Development and Application of Methods for Enantioselective Synthesis of Amines and Alcohols

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A dissertation

submitted to the Faculty of

the department of Chemistry

in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

Boston College
Morrissey College of Arts and Sciences
Graduate School

June 2020

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Abstract

Homoallylic amines and alcohols, particularly those amenable to further functionalization, are among the most widely used building blocks in chemical synthesis and are typically accessed by addition of an allyl-metal compound to an electrophile. Studies discussed herein have focused on advancing stereoselective synthesis of versatile allylboron compounds and their utilization in catalytic regio-, diastereo-, and enantioselective addition to various electrophiles. Mechanistic principles have been central to the investigations described in this thesis, and it has been on this basis that catalytic strategies for practical synthesis of bioactive molecules were developed.

Chapter One. Vicinal amino alcohols are ubiquitous in natural products and serve as versatile synthetic intermediates and we envisaged that diastereo- and enantioselective additions of *O*-substituted allyl boronates offers an attractive option to access these motifs. In the presence of zinc (II) methoxide as co-catalyst, it will be demonstrated that sequence of events may occur, wherein isomerization of an initially formed allyl complex occurs prior to addition of an aldimine with kinetic selectivity. As will be described, through the use of an optimal catalyst, *N*-protecting/activating group and appropriate reaction conditions, differentially protected vicinal amino alcohol derivatives may be synthesized in high enantiopurity. The utility of the approach is highlighted through synthesis of an NK_1 agonist.

Chapter Two. It will be demonstrated that additions of various organoboron compounds converts readily accessible and easy-to-handle silyl-substituted α-tertiary amines. Contrary to additions to aldimines, isomerization of the initially generated aminophenol-allyl complex is preempted, such

that linear products are favored. DFT analysis suggests that high enantioselectivity likely originates from attractive electrostatic interaction between a trifluoromethyl group and the catalyst's ammonium moiety. The synthetic utility was highlighted through concise, enantioselective synthesis of a key intermediate of a recently reported BACE-1 inhibitor on gram scale.

Chapter Three. This section details the development of a method for direct synthesis of homoallylic alcohols bearing a *Z*-alkenyl chloride, which may be directly subjected to stereo-retentive cross coupling without wasteful protection/deprotection or redox operations. Products were obtained in high regio- and enantioselectivity for aliphatic, alkenyl- and heteroaryl-substituted aldehydes. The approach was utilized in a concise, protecting group-free synthesis of anti-tumor agent mycothiazole.

Chapter Four. A method for stereoselective synthesis of fluorine-containing trisubstituted allyl boronates will be presented. It will then be illustrated that in the presence of an appropriate aminophenol catalyst, a large assortment of homoallylic alcohols containing a quaternary fluoro- and trifluoromethyl-substituted stereogenic center may be obtained with efficiency and high diastereo- and enantioselectivity. The obtained products were then elaborated to the furanose core of Sofosbuvir, a recently approved treatment for hepatitis C.

Acknowledgements

Five years ago, I made the decision to move to Boston to begin my graduate school experience. In this relatively short time I have grown considerably as both a person and a scientist, developing the technical skills to be a professional and striking out on my own for the first time. From filing my first insurance claim when my motorcycle was backed into, to paying my first parking ticket for misinterpreting street cleaning restrictions, Boston will always remain special to me. Reflecting now as I prepare to leave, I am astonished at how time passes and would not give up this experience despite volatile days filled with stress or anxiety.

Of course, it is not just geography that makes a place special, it is the people. I could not have done this without the support and friendship of graduate students and post-docs alike. Thursday night trivia at Common Ground, fish bowls at Tavern, mystery buckets at Patron's and infamous nights at Hong Kong were the glue that kept us together as we commiserated, laughed and got to break out clothes without holes in them for the first time in weeks. I am thankful for all those who laughed with me, and at me, shared mojitos and Bud Light, and ventured up north to spend weekends grilling and skiing

Aside from these experiences and friendships forged outside the lab, I also have to extend my gratitude to everyone in Merkert who made coming to work enjoyable. The collegial nature is the main reason I decided to pursue studies here, and I am forever grateful to everyone who opened up their inventories to let me borrow a chemical, phoned the lab from the NMR, or offered a seat in the lunch rooms or lecture halls. I would also like to thank the administrative staff for their willingness to reserve rooms, processing the load of orders I delivered every other week and keeping up morale with department wide barbeques, ice cream socials and other events.

I must also extend my thanks to my advisor, Amir Hoveyda, for his constant support and ability to push me outside of my comfort zone. I do not think I could have found another environment in which I could grow so rapidly and broadly. I was able to develop a strong

independence as well as forge effective collaborations under his direction, and I have learned to always dig deeper, never be satisfied with just one result and spend time considering outliers carefully. I will surely take these skills and philosophies with me as I begin the next chapter of my career.

Concluding this experience would not be possible without the support of my committee, and I would like to take this time to thank Professors Marc Snapper and Masa Wasa for not only reading this dissertation, but also sharing their perspective and knowledge of the craft in the courses I had the pleasure of teaching and taking with them.

Finally, this journey would not have been possible without the love and support of Molly MacPherson. I am so glad you took the leap of faith to make the move to Boston, because I truly do not think I would have made it through otherwise.

Table of Contents

Chapter One

Diastereo- and Enantioselective Synthesis of Amino Alcohols and Derivatives

1.1 Introduction

The predictable and high diastereoselectivity in which substituted allyl metal reagents add to electrophiles is an effective strategy for generating vicinal stereogenic centers, especially in acyclic systems.[1] Models for stereoselective addition, delineated as Type I, II, and III by Denmark[2] and Seebach,[3] account for stereochemical outcome based upon the identity of the crotyl-metal reagent.

Type I additions are proposed to proceed through a closed, six-membered transition state where *Z*- and *E*-substituted reagents afford *cis*- and *trans*-configured products. Additions classified as Type II afford *syn* diastereomer, regardless of the initial stereochemistry of the allyl reagent, owing to a favorable orientation of the crotyl metal compound's substituent and the Lewis acid such that steric pressure is minimized (Scheme 1.1b). Type III additions involve crotyl-metal speciess (typically Cr-, Li-, Ti- or Zn-based) with the ability to equilibrate to the more thermodynamically stable *E* isomer prior to addition, generating products with *anti*-stereochemistry.

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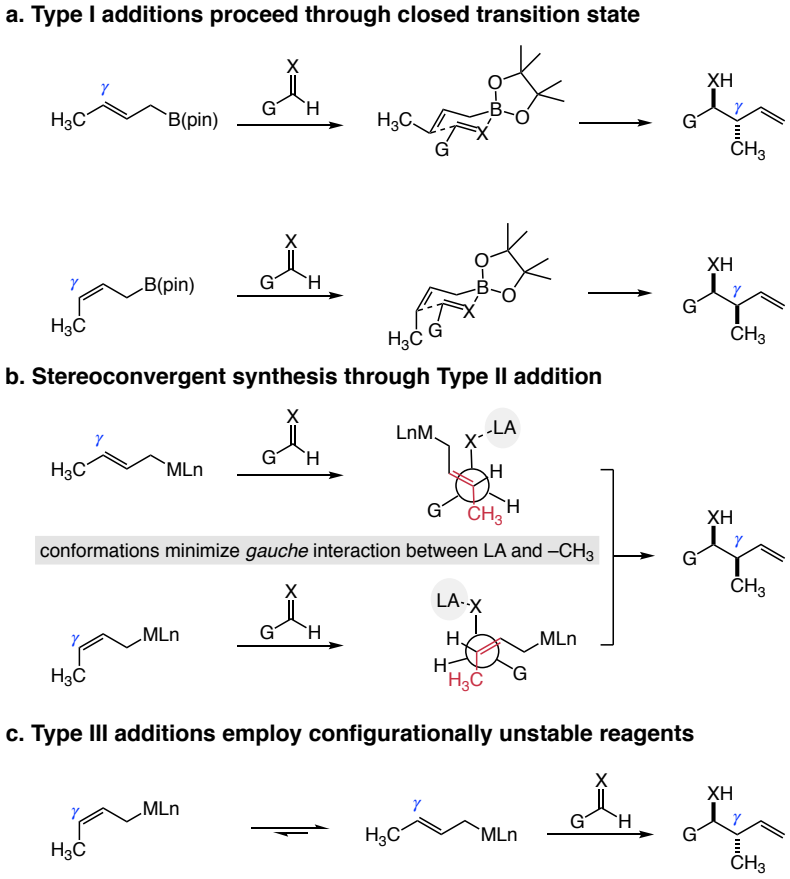
1) For a recent review regarding enantioselective addition of allyl nucleophiles to carbonyl compounds and imines, see: Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774–7854. For a recent review on diastereoselective methods for these transformations, see: Yus, M. González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595–5698.

2) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta.* **1983**, *66*, 1655–1660.

3) Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* **1982**, *21*, 654–660.

Scheme 1.1. Classification of Crotyl-Metal Additions to Carbonyl Compounds and Imines



1.2 Background

1.2.1 Highlights of the State-of-the-Art for Additions to Imines

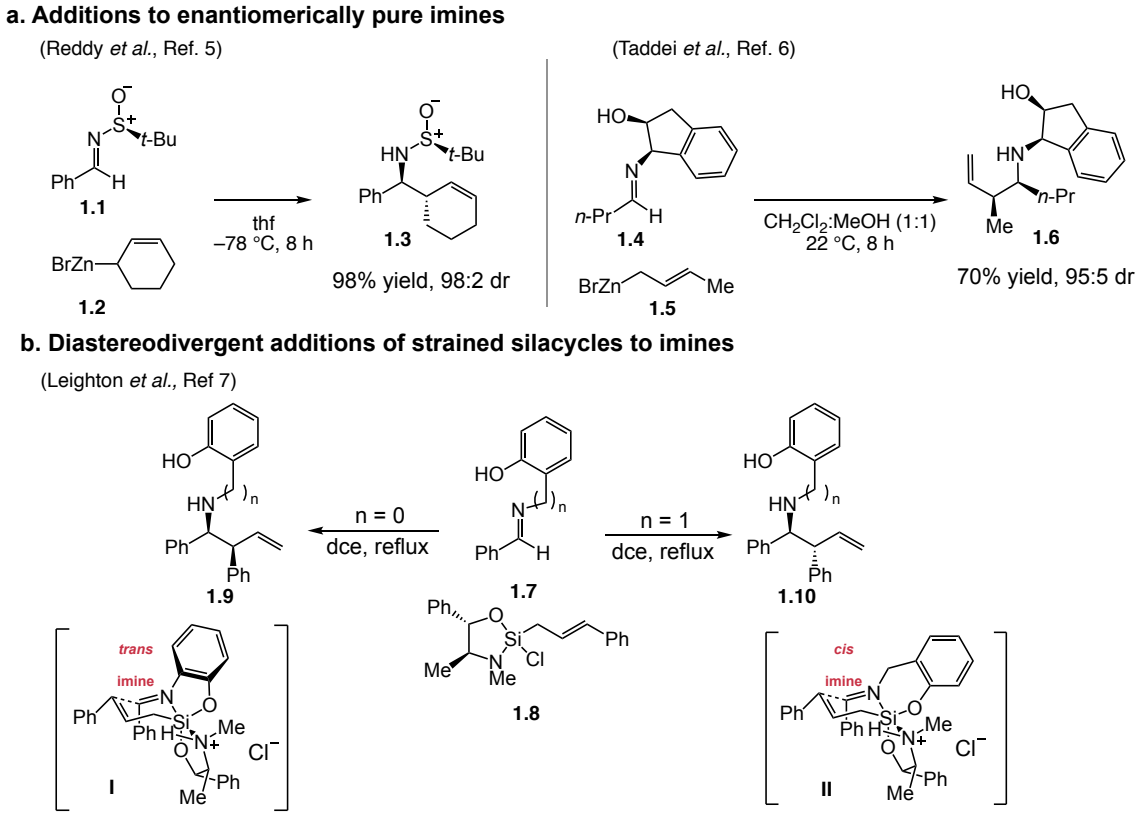
Enantiomerically enriched homoallylic amines, which serve as valuable synthetic intermediates en route to many bioactive molecules and natural products, may be accessed by addition of substituted allyl metal compounds to imines.[4] Despite major advances, the available methods are typically limited to additions to enantiomerically pure *N*-*tert*-butylsulfinyl imines **1.1**,[5] or to those derived from amino alcohol auxiliaries, such as **1.4** (Scheme 1.2a).[6]

4) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.

5) Reddy, L. R.; Bin, H.; Prashad, M.; Prashad, K. *Org. Lett.* **2008**, *10*, 3109–3112.

6) Arena, G.; Zill, N.; Salvadori, J.; Girard, N.; Mann, A.; Taddei, M. *Org. Lett.* **2011**, *13*, 2294–2297.

Scheme 1.2. Representative Additions of Crotyl Metal Reagents to Imines



Leighton and co-workers have developed strain-release strategies for synthesis of enantiomerically pure allyl-substituted silacycles **1.8** to *N*-aryl or *N*-benzyl imines. Each diastereomer may be accessed through modification of the *N*-protecting group of **1.7**. However, the method is limited to aryl-substituted silacycles.[7] In follow up studies, Leighton *et al.* expanded the method's scope to include alkyl-substituted imines and other allyl silanes.[8] Still, unmasking the NH_2 amine required strongly reducing conditions ($Pd(OH)_2/C$, ammonium carbonate), resulting in concomitant reduction of the olefin.[9]

7) Huber, J. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 14552–14553.

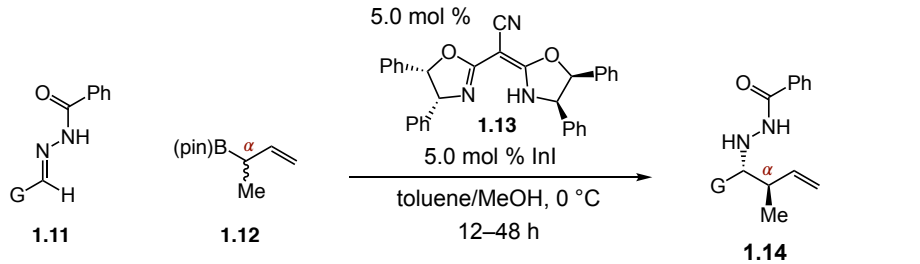
8) Huber, J. D.; Perl, N. R.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 3037–3039.

9) Feske, M. I.; Santanilla, A. B.; Leighton, J. L. *Org. Lett.* **2010**, *12*, 688–691.

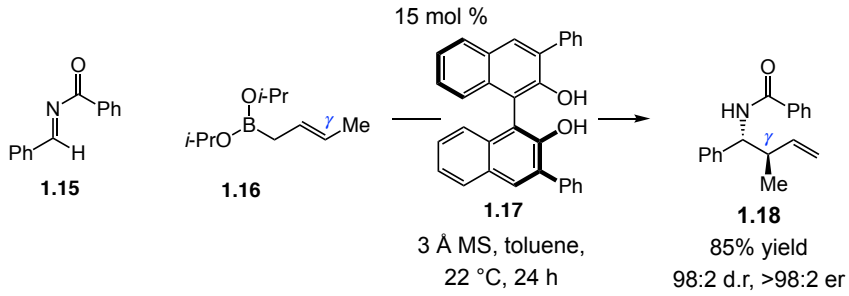
In addition to reactions involving enantiomerically pure imines or reagents, there are a handful of reports detailing strategies for additions with alkyl-substituted stannanes,[10] silanes,[11] indium-based compounds,[12] and boronates[13] to aldimines, generating products bearing vicinal stereogenic centers diastereo- and enantioselectively. Two examples of this class are highlighted in Scheme 1.3.

Scheme 1.3. Catalytic Enantioselective Addition of Allyl Boronates to Imines

a. Kobayashi's indium catalyzed additions to hydrazones



b. Schaus's chiral diol catalyzed additions to *N*-acyl imines



10) (a) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844–4849. (b) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1896–1898.

11) (a) Naodovic, M.; Wadamoto, M.; Yamamoto, H. *Eur. J. Org. Chem.* **2009**, *30*, 5129–5131. (b) Momiyama, N.; Nishimoto, H.; Terada, M. *Org. Lett.* **2011**, *13*, 2126–2129.

12) Tian, K. L.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2007**, *46*, 1315–1317.

13) (a) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398–15404. (b) Fujita, M.; Nagano, T.; Schneider, U.; Hamada, T.; Ogawa, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2914–2915. (c) Luo, Y.; Hepburn, H. B; Chotsaeng, N. Lam, H. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 8309–8313.

In 2010, Kobayashi outlined a strategy for indium(I)-catalyzed additions of racemic α-substituted allyl boronic pinacol ester **1.12** to aryl- and heteroaryl-substituted hydrazones **1.11** (Scheme 1.3a), furnishing products **1.14** in 83–98% yield, 87:5–95:5 dr, and 92:8–96.5:3.5 er.[14] Unfortunately, neither additions to aliphatic hydrazones nor unmasking the amine were addressed. In a related report involving additions of organoboron compounds, Schaus disclosed a method for addition of the air- and moisture-sensitive *E*-crotyl allyl boronate **1.16** to *N*-acyl aldimine **1.15** affording *trans*-homoallylic amide **1.18** as a single diastereomer and in >98:2 er. The scope of the approach was not expanded further, however. Under the same conditions, the *Z* isomer of **1.16** afforded the same product **1.18** in 98:2 dr and 94:6 er.

We reasoned that a more broadly applicable and versatile catalytic approach would constitute a valuable addition to the state-of-the-art, and thus became interested in additions of heteroatom-substituted allyl boronates. We were particularly keen on developing additions with *O*-substituted allyl boronates, as such transformations would provide access to differentially protected 1,2-aminoalcohols and derivatives.

1.2.2 Methods for Synthesis of Amino Alcohols

Vicinal amino alcohols are prevalent in many bioactive compounds (Scheme 1.4),[15] serve as chiral auxillaries[16] for diastereoselective synthesis, and are employed as ligands to promote

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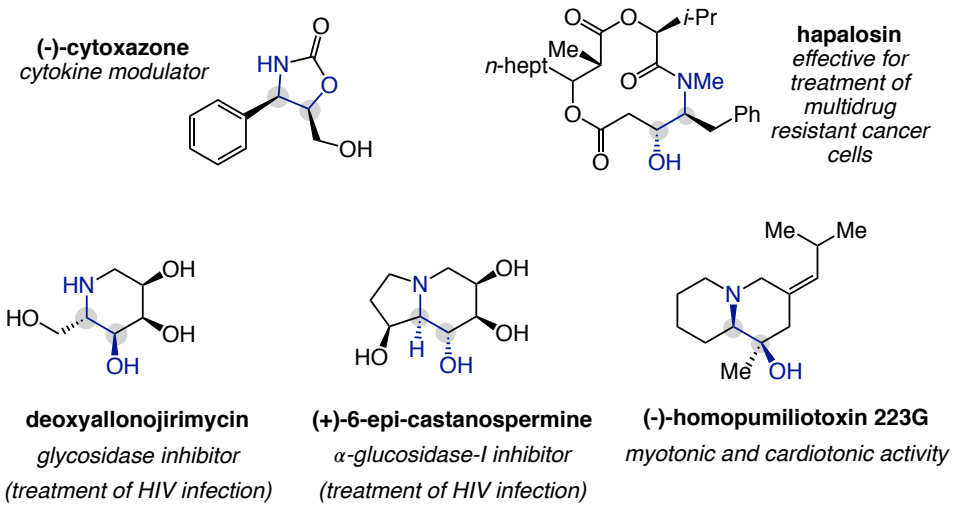
14) Chakrabarti, A.; Konishi, H.; Yamaguchi, M.; Schneider, U.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 1838–1841.

15) For synthesis and bioactivity of cytoxazone, see: Lingamurthy, M.; Nallibonia, G. R.; Rao, M. W.; Rao, B. V.; Reddy, B. S.; Kumar, H. M. S. *Tetrahedron* **2017**, *73*, 1473–1481. For synthesis and bioactivity of hapalosin, see: Okuno, T.; Ohmori, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron,* **1996**, *52*, 14723–14734. For synthesis od indolizine and pyrrolizidine alkaloids deoxyallonojirimycin and castanospermine, see: Michael, J. P.; *Nat. Prod. Rep.* **2008**, *25*, 139–165 and references therein. For synthesis of homopumiliotoxion 223G, see: Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643–652. (b) Kibayashi, C.; Aoyagi, S.; Wang, T.-C.; Saito, K.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **2000**, *63*, 1157–1159.

16) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767–796.

catalytic transformations.[17] As a result, considerable effort has been directed towards development of methods that afford these structural motifs.[18]

Scheme 1.4. Representative Bioactive Compounds Possessing Vicinal Amino Alcohol Derivatives



Among the strategies developed for enantioselective synthesis of vicinal amino alcohol derivatives, are those involving addition of oxygen-substituted enolates to imines.[19] In an early report, Kobayashi and co-workers disclosed enantioselective addition of silyl ketene acetal **1.20** to *N*-aryl substituted imine **1.19** promoted by zinc-based binapthol complex **1.21**, furnishing products **1.22** in 41–98% yield, 68:32–94:6 dr and 88:12–98:2 er (Scheme 1.5a).[20] The scope was limited to aryl imines, and three steps were required to unmask the amine, including alkylation of the phenol and subsequent oxidation with ceric ammonium nitrate (CAN). In 2004, Shibasaki outlined an approach regarding diastereo- and enantioselective synthesis of α-hydroxy-β-amino ketones **1.26** through addition of an in situ generated enolate to phosphinoyl imine **1.23** (Scheme 1.5b).

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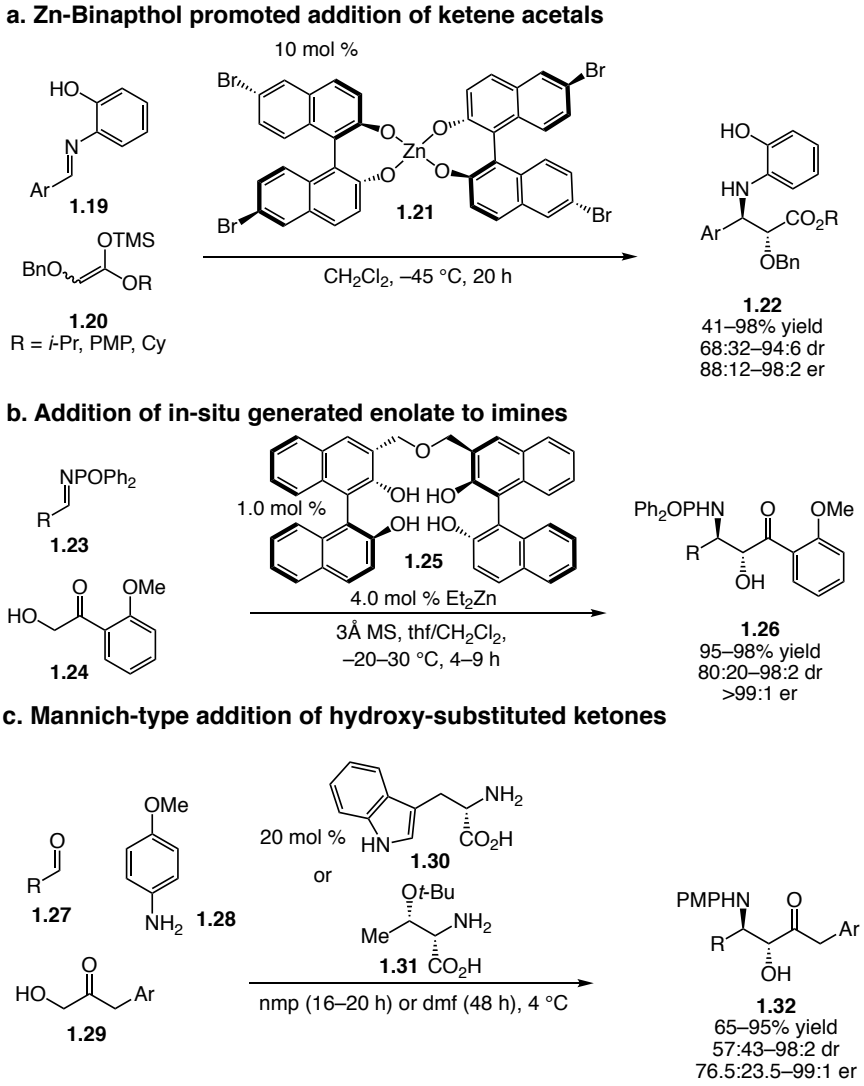
17) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–876.

18) For a recent review, see: Bergmeier, S. C. *Tetrahedron,* **2000**, *56*, 2561–2576. (b) Karjalainen, O. K.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2012**, *10*, 4311–4326.

19) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2002**, *125*, 338–339. Wu, C.; Fu, X.; Li, S. *Tetrahedron: Asymmetry* **2011**, *22*, 1063–1073.

20) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431–432.

Scheme 1.5. Catalytic Enantioselective Addition of *O*-Substituted Enolates



Transformations were promoted by binapthol-Zn complex **1.25**,[21] and either diastereomer may be accessed by this method. Nonetheless, only *o*-methoxyketone **1.24** can be used as the nucleophilic precursor. In related account, Trost has detailed the application of zinc-based prophenol complexes for highly enantioselective, but minimally diastereoselective, additions to the same class of imines.[22] In 2006, Barbas and co-workers showed that Mannich reactions of

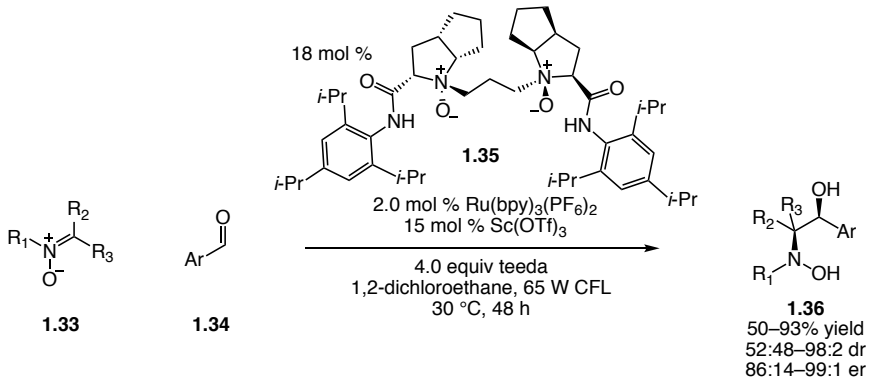
21) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777–8785.

22) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778–2779.

benzyl-substituted α-hydroxy ketones **1.29** to in-situ generated aryl imines can be catalyzed by 20 mol % of a readily available amino acid (Scheme 1.5c).[23]

Another relevant strategy entails reductive coupling of imines and aldehydes,[24] typically promoted by stoichiometric quantities of SmI_2, and accompanied by formation of side products derived from homocoupling or reduction. Recently, a method has been disclosed for intramolecular coupling for enantioselective synthesis of a limited set of amino alcohols and derivatives, wherein two catalysts, one to serve as a photosensitizer and the other, a chiral phosphoric acid, promotes enantioselective C–C bond formation.[25] Huang has introduced a more generally applicable strategy for reductive coupling of aromatic aldehydes **1.34** and nitrones **1.33** (Scheme 1.6). Reactions proceed through single electron transfer (SET) to the aldehyde, followed by C–C bond formation facilitated by Sc-based chiral complex **1.35**.[26]

Scheme 1.6. Catalytic Reductive Coupling of Nitrones and Aldehydes



23) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *129*, 288–289.

24) (a) Masson, G.; Py, S.; Vallée, Y. *Angew. Chem. Int. Ed*. **2002**, *41*, 1772–1775. (b) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956–11957. (c) Burchak, O. N.; Py, S. *Tetrahedron* **2009**, *65*, 7333–7356. (d) Wang, B.; Wang, Y.-J. *Org. Lett.* **2009**, *11*, 3410–3413.

25) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 17735–17738.

26) Ye, C.-X.; Melcamu, Y. Y.; Li, H.-H.; Cheng, J.-T.; Zhang, T.-T.; Ruan, Y.-P.; Zheng, X.; Lu, X.; Huang, P.-Q. *Nat. Commun.* **2018**, *9*, 1–9.

Catalytic enantioselective strategies for addition of hydroxyl-amines to alkenes represents another noteworthy approach.[27] Despite widespread applications in synthesis, such reactions can generate regioisomeric mixtures and chloro-containing byproducts. Incorporation of the source of nitrogen as a carbamate has led to improved selectivity in certain intramolecular examples,[28] nonetheless, the resulting cyclic amides present complications themselves. The transformation shown in Scheme 1.7 represents the most efficient available approach for synthesis of vicinal amino alcohols and derivatives.[29] Vicinal amino alcohols may be accessed through catalytic enantioselective addition of N-based nucleophiles to epoxides,[30] although regioselectivity can diminished in the absence of conjugation.[31] Catalytic hydrogenation of enantiomerically enriched

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27) (a) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 2813–2817. (b) Jiang, Y.; Chen, X.; Zheng, Y.; Xue, Z.; Chu, C.; Yuan, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 7304–7307. (c) Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. *Chem. Eur. J.* **2011**, *17*, 58–76. (d) Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2446–2449.

28) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514–2515.

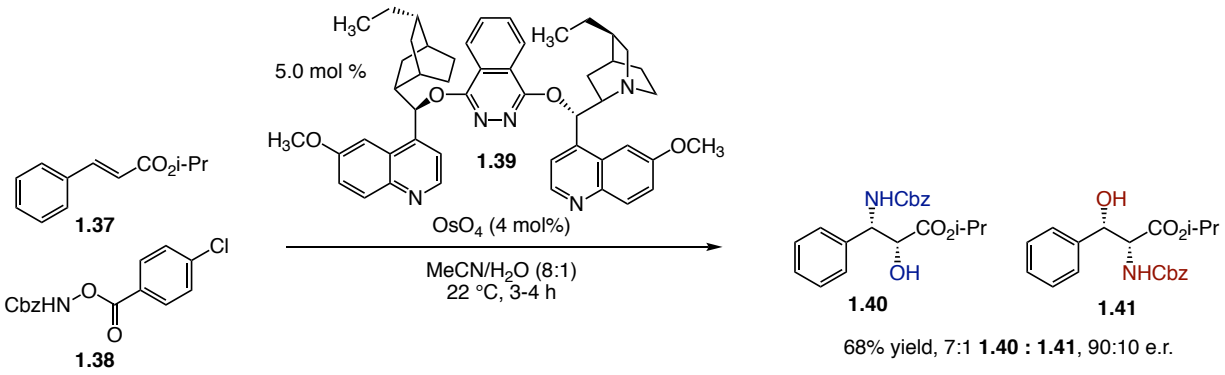
29) Harris, L.; Mee, S. P .H.; Furneaux, R. H.; Gainsford, G. J.; Luxenburger, A. *J. Org. Chem.* **2011**, *76*, 358–372.

30) (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768–2769. (b) Jacobsen, E. N.; *Acc. Chem. Res.* **2000**, *33*, 421–431. (c) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343–345. (d) Bartoli, G.; Bosco, M.; Carlone. A.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 2173–2176. (e) Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2005**, *7*, 4593–4595. (f) Carrée, F.; Gil, R.; Collin, J. *Org. Lett.* **2005**, *7*, 1023–1026. (g) Mai, E.; Schneider, C. *Chem. Eur. J.* **2007**, *13*, 2729–2741. (h) Kureshy, R. I.; Prathap, K. J.; Agrawal, S.; Khan, N.-u. H.; Abdi, S. H. R.; Jasra, R. V. *Eur. J. Org. Chem.* **2008**, *18*, 3118–3128. (i) Agarwal, J.; Duley, A.; Rani, R.; Peddinti, R. *Synthesis* **2009**, *16*, 2790–2796. (j) Bao, H.; Wu, J.; Li, H.; Wang, Z.; You, T.; Ding, K. *Eur. J. Org. Chem.* **2010**, *35*, 6722–6726. Pujala, B.; Rana, S.; Chakraborti, A. K. *J. Org. Chem.* **2011**, *76*, 8768–8780. (k) Lu, H.-F.; Sun, L.-L.; Le, W.-J.; Yang, F.-F.; Zhou, J.-T.; Gao, Y.-H. *Tetrahedron Lett.* **2012**, *53*, 42674272. (l) Birrell, J. A.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 2895–2897. (m) Weng, C.; Zhang, H.; Xiong, X.; Lu, X.; Zhou, Y.; *Asian. J. Chem.* **2014**, *26*, 3761–3768. (n) Kumar, M.; Kureshy, R. I.; Saravanan, S.; Verma, S.; Jakhar, A.; Khan, N.-u. H.; Abdi, S. H. R.; Bajaj, H. C. *Org. Lett.* **2014**, *16*, 2798–2801. (o) Srikanth, G.; Ramakrishna, K. V. S.; Sharma, G. V. M. *Org. Lett.* **2015**, *17*, 4576–4579. (p) Tak, R.; Kumar, M.; Kureshy, R. I.; Choudhary, M. K.; Khan, N.-u. H.; Bajaj, H. C. *RSC Adv.* **2016**, *6*, 7693–7700. (q) Tak. R.; Kumar, M.; Menapara, T.; Choudhary, M. K.; Kureshy, R. I.; Khan, N.-u. H. *ChemCatChem* **2017**, *9*, 322–328.

31) Jaime, C.; Ortuno, R.; Font, J. *J. Org. Chem.* **1988**, *53*, 139–141. (b) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8754–8583.

α-amino ketones[32] and catalytic enantioselective reduction of α-ketoamides,[33] represent other noteworthy strategies.

Scheme 1.7. Enantioselective Synthesis of Vicinal Amino Alcohols by Alkene Functionalization



Despite the potential utility of vicinal amino alcohols that contain a monosubstituted olefin, strategies for enantioselective allyl addition of *O*-substituted allyl boronates are uncommon.[34] In a series of related reports, Ramanchandran[35] and Soderquist[36] introduced methods for reaction of *N*-aluminoimine **1.42** with enantiomerically pure organoboron compounds to yield *syn*-1,2-aminoalcohols **1.44** and **1.46**, respectively (Scheme 1.8). The methoxyethoxymethyl ether group was removed during synthesis of β-amino acid derivatives (HCl/Et_2O). However, conditions for hydrolysis of the methoxy ether within **1.46** were not disclosed. The above methods suffer from the following shortcomings: (1) The reagent must be prepared fresh for each reaction at low temperature. (2) Stoichiometric amounts of aluminum alkoxide are formed as byproducts, leading to emulsions that can become problematic, especially upon scale up.

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32) Klingler, F. D. *Acc. Chem. Res.* **2007**, *40*, 1367–1376.

33) Mamillapalli, N. C.; Sekar, G. *Chem. Eur. J.* **2015**, *21*, 18584–18588.

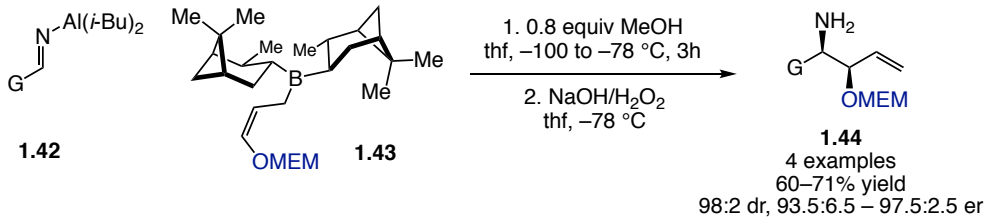
34) For synthesis of 1,2-aminoalcohols through addition of nitrogen-substituted allyl reagents to aldehydes, see: Trost, B. M.; Cregg, J. J.; Quach, N. *J. Am. Chem. Soc.* **2017**, *139*, 5133–5139. (b) Spielmann, K.; Xiang, M.; Schwartz, L. A.; Krische, M. J. *J. Am. Chem. Soc.* **2019**, *141*, 14136–14141.

35) Ramanchandran, P. V.; Burghardt, T. E. *Chem. Eur. J.* **2005**, *11*, 4387–4395.

36) Muñoz-Hernández, L.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 2571–2574. (b) Muñoz-Hernández, L.; Seda, L. A.; Wang, B.; Soderquist, J. A. *Org. Lett.* **2014**, *16*, 4052–4055.

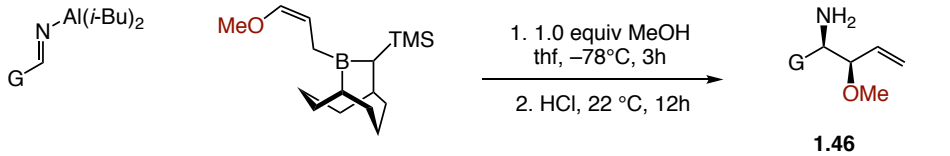
Scheme 1.8. Addition of Enantiomerically Pure *O*-Substituted Allyl Regents to Aldimines

a. Ramanchandran's allyl addition to N-aluminoimines



1.42 **1.43** **1.44**
4 examples
60–71% yield
98:2 dr, 93.5:6.5 – 97.5:2.5 er

b. Soderquist's allyl addition to N-aluminoimines



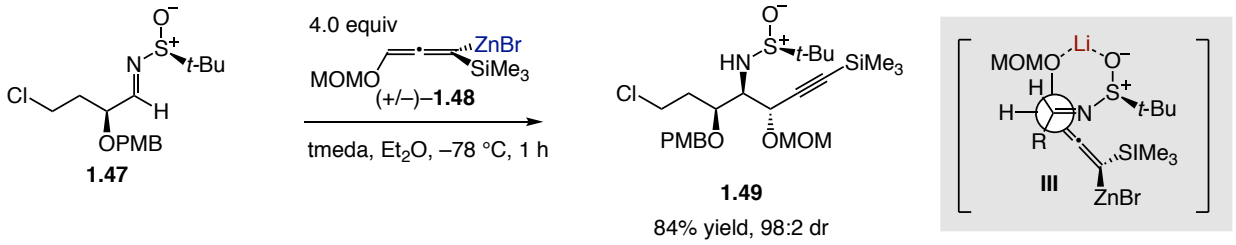
1.42 **1.45** **1.46**
5 examples
72–96% yield
98:2 dr, 78:22 – 94:6 er

Amino alcohol derivatives may be generated through addition of racemic allenyl metal compounds to enantiomerically pure sulfinyl imines, generating either diastereomer of the propargylic amine depending on the identity of the allenyl metal.[37] Accordingly, upon reaction with a Zn-based nucleophile, *anti*-amino alcohol derivatives **1.49** were furnished as a single diastereomer in 77–91% yield. Attempts to gain access to the alternative stereoisomer through the addition of additives to disrupt chelation between the sulfinyl oxygen, methyl methoxyether and the lithium cation (as shown in Scheme 1.9a) were unsuccessful. However, when treated with two equivalents of lithium cuprate **1.51** and HMPA, the desired *syn*-1,2 amino alcohols **1.52** were generated in 68–81% yield and 60:40–91:9 dr.[37b]

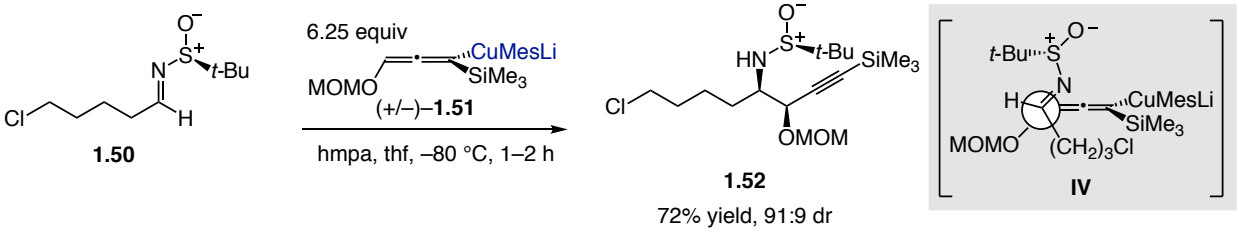
37) (a) Chemla, F.; Ferreira, F. *Synlett*, **2006**, *16*, 2613–2616. (b) Louvel, J.; Botuha, C.; Chemla, F.; Demont, E.; Ferreira, F.; Pérez-Luna, A. *Eur. J. Org. Chem.* **2010**, 2921–2926. (c) Louvel, J.; Chemla F.; Demont, E; Ferreira, F.; Pérez-Luna, A. *Adv. Synth. Catal.* **2011**, *353*, 2137–2151.

Scheme 1.9. Diastereoselective Synthesis of *Syn*- and *Anti*- 1,2–Amino Alcohols

a. Racemic allenyl zinc additions affording propargylic ethers



b. Racemic lithio cuprate additions affording propargylic ethers



Diastereoselective C–C bond formation may be effected through additions of alkenyl metal nucleophiles to enantiomerically pure α-amino aldehydes.[38] Coleman has shown that reaction with vinyl lithium **1.54** furnishes *anti*-**1.56** as predicted by the Felkin-Ahn model. Whereas, *syn*-**1.56** may be obtained by reaction with an alkenylzinc halide (eg., **1.55**) in 88:12 dr. More recently, Padron has introduced a similar strategy for diastereoselective additions of Grignard reagents to α-dibenzylamino aldehyde **1.57**.[39] Transformations may be performed in a single vessel, thereby obviating the need for reduction of the ester and subsequent oxidation to access α-amino aldehydes, as prescribed by the Reetz protocol.[40] Related derivatives were prepared through Rh-catalyzed addition of alkynes,[41] and addition of allenyl zinc compounds in 2016 and 2017, respectively.[42]

38) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697–1700.

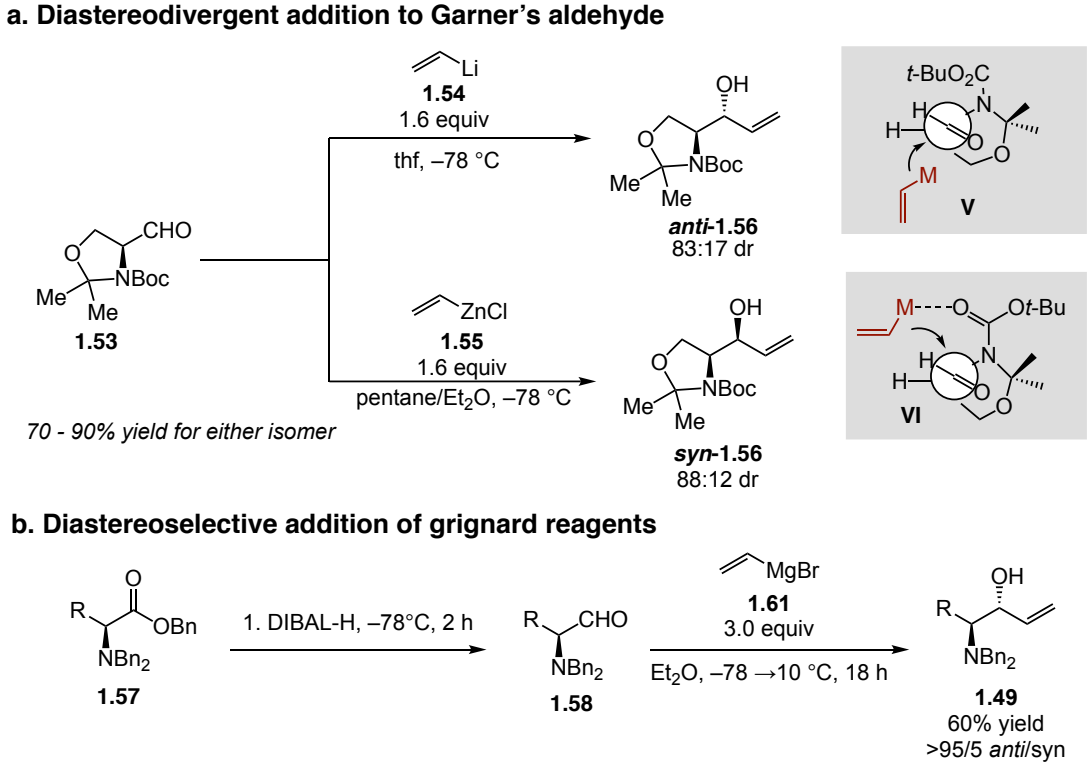
39) Silveira-Dorta, G.; Donadel, O. J.; Martín, V. S.; Padrón, J. M. *J. Org. Chem.* **2014**, *79*, 6775–6782.

40) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew Chem. Int. Ed.* **1987**, *26*, 1141–1143. (b) Reetz, M. T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1669–1972.

41) Hooper, J. F.; Seo, S.; Truscott, F. R.; Neuhaus, J. D.; Willis, M. C. *J. Am. Chem. Soc.* **2016**, *138*, 1630–1634.

42) Zamani, F.; Pyne, S. G.; Hyland, C. J. T. *J. Org. Chem.* **2017**, *82*, 6819–6830.

Scheme 1.10. Diastereoselective Addition of Alkenylmetal Compounds to α-Amino Aldehydes



In perhaps the most general transformation to date, Lin has described addition of allyl zinc compounds generated from benzoyl-substituted allyl bromide **1.62** to aryl-, heteroaryl- and alkyl-substituted sulfinyl imines **1.61**, affording **1.63** in 75–99% yield, 78:22–99:1 dr and 90:10–99:1 er. Aliphatic imines may be converted to the corresponding products in 90:10–93.5:6.5 er, nonetheless diastereoselectivity fluctuated depending on the size of the substituent (e.g., 78:22 and 98:2 dr for β- and α- branched imines, respectively). Furthermore, HMPA (hexamethylphosphoramide) was essential for optimal selectivity.[43] In a follow-up study,[44] the same authors probed the possibility of avoiding HMPA, in favor of replacing it with an alternative Lewis base additive. Such efforts were unsuccessful. However, it was determined that when allyl

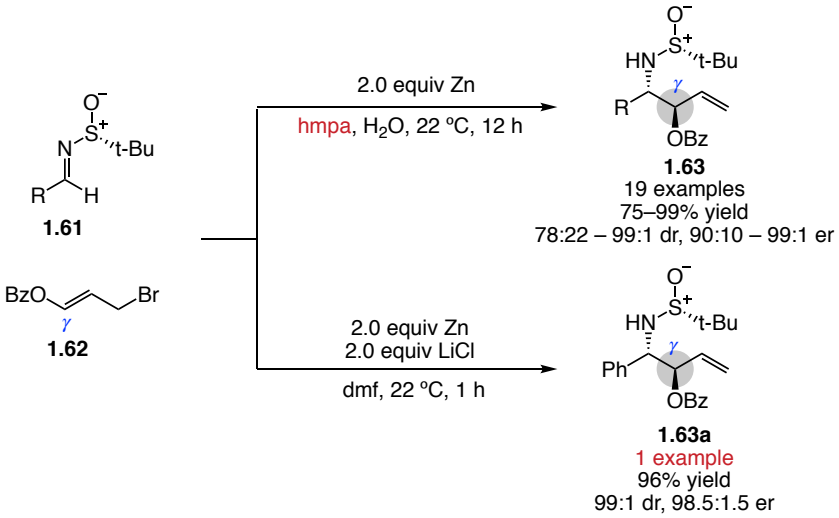
43) Lin, M.; Shen, A.; Sun, X.-W.; Xu, M.-H.; Lin, G-Q. *Chem. Eur. J.* **2010**, *15*, 10217–10224.

44) Lin, M.; Shen, A.; Sun, X.-W.; Deng, F.; Xu, M.-H.; Lin, G.-Q. *Chem. Commun.* **2010**, *46*, 8460–8462.

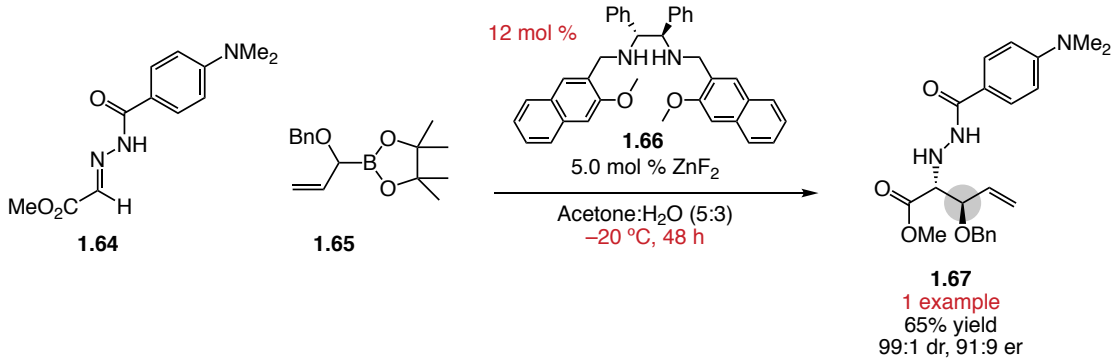
zinc compounds were synthesized according to procedures by Knochel,[45] one diastereomer is formed preferentially (e.g., **1.63a** in 96% yield, 99:1 dr and 98.5:1.5 er; Scheme 1.11a).

Scheme 1.11. Addition of Alkoxy-Substituted Allylmetal Compounds to Imines

a. Lin's diastereoselective additions to sulfinyl imines



b. Additions to hydrazono iminoesters



Kobayashi and co-workers have outlined a diastereo- and enantioselective approach for addition of allyl boronates to hydrazono imino esters **1.64** in aqueous media (Scheme 1.11b).[46] In this report, there is a single example involving allylic boronate **1.65** substituted with a benzoloxy

45) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 5376–5377.

46) Fujita, M.; Nagano, T.; Scheider, U.; Hamada, T.; Ogawa, C.; Kobayshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2914–2915.

ether affording 1,2-aminoalcohol derivative **1.67** as a in 65% yield, >99:1 α:γ ratio, 99:1 dr and 91:9 er.

1.3 Organoboron Catalysts for Enantioselective C–C Bond Formation

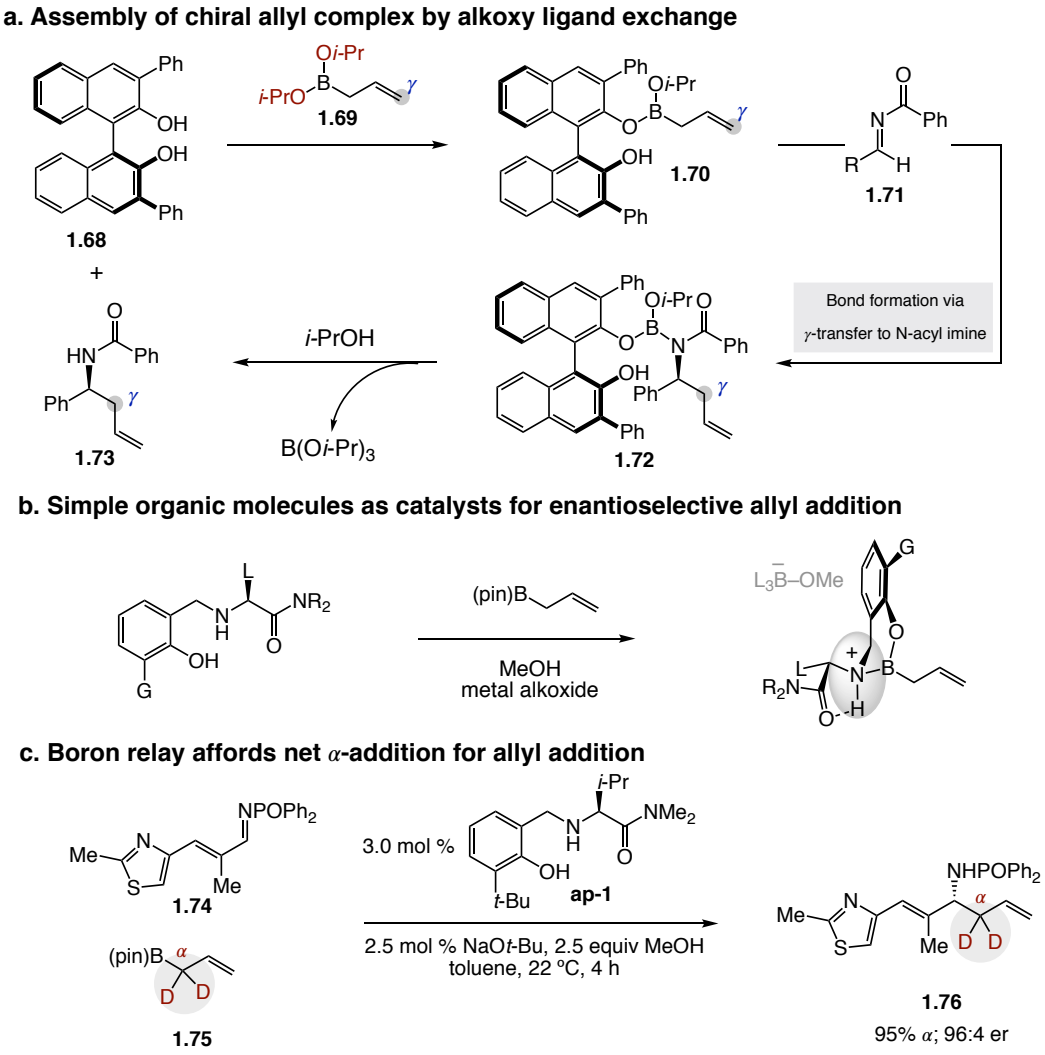
1.3.1 Aminophenol-Based Boryl Catalysts for Efficient and Enantioselective Allyl Additions

Development of enantio- and diastereoselective C–C bond forming reactions, particularly those that can operate with broad scope and predicable stereochemical outcomes and are amenable to scale-up are crucial to furthering the state-of-the-art in chemical synthesis and drug discovery. In 2013, our group identified a simple organic molecule as a catalyst for efficient, enantio- and diastereoselective addition of a variety of allyl boronates to *N*-diphenylphosphinoyl aldimines.[47] The catalyst scaffold is robust, and may be rapidly optimized, as it is derived from amino acid residues often accessible in both enantiomers, and its synthesis is straightforward, scalable and inexpensive.

It has been proposed that under the mildly acidic reaction conditions, the active complex contains an ammonium group, giving rise to unique reactivity observed and region- and enantioselectivity (Scheme 1.12b). The ammonium unit enhances boron Lewis acidity, ensures tight substrate binding, thereby rigidifying transition state structures and improving enantiofacial discrimination. Contrary to the majority of exisiting methods,[13a] additions are net α-selective (*cf.* Scheme 1.12a, 1.12c).

47) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216–221.

Scheme 1.12. Synthesis of Enantiomerically Enriched Amines Catalyzed by Organoboron Catalysts

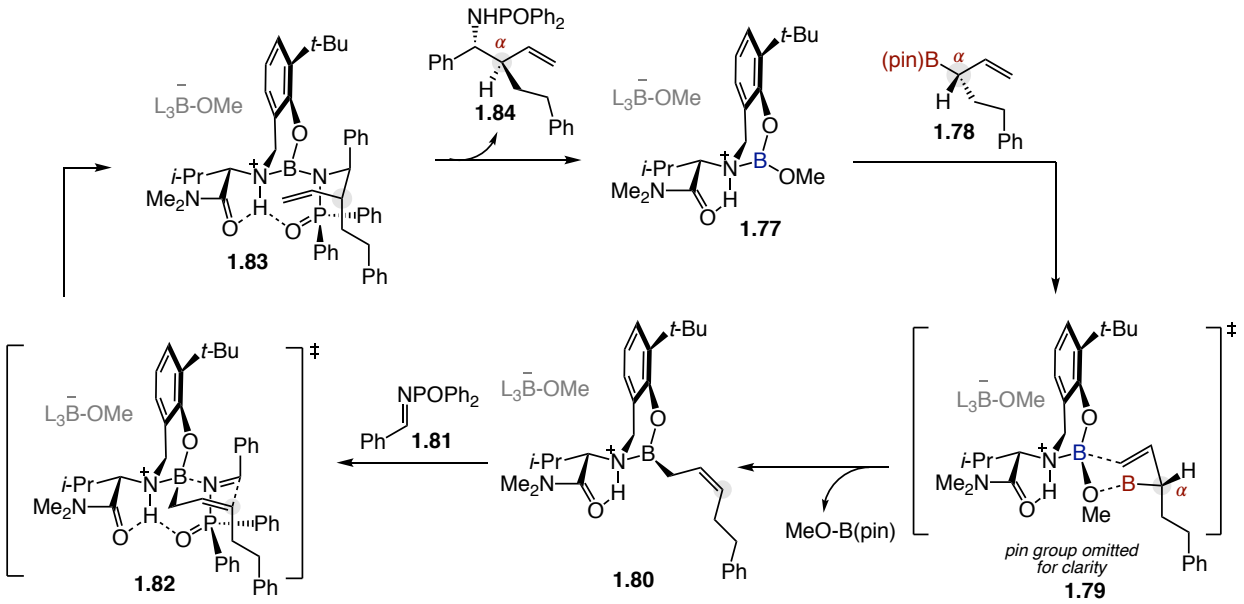


Synthesis of homoallylic amines bearing vicinal stereogenic centers, such as **1.84**, therefore required an enantioenriched allyl boronate (**1.78**, Scheme 1.13). Despite the growing number of methods to synthesize these motifs,[48] allylic boronates can undergo a 1,3-boryl shift, furnishing a more stable disubstituted olefin. We reasoned that we might take advantage of this propensity for isomerization as a design element for enantioselective transformations. That is, we could facilitate

48) For representative methods for synthesis of enantiopure allyl boronates bearing an allylic stereogenic center, see: (a) Seiber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74–75. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857. (c) Carosi, L.; Hall, D. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5913–5915. (d) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134–9135.

isomerization of the initially generated **1.87** to complex **1.89** prior to C–C bond formation. In doing so, vicinal stereogenic centers would be generated without the need for enantiomerically pure reagents.

Scheme 1.13. Formation of Vicinal Stereogenic Centers with Enantiomerically Enriched α-Substituted Allyl Boronates



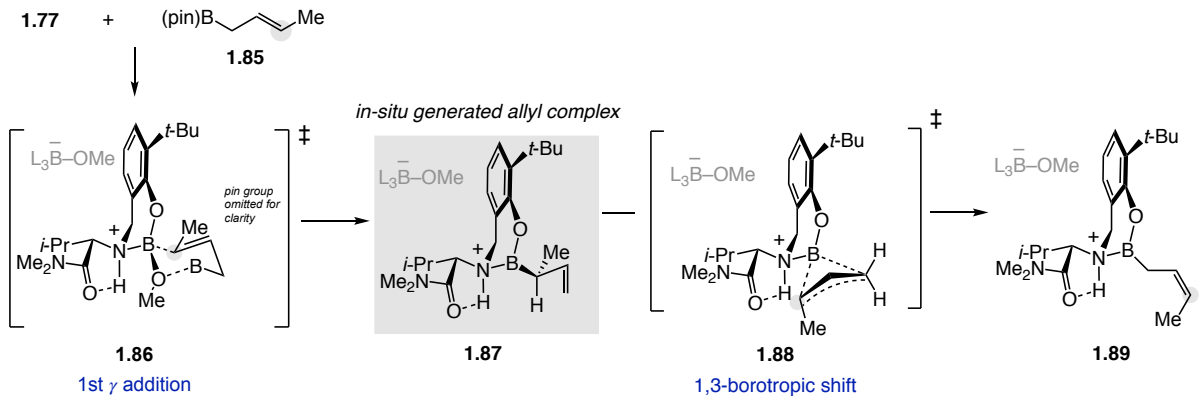
We chose to explore development of this concept by carrying out diastereo- and enantioselective addition of **1.85** to phosphinoyl aldimine **1.81**, because this particular class of imine exhibited stability under typical conditions (i.e., minimal hydrolysis in protic media).[49] Accordingly, there was only 35% conversion after 24 hr with **1.85**. We reasoned that diminished efficiency is the result of the steric pressure generated by the γ carbon (see Scheme 1.14, **1.86**). Notably, the product was obtained as a mixture of regioisomers (**1.90** and **1.91**), which is in contrast to the α-selective formerly investigated (Scheme 1.12c). Considering the transformation does not proceed (<5%) in the absence of a catalyst, formation of the minor regioisomer (**1.90**) is

49) (a) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332–3335. (b) Mszar, N. W.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 3362–3365.

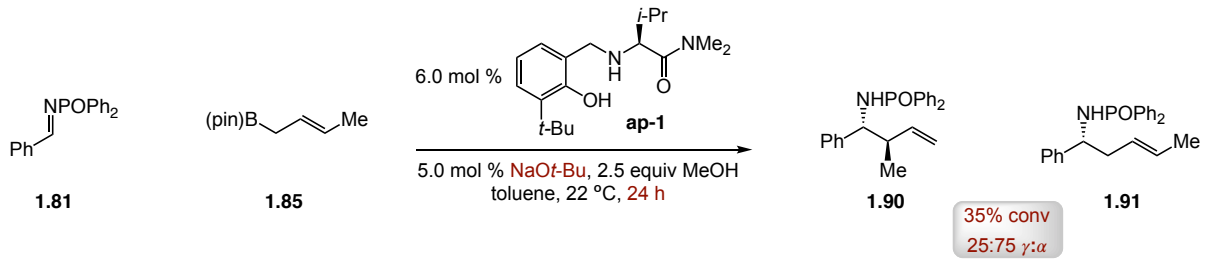
probably the result of reaction with **1.89**, indicating that isomerization of allyl complex **1.87** is competitive with direct addition. To favor isomerization further, we identified a series of reaction conditions to increase the concentration of complex **1.89**. The results of these studies are detailed below.

Scheme 1.14. Addition of Allyl Boronates Containing a Monosubstituted Olefin

a. 1,3-Boryl shift as a design element



b. Initial result for addition of substituted allyl boronate



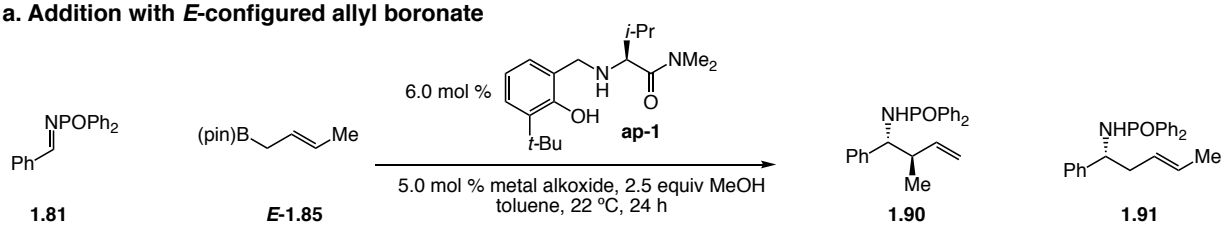
1.3.2 Reactions with Crotyl Boronates and a Zinc Alkoxide as a Co-Catalyst

Initial screening revealed that incorporation of a Lewis acid co-catalyst, namely, a zinc (II) salt improved efficiency and regioselectivity (**1.90** as the major isomer, Scheme 1.15a). We postulated that the benefit of a Lewis acid co-catalyst might originate from a more efficient allyl

exchange (**1.91**), faster 1,3-borotropic shift (**1.92**) and/or an increase in the concentration of active complex **1.94** (by disfavoring amide coordination to the boron center).[50]

Scheme 1.15. Effect of Lewis Acidic Co-Catalyst

a. Addition with *E*-configured allyl boronate

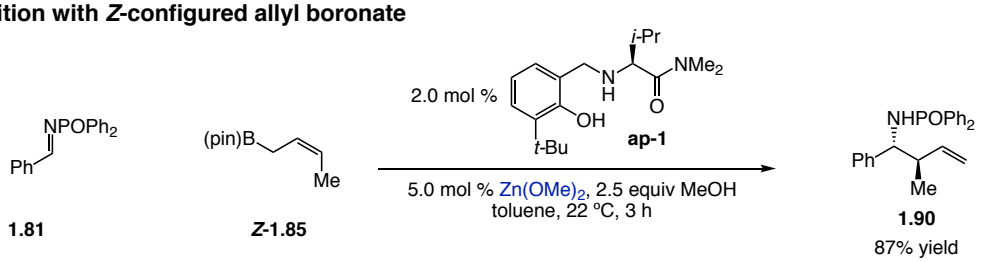


with NaO*t*-Bu
35% conv,
25:75 γ:α

with Zn(O*t*-Bu)$_2$
>98% conv, 83% yield
75:25 γ:α
89:11 dr, 95:5 er

with Zn(OMe)$_2$
>98% conv, 83% yield
90:10 γ:α
94:6 dr, 96:4 er

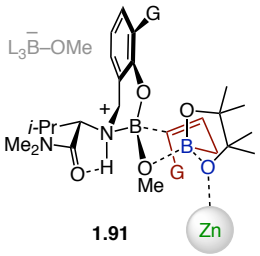
b. Addition with *Z*-configured allyl boronate



87% yield
>98:2 γ:α
93:7 dr, 96:4 er

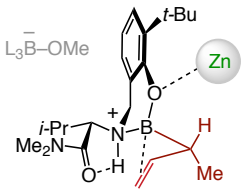
c. Benefits of zinc co-catalyst on efficiency and selectivity

More efficient allyl exchange?



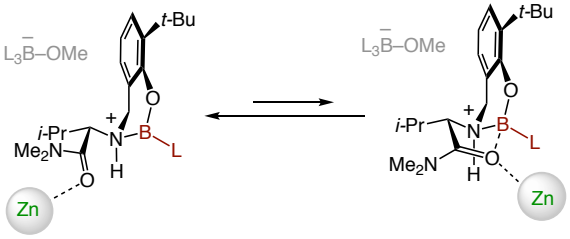
1.91

More efficient borotropic shift?



1.92

More active complex?



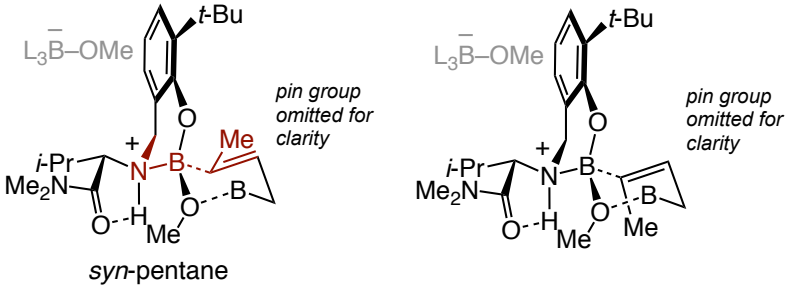
1.93 **1.94**

It is important to note that, regardless of the initial stereochemistry of the allyl reagent (i.e., either ***E*-1.85** or ***Z*-1.85**), only one diastereomer, namely, *anti*-homoallylic amine **1.90**, was

50) van der Mei, F. W.; Miyamoto, H.; Silverio, D. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4701–4706.

formed. The increased efficiency for ***Z*-1.85** may be rooted in faster allyl transfer benefiting due to release of strain inherent in a *Z* alkene and the probable *syn*-pentane interaction present in **1.86**, that is lacking in **1.95**.

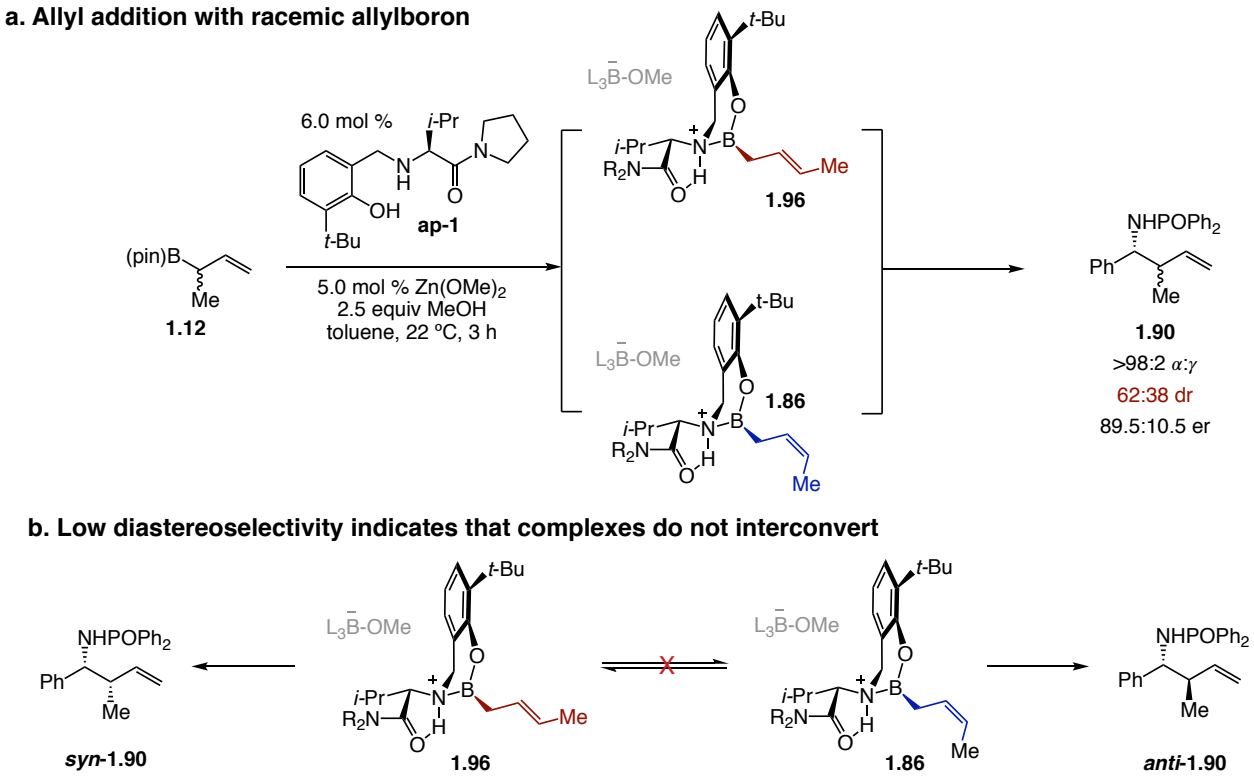
Scheme 1.16. Effect of Olefin Stereochemistry on Efficiency of Allyl Transfer



These findings are mechanistically informative, supporting idea that the same allyl complex stereoisomer may be accessed from either isomer of an *E* or *Z* allyl boronate, and intermediates **1.96** and **1.89** may interconvert prior to addition to an electrophile (Curtin-Hammett kinetics). Previous investigations had indicated that initial allyl transfer is probably stereospecific.[47] Thus, by employing racemic **1.12**, we expected a mixture of **1.96** and **1.86** would be generated in-situ. If these species were to be in rapid equilibrium prior to C–C bond formation, diastereoselectivity would be high. This was not the case, indicating that it is unlikely that **1.96** and **1.86** converge under a Curtin-Hammett scenario. [51]

51) For a detailed discussion of the role of borotropic shift in impacting the regioselectivity of addition with this class of chiral catalysts, see: van der Mei, F. W.; Miyamoto, H.; Silverio, D. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4701–4706.

Scheme 1.17 Probing Whether Allyl Boronate Isomerization/ C–C Bond Formation is Controlled by Curtin-Hammett Kinetics



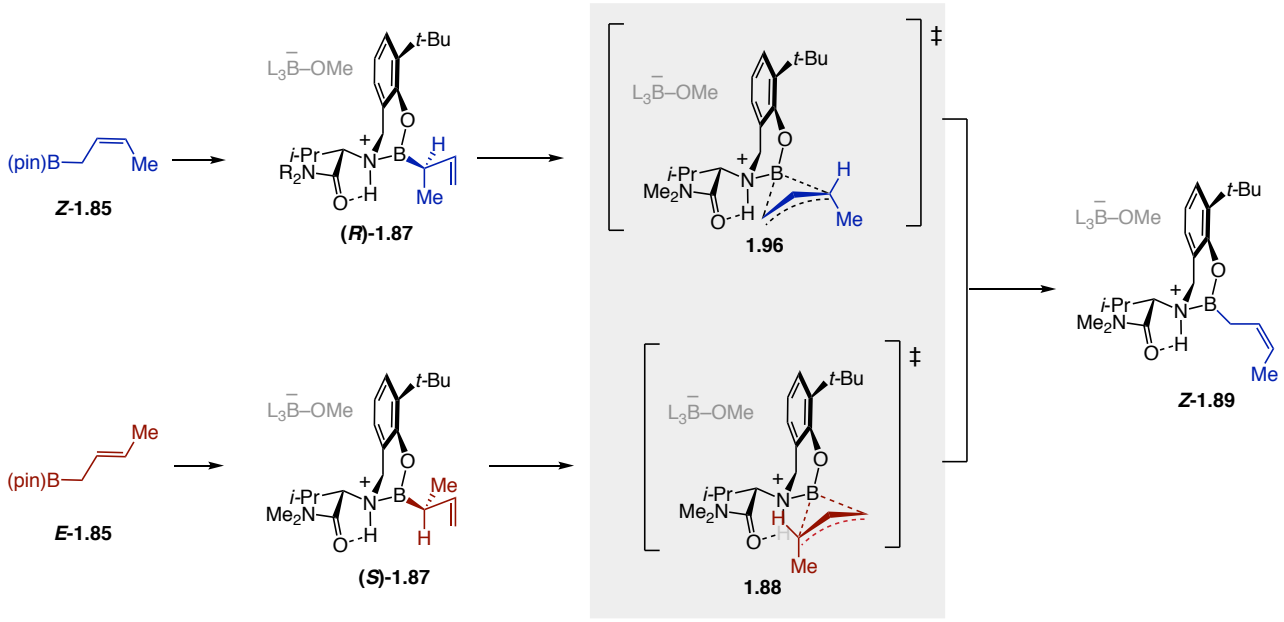
Another possible pathway would entail **1.86** being generated through a kinetically controlled 1,3-boryl shift to furnish a *Z* allyl intermediate.[52] In such a case, kinetic selectivity would likely be due to minimization of a *syn*-pentane interaction between the allyl boronate substituent and the catalyst's backbone (**1.98**, Scheme 1.18b). The efficiency with which rearrangement occurs is influenced by a number of factors. One is feasibility of alkene coordination with the partially vacant p-orbital of the boron atom. Therefore, the rate of

52) (a) Hancock, K. G.; Kramer, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6463–6465. (b) Hancock, K. G.; Kramer. J. D. *J. Organomet. Chem.* **1974**, *64*, C29–31. (c) Henriksen, U.; Snyder, J. P.; Halgren, T. A. *J. Am. Chem. Soc.* **1981**, *46*, 3767–3768. (d) Bühl, M.; Schleyer, P. v. R.; Ibrahim, M. A.; Clark, T. *J. Am. Chem. Soc.* **1991**, *113*, 2466–2471. (e) Bubnov, Y. N.; Gurskii, M. E.; Gridnev, I. D.; Ignatenko, Y. A.; Ustynyuk, Y. A.; Mstislavsky, V. I. *J. Organomet. Chem.* **1992**, *424*, 127–132. (f) Gridnev, I. D.; Gursky, M. E.; Bubnov, Y. N.; *Organometallics* **1996**, *15*, 3696–3702. (g) Bubnov, Y. N. *Pure Appl. Chem.* **1987**, *59*, 895–906. (h) Choi. J. Y.; Kim, C. K.; Lee, I.; *J. Phys. Chem. A* **2002**, *106*, 5709–5715. (i) Ess, D. H.; Kister, J.; Chen, M.; Roush, W. R. *Org. Lett.* **2009**, *11*, 5538–5541. (j) Gurskii, M. E.; Belyakov, P. A.; Lyssenko, K. A.; Semenova, A. L.; Bubnov, Y. N. *Russian Chem. Bull. Int. Ed.* **2014**, *63*, 480–486.

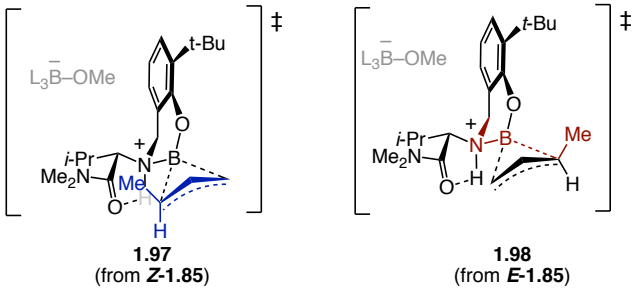
rearrangement may be hampered or increased depending on the identity of ligands substituted on the catalyst's boron center.[53]

Scheme 1.18. Mechanism of 1,3-Boryl Shift

a. Models accounting for kinetic selectiivity of 1,3-boryl shift



b. Transition states leading to *E*-1.89 are less favored due to steric hindrance



We have thus repurposed 1,3-boryl shift, previously only invoked as an explanation for isomerization of enantiomerically enriched allyl boronates,[54] as a design element. What remained was to determine the extent of substitution that could be tolerated on the γ-carbon (i.e., were

53) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 359–362.

54) Lachance, H.; Hall, D. G. Allylboration of Carbonyl Compounds in *Organic Reactions*, S. E.. Ed.; Wiley: New York, **2009**, Vol. *73*, p 17.

efficient and enantioselective additions limited to alkyl groups?). We selected *O*–substituted allylic boronates for further investigation because the corresponding processes would provide convenient access to differentially protected amino alcohols derivatives.

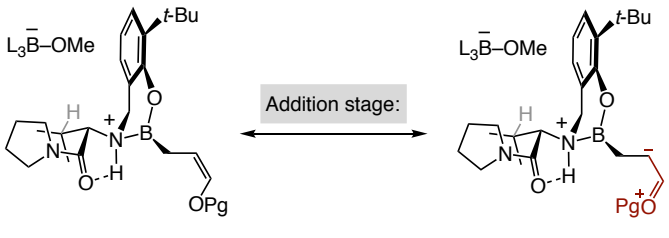
1.4 Catalytic Enantioselective Additions of O-Substituted Allyl Boronates to Aldimines

1.4.1 Further Design Considerations

A number of key issues had to be addressed. First, the reactivity of *O*-substituted organoboron reagents would be different than the corresponding alkyl-substituted derivatives. Specifically, as illustrated through resonance structures **1.100** and **1.102**, we expected a decrease in the nucleophilicity of the γ-carbon site, and diminishing the efficiency of allyl transfer as well as subsequent addition to the imine.

Scheme 1.19. Analyzing the Effect of Alkoxy Substituent on Reaction Efficiency

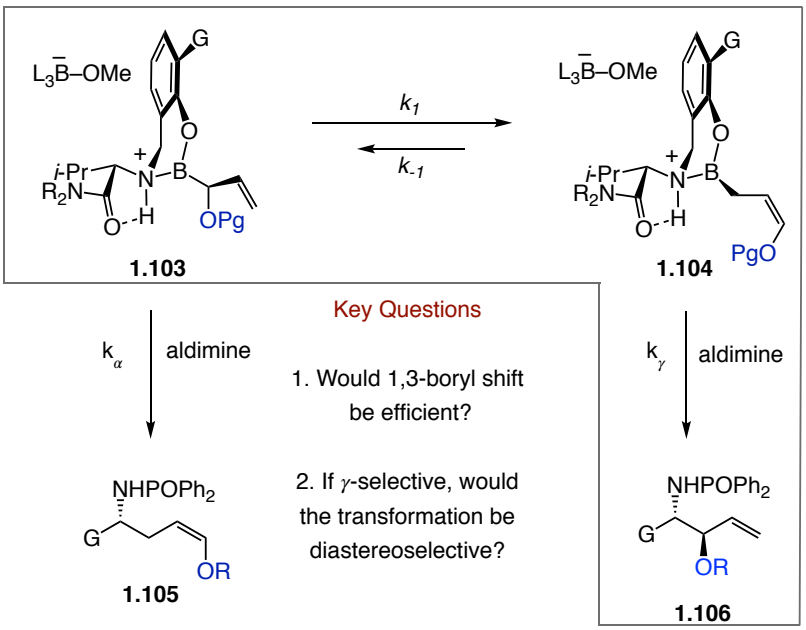
1.99 **1.100**



1.101 **1.102**

Furthermore, it was unclear whether complex **1.103** would undergo efficient rearrangement. We were encouraged by previous reports regarding organoboron reagents substituted with an allylic heteroatom being prone to borotropic shift.[55] Nonetheless, it remained to be determined what factors would favor such a process to occur for aminophenol-based boryl complexes.

Scheme 1.20. Analysis of Key Issues that Impact Regioselectivity



1.4.2 Initial Optimization and Identification of Reaction Conditions

To begin, we synthesized a several allyl boronates (***E*-1.107a-b**, ***Z*-1.107a-c**) and examined efficiency of addition (Table 1). Regardless of the stereochemical identity, reactions involving allyl boronates with a methyl ether **1.107a**[56] were inefficient at room temperature.[57] Still, we were

55) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 1039–1053.

56) For reagent preparation, see: (a) Yamamoto, Y.; Fujikawa, R.; Yamada, A.; Miyaura, N. *Chem. Lett.* **1999**, *28*, 1069–1070. (b) Zhang, P.; Roundtree, I.A.; Morken, J.P. *Org. Lett.*, **2012**, *14*, 1416–1419.

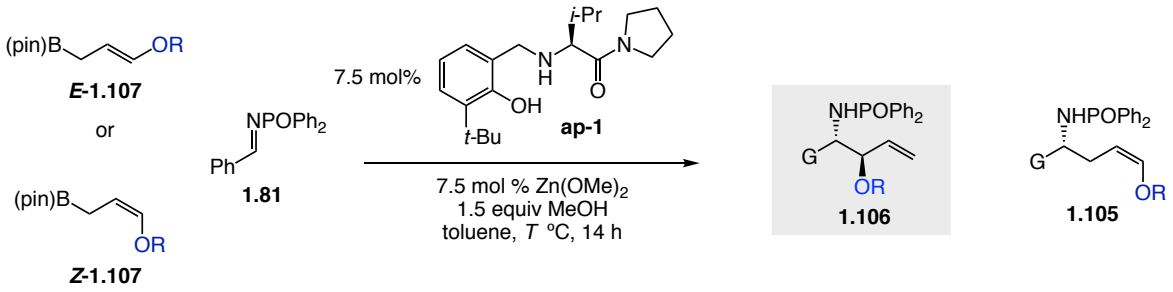
57) Low efficiency for methoxy-substituted boronates has been observed for additions to aldehydes, see: (a) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Leibigs Ann. Chem.* **1985**, 2246–2260. (b) Hoffmann, R. W.; Metternich, R. *Liebigs Ann. Chem.* **1985**, 2390–2402.

encouraged by the fact that with ***Z*-1.107a,** we were able to isolate **1.106** in 96:4 dr and 94:6 er. To improve efficiency, the reaction was performed at 60 °C. Under these conditions, there was no detectable conversion with ***E*-1.107a**; however, there was an increase in conversion to 33% with ***Z*-1.107a**. Based on precedent established by Ramanchandran for efficient additions involving *N*-aluminoimines,[35] we reasoned that an allyl boronate that is MEMO-substituted **1.107b**[58] may be more efficient and amenable to further transformation. Accordingly, under the same conditions, additions of ***Z*-** and ***E*-1.107b** were more efficient (>98% and 83% conv, respectively). For reactions involving silyl ether ***Z*-1.107c**, the transformation proceeded to 66% conv and afforded the desired homoallylic amine in 90:10 er. However, we judged that the three-step preparation for the reagent requiring a relatively costly Ru-based complex rendered this a less attractive option.[59] Attempts to synthesize other silyl-based organoborons were thwarted by poor efficiency of olefin isomerization or silyl migration to lithiated alkenyl metal reagents.[56b]

A notable observation was the difference in reactivity between the more sizable organoboron ***Z*-1.107c** and ***Z*-1.107a**, indicating that electronics might be dominant. To explore this further, we calculated the charge on the γ-carbon of these reagents. In accordance with the experimentally obtained results, we found that there is a higher amount of charge on organoboron reagents possessing methoxyethoxy methyl- or siloxy-substituent (vs the more strongly donating methyl ether).

58) For reagent preparation, see: Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs. Ann. Chem.* **1987**, 881–887.
59) Murata, M. Watanabe, S.; Masuda, Y. *J. Chem. Research (S)*, **2002**, 142–143.

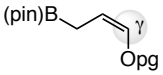
Table 1. Additions with Different Allyl Boronates Containing an *O*-Substituted Allylic Carbon[a]



entry	R, Stereochem	*T* (°C); *t* (h)	conv (%) Yield (%)	γ:α	dr	er
1	**a** Me, *E*	22; 18	<5	na	na	na
2	**a** Me, *Z*	22; 18	12; nd	>98:2	96:4	94:6
3	**a** Me, *E*	60; 14	<5	na	na	na
4	**a** Me, *Z*	60; 14	33, 21	>98:2	92:8	92:8
5	**b** MEM, *E*	60; 14	83, 56	90:10	89:11	91:9
6	**b** MEM, *Z*	60; 14	>98; 78	94:6	95:5	92:8
7[b]	**c** $SiMe_3$, *Z*	60; 14	66; 45[e]	>98:2	89:11	90:10

[a]Performed with 1.5 equiv of organoboron reagent under an atmosphere of dry N_2. Conv, α:γ and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of **1.81**. Yield of isolated and purified product as a mixture of diastereomers (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details. [b]Allylic alcohol isolated (Si-O bond cleavage upon work-up). MEM: $CH_2O(CH_2)_2OMe$; na: not applicable; nd: not determined. See Experimental Section for details.

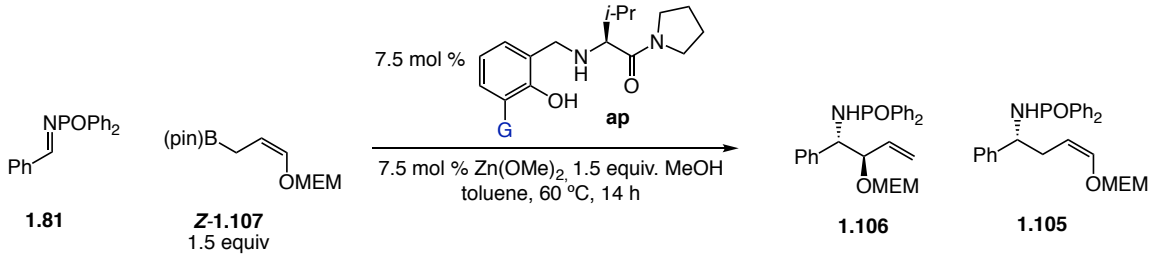
Table 2. Computed Charges on Alkoxy-Substituted Boron Reagents[a]



	Me	MEM	$SiMe_3$
Cγ	-0.12685	-0.15882	-0.16836

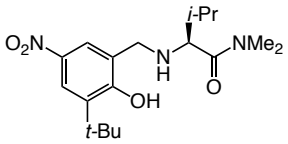
[a]Values obtained based on analysis of the Fukui function. Calculations were performed at ωB97XD/DEF2TZVPP//ωB97XD/DEF2SVP level of theory in the gas phase. MEM: $CH_2O(CH_2)_2OMe$. See Experimental Section for details.

Table 3. Identification and Evaluation of the Optimal Aminophenol[a]

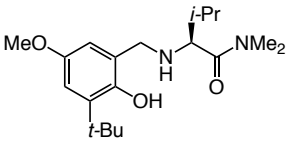


1.81 | ***Z*-1.107** 1.5 equiv | **1.106** | **1.105**

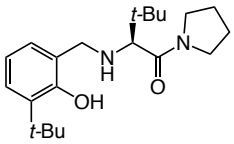
entry	G	conv (%)[b] Yield (%)[c]	γ:α[b]	dr[b]	er[d]
1	H (**2**)	>98, 81	98:2	93:7	84:16
2	Et (**3**)	>98, 88	98:2	95:5	89:11
3	*t*-Bu (**1**)	>98, 78	94:6	95:5	92:8
4	$SiPh_3$ (**4**)	94, 80	83:17	94:6	92:8



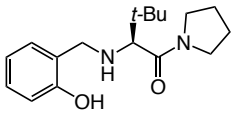
ap-5
<2% conv.



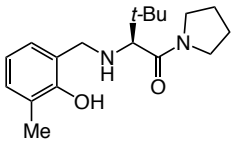
ap-6
>98% conv., 37% yield
88:12 γ:α, 94:6 dr.,
90:10 er



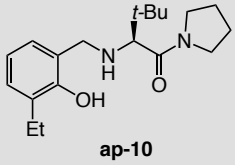
ap-7
95% conv., 77% yield
89:11 γ:α, 93:7 dr
95:5 er



ap-8
>98% conv., 82% yield
97:3 γ:α, 86:14 dr
89:11 er



ap-9
>98% conv., 82% yield
97:3 γ:α, 86:14 dr
89:11 er



ap-10
>98% conv., 86% yield
97:3 γ:α, 93:7 dr
98:2 er

[a]Performed with 1.5 equiv of organoboron reagent under an atmosphere of dry N_2. Conv, α:γ and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of **1.81**. Yield of isolated and purified product as a mixture of diastereomers (±5%). Er values were determined by HPLC analysis (±1%). MEM: $CH_2O(CH_2)_2OMe$. See Experimental Section for details.

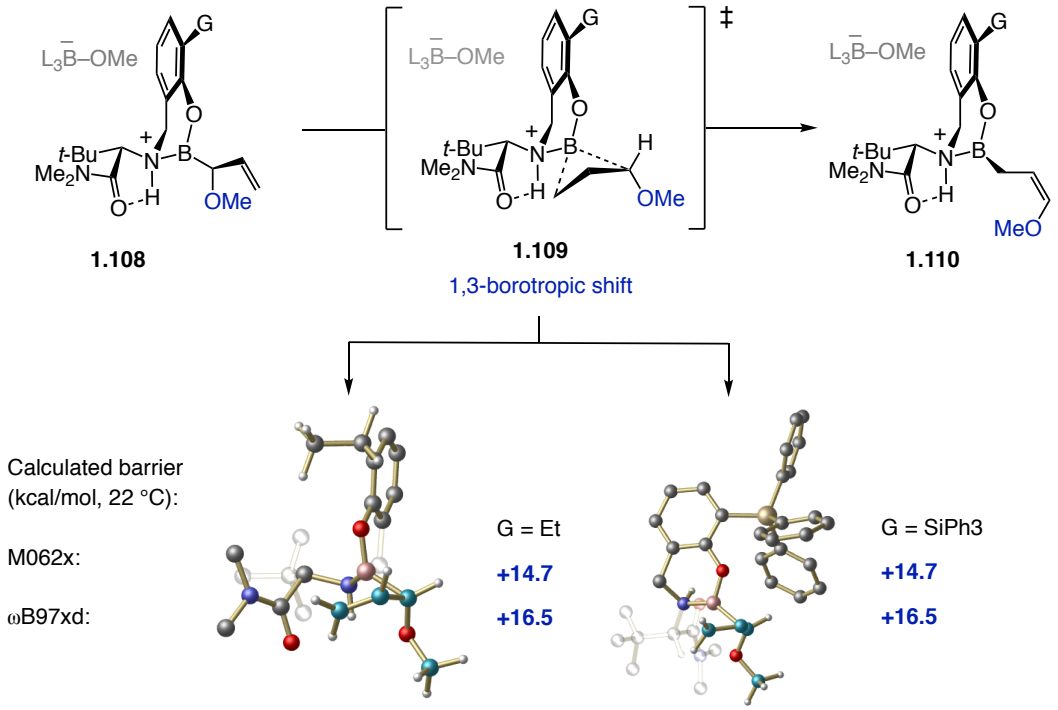
Next, we sought to improve enantioselectivity by probing the effectiveness of several catalysts. We began with modification of the phenolic substituent, finding it to have minimal impact on efficiency (Table 3, 91–98% conv). However, we found that regioselectivity is impacted

by the size of the substituent (Table 3, entry 1 vs 4). Since there was no conversion without an aminophenol, we surmised that the observed decrease in regioselectivity might be the result of a less efficient 1,3-boryl shift, which must occur prior to C–C bond fomation (Scheme 1.20). We considered two possible scenarios: (1) Increased steric pressure in the transition state for 1,3-boryl shift. (2) Less favorable coordination of the $Zn(OMe)_2$ to the catalyst's aryloxy moiety (lower boron Lewis acidity). The latter is supported by the finding that when the more sizable $Zn(O\textit{t}\text{-}Bu)_2$ was used, selectivity decreased to 55:45 γ:α.

To enhance the electrophilicity of the boron center, we synthesized and evaluated the effectiveness of **ap-5**, with contains a withdrawing nitro moiety. However, there was no discernable conversion of **1.81.** [60] In contrast, with *para*-methoxyphenyl-substituted **ap-6** conversion was high, but the product was obtained in only 37% yield. We then turned to probing the effect of the amino acid residue. In line with previous mechanistic models,[47] enantioselectivity increased with a *tert*-leucine derived aminophenol (95:5 vs 92:8 er); still 10% of the α-addition isomer was generated. To improve regioselectivity, we prepared and studied catalysts **ap-8–10**, bearing a smaller or no alkyl substituent. Optimal regio- and enantioselectivity were thus obtained by the catalyst derived from **ap-10**. To gain insight, DFT studies were carried out for analysis of 1,3-boryl shift for model systems with–$SiPh_3$ (**ap-4**) and –Et (**ap-3**) substituted complexes. We found that as hybridization at the boron center changes, there is greater steric pressure in transition state for the catalyst with a larger substituent.

60) Previous studies have indicated that catalysts possessing a more acidic phenol are less efficient for allyl addition to *N*-Phosphinoyl imines (see Ref. 50). This might be owing to more facile deprotonation of the phenolic proton.

Scheme 1.21. Transition State Analysis of Pathways for 1,3-Boryl Shift[a]

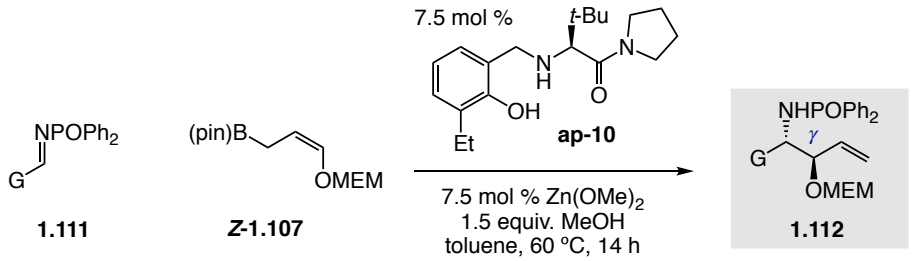


[a]Calculations were performed at the ωB97XD/DEF2SVP$_{toluene(SMD)}$ and M062x/DEF2SVP$_{toluene(SMD)}$ level of theory. See the Experimental Section for details.

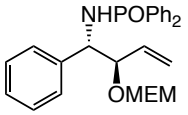
1.5 Evaluation of the Method's Scope

Ortho-substituted imines (**1.113–1.117**), such as *o*-tolyl **1.116** and *o*-napthyl **1.117** were effective substrates. Additions to imines bearing an electron-donating or electron-withdrawing group proceeded with similar selectivity (93:7 dr and 98:2 er for *para*-methoxyphenyl **1.120** and *para*-CF_3 **1.122**). We were able to determine absolute and relative stereochemistry by securing an X-ray of **1.122**. We found it noteworthy that substrates bearing electron-withdrawing substituents performed as well as those that are more electron-rich. This might arise from hemiaminal formation decreasing the availability of the more electrophilic substrates, causing 1,3-boryl shift to become more competitive with C–C bond formation.

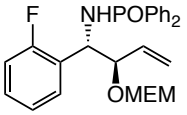
Scheme 1.22. Catalytic Enantioselective Addition of Alkoxy-Substituted Allyl Boronates *N*-Phosphinoyl Imines[a]



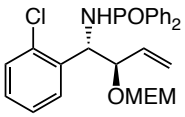
1.111 **Z-1.107** **1.112**



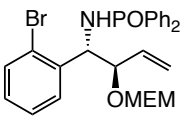
1.106
98:2 γ:α, 86% yield
93:7 dr, 97:3 er



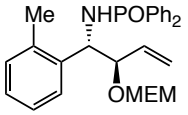
1.113
94:6 γ:α, 84% yield
93:7 dr, 99:1 er



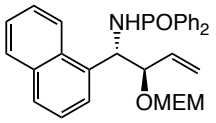
1.114
96:4 γ:α, 89% yield
97:3 dr, 97:3 er



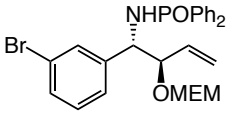
1.115
96:4 γ:α, 86% yield
97:3 dr, 97:3 er



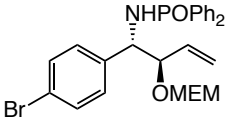
1.116
98:2 γ:α, 89% yield
93:7 dr, 99:1 er



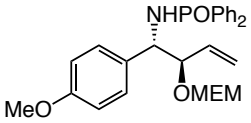
1.117
97:3 γ:α, 85% yield
89:11 dr, 98:2 er



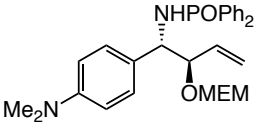
1.118
96:4 γ:α, 89% yield
89:11 dr, 95:5 er



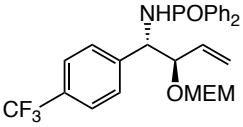
1.119
98:2 γ:α, 89% yield
91:9 dr, 98:2 er



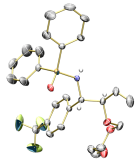
1.120
98:2 γ:α, 92% yield
93:7 dr, 98:2 er



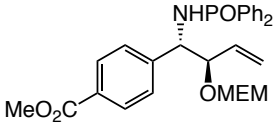
1.121[b]
98:2 γ:α, 83% yield
93:7 dr, 97:3 er



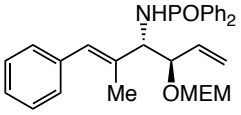
1.122
95:5 γ:α, 92% yield
93:7 dr, 98:2 er



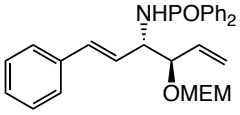
X-ray of 1.122



1.123
97:3 γ:α, 90% yield
88:12 dr, 97:3 er



1.124
97:3 γ:α, 82% yield
94:16 dr, 95:5 er



1.125
97:3 γ:α, 92% yield
94:6 dr, 98:2 er

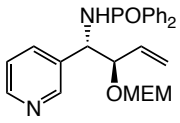
[a]Performed with 1.5 equiv of organoboron reagent under an atmosphere of dry N_2. Conv, α:γ and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of imine. Yield of isolated and purified product as a mixture of diastereomers (±5%). Er values were determined by HPLC analysis (±1%). MEM: $CH_2O(CH_2)_2OMe$. [b]7.5 mol % **ap-10**, 15 mol% $Zn(OMe)_2$, 2.5 equiv MeOH. See Experimental Section for details.

The less electrophilic imines bearing the strongly donating *para*-dimethylamino substituent (**1.121)** were less efficient. This was addressed by increasing the amount of $Zn(OMe)_2$ (15 vs 7.5 mol %) and addition of an equivalent of methanol for increased solubility of the substrate; **1.121** was thus isolated in 83% yield, 93:7 dr, and 97:3 er. Reactions with alkenyl-substituted imines, both di- and tri-substituted, were fully chemoselective (1,2 vs 1,4 addition) and afforded homoallylic amides **1.124** and **1.125** in 82 and 92% yield, 94:6 and 95:5 dr and 98:2 er, respectively. Heteroaryl-substituted imines (**1.126**–**1.130**) were equally effective substrates, but selectivities were more varied, in particular for furyl-substituted **1.127** and **1.128**. As described previously,[61] competitive electrostatic interaction involving the heterocyclic oxygen and the catalyst's ammonium unit can compete with hydrogen bonding between the phosphinoyl amide. The same trend was not observed for thienyl-substituted **1.129** and **1.130**, perhaps as a consequence of the more dispersed electron cloud for a sulfur atom. Larger amounts of the zinc alkoxide were required in the case of 3-pyridyl substituted **1.126,** perhaps due to partial coordination of the Lewis acid with the pyridine nitrogen.

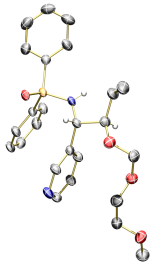
Reactions of alkyl imines were less efficient and less enantioselective. For instance, with imines possessing a less hindered, linear substituent (**1.131)**, regioselectivity decreased to 89:11 γ:α ratio. With the more sizable β-branched imine **1.132**, regioselectivity remained high (98:2 γ:α ratio); however, the diastereo- and enantioselectivity were lower (76:24 dr, 91:9 er).

61) Lee, K.; Silverio, D. L.; Torker, S.; Robbins, D. W.; Haeffner, F.; van der Mei, F. W.; Hoveyda, A. H. *Nature Chem.* **2016**, *8*, 768–777.

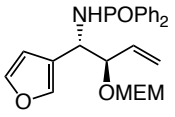
Scheme 1.23 Catalytic Enantioselective Addition of *O*-Substituted Allyl Boronates to Heteroaryl and Alkyl-Substituted Imines[a]



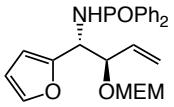
1.126[b]
96:4 γ:α, 77% yield
95:5 dr, 92:8 er



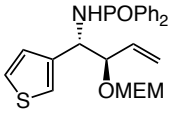
X-ray of 1.126



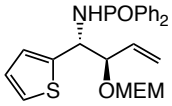
1.127
>98:2 γ:α, 91% yield.
96:4 dr, 98:2 er



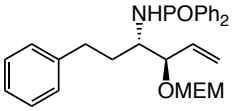
1.128
89:11 γ:α, 79% yield
86:14 dr, 90:10 er



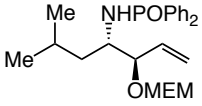
1.129
93:7 γ:α, 88% yield
94:6 dr, 98:2 er



1.130
94:6 γ:α, 92% yield
90:10 dr, 98:2 er



1.131
89:11 γ:α, 63% yield
83:17 dr, 90:10 er



1.132
98:2 γ:α, 57% yield
76:24 dr, 91:9 er

[a]Performed with 1.5 equiv of organoboron reagent under an atmosphere of dry N_2. Conv, α:γ and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of imine. Yield of isolated and purified product as a mixture of diastereomers (±5%). Er values were determined by HPLC analysis (±1%). MEM: $CH_2O(CH_2)_2OMe$. [b]7.5 mol % **ap-10**, 15 mol% $Zn(OMe)_2$, 2.5 equiv MeOH. See Experimental Section for details.

1.5.1 Product Derivatization

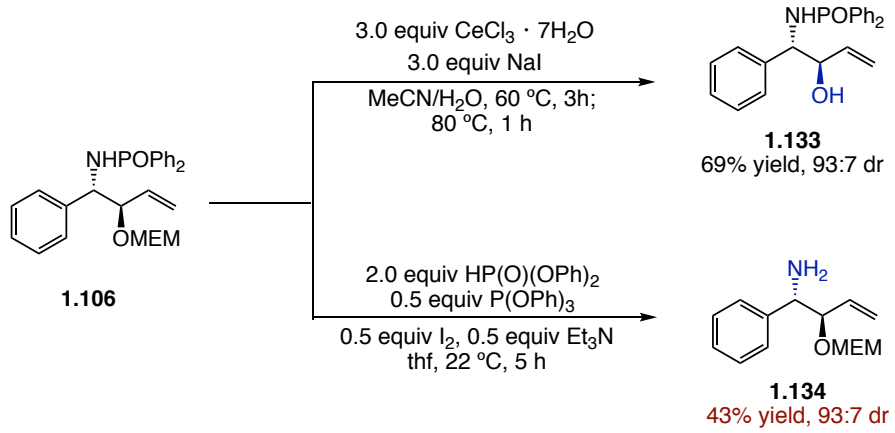
At the outset of this investigation, we sought to develop a method affording access to differentially protected vicinal amino alcohol derivatives that can be chemoselectively unmasked to reveal useful fragments represented by homoallylic amine **1.134**, allylic alcohol **1.133** or amino alcohol **1.136** (Scheme 1.24). Allylic alcohol was thus secured in 69% yield and 93:7 dr by treatment $CeCl_3$/NaI.[62] Activation of the alcohol group in **1.133** (PPh_3, diad), as outlined by Sweeney,[63] and the ensuing substitution afforded aziridine **1.135** in 73% yield and 96.5:3.5 dr.

62) Sabitha, G. S.; Babu, R. S.; Rajkumar, M.; Srividya, R.; Yadav, J. S. *Org. Lett.* **2001**, *3*, 1149–1151.

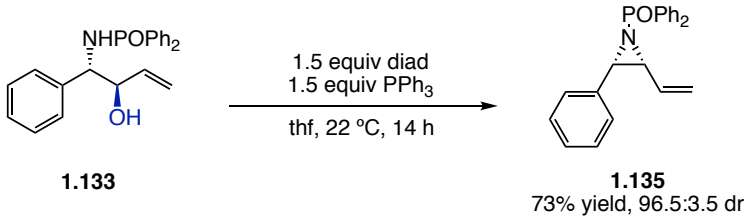
63) Jarvis, A. N.; McLaren, A. B.; Osborn, H. M. I.; Sweeney, J. *Beilstein J. Org. Chem.* **2013**, *9*, 852–859.

Scheme 1.24. Selective Functionalization of Vicinal Amino Alcohol Derivatives[a]

a. Chemoselective removal of *N*–, *O*–based protecting groups



b. Synthesis of alkenyl-substituted aziridine



[a]Performed under an atmosphere of dry N_2. Conv and dr ratios (±2%) were determined by analysis of ^1H NMR spectra of unpurified mixtures. Yield of isolated and purified product as a mixture of diastereomers (±5%). Er values were determined by HPLC analysis (±1%). diad: diisopropyl azodicarboxylate. See Experimental Section for details.

Allylic amine **1.134** was generated without harming the structural integrity of the acid sensitive alkyl ether group. Under the best circumstances, we found that mild reduction of the phosphine oxide through treatment with a combination of $HPO(OPh)_2$ and triphenylphosphite, according to a protocol recently published by Metivier,[64] and hydrolysis of the resulting iminophosphorane furnished homoallylic amine **1.134** in 43% yield. Other recently reported methods for N–P bond cleavage were less effective.[65]

Complete deprotection was performed by treatment with concentrated aqueous hydrochloric acid in ethanol for four hours at 22 °C. Attempts at deprotection under anhydrous

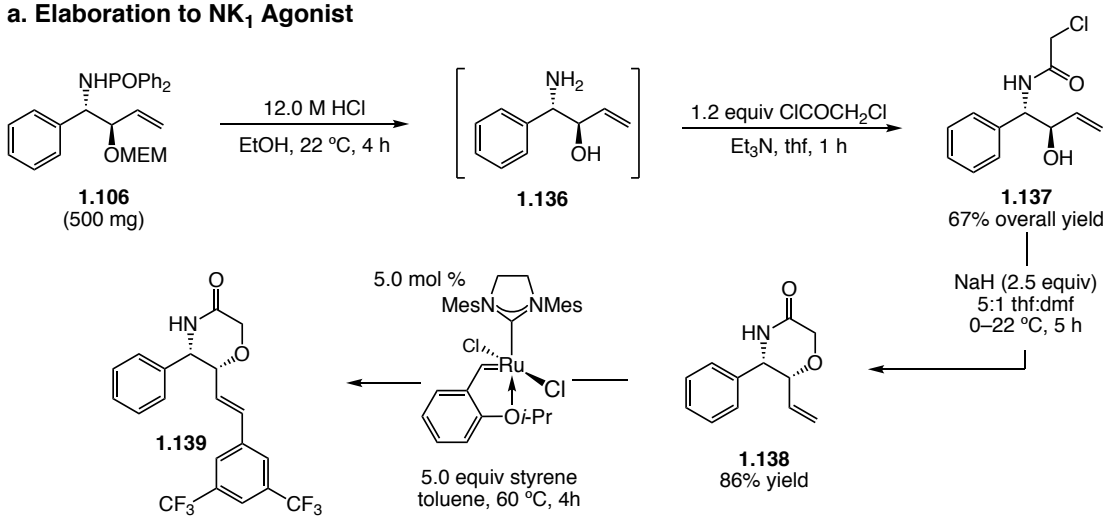
64) Li, P.; Wischert, R.; Metivier, P. *Angew. Chem. Int. Ed.* **2017**, *129*, 16205–16208.

65) Li, B.-J.; Simard, R. D.; Beauchemin, A. M. *Chem. Commun.* **2017**, *53*, 8667–8670.

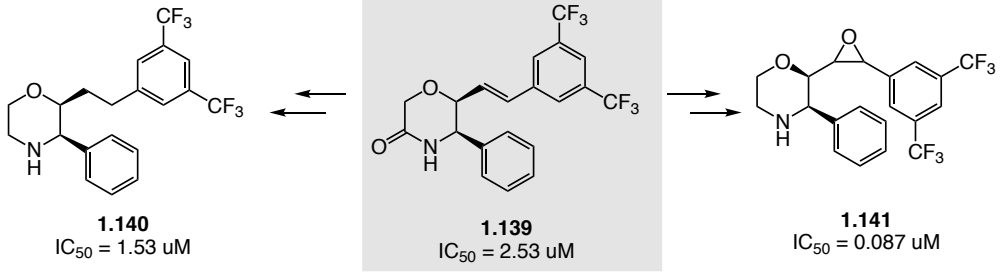
conditions, led to N→O isomerization.[66] Amino alcohol **1.136** was directly subjected to chloroacetyl chloride, affording amide **1.137** in 67% yield. Base-induced cyclization in a mixture of thf/dmf afforded lactam **1.138** in 86% yield, which was then subjected to cross-metathesis to afford NK-1 receptor antagonist **1.139**, and the precursor to the more active epoxide derivative **1.141**.[67]

Scheme 1.25 Application to Synthesis of Biologically Active Compounds[a]

a. Elaboration to NK_1 Agonist



b. Bioactivity of 1.139 and related derivatives



[a]Performed under an atmosphere of dry N_2. Conv and dr ratios (±2%) were determined by analysis of ^1H NMR spectra of unpurified mixtures. Yield of isolated and purified (±5%). Er values were determined by HPLC analysis (±1%). Mes: 2,4,6-trimethylphenyl. See Experimental Section for details.

66) Burgos, P. O.; Fernández, I.; Iglesias, M. J.; García-Granda, S.; Ortiz, F. L. *Org. Lett.* **2008**, *10*, 537–540.

67) (a) Ladduwahetty, T.; Keown, L..; Cascieri, M. A.; Sadowski, S. *Bioorg. Med. Chem.* **1994**, *4*, 1917–1920. (b) Dorn, C. P.; Finke, P. E.; Hale, J. L.; Mills, G.; Shah, S.; Chambers, M. S.; Harrison, T.; Ladduwahetty, T.; Williams, B. J. International Patent WO 95/16679, **1995**.

1.6 Conclusions

We have developed a method for regio-, diastereo- and enantioselective addition of *O*–substituted boronates to *N*-phosphinoyl aldimines. Reaction design was largely mechanism-based, allowing us to control the relative rates of 1,3-borotropic shift versus C–C bond formation. An array of otherwise difficult-to-access and readily modifiable products may be synthesized through the approach efficiently and with high region-, diastero- and enantioselectivity. The utility of the approach was showcased through chemoselective deprotection to furnish homoallylic amines, allylic alcohols, or 1,2-aminoalcohols, as well as synthesis of an NK_1 agonist.

1.7 Experimental Section

1.7.1 General

Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz) or 600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, m = multiplet, app. = apparent), and coupling constant (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). Carbons with directly attached boron atoms were not observed in some compounds, most likely due to quadrupolar relaxation.[1] High-resolution mass spectrometry was performed on a JEOL AccuTOF DART (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomeric ratios were determined by high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Chiral Technologies Chiralpak AD-H (4.6 x 250 mm), Chiralpak AZ-H (4.6 x 250 mm), Chiralcel OZ-3 (4.6 x 150 mm) in comparison to authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and hexanes were purified through a copper oxide and alumina column, CH_2Cl_2 and Et_2O were purged with Ar and purified by passage through two alumina columns. Tetrahydrofuran (thf; Fisher Chemical Co.) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher) in air. Aryl-, heteroaryl-, and alkenyl-*N*-diphenylphosphinoyl imines were synthesized through the use of a condensation promoted by $TiCl_4$ between *P,P*-diphenylphosphinic amide and the corresponding aldehyde.[2] Alkyl substituted imines, precursors to **1.131** and **1.132**, as well as the

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1) Wrackmeyer, B. *Prog. NMR Spectrosc.* **1979**, *12*, 227–259.

2) a) Jennings, W.B.; Lovely, C. J. *Tetrahedron*, **1991**, *47*, 5561–5568; b) Yamada,, K.-I.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504–3506.

imine precursor to **1.122** were synthesized through the intermediacy of the corresponding sulfinyl adducts according to previously disclosed methods.[3]

1.7.2 Reagents

Acetone oxime was purchased from Aldrich and used as received.

Allyl alcohol was purchased from Aldrich and used as received.

Aminophenol compounds (ap-1, ap-2, ap-3, ap-4, ap-5) were prepared according to previously reported procedures.[4]

Bis(1,5–cyclooctadiene)nickel (0) was purchased from Strem and used as received.

Bis(cyclopentadienyl)zirconium(IV) chloride hydride (Schwartz' Reagent) was purchased from Strem and used as received.

Bis(pinacolato)diboron [$B_2(pin)_2$] was purchased from Frontier and used as received.

3,5-Bis(trifluoromethyl)styrene was purchased from Synquest Laboratories and used as received.

Carbonylchlorohydridotris(triphenylphosphine)ruthenium(II) was purchased from Alfa and used as received.

Cerium trichloride heptahydrate was purchased from Aldrich and used as received.

Chloroacetylchloride was purchased from Oakwood and distilled from Calcium hydride immediately before use.

Chlorodiphenylphosphine was purchased from Strem and used as received.

Chlorotrimethylsilane was purchased from Oakwood and used as received.

(1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) hexafluorophosphate was purchased from Acros and used as received.

Diisopropyl azodicarboxylate was purchased from Acros and used as received.

***N,N*-Diisopropylethylamine** was purchased from Oakwood and used as received.

Diphenyl phosphite was purchased from Aldrich and used as received.

3-Ethyl-2-hydroxybenzaldehyde was prepared according to a previously reported procedure.[5]

2-Ethylphenol was purchased from Combi-Blocks and distilled from calcium hydride immediately before use.

Hydrochloric acid was purchased from Fisher and used as received.

Second-generation catalyst (Ru-1) was purchased from Ark Pharm and used as received.

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3) a) A. Côté, A. A. Boezio, A. B. Charrette, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5405–5410; b) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 3985–3989.

4) D. L. Silvero, S. Torker, T. Pilyugina, E M. Vieira, M. L. Snapper, F. Haeffner, A. H. Hoveyda, *Nature* **2013**, *494*, 216–221.

5) E. V. Johnston, K. Bogár, J.-E. Bäckvall, *J. Org. Chem.* **2010**, *75*, 4569–4599.

Iodine was purchased from Alfa and used as received.

2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was purchased from Oakwood and used as received.

Magnesium (II) chloride was purchased from Strem and dried at 130 °C overnight before use.

Methanol (extra dry) was purchased from Acros and used as received.

Methoxyallene was purchased from Aldrich and used as received.

3-((2-Methoxyethoxy)methoxy)prop-1-ene was prepared according to a previously reported procedure.[6]

3-((2-Methoxyethoxy)methoxy)prop-1-yne was prepared according to a previously reported procedure.[7]

2-Methoxyethoxymethyl chloride was purchased from Combi-Blocks and used as received.

***N*-Boc-*L*-*tert*-leucine** was purchased from Oakwood and used as received.

Paraformaldehyde was purchased from Aldrich and dried overnight over P_2O_5 *in vacuo* before use.

Pinacolborane was purchased from Oakwood and used as received.

Propargyl alcohol was purchased from Aldrich and used as received.

***sec*-Butyllithium (1.4 M in cyclohexane)** was purchased from Aldrich and titrated with *N*-Benzylbenzamide before each use.

Sodium hydride was purchased from Strem and used as received.

Sodium iodide was purchased from Alfa and used as received.

***tert*-Butyldimethylchlorosilane** was purchased from Oakwood and used as received.

Triphenylphosphite was purchased from Aldrich and used as received.

Tris(dibenzylideneacetone)platinum was prepared according to a previously reported procedure.[8]

Tricyclohexylphosphine was purchased from Strem and used as received.

Triethyl amine was purchased from Acros and distilled from calcium hydride immediately before use.

Triphenylphosphine was purchased from Aldrich and used as received.

Zinc (II) methoxide (97%, powder) was purchased from Aldrich and used as received.

Zinc (II) *tert*–butoxide was purchased from Alfa and used as received.

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6) Erb, W.; Grassot, J. M.; Linder, D.; Neuville, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1929–1932.

7) Yang, X.; Xie, X.; Fox, J. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 3960–3962.

8) Mlynarski, S. N.; Schuster, C. H., J. P. Morken, *Nature* **2014**, *505*, 386–390.

1.7.3 Alkoxy Substituted Allyl Boron Compounds

(*E*)-2-(3-Methoxyallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*E*-107a) was prepared according to a previously reported procedure, and analytical data are fully consistent with those reported previously.[9]

(*Z*)-2-(3-Methoxyallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*Z*-107a) was prepared according to a previously reported procedure and was obtained as a mixture of isomers.[10] Analytical data are fully consistent with those reported previously.[11]

(*Z*)-Trimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)oxy)silane (*Z*-107c) was prepared according to a previously reported procedure and used as a mixture of alkenyl and allylic boronates.[12] **IR (neat):** 2978 (w, br), 1646 (w), 2882 (w), 1340 (s), 1252 (s), 1145 (s), 1095 (s), 844 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.15 (dt, *J* = 5.8, 1.7 Hz, 1H), 4.60 (td, *J* = 7.6, 5.7 Hz, 1H), 1.71 – 1.60 (m, 2H), 1.23 (s, 12H), 0.15 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.0, 106.2, 83.2, 24.9, 24.7, 15.4, –0.3; **HRMS (DART):** Calcd for $C_{12}H_{26}BO_3Si$ $[M+H]^+$: 257.1739; Found: 257.1752.

(*Z*)-*tert*-Butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)oxy)silane (S-2) was prepared according to a previously reported procedure and used as a mixture of alkenyl and allylic boronates.[12] **IR (neat):** 2978 (m), 2955 (m), 2931 (m), 2887 (m), 2858 (m), 1341 (s) 1322 (s), 1258 (s), 1145 (s), 1101 (s), 838 (s), 778 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.20 (dt, *J* = 5.7, 1.7 Hz, 1H), 4.57 (td, *J* = 7.7, 5.7 Hz, 1H), 1.75 – 1.65 (m, 2H), 1.24 (s, 12H), 0.92 (s, 9H), 0.11 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.6, 105.4, 83.3, 26.1, 24.9, 18.5, –5.2; **HRMS (DART):** Calcd for $C_{15}H_{32}BO_3Si$ $[M+H]^+$: 299.2208; Found: 299.2222.

(*E*)-2-(3-((2-Methoxyethoxy)methoxy)prop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S-1): The title compound was synthesized according to a modified procedure from Wang *et al*.[13] An oven-dried vial equipped with a stir bar was charged with 3-((2-Methoxyethoxy)methoxy)prop-1-yne (1.44 g, 10.0 mmol) and 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (1.52 mL, 10.5 mmol). Bis(cyclopentadienyl)zirconium(IV) chloride hydride (Caution: gas evolution, 258.0 mg, 1.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) were then added to the solution. The vial was capped, sealed with electrical tape and allowed to stir at 60 °C for 16 h. Upon cooling to 22 °C, the solution was diluted with hexanes and filtered through a plug of celite topped with silica gel. The filtrate was concentrated to yield yellow oil, which was purified by silica gel chromatography (gradient eluting with 100:0 to 2:1 hexanes:Et_2O) to afford **S1** as colorless oil (1.93 g, 7.10 mmol, 71% yield).

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9) Zhang, P.; Roundtree, I. A.; JMorken, J. P. *Org. Lett.* **2012**, *14*, 1416–1419.

10) Yamamoto, Y.; Fujikawa, R.; Yamada, A.; Miyaura, N. *Chem. Lett.* **1999**, 1069–1070.

11) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881–887.

12) Murata, M.; Watanabe, S.; Masuda,, Y. J. *J. Chem. Research (S),* **2002**, 142–143.

13) Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y.; *Tetrahedron Lett.* **2005**, *46*, 87778780.

IR (neat): 2978 (w, br), 2928 (w), 2882 (w), 1645 (m), 1348 (s), 1322 (s), 1143 (s), 1024 (s), 972 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.79 – 6.44 (m, 1H), 5.88 – 5.46 (m, 1H), 4.73 (d, J = 0.7 Hz, 2H), 4.28 – 4.09 (m, 2H), 3.89 – 3.65 (m, 2H), 3.65 – 3.48 (m, 2H), 3.38 (s, 3H), 1.26 (d, J = 0.7 Hz, 12H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 148.8, 95.1, 83.4, 71.9, 69.0, 67.0, 59.2, 24.9; **^{11}B NMR (160 MHz, $CDCl_3$):** δ 29.36; **HRMS (DART):** Calcd for $C_{13}H_{26}BO_5$ $[M+H]^+$: 273.1873; Found: 273.1881.

(*E*)-2-(3-((2-Methoxyethoxy)methoxy)allyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*E*-107b): The title compound was synthesized according to a modified procedure of Miyaura *et al*.[14] In a nitrogen-filled glovebox, an oven-dried 6-dram vial was charged with $[Ir(cod)(PPh_2Me)_2]PF_6$ (25.4 mg, 0.0300 mmol) and dissolved in thf (3 mL). The vial was sealed with a septum, removed from the glovebox and placed under an atmosphere of hydrogen. Once the solution turned light yellow, excess hydrogen was removed by purging the system with nitrogen. **S1** (272.2 mg, 1.000 mmol) was then added as a solution in thf (2 mL) and the mixture was allowed to stir for 1 h at 22 °C. The solution was then diluted with anhydrous hexanes, and the resulting precipitate was filtered off. Concentration of the filtrate and purification by silica gel chromatography (gradient eluting with 100:0 to 1:3 hexanes: Et_2O) afforded ***E*-107b** accompanied by 28% of **S1** as clear oil (144.2 mg, 0.53 mmol, 53% yield, mixture of isomers).

IR (neat): 2978 (m), 2931 (w), 2886 (w), 1455 (s), 1358 (s), 1323 (s), 1142 (s), 1061 (s), 881 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.28 – 6.10 (m, 1H), 5.09 (dtd, J = 12.3, 7.7, 0.9 Hz, 1H), 4.94 – 4.68 (m, 2H), 3.77 – 3.62 (m, 2H), 3.61 – 3.51 (m, 2H), 3.38 (s, 3H), 1.55 – 1.48 (m, 2H), 1.24 (s, 12H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 143.6, 104.1, 94.9, 83.4, 71.8, 69.7, 67.4, 66.7, 24.9; **^{11}B NMR (160 MHz, $CDCl_3$)** δ 32.78; **HRMS (DART):** Calcd for $C_{13}H_{26}BO_5$ $[M+H]^+$: 273.1868; Found: 273.1876.

(*Z*)-2-(3-((2-Methoxyethoxy)methoxy)allyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*Z*-107b): The title compound was synthesized according to a modified procedure from Hoffmann *et al*.[11] To a cooled (–78 °C) solution of 3-((2-Methoxyethoxy)methoxy)prop-1-ene (6.0 g, 41 mmol) in thf (40 mL) was added *sec*-BuLi (26.0 mL, 1.4 M in cyclohexane) and allowed to stir for 30 min. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7.6 mL, 37.3 mmol) was then added in a dropwise manner, and the solution was allowed to warm to 22 °C and stir for 12 h. The mixture was then cooled to 0 °C, after which it was treated with a saturated solution of aqueous NH_4Cl (45 mL) followed by 1M HCl (55 mL). The mixture was allowed to stir for 1 h, and then the aqueous layer was washed with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford yellow oil, which was purified by silica gel chromatography (basic alumina, 10:1 to 0:100 hexanes:Et_2O) to yield colorless oil (contained 10–15% unreacted starting material, which was removed under high vacuum with gentle heating) to afford ***Z*-107b** (3.654 g, 13.43 mmol, 36% yield).

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14) Yamamoto, Y.; Miyairi, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem.*, **1999**, *64*, 296–298.

IR: 2978 (w), 2931 (w), 2889 (w), 1666 (w), 1351 (m), 1322 (m), 1143 (s), 1042 (s), 847 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 6.15 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.88 (s, 2H), 4.59 (td, *J* = 7.7, 6.1 Hz, 1H), 3.82 – 3.67 (m, 2H), 3.61 – 3.47 (m, 2H), 3.38 (s, 3H), 1.67 (dd, *J* = 7.5, 1.8 Hz, 2H), 1.24 (s, 12H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 142.3, 103.7, 95.3, 83.3, 71.8, 67.3, 59.1, 28.4, 25.00; **^{11}B NMR (160 MHz, $CDCl_3$):** δ 33.12; **HRMS (DART):** Calcd for $C_{13}H_{26}BO_5$ $[M+H]^+$: 273.1868; Found: 273.1877.

1.7.4 Aminophenol Compounds

(*S*)-2-((3-Ethyl-2-hydroxybenzyl)amino)-3-methyl-1-(pyrrolidin-1-yl)butan-1-one (ap-3): Viscous oil; **IR:** 3284 (w), 2961 (m), 2873 (m), 1633 (s), 1460 (s), 1428 (s), 1224 (m), 838 (m), 749 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.89 (s, 1H), 7.06 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.76 (dd, *J* = 7.5, 1.9 Hz, 1H), 6.70 (t, *J* = 7.4 Hz, 1H), 4.07 (d, *J* = 13.7 Hz, 1H), 3.70 – 3.59 (m, 1H), 3.56 – 3.44 (m, 2H), 3.29 (ddd, *J* = 10.6, 7.0, 5.4 Hz, 1H), 3.21 (dt, *J* = 10.5, 6.4 Hz, 1H), 3.09 (s, 1H), 2.92 – 2.43 (m, 2H), 2.06 – 1.70 (m, 5H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.0, 156.0, 131.5, 128.5, 126.2, 122.0, 118.9, 63.9, 51.3, 46.5, 45.9, 31.4, 26.3, 24.4, 23.1, 20.1, 18.5, 14.3; **HRMS (DART):** Calcd for $C_{18}H_{29}N_2O_2$ $[M+H]^+$: 305.2224; Found: 305.2230; **Specific rotation:** $[\alpha]^{23.9}_D$ –30.7 (*c* = 1.55, $CHCl_3$).

(*S*)-2-((2-Hydroxybenzyl)amino)-3-methyl-1-(pyrrolidin-1-yl)butan-1-one (ap-8): Viscous oil; **IR:** 3283 (w), 2960 (m), 2873 (m), 1631 (s), 1590 (m), 1489 (m), 1427 (s), 1255 (s), 755 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 10.84 (s, 1H), 7.21 – 7.11 (m, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.75 (tt, *J* = 7.4, 1.3 Hz, 1H), 4.09 (d, *J* = 13.8 Hz, 1H), 3.68 – 3.53 (m, 2H), 3.54 – 3.43 (m, 1H), 3.28 (td, *J* = 8.5, 6.9, 3.7 Hz, 1H), 3.17 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.11 (dd, *J* = 6.8, 1.1 Hz, 1H), 1.98 – 1.77 (m, 5H), 0.98 (ddd, *J* = 20.1, 6.8, 1.1 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.9, 158.3, 129.0, 128.6, 122.5, 119.2, 116.5, 63.9, 51.2, 46.5, 45.9, 31.5, 26.3, 24.3, 20.1, 18.5; **HRMS (DART):** Calcd for $C_{16}H_{25}N_2O_2$ $[M+H]^+$: 277.1911; Found: 277.1915; **Specific rotation:** $[\alpha]^{23.7}_D$ –11.2 (*c* = 1.16, $CHCl_3$).

(*S*)-2-((3-Ethyl-2-hydroxybenzyl)amino)-3,3-dimethyl-1-(pyrrolidin-1-yl)butan-1-one (ap-10): White solid; **M.p.** = 98 – 100 °C; **IR:** 3294 (w), 2958 (m), 2872 (m), 1628 (s), 1460 (s), 1426 (s), 1252 (m), 1224 (m), 839 (m), 749 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.68 (s, 1H), 7.04 (dd, *J* = 7.3, 1.9 Hz, 1H), 6.86 – 6.48 (m, 2H), 4.04 (d, *J* = 13.7 Hz, 1H), 3.62 (td, *J* = 7.5, 5.2 Hz, 1H), 3.53 – 3.39 (m, 2H, peaks overlapped), 3.34 – 3.24 (m, 1H), 3.18 (dt, *J* = 10.1, 6.3 Hz, 1H), 3.09 (s, 1H), 2.80 – 2.58 (m, 2H), 1.87 (tt, *J* = 6.1, 4.1, 3.5 Hz, 5H), 1.19 (t, *J* = 7.5 Hz, 3H), 0.98 (d, *J* = 1.0 Hz, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.4, 155.8, 131.4, 128.5, 126.1, 121.9, 118.8, 65.5, 51.1, 47.2, 45.6, 34.4, 26.9, 26.2, 24.2, 23.0, 14.2; **HRMS (DART):** Calcd for $C_{19}H_{31}O_2N_2$ $[M+H]^+$: 319.2386; Found: 319.2392; **Specific rotation:** $[\alpha]^{23.7}_D$ –12.9 (*c* = 0.90, $CHCl_3$).

1.7.5 General Procedure for Additions to N-Phosphinoyl Imines with Z-107b

In a nitrogen-filled glovebox, $Zn(OMe)_2$ (1.0 mg, 0.0075 mmol) was added to an oven dried 2-dram vial equipped with a stir bar, followed by a solution of **ap-10** in toluene (2.4 mg, 0.0075 mmol in 0.5 mL toluene). The mixture was allowed to stir at 22 °C for 5 min, after which phosphinoylimine (33.1 mg, 0.100 mmol), ***Z*-107b** (42 μL, 0.15 mmol), and MeOH (7 μL, 0.15 mmol) were added sequentially. The vial was then sealed with a cap and electrical tape and removed from the glovebox. The mixture was placed in a preheated oil bath and was allowed to stir for 14 h at 60 °C. After the solution was allowed to cool to 22 °C, it was subjected to silica gel chromatography (gradient eluting with 10:1 to 0:100 hexanes:EtOAc, ultimately thoroughly washing with 20:1 CH_2Cl_2:MeOH) to yield the desired product as a mixture of diastereomers.

Procedure for Gram-Scale Catalytic Enantioselective Addition

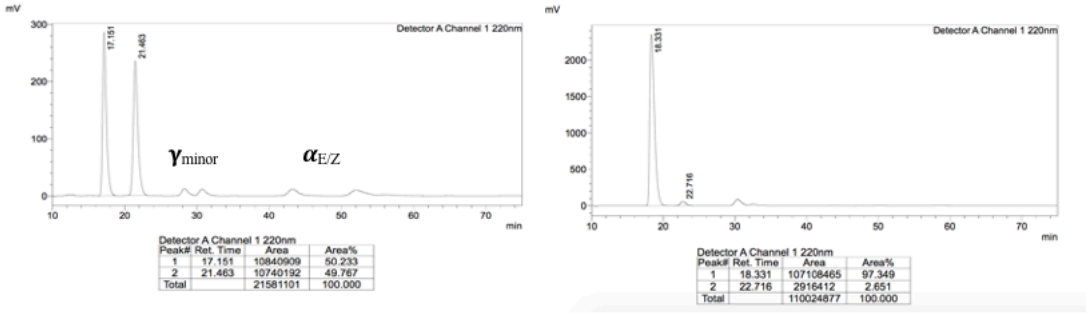
In a nitrogen-filled glovebox, $Zn(OMe)_2$ (31.3 mg, 0.245 mmol) was added to an oven-dried 6-dram vial equipped with a stir bar followed by **ap-10** (36.3 mg, 0.115 mmol). The solids were dissolved in toluene (5 mL) and the vial was sealed with a septum and removed from the glovebox. In ambient atmosphere, phosphinoyl imine **1.81** (1.00 g, 3.28 mmol) was added to an oven-dried 25 mL round bottom flask, placed under an atmosphere of N_2, and dissolved in toluene (8 mL). The solution of **ap-10** and $Zn(OMe)_2$ was then added by syringe and the vial was washed with an additional aliquot of toluene (3 mL). Compound ***Z*-107b** (1.34 g, 4.91 mmol) was added by syringe, followed by methanol (used without purification, 265 μL, 6.55 mmol). The reaction vessel was placed in an oil bath pre-heated to 60 °C and allowed to stir for 14 h. After the mixture was allowed to cool to 22 °C, it was concentrated to ~20% of its original volume in vacuo, and was purified by silica gel chromatography, as described above.

1.7.6 General Procedure for Screening of Alkoxy-Substituted Allyl Boron Compounds

Compounds ***Z*-107a, *E*-107b**, ***Z*-107c**, and ***Z*-107d** were obtained as mixtures of regioisomers. The data in Table 2 were obtained by calculating the corresponding amount of desired reagent (1.5 equiv.), with the assumption of isomeric purity and by multiplying the result by the isomeric ratio to obtain a corrected value. For example, ***E*-107b** was obtained as 72:28 regioisomeric mixture, therefore the calculated amount (assumed isomeric purity) was divided by a factor of 0.72 to obtain a true 1.5 equiv. of the desired allyl boron. For screening studies, the un-reacted imine was hydrolyzed by the addition of 3 M HCl and allowed to stir for 1h. The aqueous layer was washed with EtOAc, dried over $MgSO_4$, and the resulting residue was purified by silica gel chromatography.

1.7.7 Analytical Data for Diastereo- and Enantiomerically Enriched γ-Addition Products

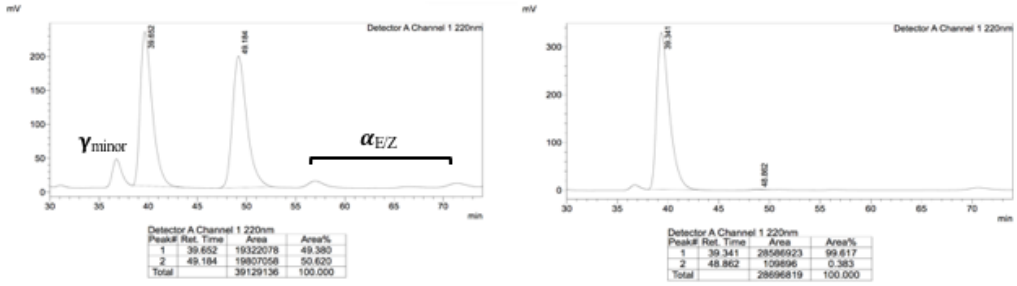
***N*-((1*S*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-phenylbut-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.106):** Viscous oil; **IR (neat):** 3195 (w, br), 2925 (w), 2885 (w), 1438 (m), 1190 (s), 1109 (s), 1032 (s), 698 (m), 535 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.92 – 7.81 (m, 2H), 7.78 – 7.66 (m, 2H), 7.55 – 7.46 (m, 1H), 7.45 – 7.36 (m, 3H), 7.32 – 7.27 (m, 2H), 7.25 – 7.21 (m, 3H), 7.18 (dd, *J* = 7.5, 2.0 Hz, 2H), 5.40 (m, 1H), 5.34 – 5.11 (m, 2H), 4.84 – 4.63 (m, 2H), 4.54 – 4.47 (m, 1H), 4.26 (td, *J* = 10.6, 4.4 Hz, 1H), 4.14 (dd, *J* = 10.6, 7.0 Hz, 1H), 3.67 – 3.48 (m, 2H), 3.48 – 3.33 (m, 2H), 3.27 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.1 (d, *J* = 4.6 Hz), 135.1, 133.2 (d, *J* = 128 Hz), 132.7 (d, *J* = 9.7 Hz), 132.2 (d, *J* = 131 Hz), 132.0 (d, *J* = 9.6 Hz), 132.0 (d, *J* = 2.8 Hz), 131.8 (d, *J* = 2.8 Hz), 128.6 (d, *J* = 12.6 Hz), 128.4 (d, *J* = 12.7 Hz), 128.2, 128.0, 127.3, 119.6, 93.7, 82.2 (d, *J* = 4.5 Hz), 71.8, 67.6, 59.0, 58.3; **HRMS (DART):** Calcd for $C_{26}H_{31}NO_4P$ $[M+H]^+$: 452.1991; Found: 452.1798; **Specific rotation:** $[\alpha]^{26.0}_D$ –7.4 (*c* = 1.45, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 18.331 min (major) and 22.716 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	17.151	50.233	1	18.331	97.349
2	21.463	49.767	2	22.716	2.651

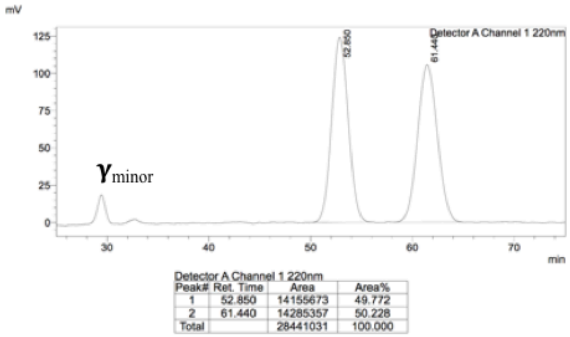
***N*-((1*S*,2*R*)-1-(2-Fluorophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.113):** White solid; **M.p.** = 87 – 89 °C; **IR (neat):** 3201 (w, br), 2928 (w), 2889 (w), 1438 (m), 1183 (s), 1108 (s), 1027 (s), 725 (m), 697 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 – 7.80 (m, 2H), 7.76 – 7.69 (m, 2H), 7.53 – 7.46 (m, 1H), 7.46 – 7.39 (m, 3H), 7.38 – 7.27 (m, 3H), 7.24 – 7.16 (m, 1H), 7.08 (td, *J* = 7.6, 1.2 Hz, 1H), 6.90 (ddd, *J* = 9.6, 8.1, 1.2 Hz, 1H), 5.57 – 5.45 (m, 1H), 5.34 – 5.19 (m, 2H), 4.79 – 4.57 (m, 2H), 4.58 (dd, *J* = 10.7, 5.1 Hz, 1H), 4.54 – 4.46 (m, 1H), 4.09 (dd, *J* = 10.7, 7.3 Hz, 1H), 3.43 – 3.38 (m, 2H), 3.38 – 3.30 (m, 2H), 3.28 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 160.2 (d, *J* = 244 Hz), 134.6, 132.8 (d, *J* = 127 Hz), 132.5 (d, *J* = 10 Hz), 132.2 (d, *J* = 130 Hz), 132.1 (d, *J* = 9.6 Hz), 132.0 (d, *J* = 2.8 Hz), 131.9 (d, *J* = 2.8 Hz), 130.2 (d, *J* = 4.2 Hz), 129.0 (d, *J* = 8.3 Hz), 128.6 (d, *J* = 12.5 Hz), 128.4 (d, *J* = 12.7 Hz), 127.6 (dd, *J* = 13.1 Hz, 4.0 Hz), 124.0 (d, *J* = 3.4 Hz), 119.9, 115.2 (d, *J* =

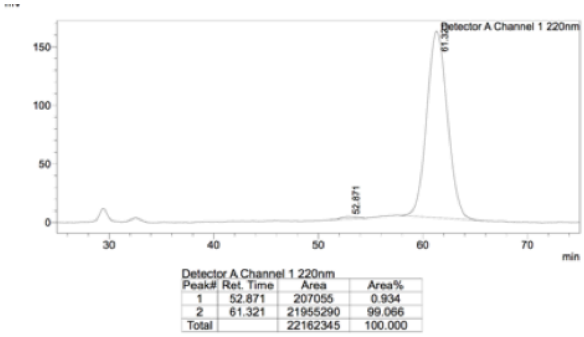
22.5 Hz), 93.6, 81.1 (dd, J = 5.3 Hz, 1.4 Hz), 71.7, 67.4, 59.0, 52.5; **^{19}F NMR**: –111.52; **HRMS (DART):** Calcd for $C_{26}H_{30}NO_4PF$ $[M+H]^+$: 470.1897; Found: 470.1901; **Specific rotation:** $[\alpha]^{28.7}_D$ –54.3 (c = 0.92, $CHCl_3$) for a 99:1 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 94:6 hexanes:*i*PrOH, 0.8 mL/min, 220 nm): t_R: 39.341 min (major) and 48.862 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	39.652	49.380	1	39.341	99.617
2	49.184	50.620	2	48.862	0.383

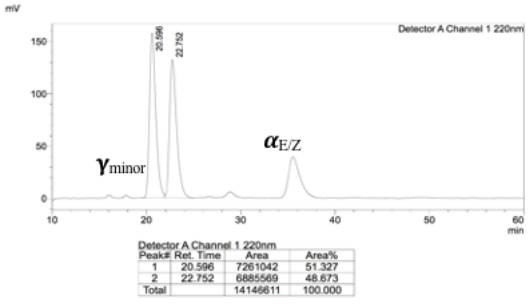
***N*-((1*S*,2*R*)-1-(2-Chlorophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.114):** Viscous yellow oil; **IR (neat):** 3201 (w, br), 2924 (w), 2887 (w), 1438 (m), 1187 (s), 1109 (s), 1033 (s), 725 (m), 696 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 – 7.80 (m, 2H), 7.77 – 7.68 (m, 2H), 7.55 – 7.45 (m, 2H), 7.45 – 7.37 (m, 3H), 7.30 (td, J = 7.6, 3.2 Hz, 2H), 7.25 – 7.11 (m, 3H), 5.48 (ddd, J = 17.0, 10.4, 6.8 Hz, 1H), 5.34 – 5.19 (m, 2H), 4.82 (s, 1H), 4.72 (t, J = 5.6 Hz, 2H), 4.56 (t, J = 5.6 Hz, 1H), 4.12 (dd, J = 10.2, 6.7 Hz, 1H), 3.54 (s, 2H), 3.49 – 3.34 (m, 2H), 3.29 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.0 (d, J = 3.7 Hz), 133.8, 133.1 (broad peak), 132.7 (d, J = 128 Hz), 132.6 (d, J = 9.7 Hz), 132.1 (d, J = 9.6 Hz), 132.1 (d, J = 129 Hz), 132.0 (d, J = 2.7 Hz), 131.9 (J = 2.7 Hz), 130.3 (broad peak), 129.2, 128.5 (d, J = 12.6 Hz), 128.5, 128.4 (d, J = 12.7 Hz), 126.6, 119.9, 80.1 (d, J = 5.2 Hz), 71.5, 67.3, 59.0; **HRMS (DART):** Calcd for $C_{26}H_{30}NO_4PCl$ $[M+H]^+$: 486.1601; Found: 486.1614; **Specific rotation:** $[\alpha]^{27.9}_D$ –29.4 (c = 1.02, $CHCl_3$) for a 99:1 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 90:10 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 52.871 min (minor) and 61.321 min (major).

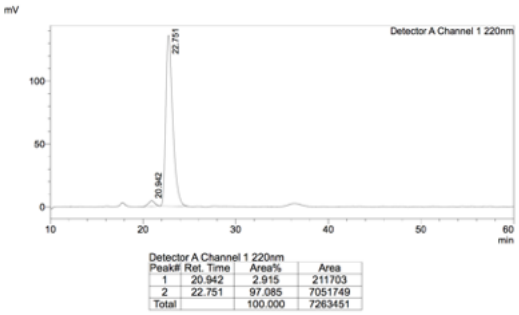




Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	52.850	49.772	1	52.871	0.934
2	61.440	50.228	2	61.321	99.066

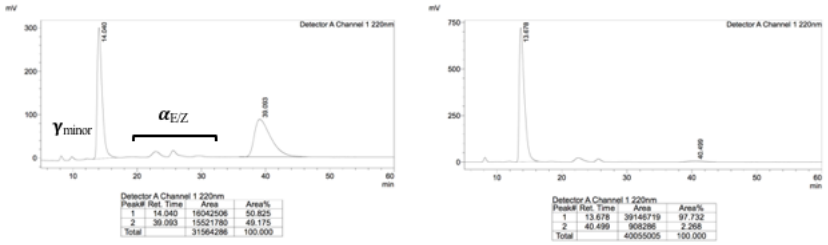
***N*-((1*S*,2*R*)-1-(2-Bromophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.115):** White solid; **M.p.** = 76 – 78 °C; **IR (neat):** 3203 (w, br), 2927 (w), 2887 (w), 1438 (m), 1189 (s), 1123 (s), 1023 (s), 725 (m), 696 (m), 541 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.92 – 7.79 (m, 2H), 7.80 – 7.67 (m, 2H), 7.59 – 7.35 (m, 6H), 7.36 – 7.28 (m, 3H), 7.18 – 6.98 (m, 1H), 5.47 (dd, *J* = 16.8, 7.9 Hz, 1H), 5.41 – 5.15 (m, 2H), 4.92 – 4.77 (m, 1H), 4.74 (s, 2H), 4.55 (t, *J* = 5.6 Hz, 1H), 4.13 (dd, *J* = 10.1, 6.5 Hz, 1H), 3.55 (br s, 2H), 3.51 – 3.37 (m, 2H), 3.30 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 139.5 (d, *J* = 3.8 Hz), 133.7, 132.7 (d, *J* = 128 Hz), 132.6 (d, *J* = 9.7 Hz), 132.6 (broad peak, peaks overlapped at 132.6), 132.2 (d, *J* = 9.6 Hz), 132.1 (d, *J* = 131 Hz), 132.0 (d, *J* = 2.8 Hz), 131.9 (d, *J* = 2.7 Hz), 131.4, 130.5 (broad peak), 128.8, 128.5 (d, *J* = 12.6 Hz peaks overlapped at 128.5), 128.4 (d, *J* = 12.8 Hz), 127.3, 123.8, 112.0, 93.5, 80.0, 71.8, 67.6, 59.1; **HRMS (DART):** Calcd for $C_{26}H_{30}NO_4PBr$ $[M+H]^+$: 530.1096; Found: 530.1113; **Specific rotation:** $[\alpha]^{28.7}_D$ –23.2 (*c* = 1.02, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 20.942 min (minor) and 22.751 min (major).





Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	20.596	51.327	1	20.942	2.915
2	22.752	48.673	2	22.752	97.085

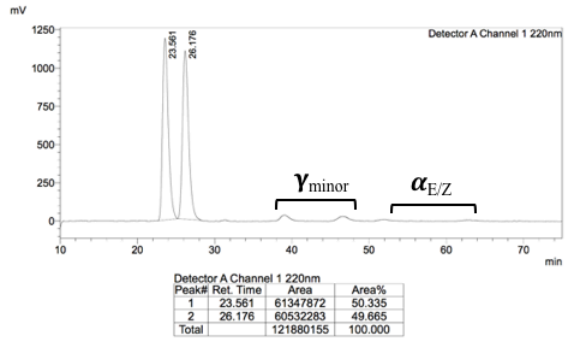
***N*-((1*S*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-(*o*-tolyl)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.116):** White solid; **M.p.** = 100 – 102 °C; **IR (neat):** 3198 (w, br), 2924 (w), 2885 (w), 1438 (m), 1186 (s), 1108 (s), 1070 (s), 1021 (s), 725 (s), 696 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.95 – 7.76 (m, 2H), 7.75 – 7.57 (m, 2H), 7.55 – 7.45 (m, 2H), 7.44 – 7.35 (m, 3H), 7.25 – 7.18 (m, 3H), 7.11 (td, *J* = 7.4, 1.5 Hz, 1H), 6.94 (ddd, *J* = 7.6, 1.5, 0.7 Hz, 1H), 5.43 (ddd, *J* = 17.4, 10.1, 7.4 Hz, 1H), 5.34 – 5.26 (m, 1H), 5.21 (ddd, *J* = 10.1, 2.1, 0.8 Hz, 1H), 4.79 – 4.56 (m, 2H), 4.54 (ddd, *J* = 11.7, 10.1, 4.9 Hz, 1H), 4.41 (dd, *J* = 7.4, 5.0 Hz, 1H), 4.09 (dd, *J* = 10.1, 6.9 Hz, 1H), 3.49 (dd, *J* = 5.1, 3.8 Hz, 2H), 3.46 – 3.32 (m, 2H), 3.29 (s, 3H), 1.79 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.9 (d, *J* = 4.2 Hz), 135.3, 134.5, 132.9 (d, *J* = 128 Hz), 132.5 (d, *J* = 9.7 Hz), 131.7 (d, *J* = 9.5 Hz), 131.6 (d, *J* = 131.2 Hz), 131.6 (d, *J* = 2 Hz, peaks overlapped at 131.6), 131.5 (d, *J* = 2.8 Hz), 129.6, 128.3 (d, *J* = 12.5 Hz), 128.0 (d, *J* = 12.5 Hz), 127.6, 126.8, 125.7, 119.9, 93.0, 81.2 (d, *J* = 4.5 Hz), 71.5, 67.1, 58.7, 52.7, 19.1; **HRMS (DART):** Calcd for $C_{27}H_{33}NO_4P$ $[M+H]^+$: 466.2147; Found: 466.2159; **Specific rotation:** $[\alpha]^{28.7}_D$ –47.8 (*c* = 0.94, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-3, 90:10 hexanes:*i*PrOH, 1.2 mL/min, 220 nm): t_R: 13.678 min (major) and 40.499 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	14.040	50.825	1	13.678	97.732
2	39.093	49.175	2	40.499	2.268

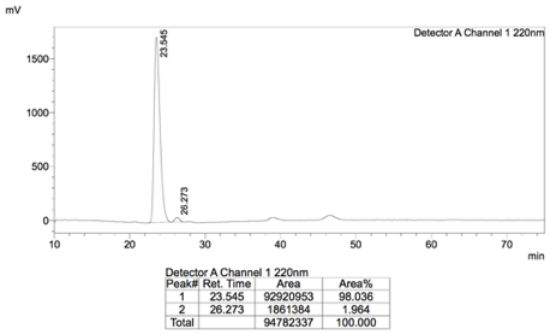
***N*-((1*S*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-(naphthalen-1-yl)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.117):** Viscous oil; **IR (neat):** 3208 (w, br), 2926 (w), 2887 (w), 1438 (m), 1324 (s), 1190 (s), 1107 (s), 1023 (s), 778 (m), 724 (s), 696 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.84 (ddd, *J* = 12.0, 8.3, 1.4 Hz, 2H), 7.80 – 7.58 (m, 7H), 7.50 – 7.41 (m, 2H), 7.41 – 7.33 (m, 3H), 7.31 – 7.25 (m, 2H), 7.16 – 7.03 (m, 2H), 5.47 – 5.32 (m, 1H), 5.22 (td, *J* = 10.4, 4.6 Hz, 1H), 5.18 – 5.12 (m, 1H), 4.73 (d, *J* = 1.5 Hz, 2H), 4.69 – 4.61 (m, 1H), 4.06 (dd, *J* = 9.8, 6.9 Hz, 1H), 3.54 (s, 1H), 3.54 – 3.44 (m, 2H), 3.43 – 3.32 (m, 2H), 3.28 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 136.6 (d, *J* = 3.8 Hz), 135.5, 134.5, 133.6, 133.0 (d, *J* = 128 Hz), 132.5 (d, *J* = 9.7 Hz), 132.1 (d, *J* = 9.6 Hz), 132.1, (d, *J* = 130 Hz, peaks overlapped at 131.6), 131.9 (d, *J* = 2.7 Hz), 131.6 (d, *J* = 2.8 Hz), 131.0, 128.7, 128.5 (d, *J* = 12.5 Hz), 128.2 (d, *J* = 12.8 Hz), 128.0, 126.0, 125.9, 125.4, 125.3, 123.2, 119.9, 93.6, 80.9 (d, *J* = 4.8 Hz), 71.8, 67.5, 59.1; **HRMS**

(DART): Calcd for $C_{30}H_{33}NO_4P$ $[M+H]^+$: 502.2147; Found: 502.2159; **Specific rotation:** $[\alpha]^{23.4}_D$ –39.9 (*c* = 1.29, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 23.545 min (major) and 26.273 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	23.561	61347872	50.335
2	26.176	60532283	49.665
Total		121880155	100.000

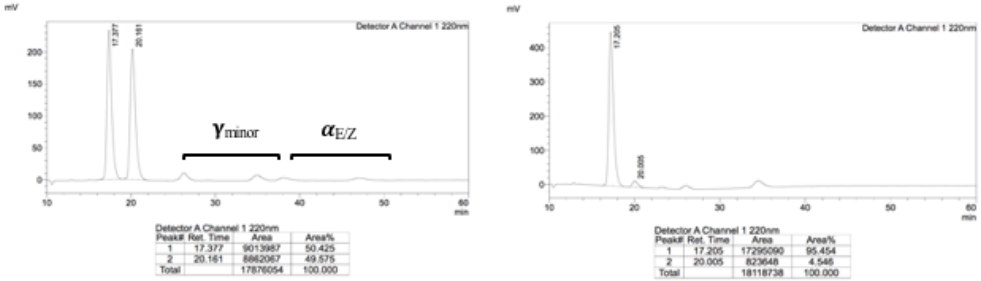


Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	23.545	92920953	98.036
2	26.273	1861384	1.964
Total		94782337	100.000

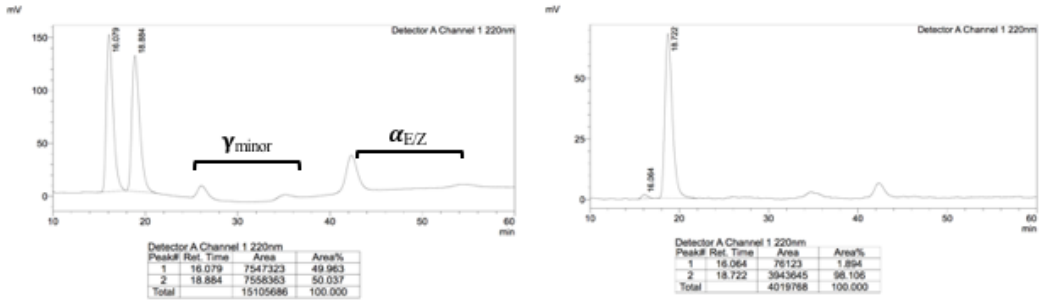
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	22.977	49.995	1	23.545	98.036
2	25.537	50.005	2	26.273	1.964

***N*-((1*S*,2*R*)-1-(3-Bromophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.118):** Viscous oil; **IR (neat):** 3178 (w, br), 2925 (w), 2886 (w), 1438 (m), 1187 (s), 1107 (s), 1023 (s), 725 (m), 698 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.85 (ddd, *J* = 12.0, 8.3, 1.4 Hz, 2H), 7.76 – 7.65 (m, 2H), 7.56 – 7.48 (m, 1H), 7.45 – 7.39 (m, 3H), 7.35 – 7.28 (m, 4H), 7.14 – 7.04 (m, 2H), 5.39 (ddd, *J* = 17.2, 10.0, 7.1 Hz, 1H), 5.31 – 5.13 (m, 2H), 4.81 – 4.64 (m, 2H), 4.48 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.34 – 4.13 (m, 2H), 3.65 – 3.49 (m, 2H), 3.49 – 3.33 (m, 2H), 3.27 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.6 (d, *J* = 4.2 Hz), 134.8, 133.0 (d, *J* = 127 Hz), 132.7 (d, *J* = 9.7 Hz), 132.0 (d, *J* = 3.0 Hz, peaks overlapped at 132.0), 132.0 (d, *J* = 130 Hz), 132.0 (d, *J* = 9.7 Hz), 131.9 (d, *J* = 2.8 Hz, peaks overlapped at 131.9), 131.3, 130.4, 129.6, 128.6 (d, *J* = 12.5 Hz), 128.4 (d, *J* = 12.7 Hz), 127.2, 122.2, 120.0, 93.7, 82.1 (d, *J* = 4.8 Hz), 71.8, 67.7, 59.0, 57.8; **HRMS (DART):** Calcd for $C_{26}H_{30}NO_4PBr$ $[M+H]^+$: 530.1096; Found: 530.1112; **Specific rotation:** $[\alpha]^{28.7}_D$ +3.05 (*c* = 2.04, $CHCl_3$) for a 95:5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 17.205 min (major) and 20.005 min (minor).



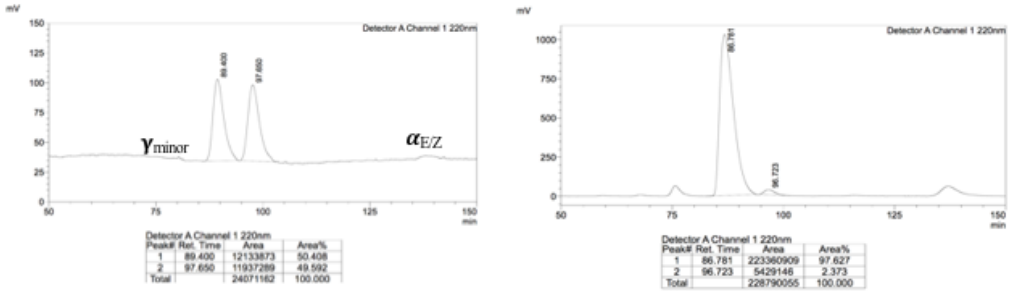
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	17.377	50.425	1	17.205	95.454
2	20.161	49.575	2	20.005	4.546

***N*-((1*S*,2*R*)-1-(4-Bromophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.119):** White solid, **M.p** = 84 – 86 °C; **IR (neat):** 3195 (w, br), 2887 (w), 2835 (w), 1513 (m), 1438 (m), 1178 (s), 1120 (s), 1109 (s), 1023 (s), 723 (s), 694 (m), 525 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.90 – 7.79 (m, 2H), 7.76 – 7.64 (m, 2H), 7.54 – 7.47 (m, 1H), 7.43 (dddd, *J* = 9.4, 4.9, 2.7, 1.4 Hz, 3H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 5.37 (ddd, *J* = 17.1, 10.0, 7.0 Hz, 1H), 5.29 – 5.09 (m, 2H), 4.77 – 4.60 (m, 2H), 4.54 – 4.44 (m, 1H), 4.26 – 4.15 (m, 2H), 3.60 (ddd, *J* = 10.8, 5.8, 3.3 Hz, 1H), 3.53 (ddd, *J* = 10.8, 6.1, 3.3 Hz, 1H), 3.40 (qdd, *J* = 10.7, 6.0, 3.3 Hz, 2H), 3.26 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 139.1 (d, *J* = 4.5 Hz), 134.9, 133.0 (d, *J* = 127 Hz), 132.6 (d, *J* = 9.6 Hz), 132.1 (d, *J* = 130 Hz), 132.0 (d, *J* = 3.0 Hz), 132.0 (d, *J* = 9.6 Hz), 131.9 (d, *J* = 2.6 Hz), 131.1, 130.1, 128.6 (d, *J* = 12.5 Hz), 128.4 (d, *J* = 12.6 Hz), 121.3, 119.8, 93.9, 82.1 (d, *J*=4.7 Hz), 71.7, 67.7, 59.0, 57.8; **HRMS (DART):** Calcd for $C_{26}H_{30}NO_4PBr$ $[M+H]^+$: 530.1096; Found: 530.1122; **Specific rotation:** $[\alpha]^{28.7}_D$ +51.9 (*c* = 2.03, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-3, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 16.064 min (minor) and 18.722 min (major).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	16.079	49.963	1	16.064	1.894
2	18.884	50.037	2	18.722	98.106

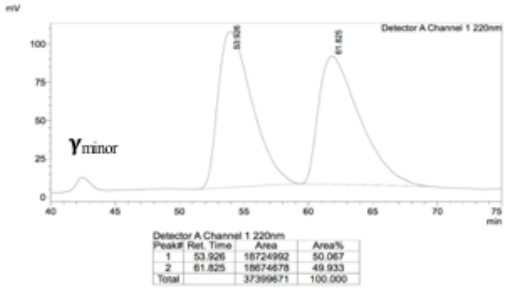
***N*-((1*S*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-(4-methoxyphenyl)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.120):** Viscous oil; **IR (neat):** 3191 (w, br), 2887 (w), 2835 (w), 1513 (m), 1438 (m), 1178 (s), 1108 (s), 1024 (s), 723 (m), 695 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.84 (ddd, *J* = 12.0, 8.3, 1.4 Hz, 2H), 7.81 – 7.65 (m, 2H), 7.59 – 7.37 (m, 4H), 7.30 (tdd, *J* = 8.1, 3.0, 1.1 Hz, 2H), 7.11 (dd, *J* = 8.7, 0.4 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.39 (ddd, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.30 – 5.13 (m, 2H), 4.82 – 4.57 (m, 2H), 4.52 – 4.39 (m, 1H), 4.21 (td, *J* = 10.6, 4.2 Hz, 1H), 4.10 (dd, *J* = 10.4, 6.9 Hz, 1H), 3.79 (s, 3H), 3.62 (ddd, *J* = 10.8, 5.7, 3.2 Hz, 1H), 3.53 (ddd, *J* = 10.8, 6.4, 3.2 Hz, 1H), 3.46 – 3.34 (m, 2H), 3.28 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 158.8, 135.3, 133.3 (d, *J* = 127 Hz), 132.8 (d, *J* = 9.6 Hz), 132.4 (d, *J* = 130 Hz), 132.3 (d, *J* = 4.7 Hz), 132.0 (d, *J* = 9.5 Hz), 131.9 (d, *J* = 2.7 Hz), 131.8 (d, *J* = 2.7 Hz), 129.4, 128.5 (d, *J* = 12.5 Hz), 128.3 (d, *J* = 12.6 Hz), 119.5, 113.4, 93.8, 82.4 (d, *J* = 4.6 Hz), 71.8, 67.6, 59.0, 57.8, 55.4; **HRMS (DART):** Calcd for $C_{27}H_{33}NO_5P$ $[M+H]^+$: 482.2096; Found: 482.2096; **Specific rotation:** $[\alpha]^{23.4}_D$ –13.4 (*c* = 0.76, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 95:5 hexanes:*i*PrOH, 0.6 mL/min, 220 nm): t_R: 86.781 min (major) and 96.723 min (minor).

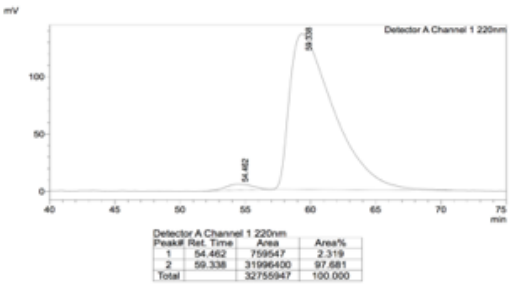


Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	89.400	50.408	1	86.781	97.627
2	97.650	49.592	2	96.723	2.373

***N*-((1*S*,2*R*)-1-(4-(Dimethylamino)phenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.121):** Viscous oil; **IR (neat):** 3215 (w, br), 2885 (w), 2813 (w), 1672 (m), 1523 (m), 1438 (m), 1190 (s), 1109 (s), 1025 (s), 754 (m), 697 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.93 – 7.82 (m, 2H), 7.80 – 7.70 (m, 2H), 7.57 – 7.34 (m, 4H), 7.37 – 7.26 (m, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 5.41 (ddd, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.34 – 5.07 (m, 2H), 4.84 – 4.60 (m, 2H), 4.47 (dd, *J* = 7.3, 4.2 Hz, 1H), 4.15 (td, *J* = 10.6, 4.2 Hz, 1H), 4.06 (dd, *J* = 10.6, 6.9 Hz, 1H), 3.64 (ddd, *J* = 10.8, 5.6, 3.1 Hz, 1H), 3.55 (ddd, *J* = 10.9, 6.6, 3.1 Hz, 1H), 3.39 (ddd, *J* = 10.7, 5.6, 3.2 Hz, 2H), 3.29 (s, 3H), 2.93 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.8, 135.5, 133.4 (d, *J* = 128 Hz), 132.8 (d, *J* = 9.7 Hz), 132.4 (d, *J* = 131 Hz), 132.0 (d, *J* = 9.6 Hz), 131.8 (d, *J* = 2.7 Hz), 131.7 (d, *J* = 2.8 Hz), 128.9, 128.5 (d, *J* = 12.5 Hz), 128.3 (d, *J* = 12.7 Hz), 119.2, 112.3, 93.7, 82.5 (d, *J* = 4.3 Hz), 71.8, 67.5, 59.0, 58.0, 57.9, 40.9; **HRMS**

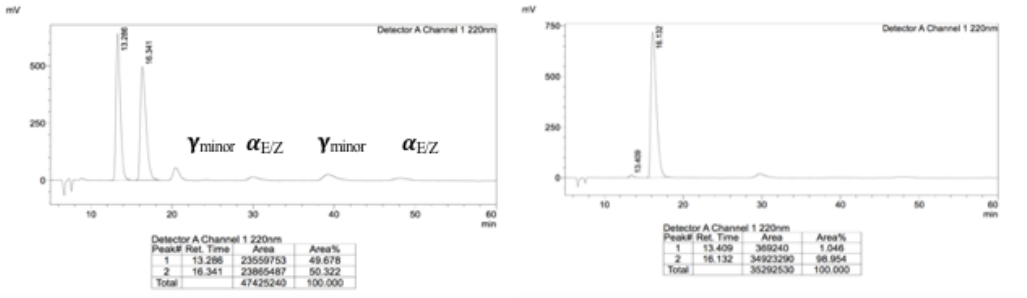
(DART): Calcd for $C_{28}H_{36}N_2O_4P$ $[M+H]^+$: 495.2413; Found: 495.2412; **Specific rotation:** $[\alpha]^{23.7}_D$ +30.6 (*c* = 1.11, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-3, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 54.462 min (minor) and 59.338 min (major).





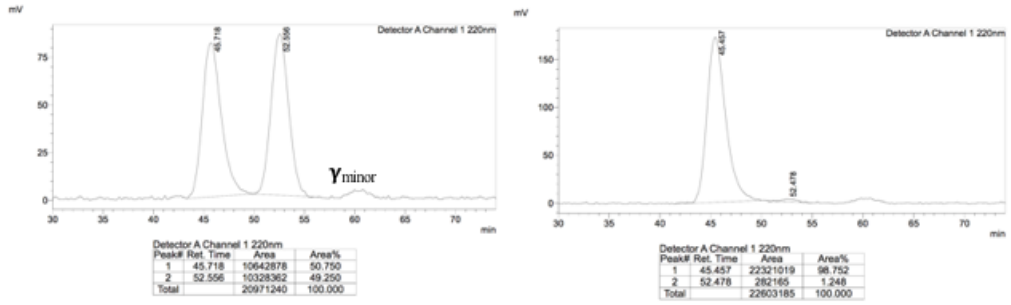
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	53.926	50.067	1	54.462	2.319
2	61.825	49.933	2	59.338	97.681

***N*-((1*S*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.122):** White solid; **M.p.** = 104 – 106 °C; **IR (neat):** 3175 (w, br), 2888 (w), 2835 (w), 1438 (m), 1324 (s), 1111 (s), 1108 (s), 986 (s), 695 (m), 534 (s) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.94 – 7.80 (m, 2H), 7.74 – 7.62 (m, 2H), 7.49 (dd, *J* = 13.6, 4.9 Hz, 3H), 7.46 – 7.39 (m, 3H), 7.38 – 7.27 (m, 4H), 5.37 (ddd, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.31 – 5.12 (m, 2H), 4.81 – 4.60 (m, 2H), 4.52 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.33 (td, *J* = 10.2, 4.2 Hz, 1H), 4.27 (dd, *J* = 10.2, 6.9 Hz, 1H), 3.63 – 3.46 (m, 2H), 3.47 – 3.30 (m, 2H), 3.25 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 144.4, 135.0, 133.0 (d, *J* = 129, peaks overlapped at 132.3), 132.9 (d, *J* = 9.7 Hz), 132.4 (d, *J*=2.7 Hz), 132.3 (d, *J* = 9.7 Hz), 132.3 (d, *J* = 2.2 Hz, peaks overlapped at 132.3), 132.2 (d, *J*=131 Hz), 129.8 (q, *J* = 32.4 Hz), 129.1, 128.9 (d, *J*=12.5 Hz), 128.7 (d, *J* = 12.6 Hz), 125.2 (q, *J* = 3.7 Hz), 124.6 (q, *J* = 272 Hz), 120.3, 94.2, 82.4 (d, *J*=5.0 Hz), 72.0, 68.1, 59.3, 58.3; **^{19}F NMR (376 MHz):** δ –62.52; **HRMS (DART):** Calcd for $C_{27}H_{30}NO_4PF_3$ $[M+H]^+$: 520.1865; Found: 520.1838; **Specific rotation:** $[\alpha]^{23.1}_D$ –5.5 (*c* = 0.91, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-3, 94:6 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 13.409 min (minor) and 16.132 min (major).



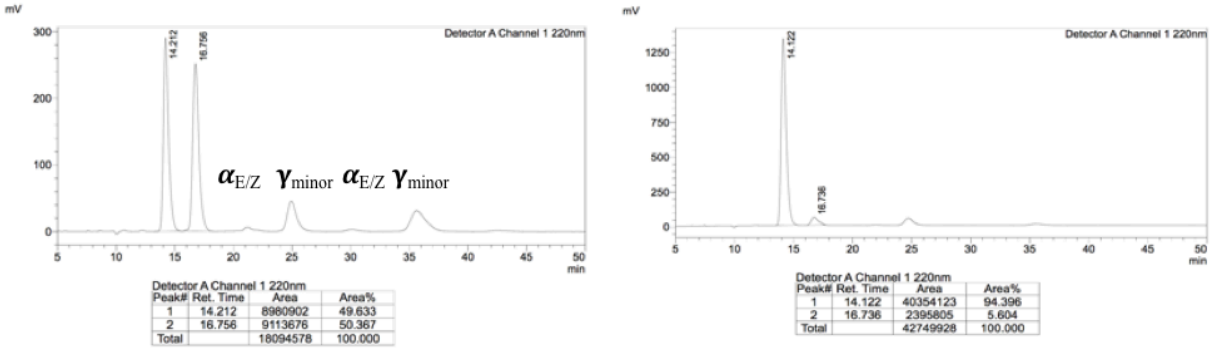
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	13.286	49.678	1	13.409	1.046
2	16.341	50.322	2	16.132	98.954

Methyl 4-((1*S*,2*R*)-1-((Diphenylphosphoryl)amino)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)benzoate (1.123): White solid; **M.p.** = 94 – 96 °C; **IR (neat):** 3201 (w, br), 2924 (w), 2887 (w), 1718 (s), 1436 (m), 1312 (s), 1184 (s), 1106 (s), 1020 (s), 696 (m), 536 (s) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.85 – 7.79 (m, 2H), 7.74 – 7.63 (m, 2H), 7.56 – 7.46 (m, 1H), 7.47 – 7.36 (m, 3H), 7.30 – 7.25 (m, 4H), 5.41 – 5.31 (m, 1H), 5.31 – 5.12 (m, 2H), 4.79 – 4.62 (m, 2H), 4.51 (dd, *J* = 7.2, 4.2 Hz, 1H), 4.32 (td, *J* = 10.6, 4.2 Hz, 1H), 4.26 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.90 (s, 3H), 3.65 – 3.48 (m, 2H), 3.46 – 3.31 (m, 2H), 3.25 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.1, 145.3 (d, *J* = 4.5 Hz), 134.7, 132.9 (d, *J* = 128 Hz), 132.6 (d, *J* = 9.7 Hz), 132.1 (d, *J* = 2.9 Hz), 132.0 (d, *J* = 9.7 Hz), 132.0 (d, *J* = 2.5 Hz), 131.9 (d, *J* = 131 Hz, peaks overlapped at 132.6), 131.9, 129.3, 128.6 (d, *J* = 12.6 Hz), 128.4 (d, *J* = 12.7 Hz), 128.4, 119.8, 93.8, 82.1 (d, *J* = 4.5 Hz), 71.7, 67.7, 59.0, 58.1, 52.2; **HRMS (DART):** Calcd for $C_{28}H_{33}NO_6P$ $[M+H]^+$: 510.2046; Found: 510.2054; **Specific rotation:** $[\alpha]^{21.2}_D$ +11.4 (*c* = 1.02, $CHCl_3$) for a 99:1 e.r. sample. Enantiomeric purity was determined by HPLC analysis of the corresponding alcohol in comparison with authentic racemic material (Chiralpak AZ-H, 90:10 hexanes:*i*PrOH, 1.2 mL/min, 220 nm): t_R: 45.457 min (minor) and 52.478 min (major).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	45.718	50.750	1	45.457	98.752
2	52.556	49.250	2	52.478	1.248

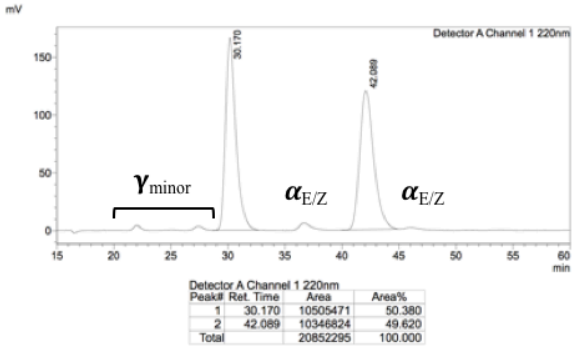
***N*-((3*S*,4*R*,*E*)-4-((2-Methoxyethoxy)methoxy)-2-methyl-1-phenylhexa-1,5-dien-3-yl)-*P*,*P*-diphenylphosphinic amide (1.124):** Viscous oil; **IR (neat):** 3198 (w, br), 2922 (w), 2887 (w), 1438 (m), 1245 (s), 1108 (s), 1108 (s), 1023 (s), 697 (s), 537 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.97 – 7.80 (m, 4H), 7.54 – 7.34 (m, 6H), δ 7.33 – 7.25 (m, 2H), 7.21 – 7.14 (m, 1H), 7.13 – 7.08 (m, 2H), 6.06 (d, *J* = 1.6 Hz, 1H), 5.68 (ddd, *J* = 17.5, 10.3, 7.3 Hz, 1H), 5.37 – 5.21 (m, 2H), 4.80 – 4.66 (m, 2H), 4.37 (dd, *J* = 7.3, 4.3 Hz, 1H), 3.93 – 3.77 (m, 2H), 3.72 (ddd, *J* = 10.9, 5.7, 3.2 Hz, 1H), 3.56 (ddd, *J* = 13.3, 6.0, 2.9 Hz, 1H), 3.51 – 3.36 (m, 2H), 3.27 (s, 3H), 1.86 (d, *J* = 1.4 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.6, 136.3 (d, *J* = 3.9 Hz), 135.3, 133.2 (d, *J* = 127 Hz), 132.8 (d, *J* = 9.6 Hz), 132.7 (d, *J* = 131 Hz), 132.0 (d, *J* = 9.6 Hz), 131.9 (d, *J* = 3.1 Hz, peaks overlapped at 131.9), 131.9 (d, *J* = 3.2 Hz, peaks overlapped at 131.9), 129.2, 129.1, 128.6 (d, *J* = 12.5 Hz), 128.4 (d, *J* = 12.7 Hz), 128.1, 126.5, 119.3, 93.9, 81.3 (d, *J* = 5.5 Hz) 71.8, 67.7, 61.6, 59.1, 15.2; **HRMS (DART):** Calcd for $C_{29}H_{35}NO_4P$ $[M+H]^+$: 492.2304; Found: 492.2314; **Specific rotation:** $[\alpha]^{23.4}_D$ –10.6 (*c* = 0.98, $CHCl_3$) for a 94:6 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 14.122 min (major) and 16.736 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	14.212	49.633	1	14.122	94.396
2	16.756	50.367	2	16.736	5.604

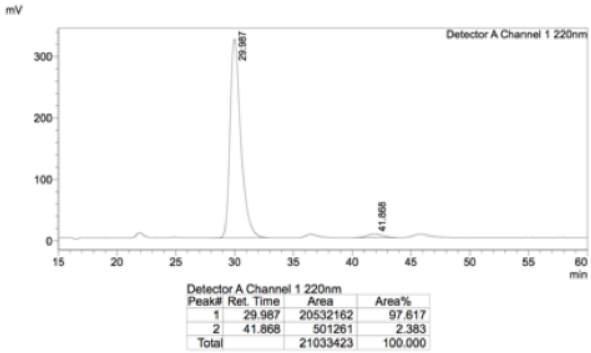
***N*-((3*S*,4*R*,*E*)-4-((2-Methoxyethoxy)methoxy)-1-phenylhexa-1,5-dien-3-yl)-*P*,*P*-diphenylphosphinic amide (1.125)**: Viscous yellow oil; **IR (neat):** 3195 (w, br), 2921 (w), 2887 (w), 1438 (m), 1191 (s), 1122 (s), 1028 (s), 721 (m), 695 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.02 – 7.76 (m, 4H), 7.54 – 7.31 (m, 6H), 7.29 – 7.25 (m, 4H), 7.22 – 7.15 (m, 1H), 6.34 (dd, *J* = 16.0, 1.0 Hz, 1H), 6.15 (dd, *J* = 15.9, 7.4 Hz, 1H), 5.68 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1H), 5.42 – 5.15 (m, 2H), 4.83 – 4.68 (m, 2H), 4.49 – 4.35 (m, 1H), 3.98 (dd, *J* = 10.1, 6.9 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.76 (ddd, *J* = 10.9, 5.9, 3.1 Hz, 1H), 3.58 (ddd, *J* = 10.9, 6.3, 3.2 Hz, 1H), 3.43 (qdd, *J* = 10.7, 6.0, 3.1 Hz, 2H), 3.24 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 136.9, 135.2, 133.3

(d, *J* = 130 Hz, overlaps with peak at 132.6), 132.8, 132.7 (d, *J*=130 Hz), 132.7 (d, *J* = 8.4 Hz), 132.0 (d, *J* = 9.5 Hz), 131.9 (d, *J*=2.8 Hz, peaks overlapped at 131.9), 131.9, 131.9 (d, *J*=2.7 Hz, peaks overlapped at 131.9) 128.6 (d, *J*=12.5 Hz), 128.5, 128.5 (d, *J*=12.5 Hz) 127.7, 119.3, 94.2, 82.6, 82.6, 71.8, 67.7, 59.0, 57.3; **HRMS (DART):** Calcd for $C_{28}H_{33}NO_4P$ $[M+H]^+$: 478.2147; Found: 478.2158; **Specific rotation:** $[\alpha]^{26.0}_D$ +9.9 (*c* = 1.01, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 94:6 hexanes:*i*PrOH, 0.8 mL/min, 220 nm): t_R: 29.987 min (major) and 41.868 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	30.170	10505471	50.380
2	42.089	10346824	49.620
Total		20852295	100.000

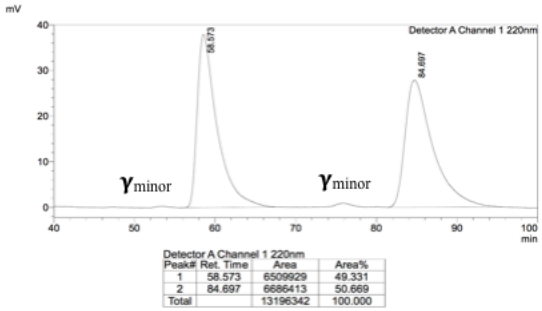


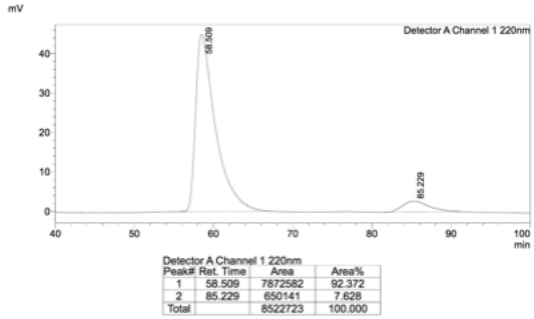
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	29.987	20532162	97.617
2	41.868	501261	2.383
Total		21033423	100.000

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	30.170	50.380	1	29.987	97.617
2	42.089	49.620	2	41.868	2.383

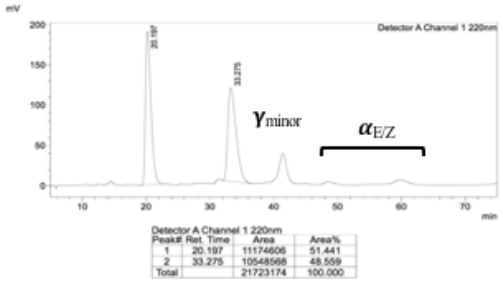
***N*-((1*S*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-(pyridin-3-yl)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.126):** White solid; **M.p.** = 79 – 81 °C; **IR (neat):** 3172 (w, br), 2978 (w), 2886 (w), 1438 (m), 1184 (s), 1108 (s), 1026 (s), 724 (s), 696 (s), 531 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.37 (d, *J* = 2.2 Hz, 1H), 7.94 – 7.79 (m, 2H), 7.69 (ddd, *J* = 12.1, 8.1, 1.4 Hz, 2H), 7.57 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.48 – 7.37 (m, 3H), 7.30 (ddd, *J* = 8.5, 4.3, 2.9 Hz, 2H), 7.21 – 7.13 (m, 1H), 5.37 (ddd, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.30 – 5.12 (m, 2H), 4.72 (q, *J* = 6.8 Hz, 2H), 4.54 (dd, *J* = 7.0, 4.0 Hz, 1H), 4.45 – 4.34 (m, 1H), 4.27 (td, *J* = 10.4, 4.1 Hz, 1H), 3.63 (ddd, *J* = 10.8, 5.8, 3.2 Hz, 1H), 3.55 (ddd, *J* = 10.9, 6.1, 3.2 Hz, 1H), 3.49 – 3.31 (m, 2H), 3.23 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.8, 148.6, 136.2, 135.6, 135.5, 132.8 (d, *J* = 128 Hz), 131.9 (d, *J* = 131 Hz), 132.0 (d, *J* = 2.8 Hz, peaks overlapped at 132.0), 132.1 (d, *J* = 2.8 Hz), 132.0 (d, *J* = 9.6 Hz), 132.6 (d, *J* = 9.8 Hz), 128.7 (d, *J* = 12.6 Hz), 128.5 (d, *J* = 12.8 Hz), 123.0, 120.1, 94.0, 82.4 (d, *J* = 4.7 Hz), 71.7, 67.8, 59.0, 56.4; **HRMS (DART):** Calcd for $C_{25}H_{30}N_2O_4P$ $[M+H]^+$: 453.1943; Found: 453.1933; **Specific rotation:** $[\alpha]^{22.9}_D$ –4.9 (*c* = 1.09, $CHCl_3$) for a 92:8 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 58.509 min (major) and 85.229 min (minor).

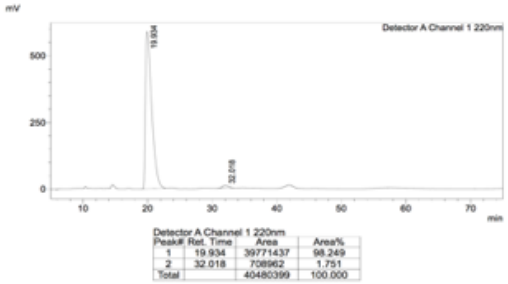




Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	58.573	49.331	1	58.509	92.372
2	84.697	50.669	2	85.229	7.628

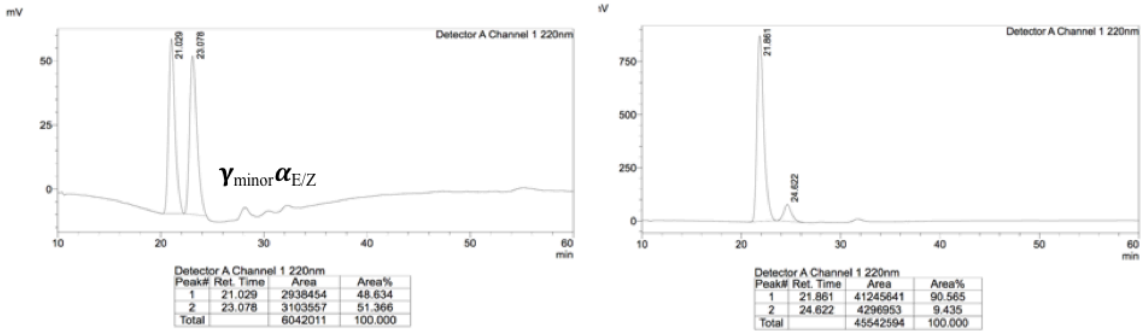
***N*-((1*S*,2*R*)-1-(Furan-3-yl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.127):** Viscous oil; **IR (neat):** 3027 (w, br), 2925 (w), 2888 (w), 1438 (m), 1190 (s), 1122 (s), 1022 (s), 726 (m), 698 (m), 529 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.93 – 7.73 (m, 4H), 7.57 – 7.36 (m, 6H), 7.32 (t, *J* = 1.7 Hz, 1H), 7.23 (dt, *J* = 1.6, 0.7 Hz, 1H), 6.41 (dd, *J* = 1.8, 0.9 Hz, 1H), 5.52 (ddd, *J* = 17.4, 10.4, 7.1 Hz, 1H), 5.36 – 5.09 (m, 2H), 4.88 – 4.66 (m, 2H), 4.51 (dd, *J* = 7.1, 3.4 Hz, 1H), 4.23 (td, *J* = 10.6, 3.5 Hz, 1H), 4.08 – 3.95 (m, 1H), 3.74 (ddd, *J* = 10.9, 5.8, 3.1 Hz, 1H), 3.59 (ddd, *J* = 10.9, 6.3, 3.2 Hz, 1H), 3.51 – 3.39 (m, 2H), 3.27 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.8, 140.6, 135.2, 133.1 (d, *J* = 127 Hz), 132.7 (d, *J* = 9.6 Hz), 132.5 (d, *J* = 130 Hz), 132.1 (d, *J* = 9.6 Hz), 131.9 (d, *J* = 2.7 Hz), 128.6 (d, *J* = 12.5 Hz), 128.5 (d, *J* = 2.7 Hz), 124.2 (d, *J* = 5.5 Hz), 119.4, 110.6, 94.2, 82.4 (d, *J* = 4.3 Hz), 71.8, 67.7, 59.0, 50.9; **HRMS (DART):** Calcd for $C_{24}H_{29}NO_5P$ $[M+H]^+$: 442.1783; Found: 442.1784; **Specific rotation:** $[\alpha]^{23.9}_D$ –36.3 (*c* = 1.1, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-3, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 19.934 min (major) and 32.018 min (minor).





Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	20.197	51.441	1	19.934	98.249
2	33.275	48.559	2	32.018	1.751

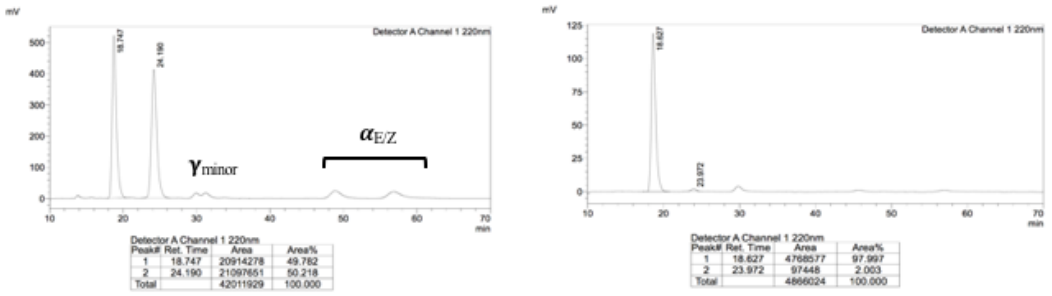
***N*-((1*R*,2*R*)-1-(Furan-2-yl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.128)**: Viscous yellow oil; **IR (neat):** 3058 (w, br), 2890 (w), 2837 (w), 1758 (m), 1438 (m), 1123 (s), 1107 (s), 1025 (s), 726 (s), 696 (s), 527 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.96 – 7.65 (m, 4H), 7.51 – 7.33 (m, 5H), 7.30 (q, *J* = 1.6 Hz, 2H), 7.23 (dt, *J* = 1.3, 0.7 Hz, 1H), 6.39 (dt, *J* = 2.0, 1.0 Hz, 1H), 5.49 (dddd, *J* = 17.4, 10.4, 7.0, 1.1 Hz, 1H), 5.32 – 5.05 (m, 2H), 4.88 – 4.70 (m, 2H), 4.48 (ddt, *J* = 7.6, 3.5, 1.1 Hz, 1H), 4.20 (td, *J* = 10.5, 3.5 Hz, 1H), 4.02 (dd, *J* = 10.9, 7.6 Hz, 1H), 3.71 (dddd, *J* = 10.2, 5.9, 3.1, 1.1 Hz, 1H), 3.57 (dddd, *J* = 10.7, 6.2, 3.2, 1.1 Hz, 1H), 3.52 – 3.34 (m, 2H), 3.26 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.6, 140.4 134.9, 132.9 (d, *J* = 128 Hz), 132.5 (d, *J* = 9.6 Hz), 132.3 (d, *J* = 131 Hz), 131.9 (d, *J* = 9.6 Hz), 131.8 (d, *J* = 4.4 Hz, peaks overlapped at 131.8), 131.8 (d, *J* = 3.0 Hz), 128.4 (d, *J* = 12.6 Hz), 128.3 (d, *J* = 12.7 Hz), 124.0 (d, *J* = 5.5 Hz), 119.2, 110.2, 94.0, 82.2 (d, *J* = 4.2 Hz), 71.2, 67.6, 58.08, 50.8; **HRMS (DART):** Calcd for $C_{24}H_{29}NO_5P$ $[M+H]^+$: 442.1783; Found: 442.1775; **Specific rotation:** $[\alpha]^{21.3}_D$ +3.6 (*c* = 0.88, $CHCl_3$) for a 90:10 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 21.861 min (major) and 24.622 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	21.029	48.634	1	21.861	90.565
2	23.078	51.366	2	24.622	9.435

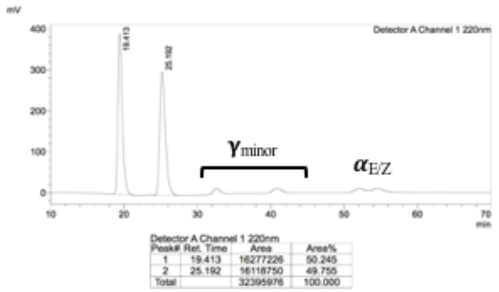
***N*-((1*S*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-(thiophen-3-yl)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.129)**: Viscous oil; **IR (neat):** 3199 (w, br), 2927 (w), 2887 (w), 1438 (m), 1190 (s), 1123 (s), 1027 (s), 698 (m), 528 (m) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.85 (ddd, *J* = 12.0, 8.3, 1.4 Hz, 2H), 7.80 – 7.71 (m, 2H), 7.57 – 7.39 (m, 4H), 7.39 – 7.28 (m, 2H), 7.20 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.09 – 6.96 (m, 2H), 5.44 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.35 – 5.11 (m, 2H), 4.85 – 4.68 (m, 2H), 4.52 (ddt, *J* = 7.1, 3.9, 1.0 Hz, 1H), 4.38 (td, *J* = 10.6,

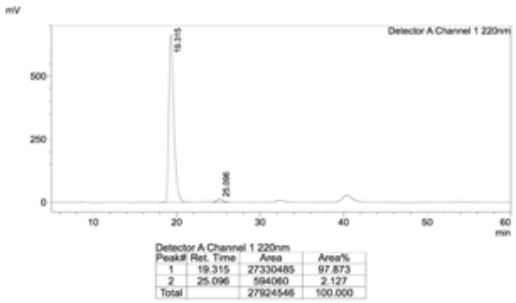
3.9 Hz, 1H), 4.09 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.67 (ddd, *J* = 10.8, 5.8, 3.1 Hz, 1H), 3.56 (ddd, *J* = 10.8, 6.3, 3.2 Hz, 1H), 3.52 – 3.37 (m, 2H), 3.27 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.0 (d, *J* = 5.0 Hz), 135.1, 133.1 (d, *J* = 128 Hz), 132.7 (d, *J* = 9.6 Hz), 132.3 (d, *J* = 131 Hz), 132.0 (d, *J* = 9.6 Hz), 131.9 (d, *J* = 2.3 Hz, peaks overlapped at 131.9), 131.9 (d, *J* = 2.8 Hz), 128.5 (d, *J* = 12.9 Hz, peaks overlapped at 128.5), 128.4 (d, *J* = 13.1 Hz, peaks overlapped at 128.5), 127.7, 125.3, 122.9, 119.5, 94.0, 82.3 (d, *J* = 4.4 Hz), 71.8, 67.7, 59.0, 54.4; **HRMS (DART):** Calcd for $C_{24}H_{29}NO_4PS$ $[M+H]^+$: 458.1555; Found: 458.1569; **Specific rotation:** $[\alpha]^{26.9}_D$ –2.8 (*c* = 1.10, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 18.627 min (major) and 23.972 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	18.747	49.782	1	18.627	97.997
2	24.190	50.218	2	23.972	2.003

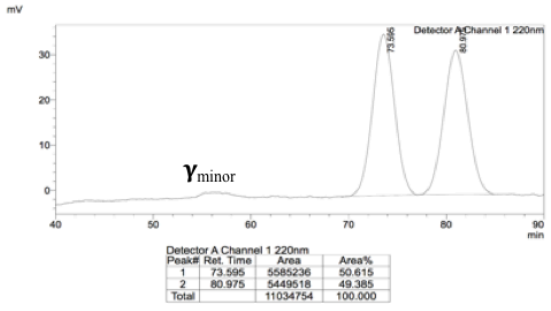
***N*-((1*R*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-(thiophen-2-yl)but-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.130):** Viscous oil; **IR (neat):** 3201 (w, br), 2922 (w), 2887 (w), 1438 (s), 1194 (s), 1123 (s), 1109 (s), 1035 (s), 725 (s), 697 (m), 530 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88 – 7.73 (m, 4H), 7.53 – 7.37 (m, 4H), 7.37 – 7.28 (m, 2H), 7.17 (ddd, *J* = 4.1, 2.9, 1.3 Hz, 1H), 6.83 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.73 (ddd, *J* = 3.5, 1.3, 0.6 Hz, 1H), 5.48 (ddd, *J* = 17.3, 10.3, 6.9 Hz, 1H), 5.31 – 5.15 (m, 2H), 4.77 (q, *J* = 6.8 Hz, 2H), 4.64 – 4.46 (m, 2H), 4.24 – 4.12 (m, 1H), 3.71 (ddd, *J* = 10.9, 5.6, 3.2 Hz, 1H), 3.58 (ddd, *J* = 10.9, 6.5, 3.3 Hz, 1H), 3.41 (qdd, *J* = 10.7, 6.1, 3.2 Hz, 2H), 3.25 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 143.1 (d, *J* = 6.1 Hz), 134.9, 133.2 (d, *J* = 128 Hz), 132.7 (d, *J* = 9.8 Hz), 132.0 (d, *J* = 128 Hz), 132.0 (d, *J* = 2.9 Hz, peaks overlapped at 132.0), 131.9 (d, *J* = 9.9 Hz), 131.9 (d, *J* = 2.9 Hz, peaks overlapped at 131.9), 128.6 (d, *J* = 12.6 Hz), 128.4 (d, *J* = 12.7 Hz), 126.4, 126.2, 125.1, 119.8, 94.1, 82.5 (d, *J* = 3.8 Hz), 71.7, 67.8, 59.0, 54.6; **HRMS (DART):** Calcd for $C_{27}H_{30}NO_4PF_3$ $[M+H]^+$: 458.1555; Found: 458.1537, **Specific rotation:** $[\alpha]^{23.4}_D$ –13.1 (*c* = 1.1, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 19.315 min (major) and 25.096 min (minor).

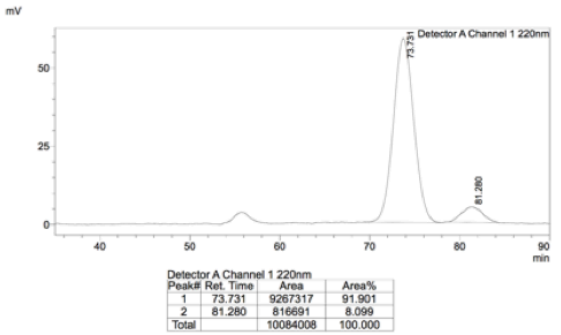




Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	19.413	50.245	1	19.315	97.873
2	25.192	49.755	2	25.096	2.127

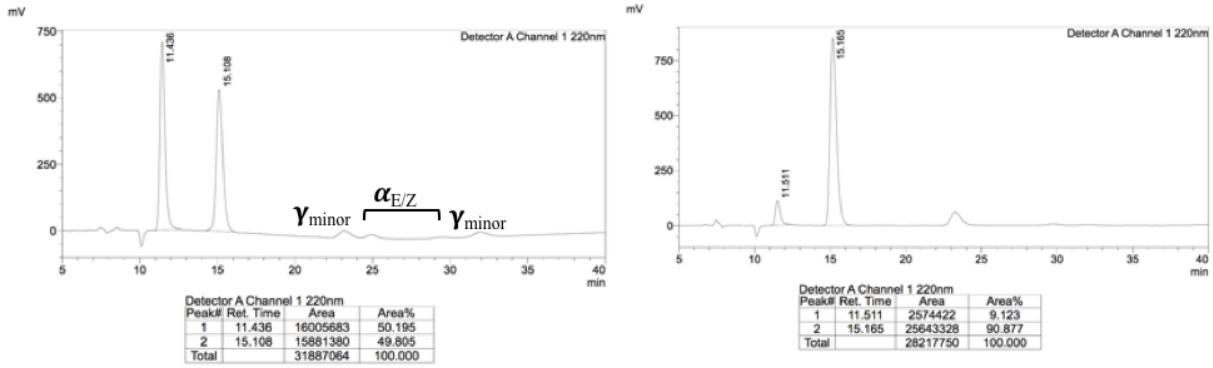
***N*-((3*S*,4*R*)-4-((2-Methoxyethoxy)methoxy)-1-phenylhex-5-en-3-yl)-*P*,*P*-diphenylphosphinic amide (1.131):** Viscous oil; **IR (neat):** 3194 (w, br), 2928 (w), 2886 (w), 1453(m), 1242 (s), 1121 (s), 1107 (s), 1027 (s), 724 (s), 696 (m), 552 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.94 (dddd, *J* = 12.0, 8.3, 5.5, 1.5 Hz, 4H), 7.55 – 7.34 (m, 6H), 7.24 – 7.18 (m, 2H), 7.14 (tt, *J* = 6.5, 1.1 Hz, 3H), 5.68 (ddd, *J* = 17.3, 10.5, 6.2 Hz, 1H), 5.31 – 5.13 (m, 2H), 4.73 (q, *J* = 6.9 Hz, 2H), 4.36 (ddt, *J* = 5.9, 2.8, 1.3 Hz, 1H), δ 3.72 (ddd, *J* = 10.9, 6.0, 3.2 Hz, 1H), 3.69 – 3.62 (m, 1H), 3.58 (ddd, *J* = 10.9, 6.0, 3.3 Hz, 1H), 3.50 – 3.37 (m, 2H), 3.25 (s, 3H), 3.23 – 3.13 (m, 1H), 3.01 – 2.84 (m, 1H), 2.67 – 2.47 (m, 1H), 1.91 – 1.73 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.4, 135.5, 133.4 (d, *J* = 130 Hz), 133.3 (d, *J* = 128 Hz), 132.5 (d, *J* = 9.4 Hz), 132.4 (d, *J* = 9.5 Hz), 131.9 (d, *J* = 2.7 Hz), 131.8 (d, *J* = 2.7 Hz), 128.6, 128.6 (d, *J* =12.5 Hz), 128.5 (d, *J* = 12.3 Hz, peaks overlapped at 128.4 Hz), 125.8, 118.2, 94.7, 82.7 (d, *J* = 4.2 Hz), 71.8, 67.8, 59.0, 55.0, 33.4, 33.4. 32.7; **HRMS (DART):** Calcd for $C_{28}H_{35}NO_4P$ $[M+H]^+$: 480.2304; Found: 480.2292; **Specific rotation:** $[\alpha]^{23.1}_D$ –2.9 (*c* = 1.82, $CHCl_3$) for a 92:8 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 73.731 min (major) and 81.280 min (minor).





Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	73.595	50.615	1	73.731	91.901
2	80.975	49.385	2	81.280	8.099

***N*-((3*R*,4*S*)-3-((2-Methoxyethoxy)methoxy)-6-methylhept-1-en-4-yl)-*P*,*P*-diphenylphosphinic amide (1.132):** Viscous oil; **IR (neat):** 3203 (w, br), 3059 (w) 2953 (m), 2870 (m), 1438 (m), 1192 (s), 1122 (s), 1109 (s), 725 (s), 698 (s), 532 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.94 (dddd, *J* = 12.0, 7.9, 6.0, 1.6 Hz, 4H), 7.55 – 7.38 (m, 6H), 5.69 (ddd, *J* = 17.0, 10.6, 6.2 Hz, 1H), 5.26 – 5.13 (m, 2H), 4.78 – 4.68 (m, 2H), 4.40 – 4.31 (m, 1H), 3.72 (ddd, *J* = 11.0, 6.0, 3.2 Hz, 1H), 3.59 (ddd, *J* = 10.9, 6.0, 3.3 Hz, 1H), 3.52 – 3.39 (m, 3H), 3.26 (s, 3H), 3.20 – 3.06 (m, 1H), 1.96 – 1.84 (m, 1H), 1.45 (ddd, *J* = 14.1, 9.5, 4.4 Hz, 1H), 1.25 (dt, *J* = 6.8, 3.6 Hz, 2H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.66 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.6, 133.4 (d, *J* =131 Hz, peaks overlapped at 132.7), 133.3 (d, *J* = 129, peaks overlapped at 132.7), 132.5 (d, *J* = 9.3 Hz), 132.4 (d, *J* = 9.3 Hz), 131.8 (d, *J* = 2.8 Hz), 131.7 (d, *J* = 2.8 Hz), 128.5 (d, *J* = 12.6 Hz), 128.4 (d, *J* = 12.5 Hz), 118.1, 94.7, 82.8 (d, *J* = 3.7 Hz), 71.8, 67.7, 59.0, 53.5, 40.9 (d, *J* = 5.5 Hz), 24.3, 23.8, 21.8; **HRMS (DART):** Calcd for $C_{24}H_{35}NO_4P$ $[M+H]^+$: 432.22982; Found: 432.2289; **Specific rotation:** $[\alpha]^{22.9}_D$ –22.4 (*c* = 1.24, $CHCl_3$) for a 91:9 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 9.123 min (minor) and 15.165 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	11.436	16005683	50.195
2	15.108	15881380	49.805
Total		31887064	100.000

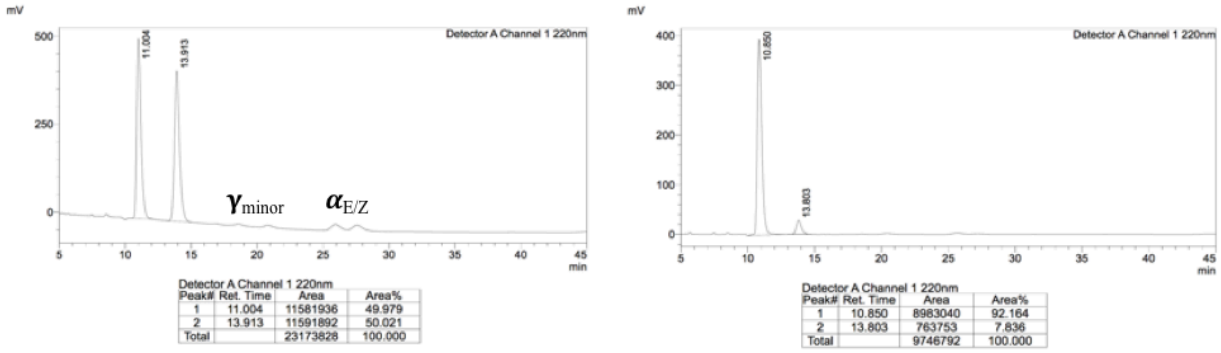
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	11.511	2574422	9.123
2	15.165	25643328	90.877
Total		28217750	100.000

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	11.436	50.195	1	11.511	9.123
2	15.106	49.805	2	15.165	90.877

***N*-((1*S*,2*R*)-2-Methoxy-1-phenylbut-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide:** White solid; **M.p.** = 133 – 135 °C (decomposition); **IR (neat):** 3193 (w, br), 3058 (w), 2930 (w), 2821 (w), 1438 (m), 1187 (s), 1123 (s), 1107 (s), 725 (s), 697 (s), 536 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.97 – 7.82 (m, 2H), 7.78 – 7.64 (m, 2H), 7.57 – 7.34 (m, 5H), 7.33 – 7.27 (m, 2H), 7.25 – 7.20 (m, 2H), 7.14 (dd, *J* = 7.4, 2.3 Hz, 2H), 5.30 – 5.21 (m, 2H), 5.19 – 5.08 (m, 1H), 4.30 – 4.16 (m, 2H), 4.15 – 4.03 (m, 1H), 3.30 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 139.7 (d, *J* = 5.9 Hz), 135.3, 133.2 (d, *J* = 131 Hz, peaks overlapped at 132.6), 132.7 (d, *J* = 9.9 Hz), 131.8 (d, *J* = 131 Hz), 131.7 (d, *J* = 9.5 Hz), 131.7 (d, *J* = 2.8 Hz), 131.6 (d, *J* = 2.8 Hz), 128.4 (d, *J* = 12.5 Hz), 128.2, 128.1 (d, *J* = 12.8 Hz), 127.8, 127.1, 119.4, 86.4 (d, *J* = 3.0 Hz), 58.3, 56.8; **HRMS**

(DART): Calcd for $C_{23}H_{25}NO_2P$ $[M+H]^+$: 378.1623; Found: 378.162; **Specific rotation:** $[\alpha]^{20.9}_D$ –3.6 (*c* = 0.94, $CHCl_3$) for a 92:8 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 10.850 min (major) and 13.803 min (minor).



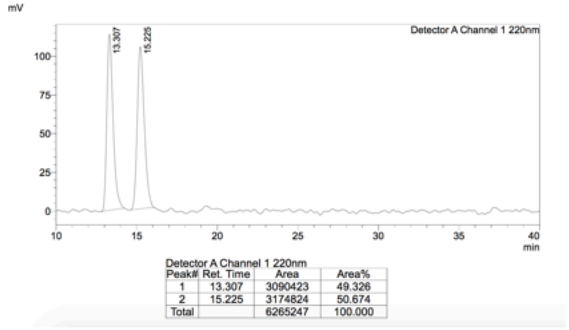
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	11.004	49.979	1	10.850	92.164
2	13.913	50.021	2	13.803	7.836

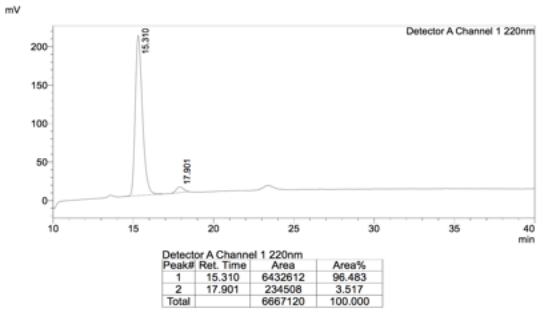
1.7.8 Product Derivatizations and Methods for Selective Removal of Protecting Groups

***N*-((1*S*,2*R*)-2-Hydroxy-1-phenylbut-3-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1.133):** To a solution of **1.106** (189.5 mg, 0.4200 mmol) in reagent-grade MeCN (2.5 mL) was added $CeCl_3 \cdot 7H_2O$ (470.0 mg, 1.260 mmol), NaI (188.0 mg, 1.260 mmol), and H_2O (4 µL). The resulting solution was heated under a stream of nitrogen to 60 °C for 3 h and then to 80 °C for one h. The mixture was allowed to cool to 22 °C, diluted with EtOAc (5.0 mL), subjected to sonication, and the white solid was removed by filtration through a short plug of oven-dried celite. The filtrate was neutralized (pH 6-7) by the addition of a saturated solution of aqueous $NaHCO_3$ (~8 mL). The resulting white solid was removed through filtration, and washed three times with EtOAc. The filtrate was then washed with EtOAc (3 x 15mL), and the combined organic layers were washed with brine (1 x 5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting yellow solid was purified by silica gel chromatography (gradient eluting with 10:1 to 1:3 hexanes:EtOAc) to afford **1.133** as off-white solid (105.3 mg, 0.29 mmol, 69% yield).

M.p. = 122 °C – decomposition; **IR (neat):** 3248 (br, w), 3060 (w), 1438 (m), 1171 (s), 1123, 925 (s), 725 (s), 695 (s), 528 (s) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.91 (dd, *J* = 12.0, 7.6 Hz, 2H), 7.83 (dd, *J* = 12.2, 7.7 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.48 (td, *J* = 7.5, 2.9 Hz, 3H), 7.37 (dd, *J* = 8.9, 6.5 Hz, 4H), 7.33 – 7.27 (m, 3H), 5.59 (ddd, *J* = 17.4, 10.4, 3.5 Hz, 1H), 5.48 (d, *J* = 17.4 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.53 (d, *J* = 7.1 Hz, 2H), 3.46 (d, *J* = 11.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 139.5 (d, *J* = 9.3 Hz), 135.0, 132.8 (d, *J* = 9.7 Hz), 132.5 (d, *J* = 2.9 Hz), 132.4 (d, *J* = 2.7 Hz), 132.3 (d, *J* = 128 Hz), 131.8 (d, *J* = 9.9 Hz), 130.2 (d, *J* = 133 Hz), 128.9 (d,

J = 12.8 Hz), 128.8 (d, J = 12.9 Hz), 128.7, 127.6, 126.6, 118.2, 75.6, 60.6; **HRMS (DART):** Calcd for $C_{22}H_{23}NO_2P$ $[M+H]^+$: 364.1461; Found: 364.1461; **Specific rotation:** $[\alpha]^{25}_D$ +52.0 (c = 2.03, $CHCl_3$) for a 96.5:3.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 15.310 min (major) and 17.901 min (minor).





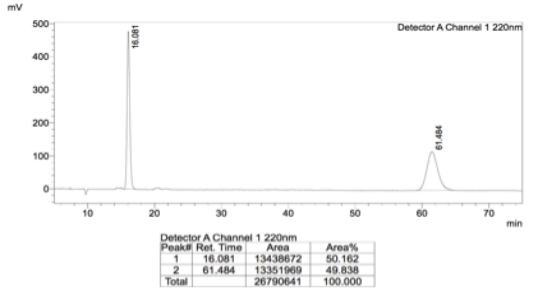
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	13.307	49.326	1	15.310	96.483
2	15.225	50.674	2	17.901	3.517

(1*S*,2*R*)-2-((2-Methoxyethoxy)methoxy)-1-phenylbut-3-en-1-amine (1.134): To a solution of homoallylamide **1.106** (45.0 mg, 0.100 mmol, 97:3 e.r.) in thf (1.0 mL) was added diphenylphosphite (38 µL, 0.20 mmol), triphenylphosphite (12 µL, 0.050 mmol), I_2 (6.3 mg, 0.050 mmol), and Et_3N (7 µL, 0.05 mmol). The solution was then purged with a stream of N_2, and sealed with a septum. The solution was allowed to stir at 22 °C for 5 h, during which it turned colorless. The reaction was then quenched by the addition of water (0.5 mL) and a 1.0 M aqueous solution of HCl (0.1 mL). The aqueous layer was washed with Et_2O (3 x 2 mL), and then basified to pH >12 by the addition of 2.0 M aqueous solution of NaOH (0.5 mL), and washed with dichloromethane (5 x 3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford **1.134** as yellow oil (10.8 mg, 0.043 mmol, 43% yield).

IR (neat): 2928 (w, br), 2885 (w, br), 1101 (s), 1019 (s), 906 (s), 725 (s), 700 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 (ddd, J = 8.2, 1.5, 0.5 Hz, 2H), 7.35 – 7.28 (m, 2H), 7.24 – 7.20 (m, 1H), 5.67 (ddd, J = 16.8, 10.8, 7.6 Hz, 1H), 5.38 – 5.20 (m, 2H), 4.70 (d, J = 7.0 Hz, 1H), 4.58 – 4.48 (m, 1H), 4.17 (ddt, J = 7.5, 6.5, 1.0 Hz, 1H), 4.01 (d, J = 6.5 Hz, 1H), 3.42 – 3.28 (m, 6H), 3.28 – 3.15 (m, 1H), 1.53 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.8, 135.0, 128.2, 127.7, 127.3, 120.2, 92.7, 81.9, 71.8, 66.7, 59.0; **HRMS (DART):** Calcd for $C_{14}H_{22}NO_3$ $[M+H]^+$: 252.1594; Found: 252.1594; **Specific rotation:** $[\alpha]^{23.3}_D$ –16.8 (c = 1.11, $CHCl_3$).

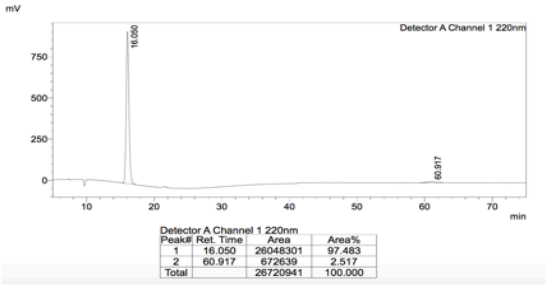
Diphenyl((2*S*,3*R*)-2-phenyl-3-vinylaziridin-1-yl)phosphine oxide (1.135): To a cooled (0 °C) solution of **1.134** (36.0 mg, 0.100 mmol) and PPh_3 (44.0 mg, 0.150 mmol) in thf (1.0 mL) was added diad (30.0 mg, 0.150 mmol) in a dropwise manner. The solution was allowed to warm to 22 °C and allowed to stir for 12 h. The volatiles were then removed in vacuo, and the resulting off-

white solid was purified by silica gel chromatography (gradient eluting with 100:0 to 0:100 hexanes:Et_2O) to furnish **1.135** as white solid (25.1 mg, 0.073 mmol, 73% yield). The analytical data are fully consistent with those reported previously.[15] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.98 – 7.90 (m, 2H), 7.90 – 7.81 (m, 2H), 7.53 – 7.36 (m, 4H), 7.35 – 7.24 (m, 7H), 6.30 (dddd, *J* = 17.0, 10.2, 9.4, 0.6 Hz, 1H), 5.24 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.13 (dd, *J* = 10.3, 1.3 Hz, 1H), 3.91 (dd, *J* = 15.8, 2.8 Hz, 1H), 3.17 (ddd, *J* = 12.4, 9.5, 2.9 Hz, 1H). **Specific rotation:** $[\alpha]^{22.2}_D$ –20.3 (*c* = 0.72, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 92:8 hexanes:*i*PrOH, 1.0 mL/min, 220 nm): t_R: 16.050 min (major) and 60.917 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	16.081	13438672	50.162
2	61.484	13351969	49.838
Total		26790641	100.000



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	16.050	26048301	97.483
2	60.917	672639	2.517
Total		26720941	100.000

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	16.081	50.162	1	16.050	97.483
2	61.484	49.838	2	60.917	2.517

1.7.9 Formal Synthesis of NK_1 Agonist

2-Chloro-*N*-((1*S*,2*R*)-2-hydroxy-1-phenylbut-3-en-1-yl)acetamide (1.136): To a cooled (0 °C) solution of **1.106** (0.5 g, 1.10 mmol) in ethanol (10 mL) was added a 12.0 M aqueous solution of HCl (10 mL). The mixture was allowed to warm to 22 °C, and then allowed to stir for an additional 4 h. The solution was then diluted with H_2O (~5 mL), washed with toluene (3 x 5 mL), and then carefully basified to pH 10–11 by the addition of 2M aqueous solution of NaOH. The mixture was filtered and subjected to continuous extraction[16] for 14 h with CH_2Cl_2 to afford unpurified **9** as yellow oil. (*Note*: In some instances, incomplete acetal deprotection was observed; however, by allowing the unpurified residue to sit on the bench open to air for 24–48 h, the desired product could be obtained). To a solution of unpurified aminoalcohol **9** in thf (5 mL) was added triethylamine (0.21 mL, 1.5 mmol). The solution was allowed to cool to 0 °C, and then treated (dropwise) with freshly distilled chloroacetyl chloride (105 µL, 1.3 mmol). The solution was then allowed to warm to 22 °C and was allowed to stir for 1h. The reaction was then quenched by the addition of a saturated solution of NH_4Cl (2.0 mL); water was added until homogeneity was

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achieved. The aqueous layer was washed with Et_2O (3 x 10 mL), and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified brown oil residue was purified by silica gel chromatography (gradient eluting with 15:1 to 0:100 hexanes: Et_2O) to afford **1.136** as yellow oil (176.6 mg, 0.74 mmol, 67% yield).

IR (neat): 3396 (w, br), 3304 (w, br), 1659 (s), 1520 (s), 1261 (w), 994 (w), 930 (w), 700 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 – 7.28 (m, 5H), 5.70 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.41 – 5.18 (m, 2H), 5.11 (dd, *J* = 8.3, 4.0 Hz, 1H), 4.52 (ddt, *J* = 4.2, 2.7, 1.3 Hz, 1H), 4.18 – 3.93 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 166.2, 136.9, 136.0, 128.8, 128.3, 127.6, 118.0, 75.1, 58.1, 42.9; **HRMS (DART):** Calcd for $C_{12}H_{15}NO_2Cl$ $[M+H]^+$: 240.0791; Found: 240.0784; **Specific rotation:** $[\alpha]^{23.9}_D$ +15.7 (*c* = 1.05, $CHCl_3$).

(5*S*,6*R*)-5-Phenyl-6-vinylmorpholin-3-one (1.138): To a cooled (0 °C) solution of **1.136** (100.0 mg, 0.42 mmol) in thf/dmf (2.0 mL/0.4 mL) was added NaH (42.0 mg, 1.05 mmol) in three portions. The solution was allowed to warm to 22 °C and to stir for 5 h before it was diluted with Et_2O (~5 mL). At this time, the reaction was quenched by the addition of a saturated solution of NH_4Cl (2.0 mL); water was added until homogeneity was achieved. The aqueous layer was washed with Et_2O (3 x 5 mL), and the combined organic layers were washed (2x) with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting viscous yellow oil residue was purified by silica gel chromatography (gradient eluting with 100:0:0 to 0:90:10 hexanes: EtOAc: acetone) to afford **1.138** as white solid (73.4 mg, 0.36 mmol, 86% yield).

M.p. = 143 – 145 °C; **IR (neat):** 3258 (w), 3219 (w), 1671 (s), 1454 (m), 1353 (m), 1109 (s), 701 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.30 (m, 3H), 7.26 – 7.21 (m, 2H), 6.22 (s, 1H), 5.39 – 5.31 (m, 1H), 5.31 – 5.22 (m, 1H), 5.15 (ddd, *J* = 10.1, 2.1, 0.9 Hz, 1H), 4.63 – 4.29 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 168.1, 136.9, 133.2, 128.4, 128.3, 128.2, 118.9, 67.8, 59.8; **HRMS (DART):** Calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.1025; Found: 204.1019; **Specific rotation:** $[\alpha]^{23.9}_D$ –44.3 (*c* = 0.91, $CHCl_3$).

(5*S*,6*R*)-6-((*E*)-3,5-Bis(trifluoromethyl)styryl)-5-phenylmorpholin-3-one (1.139): In a nitrogen-filled glovebox (with overhead lights off) **1.138** (58.0 mg, 0.29 mmol) and 3,5-bistrifluoromethyl styrene (348.2 mg, 1.45 mmol) were combined in an oven-dried 6-dram vial. The reagents were dissolved in toluene (0.7 mL) and then a solution of **Ru-1** (9.1 mg, 0.015) in toluene (0.7 mL) was added. The vial was capped, removed from the glovebox and placed in an oil bath preheated to 60 °C, covered with aluminum foil, and allowed to stir for 4 h. After the mixture was allowed to cool to 22 °C, it was diluted with EtOAc and filtered through a small plug of celite. The filtrate was concentrated in vacuo and the resulting purple oil was purified by silica gel chromatography (gradient eluting with 100:0 to 0:100 hexanes: EtOAc) to yield a mixture of the desired product and ~15% **11**. Unreacted **1.138** was removed by crystallization in a mixture of hexanes and Et_2O to yield the NK_1 agonist as white foam (78.3 mg, 0.19 mmol, 65% yield).

IR (neat): 3224 (w), 3604 (w), 2926 (w), 1671 (s), 1381 (m), 1277 (s), 1174 (m), 1128 (s), 897 (m), 700 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71 (s, 1H), 7.55 (d, *J* = 1.5 Hz, 2H), 7.41 – 7.31 (m, 3H), 7.24 (d, *J* = 2.2 Hz, 1H), 6.64 (s, 1H), 6.59 (dd, *J* = 16.0, 1.3 Hz, 1H), 5.83 (dd, *J* = 16.0, 5.9 Hz, 1H), 4.73 (ddd, *J* = 5.5, 3.6, 1.6 Hz, 1H), 4.62 (t, *J* = 3.7 Hz, 1H), 4.59 – 4.35 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 168.2, 138.2, 136.8, 132.1 (q, *J* = 33.5 Hz), 130.2, 128.9, 128.9, 128.6, 128.1, 126.4, 121.6 (q, *J* = 3.8 Hz), 123.3 (q, *J* = 273 Hz), 76.4, 68.0, 59.9; **^{19}F NMR:** δ –63.1; **HRMS (DART):** Calcd for $C_{20}H_{16}F_6NO_2$ $[M+H]^+$: 416.1085; Found: 416.1073; **Specific rotation:** $[\alpha]^{23.9}_D$ –47.9 (*c* = 1.12, $CHCl_3$).

1.7.10 DFT Studies

DFT calculations were performed with the Gaussian 09 suite of programs[17] employing the dispersion corrected ωB97XD[18] functional. The Def2SVP[19] basis set and SMD[20] solvation model (toluene) was used for geometry optimization and frequency calculation. The nature of all stationary points was checked through vibrational analysis.

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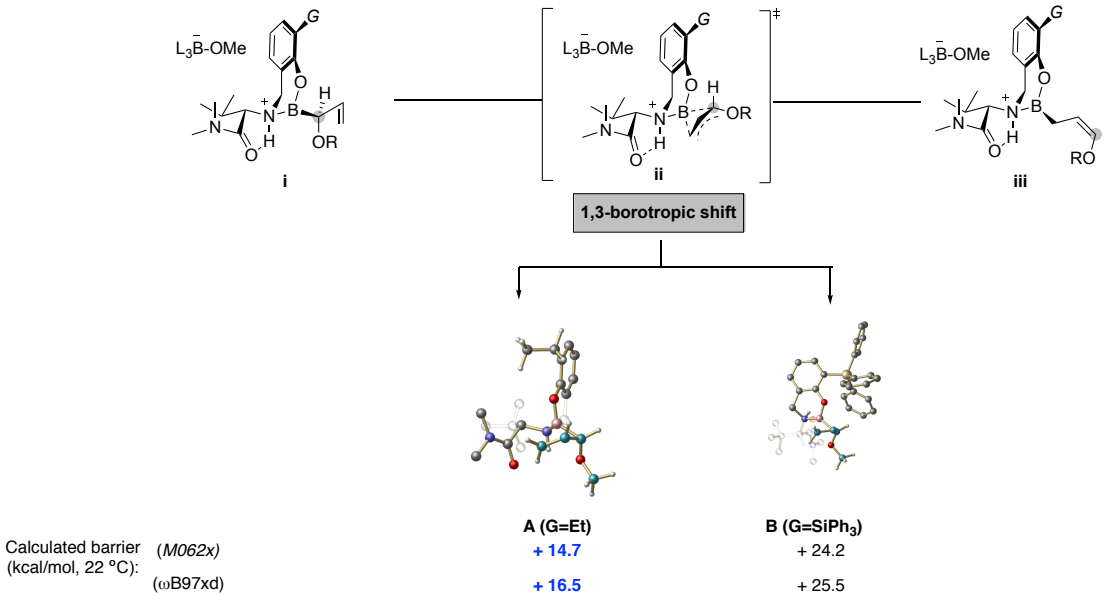

Table S1: Borotropic rearrangement energies and Gibbs free energies calculated with ωB97XD/Def2SVP, calculations were carried out in toluene with the SMD solvation model.

Structure	E [Hartree]	ΔE [kcal/mol]	G [Hartree]	ΔG [kcal/mol]	Freq [cm^{-1}]
A-gs	-1179.449824	0.00	-1178.966504	0.0	33.32
A-ts	-1179.422159	17.35	-1178.940174	16.52	-183.35
B-gs	-2083.711066	0.00	-2083.305771	0.00	12.53
B-ts	-2083.672653	25.66	-2083.265090	25.53	-348.50

Table S2: Borotropic rearrangement energies and Gibbs free energies calculated with M062x/Def2SVP, calculations were carried out in toluene with the SMD solvation model.

Structure	E [Hartree]	ΔE [kcal/mol]	G [Hartree]	ΔG [kcal/mol]	Freq [cm^{-1}]
A-gs	-1179.24481	0.00	-1178.763151	0.0	37.11
A-ts	-1179.219741	15.73	-1178.739802	14.65	-151.03
B-gs	-2083.981355	0.00	-2083.037544	0.00	21.18
B-ts	-2083.940463	25.66	-2082.998952	24.21	-317.04

Table S3: Fukui indices for *O*-substituted allyl boron reagent calculated with ωB97XD/Def2SVP, calculations were carried out in gas phase.

	$P_A(N)$	$P_A(N-1)$	**Me (*Z*-1a)**	$P_A(N)$	$P_A(N-1)$	**MEM (*Z*-1b)**
C	-0.24949	0.23611	**-0.4856**	-0.24598	0.23893	**-0.50264**
C	0.09942	0.22627	**-0.12685**	0.09833	0.25715	**-0.15882**

1.7.11 Crystallographic Data

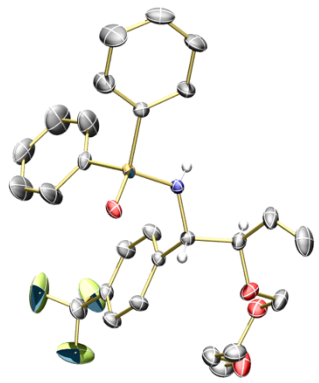

Table S4: Crystal data and structure refinement for compound **1.122**

Identification code	C27 H29 F3 N O4 P	
Empirical formula	C27 H29 F3 N O4 P	
Formula weight	519.48	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.3352(13) Å	α= 90°.
	b = 5.2931(6) Å	β= 97.645(4)°.
	c = 19.893(2) Å	γ= 90°.
Volume	1287.3(2) $Å^3$	
Z	2	
Density (calculated)	1.340 Mg/m^3	
Absorption coefficient	0.162 mm^{-1}	
F(000)	544	

Crystal size	0.1 x 0.2 x 0.4 mm^3
Theta range for data collection	1.033 to 28.927°.
Index ranges	-16<=h<=16, -7<=k<=7, -26<=l<=26
Reflections collected	46965
Independent reflections	6684 [R(int) = 0.0541]
Completeness to theta = 25.242°	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6684 / 4 / 358
Goodness-of-fit on F^2	1.064
Final R indices [I>2sigma(I)]	R1 = 0.0454, wR2 = 0.1197
R indices (all data)	R1 = 0.0483, wR2 = 0.1225
Absolute structure parameter	-0.01(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.678 and -0.392 e.$Å^{-3}$

Table S5: Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **1.122**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1A)	8154(10)	3125(16)	9779(5)	58(2)
F(2A)	7465(12)	6660(40)	9944(6)	91(4)
F(3A)	9049(8)	6410(30)	9664(7)	78(4)
F(1B)	7357(12)	6000(60)	9963(9)	75(6)
F(2B)	8860(30)	7020(70)	9711(12)	103(9)
F(3B)	8420(30)	3190(40)	9713(12)	115(10)
P(001)	4031(1)	7882(1)	6943(1)	15(1)
O(2)	4434(2)	10503(3)	6861(1)	22(1)
O(3)	7661(2)	5028(5)	6282(1)	30(1)
O(4)	8785(2)	2048(5)	6902(1)	35(1)
N(1)	4861(2)	5772(4)	6678(1)	17(1)
O(5)	10602(2)	679(6)	7908(1)	54(1)
C(1)	6603(2)	6013(5)	7470(1)	19(1)
C(22)	6044(2)	6254(5)	6744(1)	18(1)
C(17)	2720(2)	7236(5)	6457(1)	19(1)
C(23)	6536(2)	4364(5)	6268(1)	24(1)

C(3)	7573(2)	5630(6)	8815(1)	26(1)
C(10)	3864(2)	7252(5)	7819(1)	22(1)
C(5)	7358(2)	7784(6)	7744(1)	26(1)
C(00H)	6355(2)	4005(6)	7872(1)	27(1)
C(4)	7837(2)	7612(6)	8421(1)	31(1)
C(2)	6830(3)	3799(6)	8545(1)	30(1)
C(26)	8360(2)	2914(8)	6254(1)	36(1)
C(16)	2596(2)	5543(7)	5921(2)	34(1)
C(6)	8062(3)	5456(7)	9546(2)	37(1)
C(21)	1583(3)	5286(8)	5519(2)	40(1)
C(19)	808(3)	8308(8)	6192(2)	53(1)
C(32)	5956(2)	4433(7)	5551(2)	35(1)
C(20)	710(2)	6664(7)	5649(2)	39(1)
C(11)	4362(4)	8753(9)	8328(2)	53(1)
C(13)	3773(3)	6126(9)	9177(2)	49(1)
C(15)	3330(4)	5105(8)	7994(2)	51(1)
C(28)	9562(3)	3788(8)	7254(2)	42(1)
C(18)	1816(3)	8591(6)	6602(2)	40(1)
C(29)	9928(3)	2792(8)	7958(2)	40(1)
C(24)	6411(3)	5006(8)	5012(2)	44(1)
C(12)	4326(4)	8088(12)	9011(2)	62(1)
C(31)	10973(4)	-371(10)	8549(2)	56(1)
C(14)	3294(5)	4528(10)	8678(2)	63(1)

Table S6: Bond lengths [Å] and angles [°] for **1.122**.

F(1A)-C(6)	1.317(9)
F(2A)-C(6)	1.317(10)
F(3A)-C(6)	1.310(9)
F(1B)-C(6)	1.312(16)
F(2B)-C(6)	1.29(2)
F(3B)-C(6)	1.31(2)
P(001)-O(2)	1.4898(19)

P(001)-N(1)	1.648(2)
P(001)-C(17)	1.804(2)
P(001)-C(10)	1.813(2)
O(3)-C(26)	1.418(4)
O(3)-C(23)	1.428(3)
O(4)-C(26)	1.404(4)
O(4)-C(28)	1.442(4)
N(1)-C(22)	1.471(3)
N(1)-H(1)	0.86(4)
O(5)-C(29)	1.405(5)
O(5)-C(31)	1.410(5)
C(1)-C(5)	1.381(4)
C(1)-C(00H)	1.388(4)
C(1)-C(22)	1.521(3)
C(22)-C(23)	1.556(3)
C(22)-H(22)	1.0000
C(17)-C(16)	1.385(4)
C(17)-C(18)	1.388(4)
C(23)-C(32)	1.508(4)
C(23)-H(23)	1.0000
C(3)-C(4)	1.375(4)
C(3)-C(2)	1.392(4)
C(3)-C(6)	1.500(4)
C(10)-C(11)	1.366(4)
C(10)-C(15)	1.381(5)
C(5)-C(4)	1.400(3)
C(5)-H(5)	0.9500
C(00H)-C(2)	1.393(4)
C(00H)-H(00H)	0.9500
C(4)-H(4)	0.9500
C(2)-H(2)	0.9500
C(26)-H(26A)	0.9900
C(26)-H(26B)	0.9900
C(16)-C(21)	1.397(4)
C(16)-H(16)	0.9500
C(21)-C(20)	1.355(5)

C(21)-H(21)	0.9500
C(19)-C(20)	1.380(6)
C(19)-C(18)	1.401(5)
C(19)-H(19)	0.9500
C(32)-C(24)	1.310(5)
C(32)-H(32)	0.9500
C(20)-H(20)	0.9500
C(11)-C(12)	1.411(5)
C(11)-H(11)	0.9500
C(13)-C(12)	1.310(7)
C(13)-C(14)	1.377(7)
C(13)-H(13)	0.9500
C(15)-C(14)	1.401(5)
C(15)-H(15)	0.9500
C(28)-C(29)	1.506(5)
C(28)-H(28A)	0.9900
C(28)-H(28B)	0.9900
C(18)-H(18)	0.9500
C(29)-H(29A)	0.9900
C(29)-H(29B)	0.9900
C(24)-H(24A)	0.9500
C(24)-H(24B)	0.9500
C(12)-H(12)	0.9500
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800
C(14)-H(14)	0.9500

O(2)-P(001)-N(1)	111.47(11)
O(2)-P(001)-C(17)	113.98(11)
N(1)-P(001)-C(17)	104.53(11)
O(2)-P(001)-C(10)	111.02(11)
N(1)-P(001)-C(10)	109.70(11)
C(17)-P(001)-C(10)	105.79(11)
C(26)-O(3)-C(23)	113.5(2)
C(26)-O(4)-C(28)	112.4(3)

C(22)-N(1)-P(001)	120.35(16)
C(22)-N(1)-H(1)	114(2)
P(001)-N(1)-H(1)	117(2)
C(29)-O(5)-C(31)	112.0(3)
C(5)-C(1)-C(00H)	118.8(2)
C(5)-C(1)-C(22)	120.9(2)
C(00H)-C(1)-C(22)	120.3(2)
N(1)-C(22)-C(1)	112.88(19)
N(1)-C(22)-C(23)	107.30(19)
C(1)-C(22)-C(23)	111.12(19)
N(1)-C(22)-H(22)	108.5
C(1)-C(22)-H(22)	108.5
C(23)-C(22)-H(22)	108.5
C(16)-C(17)-C(18)	119.0(2)
C(16)-C(17)-P(001)	122.31(19)
C(18)-C(17)-P(001)	118.6(2)
O(3)-C(23)-C(32)	110.5(2)
O(3)-C(23)-C(22)	106.7(2)
C(32)-C(23)-C(22)	112.7(2)
O(3)-C(23)-H(23)	109.0
C(32)-C(23)-H(23)	109.0
C(22)-C(23)-H(23)	109.0
C(4)-C(3)-C(2)	120.3(2)
C(4)-C(3)-C(6)	120.3(3)
C(2)-C(3)-C(6)	119.4(3)
C(11)-C(10)-C(15)	118.3(3)
C(11)-C(10)-P(001)	120.5(2)
C(15)-C(10)-P(001)	120.8(2)
C(1)-C(5)-C(4)	120.7(3)
C(1)-C(5)-H(5)	119.6
C(4)-C(5)-H(5)	119.6
C(1)-C(00H)-C(2)	121.1(3)
C(1)-C(00H)-H(00H)	119.5
C(2)-C(00H)-H(00H)	119.5
C(3)-C(4)-C(5)	119.8(3)
C(3)-C(4)-H(4)	120.1

C(5)-C(4)-H(4)	120.1
C(3)-C(2)-C(00H)	119.2(3)
C(3)-C(2)-H(2)	120.4
C(00H)-C(2)-H(2)	120.4
O(4)-C(26)-O(3)	112.1(2)
O(4)-C(26)-H(26A)	109.2
O(3)-C(26)-H(26A)	109.2
O(4)-C(26)-H(26B)	109.2
O(3)-C(26)-H(26B)	109.2
H(26A)-C(26)-H(26B)	107.9
C(17)-C(16)-C(21)	120.1(3)
C(17)-C(16)-H(16)	119.9
C(21)-C(16)-H(16)	119.9
F(2B)-C(6)-F(3B)	107.4(15)
F(2B)-C(6)-F(1B)	104.1(17)
F(3B)-C(6)-F(1B)	105.9(16)
F(3A)-C(6)-F(2A)	106.6(9)
F(3A)-C(6)-F(1A)	105.2(9)
F(2A)-C(6)-F(1A)	105.8(9)
F(2B)-C(6)-C(3)	113.7(11)
F(3B)-C(6)-C(3)	112.5(10)
F(3A)-C(6)-C(3)	113.2(6)
F(1B)-C(6)-C(3)	112.6(9)
F(2A)-C(6)-C(3)	111.6(6)
F(1A)-C(6)-C(3)	113.8(5)
C(20)-C(21)-C(16)	120.7(3)
C(20)-C(21)-H(21)	119.6
C(16)-C(21)-H(21)	119.6
C(20)-C(19)-C(18)	120.1(3)
C(20)-C(19)-H(19)	120.0
C(18)-C(19)-H(19)	120.0
C(24)-C(32)-C(23)	125.3(3)
C(24)-C(32)-H(32)	117.3
C(23)-C(32)-H(32)	117.3
C(21)-C(20)-C(19)	120.0(3)
C(21)-C(20)-H(20)	120.0

C(19)-C(20)-H(20)	120.0
C(10)-C(11)-C(12)	120.0(4)
C(10)-C(11)-H(11)	120.0
C(12)-C(11)-H(11)	120.0
C(12)-C(13)-C(14)	119.5(3)
C(12)-C(13)-H(13)	120.2
C(14)-C(13)-H(13)	120.2
C(10)-C(15)-C(14)	120.1(4)
C(10)-C(15)-H(15)	119.9
C(14)-C(15)-H(15)	119.9
O(4)-C(28)-C(29)	109.0(3)
O(4)-C(28)-H(28A)	109.9
C(29)-C(28)-H(28A)	109.9
O(4)-C(28)-H(28B)	109.9
C(29)-C(28)-H(28B)	109.9
H(28A)-C(28)-H(28B)	108.3
C(17)-C(18)-C(19)	120.0(3)
C(17)-C(18)-H(18)	120.0
C(19)-C(18)-H(18)	120.0
O(5)-C(29)-C(28)	108.7(3)
O(5)-C(29)-H(29A)	109.9
C(28)-C(29)-H(29A)	109.9
O(5)-C(29)-H(29B)	109.9
C(28)-C(29)-H(29B)	109.9
H(29A)-C(29)-H(29B)	108.3
C(32)-C(24)-H(24A)	120.0
C(32)-C(24)-H(24B)	120.0
H(24A)-C(24)-H(24B)	120.0
C(13)-C(12)-C(11)	121.7(4)
C(13)-C(12)-H(12)	119.2
C(11)-C(12)-H(12)	119.2
O(5)-C(31)-H(31A)	109.5
O(5)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	109.5
O(5)-C(31)-H(31C)	109.5
H(31A)-C(31)-H(31C)	109.5

H(31B)-C(31)-H(31C)	109.5
C(13)-C(14)-C(15)	120.1(4)
C(13)-C(14)-H(14)	120.0
C(15)-C(14)-H(14)	120.0

Symmetry transformations used to generate equivalent atoms:

Table S7: Anisotropic displacement parameters ($Å^2x10^3$) for **1.122**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1A)	81(4)	54(4)	29(3)	15(3)	-24(2)	-10(4)
F(2A)	124(9)	126(7)	21(3)	-24(4)	-1(4)	70(7)
F(3A)	44(4)	147(11)	36(3)	17(5)	-24(2)	-40(4)
F(1B)	44(6)	163(17)	18(5)	8(7)	3(3)	-1(9)
F(2B)	160(20)	95(12)	32(6)	17(6)	-43(10)	-84(13)
F(3B)	166(19)	122(17)	41(7)	-27(8)	-48(9)	99(15)
P(001)	18(1)	15(1)	13(1)	0(1)	-1(1)	1(1)
O(2)	28(1)	16(1)	21(1)	-1(1)	-2(1)	0(1)
O(3)	21(1)	45(1)	25(1)	4(1)	4(1)	0(1)
O(4)	24(1)	47(1)	34(1)	2(1)	-2(1)	3(1)
N(1)	16(1)	15(1)	19(1)	-1(1)	1(1)	0(1)
O(5)	49(1)	75(2)	34(1)	-9(1)	-9(1)	25(2)
C(1)	19(1)	22(1)	16(1)	0(1)	1(1)	0(1)
C(22)	17(1)	21(1)	16(1)	2(1)	1(1)	-1(1)
C(17)	18(1)	22(1)	16(1)	4(1)	0(1)	-1(1)
C(23)	21(1)	32(1)	19(1)	-1(1)	3(1)	3(1)
C(3)	26(1)	34(1)	16(1)	-3(1)	-2(1)	2(1)
C(10)	24(1)	28(1)	14(1)	2(1)	2(1)	6(1)
C(5)	28(1)	28(1)	22(1)	4(1)	-1(1)	-8(1)
C(00H)	32(1)	27(1)	20(1)	4(1)	-5(1)	-6(1)
C(4)	30(1)	36(2)	24(1)	-4(1)	-4(1)	-8(1)
C(2)	35(1)	35(1)	20(1)	7(1)	-3(1)	-6(1)
C(26)	26(1)	56(2)	26(1)	-1(2)	7(1)	10(2)
C(16)	20(1)	45(2)	35(1)	-14(1)	-2(1)	-2(1)

C(6)	41(2)	50(2)	19(1)	-2(1)	-4(1)	-1(2)
C(21)	29(1)	55(2)	32(2)	-8(2)	-9(1)	-11(1)
C(19)	25(1)	52(2)	78(3)	-8(2)	-11(2)	15(2)
C(32)	25(1)	55(2)	24(1)	-12(1)	-3(1)	11(1)
C(20)	24(1)	40(2)	47(2)	16(2)	-14(1)	-6(1)
C(11)	63(2)	74(3)	21(1)	-8(2)	3(1)	-33(2)
C(13)	46(2)	83(3)	18(1)	11(2)	6(1)	11(2)
C(15)	79(3)	49(2)	26(2)	4(2)	14(2)	-15(2)
C(28)	26(1)	53(2)	43(2)	4(2)	-5(1)	-3(1)
C(18)	28(1)	37(2)	51(2)	-8(1)	-6(1)	8(1)
C(29)	32(1)	49(2)	38(2)	-10(2)	-2(1)	2(2)
C(24)	56(2)	52(2)	22(1)	-1(1)	-3(1)	17(2)
C(12)	71(2)	96(3)	17(1)	-10(2)	2(1)	-28(3)
C(31)	42(2)	71(3)	50(2)	8(2)	-13(2)	-2(2)
C(14)	88(3)	70(3)	33(2)	20(2)	18(2)	-6(2)

Table S8: Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **1.122**.

	x	y	z	U(eq)
H(22)	6161	8010	6582	22
H(23)	6488	2615	6452	29
H(5)	7555	9134	7469	32
H(00H)	5852	2751	7685	32
H(4)	8343	8862	8607	37
H(2)	6649	2425	8817	36
H(26A)	7947	1531	6002	43
H(26B)	8972	3386	6003	43
H(16)	3200	4554	5827	41
H(21)	1507	4131	5150	48
H(19)	191	9247	6289	64
H(32)	5199	4029	5485	42
H(20)	30	6500	5366	46

H(11)	4732	10244	8221	63
H(13)	3702	5806	9640	59
H(15)	2988	4017	7649	61
H(28A)	9220	5469	7282	50
H(28B)	10201	3970	7005	50
H(18)	1881	9709	6978	48
H(29A)	10337	4116	8237	48
H(29B)	9284	2306	8177	48
H(24A)	7167	5422	5056	53
H(24B)	5986	5006	4577	53
H(12)	4714	9090	9360	74
H(31A)	11280	967	8858	84
H(31B)	11538	-1638	8503	84
H(31C)	10359	-1173	8733	84
H(14)	2938	3033	8797	75
H(1)	4700(30)	4210(70)	6724(16)	16(7)

Table S9: Torsion angles [°] for **1.122**.

O(2)-P(001)-N(1)-C(22)	32.3(2)
C(17)-P(001)-N(1)-C(22)	155.92(17)
C(10)-P(001)-N(1)-C(22)	-91.0(2)
P(001)-N(1)-C(22)-C(1)	73.9(2)
P(001)-N(1)-C(22)-C(23)	-163.36(17)
C(5)-C(1)-C(22)-N(1)	-135.4(3)
C(00H)-C(1)-C(22)-N(1)	44.2(3)
C(5)-C(1)-C(22)-C(23)	104.0(3)
C(00H)-C(1)-C(22)-C(23)	-76.4(3)
O(2)-P(001)-C(17)-C(16)	113.3(2)
N(1)-P(001)-C(17)-C(16)	-8.7(3)
C(10)-P(001)-C(17)-C(16)	-124.5(2)
O(2)-P(001)-C(17)-C(18)	-63.0(3)
N(1)-P(001)-C(17)-C(18)	175.0(2)
C(10)-P(001)-C(17)-C(18)	59.2(3)
C(26)-O(3)-C(23)-C(32)	-93.8(3)

C(26)-O(3)-C(23)-C(22)	143.4(2)
N(1)-C(22)-C(23)-O(3)	174.0(2)
C(1)-C(22)-C(23)-O(3)	-62.1(3)
N(1)-C(22)-C(23)-C(32)	52.6(3)
C(1)-C(22)-C(23)-C(32)	176.5(2)
O(2)-P(001)-C(10)-C(11)	-17.7(3)
N(1)-P(001)-C(10)-C(11)	105.9(3)
C(17)-P(001)-C(10)-C(11)	-141.9(3)
O(2)-P(001)-C(10)-C(15)	169.1(3)
N(1)-P(001)-C(10)-C(15)	-67.2(3)
C(17)-P(001)-C(10)-C(15)	45.0(3)
C(00H)-C(1)-C(5)-C(4)	-2.3(4)
C(22)-C(1)-C(5)-C(4)	177.3(3)
C(5)-C(1)-C(00H)-C(2)	1.8(4)
C(22)-C(1)-C(00H)-C(2)	-177.8(3)
C(2)-C(3)-C(4)-C(5)	-0.2(4)
C(6)-C(3)-C(4)-C(5)	-178.7(3)
C(1)-C(5)-C(4)-C(3)	1.5(5)
C(4)-C(3)-C(2)-C(00H)	-0.3(5)
C(6)-C(3)-C(2)-C(00H)	178.2(3)
C(1)-C(00H)-C(2)-C(3)	-0.6(5)
C(28)-O(4)-C(26)-O(3)	-69.6(3)
C(23)-O(3)-C(26)-O(4)	-92.1(3)
C(18)-C(17)-C(16)-C(21)	2.5(5)
P(001)-C(17)-C(16)-C(21)	-173.8(3)
C(4)-C(3)-C(6)-F(2B)	-12(2)
C(2)-C(3)-C(6)-F(2B)	170(2)
C(4)-C(3)-C(6)-F(3B)	-134(2)
C(2)-C(3)-C(6)-F(3B)	48(2)
C(4)-C(3)-C(6)-F(3A)	-31.7(10)
C(2)-C(3)-C(6)-F(3A)	149.8(10)
C(4)-C(3)-C(6)-F(1B)	106.5(15)
C(2)-C(3)-C(6)-F(1B)	-72.0(15)
C(4)-C(3)-C(6)-F(2A)	88.7(11)
C(2)-C(3)-C(6)-F(2A)	-89.8(11)
C(4)-C(3)-C(6)-F(1A)	-151.7(7)

C(2)-C(3)-C(6)-F(1A)	29.8(7)
C(17)-C(16)-C(21)-C(20)	-0.6(6)
O(3)-C(23)-C(32)-C(24)	0.3(5)
C(22)-C(23)-C(32)-C(24)	119.5(4)
C(16)-C(21)-C(20)-C(19)	-1.3(6)
C(18)-C(19)-C(20)-C(21)	1.3(6)
C(15)-C(10)-C(11)-C(12)	0.3(6)
P(001)-C(10)-C(11)-C(12)	-173.1(4)
C(11)-C(10)-C(15)-C(14)	1.0(6)
P(001)-C(10)-C(15)-C(14)	174.2(4)
C(26)-O(4)-C(28)-C(29)	176.8(3)
C(16)-C(17)-C(18)-C(19)	-2.5(5)
P(001)-C(17)-C(18)-C(19)	173.9(3)
C(20)-C(19)-C(18)-C(17)	0.6(6)
C(31)-O(5)-C(29)-C(28)	-179.6(3)
O(4)-C(28)-C(29)-O(5)	71.4(3)
C(14)-C(13)-C(12)-C(11)	6.1(8)
C(10)-C(11)-C(12)-C(13)	-3.9(8)
C(12)-C(13)-C(14)-C(15)	-4.7(7)
C(10)-C(15)-C(14)-C(13)	1.2(7)

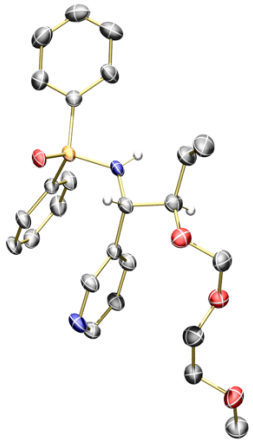

Table S10: Crystal data and structure refinement for **1.126**.

Identification code	C25H29N2O4P
Empirical formula	C25 H29 N2 O4 P
Formula weight	452.47
Temperature	100(2) K

Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.3430(2) Å	a= 90°.
	b = 12.1549(5) Å	b= 90°.
	c = 36.1182(13) Å	g = 90°.
Volume	2345.65(16) $Å^3$	
Z	4	
Density (calculated)	1.281 Mg/m^3	
Absorption coefficient	1.315 mm^{-1}	
F(000)	960	
Crystal size	0.220 x 0.070 x 0.040 mm^3	
Theta range for data collection	7.131 to 66.949°.	
Index ranges	-6<=h<=6, -14<=k<=14, -43<=l<=42	
Reflections collected	23892	
Independent reflections	4159 [R(int) = 0.0808]	
Completeness to theta = 66.949°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5931	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4159 / 1 / 293	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0410, wR2 = 0.0931	
R indices (all data)	R1 = 0.0528, wR2 = 0.0996	
Absolute structure parameter	0.055(16)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.238 and -0.280 e. $Å^{-3}$	

Table S11: Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **1.126**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	131(2)	8953(1)	3944(1)	23(1)
O(1)	7394(6)	2531(2)	3375(1)	44(1)
O(2)	5992(5)	4207(2)	3927(1)	39(1)
O(3)	2919(5)	5103(2)	4274(1)	35(1)
O(4)	-2470(4)	8521(2)	3977(1)	27(1)
N(1)	2197(5)	8050(2)	4096(1)	24(1)
N(2)	364(6)	5529(3)	3117(1)	37(1)

C(1)	8835(9)	2418(4)	3051(1)	49(1)
C(2)	5575(8)	3380(3)	3332(1)	42(1)
C(3)	4350(8)	3580(4)	3696(1)	44(1)
C(4)	5034(9)	4394(3)	4282(1)	42(1)
C(5)	3544(7)	6237(3)	4301(1)	31(1)
C(6)	1746(6)	6871(3)	4044(1)	25(1)
C(7)	741(6)	10166(3)	4214(1)	26(1)
C(8)	-451(7)	11142(3)	4113(1)	42(1)
C(9)	-164(10)	12079(3)	4333(1)	53(1)
C(10)	1318(9)	12033(4)	4648(1)	45(1)
C(11)	2521(9)	11091(4)	4741(1)	46(1)
C(12)	2227(8)	10151(3)	4526(1)	38(1)
C(13)	3393(9)	6625(4)	4698(1)	42(1)
C(14)	2759(9)	6013(4)	4979(1)	53(1)
C(15)	2037(7)	6504(3)	3641(1)	26(1)
C(16)	4097(7)	6822(3)	3435(1)	31(1)
C(17)	4235(7)	6494(3)	3068(1)	33(1)
C(18)	2341(7)	5869(3)	2924(1)	33(1)
C(19)	261(7)	5858(3)	3474(1)	33(1)
C(20)	858(6)	9316(3)	3471(1)	25(1)
C(21)	3017(7)	9922(3)	3384(1)	34(1)
C(22)	3655(8)	10113(4)	3019(1)	38(1)
C(23)	2198(8)	9693(3)	2735(1)	38(1)
C(24)	84(8)	9093(3)	2819(1)	36(1)
C(25)	-601(6)	8908(3)	3184(1)	31(1)

Table S12: Bond lengths [Å] and angles [°] for **1.126**.

P(1)-O(4)	1.490(2)
P(1)-N(1)	1.649(3)
P(1)-C(7)	1.796(4)
P(1)-C(20)	1.809(3)
O(1)-C(1)	1.408(5)
O(1)-C(2)	1.425(5)
O(2)-C(4)	1.397(5)
O(2)-C(3)	1.430(5)
O(3)-C(5)	1.420(4)
O(3)-C(4)	1.421(5)
N(1)-C(6)	1.465(4)

N(1)-H(1N)	0.87(2)
N(2)-C(18)	1.332(5)
N(2)-C(19)	1.352(4)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(3)	1.490(6)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(13)	1.514(5)
C(5)-C(6)	1.541(5)
C(5)-H(5)	1.0000
C(6)-C(15)	1.530(4)
C(6)-H(6)	1.0000
C(7)-C(12)	1.380(5)
C(7)-C(8)	1.394(5)
C(8)-C(9)	1.396(6)
C(8)-H(8)	0.9500
C(9)-C(10)	1.388(7)
C(9)-H(9)	0.9500
C(10)-C(11)	1.355(6)
C(10)-H(10)	0.9500
C(11)-C(12)	1.390(5)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500
C(13)-C(14)	1.303(6)
C(13)-H(13)	0.9500
C(14)-H(14A)	0.9500
C(14)-H(14B)	0.9500
C(15)-C(19)	1.372(5)
C(15)-C(16)	1.384(5)
C(16)-C(17)	1.386(5)
C(16)-H(16)	0.9500
C(17)-C(18)	1.369(5)
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500

C(19)-H(19)	0.9500
C(20)-C(25)	1.386(5)
C(20)-C(21)	1.404(5)
C(21)-C(22)	1.382(5)
C(21)-H(21)	0.9500
C(22)-C(23)	1.385(6)
C(22)-H(22)	0.9500
C(23)-C(24)	1.378(6)
C(23)-H(23)	0.9500
C(24)-C(25)	1.388(5)
C(24)-H(24)	0.9500
C(25)-H(25)	0.9500

O(4)-P(1)-N(1)	111.30(15)
O(4)-P(1)-C(7)	114.53(15)
N(1)-P(1)-C(7)	104.19(16)
O(4)-P(1)-C(20)	111.20(15)
N(1)-P(1)-C(20)	109.41(15)
C(7)-P(1)-C(20)	105.82(16)
C(1)-O(1)-C(2)	110.6(3)
C(4)-O(2)-C(3)	113.3(3)
C(5)-O(3)-C(4)	113.6(3)
C(6)-N(1)-P(1)	119.9(2)
C(6)-N(1)-H(1N)	113(3)
P(1)-N(1)-H(1N)	115(3)
C(18)-N(2)-C(19)	116.2(3)
O(1)-C(1)-H(1A)	109.5
O(1)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(1)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(1)-C(2)-C(3)	108.7(3)
O(1)-C(2)-H(2A)	109.9
C(3)-C(2)-H(2A)	109.9
O(1)-C(2)-H(2B)	109.9
C(3)-C(2)-H(2B)	109.9
H(2A)-C(2)-H(2B)	108.3
O(2)-C(3)-C(2)	109.4(3)
O(2)-C(3)-H(3A)	109.8

C(2)-C(3)-H(3A)	109.8
O(2)-C(3)-H(3B)	109.8
C(2)-C(3)-H(3B)	109.8
H(3A)-C(3)-H(3B)	108.2
O(2)-C(4)-O(3)	111.9(3)
O(2)-C(4)-H(4A)	109.2
O(3)-C(4)-H(4A)	109.2
O(2)-C(4)-H(4B)	109.2
O(3)-C(4)-H(4B)	109.2
H(4A)-C(4)-H(4B)	107.9
O(3)-C(5)-C(13)	110.7(3)
O(3)-C(5)-C(6)	107.4(3)
C(13)-C(5)-C(6)	112.4(3)
O(3)-C(5)-H(5)	108.8
C(13)-C(5)-H(5)	108.8
C(6)-C(5)-H(5)	108.8
N(1)-C(6)-C(15)	112.9(3)
N(1)-C(6)-C(5)	108.1(3)
C(15)-C(6)-C(5)	111.2(3)
N(1)-C(6)-H(6)	108.1
C(15)-C(6)-H(6)	108.1
C(5)-C(6)-H(6)	108.1
C(12)-C(7)-C(8)	119.1(3)
C(12)-C(7)-P(1)	122.4(3)
C(8)-C(7)-P(1)	118.4(3)
C(7)-C(8)-C(9)	119.8(4)
C(7)-C(8)-H(8)	120.1
C(9)-C(8)-H(8)	120.1
C(10)-C(9)-C(8)	119.7(4)
C(10)-C(9)-H(9)	120.1
C(8)-C(9)-H(9)	120.1
C(11)-C(10)-C(9)	120.5(4)
C(11)-C(10)-H(10)	119.7
C(9)-C(10)-H(10)	119.7
C(10)-C(11)-C(12)	120.2(4)
C(10)-C(11)-H(11)	119.9
C(12)-C(11)-H(11)	119.9
C(7)-C(12)-C(11)	120.7(4)
C(7)-C(12)-H(12)	119.6
C(11)-C(12)-H(12)	119.6

C(14)-C(13)-C(5)	125.1(4)
C(14)-C(13)-H(13)	117.5
C(5)-C(13)-H(13)	117.5
C(13)-C(14)-H(14A)	120.0
C(13)-C(14)-H(14B)	120.0
H(14A)-C(14)-H(14B)	120.0
C(19)-C(15)-C(16)	118.2(3)
C(19)-C(15)-C(6)	121.0(3)
C(16)-C(15)-C(6)	120.7(3)
C(15)-C(16)-C(17)	118.4(4)
C(15)-C(16)-H(16)	120.8
C(17)-C(16)-H(16)	120.8
C(18)-C(17)-C(16)	119.1(4)
C(18)-C(17)-H(17)	120.5
C(16)-C(17)-H(17)	120.5
N(2)-C(18)-C(17)	123.9(3)
N(2)-C(18)-H(18)	118.0
C(17)-C(18)-H(18)	118.0
N(2)-C(19)-C(15)	124.1(4)
N(2)-C(19)-H(19)	117.9
C(15)-C(19)-H(19)	117.9
C(25)-C(20)-C(21)	118.9(3)
C(25)-C(20)-P(1)	119.8(3)
C(21)-C(20)-P(1)	121.0(3)
C(22)-C(21)-C(20)	120.2(4)
C(22)-C(21)-H(21)	119.9
C(20)-C(21)-H(21)	119.9
C(21)-C(22)-C(23)	120.4(4)
C(21)-C(22)-H(22)	119.8
C(23)-C(22)-H(22)	119.8
C(24)-C(23)-C(22)	119.6(3)
C(24)-C(23)-H(23)	120.2
C(22)-C(23)-H(23)	120.2
C(23)-C(24)-C(25)	120.7(4)
C(23)-C(24)-H(24)	119.7
C(25)-C(24)-H(24)	119.7
C(20)-C(25)-C(24)	120.2(3)
C(20)-C(25)-H(25)	119.9
C(24)-C(25)-H(25)	119.9

Symmetry transformations used to generate equivalent atoms:

Table S13: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **1.126**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	18(1)	34(1)	16(1)	0(1)	0(1)	0(1)
O(1)	48(2)	45(2)	39(2)	2(1)	6(2)	12(1)
O(2)	39(1)	41(2)	36(1)	-5(1)	2(1)	3(1)
O(3)	40(2)	35(1)	30(1)	3(1)	5(1)	1(1)
O(4)	16(1)	42(1)	22(1)	-1(1)	0(1)	-1(1)
N(1)	20(1)	33(2)	19(1)	0(1)	-1(1)	-1(1)
N(2)	35(2)	49(2)	25(2)	-4(1)	-5(2)	-7(2)
C(1)	49(3)	58(3)	39(2)	-5(2)	9(2)	4(2)
C(2)	39(2)	43(2)	43(2)	-4(2)	-7(2)	6(2)
C(3)	39(2)	47(2)	47(2)	-9(2)	2(2)	1(2)
C(4)	51(2)	43(2)	32(2)	4(2)	-1(2)	12(2)
C(5)	37(2)	31(2)	26(2)	1(2)	-1(2)	0(2)
C(6)	23(2)	34(2)	19(2)	-1(1)	0(1)	-3(2)
C(7)	26(2)	32(2)	21(2)	2(1)	5(2)	0(2)
C(8)	34(2)	47(2)	46(2)	-4(2)	-3(2)	6(2)
C(9)	42(2)	39(2)	76(3)	-10(2)	3(3)	7(2)
C(10)	45(3)	41(2)	49(2)	-16(2)	16(2)	-10(2)
C(11)	56(3)	47(2)	35(2)	-9(2)	-3(2)	-11(2)
C(12)	47(2)	37(2)	30(2)	-1(2)	-10(2)	-3(2)
C(13)	56(3)	44(2)	27(2)	-1(2)	-6(2)	11(2)
C(14)	59(3)	73(3)	27(2)	-1(2)	0(2)	22(3)
C(15)	25(2)	30(2)	22(2)	1(1)	0(2)	2(2)
C(16)	29(2)	40(2)	25(2)	-2(2)	0(2)	-3(2)
C(17)	30(2)	45(2)	23(2)	-2(2)	3(2)	-1(2)
C(18)	37(2)	41(2)	20(2)	-4(2)	-1(2)	2(2)
C(19)	31(2)	44(2)	23(2)	-3(1)	0(2)	-4(2)
C(20)	24(2)	37(2)	16(2)	1(1)	3(1)	5(2)
C(21)	28(2)	50(2)	22(2)	6(2)	0(2)	-2(2)
C(22)	30(2)	54(3)	31(2)	10(2)	5(2)	0(2)
C(23)	40(2)	54(2)	20(2)	7(2)	6(2)	13(2)
C(24)	39(2)	53(2)	18(2)	0(2)	-7(2)	8(2)
C(25)	28(2)	43(2)	22(2)	1(2)	-4(2)	-1(2)

Table S14: Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **1.126**.

	x	y	z	U(eq)
H(1N)	3740(50)	8240(30)	4061(10)	29
H(1A)	7729	2265	2841	73
H(1B)	10019	1809	3081	73
H(1C)	9759	3101	3005	73
H(2A)	4308	3155	3147	50
H(2B)	6391	4062	3244	50
H(3A)	2763	3985	3659	53
H(3B)	3959	2869	3817	53
H(4A)	6353	4726	4438	50
H(4B)	4549	3683	4394	50
H(5)	5295	6342	4210	37
H(6)	-7	6708	4124	30
H(8)	-1456	11170	3897	51
H(9)	-979	12745	4267	63
H(10)	1491	12667	4800	54
H(11)	3568	11073	4953	55
H(12)	3059	9491	4595	46
H(13)	3793	7373	4747	51
H(14A)	2346	5261	4942	64
H(14B)	2709	6319	5221	64
H(16)	5386	7256	3543	37
H(17)	5625	6699	2920	39
H(18)	2444	5666	2670	39
H(19)	-1129	5626	3618	39
H(21)	4043	10202	3577	40
H(22)	5103	10535	2962	46
H(23)	2652	9818	2485	46
H(24)	-914	8802	2624	44
H(25)	-2073	8500	3239	37

Table S15: Torsion angles [°] for **1.126**.

O(4)-P(1)-N(1)-C(6)	34.1(3)
C(7)-P(1)-N(1)-C(6)	158.1(2)
C(20)-P(1)-N(1)-C(6)	-89.2(3)
C(1)-O(1)-C(2)-C(3)	-172.0(4)
C(4)-O(2)-C(3)-C(2)	-177.4(3)
O(1)-C(2)-C(3)-O(2)	76.9(4)
C(3)-O(2)-C(4)-O(3)	-67.8(4)
C(5)-O(3)-C(4)-O(2)	-89.0(4)
C(4)-O(3)-C(5)-C(13)	-94.8(4)
C(4)-O(3)-C(5)-C(6)	142.2(3)
P(1)-N(1)-C(6)-C(15)	71.9(3)
P(1)-N(1)-C(6)-C(5)	-164.6(2)
O(3)-C(5)-C(6)-N(1)	174.5(3)
C(13)-C(5)-C(6)-N(1)	52.5(4)
O(3)-C(5)-C(6)-C(15)	-61.0(4)
C(13)-C(5)-C(6)-C(15)	177.0(3)
O(4)-P(1)-C(7)-C(12)	108.6(3)
N(1)-P(1)-C(7)-C(12)	-13.3(4)
C(20)-P(1)-C(7)-C(12)	-128.6(3)
O(4)-P(1)-C(7)-C(8)	-67.7(3)
N(1)-P(1)-C(7)-C(8)	170.4(3)
C(20)-P(1)-C(7)-C(8)	55.1(3)
C(12)-C(7)-C(8)-C(9)	-1.2(6)
P(1)-C(7)-C(8)-C(9)	175.3(3)
C(7)-C(8)-C(9)-C(10)	0.4(7)
C(8)-C(9)-C(10)-C(11)	1.1(7)
C(9)-C(10)-C(11)-C(12)	-1.7(7)
C(8)-C(7)-C(12)-C(11)	0.6(6)
P(1)-C(7)-C(12)-C(11)	-175.7(3)
C(10)-C(11)-C(12)-C(7)	0.9(7)
O(3)-C(5)-C(13)-C(14)	-0.6(6)
C(6)-C(5)-C(13)-C(14)	119.5(5)
N(1)-C(6)-C(15)-C(19)	-132.1(3)
C(5)-C(6)-C(15)-C(19)	106.1(4)
N(1)-C(6)-C(15)-C(16)	47.5(4)
C(5)-C(6)-C(15)-C(16)	-74.2(4)
C(19)-C(15)-C(16)-C(17)	1.5(5)
C(6)-C(15)-C(16)-C(17)	-178.2(3)
C(15)-C(16)-C(17)-C(18)	0.0(6)
C(19)-N(2)-C(18)-C(17)	1.5(6)

C(16)-C(17)-C(18)-N(2)	-1.5(6)
C(18)-N(2)-C(19)-C(15)	0.1(6)
C(16)-C(15)-C(19)-N(2)	-1.6(6)
C(6)-C(15)-C(19)-N(2)	178.1(3)
O(4)-P(1)-C(20)-C(25)	-17.7(3)
N(1)-P(1)-C(20)-C(25)	105.6(3)
C(7)-P(1)-C(20)-C(25)	-142.7(3)
O(4)-P(1)-C(20)-C(21)	168.3(3)
N(1)-P(1)-C(20)-C(21)	-68.4(3)
C(7)-P(1)-C(20)-C(21)	43.3(3)
C(25)-C(20)-C(21)-C(22)	0.5(6)
P(1)-C(20)-C(21)-C(22)	174.5(3)
C(20)-C(21)-C(22)-C(23)	-1.1(6)
C(21)-C(22)-C(23)-C(24)	0.7(6)
C(22)-C(23)-C(24)-C(25)	0.2(6)
C(21)-C(20)-C(25)-C(24)	0.4(5)
P(1)-C(20)-C(25)-C(24)	-173.7(3)
C(23)-C(24)-C(25)-C(20)	-0.8(6)

Symmetry transformations used to generate equivalent atoms:

Table S16: Hydrogen bonds for **1.126** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(4)#1	0.87(2)	2.07(2)	2.938(4)	174(4)

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y,z

1.7.12 Coordinates for Calculated (DFT) Structures

A_GS_M062x

Cartesian coordinates (Angstroms):

61

C -4.358 0.655 0.143
C -4.461 -0.427 -0.730
C -3.158 1.358 0.302
C -3.353 -0.848 -1.463

C	-2.139	-0.178	-1.323
C	-2.071	0.911	-0.450
H	-3.428	-1.698	-2.144
H	-5.232	0.976	0.714
H	-5.413	-0.947	-0.840
O	-0.878	1.613	-0.367
C	-0.885	-0.562	-2.061
N	0.291	-0.394	-1.144
H	-0.917	-1.585	-2.448
H	-0.700	0.111	-2.916
B	0.281	1.117	-0.818
C	0.301	-1.228	0.121
C	1.614	-0.821	0.812
O	2.621	-0.850	0.119
N	1.607	-0.480	2.117
C	0.461	-0.439	3.008
C	2.880	-0.240	2.778
H	0.505	-1.266	3.734
H	-0.490	-0.494	2.472
H	2.869	0.749	3.260
H	3.048	-1.005	3.552
H	1.188	-0.567	-1.635
C	3.395	2.147	0.480
C	2.208	2.562	0.041
C	1.528	1.999	-1.188
C	0.283	-2.776	-0.106
H	-0.597	-0.949	0.681
C	1.168	-3.188	-1.287
H	1.177	-4.284	-1.365
H	2.202	-2.844	-1.149
H	0.796	-2.805	-2.250
C	-1.151	-3.289	-0.301
H	-1.812	-2.953	0.512
H	-1.141	-4.389	-0.290
H	-1.603	-2.986	-1.253
C	0.823	-3.438	1.173
H	0.720	-4.528	1.082
H	0.254	-3.127	2.063
H	1.888	-3.218	1.336
H	0.477	0.506	3.570
H	3.687	-0.282	2.041
O	2.346	1.207	-2.014
C	3.237	1.937	-2.830
H	3.897	2.585	-2.233
H	2.685	2.561	-3.555
H	3.850	1.212	-3.378
H	3.859	2.601	1.358
H	3.929	1.344	-0.035
H	1.662	3.359	0.557
H	1.115	2.856	-1.763
C	-3.018	2.531	1.237
C	-2.196	2.204	2.485
H	-1.164	1.933	2.217
H	-2.644	1.370	3.045
H	-2.149	3.073	3.155
H	-4.023	2.867	1.529

H -2.542 3.365 0.699

Frequencies -- 37.1143 48.8871 53.0716
Red. masses -- 3.5819 3.2934 3.6074
Zero-point correction= 0.537726 (Hartree/Particle)
Thermal correction to Energy= 0.566179
Thermal correction to Enthalpy= 0.567123
Thermal correction to Gibbs Free Energy= 0.481660
Sum of electronic and zero-point Energies= -1178.707084
Sum of electronic and thermal Energies= -1178.678631
Sum of electronic and thermal Enthalpies= -1178.677687
Sum of electronic and thermal Free Energies= -1178.763151

Item	Value	Threshold	Converged?
Maximum Force	0.000001	0.000015	YES
RMS Force	0.000000	0.000010	YES

A_TS_M062x

Cartesian coordinates (Angstroms):

61

C	-4.345	-0.587	-0.001
C	-4.188	-0.685	-1.385
C	-3.325	-0.100	0.816
C	-2.986	-0.308	-1.972
C	-1.939	0.183	-1.186
C	-2.127	0.291	0.198
H	-2.848	-0.398	-3.052
H	-5.287	-0.891	0.462
H	-5.003	-1.063	-2.003
O	-1.128	0.793	0.994
C	-0.627	0.578	-1.817
N	0.504	0.489	-0.828
H	-0.399	-0.048	-2.683
H	-0.629	1.622	-2.161
B	-0.049	1.395	0.341
C	0.914	-0.895	-0.376
C	2.284	-0.656	0.283
O	3.085	0.018	-0.358
N	2.554	-1.158	1.503
C	1.681	-1.968	2.331
C	3.894	-0.986	2.045
H	2.080	-2.991	2.418
H	0.664	-2.026	1.938
H	3.834	-0.534	3.046
H	4.390	-1.965	2.138
H	1.333	0.931	-1.253
C	1.558	1.910	1.526
C	0.526	2.780	1.305
C	0.040	2.979	-0.066
C	1.067	-2.000	-1.478

H	0.142	-1.222	0.326
C	1.883	-1.528	-2.687
H	1.920	-2.339	-3.429
H	2.912	-1.272	-2.404
H	1.447	-0.652	-3.191
C	-0.298	-2.559	-1.922
H	-0.970	-2.722	-1.065
H	-0.138	-3.532	-2.409
H	-0.822	-1.932	-2.651
C	1.820	-3.176	-0.826
H	1.889	-3.997	-1.552
H	1.287	-3.561	0.057
H	2.847	-2.912	-0.535
H	1.633	-1.535	3.342
H	4.480	-0.345	1.382
O	0.984	3.101	-1.074
C	1.570	4.389	-1.167
H	2.084	4.657	-0.229
H	0.806	5.150	-1.391
H	2.301	4.358	-1.983
H	1.715	1.498	2.525
H	2.341	1.768	0.779
H	-0.201	2.957	2.103
H	-0.863	3.593	-0.167
C	-3.463	-0.016	2.315
C	-2.692	-1.123	3.035
H	-1.617	-1.055	2.813
H	-3.045	-2.116	2.721
H	-2.818	-1.046	4.124
H	-4.529	-0.075	2.575
H	-3.099	0.964	2.658

Frequencies -- -151.0281 23.7125 34.8119
Red. masses -- 4.8140 4.0096 3.5426
Zero-point correction= 0.536547 (Hartree/Particle)
Thermal correction to Energy= 0.564544
Thermal correction to Enthalpy= 0.565488
Thermal correction to Gibbs Free Energy= 0.479940
Sum of electronic and zero-point Energies= -1178.683194
Sum of electronic and thermal Energies= -1178.655198
Sum of electronic and thermal Enthalpies= -1178.654253
Sum of electronic and thermal Free Energies= -1178.739802

Item	Value	Threshold	Converged?
Maximum Force	0.000001	0.000015	YES
RMS Force	0.000000	0.000010	YES

A_GS_wB97xd

Cartesian coordinates (Angstroms):

61

C	-4.347	0.657	0.110
C	-4.444	-0.421	-0.768
C	-3.149	1.360	0.283
C	-3.330	-0.841	-1.491
C	-2.118	-0.171	-1.339
C	-2.057	0.917	-0.464
H	-3.400	-1.689	-2.175
H	-5.228	0.975	0.674
H	-5.396	-0.941	-0.888
O	-0.866	1.615	-0.376
C	-0.855	-0.560	-2.059
N	0.309	-0.399	-1.129
H	-0.885	-1.581	-2.448
H	-0.658	0.108	-2.916
B	0.294	1.114	-0.814
C	0.315	-1.245	0.128
C	1.614	-0.836	0.841
O	2.639	-0.873	0.174
N	1.576	-0.470	2.141
C	0.412	-0.436	3.004
C	2.832	-0.200	2.819
H	0.455	-1.246	3.749
H	-0.527	-0.528	2.450
H	2.797	0.793	3.291
H	3.010	-0.955	3.601
H	1.209	-0.563	-1.616
C	3.386	2.223	0.490
C	2.202	2.606	0.016
C	1.534	2.001	-1.200
C	0.291	-2.797	-0.101
H	-0.588	-0.971	0.682
C	1.183	-3.214	-1.276
H	1.188	-4.310	-1.361
H	2.219	-2.877	-1.134
H	0.822	-2.827	-2.242
C	-1.145	-3.304	-0.310
H	-1.818	-2.959	0.489
H	-1.146	-4.404	-0.292
H	-1.583	-3.007	-1.270
C	0.814	-3.463	1.186
H	0.717	-4.554	1.090
H	0.230	-3.162	2.069
H	1.875	-3.245	1.372
H	0.387	0.522	3.545
H	3.651	-0.229	2.094
O	2.355	1.199	-2.011
C	3.236	1.903	-2.855
H	3.909	2.565	-2.285
H	2.682	2.511	-3.593
H	3.843	1.160	-3.389
H	3.826	2.711	1.362
H	3.945	1.411	0.018
H	1.640	3.413	0.500
H	1.108	2.839	-1.793
C	-3.025	2.527	1.229
C	-2.234	2.198	2.495

H -1.189 1.947 2.258
H -2.682 1.349 3.035
H -2.220 3.059 3.178
H -4.036 2.865 1.500
H -2.541 3.368 0.707

Frequencies -- 33.3194 47.1567 55.6993
Red. masses -- 3.6642 3.6215 3.5967
Zero-point correction= 0.539084 (Hartree/Particle)
Thermal correction to Energy= 0.567362
Thermal correction to Enthalpy= 0.568306
Thermal correction to Gibbs Free Energy= 0.483321
Sum of electronic and zero-point Energies= -1178.910741
Sum of electronic and thermal Energies= -1178.882463
Sum of electronic and thermal Enthalpies= -1178.881518
Sum of electronic and thermal Free Energies= -1178.966504

Item	Value	Threshold	Converged?
Maximum Force	0.000001	0.000015	YES
RMS Force	0.000000	0.000010	YES

A_TS_wb97xd

Cartesian coordinates (Angstroms):

61

C -4.330 -0.638 -0.120
C -4.129 -0.730 -1.498
C -3.344 -0.136 0.730
C -2.917 -0.332 -2.047
C -1.905 0.176 -1.228
C -2.136 0.279 0.148
H -2.745 -0.418 -3.123
H -5.281 -0.961 0.311
H -4.919 -1.122 -2.142
O -1.168 0.784 0.969
C -0.582 0.597 -1.816
N 0.526 0.502 -0.805
H -0.328 -0.012 -2.686
H -0.589 1.642 -2.152
B -0.055 1.386 0.371
C 0.948 -0.891 -0.396
C 2.241 -0.661 0.398
O 3.087 0.058 -0.128
N 2.402 -1.219 1.614
C 1.455 -2.060 2.321
C 3.670 -1.040 2.300
H 1.893 -3.055 2.498
H 0.520 -2.196 1.771
H 3.504 -0.600 3.296
H 4.169 -2.013 2.432
H 1.357 0.971 -1.195

C	1.413	1.890	1.625
C	0.431	2.805	1.337
C	0.031	2.988	-0.055
C	1.231	-1.925	-1.549
H	0.130	-1.279	0.216
C	2.043	-1.315	-2.701
H	2.253	-2.095	-3.447
H	3.002	-0.915	-2.347
H	1.514	-0.508	-3.229
C	-0.069	-2.564	-2.068
H	-0.701	-2.923	-1.241
H	0.181	-3.433	-2.694
H	-0.681	-1.901	-2.690
C	2.062	-3.075	-0.943
H	2.209	-3.851	-1.707
H	1.549	-3.551	-0.093
H	3.061	-2.751	-0.617
H	1.216	-1.613	3.299
H	4.317	-0.382	1.713
O	1.018	3.104	-1.019
C	1.611	4.386	-1.108
H	2.109	4.661	-0.162
H	0.860	5.153	-1.359
H	2.362	4.343	-1.907
H	1.489	1.480	2.634
H	2.261	1.743	0.951
H	-0.342	3.003	2.087
H	-0.874	3.588	-0.218
C	-3.534	-0.064	2.224
C	-2.793	-1.173	2.973
H	-1.707	-1.104	2.807
H	-3.127	-2.168	2.641
H	-2.972	-1.102	4.057
H	-4.609	-0.123	2.448
H	-3.187	0.915	2.589

Frequencies -- -183.3496 28.0787 39.1557
Red. masses -- 5.4910 4.2069 3.3466
Zero-point correction= 0.537998 (Hartree/Particle)
Thermal correction to Energy= 0.565731
Thermal correction to Enthalpy= 0.566675
Thermal correction to Gibbs Free Energy= 0.481985
Sum of electronic and zero-point Energies= -1178.884161
Sum of electronic and thermal Energies= -1178.856428
Sum of electronic and thermal Enthalpies= -1178.855484
Sum of electronic and thermal Free Energies= -1178.940174

Item	Value	Threshold	Converged?
Maximum Force	0.000000	0.000015	YES
RMS Force	0.000000	0.000010	YES

B_GS_M062x

Cartesian coordinates (Angstroms):

88

C	2.245	-2.516	-1.498
C	1.399	-3.405	-2.165
C	1.815	-1.239	-1.107
C	0.071	-3.060	-2.412
C	-0.391	-1.799	-2.039
C	0.501	-0.914	-1.440
H	-0.611	-3.774	-2.880
H	3.261	-2.836	-1.252
H	1.765	-4.389	-2.457
O	0.013	0.335	-1.110
C	-1.820	-1.344	-2.152
N	-2.187	-0.695	-0.836
H	-1.973	-0.604	-2.951
H	-2.468	-2.201	-2.331
B	-1.247	0.527	-0.688
C	-3.628	-0.445	-0.421
C	-3.546	-0.757	1.099
O	-2.721	-1.619	1.418
N	-4.357	-0.172	1.984
C	-5.188	0.996	1.755
C	-4.317	-0.625	3.367
H	-6.253	0.739	1.844
H	-4.996	1.445	0.778
H	-3.698	0.050	3.979
H	-5.339	-0.626	3.770
H	-1.913	-1.379	-0.071
C	-3.330	2.920	-1.977
C	-2.074	2.608	-1.655
C	-1.661	2.007	-0.323
H	-1.266	2.756	-2.379
H	-4.147	2.802	-1.258
C	-4.718	-1.319	-1.120
H	-3.854	0.605	-0.620
C	-4.539	-2.818	-0.843
H	-5.257	-3.387	-1.452
H	-4.737	-3.052	0.213
H	-3.534	-3.204	-1.070
C	-4.792	-1.009	-2.629
H	-4.673	0.069	-2.822
H	-5.785	-1.300	-3.001
H	-4.066	-1.551	-3.244
C	-6.086	-0.909	-0.548
H	-6.864	-1.500	-1.052
H	-6.303	0.153	-0.739
H	-6.171	-1.109	0.527
H	-4.950	1.744	2.526
H	-3.902	-1.637	3.417
Si	2.828	-0.099	0.033
C	1.610	0.534	1.333
C	1.663	1.859	1.787
C	0.579	-0.290	1.820
C	0.717	2.349	2.692

C	-0.373	0.195	2.716
C	-0.305	1.521	3.152
H	-1.047	1.906	3.854
H	0.781	3.383	3.035
H	-1.165	-0.468	3.068
H	0.507	-1.332	1.486
H	2.446	2.530	1.422
C	3.593	1.337	-0.902
C	3.049	1.844	-2.092
C	3.619	2.948	-2.726
C	4.745	3.564	-2.178
C	5.301	3.073	-0.997
C	4.730	1.968	-0.368
H	2.171	1.367	-2.537
H	5.194	4.425	-2.675
H	3.190	3.327	-3.655
H	5.182	1.586	0.552
H	6.184	3.548	-0.567
C	4.185	-1.130	0.822
C	4.046	-1.657	2.115
C	5.361	-1.419	0.107
C	5.046	-2.453	2.675
C	6.360	-2.216	0.663
C	6.202	-2.734	1.949
H	3.150	-1.437	2.702
H	7.267	-2.430	0.095
H	5.502	-1.008	-0.897
H	6.985	-3.355	2.388
H	4.924	-2.852	3.684
O	-2.648	2.101	0.669
C	-2.701	3.383	1.262
H	-2.921	4.167	0.519
H	-1.746	3.622	1.757
H	-3.499	3.372	2.015
H	-0.723	2.494	0.011
H	-3.575	3.340	-2.955

Frequencies -- 21.1802 25.9989 34.8302
Red. masses -- 4.3211 4.7984 3.7751
Zero-point correction= 0.747759 (Hartree/Particle)
Thermal correction to Energy= 0.789940
Thermal correction to Enthalpy= 0.790884
Thermal correction to Gibbs Free Energy= 0.673522
Sum of electronic and zero-point Energies= -2082.963307
Sum of electronic and thermal Energies= -2082.921126
Sum of electronic and thermal Enthalpies= -2082.920182
Sum of electronic and thermal Free Energies= -2083.037544

Item	Value	Threshold	Converged?
Maximum Force	0.000001	0.000015	YES
RMS Force	0.000000	0.000010	YES

B_TS_M062x

Cartesian coordinates (Angstroms):

88

C	-2.069	2.931	-0.349
C	-1.175	3.956	-0.671
C	-1.717	1.583	-0.496
C	0.110	3.649	-1.118
C	0.487	2.316	-1.287
C	-0.439	1.314	-0.995
H	0.825	4.446	-1.332
H	-3.056	3.186	0.044
H	-1.470	4.998	-0.544
O	-0.080	0.021	-1.181
C	1.862	1.869	-1.698
N	2.256	0.710	-0.799
H	1.908	1.521	-2.739
H	2.560	2.693	-1.574
B	1.258	-0.442	-1.204
C	3.706	0.422	-0.449
C	3.603	0.205	1.092
O	2.678	0.791	1.657
N	4.512	-0.506	1.770
C	5.433	-1.475	1.208
C	4.400	-0.543	3.221
H	6.476	-1.183	1.396
H	5.282	-1.593	0.131
H	3.763	-1.384	3.540
H	5.402	-0.674	3.650
H	1.926	0.997	0.164
C	1.801	-1.304	-2.649
C	1.103	-2.087	-1.704
C	1.495	-2.050	-0.349
H	0.031	-2.223	-1.874
H	2.895	-1.269	-2.624
C	4.745	1.544	-0.786
H	4.010	-0.491	-0.967
C	4.491	2.838	0.004
H	5.150	3.632	-0.375
H	4.732	2.689	1.067
H	3.460	3.213	-0.029
C	4.842	1.762	-2.310
H	4.920	0.795	-2.832
H	5.761	2.322	-2.530
H	4.020	2.324	-2.762
C	6.148	1.059	-0.373
H	6.871	1.836	-0.658
H	6.436	0.135	-0.895
H	6.239	0.914	0.709
H	5.256	-2.446	1.694
H	3.965	0.392	3.587
Si	-2.754	0.120	0.101
C	-1.643	-0.874	1.273
C	-1.861	-2.243	1.498
C	-0.576	-0.259	1.949
C	-1.052	-2.968	2.375

C	0.239	-0.979	2.825
C	-0.001	-2.336	3.043
H	0.627	-2.903	3.733
H	-1.247	-4.030	2.541
H	1.066	-0.471	3.323
H	-0.364	0.804	1.792
H	-2.673	-2.760	0.981
C	-3.332	-0.945	-1.343
C	-2.790	-0.808	-2.631
C	-3.218	-1.617	-3.683
C	-4.202	-2.582	-3.466
C	-4.763	-2.726	-2.197
C	-4.335	-1.911	-1.149
H	-2.027	-0.049	-2.819
H	-4.539	-3.215	-4.289
H	-2.791	-1.489	-4.680
H	-4.803	-2.023	-0.166
H	-5.543	-3.470	-2.026
C	-4.251	0.780	1.026
C	-4.199	1.024	2.408
C	-5.430	1.105	0.335
C	-5.290	1.578	3.078
C	-6.522	1.659	1.002
C	-6.452	1.896	2.375
H	-3.297	0.774	2.973
H	-7.431	1.904	0.450
H	-5.499	0.919	-0.740
H	-7.307	2.328	2.899
H	-5.235	1.759	4.153
O	2.821	-2.234	-0.031
C	3.112	-3.621	0.102
H	2.821	-4.165	-0.811
H	2.575	-4.049	0.964
H	4.191	-3.730	0.253
H	0.762	-2.342	0.414
H	1.321	-1.117	-3.610

Frequencies -- -317.0407 15.4358 24.7836
Red. masses -- 7.4933 4.7089 4.2260
Zero-point correction= 0.747594 (Hartree/Particle)
Thermal correction to Energy= 0.788912
Thermal correction to Enthalpy= 0.789857
Thermal correction to Gibbs Free Energy= 0.673701
Sum of electronic and zero-point Energies= -2082.925059
Sum of electronic and thermal Energies= -2082.883740
Sum of electronic and thermal Enthalpies= -2082.882796
Sum of electronic and thermal Free Energies= -2082.998952

Item	Value	Threshold	Converged?
Maximum Force	0.000000	0.000015	YES
RMS Force	0.000000	0.000010	YES

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Cartesian coordinates (Angstroms):

88

C	2.276	-2.530	-1.442
C	1.434	-3.407	-2.130
C	1.835	-1.267	-1.023
C	0.108	-3.060	-2.385
C	-0.363	-1.811	-1.985
C	0.520	-0.945	-1.349
H	-0.562	-3.763	-2.885
H	3.297	-2.845	-1.211
H	1.809	-4.382	-2.446
O	0.033	0.293	-0.990
C	-1.782	-1.339	-2.132
N	-2.188	-0.693	-0.830
H	-1.895	-0.595	-2.935
H	-2.437	-2.184	-2.341
B	-1.240	0.509	-0.637
C	-3.637	-0.447	-0.447
C	-3.588	-0.801	1.065
O	-2.761	-1.666	1.378
N	-4.415	-0.244	1.954
C	-5.224	0.943	1.752
C	-4.378	-0.730	3.325
H	-6.295	0.708	1.839
H	-5.030	1.408	0.783
H	-3.725	-0.094	3.945
H	-5.394	-0.702	3.743
H	-1.950	-1.385	-0.056
C	-3.292	2.994	-1.857
C	-2.041	2.648	-1.548
C	-1.626	1.991	-0.246
H	-1.231	2.815	-2.268
H	-4.114	2.861	-1.147
C	-4.728	-1.276	-1.208
H	-3.845	0.612	-0.615
C	-4.590	-2.790	-0.983
H	-5.312	-3.321	-1.621
H	-4.810	-3.060	0.060
H	-3.594	-3.196	-1.211
C	-4.740	-0.913	-2.709
H	-4.574	0.165	-2.865
H	-5.726	-1.155	-3.131
H	-4.010	-1.462	-3.313
C	-6.107	-0.860	-0.664
H	-6.883	-1.417	-1.209
H	-6.305	0.211	-0.819
H	-6.232	-1.098	0.400
H	-4.970	1.676	2.531
H	-4.002	-1.757	3.352
Si	2.849	-0.092	0.074
C	1.676	0.447	1.457
C	1.687	1.756	1.957
C	0.704	-0.439	1.954
C	0.756	2.171	2.912

C	-0.239	-0.027	2.895
C	-0.215	1.284	3.374
H	-0.951	1.613	4.111
H	0.788	3.195	3.291
H	-0.996	-0.732	3.243
H	0.661	-1.469	1.586
H	2.422	2.478	1.589
C	3.424	1.389	-0.931
C	2.875	1.684	-2.189
C	3.281	2.808	-2.907
C	4.248	3.661	-2.377
C	4.813	3.381	-1.133
C	4.407	2.254	-0.420
H	2.122	1.023	-2.625
H	4.568	4.543	-2.938
H	2.844	3.016	-3.886
H	4.872	2.043	0.548
H	5.578	4.042	-0.719
C	4.319	-1.039	0.757
C	4.257	-1.671	2.008
C	5.494	-1.179	-0.002
C	5.328	-2.427	2.484
C	6.566	-1.935	0.471
C	6.483	-2.560	1.715
H	3.361	-1.571	2.628
H	7.474	-2.031	-0.130
H	5.578	-0.688	-0.976
H	7.324	-3.150	2.088
H	5.261	-2.911	3.461
O	-2.590	2.062	0.769
C	-2.606	3.301	1.440
H	-2.844	4.136	0.759
H	-1.633	3.503	1.919
H	-3.377	3.251	2.220
H	-0.675	2.451	0.088
H	-3.529	3.458	-2.817

Frequencies -- 12.5265 27.0812 31.7303
Red. masses -- 5.3221 4.8735 4.8615
Zero-point correction= 0.750373 (Hartree/Particle)
Thermal correction to Energy= 0.792166
Thermal correction to Enthalpy= 0.793110
Thermal correction to Gibbs Free Energy= 0.675584
Sum of electronic and zero-point Energies= -2083.230982
Sum of electronic and thermal Energies= -2083.189190
Sum of electronic and thermal Enthalpies= -2083.188245
Sum of electronic and thermal Free Energies= -2083.305771

Item	Value	Threshold	Converged?
Maximum Force	0.000000	0.000015	YES
RMS Force	0.000000	0.000010	YES

B_TS_wb97xd

Cartesian coordinates (Angstroms):

XXX
88

C	-2.066	2.938	-0.249
C	-1.159	3.972	-0.499
C	-1.720	1.596	-0.452
C	0.132	3.678	-0.934
C	0.502	2.352	-1.162
C	-0.433	1.345	-0.940
H	0.858	4.480	-1.092
H	-3.059	3.182	0.138
H	-1.451	5.009	-0.326
O	-0.072	0.066	-1.178
C	1.877	1.917	-1.579
N	2.269	0.715	-0.747
H	1.931	1.633	-2.638
H	2.580	2.728	-1.401
B	1.261	-0.408	-1.200
C	3.727	0.410	-0.443
C	3.680	0.226	1.104
O	2.782	0.837	1.689
N	4.593	-0.492	1.772
C	5.473	-1.503	1.219
C	4.527	-0.479	3.226
H	6.530	-1.238	1.374
H	5.300	-1.656	0.151
H	3.870	-1.284	3.596
H	5.537	-0.632	3.630
H	1.973	0.971	0.234
C	1.805	-1.237	-2.660
C	1.091	-2.052	-1.753
C	1.448	-2.042	-0.384
H	0.020	-2.178	-1.947
H	2.900	-1.229	-2.633
C	4.798	1.481	-0.869
H	3.982	-0.528	-0.944
C	4.695	2.790	-0.067
H	5.412	3.521	-0.469
H	4.954	2.625	0.990
H	3.705	3.264	-0.074
C	4.764	1.721	-2.395
H	4.600	0.781	-2.945
H	5.737	2.115	-2.720
H	4.016	2.447	-2.729
C	6.198	0.909	-0.579
H	6.949	1.632	-0.930
H	6.382	-0.037	-1.110
H	6.376	0.763	0.492
H	5.287	-2.455	1.738
H	4.137	0.481	3.580
Si	-2.776	0.125	0.088
C	-1.694	-0.897	1.261
C	-1.890	-2.276	1.432
C	-0.656	-0.289	1.987

C	-1.085	-3.019	2.297
C	0.158	-1.026	2.847
C	-0.058	-2.395	3.006
H	0.573	-2.976	3.683
H	-1.262	-4.091	2.419
H	0.966	-0.525	3.382
H	-0.467	0.783	1.875
H	-2.681	-2.790	0.880
C	-3.336	-0.916	-1.380
C	-2.780	-0.764	-2.660
C	-3.191	-1.565	-3.726
C	-4.171	-2.538	-3.530
C	-4.746	-2.697	-2.270
C	-4.336	-1.890	-1.209
H	-2.017	-0.002	-2.834
H	-4.495	-3.166	-4.364
H	-2.750	-1.425	-4.715
H	-4.815	-2.017	-0.234
H	-5.525	-3.448	-2.115
C	-4.284	0.775	1.005
C	-4.268	0.958	2.397
C	-5.439	1.153	0.299
C	-5.366	1.504	3.062
C	-6.538	1.698	0.960
C	-6.502	1.875	2.343
H	-3.386	0.669	2.976
H	-7.429	1.983	0.395
H	-5.485	1.014	-0.785
H	-7.364	2.301	2.862
H	-5.335	1.639	4.145
O	2.748	-2.258	-0.007
C	2.960	-3.624	0.314
H	2.648	-4.276	-0.520
H	2.398	-3.907	1.220
H	4.031	-3.770	0.491
H	0.683	-2.342	0.342
H	1.342	-1.024	-3.625

Frequencies -- -348.2968 11.1715 27.1389
Red. masses -- 7.5547 4.8363 4.2023
Zero-point correction= 0.749806 (Hartree/Particle)
Thermal correction to Energy= 0.791045
Thermal correction to Enthalpy= 0.791989
Thermal correction to Gibbs Free Energy= 0.675374
Sum of electronic and zero-point Energies= -2083.190657
Sum of electronic and thermal Energies= -2083.149419
Sum of electronic and thermal Enthalpies= -2083.148474
Sum of electronic and thermal Free Energies= -2083.265090

Item	Value	Threshold	Converged?
Maximum Force	0.000000	0.000015	YES
RMS Force	0.000000	0.000010	YES

Allyl_OMe_GS_wb97xd

charge= 0 multiplicity= 1

Cartesian coordinates (Angstroms):

33

B	0.037	0.349	0.799
C	-1.358	0.725	1.420
C	-2.221	1.346	0.356
H	-1.202	1.446	2.241
H	-1.843	-0.170	1.835
C	-3.199	0.710	-0.296
H	-2.007	2.372	0.047
O	-3.513	-0.585	-0.051
H	-3.786	1.205	-1.081
C	-4.750	-1.022	-0.542
H	-4.832	-0.873	-1.635
H	-5.593	-0.502	-0.053
H	-4.827	-2.095	-0.330
O	0.500	-0.928	0.645
O	0.910	1.283	0.302
C	1.851	-0.857	0.163
C	1.904	0.586	-0.463
C	2.769	-1.018	1.375
H	2.523	-1.961	1.883
H	2.626	-0.198	2.094
H	3.828	-1.045	1.082
C	2.086	-1.990	-0.825
H	2.033	-2.955	-0.302
H	3.082	-1.904	-1.286
H	1.329	-1.995	-1.619
C	1.445	0.620	-1.922
H	2.183	0.156	-2.593
H	1.309	1.668	-2.225
H	0.481	0.106	-2.047
C	3.240	1.297	-0.317
H	4.039	0.730	-0.818
H	3.512	1.433	0.738
H	3.183	2.292	-0.781

Frequencies --	10.2718	18.7164	47.3847
Red. masses --	3.5470	3.7593	2.5053

Zero-point correction= 0.287374 (Hartree/Particle)
Thermal correction to Energy= 0.303275
Thermal correction to Enthalpy= 0.304219
Thermal correction to Gibbs Free Energy= 0.242094
Sum of electronic and zero-point Energies= -642.171110
Sum of electronic and thermal Energies= -642.155210
Sum of electronic and thermal Enthalpies= -642.154265
Sum of electronic and thermal Free Energies= -642.216390

Item	Value	Threshold	Converged?
Maximum Force	0.000000	0.000015	YES
RMS Force	0.000000	0.000010	YES

Summary of Natural Population Analysis:

$P_A(N)$

Atom	No	Charge	Natural Population Core	Valence	Rydberg	Total
B	1	1.13132	1.99930	1.83695	0.03243	3.86868
C	2	-0.79430	1.99911	4.77708	0.01810	6.79430
C	3	-0.24949	1.99910	4.23035	0.02004	6.24949
H	4	0.23901	0.00000	0.75903	0.00196	0.76099
H	5	0.24696	0.00000	0.75081	0.00222	0.75304
C	6	0.09942	1.99881	3.88010	0.02167	5.90058
H	7	0.21363	0.00000	0.78480	0.00157	0.78637
O	8	-0.48625	1.99974	6.45574	0.03077	8.48625
H	9	0.16553	0.00000	0.83141	0.00306	0.83447
C	10	-0.24867	1.99934	4.23575	0.01358	6.24867
H	11	0.16359	0.00000	0.83387	0.00254	0.83641
H	12	0.16623	0.00000	0.83112	0.00265	0.83377
H	13	0.19285	0.00000	0.80544	0.00171	0.80715
O	14	-0.69710	1.99969	6.67331	0.02410	8.69710
O	15	-0.70547	1.99969	6.68200	0.02378	8.70547
C	16	0.23939	1.99923	3.74076	0.02061	5.76061
C	17	0.24013	1.99924	3.73994	0.02069	5.75987
C	18	-0.62799	1.99939	4.61527	0.01332	6.62799
H	19	0.22044	0.00000	0.77778	0.00179	0.77956
H	20	0.21313	0.00000	0.78532	0.00155	0.78687
H	21	0.21015	0.00000	0.78841	0.00144	0.78985
C	22	-0.62086	1.99939	4.60850	0.01297	6.62086
H	23	0.21846	0.00000	0.77978	0.00176	0.78154
H	24	0.20831	0.00000	0.79024	0.00144	0.79169
H	25	0.22004	0.00000	0.77844	0.00152	0.77996
C	26	-0.62966	1.99939	4.61684	0.01342	6.62966
H	27	0.20963	0.00000	0.78892	0.00144	0.79037
H	28	0.21965	0.00000	0.77855	0.00180	0.78035
H	29	0.21676	0.00000	0.78168	0.00156	0.78324
C	30	-0.62094	1.99939	4.60854	0.01301	6.62094
H	31	0.20901	0.00000	0.78955	0.00144	0.79099
H	32	0.21871	0.00000	0.77977	0.00152	0.78129
H	33	0.21836	0.00000	0.77986	0.00177	0.78164

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Natural Population

$P_A(N-1)$

Atom	No	Charge	Core	Valence	Rydberg	Total
B	1	1.13132	1.99930	1.83695	0.03243	3.86868
C	2	-0.79430	1.99911	4.77708	0.01810	6.79430
C	3	-0.24949	1.99910	4.23035	0.02004	6.24949
H	4	0.23901	0.00000	0.75903	0.00196	0.76099
H	5	0.24696	0.00000	0.75081	0.00222	0.75304
C	6	0.09942	1.99881	3.88010	0.02167	5.90058

H	7	0.21363	0.00000	0.78480	0.00157	0.78637
O	8	-0.48625	1.99974	6.45574	0.03077	8.48625
H	9	0.16553	0.00000	0.83141	0.00306	0.83447
C	10	-0.24867	1.99934	4.23575	0.01358	6.24867
H	11	0.16359	0.00000	0.83387	0.00254	0.83641
H	12	0.16623	0.00000	0.83112	0.00265	0.83377
H	13	0.19285	0.00000	0.80544	0.00171	0.80715
O	14	-0.69710	1.99969	6.67331	0.02410	8.69710
O	15	-0.70547	1.99969	6.68200	0.02378	8.70547
C	16	0.23939	1.99923	3.74076	0.02061	5.76061
C	17	0.24013	1.99924	3.73994	0.02069	5.75987
C	18	-0.62799	1.99939	4.61527	0.01332	6.62799
H	19	0.22044	0.00000	0.77778	0.00179	0.77956
H	20	0.21313	0.00000	0.78532	0.00155	0.78687
H	21	0.21015	0.00000	0.78841	0.00144	0.78985
C	22	-0.62086	1.99939	4.60850	0.01297	6.62086
H	23	0.21846	0.00000	0.77978	0.00176	0.78154
H	24	0.20831	0.00000	0.79024	0.00144	0.79169
H	25	0.22004	0.00000	0.77844	0.00152	0.77996
C	26	-0.62966	1.99939	4.61684	0.01342	6.62966
H	27	0.20963	0.00000	0.78892	0.00144	0.79037
H	28	0.21965	0.00000	0.77855	0.00180	0.78035
H	29	0.21676	0.00000	0.78168	0.00156	0.78324
C	30	-0.62094	1.99939	4.60854	0.01301	6.62094
H	31	0.20901	0.00000	0.78955	0.00144	0.79099
H	32	0.21871	0.00000	0.77977	0.00152	0.78129
H	33	0.21836	0.00000	0.77986	0.00177	0.78164

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Allyl_OMEM_GS_wb97xd

charge= 0 multiplicity= 1

Cartesian coordinates (Angstroms):

44

B	-2.259	1.113	-0.228
C	-1.677	2.562	-0.434
C	-0.426	2.863	0.343
H	-2.472	3.273	-0.154
H	-1.516	2.714	-1.516
C	0.634	2.057	0.384
H	-0.347	3.803	0.895
O	0.649	0.880	-0.310
H	1.552	2.295	0.929
C	1.590	-0.046	0.093
O	2.866	0.426	-0.203
H	1.373	-0.978	-0.463
H	1.505	-0.254	1.183
C	3.900	-0.391	0.266
C	5.221	0.264	-0.117
H	3.828	-1.407	-0.174
H	3.856	-0.510	1.367
O	6.323	-0.470	0.331

H	5.269	1.258	0.353
H	5.246	0.414	-1.213
C	6.725	-1.510	-0.511
H	6.995	-1.140	-1.519
H	5.950	-2.291	-0.632
H	7.612	-1.977	-0.063
O	-2.918	0.426	-1.213
O	-2.247	0.433	0.960
C	-3.568	-0.701	-0.607
C	-2.730	-0.894	0.711
C	-5.017	-0.294	-0.337
H	-5.476	0.031	-1.282
H	-5.070	0.545	0.371
H	-5.606	-1.130	0.066
C	-3.527	-1.878	-1.570
H	-4.141	-1.654	-2.454
H	-3.931	-2.785	-1.093
H	-2.506	-2.083	-1.913
C	-3.530	-1.369	1.915
H	-3.993	-2.347	1.714
H	-4.318	-0.654	2.182
H	-2.863	-1.476	2.782
C	-1.506	-1.788	0.507
H	-1.787	-2.844	0.386
H	-0.854	-1.699	1.387
H	-0.935	-1.470	-0.376

Frequencies --	9.7138	23.3411	30.1984
Red. masses --	4.0269	4.3979	4.0213

Zero-point correction= 0.383059 (Hartree/Particle)
Thermal correction to Energy= 0.404917
Thermal correction to Enthalpy= 0.405861
Thermal correction to Gibbs Free Energy= 0.328947
Sum of electronic and zero-point Energies= -910.151847
Sum of electronic and thermal Energies= -910.129990
Sum of electronic and thermal Enthalpies= -910.129046
Sum of electronic and thermal Free Energies= -910.205960

Item	Value	Threshold	Converged?
Maximum Force	0.000000	0.000015	YES
RMS Force	0.000000	0.000010	YES

Summary of Natural Population Analysis:
$P_A(N)$

			Natural Population			
Atom	No	Charge	Core	Valence	Rydberg	Total
B	1	1.14250	1.99930	1.82124	0.03696	3.85750
C	2	-0.80252	1.99912	4.78706	0.01634	6.80252
C	3	-0.23697	1.99911	4.21829	0.01957	6.23697
H	4	0.24294	0.00000	0.75534	0.00172	0.75706
H	5	0.24715	0.00000	0.75087	0.00198	0.75285
C	6	0.09833	1.99879	3.87971	0.02318	5.90167

H	7	0.21090	0.00000	0.78759	0.00150	0.78910
O	8	-0.49040	1.99972	6.46173	0.02895	8.49040
H	9	0.18472	0.00000	0.81307	0.00221	0.81528
C	10	0.23781	1.99937	3.74102	0.02180	5.76219
O	11	-0.51237	1.99973	6.48703	0.02561	8.51237
H	12	0.15053	0.00000	0.84620	0.00327	0.84947
H	13	0.12544	0.00000	0.86974	0.00481	0.87456
C	14	-0.09538	1.99930	4.07678	0.01930	6.09538
C	15	-0.07901	1.99929	4.05956	0.02016	6.07901
H	16	0.15448	0.00000	0.84266	0.00286	0.84552
H	17	0.16455	0.00000	0.83292	0.00254	0.83545
O	18	-0.49591	1.99977	6.47016	0.02597	8.49591
H	19	0.18832	0.00000	0.80961	0.00206	0.81168
H	20	0.16453	0.00000	0.83278	0.00269	0.83547
C	21	-0.25230	1.99935	4.23833	0.01462	6.25230
H	22	0.15940	0.00000	0.83759	0.00302	0.84060
H	23	0.15467	0.00000	0.84237	0.00297	0.84533
H	24	0.19134	0.00000	0.80688	0.00178	0.80866
O	25	-0.70422	1.99969	6.68125	0.02328	8.70422
O	26	-0.70557	1.99969	6.68251	0.02338	8.70557
C	27	0.23884	1.99923	3.74058	0.02135	5.76116
C	28	0.23966	1.99923	3.73910	0.02201	5.76034
C	29	-0.62818	1.99940	4.61581	0.01297	6.62818
H	30	0.22038	0.00000	0.77792	0.00169	0.77962
H	31	0.21340	0.00000	0.78512	0.00148	0.78660
H	32	0.21037	0.00000	0.78822	0.00141	0.78963
C	33	-0.62069	1.99939	4.60857	0.01273	6.62069
H	34	0.21891	0.00000	0.77941	0.00168	0.78109
H	35	0.20833	0.00000	0.79026	0.00141	0.79167
H	36	0.21909	0.00000	0.77940	0.00152	0.78091
C	37	-0.62065	1.99939	4.60854	0.01271	6.62065
H	38	0.20849	0.00000	0.79011	0.00140	0.79151
H	39	0.21925	0.00000	0.77924	0.00151	0.78075
H	40	0.21808	0.00000	0.78023	0.00169	0.78192
C	41	-0.63177	1.99940	4.61843	0.01395	6.63177
H	42	0.21062	0.00000	0.78794	0.00143	0.78938
H	43	0.21709	0.00000	0.78106	0.00184	0.78291
H	44	0.21581	0.00000	0.78214	0.00206	0.78419

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Natural Population
P_A(N-1)

Natural Population

Atom	No	Charge	Core	Valence	Rydberg	Total
B	1	0.57429	0.99955	0.90848	0.01768	1.92571
C	2	-0.40709	0.99954	2.39946	0.00809	3.40709
C	3	0.26567	0.99957	1.72629	0.00847	2.73433
H	4	0.14268	0.00000	0.35655	0.00077	0.35732
H	5	0.17931	0.00000	0.31991	0.00078	0.32069
C	6	0.25715	0.99943	1.73339	0.01004	2.74285
H	7	0.11679	0.00000	0.38262	0.00059	0.38321
O	8	-0.04807	0.99986	3.03575	0.01245	4.04807
H	9	0.11119	0.00000	0.38783	0.00098	0.38881
C	10	0.09810	0.99968	1.89173	0.01049	2.90190

O	11	-0.24749	0.99986	3.23531	0.01232	4.24749
H	12	0.09405	0.00000	0.40445	0.00151	0.40595
H	13	0.08928	0.00000	0.40859	0.00213	0.41072
C	14	-0.05264	0.99965	2.04334	0.00966	3.05264
C	15	-0.03945	0.99964	2.02959	0.01022	3.03945
H	16	0.08606	0.00000	0.41266	0.00127	0.41394
H	17	0.08722	0.00000	0.41165	0.00112	0.41278
O	18	-0.24206	0.99989	3.22931	0.01286	4.24206
H	19	0.09462	0.00000	0.40437	0.00100	0.40538
H	20	0.08576	0.00000	0.41294	0.00130	0.41424
C	21	-0.12885	0.99968	2.12191	0.00727	3.12885
H	22	0.08344	0.00000	0.41520	0.00135	0.41656
H	23	0.07669	0.00000	0.42197	0.00134	0.42331
H	24	0.10262	0.00000	0.39655	0.00083	0.39738
O	25	-0.34356	0.99984	3.33191	0.01181	4.34356
O	26	-0.35390	0.99984	3.34245	0.01162	4.35390
C	27	0.12144	0.99961	1.86861	0.01034	2.87856
C	28	0.12174	0.99961	1.86795	0.01070	2.87826
C	29	-0.31586	0.99970	2.30961	0.00655	3.31586
H	30	0.11541	0.00000	0.38382	0.00078	0.38459
H	31	0.10542	0.00000	0.39387	0.00071	0.39458
H	32	0.11329	0.00000	0.38605	0.00066	0.38671
C	33	-0.31219	0.99969	2.30604	0.00646	3.31219
H	34	0.11592	0.00000	0.38330	0.00078	0.38408
H	35	0.11135	0.00000	0.38799	0.00066	0.38865
H	36	0.10860	0.00000	0.39067	0.00073	0.39140
C	37	-0.31281	0.99969	2.30664	0.00647	3.31281
H	38	0.11246	0.00000	0.38688	0.00065	0.38754
H	39	0.11350	0.00000	0.38579	0.00071	0.38650
H	40	0.11161	0.00000	0.38760	0.00079	0.38839
C	41	-0.31616	0.99970	2.30960	0.00686	3.31616
H	42	0.11748	0.00000	0.38185	0.00068	0.38252
H	43	0.10718	0.00000	0.39191	0.00092	0.39282
H	44	0.09982	0.00000	0.39916	0.00102	0.40018

==========

Allyl_OTMS_wb97xd

charge= 0 multiplicity= 1

Cartesian coordinates (Angstroms):

42

B	-1.137	-0.968	0.715
C	-0.033	-1.947	1.256
C	0.803	-2.436	0.104
H	-0.521	-2.802	1.754
H	0.602	-1.435	1.993
C	2.002	-1.942	-0.220
H	0.400	-3.229	-0.531
O	2.619	-0.974	0.499
H	2.563	-2.332	-1.081
Si	3.087	0.541	-0.087
C	3.552	1.521	1.431

H	2.683	1.631	2.098
H	3.906	2.527	1.159
H	4.352	1.016	1.993
C	1.629	1.292	-0.989
H	0.745	1.270	-0.333
H	1.395	0.719	-1.900
H	1.827	2.335	-1.284
O	-1.148	0.385	0.934
O	-2.176	-1.371	-0.081
C	-2.379	0.910	0.407
C	-2.786	-0.195	-0.636
C	-3.357	1.016	1.578
H	-2.905	1.641	2.361
H	-3.569	0.028	2.011
H	-4.308	1.476	1.272
C	-2.126	2.286	-0.189
H	-1.834	2.986	0.607
H	-3.039	2.673	-0.667
H	-1.322	2.266	-0.934
C	-2.155	0.026	-2.011
H	-2.616	0.872	-2.540
H	-2.296	-0.882	-2.615
H	-1.074	0.211	-1.926
C	-4.283	-0.424	-0.773
H	-4.787	0.496	-1.105
H	-4.730	-0.750	0.174
H	-4.470	-1.207	-1.522
C	4.552	0.325	-1.240
H	5.395	-0.156	-0.720
H	4.898	1.300	-1.621
H	4.289	-0.297	-2.110

Frequencies -- 15.9598 29.0765 41.2154
Red. masses -- 3.1973 3.5680 4.3082
Zero-point correction= 0.360926 (Hartree/Particle)
Thermal correction to Energy= 0.382666
Thermal correction to Enthalpy= 0.383611
Thermal correction to Gibbs Free Energy= 0.310203
Sum of electronic and zero-point Energies= -1011.343687
Sum of electronic and thermal Energies= -1011.321946
Sum of electronic and thermal Enthalpies= -1011.321002
Sum of electronic and thermal Free Energies= -1011.394410

Item	Value	Threshold	Converged?
Maximum Force	0.000001	0.000015	YES
RMS Force	0.000000	0.000010	YES

Summary of Natural Population Analysis:
$P_A(N)$

Atom	No	Charge	Core	Valence	Rydberg	Total
B	1	1.13941	1.99929	1.82604	0.03526	3.86059
C	2	-0.80064	1.99912	4.78218	0.01935	6.80064

C	3	-0.24450	1.99908	4.22509	0.02033	6.24450
H	4	0.24067	0.00000	0.75744	0.00189	0.75933
H	5	0.24586	0.00000	0.75150	0.00264	0.75414
C	6	0.11089	1.99884	3.86174	0.02853	5.88911
H	7	0.21144	0.00000	0.78699	0.00157	0.78856
O	8	-0.84299	1.99973	6.82424	0.01902	8.84299
H	9	0.16634	0.00000	0.83163	0.00203	0.83366
Si	10	1.91172	9.99795	2.05373	0.03659	12.08828
C	11	-1.13832	1.99944	5.11882	0.02006	7.13832
H	12	0.24388	0.00000	0.75458	0.00154	0.75612
H	13	0.23383	0.00000	0.76473	0.00144	0.76617
H	14	0.24126	0.00000	0.75719	0.00155	0.75874
C	15	-1.16481	1.99943	5.14289	0.02249	7.16481
H	16	0.25815	0.00000	0.74011	0.00174	0.74185
H	17	0.23593	0.00000	0.76220	0.00187	0.76407
H	18	0.23564	0.00000	0.76277	0.00159	0.76436
O	19	-0.71091	1.99969	6.68762	0.02360	8.71091
O	20	-0.70610	1.99969	6.68271	0.02370	8.70610
C	21	0.24137	1.99923	3.73755	0.02185	5.75863
C	22	0.23947	1.99923	3.74069	0.02061	5.76053
C	23	-0.62876	1.99940	4.61631	0.01305	6.62876
H	24	0.22045	0.00000	0.77783	0.00172	0.77955
H	25	0.21434	0.00000	0.78421	0.00146	0.78566
H	26	0.21117	0.00000	0.78741	0.00142	0.78883
C	27	-0.62588	1.99939	4.61355	0.01294	6.62588
H	28	0.21881	0.00000	0.77945	0.00173	0.78119
H	29	0.21123	0.00000	0.78735	0.00142	0.78877
H	30	0.22220	0.00000	0.77633	0.00148	0.77780
C	31	-0.63081	1.99939	4.61808	0.01334	6.63081
H	32	0.21033	0.00000	0.78824	0.00143	0.78967
H	33	0.22115	0.00000	0.77715	0.00170	0.77885
H	34	0.21766	0.00000	0.78083	0.00151	0.78234
C	35	-0.62073	1.99939	4.60854	0.01280	6.62073
H	36	0.20930	0.00000	0.78927	0.00143	0.79070
H	37	0.21914	0.00000	0.77934	0.00152	0.78086
H	38	0.21932	0.00000	0.77899	0.00169	0.78068
C	39	-1.14599	1.99945	5.12533	0.02120	7.14599
H	40	0.23895	0.00000	0.75954	0.00151	0.76105
H	41	0.23553	0.00000	0.76302	0.00145	0.76447
H	42	0.23502	0.00000	0.76338	0.00159	0.76498

==========

Natural Population
P_A(N-1)

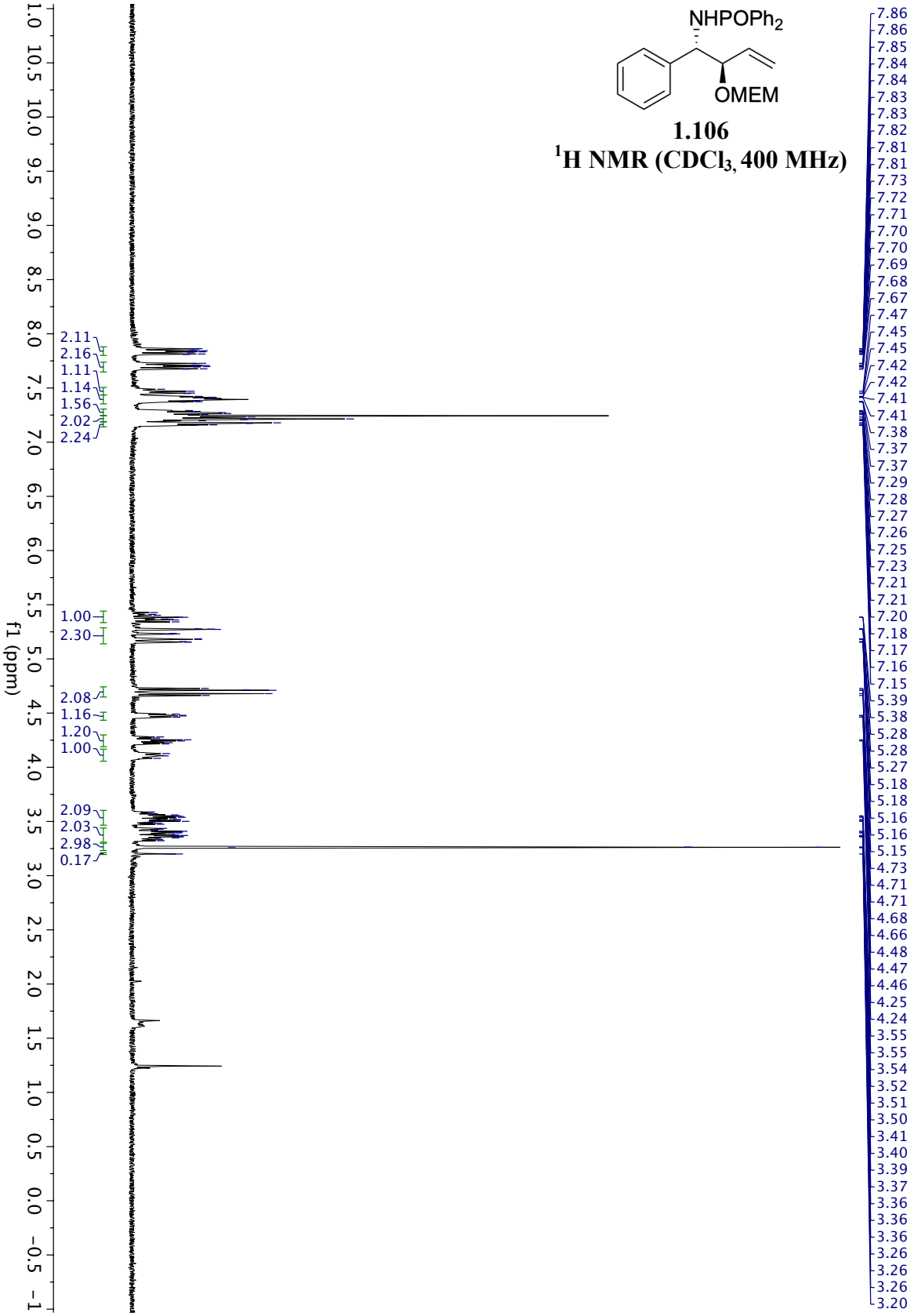
Atom	No	Charge	Core	Valence	Rydberg	Total
B	1	0.58121	0.99943	0.90076	0.01860	1.91879
C	2	-0.38084	0.99954	2.37143	0.00987	3.38084
C	3	0.23966	0.99956	1.75234	0.00844	2.76034
H	4	0.15980	0.00000	0.33934	0.00086	0.34020
H	5	0.14167	0.00000	0.35723	0.00110	0.35833
C	6	0.27925	0.99945	1.70880	0.01251	2.72075
H	7	0.11719	0.00000	0.38215	0.00065	0.38281
O	8	-0.23477	0.99986	3.22655	0.00836	4.23477

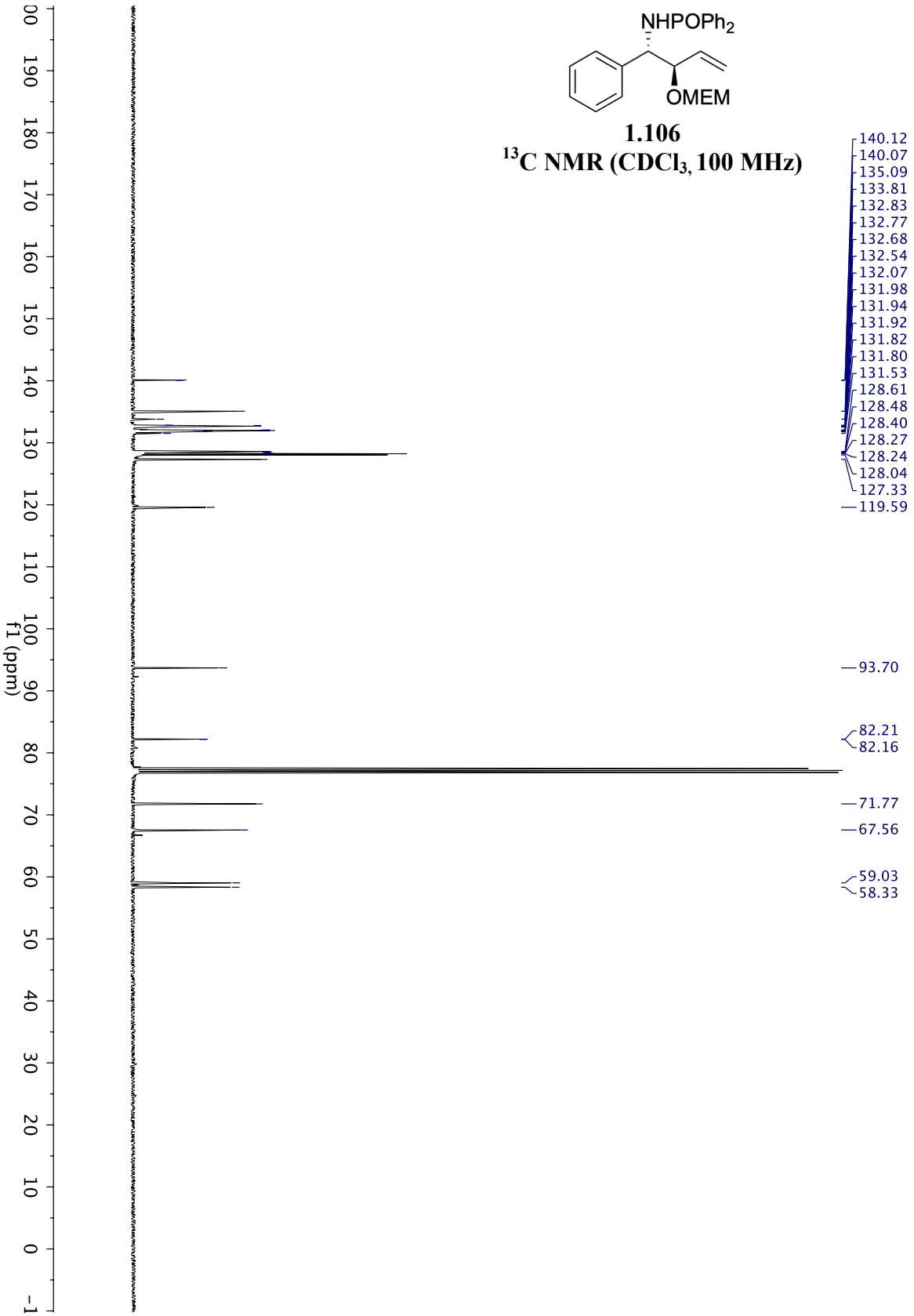
H	9	0.10105	0.00000	0.39814	0.00081	0.39895
Si	10	0.92795	4.99885	1.05636	0.01684	6.07205
C	11	-0.57027	0.99971	2.56026	0.01030	3.57027
H	12	0.12546	0.00000	0.37379	0.00075	0.37454
H	13	0.13042	0.00000	0.36888	0.00070	0.36958
H	14	0.12718	0.00000	0.37209	0.00073	0.37282
C	15	-0.56478	0.99971	2.55405	0.01102	3.56478
H	16	0.13019	0.00000	0.36895	0.00086	0.36981
H	17	0.11854	0.00000	0.38058	0.00088	0.38146
H	18	0.13470	0.00000	0.36450	0.00080	0.36530
O	19	-0.34794	0.99984	3.33642	0.01168	4.34794
O	20	-0.34687	0.99984	3.33523	0.01181	4.34687
C	21	0.12352	0.99961	1.86626	0.01061	2.87648
C	22	0.12237	0.99961	1.86794	0.01008	2.87763
C	23	-0.31632	0.99970	2.31004	0.00659	3.31632
H	24	0.11420	0.00000	0.38501	0.00080	0.38580
H	25	0.10725	0.00000	0.39206	0.00069	0.39275
H	26	0.11407	0.00000	0.38527	0.00066	0.38593
C	27	-0.31441	0.99969	2.30818	0.00654	3.31441
H	28	0.11429	0.00000	0.38490	0.00082	0.38571
H	29	0.11444	0.00000	0.38490	0.00066	0.38556
H	30	0.10813	0.00000	0.39114	0.00073	0.39187
C	31	-0.31527	0.99970	2.30894	0.00663	3.31527
H	32	0.11525	0.00000	0.38408	0.00067	0.38475
H	33	0.11348	0.00000	0.38570	0.00081	0.38652
H	34	0.09960	0.00000	0.39965	0.00076	0.40040
C	35	-0.31299	0.99969	2.30678	0.00652	3.31299
H	36	0.11191	0.00000	0.38743	0.00066	0.38809
H	37	0.11325	0.00000	0.38602	0.00072	0.38675
H	38	0.11394	0.00000	0.38528	0.00078	0.38606
C	39	-0.57373	0.99972	2.56327	0.01074	3.57373
H	40	0.12668	0.00000	0.37259	0.00073	0.37332
H	41	0.13228	0.00000	0.36700	0.00072	0.36772
H	42	0.11927	0.00000	0.37997	0.00077	0.38073

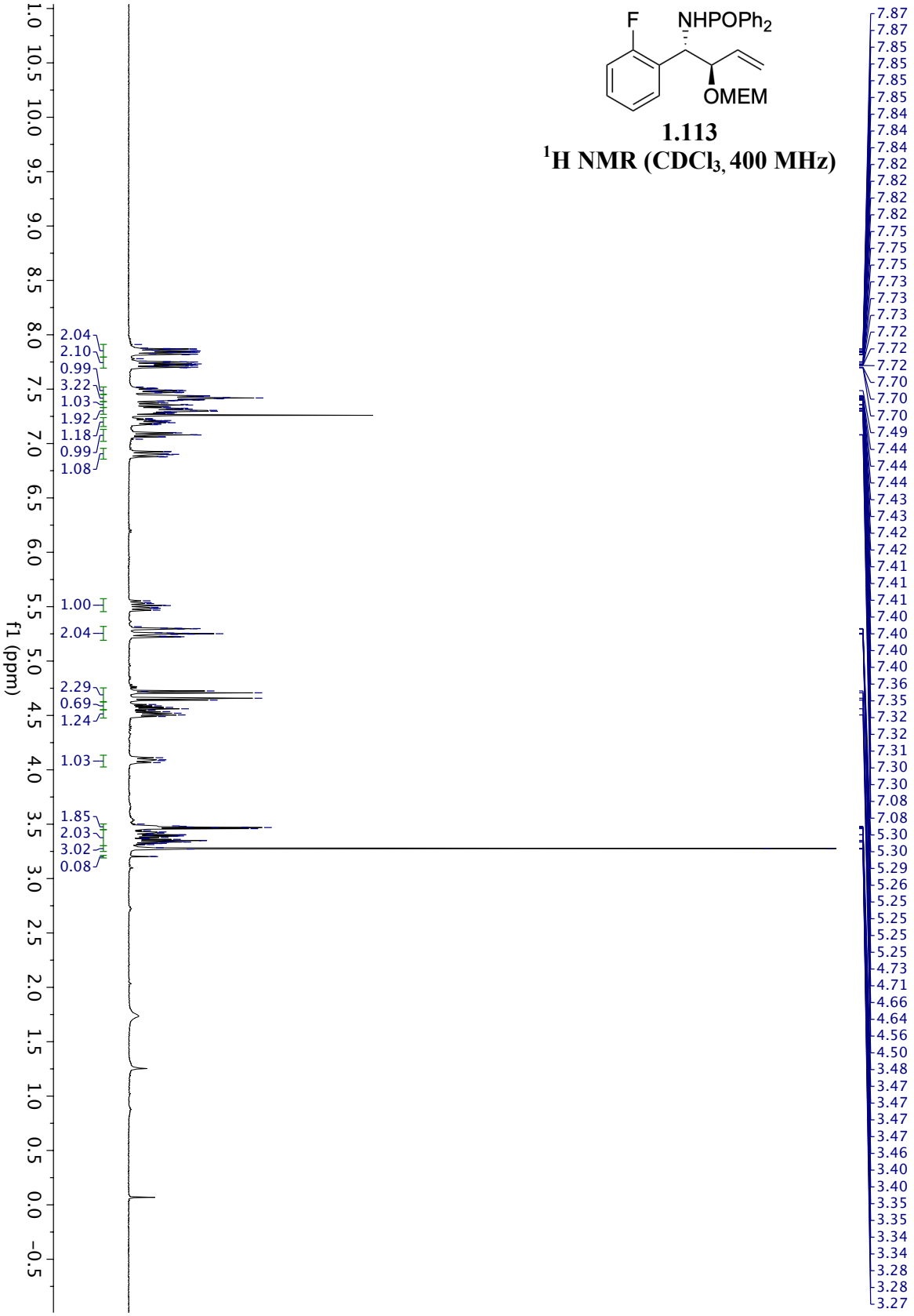
==========

1.7.13 NMR Spectra

(appear on the following pages)

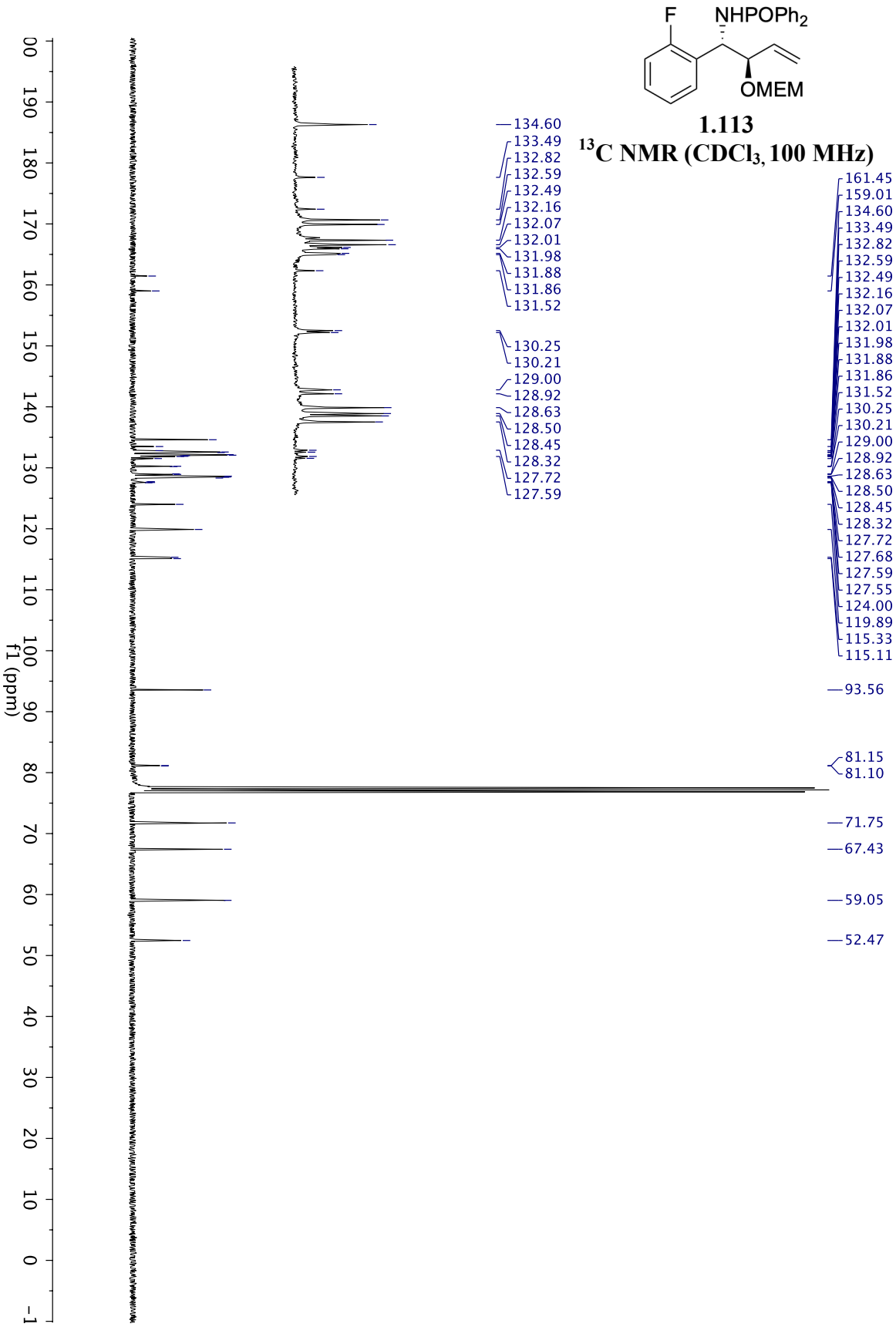

NHPOPh2
OMEM
1.106
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.11
2.16
1.11
1.14
1.56
2.02
2.24
1.00
2.30
2.08
1.16
1.20
1.00
2.09
2.03
2.98
0.17

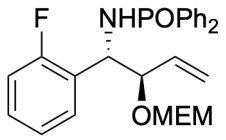

NHPOPh2
OMEM
1.106
13C NMR (CDCl3, 100 MHz)
140.12
140.07
135.09
133.81
132.83
132.77
132.68
132.54
132.07
131.98
131.94
131.92
131.82
131.80
131.53
128.61
128.48
128.40
128.27
128.24
128.04
127.33
119.59
93.70
82.21
82.16
71.77
67.56
59.03
58.33
f1 (ppm)



1.113

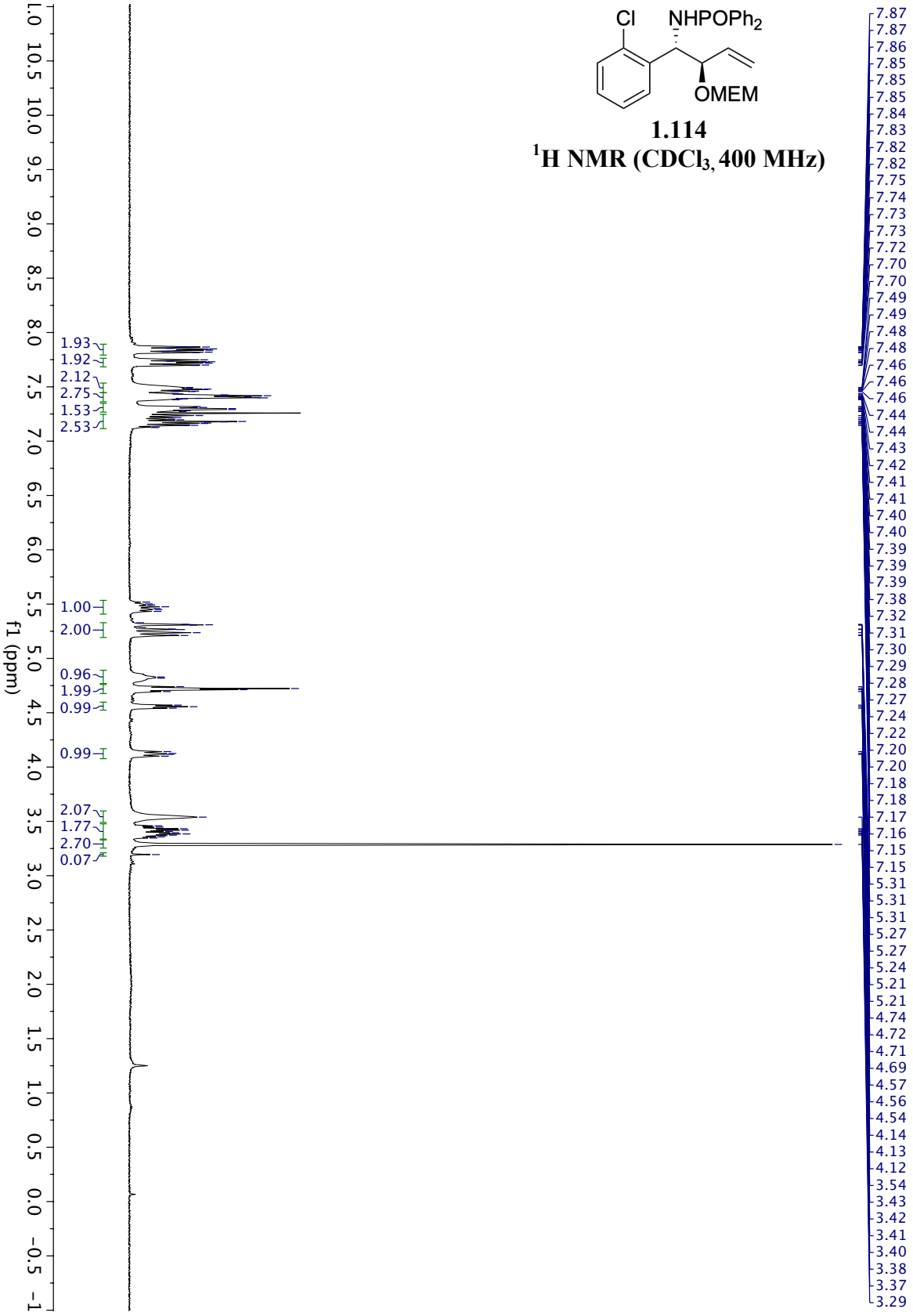
^{1}H NMR ($CDCl_3$, 400 MHz)

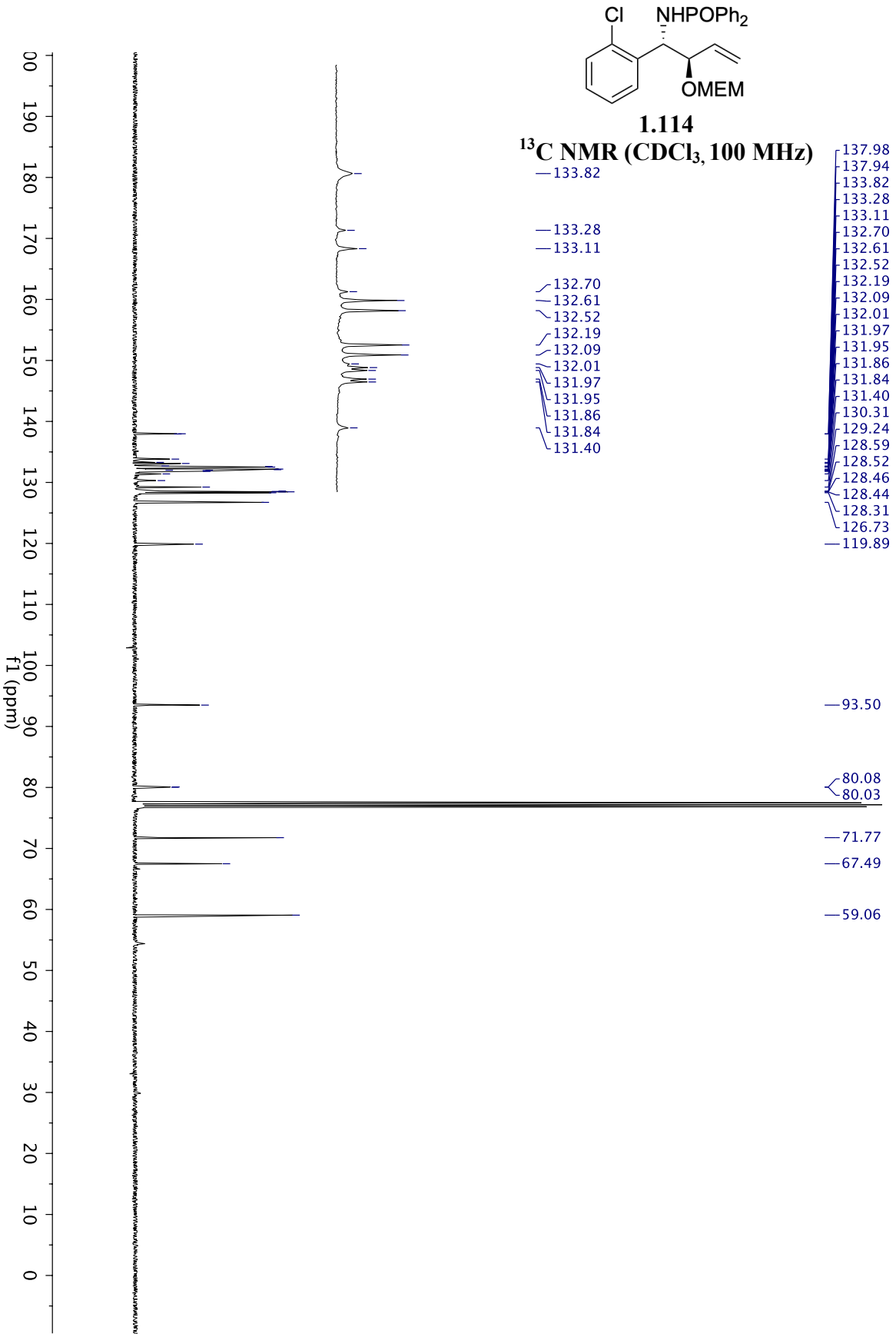

F
NHPOPh2
OMEM
1.113
13C NMR (CDCl3, 100 MHz)
134.60
133.49
132.82
132.59
132.49
132.16
132.07
132.01
131.98
131.88
131.86
131.52
130.25
130.21
129.00
128.92
128.63
128.50
128.45
128.32
127.72
127.59
161.45
159.01
134.60
133.49
132.82
132.59
132.49
132.16
132.07
132.01
131.98
131.88
131.86
131.52
130.25
130.21
129.00
128.92
128.63
128.50
128.45
128.32
127.72
127.68
127.59
127.55
124.00
119.89
115.33
115.11
93.56
81.15
81.10
71.75
67.43
59.05
52.47
f1 (ppm)

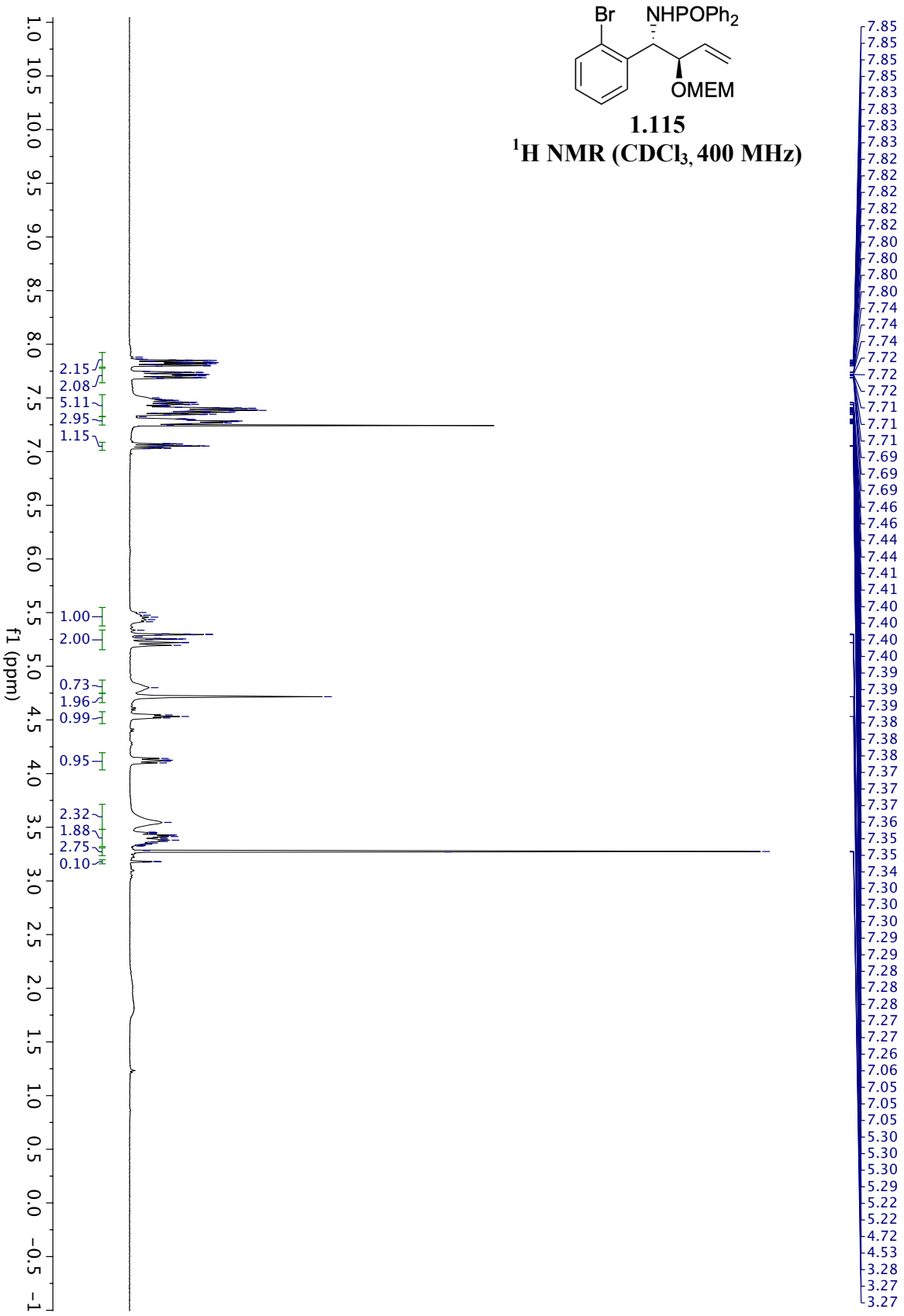


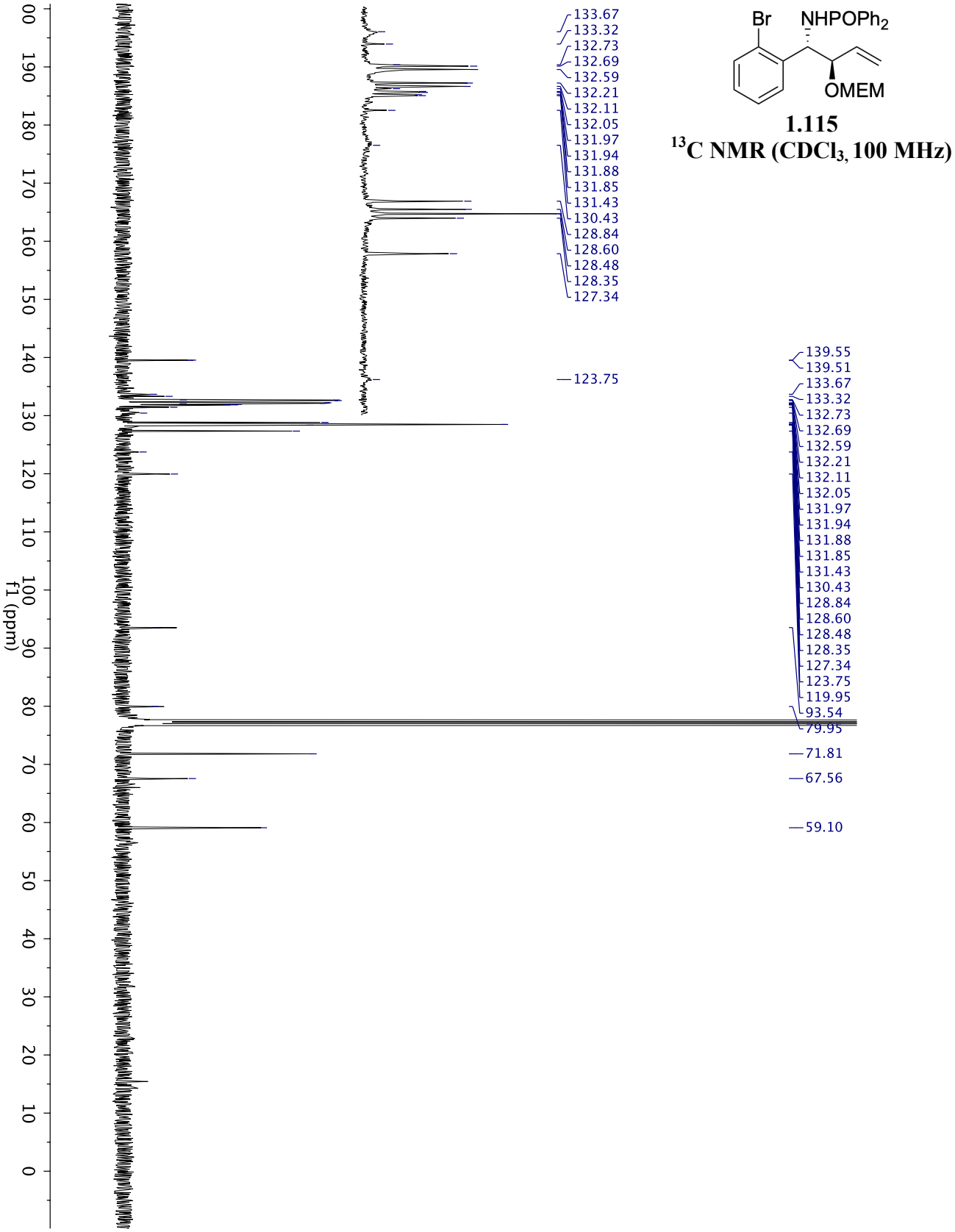
1.113

^{19}F NMR ($CDCl_3$, 376 MHz)


Cl
NHPOPh2
OMEM
1.114
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.93
1.92
2.12
2.75
1.53
2.53
1.00
2.00
0.96
1.99
0.99
0.99
2.07
1.77
2.70
0.07

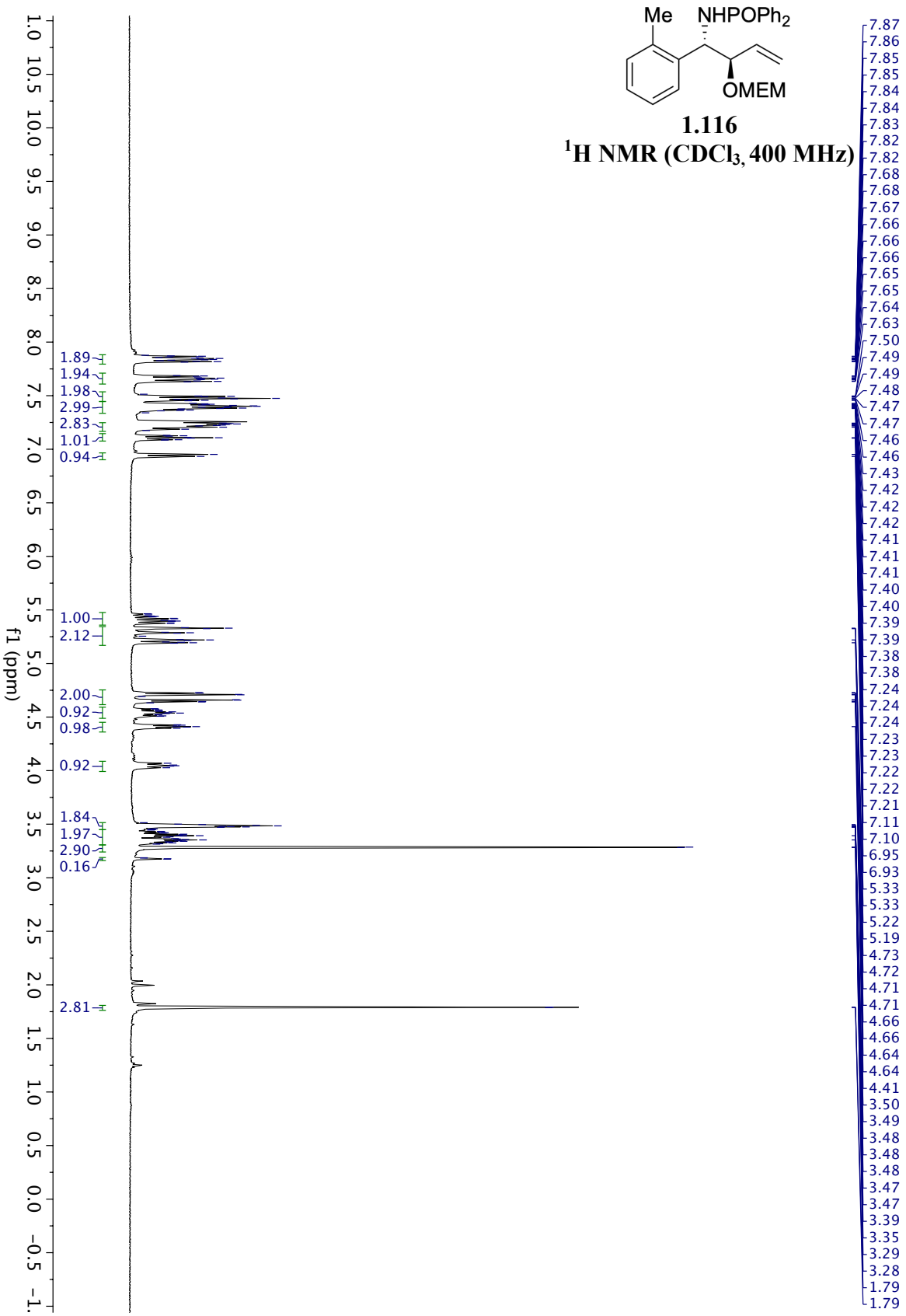

Cl
NHPOPh2
OMEM
1.114
13C NMR (CDCl3, 100 MHz)
133.82
133.28
133.11
132.70
132.61
132.52
132.19
132.09
132.01
131.97
131.95
131.86
131.84
131.40
137.98
137.94
133.82
133.28
133.11
132.70
132.61
132.52
132.19
132.09
132.01
131.97
131.95
131.86
131.84
131.40
130.31
129.24
128.59
128.52
128.46
128.44
128.31
126.73
119.89
93.50
80.08
80.03
71.77
67.49
59.06
f1 (ppm)

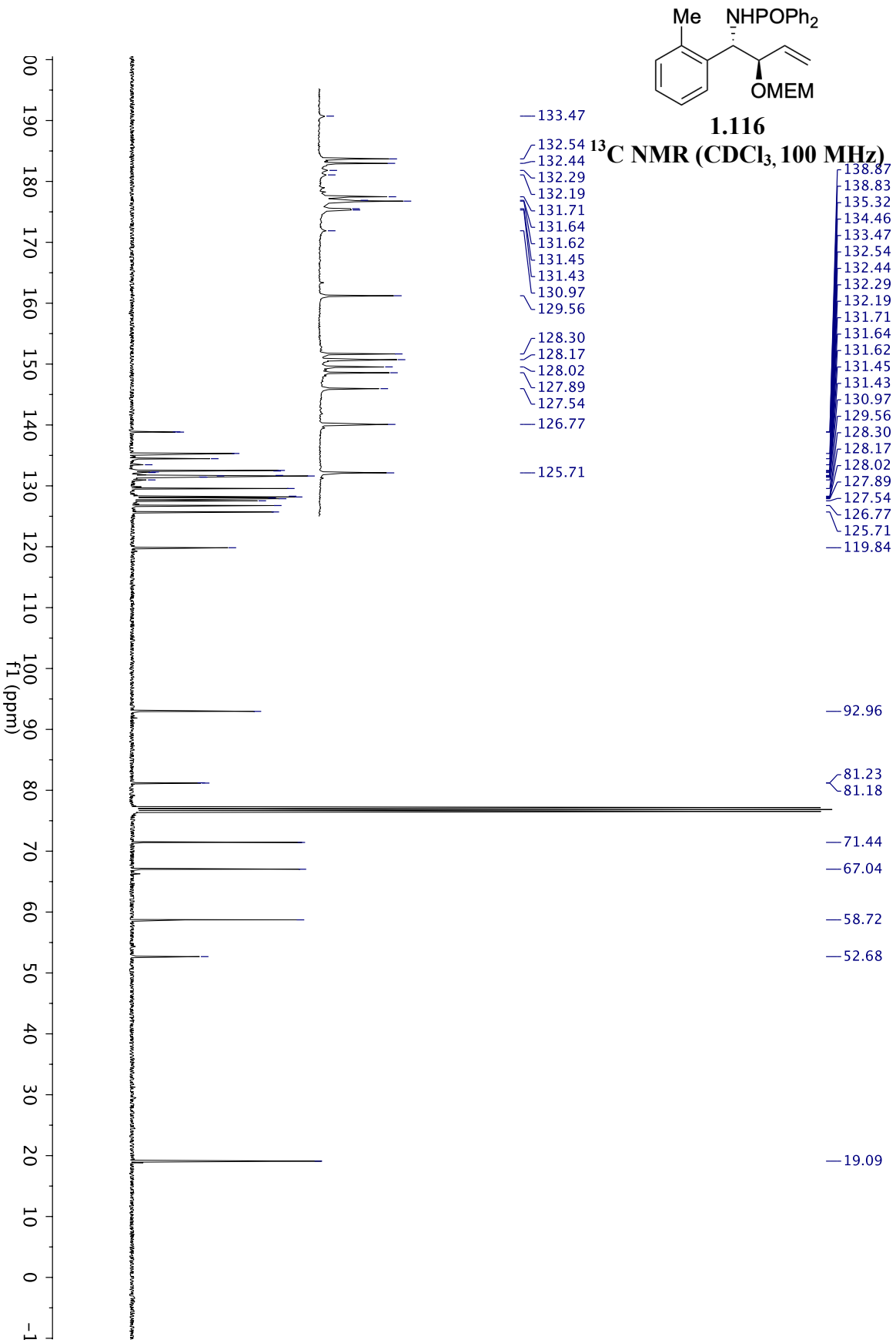

Br
NHPOPh2
OMEM
1.115
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.15
2.08
5.11
2.95
1.15
1.00
2.00
0.73
1.96
0.99
0.95
2.32
1.88
2.75
0.10

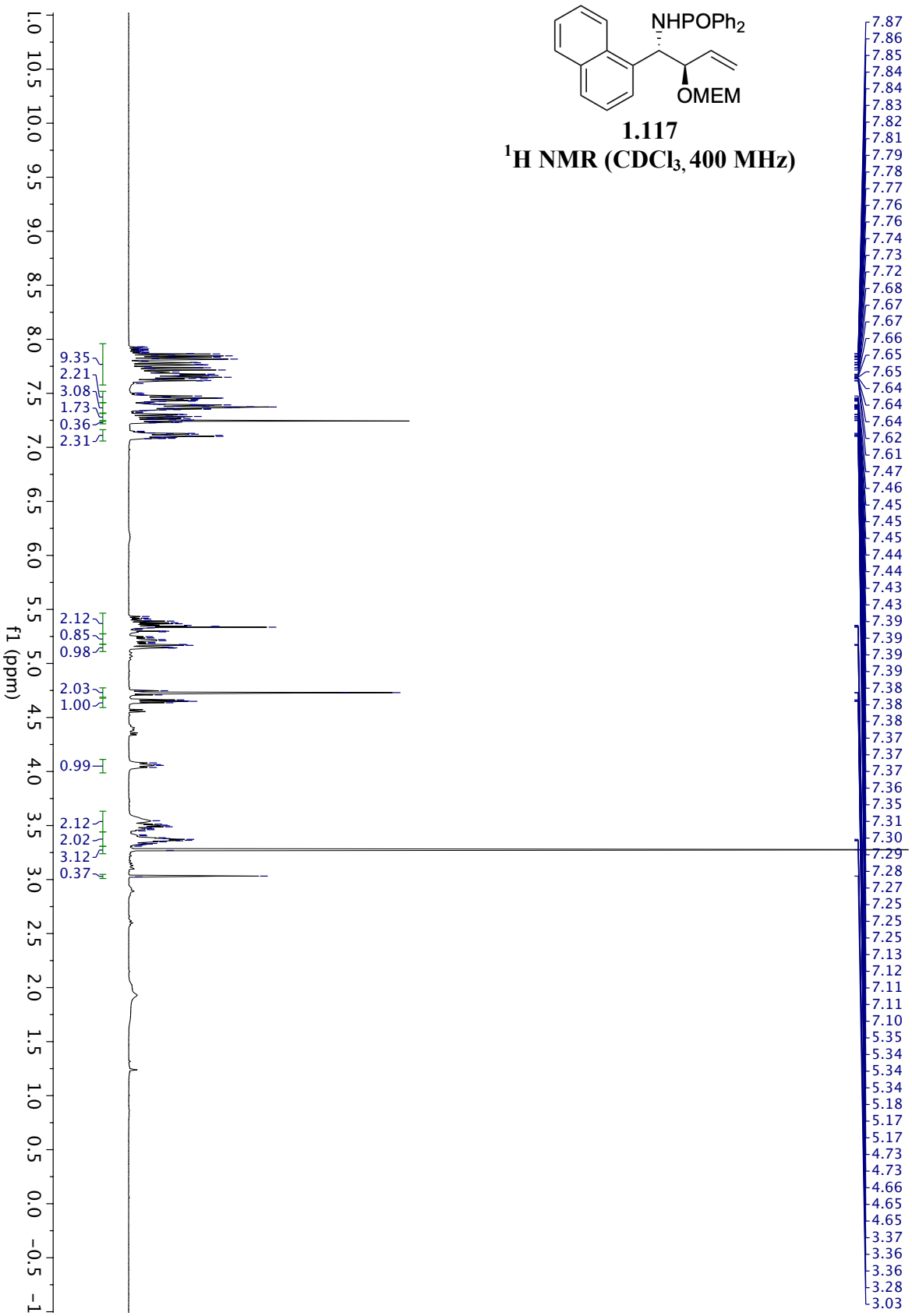


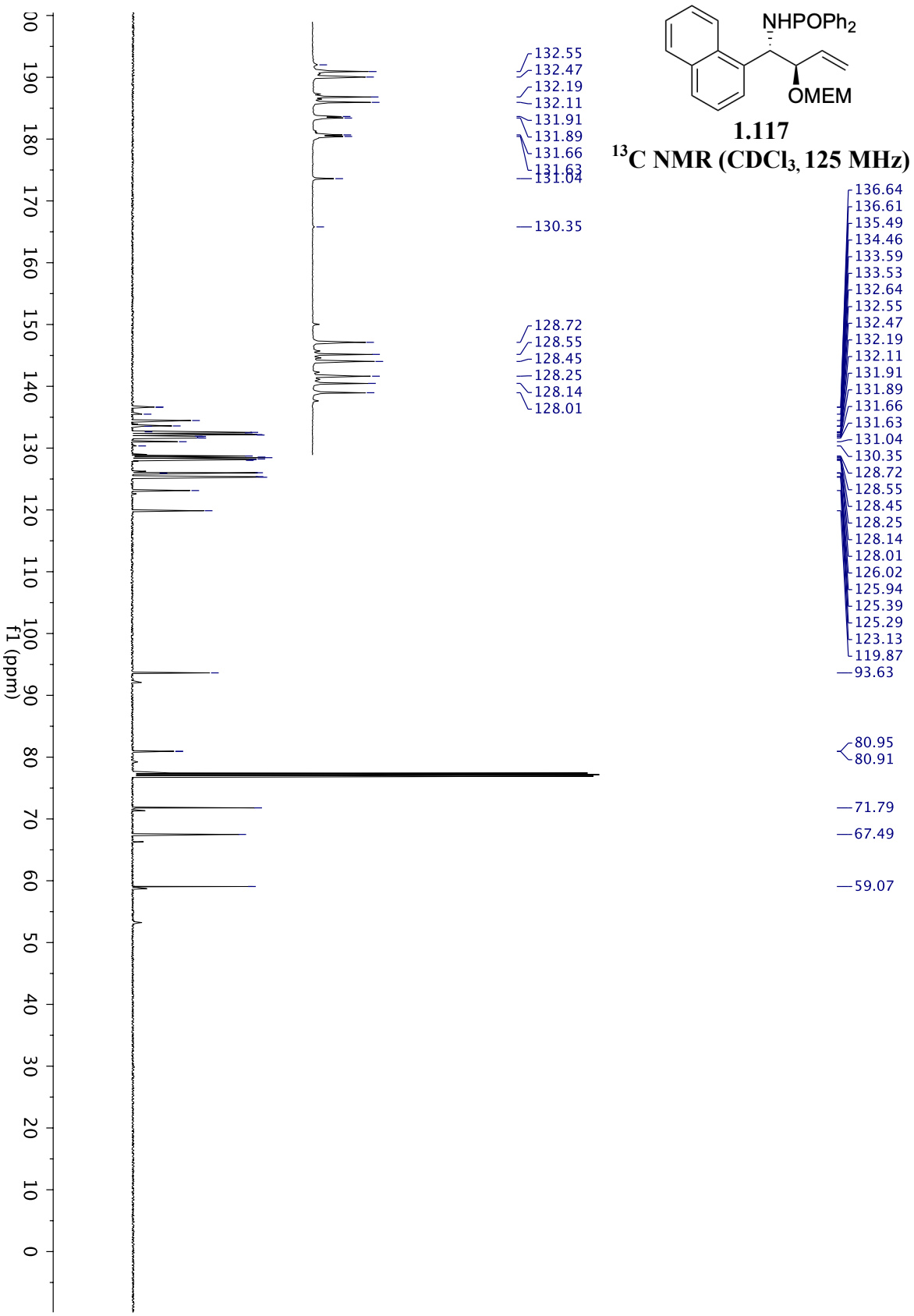
1.115

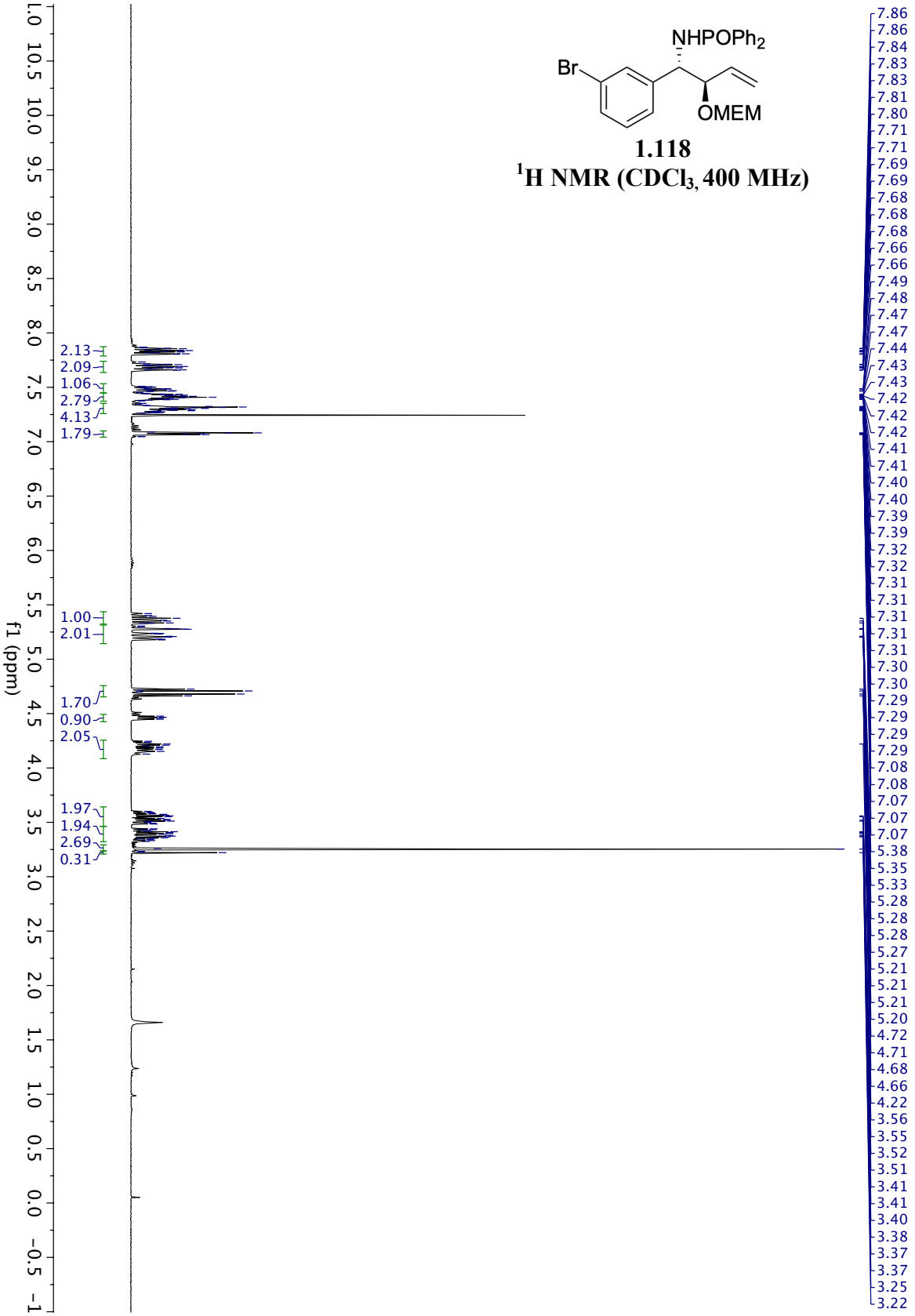
^{13}C NMR ($CDCl_3$, 100 MHz)


Me
NHPOPh2
OMEM
1.116
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.89
1.94
1.98
2.99
2.83
1.01
0.94
1.00
2.12
2.00
0.92
0.98
0.92
1.84
1.97
2.90
0.16
2.81


Me
NHPOPh2
OMEM
1.116
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
133.47
132.54
132.44
132.29
132.19
131.71
131.64
131.62
131.45
131.43
130.97
129.56
128.30
128.17
128.02
127.89
127.54
126.77
125.71
119.84
92.96
81.23
81.18
71.44
67.04
58.72
52.68
19.09

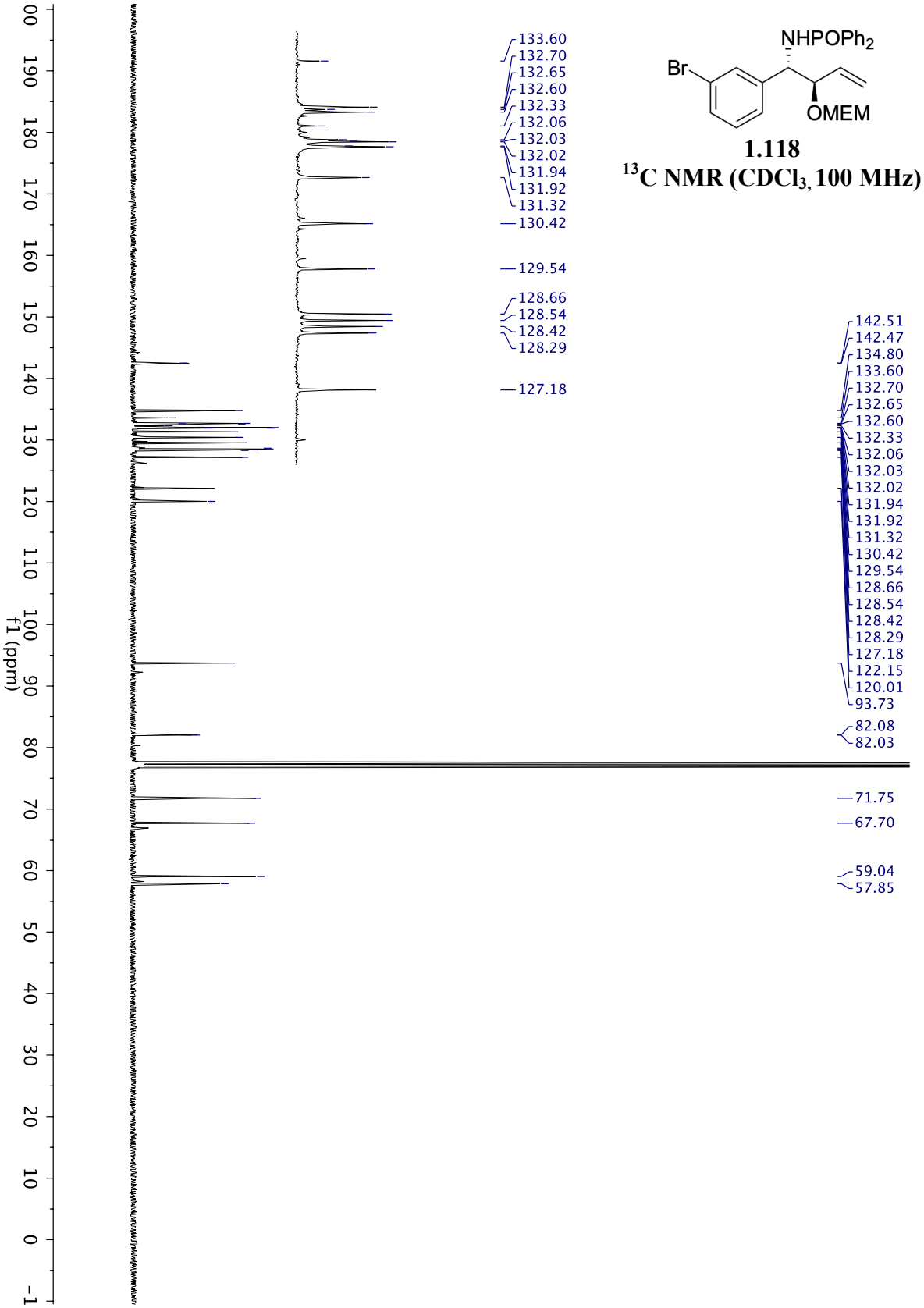

NHPOPh2
OMEM
1.117
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
9.35
2.21
3.08
1.73
0.36
2.31
2.12
0.85
0.98
2.03
1.00
0.99
2.12
2.02
3.12
0.37

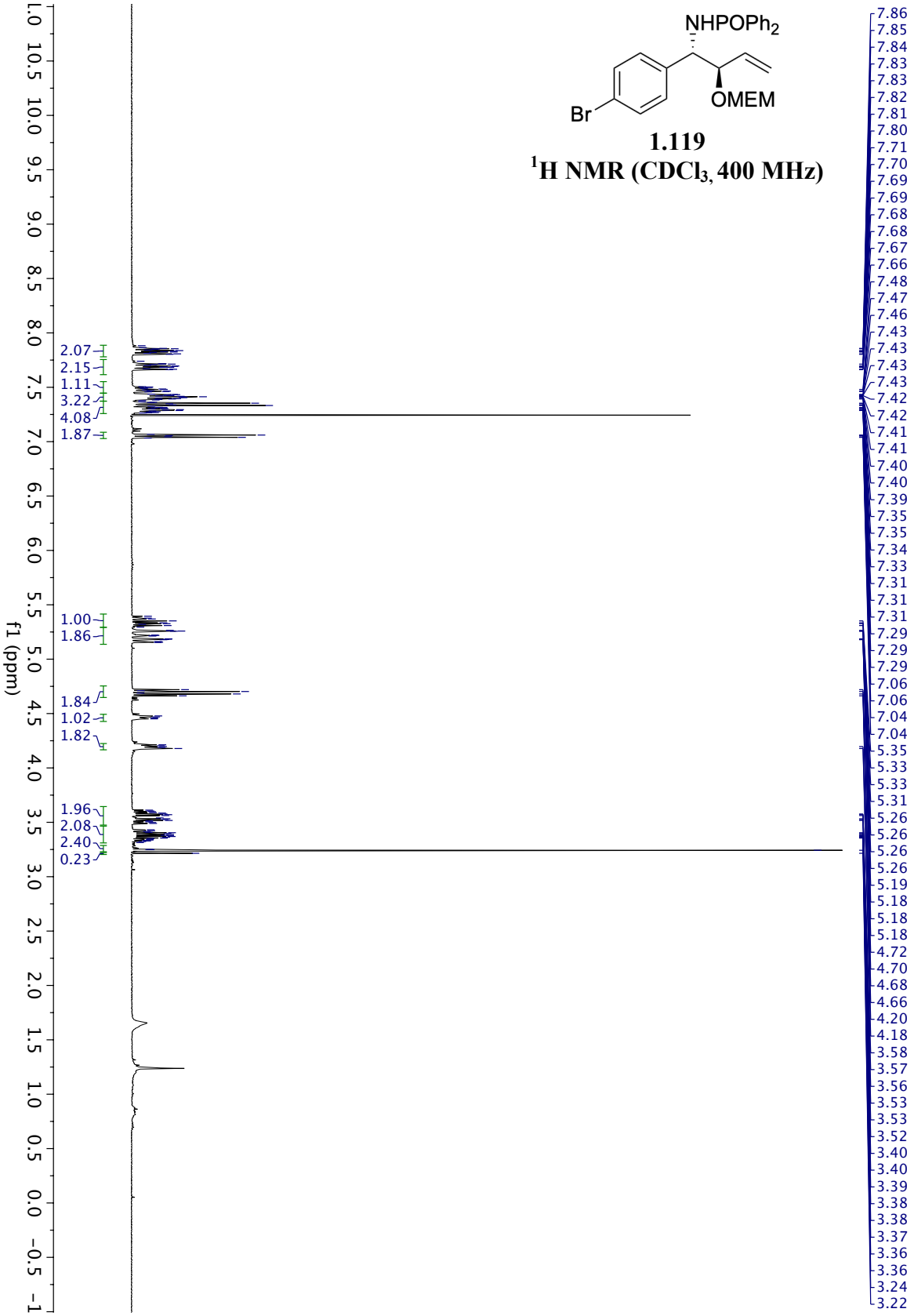

NHPOPh2
OMEM
1.117
13C NMR (CDCl3, 125 MHz)
f1 (ppm)
132.55
132.47
132.19
132.11
131.91
131.89
131.66
131.63
131.04
130.35
128.72
128.55
128.45
128.25
128.14
128.01
136.64
136.61
135.49
134.46
133.59
133.53
132.64
132.55
132.47
132.19
132.11
131.91
131.89
131.66
131.63
131.04
130.35
128.72
128.55
128.45
128.25
128.14
128.01
126.02
125.94
125.39
125.29
123.13
119.87
93.63
80.95
80.91
71.79
67.49
59.07

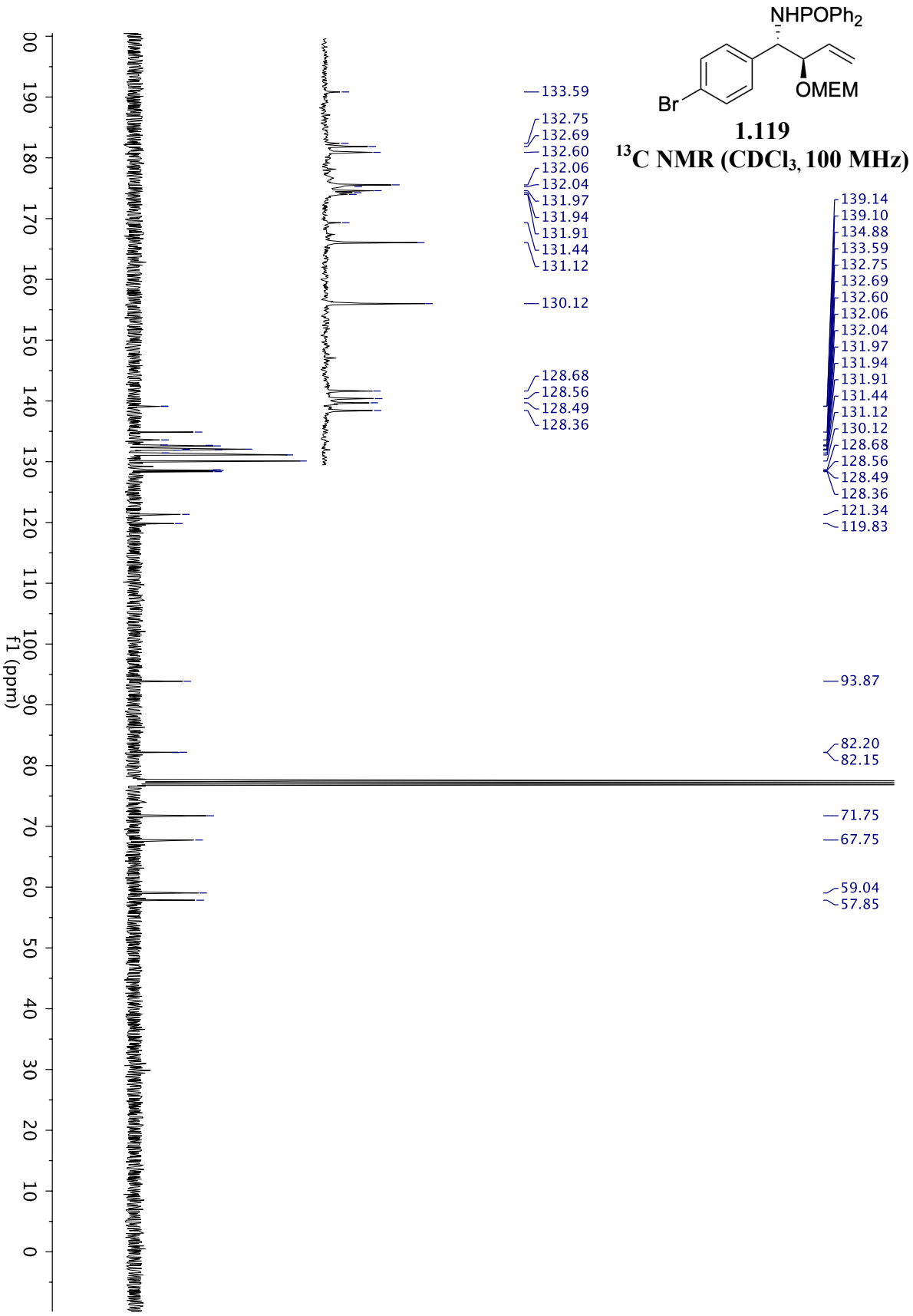


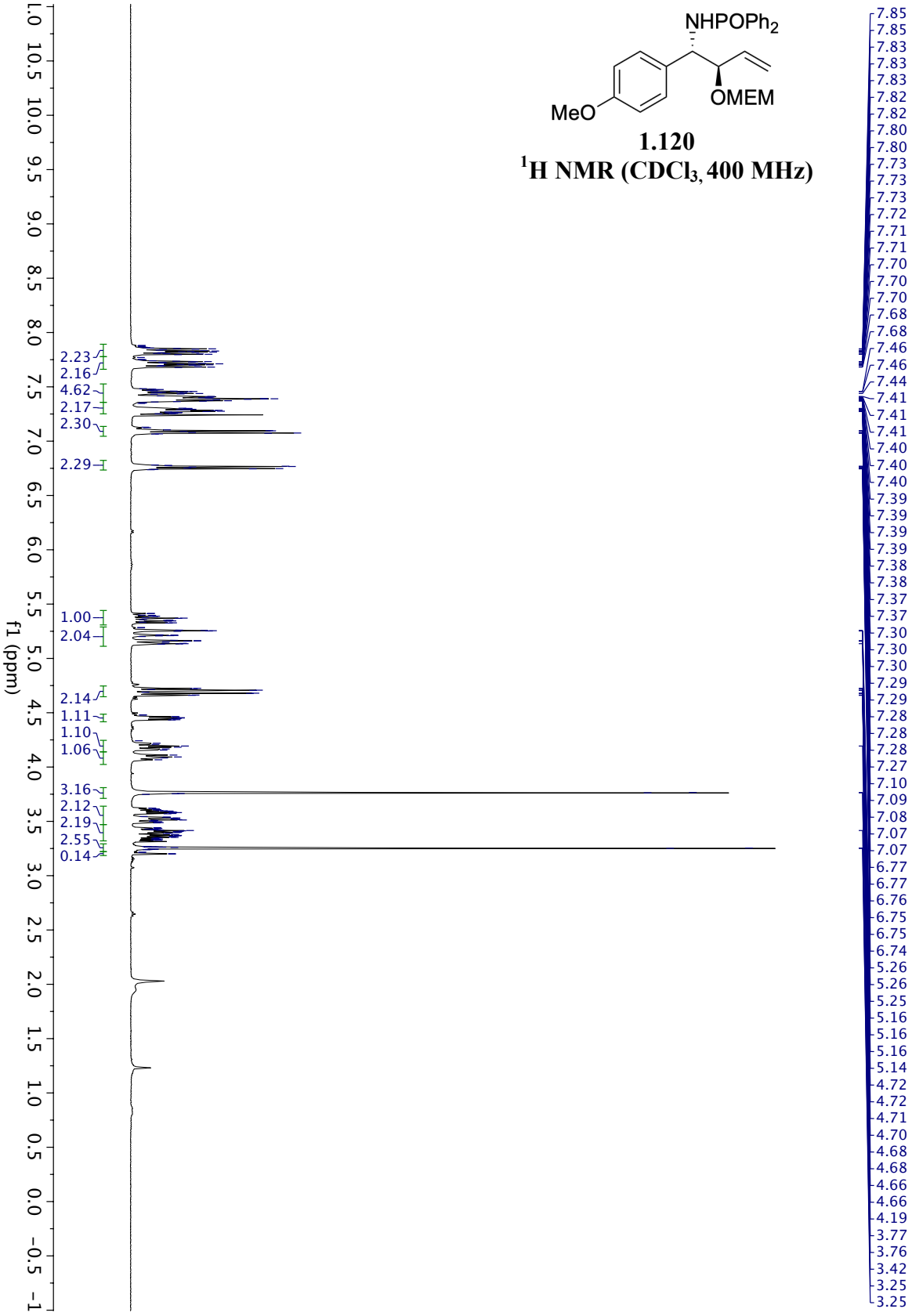
1.118

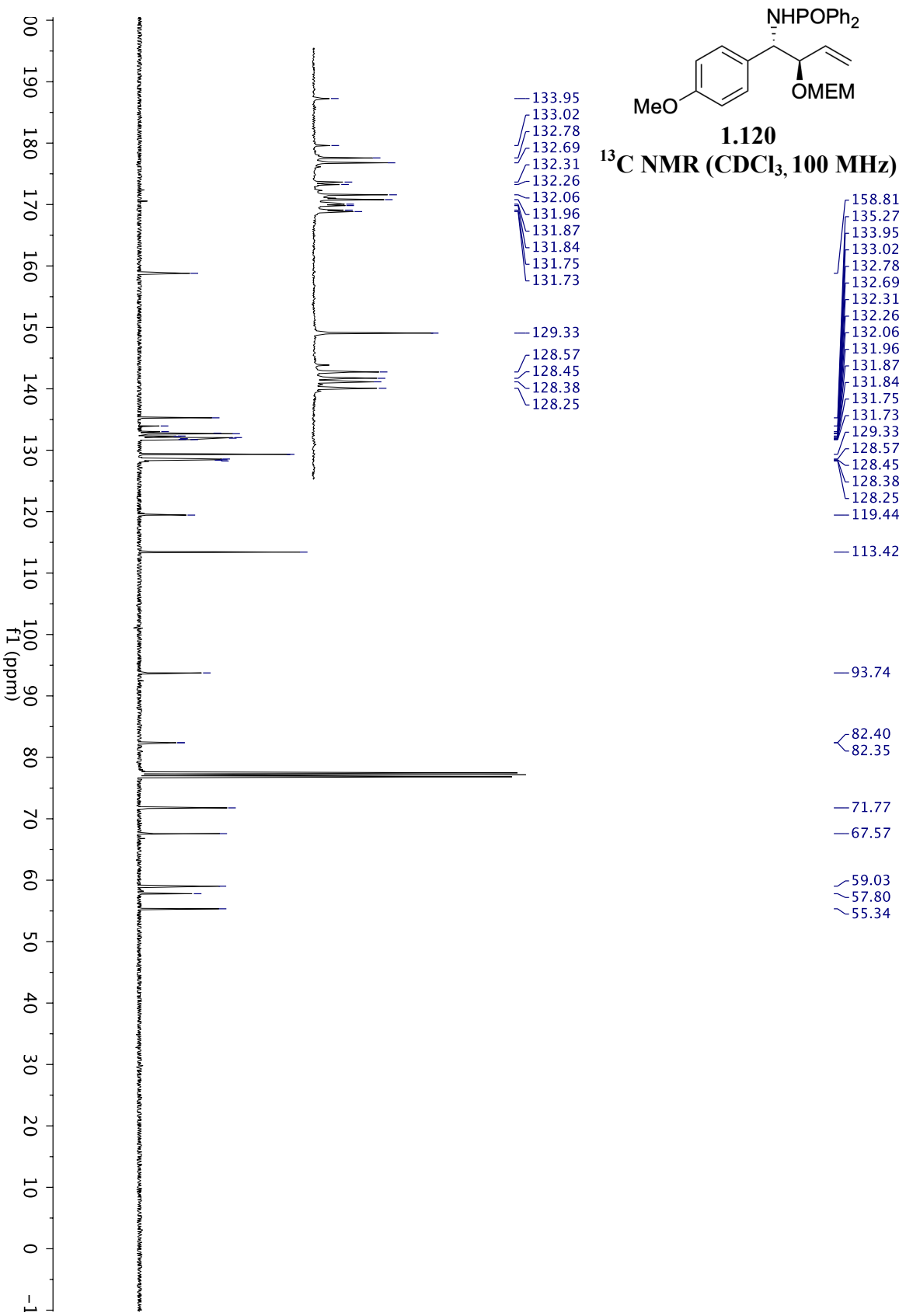
^{1}H NMR ($CDCl_3$, 400 MHz)

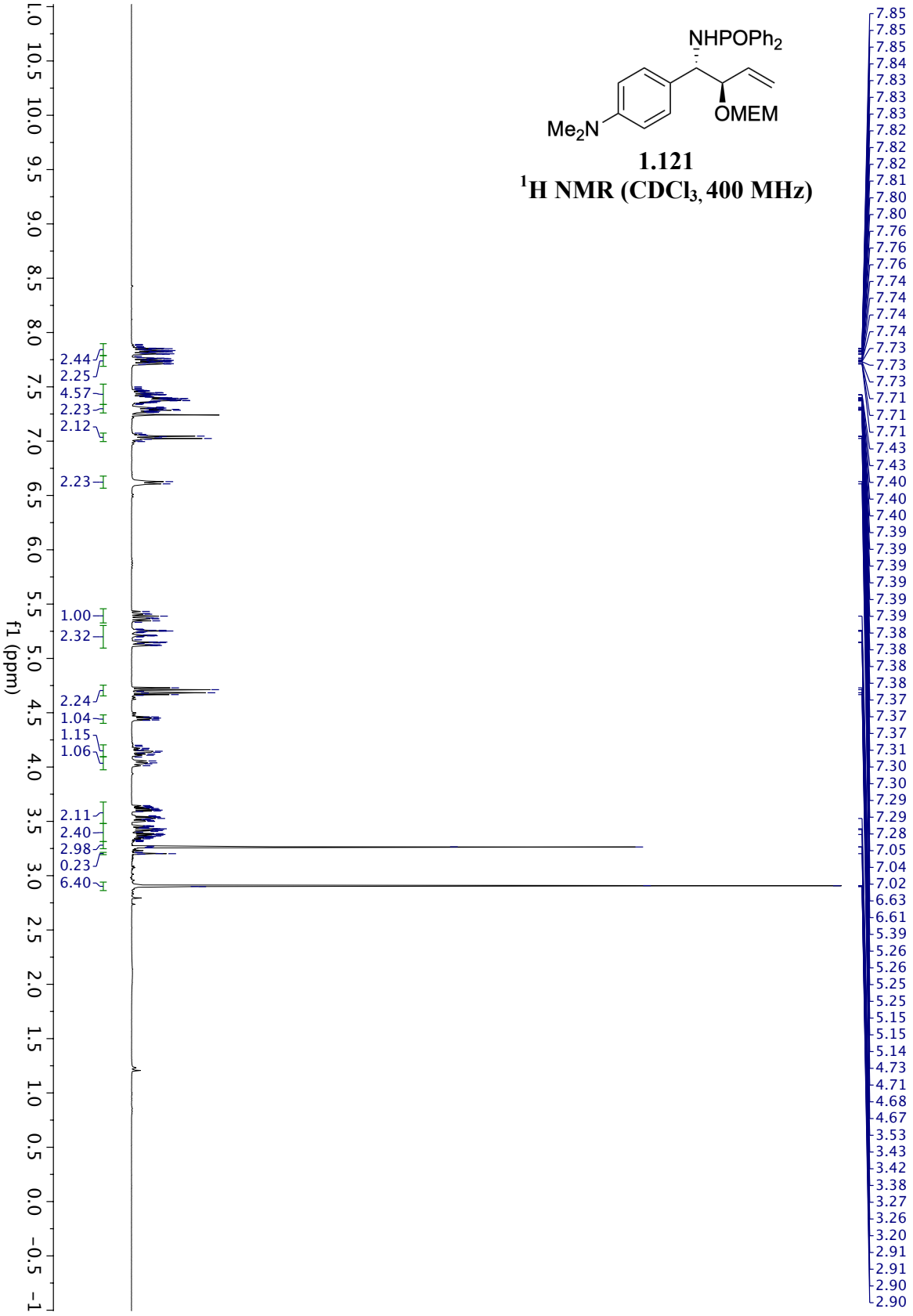

NHPOPh2
Br
OMEM
1.118
13C NMR (CDCl3, 100 MHz)
133.60
132.70
132.65
132.60
132.33
132.06
132.03
132.02
131.94
131.92
131.32
130.42
129.54
128.66
128.54
128.42
128.29
127.18
142.51
142.47
134.80
133.60
132.70
132.65
132.60
132.33
132.06
132.03
132.02
131.94
131.92
131.32
130.42
129.54
128.66
128.54
128.42
128.29
127.18
122.15
120.01
93.73
82.08
82.03
71.75
67.70
59.04
57.85
f1 (ppm)

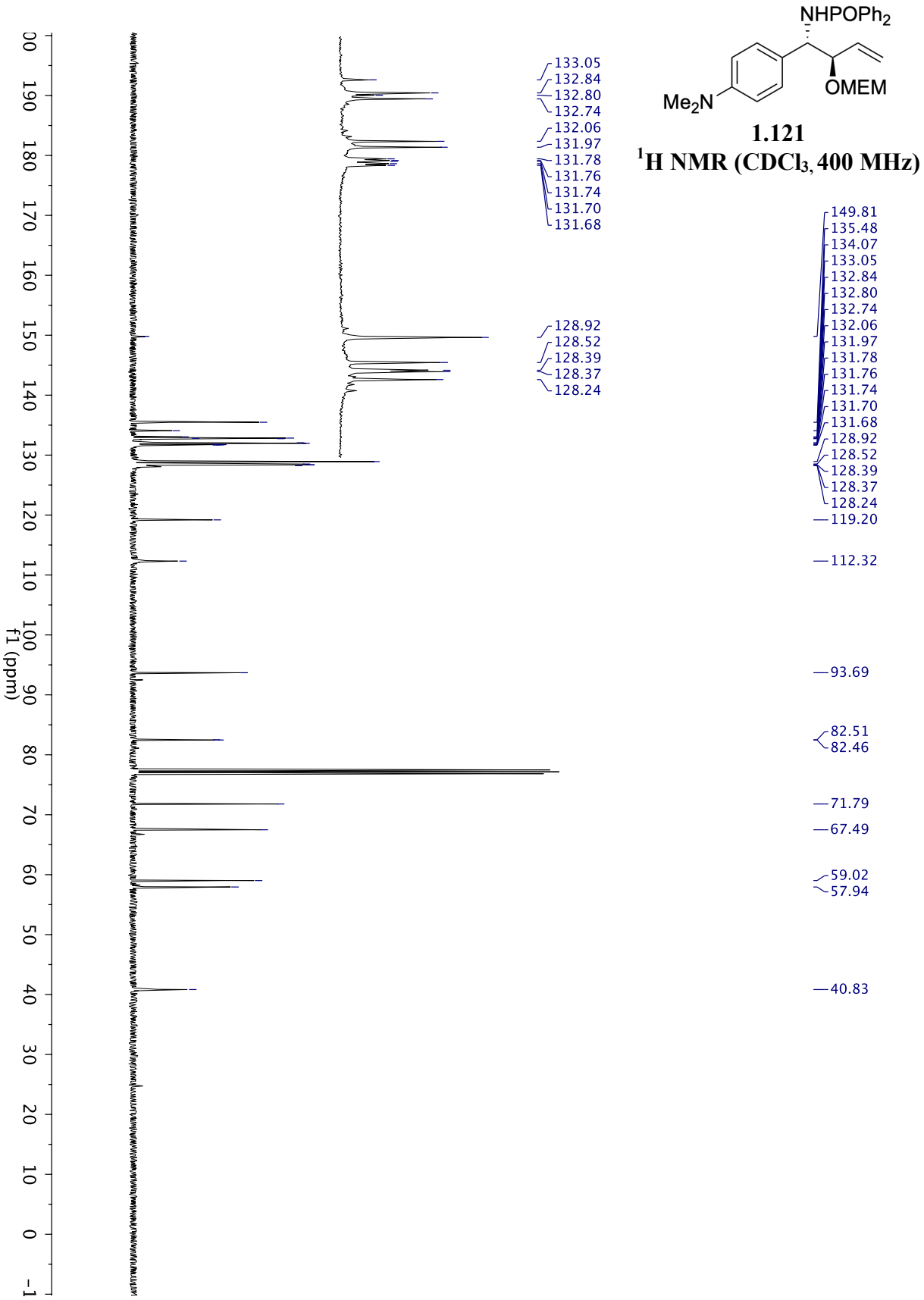

NHPOPh2
Br
OMEM
1.119
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.07
2.15
1.11
3.22
4.08
1.87
1.00
1.86
1.84
1.02
1.82
1.96
2.08
2.40
0.23

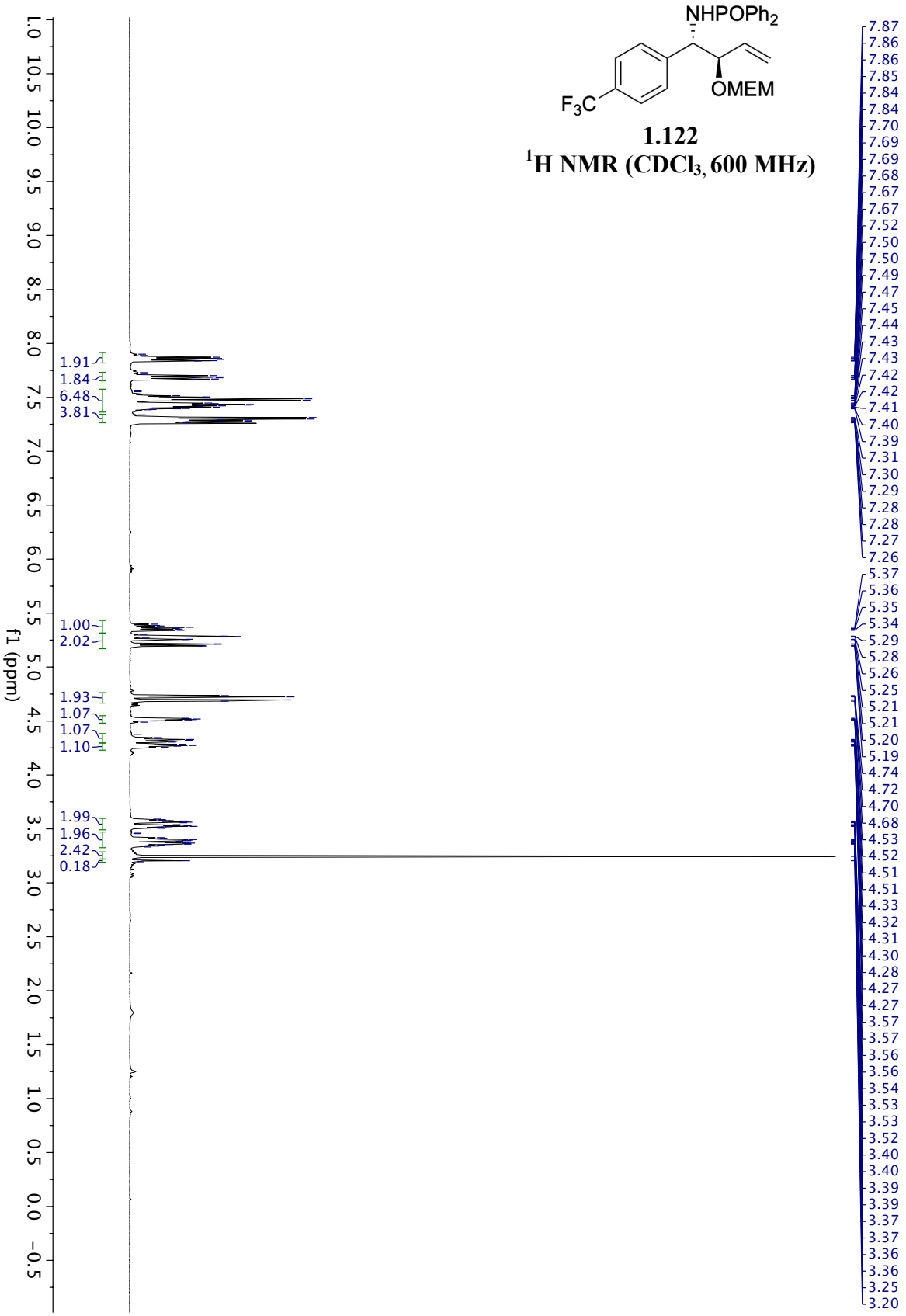

NHPOPh2
Br
OMEM
1.119
13C NMR (CDCl3, 100 MHz)
133.59
132.75
132.69
132.60
132.06
132.04
131.97
131.94
131.91
131.44
131.12
130.12
128.68
128.56
128.49
128.36
139.14
139.10
134.88
133.59
132.75
132.69
132.60
132.06
132.04
131.97
131.94
131.91
131.44
131.12
130.12
128.68
128.56
128.49
128.36
121.34
119.83
93.87
82.20
82.15
71.75
67.75
59.04
57.85
f1 (ppm)

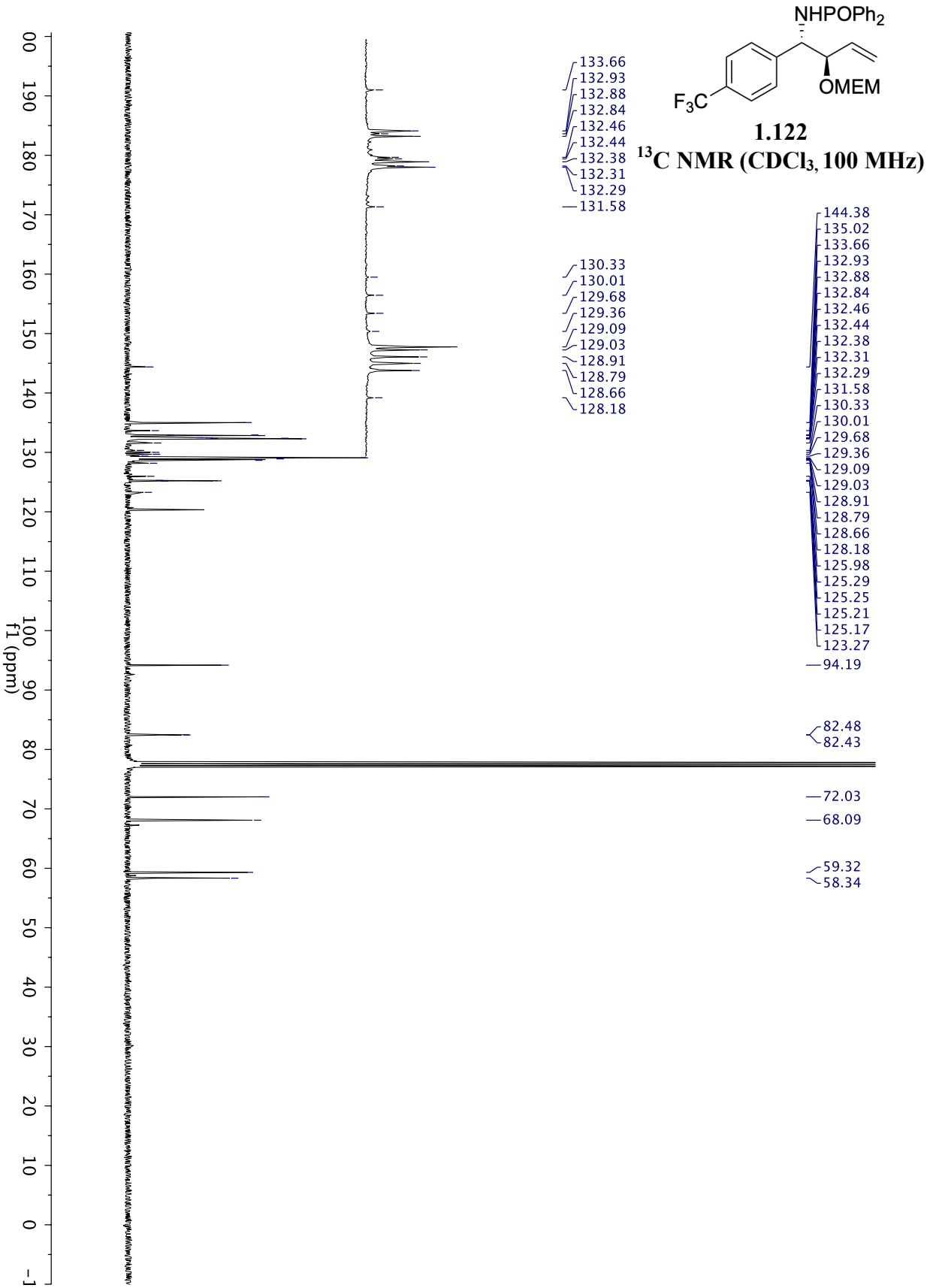

NHPOPh2
MeO
OMEM
1.120
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.23
2.16
4.62
2.17
2.30
2.29
1.00
2.04
2.14
1.11
1.10
1.06
3.16
2.12
2.19
2.55
0.14

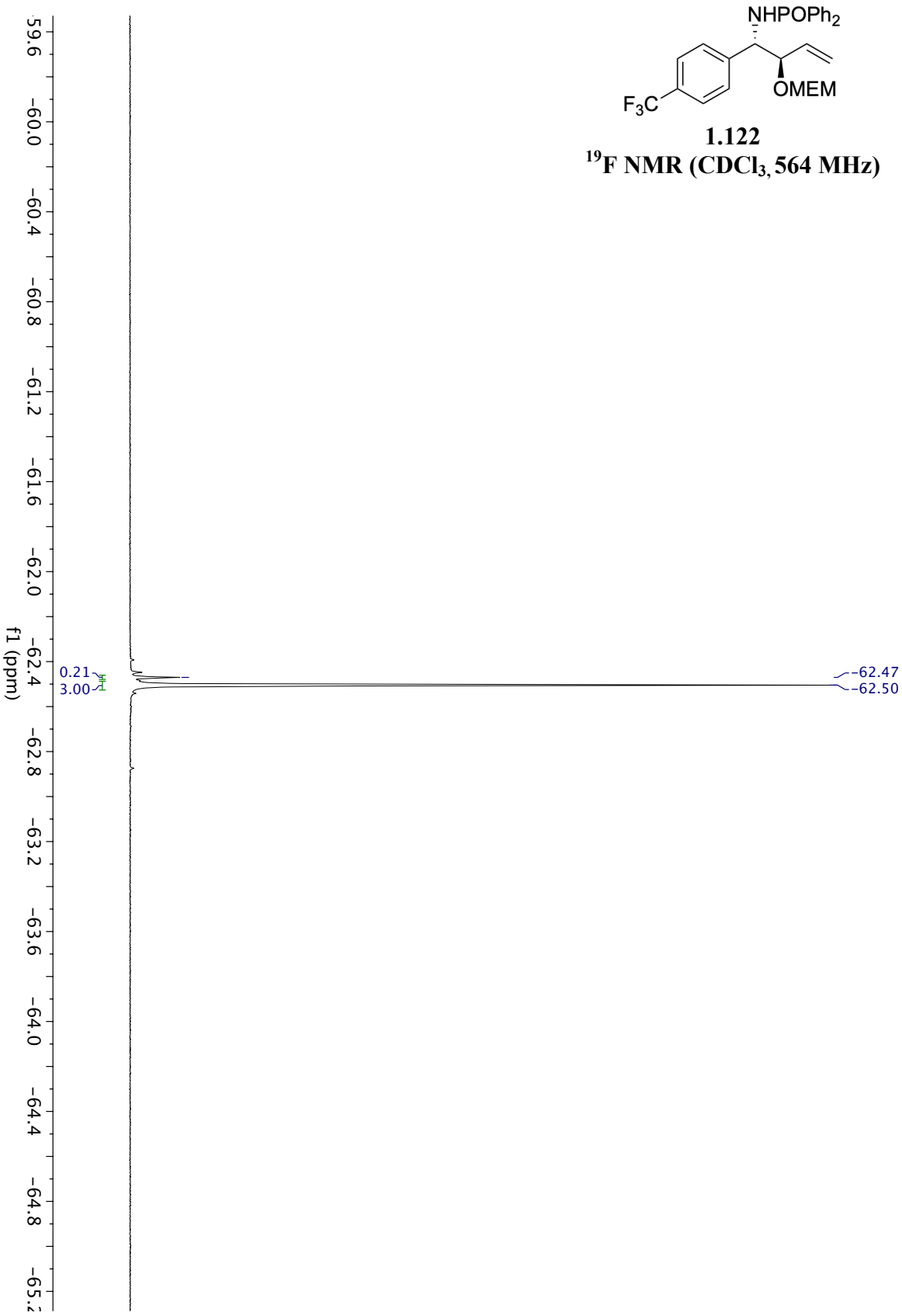

NHPOPh2
MeO
OMEM
1.120
13C NMR (CDCl3, 100 MHz)
133.95
133.02
132.78
132.69
132.31
132.26
132.06
131.96
131.87
131.84
131.75
131.73
129.33
128.57
128.45
128.38
128.25
158.81
135.27
133.95
133.02
132.78
132.69
132.31
132.26
132.06
131.96
131.87
131.84
131.75
131.73
129.33
128.57
128.45
128.38
128.25
119.44
113.42
93.74
82.40
82.35
71.77
67.57
59.03
57.80
55.34
f1 (ppm)

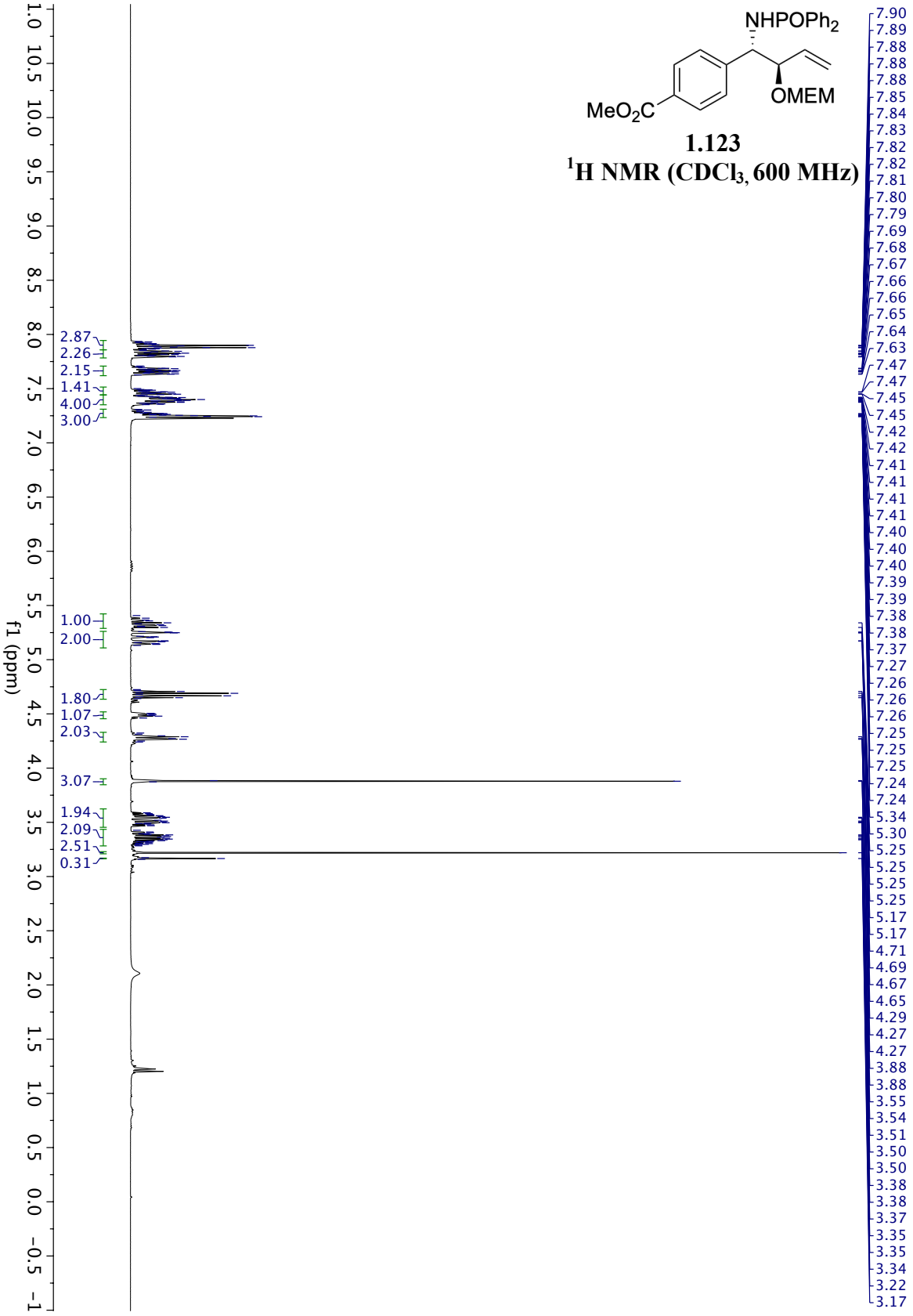

NHPOPh2
Me2N
OMEM
1.121
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.44
2.25
4.57
2.23
2.12
2.23
1.00
2.32
2.24
1.04
1.15
1.06
2.11
2.40
2.98
0.23
6.40

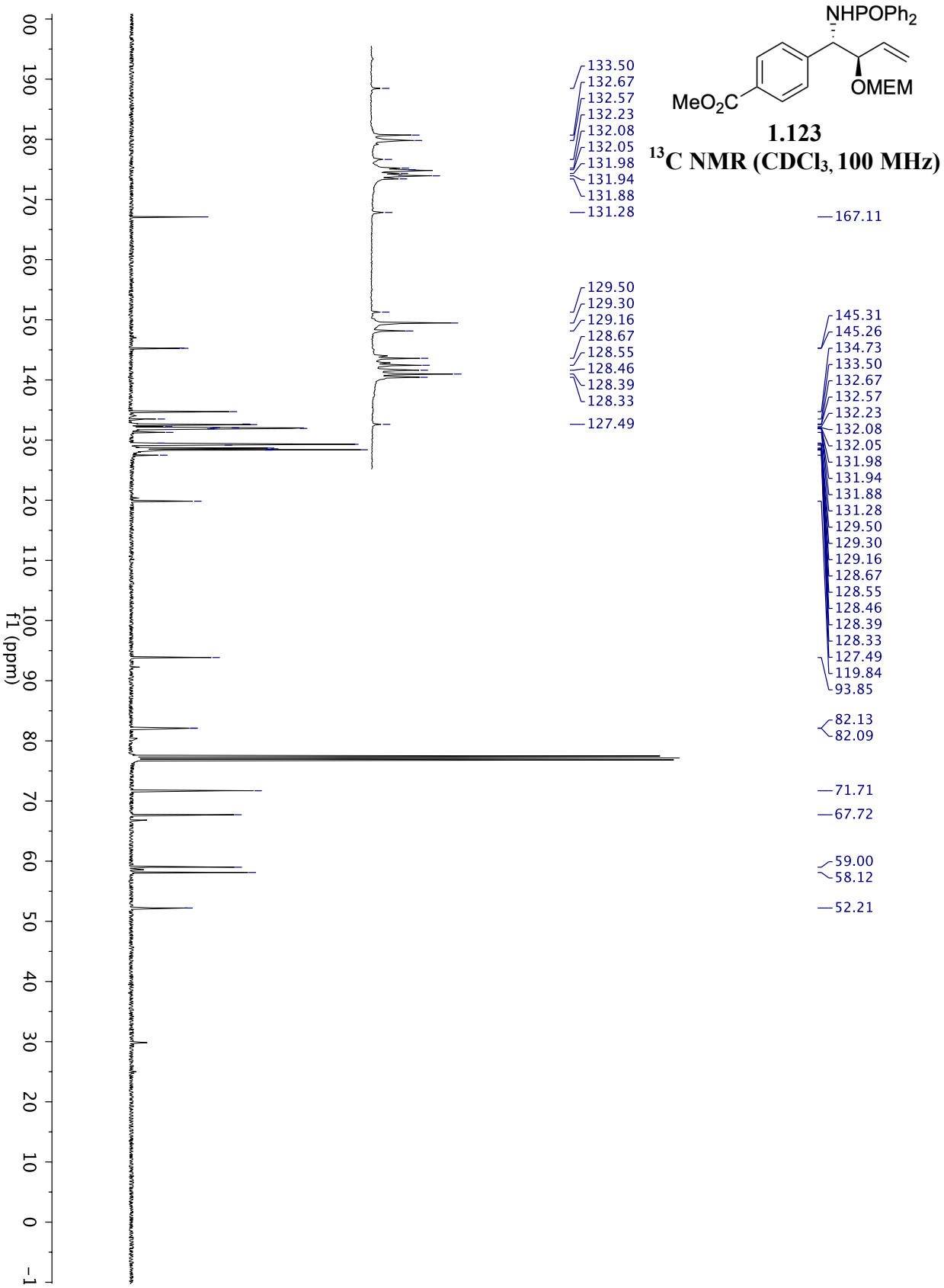

NHPOPh2
Me2N
OMEM
1.121
1H NMR (CDCl3, 400 MHz)
133.05
132.84
132.80
132.74
132.06
131.97
131.78
131.76
131.74
131.70
131.68
128.92
128.52
128.39
128.37
128.24
149.81
135.48
134.07
133.05
132.84
132.80
132.74
132.06
131.97
131.78
131.76
131.74
131.70
131.68
128.92
128.52
128.39
128.37
128.24
119.20
112.32
93.69
82.51
82.46
71.79
67.49
59.02
57.94
40.83
f1 (ppm)

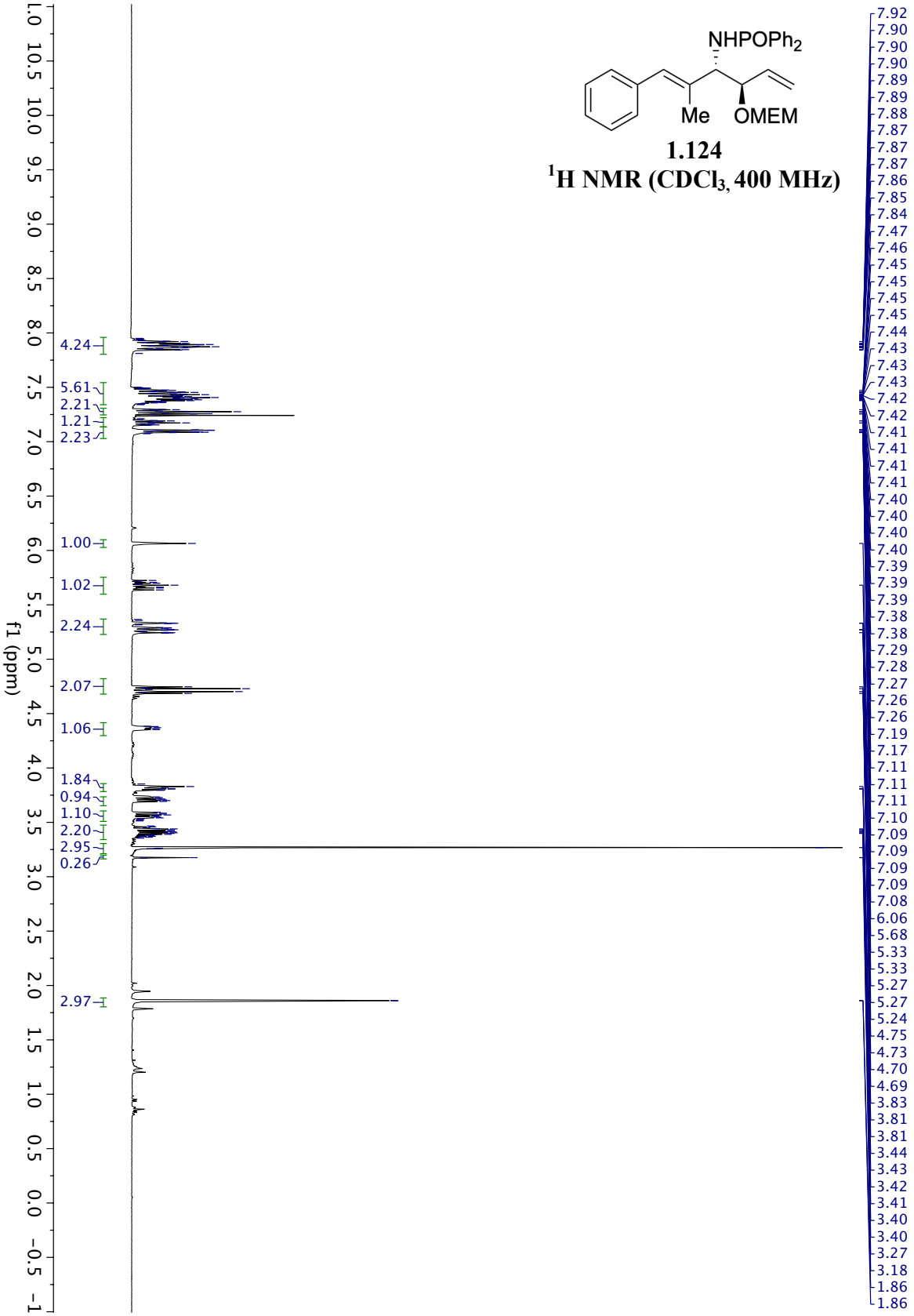

NHPOPh2
F3C
OMEM
1.122
1H NMR (CDCl3, 600 MHz)
f1 (ppm)
1.91
1.84
6.48
3.81
1.00
2.02
1.93
1.07
1.07
1.10
1.99
1.96
2.42
0.18

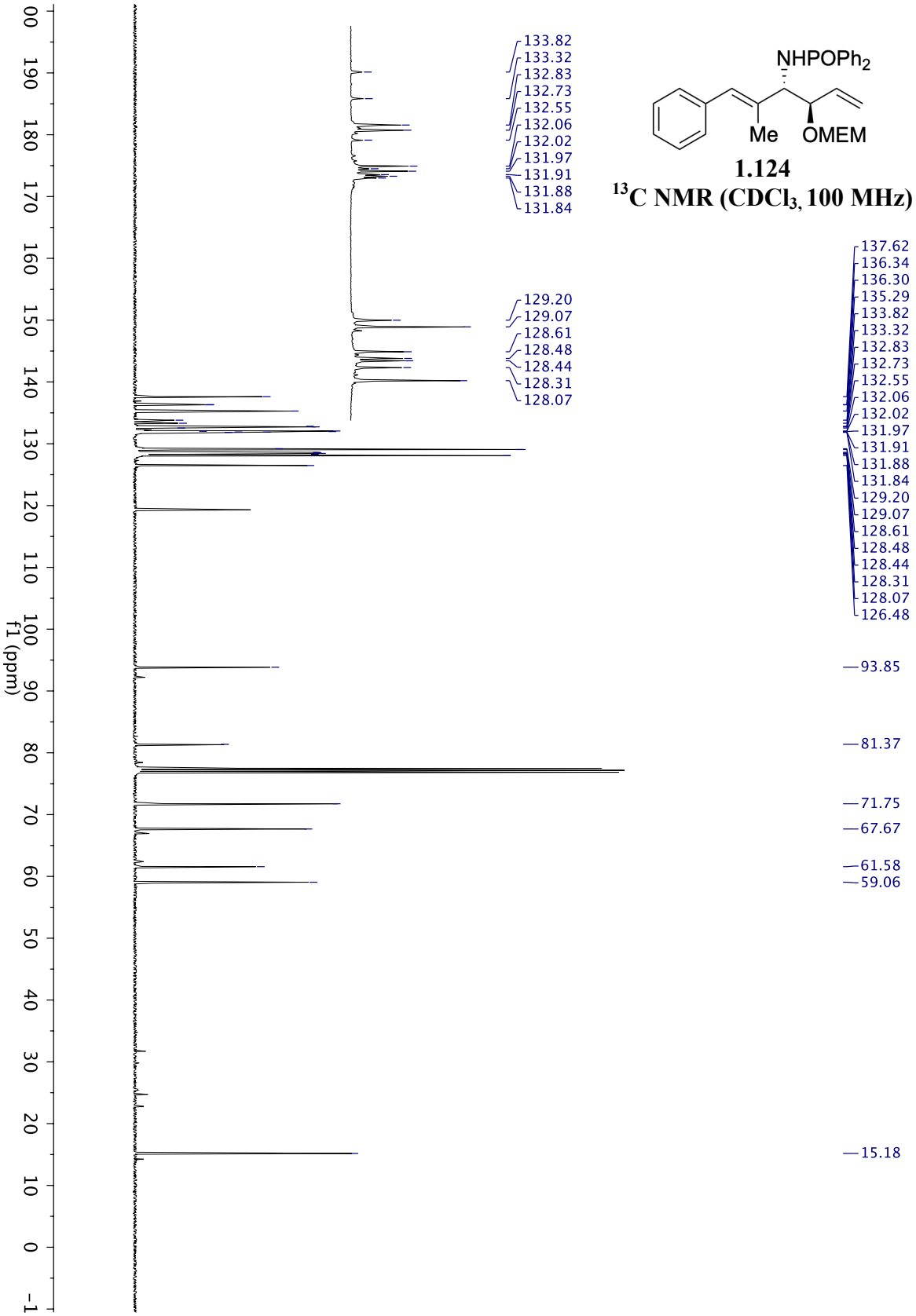

NHPOPh2
F3C
OMEM
1.122
13C NMR (CDCl3, 100 MHz)
133.66
132.93
132.88
132.84
132.46
132.44
132.38
132.31
132.29
131.58
130.33
130.01
129.68
129.36
129.09
129.03
128.91
128.79
128.66
128.18
144.38
135.02
133.66
132.93
132.88
132.84
132.46
132.44
132.38
132.31
132.29
131.58
130.33
130.01
129.68
129.36
129.09
129.03
128.91
128.79
128.66
128.18
125.98
125.29
125.25
125.21
125.17
123.27
94.19
82.48
82.43
72.03
68.09
59.32
58.34
f1 (ppm)

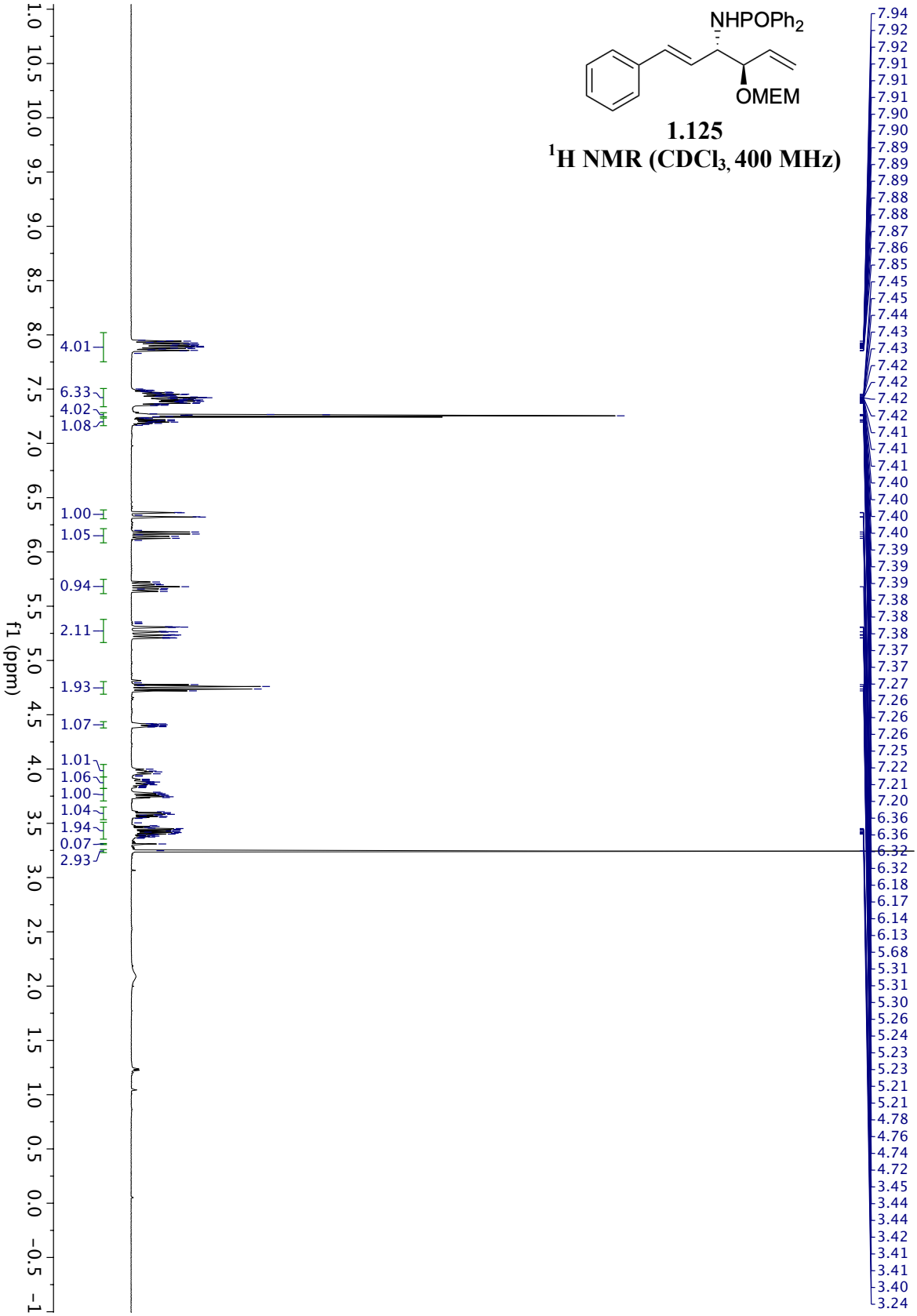

NHPOPh2
F3C
OMEM
1.122
19F NMR (CDCl3, 564 MHz)
f1 (ppm)
-59.6
-60.0
-60.4
-60.8
-61.2
-61.6
-62.0
-62.4
-62.8
-63.2
-63.6
-64.0
-64.4
-64.8
-65.2
0.21
3.00
-62.47
-62.50

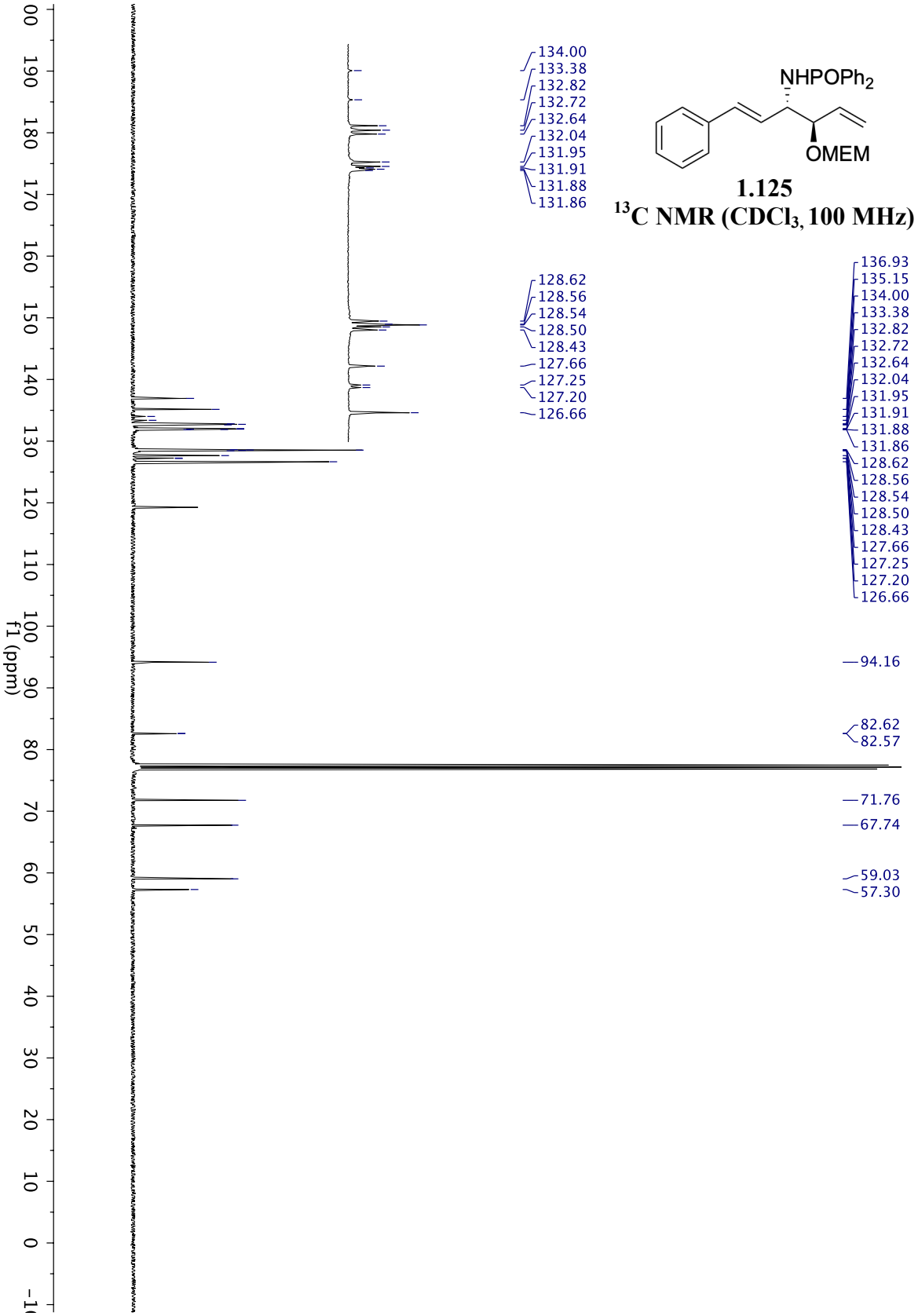

NHPOPh2
MeO2C
OMEM
1.123
1H NMR (CDCl3, 600 MHz)
f1 (ppm)
2.87
2.26
2.15
1.41
4.00
3.00
1.00
2.00
1.80
1.07
2.03
3.07
1.94
2.09
2.51
0.31

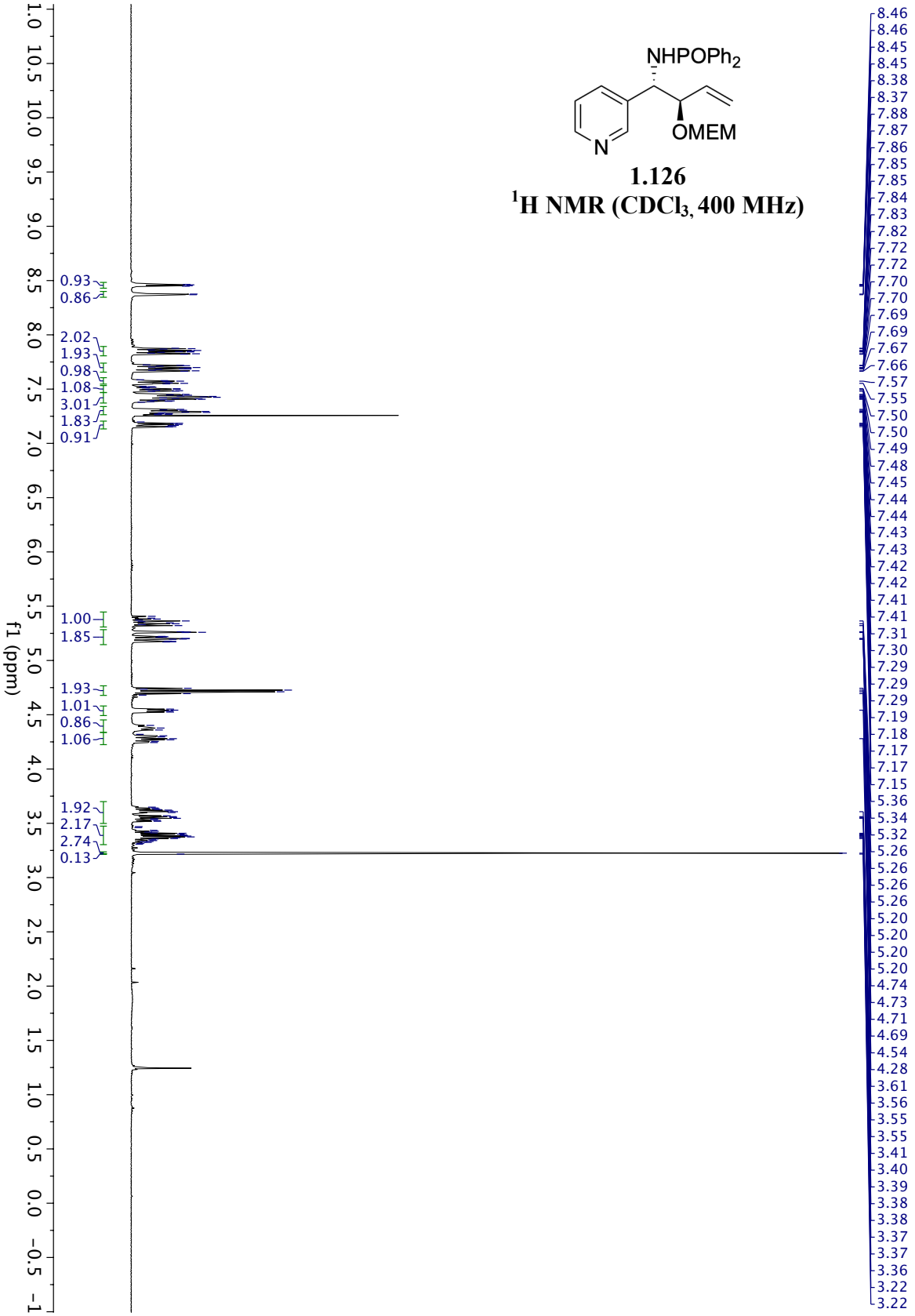

NHPOPh2
MeO2C
OMEM
1.123
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
133.50
132.67
132.57
132.23
132.08
132.05
131.98
131.94
131.88
131.28
129.50
129.30
129.16
128.67
128.55
128.46
128.39
128.33
127.49
167.11
145.31
145.26
134.73
119.84
93.85
82.13
82.09
71.71
67.72
59.00
58.12
52.21

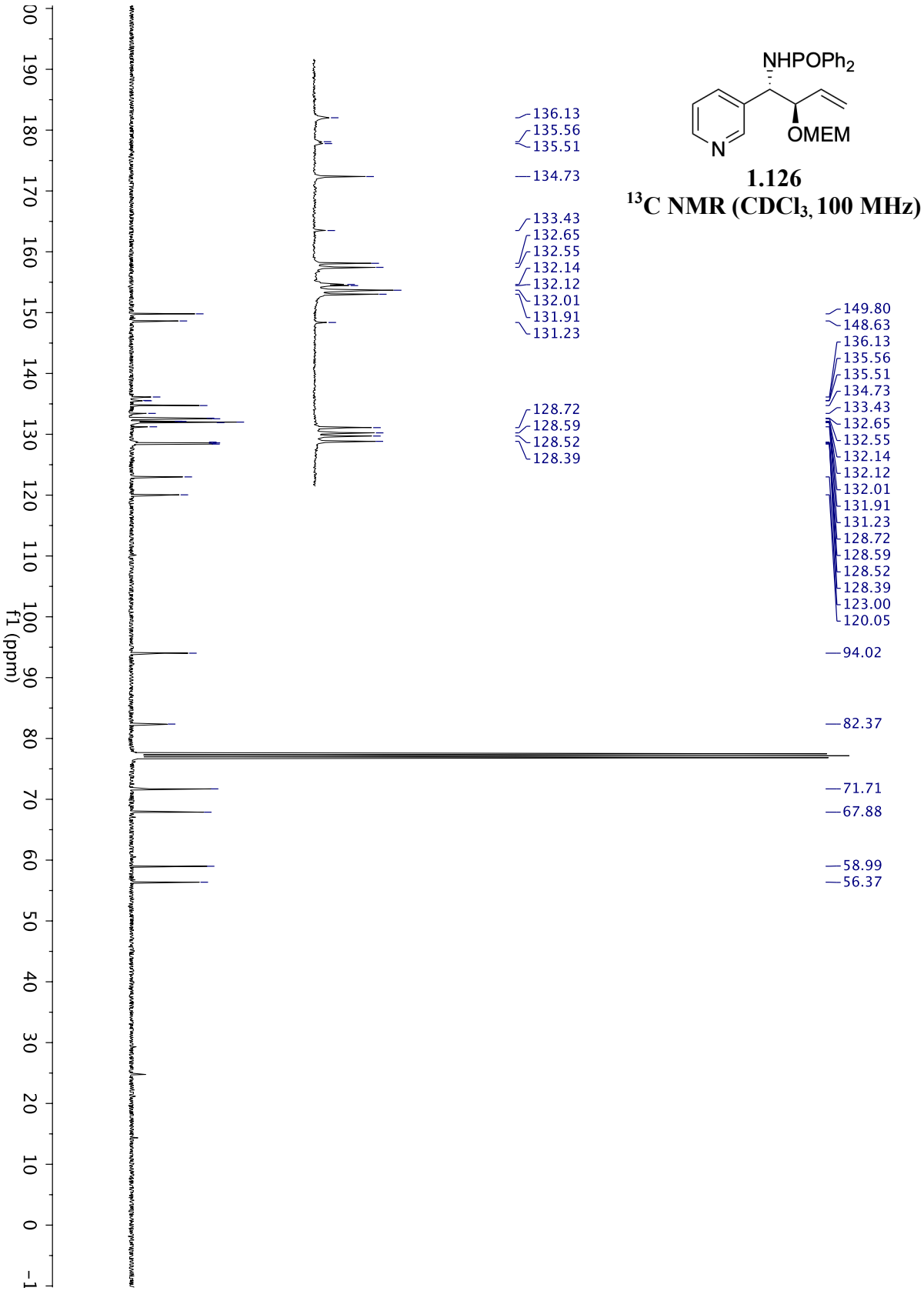

NHPOPh2
Me
OMEM
1.124
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.24
5.61
2.21
1.21
2.23
1.00
1.02
2.24
2.07
1.06
1.84
0.94
1.10
2.20
2.95
0.26
2.97

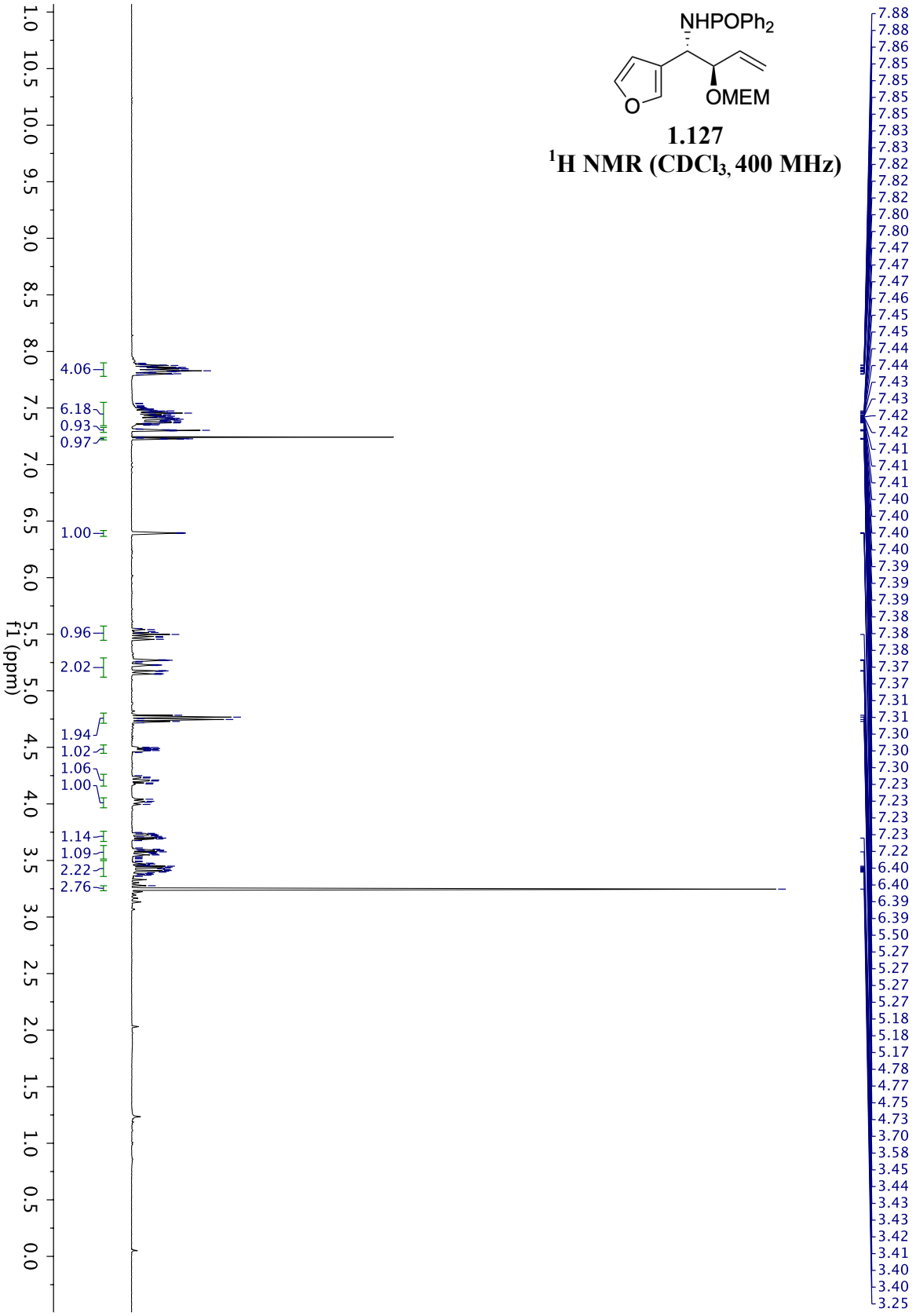

NHPOPh2
Me
OMEM
1.124
13C NMR (CDCl3, 100 MHz)
133.82
133.32
132.83
132.73
132.55
132.06
132.02
131.97
131.91
131.88
131.84
129.20
129.07
128.61
128.48
128.44
128.31
128.07
137.62
136.34
136.30
135.29
126.48
93.85
81.37
71.75
67.67
61.58
59.06
15.18
f1 (ppm)

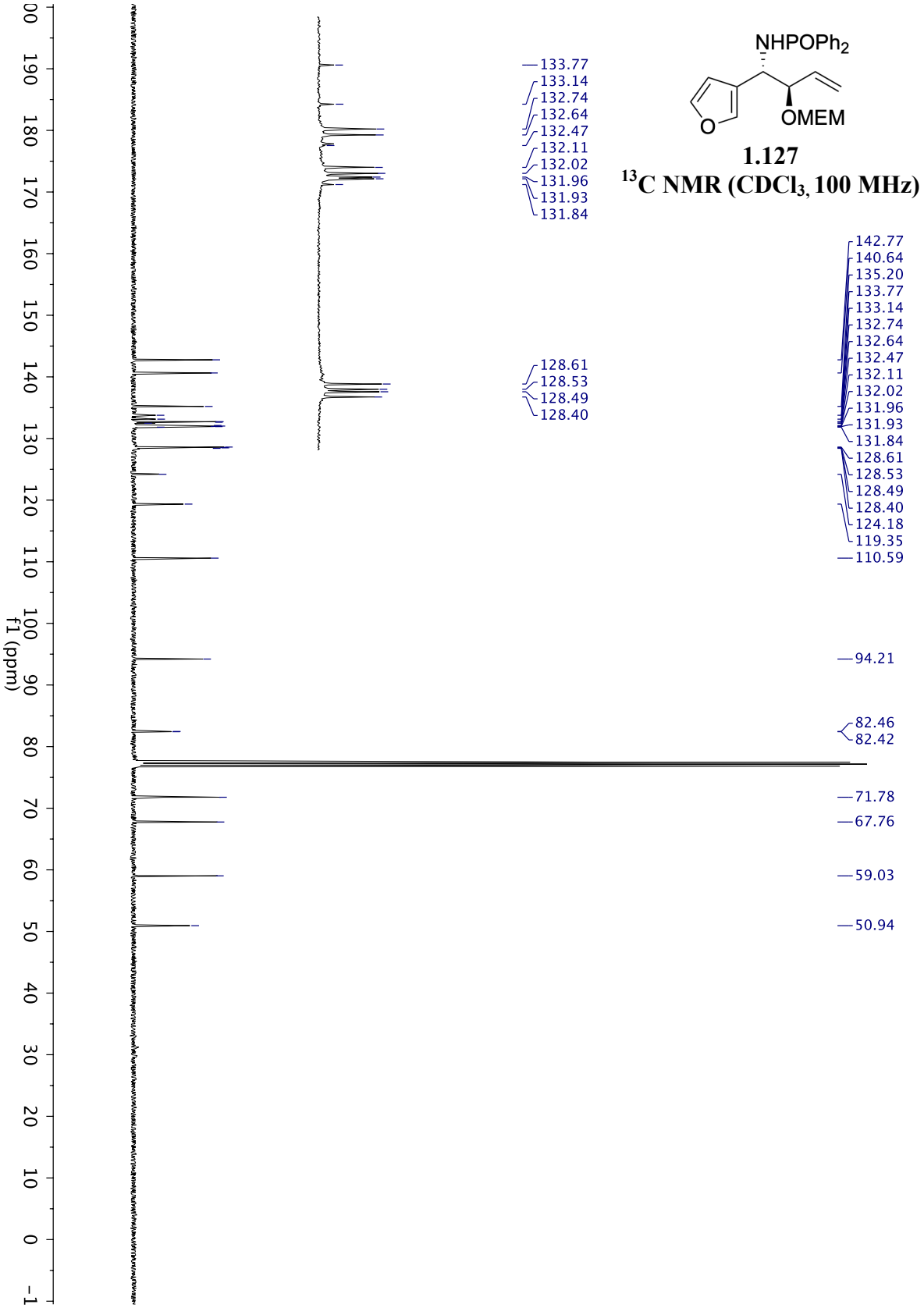

NHPOPh2
OMEM
1.125
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.01
6.33
4.02
1.08
1.00
1.05
0.94
2.11
1.93
1.07
1.01
1.06
1.00
1.04
1.94
0.07
2.93

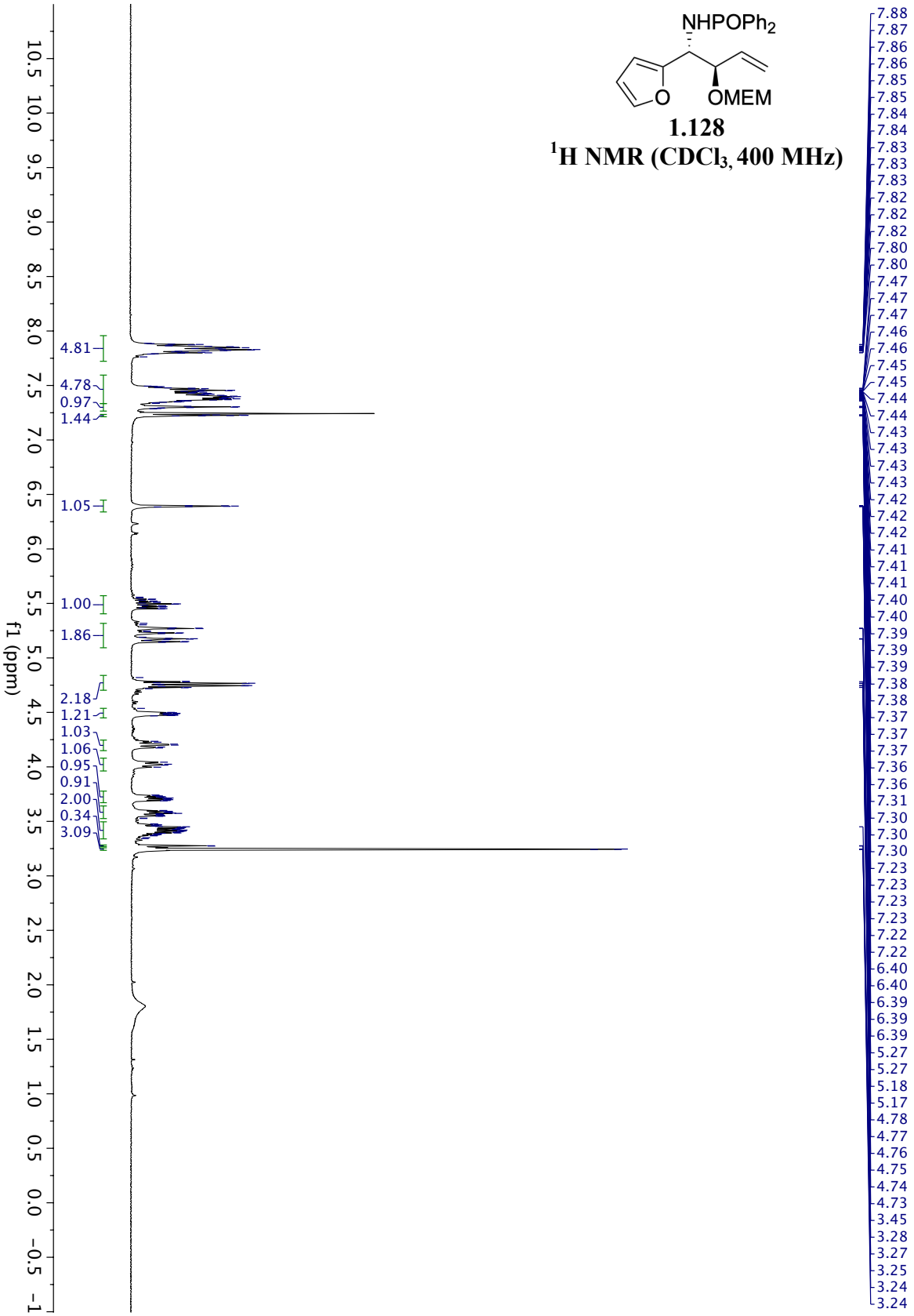

NHPOPh2
OMEM
1.125
13C NMR (CDCl3, 100 MHz)
134.00
133.38
132.82
132.72
132.64
132.04
131.95
131.91
131.88
131.86
128.62
128.56
128.54
128.50
128.43
127.66
127.25
127.20
126.66
136.93
135.15
94.16
82.62
82.57
71.76
67.74
59.03
57.30
f1 (ppm)

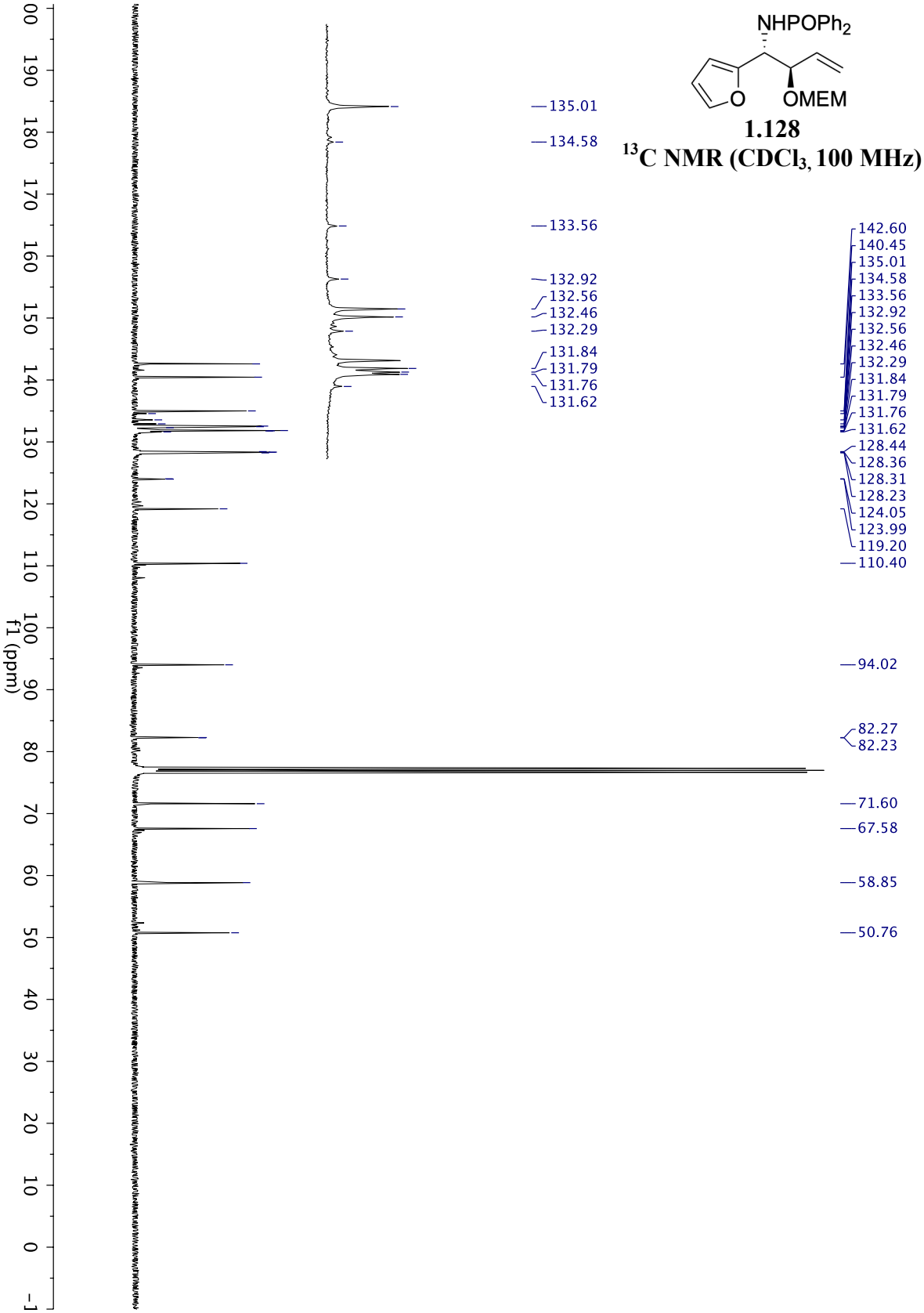

NHPOPh2
OMEM
N
1.126
1H NMR (CDCl3, 400 MHz)
f1 (ppm)

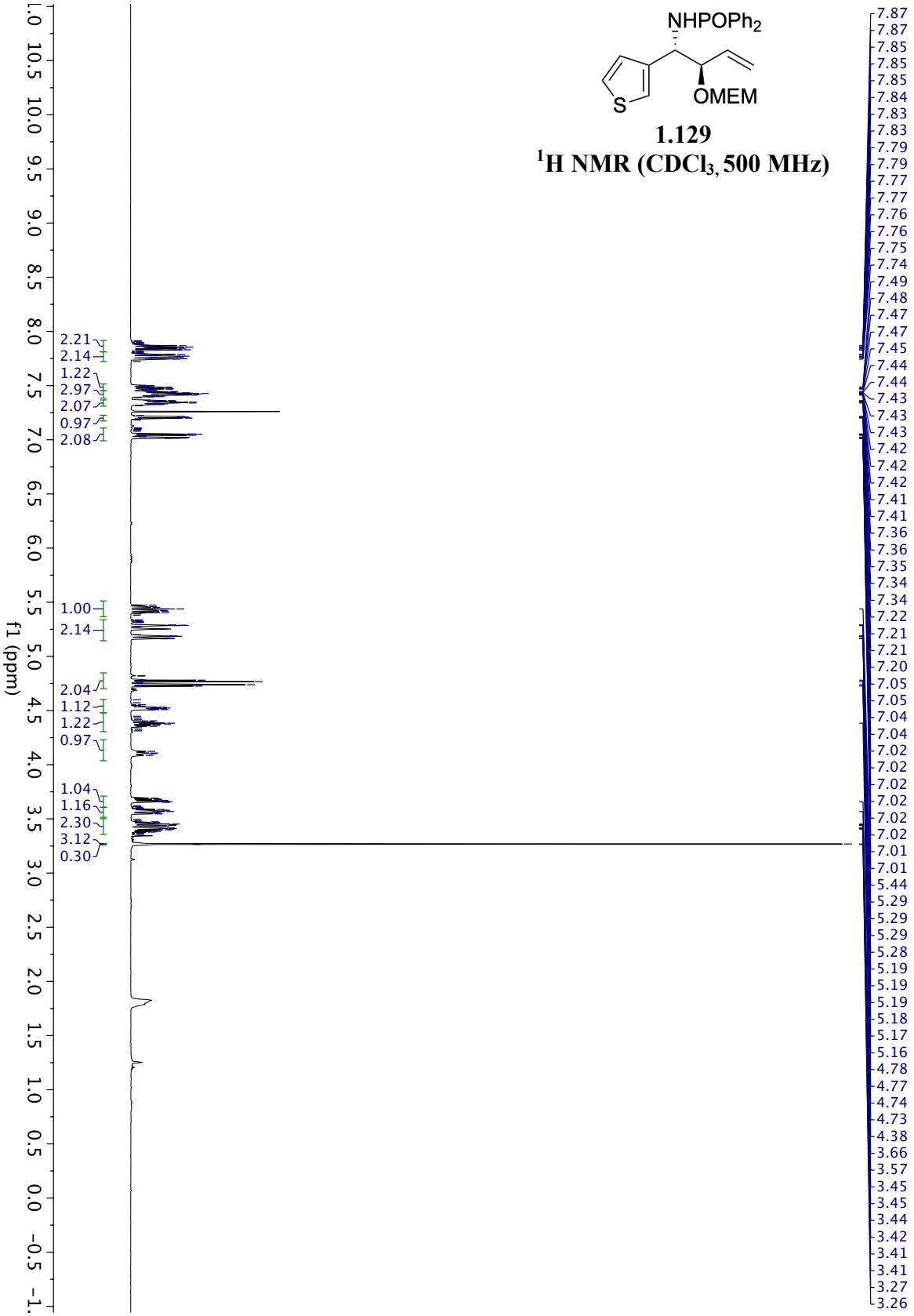

NHPOPh2
OMEM
N
1.126
13C NMR (CDCl3, 100 MHz)
136.13
135.56
135.51
134.73
133.43
132.65
132.55
132.14
132.12
132.01
131.91
131.23
128.72
128.59
128.52
128.39
149.80
148.63
136.13
135.56
135.51
134.73
133.43
132.65
132.55
132.14
132.12
132.01
131.91
131.23
128.72
128.59
128.52
128.39
123.00
120.05
94.02
82.37
71.71
67.88
58.99
56.37
f1 (ppm)

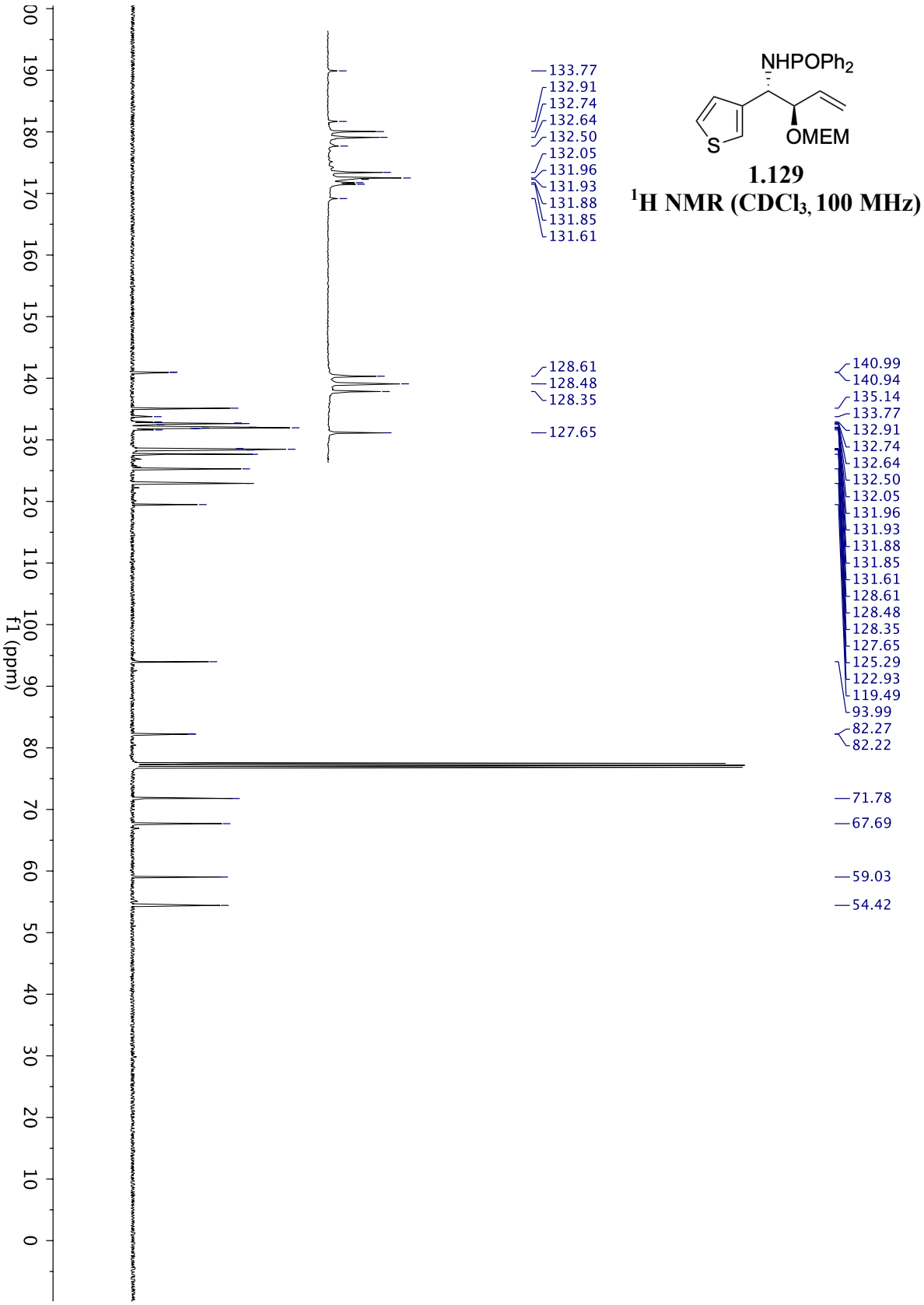

NHPOPh2
OMEM
O
1.127
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.06
6.18
0.93
0.97
1.00
0.96
2.02
1.94
1.02
1.06
1.00
1.14
1.09
2.22
2.76

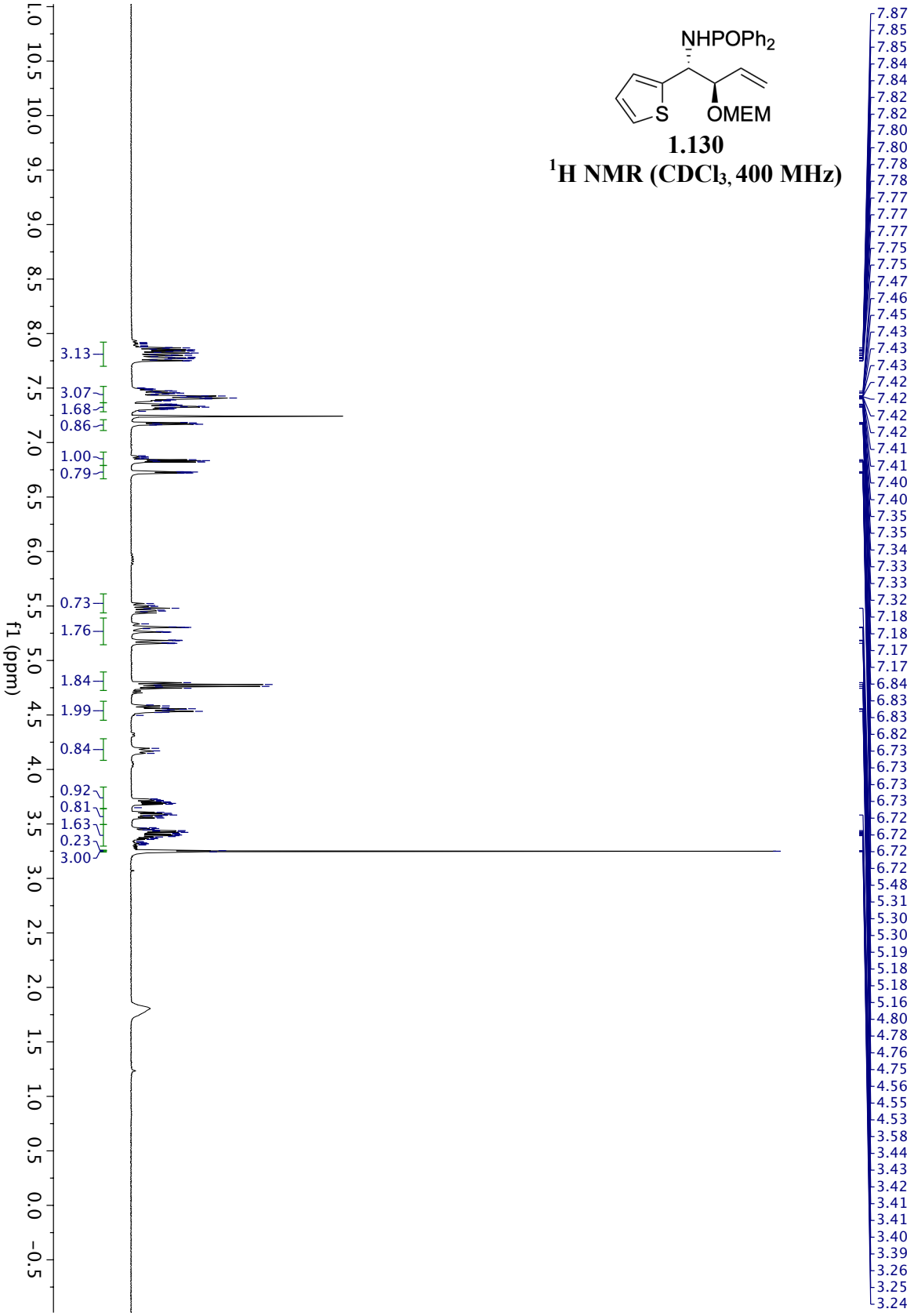

NHPOPh2
O
OMEM
1.127
13C NMR (CDCl3, 100 MHz)
133.77
133.14
132.74
132.64
132.47
132.11
132.02
131.96
131.93
131.84
128.61
128.53
128.49
128.40
142.77
140.64
135.20
133.77
133.14
132.74
132.64
132.47
132.11
132.02
131.96
131.93
131.84
128.61
128.53
128.49
128.40
124.18
119.35
110.59
94.21
82.46
82.42
71.78
67.76
59.03
50.94
f1 (ppm)

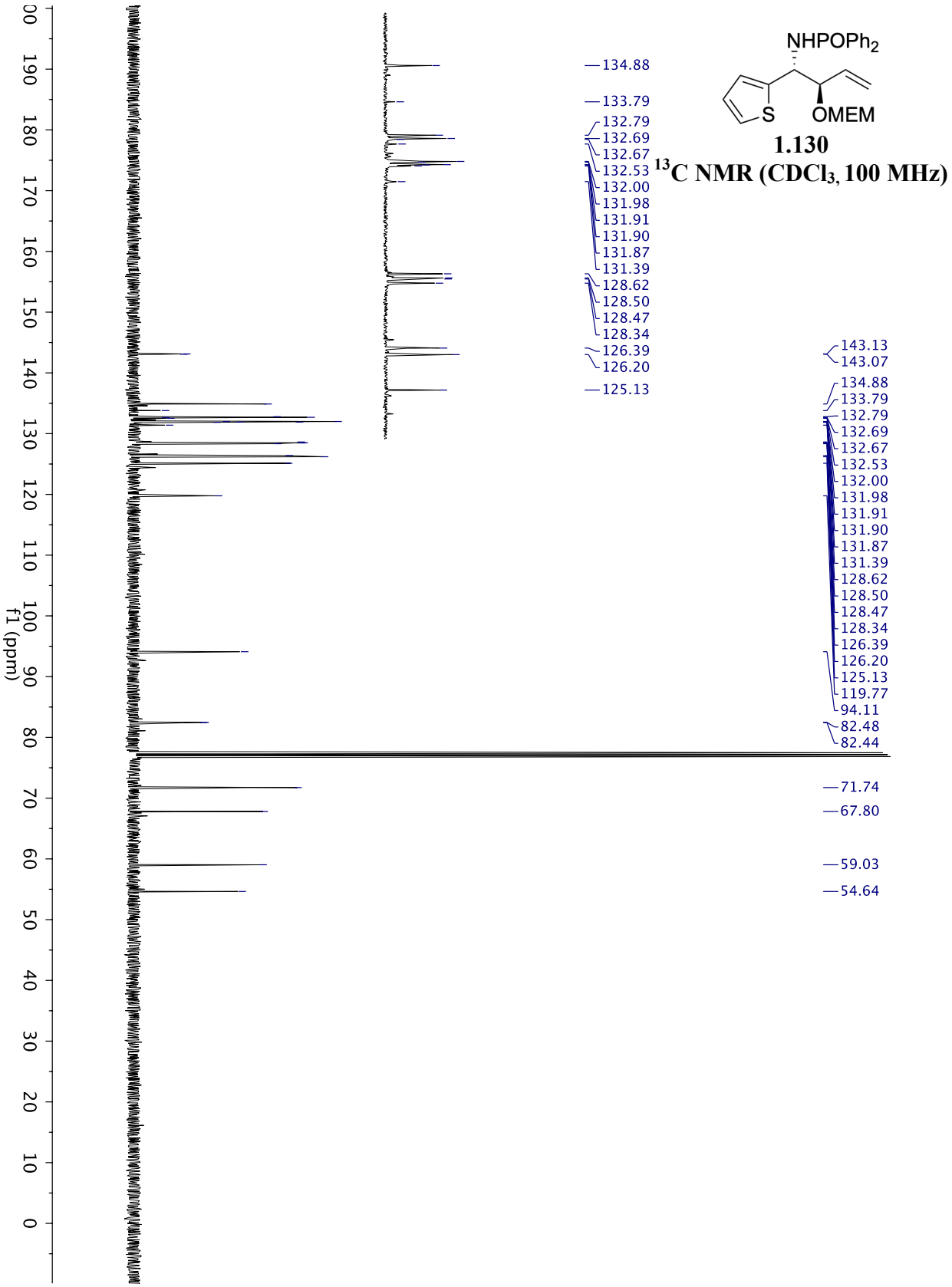

NHPOPh2
O
OMEM
1.128
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.81
4.78
0.97
1.44
1.05
1.00
1.86
2.18
1.21
1.03
1.06
0.95
0.91
2.00
0.34
3.09

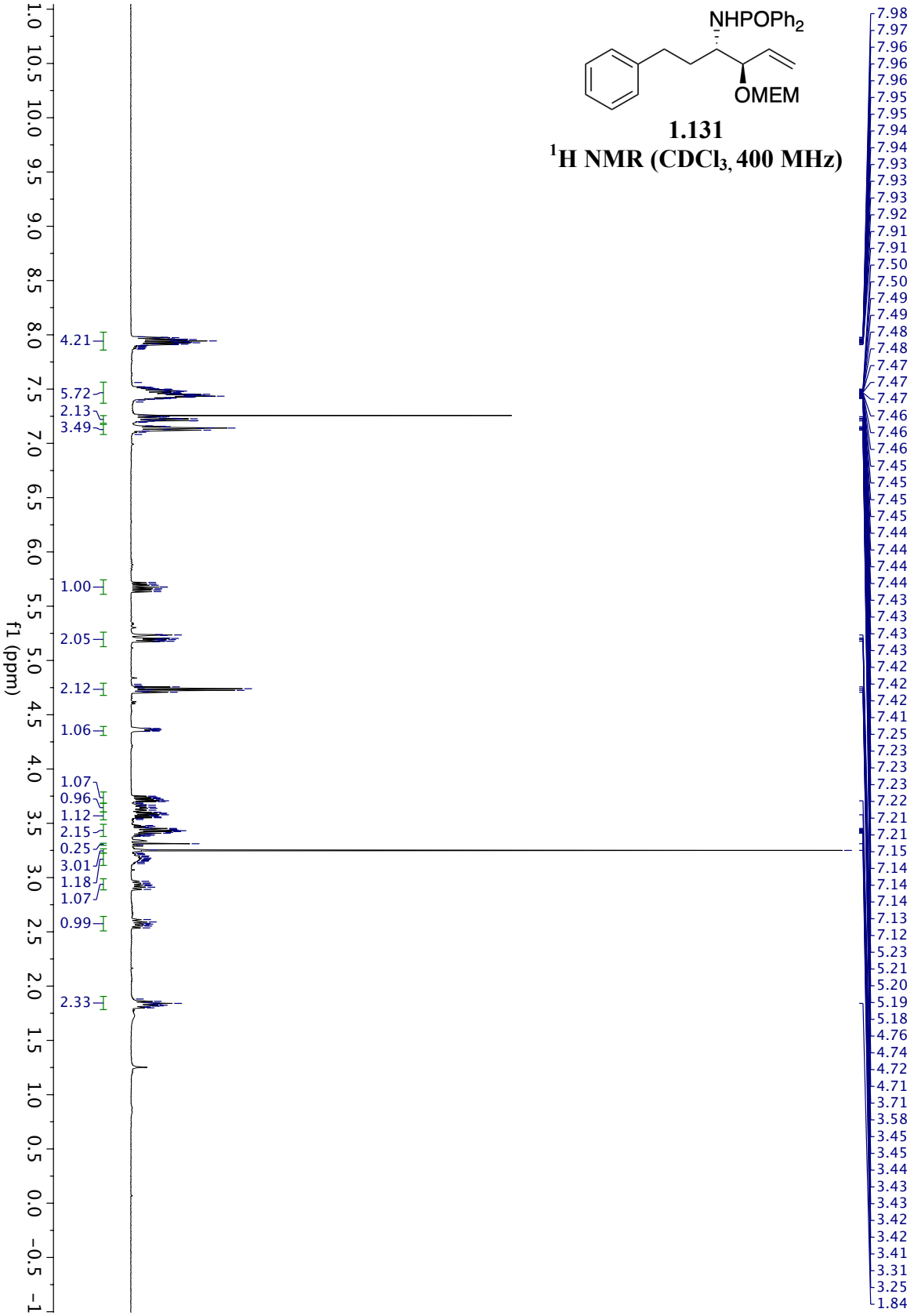

NHPOPh2
O
OMEM
1.128
13C NMR (CDCl3, 100 MHz)
135.01
134.58
133.56
132.92
132.56
132.46
132.29
131.84
131.79
131.76
131.62
142.60
140.45
135.01
134.58
133.56
132.92
132.56
132.46
132.29
131.84
131.79
131.76
131.62
128.44
128.36
128.31
128.23
124.05
123.99
119.20
110.40
94.02
82.27
82.23
71.60
67.58
58.85
50.76
f1 (ppm)

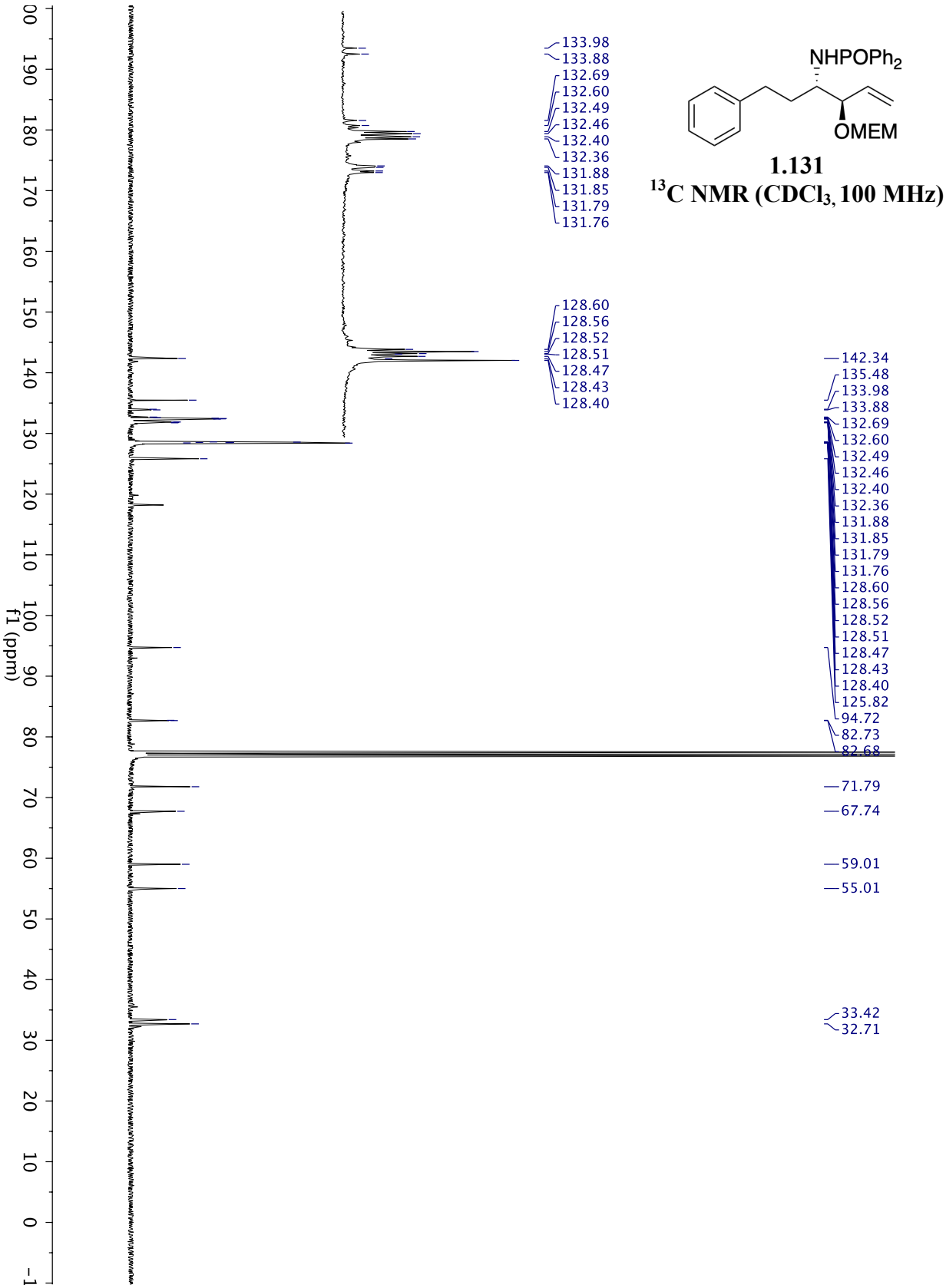

NHPOPh2
S
OMEM
1.129
1H NMR (CDCl3, 500 MHz)
f1 (ppm)
2.21
2.14
1.22
2.97
2.07
0.97
2.08
1.00
2.14
2.04
1.12
1.22
0.97
1.04
1.16
2.30
3.12
0.30

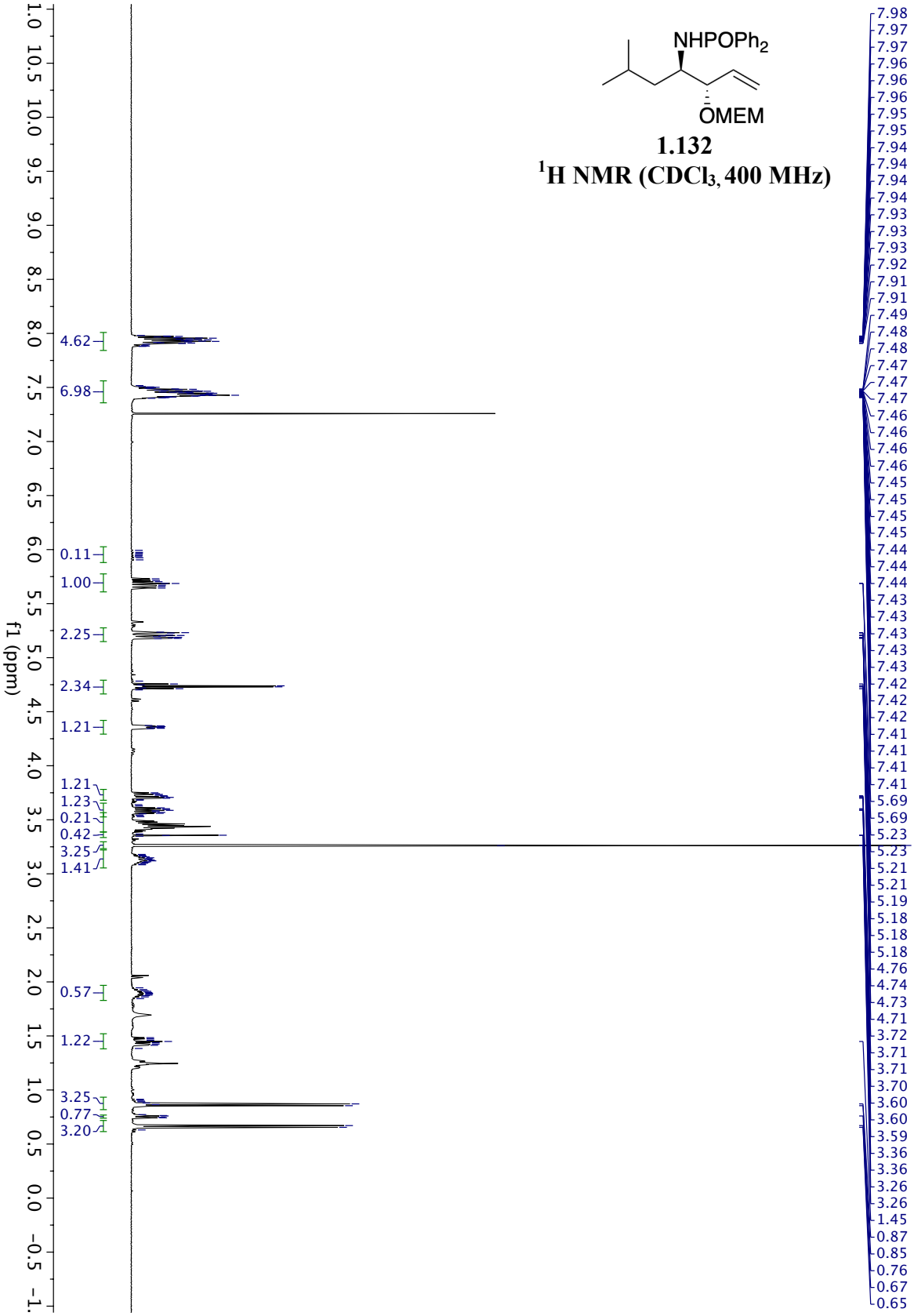

NHPOPh2
S
OMEM
1.129
1H NMR (CDCl3, 100 MHz)
133.77
132.91
132.74
132.64
132.50
132.05
131.96
131.93
131.88
131.85
131.61
128.61
128.48
128.35
127.65
140.99
140.94
135.14
133.77
132.91
132.74
132.64
132.50
132.05
131.96
131.93
131.88
131.85
131.61
128.61
128.48
128.35
127.65
125.29
122.93
119.49
93.99
82.27
82.22
71.78
67.69
59.03
54.42
f1 (ppm)

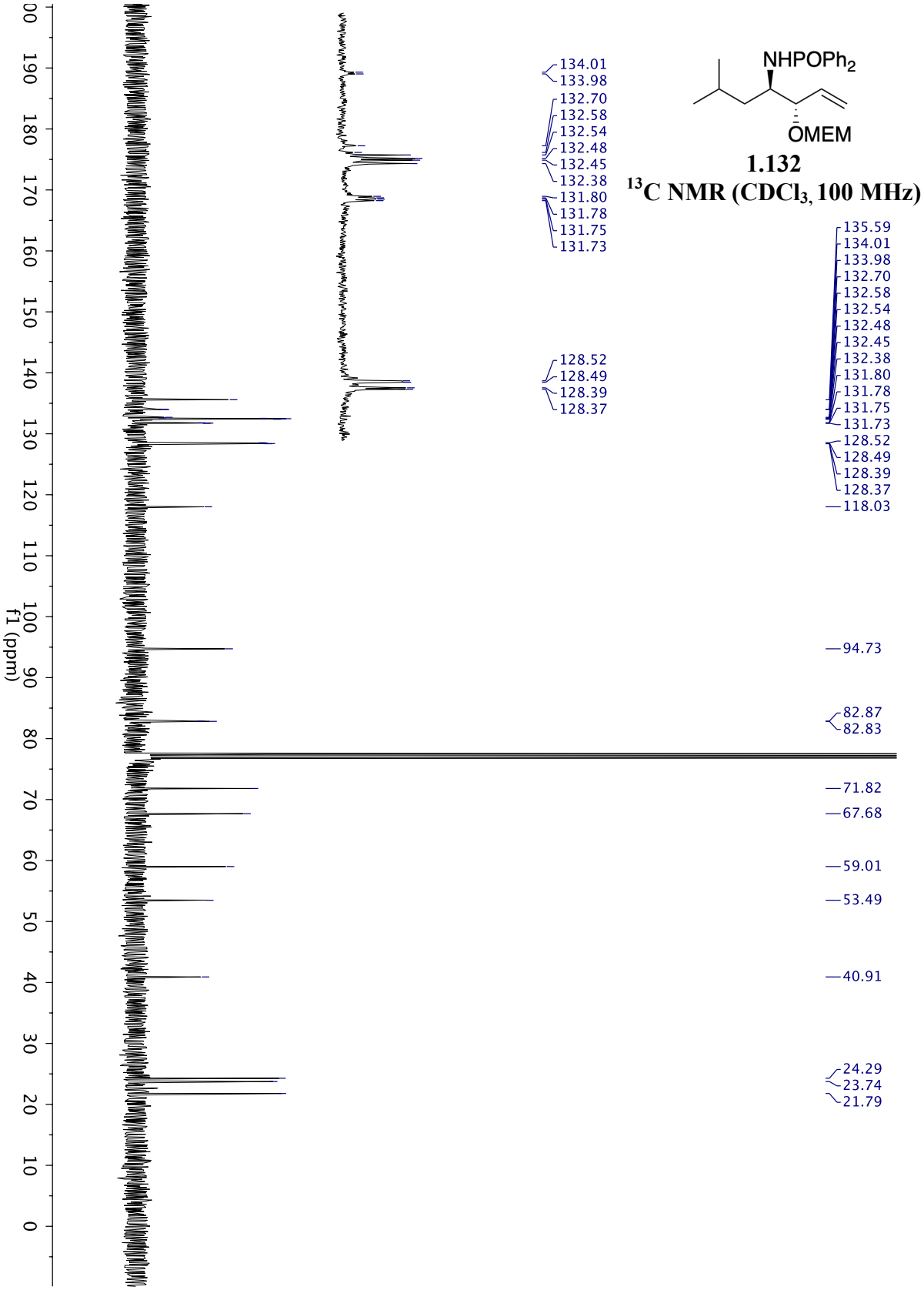

NHPOPh2
S
OMEM
1.130
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
3.13
3.07
1.68
0.86
1.00
0.79
0.73
1.76
1.84
1.99
0.84
0.92
0.81
1.63
0.23
3.00

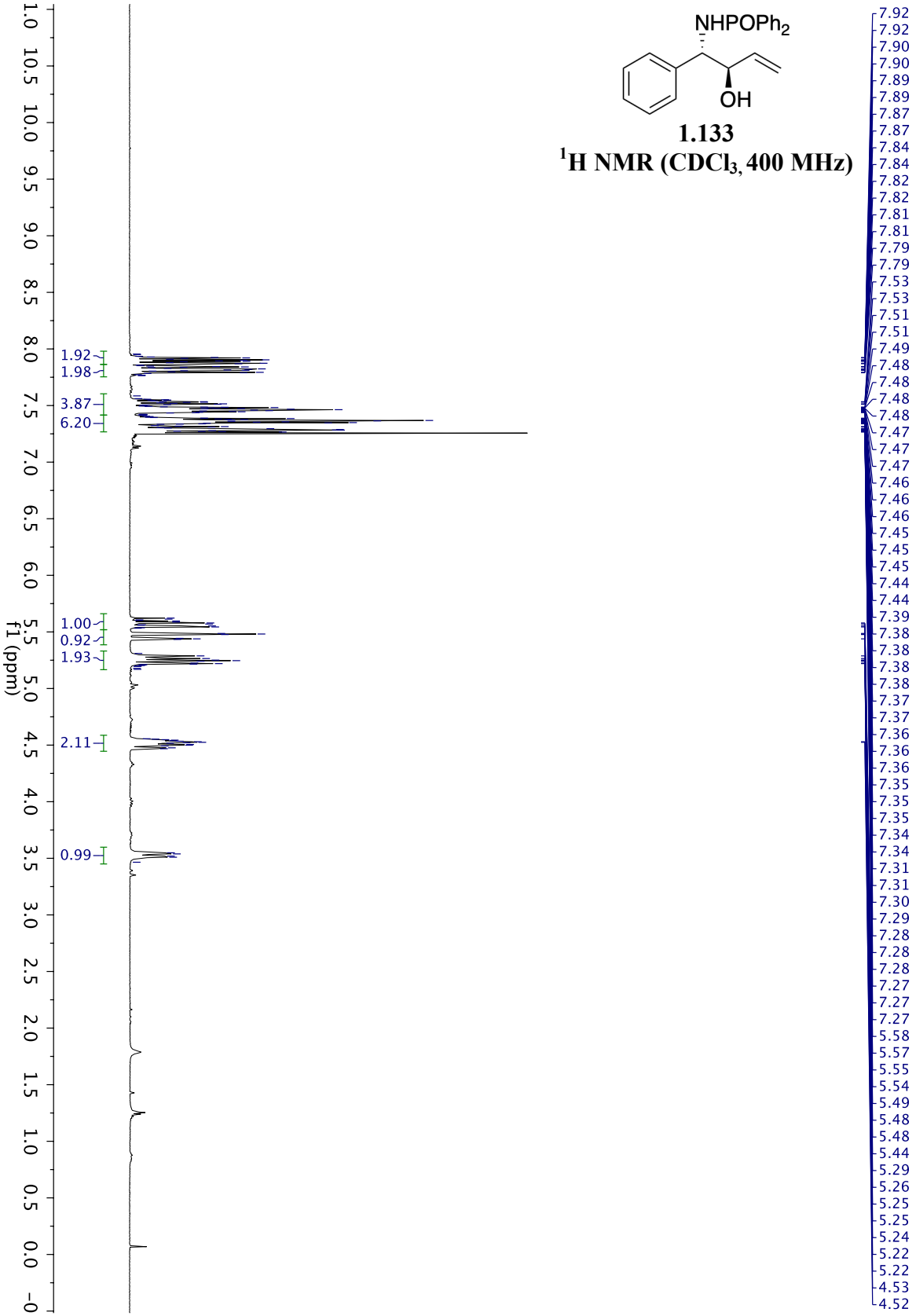

NHPOPh2
S
OMEM
1.130
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
134.88
133.79
132.79
132.69
132.67
132.53
132.00
131.98
131.91
131.90
131.87
131.39
128.62
128.50
128.47
128.34
126.39
126.20
125.13
143.13
143.07
71.74
67.80
59.03
54.64
119.77
94.11
82.48
82.44

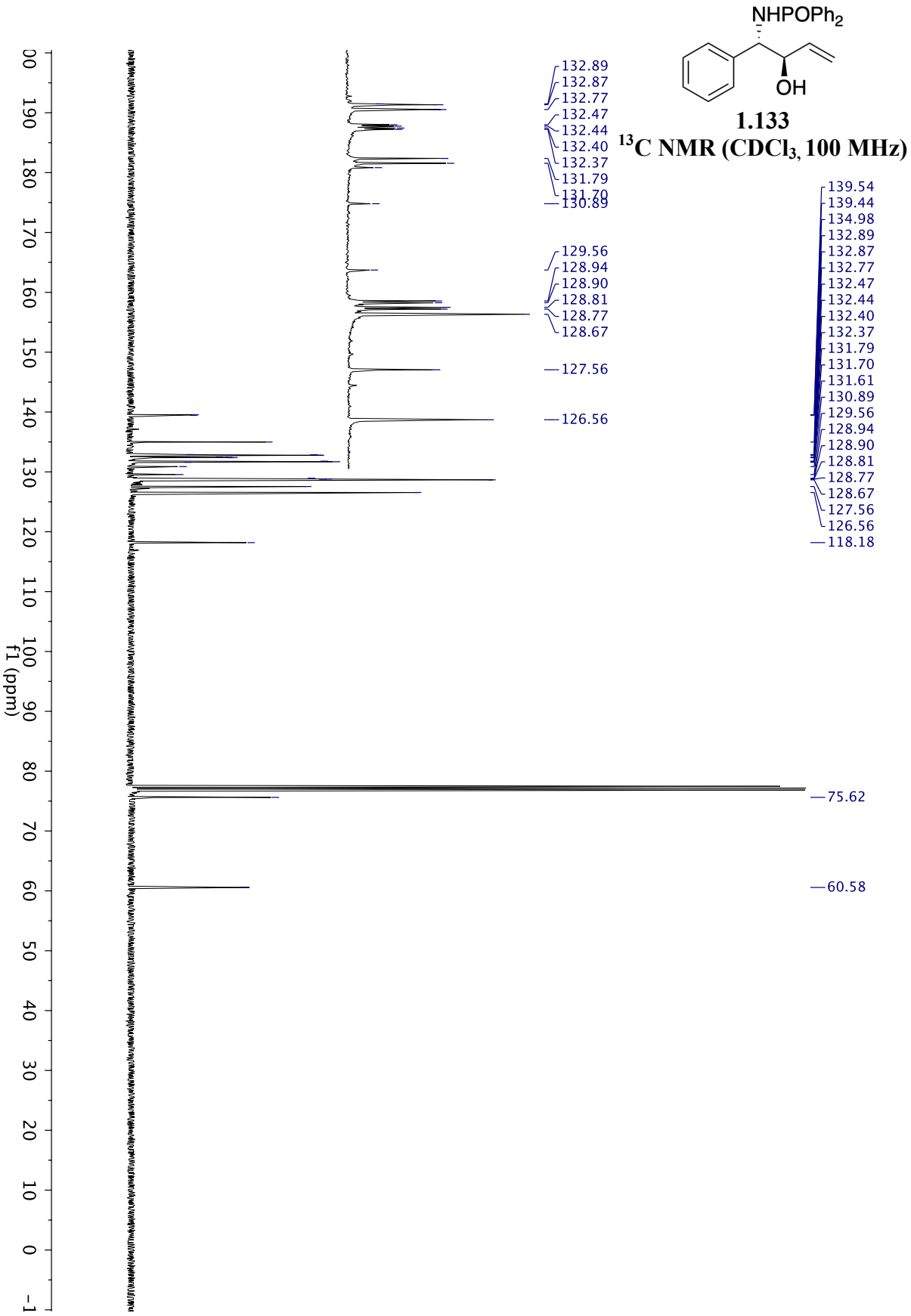

NHPOPh2
OMEM
1.131
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.21
5.72
2.13
3.49
1.00
2.05
2.12
1.06
1.07
0.96
1.12
2.15
0.25
3.01
1.18
1.07
0.99
2.33

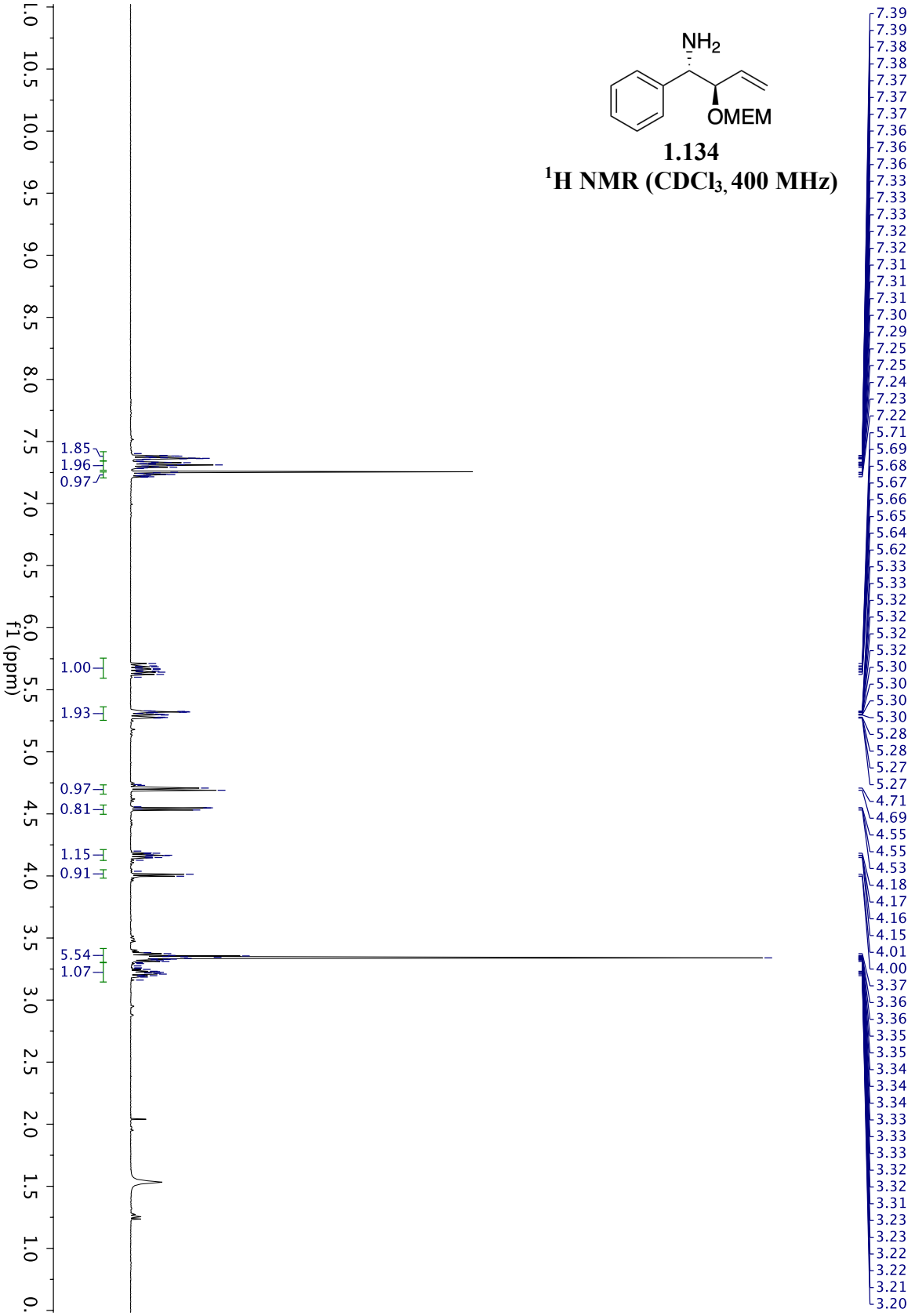

NHPOPh2
OMEM
1.131
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
133.98
133.88
132.69
132.60
132.49
132.46
132.40
132.36
131.88
131.85
131.79
131.76
128.60
128.56
128.52
128.51
128.47
128.43
128.40
142.34
135.48
133.98
133.88
132.69
132.60
132.49
132.46
132.40
132.36
131.88
131.85
131.79
131.76
128.60
128.56
128.52
128.51
128.47
128.43
128.40
125.82
94.72
82.73
82.68
71.79
67.74
59.01
55.01
33.42
32.71

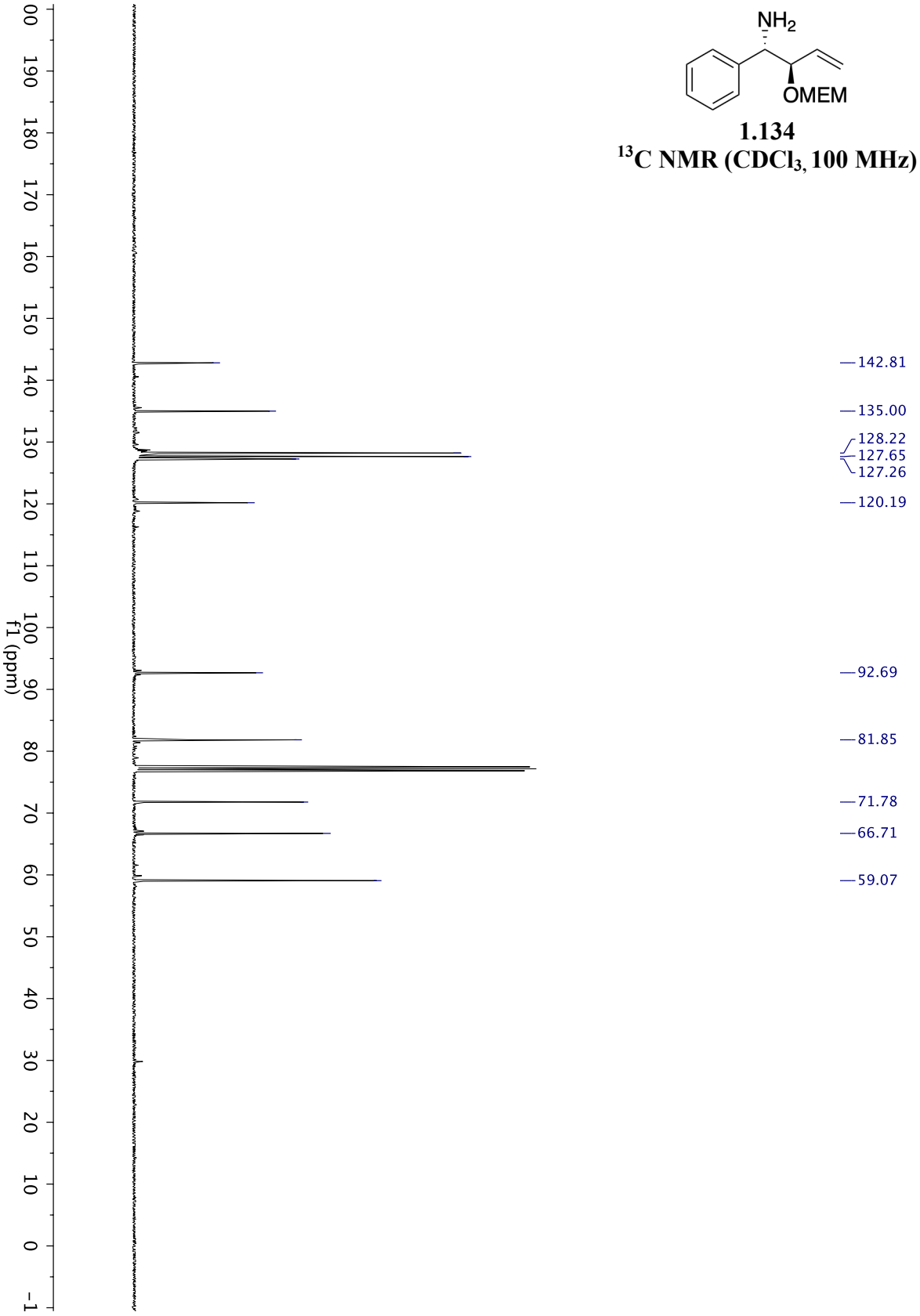

NHPOPh2
OMEM
1.132
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.62
6.98
0.11
1.00
2.25
2.34
1.21
1.21
1.23
0.21
0.42
3.25
1.41
0.57
1.22
3.25
0.77
3.20


NHPOPh2
OMEM
1.132
13C NMR (CDCl3, 100 MHz)
134.01
133.98
132.70
132.58
132.54
132.48
132.45
132.38
131.80
131.78
131.75
131.73
128.52
128.49
128.39
128.37
135.59
118.03
94.73
82.87
82.83
71.82
67.68
59.01
53.49
40.91
24.29
23.74
21.79
f1 (ppm)


NHPOPh2
OH
1.133
1H NMR (CDCl3, 400 MHz)
1.92
1.98
3.87
6.20
1.00
0.92
1.93
2.11
0.99
f1 (ppm)

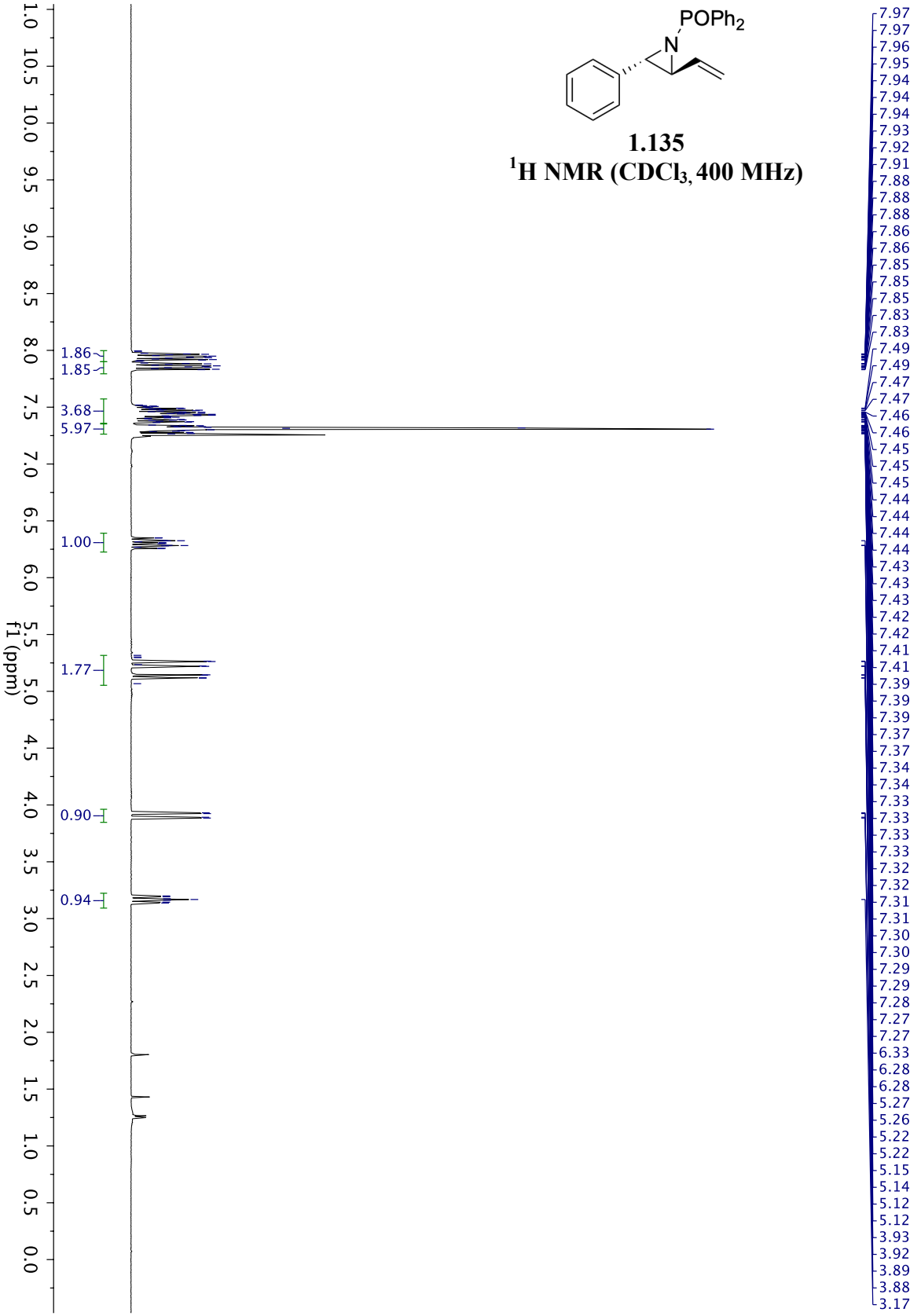

NHPOPh2
OH
1.133
13C NMR (CDCl3, 100 MHz)
132.89
132.87
132.77
132.47
132.44
132.40
132.37
131.79
131.70
130.89
129.56
128.94
128.90
128.81
128.77
128.67
127.56
126.56
139.54
139.44
134.98
132.89
132.87
132.77
132.47
132.44
132.40
132.37
131.79
131.70
131.61
130.89
129.56
128.94
128.90
128.81
128.77
128.67
127.56
126.56
118.18
75.62
60.58
f1 (ppm)

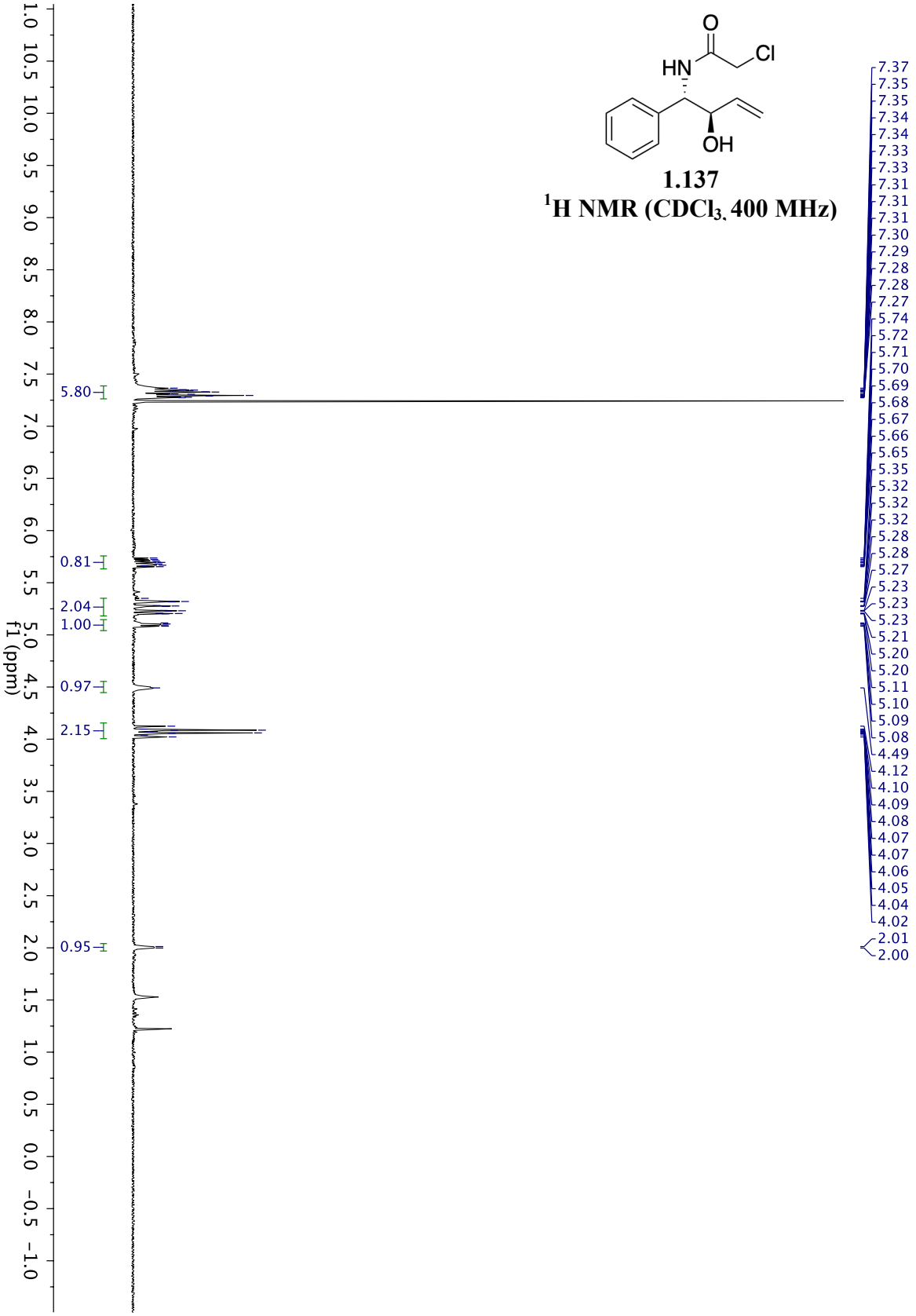

NH2
OMEM
1.134
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.85
1.96
0.97
1.00
1.93
0.97
0.81
1.15
0.91
5.54
1.07

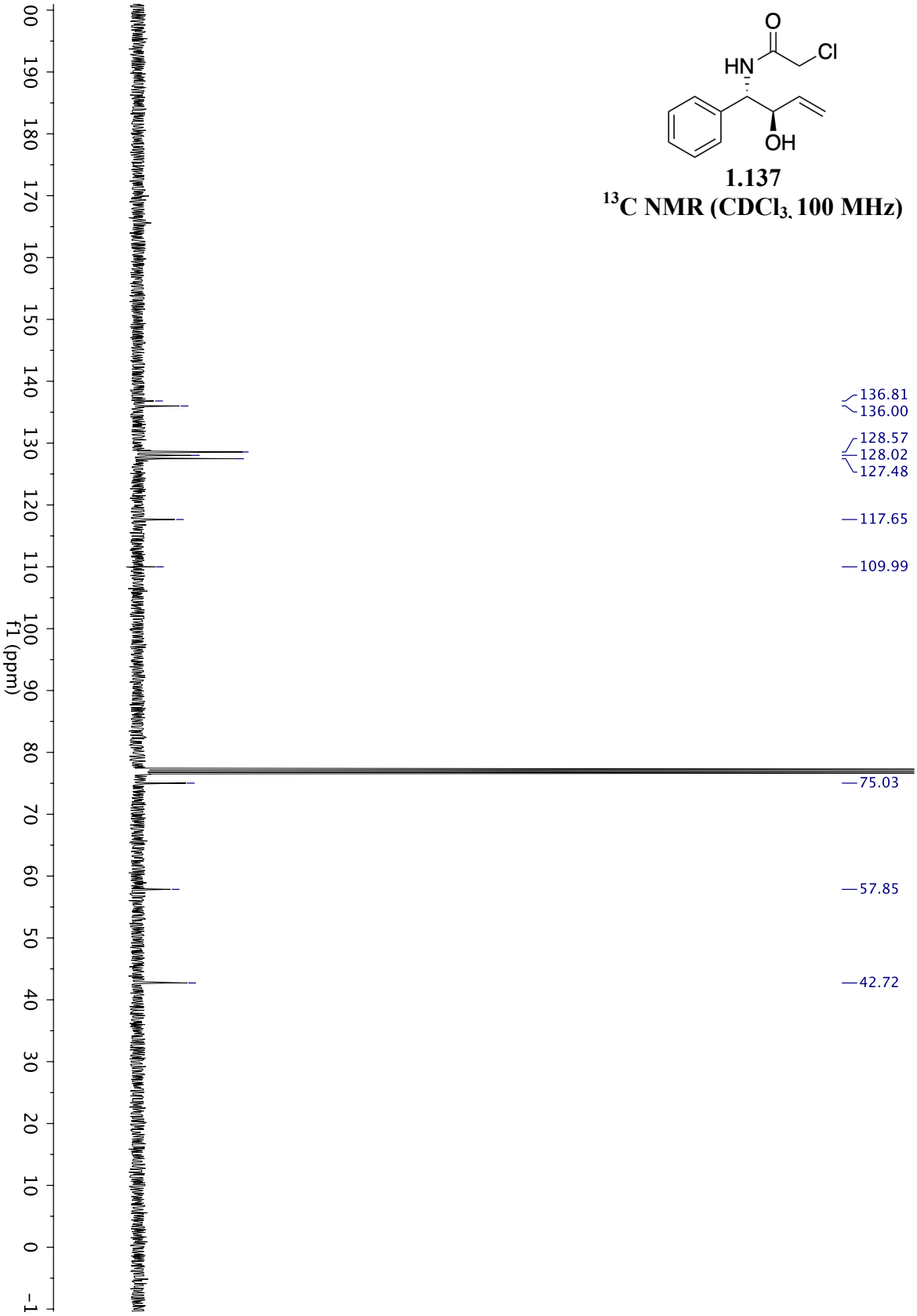


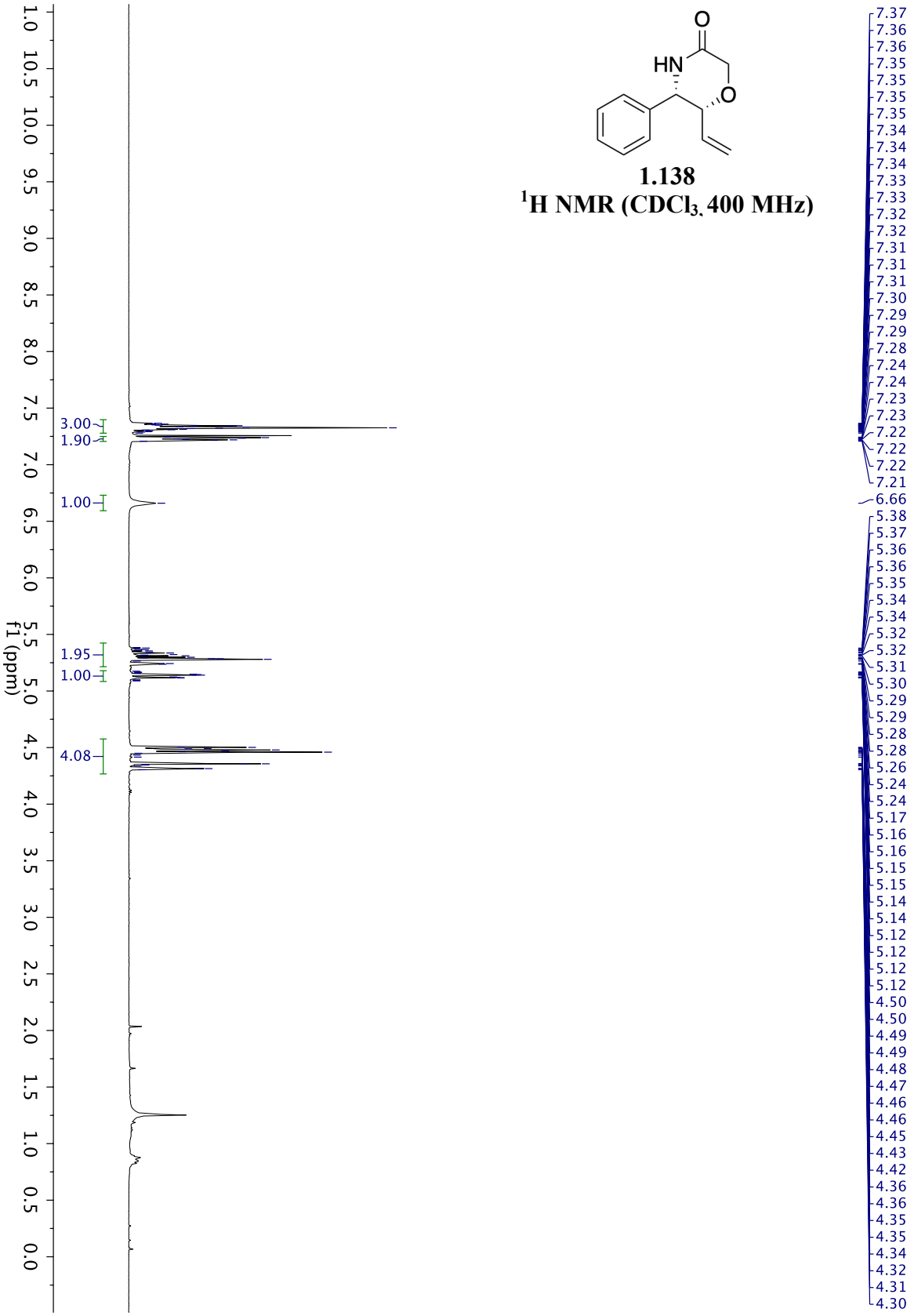
1.134

^{13}C NMR ($CDCl_3$, 100 MHz)


POPh2
N
1.135
1H NMR (CDCl3, 400 MHz)
1.86
1.85
3.68
5.97
1.00
1.77
0.90
0.94
f1 (ppm)

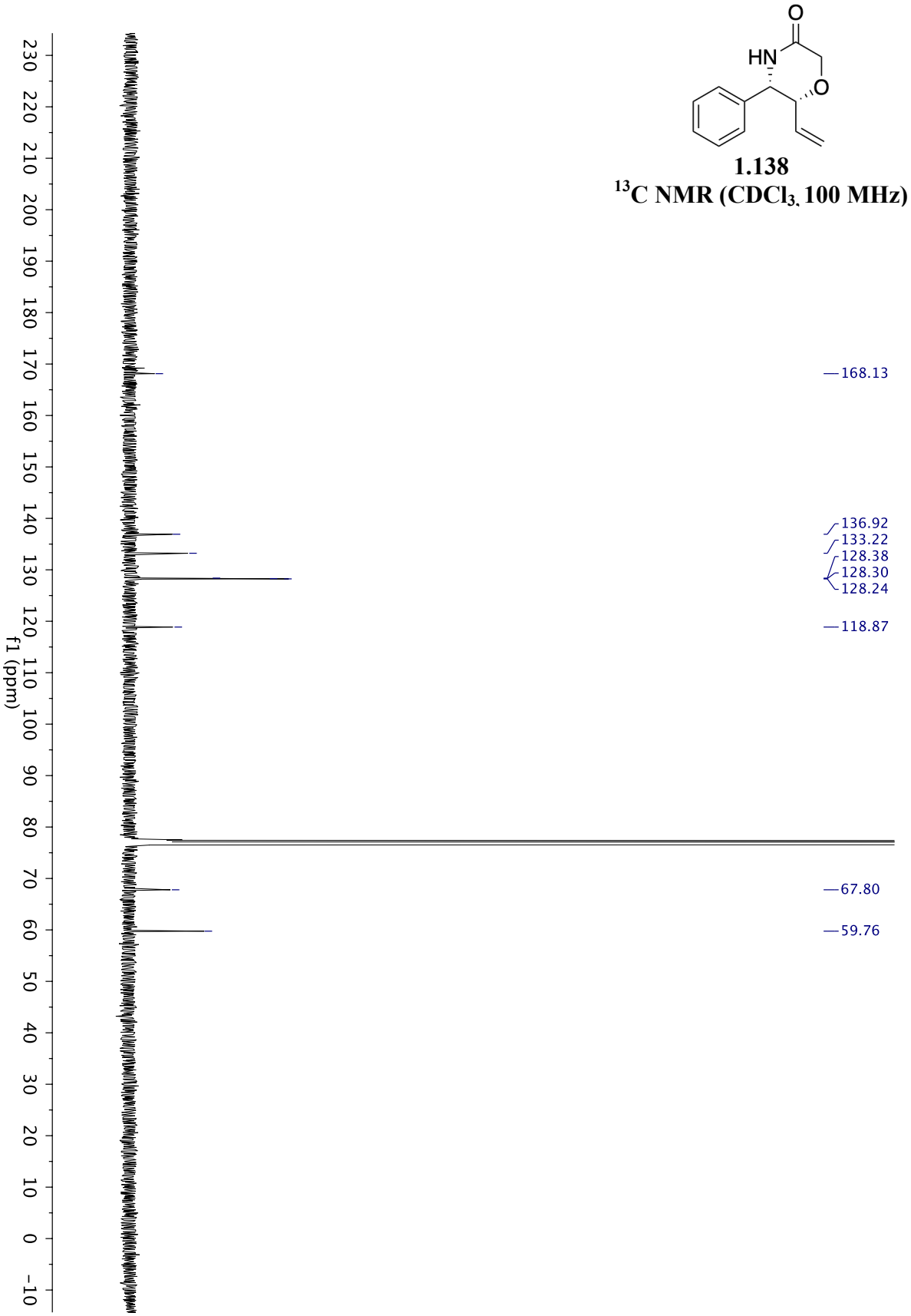

O
HN
Cl
OH
1.137
1H NMR (CDCl3, 400 MHz)
7.37
7.35
7.35
7.34
7.34
7.33
7.33
7.31
7.31
7.31
7.30
7.29
7.28
7.28
7.27
5.74
5.72
5.71
5.70
5.69
5.68
5.67
5.66
5.65
5.35
5.32
5.32
5.32
5.28
5.28
5.27
5.23
5.23
5.23
5.21
5.20
5.20
5.11
5.10
5.09
5.08
4.49
4.12
4.10
4.09
4.08
4.07
4.07
4.06
4.05
4.04
4.02
2.01
2.00
5.80
0.81
2.04
1.00
0.97
2.15
0.95
f1 (ppm)

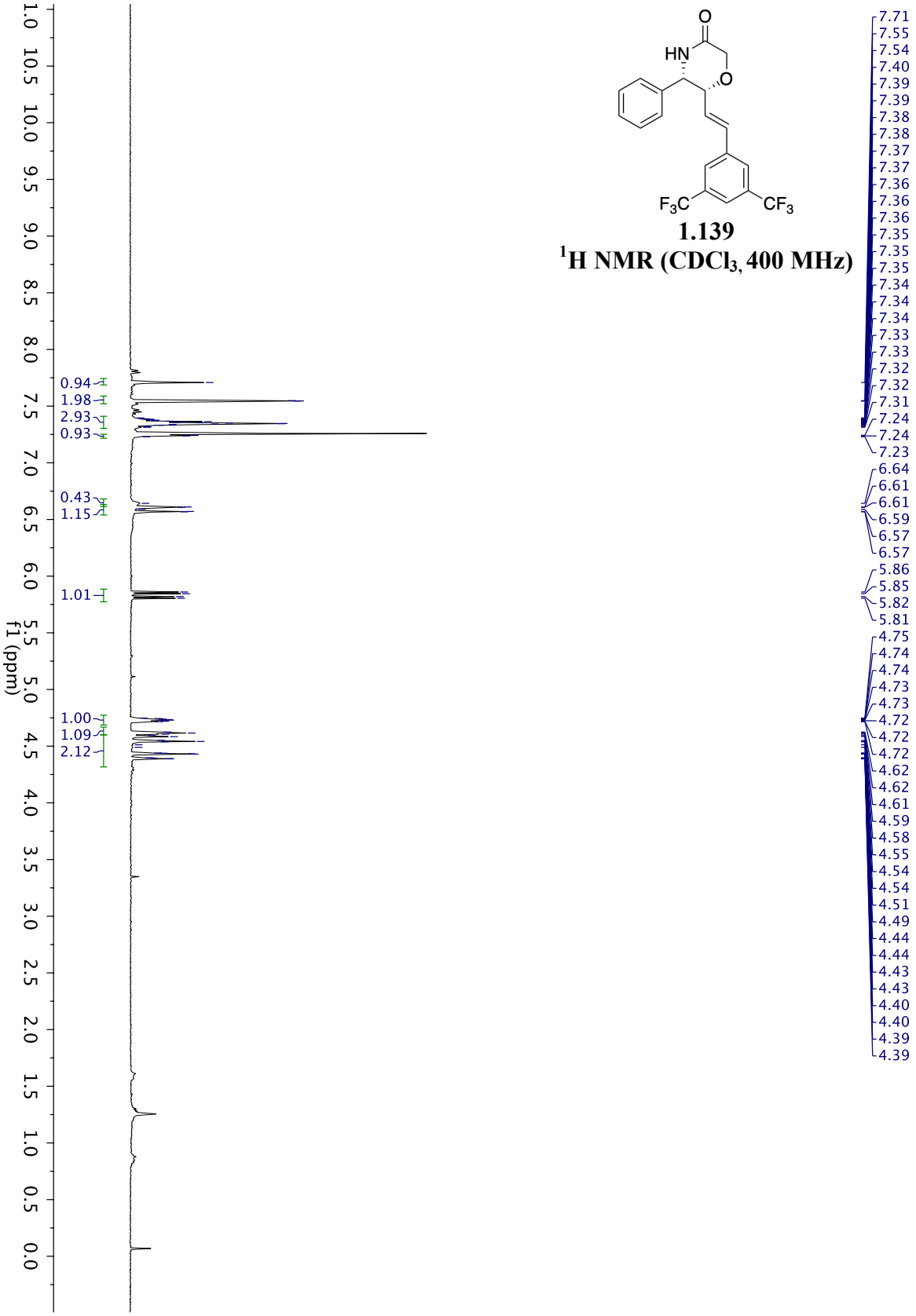

O
HN
Cl
OH
1.137
13C NMR (CDCl3, 100 MHz)
136.81
136.00
128.57
128.02
127.48
117.65
109.99
75.03
57.85
42.72
f1 (ppm)

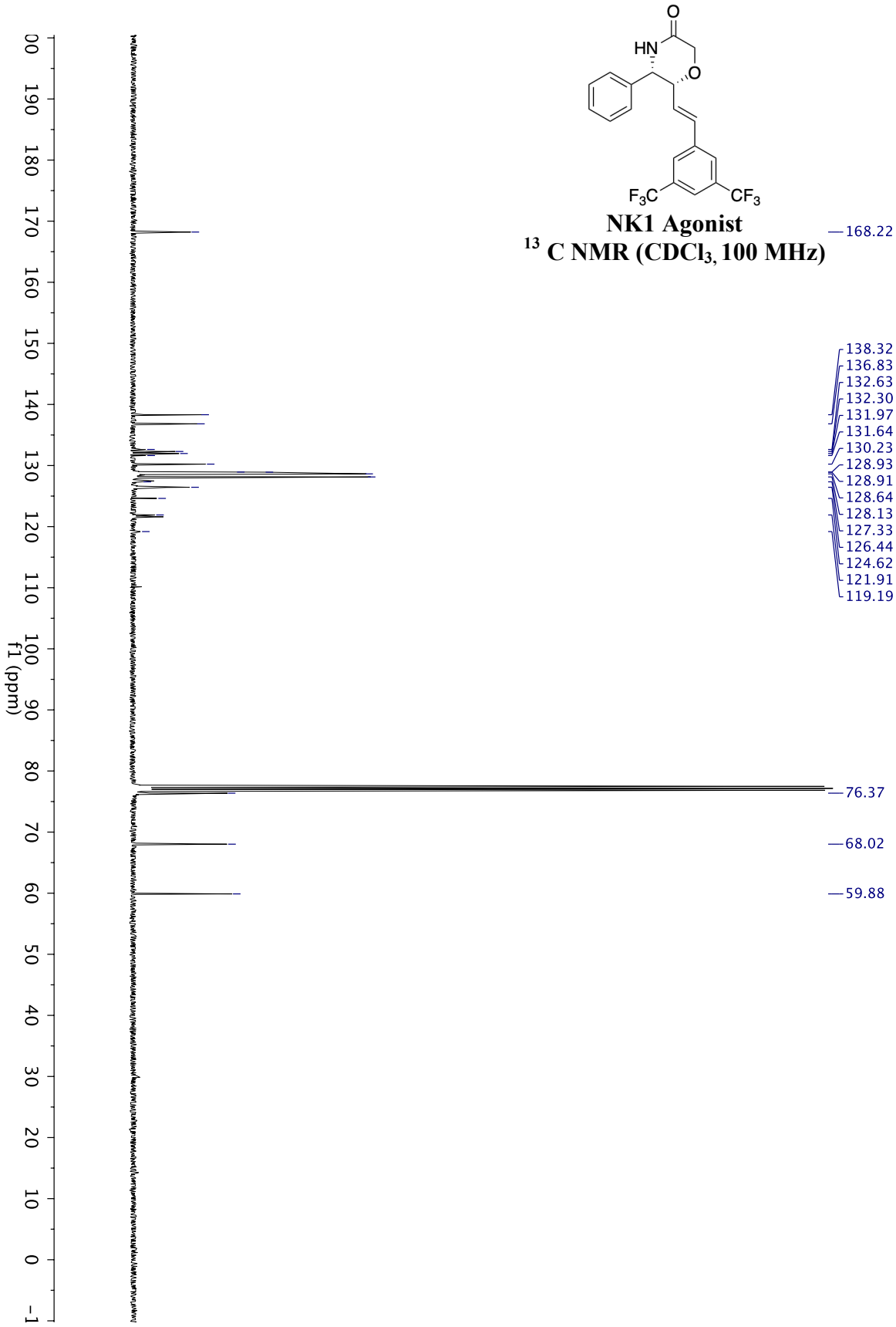


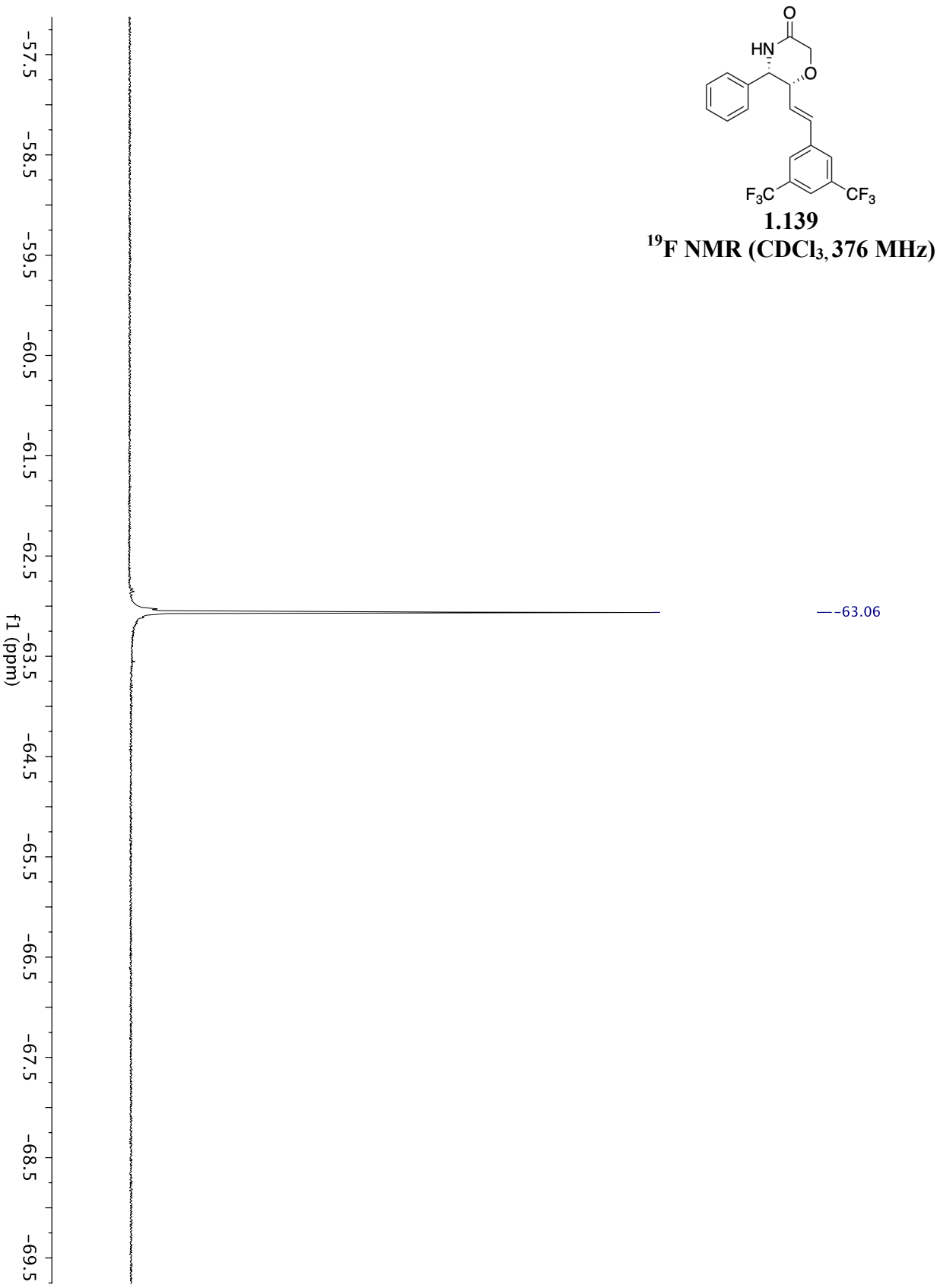
1.138

^{1}H NMR ($CDCl_3$, 400 MHz)


O
HN
O
1.138
13C NMR (CDCl3, 100 MHz)
168.13
136.92
133.22
128.38
128.30
128.24
118.87
67.80
59.76
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

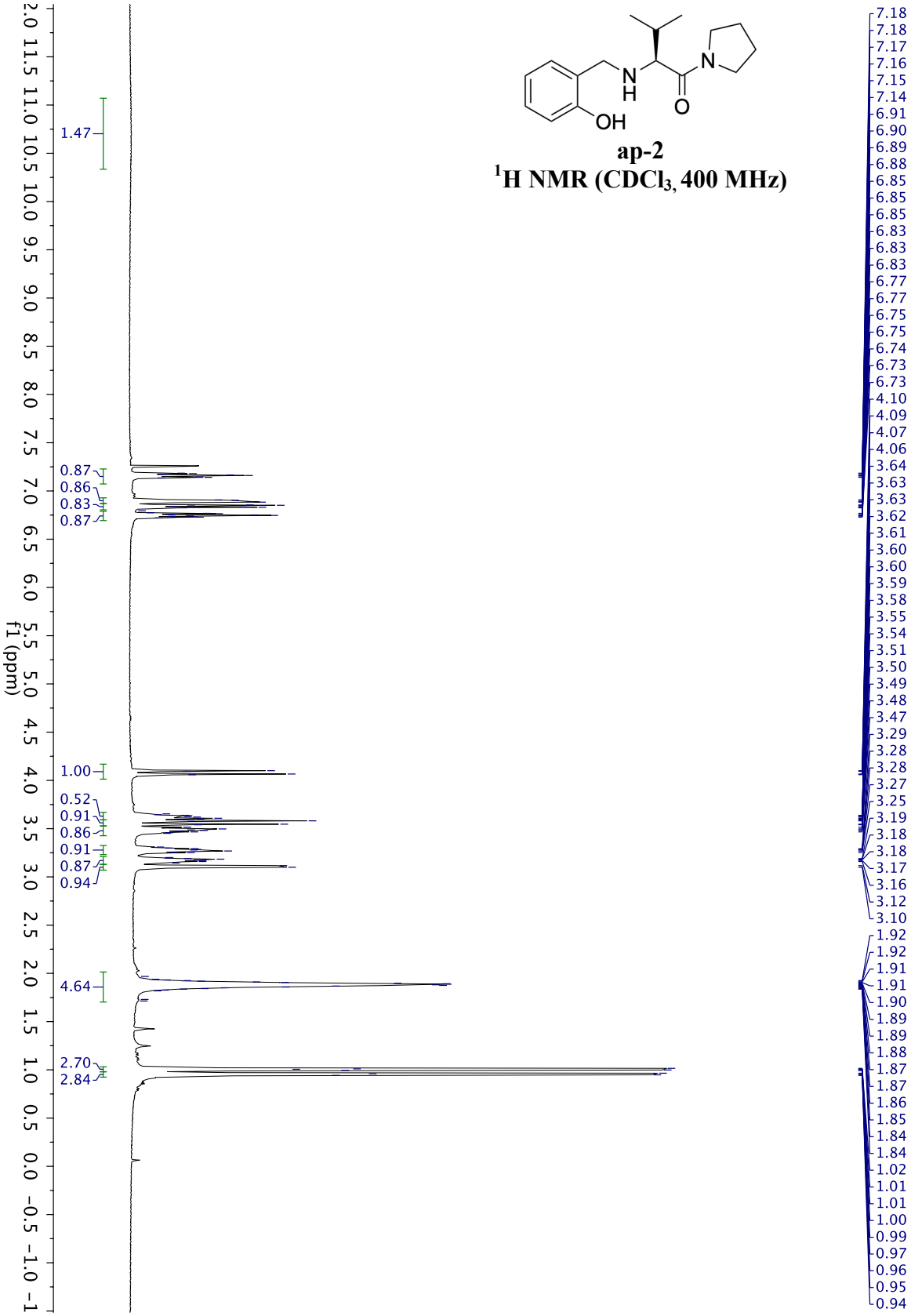

O
HN
O
F3C
CF3
1.139
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.94
1.98
2.93
0.93
0.43
1.15
1.01
1.00
1.09
2.12
7.71
7.55
7.54
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.36
7.35
7.35
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.24
7.24
7.23
6.64
6.61
6.61
6.59
6.57
6.57
5.86
5.85
5.82
5.81
4.75
4.74
4.74
4.73
4.73
4.72
4.72
4.72
4.62
4.62
4.61
4.59
4.58
4.55
4.54
4.54
4.51
4.49
4.44
4.44
4.43
4.43
4.40
4.40
4.39
4.39

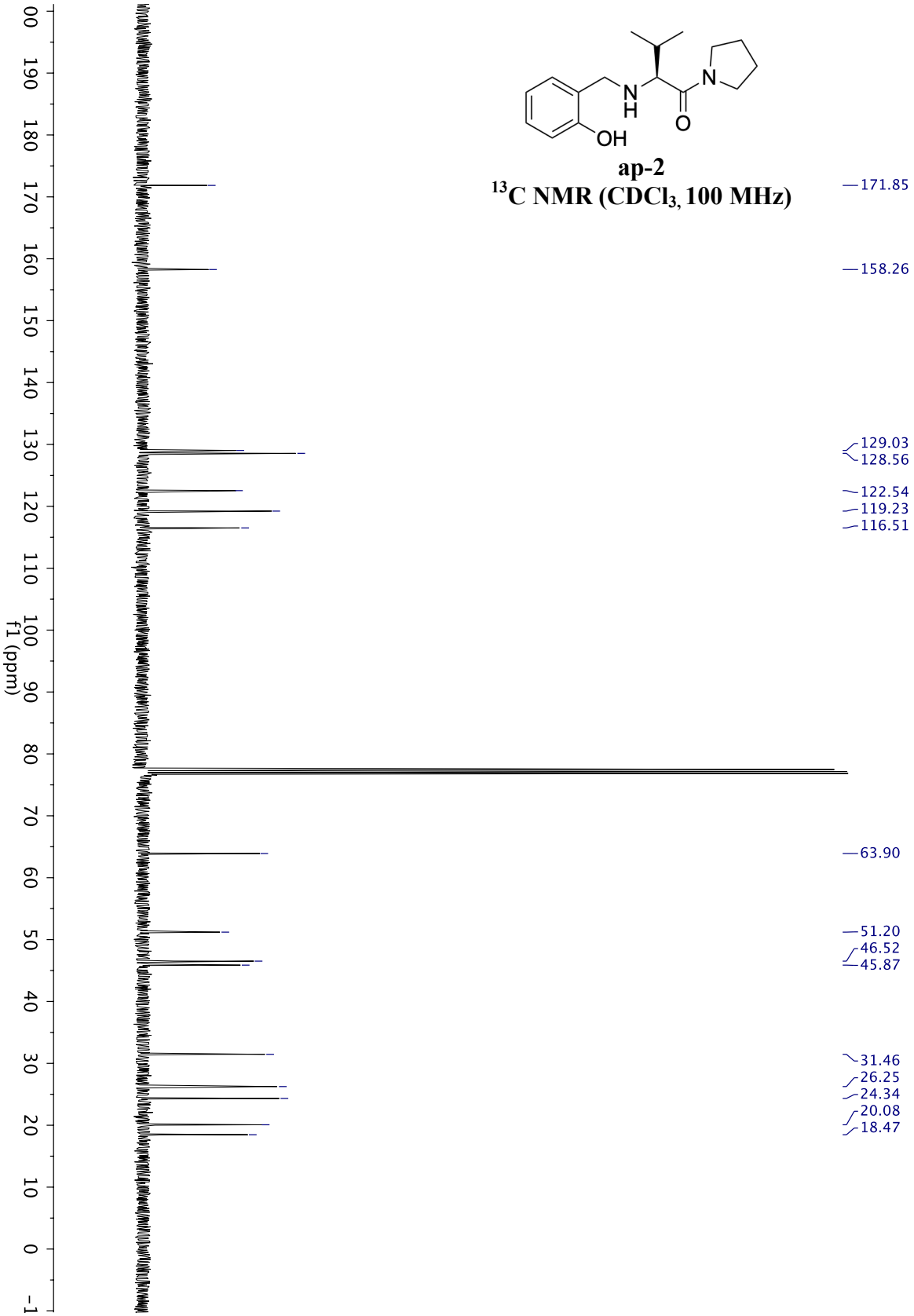

O
HN
O
F3C
CF3
NK1 Agonist
13 C NMR (CDCl3, 100 MHz)
168.22
138.32
136.83
132.63
132.30
131.97
131.64
130.23
128.93
128.91
128.64
128.13
127.33
126.44
124.62
121.91
119.19
76.37
68.02
59.88
f1 (ppm)

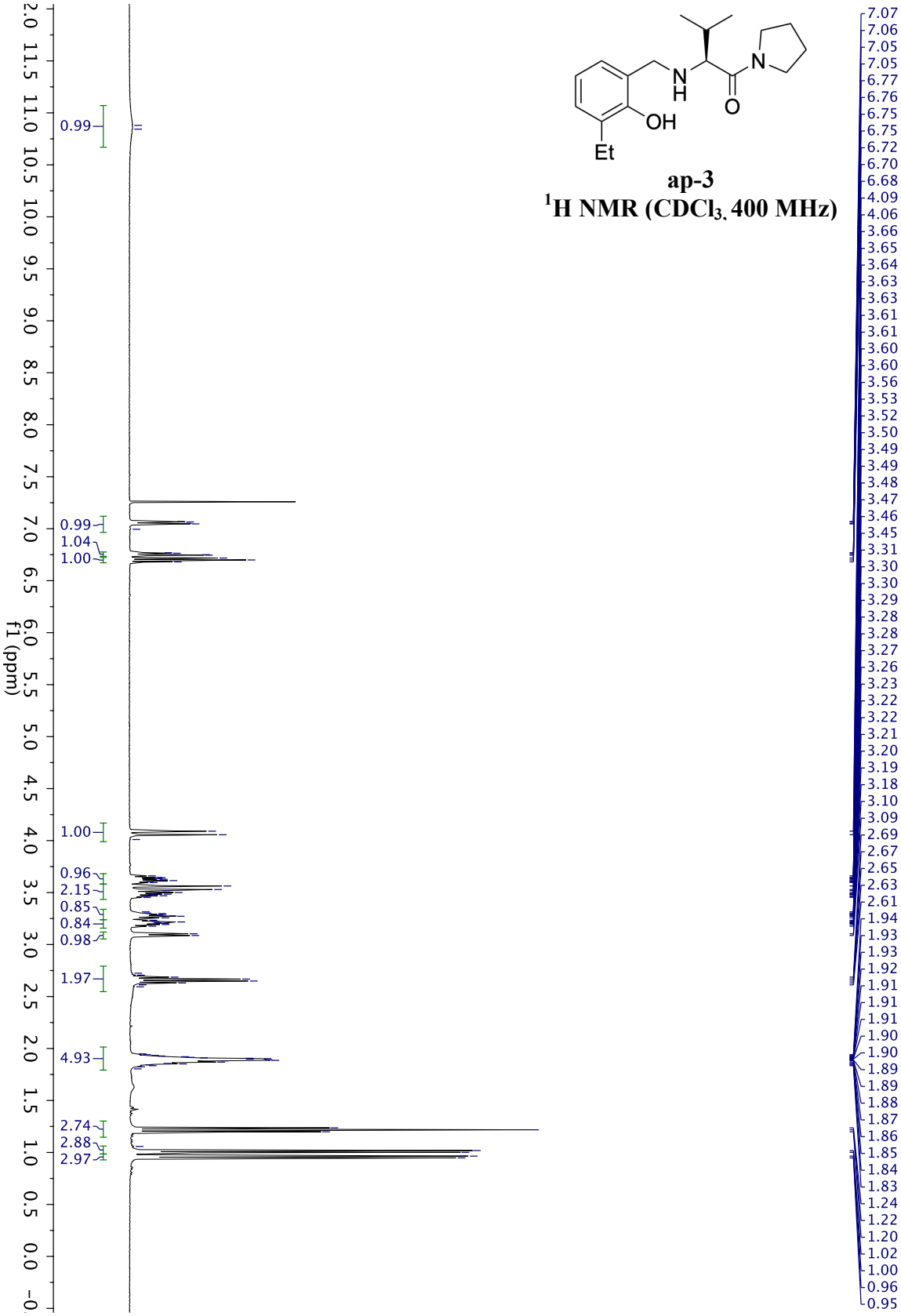


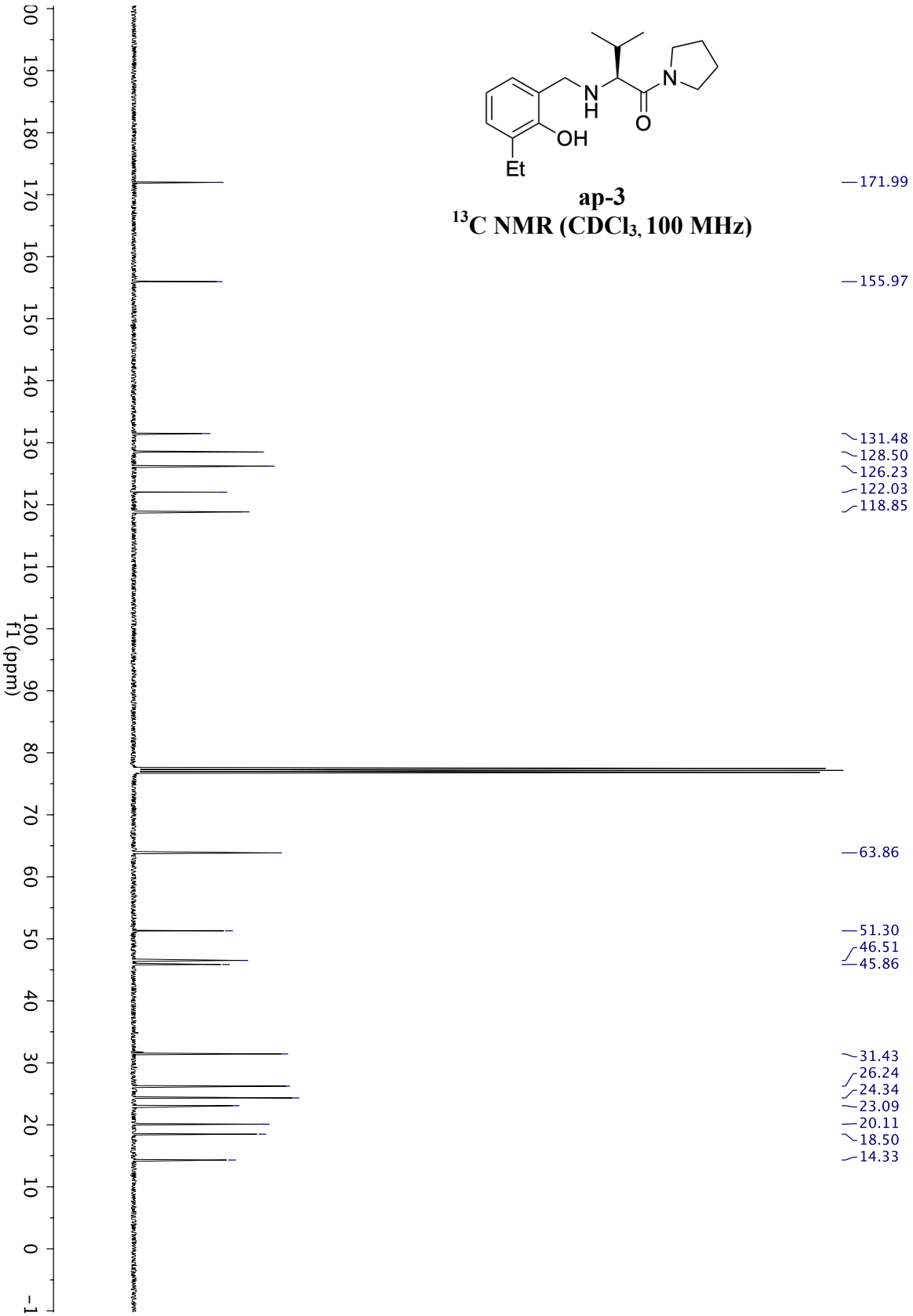
1.139

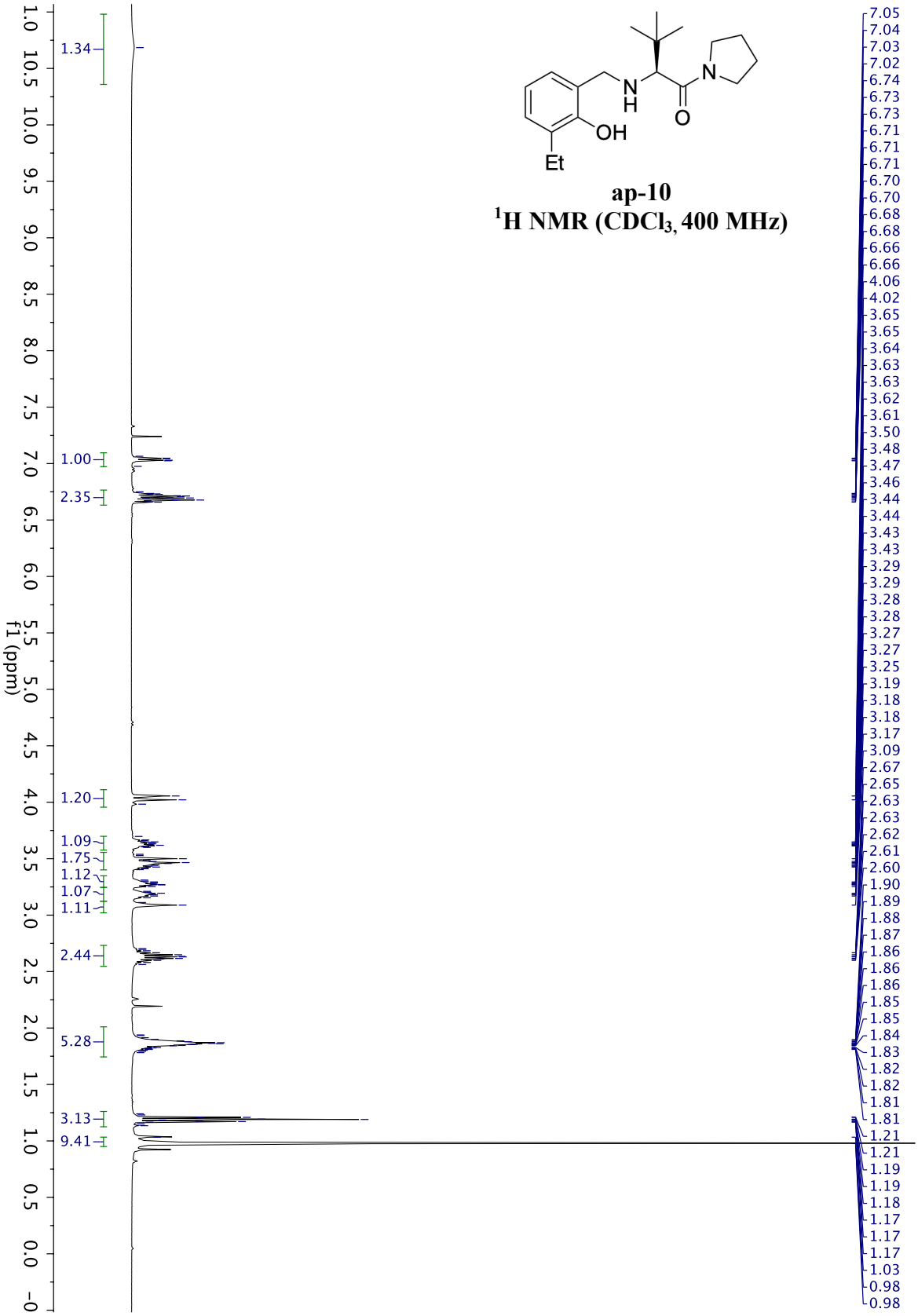
^{19}F NMR ($CDCl_3$, 376 MHz)

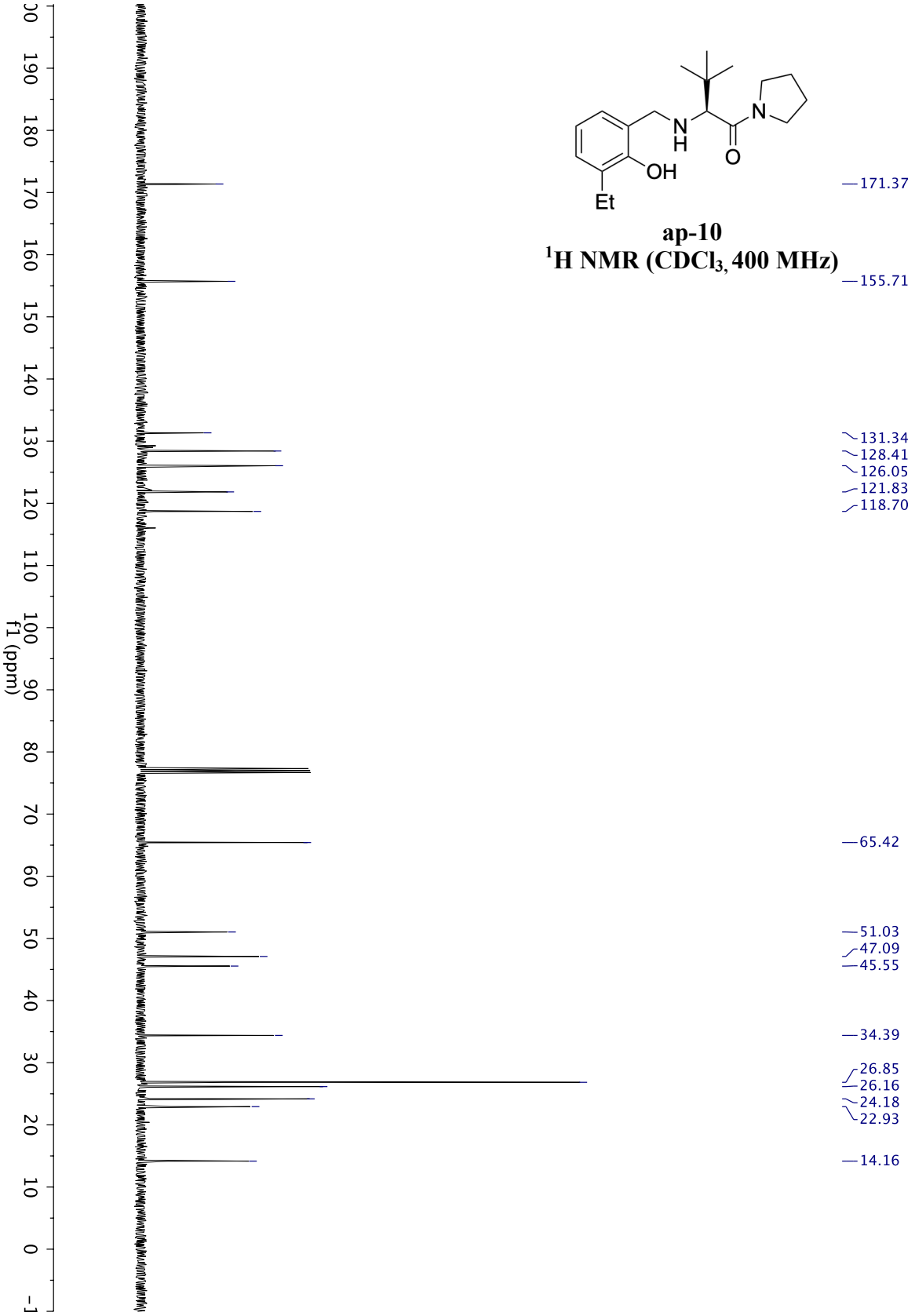

ap-2
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.47
0.87
0.86
0.83
0.87
1.00
0.52
0.91
0.86
0.91
0.87
0.94
4.64
2.70
2.84

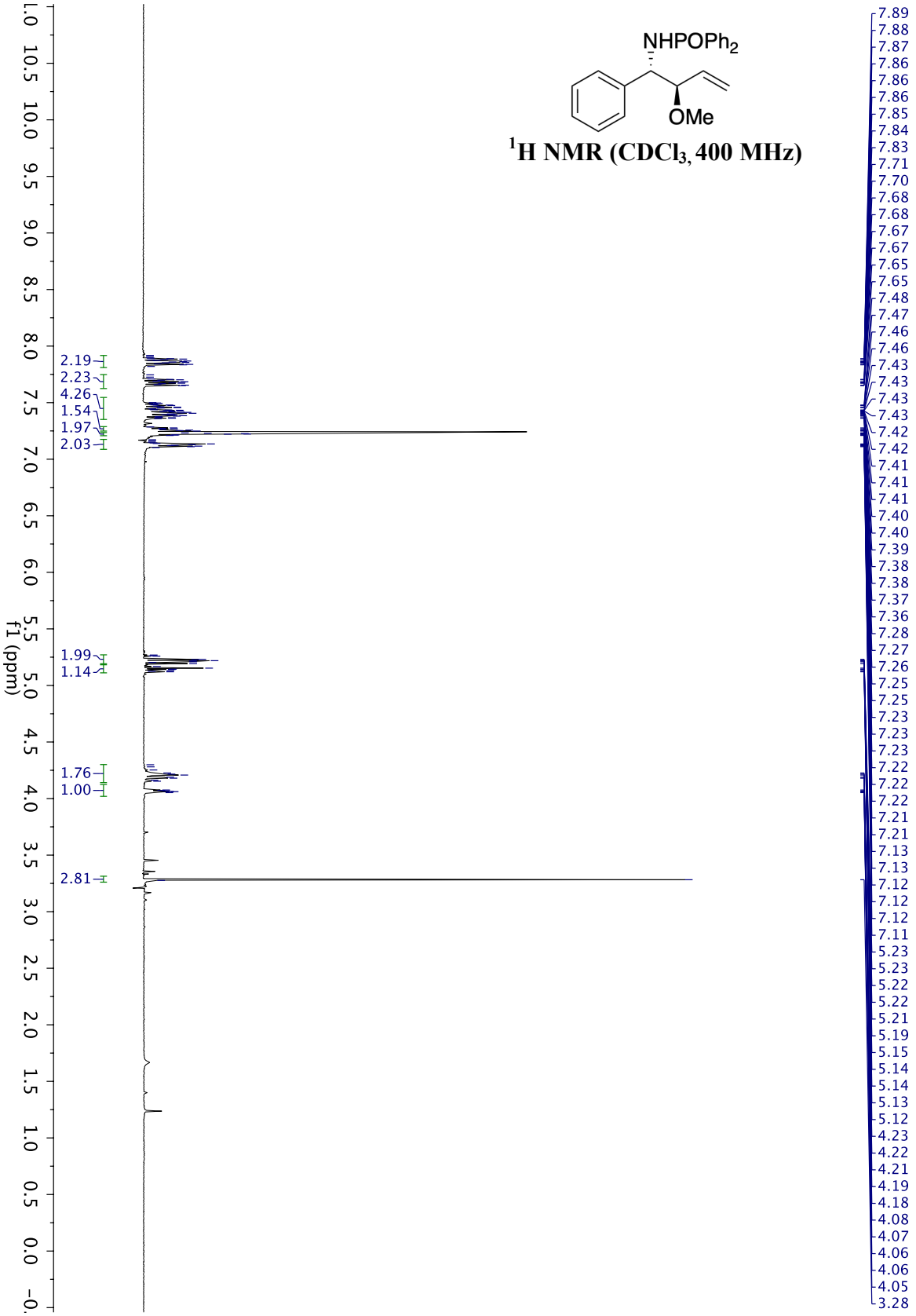

ap-2
13C NMR (CDCl3, 100 MHz)
171.85
158.26
129.03
128.56
122.54
119.23
116.51
63.90
51.20
46.52
45.87
31.46
26.25
24.34
20.08
18.47
f1 (ppm)

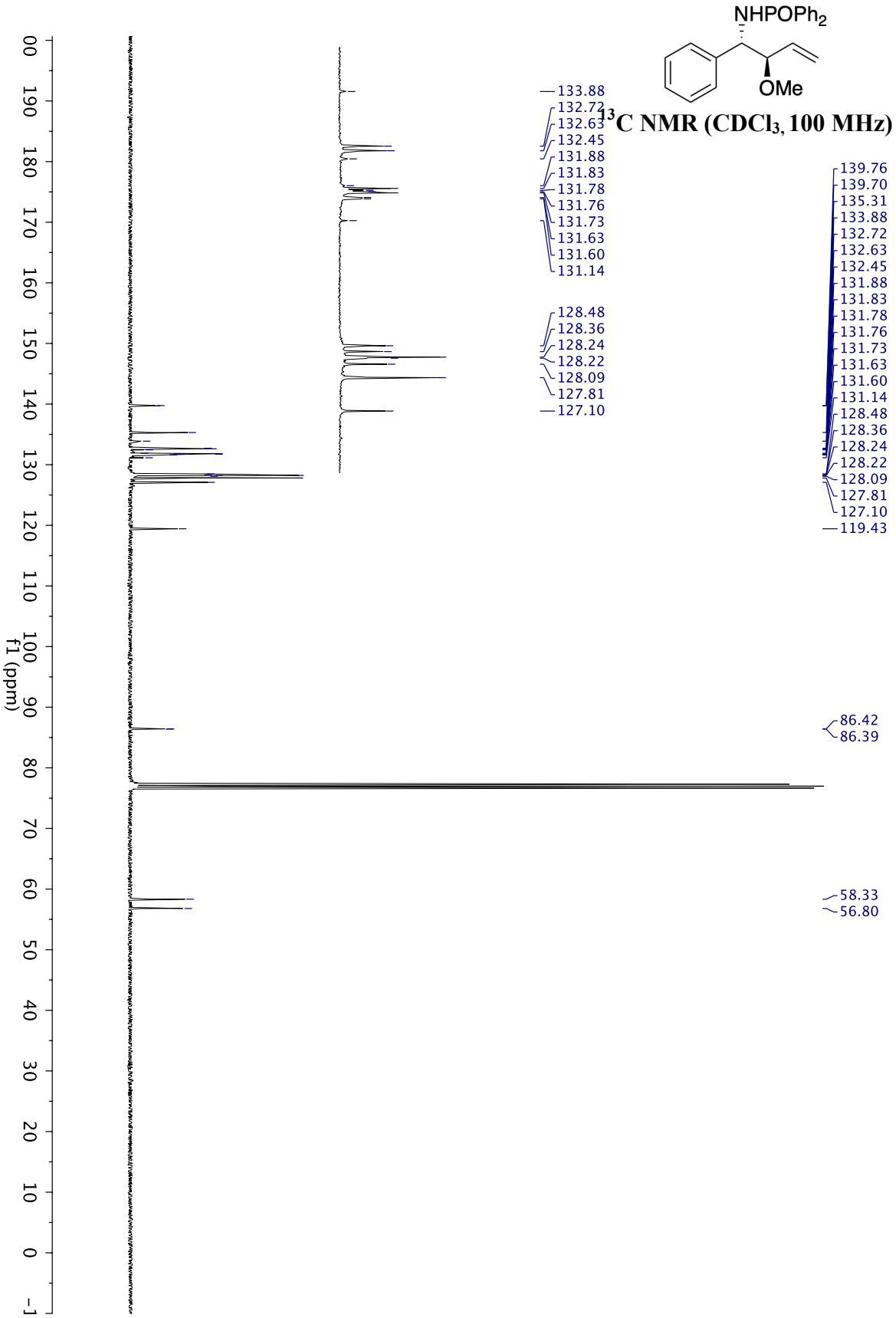

ap-3
^{1}H NMR ($CDCl_3$, 400 MHz)
f1 (ppm)
0.99
0.99
1.04
1.00
1.00
0.96
2.15
0.85
0.84
0.98
1.97
4.93
2.74
2.88
2.97

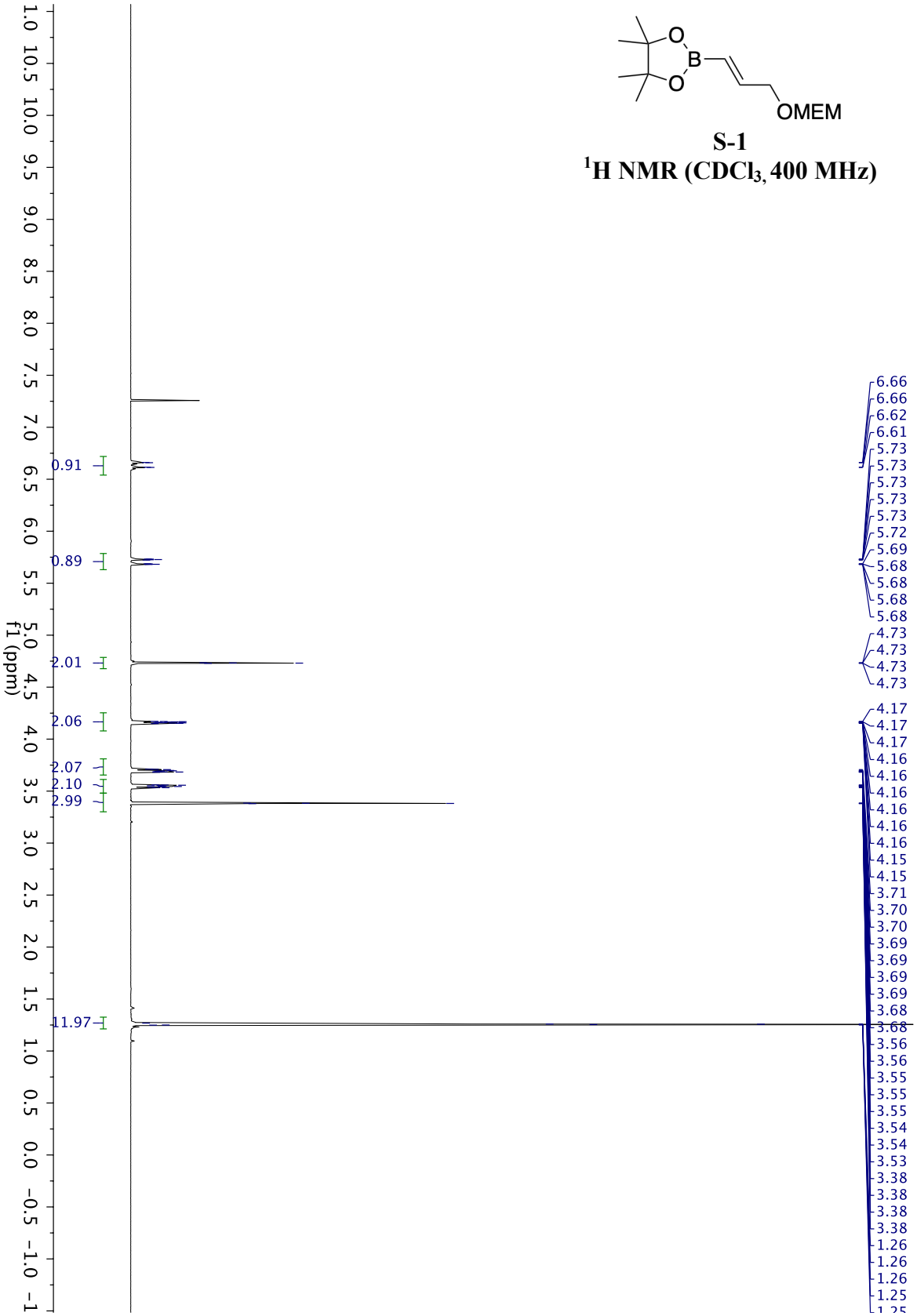

ap-3
13C NMR (CDCl3, 100 MHz)
171.99
155.97
131.48
128.50
126.23
122.03
118.85
63.86
51.30
46.51
45.86
31.43
26.24
24.34
23.09
20.11
18.50
14.33
f1 (ppm)


ap-10
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.34
1.00
2.35
1.20
1.09
1.75
1.12
1.07
1.11
2.44
5.28
3.13
9.41


ap-10
^{1}H NMR ($CDCl_3$, 400 MHz)
171.37
155.71
131.34
128.41
126.05
121.83
118.70
65.42
51.03
47.09
45.55
34.39
26.85
26.16
24.18
22.93
14.16
f1 (ppm)

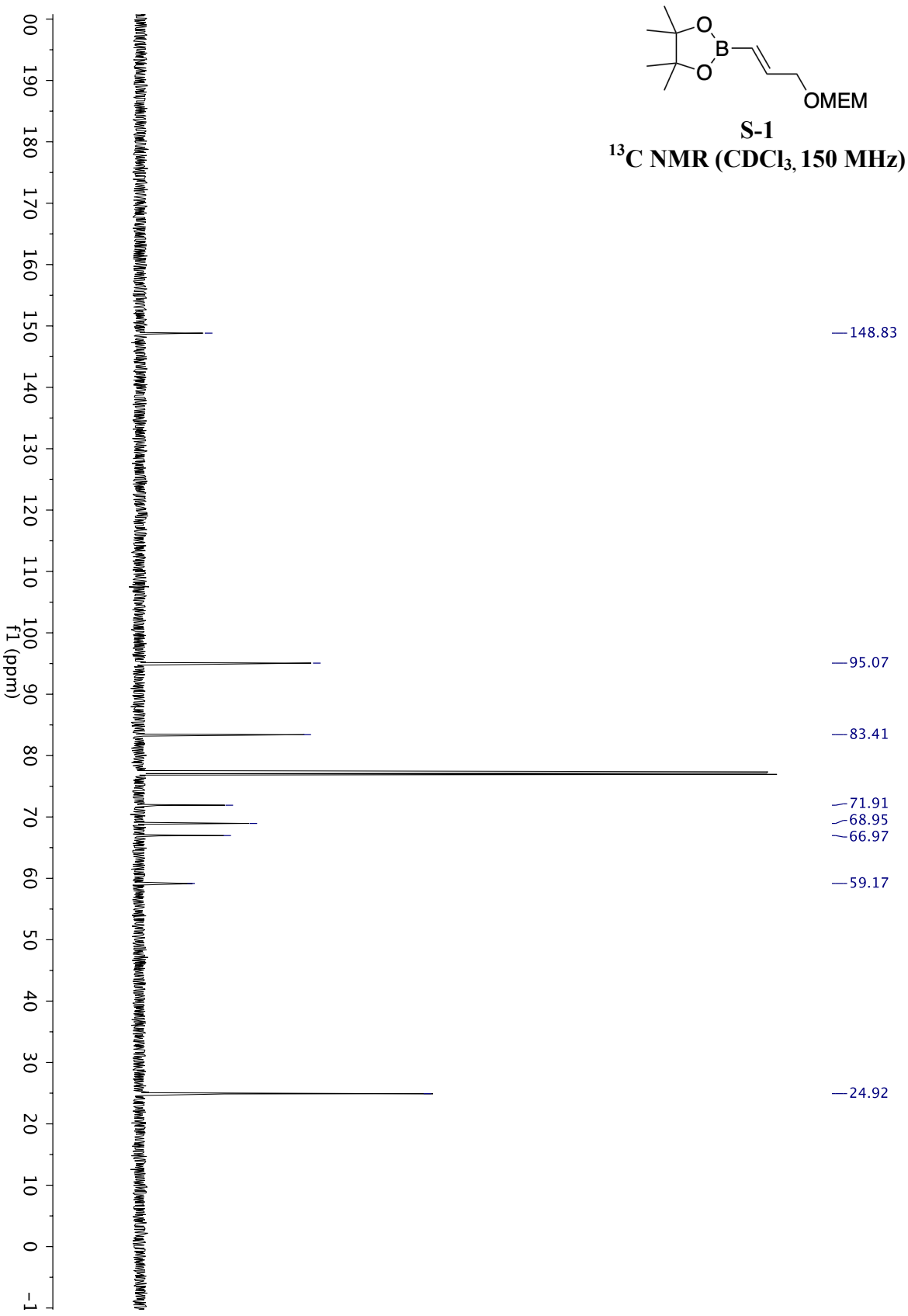

NHPOPh2
OMe
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.19
2.23
4.26
1.54
1.97
2.03
1.99
1.14
1.76
1.00
2.81


NHPOPh2
OMe
13C NMR (CDCl3, 100 MHz)
133.88
132.72
132.63
132.45
131.88
131.83
131.78
131.76
131.73
131.63
131.60
131.14
128.48
128.36
128.24
128.22
128.09
127.81
127.10
139.76
139.70
135.31
133.88
132.72
132.63
132.45
131.88
131.83
131.78
131.76
131.73
131.63
131.60
131.14
128.48
128.36
128.24
128.22
128.09
127.81
127.10
119.43
86.42
86.39
58.33
56.80
f1 (ppm)



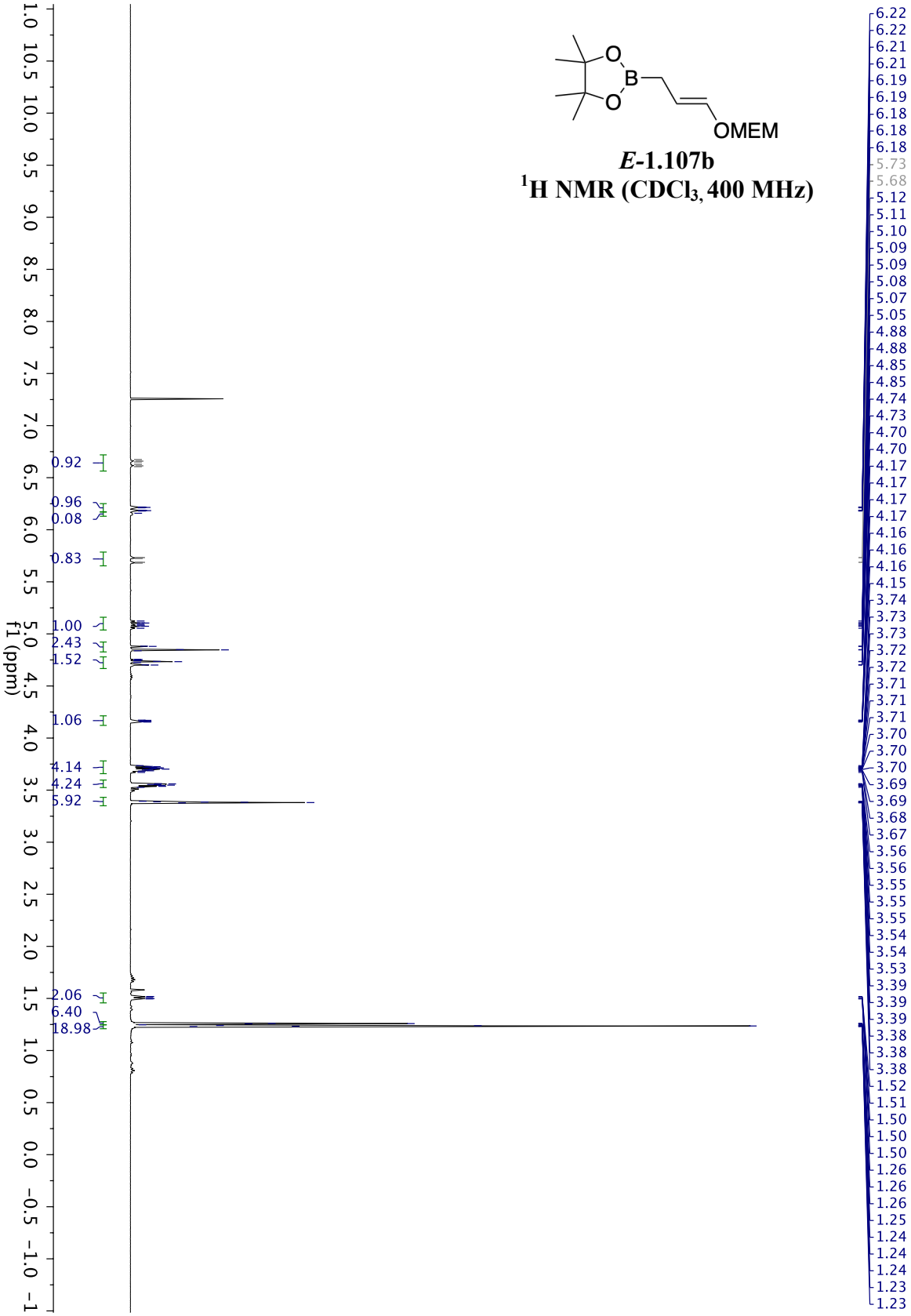
S-1

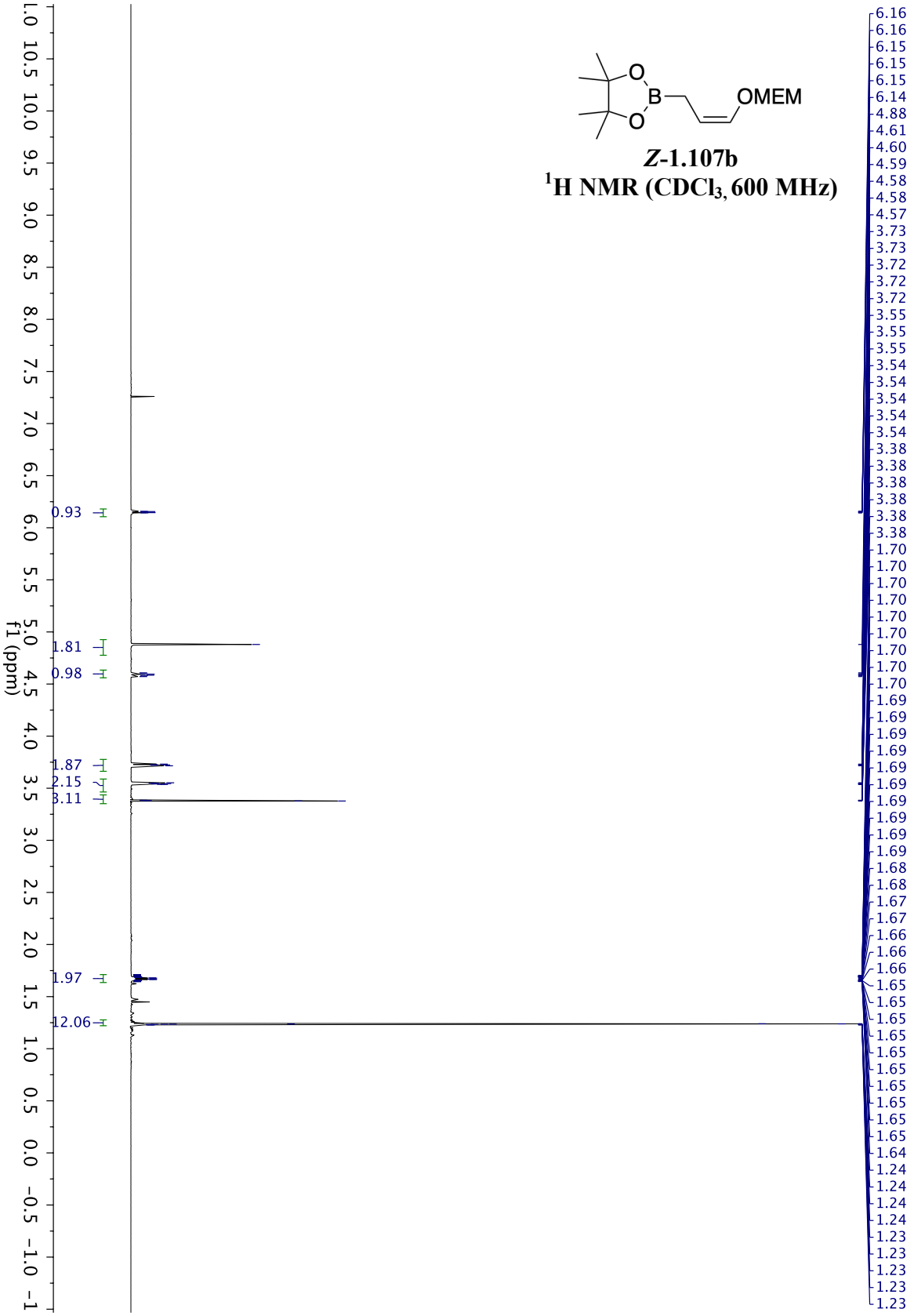
^{1}H NMR ($CDCl_3$, 400 MHz)

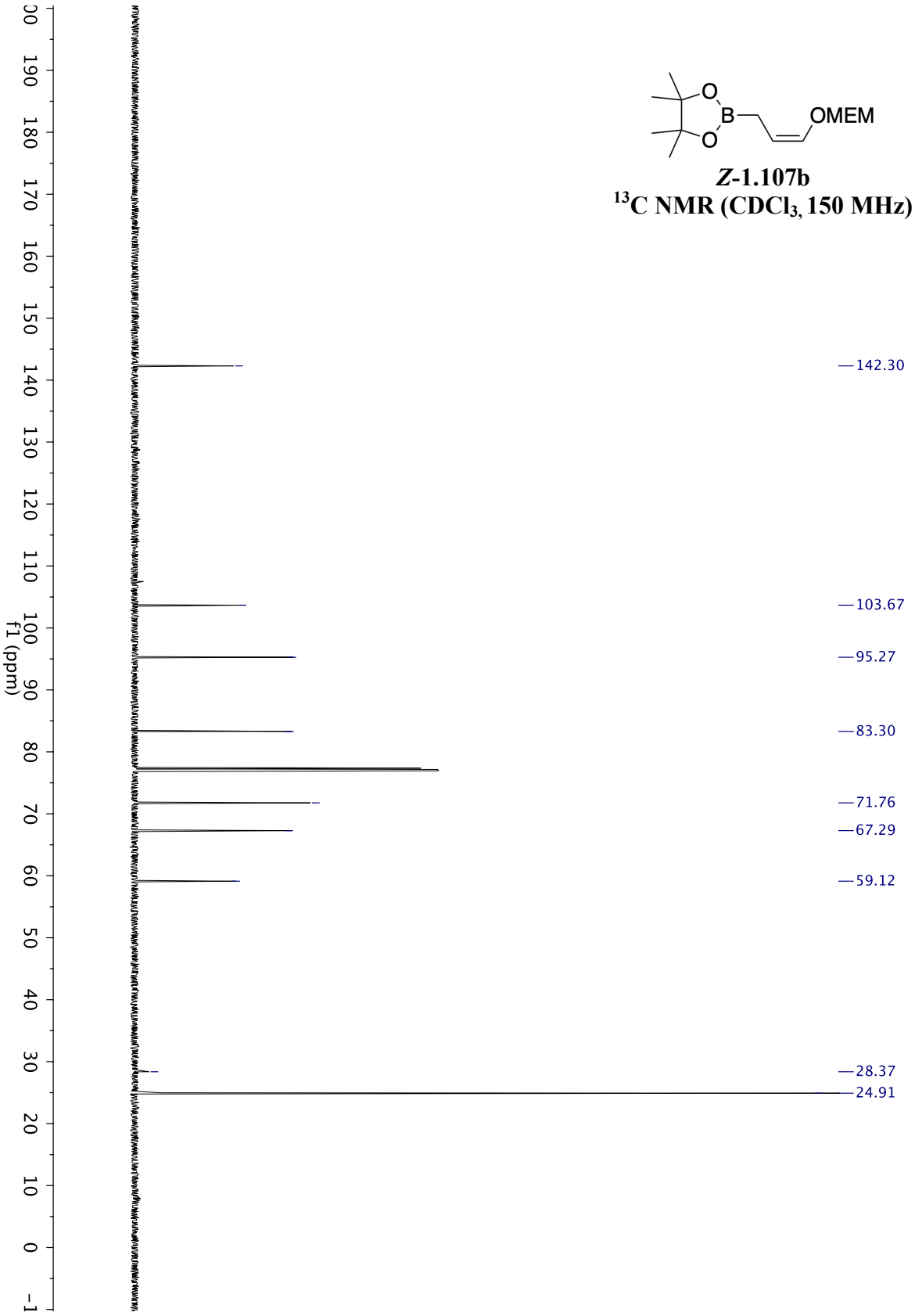


S-1

^{13}C NMR ($CDCl_3$, 150 MHz)

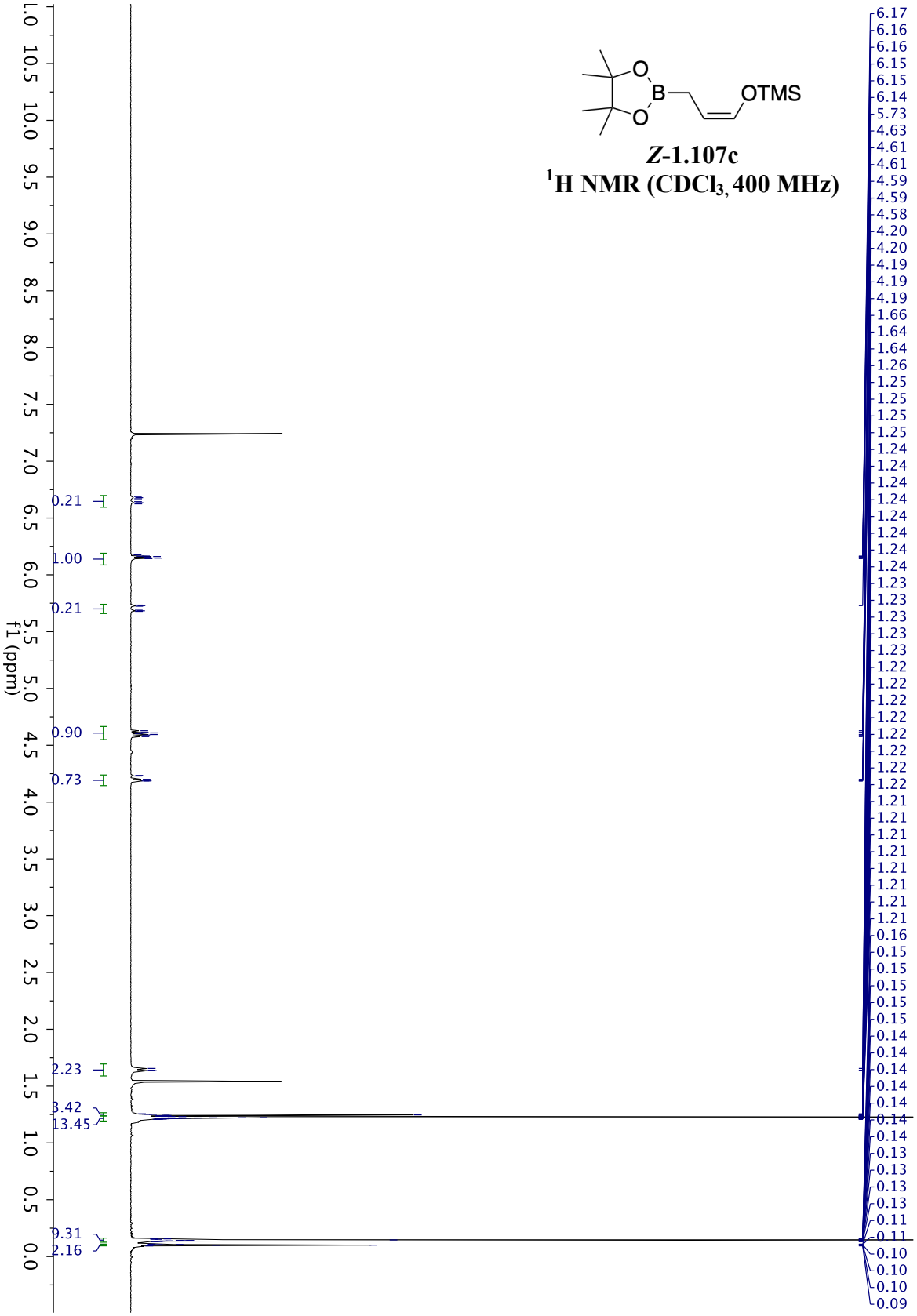

O
B
O
OMEM
E-1.107b
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.92
0.96
0.08
0.83
1.00
2.43
1.52
1.06
4.14
4.24
5.92
2.06
6.40
18.98

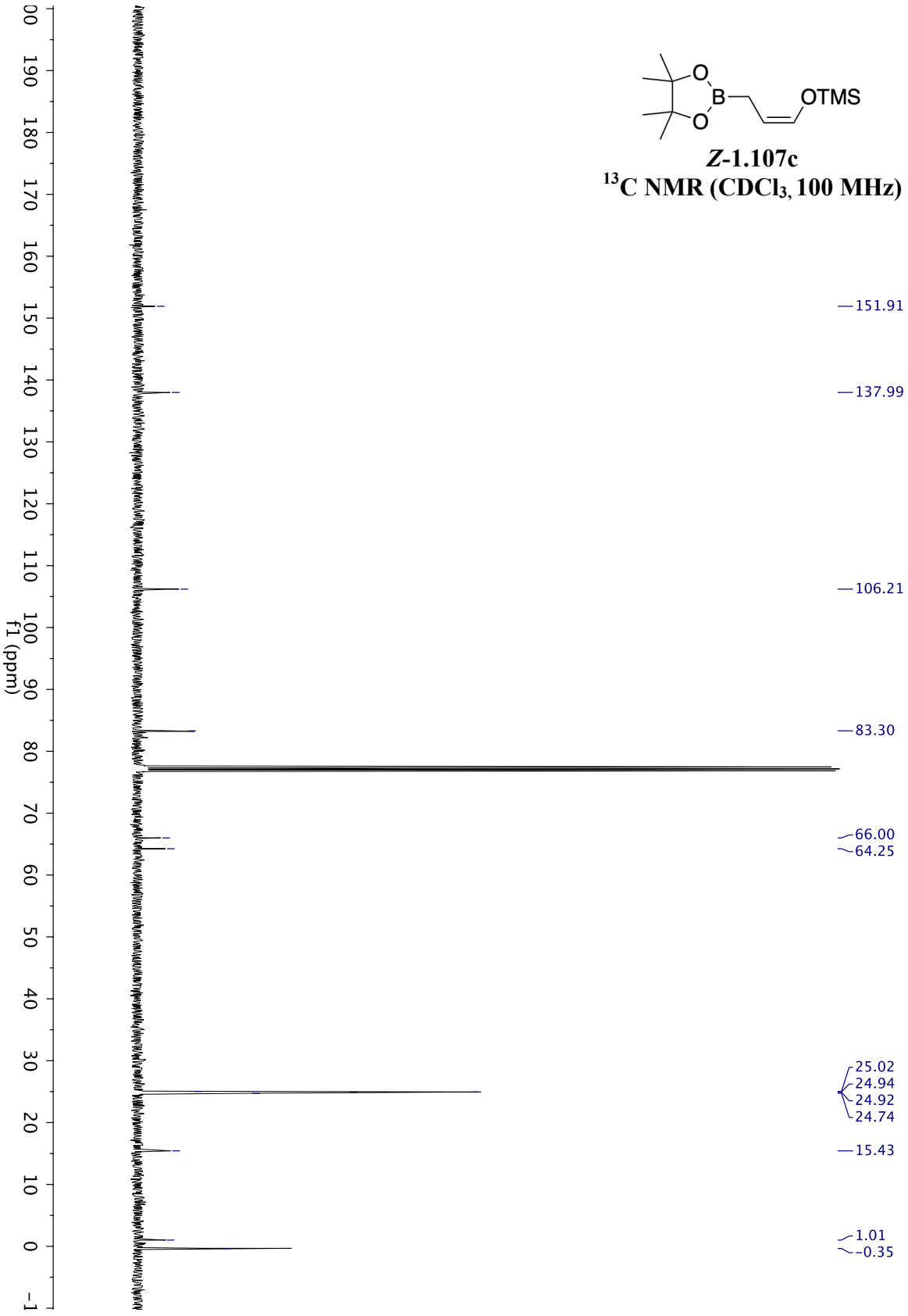

O
B
O
OMEM
Z-1.107b
1H NMR (CDCl3, 600 MHz)
f1 (ppm)
0.93
1.81
0.98
1.87
2.15
3.11
1.97
12.06



***Z*-1.107b**

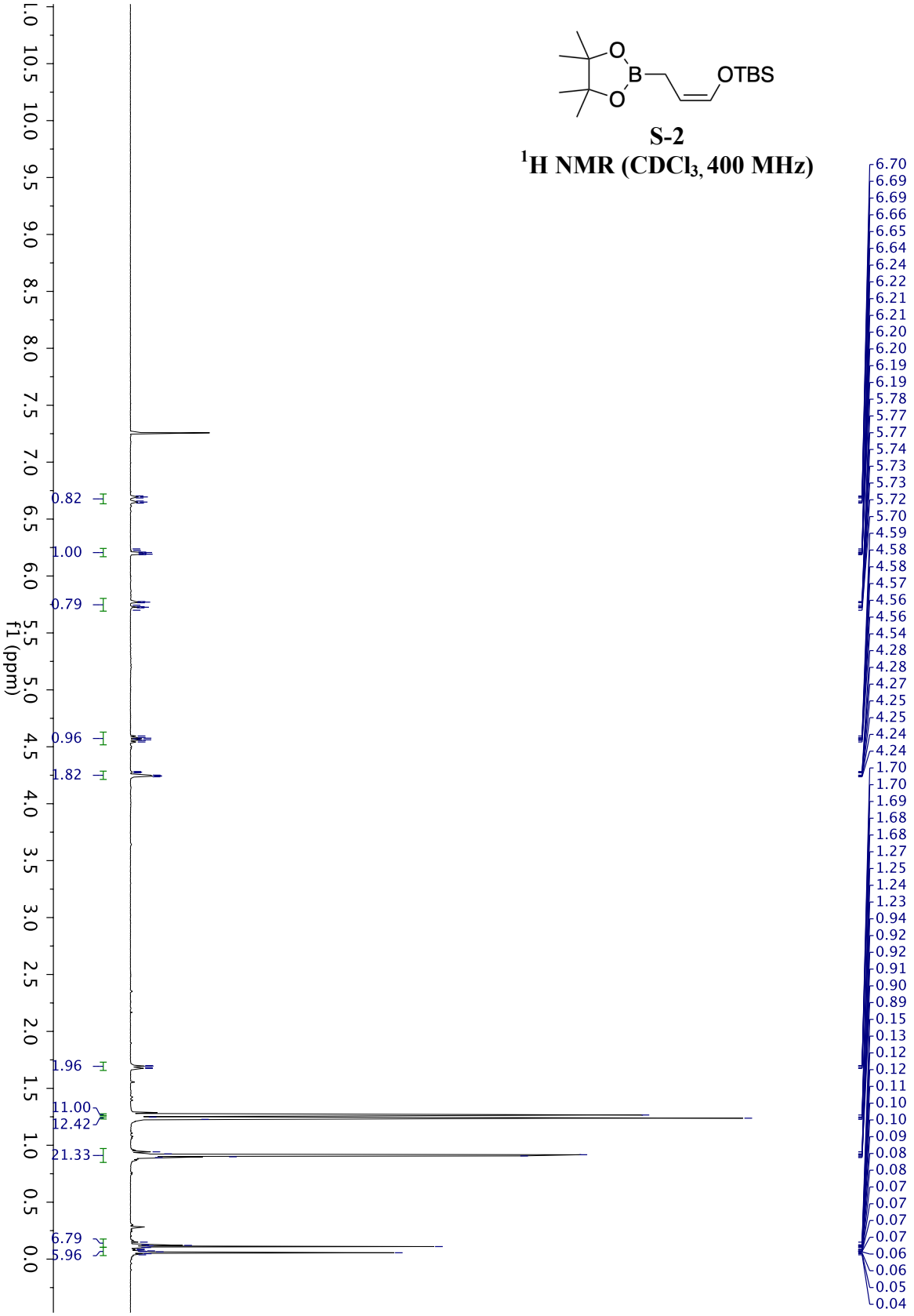
^{13}C NMR ($CDCl_3$, 150 MHz)


OTMS
Z-1.107c
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.21
1.00
0.21
0.90
0.73
2.23
3.42
13.45
9.31
2.16



***Z*-1.107c**

^{13}C NMR ($CDCl_3$, 100 MHz)


O
B
O
OTBS
S-2
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
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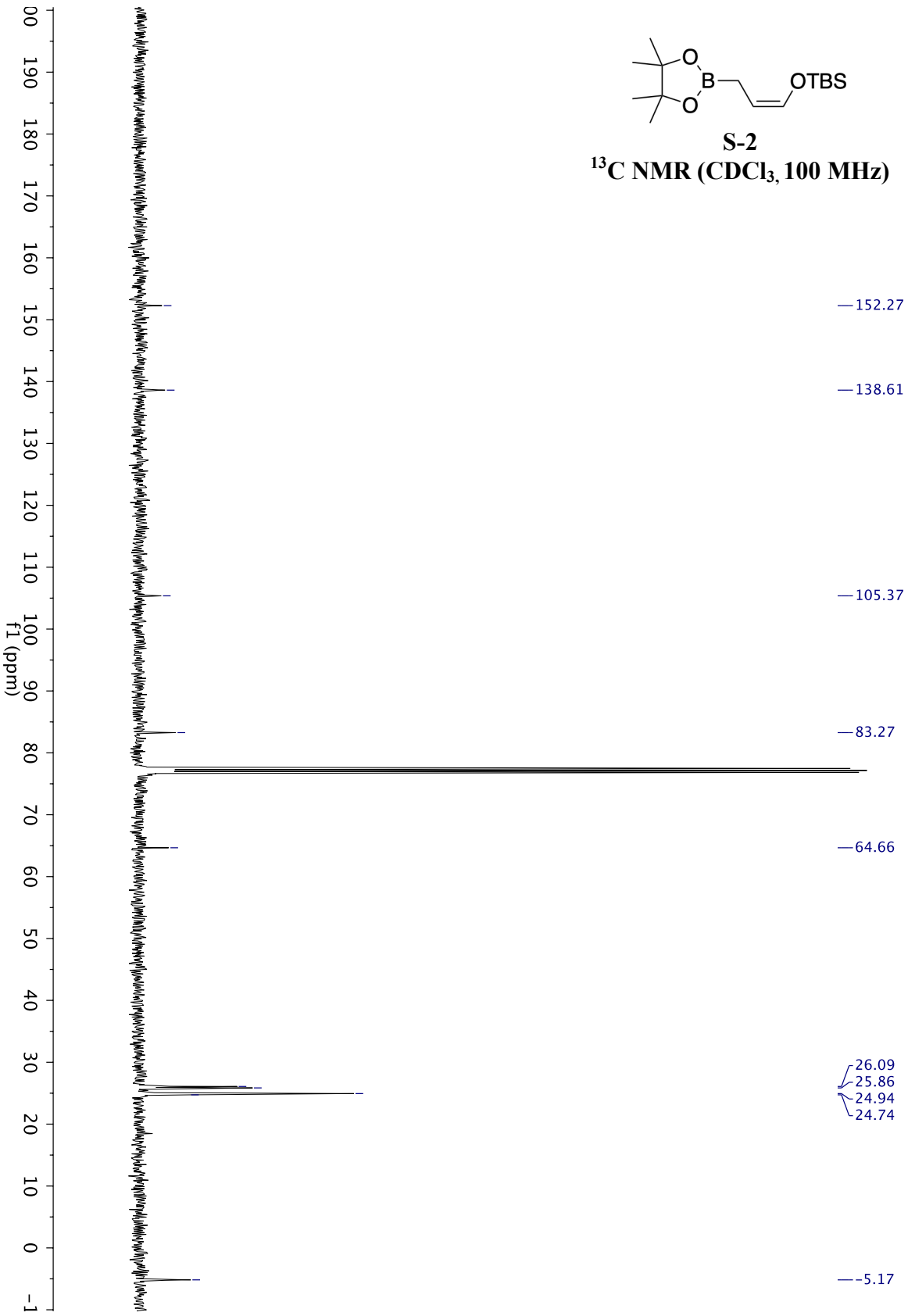
1.00
0.79
0.96
1.82
1.96
11.00
12.42
21.33
6.79
5.96


O
B
O
OTBS
S-2
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
152.27
138.61
105.37
83.27
64.66
26.09
25.86
24.94
24.74
-5.17

Chapter Two

Regio- and Enantioselective Synthesis of Trifluoromethyl-Substituted α-Tertiary NH_2 Amines

2.1 Introduction

The incorporation of one or more fluorine atoms as a strategy to modify chemical properties of a compound has emerged as a crucial approach for discovery of new classes of therapeutics,[1] agrichemicals[2] or materials.[3] One important class of fluorine-containing compounds are those with a trifluoromethyl group adjacent to an amine, since this motif may modulate basicity, lipophilicity[4] or increase metabolic stability.[5] Despite considerable efforts directed towards the preparation of enantioenriched amines,[6] the efficiency with which an α-tertiary trifluoromethyl substituted amine bearing a *Z* alkene can be accessed remains lacking.

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1) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315–8359.

2) Fugiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16–29.

3) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hullinger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

4) Smart, B. E.; *J. Fluorine Chem.* **2001**, *109,* 3–11.

5) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Med. Chem.* **2015**, *58*, 9041–9060.

6) (a) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743–2745. (b) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530–5541. (c) Enders, D.; Gottfried, K.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 3147–3152. (d) Huang, G.; Yang, J.; Zhang, X. *Chem. Commun.* **2011**, *47*, 5587–5589. (e) Husmann, R.; Sugiono, E.; Mersmann, S.; Raabe, G.; Rueping, M.; Bolm, C. *Org. Lett.* **2011**, *13*, 1044–1047. (f) Liu, Y.-L.; Shi, T. D.; Zhou, F.; Zhao, X.-L.; Wang, X.; Zhou, J. *Org. Lett.* **2011**, *13*, 3826–3829. (g) Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. *Angew. Chem. Int. Ed.* **2011**, *50*, 11773–11776. (g) Sun, L.-H.; Liang, Z.-Q.; Jia, W.-Q.; Ye, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 5803–5806. (h) Yuan, H.-N.; Li, S.; Nie, J.; Zheng, Y.; Ma, J.-A. *Chem. Eur. J.* **2013**, *19*, 15856–15860. (h) Grellepois, F. *J. Org. Chem.* **2013**, *78*, 1127–1137. (i) Wang, H.; Jiang, T.; Xu, M.-H. *J. Am. Chem. Soc.* **2013**, *135*, 971–974. (j) Wang, L.; Chen, J.; Huang, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 15414–15418. (k) Zhang, S.; Li, L.; Hu, Y.; Li, Y.; Yang, Y.; Wang, Z. *Org. Lett.* **2015**, *17*, 5036–5039. (k) Trost, B. M.; Hung, C.-I.; Scharf, M. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 11408–11412.

2.2 Background

2.2.1 State-of-the-art for Diastereoselective Synthesis of Enantioenriched α-Tertiary Trifluoromethyl Amines

Diastereoselective addition of allyl metal reagents to enantiomerically pure trifluoromethyl substituted imines (**2.1**, **2.6**) is an effective strategy for synthesis of enantioenriched homoallylic amines. In an early report, Brigaud outlined diastereoselective addition to phenyl glycinol derived iminoester **2.1** affording a mixture of the desired homoallylic amine **2.3** and the closely related derivative **2.4** in 85:15 dr and 78% combined yield. However, to expose the free NH_2 amine **2.5**, a four-step procedure mandating cleavage of the ester, followed by treatment with lead acetate was required.[7] In a related disclosure, Zhang detailed addition of allyl indium reagents to imino ester **2.6** generating homoallylic amine **2.8** in 85% yield and 95:5 dr. The free amine **2.9** was unmasked through hydrogenolysis of the glycinol auxiliary with concomitant reduction of the terminal olefin.[8]

Grellepois has reported on diastereoselective addition of Grignard reagents to *N*–sulfinyl hemiaminals **2.10**, furnishing homoallylic amines **2.12** in 42–83% yield and 89:11 – 95:5 dr.[9] In a follow-up study, the same authors showcased addition of allyl zinc and indium compounds to methyl or phenyl-substituted hemiacetals **2.10** in 26–77% yield and 79:21–99:1 dr.[10] Deprotection of an aryl substituted α-tertiary trifluoromethyl amine was not reported, likely due to the sensitivity of the benzylic stereogenic center.

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7) Chaume, G.; Van Severen, M.-C.; Marinkovic, S.; Brigaud, T. *Org. Lett.* **2006**, *8*, 6123–6126.

8) Min, Q.-Q.; He, C.-Y.; Zhou, H.; Zhang, X. *Chem. Commun.* **2010**, *46*, 8029–8031.

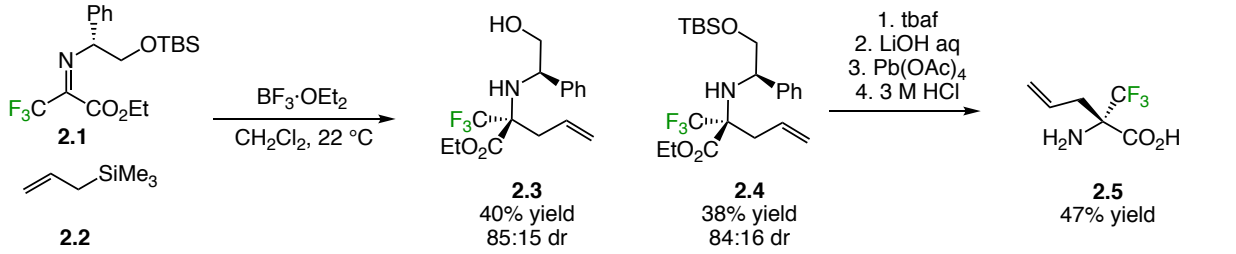
9) Grellepois, F.; Jamaa, A. B.; Gassama, A. *Eur. J. Org. Chem.* **2013**, *29*, 6694–6701.

10) Grellepois, F.; Jamaa, A. B.; Rosa, N. S. *Org. Biomol. Chem.* **2017**, *15*, 9696–9709. For a related report, see: Guo, T.; Song, R.; Yuan, B.-H.; Chen, X.-Y.; Sun, X.-W.; Lin, G.-Q. *Chem. Commun.* **2013**, *49*, 5402–5404.

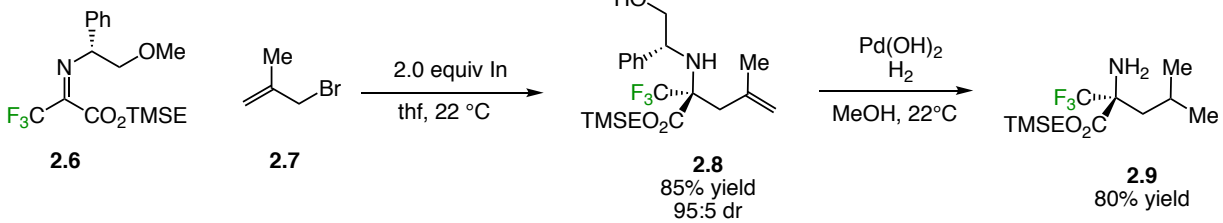
Scheme 2.1. Addition of Allyl Metal Nucleophiles to Enantiomerically Pure Aldimines

a. Addition of allyl reagents to phenylglycinol based imines

(Briguard *et al.*, Ref 7)

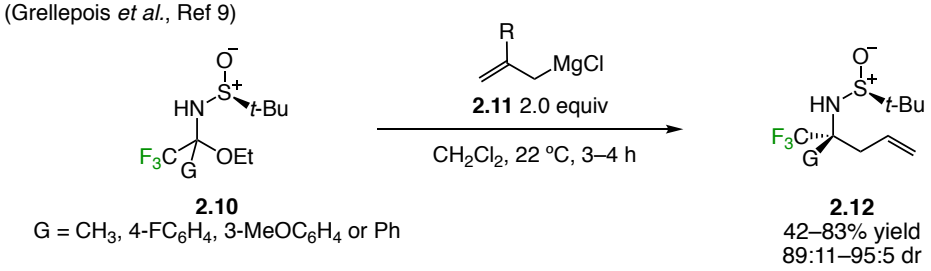


(Zhang *et al.*, Ref 8)

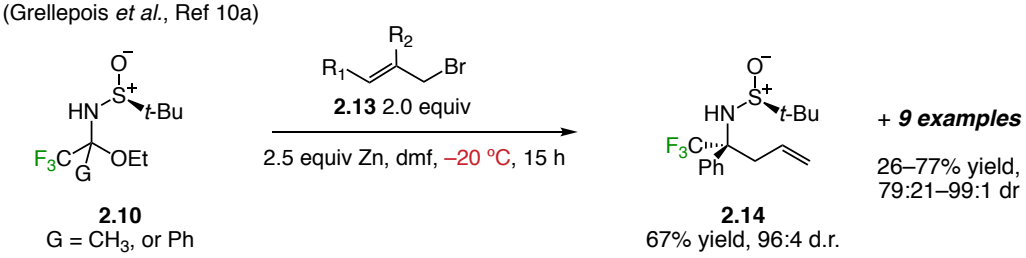


b. Addition of allyl reagents to sulfinyl based imines

(Grellepois *et al.*, Ref 9)



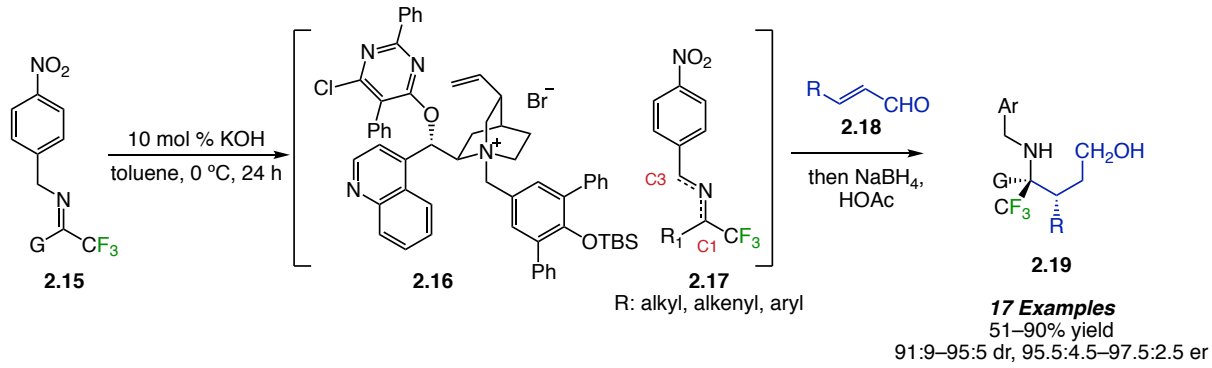
(Grellepois *et al.*, Ref 10a)



2.2.2 State-of-the-art for Catalytic Enantioselective Synthesis of Enantioenriched α Tertiary Trifluoromethyl Amines

As originally shown by Deng, umpolung addition of trifluoromethyl containing aza-allyl anions **2.17** to enones **2.18**[11] is an attractive strategy for enantioselective synthesis of α-tertiary trifluoromethyl amines with vicinal stereocenters **2.19**.[12] In these cases, enantiotopic discrimination is probably the result of transition state organization through interaction between the aza-allyl anion and the quaternary ammonium phase transfer catalyst **2.16**. Accordingly, in the presence of cinchona alkaloid **2.16** (with loadings as low as 0.01 mol %), diastereo- and enantioselective addition of alkyl, alkenyl and aromatic aza-allyl anions **2.17** afforded homoallylic amine **2.19** in up to 90% yield, 95:5 dr and 97.5:2.5 er.

Scheme 2.2. Enantio- and Diastereoselective Addition of Aza-allyl Anions to Enals



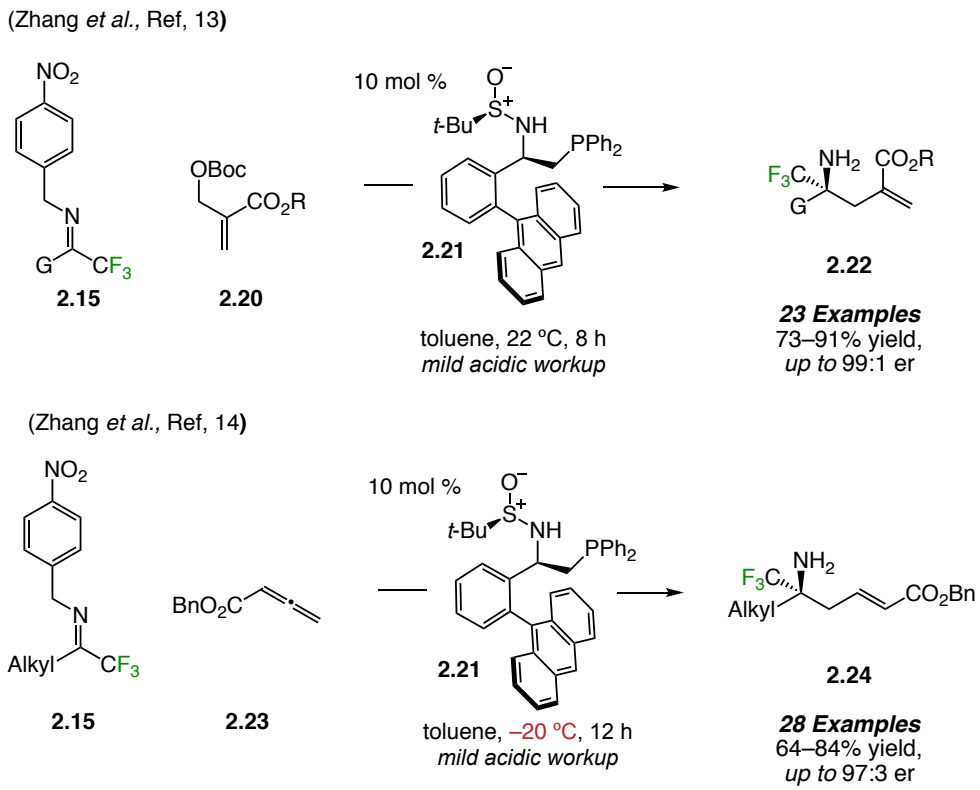
Zhang has reported a highly enantioselective umpolung addition of aryl-, heteroaryl- and alkyl-substituted trifluoromethyl aza-allyl anions to Morita-Baylis-Hillman carbonates **2.20** promoted by phosphine **2.21** in 73–91% yield and 96.5:3.5–99:1 er and subsequent elaboration of

11) (a) Wu, Y.; Hu, L.; Li, Z.; Deng, L. *Nature*, **2015**, *523*, 445–450. (b) Hu, L.; Wu, Y.; Li, Z.; Deng, L. *J. Am. Chem. Soc.* **2016**, *138*, 15817–15820. (c) Li, Z.; Hu, B.; Wu, Y.; Fei, C.; Deng, L. *Proc. Natl. Acad. Sci. U. S.* A. **2018**, 115, 1730−1735. (d) Hu, B.; Deng, L. *J. Org. Chem.* **2019**, *84*, 994–1005.

12) For related studies, see (a) Wu, Y.; Deng, L. *J. Am. Chem. Soc.* **2012**, *134*, 14334–14337. (b) Hu, B.; Deng, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 2233–2237.

the products to α-methylene γ-lactams.[13] An ensuing disclosure detailed additions of aza-allyl anions promoted by the same catalyst to allenoate **2.23**, affording β,γ-unsaturated amino esters **2.24**. The scope is broad for alkyl substituted imines **2.15**, affording **2.24** in 64–84% yield and 90:10–97.5:2.5 er with complete *E* selectivity.[14]

Scheme 2.3. Phosphine-Catalyzed Umpolung Addition of Aza-Allyl Anions



Almost simultaneously, Niu[15] and Wang[16a] introduced a strategy of umpolung addition of fluorenyl imine **2.28** to allyl carbonates **2.26** and **2.32** promoted by iridium-based phosphoramidite complex **2.27**, followed by aza-Cope rearrangement of intermediate **2.29** furnishing α-tertiary

13) Chen, P.; Yue, Z.; Zhang, J.; Lv, Z.; Wang, L.; Zhang, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 13316–13320.

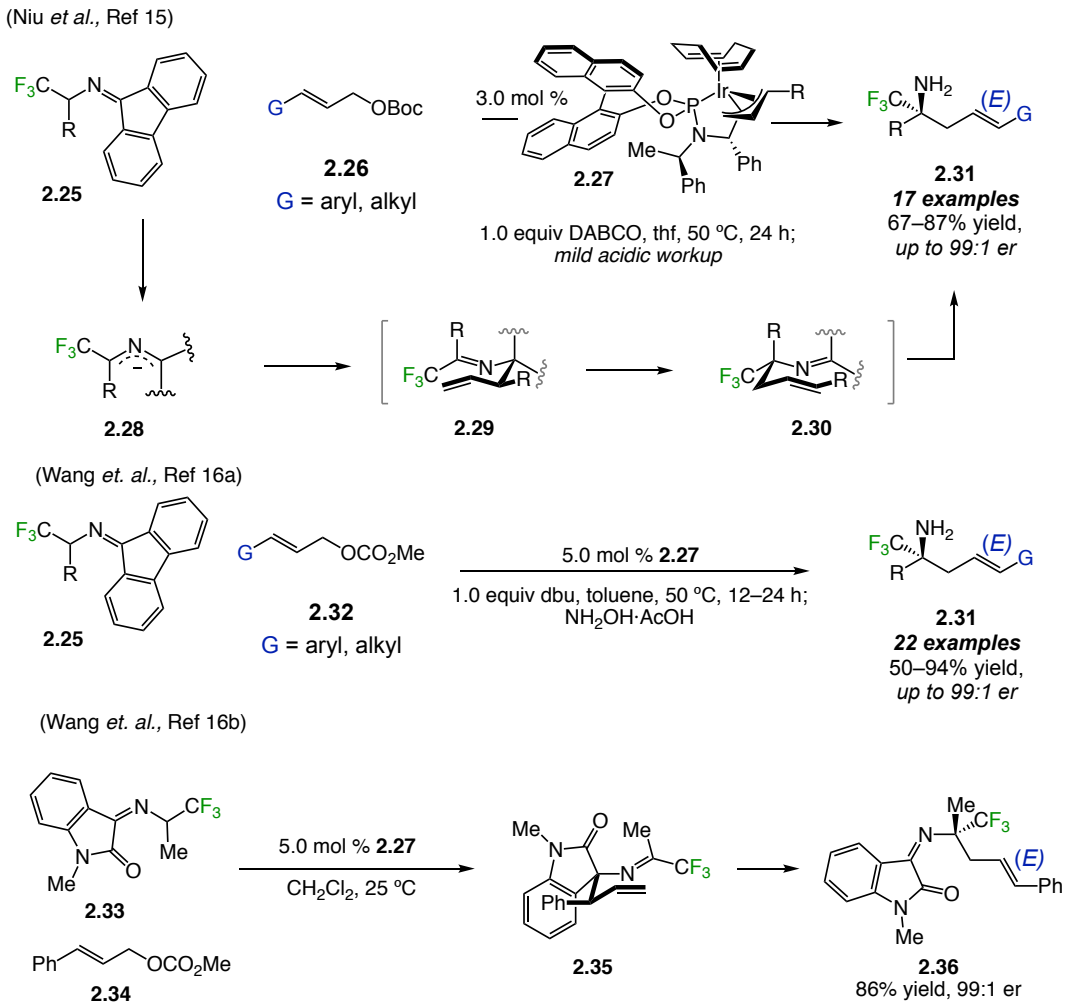
14) Chen, P.; Zhang. J. *Org. Lett.* **2017**, *19*, 6550–6553.

15) Wang, Y.; Deng, L.-F.; Zhang, X.; Niu, D. *Org. Lett.* **2019**, *21*, 6951–6956.

16) (a) Shen, C.; Wang, R.-Q.; Wei, L.; Wang, Z.-F.; Tao, H.-Y.; Wang, C.-J. *Org. Lett.* **2019**, *21*, 6940–6945. (b) Shi, L.-M.; Sun, X.-S.; Shen, C.; Wang, Z.-F.; Tao, H.-Y.; Wang, C.J. *Org. Lett.* **2019**, *21*, 4842–4848.

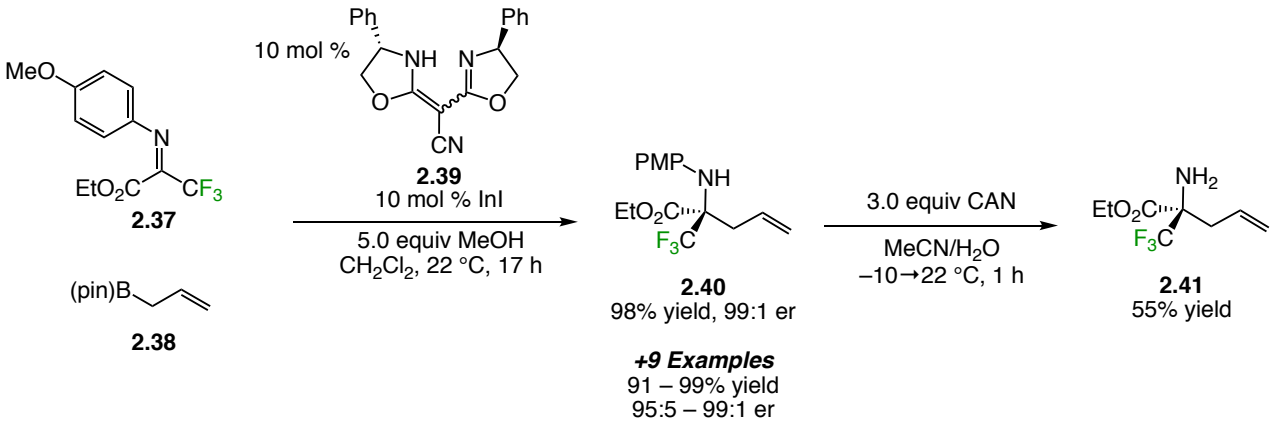
trifluoromethyl amines **2.31**. Niu has outlined a method for addition to aromatic imines affording α-tertiary trifluoromethyl amines **2.31** in 67–87% yield and 96:4–99:1 er, and in a related study Wang shows that the same class of compounds may be accessed in 50–94% yield and up to 99:1 er. A distinct advantage of Niu's system is applicability to heteroaryl aza-allyl species. A separate, but closely related disclosure by the Wang group described a single example of synthesis of α-tertiary imine **2.36** in 86% yield and 99:1 er; hydrolysis of analogous α-secondary imines were outlined, but unmasking of **2.36** was not included.[16b]

Scheme 2.4. Tandem Aza-Allyl Umpolung Addition and Aza-Cope Rearrangement



Kurti has recently disclosed enantioselective addition of allyl boronates to *N*-aryl iminoesters **2.37**,[17] promoted by indium-based semicorrin complex **2.39**. Addition proceeds readily to deliver an array of iminoesters exhibiting electronically diverse *N*-aryl substitution. However, the free amine **2.41** could only be accessed through oxidative cleavage (treatment with ceric ammonium nitrate) of the *para*-methoxyphenyl group **2.40** in 55% yield.

Scheme 2.5. Allyl Addition to Iminoesters Promoted by Indium-Based Complexes



2.2.3 N-H Ketimines as Electrophiles in Catalytic Transformations

There are only a small number of examples detailing addition to unprotected ketimines,[18] and even fewer that do not require activated substrates such as those derived from trifluoropyruvate. Over a decade ago, Vovk first described proline-catalyzed Mannich-type reactions of aryl trifluoromethyl ketimines **2.42** affording **2.45** in 75–86% yield and 87:13–96:4 er.[19] In a related study (Scheme 2.6a), Nakamura described a class of heterosulfonyl prolinamide

17) Bhakta, U.; Kattamuri, P. V.; Siitonen, J. H.; Alemany, L. B.; Kürti, L. *Org. Lett.* **2019**, *21*, 9208–9211.

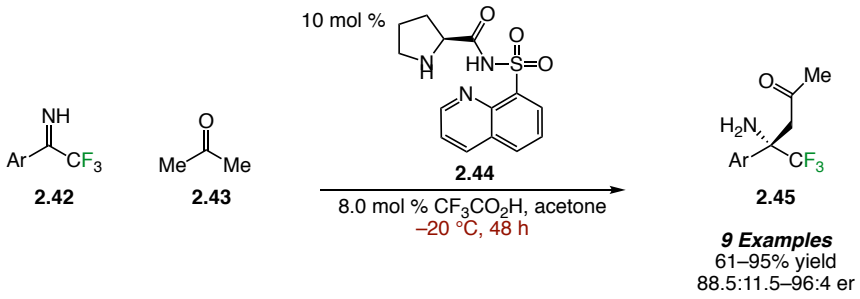
18) (a) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551–5553. (b) Tran, D. C.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 11098–11102. (c) Tran, D. C.; Cramer, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 10630–10634.

19) Sukach, V. A.; Golovach, N. M.; Pirozhenko, V. V.; Rusanov, E. B.; Vovk, M. V. *Tetrahedron: Asymmetry* **2008**, *19*, 761–764.

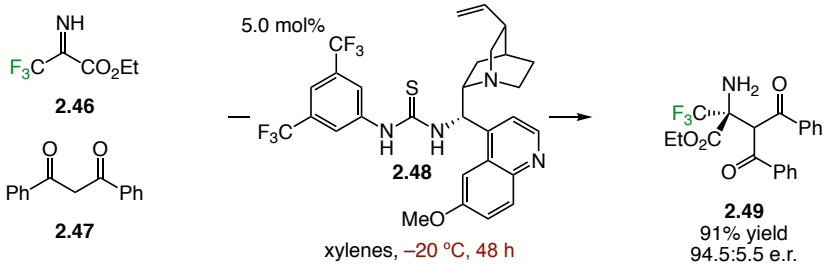
catalysts **2.44** for enantioselective addition with a larger scope of aromatic trifluoromethyl ketimines furnishing **2.45** in 61–95% yield and 88.5:11.5–96:4 er.[20]

Scheme 2.6. Scheme 2.26 Mannich-Type Transformations Involving *N*-H Ketimines

a. Representative prolinamide catalyzed Mannich addition involving trifluoromethyl ketimines



b. Representative Mannich addition of 1,3-dicarbonyl compounds to trifluoromethyl ketimines



Oshima and Morimoto were able to accomplish enantioselective Mannich-type addition of 1,3-dicarbonyl compound **2.47**, but the scope was limited to the activated iminoester **2.46** as the substrate. Products were isolated in 77–91% yield and 88.5:11.5–99:1 er, but required low temperatures and reaction times up to 48 hours.[21] The same authors subsequently disclosed synthesis of propargylamines through addition of alkynyl-Zn reagents to aromatic and aliphatic trifluoromethyl substituted ketimines affording racemic α-tertiary trifluoromethyl amines in 82–99% yield.[22] Also attempted was the development of an enantioselective variant, where in the presence of a chiral phosphoric acid **2.51,** addition proceeded efficiently (88% and 96% yield)

20) Hara, N.; Tamura, R.; Funahashi, Y.; Nakamura, S. *Org. Lett.* **2011**, *13*, 1662–1665.

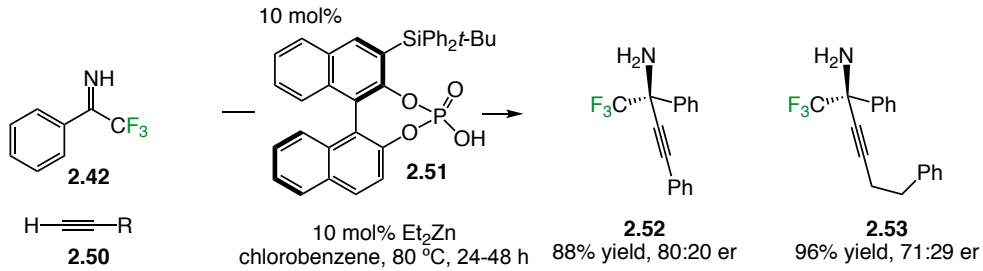
21) Sawa, M.; Morisaki, K.; Kondo, Y.; Morimoto, H.; Ohshima, T. *Chem. Eur. J.* **2017**, *23*, 17022–17028.

22) Morisaki, K.; Morimoto, H.; Ohshima, T. *Chem. Commun.* **2017**, *53*, 6319–6322.

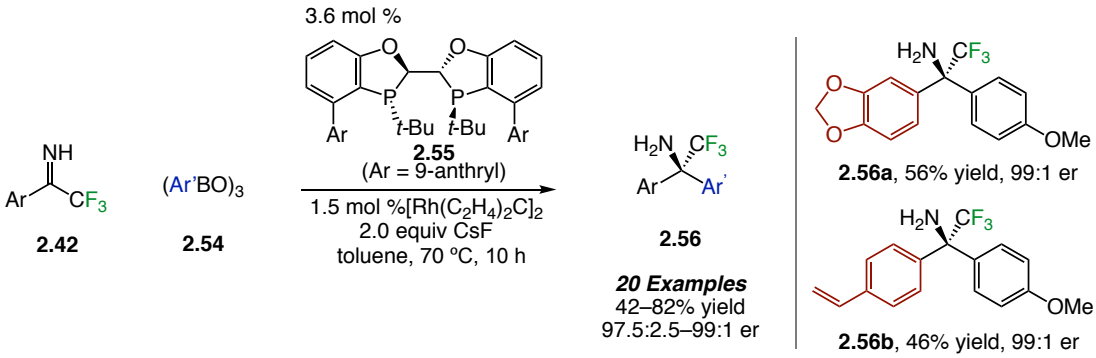
but with only modest levels of enantioselectivity (80:20 er and 71:29 er for **2.52** and **2.53**, respectively).

Scheme 2.7. Catalytic Enantioselective Addition of Alkynyl and Aryl Metal Nucleophiles

a. Phosphoric acid catalyzed alkynyl metal addition to trifluoromethyl ketimines



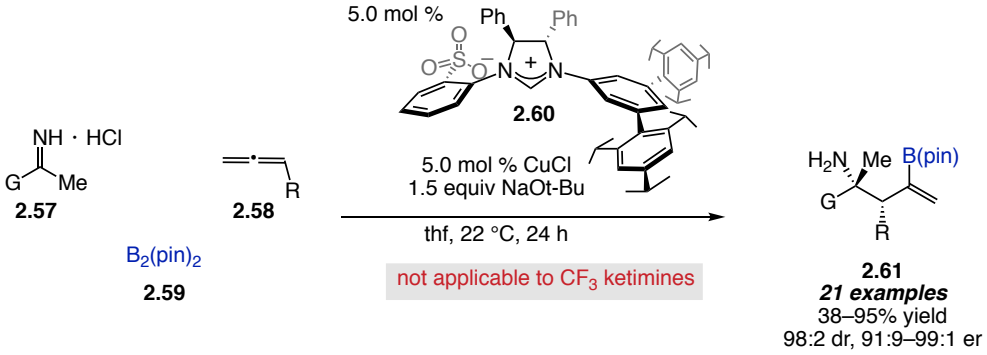
b. Rhodium-catalyzed addition of arylboroxines to trifluoromethyl ketimines



Most recently, Deng and Teng reported enantioselective addition of aryl boroximes **2.54** to trifluoroketimine **2.42,** promoted by a phosphine-Rh complex, generating enantioenriched diaryl amino methanes **2.55**.[23] Enantioselectivity was high (97.5:2.5–99:1 er), and a range of electronically diverse ketimines were suitable as substrates. Somewhat discouragingly, however, sterically encumbered *ortho*-substituted ketimines or boroximes were not tolerated, and substrates possessing sensitive functionality, such as acetal **2.56a** and alkenyl **2.56b,** were isolated in significantly lower yield (56 and 46% yield, respectively).

23) Zhu, J.; Huang, L.; Dong, W.; Li, N.; Yu, X.; Deng, W.-P.; Tang, W. *Angew. Chem. Int. Ed.* **2019**, *58*, 16119–16123.

Scheme 2.8. Catalytic, Enantioselective Allyl Addition Promoted by NHC-Cu Complexes



In 2017, our group reported a catalytic method for enantioselective synthesis of α-tertiary homoallylic amines **2.61** promoted by sulfonate-containing NHC-copper complex **2.60** in up to 95% yield, 98:2 dr and 99:1 er.[24] Nonetheless, the transformation did not tolerate trifluoromethyl ketimines as substrates (i.e., only alkyl substituted ketimines were compatible). Considering the inefficiencies surrounding the unmasking of phosphinoyl imines, as discussed in Chapter One, and the low-yielding transformation described in Scheme 2.5, we questioned whether *N*-H ketimines could be viable substrates for allyl addition promoted by aminophenol complexes. This would afford access to highly desirable NH_2 amines without the need for treating the obtained products with acidic or oxidizing conditions typically needed for deprotection strategies.

2.3 Additions to Halogen-Containing Substrates Promoted by Aminophenol Boron-Based Complexes

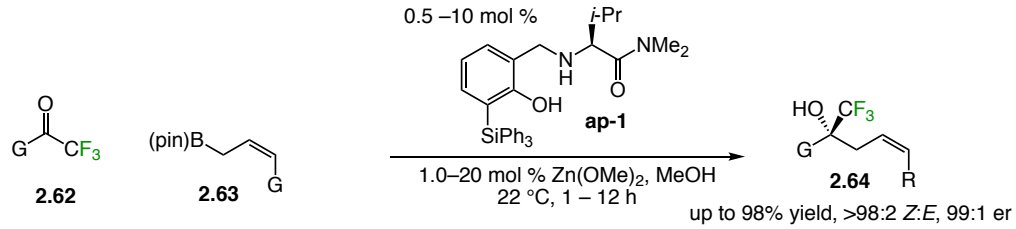
In 2016, our group detailed catalytic, enantioselective addition to trifluoromethyl ketones promoted by an aminophenol boron-based complex. Enantiofacial discrimination was influenced through an electrostatic attraction between the trifluoromethyl group of the ketone and the embedded ammonium group within the complex. Through the use of just 2.5 mol % of an

24) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H. *Nature Chem.* **2017**, *9*, 1269–1275.

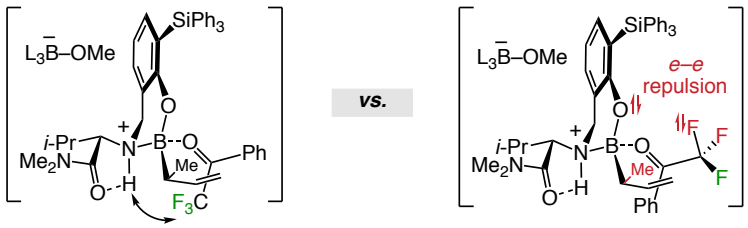
appropriate aminophenol and 10 mol % NaO*t*-Bu, homoallylic alcohols bearing a trifluoromethyl-substituted stereogenic center were isolated in up to 98% yield and 99:1 er.[25]

Scheme 2.9. Previous Work and Goals of the Present Study

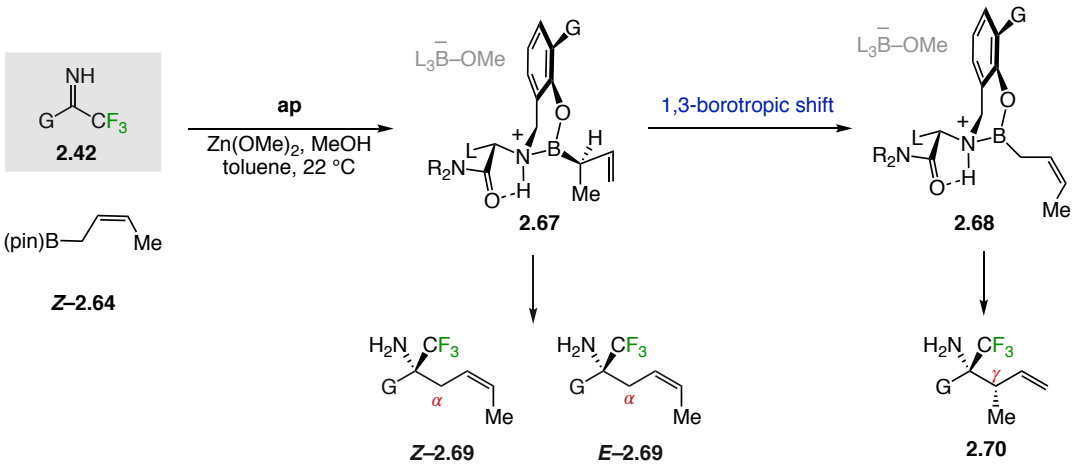
a. Aminophenol boron-based complexes as catalysts for addition to trifluoroketones



b. Coulombic attraction drives selectivity



c. Possible scenarios for additions to ketimines



25) For a detailed account, see: Lee, K.; Silverio, D. L.; Torker, S.; Robbins, D. W.; Haeffner, F.; van der Mei, F. W.; Hoveyda, A. H. *Nature Chem.* **2016**, *8*, 768–777. For transformations of the same class, see: Fager, D. C.; Lee, K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 16125–16138. For propargyl addition, see: Mszar, N. W.; Mikus, M. S.; Torker, S.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 8736–8741.

We expanded this to α selective addition of *Z*-substituted allyl boronate ***Z*–2.64** in 2018, generating products in up to 98% yield, >98:2 *Z*:*E* and 99:1 er.[26] We were somewhat surprised to find that contrary to additions to phosphinoyl imines (see Chapter One), direct addition of the initially generated allyl complex **2.65** was more competitive than 1,3-boyl shift. To develop a method for synthesis of α-tertiary trifluoromethyl amines, particularly those with defined olefin geometry, we initiated an investigation into *N*-H ketimines substituted with a trifluoromethyl group. It was not clear to us whether the smaller size difference between the two substituents would afford enantiotopic discrimination of if the product, a basic primary amine, could sequester the ammonium-based catalyst.

2.4 Development of Catalytic, Enantioselective Synthesis Of α-Tertiary Trifluoromethyl Amines

2.4.1 Methods for Synthesis of N-H Ketimines (Survey of the State-of-the-Art)

Our first objective was to identify a method to access the requisite ketimine **2.42**. After a survey of the literature, we found three methods for synthesis of *N*-H trifluoromethyl ketimines: (1) Addition of Grignard reagent **2.73** to trifluoroacetonitrile **2.72,**[27] (2) Reaction of trifluoroketone **2.62** with methylchloroaluminum amide **2.74**,[28] and (3) Aza-Wittig reaction of trifluoroketone **2.62** with imino triphenylphosphorane **2.75**.[22] Each has its own drawback, including multiple step preparation requiring pyrophoric reagents for synthesis of aluminum complex **2.74**, trifluoroacetonitrile **2.72** is a toxic gas, and the aza-Wittig reaction generates an equivalent of triphenylphosphine oxide **2.76** as a byproduct.

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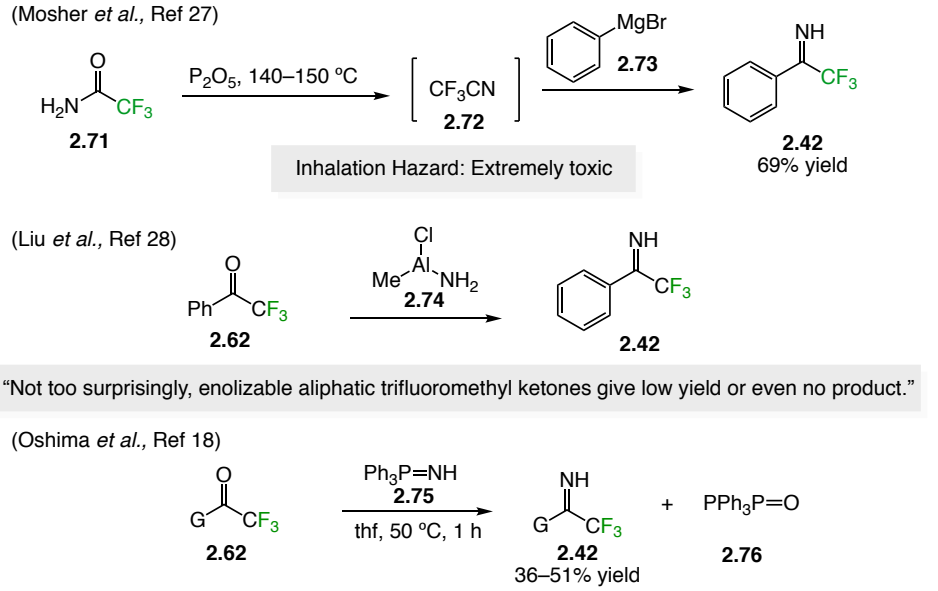
26) van der Mei, F. W.; Qin, C.; Morrison, R. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 9053–9065.

27) Koos, M.; Mosher, H. S. *Tetrahedron* **1993**, *49*, 1541–1546.

28) Kende, A. S.; Liu, K. *Tetrahedron Lett.* **1995**, *36*, 4035–4038.

Scheme 2.10. Methods to Directly Access *N*-H Ketimines



Recognizing that silyl-substituted aldimines are *N*-H surrogates[29] and have been widely employed in enantioselective transformations involving alkyl nucleophiles,[30] allyl addition,[31] propargyl addition,[32] cycloaddition,[33] and Mannich-type reactions,[34] we reasoned that silyl ketimines may be well suited for our purpose.

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29) Chen, G.-M.; Brown, H. C. *J. Am. Chem. Soc.* **2000**, *122*, 4217–4218.

30) Itsuno, S.; Sasaki, M.; Kuroda, S.; Ito, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1507–1510.

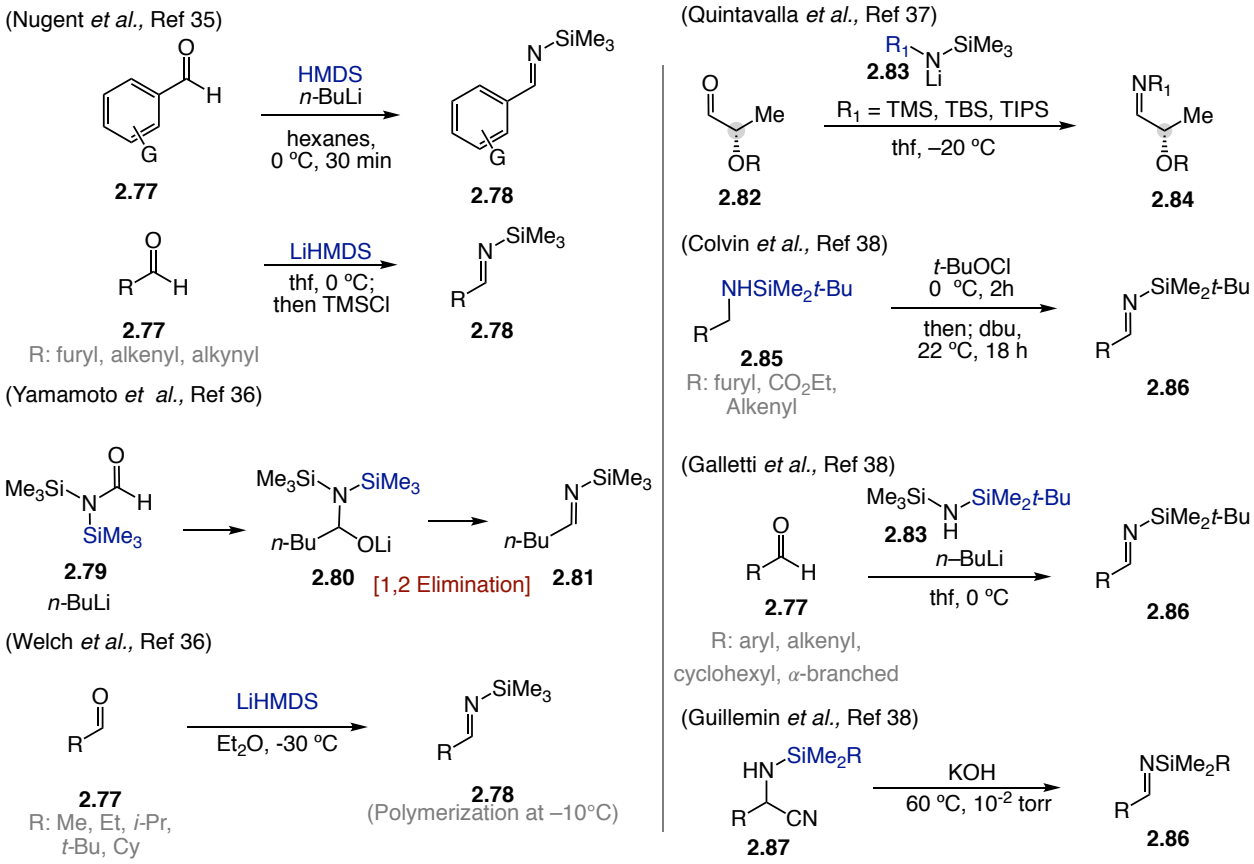
31) (a) El-Shehawy, A. A.; Abdelaal, M. Y.; Watanabe, K.; Ito, K.; Isuno, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1731–1734. (b) Chen, G.-M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 825–826. (c) Ramachandran, P. V.; Burghardt, T. E. *Chem. Eur. J.* **2005**, *11*, 4387–4395. (d) Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712–8713. (e) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74–75. (f) Román, J. G.; Soderquist, J. A. *J. Org. Chem.* **2007**, *72*, 9772–9775. (g) Chataigner, I.; Zammattio, F.; Lebreton, J.; Villiéras, J. *Tetrahedron* **2008**, *64*, 2441–2455. (h) Kuznetsov, N. Y.; Maleev, V. I.; Khrustalev, V. N.; Mkrtchyan, A. F.; Godovikov, I. A.; Strelkova, T. V.; Bubnov, Y. N. *Eur. J. Org. Chem.* **2012**, 334–344. (i) Chen, J. L.-Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 10992–10996.

32) (a) Chemla, F.; Ferreira, F.; Hebbe, V.; Stercklen, E. *Eur. J. Org. Chem.* **2002**, 1385–1391. (b) Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081–1084.

33) (a) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, Fernández, M.; Cabal, M.-P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805–811. (b) Bongini, A.; Panunzio, M.; Bandini, E.; Campana, E.; Martelli, G.; Spunta, G. *Tetrahedron: Asymmetry* **2001**, *12*, 439–454. (c) Fernández-Garcia, J. M.; Fernández-Rodriguez, M. A.; Aguilar, E. *Org. Lett.* **2011**, *13*, 5172–5175.

34) (a) Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron*, **1997**, *53*, 5909–5924. (b) Fujieda, H.; Hata, S.; Yamada, K.-i.; Tomioka, K. *Hetereocycles* **2005**, *66*, 603–610.

Scheme 2.11. Methods to Access Silyl-Substituted Imines



Additionally, as a result of such widespread use, an array of methods have been developed to address synthesis of aryl–[35] and alkyl–substituted imines,[36] including compounds with an α-stereogenic centers[37] and other silyl protecting groups.[38] We hoped these advances could extend to synthesis of ketimines and were pleased to find a report from Merck describing synthesis of *N*-

35) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron*, **1988**, *44*, 4157-4172.

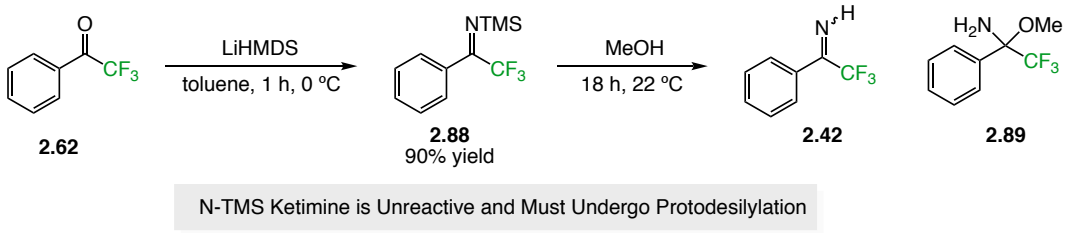
36) (a) Uyehara, T.; Suzuki, I.; Yamamoto, Y. *Tetrahedron Lett.*, **1989**, *30*, 4275-7278. (b) Gyenes, F.; Bergmann, K. E.; Welch, J. T. *J. Org. Chem.* **1998**, *63*, 2824-2828.

37) Cainelli, G.; Giacomini, D.; Galletti, P.; Quintavalla, A. *Eur. J. Org. Chem.* **2002**, 3153-3161.

38) (a) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron*, **1988**, *13*, 4157-4172. (b) Guillemin, J.-C.; Ammi, L.; Denis, J. M. *Tetrahedron Lett.* **1988**, *29*, 1287-1288. (c) Cainelli, G.; Giacomini, D.; Galletti, P. *Synthesis*, **1997**, 886-890. (d) Richy, N.; Ghoraf, M.; Vidal, J. *J. Org. Chem*. **2012**, *77*, 10972−10977.

silyl trifluoromethylketimines, which we considered an excellent starting point to commence investigations.[39]

Scheme 2.12. Synthesis of Silyl-Substituted Trifluoromethyl Ketimines



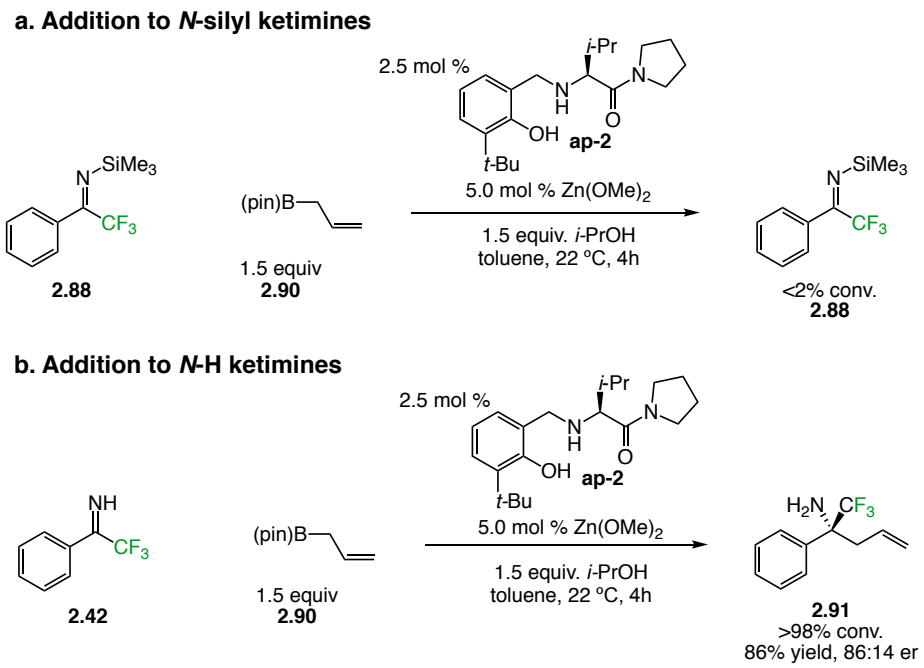
2.4.2 Catalytic Enantioselective Addition to Ketimines

We first synthesized silyl imine **2.88** as previously described[39] and subjected it to conditions typically employed for aminophenol promoted allyl addition (5.0 mol % aminophenol, 10 mol % $Zn(OMe)_2$, 1.5 equiv iPrOH).[40] The transformation was inefficient, however (<2% conv). Recognizing that the silyl group was likely excised under the reaction conditions in the original report by Merck chemists, we synthesized *N*-H ketimine **2.42** to ascertain whether this species would be an appropriate electrophile, and thus we were able to isolate homoallylic amine **2.91** in 86% yield and 86:14 er.

39) Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 355–358. In the course of preparing this manuscript, another report appeared detailing silyl imine synthesis: Sukach, V.; Melnykov, S.; Bertho, S.; Diachenko, I.; Retailleau, P.; Vovk. M.; Gillaizeau, I. *Org. Lett.* **2019**, *21*, 2340–2345.

40) Typically, MeOH is employed as the proton source; however, under these conditions we observed ~20% hemiaminal formation that complicated purification and accurate determination of enantioselectivity.

Scheme 2.13. Probing the Catalytic Reaction: The Need for *N*-H Ketimines[a]



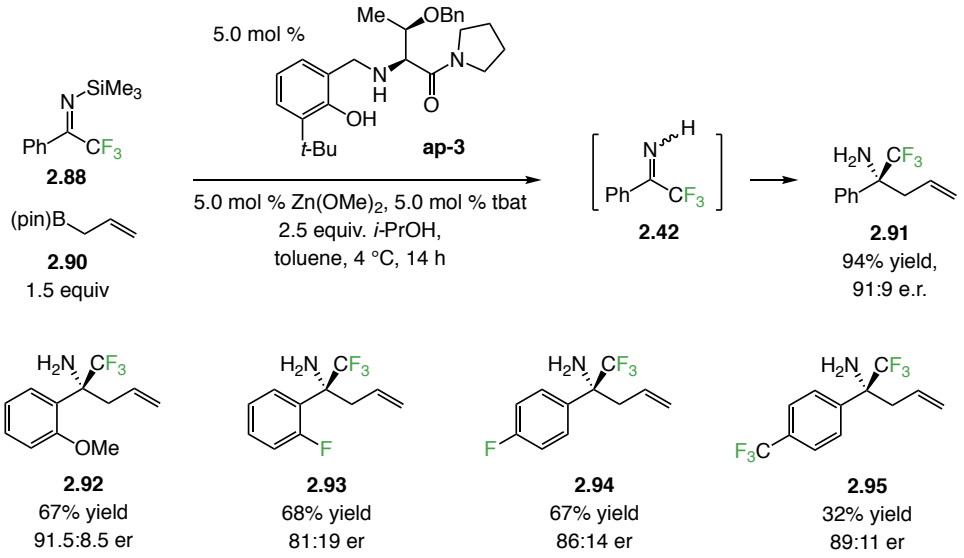
[a]All reactions were performed under N_2 atm. Conv (±2%) determined by analysis of ^{19}F NMR spectra of unpurified mixtures; Conv refers to disappearance of **2.88** and **2.42**, respectively. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

As a result of low yields for preparation of **2.42**, we sought to find a method that could incorporate the easier-to-handle silyl derivative **2.88.** We knew silyl removal could be effected by treatment with solvent quantities of methanol per the original disclosure, but then *N*-H ketimine **2.42** could react further, furnishing stable hemiaminal **2.89**, a species that was not suitable for allyl addition. To circumvent this, we opted to include an appropriate fluoride reagent and MeOH as the proton source. To our delight, soluble and non-hygroscopic tetrabutylammonium difluorotriphenylsilicate (tbat) yielded clean silyl removal in a matter of minutes without significant formation of **2.89**.[41] Despite considerable efforts towards optimization, the highest levels of enantioselectivity we could obtain for allyl addition were 91.5:8.5 er when promoted by

41) See Experimental Section for details.

benzyl-threonine catalyst **ap-3** (more on this later). What is more, screening of a subset of substrates revealed a broad distribution of yield and enantioselectivities.

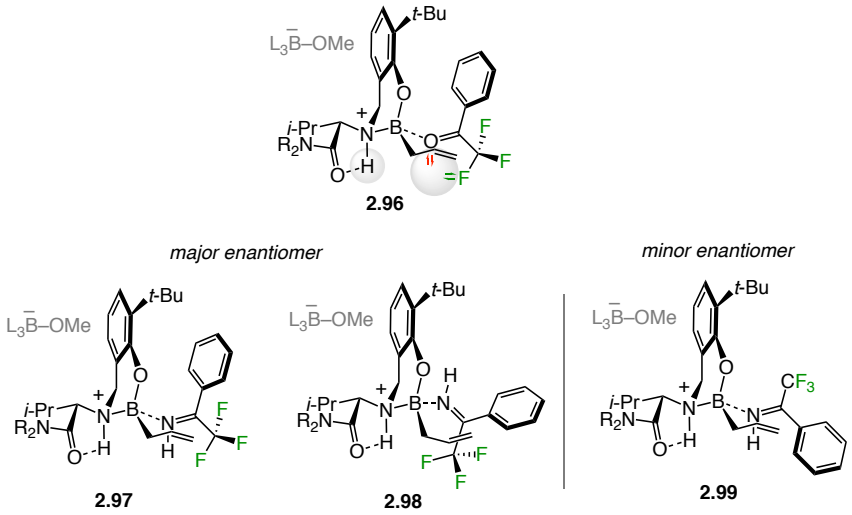
Scheme 2.14. Scope of Allyl Addition to Trifluoroketimines[a]



[a]All reactions were performed under N_2 atm. Conv (±2%) determined by analysis of ^{19}F NMR spectra of unpurified mixtures; Conv refers to disappearance of the ketimine. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). tbat: tetrabutylammonium difluorotriphenylsilicate. See Experimental Section for details.

We could rationalize the lower selectivity obtained for addition to trifluoromethyl ketimines, as opposed to ketones,[25] through analysis of transition state models. We reasoned that for ketones, enantiofacial discrimination is favored by an alleviation of electron-electron repulsion between the carbonyl oxygen and fluorine of the trifluoromethyl group (highlighted in Scheme 2.15, **2.96**) through coulombic attraction with the ammonium ion. For additions to ketimines (**2.97**), the benefit of a stabilizing interaction is no longer existent due to the *N*-H, and in these cases steric pressure between the catalyst's *tert*-butyl group and the aryl fragment of the ketimine can cause the pathway involving **2.99** to become more competitive.

Scheme 2.15. Stereochemical Models for Additions to Ketones and Ketimines

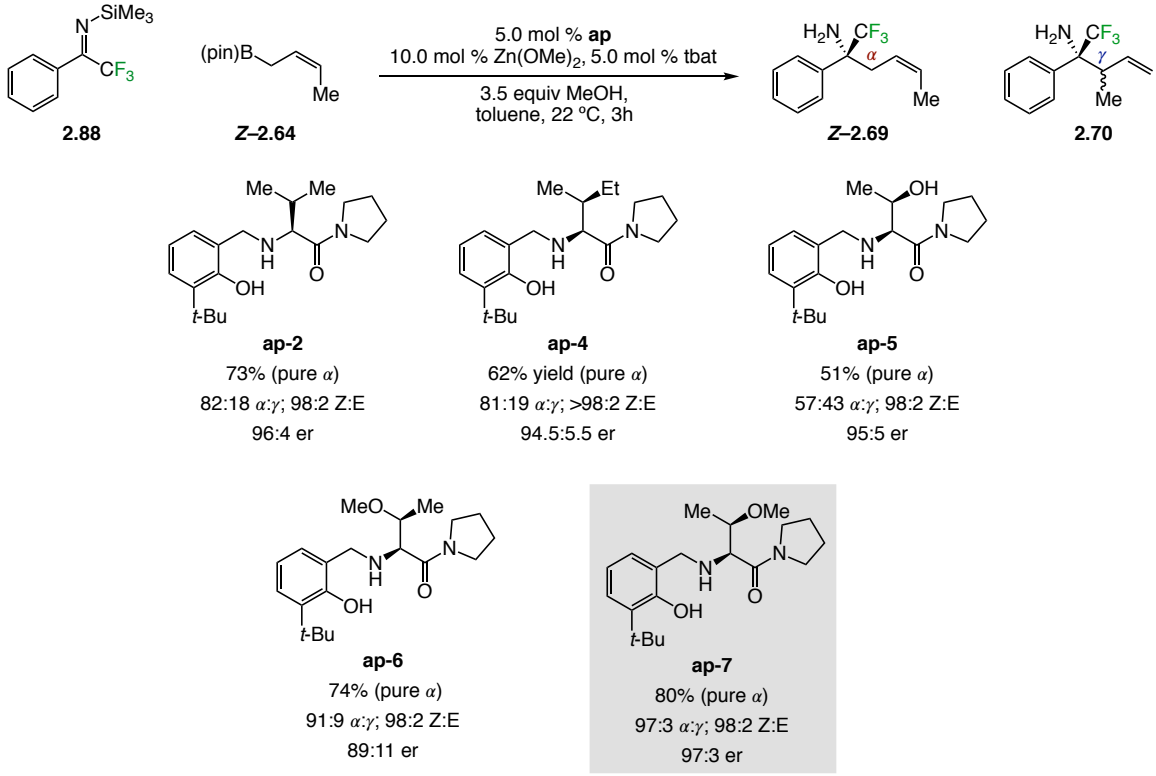


To address poor regioselectivity, we considered addition of substituted allyl boronates because for additions to ketones, enantiomeric ratios were higher than the corresponding allyl additions. This is likely due to the influence of the additional allylic stereogenic center that is favorably oriented pseudo-axially (**2.65**, Scheme 2.9). Under these conditions, enantiotopic discrimination is favored by steric *and* electronic factors leading to larger energy differences between competitive transition states. Accordingly, we subjected trifluoroketimine **2.88** to ***Z*–2.64** promoted by 5.0 mol % **ap-2**, 10 mol % $Zn(OMe)_2$ and 3.5 equiv MeOH affording ***Z*–2.69** in 73% yield, 82:18 α:γ ratio, 98:2 *Z*:*E* and 96:4 er. We were pleased to observe moderate levels of α selectivity, indicating that despite decreased electrophilicity, relative to ketones, a combination of the inductive and steric effects of the trifluoromethyl group were sufficient to favor direct addition versus 1,3-boryl shift. To circumvent pathways accounting for 18% of γ-addition product **2.70**, we turned to modifying the catalyst structure, which could be rapidly carried out due to modular synthesis of the scaffold.

We began by synthesizing **ap-4**, bearing an isoleucine residue, to probe whether increased steric bulk and the presence of an additional stereogenic center would affect the observed regioselectivity. However, these modifications proved ineffective. We thus incorporated the more polar threonine residue with hopes that a catalyst bearing an alternate ligation site may sequester

the zinc (II) co-catalyst or reversibly coordinate to the boron center preempting olefin association, nonetheless the impact was deleterious and favored the undesired γ-product. In line with optimal results obtained for allyl addition to ketimines (Scheme 2.14), we found that reaction promoted by catalysts derived from *O*–methyl threonine proved more effective. Specifically, with **ap-6** and **ap-7**, regioselectivity improved to 91:9 and 97:3 α:γ ratio, while retaining high *Z* selectivity, and in the case of **ap-7**, enantioselectivity was further improved to 97:3 er.

Scheme 2.16. Identification and Evaluation of an Optimal Aminophenol[a]

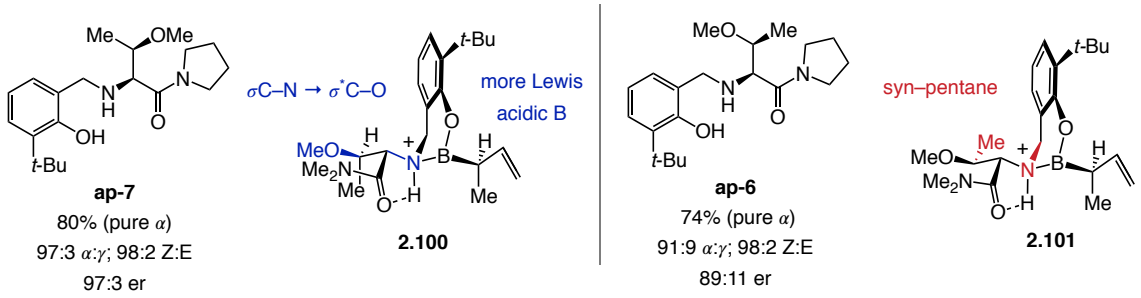


[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures; Conv refers to disappearance of **2.88**. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

Recognizing that improvement was not due to a steric effect (Scheme 2.16, c.f. **ap-4** and **ap-7**), we reasoned that the benefit must be largely electronic. One possible explanation is that for **ap-7**, there is orbital overlap between the C–N and C–O bonds allowing for beneficial σC–N →

σ^*C–O hyperconjugation. The reduced electron density on nitrogen increases the vacancy of the p-orbital on boron facilitating substrate coordination. Alternatively, in **ap-6**, in order for similar overlap to be feasible, a *syn*-pentane interaction develops between the methyl substituent and the catalyst backbone (Scheme 2.17, **2.106**). The latter conformation is thereby higher in energy and affords greater chance for addition to occur through competitive modes, resulting in diminished α:γ ratios and er.

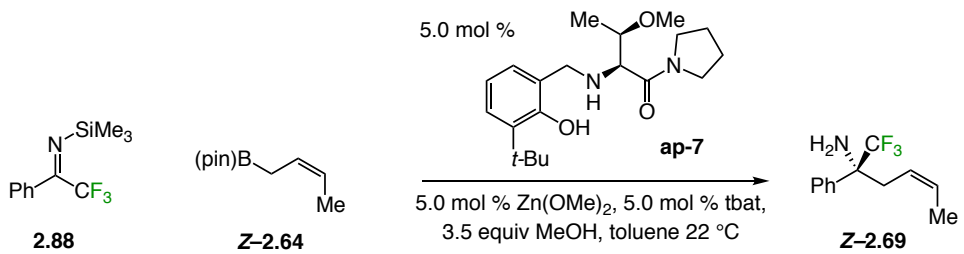
Scheme 2.17. Rationale for Selectivities Obtained with Diastereomeric Complexes[a]



[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures; Conv refers to disappearance of **2.88**. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

For further optimization, we investigated additions to **2.88** in the presence of a variety of known promoters for Si–O bond cleavage to determine the effect. Under all conditions we observed complete consumption of **2.88**, however the less soluble fluoride sources (CsF, $(CH_3)_4NF$; Table 1, entry 1 and 4) led to lower yields. The more basic and hygroscopic (n-Bu_4)NF was less effective and afforded ***Z*–2.69** with diminished *Z* selectivity (84:16–96:4 *Z*:*E*, Table 1, entry 2-3).

Table 1. Examination of Different Fluoride Reagents[a]



2.88 | ***Z*–2.64** (1.3 equiv) | ***Z*–2.69**

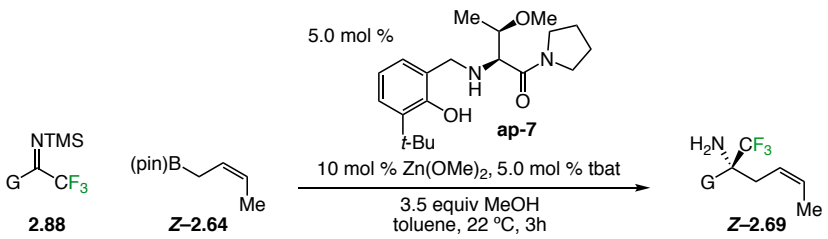
Entry	Reagent	N-H Ketimine (%)	Conv. to ***Z*–2.69** (%)	Hemiaminal (%)	*Z*:*E* (α-add. isomer)	e.r. (α-add. isomer)
1	CsF	>98	36	19	>98:2	97:3
2	$(n\text{-Bu})_4NF$ (solid)	>98	58	15	84:16	97:3
3	$(n\text{-Bu})_4NF$ (1.0 M, thf)	>98	88	<5	96:4	97:3
4	$(Me)_4NF$	>98	25	<10	>98:2	97:3
5	tbat	>98	>98	<10	>98:2	97:3

[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures; Conv refers to disappearance of **2.88**. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

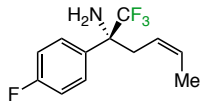
2.4.3 Scope

With optimal conditions in hand, we explored the scope of the method. In most instances, the substitution on the aryl group had little effect on enantioselectivity, as electron-deficient *para*-trifluoromethyl ***Z*–2.105** and electron-rich *para*-methoxyphenyl ***Z*–2.106** and were isolated in 61% and 78% yield, 98:2 and 94:6 α:γ ratio, 96:4 and 92:2 *Z*:*E* and 97:3 and 98:2 er, respectively. Under the same conditions, for *para*-dimethylamino substituted ***Z*–2.107** we observed <2% Si–O bond cleavage and recovery of starting material. Fortunately, subjecting the imine to silyl removal (tbat and 1.75 equivalents of MeOH) prior to the addition of an aminophenol and $Zn(OMe)_2$ solution allowed us to isolate ***Z*–2.107** in 50% yield, 87:13 α:γ ratio, 98:2 *Z*:*E* and 98:2 er. The diminished regioselectivity is likely a consequence of the less electrophilic ketimine which affords greater chance for competitive boryl shift.

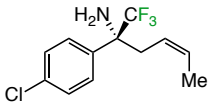
Scheme 2.18. Scope of Addition to Trifluoromethyl Ketimines[a]



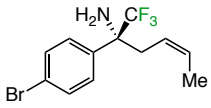
2.88 **Z–2.64** **Z–2.69**



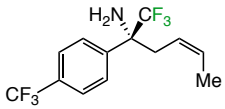
Z–2.102
68% (pure α)
93:7 α:γ; 98:2 *Z*:*E*
97:3 er



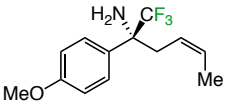
Z–2.103
87% yield
95:5 α:γ, 95:5 *Z*:*E*
96:4 er



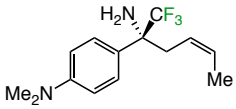
Z–2.104
67% (pure α)
96:4 α:γ; 97:3 *Z*:*E*
98:2 er



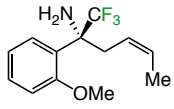
Z–2.105
61% (pure α)
98:2 α:γ; 96:4 *Z*:*E*
97:3 er



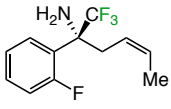
Z–2.106
78% yield
94:6 α:γ; 98:2 *Z*:*E*
98:2 er



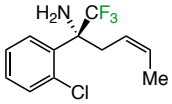
Z–2.107[e]
50% (pure α)
87:13 α:γ; 98:2 *Z*:*E*
98:2 er



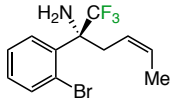
Z–2.108
70% (pure α)
96:4 α:γ; 98:2 *Z*:*E*
99:1 e.r.



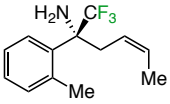
Z–2.109
89% yield
96:4 α:γ; 98:2 *Z*:*E*
97:3 er



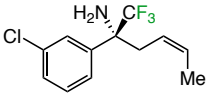
Z–2.110[b]
79% yield
74:26 α:γ; 98:2 *Z*:*E*
96:4 er



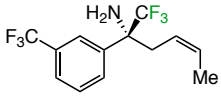
Z–2.111
53% yield
59:41 α:γ; 97:3 *Z*:*E*
90:10 er



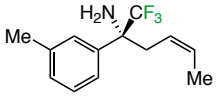
Z–2.112
52% yield,
45:55 α:γ; 98:2 *Z*:*E*
95:5 er



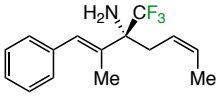
Z–2.113
90% (pure α)
>98:2 α:γ; 97:3 *Z*:*E*
96:4 er



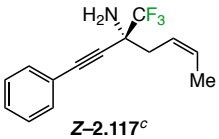
Z–2.114
82% (pure α)
98:2 α:γ; 98:2 *Z*:*E*
97:3 er



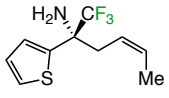
Z–2.115
67% yield
91:9 α:γ, >98:2 *Z*:*E*
96:4 er



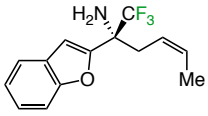
Z–2.116
64% yield
91:9 α:γ; 96:4 *Z*:*E*
98:2 er



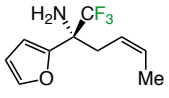
Z–2.117[c]
81% yield
80:20 α:γ; 96:4 *Z*:*E*
93:7 er



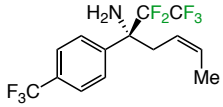
Z–2.118
84% yield
98:2 α:γ; 97:3 *Z*:*E*
93:7 er



Z–2.119[b]
77% yield
87:13 α:γ; >98:2 *Z*:*E*
97.5:2.5 er



Z–2.120
32% yield
89:11 α:γ; 98:2 *Z*:*E*,
97:3 er



Z–2.121
72% yield
98:2 α:γ, 98:2 *Z*:*E*
97:3 er

[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures; Conv refers to disappearance of silyl ketimine. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). [b]Ketimine was fully desilylated in situ prior to addition of other reagents. [c]2.5 equiv MeOH were employed, and reaction was allowed to stir for 14 h. Experiments run at least in triplicate. See Experimental Section for details.

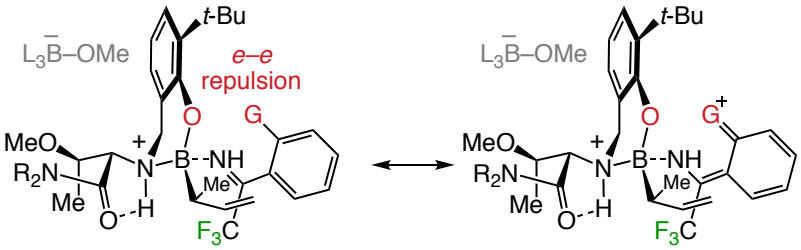
Additions to alkenyl[42] **(*Z*–2.116**) and alkynyl-substituted ***Z*–2.117** proceeded with high efficiency, but α:γ selectivity was notably lower for ***Z*–2.117**. Competitive addition of methanol to less hindered ***Z*–2.117** resulted in significant (~20%) hemiaminal formation. The reversible formation of hemiaminal probably diminishes the effective concentration of ketimine present in solution, rendering boryl shift more competitive. Substitution of methanol for larger *i*-PrOH required elevated temperature and extended reaction time (60 °C, 14 h). While these conditions reduced hemiaminal formation, it was at the expense of enantioselectivity (86:14 vs 96.5:3.5 er). Heteroaryl-substituted ketimines may be used, as indicated by thienyl-***Z*–2.118** and benzofuranyl-***Z*–2.119**. Additions to the somewhat moisture-sensitive furyl substituted ketimines were less efficient (32% yield, 89:11 α:γ ratio, 98:2 *Z*:*E*, 97:3 er). A noteworthy observation, however, is that, unlike additions to the corresponding ketones, additions to 2-substituted heterocycles did not afford products in lower er. Furthermore, the trend is reversed (i.e. thienyl-substituted ***Z*–2.118** was isolated with lower enantioselectivity than ***Z*–2.120).** The exact origin of this discrepancy remains to be investigated further, but demonstrates that the *N*-H may be involved.

These data suggest that steric repulsion between an *ortho* substituent and the catalyst dramatically affects the efficiency. With larger substrates ***Z*–2.108–2.112**, repulsion between the *ortho*-substituent and the catalyst can disfavor addition and allow alternative pathways (either catalyzed or non-catalyzed) to become more competitive. While steric factors could be playing a role, electronic factors might be operative as well, as underscored by the highly selective additions to *o*-OMe substituted ***Z*–2.108** and *o*-F ***Z*–2.109**. In the proposed mode of addition (**2.122**) electron-electron repulsion between the phenoxy oxygen of the catalyst and the lone pair of the *ortho* substituent cannot be relieved and the alternative ketimine conformer positioning the *ortho*-substituent and the trifluoromethyl group in a proximal manner suffers from severe steric hindrance. Substrates possessing *ortho*-substitution with better orbital overlap with the arene, (i.e., *o*-F and *o*-OMe) underwent more efficient reactions, perhaps because of resonance structure **2.123**

42) Synthesis of a disubstituted ketimines were not accomplished due to a facile [4+2] cycloaddition.

wherein repulsion can be reduced. Accordingly, we isolated ***Z*–2.109** in synthetically useful yield, which may be elaborated to a BACE-1 inhibitor, developed by Novartis.[43]

Scheme 2.19. Resonance Structures Leading to Reduced Repulsion

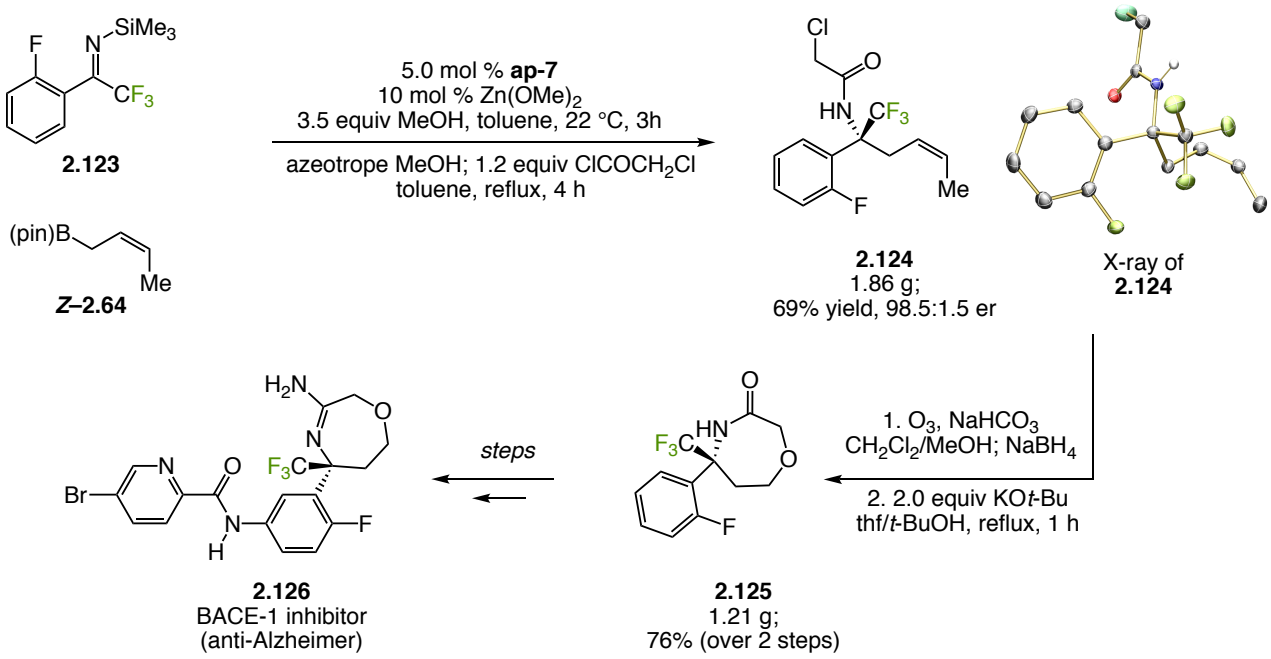


2.4.4 Derivatization of the Obtained Homoallylic Amines

The method is amenable to gram-scale synthesis allowing us to secure 1.86 g of **2.124**, upon treating the unpurified amine with 1.5 equivalents of chloroacetyl chloride in refluxing toluene for four hours. The crystalline nature of the amide aided us in purifying the product, and allowed us to secure the X-ray structure for absolute and relative stereochemistry determination. Subsequent oxidative cleave of the olefin by treatment with ozone, followed by reductive work-up ($NaBH_4$) afforded an unpurified alcohol that was directly subjected to alkylation by treatment with KO*t*-Bu (thf/*t*-BuOH), affording 1.21 g of **2.125**. The efficiency with which this core was assembled is expected to facilitate preparation of diverse azepanes with potential bioactivity.

43) Badiger, S.; Chebrolu, M.; Frederiksen, M.; Holzer, P.; Hurth, K.; Li, L.; Liu, H.; Lueoend, R. M.; Machauer, R.; Moebitz, H.; Meumann, U.; Ramos, R.; Rueeger, H.; Schaefer, M.; Tintelnot-Blomley, M.; Veenstra, S. J.; Voegtle, M.; Xiong, X. PCT. Int. Appl. 2012006953.

Scheme 2.20. Gram-Scale Formal Synthesis of BACE-1 Inhibitor[a]



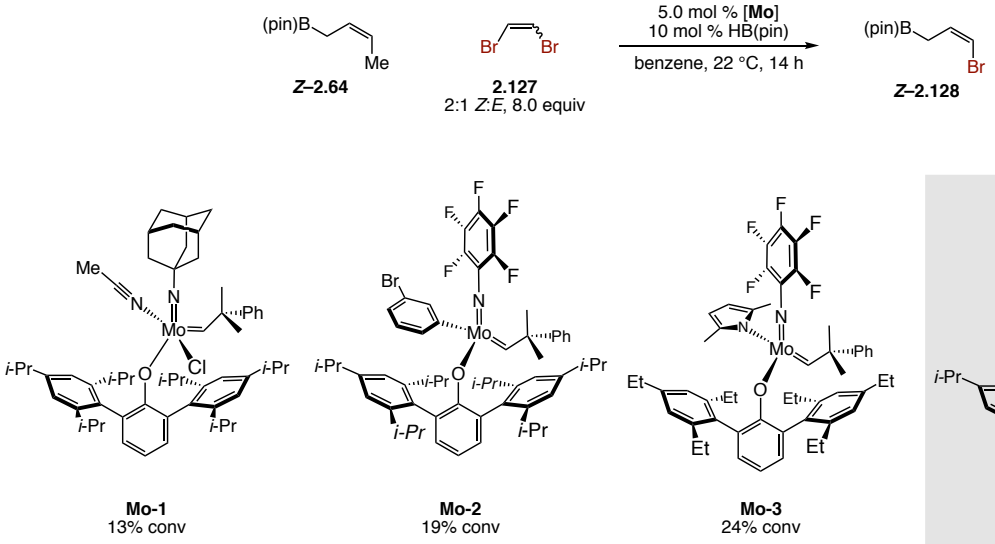
[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

The utility of the method extends beyond addition of methyl-substituted allyl boronate ***Z*–2.64**. Additions of *Z*-Cl substituted allyl boronate furnished alkenyl chloride **2.129,** albeit in lower er. We considered that perhaps selectivity could be improved with the sizable bromo-substituted reagent ***Z*–2.128**. To access the requisite reagent, we explored the possibility of stereoretentive cross-metathesis. A survey of molybdenum-based monoaryloxide pyrrolide complexes[44] allowed us to identify **Mo-4** as optimal.

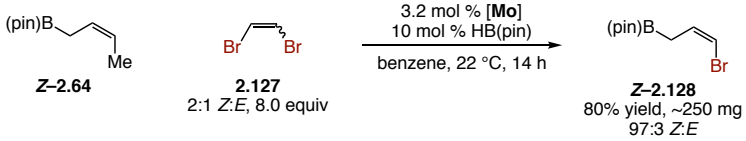
44) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465.

Scheme 2.21. Identification and Application of Mo-Based Complex for Cross-Metathesis[a]

a. Initial evaluation of complexes



b. Optimized reaction conditions and scale-up

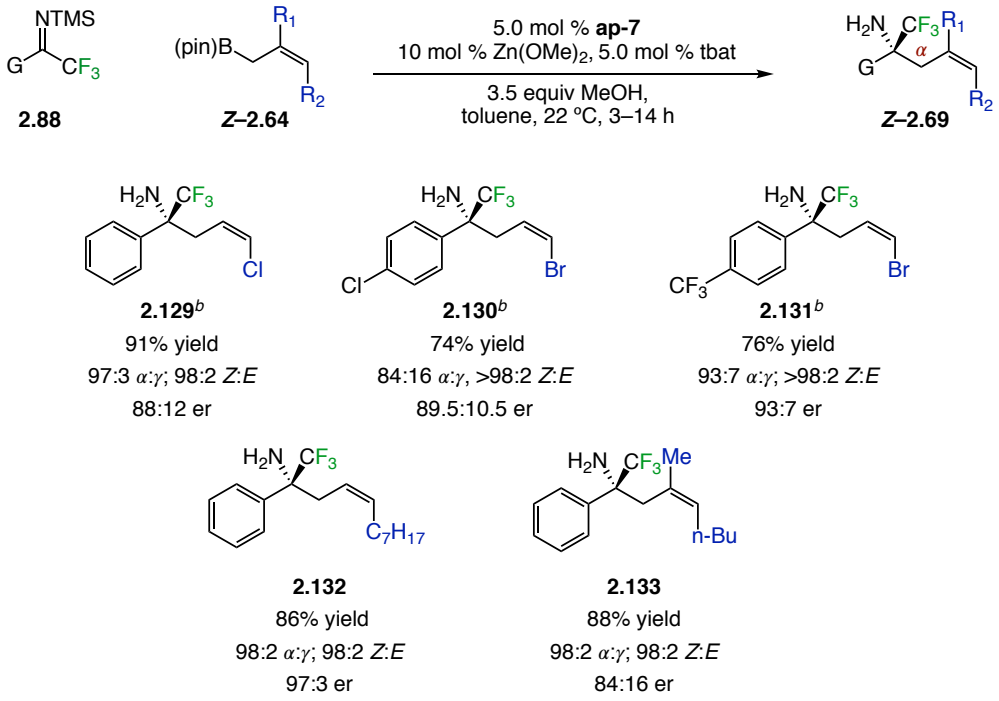


[a]All reactions were performed under N_2 atm. Conv and *Z*:*E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of ***Z*–2.64**. Yield of isolated and purified product (±5%). pin: pinacolato. See Experimental Section for details.

With phenyl-substituted ketimine **2.88**, we found that although Si-O bond cleavage was readily accomplished, addition was sluggish, and afforded product in 35% yield and 89:11 er. We attributed the lower efficiency to the larger bromine substituent and longer C–Br bond (vs C–Cl) which could impede allyl transfer to the aminophenol boron-based complex. In such cases, competitive and non-selective processes, such as addition of methanol or hydrolysis of the ketimine, can become prevalent. This issue was addressed through the use of a ketimine possessing the strongly electron-withdrawing *para*-trifluoromethyl group, allowing us to secure ***Z*–2.131** in 76% yield, 93:7 α:γ ratio, and 93:7 er, as a single olefin isomer. With *para*-chloro-substituted imine, ***Z*–2.132** was generated efficiently; however, there was an erosion in α selectivity. Addition

to the less electrophilic halo-substituted substrate (vs trifluoromethyl) was not as competitive, likely as a result of the impetus to reduce steric pressure between the catalyst and bromo-substituent through boryl shift.

Scheme 2.22 Addition of γ-Substituted Organoboron Reagents[a]



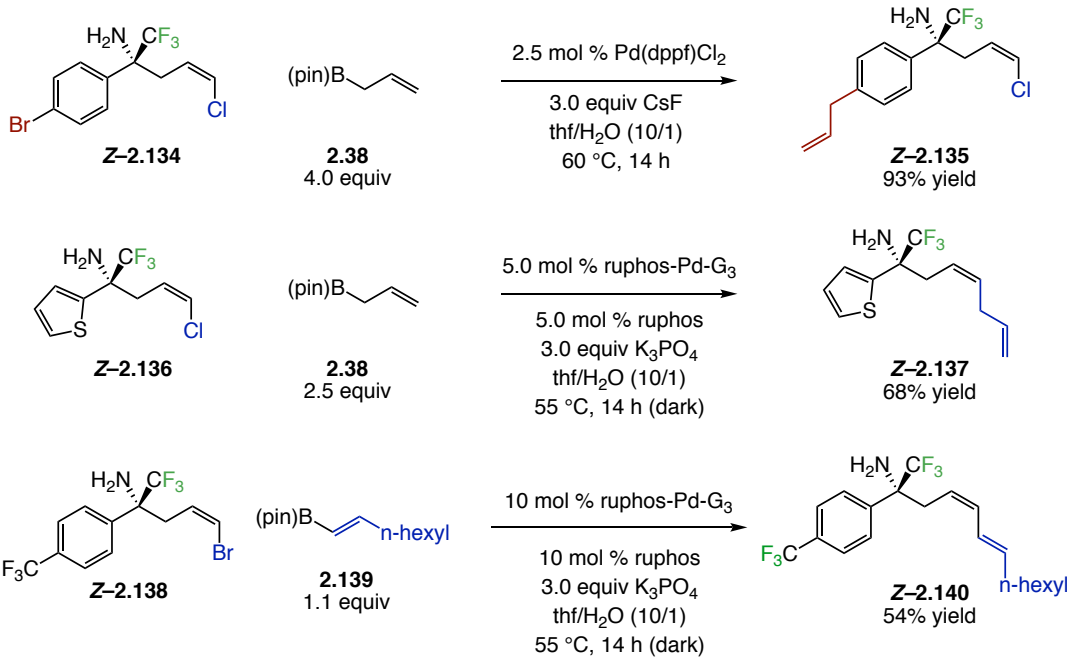
[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures; Conv refers to disappearance of silyl ketimine. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). [b]Ketimine was fully desilylated in situ prior to addition of other reagents. Experiments run at least in triplicate. See Experimental Section for details.

Addition of *n*-heptyl-substituted allyl boronic ester, accessed through catalytic 1,4-boron hydride addition to a diene,[45] proceeded with similar efficiency and enantioselectivity, furnishing ***Z*–2.132** in 86% yield and 97:3 er. Equally notable, ***Z*–2.133** bearing a trisubstituted olefin was isolated, albeit in 84:16 er, likely a consequence of increased steric pressure in the transition state caused by the C_2 methyl on the corresponding allyl reagent.

45) Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534–2535.

The utility of homoallylic amines bearing a *Z*-halo substituent was highlighted through a series of representative stereoretentive cross-coupling reactions. Such processes allow for the rapid synthesis of a diverse series of derivatives from a common intermediate.

Scheme 2.23. Product Utility Highlighted Through Cross-Coupling Methodologies[a]



[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). dppf: 1,1'-bis(diphenylphosphino)ferrocene; ruphos: 2-dicyclohexylphosphino-2,6'-diisopropoxybiphenyl. See Experimental Section for details.

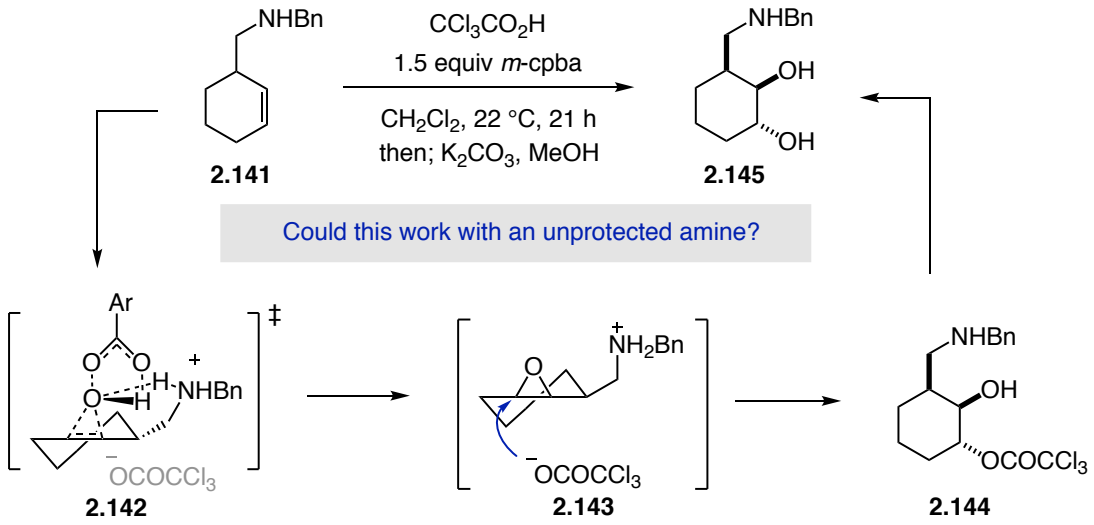
Chemoselective coupling of the more reactive aryl bromide within ***Z*-2.134** was accomplished through Suzuki coupling of allyl boronic pinacol ester **2.38**, promoted by a organophosphine-Pd complex under conditions reported by Aggarwal.[46] Stereoretentive coupling of *Z*-alkenyl chloride ***Z*-2.136** was accomplished through a phosphine-Pd-catalyzed reaction.[47]

46) Zhurakovsky, O.; Türkmen, Y. E.; Löffler, L. E.; Moorthie, V. A.; Chen, C. C.; Shaw, M. A.; Crimmin, M. R.; Ferrara, M.; Ahmad, M.; Ostovar, M.; Matlock, J. C.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2018**, *57*, 1346–1350.

47) (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916–920. (b) Bruno, N. C.; Niljiasnskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161–4166.

When shielded from light and kept at 55 °C, olefin isomerization was minimized and skipped diene ***Z*-2.137** was isolated in 68% yield. Cross-coupling of alkenyl bromide ***Z*-2.138** was accomplished in a similar manner (**2.140** in 54% yield).

Scheme 2.24. Diastereoselective Transformation Directed by Homoallylic Amine

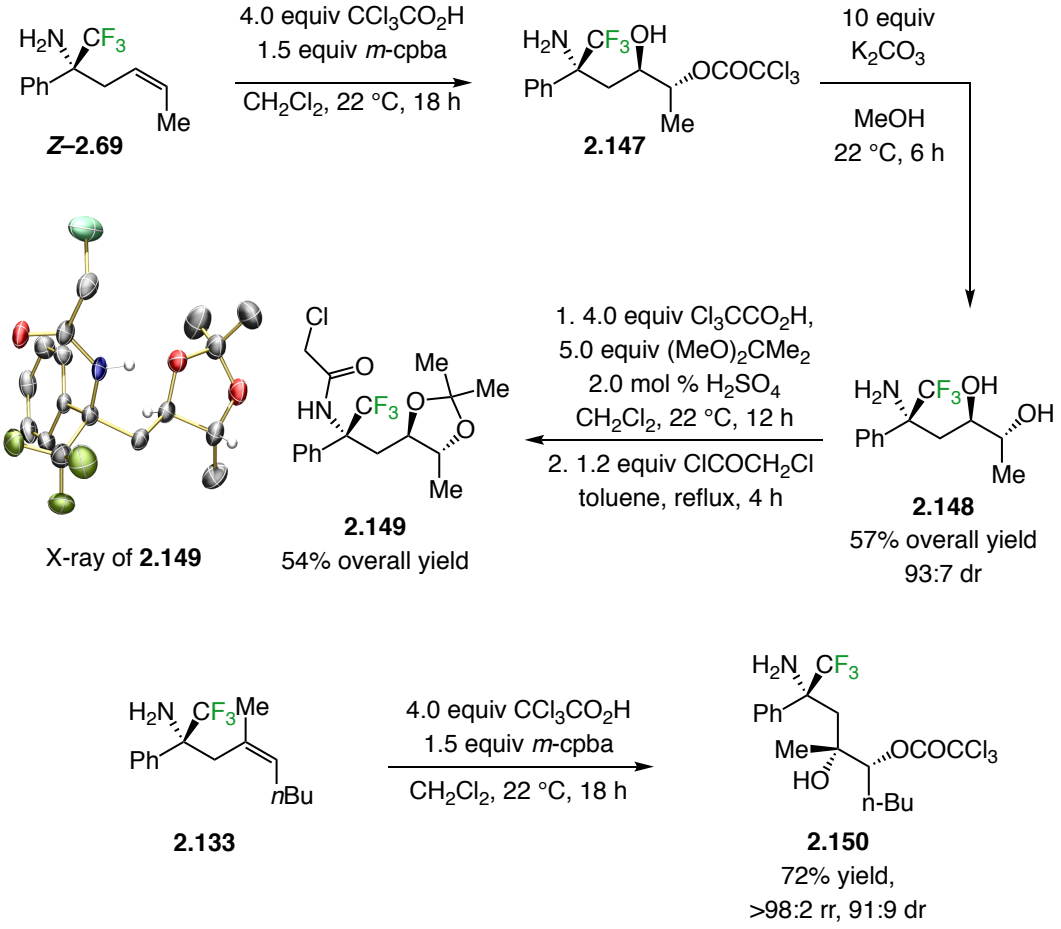


To highlight the utility of alkyl-substituted *Z* olefins, we explored diastereoselective functionalization directed by the homoallylic amine, based on studies by Davies,[48] who reported directed epoxidation of *N*-benzyl homoallylic amine **2.141**. Subsequent ring opening through addition of an acetate anion, leading to the formation of differentially protected diol **2.144**. followed by saponification with mild base furnished diol **2.145**. As we considered applying this strategy to products obtained from our method, two important questions arose: (1) Would the reaction be efficient with an unprotected amine, particularly one that does not bear a donating benzyl substituent and possesses a withdrawing trifluoromethyl group? (2) Would an acyclic system afford similar regio- and stereoselectivity? Our hope was that the Z olefin would greatly

48) Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J. Org. Chem.* **2009**, *74*, 6735–6748.

benefit us, as these transformations are typically more diastereoselective (vs *E* isomers) due to allylic strain in the transition state.[49]

Scheme 2.25. Diastereoselective Epoxidation and Regioselective Ring Opening[a]



[a]All reactions were performed under N_2 atm. Conv, and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

Treatment of ***Z*–2.69** with four equivalents of trichloroacetic acid, followed by addition of 1.5 equivalents of *m*-cpba afforded differentially protected diol **2.147**. Subsequent saponification under conditions outlined by Davies furnished diol **2.148** in 57% yield and 93:7 dr. We were able

49) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

to confirm absolute and relative stereochemistry through treatment with trichloroacetic acid to mask the nucleophilic amine, and protect the diol as an acetal. Ensuing treatment with an acid chloride afforded amide **2.149** in 54% yield**.** The same procedure was applied to synthesis of trisubstituted **2.133**, delivering **2.150** in 72% yield and 91:9 dr.

2.5 *Mechanism of Additions to Trifluoromethyl Ketimines*

2.5.1 Reactions with E- and Z-Crotyl Boronates

We have observed that for addition to phosphinoyl imines, regardless of the configuration of the allyl boronate (i.e. *E*- or *Z*-) *anti*-homoallylic amines are afforded exclusively.[50] In contrast, for additions of *E*-substituted compounds to trifluoroketones possessing an *ortho*-substituent, the transformations remain highly *Z* selective, however the opposite enantiomer is obtained.[51] To probe the effect of olefin configuration on additions to ketimines, we carried out reaction with ***E*-2.64** and ***Z*-2.64**. We found that addition of the former promoted by **ap-7** was highly inefficient (<7% conv), which is unlike transformations involving ketones and highlights the benefit of utilizing the higher energy ***Z*-2.64** for addition to less electrophilic ketimines. Moreover, we performed a parallel set of experiments promoted by diastereomeric **ap-6**. We found that, under these conditions, addition of ***E*-2.64** is comparatively more efficient (38% conv).[52] However, in accordance with our previous analysis, we found that additions promoted by **ap-6** were less α-selective, regardless of olefin stereochemistry.

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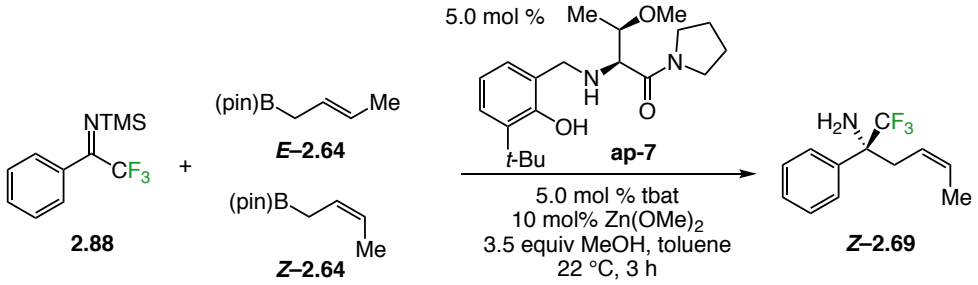
50) van der Mei, F. W.; Miyamoto, H.; Silverio, D. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4701–4706.

51) For a detailed account of this phenomenon, see ref 23.

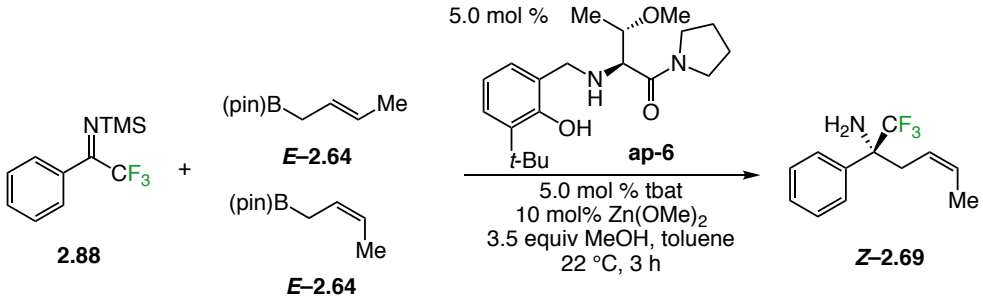
52) The difference in efficiency likely arises from a more efficient allyl transfer due to a reduction in steric hindrance between the methyl substituent of the reagent and the backbone of the catalyst.

Table 2. Effect of Olefin Stereochemistry on Selectivity and Efficiency[a]



Entry	Reagent	Conv. to ***Z*–2.69** (%)[b]	α:γ	*Z*:*E* (α-add. isomer)[b]	e.r. (α-add. isomer)[c]
1	***E*–2.64**	7 (nd)	98:2	94:6	nd
2	***Z*–2.64**	98 (84)	98:2	98:2	98:2

b. Reaction with diastereomeric aminophenol



Entry	Reagent	Conv. to ***Z*–2.69** (%)[b]	α:γ	*Z*:*E* (α-add. isomer)[b]	e.r. (α-add. isomer)[c]
1	***E*–2.64**	38 (22)	84:16	76:24	85:15
2	***Z*–2.64**	98 (88)	89:11	97:3	92:8

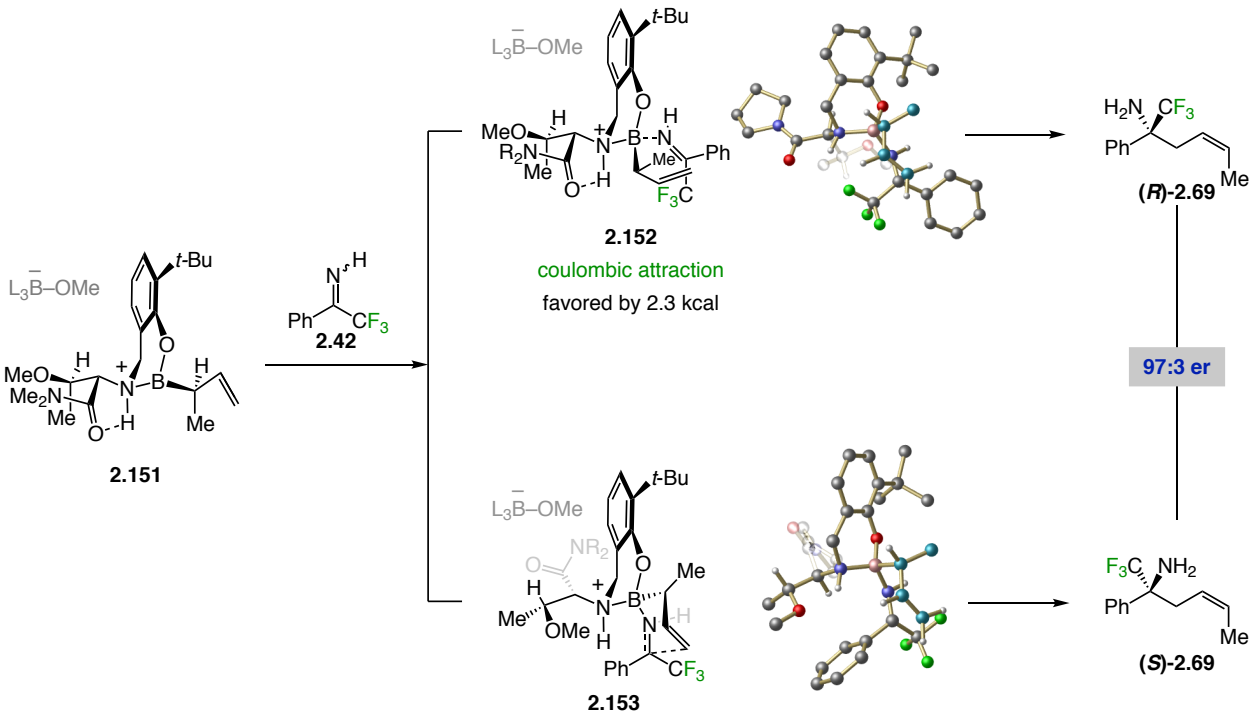
[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures; Conv refers to disappearance of **2.88**. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

2.5.2 Computational Modeling of Transition States

As introduced in section 2.3, high levels of enantioselectivity can result from electrostatic interaction involving the catalyst's ammonium group.[25] For further insight, we carried out DFT

studies for the C–C bond forming step, be it via a chair or boat transition state or either of the ketimine stereoisomers (i.e., H *syn* to $–CF_3$ or –Ph).[53] The lowest energy transition state was thus found to lead to ***R*-2.69** as the major enantiomer and ***S*-2.69** as the minor product (along with ***E*–2.70**, Schemes 2.26 and 2.27).

Scheme 2.26. Transition State Analysis to Account for Enantioselectivity[a]



[a] *Calculations performed at M06/DEF2TZVPP//M062X/DEF2SVP$_{toluene(SMD)}$. See Experimental Section for details.*

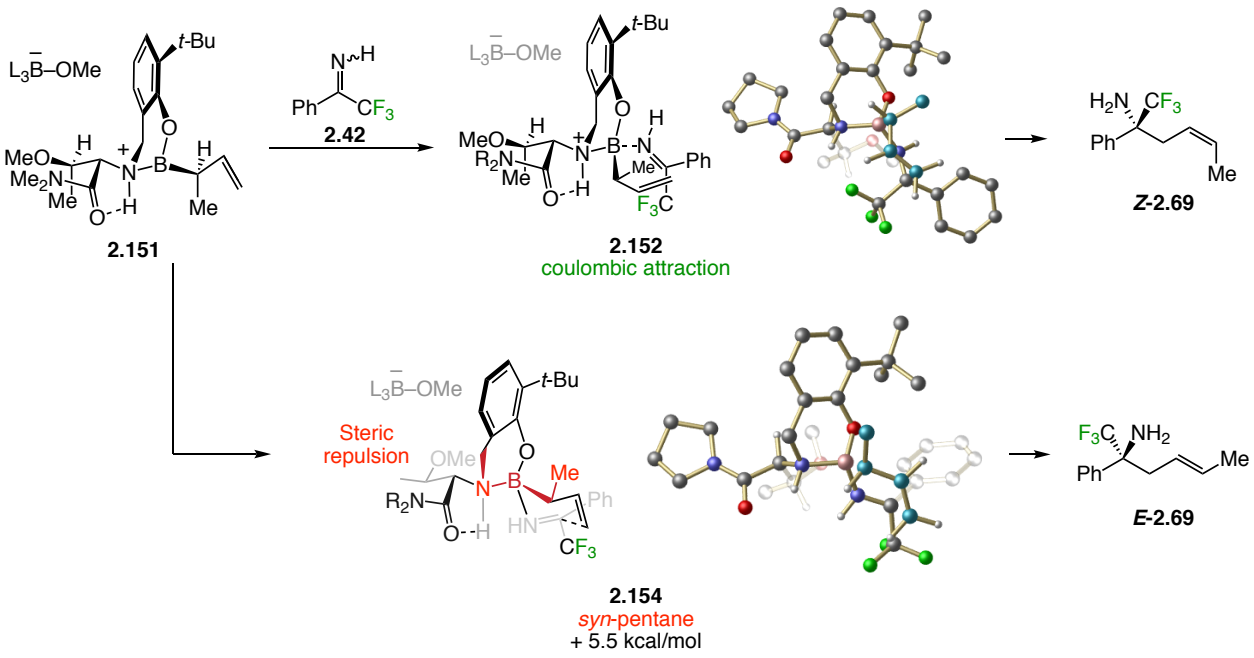
We found that in the lowest energy transition state **2.152**, which leads to the experimentally observed enantiomer, despite the imine reacting through its higher energy conformation (H *syn* to Ph, causing poor overlap between the non-bonding electron pair on nitrogen and $\sigma^*C–CF_3$) the trifluoromethyl group is oriented towards the ammonium group. We believe that this is the result of a stabilizing coulombic interaction (ion-dipole). Addition to the opposite enantiotopic face lies

53) See Supporting Information for details.

2.3 kcal/mol higher on the energy profile, in agreement with the experimentally observed enantiomeric ratio.

Steric elements play a role in rendering the transformation enantioselective as well. There is probable repulsion between the pseudo-axially oriented methyl substituent and the catalyst's *t*-Bu unit (**2.153**) in the mode delivering minor enantiomer ***(S)*–2.69**. Interaction between the allylic substituent and the catalyst framework likely contribute to the high *Z* selectivity as well. The preference to orient the methyl substituent in a pseudo-axial position is probably owing to minimization of a costly *syn*-pentane interaction between the methyl group and the C–N bond of the catalyst framework (highlighted in red, Scheme 2.27). The computed energy difference (5.5 kcal/mol) between **2.152**, the lowest accessible state leading to an *E*-alkene, **2.154**, agrees with the observed *Z* selectivity.

Scheme 2.27. Transition State Analysis to Account for High *Z* Selectivity[a]



[a] *Calculations performed at M06/DEF2TZVPP//M062X/DEF2SVP$_{toluene(SMD)}$. See Experimental Section for details.*

2.6 Conclusions

In summary, we have developed the first enantioselective method for additions of various *Z*-allyl boronates to trifluoromethyl ketimines, generating desirable α-tertiary trifluoromethyl-substituted amines that contain a *Z* olefin. The requisite *N*-silyl ketimines are easily prepared and robust, and silyl deprotection and formation of the *N*-H ketimines takes place in situ through treatment with a combination of tbat and methanol. We have thus advanced the state-of-the-art by developing a catalytic method that can be used to prepare α-tertiary NH_2 amines thereby obviating the need for inefficient deprotection sequences. Additionally, these investigations have offered further insight into factors that can lead to enhanced efficiency and enantioselectivity in reactions promoted by aminophenol boron-based catalysts. The utility of the approach was highlighted through a series of chemoselective and stereoretentive cross-coupling reactions, as well as a regio- and diastereoselective synthesis of differentially protected diols through a directed epoxidation/ring-opening sequence.

2.7 Experimental Section

2.7.1 General

Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, λ_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) or a Varian Premium Shielded 600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) or a Varian Premium Shielded 600 (125 MHz) spectrometer with complete proton decoupling. ^{19}F NMR spectra were recorded on a Varian Unity INOVA 400 (376 MHz) or a Varian Premium Shielded 600 (564 MHz) spectrometer using trifluorotoluene as an external standard. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). Data are reported as follows: chemical shift, multiplicity (singlet unless otherwise noted), and coupling constant (Hz). High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomeric ratios (e.r.) were determined by HPLC analysis through the use of either a Shimadzu LC-2010AHT or SCL-10AVP chromatograph (Chiral Technologies Chiralcel OD-H (4.6 x 250 mm), Chiral Technologies Chiralcel OJ-H (4.6 x 250 mm), Chiral Technologies Chiralpak AD-H (4.6 x 250 mm), Chiral Technologies Chiralpak AZ-H (4.6 x 250 mm), Chiral Technologies Chiralpak AS-H (4.6 x 250 mm) columns). Authentic racemic samples for HPLC analysis were obtained by performing the reaction with *rac*-**ap-1a**. Specific rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter. Melting points were determined by the use of a Thomas Hoover Uni-melt capillary melting point apparatus. Unless otherwise noted, reactions were carried out under an atmosphere of dry N_2 in oven-dried (135 ºC) glassware. Unless otherwise noted, solvents were purged with Argon and purified under a positive pressure of dry Argon by a modified Innovative Technologies purification system. Toluene (Fisher, ACS Grade) was passed successively through activated copper and alumina columns. Dichloromethane (Fisher, ACS Grade) and diethyl ether (Aldrich, Chromasolv®) were passed successively through two activated alumina columns. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl immediately prior to use. $CDCl_3$ was purchased from Cambridge Isotope Laboratories and stored over activated 4Å molecular sieves prior to use. All work-up and purification procedures were carried out in air with reagent grade solvents (purchased from Fisher).

2.7.2 Reagents

1-(Benzofuran-2-yl)-2,2,2-trifluoroethan-1-one was synthesized according to a procedure in the

literature and the analytical data are consistent with those reported previously.[1]

Bis(pinacolato)diboron was purchased from Frontier and recrystallized from pentane prior to use.

Bis(trimethylsilyl)amine was purchased from Acros and used as received.

Boc-D-Allo-Thr-OBn was purchased from Advanced ChemTech and used as received.

Boc-Ile-OH was purchased from Advanced ChemTech and used as received.

Boc-Thr-OH was purchased from ArkPharm and used as received.

Boc-Thr(Bzl)-OH was purchased from ArkPharm and used as received.

Boc-Thr(Me)-OH was purchased from Alfa Aesar and used as received.

Boc-Val-OH was purchased from Advanced ChemTech and used as received.

1-(2-Bromophenyl)-2,2,2-trifluoroethan-1-one was synthesized from the corresponding aldehyde (Aldrich, used as received).

4'-Bromo-2,2,2-trifluoroacetophenone was purchased from Combi Blocks and used as received.

1-Chloro-3-methyl-2-butene was purchased from Alfa Aesar and used as received.

1-(2-Chlorophenyl)-2,2,2-trifluoroethan-1-one was synthesized from the corresponding aldehyde (Aldrich, used as received).

1-(3-Chlorophenyl)-2,2,2-trifluoroethan-1-one was synthesized from the corresponding aldehyde (Aldrich, used as received).

4'-Chloro-2,2,2-trifluoroacetophenone was purchased from Oakwood and used as received.

Dess-Martin periodinane was purchased from Oakwood and used as received.

1,2-Dibromoethylene was purchased from Aldrich and used as received.

Dimethylamine (40 wt % in H_2O) was purchased from Aldrich and used as received.

4′-(Dimethylamino)-2,2,2-trifluoroacetophenone was purchased from Aldrich and used as received.

1-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-1-(((1'*r*,3'*r*)-2,2'',4,4'',6,6''-hexaisopropyl-[1,1':3',1''-terphenyl]-2'-yl)oxy)-1-(2-methyl-2-phenylpropylidene)-*N*-(perfluorophenyl)molybdenumimine (Mo-1) was synthesized according to a procedure in the literature and the analytical data are consistent with those reported previously.[2]

1-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-1-(((1'*r*,3'*r*)-2,2'',4,4'',6,6''-hexamethyl-[1,1':3',1''-terphenyl]-2'-yl)oxy)-1-(2-methyl-2-phenylpropylidene)-*N*-(perfluorophenyl)molybdenumimine (Mo-2) was purchased from Strem and used as received.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride (EDC•HCl) was purchased from Advanced ChemTech and used as received.

2'-Fluorobenzaldehyde was purchased from Aldrich and used as received.

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1) Debien, L.; Trost, B. M. *J. Am. Chem. Soc.* **2015**, *137*, 11606–11609.

2) Zhang, H.; Yu, E.; Torker S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16493–16496.

Hydrochloric Acid (4.0 M in 1,4-dioxane) was purchased from Aldrich and used as received.

1-Hydroxy-benzotriazole hydrate (HOBt•H_2O) was purchased from Advanced ChemTech and used as received.

Lithium bis(trimethylsilyl)amide (1.0 M in thf) was purchased from Aldrich and used as received.

Magnesium Sulfate was purchased from Fisher and flame-dried under vacuum prior to use.

Methanol (99.8% anhydrous) was purchased from Alfa Aesar and used as received.

2'-Methoxy-2,2,2-trifluoroacetophenone as purchased from Oakwood and used as received.

4'-Methoxy-2,2,2-trifluoroacetophenone was purchased from Aldrich and used as received.

***n*-Butyllithium (1.6 or 2.5 M in hexanes)** was purchased from Aldrich and titrated with *n*-benzylbenzamide prior to use.

Palladium on carbon was purchased from Strem and used as received.

2,2,3,3,3-Pentafluoro-1-(4-(trifluoromethyl)phenyl)propan-1-one was synthesized according to a procedure in the literature and the analytical data are consistent with those reported previously.[3]

Pyrrolidine was purchased from Aldrich and used as received.

Sodium Borohydride was purchased from Aldrich and used as received.

3-*tert*-Butyl-2-hydroxybenzaldehyde was purchased from Aldrich and used as received.

Tetrabutylammonium fluoride (1M in thf) was purchased from Oakwood and used as received.

2,2,2,4'-Tetrafluoroacetophenone was purchased from Oakwood and used as received.

Triethylamine was purchased from Aldrich and distilled from to use.

2,2,2-Trifluoroacetophenone was purchased from Oakwood and used as received.

4-(Trifluoroacetyl)toluene was purchased from Oakwood and used as received.

2,2,2-Trifluoro-1-(2-fluorophenyl)ethan-1-one was synthesized from the corresponding aldehyde (Aldrich, used as received).

2,2,2-Trifluoro-1-(furan-2-yl)ethan-1-one was purchased from Enamine and used as received.

(*E*)-1,1,1-Trifluoro-3-methyl-4-phenylbut-3-en-2-one was synthesized according to a procedure in the literature and the analytical data are consistent with those reported previously.[4]

1,1,1-Trifluoro-4-phenylbut-3-yn-2-one was synthesized according to a procedure in the literature and the analytical data are consistent with those reported previously.[5]

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3).Antúnez, D-J. B.; Greenhalgh, M. D.; Brueckner, A. C.; Walden, D. M.; Elías-Rodríguez, P.; Roberts, P.; Young, B. G.; West, T. H.; Slawin, .A. M. Z.; Cheong, R. H-Y.; Smith, A. D. *Chem. Sci.* **2019**, *10*, 6162–6173.

4) Buesking, A. W.; Ellman, J. A. *Chem. Sci.* **2014**, *5*, 1983–1987.

5) Hung, C-I.; Scharf, M. J.; Trost, B. M. *Angew. Chem., Int. Ed.* **2018**, *57*, 11408–11412.

2,2,2-Trifluoro-1-(thiophen-2-yl)ethan-1-one was purchased from Oakwood and used as received.

2,2,2-Trifluoro-1-(*m*-tolyl)ethan-1-one was purchased from Oakwood and used as received.

2,2,2-Trifluoro-1-(*o*-tolyl)ethan-1-one was synthesized from the corresponding aldehyde (TCI America, used as received).

2,2,2-Trifluoro-4′-(trifluoromethyl)acetophenone was purchased from Oakwood and used as received.

2,2,2-Trifluoro-1-(3-(trifluoromethyl)phenyl)ethan-1-one was synthesized from the corresponding aldehyde (Aldrich, used as received).

Trifluoromethyltrimethylsilane was purchased from Oakwood and used as received.

Tris(dibenzylideneacetone)dipalladium(0) was purchased from Strem and used as received.

Zinc (II) methoxide was purchased from Aldrich and used as received.

2.7.3 Synthesis of N-Trimethylsilyl Ketimines

Two different methods were used to synthesize N-trimethylsilyl (N-TMS) ketimines. In general, ketones possessing electron-withdrawing substituents were synthesized by Method A, whereas condensation of electron-rich and/or hindered ketones were carried out under conditions outlined by Method B. Note: In some cases, hexamethyldisilazide co-distills along with the ketimine product, but this does not affect the catalytic transformation. Weight percent was determined and substrates were revised accordingly.

Method A: Condensation was carried out according to a procedure described by Gosselin *et. al*.[6] To an oven-dried six-dram vial equipped with a magnetic stir-bar was added ketone (1.0 equiv.) and toluene (1.0 M). The solution was cooled to 0 °C, then LiHMDS (1.0 M in thf, 1.1 equiv.) was added dropwise anner. The solution was allowed to stir at 0 °C for one h, then the reaction was quenched by the addition of water (5 mL). The organic layer was washed with water (2 x 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the product as yellow oil, which was used without purification.

Method B: Condensation was carried out according to a procedure described by Hart *et. al*.[7] To an oven-dried six-dram vial equipped with a magnetic stir-bar was added HMDS (1.1 equiv.). The vial was allowed to cool to 0 °C for 10 min, then *n*-BuLi (2.6 M in hexanes, 1.05 equiv.) was added in a dropwise manner. The suspension was allowed to stir at 0 °C for five min and then allowed to warm to 22 °C for 10 min. After re-cooling to 0 °C again, trifluoromethyl ketone (1.0 equiv.)

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6) Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.; Volante, R. P. *Org. Lett.* **2005**, *7*, 355–358.

7) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T-K. *J. Org. Chem.* **1983,** *48*, 289-294.

was added dropwise. The yellow solution was allowed to stir at 0 °C for one h, then concentrated under reduced pressure (rotary evaporator) and the desired ketimine was distilled directly form the reaction flask under vacuum to afford the product as cololess or yellow oil.

2,2,2-Trifluoro-1-phenyl-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method A and the analytical data are consistent with those reported previously.[6] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57–7.51 (m, 2H), 7.50–7.38 (m, 3H), 0.17 (s, 9H).

2,2,2-Trifluoro-1-(2-fluorophenyl)-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method B. Yellow oil, 0.895 g, 65% yield, 3.39 mmol; **IR (neat):** 2962 (w), 1708 (m), 1489 (m), 1452 (m), 1182 (s), 1133 (s), 822 (m), 758 (m), 744 (s), 612 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43 (m, 1H), 7.25–7.15 (m, 2H), 7.11 (ddt, *J* = 9.4, 8.3, 1.0 Hz, 1H), 0.05 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.0 (d, *J* = 248.4 Hz), 156.7 (q, *J* = 36.8 Hz), 131.7 (d, *J* = 8.0 Hz), 129.0 (d, *J* = 3.2 Hz), 124.2 (d, *J* = 18.9 Hz), 124.1 (d, *J* = 3.6 Hz), 117.7 (q, *J* = 285.8 Hz), 115.9 (d, *J* = 21.4 Hz), –0.6; **^{19}F NMR (376 MHz, $CDCl_3$):** –74.0 (d, *J* = 5.1 Hz, 3F), –113.9 (dq, *J* = 10.8, 5.5 Hz, 1F); **HRMS (DART):** Calcd for $C_{11}H_{14}NF_4Si$ $[M+H]^+$: 264.0832; Found: 264.0842.

1-(2-Chlorophenyl)-2,2,2-trifluoro-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method B. Yellow oil, 0.338 g, 50% yield, 1.21 mmol; **IR (neat):** 2962 (w), 1708 (m), 1186 (s), 1126 (s), 1059 (m), 950 (s), 839 (s), 756 (s), 648 (m), 471 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44–7.40 (m, 1H), 7.40–7.34 (m, 1H), 7.34–7.27 (m, 1H), 7.21–7.16 (m, 1H), 0.02 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.1, 135.8, 131.8, 131.0, 129.9, 128.8, 126.8, 117.9 (q, *J* = 284.7 Hz), –0.6; **^{19}F NMR (376 MHz, $CDCl_3$):** –73.5 (s, 3F); **HRMS (DART):** Calcd for $C_{11}H_{14}NF_3SiCl$ $[M+H]^+$: 280.0531; Found: 280.0533.

2,2,2-Trifluoro-1-(2-methoxyphenyl)-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method B. Yellow oil, 0.624 g, 97% yield, 2.26 mmol; **IR (neat):** 2958 (w), 1702 (m), 1488 (m), 1247 (m), 1180 (s), 1125 (s), 944 (m), 802 (s), 751 (s), 657 (m), 575 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H), 7.09 (m, 1H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.90 (dd, *J* = 8.4, 0.9 Hz, 1H), 3.81 (s, 3H), –0.01 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.7, 132.7, 131.2, 130.8 (q, *J* = 288.0 Hz), 128.5, 120.8, 120.4, 111.9, 111.0, 55.9 (q, *J* = 27.3 Hz), 1.5, -0.4; **^{19}F NMR (376 MHz, $CDCl_3$):** –73.9 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{17}NOF_3Si$ $[M+H]^+$: 276.1026; Found: 276.1022.

(*Z*)-2,2,2-Trifluoro-1-(*o*-tolyl)-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method B. Yellow oil, 0.912 g, 89% yield, 3.52 mmol; **IR (neat):** 3051 (w), 1702 (w), 1420 (m), 1304 (m), 1263 (m), 1184 (m), 930 (m), 859 (m), 730 (s), 702 (m), 513 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35–7.28 (m, 1H), 7.20 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 2.25 (s, 3H), –0.02 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 163.7 (q, *J* = 35.5 Hz), 136.7, 135.2, 130.4, 129.6, 127.3, 125.7, 118.3 (q, *J* = 285 Hz), 19.7, –0.4; **^{19}F NMR (376 MHz, $CDCl_3$):** –73.6 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{17}NF_3Si$ $[M+H]^+$: 260.1077; Found: 260.1072.

1-(3-Chlorophenyl)-2,2,2-trifluoro-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method A. Yellow oil, 0.439 g, 66% yield, 1.57 mmol; **IR (neat):** 2957 (w), 1707 (m), 1568 (w), 1251 (m), 1224 (s), 1178 (s), 840 (s), 674 (m), 622 (m), 540 (w) cm^{-1}; **^{1}H NMR (400 MHz,**

$CDCl_3$): δ 7.58 (m, 1H), 7.46 (m, 2H), 7.42–7.30 (m, 1H), 0.27–0.14 (m, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.4 (q, *J* = 34.3 Hz), 137.2, 134.7, 131.0, 129.8, 128.1 (d, *J* = 1.8 Hz), 126.0 (d, *J* = 1.9 Hz), 117.7 (d, *J* = 287.3 Hz), 0.5; **^{19}F NMR (376 MHz, $CDCl_3$):** –68.9 (s, 3F); **HRMS (DART):** Calcd for $C_{11}H_{14}NF_3SiCl$ $[M+H]^+$: 280.0531; Found: 280.0533.

2,2,2-Trifluoro-1-(3-(trifluoromethyl)phenyl)-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method A. Yellow oil, 0.303 g, 55% yield, 0.968 mmol; **IR (neat):** 2959 (w), 1960 (m), 1332 (m), 1165 (s), 1126 (s), 1099 (m), 863 (m), 842 (m), 648 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (m, 1H), 7.46 (m, 2H), 7.35 (m, 1H), 0.23–0.18 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.4 (q, *J* = 34.3 Hz), 137.2, 134.7, 131.3 (q, *J* = 230.0 Hz), 131.1, 129.8, 128.1 (d, *J* = 1.6 Hz), 126.0 (q, *J* = 1.8 Hz), 117.7 (q, *J* = 288.9 Hz), 0.5 (d, *J* = 1.4 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** –68.9 (s, 3F), –62.9 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_6Si$ $[M+H]^+$: 314.0794; Found: 314.0806.

2,2,2-Trifluoro-1-(4-fluorophenyl)-*N*-(trimethylsilyl)ethan-1-imine was synthesized according Method A. Yellow oil, 2.09 g, 80% yield, 7.92 mmol; **IR (neat):** 2961 (w), 1704 (m), 1602 (m), 1509 (m), 1237 (m), 1160 (s), 1129 (s), 862 (s), 840 (s) 687 (m), 528 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.64 (m, *J* = 7.1, 5.3, 0.9 Hz, 2H), 7.17–7.02 (m, 2H), 0.22 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.7, 163.2, 130.3 (dq, *J* = 8.7, 1.8 Hz), 117.8 (d, *J* = 287.9 Hz), 115.7, 115.5, 0.5; **^{19}F NMR (376 MHz, $CDCl_3$):** –68.5 (s, 3F), –108.9 (ddd, *J* = 8.2, 5.4, 3.1 Hz, 1F); **HRMS (DART):** Calcd for $C_{11}H_{14}F_4NSi$ $[M+H]^+$: 264.0832; Found: 264.0826.

(*Z*)-1-(4-Chlorophenyl)-2,2,2-trifluoro-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method A. Yellow oil, 0.573 g, 77% yield, 2.05 mmol; **IR (neat):** 2960 (w), 1702 (m), 1609 (w), 1252 (m), 1174 (s), 1131 (s), 1023 (s), 952 (s), 726 (s), 528 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.62–7.51 (m, 2H), 7.47–7.33 (m, 2H), 0.21 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.5 (q, *J* = 33.8 Hz), 137.3, 133.9, 129.4 (q, *J* = 1.8 Hz), 128.8, 117.7 (q, *J* = 287.8 Hz), 0.5; **^{19}F NMR (376 MHz, $CDCl_3$):** –68.7 (d, *J* = 4.0 Hz, 3F); **HRMS (DART):** Calcd for $C_{11}H_{14}NF_3SiCl$ $[M+H]^+$: 260.1077; Found: 260.1072.

(*Z*)-1-(4-Bromophenyl)-2,2,2-trifluoro-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method A and the analytical data are consistent with those reported previously.[6]

2,2,2-Trifluoro-1-(4-(trifluoromethyl)phenyl)-N-(trimethylsilyl)ethan-1-imine was synthesized according to Method A. Yellow oil, 0.480 g, 87% yield, 1.53 mmol; **IR (neat):** 2254 (w), 1712 (w), 1327 (m), 1188 (m), 1020 (m), 903 (s), 847 (s), 724 (s), 650 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.75–7.62 (m, 4H), 0.20 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.5 (q, *J* = 34.4 Hz), 138.7, 132.5 (q, *J* = 32.6 Hz), 128.9, 122.3 (q, *J* = 272.5 Hz), 117.5 (q, *J* = 287.3 Hz), 29.7, 0.2; **^{19}F NMR (376 MHz, $CDCl_3$):** –63.0 (d, *J* = 6.1 Hz, 3F), –69.1 (d, *J* = 6.3 Hz, 3F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_6Si$ $[M+H]^+$: 314.0800; Found: 314.0811.

2,2,2-Trifluoro-1-(4-methoxyphenyl)-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method B. Yellow oil, 0.371 g, 55% yield, 1.35 mmol; **IR (neat):** 2957 (w), 2834 (w), 1697 (m), 1602 (m), 1577 (m), 1251 (s), 1164 (s), 1126 (s), 1032 (m), 862 (s), 837 (s), 761 (m), 560 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.62 (m, *J* = 7.8, 1.2 Hz, 2H), 7.01–6.78 (m,

2H), 3.85 (d, J = 1.2 Hz, 3H), 0.22 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.7, 156.6 (q, J = 33.1 Hz), 129.6 (q, J = 26.8 Hz), 128.0, 116.5 (q, J = 288.1 Hz), 113.5 (d, J = 13.2 Hz), 55.3 (q, J = 22.5 Hz), 0.5; **^{19}F NMR (376 MHz, $CDCl_3$):** –68.0 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{17}NF_3SiO$ $[M+H]^+$: 276.1032; Found: 276.1044.

***N*,*N*-Dimethyl-4-(2,2,2-trifluoro-1-((trimethylsilyl)imino)ethyl)aniline** was synthesized according to Method B. Yellow solid, 0.349 g, 52% yield, 1.21 mmol; **M.p.** = 56–58 °C; **IR (neat):** 2956 (w), 2899 (w), 1690 (m), 1602 (s), 1527 (w), 1369 (m), 1164 (s), 1129 (s), 864 (m), 842 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.64 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 8.9 Hz, 2H), 3.03 (s, 6H), 0.23 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 152.1, 129.8 (q, J = 26.2 Hz), 122.8, 118.0 (q, J = 289.0 Hz), 110.9, 110.8, 40.1, 40.0, 0.7; **^{19}F NMR (376 MHz, $CDCl_3$):** –66.9 (s, 3F); **HRMS (DART):** Calcd for $C_{13}H_{20}N_2F_3Si$ $[M+H]^+$: 289.1342; Found: 289.1334.

2,2,2-Trifluoro-1-(furan-2-yl)-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method A and the analytical data are consistent with those reported previously.[8]

1-(Benzofuran-2-yl)-2,2,2-trifluoro-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method B. Yellow solid, 0.649 g, 79% yield, 2.25 mmol; **M.p.** = 59–61°C; **IR (neat):** 2958 (w), 1686 (s), 1407 (w), 1251 (s), 1200 (m), 1154 (s), 1129 (s), 982 (s), 905 (s), 843 (s), 743 (s), 626 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71 (dt, J = 7.9, 0.9 Hz, 1H), 7.54 (dd, J = 8.3, 1.1 Hz, 1H), 7.44 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.36–7.28 (m, 2H), 0.38 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.1, 147.6, 127.5, 127.4, 124.0, 123.3, 117.1 (q, J = 285.4 Hz), 111.6, 111.5, 111.5 (q, peaks overlapped), 0.7; **^{19}F NMR (376 MHz, $CDCl_3$):** –70.1 (d, J = 1.8 Hz, 3F); **HRMS (DART):** Calcd for $C_{13}H_{15}NOF_3Si$ $[M+H]^+$: 286.0870; Found: 286.0868.

2,2,2-Trifluoro-1-(thiophen-2-yl)-*N*-(trimethylsilyl)ethan-1-imine was synthesized according to Method B. Yellow oil, 0.289 g, 41% yield, 1.14 mmol; **IR (neat):** 2960 (w), 1682 (s), 1421 (m), 1251 (m), 1184 (s), 1136 (s), 1061 (m), 841 (s), 712 (s), 567 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.56–7.45 (m, 2H), 7.09 (dt, J = 5.1, 2.3 Hz, 1H), 0.28 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.9, 131.8, 130.01 (q, J = 3.2 Hz), 128.4, 117.1 (q, J = 289 Hz), 105.6, 0.7; **^{19}F NMR (376 MHz, $CDCl_3$):** –67.6 (s, 3F); **HRMS (DART):** Calcd for $C_9H_{13}NF_3Si$ $[M+H]^+$: 252.0485; Found: 252.0489.

(*E*)-1,1,1-Trifluoro-3-methyl-4-phenyl-*N*-(trimethylsilyl)but-3-en-2-imine was synthesized according to Method B. Yellow oil, 0.295 g, 52% yield, 1.04 mmol; **IR (neat):** 3298 (w), 2959 (w), 1696 (m), 1608 (m), 1184 (s), 1129 (s), 953 (s), 839 (s), 696 (s), 626 (m), 506 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43–7.27 (m, 5H), 6.80 (s, 1H), 2.05 (dt, J = 1.6, 0.8 Hz, 3H), 0.27 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.7 (q, J = 32.6 Hz), 136.0, 134.7, 133.8 (q, J = 2.0 Hz), 129.2, 128.4, 127.8, 117.9 (q, J = 287.9 Hz), 15.7 (q, J = 1.5 Hz), 0.5; **^{19}F NMR (376 MHz, $CDCl_3$):** –68.4 (d, J = 5.8 Hz, 3F); **HRMS (DART):** Calcd for $C_{14}H_{19}NF_3Si$ $[M+H]^+$: 286.1233; Found: 286.1231.

1,1,1-Trifluoro-4-phenyl-*N*-(trimethylsilyl)but-3-yn-2-imine was synthesized according to

8) Zhu, J.; Huang, L.; Dong, W.; Li, N.; Yu, X.;. Deng T. W, *Angew. Chem., Int. Ed.* **2019**, *58*, 16119–16123.

Method B. Yellow oil, 0.434 g, 64% yield, 1.61 mmol; **IR (neat):** 2959 (w), 2199 (m), 1654 (m), 1319 (m), 1247 (s), 1196 (s), 1138 (s), 860 (s), 843 (s), 755 (s), 687 (m), 533 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57–7.51 (m, 2H), 7.49–7.43 (m, 1H), 7.43–7.36 (m, 2H), 0.37 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 145.1 (q, J = 39.6 Hz), 132.4, 130.6, 128.7, 120.1, 117.1 (q, J = 281.9), 94.3, 82.2, –0.7; **^{19}F NMR (376 MHz, $CDCl_3$):** –74.5 (s, 3F); **HRMS (DART):** Calcd for $C_{13}H_{15}NF_3Si$ $[M+H]^+$: 270.0920; Found: 270.0922.

2.7.4 Boronic ester reagents

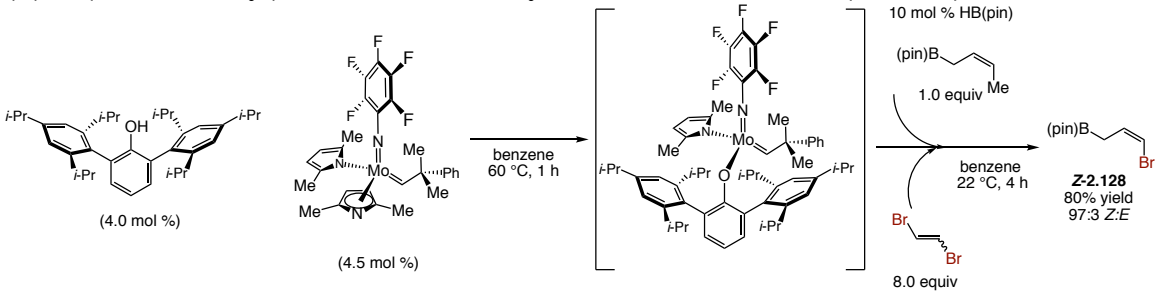
2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was purchased from Frontier Scientific and distilled from calcium hydride prior to use.

(*Z*)-2-(But-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was purchased from Aldrich or Santa Cruz and used as received.

(*Z*)-1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)dec-2-en-5-one (S-1) was synthesized according to a procedure in the literature and the analytical data are consistent with those reported previously.[9]

(*Z*)-2-(3-Chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S-2) was synthesized according to a procedure in the literature and the analytical data are consistent with those reported previously.[10]

(*Z*)-2-(3-Bromoallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*Z*-2.128):



In a N_2-filled glovebox, an oven-dried one-dram vial was charged with aryl-oxide (24.9 mg, 0.05 mmol), bis-imidomolybdenum (33.7 mg, 0.055 mmol), and benzene (0.4 mL). The vial was sealed with a Teflon cap and the solution was allowed to stir at 60 °C for one h. A separate oven-dried one-dram vial was charged with ***Z*-2.64** (227.6 mg, 1.25 mmol), 1,2-dibromoethylene (mixture of *cis*- and *trans*-, 1.85 g, 10.0 mmol), HB(pin) (16.0 mg, 0.125 mmol) and benzene (0.1 mL). The solution was allowed to stir at 22 °C for 10 min. The freshly prepared catalyst solution was allowed to cool to 22 °C before it was added in a dropwise manner (0.3 mL) to the vial containing the cross partners. The solution was allowed to stir at 22 °C for two h, after which the

9) Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534–2535.

10) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465.

remaining catalyst stock solution (0.1 mL) was added. The solution was allowed to stir at 22 °C for an additional two 2, then reaction was quenched by the addition of $CDCl_3$ and analyzed by ^{1}H-NMR spectroscopy affording the desired allyl boron in 95% conv, 97:3 *Z*:*E*. The volatiles were removed in vacuo prior and the remaining brown oil was purified by Kugelrohr distillation (90–120 °C, 0.5 torr) to afford ***Z*-2.128** (247.3 mg, 1.00 mmol, 80% yield) as light brown oil. **IR (neat):** 2977 (m), 2930 (w), 1619 (w), 1468 (s), 1369 (s), 1302 (s), 1108 (s), 966 (m), 846 (m) 718 (m), 675 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.23 (td, *J* = 7.6, 6.8 Hz, 1H), 6.15 (dt, *J* = 6.8, 1.4 Hz, 1H), 1.86–1.83 (m, 2H), 1.26 (s, 12H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 130.7, 108.0, 83.7, 24.9, 24.7; **HRMS (DART):** Calcd for $C_9H_{17}BO_2Br$ $[M+H]^+$: 247.0500; Found: 247.0497.

(*Z*)-4,4,5,5-Tetramethyl-2-(2-methylhept-2-en-1-yl)-1,3,2-dioxaborolane (S-3) was synthesized according to a procedure in the literature.[9] **IR (neat):** 2975 (m), 2924 (m), 1350 (s), 1320 (s), 1141 (s), 967 (m), 847 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.11 (tq, *J* = 7.1, 1.3 Hz, 1H), 1.94 (q, *J* = 6.6 Hz, 2H), 1.73 (q, *J* = 1.3 Hz, 3H), 1.65 (s, 2H), 1.30 (tt, *J* = 5.1, 2.4 Hz, 4H), 1.23 (s, 12H), 0.93 – 0.78 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 167.6, 131.8, 124.0 (d, *J* = 13.5 Hz) 97.6, 83.1, 32.0, 28.0, 25.7 (m), 24.7, 22.4, 14.1; **HRMS (DART):** Calcd for $C_{14}H_{28}BO_2$ $[M+H]^+$: 239.21769; Found: 239.21758.

2.7.5 Aminophenol ligands

(*S*)-2-((3-(*tert*-Butyl)-2-hydroxybenzyl)amino)-3-methyl-1-(pyrrolidin-1-yl)butan-1-one (ap-1) was synthesized in accordance to a procedure in the literature and the analytical data are consistent with those reported previously.[11]

(2*S*,3*S*)-2-((3-(*tert*-Butyl)-2-hydroxybenzyl)amino)-3-methyl-1-(pyrrolidin-1-yl)pentan-1-one (ap-4) was synthesized analogous to **ap-1a** except Boc-Ile-OH was used as the starting material. Colorless oil; **IR (neat):** 3279 (w), 3042 (m, br), 1631 (s), 1433 (s), 1238 (m), 1023 (m), 840 (m), 748 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.95 (s, 1H), 7.18 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.76 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.69 (t, *J* = 7.5 Hz, 1H), 4.11 (d, *J* = 13.7 Hz, 3H), 3.68–3.56 (m, 1H), 3.49 (dd, *J* = 13.1, 8.9 Hz, 2H), 3.24 (ddd, *J* = 9.3, 7.0, 5.1 Hz, 1H), 3.19–3.10 (m, 2H), 1.96–1.81 (m, 4H), 1.76–1.58 (m, 1H), 1.41 (s, 9H), 1.26–1.12 (m, 1H), 0.92–0.81 (m, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.2, 158.6, 138.3, 127.8, 126.2, 123.8, 118.4, 62.1, 51.3, 46.9, 45.1, 37.7, 34.2, 29.6, 26.2, 24.5, 23.5, 15.3, 11.1; **HRMS (DART):** Calcd for $C_{21}H_{35}N_2O_2$ $[M+H]^+$: 347.2693; Found: 347.2684; **Specific rotation:** $[\alpha]_D^{25}$ –36.5 (*c* 2.24, $CHCl_3$).

(2*S*,3*S*)-2-((3-(*tert*-Butyl)-2-hydroxybenzyl)amino)-3-methoxy-1-(pyrrolidin-1-yl)butan-1-one (ap-6) was synthesized analogous to **ap-1a**. The requisite amino acid was obtained by alkylating Boc-allo-Thr-OBn with trimethyloxonium tetrafluoroborate (Meerwein's Salt)

11) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216–221.

according to a reported procedure[12] and subsequent hydrolysis of the benzyl ester according to a known protocol.[13] Colorless oil; **IR (neat):** 3269 (w), 2948 (m, br), 1631 (s), 1434 (s), 1238 (m), 1103 (m), 841 (m), 749 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.78 (s, 1H), 7.20 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.79 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.71 (t, *J* = 7.5 Hz, 1H), 4.11 (d, *J* = 13.5 Hz, 1H), 3.65 – 3.36 (m, 5H), 3.35 – 3.28 (m, 1H), 3.24 (s, 3H), 3.14 (dt, *J* = 8.9, 6.6 Hz, 1H), 1.88 (dq, *J* = 6.2, 3.8, 2.2 Hz, 4H), 1.41 (s, 9H), 1.24 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.1, 156.8, 137.0, 126.7, 126.1, 122.5, 118.4, 78.4, 62.2, 57.1, 50.8, 46.3, 45.9, 34.6, 29.4, 25.9, 24.3, 16.6; **HRMS (DART):** Calcd for $C_{20}H_{33}N_2O_3$ $[M+H]^+$: 349.2486; Found: 349.2475; **Specific rotation:** $[\alpha]^{24}_D$ –35.7 (*c* 2.35, $CHCl_3$).

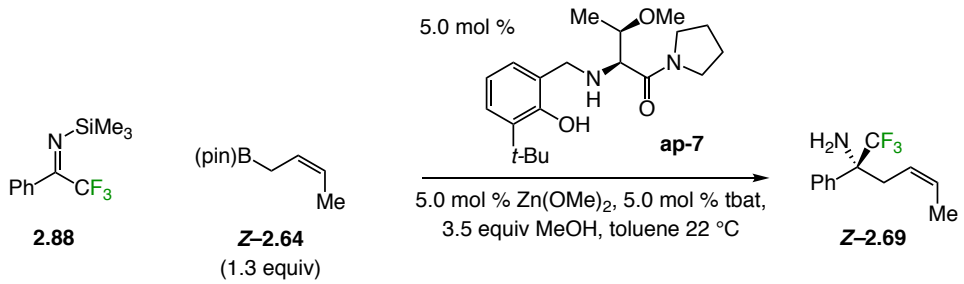
(2*S*,3*R*)-2-((3-(*tert*-Butyl)-2-hydroxybenzyl)amino)-3-methoxy-1-(pyrrolidin-1-yl)butan-1-one (ap-7) was synthesized analogous to **ap-1a** in accordance to a reported procedure except Boc-Thr(OMe)-OH was used as the starting material. Colorless oil; **IR (neat):** 3288 (w), 2949 (m, br), 1631 (s), 1434 (s), 1238 (m), 1090 (s), 877 (s), 748 (m), 619 (s), 509 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.20 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.81 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 4.11 (d, *J* = 13.5 Hz, 1H), 3.68 (d, *J* = 13.5 Hz, 1H), 3.64 – 3.39 (m, 5H), 3.31 (s, 3H), 3.24 (dt, *J* = 10.5, 6.6 Hz, 1H), 1.89 (qt, *J* = 11.7, 5.1 Hz, 4H), 1.42 (s, 9H), 1.16 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.7, 157.1, 137.0, 126.7, 126.1, 122.7, 118.3, 78.4, 61.5, 57.1, 51.2, 46.5, 45.9, 34.7, 29.5, 26.1, 24.1, 15.5; **HRMS (DART):** Calcd for $C_{20}H_{33}N_2O_3$ $[M+H]^+$: 349.2486; Found: 349.2478; **Specific rotation:** $[\alpha]^{24}_D$ –21.6 (*c* 1.41, $CHCl_3$).

12) Kiho, T.; Nakayama, M.; Yasuda, K.; Miyakoshi, S.; Inukai, M.;Kogen, H. *Bioorg. Med. Chem.* **2004**, *12*, 337–361.

13) Xiao, K.-J.; Chu, L.; Yu, J.-Q., *Angew. Chem. Int. Ed.* **2016**, *55*, 2856-2860.

2.7.6 In Situ Silyl Removal

2.7.6.1 Screening of Fluoride Reagents

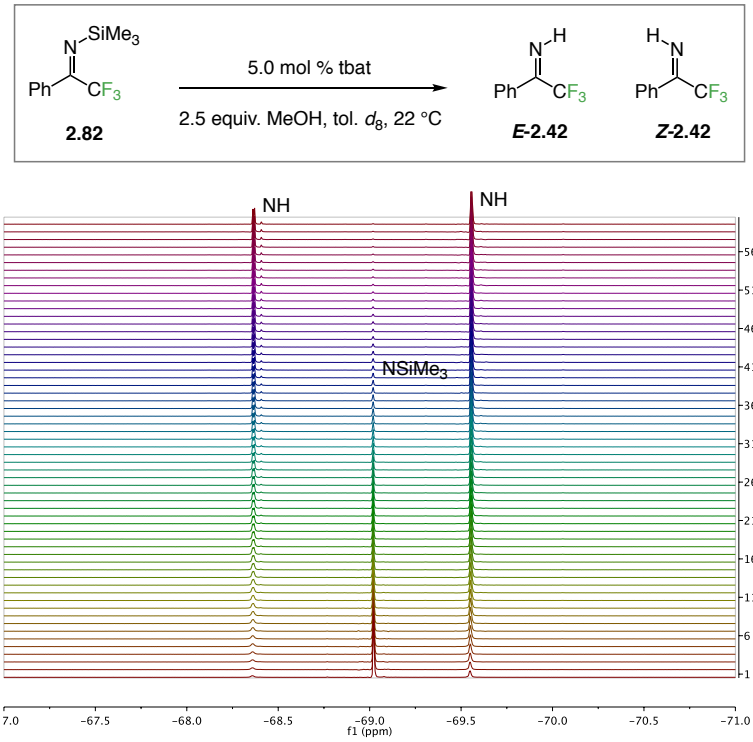


Entry	Reagent	N-H Ketimine (%)	Conv. to ***Z*–2.69** (%)	Hemiaminal (%)	*Z*:*E* (α-add. isomer)	e.r. (α-add. isomer)
1	CsF	>98	36	19	>98:2	97:3
2	$(n\text{-Bu})_4$NF (solid)	>98	58	15	84:16	97:3
3	$(n\text{-Bu})_4$NF (1.0 M, thf)	>98	88	<5	96:4	97:3
4	$(Me)_4$NF	>98	25	<10	>98:2	97:3
5	tbat	>98	>98	<10	>98:2	97:3

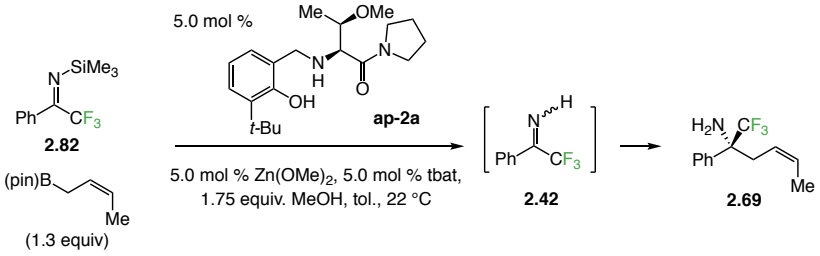
[a] All reactions were performed under N_2 atm. [b] Conv., α:γ, and *Z*:*E* ratios were determined by analysis of ^{19}F NMR spectra (±2%) of unpurified mixtures; Conv. refers to disappearance of **2.88**. [c] er values were determined by HPLC analysis (± 1%). See Supporting Information for details. tbat: tetrabutylammonium difluorotriphenylsilicate

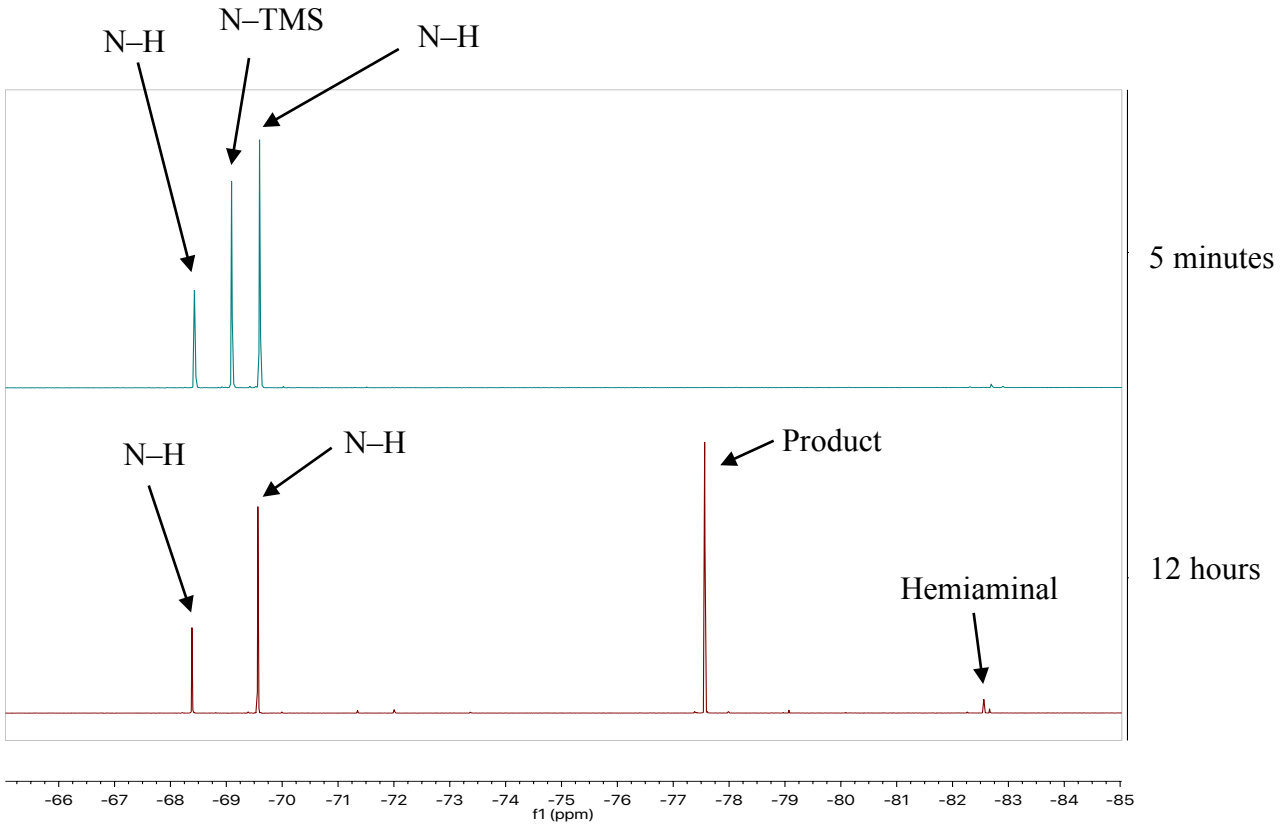
2.7.6.2 Spectroscopic Analysis

In a N_2-filled glovebox, NTMS ketimine (0.1 mmol), tbat (5.0 mol %), and toluene (0.5 mL) were combined in a J-Young NMR tube. Immediately prior to placing the tube in the spectrometer, the solution was charged with *i*PrOH (2.5 equiv.) after which the tube was turned several times to ensure complete mixing. Spectra (^{19}F NMR) were collected every minute until complete disappearance of the N-TMS ketimine (~60 min). The signals corresponding to *E* and *Z* isomers of the N-H ketimine can be observed increasing in intensity at the left and right of the N-TMS ketimine peak. It was not determined which peak corresponds to the *E*- and *Z*-N–H imine isomers.



N-H ketimine generation and crotyl addition: In a N_2-filled glovebox, ketimine (0.1 mmol), tbat (5.0 mol %), and toluene (0.25 mL) were combined in a J-Young NMR tube, after which the solution was charged with a solution of aminophenol (5.0 mol %) and $Zn(OMe)_2$ (10.0 mol %) in tol. (0.25 mL). Immediately prior to placement of the tube within the NMR instrument, MeOH (1.75 equiv.) was added and the tube was turned ~10 times to ensure complete mixing. (Note: MeOH (1.75 equiv.) so that formation of N-H ketimine and homoallylamine formation could be monitored.) Spectra (^{19}F NMR) were collected until complete disappearance of N–TMS ketimine and appearance of the final product.





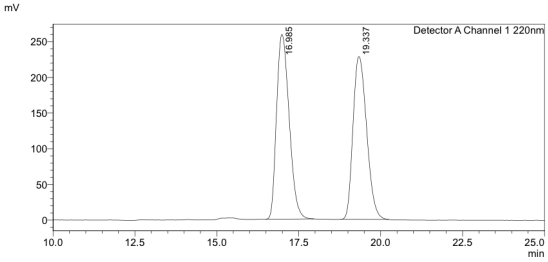
2.7.7 Additions of Allyl–B(Pin) To Trifluoromethyl N-H Ketimines

General procedure for addition of allyl–B(pin): In a N_2-filled glovebox, an oven-dried two-dram vial equipped with a magnetic stir-bar was charged with **ap-3** (3.3 mg, 0.01 mmol), $Zn(OMe)_2$ (1.7 mg, 0.01 mmol) and the solids were dissolved in toluene (0.20 mL). A second oven-dried two-dram vial was charged with ketimine (0.1 mmol), tol. (0.10 mL), and tbat (2.7 mg, 0.005 mmol) to which was added the freshly prepared catalyst stock solution (0.1 mL) followed by allylboronic acid pinacol ester (25.3 mg, 0.15 mmol). The vial was sealed (septum and electrical tape), and removed from the glovebox, and the solution was allowed to cool to 4 °C in a cold room. To this solution was added *i*PrOH (19 μL, 0.25 mmol) and the mixture was allowed to stir for 3 h. Reaction progress (conv) was monitored by ^{19}F NMR spectroscopy (aliquot removed). Once transformation reached completion, the mixture was loaded onto a silica gel column and eluted with hexanes/Et_2O to afford the α-tertiary amine as colorless oil.

(*R*)-1,1,1-Trifluoro-2-phenylpent-4-en-2-amine (2.91): The title compound was synthesized according to the general procedure and purified by silica gel chromatography to afford the product as colorless oil. The analytical data are consistent with those reported previously.[14] Colorless oil,

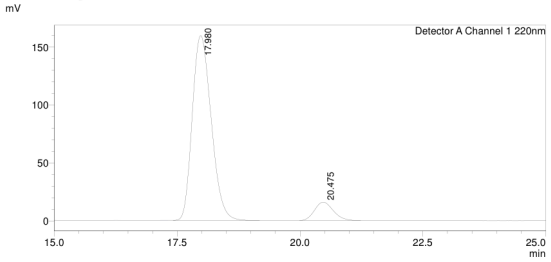
14) Morisaki, K.; Kondo, Y.; Sawa, M.; Morimoto, H.; Ohshima, T. *Chem. Pharm. Bull.* **2017**, *65*, 1089–1092.

20.2 mg, 94% yield, 0.094 mmol; **Specific Rotation:** $[\alpha]^{24}_{D}$ +38.7 (*c* 2.57, $CHCl_3$) for a 91:9 e.r. sample. The enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm) : t_R: 17.980 min (major) and 20.475 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	16.985	6930915	51.194	258584
2	19.337	6607487	48.806	228035
Total		13538401	100.000	486619

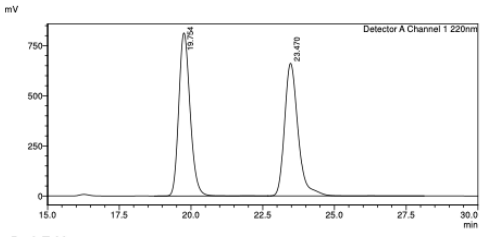


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area%
1	17.980	4271190	159486	91.006
2	20.475	422106	15899	8.994
Total		4693296	175384	100.000

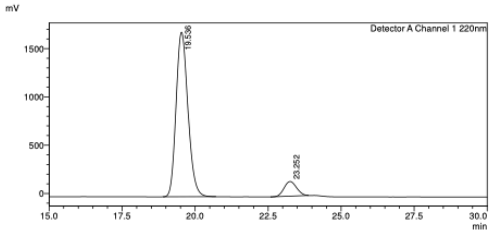
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	16.985	51.194	1	17.980	91.006
2	19.337	48.806	2	20.475	8.994

(*R*)-1,1,1-Trifluoro-2-(2-methoxyphenyl)pent-4-en-2-amine (2.92): Colorless oil, 16.4 mg, 67% yield, 0.067 mmol; **IR (neat):** 2254 (w), 2014 (w), 1495 (w), 1381 (w), 903 (s), 723 (s), 650 (m), 543 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46–7.40 (m, 1H), 7.32 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H), 7.01–6.92 (m, 2H), 5.73–5.61 (m, 1H), 5.24–5.07 (m, 2H), 3.86 (s, 3H), 3.30 (ddt, *J* = 14.5, 6.3, 1.5 Hz, 1H), 2.61 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.35 (br, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.1, 132.5, 130.2, 130.0, 127.2 (q, *J* = 286.7 Hz), 120.7, 119.7, 112.7, 62.0 (q, *J* = 26.6 Hz), 55.8, 39.4; **^{19}F NMR (376 MHz, $CDCl_3$):** –78.44 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{15}NOF_3$ $[M+H]^+$: 246.1106; Found: 246.1118; **Specific rotation:** $[\alpha]^{24}_{D}$ = +18.8 (*c* 2.08, $CHCl_3$) for a 91.5:8.5 e.r. sample. The enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 19.536 min (major) and 23.252 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area%
1	19.754	22308615	812925	50.671
2	23.470	21718038	661467	49.329
Total		44026654	1474392	100.000



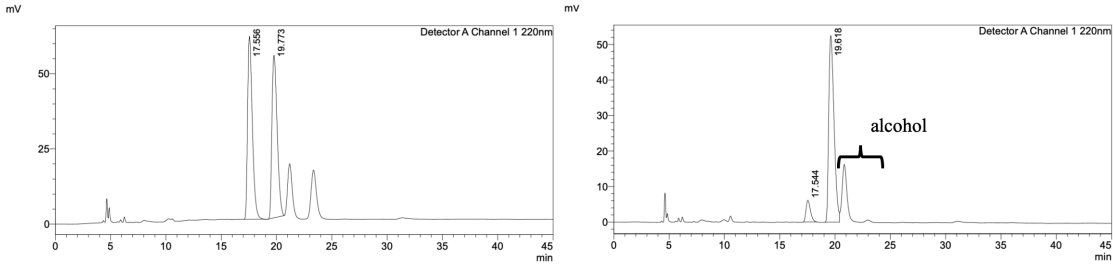
<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area%
1	19.536	48230817	1702737	91.455
2	23.252	4506163	151715	8.545
Total		52736980	1854452	100.000

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	19.754	50.671	1	19.536	91.455
2	23.470	49.329	2	23.252	8.545

(*R*)-1,1,1-Trifluoro-2-(2-fluorophenyl)pent-4-en-2-amine (2.93): Colorless oil, 15.9 mg, 68% yield, 0.068 mmol; **IR (neat):** 3444 (w), 3084 (w), 2933 (w), 1642 (m), 1489 (m), 1219 (m), 1149

(s), 818 (m), 757 (s), 573 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58–7.51 (m, 1H), 7.36 (ddd, *J* = 14.0, 10.6, 4.5 Hz, 1H), 7.22–7.14 (m, 1H), 7.08 (ddd, *J* = 13.1, 8.3, 1.5 Hz, 1H), 5.76–5.52 (m, 1H), 5.31–5.05 (m, 2H), 3.30 (dd, *J* = 14.5, 6.4 Hz, 1H), 2.61 (dd, *J* = 14.5, 7.8 Hz, 1H), 1.87 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.4 (d, *J* = 249.6 Hz), 135.1, 131.5, 130.6, 130.1, 129.3 (q, *J* = 278.3 Hz), 124.3 (d, *J* = 3.5 Hz), 120.4, 117.0 (d, *J* = 25.4 Hz), 61.2 (q, *J* = 20.0 Hz), 39.1 (d, *J* = 6.2 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –79.2 (d, *J* = 15.0 Hz, 3F), –108.5 (dt, *J* = 21.3, 12.4 Hz, 1F); **HRMS (DART):** Calcd for $C_{11}H_{12}F_4N$ $[M+H]^+$: 234.0906; Found: 234.0905; **Specific rotation:** $[\alpha]^{24}_D$ = +28.1 (*c* 1.42, $CHCl_3$) for a 91:9 e.r. sample. The enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 17.544 min (minor) and 19.618 min (major).



<Peak Table>
Detector A Channel 1 220nm

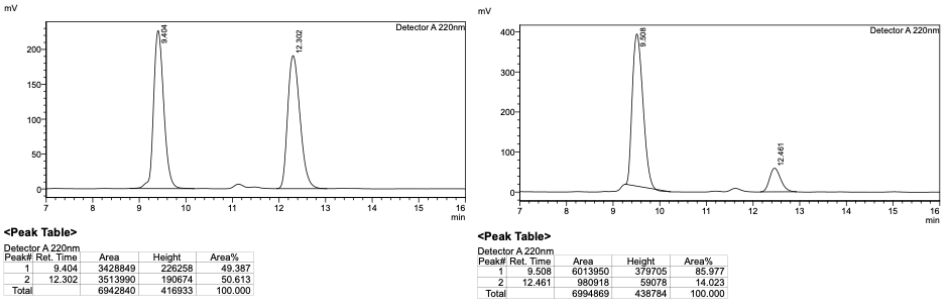
Peak#	Ret. Time	Area	Height	Area%
1	17.556	1824963	60867	50.556
2	19.773	1784848	54080	49.444
Total		3609811	114947	100.000

<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area%
1	17.544	168514	6098	8.805
2	19.618	1745224	52511	91.195
Total		1913738	58609	100.000

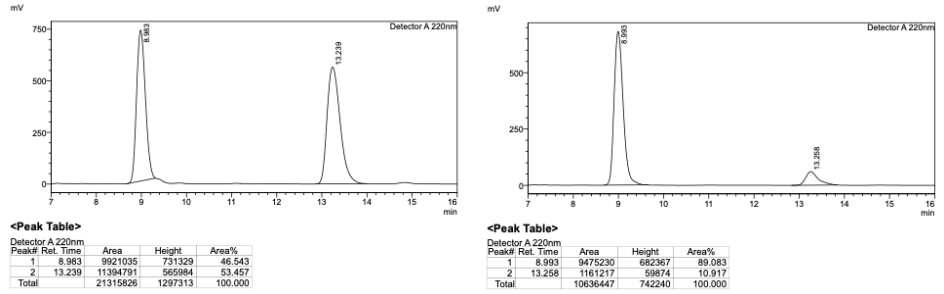
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	17.6 min	1824963	50.556	1	17.5 min	168514	8.805
2	19.8 min	1784848	49.444	2	10.6 min	1745224	91.195

(*R*)-1,1,1-Trifluoro-2-(4-fluorophenyl)pent-4-en-2-amine (2.94): Colorless oil, 15.6 mg, 67% yield, 0.067 mmol; **IR (neat):** 2047 (w), 3083 (w), 2985 (w), 1642 (m), 1510 (m), 1147 (s), 830 (s), 735 (m), 583 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.55 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.06 (dd, *J* = 9.0, 1.9 Hz, 2H), 5.50 (dq, *J* = 16.8, 7.9 Hz, 1H), 5.17–5.05 (m, 2H), 2.88 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.63 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.73 (br, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.6 (d, *J* = 247.6 Hz), 134.3 (d, *J* = 171.1 Hz), 131.0, 128.8 (d, *J* = 8.2 Hz), 126.9 (q, *J* = 285.2 Hz), 120.5, 115.4 (d, *J* = 21.4 Hz), 60.9 (q, *J* = 26.0 Hz), 41.1; **^{19}F NMR (376 MHz, $CDCl_3$):** –78.20 (d, *J* = 13.8 Hz, 3F), –114.48 (s, 1F); **HRMS (DART):** Calcd for $C_{11}H_{12}F_4N$ $[M+H]^+$: 234.0906; Found: 234.0911; **Specific rotation:** $[\alpha]^{24}_D$ = +34.8 (*c* 1.35, $CHCl_3$) for a 86:14 e.r. sample. The enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*-PrOH, 0.7 mL/min, 220 nm): t_R: 9.508 min (major) and 12.461 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	9.404	49.387	1	9.508	85.977
2	12.302	50.613	2	12.461	14.023

(*R*)-1,1,1-Trifluoro-2-(4-(trifluoromethyl)phenyl)pent-4-en-2-amine (2.95): Colorless oil, 9.06 mg, 32% yield, 0.032 mmol; **IR (neat):** 2991 (w), 2942 (w), 2849 (w), 2053 (w), 1622 (m), 1325 (s), 1117 (s), 1068 (s), 1019 (s), 839 (m), 579 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.69–7.57 (m, 2H), 5.49 (ddd, *J* = 16.9, 9.5, 7.2 Hz, 1H), 5.24–5.05 (m, 2H), 2.91 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.69 (dd, *J* = 14.4, 7.6 Hz, 1H), 1.79 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.8, 135.6, 130.7, 130.1 (q, *J* = 22.7 Hz), 127.6, 125.4 (d, *J* = 4.2 Hz), 124.6 (q, *J* = 274.2 Hz), 120.9, 61.4 (q, *J* = 26.6 Hz), 41.1; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –62.79 (s, 3F), –77.63 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{12}F_6N$ $[M+H]^+$: 284.0874; Found: 284.0882; **Specific rotation:** $[\alpha]^{24}_D$ = +26.6 (*c* 0.93, $CHCl_3$) for a 89:11 e.r. sample. The enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 8.993 min (major) and 13.258 min (minor).



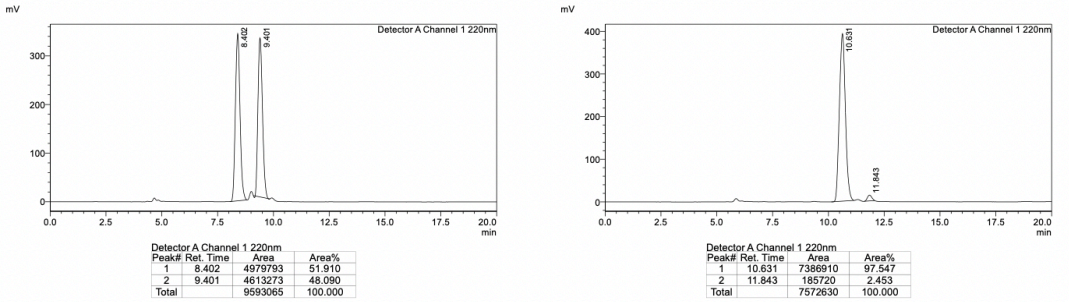
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	8.983	46.543	1	8.993	89.083
2	13.239	53.457	2	13.258	10.917

2.7.8 Additions of Z-Substituted Allyl Boronates to Trifluoromethyl N-H Ketimines

In a N_2-filled glovebox, an oven-dried two-dram vial was charged with a stock solution of aminophenol **ap-7** (3.5 mg, 0.01 mmol), $Zn(OMe)_2$ (2.6 mg, 0.02 mmol), and tol. (0.5 mL). A

separate oven-dried two-dram vial equipped with a magnetic stir-bar was charged with ketimine (0.1 mmol), tol. (0.25 mL), and tbat (2.7 mg, 0.005 mmol), followed by the freshly prepared stock solution of the catalyst (0.25 mL) and ***Z*-2.64** (27 μL, 0.13 mmol) and MeOH (14 μL, 0.35 mmol). The mixture was allowed to stir for five min after which the vial was capped, removed from the glovebox, and the mixture was allowed to stir for 3 h at 22 °C. Conversion and α:γ ratio were determined by spectroscopic analysis (^{19}F NMR) of an aliquot sample. The mixture was loaded onto silica gel and eluted with 100:0 → 3:1 hexanes:Et_2O, resulting in the isolation of α-tertiary amine as colorless oil. Note: In some cases, and as explicitly indicated in the body of the manuscript, yields of isolated products are reported as mixtures of α and γ isomers. The minor γ isomer accounts for the minor signals in the corresponding NMR spectra.

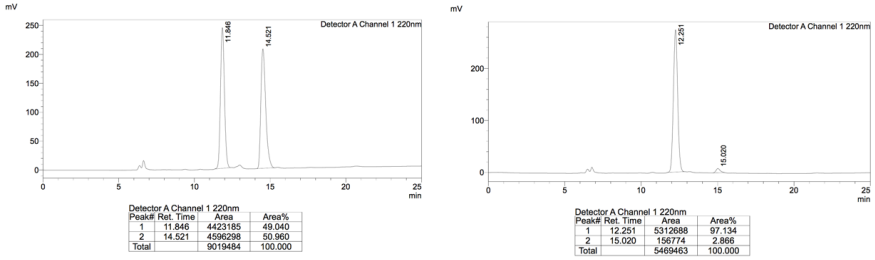
(*R*,*Z*)-1,1,1-Trifluoro-2-phenylhex-4-en-2-amine (2.69): Colorless oil, 19.9 mg, 80% yield, 0.080 mmol; **IR (neat):** 2254 (w), 1156 (w), 903 (s), 722 (s), 650 (s), 543 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61–7.53 (m, 2H), 7.52–7.31 (m, 3H), 5.60 (m, 1H), 5.25–5.03 (m, 1H), 2.88 (dd, *J* = 14.9, 6.7 Hz, 1H), 2.82–2.63 (m, 1H), 1.77 (s, 2H), 1.62 (ddt, *J* = 6.9, 1.8, 0.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.8, 128.7, 128.4, 128.2, 127.3 (q, *J* = 285.3 Hz), 126.1 (q, *J* = 1.6 Hz), 123.0, 61.6 (q, *J* = 25.8 Hz), 33.6, 13.3; **^{19}F NMR (376 MHz, $CDCl_3$):** –77.9 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{15}NF_3$ $[M+H]^+$: 230.1151; Found: 230.1156; **Specific rotation:** $[\alpha]^{24}_D$ = –6.1 (*c* 1.40, $CHCl_3$) for a 97:3 e.r. sample; The enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 10.631 min (major) and 11.843 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	8.402	51.910	1	10.631	97.547
2	9.401	48.090	2	11.843	2.453

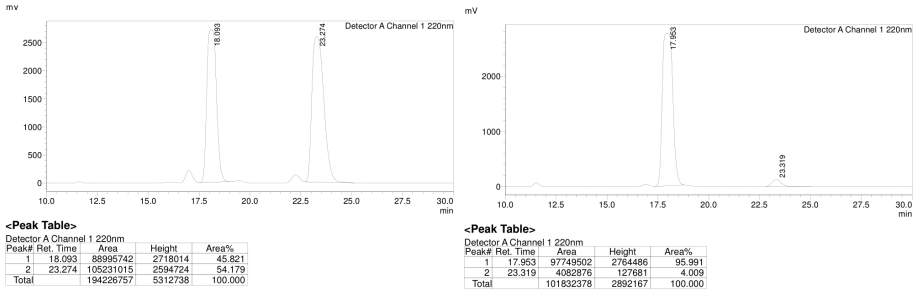
(*R*,*Z*)-1,1,1-Trifluoro-2-(4-fluorophenyl)hex-4-en-2-amine (2.102): Colorless oil, 16.8 mg, 68% yield, 0.068 mmol; **IR (neat):** 2924 (w), 1606 (m), 1511 (s), 1237 (m), 1145 (s), 831 (s), 737 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.62–7.45 (m, 2H), 7.17–6.98 (m, 2H), 5.72–5.54 (m, 1H), 5.25–5.07 (m, 1H), 2.84 (dd, *J* = 15.0, 6.9 Hz, 1H), 2.70 (dd, *J* = 15.0, 7.6 Hz, 1H), 1.74 (s, 2H), 1.61 (ddt, *J* = 6.8, 1.9, 0.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.6 (d, *J* = 247.5 Hz), 133.6 (d, *J* = 3.2 Hz), 129.0, 128.9, 127.2 (q, *J* = 285.2 Hz), 122.7, 115.3 (d, *J* = 21.3 Hz), 61.4 (q, *J* = 25.9 Hz), 33.7, 13.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.2 (s, 3F), –114.6 (s, 1F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_4$ $[M+H]^+$: 248.1057; Found: 248.1064; **Specific rotation:** $[\alpha]^{25.1}_D$ +14.6 (*c* 0.77, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC

analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 12.251 min (major) and 15.020 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	11.846	49.040	1	12.251	97.134
2	14.521	50.960	2	15.020	2.866

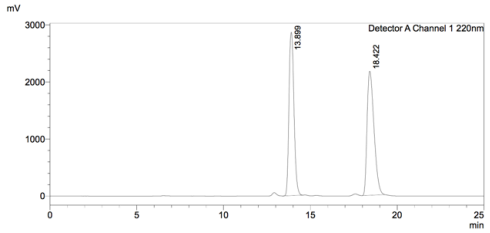
(*R*,*Z*)-2-(4-Chlorophenyl)-1,1,1-trifluorohex-4-en-2-amine (2.103): Colorless oil, 22.9 mg, 87% yield, 0.087 mmol; **IR (neat):** 3397 (w), 3025 (w), 2925 (w), 1597 (m), 1493 (m), 1525 (m), 1148 (s), 1096 (s), 820 (m), 692 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 5.61 (m, 1H), 5.14 (m, 1H), 2.83 (dd, *J* = 15.0, 6.9 Hz, 1H), 2.70 (dd, *J* = 14.9, 7.6 Hz, 1H), 1.72 (s, 2H), 1.61 (ddt, *J* = 6.9, 2.0, 1.0 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 136.4, 134.3, 129.0, 128.6, 128.6, 127.1 (q, *J* = 143.5 Hz), 122.5, 61.5 (q, *J* = 26.3Hz), 33.7, 13.3; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.0 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_3Cl$ $[M+H]^+$: 264.0761; Found: 264.0760; **Specific rotation:** $[\alpha]^{24.3}_D$ +18.9 (*c* 2.1, $CHCl_3$) for a 96:4 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AS-H, 98:2 hexanes:*i*PrOH, 0.5 mL/min, 220 nm): t_R: 17.953 min (major) and 23.319 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	18.093	45.821	1	17.953	95.991
2	23.274	54.179	2	23.319	4.009

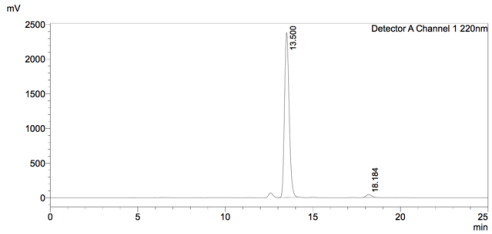
(*R*,*Z*)-2-(4-Bromophenyl)-1,1,1-trifluorohex-4-en-2-amine (2.104): Colorless oil, 20.6 mg, 67% yield, 0.067 mmol; **IR (neat):** 3026 (w), 1591 (m), 1490 (m), 1250 (m), 1137 (s), 1010 (m), 818 (m), 751 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54–7.48 (m, 2H), 7.48–7.43 (m, 2H), 5.61 (m, 1H), 5.24–4.99 (m, 1H), 2.83 (dd, *J* = 15.0, 6.9 Hz, 1H), 2.79–2.61 (m, 1H), 1.73 (s, 2H), 1.61 (ddt, *J* = 6.8, 1.8, 0.9 Hz, 3H).; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.0, 131.6, 129.1, 129.0 (q, *J* = 1.5 Hz), 127.01 (q, *J* = 285.4 Hz), 122.6, 122.5, 61.6 (q, *J* = 26.0 Hz), 33.6, 13.3; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.0 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_3Br$ $[M+H]^+$: 308.0256;

Found: 308.0252; **Specific rotation:** $[\alpha]^{25.2}_{D}$ +31.0 (*c* 1.3, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 13.500 min (major) and 18.184 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	13.899	57297739	48.771
2	18.422	60185373	51.229
Total		117483113	100.000

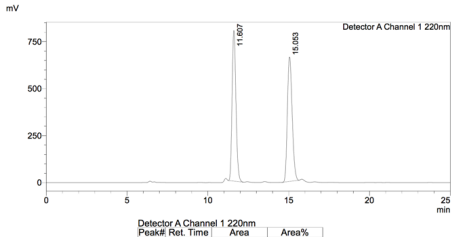


Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	13.500	43826395	98.021
2	18.184	885059	1.979
Total		44711454	100.000

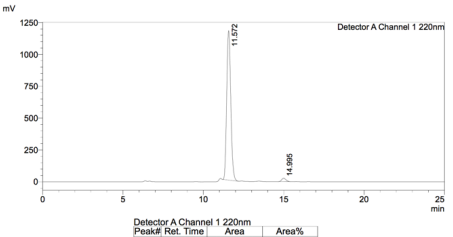
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	13.809	48.771	1	13.500	98.021
2	18.422	51.229	2	18.184	1.979

(*R,Z*)-1,1,1-Trifluoro-2-(4-(trifluoromethyl)phenyl)hex-4-en-2-amine (2.105): Colorless oil, 18.1 mg, 61% yield, 0.061 mmol; **IR (neat):** 2939 (w), 1622 (m), 1325 (s), 1152 (s), 1070 (s), 1018 (m), 834 (m), 733 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.82–7.69 (m, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 5.62 (m, 1H), 5.22–5.07 (m, 1H), 2.87 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.73 (dd, *J* = 15.1, 7.5 Hz, 1H), 1.77 (s, 2H), 1.61 (ddt, *J* = 6.9, 1.9, 0.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.0, 130.5 (q, *J* = 32.6 Hz), 129.3, 127.6 (q, *J* = 1.7 Hz), 127.0, 125.4 (q, *J* = 3.8 Hz), 124.1, 122.3 (q, *J* = 274 Hz), 61.9 (q, *J* = 26.1 Hz), 33.8, 13.3; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –62.8 (s, 3F), –77.7 (s, 3F); **HRMS (DART):** Calcd for $C_{13}H_{14}NF_6$ $[M+H]^+$: 298.1025; Found: 298.1035; **Specific rotation:** $[\alpha]^{26.0}_{D}$ +19.9 (*c* 1.5, $CHCl_3$) for a 97.5:2.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 11.572 min (major) and 14.955 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	11.607	13222387	49.194
2	15.053	13655692	50.806
Total		26878079	100.000



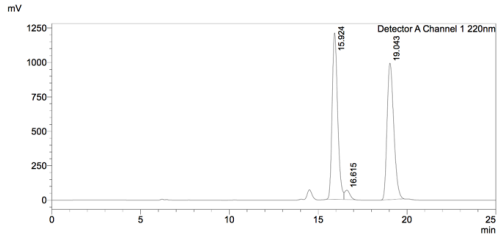
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	11.572	20621210	97.672
2	14.995	491469	2.328
Total		21112680	100.000

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	11.607	49.194	1	11.572	97.672
2	15.053	50.806	2	14.995	2.328

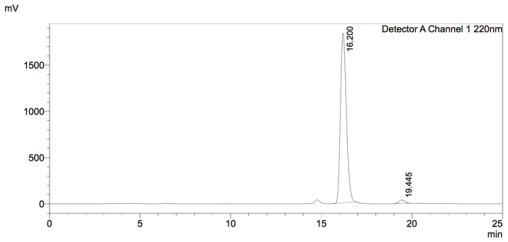
(*R,Z*)-1,1,1-Trifluoro-2-(4-methoxyphenyl)hex-4-en-2-amine (2.106): Colorless oil, 20.2 mg, 78% yield, 0.078 mmol; **IR (neat):** 2937 (w), 2839 (w), 1612 (m), 1515 (s), 1254 (s), 1149 (s), 1035 (m), 829 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58–7.38 (m, 2H), 7.03–6.81 (m, 2H), 5.74–5.49 (m, 1H), 5.27–5.07 (m, 1H), 3.81 (s, 3H), 2.85 (dd, *J* = 15.0, 6.7 Hz, 1H), 2.70 (dd, *J* =

14.9, 7.7 Hz, 1H), 1.72 (s, 2H), 1.63 (ddt, *J* = 6.9, 1.9, 0.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.4, 129.7 (br), 128.6, 128.4 (q, *J* = 1.3 Hz), 127.3 (q, *J* = 285 Hz), 123.1, 113.7, 61.2 (q, *J* = 26.0 Hz), 53.4, 35.6, 13.3; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.4 (s, 3F); **HRMS (DART):** Calcd for $C_{13}H_{17}NOF_3$ $[M+H]^+$: 260.1257; Found: 260.1261; **Specific rotation:** $[\alpha]^{24.2}_D$ +23.6 (*c* 1.3, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 16.220 min (major) and 19.445 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	15.924	26050564	48.768
2	16.615	1376459	2.577
3	19.043	25990583	48.655
Total		53417607	100.000

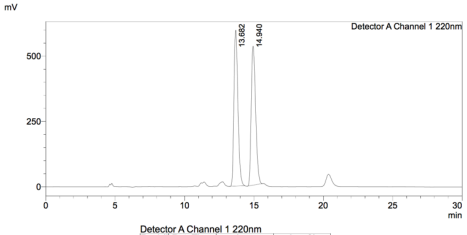


Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	16.200	41331980	97.996
2	19.445	845435	2.004
Total		42177414	100.000

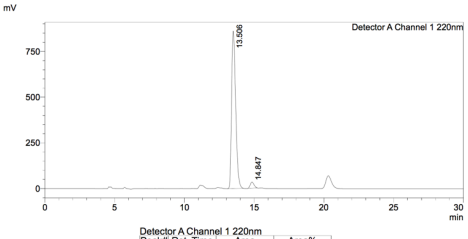
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	15.924	48.768	1	16.200	97.996
2	19.043	48.655	2	19.445	2.004

(*R,Z*)-4-(2-Amino-1,1,1-trifluorohex-4-en-2-yl)-*N*,*N*-dimethylaniline (2.107): Pale yellow oil, 13.6 mg, 50% yield, 0.050 mmol; **IR (neat):** 2890 (w), 1614 (m), 1523 (m), 1355 (m), 1139 (s), 947 (m), 909 (m), 813 (m), 734 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52–7.25 (m, 2H), 6.71 (d, *J* = 9.0 Hz, 2H), 5.74–5.46 (m, 1H), 5.34–4.99 (m, 1H), 2.96 (s, 6H), 2.90–2.77 (m, 1H), 2.70 (dddd, *J* = 14.9, 7.8, 1.6, 0.8 Hz, 1H), 1.71 (s, 2H), 1.64 (dt, *J* = 6.9, 1.0 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.0, 128.2, 127.7, 127.3 (q, *J* = 285 Hz), 124.7, 123.3, 111.8, 60.9 (q, *J* = 25.7 Hz), 40.3, 33.2, 13.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.6 (s, 3F); **HRMS (DART):** Calcd for $C_{14}H_{20}N_2F_3$ $[M+H]^+$: 273.1573; Found: 273.1580; **Specific rotation:** $[\alpha]^{24.2}_D$ +23.6 (*c* 1.3, $CHCl_3$) for a 96.5:3.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 13.506 min (major) and 14.847 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	13.682	11707795	50.335
2	14.940	11552163	49.665
Total		23259958	100.000

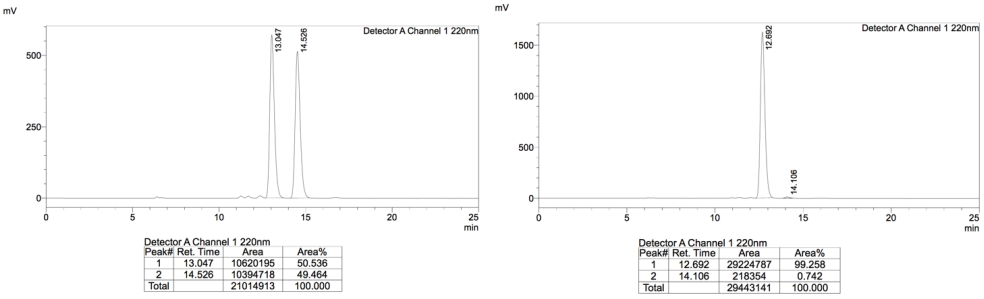


Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	13.506	17315969	96.559
2	14.847	617070	3.441
Total		17933040	100.000

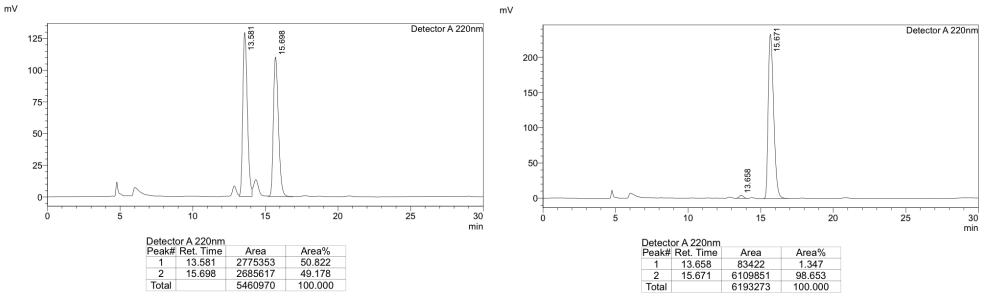
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	13.682	50.335	1	13.506	96.559
2	14.940	49.665	2	14.847	3.441

(*R*,*Z*)-1,1,1-Trifluoro-2-(2-methoxyphenyl)hex-4-en-2-amine (2.108): Colorless oil, 18.1 mg, 70% yield, 0.070 mmol; **IR (neat):** 2941 (w, br), 1601 (w), 1492 (m), 1244 (m), 1218 (s), 1026 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 (td, *J* = 8.1, 1.8 Hz, 1H), 7.34 (dddd, *J* = 8.1, 7.3, 4.8, 1.7 Hz, 1H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 (m, 1H), 5.69–5.55 (m, 1H), 5.23 (m, 1H), 3.86 (s, 3H), 3.29–3.12 (m, 1H), 2.78–2.57 (m, 1H), 2.00 (s, 2H), 1.76–1.58 (m, 3H)**; ^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.2, 130.3, 129.9, 127.4 (q, *J* = 286.8 Hz), 127.9, 124.7, 124.2, 120.7, 112.7, 62.6 (q, *J* = 26.6 Hz), 55.8, 32.3, 13.4; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.5 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_4$ $[M+H]^+$: 248.1057; Found: 248.1068; **Specific rotation:** $[\alpha]^{24.8}_D$ –4.2 (*c* 1.6, $CHCl_3$) for a 99:1 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 12.692 min (major) and 14.106 min (minor).



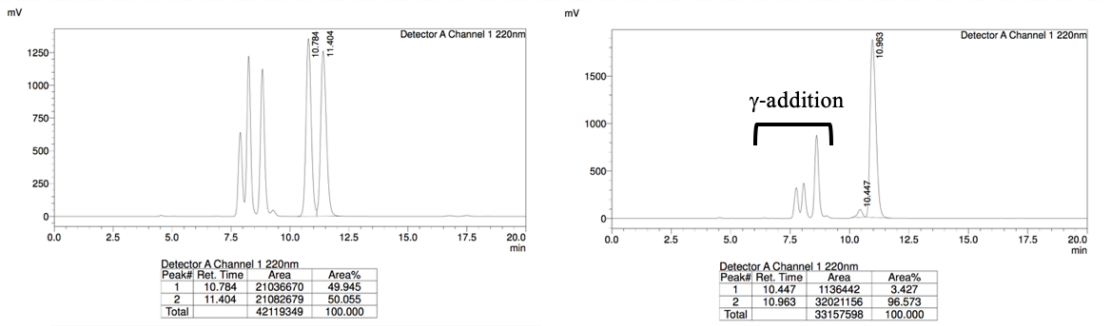
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	13.047	50.536	1	12.692	99.258
2	14.536	49.464	2	14.106	0.742

(*R*,*Z*)-1,1,1-Trifluoro-2-(2-fluorophenyl)hex-4-en-2-amine (2.109): Colorless oil, 22.0 mg, 89% yield, 0.089 mmol; **IR (neat):** 3030 (w), 2158 (w), 1614 (m), 1489 (m), 1445 (m), 1221 (s), 1151 (s), 759 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 (td, *J* = 8.1, 1.8 Hz, 1H), 7.34 (dddd, *J* = 8.1, 7.3, 4.8, 1.7 Hz, 1H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 (ddd, *J* = 13.0, 8.2, 1.3 Hz, 1H), 5.69–5.55 (m, 1H), 5.23 (m, 1H), 3.29–3.12 (m, 1H), 2.78–2.57 (m, 1H), 2.00 (s, 2H), 1.76–1.58 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.6 (d, *J* = 249.5 Hz), 138.0 (d, *J* = 74.0 Hz), 130.6 (d, *J* = 9.3 Hz), 130.2 (d, *J* = 3.8 Hz), 128.8, 126.9 (q, *J* = 286.1 Hz), 124.2 (d, *J* = 3.4 Hz), 123.1, 117.0 (d, *J* = 25.4 Hz), 61.6 (q, *J* = 26.7 Hz), 32.0 (d, *J* = 5.7 Hz), 13.3; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –79.2 (d, *J* = 15.0 Hz, 3F), –108.7 (ddt, *J* = 26.5, 18.5, 9.4 Hz, 1F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_4$ $[M+H]^+$: 248.1057; Found: 248.1068; **Specific rotation:** $[\alpha]^{24.0}_D$ +16.0 (*c* 1.4, $CHCl_3$) for a 98.5:1.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis of the derived chloroacetamide in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 13.658 min (minor) and 15.671 min (major).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	13.581	50.822	1	13.658	1.347
2	15.698	49.178	2	15.671	98.563

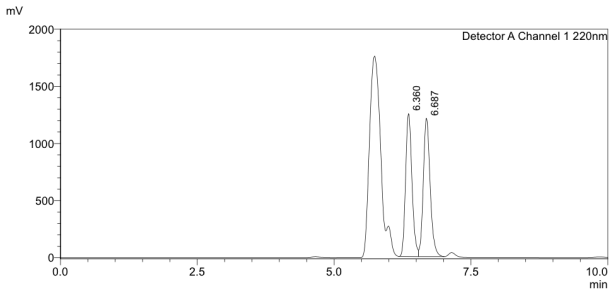
(*R,Z*)-2-(2-Chlorophenyl)-1,1,1-trifluorohex-4-en-2-amine (2.110): Colorless oil, 20.8 mg, 79% yield, 0.079 mmol; **IR (neat):** 2981 (w), 2160 (w), 1429 (m), 1245 (m), 1153 (s), 1042 (m), 755 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.75–7.48 (m, 1H), 7.47–7.36 (m, 1H), 7.32–7.23 (m, 2H), 5.62 (m, 1H), 5.39–5.15 (m, 1H), 3.39 (ddt, *J* = 15.6, 6.5, 1.5 Hz, 1H), 2.93–2.69 (m, 1H), 2.24 (s, 2H), 1.69 (ddt, *J* = 6.8, 1.9, 1.0 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.6, 134.2, 132.6, 131.1 (q, *J* = 1.5 Hz), 130.48 (q, *J* = 156.6 Hz), 129.5, 128.6, 126.7, 123.1, 63.3 (q, *J* = 26.6 Hz), 32.6, 13.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –76.8 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_3Cl$ $[M+H]^+$: 264.0761; Found: 264.0770; **Specific rotation:** $[\alpha]^{24.9}_D$ +7.4 (*c* 1.2, $CHCl_3$) for a 96.5:3.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 10.447 min (minor) and 10.963 min (major).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	10.784	49.945	1	10.447	3.427
2	11.404	50.055	2	10.963	96.573

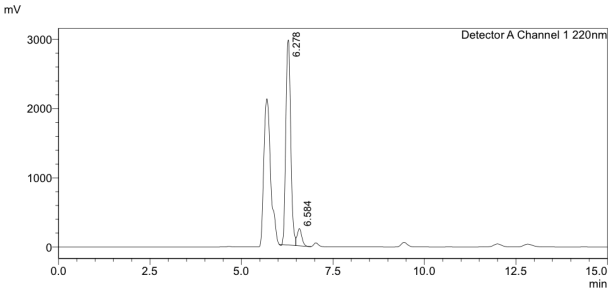
(*Z*)-2-(2-Bromophenyl)-1,1,1-trifluorohex-4-en-2-amine (2.111): Clear oil; **IR (neat):** 2984 (w,), 1621 (w), 1464 (m), 1424 (m), 1244 (m), 1155 (s), 1019 (m), 755 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.67 7.66f (m, 1H), 7.64 – 7.60 (m, 1H), 7.33 (dtd, *J* = 8.6, 7.3, 1.4 Hz, 2H), 7.16 (m, 1H, peaks overlapped with γ-addition product), 5.75 – 5.56 (m, 1H), 5.34 – 5.17 (m, 1H, peaks overlapped with γ-addition product),), 3.38 (dd, *J* = 15.7, 6.5 Hz, 1H), 2.84 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.29 (s, 2H), 1.69 (ddt, *J* = 6.9, 2.0, 1.0 Hz, 3H)**; ^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.8, 136.7, 131.5 (q, *J* = 1.9 Hz), 129.8, 128.7, 127.1 (q, *J* = 285 Hz), 127.3,

123.3, 117.7, 63.8 (q, J = 26.3 Hz), 32.9 (q, J =1.3 Hz), 13.4; **^{19}F NMR (376 MHz, $CDCl_3$):** –76.1 (s, 3F), –106.2 (m, 2F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_3Br$ $[M+H]^+$: 308.0256; Found: 308.0248; **Specific rotation:** $[\alpha]^{24.6}_D$ +1.5 (c = 1.1, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 6.278 min (major) and 6.584 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	6.360	9995624	48.648	1250476
2	6.687	10551083	51.352	1209830
Total		20546707	100.000	2460306

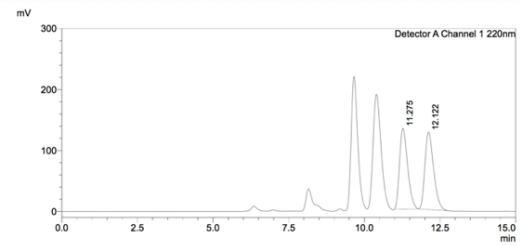


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	6.278	27681317	92.634	2963272
2	6.584	2201194	7.366	248668
Total		29882511	100.000	3211939

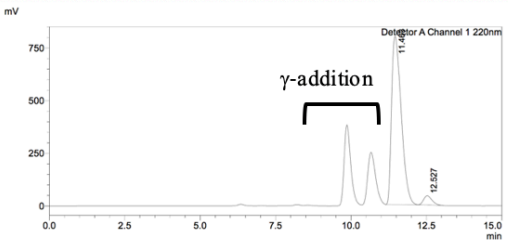
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	6.360	48.648	1	6.278	92.634
2	6.687	51.352	2	6.584	7.366

(*R*,*Z*)-1,1,1-Trifluoro-2-(*o*-tolyl)hex-4-en-2-amine (2.112): Colorless oil, 12.7 mg, 52% yield, 0.052 mmol; **IR (neat):** 3315 (w, br), 2956 (w), 1762 (m), 1449 (m), 1239 (s), 1151 (s), 989 (m), 676 (s), 623 (s), 573 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (m, 1H), 7.24–7.13 (m, 3H), 5.75–5.46 (m, 1H), 5.33–5.06 (m, 1H, overlapped with γ-addn product), 3.16 (dd, J = 15.8, 6.4 Hz, 1H), 2.70 (dd, J = 15.7, 7.5 Hz, 1H), 2.64 (s, 3H), 1.81 (s, 2H, overlapped with γ-addition product), 1.68 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.2, 135.1, 133.7, 129.5, 128.5, 128.3, 127.6 (q, J = 286.1 Hz), 125.9, 123.6, 63.6 (q, J = 25.8 Hz), 34.0, 23.7, 13.4; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –77.4 (s, 3F); **HRMS (DART):** Calcd for $C_{13}H_{17}NF_3$ $[M+H]^+$: 244.1308; Found: 244.1319; **Specific rotation:** $[\alpha]^{26.0}_D$ +29.5 (c 1.48, $CHCl_3$) for a 95.5:4.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 11.463 min (major) and 12.557 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	11.275	2473974	49.404
2	12.122	2533673	50.596
Total		5007647	100.000

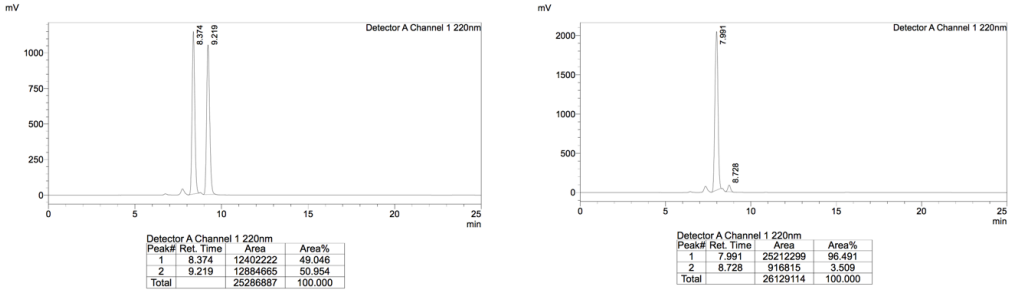


Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	11.463	17780260	95.445
2	12.527	848456	4.555
Total		18628716	100.000

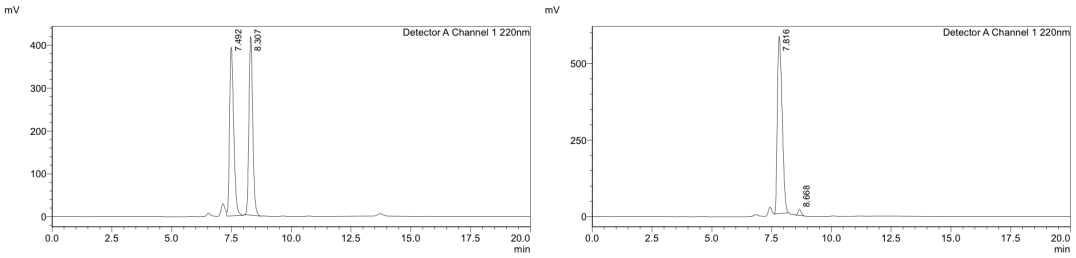
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	11.275	49.404	1	11.463	95.445
2	12.122	50.596	2	12.527	4.555

(*R,Z*)-2-(3-Chlorophenyl)-1,1,1-trifluorohex-4-en-2-amine (2.113): Colorless oil, 23.7 mg, 90% yield, 0.090 mmol; **IR (neat):** 2232 (w), 2032 (w), 1573 (m), 1251 (m), 1141 (s), 780 (s), 700 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 (m, 1H), 7.47 (m, 1H), 7.36–7.29 (m, 2H), 5.78–5.41 (m, 1H), 5.22–4.94 (m, 1H), 2.83 (dd, *J* = 14.9, 7.0 Hz, 1H), 2.71 (dddd, *J* = 14.9, 7.7, 1.7, 0.9 Hz, 1H), 1.74 (s, 2H), 1.67–1.49 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 139.9, 134.4, 129.5, 129.0, 128.3, 127.4 (q, *J* = 1.4 Hz), 126.8 (q, *J* = 285.5 Hz), 125.1 (q, *J* = 1.8 Hz), 122.3, 61.6 (q, *J* = 26.0 Hz), 33.5, 13.1; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –77.8 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{14}NF_3Cl$ $[M+H]^+$: 264.0761; Found: 264.0770; **Specific rotation:** $[\alpha]^{24.9}_D$ +25.6 (*c* 1.2, $CHCl_3$) for a 96.5:3.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 7.991 min (major) and 8.728 min (minor).



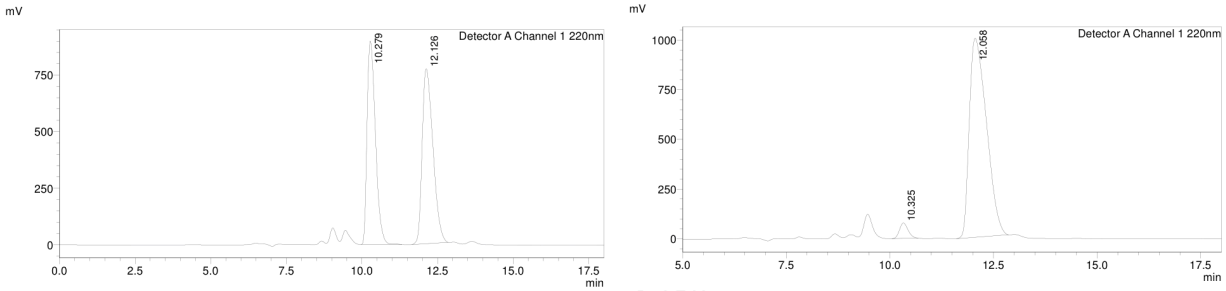
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	8.374	49.046	1	7.991	96.491
2	9.219	50.954	2	8.728	3.509

(*R,Z*)-1,1,1-Trifluoro-2-(3-(trifluoromethyl)phenyl)hex-4-en-2-amine (2.114): Colorless oil, 24.4 mg, 82% yield, 0.082 mmol; **IR (neat):** 2926 (w), 1617 (m), 1444 (m), 1329 (s), 1129 (s), 1079 (m), 802 (m), 703 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61 (m, 1H), 7.50–7.42 (m, 1H), 7.38–7.27 (m, 2H), 5.74–5.51 (m, 1H), 5.27–4.97 (m, 1H), 2.83 (dd, *J* = 14.9, 7.0 Hz, 1H), 2.71 (dddd, *J* = 14.9, 7.7, 1.7, 0.9 Hz, 1H), 1.74 (s, 2H), 1.69–1.45 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 139.1, 130.9 (q, *J* = 32.1 Hz), 130.6 (m), 129.3, 128.9, 126.9 (q, *J* = 269.2 Hz), 125.2 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.3 Hz), 124.1 (m), 122.2, 61.8 (q, *J* = 26.0 Hz), 33.8 (q, *J* =1.4 Hz), 13.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –62.6 (s, 3F), –77.8 (s, 3F); **HRMS (DART):** Calcd for $C_{13}H_{14}NF_6$ $[M+H]^+$: 298.1025; Found: 298.1038; **Specific rotation:** $[\alpha]^{24.3}_D$ +20.9 (*c* 1.4, $CHCl_3$) for a 98:2 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak OZ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 7.816 min (major) and 8.668 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	7.492	50.801	1	7.816	97.904
2	8.307	49.199	2	8.668	2.096

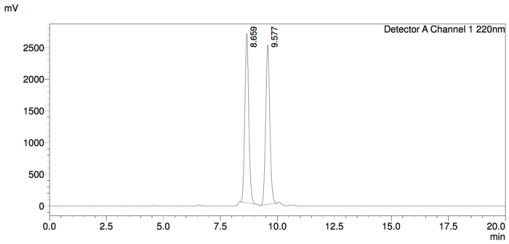
(*R*,*Z*)-1,1,1-Trifluoro-2-(*m*-tolyl)hex-4-en-2-amine (2.115): Clear oil; **IR (neat):** 3397 (w), 3027 (w), 2923 (w), 1608 (w), 1446 (m), 1252 (m), 1142 (s), 839 (s), 785 (s), 717 (s), 532 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 – 7.31 (m, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 5.59 (dddd, *J* = 11.6, 8.6, 5.9, 3.5 Hz, 1H), 5.15 (q, *J* = 8.1 Hz, 1H), 2.79 (ddd, *J* = 56.1, 14.9, 7.2 Hz, 2H), 2.37 (s, 3H), 1.73 (s, 2H), 1.68 – 1.55 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.00, 137.68, 128.94, 128.66, 128.27, 127.71, 127.1 (q, *J* = 219.1 Hz), 124.12, 123.06, 61.55 (q, *J* = 27.7, 27.0 Hz), 33.64, 21.79, 13.28; **^{19}F NMR (376 MHz, $CDCl_3$):** –77.9 (s, 3F); **HRMS (DART):** Calcd for $C_{13}H_{17}NF_3$ $[M+H]^+$: 244.1308; Found: 244.1303; **Specific rotation:** $[\alpha]^{24.3}_D$ +18.4 (*c* = 1.3, $CHCl_3$) for a 96:4 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak OJ-H, 97:3 hexanes:*i*PrOH, 0.5 mL/min, 220 nm): t_R: 12.058 min (major) and 10.325 min (minor).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	10.279	47.612	1	10.325	3.736
2	12.126	52.388	2	12.058	96.264

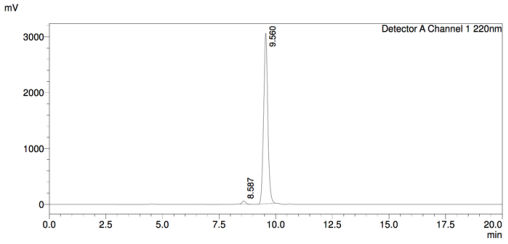
(*R*,1*E*,5*Z*)-2-Methyl-1-phenyl-3-(trifluoromethyl)hepta-1,5-dien-3-amine (2.116): Colorless oil, 17.2 g, 64% yield, 0.064 mmol; **IR (neat):** 3024 (w), 2935 (w), 1444 (m), 1250 (m), 1147 (m), 1003 (m), 700 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.34 (m, 2H), 7.26–7.22 (m, 3H), 6.90

(s, 1H), 5.78–5.62 (m, 1H), 5.37 (m, 1H), 2.71 (dd, *J* = 15.1, 6.7 Hz, 1H), 2.51 (dd, *J* = 15.1, 7.5 Hz, 1H), 1.90 (t, *J* = 1.3 Hz, 3H), 1.71 (dt, *J* = 6.8, 1.1 Hz, 3H), 1.57 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.7, 134.3, 129.8, 129.1, 128.2, 128.1, 127.3 (q, *J* = 286.8 Hz), 126.7, 122.9, 62.9 (q, *J* = 25.0 Hz), 30.9, 15.0, 13.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –76.8 (s, 3F); **HRMS (DART):** Calcd for $C_{15}H_{19}NF_3$ $[M+H]^+$: 270.1464; Found: 270.1474; **Specific rotation:** $[\alpha]^{24.8}_D$ +4.4 (*c* 0.9, $CHCl_3$) for a 98.5:1.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 8.587 min (minor) and 9.560 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	8.659	31586105	50.025
2	9.577	31554977	49.975
Total		63141082	100.000

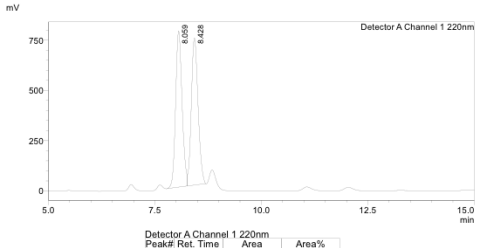


Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	8.587	631422	1.602
2	9.560	38791988	98.398
Total		39423410	100.000

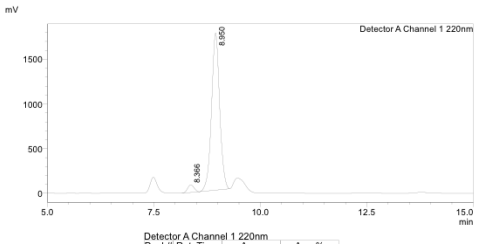
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	8.659	50.025	1	8.587	1.602
2	9.577	49.975	2	9.560	98.398

(*R,Z*)-1-Phenyl-3-(trifluoromethyl)hept-5-en-1-yn-3-amine (2.117): Colorless oil, 20.5 mg, 81% yield, 0.081 mmol; **IR (neat):** 3026 (w), 1617 (m), 1436 (m), 1143 (s), 1052 (m), 832 (m), 701 (s) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.52–7.37 (m, 2H), 7.36–7.27 (m, 3H), 5.84 (dqt, *J* = 12.3, 6.8, 1.5 Hz, 1H), 5.68 (td, *J* = 9.0, 6.8 Hz, 1H), 2.63 (d, *J* = 7.4 Hz, 2H), 1.83 (s, 2H), 1.72 (dq, *J* = 6.7, 0.9 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 140.8 (q, *J* = 15.1 Hz), 134.5, 132.3, 131.5, 128.9 (q, *J* = 190.1 Hz), 125.1, 124.5, 88.5, 87.8, 59.2 (q, *J* = 29.1 Hz), 35.5, 15.8; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –80.5 (s, 3F); **HRMS (DART):** Calcd for $C_{14}H_{15}NF_3$ $[M+H]^+$: 254.1151; Found: 254.1153; **Specific rotation:** $[\alpha]^{26.0}_D$ +11.4 (*c* 1.85, $CHCl_3$) for a 96.5:3.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 8.366 min (major) and 8.950 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	8.059	8200707	50.368
2	8.428	8080741	49.632
Total		16281448	100.000

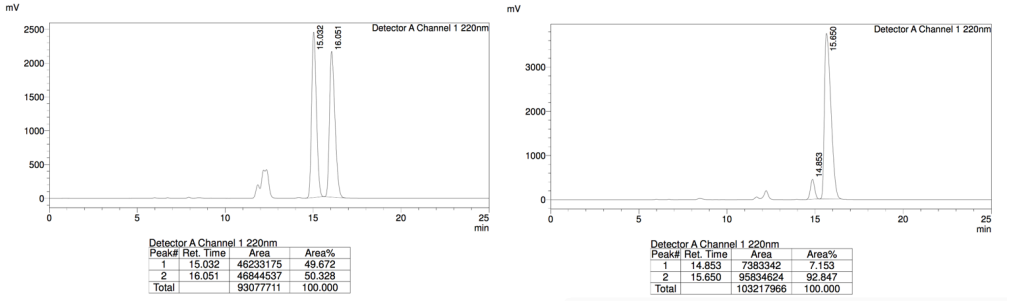


Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	8.366	909252	3.724
2	8.950	23509180	96.276
Total		24418432	100.000

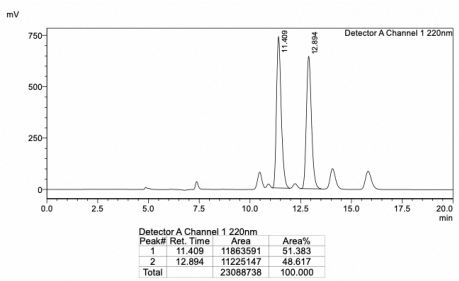
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	8.059	50.368	1	8.366	3.724
2	8.428	49.632	2	8.950	96.276

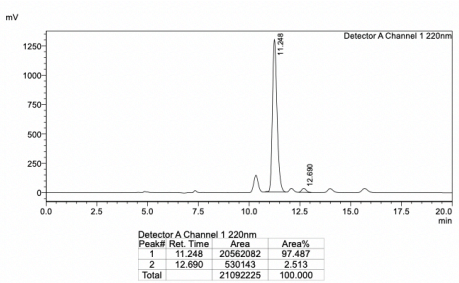
(*R*,*Z*)-1,1,1-Trifluoro-2-(thiophen-2-yl)hex-4-en-2-amine (2.118): Pale yellow oil, 19.8 mg, 84% yield, 0.084 mmol; **IR (neat):** 3026 (w), 1617 (m), 1436 (m), 1143 (s), 1052 (m), 832 (m), 701 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35–7.25 (m, 1H), 7.11 (m, 1H), 7.02 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.67 (m, 1H), 5.43–5.14 (m, 1H), 2.76 (d, *J* = 7.4 Hz, 2H), 1.91 (s, 2H), 1.72–1.31 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 143.1, 129.2, 127.2, 126.4 (q, *J* = 285.2 Hz), 125.5 (q, *J* = 1.4 Hz), 125.4, 122.3, 61.0 (q, *J* = 27.1 Hz), 34.7, 13.1; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –79.2 (s, 3F); **HRMS (DART):** Calcd for $C_{10}H_{13}NF_3S$ $[M+H]^+$: 236.0715; Found: 236.0717; **Specific rotation:** $[\alpha]^{26.0}_D$ –20.0 (*c* 0.5, $CHCl_3$) for a 93:7 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 14.853 min (minor) and 15.650 min (major).



Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	15.032	49.672	1	14.853	7.153
2	16.051	50.328	2	15.650	92.847

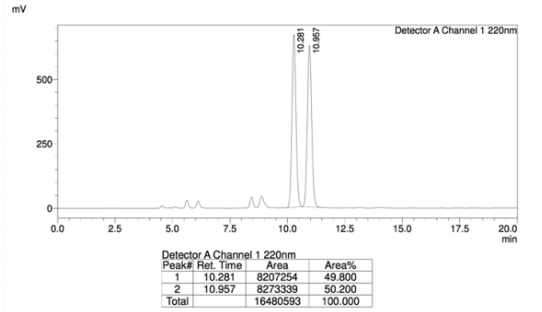
(*R*,*Z*)-2-(Benzofuran-2-yl)-1,1,1-trifluorohex-4-en-2-amine (2.119): Pale yellow oil, 20.7 mg, 77% yield, 0.077 mmol; **IR (neat):** 3400 (w), 3025 (w), 1705 (w), 1473 (m), 1138 (s), 1004 (m), 739 (s), 629 (m), 429 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (ddd, *J* = 7.6, 1.5, 0.8 Hz, 1H), 7.49 (dq, *J* = 8.2, 0.9 Hz, 1H), 7.30 (ddd, *J* = 8.3, 7.2, 1.5 Hz, 1H), 7.23 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.80 (d, *J* = 0.9 Hz, 1H), 5.67 (m, 1H), 5.33–5.17 (m, 1H), 2.95 (dd, *J* = 14.6, 6.6 Hz, 1H), 2.79 (dd, *J* = 14.6, 8.2 Hz, 1H), 1.95 (s, 2H), 1.66 (ddt, *J* = 6.9, 1.9, 0.9 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.0, 154.3, 129.5, 127.8, 124.6, 124.4 (q, *J* = 204.4 Hz), 123.0, 122.0, 121.2, 111.4, 105.7, 60.2 (q, *J* = 22.6 Hz), 31.3, 13.1; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.7 (s, 3F); **HRMS (DART):** Calcd for $C_{14}H_{15}NOF_3$ $[M+H]^+$: 270.1100; Found: 270.1098; **Specific rotation:** $[\alpha]^{26.0}_D$ +37.9 (*c* 10.7, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 11.248 min (major) and 12.690 min (minor).

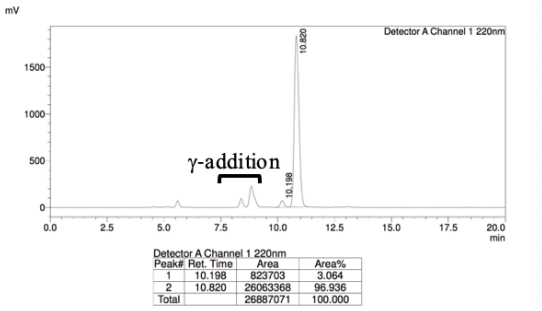




Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	11.409	51.383	1	11.248	97.487
2	12.894	48.617	2	12.690	2.513

(*R*,*Z*)-1,1,1-Trifluoro-2-(furan-2-yl)hex-4-en-2-amine (2.120): Pale yellow oil, 7.0 mg, 32% yield, 0.032 mmol; **IR (neat):** 3999 (w, br), 3025 (w), 1759 (w), 1616 (m), 1257 (m), 1144 (s), 1016 (m), 738 (s), 556 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 (s, 1H), 6.55 – 6.01 (m, 2H), 5.81 – 5.58 (m, 1H), 5.35 – 5.10 (m, 1H), 2.82 (dd, *J* = 14.6, 6.6 Hz, 1H), 2.70 (dd, *J* = 14.4, 8.1 Hz, 1H), 1.81 (s, 2H), 1.64 (dt, *J* = 6.9, 0.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 151.6, 142.9, 129.4, 126.1 (q, *J* = 285.4 Hz), 122.4, 110.6, 108.8, 59.8 (q, *J* = 27.3 Hz), 31.4, 13.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –79.3 (s, 3F); **HRMS (DART):** Calcd for $C_{10}H_{13}NOF_3$ $[M+H]^+$: 220.0944; Found: 220.0940; **Specific rotation:** $[\alpha]^{26.0}_D$ +27.9 (*c* 1.72, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 10.198 min (minor) and 10.820 min (minor).

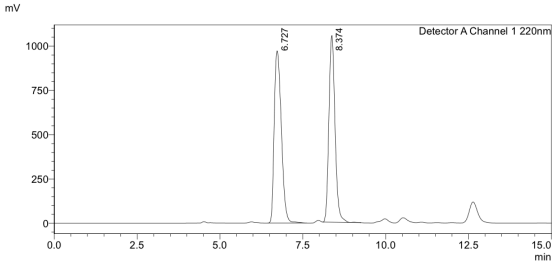




Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	10.281	49.800	1	10.198	3.064
2	10.957	50.200	2	10.820	96.936

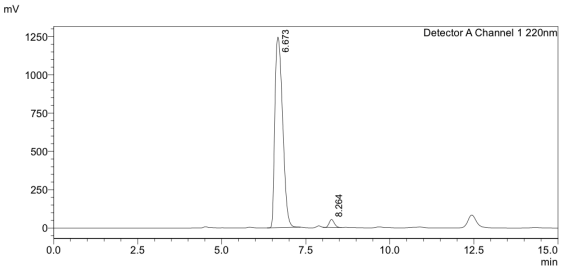
(*R*,*Z*)-1,1,1,2,2-Pentafluoro-3-(4-(trifluoromethyl)phenyl)hept-5-en-3-amine (2.121): Pale yellow oil; **IR (neat):** 3027 (w), 2919 (w), 1620 (m), 1324 (s), 1209 (m), 1164 (s), 1121 (s), 1069 (m), 751 (m), 599 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72–7.58 (m, 4H), 5.61 (dtd, *J* = 12.0, 8.4, 7.8, 6.3 Hz, 1H), 4.97 (q, *J* = 8.6 Hz, 1H), 3.02–2.79 (m, 2H), 1.78 (s, 2H), 1.63 (ddt, *J* = 6.8, 1.7, 0.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.66, 130.50 (dd, *J* = 65.6, 32.8 Hz), 129.71, 127.86, 125.30, 124.11 (q, *J* = 272.0 Hz), 122.05, 121.03 (t, *J* = 37.1 Hz), 115.99 (tq, *J* =

37.2 Hz, *J* = 33.6 Hz, *J* = 33.6 Hz, *J* = 36.8, 34.9 Hz), 61.70 (t, *J* = 21.3 Hz), 33.61, 13.35; **^{19}F NMR (376 MHz, $CDCl_3$):** –62.7 (s, 3F), –77.0 (s, 3F), –120.1 (dd, *J* = 73.8 Hz, *J* = 124.1 Hz, 2F); **HRMS (DART):** Calcd for $C_{14}H_{14}NF_8$ $[M+H]^+$: 348.0993; Found: 348.1002; **Specific rotation:** $[\alpha]^{26.0}_D$ +13.9 (*c* = 2.75, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel AD-H, 97:3 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 6.673 min (minor) and 8.264 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	6.727	14507897	51.575	972360
2	8.374	13621924	48.425	1054252
Total		28129820	100.000	2026612



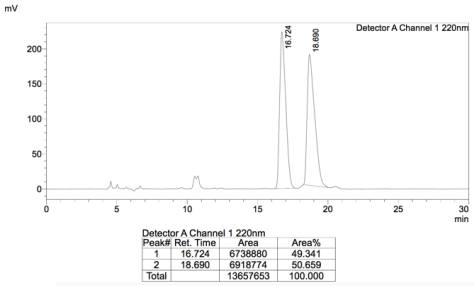
<Peak Table>
Detector A Channel 1 220nm

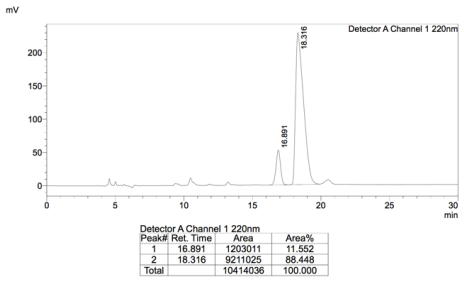
Peak#	Ret. Time	Area	Area%	Height
1	6.673	19942733	97.314	1244168
2	8.264	550433	2.686	52409
Total		20493165	100.000	1296577

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	6.727	51.574	1	6.673	97.314
2	8.374	48.425	2	8.264	2.686

In a N_2-filled glovebox, a stock solution of **ap-7** (3.5 mg, 0.01 mmol), $Zn(OMe)_2$ (2.6 mg, 0.02 mmol), and tol. (0.5 mL) was prepared. A separate oven-dried two-dram vial equipped with a magnetic stir-bar was charged with NTMS-ketimine (0.1 mmol), tol. (0.25 mL), tbat (2.7 mg, 0.005 mmol) and MeOH (7 μL, 0.175 mmol), and was subsequently charged with the freshly prepared catalyst stock solution (0.25 mL) followed by (*Z*)-2-(3-Chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (26.3 mg, 0.13 mmol), and MeOH (7 μL, 0.175 mmol). The mixture was allowed to stir for five min prior and then the vessel was capped, removed from the glovebox, and the solution was allowed to stir for 14 h at 22 °C. Conversion and α:γ ratio were determined by spectroscopic analysis (^{19}F NMR) of an aliquot sample. The mixture was directly loaded onto silica gel and eluted with 100:0 → 3:1 hexanes:Et_2O to afford the desired α-tertiary amine as colorless oil.

(*R,Z*)-5-Chloro-1,1,1-trifluoro-2-phenylpent-4-en-2-amine (2.129): Colorless oil, 22.7 mg, 91% yield, 0.091 mmol; **IR (neat):** 2924 (m), 2853 (m), 1630 (m), 1449 (m), 1255 (m), 1152 (s), 756 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.60–7.52 (m, 2H), 7.45–7.32 (m, 3H), 6.10 (dt, *J* = 7.2, 1.7 Hz, 1H), 5.54 (q, *J* = 7.0 Hz, 1H), 3.11 (ddd, *J* = 15.5, 6.6, 1.8 Hz, 1H), 2.89 (ddd, *J* = 15.5, 7.2, 1.7 Hz, 1H), 1.81 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 136.6, 128.4, 128.3, 126.9 (q, *J* = 285.4 Hz), 126.8, 125.0, 121.7, 61.2 (q, *J* = 26.2 Hz), 33.8; **^{19}F NMR (564 MHz, $CDCl_3$):** δ –78.7 (s, 3F); **HRMS (DART):** Calcd for $C_{11}H_{12}NF_3Cl$ $[M+H]^+$: 250.0605; Found: 250.0616; **Specific rotation:** $[\alpha]^{24.5}_D$ +4.1 (*c* 1.3, $CHCl_3$) for a 88.5:11.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 16.891 min (minor) and 18.316 min (major).

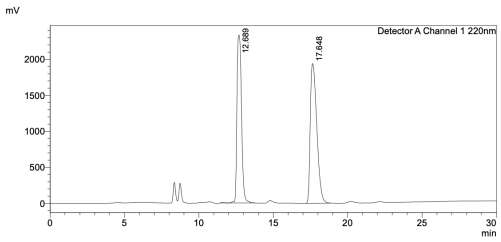




Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	16.724	49.341	1	16.891	11.552
2	18.690	50.659	2	18.316	88.448

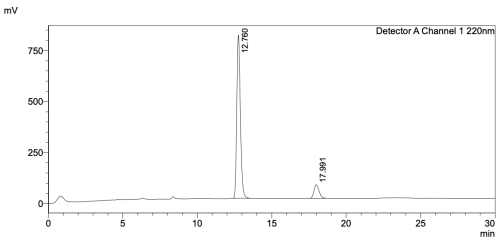
In a N_2-filled glovebox, a stock solution of aminophenol **ap-7** (3.5 mg, 0.01 mmol), $Zn(OMe)_2$ (2.6 mg, 0.02 mmol), and toluene (0.5 mL) was prepared. A separate oven-dried two-dram vial equipped with a magnetic stir-bar was charged with NTMS-ketimine (0.1 mmol), toluene (0.25 mL), TBAT (2.7 mg, 0.005 mmol) and MeOH (7 μL, 0.175 mmol). The freshly prepared catalyst stock solution (0.25 mL) was then added followed by (*Z*)-2-(3-Bromoallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (32.1 mg, 0.13 mmol), and MeOH (7 μL, 0.175 mmol). The mixture was allowed to stir for five minutes prior to being sealed with a Teflon cap, removed from the glovebox, and allowed to stir at 22 °C for 14 h. Conversion and α:γ ratio were determined by ^{19}F NMR of an aliquot. The mixture was loaded onto silica gel and eluted with 100:0 → 3:1 hexanes:Et_2O to afford the α-tertiary amine as colorless oil.

(*R*,*Z*)-5-Bromo-2-(4-chlorophenyl)-1,1,1-trifluoropent-4-en-2-amine (2.130): Yellow oil, 24.3 mg, 74 % yield, 0.074 mmol; **IR (neat):** 3402 (w), 3334 (w), 2926 (w), 1624 (w), 1494 (m), 1151 (s), 1075 (m), 824 (m), 699 (m), 581 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.39–7.33 (m, 2H), 6.26 (dt, *J* = 7.3, 1.7 Hz, 1H), 5.86 (q, *J* = 6.9 Hz, 1H), 3.05 (dd, *J* = 15.5, 6.7 Hz, 1H), 2.82 (ddd, *J* = 15.4, 6.8, 1.7 Hz, 1H), 1.79 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.4, 134.7, 129.9, 128.6, 128.0, 126.8 (q, *J* = 285.8 Hz), 112.1, 62.1 (q, *J* = 26.4 Hz), 36.6; **^{19}F NMR (564 MHz, $CDCl_3$):** δ –78.8 (s, 3F); **HRMS (DART):** Calcd for $C_{11}H_{11}NF_3ClBr$ $[M+H]^+$: 327.9710; Found: 327.9718; **Specific rotation:** $[\alpha]^{24.5}_D$ –3.5 (*c* 0.85, $CHCl_3$) for a 92:8 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 12.760 min (major) and 17.991 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area%
1	12.689	50119875	2334559	46.147
2	17.648	58488202	1940051	53.853
Total		108608076	4274609	100.000

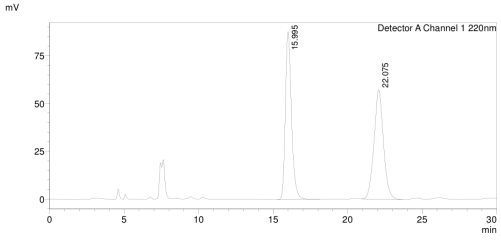


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area%
1	12.760	13433502	799630	89.499
2	17.991	1576140	66681	10.501
Total		15009642	866311	100.000

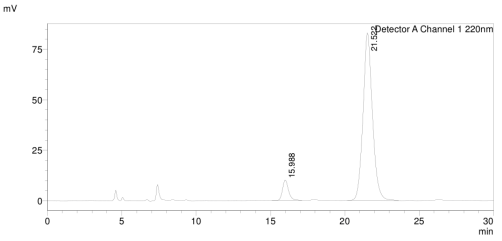
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	12.689	46.147	1	12.760	89.499
2	17.648	53.853	2	17.991	10.501

(*R*,*Z*)-5-Bromo-1,1,1-trifluoro-2-(4-(trifluoromethyl)phenyl)pent-4-en-2-amine (2.131): Colorless oil, 27.5 mg, 76% yield, 0.076 mmol; **IR (neat):** 3401 (w), 2993 (w), 2855 (w), 1623 (w), 1324 (s), 1253 (m), 1158 (s), 1125 (s), 735 (m), 625 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 6.27 (dt, *J* = 7.3, 1.7 Hz, 1H), 5.85 (q, *J* = 6.9 Hz, 1H), 3.10 (ddd, *J* = 15.5, 6.8, 1.6 Hz, 1H), 2.85 (ddd, *J* = 15.5, 6.7, 1.7 Hz, 1H), 1.80 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.6 (d, *J* = 249.5 Hz), 130.6, 130.4 (q, *J* = 35.8 Hz), 128.8, 126.9 (q, *J* = 286.1 Hz), 124.2 (q, *J* = 3.4 Hz), 123.1, 117.0 (q, *J* = 25.4 Hz), 61.6 (q, *J* = 26.7 Hz), 32.0; **^{19}F NMR (564 MHz, $CDCl_3$):** δ –62.41 to –63.28 (m, 3F), –78.13 to –78.89 (m, 3F); **HRMS (DART):** Calcd for $C_{12}H_{11}NF_6Br$ $[M+H]^+$: 361.9974; Found: 361.9980; **Specific rotation:** $[\alpha]^{24.5}_D$ –6.2 (*c* 7.8, $CHCl_3$) for a 93:7 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 98:2 hexanes:*i*PrOH, 0.5 mL/min, 220 nm): t_R: 15.988 min (major) and 21.552 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area%
1	15.995	2504363	87792	49.717
2	22.075	2532849	57415	50.283
Total		5037212	145207	100.000



<Peak Table>
Detector A Channel 1 220nm

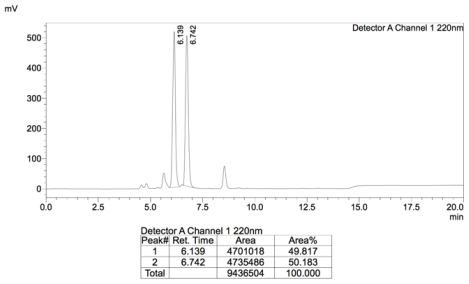
Peak#	Ret. Time	Area	Height	Area%
1	15.988	281278	10071	7.159
2	21.522	3647724	82920	92.841
Total		3929002	92991	100.000

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	15.995	49.717	1	15.988	7.159
2	22.075	50.283	2	21.552	92.841

In a N_2-filled glovebox, a stock solution of **ap-7** (3.5 mg, 0.01 mmol), $Zn(OMe)_2$ (2.6 mg, 0.02 mmol), and tol. (0.5 mL) was prepared. A separate oven-dried two-dram vial equipped with a magnetic stir-bar was charged with NTMS-ketimine (0.1 mmol), toluene (0.25 mL), and tbat (2.7 mg, 0.005 mmol). The freshly prepared catalyst stock solution (0.25 mL) was then added followed

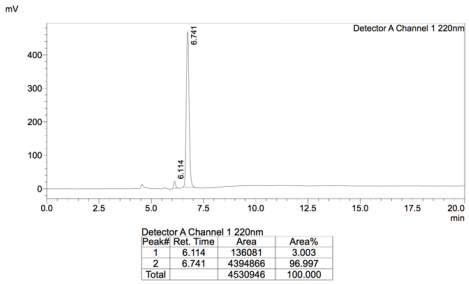
by (*Z*)-1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)dec-2-en-5-one (34.6 mg, 0.13 mmol), and MeOH (14 μL, 0.35 mmol). The mixture was allowed to stir for five min before the vial was capped, removed from the glovebox, and the mixture was allowed to stir for 3 h at 22 °C. Conversion and α:γ ratio were determined by spectroscopic analysis (^{19}F NMR) of an aliquot sample. The mixture was loaded onto silica gel and eluted with 100:0 → 3:1 hexanes:Et_2O to afford the expected α-tertiary amine as colorless oil.

(*R*,*Z*)-1,1,1-Trifluoro-2-phenyldodec-4-en-2-amine (2.132): Colorless oil, 27.0 mg, 86% yield, 0.086 mmol; **IR (neat):** 2925 (m), 2855 (m), 1449 (m), 1252 (m), 1147 (s), 763 (m), 699 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.63–7.52 (m, 2H), 7.45–7.31 (m, 3H), 5.58–5.41 (m, 1H), 5.20–5.01 (m, 1H), 2.88 (dd, *J* = 15.1, 6.9 Hz, 1H), 2.79–2.64 (m, 1H), 2.13–1.95 (m, 2H), 1.74 (s, 2H), 1.38–1.18 (m, 10H), 1.00–0.76 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.8, 134.9, 128.4, 128.2, 127.3 (q, *J* = 285.4 Hz), 127.1 127.0, 121.7, 61.6 (q, *J* = 25.8 Hz), 32.0, 29.6, 29.4, 29.3, 27.7, 22.8, 14.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.0 (s, 3F); **HRMS (DART):** Calcd for $C_{18}H_{27}NF_3$ $[M+H]^+$: 314.2090; Found: 314.2091; **Specific rotation:** $[\alpha]^{24.7}_D$ +16.4 (*c* 0.9, $CHCl_3$) for a 97:3 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 6.114 min (minor) and 6.741 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	6.139	4701018	49.817
2	6.742	4735486	50.183
Total		9436504	100.000



Detector A Channel 1 220nm

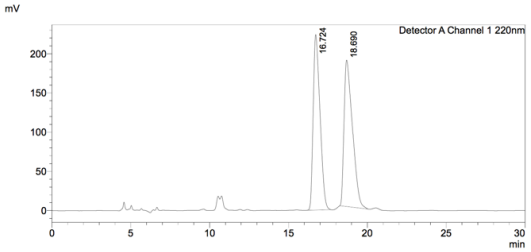
Peak#	Ret. Time	Area	Area%
1	6.114	136081	3.003
2	6.741	4394866	96.997
Total		4530946	100.000

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	6.139	49.817	1	6.114	3.003
2	6.742	50.183	2	6.741	96.997

In a N_2-filled glovebox, a stock solution of aminophenol **ap-7** (3.5 mg, 0.01 mmol), $Zn(OMe)_2$ (2.6 mg, 0.02 mmol), and tol. (0.5 mL) was prepared. A separate oven-dried two-dram vial equipped with a magnetic stir-bar was charged with NTMS-ketimine (0.1 mmol), tol. (0.25 mL), and TBAT (2.7 mg, 0.005 mmol), which was charged with the freshly prepared catalyst stock solution (0.25 mL) followed by (*Z*)-4,4,5,5-tetramethyl-2-(2-methylhept-2-en-1-yl)-1,3,2-dioxaborolane (31.0 mg, 0.13 mmol), and MeOH (14 μL, 0.35 mmol). The mixture was allowed to stir for five min after which the vial was capped, removed from the glovebox, and the mixture was allowed to stir for 3 h at 22 °C. Conversion and α:γ ratio were determined by ^{19}F NMR of an aliquot The mixture was loaded onto silica gel and eluted with 100:0 → 3:1 hexanes:Et_2O to afford the α-tertiary amine as colorless oil.

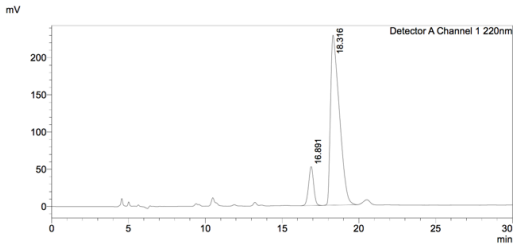
(*R*,*Z*)-1,1,1-Trifluoro-4-methyl-2-phenylnon-4-en-2-amine (2.133): Colorless oil, 25.1 mg,

88% yield, 0.088 mmol; **IR (neat):** 2955 (m), 2855 (m), 1603 (w), 1143 (s), 760 (m), 700 (s), 509 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.43–7.28 (m, 3H), 5.56–5.44 (m, 1H), 5.11 (q, *J* = 7.8 Hz, 1H), 2.88 (dd, *J* = 14.9, 6.6 Hz, 1H), 2.77–2.66 (m, 1H), 2.02 (m, 2H), 1.75 (s, 1H), 1.28 (d, *J* = 8.3 Hz, 7H), 0.93–0.84 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.8, 134.9, 128.4, 128.2, 127.3 (q, *J* = 285.4 Hz), 127.1 (q, *J* = 1.5 Hz), 121.7, 61.6 (q, *J* = 25.9 Hz), 34.0 (d, *J* = 1.4 Hz), 32.0, 29.6, 29.4, 29.3, 27.7, 22.8; **^{19}F NMR (564 MHz, $CDCl_3$):** δ –78.0 (s, 3F); **HRMS (DART):** Calcd for $C_{16}H_{23}NF_3$ $[M+H]^+$: 286.1777; Found: 286.1778; **Specific rotation:** $[\alpha]^{24.5}_D$ +34.7 (*c* 1.77, $CHCl_3$) for a 88.5:11.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 16.891 min (minor) and 18.316 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	16.724	6738880	49.341
2	18.690	6918774	50.659
Total		13657653	100.000



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	16.891	1203011	11.552
2	18.316	9211025	88.448
Total		10414036	100.000

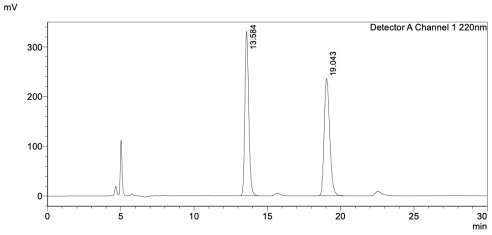
Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	16.724	49.341	1	16.891	11.552
2	18.690	50.659	2	18.316	88.448

2.7.9 Functionalization of Olefins

In a N_2-filled glovebox, a stock solution of **ap-7** (3.5 mg, 0.01 mmol), $Zn(OMe)_2$ (2.6 mg, 0.02 mmol), and tol. (0.5 mL) was prepared. A separate oven-dried two-dram vial equipped with a magnetic stir-bar was charged with imine (0.1 mmol), toluene (0.25 mL), tbat (2.7 mg, 0.005 mmol) and MeOH (7 μL, 0.175 mmol), and was subsequently charged with the freshly prepared catalyst stock solution (0.25 mL) followed by (*Z*)-2-(3-Chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (26.3 mg, 0.13 mmol), and MeOH (7 μL, 0.175 mmol). The mixture was allowed to stir for five min prior and then the vessel was capped, removed from the glovebox, and the solution was allowed to stir for 14 h at 22 °C. Conversion and α:γ ratio were determined by spectroscopic analysis (^{19}F NMR) of an aliquot sample. The mixture was directly loaded onto silica gel and eluted with 100:0 → 3:1 hexanes:Et_2O to afford the α-tertiary amine as colorless oil.

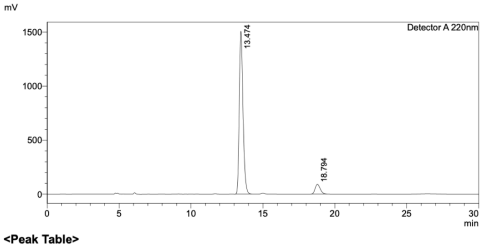
(*R*,*Z*)-2-(4-Bromophenyl)-5-chloro-1,1,1-trifluoropent-4-en-2-amine (2.134): Colorless oil, 25.0 mg, 76% yield, 0.076 mmol; **IR (neat):** 3402 (w), 3337 (w), 2917 (w), 2848 (w), 1719 (w), 1488 (m), 1151 (s), 1075 (m), 1009 (m), 821 (m), 541 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ

7.57–7.48 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.14–6.07 (m, 1H), 5.52 (q, J = 7.0 Hz, 1H), 3.06 (ddd, J = 15.4, 6.9, 1.6 Hz, 1H), 2.89–2.79 (m, 1H), 1.79 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.9, 131.9, 131.7, 130.2, 128.9, 126.8 (q, J = 285.5 Hz), 124.6, 122.2, 61.3 (q, J = 26.3 Hz); **^{19}F NMR (564 MHz, $CDCl_3$):** δ –79.0 (s, 3F); **HRMS (DART):** Calcd for $C_{11}H_{11}NF_3ClBr$ $[M+H]^+$: 327.9710; Found: 327.9709; **Specific rotation:** $[\alpha]^{24.5}_D$ –1.3 (*c* 2.1, $CHCl_3$) for a 92.5:7.5 e.r. sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel AD-H, 99:1 hexanes:*i*PrOH, 0.7 mL/min, 220 nm): t_R: 13.474 min (major) and 18.794 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	13.584	5927017	49.330	330125
2	19.043	6088017	50.670	235898
Total		12015034	100.000	566023



<Peak Table>
Detector A 220nm

Peak#	Ret. Time	Area	Height	Area%
1	13.474	27184458	1505497	92.554
2	18.794	2186939	90348	7.446
Total		29371397	1595845	100.000

Peak #	Ret. Time (min)	Area %	Peak #	Ret. Time (min)	Area %
1	13.584	49.330	1	13.474	92.554
2	19.043	50.670	2	18.794	7.446

(*R*,*Z*)-2-(4-Allylphenyl)-5-chloro-1,1,1-trifluoropent-4-en-2-amine (2.135): In a N_2-filled glovebox, an oven-dried two-dram vial equipped with a stir bar was charged with amine **Z-2.134** (20.8 mg, 0.063 mmol), Pd(dppf)Cl_2•CH_2Cl_2 (1.3 mg, 0.00158 mmol) and thf (0.62 mL). The solution was stirred for five minutes at 22 °C, then allyl–B(pin) (47.3 μL, 0.252 mmol) and CsF (28.7 mg, 0.186 mmol) were added. The vial was sealed with a Teflon septa cap and removed from the glovebox. Water (0.6 mL) was added to the vial and the solution was allowed stir at 60 °C for 14 h. The solution was then allowed to cool to 22 °C, filtered through a small (~5 cm) plug of silica gel eluting with Et_2O after which the volatiles were removed in vacuo to afford brown residue, which was purified by silica gel chromatography (gradient: 100:00 → 2:1 hexanes/Et_2O) to afford **17** as colorless oil (26.9 mg, 93% yield, 0.059 mmol). **IR (neat):** 3078 (m), 2921 (m), 2851 (m), 1637 (w), 1149 (s), 915 (m), 804 (m), 721 (m), 527 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.48 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.10 (d, J = 7.3 Hz, 1H), 5.97 (dq, J = 15.8, 7.2 Hz, 1H), 5.55 (q, J = 7.1 Hz, 1H), 5.14–5.04 (m, 2H), 3.40 (d, J = 6.7 Hz, 2H), 3.08 (dd, J = 15.5, 6.6 Hz, 1H), 2.87 (dd, J = 15.5, 7.1 Hz, 1H), 1.79 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.5, 137.1, 135.1, 130.3, 128.1, 126.7 (q, J = 287.9 Hz), 125.2, 121.8, 116.3, 61.2 (q, J = 26.7 Hz), 39.8, 33.9; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –78.8 (s, 3F); **HRMS (DART):** Calcd for $C_{14}H_{16}NF_3Cl$ $[M+H]^+$: 290.0918; Found: 290.0914; **Specific rotation:** $[\alpha]^{25.0}_D$ +0.8 (*c* 1.1, $CHCl_3$).

(*R*,4*Z*,6*E*)-1,1,1-Trifluoro-2-(4-(trifluoromethyl)phenyl)trideca-4,6-dien-2-amine (2.140): In

a N_2-filled glovebox, an oven-dried two-dram vial equipped with a stir bar was charged with **Z-2.138** (20.9 mg, 0.058 mmol), **2.139** (16.5 mg, 0.69 mmol), and thf (0.53 mL). The mixture was allowed to stir for five min at 22 °C after which ruphos–Pd-G_3 (4.85 mg, 0.0058 mmol), ruPhos (2.71 mg, 0.0058 mmol), and K_3PO_4 (12.3 mg, 0.17 mmol) were added. The vial was capped and removed from the glovebox, after which water (53 μL) was added, and the vial was wrapped in aluminum foil. The solution was then allowed stir for 14 h at 60 °C, after which it was allowed to cool to room temperature, and % conv determined by analysis of ^{1}H and ^{19}F NMR spectra. Removal of the volatiles in vacuo and purification of the orange oil by silica gel chromatography (elution with hexanes/Et_2O) to afford **2.140** as yellow oil (12.2 mg, 54% yield, 0.031 mmol). **IR (neat):** 2955 (m), 1621 (w), 1412 (w), 1325 (s), 1156 (s), 1125 (s), 1070 (s), 834 (m), 725 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 6.34–6.14 (m, 1H), 6.07 (dd, *J* = 11.8, 10.1 Hz, 1H), 5.73 (dt, *J* = 14.5, 7.0 Hz, 1H), 4.97 (q, *J* = 8.1 Hz, 1H), 2.99 (dd, *J* = 15.1, 7.1 Hz, 1H), 2.86 (dd, *J* = 15.1, 7.9 Hz, 1H), 2.10 (q, *J* = 7.2 Hz, 2H), 1.78 (s, 2H), 1.49–1.17 (m, 8H), 0.96–0.79 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.8, 138.0, 133.7, 130.6 (q, *J* = 32.7 Hz), 127.7, 125.4, 125.4 (q, *J* = 286.4 Hz), 124.73, 124.3 (q, *J* = 221.6 Hz), 120.2, 61.9 (q, *J* = 26.0 Hz), 34.4, 33.1, 31.9, 29.4, 29.1, 22.8, 14.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –62.8 (s, 3F), –77.7 (s, 3F); **HRMS (DART):** Calcd for $C_{20}H_{26}NF_6$ $[M+H]^+$: 394.1964; Found: 394.1961; **Specific rotation:** $[\alpha]^{25.0}_D$ +16.0 (*c* 1.3, $CHCl_3$).

2.7.10 Directed Epoxidation/Ring-Opening

This sequence was carried out based on a procedure by Davies.[15] To a cooled (0 °C) solution of amine **Z-2.69** (126.0 mg, 0.55 mmol) in CH_2Cl_2 (2.0 mL) was added trichloroacetic acid (220 μL, 2.20 mmol) and the solution was allowed to stir for 30 min. The mixture was charged with *m*-cpba (188.7 mg, 0.82 mmol; single portion), after which it was allowed to warm to 22 °C, and stir for 18 h. The solution was diluted with CH_2Cl_2 (7.0 mL), and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$. The pH was adjusted to 8 by the addition of a saturated solution of aqueous $NaHCO_3$. The aqueous layer was washed with CH_2Cl_2 (2 x 5.0 mL) and the combined organics were dried over Na_2SO_4 and concentrated to afford yellow residue which was purified by silica gel chromatography to afford the desired product as white solid.

(2*R*,3*R*,5*R*)-5-Amino-6,6,6-trifluoro-3-hydroxy-5-phenylhexan-2-yl-2,2,2-trichloroacetate (2.147): IR (neat): 3386 (w), 1760 (m), 1263 (m), 1155 (m), 1040 (w), 733 (s), 701 (s), 620 (m), 502 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.3 Hz, 2H), 7.45–7.33 (m, 3H), 4.94–

15) Bond, C. W.; Cresswell, A. G.; Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J.* Org. *Chem.* **2009**, *74*, 6735–6748.

4.84 (m, 1H), 3.46 (dd, *J* = 10.8, 3.6 Hz, 1H), 2.30 (d, *J* = 1.5 Hz, 1H), 2.26 (d, *J* = 1.5 Hz, 1H), 2.05 (dd, *J* = 14.2, 10.6 Hz, 2H), 1.36–1.28 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 166.1, 131.6, 129.8, 129.5, 127.3 (q, *J* = 157.3 Hz), 126.3, 94.5, 72.0, 70.8, 64.0 (q, *J* =27.3 Hz), 35.2, 19.4; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –79.5 (s, 3F); **HRMS (DART):** Calcd for $C_{14}H_{16}NO_2F_3Cl_3$ $[M+H]^+$: 408.0142; Found: 408.0137; **Specific rotation:** $[\alpha]^{25.0}_D$ +9.4 (*c* 13.4, $CHCl_3$).

Trichloroacetate cleavage (2.148): To a solution of **2.147** in MeOH (8.0 mL) was added granular K_2CO_3 (304 mg, 5.5 mmol). The mixture was allowed to stir for 4 h at 22 °C, after which the volatiles were removed to ~10% of the original volume. The resulting yellow oil was passed through a (~5 cm) plug of silica gel eluting with Et_2O and then thoroughly flushed with EtOAc. The filtrate was concentrated, diluted with EtOAc, and dried over $MgSO_4$. The solids were filtered off and the filtrate was concentrated to afford yellow oil (82.5 mg, 57% yield, 0.314 mmol).

(2*R*,3*R*,5*R*)-5-Amino-6,6,6-trifluoro-5-phenylhexane-2,3-diol (2.158): IR (neat): 3526 (br), 2920 (m), 1799 (m), 1763 (m), 1249 (s), 1153 (s), 644 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.55–7.32 (m, 5H), 5.12 (br, 1H), 3.52 (p, *J* = 6.1 Hz, 1H), 3.11 (ddd, *J* = 10.6, 5.0, 1.8 Hz, 1H), 2.38 (s, 1H), 2.22 (dd, *J* = 14.4, 1.8 Hz, 1H), 2.18 (s, 2H), 2.02 (dd, *J* = 14.4, 10.6 Hz, 1H), 1.07 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.2, 129.0, 128.8, 126.6 (q, *J* = 286.8 Hz), 126.3 (q, *J* = 1.7 Hz), 72.2, 70.7, 62.3 (q, *J* = 26.4 Hz), 37.1, 19.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –80.9 (s, 3F); **HRMS (DART):** Calcd for $C_{12}H_{17}NO_2F_3$ $[M+H]^+$: 264.1206; Found: 264.1208; **Specific rotation:** $[\alpha]^{25.0}_D$ +21.8 (*c* 2.3, $CHCl_3$).

Acetonide Formation (S-1): To a solution of diol 2.**158** (82.2 mg, 0.30 mmol) in CH_2Cl_2 (0.6 mL) was added trichloroacetic acid (120 µL, 1.20 mmol) and the solution was allowed to stir for 30 min. Dimethoxypropane (183 µL, 1.50 mmol) was then added followed by conc. H_2SO_4 (25 µL). The solution was allowed to stir for 12 h, and then allowed to cool to 0 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$. At this point, NaOH (1M, 0.1 mL) was added until pH was ~9. The aqueous layer was washed with CH_2Cl_2 (2 x 5.0 mL) and the combined organic layerss were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated to afford yellow oil, which was purified by silica gel chromatography (gradient: 100:0 → 3:1 hexanes:Et_2O) to afford the desired product as colorless oil (72.8 mg, 80% yield, 0.24 mmol).

(*R*)-1,1,1-Trifluoro-2-phenyl-3-((4*R*,5*R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)propan-2-amine (S-1): IR (neat): 3413 (w), 2983 (w), 1616 (w), 1311 (m), 1148 (s), 1094 (s), 763 (m), 701 (s), 577 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.57 (d, *J* = 7.7 Hz, 2H), 7.40 (m, 3H), 3.77–3.66 (m, 1H), 3.18 (m, 1H), 2.42 (m, 1H), 2.12 (m, 3H), 2.08 (m, 1H), 1.37 (s, 3H), 1.25 (s, 3H), 1.10–1.02 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.6, 128.6, 128.4, 128.2 (q, *J* = 181.1 Hz), 127.2, 108.8, 78.4, 77.0, 61.8 (q, *J* =214.1 Hz), 38.0, 27.4, 27.3, 16.6; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –79.2 (s, 3F): **HRMS (DART):** Calcd for $C_{15}H_{21}NO_2F_3$ $[M+H]^+$: 304.1519; Found: 304.1523; **Specific rotation:** $[\alpha]^{25.0}_D$ +32.6 (*c* 5.7, $CHCl_3$).

Amide Formation (2.149): To a solution of **S-1** (22.5 mg, 0.074 mmol) in tol. (0.5 mL) was added dropwise chloroacetyl chloride (12.5 mg, 0.11 mmol), and the resulting solution was allowed to

heat to 100 °C in a sealed vial for 4 h. The mixture was then allowed to cool to 22 °C, the volatiles were removed in vacuo, and the resulting brown residue was purified by silica gel chromatography (hexanes → 2:1 hexanes:Et_2O) to afford **2.149** (19.0 mg, 68% yield, 0.50 mmol) as white solid.

2-Chloro-*N*-((*R*)-1,1,1-trifluoro-2-phenyl-3-((4*R*,5*R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)propan-2-yl)acetamide (2.149): White solid, m.p. = 129–131°C; **IR (neat):** 3321 (br), 2982 (w), 1704 (m), 11542 (m), 1233 (s), 1165 (s), 1025 (m), 700 (m), 628 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.30 (s, 1H), 7.38 (m, 5H), 4.18–4.05 (m, 2H), 3.80–3.69 (m, 1H), 3.21 (t, *J* = 9.2 Hz, 1H), 2.30 (dd, *J* = 14.6, 9.8 Hz, 1H), 2.20 (d, *J* = 14.4 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.03 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.3, 134.1, 128.9, 128.7, 126.0, 124.8 (q, *J* = 122.1 Hz), 109.4, 77.7, 77.3, 62.4 (q, *J* = 44.1 Hz), 43.0, 39.1, 27.4, 27.2, 16.5; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –68.5 (s, 3F); **HRMS (DART):** Calcd for $C_{17}H_{22}NO_3F_3Cl$ $[M+H]^+$: 380.1223; Found: 380.1229; **Specific rotation:** $[\alpha]^{25.0}_D$ +21.5 (*c* 1.9, $CHCl_3$).

(2*R*,4*R*,5*R*)-2-Amino-1,1,1-trifluoro-4-hydroxy-4-methyl-2-phenylnonan-5-yl-2,2,2-trichloroacetate (2.150) was synthesized according to the above procedure to afford the product as yellow oil (66.9 mg, 72% yield, 0.144 mmol). **IR (neat):** 3383 (w), 2955 (m), 1761 (m), 1233 (s), 1155 (s), 990 (m), 825 (s), 737 (s), 704 (s), 676 (s), 576 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$ & CD_2Cl_2):** δ 7.56–7.50 (m, 2H), 7.44–7.38 (m, 3H), 4.83 (dd, *J* = 10.7, 2.1 Hz, 1H), 2.38 (d, *J* = 14.7 Hz, 1H), 2.22 (d, *J* = 14.6 Hz, 1H), 1.42–1.28 (m, 6H), 1.27 (s, 2H), 0.93–0.90 (m, 3H), 0.63 (s, 3H); **^{13}C NMR (100 MHz, Acetone-d6):** δ 162.4, 138.1, 135.8, 129.7 (q, *J* = 93.9 Hz), 129.2, 128.2, 88.2, 74.4, 62.9 (q, *J* = 25.6 Hz), 55.1, 38.1, 29.2, 29.2, 24.6, 23.1, 14.3; **^{19}F NMR (376 MHz, acetone-d_6):** δ –79.5 (s, 3F); **HRMS (DART):** Calcd for $C_{18}H_{24}NO_3F_3Cl_3$ $[M+H]^+$: 464.0768; Found: 464.0774; **Specific rotation:** $[\alpha]^{25.0}_D$ +27.6 (*c* 7.3, $CHCl_3$).

2.7.11 Gram-Scale Enantioselective Formal Synthesis of Bace-1 Inhibitor

In a N_2-filled glovebox, an oven-dried vial containing a stir bar was charged with **ap-7** (0.146 g, 0.42 mmol) and $Zn(OMe)_2$ (0.107 g, 0.84 mmol). The solids were dissolved in tol. (42.0 mL) and the mixture was allowed to stir for 10 min, after which it was sequentially charged with NTMS-ketimine **2.88j** (2.21 g, 8.38 mmol), tbat (0.227 g, 0.42 mmol), *Z*-crotyl boronic pinacol ester (1.83 g, 10.1 mmol) and MeOH (0.940 g, 29.3 mmol). The solution was allowed to stir for five min in open vial and then the vial was capped and removed from the glovebox, after which the mixture was allowed to stir for three h at 22 °C. Reaction progress was monitored spectroscopically (^{19}F NMR) of aliquot samples until >98% conv was reached. The volatiles were removed in vacuo to ~50 % of original volume (rotary evaporator), the solution was diluted with tol. (10 mL), and the volatiles were removed to ~50% volume; the azeotrope was carried out a total of three times.

Toluene (5 mL) was added such that total volume was 20 mL and the resulting solution was allowed to cool to 0 °C (ice-bath). Chloroacetyl chloride (1.0 mL, 12.6 mmol) was added dropwise, the ice-bath was removed, and the mixture was allowed to heat for four h to 100 °C. The mixture was allowed to cool to 22 °C, the volatiles were removed in vacuo, and the resulting brown residue was purified by silica gel chromatography (hexanes → 2:1 hexanes:Et_2O) to afford white solid (1.86 g, 69% yield, 5.75 mmol).

(*R*,*Z*)-2-Chloro-*N*-(1,1,1-trifluoro-2-(2-fluorophenyl)hex-4-en-2-yl)acetamide (2.124): White solid, **M.p**. = 88–90 °C; **IR (neat):** 3298 (m), 3078 (m), 1682 (s), 1528 (s), 1490 (m), 1327 (m), 1227 (s), 759 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43 (ddt, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.36 (dddd, *J* = 8.2, 7.4, 4.8, 1.7 Hz, 1H), 7.24–7.21 (m, 1H), 7.18 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 7.08 (ddd, *J* = 13.1, 8.2, 1.4 Hz, 1H), 5.88–5.65 (m, 1H), 5.50–5.20 (m, 1H), 4.04 (s, 2H), 3.32–3.05 (m, 2H), 1.70 (ddt, *J* = 7.0, 1.9, 0.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.8, 160.6 (d, *J* = 249.8 Hz), 130.7 (d, *J* = 9.5 Hz), 130.1, 128.9 (q, *J* = 88.9 Hz), 125.5 (q, *J* = 287.2 Hz), 124.4 (d, *J* = 3.4 Hz), 122.6 (d, *J* = 8.6 Hz), 122.2 (d, *J* = 1.6 Hz), 117.1 (d, *J* = 24.4 Hz), 63.7 (q, *J* = 27.7 Hz), 42.7, 31.4 (d, *J* = 3.4 Hz), 13.0; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –72.9 (d, *J* = 8.6 Hz, 3F), –110.4 (dq, *J* = 13.6, 7.4 Hz, 1F); **HRMS (DART):** Calcd for $C_{14}H_{15}NF_4Cl$ $[M+H]^+$: 324.0773; Found: 324.0780; **Specific rotation:** $[\alpha]^{24.5}_D$ +14.7 (*c* 1.3, $CHCl_3$) for a 97:3 e.r. sample.

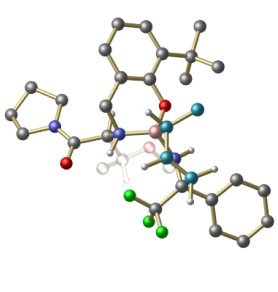
The oxidation and cyclization steps were carried out according to a reported procedure.[16] An oven-dried flask equipped with a stir bar was charged with **2.124** (1.86 g, 5.75 mmol) and $NaHCO_3$ (0.745 g, 8.60 mmol). The solids were dissolved in CH_2Cl_2:MeOH (50.0:12.5 mL) and the resulting mixture was allowed to cool to –78 °C. Ozone was then introduced until blue color persisted (after ~ 45 min); the mixture was then purged with a stream of oxygen. At this time, $NaBH_4$ (435.1 mg, 11.5 mmol) was added (2 portions) and the solution was allowed to stir for 10 min, before allowing it to warm to 0 °C. The mixture was poured into a cold (0 °C) aqueous solution of 1M HCl (30 mL) and washed with Et_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford colorless oil.

An oven-dried flask was charged with KO*t*-Bu (1.30 g, 11.6 mmol, 2.0 equiv.), *t*-BuOH (44 mL), and the solution was allowed to reach reflux (85 °C). A solution of the aforementioned alcohol, dissolved in thf (35 mL), was added slowly (over ~5 min), and the mixture was allowed to stir at reflux (85 °C) for 14 h before it allowed to cool to 0 °C. At this time, the reaction was quenched by addition of an aqueous solution of 1 M HCl (25 mL). The mixture was diluted with EtOAc (50 mL) and the organic layerss were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to afford brown solid, which was purified by silica gel chromatography (100:0 → 1:2 hexanes:EtOAc) to afford **2.125** as white solid (1.21 g, 76% over 2 steps, 4.36 mmol).

(*R*)-5-(2-Fluorophenyl)-5-(trifluoromethyl)-1,4-oxazepan-3-one (2.125): White solid, m.p. =

16) Badiger, S.; Chebrolu, M.; Frederiksen, M.; Holzer, P.; Hurth, K.; Li, L.; Liu, H.; Lueoend, R.M.; Machauer, R.; Moebitz, H.; Meumann, U.; Ramos, R.; Rueeger, H.; Schaefer, M; Tintelnot-Blomley, M.; Veenstra, S. J.; Voegtle, M.; Xiong, X. PCT. Int. Appl. 2012006953.

129–131°C; **IR (neat):** 2953 (w), 2918 (w), 1628 (m), 1489 (m), 1247 (m), 1159 (s), 1009 (m), 819 (m), 784 (m), 643 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.55 (td, *J* = 8.0, 1.8 Hz, 1H), 7.44 (dddd, *J* = 8.2, 7.5, 4.8, 1.7 Hz, 1H), 7.29–7.24 (m, 1H), 7.14 (ddd, *J* = 12.5, 8.2, 1.3 Hz, 1H), 6.47 (s, 1H), 4.13 (q, *J* = 16.9 Hz, 2H), 3.91 (dd, *J* = 12.2, 6.1 Hz, 1H), 3.79–3.67 (m, 1H), 3.11 (dddt, *J* = 15.3, 4.6, 3.1, 1.6 Hz, 1H), 2.71 (tdd, *J* = 15.0, 6.2, 2.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.6, 159.7 (d, *J* = 248.9 Hz), 130.1 (d, *J* = 3.4 Hz), 126.4, 125.0 (d, *J* = 3.4 Hz), 123.6, 121.7 (d, *J* = 12.0 Hz), 117.0 (d, *J* = 25.0 Hz), 70.0, 65.9, 63.7 (q, *J* = 28.9 Hz), 32.3 (d, *J* = 7.5 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –79.9 (d, *J* = 16.1 Hz, 3F), –109.9 to –110.3 (m, 1F); **HRMS (DART):** Calcd for $C_{12}H_{12}NO_2F_4$ $[M+H]^+$: 278.0799; Found: 278.0805; **Specific rotation:** $[\alpha]^{25.0}_D$ +26.2 (*c* 1.7, $CHCl_3$).



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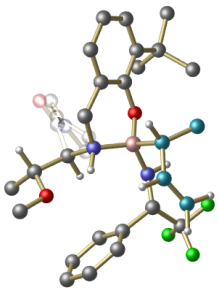

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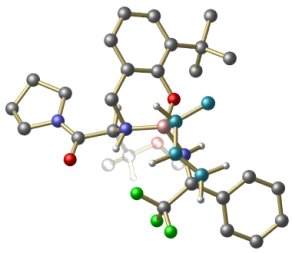

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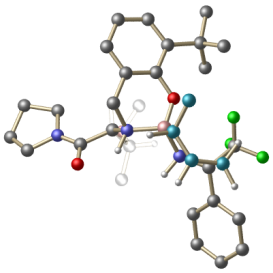

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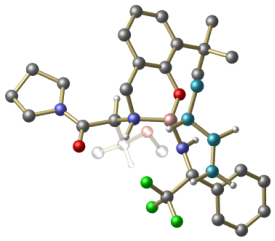

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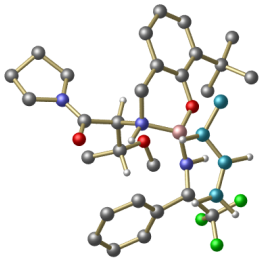

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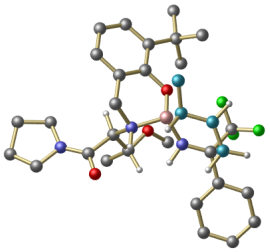

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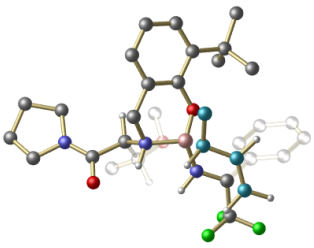
+7.1



E-4
+9.2

2.7.12 DFT Calculations

DFT calculations were performed with the Gaussian 09 suite of programs[17] employing ωB97XD the functional. The DEF2SVP[18] basis set and SMD[19] solvation model (toluene) was used for geometry optimization and frequency calculation. The nature of all stationary points was checked through vibrational analysis. [20] Single point electronic energy (ΔE_{sp}) calculations applying the ωB97XD functional and the DEF2TZVPP basis set in solution with the SMD solvation model were performed on the geometries obtained with the DEF2SVP basis set. The single point electronic energies (ΔE_{sp}) at the DEF2TZVPP level were corrected by addition of thermal corrections to the Gibbs free energy (ΔG_{corr}) obtained at the corresponding DEF2SVP level.

Structure	E [Hartree]	ΔE [kcal/mol]	G [Hartree]	ΔG [kcal/mol]	ΔG_{corr} [kcal/mol]	Freq cm^{-1}
Z-1	-1957.394992	0.00	-1957.503140	0.00	0.00	-330.2836
Z-2	-1957.396999	-1.2	-1957.501356	1.1	2.4	-267.5422
Z-3	-1957.381746	8.3	-1957.488634	9.1	0.8	-281.9097
Z-4	-1957.373275	13.6	-1957.481719	13.4	-0.2	-376.1261
E-1	-1957.385416	6.0	-1957.493726	5.9	-0.1	-407.0333
E-2	-1957.385751	5.8	-1957.492660	6.5	0.8	-311.3443

17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G.E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y. Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr. J.A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayshi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyenger, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, **2009**.

18) Weigend, F.; Ahlrichs, R, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.

19) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G.; *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

E-3	-1957.381513	8.4	-1957.489439	8.6	0.1	-337.9035
E-4	-1957.379454	9.8	-1957.487654	9.7	-0.03	-414.9864

Structure	E_{sp} [Hartree]	ΔE_{sp} [kcal/mol]	ΔG_{sp} [kcal/mol]
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Z-2	-1959.605717	-0.10	2.3
Z-3	-1959.591430	7.0	9.6
Z-4	-1959.586339	12.1	11.9
E-1	-1959.597046	5.3	5.2
E-2	-1959.597235	5.2	6.0
E-3	-1959.591440	8.9	7.1
E-4	-1959.590708	9.3	9.2

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Z-1

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C    -1.377     2.004     0.602
C    -3.475     1.766     1.797
C    -2.222     1.259     1.443
H    -4.128     1.178     2.447
H    -3.415     4.658     0.054
H    -4.853     3.412     1.602
C    -0.953     3.978    -1.004
C     0.434     4.342    -0.444
H     0.345     4.939     0.477
H     0.988     4.946    -1.180
H     1.029     3.450    -0.219
C    -0.805     3.075    -2.245
H    -0.155     3.560    -2.992
H    -1.784     2.904    -2.719
H    -0.379     2.095    -1.994
C    -1.621     5.286    -1.451
H    -0.992     5.771    -2.213
H    -1.737     6.000    -0.620
H    -2.608     5.119    -1.907
O    -0.159     1.522     0.278
C    -1.824    -0.116     1.916
N    -0.786    -0.702     1.013
H    -1.430    -0.119     2.939
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C    -2.368    -2.288     0.147
N    -3.640    -2.287    -0.269
C    -4.347    -1.200    -0.960
C    -4.510    -3.436    -0.002
C    -5.738    -3.153    -0.862
H    -4.757    -3.477     1.072
H    -3.993    -4.372    -0.256
C    -5.812    -1.626    -0.874
H    -4.012    -1.123    -2.007
H    -4.165    -0.232    -0.470
H    -6.409    -1.222    -1.702
H    -6.253    -1.260     0.067
H    -6.644    -3.629    -0.465
H    -5.579    -3.534    -1.883
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C     1.962    -0.172     2.909
C     1.568     2.262     2.370
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H     2.273     2.370     1.534
H     2.092     2.557     3.291
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O    -0.072    -0.366    -2.015
H    -2.039    -0.250    -0.624
C     1.011    -0.510    -2.892
H     1.828    -1.106    -2.445
H     1.389     0.498    -3.115
H     0.725    -0.979    -3.849
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C     3.998    -0.378    -0.277
C     2.519    -2.236     0.727
C     4.260     0.983    -0.514
C     4.919    -1.330    -0.735
C     5.395     1.379    -1.209
C     6.056    -0.927    -1.432
C     6.298     0.422    -1.673
H     5.582     2.441    -1.377
H     7.193     0.730    -2.217
H     3.584     1.750    -0.127
H     6.759    -1.683    -1.789
H     4.766    -2.396    -0.572
F     1.403    -2.469     1.424
F     3.521    -2.798     1.385
F     2.388    -2.882    -0.436
H     1.840     0.724    -0.531
H     1.576    -1.053     3.433
C     3.272    -0.182     2.498
H     3.952    -0.970     2.826
H     3.746     0.741     2.161
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H    -0.566    -2.695    -3.250
H    -2.129    -1.937    -2.871
H    -1.571    -3.391    -1.980
H     0.295    -2.128    -1.002
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                      A                     A                     A
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 Thermal correction to Enthalpy=                  0.779006
 Thermal correction to Gibbs Free Energy=         0.669913
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 Sum of electronic and thermal Energies=             -1957.394992
 Sum of electronic and thermal Enthalpies=           -1957.394047
 Sum of electronic and thermal Free Energies=        -1957.503140

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MP2: no data
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Z-2

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H    -2.696    -0.249     1.765
C    -5.698    -1.592     0.704
H    -5.942    -2.054     1.673
H    -6.070    -2.266    -0.083
H    -6.256    -0.646     0.644
O    -1.443    -0.745    -0.152
C    -0.683     0.840    -2.419
N     0.262     0.572    -1.285
H    -0.267     0.346    -3.308
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B    -0.115    -0.843    -0.654
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C    -0.935     2.287     0.194
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C    -2.323     2.926     2.084
C    -2.047     2.876     3.584
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C     1.467    -2.280    -2.063
C    -0.747    -3.316    -1.417
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H    -0.481    -3.667    -0.410
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C     3.109    -0.588     0.155
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C     3.225     0.408     1.139
O     2.270     2.174    -1.614
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C     2.226    -3.134    -1.314
H     3.296    -3.254    -1.491
H     1.746    -3.938    -0.752
O    -1.640     2.919    -0.578
F     1.593    -3.626     1.650
C     5.010     0.381    -0.988
C     4.225     1.371     1.059
C     5.120     1.363    -0.008
H     3.979    -1.361    -1.674
H     5.907     2.117    -0.071
H     5.712     0.359    -1.824
H     4.309     2.128     1.841
H     2.542     0.412     1.991
H     0.229    -1.986     1.056
C     3.078     2.984    -2.430
H     3.696     2.320    -3.049
H     3.748     3.630    -1.838
H     2.466     3.622    -3.094
H     0.823     4.255     0.639
H     2.217     4.662    -0.363
H     2.354     3.349     0.836
YYY
                      1                      2                      3
                      A                      A                      A
 Frequencies --   -267.5422               32.3312               42.7069
 Red. masses --      6.6424                5.0313                5.3424
 Zero-point correction=                          0.740397 (Hartree/Particle)
 Thermal correction to Energy=                   0.778891
 Thermal correction to Enthalpy=                 0.779835
```

```
 Thermal correction to Gibbs Free Energy=         0.674534
 Sum of electronic and zero-point Energies=          -1957.435493
 Sum of electronic and thermal Energies=             -1957.396999
 Sum of electronic and thermal Enthalpies=           -1957.396055
 Sum of electronic and thermal Free Energies=        -1957.501356

         Item               Value     Threshold  Converged?
 Maximum Force            0.000001     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1958.17589022', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 423.27683034 kcal/mol
H_corr: 489.35426085 kcal/mol
S_corr: 66.0777919 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.4137685 kcal/mol
S_rot: 11.1728731 kcal/mol
S_vib: 41.4911503 kcal/mol
```

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-----------------------------------------
Z-3
-----------------------------------------

#P Geom=AllCheck Guess=TCheck SCRF=Check GenChk RwB97XD/def2SVP Freq

charge= 1    multiplicity= 1
-----------------------------------------
 Cartesian coordinates (Angstroms):
-----------------------------------------
XXX
86

C    -4.860    -0.325    -1.115
C    -4.675     0.359    -2.317
C    -3.792    -0.758    -0.325
C    -2.492    -0.481    -0.812
C    -3.393     0.647    -2.752
C    -2.292     0.229    -2.002
H    -3.232     1.210    -3.675
H    -5.881    -0.522    -0.792
H    -5.541     0.679    -2.900
C    -4.023    -1.487     1.012
C    -3.394    -2.891     0.988
H    -3.806    -3.496     0.165
H    -3.613    -3.416     1.931
H    -2.305    -2.846     0.871
C    -3.407    -0.657     2.151
H    -3.553    -1.164     3.119
H    -3.888     0.331     2.215
H    -2.330    -0.510     2.000
C    -5.518    -1.659     1.316
H    -5.635    -2.173     2.282
H    -6.029    -2.269     0.556
H    -6.042    -0.694     1.395
O    -1.413    -0.907    -0.102
C    -0.912     0.576    -2.501
N     0.142     0.418    -1.449
H    -0.629    -0.059    -3.352
H    -0.902     1.616    -2.846
B    -0.116    -0.957    -0.672
C     0.345     1.636    -0.593
C     1.253     2.614    -1.356
C    -0.950     2.359    -0.189
```

```
N    -1.292     2.323     1.111
C    -0.530     1.729     2.214
C    -2.448     3.086     1.584
C    -2.162     3.280     3.069
H    -3.371     2.509     1.408
H    -2.534     4.024     1.020
C    -1.386     2.018     3.449
H     0.455     2.218     2.302
H    -0.369     0.652     2.055
H    -0.774     2.139     4.353
H    -2.082     1.186     3.628
H    -3.079     3.416     3.658
H    -1.535     4.174     3.216
C     0.080    -2.281    -1.822
C     1.341    -2.978    -1.651
C    -1.129    -3.213    -1.849
H    -2.066    -2.672    -2.027
H    -1.234    -3.752    -0.897
H    -1.026    -3.963    -2.647
H     0.154    -1.717    -2.767
H     1.050     0.362    -1.935
C     1.737     3.734    -0.450
H     0.896     1.288     0.283
N     0.863    -1.306     0.464
C     2.177    -1.516     0.418
C     2.659    -2.699     1.282
C     3.152    -0.375     0.420
F     2.760    -2.312     2.552
F     3.841    -3.149     0.893
C     4.335    -0.311    -0.323
C     2.924     0.586     1.416
O     2.293     1.809    -1.868
H     0.680     3.055    -2.194
C     2.551    -2.351    -1.667
H     1.309    -4.028    -1.334
O    -1.578     2.986    -1.029
F     1.786    -3.709     1.241
C     5.242     0.722    -0.110
C     3.843     1.607     1.640
C     5.000     1.686     0.868
H     4.569    -1.062    -1.073
H     5.722     2.487     1.039
H     6.156     0.765    -0.706
H     3.656     2.340     2.428
H     2.038     0.504     2.046
H     0.372    -2.053     0.961
C     3.220     2.446    -2.712
H     3.828     1.662    -3.181
H     3.891     3.118    -2.153
H     2.714     3.025    -3.505
H     0.884     4.274    -0.015
H     2.328     4.467    -1.015
H     2.363     3.332     0.359
H     2.631    -1.348    -2.096
H     3.476    -2.919    -1.559
YYY
                     1                     2                     3
                     A                     A                     A
 Frequencies --   -281.9097              33.6336               41.3204
 Red. masses --      7.2842               4.3910                5.1218
 Zero-point correction=                          0.738687 (Hartree/Particle)
 Thermal correction to Energy=                   0.777897
 Thermal correction to Enthalpy=                 0.778841
 Thermal correction to Gibbs Free Energy=        0.671010
 Sum of electronic and zero-point Energies=          -1957.420956
```

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 Sum of electronic and thermal Energies=            -1957.381746
 Sum of electronic and thermal Enthalpies=          -1957.380802
 Sum of electronic and thermal Free Energies=       -1957.488634

         Item               Value     Threshold  Converged?
 Maximum Force            0.000001     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1958.15964342', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 421.0654851 kcal/mol
H_corr: 488.73051591 kcal/mol
S_corr: 67.6651425 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.4137685 kcal/mol
S_rot: 11.17496015 kcal/mol
S_vib: 43.07641385 kcal/mol
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Z-4

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#P Geom=AllCheck Guess=TCheck SCRF=Check GenChk RwB97XD/def2SVP Freq

charge= 1    multiplicity= 1
----------------------------------------
 Cartesian coordinates (Angstroms):
----------------------------------------
XXX
86

C    -2.502     3.953    -0.132
C    -3.499     3.452     0.703
C    -1.252     3.342    -0.279
C    -1.029     2.162     0.473
C    -3.263     2.292     1.423
C    -2.031     1.649     1.315
H    -4.033     1.874     2.077
H    -2.716     4.863    -0.690
H    -4.457     3.969     0.782
C    -0.168     3.963    -1.177
C    -0.684     5.193    -1.939
H    -1.529     4.950    -2.601
H     0.125     5.585    -2.574
H    -0.991     6.007    -1.266
C     0.991     4.431    -0.279
H     1.809     4.844    -0.890
H     1.394     3.610     0.320
H     0.649     5.220     0.409
C     0.316     2.950    -2.230
O     0.153     1.501     0.364
C    -1.782     0.377     2.071
N    -0.893    -0.523     1.266
H    -1.310     0.557     3.044
H    -2.724    -0.149     2.274
B     0.480     0.292     1.028
C    -1.719    -1.022     0.111
C    -0.970    -1.534    -1.155
C    -2.587    -2.132     0.731
C     1.200     0.610     2.678
C     2.451    -0.088     2.737
C     1.250     2.128     2.871
H     0.255     2.580     2.766
H     1.906     2.617     2.140
H     1.621     2.367     3.879
```

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H     0.503     0.144     3.387
H    -0.750    -1.378     1.833
H    -2.329    -0.175    -0.220
N     1.495    -0.606     0.335
C     2.830    -0.458     0.210
C     3.286     0.754    -0.625
C     3.623    -1.704    -0.089
N    -3.794    -2.369     0.215
C    -4.504    -1.591    -0.812
C    -4.603    -3.484     0.720
C    -5.784    -3.532    -0.246
H    -4.921    -3.273     1.754
H    -4.008    -4.408     0.741
C    -5.946    -2.073    -0.673
H    -6.685    -3.953     0.219
H    -5.533    -4.156    -1.119
O    -2.111    -2.773     1.668
H    -4.086    -1.811    -1.804
H    -4.399    -0.510    -0.634
H    -6.464    -1.502     0.114
H    -6.511    -1.950    -1.606
H    -0.494     2.716    -2.939
H     0.666     2.015    -1.781
H     1.149     3.379    -2.809
C     3.602     0.296     2.085
C    -0.628    -3.012    -1.112
O    -1.794    -1.323    -2.269
C    -1.722    -0.031    -2.815
H    -2.471     0.032    -3.615
H    -0.725     0.165    -3.246
H    -1.941     0.758    -2.071
H    -0.097    -3.286    -0.189
H    -0.013    -3.280    -1.982
H    -1.547    -3.615    -1.155
H    -0.050    -0.938    -1.269
H     1.289    -1.576     0.573
F     4.607     0.896    -0.614
F     2.760     1.902    -0.223
F     2.905     0.547    -1.886
C     4.993    -1.825     0.186
C     2.981    -2.765    -0.744
C     5.679    -2.992    -0.133
C     3.669    -3.934    -1.061
C     5.019    -4.055    -0.748
H     1.940    -2.673    -1.048
H     6.743    -3.068     0.100
H     5.543    -1.008     0.651
H     5.562    -4.970    -0.993
H     3.145    -4.745    -1.570
H     4.505    -0.295     2.234
H     3.754     1.345     1.823
H     2.431    -1.115     3.123
YYY
                     1                     2                     3
                     A                     A                     A
 Frequencies --   -376.1261              19.1149               28.8033
 Red. masses --      8.6408               4.3568                5.2319
 Zero-point correction=                          0.738813 (Hartree/Particle)
 Thermal correction to Energy=                   0.778079
 Thermal correction to Enthalpy=                 0.779023
 Thermal correction to Gibbs Free Energy=        0.669634
 Sum of electronic and zero-point Energies=          -1957.412540
 Sum of electronic and thermal Energies=             -1957.373275
 Sum of electronic and thermal Enthalpies=           -1957.372330
 Sum of electronic and thermal Free Energies=        -1957.481719
```

```
         Item               Value     Threshold  Converged?
 Maximum Force            0.000000     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1958.15135309', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 420.20203134 kcal/mol
H_corr: 488.84472273 kcal/mol
S_corr: 68.64218005 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.4137685 kcal/mol
S_rot: 11.26679035 kcal/mol
S_vib: 43.9616212 kcal/mol
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————————————————————————————————————

E-1

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#P Geom=AllCheck Guess=TCheck SCRF=Check GenChk RwB97XD/def2SVP Freq

charge= 1    multiplicity= 1
----------------------------------------
 Cartesian coordinates (Angstroms):
----------------------------------------
XXX
86

C    -2.811     3.850     0.063
C    -3.794     3.182     0.793
C    -1.522     3.337    -0.112
C    -1.243     2.097     0.508
C    -3.506     1.952     1.366
C    -2.229     1.404     1.231
H    -4.271     1.406     1.925
H    -3.071     4.807    -0.388
H    -4.786     3.624     0.902
C    -0.456     4.073    -0.944
C     0.755     4.427    -0.060
H     0.450     5.060     0.788
H     1.498     4.991    -0.646
H     1.245     3.530     0.340
C    -0.015     3.183    -2.122
H     0.761     3.695    -2.713
H    -0.863     2.969    -2.791
H     0.382     2.221    -1.777
C    -0.999     5.385    -1.527
H    -0.210     5.873    -2.119
H    -1.305     6.095    -0.744
H    -1.855     5.218    -2.199
O    -0.006     1.572     0.385
C    -1.907     0.065     1.841
N    -0.868    -0.629     1.017
H    -1.528     0.147     2.868
H    -2.806    -0.563     1.890
B     0.415     0.342     0.961
C    -1.538    -1.064    -0.266
C    -2.457    -2.212     0.171
C     1.013     0.633     2.631
C     2.446     0.663     2.555
C     0.442     1.932     3.211
H    -0.652     1.951     3.251
H     0.756     2.798     2.612
```

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H     0.805     2.082     4.238
H    -0.628    -1.516     1.482
N     1.585    -0.178     0.145
C     2.679    -0.888     0.479
C     3.930    -0.571    -0.282
C     2.405    -2.370     0.786
C     4.226     0.781    -0.517
C     4.801    -1.550    -0.777
C     5.351     1.148    -1.244
C     5.929    -1.178    -1.506
C     6.207     0.166    -1.744
H     5.565     2.204    -1.413
H     7.095     0.450    -2.313
H     3.579     1.561    -0.107
H     6.596    -1.951    -1.891
H     4.613    -2.611    -0.617
F     1.321    -2.513     1.557
F     3.412    -2.991     1.383
F     2.165    -3.016    -0.359
H     1.802     0.551    -0.532
C     3.248    -0.452     2.487
H     4.331    -0.338     2.408
H     2.900    -1.366     2.970
H     2.904     1.636     2.333
H     0.680    -0.269     3.174
C    -0.612    -1.518    -1.403
O    -1.989    -3.079     0.902
N    -3.721    -2.211    -0.269
C    -4.406    -1.142    -1.008
C    -4.608    -3.340     0.028
C    -5.879    -1.537    -0.903
H    -4.073    -1.119    -2.058
H    -4.205    -0.157    -0.564
C    -5.833    -3.063    -0.839
H    -4.854    -3.350     1.103
H    -4.106    -4.290    -0.202
H    -6.747    -3.509    -0.424
H    -5.685    -3.482    -1.847
H    -6.471    -1.150    -1.742
H    -6.309    -1.130     0.026
H    -2.093    -0.202    -0.648
O    -0.158    -0.337    -2.019
C     0.899    -0.498    -2.925
H     1.690    -1.157    -2.523
H     1.329     0.496    -3.113
H     0.566    -0.907    -3.895
C    -1.307    -2.446    -2.395
H    -2.182    -1.965    -2.856
H    -1.617    -3.384    -1.915
H    -0.607    -2.717    -3.197
H     0.236    -2.069    -0.970
YYY
                      1                     2                     3
                      A                     A                     A
 Frequencies --   -407.0333              24.4120               33.2003
 Red. masses --      8.4451               4.7693                5.1749
 Zero-point correction=                          0.738241 (Hartree/Particle)
 Thermal correction to Energy=                   0.777637
 Thermal correction to Enthalpy=                 0.778581
 Thermal correction to Gibbs Free Energy=        0.669326
 Sum of electronic and zero-point Energies=          -1957.424812
 Sum of electronic and thermal Energies=             -1957.385416
 Sum of electronic and thermal Enthalpies=           -1957.384471
 Sum of electronic and thermal Free Energies=        -1957.493726
```

```
         Item               Value     Threshold  Converged?
 Maximum Force            0.000000     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1958.16305252', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 420.00875826 kcal/mol
H_corr: 488.56736331 kcal/mol
S_corr: 68.5583999 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.4137685 kcal/mol
S_rot: 11.24711245 kcal/mol
S_vib: 43.89751895 kcal/mol
```

E-2

```
----------------------------------------

#P Geom=AllCheck Guess=TCheck SCRF=Check GenChk RwB97XD/def2SVP Freq

charge= 1    multiplicity= 1
----------------------------------------
 Cartesian coordinates (Angstroms):
----------------------------------------
XXX
86

C    -0.533     4.437     0.384
C    -1.754     4.337     1.049
C     0.273     3.329     0.105
C    -0.199     2.066     0.540
C    -2.197     3.094     1.470
C    -1.422     1.957     1.230
H    -3.145     2.994     2.004
H    -0.202     5.428     0.073
H    -2.347     5.233     1.240
C     1.604     3.487    -0.650
C     1.469     2.797    -2.017
H     1.253     1.731    -1.895
H     2.406     2.894    -2.588
H     0.661     3.259    -2.607
C     1.949     4.962    -0.901
H     2.911     5.022    -1.431
H     2.056     5.529     0.037
H     1.202     5.469    -1.530
C     2.772     2.873     0.146
H     3.718     3.038    -0.391
H     2.652     1.793     0.285
H     2.866     3.351     1.135
O     0.541     0.956     0.288
C    -1.885     0.646     1.809
N    -1.281    -0.500     1.077
H    -1.614     0.547     2.867
H    -2.981     0.566     1.763
B     0.324    -0.239     1.022
C    -2.100    -0.707    -0.173
C    -1.467    -1.570    -1.291
C    -2.506    -2.211    -2.211
C    -3.374    -1.386     0.346
C     0.984    -0.114     2.668
C     2.382    -0.498     2.587
C     0.886     1.276     3.324
H    -0.139     1.610     3.512
H     1.374     2.040     2.702
H     1.397     1.265     4.298
```

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H     0.416    -0.871     3.238
H    -1.483    -1.352     1.625
O    -0.493    -0.849    -1.998
H    -2.303     0.289    -0.584
C    -0.926     0.204    -2.819
H    -1.676    -0.118    -3.560
H    -0.046     0.563    -3.367
H    -1.331     1.056    -2.244
H    -0.921    -2.400    -0.826
H    -3.225    -1.494    -2.631
H    -3.068    -2.990    -1.678
H    -1.976    -2.694    -3.044
N     0.929    -1.531     0.501
C     2.221    -1.818     0.395
C     3.145    -0.936    -0.386
C     2.684    -0.533    -1.645
C     4.457    -0.636    -0.003
C     5.287     0.079    -0.861
C     3.529     0.163    -2.506
C     4.828     0.476    -2.116
H     5.485     1.030    -2.789
H     3.161     0.470    -3.487
H     6.305     0.319    -0.547
H     4.844    -0.948     0.966
H     1.661    -0.778    -1.937
C     2.504    -3.321     0.189
F     1.660    -4.075     0.905
F     2.313    -3.623    -1.092
F     3.741    -3.654     0.514
C     2.843    -1.783     2.500
H     2.194    -2.615     2.784
H     3.913    -1.994     2.498
H     3.107     0.315     2.456
N    -4.560    -0.968    -0.108
C    -4.834     0.225    -0.921
C    -5.785    -1.691     0.249
C    -6.827    -1.094    -0.690
H    -6.030    -1.511     1.309
H    -5.635    -2.772     0.125
C    -6.357     0.352    -0.850
H    -7.846    -1.178    -0.291
H    -6.801    -1.613    -1.661
O    -3.236    -2.304     1.151
H    -4.493     0.079    -1.959
H    -4.324     1.111    -0.516
H    -6.642     0.943     0.035
H    -6.770     0.853    -1.735
H     0.380    -2.347     0.766
YYY
                      1                      2                      3
                      A                      A                      A
 Frequencies --   -311.3443               19.3548               33.5629
 Red. masses --      7.8037                4.9433                4.9624
 Zero-point correction=                          0.739347 (Hartree/Particle)
 Thermal correction to Energy=                   0.778225
 Thermal correction to Enthalpy=                 0.779169
 Thermal correction to Gibbs Free Energy=        0.671316
 Sum of electronic and zero-point Energies=          -1957.424628
 Sum of electronic and thermal Energies=             -1957.385751
 Sum of electronic and thermal Enthalpies=           -1957.384807
 Sum of electronic and thermal Free Energies=        -1957.492660

         Item               Value     Threshold  Converged?
 Maximum Force            0.000000     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
```

SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1958.16397592', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 421.25750316 kcal/mol
H_corr: 488.93633919 kcal/mol
S_corr: 67.67915555 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.4137685 kcal/mol
S_rot: 11.23220495 kcal/mol
S_vib: 43.03288395 kcal/mol

E-3

#P Geom=AllCheck Guess=TCheck SCRF=Check GenChk RwB97XD/def2SVP Freq

charge= 1 multiplicity= 1

Cartesian coordinates (Angstroms):

XXX
86

C	-2.913	3.724	-0.269
C	-3.903	3.086	0.477
C	-1.604	3.243	-0.363
C	-1.305	2.055	0.350
C	-3.596	1.917	1.155
C	-2.300	1.400	1.099
H	-4.360	1.392	1.735
H	-3.183	4.637	-0.799
H	-4.911	3.503	0.519
C	-0.532	3.985	-1.179
C	0.553	4.509	-0.220
H	0.125	5.232	0.493
H	1.346	5.024	-0.785
H	1.019	3.698	0.349
C	0.079	3.045	-2.236
H	0.836	3.586	-2.825
H	-0.697	2.688	-2.931
H	0.554	2.172	-1.778
C	-1.115	5.194	-1.924
H	-0.314	5.683	-2.499
H	-1.530	5.950	-1.240
H	-1.900	4.903	-2.639
O	-0.053	1.553	0.291
C	-1.977	0.116	1.814
N	-0.933	-0.621	1.044
H	-1.604	0.267	2.833
H	-2.874	-0.513	1.898
B	0.367	0.370	0.945
C	-1.632	-1.202	-0.166
C	-2.374	-2.417	0.412
C	0.935	0.750	2.587
C	2.379	0.881	2.562
C	0.301	2.037	3.140
H	-0.790	2.002	3.222
H	0.547	2.892	2.495
H	0.690	2.251	4.147
H	-0.676	-1.456	1.592
N	1.476	-0.498	0.342
C	2.802	-0.363	0.318
C	3.343	0.959	-0.266
C	3.649	-1.573	0.023

```
C     3.267    -0.151     2.408
H     4.341     0.045     2.438
H     2.962    -1.181     2.612
H     2.781     1.900     2.521
H     0.650    -0.146     3.167
C    -0.757    -1.634    -1.349
O    -1.733    -3.167     1.146
N    -3.662    -2.603     0.111
C    -4.551    -1.704    -0.639
C    -4.367    -3.793     0.602
C    -5.942    -2.219    -0.279
H    -4.363    -1.792    -1.721
H    -4.398    -0.654    -0.350
C    -5.720    -3.721    -0.100
H    -4.465    -3.737     1.699
H    -3.792    -4.701     0.370
H    -6.515    -4.213     0.476
H    -5.663    -4.216    -1.083
H    -6.685    -1.973    -1.050
H    -6.277    -1.768     0.668
H    -2.301    -0.425    -0.549
O    -0.240    -0.459    -1.896
C     0.811    -0.614    -2.812
H     1.604    -1.275    -2.416
H     1.241     0.380    -2.989
H     0.469    -1.018    -3.780
C    -1.551    -2.441    -2.373
H    -2.385    -1.846    -2.774
H    -1.943    -3.375    -1.948
H    -0.899    -2.719    -3.212
H     0.054    -2.291    -0.978
F     2.497     1.960    -0.090
F     3.525     0.799    -1.575
F     4.507     1.335     0.263
C     3.059    -2.806    -0.294
C     5.052    -1.504     0.061
C     3.837    -3.929    -0.558
C     5.828    -2.627    -0.208
C     5.226    -3.845    -0.515
H     5.556    -0.573     0.307
H     5.837    -4.726    -0.724
H     6.915    -2.544    -0.172
H     1.978    -2.927    -0.373
H     3.348    -4.873    -0.805
H     1.232    -1.480     0.418
YYY
                      1                      2                      3
                      A                      A                      A
 Frequencies --   -337.9035               26.1277               26.8952
 Red. masses --      8.7865                5.4981                4.8441
 Zero-point correction=                          0.738915 (Hartree/Particle)
 Thermal correction to Energy=                   0.778117
 Thermal correction to Enthalpy=                 0.779061
 Thermal correction to Gibbs Free Energy=        0.670191
 Sum of electronic and zero-point Energies=          -1957.420715
 Sum of electronic and thermal Energies=             -1957.381513
 Sum of electronic and thermal Enthalpies=           -1957.380569
 Sum of electronic and thermal Free Energies=        -1957.489439

         Item               Value     Threshold  Converged?
 Maximum Force            0.000000     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1958.15963005', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
```

G_corr: 420.55155441 kcal/mol
H_corr: 488.86856811 kcal/mol
S_corr: 68.31719655 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.4137685 kcal/mol
S_rot: 11.2623181 kcal/mol
S_vib: 43.64110995 kcal/mol

E-4

#P Geom=AllCheck Guess=TCheck SCRF=Check GenChk RwB97XD/def2SVP Freq

charge= 1 multiplicity= 1

Cartesian coordinates (Angstroms):

XXX
86

C	-3.803	-2.984	-0.171
C	-4.442	-2.039	-0.977
C	-2.430	-2.949	0.089
C	-1.698	-1.909	-0.525
C	-3.705	-1.010	-1.545
C	-2.329	-0.944	-1.328
H	-4.192	-0.250	-2.163
H	-4.412	-3.771	0.271
H	-5.517	-2.109	-1.148
C	-1.744	-3.972	1.012
C	-0.662	-4.749	0.237
H	-1.098	-5.272	-0.629
H	-0.206	-5.509	0.890
H	0.137	-4.090	-0.126
C	-1.115	-3.239	2.213
H	-0.611	-3.961	2.875
H	-1.886	-2.721	2.804
H	-0.384	-2.486	1.893
C	-2.745	-4.997	1.562
H	-2.217	-5.704	2.219
H	-3.219	-5.586	0.762
H	-3.538	-4.524	2.161
O	-0.366	-1.836	-0.319
C	-1.510	0.168	-1.922
N	-0.386	0.520	-0.995
H	-1.074	-0.097	-2.893
H	-2.127	1.059	-2.092
B	0.487	-0.816	-0.808
C	-0.984	1.200	0.211
C	-1.471	2.550	-0.330
C	1.153	-1.322	-2.437
C	2.512	-1.745	-2.259
C	0.272	-2.413	-3.054
H	-0.785	-2.133	-3.135
H	0.310	-3.332	-2.451
H	0.619	-2.658	-4.068
H	0.162	1.270	-1.443
N	1.697	-0.735	0.095
C	2.927	-0.246	-0.126
C	4.008	-0.988	0.682
C	3.097	1.244	-0.279
C	3.594	-0.916	-2.068
H	1.116	-0.370	-2.997
C	-0.039	1.374	1.409
O	-0.735	3.167	-1.095

```
N    -2.675     2.991     0.050
C    -3.698     2.268     0.817
C    -3.142     4.310    -0.391
C    -4.968     3.069     0.535
H    -3.454     2.273     1.892
H    -3.779     1.221     0.490
C    -4.451     4.498     0.371
H    -3.296     4.302    -1.483
H    -2.385     5.076    -0.173
H    -5.151     5.155    -0.162
H    -4.255     4.947     1.357
H    -5.712     2.960     1.336
H    -5.429     2.719    -0.402
H    -1.808     0.570     0.562
O    -0.117     0.158     2.108
C     0.829    -0.012     3.128
H     1.834     0.315     2.811
H     0.868    -1.083     3.371
H     0.556     0.535     4.048
C    -0.391     2.571     2.286
H    -1.398     2.476     2.717
H    -0.318     3.511     1.723
H     0.328     2.641     3.114
H     0.985     1.532     1.029
F     3.902    -2.307     0.499
F     3.859    -0.777     1.996
F     5.232    -0.614     0.348
C     3.733     1.963     0.744
C     2.520     1.962    -1.335
C     3.772     3.356     0.711
C     2.550     3.352    -1.360
C     3.176     4.056    -0.333
H     2.053     1.441    -2.171
H     4.273     3.893     1.519
H     4.191     1.454     1.590
H     3.204     5.147    -0.353
H     2.078     3.884    -2.186
H     4.578    -1.365    -1.917
H     2.659    -2.812    -2.043
H     3.605     0.082    -2.505
H     1.717    -1.644     0.563
YYY
                     1                     2                     3
                     A                     A                     A
 Frequencies --   -414.9864              24.6148               29.8483
 Red. masses --      8.7179               4.6219                4.9298
 Zero-point correction=                          0.738225 (Hartree/Particle)
 Thermal correction to Energy=                   0.777667
 Thermal correction to Enthalpy=                 0.778611
 Thermal correction to Gibbs Free Energy=        0.669468
 Sum of electronic and zero-point Energies=          -1957.418896
 Sum of electronic and thermal Energies=             -1957.379454
 Sum of electronic and thermal Enthalpies=           -1957.378510
 Sum of electronic and thermal Free Energies=        -1957.487654

         Item               Value     Threshold  Converged?
 Maximum Force            0.000000     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1958.15712157', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 420.09786468 kcal/mol
H_corr: 488.58618861 kcal/mol
S_corr: 68.4886328 kcal/mol
S_elec: 0.0 kcal/mol
```

```
S_trans: 13.4137685 kcal/mol
S_rot: 11.22027895 kcal/mol
S_vib: 43.8542872 kcal/mol
----------------------------------------
```

2.7.13 Crystallographic Data

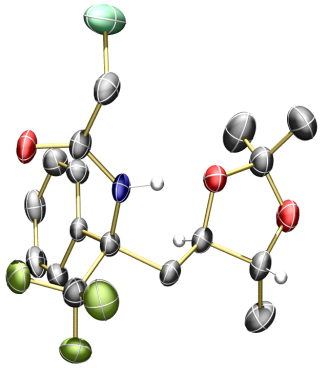


Table S2. Crystal data and structure refinement for C17H21ClF3NO3

Identification code	C17H21ClF3NO3	
Empirical formula	C17 H21 Cl F3 N O3	
Formula weight	379.80	
Temperature	173(2) K	
Wavelength	1.54178 ≈	
Crystal system	Tetragonal	
Space group	$P4_32_12$	
Unit cell dimensions	a = 9.6003(2) ≈	a= 90∞.
	b = 9.6003(2) ≈	b= 90∞.
	c = 41.0420(14) ≈	c = 90∞.
Volume	3782.7(2) ≈^{3}	
Z	8	
Density (calculated)	1.334 Mg/m^3	
Absorption coefficient	2.191 mm^{-1}	
F(000)	1584	
Crystal size	0.460 x 0.370 x 0.220 mm^3	
Theta range for data collection	4.730 to 66.407∞.	
Index ranges	-11<=h<=11, -10<=k<=11, -48<=l<=48	
Reflections collected	40047	
Independent reflections	3300 [R(int) = 0.0240]	

Completeness to theta = 66.407∞	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7528 and 0.6464
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3300 / 1 / 230
Goodness-of-fit on F^2	1.072
Final R indices [I>2sigma(I)]	R1 = 0.0298, wR2 = 0.0800
R indices (all data)	R1 = 0.0304, wR2 = 0.0806
Absolute structure parameter	0.03(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.224 and -0.342 e.≈$^{-3}$

Table S3. Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (≈^{2}x10^3) for C17H21ClF3NO3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
Cl(1)	8272(1)	-232(1)	6572(1)	75(1)
F(1)	7089(2)	4861(2)	5913(1)	53(1)
F(2)	8189(2)	6719(2)	6042(1)	53(1)
F(3)	9301(2)	4970(2)	5852(1)	60(1)
N(1)	8919(2)	3293(2)	6364(1)	30(1)
O(1)	6881(2)	2306(2)	6199(1)	41(1)
O(2)	10243(2)	3902(2)	6978(1)	39(1)
O(3)	11605(2)	5220(2)	7316(1)	47(1)
C(1)	8879(2)	843(2)	6254(1)	41(1)
C(2)	8117(2)	2222(2)	6267(1)	32(1)
C(3)	8503(2)	4743(2)	6398(1)	29(1)
C(4)	9769(2)	5538(2)	6542(1)	32(1)
C(5)	9993(2)	5331(2)	6904(1)	32(1)
C(6)	10973(3)	3876(3)	7282(1)	45(1)
C(7)	11304(2)	6026(3)	7032(1)	38(1)
C(8)	11144(3)	7537(3)	7121(1)	54(1)
C(9)	7234(2)	4944(2)	6620(1)	27(1)
C(10)	6834(2)	3907(2)	6835(1)	33(1)
C(11)	5765(2)	4126(3)	7055(1)	41(1)

C(12)	5086(2)	5388(3)	7067(1)	42(1)
C(13)	5489(2)	6434(3)	6862(1)	42(1)
C(14)	6553(2)	6222(2)	6637(1)	35(1)
C(15)	8253(2)	5321(3)	6051(1)	40(1)
C(16)	12072(4)	2763(4)	7257(1)	69(1)
C(17)	9963(3)	3676(4)	7561(1)	76(1)

Table S4. Bond lengths [≈] and angles [∞] for C17H21ClF3NO3

Cl(1)-C(1)	1.762(3)
F(1)-C(15)	1.328(3)
F(2)-C(15)	1.344(3)
F(3)-C(15)	1.338(3)
N(1)-C(2)	1.344(3)
N(1)-C(3)	1.455(3)
N(1)-H(1N)	0.847(19)
O(1)-C(2)	1.222(3)
O(2)-C(5)	1.426(3)
O(2)-C(6)	1.433(3)
O(3)-C(7)	1.428(3)
O(3)-C(6)	1.433(3)
C(1)-C(2)	1.513(3)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(3)-C(9)	1.534(3)
C(3)-C(15)	1.549(3)
C(3)-C(4)	1.551(3)
C(4)-C(5)	1.515(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(7)	1.519(3)
C(5)-H(5A)	1.0000
C(6)-C(16)	1.505(4)
C(6)-C(17)	1.511(4)
C(7)-C(8)	1.503(4)

C(7)-H(7)	1.0000
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-C(10)	1.384(3)
C(9)-C(14)	1.392(3)
C(10)-C(11)	1.384(3)
C(10)-H(10)	0.9500
C(11)-C(12)	1.376(3)
C(11)-H(11)	0.9500
C(12)-C(13)	1.369(4)
C(12)-H(12)	0.9500
C(13)-C(14)	1.390(3)
C(13)-H(13)	0.9500
C(14)-H(14)	0.9500
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800

C(2)-N(1)-C(3)	127.11(17)
C(2)-N(1)-H(1N)	117.4(17)
C(3)-N(1)-H(1N)	115.3(17)
C(5)-O(2)-C(6)	106.56(17)
C(7)-O(3)-C(6)	108.82(16)
C(2)-C(1)-Cl(1)	109.07(15)
C(2)-C(1)-H(1A)	109.9
Cl(1)-C(1)-H(1A)	109.9
C(2)-C(1)-H(1B)	109.9
Cl(1)-C(1)-H(1B)	109.9
H(1A)-C(1)-H(1B)	108.3
O(1)-C(2)-N(1)	125.0(2)
O(1)-C(2)-C(1)	121.2(2)
N(1)-C(2)-C(1)	113.77(18)

N(1)-C(3)-C(9)	113.35(16)
N(1)-C(3)-C(15)	107.26(16)
C(9)-C(3)-C(15)	112.28(16)
N(1)-C(3)-C(4)	106.99(15)
C(9)-C(3)-C(4)	109.52(15)
C(15)-C(3)-C(4)	107.13(16)
C(5)-C(4)-C(3)	114.81(16)
C(5)-C(4)-H(4A)	108.6
C(3)-C(4)-H(4A)	108.6
C(5)-C(4)-H(4B)	108.6
C(3)-C(4)-H(4B)	108.6
H(4A)-C(4)-H(4B)	107.5
O(2)-C(5)-C(4)	111.05(16)
O(2)-C(5)-C(7)	102.06(16)
C(4)-C(5)-C(7)	113.67(17)
O(2)-C(5)-H(5A)	109.9
C(4)-C(5)-H(5A)	109.9
C(7)-C(5)-H(5A)	109.9
O(2)-C(6)-O(3)	106.05(18)
O(2)-C(6)-C(16)	107.2(2)
O(3)-C(6)-C(16)	110.4(2)
O(2)-C(6)-C(17)	110.4(2)
O(3)-C(6)-C(17)	108.2(2)
C(16)-C(6)-C(17)	114.2(3)
O(3)-C(7)-C(8)	110.26(19)
O(3)-C(7)-C(5)	102.31(17)
C(8)-C(7)-C(5)	115.0(2)
O(3)-C(7)-H(7)	109.7
C(8)-C(7)-H(7)	109.7
C(5)-C(7)-H(7)	109.7
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5

C(10)-C(9)-C(14)	118.11(18)
C(10)-C(9)-C(3)	120.56(17)
C(14)-C(9)-C(3)	120.95(17)
C(11)-C(10)-C(9)	120.8(2)
C(11)-C(10)-H(10)	119.6
C(9)-C(10)-H(10)	119.6
C(12)-C(11)-C(10)	120.6(2)
C(12)-C(11)-H(11)	119.7
C(10)-C(11)-H(11)	119.7
C(13)-C(12)-C(11)	119.3(2)
C(13)-C(12)-H(12)	120.3
C(11)-C(12)-H(12)	120.3
C(12)-C(13)-C(14)	120.6(2)
C(12)-C(13)-H(13)	119.7
C(14)-C(13)-H(13)	119.7
C(13)-C(14)-C(9)	120.5(2)
C(13)-C(14)-H(14)	119.7
C(9)-C(14)-H(14)	119.7
F(1)-C(15)-F(3)	106.86(18)
F(1)-C(15)-F(2)	106.48(19)
F(3)-C(15)-F(2)	105.70(18)
F(1)-C(15)-C(3)	113.74(17)
F(3)-C(15)-C(3)	110.69(19)
F(2)-C(15)-C(3)	112.87(18)
C(6)-C(16)-H(16A)	109.5
C(6)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(6)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(6)-C(17)-H(17A)	109.5
C(6)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(6)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S5. Anisotropic displacement parameters ($\approx^2$x 10^3) for C17H21ClF3NO3. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	65(1)	53(1)	108(1)	26(1)	25(1)	11(1)
F(1)	48(1)	68(1)	43(1)	14(1)	-18(1)	-14(1)
F(2)	61(1)	50(1)	49(1)	20(1)	-4(1)	-9(1)
F(3)	55(1)	90(1)	36(1)	8(1)	12(1)	3(1)
N(1)	15(1)	37(1)	37(1)	-5(1)	0(1)	1(1)
O(1)	21(1)	47(1)	55(1)	-6(1)	-6(1)	-2(1)
O(2)	38(1)	41(1)	38(1)	3(1)	-9(1)	-6(1)
O(3)	40(1)	59(1)	42(1)	-1(1)	-12(1)	-9(1)
C(1)	30(1)	39(1)	54(1)	-12(1)	4(1)	-1(1)
C(2)	22(1)	39(1)	34(1)	-6(1)	3(1)	-3(1)
C(3)	21(1)	33(1)	32(1)	2(1)	0(1)	-2(1)
C(4)	22(1)	36(1)	38(1)	1(1)	1(1)	-6(1)
C(5)	24(1)	36(1)	36(1)	-3(1)	2(1)	-4(1)
C(6)	41(1)	56(2)	39(1)	6(1)	-8(1)	-9(1)
C(7)	28(1)	52(1)	36(1)	-4(1)	-1(1)	-10(1)
C(8)	61(2)	52(2)	51(1)	-11(1)	-2(1)	-18(1)
C(9)	18(1)	32(1)	31(1)	0(1)	-3(1)	-1(1)
C(10)	29(1)	34(1)	36(1)	3(1)	1(1)	3(1)
C(11)	36(1)	53(1)	36(1)	5(1)	6(1)	1(1)
C(12)	27(1)	66(2)	34(1)	-8(1)	1(1)	9(1)
C(13)	32(1)	45(1)	47(1)	-12(1)	-9(1)	13(1)
C(14)	29(1)	33(1)	44(1)	4(1)	-6(1)	2(1)
C(15)	34(1)	50(1)	36(1)	6(1)	0(1)	-5(1)
C(16)	66(2)	66(2)	75(2)	14(2)	-25(2)	4(2)
C(17)	70(2)	115(3)	42(1)	11(2)	1(1)	-34(2)

Table S6. Hydrogen coordinates (x10^4) and isotropic displacement parameters ($\approx^2$x10^3)

for C17H21ClF3NO3

	x	y	z	U(eq)
H(1N)	9780(20)	3130(30)	6393(6)	36
H(1A)	9893	999	6278	49
H(1B)	8712	387	6042	49
H(4A)	10619	5235	6425	39
H(4B)	9644	6545	6499	39
H(5A)	9162	5671	7027	38
H(7)	12075	5917	6870	46
H(8A)	10939	8078	6924	82
H(8B)	10379	7641	7277	82
H(8C)	12010	7876	7219	82
H(10)	7300	3034	6832	39
H(11)	5497	3400	7199	50
H(12)	4344	5530	7217	51
H(13)	5038	7314	6872	50
H(14)	6818	6955	6495	42
H(16A)	12594	2716	7462	103
H(16B)	11628	1862	7215	103
H(16C)	12710	2987	7078	103
H(17A)	10477	3660	7767	114
H(17B)	9293	4445	7563	114
H(17C)	9466	2792	7533	114

Table S7. Torsion angles [∞] for C17H21ClF3NO3

C(3)-N(1)-C(2)-O(1)	-1.6(3)
C(3)-N(1)-C(2)-C(1)	179.40(18)
Cl(1)-C(1)-C(2)-O(1)	-69.5(2)
Cl(1)-C(1)-C(2)-N(1)	109.50(18)
C(2)-N(1)-C(3)-C(9)	54.8(3)
C(2)-N(1)-C(3)-C(15)	-69.8(2)

C(2)-N(1)-C(3)-C(4)	175.58(18)
N(1)-C(3)-C(4)-C(5)	-77.2(2)
C(9)-C(3)-C(4)-C(5)	46.0(2)
C(15)-C(3)-C(4)-C(5)	168.02(18)
C(6)-O(2)-C(5)-C(4)	157.29(17)
C(6)-O(2)-C(5)-C(7)	35.8(2)
C(3)-C(4)-C(5)-O(2)	61.0(2)
C(3)-C(4)-C(5)-C(7)	175.36(18)
C(5)-O(2)-C(6)-O(3)	-22.1(2)
C(5)-O(2)-C(6)-C(16)	-140.1(2)
C(5)-O(2)-C(6)-C(17)	94.9(3)
C(7)-O(3)-C(6)-O(2)	-2.0(2)
C(7)-O(3)-C(6)-C(16)	113.8(2)
C(7)-O(3)-C(6)-C(17)	-120.5(2)
C(6)-O(3)-C(7)-C(8)	146.2(2)
C(6)-O(3)-C(7)-C(5)	23.4(2)
O(2)-C(5)-C(7)-O(3)	-35.9(2)
C(4)-C(5)-C(7)-O(3)	-155.57(18)
O(2)-C(5)-C(7)-C(8)	-155.46(19)
C(4)-C(5)-C(7)-C(8)	84.9(2)
N(1)-C(3)-C(9)-C(10)	18.1(2)
C(15)-C(3)-C(9)-C(10)	139.82(19)
C(4)-C(3)-C(9)-C(10)	-101.3(2)
N(1)-C(3)-C(9)-C(14)	-169.13(17)
C(15)-C(3)-C(9)-C(14)	-47.4(2)
C(4)-C(3)-C(9)-C(14)	71.5(2)
C(14)-C(9)-C(10)-C(11)	1.6(3)
C(3)-C(9)-C(10)-C(11)	174.56(19)
C(9)-C(10)-C(11)-C(12)	-0.7(3)
C(10)-C(11)-C(12)-C(13)	-0.7(3)
C(11)-C(12)-C(13)-C(14)	1.4(3)
C(12)-C(13)-C(14)-C(9)	-0.5(3)
C(10)-C(9)-C(14)-C(13)	-0.9(3)
C(3)-C(9)-C(14)-C(13)	-173.91(18)
N(1)-C(3)-C(15)-F(1)	73.5(2)
C(9)-C(3)-C(15)-F(1)	-51.6(3)

C(4)-C(3)-C(15)-F(1)	-171.89(18)
N(1)-C(3)-C(15)-F(3)	-46.8(2)
C(9)-C(3)-C(15)-F(3)	-171.93(17)
C(4)-C(3)-C(15)-F(3)	67.8(2)
N(1)-C(3)-C(15)-F(2)	-165.02(17)
C(9)-C(3)-C(15)-F(2)	69.8(2)
C(4)-C(3)-C(15)-F(2)	-50.4(2)

Symmetry transformations used to generate equivalent atoms:

Table S8. Hydrogen bonds for C17H21ClF3NO3 [≈ and ∞]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.847(19)	2.10(2)	2.913(2)	161(2)

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+1/2,-z+5/4

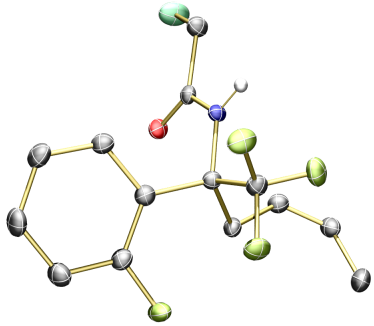


Table S9. Crystal data and structure refinement for C14 H14 Cl F4 N O

Identification code	C14 H14 Cl F4 N O	
Empirical formula	C14 H14 Cl F4 N O	
Formula weight	323.71	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Tetragonal	
Space group	$P4_3$	
Unit cell dimensions	a = 9.6746(3) Å	a= 90°.

	b = 9.6746(3) Å	b= 90°.
	c = 15.2638(5) Å	c = 90°.
Volume	1428.66(10) $Å^3$	
Z	4	
Density (calculated)	1.505 Mg/m^3	
Absorption coefficient	2.793 mm^{-1}	
F(000)	664	
Crystal size	0.250 x 0.100 x 0.100 mm^3	
Theta range for data collection	7.093 to 66.613°.	
Index ranges	-11<=h<=11, -10<=k<=8, -17<=l<=15	
Reflections collected	6738	
Independent reflections	2293 [R(int) = 0.0268]	
Completeness to theta = 67.679°	97.5 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2293 / 1 / 191	
Goodness-of-fit on F^2	1.658	
Final R indices [I>2sigma(I)]	R1 = 0.0245, wR2 = 0.0605	
R indices (all data)	R1 = 0.0246, wR2 = 0.0607	
Absolute structure parameter	0.086(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.195 and -0.255 e.$Å^{-3}$	

Table S10. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for C14 H14 Cl F4 N O. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
Cl(01)	7488(1)	3176(1)	3774(1)	38(1)
F(002)	5562(1)	10537(1)	4621(1)	26(1)
F(003)	4660(1)	9303(1)	3600(1)	27(1)
F(004)	6834(1)	9762(1)	3573(1)	28(1)
F(005)	5428(1)	9492(1)	6307(1)	27(1)
O(001)	6791(2)	5391(1)	4992(1)	21(1)
N(001)	6275(2)	7035(2)	3994(1)	15(1)
C(001)	6601(2)	5744(2)	4232(1)	17(1)
C(002)	7403(2)	8363(2)	5206(1)	18(1)

C(003)	4788(2)	7847(2)	5218(1)	18(1)
C(004)	5780(2)	9442(2)	4105(1)	20(1)
C(005)	6075(2)	8134(2)	4644(1)	17(1)
C(006)	3785(2)	6893(2)	4953(1)	21(1)
C(014)	4541(2)	8508(2)	6008(1)	21(1)
C(007)	3413(2)	8235(2)	6535(1)	26(1)
C(008)	9753(2)	8990(2)	4605(1)	23(1)
C(009)	6704(2)	4743(2)	3463(1)	23(1)
C(010)	9730(2)	10515(2)	4771(2)	29(1)
C(011)	8758(2)	8073(2)	4758(1)	21(1)
C(012)	2453(2)	7264(2)	6264(2)	27(1)
C(013)	2634(2)	6600(2)	5464(2)	26(1)

Table S11. Bond lengths [Å] and angles [°] for C14 H14 Cl F4 N O

Cl(01)-C(009)	1.760(2)
F(002)-C(004)	1.338(2)
F(003)-C(004)	1.337(2)
F(004)-C(004)	1.340(3)
F(005)-C(014)	1.361(2)
O(001)-C(001)	1.224(3)
N(001)-C(001)	1.339(3)
N(001)-C(005)	1.467(2)
N(001)-H(007)	0.8800
C(001)-C(009)	1.525(3)
C(002)-C(011)	1.505(3)
C(002)-C(005)	1.561(3)
C(002)-H(00A)	0.9900
C(002)-H(00B)	0.9900
C(003)-C(014)	1.385(3)
C(003)-C(006)	1.400(3)
C(003)-C(005)	1.548(3)
C(004)-C(005)	1.536(3)
C(006)-C(013)	1.389(3)
C(006)-H(00D)	0.9500

C(014)-C(007)	1.382(3)
C(007)-C(012)	1.384(3)
C(007)-H(00F)	0.9500
C(008)-C(011)	1.330(3)
C(008)-C(010)	1.497(3)
C(008)-H(00G)	0.9500
C(009)-H(00C)	0.9900
C(009)-H(00E)	0.9900
C(010)-H(00H)	0.9800
C(010)-H(00I)	0.9800
C(010)-H(00J)	0.9800
C(011)-H(00K)	0.9500
C(012)-C(013)	1.391(4)
C(012)-H(00L)	0.9500
C(013)-H(00M)	0.9500

C(001)-N(001)-C(005)	121.58(16)
C(001)-N(001)-H(007)	119.2
C(005)-N(001)-H(007)	119.2
O(001)-C(001)-N(001)	123.59(18)
O(001)-C(001)-C(009)	122.89(19)
N(001)-C(001)-C(009)	113.52(17)
C(011)-C(002)-C(005)	116.17(16)
C(011)-C(002)-H(00A)	108.2
C(005)-C(002)-H(00A)	108.2
C(011)-C(002)-H(00B)	108.2
C(005)-C(002)-H(00B)	108.2
H(00A)-C(002)-H(00B)	107.4
C(014)-C(003)-C(006)	115.89(19)
C(014)-C(003)-C(005)	123.28(17)
C(006)-C(003)-C(005)	120.82(18)
F(003)-C(004)-F(002)	106.92(16)
F(003)-C(004)-F(004)	106.97(17)
F(002)-C(004)-F(004)	107.12(16)
F(003)-C(004)-C(005)	112.12(16)
F(002)-C(004)-C(005)	111.47(16)

F(004)-C(004)-C(005)	111.93(16)
N(001)-C(005)-C(004)	105.01(15)
N(001)-C(005)-C(003)	111.05(15)
C(004)-C(005)-C(003)	107.54(16)
N(001)-C(005)-C(002)	111.50(15)
C(004)-C(005)-C(002)	109.28(16)
C(003)-C(005)-C(002)	112.12(15)
C(013)-C(006)-C(003)	121.9(2)
C(013)-C(006)-H(00D)	119.1
C(003)-C(006)-H(00D)	119.1
F(005)-C(014)-C(007)	115.85(18)
F(005)-C(014)-C(003)	120.44(18)
C(007)-C(014)-C(003)	123.71(19)
C(014)-C(007)-C(012)	119.02(19)
C(014)-C(007)-H(00F)	120.5
C(012)-C(007)-H(00F)	120.5
C(011)-C(008)-C(010)	128.1(2)
C(011)-C(008)-H(00G)	115.9
C(010)-C(008)-H(00G)	115.9
C(001)-C(009)-Cl(01)	111.58(15)
C(001)-C(009)-H(00C)	109.3
Cl(01)-C(009)-H(00C)	109.3
C(001)-C(009)-H(00E)	109.3
Cl(01)-C(009)-H(00E)	109.3
H(00C)-C(009)-H(00E)	108.0
C(008)-C(010)-H(00H)	109.5
C(008)-C(010)-H(00I)	109.5
H(00H)-C(010)-H(00I)	109.5
C(008)-C(010)-H(00J)	109.5
H(00H)-C(010)-H(00J)	109.5
H(00I)-C(010)-H(00J)	109.5
C(008)-C(011)-C(002)	125.83(19)
C(008)-C(011)-H(00K)	117.1
C(002)-C(011)-H(00K)	117.1
C(007)-C(012)-C(013)	119.48(19)
C(007)-C(012)-H(00L)	120.3

C(013)-C(012)-H(00L)	120.3
C(006)-C(013)-C(012)	119.99(19)
C(006)-C(013)-H(00M)	120.0
C(012)-C(013)-H(00M)	120.0

Symmetry transformations used to generate equivalent atoms:

Table S12. Anisotropic displacement parameters ($Å^2x10^3$) for C14 H14 Cl F4 N O. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(01)	59(1)	18(1)	37(1)	-2(1)	-8(1)	14(1)
F(002)	36(1)	15(1)	29(1)	-4(1)	-2(1)	4(1)
F(003)	32(1)	21(1)	29(1)	2(1)	-12(1)	5(1)
F(004)	33(1)	24(1)	27(1)	8(1)	6(1)	2(1)
F(005)	23(1)	32(1)	27(1)	-13(1)	2(1)	-7(1)
O(001)	25(1)	19(1)	18(1)	3(1)	-3(1)	-1(1)
N(001)	20(1)	14(1)	13(1)	1(1)	-1(1)	1(1)
C(001)	14(1)	18(1)	19(1)	1(1)	0(1)	-2(1)
C(002)	17(1)	20(1)	18(1)	1(1)	-1(1)	-2(1)
C(003)	17(1)	17(1)	20(1)	1(1)	-2(1)	3(1)
C(004)	21(1)	17(1)	22(1)	-1(1)	0(1)	1(1)
C(005)	18(1)	15(1)	17(1)	-1(1)	-1(1)	1(1)
C(006)	20(1)	22(1)	22(1)	-3(1)	-3(1)	1(1)
C(014)	18(1)	22(1)	23(1)	-1(1)	-3(1)	-1(1)
C(007)	22(1)	31(1)	25(1)	-5(1)	3(1)	3(1)
C(008)	18(1)	28(1)	22(1)	-4(1)	1(1)	-1(1)
C(009)	28(1)	18(1)	22(1)	-1(1)	0(1)	2(1)
C(010)	30(1)	27(1)	30(1)	-1(1)	4(1)	-9(1)
C(011)	20(1)	20(1)	23(1)	-3(1)	-1(1)	2(1)
C(012)	18(1)	32(1)	32(1)	1(1)	7(1)	0(1)
C(013)	19(1)	24(1)	34(1)	-3(1)	-2(1)	-2(1)

Table S13. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$)

for C14 H14 Cl F4 N O

	x	y	z	U(eq)
H(007)	6178	7230	3434	18
H(00A)	7411	9335	5409	22
H(00B)	7341	7769	5732	22
H(00D)	3894	6432	4408	25
H(00F)	3297	8707	7076	31
H(00G)	10582	8633	4360	27
H(00C)	7251	5175	2988	27
H(00E)	5766	4554	3233	27
H(00H)	8866	10764	5067	43
H(00I)	9792	11009	4212	43
H(00J)	10516	10769	5142	43
H(00K)	8917	7151	4568	25
H(00L)	1678	7052	6622	33
H(00M)	1969	5947	5267	31

Table S14. Torsion angles [°] for C14 H14 Cl F4 N O

C(005)-N(001)-C(001)-O(001)	-2.0(3)
C(005)-N(001)-C(001)-C(009)	177.59(16)
C(001)-N(001)-C(005)-C(004)	177.74(16)
C(001)-N(001)-C(005)-C(003)	-66.3(2)
C(001)-N(001)-C(005)-C(002)	59.5(2)
F(003)-C(004)-C(005)-N(001)	59.6(2)
F(002)-C(004)-C(005)-N(001)	179.39(15)
F(004)-C(004)-C(005)-N(001)	-60.7(2)
F(003)-C(004)-C(005)-C(003)	-58.8(2)
F(002)-C(004)-C(005)-C(003)	61.0(2)
F(004)-C(004)-C(005)-C(003)	-179.00(16)
F(003)-C(004)-C(005)-C(002)	179.28(16)
F(002)-C(004)-C(005)-C(002)	-60.9(2)

F(004)-C(004)-C(005)-C(002)	59.1(2)
C(014)-C(003)-C(005)-N(001)	163.62(17)
C(006)-C(003)-C(005)-N(001)	-17.0(3)
C(014)-C(003)-C(005)-C(004)	-82.0(2)
C(006)-C(003)-C(005)-C(004)	97.4(2)
C(014)-C(003)-C(005)-C(002)	38.1(2)
C(006)-C(003)-C(005)-C(002)	-142.46(18)
C(011)-C(002)-C(005)-N(001)	30.6(2)
C(011)-C(002)-C(005)-C(004)	-85.0(2)
C(011)-C(002)-C(005)-C(003)	155.82(17)
C(014)-C(003)-C(006)-C(013)	-1.7(3)
C(005)-C(003)-C(006)-C(013)	178.84(18)
C(006)-C(003)-C(014)-F(005)	-177.48(17)
C(005)-C(003)-C(014)-F(005)	1.9(3)
C(006)-C(003)-C(014)-C(007)	2.2(3)
C(005)-C(003)-C(014)-C(007)	-178.37(19)
F(005)-C(014)-C(007)-C(012)	178.8(2)
C(003)-C(014)-C(007)-C(012)	-0.9(3)
O(001)-C(001)-C(009)-Cl(01)	-13.2(2)
N(001)-C(001)-C(009)-Cl(01)	167.24(14)
C(010)-C(008)-C(011)-C(002)	-5.2(3)
C(005)-C(002)-C(011)-C(008)	117.5(2)
C(014)-C(007)-C(012)-C(013)	-1.0(3)
C(003)-C(006)-C(013)-C(012)	0.0(3)
C(007)-C(012)-C(013)-C(006)	1.4(3)

Symmetry transformations used to generate equivalent atoms:

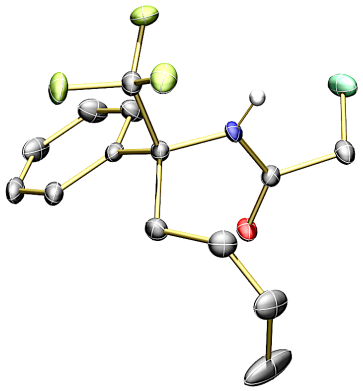


Table S15. Crystal data and structure refinement for C14H15ClF3NO

Identification code	C14H15ClF3NO	
Empirical formula	C14 H15 Cl F3 N O	
Formula weight	305.72	
Temperature	100(2) K	
Wavelength	1.54178 ≈	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.1349(4) ≈	α= 90∞.
	b = 9.3369(4) ≈	β= 90∞.
	c = 17.2799(7) ≈	γ = 90∞.
Volume	1473.83(11) ≈^{3}	
Z	4	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	2.573 mm^{-1}	
F(000)	632	
Crystal size	0.600 x 0.380 x 0.260 mm^3	
Theta range for data collection	5.385 to 69.524∞.	
Index ranges	-11<=h<=11, -11<=k<=11, -21<=l<=20	
Reflections collected	18445	
Independent reflections	2753 [R(int) = 0.0258]	
Completeness to theta = 67.679∞	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7532 and 0.6007	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2753 / 1 / 186	
Goodness-of-fit on F^2	1.088	

Final R indices [I>2sigma(I)]	R1 = 0.0238, wR2 = 0.0626
R indices (all data)	R1 = 0.0238, wR2 = 0.0626
Absolute structure parameter	0.011(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.226 and -0.262 e.≈$^{-3}$

Table S16. Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (≈^{2}x10^3) for C14H15ClF3NO. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
Cl(1)	2344(1)	5556(1)	7013(1)	30(1)
F(1)	7180(1)	3967(1)	5982(1)	26(1)
F(2)	8341(1)	3366(1)	7011(1)	24(1)
F(3)	9340(1)	4806(1)	6199(1)	26(1)
O(1)	5285(1)	7473(1)	7680(1)	19(1)
N(1)	5922(2)	5311(2)	7188(1)	14(1)
C(1)	7261(5)	7188(3)	9303(1)	60(1)
C(2)	7551(3)	5679(2)	9063(1)	31(1)
C(3)	8000(2)	5223(2)	8379(1)	21(1)
C(4)	8336(2)	6141(2)	7684(1)	18(1)
C(5)	7395(2)	5764(2)	6957(1)	14(1)
C(6)	5015(2)	6204(2)	7559(1)	15(1)
C(7)	3585(2)	5538(2)	7814(1)	19(1)
C(8)	8066(2)	4474(2)	6537(1)	18(1)
C(9)	7335(2)	6991(2)	6364(1)	16(1)
C(10)	8519(2)	7922(2)	6283(1)	20(1)
C(11)	8491(2)	8990(2)	5719(1)	24(1)
C(12)	7297(3)	9138(2)	5242(1)	28(1)
C(13)	6111(3)	8217(2)	5322(1)	30(1)
C(14)	6131(2)	7142(2)	5879(1)	23(1)

Table S17. Bond lengths [≈] and angles [∞] for C14H15ClF3NO

Cl(1)-C(7)	1.789(2)

F(1)-C(8)	1.341(2)
F(2)-C(8)	1.344(2)
F(3)-C(8)	1.339(2)
O(1)-C(6)	1.228(2)
N(1)-C(6)	1.339(2)
N(1)-C(5)	1.465(2)
N(1)-H(1N)	0.864(19)
C(1)-C(2)	1.492(3)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(3)	1.322(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.507(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.562(2)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(8)	1.534(2)
C(5)-C(9)	1.538(2)
C(6)-C(7)	1.513(3)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(9)-C(14)	1.390(3)
C(9)-C(10)	1.395(3)
C(10)-C(11)	1.394(3)
C(10)-H(10)	0.9500
C(11)-C(12)	1.375(3)
C(11)-H(11)	0.9500
C(12)-C(13)	1.390(3)
C(12)-H(12)	0.9500
C(13)-C(14)	1.391(3)
C(13)-H(13)	0.9500
C(14)-H(14)	0.9500

C(6)-N(1)-C(5)	121.24(15)

C(6)-N(1)-H(1N)	116.7(16)
C(5)-N(1)-H(1N)	120.1(16)
C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
C(3)-C(2)-C(1)	127.4(2)
C(3)-C(2)-H(2)	116.3
C(1)-C(2)-H(2)	116.3
C(2)-C(3)-C(4)	126.37(19)
C(2)-C(3)-H(3)	116.8
C(4)-C(3)-H(3)	116.8
C(3)-C(4)-C(5)	113.61(15)
C(3)-C(4)-H(4A)	108.8
C(5)-C(4)-H(4A)	108.8
C(3)-C(4)-H(4B)	108.8
C(5)-C(4)-H(4B)	108.8
H(4A)-C(4)-H(4B)	107.7
N(1)-C(5)-C(8)	105.62(14)
N(1)-C(5)-C(9)	111.31(14)
C(8)-C(5)-C(9)	106.44(14)
N(1)-C(5)-C(4)	110.59(14)
C(8)-C(5)-C(4)	109.75(15)
C(9)-C(5)-C(4)	112.79(14)
O(1)-C(6)-N(1)	123.94(17)
O(1)-C(6)-C(7)	121.37(17)
N(1)-C(6)-C(7)	114.69(15)
C(6)-C(7)-Cl(1)	108.58(13)
C(6)-C(7)-H(7A)	110.0
Cl(1)-C(7)-H(7A)	110.0
C(6)-C(7)-H(7B)	110.0
Cl(1)-C(7)-H(7B)	110.0
H(7A)-C(7)-H(7B)	108.4
F(3)-C(8)-F(1)	107.11(14)

F(3)-C(8)-F(2)	106.39(15)
F(1)-C(8)-F(2)	106.06(15)
F(3)-C(8)-C(5)	111.86(15)
F(1)-C(8)-C(5)	112.01(15)
F(2)-C(8)-C(5)	112.98(15)
C(14)-C(9)-C(10)	119.35(17)
C(14)-C(9)-C(5)	120.38(17)
C(10)-C(9)-C(5)	120.20(17)
C(11)-C(10)-C(9)	120.11(19)
C(11)-C(10)-H(10)	119.9
C(9)-C(10)-H(10)	119.9
C(12)-C(11)-C(10)	120.36(19)
C(12)-C(11)-H(11)	119.8
C(10)-C(11)-H(11)	119.8
C(11)-C(12)-C(13)	119.78(18)
C(11)-C(12)-H(12)	120.1
C(13)-C(12)-H(12)	120.1
C(12)-C(13)-C(14)	120.3(2)
C(12)-C(13)-H(13)	119.8
C(14)-C(13)-H(13)	119.8
C(9)-C(14)-C(13)	120.06(19)
C(9)-C(14)-H(14)	120.0
C(13)-C(14)-H(14)	120.0

Symmetry transformations used to generate equivalent atoms:

Table S18. Anisotropic displacement parameters ($\approx^2$x10^3) for C14H15ClF3NO. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	18(1)	32(1)	41(1)	-14(1)	-3(1)	0(1)
F(1)	32(1)	23(1)	22(1)	-10(1)	2(1)	-1(1)
F(2)	28(1)	13(1)	29(1)	2(1)	6(1)	5(1)
F(3)	22(1)	21(1)	35(1)	-1(1)	15(1)	1(1)

O(1)	20(1)	11(1)	25(1)	-1(1)	5(1)	0(1)
N(1)	14(1)	9(1)	17(1)	2(1)	2(1)	-2(1)
C(1)	136(3)	26(1)	19(1)	2(1)	8(2)	11(2)
C(2)	51(1)	21(1)	19(1)	5(1)	-3(1)	1(1)
C(3)	25(1)	18(1)	21(1)	2(1)	-5(1)	4(1)
C(4)	16(1)	19(1)	19(1)	-1(1)	-2(1)	-1(1)
C(5)	14(1)	14(1)	16(1)	-1(1)	2(1)	-1(1)
C(6)	17(1)	12(1)	15(1)	2(1)	1(1)	2(1)
C(7)	18(1)	13(1)	26(1)	0(1)	4(1)	0(1)
C(8)	19(1)	16(1)	21(1)	-1(1)	5(1)	-1(1)
C(9)	21(1)	13(1)	14(1)	-2(1)	4(1)	-1(1)
C(10)	21(1)	17(1)	21(1)	-2(1)	6(1)	-1(1)
C(11)	30(1)	18(1)	26(1)	1(1)	12(1)	-5(1)
C(12)	50(1)	18(1)	17(1)	4(1)	3(1)	-4(1)
C(13)	43(1)	25(1)	21(1)	4(1)	-11(1)	-4(1)
C(14)	28(1)	19(1)	20(1)	2(1)	-4(1)	-6(1)

Table S19. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($\approx^2 x\ 10^3$) for C14H15ClF3NO

	x	y	z	U(eq)
H(1N)	5700(30)	4410(20)	7198(13)	18(6)
H(1A)	7336	7819	8852	90
H(1B)	7982	7478	9693	90
H(1C)	6274	7257	9523	90
H(2)	7395	4964	9445	37
H(3)	8124	4219	8319	26
H(4A)	9384	6032	7551	21
H(4B)	8167	7158	7821	21
H(7A)	3167	6087	8251	23
H(7B)	3752	4541	7988	23
H(10)	9345	7828	6613	24
H(11)	9303	9618	5665	29

H(12)	7282	9867	4859	34
H(13)	5283	8323	4994	36
H(14)	5320	6512	5929	27

Table S20. Torsion angles [∞] for C14H15ClF3NO

C(1)-C(2)-C(3)-C(4)	0.6(5)
C(2)-C(3)-C(4)-C(5)	-121.3(2)
C(6)-N(1)-C(5)-C(8)	-178.66(15)
C(6)-N(1)-C(5)-C(9)	-63.5(2)
C(6)-N(1)-C(5)-C(4)	62.7(2)
C(3)-C(4)-C(5)-N(1)	34.3(2)
C(3)-C(4)-C(5)-C(8)	-81.80(19)
C(3)-C(4)-C(5)-C(9)	159.70(16)
C(5)-N(1)-C(6)-O(1)	5.9(3)
C(5)-N(1)-C(6)-C(7)	-175.28(15)
O(1)-C(6)-C(7)-Cl(1)	95.92(19)
N(1)-C(6)-C(7)-Cl(1)	-82.94(17)
N(1)-C(5)-C(8)-F(3)	171.25(14)
C(9)-C(5)-C(8)-F(3)	52.83(19)
C(4)-C(5)-C(8)-F(3)	-69.52(18)
N(1)-C(5)-C(8)-F(1)	50.98(18)
C(9)-C(5)-C(8)-F(1)	-67.44(18)
C(4)-C(5)-C(8)-F(1)	170.21(14)
N(1)-C(5)-C(8)-F(2)	-68.72(18)
C(9)-C(5)-C(8)-F(2)	172.86(15)
C(4)-C(5)-C(8)-F(2)	50.5(2)
N(1)-C(5)-C(9)-C(14)	-26.8(2)
C(8)-C(5)-C(9)-C(14)	87.8(2)
C(4)-C(5)-C(9)-C(14)	-151.82(17)
N(1)-C(5)-C(9)-C(10)	156.11(16)
C(8)-C(5)-C(9)-C(10)	-89.28(19)
C(4)-C(5)-C(9)-C(10)	31.1(2)
C(14)-C(9)-C(10)-C(11)	-0.2(3)
C(5)-C(9)-C(10)-C(11)	176.87(16)

C(9)-C(10)-C(11)-C(12)	0.3(3)
C(10)-C(11)-C(12)-C(13)	-0.1(3)
C(11)-C(12)-C(13)-C(14)	-0.3(3)
C(10)-C(9)-C(14)-C(13)	-0.2(3)
C(5)-C(9)-C(14)-C(13)	-177.27(18)
C(12)-C(13)-C(14)-C(9)	0.5(3)

Symmetry transformations used to generate equivalent atoms:

Table S21. Hydrogen bonds for C14H15ClF3NO [≈ and ∞].

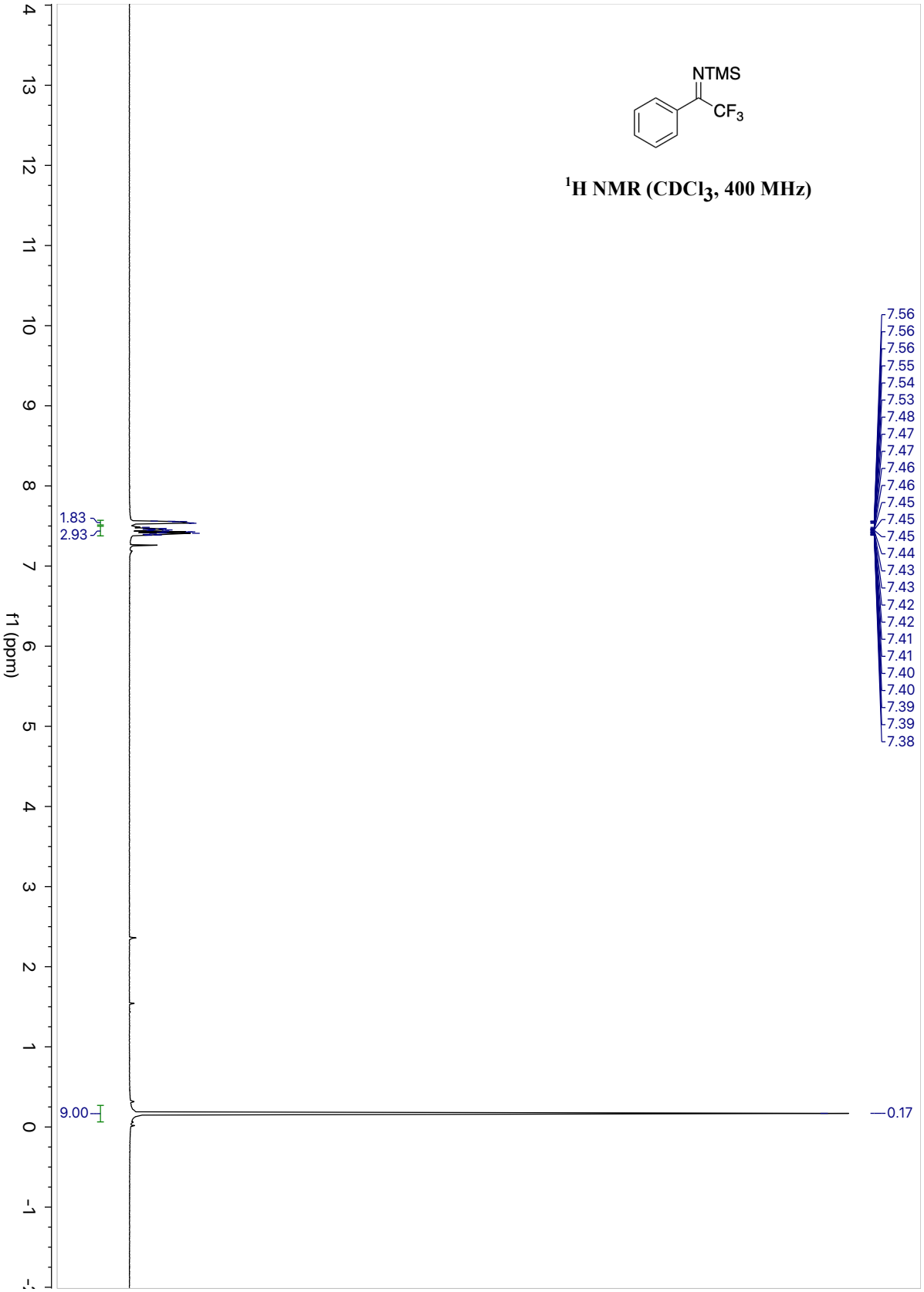
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.864(19)	2.03(2)	2.879(2)	166(2)

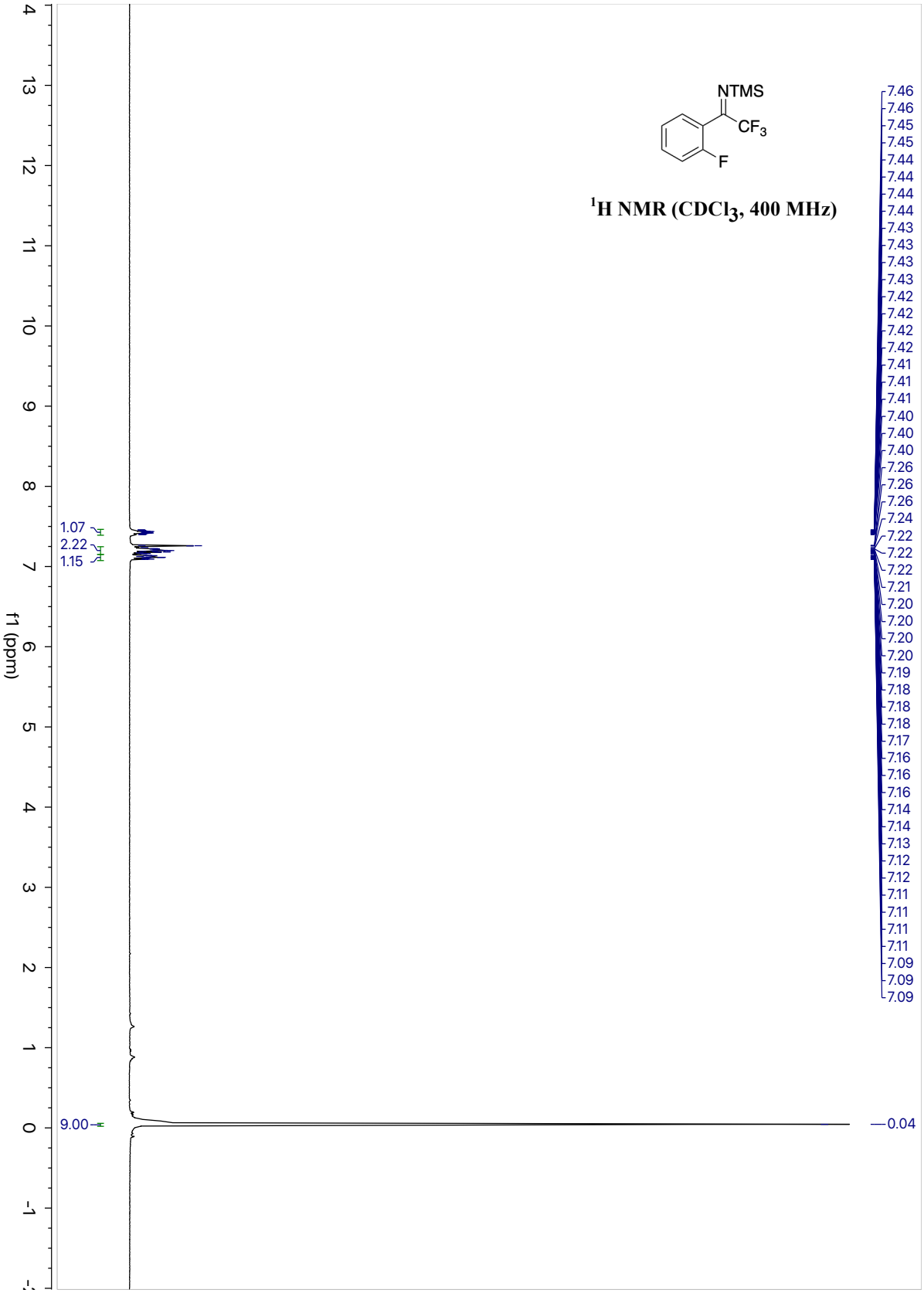
Symmetry transformations used to generate equivalent atoms:

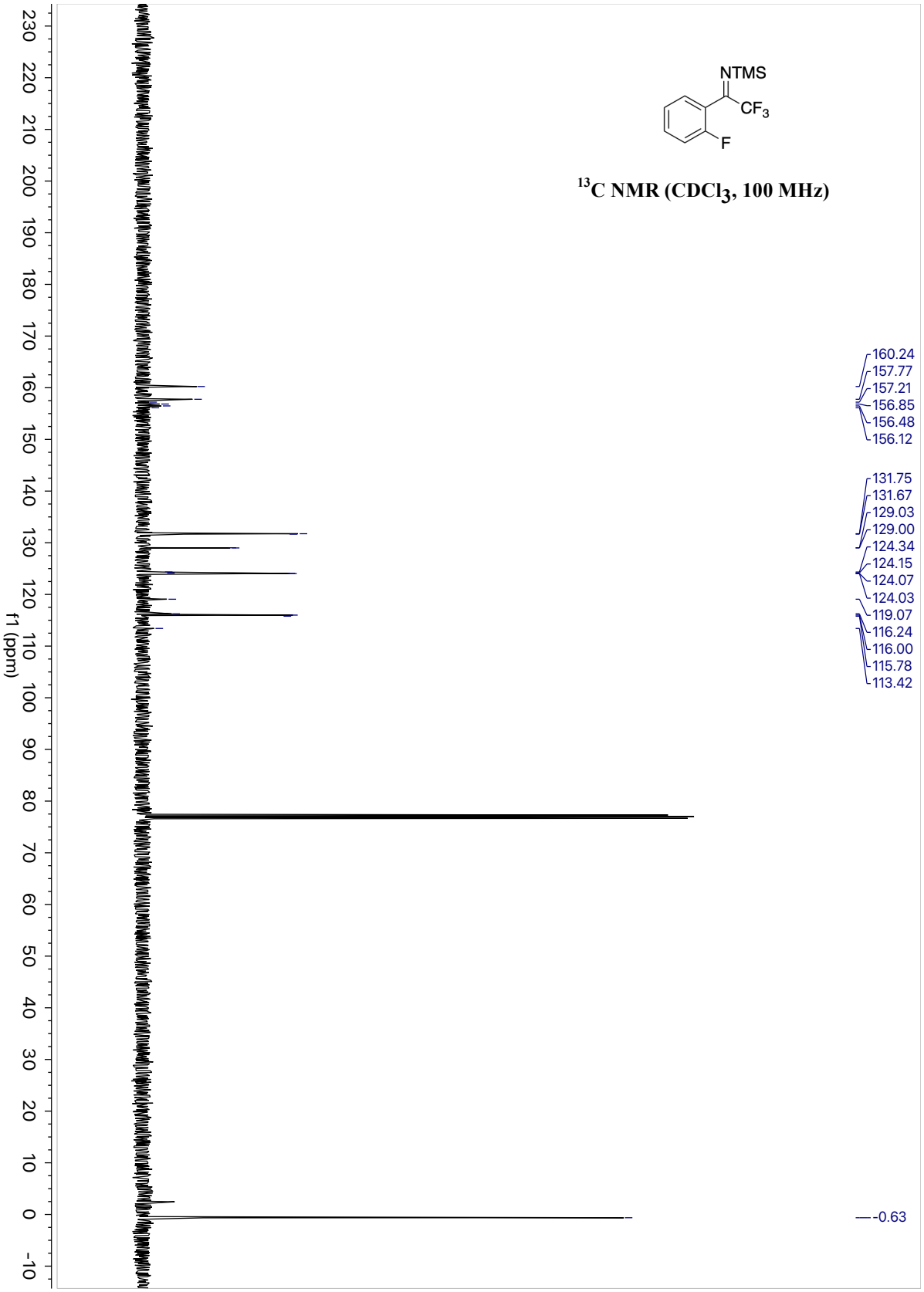
#1 -x+1, y-1/2, -z+3/2

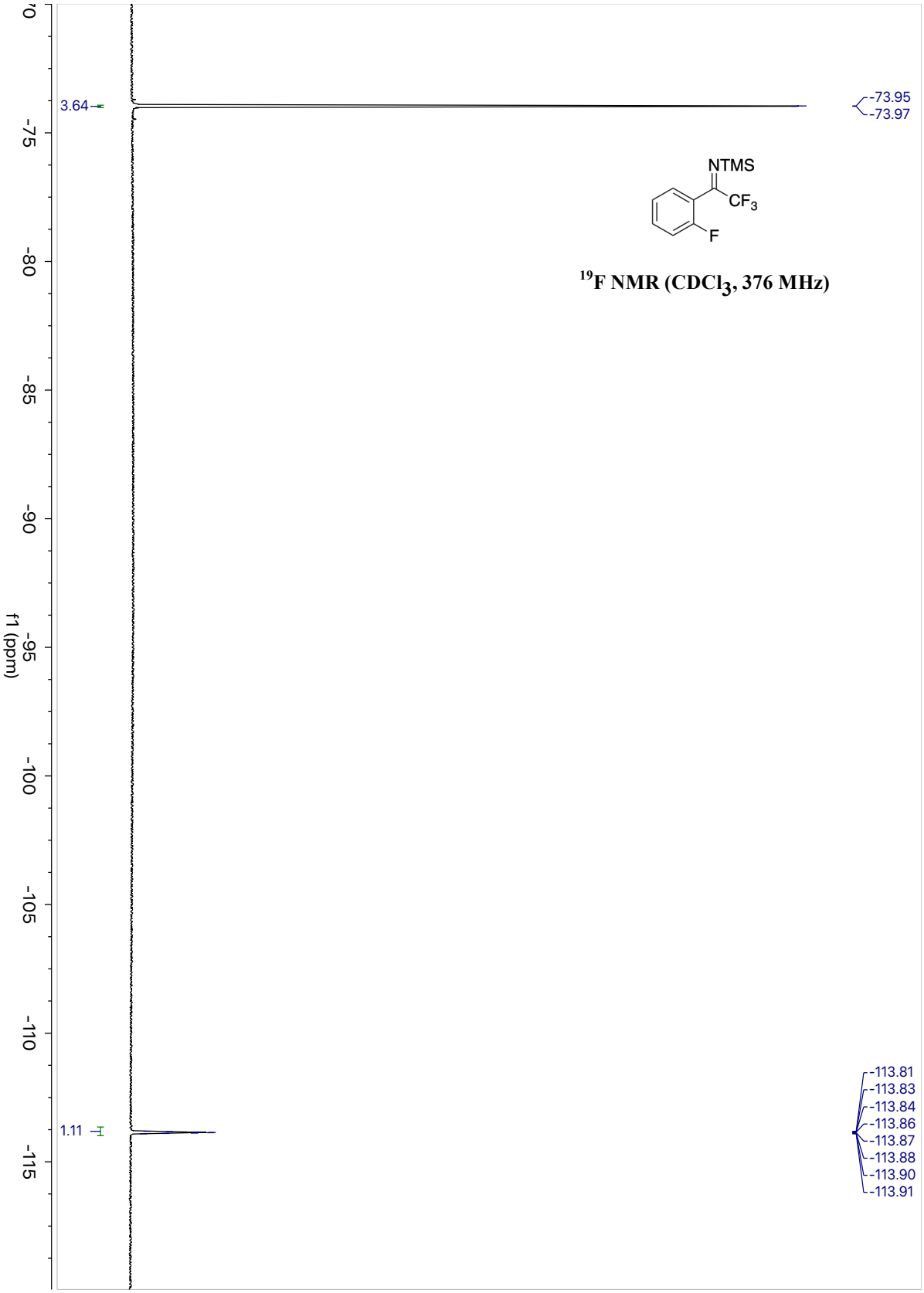
2.7.14 NMR Spectra

NMR spectra appear on the following pages:

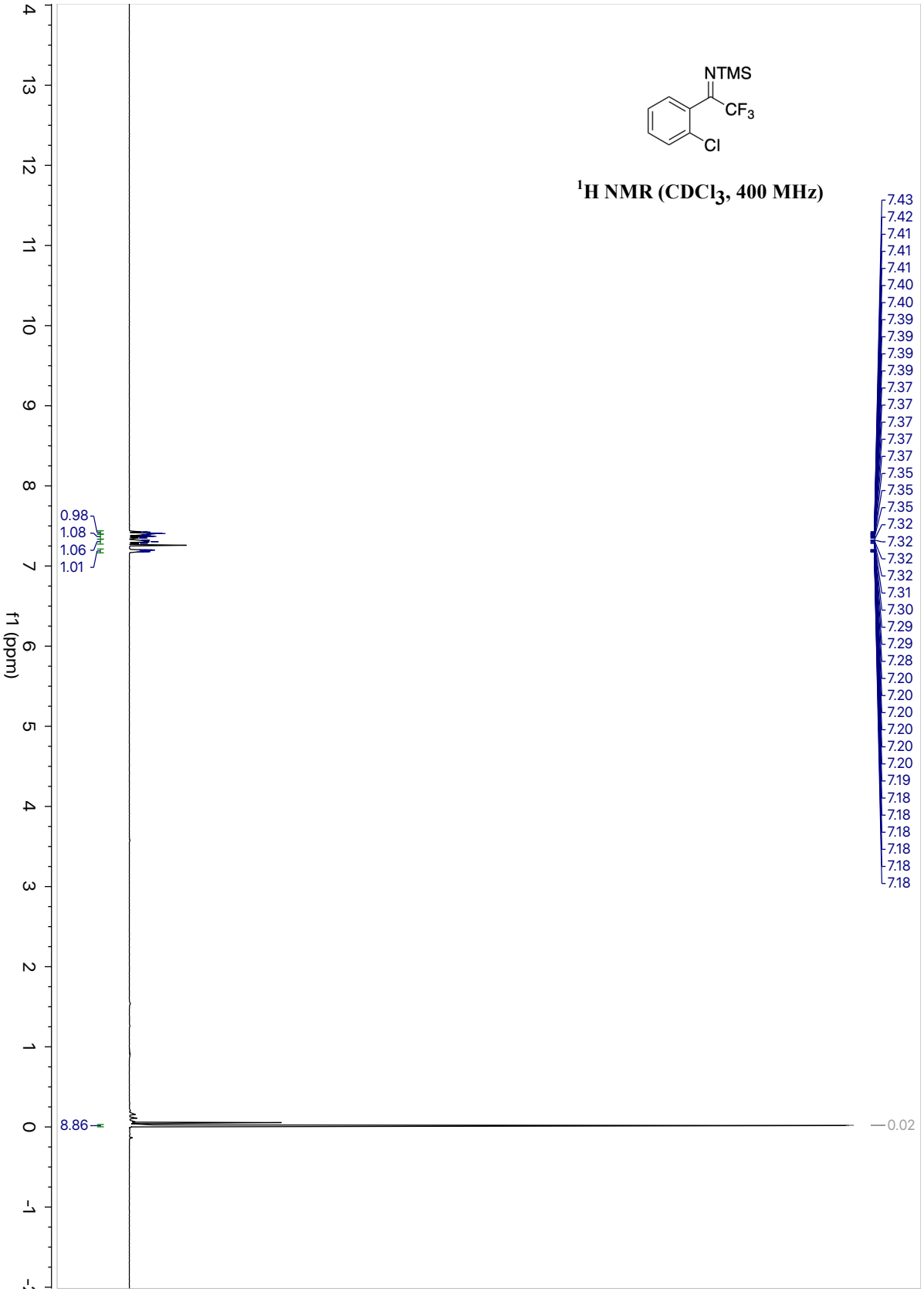

NTMS
CF3
1H NMR (CDCl3, 400 MHz)
7.56
7.56
7.56
7.55
7.54
7.53
7.48
7.47
7.47
7.46
7.46
7.45
7.45
7.45
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.38
1.83
2.93
9.00
0.17
f1 (ppm)

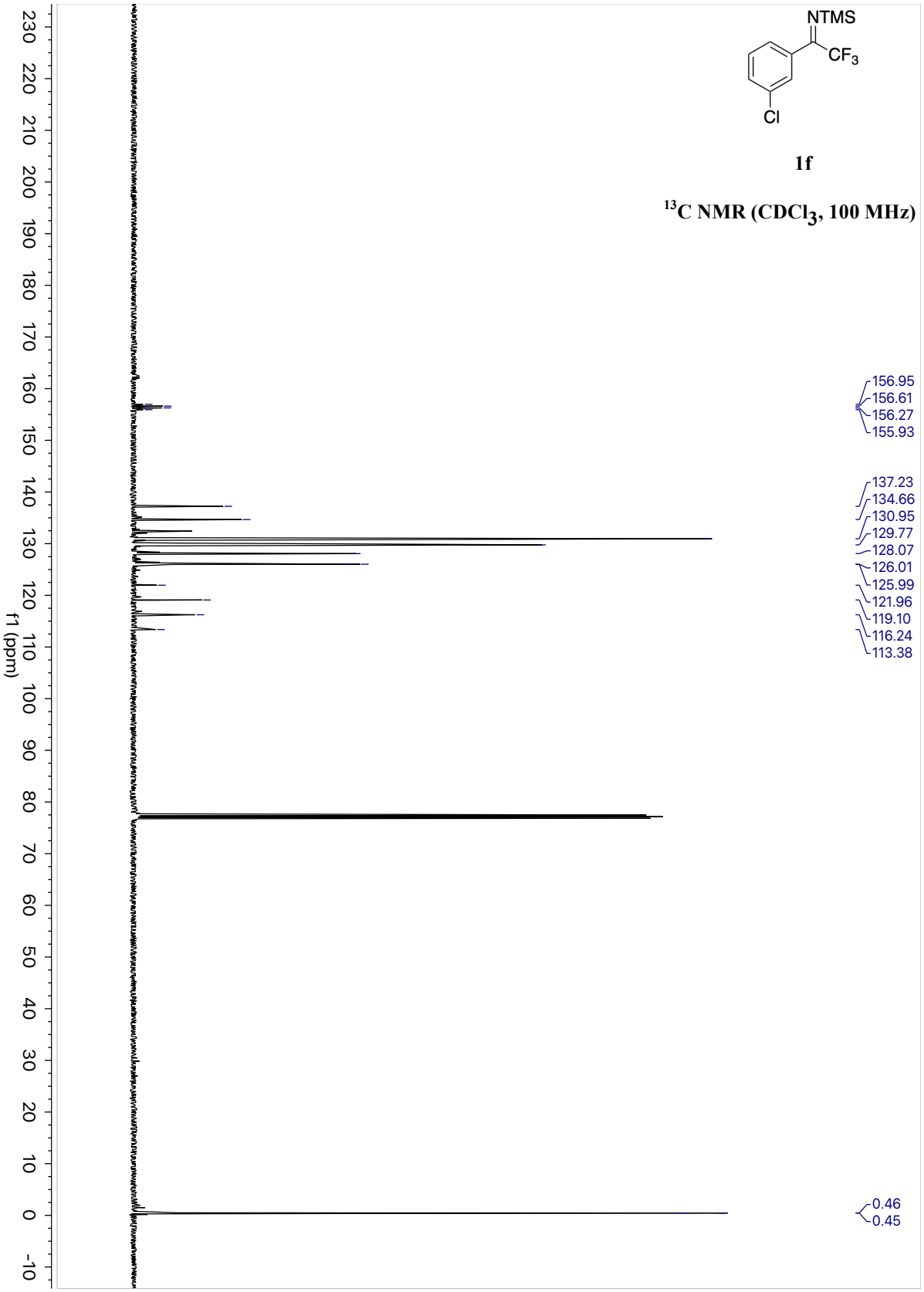

NTMS
CF3
F
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.07
2.22
1.15
9.00
0.04

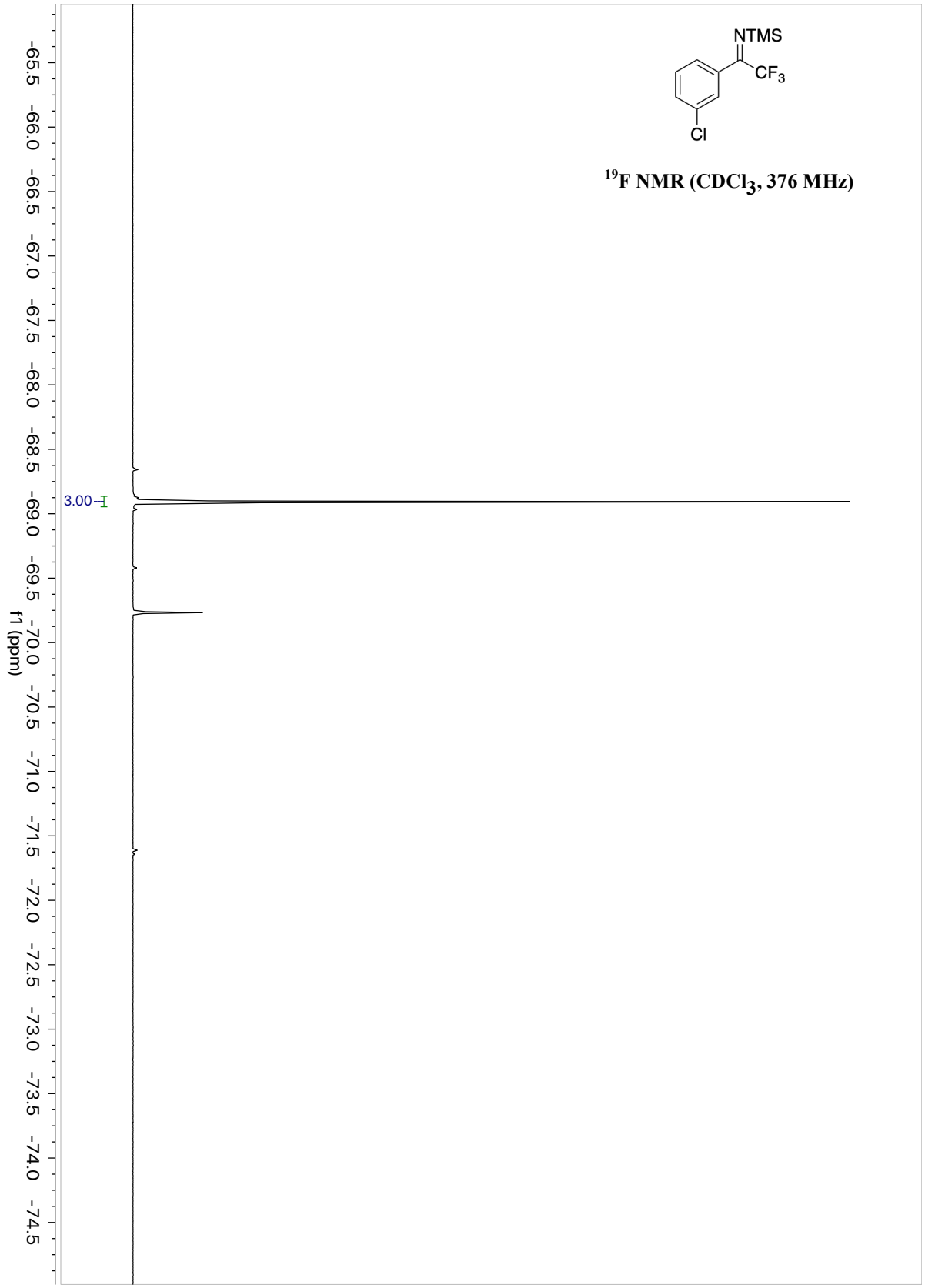

NTMS
CF3
F
13C NMR (CDCl3, 100 MHz)
160.24
157.77
157.21
156.85
156.48
156.12
131.75
131.67
129.03
129.00
124.34
124.15
124.07
124.03
119.07
116.24
116.00
115.78
113.42
-0.63
f1 (ppm)



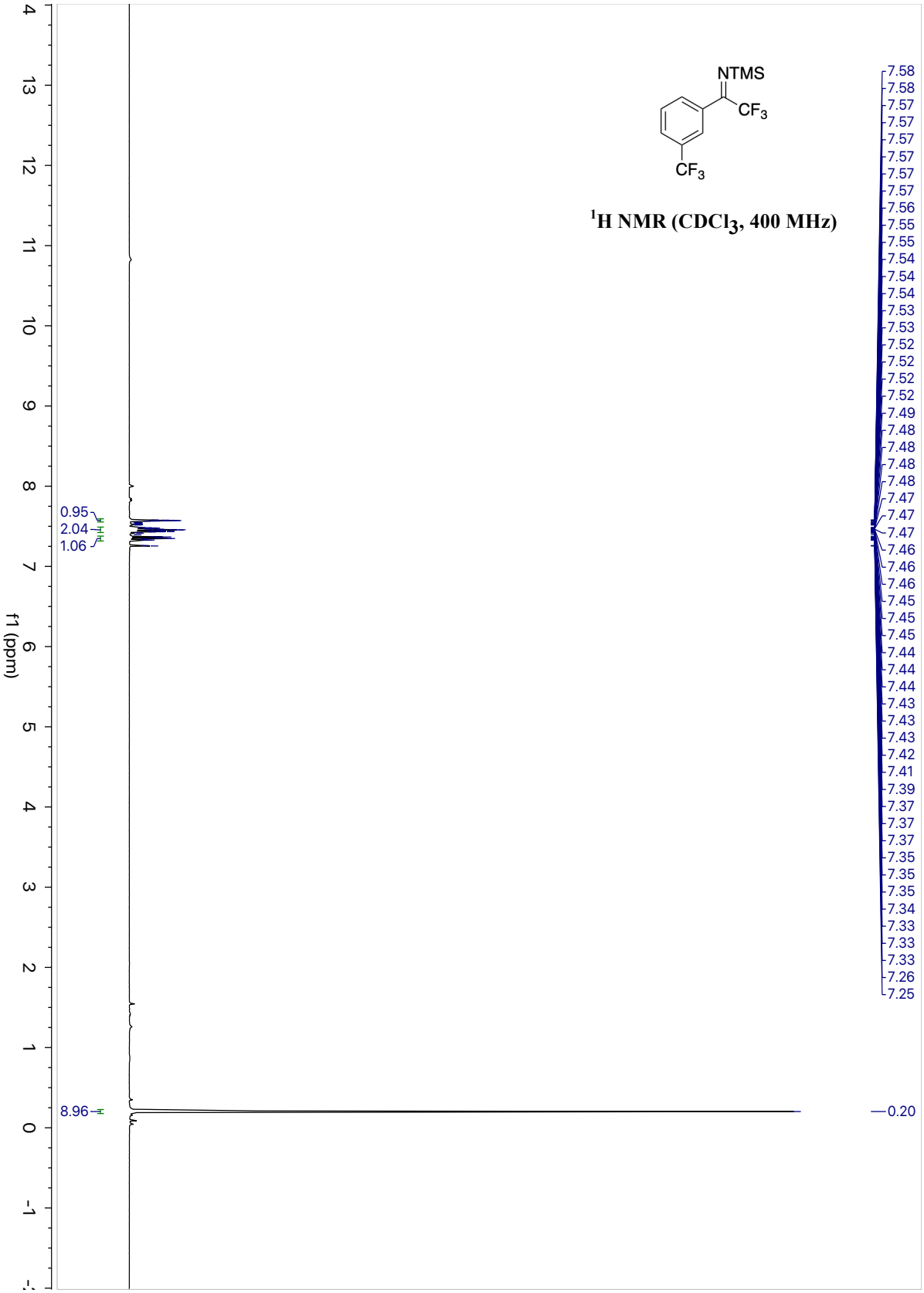
^{19}F NMR ($CDCl_3$, 376 MHz)


NTMS
CF3
Cl
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.98
1.08
1.06
1.01
8.86
0.02
7.43
7.42
7.41
7.41
7.41
7.40
7.40
7.39
7.39
7.39
7.39
7.37
7.37
7.37
7.37
7.37
7.35
7.35
7.35
7.32
7.32
7.32
7.32
7.31
7.30
7.29
7.29
7.28
7.20
7.20
7.20
7.20
7.20
7.20
7.19
7.18
7.18
7.18
7.18
7.18
7.18


NTMS
CF3
Cl
1f
13C NMR (CDCl3, 100 MHz)
156.95
156.61
156.27
155.93
137.23
134.66
130.95
129.77
128.07
126.01
125.99
121.96
119.10
116.24
113.38
0.46
0.45
f1 (ppm)



^{19}F NMR ($CDCl_3$, 376 MHz)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CF3
CF3
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
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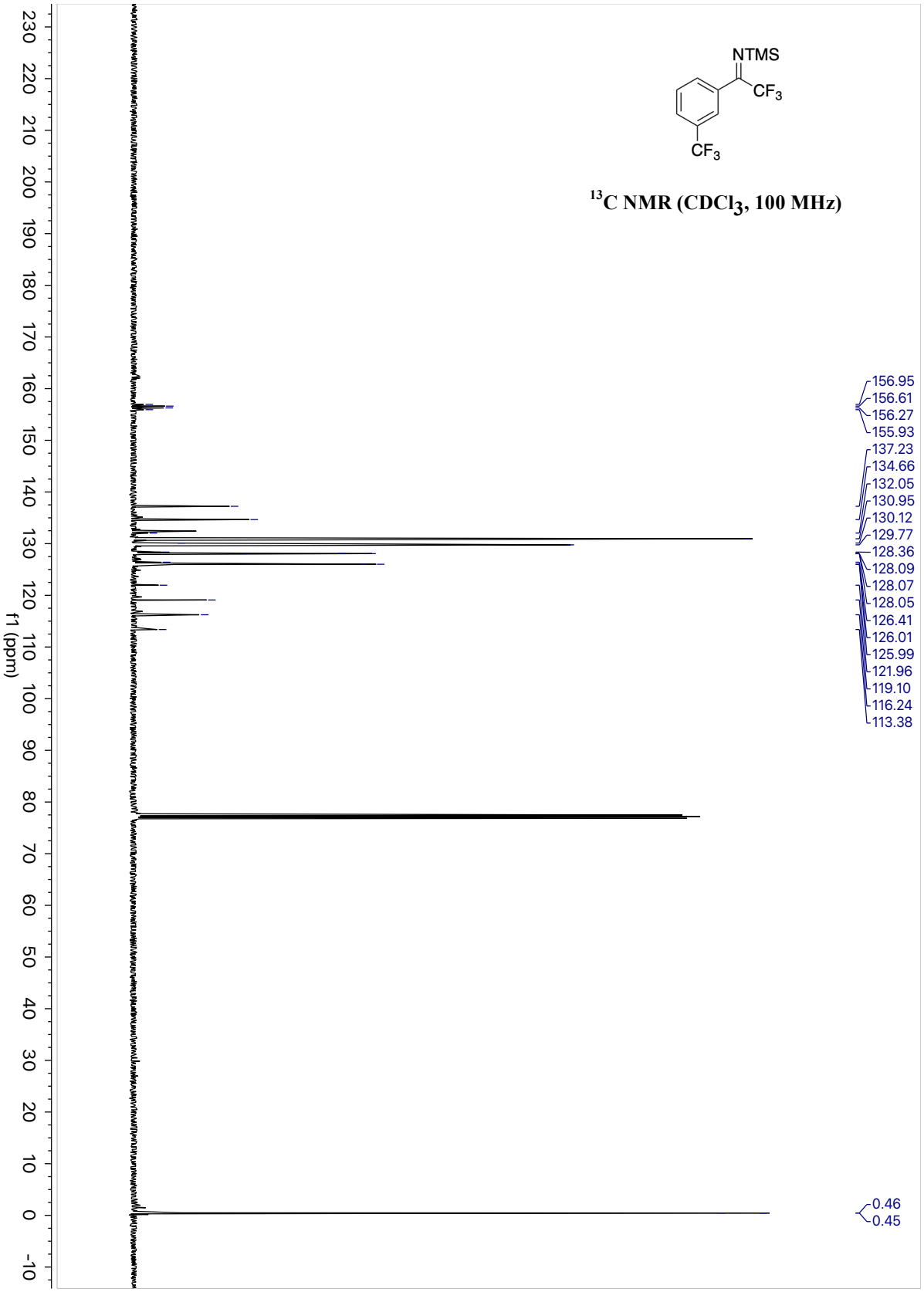
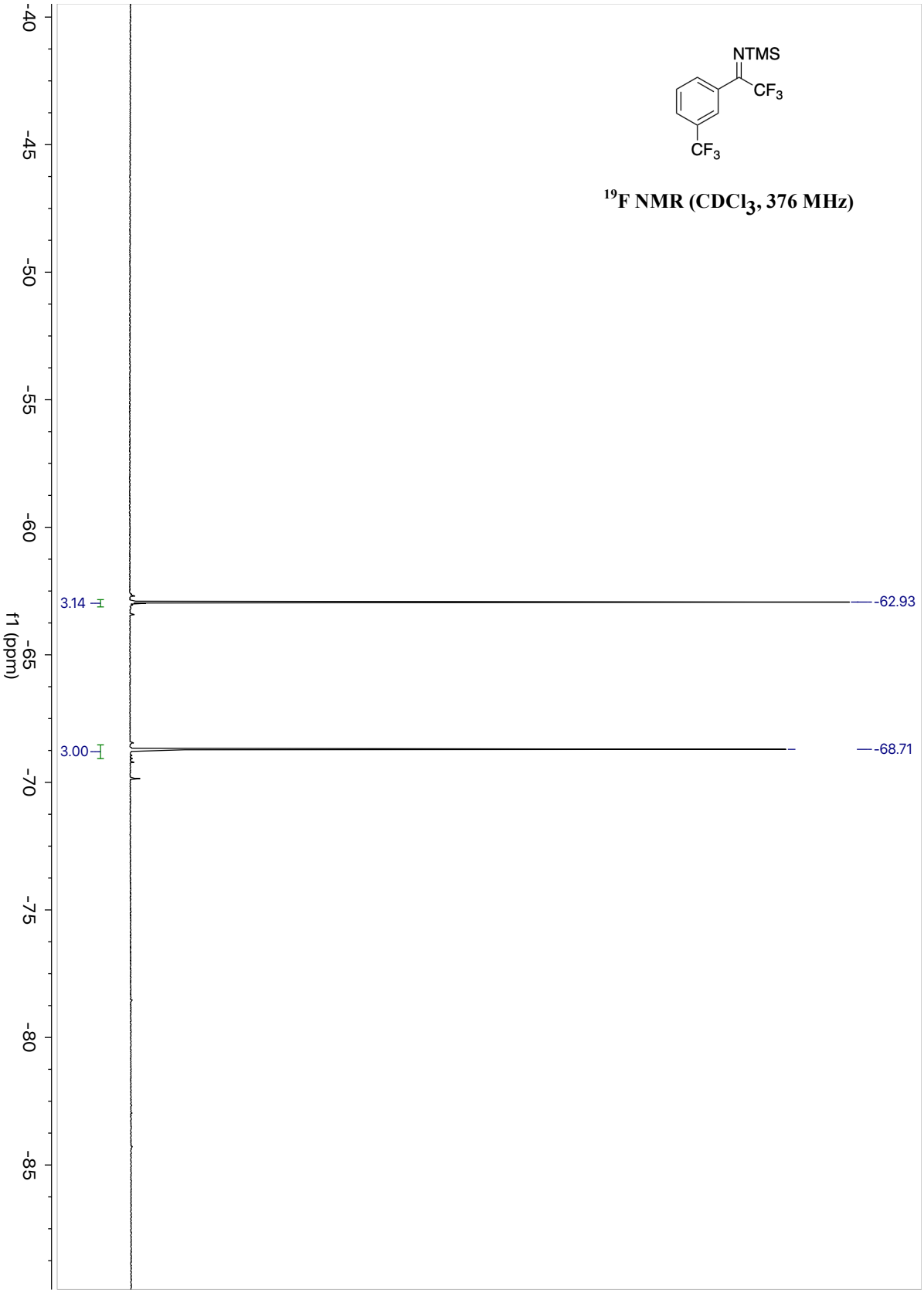
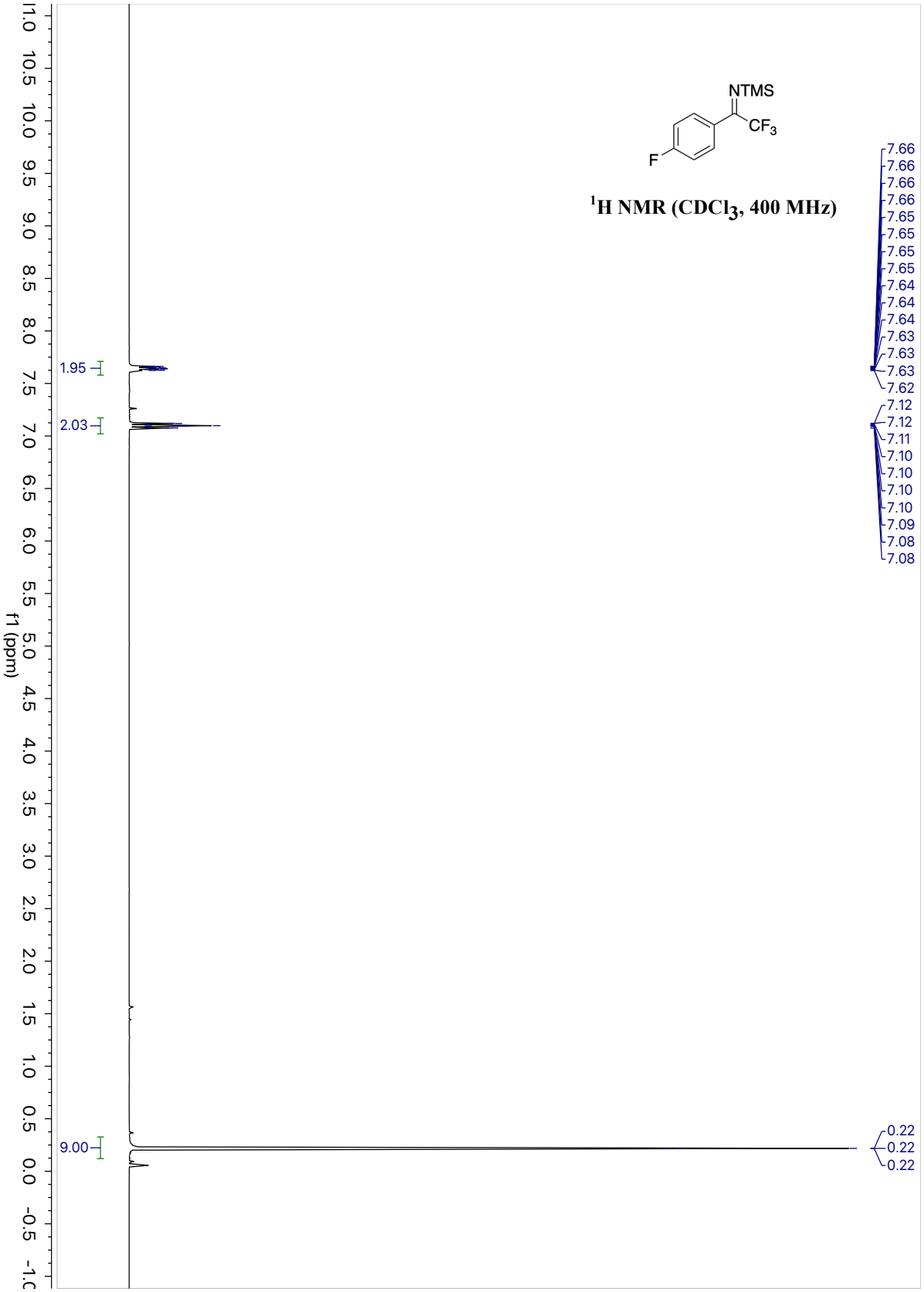
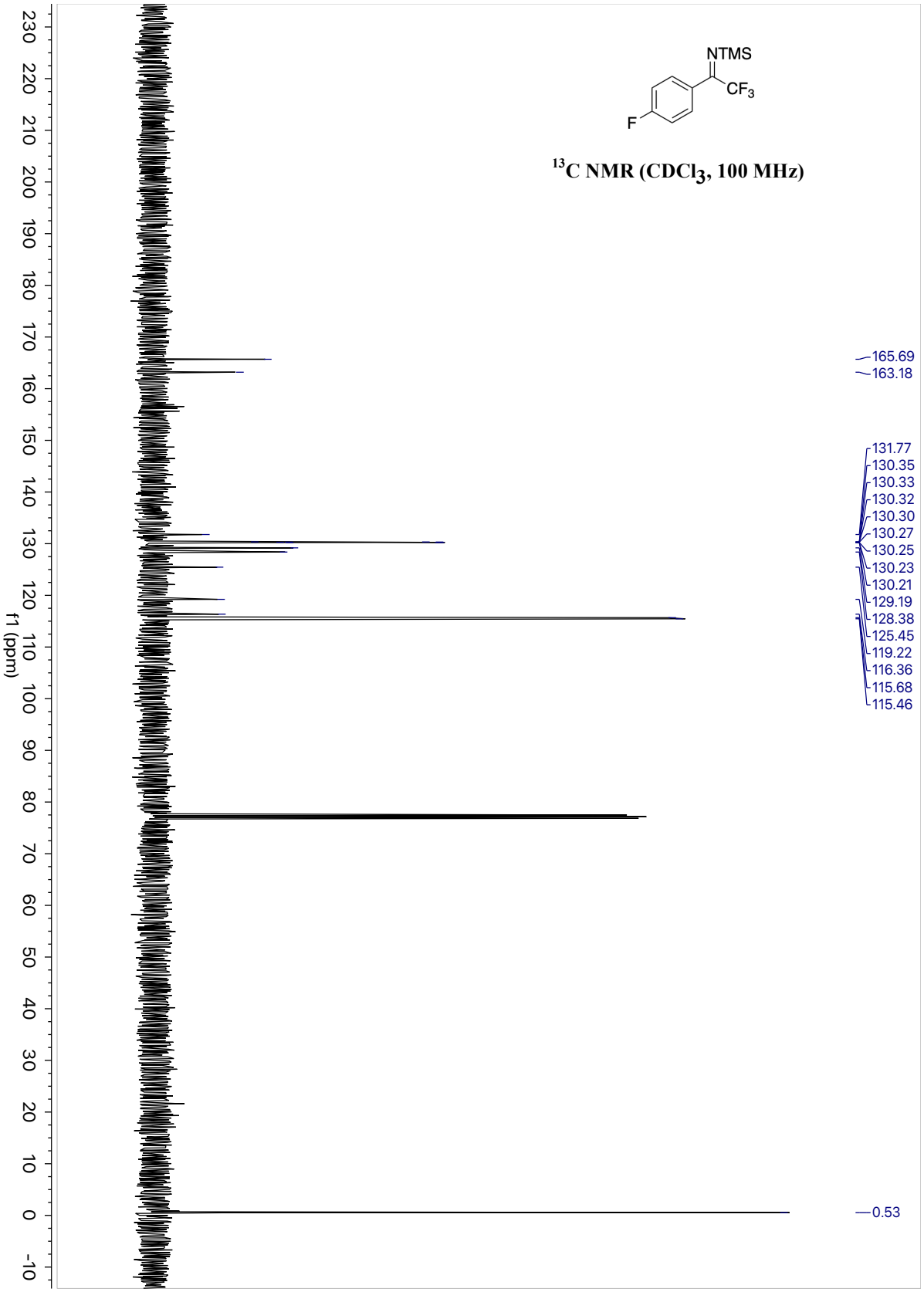
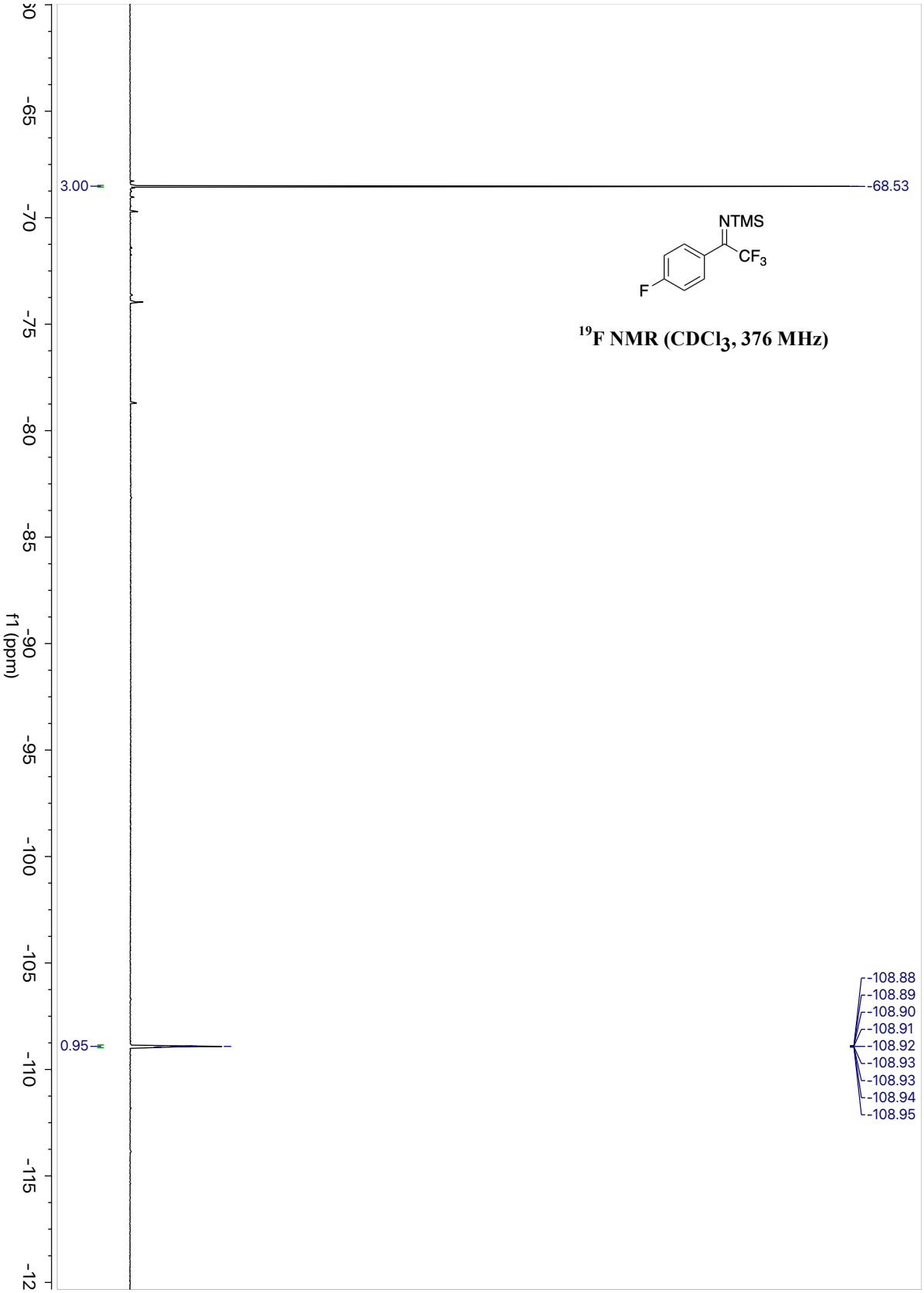
2.04
1.06
8.96
0.20


NTMS
CF3
CF3
13C NMR (CDCl3, 100 MHz)
156.95
156.61
156.27
155.93
137.23
134.66
132.05
130.95
130.12
129.77
128.36
128.09
128.07
128.05
126.41
126.01
125.99
121.96
119.10
116.24
113.38
0.46
0.45
f1 (ppm)

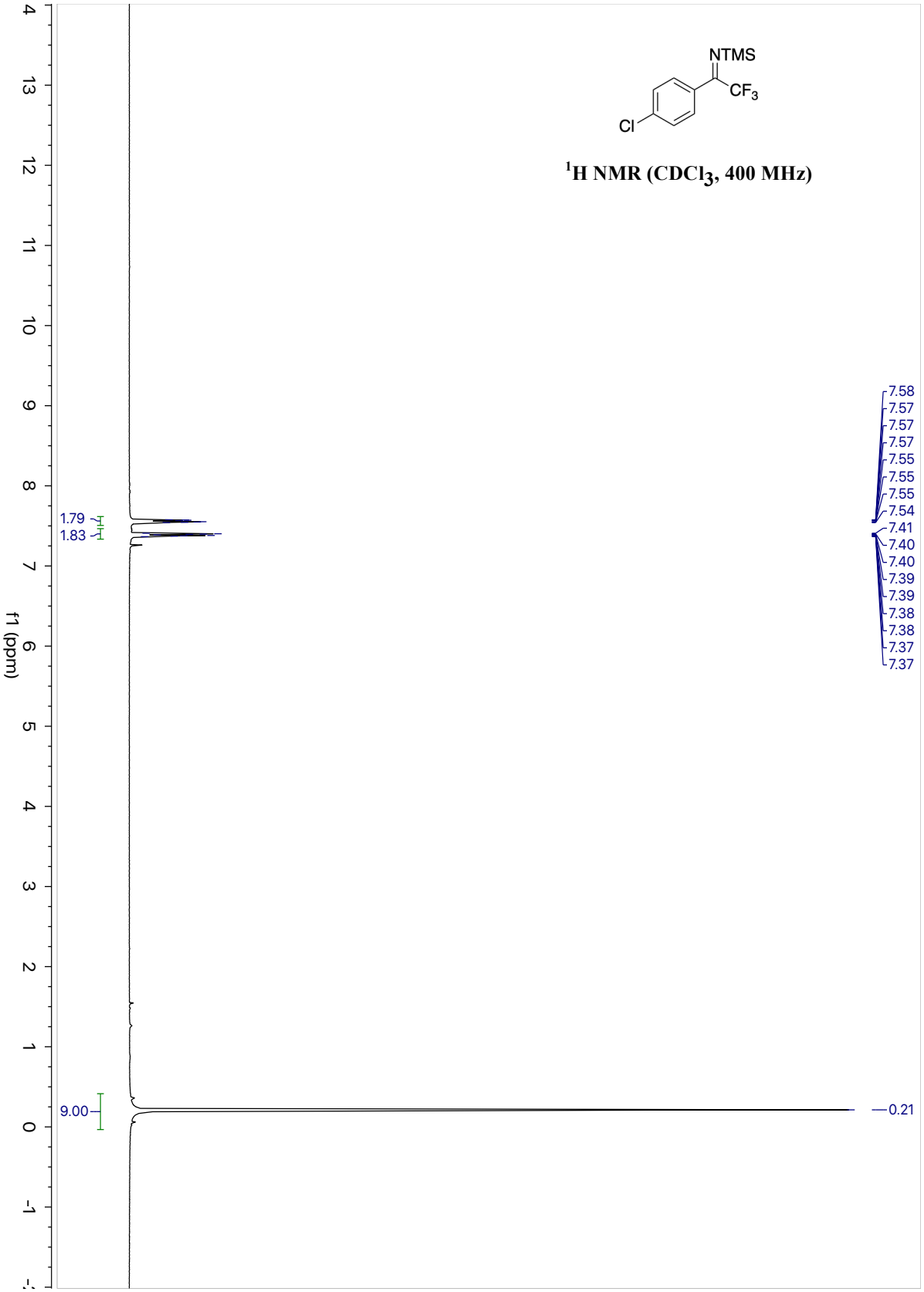

NTMS
CF3
CF3
19F NMR (CDCl3, 376 MHz)
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
f1 (ppm)
3.14
3.00
-62.93
-68.71

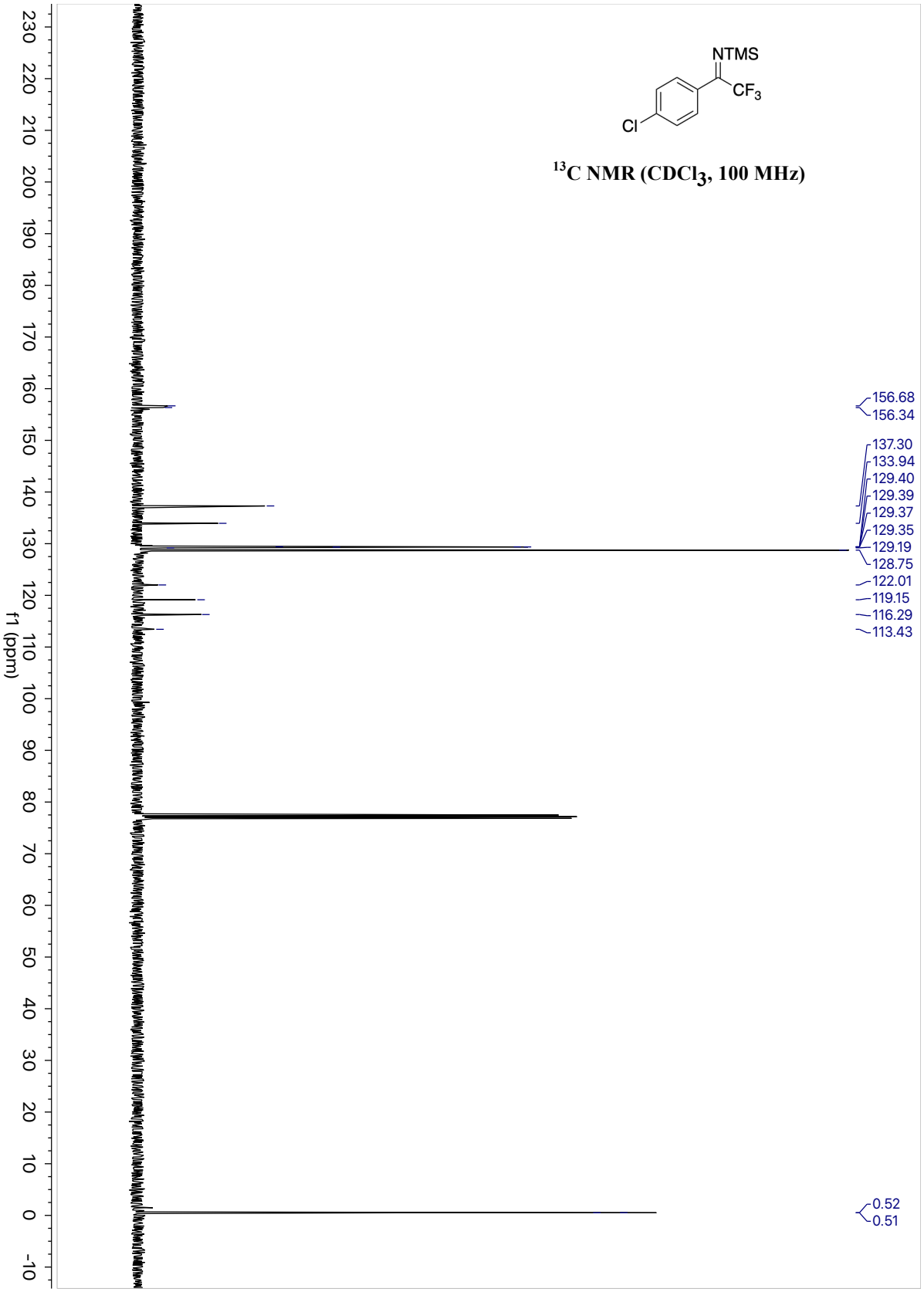

NTMS
CF3
F
1H NMR (CDCl3, 400 MHz)
7.66
7.66
7.66
7.66
7.65
7.65
7.65
7.65
7.64
7.64
7.64
7.63
7.63
7.63
7.62
7.12
7.12
7.11
7.10
7.10
7.10
7.10
7.09
7.08
7.08
1.95
2.03
9.00
0.22
0.22
0.22
f1 (ppm)

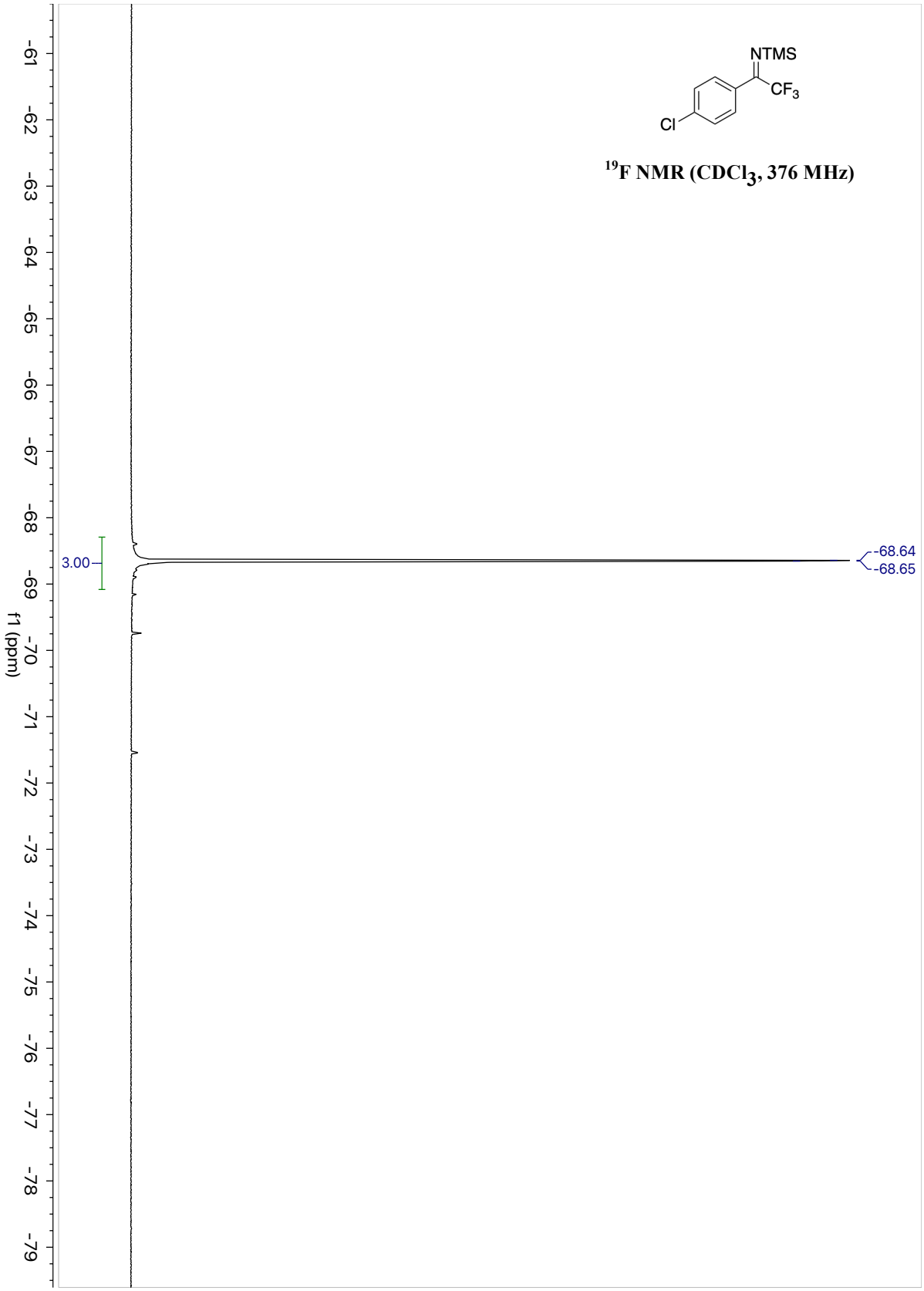

NTMS
CF3
F
13C NMR (CDCl3, 100 MHz)
165.69
163.18
131.77
130.35
130.33
130.32
130.30
130.27
130.25
130.23
130.21
129.19
128.38
125.45
119.22
116.36
115.68
115.46
0.53
f1 (ppm)



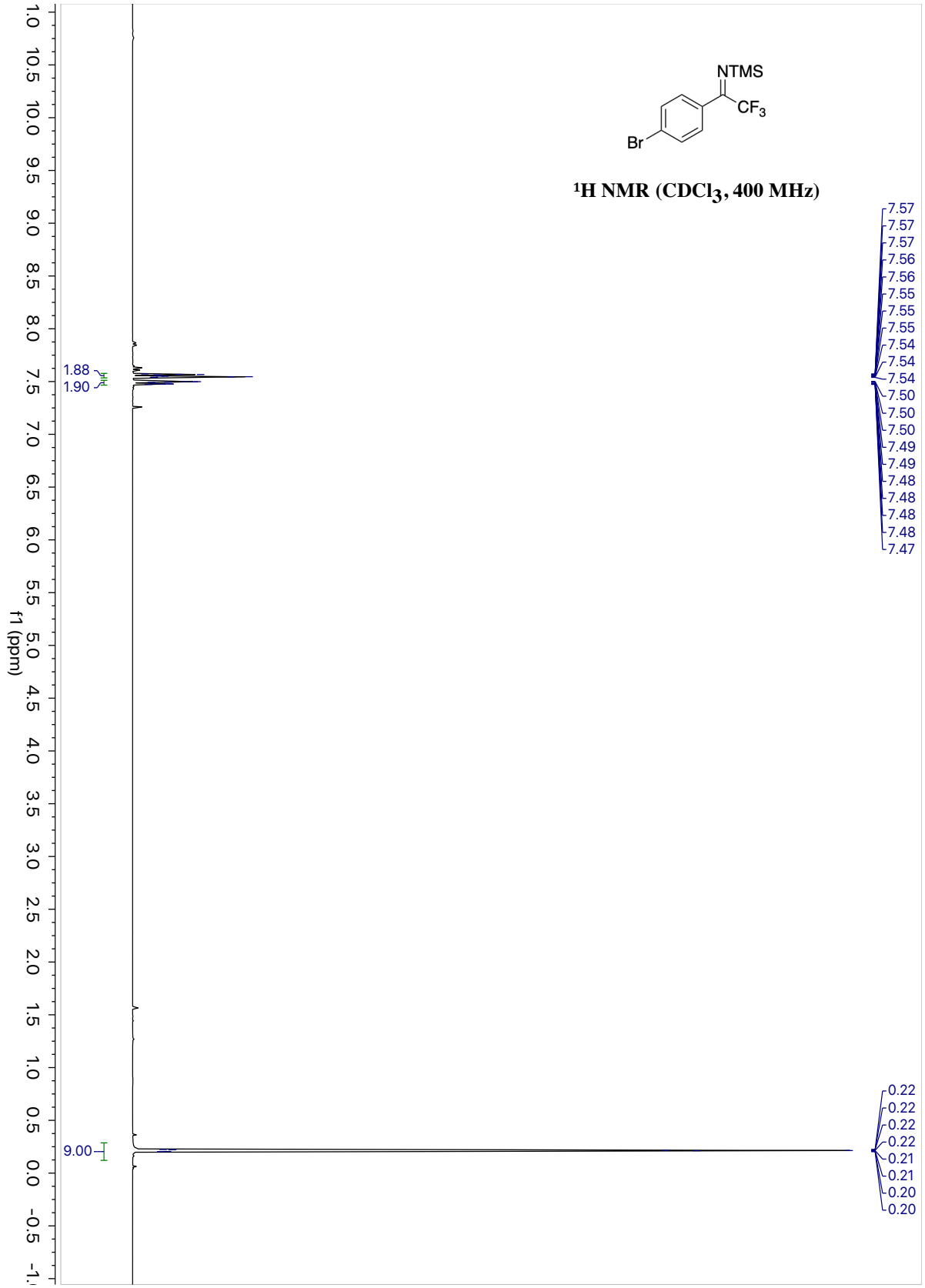
^{19}F NMR ($CDCl_3$, 376 MHz)

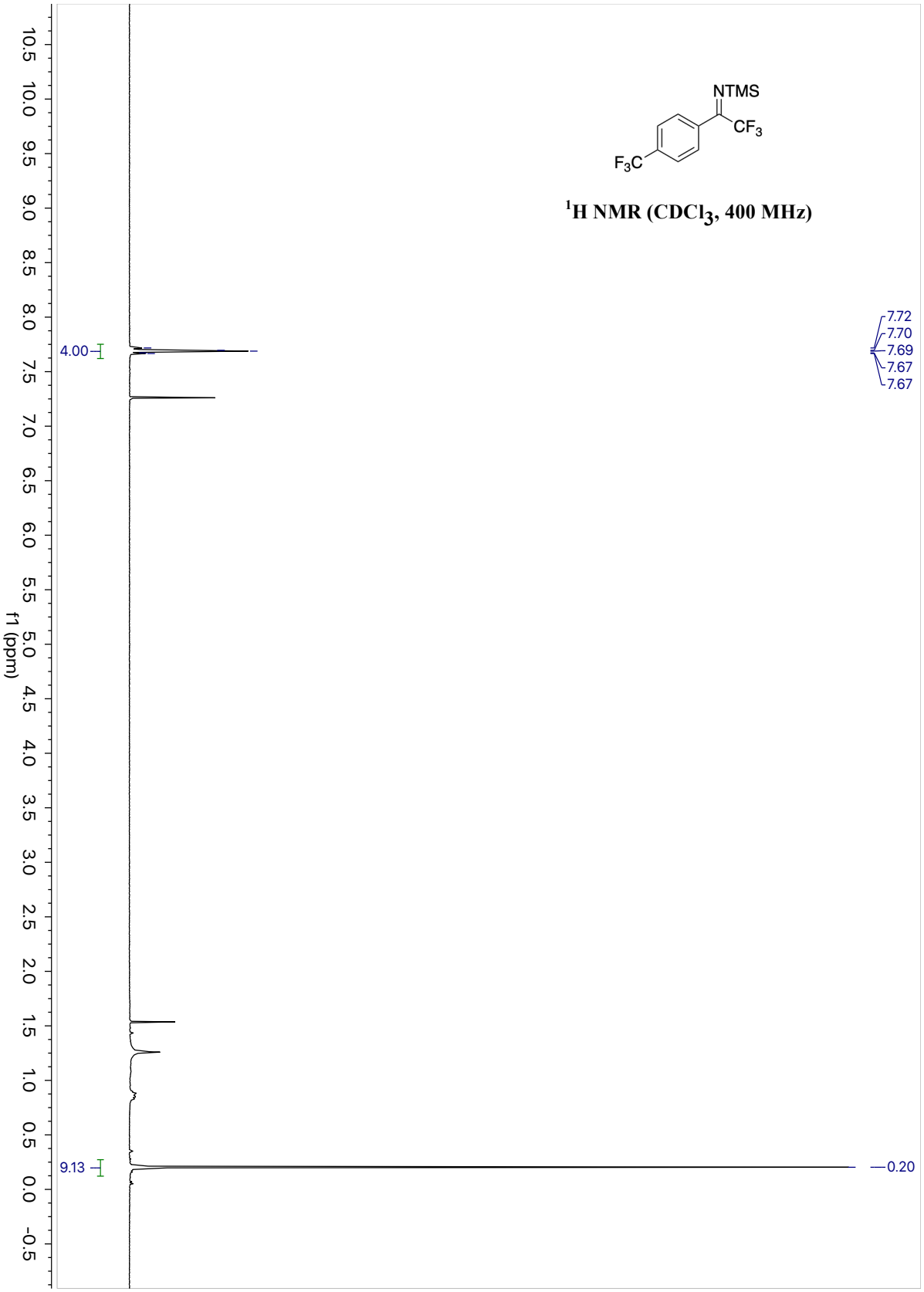

NTMS
CF3
Cl
1H NMR (CDCl3, 400 MHz)
7.58
7.57
7.57
7.57
7.55
7.55
7.55
7.54
7.41
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.37
1.79
1.83
9.00
0.21
f1 (ppm)

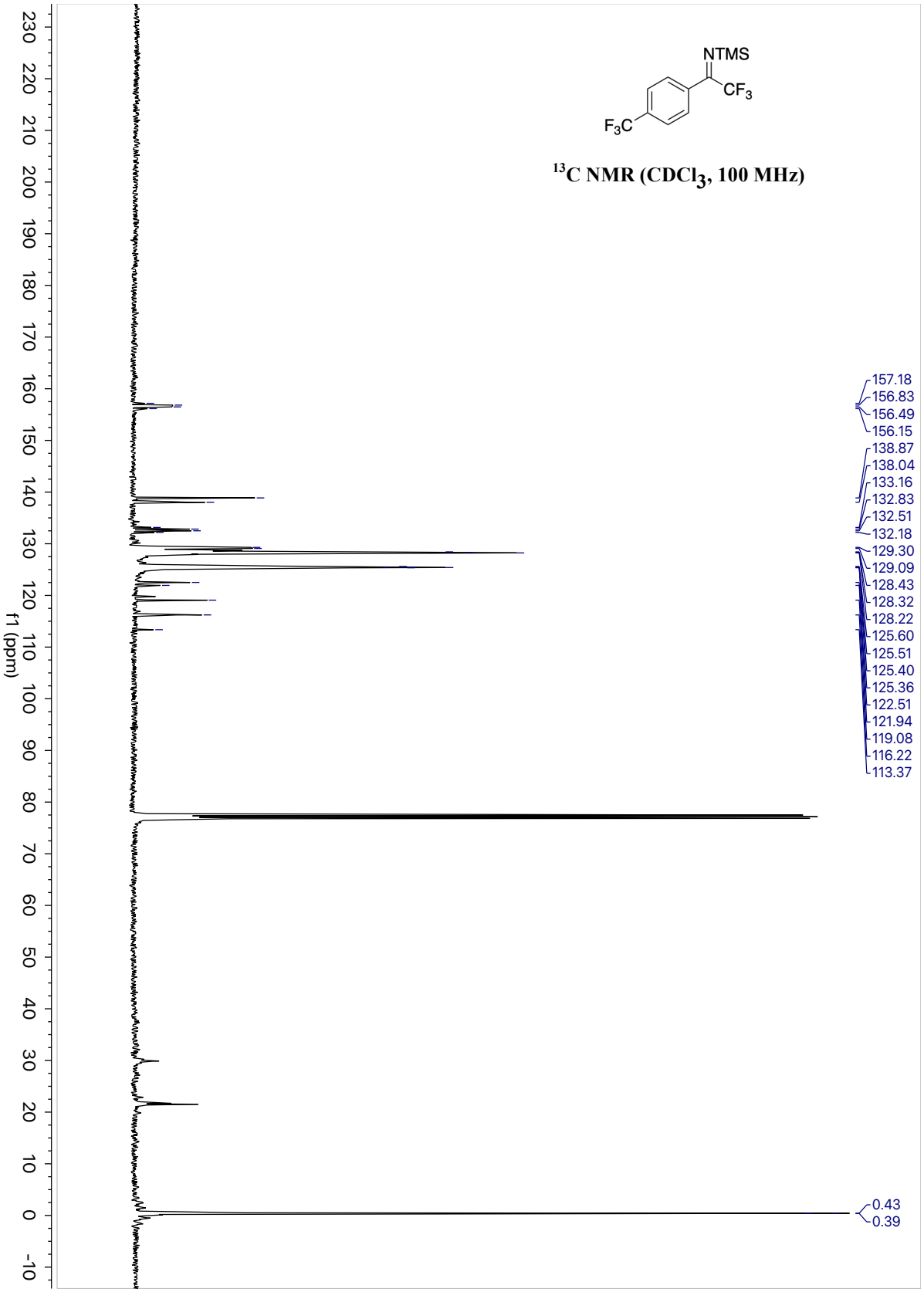

NTMS
CF3
Cl
13C NMR (CDCl3, 100 MHz)
156.68
156.34
137.30
133.94
129.40
129.39
129.37
129.35
129.19
128.75
122.01
119.15
116.29
113.43
0.52
0.51
f1 (ppm)

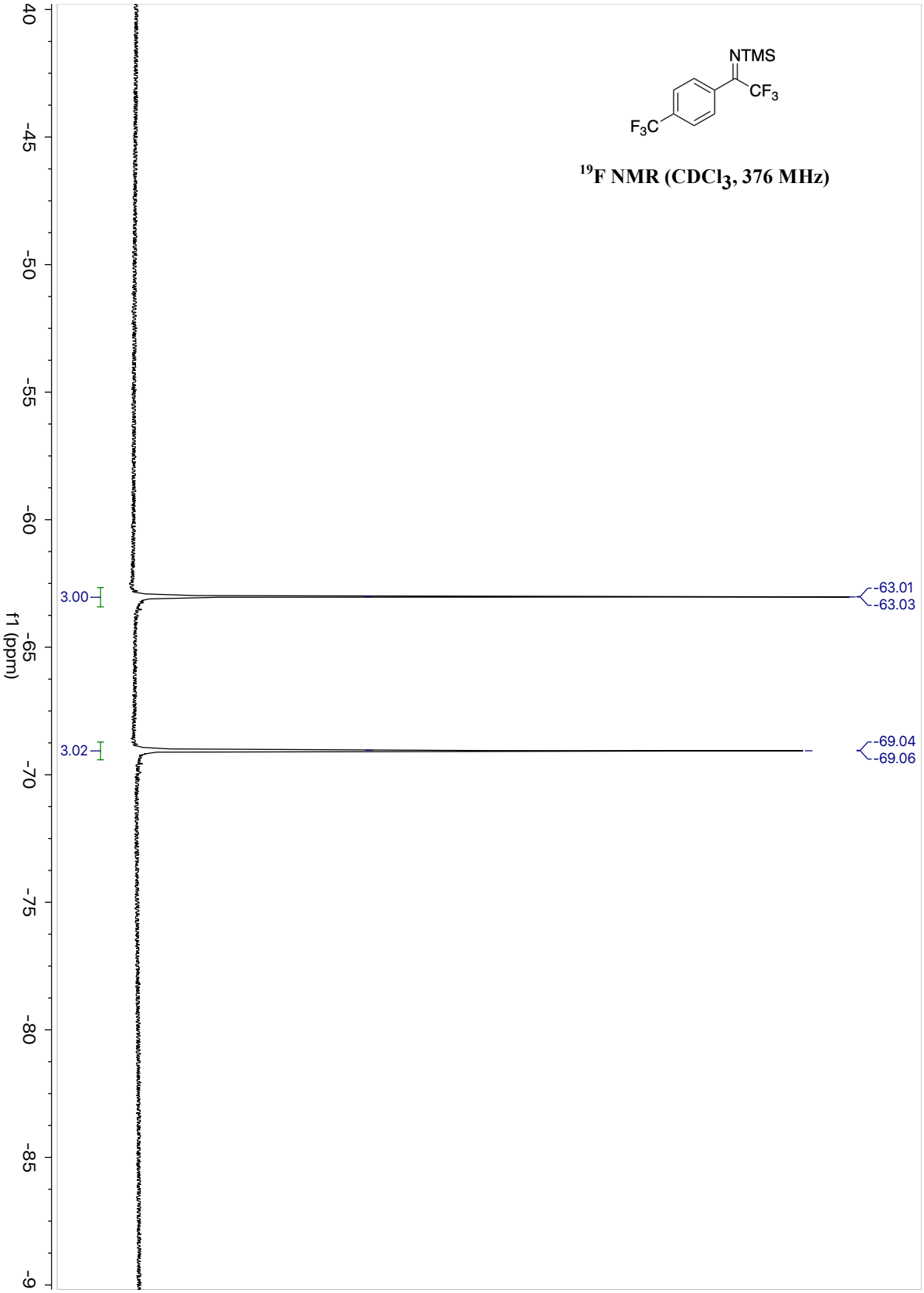


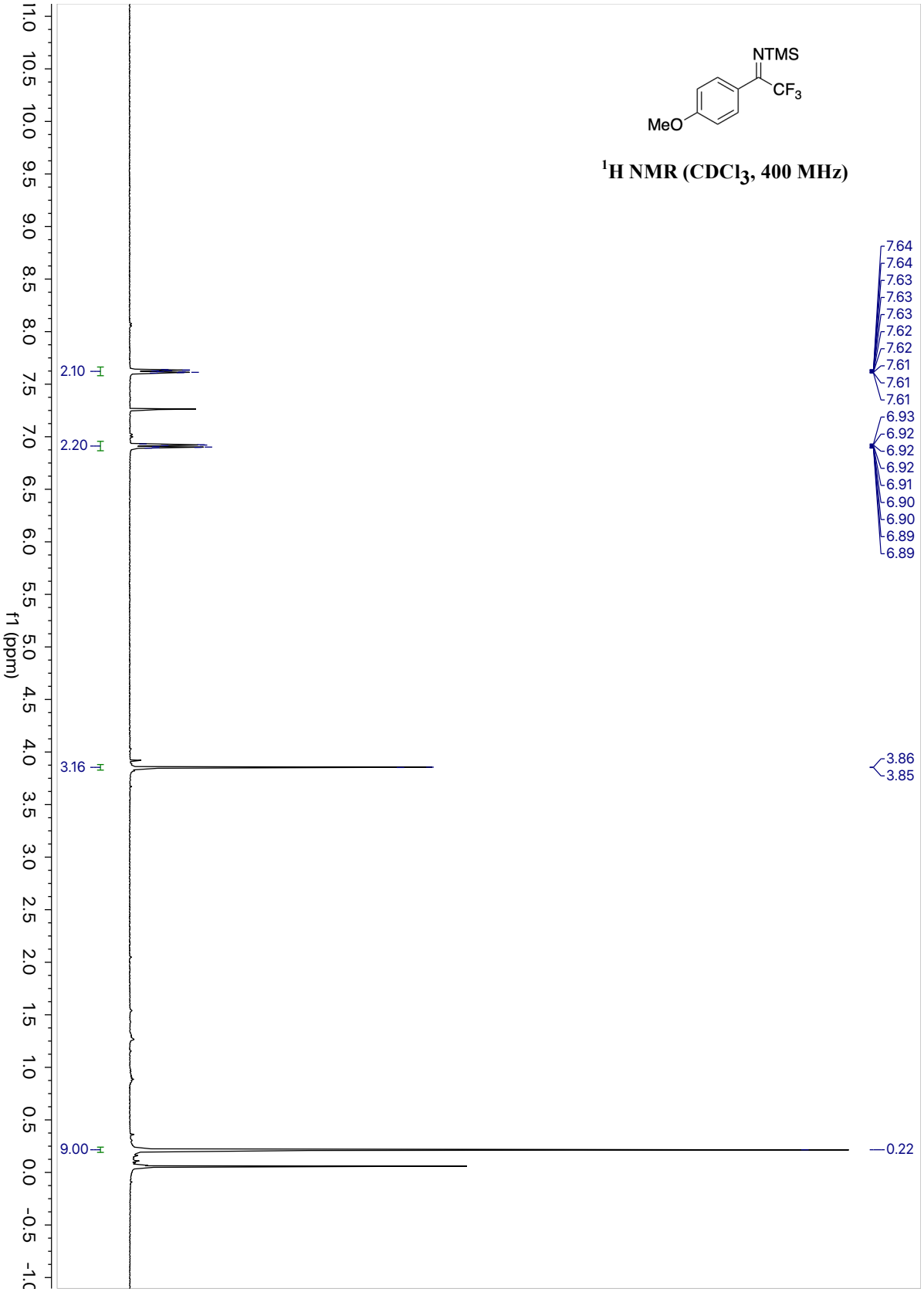
^{19}F NMR ($CDCl_3$, 376 MHz)

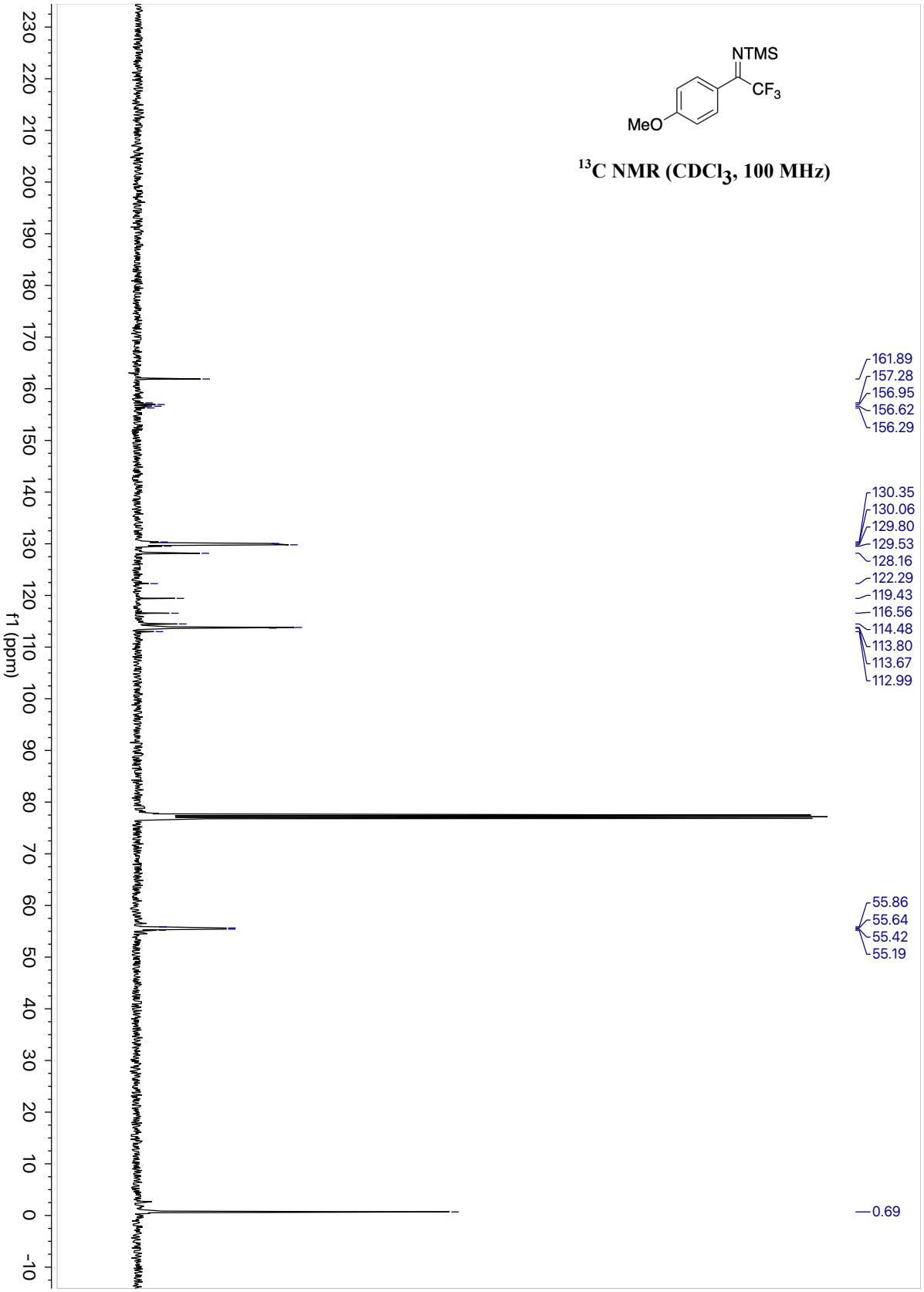

NTMS
CF3
Br
1H NMR (CDCl3, 400 MHz)
7.57
7.57
7.57
7.56
7.56
7.55
7.55
7.55
7.54
7.54
7.54
7.50
7.50
7.50
7.49
7.49
7.48
7.48
7.48
7.48
7.47
1.88
1.90
9.00
0.22
0.22
0.22
0.22
0.21
0.21
0.20
0.20
f1 (ppm)

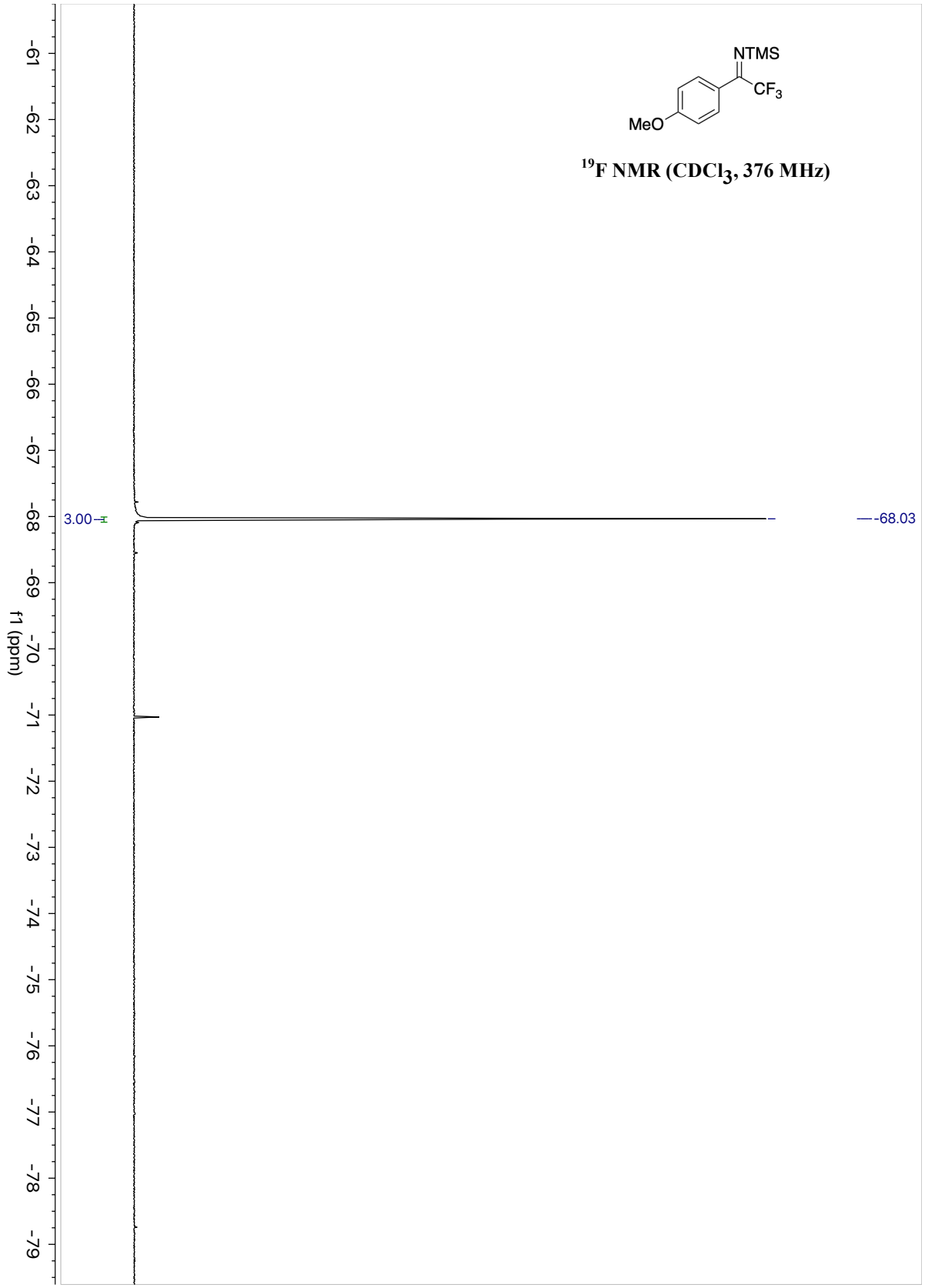

NTMS
CF3
F3C
1H NMR (CDCl3, 400 MHz)
7.72
7.70
7.69
7.67
7.67
4.00
9.13
0.20
f1 (ppm)

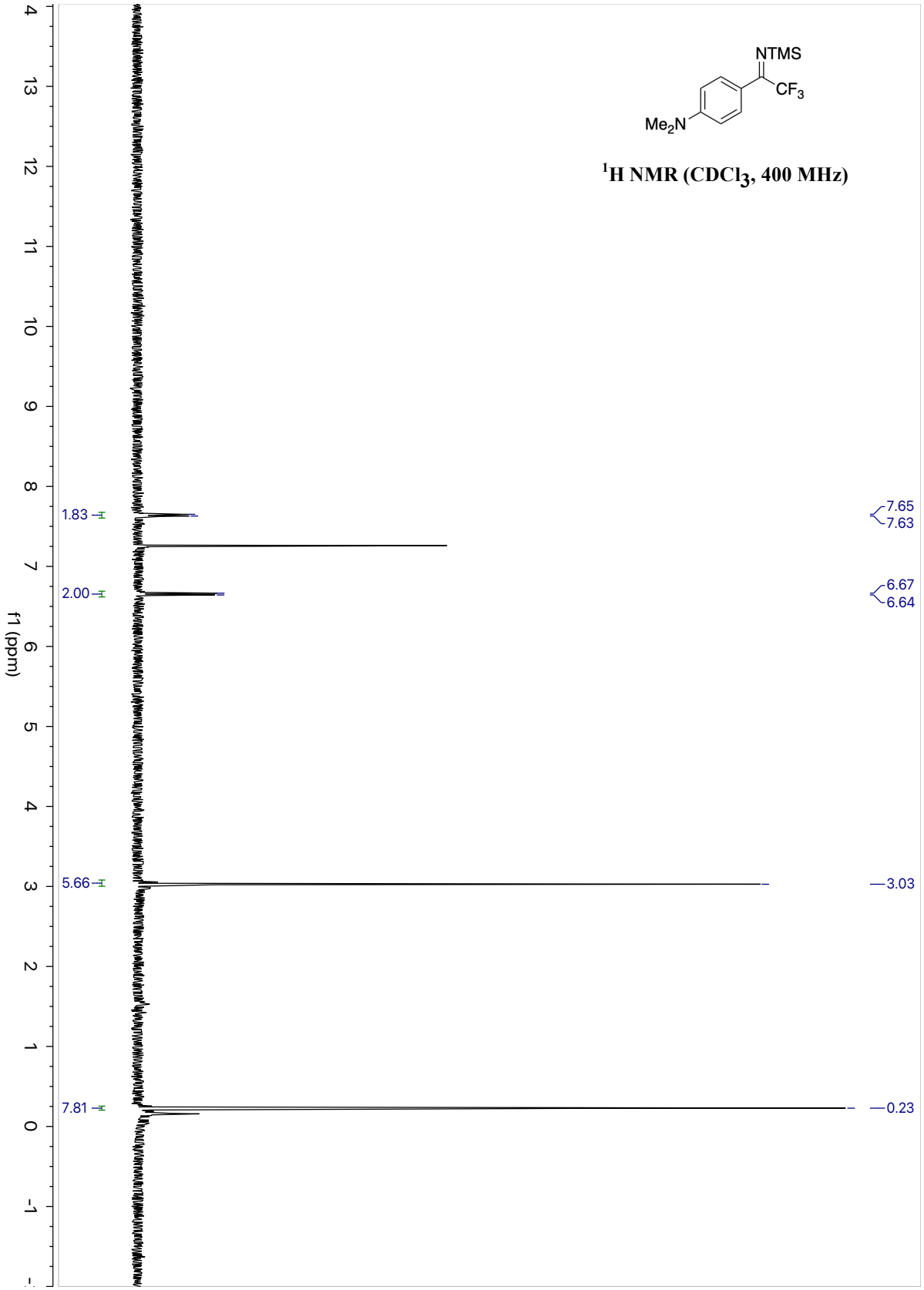

NTMS
CF3
F3C
13C NMR (CDCl3, 100 MHz)
157.18
156.83
156.49
156.15
138.87
138.04
133.16
132.83
132.51
132.18
129.30
129.09
128.43
128.32
128.22
125.60
125.51
125.40
125.36
122.51
121.94
119.08
116.22
113.37
0.43
0.39
f1 (ppm)

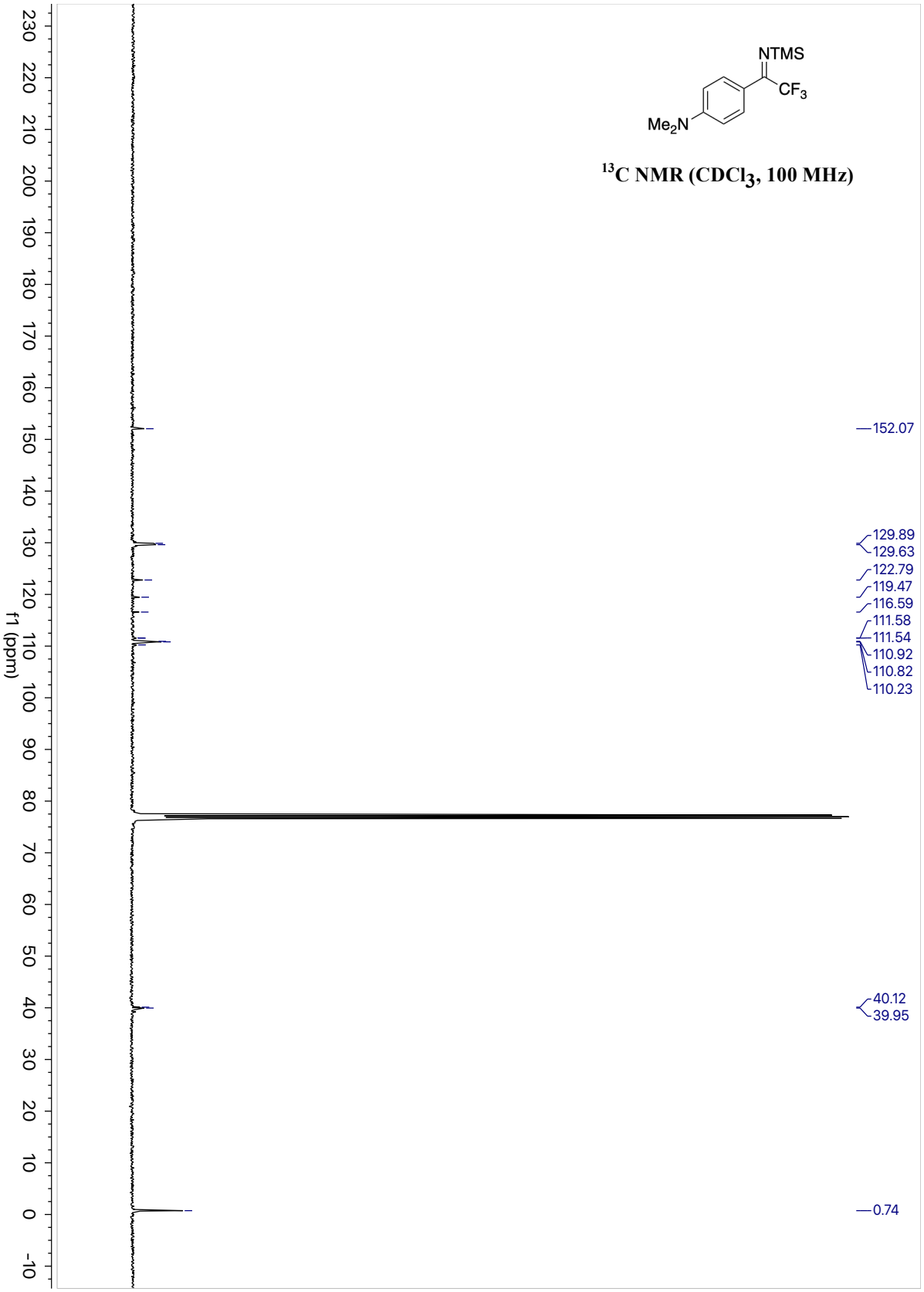

NTMS
CF3
F3C
19F NMR (CDCl3, 376 MHz)
40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-9
f1 (ppm)
3.00
3.02
-63.01
-63.03
-69.04
-69.06

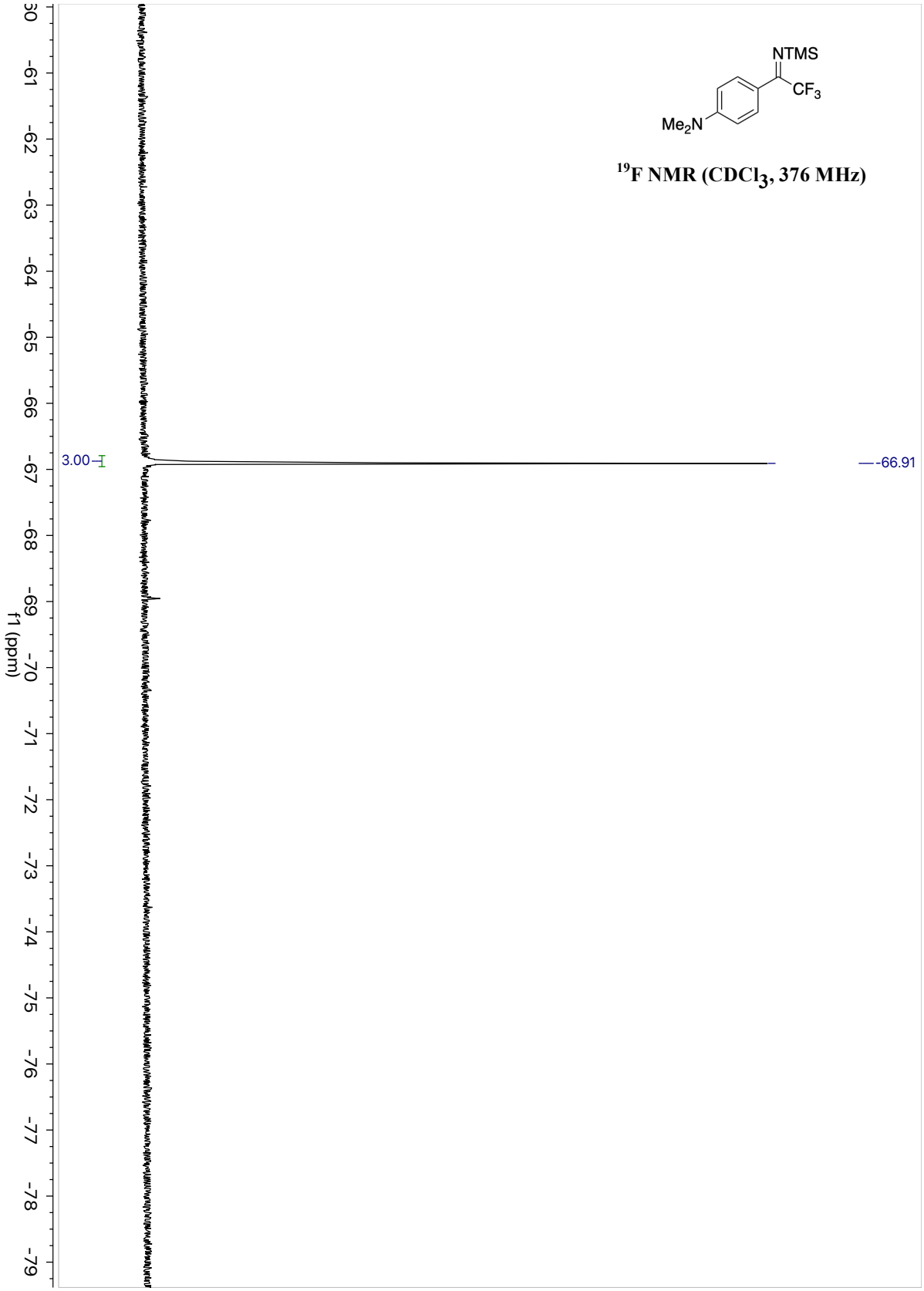

NTMS
CF3
MeO
1H NMR (CDCl3, 400 MHz)
7.64
7.64
7.63
7.63
7.63
7.62
7.62
7.61
7.61
7.61
6.93
6.92
6.92
6.92
6.91
6.90
6.90
6.89
6.89
3.86
3.85
0.22
2.10
2.20
3.16
9.00
f1 (ppm)

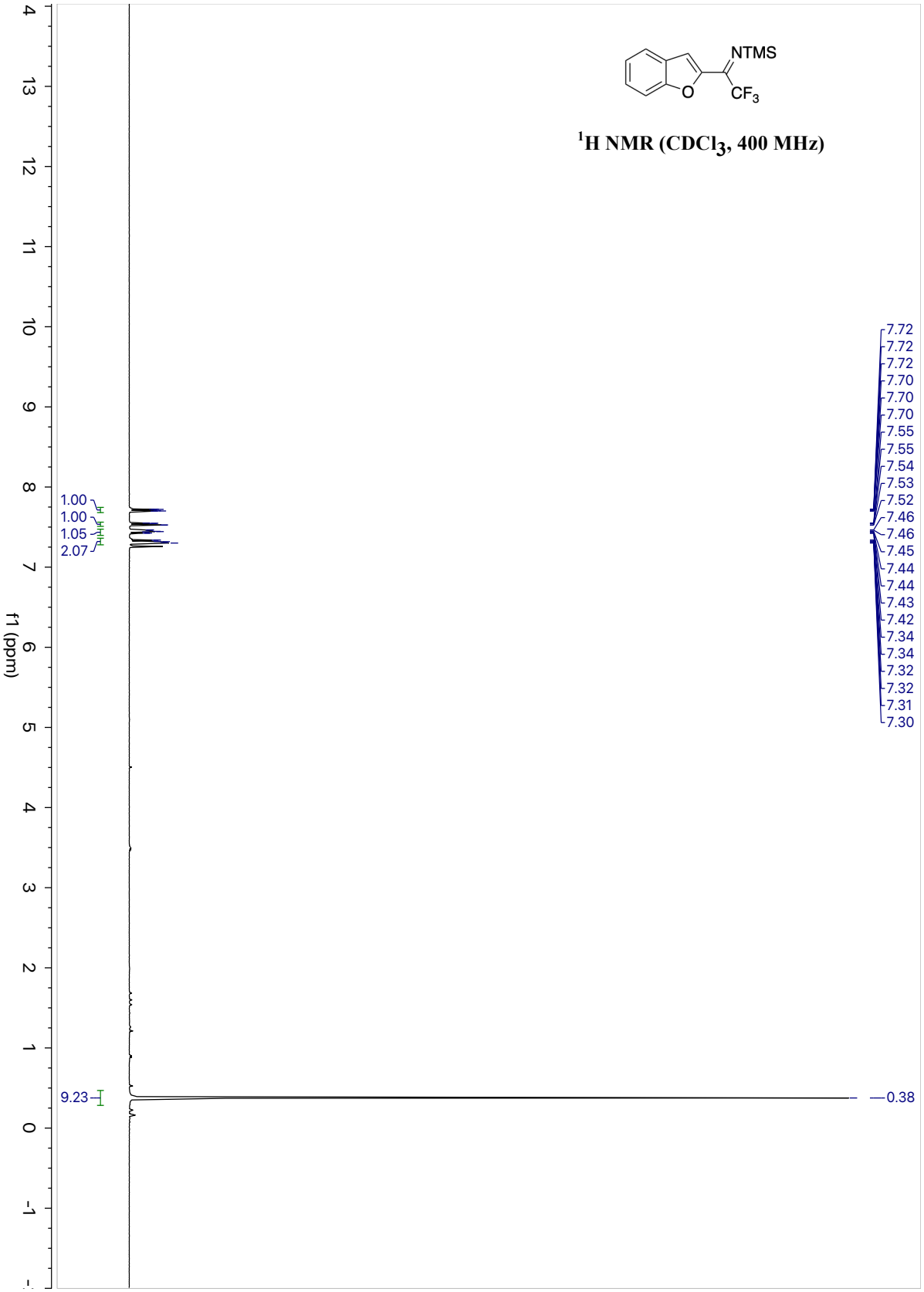

NTMS
CF3
MeO
13C NMR (CDCl3, 100 MHz)
161.89
157.28
156.95
156.62
156.29
130.35
130.06
129.80
129.53
128.16
122.29
119.43
116.56
114.48
113.80
113.67
112.99
55.86
55.64
55.42
55.19
0.69
f1 (ppm)

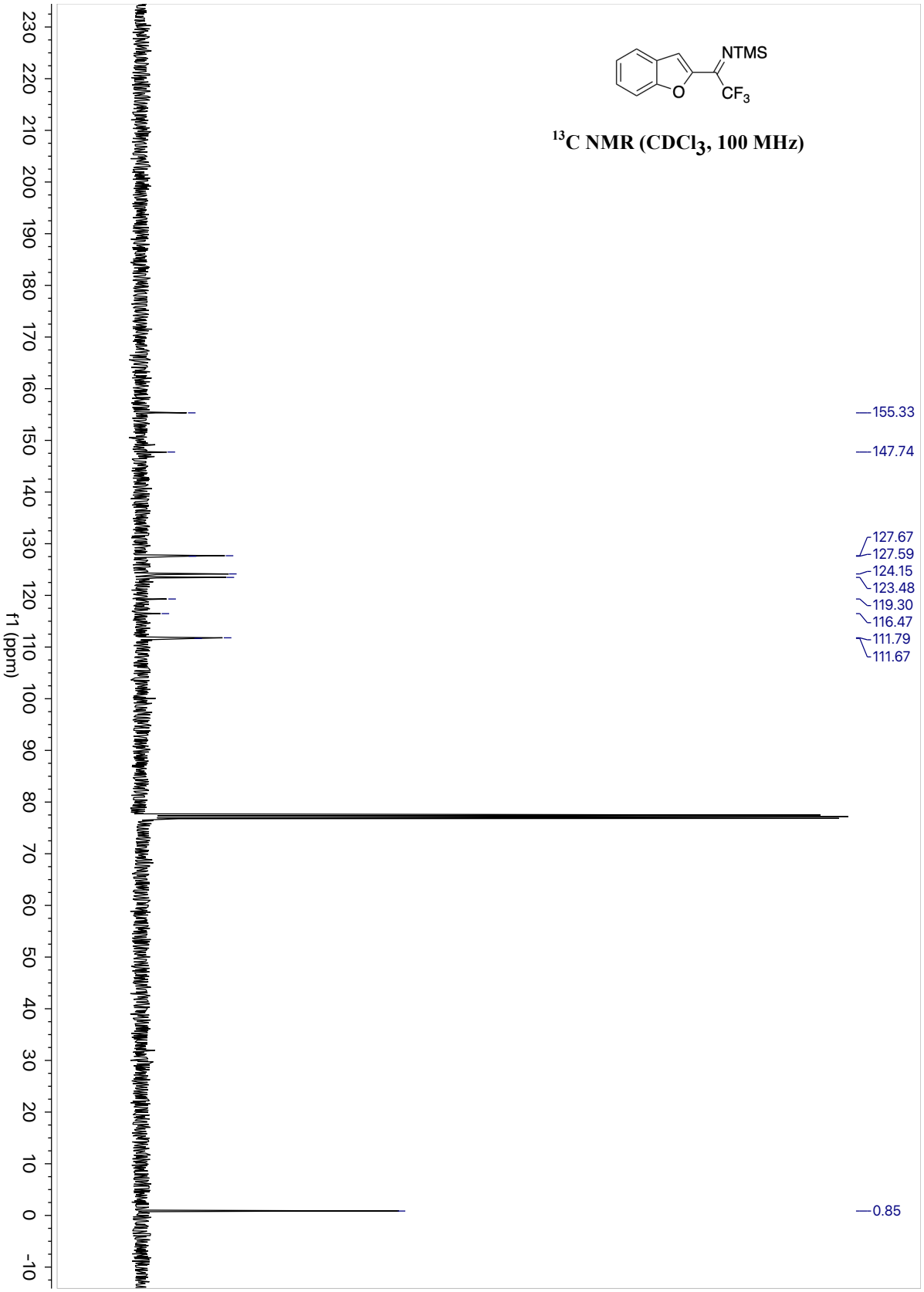

NTMS
CF3
MeO
19F NMR (CDCl3, 376 MHz)
3.00
-68.03
f1 (ppm)
-61
-62
-63
-64
-65
-66
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79

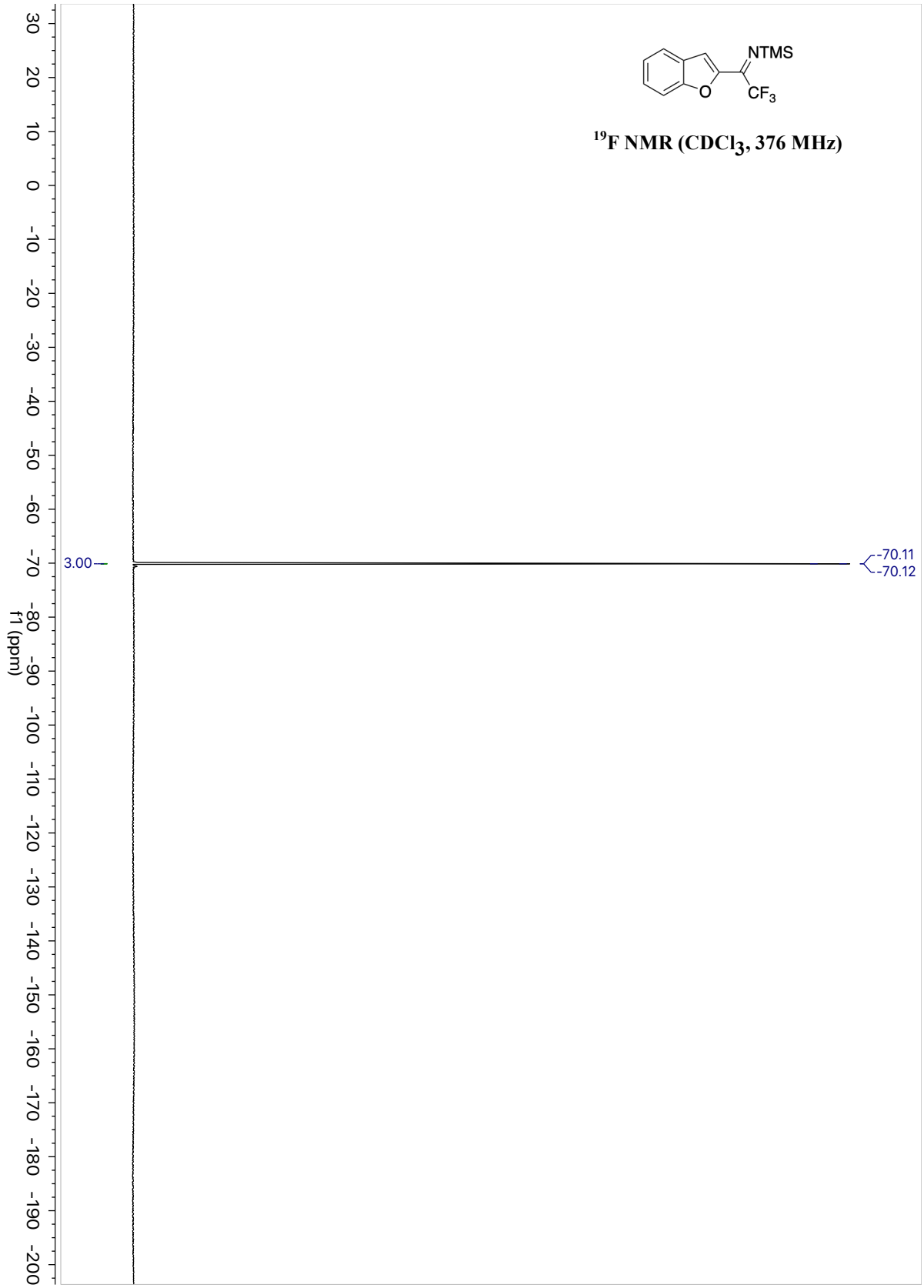

NTMS
CF3
Me2N
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.83
2.00
5.66
7.81
7.65
7.63
6.67
6.64
3.03
0.23

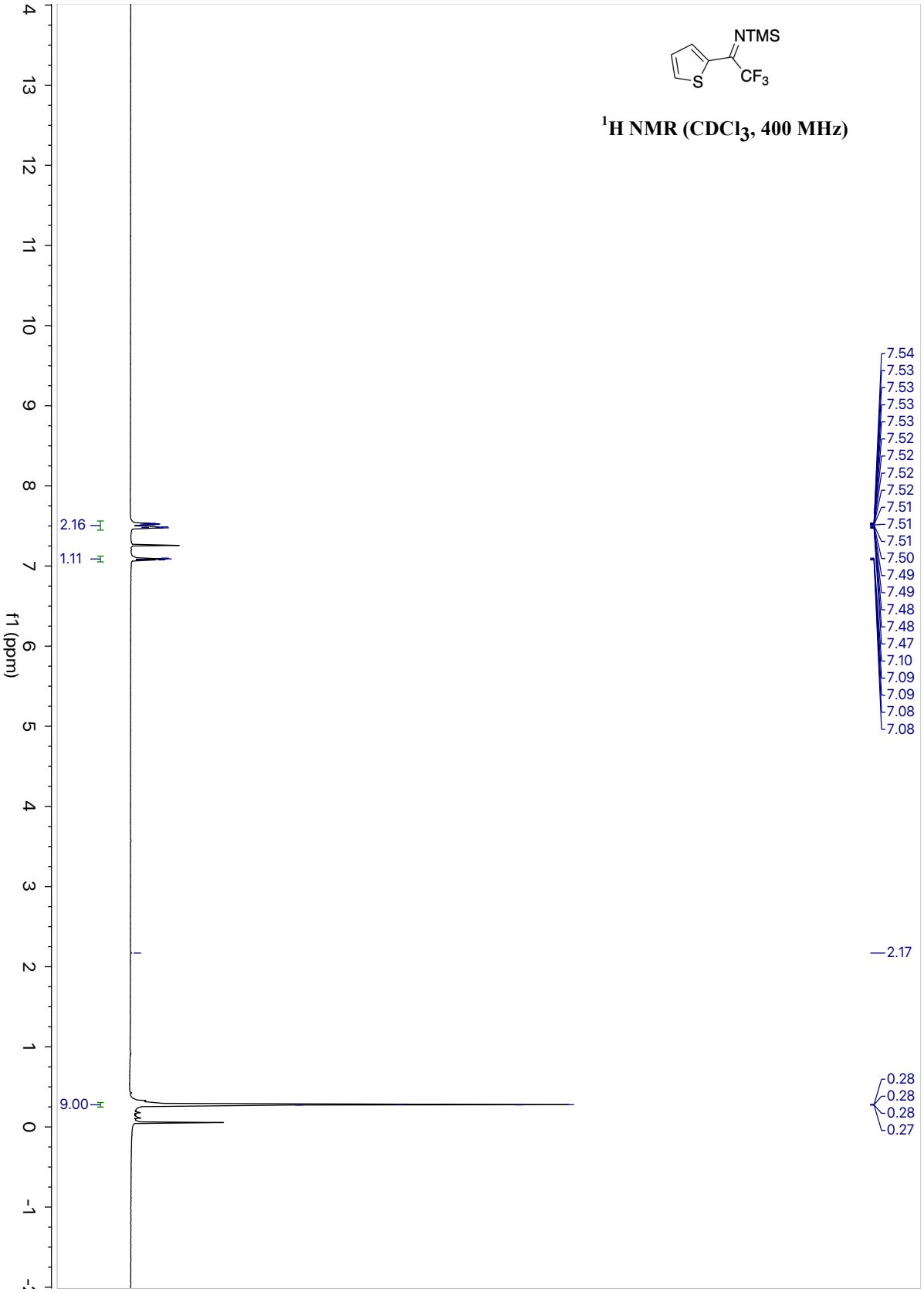

NTMS
CF3
Me2N
13C NMR (CDCl3, 100 MHz)
152.07
129.89
129.63
122.79
119.47
116.59
111.58
111.54
110.92
110.82
110.23
40.12
39.95
0.74
f1 (ppm)

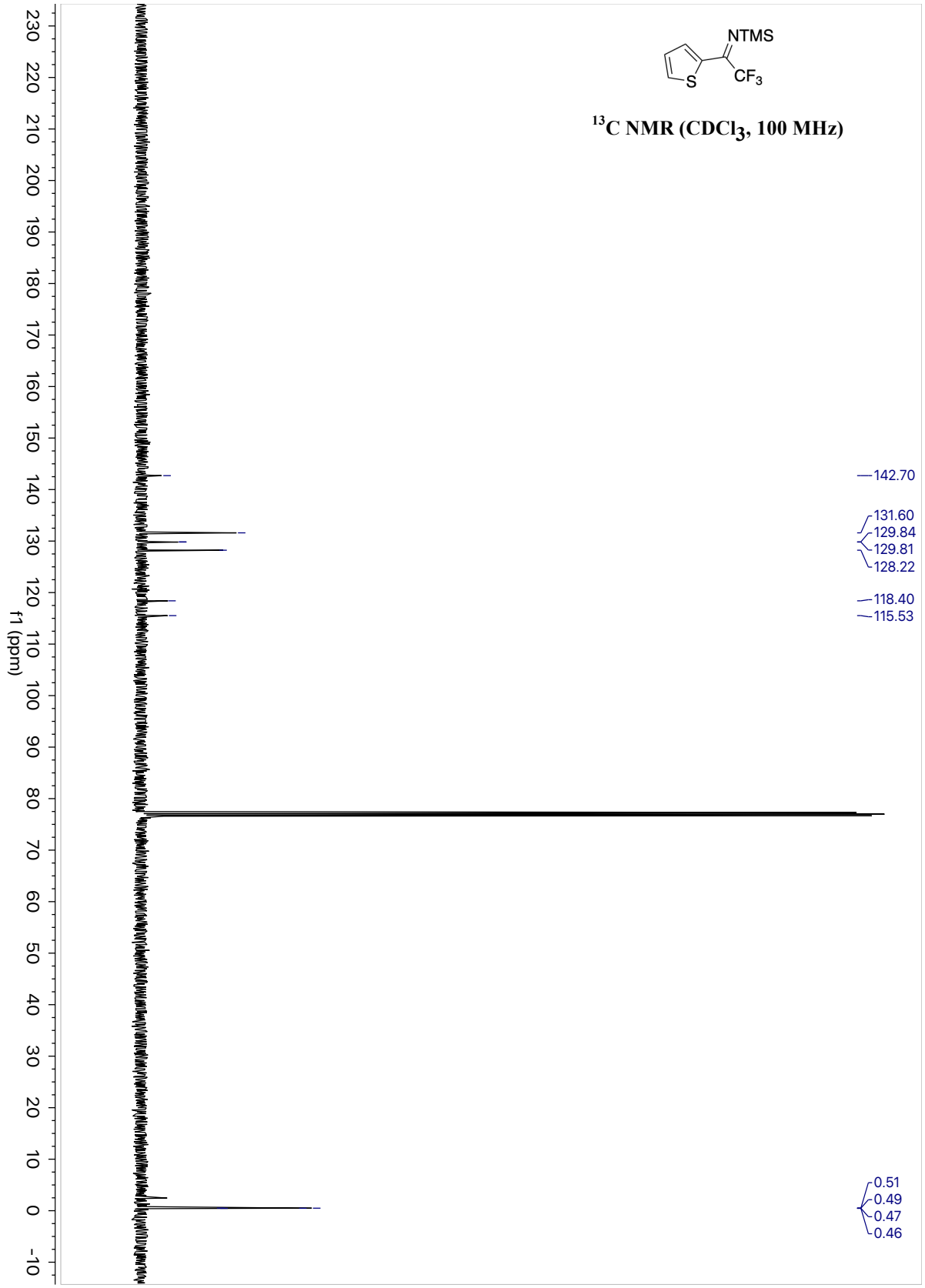

NTMS
CF3
Me2N
19F NMR (CDCl3, 376 MHz)
3.00
-66.91
f1 (ppm)
-60
-61
-62
-63
-64
-65
-66
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79

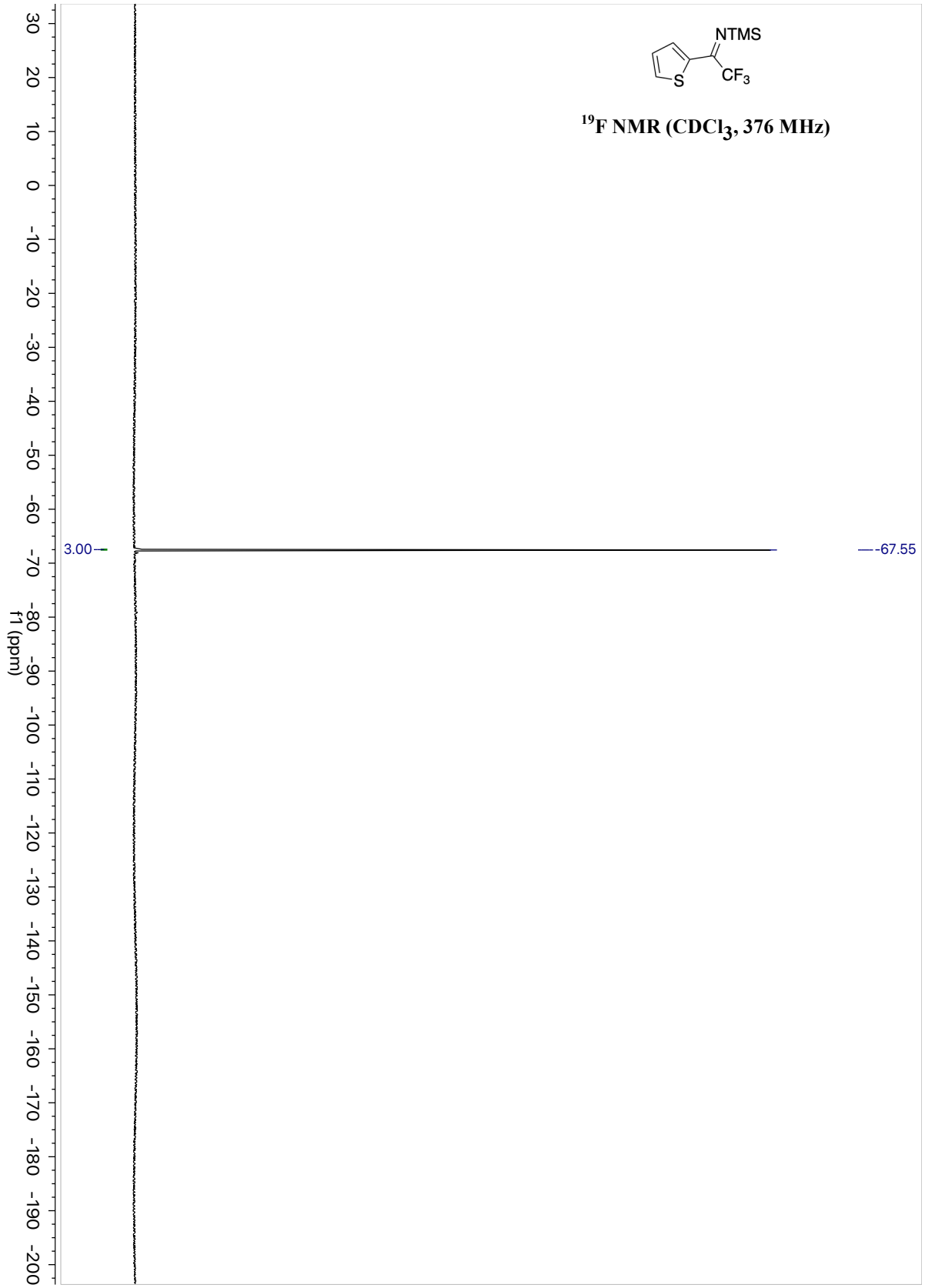

NTMS
O
CF3
1H NMR (CDCl3, 400 MHz)
7.72
7.72
7.72
7.70
7.70
7.70
7.55
7.55
7.54
7.53
7.52
7.46
7.46
7.45
7.44
7.44
7.43
7.42
7.34
7.34
7.32
7.32
7.31
7.30
1.00
1.00
1.05
2.07
9.23
0.38
f1 (ppm)

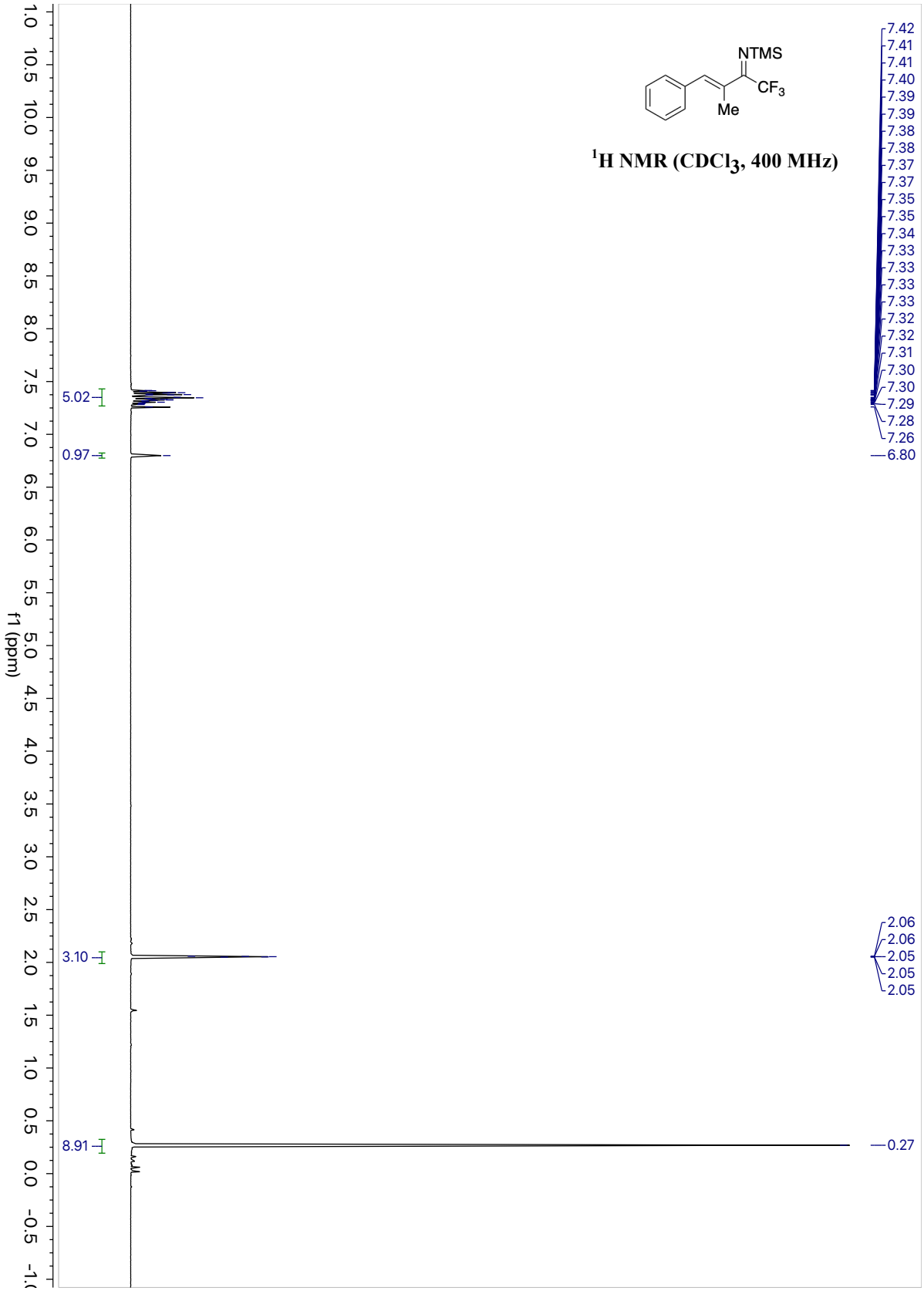

NTMS
O
CF3
13C NMR (CDCl3, 100 MHz)
155.33
147.74
127.67
127.59
124.15
123.48
119.30
116.47
111.79
111.67
0.85
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

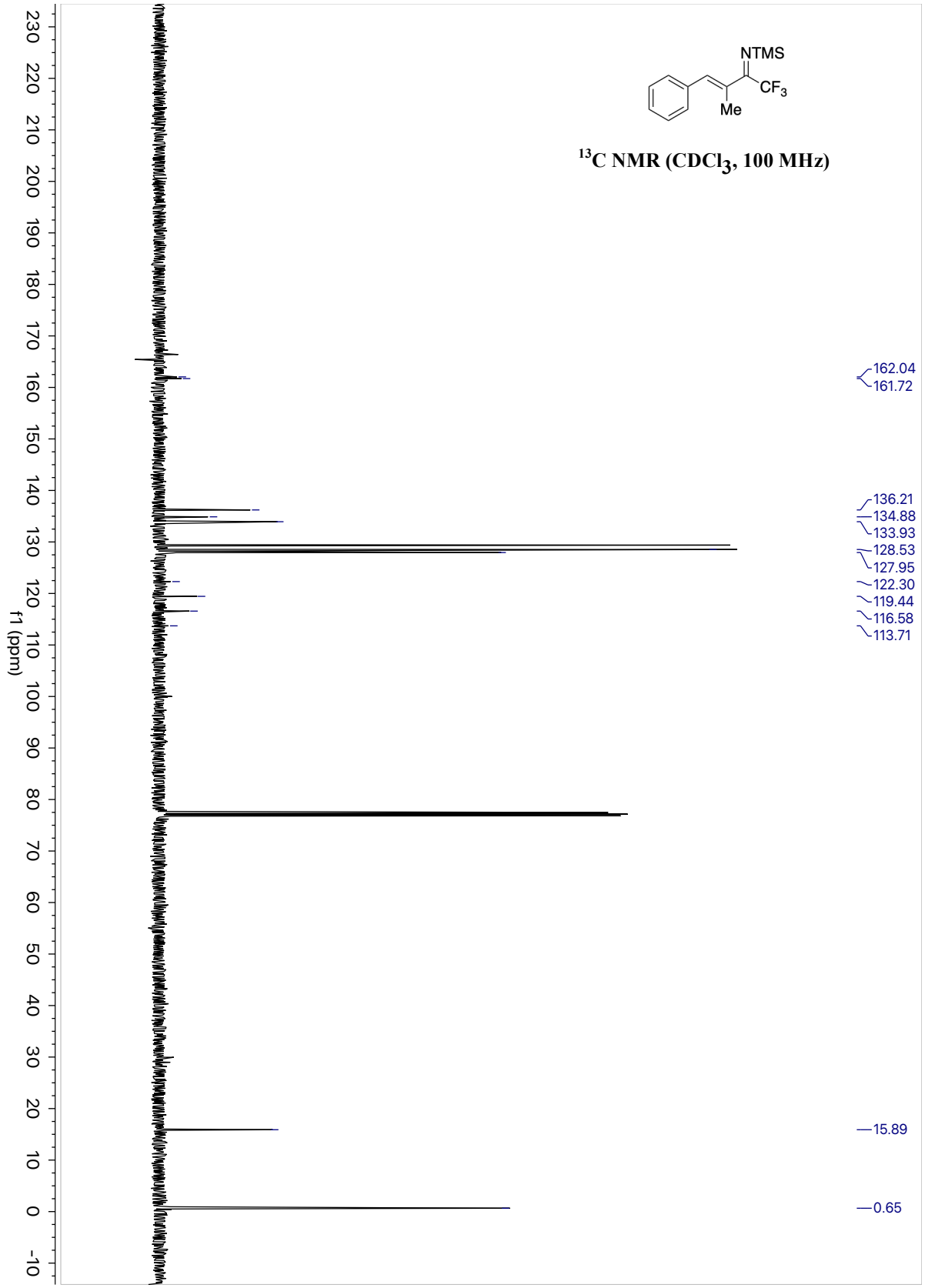

NTMS
O
CF3
19F NMR (CDCl3, 376 MHz)
3.00
-70.11
-70.12
f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

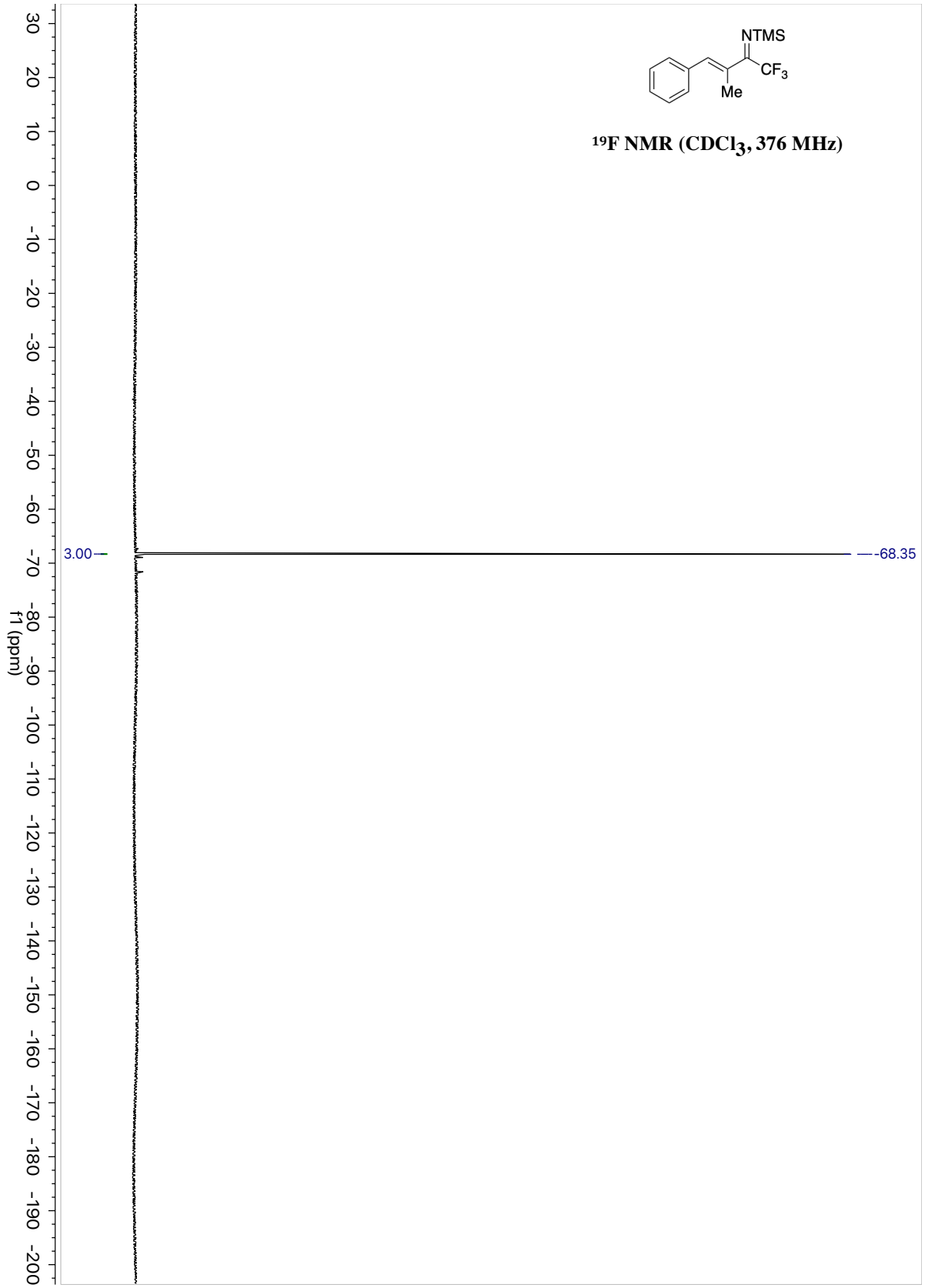

NTMS
S
CF3
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.16
1.11
9.00
7.54
7.53
7.53
7.53
7.53
7.52
7.52
7.52
7.52
7.51
7.51
7.51
7.50
7.49
7.49
7.48
7.48
7.47
7.10
7.09
7.09
7.08
7.08
2.17
0.28
0.28
0.28
0.27

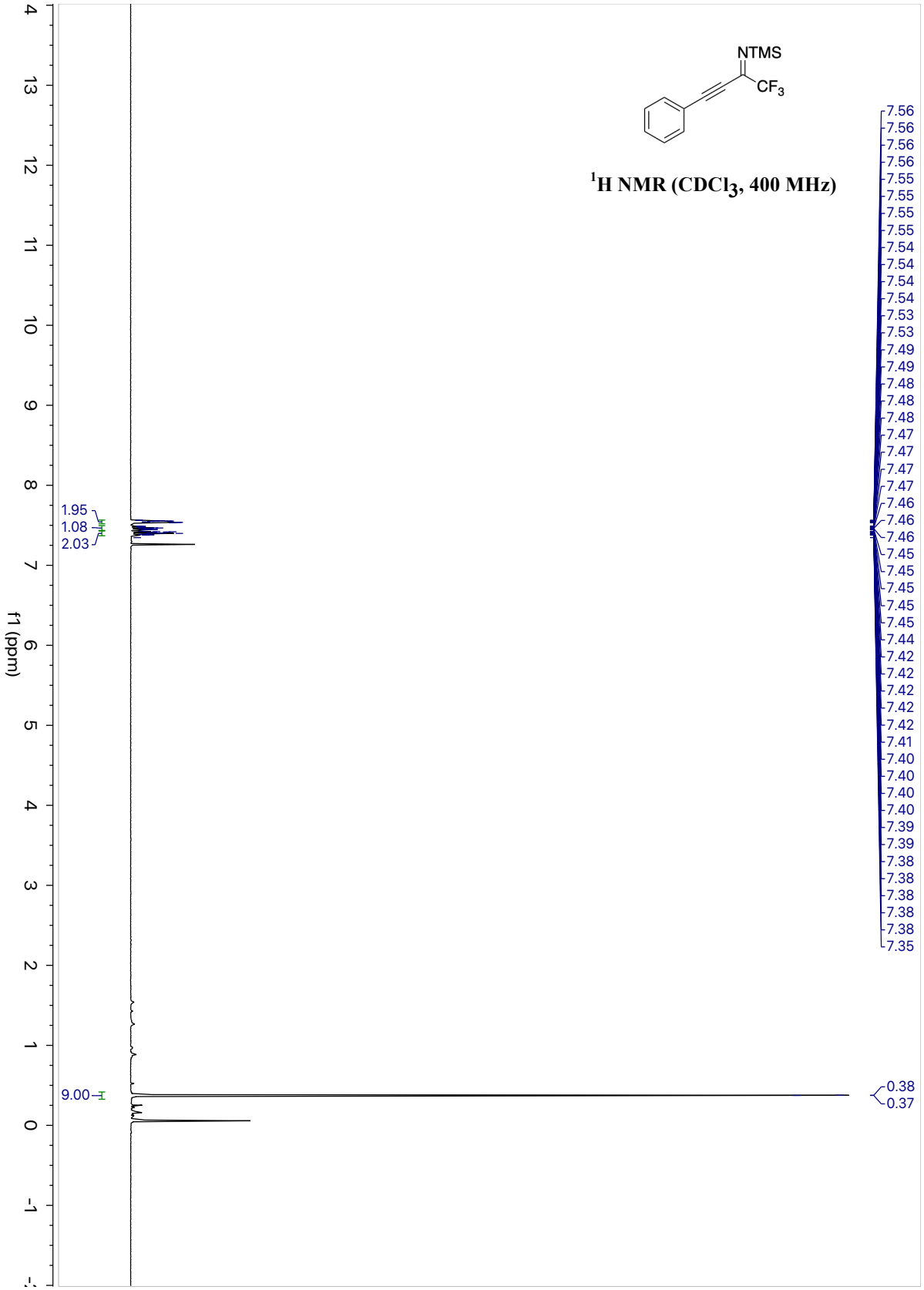

NTMS
S
CF3
13C NMR (CDCl3, 100 MHz)
142.70
131.60
129.84
129.81
128.22
118.40
115.53
0.51
0.49
0.47
0.46
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

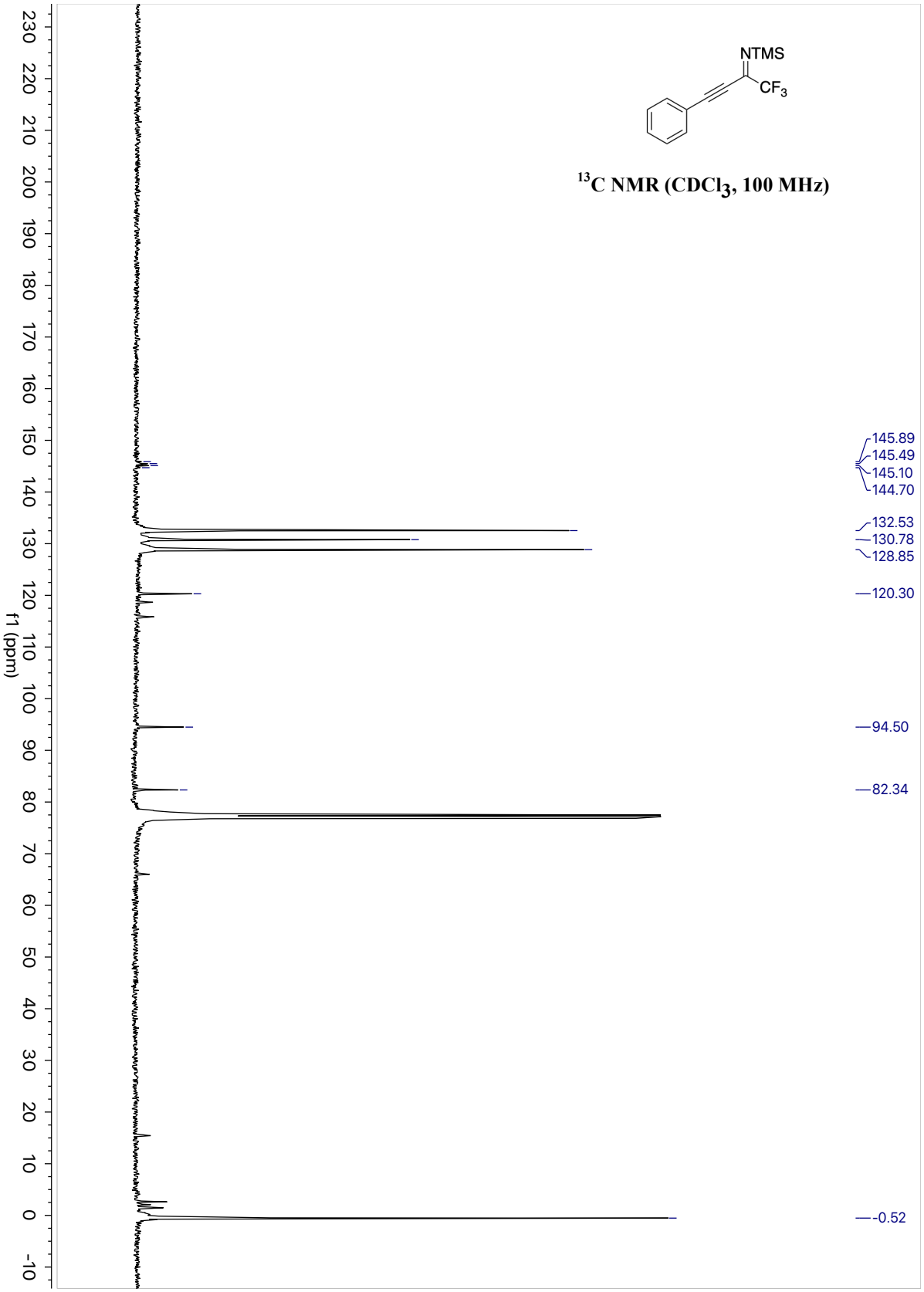

NTMS
S
CF3
19F NMR (CDCl3, 376 MHz)
3.00
-67.55
f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

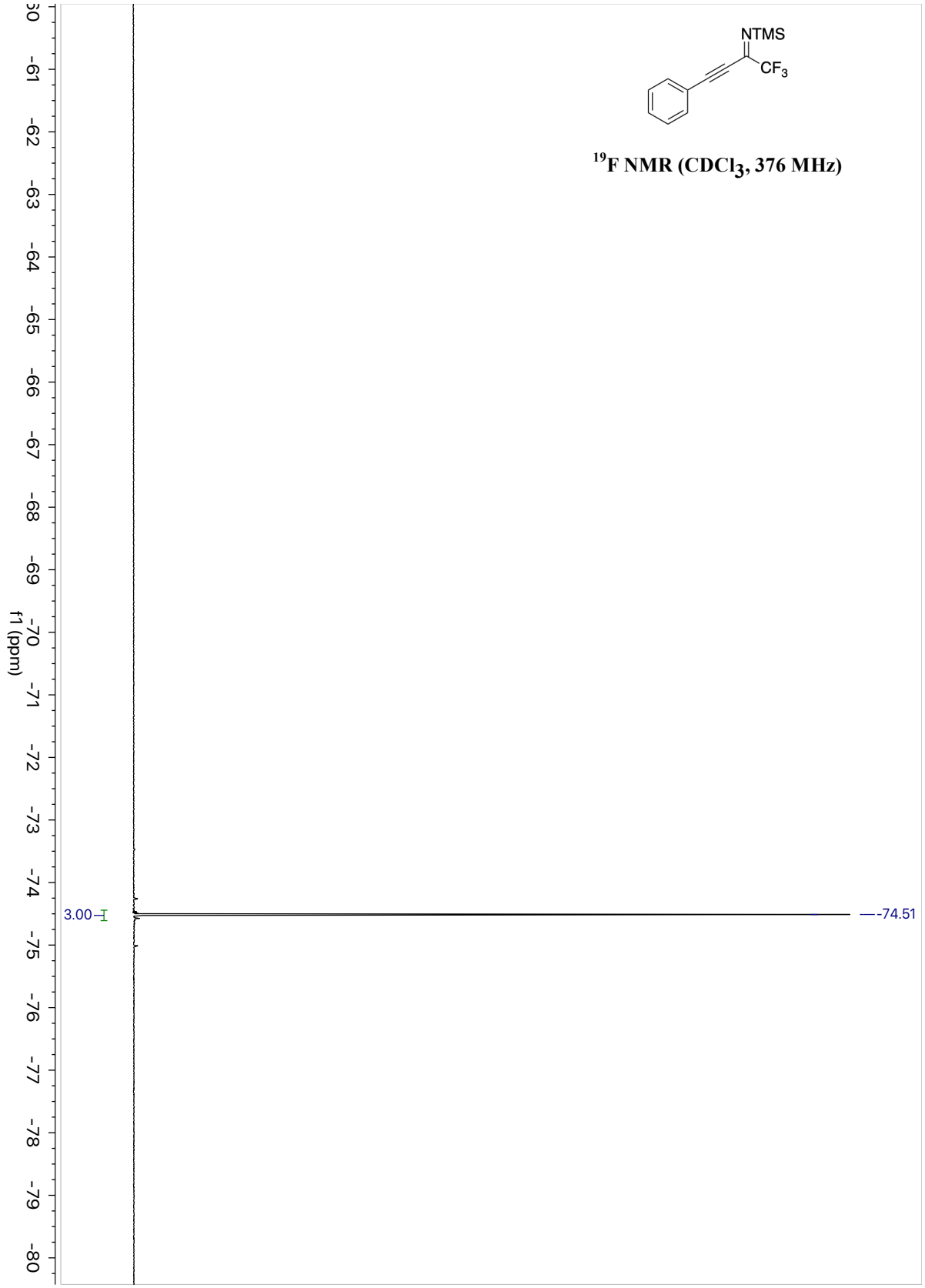

NTMS
CF3
Me
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
5.02
0.97
3.10
8.91
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.35
7.35
7.34
7.33
7.33
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.29
7.28
7.26
6.80
2.06
2.06
2.05
2.05
2.05
0.27

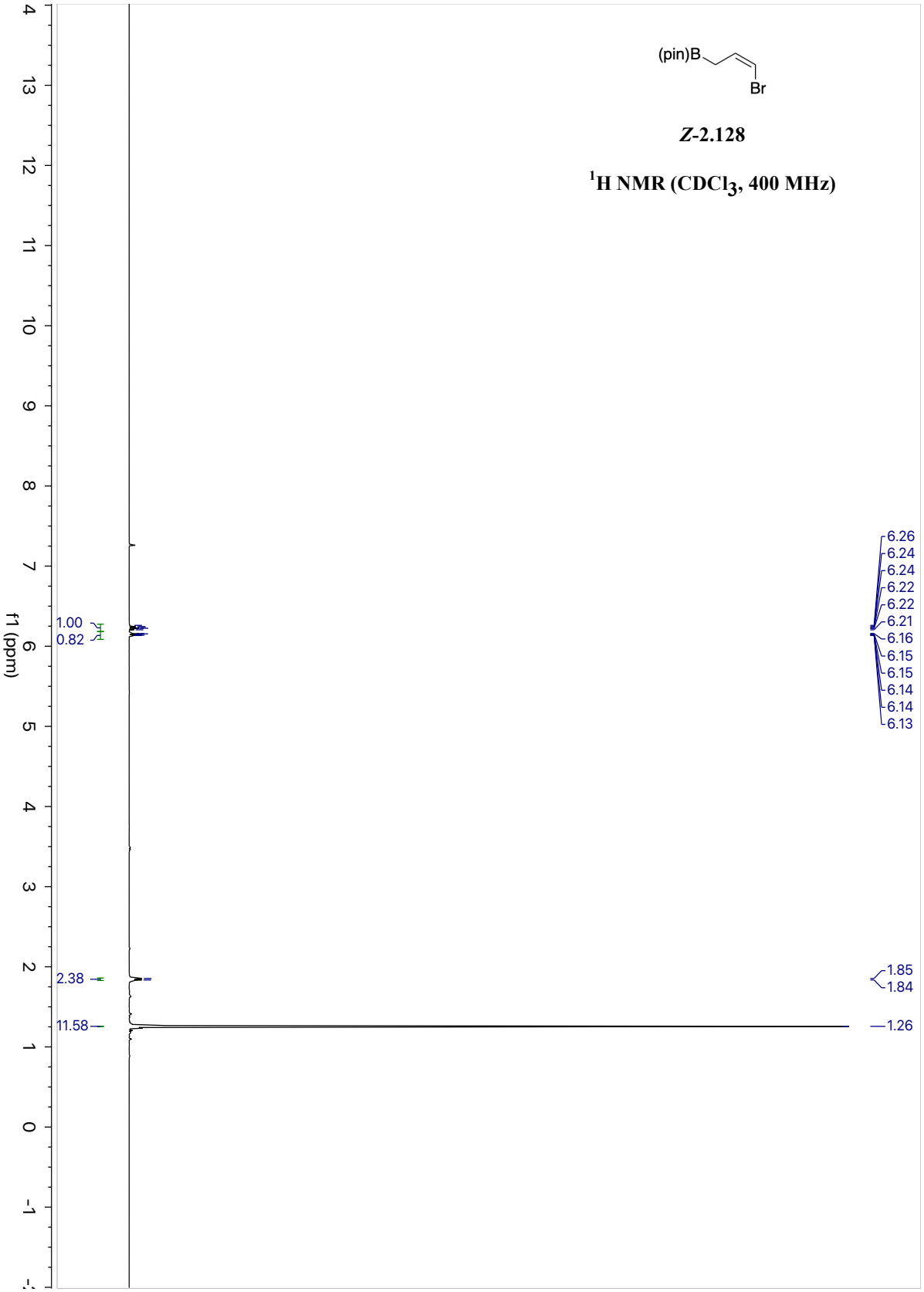

NTMS
CF3
Me
13C NMR (CDCl3, 100 MHz)
162.04
161.72
136.21
134.88
133.93
128.53
127.95
122.30
119.44
116.58
113.71
15.89
0.65
f1 (ppm)

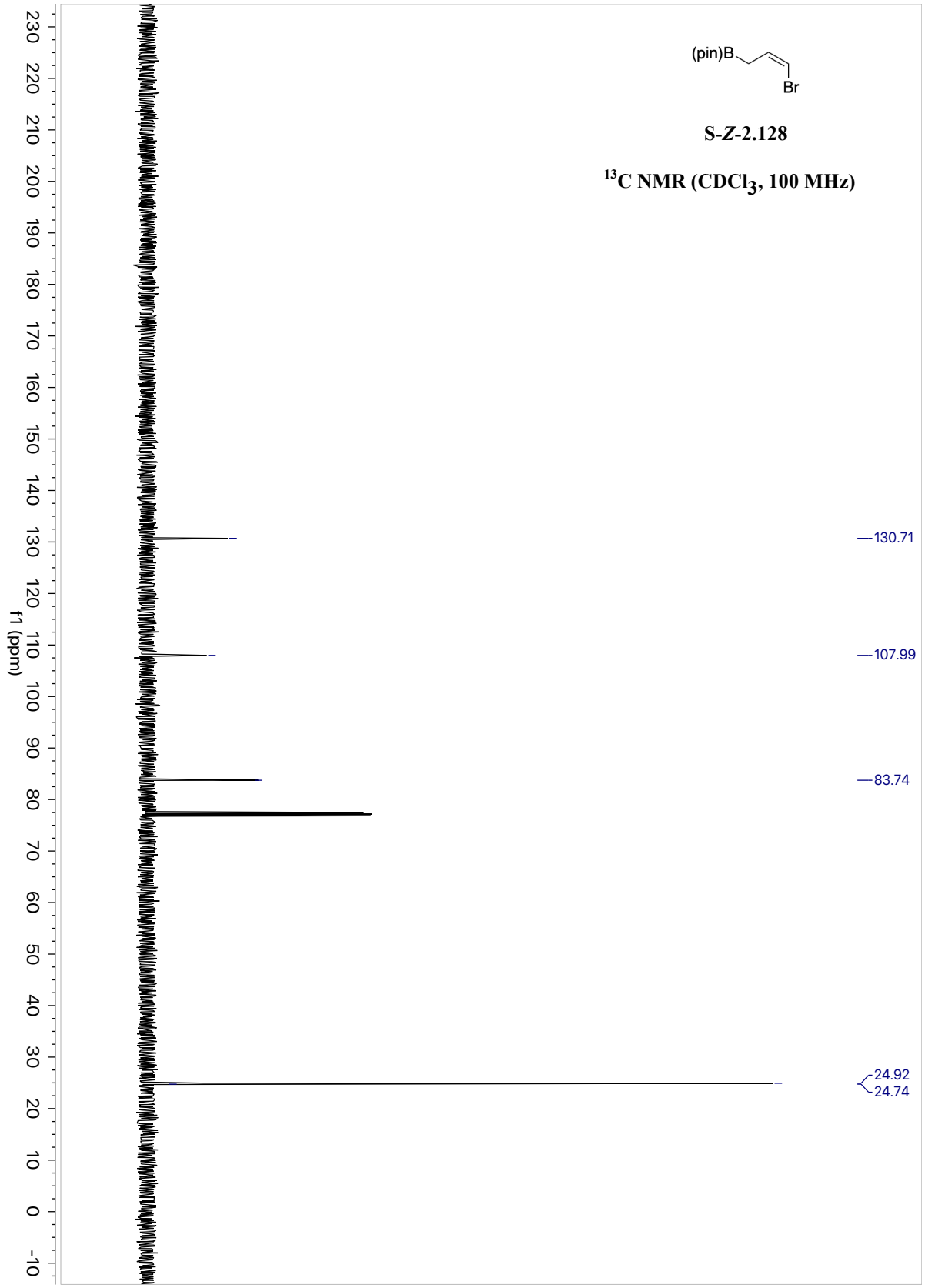

NTMS
CF3
Me
19F NMR (CDCl3, 376 MHz)
3.00
-68.35
f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

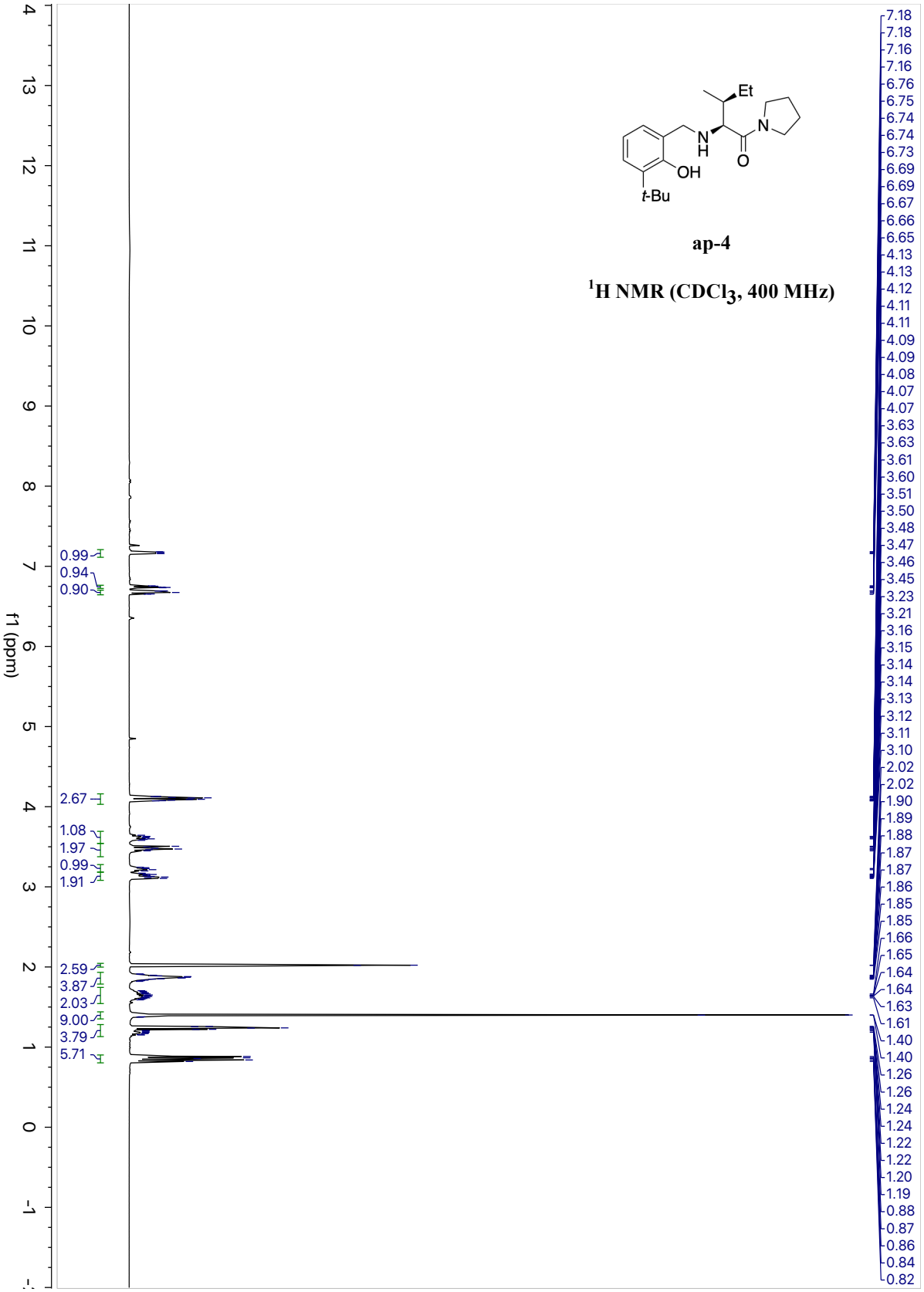

NTMS
CF3
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.95
1.08
2.03
9.00
7.56
7.55
7.54
7.53
7.49
7.48
7.47
7.46
7.45
7.44
7.42
7.41
7.40
7.39
7.38
7.35
0.38
0.37


NTMS
CF3
13C NMR (CDCl3, 100 MHz)
145.89
145.49
145.10
144.70
132.53
130.78
128.85
120.30
94.50
82.34
-0.52
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


NTMS
CF3
19F NMR (CDCl3, 376 MHz)
f1 (ppm)
-60
-61
-62
-63
-64
-65
-66
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
3.00
-74.51

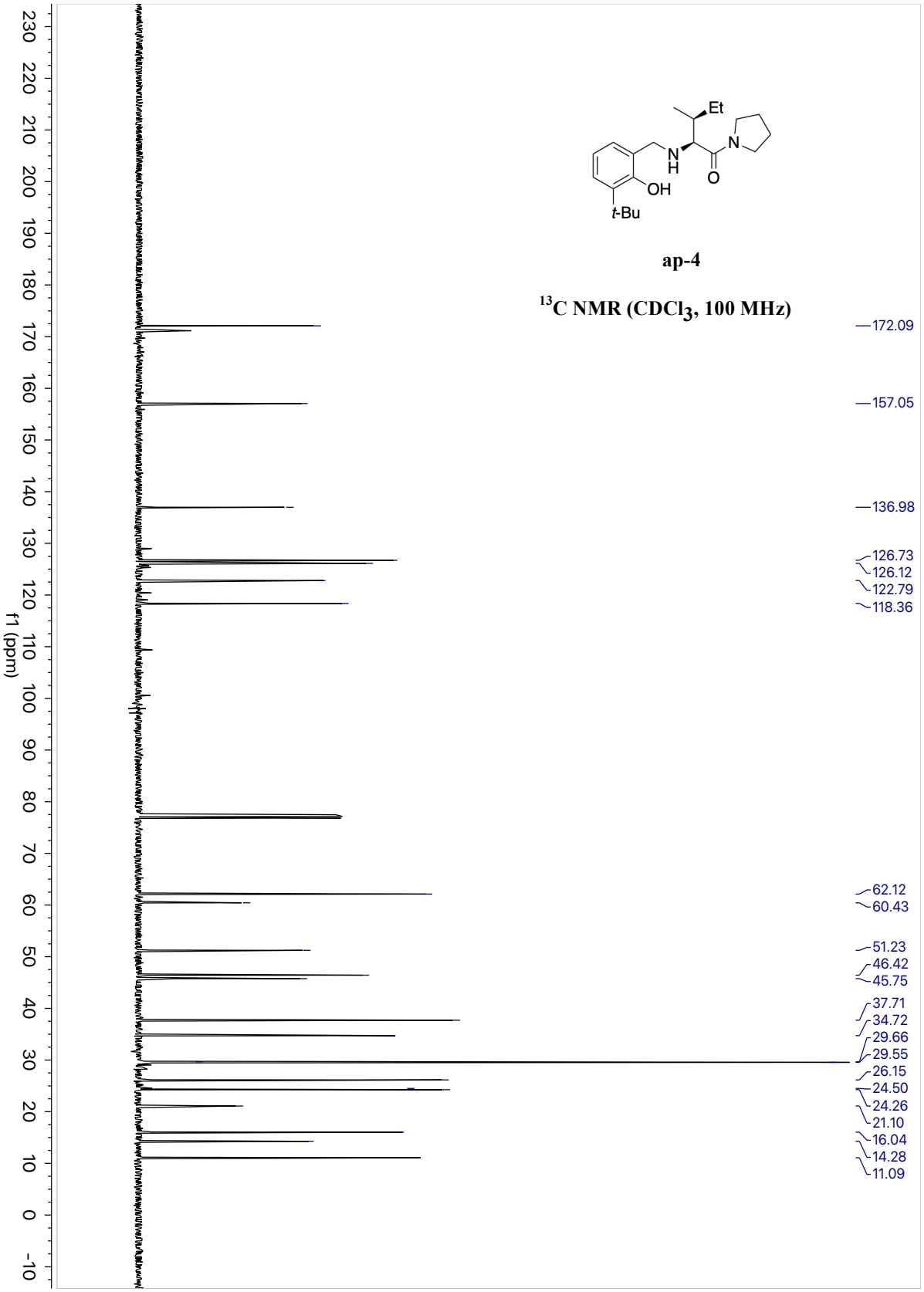

(pin)B
Br
Z-2.128
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.00
0.82
2.38
11.58
6.26
6.24
6.24
6.22
6.22
6.21
6.16
6.15
6.15
6.14
6.14
6.13
1.85
1.84
1.26

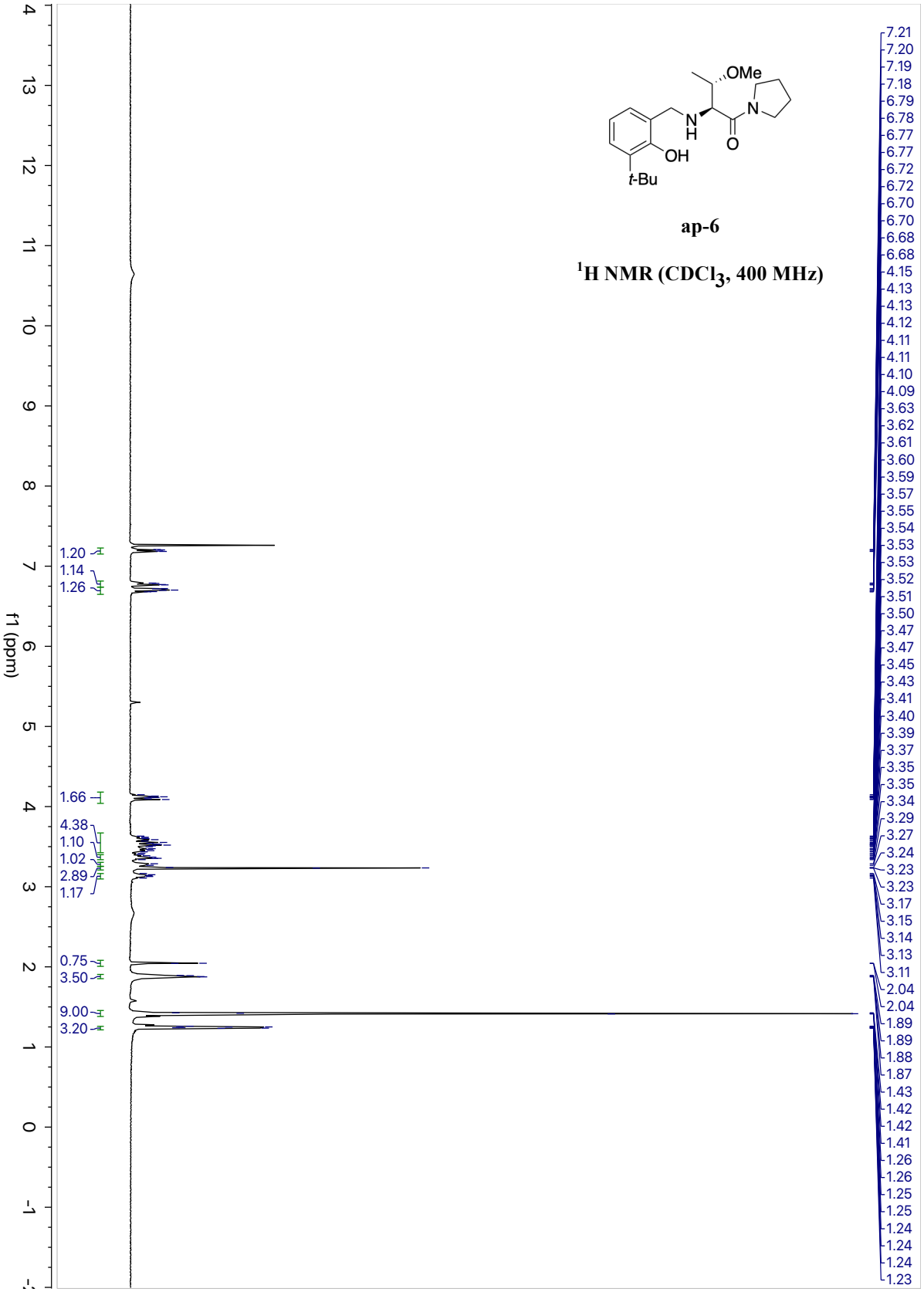

(pin)B
Br
S-Z-2.128
13C NMR (CDCl3, 100 MHz)
130.71
107.99
83.74
24.92
24.74
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

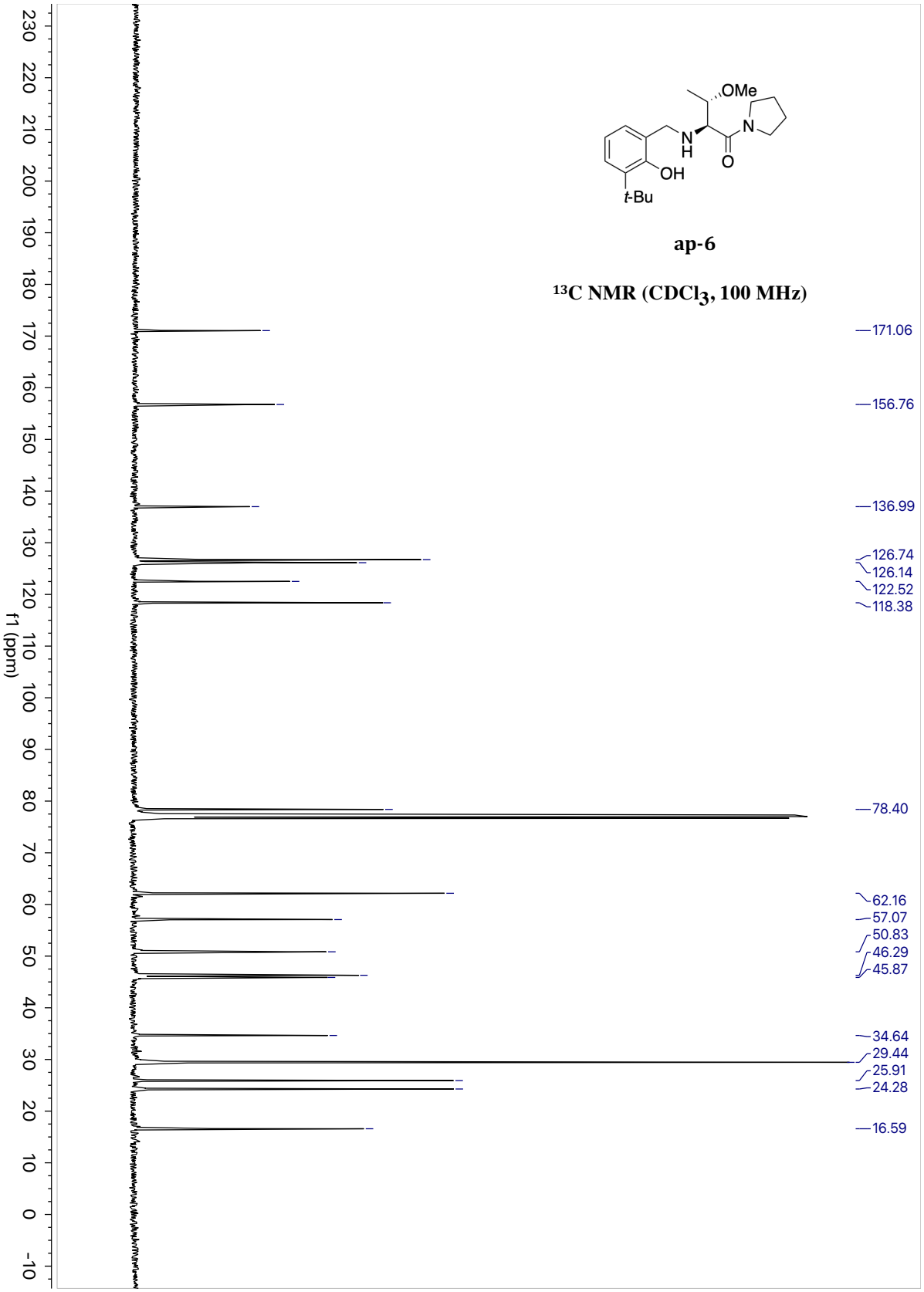


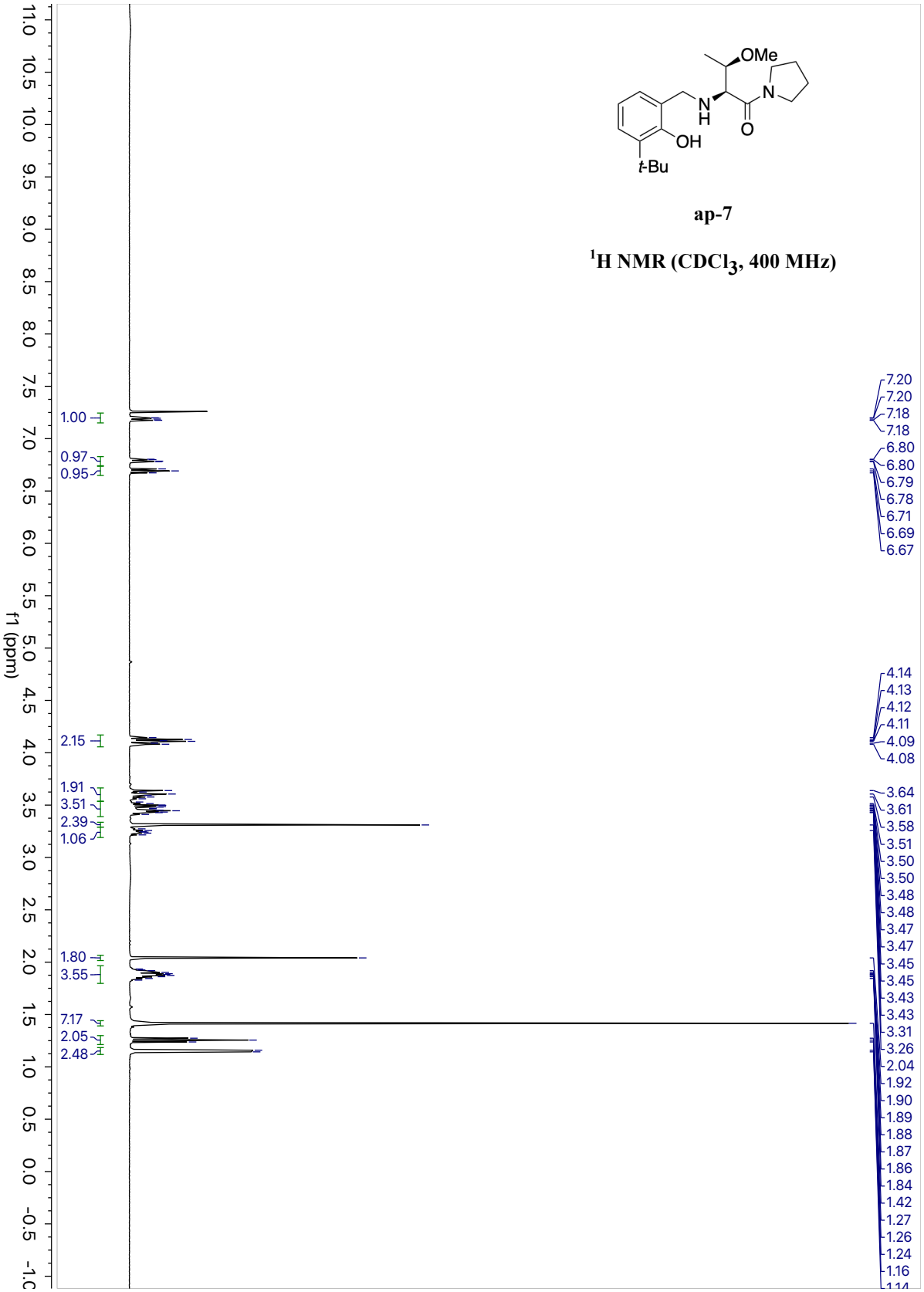
ap-4

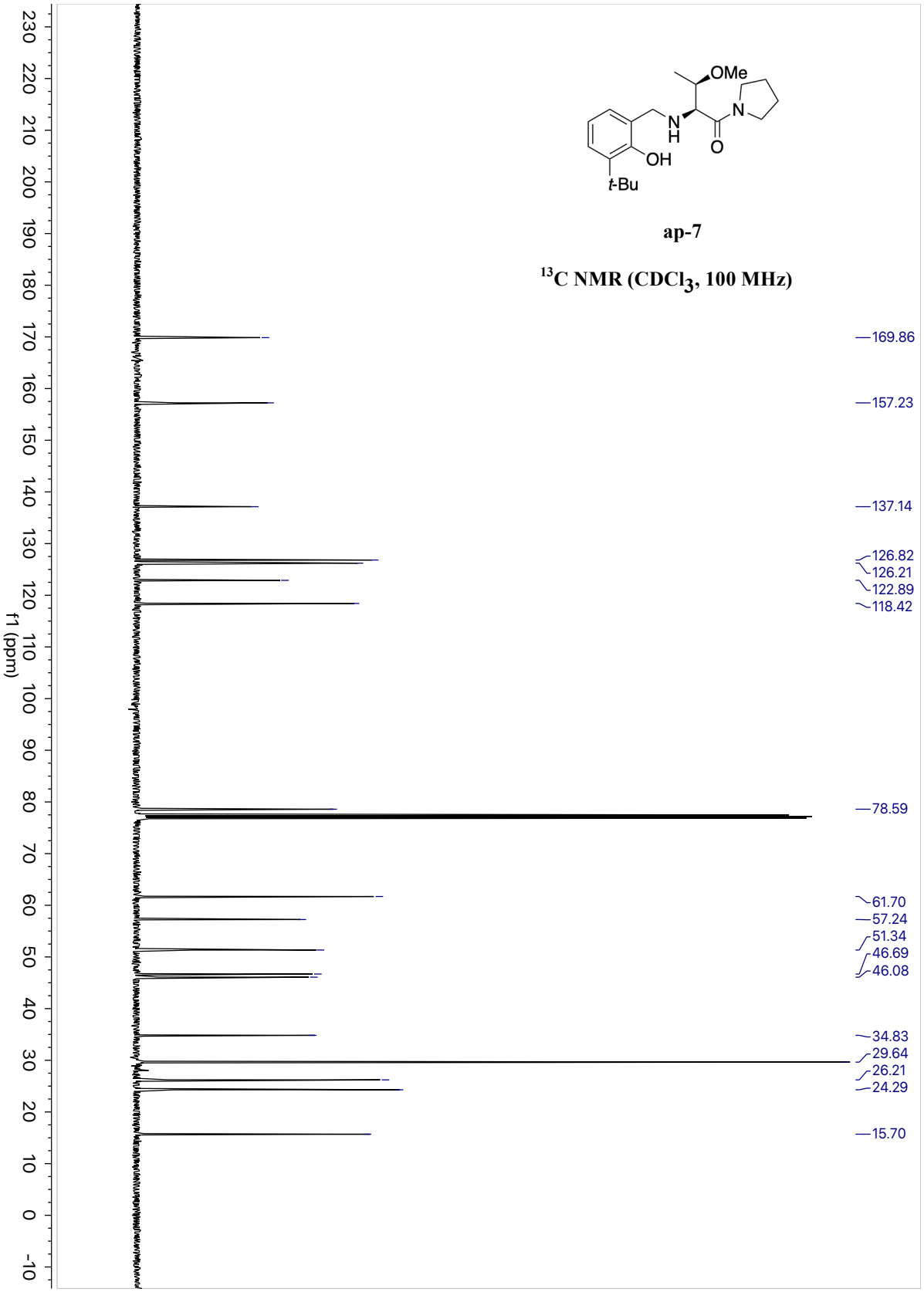
^{1}H NMR ($CDCl_3$, 400 MHz)

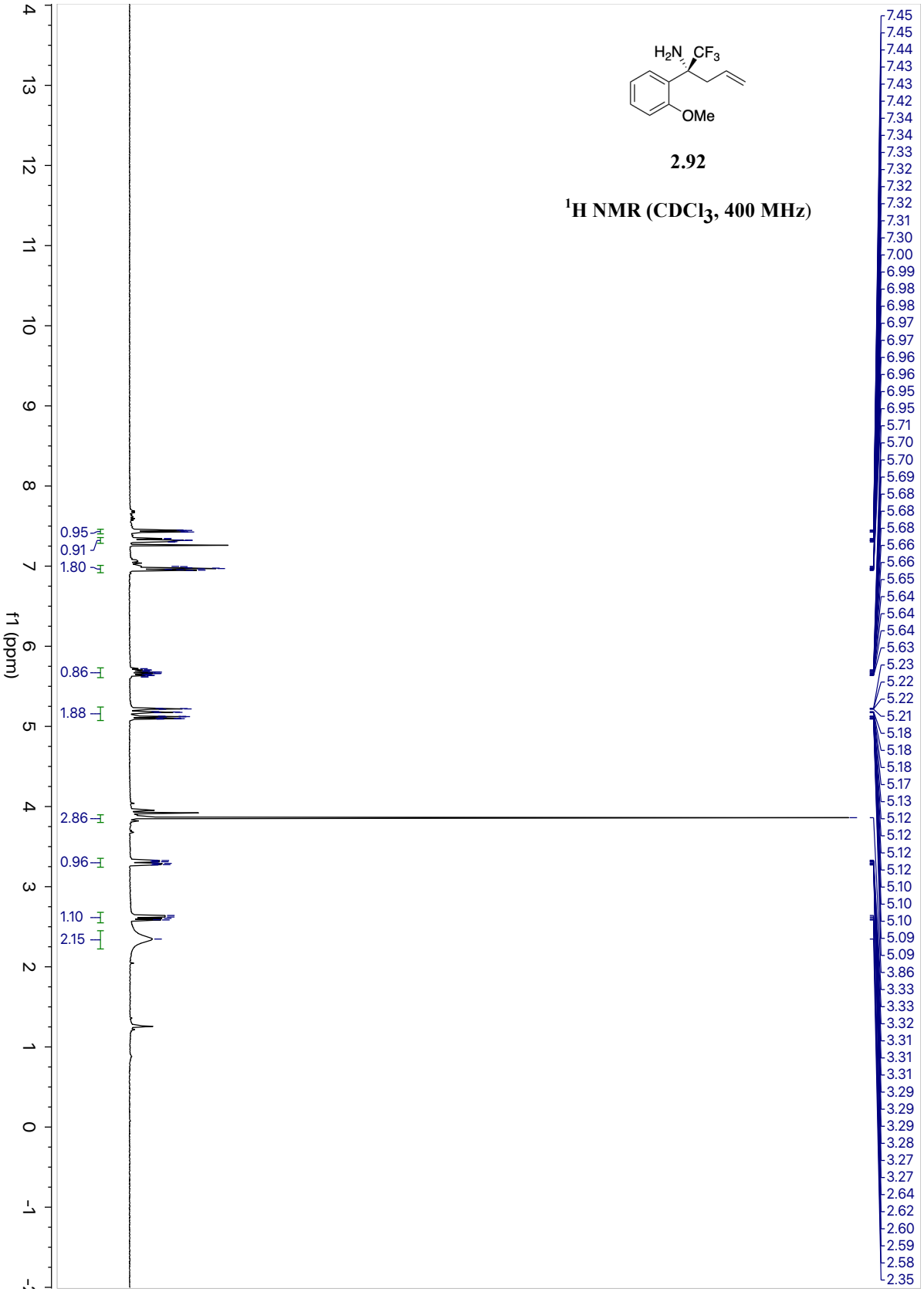

Et
N
H
N
O
OH
t-Bu
ap-4
13C NMR (CDCl3, 100 MHz)
172.09
157.05
136.98
126.73
126.12
122.79
118.36
62.12
60.43
51.23
46.42
45.75
37.71
34.72
29.66
29.55
26.15
24.50
24.26
21.10
16.04
14.28
11.09
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

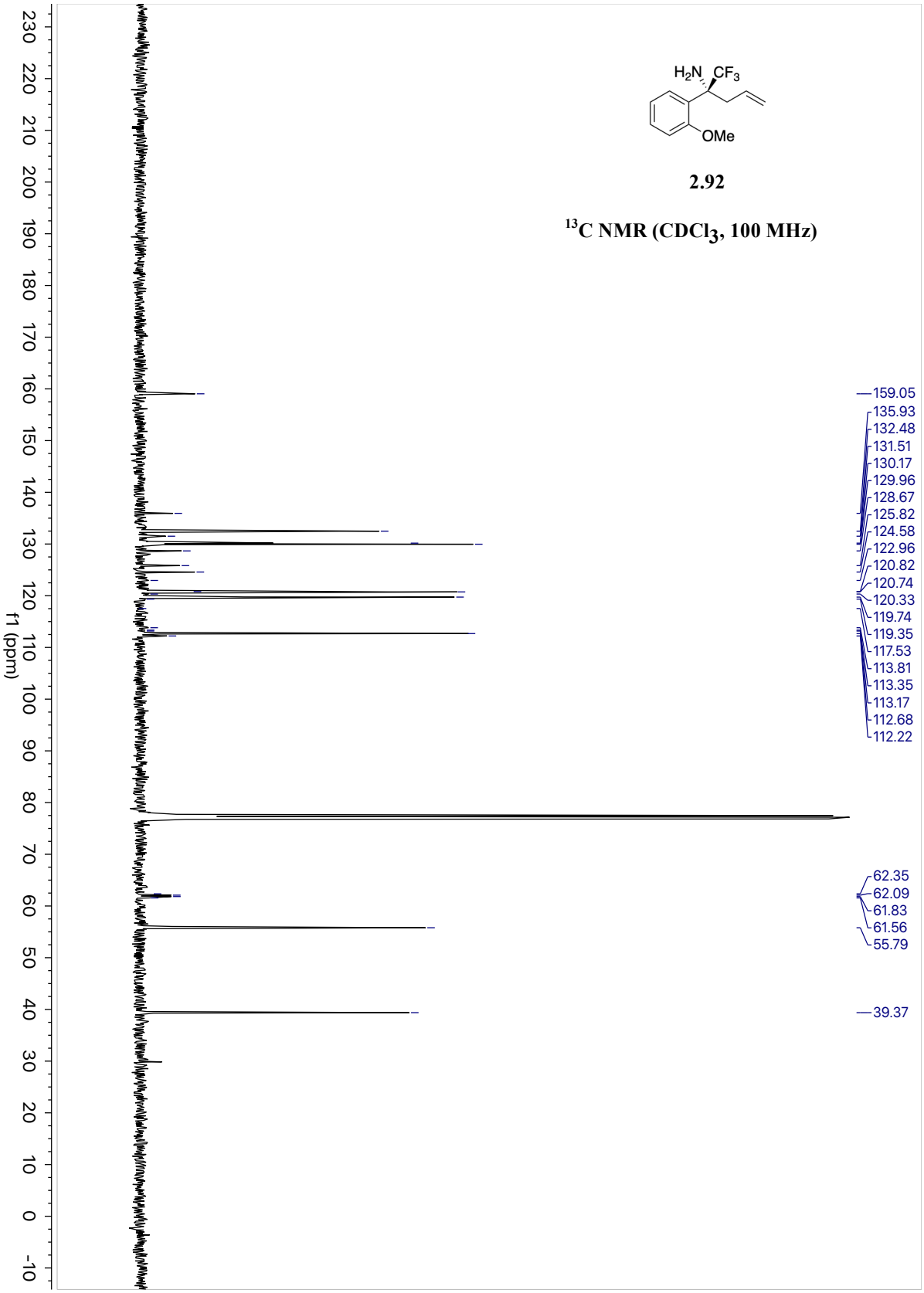

OMe
N
H
N
O
OH
t-Bu
ap-6
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.20
1.14
1.26
1.66
4.38
1.10
1.02
2.89
1.17
0.75
3.50
9.00
3.20

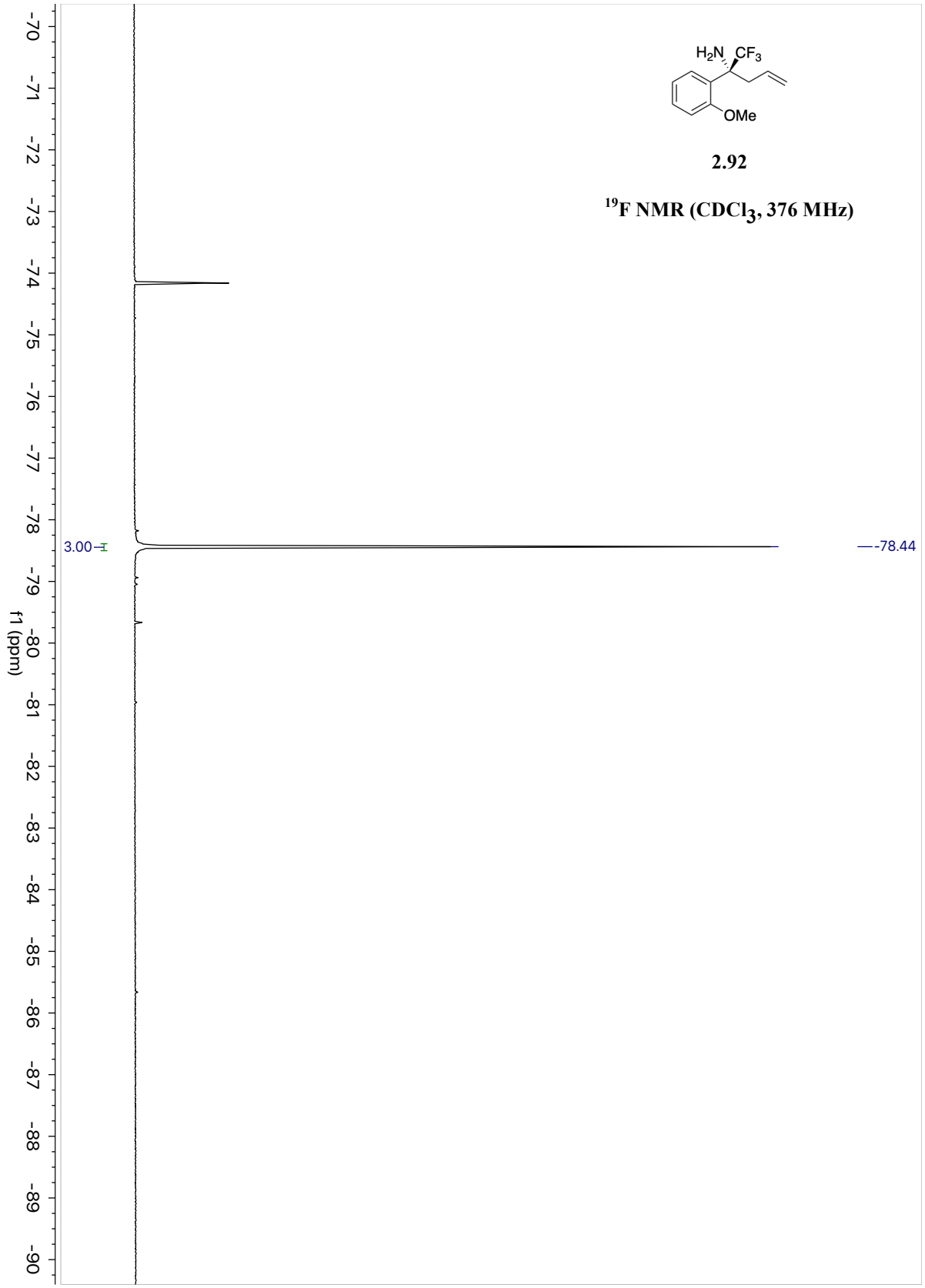

OMe
N
H
N
O
OH
t-Bu
ap-6
13C NMR (CDCl3, 100 MHz)
171.06
156.76
136.99
126.74
126.14
122.52
118.38
78.40
62.16
57.07
50.83
46.29
45.87
34.64
29.44
25.91
24.28
16.59
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

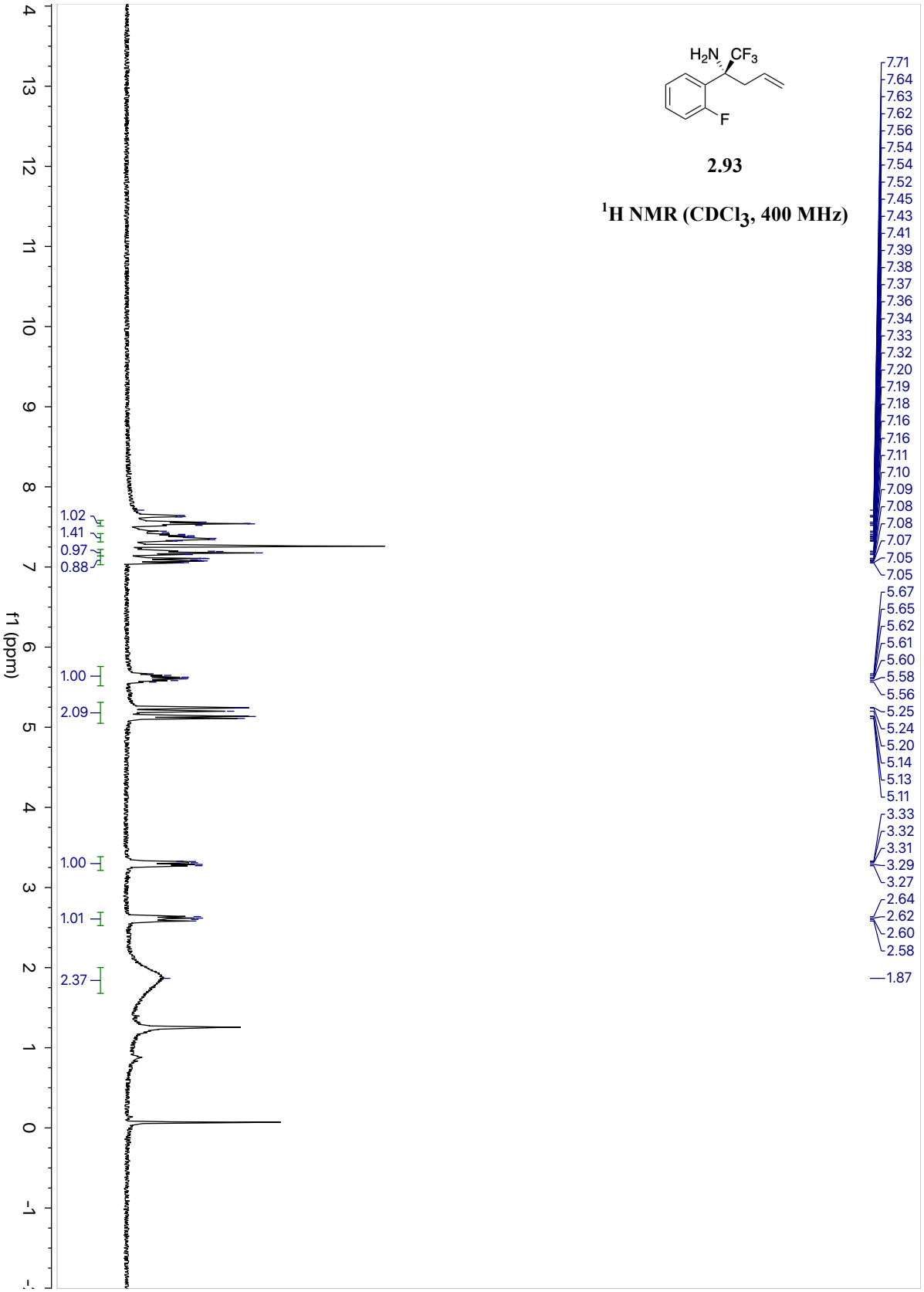

OMe
N
H
N
O
OH
t-Bu
ap-7
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.00
0.97
0.95
2.15
1.91
3.51
2.39
1.06
1.80
3.55
7.17
2.05
2.48
7.20
7.18
6.80
6.79
6.78
6.71
6.69
6.67
4.14
4.13
4.12
4.11
4.09
4.08
3.64
3.61
3.58
3.51
3.50
3.48
3.47
3.45
3.43
3.31
3.26
2.04
1.92
1.90
1.89
1.88
1.87
1.86
1.84
1.42
1.27
1.26
1.24
1.16

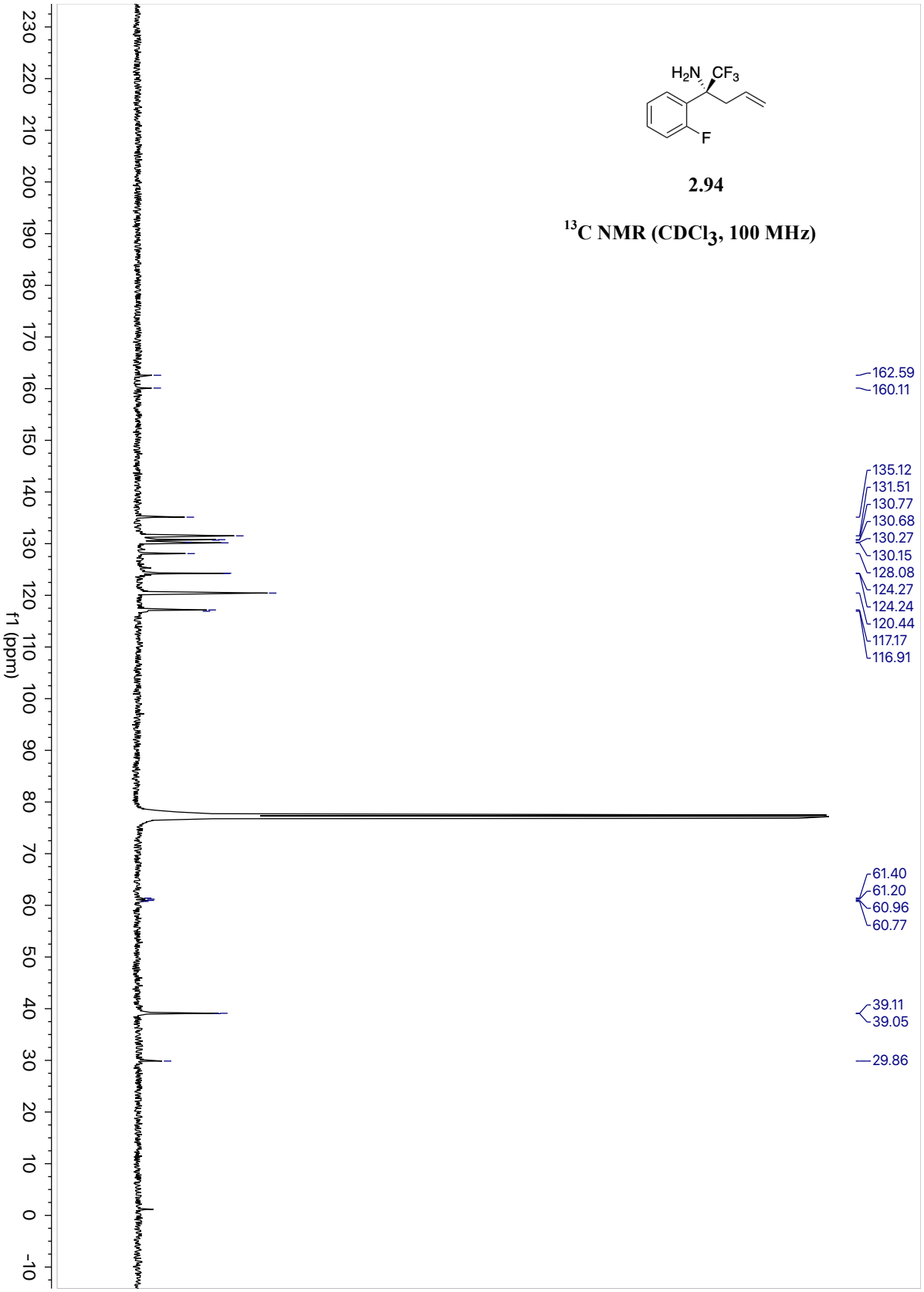

OMe
N
H
N
O
OH
t-Bu
ap-7
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
169.86
157.23
137.14
126.82
126.21
122.89
118.42
78.59
61.70
57.24
51.34
46.69
46.08
34.83
29.64
26.21
24.29
15.70

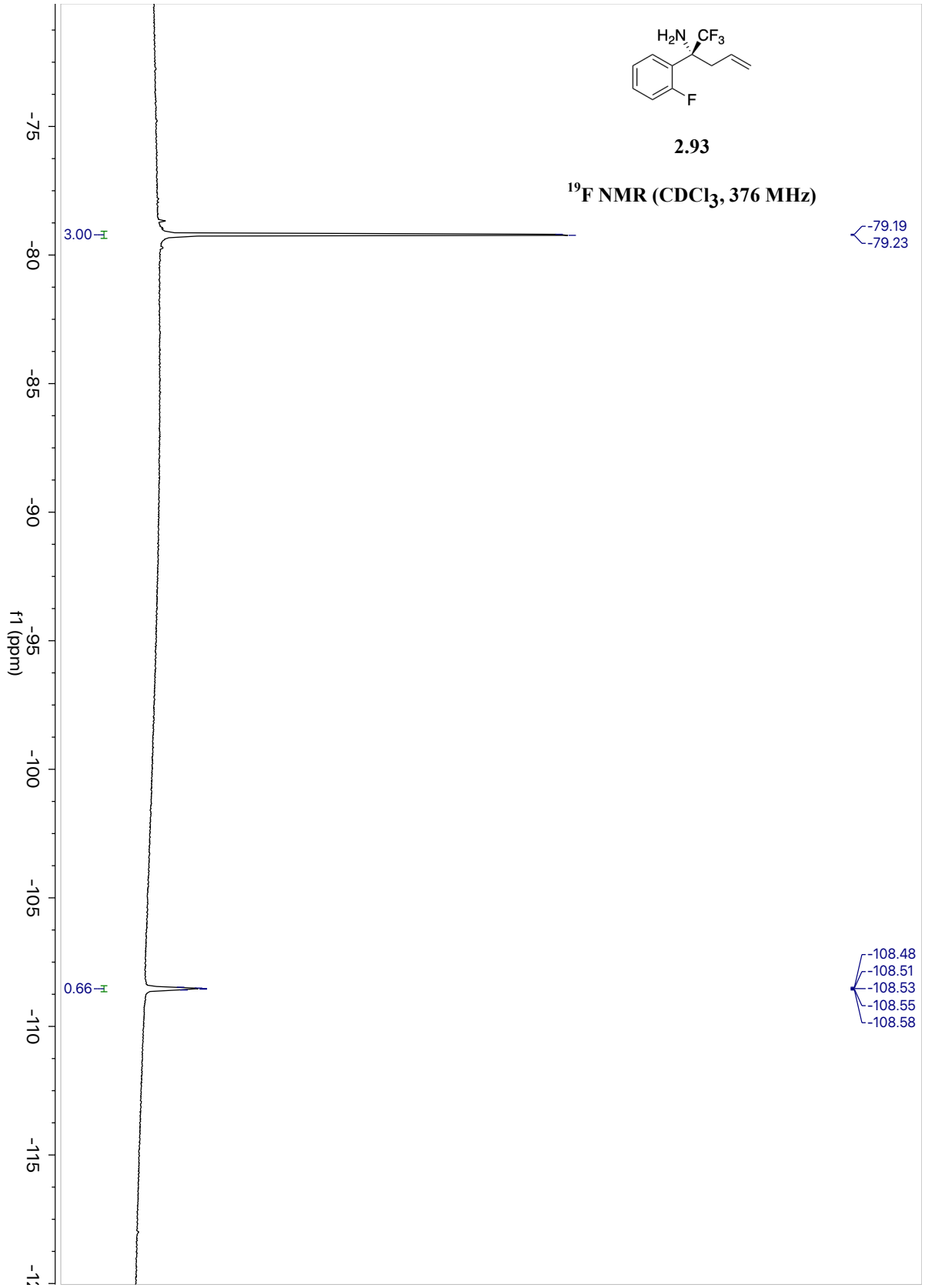

H2N CF3
OMe
2.92
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.95
0.91
1.80
0.86
1.88
2.86
0.96
1.10
2.15

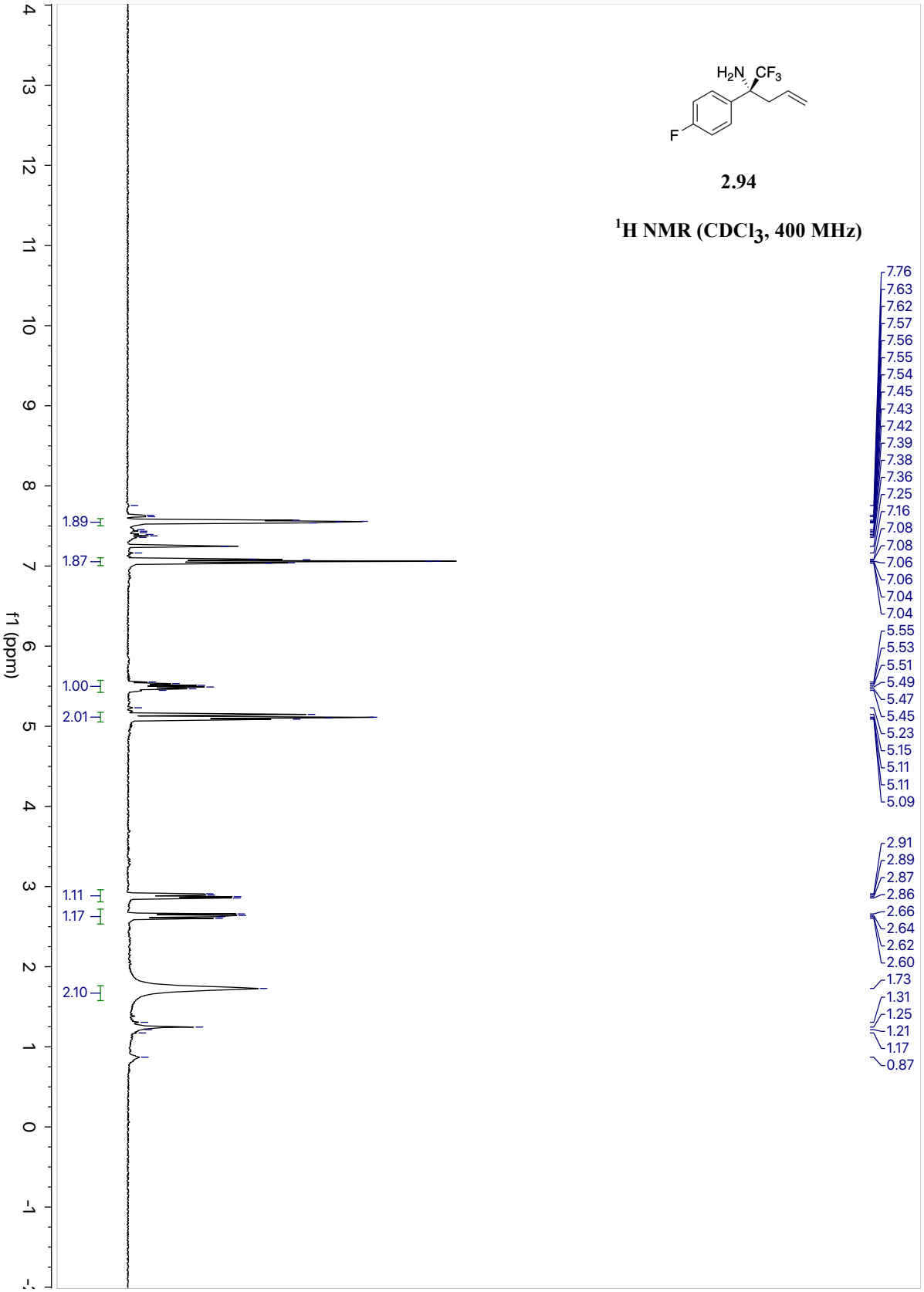

H2N CF3
OMe
2.92
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
159.05
135.93
132.48
131.51
130.17
129.96
128.67
125.82
124.58
122.96
120.82
120.74
120.33
119.74
119.35
117.53
113.81
113.35
113.17
112.68
112.22
62.35
62.09
61.83
61.56
55.79
39.37

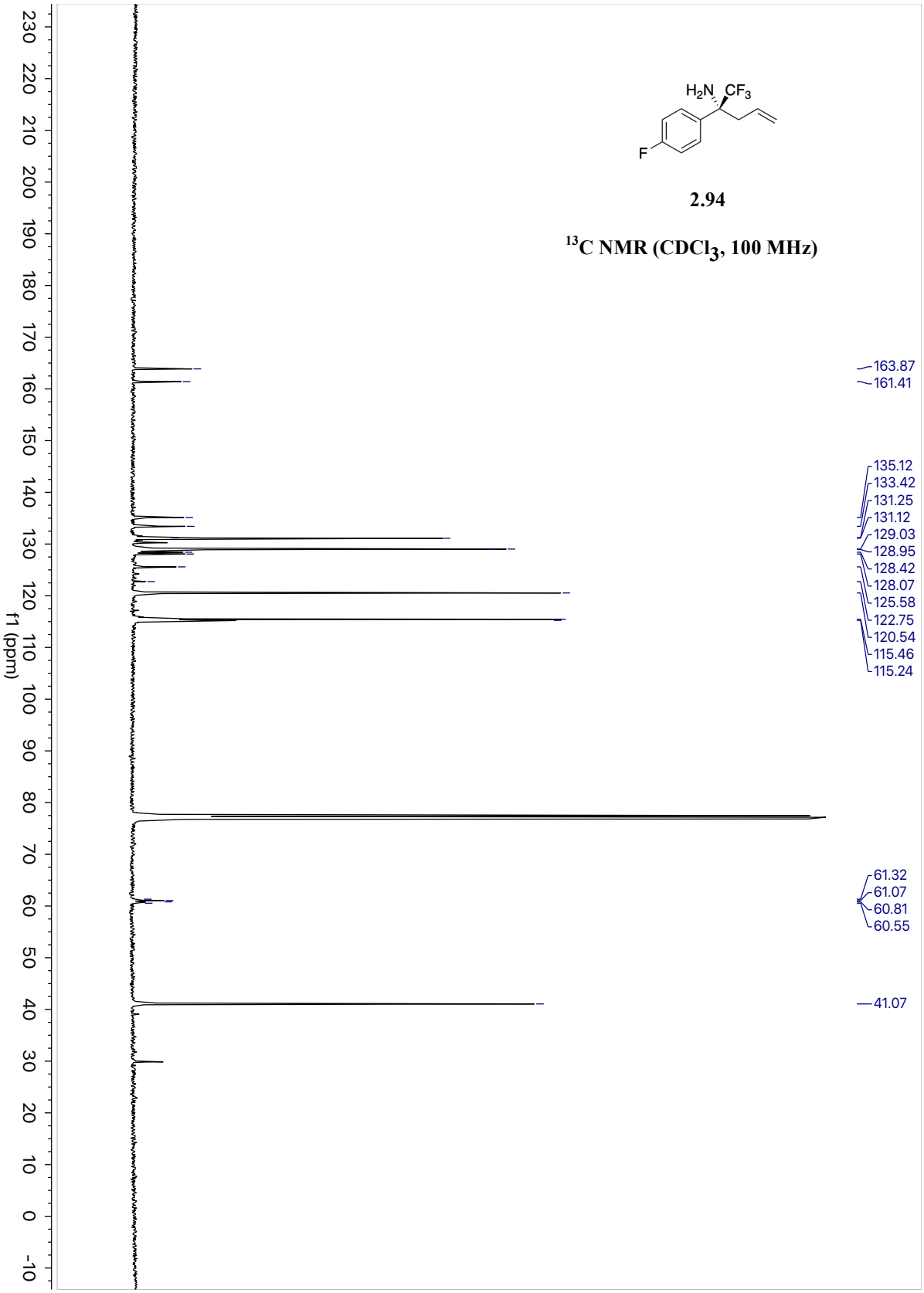

H2N CF3
OMe
2.92
19F NMR (CDCl3, 376 MHz)
3.00
-78.44
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

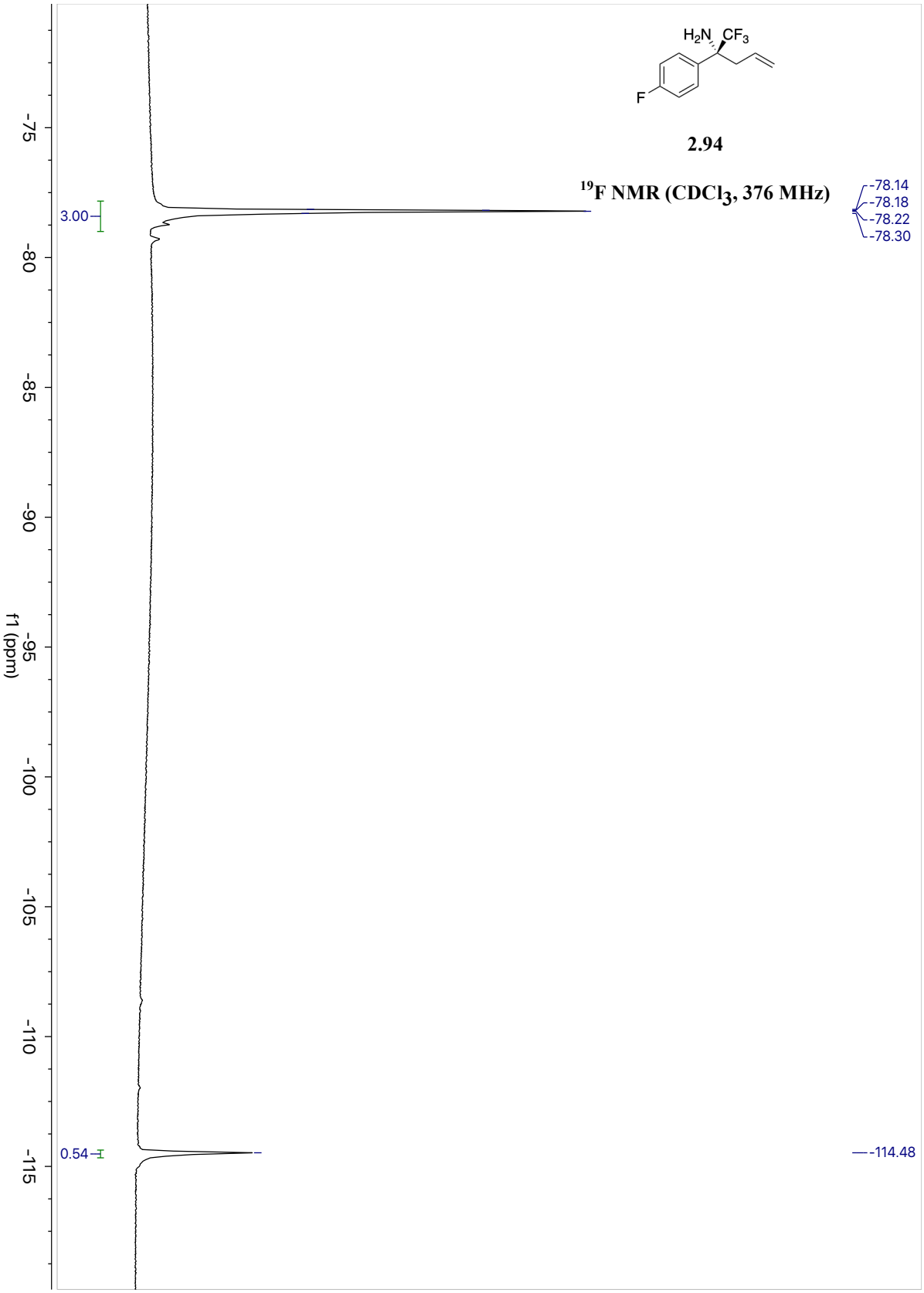

H2N
CF3
F
2.93
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.02
1.41
0.97
0.88
1.00
2.09
1.00
1.01
2.37
7.71
7.64
7.63
7.62
7.56
7.54
7.54
7.52
7.45
7.43
7.41
7.39
7.38
7.37
7.36
7.34
7.33
7.32
7.20
7.19
7.18
7.16
7.16
7.11
7.10
7.09
7.08
7.08
7.07
7.05
7.05
5.67
5.65
5.62
5.61
5.60
5.58
5.56
5.25
5.24
5.20
5.14
5.13
5.11
3.33
3.32
3.31
3.29
3.27
2.64
2.62
2.60
2.58
1.87

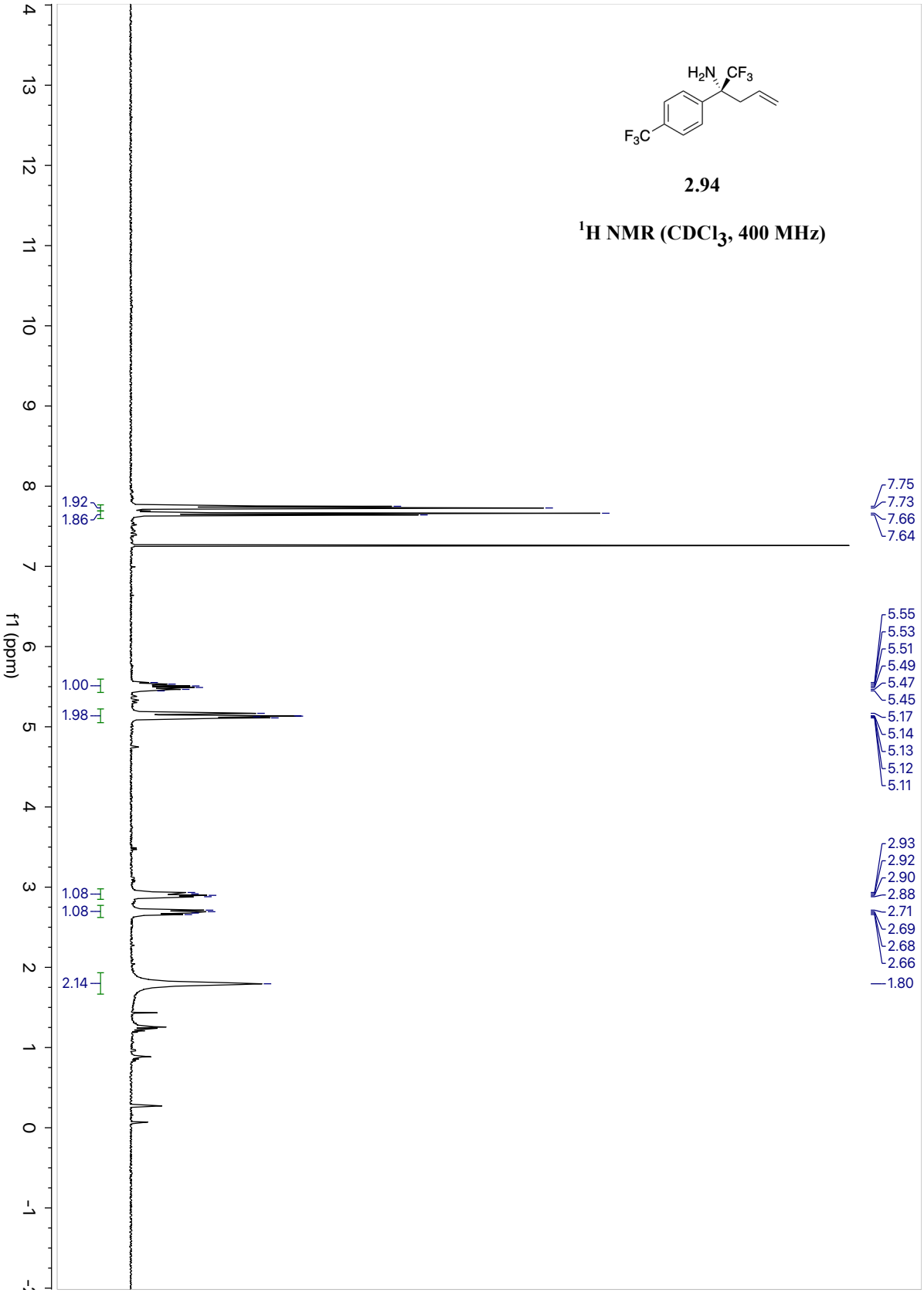

H2N
CF3
F
2.94
13C NMR (CDCl3, 100 MHz)
162.59
160.11
135.12
131.51
130.77
130.68
130.27
130.15
128.08
124.27
124.24
120.44
117.17
116.91
61.40
61.20
60.96
60.77
39.11
39.05
29.86
f1 (ppm)

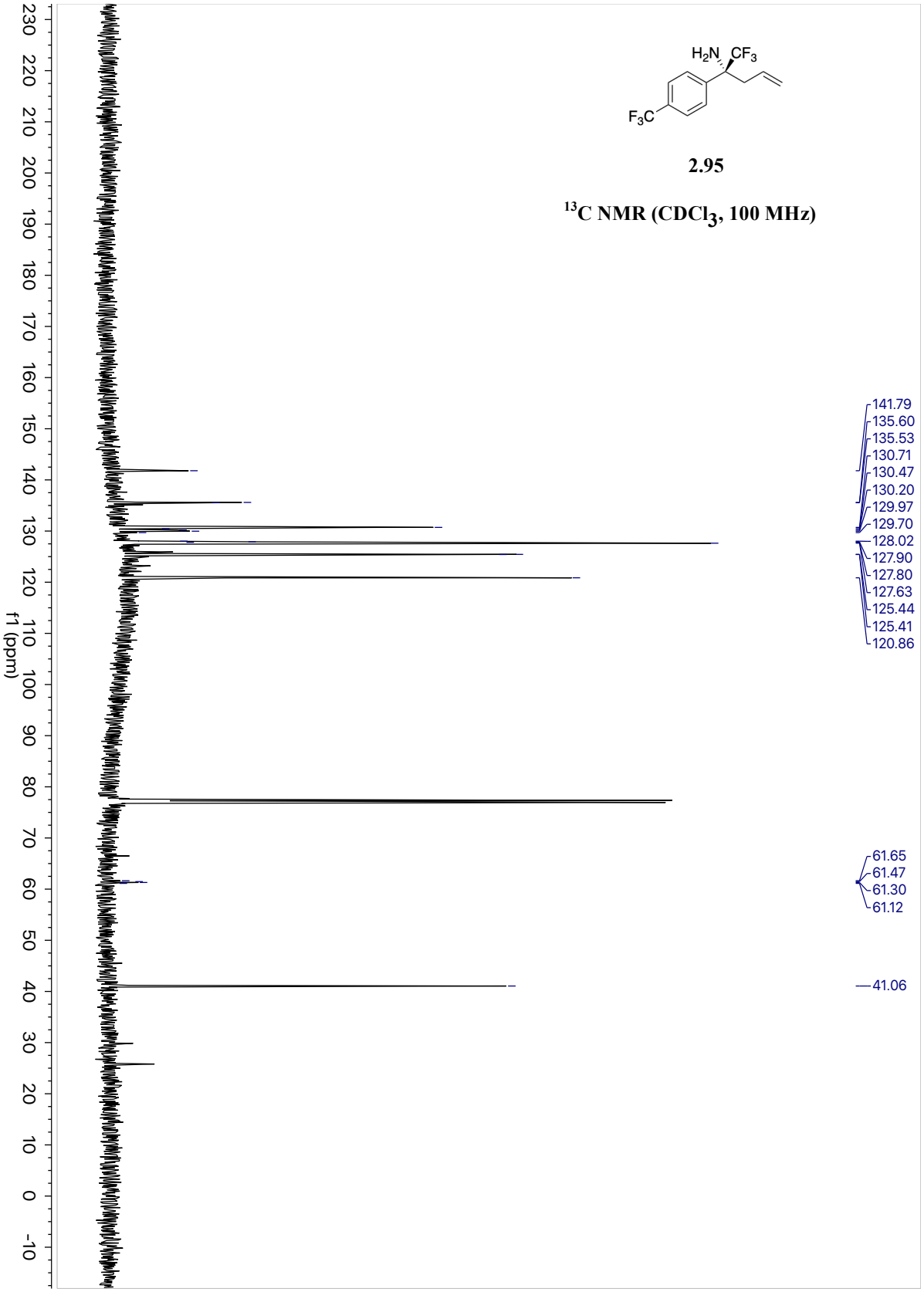

H2N CF3
F
2.93
19F NMR (CDCl3, 376 MHz)
3.00
0.66
-79.19
-79.23
-108.48
-108.51
-108.53
-108.55
-108.58
f1 (ppm)
-75
-80
-85
-90
-95
-100
-105
-110
-115

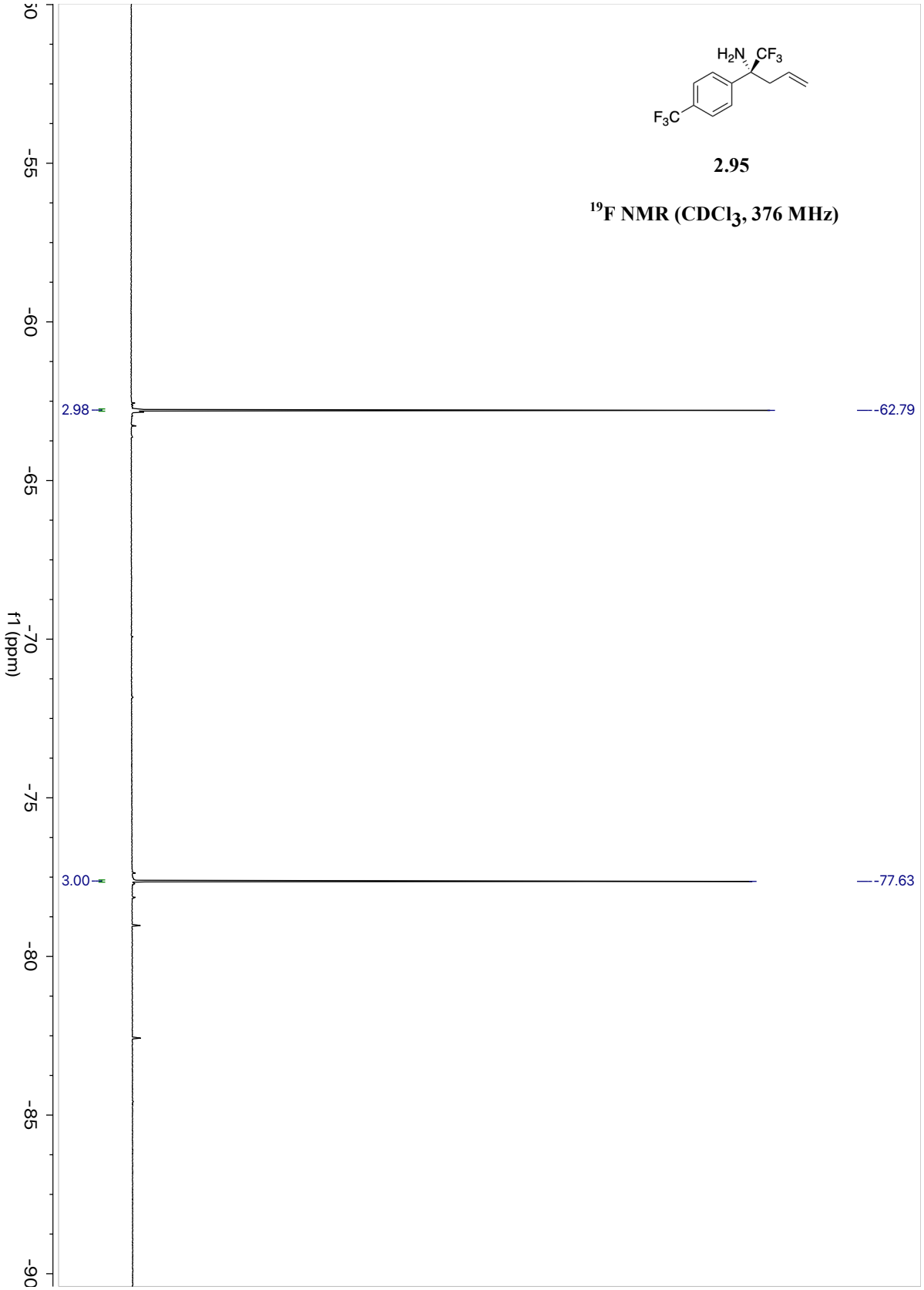

H2N CF3
F
2.94
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.89
1.87
1.00
2.01
1.11
1.17
2.10
7.76
7.63
7.62
7.57
7.56
7.55
7.54
7.45
7.43
7.42
7.39
7.38
7.36
7.25
7.16
7.08
7.08
7.06
7.06
7.04
7.04
5.55
5.53
5.51
5.49
5.47
5.45
5.23
5.15
5.11
5.11
5.09
2.91
2.89
2.87
2.86
2.66
2.64
2.62
2.60
1.73
1.31
1.25
1.21
1.17
0.87

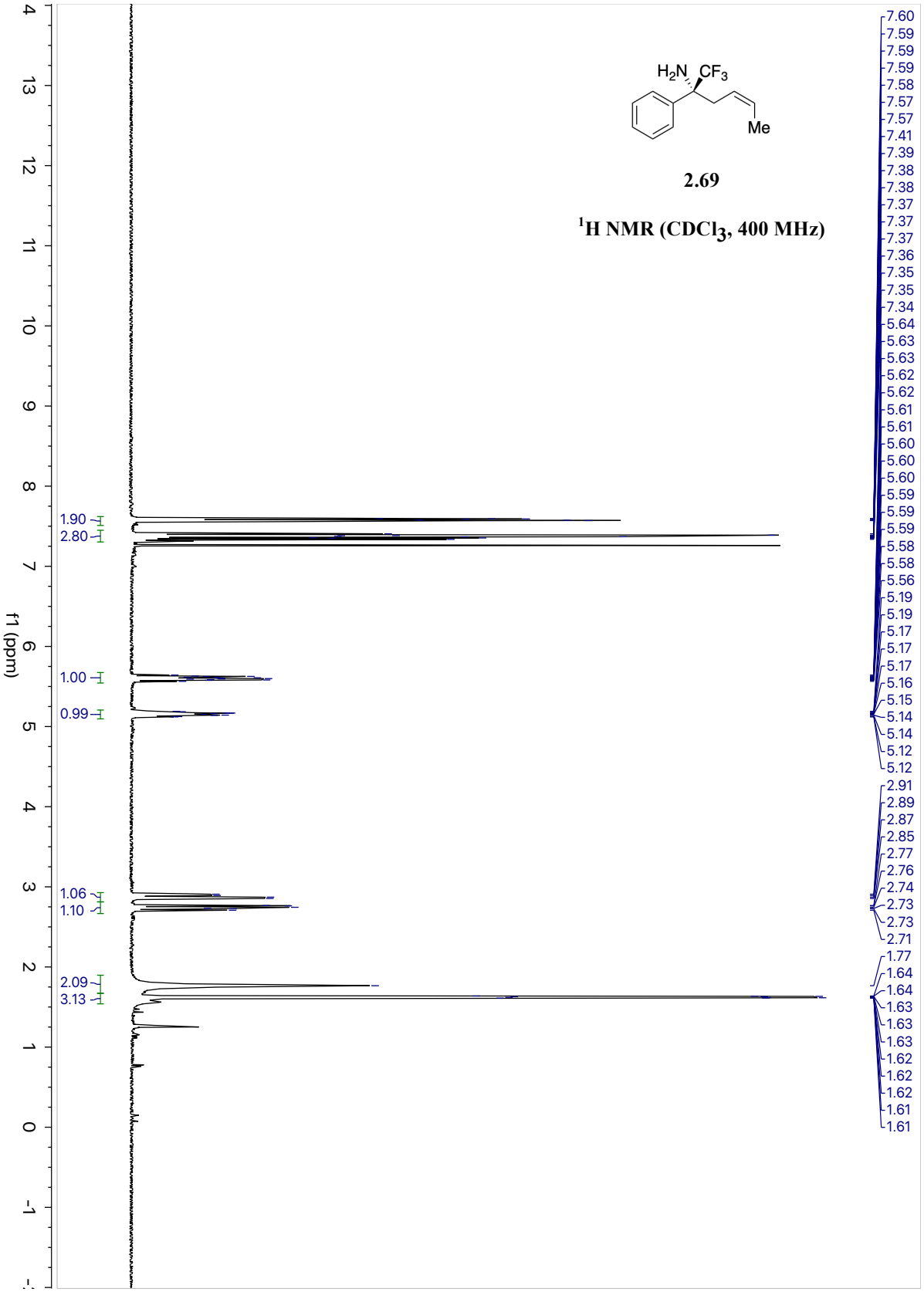

H2N
CF3
F
2.94
13C NMR (CDCl3, 100 MHz)
163.87
161.41
135.12
133.42
131.25
131.12
129.03
128.95
128.42
128.07
125.58
122.75
120.54
115.46
115.24
61.32
61.07
60.81
60.55
41.07
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

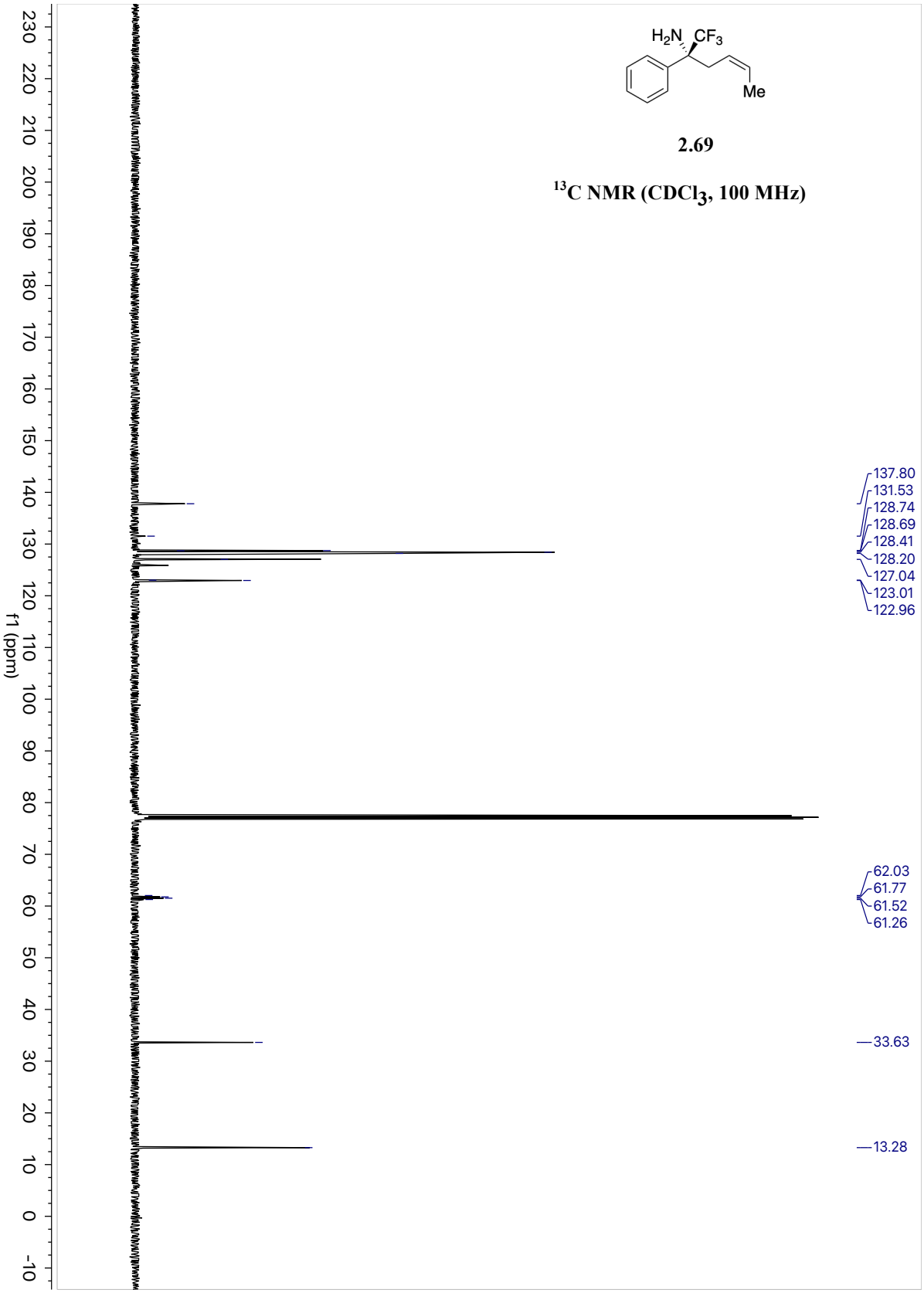

H2N CF3
F
2.94
19F NMR (CDCl3, 376 MHz)
-78.14
-78.18
-78.22
-78.30
3.00
0.54
-114.48
-75
-80
-85
-90
-95
-100
-105
-110
-115
f1 (ppm)

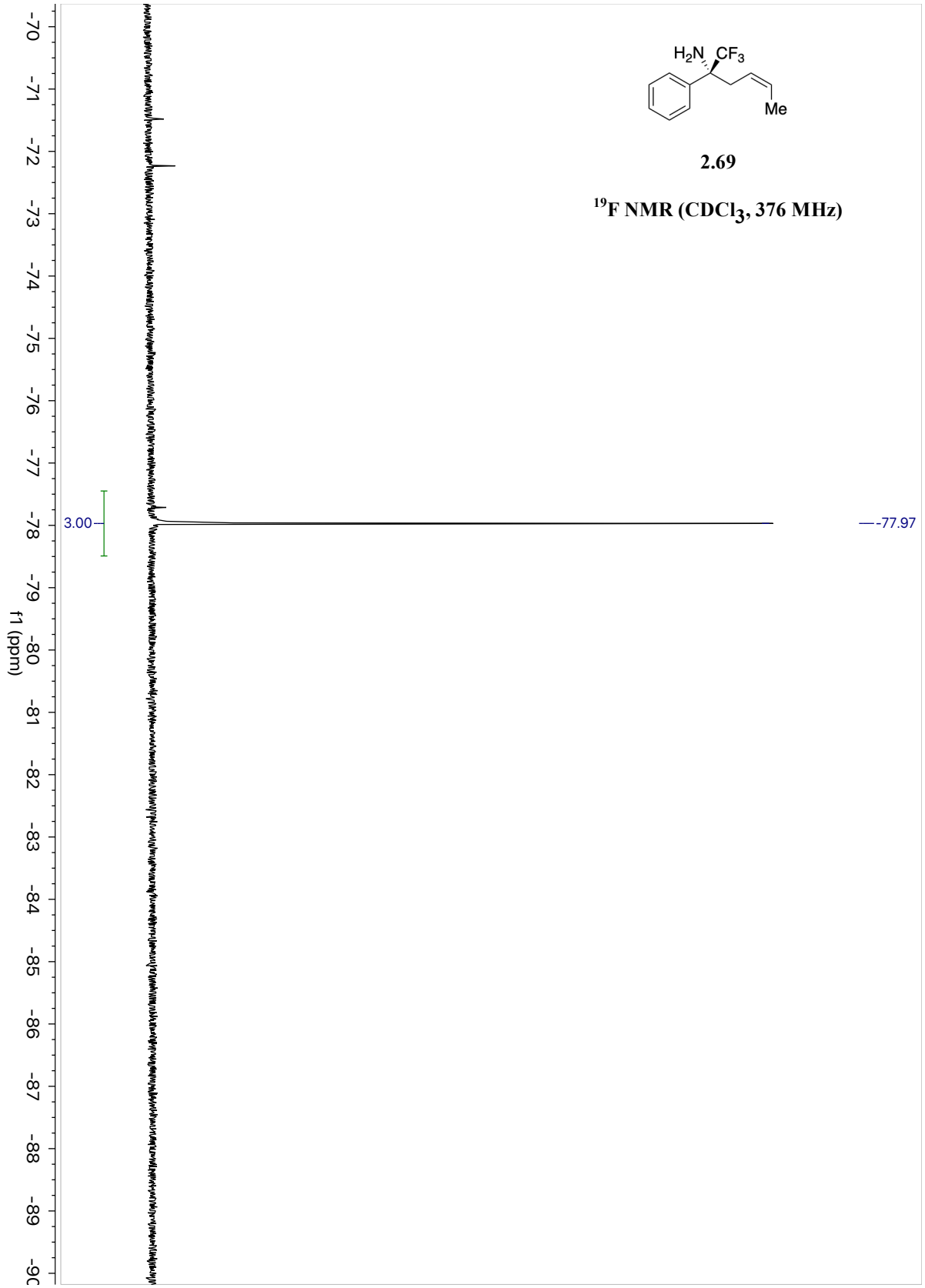

H2N
CF3
F3C
2.94
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.92
1.86
1.00
1.98
1.08
1.08
2.14
7.75
7.73
7.66
7.64
5.55
5.53
5.51
5.49
5.47
5.45
5.17
5.14
5.13
5.12
5.11
2.93
2.92
2.90
2.88
2.71
2.69
2.68
2.66
1.80

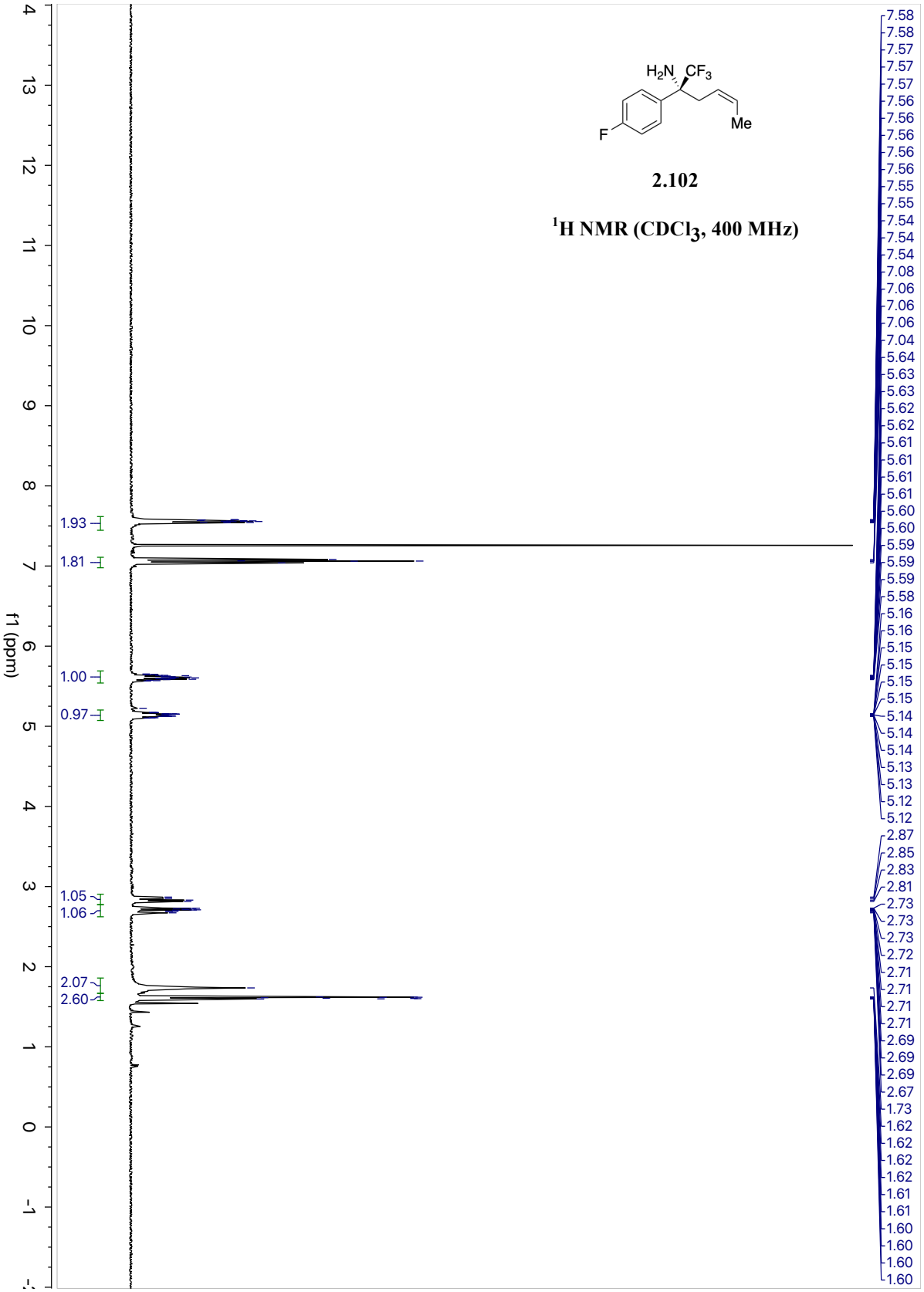

H2N
CF3
F3C
2.95
13C NMR (CDCl3, 100 MHz)
141.79
135.60
135.53
130.71
130.47
130.20
129.97
129.70
128.02
127.90
127.80
127.63
125.44
125.41
120.86
61.65
61.47
61.30
61.12
41.06
f1 (ppm)

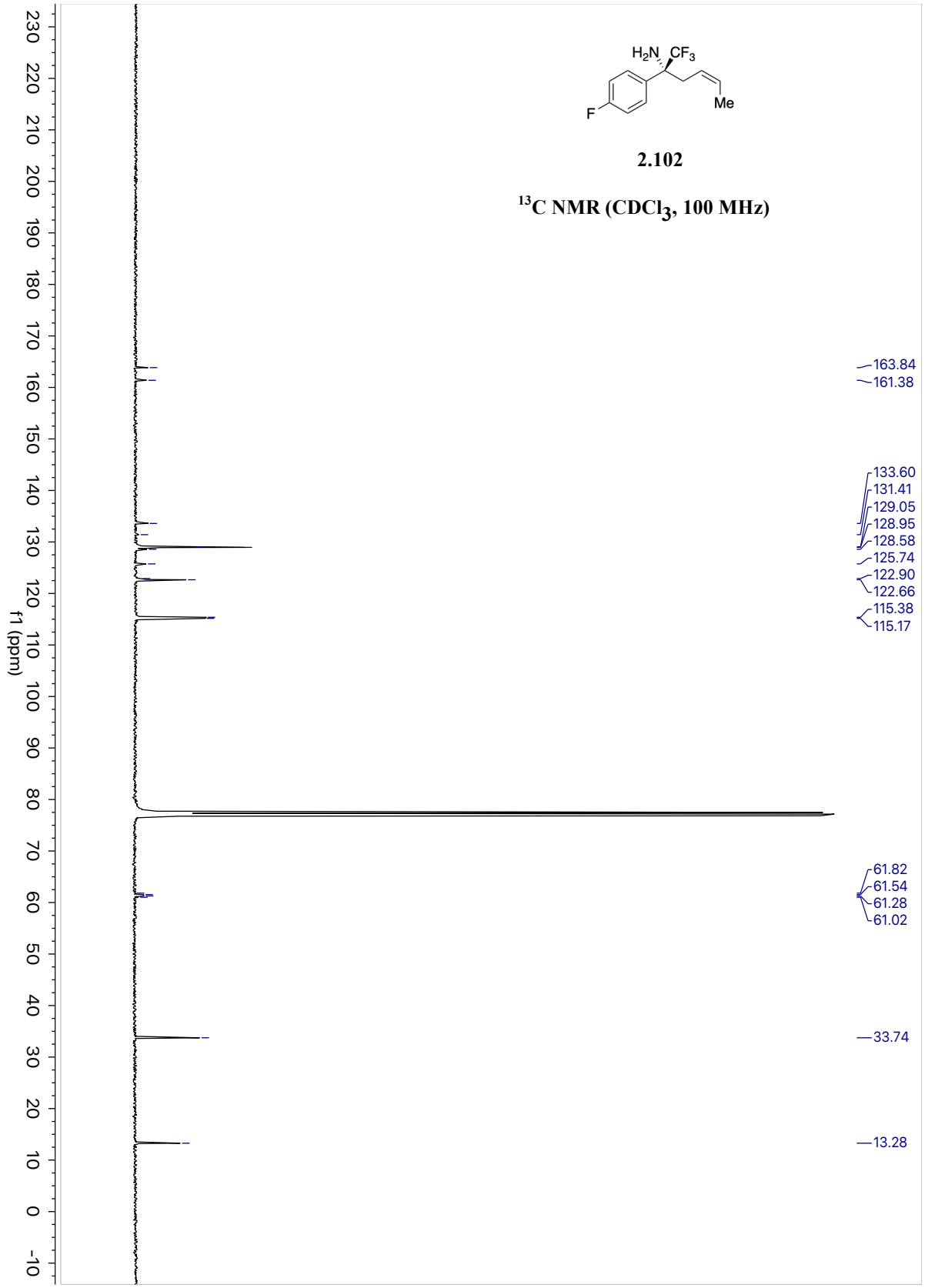

H2N
CF3
F3C
2.95
19F NMR (CDCl3, 376 MHz)
f1 (ppm)
-55
-60
-65
-70
-75
-80
-85
-90
2.98
-62.79
3.00
-77.63

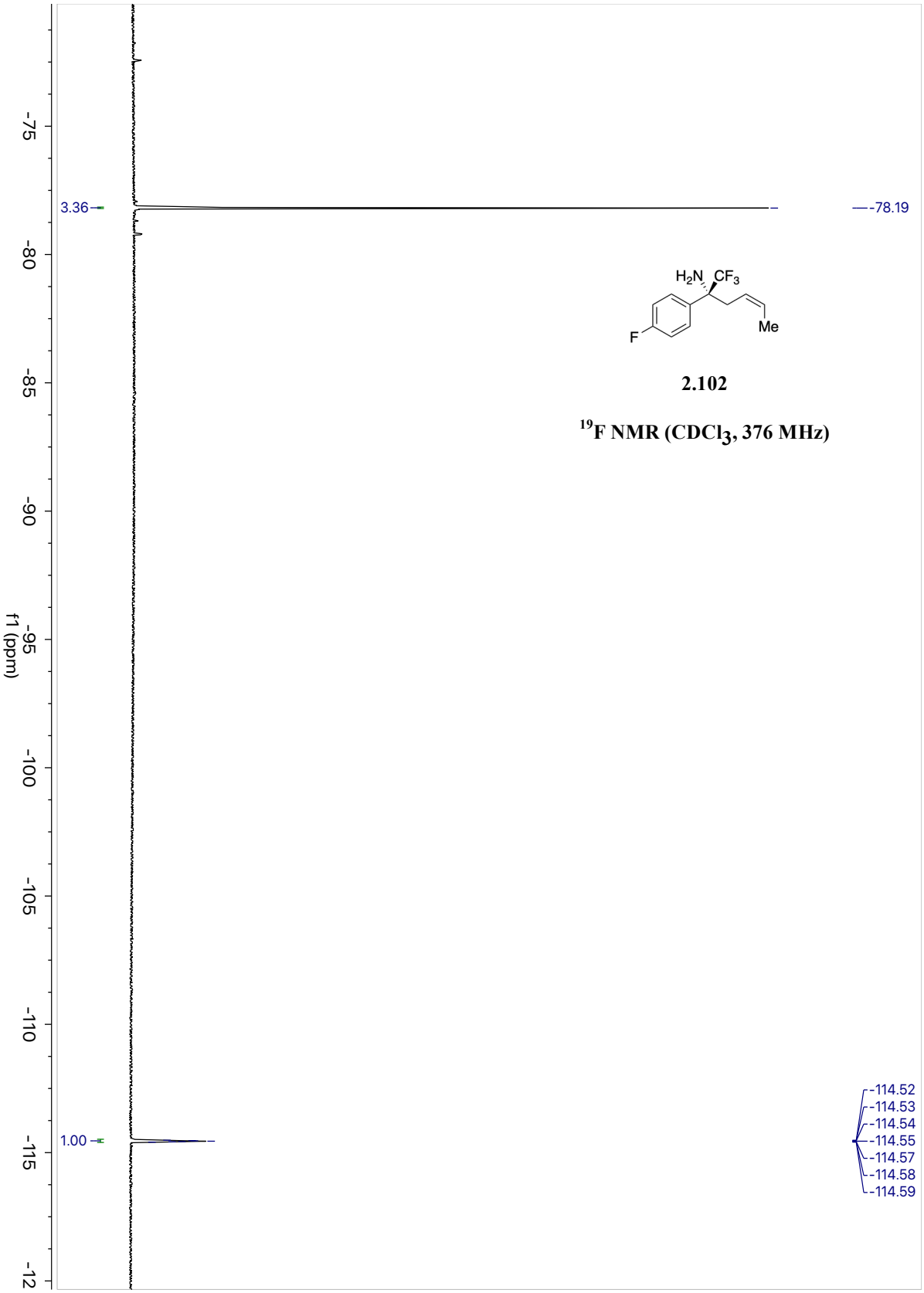

H2N CF3
Me
2.69
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.90
2.80
1.00
0.99
1.06
1.10
2.09
3.13


H2N CF3
Me
2.69
13C NMR (CDCl3, 100 MHz)
137.80
131.53
128.74
128.69
128.41
128.20
127.04
123.01
122.96
62.03
61.77
61.52
61.26
33.63
13.28
f1 (ppm)


H2N
CF3
Me
2.69
19F NMR (CDCl3, 376 MHz)
3.00
-77.97
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

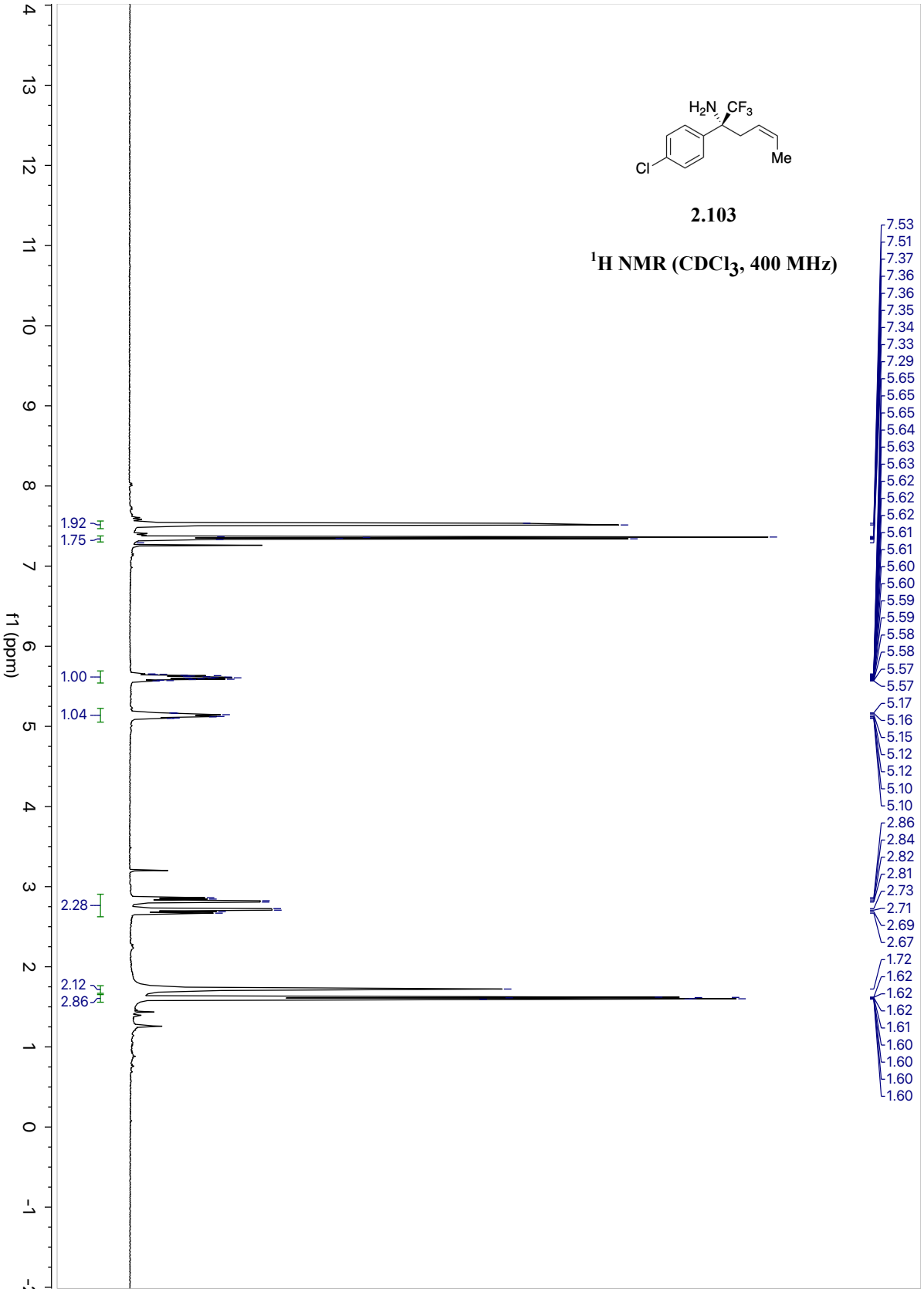

H2N
CF3
F
Me
2.102
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.93
1.81
1.00
0.97
1.05
1.06
2.07
2.60

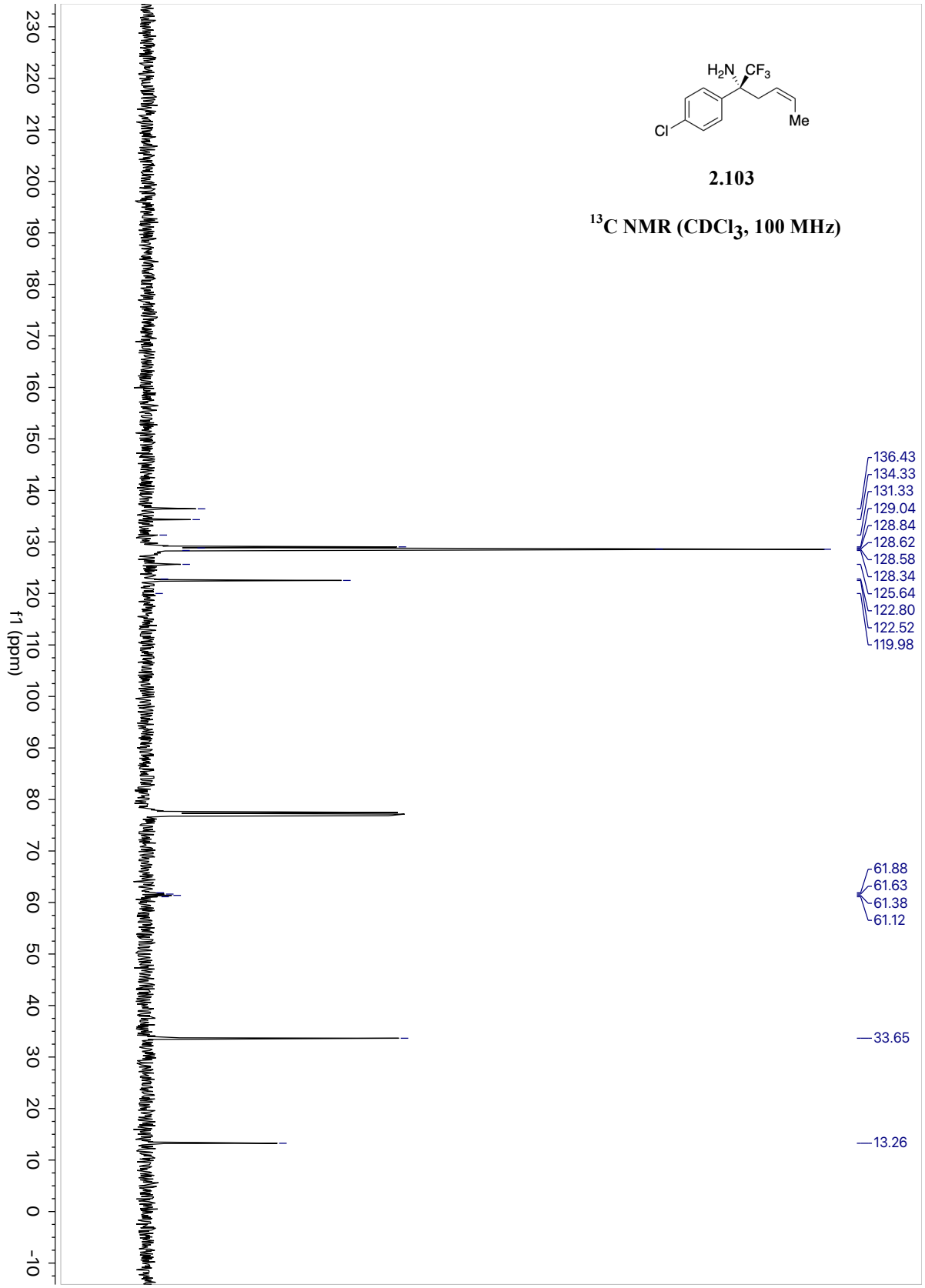

H2N CF3
F
Me
2.102
13C NMR (CDCl3, 100 MHz)
163.84
161.38
133.60
131.41
129.05
128.95
128.58
125.74
122.90
122.66
115.38
115.17
61.82
61.54
61.28
61.02
33.74
13.28
f1 (ppm)

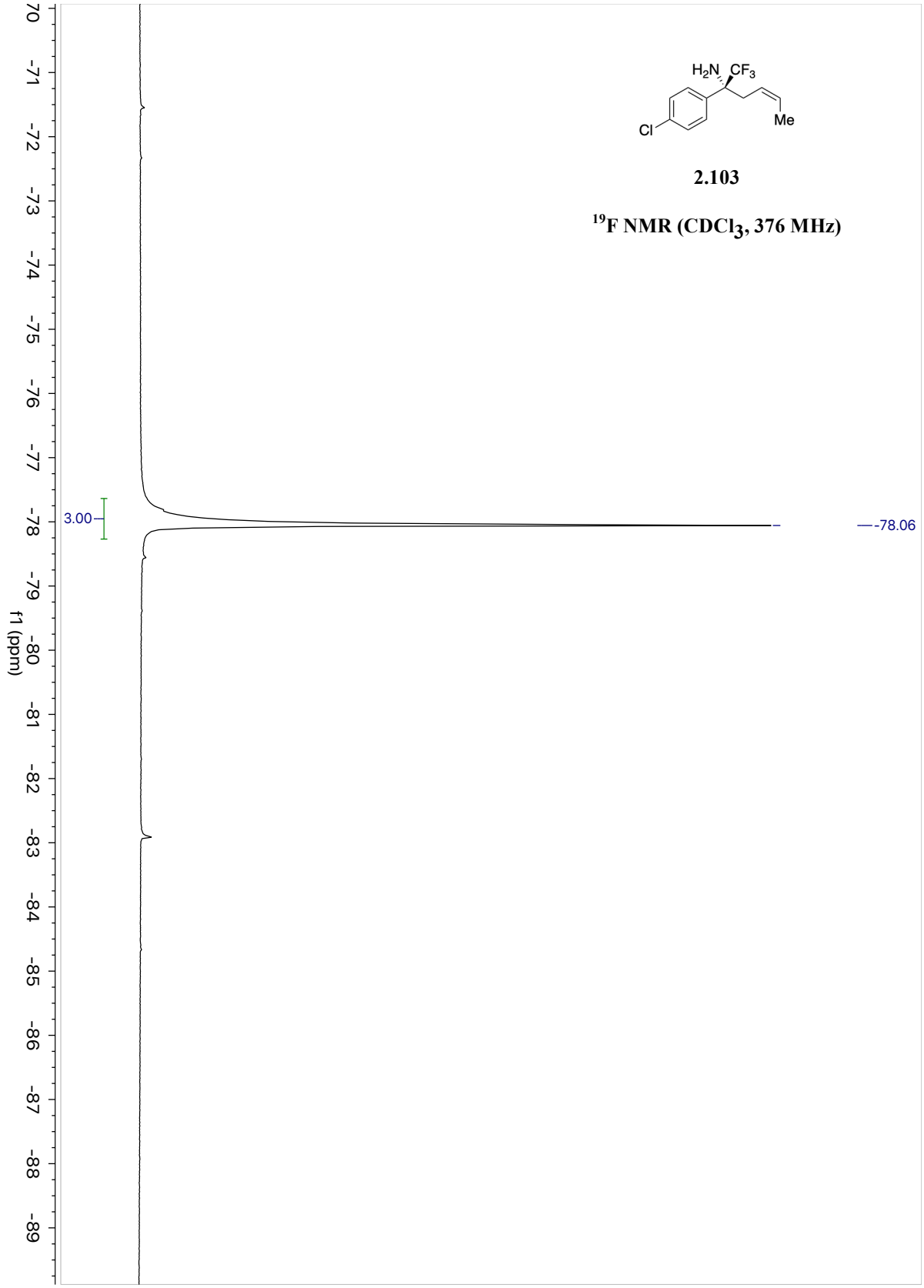


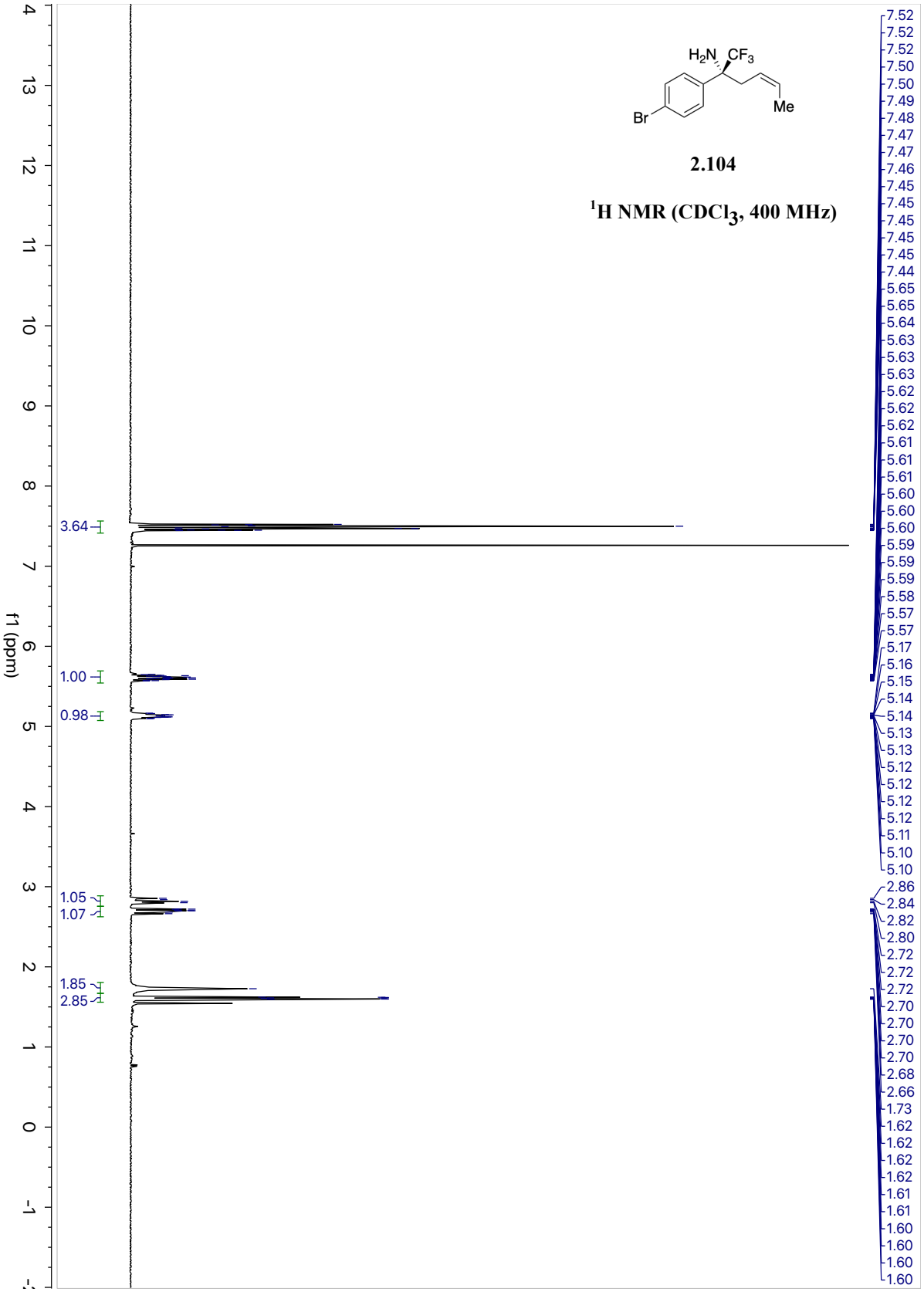
2.102

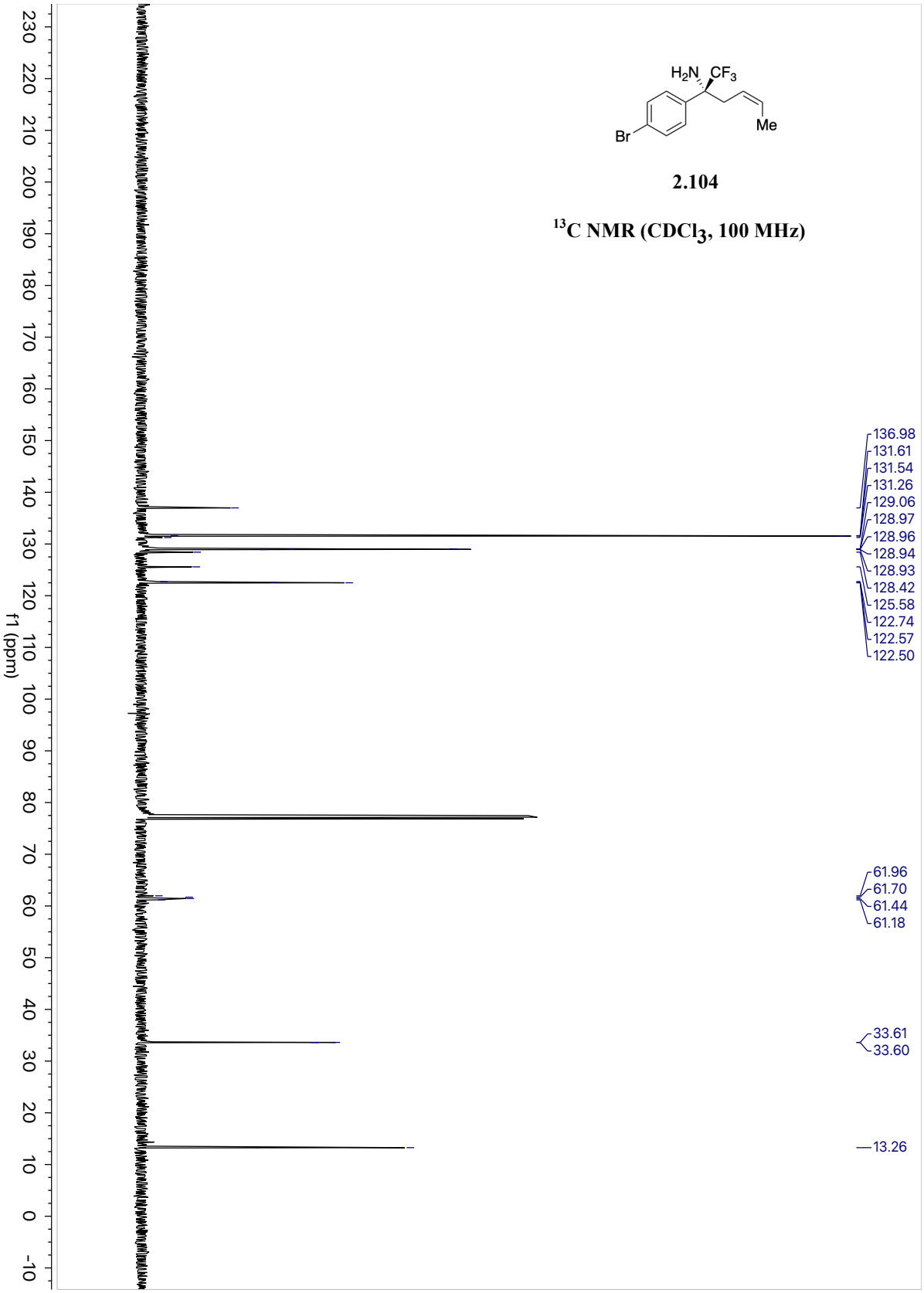
^{19}F NMR ($CDCl_3$, 376 MHz)

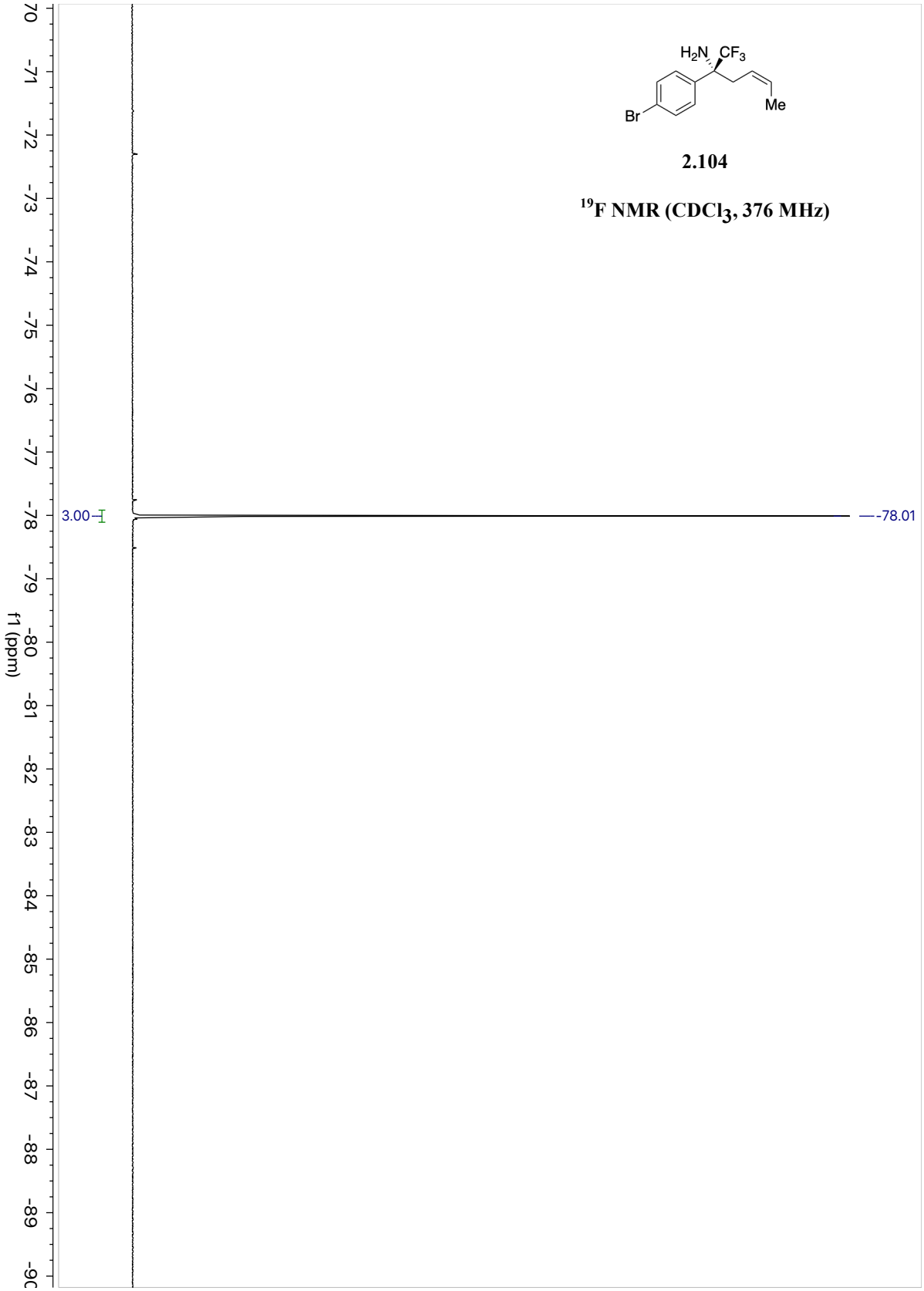

H2N
CF3
Cl
Me
2.103
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.92
1.75
1.00
1.04
2.28
2.12
2.86
7.53
7.51
7.37
7.36
7.36
7.35
7.34
7.33
7.29
5.65
5.65
5.65
5.64
5.63
5.63
5.62
5.62
5.62
5.61
5.61
5.60
5.60
5.59
5.59
5.58
5.58
5.57
5.57
5.17
5.16
5.15
5.12
5.12
5.10
5.10
2.86
2.84
2.82
2.81
2.73
2.71
2.69
2.67
1.72
1.62
1.62
1.62
1.61
1.60
1.60
1.60
1.60

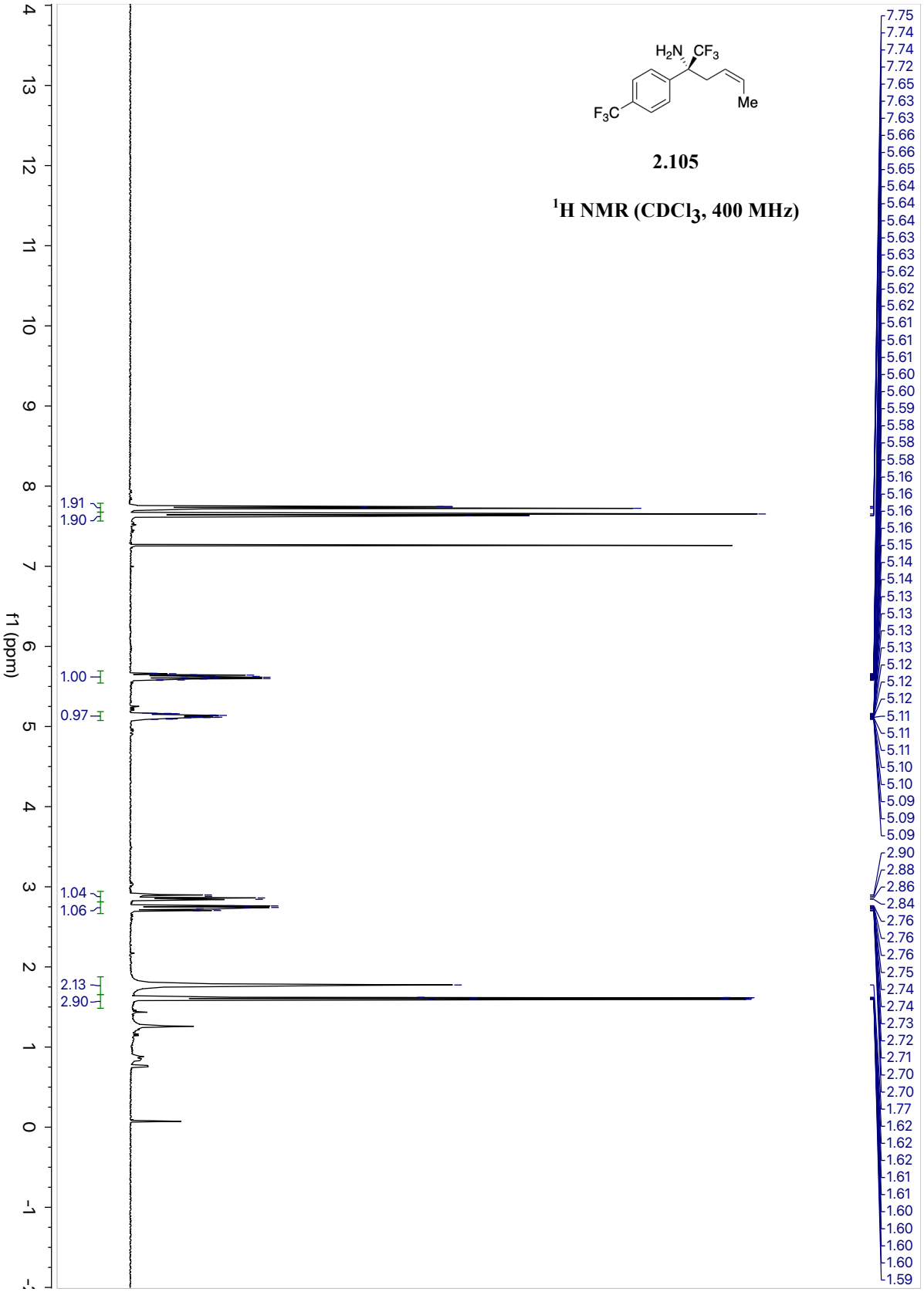

H2N
CF3
Cl
Me
2.103
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
136.43
134.33
131.33
129.04
128.84
128.62
128.58
128.34
125.64
122.80
122.52
119.98
61.88
61.63
61.38
61.12
33.65
13.26

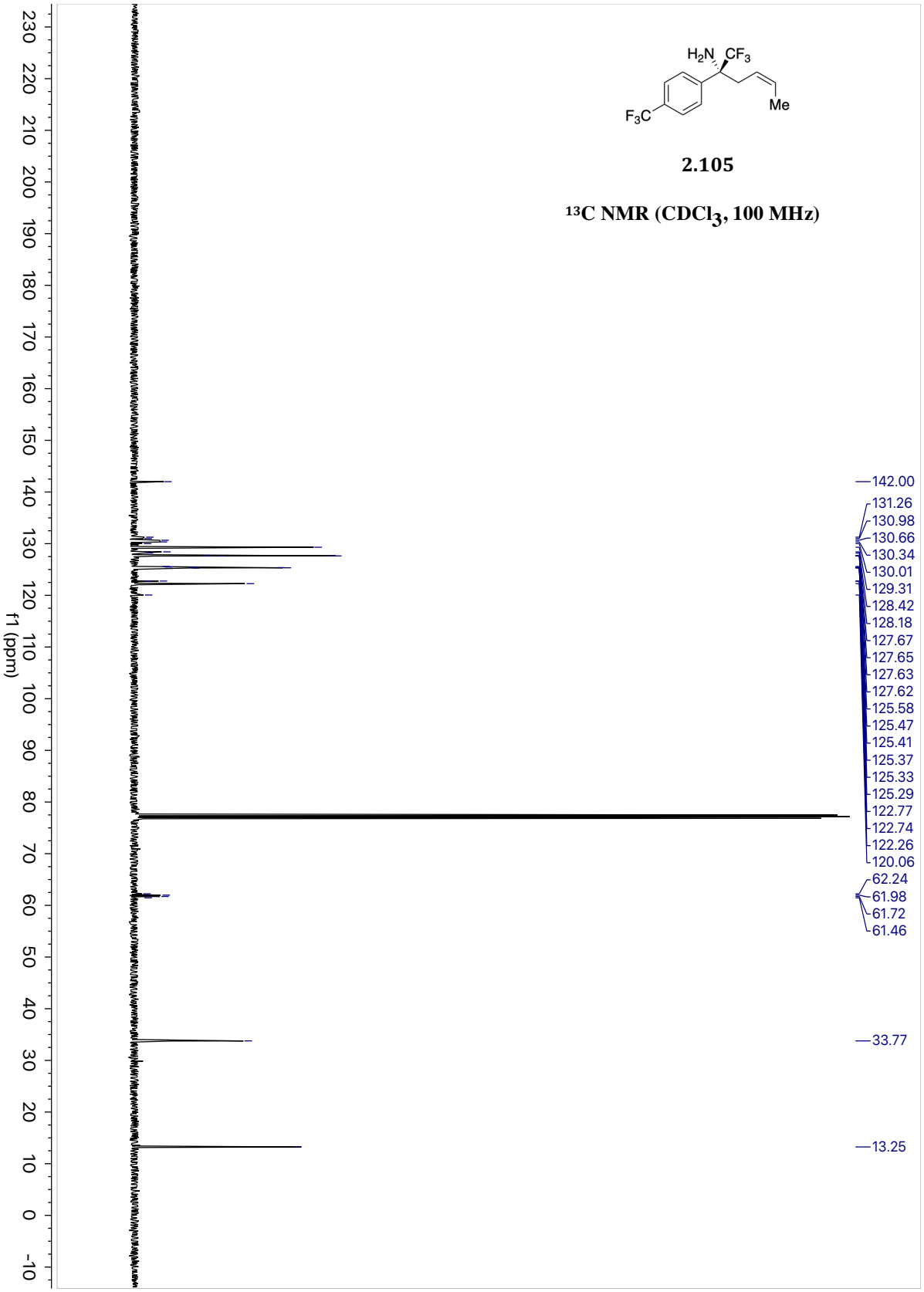

H2N
CF3
Cl
Me
2.103
19F NMR (CDCl3, 376 MHz)
3.00
-78.06
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89

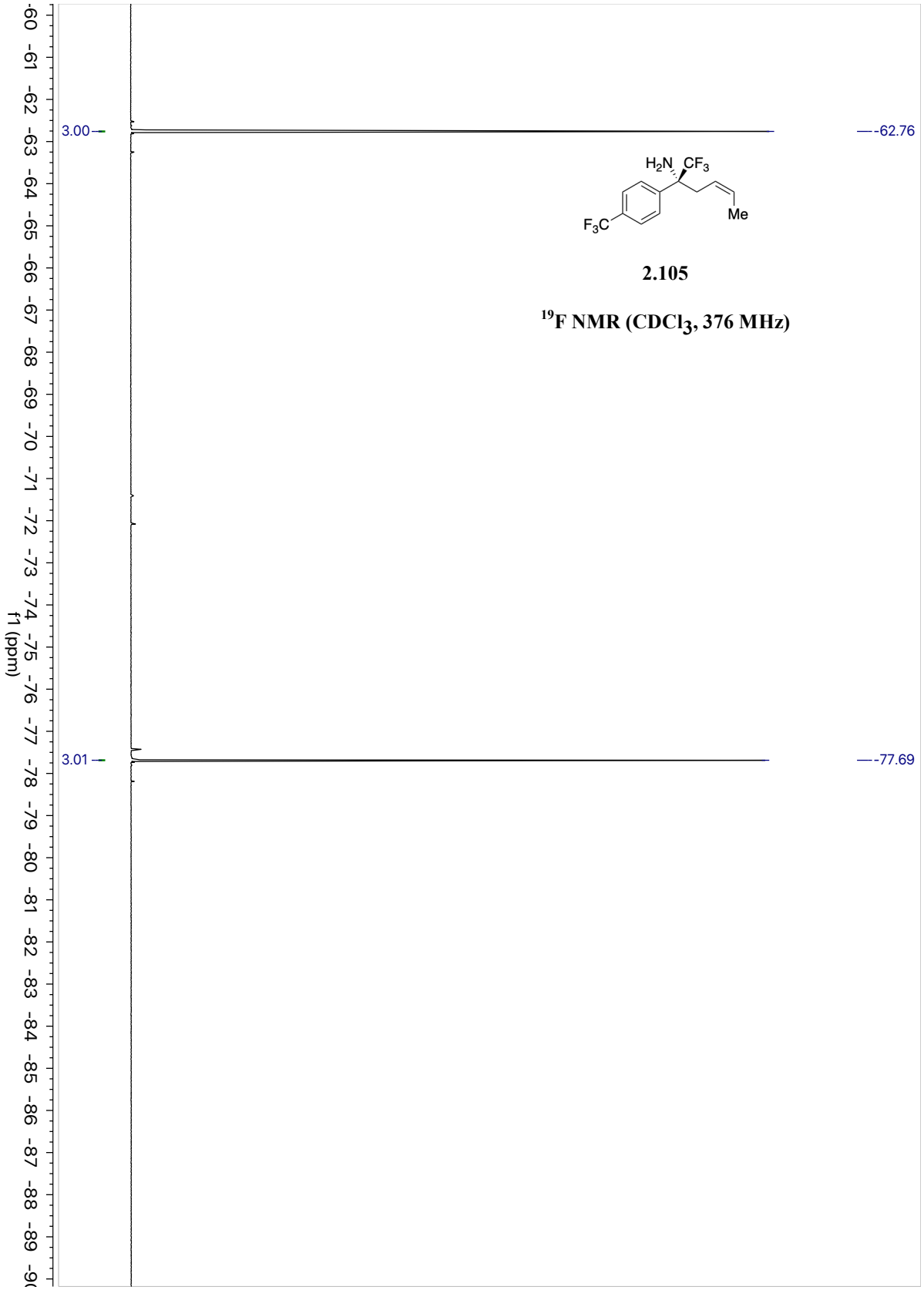

H2N
CF3
Br
Me
2.104
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
3.64
1.00
0.98
1.05
1.07
1.85
2.85


H2N CF3
Br
Me
2.104
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
136.98
131.61
131.54
131.26
129.06
128.97
128.96
128.94
128.93
128.42
125.58
122.74
122.57
122.50
61.96
61.70
61.44
61.18
33.61
33.60
13.26


H2N
CF3
Br
Me
2.104
19F NMR (CDCl3, 376 MHz)
3.00
-78.01
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

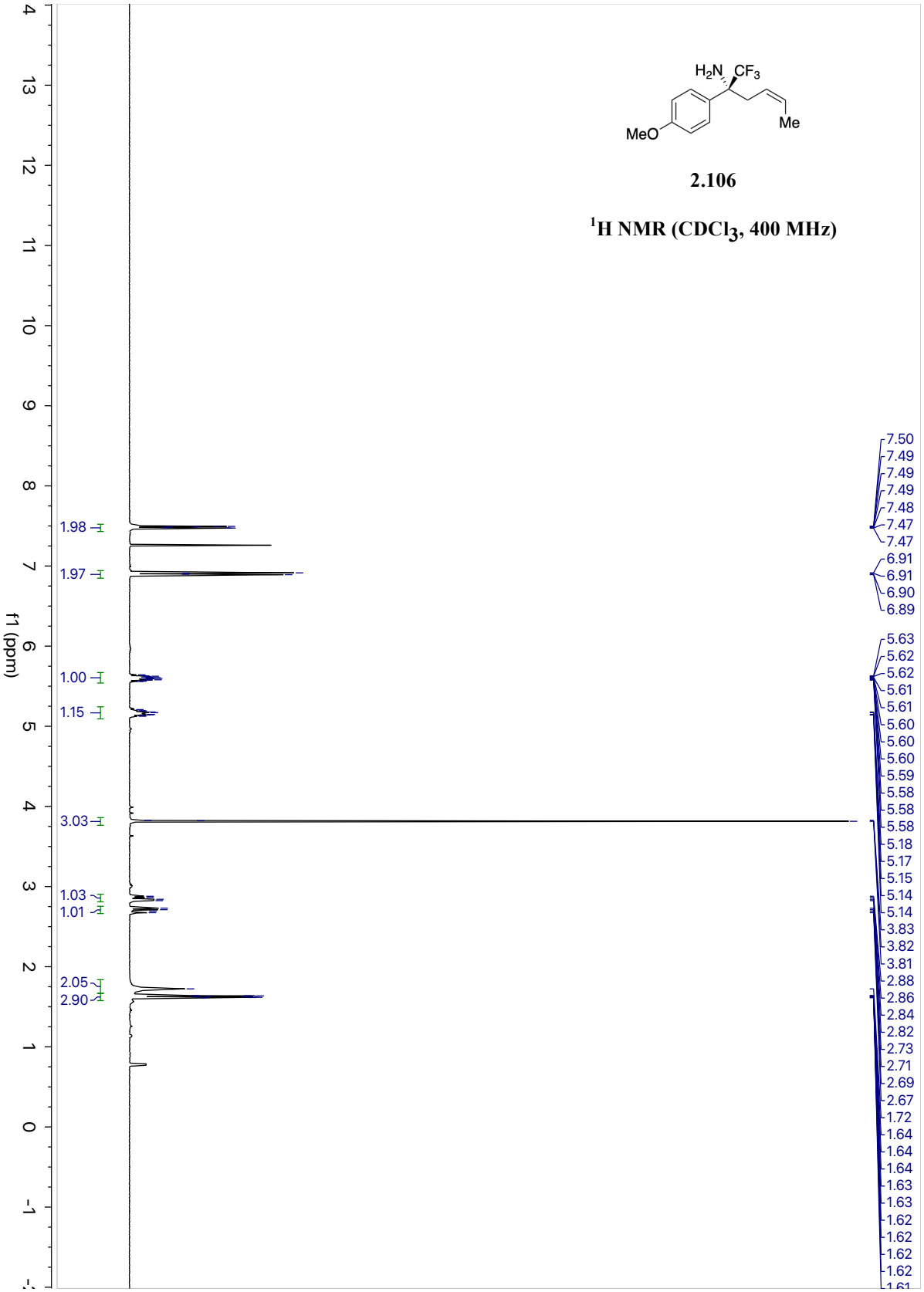

H2N
CF3
F3C
Me
2.105
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.91
1.90
1.00
0.97
1.04
1.06
2.13
2.90


H2N
CF3
F3C
Me
2.105
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
142.00
131.26
130.98
130.66
130.34
130.01
129.31
128.42
128.18
127.67
127.65
127.63
127.62
125.58
125.47
125.41
125.37
125.33
125.29
122.77
122.74
122.26
120.06
62.24
61.98
61.72
61.46
33.77
13.25



2.105

^{19}F NMR ($CDCl_3$, 376 MHz)


H2N
CF3
MeO
Me
2.106
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.98
1.97
1.00
1.15
3.03
1.03
1.01
2.05
2.90
7.50
7.49
7.49
7.49
7.48
7.47
7.47
6.91
6.91
6.90
6.89
5.63
5.62
5.62
5.61
5.61
5.60
5.60
5.60
5.59
5.58
5.58
5.58
5.18
5.17
5.15
5.14
5.14
3.83
3.82
3.81
2.88
2.86
2.84
2.82
2.73
2.71
2.69
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1.72
1.64
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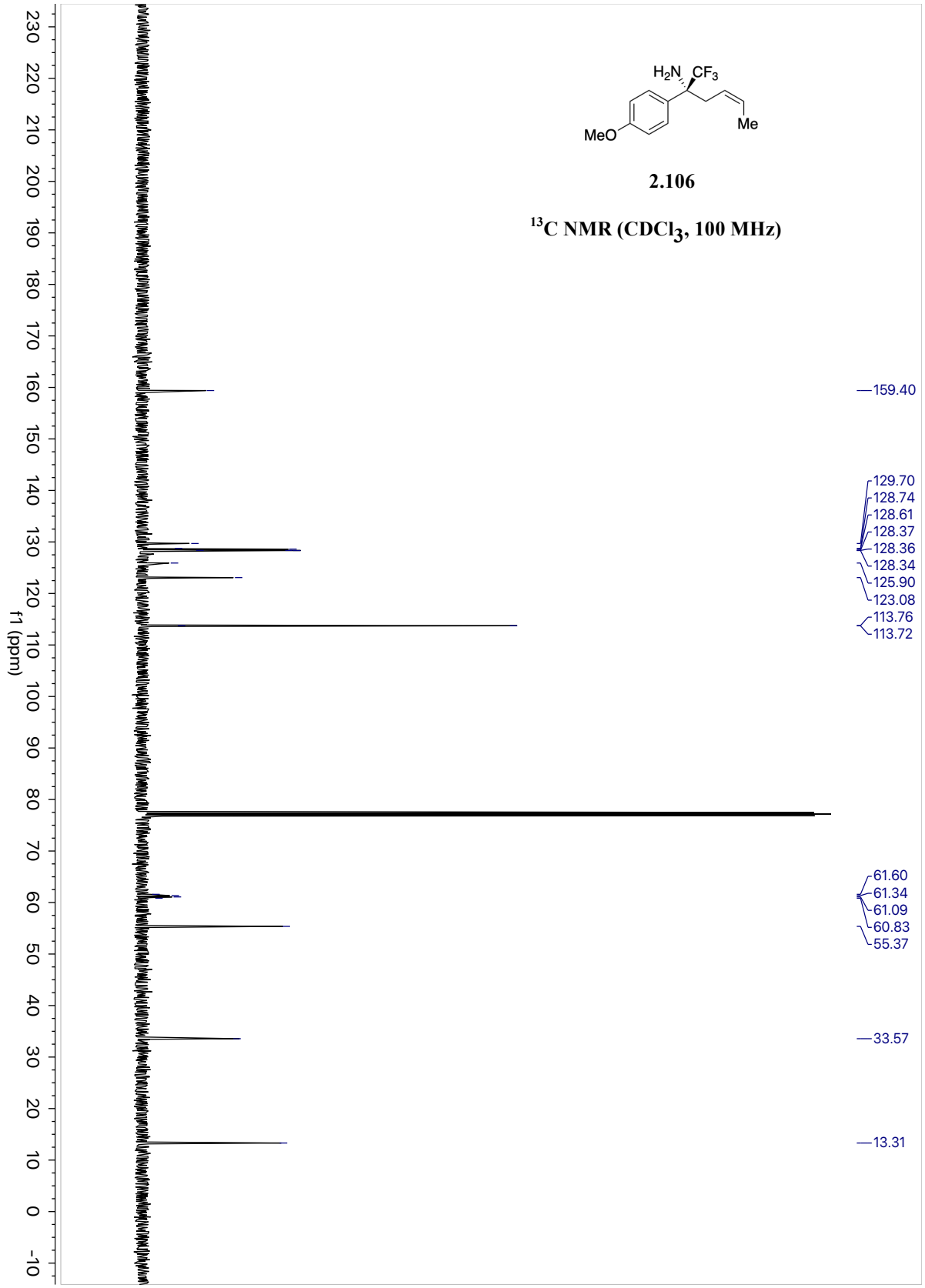
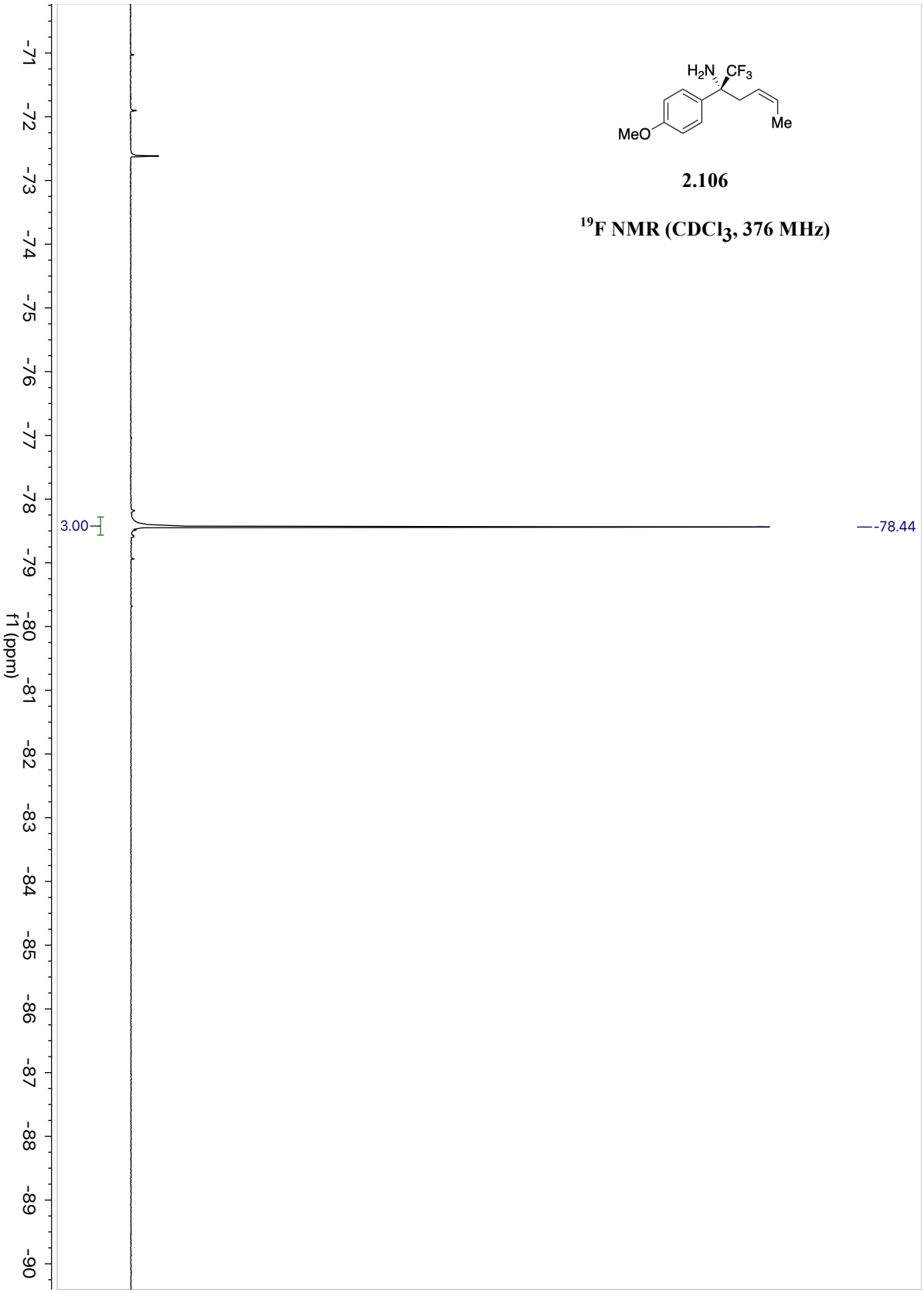
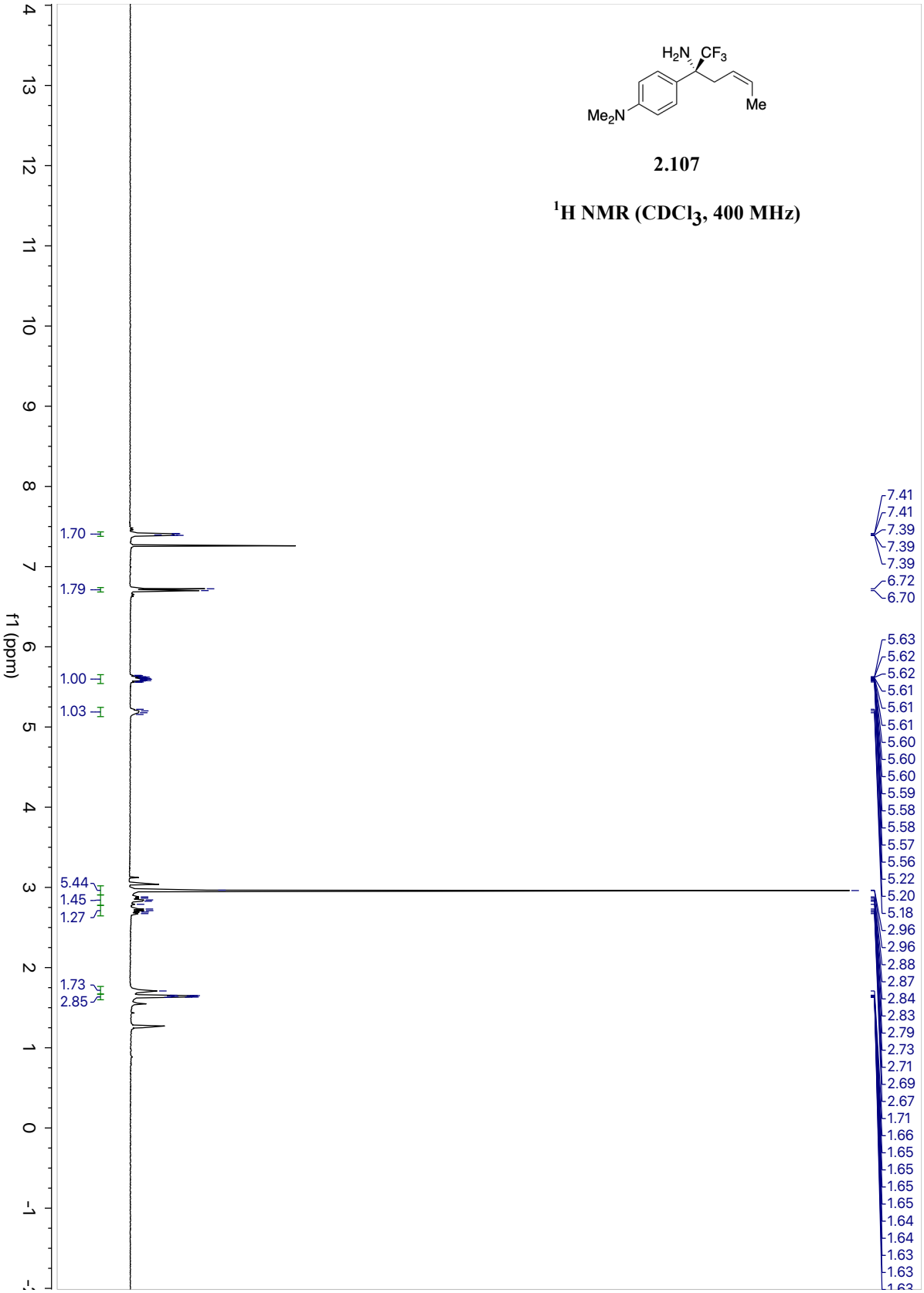
1.64
1.63
1.63
1.62
1.62
1.62
1.62



2.106

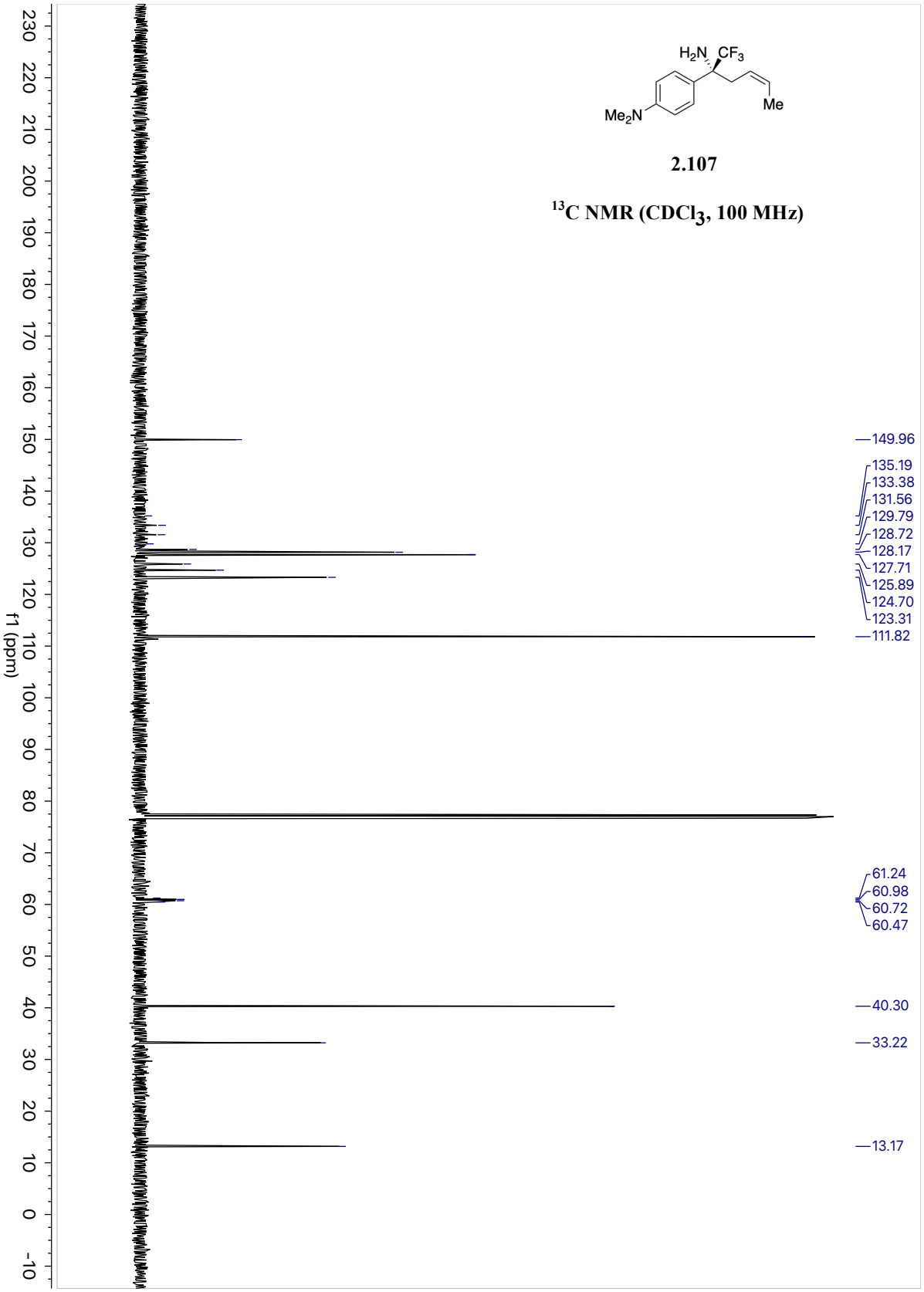
^{13}C NMR ($CDCl_3$, 100 MHz)

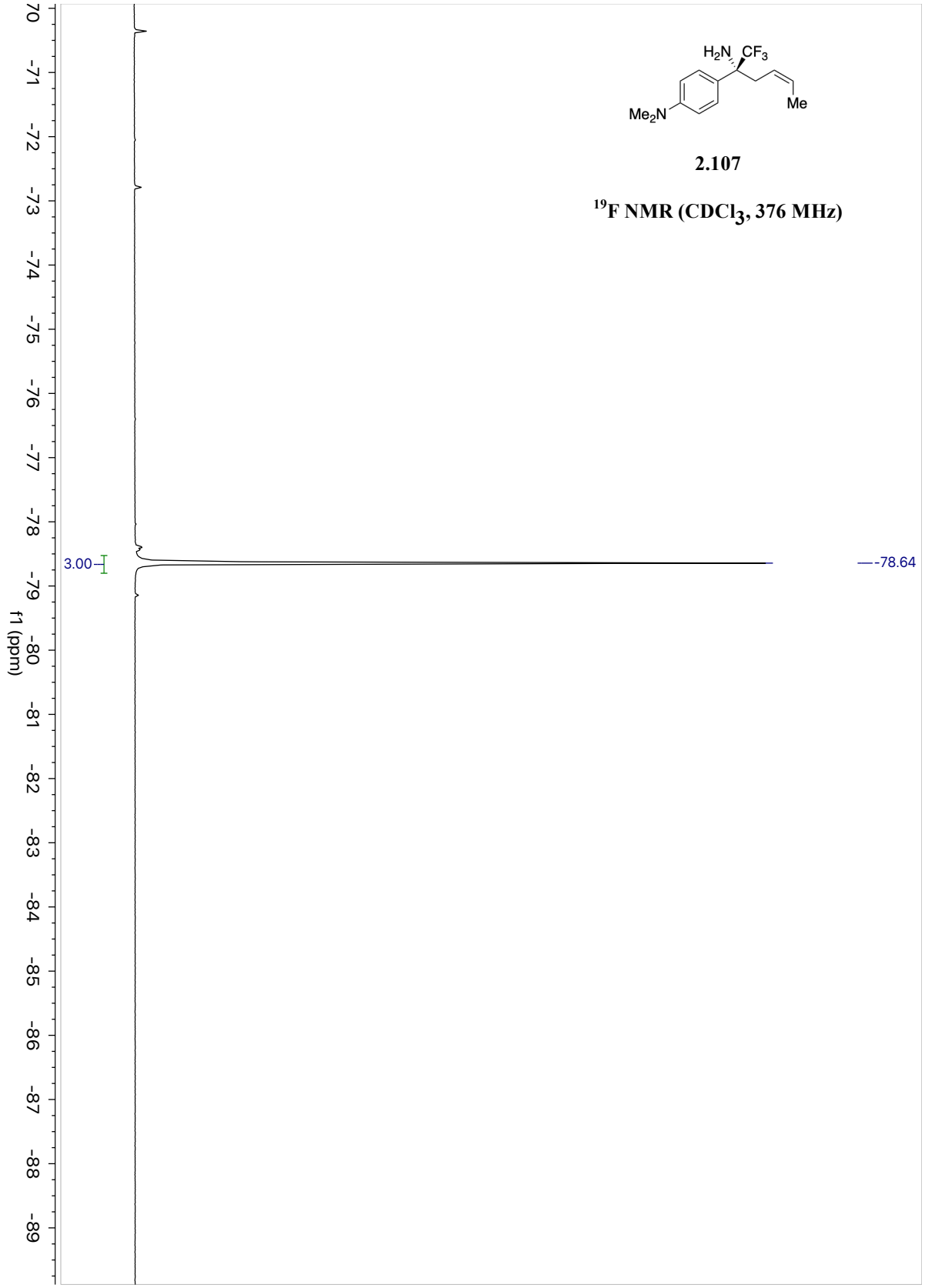

H2N
CF3
MeO
Me
2.106
19F NMR (CDCl3, 376 MHz)
3.00
-78.44
f1 (ppm)
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

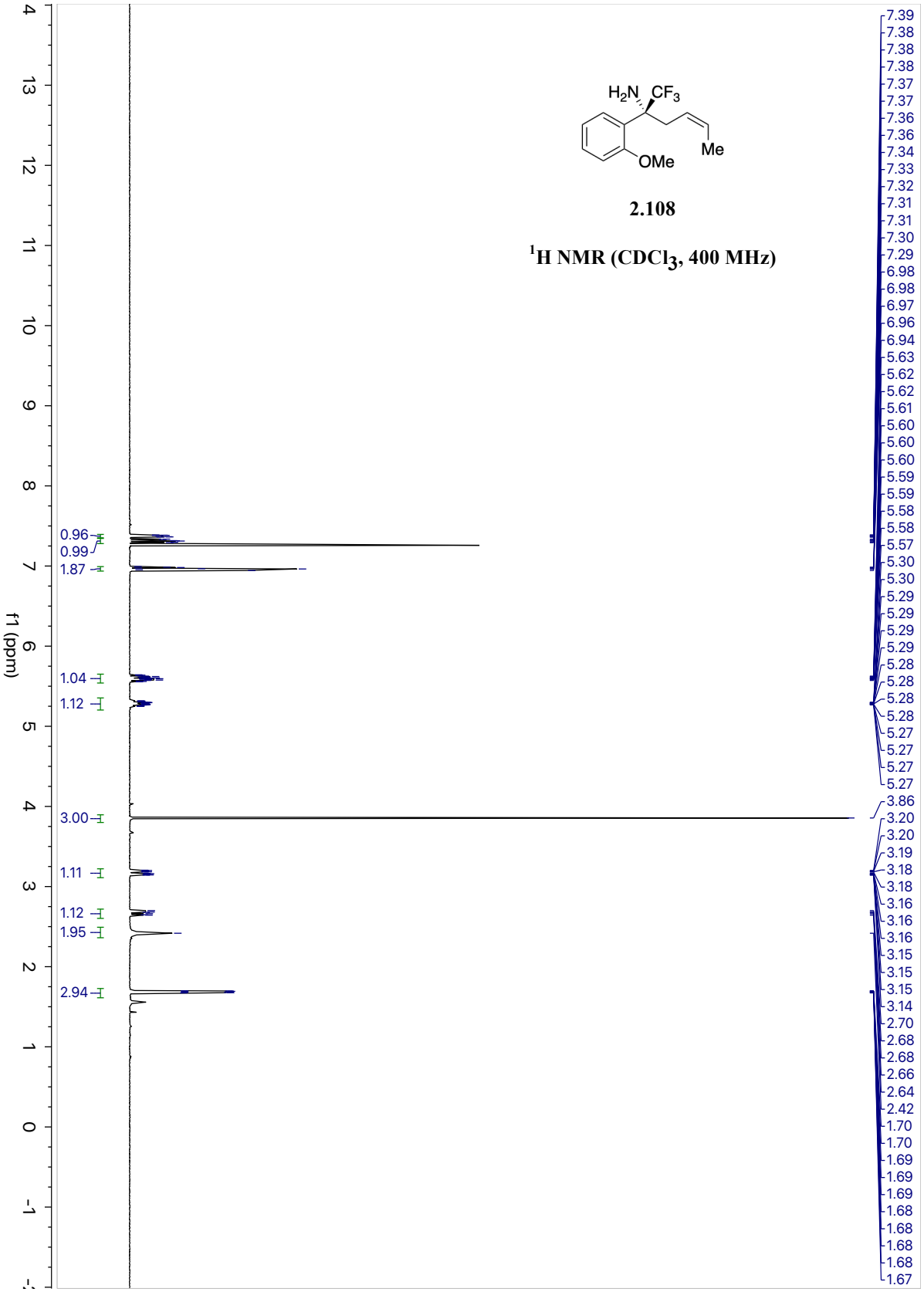


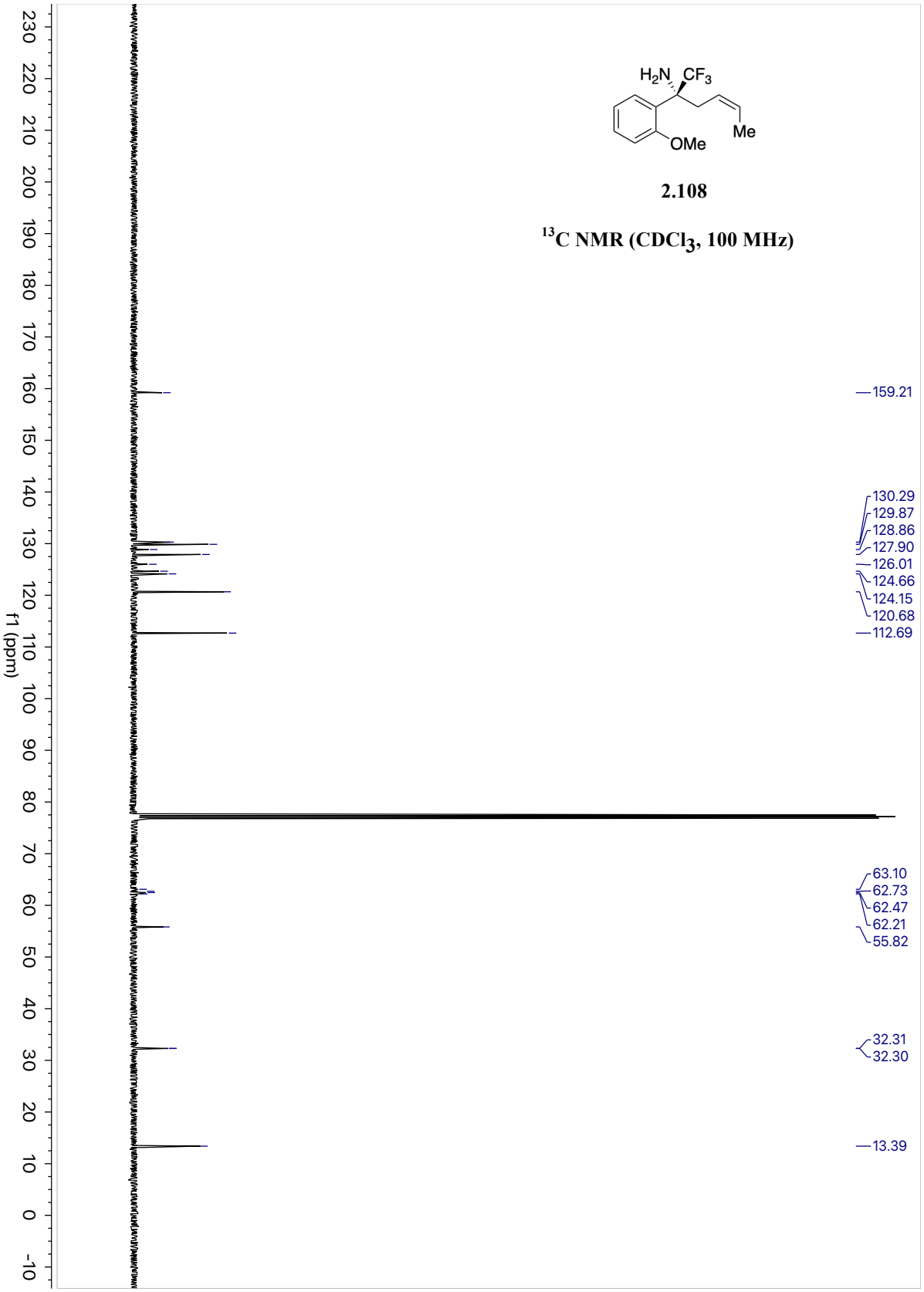
2.107

^{1}H NMR ($CDCl_3$, 400 MHz)


H2N CF3
Me2N
Me
2.107
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
149.96
135.19
133.38
131.56
129.79
128.72
128.17
127.71
125.89
124.70
123.31
111.82
61.24
60.98
60.72
60.47
40.30
33.22
13.17

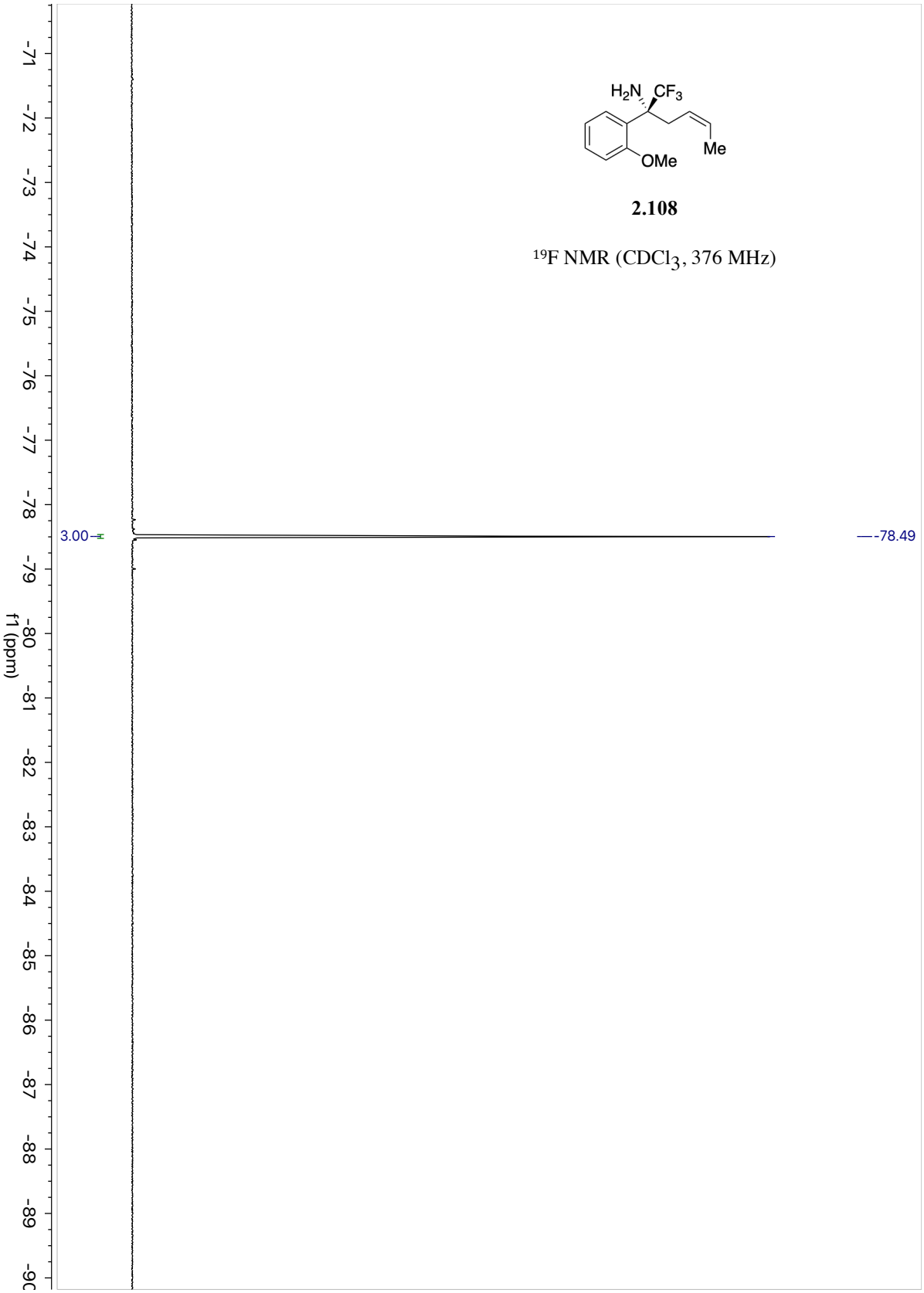

H2N
CF3
Me2N
Me
2.107
19F NMR (CDCl3, 376 MHz)
3.00
-78.64
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89


H2N
CF3
Me
OMe
2.108
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.96
0.99
1.87
1.04
1.12
3.00
1.11
1.12
1.95
2.94



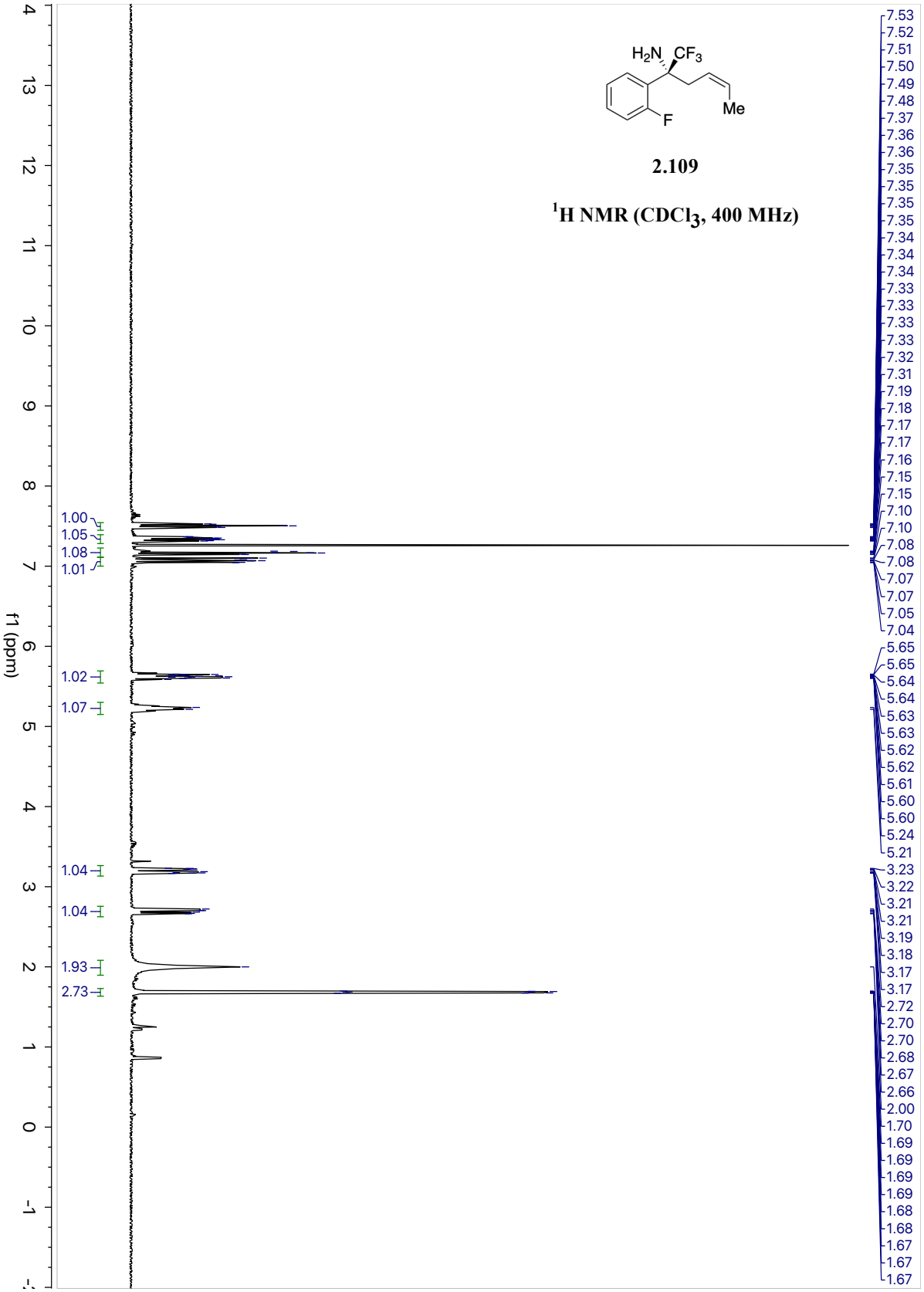
2.108

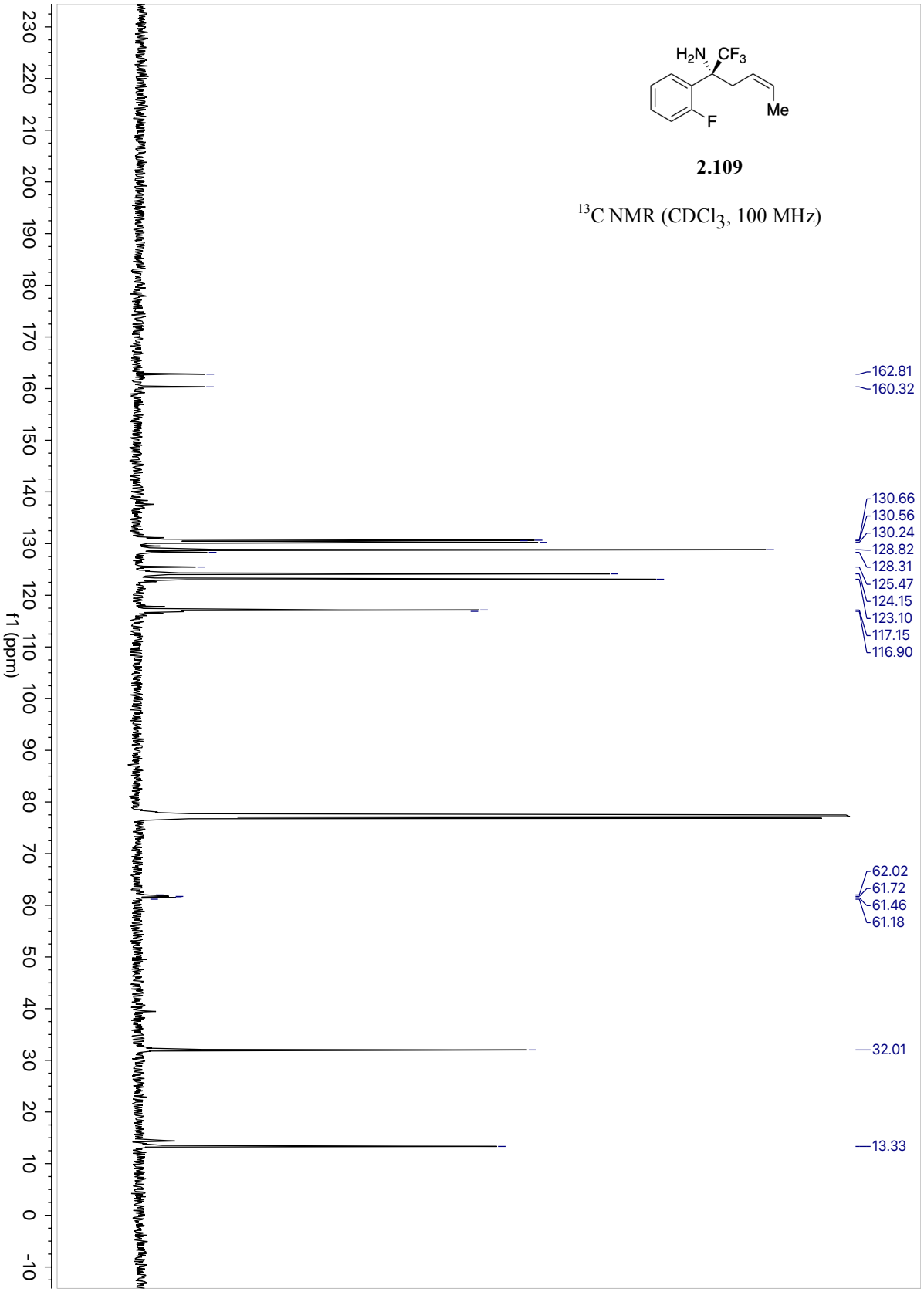
^{13}C NMR ($CDCl_3$, 100 MHz)

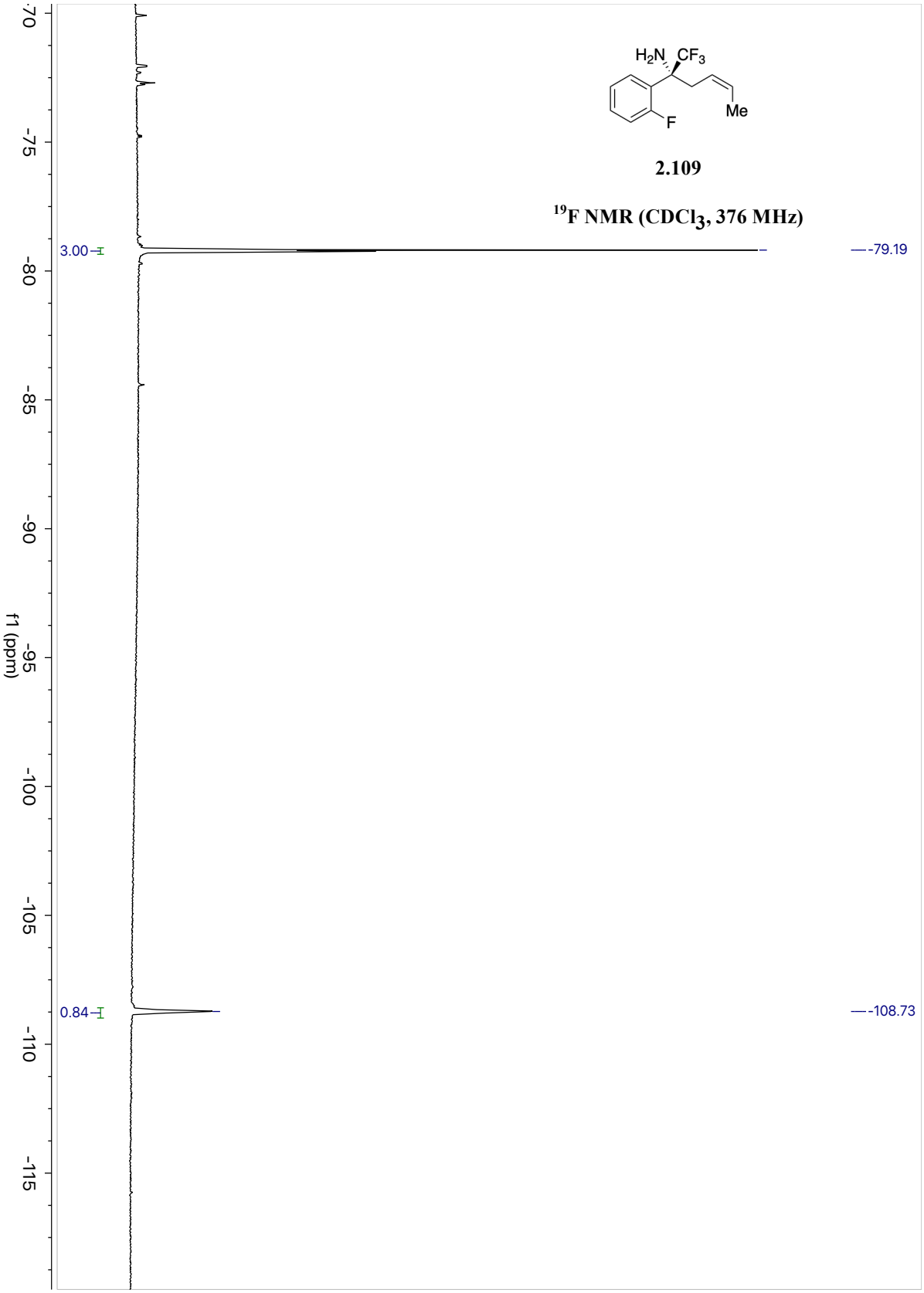


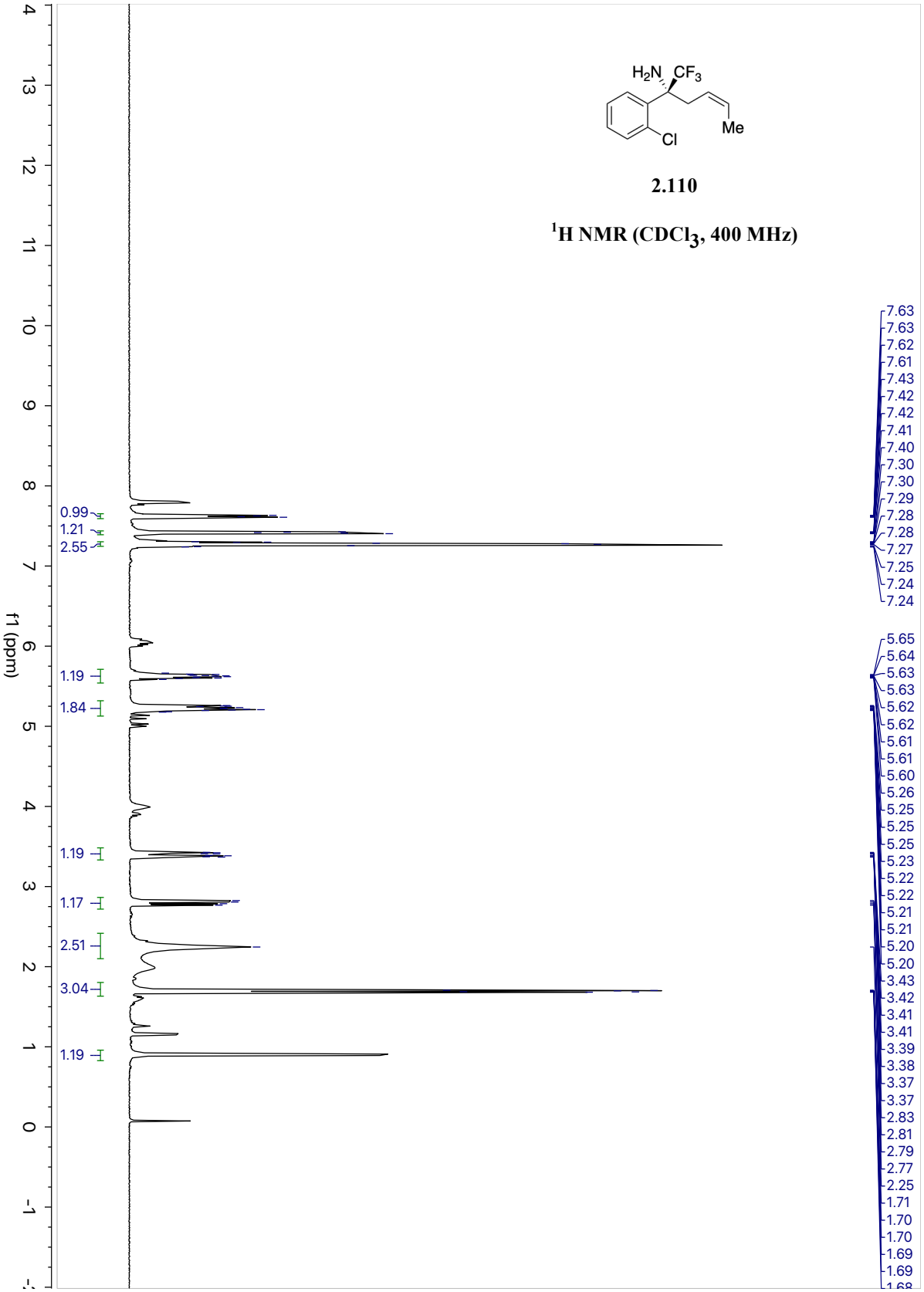
2.108

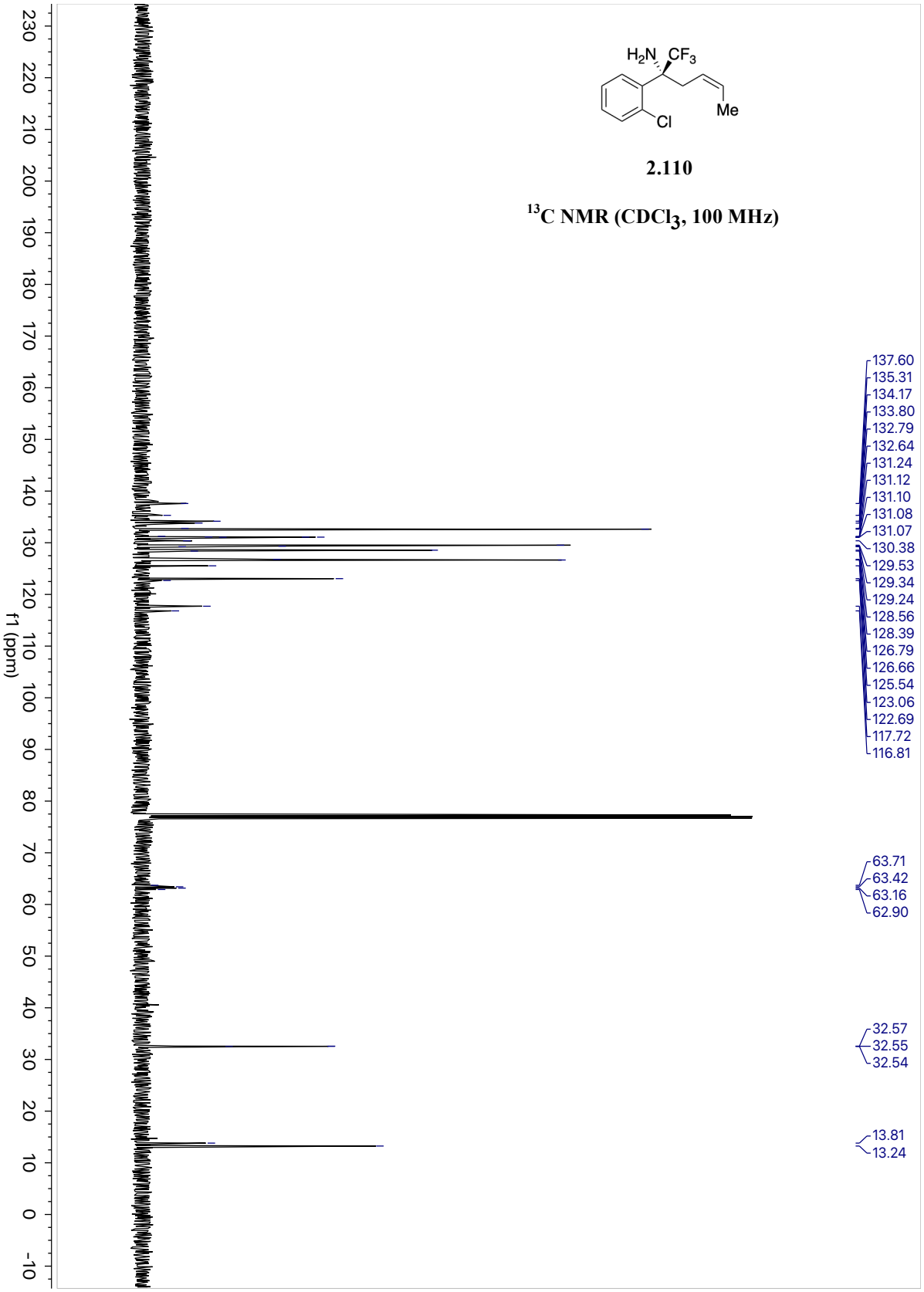
^{19}F NMR ($CDCl_3$, 376 MHz)

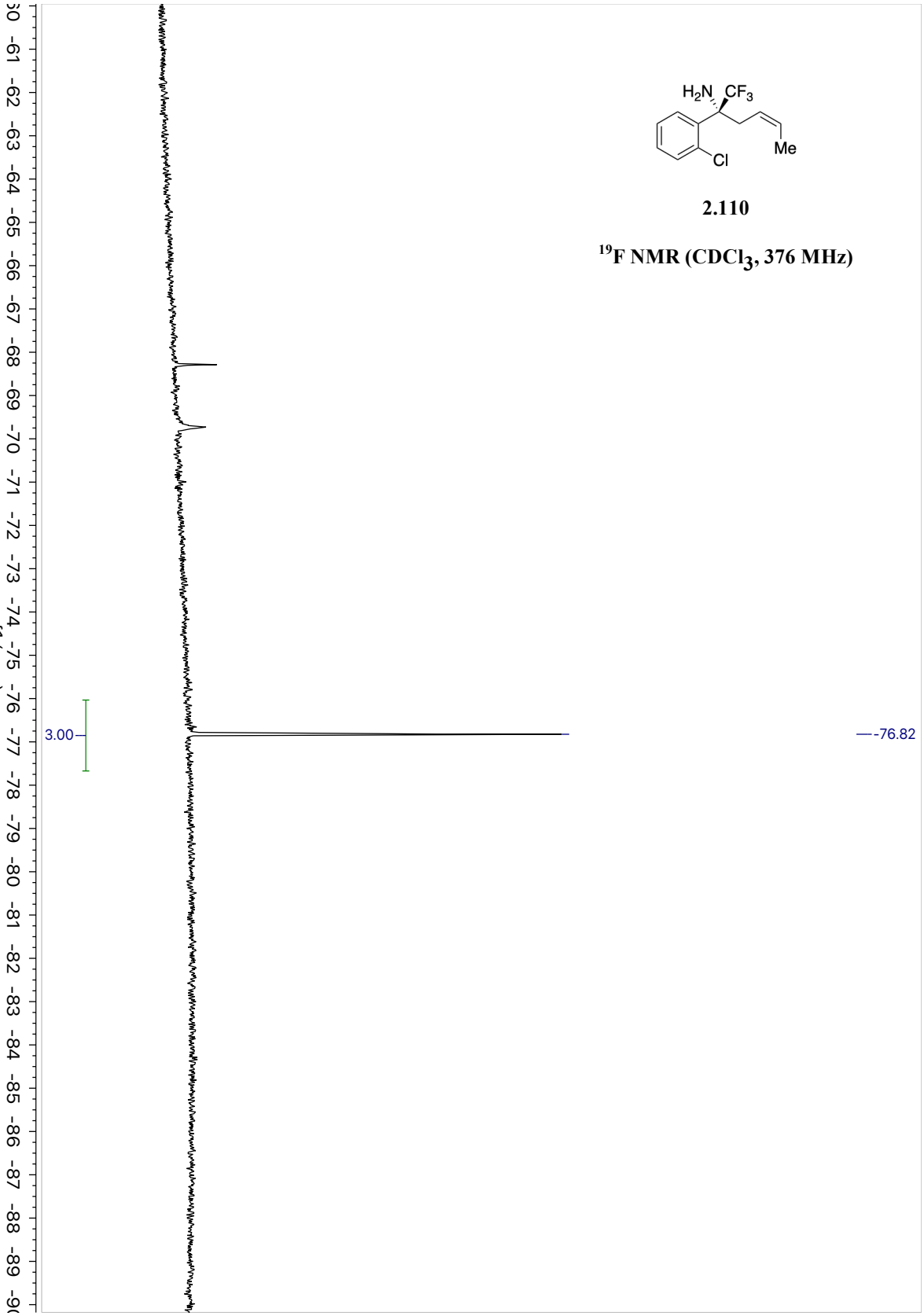

H2N
CF3
F
Me
2.109
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.00
1.05
1.08
1.01
1.02
1.07
1.04
1.04
1.93
2.73

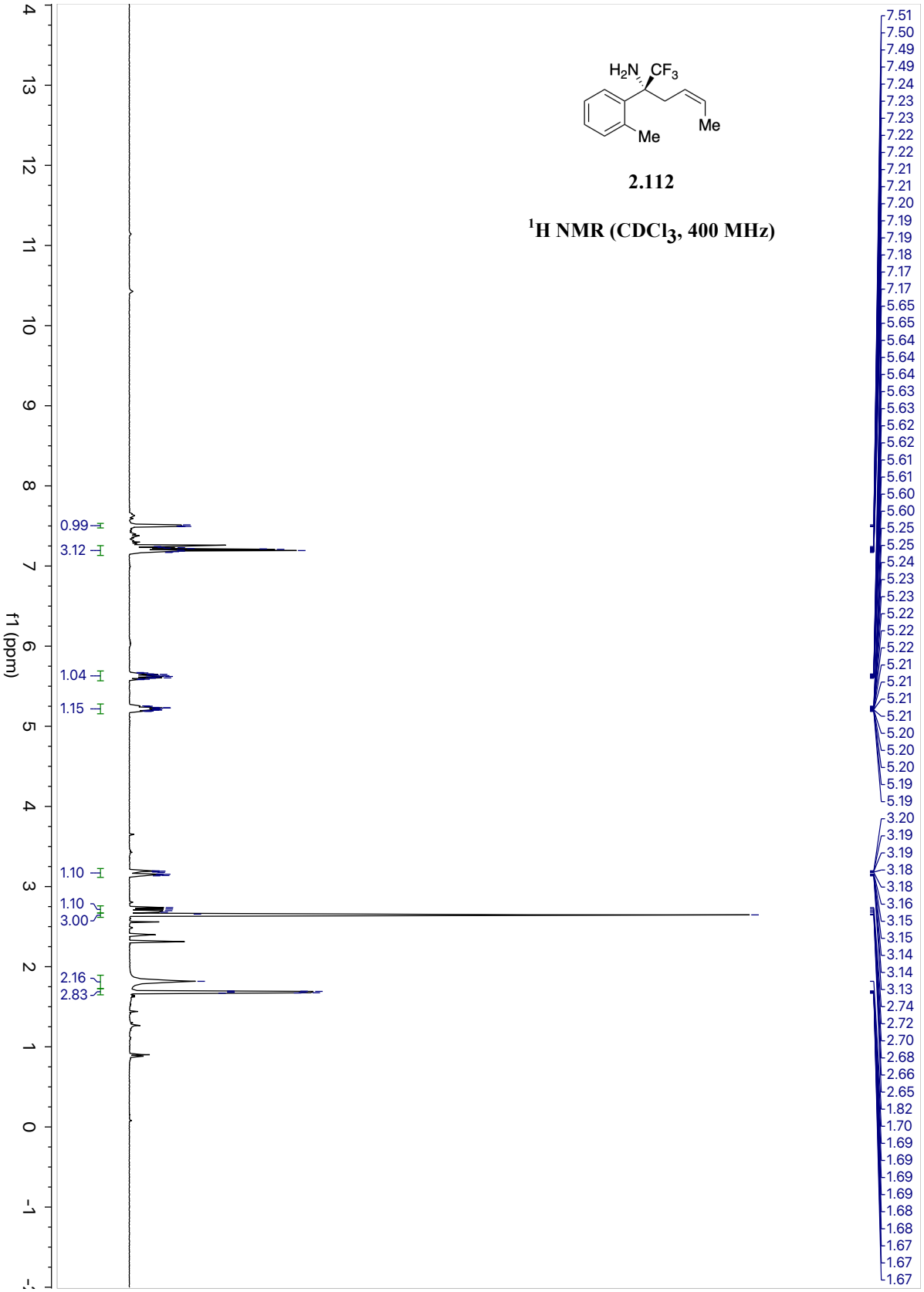

H2N
CF3
F
Me
2.109
13C NMR (CDCl3, 100 MHz)
162.81
160.32
130.66
130.56
130.24
128.82
128.31
125.47
124.15
123.10
117.15
116.90
62.02
61.72
61.46
61.18
32.01
13.33
f1 (ppm)

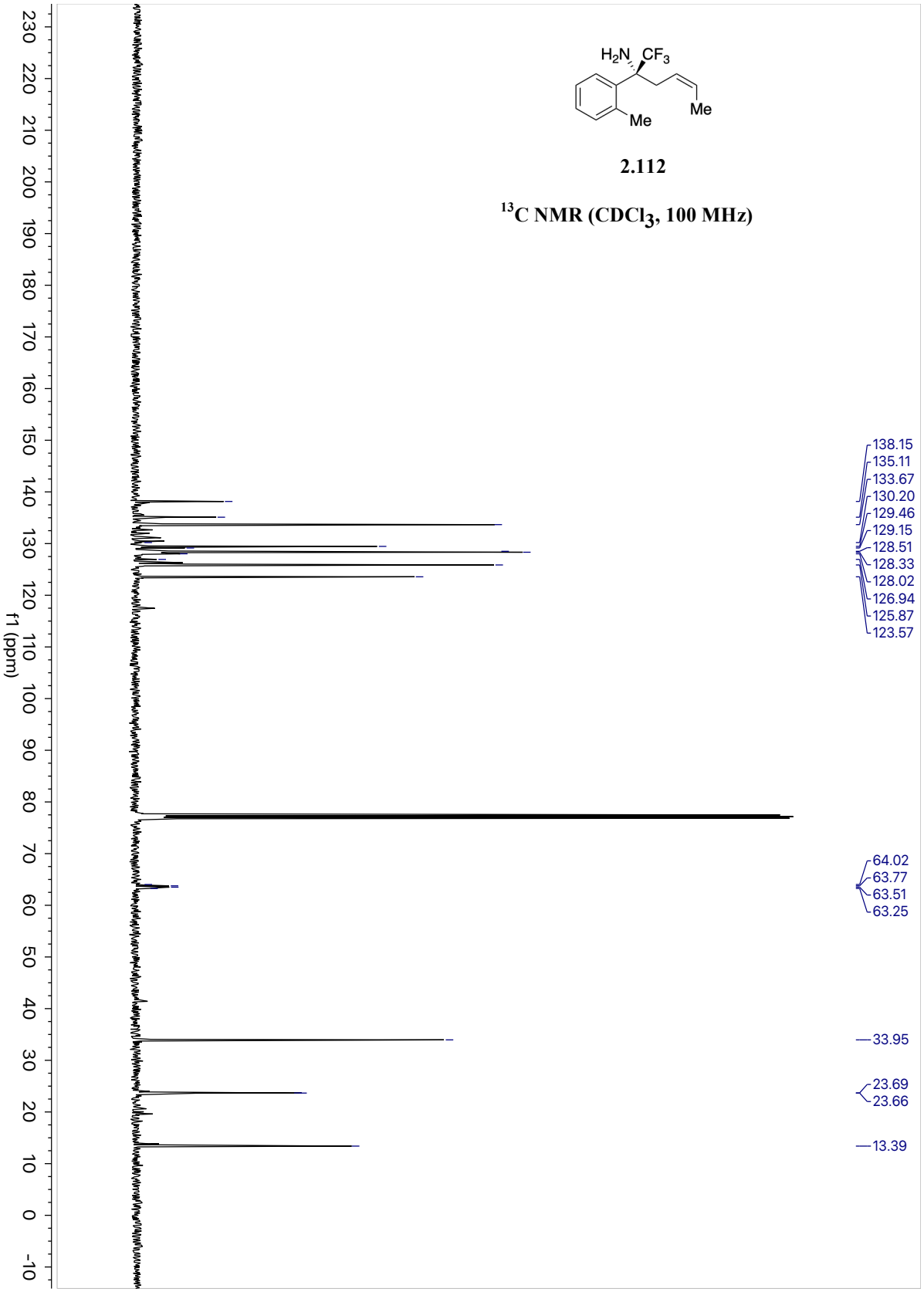

H2N CF3
F
Me
2.109
19F NMR (CDCl3, 376 MHz)
3.00
-79.19
0.84
-108.73
f1 (ppm)
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115


H2N
CF3
Cl
Me
2.110
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.99
1.21
2.55
1.19
1.84
1.19
1.17
2.51
3.04
1.19
7.63
7.63
7.62
7.61
7.43
7.42
7.42
7.41
7.40
7.30
7.30
7.29
7.28
7.28
7.27
7.25
7.24
7.24
5.65
5.64
5.63
5.63
5.62
5.62
5.61
5.61
5.60
5.26
5.25
5.25
5.25
5.23
5.22
5.22
5.21
5.21
5.20
5.20
3.43
3.42
3.41
3.41
3.39
3.38
3.37
3.37
2.83
2.81
2.79
2.77
2.25
1.71
1.70
1.70
1.69
1.69


H2N
CF3
Cl
Me
2.110
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
137.60
135.31
134.17
133.80
132.79
132.64
131.24
131.12
131.10
131.08
131.07
130.38
129.53
129.34
129.24
128.56
128.39
126.79
126.66
125.54
123.06
122.69
117.72
116.81
63.71
63.42
63.16
62.90
32.57
32.55
32.54
13.81
13.24

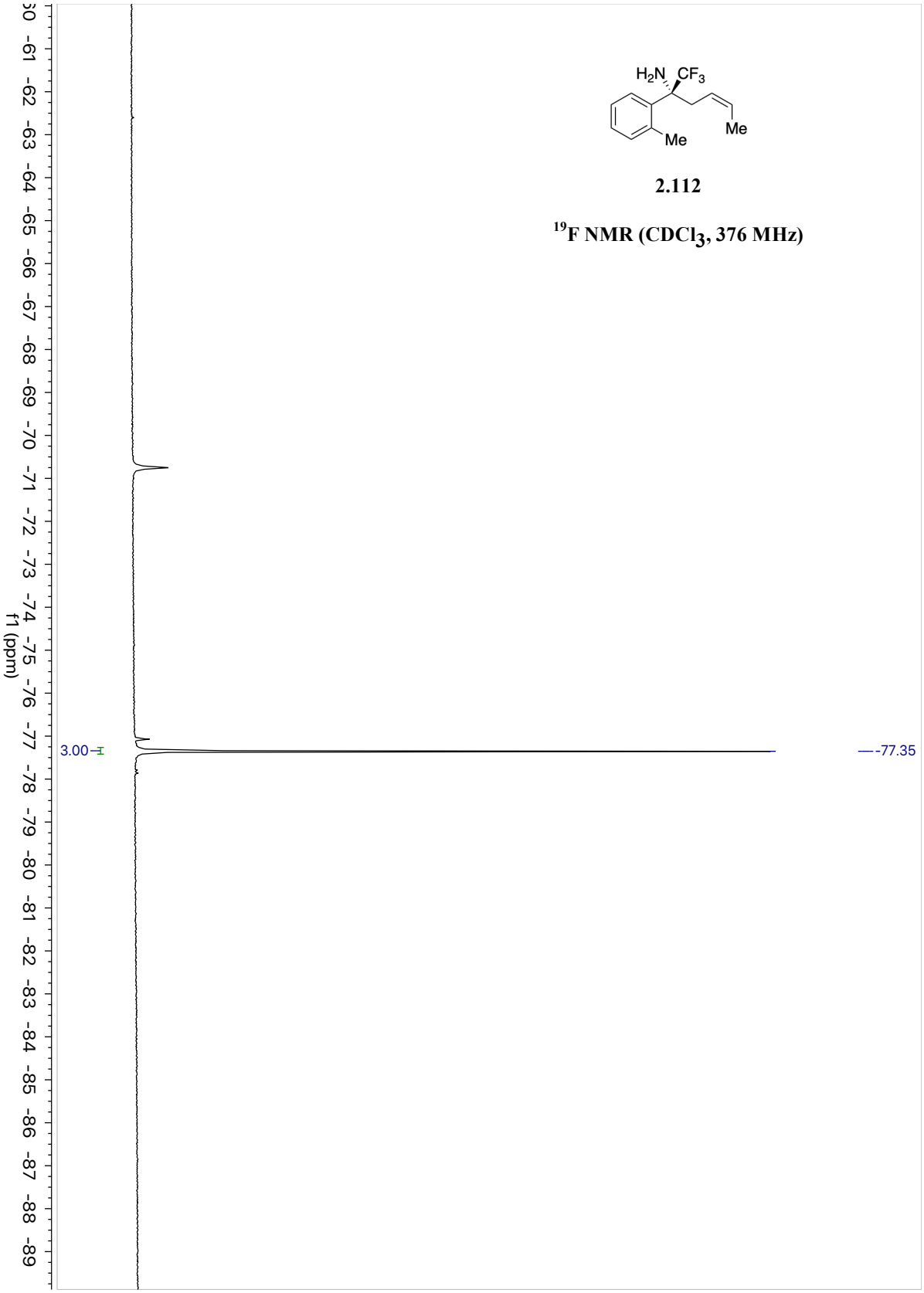

H2N
CF3
Cl
Me
2.110
19F NMR (CDCl3, 376 MHz)
3.00
-76.82
f1 (ppm)


H2N
CF3
Me
Me
2.112
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.99
3.12
1.04
1.15
1.10
1.10
3.00
2.16
2.83



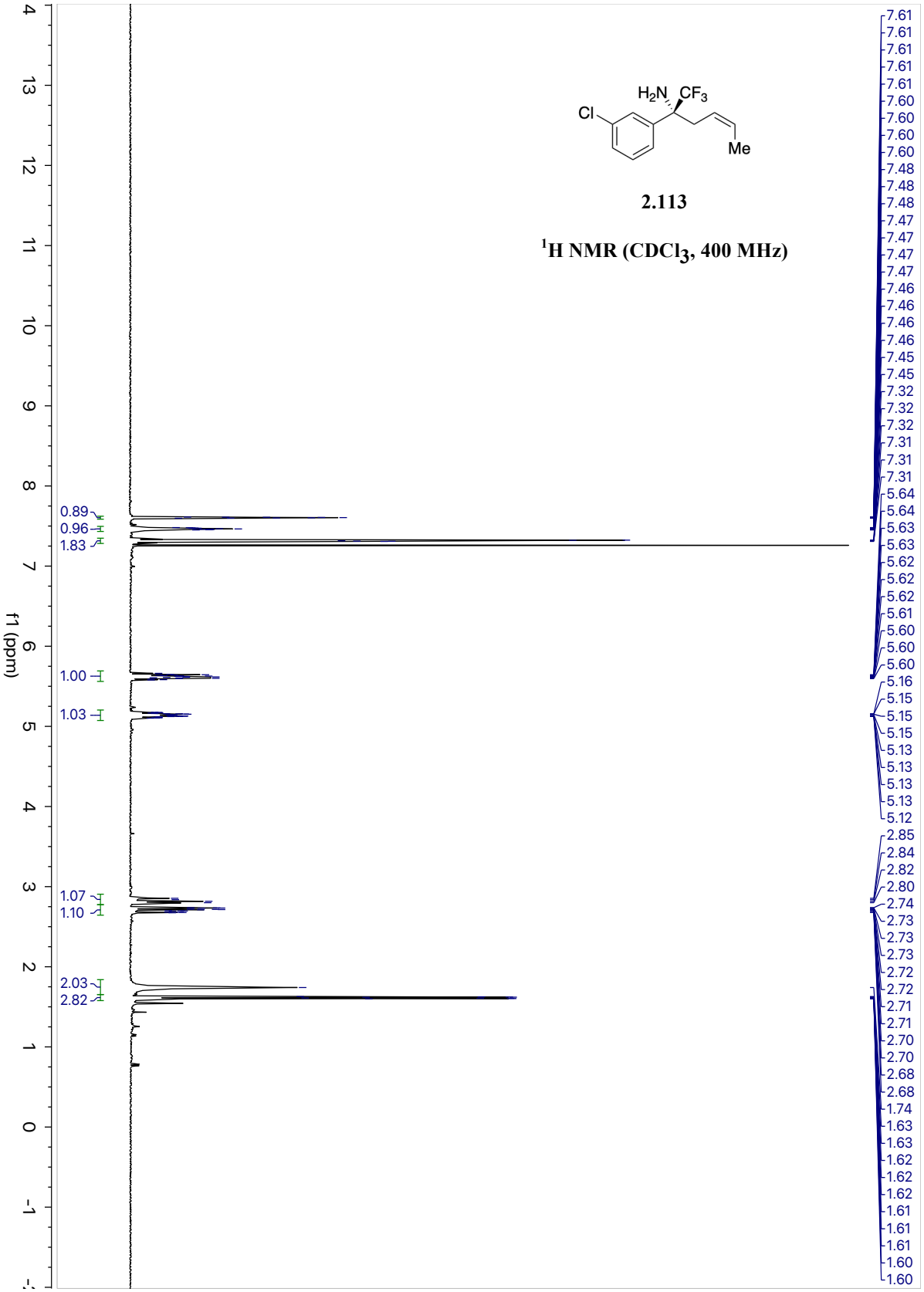
2.112

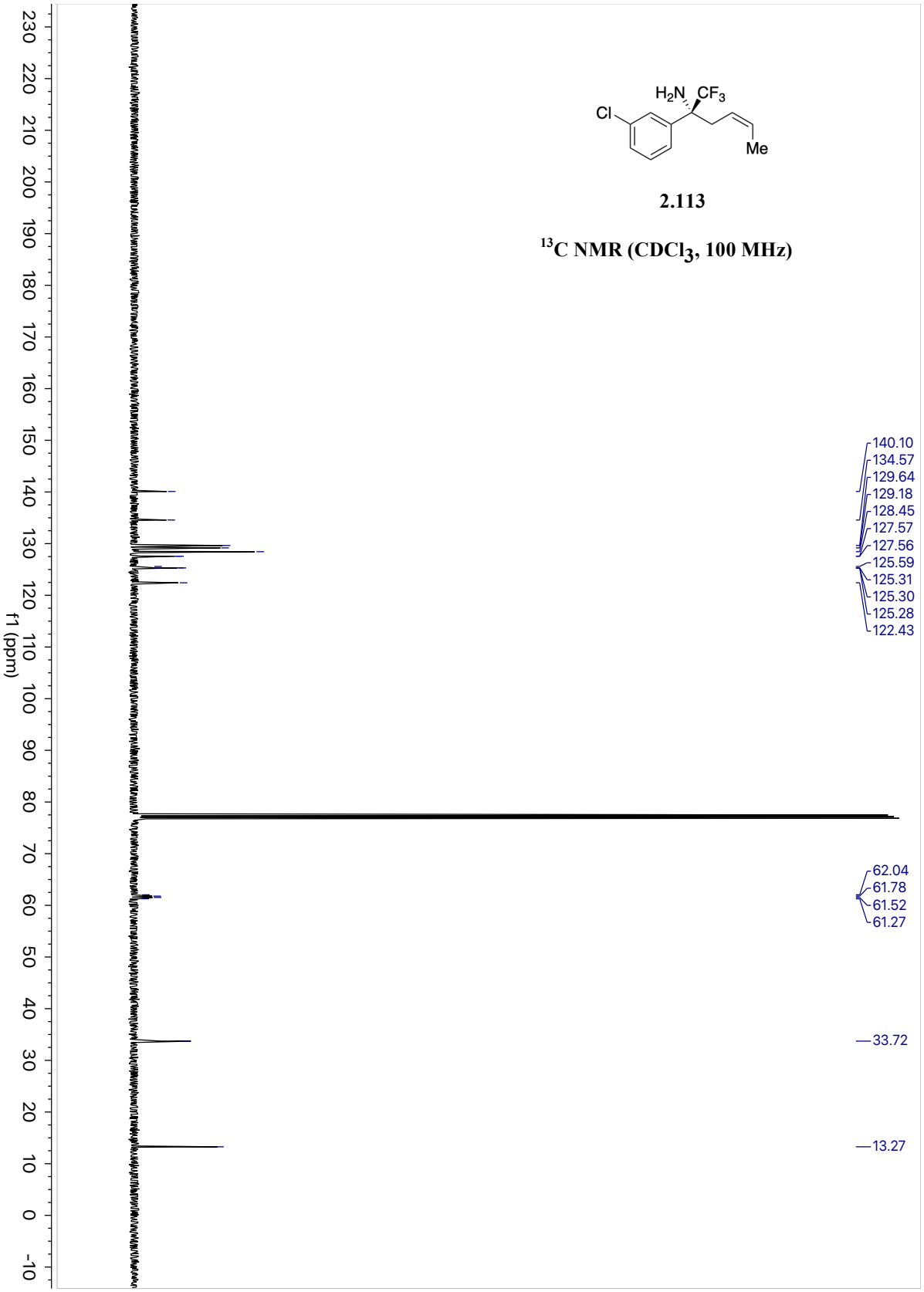
^{13}C NMR ($CDCl_3$, 100 MHz)

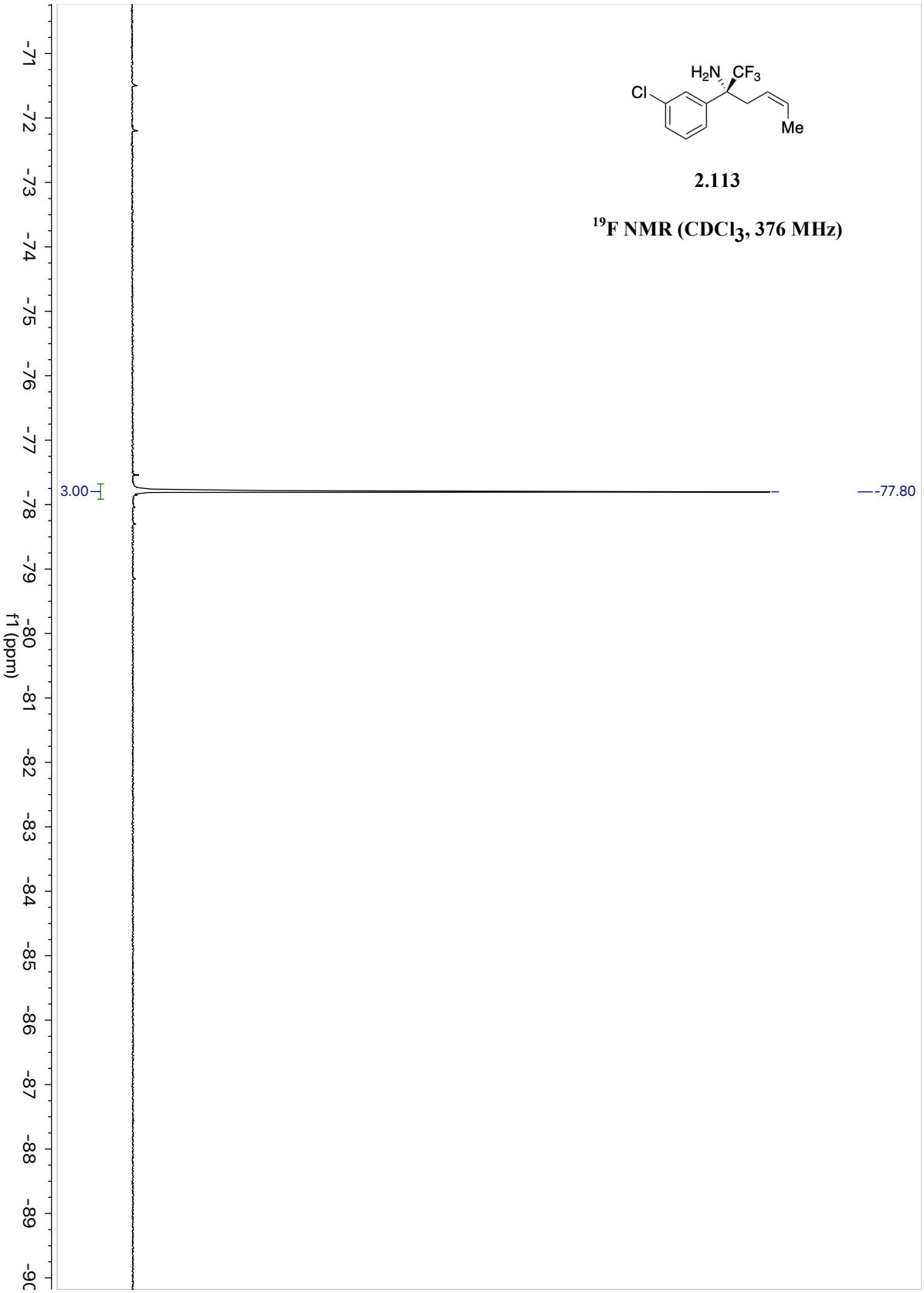


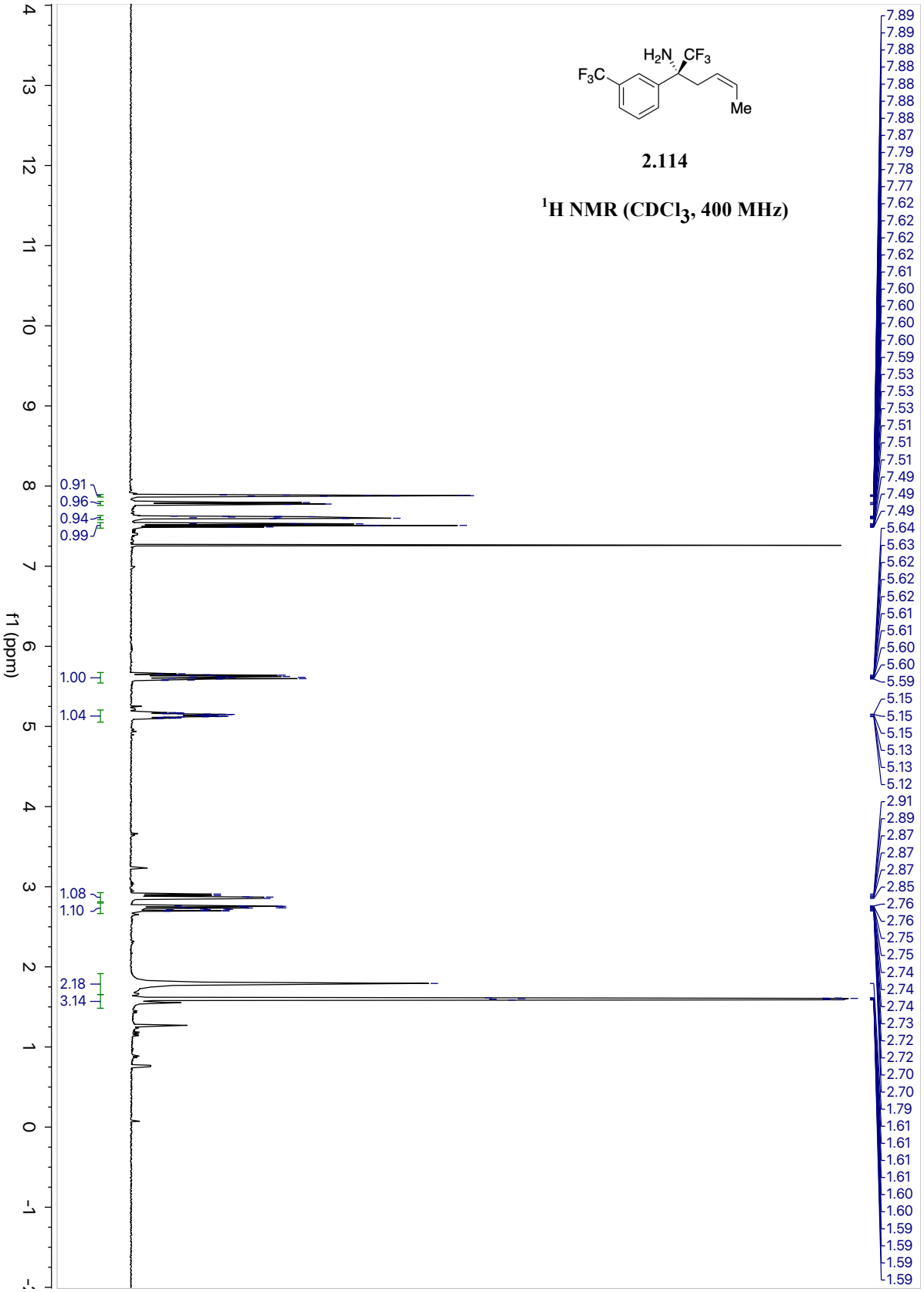
2.112

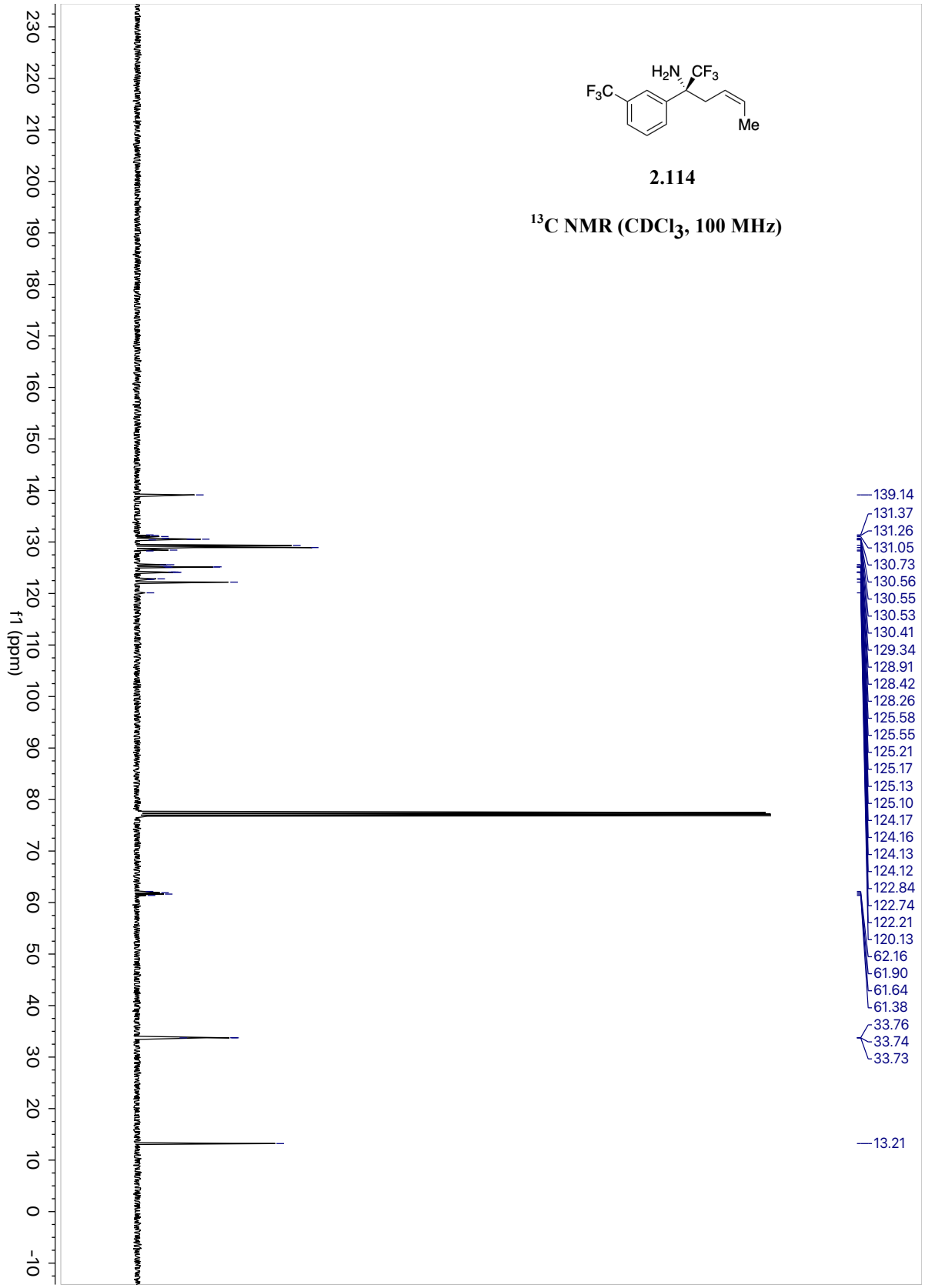
^{19}F NMR ($CDCl_3$, 376 MHz)

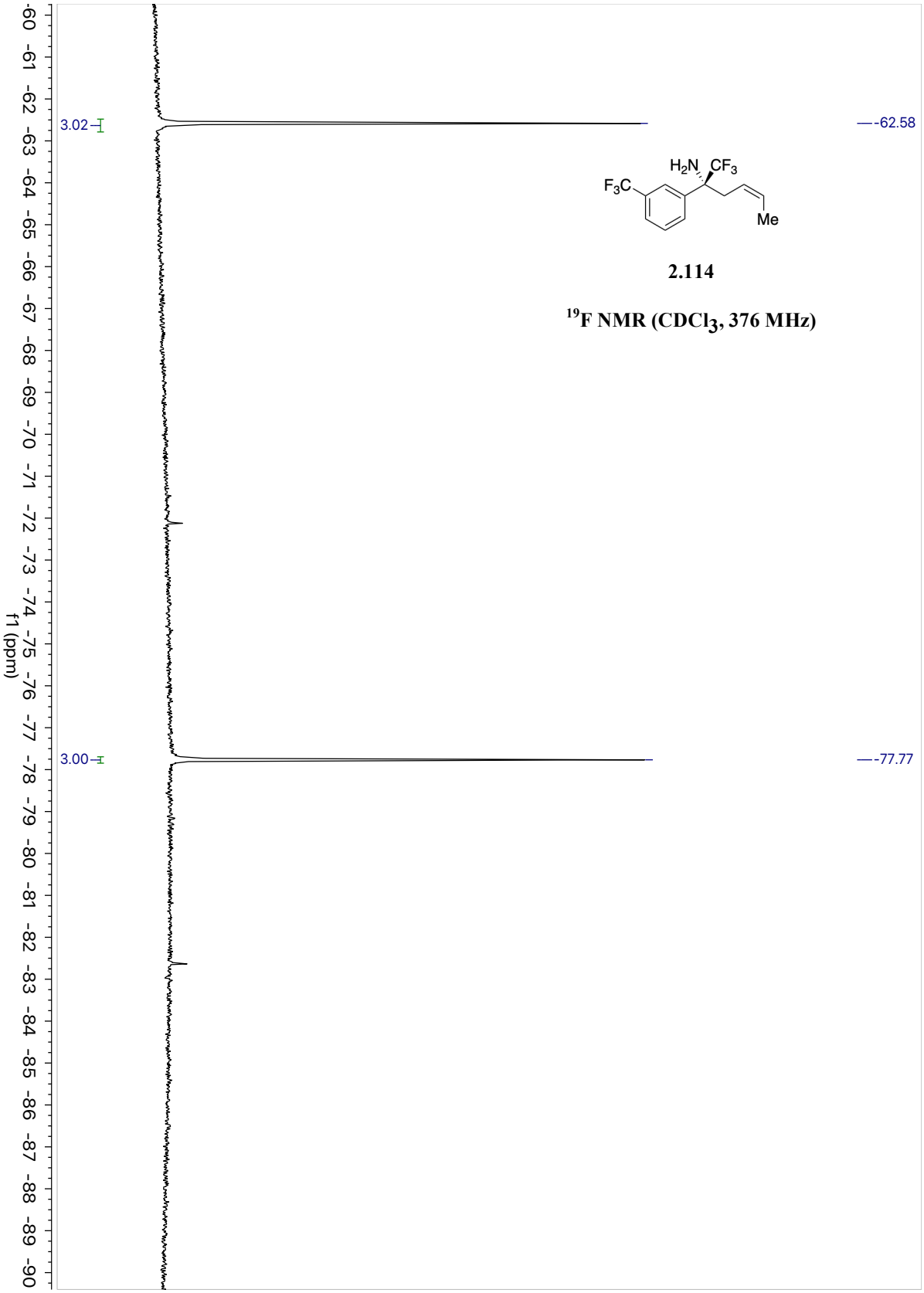

H2N CF3
Cl
Me
2.113
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.89
0.96
1.83
1.00
1.03
1.07
1.10
2.03
2.82


H2N
CF3
Cl
Me
2.113
13C NMR (CDCl3, 100 MHz)
140.10
134.57
129.64
129.18
128.45
127.57
127.56
125.59
125.31
125.30
125.28
122.43
62.04
61.78
61.52
61.27
33.72
13.27
f1 (ppm)


H2N
CF3
Cl
Me
2.113
19F NMR (CDCl3, 376 MHz)
3.00
-77.80
f1 (ppm)
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

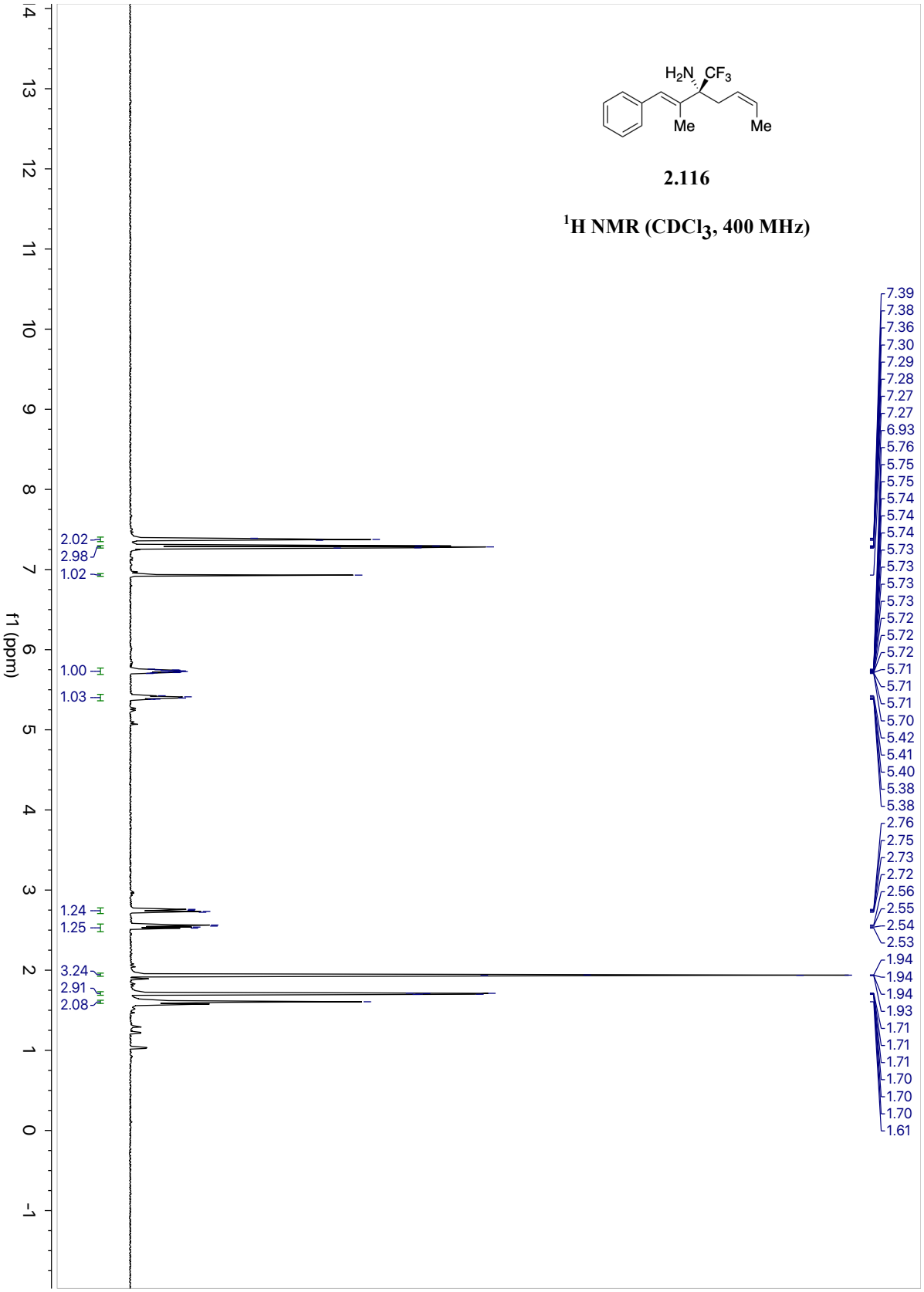

H2N
CF3
F3C
Me
2.114
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.91
0.96
0.94
0.99
1.00
1.04
1.08
1.10
2.18
3.14


H2N CF3
F3C
Me
2.114
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
139.14
131.37
131.26
131.05
130.73
130.56
130.55
130.53
130.41
129.34
128.91
128.42
128.26
125.58
125.55
125.21
125.17
125.13
125.10
124.17
124.16
124.13
124.12
122.84
122.74
122.21
120.13
62.16
61.90
61.64
61.38
33.76
33.74
33.73
13.21



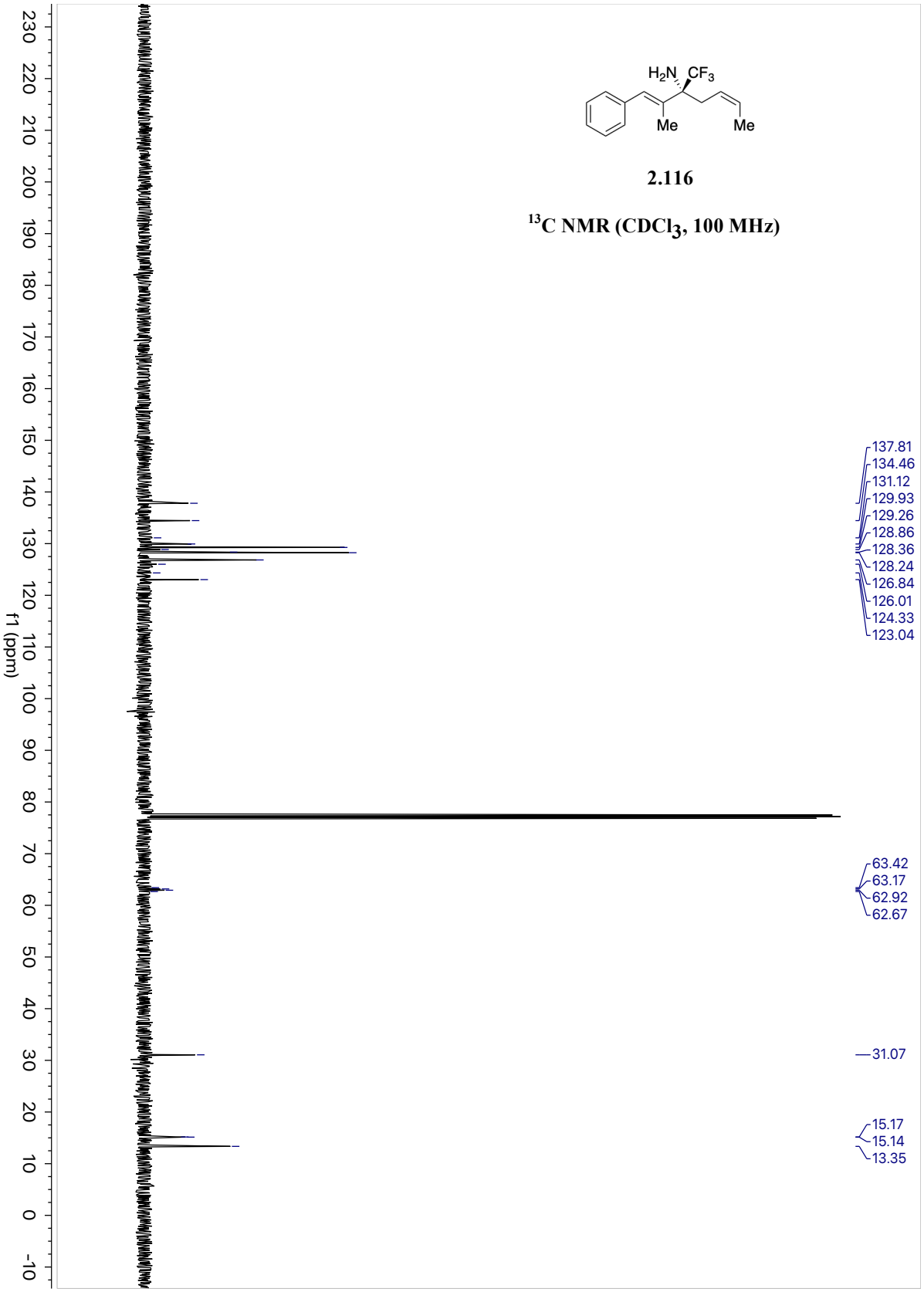
2.114

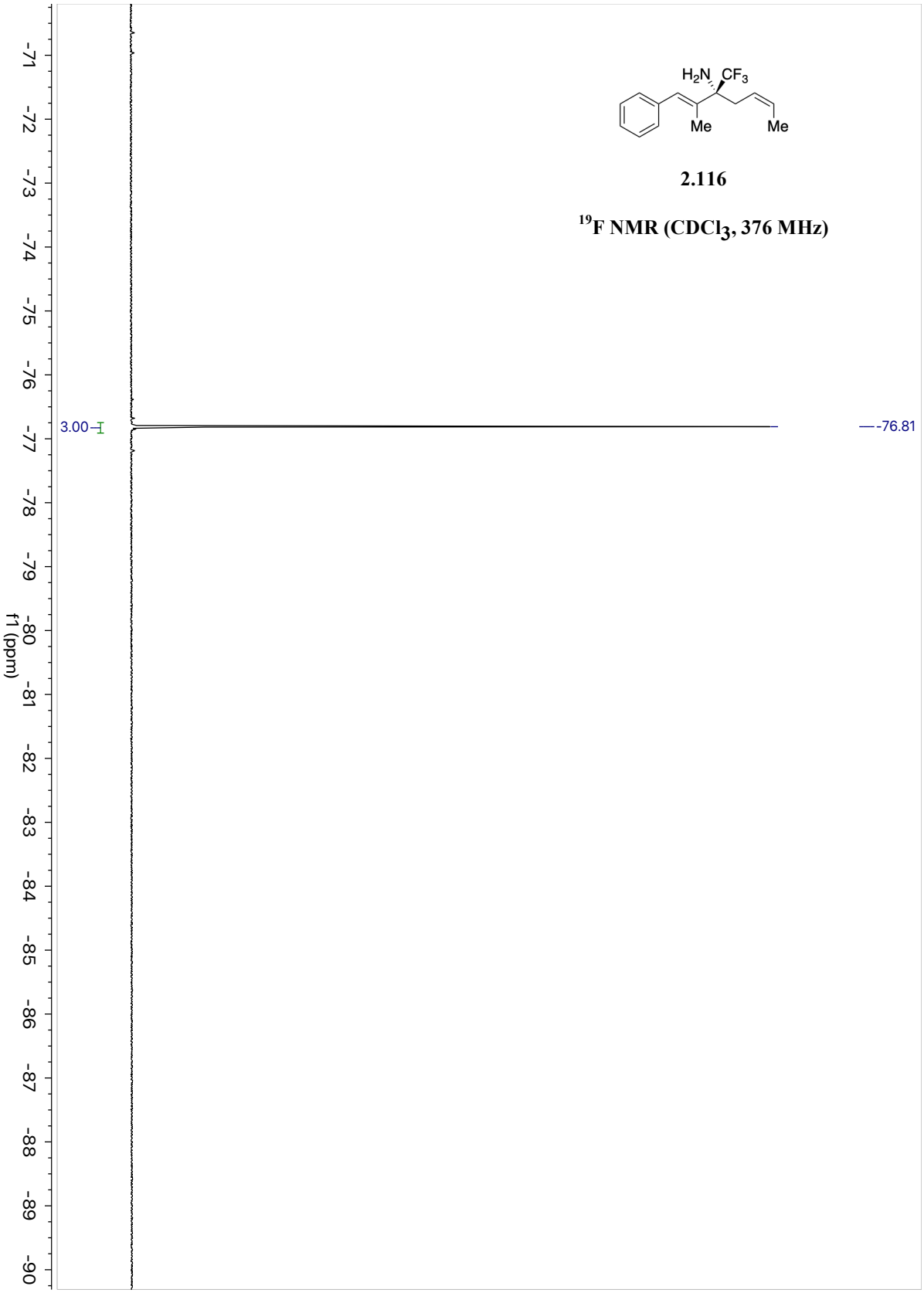
^{19}F NMR ($CDCl_3$, 376 MHz)

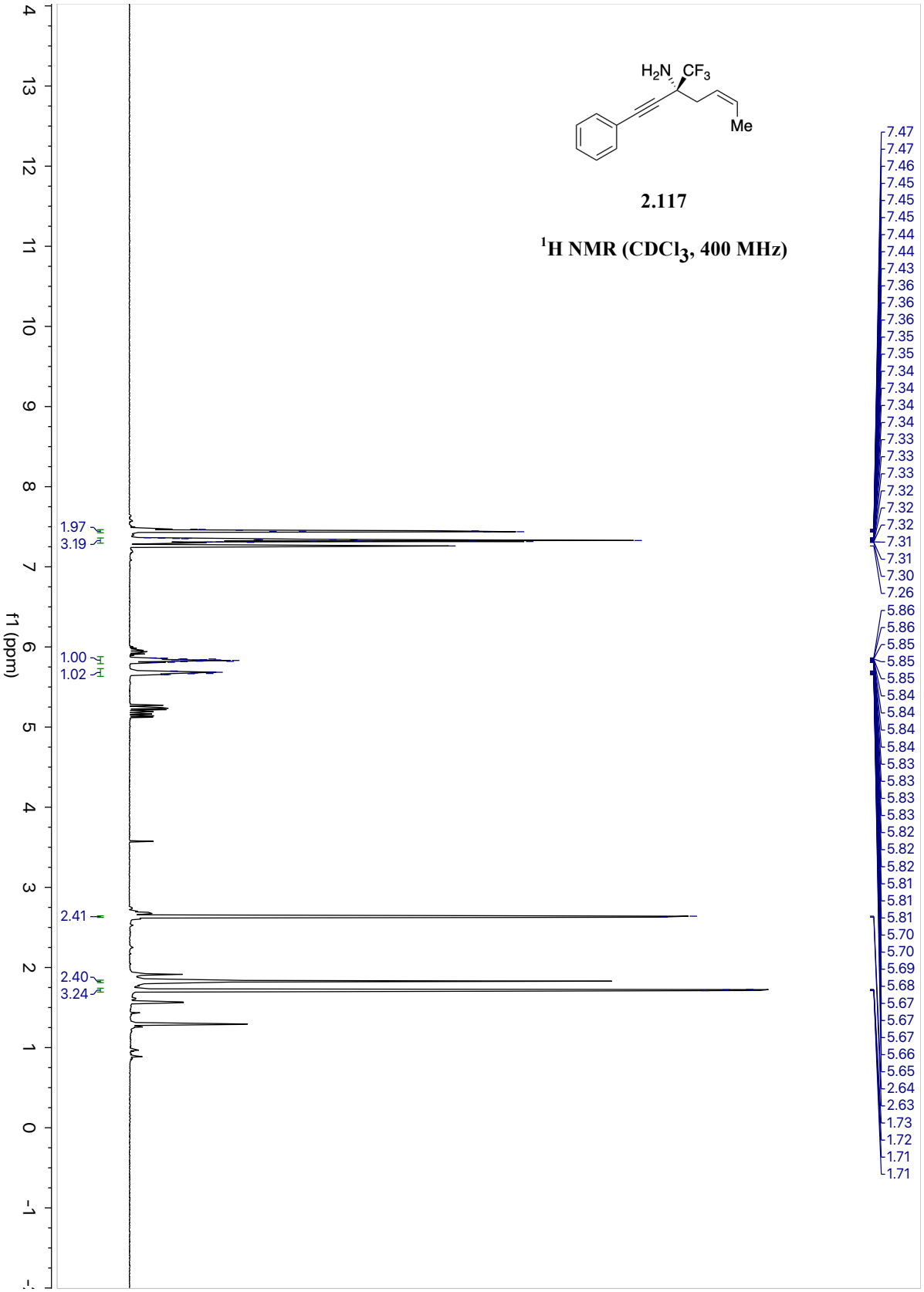


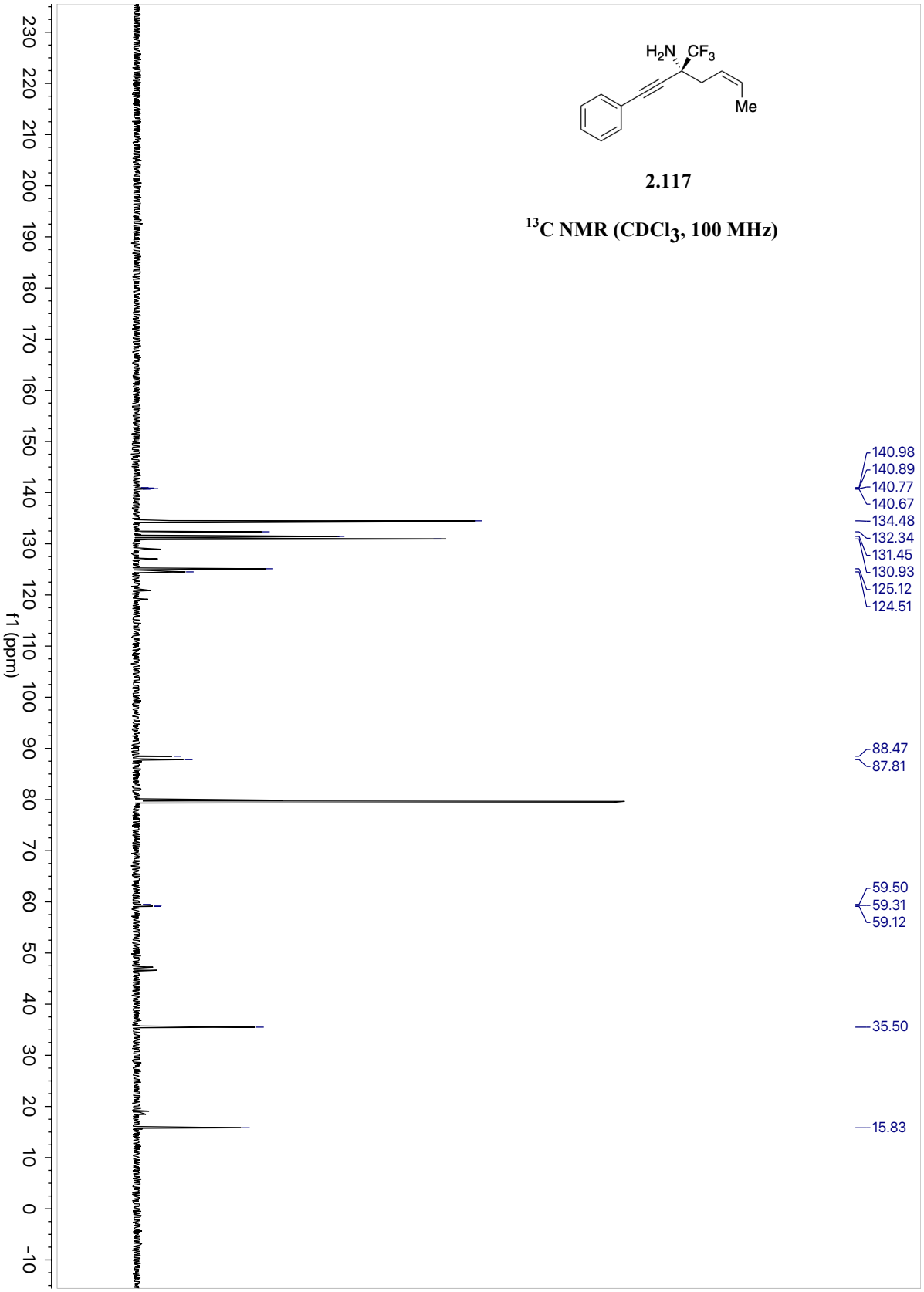
2.116

^{1}H NMR ($CDCl_3$, 400 MHz)


H2N CF3
Me
Me
2.116
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
137.81
134.46
131.12
129.93
129.26
128.86
128.36
128.24
126.84
126.01
124.33
123.04
63.42
63.17
62.92
62.67
31.07
15.17
15.14
13.35

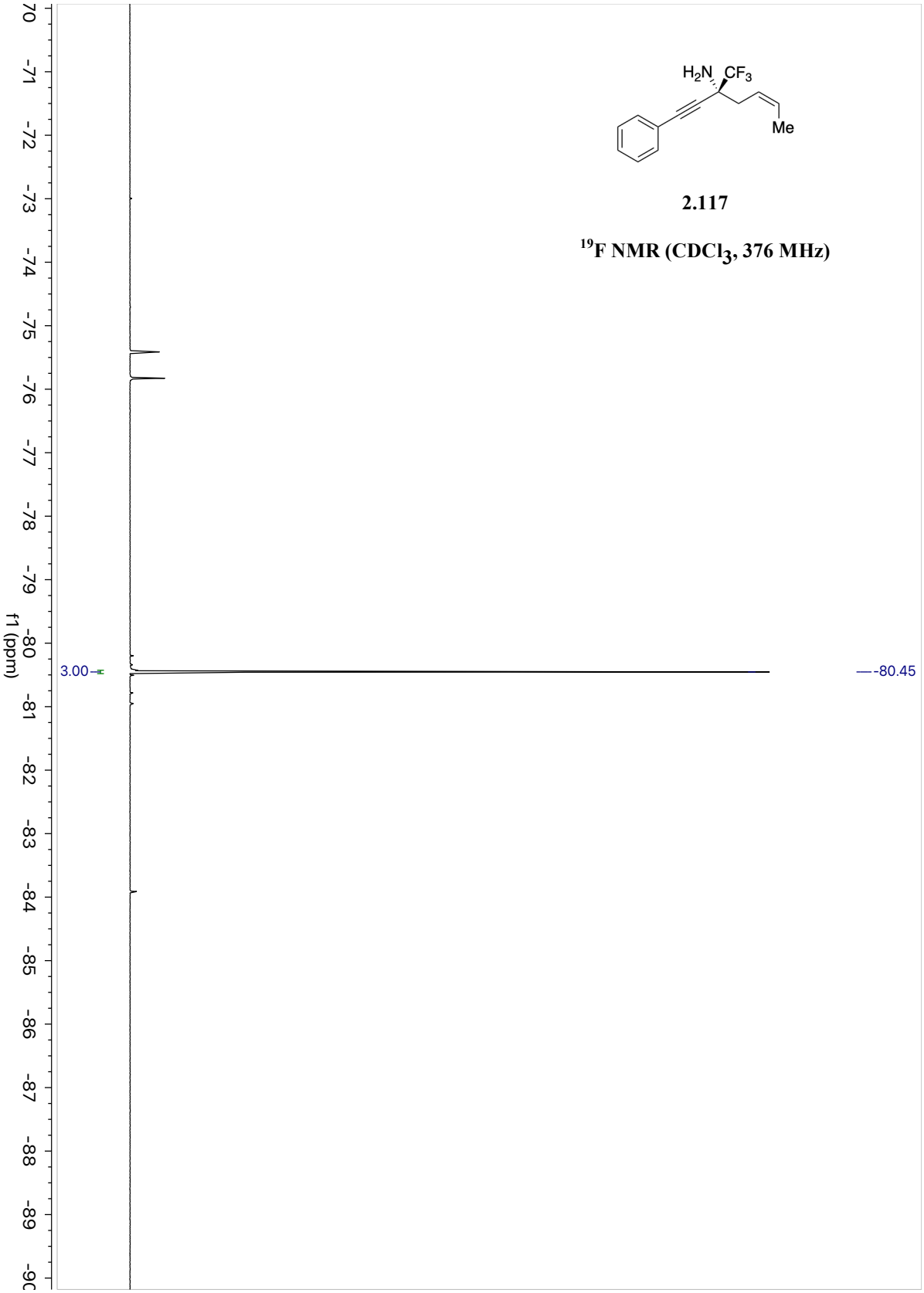

H2N CF3
Me
Me
2.116
19F NMR (CDCl3, 376 MHz)
3.00
-76.81
f1 (ppm)
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

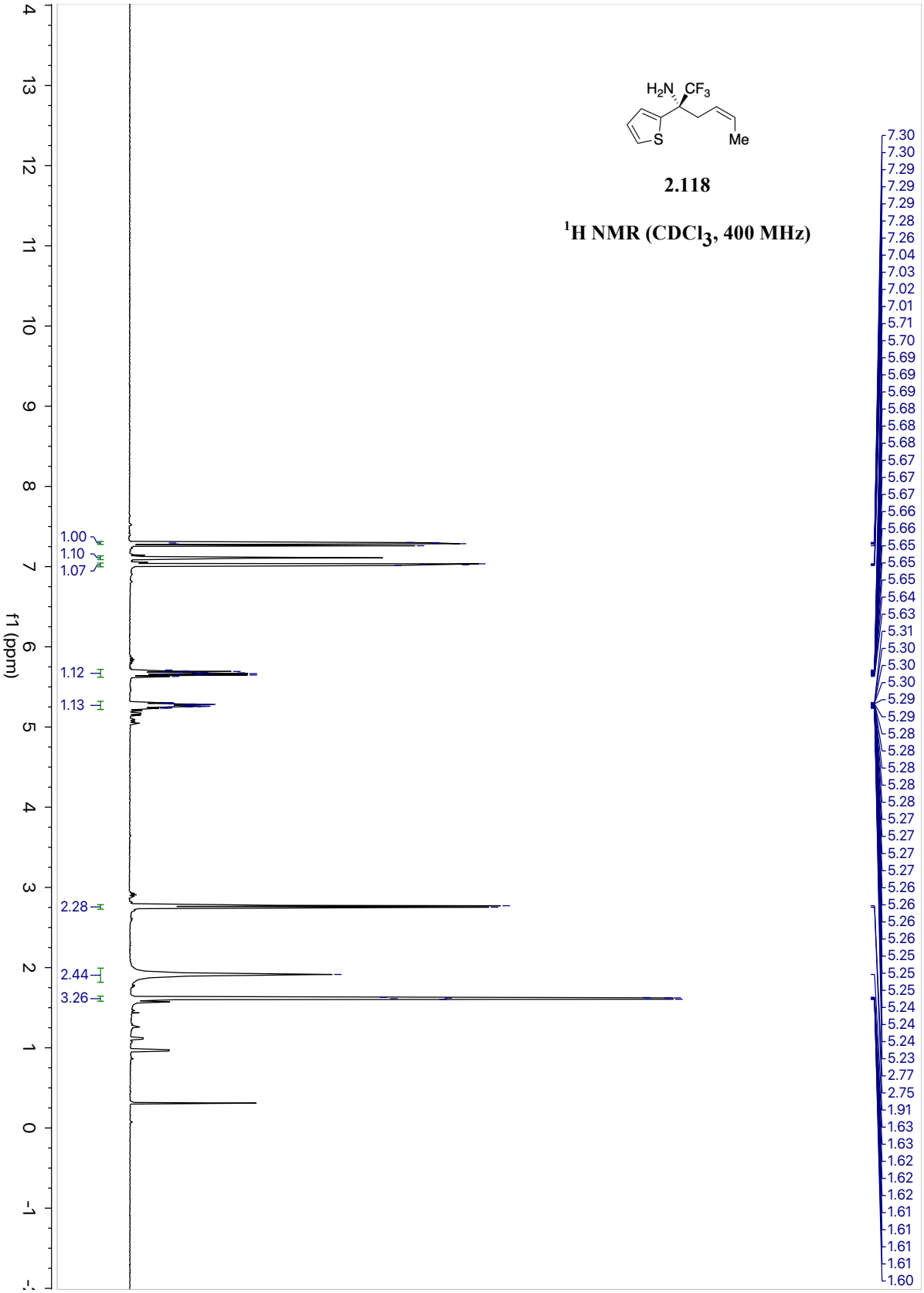

H2N
CF3
Me
2.117
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.97
3.19
1.00
1.02
2.41
2.40
3.24
7.47
7.47
7.46
7.45
7.45
7.45
7.45
7.44
7.44
7.43
7.36
7.36
7.36
7.35
7.35
7.34
7.34
7.34
7.34
7.34
7.33
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.26
5.86
5.86
5.85
5.85
5.85
5.84
5.84
5.84
5.84
5.83
5.83
5.83
5.83
5.82
5.82
5.82
5.81
5.81
5.81
5.70
5.70
5.69
5.68
5.67
5.67
5.67
5.66
5.65
2.64
2.63
1.73
1.72
1.71
1.71

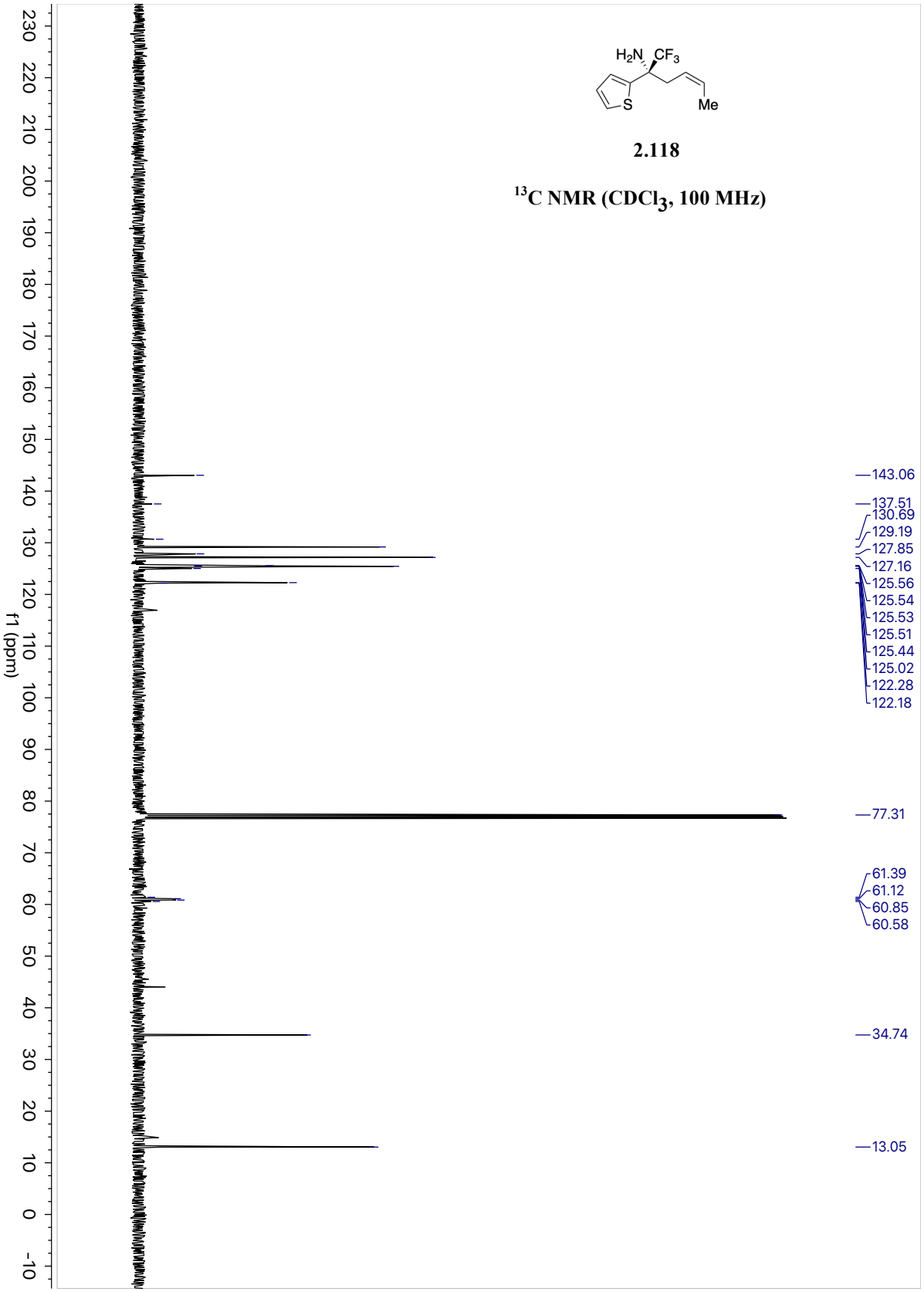


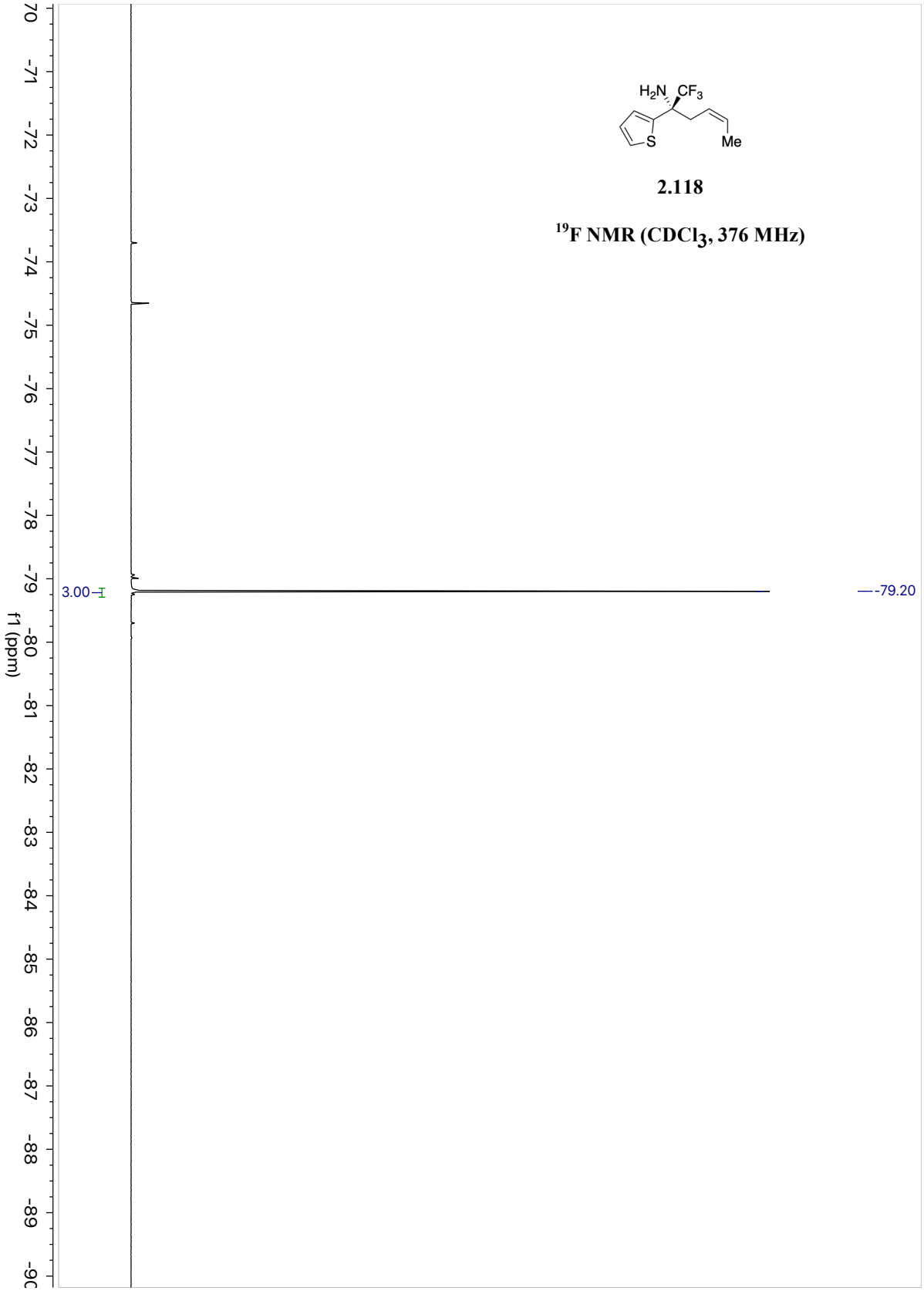
2.117

^{13}C NMR ($CDCl_3$, 100 MHz)


H2N
CF3
Me
2.117
19F NMR (CDCl3, 376 MHz)
f1 (ppm)
3.00
-80.45

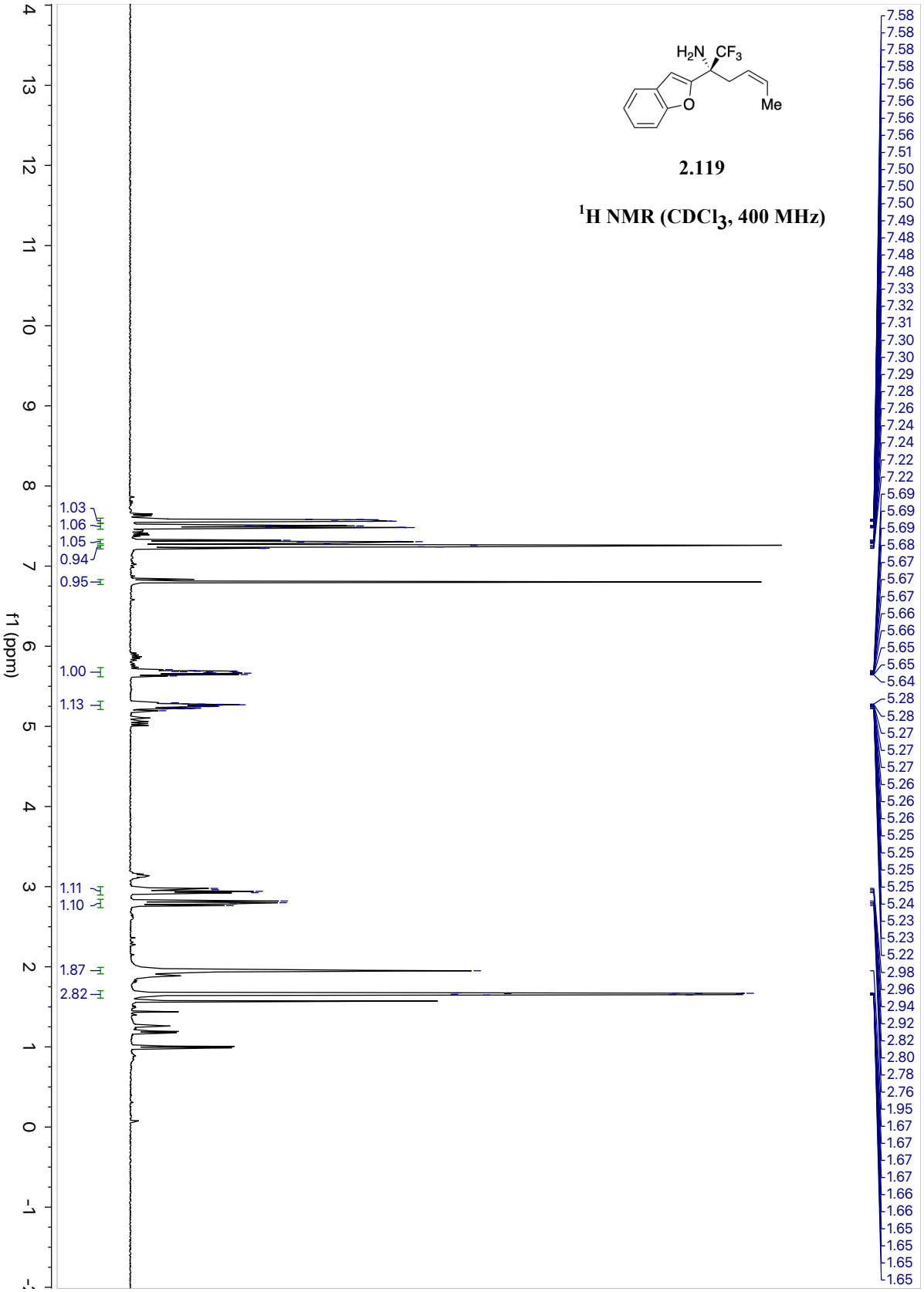

H2N
CF3
S
Me
2.118
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.00
1.10
1.07
1.12
1.13
2.28
2.44
3.26
7.30
7.30
7.29
7.29
7.29
7.28
7.26
7.04
7.03
7.02
7.01
5.71
5.70
5.69
5.69
5.69
5.68
5.68
5.68
5.67
5.67
5.67
5.66
5.66
5.65
5.65
5.65
5.64
5.63
5.31
5.30
5.30
5.30
5.29
5.29
5.28
5.28
5.28
5.28
5.28
5.27
5.27
5.27
5.27
5.26
5.26
5.26
5.26
5.25
5.25
5.25
5.24
5.24
5.24
5.23
2.77
2.75
1.91
1.63
1.63
1.62
1.62
1.62
1.61
1.61
1.61
1.61
1.60

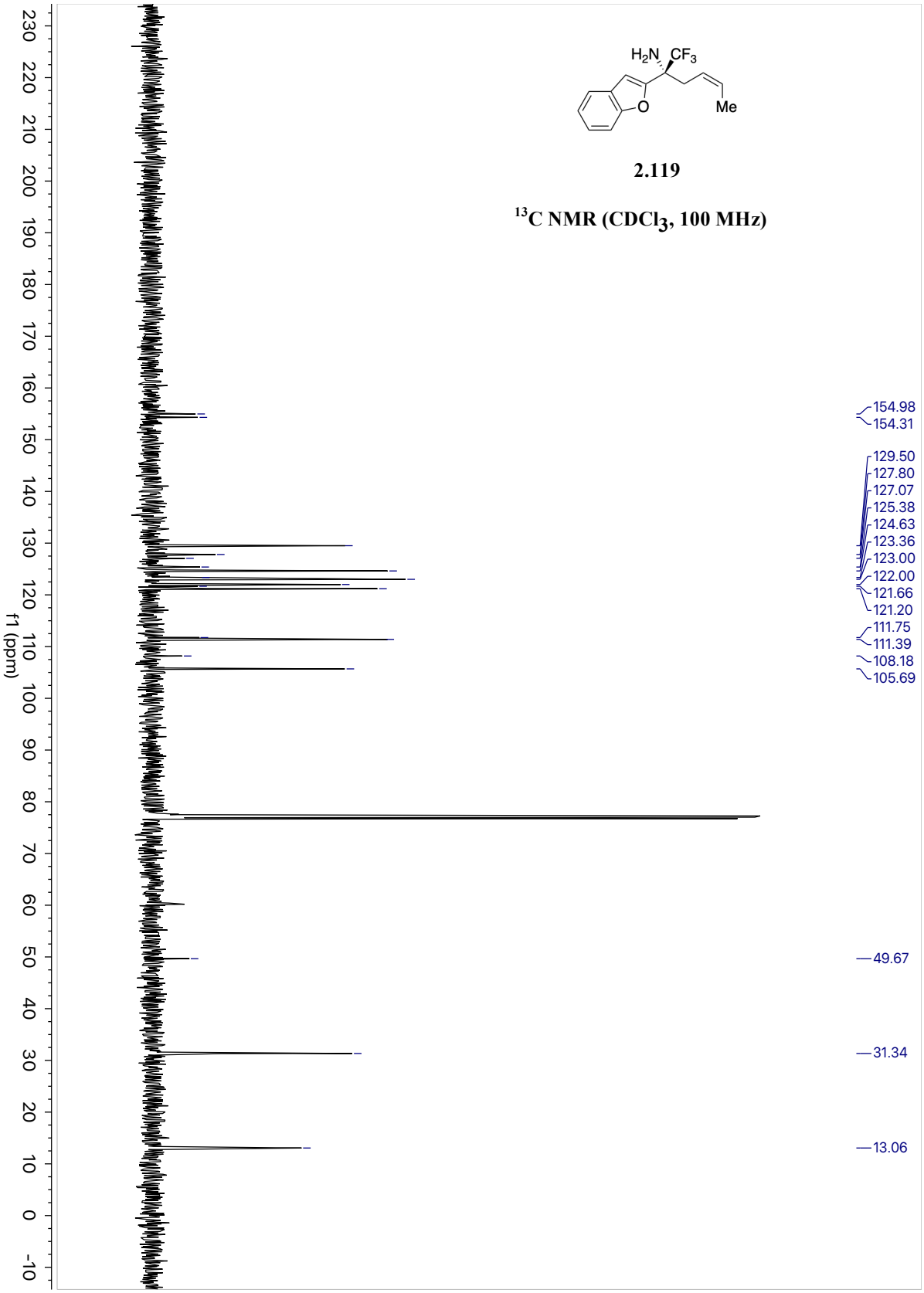

H2N
CF3
S
Me
2.118
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
143.06
137.51
130.69
129.19
127.85
127.16
125.56
125.54
125.53
125.51
125.44
125.02
122.28
122.18
77.31
61.39
61.12
60.85
60.58
34.74
13.05

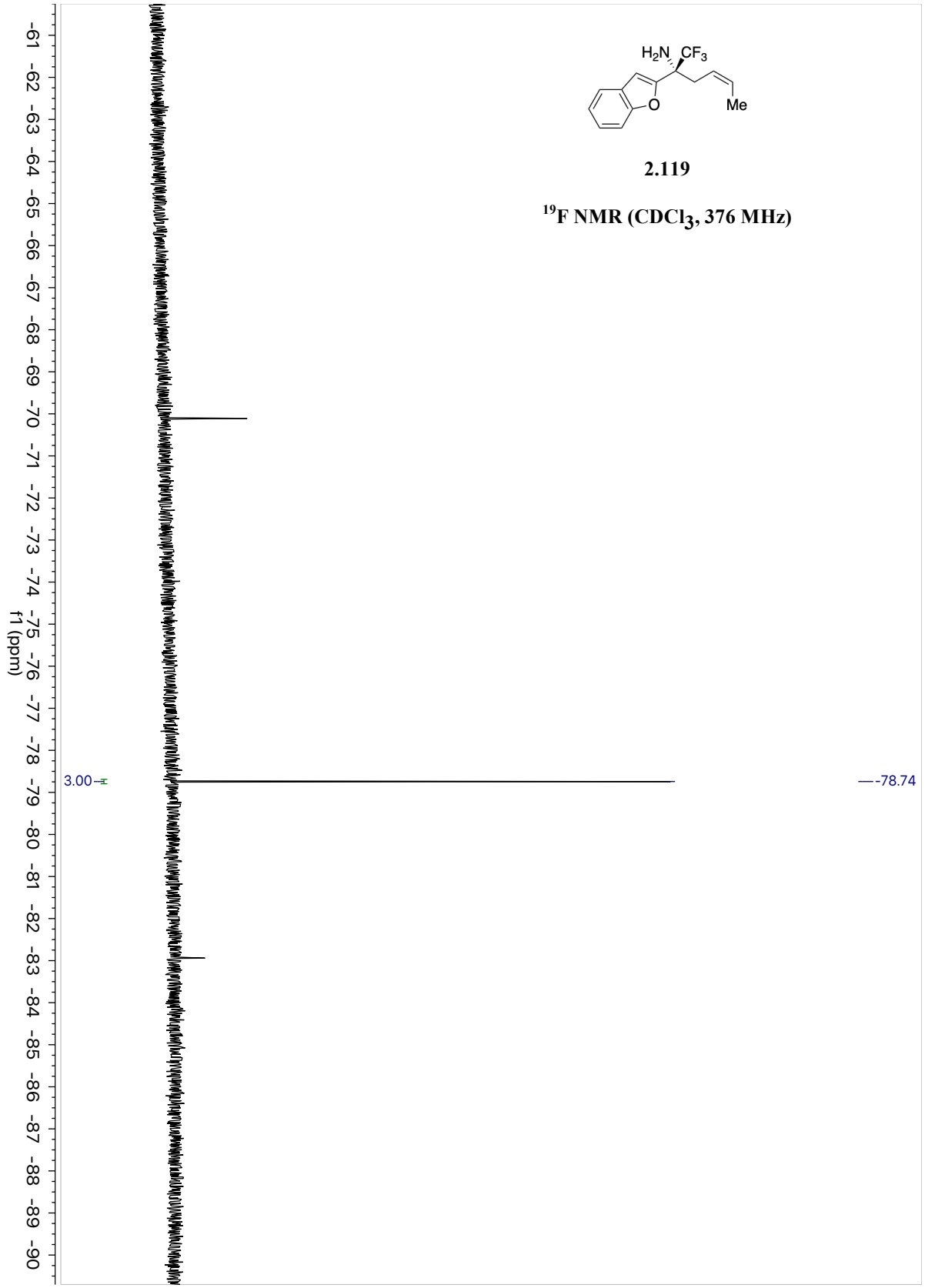


2.118

^{19}F NMR ($CDCl_3$, 376 MHz)

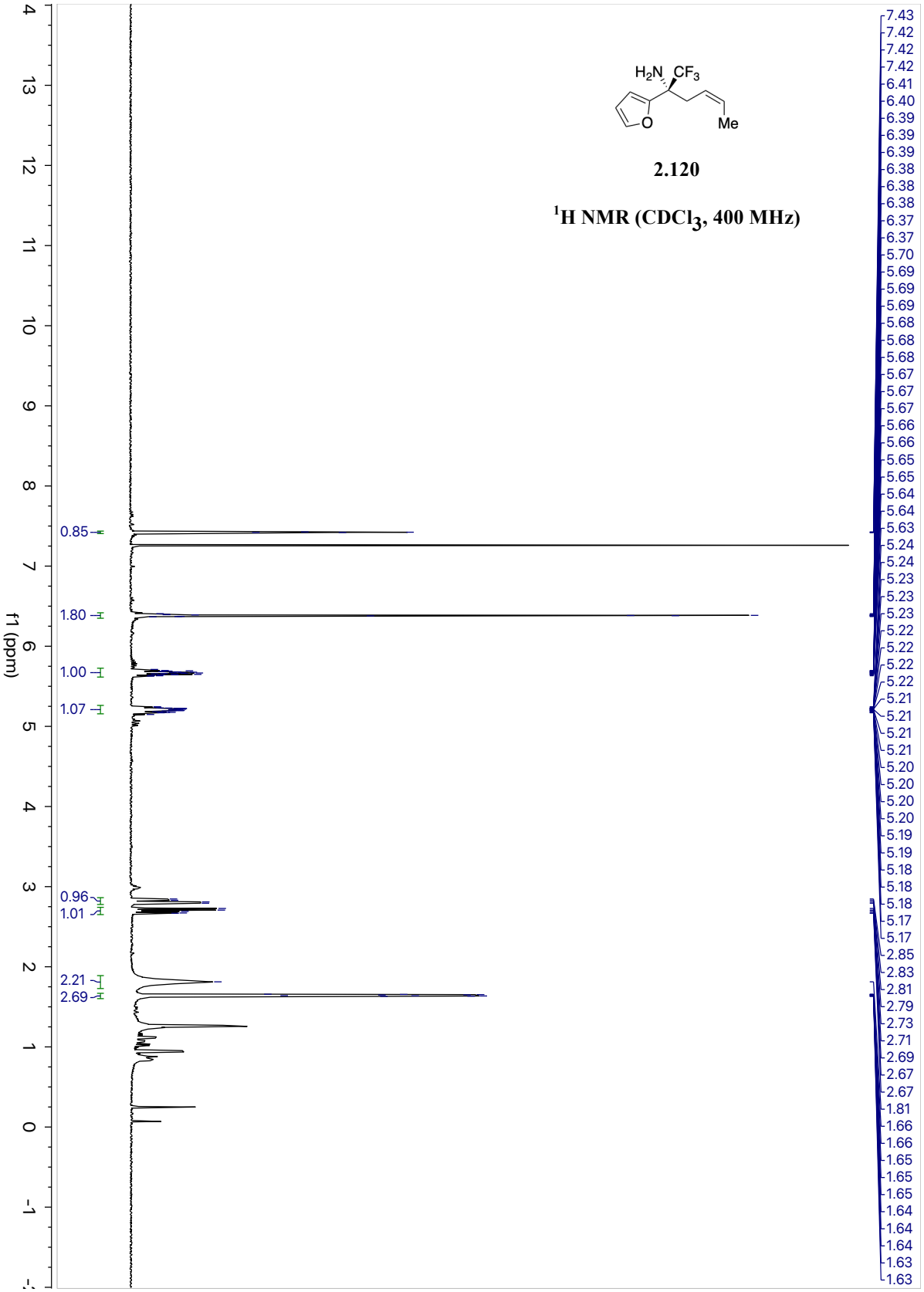

H2N CF3
O
Me
2.119
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.03
1.06
1.05
0.94
0.95
1.00
1.13
1.11
1.10
1.87
2.82

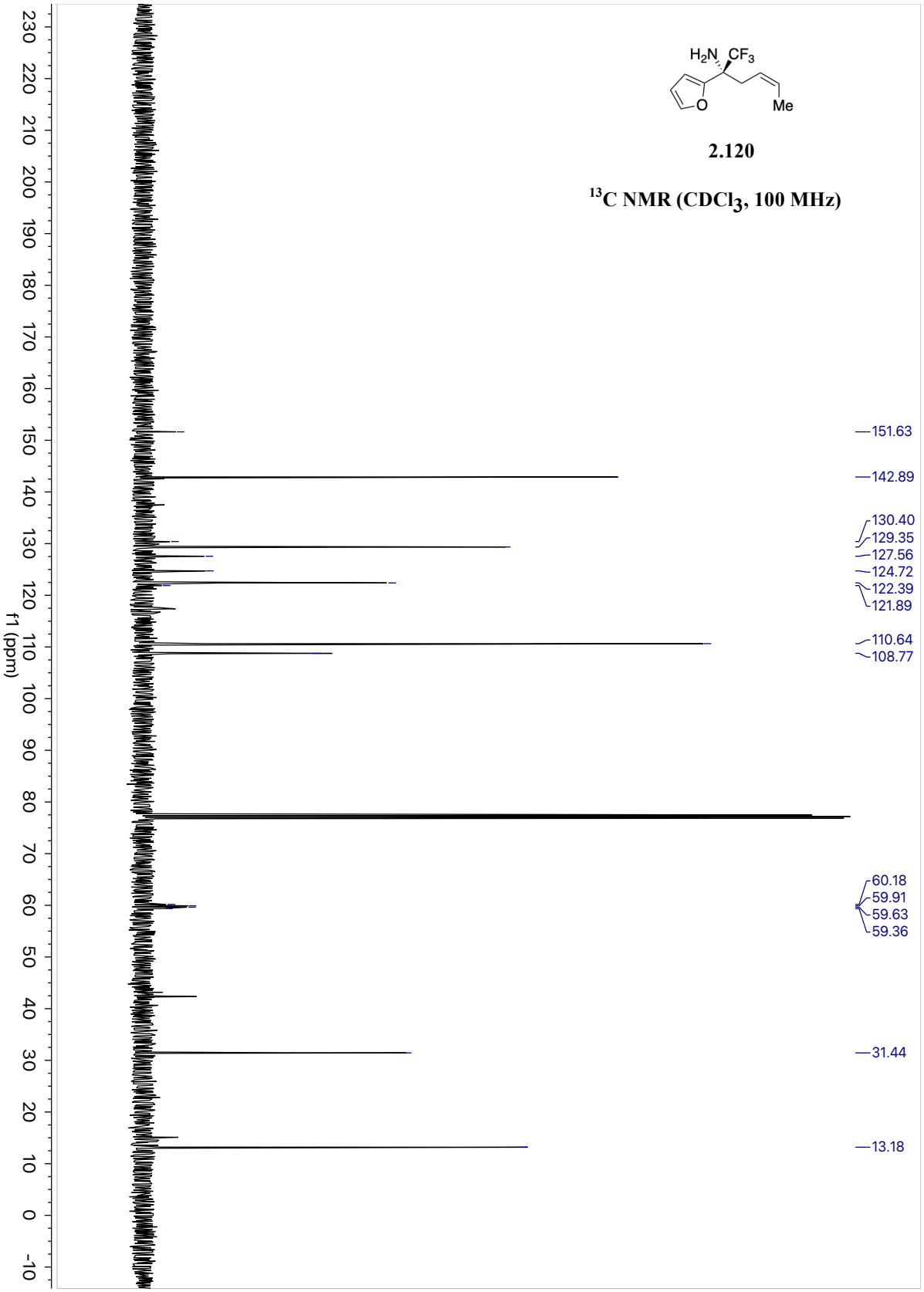

H2N
CF3
O
Me
2.119
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
154.98
154.31
129.50
127.80
127.07
125.38
124.63
123.36
123.00
122.00
121.66
121.20
111.75
111.39
108.18
105.69
49.67
31.34
13.06

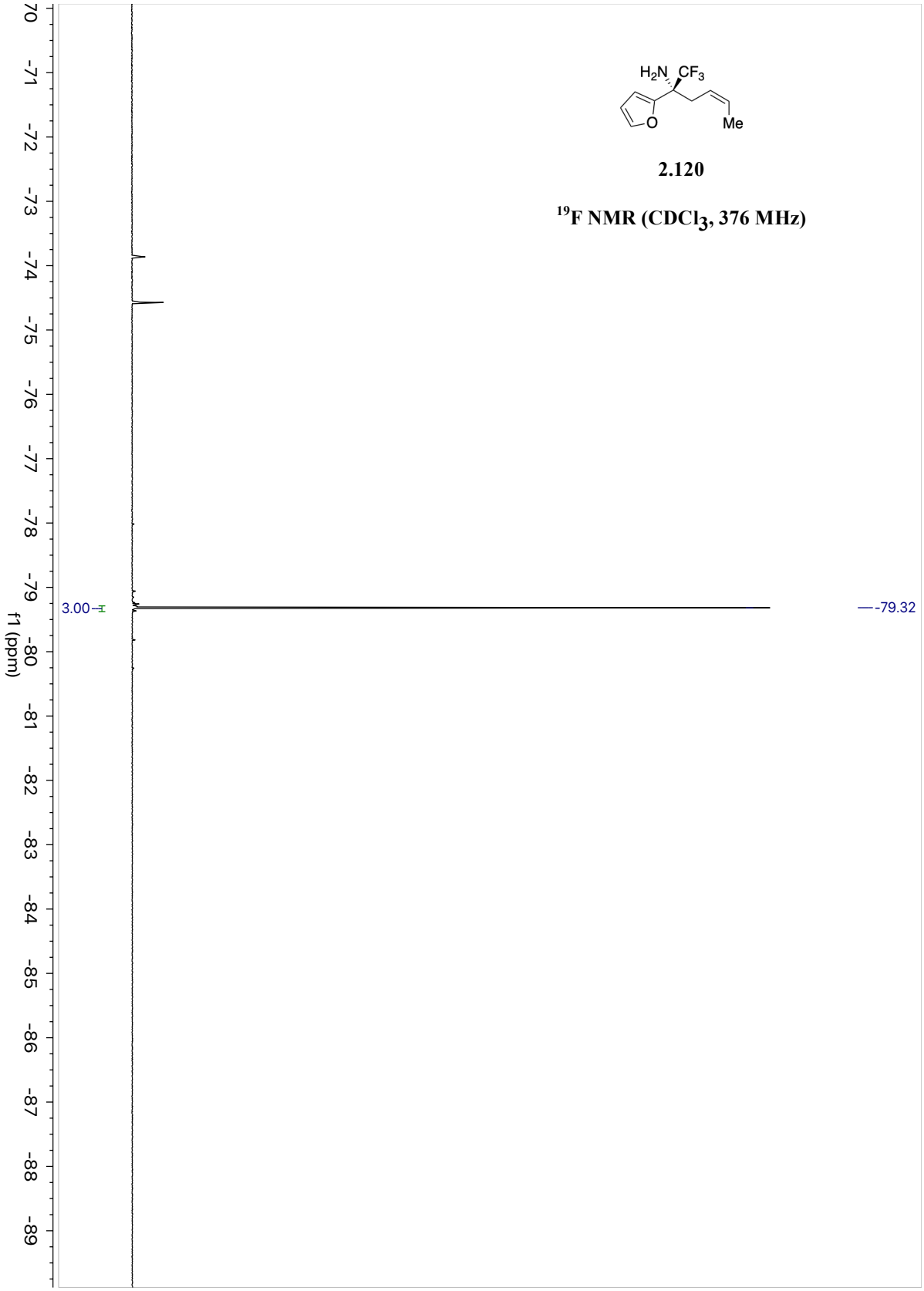


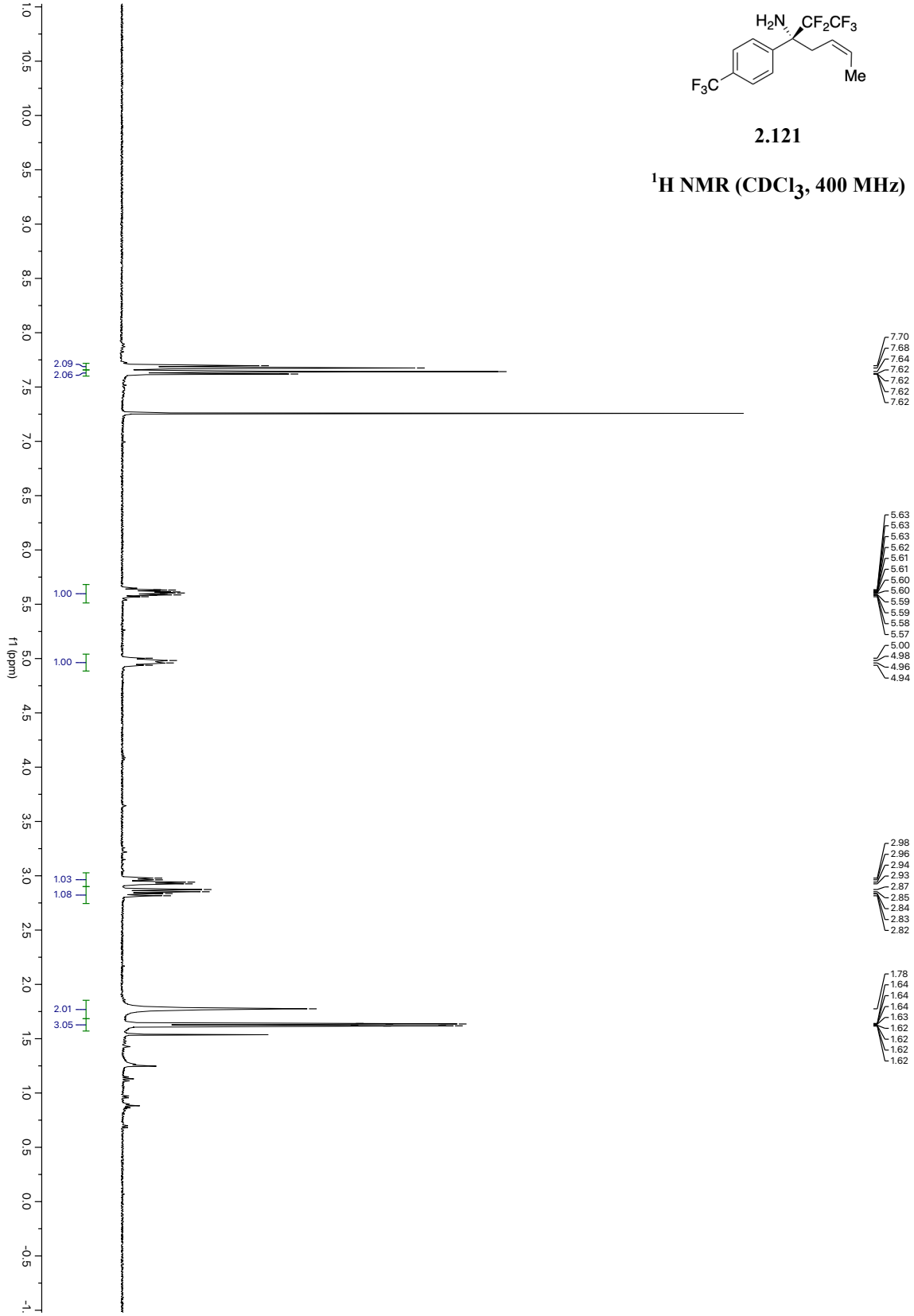
2.119

^{19}F NMR ($CDCl_3$, 376 MHz)


H2N
CF3
O
Me
2.120
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.85
1.80
1.00
1.07
0.96
1.01
2.21
2.69


H2N
CF3
O
Me
2.120
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
151.63
142.89
130.40
129.35
127.56
124.72
122.39
121.89
110.64
108.77
60.18
59.91
59.63
59.36
31.44
13.18


H2N CF3
O
Me
2.120
19F NMR (CDCl3, 376 MHz)
3.00
-79.32
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89


H2N
CF2CF3
F3C
Me
2.121
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.09
2.06
1.00
1.00
1.03
1.08
2.01
3.05
7.70
7.68
7.64
7.62
7.62
7.62
7.62
5.63
5.63
5.63
5.62
5.61
5.61
5.60
5.60
5.59
5.59
5.58
5.57
5.00
4.98
4.96
4.94
2.98
2.96
2.94
2.93
2.87
2.85
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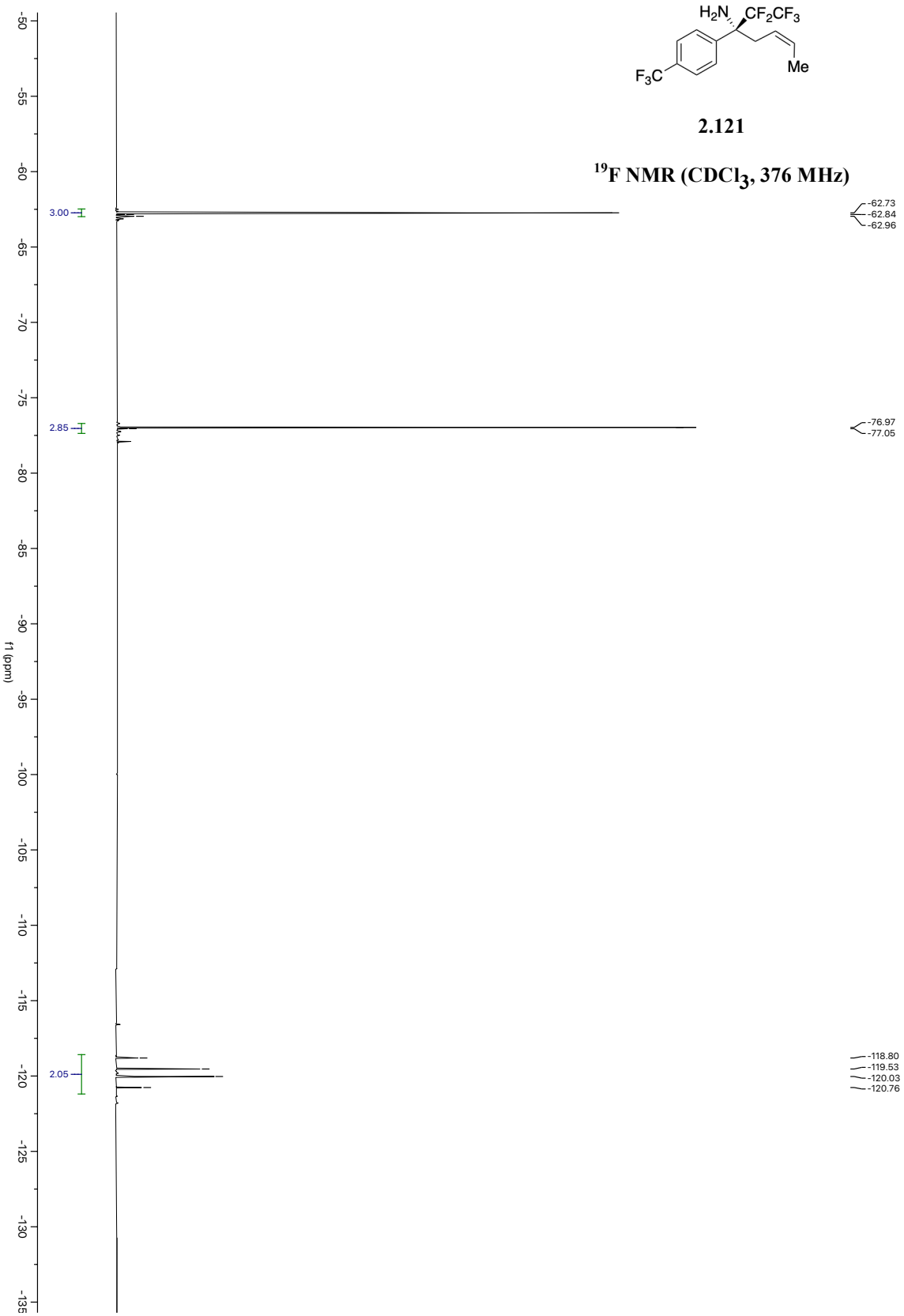
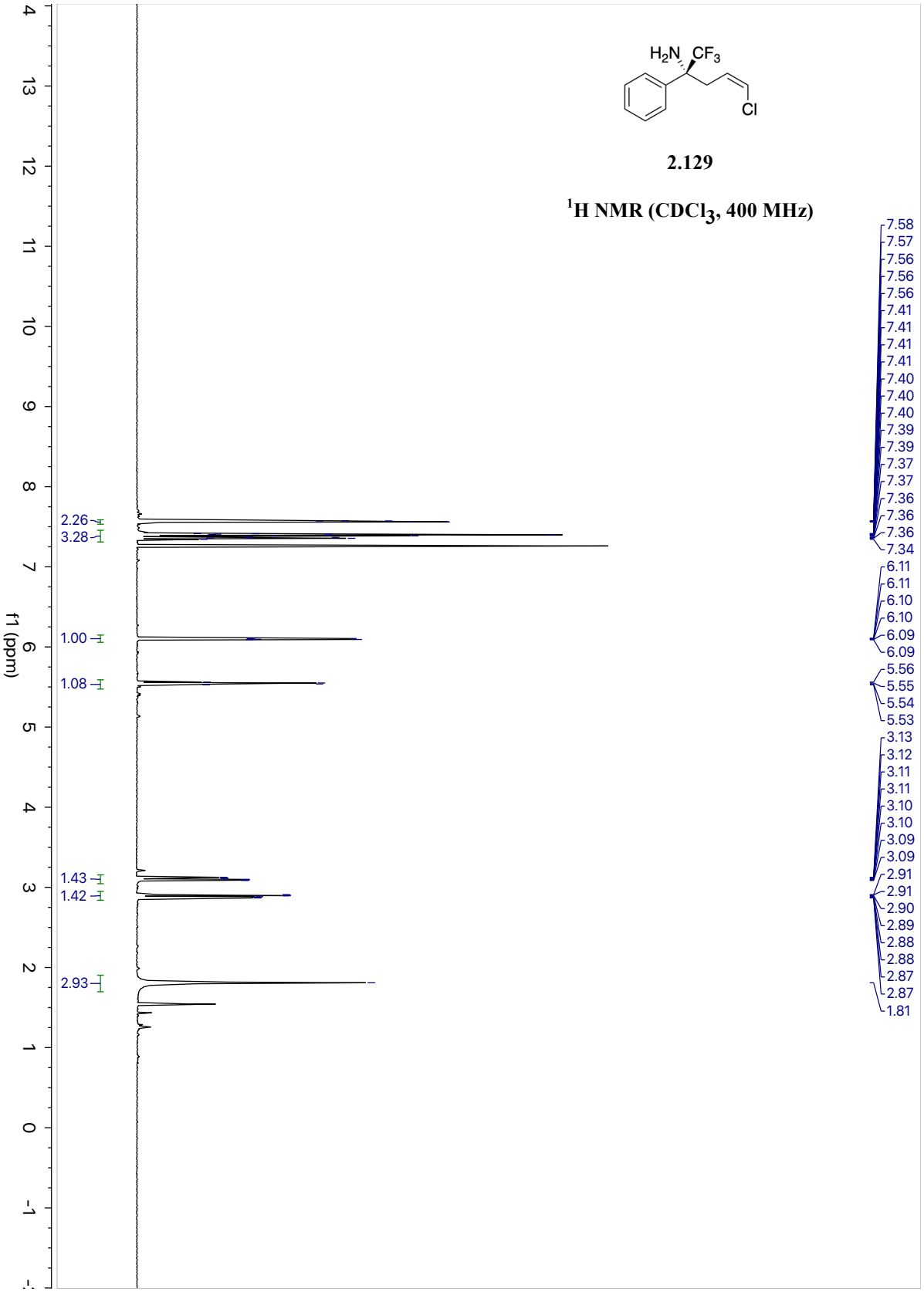
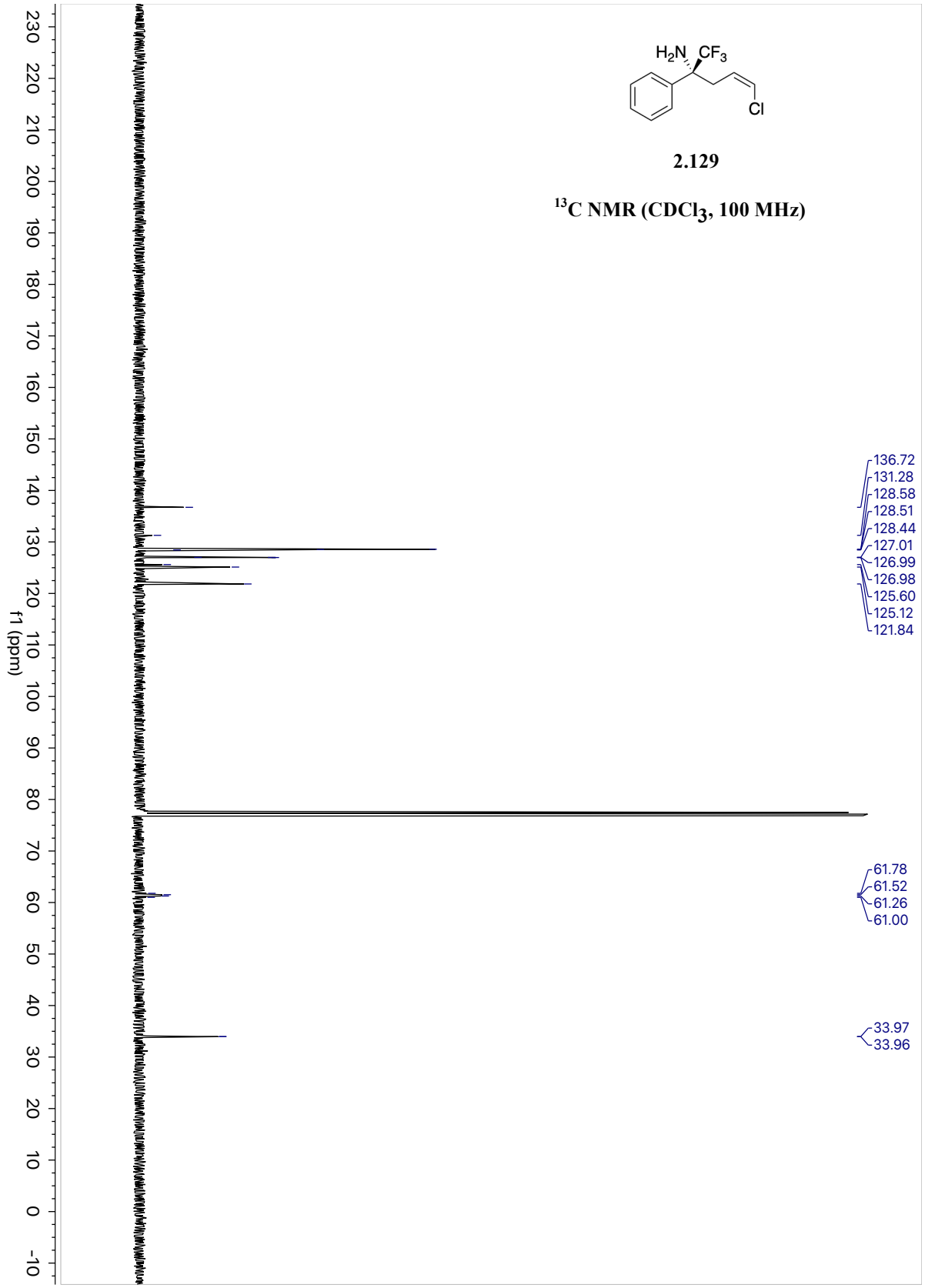
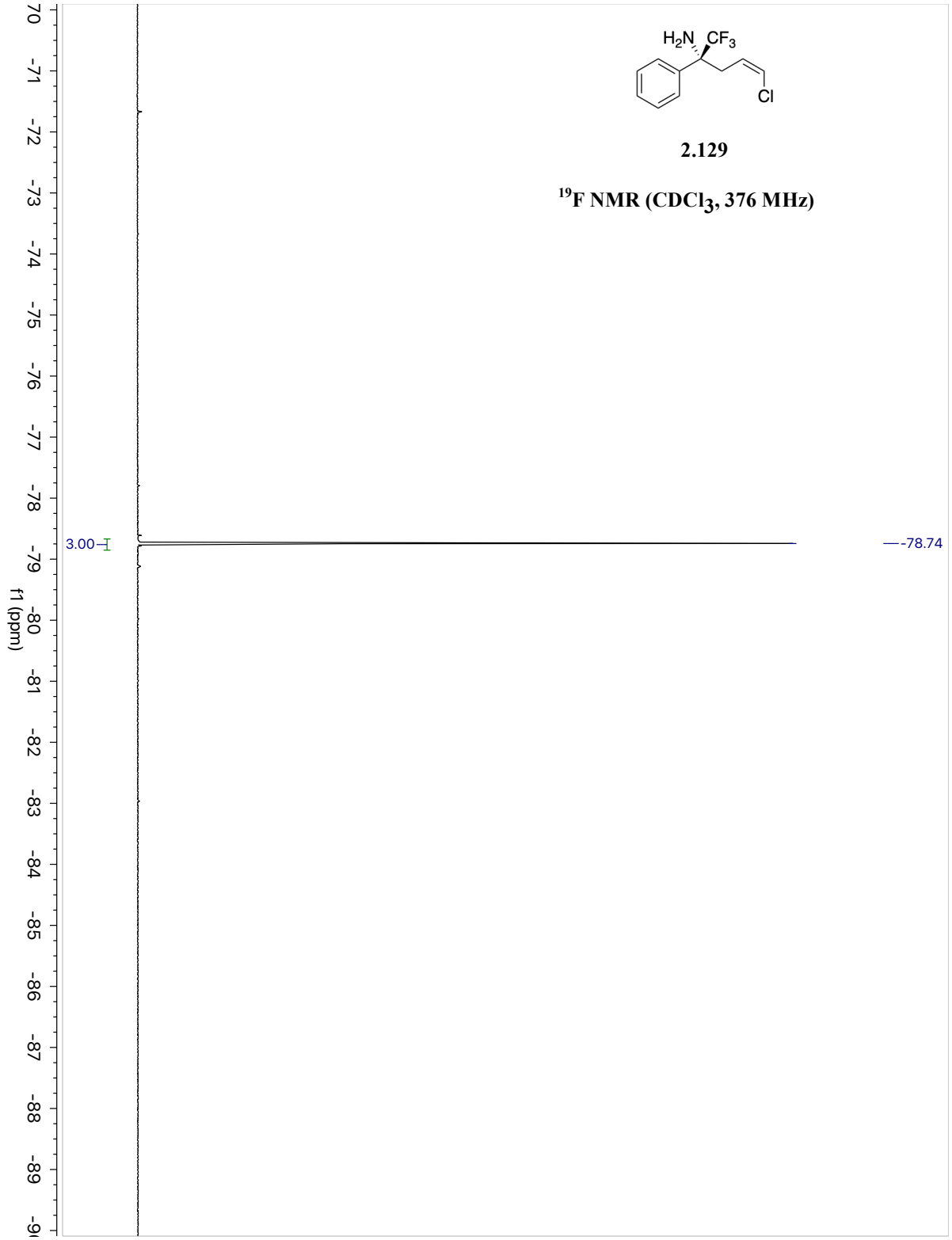
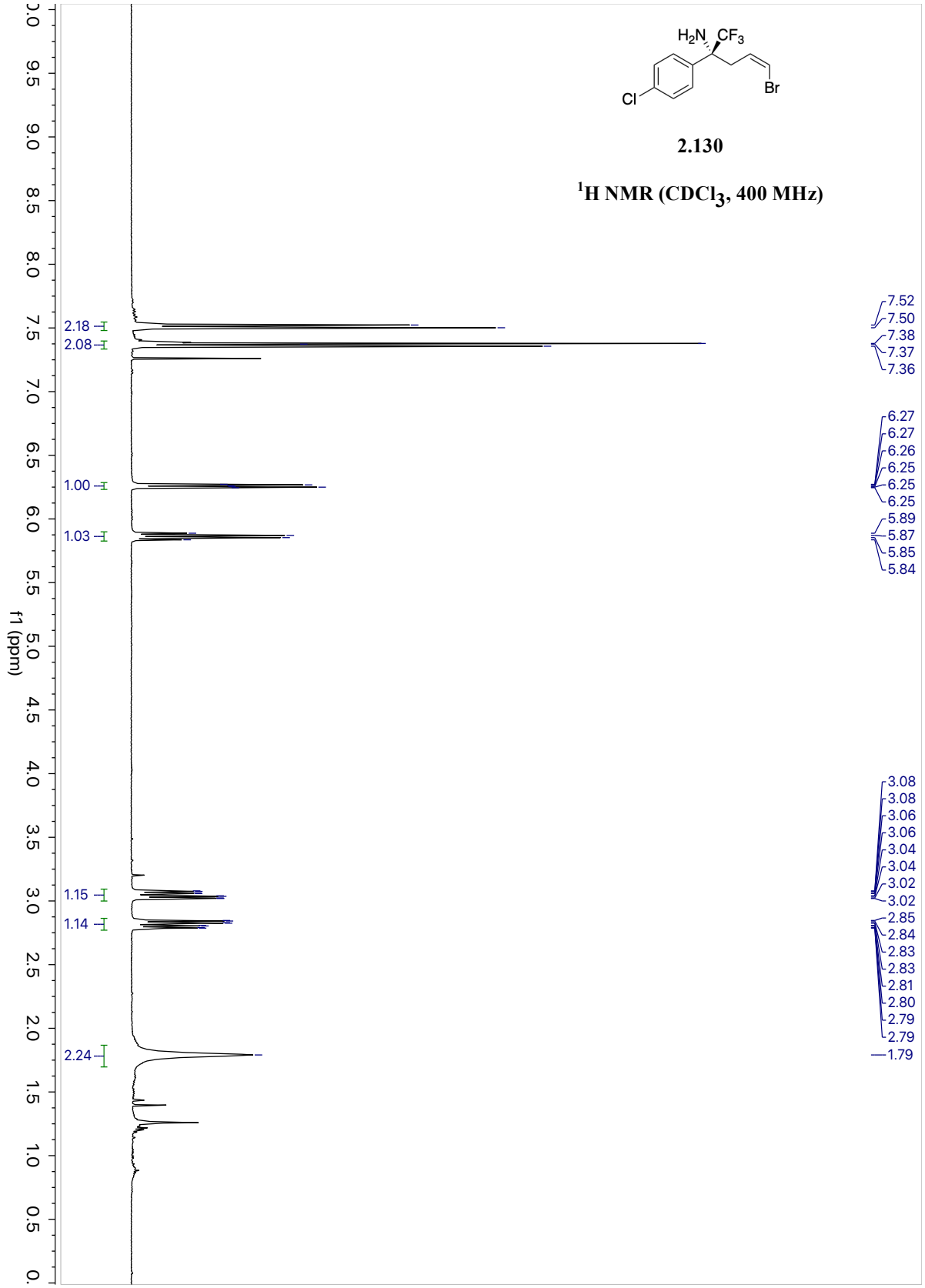
1.64
1.63
1.62
1.62
1.62
1.62


H2N
CF2CF3
F3C
Me
2.121
19F NMR (CDCl3, 376 MHz)
3.00
2.85
2.05
-62.73
-62.84
-62.96
-76.97
-77.05
-118.80
-119.53
-120.03
-120.76
f1 (ppm)
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135


H2N CF3
Cl
2.129
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.26
3.28
1.00
1.08
1.43
1.42
2.93
7.58
7.57
7.56
7.56
7.56
7.41
7.41
7.41
7.41
7.40
7.40
7.40
7.39
7.39
7.37
7.37
7.36
7.36
7.36
7.34
6.11
6.11
6.10
6.10
6.09
6.09
5.56
5.55
5.54
5.53
3.13
3.12
3.11
3.11
3.10
3.10
3.09
3.09
2.91
2.91
2.90
2.89
2.88
2.88
2.87
2.87
1.81


H2N CF3
Cl
2.129
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
136.72
131.28
128.58
128.51
128.44
127.01
126.99
126.98
125.60
125.12
121.84
61.78
61.52
61.26
61.00
33.97
33.96


H2N
CF3
Cl
2.129
19F NMR (CDCl3, 376 MHz)
3.00
-78.74
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-91


H2N
CF3
Cl
Br
2.130
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.18
2.08
1.00
1.03
1.15
1.14
2.24
7.52
7.50
7.38
7.37
7.36
6.27
6.27
6.26
6.25
6.25
6.25
5.89
5.87
5.85
5.84
3.08
3.08
3.06
3.06
3.04
3.04
3.02
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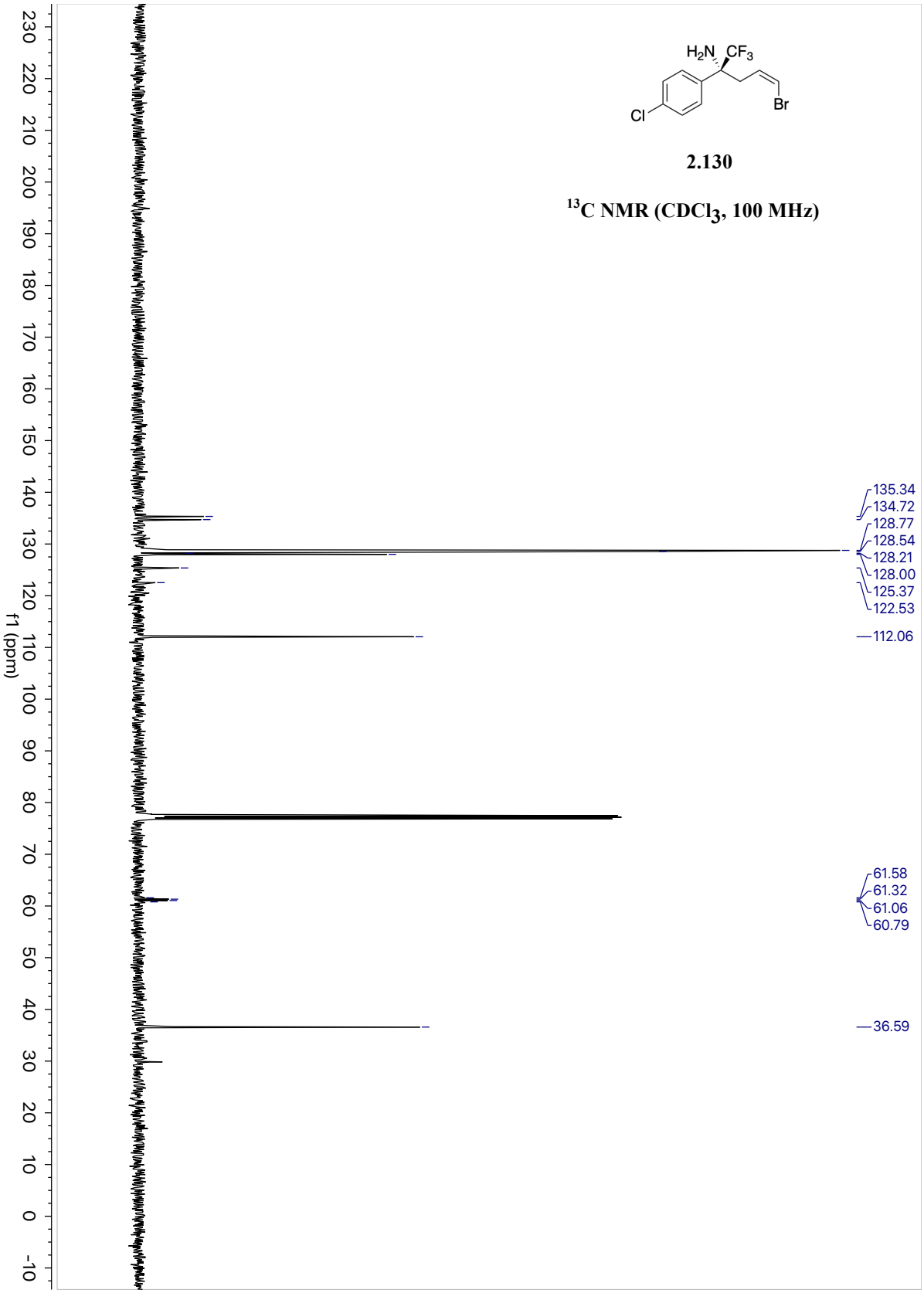
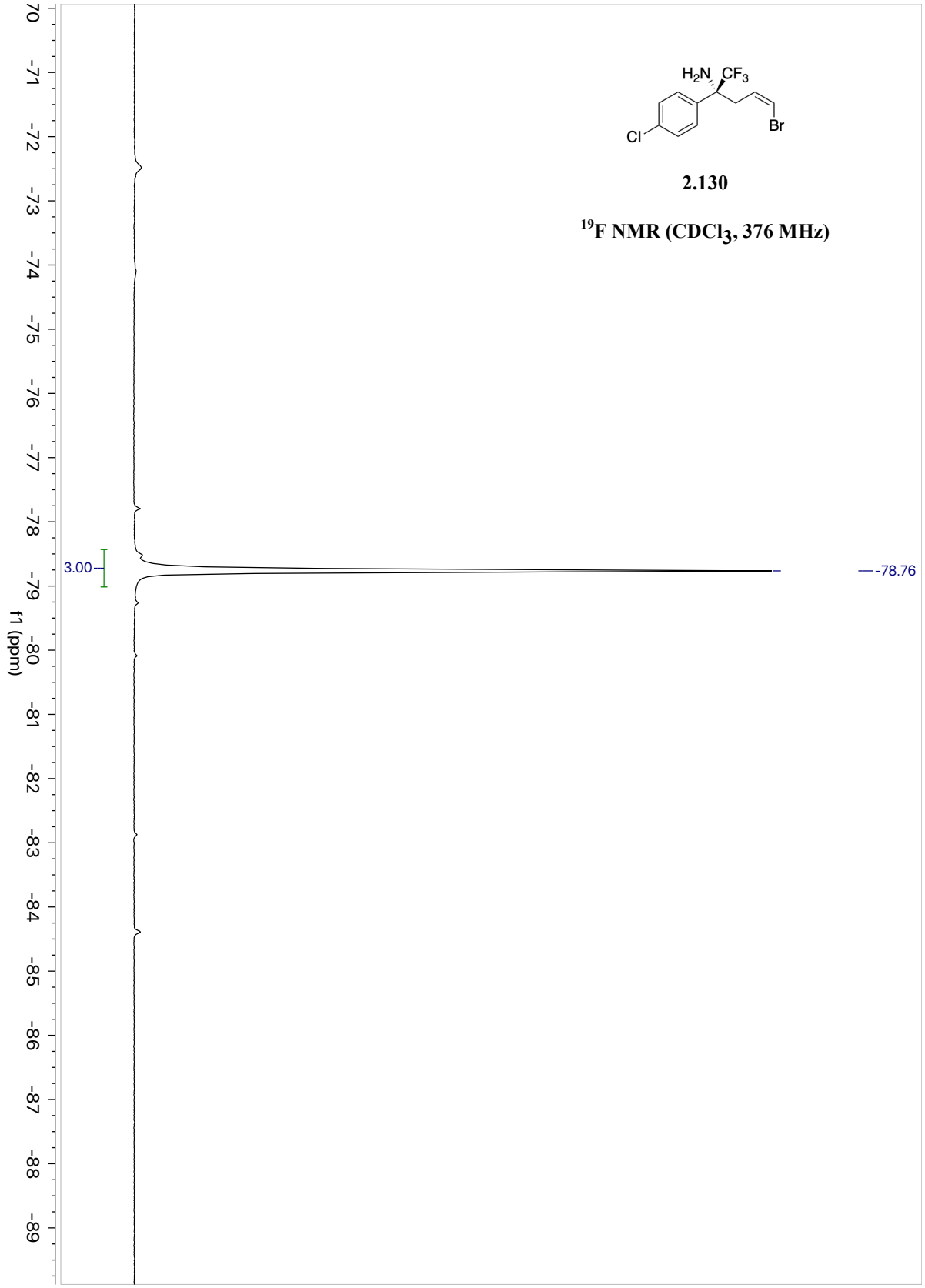
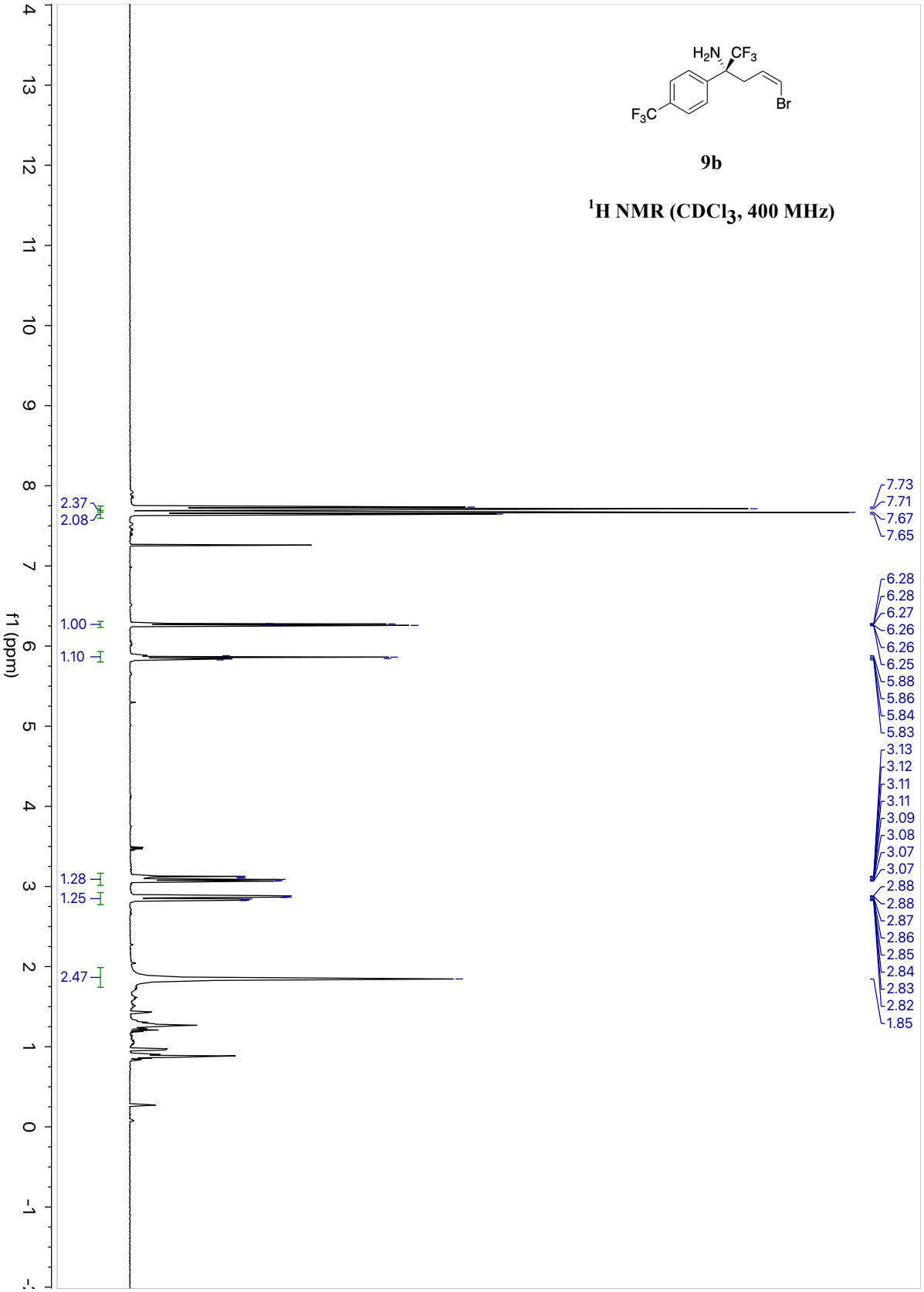
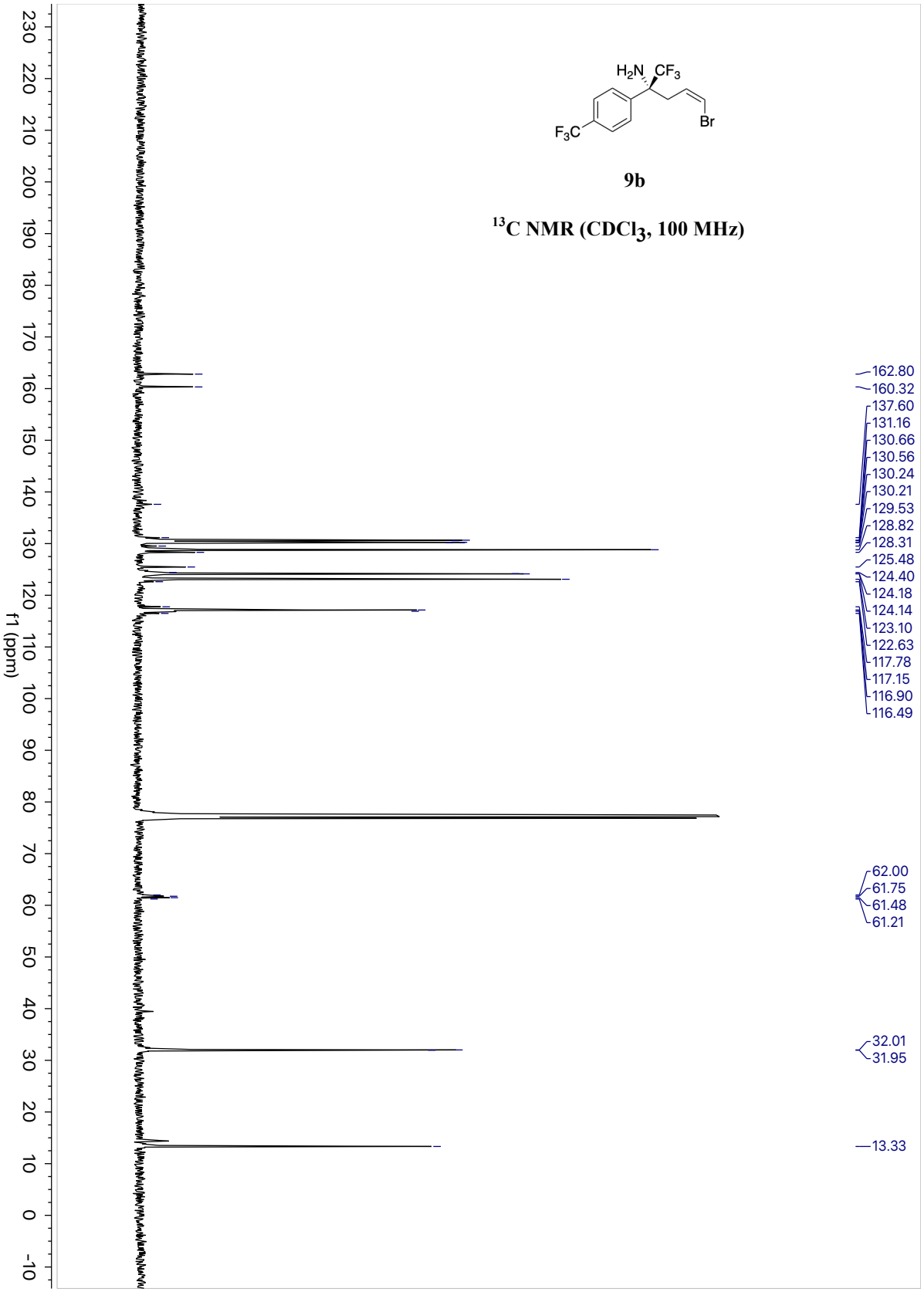
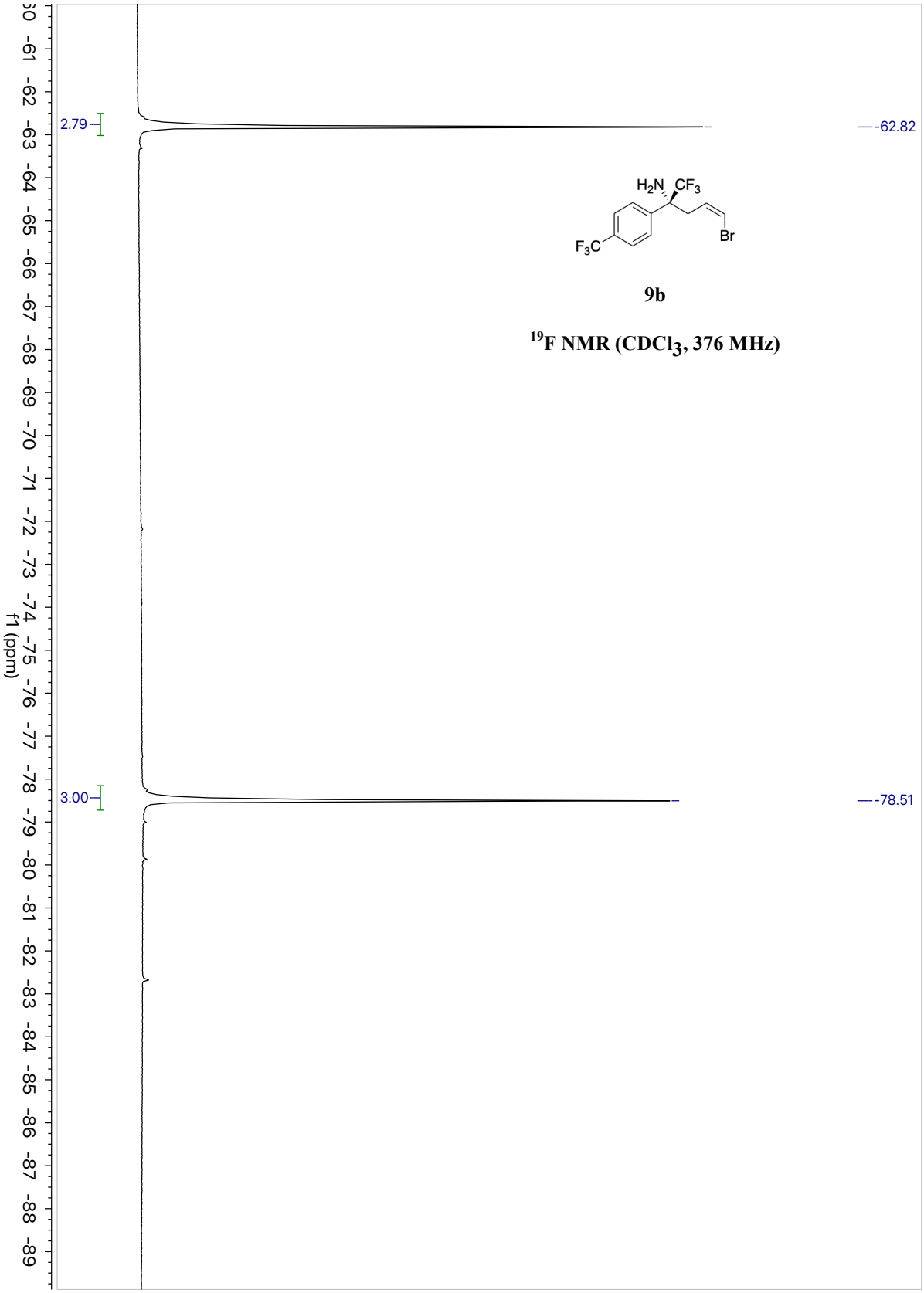
2.85
2.84
2.83
2.83
2.81
2.80
2.79
2.79
1.79


H2N
CF3
Cl
Br
2.130
13C NMR (CDCl3, 100 MHz)
135.34
134.72
128.77
128.54
128.21
128.00
125.37
122.53
112.06
61.58
61.32
61.06
60.79
36.59
f1 (ppm)


H2N
CF3
Cl
Br
2.130
19F NMR (CDCl3, 376 MHz)
3.00
-78.76
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89

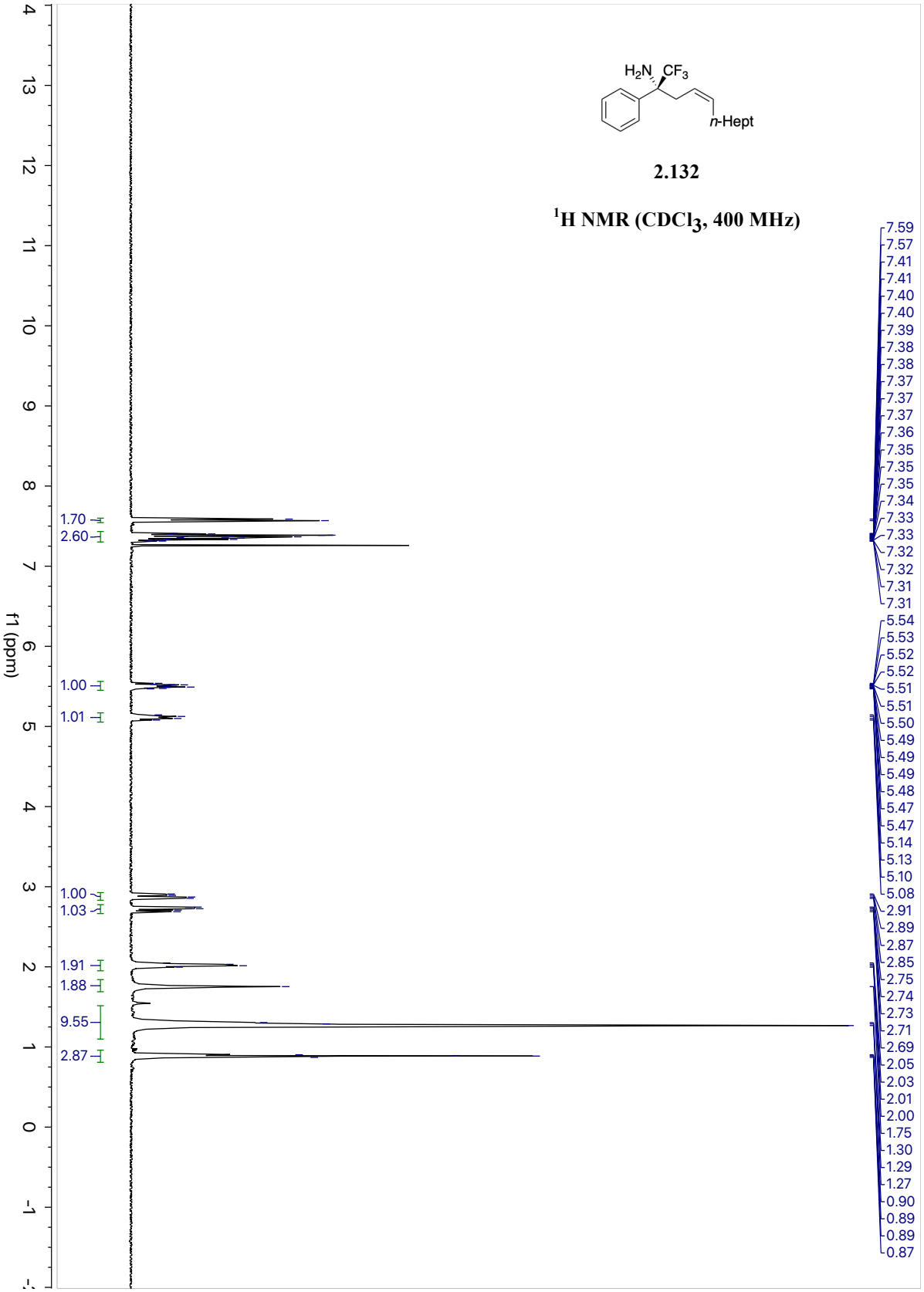

H2N CF3
F3C
Br
9b
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.37
2.08
1.00
1.10
1.28
1.25
2.47
7.73
7.71
7.67
7.65
6.28
6.28
6.27
6.26
6.26
6.25
5.88
5.86
5.84
5.83
3.13
3.12
3.11
3.11
3.09
3.08
3.07
3.07
2.88
2.88
2.87
2.86
2.85
2.84
2.83
2.82
1.85

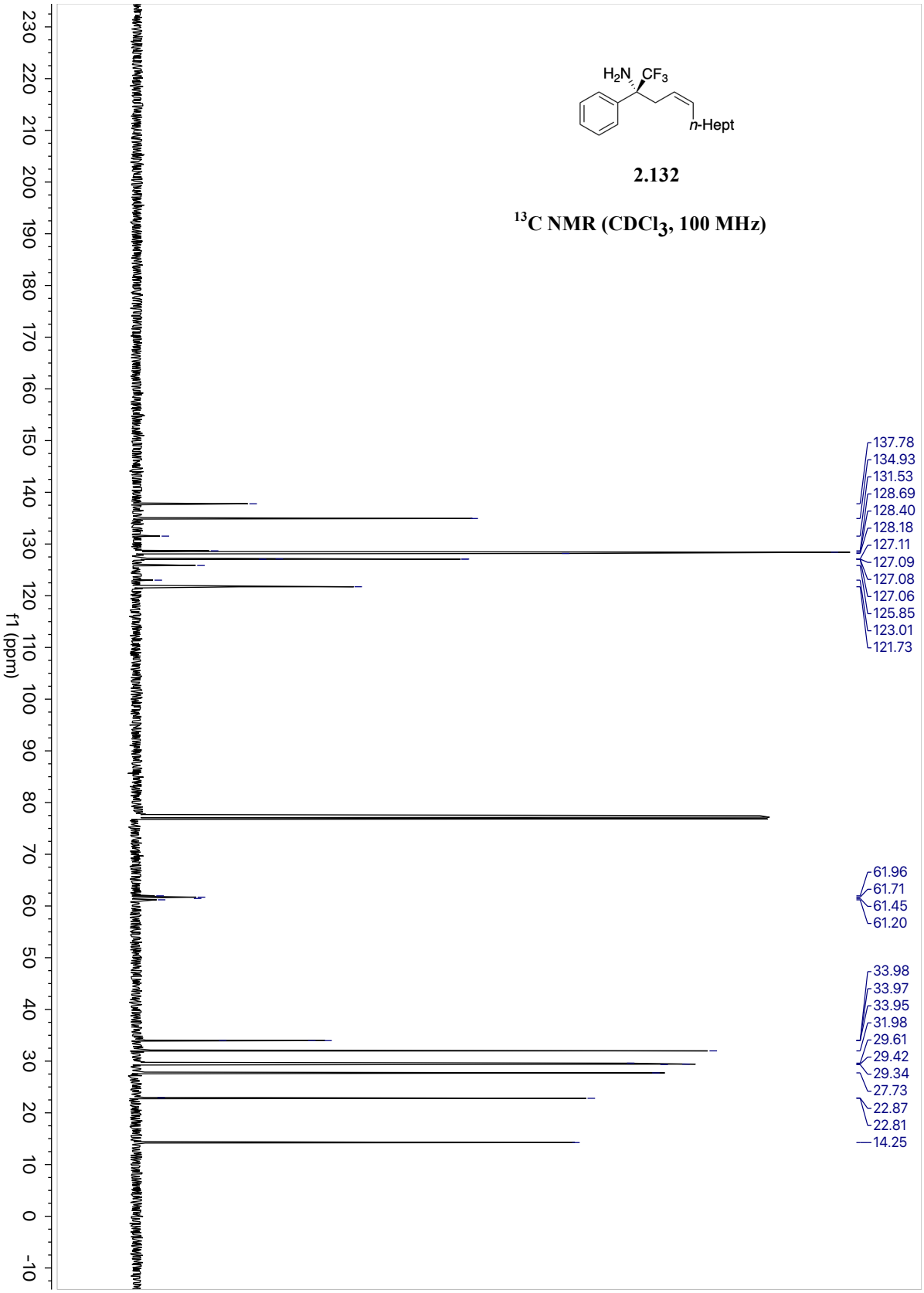

H2N
CF3
F3C
Br
9b
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
162.80
160.32
137.60
131.16
130.66
130.56
130.24
130.21
129.53
128.82
128.31
125.48
124.40
124.18
124.14
123.10
122.63
117.78
117.15
116.90
116.49
62.00
61.75
61.48
61.21
32.01
31.95
13.33

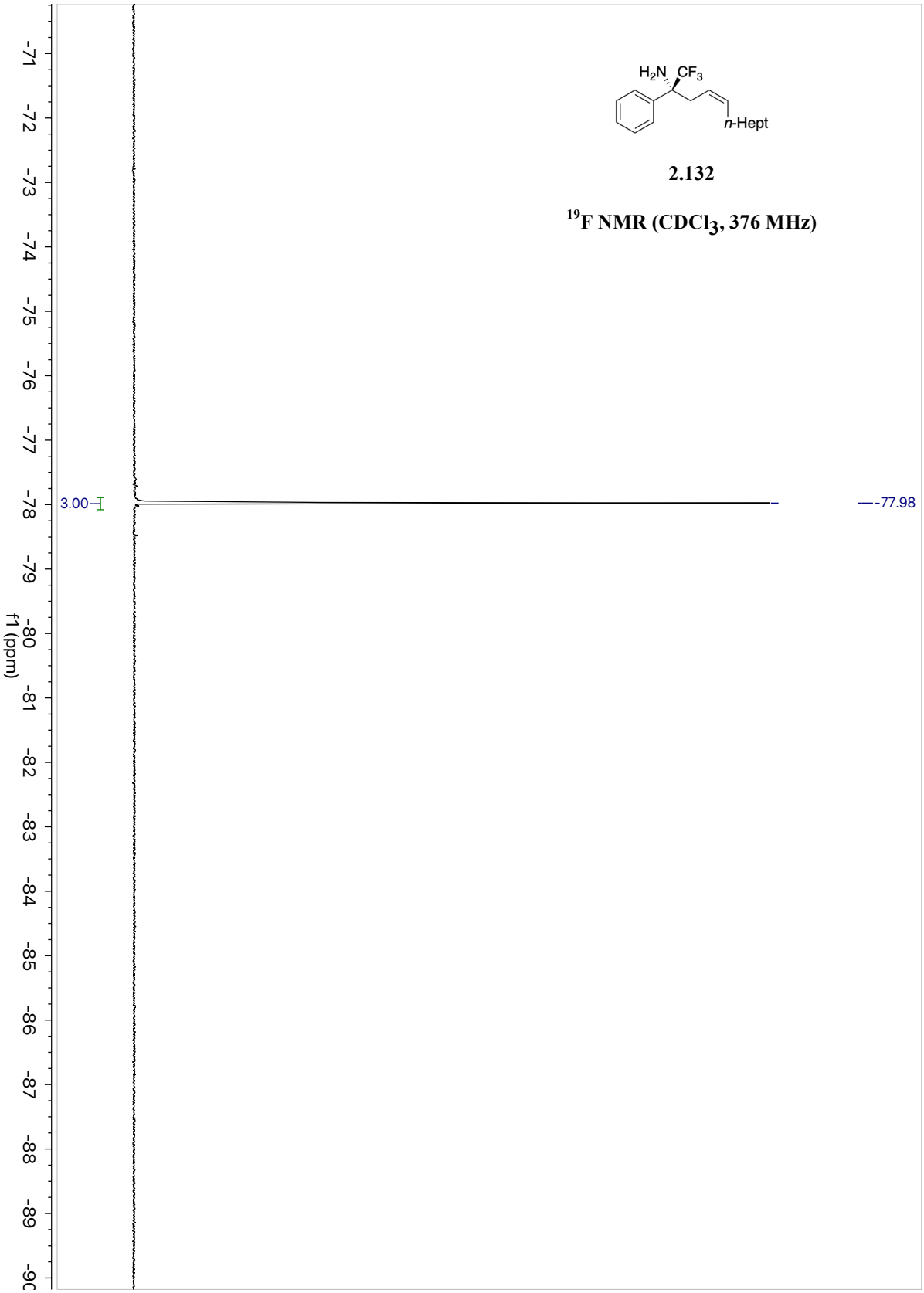


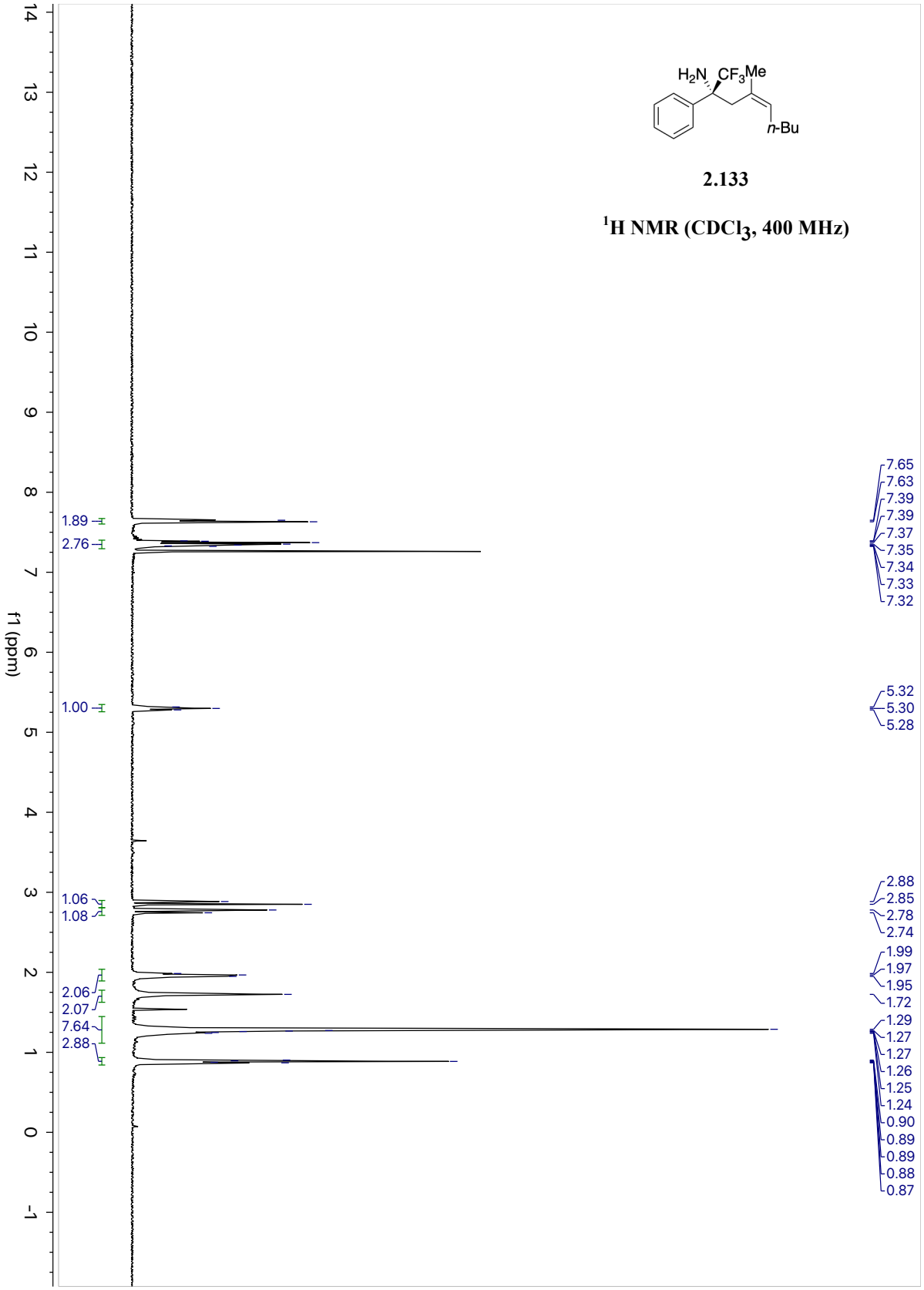
9b

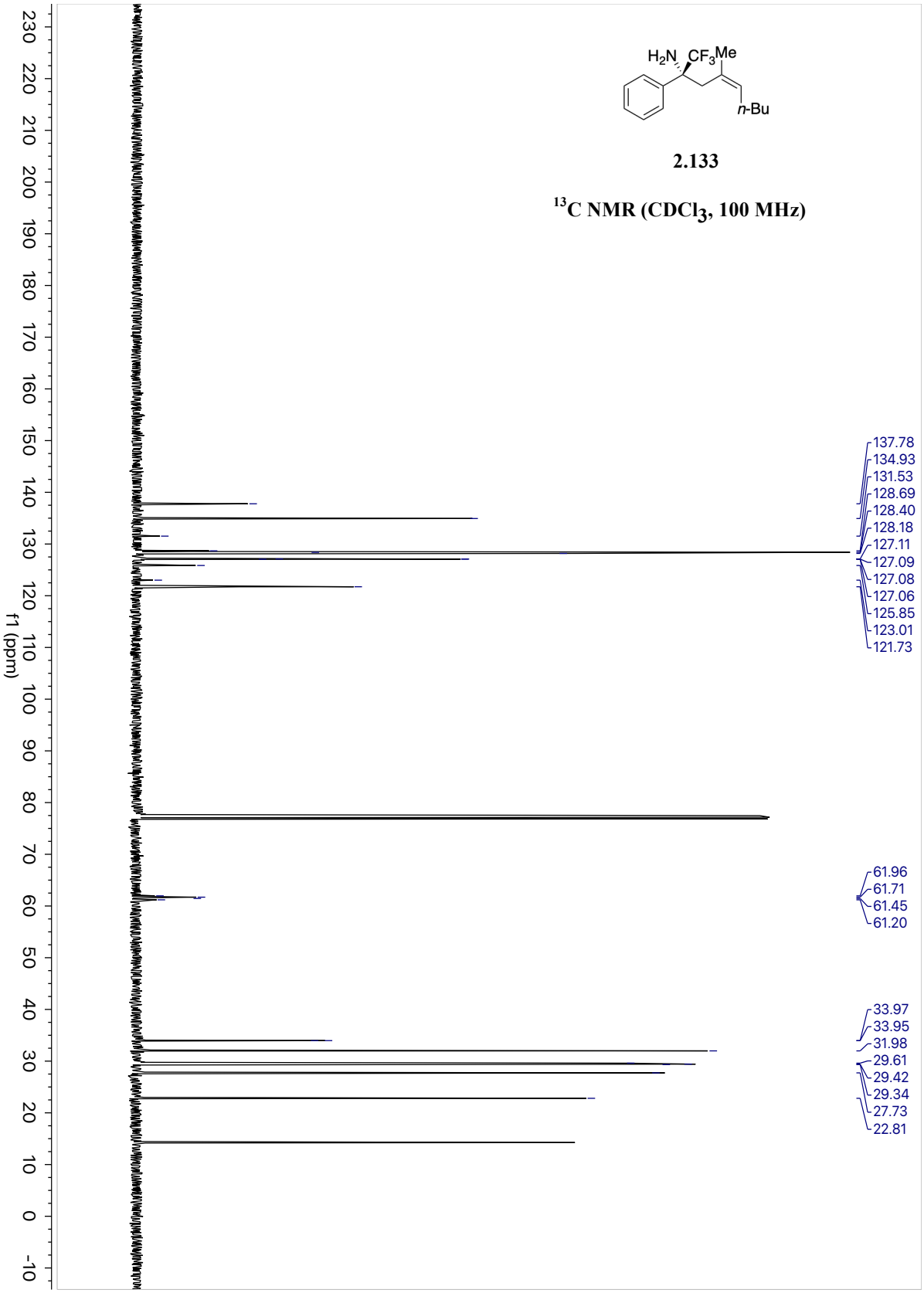
^{19}F NMR ($CDCl_3$, 376 MHz)


H2N
CF3
n-Hept
2.132
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.70
2.60
1.00
1.01
1.00
1.03
1.91
1.88
9.55
2.87
7.59
7.57
7.41
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.31
5.54
5.53
5.52
5.52
5.51
5.51
5.50
5.49
5.49
5.49
5.48
5.47
5.47
5.14
5.13
5.10
5.08
2.91
2.89
2.87
2.85
2.75
2.74
2.73
2.71
2.69
2.05
2.03
2.01
2.00
1.75
1.30
1.29
1.27
0.90
0.89
0.89
0.87


H2N CF3
n-Hept
2.132
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
137.78
134.93
131.53
128.69
128.40
128.18
127.11
127.09
127.08
127.06
125.85
123.01
121.73
61.96
61.71
61.45
61.20
33.98
33.97
33.95
31.98
29.61
29.42
29.34
27.73
22.87
22.81
14.25

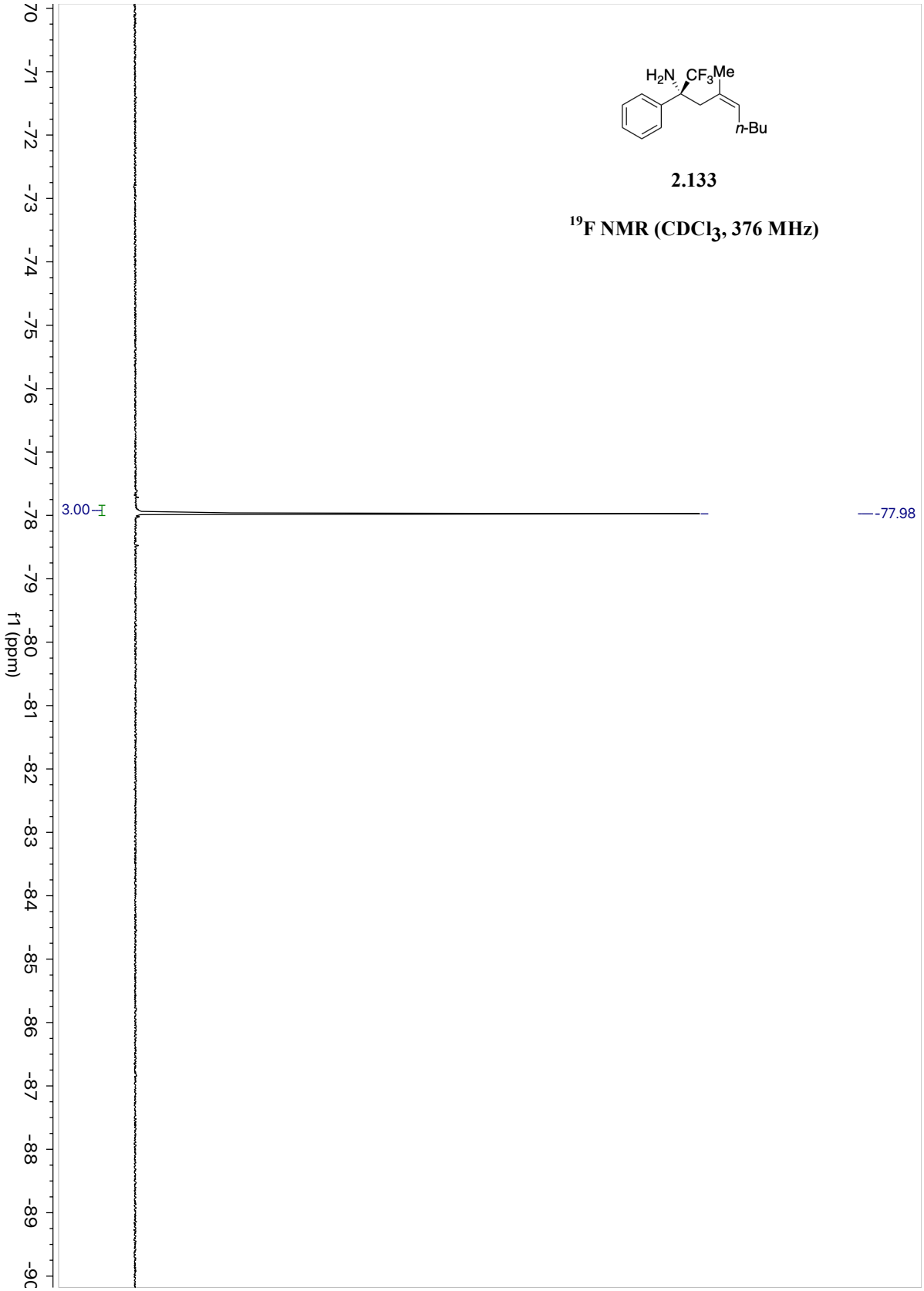

H2N CF3
n-Hept
2.132
19F NMR (CDCl3, 376 MHz)
3.00
-77.98
f1 (ppm)
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

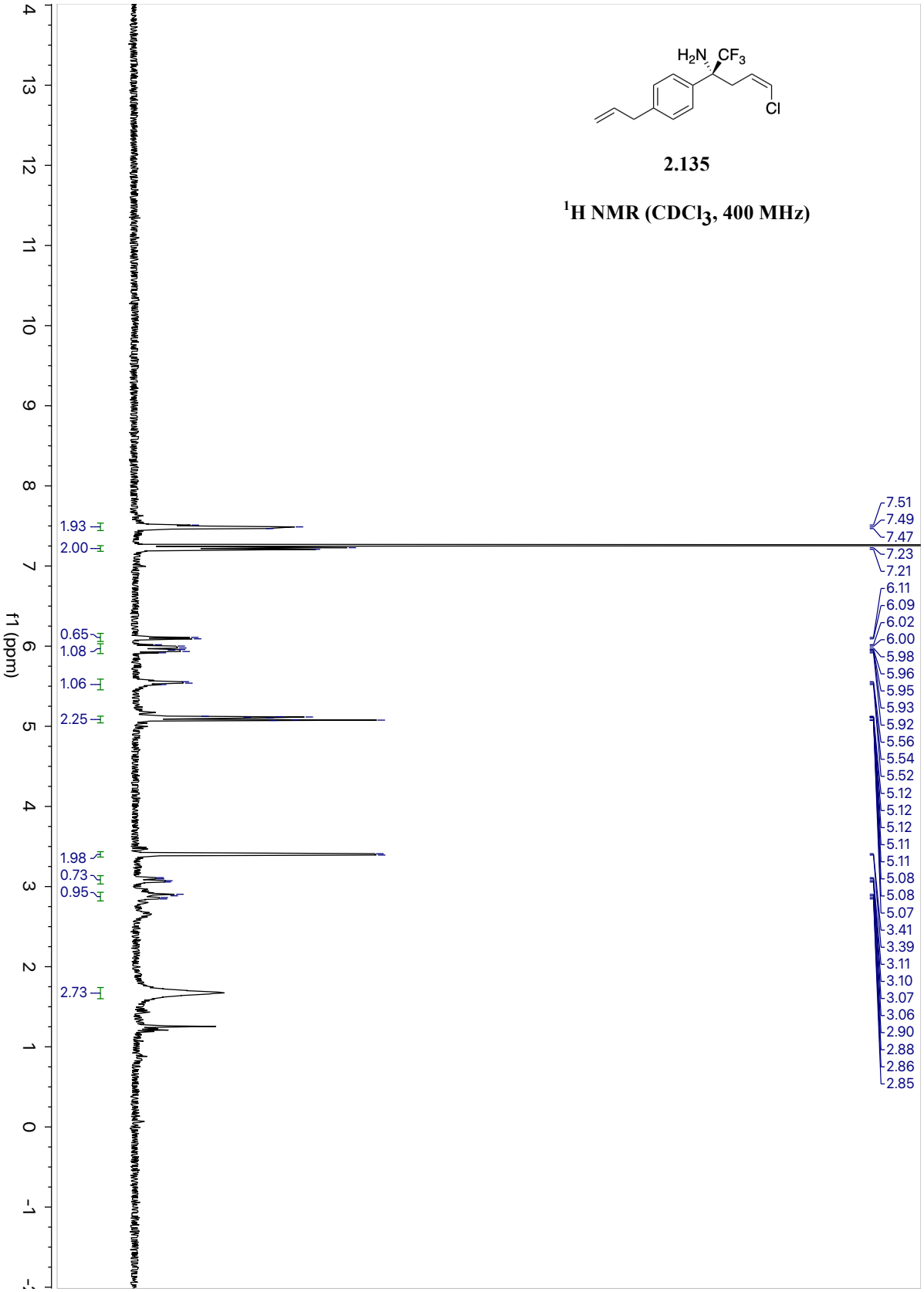

H2N
CF3Me
n-Bu
2.133
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
1.89
2.76
1.00
1.06
1.08
2.06
2.07
7.64
2.88
7.65
7.63
7.39
7.39
7.37
7.35
7.34
7.33
7.32
5.32
5.30
5.28
2.88
2.85
2.78
2.74
1.99
1.97
1.95
1.72
1.29
1.27
1.27
1.26
1.25
1.24
0.90
0.89
0.89
0.88
0.87

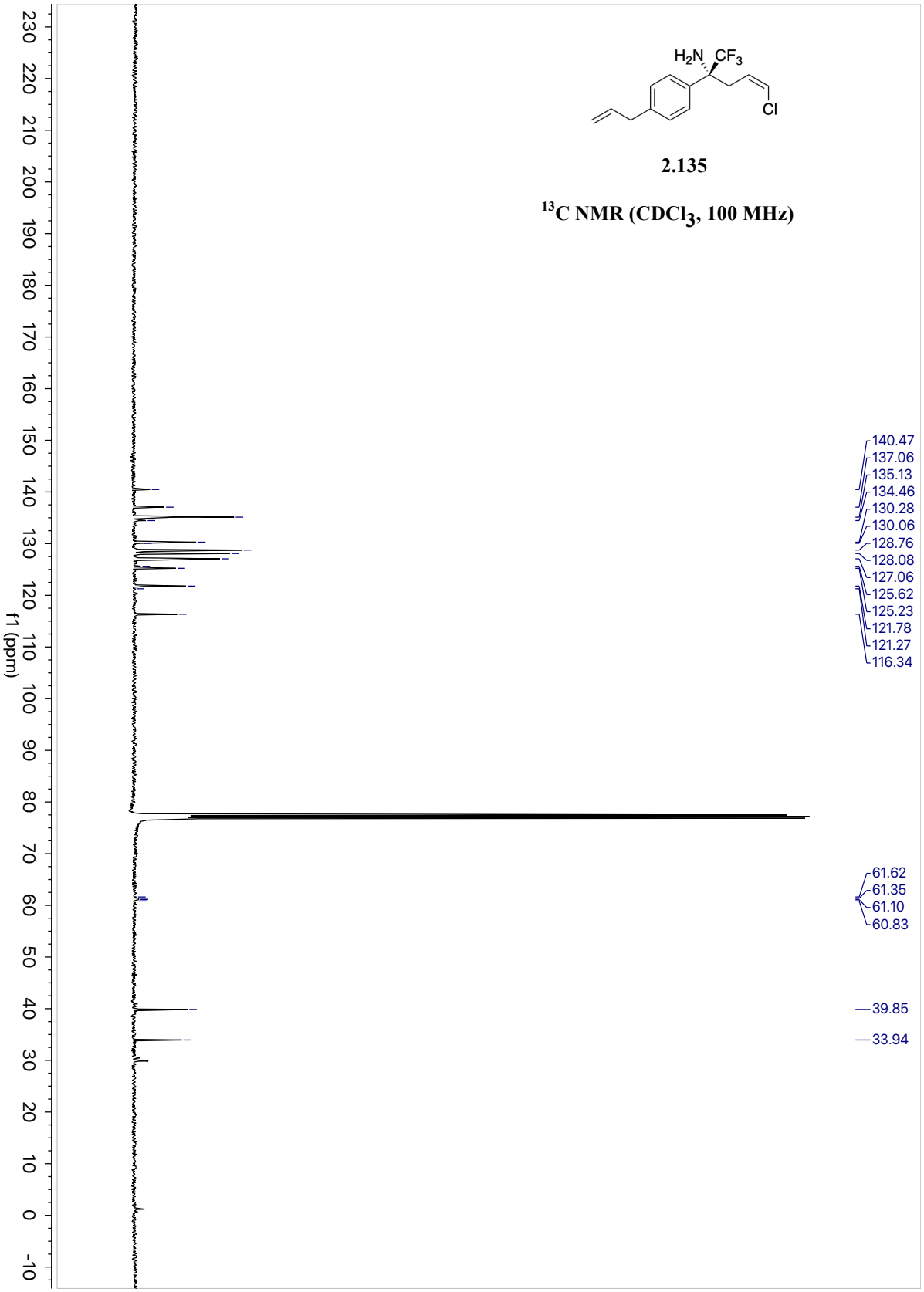


2.133

^{13}C NMR ($CDCl_3$, 100 MHz)

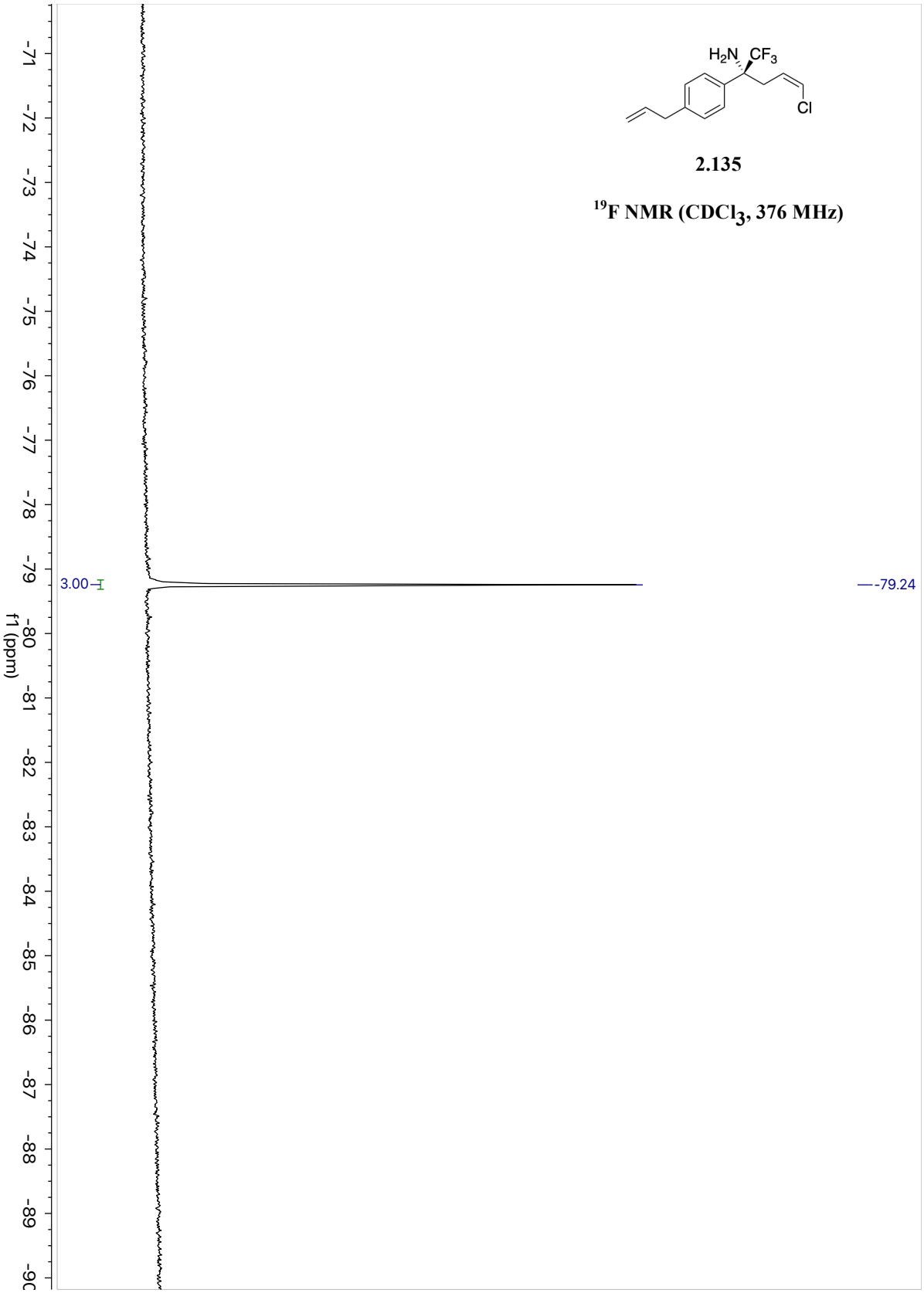

H2N
CF3Me
n-Bu
2.133
19F NMR (CDCl3, 376 MHz)
3.00
-77.98
f1 (ppm)
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

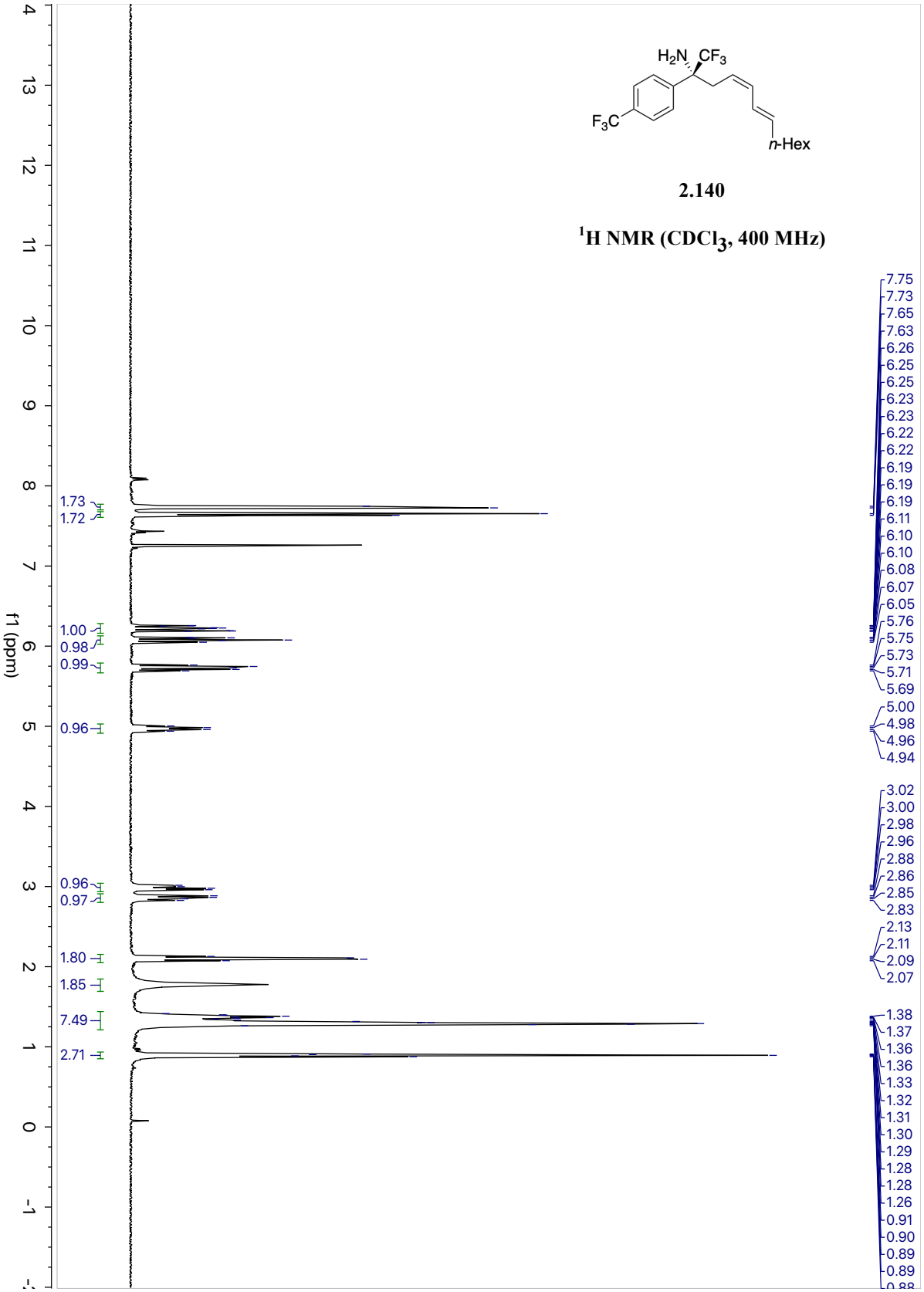

H2N
CF3
Cl
2.135
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.93
2.00
0.65
1.08
1.06
2.25
1.98
0.73
0.95
2.73
7.51
7.49
7.47
7.23
7.21
6.11
6.09
6.02
6.00
5.98
5.96
5.95
5.93
5.92
5.56
5.54
5.52
5.12
5.12
5.12
5.11
5.11
5.08
5.08
5.07
3.41
3.39
3.11
3.10
3.07
3.06
2.90
2.88
2.86
2.85

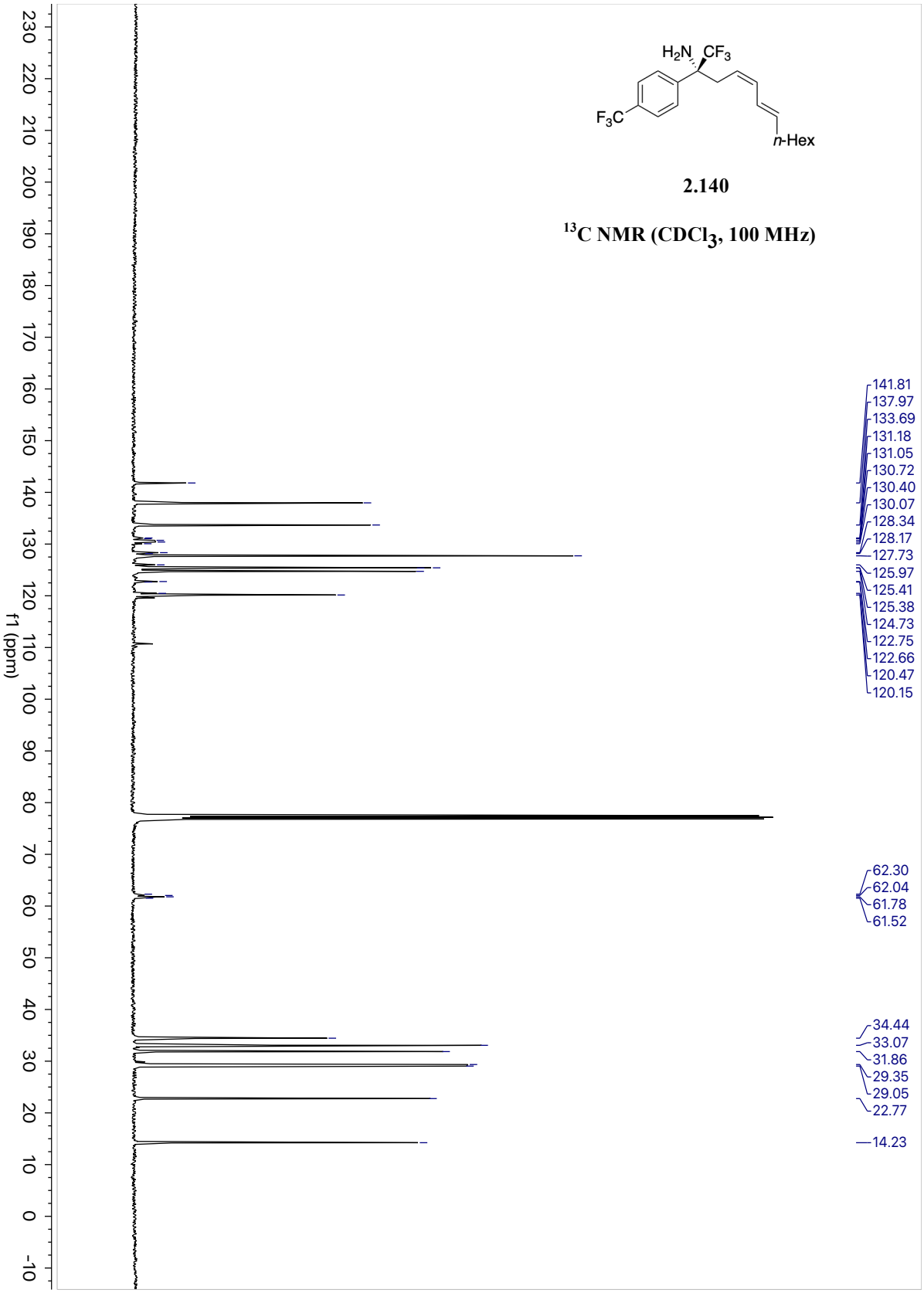


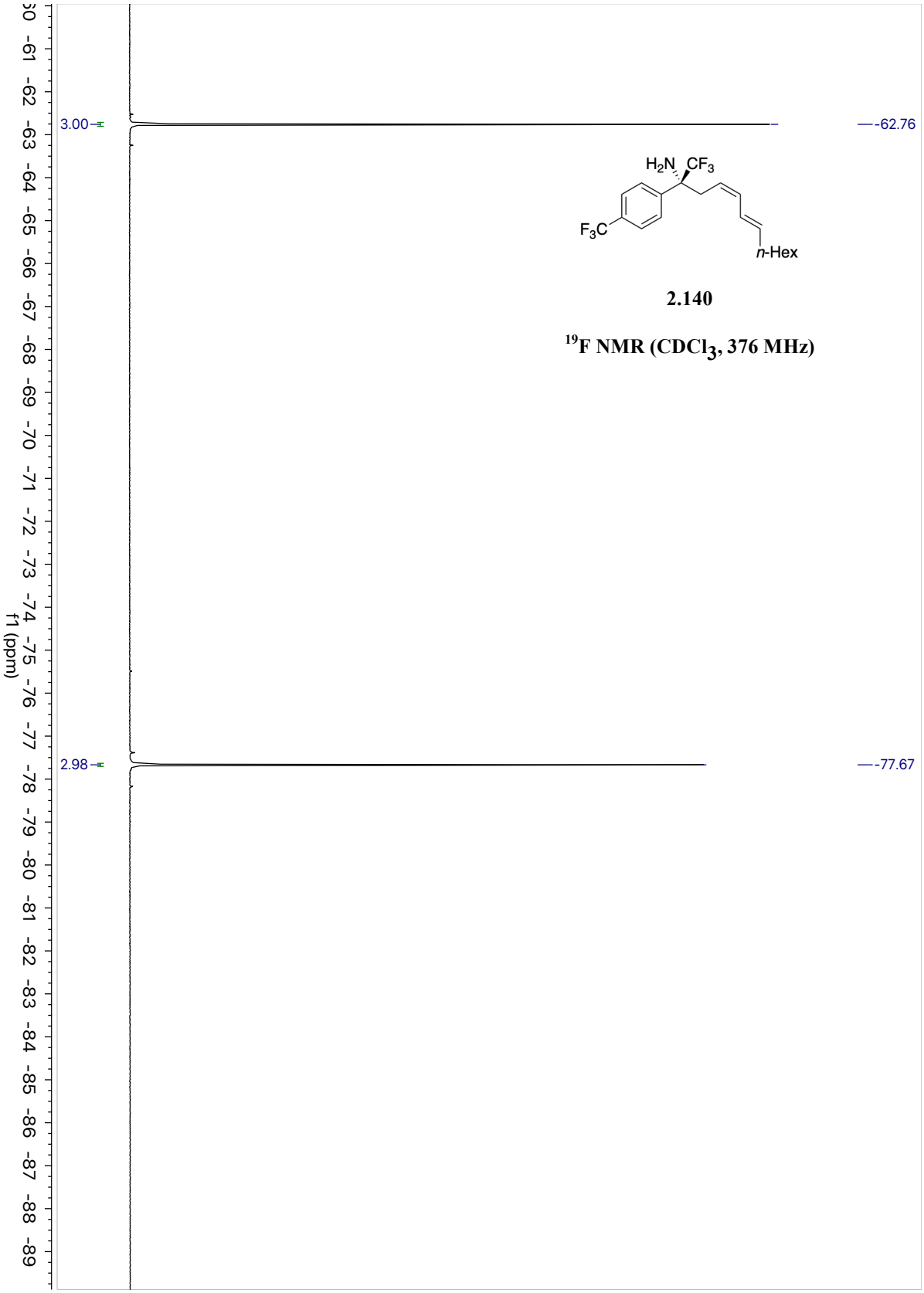
2.135

^{13}C NMR ($CDCl_3$, 100 MHz)


H2N
CF3
Cl
2.135
19F NMR (CDCl3, 376 MHz)
3.00
-79.24
f1 (ppm)
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

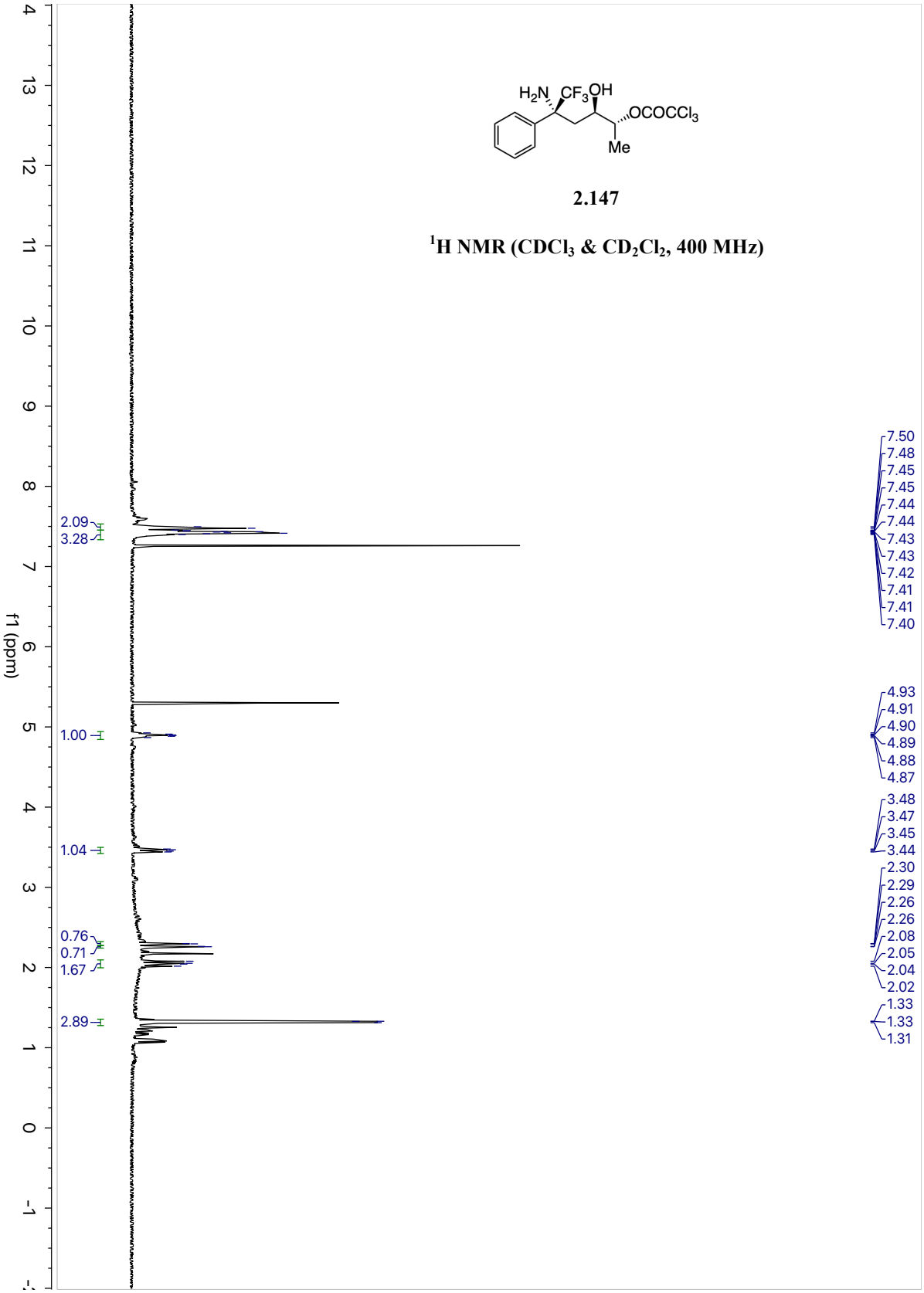

H2N CF3
F3C
n-Hex
2.140
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.73
1.72
1.00
0.98
0.99
0.96
0.96
0.97
1.80
1.85
7.49
2.71
7.75
7.73
7.65
7.63
6.26
6.25
6.25
6.23
6.23
6.22
6.22
6.19
6.19
6.19
6.11
6.10
6.10
6.08
6.07
6.05
5.76
5.75
5.73
5.71
5.69
5.00
4.98
4.96
4.94
3.02
3.00
2.98
2.96
2.88
2.86
2.85
2.83
2.13
2.11
2.09
2.07
1.38
1.37
1.36
1.36
1.33
1.32
1.31
1.30
1.29
1.28
1.28
1.26
0.91
0.90
0.89
0.89


H2N CF3
F3C
n-Hex
2.140
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
141.81
137.97
133.69
131.18
131.05
130.72
130.40
130.07
128.34
128.17
127.73
125.97
125.41
125.38
124.73
122.75
122.66
120.47
120.15
62.30
62.04
61.78
61.52
34.44
33.07
31.86
29.35
29.05
22.77
14.23



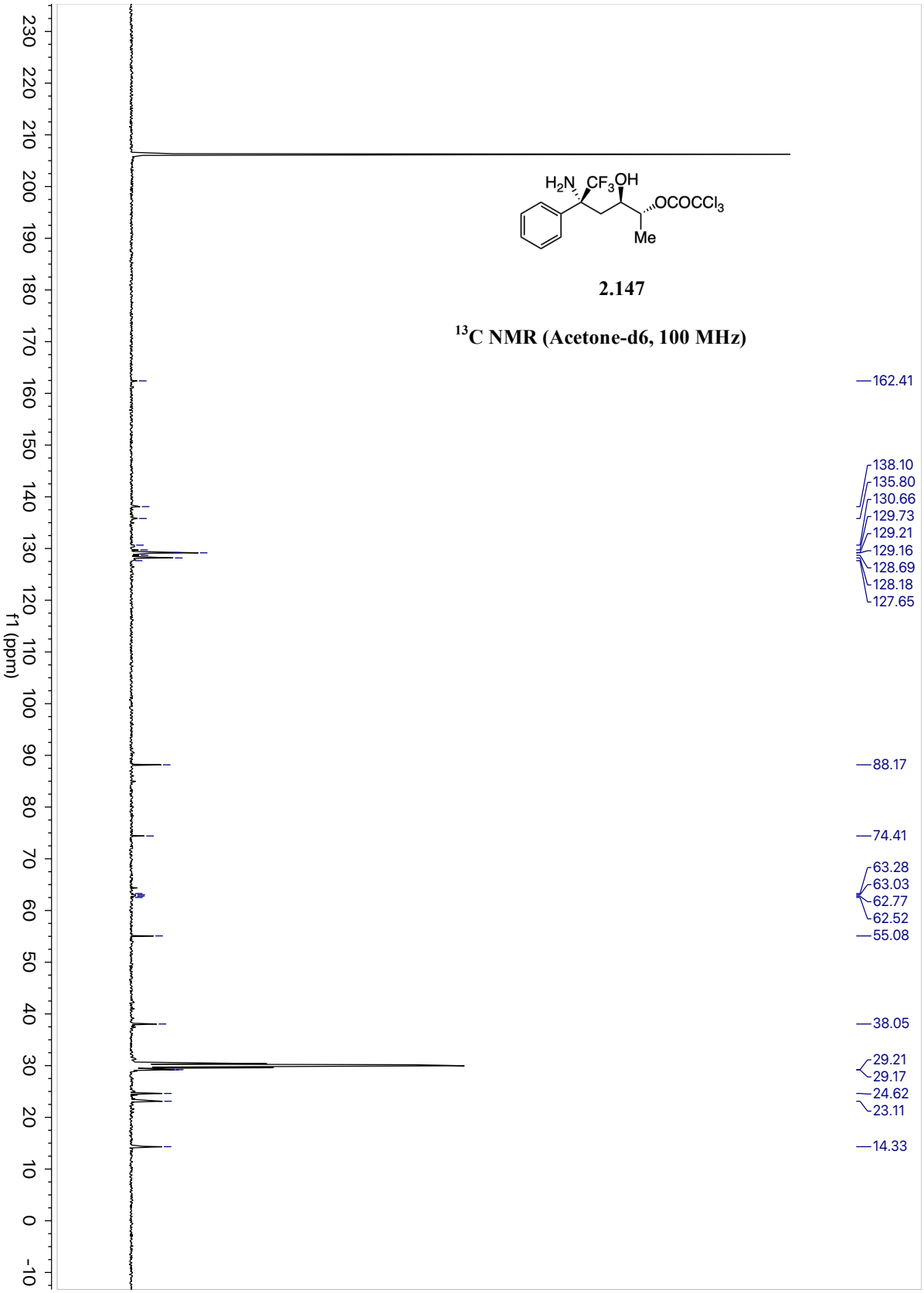
2.140

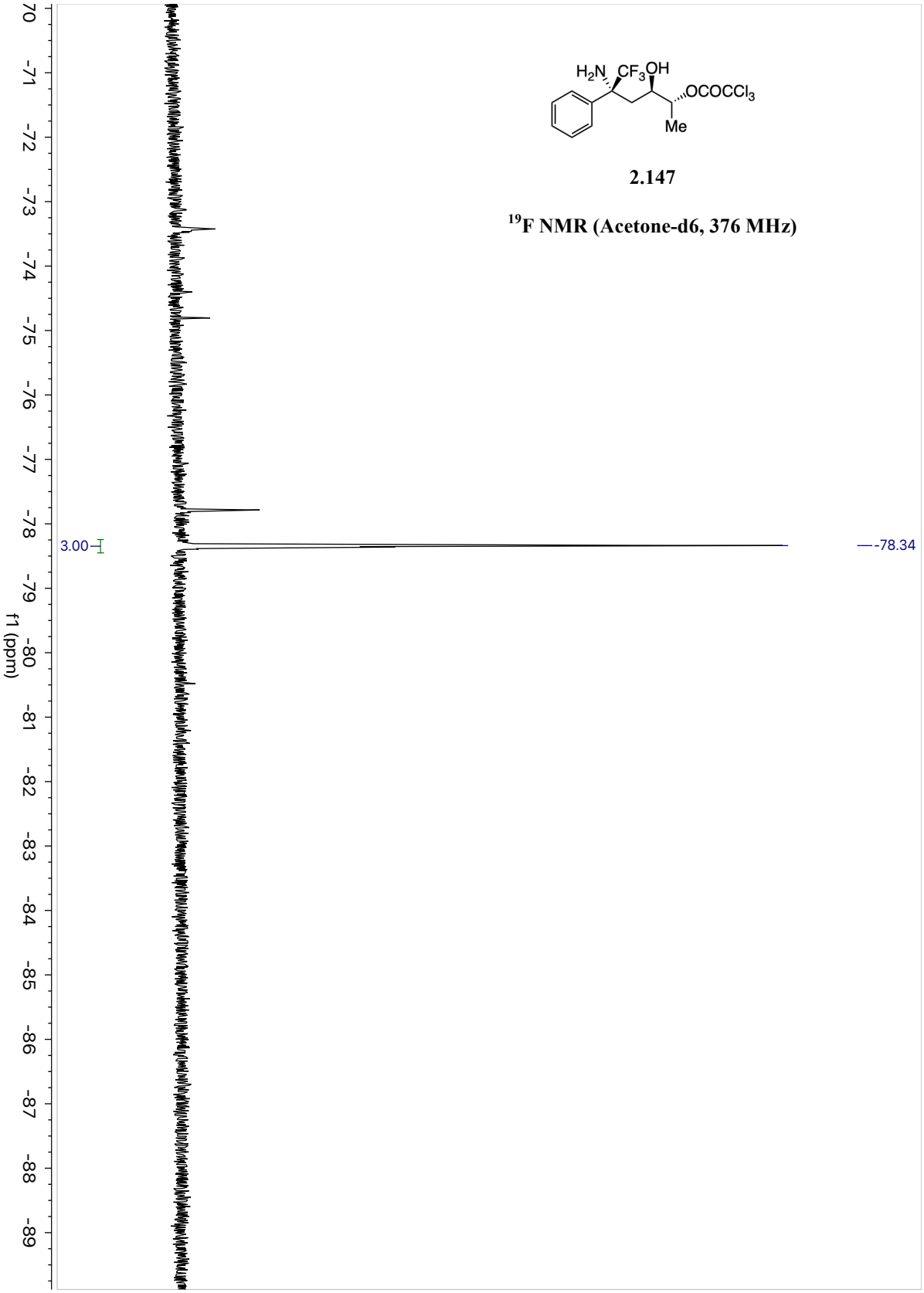
^{19}F NMR ($CDCl_3$, 376 MHz)



2.147

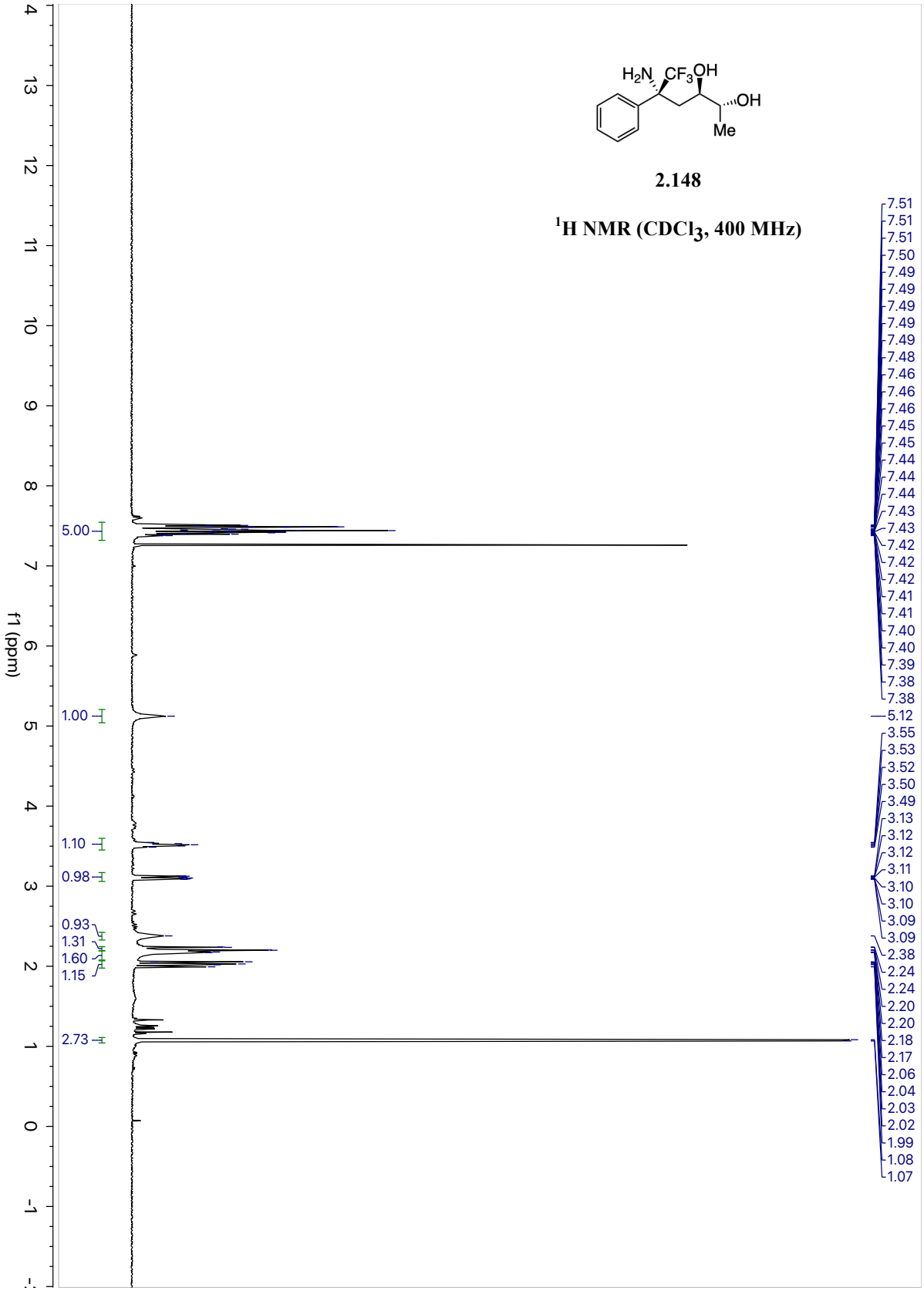
^{1}H NMR ($CDCl_3$ & CD_2Cl_2, 400 MHz)

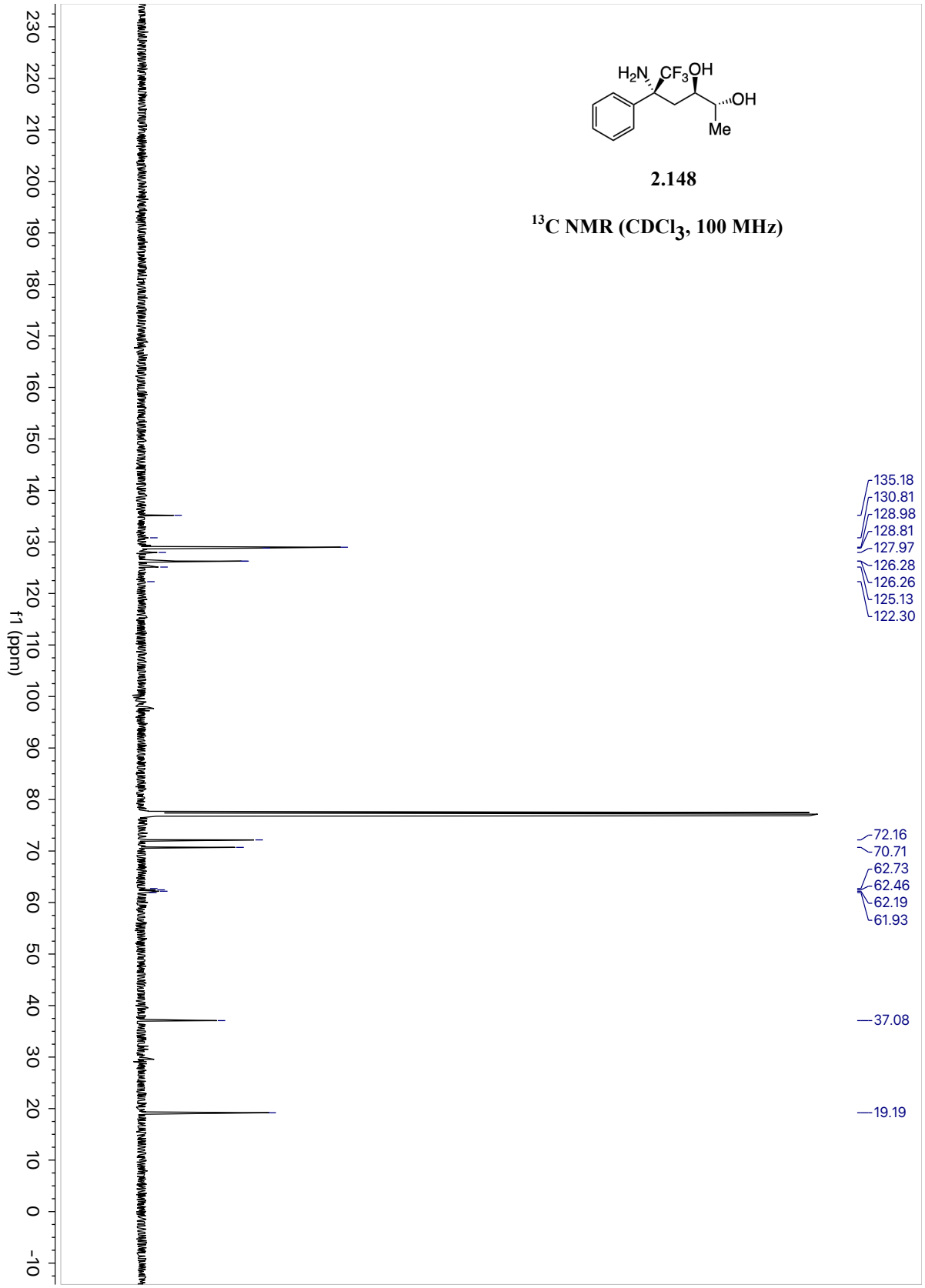

H2N
CF3
OH
OCOCCl3
Me
2.147
13C NMR (Acetone-d6, 100 MHz)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
162.41
138.10
135.80
130.66
129.73
129.21
129.16
128.69
128.18
127.65
88.17
74.41
63.28
63.03
62.77
62.52
55.08
38.05
29.21
29.17
24.62
23.11
14.33



2.147

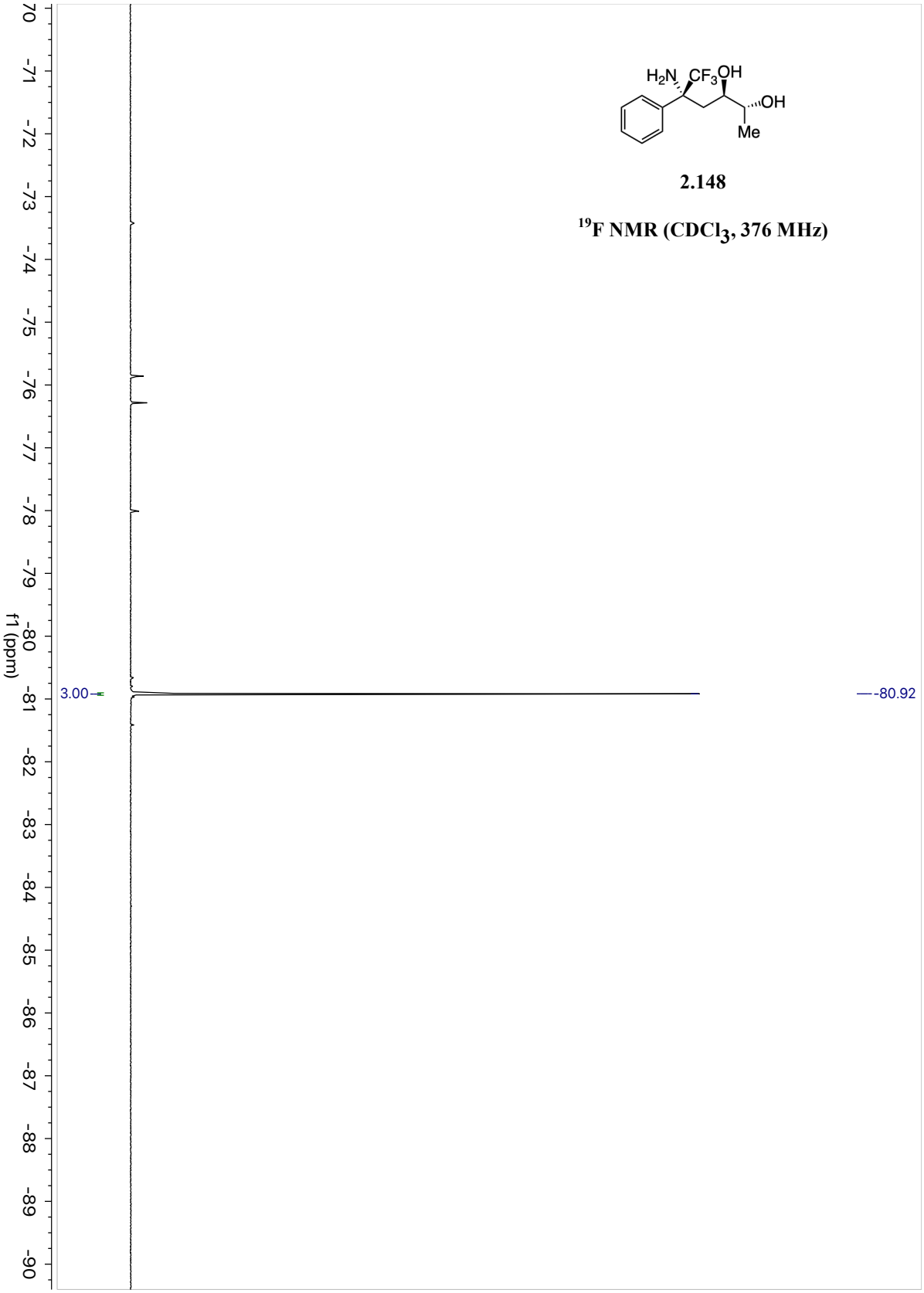
^{19}F NMR (Acetone-d6, 376 MHz)

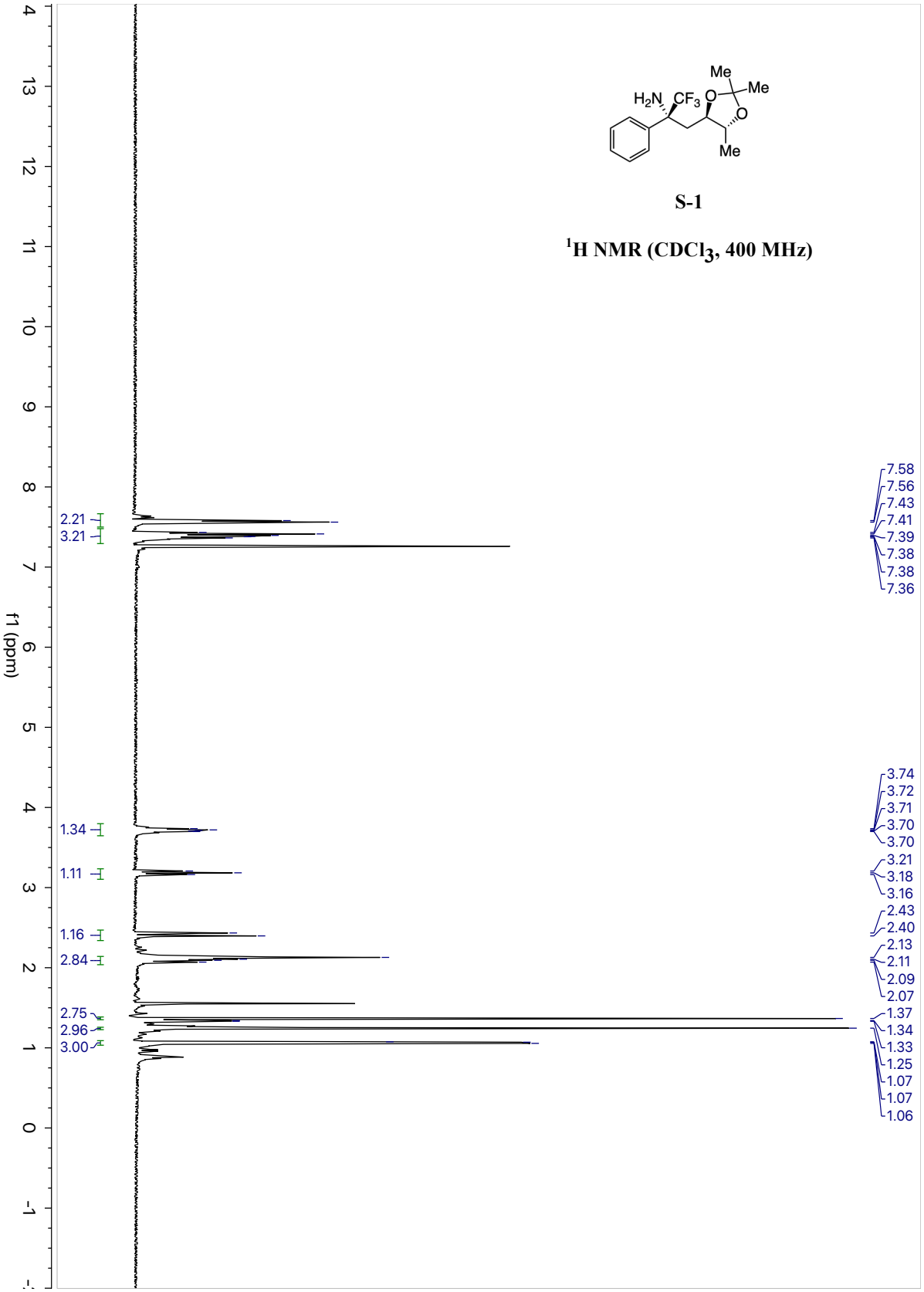

H2N
CF3
OH
OH
Me
2.148
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
5.00
1.00
1.10
0.98
0.93
1.31
1.60
1.15
2.73
7.51
7.51
7.51
7.50
7.49
7.49
7.49
7.49
7.49
7.48
7.46
7.46
7.46
7.45
7.45
7.44
7.44
7.44
7.43
7.43
7.42
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.38
7.38
5.12
3.55
3.53
3.52
3.50
3.49
3.13
3.12
3.12
3.11
3.10
3.10
3.09
3.09
2.38
2.24
2.24
2.20
2.20
2.18
2.17
2.06
2.04
2.03
2.02
1.99
1.08
1.07

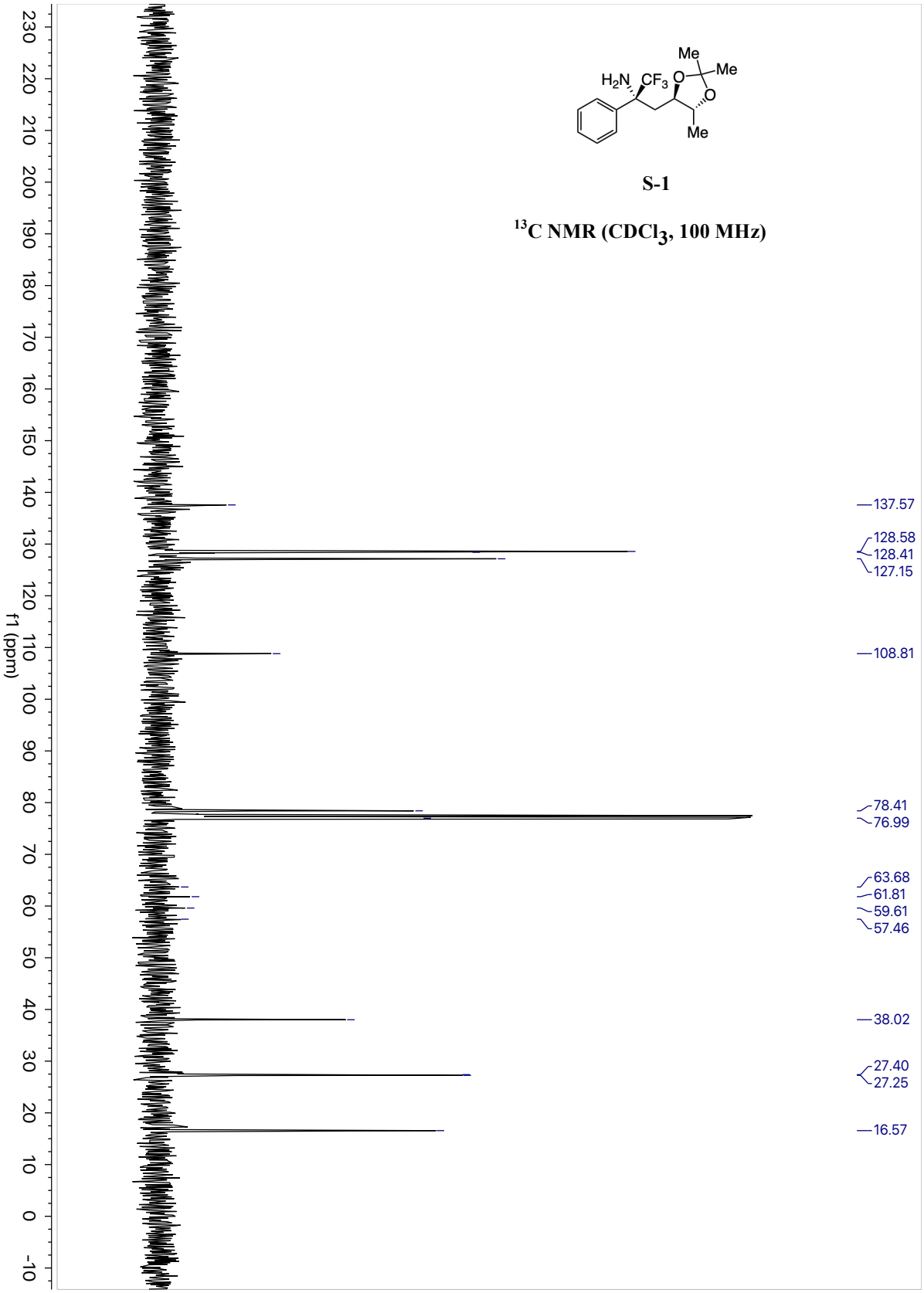


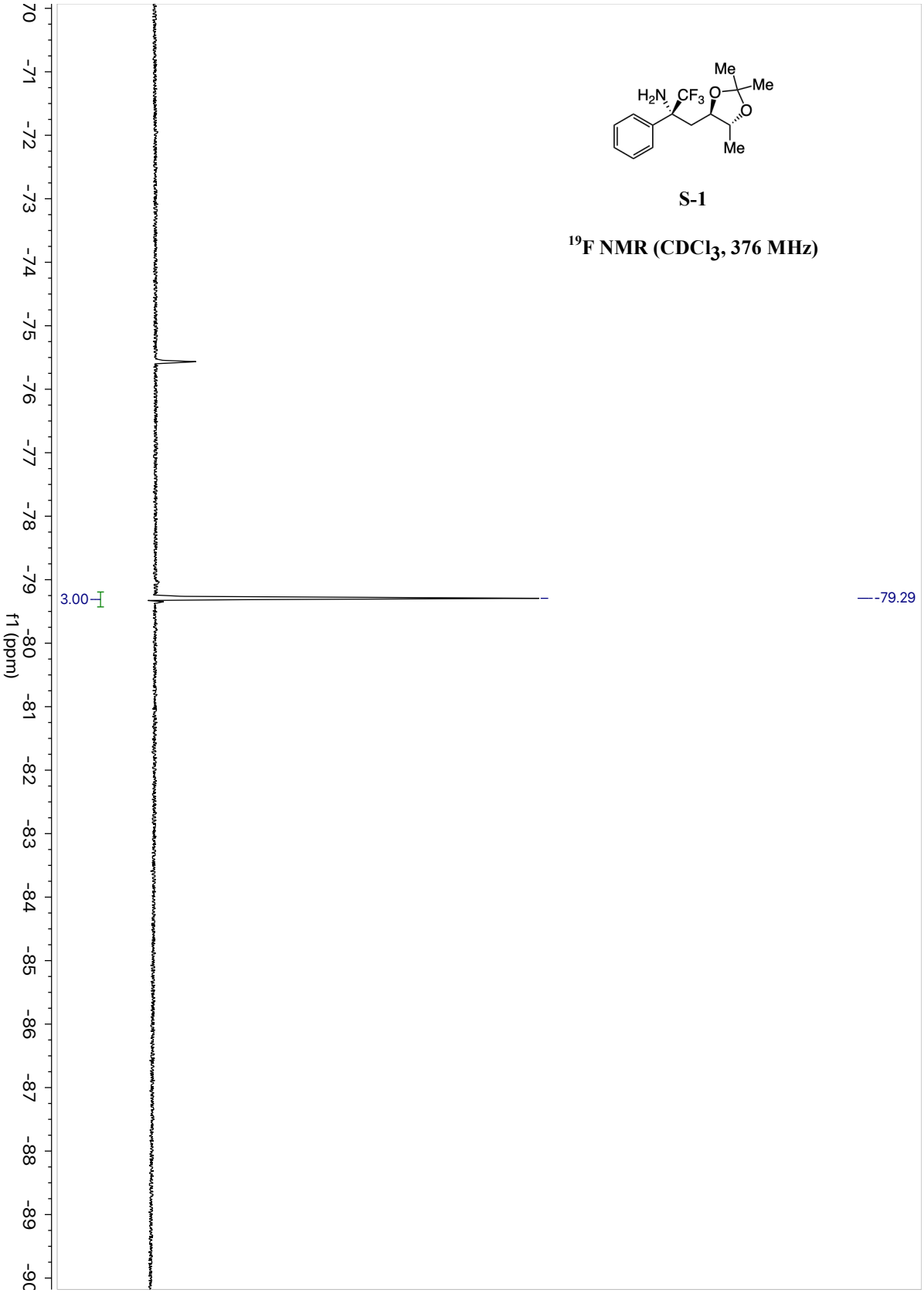
2.148

^{13}C NMR ($CDCl_3$, 100 MHz)


H2N
CF3
OH
OH
Me
2.148
19F NMR (CDCl3, 376 MHz)
f1 (ppm)
70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90
3.00
-80.92

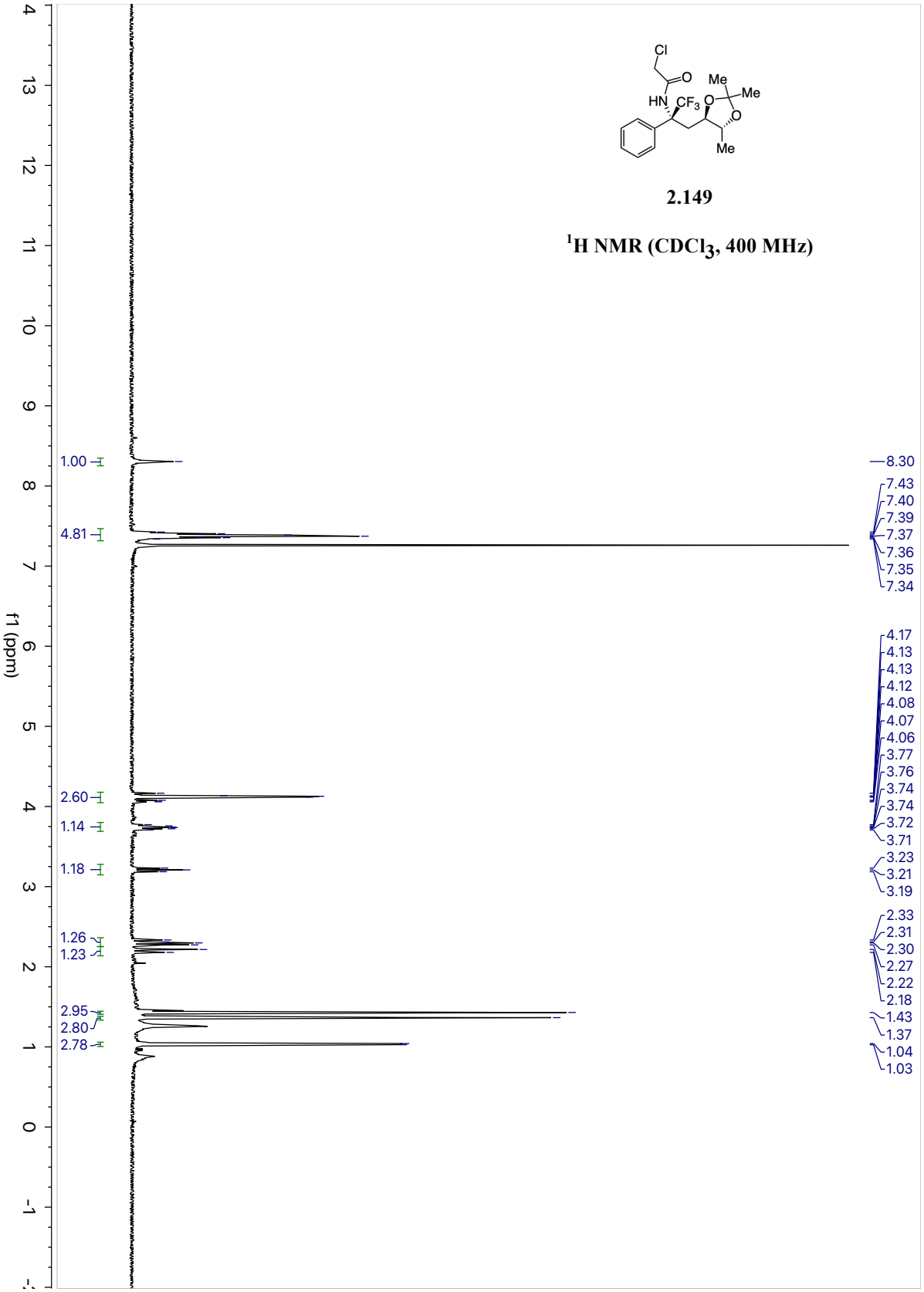

Me
Me
H2N
CF3
O
O
Me
S-1
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
7.58
7.56
7.43
7.41
7.39
7.38
7.38
7.36
3.74
3.72
3.71
3.70
3.70
3.21
3.18
3.16
2.43
2.40
2.13
2.11
2.09
2.07
1.37
1.34
1.33
1.25
1.07
1.07
1.06
2.21
3.21
1.34
1.11
1.16
2.84
2.75
2.96
3.00


Me
Me
H2N
CF3
O
O
Me
S-1
13C NMR (CDCl3, 100 MHz)
137.57
128.58
128.41
127.15
108.81
78.41
76.99
63.68
61.81
59.61
57.46
38.02
27.40
27.25
16.57
f1 (ppm)



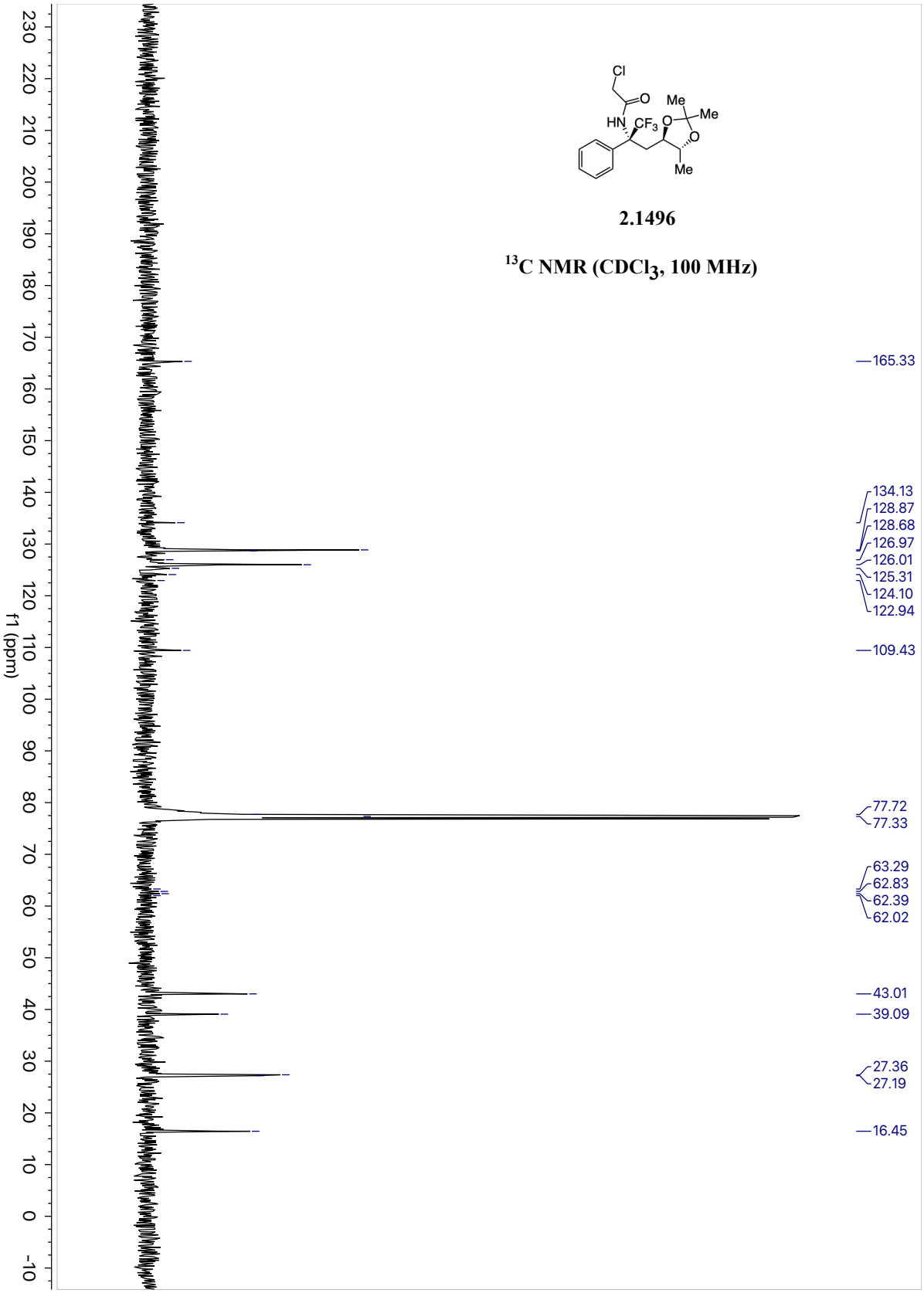
S-1

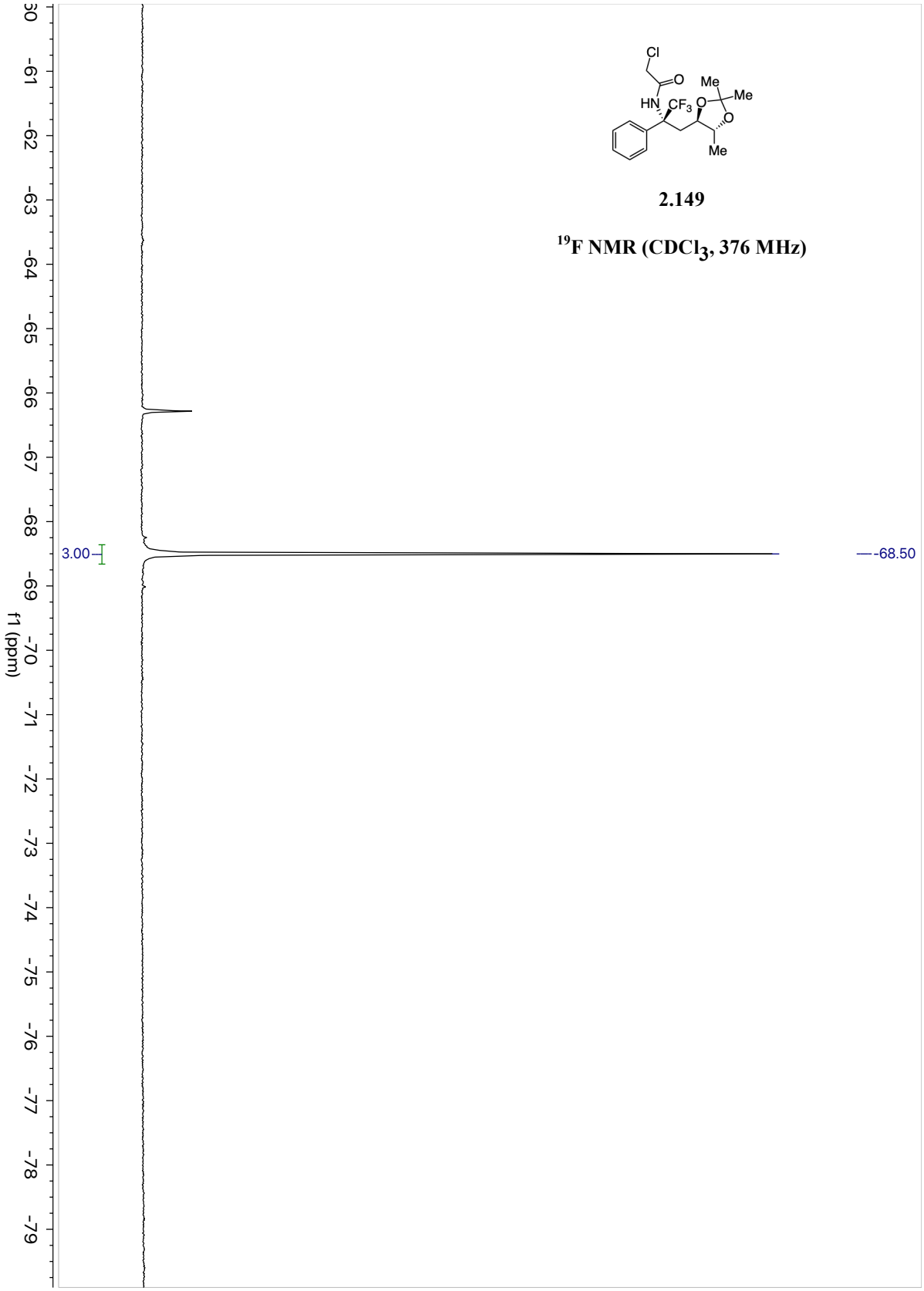
^{19}F NMR ($CDCl_3$, 376 MHz)



2.149

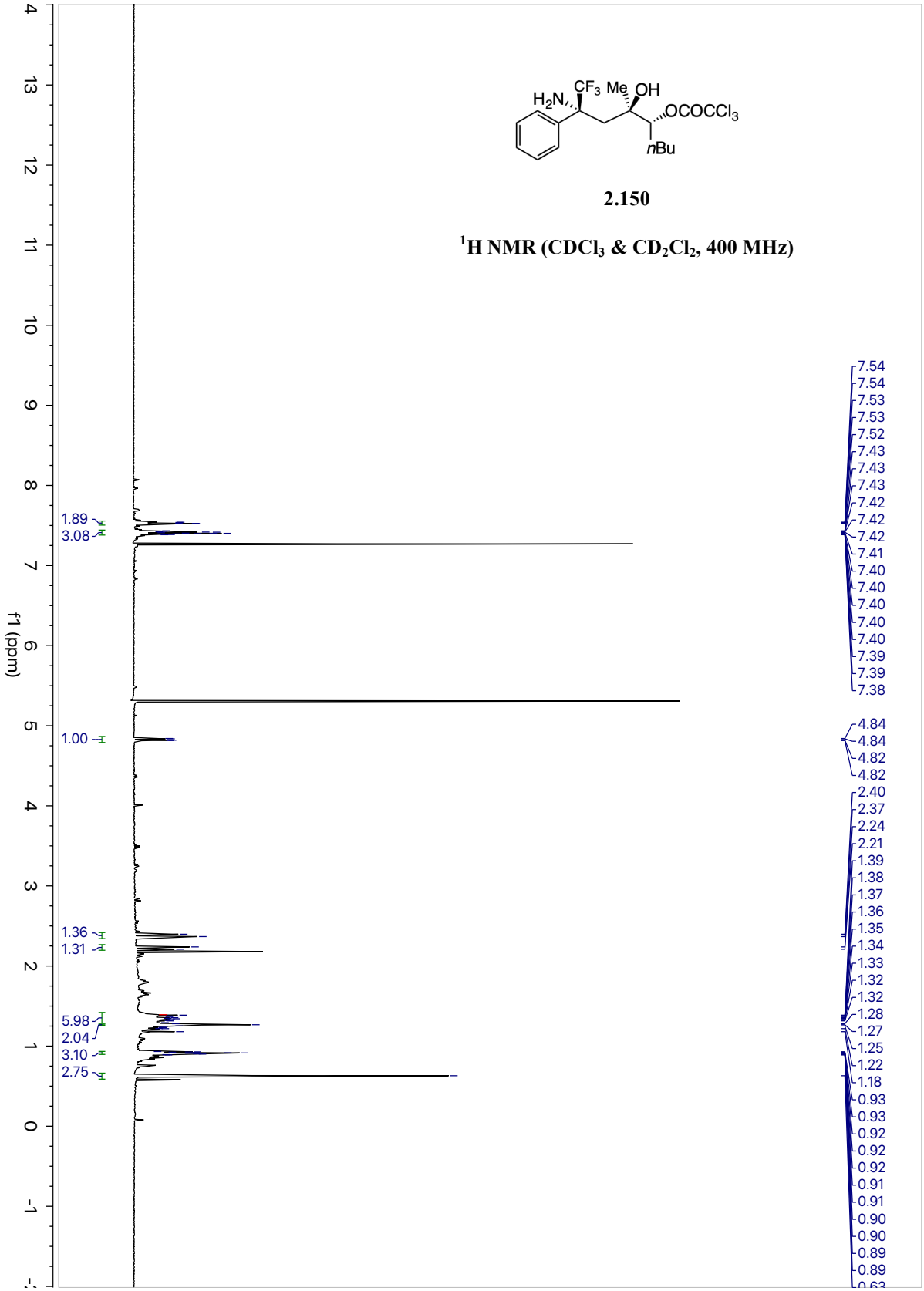
^{1}H NMR ($CDCl_3$, 400 MHz)


Cl
O
Me
HN
CF3
O
Me
O
Me
2.1496
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
165.33
134.13
128.87
128.68
126.97
126.01
125.31
124.10
122.94
109.43
77.72
77.33
63.29
62.83
62.39
62.02
43.01
39.09
27.36
27.19
16.45



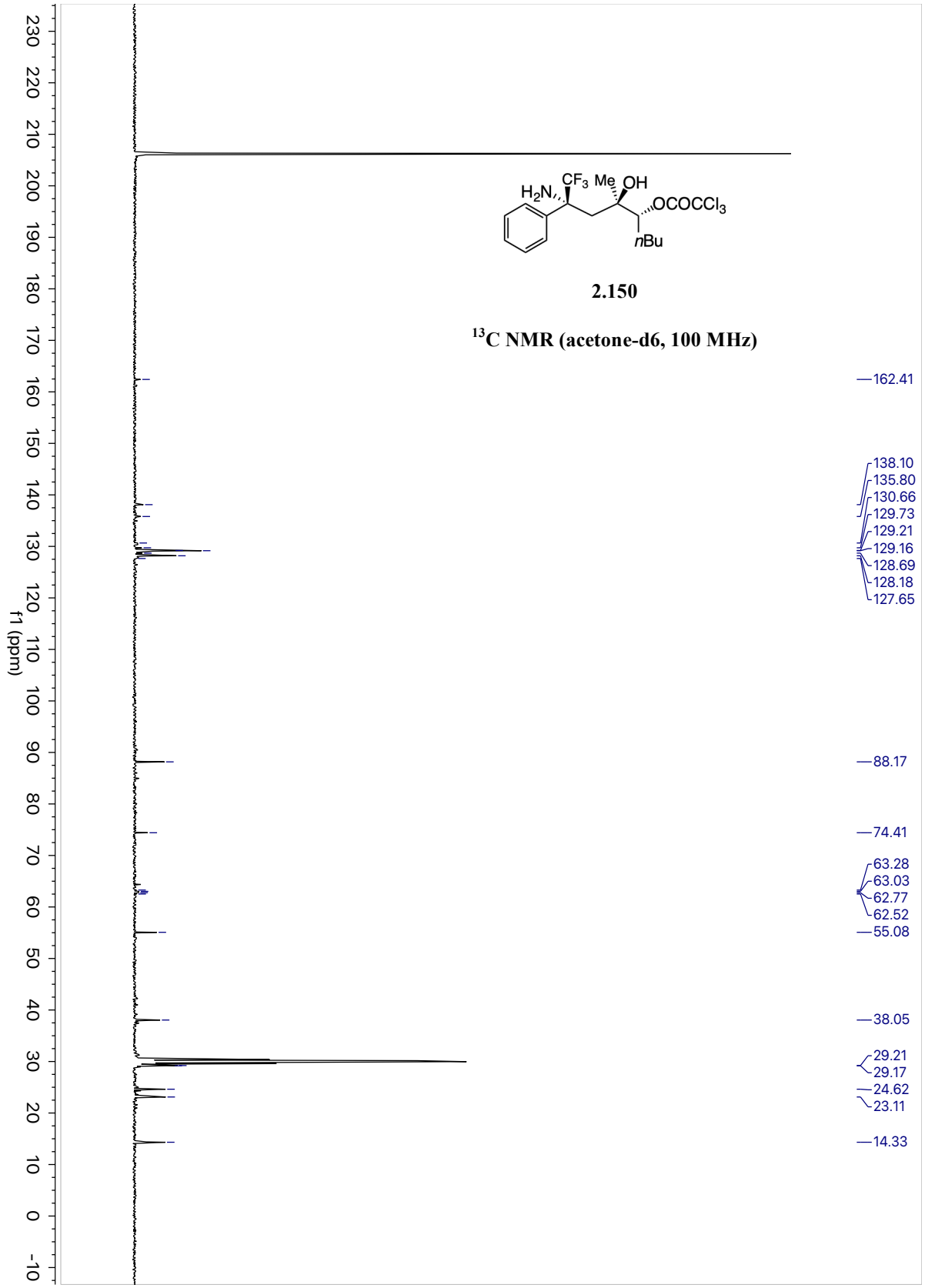
2.149

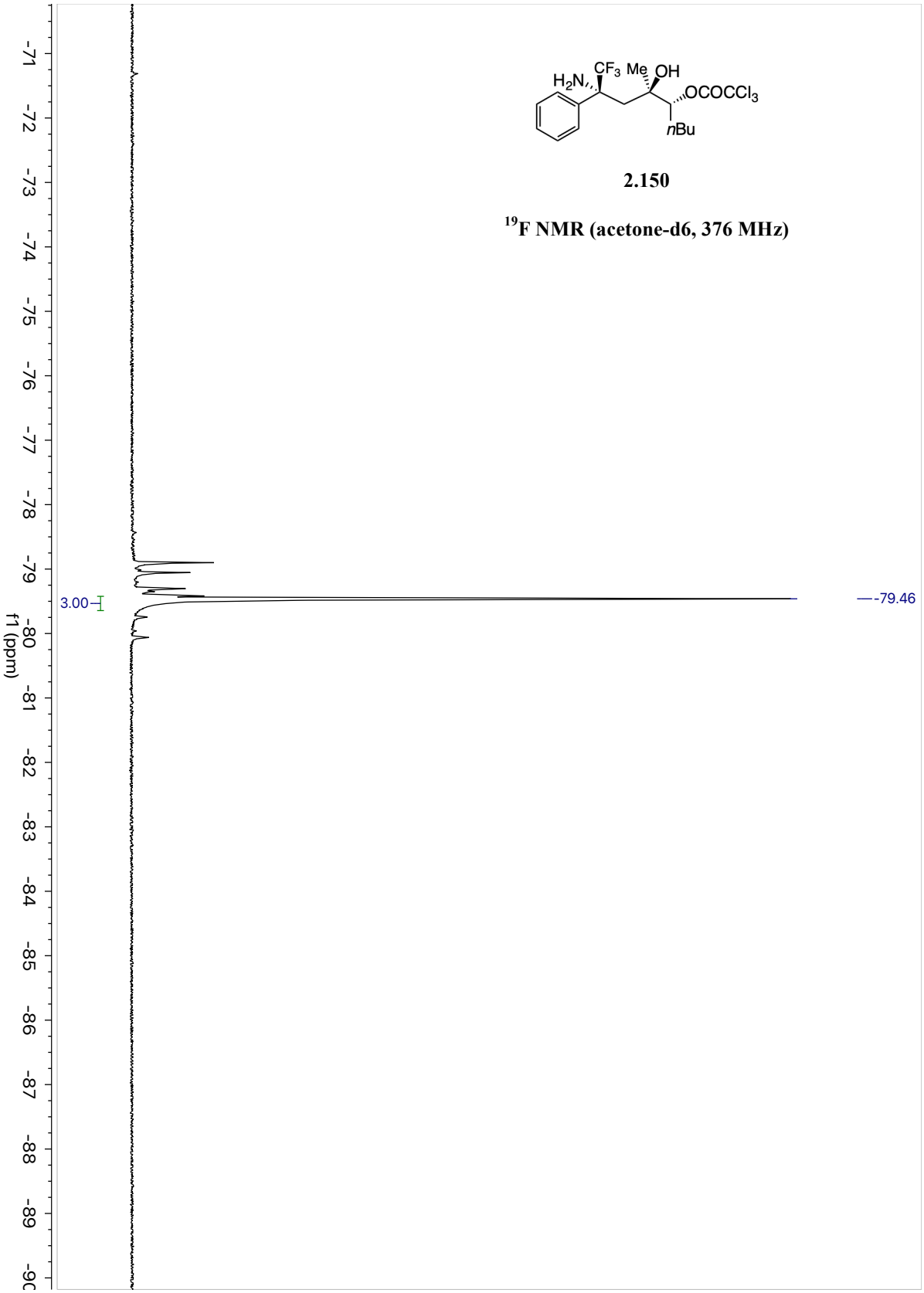
^{19}F NMR ($CDCl_3$, 376 MHz)

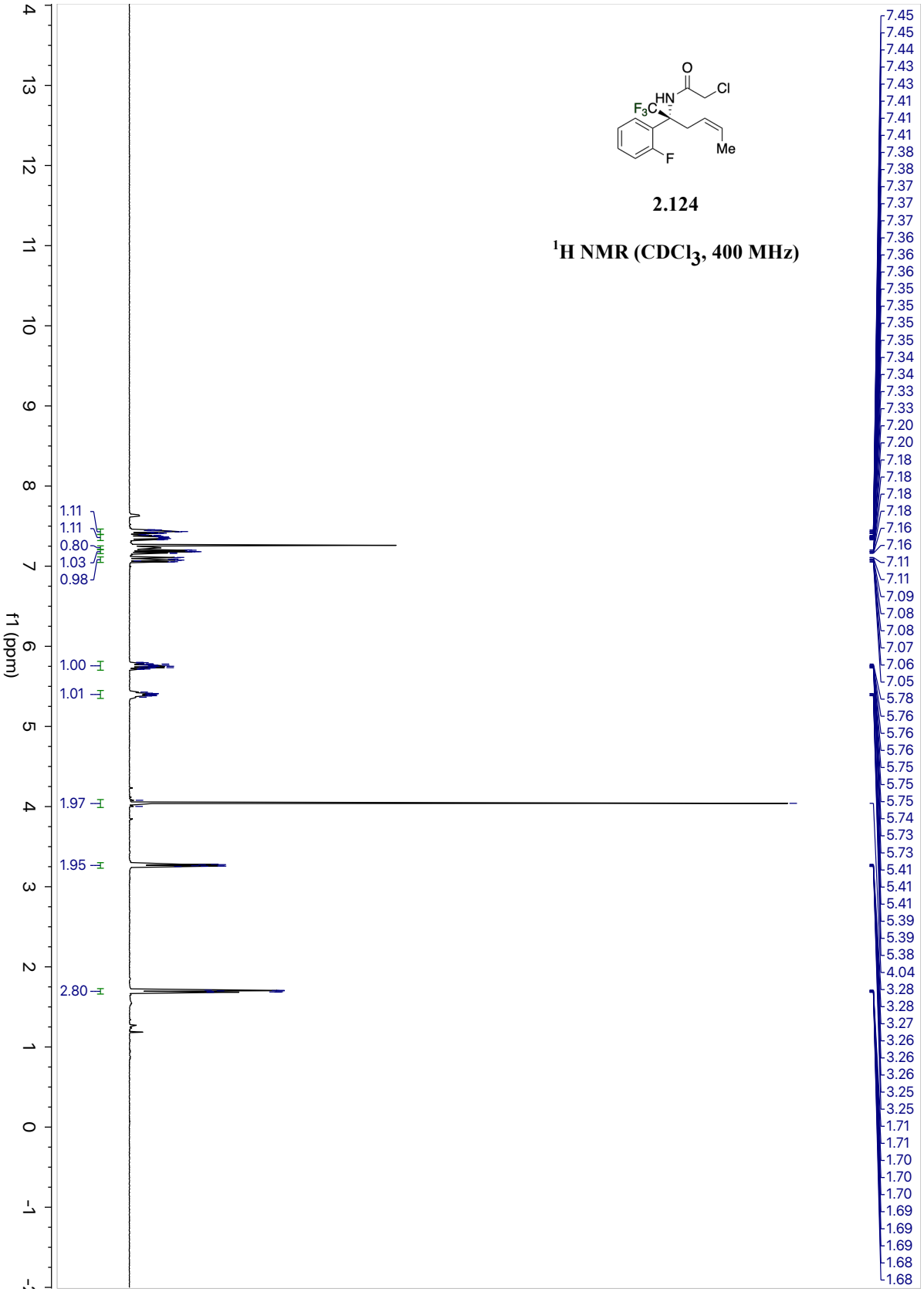


2.150

^{1}H NMR ($CDCl_3$ & CD_2Cl_2, 400 MHz)

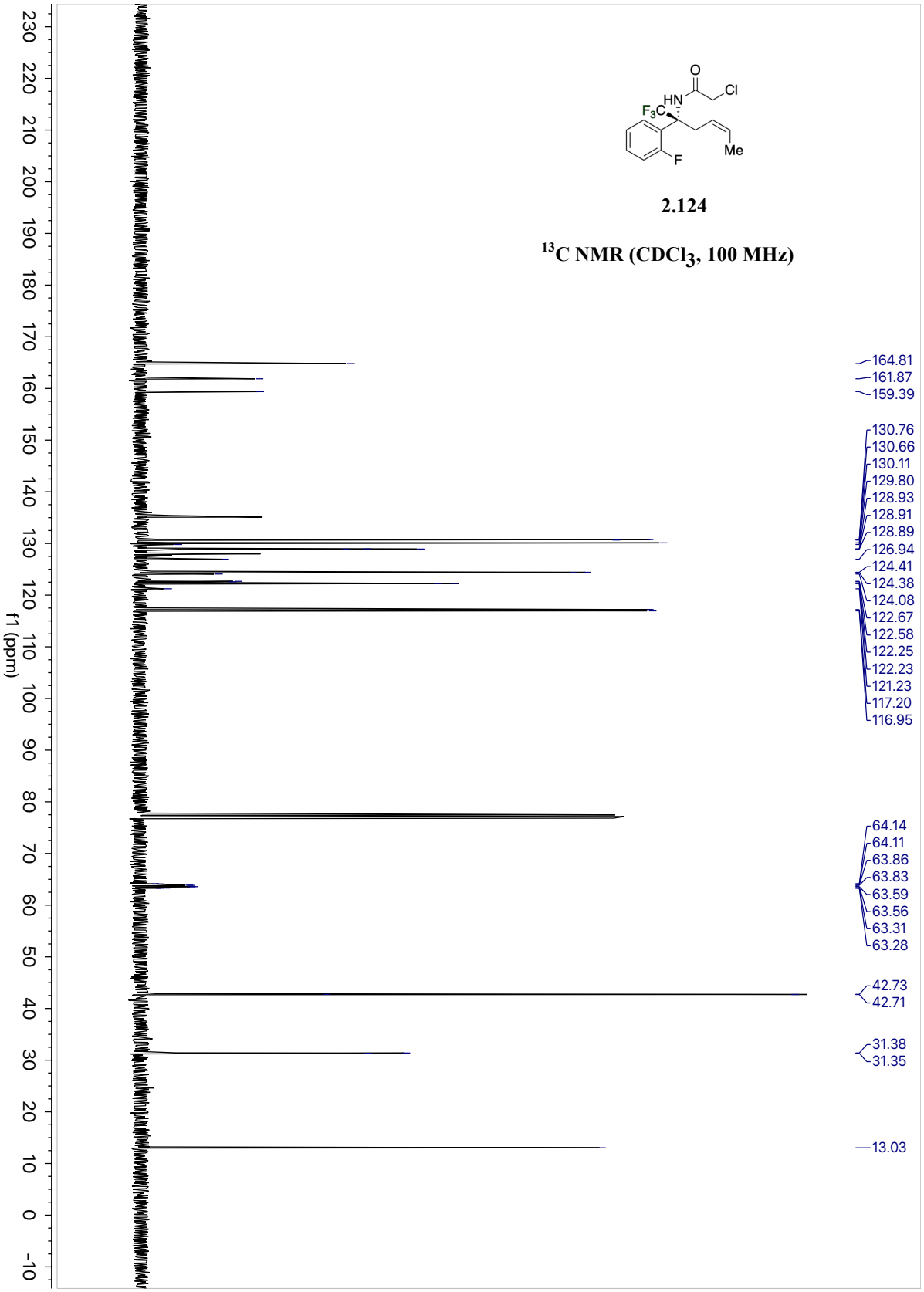

CF3 Me OH
H2N
OCOCCl3
nBu
2.150
13C NMR (acetone-d6, 100 MHz)
162.41
138.10
135.80
130.66
129.73
129.21
129.16
128.69
128.18
127.65
88.17
74.41
63.28
63.03
62.77
62.52
55.08
38.05
29.21
29.17
24.62
23.11
14.33
f1 (ppm)

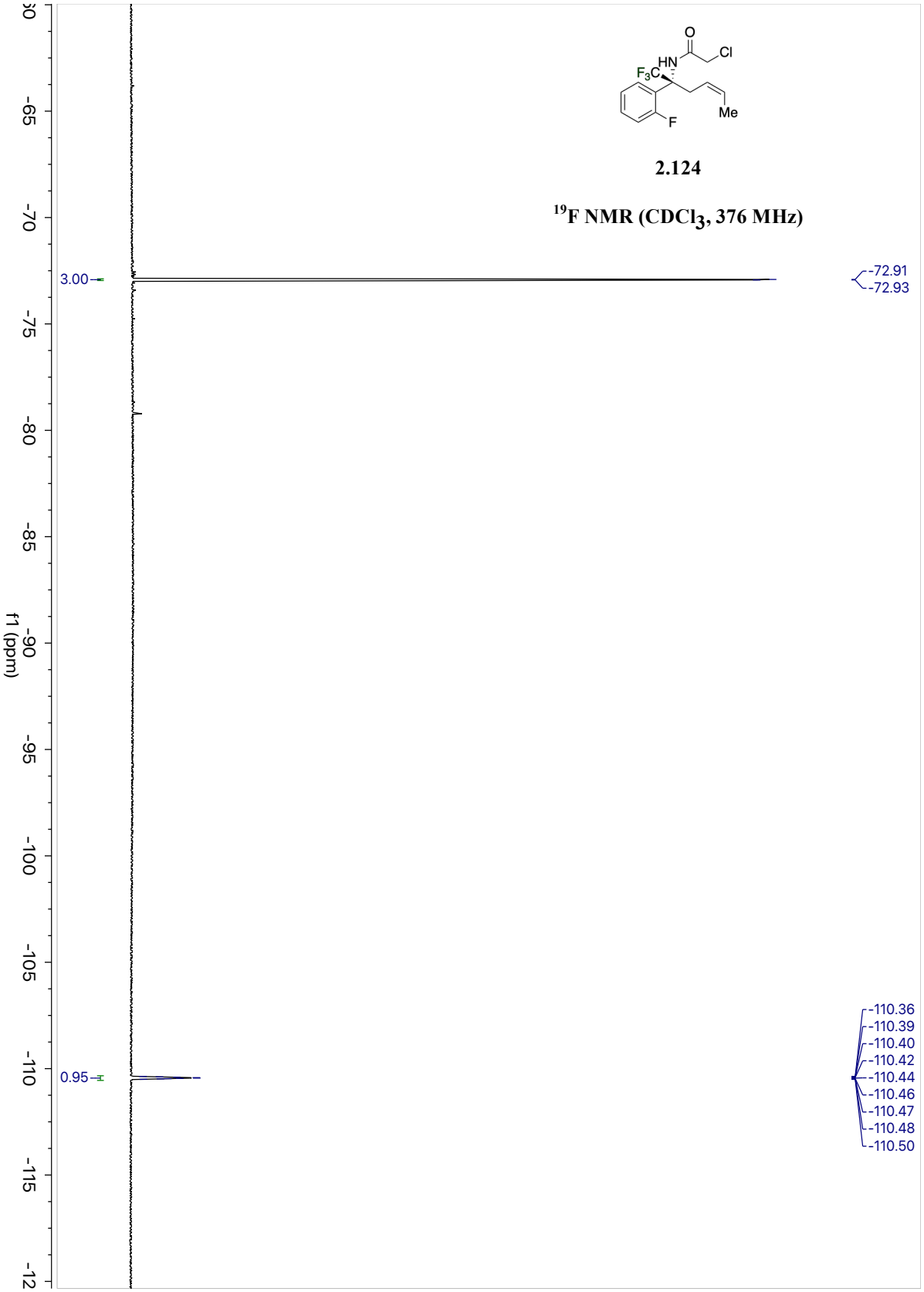

CF3 Me OH
H2N
OCOCCl3
nBu
2.150
19F NMR (acetone-d6, 376 MHz)
3.00
-79.46
f1 (ppm)
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
-89
-90

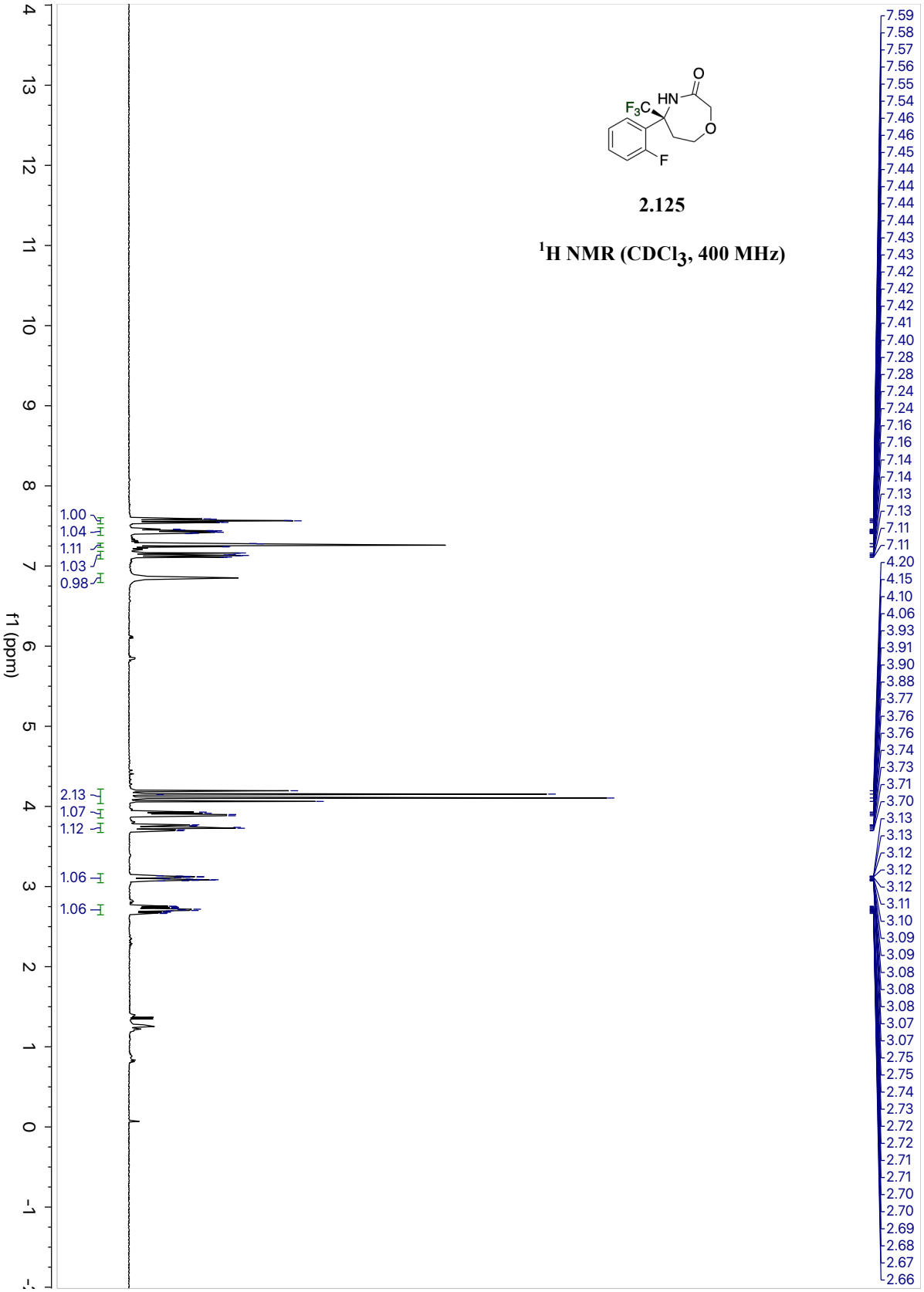


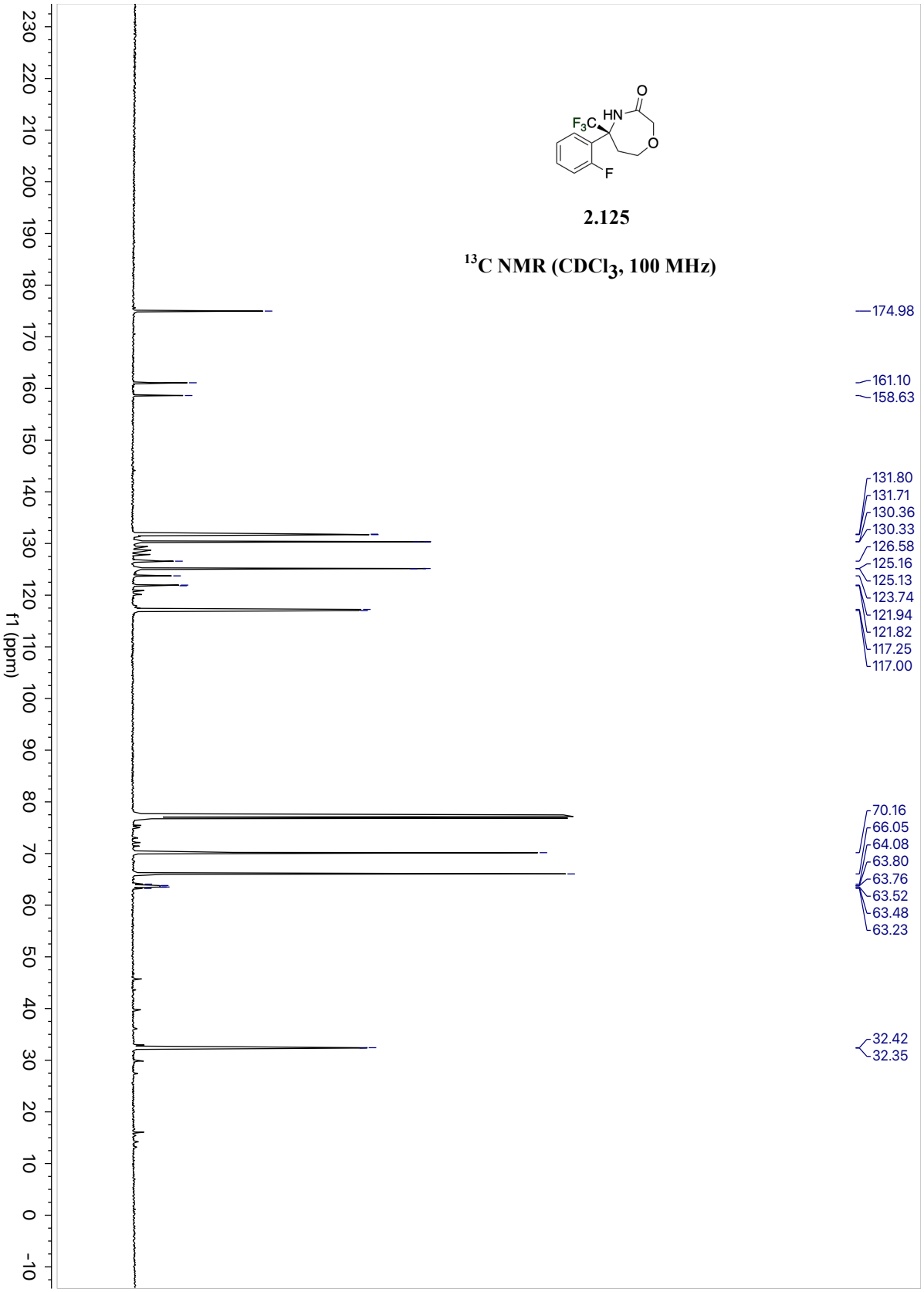
2.124

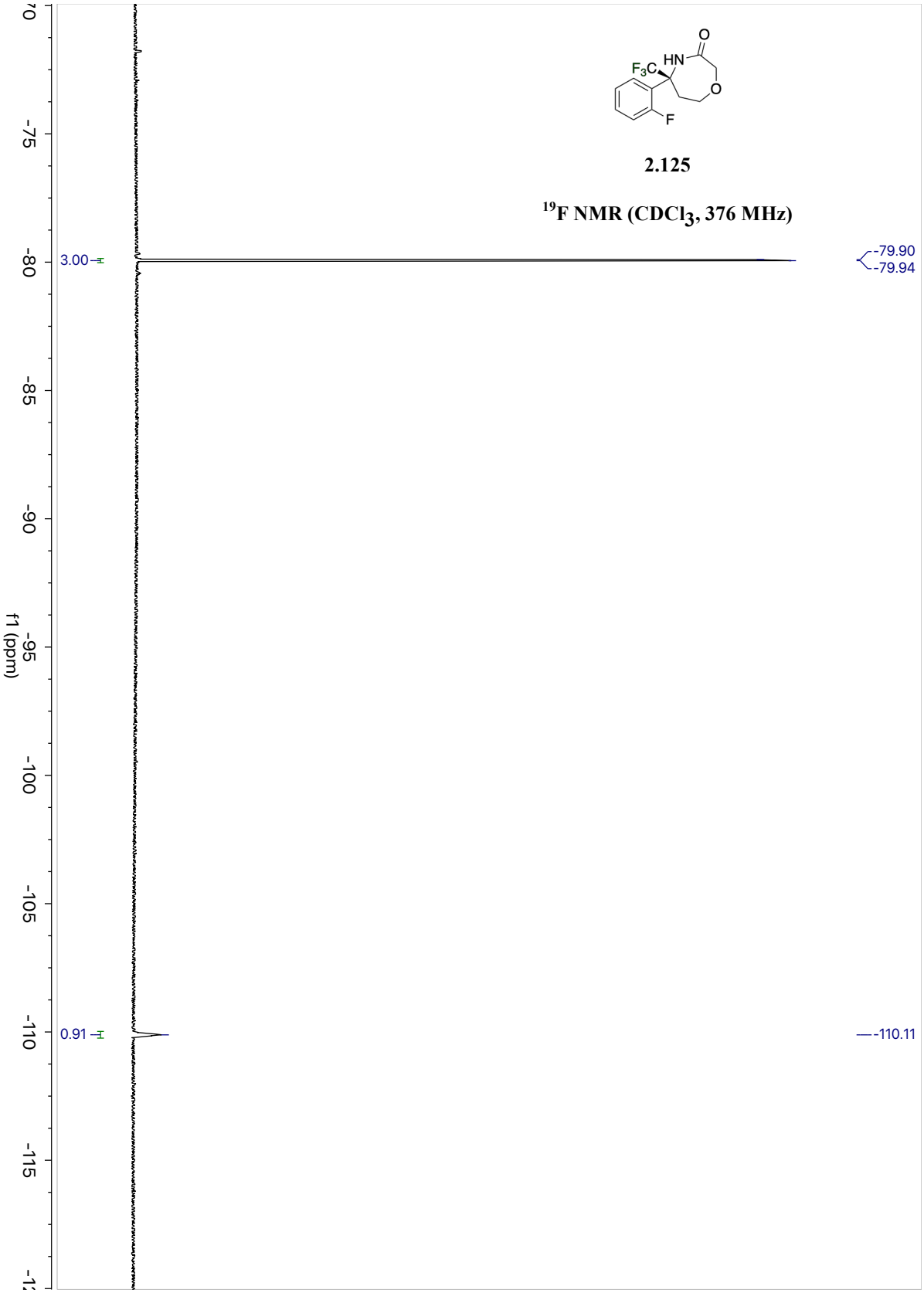
^{1}H NMR ($CDCl_3$, 400 MHz)


O
Cl
HN
F3C
F
Me
2.124
13C NMR (CDCl3, 100 MHz)
164.81
161.87
159.39
130.76
130.66
130.11
129.80
128.93
128.91
128.89
126.94
124.41
124.38
124.08
122.67
122.58
122.25
122.23
121.23
117.20
116.95
64.14
64.11
63.86
63.83
63.59
63.56
63.31
63.28
42.73
42.71
31.38
31.35
13.03
f1 (ppm)


O
Cl
HN
F3C
Me
F
2.124
19F NMR (CDCl3, 376 MHz)
3.00
0.95
-72.91
-72.93
-110.36
-110.39
-110.40
-110.42
-110.44
-110.46
-110.47
-110.48
-110.50
f1 (ppm)
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115


2.125
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.00
1.04
1.11
1.03
0.98
2.13
1.07
1.12
1.06
1.06


O
HN
F3C
O
F
2.125
13C NMR (CDCl3, 100 MHz)
174.98
161.10
158.63
131.80
131.71
130.36
130.33
126.58
125.16
125.13
123.74
121.94
121.82
117.25
117.00
70.16
66.05
64.08
63.80
63.76
63.52
63.48
63.23
32.42
32.35
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
HN
F3C
O
F
2.125
19F NMR (CDCl3, 376 MHz)
3.00
0.91
-79.90
-79.94
-110.11
f1 (ppm)
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115

Chapter Three

Catalytic, Enantioselective Addition of Terminally Substituted Allyl Boronates to Aldehydes

3.1 Introduction

Homoallylic alcohols and their derivatives are ubiquitous motifs in polyketide scaffolds, many of which possess potent bioactivity. As a result, considerable effort has been directed towards enantioselective synthesis of these moieties.[1] Of the strategies developed, those attributed to Brown,[2] Roush,[3] Leighton[4] and Krische[5] are employed due to high levels of selectivity, operational simplicity and/or predictable models for stereoselectivity. Despite these advances, the majority of these methods only address synthesis of products containing an internal allylic

1) For a recent review, see: Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774–7854. For representative examples, see: (a) Corey, E. J.; Mu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495–5496. (b) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044–8049. (c) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884–11886. Xing, C.-H.; Liao, Y.-X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q.-S. *Eur. J. Org. Chem.* **2012**, *6*, 1115–1118. (d) Clot-Almenara, L.; Rodríguez-Escrich, C.; Osorio-Planes, L.; Pericàs, M. A. *ACS Catalysis* **2016**, *6*, 7647–7651. (e) Gao, S.; Chen, M. *Org. Lett.* **2018**, *20*, 6174–6177.

2) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093.

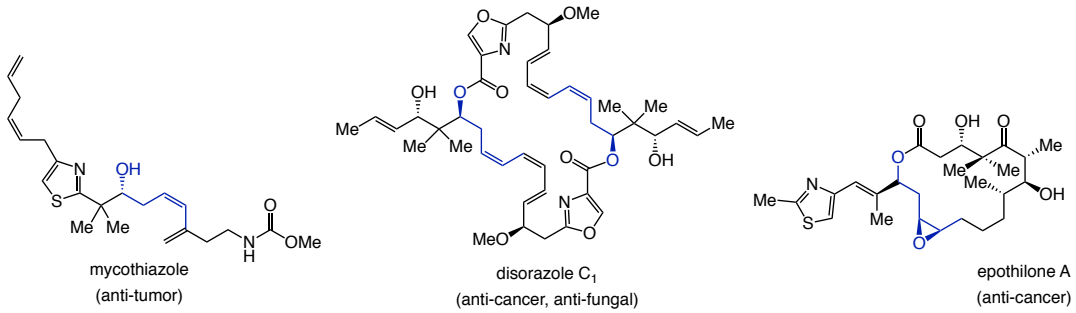
3) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190.

4) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946–948.

5) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891–14899. (b) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5018–5021. (c) Hassan, A.; Townsend, I. A.; Krische, M. J. *Chem. Commun.* **2011**, *47*, 10028–10030. (d) Zbeig, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science*, **2012**, *336*, 324–327. (e) Feng, J.; Garza, V. J.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8911–8914. (f) Brito, G. A.; Della-Felice, F.; Luo, G.; Burns, A. S.; Pilli, R. A.; Rychnovsky, S. D.; Krische, M. J. *Org. Lett.* **2018**, *20*, 4144–4147.

substituent (commonly referred to as the branched product),[6] and there are far fewer reports detailing synthesis of the regioisomeric linear products (more on this below).[7]

Scheme 3.1. Representative Bioactive Compounds Possessing *Z*-Homoallylic Alcohol Motifs



3.2 Background

3.2.1 Z-Homoallylic Alcohols in Synthesis

To access compounds such as those shown in Scheme 3.1, synthetic routes often require protection and deprotection sequences or extensive redox manipulations. A representative example, taken from Panek's synthesis of epothilone A, is illustrated below (Scheme 3.2).[8] A seven-step sequence involving resolution of allylic alcohol **3.2**, followed by hydroboration of the alkene and subsequent oxidation to aldehyde **3.6** were all required before obtaining alkenyl iodide **3.7**. While this remains a reliable and stereoselective strategy for synthesis of homoallylic alcohols bearing a *Z*-alkenyl halide, in fact the lowest reported ratio for selectivity we could identify was 94:6 *Z*:*E*,[9] the sequence generates a large amount of waste and consumes valuable time to carry out.

---

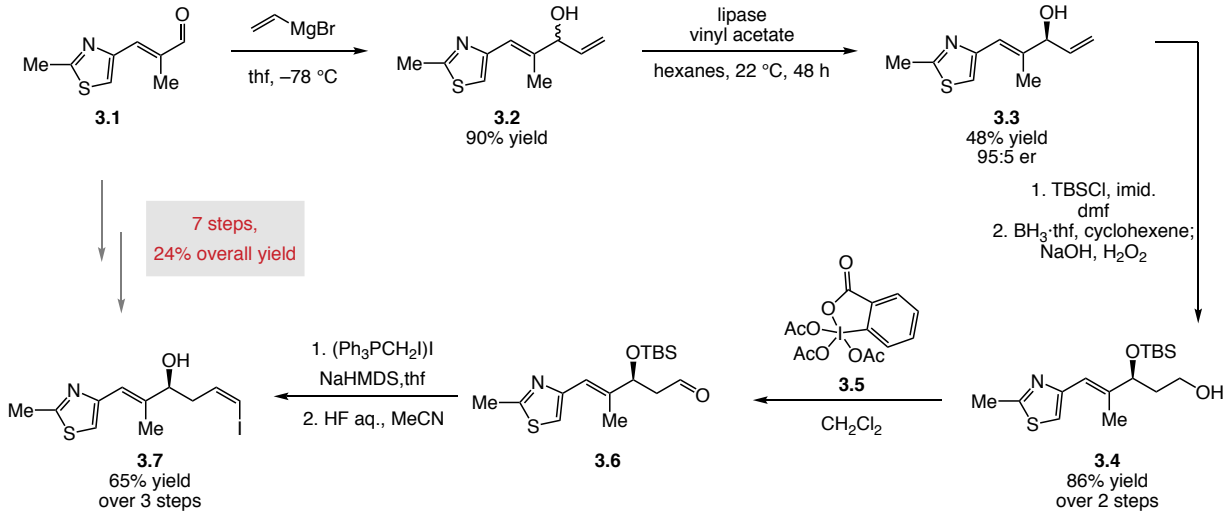
6) (a) Denmark, S. E.; Wilson, T. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 3236–3239. (b) Miura, T.; Nishida, Y.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 11497–11500.

7) (a) Kobayashi, S.; Endo, T.; Schneider, U.; Ueno, M. *Chem. Commun.* **2010**, *46*, 1260–1262. (b) Kobayashi, S.; Endo, T.; Yoshino, T.; Schneider, U.; Ueno, M. *Chem. Asian. J.* **2013**, *8*, 2033–2045.

8) Zhu, B.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2575–2578.

9) Yadav, J. S.; Dutta, P. *J. Org. Chem.* **2016**, *81*, 1786–1797.

Scheme 3.2. Synthesis of *Z*-Alkenyl Iodide En Route to Epothilone A



With this insight, we reasoned that development of a method for direct enantioselective synthesis of *Z*–substituted homoallylic alcohols would be a compelling objective. There are several examples addressing synthesis of such motifs that possess an allylic substituent through addition of enantiomerically pure reagents;[10] however, there are far fewer describing synthesis of those without an allylic substituent.[11] Two representative examples are shown in Scheme 3.3.

In the presence of a camphor-based auxiliary, Loh described stereoselective synthesis of homoallylic alcohols **3.10** through [3,3]-sigmatropic rearrangement of oxonium **3.12** formed upon reaction of diastereoenriched homoallylic alcohol **3.9** and an aldehyde (Scheme 3.3b).[12] The scope is limited to aliphatic aldehydes, and those that are more sizable required extended reaction times (up to 240 h). In a different approach, Malkov reported synthesis of *Z*-homoallylic alcohols

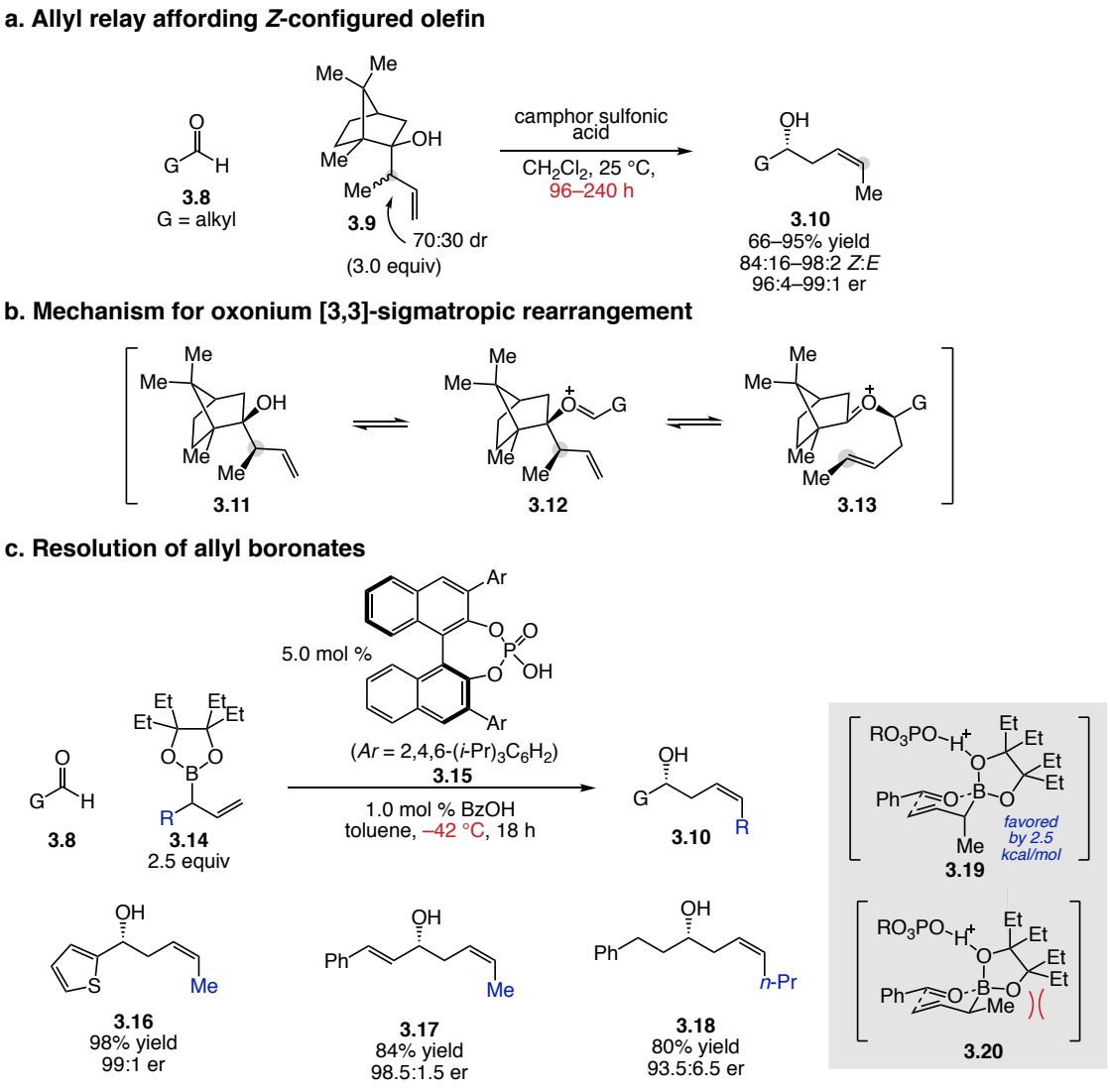
10) (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229–3231. (b) Pietruska, J.; Schöne, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 5638–5641. (c) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, 2275–2280. (d) Beckmann, E.; Hoppe, D. *Synthesis* **2005**, 217–222. (e) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 359–362. (f) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025–4028. (g) Binanzer, M.; Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 4264–4268. (h) Chen, J. L-Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 5316–5319.

11) Pietruszka, J.; Schöne, N.; Frey, W.; Grundl, L. *Chem. Eur. J.* **2008**, *14*, 5178–5197.

12) Lee, C.-K.; Lee, C-H. A.; Tan, K.-T.; Loh, T.-P. *Org. Lett.* **2004**, *6*, 1281–1283.

through resolution of secondary allyl boronate **3.14** promoted by phosphoric acid catalyst **3.15**.[13] *Z* selectivity is likely the result of a preference to orient the methyl substituent in a pseudo-axial position (**3.19)** in order to alleviate steric hindrance between the alkyl substituent of the pinacolato ester and the methyl group. As indicated, alkyl, alkenyl, aryl, and heteroaryl-substituted aldehydes were all suitable affording products in 70–97% yield and 93.5:6.5–99:1 er.

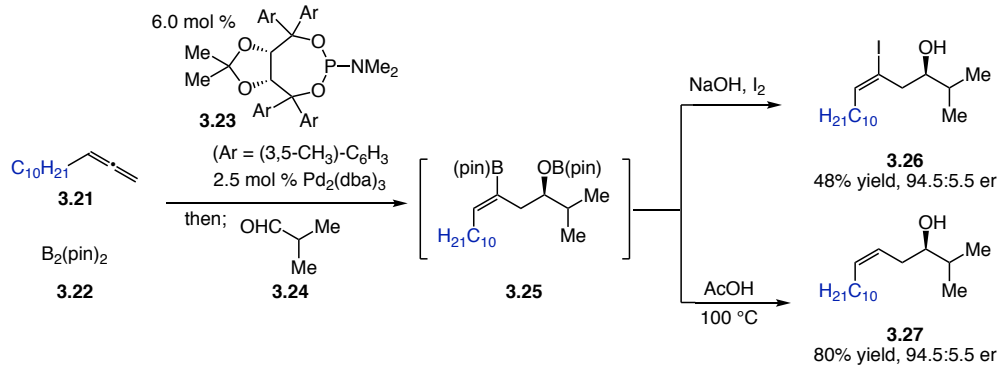
Scheme 3.3. State-of-the-Art for Synthesis of *Z*-Homoallylic Alcohols



13) Incerti-Pradillos, C. A.; Kabeshov, M. A.; Malkov, A. V. *Angew. Chem. Int. Ed.* **2013**, *52*, 5338–5341.

Morken has detailed a method for catalytic, enantioselective diboryl addition to allene **3.21** (Scheme 3.4). The resulting enantioenriched allyl boronate reacts with aldehyde **3.24**, furnishing homoallylic alcohol **3.25** bearing a trisubstituted olefin.[14] The utility of the obtained products were highlighted through conversion to alkenyl iodide **3.26** in 48% yield and stereoretentive proto-deboronation through treatment with refluxing acetic acid for synthesis of *Z*-homoallylic alcohol **3.27** in 80% yield.

Scheme 3.4. Catalytic Enantioselective Diboryl Addition to Allenes



3.2.2 Synthesis of Z-Homoallylic Alcohols Without Alkyl Substitution

These are key studies in light of recent advances in stereo-retentive cross-metathesis have benefited from higher efficiency when cross partners with stereodefined disubstituted olefins are employed.[15] However, we could only find limited examples for synthesis of *Z*-homoallylic alcohols that do not bear an alkyl substituent. One example is addition of α-silyl substituted allyl boronate **3.28** to **3.8a** (Scheme 3.5),[16] although *Z* selectivity is moderate and competitive addition of the allyl silane led to lower yields. In a different approach, Krische has reported stereoselective formation of *Z*-enol ether **3.34**, wherein an iridium-based allyl species, generated through a 1,2-

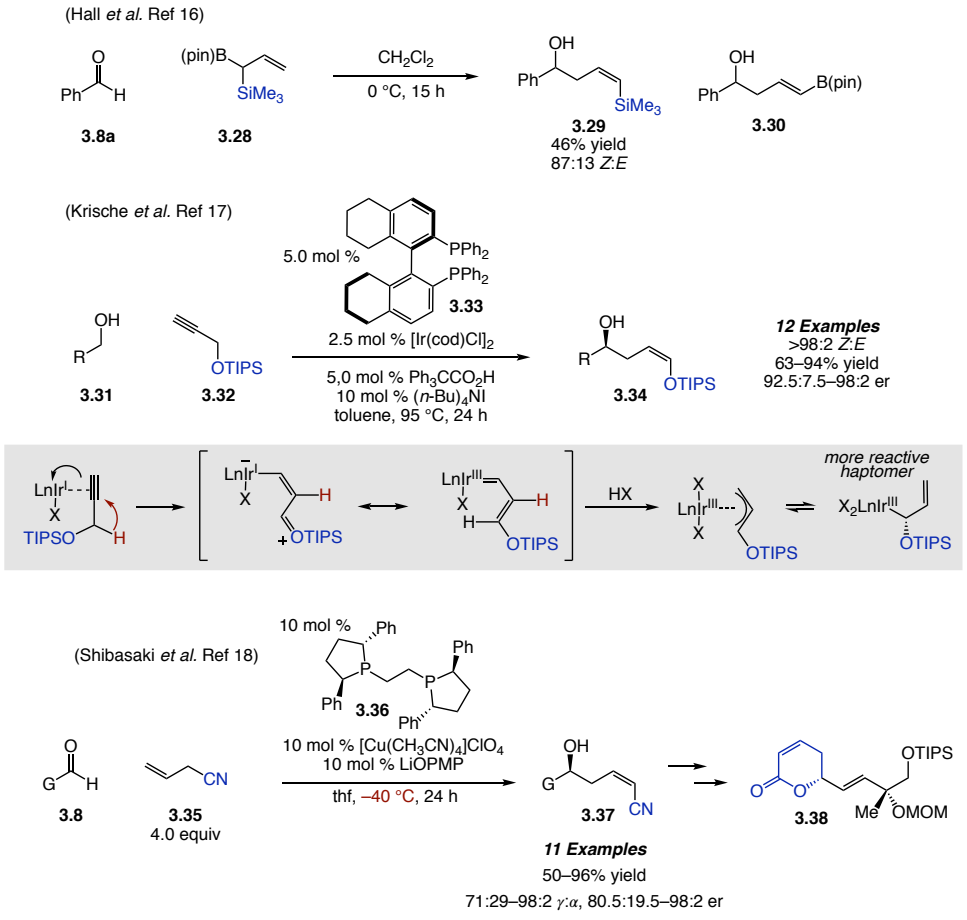
14) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505–5507.

15) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919–10928.

16) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981–8985.

hydride shift, as shown in Scheme 3.5, adds to an aldehyde.[17] Selectivity is likely a result of reaction through the iridium-based haptomer shown due to the inductive effect of the oxygen atom in combination with a preference for formation of a less hindered C–C bond. Shibasaki has described synthesis of *Z*-alkenyl nitriles **(3.37)** through addition of allyl cyanide **3.35** to aldehydes promoted by a copper bis-phosphine complex. The method is not applicable to aliphatic aldehydes and substrates possessing alkenyl side chains were isolated with lower levels of γ selectivity (71:29–77:23 γ:α ratio). The obtained products were subsequently elaborated to lactone **3.38,** a key intermediate in the synthesis of fostriecin.[18]

Scheme 3.5. Additions of Allyl Reagents for Synthesis of *Z*-Homoallylic Alcohols



17) Liang, T.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 16024–16027.

18) Otuska, Y.; Takada, H.; Yasuda, S.; Kumagai, N.; Shibasaki, M. *Chem. Asian. J.* **2013**, *8*, 354–358.

3.2.3 State-of-the-Art for Addition of Halo-Substituted Allyl Nucleophiles

Given the advances in modern cross-coupling methodologies and the prevalence of *Z*-halo homoallylic alcohols as synthetic intermediates,[19] we were somewhat surprised to find few examples detailing direct synthesis of these motifs,[20] and only one exhibiting appreciable enantioselectivity.[20c] Methods, however, for additions of halogen containing compounds affording the regioisomeric chlorohydrin product **3.41** are more prevalent,[21] and three representative examples are illustrated in Scheme 3.6. Kobayashi disclosed addition of α-chloro allyl boronate **3.39** to a variety of aliphatic and aromatic aldehydes promoted by readily accessible diol **3.40** affording *syn*-chlorohydrin **3.41** in 73–99% yield, 87.5:12.5–98:2 dr and 92.5:7.5–99:1 er.[22] Umani-Ronchi and co-workers accessed the same class of compounds through addition of dichloropropene **3.42** promoted by chromium-based salen **3.43** complexes, obtaining regioisomeric mixtures (i.e., α- and γ-addition), which led to low yields upon separation.[23] Finally, Leighton accomplished diastereodivergent synthesis of *syn*- and *anti*-**3.47** through addition of allyl silanes **3.44** and **3.45**, respectively. Despite the use of stoichiometric diamine, which can be recycled upon work-up, the reaction is efficient, as well as diastereo- and enantioselective.[24]

---

19) For recent examples, see: (a) Reddy, K. M.; Yamini, V.; Singarapu, K. K.; Ghosh, S. *Org. Lett.* **2014**, *16*, 2658–2660. (b) Speed, A. W. H.; Mann, T. J.; O'Brien, R. V.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16136–16139. (c) Lei, H.; Yan. J.; Yu, J.; Liu, Y.; Wang, Z.; Xu, Z.; Ye, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 6533–6537. (d) Franke, J.; Bock, M.; Dehn, R.; Fohrer, J.; Mhaske, S. B.; Migliorini, A.l Kanakis, A. A.; Jansen, R.; Herrmann, J.; Müller, R.; Kirschning, A. *Chem. Eur. J.* **2015**, *21*, 4272–4284. (e) Yadav, J. S.; Dutta, P. *J. Org. Chem.* **2016**, *81*, 1786–1797. (f) Nguyen, M. H.; Imanishi, M.; Kurogi, T.; Smith, A. N. *J. Am. Chem. Soc.* **2016**, *138*, 3675–3678. (g) Yoshikawa, Y.; Yamakawa, M.; Kobayashi, T.; Murai, K.; Arisawa, M.; Sumimoto, M.; Fujioka, H. *Eur. J. Org. Chem.* **2017**, 2715–2718.

20) (a) Hoffmann, R. W.; Landmann, B.; *Tetrahedron Lett.* **1983**, *24*, 3209–3212. (b) Hoffmann, R. W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903–909. (c) Sturmer, R.; Hoffmann, R. W. *Synlett* **1990**, 759–760. (d) Mallaiah, K.; Satyamarayana, J.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993**, *34*, 3145–3148.

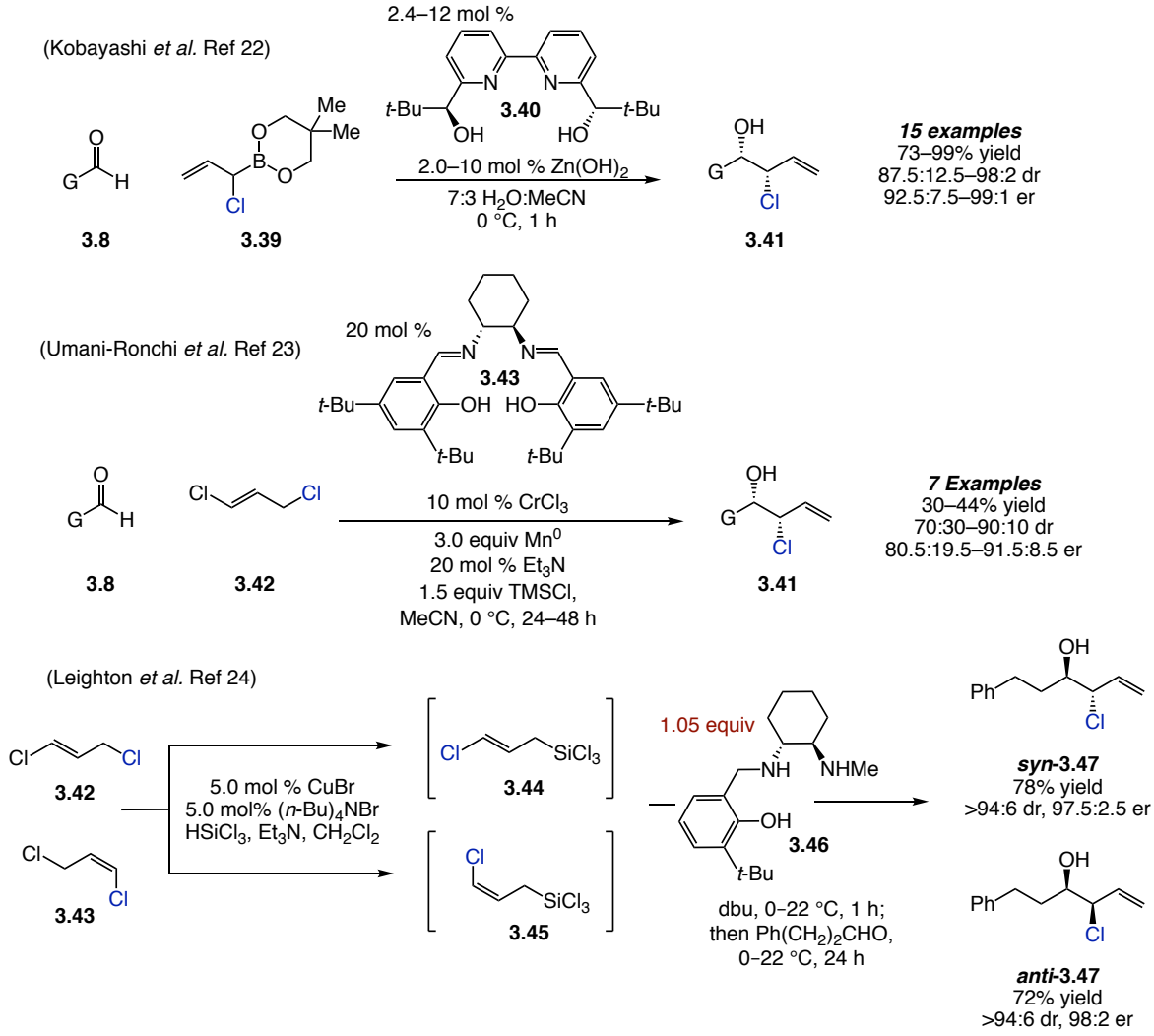
21) (a) Jayaraman, S.; Hu, S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1995**, *36*, 4765–4768. Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513–7520. (b) Hertweck, C.; Boland, W. *Eur. J. Org. Chem.* **1998**, 2143–2148. Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1998**, *63*, 8843–8849.

22) Kobayashi, S.; Endo, T.; Ueno, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 12262–12265.

23) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Morganti, S.; Umani-Ronchi, A. *Org. Lett.* **2001**, *3*, 1153–1155.

24) Tekle-Smith, M. A.; Williamson, K. S.; Hughes, I. F.; Leighton, J. L. *Org. Lett.* **2017**, *19*, 6024–6027.

Scheme 3.6. Enantioselective Addition of Chloro-Substituted Allyl Reagents



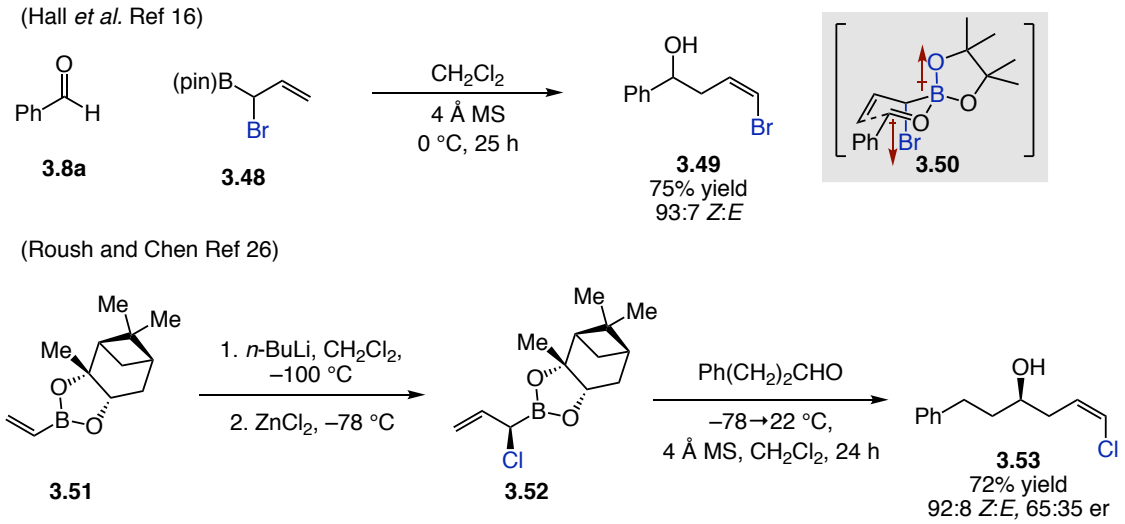
In 2005, Hall and co-workers outlined addition of allyl reagent **3.48** furnishing *Z*-bromo substituted alcohol **3.49**.[16] The high levels of *Z* selectivity are the result of minimization of dipole interaction between the polar halogen bond and the B–O bond of the boronate, as shown in **3.50**.[25] Five years later, Roush and Chen[26] reported synthesis and application of enantioenriched allyl

25) For other factors governing *Z* selectivity, see: (a) Hoffmann, R. W.; Landmann, B. *Angew. Chem. Int. Ed.* **1986**, *25*, 189–190. (b) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123–130. (c) Hoffmann, R. W.; Wolff, J. J. *Chem. Ber.* **1991**, *124*, 563–569.

26) (a) Hoffmann, R. W.; Landmann, B. *Angew. Chem. Int. Ed.* **1984**, *23*, 437–438. (b) Chen, M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 2706–2709.

boronate **3.52**; although the transformation is *Z*-selective, enantiomeric ratios did not exceed 65:35, probably owing to epimerization of the allylic position during reagent preparation.

Scheme 3.7. State-of-the-Art for Synthesis of *Z*-Halo Substituted Alcohols



3.3 Additions to Aldehydes Promoted by Aminophenol Complexes

3.3.1 Challenges Surrounding Additions

To address these shortcomings, we envisaged that a class of aminophenol boron-based catalysts, known to be α-selective,[27] could be well suited to advance the state-of-the-art. Our group has previously utilized these for enantioselective addition of allyl boronates to phosphinoyl aldimines,[27] ketones,[28] and as discussed in Chapter Two, trifluoromethyl ketimines. Enantiotopic discrimination for additions to *N*-diphenylphosphinoyl aldimines was likely the result of an

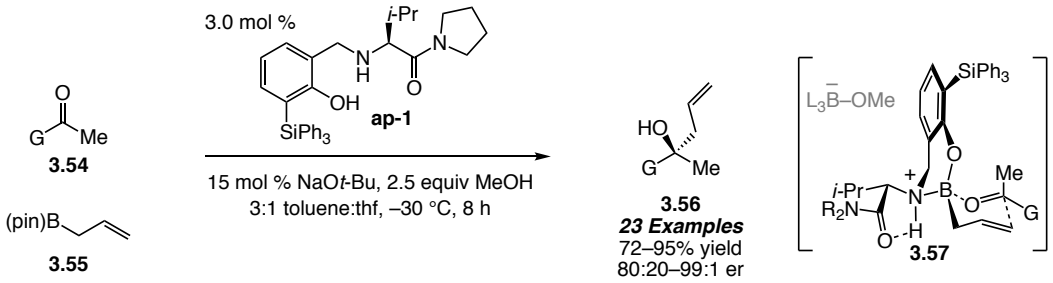
27) (a) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216–221. (b) van der Mei, F. W.; Qin, C.; Morrison, R. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 9053–9065.

28) Robbins, D. W.; Lee, K.; Silverio, D. L.; Volkov, A.; Torker, S.; Hoveyda, A. H. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 9610–9614. Lee, K.; Silverio, D. L.; Torker, S.; Robbins, D. W.; Haeffner, F.; van der Mei, F. W.; Hoveyda, A. H. *Nature Chem.* **2016**, *8*, 768–777. Fager, D. C.; Lee, K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 16125–16138.

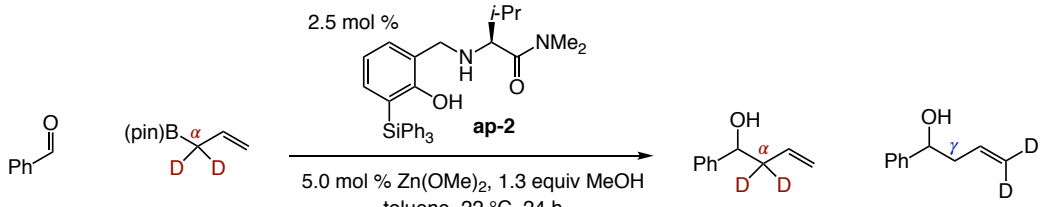
interaction between the phosphine oxide and ammonium ion within the catalyst, and selectivity for trifluoromethyl substituted ketones and ketimines was probably as a result of coulombic attraction with the ammonium. Aminophenol boron-based catalysts may also be employed for additions to methyl ketones **3.54**, wherein selectivity is governed by steric factors (Scheme 3.8a). Based on this past experience, we reasoned that with an appropriate catalyst and reaction conditions, enantioselective additions to aldehydes could be achieved due the larger size difference between –H and –Ph (vs $–CH_3$ and –Ph in the case of methyl ketone **3.54**).

Scheme 3.8. Past Investigations and Objective of Our Investigations[a]

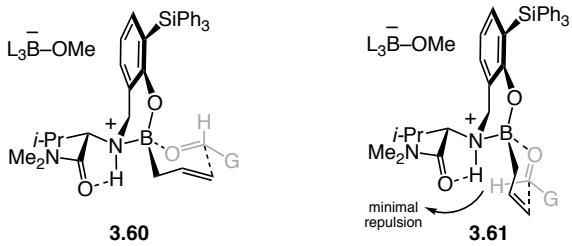
a. Additions to ketones: enantiotopic discrimination based on steric control



b. Additions to aldehydes: efficient but non-selective



c. Competitive modes of addition



[a]All reactions were performed under N_2 atm. Conv and α:γ ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). pin: pinacaloto See Experimental Section for details.

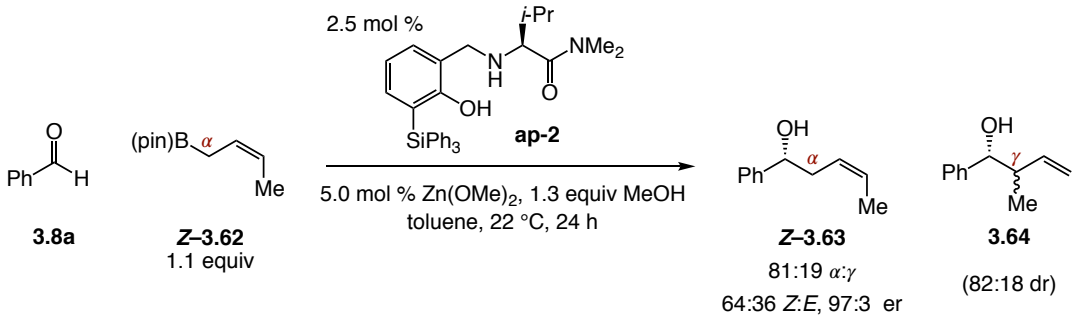
However, under the best of circumstances, enantiomeric ratios did not exceed 62:38 er (Scheme 3.8b), which we attributed to competitive uncatalyzed addition to these more electrophilic substrates. To determine if this was the case, we prepared deuterated allyl boronate ***d*$_2$–3.55** with the rationale that, if a competitive non-selective process were to dominate, two deuterium atoms would be incorporated on the terminal carbon as shown in **3.59**; however, we isolated **3.58** as the major product (95%). This indicated that additions promoted by an aminophenol boron-based complex were efficient, but non-selective.

Analysis of transition state models, based on those previously disclosed, led us to consider two possible modes of addition, **3.60** and **3.61**. Unlike additions to ketone **3.54**, the smaller hydrogen atom probably renders addition through **3.61** more competitive resulting in a smaller $\Delta\Delta G^{\ddagger}$. In previous investigations,[27] we have observed that reaction of substituted allyl boronates and trifluoroketones and ketimines are typically more enantioselective due to an allylic substituent that generates a degree of steric pressure in modes leading to the minor enantiomer (see Chapter Two). If the same lessons could extend to addition to aldehydes, we sought to address two longstanding challenges: (1) Development of a robust, catalytic, and enantioselective method for additions to aldehydes promoted by aminophenol boron-based catalysts. (2) Directly synthesis of homoallylic alcohols that contain a *Z*-olefin.

3.3.2 Initial Optimization and Method Development

We commenced our investigation with ***Z*-3.62** to ascertain whether addition of substituted allyl boronates proceeded with the same levels of α selectivity as those for ***d*$_2$-3.55**. Addition proved to be efficient and in moderate preference the desired isomer (81:19 α:γ ratio); however, both diastereo- and *Z* selectivity were low (82:18 dr and 64:36 *Z*:*E*). We reasoned that may arise from a competitive non-catalyzed process, and considered employing a set of less nucleophilic reagents.

Scheme 3.9. Initial Result for Addition of Crotyl Boronate to Aldehydes[a]



3.8a

***Z*–3.62**
1.1 equiv

***Z*–3.63**
81:19 α:γ
64:36 *Z*:*E*, 97:3 er

3.64
(82:18 dr)

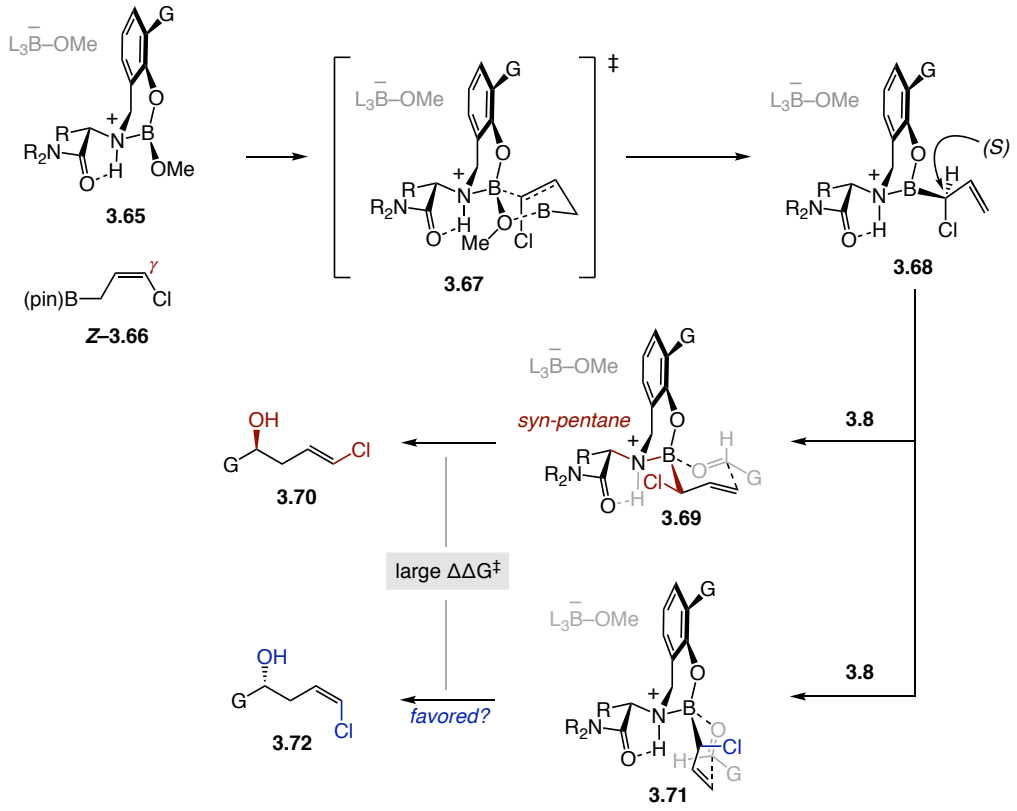
[a]All reactions were performed under N_2 atm. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of **3.8a**. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

Accordingly, we selected ***Z*-3.66**, accessible due to recent advances in *Z*-selective cross-metathesis promoted by Mo-based complexes[29] to address the need for enantioselective synthesis of *Z*-halo homoallylic alcohols. We are not the first to consider preparation of allyl reagents through catalytic cross-metathesis, but typically these transformations are promoted by Ru-based complexes and are highly *E* selective.[30] With the requisite reagent in hand, we considered the orchestrated series of events that must occur in order to furnish the desired product stereoselectively.

29) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465.

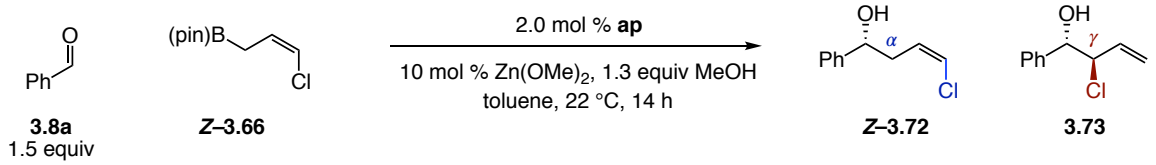
30) Feske, M. I.; Santanilla, A. B.; Leighton, J. L. *Org. Lett.* **2010**, *12*, 688–691.

Scheme 3.10. Possible Modes of Addition for Chloro-Substituted Aminophenol Complex

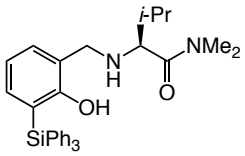


Stereospecific γ-transfer of ***Z*-3.66** to aminophenol boron-based complex **3.65** proceeds via **3.67**, affording complex **3.68** with a chloro-substituted stereogenic center. If, for a moment, we ignore the possibility of 1,3-boryl shift, allyl addition can proceed through two possible modes. In **3.69**, the chloro substituent is oriented pseudo-equatorially generating steric hindrance between the chloride and the amide, as well as a *syn*-pentane-like interaction with the catalyst backbone. Alternatively, addition through **3.71**, wherein the chloride is pseudo-axial, these repulsive interactions are minimized. It was unclear, however, if such interactions could lead to a sufficient energy difference between **3.69** and **3.71** (Scheme 3.8).

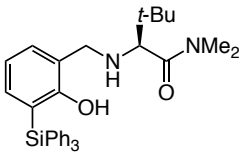
Scheme 3.11. Initial Evaluation and Optimization of Aminophenol Catalyst[a]



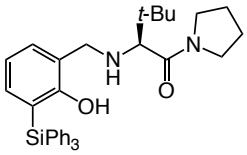
3.8a 1.5 equiv | ***Z*–3.66** | ***Z*–3.72** | **3.73**



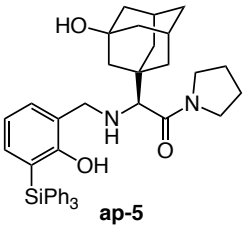
ap-2
91:9 α:γ
79% yield (α), 98:2 Z:E
87:13 er



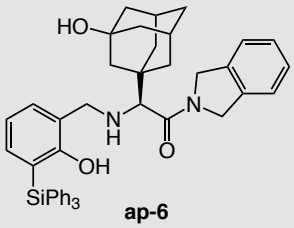
ap-3
98:2 α:γ
94% yield (α), 97:3 Z:E
91:9 er



ap-4
98:2 α:γ
84% yield (α), 98:2 Z:E
92:8 er



ap-5
98:2 α:γ
83% yield (α), 98:2 Z:E
93:7 er



ap-6
>98:2 α:γ
95% yield (α), >98:2 Z:E
94:6 er

[a]Performed under an atmosphere of dry N_2. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

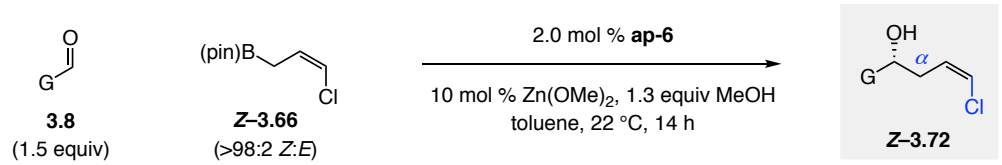
We began optimization by using 1.5 equivalents of aldehyde **3.8a** to ensure efficiency and maintain an excess of substrate to favor direct addition over competitive 1,3-boryl shift.[31] Under these conditions, additions promoted by a triphenylsilyl-substituted aminophenol compound, the transformation was largely α- and *Z*–selective. In accordance with previous models, we found that enantioselectivity was correlated to the size of the amino acid residue (Scheme 3.11, c.f. **ap-2** and **ap-3**), with hydroxyl-substituted adamantane **ap-6** affording optimal results.

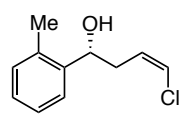
31) Excess aldehyde can be recovered in up to 97% yield.

3.3.3 Scope of the Method

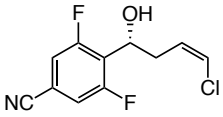
We explored the scope of the transformation. Substrates possessing an *ortho*-substituent, such as *o*-tolyl ***Z*–3.73** and 2,6-difluorosubstituted ***Z*–3.74** furnished products with exclusive α selectivity and in 95:5 and 94:6 er, respectively, indicating that association with complex **3.68** is favored over 1,3-shift even with more sizable substrates. Aryl halides such as ***Z*–3.75** and ***Z*–3.76** were tolerated affording products in >98:2 α:γ ratio and 96:4 and 93:7 er, respectively. Furthermore, the reaction proceeded with complete chemoselectivity as evidenced by ***Z*–3.77**. Electronic factors had little effect on the enantioselectivity of the reaction, although addition to *para*-methoxyphenyl substituted ***Z*–3.78** resulted in diminished regioselectivity, likely due to a more competitive 1,3-boryl shift for this electron-rich case. This supports the idea that steric factors are underscored by electronics for kinetics of 1,3-boryl shift. Notably, aldehydes that contain *para*-substitution were isolated in lower er (88:12–90:10 er for ***Z*–3.77–3.79**, compared to 94:6 er for ***Z*-3.72**) regardless of the electronics of the arene. To determine if this was the consequence of a competitive, non-catalyzed process, we carried out addition in the absence of aminophenol and found no indication of increased reactivity due to *para*-substitution. The implications of these findings, and how this pattern of substitution disfavors the major mode of addition still require investigation. The method is suitable for substrates that contain an acetal moiety ***Z*–3.77**, as well as those with a heterocyclic substituent. Both indole ***Z*–3.81** and 3-pyridyl substituted ***Z*–3.82** were isolated with exclusive α selectivity in 96:4 and 94:6 er, respectively.

Scheme 3.12. Scope of Aryl and Heteroaryl-Substituted Aldehydes[a]

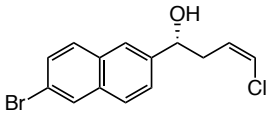




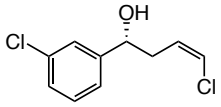
Z–3.73
>98:2 α:γ
83% yield, 98:2 *Z*:*E*
95:5 er



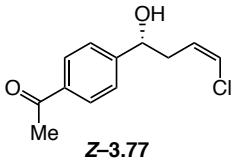
Z–3.74
>98:2 α:γ
86% yield, >98:2 *Z*:*E*
94:6 er



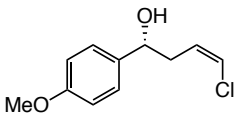
Z–3.75
>98:2 α:γ
95% yield, 97:3 *Z*:*E*
96:4 er



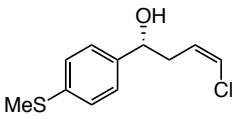
Z–3.76
98:2 α:γ
90% yield, >92:8 *Z*:*E*
93:7 er



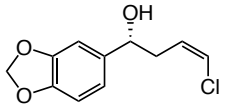
Z–3.77
>98:2 α:γ
92% yield, 97:3 *Z*:*E*
88:12 er



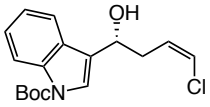
Z–3.78
93:7 α:γ
92% yield, >92:8 *Z*:*E*
89:11 er



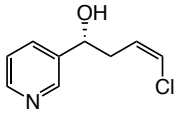
Z–3.79
97:3 α:γ
90% yield, >98:2 *Z*:*E*
90:10 er



Z–3.80
>98:2 α:γ
95% yield, >98:2 *Z*:*E*
95:5 er



Z–3.81
>98:2 α:γ
96% yield, >98:2 *Z*:*E*
96:4 er



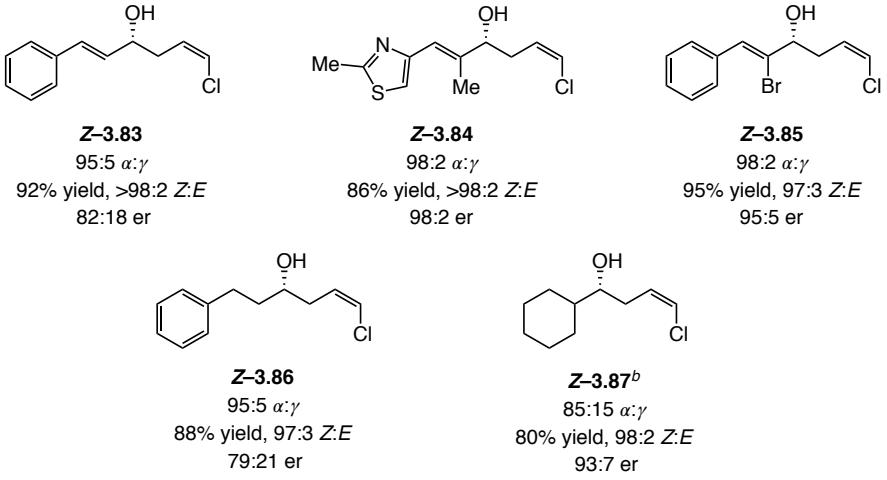
Z–3.82
>98:2 α:γ
91% yield, >98:2 *Z*:*E*
94:6 er

[a]Performed under an atmosphere of dry N_2. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Experiments run at least in triplicate. Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

Enals, both di-(***Z*–3.83)** and trisubstituted (***Z*–3.84–85)**, furnished product with efficiency, however, enantiomeric ratios for the former were lower probably owing to the small and linear nature of the alkyl group. This is indeed a consequence of reliance on steric factors for high levels of enantioselectivity. Nonetheless, replacement of an alkenyl hydrogen with a methyl or bromo substituent afforded access to ***Z*–3.84** and ***Z*–3.85** in 98:2 and 95:5 er, respectively. Additions to aliphatic aldehydes with an α-substituent were also efficient and enantioselective, although the

decrease in regioselectivity may be the result of competitive 1,3-boryl shift for these less electrophilic and hindered substrates.

Scheme 3.13. Scope of Alkenyl and Aliphatic Aldehydes[a]

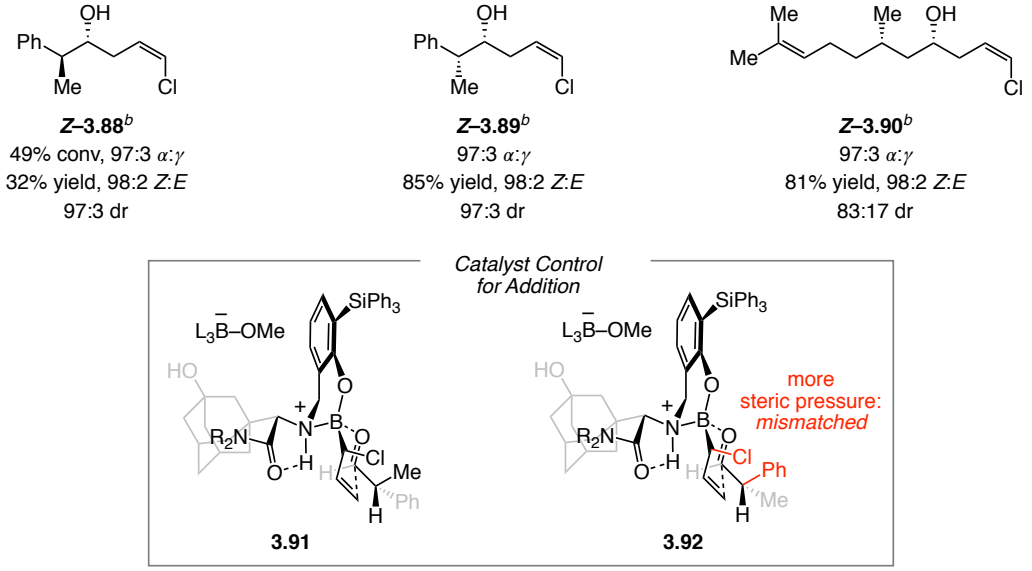


[a]Performed under an atmosphere of dry N_2. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Experiments run at least in triplicate. Er values were determined by HPLC analysis (±1%). [b]Conducted in the absence of methanol. See Experimental Section for details.

The transformation is applicable to compounds that contain an α-stereogenic center (***Z*–3.88-89)**. We found that by forgoing addition of methanol (trace amounts of moisture are sufficient to generate the ammonium ion), optimal α selectivity could be achieved. For example, when addition was carried out in the presence of 1.3 equivalents of MeOH, ***Z*–3.88** and **3.89** were isolated in 53:47 and 62:38 α:γ ratio, respectively. The precise origin of this phenomenon requires further investigation. However, it is reasonable to postulate that a less polar medium may affect the efficiency with which boryl shift proceeds or hamper the formation of extensive networks of hydrogen bonding that facilitate competitive and non-selective pathways. Addition proceeds under catalyst control, with the matched case (Felkin-Ahn model), generating product in 85% yield and 97:3 dr. For the mismatched case, ***Z*–3.88**, diastereoselectivity remained high (97:3 dr), but increased steric pressure between the pseudo-axial chloride and the phenyl ring reduced the efficiency (**3.92**, Scheme 3.14). In accordance with results for additions to aldehydes possessing a

linear alkyl substituent, reaction with (+)-citronellal, although α-selective afforded ***Z*–3.90** in 83:17 dr.

Scheme 3.14. Additions to Aldehydes Possessing a Stereogenic Center[a]



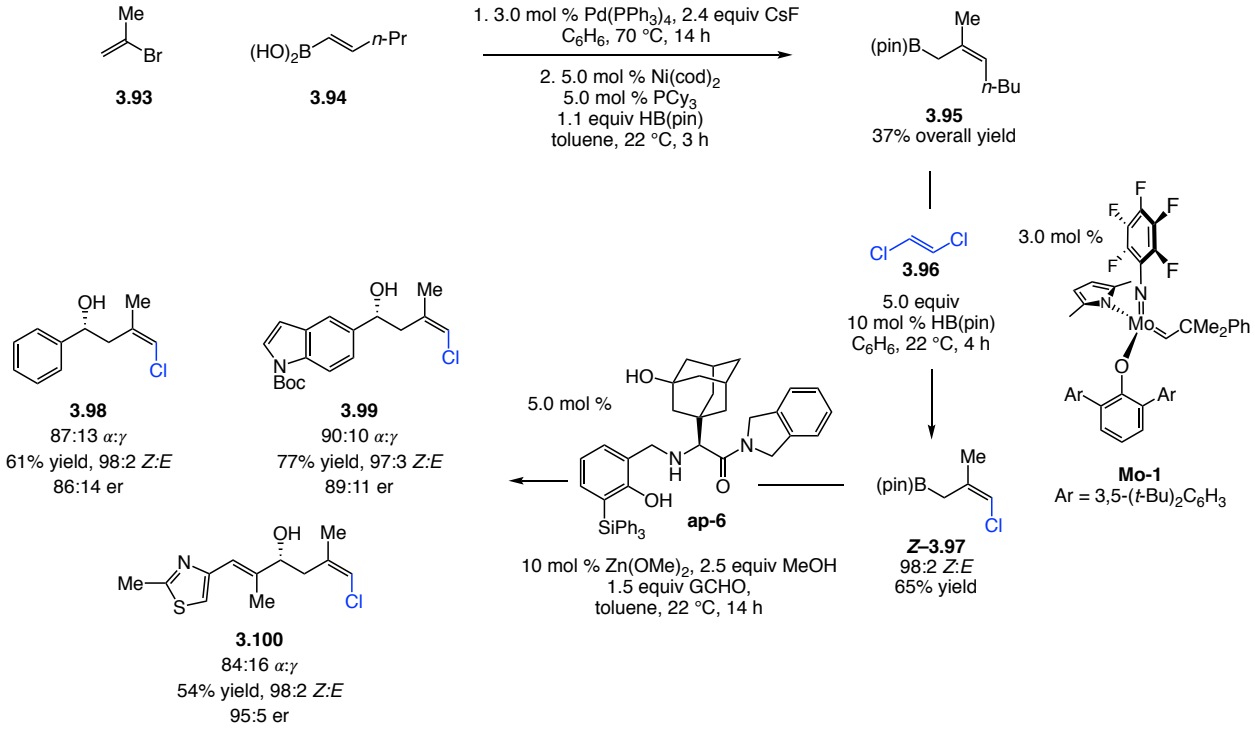
[a]Performed under an atmosphere of dry N_2. Conv, α:γ , dr and *Z:E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Experiments run at least in triplicate. [b]Conducted in the absence of methanol. See Experimental Section for details.

Trisubstituted alkenyl chlorides were efficiently prepared. The requisite reagent, ***Z*–3.97,** which may be synthesized through cross-metathesis, promoted by Mo-based complex **Mo-1**,[32] of trisubstituted allyl boronate **3.95**[33] and dichloroethylene **3.96**. Reaction with the more sizable reagent required higher catalyst loading (5.0 mol %) and an additional equivalent of methanol for efficiency. Under these conditions, additions to aryl, heteroaryl, and alkenyl-substituted aldehydes furnished products in 54–77% yield, 97:3–98:2 Z:*E* ratio and 86:14–95:5 er.

32) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347–354.

33) Allyl boronate was synthesized through Ni-catalyzed 1,4-hydroboration, see: Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534–2535.

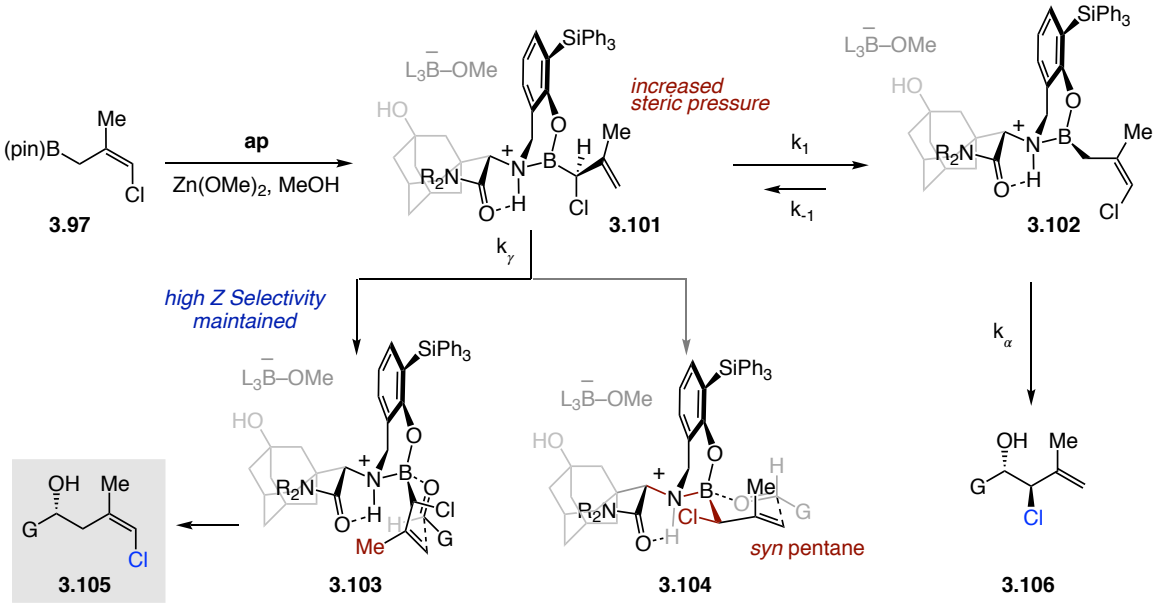
Scheme 3.15. Synthesis of Application of Trisubstituted Allyl Boronates[a]



[a]Performed under an atmosphere of dry N_2. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of ***Z*–3.97** Yield of isolated and purified product (±5%). Experiments run at least in triplicate. Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

We reasoned that the diminished regioselectivity might be a consequence of increased steric pressure exerted on the complex by the C_2 methyl substituent, impeding substrate coordination and allow a greater chance for boryl shift (Scheme 3.16). The diminution in enantioselectivity is likely affected by the same factors, as it is possible that the methyl substituent can cause distortion of the complex through interaction with the proximal amide, disrupting transition state organization. It is noteworthy, that addition remains *Z*-selective, indicating that factors previously described (including *syn*-pentane interaction in **3.104**) are probably significant.

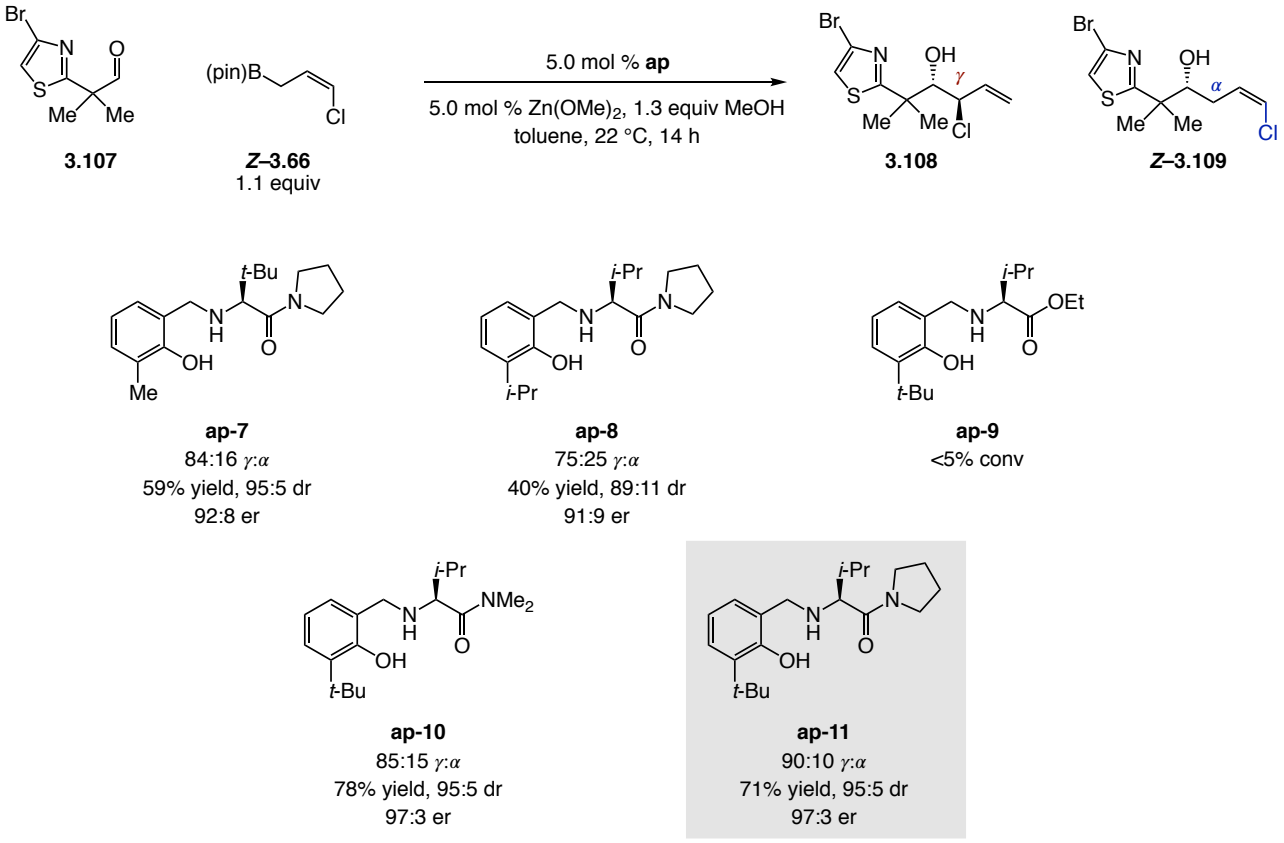
Scheme 3.16. Rationale for Diminished Selectivity



3.3.4 γ-Selective Additions to Aldehydes

Another notable observation was that the minor γ-product was enantioenriched. We reasoned that with appropriate adjustments to the structure of the aminophenol and altered reaction conditions, we might be able to access both *Z*-alkenyl chlorides and chlorohydrins. For initial optimization, we carried out additions to aliphatic aldehyde **3.107**, reasoning that hindrance engendered by the *gem*-dimethyl group would afford a greater chance for competitive boryl shift.

Scheme 3.17. Identification of an Effective Catalyst for γ-Addition[a]



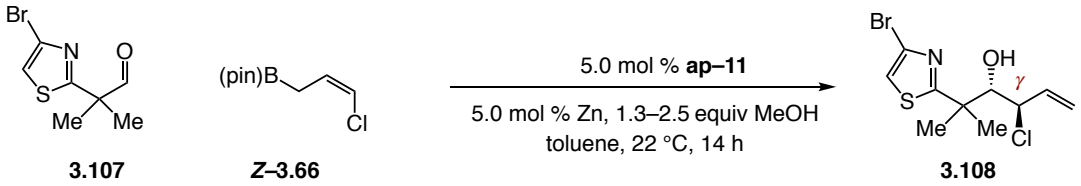
[a]Performed reagent under an atmosphere of dry N_2. Conv, α:γ and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of **3.107.** Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

As discussed in Section 3.3.3, to achieve α selectivity, the effective concentration of aldehyde must remain sufficiently high. We reasoned if the concentration of substrate could be decreased through a combination of diluting the reaction mixtures and forgoing excess aldehyde, boryl shift (which proceeds in an intramolecular fashion and is likely not dependent on aldehyde concentration) could be favored. Indeed, this was the case.

We probed a series of aminophenol compounds. Drawing upon insight from studies regarding γ-addition to phosphinoyl imines (Chapter One), we hoped a combination of a small aryl substituent and a *tert*-leucine residue may lead to optimal regio- and enantioselectivity.

Accordingly, we synthesized **ap-7** and isolated **3.108** in 84:16 γ:α ratio, 95:5 dr and 92:8 er. We found that similar selectivity, and improved enantioselectivity were obtained with catalysts bearing a *t*-Bu group on the arene, **ap-10–11**, and optimal results were obtained with **ap-11**.

Table 1. Further Optimization Towards γ-Selective Addition[a]



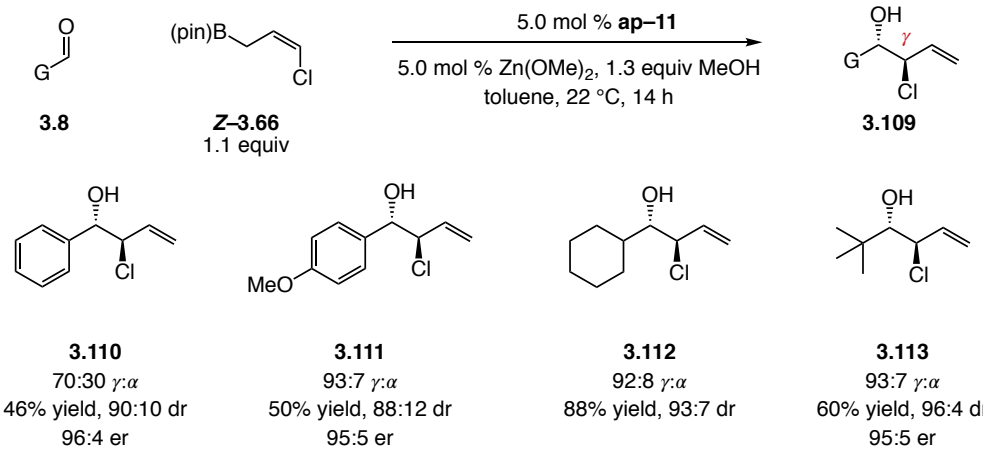
3.107 ***Z*–3.66** **3.108**

Entry	Modification of Reaction Conditions	γ:α	yield	dr	er (γ-add. isomer)[c]
1	[c] = 0.08 M	82:18	68	81:19	97:3
2	2.5 mol % $Zn(OMe)_2$	83:17	71	90:10	97:3
3	5.0 mol % $Zn(O\textit{t}\text{-Bu})_2$	85:15	77	95:5	96:4
4	1.5 equiv ***Z*–3.66**	80:20	65	93:7	97:3
5	2.5 equiv MeOH	83:17	73	94:6	96:4

[a]Performed under an atmosphere of dry N_2. Conv, α:γ and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of **3.107.** Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

Further dilution of the reaction mixture led to efficient addition; however, this was at the expensive of diastereoselectivity (Table 1, entry 1). Altering the loading or the identity of the zinc(II) salt, or increasing the polarity of the media (entries 2-3, 5) had little effect. Thus, with 5.0 mol % **ap-11**, 5.0 mol % $Zn(OMe)_2$ and 1.3 equivalents of methanol, we explored the scope of the method. In each case, the transformation was γ-selective, although electron-rich *para*-methoxyphenyl substituted **3.111** and hindered aliphatic aldehydes **3.112–113** were more suitable as compared to benzaldehyde **3.110**.

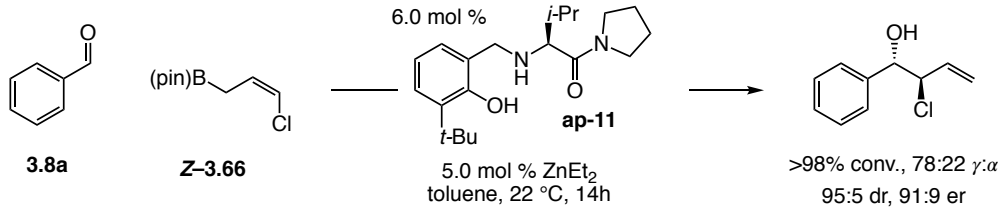
Scheme 3.18. Representative γ-Selective Addition[a]



[a]Performed under an atmosphere of dry N_2. Conv, α:γ and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of **3.8.** Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

It is noteworthy that the transformation may be carried out with diethyl zinc in the absence of an alcohol. γ Selectivity, as well as diastereoselectivity were improved compared to trials carried out with $Zn(OMe)_2$, nonetheless, this was at the expense of enantioselectivity (91:9 vs 96:4 er). This corresponds to a significant energetic difference and indicates that in the presence of the more nucleophilic promoter, competitive non-catalyzed pathways might be responsible for such erosion.

Scheme 3.19. Transformation Promoted by Dialkyl Zinc[a]

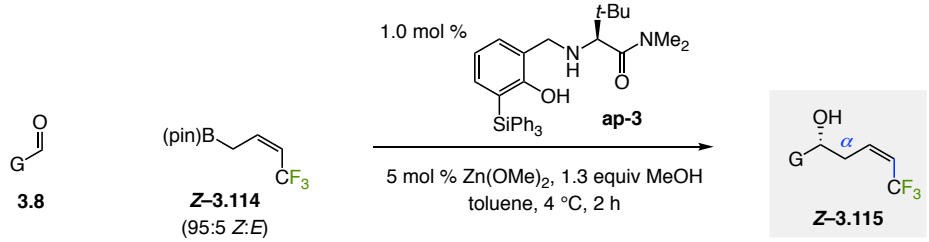


[a]Performed reagent under an atmosphere of dry N_2. Conv, α:γ and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of **3.8a.** Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

3.3.5 Synthesis of Homoallylic Alcohols Bearing a Z–CF_3 Motif

The scope of the method is not limited to synthesis of *Z*-alkenyl halides; boronates possessing a withdrawing trifluoromethyl methyl group may be employed with efficiency and α selectivity.

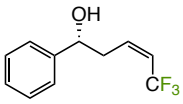
Scheme 3.20. Scope of Aryl and Heteroaryl-Substituted Homoallylic Alcohols[a]



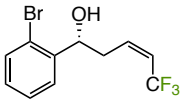
3.8

***Z*–3.114**
(95:5 *Z*:*E*)

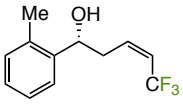
***Z*–3.115**



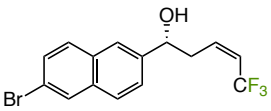
***Z*–3.116**
95:5 α:γ
83% yield, 94:6 *Z*:*E*
95:5 er



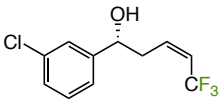
***Z*–3.117**
>98:2 α:γ
91% yield, 93:7 *Z*:*E*
98:2 er



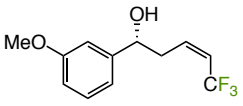
***Z*–3.118**
93:7 α:γ
91% yield, 94:6 *Z*:*E*
97:3 er



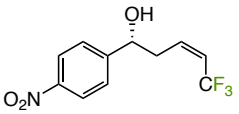
***Z*–3.119**
97:3 α:γ
93% yield, 95:5 *Z*:*E*
98:2 er



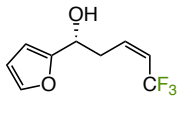
***Z*–3.120**
97:3 α:γ
93% yield, 94:6 *Z*:*E*
98:2 er



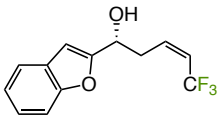
***Z*–3.121**
91:9 α:γ
86% yield, 92:8 *Z*:*E*
97:3 er



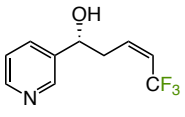
***Z*–3.122**
>98:2 α:γ
98% yield, 98:2 *Z*:*E*
98:2 er



***Z*–3.123**
91:9 α:γ
82% yield, 81:19 *Z*:*E*
93:7 er



***Z*–3.124**
>98:2 α:γ
94% yield, 87:13 *Z*:*E*
95:5 er



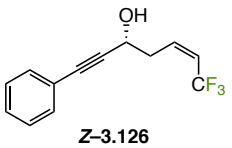
***Z*–3.125**
98:2 α:γ
89% yield, 91:9 *Z*:*E*
92.5:7.5 er

[a]Performed under an atmosphere of dry N_2. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). Experiments were conducted at least in triplicate. See Experimental Section for details.

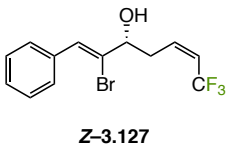
Methods for synthesis of this class of compounds in a stereoselective manner are crucial to advancing recent developments for 1,2-functionalization of trifluoromethyl substituted alkenes.[34] Sterically hindered substrates, such as ***Z*–3.117** and ***Z*–3.118**, were subjected to addition with efficiency and α selectivity (>98:2 and 93:7 α:γ ratio, respectively). With electron-deficient *para*-NO_2-substituted ***Z*–3.122**, boryl shift may be preempted and the product was isolated as a single regioisomer. Heteroaryl cases are suitable as evidenced by ***Z*–3.123-125**, although *Z* selectivity was diminished for 2-substituted cases. This is likely owing to development of electron-electron repulsion between the oxygen of the heterocycle and the allylic trifluoromethyl group, allowing greater chance for competitive modes to become more predominant. It is evident that in these cases, steric factors play a role, as the larger benzofuranyl-substituted ***Z*–3.118** underwent reaction with higher *Z* selectivity, as compared to the furanyl case. Electron-deficient and unhindered alkyne ***Z*–3.126** was generated as a single regioisomer in 94:6 *Z*:*E* ratio and 97:3 er. Substrates bearing trisubstituted olefins ***Z*-3.127** and ***Z*-3.128** reacted smoothly, furnishing product in 98.5:1.5 and 92:8 er, respectively. Furthermore, in accordance with results obtained for additions of chloro-substituted boronates, aldehydes lacking an α-substituent were found to be less enantioselective and alkyl-subsituted ***Z*–3.129** was generated in 88:12 er.

34) (a) Corberan, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079–7082. (b) Liu, Y.; Zhou, Y.; Zhao, Y.; Qu, J. *Org. Lett.* **2017**, *19*, 946–949. (c) Kojima, R.; Akiyama, S.; Ito, H. *Angew. Chem. Int. Ed.* **2018**, *57*, 7196–7199. (d) Gao, P.; Yuan, C.; Zhao, Y.; Shi, Z. *Chem* **2018**, *4*, 2201–2211. (e) Zhao, X.; Li, C.; Wang, B.; Cao, S. *Tetrahedron Lett.* **2019**, *60*, 129–132.

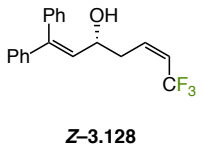
Scheme 3.21. Additions of Cl-Substituted Allyl Boronates to Alkynyl-, Alkenyl- and Aliphatic Aldehydes[a]



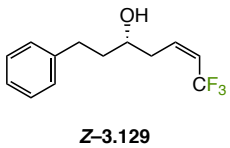
***Z*–3.126**
>98:2 α:γ
93% yield, 94:6 *Z*:*E*
97:3 er



***Z*–3.127**
97:3 α:γ
93% yield, 90:10 *Z*:*E*
98.5:1.5 er



***Z*–3.128**
92:8 α:γ
78% yield, 92:8 *Z*:*E*
92:8 er



***Z*–3.129**
70:30 α:γ
65% yield, 83:17 *Z*:*E*
88:12 er

[a]Performed under an atmosphere of dry N_2. Conv, α:γ and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). Experiments were conducted at least in triplicate. See Experimental Section for details.

3.3.6 Application to Synthesis of Mycothiazole

Next, we set out to demonstrate the utility of the method by a concise total synthesis of anti-tumor agent mycothiazole (Scheme 3.1).[35] Isolated from *Cacospongia mycofijiensis*, the marine alkaloid exhibits nanomolar (0.36–13.8 nM) activity against small and non-small cell lung cancer lines. Degradation studies have elucidated that the thiazole component is essential for bioactivity, and the compound is cytostatic rather than cytotoxic, requiring a 12 hour incubation period before activation.[36] We envisaged a method affording access to the heterocyclic core that is amenable to further functionalization and the development of new therapeutic candidates.

Synthesis of mycothiazole has been previously reported by Hale and co-workers in 2015,[37] commencing from enantioenriched epoxy alcohol **3.131**. Similar to Panek's work (see section

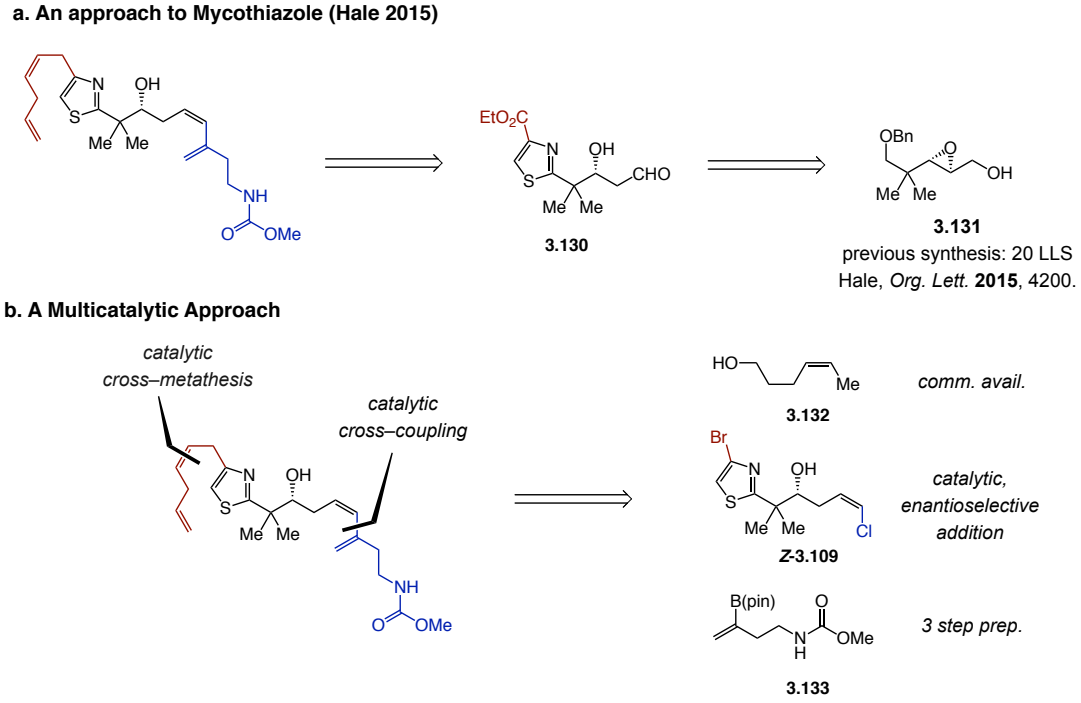
35) (a) Crews, P.; Kakou, Y.; Quiñoà, E. *J. Am. Chem. Soc.* **1998**, *110*, 4365–4368. (b) Sonnenschein, R. N.; Johnson, T. A.; Tenney, K.; Valeriote, F. A.; Crews, P. *J. Nat. Prod.* **2006**, *69*, 145–147. (c) Morgan, J. B.; Mahdi, F.; Liu, Y.; Coothankandaswamy, V.; Jekabsons, M. B.; Johnson, T. A.; Sashidhara, K. V.; Crews. P.; Nagle, D. G.; Zhou, Y.-D. *Bioorg. Med. Chem.* **2010**, *18*, 5988–5994.

36) Meyer, K. J.; Singh, A. J.; Cameron, A.; Tan, A. S.; Leahy, D. C.; O'Sullivan, D.; Joshi, P.; La Flamme, A. C.; Northcote, P. T.; Berridge, M. V.; Miller, J. H. *Mar. Drugs* **2012**, *10*, 900–917.

37) Wang, L.; Hale, K. J. *Org. Lett.* **2015**, *17*, 4200–4203. For other studies describing synthesis towards mycothiazole, see: (a) Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Org. Lett.* **2000**, *2*, 2149–2152. (b) Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Tetrahedron* **2003**, *59,* 6579–6593. (c) Le Flohic, A.; Meyer, C.; Cossy, J. *Org. Lett.* **2005**, *7*, 339–342. (d) Le Flohic, A.; Meyer, C.; Cossy, J. *Tetrahedron* **2006**, *62*, 9017–9037. (e) Rega, M.; Candal, P.;

3.2.1), the *Z*-homoallylic alcohol was introduced through a series of oxidation state manipulations affording aldehyde **3.130**, which may be then be converted to a *Z*-alkenyl iodide through Wittig olefination and then elaborated further by a cross-coupling reaction. Alternatively, the heterocyclic core ***Z*–3.109** may be accessed through catalytic, enantioselective α addition to the corresponding aldehyde. The *Z*-diene could then be appended through catalytic stereoretentive cross-coupling and the skipped diene could be introduced by cross-metathesis,[38] followed by dehydration.

Scheme 3.22. Strategies for Synthesis of Mycothiazole

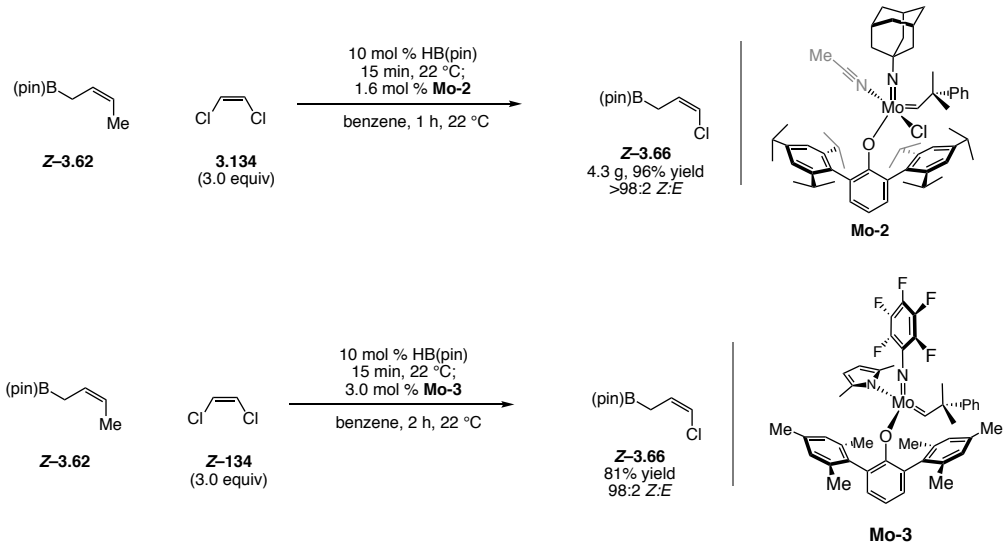


Jiménez, C.; Rodríquez, J.; *Eur. J. Org. Chem.* **2007**, 934–942. (f) Batt, F.; Fache, F. *Eur. J. Org. Chem.* **2011**, 6039–6055.

38) (a) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 10258–10261. (b) Koh, M. J.; Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 1968–1972. (c) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. *Nature* **2015**, *517*, 181–186.

We began by identifying an efficient catalyst for scalable preparation of ***Z*–3.66**. We found **Mo-2** to be optimal, furnishing the desired allylic boronate in one hour, as a single stereoisomer.[39] Recent studies had informed us that if cross partners ***Z*-3.62** and **3.134** were treated with 10 mol % of pinacolborane, prior to addition of a solution of Mo-based complex, trace amounts of moisture or residual pinacol that can sequester the catalyst may be consumed, thus enabling catalyst loadings to be lowered to 1.6 mol %.[40] Furthermore, olefin metathesis was efficient when promoted by commercially available **Mo-3**. Following the same procedure for pretreatment with pinacolborane, just 3.0 mol % of the complex was required, generating ***Z*–3.66** in 81% yield and 98:2 *Z*:*E* ratio. An added benefit of employing a Mo-based complex is that purification may be carried out by distillation, allowing for efficient separation from residual metal salts.

Scheme 3.23. Efficient, Scalable Access to *Z*-Alkenyl Halides[a]



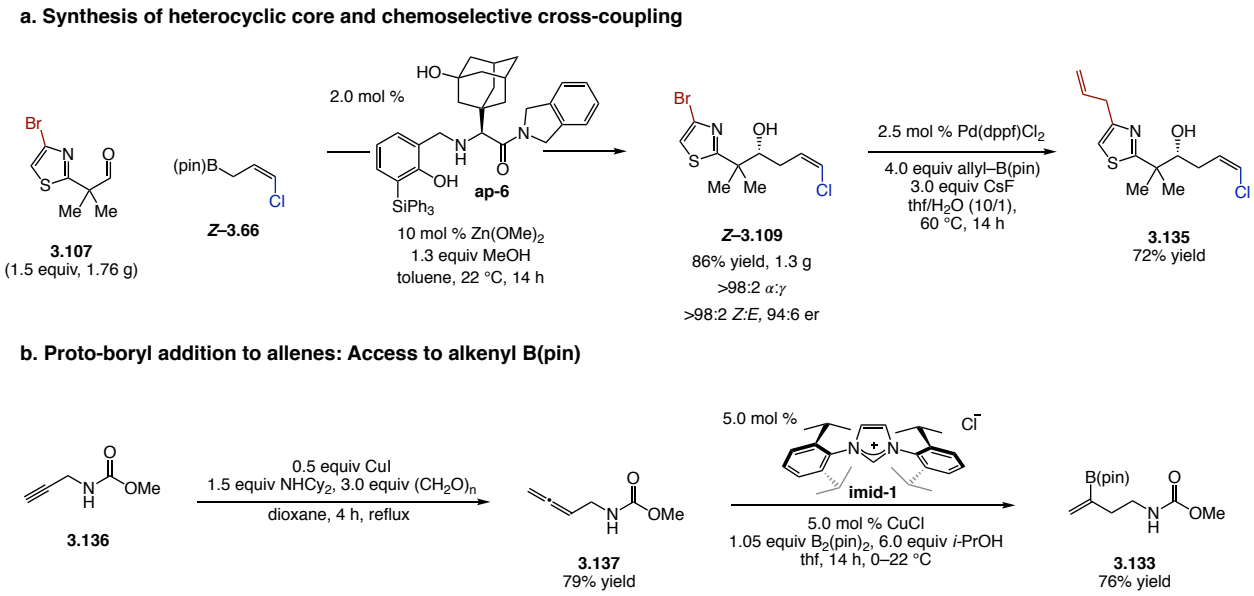
[a]All reactions were performed under N_2 atm. Conv and *Z*:*E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Conv refers to disappearance of ***Z*–3.62**. Yield of isolated and purified product (±5%). pin: pinacolato. See Experimental Section for details.

39) (a) Lam, J. K.; Zhu, C.; Bukhryakov, K. V.; Müller, P.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2016**, *138*, 15774–15783. (b) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature*, **2017**, *542*, 80–85.

40) Mu, Y.; Nguyen, T.; van der Mei, F. W.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 5365–5370.

Addition of ***Z*–3.66** to aldehyde **3.107**, accessible in two steps according to a protocol reported by Cossy,[37d] proceeded under optimal conditions affording ***Z*–3.109** in 86% yield, >98:2 α:γ ratio and 94:6 er. The excess aldehyde was recovered in 97% yield. Next, we carried out a chemoselective cross-coupling of the aryl bromide within the thiazole and allyl–B(pin), through a phosphine-Pd-catalyzed reaction under conditions outlined by Aggarwal.[41]

Scheme 3.24. Preparation of Fragments for Cross-Coupling[a]



[a]Performed under an atmosphere of dry N_2. Conv, α:γ and *Z:E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

To obtain the desired boronate to be employed for stereoretentive cross-coupling, we employed catalytic proto-boryl addition under modified conditions, previously developed in our laboratory. [42] Allene **3.137** was synthesized through Crabbé homologation [43] of propargyl carbamate **3.136**. We found that in this case, sterically hindered **imid-1** was essential for

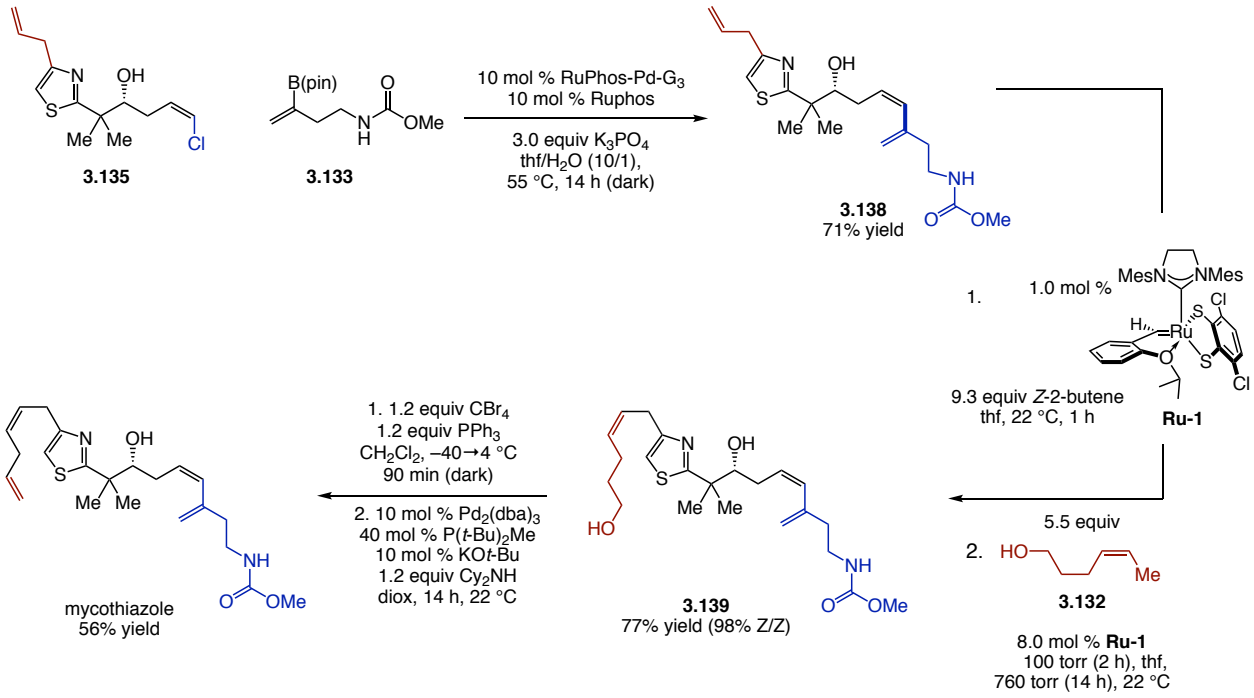
41) Zhurakovsky, O.; Türkmen, Y. E.; Löffler, L. E.; Moorthie, V. A.; Chen, C. C.; Shaw, M. A.; Crimmin, M. R.; Ferrara, M.; Ahmad, M.; Ostovar, M.; Matlock, J. C.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2018**, *57*, 1346–1350.

42) Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett.* **2013**, *15*, 1414–1417.

43) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763–1765.

regioselective copper-boryl additon since the sizable *ortho* substituents of the *N*-aryl rings favored positioning of the NHC-Cu complex in the least hindered terminal site. Selectivity could be further improved when isopropanol was employed as the proton source, allowing us to isolate **3.133** in 76% yield.

Scheme 3.25. Endgame of Synthesis of Mycothiazole[a]



[a]Performed under an atmosphere of dry N_2. Conv, and *Z:E* ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; Yield of isolated and purified product (±5%). Reactions run at least in triplicate. dba: dibenzylidene acetone; dppf: 1,1'-bis(diphenylphosphino)ferrocene; ruphos: 2-dicyclohexylphosphino-2,6'-diisopropoxybiphenyl; diox: 1.4-dioxane. See Experimental Section for details.

Out next objective was to join fragments **3.135** and **3.133** to forge the desired diene. After considerable optimization, we discovered that a class of Pd-based complexes developed by Buchwald[44] were competent, although the reaction was not stereoretentive. Control experiments allowed us to identify that the diene was prone to isomerization in the presence of a Pd-based complex (at >65 °C); this was circumvented by carrying out the transformation at 55 °C in the

44) (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916–920. (b) Bruno, N. C.; Niljiasnskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161–4166.

absence of light. Upon filtration through silica gel to remove palladium salts, the desired compound **3.138** was isolated as a single stereoisomer.

To complete the synthesis, we carried out *Z*-selective cross-metathesis of **3.138** and **3.132** in the presence of **Ru-1**. For maximum efficiency, we first treated **3.138** with an excess of *Z*-2-butene and **Ru-1** to convert the terminal olefin to the derived disubstituted olefin. This was necessary because previous studies had indicated that Ru-methylidene are more susceptible to decomposition.[45]

We were then able to complete the total synthesis of mycothiazole through a two-step sequence for preparation of the skipped diene. First, the primary alcohol was converted to an alkyl bromide according to a modified procedure disclosed by Shiori,[46] in a dilute solution coupled with slow addition of triphenyl phosphine to prevent decomposition of reaction intermediates. The freshly prepared bromide was then subjected to elimination under conditions outlined by Fu, which prevented isomerization of the newly formed diene.[47] We were thus able to generate ~250 mg of mycothiazole.

3.4 Conclusions

In summary, through mechanistic understanding we were able to determine that additions of *Z*-substituted allyl boronates to aldehydes may be carried out with exceptional enantio- and *Z* selectivity. We adopted a similar approach to identify an effective way to synthesize regioisomeric chlorohydrin products. The protecting group free total synthesis of mycothiazole highlights the considerable utility of the catalytic approach, and is expected to be applicable to preparation of a variety of other complex bioactive molecules.

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45) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919–10928.

46) Sugiyama, H.; Yokokawa, F.; Shiori, T. *Org. Lett.* **2000**, *2*, 2149–2152.

47) Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232–14337.

3.5 Experimental Section

3.5.1 General

Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz), or 600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br s = broad singlet, m = multiplet, app = apparent), coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). ^{19}F NMR spectra were recorded on a Varian Unity INOVA 400 (376 MHz) spectrometer. Chemical shifts are reported in ppm with $C_6H_5CF_3$ as an external standard ($C_6H_5CF_3$: –63.72 ppm). Data are reported as follows: chemical shift, multiplicity, coupling constants (Hz), and integration. Carbons with directly attached boron atoms were not observed in some compounds, most likely due to quadrupolar relaxation.[1] High-resolution mass spectrometry was performed on a JEOL AccuTOF DART (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomeric ratios were determined by high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Chiral Technologies Chiralcel OD-H (4.6 x 250 mm), Chiralcel OJ-H (4.6 x 250 mm), Chiralcel OZ-H (4.6 x 250 mm), Chiralpak AD-H (4.6 x 250 mm), Chiralpak AS-H (4.6 x 250 mm)) in comparison with authentic racemic materials. Specific rotations were measured using either an Atago AP-300 Automated Polarimeter or a Rudolph Research Analytical Autopol IV Polarimeter. Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene was purified through a copper oxide and alumina column. Dimethoxy ethane and tetrahydrofuran were freshly distilled from a sodium and benzophenone ketyl solution. $CDCl_3$ was purchased from Cambridge Isotope Laboratories and store over activated 4Å molecular sieves prior to use. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher Scientific) in air.

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1) Wrackmeyer, B. *Prog. NMR Spectrosc.* **1979**, *12*, 227–259.

3.5.2 Reagents

Aldehydes were purchased from commercial sources. Liquid aldehydes were distilled over CaH_2 prior to use. Crystalline aldehydes were purified by silica gel chromatography.
Allylboronic acid pinacol ester was purchased from Frontier and distilled over CaH_2.
Bis(1,5-cyclooctadiene)nickel(0) (Ni(cod)) was purchased from Strem and used as received.
1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride (imid-1) was purchased from Strem and used as received.
[(*S*)-(-)-5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole][4-cyano-3-nitrobenzenecarboxylato][1,2,3-η-2-propenyl]iridium(III) was synthesized according to a literature procedure.[2]
[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane was purchased from Sigma-Aldrich and used as received.
Bis(pinacolato)diboron was purchased from Frontier Scientific and recrystallized from pentane.
2-Bromopropene was purchased from Sigma-Aldrich and used as received.
(2*S*)-[(*tert*-Butoxycarbonyl)amino](3-hydroxytricyclo[3.3.1.13,7]decan-1-yl)ethanoic acid was purchased from ArkPharm and used as received.
***Z*-2-Butene** was purchased from Sigma-Aldrich and stored as a solution in tetrahydrofuran over 4Å molecular sieves.
Calcium Hydride was purchased from Strem and used as received.
Carbon tetrabromide was purchased from Alfa Aesar and used as received.
Cesium fluoride was purchased from Sigma-Aldrich and used as received.
Chloro-3-methyl-2-butene was purchased from Alfa Aesar and used as received.
Chlorotriethylsilane was purchased from Oakwood and used as received.
Cis-1,1,1,4,4,4,-Hexafluoro-2-butene was purchased from CarboSynth.
***Z*-Crotylboronic acid pinacol ester, 97% (*Z*-1a)** was purchased from Sigma-Aldrich or Santa-Cruz and distilled over CaH_2 prior to use.
Copper(I) chloride was purchased from Strem and used as received.
Copper(I) iodide was purchased from Strem and used as received.
***d_2*-Allyl boronic pinacol ester** was synthesized according to a literature procedure.[3]
2,4-Dibromothiazole was purchased from Combi-Blocks and used as received.
***E*-1,2-Dichloroethylene** was purchased from TCI and used as received.
***Z*-1,2-Dichloroethylene** was purchased from TCI and distilled over CaH_2 prior to use.
Dicyclohexylamine was purchased from Sigma-Aldrich and used as received.
2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (ruphos) was purchased from Strem and used as received.

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2) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350–2354.

3) Sieber, J. D.; Morken, J. P.. *J. Am. Chem. Soc.* **2008**, *130*, 4978–4983.

(2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (ruPhos-Pd-G3) was purchased from Strem and used as received.
***N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC•HCl)** was purchased from Advanced ChemTech and used as received.
4-Dimethylaminopyridine was purchased from Oakwood and used as received.
Di-*tert*-butylmethylphosphine was purchased from Strem and used as received.
***Z*-4-Hexenol** was purchased from Alfa Aesar and used as received.
Hexylzinc bromide solution 0.5 M in THF was purchased from Alfa Aesar and used as received.
Hydrochloric acid (4M in dioxane) was purchased from Acros and used as received.
1-Hydroxybenzotriazole hydrate was purchased from Oakwood and used as received.
Isoindoline hydrochloride was purchased from Combi-Blocks and used as received.
Magnesium Sulfate was purchased from Oakwood and used as received.
Magnesium turnings were purchased from Sigma-Aldrich and used as received.
Methanol was purchased from Acros (99.8% anhydrous) and used as received.
Methyl chloroformate was purchased Sigma-Aldrich and used as received.
4-Nitrobenzoyl chloride was purchased from Sigma-Aldrich and used as received.
N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester was purchased from Alfa Aesar and used as received.
Osmium tetroxide (4 wt % in H_2O) was purchased from Strem and used as received.
Paraformaldehyde was purchased from Sigma-Aldrich and used as received.
Pinacolborane was purchased from Oakwood and distilled over CaH_2 prior to use.
Potassium phosphate tribasic (K_3PO_4) was purchased from Fisher Scientific and dried under vacuum at 60 °C overnight prior to use.
Potassium *tert*-butoxide was purchased from Strem and used as received.
Propargyl amine was purchased from Combi-Blocks and used as received.
Sodium borohydride was purchased from Sigma-Aldrich and used as received.
Sodium periodate was purchased from Alfa Aesar and used as received.
Sodium *tert*-Butoxide was purchased from Strem and used as received.
Tetrakis(triphenylphosphine)palladium(0) was purchased from Strem and used as received.
***Trans*-1-octen-1-ylboronic acid pinacol ester** was purchased from Sigma-Aldrich and used as received.
Tricyclohexylphosphine was purchased from Strem and used as received.
Triethylamine was purchased from Sigma-Aldrich and used as received.
Triphenylphosphine was purchased from Sigma-Aldrich and used as received.
Tris(dibenzylideneacetone)dipalladium(0) was purchased from Oakwood and used as received.
Zinc methoxide was purchased from Sigma-Aldrich and used as received.
(*Z*)-4,4,5,5-Tetramethyl-2-(2-methylhept-2-en-1-yl)-1,3,2-dioxaborolane (3.95) was prepared as described in Scheme 7 of the manuscript. Cross-coupling was carried out under the conditions

reported previously,[4] and described as follows. In an N_2-filled glove box, an oven-dried flask equipped with a stir bar was charged with CsF (1.09 g, 7.3 mmol), 1-pentenylboronic acid (376.0 mg, 3.3 mmol), $Pd(PPh_3)_4$ (104.0 mg, 0.09 mmol) and 2-bromopropene (0.27 mL, 3.0 mmol). The flask was then equipped with an oven-dried reflux condenser, sealed (septum and electrical tape) and removed from the glovebox. The mixture was diluted with benzene (15 mL) and allowed to stir for 16 h at 70 °Che mixture was then allowed to cool to 22 °C and pass through a short (~3 cm high x 5 cm wide; pentane). The filtrate was concentrated in an ice bath (4 °C) to ~4 mL of solution volume to obtain a 4.7 wt% solution of (*E*)-2-methylhepta-1,3-diene in benzene. Catalytic 1,4-hydroboration was then performed as described formerly,[5] and as follows. In an N_2-filled glove box, an oven-dried flask equipped with a stir bar was charged with $Ni(cod)_2$ (20.7 mg, 0.075 mmol), PCy_3 (21.0 mg, 0.075 mmol), pinacolborane (0.24 mL, 1.65 mmol) and (*E*)-2-methylhepta-1,3-diene (3.47 g, 4.7 wt% in benzene). The flask was sealed (septum and electrical tape) and removed from the glovebox and the solution was allowed to stir for 3 h. The volatiles were removed to ~20% of the original volume and the resulting oil residue was purified by silica gel chromatography (silica gel dried at 130 °C for 12 h before use; 50:1 pentane:Et_2O) to afford **3.95** as colorless oil (266.8 mg, 34% overall yield). **IR (neat):** 2975 (m), 2924 (m), 1350 (s), 1320 (s), 1141 (s), 967 (m), 847 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.11 (tq, *J* = 7.1, 1.3 Hz, 1H), 1.94 (q, *J* = 6.6 Hz, 2H), 1.73 (q, *J* = 1.3 Hz, 3H), 1.65 (s, 2H), 1.30 (tt, *J* = 5.1, 2.4 Hz, 4H), 1.23 (s, 12H), 0.93 – 0.78 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 167.6, 131.8, 124.0 (d, *J* = 13.5 Hz) 97.6, 83.1, 32.0, 28.0, 25.7 (m), 24.7, 22.4, 14.1; **HRMS (DART):** Calcd for $C_{14}H_{28}BO_2$ $[M+H]^+$: 239.21769; Found: 239.21758.

(*Z*)-2-(3-Chloro-2-methylallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*Z*-3.97) was synthesized as described in Scheme 7 in the manuscript and described as follows. In a N_2-filled glovebox, an oven-dried vial equipped with a stir bar was charged with **3.95** (238.0 mg, 1.0 mmol, dried azeotropically with anhydrous benzene), *trans*-1,2-dichloroethylene (484.8 mg, 5.0 mmol) and pinacolborane (12.8 mg, 0.1 mmol) and the mixture was allowed to stir for 10 min. A solution of **Mo-1b** (1.0 M in benzene, 300 μL, 0.03 mmol) was added dropwise. The vial was sealed and the solution was allowed to stir for 4 h, at which point an aliquot was removed and analyzed by ^{1}H NMR spectroscopy, revealing ~98% consumption of **3.95**. The vial was removed from the glovebox and concentrated to ~50% of the original solution volume and passed through a small (3 cm high x 1 cm wide) plug of oven-dried silica (20:1 hexanes:Et_2O). The volatiles were removed in vacuo to afford yellow oil, which was purified by distillation (70–100 °C, 0.5 torr), furnishing ***Z*-3.97** as colorless oil. Analytical data is fully consistent with those reported previously.[6]

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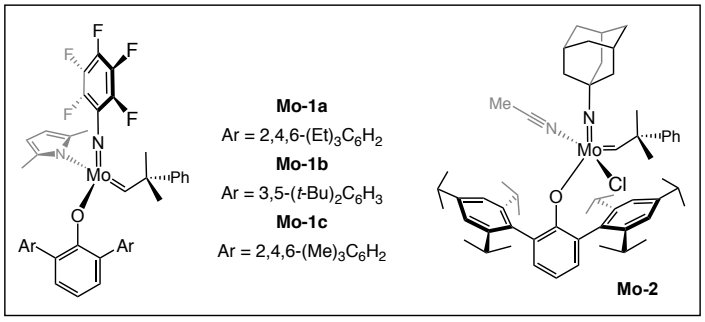
4) Burks, H. E.; Kilman, L. T. *J. Am. Chem. Soc.* **2009**, *131*, 9134–9135.

5) Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534–2535.

6) Nguyen, T. T.; Koh, M. J. Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature*, **2017**, *552*, 347–354.

(*Z*)-4,4,5,5-tetramethyl-2-(4,4,4-trifluorobut-2-en-1-yl)-1,3,2-dioxaborolane (*Z*-3.114) was synthesized according to a previously reported procedure.[7]

3.5.3 Olefin Metathesis Complexes



Mo-1a-b,[8] **Mo-2**[9] and **Ru-1**[10] was prepared according to a previously reported procedure, and **Mo-1c** was purchased from Strem and used as received.

3.5.4 Aminophenols

(2*S*)-2-((2-Hydroxy-3-(triphenylsilyl)benzyl)amino)-2-((1s,3*R*)-3-hydroxyadamantan-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one (ap-5): White crystalline solid; synthesized according to a reported procedure.[11] **M.p.** 155 – 158 °C, **IR (neat):** 3375 (br, m), 2915 (s), 2849 (m), 1623 (s), 1427 (s), 1107 (s), 908 (m), 735 (m), 701 (s), 508 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.61 (s, 1H), 7.66 – 7.57 (m, 6H), 7.45 – 7.30 (m, 9H), 7.12 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.73 (t, *J* = 7.3 Hz, 1H), 4.23 (d, *J* = 14.1 Hz, 1H), 3.64 (dt, *J* = 11.2, 6.6 Hz, 1H), 3.46 (d, *J* = 14.1 Hz, 2H), 3.21 (q, *J* = 8.4, 7.2 Hz, 1H), 3.05 – 2.81 (m, 2H), 2.56 (s, 1H), 2.09 (s, 2H), 1.85 (td, *J* = 10.4, 9.1, 4.6 Hz, 4H), 1.60 – 1.37 (m, 10H), 1.27 – 0.96 (m, 4H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.3, 163.2, 137.9, 136.4, 135.1, 131.1, 129.2, 127.6, 121.3, 120.8, 119.0, 68.5, 64.7, 50.3, 47.0, 46.4, 45.5, 44.4, 39.7, 37.9, 37.0, 35.2, 30.3, 30.2, 26.2, 24.2; **HRMS**

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7) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S. Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature*, **2017**, *542*, 80–85.

8) Lam, J. K.; Zhu, C.; Bukhryakov, K. V.; Müller, P.; Hoveyda A.; Schrock, R. R. *J. Am. Chem. Soc.* **2016**, *138*, 15774–15783.

9) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352,* 569–575.

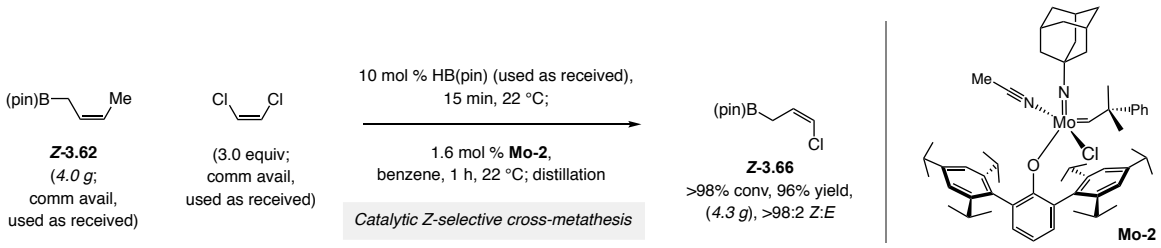
10) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. *Nature* **2015**, *517*, 181–186.

11) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H *Nature* **2013**, *494*, 216–221.

(DART): Calcd for $C_{41}H_{47}N_2O_3Si$ $[M+H]^+$: 643.33505; Found: 643.33497; **Specific Rotation:** $[\alpha]^{24.2}$ 23.0° (*c* 1.0, $CHCl_3$).

(2*S*)-2-((2-Hydroxy-3-(triphenylsilyl)benzyl)amino)-2-((1s,3*R*)-3-hydroxyadamantan-1-yl)-1-(isoindolin-2-yl)ethan-1-one (ap-6): White crystalline solid; **M.p.** 142 144 °C, **IR (neat):** 3303 (br, m), 2908 (m), 2849 (m), 1632 (s), 1425 (s), 1133 (s), 942 (s), 730 (s), 700 (s), 507 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.53 (s, 1H), 7.67 – 7.59 (m, 6H), 7.44 – 7.26 (m, 12H),7.22 – 7.00 (m, 2H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.64 (dd, *J* = 8.3, 6.6 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.79 (d, *J* = 16.2 Hz, 1H), 4.65 (d, *J* = 13.6 Hz, 1H), 4.39 (d, *J* = 13.6 Hz, 1H), 4.25 (d, *J* = 14.1 Hz, 1H), 3.48 (d, *J* = 14.0 Hz, 1H), 3.06 (s, 1H), 2.62 (s, 1H), 2.10 (s, 2H), 1.66 (m, 3H), 1.57 – 1.40 (m, 7H), 1.36 – 1.11 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.1, 163.2, 138.1, 136.4, 135.9, 135.8, 135.1, 131.3, 129.2, 128.0, 127.7, 127.6, 123.1, 122.6, 121.2, 120.9, 119.2, 68.5, 64.7, 52.7, 52.0, 50.5, 46.4, 44.5, 44.4, 39.9, 38.1, 37.1, 35.2, 30.3, 30.2; **HRMS (DART):** Calcd for $C_{45}H_{47}N_2O_3Si$ $[M+H]^+$:691.33505; Found: 691.33623; **Specific Rotation:** $[\alpha]^{25.2}$ 20.2° (*c* 0.8, $CHCl_3$).

3.5.5 Preparation of Z-Cl-Substituted Allyl Boronate Z-3.66



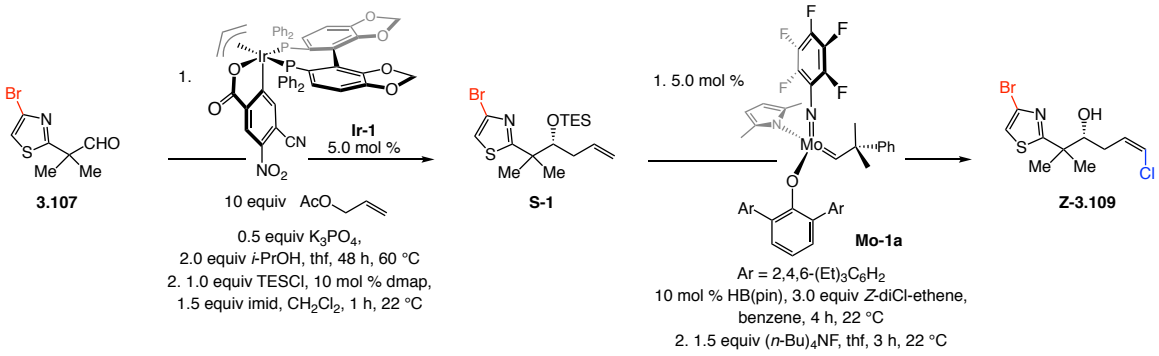
(*Z*)-2-(3-Chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*Z*-3.66). A previously reported procedure was used.[12] In a N_2-filled glovebox, *Z*-crotyl–B(pin) (**3.62**) (4.0 g, 21.9 mmol) and *Z*-dichloroethylene (6.4 g, 66 mmol) were added to an oven-dried 40 mL vial equipped with a stir bar. Pinacolborane (320 μL, 2.2 mmol) was added (gentle release of gas). The mixture was sealed with a cap and allowed to stir for 10 min (22 °C). A solution of **Mo-2** (333 mg, 0.35 mmol) in benzene (3.5 mL) was slowly added to the solution. The vial was capped and the mixture was allowed to stir for 1 h. The vial was removed from the glovebox and the volatiles were evaporated in vacuo. The resulting black oil residue was purified by (short path) distillation to afford the desired product as colorless oil (4.3 g, 96% yield, >98:2 *Z*:*E*). When performing the cross-metathesis reaction with complex **Mo-1c**, the volatiles must first be removed from the unpurified mixture, the residue triturated with pentane and then passed through a small cotton plug prior to distillation to afford yellow oil.

12) (a) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347–354. (b) Mu, Y.; Nguyen, T. T.; van der Mei, F. W.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2019**, *58*, 5365–5370.

3.5.6 Representative Procedure for Catalytic Enantioselective Additon

In a N_2-filled glovebox, a stock solution of **ap-6** and zinc(II) methoxide was prepared. An oven-dried vial (8 mL) equipped with a stir bar was charged with aminophenol (**ap-6**) (5.5 mg, 0.008 mmol), zinc methoxide (5.1 mg, 0.04 mmol) and toluene (2.0 mL). The freshly prepared stock solution was allowed to stir for 15 min at 22 °C. In another vial (8 mL), aldehyde (0.15 mmol) was weighed out. The aminophenol/$Zn(OMe)_2$ stock solution was then added by syringe (500 μL). *Z*-Chloro-allyl–B(pin) (***Z*-3.66**) (20.2 mg, 0.1 mmol), was added followed by MeOH (5 μL, 0.13 mmol). The reaction vessel was equipped with a stir bar, sealed with a cap removed from the glovebox. The mixture was allowed to stir for 14 h at 22 °C, at which time the reaction was quenched by the addition of MeOH (1.5 mL). The mixture was then allowed to stir for 0.5 h at 22 °C. The volatiles were removed in vacuo and the resulting opaque oil was purified by silica gel chromatography (10:1–4:1 hexanes:Et_2O) to afford the desired homoallylic alcohol typically as colorless oil).

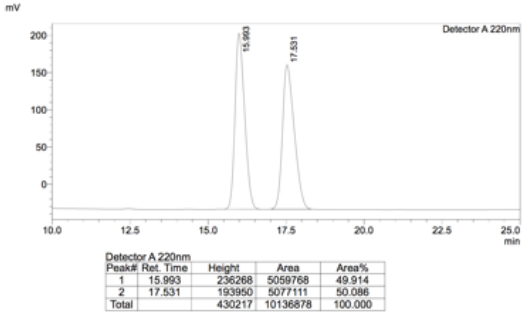
3.5.7 Terminal Olefin Approach

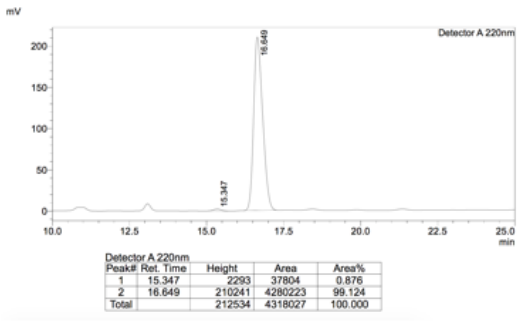


Enantiomerically enriched homoallylic alcohol **S-1** was synthesized according to a previously reported procedure,[2] and as follows. In a N_2-filled glovebox, an oven-dried vial equipped with a magnetic stir bar was charged with aldehyde **3.107** (46.8 mg, 0.2 mmol), **Ir-1** (10.3 mg, 0.01 mmol), K_3PO_4 (21.5 mg, 0.1 mmol) and thf (1.0 mL). The vial was sealed (septum and electrical tape) before being removed from the glovebox. Isopropanol (31 μL, 0.4 mmol), H_2O (18 μL, 1.0 mmol) and allyl acetate (214 μL, 2.0 mmol) were added sequentially and the mixture was allowed to stir for 30 min before being placed in an oil bath at 60 °C and allowed to stir for 48 h. The mixture was then allowed to cool to 22 °C and the volatiles were removed in vacuo to afford yellow oil (^{1}H NMR analysis revealed ~83% consumption of **3.107**), which was purified by silica gel chromatography (gradient 100:0 → 3:1 hexanes:Et_2O) to afford colorless oil (28.4 mg, 52% yield). **Please note:** this yield is unoptimized. An oven-dried vial was charged with a solution of the aforementioned homoallylic alcohol in CH_2Cl_2 (1.0 mL), imidazole (10.5 mg, 0.15 mmol) and TESCl (18 μL, 0.1 mmol) and the mixture was allowed to stir for 1 h. The volatiles were removed

in vacuo to afford white oil, which was purified by silica gel chromatography (gradient 100:0 to 10:1 hexanes:Et_2O) to afford **S-1** as colorless oil (39.1 mg, 82% yield).

(*R*)-4-Bromo-2-(2-methyl-3-((triethylsilyl)oxy)hex-5-en-2-yl)thiazole (S-1): IR (neat): 2952 (m), 2873 (m), 1463 (m), 1257 (s), 1097 (s), 1002 (s), 910 (m), 725 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.09 (s, 1H), 5.85–5.52 (m, 1H), 5.10–4.74 (m, 2H), 4.01 (dd, *J* = 7.0, 4.0 Hz, 1H), 2.52–2.17 (m, 1H), 2.10–1.89 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.68–0.22 (m, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 179.5, 135.9, 123.7, 116.5, 116.1, 79.2, 46.6, 38.3, 25.6, 24.5, 7.0, 5.3; **HRMS (DART):** Calcd for $C_{16}H_{29}OSiSBr$ $[M+H]^+$: 390.09170; Found: 390.09159; **Specific Rotation:** $[\alpha]^{23.8}$ 2.0° (*c* 1.2, $CHCl_3$) for a 99:1 er sample of the derived alcohol. Enantiomeric purity of the derived alcohol was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 99:1 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 15.4 min (minor) and 16.6 min (major).





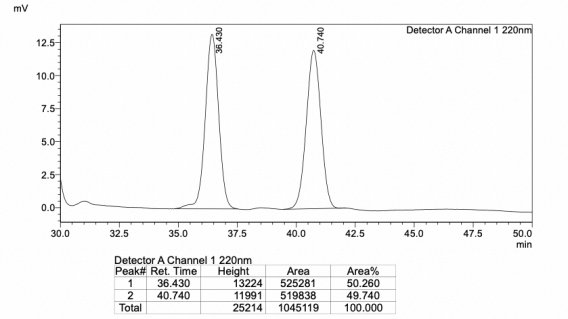
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	15.993 min	5059768	49.914	1	15.347 min	37804	0.876
2	17.531 min	5077111	50.086	2	16.649 min	4280228	99.124

In a N_2-filled glovebox, an oven-dried vial equipped with a stir bar was charged with **S-1** (39.0 mg, 0.1 mmol, azeotropically dried with anhydrous benzene), *cis*-1,2-dichloroethylene (29.1 mg, 0.3 mmol), and pinacolborane (1.3 mg, 0.01 mmol) and the mixture was allowed to stir for 10 min. To the solution was added a solution of **Mo-1a** (1.0 M in benzene, 50 μL, 0.005 mmol) dropwise. The vial was sealed and the mixture was allowed to stir for 4 h, at which point an aliquot was removed and analyzed by 1H NMR spectroscopy, revealing ~48% consumption of **S-1**. The vial was removed from the glovebox and the volatiles were removed in vacuo to afford brown oil, which was diluted with thf (0.5 mL). Tetra(*n*-butyl)ammonium fluoride (0.15 mL, 1M in thf) was added and allowed to stir for 3 h. The mixture was concentrated to afford brown oil, which was purified by silica gel chromatography (100:0 → 3:1 hexanes:Et_2O) to afford afford **3.109** as colorless oil (10.5 mg, 34% overall yield). **(*R*,*Z*)-2-(4-Bromothiazol-2-yl)-6-chloro-2-methylhex-5-en-3-ol (*Z*-3.109)**. IR (neat): 3421 (br, m), 2968 (m), 2931 (w), 1630 (w), 1465 (s), 1387 (m), 1366 (m), 1257 (s), 1081 (s), 1050 (s), 885 (m), 838 (m), 748 (s) cm-1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (s, 1H), 6.09 (dt, J = 7.1, 1.5 Hz, 1H), 5.95 (q, J = 7.0 Hz, 1H), 3.82 (ddd, *J* = 10.2, 6.3, 2.7 Hz, 1H), 3.52 (dd, *J* = 6.3, 0.6 Hz, 1H), 2.56–2.47 (m, 1H), 2.15 (dddd, *J* = 14.8, 10.2, 6.6, 1.5 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): 179.9, 128.9,

124.3, 119.5, 116.0, 77.5, 45.3, 30.1, 26.7, 24.0; HRMS (DART): Calcd for $C_{10}H_{14}BrClNOS$ [M+H]+: 309.9668; Found: 309.9673.

3.5.8 Addition of d_2-Allyl–B(pin)

In a N_2-filled glovebox, an oven-dried vial containing a magnetic stir bar was charged with **ap-2** (5.1 mg, 0.01 mmol), zinc(II) methoxide (2.6 mg, 0.02 mmol) and toluene (2.0 mL). The mixture was allowed to stir for 10 min at 22 °C. A separate oven dried vial was charged with benzaldehyde (20 μL, 0.2 mmol), and was then charged with the initial stock solution of **ap-2**/$Zn(OMe)_2$ (1.0 mL), which was added by syringe. d_2-Allyl–B(pin) (41.0 mg, 0.24 mmol) was added followed by MeOH (11 μL), and the vial was sealed (septum and electrical tape) and removed from the glovebox, and the mixture was allowed to stir for 24 h at 22 °C. The reaction was quenched by the addition of MeOH (1.5 mL) and the mixture was allowed to stir for 30 min at 22 °C. The volatiles were removed in vacuo and the resulting opaque oil was purified by silica gel chromatography (gradient 10:1–4:1 hexanes:Et_2O) to afford the desired homoallylic alcohol as colorless oil with spectral data in agreement with the previously reported values.[13] Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 25.3 min (minor) and 28.8 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
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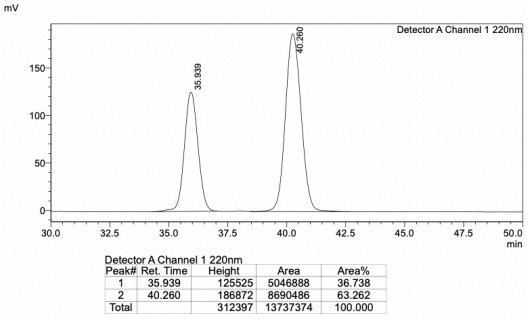
2	40.740	11991	519838	49.740
Total		25214	1045119	100.000



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	35.939	125525	5046888	36.738
2	40.260	186872	8690486	63.262
Total		312397	13737374	100.000

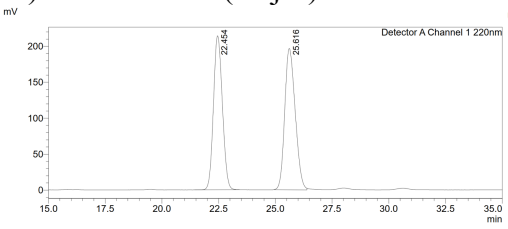
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	36.430 min	525281	50.260	1	35.939 min	5046888	36.738
2	40.740 min	519838	49.740	2	40.260 min	8690486	63.262

3.5.9 Analytical Data for Addition of Chloro–Substituted Allyl Boronates

(*R*,*Z*)-4-Chloro-1-phenylbut-3-en-1-ol (*Z*-3.72): Following the general procedure for addition, benzaldehyde (15.9 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (17.4 mg, 0.095 mmol). **IR (neat):** 3366 (br, m), 1630 (w), 1453 (w), 1335 (w), 1307 (w), 1053 (m), 743 (m), 699 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41–7.34

13) Kobayashi, S.; Endo, T.; Yoshino, T.; Schneider, U.; Ueno, M. *Chem. Asian J.* **2013**, *8*, 2033-2045.

(m, 4H), 7.32–7.27 (m, 1H), 6.14 (dt, J = 7.1, 1.6 Hz, 1H), 5.84 (q, J = 7.1 Hz, 1H), 4.82 (ddd, J = 7.6, 5.6, 3.5 Hz, 1H), 2.86–2.60 (m, 2H), 1.90 (d, J = 3.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 143.8, 128.7, 128.0, 127.6, 125.9, 120.5, 73.4, 36.8; **HRMS (DART):** Calcd for $C_{10}H_{10}Cl$ $[M+H–H_2O]^+$: 165.0471; Found: 165.0469; **Specific Rotation:** $[\alpha]^{24.6}$ +46.6° (*c* 1.0, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 99:1 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 25.3 min (minor) and 28.8 min (major).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
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2	25.616	196684	6322284	51.907
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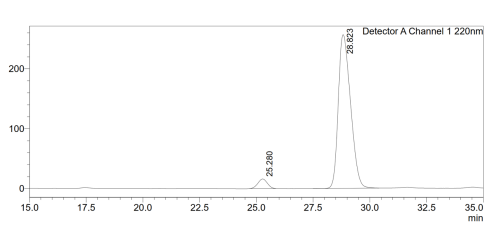
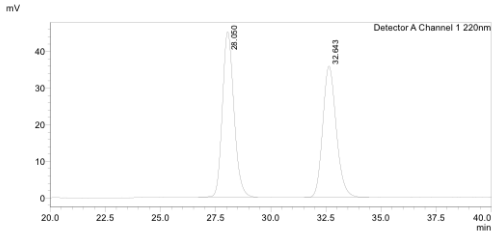


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	25.280	16024	462755	4.581
2	28.823	256470	9638657	95.419
Total		272494	10101412	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	22.454 min	5857752	48.093	1	25.280 min	462755	4.581
2	25.616 min	6322284	51.907	2	28.823 min	9638657	95.419

(*R*,*Z*)-4-Chloro-1-(*o*-tolyl)but-3-en-1-ol (*Z*-3.73): Following the general procedure for addition, 2-methylbenzaldehyde (18.0 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (16.3 mg, 0.083 mmol). **IR (neat):** 3365 (br, m), 2924 (w), 1629 (m), 1459 (m), 1331 (m), 1046 (s), 743 (s) cm^{-1}; **H NMR (400 MHz, $CDCl_3$):** δ 7.50 (dd, J = 7.6, 1.5 Hz, 1H), 7.24–7.10 (m, 3H), 6.29–6.08 (m, 1H), 5.89 (q, J = 7.1 Hz, 1H), 5.04 (ddd, J = 8.0, 4.9, 3.0 Hz, 1H), 3.01–2.46 (m, 2H), 2.36 (s, 3H), 1.82 (d, J = 3.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.7, 134.5, 130.5, 127.7, 127.5, 126.3, 125.1, 120.2, 69.7, 35.5, 19.0; **HRMS (DART):** Calcd for $C_{11}H_{12}Cl$ $[M+H–H_2O]^+$: 179.06220; Found: 179.06140; **Specific Rotation:** $[\alpha]^{25.4}$ +47.3° (*c* 0.77, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*-PrOH, 0.7 mL/min, 220 nm): t_R: 27.7 min (major) and 32.5 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
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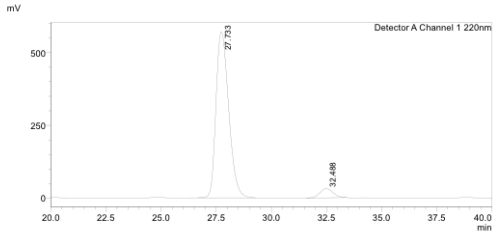
2	32.643	35851	1531810	48.091
Total		81065	3185232	100.000

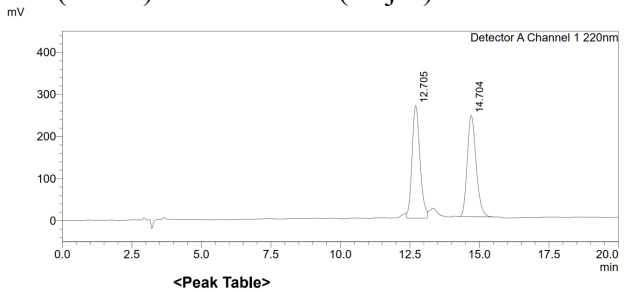


Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	27.733	570829	22833378	94.605
2	32.488	31711	1302195	5.395
Total		602541	24135573	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	28.050 min	1653422	51.909	1	27.733 min	22833378	94.605
2	32.643 min	1531810	48.091	2	32.488 min	13202195	5.395

(*R*,*Z*)-4-(4-Chloro-1-hydroxybut-3-en-1-yl)-3,5-difluorobenzonitrile (*Z*-3.74): Following the general procedure, except the reaction was carried out at 40 °C, 3,5-Difluoro-4-formylbenzonitrile (25.0 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (21.0 mg, 0.086 mmol). **IR (neat):** 3443 (br, m), 2237 (w), 1626 (m), 1573 (s), 1423 (s), 1320 (s), 1203 (m), 1190 (m), 1048 (s), 1018 (s), 971 (m), 863 (s), 755 (m), 727 (m), 710 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.25–7.18 (m, 2H), 6.17 (dt, *J* = 7.2, 1.5 Hz, 1H), 5.81 (q, *J* = 7.2 Hz, 1H), 5.18 (dt, *J* = 8.8, 7.1 Hz, 1H), 2.98–2.79 (m, 2H), 2.35 (dt, *J* = 8.8, 1.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 160.8 (dd, *J* = 252.2, 9.2 Hz), 125.7, 124.8 (t, *J* = 16.4 Hz), 121.9, 116.4 (t, *J* = 3.5 Hz), 116.1 (dd, *J* = 21, 9.0 Hz), 113.2 (t, *J* = 12.6 Hz), 65.3, 34.6; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –110.74 (d, *J* = 6.7 Hz). **HRMS (DART):** Calcd for $C_{11}H_9NOF_2Cl$ $[M+H]^+$: 244.03352; Found: 244.03341; **Specific Rotation:** $[\alpha]^{20.0}_D$ +25.1° (*c* 1.25, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 95:5 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 12.6 min (minor) and 14.5 min (major).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
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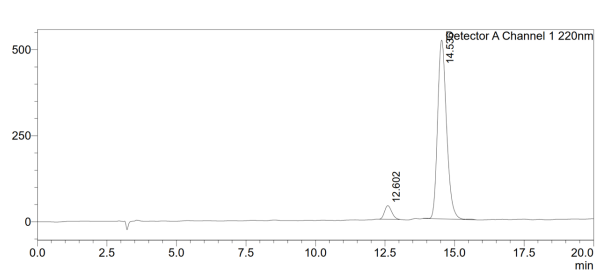
2	14.704	240090	5334966	50.338
Total		507130	10598255	100.000

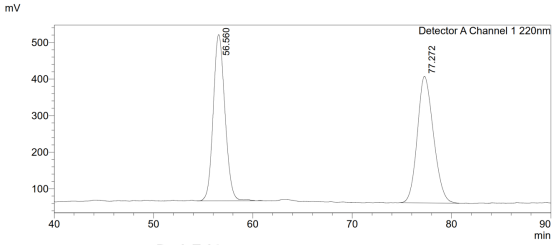


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	12.602	39777	715068	5.788
2	14.536	519279	11639151	94.212
Total		559056	12354219	100.000

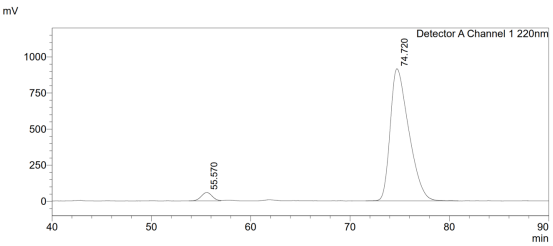
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	12.705 min	5263289	49.662	1	12.602 min	715068	5.788
2	14.704 min	5334966	50.338	2	14.536 min	11639151	94.212

(*R*,*Z*)-1-(6-Bromonaphthalen-2-yl)-4-chlorobut-3-en-1-ol (*Z*-*3.75*): Following the general procedure for addition, 6-Bromo-2-napthaldehyde (35.3 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (29.6 mg, 0.095 mmol). **IR (neat):** 3387 (br, m), 1630 (m), 1590 (m), 1497 (m), 1463 (w), 1337 (m), 1314 (m), 1161 (m), 1127 (m), 1061 (s), 877 (s), 805 (s), 746 (s), 475 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 1.9 Hz, 1H), 7.77 (d, *J* = 1.1 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.55 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.51 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.15 (dt, *J* = 7.1, 1.5 Hz, 1H), 5.83 (q, *J* = 7.1 Hz, 1H), 4.96 (td, *J* = 6.8, 2.9 Hz, 1H), 2.85 – 2.71 (m, 2H), 2.13 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** 141.7, 134.2, 131.8, 129.9, 129.8, 129.7, 127.6, 127.3, 125.0, 124.6, 120.8, 120.1, 73.3, 36.7; **HRMS (DART):** Calcd for $C_{14}H_{11}BrCl$ $[M+H–H_2O]^+$: 292.9733; Found: 292.9737; **Specific Rotation:** $[\alpha]^{24.6}_D$ +13.5° (*c* 1.97, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 96:5 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 55.5 min (minor) and 74.7 min (major).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	56.560	454327	37160771	48.726
2	77.272	346013	39103354	51.274
Total		800341	76264126	100.000

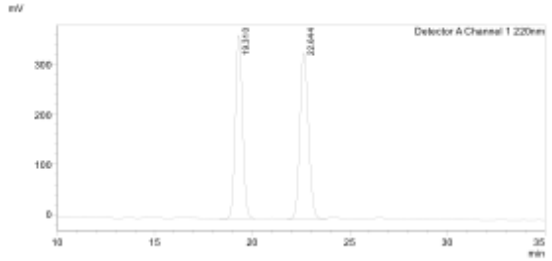


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	55.570	58400	4473795	3.615
2	74.720	915368	119267933	96.385
Total		973769	123741727	100.000

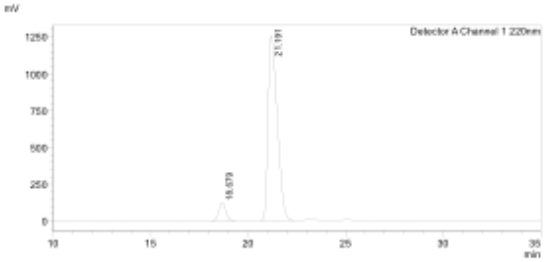
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	56.560 min	37160771	48.726	1	55.570 min	4473795	3.615
2	77.272 min	39103354	51.274	2	74.720 min	119267933	96.385

(*R*,*Z*)-4-Chloro-1-(3-chlorophenyl)but-3-en-1-ol (*Z*-3.76): Following the general procedure for addition, 3-Chlorobenzaldehyde (21.1 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (19.5 mg, 0.090 mmol). **IR (neat):** 3352 (br, m), 2912 (w), 1630 (m), 1596 (m), 1573 (m), 1431 (s), 1199 (s), 1052 (s), 787 (s), 751 (s), 696 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 (td, *J* = 1.7, 0.8 Hz, 1H), 7.34–7.19 (m, 3H), 6.16 (dt, *J* = 7.2, 1.5 Hz, 1H), 5.81 (q, *J* = 7.2 Hz, 1H), 4.98–4.65 (m, 1H), 2.69 (dddq, *J* = 7.2, 5.7, 2.9, 1.5 Hz, 2H), 1.98 (d, *J* = 3.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 145.6, 134.4, 129.8, 127.9, 126.9, 126.0, 123.9, 120.9, 72.6, 36.6; **HRMS (DART):** Calcd for $C_{10}H_9Cl_2$ $[M+H–H_2O]^+$: 199.00758; Found: 199.00699; **Specific Rotation:** $[\alpha]^{21.8}_D$ +22.2° (*c* 0.83, $CHCl_3$) for a 93:7 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak OD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 18.7 min (minor) and 21.2 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	19.310	366384	9399265	48.221
2	22.644	331682	10092938	51.779
Total		698066	19492203	100.000



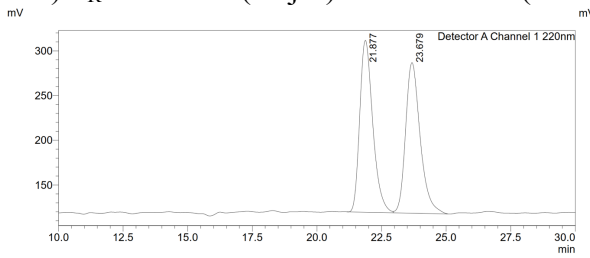
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	18.679	124385	2978878	6.757
2	21.191	1254409	41105908	93.243
Total		1378794	44084786	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	19.310 min	9399265	48.221	1	18.679 min	2978878	6.757
2	22.644 min	10092938	51.779	2	21.191 min	44084786	93.243

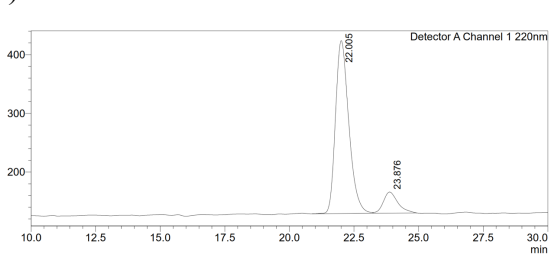
(*R*,*Z*)-1-(4-(4-Chloro-1-hydroxybut-3-en-1-yl)phenyl)ethan-1-one (*Z*-3.77): Following the general procedure for addition, 4-Acetylbenzaldehyde (22.2 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (20.7 mg, 0.092 mmol). **IR (neat):** 3424 (br, m), 1671 (w), 1630 (w), 1607 (s), 1412 (m), 1359 (s), 1304 (m), 1268 (s), 1065 (m), 853 (m), 752 (m), 722 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J*

= 8.3 Hz, 2H), 6.16 (dt, *J* = 7.1, 1.5 Hz, 1H), 5.82 (q, *J* = 7.1 Hz, 1H), 4.90 (td, *J* = 6.4, 3.2 Hz, 1H), 2.74–2.69 (m, 2H), 2.60 (s, 3H), 2.10 (d, *J* = 3.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 197.9, 149.0, 136.6, 128.7, 126.9, 126.0, 121.0, 72.7, 36.7, 26.7; **HRMS (DART):** Calcd for $C_{12}H_{14}O_2Cl$ $[M+H]^+$: 225.06768; Found: 225.06659; **Specific Rotation:** $[\alpha]^{20.0}_D$ +21.4° (*c* 1.33, $CHCl_3$) for a 88:12 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 95:5 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 22.0 min (major) and 23.8 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	21.877	192221	6743165	50.457
2	23.679	168437	6621097	49.543
Total		360658	13364263	100.000

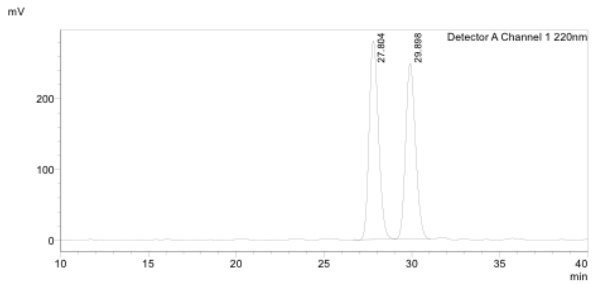


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	22.005	294635	10588026	88.248
2	23.876	35971	1410016	11.752
Total		330606	11998042	100.000

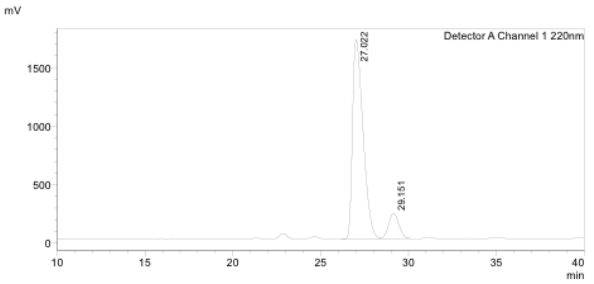
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	21.877 min	6743165	50.457	1	22.005 min	10588026	88.248
2	23.679 min	6621097	49.543	2	23.876 min	1410016	11.752

(*R*,*Z*)-4-Chloro-1-(4-methoxyphenyl)but-3-en-1-ol (*Z*-3.78): Following the general procedure for addition, 4-Methoxybenzaldehyde (20.4 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (19.6 mg, 0.092 mmol). **IR (neat):** 3407 (br, m), 1611 (m), 1512 (s), 1463 (w), 1441 (w), 1303 (m), 1246 (s), 1175 (m), 1034 (s), 832 (m), 746 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.31 – 7.28 (m, 2H), 6.91 – 6.87 (m, 2H), 6.12 (dt, *J* = 7.1, 1.5 Hz, 1H), 5.80 (q, *J* = 7.1 Hz, 1H), 4.75 (ddd, *J* = 7.8, 5.6, 2.3 Hz, 1H), 3.81 (s, 3H), 2.73 (dddd, *J* = 14.8, 7.6, 7.0, 1.5 Hz, 1H), 2.65 (dddd, *J* = 14.7, 7.1, 5.6, 1.6 Hz, 1H), 1.95 (d, *J* = 3.1 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 159.3, 135.9, 127.7, 127.2, 120.3, 114.0, 72.9, 55.4, 36.7; **HRMS (DART):** Calcd for $C_{11}H_{12}OCl$ $[M+H–H_2O]^+$: 195.05712; Found: 195.05662; **Specific Rotation:** $[\alpha]^{20.0}_D$ +28.1° (*c* 1.00, $CHCl_3$) for a 89:11 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 27.0 min (major) and 29.1 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	27.804	280734	10380801	51.550
2	29.898	248125	9756582	48.450
Total		528859	20137383	100.000

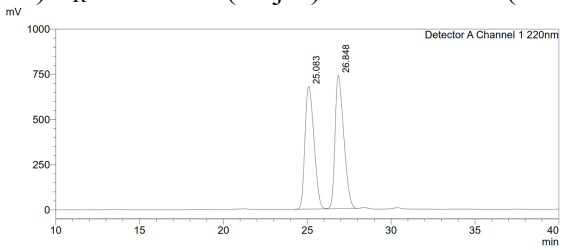


Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	27.022	1702650	71138610	89.010
2	29.151	217974	8783690	10.990
Total		1920624	79922300	100.000

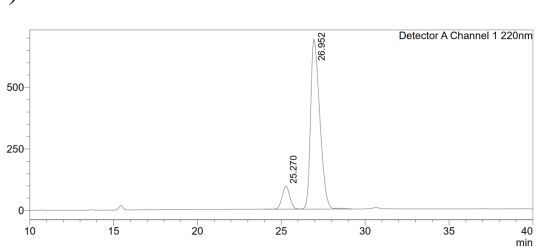
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	27.804 min	10380801	51.528	1	27.022 min	71138610	89.010
2	29.898 min	9756582	48.429	2	29.151 min	8783690	10.990

(*R,Z*)-4-Chloro-1-(4-(methylthio)phenyl)but-3-en-1-ol (*Z*-3.79): Following the general procedure for addition, 4-(Methylthio)benzaldehyde (22.8 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (20.6 mg, 0.090 mmol). **IR (neat):** 3377 (br, m), 2920 (m), 1630 (m), 1599 (m), 1494 (s), 1435 (m), 1406 (m), 1300 (m), 1092 (s), 1055 (s), 1014 (m), 968 (m), 821 (m), 749 (s), 729 (s), 712 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 – 7.10 (m, 4H), 6.14 (dt, *J* = 7.1, 1.6 Hz, 1H), 5.81 (q, *J* = 7.1 Hz, 1H), 4.78 (ddd, *J* = 7.4, 5.5, 3.4 Hz, 1H), 2.85 – 2.59 (m, 2H), 2.49 (s, 3H), 1.91 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.6, 138.0, 127.4, 126.8, 126.4, 120.5, 72.9, 36.7, 16.0; **HRMS (DART):** Calcd for $C_{11}H_{12}SCl$ $[M+H–H_2O]^+$: 211.03428; Found: 211.03309; **Specific Rotation:** $[\alpha]^{20.0}_D$ +16.0° (*c* 1.35, $CHCl_3$) for a 90:10 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 26.9 min (major) and 25.2 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	25.083	677561	25284391	48.507
2	26.848	737126	26840597	51.493
Total		1414687	5124987	100.000

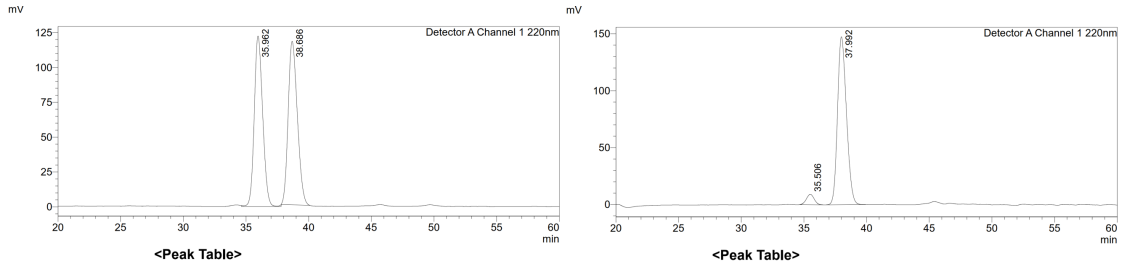


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	25.270	93198	2994430	10.124
2	26.952	689289	26583250	89.876
Total		782487	29577680	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	25.083 min	25284391	48.507	1	25.270 min	2994430	10.124
2	26.848 min	26840597	51.493	2	26.952 min	26583250	89.876

(*R,Z*)-1-(Benzo[d][1,3]dioxol-5-yl)-4-chlorobut-3-en-1-ol (*Z*-3.80): Following the general procedure for addition, Piperonal (22.5 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (21.5 mg, 0.095 mmol). **IR (neat):** 3384 (br, m), 2894 (w), 1738 (m), 1503 (m), 1487 (s), 1442 (m), 1365 (w), 1321 (w), 1244 (s), 1095 (w), 1039 (s), 933 (m), 747 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.89 (dd, *J* = 1.7, 0.5 Hz, 1H), 6.82 (ddd, *J* = 7.9, 1.7, 0.5 Hz, 1H), 6.78 (dd, *J* = 7.9, 0.5 Hz, 1H), 6.13 (dt, *J* = 7.2, 1.6 Hz, 1H), 5.96 (s, 2H), 5.80 (q, *J* = 7.1 Hz, 1H), 4.73 (ddd, *J* = 7.7, 5.6, 3.3 Hz, 1H), 2.77 – 2.57 (m, 2H), 1.85 (d, *J* = 3.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 147.9, 147.2, 137.8, 127.5, 120.4, 119.3, 108.2, 106.4, 101.1, 73.2, 36.8; **HRMS (DART):** Calcd for $C_{11}H_{10}O_2Cl$ $[M+H–H_2O]^+$: 209.03638; Found: 209.03521; **Specific Rotation:** $[\alpha]^{20.0}_D$ +16.9° (*c* 1.40, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 37.9 min (major) and 35.5 min (minor).



<Peak Table>
Detector A Channel 1 220nm

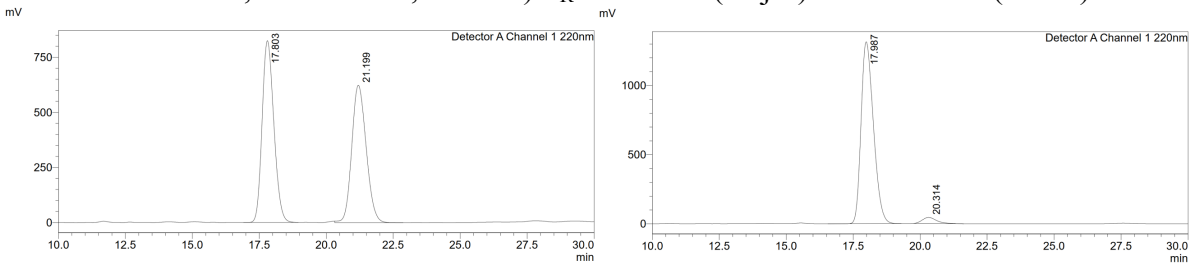
Peak#	Ret. Time	Height	Area	Area%
1	35.962	122288	5711093	48.930
2	38.686	117220	5960792	51.070
Total		239508	11671884	100.000

<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	35.506	9218	399379	5.163
2	37.992	147564	7336485	94.837
Total		156782	7735864	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	35.962 min	5711093	48.930	1	35.506 min	399379	5.163
2	38.686 min	5960792	51.070	2	37.992 min	7336485	94.837

***tert*-Butyl-(*R*,*Z*)-3-(4-Chloro-1-hydroxybut-3-en-1-yl)-1H-indole-1-carboxylate (*Z*-3.81):** Following the general procedure for addition, *tert*-Butyl 3-formyl-1*H*-indole-1-carboxylate (36.8 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (30.9 mg, 0.096 mmol). **IR (neat):** 3421 (br, w), 2979 (w), 1732 (s), 1452 (s), 1370 (s), 1255 (m), 1224 (m), 1156 (s), 1090 (m), 1056 (w), 1019 (w), 856 (w), 766 (m), 746 (s) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.15 (d, *J* = 5.9 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.58 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 6.17 (dd, *J* = 7.2, 1.4 Hz, 1H), 5.97 – 5.87 (m, 1H), 5.08 (t, *J* = 6.7 Hz, 1H), 3.03 – 2.77 (m, 2H), 2.08 (s, 1H), 1.67 (s, 9H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 149.7, 135.9, 128.5, 127.7, 127.5, 124.9, 124.5, 123.2, 123.0, 122.8, 122.5, 122.4, 120.6, 120.4, 119.9, 119.6, 115.5, 83.9, 67.2, 66.7, 35.1, 28.3, 28.2 (extra peaks were observed due to rotamers); **HRMS (DART):** Calcd for $C_{17}H_{19}NO_2Cl$ $[M+H-H_2O]^+$: 304.10988; Found: 304.10987; **Specific Rotation:** $[\alpha]^{20.0}_D$ +19.5° (*c* 1.35, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 17.9 min (major) and 20.3 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	17.803	824805	25116671	51.727
2	21.199	624208	23439094	48.273
Total		1449013	48555765	100.000

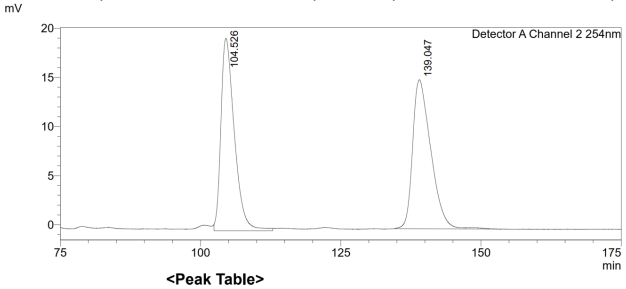
<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	17.987	1315424	42194991	96.228
2	20.314	44349	1653955	3.772
Total		1359773	43848946	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	17.803 min	25116671	51.727	1	17.987 min	42194991	96.228
2	21.199 min	23439094	48.273	2	20.314 min	1653955	3.772

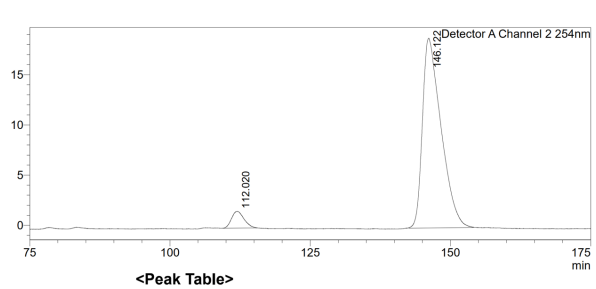
(*R*,*Z*)-4-Chloro-1-(pyridin-3-yl)but-3-en-1-ol (*Z*-3.82): Following the general procedure for addition, (16.1 mg, 0.15 mmol) was transferred to an oven-dried vial and purified by silica gel

chromatography (gradient eluting with 100:0 → 95:5 CH_2Cl_2:MeOH) to afford the title compound as colorless oil (16.7 mg, 0.091 mmol). **IR (neat):** 3184 (br, s), 2916 (br, m), 2854 (br, m), 1630 (w), 1594 (w), 1580 (w), 1480 (w), 1427 (m), 1339 (w), 1314 (w), 1071 (m), 1028 (m), 748 (m), 712 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** 8.60 (d, *J* = 2.3 Hz, 1H), 8.54 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.74 (dddd, *J* = 7.9, 2.3, 1.7, 0.6 Hz, 1H), 7.35 – 7.27 (m, 1H), 6.18 (dt, *J* = 7.2, 1.5 Hz, 1H), 5.83 (q, *J* = 7.2 Hz, 1H), 4.94 – 4.85 (m, 1H), 2.89 – 2.62 (m, 2H), 2.18 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 148.9, 147.6, 139.4, 133.8, 126.8, 123.6, 121.0, 70.8, 36.7; **HRMS (DART):** Calcd for $C_9H_{11}ClNO$ $[M+H]^+$: 184.0529; Found: 184.053; **Specific Rotation:** $[\alpha]^{20.0}_D$ +28.8° (*c* 1.27, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 97:3 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R: 112.0 min (minor) and 146.1 min (major).



<Peak Table>
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	104.526	19601	3280059	48.927
2	139.047	15164	3423948	51.073
Total		34766	6704007	100.000

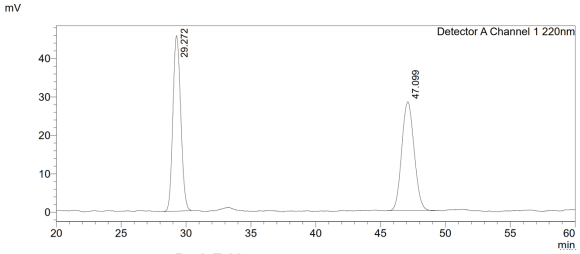


<Peak Table>
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	112.020	1667	258022	5.593
2	146.122	18899	4355131	94.407
Total		20566	4613153	100.000

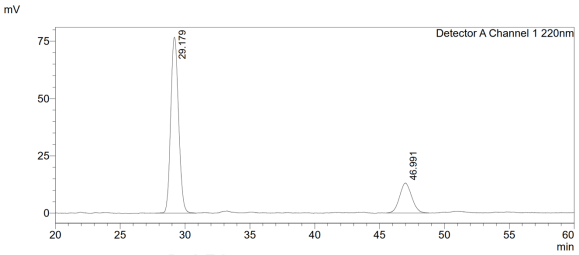
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	104.526 min	3280059	48.927	1	112.020 min	258022	5.593
2	139.047 min	3423948	51.073	2	146.122 min	4355131	94.407

(S,*Z*)-6-Chloro-1-phenylhex-5-en-3-ol (*Z*-3.83): IR (neat): 3356 (br, m), 2924 (m), 1630 (m), 1495 (w), 1453 (m), 1331 (w), 1081 (m), 1046 (m), 1030 (m), 931 (w), 861 (m), 744 (s), 696 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.27 (m, 2H), 7.20 (ddt, *J* = 10.6, 6.4, 1.6 Hz, 3H), 6.17 (dt, *J* = 7.1, 1.6 Hz, 1H), 5.87 (q, *J* = 7.2 Hz, 1H), 3.83 – 3.72 (m, 1H), 2.81 (ddd, *J* = 13.8, 8.4, 6.6 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.51 – 2.42 (m, 2H), 1.90 – 1.78 (m, 2H), 1.46 (d, *J* = 4.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.9, 128.5, 128.5, 127.7, 126.0, 120.4, 70.3, 38.7, 35.2, 32.1; **HRMS (DART):** Calcd for $C_{11}H_{14}BrF_3NSO$ $[M+H–H_2O]^+$: 193.0784; Found: 193.0783; **Specific Rotation:** $[\alpha]^{21.5}_D$ –27.4° (*c* 1.82, $CHCl_3$) for a 79:21 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 29.1 min (major) and 46.9 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	29.272	45682	1923131	50.679
2	47.099	28275	1871631	49.321
Total		73957	3794762	100.000

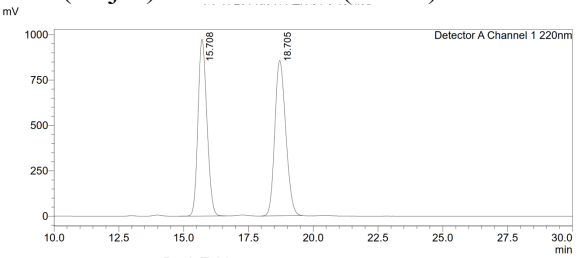


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	29.179	76766	3237834	79.212
2	46.991	13075	849731	20.788
Total		89841	4087565	100.000

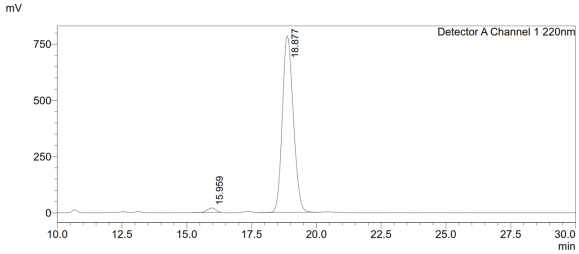
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	29.727 min	1923131	50.679	1	29.179 min	3237834	79.212
2	47.099 min	1871631	49.321	2	46.991 min	849731	20.788

(*R*,1*E*,5*Z*)-6-Chloro-2-methyl-1-(2-methylthiazol-4-yl)hexa-1,5-dien-3-ol (*Z*-3.84): Following the general procedure for addition, (*E*)-2-methyl-3-(2-methylthiazole-4-yl)acrylaldehyde (25.1 mg, 0.15 mmol) was transferred to an oven-dried vial. The reaction was quenched by addition of a saturated aqueous solution of sodium periodate (1.0 mL), extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to afford an unpurified residue that was purified by silica gel chromatography to afford the title compound as colorless oil (20.9 mg, 0.086 mmol). **IR (neat):** 3282 (br, s), 2921 (m), 1630 (w), 1507 (m), 1438 (m), 1306 (m), 1188 (s), 1046 (s), 879 (m), 746 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.94 (s, 1H), 6.56 (tt, *J* = 1.1, 0.6 Hz, 1H), 6.12 (ddd, *J* = 7.1, 1.8, 1.3 Hz, 1H), 5.85 (q, *J* = 7.0 Hz, 1H), 4.28 (t, *J* = 6.5 Hz, 1H), 2.70 (s, 2H), 2.67 – 2.51 (m, 2H), 2.41 (s, 1H), 2.04 (d, *J* = 1.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.8, 152.6, 141.4, 127.7, 120.1, 119.4, 115.8, 76.3, 33.1, 19.2, 14.3; **HRMS (DART):** Calcd for $C_{11}H_{14}NOSCl$ $[M+H]^+$: 243.04791; Found: 243.04791; **Specific Rotation:** $[\alpha]^{25.0}_D$ +13.9° (*c* 1.44, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 94:6 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 18.8 min (major) and 15.9 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	15.708	973708	23419221	48.167
2	18.705	855295	25201872	51.833
Total		1829003	48621093	100.000



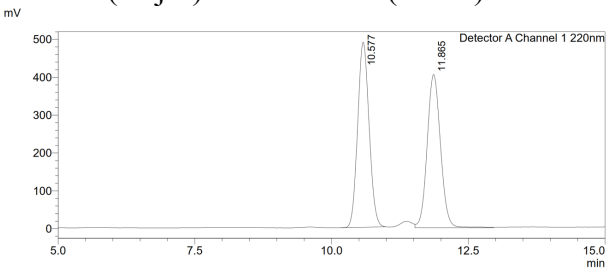
<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	15.959	20235	462922	1.959
2	18.877	785862	23169985	98.041
Total		806097	23632907	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	15.708 min	23419221	48.167	1	15.959 min	462922	1.959

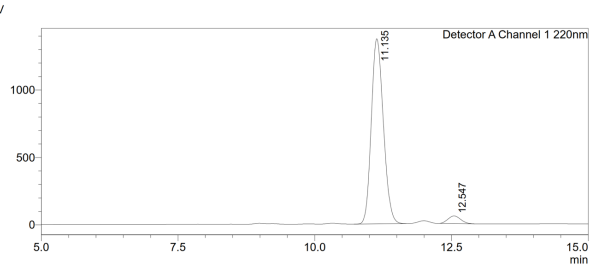
2	18.705 min	25201872	51.833	2	18.877 min	23169985	98.041

(*R*,1*Z*,5*Z*)-2-Bromo-6-chloro-1-phenylhexa-1,5-dien-3-ol (*Z*-3.85): Following the general procedure for addition, *α*-Bromocinnamaldehyde (31.7 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (27.1 mg, 0.095 mmol). **IR (neat):** 3381 (br, m), 1631 (w), 1491 (w), 1445 (w), 1338 (w), 1303 (w), 1275 (w), 1050 (m), 1030 (m), 920 (w), 867 (w), 752 (s), 717 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72 – 7.53 (m, 2H), 7.43 – 7.29 (m, 3H), 7.09 (s, 1H), 6.20 (dt, *J* = 7.1, 1.5 Hz, 1H), 5.86 (q, *J* = 7.1 Hz, 1H), 4.40 (q, *J* = 6.3 Hz, 1H), 2.76 (tt, *J* = 7.0, 1.6 Hz, 2H), 2.18 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 134.9, 129.2, 128.9, 128.7, 128.4, 128.3, 126.5, 121.0, 76.4, 33.8; **HRMS (DART):** Calcd for $C_{12}H_{11}BrCl$ $[M+H–H_2O]^+$: 268.9733; Found: 268.9736; **Specific Rotation:** $[\alpha]^{25.3}_D$ –31.4° (*c* 2.4, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 11.1 min (major) and 12.5 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	10.577	489192	7137557	50.882
2	11.865	405090	6890042	49.118
Total		894282	14027599	100.000

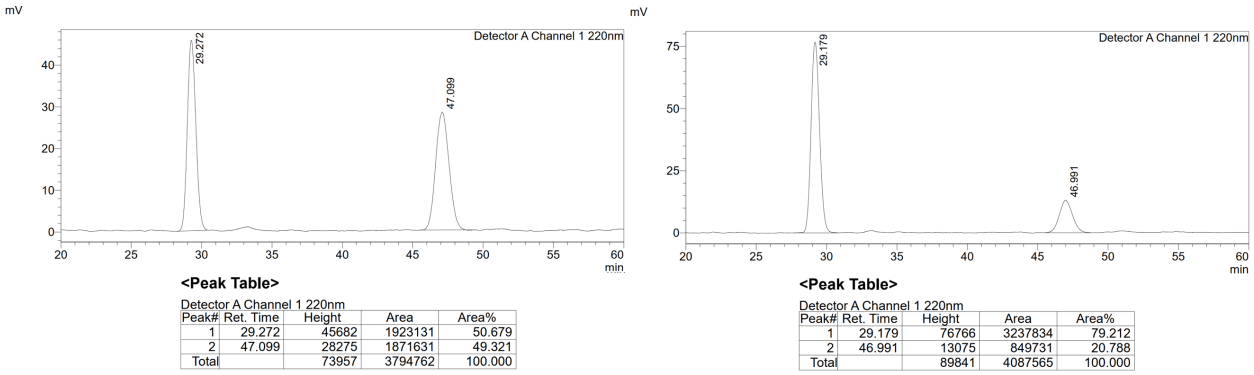


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	11.135	1372907	21193634	95.878
2	12.547	56580	911046	4.122
Total		1429488	22104680	100.000

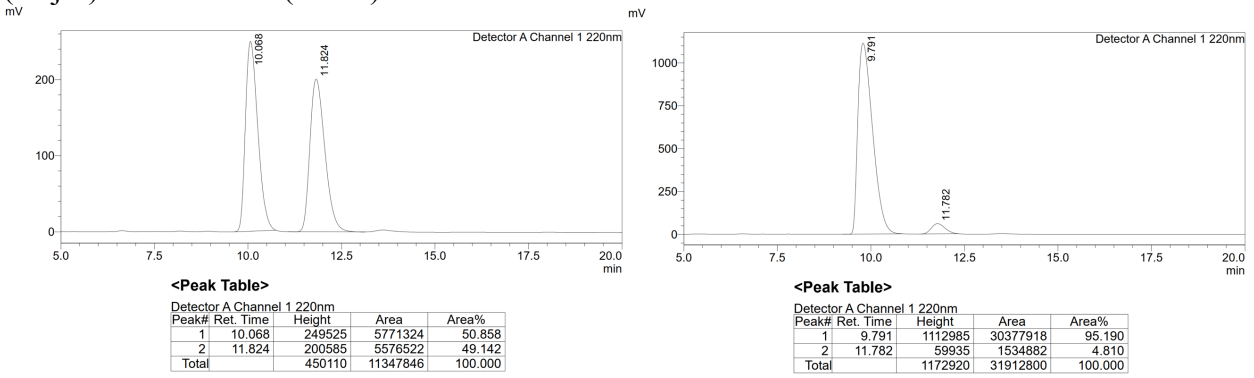
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	10.577 min	7137557	50.882	1	11.135 min	21193634	95.878
2	11.865 min	6890042	49.118	2	12.547 min	911046	4.122

(*S*,*Z*)-6-Chloro-1-phenylhex-5-en-3-ol (*Z*-3.86): Following the general procedure for addition, hydrocinnamaldehyde (20.1 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (18.5 mg, 0.088 mmol). **IR (neat):** 3356 (br, m), 2924 (m), 1630 (m), 1495 (w), 1453 (m), 1331 (w), 1081 (m), 1046 (m), 1030 (m), 931 (w), 861 (m), 744 (s), 696 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.27 (m, 2H), 7.20 (ddt, *J* = 10.6, 6.4, 1.6 Hz, 3H), 6.17 (dt, *J* = 7.1, 1.6 Hz, 1H), 5.87 (q, *J* = 7.2 Hz, 1H), 3.83 – 3.72 (m, 1H), 2.81 (ddd, *J* = 13.8, 8.4, 6.6 Hz, 1H), 2.76–2.65 (m, 1H), 2.51–2.42 (m, 2H), 1.90–1.78 (m, 2H), 1.46 (d, *J* = 4.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.9, 128.5, 128.5, 127.7, 126.0, 120.4, 70.3, 38.7, 35.2, 32.1; **HRMS (DART):** Calcd for $C_{12}H_{13}ClO$ $[M+H–H_2O]^+$: 193.0784; Found: 193.0783; **Specific Rotation:** $[\alpha]^{21.5}_D$ –27.4° (*c* 1.82, $CHCl_3$) for a 79:21 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 29.1 min (major) and 46.9 min (minor).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	29.727 min	1923131	50.679	1	29.179 min	3237834	79.212
2	47.099 min	1871631	49.321	2	46.991 min	849731	20.788

(*R*,*Z*)-4-Chloro-1-cyclohexylbut-3-en-1-ol (*Z*-3.87): Following the general procedure for addition, (16.8 mg, 0.15 mmol) was transferred to an oven-dried vial that was carefully concentrated under reduced pressure in an ice-bath to afford the title compound as *volatile* colorless oil (15.1 mg, 0.080 mmol). **IR (neat):** 3361 (br, m), 2922 (s), 2851 (s), 1449 (m), 1334 (w), 1102 (w), 1086 (w), 1059 (w), 1036 (m), 892 (w), 860 (w), 748 (m), 714 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.14 (dt, *J* = 7.1, 1.6 Hz, 1H), 5.90 (q, *J* = 7.1 Hz, 1H), 3.53–3.42 (m, 1H), 2.47 (dddd, *J* = 15.0, 6.9, 4.0, 1.7 Hz, 1H), 2.43–2.32 (m, 1H), 1.87 (dtt, *J* = 12.2, 3.3, 1.8 Hz, 1H), 1.83–1.73 (m, 2H), 1.69 (dddd, *J* = 13.9, 8.0, 3.9, 2.3 Hz, 2H), 1.42 (d, *J* = 5.0 Hz, 1H), 1.40 – 0.96 (m, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 128.6, 119.9, 75.3, 43.5, 32.2, 29.2, 28.0, 26.5, 26.3, 26.2; **HRMS (DART):** Calcd for $C_{10}H_{16}Cl$ $[M+H-H_2O]^+$: 171.09350; Found: 171.09304; **Specific Rotation:** $[\alpha]^{20.0}_D$ +8.1° (*c* 1.1, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity was determined by HPLC analysis of the *p*-nitrobenzoyl derived product in comparison with authentic racemic material (Chiralpak AS-H, 99:1 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 9.7 min (major) and 11.7 min (minor).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	10.068 min	5771324	50.858	1	9.791 min	30377918	95.190
2	11.824 min	5576522	49.142	2	11.782 min	1534882	4.810

3.5.10 Analytical Data for Diastereoselective Addition to Chiral Aldehydes

(2*R*,3*R*,*Z*)-6-Chloro-2-phenylhex-5-en-3-ol (*Z*-3.88). Freshly prepared (*R*)-2-phenylpropanal (20.1 mg, 0.15 mmol) was transferred to an oven-dried vial and purified as described to afford the title compound as colorless oil (6.7 mg, 0.032 mmol). **IR (neat):** 3281 (br, m), 3024 (m), 2963 (m), 1629 (m), 1492 (m), 1451 (m), 1008 (m), 699 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31 (dd, *J* = 8.5, 6.4 Hz, 2H), 7.24 – 7.18 (m, 3H), 6.11 (dt, *J* = 7.1, 1.6 Hz, 1H), 5.84 (q, *J* = 7.1 Hz, 1H), 3.79 (ddt, *J* = 8.8, 6.2, 4.4 Hz, 1H), 2.81 (p, *J* = 6.9 Hz, 1H), 2.36 (dddd, *J* = 15.0, 7.1, 4.2, 1.7 Hz, 1H), 2.30 – 2.21 (m, 1H), 1.50 (d, *J* = 5.0 Hz, 1H), 1.35 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 144.0, 128.6, 128.2, 127.7, 126.6, 120.0, 75.3, 45.6, 32.8, 15.8; **HRMS (DART):** Calcd for $C_{11}H_{14}Cl$ $[M+H–H_2O]^+$: 193.07785; Found: 193.07763; **Specific Rotation:** $[\alpha]^{24.7}_D$ +45.6° (*c* 0.9, $CHCl_3$).

(2*S*,3*R*,*Z*)-6-Chloro-2-phenylhex-5-en-3-ol (*Z*-3.89). Freshly prepared (*S*)-2-phenylpropanal (20.1 mg, 0.15 mmol) was transferred to an oven-dried vial and purified as described to afford the title compound as colorless oil (17.9 mg, 0.085 mmol). **IR (neat): IR (neat):** 3438 (br, m), 3060 (m), 2965 (m), 1629 (m), 1493 (s), 1442 (s), 1037 (m), 701 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 – 7.22 (m, 5H), 6.15 (dt, *J* = 7.1, 1.7 Hz, 1H), 5.96 (q, *J* = 7.0 Hz, 1H), 3.78 (d, *J* = 9.4 Hz, 1H), 2.78 (p, *J* = 7.2 Hz, 1H), 2.56 (dddd, *J* = 15.1, 6.6, 3.7, 1.8 Hz, 1H), 2.42 – 2.25 (m, 1H), 1.41 (s, 1H), 1.32 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.9, 128.7, 128.10, 128.08, 126.9, 119.7, 75.1, 45.9, 32.2, 17.9; **HRMS (DART):** Calcd for $C_{11}H_{12}Cl$ $[M+H–H_2O]^+$: 193.07785; Found: 193.07751; **Specific Rotation:** $[\alpha]^{25.6}_D$ 9.6° (*c* 1.0, $CHCl_3$).

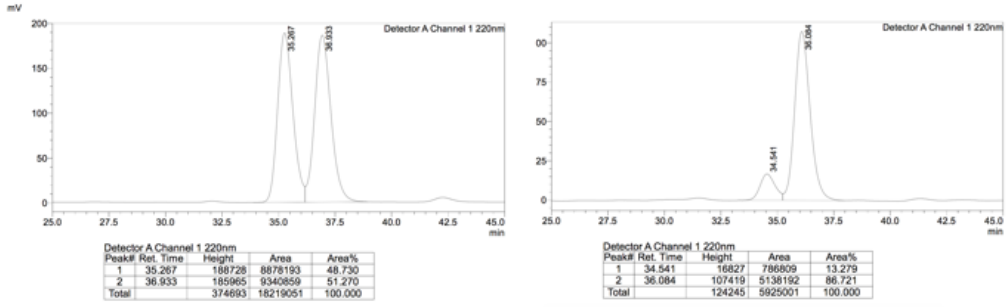
(4*S*,6*S*,*Z*)-1-Chloro-6,10-dimethylundeca-1,9-dien-4-ol (*Z*-3.90). Following the general procedure for addition, (23.1 mg, 0.15 mmol) was transferred to an oven-dried to afford the title compound as colorless oil (15.7 mg, 0.081 mmol). **IR (neat):** 3341 (br, m), 2959 (s), 2915 (s), 2850 (m), 1630 (m), 1451 (m), 1376 (m), 1043 (s), 746 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.17 (dq, *J* = 7.2, 1.4 Hz, 1H), 5.90 (qd, *J* = 6.6, 5.9, 0.9 Hz, 1H), 5.11 (ddq, *J* = 7.2, 4.2, 1.4 Hz, 1H), 3.85 (td, *J* = 7.5, 3.7 Hz, 1H), 2.44 (tdd, *J* = 8.7, 7.6, 3.8 Hz, 1H), 2.41–2.29 (m, 1H), 2.10–1.89 (m, 2H), 1.69 (s, 3H), 1.62 (s, 4H), 1.51–1.31 (m, 4H), 1.30–1.11 (m, 1H), 0.95 (dd, *J* = 6.7, 0.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 131.4, 127.8, 124.6, 120.1, 69.0, 44.6, 36.7, 35.2, 29.3, 25.7, 25.3, 20.2, 17.7; **HRMS (DART):** Calcd for $C_{13}H_{24}OCl$ $[M+H]^+$: 231.15102; Found: 231.15018; **Specific Rotation:** $[\alpha]^{23.0}_D$ –1.8° (*c* 0.77, $CHCl_3$).

3.5.11 Analytical Data for Addition of Trisubstituted Allyl Boronates to Aldehydes

(*R*,*Z*)-4-Chloro-3-methyl-1-phenylbut-3-en-1-ol (3.98): In a N_2-filled glovebox, a stock solution of **ap-6** and zinc(II) methoxide was prepared. An oven-dried vial (8 mL) equipped with a stir bar

was charged with aminophenol (**ap-6**) (13.8 mg, 0.02 mmol), zinc methoxide (5.1 mg, 0.04 mmol) and toluene (2.0 mL). The freshly prepared stock solution was allowed to stir for 15 min at 22 °C. In another vial (8 mL), benzaldehyde (15.9 mg, 0.15 mmol) was weighed out. The aminophenol/$Zn(OMe)_2$ stock solution was then added by syringe (500 μL). *Z*-Chloro-allyl–B(pin) (***Z*-3.96**) (32.5 mg, 0.1 mmol), was added followed by MeOH (10 μL, 0.25 mmol). The reaction vessel was equipped with a stir bar, sealed with a cap removed from the glovebox. The mixture was allowed to stir for 14 h at 22 °C, at which time the reaction was quenched by the addition of MeOH (1.5 mL). The mixture was then allowed to stir for 0.5 h at 22 °C. The volatiles were removed in vacuo and the resulting opaque oil was purified by silica gel chromatography (10:1–4:1 hexanes:Et_2O) to afford the title compound (12.0 mg, 0.061 mmol) as colorless oil.

IR (neat): 3392 (br, m), 2949 (m), 3062 (m), 3028 (m), 2914 (m), 1451 (s), 1048 (s), 1024 (s), 752 (s), 699 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** 7.49 – 7.32 (m, 4H), 7.32 – 7.26 (m, 1H), 5.92 (d, *J* = 1.8 Hz, 1H), 4.92 (ddd, *J* = 8.7, 5.0, 3.4 Hz, 1H), 2.80 (dd, *J* = 13.5, 8.8 Hz, 1H), 2.51 (dd, *J* = 13.5, 5.1 Hz, 1H), 1.91 (d, *J* = 3.5 Hz, 1H), 1.74 (d, *J* = 1.5 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 144.0, 135.7, 128.5, 127.7, 125.8, 114.2, 72.5, 41.8, 21.8; **HRMS (DART):** Calcd for $C_{11}H_{12}Cl$ $[M+H–H_2O]^+$: 179.06220; Found: 179.06137; **Specific Rotation:** $[\alpha]^{23.5}_D$ +14.8° (*c* 0.54, $CHCl_3$) for a 86:14 er sample. Enantiomeric purity was determined by HPLC in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*-PrOH, 0.7 mL/min, 220 nm): t_R: 34.5 min (minor) and 36.1 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	35.267	188728	8878193	48.730
2	36.933	185965	9340859	51.270
Total		374693	18219051	100.000

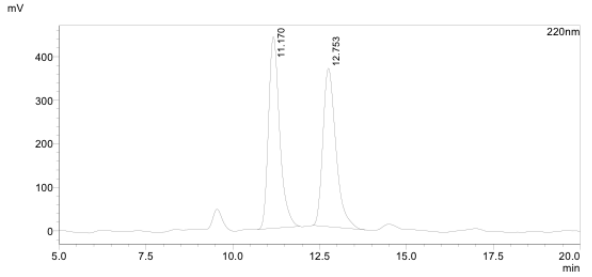
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	34.541	16827	786809	13.279
2	36.084	107419	5138192	86.721
Total		124245	5925001	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	35.267 min	8878193	48.730	1	34.541min	786809	13.279
2	36.933 min	9340859	51.270	2	36.084 min	5138192	86.721

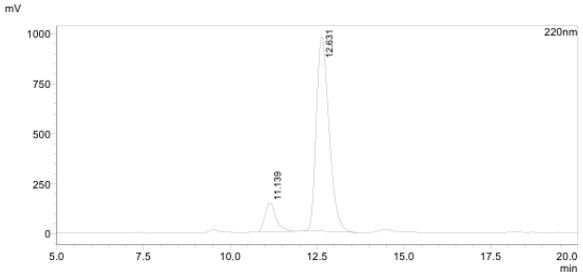
***tert*-Bu-(*R*,*Z*)-5-(4-Chloro-1-hydroxy-3-methylbut-3-en-1-yl)-1*H*-indole-1-carboxylate (3.99):** Following the general procedure for addition, (36.8 mg, 0.15 mmol) was transferred to an oven-dried vial that was carefully concentrated under reduced pressure in an ice-bath to afford the title compound as yellow oil (25.8 mg, 0.077 mmol). **IR (neat):** 3430 (br, m), 2974 (m), 2915 (m), 1730 (s), 1470 (m), 1369 (m), 1255 (m), 1159 (s), 1022 (s), 766 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.58 (m, 2H), 7.35 –7.33 (m, 1H), 6.55 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.90 (dt, *J* = 1.5, 0.7 Hz, 1H), 5.01 (ddd, *J* = 8.6, 5.3, 3.1 Hz, 1H), 3.01 – 2.74 (m, 1H), 2.56 (dd, *J* = 13.5, 5.3 Hz, 1H), 1.94 (d, *J* = 3.3 Hz, 1H), 1.72 (d, *J* = 1.6 Hz, 3H), 1.66 (s, 9H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 149.7, 138.6, 135.9, 134.8, 130.6, 126.4, 122.2, 118.1, 115.1,

114.0, 107.3, 83.7, 72.7, 42.1, 28.2, 21.9. **HRMS (DART):** Calcd for $C_{18}H_{21}NO_2Cl$ $[M+HH_2O]^+$: 318.12553; Found: 318.12483; **Specific Rotation:** $[\alpha]^{22.8}_D$ +5.8° (*c* 1.0, $CHCl_3$) for a 89:11 er sample. Enantiomeric purity was determined by HPLC in comparison with authentic racemic material (Chiralpak OZ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R 11.1 min (minor) and 12.6 min (major).



220nm

Peak#	Ret. Time	Height	Area	Area%
1	11.170	440263	9780776	50.690
2	12.753	363575	9514321	49.310
Total		803838	19295097	100.000

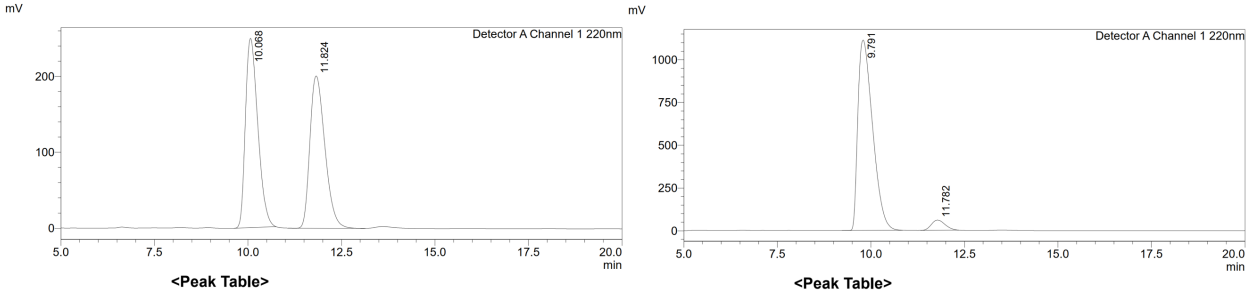


220nm

Peak#	Ret. Time	Height	Area	Area%
1	11.139	145131	3123440	11.159
2	12.631	972941	24866467	88.841
Total		1118072	27989908	100.000

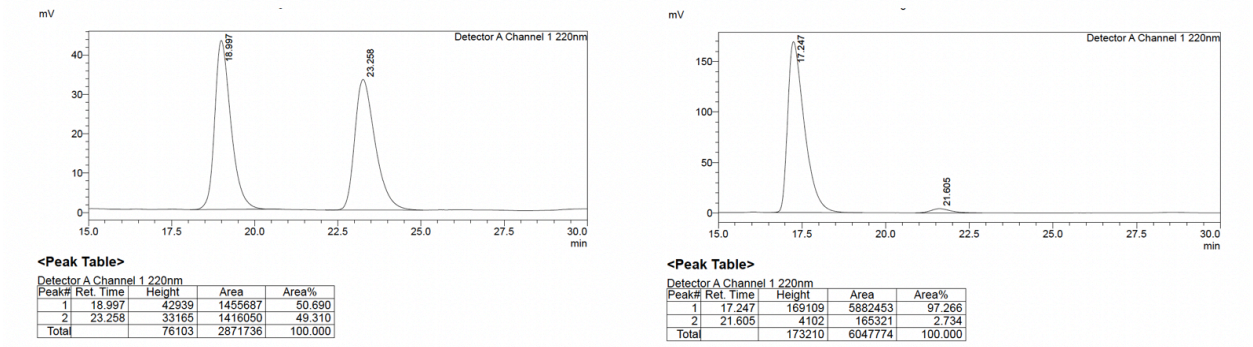
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	11.170 min	9780776	50.690	1	11.139 min	3123440	11.159
2	12.753 min	9514321	49.310	2	12.631 min	24866467	88.841

(*R*,1*E*,5*Z*)-6-Chloro-5-methyl-1-(2-methylthiazol-4-yl)hexa-1,5-dien-3-ol (3.100): Following the general procedure for addition, (*E*)-2-methyl-3-(2-methylthiazole-4-yl)acrylaldehyde (25.1 mg, 0.15 mmol) was transferred to an oven-dried vial. The reaction was quenched by addition of a saturated aqueous solution of sodium periodate (1.0 mL), extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to afford an unpurified residue that was purified by silica gel chromatography to afford the title compound as colorless oil (13.2 mg, 0.054 mmol). **IR (neat):** 3314 (br, m), 2949 (m), 2918 (m), 1506 (m), 1440 (s), 1189 (s), 1047 (s), 1015 (m), 875 (m), 782 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.95 (s, 1H), 6.66 – 6.42 (m, 1H), 5.90 (dt, *J* = 1.6, 0.8 Hz, 1H), 4.38 (dd, *J* = 8.4, 5.3 Hz, 1H), 2.69 (s, 3H), 2.60 – 2.42 (m, 2H), 2.08 (d, *J* = 1.3 Hz, 3H), 1.95 – 1.87 (br s, 1H), 1.82 (d, *J* = 1.6 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.6, 152.6, 141.5, 135.8, 119.1, 115.7, 113.9, 75.7, 38.1, 21.7, 14.2; **HRMS (DART):** Calcd for $C_{11}H_{17}NOSCl$ $[M+H]^+$: 258.07139; Found: 258.07166; **Specific Rotation:** $[\alpha]^{25.6}_D$ +5.7° (*c* 1.4, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*-PrOH, 0.7 mL/min, 220 nm): t_R: 9.7 min (major) and 11.7 min (minor).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	10.068 min	5771324	50.858	1	9.791 min	30377918	95.190
2	11.824 min	5576522	49.142	2	11.782 min	1534882	4.810

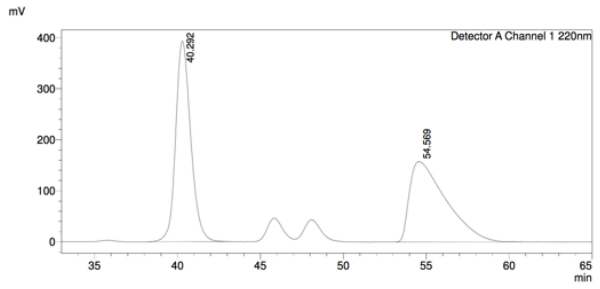
(3*S*,4*R*)-2-(4-Bromothiazol-2-yl)-4-chloro-2-methylhex-5-en-3-ol (3.108): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1H), 5.85 (dt, *J* = 17.1, 9.9 Hz, 1H), 5.11 – 4.94 (m, 2H), 4.56 (ddt, *J* = 9.7, 2.4, 0.5 Hz, 1H), 4.11 (dd, *J* = 6.5, 2.4 Hz, 1H), 3.82 (d, *J* = 6.5 Hz, 1H), 1.51 (d, *J* = 4.0 Hz, 6H.; **^{13}C NMR (150 MHz, $CDCl_3$):** 178.5, 133.6, 124.1, 118.3, 116.3, 81.9, 64.6, 44.8, 27.4, 25.0; **HRMS (DART):** Calcd for $C_{10}H_{14}BrClNOS$ $[M+H]^+$: 309.96625; Found: 309.96681. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 99:1 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 17.3 min (major) and 21.6 min (minor).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	18.997 min	1455687	50.690	1	17.247 min	5882453	97.266
2	23.258 min	1416050	49.310	2	21.605 min	165321	2.734

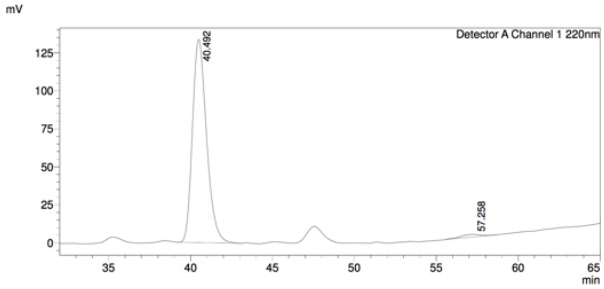
(1*S*,2*R*)-2-chloro-1-(4-Methoxyphenyl)but-3-en-1-ol (3.111): **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.27 (m, 2H), 6.92 – 6.85 (m, 2H), 5.93 (ddd, *J* = 17.0, 10.2, 8.6 Hz, 1H), 5.34 – 5.17 (m, 2H), 4.88 (dd, *J* = 4.9, 2.8 Hz, 1H), 4.54 (ddt, *J* = 8.6, 4.9, 0.8 Hz, 1H), 3.81 (s, 3H), 2.45 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.6, 133.8, 131.5, 128.1, 120.1, 113.8. 69.6, 67.6, 55.4; **HRMS (DART):** Calcd for $C_{11}H_{12}OCl$ $[M+H–H_2O]^+$: 195.05712; Found: 195.05650;

Specific Rotation: $[\alpha]^{22.7}$ +8.03° (*c* 0.56, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99:1 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 40.5 min (major) and 57.3 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	40.292	393307	24840186	50.881
2	54.569	157527	23979813	49.119
Total		550833	48819999	100.000



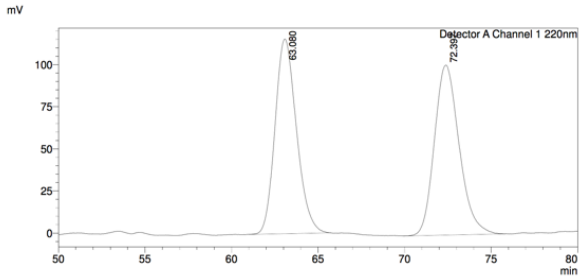
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	40.492	133606	8010680	98.164
2	57.258	1705	149838	1.836
Total		135312	8160518	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	40.292 min	24840186	50.881	1	40.491 min	8010680	98.164
2	54.569 min	23979813	49.119	2	57.258 min	149838	1.836

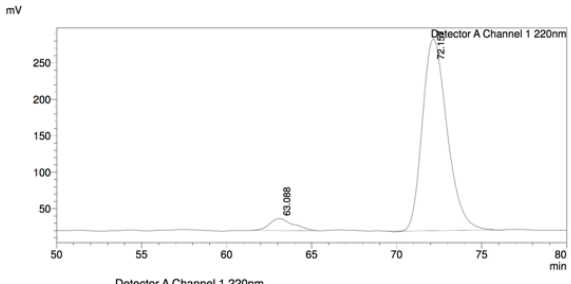
(1*S*,2*R*)-2-Chloro-1-cyclohexylbut-3-en-1-ol (3.112): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (ddd, *J* = 17.0, 10.1, 9.1 Hz, 1H), 5.47 – 5.15 (m, 2H), 4.54 (dd, *J* = 9.1, 4.1 Hz, 1H), 3.59 – 3.30 (m, 1H), 2.12 (d, *J* = 3.4 Hz, 1H), 2.06 – 1.90 (m, 1H), 1.83 – 1.36 (m, 5H), 1.32 – 0.80 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 134.0, 119.7, 78.5, 65.8, 40.0, 29.1, 28.6, 26.4, 26.1, 25.9; **HRMS (DART):** Calcd for $C_{10}H_{16}Cl$ $[M+H–H_2O]^+$: 171.09350; Found: 171.09280; **Specific Rotation:** $[\alpha]^{22.4}$ +14.4° (*c* 1.39, $CHCl_3$).

(3*S*,4*R*)-4-Chloro-2,2-dimethylhex-5-en-3-ol (3.113): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (dt, *J* = 17.2, 9.9 Hz, 1H), 5.51 – 5.03 (m, 2H), 4.74 (dd, *J* = 9.7, 2.1 Hz, 1H), 3.64 (dd, *J* = 3.7, 2.1 Hz, 1H), 2.27 (dd, *J* = 3.6, 0.8 Hz, 1H), 0.97 (s, 9H); **HRMS (DART):** Calcd for $C_{10}H_{10}Cl$ $[M+H–H_2O]^+$: 145.07785; Found: 145.07815; **Specific Rotation:** $[\alpha]^{22.4}$ +19.9° (*c* 0.71, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 63.1 min (minor) and 72.2 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	63.080	115577	9978135	49.826
2	72.397	100892	10047633	50.174
Total		216469	20025768	100.000



Detector A Channel 1 220nm

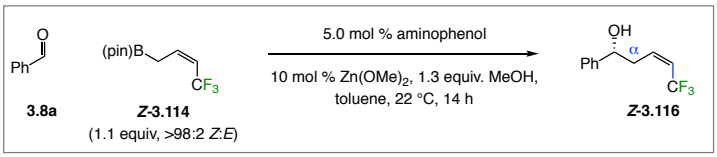
Peak#	Ret. Time	Height	Area	Area%
1	63.088	16483	1593128	5.646
2	72.157	263193	26626055	94.354
Total		279676	28219183	100.000

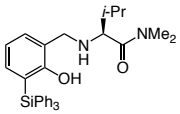
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	63.080 min	9978135	49.826	1	63.088 min	1593128	5.646
2	72.397 min	10047633	50.174	2	72.157 min	26626055	94.354

3.5.12 Representative Procedure for Catalytic Enantioselective Additions of Z–CF_3 Substituted Allyl Boronate

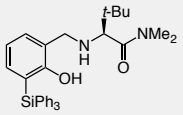
In an N_2-filled glovebox, an oven-dried vial equipped with a stir bar was charged with **ap-3** (2.6 mg, 0.005 mmol), zinc methoxide (3.2 mg, 0.025 mmol) and toluene (2.0 mL), and the resulting mixture was allowed to stir for 15 min at 22 °C. In another vial, an aldehyde was dissolved in toluene (1.0 mL). A third oven-dried vial was charged with the aforementioned aldehyde (stock) solution (100 µL, 0.1 mmol) and **ap-3**/$Zn(OMe)_2$ (stock) solution (400 µL), followed by MeOH (5 µL, 0.13 mmol). The vial was sealed (septum cap and electrical tape), brought out of the glovebox and allowed to cool to 4 °C. After 5 min, ***Z*-3.114** (25 mg, 0.105 mmol) was added by syringe, and the mixture was allowed to stir for 2 h at 4 °C. The reaction was quenched by the addition of MeOH (1.5 mL) and the resulting solution was allowed to stir for 30 min at 22 °C. The volatiles were removed in vacuo and the resulting opaque oil was purified by silica gel column chromatography (gradient eluting with 10:1 → 4:1 hexanes:Et_2O).

3.5.13 Catalyst Screening for Additions of Z-CF_3-Substituted Allyl Boronate

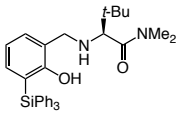




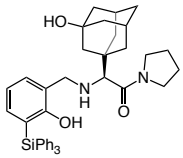
ap-1
>98% conv, 74:26 α:γ,
64% yield (α), 96:4 *Z*:*E*,
86:14 er



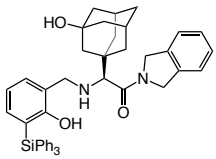
ap-3
>98% conv, 86:14 α:γ,
68% yield (α), 94:6 *Z*:*E*,
92:8 er



ap-4
>98% conv, 83:17 α:γ,
71% yield (α), 95:5 *Z*:*E*,
93:7er



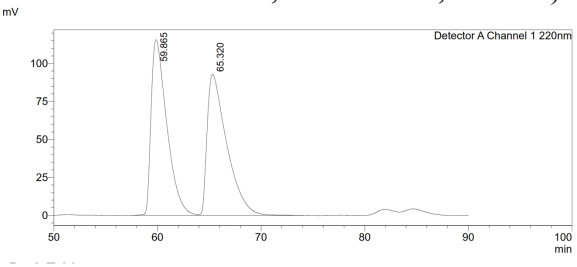
ap-5
>98% conv, 88:12 α:γ,
81% yield (α), 94:6 *Z*:*E*,
95:5er



ap-6
>98% conv, 89:11 α:γ,
80% yield (α), 93:7 *Z*:*E*,
95:5 er

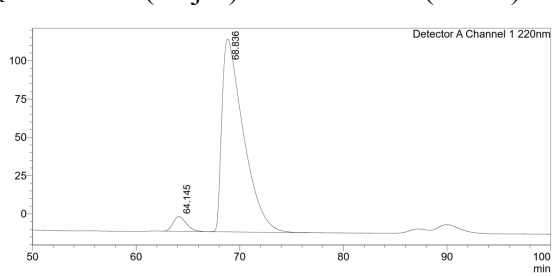
3.5.14 Analytical Data for Addition of Z-CF_3-Substituted Allyl Boronate 4d to Aldehydes

(*R*,*Z*)-5,5,5-Trifluoro-1-phenylpent-3-en-1-ol (*Z*-3.116): Following the general procedure for addition, benzaldehyde (15.9 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (19.0 mg, 0.088 mmol). **IR (neat):** 3375 (br, w), 2920 (w), 1671 (w), 1454 (w), 1418 (w), 1274 (m), 1226 (m), 1195 (m), 1112 (s), 1051 (m), 698 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41 – 7.28 (m, 5H), 6.10 (dt, *J* = 11.7, 7.6 Hz, 1H), 5.70 (dqt, *J* = 11.9, 8.5, 1.8 Hz, 1H), 4.80 (dd, *J* = 7.6, 5.5 Hz, 1H), 2.86 – 2.68 (m, 2H), 1.99 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 143.4, 138.6 (q, *J* = 5.4 Hz), 128.8, 128.2, 125.9, 123.3 (q, *J* = 271.8 Hz), 120.4 (q, *J* = 33.4 Hz), 73.6, 37.7; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –57.97 (3F, dt, *J* = 8.5, 2.2 Hz); **HRMS (DART):** Calcd for $C_{11}H_{10}F_3$ $[M+H–H_2O]^+$: 199.0735; Found: 199.0741; **Specific Rotation:** $[\alpha]^{20.0}_D$ +34.97° (*c* 0.74, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 68.8 min (major) and 64.1 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	59.865	115796	12218876	49.924
2	65.320	92858	12256231	50.076
Total		208653	24475107	100.000



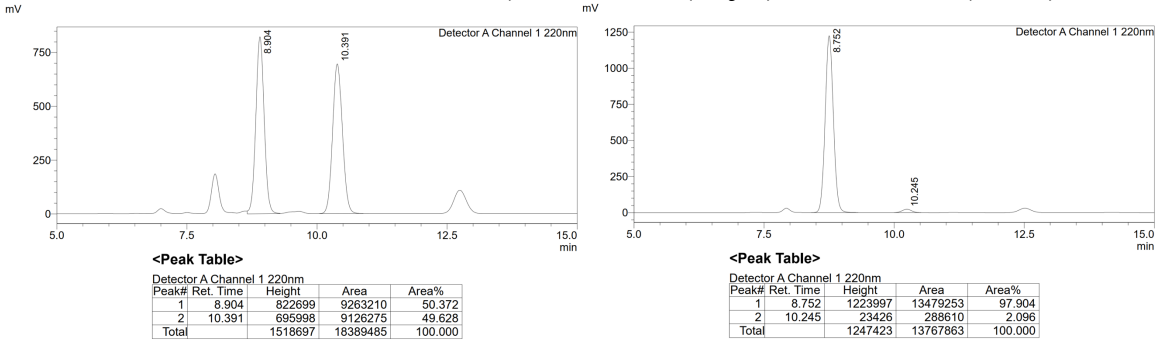
<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Conc.
1	64.145	856550	9611	4.501
2	68.836	18174970	125917	95.499
Total		19031520	135528	

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	59.865 min	12218876	49.924	1	64.145 min	856550	4.501

2	65.320 min	12256231	50.076	2	68.836 min	18174970	95.499

(*R*,*Z*)-1-(2-Bromophenyl)-5,5,5-trifluoropent-3-en-1-ol (*Z*-3.117): Following the general procedure for addition, 2-Bromobenzaldehyde (27.8 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (26.9 mg, 0.095 mmol). **IR (neat):** 3385 (br, m), 1671 (w), 1468 (w), 1419 (m), 1275 (m), 1224 (m), 1196 (m), 1117 (s), 1062 (m), 1045 (m), 1022 (m), 756 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.36 (tdd, *J* = 7.8, 1.2, 0.5 Hz, 1H), 7.16 (ddd, *J* = 7.9, 7.3, 1.7 Hz, 1H), 6.18 (dt, *J* = 11.7, 7.5 Hz, 1H), 5.78 – 5.68 (dqt, *J* = 12.0, 8.4, 1.8 Hz, 1H), 5.21 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.79 – 2.67 (m, 1H), 2.02 (d, *J* = 3.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.2, 138.3 (q, *J* = 5.4 Hz), 132.9, 129.4, 128.0, 123.2 (q, *J* = 271.7 Hz), 121.9, 120.7 (q, *J* = 33.5 Hz), 71.9, 36.0; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.22 (3F, dt, *J* = 8.5, 2.1 Hz); **HRMS (DART):** Calcd for $C_{11}H_9BrF_3$ $[M+H–H_2O]^+$: 276.984; Found: 276.9834; **Specific Rotation:** $[\alpha]^{20.0}_D$ +59.6° (*c* 1.25, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 8.7 min (major) and 10.2 min (minor).



<Peak Table>
Detector A Channel 1 220nm

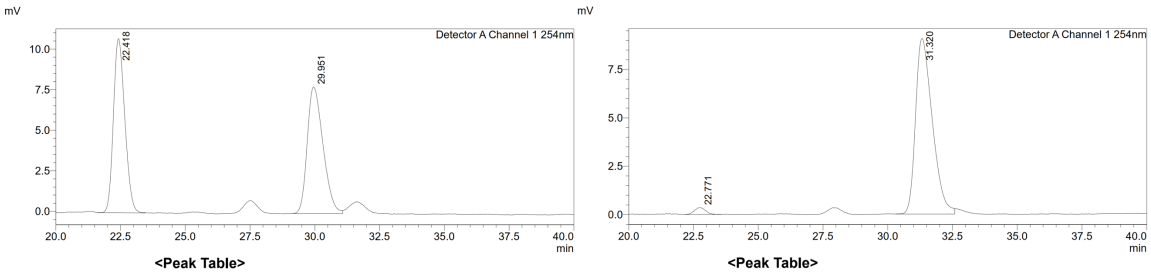
Peak#	Ret. Time	Height	Area	Area%
1	8.904	822699	9263210	50.372
2	10.391	695998	9126275	49.628
Total		1518697	18389485	100.000

<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	8.752	1223997	13479253	97.904
2	10.245	23426	288610	2.096
Total		1247423	13767863	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	8.904 min	9263210	50.372	1	8.752 min	13479253	97.904
2	10.391 min	9126275	49.628	2	10.245 min	288610	2.096

(*R*,*Z*)-5,5,5-Trifluoro-1-(o-tolyl)pent-3-en-1-ol (*Z*-3.118): Following the general procedure for addition, 2-Methylbenzaldehyde (18.0 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (20.9 mg, 0.091 mmol). **IR (neat):** 3365 (br, m), 2930 (w), 1670 (w), 1488 (w), 1461 (m), 1275 (m), 1228 (m), 1119 (s), 1049 (m), 758 (m), 729 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.29 – 7.12 (m, 3H), 6.19 (dtd, *J* = 11.7, 7.7, 0.7 Hz, 1H), 5.78 – 5.65 (m, 1H), 5.05 (ddd, *J* = 8.0, 5.1, 3.2 Hz, 1H), 2.77 – 2.66 (m, 2H), 2.34 (s, 3H), 1.79 (d, *J* = 3.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.6, 139.0 (q, *J* = 5.4 Hz), 134.5, 130.7, 127.8, 126.6, 125.2, 123.3 (q, *J* = 271.8 Hz), 120.3 (q, *J* = 33.4 Hz), 69.9, 36.5, 19.0; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –59.09 (3F, dt, *J* = 8.4, 2.2 Hz); **HRMS (DART):** Calcd for $C_{12}H_{12}F_3$ $[M+H–H_2O]^+$: 213.0891; Found: 213.0886; **Specific Rotation:** $[\alpha]^{20.0}_D$ +59.9° (*c* 0.95, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 99:1 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R: 31.3 min (major) and 22.7 min (minor).



<Peak Table>
Detector A Channel 1 254nm

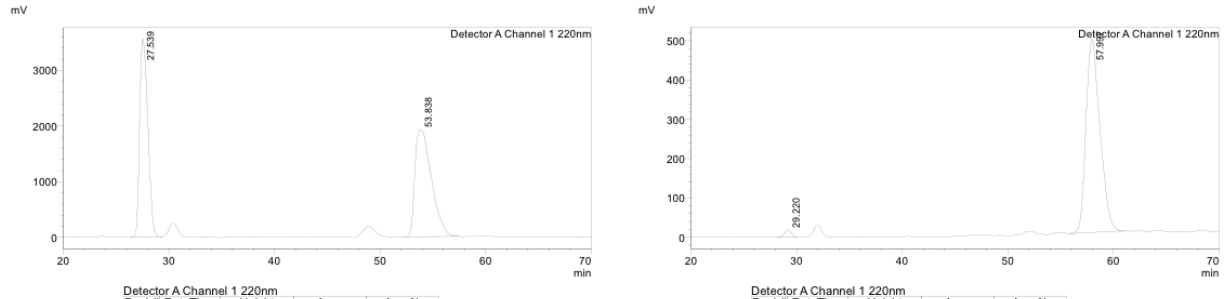
Peak#	Ret. Time	Height	Area	Area%
1	22.418	10727	327530	49.706
2	29.951	7805	331402	50.294
Total		18533	658932	100.000

<Peak Table>
Detector A Channel 1 254nm

Peak#	Ret. Time	Height	Area	Area%
1	22.771	355	10671	2.543
2	31.320	9078	408954	97.457
Total		9433	419625	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	22.418 min	327530	49.706	1	22.771 min	10671	2.543
2	29.951 min	331402	50.294	2	31.320 min	408954	97.457

(*R*,*Z*)-1-(6-Bromonaphthalen-2-yl)-5,5,5-trifluoropent-3-en-1-ol (*Z*-3.119): Following the general procedure for addition, 6-Bromo-2-napthaldehyde (35.3 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (32.1 mg, 0.093 mmol). **IR (neat):** 3367 (br, m), 1671 (w), 1591 (w), 1418 (w), 1275 (m), 1228 (w), 1118 (s), 1062 (m), 877 (m), 807 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.02 – 7.98 (m, 1H), 7.78 – 7.72 (m, 2H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.49 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.11 (dt, *J* = 11.7, 7.6 Hz, 1H), 5.76 – 7.66 (m, 1H), 4.96 (dd, *J* = 7.3, 5.7 Hz, 1H), 2.91 – 2.78 (m, 2H), 2.11 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.2, 138.3 (q, *J* = 5.4 Hz), 134.3, 131.8, 129.92, 129.89, 129.8, 127.8, 124.9, 124.6, 123.2 (q, *J* = 270 Hz), 120.7 (q, *J* = 33.3 Hz), 120.2, 73.5, 37.5; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –59.13 (3F ,dt, *J* = 8.4, 2.2 Hz); **HRMS (DART):** Calcd for $C_{15}H_{11}BrF_3$ $[M+H–H_2O]^+$: 326.9996; Found: 327.0002; **Specific Rotation:** $[\alpha]^{20.0}_D$ +21.9° (*c* 1.50, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 57.9 min (major) and 29.2 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	27.539	3554528	191905224	47.936
2	53.838	1925812	208427305	52.064
Total		5480340	400332529	100.000

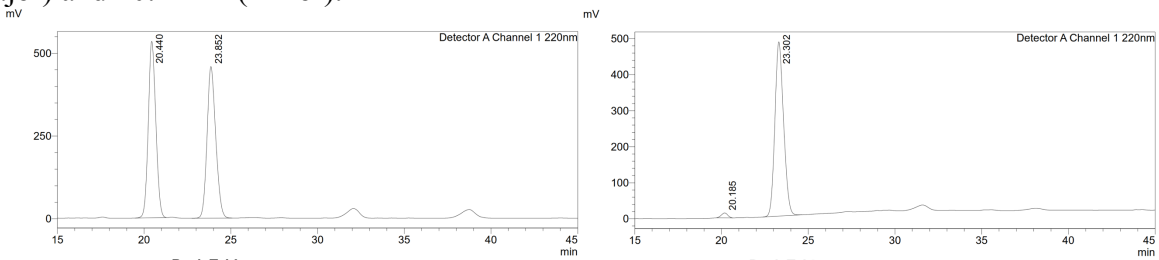
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	29.220	18218	766234	1.668
2	57.997	492342	45176814	98.332
Total		510561	45943048	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	27.539 min	191905224	47.936	1	29.220 min	766234	1.668
2	53.838 min	2208427305	52.064	2	57.997 min	45176814	98.332

(*R*,*Z*)-1-(3-Chlorophenyl)-5,5,5-trifluoropent-3-en-1-ol (*Z*-3.120): Following the general procedure for addition, 3-Chlorobenzaldehyde (21.1 mg, 0.15 mmol) was transferred to an oven-

dried vial to afford the title compound as colorless oil (23.3 mg, 0.093 mmol). **IR (neat):** 3354 (br, m), 1671 (w), 1598 (w), 1576 (w), 1419 (m), 1276 (m), 1227 (m), 1197 (m), 1120 (s), 788 (m), 698 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 – 7.34 (m, 1H), 7.35 – 7.19 (m, 3H), 6.09 (dt, *J* = 11.7, 7.6 Hz, 1H), 5.77 – 5.67 (m, 1H), 4.87 – 4.74 (m, 1H), 2.77 – 2.72 (m, 2H), 1.93 (d, *J* = 3.6 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 145.4, 138.0 (q, *J* = 5.3 Hz), 134.7, 130.1, 128.3, 126.1, 124.0, 123.2 (q, *J* = 270.0 Hz) 120.9 (q, *J* = 33.5 Hz), 72.9, 37.7; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.26 (3F, dt, *J* = 8.5, 2.1 Hz); **HRMS (DART):** Calcd for $C_{11}H_9F_3Cl$ $[M+H–H_2O]^+$: 233.0345; Found: 233.0353; **Specific Rotation:** $[\alpha]^{20.0}_D$ +24.55° (*c* 1.00, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 23.3 min (major) and 20.1 min (minor).



<Peak Table>
Detector A Channel 1 220nm

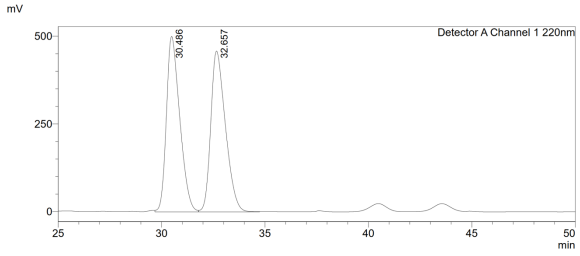
Peak#	Ret. Time	Height	Area	Area%
1	20.440	532858	15920649	49.826
2	23.852	457790	16032077	50.174
Total		990648	31952727	100.000

<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	20.185	13538	343979	2.010
2	23.302	483546	16769906	97.990
Total		497084	17113885	100.000

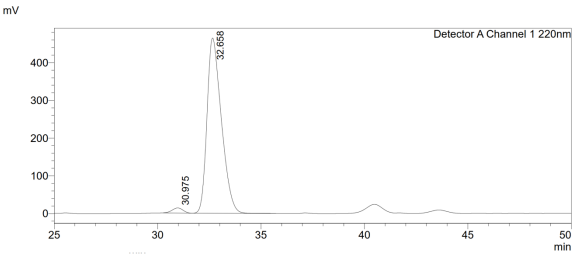
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	20.440 min	15920649	49.826	1	20.185 min	343979	2.010
2	23.852 min	16032077	50.174	2	23.302 min	16769906	97.990

(*R*,*Z*)-5,5,5-Trifluoro-1-(3-methoxyphenyl)pent-3-en-1-ol (*Z*-3.121): Following the general procedure for addition, 3-Methoxybenzaldehyde (20.4 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (21.2 mg, 0.086 mmol). **IR (neat):** 3406 (br, m), 1602 (w), 1587 (w), 1488 (w), 1419 (w), 1268 (m), 1118 (s), 1043 (m), 871 (w), 699 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.26 (m, 1H), 6.99 – 6.90 (m, 2H), 6.89 – 6.80 (m, 1H), 6.10 (dt, *J* = 11.7, 7.6 Hz, 1H), 5.77 – 5.63 (m, 1H), 4.81 – 4.77 (m, 1H), 3.82 (d, *J* = 0.9 Hz, 3H), 2.83 – 2.72 (m, 2H), 1.89 (d, *J* = 3.5 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 160.0, 145.1, 138.6 (q, *J* = 5.4 Hz), 129.9, 123.3 (q, *J* = 271.8 Hz), 120.4 (q, *J* = 33.4 Hz), 118.1, 113.5, 111.4, 73.5, 55.4, 37.6; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.25 (3F, dt, *J* = 8.5, 2.2 Hz); **HRMS (DART):** Calcd for $C_{12}H_{12}F_3O$ $[M+H–H_2O]^+$: 229.084; Found: 229.085; **Specific Rotation:** $[\alpha]^{20.0}_D$ +15.2° (*c* 1.39, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 30.9 min (major) and 32.6 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	30.486	500336	22474231	49.830
2	32.657	458433	22627254	50.170
Total		958769	45101485	100.000

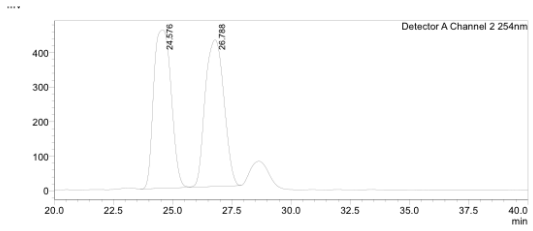


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	30.975	13666	490854	2.139
2	32.658	464694	22462335	97.861
Total		478360	22953190	100.000

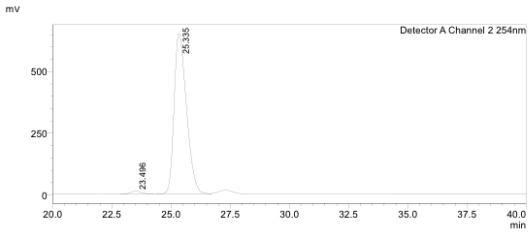
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	30.486 min	22474231	49.830	1	30.975 min	490854	2.139
2	32.657 min	22627254	50.170	2	32.658 min	22462335	97.861

(*R*,*Z*)-5,5,5-Trifluoro-1-(4-nitrophenyl)pent-3-en-1-ol (*Z*-3.122): Following the general procedure for addition, 4-Nitrobenzaldehyde (22.7 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (25.5 mg, 0.098 mmol). **IR (neat):** 3444 (br, m), 1671 (w), 1605 (w), 1519 (s), 1418 (w), 1346 (s), 1276 (m), 1226 (m), 1198 (m), 1118 (s), 1013 (m), 856 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.33 – 8.11 (m, 2H), 7.61 – 7.43 (m, 2H), 6.10 (dt, *J* = 11.7, 7.7 Hz, 1H), 5.79 – 5.69 (m, 1H), 4.97 (t, *J* = 6.3 Hz, 1H), 2.79 – 2.74 (m, 2H), 2.24 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.5, 147.6, 137.3 (q, *J* = 5.4 Hz), 126.6, 123.9, 123.0 (q, *J* = 271.9 Hz), 121.3 (q, *J* = 33.5 Hz), 72.5, 37.7; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.27 (3F, dt, *J* = 8.5, 2.1 Hz); **HRMS (DART):** Calcd for $C_{11}H_{11}F_3NO_3$ $[M+H]^+$: 262.0691; Found: 262.0694; **Specific Rotation:** $[\alpha]^{20.0}_D$ +16.9° (*c* 1.21, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R: 23.6 min (major) and 22.0 min (minor).



<Peak Table>
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	24.576	458244	23619537	50.258
2	26.788	423778	23376975	49.742
Total		882022	46996512	100.000



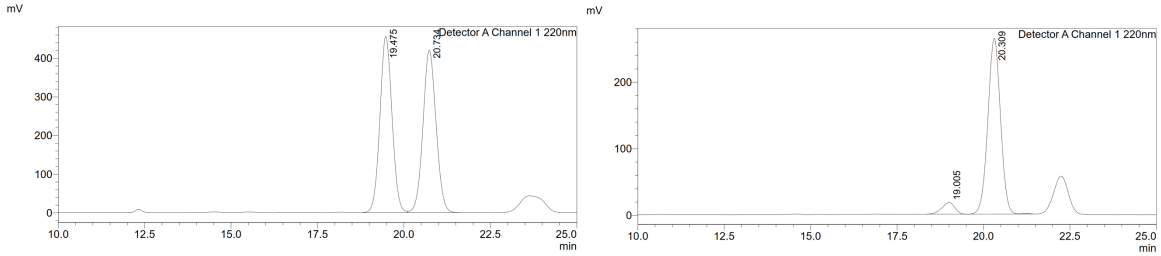
<Peak Table>
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	23.496	11877	389560	1.609
2	25.335	650789	23816871	98.391
Total		662666	24206432	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	24.576 min	23619537	50.258	1	23.496 min	389560	1.609
2	26.788 min	23376975	49.742	2	25.335 min	23816871	98.391

(*R*,*Z*)-5,5,5-Trifluoro-1-(furan-2-yl)pent-3-en-1-ol (*Z*-3.123): Following the general procedure for addition, furfural (14.4 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (16.9 mg, 0.083 mmol). **IR (neat):** 3373 (br, m), 1672 (w), 1420 (w),

1329 (m), 1278 (m), 1118 (s), 1011 (m), 740 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.35 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.27 (dt, *J* = 3.2, 0.7 Hz, 1H), 6.10 (dt, *J* = 11.7, 7.4 Hz, 1H), 5.79 – 5.66 (m, 1H), 4.84 – 4.78 (m, 1H), 2.93 – 2.83 (m, 2H), 2.04 (d, *J* = 5.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.3, 142.5, 137.8 (q, *J* = 5.5 Hz), 123.2 (q, *J* = 270 Hz), 120.6 (q, *J* = 33.5 Hz), 110.4, 106.6, 66.8, 37.6; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.43 (3F, dt, *J* = 8.5, 2.3 Hz); **HRMS (DART):** Calcd for $C_9H_8F_3O$ $[M+H–H_2O]^+$: 189.0527.0891; Found: 189.0532; **Specific Rotation:** $[\alpha]^{20.0}_D$ +10.9° (*c* 0.74, $CHCl_3$) for a 93:7 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 20.3 min (major) and 19.0 min (minor).



<Peak Table>
Detector A Channel 1 220nm

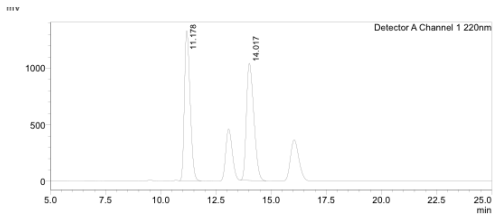
Peak#	Ret. Time	Height	Area	Area%
1	19.475	455959	11090925	49.991
2	20.734	420351	11095040	50.009
Total		876310	22185966	100.000

<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	19.005	17535	453316	6.325
2	20.309	263982	6714278	93.675
Total		281517	7167594	100.000

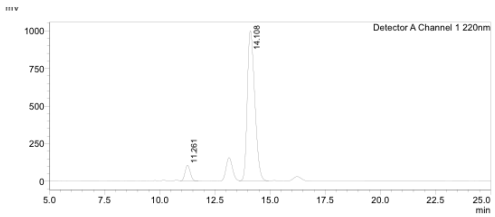
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	19.475 min	11090925	49.991	1	19.005 min	453316	6.325
2	20.734 min	11095040	50.009	2	20.309 min	6714278	93.675

(*R*,*Z*)-1-(Benzofuran-2-yl)-5,5,5-trifluoropent-3-en-1-ol (*Z*-3.124): Following the general procedure for addition, 2-Benzofurancarboxaldehyde (21.9 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (24.1 mg, 0.094 mmol). **IR (neat):** 3364 (br, m), 1672 (w), 1454 (m), 1420 (w), 1278 (m), 1253 (m), 1229 (m), 1120 (s), 1072 (m), 880 (w), 810 (m), 750 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.56 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.47 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.24 (td, *J* = 7.5, 1.2 Hz, 1H), 6.66 (s, 1H), 6.15 (dt, *J* = 11.7, 7.4 Hz, 1H), 5.83 – 5.67 (m, 1H), 4.96 (dt, *J* = 7.1, 5.5 Hz, 1H), 3.05 – 2.92 (m, 2H), 2.22 (d, *J* = 5.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 157.8, 154.9, 137.4 (q, *J* = 5.4 Hz), 128.0, 124.6, 123.2 (q, *J* = 271.8 Hz), 123.1, 121.3, 120.9 (q, *J* = 33.5 Hz), 111.4, 103.3, 67.3, 34.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.37 (3F, dt, *J* = 8.5, 2.2 Hz); **HRMS (ESI+):** Calcd for $C_{13}H_{10}F_3O$ $[M+H–H_2O]^+$: 239.068374; Found: 239.068298; **Specific Rotation:** $[\alpha]^{20.0}_D$ +11.3° (*c* 1.14, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R: 14.7 min (major) and 11.7 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	11.178	1328058	23883206	49.505
2	14.017	1037213	24360839	50.495
Total		2365270	48244045	100.000

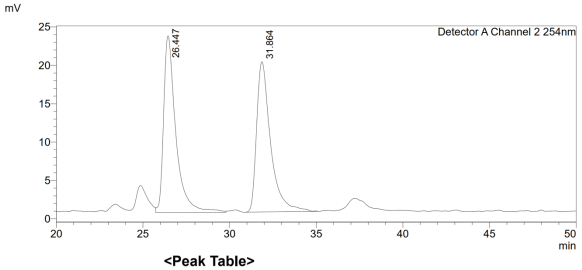


<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	11.261	104535	1717733	6.844
2	14.108	995565	23379882	93.156
Total		1100100	25097615	100.000

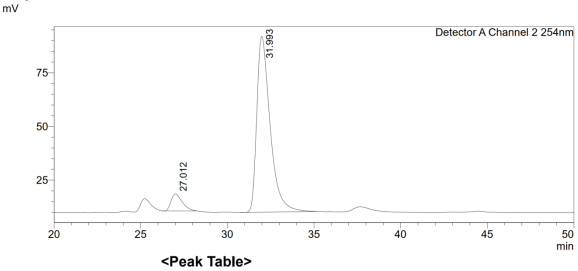
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	11.178 min	23883206	49.505	1	11.261 min	1717733	6.844
2	14.017 min	24360839	50.495	2	14.108 min	23379882	93.156

(*R*,*Z*)-5,5,5-Trifluoro-1-(pyridin-3-yl)pent-3-en-1-ol (*Z*-3.125): Following the general procedure for addition, 3-Pyridinecarboxaldehyde (16.1 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (19.3 mg, 0.089 mmol). **IR (neat):** 3192 (br, m), 2917 (w), 1671 (w), 1422 (m), 1320 (m), 1277 (m), 1118 (s), 1070 (m), 1029 (w), 714 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.56 – 8.31 (m, 2H), 7.72 (dt, *J* = 7.9, 2.1 Hz, 1H), 7.28 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 6.10 (dt, *J* = 11.7, 7.6 Hz, 1H), 5.76 – 5.65 (m, 1H), 4.84 (dd, *J* = 7.4, 5.6 Hz, 1H), 3.82 (s, 1H), 2.83 – 2.68 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.0, 147.4, 139.3, 137.8 (q, *J* = 5.2 Hz), 133.9, 123.8, 123.1 (q, *J* = 271.8 Hz), 120.8 (q, *J* = 34.0 Hz), 70.9, 37.6; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.31 (3F, dt, *J* = 8.4, 2.1 Hz); **HRMS (DART):** Calcd for $C_{10}H_{11}F_3NO$ $[M+H]^+$: 218.0793; Found: 218.0793; **Specific Rotation:** $[\alpha]^{20.0}_D$ +46.1° (*c* 0.54, $CHCl_3$) for a 93:7 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 95:5 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R: 31.9 min (major) and 27.0 min (minor).



<Peak Table>
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	26.447	23032	1131463	50.678
2	31.864	19580	1101207	49.322
Total		42611	2232669	100.000



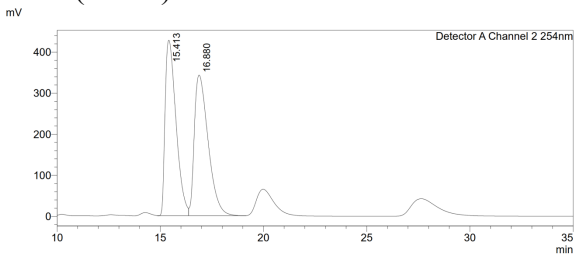
<Peak Table>
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	27.012	7874	351261	7.422
2	31.993	81996	4381557	92.578
Total		89870	4732818	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	26.447 min	1131463	50.678	1	27.012 min	351261	7.422
2	31.864 min	1101207	49.322	2	31.993 min	4381557	92.578

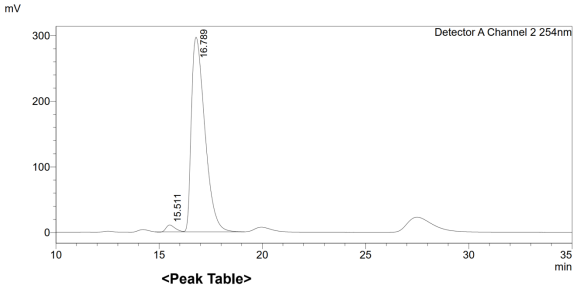
(*R*,*Z*)-7,7,7-Trifluoro-1-phenylhept-5-en-1-yn-3-ol (*Z*-3.126): Following the general procedure for addition, 3-Phenyl-2-propynal (19.5 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (22.3 mg, 0.093 mmol). **IR (neat):** 3359 (br, m), 1672 (w), 1492 (w), 1419 (w), 1277 (m), 1228 (m), 1120 (s), 1041 (m), 966 (m), 756 (m), 722 (m) cm^{-}

[1]; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46 – 7.39 (m, 2H), 7.37 – 7.29 (m, 3H), 6.25 (dt, *J* = 11.8, 7.5 Hz, 1H), 5.89 – 5.70 (m, 1H), 4.74 (app q, *J* = 5.9 Hz, 1H), 2.86 – 2.82 (m, 2H), 1.96 (d, *J* = 5.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.1, 137.1 (q, *J* = 5.4 Hz), 131.8, 128.8, 128.4, 123.2 (q, *J* = 271.9 Hz), 121.1 (q, *J* = 33.6 Hz), 88.4, 86.1, 61.7, 36.5; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –59.26 (3F, dt, *J* = 8.5, 2.1 Hz); **HRMS (DART):** Calcd for $C_{13}H_{10}F_3$ $[M+H-H_2O]^+$: 223.0735; Found: 223.0735; **Specific Rotation:** $[\alpha]^{20.0}_D$ –3.4° (*c* 1.1, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AY-3, 99:1 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R: 16.7 min (major) and 15.5 min (minor).



<Peak Table>
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	15.413	427350	15667125	49.536
2	16.880	342258	15960613	50.464
Total		769608	31627738	100.000

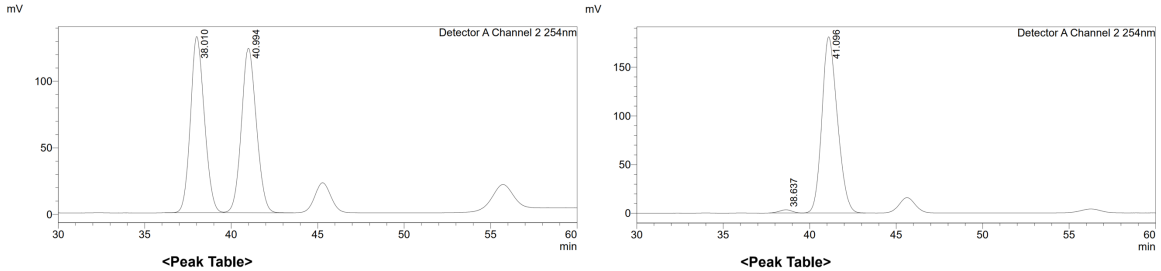


<Peak Table>
Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Height	Conc.
1	15.511	312897	10524	2.267
2	16.789	13489402	296461	97.733
Total		13802299	306985	

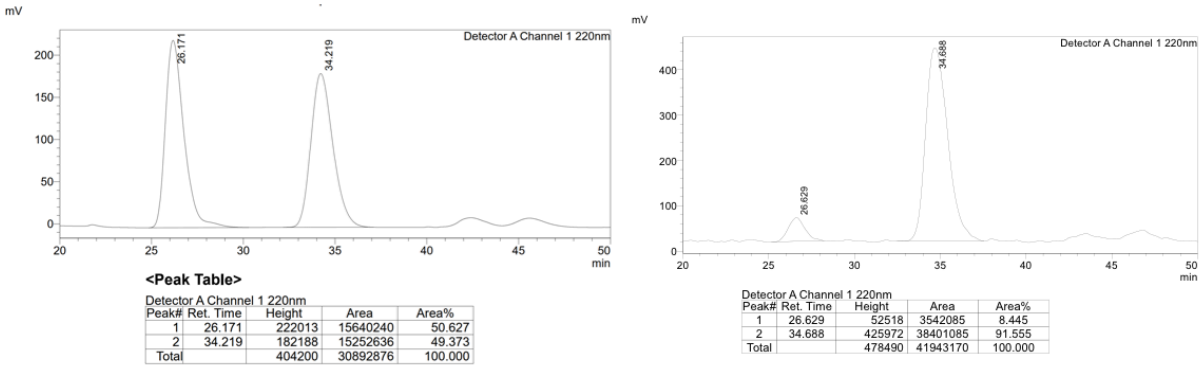
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	15.413 min	15667125	49.536	1	15.511 min	312897	2.267
2	16.880 min	15960613	50.464	2	16.789 min	13489402	97.733

(*R*,1*Z*,5*Z*)-2-Bromo-7,7,7-trifluoro-1-phenylhepta-1,5-dien-3-ol (*Z*-3.127): Following the general procedure for addition, *α*-Bromocinnamaldehyde (31.7 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (29.8 mg, 0.093 mmol). **IR (neat):** 3386 (br, m), 1672 (w), 1429 (w), 1446 (w), 1418 (w), 1276 (m), 1228 (m), 1195 (m), 1119 (s), 1074 (m), 1050 (m), 754 (m), 693 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 – 7.58 (m, 2H), 7.43 – 7.32 (m, 3H), 7.12 (s, 1H), 6.12 (dt, *J* = 11.7, 7.6 Hz, 1H), 5.83 – 5.71 (m, 1H), 4.43 – 4.37 (m, 1H), 2.89 – 2.76 (m, 2H), 2.22 (d, *J* = 5.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.3 (q, *J* = 5.4 Hz), 134.7, 129.2, 128.9, 128.5, 128.3, 128.3, 123.2 (q, *J* = 271.9 Hz), 120.9 (q, *J* = 33.6 Hz), 76.5, 34.7; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.24 (3F, dt, *J* = 8.5, 2.1 Hz); **HRMS (ESI+):** Calcd for $C_{13}H_{11}BrF_3$ $[M+H-H_2O]^+$: 302.9996; Found: 302.9992; **Specific Rotation:** $[\alpha]^{20.0}_D$ – 10.9° (*c* 1.37, $CHCl_3$) for a 98.5:1.5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OJ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R: 41.0 min (major) and 38.6 min (minor).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	38.010 min	7419559	49.923	1	38.673 min	166532	1.456
2	40.994 min	7442395	50.077	2	41.096 min	11270414	98.544

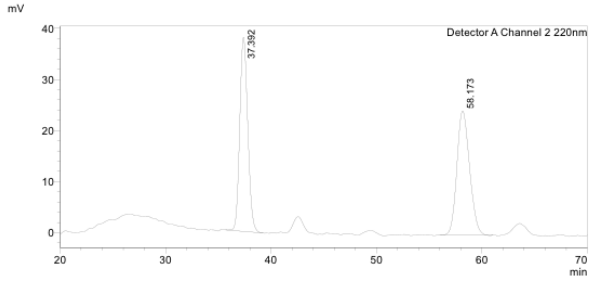
(*R*,*Z*)-7,7,7-Trifluoro-1,1-diphenylhepta-1,5-dien-3-ol (*Z*-3.128): Following the general procedure for addition, β-Phenylcinnamaldehyde (31.2 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (24.8 mg, 0.078 mmol). **IR (neat):** 3343 (br, m), 3057 (w), 3024 (w), 1670 (w), 1493 (w), 1444 (w), 1275 (m), 1228 (m), 1197 (m), 1119 (s), 1030 (m), 764 (m), 730 (w), 699 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44 – 7.33 (m, 3H), 7.33 – 7.16 (m, 7H), 6.16 – 6.01 (m, 2H), 5.75 – 5.65 (m, 1H), 4.41 – 4.22 (m, 1H), 2.67 – 2.63 (m, 2H), 1.66 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 144.7, 141.4, 139.0, 138.3 (q, J = 5.4 Hz), 129.6, 129.6, 128.5, 128.3, 128.0, 127.8, 127.6, 123.2 (q, J = 271.8 Hz), 120.3 (q, J = 33.4 Hz), 68.6, 36.3; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.06 (3F, dt, J = 8.3, 2.0 Hz); **HRMS (DART):** Calcd for $C_{19}H_{16}F_3$ $[M+H–H_2O]^+$: 301.1204; Found: 301.1199; **Specific Rotation:** $[\alpha]^{20.0}_D$ +22.7° (*c* 1.76, $CHCl_3$) for a 92:8 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 35.7 min (major) and 27.4 min (minor).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	26.171 min	15640240	50.627	1	27.495 min	3931398	8.194
2	34.219 min	15252636	49.373	2	35.715 min	44047550	91.806

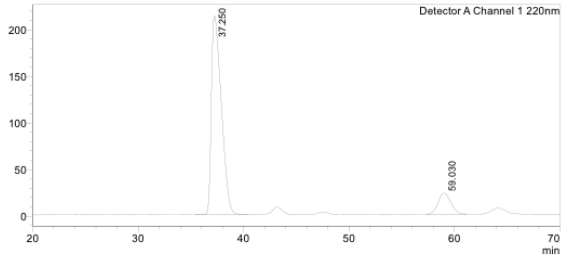
(*S*,*Z*)-7,7,7-Trifluoro-1-phenylhept-5-en-3-ol (*Z*-3.129): Following the general procedure for addition, hydrocinnamaldehyde (20.1 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (15.9 mg, 0.088 mmol). **IR (neat):** 3390 (br, m), 2921

(w), 1670 (w), 1496 (w), 1454 (w), 1418 (w), 1275 (m), 1227 (m), 1117 (s), 1083 (m), 1055 (m), 747(w), 699 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ δ 7.33 – 7.27 (m, 2H), 7.22 – 7.19 (m, 3H), 6.13 (dt, *J* = 11.7, 7.7 Hz, 1H), 5.72 (dqt, *J* = 12.0, 8.5, 1.8 Hz, 1H), 3.76 (tq, *J* = 7.3, 5.1 Hz, 1H), 2.86 – 2.75 (m, 1H), 2.75 – 2.64 (m, 1H), 2.59 – 2.44 (m, 2H), 1.88 – 1.75 (m, 2H), 1.43 (d, *J* = 5.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.6, 138.9 (q, *J* = 5.4 Hz), 128.6, 128.5, 126.1, 123.3 (q, *J* = 271.7 Hz), 120.4 (q, *J* = 33.3 Hz), 70.3, 38.8, 36.2, 32.0; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –58.05 (3F, dt, *J* = 8.4, 2.2 Hz); **HRMS (DART):** Calcd for $C_{13}H_{14}F_3$ $[M+H–H_2O]^+$: 227.1048; Found: 227.1039; **Specific Rotation:** $[\alpha]^{20.0}_D$ –11.6° (*c* 0.25, $CHCl_3$) for a 87:13 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 92:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 37.2 min (major) and 59.0 min (minor).



Detector A Channel 2 220nm

Peak#	Ret. Time	Height	Area	Area%
1	37.392	37988	2007374	49.762
2	58.173	24297	2026611	50.238
Total		62285	4033985	100.000



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	37.250	213221	13997478	88.166
2	59.030	22397	1878879	11.834
Total		235619	15876357	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	37.392 min	2007374	49.762	1	37.250 min	13997478	88.166
2	58.173 min	2026611	50.238	2	59.030 min	1878879	11.834

3.5.15 Determination of Absolute Stereochemistry for Additions with Z-CF_3-Substituted Allyl Boronate Z-3.114

(*R*)-1-Phenylpropane-1,3-diol: An 8-dram vial equipped with a stir bar was charged with **S-2** (0.07 mmol, 15.2 mg), $NaHCO_3$ (47 mg, 0.56 mmol), MeOH (5 mL), and CH_2Cl_2 (10 mL). The solution was allowed to cool to –78 °C and a stream of ozone was introduced to the solution until it turned light blue. Oxygen was passed through the solution until it became colorless, after which it was charged with $NaBH_4$ (80 mg, 2.1 mmol). The mixture was allowed to warm to 22 °C and stir for 12 h. The mixture was allowed to cool to 0 °C and then the reaction was quenched by the addition of water. The organic layer was removed and the aqueous layer was washed with EtOAc (3 x 10 mL). The combined organic layers were combined and dried over MgSO4 and filtered. The resulting oil was purified by silica gel chromatography (gradient 1:0 hexanes:EtOAc → 0:1 hexanes:EtOAc) to afford the desired product as colorless oil (6.1 mg, 0.04 mmol, 57% yield). The

analytical data for this compound was fully consistent with those reported previously.[14] **Specific Rotation:** $[\alpha]^{20.0}_{D}$ +36.8° (*c* 0.61, $CHCl_3$) [literature: [✔]$^{24}_{D}$ +65.1° (*c* 1.05, $CHCl_3$)].

3.5.16 Procedures and Analytical Data for Total Synthesis of Mycothiazole

2-(4-bromothiazol-2-yl)-2-methylpropanal (3.107). The procedures used were exactly the same as those reported by Cossy et al. The spectral data for the products were identical to those formerly disclosed.[15]

Methyl buta-2,3-dien-1-ylcarbamate (3.137). Copper iodide (952 mg, 5.0 mmol) and paraformaldehyde (900 mg, 30 mmol) were added to a flame-dried round bottom flask equipped with stir bar and a reflux condenser. Dioxane (45 mL) was introduced after which a solution of propargyl amide[16] (**3.136**, 1.0 g, 8.8 mmol) in dioxane (5 mL) and dicyclohexylamine (5.0 mL, 25 mmol) were added. The mixture was heated to reflux and allowed to stir for 4 h under these conditions; it was then allowed to cool to 22 °C and diluted with water (50 mL) and Et_2O (100 mL). The aqueous layer was separated and washed with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to ~20% of the original volume, after which silica gel was added to generate a heterogenous mixture, and the volatiles were removed to dryness. The resulting brown powder was then purified by silica gel chromatography eluting with 100:0 to 9:1 hexanes/EtOAc to afford allene **3.137** as pale yellow oil (880 mg, 79% yield). **IR (neat):** 3327 (br, m), 2936 (w), 1704 (s), 1530 (s), 1462 (w), 1467 (m), 1261 (s), 1193 (w), 850 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.20 (p, *J* = 6.3 Hz, 1H), 4.90 – 4.73 (m, 3H), 3.78 (s, 2H), 3.67 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 207.9, 156.9, 88.3, 77.7, 52.3, 39.2; **HRMS (DART):** Calcd for $C_6H_{10}NO_2$ $[M+H]^+$: 128.0712; Found: 128.0718.

Methyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)carbamate (3.133). In a N_2-filled glovebox, an oven-dried 100 mL round bottom flask equipped with stir bar was charged with copper chloride (38 mg, 0.39 mmol), **imid-1** (166 mg, 0.39 mmol) and NaO*t*-Bu (300 mg, 3.13 mmol). Anhydrous tetrahydrofuran (39 mL) was added and the reaction vessel sealed with septum. The mixture was allowed to stir for 2 h at 22 °C, after which $B_2(pin)_2$ (2.01 g, 7.9 mmol) and allene **7** (1.0 g, 7.8 mmol) were added. The vial was re-sealed with septum, removed from the glovebox and solution was allowed to cool to 0 °C. At this point, *i*-PrOH (3.6 mL, 46.9 mmol) was added dropwise. The ice bath was then removed and the mixture allowed to warm to 22 °C and stir for 14 h, after which the mixture was diluted by the addition of Et_2O (50 mL) and passed

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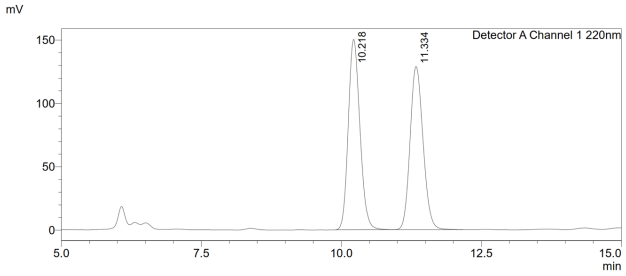
14) Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10190–10193.

15) Le Flohic, A.; Meyer, C.; Cossy, J. *Tetrahedron*, **2006**, *62*, 9017–9037.

16) This compound has been previously synthesized in quantitative yield in a single step from commercially available starting materials; see: Teller, H.; Corbet, M.; Mantilli, L; Gopakumar, G.; Goddard, G.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331–15342.

through a plug (3 cm high x 6 cm wide) of silica gel topped with a layer of celite (~1 cm) . The volatiles were removed to ~20% of the original volume, after which silica gel was added to generate a hetereogeneous mixture, which was concentrated to dryness. The resulting yellow powder was purified by silica gel chromatography (gradient elution, 10:1 → 2:1 hexanes/EtOAc) to afford alkenyl–B(pin) compound **3.133** as colorless oil (1.5 g, 76% yield). **IR (neat):** 3350 (br, w), 2977 (m), 1703 (s), 1526 (m), 1439 (m), 1371 (s), 1309 (s), 1249 (s), 1215 (s), 1192 (m), 1167 (m), 1139 (s), 854 (w), 832 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.88 (d, *J* = 3.3 Hz, 1H), 5.68 (s, 1H), 4.93 (s, 1H), 3.64 (s, 3H), 3.28 (q, *J* = 6.3 Hz, 2H), 2.34 (t, *J* = 6.5 Hz, 2H), 1.27 (s, 12H); **^{13}C NMR (100 MHz, $CDCl_3$):** 157.1, 132.1, 83.8, 51.9, 40.9, 35.6, 24.8; **HRMS (DART):** Calcd for $C_{12}H_{23}BNO_4$ $[M+H]^+$: 256.172; Found: 256.1733.

(*R*,*Z*)-2-(4-Bromothiazol-2-yl)-6-chloro-2-methylhex-5-en-3-ol (*Z*-3.109): In a N_2-filled glovebox, an oven-dried round bottom flask (25 mL) containing a stir bar was charged with **ap-5** (69 mg, 0.1 mmol), $Zn(OMe)_2$ (64 mg, 0.5 mmol) and toluene (25 mL). After the mixture was allowed to stir for 15 min at 22 °C, aldehyde **3.107** (1.76 g, 7.5 mmol), allyl boronate ***Z*-3.66** (1.01 g, 5.0 mmol), and MeOH (260 μL, 6.5 mmol) were added. The vessel was sealed with a septum, removed from the glovebox and the solution was allowed to stir at for 14 h 22 °C. The volatiles were removed and the resulting opaque oil was purified by silica gel chromatography (10:1 hexanes:Et_2O → 4:1 hexanes:Et_2O) to afford ***Z*-3.109** as colorless oil (1.32 g, 4.3 mmol, 86% yield, >98:2 *Z*:*E*). The unreacted aldehyde (**3.107**) was collected and further purified by short path distillation to give pure **3.107** as colorless oil (570 mg, 2.4 mmol, 97% recovered). **IR (neat):** 3421 (br, m), 2968 (m), 2931 (w), 1630 (w), 1465 (s), 1387 (m), 1366 (m), 1257 (s), 1081 (s), 1050 (s), 885 (m), 838 (m), 748 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.14 (s, 1H), 6.09 (dt, *J* = 7.1, 1.5 Hz, 1H), 5.95 (q, *J* = 7.0 Hz, 1H), 3.82 (ddd, *J* = 10.2, 6.3, 2.7 Hz, 1H), 3.52 (dd, *J* = 6.3, 0.6 Hz, 1H), 2.56 – 2.47 (m, 1H), 2.15 (dddd, *J* = 14.8, 10.2, 6.6, 1.5 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** 179.9, 128.9, 124.3, 119.5, 116.0, 77.5, 45.3, 30.1, 26.7, 24.0; **HRMS (DART):** Calcd for $C_{10}H_{14}BrClNOS$ $[M+H]^+$: 309.9668; Found: 309.9673; **Specific Rotation:** $[\alpha]^{24.5}$ +13.3° (*c* 1.0, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 10.4 min (major) and 11.6 min (minor).



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
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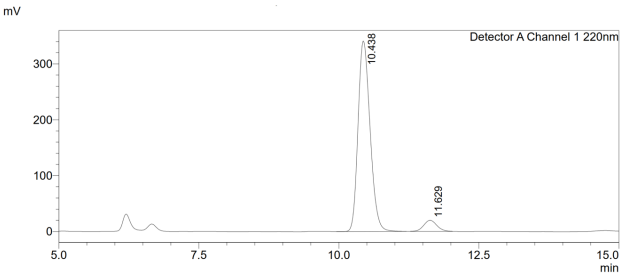
2	11.334	128751	2069486	48.660
Total		278981	4252964	100.000



<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	10.438	340584	5064993	94.056
2	11.629	19665	320096	5.944
Total		360248	5385089	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	10.218 min	2183478	51.340	1	10.438 min	5064993	94.056
2	11.334 min	2069486	48.660	2	11.629 min	320096	5.944

(*R*,*Z*)-2-(4-Allylthiazol-2-yl)-6-chloro-2-methylhex-5-en-3-ol (3.135): The procedure used was based on that reported by Aggarwal et al.[17] In a N_2-filled glovebox, aryl bromide ***Z*-3.109** (2.54 g, 8.17 mmol) was added to an oven-dried round bottom flask that contained a stir bar. Complex $Pd(dppf)Cl_2•CH_2Cl_2$ (166.8 mg, 0.2 mmol) was then added, followed by tetrahydrofuran (80 mL). The mixture was charged with allyl–B(pin) (5.49 g, 32.7 mmol) and then CsF (3.72 g, 24.5 mmol; added in portions (~0.5 g/addition). At this point, the vial was sealed with a septum and removed from the glovebox. The solution was charged with water (8 mL) and heated to 60 °C and allowed to stir for 14 h at this temperature. After the solution was allowed to cool to 22 °C, it was diluted with Et_2O (100 mL) and passed through silica gel. The filtrate was concentrated to afford an orange residue, which was purified by silica gel chromatography (10:1 → 4:1 hexanes/Et_2O) to afford **3.135** as light-yellow oil (1.6 g, 72% yield). **IR (neat):** 3383 (br, m), 2963 (m), 2923 (s), 2854 (m), 1638 (w), 1519 (m), 1466 (m), 1426 (s), 1327 (m), 1051 (s), 993 (m), 916 (s), 747 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.79 (d, *J* = 1.0 Hz, 1H), 6.10 – 5.95 (m, 3H), 5.19 – 5.09 (m, 2H), 4.90 (d, *J* = 6.3 Hz, 1H), 3.75 (ddd, *J* = 10.3, 6.3, 2.8 Hz, 1H), 3.51 (dq, *J* = 6.8, 1.3 Hz, 2H), 2.59 – 2.46 (m, 1H), 2.13 (dddd, *J* = 14.8, 10.1, 6.3, 1.5 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** 179.0, 154.8, 135.1, 129.4, 118.9, 117.0, 112.2, 77.8, 44.6, 35.9, 30.2, 27.5, 24.2; **HRMS (DART):** Calcd for $C_{13}H_{19}ClNOS$ $[M+H]^+$: 272.0876; Found: 272.0881; **Specific Rotation:** $[\alpha]^{21.5}_D$ +10.3° (*c* 2.58, $CHCl_3$) for a 94:6 er sample.

Methyl-(*R*,*Z*)-(8-(4-Allylthiazol-2-yl)-7-hydroxy-8-methyl-3-methylenenon-4-en-1-yl)carbamate (3.138): The procedure used was based on that reported by Buchwald and co-workers.[18] In a N_2-filled glovebox, an oven-dried 40 mL vial equipped containing a stir bar was charged with **3.135** (500 mg, 1.84 mmol), alkenyl boronate **3.133** (492 mg, 1.93 mmol), ruphos-Pd-G_3 (150 mg, 0.18 mmol), ruphos (84 mg, 0.18 mmol) and K_3PO_4 (1.2 g, 5.52 mmol). Tetrahydrofuran (18 mL) was added and the vial was sealed with septum and removed from the glovebox. After addition of water (1.8 mL), the vial was then covered in aluminum foil, and the mixture was heated to 55 °C and allowed to stir for 14 h under such conditions. The solution was allowed to cool to 22 °C, diluted with Et_2O (40 mL), and passed through silica gel. The filtrate was concentrated to give a yellow residue that was purified by medium pressure liquid chromatography (MPLC) with a Teledyne ISCO Combiflash RF instrument paired with a 24 g RediSep Rf Gold column (catalog number 69-2203-345) and a gradient elution method: 100% hexanes → 100% EtOAc) to furnish diene **3.138** as yellow oil (480 mg, 71% yield). **IR (neat):**

17) Zhurakovskyi, O.; Türkmen, Y. E.; Löffler, L. E.; Moorthie, V. A.; Chen, C. C.; Shaw, M. A.; Crimmin, M. R.; Ferrara, M.; Ahmad, M.; Ostovar, M.; Matlock, J. V.; Aggarwal, V. K.. *Angew. Chem., Int. Ed.* **2018**, *57*, 1346–1350.

18) (a) Bruno, N. C.; Niljiasnskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161–4166. (b) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916–920.

3340 (br, m), 2965 (m), 1703 (s), 1521 (s), 1466 (m), 1447 (m), 1385 (w), 1364 (w), 1268 (s), 1052 (m), 904 (m), 776 (w), 732 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.79 (s, 1H), 6.00 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.87 (d, *J* = 11.6 Hz, 1H), 5.70 – 5.64 (m, 1H), 5.43 (s, 1H), 5.17 – 5.08 (m, 2H), 5.00 (s, 1H), 4.89 (d, *J* = 3.6 Hz, 1H), 4.87 (s, 1H), 3.78 (d, *J* = 9.9 Hz, 1H), 3.62 (s, 3H), 3.49 (d, *J* = 6.7 Hz, 2H), 3.37 – 3.10 (m, 2H), 2.45 – 2.19 (m, 4H), 1.43 (s, 3H), 1.38 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 179.5, 157.2, 154.7, 142.5, 135.0, 131.0, 130.7, 117.0, 115.9, 112.3, 78.2, 51.9, 44.7, 39.5, 37.2, 35.9, 30.7, 26.8, 24.0; **HRMS (DART):** Calcd for $C_{19}H_{29}N_2O_3S$ $[M+H]^+$: 365.1899; Found: 365.1904; **Specific Rotation:** $[\alpha]^{23.9}_D$ –28.5° (*c* 2.45, $CHCl_3$) for a 94:6 er sample.

Methyl ((*R*,*Z*)-7-Hydroxy-8-(4-((*Z*)-6-hydroxyhex-2-en-1-yl)thiazol-2-yl)-8-methyl-3-methylenenon-4-en-1-yl)carbamate (3.139): A previously reported procedure was used.[19] In a N_2-filled glovebox, an oven-dried 40 mL vial equipped containing a stir bar was charged with **3.138** (410 mg, 1.12 mmol) and a thf solution of *Z*-2-butene (28 wt %, 2.08 g, 10.4 mmol). A solution of **Ru-1** (10.7 mg, 0.014 mmol, 200 μL thf) was added, the vial was sealed with a cap, and mixture was allowed to stir for 1 h at 22 °C. Excess *Z*-2-butene was then removed in vacuo (5 min, 100 torr). At this point, alcohol **3.132** (730 μL, 6.24 mmol) was added followed by a solution of **Ru-1** (86 mg, 0.08 mmol, 2 mL thf), and the mixture was subjected to vacuum for 2 h (100 torr). The vial was then capped and sealed with electrical tape, and the solution was allowed to stir for 12 h at 22 °C. The volatiles were removed, leaving behind a dark oil, which was purified by medium pressure liquid chromatography (MPLC) with a Teledyne ISCO Combiflash RF instrument paired with a 24 g RediSep Rf Gold column (catalog number 69-2203-345) and a gradient elution method: 100% CH_2Cl_2 → 9:1 CH_2Cl_2/MeOH to give primary alcohol **3.139** as dark oil (405 mg, 77% yield; along with ~5% of homocoupled thiazole impurity). **IR (neat):** 3322 (br, m), 2934 (m), 1699 (s), 1520 (s), 1439 (m), 1385 (w), 1364 (w), 1271 (s), 1192 (m), 1144 (m), 1051 (s), 1014 (s), 899 (m), 775 (m), 734 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** 6.79 (s, 1H), 5.87 (d, *J* = 11.5 Hz, 1H), 5.72 – 5.46 (m, 3H), 5.39 (s, 1H), 5.00 (s, 1H), 4.87 (s, 1H), 4.47 (d, *J* = 3.4 Hz, 1H), 3.81 (ddd, *J* = 10.3, 4.5, 2.5 Hz, 1H), 3.66 – 3.63 (m, 5H), 3.51 (d, *J* = 7.3 Hz, 2H), 3.21 (ddq, *J* = 33.6, 13.6, 6.6 Hz, 2H), 2.48 (s, 1H), 2.45 – 2.13 (m, 6H), 1.72 – 1.62 (m, 2H), 1.43 (s, 3H), 1.40 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 179.6, 157.2, 155.2, 142.5, 131.1, 131.0, 130.5, 126.8, 116.0, 112.1, 78.2, 61.3, 51.9, 44.8, 39.5, 37.2, 32.0, 30.8, 29.6, 26.1, 24.1, 23.4; **HRMS (DART):** Calcd for $C_{22}H_{35}N_2O_4S$ $[M+H]^+$: 423.23120; Found: 423.23033; **Specific Rotation:** $[\alpha]^{20.0}_D$ –6.7° (*c* 1.9, $CHCl_3$) for a 94:6 er sample.

Methyl ((*R*,*Z*)-8-(4-((*Z*)-6-bromohex-2-en-1-yl)thiazol-2-yl)-7-hydroxy-8-methyl-3-methylenenon-4-en-1-yl)carbamate (S-3). In a N_2-filled glovebox, an oven-dried 8 mL vial was charged with primary alcohol **3.139** (50.0 mg, 0.118 mmol) and CH_2Cl_2 (1.5 mL); the mixture was allowed to cool to 40 °C (freezer) and kept at this temperature for 1 h. In a separate oven-dried 8 mLvial, a solution of CBr_4 (47.1 mg, 0.142 mmol, 1.0 mL CH_2Cl_2) was allowed to cool to 40 °C

19) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919–10928.

(freezer). Triphenylphosphine (37.2 mg, 0.142 mmol) was added to the solution containing **3.139** followed by addition of the solution of CBr_4 in CH_2Cl_2 and the vessel was placed back in the –40 °C freezer and allowed to remain there for 45 min. The vial was sealed with electrical tape, removed from the glovebox and wrapped in aluminum foil. The mixture was allowed to warm to +4 °C (cold room), and remain under these conditions for 45 min, after which the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (2.0 mL). The aqueous layer was washed with CH_2Cl_2 (5 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to ~10% of the original volume. The resulting light yellow oil was purified by silica gel chromatography (silica dried overnight at 120 °C; 100% hexanes–3:1 hexanes:Et_2O) to afford the desired primary bromide **S-3** as colorless oil (38.9 mg, 68% yield). **IR (neat):** 3336 (br, m), 2962 (m), 2936 (m), 1703 (s), 1519 (s), 1440 (m), 1244 (s), 1052 (m), 900 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.77 (d, *J* = 1.0 Hz, 1H), 5.87 (d, *J* = 11.6 Hz, 1H), 5.78 – 5.59 (m, 2H), 5.54 – 5.44 (m, 1H), 5.40 (s, 1H), 5.00 (d, *J* = 2.3 Hz, 1H), 4.86 (d, *J* = 5.2 Hz, 2H), 3.77 (ddd, *J* = 9.9, 4.4, 2.7 Hz, 1H), 3.62 (s, 3H), 3.52 (d, *J* = 7.4 Hz, 2H), 3.41 (t, *J* = 6.6 Hz, 2H), 3.31 – 3.09 (m, 2H), 2.53 – 2.09 (m, 4H), 1.94 (dq, *J* = 7.8, 6.6 Hz, 2H), 1.42 (s, 3H), 1.39 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 179.5, 157.1, 154.9, 142.5, 130.9, 130.6, 129.6, 127.4, 115.8, 111.8, 78.1, 44.6, 39.4, 37.1, 33.3, 32.3, 30.6, 29.6, 26.6, 25.6, 23.8. **HRMS (DART):** Calcd for $C_{22}H_{34}N_2O_3SBr$ $[M+H]^+$: 485.14680; Found: 485.14443; **Specific Rotation:** $[\alpha]^{24.2}_D$ – 5.8° (*c* 0.43, $CHCl_3$) for a 94:6 er sample.

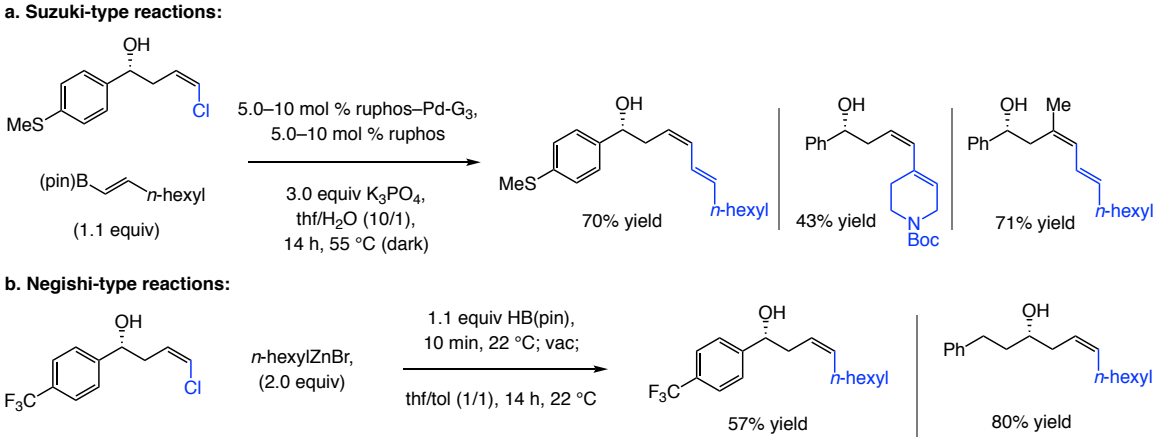
Mycothiazole [methyl ((*R*,*Z*)-8-(4-((*Z*)-Hexa-2,5-dien-1-yl)thiazol-2-yl)-7-hydroxy-8-methyl-3-methylenenon-4-en-1-yl)carbamate]. The procedure used was based on that reported by Fu et al.[20] In an N_2-filled glovebox, an oven dried 4.0 mL vial equipped with a stir bar was charged with $Pd_2(dba)_3$ (19.1 mg, 0.021 mmol), P(*t*-Bu)$_2$Me (13.3 mg, 0.083 mmol), KO*t*-Bu (2.4 mg, 0.021 mmol) and dioxane (0.125 mL). To this was added Cy_2NH (45.3 mg, 0.25 mmol) and the resulting mixture was allowed to stir for 2 h at 22 °C. A solution of the freshly prepared bromide **S-3** was then added (101.3 mg, 0.21 mmol, 0.2 mL dioxane; to ensure complete transfer, the vial was carefully rinsed with additional dioxane (0.2 mL), which was then added to the mixture). The vial was capped and sealed with electrical tape and the mixture was allowed to stir for 8 h. The vial was removed from the glovebox and the volatiles were removed and the resulting yellow oil was loaded directly onto oven-dried silica gel for purification (100% hexanes–1:3 hexanes:Et_2O) to afford mycothiazole as light yellow oil (68.8 mg, 82% yield). The analytical data was fully consistent with those found in the literature.[21] **IR (neat):** 3334 (br, m), 2923 (s), 2851 (m), 1705 (m), 1520 (s), 1465 (m), 1441 (m), 1269 (s), 1055 (m), 908 (m), 777 (w), 735 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.77 (s, 1H), 5.88 (d, *J* = 13.2 Hz, 1H), 5.88 – 5.76 (m, 1H), 5.76 – 5.64 (m, 2H), 5.64 – 5.55 (m, 1H), 5.42 (s, 1H), 5.10 – 4.97 (m, 3H), 4.92 – 4.84 (m, 2H), 3.78 (d, *J* = 10.0 Hz, 1H), 3.63 (s, 3H), 3.51 (d, *J* = 7.3 Hz, 2H), 3.37 – 3.11 (m, 2H), 2.88 (td, *J* = 6.8, 1.7 Hz,

20) Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232–143237.

21) Wang, L.; Hale, K. J. *Org. Lett.* **2015**, *17*, 4200–4203.

2H), 2.48 – 2.11 (m, 4H), 1.43 (s, 3H), 1.39 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 179.6, 157.2, 155.1, 142.6, 136.5, 131.0, 130.7, 129.0, 126.8, 115.9, 115.1, 111.9, 78.2, 51.9, 44.7, 39.5, 37.3, 31.6, 30.7, 29.5, 26.8, 23.9. **HRMS (DART):** Calcd for $C_{22}H_{33}N_2O_3S$ $[M+H]^+$: 405.22064; Found: 405.22066; **Specific Rotation:** $[\alpha]^{20.0}_D$ –22.3° (*c* 0.2, $CHCl_3$) for a 94:6 er sample.

3.5.17 Representative Exampples of Cross-Coupling Involving a Z–Alkenyl Chloride



(*R*,3*Z*,5*E*)-1-(4-(methylthio)phenyl)dodeca-3,5-dien-1-ol. In a N_2-filled glovebox, an oven-dried vial equipped with a stir bar was charged with ruphos-Pd-G_3 (3.1 mg, 0.0037 mmol), ruphos (1.7 mg, 0.0037 mmol, K_3PO_4 (46.5 mg, 0.220 mmol) and *trans*-1-octen-ylboronic acid pinacol ester (19.0 mg, 0.080 mmol). ***Z*-3.79** (16.6 mg, 0.073 mmol) was added as a solution in tetrahydrofuran (0.5 mL) and the vial was carefully rinsed with additional tetrahydrofuran (0.2 mL). The vial was sealed with septum and removed from the glovebox. After addition of water (70 μL), the vial was then covered in aluminum foil, and the mixture was heated to 55 °C and allowed to stir for 14 h under such conditions. The solution was allowed to cool to 22 °C, diluted with Et_2O (5 mL), and passed through silica gel to afford an unpurified brown residue that was purified by silica gel chromatography (gradient eluting with 100:0 → 3:1 Hexanes:Et_2O) to afford the title compound as colorless oil (15.5 mg, 0.051 mmol).

IR (neat): 3391 (br, m), 2921 (m), 2852 (m), 1492 (m), 1435 (m), 1092 (m), 1047 (m), 1013 (m), 818 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.28 (m, 2H), 7.26 – 7.21 (m, 2H), 6.28 (ddq, *J* = 14.9, 10.9, 1.3 Hz, 1H), 6.12 (tt, *J* = 11.0, 1.6 Hz, 1H), 5.72 (dt, *J* = 14.6, 7.0 Hz, 1H), 5.28 (dt, *J* = 10.6, 7.7 Hz, 1H), 4.70 (ddd, *J* = 8.0, 5.1, 2.9 Hz, 1H), 2.67 (dtd, *J* = 14.4, 8.0, 1.4 Hz, 1H), 2.56 (dddd, *J* = 14.3, 7.0, 5.2, 1.5 Hz, 1H), 2.49 (s, 3H), 2.14 – 2.02 (m, 2H), 1.98 (d, *J* = 3.2 Hz, 1H), 1.53 – 1.08 (m, 8H), 0.93 – 0.85 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.3, 138.1, 136.6, 132.6, 127.5, 126.4, 125.1, 124.0, 73.9, 40.0, 32.9, 31.7, 29.7, 28.9, 23.1, 17.5, 13.3; **HRMS (DART):** Calcd for $C_{19}H_{27}S$ $[M+H–H_2O]^+$: 287.18280; Found: 287.18293; **Specific Rotation:** $[\alpha]^{23.7}_D$ +37.8° (*c* 1.01, $CHCl_3$).

***tert*-butyl (*R*,*Z*)-4-(4-hydroxy-4-phenylbut-1-en-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate.** In a N_2-filled glovebox, an oven-dried vial equipped with a stir bar was charged with ruphos-Pd-G_3 (6.5 mg, 0.0078 mmol), ruphos (3.6 mg, 0.0078 mmol, K_3PO_4 (48.8 mg, 0.230 mmol) and N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (19.0 mg, 0.080 mmol). ***Z*-3.72** (14.2 mg, 0.078 mmol) was added as a solution in tetrahydrofuran (0.5 mL) and the vial was carefully rinsed with additional tetrahydrofuran (0.3 mL). The vial was sealed with septum and removed from the glovebox. After addition of water (80 μL), the vial was then covered in aluminum foil, and the mixture was heated to 55 °C and allowed to stir for 14 h under such conditions. The solution was allowed to cool to 22 °C, diluted with Et_2O (5 mL), and passed through silica gel to afford an unpurified brown residue that was purified by silica gel chromatography (gradient eluting with 100:0 → 1:1 Hexanes:Et_2O) to afford the title compound as yellow oil (12.3 mg, 0.034 mmol).

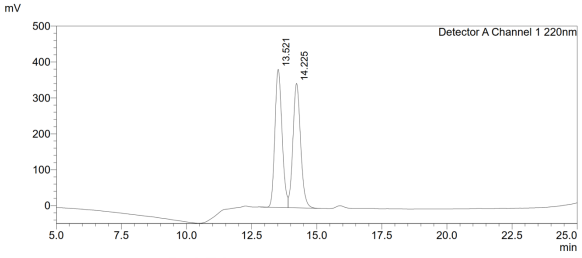
IR (neat): 3439 (br, m), 3001 (m), 2973 (m), 2928 (m), 1693 (s), 1420 (s), 1365 (m), 1240 (m), 1168 (s), 1113 (m), 700 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 (d, *J* = 4.4 Hz, 4H), 7.31 – 7.27 (m, 1H), 5.92 (d, *J* = 11.8 Hz, 1H), 5.55 (s, 1H), 5.42 (dt, *J* = 11.9, 7.5 Hz, 1H), 4.74 (ddd, *J* = 8.0, 5.2, 2.9 Hz, 1H), 3.97 – 3.92 (m, 2H), 3.57 – 3.43 (m, 2H), 2.84 – 2.71 (m, 2H), 2.71 – 2.60 (m, 1H), 2.22 (s, 2H), 1.96 (d, *J* = 3.2 Hz, 1H), 1.47 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.8, 143.9, 132.8, 128.5, 127.7, 125.8, 125.8, 123.1 (broad signal), 79.6, 73.3, 43.2 (broad signal), 40.6 (broad signal), 39.7 (broad signal), 38.6, 28.5; **HRMS (DART):** Calcd for $C_{20}H_{26}NO_2$ $[M+H–H_2O]^+$: 312.19581; Found: 312.19617; **Specific Rotation:** $[\alpha]^{22.7}_D$ +26.4° (*c* 0.50, $CHCl_3$).

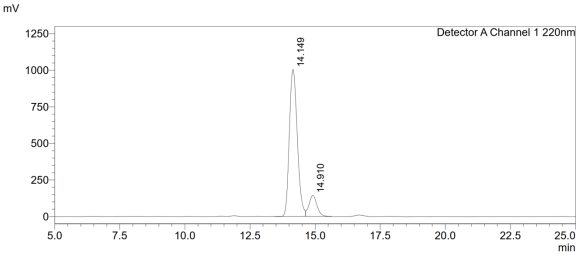
(*R*,3*Z*,5*E*)-3-methyl-1-phenyldodeca-3,5-dien-1-ol. In a N_2-filled glovebox, an oven-dried vial equipped with a stir bar was charged with ruphos-Pd-G_3 (2.4 mg, 0.0029 mmol), ruphos (1.3 mg, 0.0029 mmol, K_3PO_4 (36.3 mg, 0.220 mmol) and *trans*-1-octen-ylboronic acid pinacol ester (14.9 mg, 0.063 mmol). **3.98** (11.2 mg, 0.057 mmol) was added as a solution in tetrahydrofuran (0.4 mL) and the vial was carefully rinsed with additional tetrahydrofuran (0.2 mL). The vial was sealed with septum and removed from the glovebox. After addition of water (60 μL), the vial was then covered in aluminum foil, and the mixture was heated to 55 °C and allowed to stir for 14 h under such conditions. The solution was allowed to cool to 22 °C, diluted with Et_2O (5 mL), and passed through silica gel to afford an unpurified yellow residue that was purified by silica gel chromatography (gradient eluting with 100:0 → 3:1 Hexanes:Et_2O) to afford the title compound as colorless oil (11.0 mg, 0.040 mmol).

IR (neat): 3414 (br, m), 2953 (m), 2922 (s), 2852 (m), 1451 (m), 1376 (m), 1325 (m), 1047 (m), 961 (m), 753 (s), 699 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.47 – 7.32 (m, 4H), 7.32 – 7.20 (m, 1H), 6.24 (ddt, *J* = 14.9, 10.9, 1.5 Hz, 1H), 6.01 (d, *J* = 10.9 Hz, 1H), 5.62 (dt, *J* = 14.6, 7.0 Hz, 1H), 4.82 (ddd, *J* = 9.1, 4.5, 2.3 Hz, 1H), 2.78 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.38 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.08 (q, *J* = 7.1 Hz, 2H), 2.00 (d, *J* = 2.5 Hz, 1H), 1.79 (s, 3H), 1.45 – 1.17 (m, 8H), 0.93 – 0.84 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 144.2, 134.3, 131.8, 129.3, 128.9, 127.5,

125.8, 125.7, 72.1, 42.8, 32.5, 31.7, 29.4, 28.9, 24.0, 22.6, 14.1; **HRMS (DART):** Calcd for $C_{19}H_{27}$ $[M+H–H_2O]^+$: 255.21073; Found: 255.21006; **Specific Rotation:** $[\alpha]^{23.7}_D$ +48.0° (*c* 0.82, $CHCl_3$).

(*R*,*Z*)-4-Chloro-1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (S-4): Following the general procedure for addition, 4-(Trifluoromethyl)benzaldehyde (26.1 mg, 0.15 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (22.5 mg, 0.090 mmol). **IR (neat):** 3359 (br, m), 1621 (w), 1418 (w), 1322 (s), 1162 (m), 1109 (s), 1065 (s), 1015 (m), 842 (m), 753 (m), 737 (m), 710 (m), 607 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.67 – 7.56 (m, 2H), 7.55 – 7.44 (m, 2H), 6.17 (dt, *J* = 7.1, 1.5 Hz, 1H), 5.82 (q, *J* = 7.2 Hz, 1H), 4.90 (td, *J* = 6.5, 3.6 Hz, 1H), 2.83 – 2.60 (m, 2H), 2.01 (d, *J* = 3.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 147.6, 130.1(q, *J* = 32.4 Hz), 126.8, 126.2, 125.6 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271 Hz), 121.2, 72.7, 36.8; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –62.53 (s, 3F); **HRMS (DART):** Calcd for $C_{11}H_9F_3Cl$ $[M+H–H_2O]^+$: 233.03394; Found: 233.03349; **Specific Rotation:** $[\alpha]^{20.0}_D$ +20.7° (*c* 1.48, $CHCl_3$) for a 87:13 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 14.1 min (major) and 14.9 min (minor).





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Total		731323	14527855	100.000

<Peak Table>
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
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2	14.910	143842	3115505	12.753
Total		1149073	24429872	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	13.521 min	7375322	50.767	1	14.149 min	21314367	87.247
2	14.225 min	7152534	49.233	2	14.910 min	3115505	12.753

(*R*,*Z*)-1-(4-(trifluoromethyl)phenyl)dec-3-en-1-ol. The procedure used was based on that reported by Buchwald et al.[22] In a N_2-filled glovebox, an oven-dried vial equipped with a stir bar was charged with (*R*,*Z*)-4-chloro-1-(4-(trifluoromethyl)phenyl)but-3-en 1-ol **S-4** (16.9 mg, 0.067 mmol) and diluted with tetrahydrofuran (0.3 mL). Pinacolborane (10.3 mg, 0.080 mmol) was added and allowed to stir at 22 °C for 10 minutes. The solution was then concentrated under vacuum to afford a yellow residue that was diluted with toluene (0.1 mL). In a separate oven-dried vial ruphos-Pd-G_3 (1.8 mg, 0.0022 mmol) was weighed out, and the toluene solution was then added and the vial was carefully rinsed with additional toluene (0.1 mL). *n*-hexyl Zinc bromide

22) Buchwald, S. L.; Han, C. *J. Am. Chem. Soc.* **2009**, *131*, 7532–7533.

(0.5 M in thf, 0.17 mL) was then added in a dropwise manner. The vial was sealed with a cap and removed from the glovebox and allowed to stir at 22 °C for 14 h. The reaction was quenched by the addition of solid $Na_2SO_4 \bullet 10H_2O$ (100 mg) and then diluted with Et_2O (5 mL) and passed through a small plug of silica gel to afford an unpurified yellow residue that was purified by silica gel chromatography (gradient eluting with 100:0 → 3:1 Hexanes:Et_2O) to afford the title compound as colorless oil (11.5 mg, 0.038 mmol).

IR (neat): 3355 (br, m), 2954 (m), 2925 (m), 2854 (m), 1324 (s), 1164 (m), 1126 (m), 1067 (m), 841 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 5.67 – 5.54 (m, 1H), 5.43 – 5.31 (m, 1H), 4.80 – 4.76 (m, 1H), 2.61 – 2.42 (m, 2H), 2.05 (d, *J* = 3.2 Hz, 1H), 2.03 – 1.95 (m, 9H), 1.30 – 1.23 (m, 3H), 0.88 (t, *J* = 6.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 134.7, 126.1, 125.3 (q, *J* = 3.8 Hz), 123.7, 73.2, 37.4, 31.7, 29.5, 28.9, 25.7, 22.1, 13.1; **^{19}F NMR (376 MHz):** δ –62.5 (s, 3F); **HRMS (DART):** Calcd for $C_{17}H_{22}F_3$ $[M+H–H_2O]^+$: 283.16681; Found: 283.16733; **Specific Rotation:** $[\alpha]^{24.9}_D$ +24.9° (*c* 0.45, $CHCl_3$).

(*S*,*Z*)-1-phenyldodec-5-en-3-ol. The procedure used was based on that reported by Buchwald et al.[23] In a N_2-filled glovebox, an oven-dried vial equipped with a stir bar was charged with ***Z*-3.86** (15.4 mg, 0.073 mmol) and diluted with tetrahydrofuran (0.3 mL). Pinacolborane (11.2 mg, 0.088 mmol) was added and allowed to stir at 22 °C for 10 minutes. The solution was then concentrated under vacuum to afford a yellow residue that was diluted with toluene (0.15 mL). In a separate oven-dried vial ruphos-Pd-G_3 (3.1 mg, 0.0036 mmol) was weighed out, and the toluene solution was then added and the vial was carefully rinsed with additional toluene (0.15 mL). *n*-hexyl Zinc bromide (0.5 M in thf, 0.30 mL) was then added in a dropwise manner. The vial was sealed with a cap and removed from the glovebox and allowed to stir at 22 °C for 14 h. The reaction was quenched by the addition of solid $Na_2SO_4 \bullet 10H_2O$ (100 mg) and then diluted with Et_2O (5 mL) and passed through a small plug of silica gel to afford an unpurified yellow residue that was purified by silica gel chromatography (gradient eluting with 100:0 → 3:1 Hexanes:Et_2O) to afford the title compound as colorless oil (15.2 mg, 0.058 mmol).

IR (neat): 3415 (br, m), 2953 (m), 2921 (s), 2851 (s), 1451 (s), 1047 (m), 1026 (m), 971 (s), 753 (s), 699 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 5.64 – 5.50 (m, 1H), 5.45 – 5.30 (m, 1H), 3.65 (ddd, *J* = 12.4, 7.1, 5.3 Hz, 1H), 2.82 (ddd, *J* = 13.7, 8.9, 6.6 Hz, 1H), 2.69 (ddd, *J* = 13.8, 9.0, 7.2 Hz, 1H), 2.34 – 2.18 (m, 2H), 2.06 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.89 – 1.71 (m, 2H), 1.57 (s, 1H), 1.41 – 1.19 (m, 9H), 0.92 – 0.84 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.1, 133.9, 128.43, 128.37, 125.8, 124.8, 70.1, 39.5, 35.5, 33.0, 31.7, 29.6, 28.3, 27.4, 21.6, 13.6; **HRMS (DART):** Calcd for $C_{18}H_{32}NO$ $[M+NH_4]^+$: 278.24784; Found: 278.24744; **Specific Rotation:** $[\alpha]^{23.2}_D$ –3.2° (*c* 0.94, $CHCl_3$).

23) Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232–143237.

3.5.17 Comparison of Natural and Synthetic Mycothiazole and Confirmation of Absolute Stereochemistry of the Addition Process

Absolute configurations of all products were assigned as *R*, based on agreement between an optical rotation of –22.3° for synthetic material, and a reported[21] value of –21.3° for (8*R*)-mycothiazole.

Table S-1. Comparison of ^{1}H NMR Data for Mycothiazole

Natural Mycothiazole[24] **(300/500 MHz, $CDCl_3$)**	Synthetic Mycothiazole **(400 MHz, $CDCl_3$)**	Hale, K. J. *et al*.[21] **(400 MHz, $CDCl_3$)**
6.73 (7, *J* = 2.0 Hz, 1H)	6.77 (s, 1H)	6.76 (s, 1H)
5.83 (m, 1H)	5.88 (d, *J* = 13.2 Hz, 1H)	5.86 (d, *J* = 11.6 Hz, 1H)
5.73 (m, 1H)	5.88 – 5.76 (m, 1H)	5.79 (m, 1H)
5.68 (m, 1H), 5.65 (m, 1H)	5.76 – 5.64 (m, 2H)	5.68 (m, 2H)
5.50 (m, 1H)	5.64 – 5.55 (m, 1H)	5.57 (m, 1H)
NH not observed	5.42 (s, 1H)	5.40 (s, 1H)
4.96 (m, 3H)	5.10 – 4.97 (m, 3H)	5.04 (m, 1H), 4.99 (m, 1H), 4.96 (m, 1H)
4.83 (m, 1H), OH not observed	4.92 – 4.84 (m, 2H)	4.83 (m, 1H), OH not observed
3.74 (dd, *J* = 10.2, 3.0 Hz, 1H)	3.78 (d, *J* = 10.0 Hz, 1H)	3.78 (dd, *J* = 10.4, 2.4 Hz, 1H)
3.56 (s, 3H)	3.63 (s, 3H)	3.61 (s, 3H)
3.46 (d, *J* = 7.2 Hz, 2H)	3.51 (d, *J* = 7.3 Hz, 2H)	3.51 (d, *J* = 7.2 Hz, 2H)

24) Crews, P.; Kakou, Y.; Quiñoà, E.. *J. Am. Chem. Soc.* **1998**, *110*, 4365–4368. (b) Sonnenschein, R. N.; Johnson, T. A.; Tenney, K.; Valeriote, F. A.; Crews, P. *J. Nat. Prod.* **2006**, *69*, 145–147.

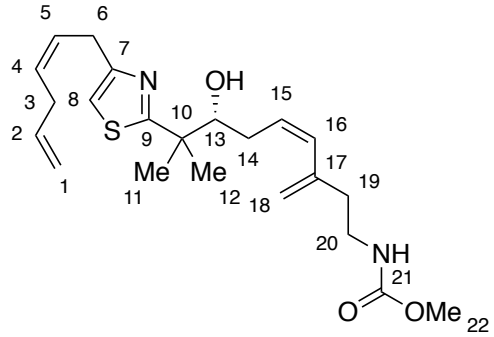
3.23 (m, 1H), 3.14 (m, 1H)	3.37 – 3.11 (m, 2H)	3.27 (m, 1H), 3.16 (m, 1H)
2.84 (dt, *J* = 6.3, 1.5 Hz, 2H)	2.88 (td, *J* = 6.4, 1.7 Hz, 2H)	2.86 (apparent t, *J* = 6.4, 1.5 Hz, 2H)
2.39 (m, 1H), 2.29 (m, 1H), 2.24 (m, 1H), 2.18 (m, 1H)	2.48 – 2.11 (m, 4H)	2.36 (m, 2H), 2.31 (m, 1H), 2.21 (m, 1H)
1.39 (s, 3H)	1.42 (s, 3H)	1.42 (s, 3H)
1.35 (s, 3H)	1.39 (s, 3H)	1.38 (s, 3H)

Table S-2. **Comparison of ^{13}C NMR Data for Mycothiazole**

Natural Mycothiazole **(75 MHz, $CDCl_3$)**	Synthetic Mycothiazole **(101 MHz, $CDCl_3$)**	Hale, K. J. *et al.* **(101 MHz, $CDCl_3$)**
179.4	179.6	179.6
157.1	157.2	157.1
154.9	155.1	154.8
142.4	142.6	142.5
136.4	136.5	136.4
130.8	131.0	131.0
130.8	130.7	130.5
128.8	129.0	129.0
126.7	126.8	126.6
115.8	115.9	115.8
115.0	115.1	115.0
111.8	111.9	111.9
78.1	78.2	78.1
51.8	51.9	51.8
44.5	44.7	44.7

39.4	39.5	39.4
37.1	37.3	37.2
31.5	31.6	31.5
30.6	30.7	30.6
29.4	29.5	29.3
26.6	26.8	26.6
23.9	23.9	23.8

Table S-3. Assignments of ^{13}C and ^{1}H Signals.

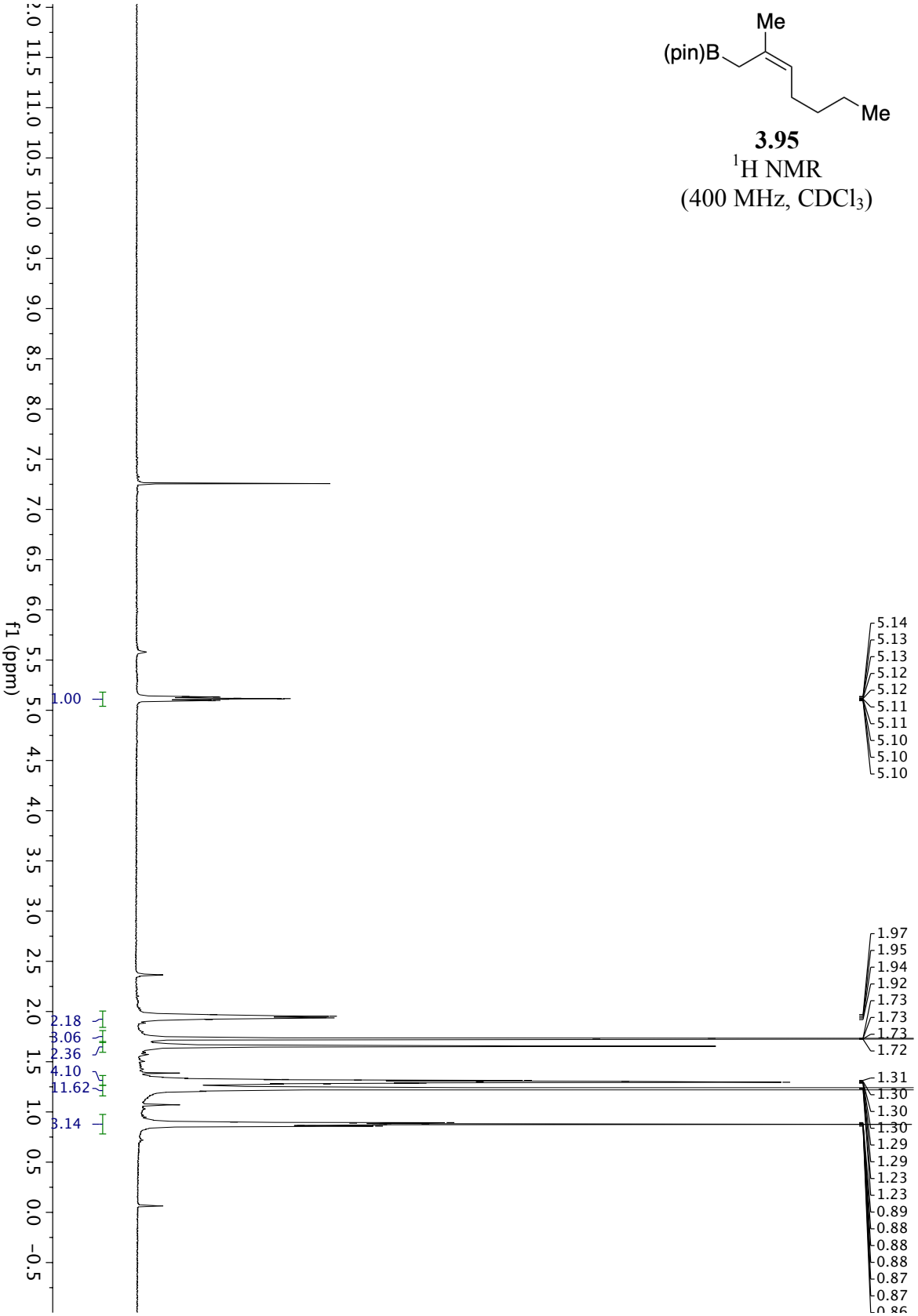


Carbon	^{13}C NMR Signal (100 MHz)	^{1}H NMR Signal (400 MHz)
1	115.1	5.10 – 4.97 (m, 2H)
2	136.5	5.88 – 5.76 (m, 1H)
3	31.6	2.88 (td, *J* = 6.4, 1.7 Hz, 2H)
4	129.0	5.64 – 5.55 (m, 1H)
5	126.8	5.76 – 5.64 (m, 1H)
6	29.5	3.51 (d, *J* = 7.3 Hz, 2H)
7	155.1	
8	111.9	6.77 (s, 1H)
9	179.6	
10	44.7	
11	26.8	1.42 (s, 3H)

12	23.9	1.39 (s, 3H)
13	78.2	3.78 (d, *J* = 10.0 Hz, 1H)
14	30.7	2.48 – 2.11 (m, 2H)
15	130.7	5.76 – 5.64 (m, 1H)
16	130.1	5.88 (d, *J* = 13.2 Hz, 1H)
17	142.6	
18	115.9	5.10 – 4.97 (m, 1H), 4.92 – 4.84 (m, 1H)
19	37.3	2.48 – 2.11 (m, 2H)
20	39.5	3.37 – 3.11 (m, 2H)
21	157.2	
22	51.9	3.63s, 3H)

3.5.18 NMR spectra

(Appear on the following pages)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1H NMR
(400 MHz, CDCl3)
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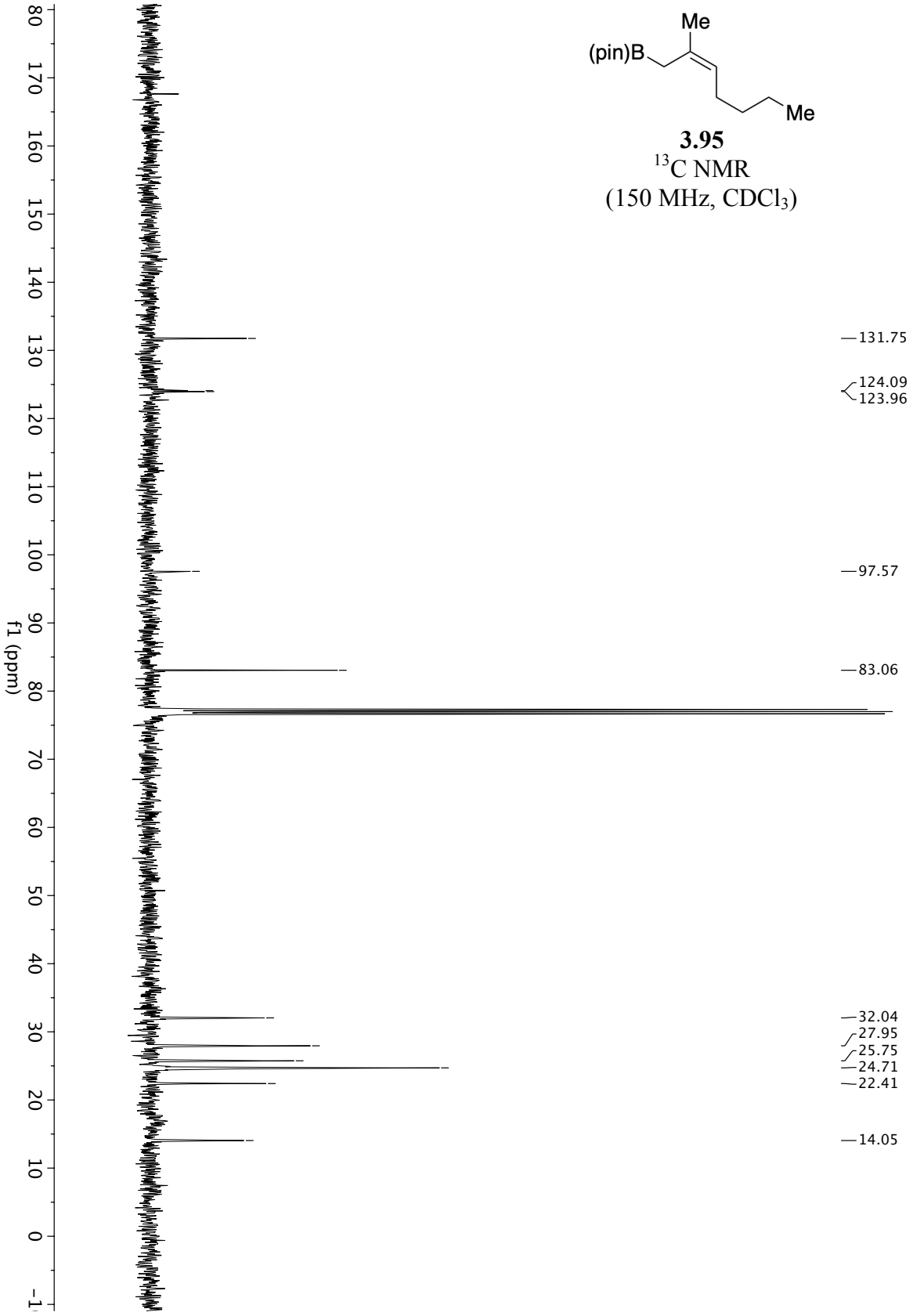
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13C NMR
(150 MHz, CDCl3)
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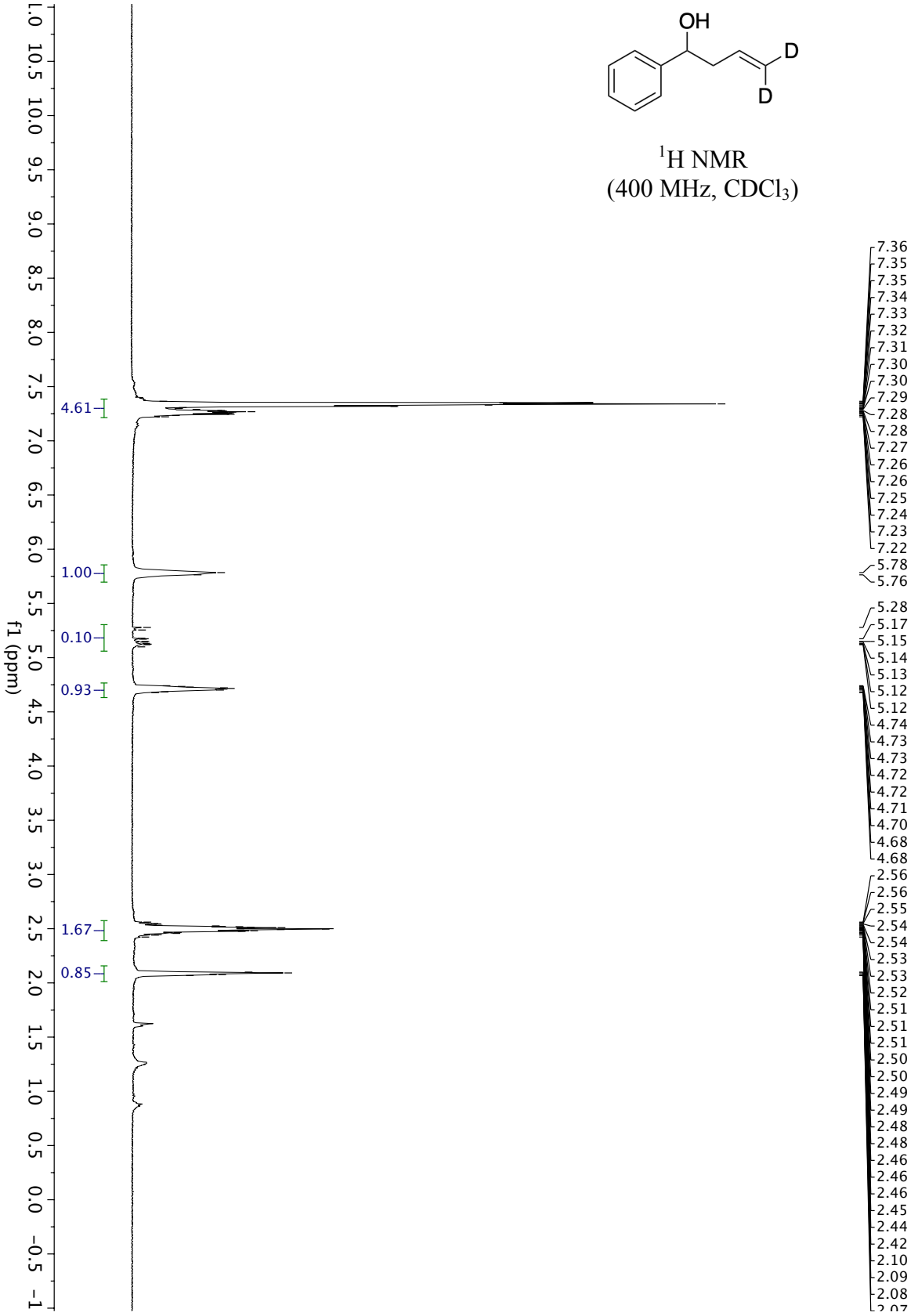
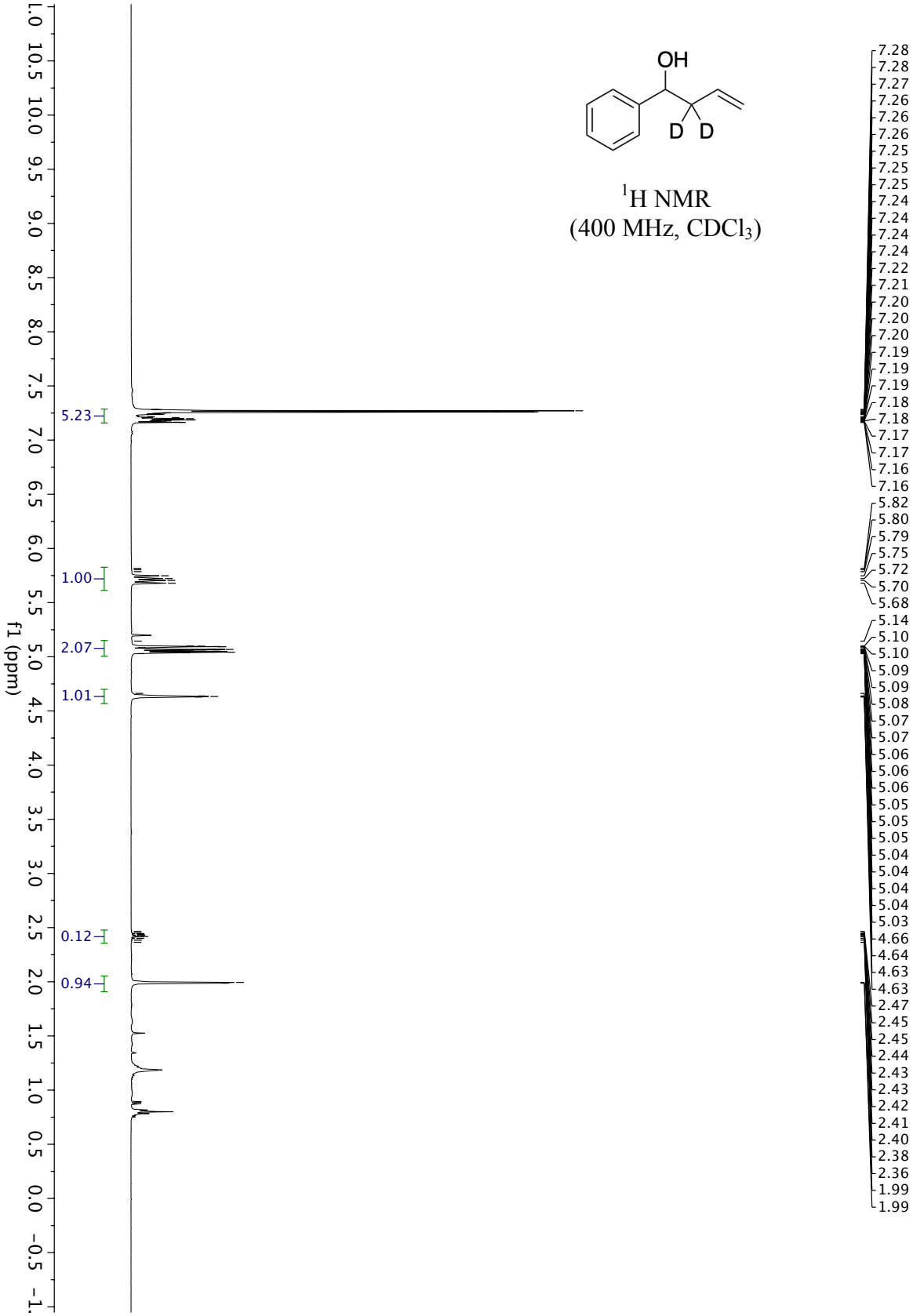
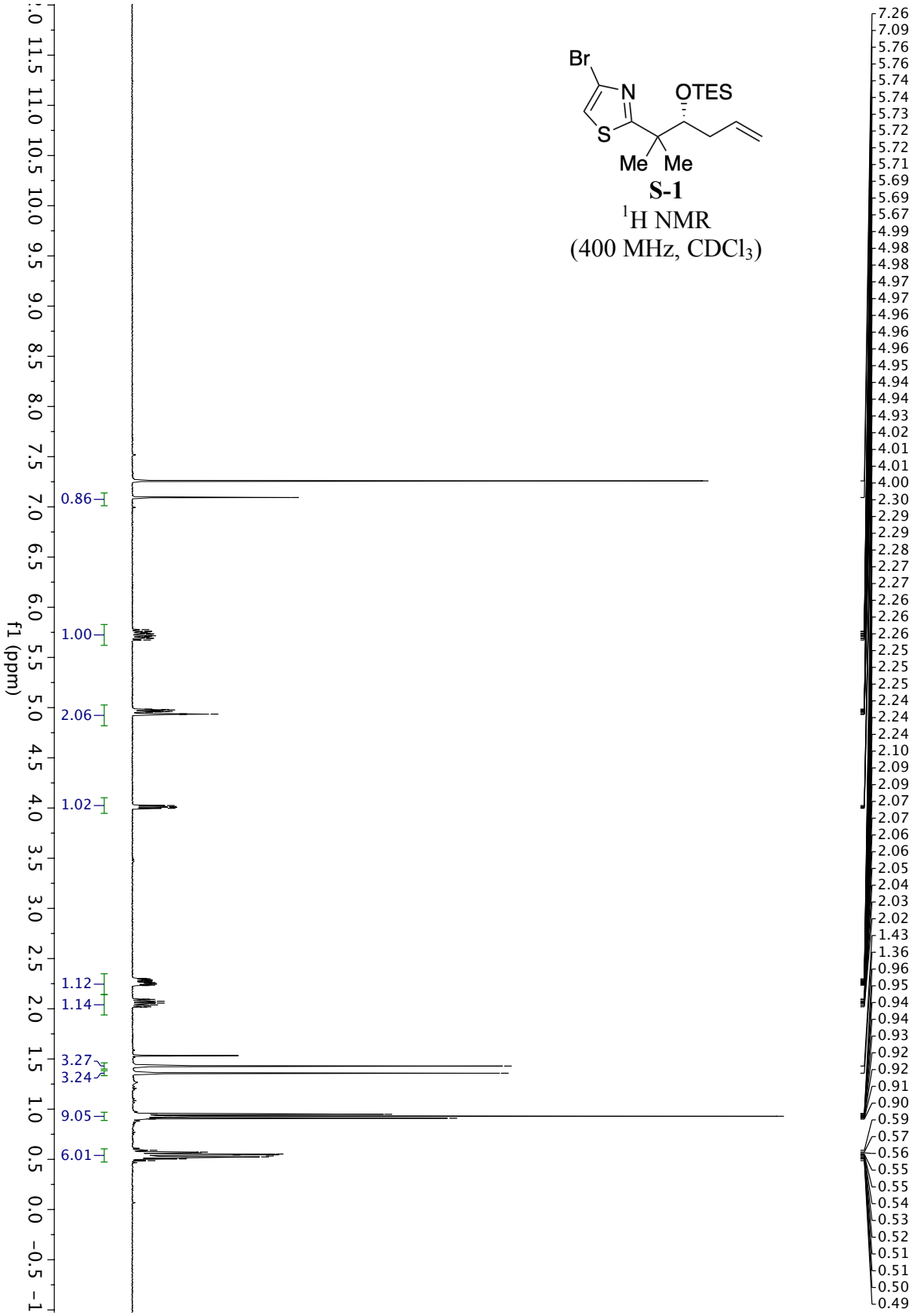
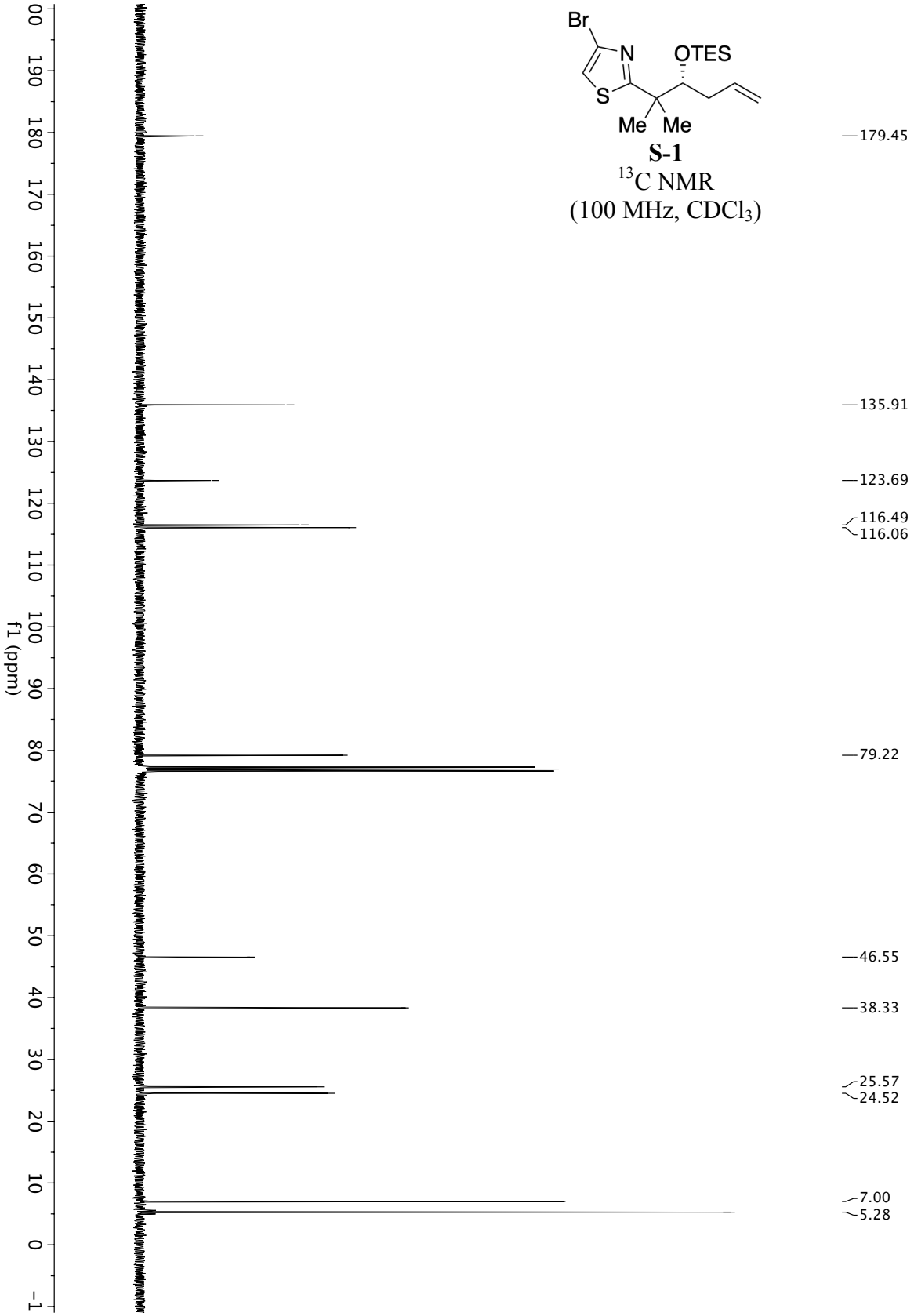
27.95
25.75
24.71
22.41
14.05
f1 (ppm)


OH
D
D
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
4.61
1.00
0.10
0.93
1.67
0.85
7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.30
7.30
7.29
7.28
7.28
7.27
7.26
7.26
7.25
7.24
7.23
7.22
5.78
5.76
5.28
5.17
5.15
5.14
5.13
5.12
5.12
4.74
4.73
4.73
4.72
4.72
4.71
4.70
4.68
4.68
2.56
2.56
2.55
2.54
2.54
2.53
2.53
2.52
2.51
2.51
2.51
2.50
2.50
2.49
2.49
2.48
2.48
2.46
2.46
2.46
2.45
2.44
2.42
2.10
2.09
2.08


OH
D D
^{1}H NMR
(400 MHz, $CDCl_3$)
f1 (ppm)
5.23
1.00
2.07
1.01
0.12
0.94

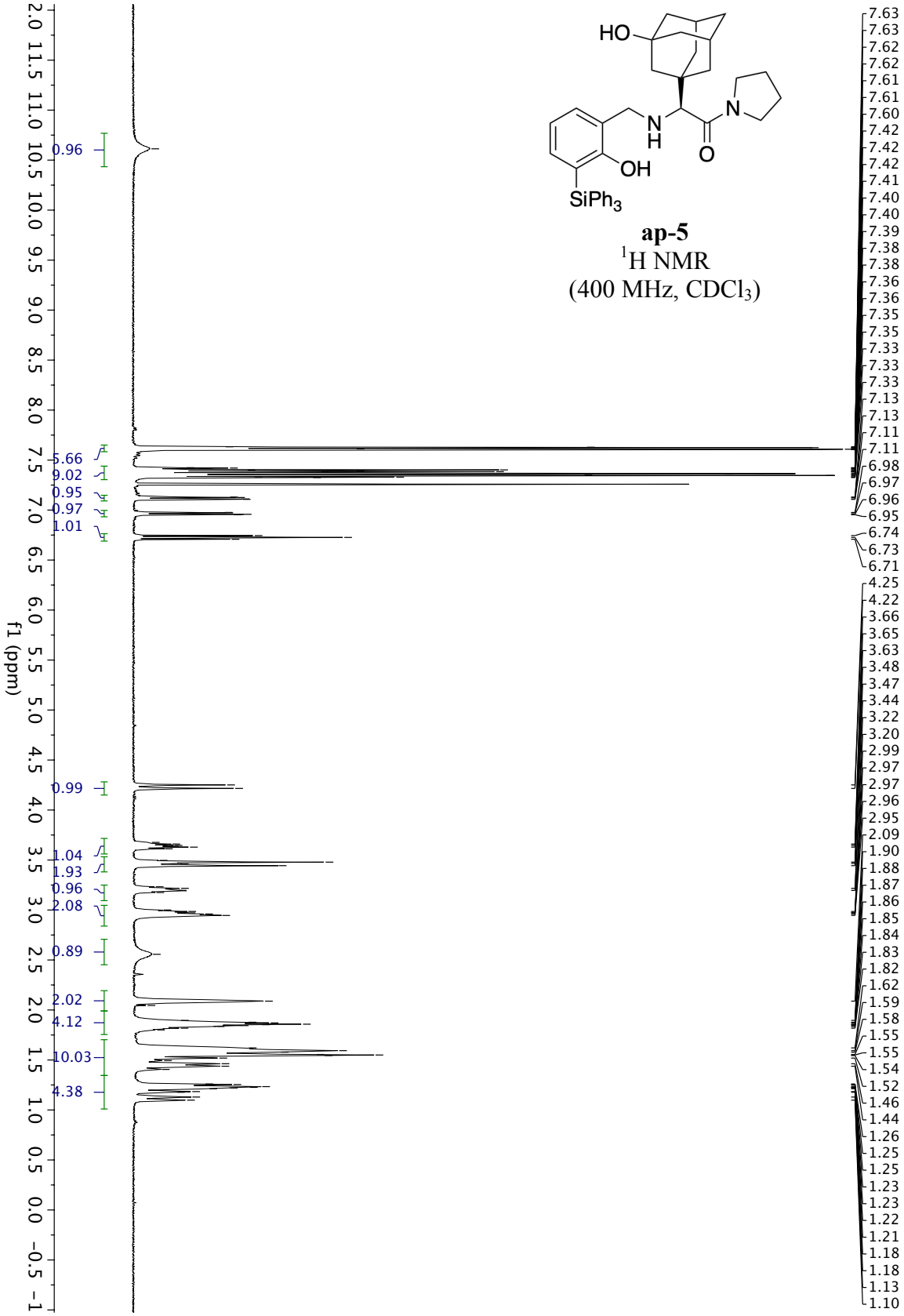

Br
N
OTES
S
Me Me
S-1
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
0.86
1.00
2.06
1.02
1.12
1.14
3.27
3.24
9.05
6.01

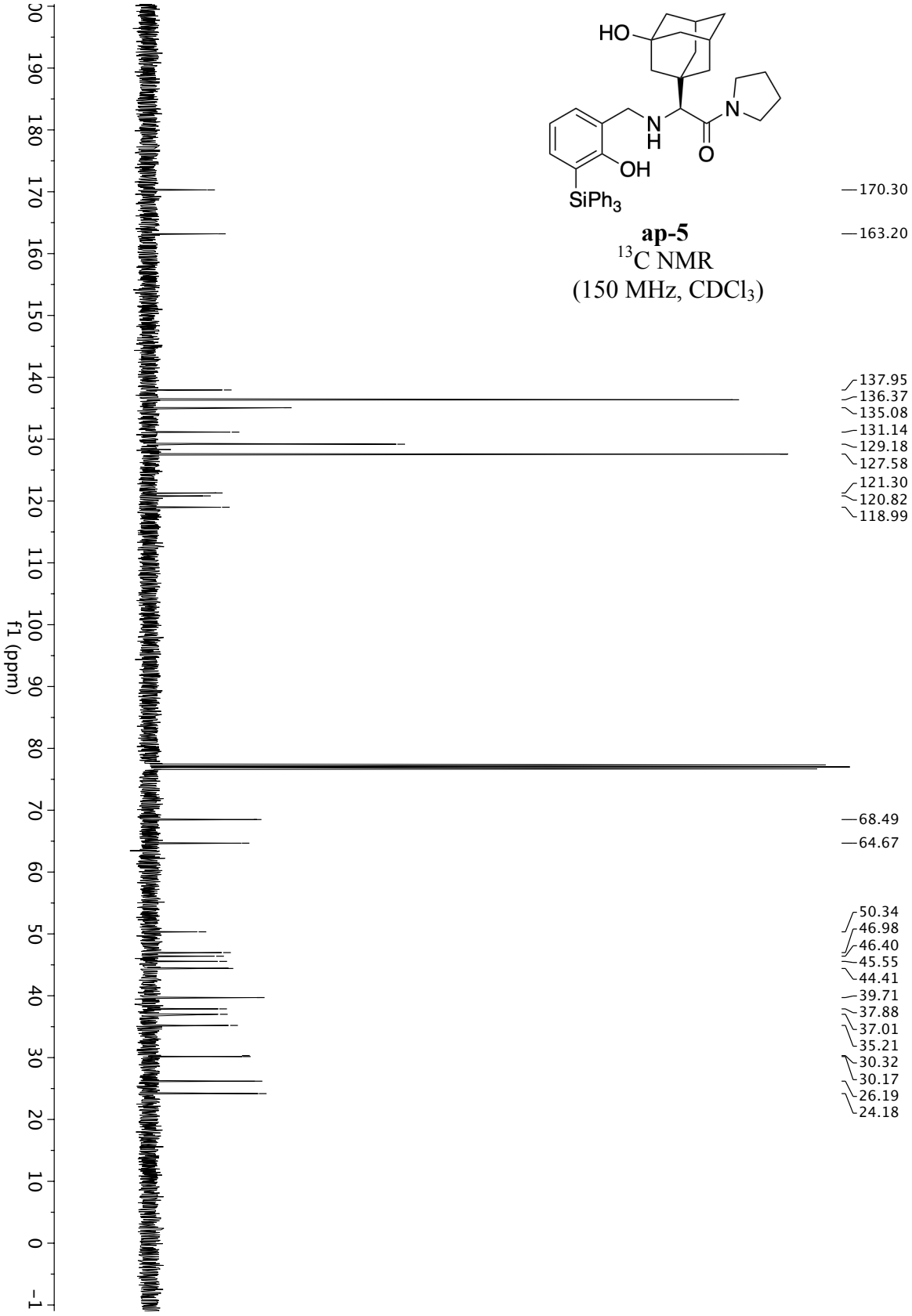


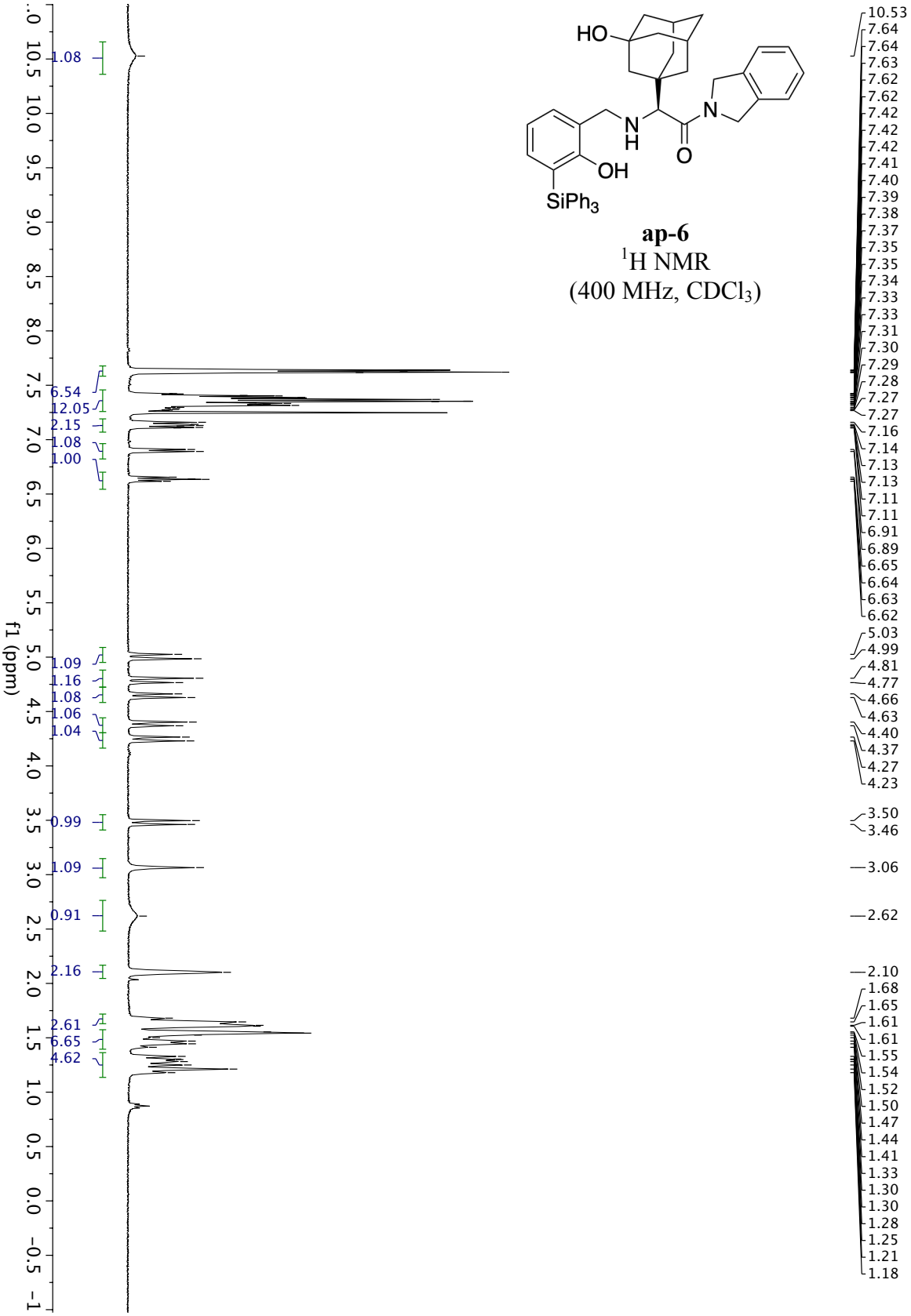
S-1

^{13}C NMR

(100 MHz, $CDCl_3$)


HO
N
H
N
O
OH
SiPh3
ap-5
1H NMR
(400 MHz, CDCl3)
f1 (ppm)

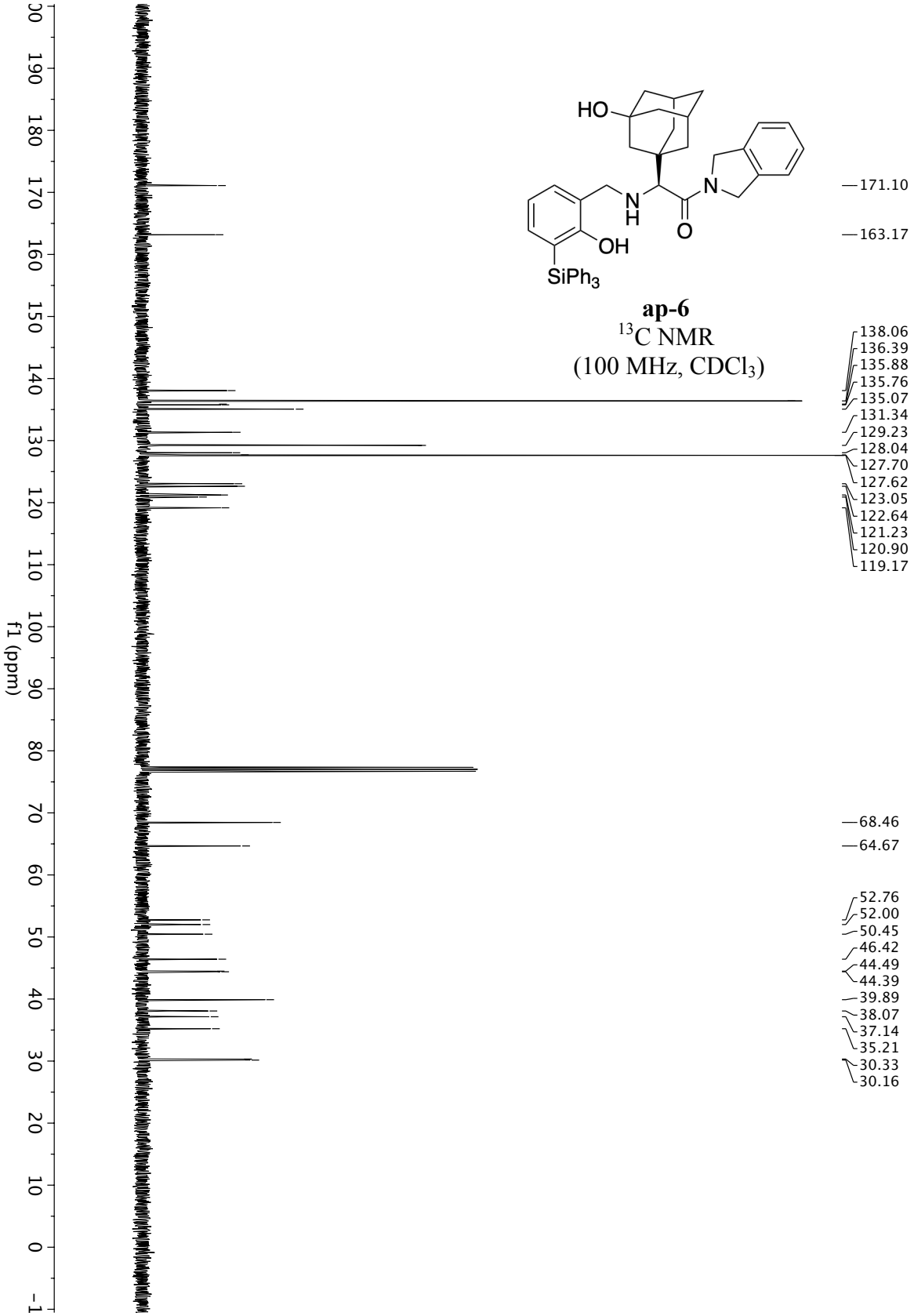

HO
N
H
N
O
OH
SiPh3
ap-5
13C NMR
(150 MHz, CDCl3)
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
170.30
163.20
137.95
136.37
135.08
131.14
129.18
127.58
121.30
120.82
118.99
68.49
64.67
50.34
46.98
46.40
45.55
44.41
39.71
37.88
37.01
35.21
30.32
30.17
26.19
24.18

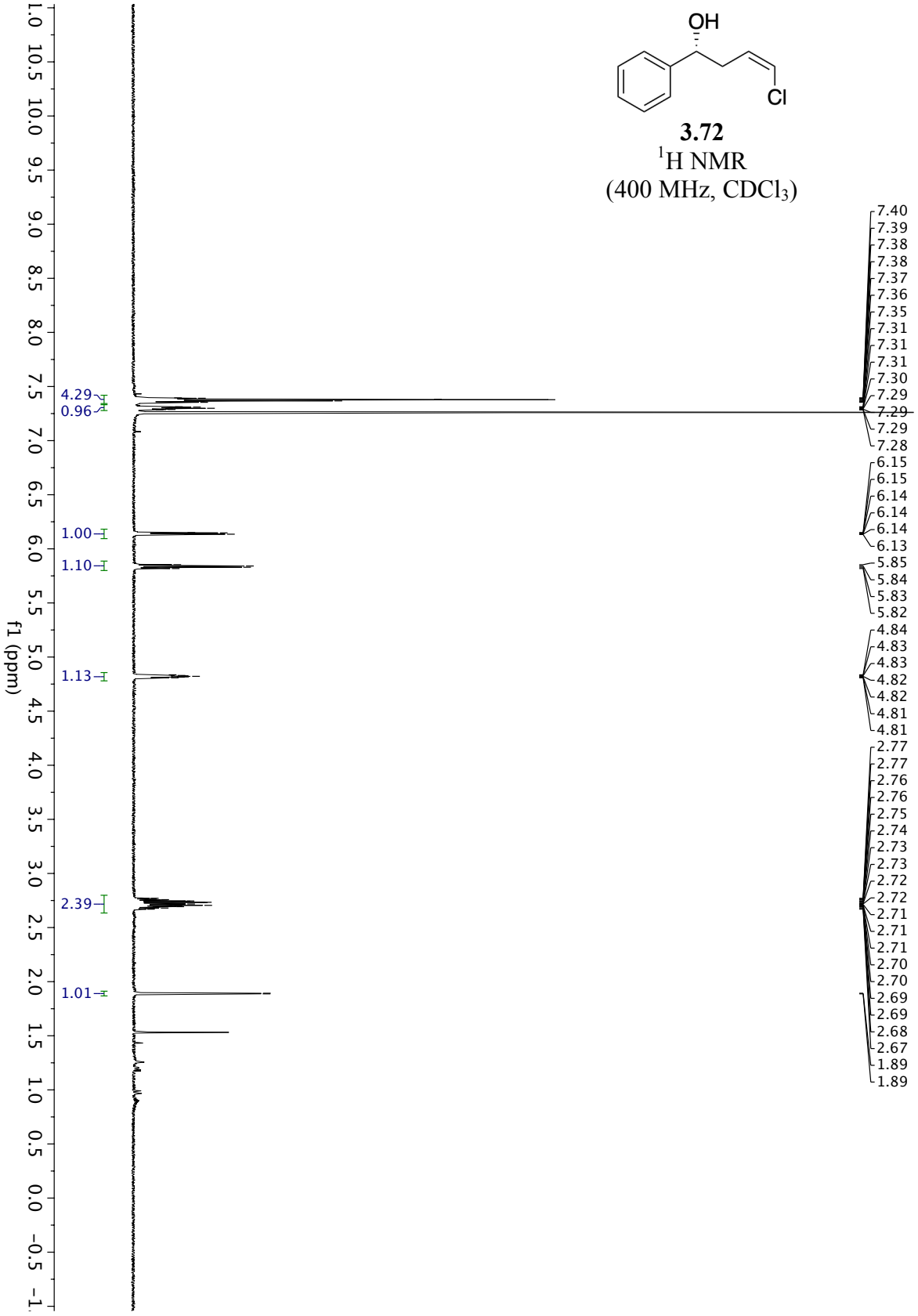


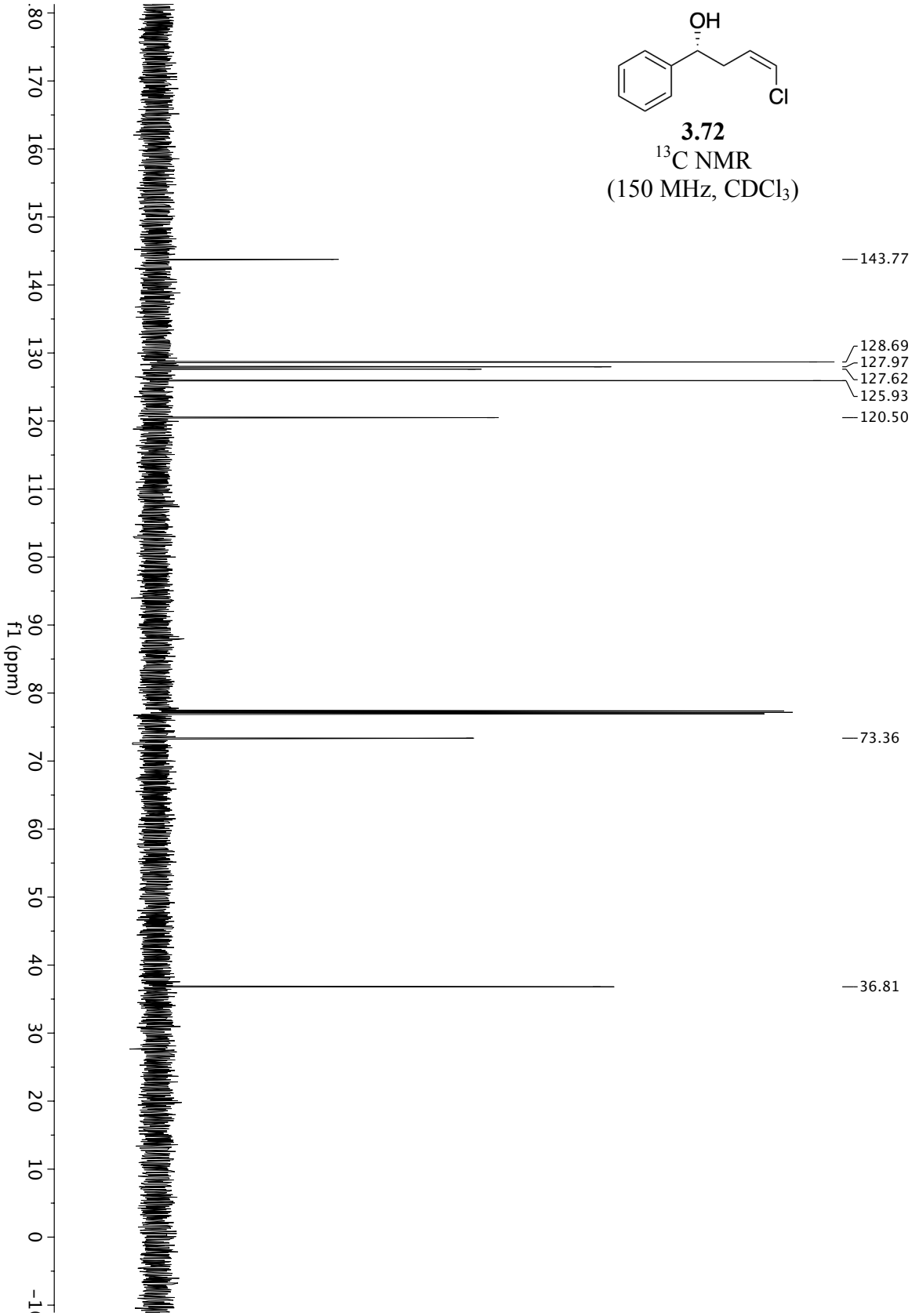
ap-6

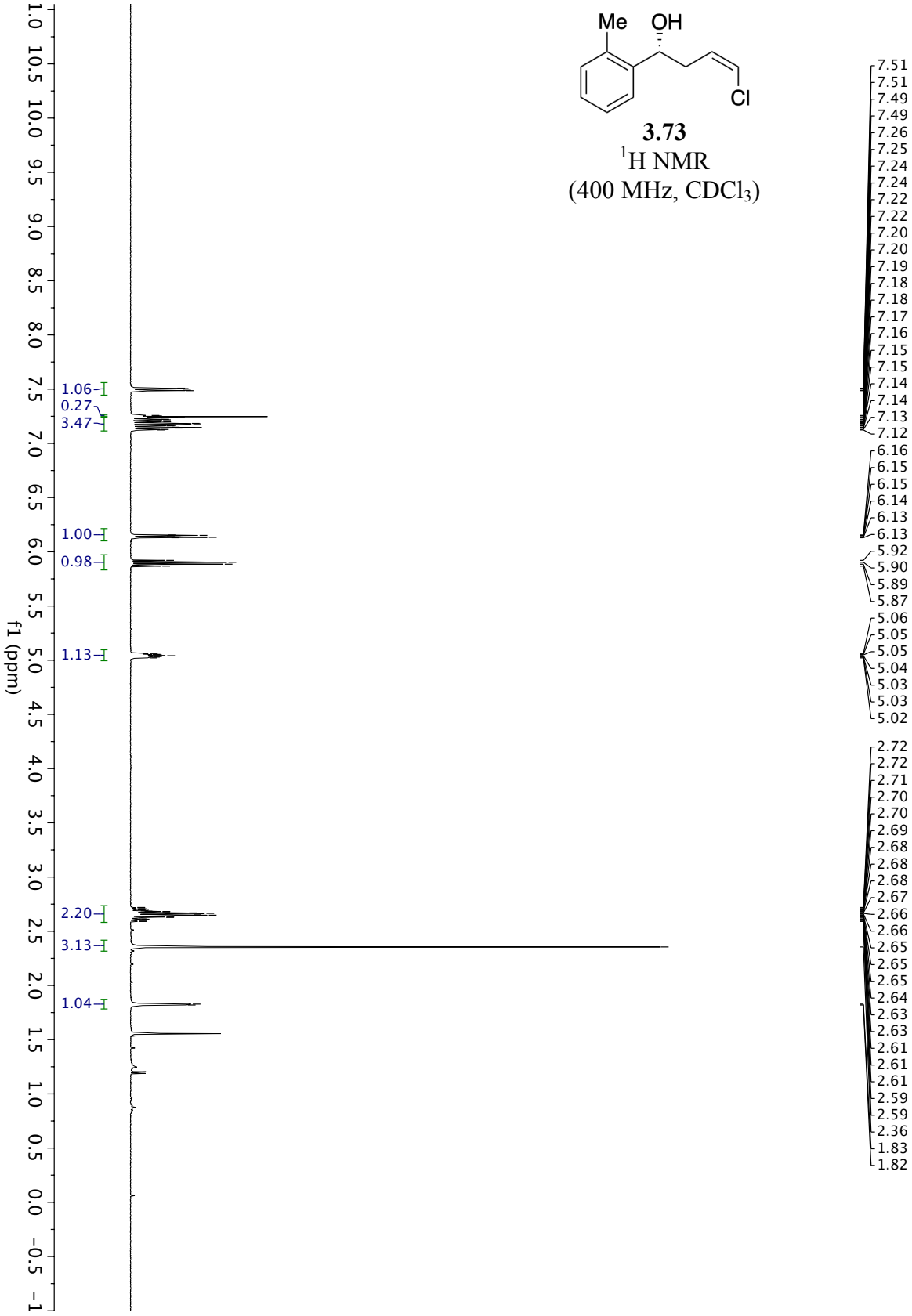
^{1}H NMR

(400 MHz, $CDCl_3$)


HO
N
H
N
O
OH
SiPh3
ap-6
13C NMR
(100 MHz, CDCl3)
171.10
163.17
138.06
136.39
135.88
135.76
135.07
131.34
129.23
128.04
127.70
127.62
123.05
122.64
121.23
120.90
119.17
68.46
64.67
52.76
52.00
50.45
46.42
44.49
44.39
39.89
38.07
37.14
35.21
30.33
30.16
f1 (ppm)


OH
Cl
3.72
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
4.29
0.96
1.00
1.10
1.13
2.39
1.01
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.31
7.31
7.31
7.30
7.29
7.29
7.29
7.28
6.15
6.15
6.14
6.14
6.14
6.13
5.85
5.84
5.83
5.82
4.84
4.83
4.83
4.82
4.82
4.81
4.81
2.77
2.77
2.76
2.76
2.75
2.74
2.73
2.73
2.72
2.72
2.71
2.71
2.71
2.70
2.70
2.69
2.69
2.68
2.67
1.89
1.89


OH
Cl
3.72
13C NMR
(150 MHz, CDCl3)
143.77
128.69
127.97
127.62
125.93
120.50
73.36
36.81
f1 (ppm)


Me
OH
Cl
3.73
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.06
0.27
3.47
1.00
0.98
1.13
2.20
3.13
1.04
7.51
7.51
7.49
7.49
7.26
7.25
7.24
7.24
7.22
7.22
7.20
7.20
7.19
7.18
7.18
7.17
7.16
7.15
7.15
7.14
7.14
7.13
7.12
6.16
6.15
6.15
6.14
6.13
6.13
5.92
5.90
5.89
5.87
5.06
5.05
5.05
5.04
5.03
5.03
5.02
2.72
2.72
2.71
2.70
2.70
2.69
2.68
2.68
2.68
2.67
2.66
2.66
2.65
2.65
2.65
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2.63
2.61
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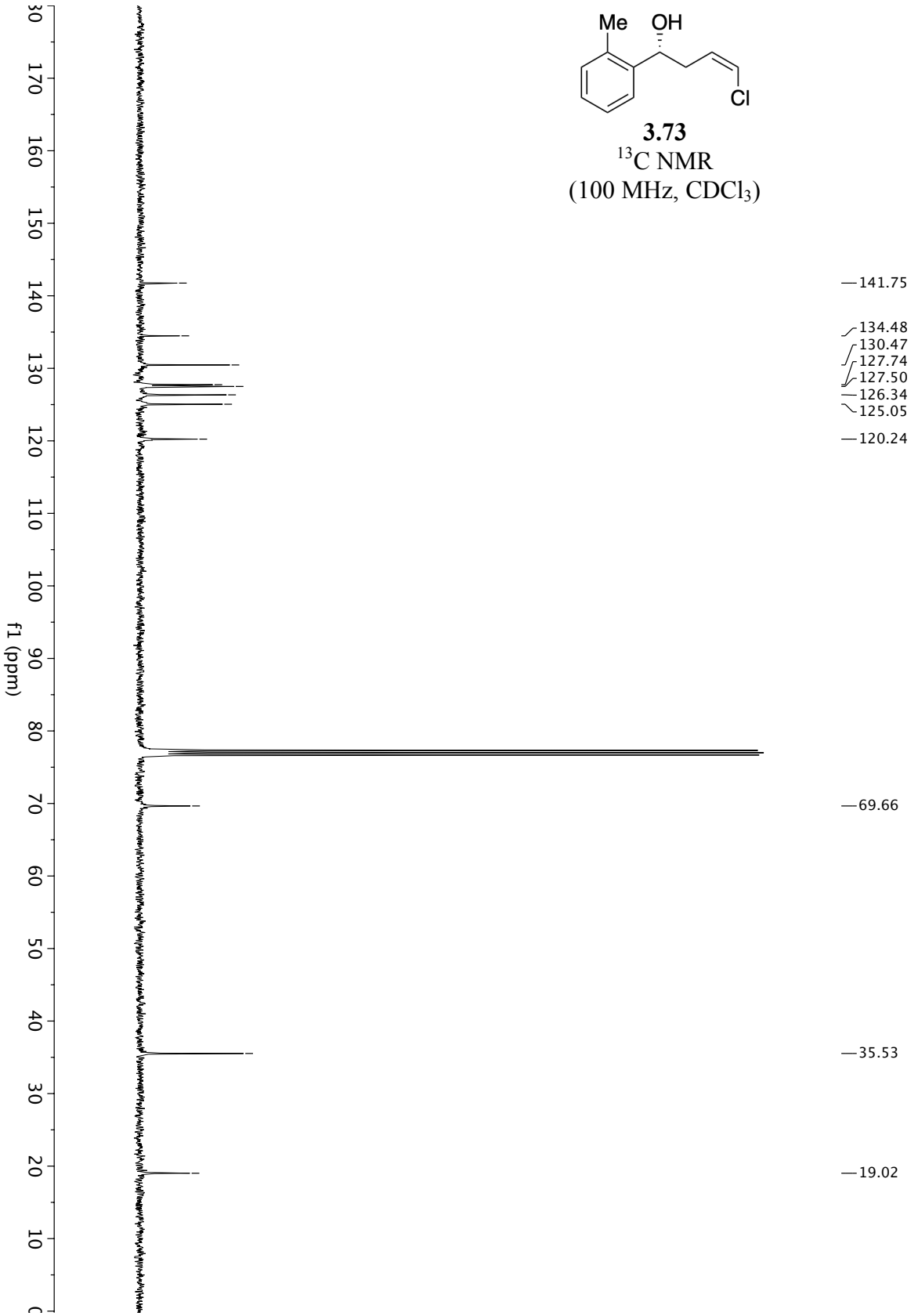
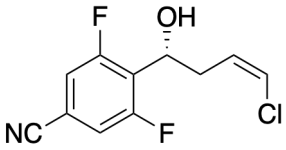
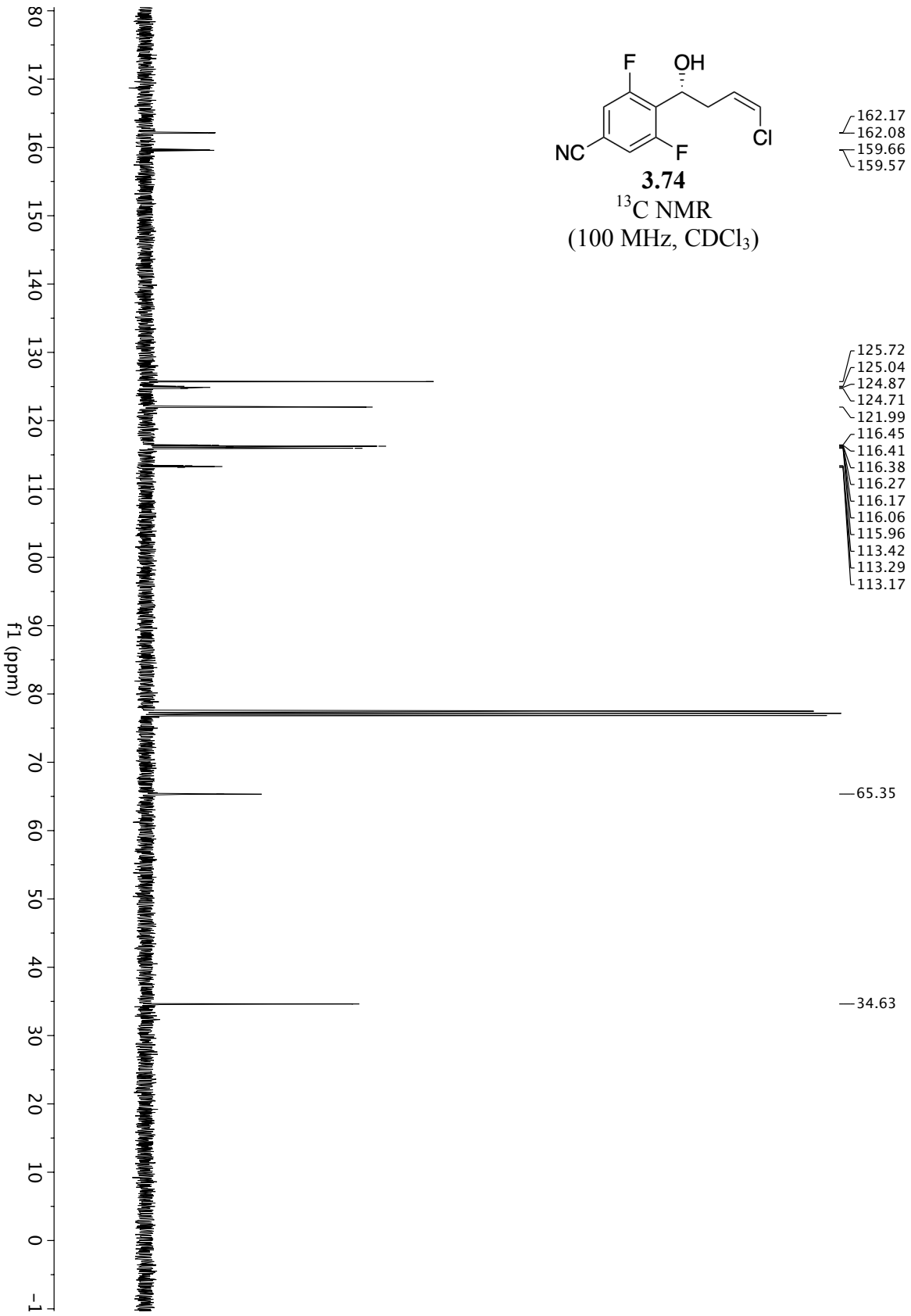
2.61
2.59
2.59
2.36
1.83
1.82


Me
OH
Cl
3.73
^{13}C NMR
(100 MHz, $CDCl_3$)
141.75
134.48
130.47
127.74
127.50
126.34
125.05
120.24
69.66
35.53
19.02
f1 (ppm)



3.74

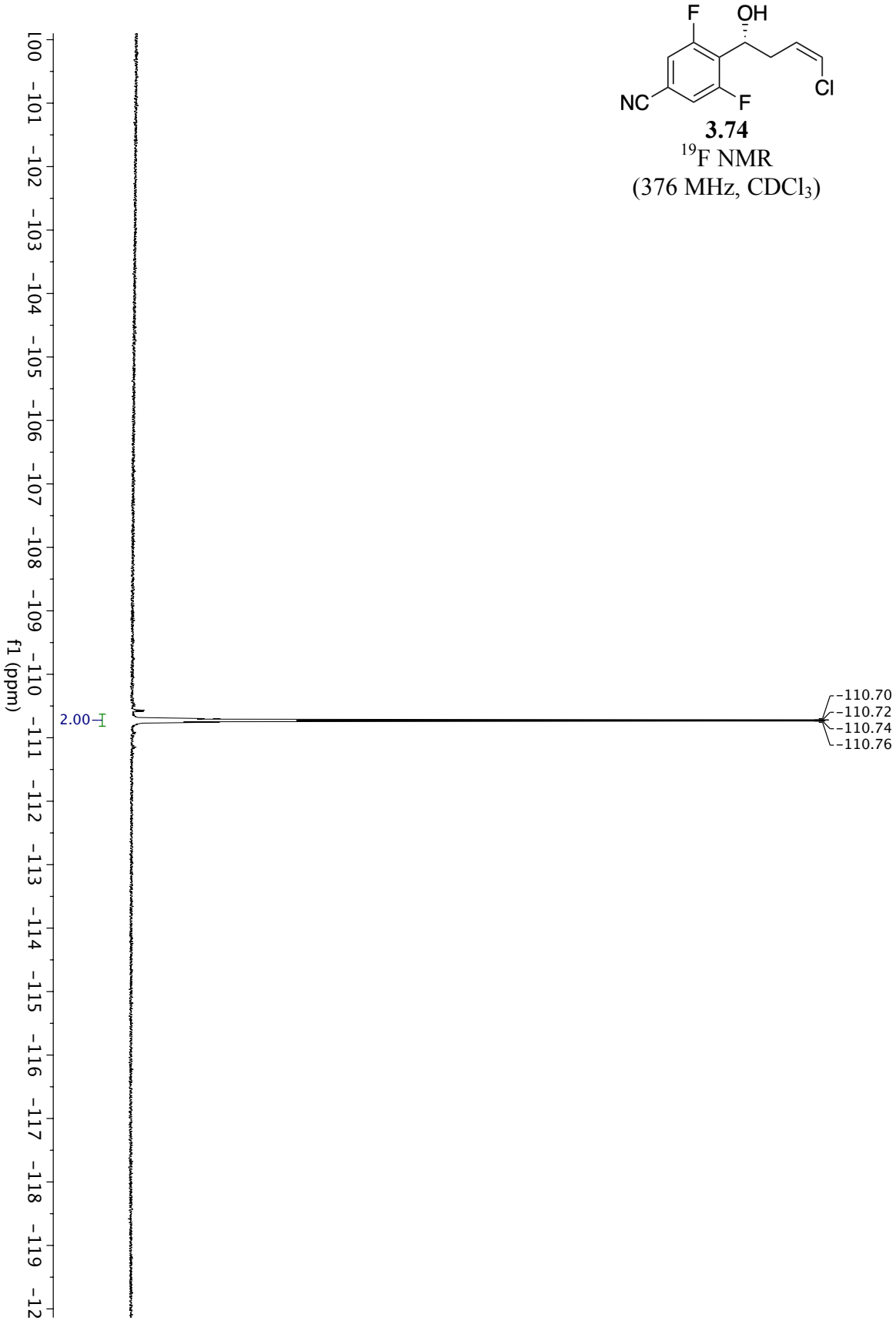
^{1}H NMR
(400 MHz, $CDCl_3$)

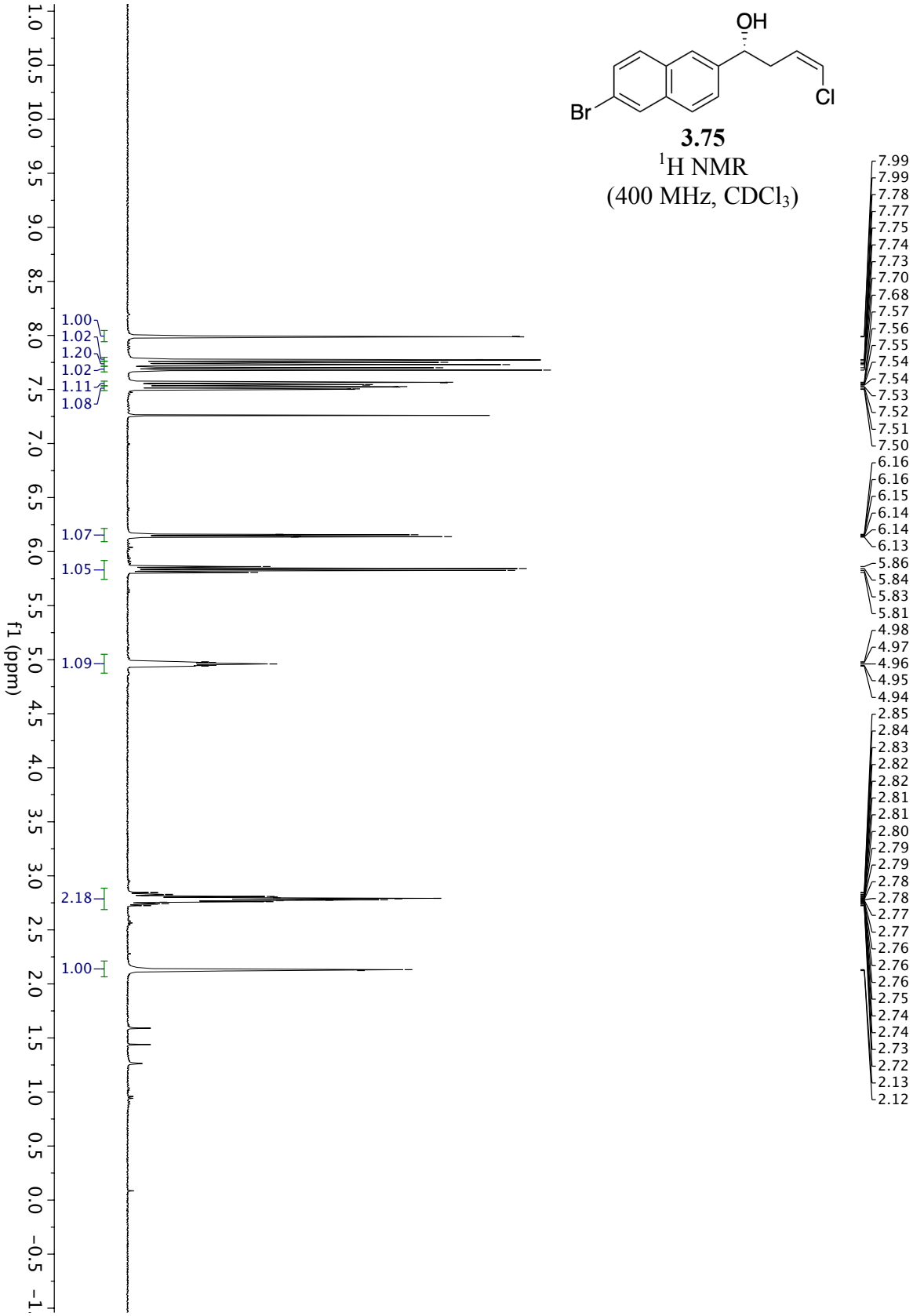


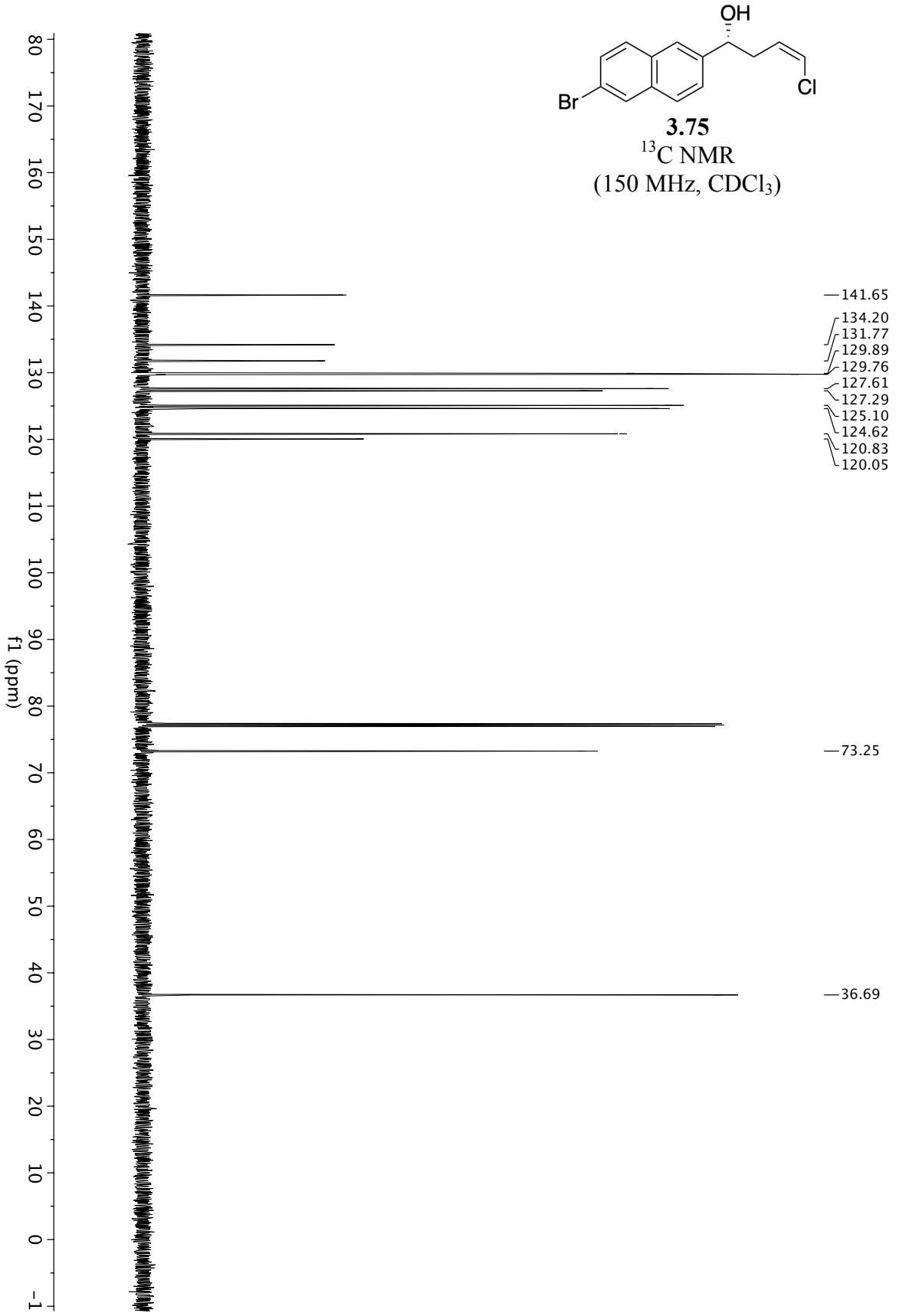
3.74

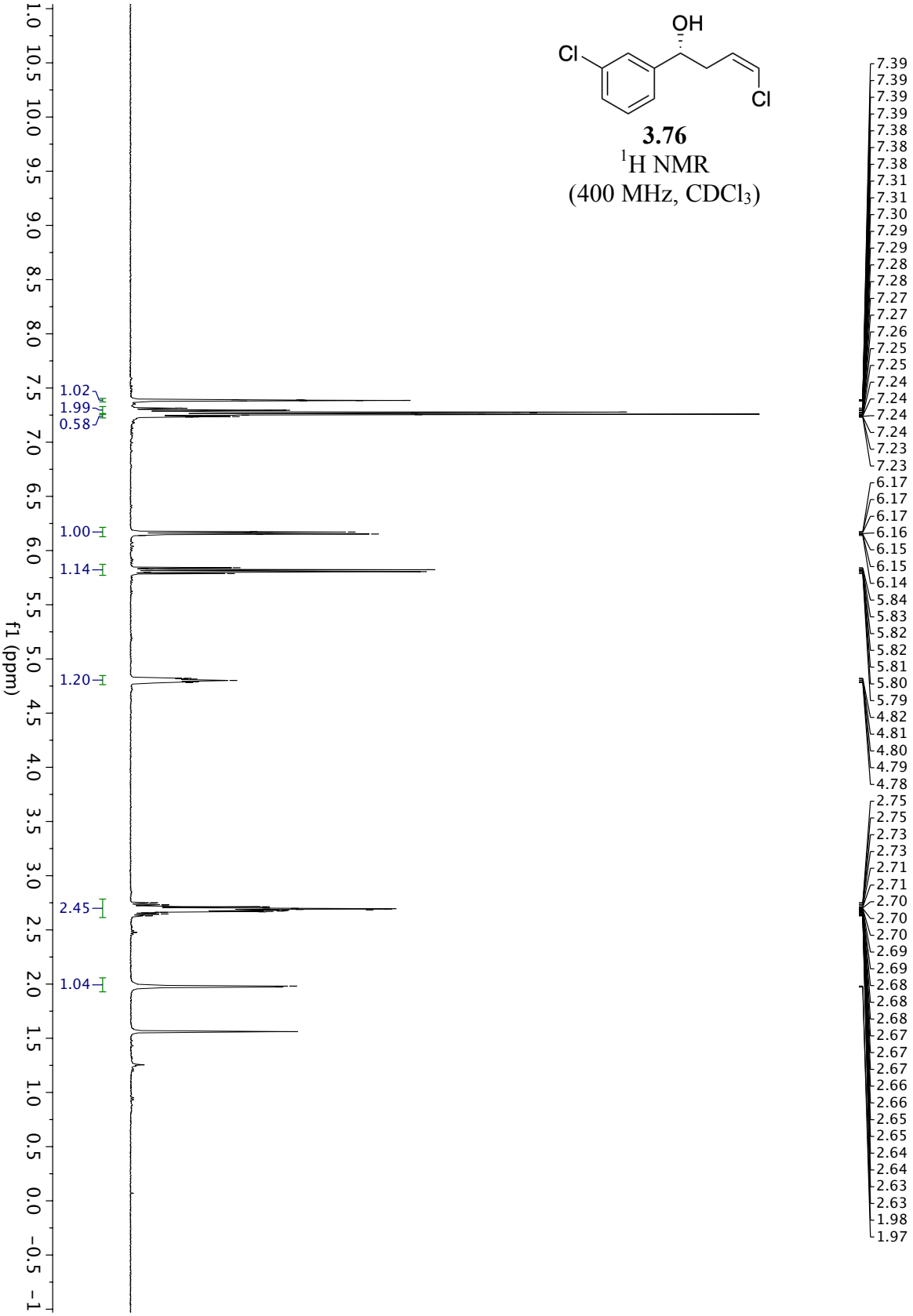
^{13}C NMR

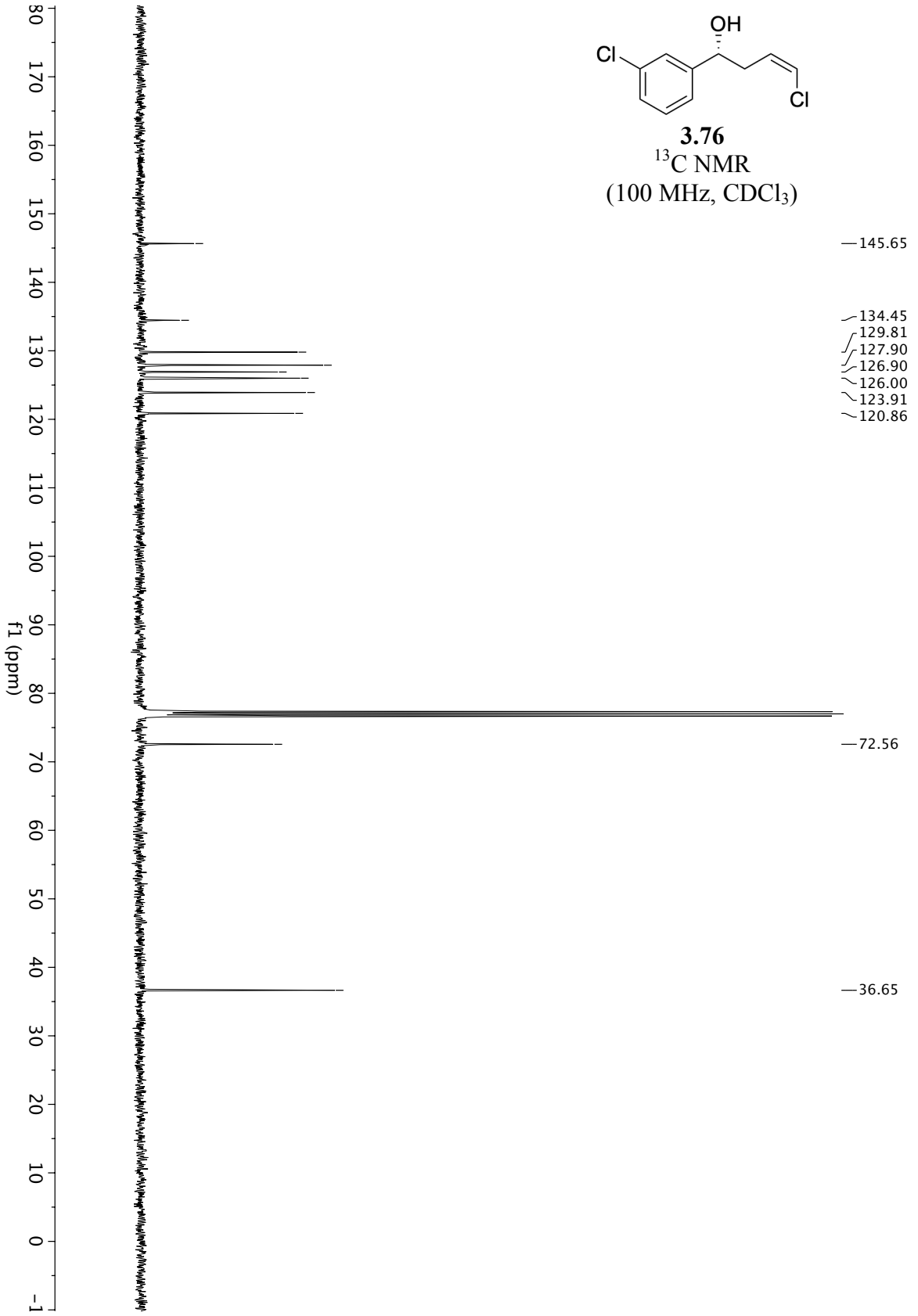
(100 MHz, $CDCl_3$)

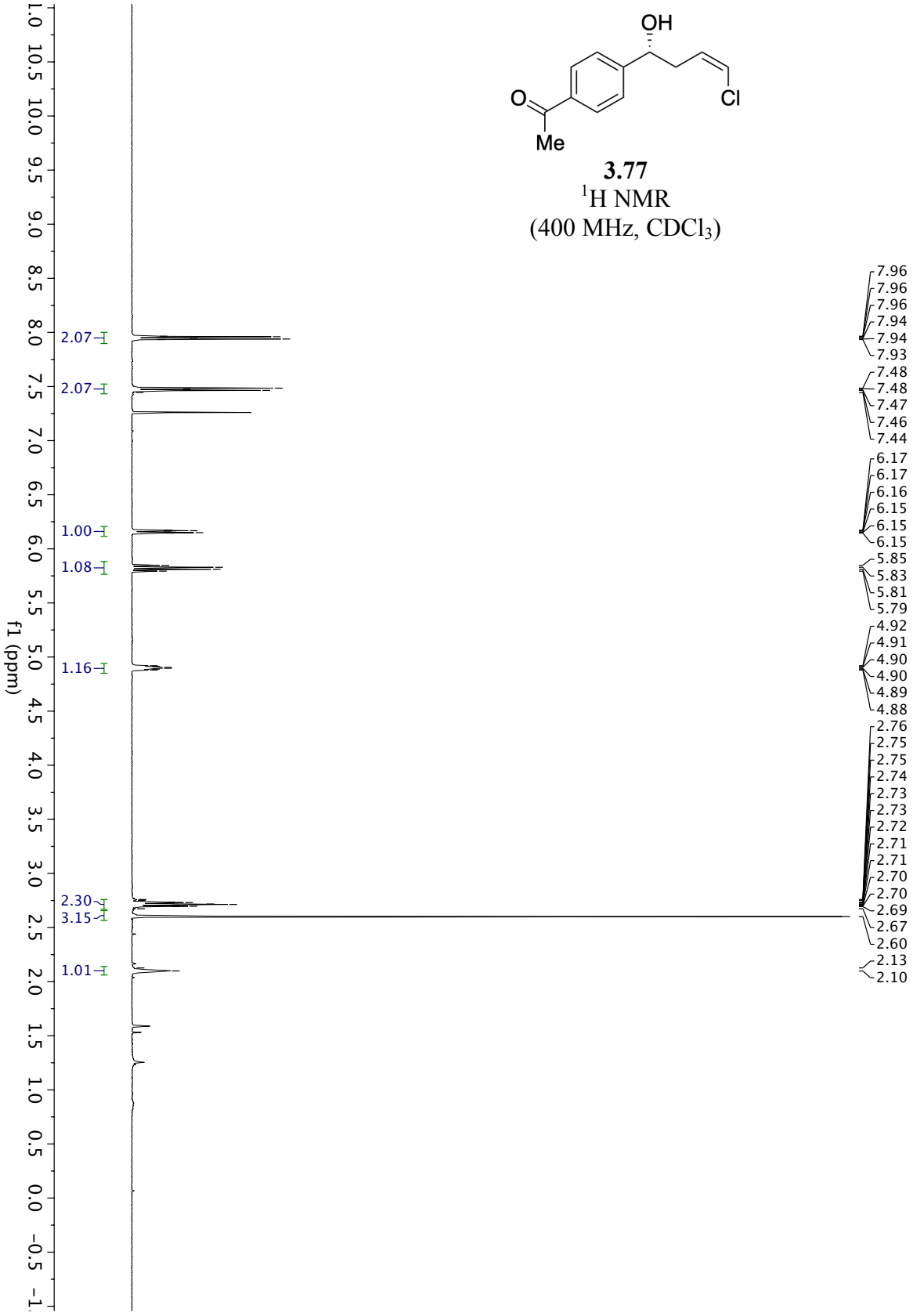

F
OH
NC
F
Cl
3.74
19F NMR
(376 MHz, CDCl3)
-100
-101
-102
-103
-104
-105
-106
-107
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-12
f1 (ppm)
2.00
-110.70
-110.72
-110.74
-110.76

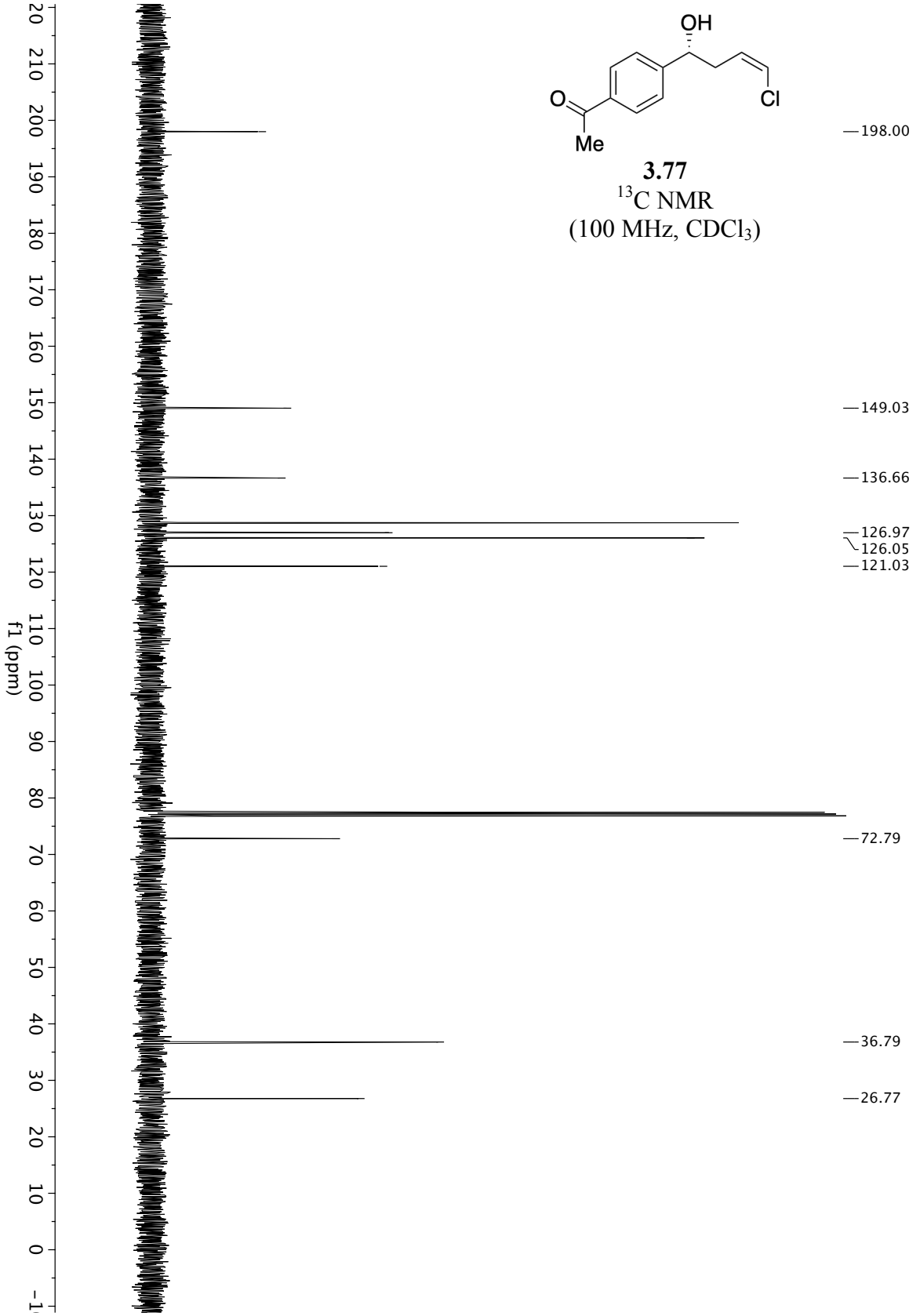

OH
Br
Cl
3.75
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
1.02
1.20
1.02
1.11
1.08
1.07
1.05
1.09
2.18
1.00
7.99
7.99
7.78
7.77
7.75
7.74
7.73
7.70
7.68
7.57
7.56
7.55
7.54
7.54
7.53
7.52
7.51
7.50
6.16
6.16
6.15
6.14
6.14
6.13
5.86
5.84
5.83
5.81
4.98
4.97
4.96
4.95
4.94
2.85
2.84
2.83
2.82
2.82
2.81
2.81
2.80
2.79
2.79
2.78
2.78
2.77
2.77
2.76
2.76
2.76
2.75
2.74
2.74
2.73
2.72
2.13
2.12


OH
Br
Cl
3.75
13C NMR
(150 MHz, CDCl3)
141.65
134.20
131.77
129.89
129.76
127.61
127.29
125.10
124.62
120.83
120.05
73.25
36.69
f1 (ppm)

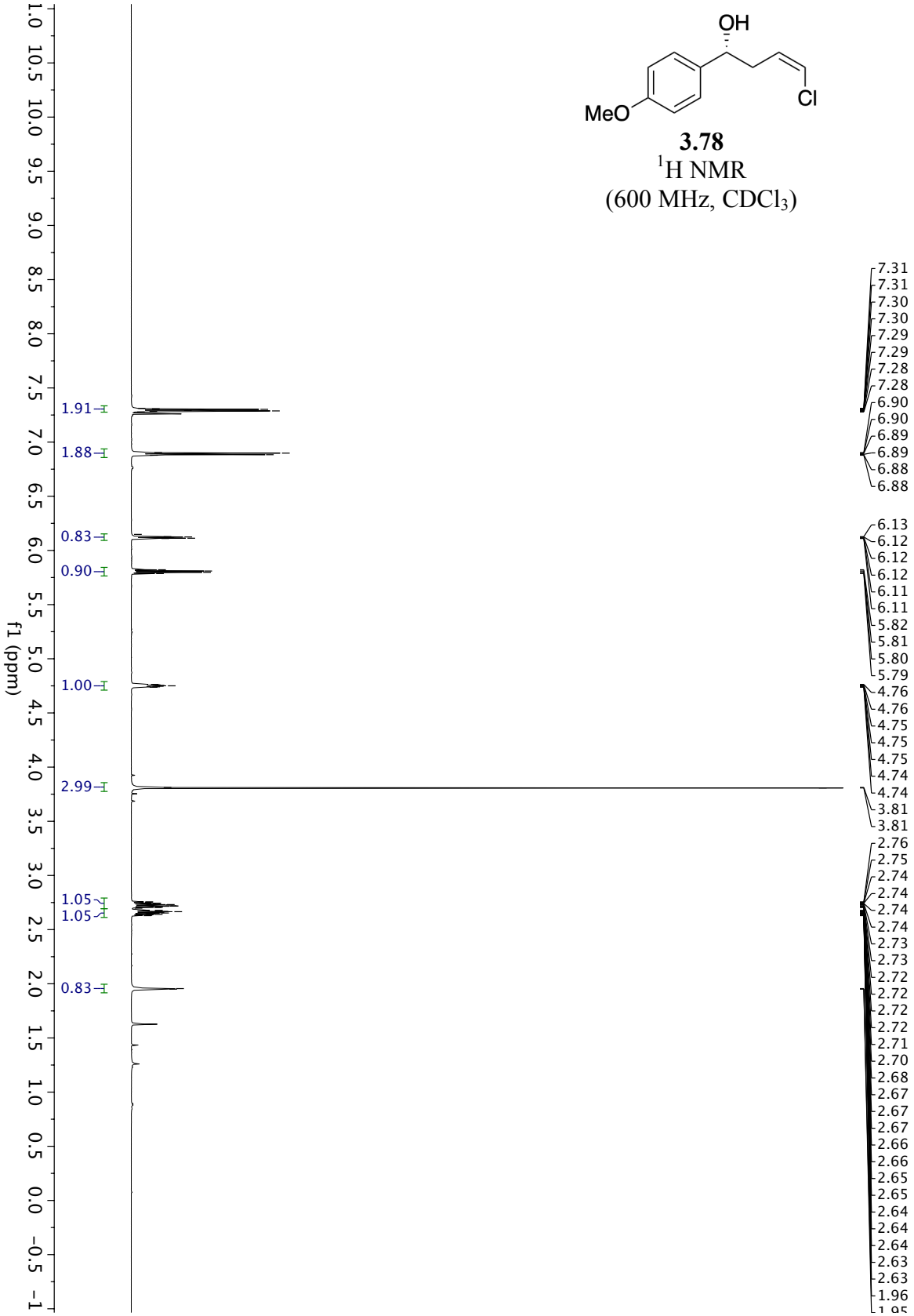

OH
Cl
Cl
3.76
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.02
1.99
0.58
1.00
1.14
1.20
2.45
1.04
7.39
7.39
7.39
7.39
7.38
7.38
7.38
7.31
7.31
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26
7.25
7.25
7.24
7.24
7.24
7.24
7.23
7.23
6.17
6.17
6.17
6.16
6.15
6.15
6.14
5.84
5.83
5.82
5.82
5.81
5.80
5.79
4.82
4.81
4.80
4.79
4.78
2.75
2.75
2.73
2.73
2.71
2.71
2.70
2.70
2.70
2.69
2.69
2.68
2.68
2.68
2.67
2.67
2.67
2.66
2.66
2.65
2.65
2.64
2.64
2.63
2.63
1.98
1.97


OH
Cl
Cl
3.76
13C NMR
(100 MHz, CDCl3)
145.65
134.45
129.81
127.90
126.90
126.00
123.91
120.86
72.56
36.65
f1 (ppm)


OH
O
Cl
Me
3.77
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.07
2.07
1.00
1.08
1.16
2.30
3.15
1.01
7.96
7.96
7.96
7.94
7.94
7.93
7.48
7.48
7.47
7.46
7.44
6.17
6.17
6.16
6.15
6.15
6.15
5.85
5.83
5.81
5.79
4.92
4.91
4.90
4.90
4.89
4.88
2.76
2.75
2.75
2.74
2.73
2.73
2.72
2.71
2.71
2.70
2.70
2.69
2.67
2.60
2.13
2.10



3.77
^{13}C NMR
(100 MHz, $CDCl_3$)


OH
MeO
Cl
3.78
1H NMR
(600 MHz, CDCl3)
f1 (ppm)
1.91
1.88
0.83
0.90
1.00
2.99
1.05
1.05
0.83
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.28
6.90
6.90
6.89
6.89
6.88
6.88
6.13
6.12
6.12
6.12
6.11
6.11
5.82
5.81
5.80
5.79
4.76
4.76
4.75
4.75
4.75
4.74
4.74
3.81
3.81
2.76
2.75
2.74
2.74
2.74
2.74
2.73
2.73
2.72
2.72
2.72
2.72
2.71
2.70
2.68
2.67
2.67
2.67
2.66
2.66
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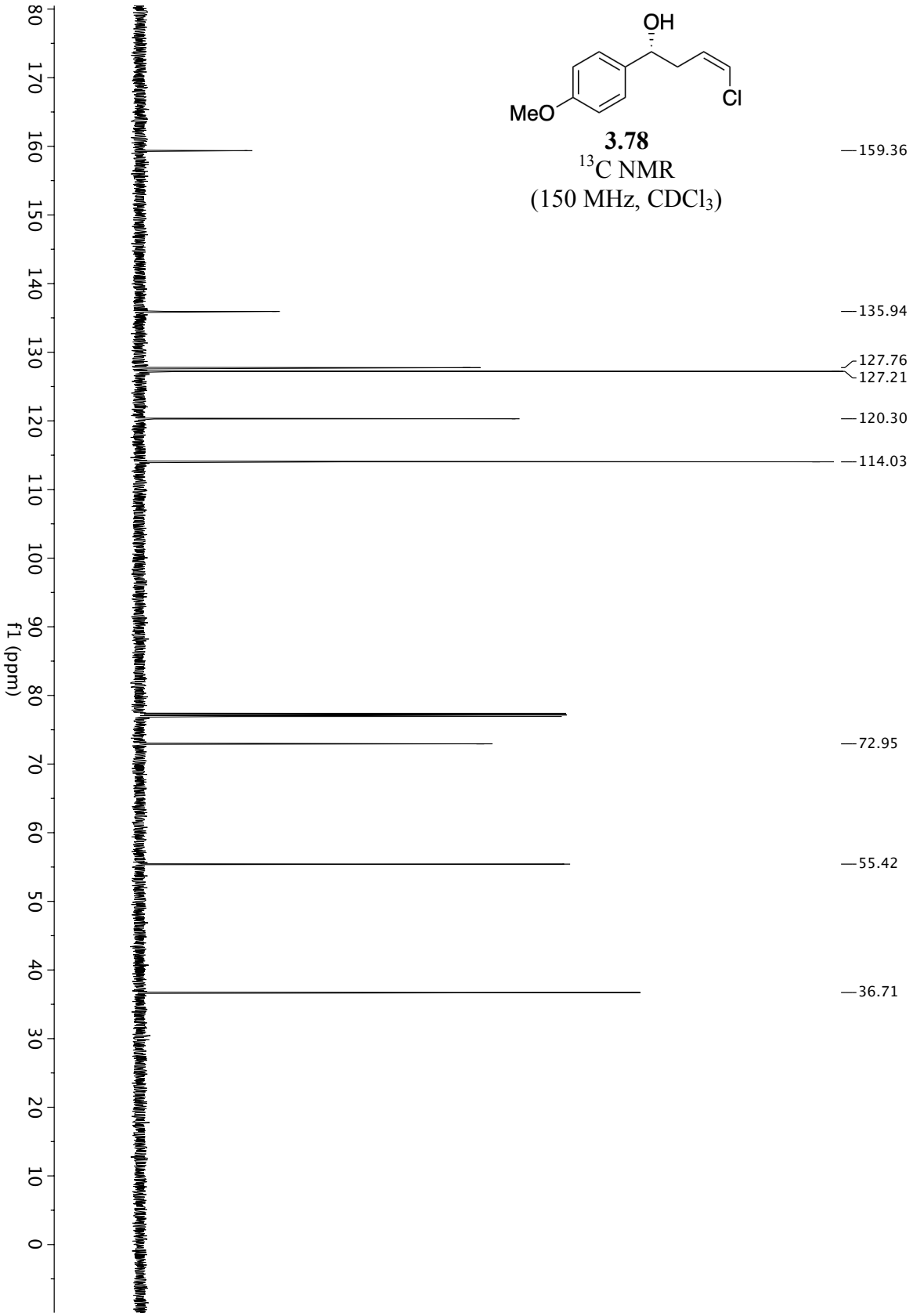
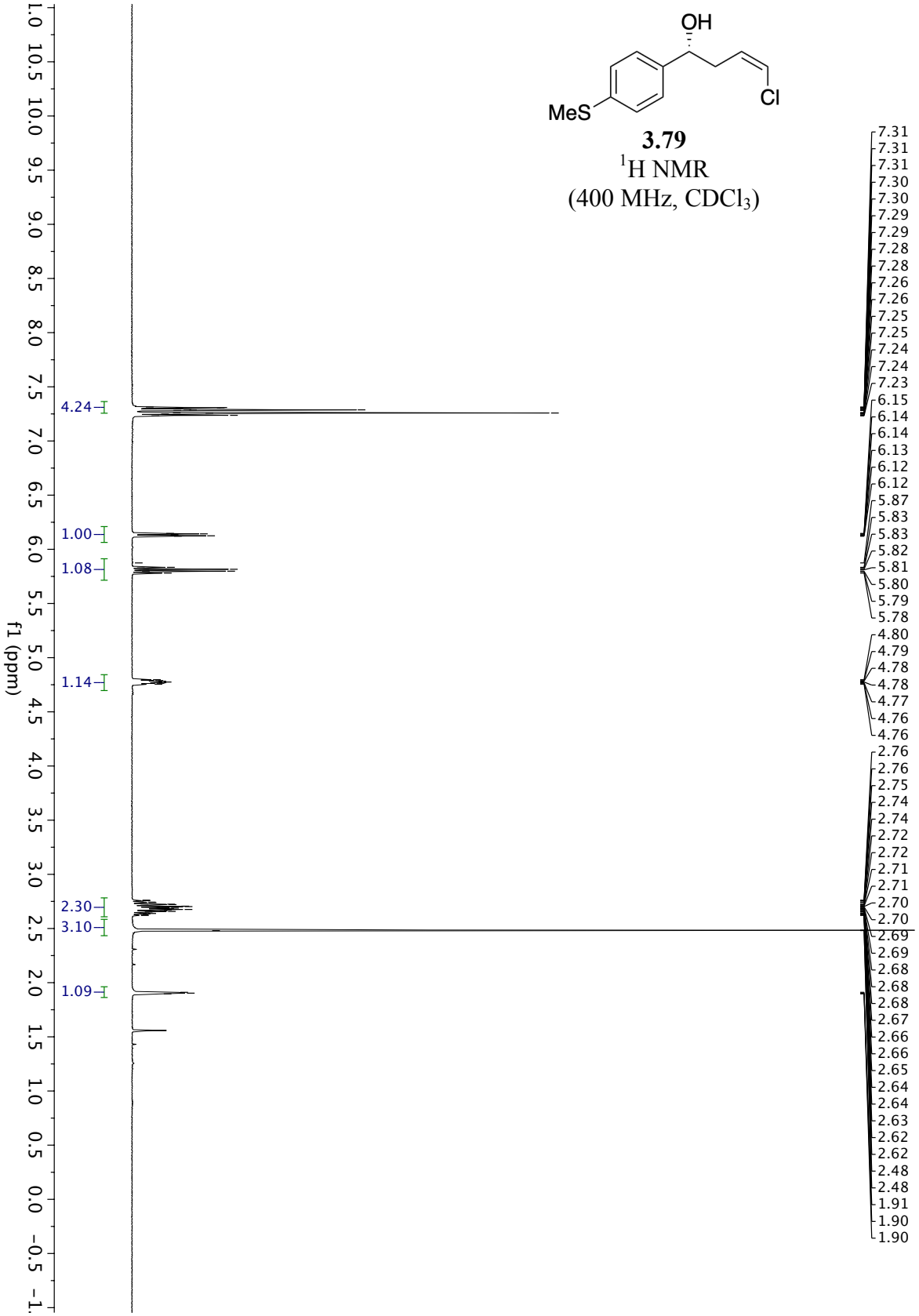
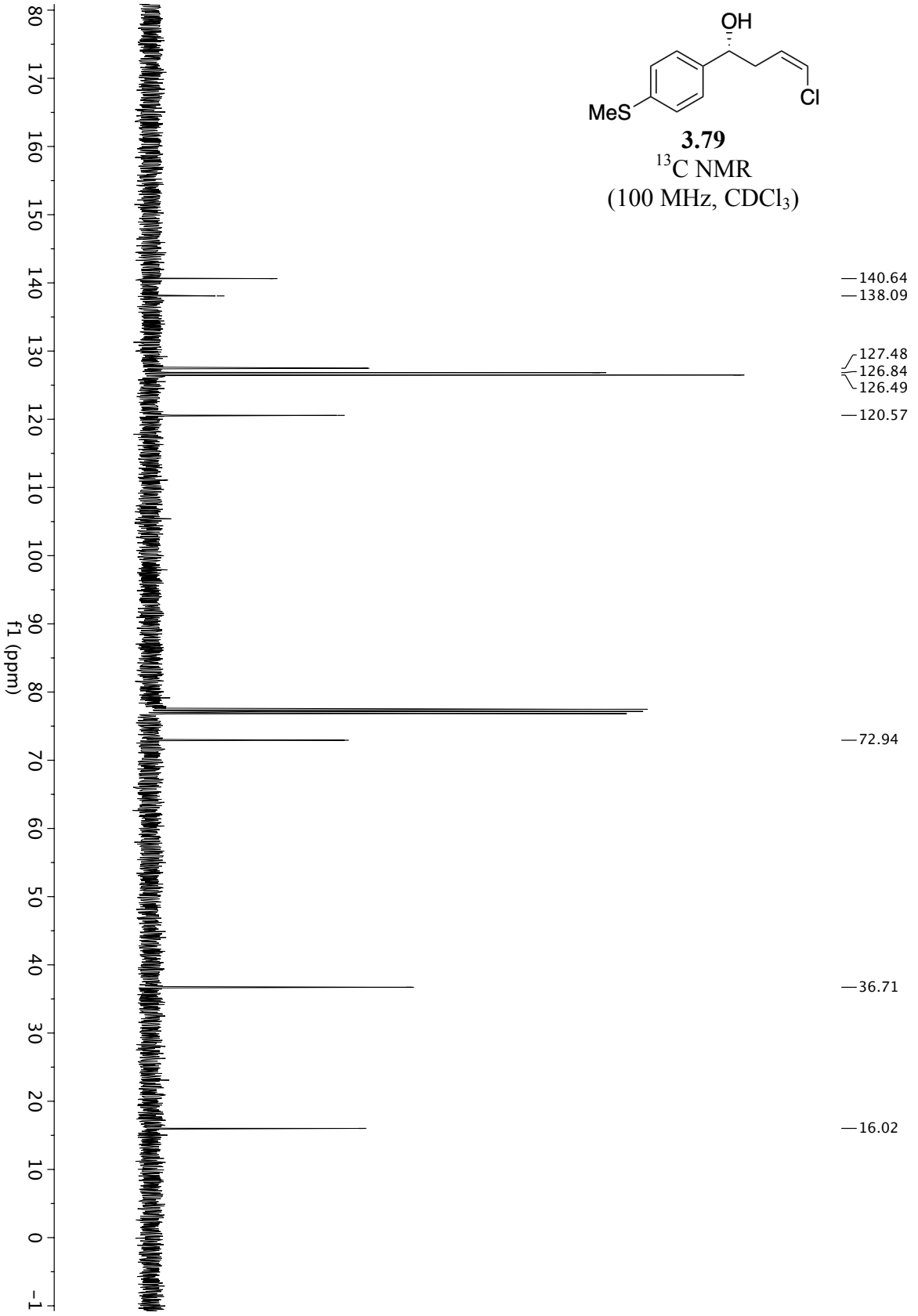
2.64
2.64
2.64
2.63
2.63
1.96


OH
MeO
Cl
3.78
^{13}C NMR
(150 MHz, $CDCl_3$)
159.36
135.94
127.76
127.21
120.30
114.03
72.95
55.42
36.71
f1 (ppm)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

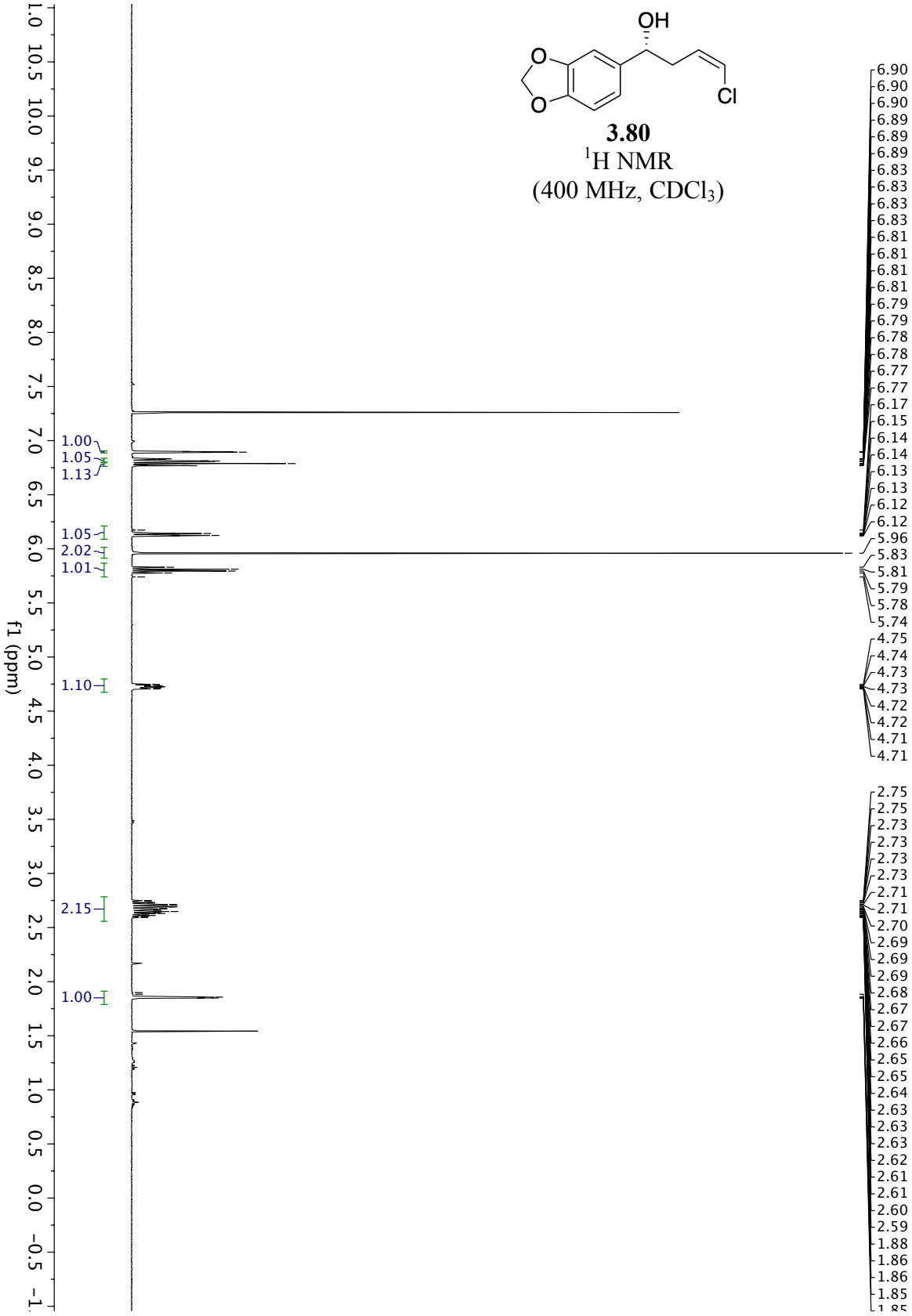

OH
MeS
Cl
3.79
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
4.24
1.00
1.08
1.14
2.30
3.10
1.09

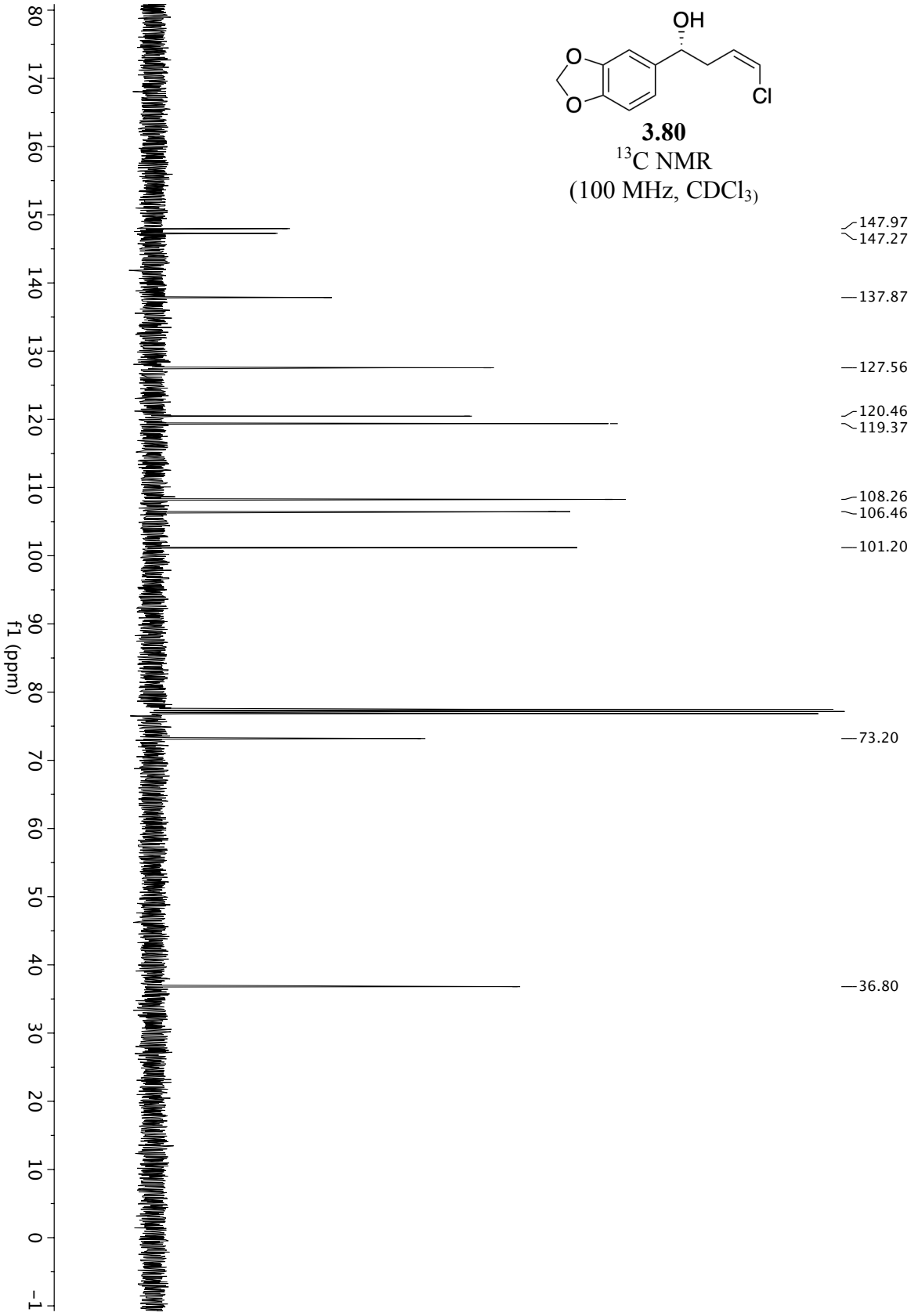


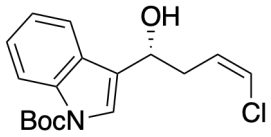
3.79

^{13}C NMR

(100 MHz, $CDCl_3$)


OH
O
O
Cl
3.80
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
1.05
1.13
1.05
2.02
1.01
1.10
2.15
1.00

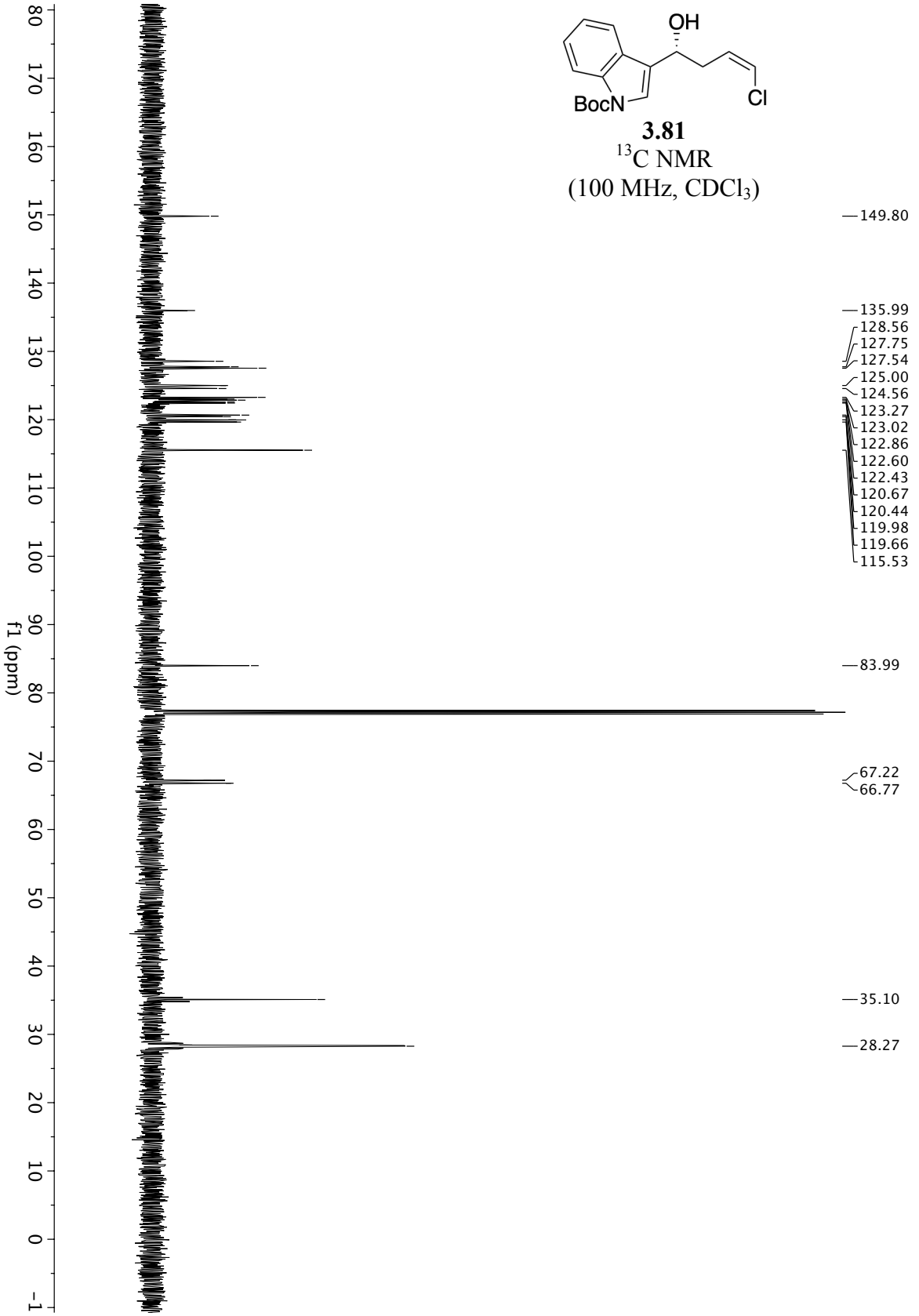

OH
O
O
Cl
3.80
13C NMR
(100 MHz, CDCl3)
147.97
147.27
137.87
127.56
120.46
119.37
108.26
106.46
101.20
73.20
36.80
f1 (ppm)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

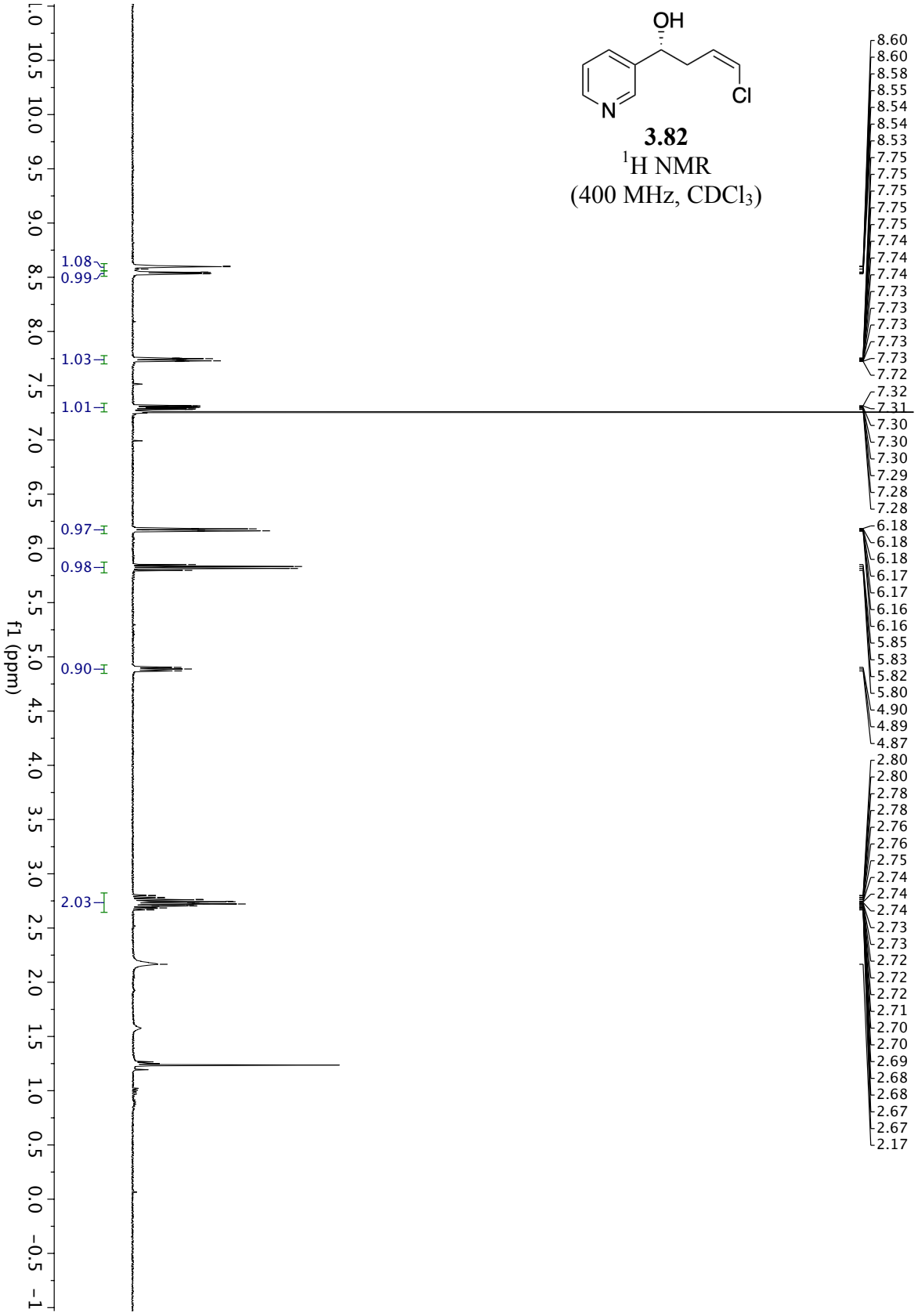


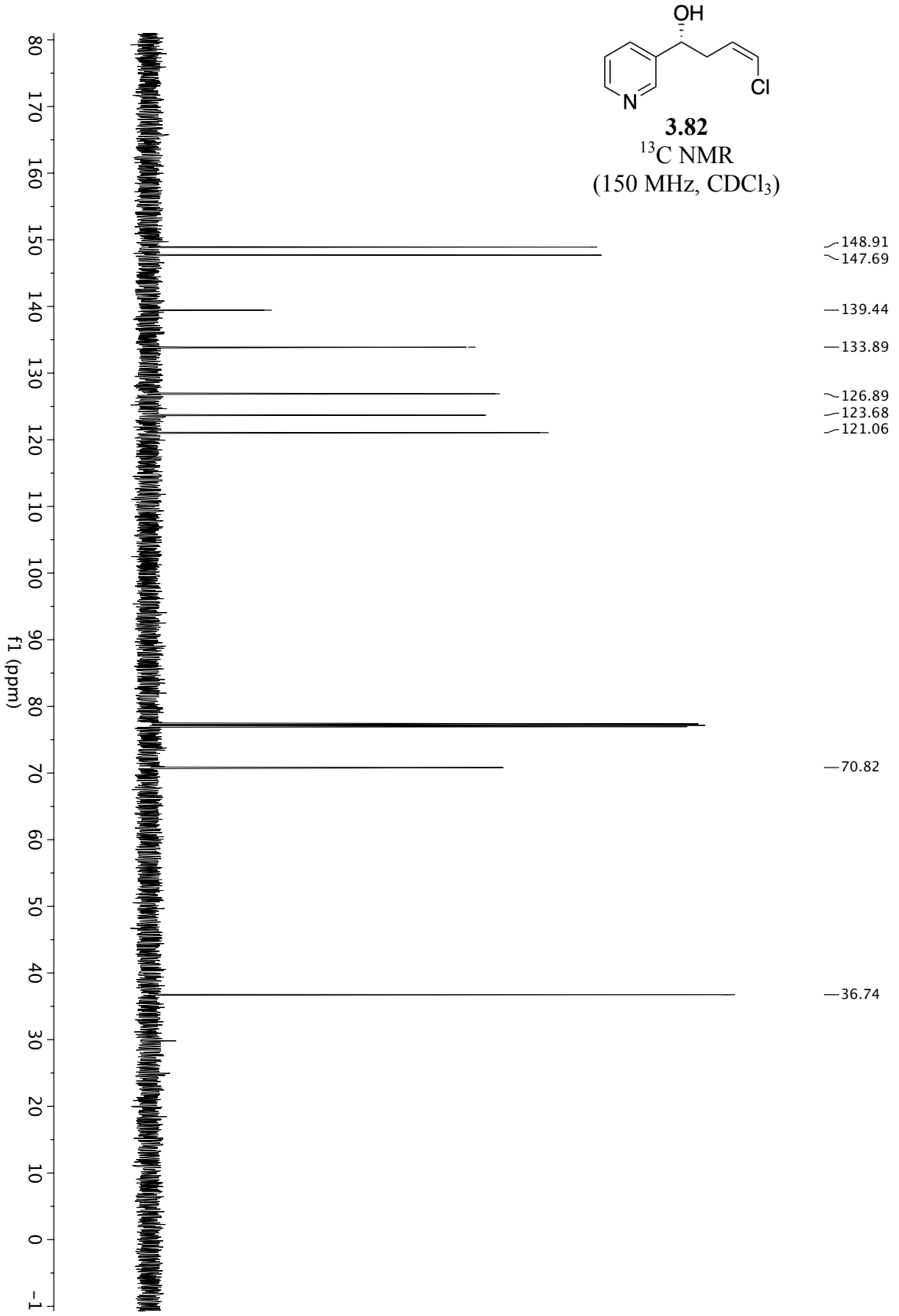
3.81

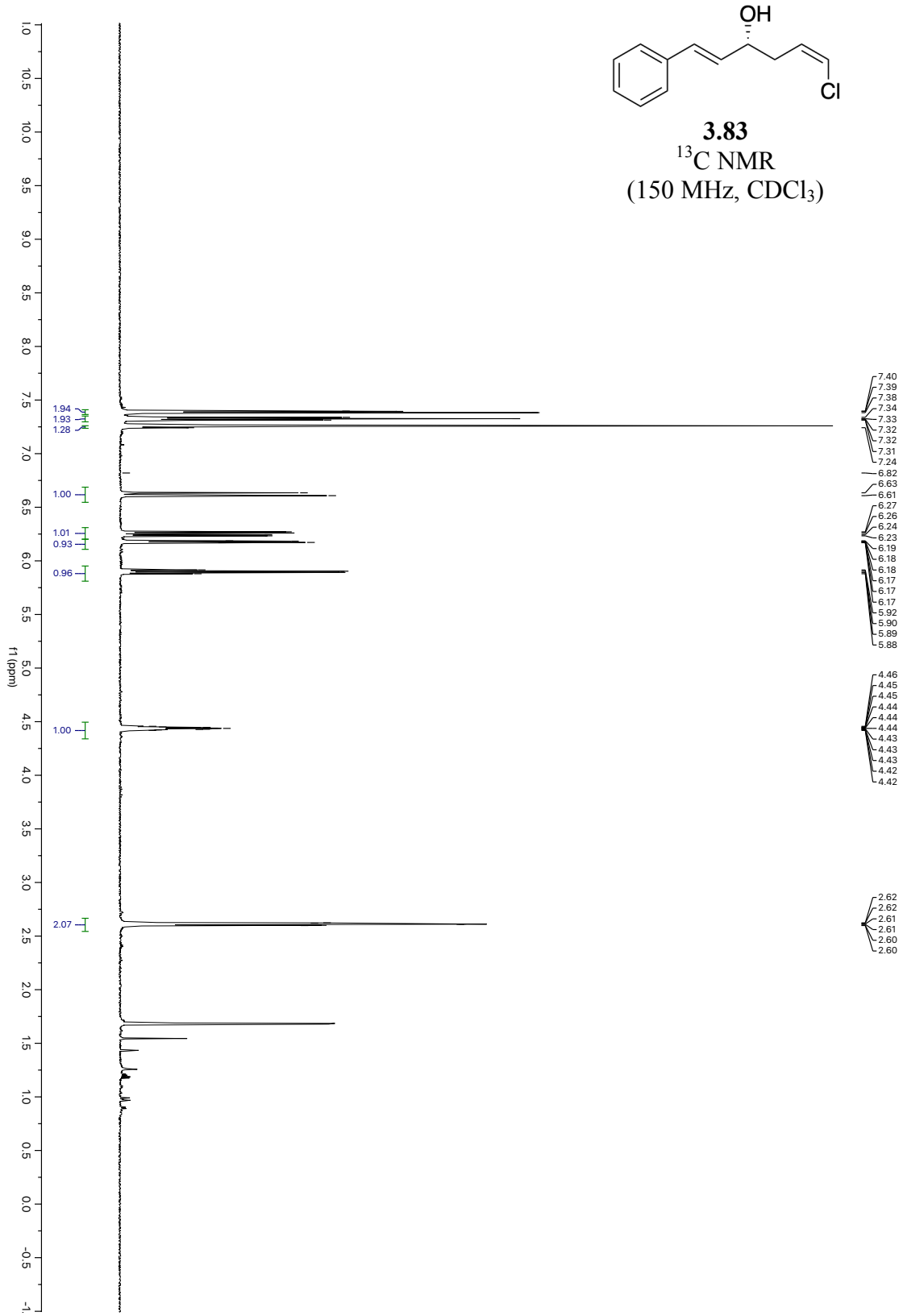
^{1}H NMR

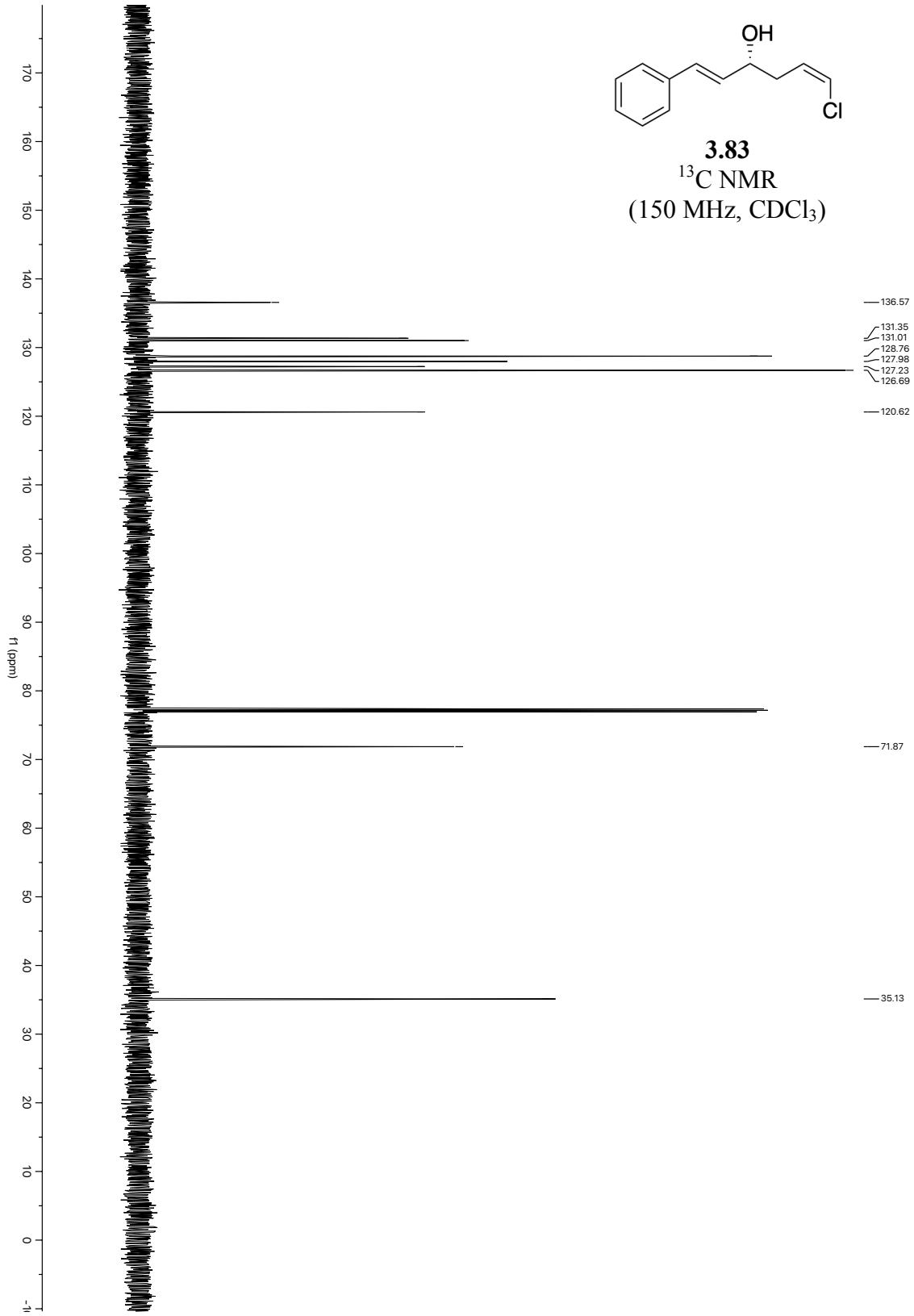
(500 MHz, $CDCl_3$)


OH
BocN
Cl
3.81
13C NMR
(100 MHz, CDCl3)
149.80
135.99
128.56
127.75
127.54
125.00
124.56
123.27
123.02
122.86
122.60
122.43
120.67
120.44
119.98
119.66
115.53
83.99
67.22
66.77
35.10
28.27
f1 (ppm)

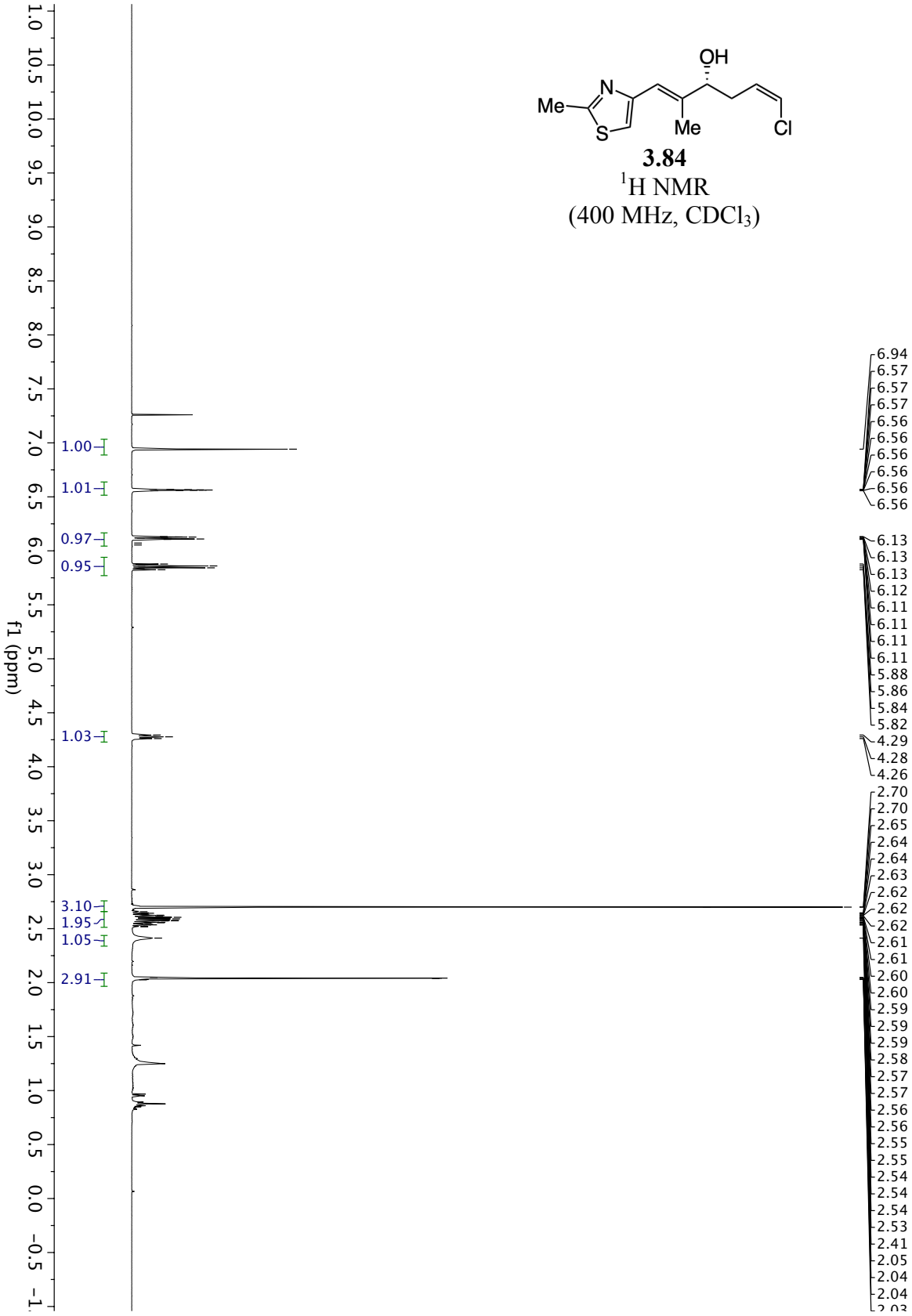

OH
N
Cl
3.82
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.08
0.99
1.03
1.01
0.97
0.98
0.90
2.03


OH
N
Cl
3.82
13C NMR
(150 MHz, CDCl3)
148.91
147.69
139.44
133.89
126.89
123.68
121.06
70.82
36.74
f1 (ppm)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1


OH
Cl
3.83
13C NMR
(150 MHz, CDCl3)
f1 (ppm)
1.94
1.93
1.28
1.00
1.01
0.93
0.96
1.00
2.07
7.40
7.39
7.38
7.34
7.33
7.32
7.32
7.31
7.24
6.82
6.63
6.61
6.27
6.26
6.24
6.23
6.19
6.18
6.18
6.17
6.17
6.17
5.92
5.90
5.89
5.88
4.46
4.45
4.45
4.44
4.44
4.44
4.43
4.43
4.43
4.42
4.42
2.62
2.62
2.61
2.61
2.60
2.60



3.83
^{13}C NMR
(150 MHz, $CDCl_3$)


OH
N
Me
S
Me
Cl
3.84
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
1.01
0.97
0.95
1.03
3.10
1.95
1.05
2.91
6.94
6.57
6.57
6.57
6.56
6.56
6.56
6.56
6.56
6.56
6.13
6.13
6.13
6.12
6.11
6.11
6.11
6.11
5.88
5.86
5.84
5.82
4.29
4.28
4.26
2.70
2.70
2.65
2.64
2.64
2.63
2.62
2.62
2.62
2.61
2.61
2.60
2.60
2.59
2.59
2.59
2.58
2.57
2.57
2.56
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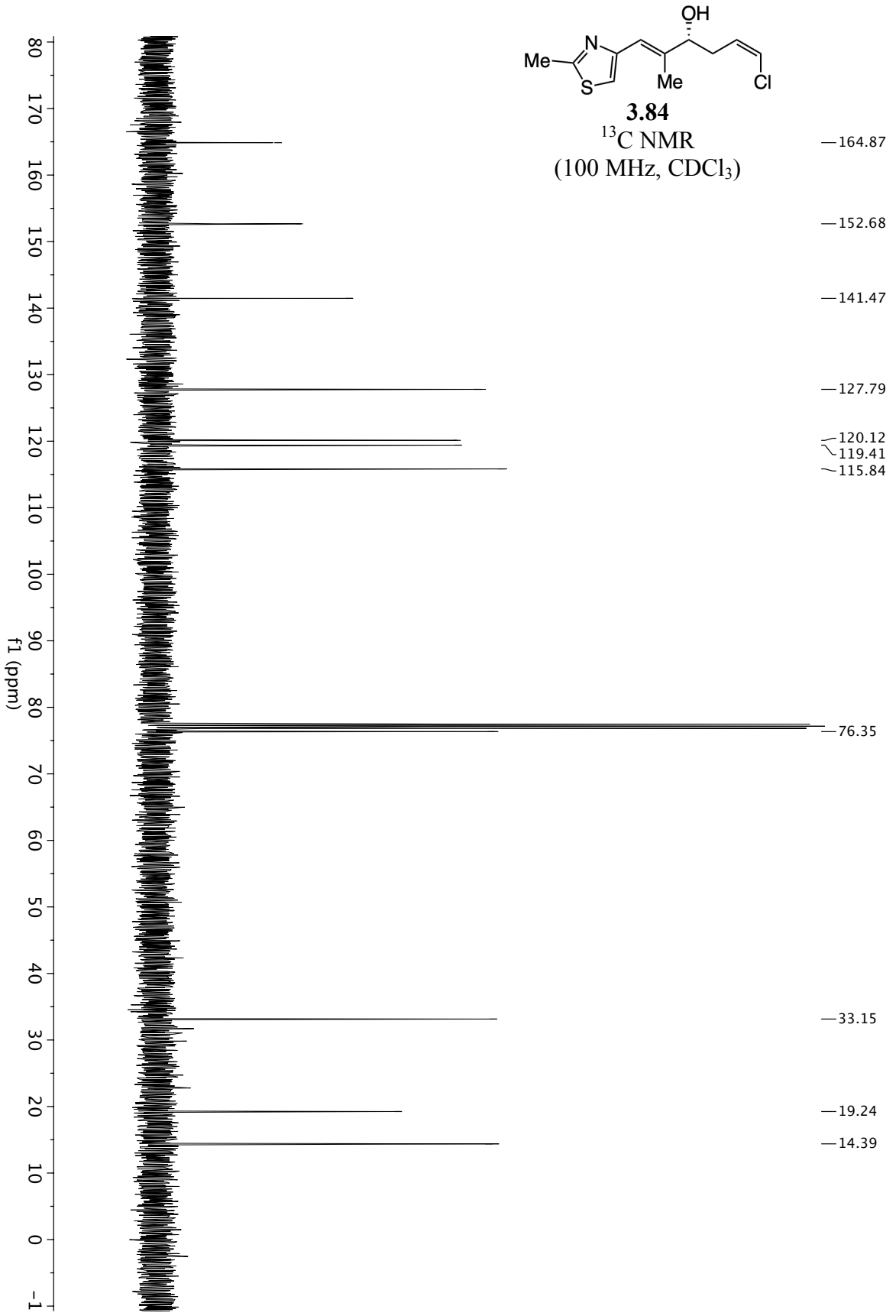
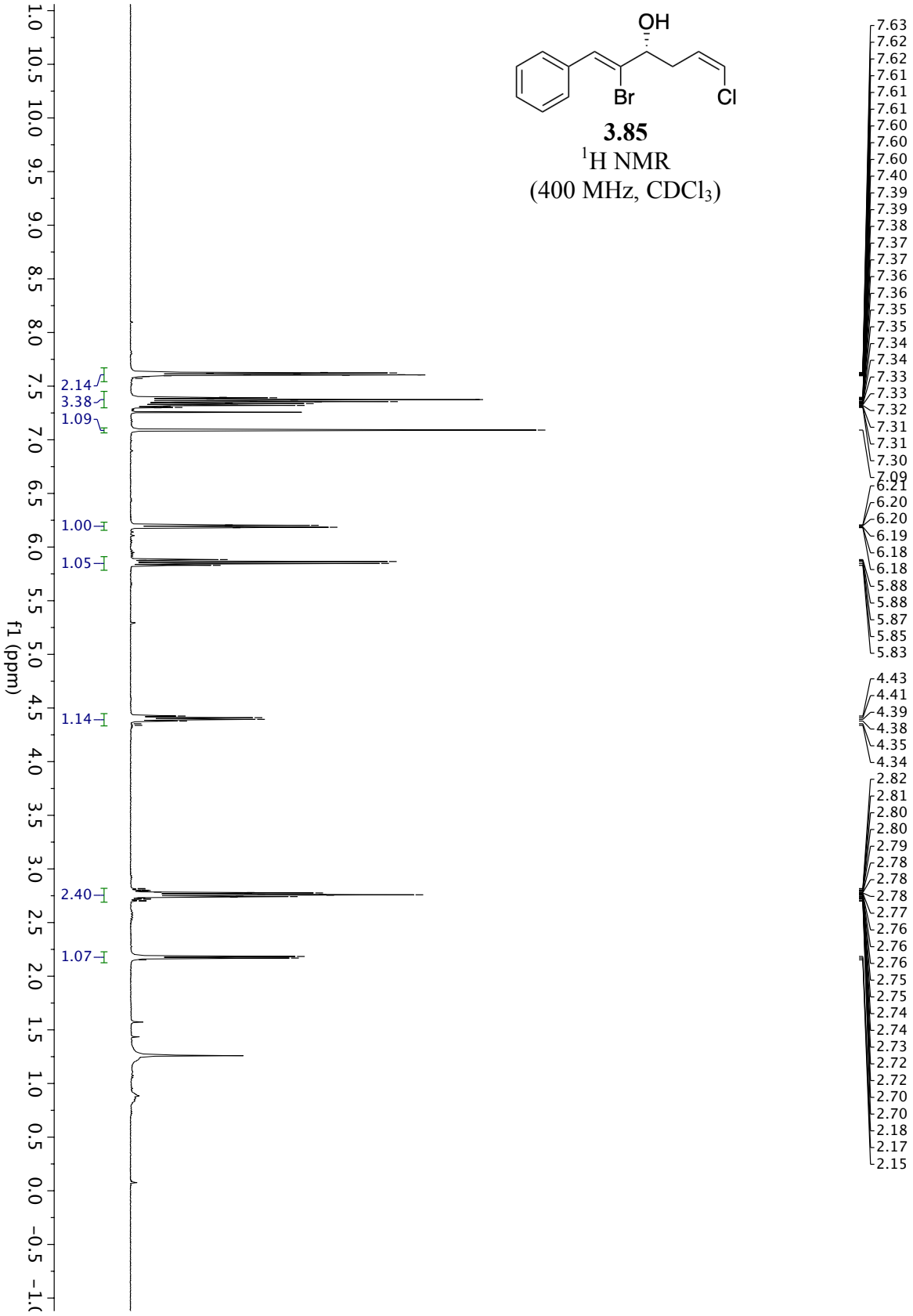
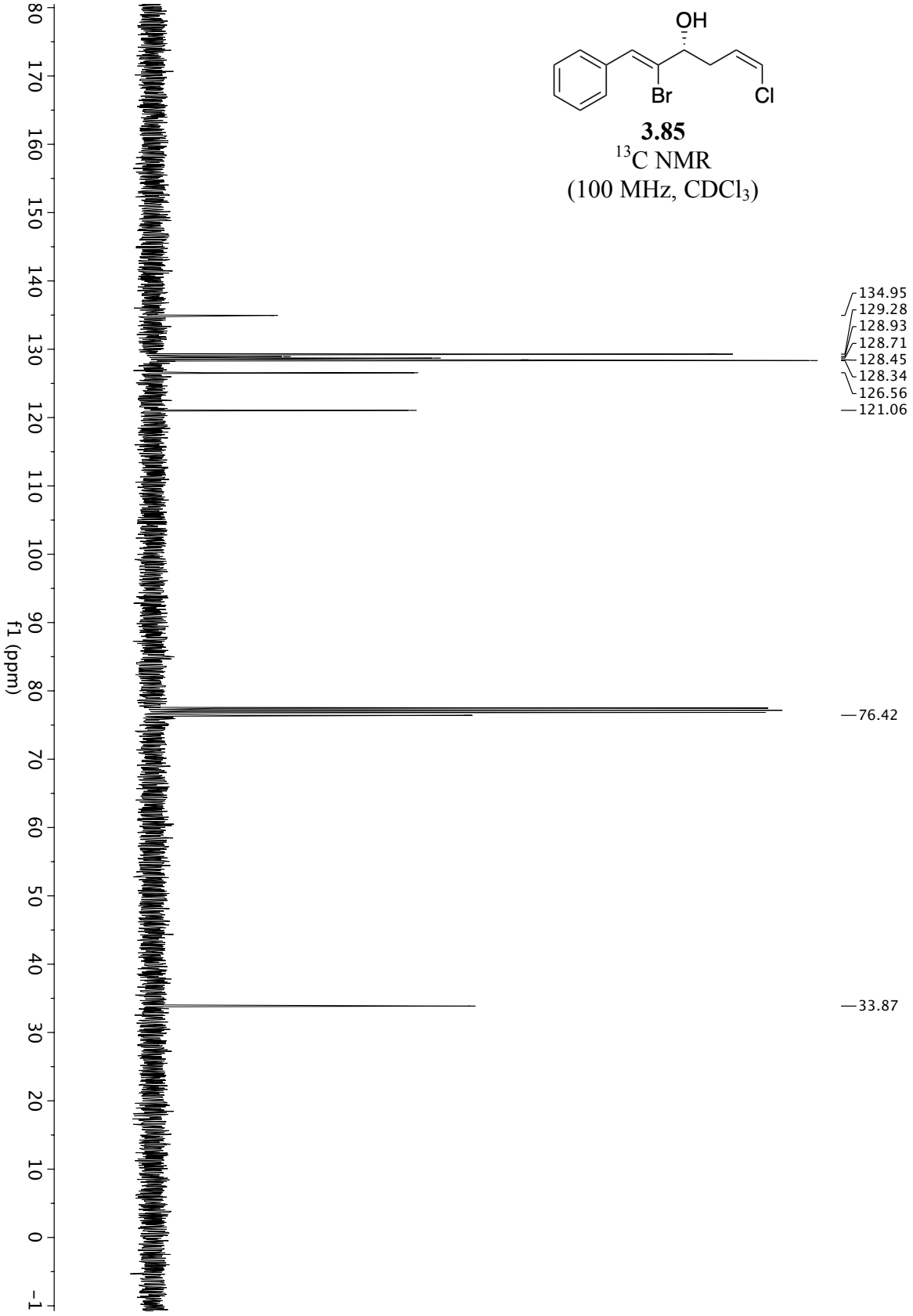
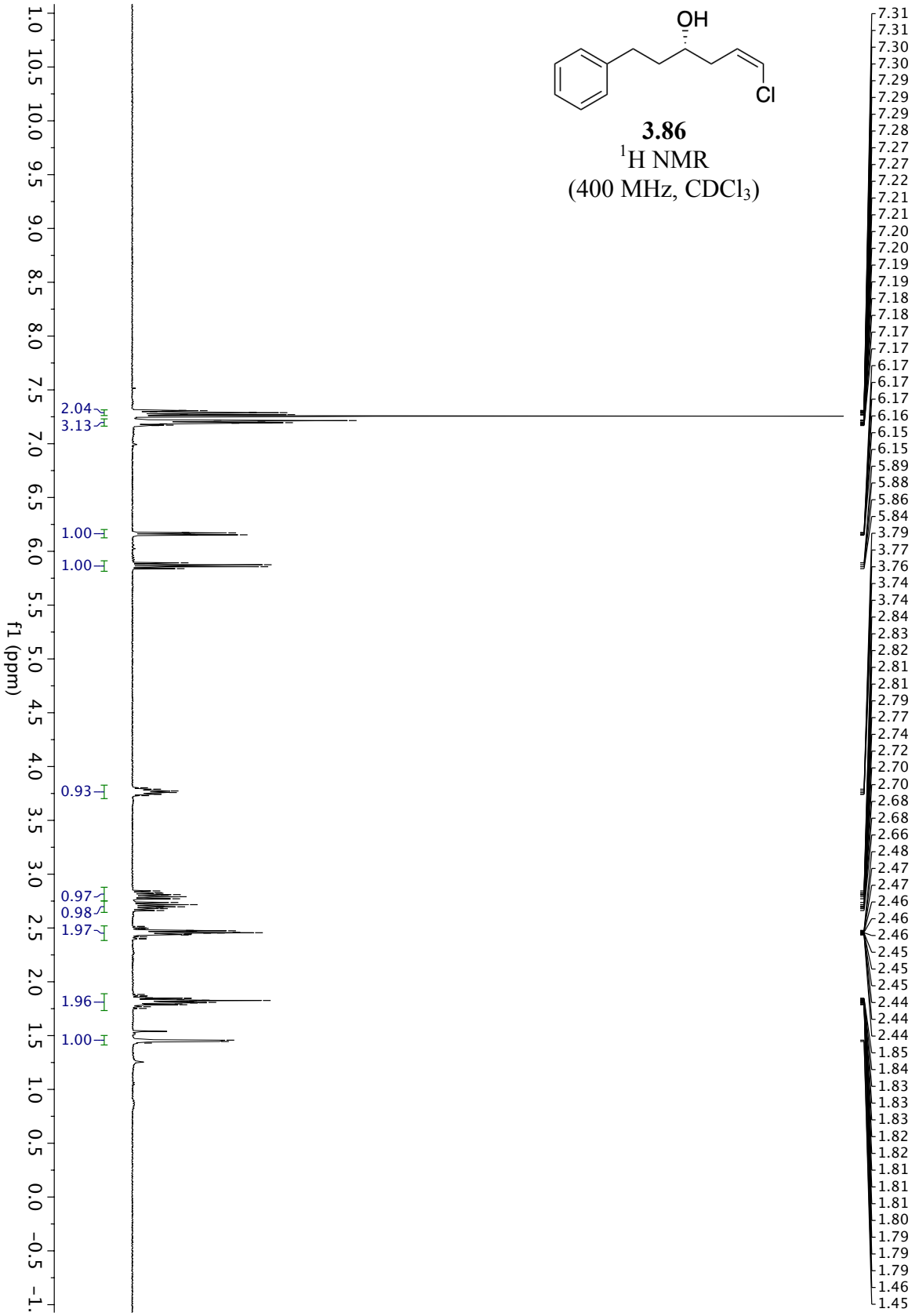
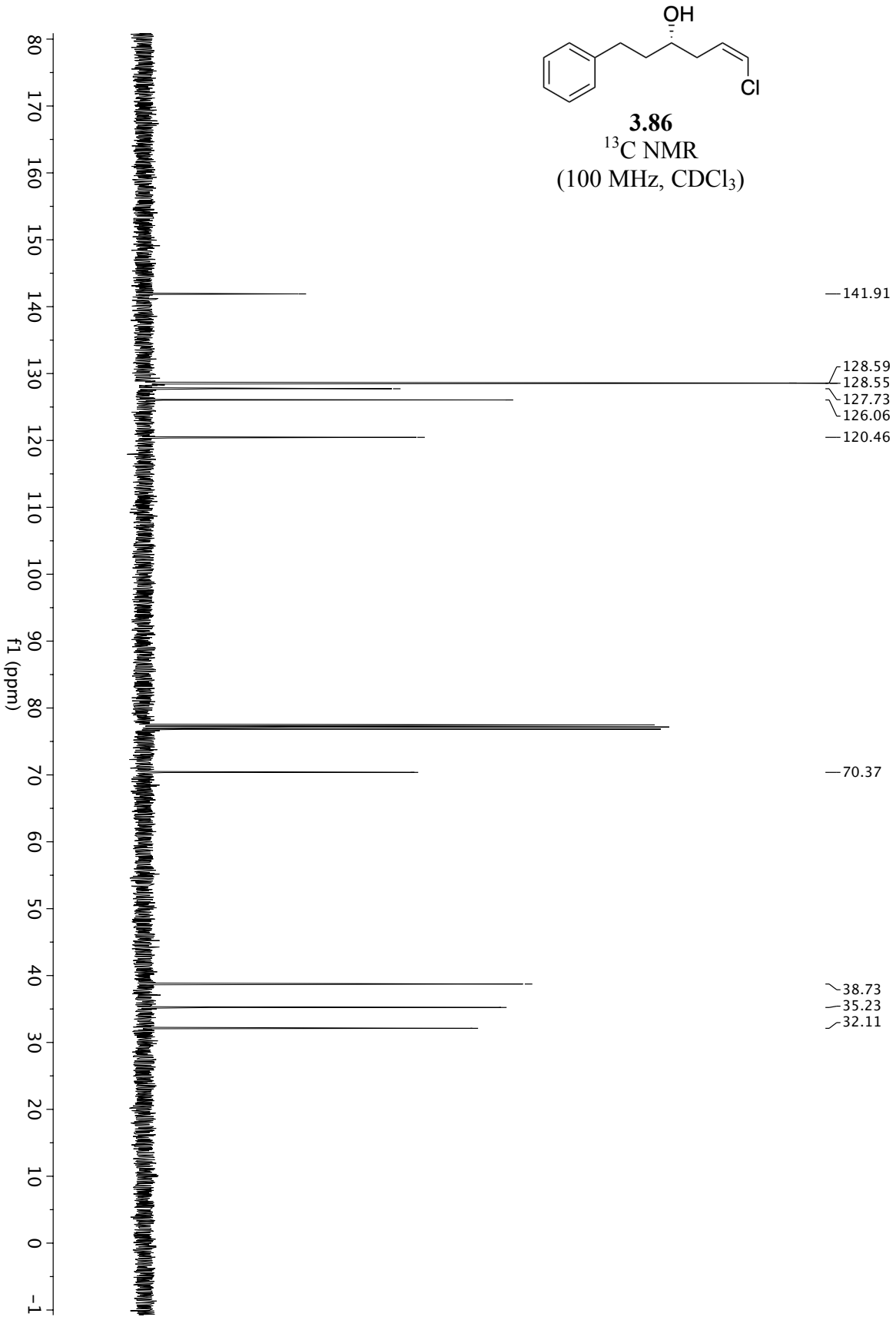
2.55
2.55
2.54
2.54
2.54
2.53
2.41
2.05
2.04
2.04

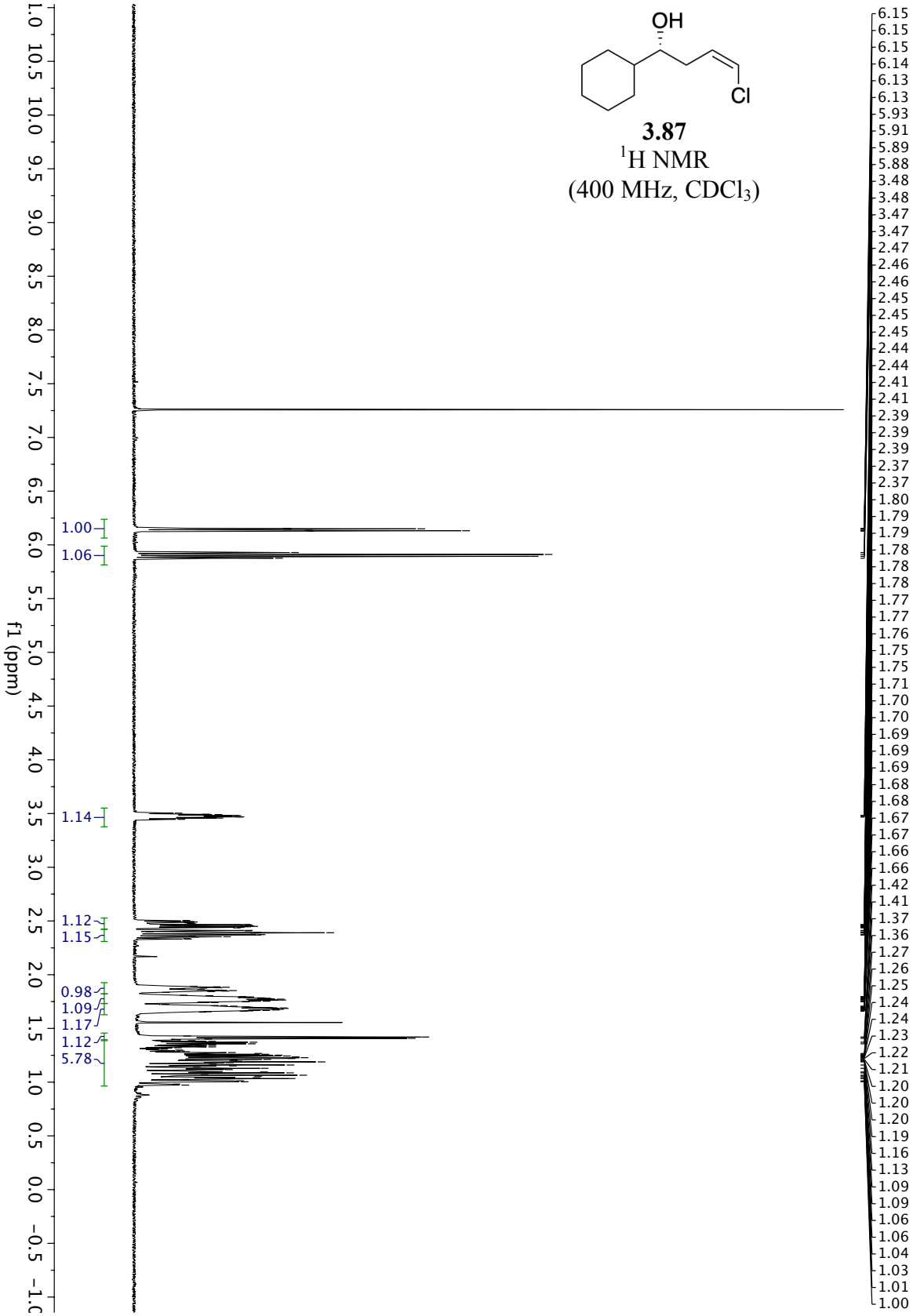

OH
N
Me
S
Me
Cl
3.84
13C NMR
(100 MHz, CDCl3)
164.87
152.68
141.47
127.79
120.12
119.41
115.84
76.35
33.15
19.24
14.39
f1 (ppm)

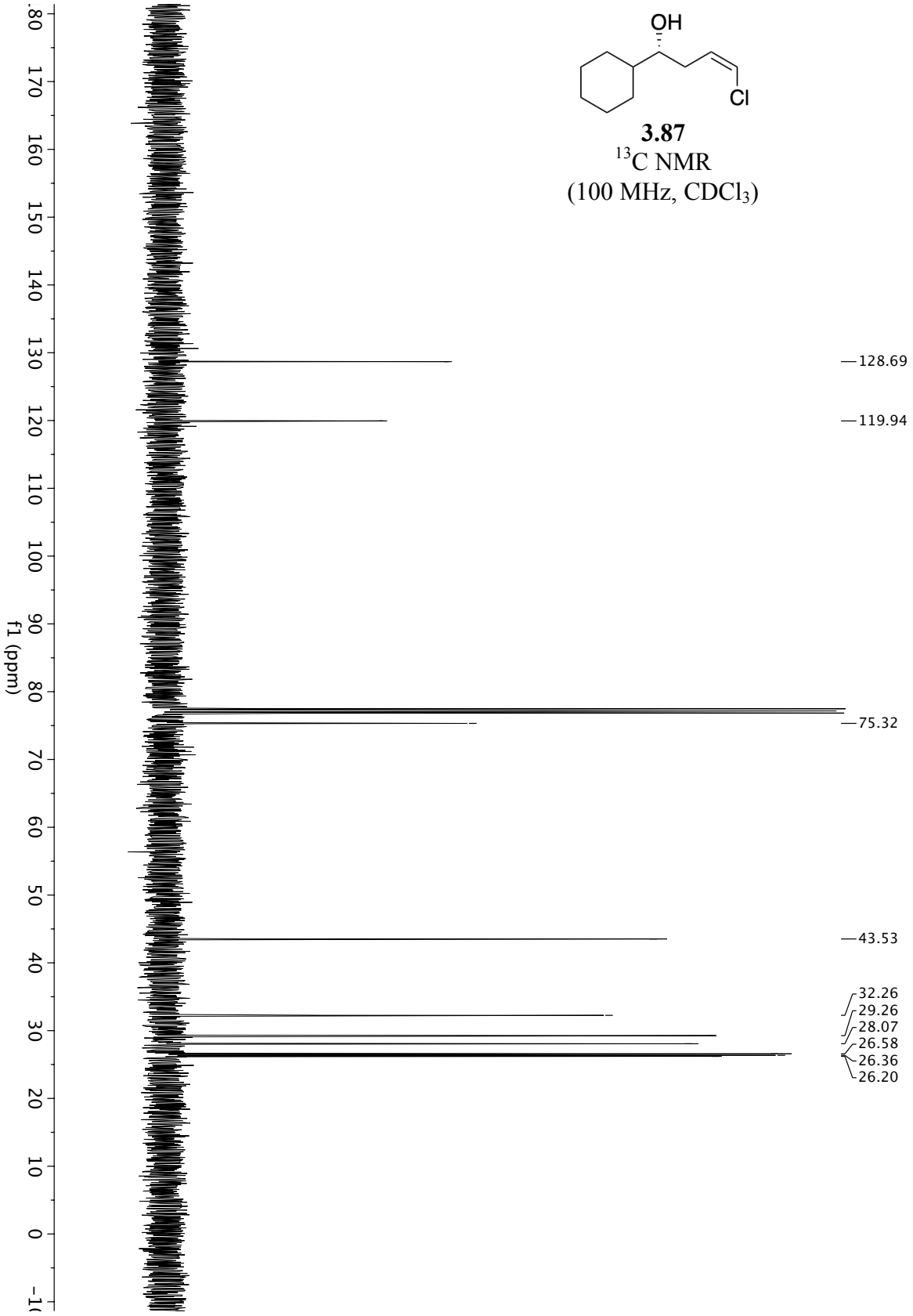

OH
Br
Cl
3.85
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.14
3.38
1.09
1.00
1.05
1.14
2.40
1.07
7.63
7.62
7.62
7.61
7.61
7.61
7.60
7.60
7.60
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.09
6.21
6.20
6.20
6.19
6.18
6.18
5.88
5.88
5.87
5.85
5.83
4.43
4.41
4.39
4.38
4.35
4.34
2.82
2.81
2.80
2.80
2.79
2.78
2.78
2.78
2.77
2.76
2.76
2.76
2.75
2.75
2.74
2.74
2.73
2.72
2.72
2.70
2.70
2.18
2.17
2.15

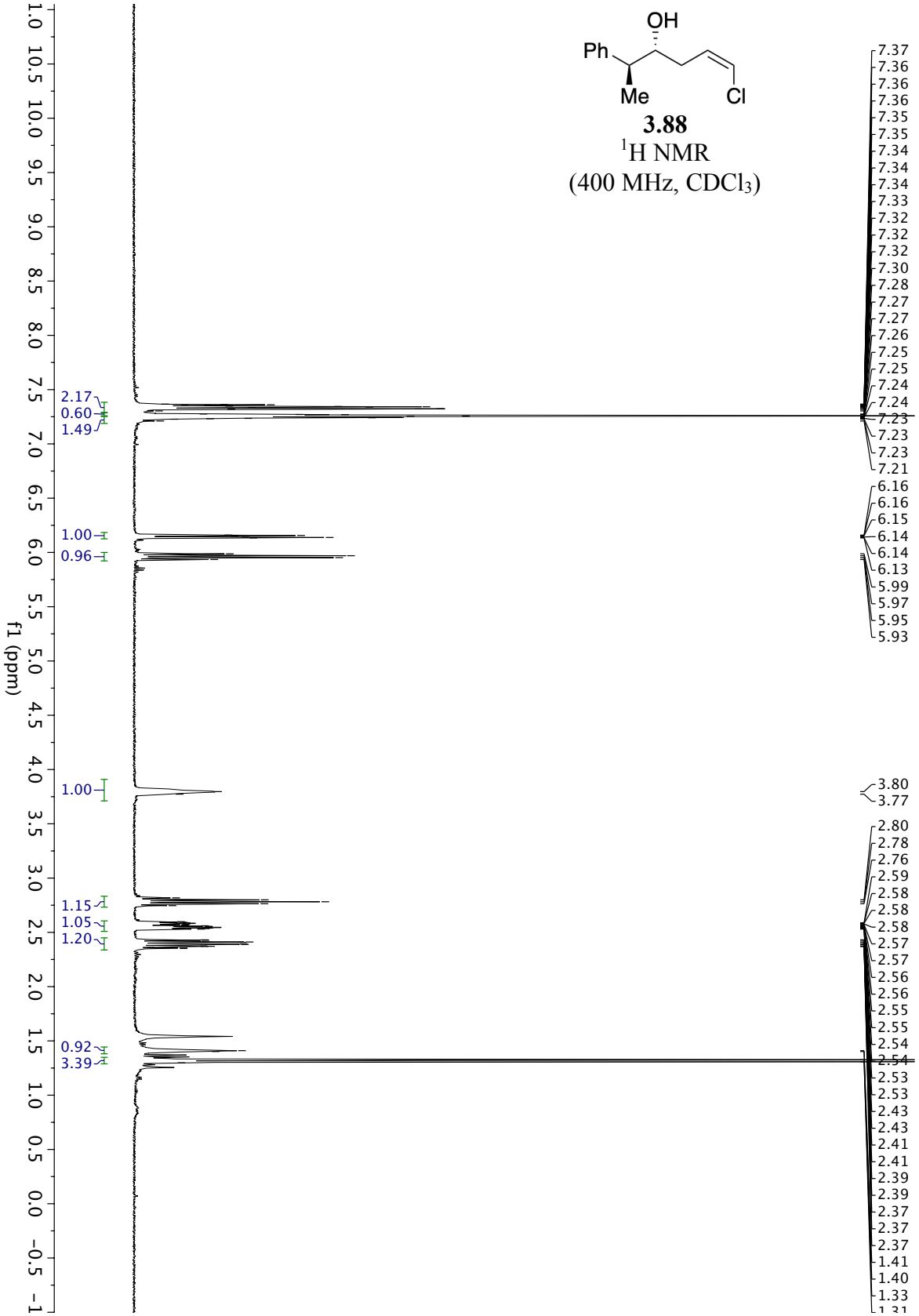

OH
Br
Cl
3.85
13C NMR
(100 MHz, CDCl3)
134.95
129.28
128.93
128.71
128.45
128.34
126.56
121.06
76.42
33.87
f1 (ppm)


OH
Cl
3.86
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.04
3.13
1.00
1.00
0.93
0.97
0.98
1.97
1.96
1.00


OH
Cl
3.86
13C NMR
(100 MHz, CDCl3)
141.91
128.59
128.55
127.73
126.06
120.46
70.37
38.73
35.23
32.11
f1 (ppm)


OH
Cl
3.87
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
1.06
1.14
1.12
1.15
0.98
1.09
1.17
1.12
5.78


OH
Cl
3.87
13C NMR
(100 MHz, CDCl3)
f1 (ppm)
128.69
119.94
75.32
43.53
32.26
29.26
28.07
26.58
26.36
26.20


OH
Ph
Me
Cl
3.88
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.17
0.60
1.49
1.00
0.96
1.00
1.15
1.05
1.20
0.92
3.39
7.37
7.36
7.36
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.32
7.32
7.32
7.30
7.28
7.27
7.27
7.26
7.25
7.25
7.24
7.24
7.23
7.23
7.23
7.21
6.16
6.16
6.15
6.14
6.14
6.13
5.99
5.97
5.95
5.93
3.80
3.77
2.80
2.78
2.76
2.59
2.58
2.58
2.58
2.57
2.57
2.56
2.56
2.55
2.55
2.54
2.54
2.53
2.53
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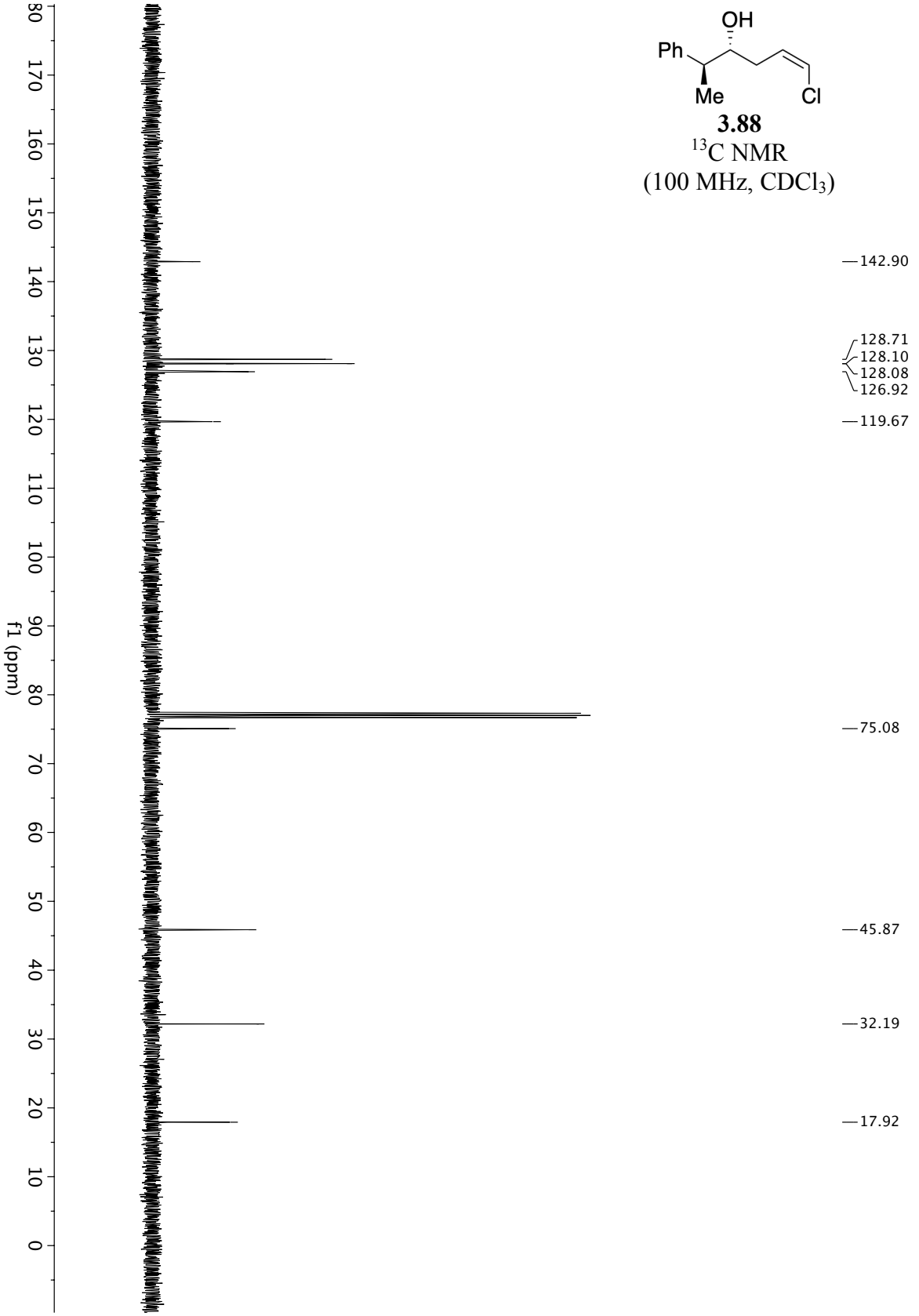
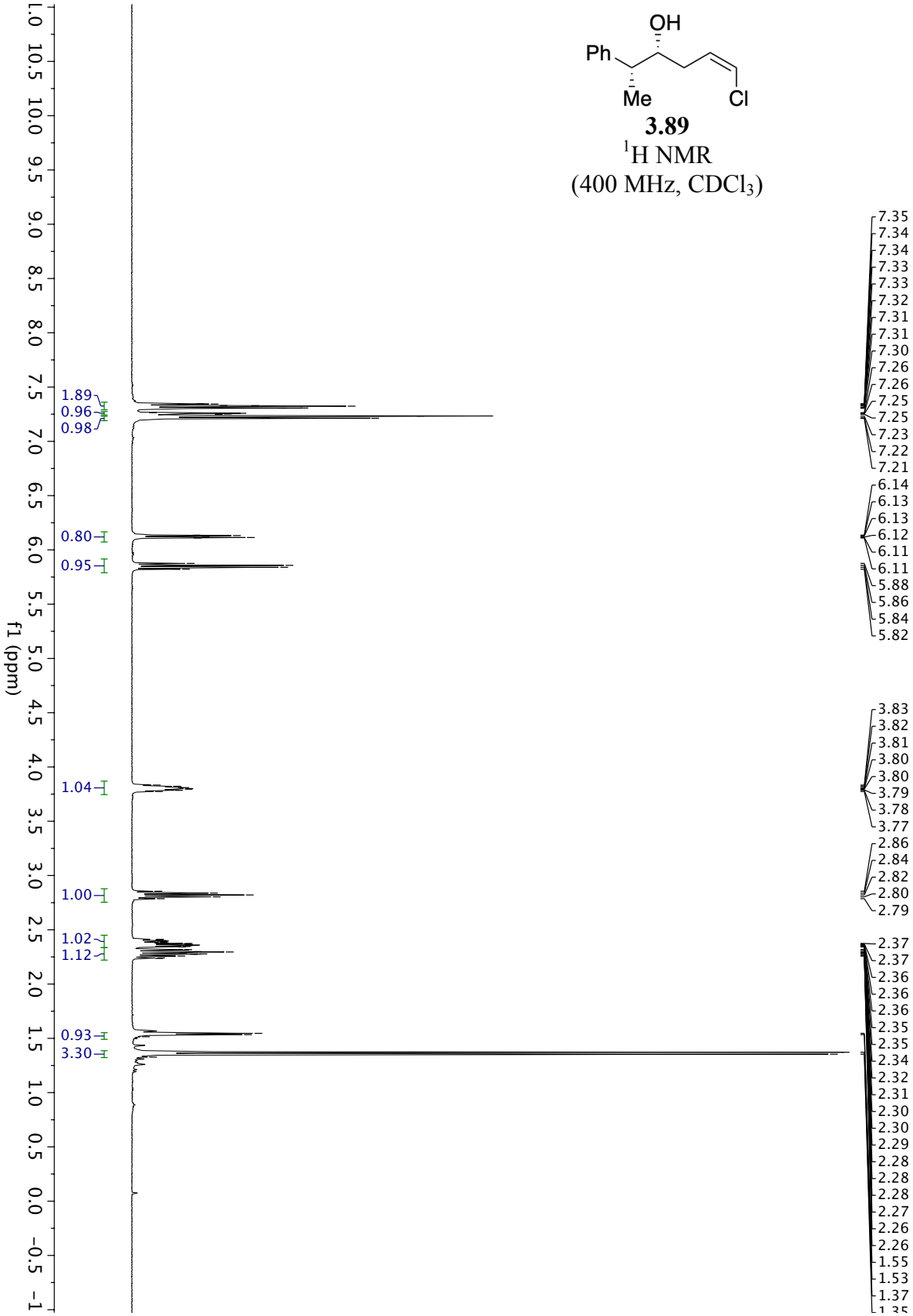
2.37
2.37
2.37
1.41
1.40
1.33


OH
Ph
Me
Cl
3.88
13C NMR
(100 MHz, CDCl3)
142.90
128.71
128.10
128.08
126.92
119.67
75.08
45.87
32.19
17.92
f1 (ppm)


OH
Ph
Me
Cl
3.89
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.89
0.96
0.98
0.80
0.95
1.04
1.00
1.02
1.12
0.93
3.30
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.26
7.26
7.25
7.25
7.23
7.22
7.21
6.14
6.13
6.13
6.12
6.11
6.11
5.88
5.86
5.84
5.82
3.83
3.82
3.81
3.80
3.80
3.79
3.78
3.77
2.86
2.84
2.82
2.80
2.79
2.37
2.37
2.36
2.36
2.36
2.35
2.35
2.34
2.32
2.31
2.30
2.30
2.29
2.28
2.28
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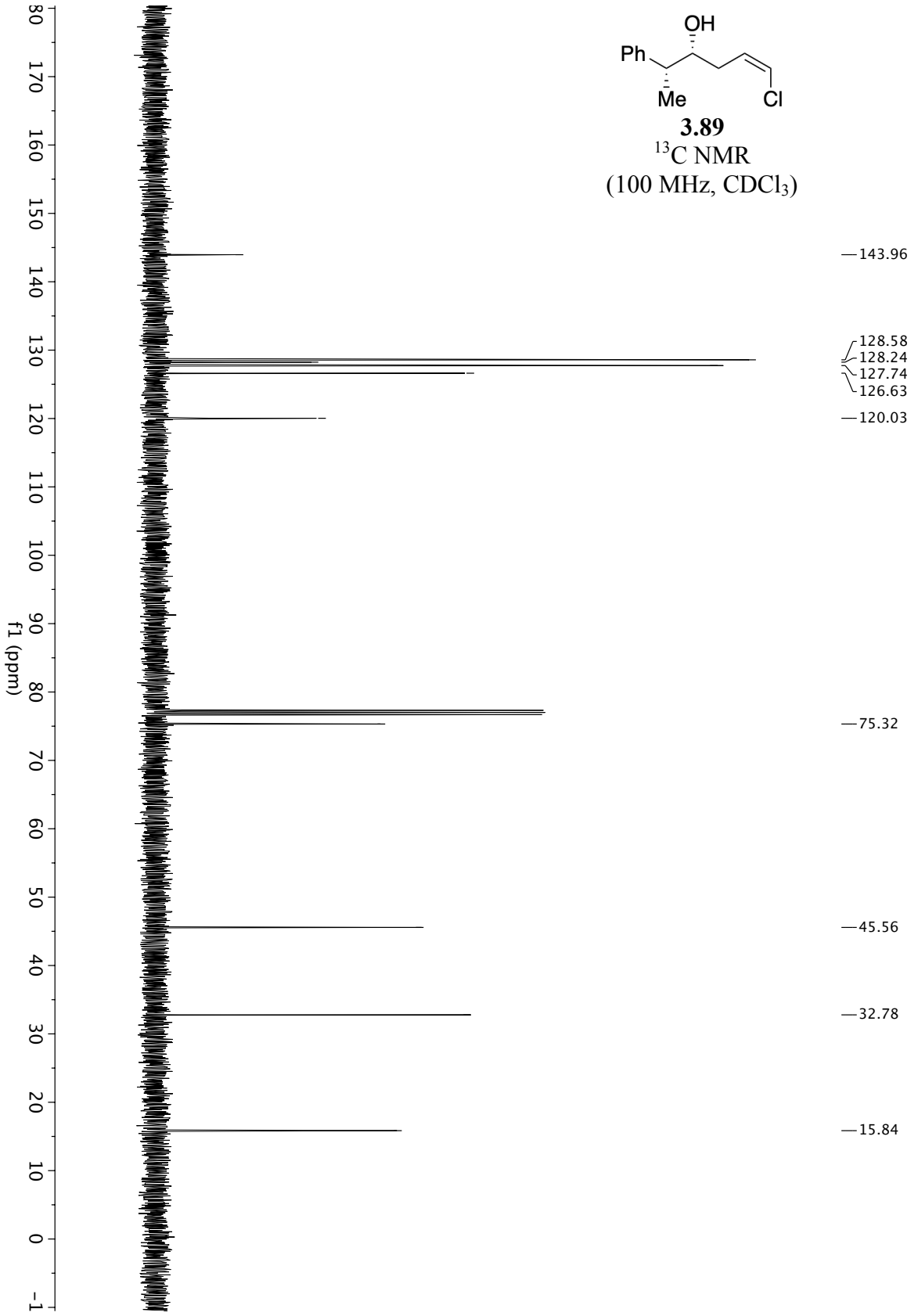
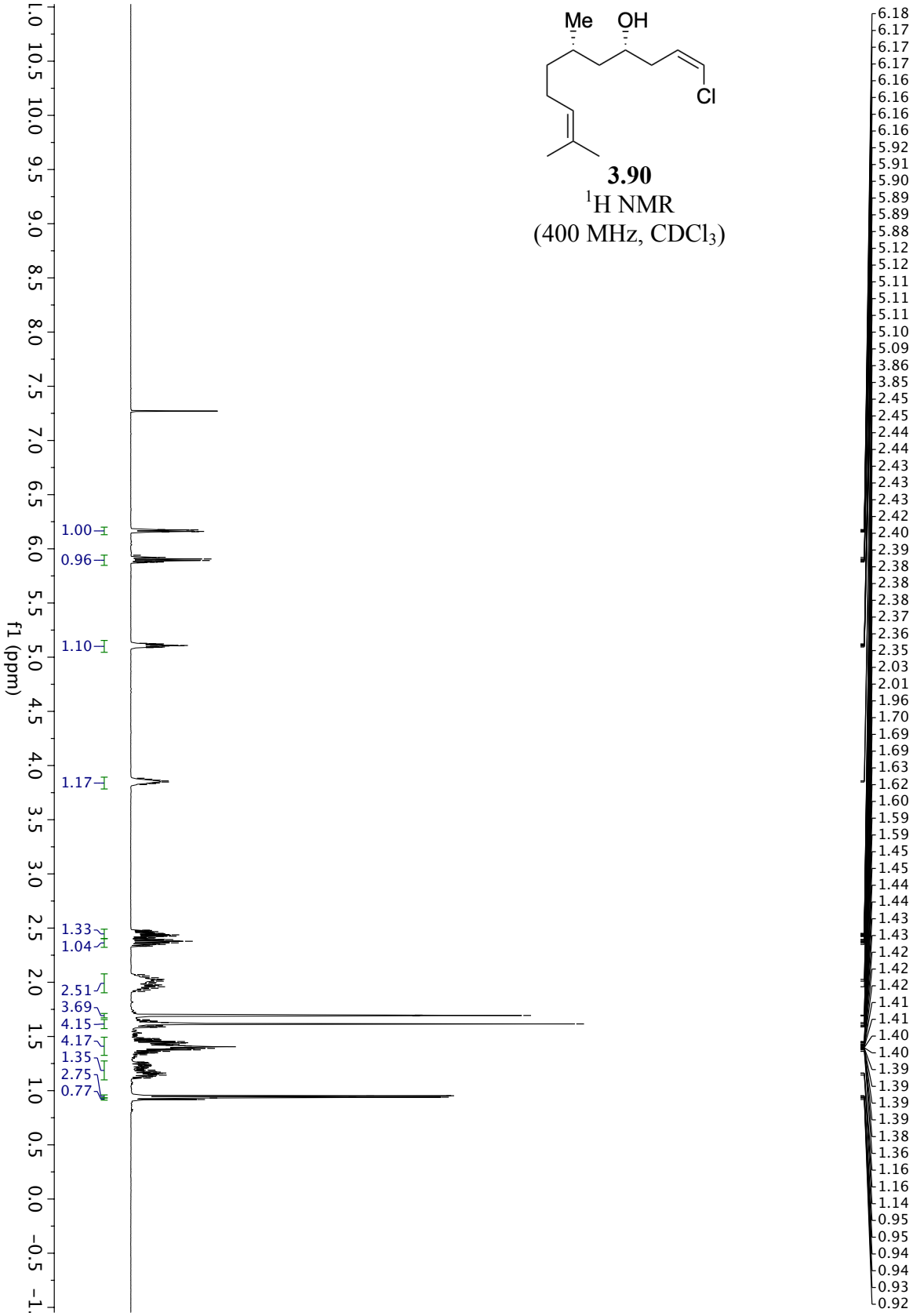
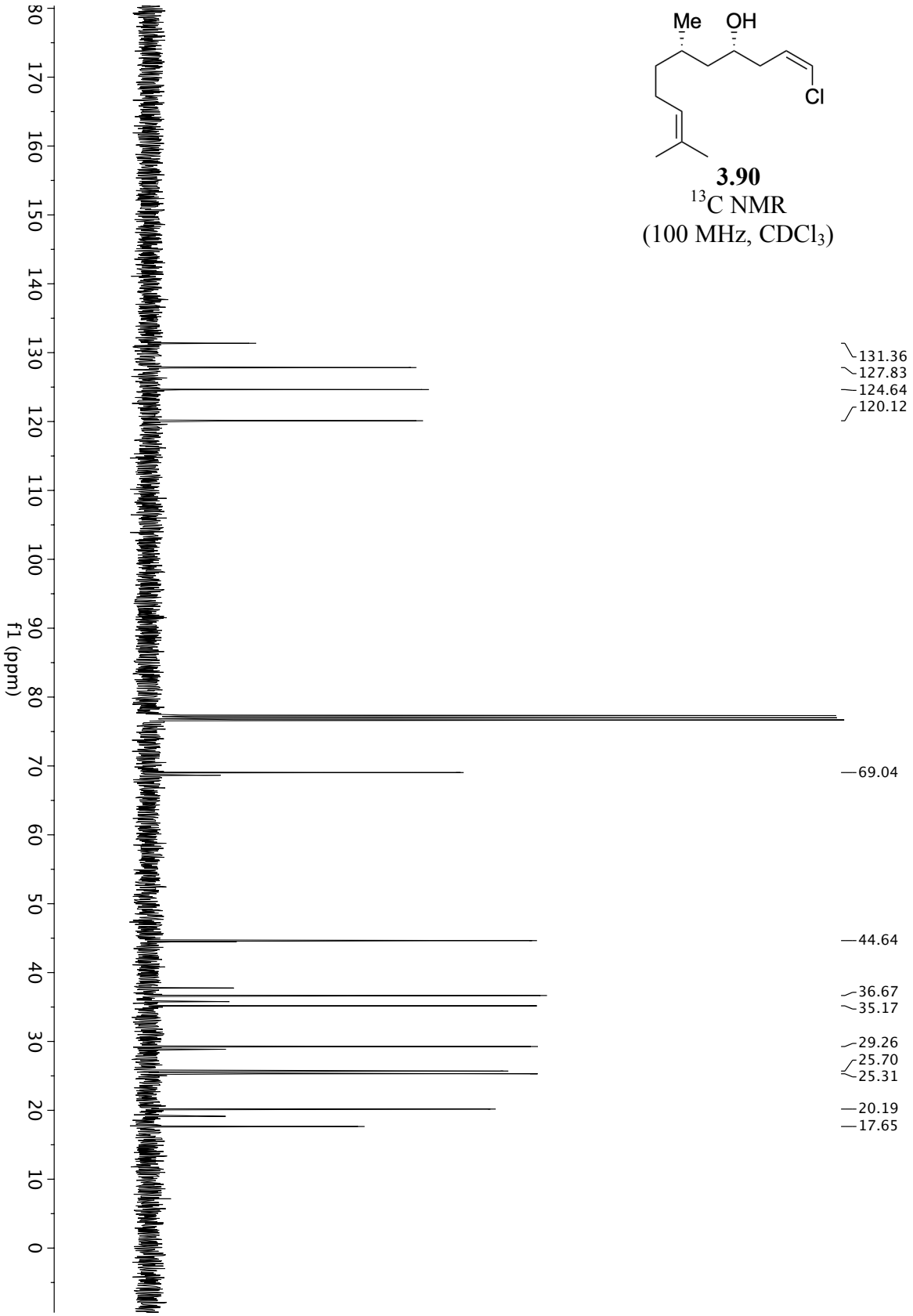
2.27
2.26
2.26
1.55
1.53
1.37


OH
Ph
Me
Cl
3.89
13C NMR
(100 MHz, CDCl3)
143.96
128.58
128.24
127.74
126.63
120.03
75.32
45.56
32.78
15.84
f1 (ppm)

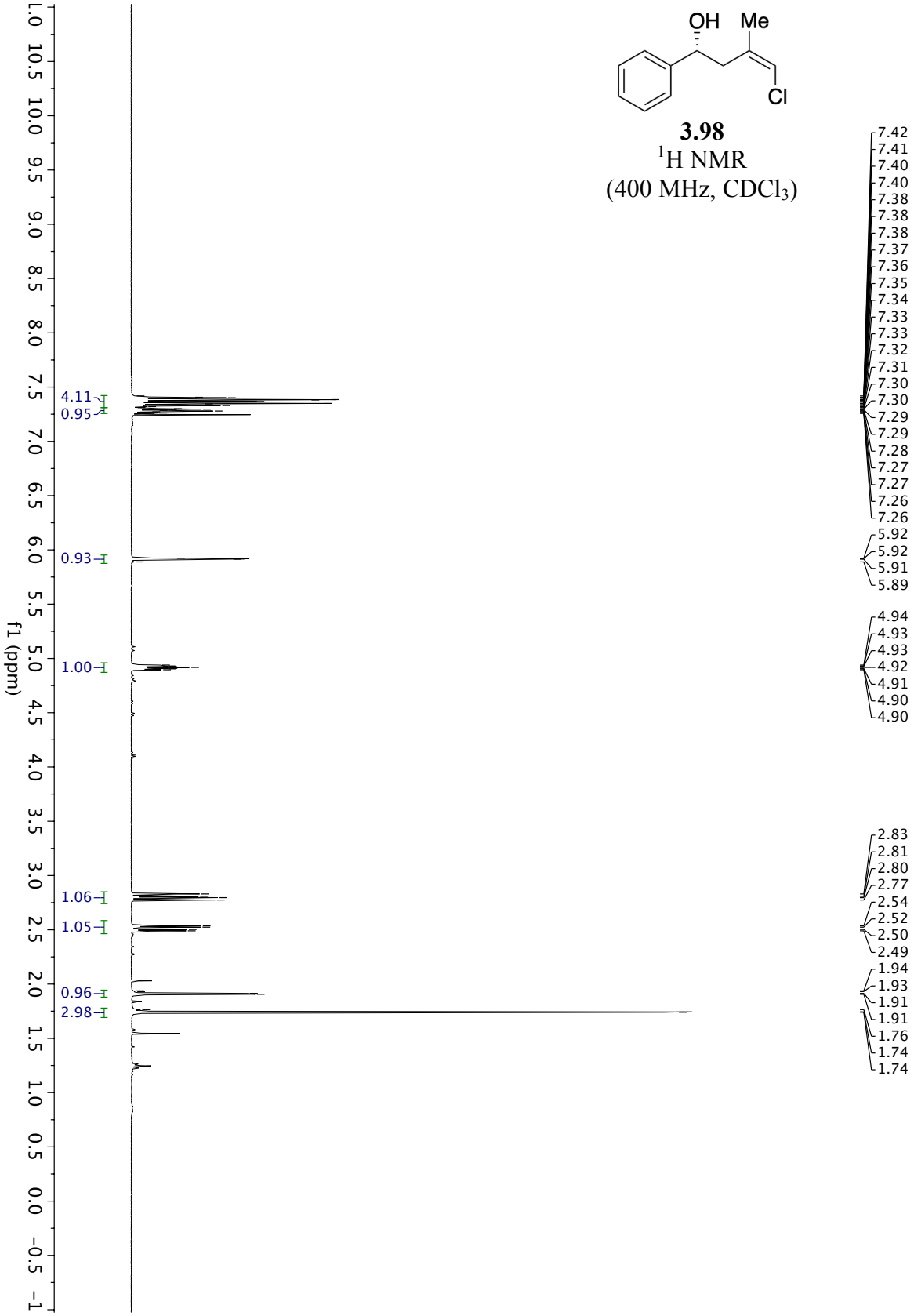

Me
OH
Cl
3.90
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
0.96
1.10
1.17
1.33
1.04
2.51
3.69
4.15
4.17
1.35
2.75
0.77



3.90

^{13}C NMR

(100 MHz, $CDCl_3$)


OH
Me
Cl
3.98
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
4.11
0.95
0.93
1.00
1.06
1.05
0.96
2.98
7.42
7.41
7.40
7.40
7.38
7.38
7.38
7.37
7.36
7.35
7.34
7.33
7.33
7.32
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.27
7.26
7.26
5.92
5.92
5.91
5.89
4.94
4.93
4.93
4.92
4.91
4.90
4.90
2.83
2.81
2.80
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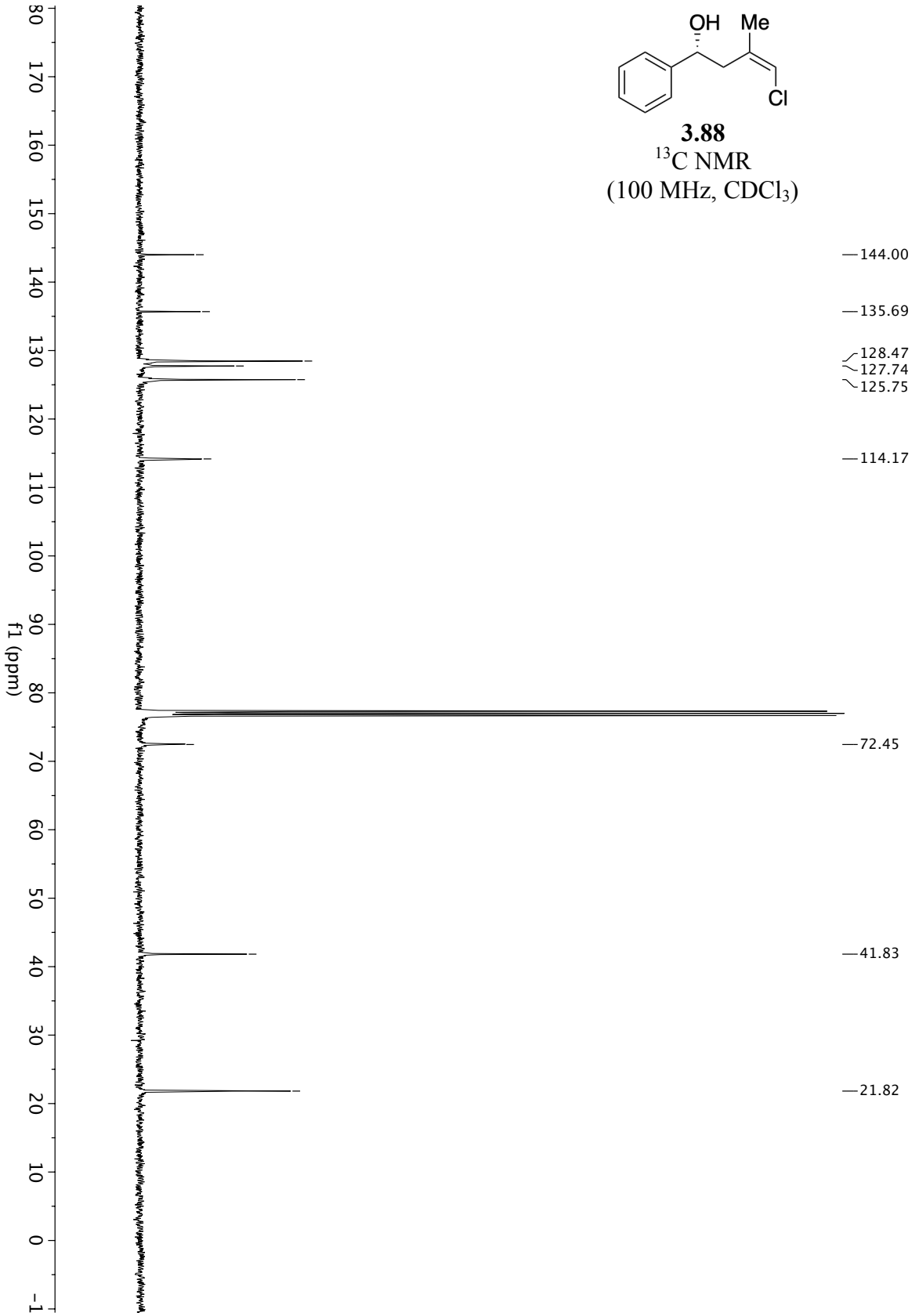
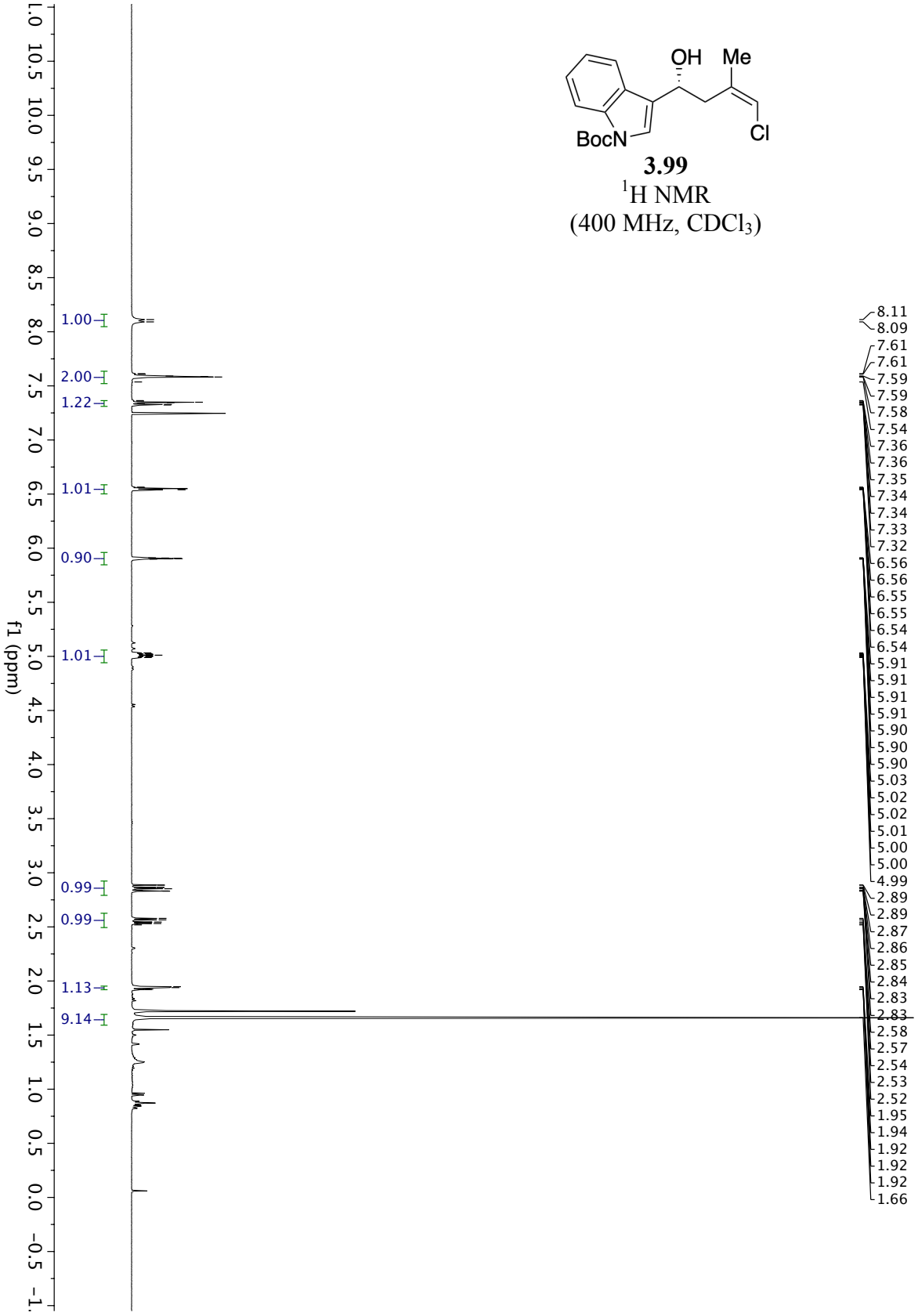
1.93
1.91
1.91
1.76
1.74
1.74



3.88

^{13}C NMR

(100 MHz, $CDCl_3$)


OH
Me
BocN
Cl
3.99
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
2.00
1.22
1.01
0.90
1.01
0.99
0.99
1.13
9.14
8.11
8.09
7.61
7.61
7.59
7.59
7.58
7.54
7.36
7.36
7.35
7.34
7.34
7.33
7.32
6.56
6.56
6.55
6.55
6.54
6.54
5.91
5.91
5.91
5.91
5.90
5.90
5.90
5.03
5.02
5.02
5.01
5.00
5.00
4.99
2.89
2.89
2.87
2.86
2.85
2.84
2.83
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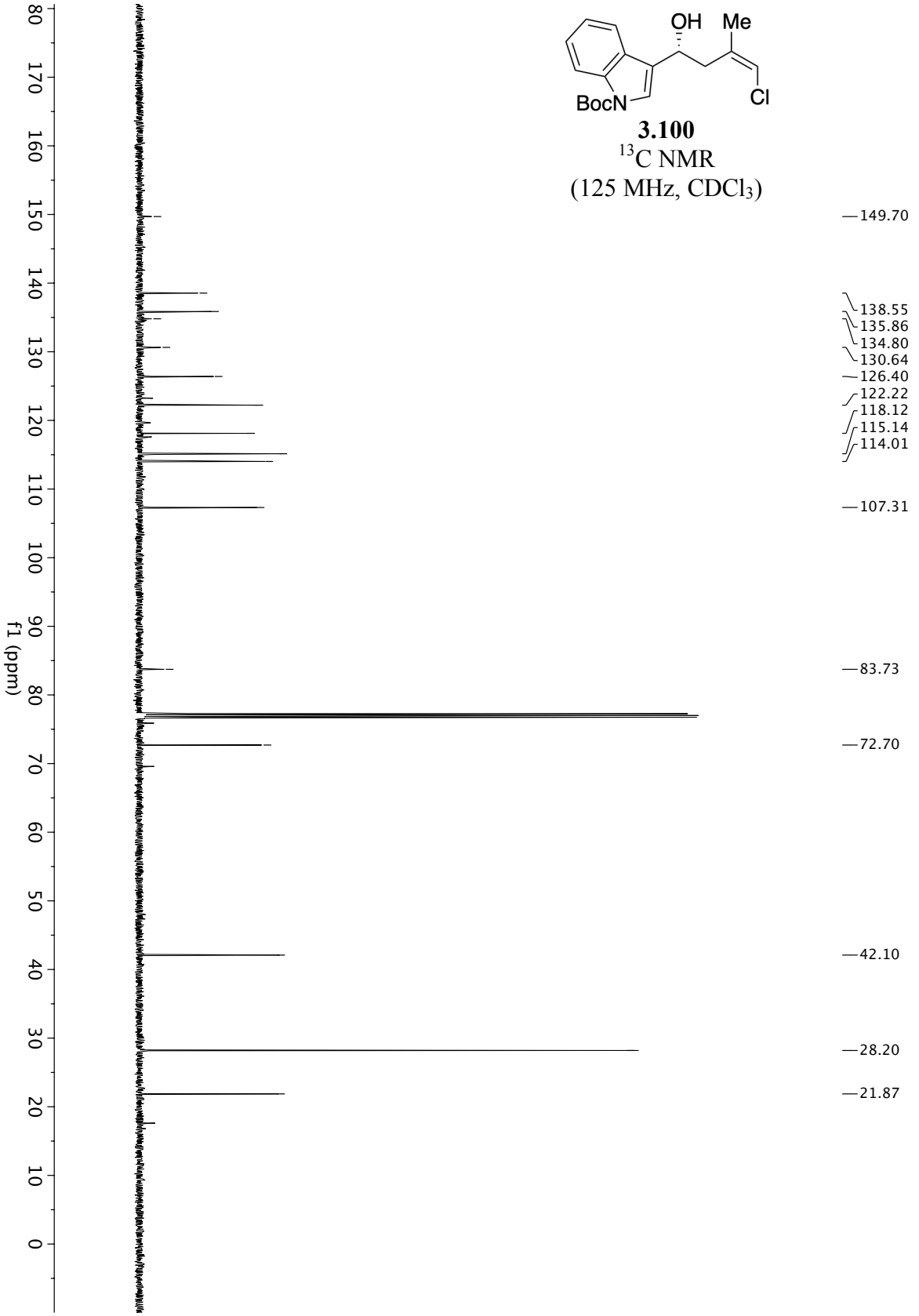
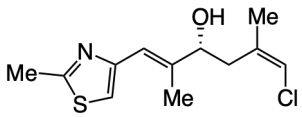
1.95
1.94
1.92
1.92
1.92
1.66

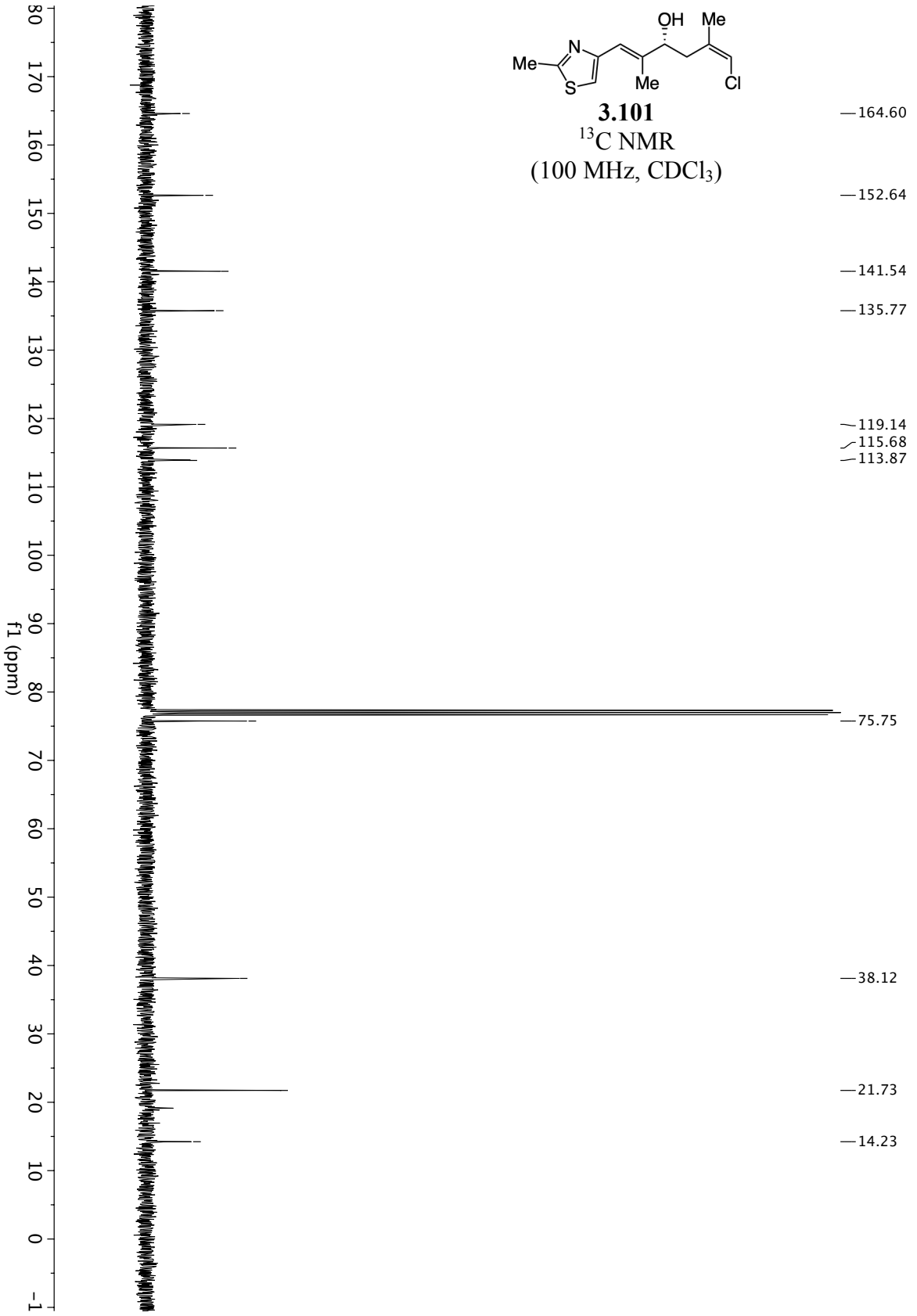

OH
Me
BocN
Cl
3.100
13C NMR
(125 MHz, CDCl3)
f1 (ppm)
149.70
138.55
135.86
134.80
130.64
126.40
122.22
118.12
115.14
114.01
107.31
83.73
72.70
42.10
28.20
21.87

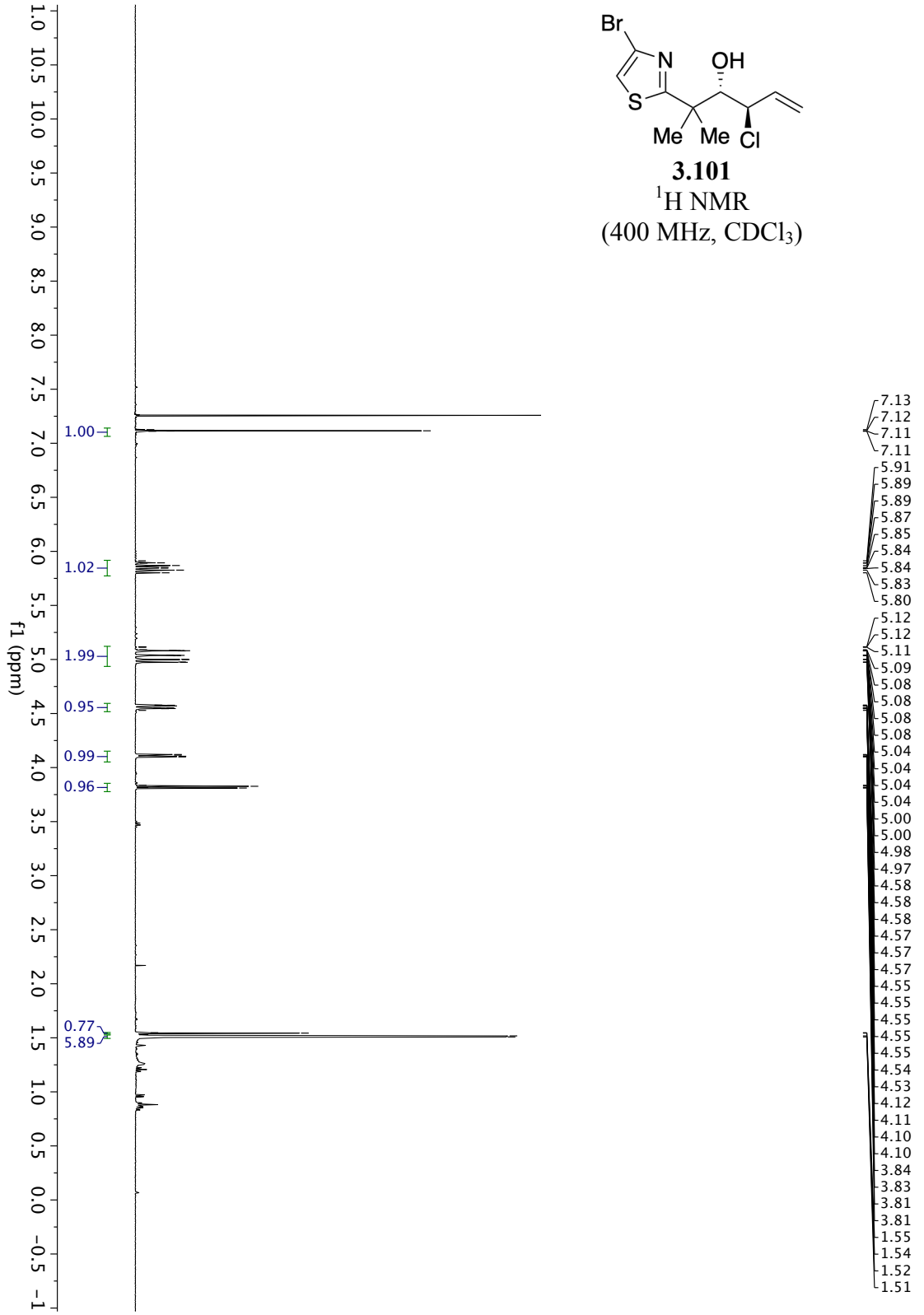


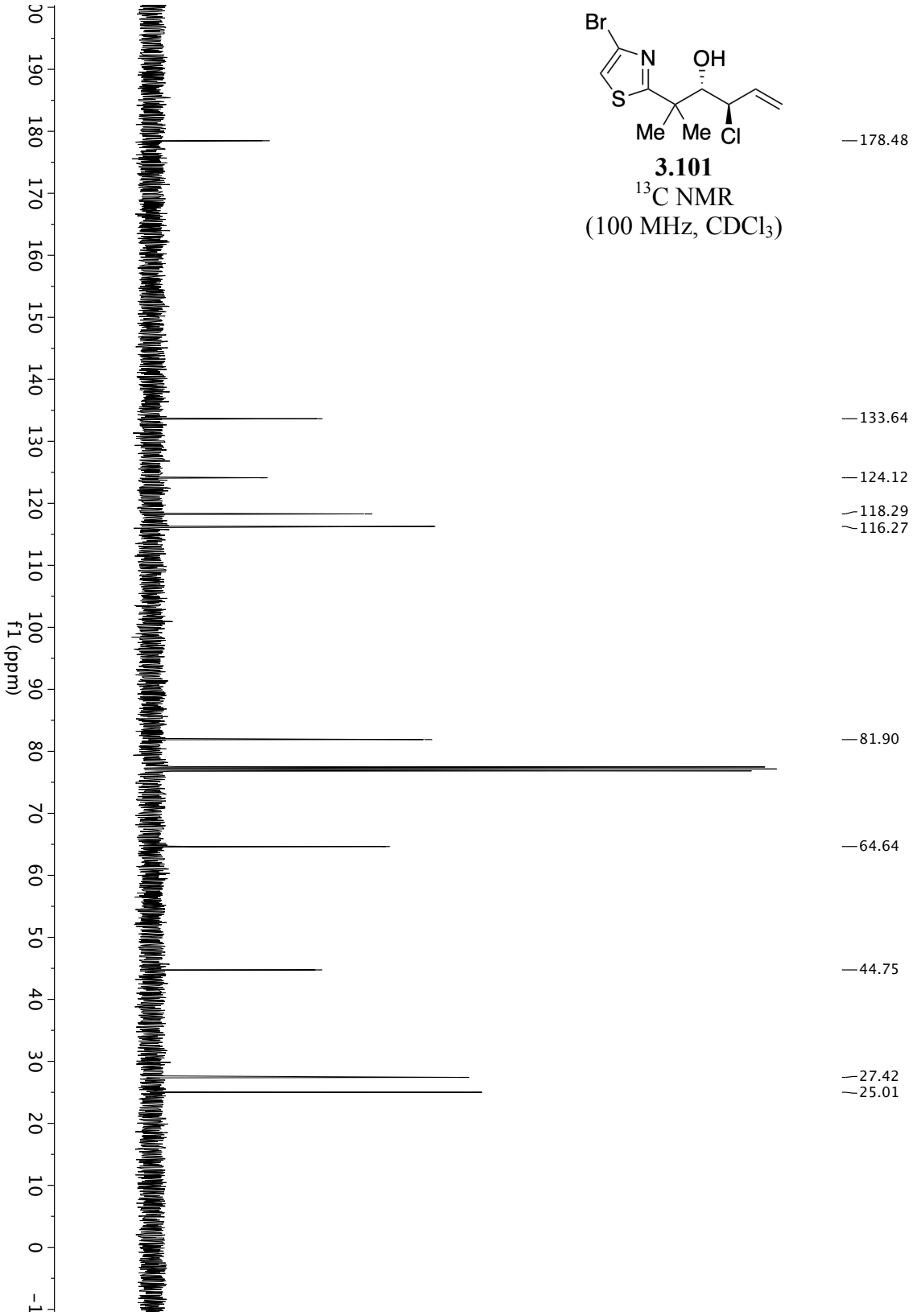
3.101

^{1}H NMR

(400 MHz, $CDCl_3$)


OH
Me
N
Me
S
Me
Cl
3.101
13C NMR
(100 MHz, CDCl3)
164.60
152.64
141.54
135.77
119.14
115.68
113.87
75.75
38.12
21.73
14.23
f1 (ppm)

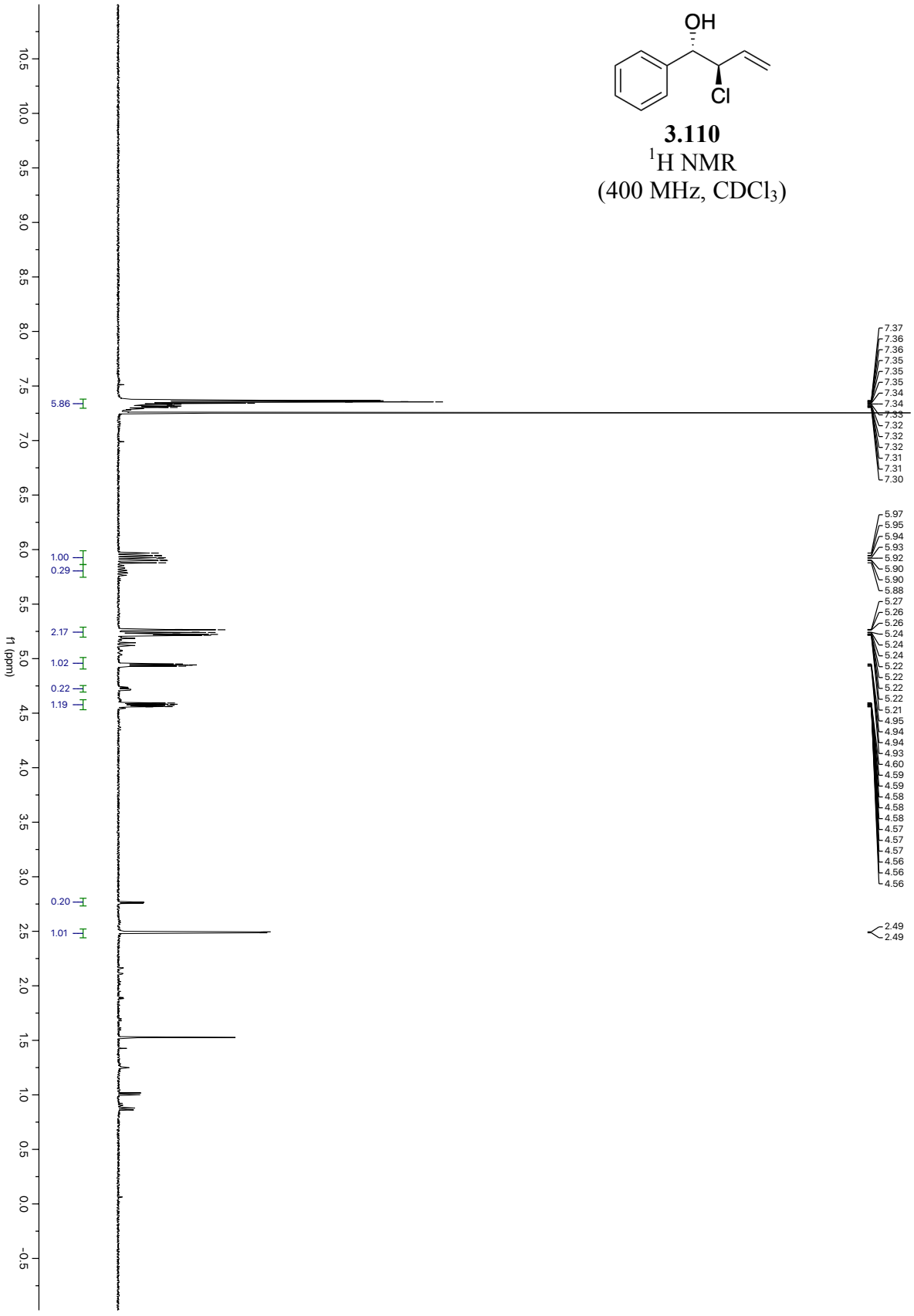

Br
N
OH
S
Me
Me
Cl
3.101
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
1.02
1.99
0.95
0.99
0.96
0.77
5.89
7.13
7.12
7.11
7.11
5.91
5.89
5.89
5.87
5.85
5.84
5.84
5.83
5.80
5.12
5.12
5.11
5.09
5.08
5.08
5.08
5.08
5.04
5.04
5.04
5.04
5.00
5.00
4.98
4.97
4.58
4.58
4.58
4.57
4.57
4.57
4.55
4.55
4.55
4.55
4.55
4.54
4.53
4.12
4.11
4.10
4.10
3.84
3.83
3.81
3.81
1.55
1.54
1.52
1.51

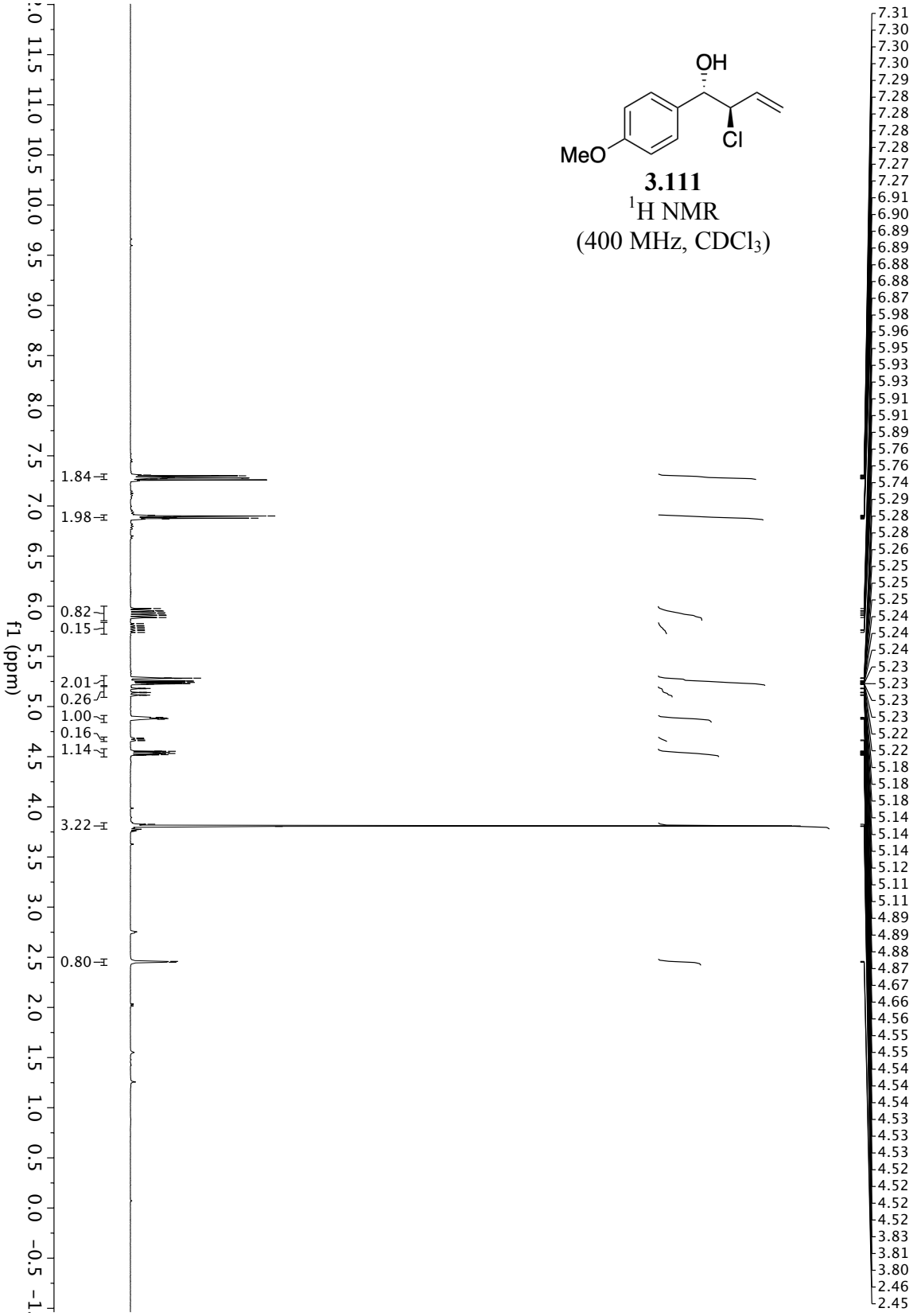


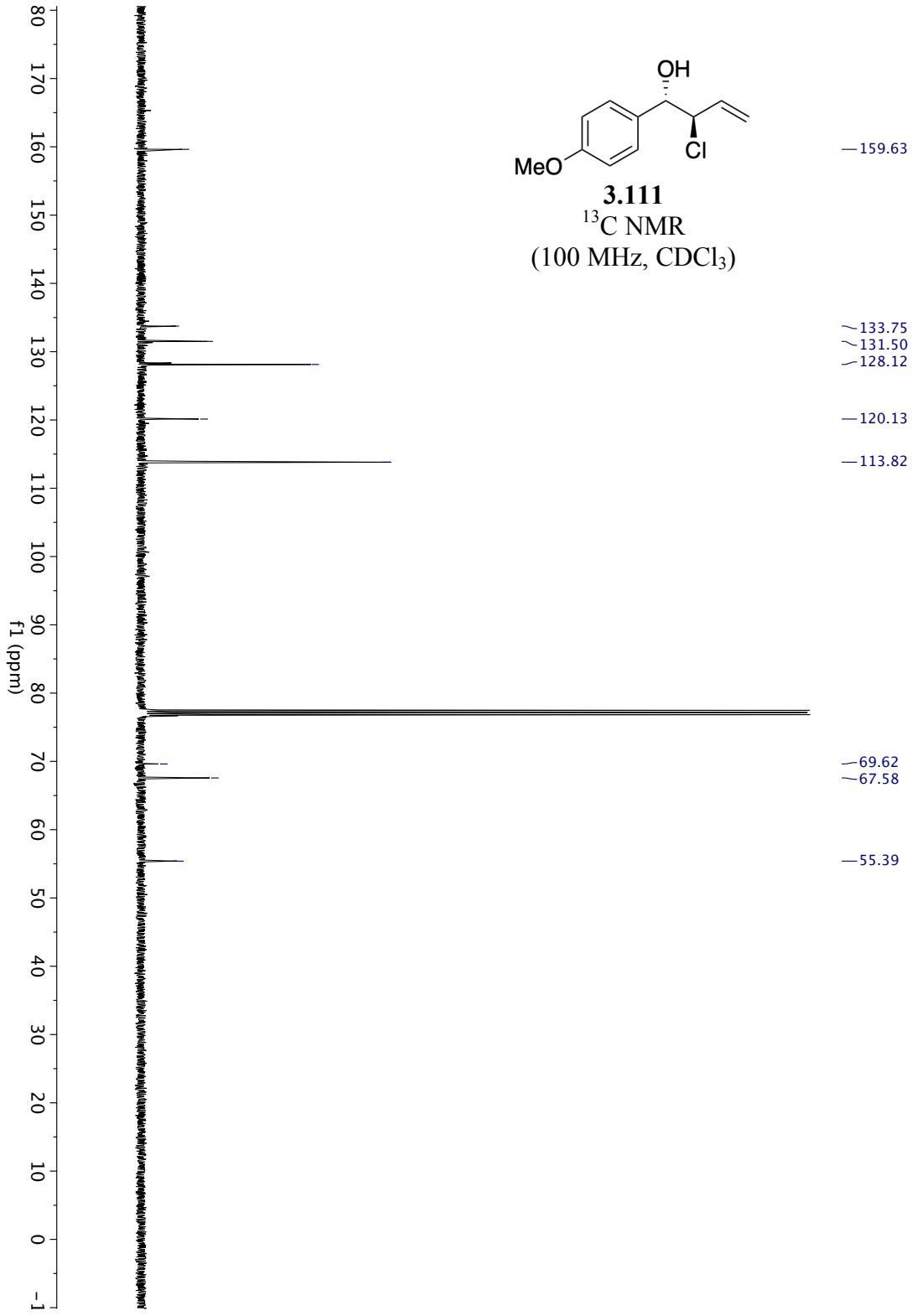
3.101

^{13}C NMR

(100 MHz, $CDCl_3$)


OH
Cl
3.110
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
5.86
1.00
0.29
2.17
1.02
0.22
1.19
0.20
1.01
7.37
7.36
7.36
7.35
7.35
7.35
7.34
7.34
7.33
7.32
7.32
7.32
7.31
7.31
7.30
5.97
5.95
5.94
5.93
5.92
5.90
5.90
5.88
5.27
5.26
5.26
5.24
5.24
5.24
5.22
5.22
5.22
5.22
5.21
4.95
4.94
4.94
4.93
4.60
4.59
4.59
4.58
4.58
4.58
4.57
4.57
4.57
4.56
4.56
4.56
2.49
2.49

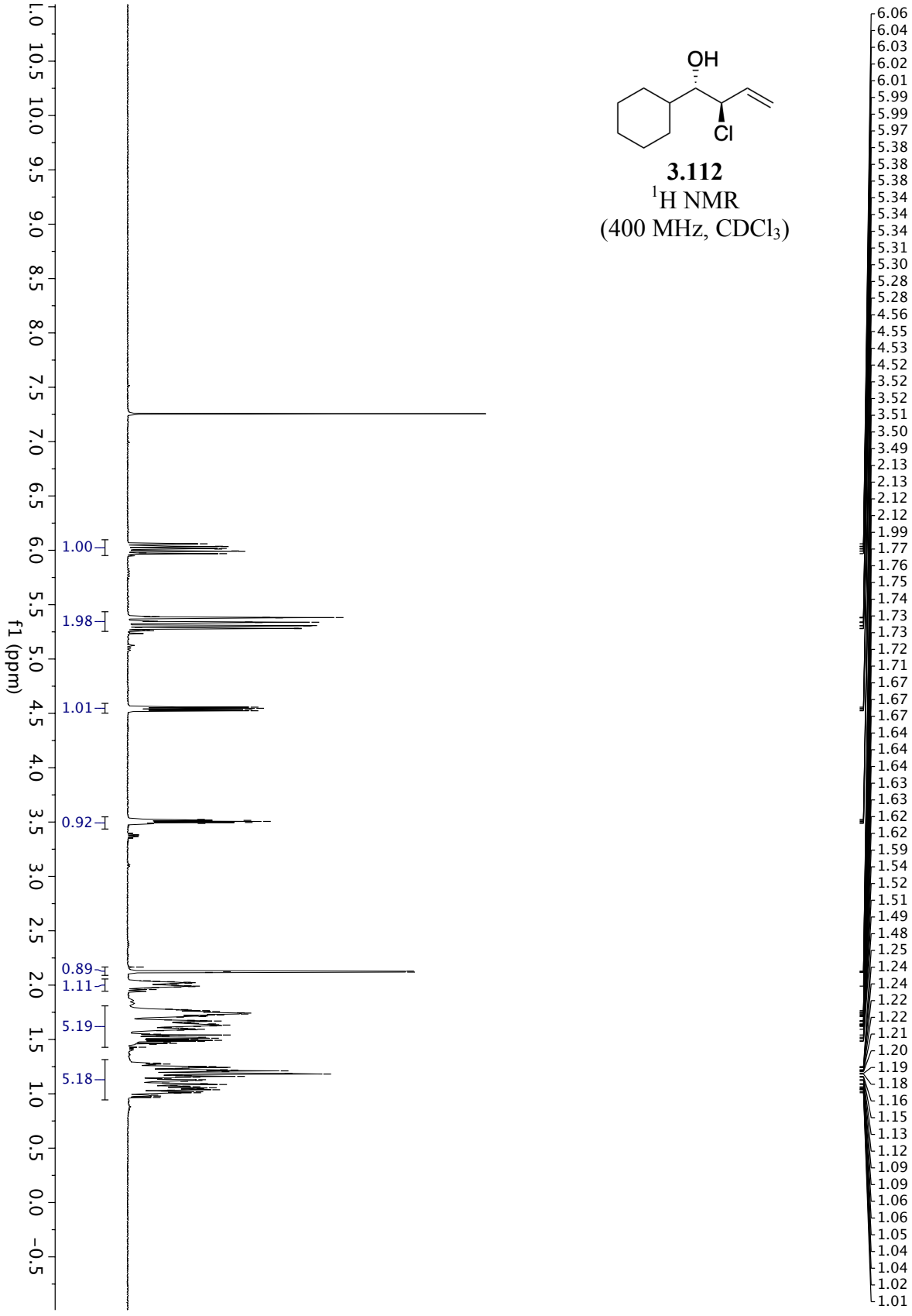

OH
Cl
MeO
3.111
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.84
1.98
0.82
0.15
2.01
0.26
1.00
0.16
1.14
3.22
0.80

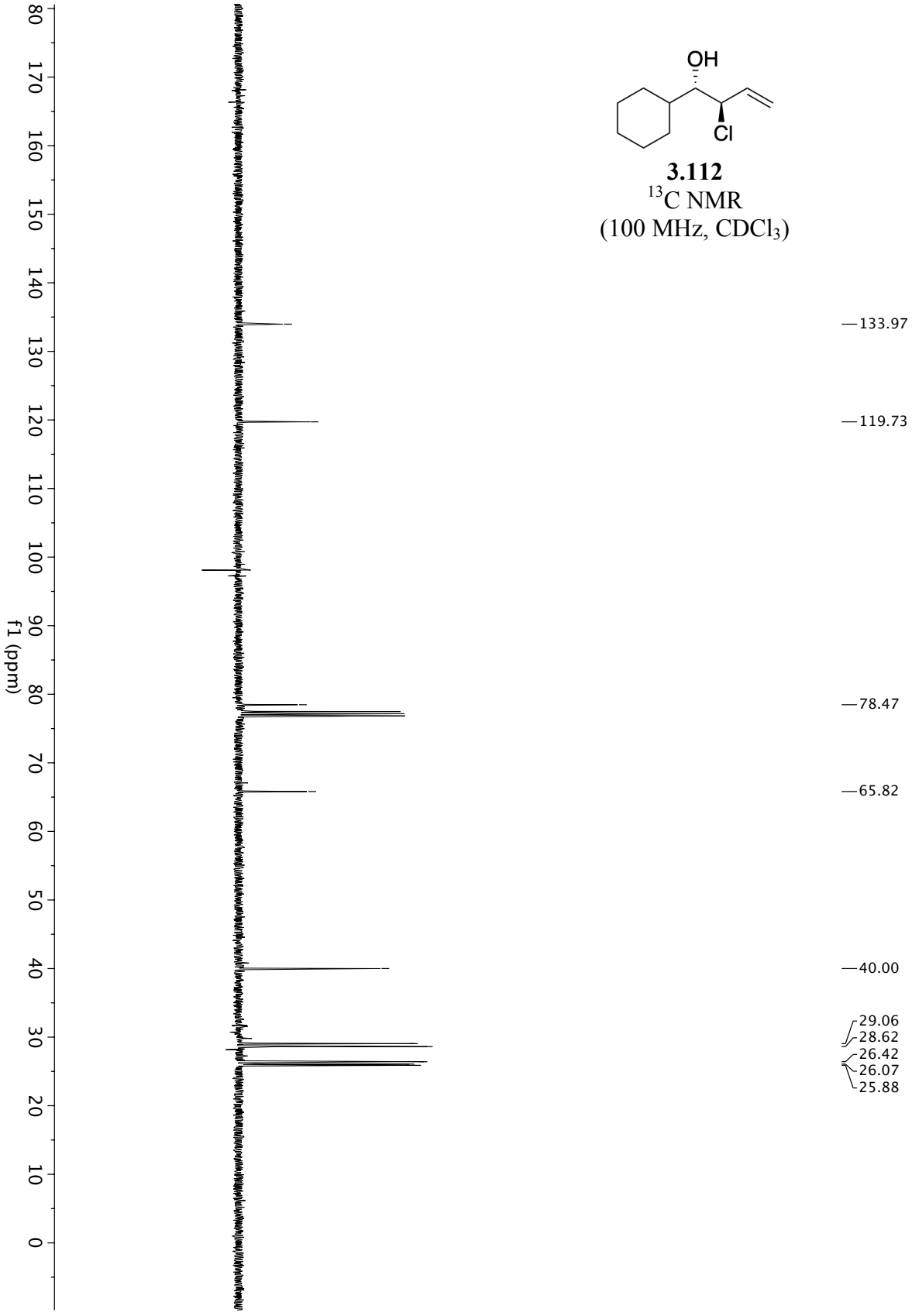


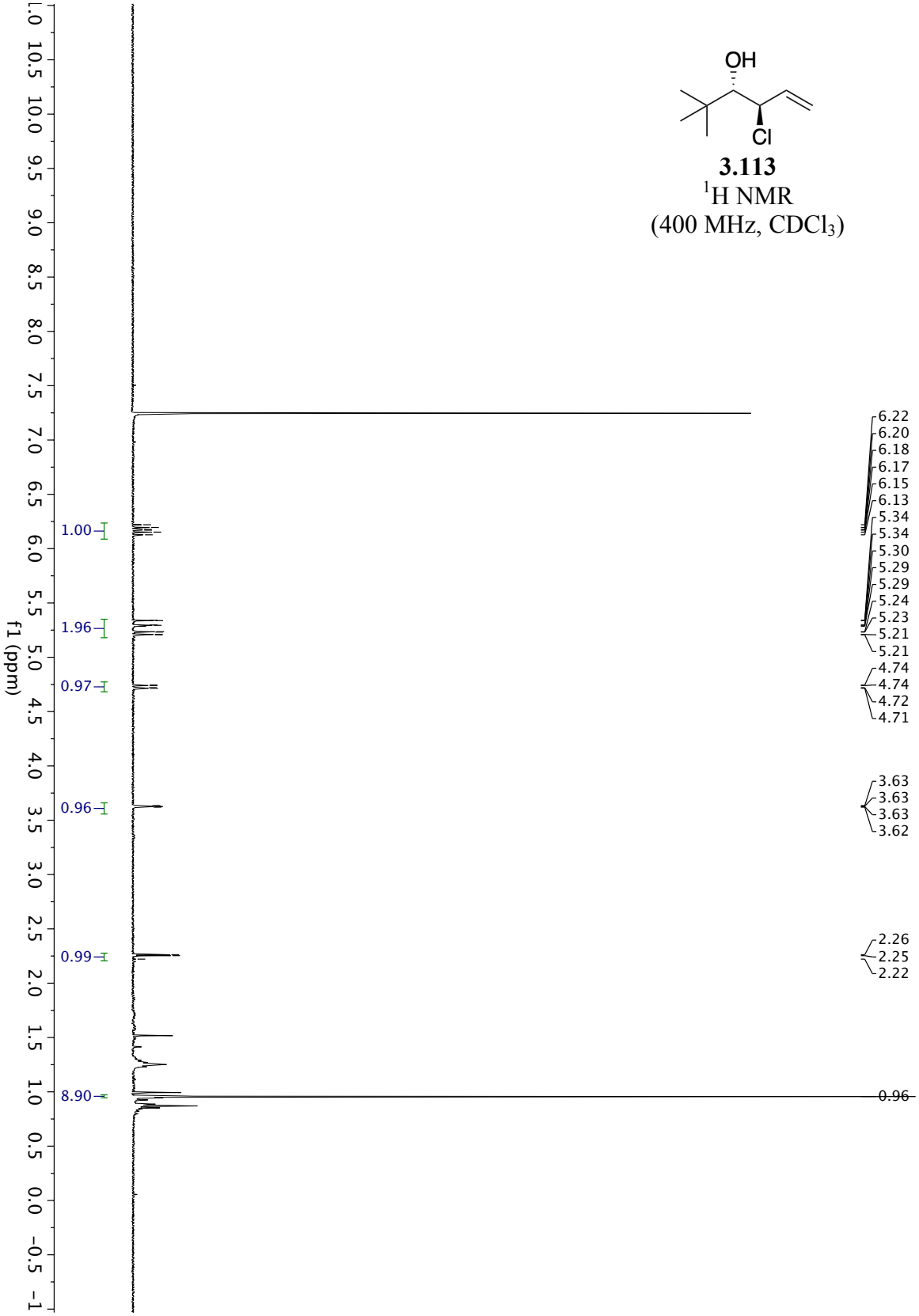
3.111

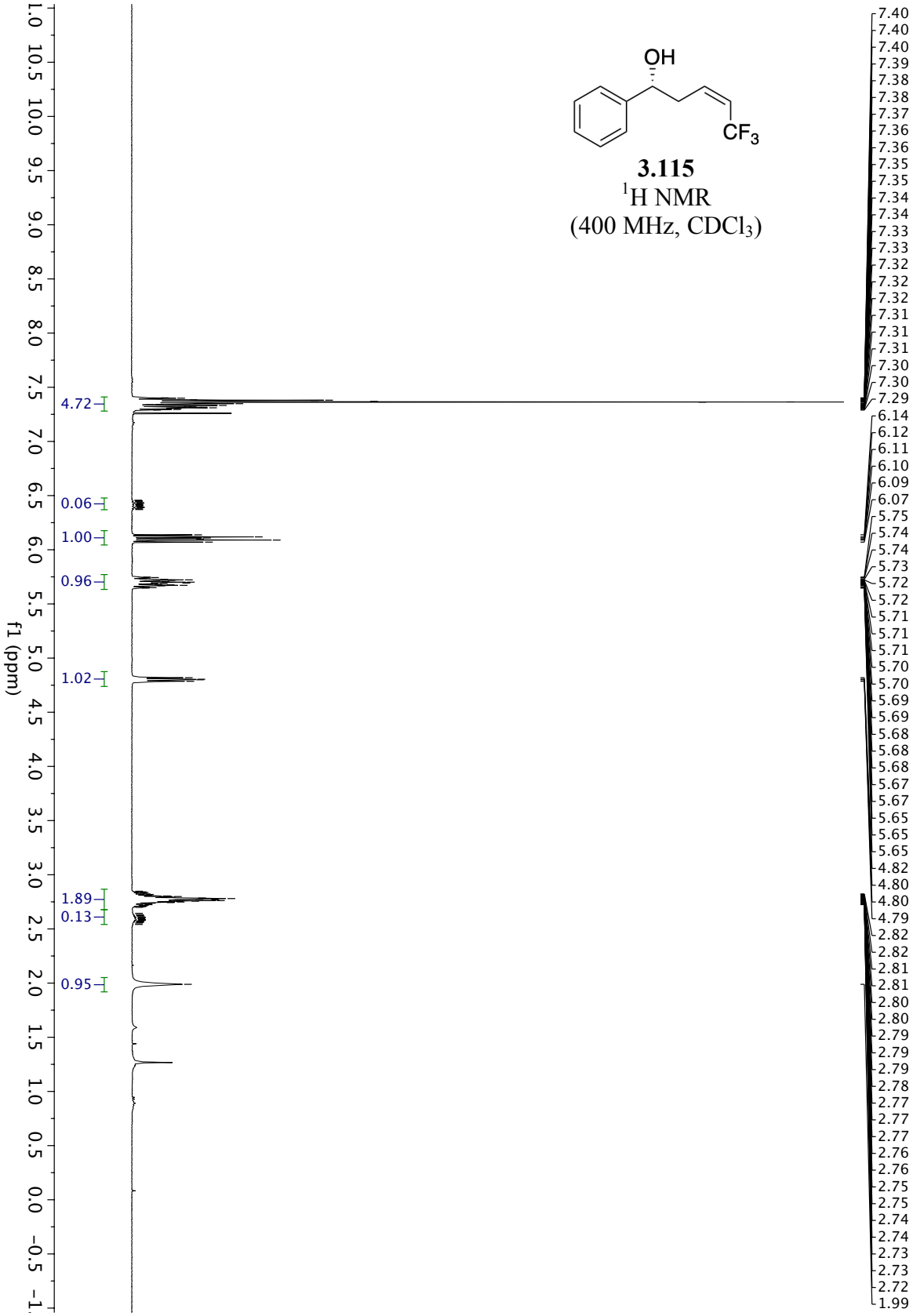
^{13}C NMR

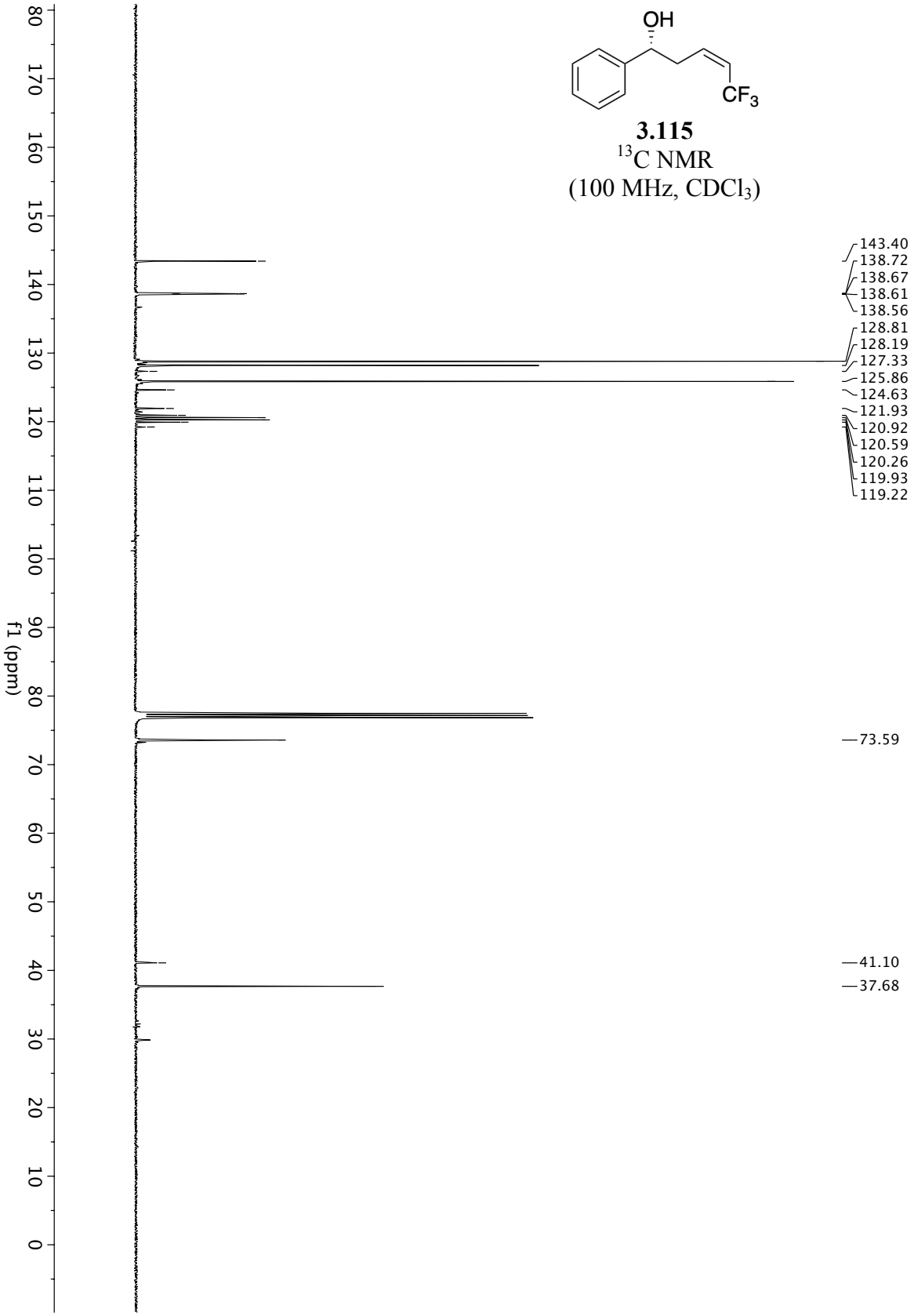
(100 MHz, $CDCl_3$)

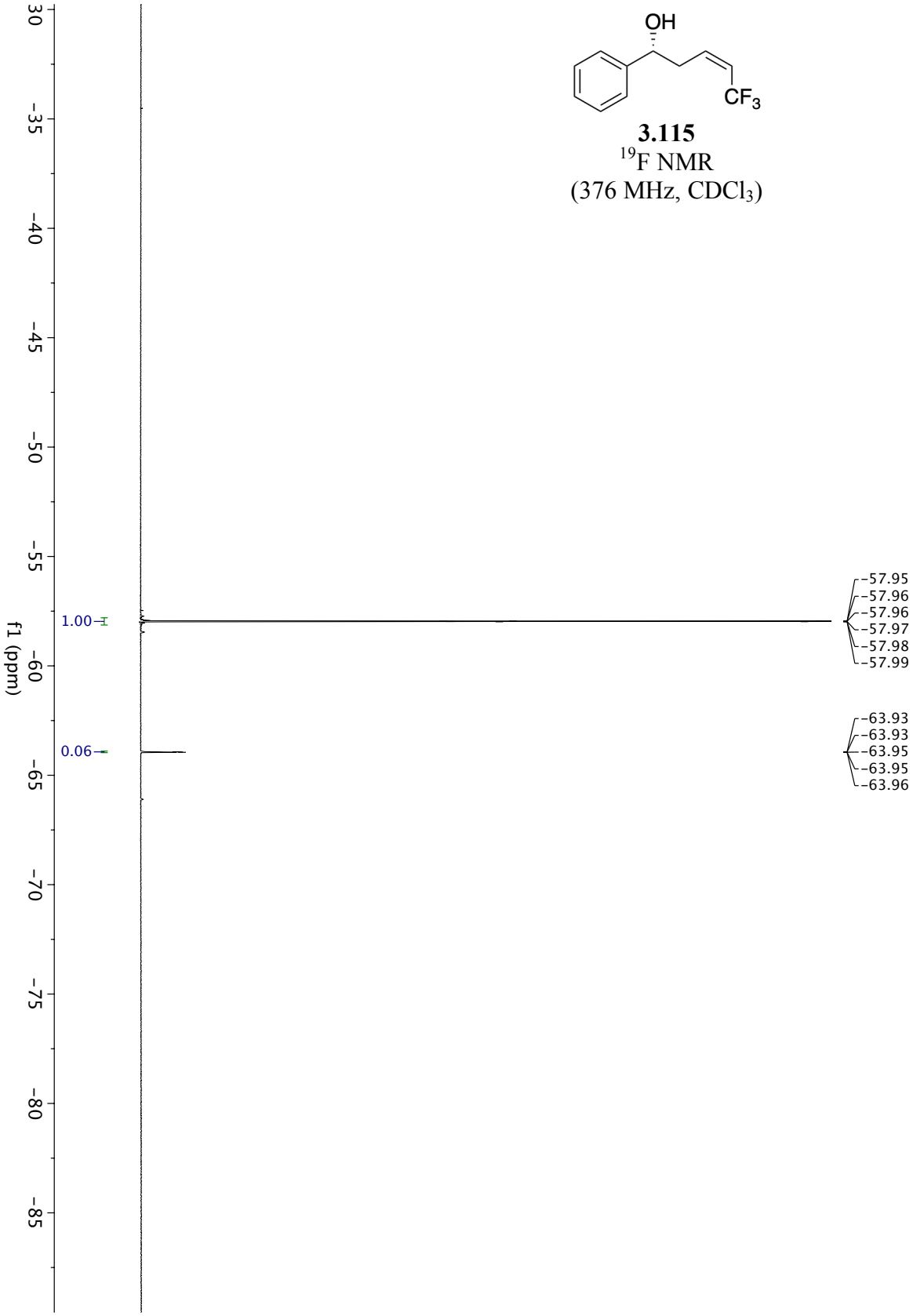

OH
Cl
3.112
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
1.98
1.01
0.92
0.89
1.11
5.19
5.18

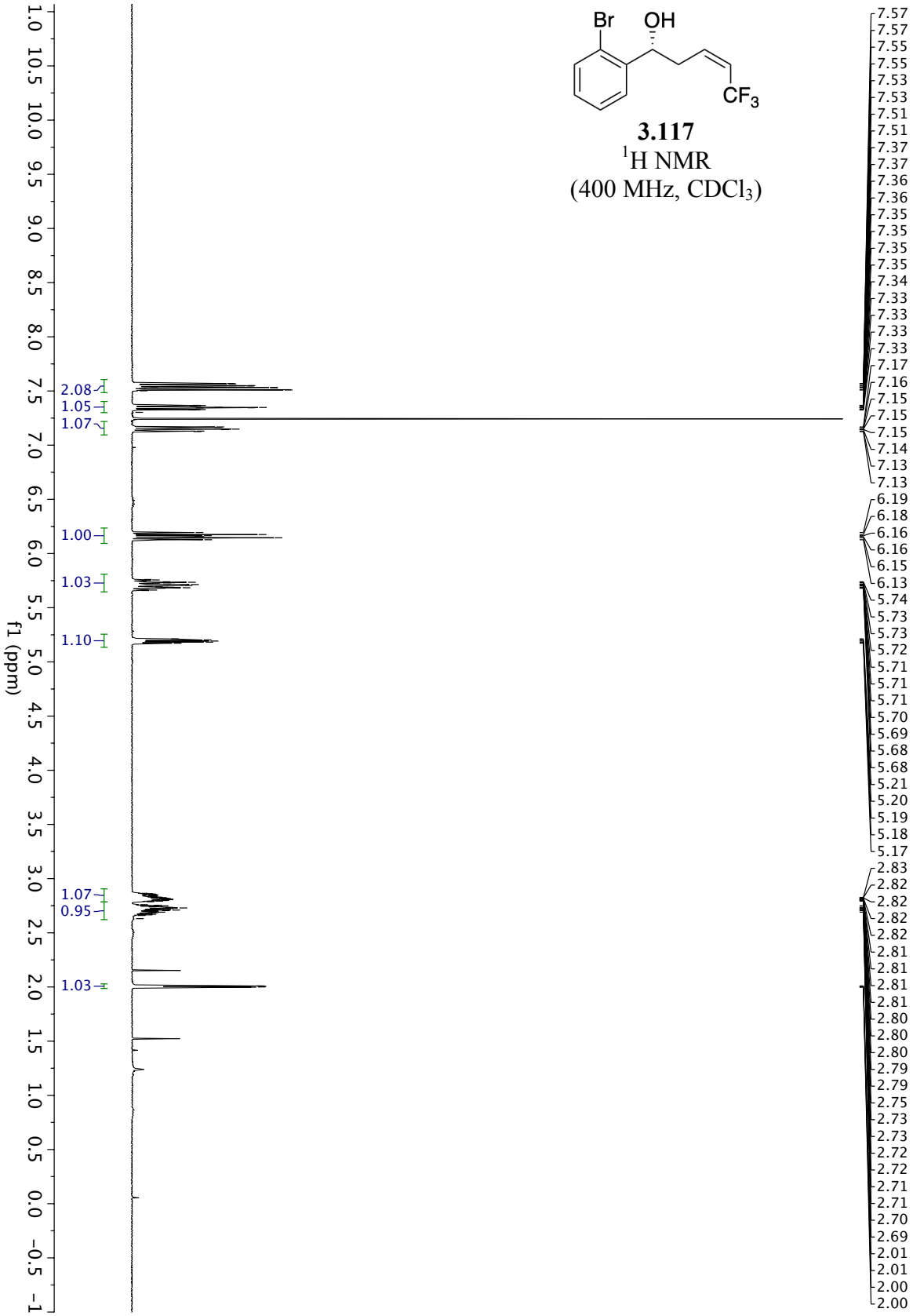

OH
Cl
3.112
13C NMR
(100 MHz, CDCl3)
f1 (ppm)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
133.97
119.73
78.47
65.82
40.00
29.06
28.62
26.42
26.07
25.88

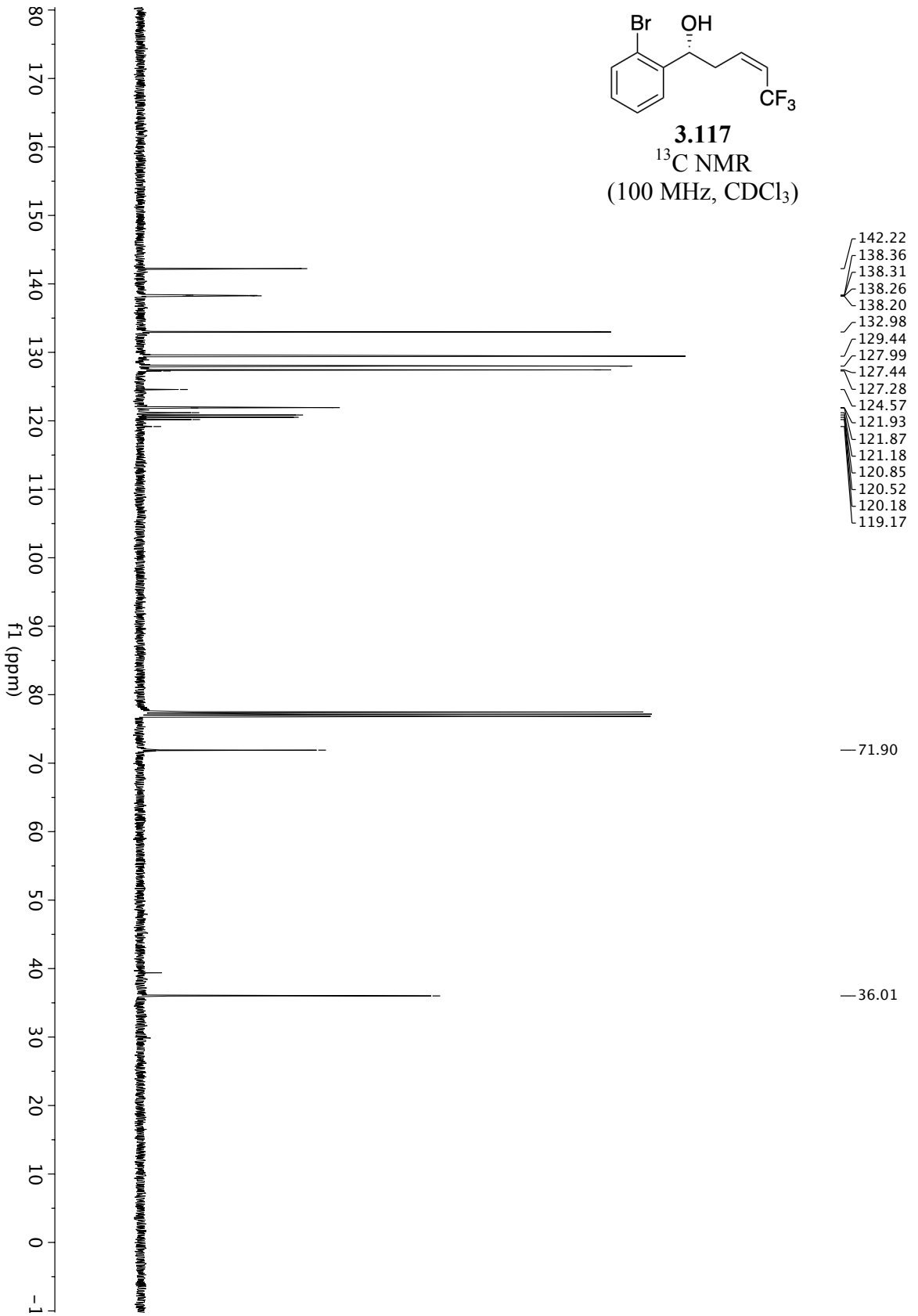

OH
Cl
3.113
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
1.96
0.97
0.96
0.99
8.90
6.22
6.20
6.18
6.17
6.15
6.13
5.34
5.34
5.30
5.29
5.29
5.24
5.23
5.21
5.21
4.74
4.74
4.72
4.71
3.63
3.63
3.63
3.62
2.26
2.25
2.22
0.96

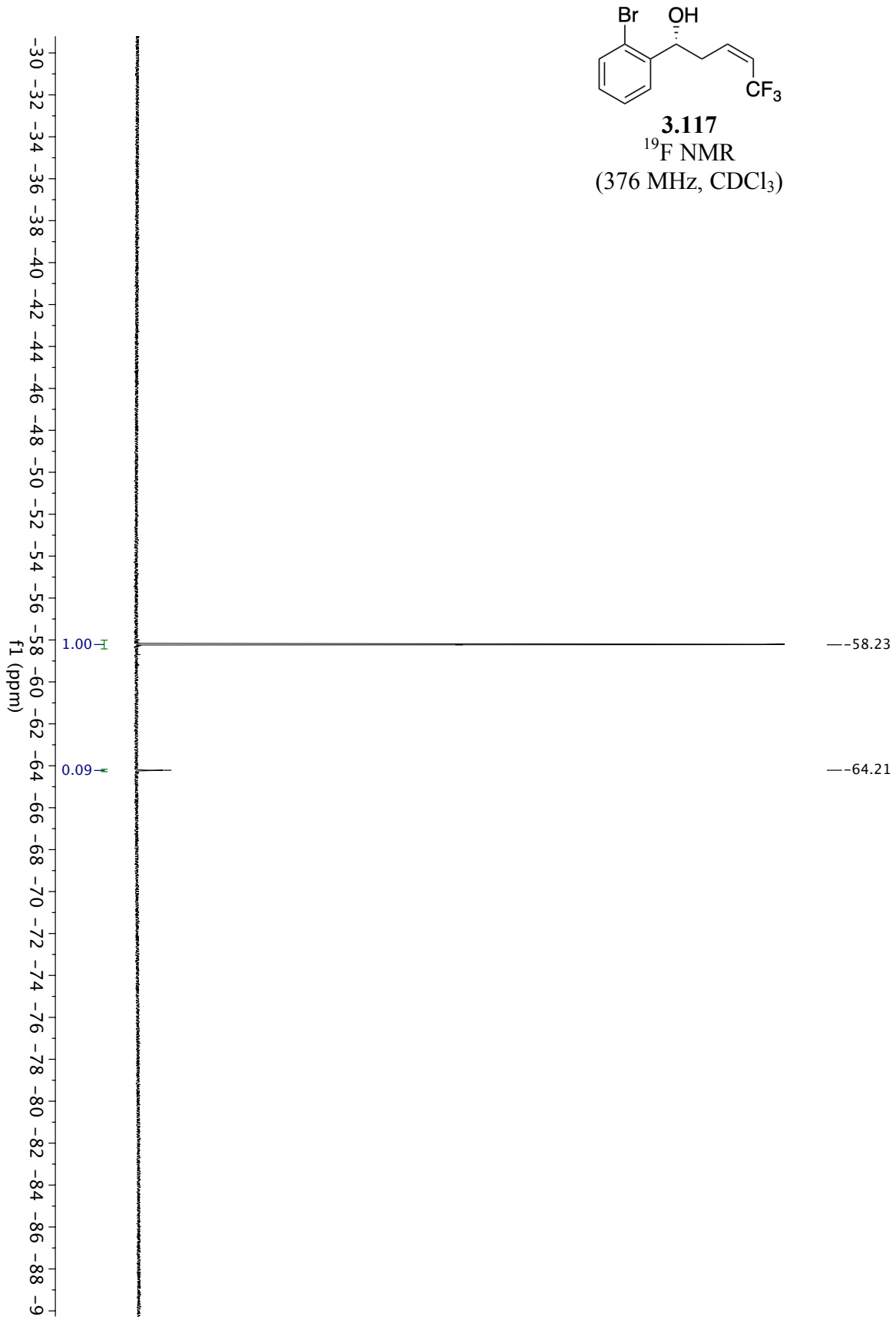

OH
CF3
3.115
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
4.72
0.06
1.00
0.96
1.02
1.89
0.13
0.95


OH
CF3
3.115
13C NMR
(100 MHz, CDCl3)
143.40
138.72
138.67
138.61
138.56
128.81
128.19
127.33
125.86
124.63
121.93
120.92
120.59
120.26
119.93
119.22
73.59
41.10
37.68
f1 (ppm)


OH
CF3
3.115
19F NMR
(376 MHz, CDCl3)
f1 (ppm)
30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
1.00
0.06
-57.95
-57.96
-57.96
-57.97
-57.98
-57.99
-63.93
-63.93
-63.95
-63.95
-63.96


Br
OH
CF3
3.117
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.08
1.05
1.07
1.00
1.03
1.10
1.07
0.95
1.03

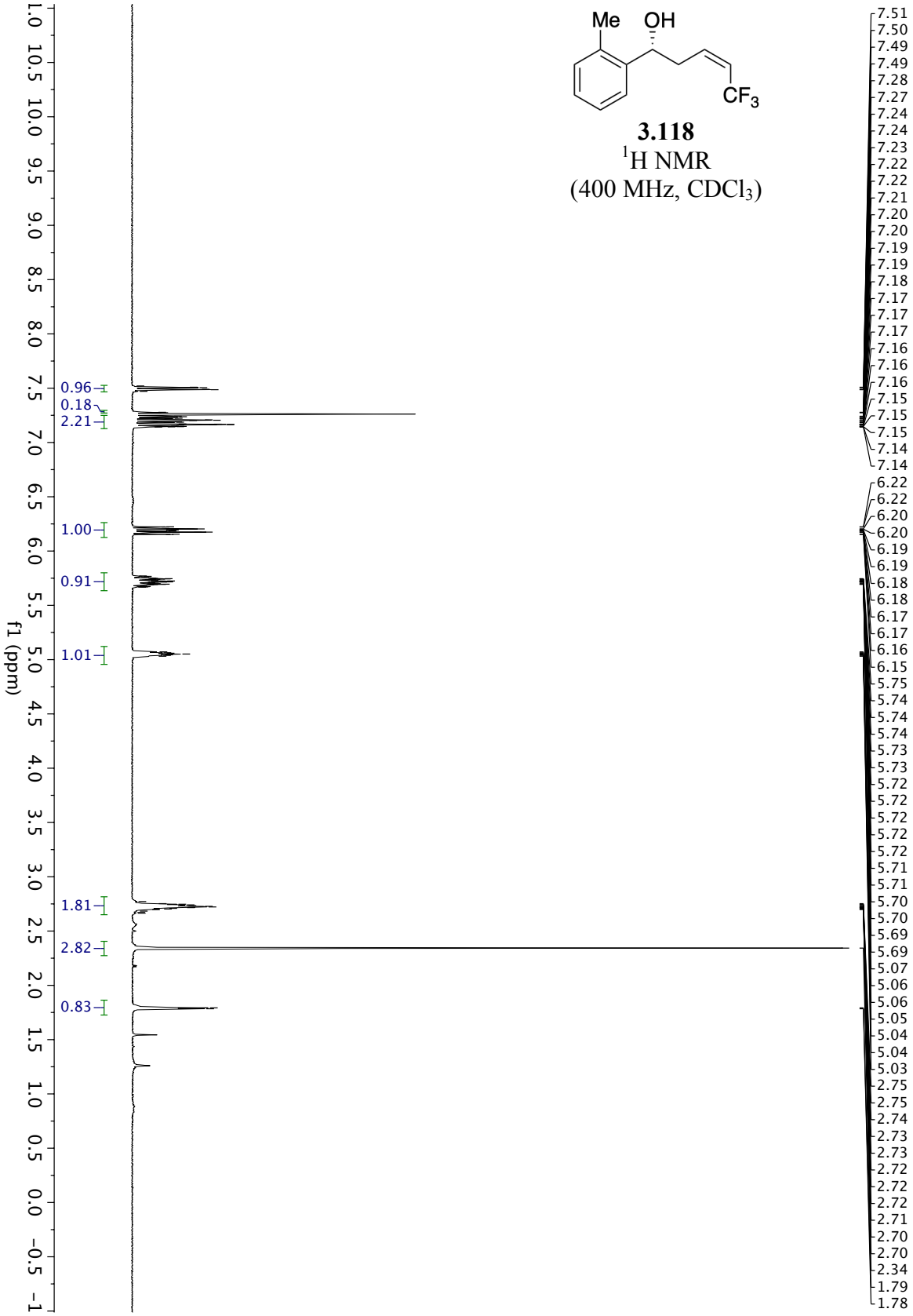

Br
OH
CF3
3.117
13C NMR
(100 MHz, CDCl3)
142.22
138.36
138.31
138.26
138.20
132.98
129.44
127.99
127.44
127.28
124.57
121.93
121.87
121.18
120.85
120.52
120.18
119.17
71.90
36.01
f1 (ppm)

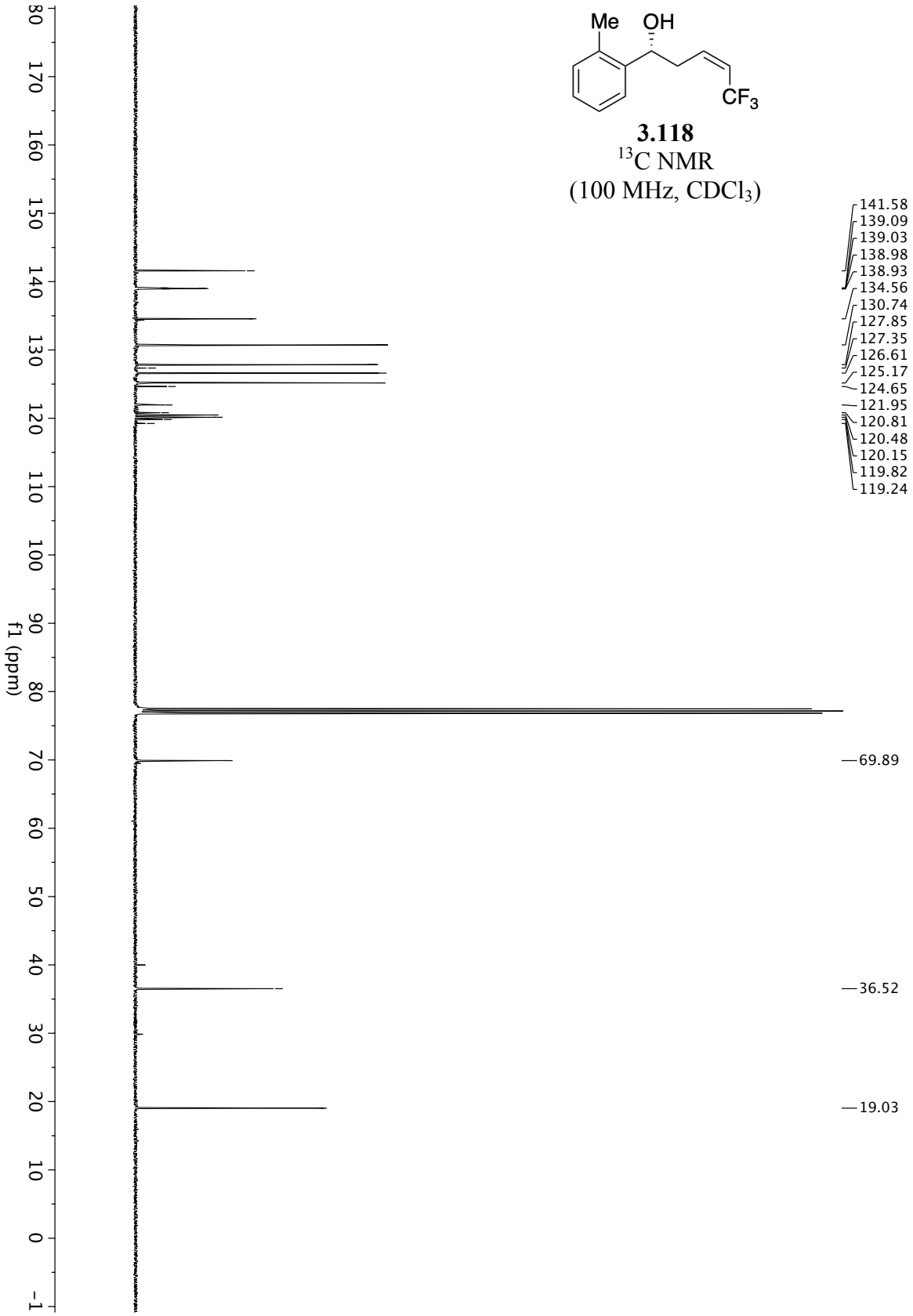


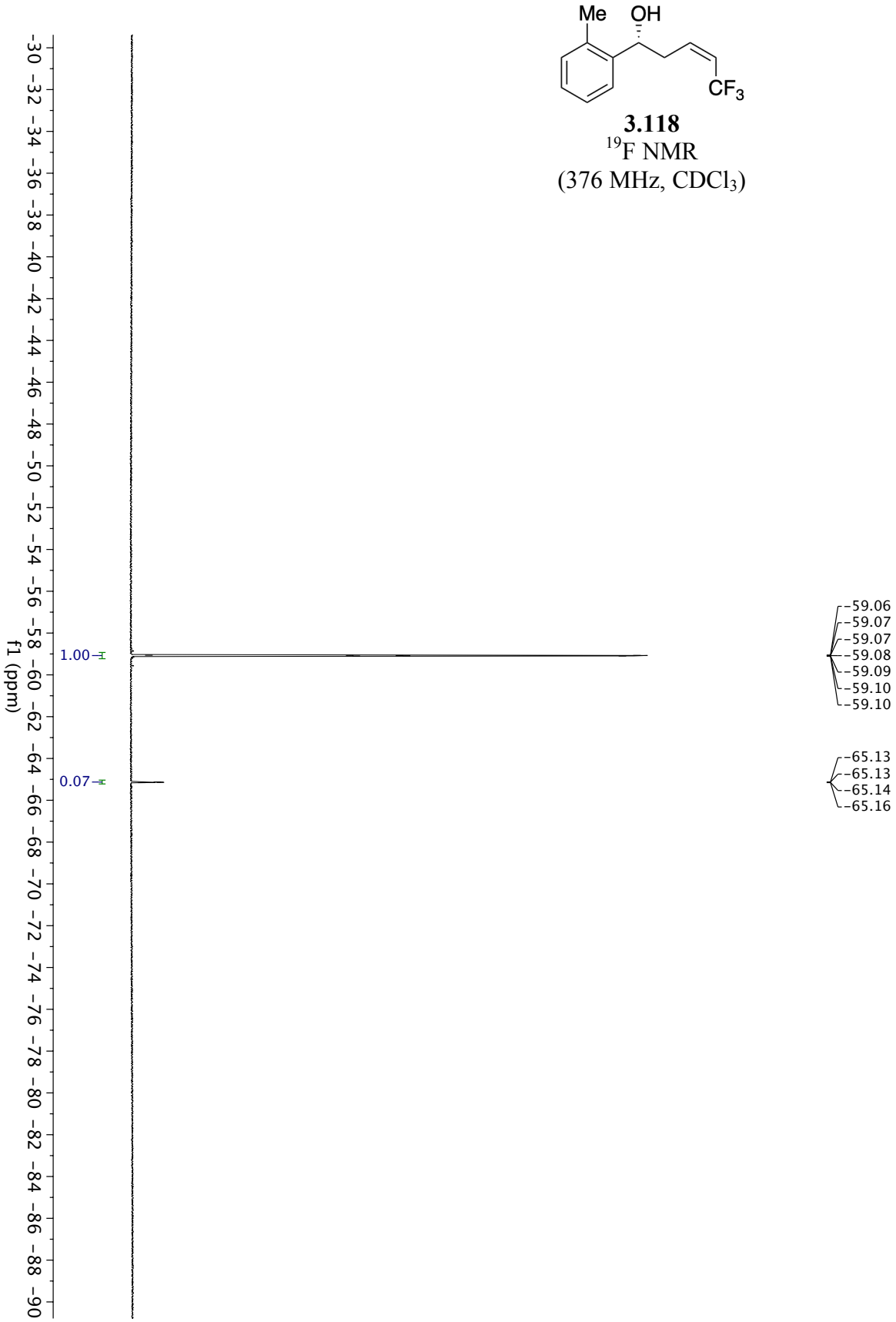
3.117

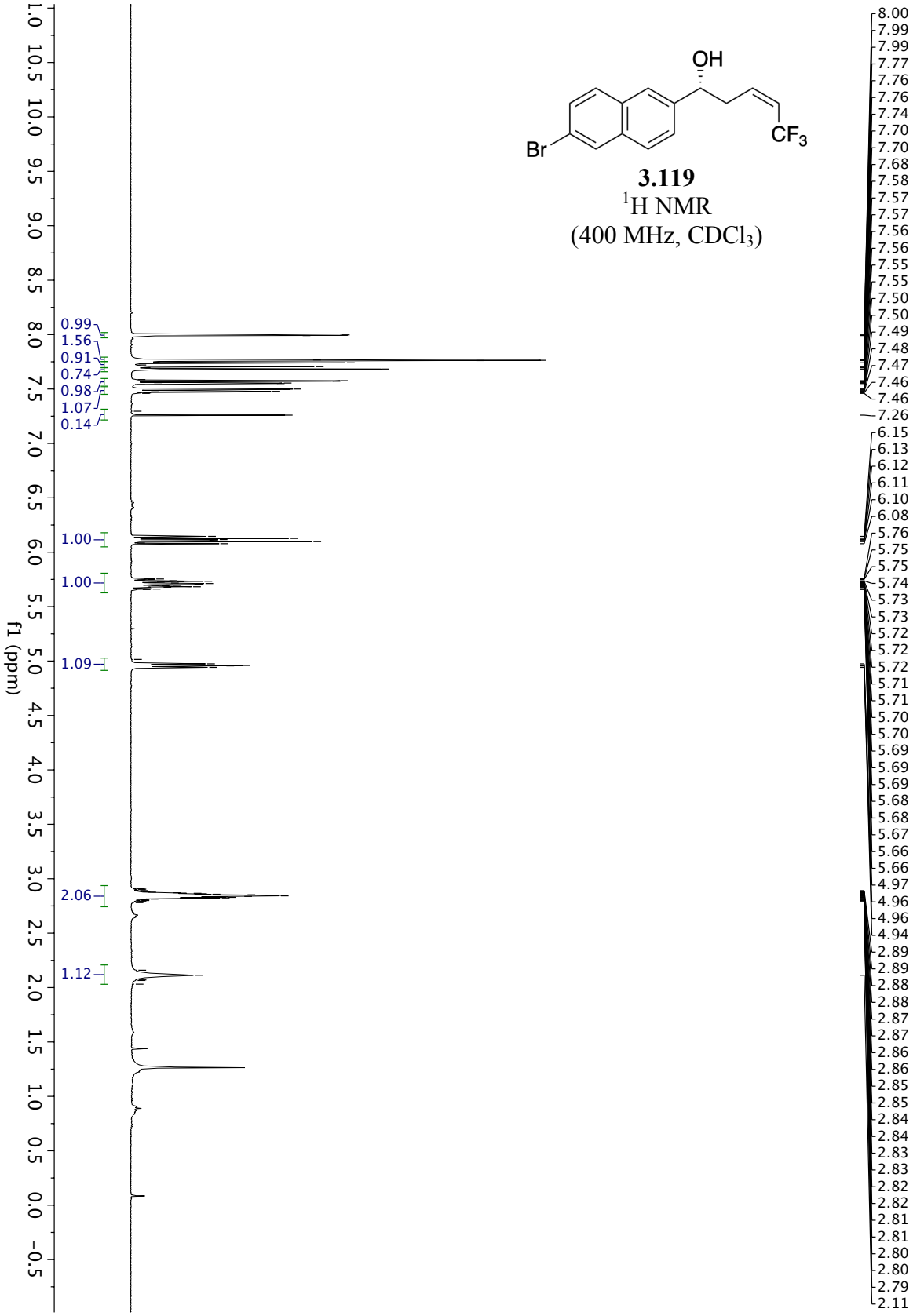
^{19}F NMR

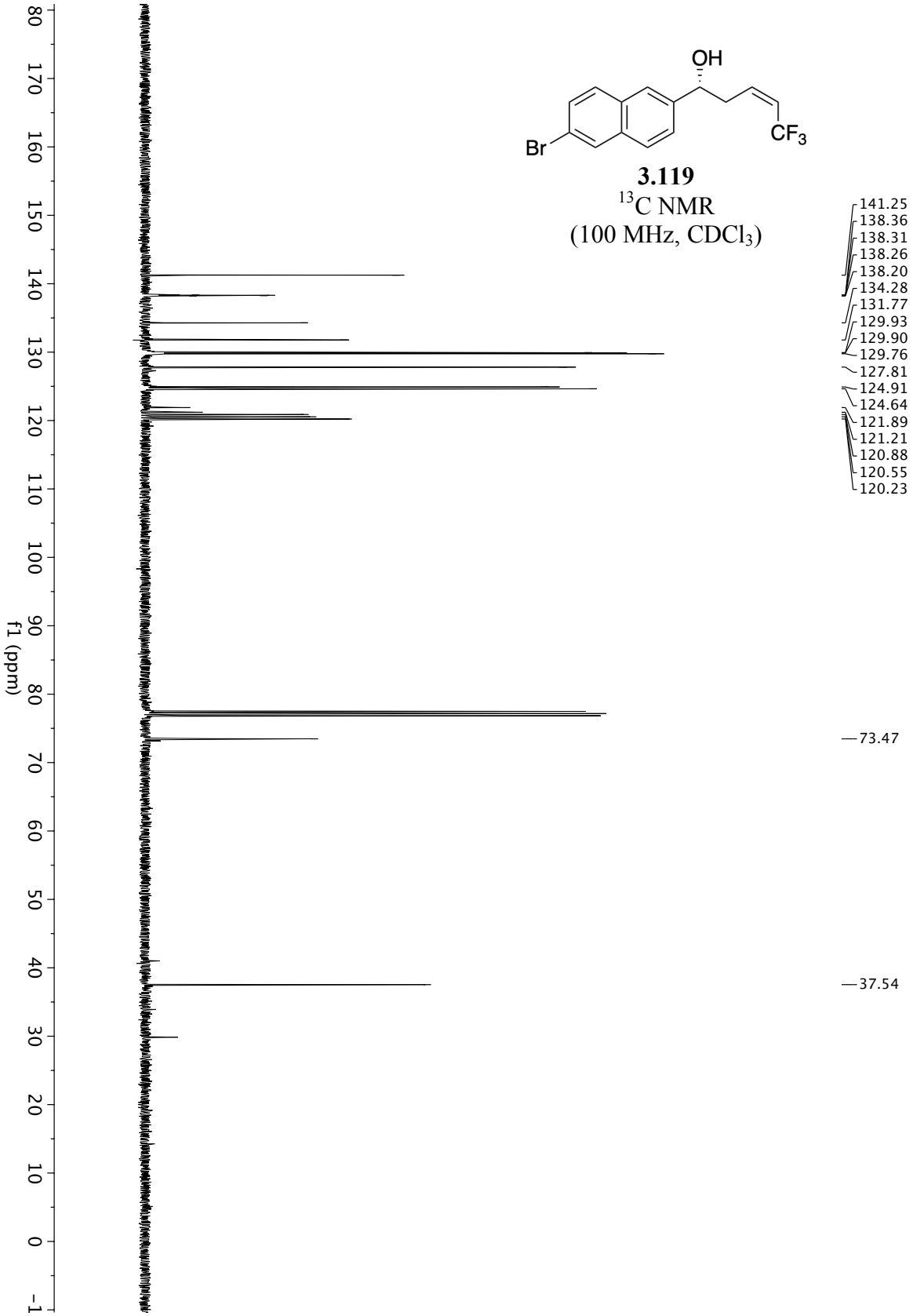
(376 MHz, $CDCl_3$)

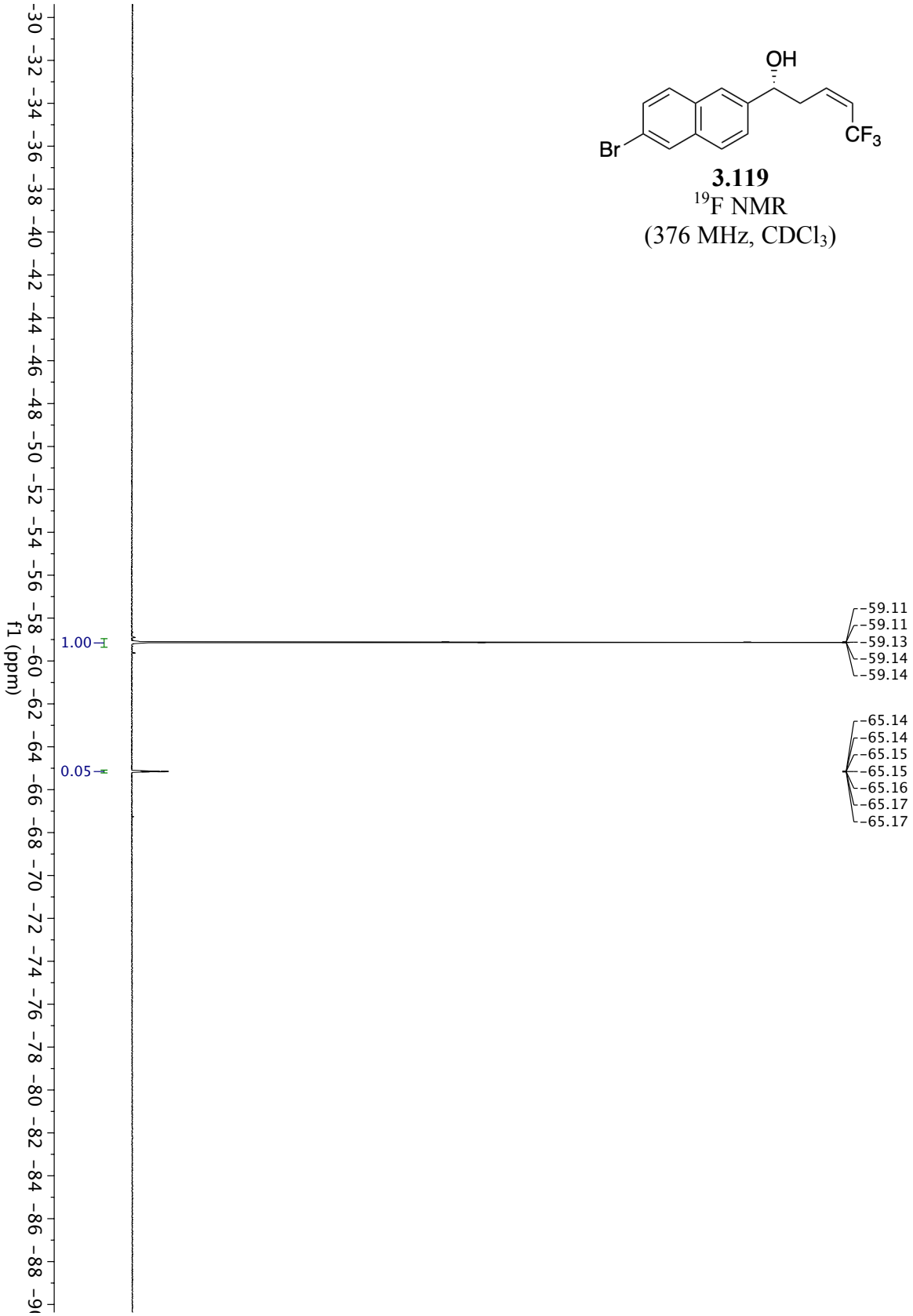

Me
OH
CF3
3.118
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
0.96
0.18
2.21
1.00
0.91
1.01
1.81
2.82
0.83

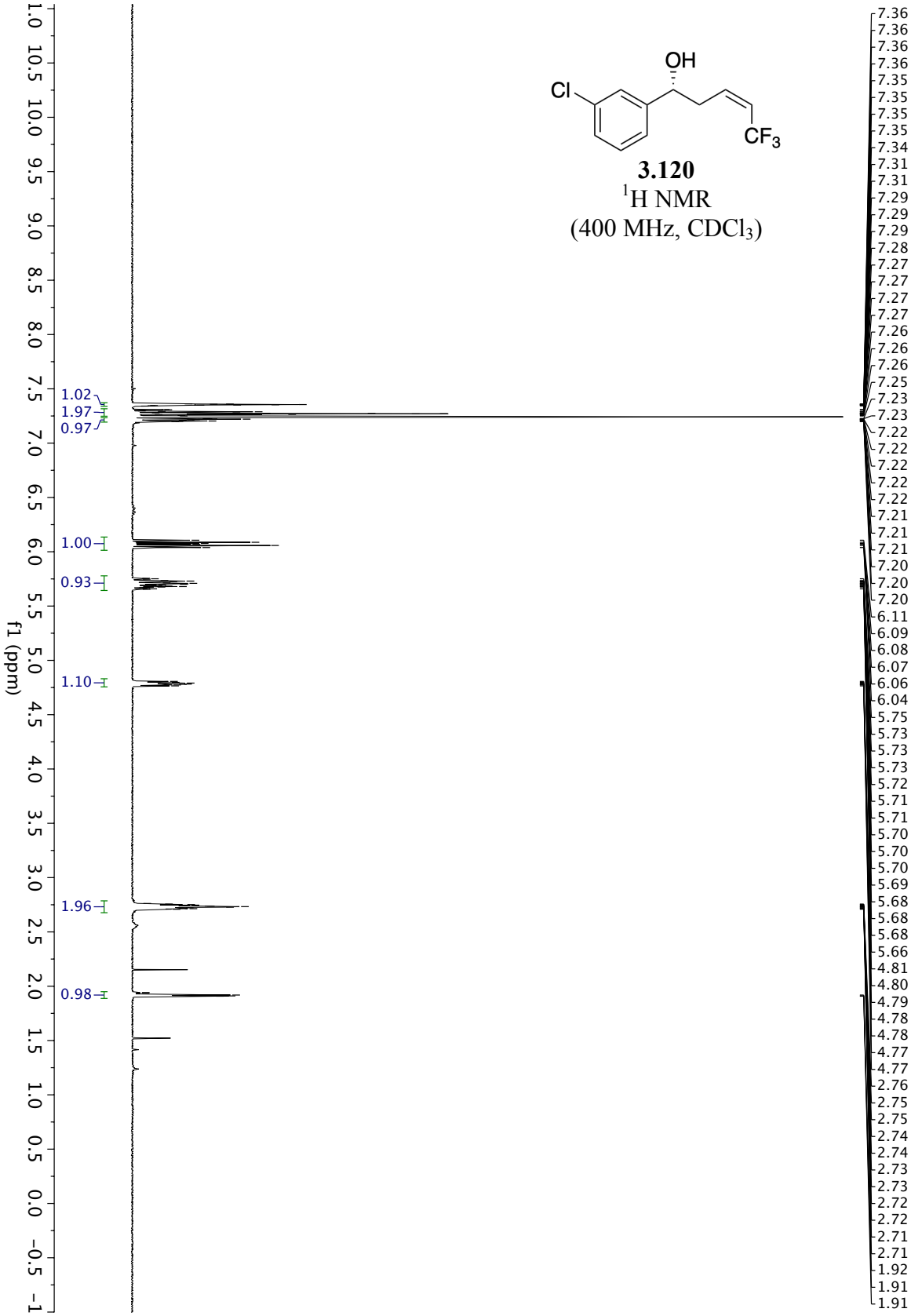

Me
OH
CF3
3.118
13C NMR
(100 MHz, CDCl3)
141.58
139.09
139.03
138.98
138.93
134.56
130.74
127.85
127.35
126.61
125.17
124.65
121.95
120.81
120.48
120.15
119.82
119.24
69.89
36.52
19.03
f1 (ppm)

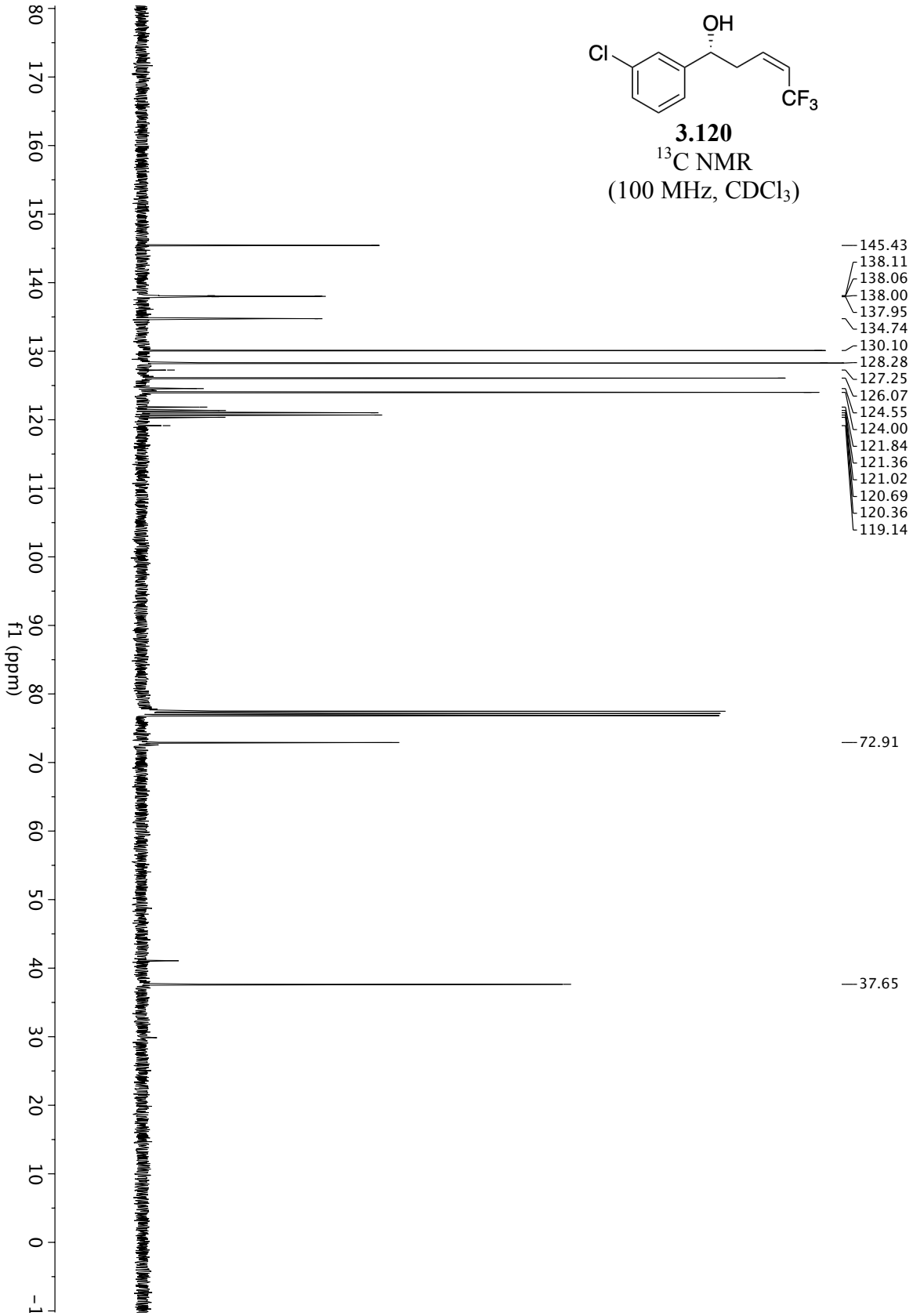

Me
OH
CF3
3.118
19F NMR
(376 MHz, CDCl3)
-30 -32 -34 -36 -38 -40 -42 -44 -46 -48 -50 -52 -54 -56 -58 -60 -62 -64 -66 -68 -70 -72 -74 -76 -78 -80 -82 -84 -86 -88 -90
f1 (ppm)
1.00
0.07
-59.06
-59.07
-59.07
-59.08
-59.09
-59.10
-59.10
-65.13
-65.13
-65.14
-65.16

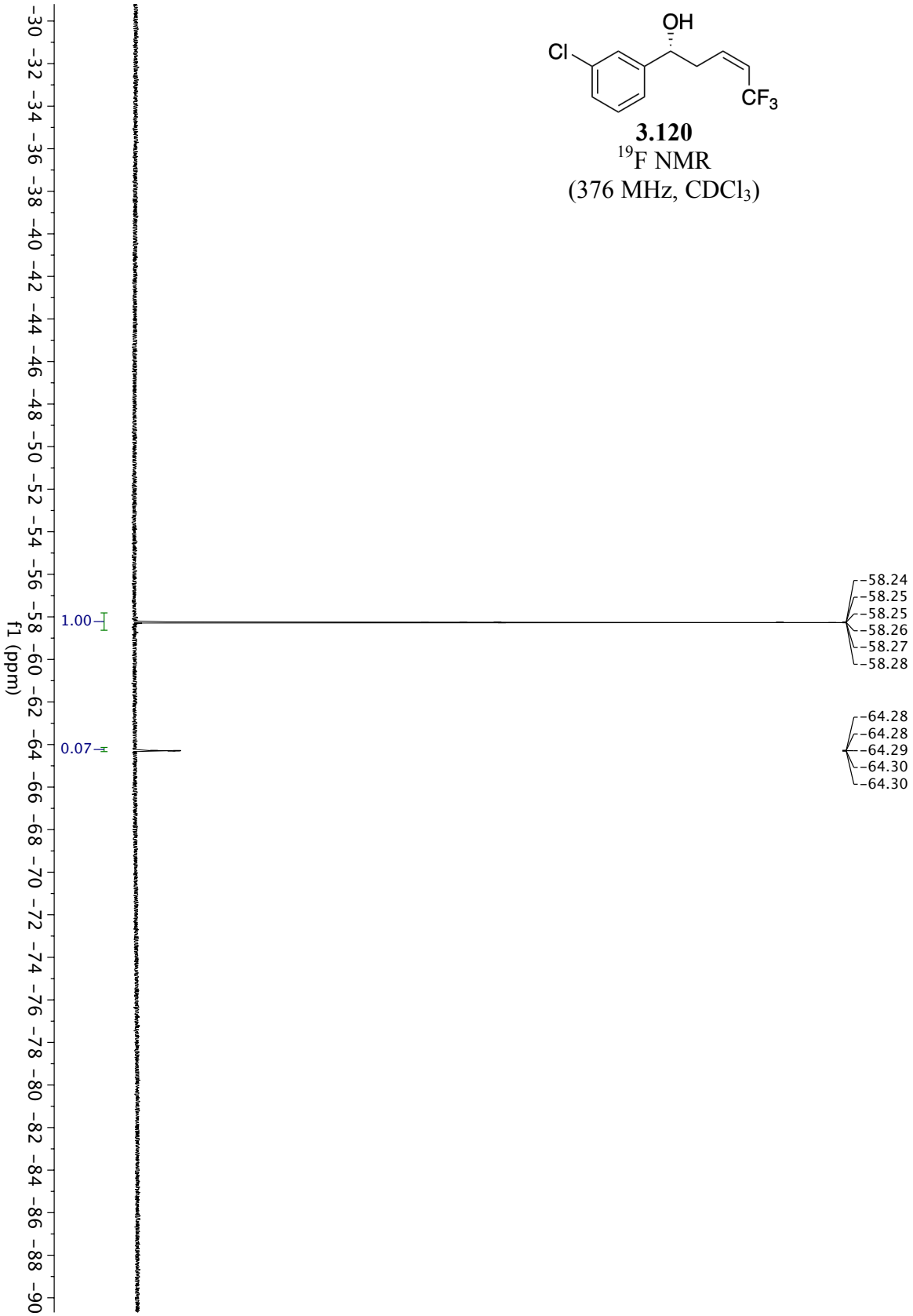

OH
Br
CF3
3.119
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
0.99
1.56
0.91
0.74
0.98
1.07
0.14
1.00
1.00
1.09
2.06
1.12

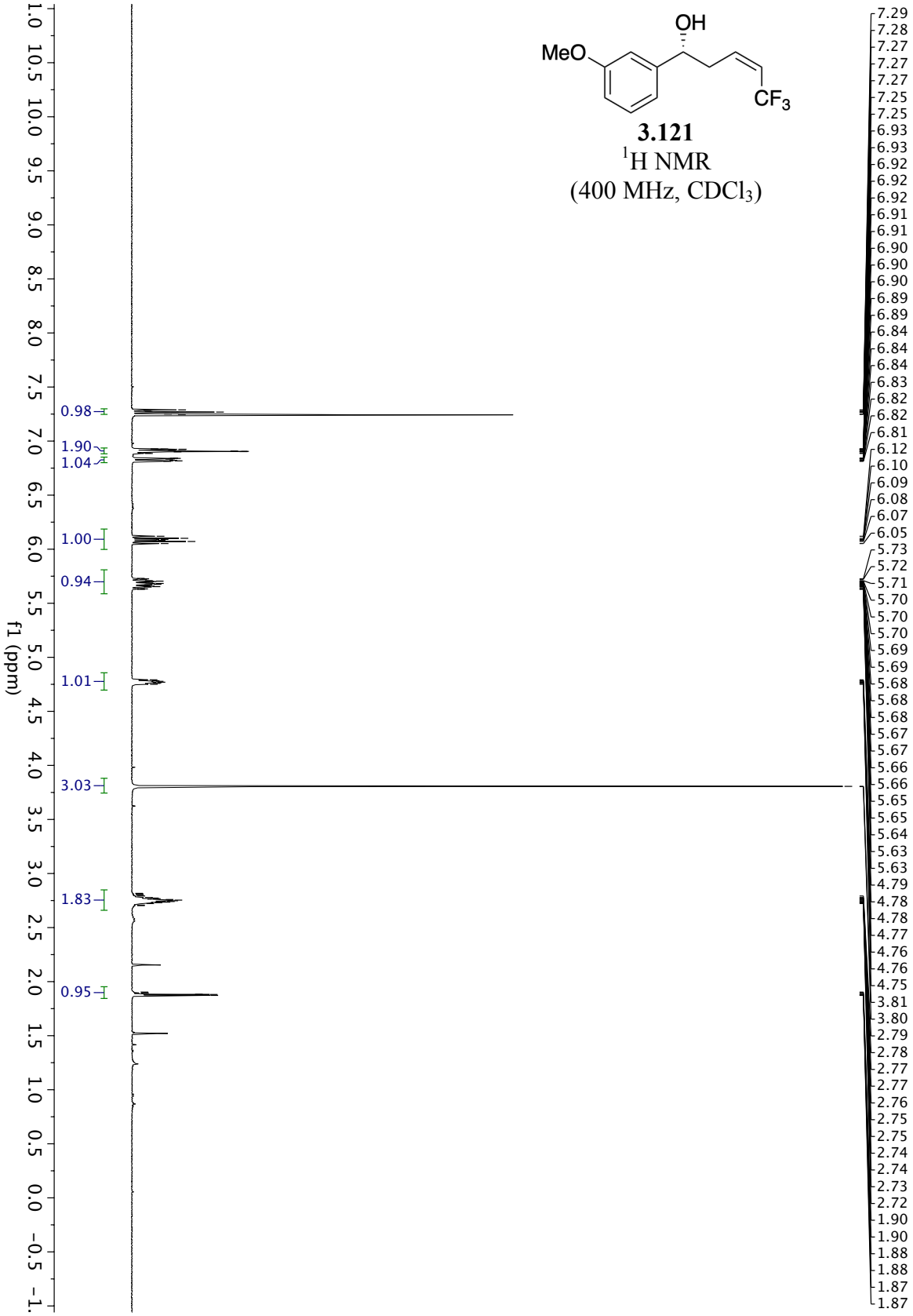

OH
Br
CF3
3.119
13C NMR
(100 MHz, CDCl3)
141.25
138.36
138.31
138.26
138.20
134.28
131.77
129.93
129.90
129.76
127.81
124.91
124.64
121.89
121.21
120.88
120.55
120.23
73.47
37.54
f1 (ppm)

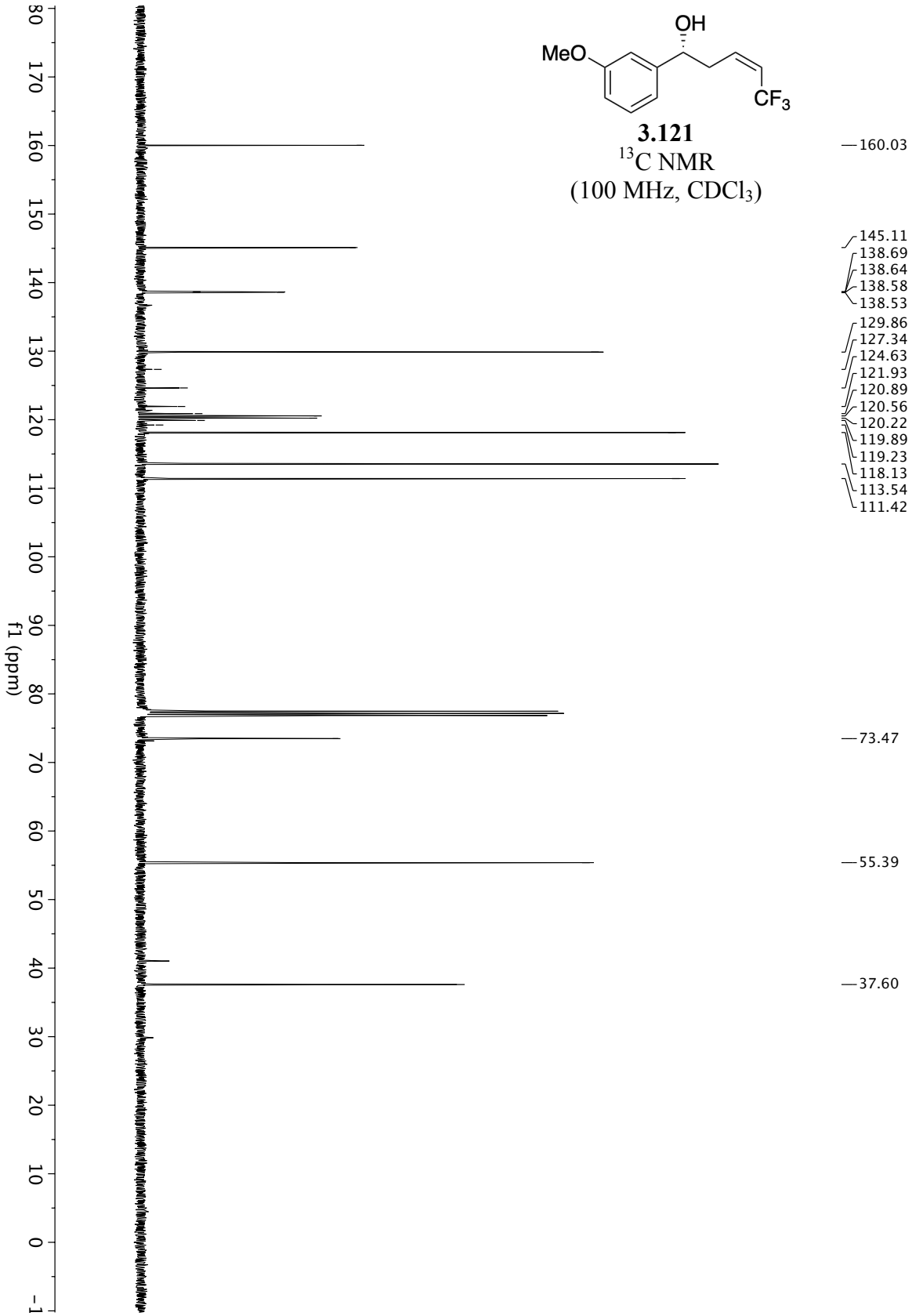

OH
Br
CF3
3.119
19F NMR
(376 MHz, CDCl3)
f1 (ppm)
1.00
0.05
-59.11
-59.11
-59.13
-59.14
-59.14
-65.14
-65.14
-65.15
-65.15
-65.16
-65.17
-65.17

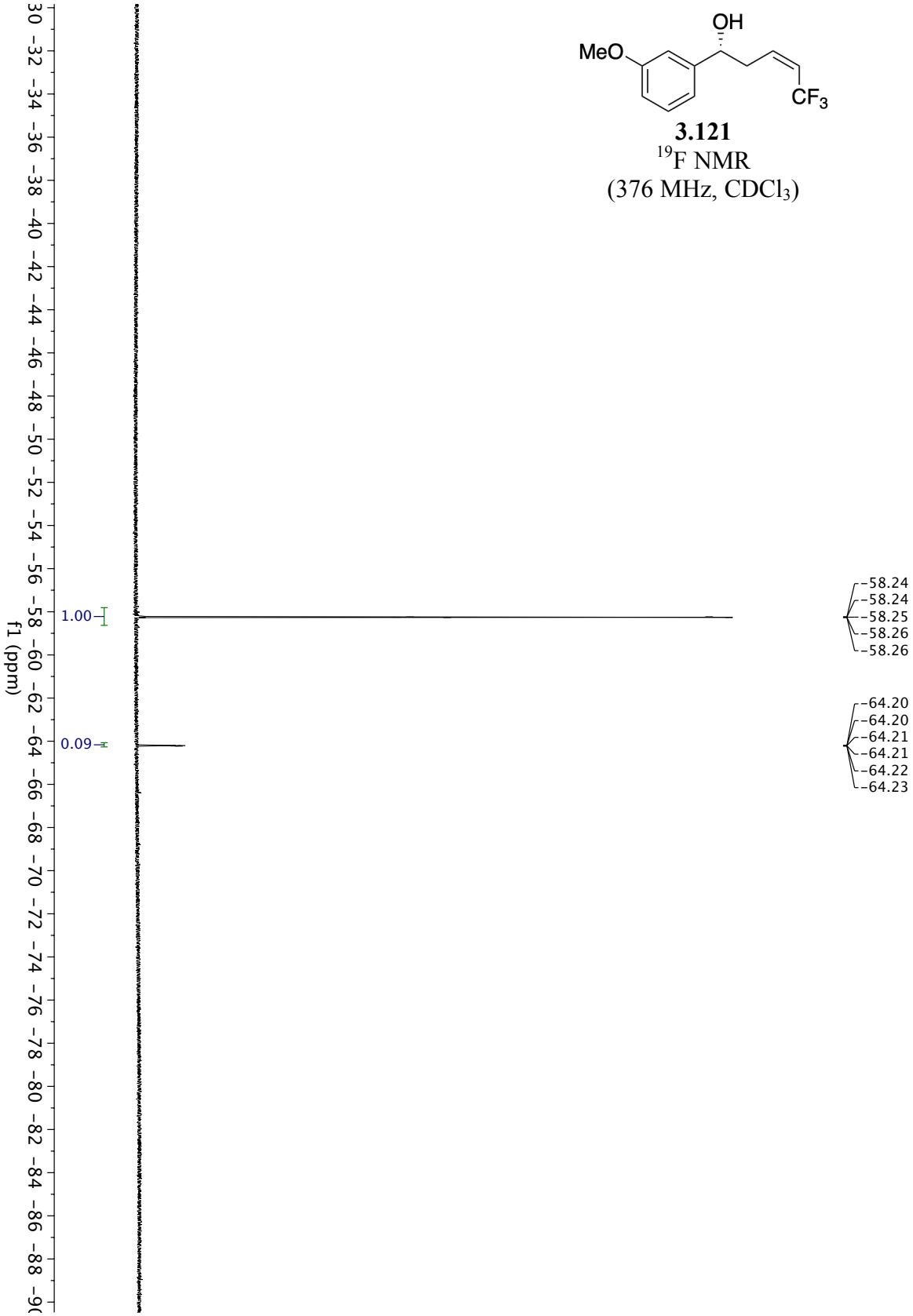

OH
Cl
CF3
3.120
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.02
1.97
0.97
1.00
0.93
1.10
1.96
0.98

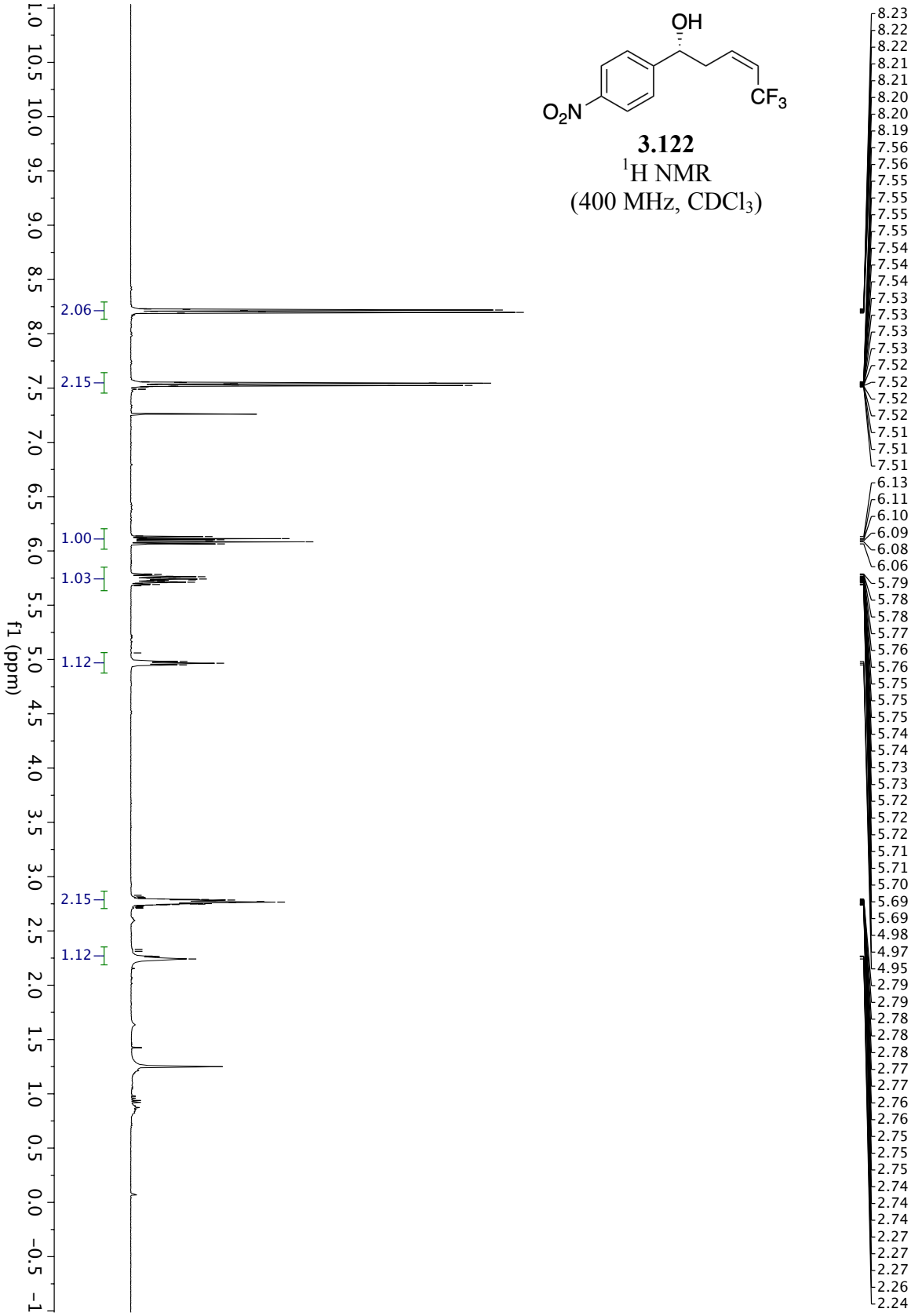

OH
Cl
CF3
3.120
13C NMR
(100 MHz, CDCl3)
145.43
138.11
138.06
138.00
137.95
134.74
130.10
128.28
127.25
126.07
124.55
124.00
121.84
121.36
121.02
120.69
120.36
119.14
72.91
37.65
f1 (ppm)


OH
Cl
CF3
3.120
19F NMR
(376 MHz, CDCl3)
f1 (ppm)
1.00
0.07
-58.24
-58.25
-58.25
-58.26
-58.27
-58.28
-64.28
-64.28
-64.29
-64.30
-64.30


OH
MeO
CF3
3.121
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
0.98
1.90
1.04
1.00
0.94
1.01
3.03
1.83
0.95


OH
MeO
CF3
3.121
13C NMR
(100 MHz, CDCl3)
160.03
145.11
138.69
138.64
138.58
138.53
129.86
127.34
124.63
121.93
120.89
120.56
120.22
119.89
119.23
118.13
113.54
111.42
73.47
55.39
37.60
f1 (ppm)

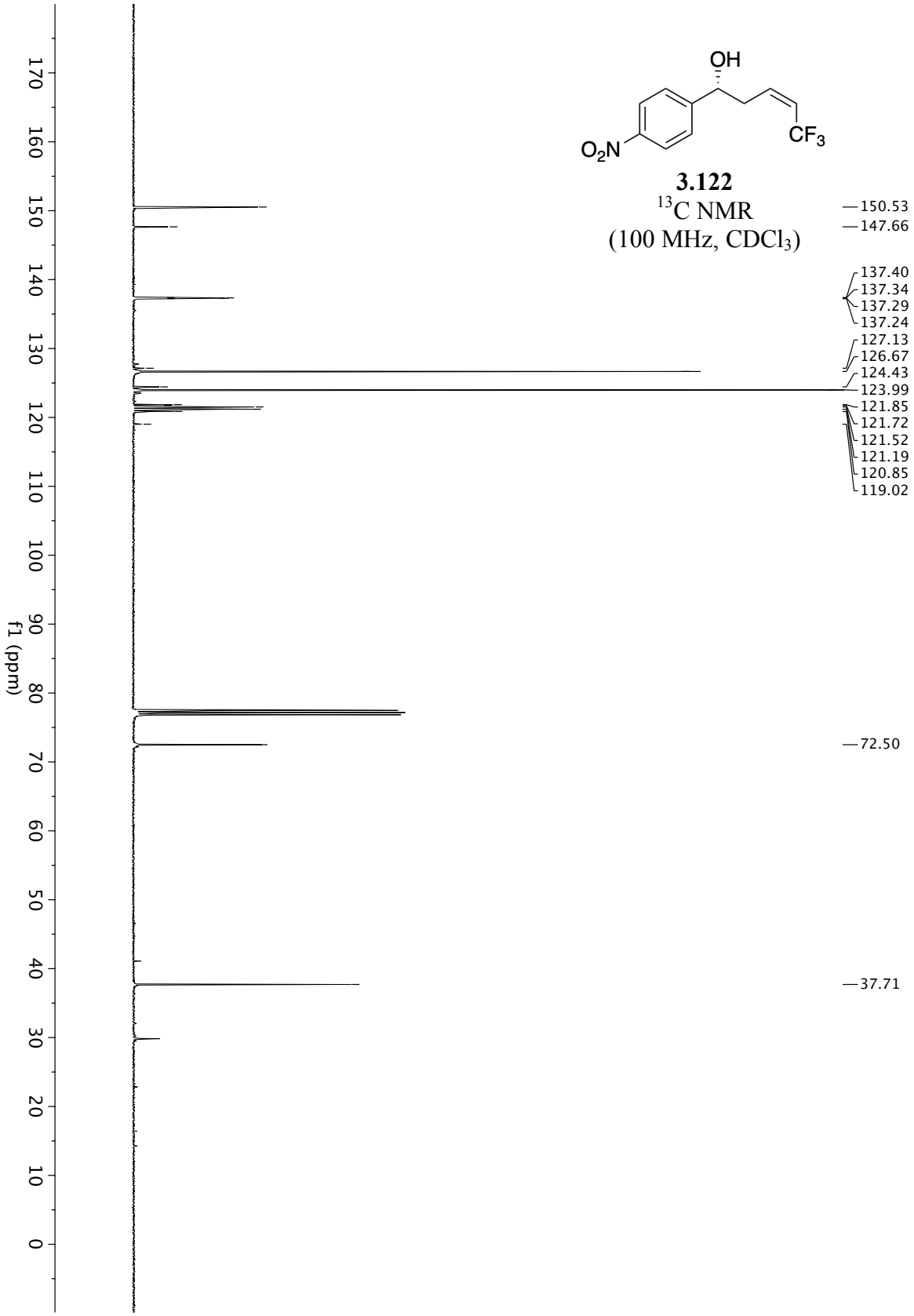

OH
MeO
CF3
3.121
19F NMR
(376 MHz, CDCl3)
-58.24
-58.24
-58.25
-58.26
-58.26
-64.20
-64.20
-64.21
-64.21
-64.22
-64.23
1.00
0.09
f1 (ppm)

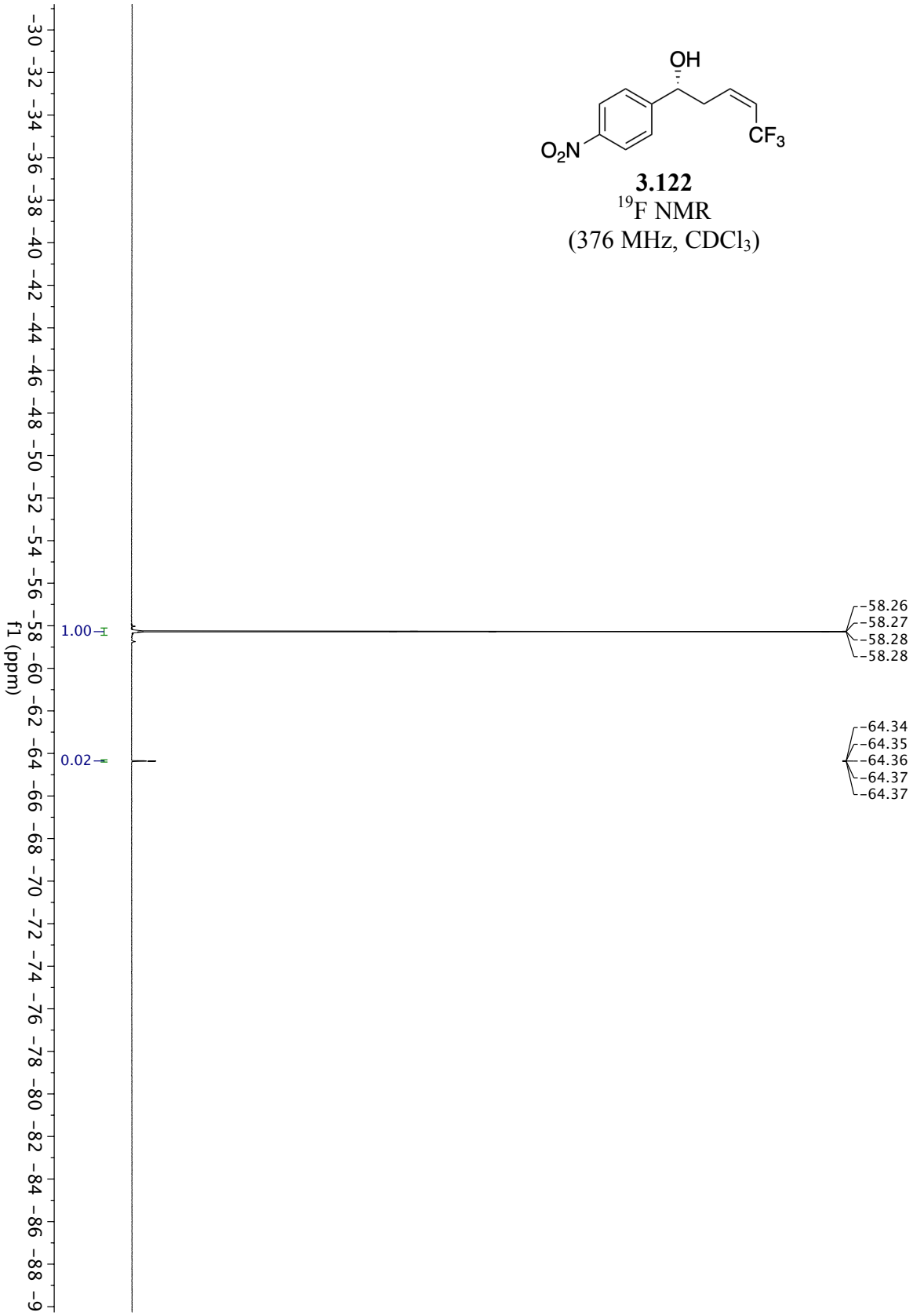


3.122

^{1}H NMR

(400 MHz, $CDCl_3$)

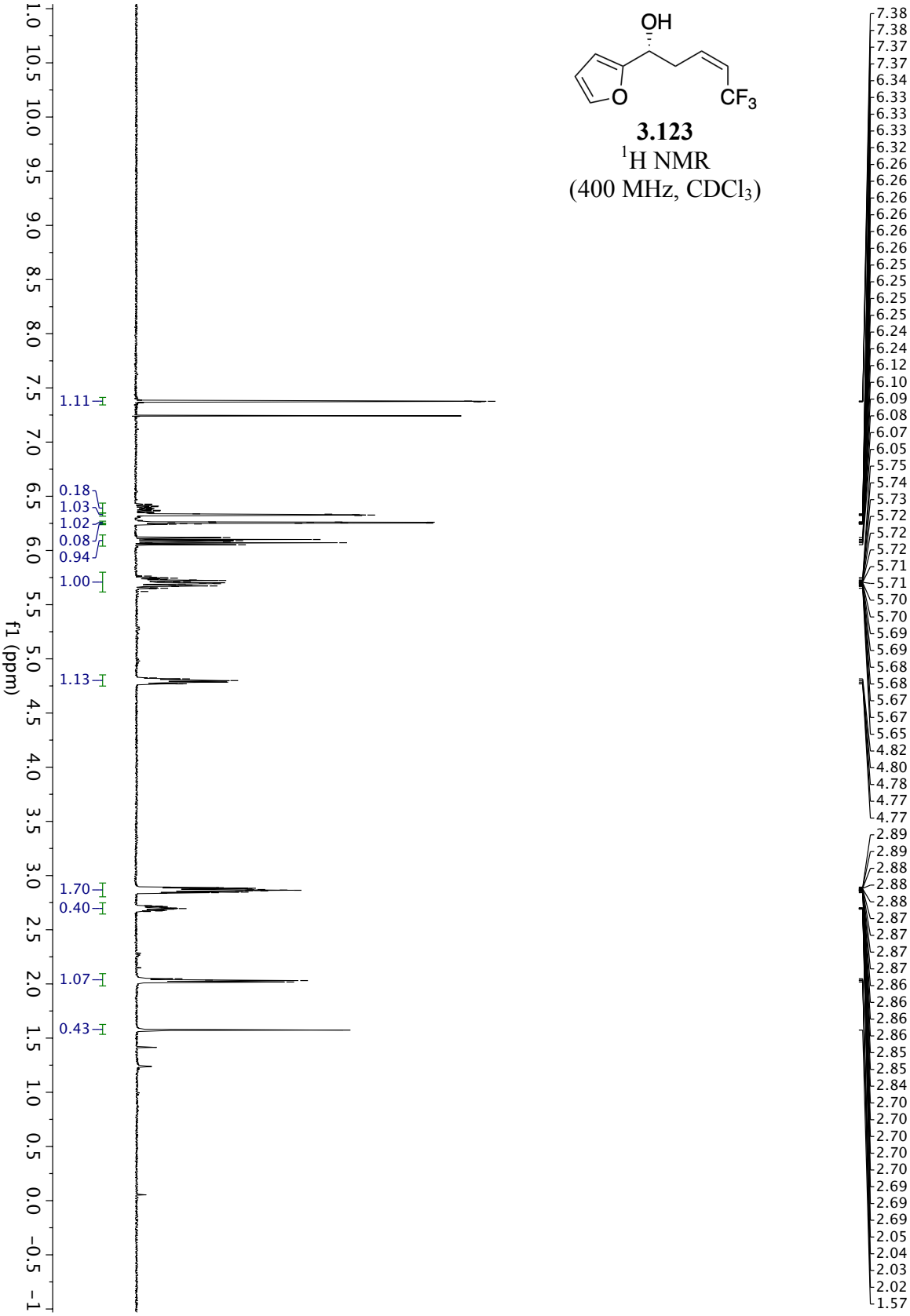

OH
O2N
CF3
3.122
13C NMR
(100 MHz, CDCl3)
150.53
147.66
137.40
137.34
137.29
137.24
127.13
126.67
124.43
123.99
121.85
121.72
121.52
121.19
120.85
119.02
72.50
37.71
f1 (ppm)

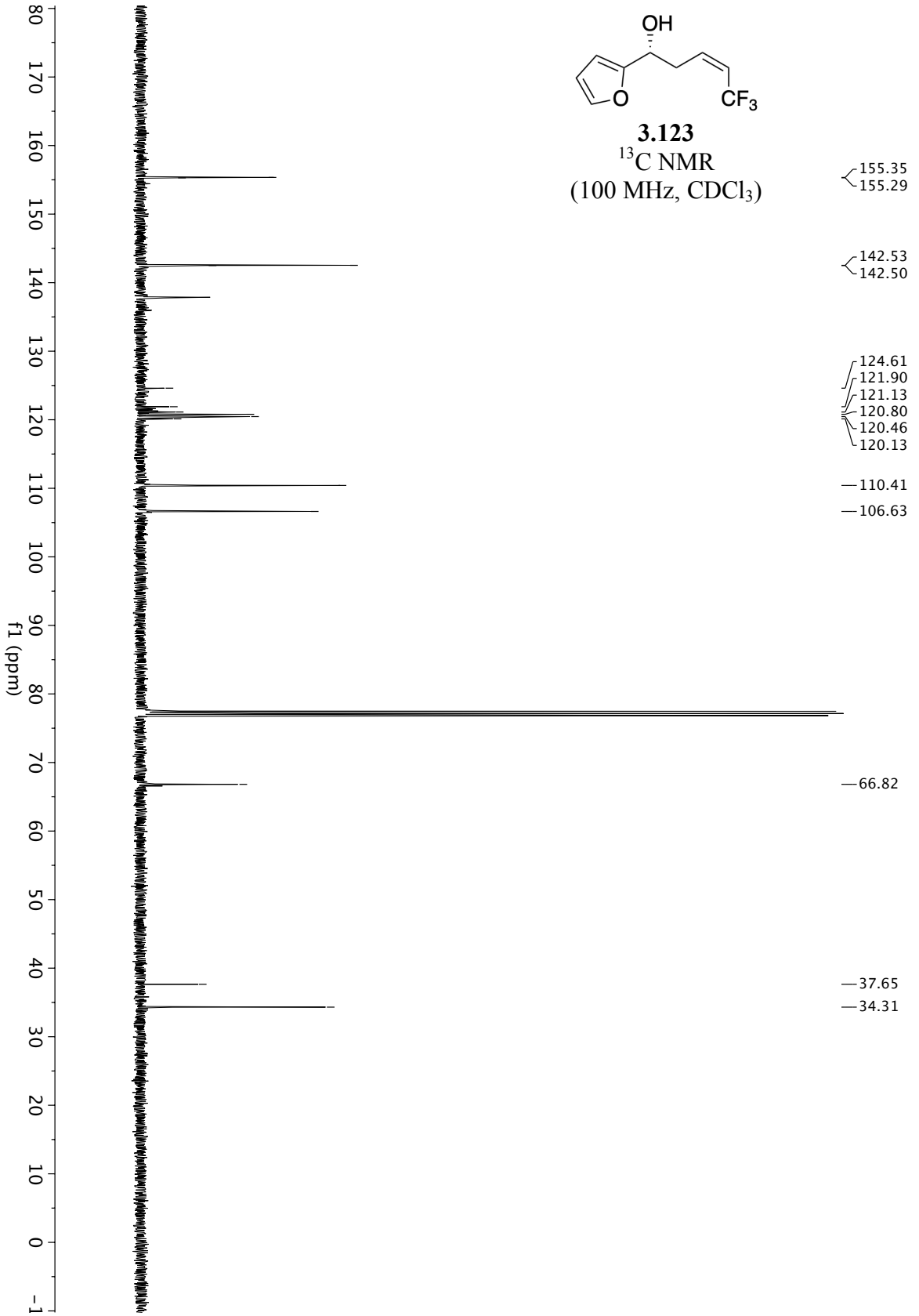


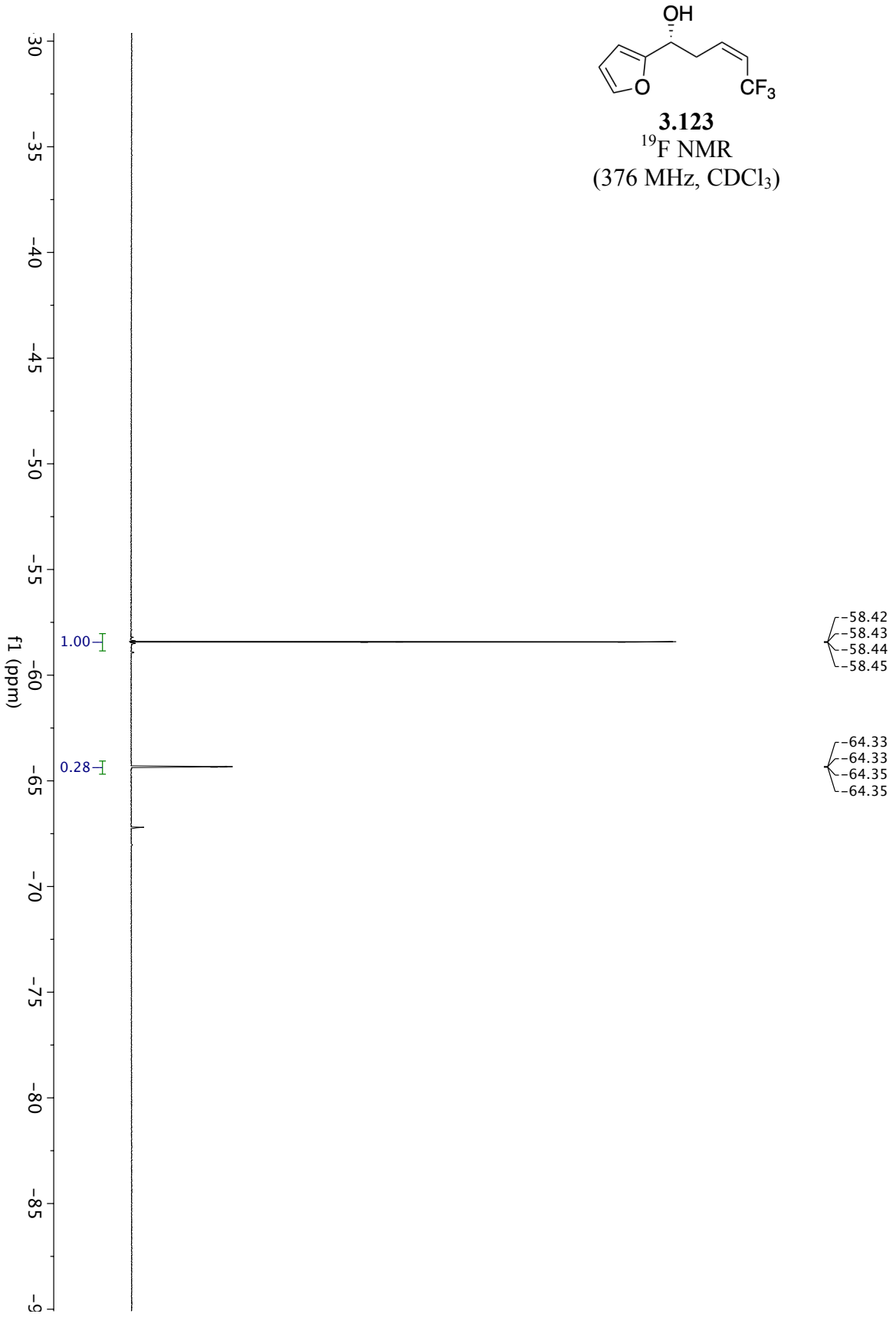
3.122

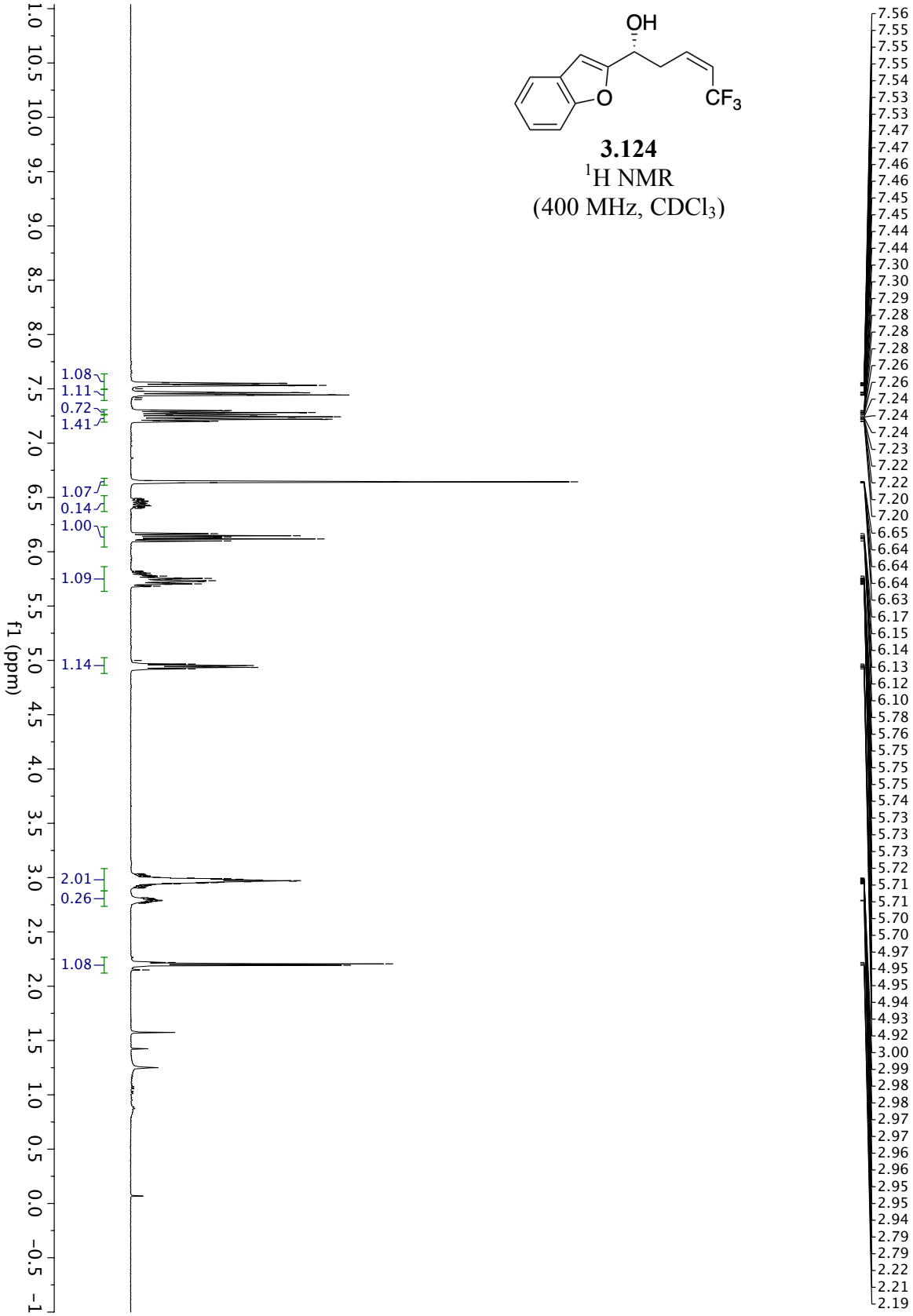
^{19}F NMR

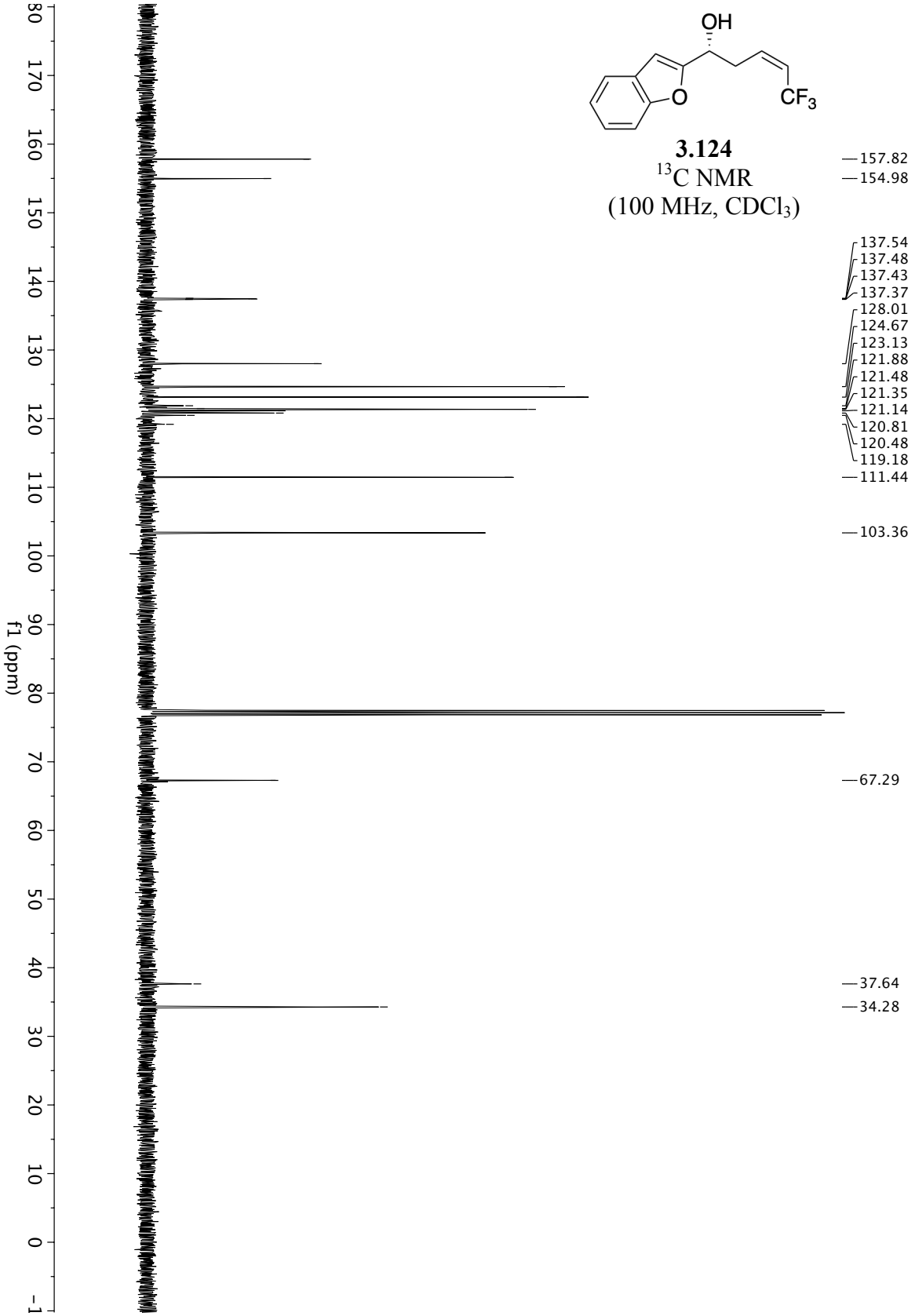
(376 MHz, $CDCl_3$)

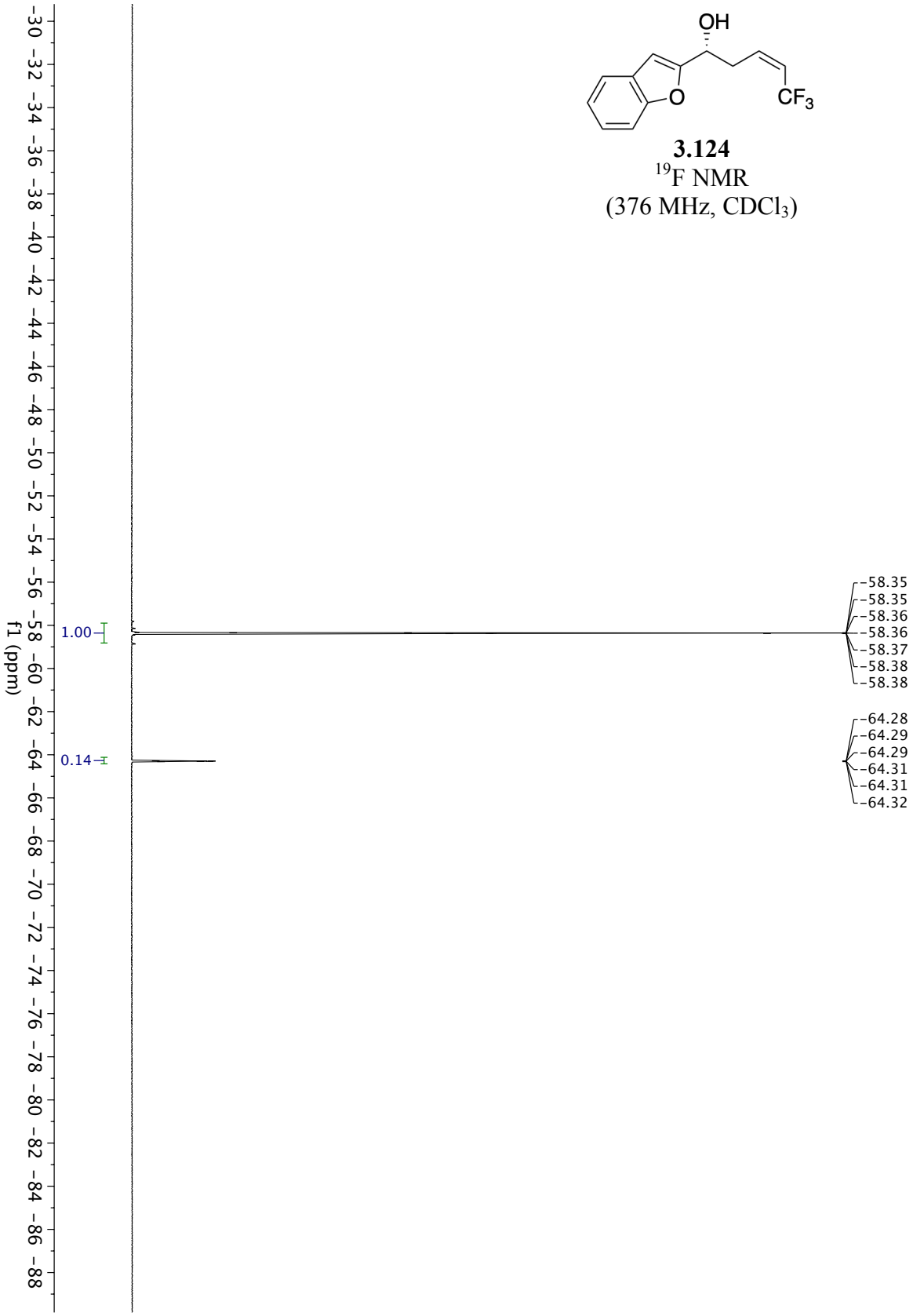

OH
O
CF3
3.123
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.11
0.18
1.03
1.02
0.08
0.94
1.00
1.13
1.70
0.40
1.07
0.43

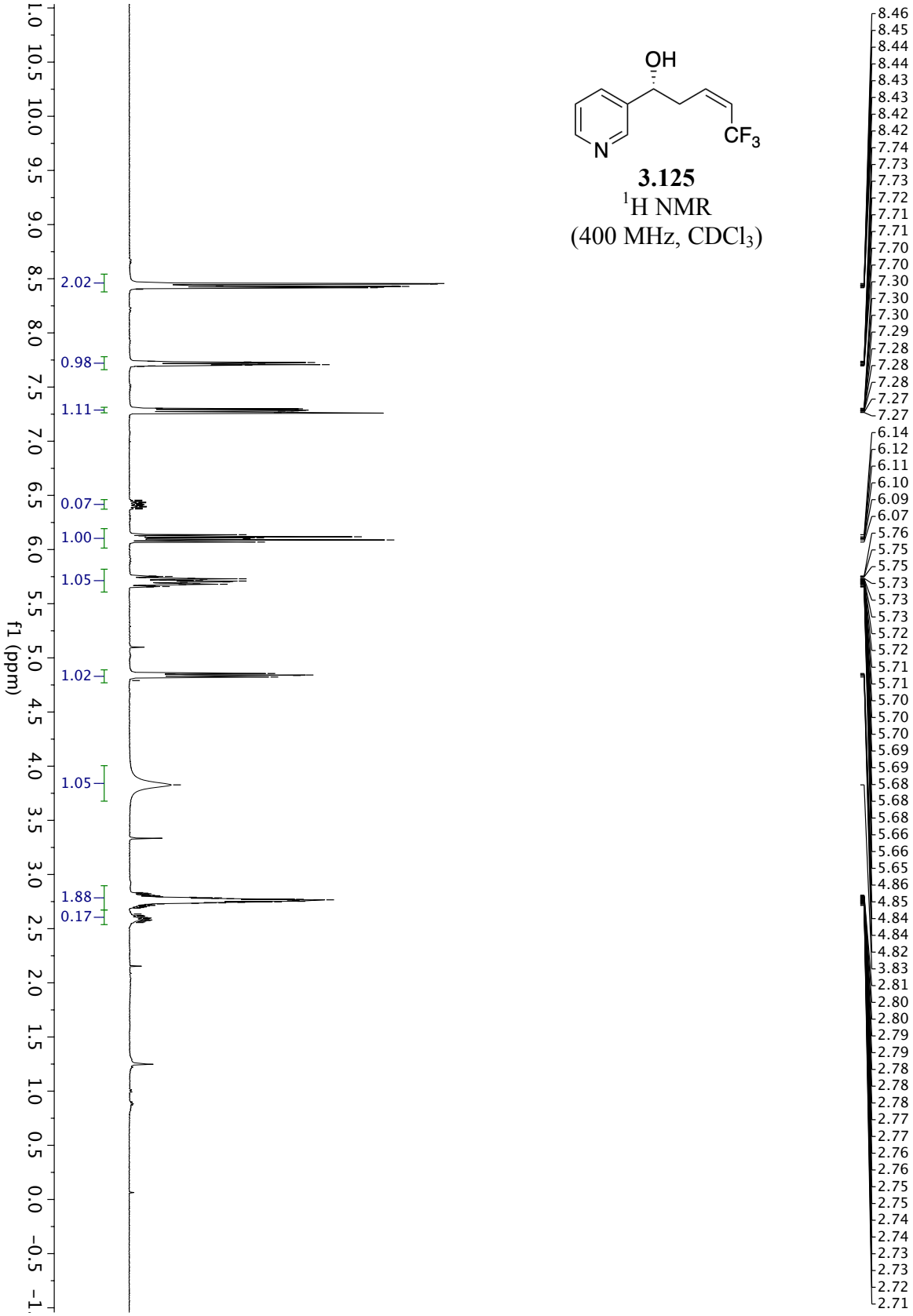

OH
O
CF3
3.123
13C NMR
(100 MHz, CDCl3)
155.35
155.29
142.53
142.50
124.61
121.90
121.13
120.80
120.46
120.13
110.41
106.63
66.82
37.65
34.31
f1 (ppm)

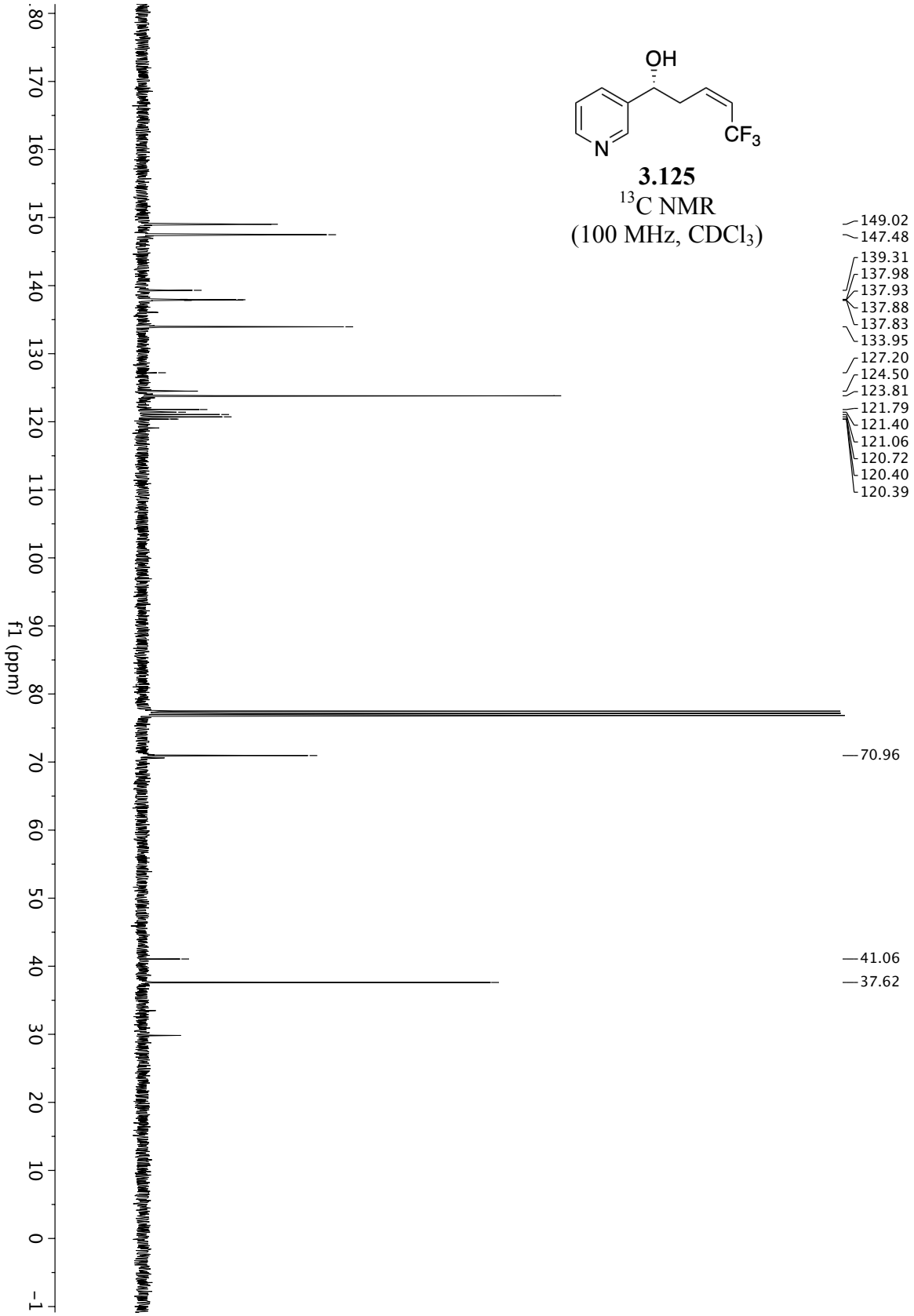

OH
O
CF3
3.123
19F NMR
(376 MHz, CDCl3)
f1 (ppm)
1.00
0.28
-58.42
-58.43
-58.44
-58.45
-64.33
-64.33
-64.35
-64.35

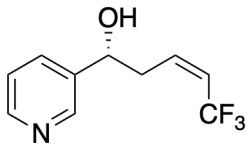

OH
O
CF3
3.124
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.08
1.11
0.72
1.41
1.07
0.14
1.00
1.09
1.14
2.01
0.26
1.08


OH
O
CF3
3.124
13C NMR
(100 MHz, CDCl3)
157.82
154.98
137.54
137.48
137.43
137.37
128.01
124.67
123.13
121.88
121.48
121.35
121.14
120.81
120.48
119.18
111.44
103.36
67.29
37.64
34.28
f1 (ppm)


OH
O
CF3
3.124
19F NMR
(376 MHz, CDCl3)
-58.35
-58.35
-58.36
-58.36
-58.37
-58.38
-58.38
-64.28
-64.29
-64.29
-64.31
-64.31
-64.32
1.00
0.14
f1 (ppm)
-30 -32 -34 -36 -38 -40 -42 -44 -46 -48 -50 -52 -54 -56 -58 -60 -62 -64 -66 -68 -70 -72 -74 -76 -78 -80 -82 -84 -86 -88


OH
N
CF3
3.125
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.02
0.98
1.11
0.07
1.00
1.05
1.02
1.05
1.88
0.17

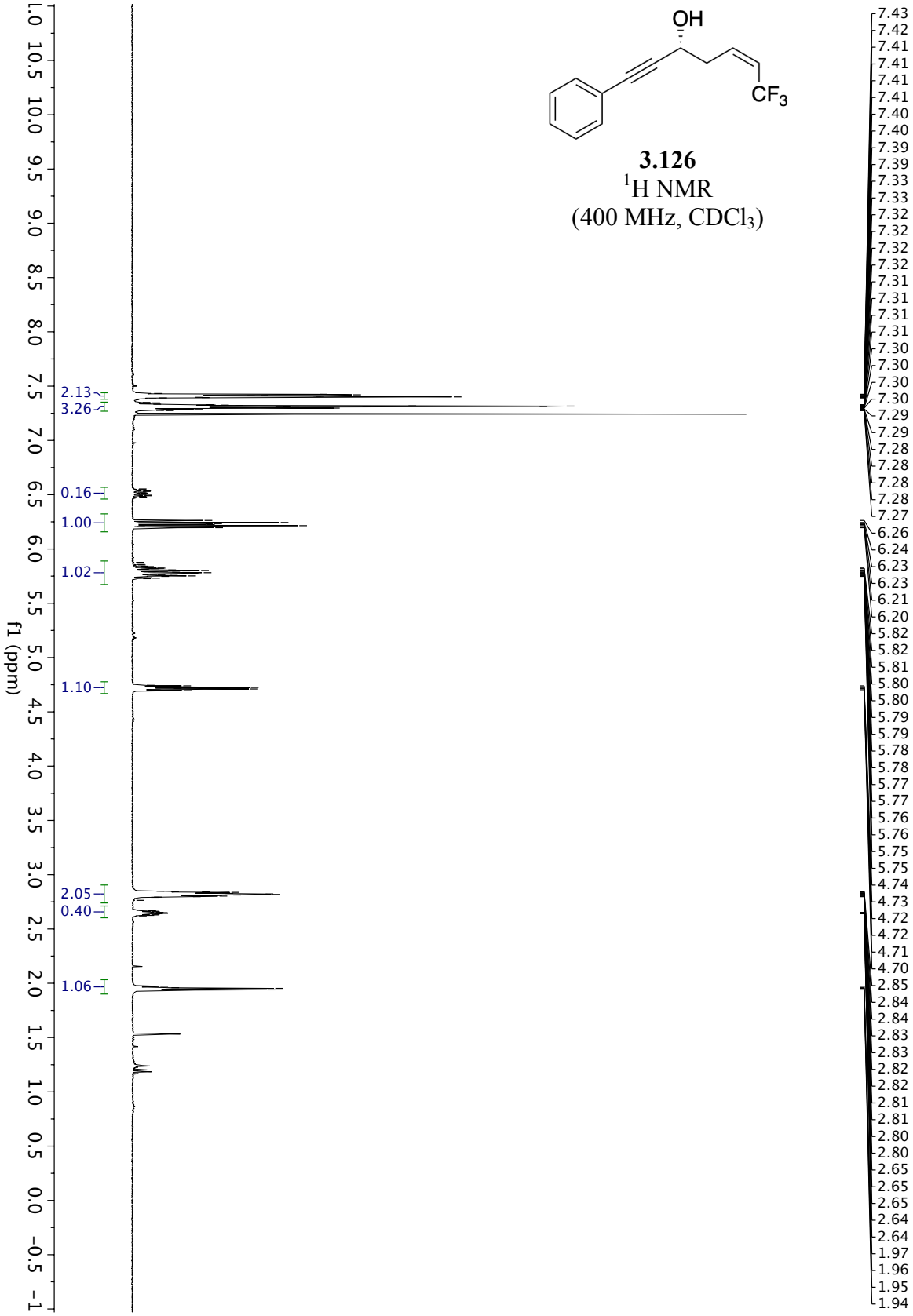

OH
N
CF3
3.125
13C NMR
(100 MHz, CDCl3)
149.02
147.48
139.31
137.98
137.93
137.88
137.83
133.95
127.20
124.50
123.81
121.79
121.40
121.06
120.72
120.40
120.39
70.96
41.06
37.62
f1 (ppm)

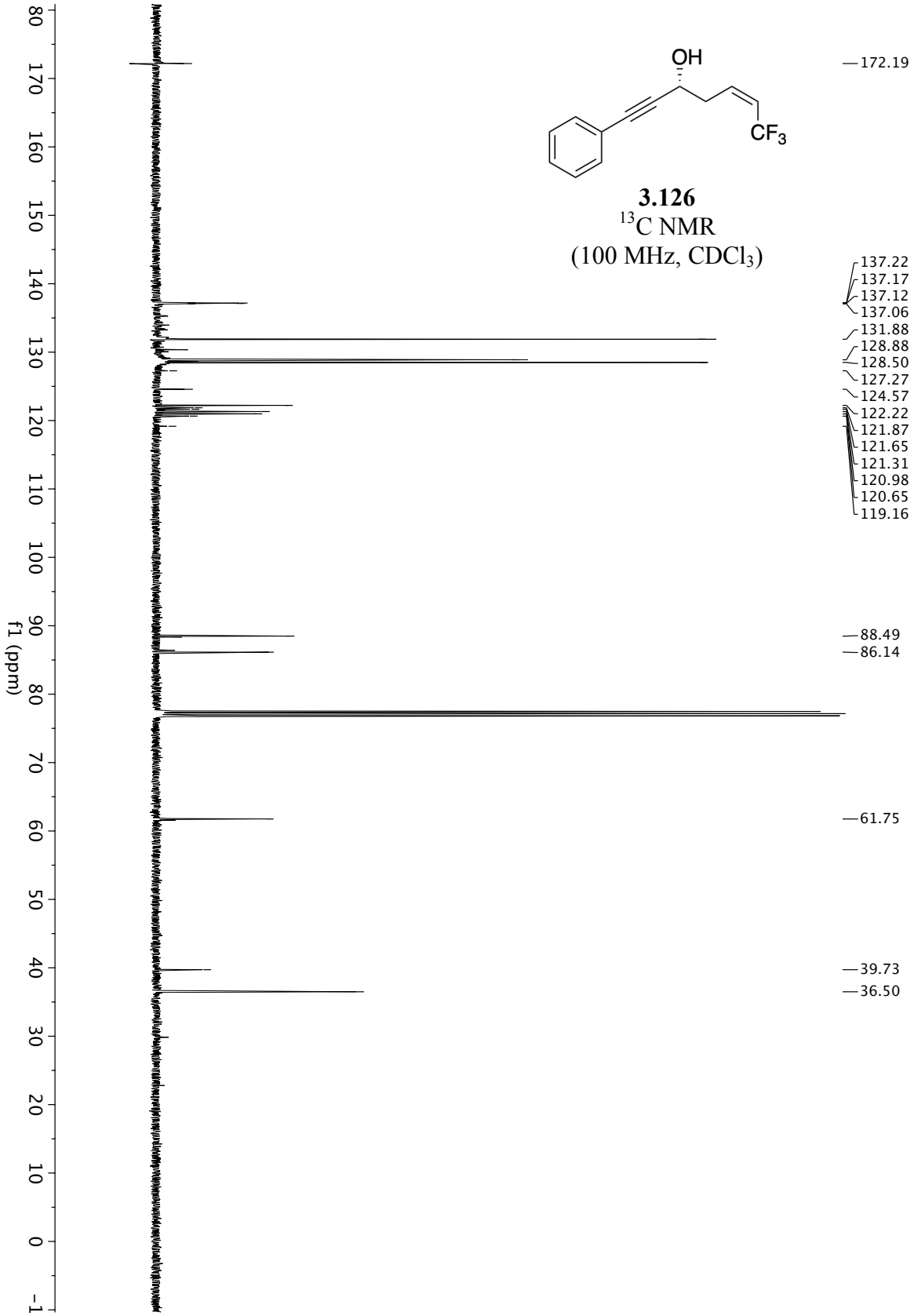


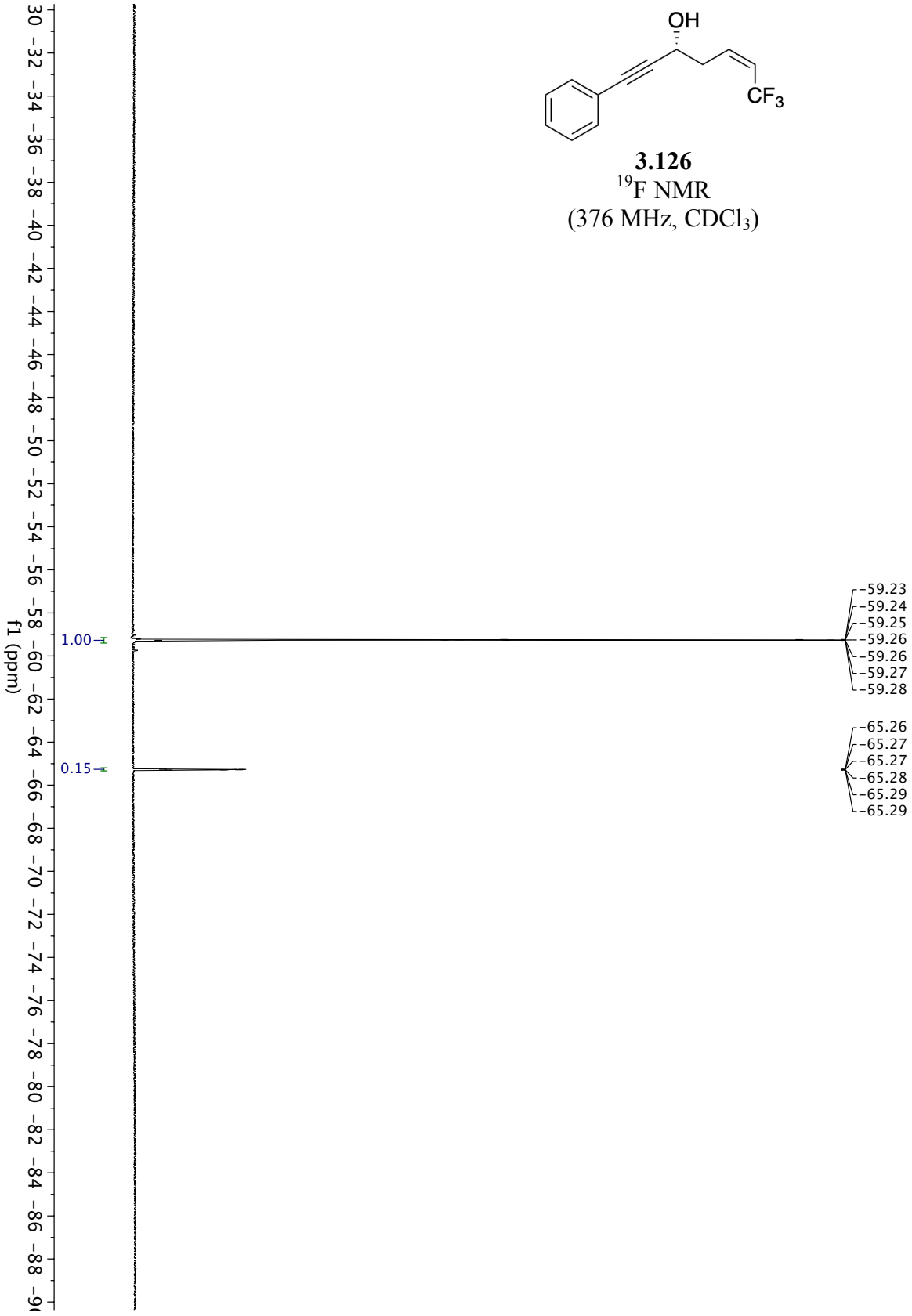
3.125

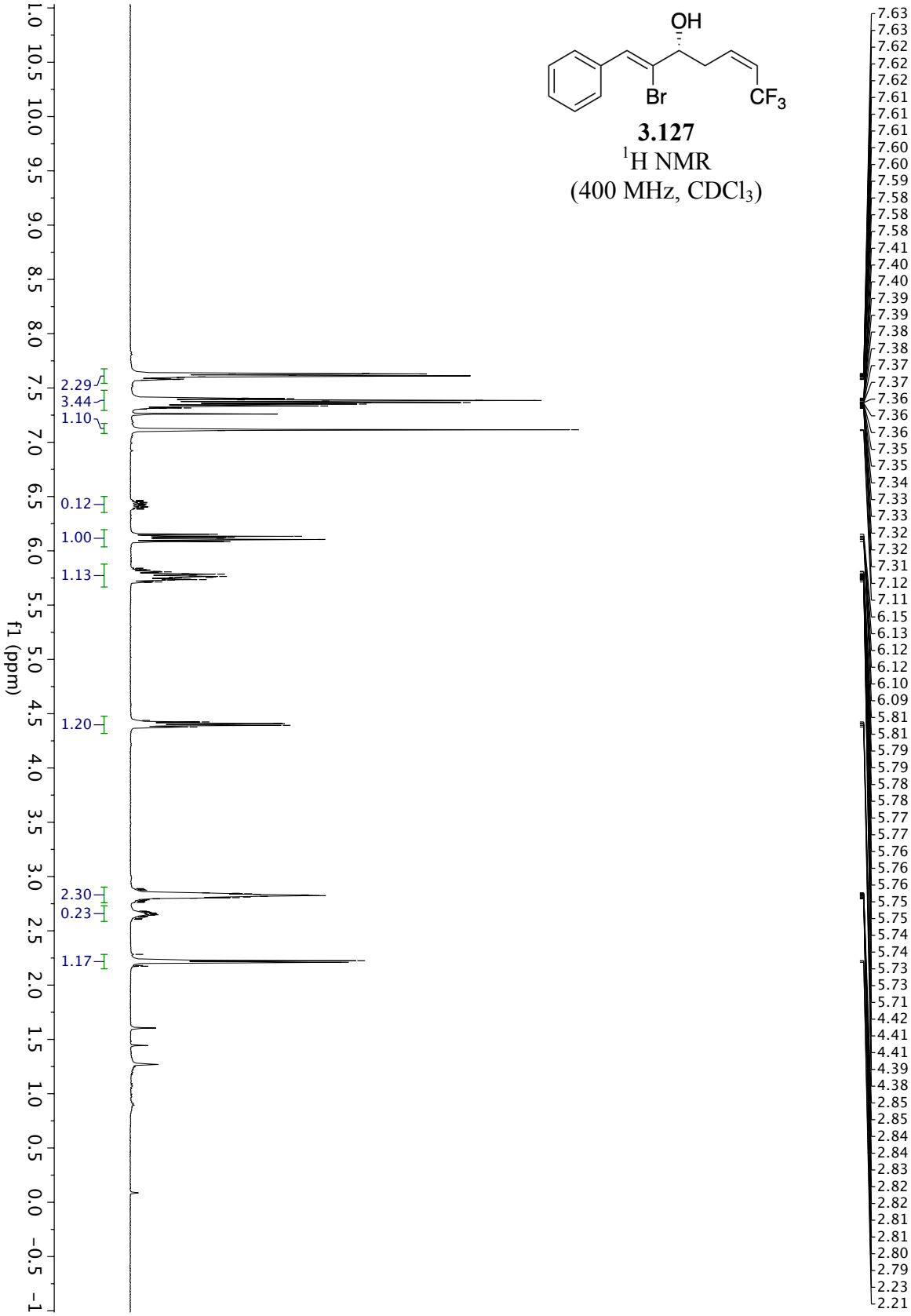
^{19}F NMR

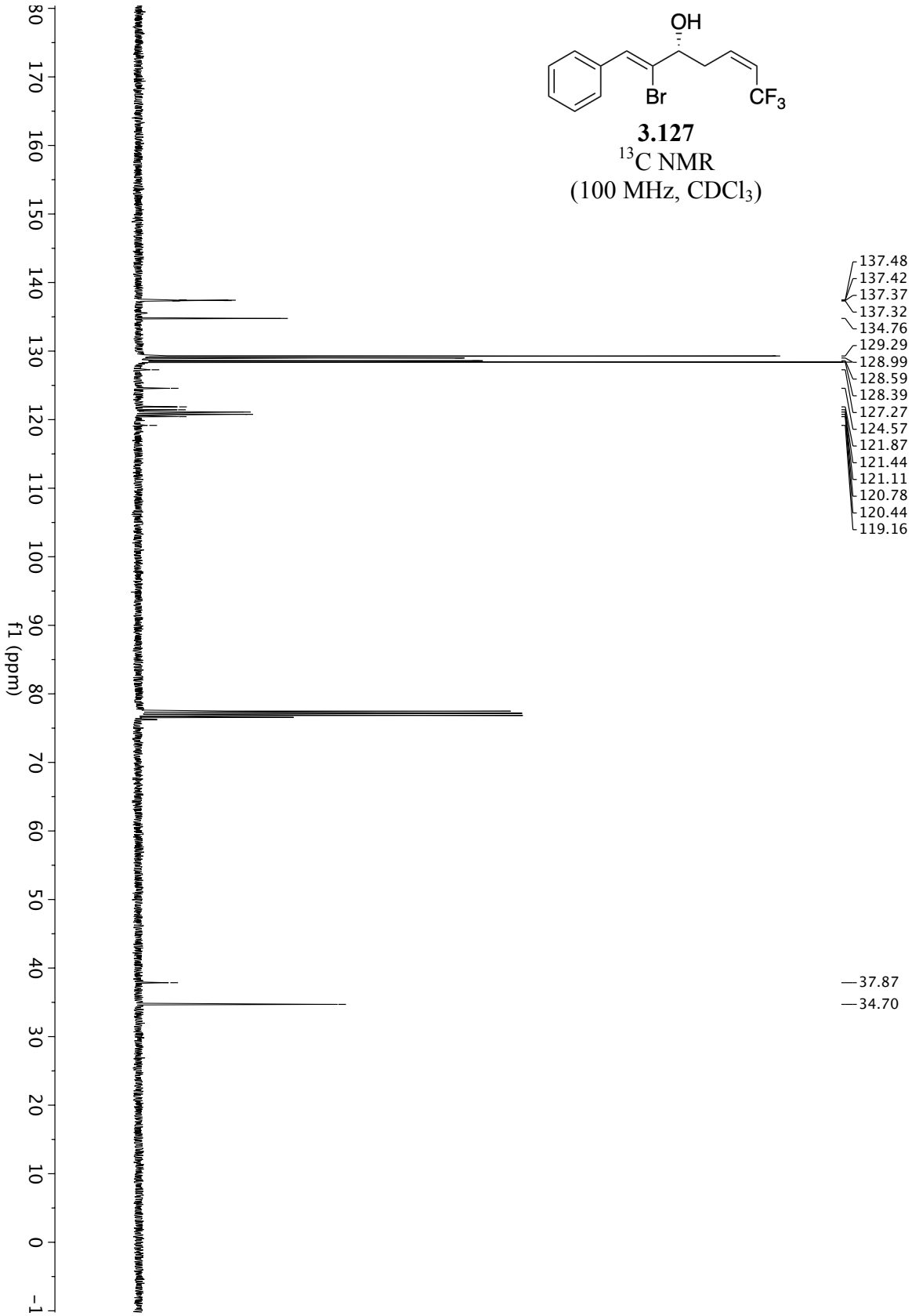
(376 MHz, $CDCl_3$)

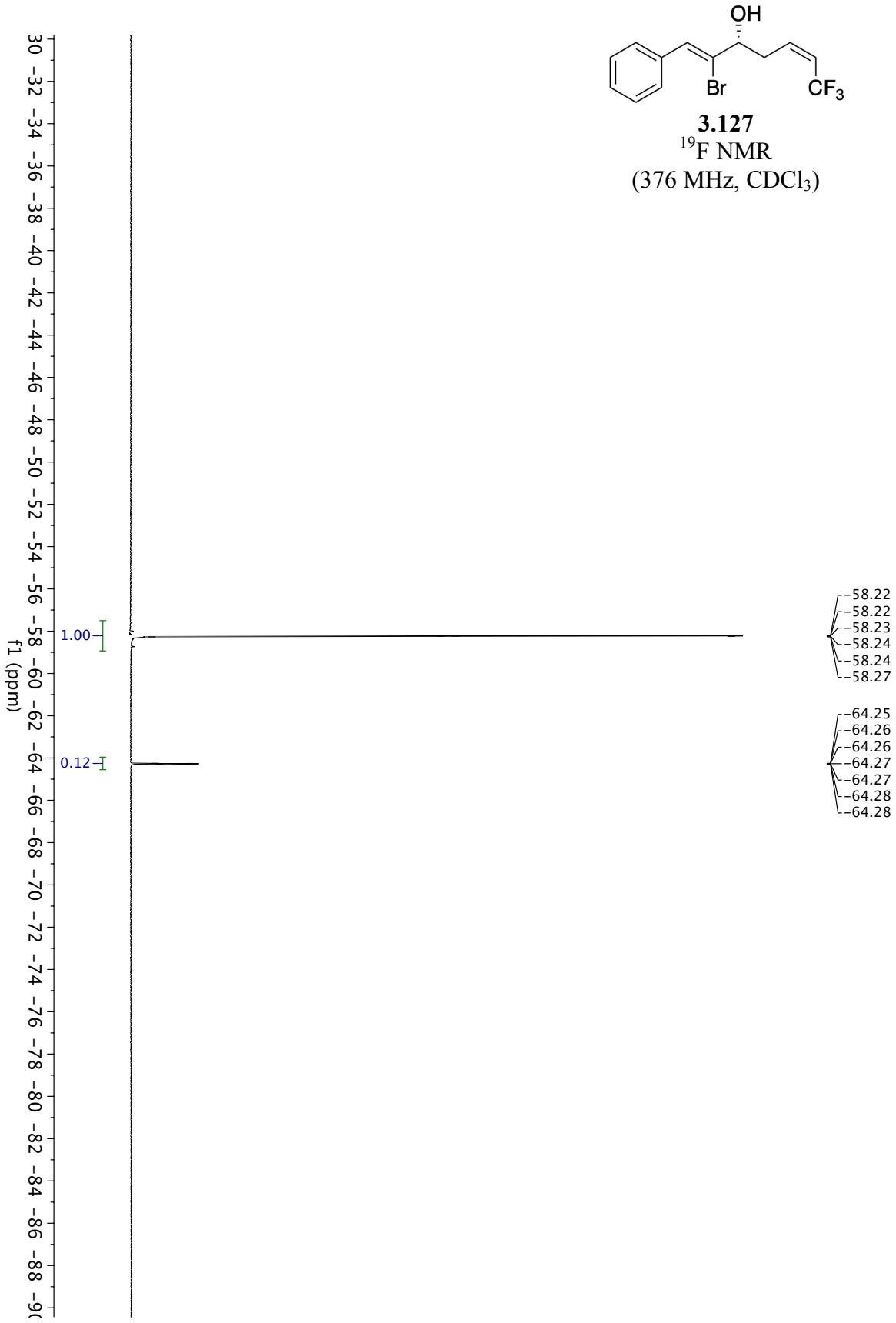

OH
CF3
3.126
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.13
3.26
0.16
1.00
1.02
1.10
2.05
0.40
1.06

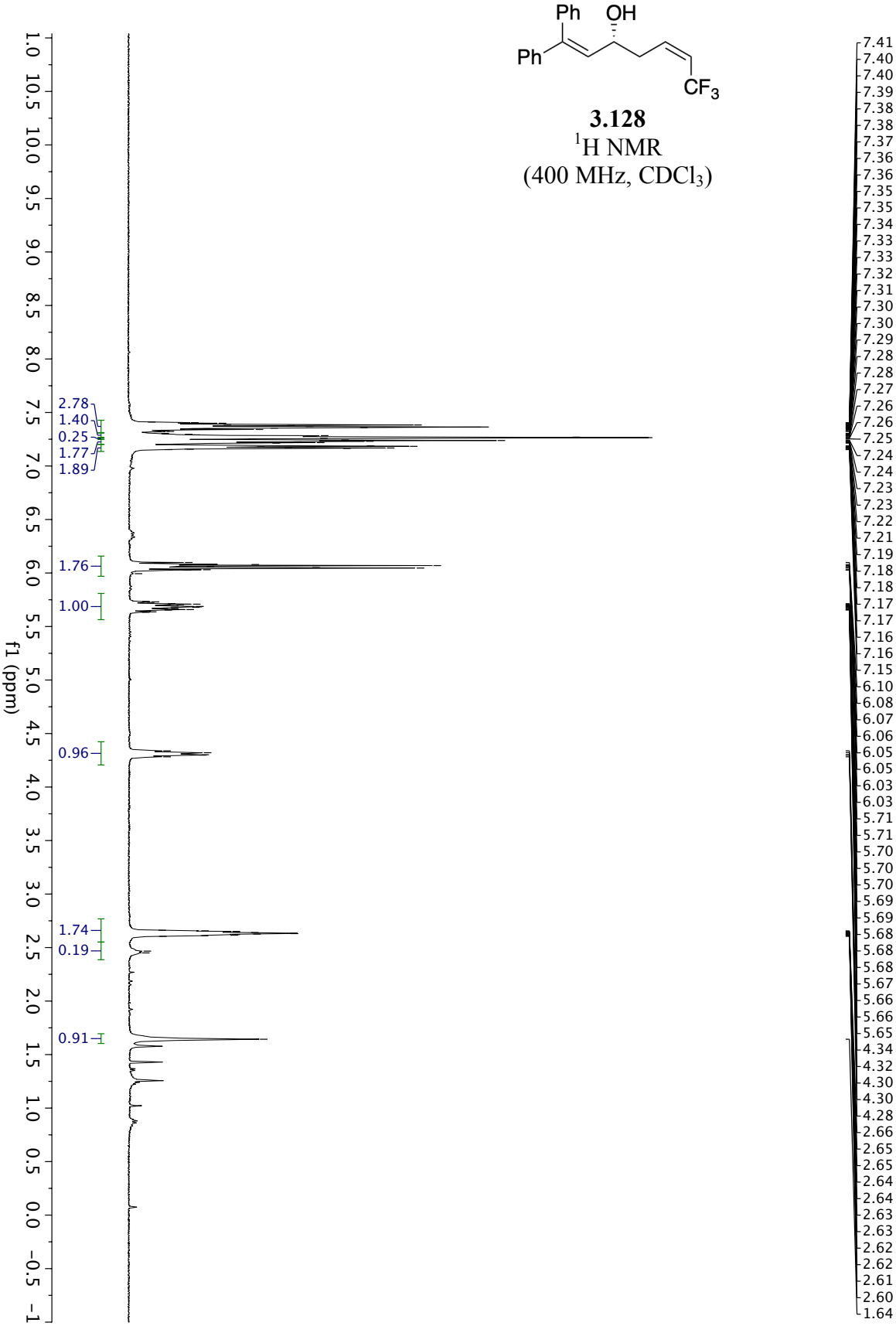

OH
CF3
3.126
13C NMR
(100 MHz, CDCl3)
172.19
137.22
137.17
137.12
137.06
131.88
128.88
128.50
127.27
124.57
122.22
121.87
121.65
121.31
120.98
120.65
119.16
88.49
86.14
61.75
39.73
36.50
f1 (ppm)

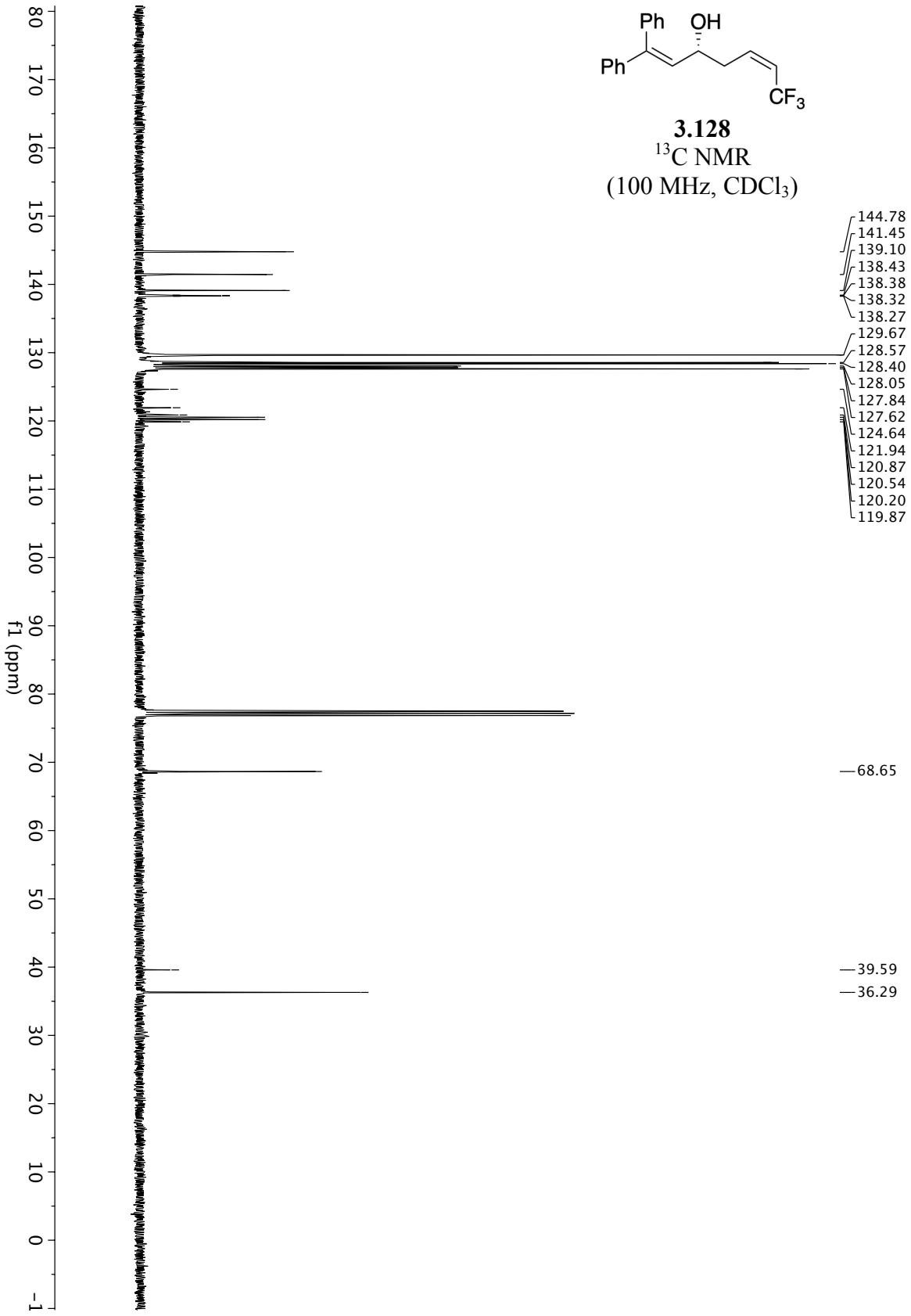

OH
CF3
3.126
19F NMR
(376 MHz, CDCl3)
f1 (ppm)
1.00
0.15
-59.23
-59.24
-59.25
-59.26
-59.26
-59.27
-59.28
-65.26
-65.27
-65.27
-65.28
-65.29
-65.29


OH
Br
CF3
3.127
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.29
3.44
1.10
0.12
1.00
1.13
1.20
2.30
0.23
1.17


OH
Br
CF3
3.127
13C NMR
(100 MHz, CDCl3)
137.48
137.42
137.37
137.32
134.76
129.29
128.99
128.59
128.39
127.27
124.57
121.87
121.44
121.11
120.78
120.44
119.16
37.87
34.70
f1 (ppm)


OH
Br
CF3
3.127
19F NMR
(376 MHz, CDCl3)
f1 (ppm)
1.00
0.12
-58.22
-58.22
-58.23
-58.24
-58.24
-58.27
-64.25
-64.26
-64.26
-64.27
-64.27
-64.28
-64.28

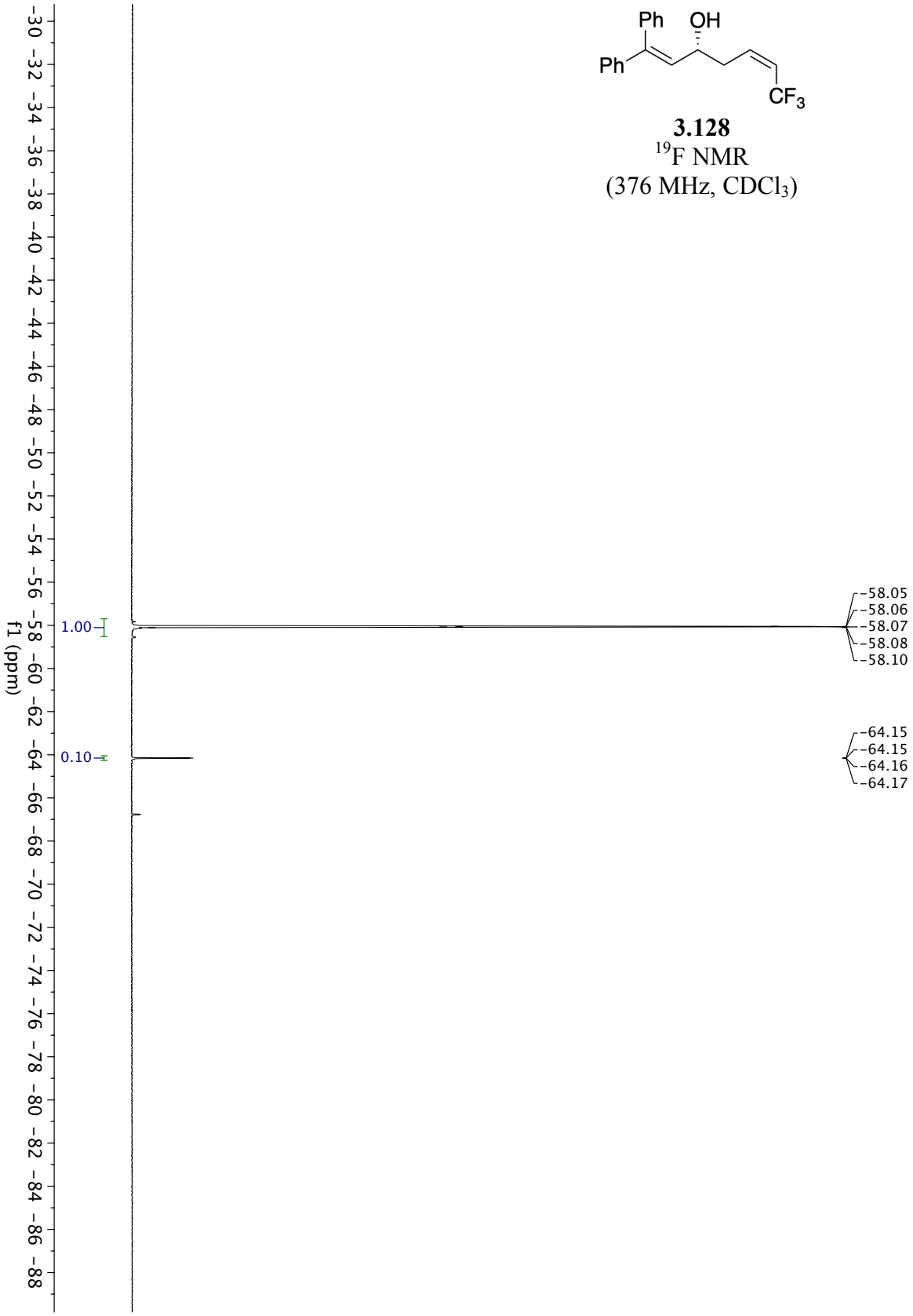

Ph
OH
Ph
CF3
3.128
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.78
1.40
0.25
1.77
1.89
1.76
1.00
0.96
1.74
0.19
0.91

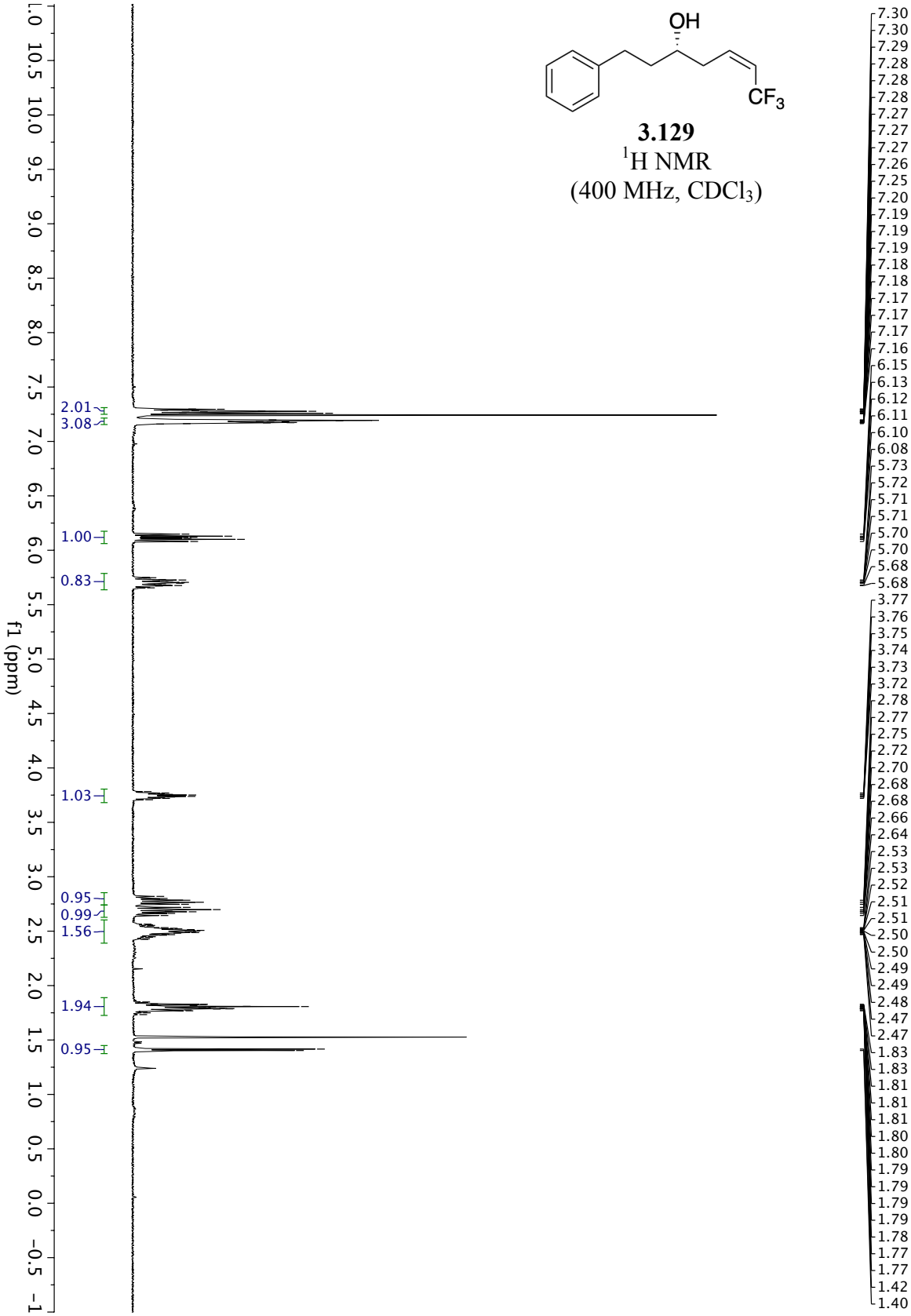


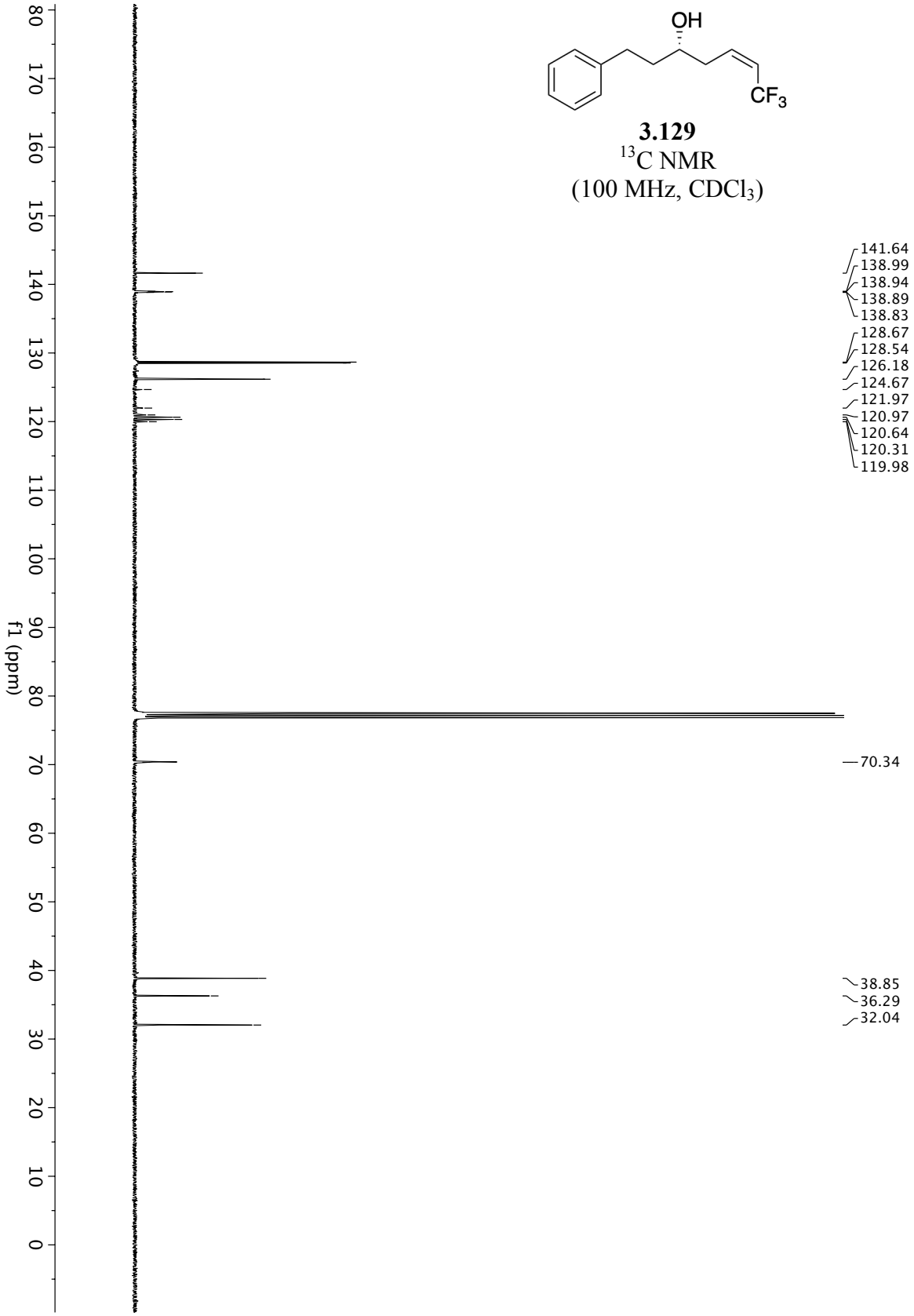
3.128

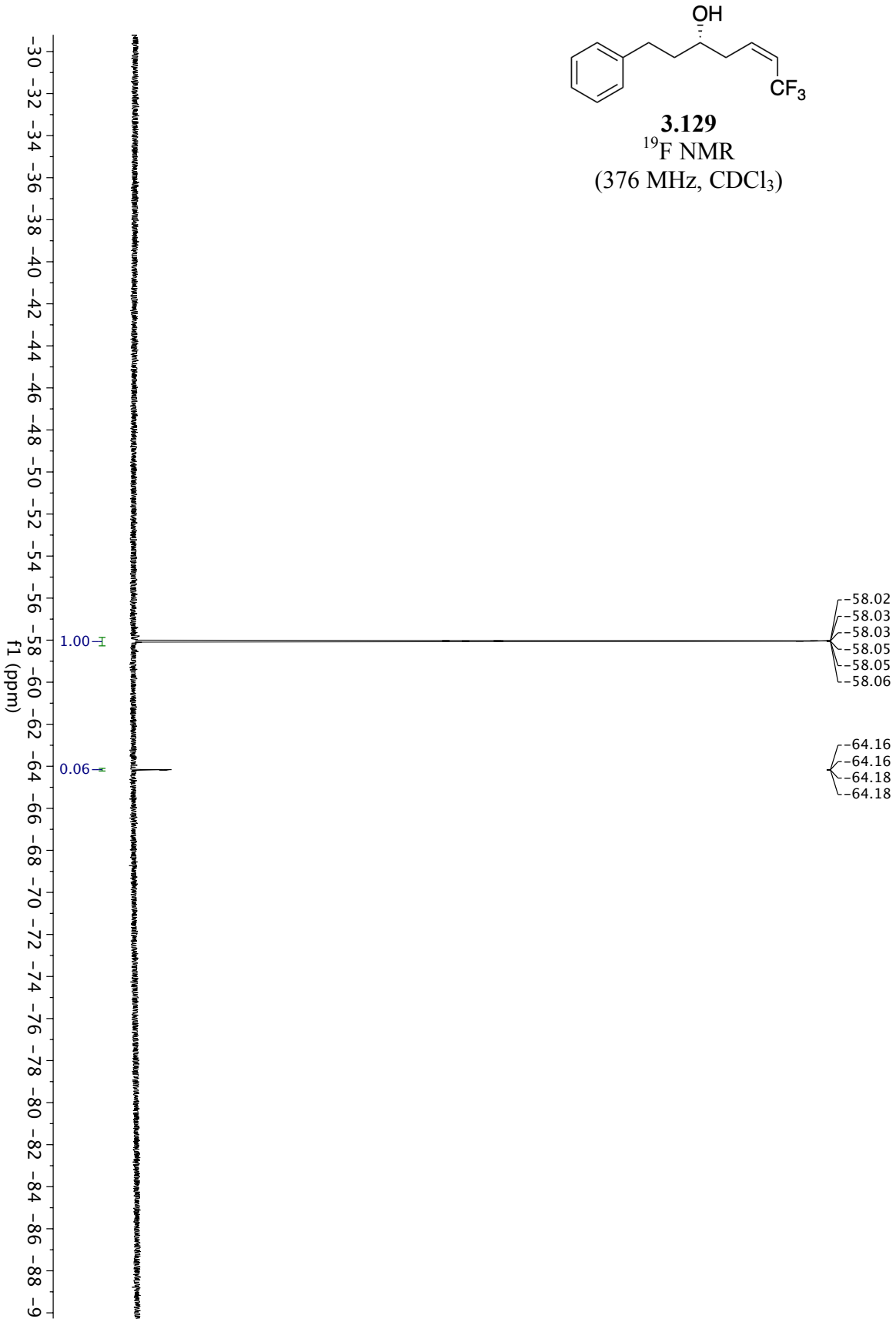
^{13}C NMR

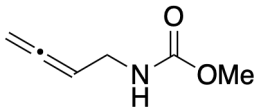
(100 MHz, $CDCl_3$)


Ph
OH
Ph
CF3
3.128
19F NMR
(376 MHz, CDCl3)
-58.05
-58.06
-58.07
-58.08
-58.10
-64.15
-64.15
-64.16
-64.17
1.00
0.10
f1 (ppm)
-30 -32 -34 -36 -38 -40 -42 -44 -46 -48 -50 -52 -54 -56 -58 -60 -62 -64 -66 -68 -70 -72 -74 -76 -78 -80 -82 -84 -86 -88

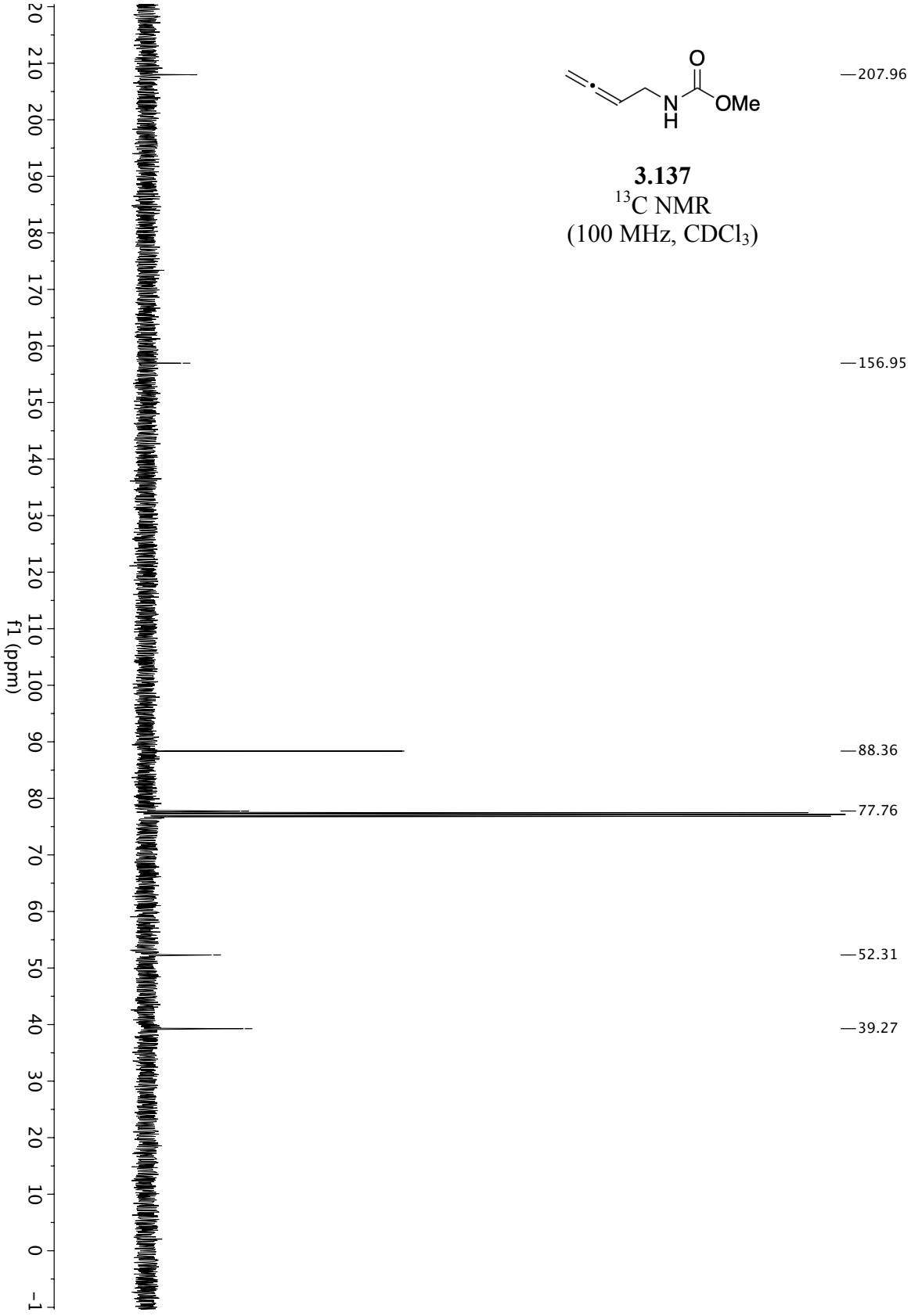

OH
CF3
3.129
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.01
3.08
1.00
0.83
1.03
0.95
0.99
1.56
1.94
0.95


OH
CF3
3.129
13C NMR
(100 MHz, CDCl3)
141.64
138.99
138.94
138.89
138.83
128.67
128.54
126.18
124.67
121.97
120.97
120.64
120.31
119.98
70.34
38.85
36.29
32.04
f1 (ppm)

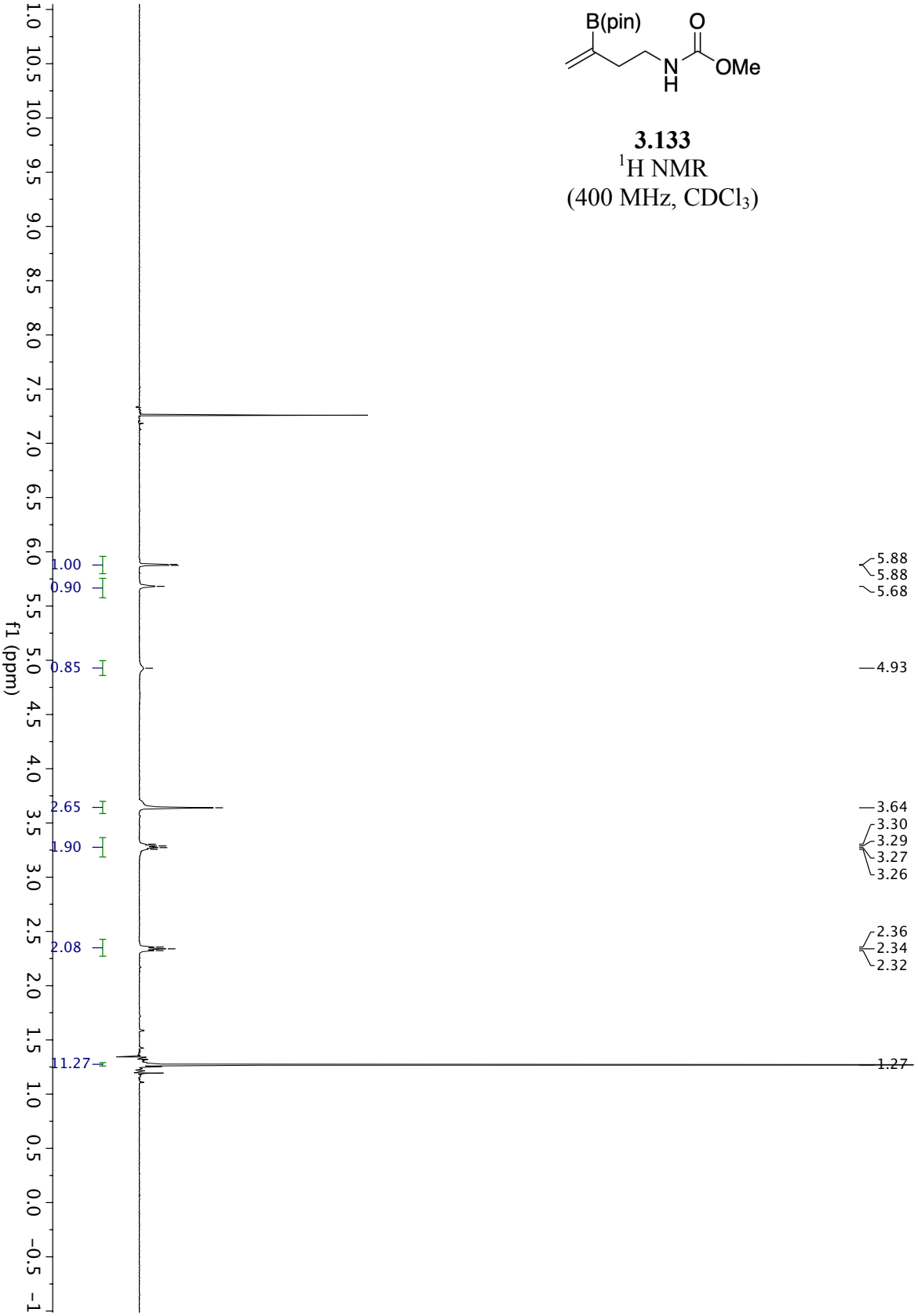

OH
CF3
3.129
19F NMR
(376 MHz, CDCl3)
f1 (ppm)
1.00
0.06
-58.02
-58.03
-58.03
-58.05
-58.05
-58.06
-64.16
-64.16
-64.18
-64.18

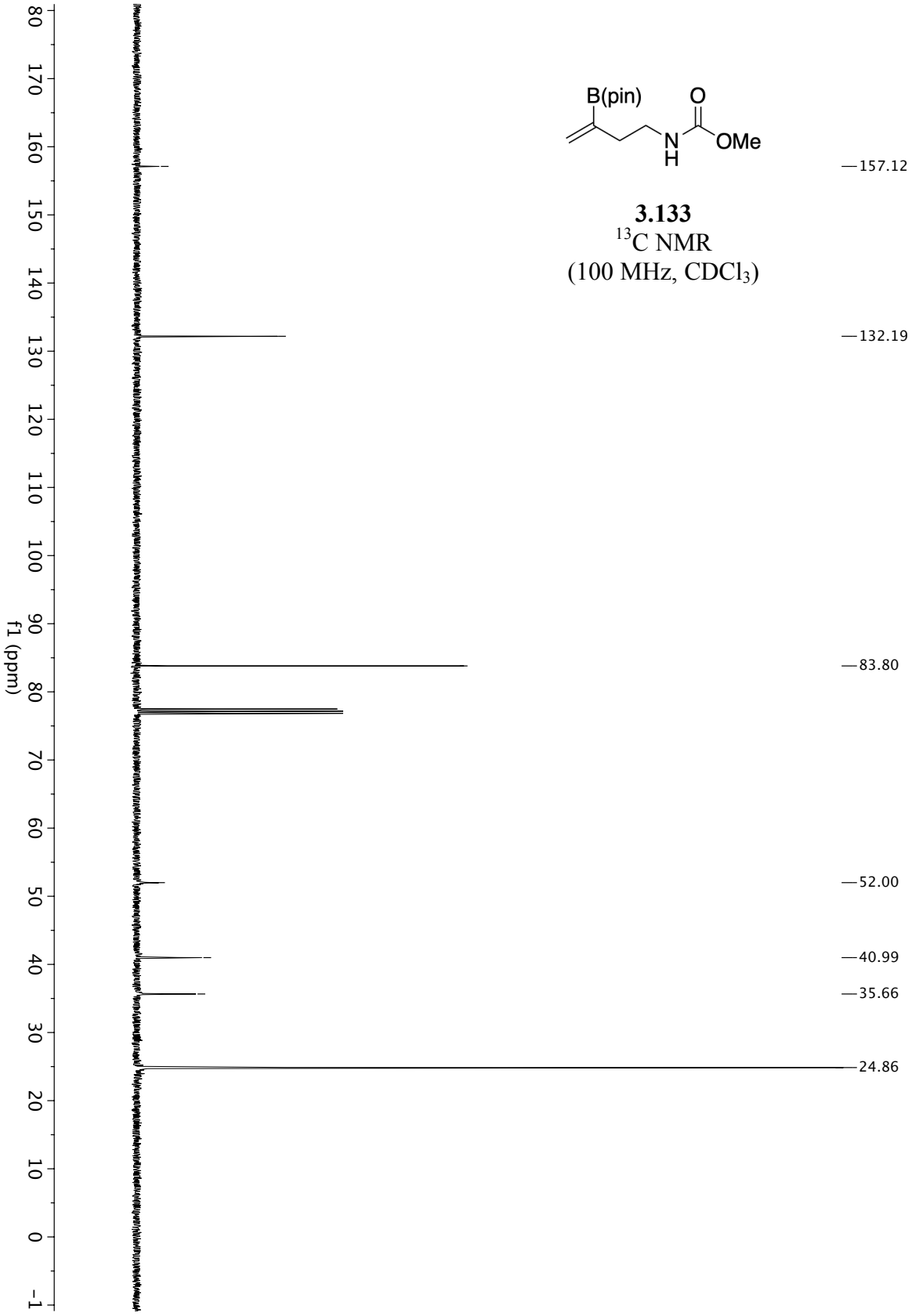


3.137
^{1}H NMR
(400 MHz, $CDCl_3$)

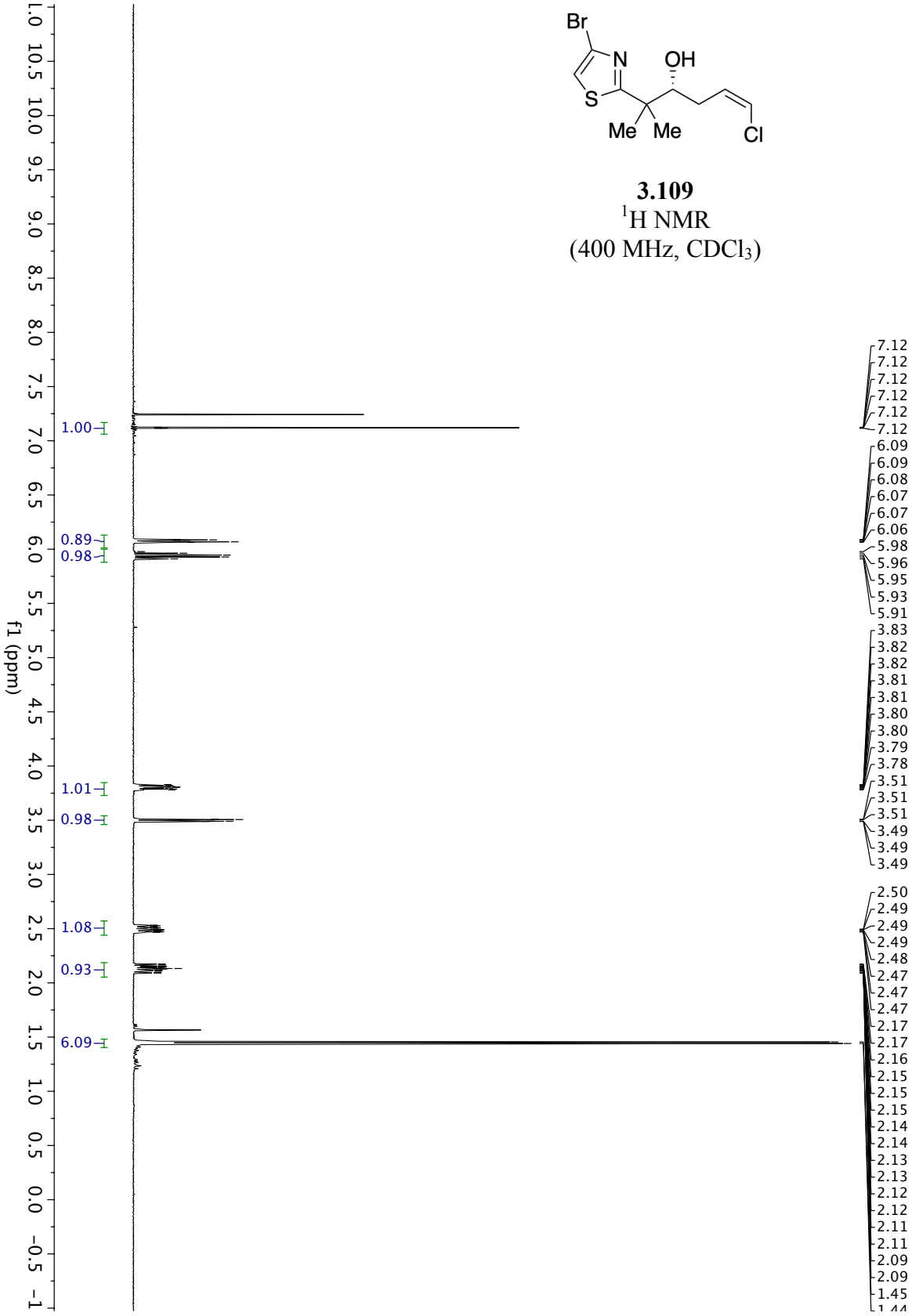


3.137
^{13}C NMR
(100 MHz, $CDCl_3$)

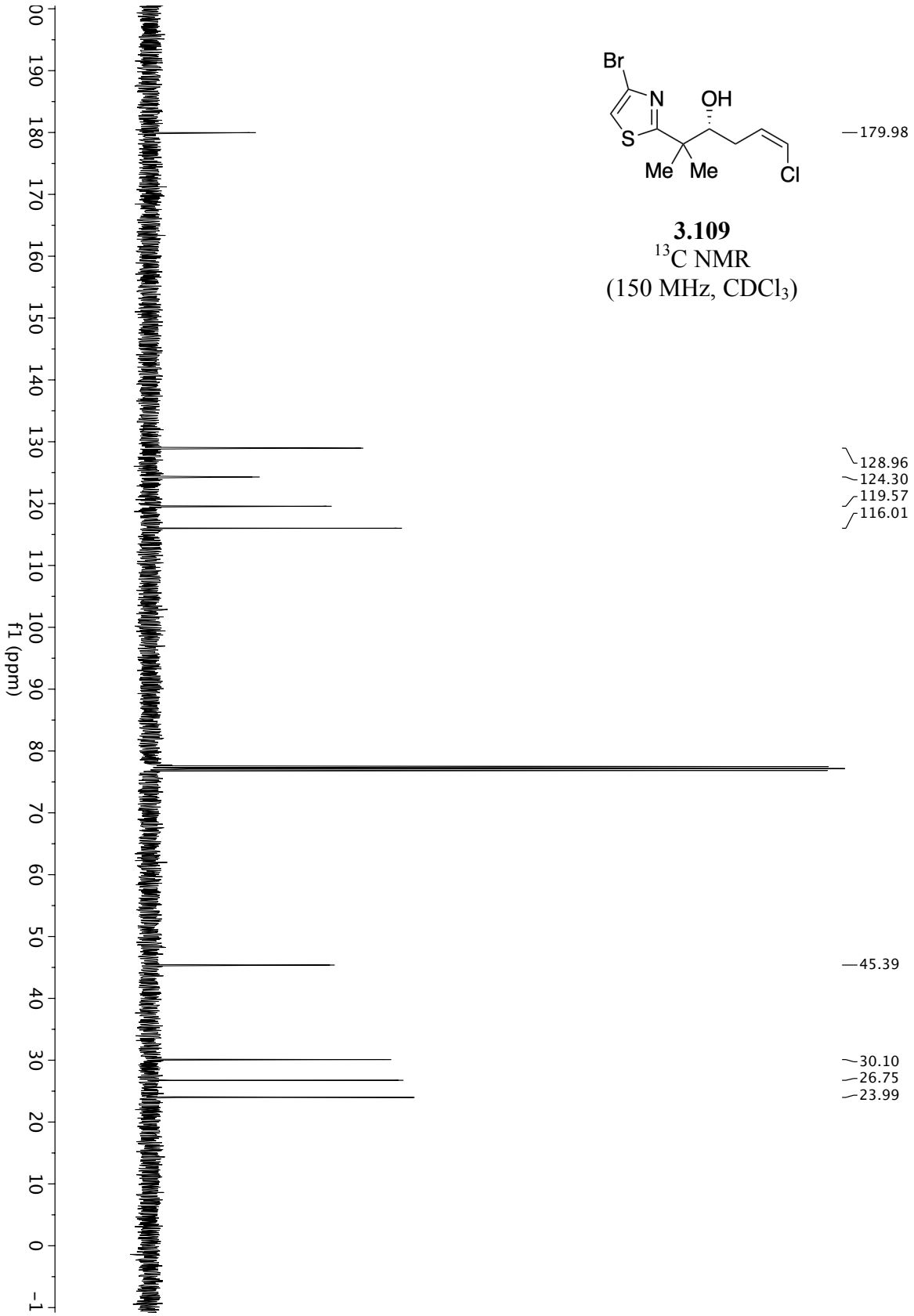

B(pin)
O
N
H
OMe
3.133
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.00
0.90
0.85
2.65
1.90
2.08
11.27
5.88
5.88
5.68
4.93
3.64
3.30
3.29
3.27
3.26
2.36
2.34
2.32
1.27



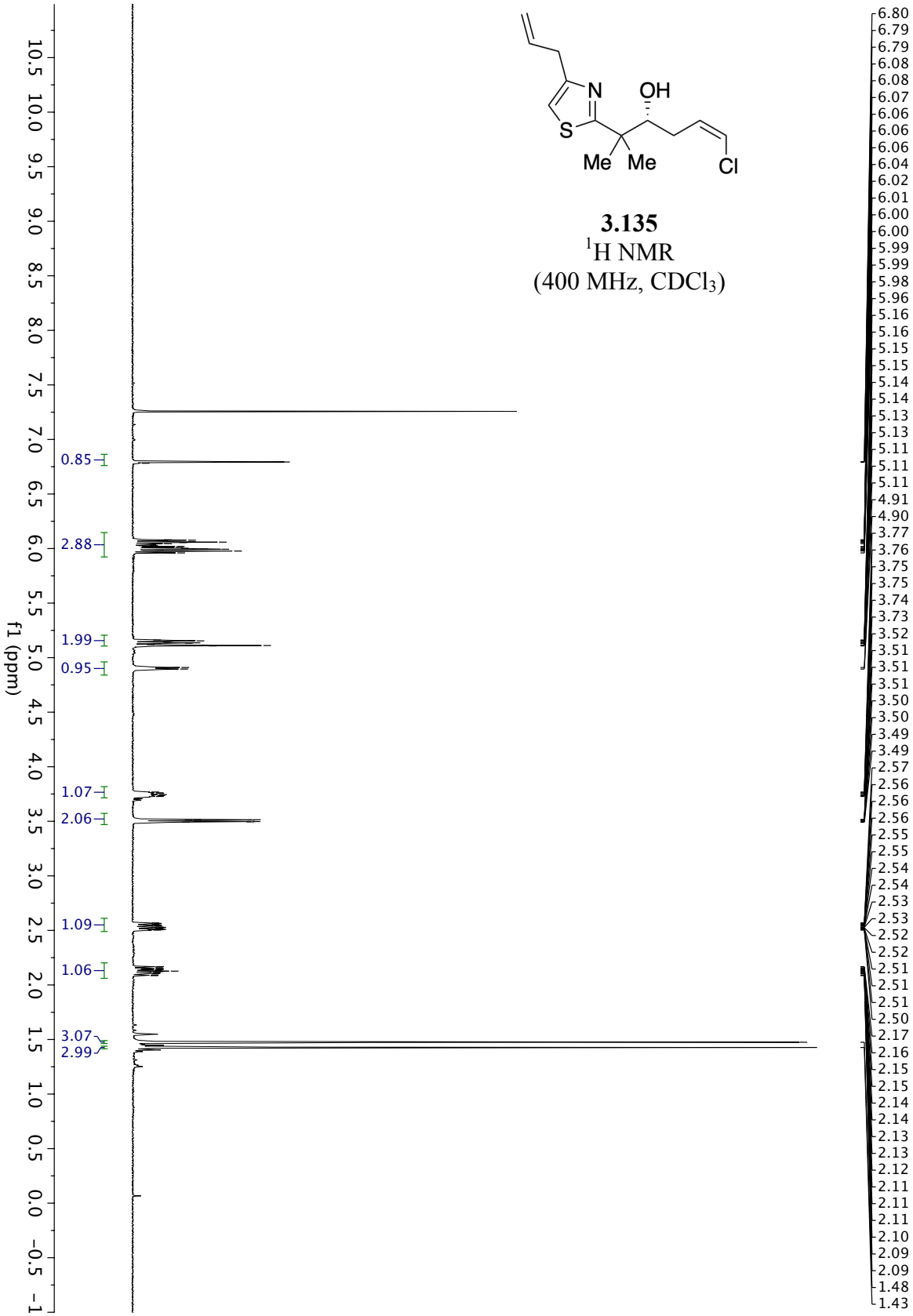
3.133
^{13}C NMR
(100 MHz, $CDCl_3$)



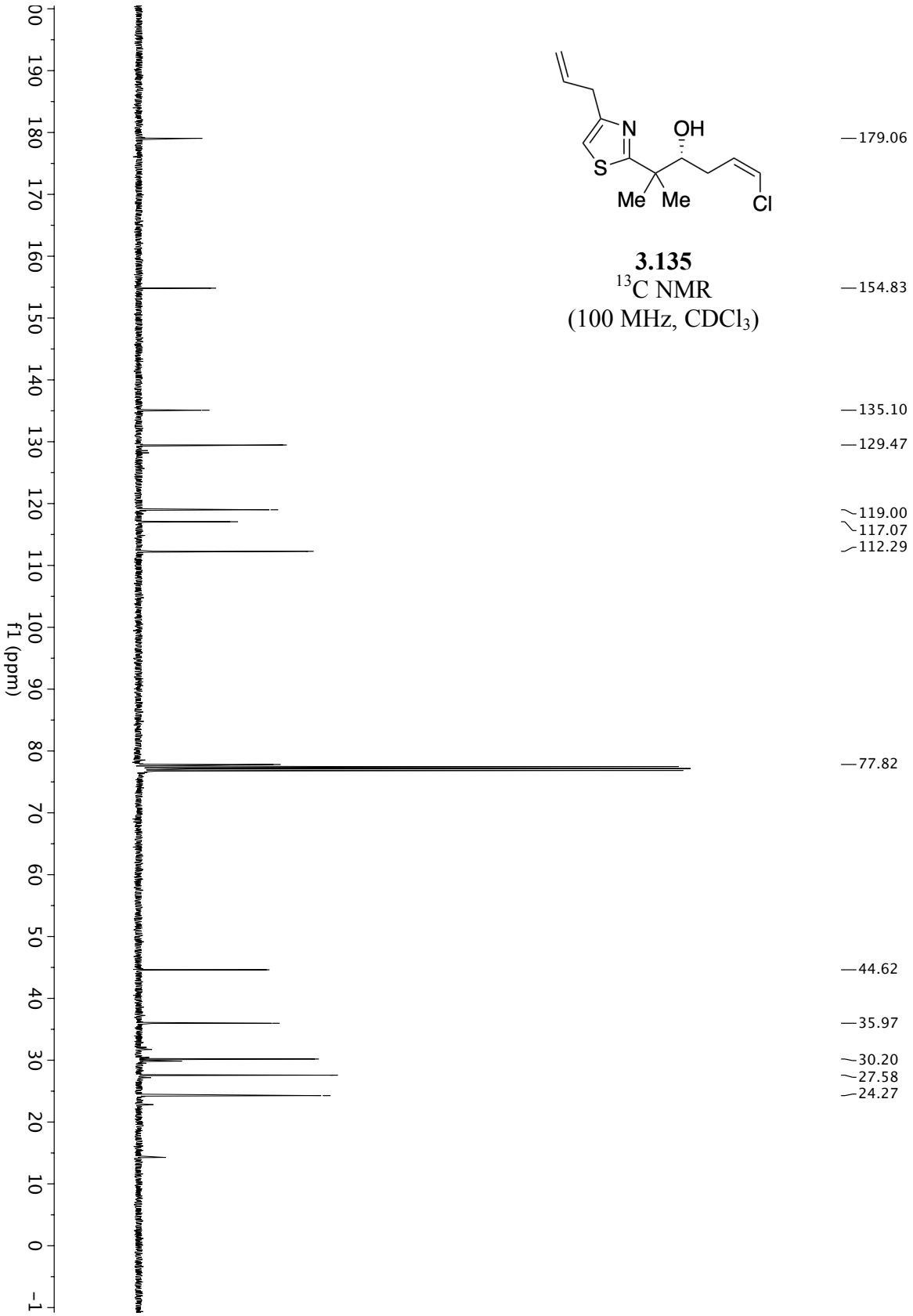
3.109
^{1}H NMR
(400 MHz, $CDCl_3$)

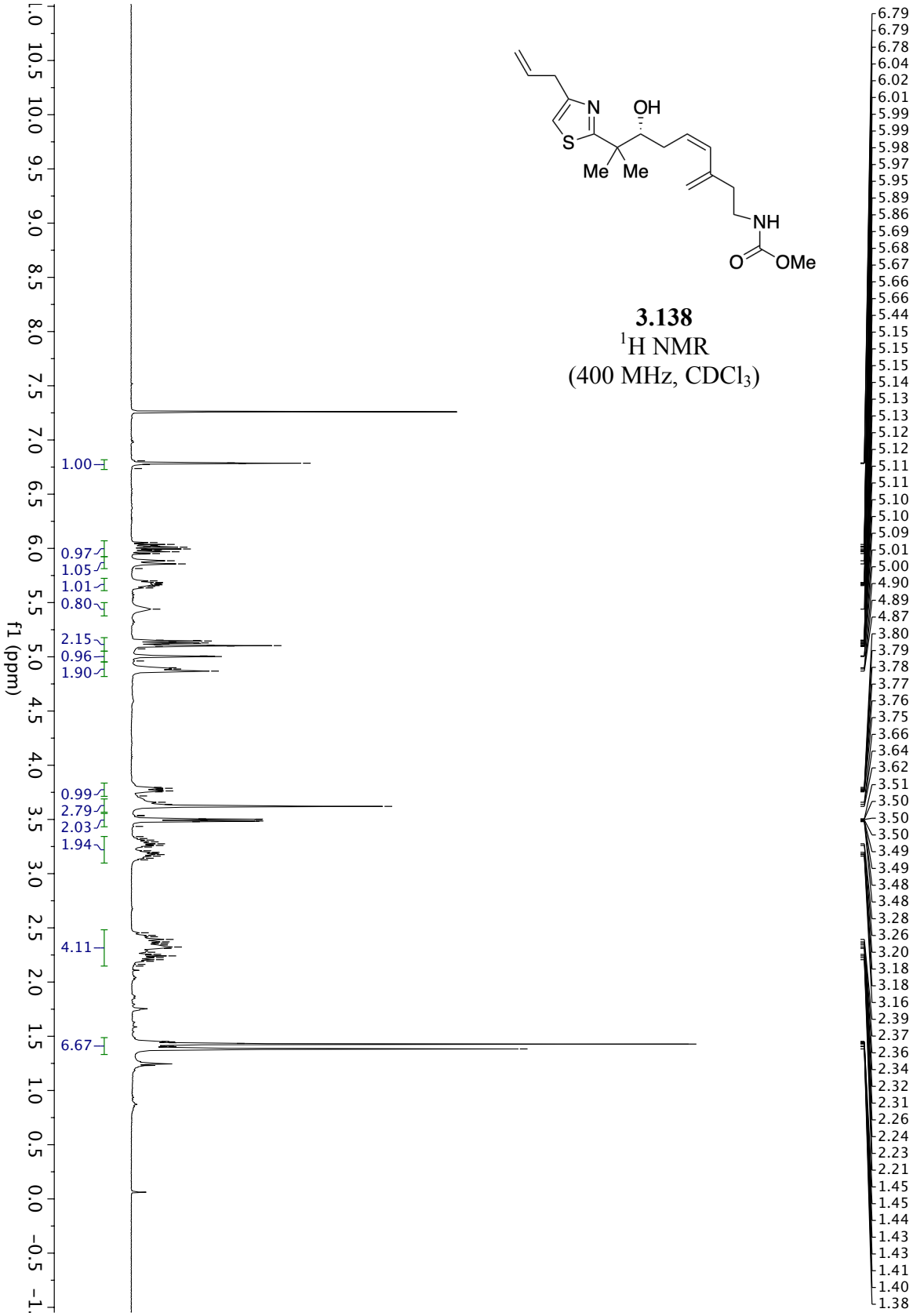


3.109
^{13}C NMR
(150 MHz, $CDCl_3$)

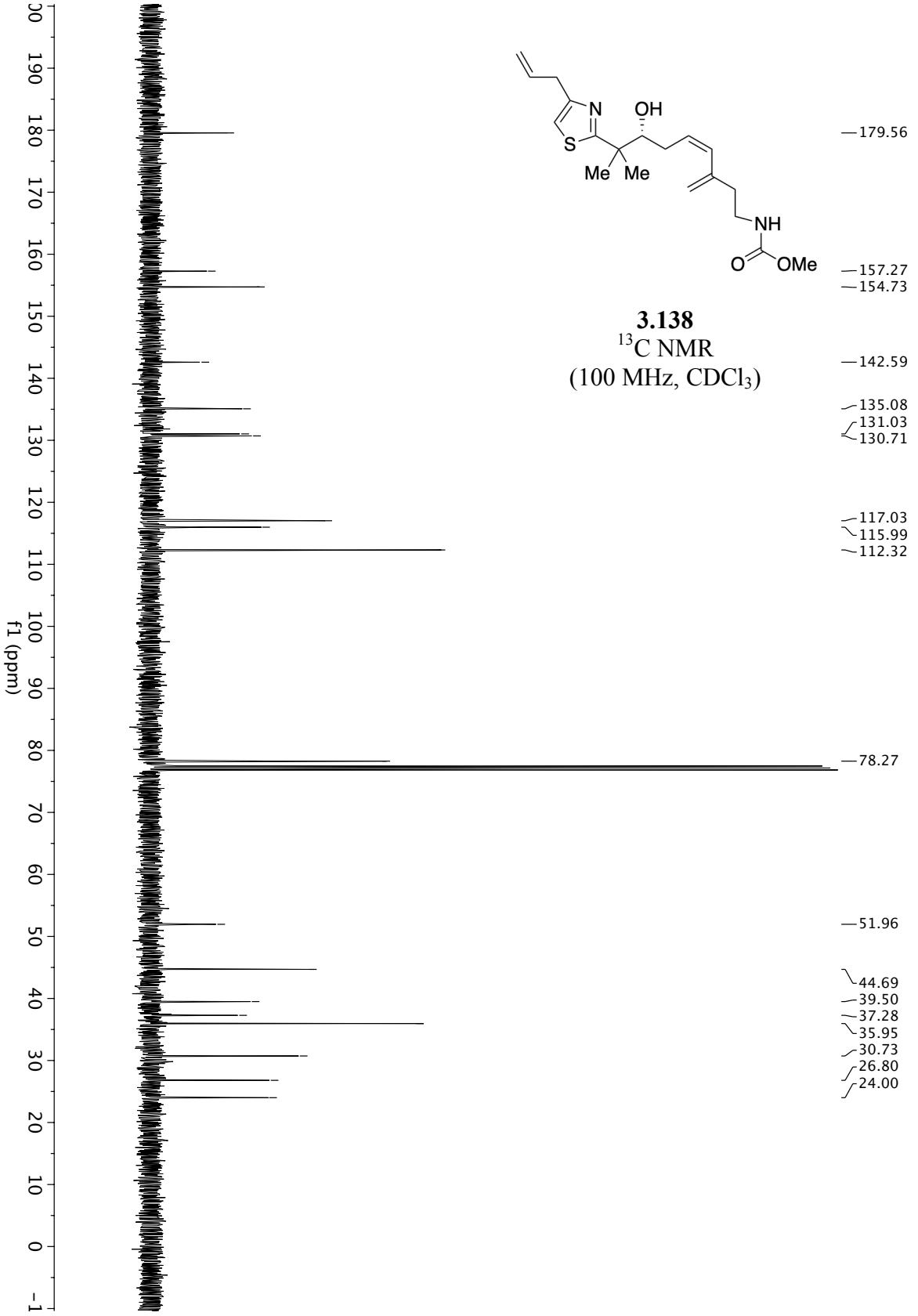


3.135
^{1}H NMR
(400 MHz, $CDCl_3$)

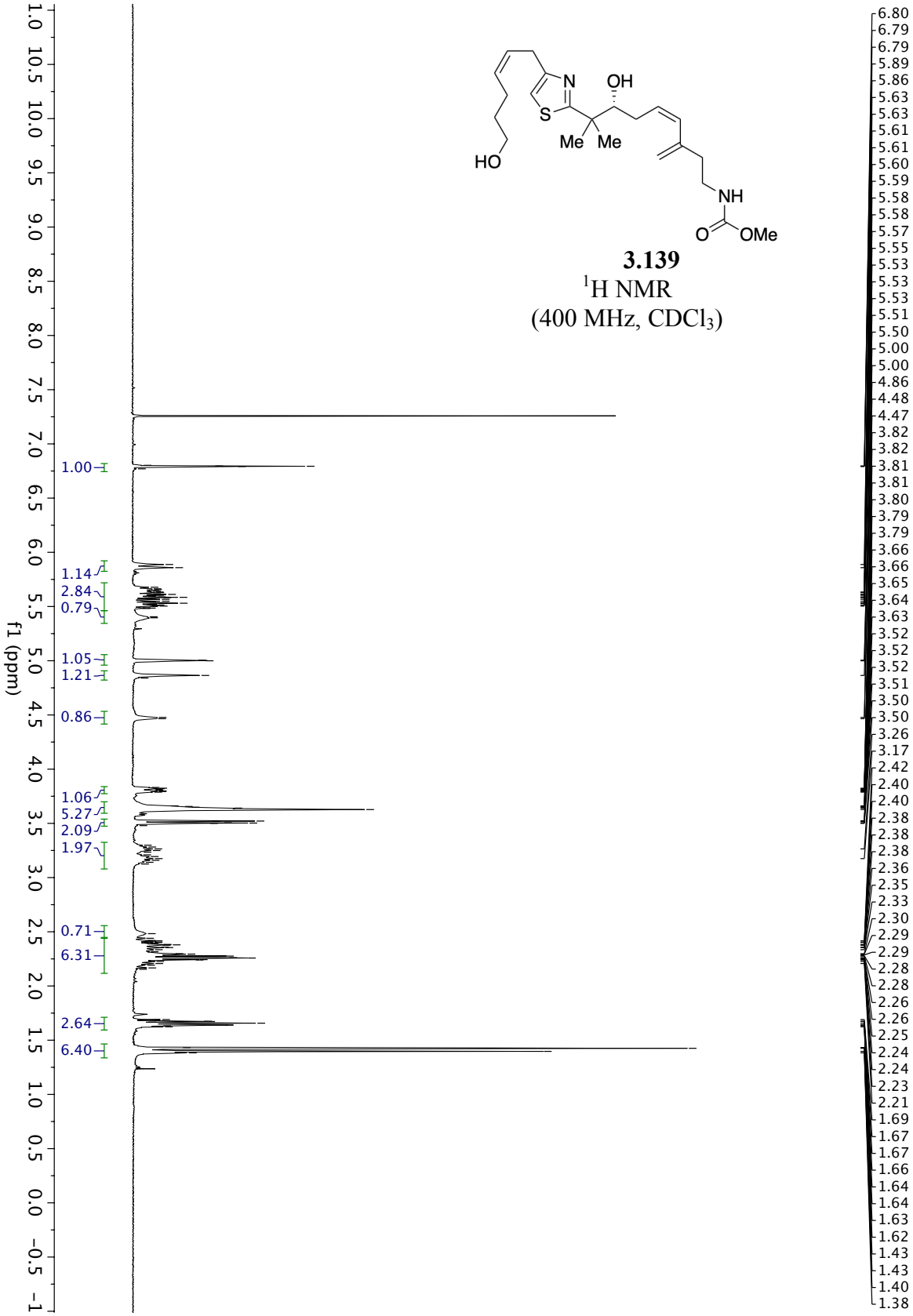

N
OH
S
Me
Me
Cl
3.135
13C NMR
(100 MHz, CDCl3)
179.06
154.83
135.10
129.47
119.00
117.07
112.29
77.82
44.62
35.97
30.20
27.58
24.27
f1 (ppm)



3.138
^{1}H NMR
(400 MHz, $CDCl_3$)



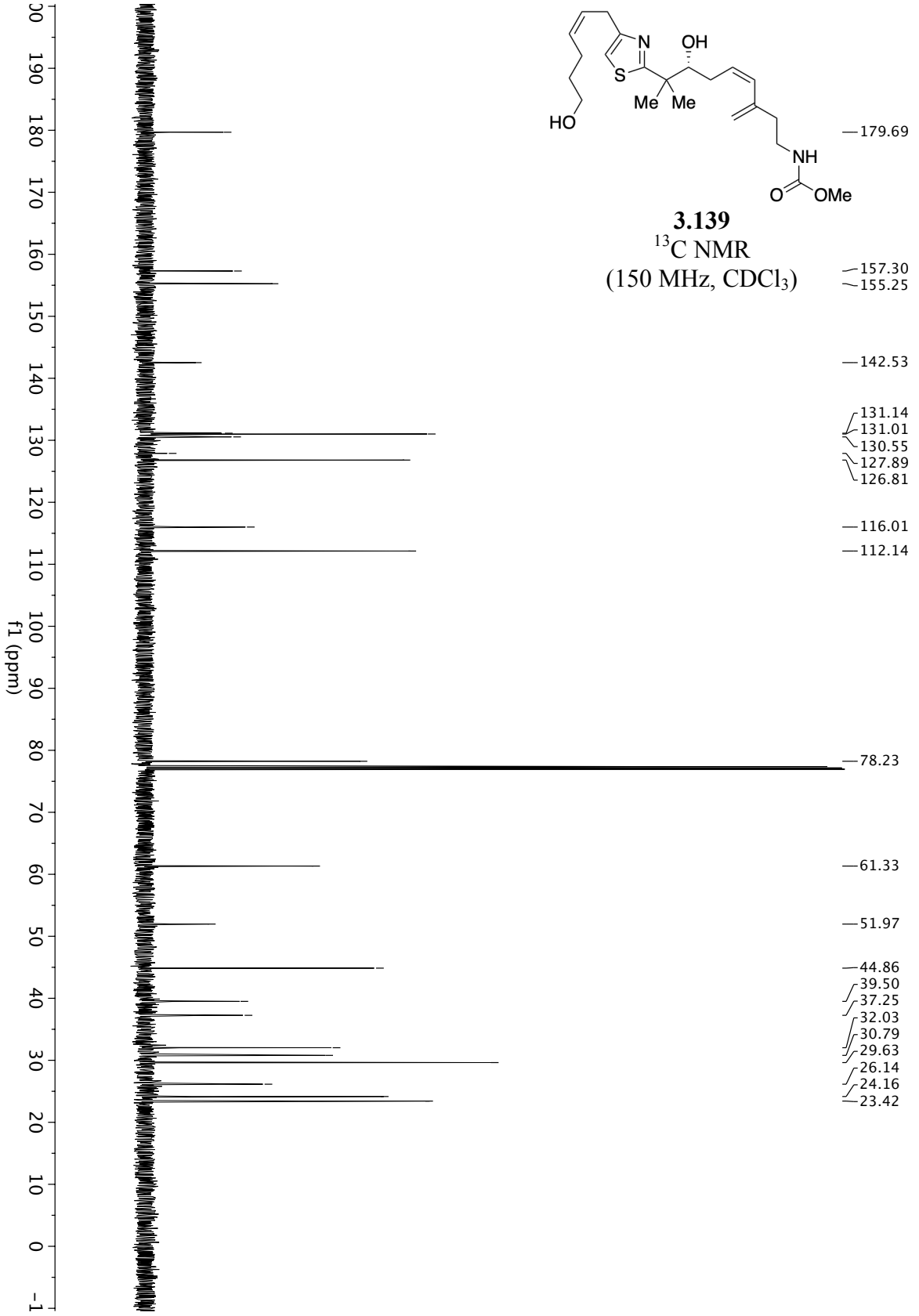
3.138
^{13}C NMR
(100 MHz, $CDCl_3$)

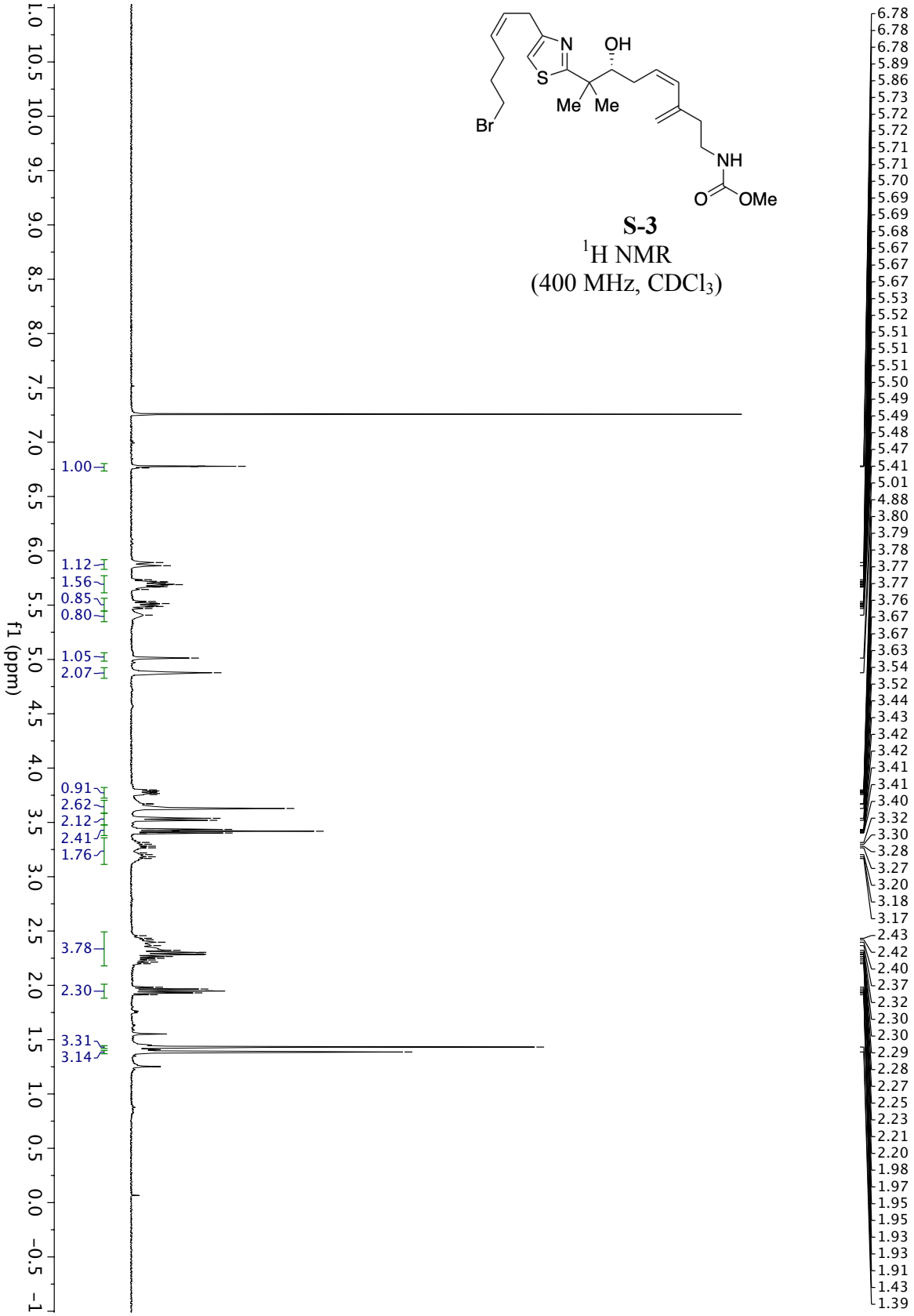


3.139

^{1}H NMR

(400 MHz, $CDCl_3$)

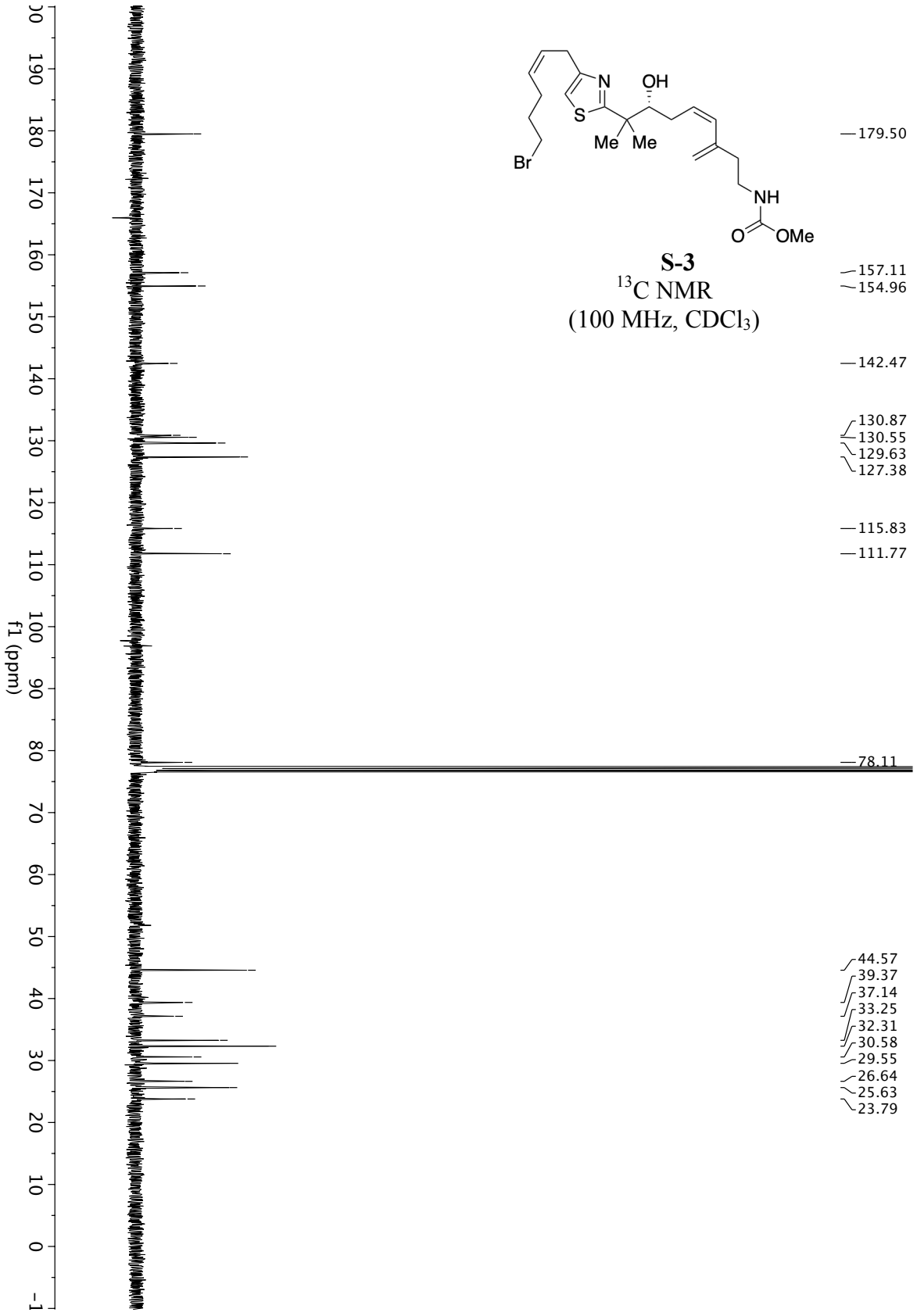

HO
N
S
OH
Me
Me
NH
O
OMe
3.139
13C NMR
(150 MHz, CDCl3)
179.69
157.30
155.25
142.53
131.14
131.01
130.55
127.89
126.81
116.01
112.14
78.23
61.33
51.97
44.86
39.50
37.25
32.03
30.79
29.63
26.14
24.16
23.42
f1 (ppm)



S-3

^{1}H NMR

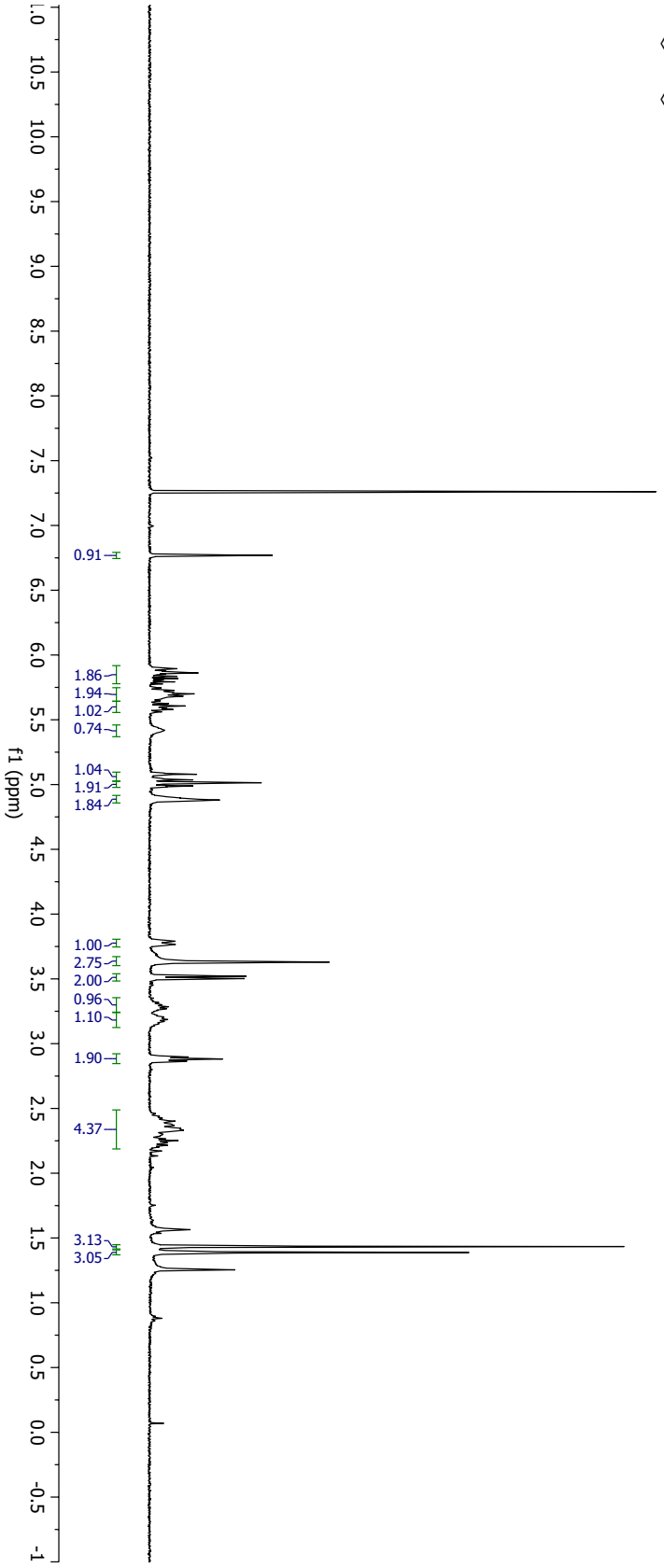
(400 MHz, $CDCl_3$)

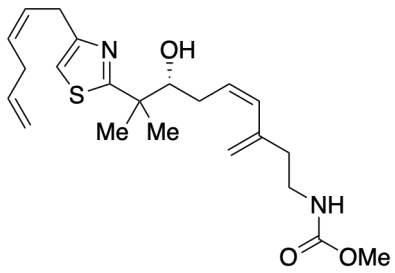


S-3

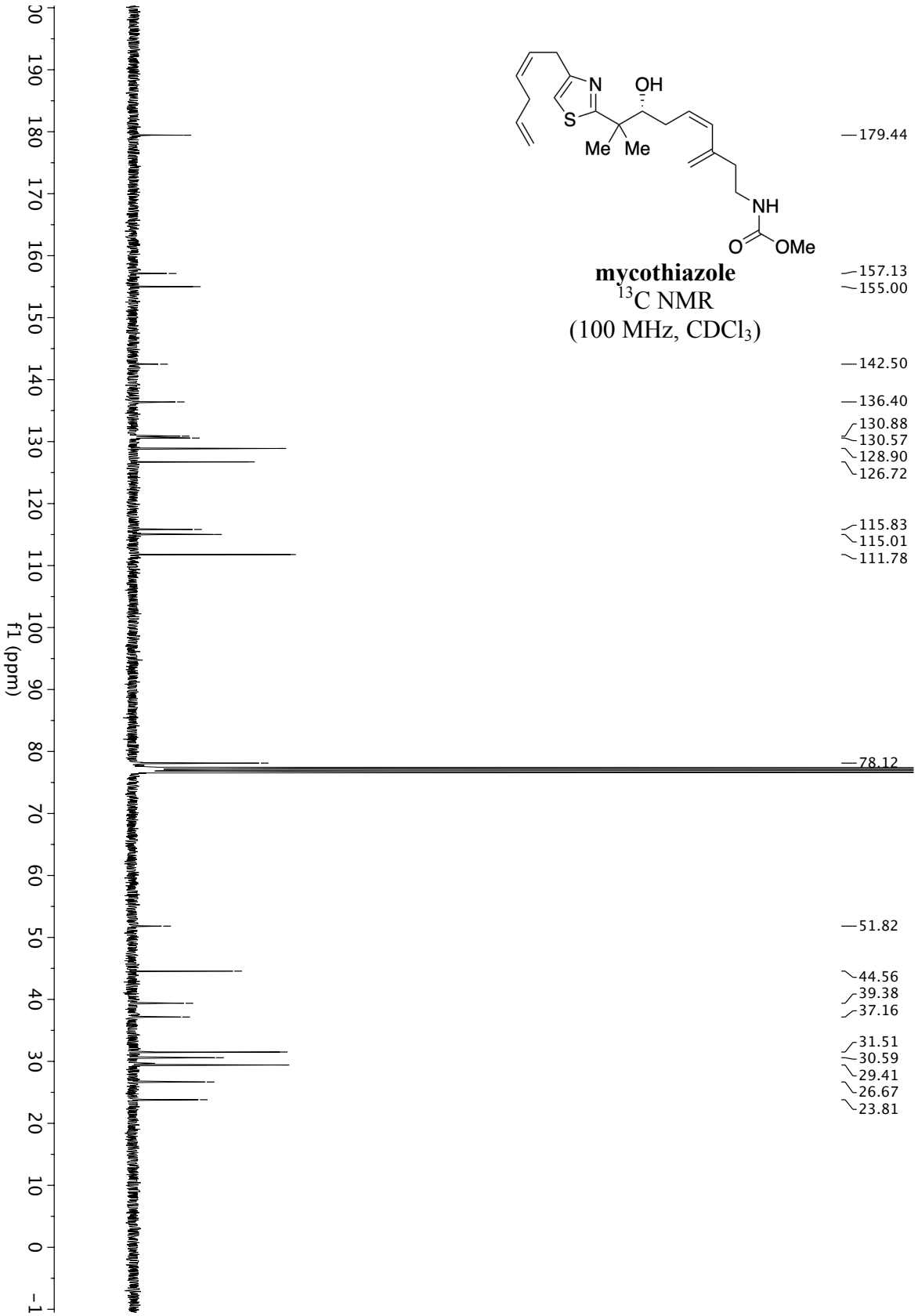
^{13}C NMR

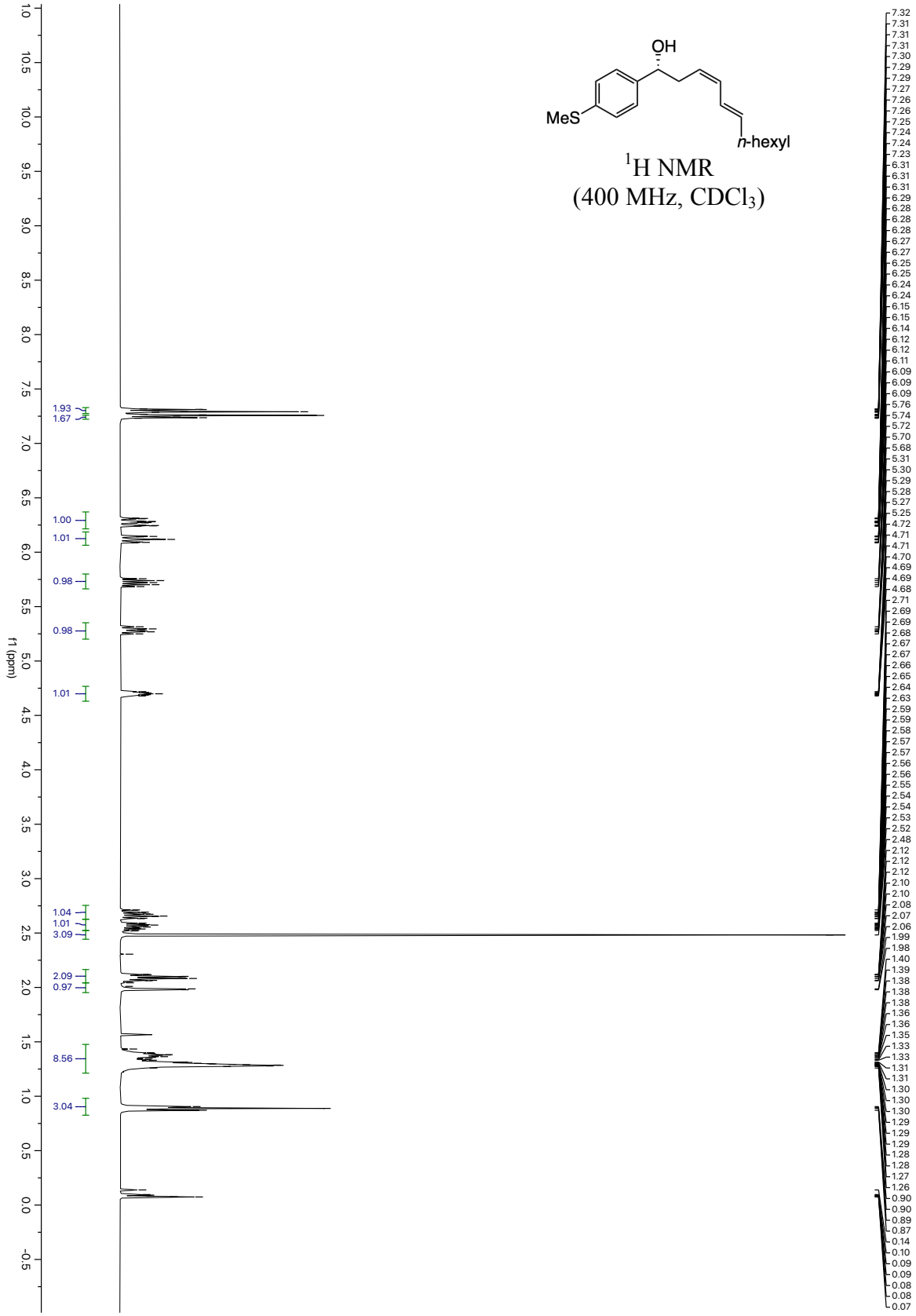
(100 MHz, $CDCl_3$)

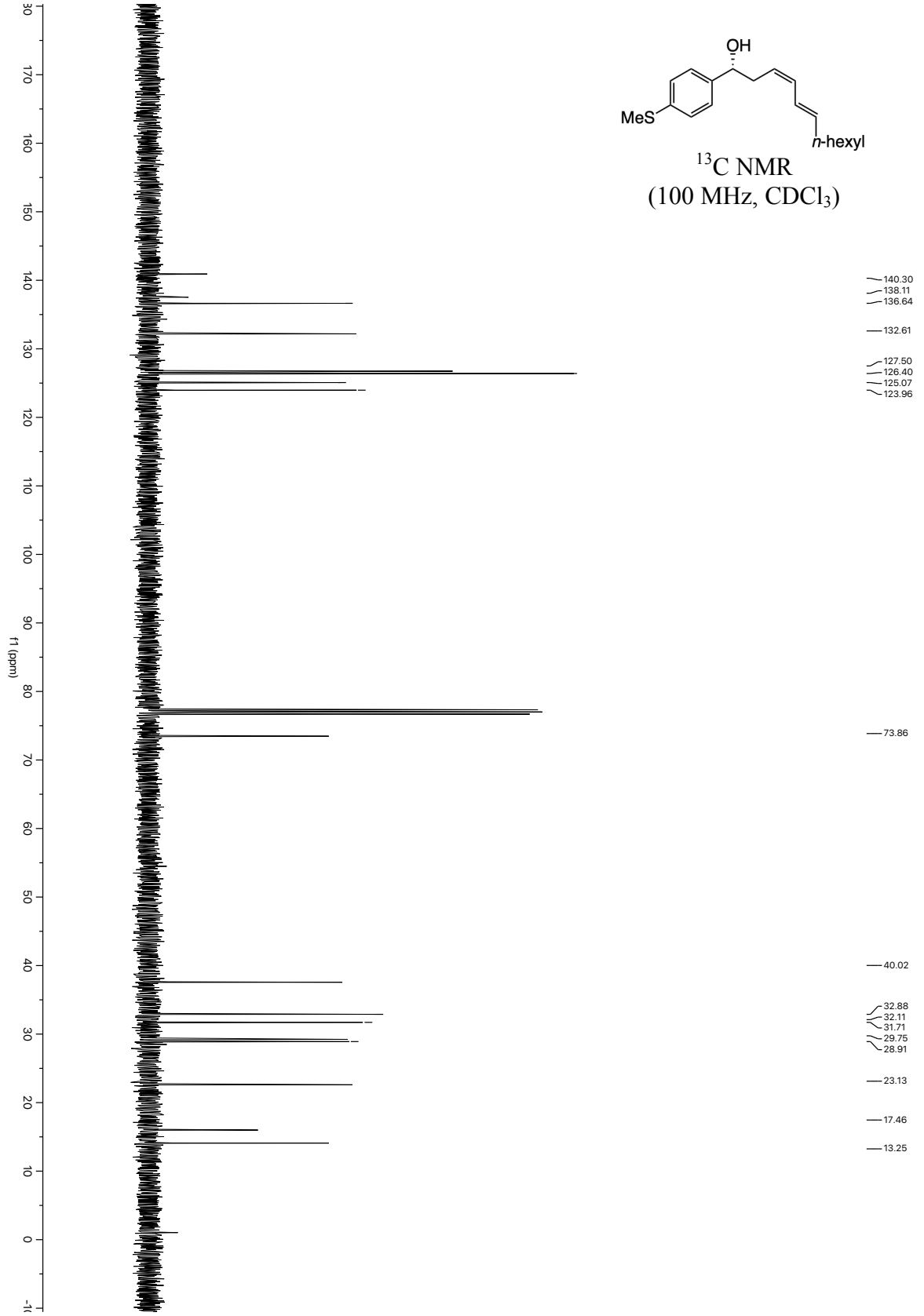




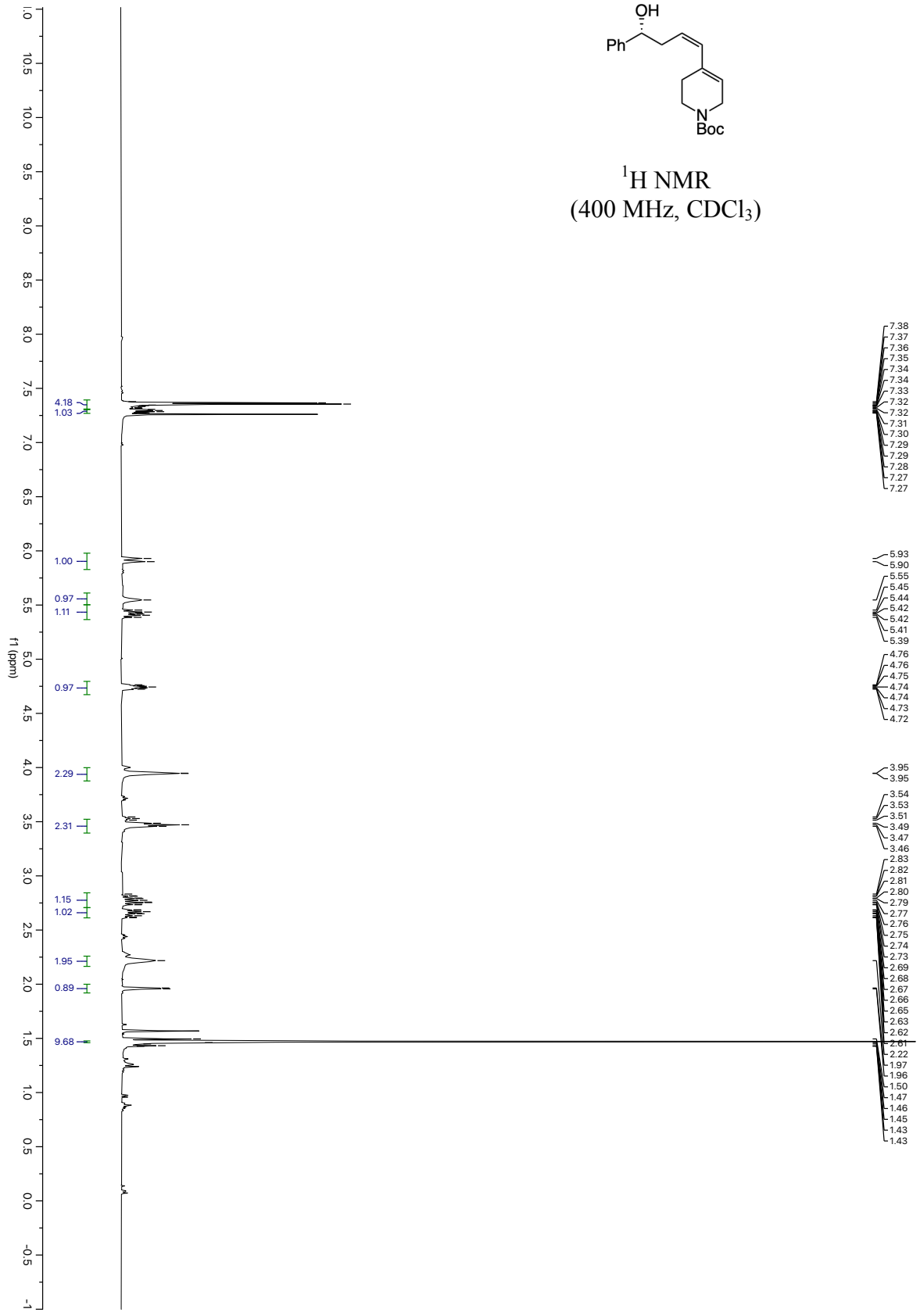
mycothiazole
^{1}H NMR
(400 MHz, $CDCl_3$)

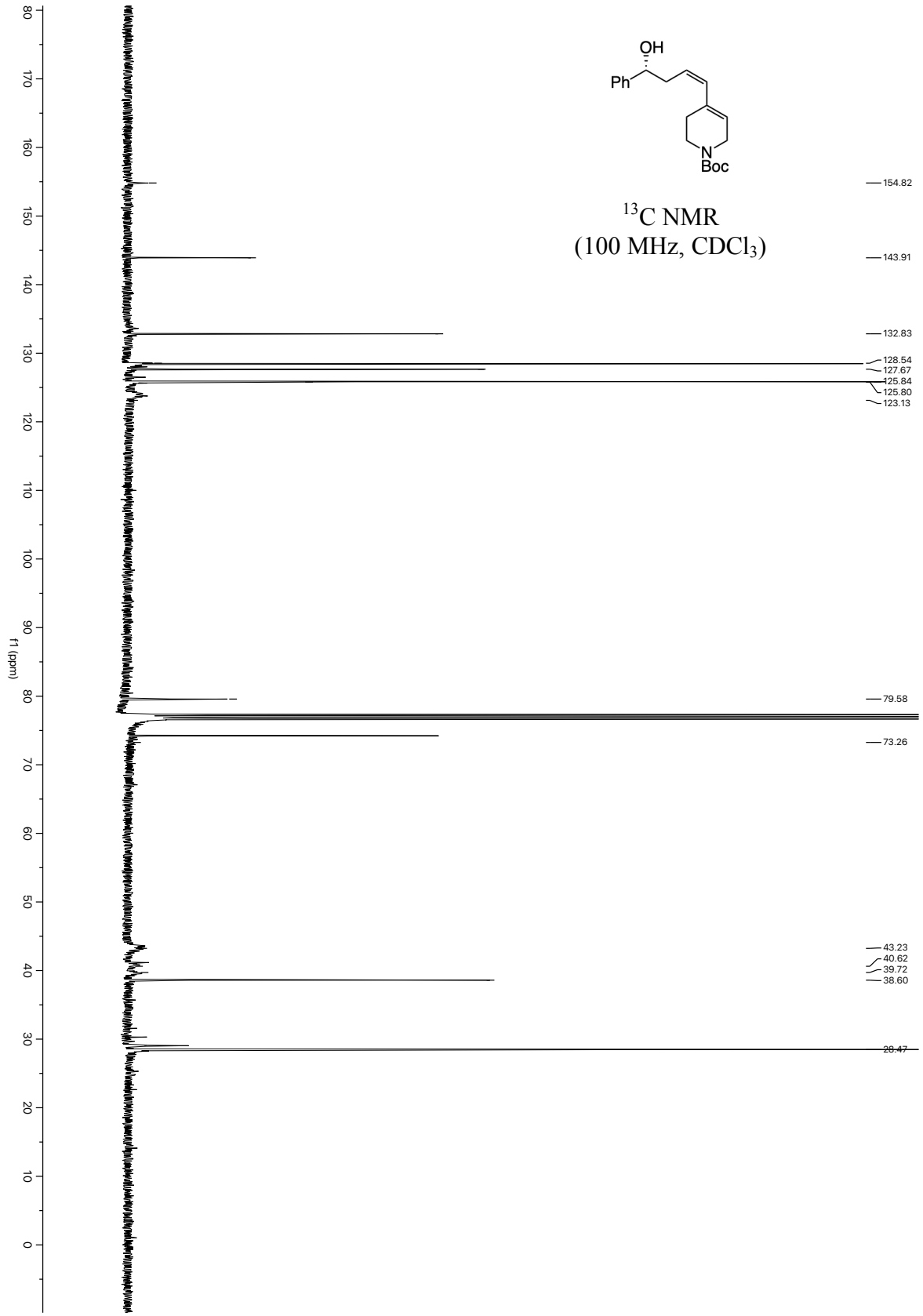

N
OH
S
Me Me
NH
O
OMe
mycothiazole
^{13}C NMR
(100 MHz, $CDCl_3$)
179.44
157.13
155.00
142.50
136.40
130.88
130.57
128.90
126.72
115.83
115.01
111.78
78.12
51.82
44.56
39.38
37.16
31.51
30.59
29.41
26.67
23.81
f1 (ppm)

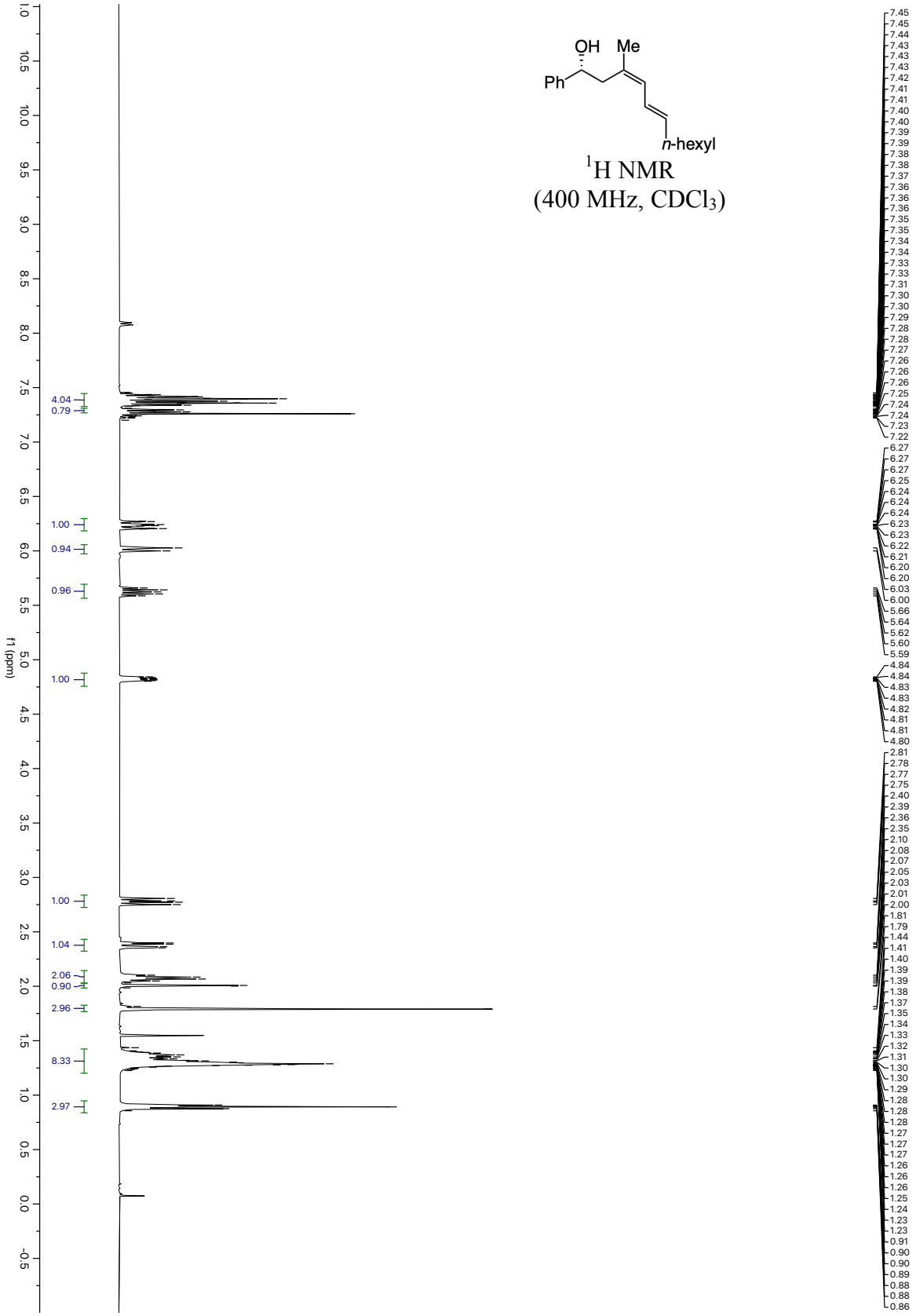

OH
MeS
n-hexyl
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
1.93
1.67
1.00
1.01
0.98
0.98
1.01
1.04
1.01
3.09
2.09
0.97
8.56
3.04

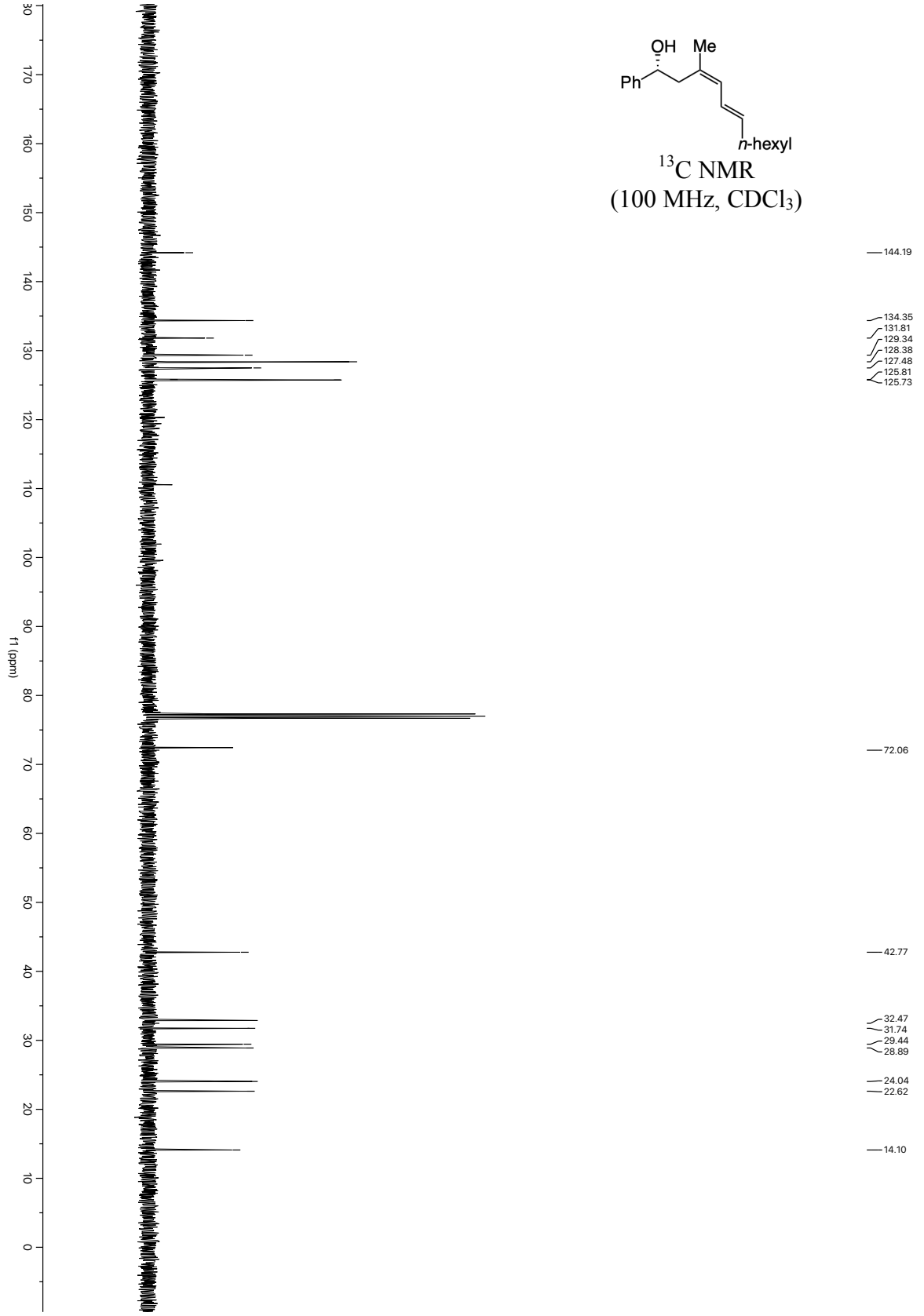


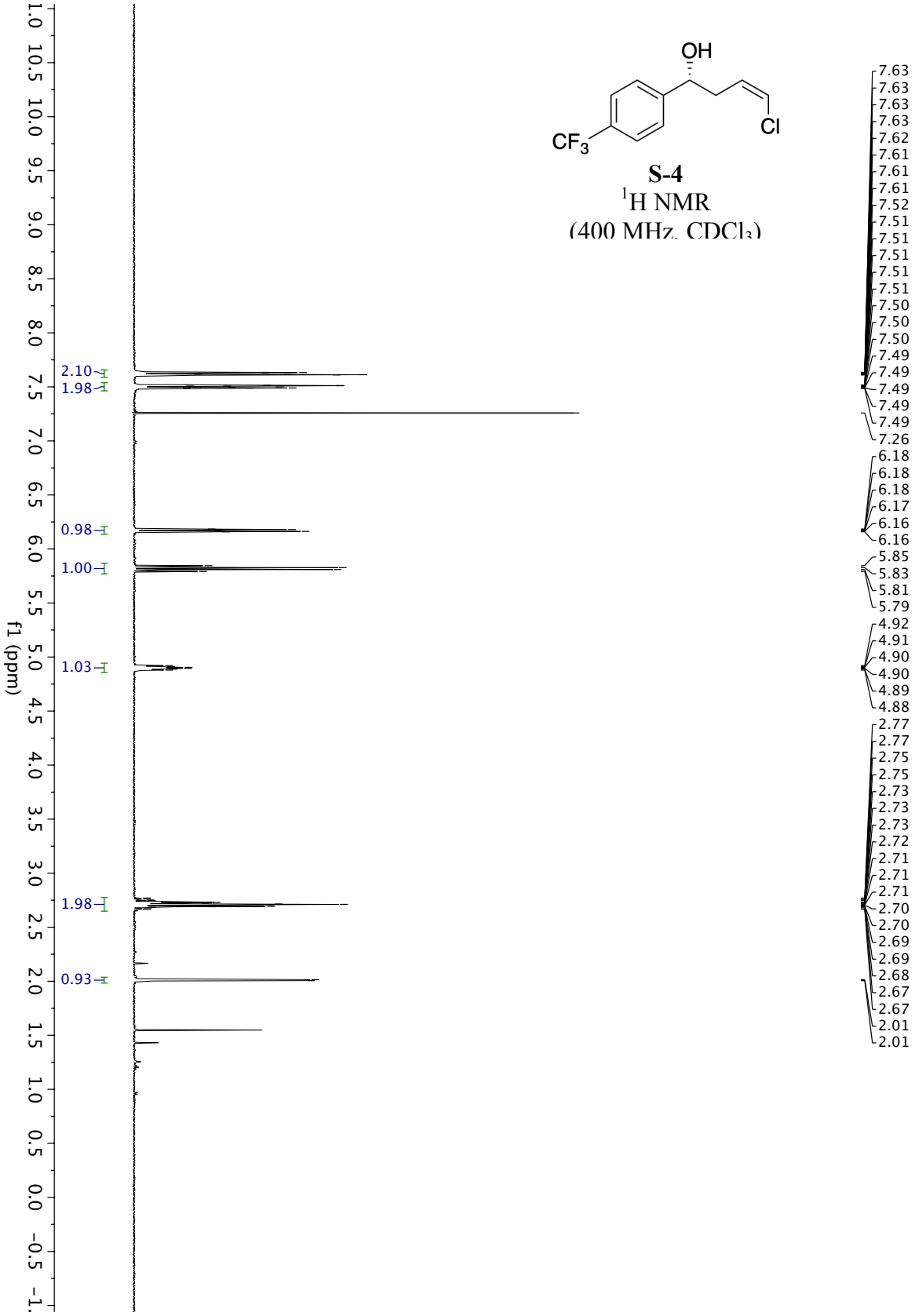
^{13}C NMR
(100 MHz, $CDCl_3$)

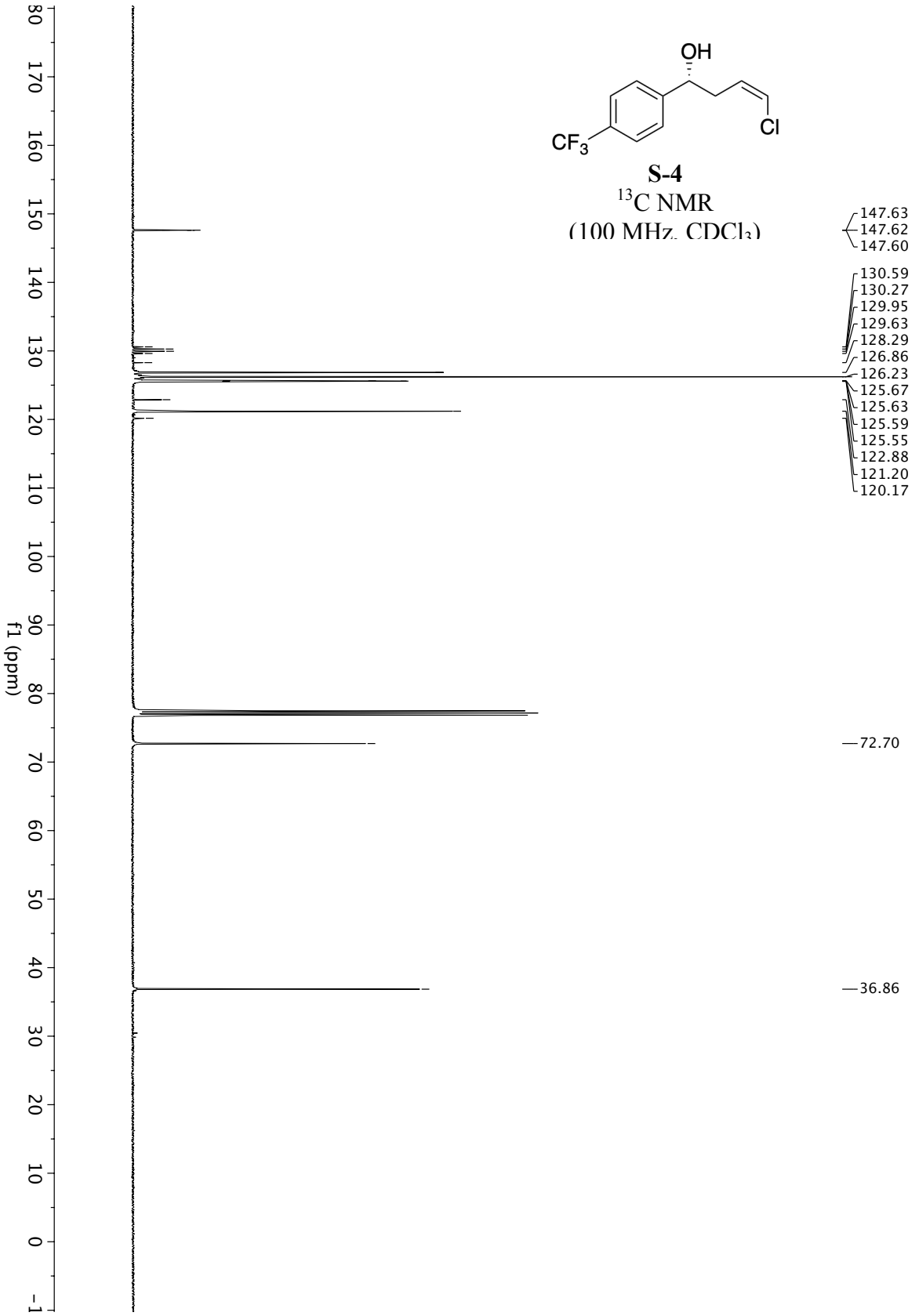

OH
Ph
N
Boc
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
4.18
1.03
1.00
0.97
1.11
0.97
2.29
2.31
1.15
1.02
1.95
0.89
9.68

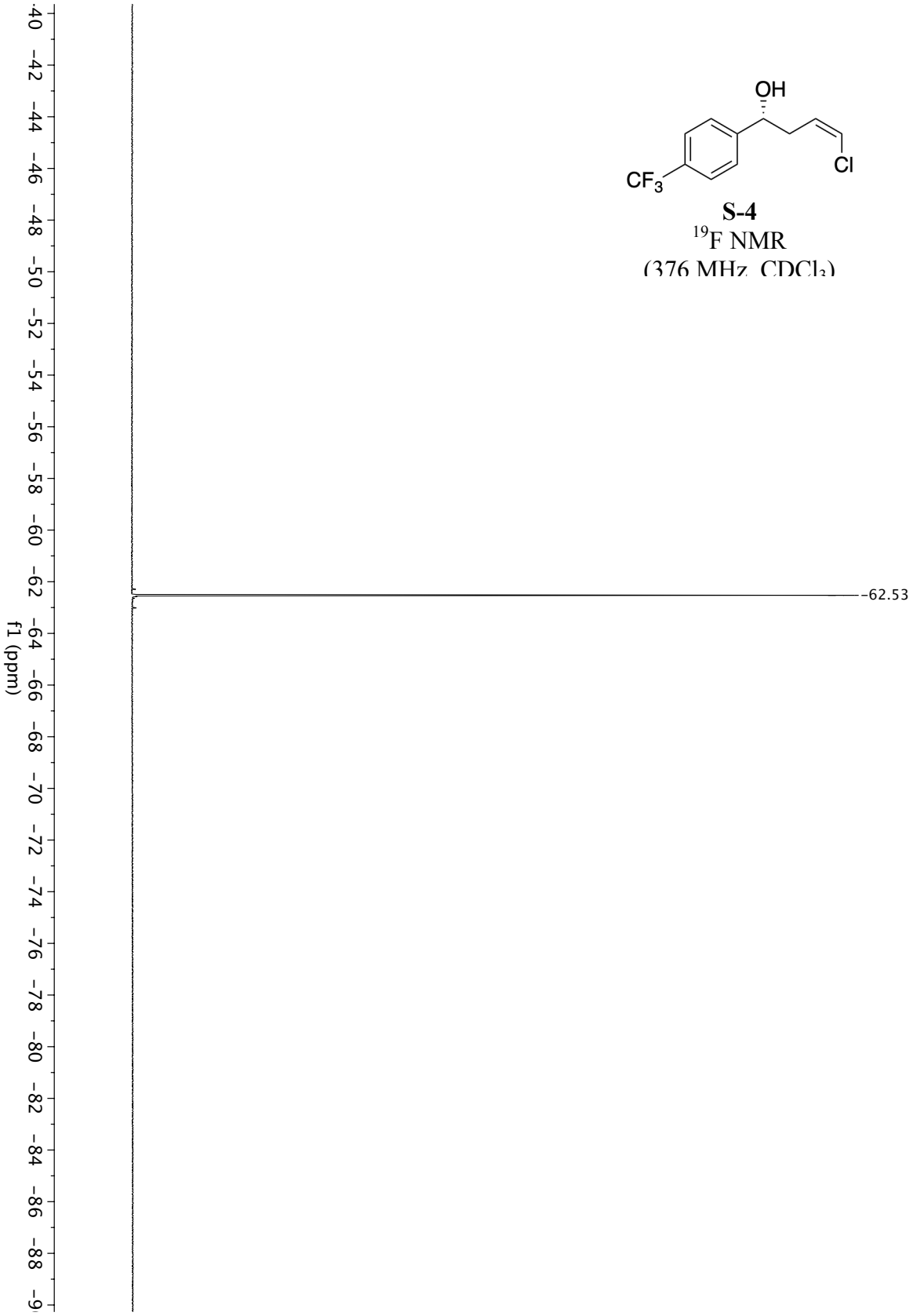

OH
Ph
N
Boc
^{13}C NMR
(100 MHz, $CDCl_3$)
154.82
143.91
132.83
128.54
127.67
125.84
125.80
123.13
79.58
73.26
43.23
40.62
39.72
38.60
28.47
f1 (ppm)


OH
Me
Ph
n-hexyl
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
4.04
0.79
1.00
0.94
0.96
1.00
1.00
1.04
2.06
0.90
2.96
8.33
2.97


OH
Me
Ph
n-hexyl
13C NMR
(100 MHz, CDCl3)
144.19
134.35
131.81
129.34
128.38
127.48
125.81
125.73
72.06
42.77
32.47
31.74
29.44
28.89
24.04
22.62
14.10
f1 (ppm)


OH
CF3
Cl
S-4
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.10
1.98
0.98
1.00
1.03
1.98
0.93
7.63
7.62
7.61
7.52
7.51
7.50
7.49
7.26
6.18
6.17
6.16
5.85
5.83
5.81
5.79
4.92
4.91
4.90
4.89
4.88
2.77
2.75
2.73
2.72
2.71
2.70
2.69
2.68
2.67
2.01

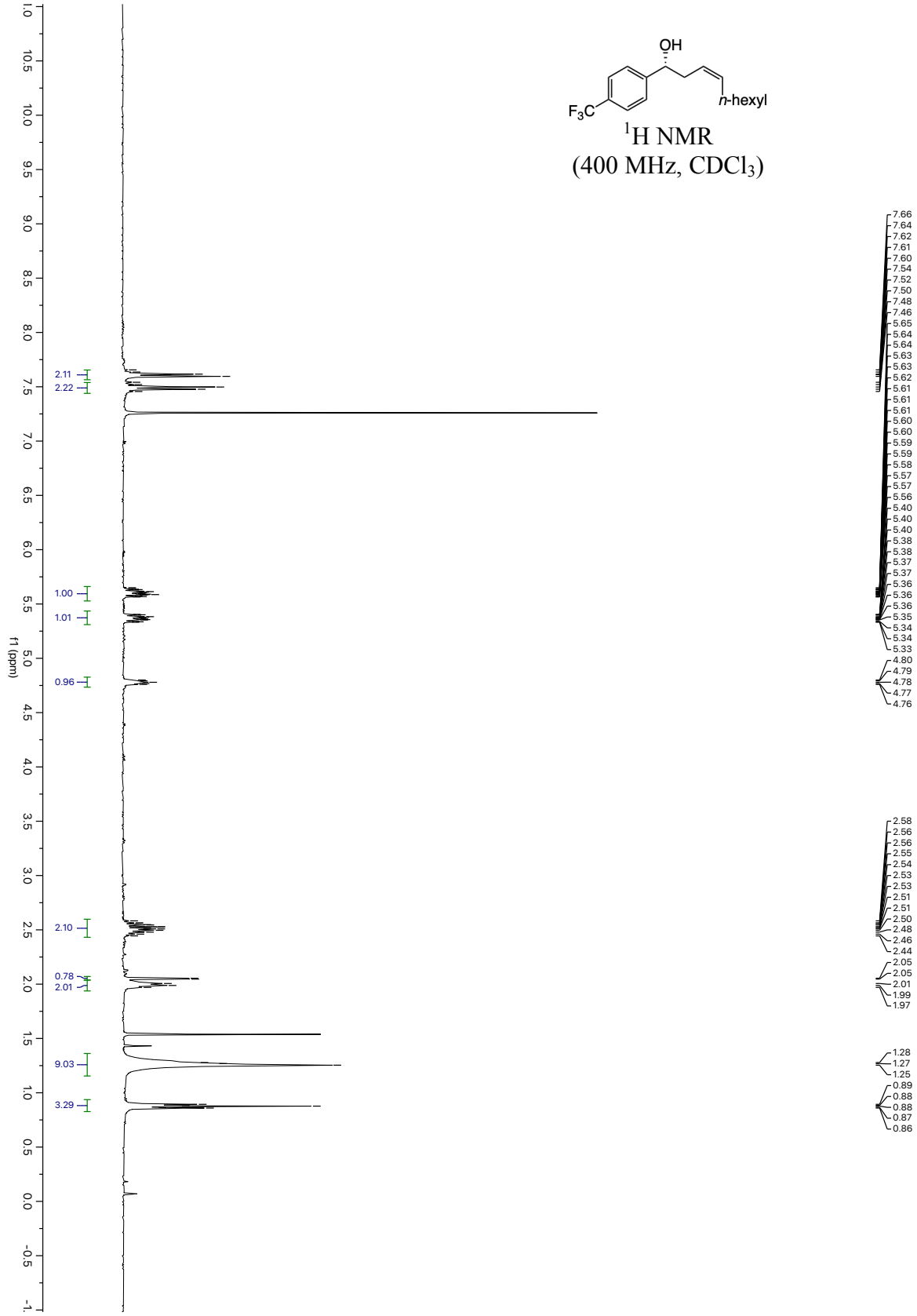

OH
CF3
Cl
S-4
13C NMR
(100 MHz, CDCl3)
147.63
147.62
147.60
130.59
130.27
129.95
129.63
128.29
126.86
126.23
125.67
125.63
125.59
125.55
122.88
121.20
120.17
72.70
36.86
f1 (ppm)

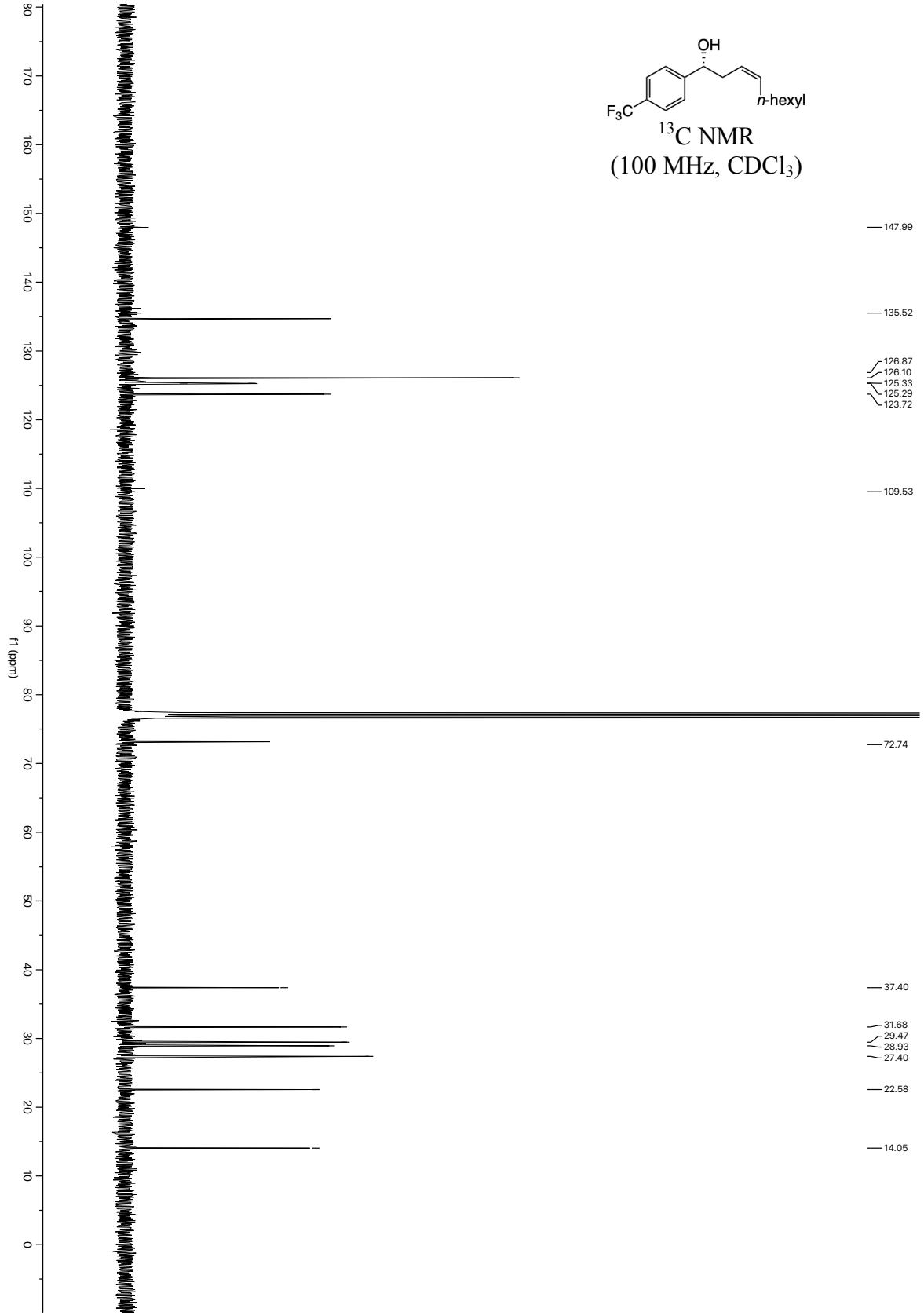


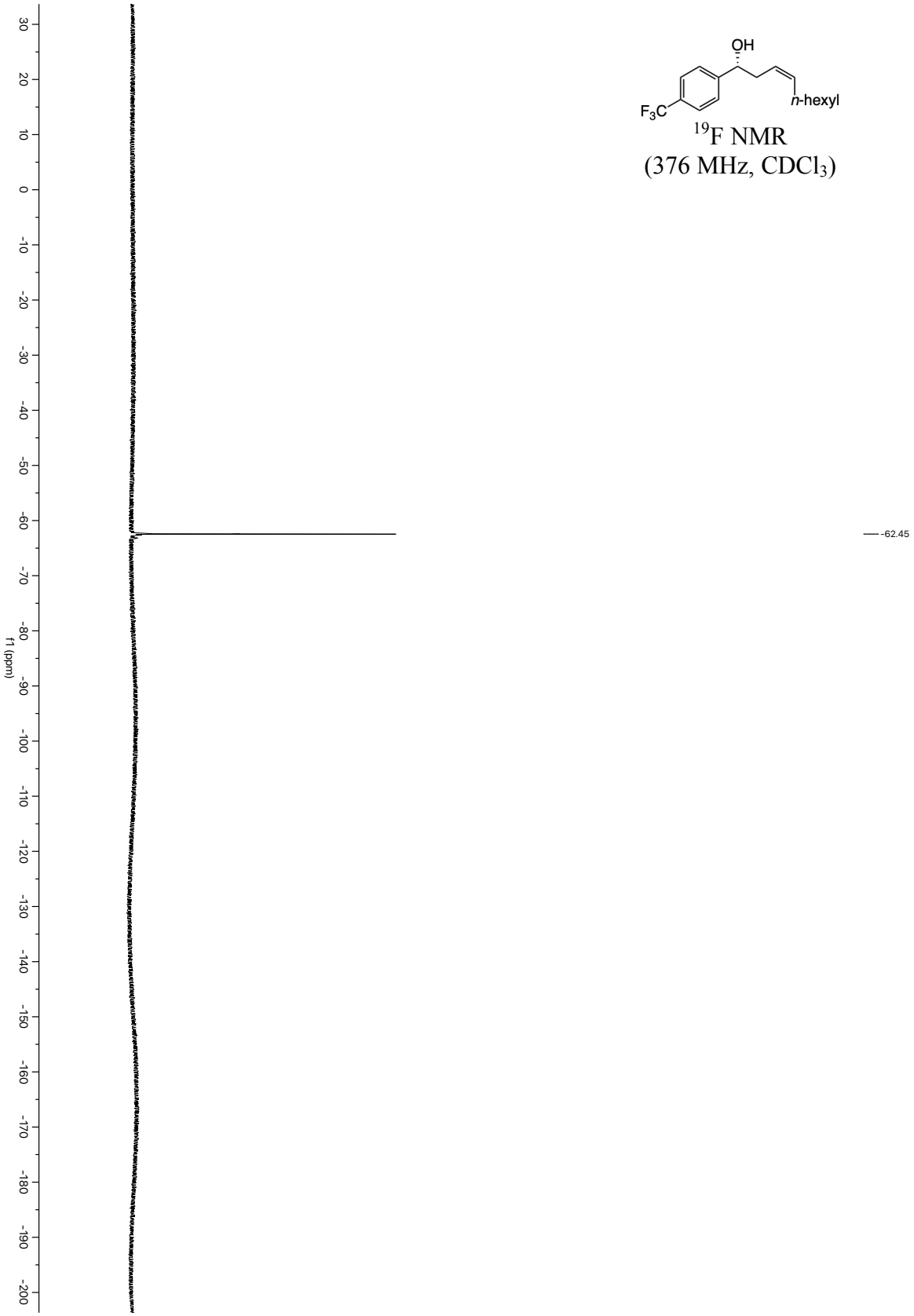
S-4

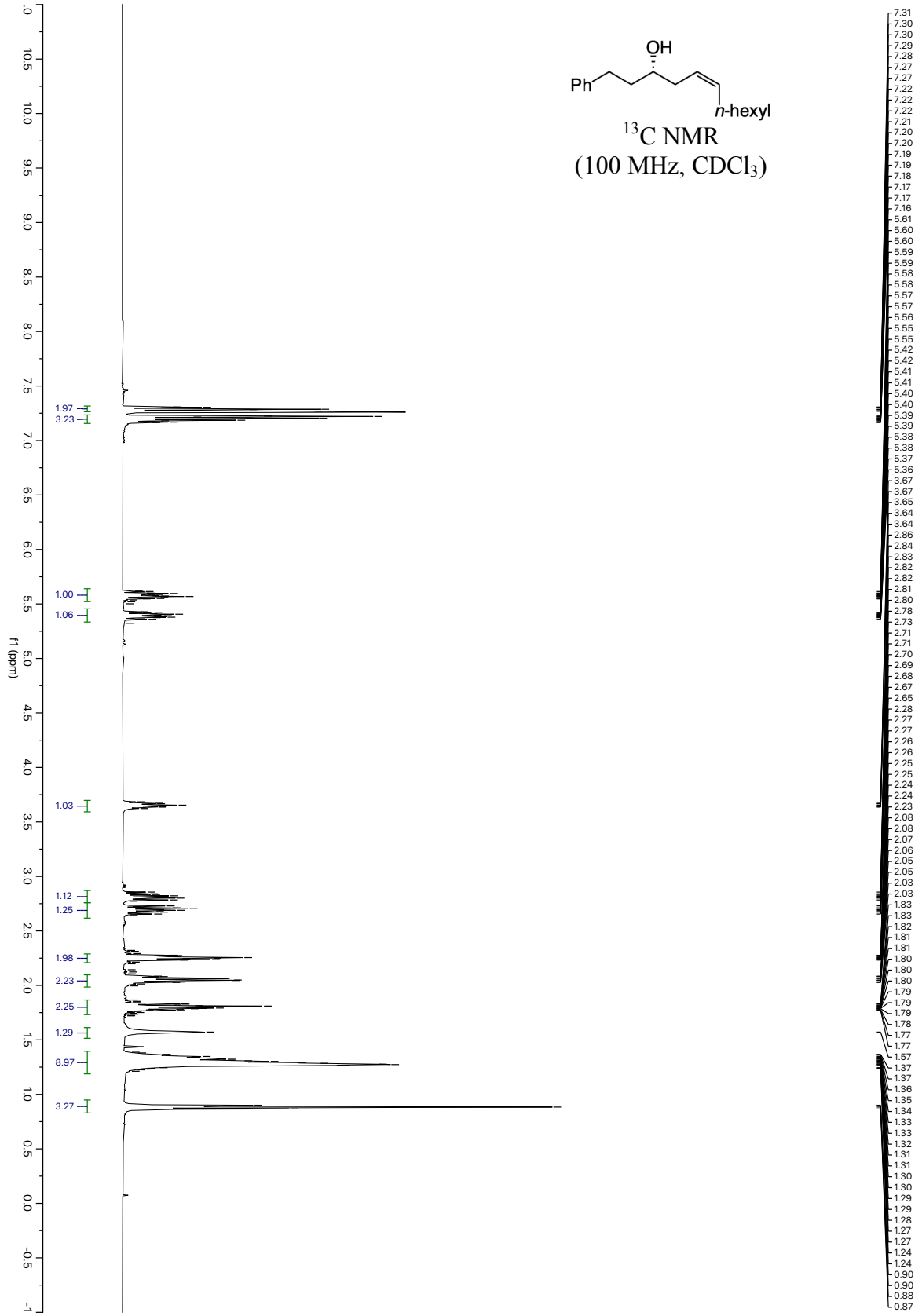
^{19}F NMR

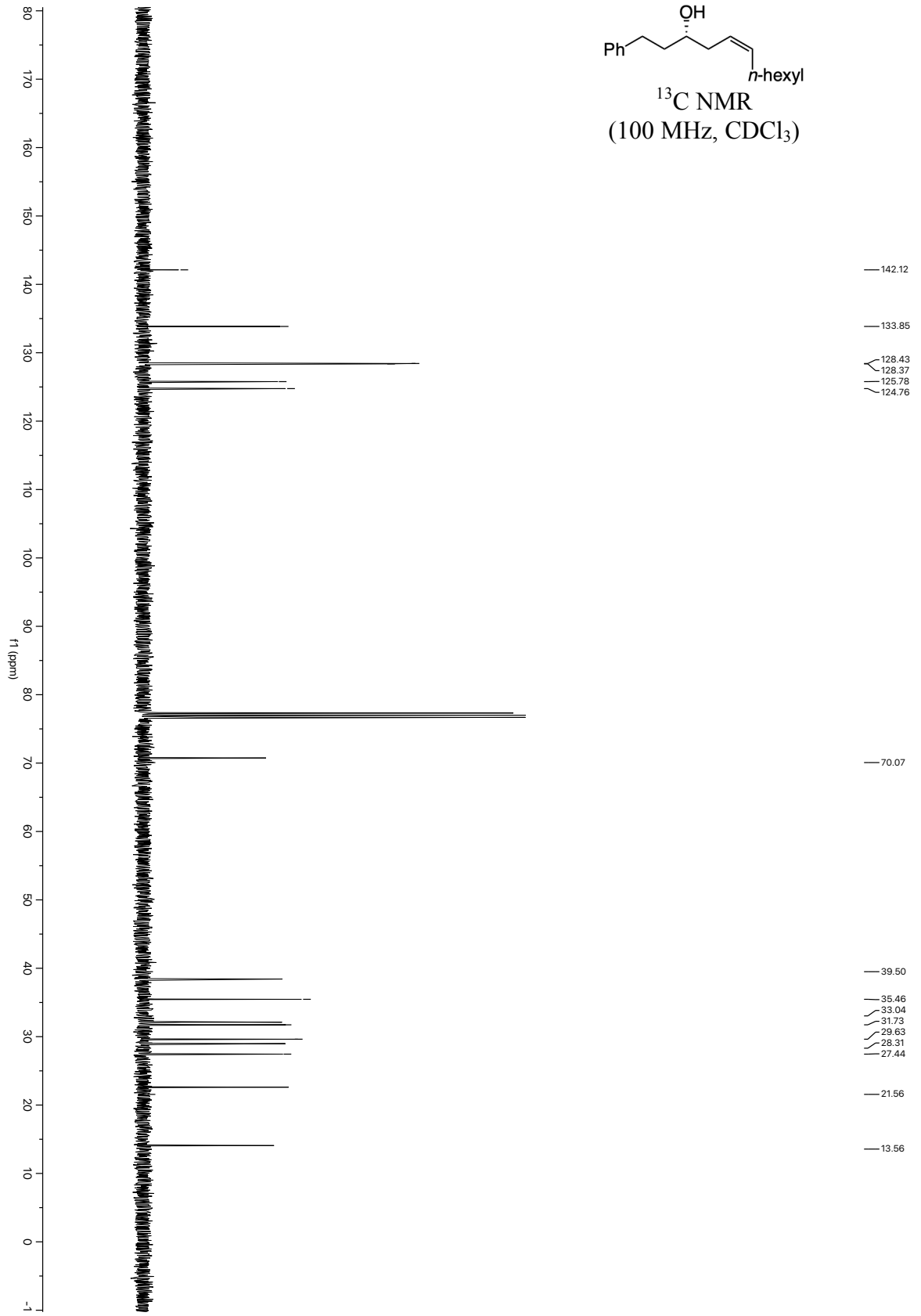
(376 MHz, $CDCl_3$)


OH
F3C
n-hexyl
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
2.11
2.22
1.00
1.01
0.96
2.10
0.78
2.01
9.03
3.29
7.66
7.64
7.62
7.61
7.60
7.54
7.52
7.50
7.48
7.46
5.65
5.64
5.64
5.64
5.63
5.63
5.62
5.61
5.61
5.61
5.61
5.60
5.60
5.59
5.59
5.58
5.57
5.57
5.56
5.40
5.40
5.40
5.38
5.38
5.37
5.37
5.36
5.36
5.36
5.35
5.34
5.34
5.33
4.80
4.79
4.78
4.77
4.76
2.58
2.56
2.56
2.55
2.54
2.53
2.53
2.51
2.51
2.50
2.48
2.46
2.44
2.05
2.05
2.01
1.99
1.97
1.28
1.27
1.25
0.89
0.88
0.88
0.87
0.86


OH
F3C
n-hexyl
13C NMR
(100 MHz, CDCl3)
147.99
135.52
126.87
126.10
125.33
125.29
123.72
109.53
72.74
37.40
31.68
29.47
28.93
27.40
22.58
14.05
f1 (ppm)


OH
F3C
n-hexyl
19F NMR
(376 MHz, CDCl3)
-62.45
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


OH
Ph
n-hexyl
13C NMR
(100 MHz, CDCl3)
f1 (ppm)
1.97
3.23
1.00
1.06
1.03
1.12
1.25
1.98
2.23
2.25
1.29
8.97
3.27


OH
Ph
n-hexyl
13C NMR
(100 MHz, CDCl3)
f1 (ppm)
142.12
133.85
128.43
128.37
125.78
124.76
70.07
39.50
35.46
33.04
31.73
29.63
28.31
27.44
21.56
13.56

Chapter Four

Catalytic Enantioselective Addition of Fluorine-Containing Trisubstituted Allyl Boronates to Aldehydes

4.1 Introduction

As discussed in Chapter Two, the incorporation of stereogenic centers possessing fluorine into compounds may modulate biological activity, influence pharmokinetic properties,[1] or improve catalytic activity through conformational bias.[2] While methods for the introduction of such motifs through additions to pro-chiral substrates[3] or synthesis of tertiary C–CF_3 bonds[4] are well established, much less developed are strategies to access molecules possessing trifluoromethyl-substituted all-carbon quaternary centers. The need for efficient methods to synthesize such compounds is evidenced by the effective agrichemicals and new therapeutics represented in Scheme 4.1[5]

---

1) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422–518.

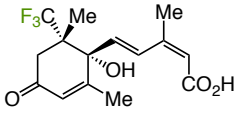
2) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 11860–11871. (b) Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135–147.

3) Zheng, Y.;.Ma, J.-A. *Adv. Synth. Catal.* **2010**, *352*, 2745–2750. (b) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455–529. (c) Dilman, A. D.; Levin, V. V. *Eur. J. Org. Chem.* **2011**, 831–841.

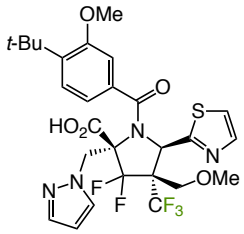
4) For recent examples, see: (a) Li, G.; Gagare, P. D.; Ramachandran, P. V. *Tetrahedron Lett.* **2014**, *55*, 5736–5738. (b) Gao, X.; Zhang, Y. J.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 4173–4175. (c) Guo, R.; Yang, Q.; Tian, Q.; Zhang, G. *Scientific Reports* **2017**, *7*, 4873. (d) Tauber, J.; Schwartz, L. A.; Krische, M. J. *Org. Process Res. Dev.* **2019**, *23*, 730–736.

5) For abscisic acid analogue, see: Todoroki, Y.; Hirai, N.; Koshimizu, K. *Phytochemistry* **1995**, *38*, 561–568. (b) Kim, B. T.; Min, Y. K.; Asami, T.; Park, N. K.; Jeong, I. H.; Cho, K. Y.; Yoshida, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 275–278. (c) Balko, T. W.; Fields, S. C.; Webster, J. D. *Tetrahedron Lett.* **1999**, *40*, 6347–6351. For anti-viral pyrrolidine, see: Or, Y. S.; Ying, L.; Wang, C.; Long, J.; Qui, Y.-L. *PCT. Int. Appl.* **2008**, WO 2009003009. For fungicide, see: Jennings, L. D.; Rayner, D. R.; Jordan, D. B.; Okonya, J. F.;

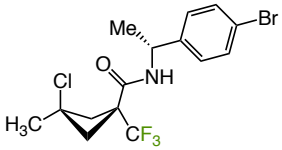
Scheme 4.1. The Need for Efficient Methods for Synthesis of Trifluoromethyl Substituted Quaternary Centers



abscisic acid analogue
(herbicide)



treatment of Hepatitis C
(anti-viral)



Blast disease mitigator
(fungicide)

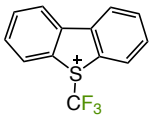
4.2 Background

4.2.1 Accessing Quaternary Carbon Centers Bearing Trifluoromethyl Substitution

Methods for synthesis of these compounds can be divided into two categories: (1) Trapping of an electrophilic source of a trifluoromethyl group such as those depicted in Scheme 4.2. (2) Manipulation of trifluoromethyl-containing building blocks. The former relies on hypervalent iodine, or thio-based reagents developed by Togni[6] and Umemoto,[7] which in addition to poor atom-economy, have been shown to be shock sensitive.[8]

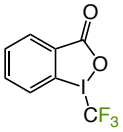
Scheme 4.2. Common Sources of a Trifluoromethyl Group

Umemoto's Reagent

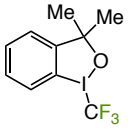


4.1

Togni's Reagents



4.2



4.3

Langlois Reagent

4.4

Basarab, G. S.; Amorose, D. K.; Anaclerio, B. M.; Lee, J. K.; Schwartz, R. S.; Whitmore, K. A. *Bioorg. Med. Chem. Lett.* **2000**, *8*, 897–907.

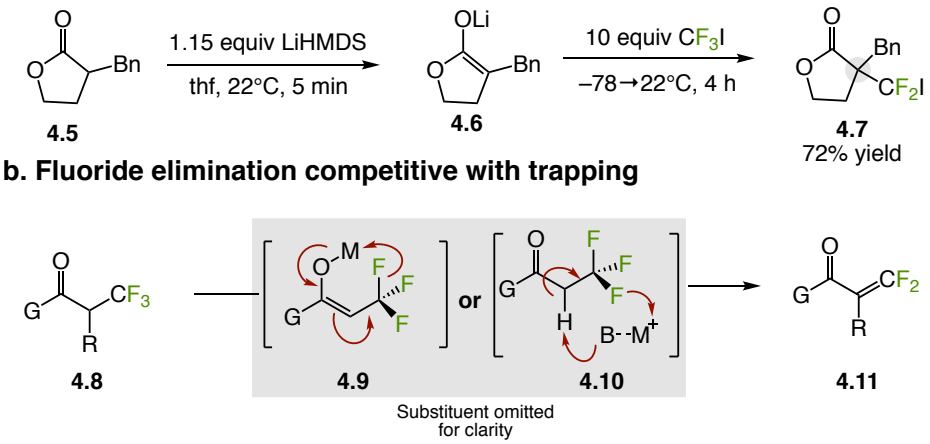
6) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650–682.

7) Barata-Vallejo, S.; Lantaño, B.; Postigo, A. *Chem. Eur. J.* **2014**, *20*, 16806–16829.

8) Fiederling, N.; Haller. J.; Schramm, H. *Org. Process. Res. Dev.* **2013**, *17*, 318–319.

Despite these drawbacks, there are several reports detailing synthesis of quaternary stereogenic centers involving additions to enolates,[9] in addition to an isolated example describing reaction of silyl ketene imines for synthesis of α-trifluoromethyl substituted nitriles.[10] One may consider that reaction with trifluoroiodomethane may be a viable strategy; however, in the presence of lithium-based ester enolates, the major product obtained is difluoromethyl-substituted **4.7** (C–F bond cleavage vs. C–I, Scheme 4.3a).[11] Radical-based strategies have been demonstrated to minimize fluoride elimination to some extent when involving titanium- or ammonium-based enolates, nonetheless these solutions are far from general.[12]

Scheme 4.3. Challenges Surrounding Introduction of a Trifluoromethyl Group



9) (a) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164. (b) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692–5699. (c) Ma, J.-A.; Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726–8729. (d) Sato, K.; Yuki, T.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Tetrahedron Lett.* **2008**, *49*, 3558–3561. (e) Li, L.; Chen, Q.-Y.; Guo, Y. *J. Org. Chem.* **2014**, *79*, 5145–5152.

10) Früh, N.; Togni, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 10813–10816.

11) Mikami, K.; Tomita, Y.; Itoh, Y. *Angew, Chem. Int. Ed.* **2010**, *49*, 3819–3822.

12) (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649–651. (b) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 4883–4885. (c) Petrik, V.; Cahard, D. *Tetrahedron Lett.* **2007**, *48*, 3327–3330.

C–C bond forming reactions involving nucleophiles that possess an α-CF_3 anion are underdeveloped, as these moieties are prone to elimination of fluoride and generation of 1,1-difluoro-olefins **4.11** (Scheme 4.3b).[13] The rate of decomposition (**4.9, 4.10**) is dependent on the counter ion, and those that are more fluorophilic, accelerate elimination.[14] In a single report, Nakagawa identified that in the presence of base generated electrochemically from α-pyrrolidone in conjunction with a tetraethyl ammonium cation, trifluoromethyl-substituted malonates may react with alkyl, allyl and benzyl electrophiles.[15]

Fluorine-containing nucleophiles are more common in methods for allylic substitution, a strategy that has received considerable attention for synthesis of all-carbon quaternary centers,[16] nonetheless, these methods are not immune to facile fluoride elimination.[17] In the state-of-the-art, illustrated in Scheme 4.4, α-trifluoromethyl β-keto carboxylates may be employed for Tsuji-Trost alkylation promoted by a phosphine-Pd complex.[18] However, despite enantioselective transformations of closely related, but non-fluorine containing substrates,[19] the method could not furnish trifluoromethyl substituted stereogenic centers under catalyst control or with non-racemic starting material.

---

13) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2008**, 1006–1007. For a comprehensive review, see: Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817–829.

14) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *26*, 3987.

15) Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276–5277. For a review, see: Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975–996.

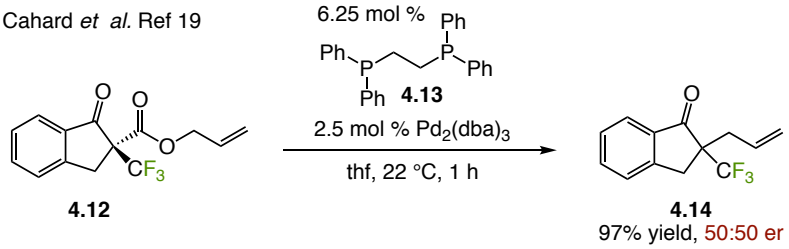
16) For recent reviews detailing methods to access quaternary centers, see: (a) Quasdorf, K. W.; Overman, L. E. *Nature*, **2014**, *516*, 181–191. (b) Feng, J.; Holmes, M.; Krische, M. J. *Chem. Rev.* **2017**, *117*, 12564–12580.

17) (a) Hiraoka, S.; Yamazaki, T.; Kitazume, T. *Chem. Commun.* **1997**, 1497–1498. (b) Li, L.; Chen, Q.-Y.; Guo, Y. *Chem. Commun.* **2013**, *49*, 8764–8766. (c) Li, L.; Huang, D.; Chen, Q.-Y.; Guo, Y. *Synlett*, **2013**, *24*, 611–614. (d) Trost, B. M.; Debien, L. *J. Am. Chem. Soc.* **2015**, *137*, 11606–11609.

18) Shibata, N.; Suzuki, S.; Furukawa, T.; Kawai, H.; Tokunaga, E.; Yuan, Z.; Cahard, D. *Adv. Synth. Catal.* **2011**, *353*, 2037–2041.

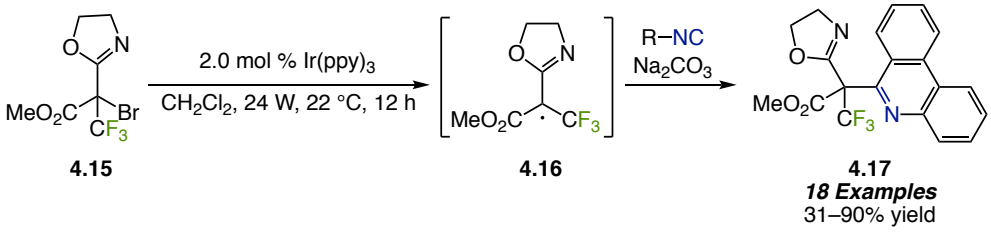
19) (a) Mohr, J. T.; Stoltz, B. M. *Chem. Asian. J.* **2007**, *2*, 1476–1491. (b) Mukherjee, H.; McDougal, N. T.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 825–827.

Scheme 4.4. Erosion of Enantiomeric Purity Under Tsuji-Trost Conditions



In a related disclosure, Ando has outlined a strategy for alkylation of α-trifluoromethyl substituted ketones, yet attempts at extending the method for synthesis of stereogenic centers bearing a trifluoromethyl group were equally unsuccessful.[20] Most recently, Guo and Chen have detailed a method for enantioselective addition of trifluoromethyl-substituted ketene aminoacetals to allylic carbonates in the presence of an unspecified palladium complex. However, the scope of products, furnished in 0–86% yield and 50:50–87:13 er, lack generality and further serve as a testament to what is lacking in the current state-of-the-art.[21]

Scheme 4.5. Synthesis of Quaternary Stereogenic Centers through Addition of Tertiary Radical Species to Isonitriles



Wang and Chen have outlined an approach involving generation of trifluoromethyl-containing radicals from bromine-containing ketene aminoacetals and subsequent addition

20) Sato, K.; Takiguchi, Y.; Yoshizawa, Y.; Iwase. K.; Shimizu, Y.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Chem. Pharm. Bull.* **2007**, *55*, 1593–1596.

21) Wang, W.; Huan, F.; Sun, Y.; Fang, J.; Liu, X.-Y.; Chen, Q.-Y.; Guo, Y. *J. Fluorine Chem*. **2015**, *171*, 46–55.

to electron deficient olefins[22] and isonitriles (Scheme 4.5).[23] The mild reaction conditions are tolerant of diverse functionality, but are neither diastereo- nor enantioselective. In a related disclosure, Murahashi outlined a catalytic strategy wherein phosphine-Ir complexes are proposed to insert into C–H bonds of trifluoromethyl containing alkanes and then react with acrylates and alkenyl nitriles.[24] However, in a follow-up study, the authors discovered that the transformation can be carried out in the absence of a metal-based catalyst, and only requires a phosphine ligand (XPhos) for efficient carbon-carbon bond formation.[24b] Other notable strategies for synthesis of all-carbon trifluoromethyl substituted quaternary centers include cycloaddition,[25] addition of trifluoromethyl substituted allyl zinc compounds to aldehydes,[26] and Claisen rearrangement of γ-substituted allylic alcohols.[27]

4.2.2 Catalytic Enantioselective Formation of All-Carbon Quaternary Centers Bearing a Trifluoromethyl Group

There are even fewer methods for catalytic, enantioselective synthesis of quaternary trifluoromethyl substituted stereogenic centers. In one of the earliest reports, Davies and co-workers outlined diastereo- and enantioselective construction of trifluoromethyl-

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22) Huan, F.; Chen, Q.-Y.; Guo, Y. *J. Org. Chem.* **2016**, *81*, 7051–7063.

23) Wang, W.; Guo, Y.; Sun, K.; Wang, S.; Zhang, S.; Liu, C.; Chen, Q.-Y. *J. Org. Chem.* **2018,** *83*, 14588–14599.

24) (a) Guo, Y.; Zhao, X.; Zhang, D.; Murahashi, S.-I. *Angew. Chem. Int. Ed.* **2009**, *48*, 2047–2049. (b) Wang, Q.; Huan, F.; Shen, H.; Xiao, J.-C.; Gao, M.; Yang, X.; Murahashi. S.-I.; Chen, Q.-Y.; Guo, Y. *J. Org. Chem.* **2013**, *78*, 12525–12531.

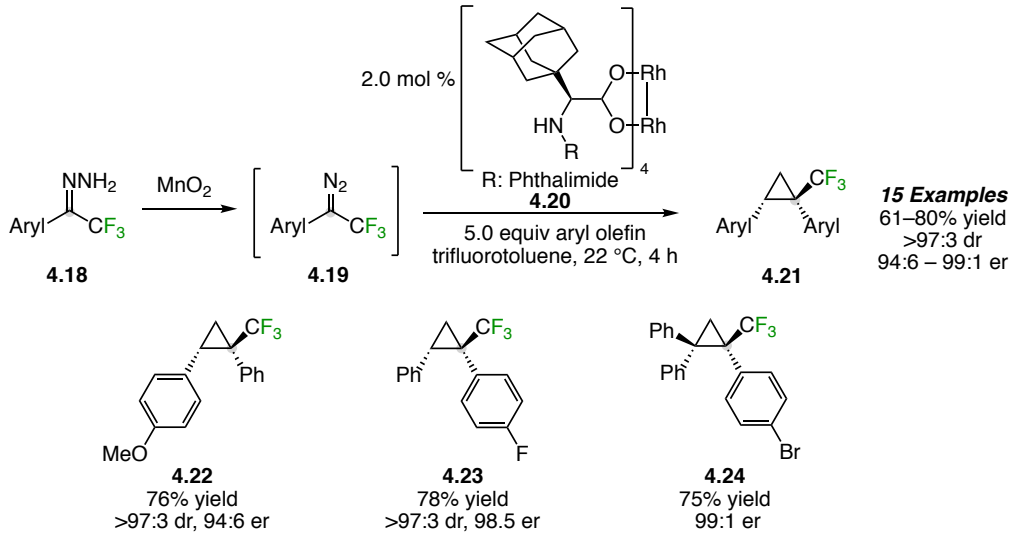
25) (a) Hanzawa, Y.; Suzuki, M.; Kobayashi, Y. *Tetrahedron Lett.* **1989**, *30*, 571–574. (b) Hanzawa, Y.; Suzuki, M.; Kobayshi, Y.; Taguchi, T. *J. Org. Chem.* **1991**, *56*, 1718–1724. (c) Ogawa, S.; Nishimine, T.; Tokunaga, E.; Shibata, N. *Synthesis*, **2010**, *19*, 3274–3281. (d) Nikolaev, V. A.; Supurgibekov, M. B.; Davies, H. M. L.; Sieler, J.; Zakharova, V. M. *J. Org. Chem.* **2013**, *78*, 4239–4244. (e) Loska, R. *Targets in Heterocyclic Systems–Chemistry and Properties*, **2015**, *19*, 101–127.

26) Gosmini, C.; Rollin, Y.; Perichon, J.; Wakselman, C.; Tordeux, M.; Marival, L. *Tetrahedron*, **1997**, *53*, 6027–6034.

27) Bouvet, D.; Sdassi, H.; Ourévitch, M.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 2104–2107.

substituted cyclopropanes through addition of rhodium-based carbenoids to aryl olefins (Scheme 4.6), affording products as a single diastereomer in 61–80% yield and 94:6–99:1 er. A notable feature of the method is that isolation of the volatile diazo compound **4.19** is obviated by in-situ preparation through mild oxidation of the corresponding hydrazone.[28]

Scheme 4.6. Diastereo- and Enantioselective Synthesis of Cyclopropanes Bearing Trifluoromethyl Substituents

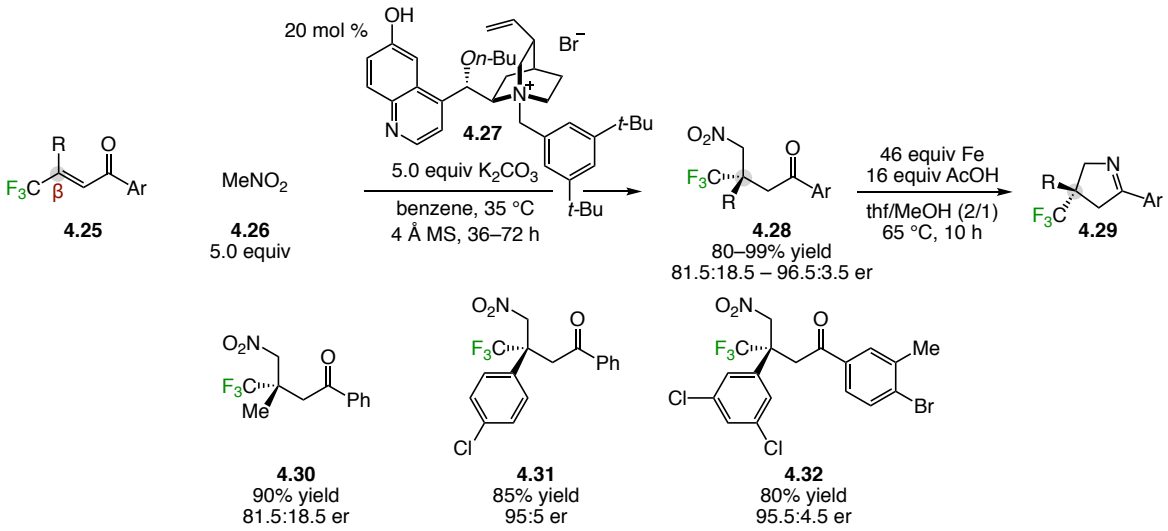


Enantioenriched quaternary stereogenic centers may be prepared through conjugate addition of various nucleophiles to β,β–disubstituted enones **4.25**. In 2012, Shibata described the first example of cyanide conjugate addition to a number of enones including 2-naphthyl, nitro, and various halo-substituted examples in high er. [29] However, in order to access 5-membered heterocycles such as **4.29**, reduction of the nitrile required treatment with Raney-Ni, which furnished the desire amines in no more than 50% yield.

28) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625–2628.

29) Kawai, H.; Okusu, S.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 4959–4962.

Scheme 4.7 Conjugate Addition of Nitromethane to Trifluoromethyl Substituted Enones



To address these shortcomings, an ensuing disclosure by the same authors detailed enantioselective conjugate addition of nitromethane to a variety of structurally diverse enones (**4.30–32**), including one β-alkyl substrate (Scheme 4.7).[30] Partially saturated pyrrolidines could then be accessed through reduction of the nitro group and subsequent condensation in up to 92% yield. In an almost identical, but less efficient process, Kwiatowski reported conjugate addition of nitromethane at high-pressure (10 kbar) for access to the same class of compounds in 56–99% yield and 72.5:27.5–97.5:2.5 er.[31]

Another strategy entails addition to trifluoromethyl-substituted nitroalkenes.[32] In 2014, Wang detailed reaction of vinylogous enolates **4.33** with tri- and tetra-substituted alkenes **4.34** promoted by thiourea **4.35** in 60–92% yield and 99:1 er (Scheme 4.8a).[33] Shortly thereafter, Ma outlined a method for catalytic enantioselective addition of malonate derivatives **4.40** to indole-containing nitroalkenes **4.41**. Considerable diversity was

30) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 5575–5579.

31) Kwiatkowski, P.; Cholewiak, A.; Kasztelan, A. *Org. Lett.* **2014**, *16*, 5930–5933.

32) Du, D.; Jiang, Y.; Xu, Q.; Tang, X.-Y.; Shi, M. *ChemCatChem*, **2015**, *7*, 1366–1371.

33) Chen, Q.; Wang, G.; Jiang, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1394–1397.

tolerated among the alkene and malonate compounds, including different patterns of ester substitution, *N*-tosyl or *N*-Boc protecting groups, and substitution on the aryl ring. The derived products possessing quaternary stereogenic centers were obtained in 63–93% yield, however extended reaction times (24–96 h) were required for efficiency (Scheme 4.8b).[34]

In 2016, Shen described addition of cyclic 1,3-dicarbonyl compounds promoted by squaramide catalyst **4.48** to nitroalkenes affording hydroxyimino tetrahydrobenzofuranones in 65–81% yield and 78:22–94.5:5.5 er.[35] In a follow-up study, the same authors carried out addition of pyrazolinones **4.47** to trifluoromethyl substituted nitroalkenes (Scheme 4.8c).[36] Neither method is tolerant of *ortho*-substitution on the aryl ring or the nitroalkene (<2% conv) and require extended reaction times for efficient addition. Jiang has reported similar squaramide catalysts to be effective for promoting enantioselective addition of maleonitrile to trifluoromethyl-substituted acrylates. In these cases, quaternary stereogenic centers bearing a trifluoromethyl group were furnished in 61–99% yield and 73.5:26.5–99:1 er; however, the reaction required up to 120 h at –20°C.[37]

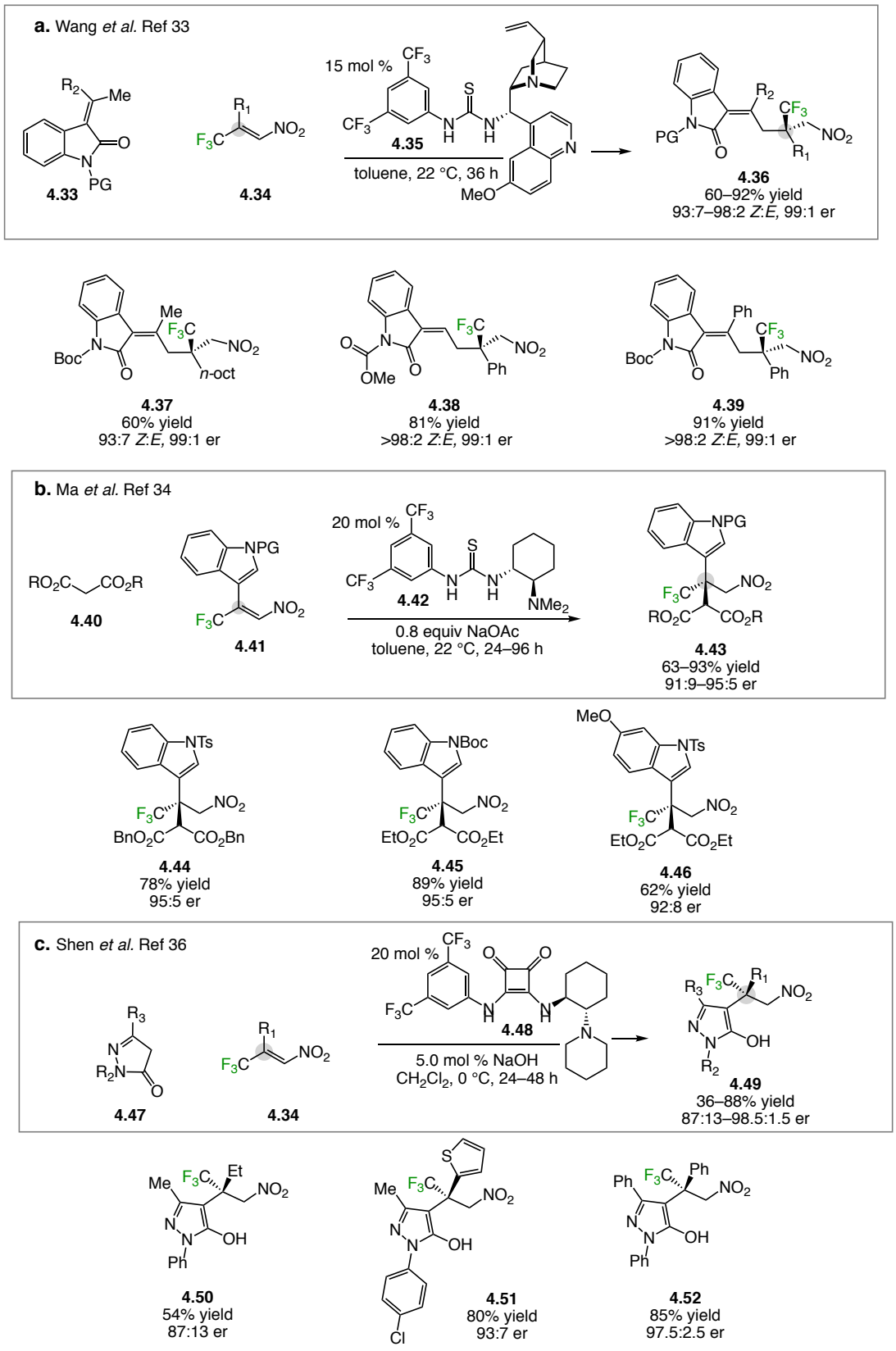
34) Ma, C.-H.; Kang, T.-R.; He, L.; Liu, Q.-Z. *Eur. J. Org. Chem.* **2014**, 3981–3985.

35) Liu, W.; Lai, X.; Zha, G.; Xu, Y.; Sun, P.; Xia, T.; Shen, Y. *Org. Biomol. Chem.* **2016**, *14*, 3603–3607.

36) Lai, A.; Zha, G.; Liu, W.; Xu, Y.; Sun, P.; Xia, T.; Shen, Y. *Synlett*, **2016**, *27*, 1983–1988.

37) Lou, Q.; Ding, Y.; Xu, D.; Liu, G.; Zhao, J. *Adv. Synth. Catal.* **2017**, *359*, 2557–2563.

Scheme 4.8. Methods for Catalytic Enantioselective Addition to Nitroalkenes



Fu has outlined construction of all carbon quaternary centers through addition of nickel-based enolates to nitro alkenes.[38] Thiazoyl, pyridyl and pyrazinyl ketones **4.53** proved to be effective under the reaction conditions affording **4.55** in 71–97% yield and 95.5:4.5–99:1 er (Scheme 4.9a). The reaction is promoted by a readily accessible bis-oxazoline ligand under mild conditions, however, reaction times of up to 120 h were required for efficiency. Furthermore, more sizable *ortho*-substituted nitroalkenes were unreactive and attempts to extend the scope to other Michael acceptors such as acrylates or acrylonitrile were unsuccessful.

Jia has developed a method for Friedel-Crafts alkylation of indole **4.59** and pyrrole with disubstituted nitro-olefins in the presence of a related nickel complex, generating products **4.61** in 51–97% yield and 66.5:33.5–98:2 er (Scheme 4.9b).[39] The utility was highlighted through conversion to valuable tryptamine derivatives possessing an enantioenriched benzylic stereogenic center. Analogous to Fu's method, *ortho*-substituted nitroalkenes were unreactive, however the authors do include examples of alkyl (benzyl and *n*-octyl **4.63**) substituted nitro alkenes.

Suresh found that titanium-based salen complexes could effectively catalyze conjugate addition of cyanide **4.65** to aromatic nitroalkenes in 52–92% yield and 76:24–95.5:4.5 er (Scheme 4.9c).[40] The obtained products may then be converted to trifluoromethyl-substituted β-amino acids. It is noteworthy that, contrary to the Ni-based protocols detailed above, this method can tolerate *o*-fluoro- and *o*-methoxy-substituted arenes furnishing products in 99:1 and 87.5:12.5 er, respectively.

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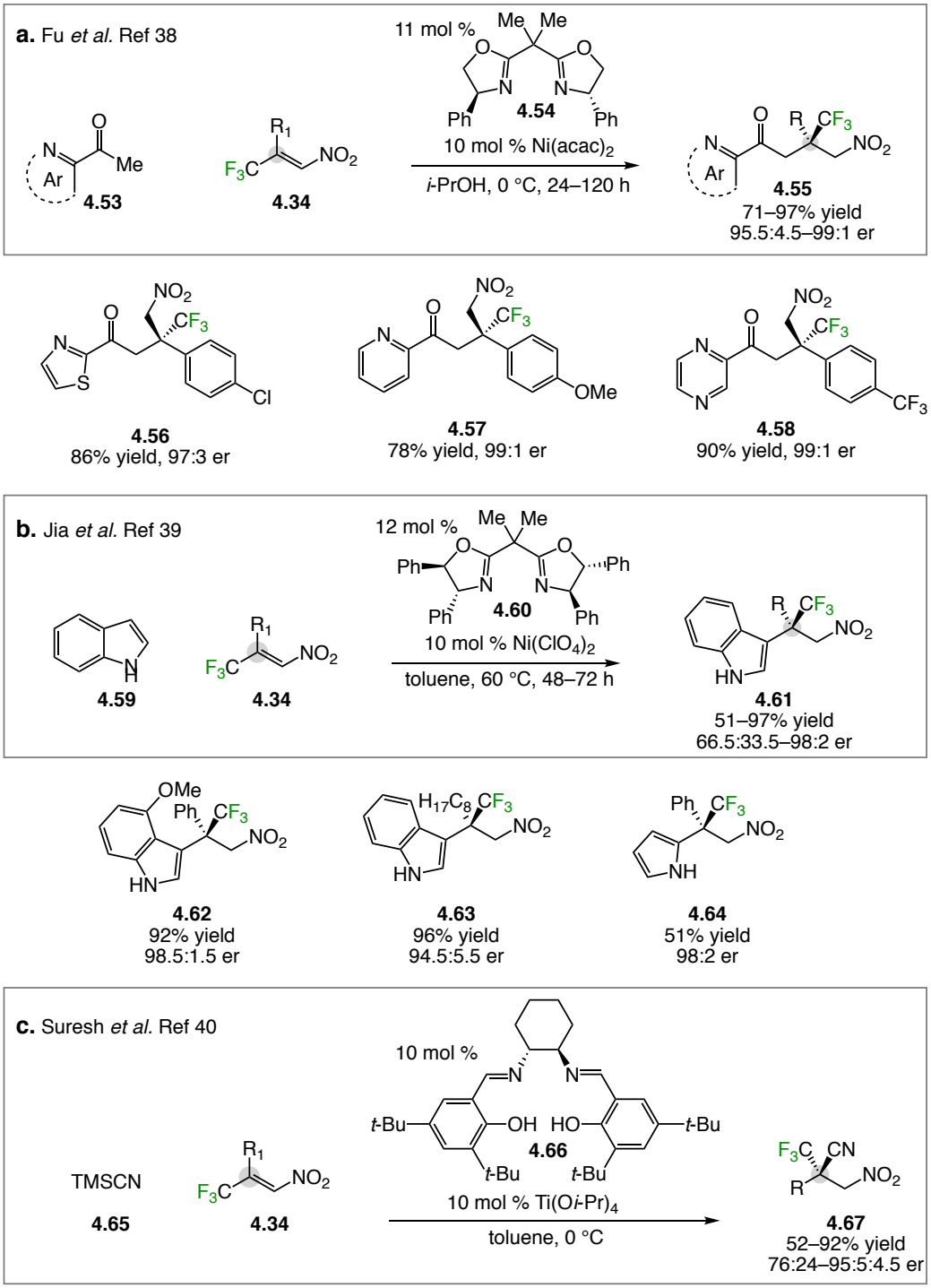
38) Hou, X.; Ma, H.; Zhang, Z.; Xie, L.; Qin, A.; Fu, B. *Chem. Commun.* **2016**, *52*, 1470–1473. For a related report involving a Co-based complex, see: Hao, X.-Q.; Wang, C.; Liu, S.-L.; Wang, X.; Wang, L.; Gong, J.-F.; Song, M.-P. *Org. Chem. Front.* **2017**, *4*, 308–312.

39) Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, L.; Jia, Y-X. *J. Am. Chem. Soc.* **2013**, *135*, 2983–2986.

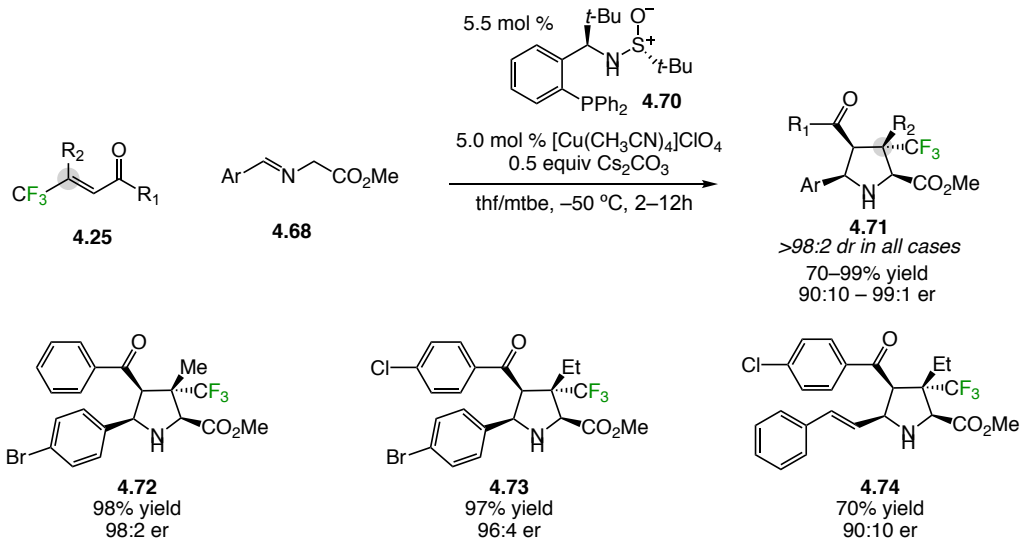
40) Jakhar, A.; Kumari, P.; Nazish, M.; Khan, N. H.; Kureshy, R. I.; Abdi, S, H. R.; Suresh, E. *RSC Adv.* **2016**, *6*, 29977–29982.

Scheme 4.9. Catalytic Enantioselective Additions to Nitroalkenes Promoted by Ni and Ti-Based Complexes



Zhang has disclosed diastereo- and enantioselective [3+2] cycloaddition of azomethine ylides **4.68** and trifluoromethyl substituted enones[41] and esters[42] for synthesis of pyrrolidines **4.71**. The method exhibits a broad scope, affording products in 70–99% yield and 90:10–99:1 er and is promoted by a ligand well suited to rapid library generation due to its modular synthesis. In a related account, Zhou accomplished synthesis of the same class of pyrrolidines through dipolar cycloaddition of azomethine ylides and nitro alkenes furnishing nitro-substituted pyrrolidines in 71–86% yield and 95.5:4.5–99:1 er.[43]

Scheme 4.10. Synthesis of Trifluoromethyl-Substituted Pyrrolidines through Catalytic Diastereo- and Enantioselective [3+2] Addition



41) Zhang, Z.-M.; Xu, B.; Xu, S.; Wu, H.-H.; Zhang, J. *Angew, Chem. Int. Ed.* **2016**, *55*, 6324–6328.

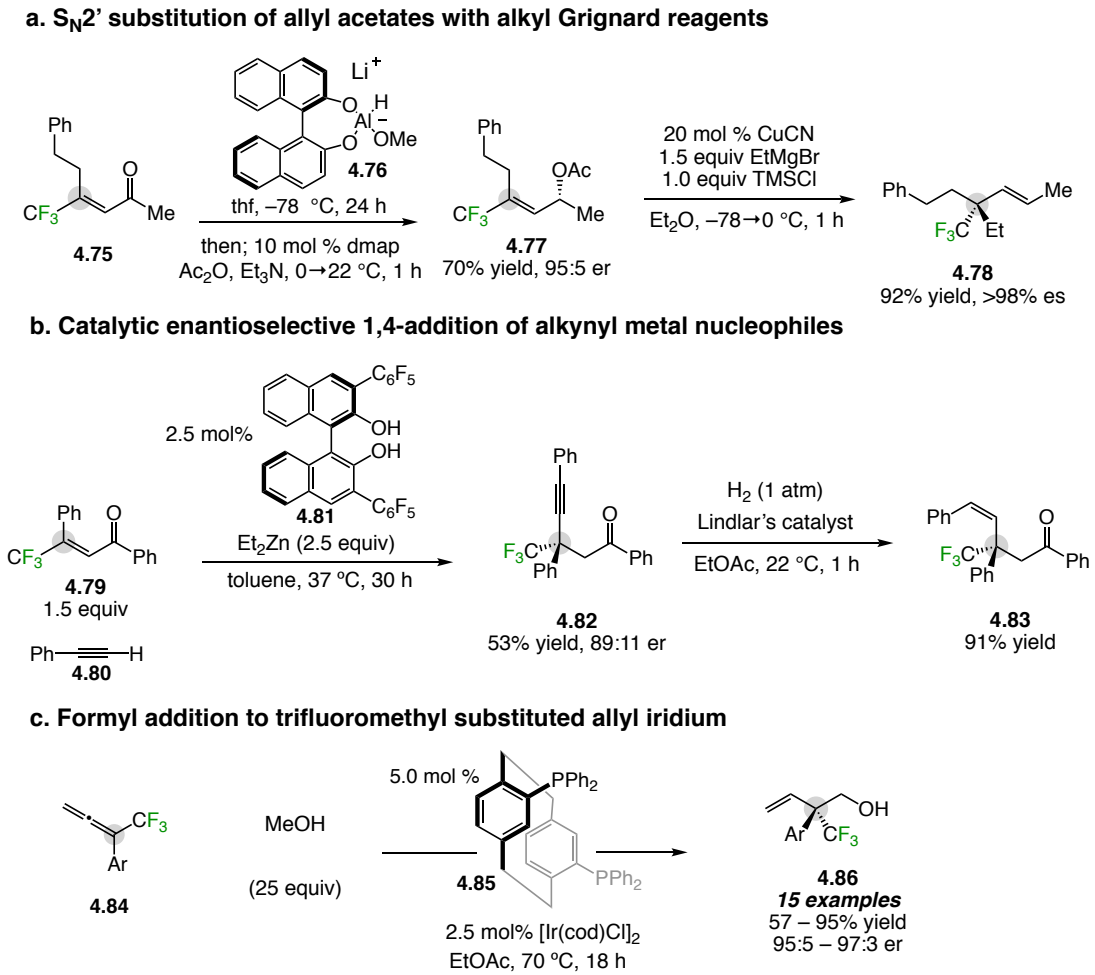
42) Xu, B.; Zhang, Z.-M.; Xu, S.; Liu, B.; Xiao, Y.; Zhang, J. *ACS Catal.* **2017**, *7*, 210–214.

43) Tang, L.-W.; Zhao, B.-J.; Daie, L.; Zhang, M.; Zhou, Z.-M. *Chem. Asian J.* **2016**, *11*, 2470–2477.

4.2.3 Enantioselective Synthesis of Allylic or Propargylic Quaternary Stereogenic Centers Bearing a Trifluoromethyl Group

There are few examples detailing synthesis of an allylic trifluoromethyl-substituted quaternary stereogenic center, despite the potential of these motifs as synthetic building blocks.

Scheme 4.11. Methods for Synthesis of Allylic F_3C-Subsituted Stereogenic Centers



In 2004, Yamazaki reported S_N2' addition of alkyl Grignard reagents to enantioenriched allylic acetate **4.77,** obtained through reduction of the corresponding

enone with stoichiometric (*R*)-BINAL-H.[44] In the presence of a suitable copper salt, namely CuCN, and chlorotrimethylsilane as an additive to promote rapid reductive elimination as a result of a favorable β-silicon effect,[45] **4.78** was isolated as a single olefin isomer with >98% enantiospecificity and in 92% yield (Scheme 4.11a).

In a different approach, Pedro described the first example of addition of alkynyl-Zn compounds to trifluoromethyl-substituted enones (Scheme 4.11b).[46] The method is suitable for additions to compounds that are alkyl or aryl-substituted, albeit the former was obtained in 71.5:28.5 er for one containing a methyl substituent. The utility of the propargylic stereocenter in **4.82** was highlighted through stereoselective reduction to *Z*-olefin **4.83**, in addition to iodine-induced cyclization for synthesis of pyran derivatives.

Krische has developed a method for synthesis of allylic quaternary stereogenic centers by reductive coupling of trifluoromethyl-substituted allenes and in-situ generated formaldehyde.[47] The method has broad scope, affording **4.86** in 57–95% yield and 95:5–97:3 er. Nonetheless, applicability is limited to aryl-substituted allenes. This is likely due to low yielding or inefficient preparations of trifluoromethyl-containing alkyl-substituted allenes,[47b] a fact that highlights current deficiencies in the state-of-the-art.

Most recently, Aggarwal and co-workers described ring opening of trifluoromethyl-substituted epoxide **4.87**, furnishing boronic ester **4.91**.[48] Notably, the reaction affords a mixture of separable regioisomers resulting from [1,2]-shift of either the alkyl group or the oxygen substituent on boron. The fact that the latter is observed is likely

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44) Kimura, M.; Yamazaki, T.; Kitazume, T.; Kubota, T. *Org. Lett.* **2004**, *6*, 4651–4654.

45) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023–11024.

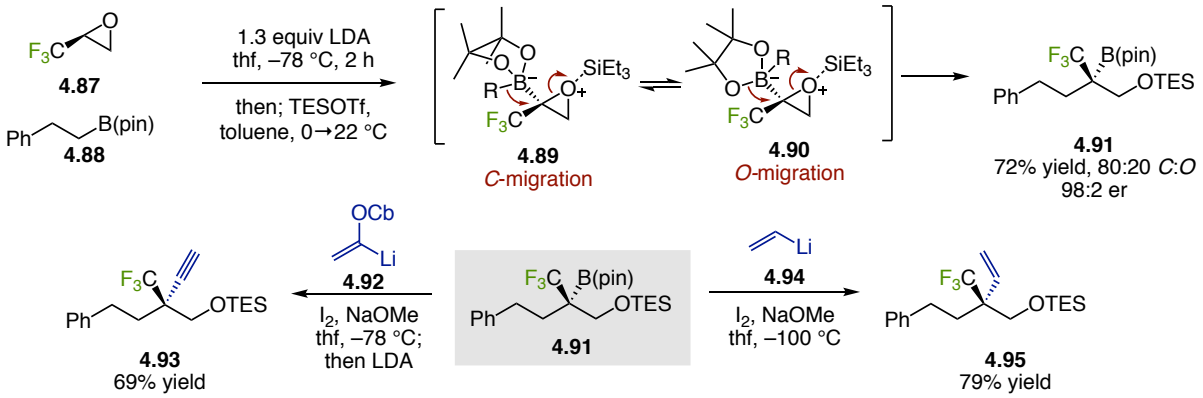
46) Sanz-Marco, A.; Blay, G.; Vila, C.; Pedro, J. R. *Org. Lett.* **2016**, *18*, 3538–3541.

47) Holmes, M.; Nguyen, K. D.; Schwartz, L. A.; Luong, T.; Krische, M. J. *J. Am. Chem. Soc.* **2017**, *139*, 8114–8117. For examples of preparation of alkyl-substituted allenes, see: Miyake, Y.; Ota, S.-i.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commu.* **2013**, *49*, 7809–7811.

48) Nandakumur, M.; Rubial, B.; Noble, A. Myers, E. L.; Aggarwal, V. K. *Angew. Chem, Int. Ed.* **2020**, *59*, 1187–1191.

consequence of the trifluoromethyl group and emphasizes how incorporation of such motifs can alter the reactivity of organic compounds. Products bearing otherwise difficult-to-access quaternary allylic and propargylic stereogenic centers were accessed through well-known methods for conversion of the obtained boronic esters.

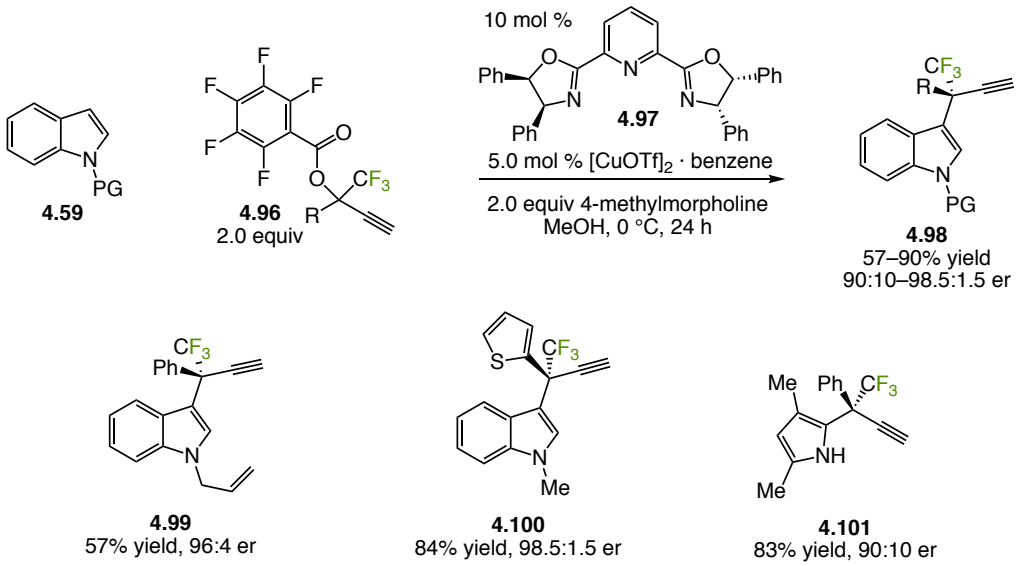
Scheme 4.12. Ring Opening of Trifluoromethyl-Substitued Epoxides through [1,2]-Metallate Shift



In a different approach, Nishibayashi developed a method for substitution of racemic propargylic perfluorobenzoates **4.96** with indole.[49] In the presence of a Cu-based pybox complex, **4.98** was obtained in 71–86% yield and 96.5:3.5–98.5:1.5 er, with similar results for reaction with other nitrogen-containing heterocyles such as pyrrole **4.101**. The utility of the terminal alkyne was highlighted by conversion to various triazoles through cycloaddition in a single vessel.

49) Tsuchida, K.; Senda, Y.; Nakajima, K.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 9728–9732.

Scheme 4.13. Synthesis of Propargylic F_3C-Substitued Stereogenic Centers



4.2.4 Catalytic Enantioselective Formation of All-Carbon Quaternary Centers Bearing a Trifluoromethyl Group (Cyclic Systems)

Access to compounds containing trifluoromethyl-substituted quaternary stereogenic centers in cyclic systems are lacking,[50] and there are just five reports to date describing their synthesis. The earliest, disclosed by Gade in 2012, relates to enantioselective trapping of Cu-based enolates with Togni's reagent **4.3** furnishing products (**4.104**) in 83–94% yield and 90:10–99:1 er (Scheme 4.14a).[51] The method is suitable for reaction of 5- and 6-membered ketoesters, although enantioselectivities were diminished for the latter. Cahard has contributed to the field, developing a method for enantioselective synthesis of identical compounds promoted by chiral guanidine bases, however, selectivity did not exceed 85:15 er, even at –80°C.[52] Most recently, Togni

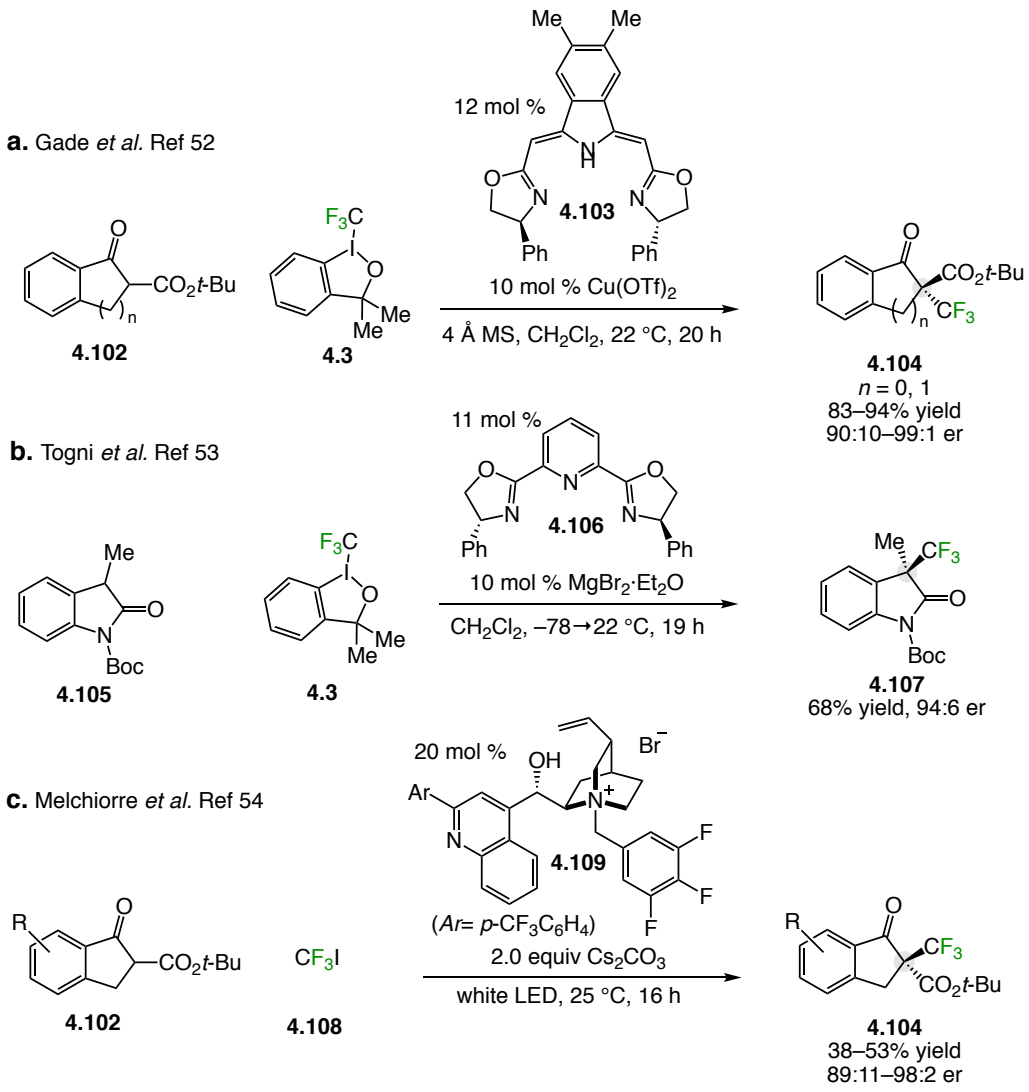
50) For an example of this motif in a bioactive molecule, see: Luzina, E. L.; Popov, A. V. *J. Fluorine Chem.* **2014**, *168*, 121–127.

51) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769–10772.

52) Noritake, S.; Shibata, N.; Nomura, Y.; Huang, Y.; Matsnev, A.; Nakamura, S.; Toru, T.; Cahard, D. *Org. Biomol. Chem.* **2009**, *7*, 3599–3604.

provided a single example of enantioselective synthesis of trifluoromethyl-substituted oxidole **4.107** in 68% yield and 94:6 er (Scheme 4.14b).[53]

Scheme 4.14. Enantioselective Synthesis of Cyclic Motifs Possessing a Quaternary Stereogenic Center



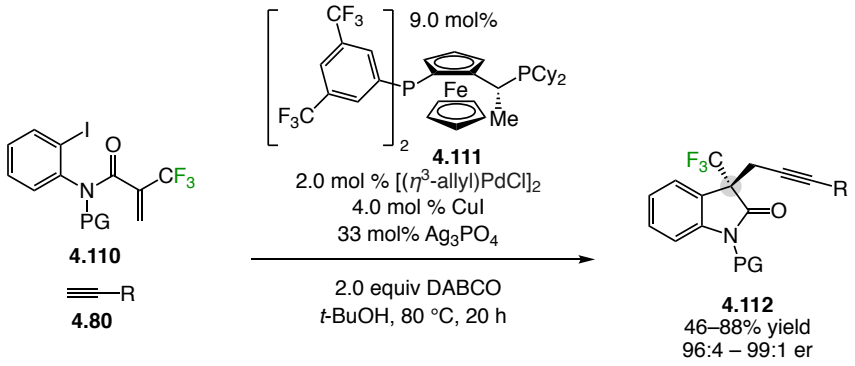
In 2015, Melchoirre developed a catalytic enantioselective method for introduction of perfluoro alkyl groups through reaction of ketoesters **4.102** and alkyl iodides. The authors found that the method could be extended to reaction with CF_3I when promoted by

53) Katayev, D.; Kajita, H.; Togni, A. *Chem. Eur. J.* **2017**, *23*, 8353–8357.

cinchona alkaloid phase transfer catalyst **4.109**.[54] Thus, under these reaction conditions, compounds containing quaternary stereogenic centers were isolated, however enantioselectivity fluctuated depending on the substitution pattern of the aromatic ring (e.g., R=H, 98:2 er; R=3-CH_3, 89:11 er) and yields did not exceed 53% (Scheme 4.14c).

This year, Ge and Lu disclosed a method for synthesis of oxindoles **4.112** bearing a trifluoromethyl-substituted quaternary center through sequential Heck coupling of iodoacrylanilides **4.110** and a terminal alkyne **4.80**.[55] The method has considerable scope, tolerating a variety of nitrogen protecting groups including alkyl (–CH_3, –Bn) and aryl (paramethoxybenzyl) substitution, in addition to alkyl, aryl and silyl substituents on the alkyne affording products **4.122** in 46–88% yield and 96:4–99:1 er.

Scheme 4.15. Synthesis of Trifluoromethyl Substituted Oxindoles



54) Woźniak, L.; Murphy, J. J.; Melchiorre, P. *J. Am. Chem. Soc.* **2015**, *137*, 5678–5681.

55) Bai, X.; Wu, C.; Ge, S; Lu, Y. *Angew. Chem. Int. Ed.* **2020**, *59*, 2764–2768.

4.2.5 Synthesis and Unique Reactivity of Allyl Fluorides

Due to the well-known benefits of incorporation of fluorine[56] countless methods have been developed for synthesis of these motifs.[57] In fact, in 2018 alone, 17 new therapeutics approved by the FDA contained fluorine,[58] however, the majority of these moieties are substituted on Csp^2 atoms, as a result of advances enabled by metal-mediated reactions.[59] Far less common are methods for synthesis Csp^3 fluoro-substituted centers, despite emerging evidence of the benefits of such a motif, as indicated by the recently developed therapeutic candidates shown in Scheme 4.16.[60]

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56) (a) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (c) Purser, S.; Moore, P. R.; Swallow, S. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (d) Hunter, L. *Bielstein J. Org. Chem.* **2010**, *6*, doi 10.3762/bjoc.6.38. (e) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432–2506. (f) Ilardi, E. A.; Vitaku, E.; Njardson, J. T. *J. Med. Chem.* **2014**, *57*, 2832–2842. (g) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Med. Chem.* **2015**, *58*, 9041–9060. (h) Berger, A. A.; Völler, J.-S.; Budisa, N.; Koksch, N. *Acc. Chem. Res.* **2017**, *50*, 2093–2103. (i) Huhmann, S.; Koksch, B. *Eur. J. Org. Chem.* **2018**, 3667–3679. Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822–5880.

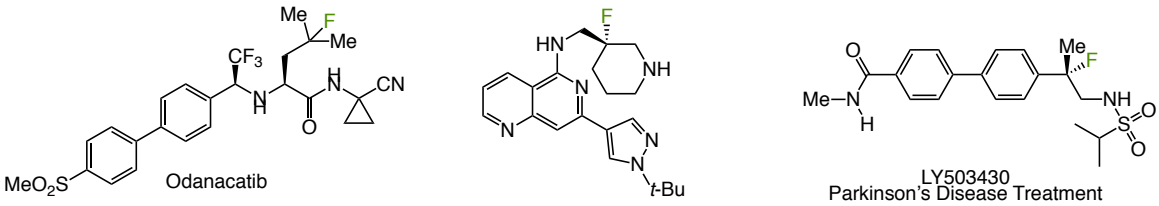
57) (a) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065–2075. (b) Cahard, D,; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev*. **2010**, *39*, 558–568. (c) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708–2732. (d) Yerien, D. E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 8398–8427.

58) Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D. M.; Santi, C.; Ruzziconi, R.; Soloshonok, V. A. *Chem. Eur. J.* **2019***, 25*, 11797–11819.

59) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477.

60) For synthesis of odanacatib, see: O'Shea, P. D.; Chen, C.-y.; Gauvreau, D.; Gosselin, F.; Hughes, G.; Nadeau, C.; Volante, R. P. *J. Org. Chem.* **2009**, *74*, 1605–1610. For synthesis of tyrosine kinase inhibitor, see, Curtis, N. R.; Davies, S.; Gray, M.; Leach, S. G.; McKie, R. A.; Vernon, L. E.; Walkington, A. *Org. Process Res. Dev.* **2015**, *19*, 865–871. For synthesis of LY503430, see: Duthion, B.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2010**, *12*, 4620–4623.

Scheme 4.16. Representative Bioactive Compounds with Quaternary Fluoro-Substituted Stereogenic Centers



A common method for introduction of fluorine at a Csp^3 center is substitution of an alcohol with DAST (diethylaminosulfur trifluoride) or Deoxo-fluor (bis-2-methoxyethylaminosulfur trifluoride). In addition to poor functional group tolerance, these reactions can lead to mixtures of regioisomeric products when allylic alcohols are the substrate. A representative example is shown in Scheme 4.17a, where Rapp attempted synthesis of allylic fluoride **4.114**, obtaining the desired quaternary fluoro-substituted center in 26% yield.[61] Further complicating the issue, the reaction proceeds with inversion of stereochemistry. In fact, the stereochemical outcomes for substitution are often unpredictable and substrate dependent. For instance, in a campaign to synthesize fluorinated prostaglandins, Kurozumi and co-workers found that no matter the epimer of allylic alcohol **4.116** they attempted to transform, only a single diastereomeric product **4.117** was isolated (Scheme 4.17b).[62] This is contrary to reports by Erasmuson, wherein stereochemistry was inverted for cases involving acyclic allylic alcohols,[63] and those by Troupet where introduction of fluorine was stereoretentive in the presence of an iron

61) Rapp, M.; Bilska, M.; Koroniak, H. *J. Fluorine Chem.* **2011**, *132*, 1232–1240. For a detailed review regarding allylic and propargylic fluorides, see: Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943–1981.

62) (a) Bannai, K.; Toru, T.; Oba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Hazato, A.; Kurozumi, S. *Tetrahedron,* **1983**, *39*, 3807–3819. (b) Sugiura, S.; Toru, T.; Tanaka, T.; Okamura, N.; Hazato, A.; Bannai, K.; Manabe, K.; Kurozumi, S. *Chem. Pharm. Bull.* **1984**, *32*, 1248–1251.

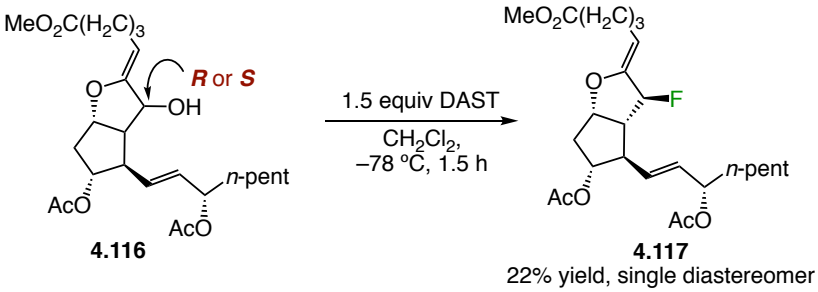
63) Cross, B. E.; Erasmuson, A. *J. Chem. Soc, Chem. Commun.* **1978**, 1013–1015.

carbonyl co-catalyst.[64] Furthermore, the activated intermediate is susceptible to intramolecular displacement even in the presence of weakly nucleophilic groups. For instance, when transformation of Boc-protected amino alcohol **4.118** was attempted, the corresponding aziridine **4.119** was isolated in 65% yield (Scheme 4.17c).[65]

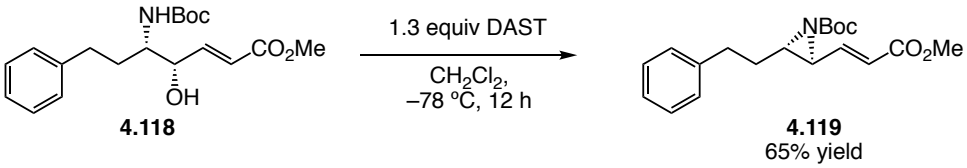
Scheme 4.17. Challenges Associated with Conventional Strategies for Substitution of Allylic Alcohols

a. Inversion of configuration

b. Diastereoconvergent fluorination of prostaglandins



c. Intramolecular displacement of activated allyic alcohol



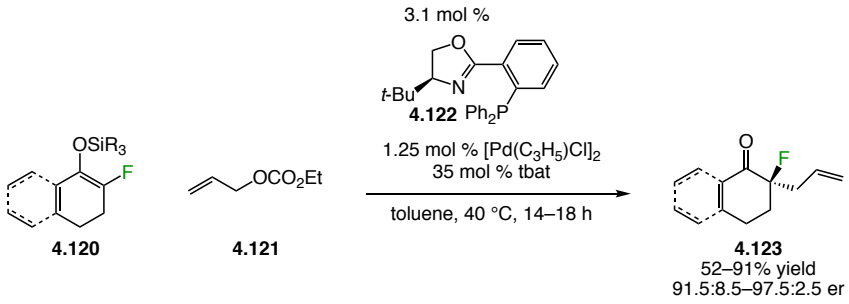
64) Gree, D. M.; Kermarrec, C. J. M.; Martelli, J. T.; Gree, R. L.; Lellouche, J.-P.; Troupet, L. J. *J. Org. Chem.* **1996**, *61*, 1918–1919.

65) Li, Y.-L.; Luthman, K.; Hacksell, U. *Tetrahedron Lett.* **1992**, *33,* 4487–4490.

4.2.6 Catalytic Enantioselective Synthesis of Quaternary Carbons Containing Fluorine

Strategies for synthesis of cyclic and acyclic carbonyl compounds possessing an α-fluoro-substituted stereogenic center are well established.[66] One representative example, as described by Paquin,[67] furnishes these motifs through addition of silyl enol ether **4.120** to allyl carbonate **4.121** (Scheme 4.18). Since the method does not require *β*-ketoesters as the substrate, as most others do, the need to extrude carbon dioxide in a subsequent synthetic manipulation is obviated.

Scheme 4.18. Reaction of Silyl Enol Ethers with Allyl Carbonates



A more recent example, involves conversion of racemic branched aldehydes to homobenzylic alcohols (**4.128-129)** with a fluoro-substituted stereogenic center (Scheme 4.19).[68] Upon reaction with primary amine catalyst **4.126**, the likely in situ generated enamine may be quenched by reaction with NFSI. After reductive work-up,

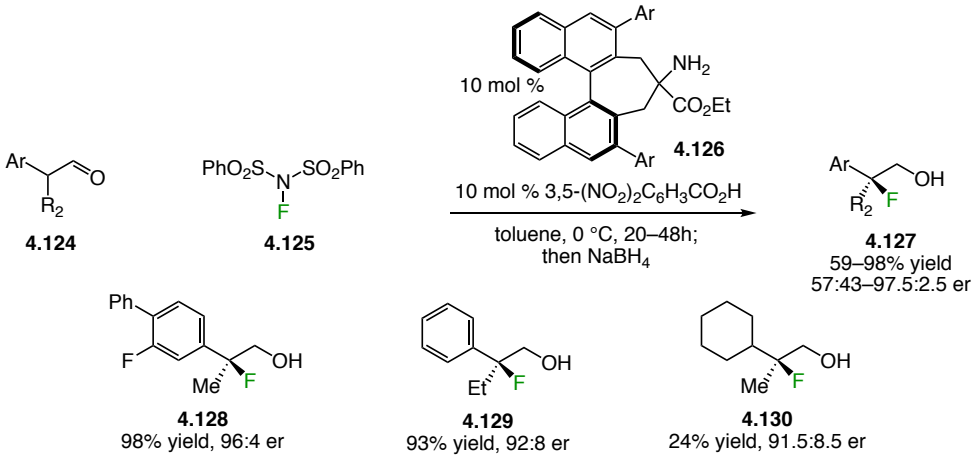
66) For a comprehensive review, see: Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. *Chem. Rev.* **2018**, *118*, 3887–3964.

67) Bélanger, E.; Cantin, K.; Messe, O.; Trembaly, M.; Paquin, J. F. *J. Am. Chem. Soc.* **2007**, *129,* 1034–1035.

68) Shibatomi, K.; Kitahara, K.; Okimi, T.; Abe, Y.; Iwasa, S. *Chem. Sci.* **2016**, *7*, 1388–1392. For other examples of fluorination of aldehydes, see: (a) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jϕrgensen, K. A. *Chem. Eur. J.* **2006**, *12*, 6039–6052. (b) Shibatomu, K.; Yamamoto, H. *Angew. Chem, Int. Ed.* **2008**, *47*, 5796–5798. (c) Witten, M. R.; Jacobsen, E. N. *Org. Lett.* **2015**, *17*, 2772–2775. (d) Emma, M. G.; Lombardo, M.; Trombini, C.; Quintavalla, A. *Eur. J. Org. Chem.* **2016**, 3223–3232.

enantiomerically enriched alcohols were generated in 59–98% yield and 57:43–97.5:2.5 er. Additions to aliphatic aldehydes **4.130**, however, were less efficient (24% yield).

Scheme 4.19. Synthesis of Homobenzylic Alcohols Containing a F-Substituted Stereogenic Center



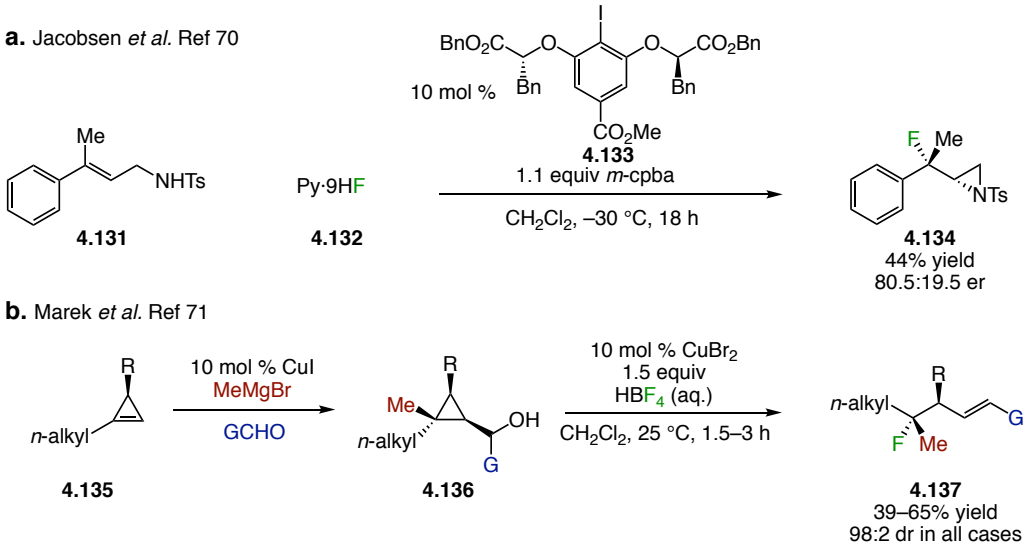
Strategies for synthesis of quaternary fluoro-substituted stereogenic centers that are not adjacent to a carbonyl may be divided into two classes: (1) Reaction with a source of electrophilic fluorine (e.g., NFSI or Selectfluor)[69] or addition of fluoride to an activated substrate. (2) Employing a building block that already contains fluorine. Representative examples for each of these cases are described below.

In 2018, Jacobsen accomplished synthesis of β-fluoroaziridines through oxidative functionalization of homoallylic amines.[70] In the presence of C_2-symmetric iodoarene catalyst **4.133**, the alkene may be sufficiently activated for addition of fluoride, thus forming an intermediary $C_{sp}{}^3$-I^{III} species, and ensuing substitution furnished aziridine **4.134**. However, only a single example of synthesis of a compound bearing a quaternary stereogenic center was addressed (**4.134**, 44% yield and 80.5:19.5 er; Scheme 4.20a).

69) For reviews, see: (a) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065–2075. (b) Brunet, V. A.; O'Hagan, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 1179–1182.

70) Mennie, K. M.; Banik, S. M.; Reichert, E. C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2018**, *140*, 4797–4802.

Scheme 4.20. Nucleophilic Addition of Fluoride for Synthesis of Quaternary Stereogenic Centers



This year, Marek detailed an approach for synthesis of quaternary fluoro-substituted stereogenic centers through nucleophilic displacement of cyclic carbinols with tetrafluoroboric acid (Scheme 4.20b). Compounds **4.137**, possessing valuable vicinal stereocenters, were obtained in 39–65% yield as a single diastereomer.[71] Nonetheless, due to the requirement for an aqueous solution of HBF_4, competitive formation of tertiary alcohols was observed leading to diminished yields.

Among the approaches for synthesis of fluoro-substituted stereogenic centers,[72] methods for synthesis allylic moieties have received little attention. These compounds are known to induce conformational preferences for highly selective cycloadditions,[73] or may be elaborated through ozonolysis [74] or dihydroxylation [75] to access to high-value

71) Lanke, V.; Marek, I. *J. Am. Chem. Soc.* **2020**, *142*, 5543–5548.

72) (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1–PR43. (b) Valero, F.; Companyó, X.; Rios, R. *Chem. Eur. J.* **2011**, *17*, 2018–2037. (c) Yang, A.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826–870.

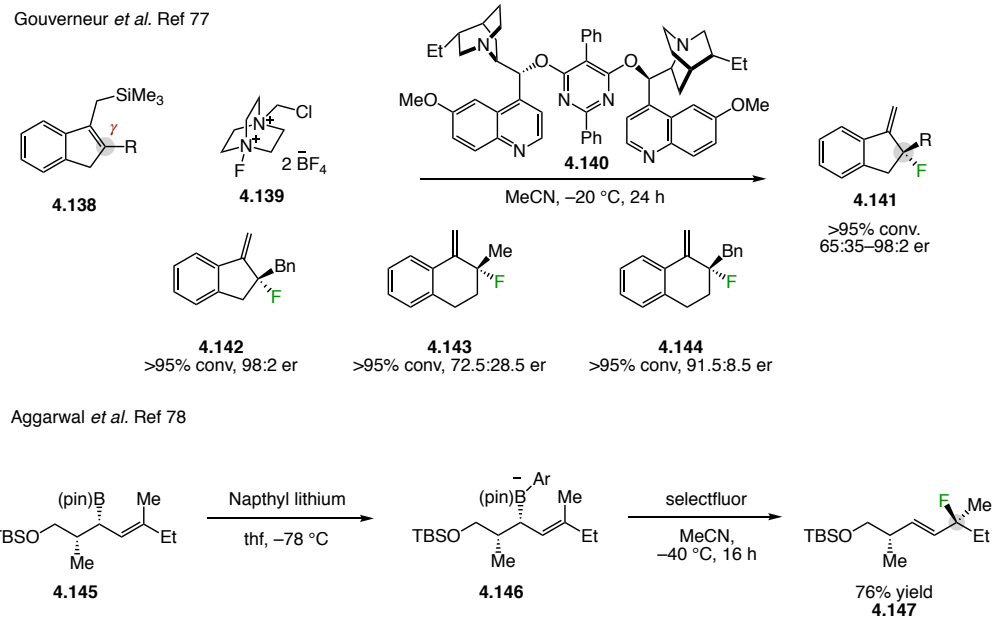
73) Grée, D.; Vallerie, L.; Grée, R.; Toupet, L.; Washington, I.; Pelicier, J.-P.; Villacampa, M.; Pérez, J. M.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 2374–2381.

74) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422–16423.

75) Hong, J. H.; Lee, K.; Choi, Y.; Chu, C. K.; *Tetrahedron Lett.* **1998**, *39*, 3443–3446.

organofluorine compounds. One strategy for preparation involves reaction of an allyl silane with Selectfluor.[76] In 2003, Gouverneur reported an enantioselective variant wherein cinchona alkoid **4.140** and selectfluor react in situ to generate an enantiomerically enriched source of fluorine. (Scheme 4.21a).

Scheme 4.21. Transformation Involving Allyl Silanes and Boronates



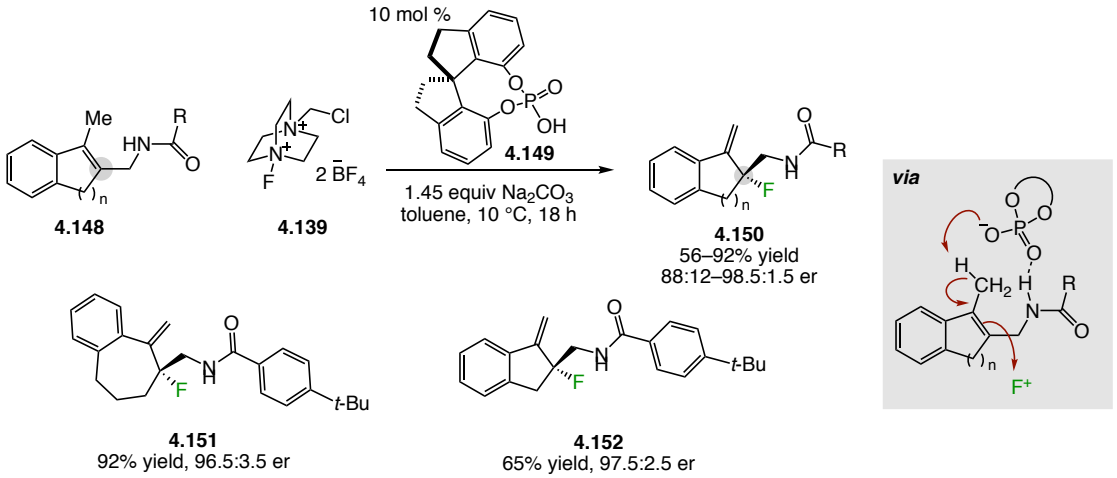
Despite high efficiency, enantiomeric ratios were dependent on the identity of the γ-substituent, with a benzyl group being optimal.[77] In the first example of enantioselective synthesis of acyclic allyl fluorides bearing a quaternary stereogenic center, Aggarwal

76) (a) Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891–4893.; (b) Tredwell, M.; Tenza, K.; Pacheco, M. C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 4495–4497. (c) Tredwell, M.; Gouverneur, V.; *Org. Biomol. Chem.* **2006**, *4*, 26–32. (d) Purser, S.; Odell, B.; Claridge, T. D. W.; Moore, P. R.; Gouverneur, V. *Chem. Eur. J.* **2006**, *12*, 9176–9185. (e) Purser, S.; Wilson, C.; Moore, P. R.; Gouverneur, V. *Synlett*, **2007**, 1166–1168. (f) Lam, Y.-H.; Bobbio, C.; Cooper, I. R.; Gouverneur, V.; *Angew. Chem. Int. Ed.* **2007**, *46*, 5106–5110. (g) Lam, Y.-H.; Hopkinson, M. N.; Stanway, S. J.; Gouverneur, V. *Synlett*, **2007**, 3022–3026. (h) Teare, H.; Robins, E. G.; Årstad, E.; Luthra, S. K.; Gouverneur, V. *Chem. Commun.* **2007**, *23*, 2330–2332.

77) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 3291–3294.

documented stereoselective tapping of enantiomerically pure boron-ate complex **4.146** with selectfluor furnishing allyl fluoride **4.147** in 76% yield and 95:5 dr. [78]

Scheme 4.22. Phosphoric Acid Promoted Synthesis of Exocyclic Allyl Fluorides



In 2013, Toste detailed an approach for synthesis of five to seven membered cyclic allyl fluorides. [79] In the presence of an ion pair comprised of phosphate **4.149** and Selectfluor **4.139,** obtained through exchange of one tetrafluoroborate anion, concerted deprotonation and incorporation of fluorine is proposed to generates β-fluoroamine derivatives **4.150** with an exocyclic olefin (Scheme 4.22).

In an ensuing report, the same authors developed a strategy for synthesis of enantioenriched allyl fluorides through 1,4-addition across conjugated dienes **4.153**, wherein 6-*endo*-trig cyclization furnished isoquinoline derivatives.[80] Di-**4.157–158** and tri-substituted olefins **4.156** with various styrenyl substituents and aryl amides were suitable substrates, as illustrated in Scheme 4.23. Attempts to synthesize to the opposite

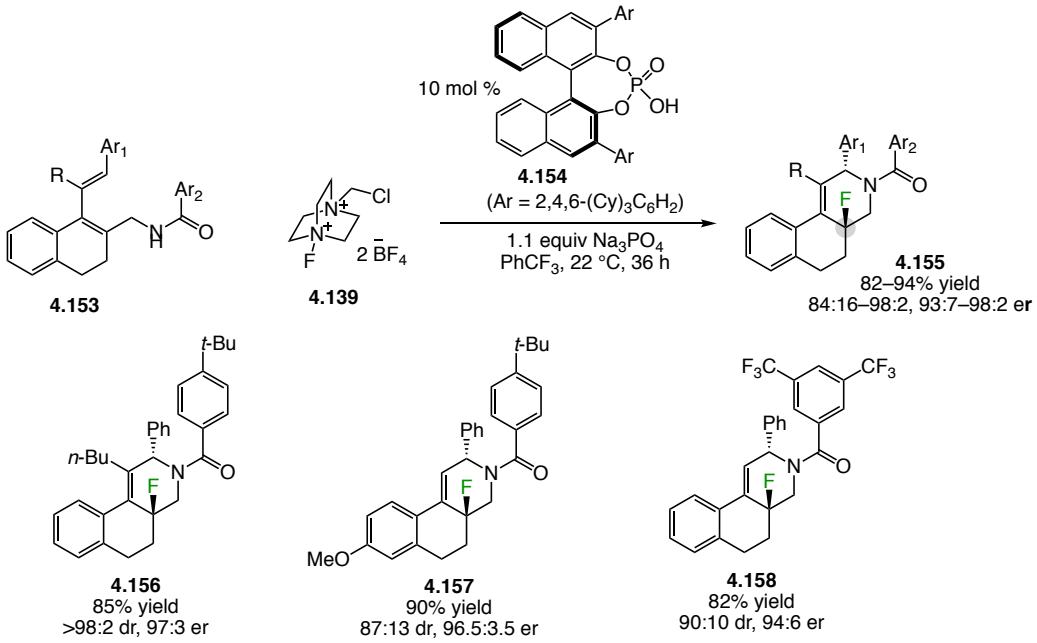
78) García-Ruiz, C.; Chen, J. L.-Y.; Sandford, C.; Feeney, K.; Lorenzo, P.; Berionni, G.; Mayr, H.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2017**, *139*, 15324–15327.

79) Wu, J.; Wang, Y.-M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 13729–13733.

80) Shunatona, H. P.; Früh, N.; Wang, Y.-M.; Rauniyar, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 7724–7727.

diastereomer, i.e., a *Z*-aryl olefin was utilized, were inefficient due to a buildup of allylic strain in the transition state.

Scheme 4.23. Toste's Method for Catalytic Enantioselective Addition to Dienes



In 2018, Hartwig outlined the first catalytic enantioselective method for allylic substitution affording acyclic allylic fluorides **4.162**,[81] previously only accessible in a racemic manner.[82] Additions of malonic acid derivatives **4.160** (including maleonitrile) to a variety of aryl and alkyl-substituted allyl carbonates furnished **4.162** in 56–98% yield and 74:26–99:1 er (Scheme 4.24a). In a subsequent disclosure,[83] the authors described diastereodivergent synthesis of organofluorine compounds, wherein two catalysts,

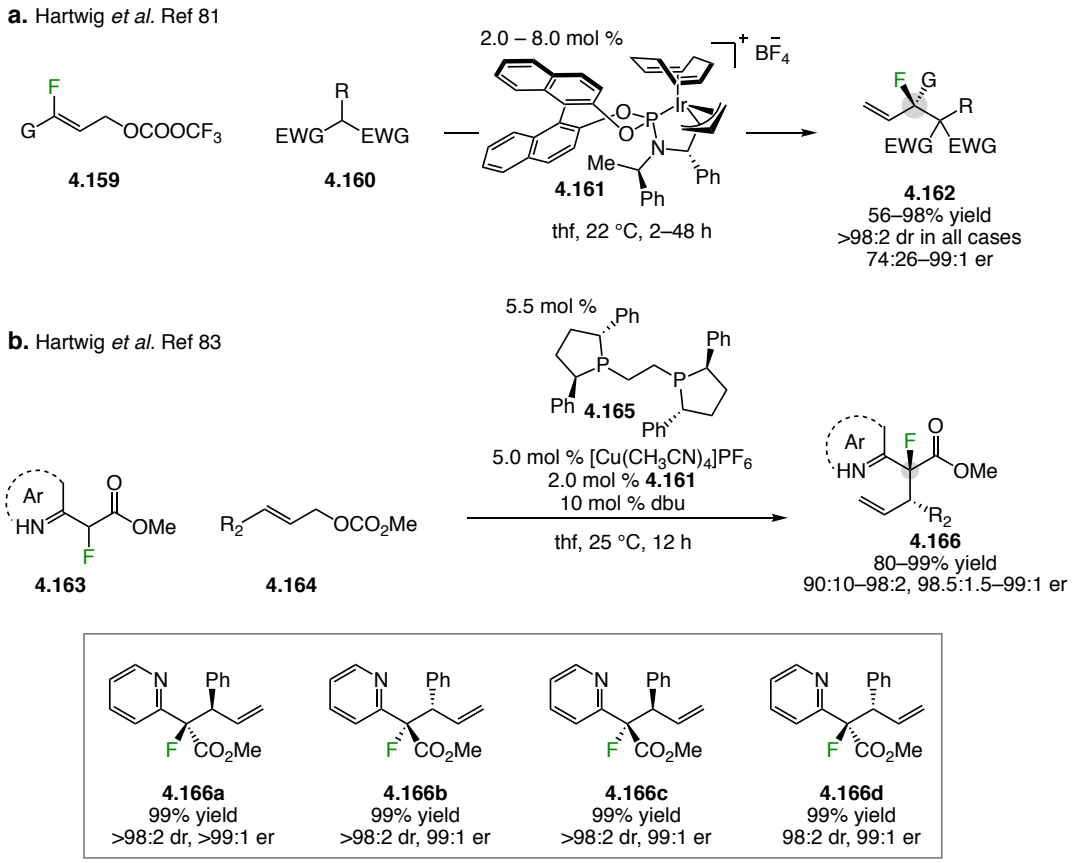
81) Butcher, T. W.; Hartwig, J. F. *Angew. Chem, Int. Ed.* **2018**, *57*, 13125–13129.

82) (a) Topczewski, J. J.; Tewson, T. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2011**, *133*, 19318–19321. (b) Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 15902–15905. (c) Konno, T.; Ikemoto, A.; Ishihara, T. *Org. Biomol. Chem.* **2012**, *10*, 8154–8163.

83) He, Z. T.; Jiang, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2019**, *141*, 13066–13073

phosphine-Cu complex **4.165** and iridium complex **4.161,** function cooperatively[84] to generate all four possible isomers in 99% yield and 99:1 er (Scheme 4.24b).

Scheme 4.24. Strategies for Allylic Substitution Involving Fluorine-Containing Species



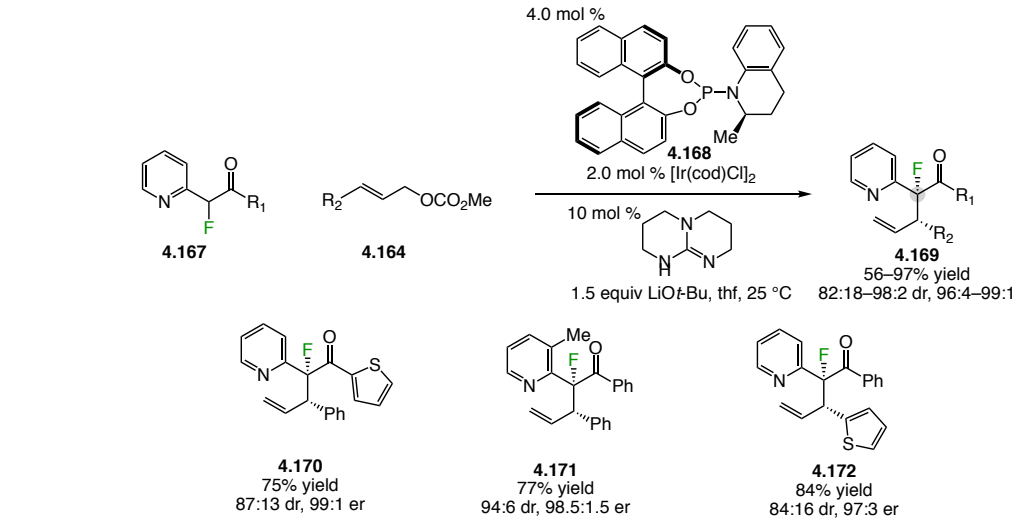
More recently, You has developed an approach for diastereodivergent allylic substitution involving acyclic pyridyl-substituted ketones **4.167**.[85] In contrast to Hartwig's method, only a single catalyst, **4.168**, was required to access to all four possible stereoisomers. This was accomplished by selecting an appropriate sequence i.e., C–C bond

84) This is an example of cooperative catalysis, formally designated as Type I, see: Romiti, F.; del Pozo, J.; Paioti, P. H. S.; Gonsales, S. A.; Li, X.; Hartrampf, F. W. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 17952–17961.

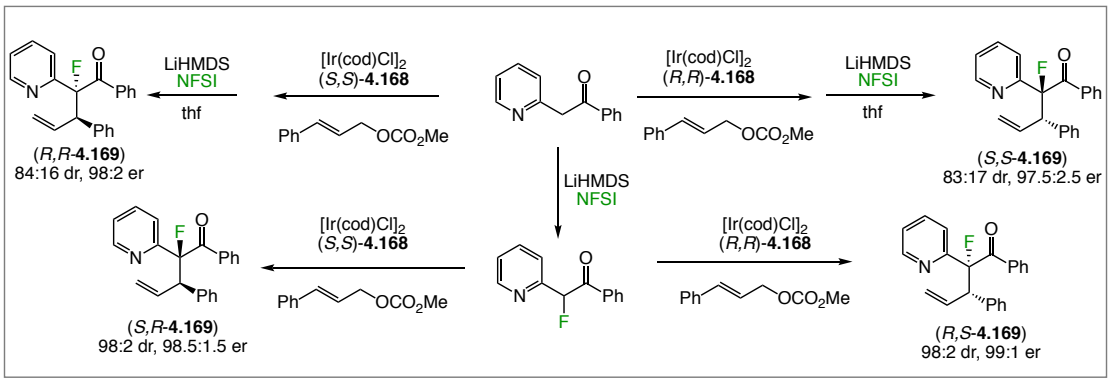
85) Xiu, X.-J.; Jin, S.; Zhang, W.-Y.; Liu, Q.-Q.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed.* **2020**, *59*, 2039–2043.

formation or introduction of fluorine as the first synthetic manipulation. Products **4.169**, were thus generated in 56–97% yield, 82:18–98:2 dr and 96:4–99:1 er.

Scheme 4.25. Sequence Specific Synthesis of Diastereomeric Quaternary F-Substituted Stereogenic Centers



b. Access to all diastereomers through sequence specific fluorination

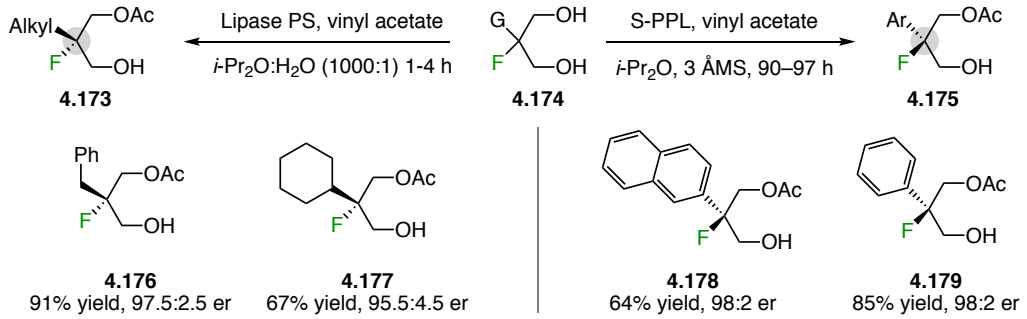


Resolution of fluorine containing diols represents another notable strategy.[86] Narisano has shown that porcine pancreas (PPL) is an effective catalyst for enantioselective acylation of fluorine-containing diols **4.178-179**. Under the same conditions, transformation of alkyl substituted cases were less efficient, however, synthesis of **4.176–**

86) (a) Guanti, G.; Marisans, E.; Riva, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1859–1862. (b) Narisano, E.; Riva, R. *Tetrahedron: Asymmetry,* **1999,** *10*, 1223–1242.

177 were accomplished with Lipase PS in non-anhydrous media, generating the corresponding products in up to 97.5:2.5 er.

Scheme 4.26. Enzymatic Resolution of Symmetrical Diols



4.2.7 Enantioselective Synthesis of Fluorine-Containing Homoallylic Alcohols

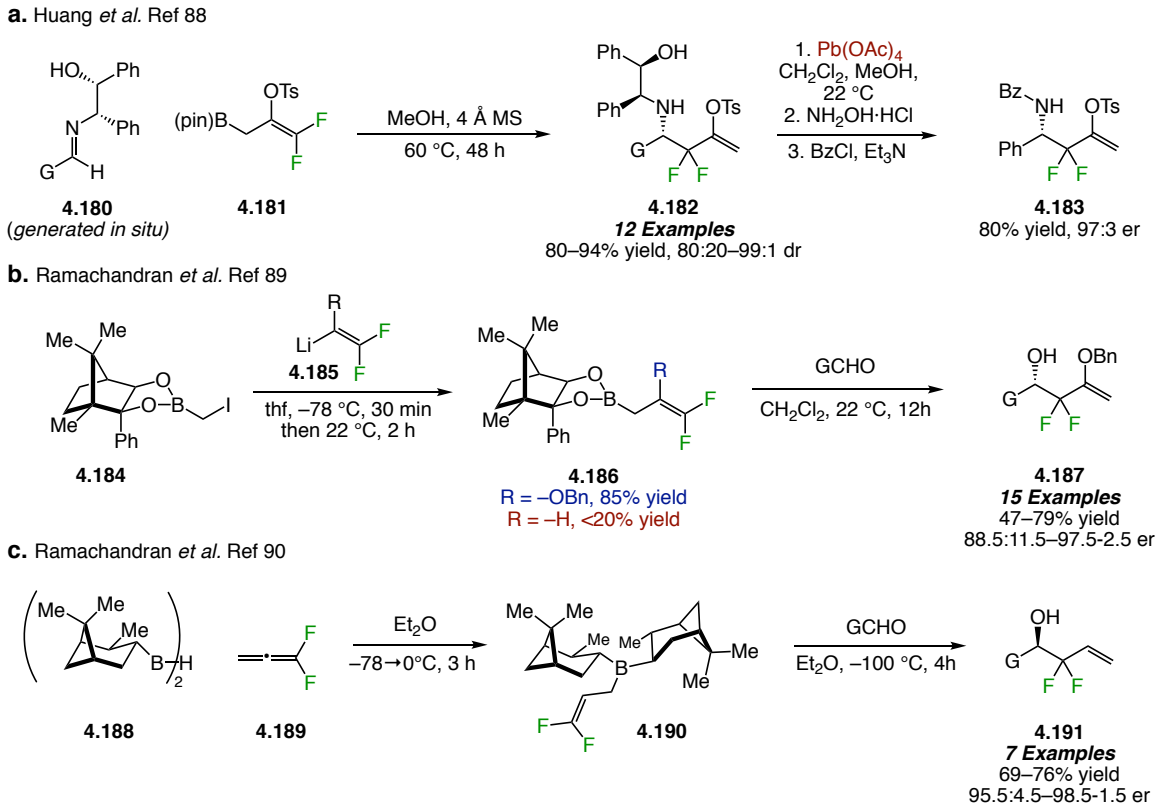
We are only aware of a few examples addressing synthesis of homoallylic alcohols[87] or amines through addition of fluoro-substituted allylmetal compounds. In a disclosure by Huang, enantiomerically pure imines **4.180**, generated in-situ, react with γ,γ-difluoroallyl boronate **4.181**, generating **4.182** in 80:20–99:1 dr and 80–94% yield (Scheme 4.27a).[88] However, the transformation requires 48 h at 60 °C for efficiency, and additions to aliphatic imines were not addressed. Furthermore, removal of the auxiliary required a three-step sequence involving reaction with $Pb(OAc)_4$, followed by treatment with hydroxylamine. Homoallylic alcohols containing a fluoro-substituted allylic carbon may be accessed through addition of enantiomerically pure γ,γ-difluoroallyl boronate **4.186**, however, an inherent limitation is that the C_2 substituent is required for efficient

87) For a radical-based transformation, see: Lang, S. B.; Wiles, R. J.; Kelly, C. B.; Molander, G. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 15073–15077.

88) Yang, X.; Cao, Z.-H,; Zhou, Y.; Cheng, F.; Lin, Z.-W.; Ou, Z.; Yuan, Y.; Huang, Y. Y. *Org. Lett.* **2018**, *20*, 2585–2589. Yang, X.; Zhang, F.; Zhou, Y.; Huang, Y-Y. *Org. Biomol. Chem.* **2018**, *16*, 3367–3371.

preparation of the boronate (Scheme 4.27b).[89] To access similar compounds without substitution (**4.191**), additions involving the more reactive alkyl borane **4.190** (prepared through treatment of fluorine-containing allene **4.189** with a pinene-derived borohydride) were required (Scheme 4.27c).[90]

Scheme 4.27. Additions of Fluorine-Containing Allyl Boron Reagents to Aldehydes and Imines

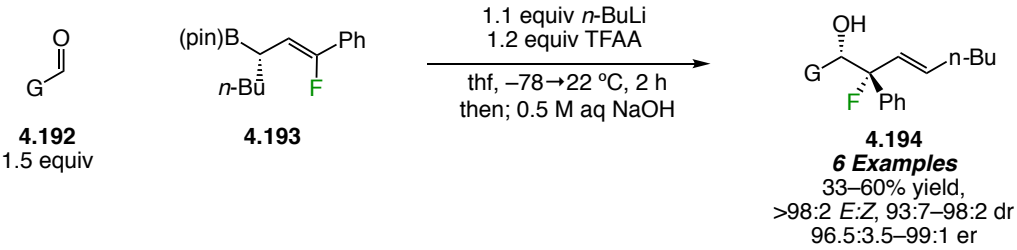


89) Ramachandran, P. V.; Tafelska-Kaczmarek, A.; Sakavuyi, K. *Org. Lett.* **2011**, *13*, 4044–4047. For examples of diastereoselective addition, see: (a) Ramanchandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195–1198. (b) Ramachandran, P. V.; Chatterjee, A. *J. Fluorine Chem.* **2009**, *130*, 144–150. (c) Ramachandran, P. V.; Tafelska-Kaczmarek, A.; Sakavuyi, K.; Chatterjee, A. *Org. Lett.* **2011**, *13*, 1302–1305.

90) Ramachandran, P. V.; Tafelska-Kaczmarek, A.; Chatterjee, A. *J. Org. Chem.* **2012**, *77*, 9329–9333.

Recently, our group [91] and others [92] have developed catalytic methods for preparation of fluorine-containing allyl boronates through boryl allylic substitution of trifluoromethyl substituted alkenes. Subsequent addition of the obtained γ,γ-difluoroallyl boronates to imines and aldehydes furnished homoallylic amines and alcohols with gem difluoromethyl motifs.[93] In 2019, in collaboration with Ito, we reported the first examples of regio- and stereoselective synthesis of trisubstituted fluorine-containing allyl boronates.[94] Subsequent addition to aldehydes generated homoallylic alcohols **4.194,** possessing a fluoro-substituted quaternary center in 33–60% yield.

Scheme 4.28. Reaction of Enantiomerically Enriched Trisubstituted Allyl Boronates



4.192
1.5 equiv

4.193

4.194
6 Examples
33–60% yield,
>98:2 *E*:*Z*, 93:7–98:2 dr
96.5:3.5–99:1 er

We reasoned that a more broadly applicable catalytic approach for additions would constitute a valuable addition to the state-of-the-art. Based on the benefits of incorporation of a fluoro- and trifluoromethyl motif, we reasoned a stereogenic center which incorporates each of these motifs could have a synergistic benefit.[95] Furthermore, the current state of-

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91) Corberan, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079–7082.

92) Liu, Y.; Zhou, Y.; Zhao, Y.; Qu, J. *Org. Lett.* **2017**, *19*, 946–949. Kojima, R.; Akiyama, S.; Ito, H. *Angew. Chem. Int. Ed.* **2018**, *57*, 7196–7199. Gao, P.; Yuan, C.; Zhao, Y.; Shi, Z. *Chem* **2018**, *4*, 2201–2211. Zhao, X.; Li, C.; Wang, B.; Cao, S. *Tetrahedron Lett.* **2019**, *60*, 129–132. For synthetic methods regarding synthesis of other fluorinated allyl compounds, see: Novikov, M. A.; Nefedov, O. M. *Org. Biomol. Chem.* **2018**, *16*, 4963–4967.

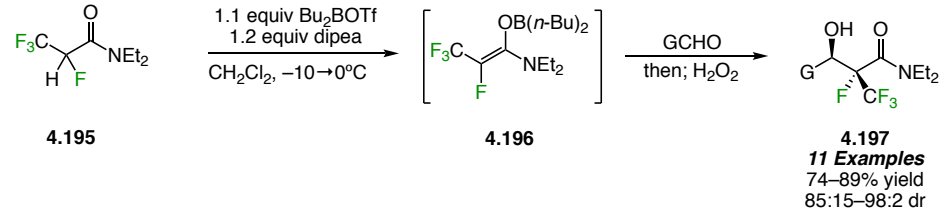
93) Liu, Y.-L.; Yu, J.-S.; Zhao, J. *Asian J. Org. Chem.* **2013**, *2*, 194–206.

94) Akiyama, S.; Kubota, K.; Mikus, M. S.; Paioti, P. H. S.; Romiti, F.; Liu, Q.; Zhou, Y.; Hoveyda, A. H.; Ito, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 11998–12003.

95) For a recent example of a bioactive compound with a halogenated quaternary center, see: Cherney, R. J.; Cornelius, L. A. M.; Srivastava, A.; Weigelt, C. A.; Marcoux, D.; Duan, J. J.-W.; Shi, Q.; Batt, D. G.; Liu, Q.; Yip, S.; Wu, D.-R.; Ruzanov, M.; Sack, J.; Khan, J.; Wang, J.; Yarde, M.; Cvijic, M. E.; Mathur, A.; Li,

the-art to access products of this sort was reported by Ishihara nearly three decades ago, and surrounds diastereoselective addition of boron-based enolates to aldehydes (Scheme 4.29).[96]

Scheme 4.29. Diastereoselective Addition of Boron-Based Enolates to Aldehydes



4.3 Transformations Involving Fluorine-Containing Allyl Boronates

4.3.1 Prior Work and Reaction Design

As we considered which catalytic platform might be best suited to promote addition, we were attracted to aminophenol boron-based complexes, an emerging class of catalysts capable of promoting efficient and enantioselective addition to a variety of electrophiles, particularly those containing fluorine.[97] For additions to trifluoromethyl-substituted ketimines and ketones, enantiofacial discrimination is likely the result of coulombic attraction between the trifluoromethyl group and the embedded ammonium

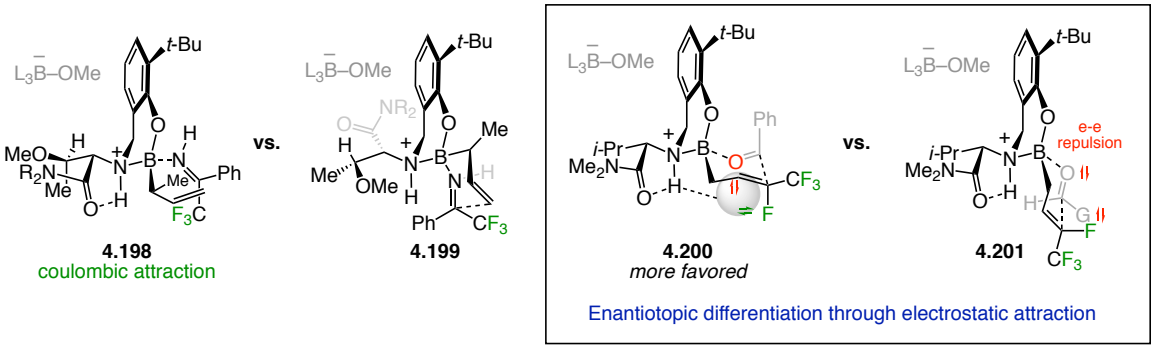
S.; Shuster, D.; Khandelwal, P.; Borowski, V.; Xie, J.; Obermier, M.; Fura, A.; Stefanski, K.; Cornelius, G.; Tino, J. A.; Macor, J. E.; Salter-Cid, L.; Denton, R.; Zhao, Q.; Carter, P. H.; Dhar, T. G. M. *ACS Med. Chem. Lett.* **2020**, doi: https://doi.org/10.1021/acsmedchemlett.0c00063

96) (a) Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc, Jpn.* **1990**, *63*, 1191–1195. Ishihara, T.; Kuroboshi, M.; Yamaguchi, K. *Chem. Lett.* **1990**, 211–214. (b) For non-selective addition of aluminum-based enolates to aldehydes, see: Ishihara, T.; Kuroboshi, M.; Yamaguchi, K.; Okada, Y. *J. Org. Chem.* **1990**, *55*, 3107–3114. (c) For diastereoselective reduction of related products, see: Ishihara, T.; Yamaguchi, K.; Kuroboshi, M.; Utimoro, K. *Tetrahedron Lett.* **1994**, *35*, 5263–5266.

97) Lee, K.; Silverio, D. L.; Torker, S.; Robbins, D. W.; Haeffner, F.; van der Mei, F. W.; Hoveyda, A. H. *Nature Chem.* **2016**, *8*, 768–777. For transformations of the same class, see: Fager, D. C.; Lee, K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 16125–16138. For propargyl addition, see: Mszar, N. W.; Mikus, M. S.; Torker, S.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 8736–8741.

(Scheme 4.30, **4.198)**. As illustrated in **4.200**, we questioned whether repulsion between fluorine on the catalyst's allyl unit and the oxygen lone pair may be alleviated through attraction with the ammonium ion, a stabilizing interaction that is not present in **4.201**. Whether these factors would be sufficient to render the transformation enantioselective remained to be determined.

Scheme 4.30. Elements of Reaction Design for Enantiofacial Discrimination

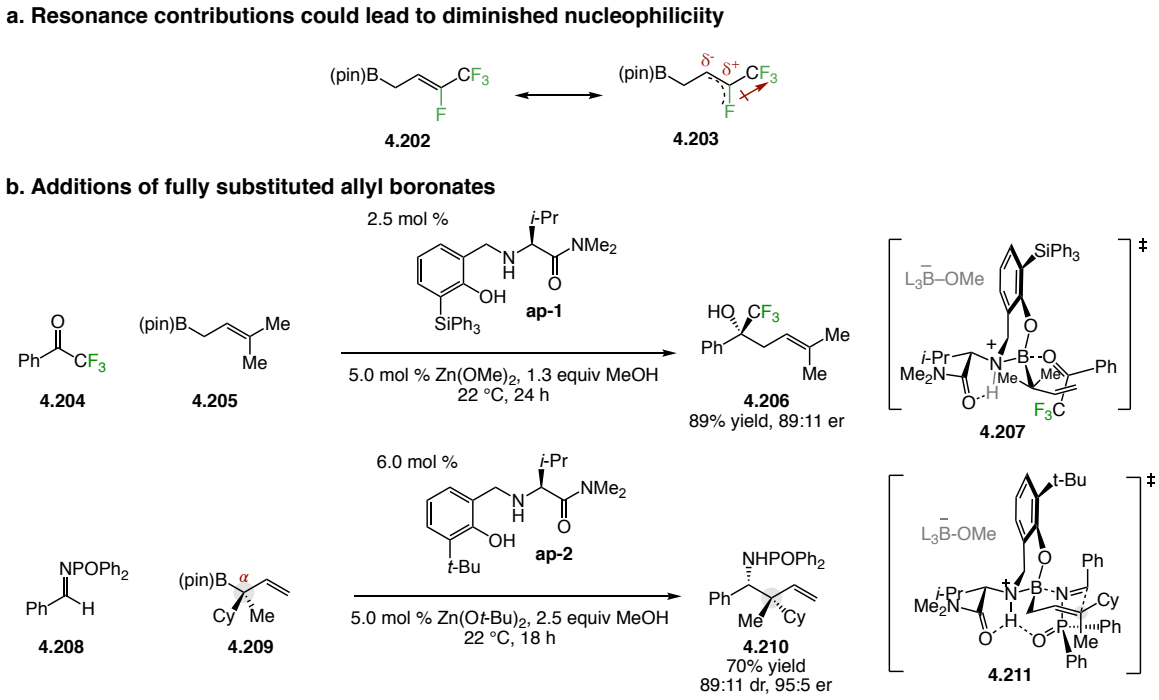


We then needed to address whether trisubstituted allyl boronates, particularly those possessing fluorine would efficiently react. As depicted in Scheme 4.31, π-donation from fluorine coupled with withdrawal of electron density through the σ-framework polarizes the alkene, thereby decreasing nucleophilicity (**4.203**). Making the situation even more tenuous, we had devoted previous effort almost exclusively to additions of disubstituted allyl boronates for synthesis of *Z* alkenes or tertiary allylic stereogenic centers. In fact, since our first disclosure, we have only accessed quaternary centers on two occasions. The first involves addition of enantioenriched allyl boronates to phosphinoyl aldimines, wherein γ-transfer of allyl boronate **4.209** furnishes a trisubstituted aminophenol allyl complex **4.211** that may subsequently react with a phosphinoyl imine.[98] The second

98) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216–221.

involves a single example of addition of prenyl-substituted allyl boronate **4.205** to trifluoroketone **4.204**,[99] wherein α-product **4.206** was furnished in 89% yield and 89:11 er.

Scheme 4.31. Additions of Substituted Allyl Boronates Promoted by Aminophenol Boron-Based Complexes



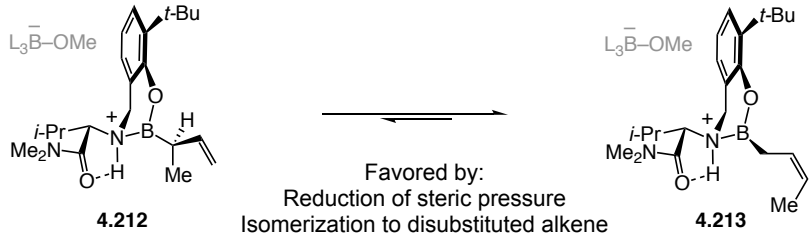
To access quaternary stereogenic centers possessing fluoro- and trifluoromethyl substitution, we rationalized that 1,3-boryl shift must preempt direct addition (Scheme 4.32c). It is plausible, that for additions to ketones, increased steric pressure, engendered by the two methyl substituents as a result of a change in hybridization at the boron center disfavors isomerization. While these factors may be implicated for an allyl boronate bearing two methyl groups, we postulated that one incorporating electron-withdrawing fluoro and trifluoromethyl moieties may enhance boron Lewis acidity. Thus, the strength of alkene coordination with the partially vacant p-orbital may be increased. We did have to contend with prior knowledge that addition of trifluoromethyl-substituted allyl boronate

99) van der Mei, F. W.; Qin, C.; Morrison, R. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 9053–9065.

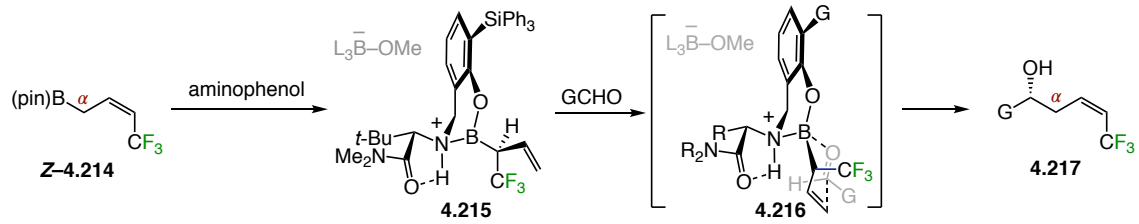
***Z*-4.214** was predominately α-selective. Nonetheless, it is possible that the fully substituted allylic carbon (**4.218** vs **4.215**) could hinder initial substrate coordination. Compounds containing quaternary stereogenic centers may then be generated; however, if the products could be isolated with diastereo- or enantioselectivity remained to be determined.

Scheme 4.32. Factors Influencing Additions of F-, F_3C-Substituted Allyl Boronates

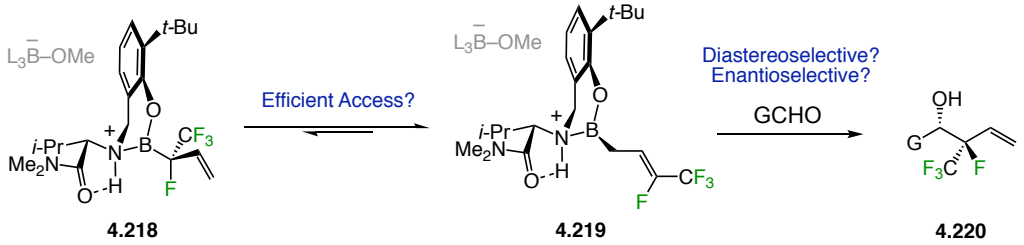
a. Kinetically controlled 1,3-boryl shift



b. α-Selective addition of *Z*-trifluoromethyl substituted boronates



c. Objective of this work

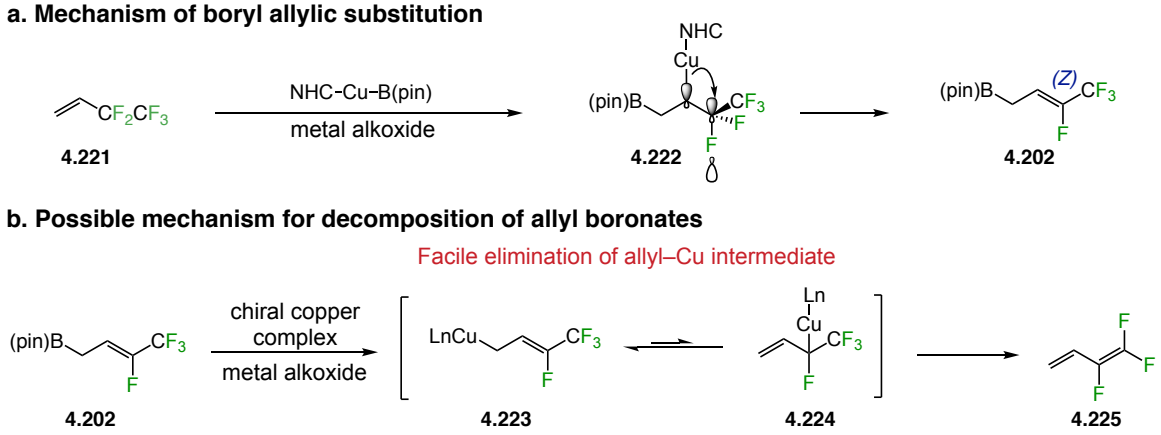


4.3.2 Synthesis of Fluorine-Containing Allyl Boronates

To begin, we required a method for regio- and stereoselective synthesis of fluorine containing allyl boronates. We surveyed a series of imidazolinium salts (**imid 1-4**) to promote synthesis of trisubstituted allyl boronate **4.202**. Copper-boryl addition generates an intermediary Cu-alkyl species **4.222** which readily eliminates fluoride due to a

weakened C-F bond as a result of overlap between σCu–C and σ*C-F.[100] Two practical considerations merit brief note before continued discussion: (1) The transformation must be carried out with excess $B_2(pin)_2$, otherwise the newly formed allyl boronate may react with the copper alkoxide species present in solution, generating allyl copper **4.224** that can eliminate fluoride. (2) Optimal efficiency and stereoselectivity required non-polar media. Under these conditions, in the absence of ligand, the transformation proceeds with to 78% conversion, furnishing the allyl boronate in 91:9 *Z:E* ratio (Scheme 4.33c). Previously, for additions of disubstituted allyl boronates to phosphinoyl imines, the stereochemistry of the compound did not affect selectivity;[101] however, if the same would be true for additions of trisubstituted reagents was unclear. Improved stereoisomeric purity was obtained when the transformation was promoted by sulfonate containing **imid-3** and phenyl glycinol based **imid-4**. could afford the allyl boronate with improved *Z* selectivity (Scheme 4.33c). We judged the cost and time required for preparation of **imid-3** rendered it less attractive.

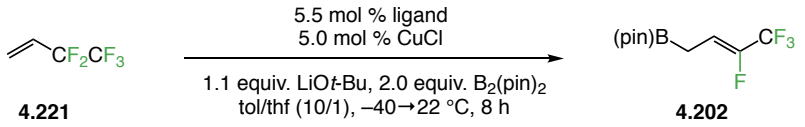
Scheme 4.33. Stereoselective Synthesis of Trisubstituted Fluorine-Containing Allyl Boron Compounds[a]



100) For a detailed mechanistic analysis, see: Paioti, P. H. S.; del Pozo, J.; Mikus, M. S.; Lee, J.; Koh, M. J.; Romiti, F.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 19917–19934.

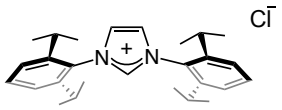
101) van der Mei, F. W.; Miyamoto, H.; Silverio, D. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4701–4706.

c. Evaluation and optimization of ligands

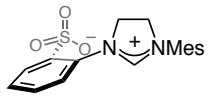


4.221 **4.202**

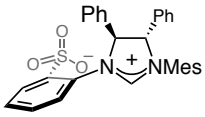
no ligand
78% conv., 91:9 *Z*:*E*



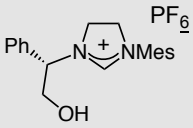
imid-1
50% conv., 92:8 *Z*:*E*



imid-2
56% conv., 95:5 *Z*:*E*



imid-3
75% conv., 98:2 *Z*:*E*



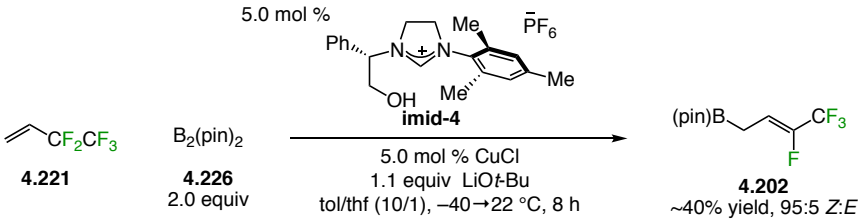
imid-4
80% conv., 95:5 *Z*:*E*

[a]All reactions were performed under an atmosphere of dry N_2. Conv. and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Experiments were conducted at least in triplicate. pin: pinacolato. See Experimental Section for details.

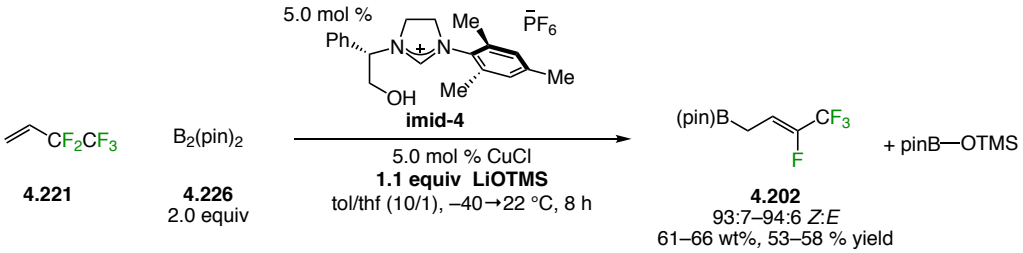
Isolation of the moisture-sensitive boronate was not so straightforward, although this could be circumvented through purification with anhydrous solvent and oven-dried silica. In the event that LiO*t*-Bu was replaced with LiOTMS, the desired reagent **4.202** could be isolated following filtration and distillation to remove residual salts, thereby eliminating silica gel chromatography (Scheme 4.34b).

Scheme 4.34. Preparative Scale Synthesis of Fluorine-Containing Allyl Boronates[a]

a. Synthesis of fluoroallyl boronate



b. Modification of reaction conditions for scalable preparation

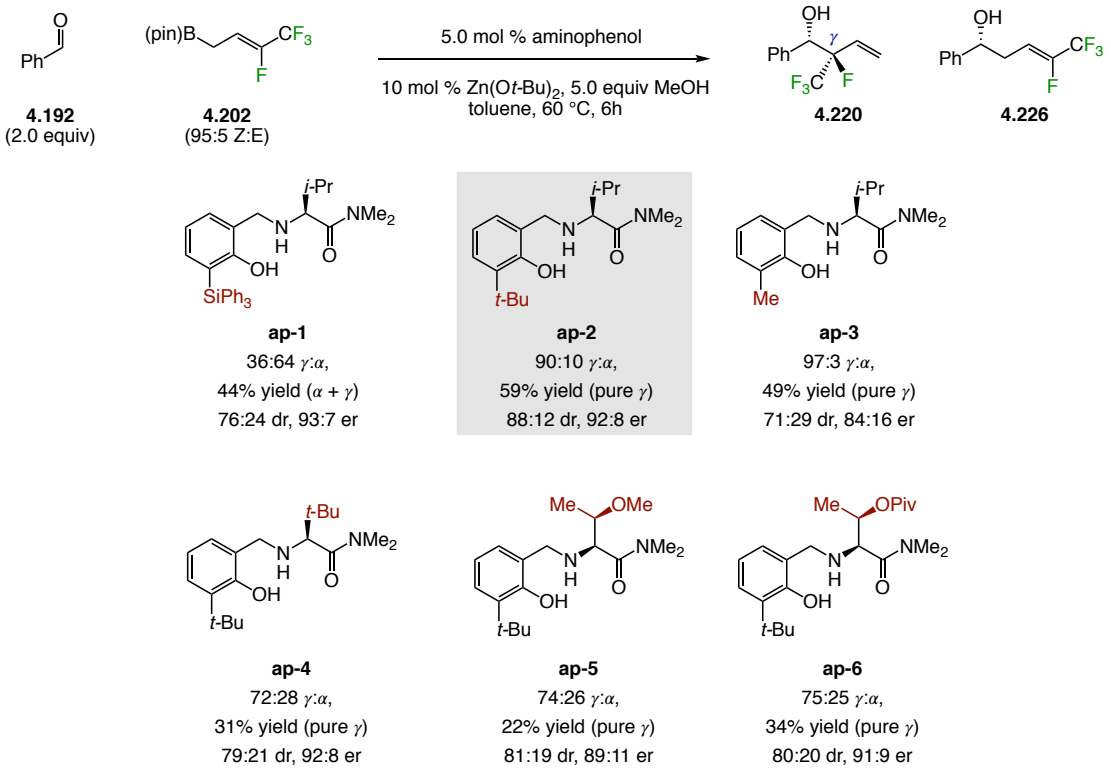


[a]All reactions were performed under an atmosphere of dry N_2. Conv. and *Z*:*E* ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Experiments were conducted at least in triplicate. See Experimental Section for details.

4.3.3 Initial Evaluation and Optimization

In line with previous investigations,[98] the less acidic, and more soluble, Zn(O*t*-Bu)$_2$ was optimal for efficiency. Furthermore, we found that there was no detectable conversion at 22 °C, likely a consequence of the steric pressure generated by the γ-carbon and the reversed polarity of the reagent. To improve efficiency, the reaction was performed at 60 °C. Under the latter conditions, the aldehyde was consumed within six hours.

Scheme 4.35. Initial Evaluation and Identification of an Optimal Aminophenol[a]



[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). Er values were determined by HPLC analysis (±1%). Experiments were conducted at least in triplicate. piv: pivaloyl. See Experimental Section for details.

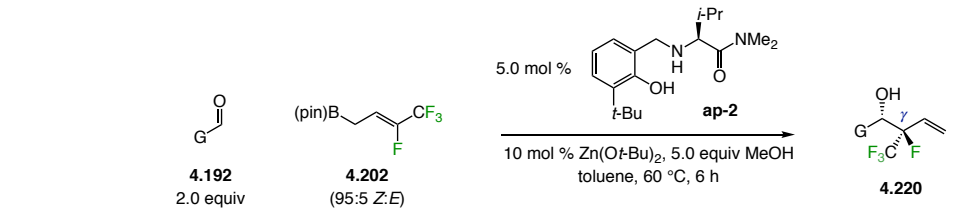
Next, we sought to identity an effective catalyst to promote the transformation. We identified that regioselectivity was impacted by the size of the aryloxide substituent. In line with previous mechanistic models (see Chapter One), those possessing a smaller substituent, such as **ap-3**, exhibited increased γ selectivity, however this was at the expense of diastero- and enatioselectivity. Reactions promoted by a catalyst with a more sizable *tert*-butyl group, afforded **4.220** in 88:12 dr and 92:8 er, and aminophenol compounds that were substituted with a sizable triphenylsilyl group were largely α-selective. We then probed a variety of compounds possessing different amino acid residues. Those containing a larger *tert*-leucine residue (**ap-4**) led to diminished regioselectivity, probably owing to

increased steric pressure in the transition state for 1,3-boryl shift. Threonine-based catalysts **ap-5** and **ap-6** offered little improvement. Thus, we selected **ap-2** as optimal.

4.3.4 Scope of the Catalytic Method

Additions to electron-rich aldehydes proceeded with efficiency, and *para*-methoxyphenyl-substituted **4.228** and 4-methylthio-**4.229** furnished products in 63 and 67% yield and 96:4 and 96.5:4.5 er, respectively. The more electron-donating methyl ether (more efficient C–O overlap, as opposed to C–S) affords higher levels of γ selectivity probably owing to decreased electrophilicity. Thus, allowing pathways for 1,3-boryl shift to be more viable. Heteroaryl-substituted aldehydes were equally effective, as evidenced by 3-thienyl **4.232** and 3-furyl **4.233,** generated in 69 and 77% yield and 92:8 dr and 96:4 er. Indole containing **4.234** was in 54% yield, 86:14 dr and 95:5 er, and the crystalline nature of the product allowed us to obtain an X-ray structure to determine relative and absolute stereochemistry. Contrary to additions of chloro-substituted allyl boronates (see Chapter Three), which rely on steric factors for enantiofacial discrimination, additions to more diminutive alkenyl and alkyl-substituted aldehydes furnished products **4.235-237** in 89:11–92:8 dr and 91:9–94:6 er. Furthermore, the transformation is suitable with compounds possessing a stereogenic center, as the product derived from (+)-citronellal was obtained in 84:16 γ:α ratio and 92:8 dr.

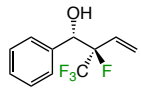
Scheme 4.36 Scope of Catalytic Enantioselective Addition of Fluoro-Substituted Allyl Boronates[a]



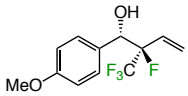
4.192 2.0 equiv

4.202 (95:5 *Z*:*E*)

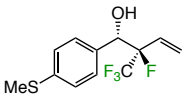
4.220



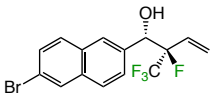
4.227
90:10 γ:α
59% yield (pure γ)
88:12 dr, 92:8 er



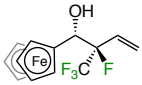
4.228
93:7 γ:α
63% yield (pure γ)
85:15 dr, 96:4 er



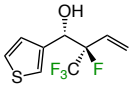
4.229
89:11 γ:α
67% yield (pure γ)
84:16 dr, 95.5:4.5 er



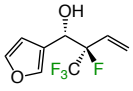
4.230
80:20 γ:α
50% yield (pure γ)
82:18 dr, 94:6 er



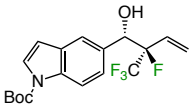
4.231
95:5 γ:α
73% yield (pure γ)
96:4 dr, 95:5 er



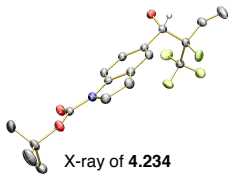
4.232
90:10 γ:α
69% yield (pure γ)
92:8 dr, 96:4 er



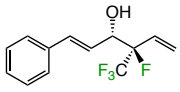
4.233
92:8 γ:α
77% yield (pure γ)
92:8 dr, 96:4 er



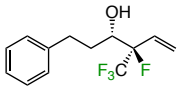
4.234
93:7 γ:α
54% yield (pure γ)
86:14 dr, 95:5 er



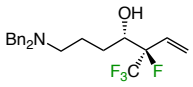
X-ray of **4.234**



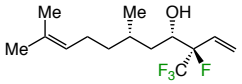
4.235
90:10 γ:α
53% yield (pure γ)
90:10 dr, 91:9 er



4.236
87:13 γ:α
65% yield (pure γ)
89:11 dr, 92:8 er



4.237
88:12 γ:α
61% yield (pure γ)
92:8 dr, 94:6 er



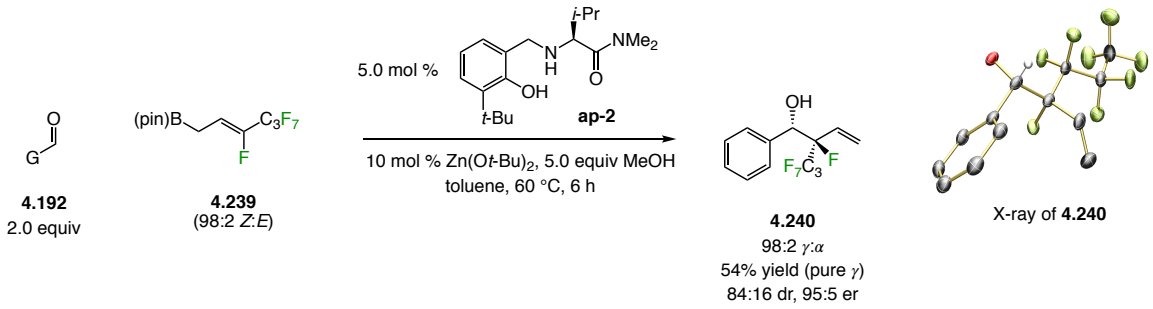
4.238
84:16 γ:α
58% yield (pure γ)
92:8 dr

[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). Er values were determined by HPLC analysis (±1%). Experiments were conducted at least in triplicate. Bn: benzyl. See Experimental Section for details.

Boronates possessing perfluoroalkyl substitution were prepared analogously through reaction with perfluoro hexane, affording **4.239.** Under the same conditions for addition of trifluoromethyl-substituted boronates, **4.240** was obtained with exclusive γ selectivity, 84:16 dr and 95:5 er. The higher proportion of γ-isomer in the reaction mixture is likely consequence of the more sizable perfluoroalkyl substituent, which may hamper association of the aldehyde and/or exert greater pressure with the catalyst, favoring boryl

shift. We were able to secure an X-ray structure to confirm our previously assigned absolute and relative stereochemistry.

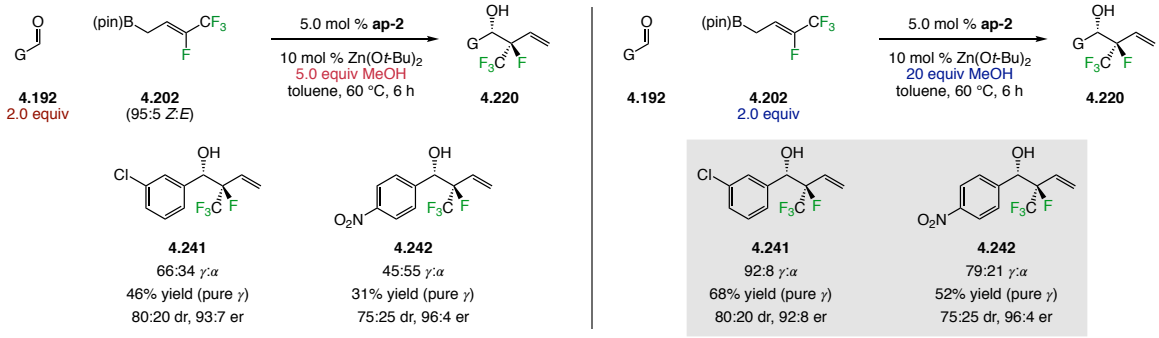
Scheme 4.37 Additions of Perfluoroalkyl-Substituted Allyl Boronates[a]



[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). Er values were determined by HPLC analysis (±1%). Experiments were conducted at least in triplicate. See Experimental Section for details.

Aldehydes possessing electron-withdrawing substituents exhibited diminished γ selectivity. Under optimal conditions, *m*-Cl **4.241** and *para*-NO_2 substituted **4.242** were isolated in 66:34 and 45:55 γ:α ratio, respectively. Since the rate of addition is dependent on the concentration of aldehyde, whereas boryl shift likely does not exhibit the same concentration dependence, we rationalized that if the availability of these more electrophilic substrates was decreased, then γ:α ratios may be improved. We went about this by modifying the reaction conditions, first reversing the stoichiometry of the reagents such that the allyl boronate was now in excess. Furthermore, we sought to take advantage of the reactivity of these more electrophilic aldehydes through reversible formation of their corresponding hemiacetals. Accordingly, when addition was carried out with 20 equivalents of methanol, **4.241** and **4.242** were accessed in 92:8 and 79:21 γ:α ratio, respectively.

Scheme 4.38. Improved Conditions for Additions to Electron-Deficient Aldehydes[a]



[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). Er values were determined by HPLC analysis (±1%). Experiments were conducted at least in triplicate. See Experimental Section for details.

4.3.5 Application to Synthesis of Sofosbuvir Analogue

One example of an organofluorine compound possessing a quaternary stereogenic center is HCV inhibitor Sofosbuvir,[102] a recently developed treatment for Hepatitis C, a liver disease that effects millions annually.[103] We envisaged that a fluoro- and trifluoromethyl-substituted derivative of the furanose core may be efficiently synthesized through addition of fluorine-containing allyl boronates. Initial attempts for optimization (antipode of **ap-2** employed for desired stereochemistry) revealed the benefit of an excess

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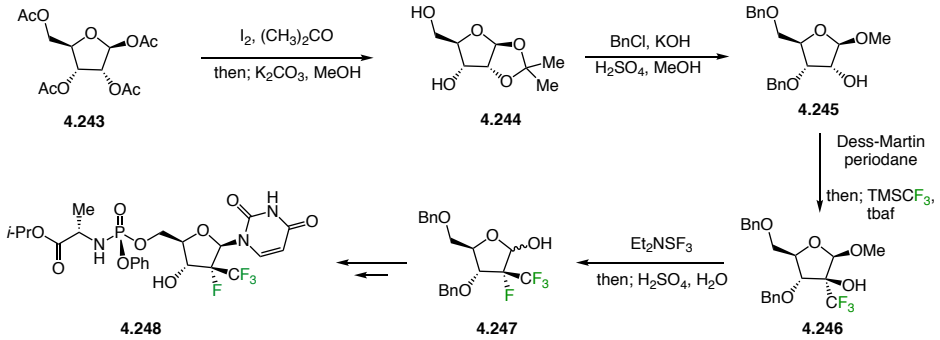
102) (a) Liotta, D. C.; Painter, G. R.; Bluemling, G. R. PCT. Int. Appl. 2014124430 (b) Liotta, D. C.; Painter, G. R.; Blueming, G. R.; De La Rosa, A. PCT. Int. Appl. 2015038596. (c) Liotta, D. C.; Painter, G. R.; Blueming, G. R.; De La Rosa, A. PCT. Int. Appl. 2016145142.

103) Sofia, M. J.; Bao, D.; Chang, W.; Du, J.; Nagarathnam, D.; Rachakonda, S.; Reddy, P. G.; Ross, B. S.; Wang, P.; Zhang, H.-R.; Bansal, S.; Espiritu, C.; Keilman, M.; Lam, A. M.; Micolochick Steuer, H. M.; Niu, C.; Otto, M. J.; Furman, P. A. *J. Med. Chem*. **2010**, *53*, 7202−7218. For bioactivity, see: (a) Lawitz, E.; Mangia, A.; Wyles, D.; Rodriguez-Torres, M.; Hassanein, T.; Gordon, S. C.; Schultz, M.; Davis, M. N.; Kayali, Z.; Reddy, K. R.; Jacobson, I. M.; Kowdley, K. V.;Nyberg, L.; Subramanian, G. M.; Hyland, R. H.; Arterburn, S.; Jiang, D.; McNally, J.; Brainard, D.; Symonds, W. T.; McHutchinson, J. G.; Sheikh, A. M.; Younossi, Z.; Gane, E. J. *New England J. Medicine.* **2013**, *368*, 1878–1887. (b) Fung, A.; Jin, Z.; Dyatkina, N.; Wang, G.; Beigelman, L.; Deval, J. *Antivir. Chem. Chemother.* **2014**, *58*, 3636–3645. (c) Kirby, B. J.; Symonds, W. T.; Kearney, B. P.; Mathias, A. A. *Clin. Pharmokinet.* **2015**, *54*, 677–670. For recent studies regarding synthesis, see: Simmons, B.; Liu, Z.; Klapars, A.; Bellomo, A.; Silverman, S. M. *J. Org. Chem.* **2017**, *19*, 2218–2221. (b) Cini, E.; Barreca, G.; Carcone, L.; Manetti, F.; Rasparini, M.; Taddei, M. *Eur. J. Org. Chem*. **2018**, 2262–2628.

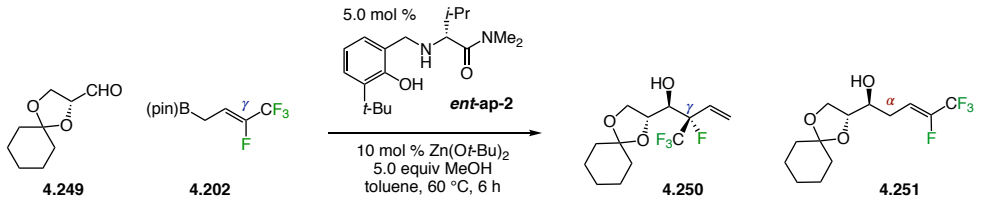
of allyl boronate **4.202** for additions to α-alkoxy aldehyde **4.249**; however, γ selectivity did not exceed 80:20 γ:α ratio. To overcome this, we considered applying insight obtained for additions to other electrophilic aldehydes, wherein the concentration of the aldehyde may likely be reduced through reversible formation of the corresponding hemiacetal. Accordingly, in the presence of 20 equivalents of methanol, selectivity increased to 97:3 γ:α ratio, without any discernable impact on the diastereoselectivity of the transformation (Scheme 4.39c). To complete the formal synthesis, the secondary alcohol was converted to a benzyl ether by treatment with sodium hydride and benzyl bromide, and the diol was unmasked through treatment with camphor sulfonic acid in ethylene glycol to afford **4.252** in 73% yield over two steps. With **4.252** in hand, we attempted the penultimate step; namely protection of the primary alcohol, however, to our surprise, the product obtained was the result of reaction with the secondary alcohol. Oxidative cleavage of the olefin through treatment with ozone and subsequent cyclization afforded puranose **4.254**, the identity of which was confirmed by an X-ray structure of the derived benzoate.

Scheme 4.39. Sofosbuvir Analogue and Discovery of Unusual Reactivity Profile[a]

a. Medicinal chemistry route towards furanose core of Sofosbuvir analogue

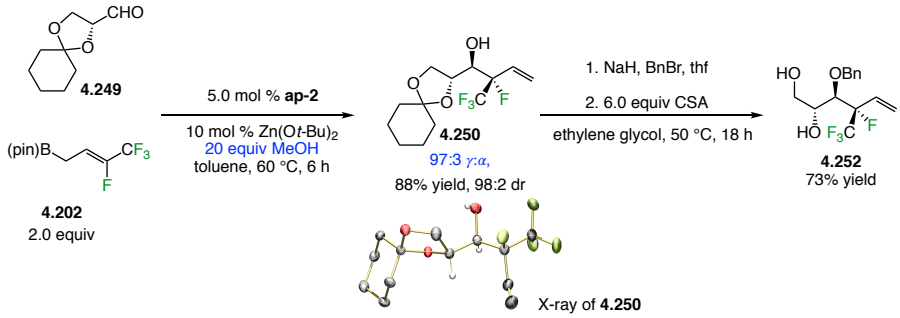


b. Poor regioselectivity for electron deficient α-alkoxy aldehydes

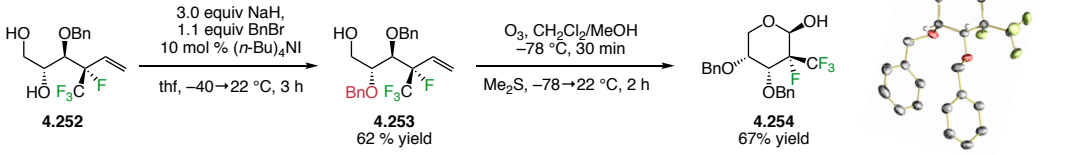


Entry	4.249 / 4.202	γ:α	dr (γ)
1	2:1	34:66	98:2
2	1:2	75:25	98:2
3	1:3	80:20	98:2

c. A catalytic approach towards furanose core: beneficial effect of more polar media



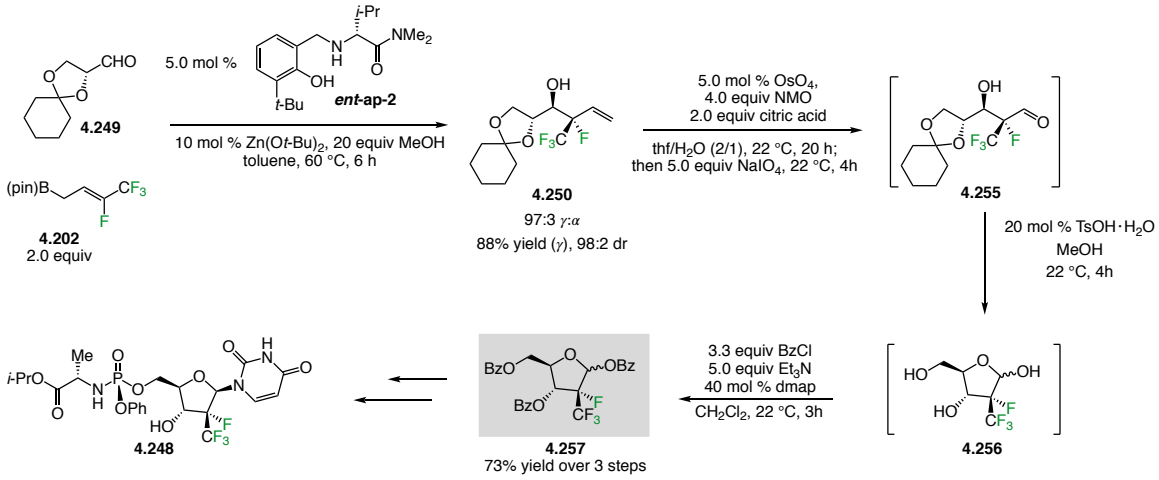
d. Endgame of synthesis and unexpected synthesis of puranose



[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). Er values were determined by HPLC analysis (±1%). Experiments were conducted at least in triplicate. CSA: camphorsulfonic acid. See Experimental Section for details.

To access the furanoside, an alternative route was developed. Oxidative cleavage through treatment with catalytic osmium and NMO, with citric acid to promote efficiency,[104] furnished an unpurified aldehyde **4.255,** which was immediately subjected to cyclization upon treatment with *para*-toluenesulfonic acid generating hemiacetal **4.256**, instead of the expected methanol adduct. After filtration through $NaHCO_3$ to neutralize excess acid, the water-soluble hemiacetal could then be protected and isolated as tris-benzoate **4.257** in 73% yield over three-steps.

Scheme 4.40. Synthesis of Furanoside Core of Sofosbuvir Analogue[a]



[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). See Experimental Section for details.

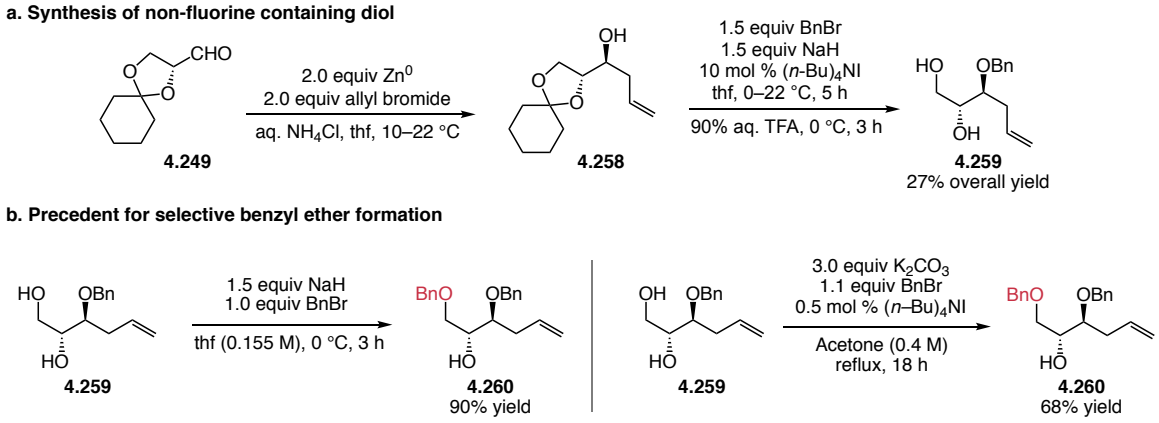
104) (a) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421–433. (b) Chu, H.; Smith, J. M.; Felding, J.; Baran, P. S. *ACS Cent. Sci.* **2017**, *3*, 47–51.

4.4 *Analysis of Mechanism*

4.4.1 *Unique Selectivity for Benzyl Protection*

The origins of the unusual selectivity for benzyl ether formation intrigued us, especially considering precedent that in similar, but non-halogen containing compounds, the primary alcohol was selectively protected (Scheme 4.41). In one reported case, treatment with sodium hydride and benzyl bromide afforded benzyl ether **4.260** in 90% yield,[105] and a second detailed isolation of the primary benzyl ether in 68% yield upon refluxing in acetone with K_2CO_3 as a mild buffer.[106] Thus, we reasoned reaction at the secondary alcohol was likely a consequence of the incorporation fluorine, however, it had yet to be determined whether this was due to the allylic fluoride, trifluoromethyl group or a combination of the two. To probe these effects, we set out to prepare a series of derivatives.

Scheme 4.41 Precedent for Selective Reaction at Primary Alcohol[a]

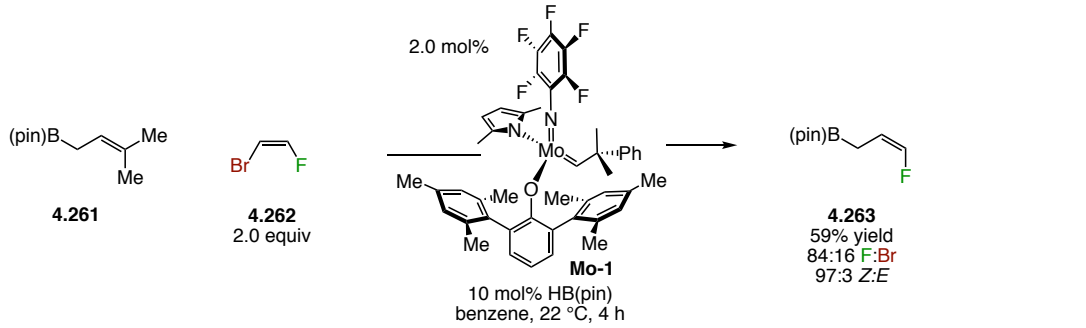


[a]All reactions were performed under an atmosphere of dry N_2. Conv. and dr ratios (±2%) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). See Experimental Section for details.

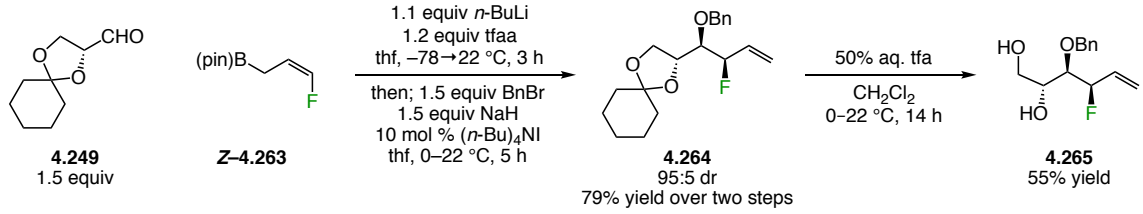
105) Li, M.; Xiong, J.; Huang, Y.; Wang, L.-J.; Tang, Y.; Yang, G-X.; Liu, Z.-H.; Wei, B.-G.; Fan, H.; Zhao, Y.; Zhai. W.-Z.; Hu. J.-F. *Tetrahedron*, **2015,** *71*, 5285–5295.
106) Krishna, P. R.; Reddy, V. V. R.; Srinivas, R. *Tetrahedron*, **2007,** *63*, 9871–9880.

We first synthesized allyl alcohol **4.259** under standard Barbier conditions as outlined by Fadnavis.[107] Homoallylic alcohol **4.258** was isolated as a mixture of isomers, which upon conversion to the corresponding benzyl ethers were separable by chromatography. The diol could then be unmasked through treatment with trifluoroacetic acid.

Scheme 4.42. Synthesis and Application of Fluoro-Substituted Allyl Boronate[a]



b. Diastereoselective allyl addition of fluoroallyl boronate



[a]All reactions were performed under an atmosphere of dry N_2. Conv., *Z:E* and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). Er values were determined by HPLC analysis (±1%). Bn: benzyl. See Experimental Section for details.

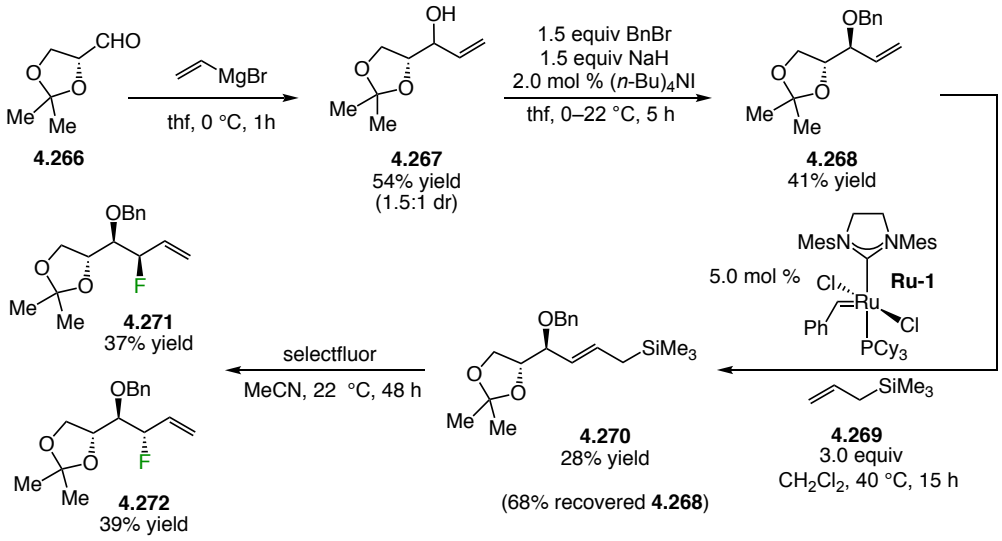
A direct strategy for access to an analog possessing an allylic fluoride would involve allyl addition of a fluoro-substituted allyl boronate. Based on our own experience,[108] we recognized the requisite reagent ***Z*–4.263** could be synthesized through

107) Venkataiah, M.; Somaiah, P.; Reddipalli, G.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2009**, *20*, 2230–2233.

108) Mu, Y.; Nguyen, T.; van der Mei, F. W.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 5365–5370.

cross-metathesis of prenyl–B(pin) **4.261** and bromo fluoro ethylene **4.262**. Diastereoselective allyl addition, under conditions previously employed for fluorine-containing allyl boronates, [109] then afforded a homoallylic alcohol which was protected as a benzyl ether prior to unmasking the diol (Scheme 4.42b).[110] Unfortunately, attempts to access the alternative diastereomer through synthesis of an *E*–fluoro allyl boronate by cross-metathesis were unsuccessful.[111]

Scheme 4.43. Establishment of Fluoro-Substituted Stereogenic Center Through Reaction with an Allyl Silane[a]



[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^1H or ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). See Experimental Section for details.

Instead, we pursed a different strategy, wherein fluorine was introduced at a later stage in the synthesis. We commenced with non-selective addition of vinyl magnesium

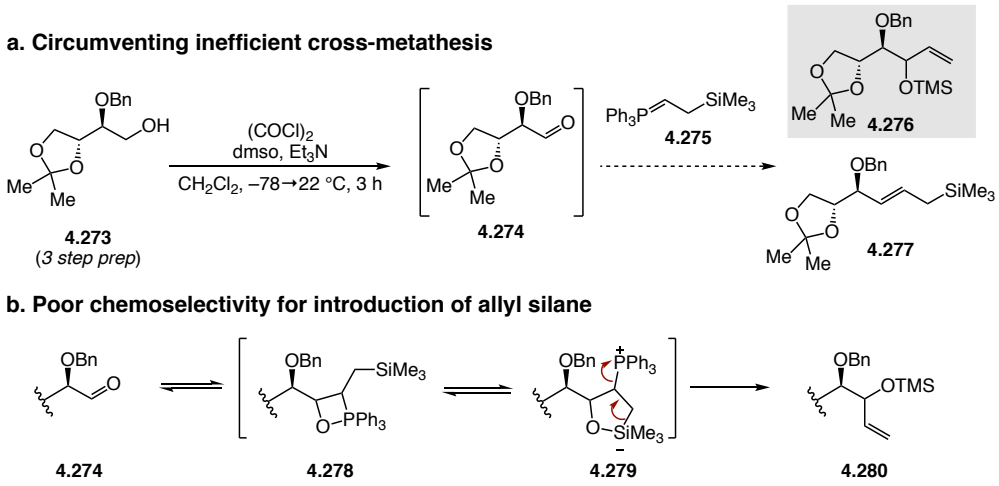
109) Kojima, R.; Akiyama, S.; Ito, H. *Angew. Chem. Int. Ed.* **2018**, *57*, 7196–7199.

110) Interestingly, when deprotection was attempted by treatment with CSA in ethylene glycol, fluorine was excised from the molecule.

111) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, R.; Schrock, R. R.; Hoveyda, A. H, *Science*, **2016**, *352*, 569–575.

bromide to aldehyde **4.266** affording a 1:1 mixture of diastereomers in 54% yield,[112] and subsequent conversion to benzyl ether **4.268** allowed for separation of the diastereomeric products.[113] At this stage, we carried out cross-metathesis of allylic benzyl ether **4.268** and allyl silane **4.269** promoted by Grubbs' Second-Generation catalyst **Ru-1** according to a procedure by Vankar.[114] Finally, we secured allylic fluorides **4.271** and **4.272** by subjecting the obtained allyl silane to selectfluor and separating the diastereomeric products.[76a] To address the poor efficiency for synthesis of allyl silane **4.270**, we considered reaction with phosphorane **4.275** and α-alkoxy aldehyde **4.274**. Despite straightforward preparation of each of the components,[115] reaction with branched aldehydes favors formation of **4.276** as the major product due to silyl migration over retro [2+2] collapse of oxaphosphatane **4.278** (Scheme 4.44b).

Scheme 4.44. An Alternative Strategy for Allyl Silane Synthesis



112) Bilska-Markowska, M.; Koroniak, H. *J. Fluorine Chem.* **2003***, 203*, 185–192.

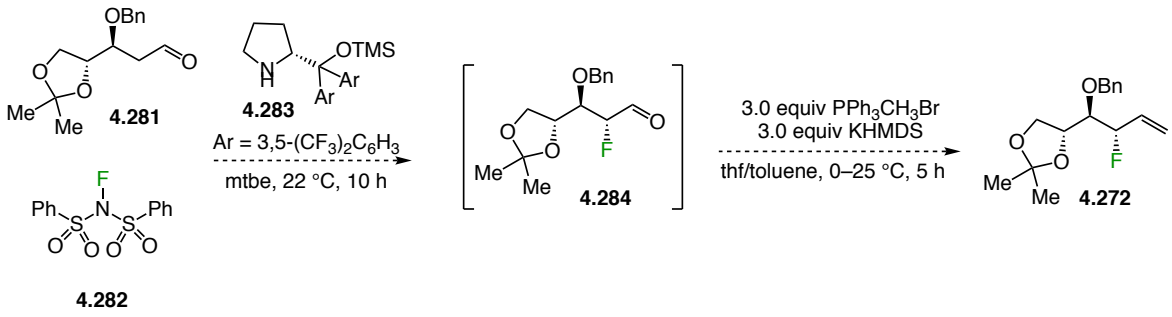
113) Allylic alcohol may be accessed in diastereomerically pure form in 3 steps from commercially available 2,3:4,5-Di-o-isopropylidene-d-arabitol (CarboSynth, 500 mg, $70), see: Schneider, C.; Kazmaier, U. *Synthesis* **1998**, *9*, 1314–1320.

114) Dubbu, S.; Bardhan, A.; Chennaiah, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2018**, 6800–6808.

115) For phosphorane prep, see: Fleming, I.; Paterson, I. *Synthesis* **1979**, 446–448. For aldehyde prep, see: Palík, M.; Kožíšek, J. Kóóš, P.; Gracza, T. *Bielstein J. Org. Chem.* **2014**, *10*, 2077–2086.

Alternatively, allyl fluoride **4.272** may be accessed through treatment of aldehyde **4.281** under conditions previously reported for α-fluorination (Scheme 4.45). When promoted with the matched antipode of pyrrolidine **4.283**, diastereomeric ratios are reported to be excellent (>95:5),[116] and unlike the branched examples discussed in Section 4.2.5, linear aliphatic aldehydes afford the corresponding tertiary fluorides with efficiency and in high er.[117] The somewhat sensitive aldehyde **4.284,** may then be converted to an alkene as previously described by Guindon.[118]

Scheme 4.45 Proposed Synthetic Strategy for Synthesis of a Fluoro-Substituted Derivative



For synthesis of **4.295**, we considered recent advances in preparation of fluorine-containing allyl boronates that are fluoro- and alkyl-substituted; however, *Z* selectivity is lower than the analogous aryl substituted examples (Scheme 4.46a). Furthermore, the product of addition to an aldehyde would be a homoallylic alcohol containing a disubstituted olefin, requiring cleavage in a further synthetic manipulation. Furthermore,

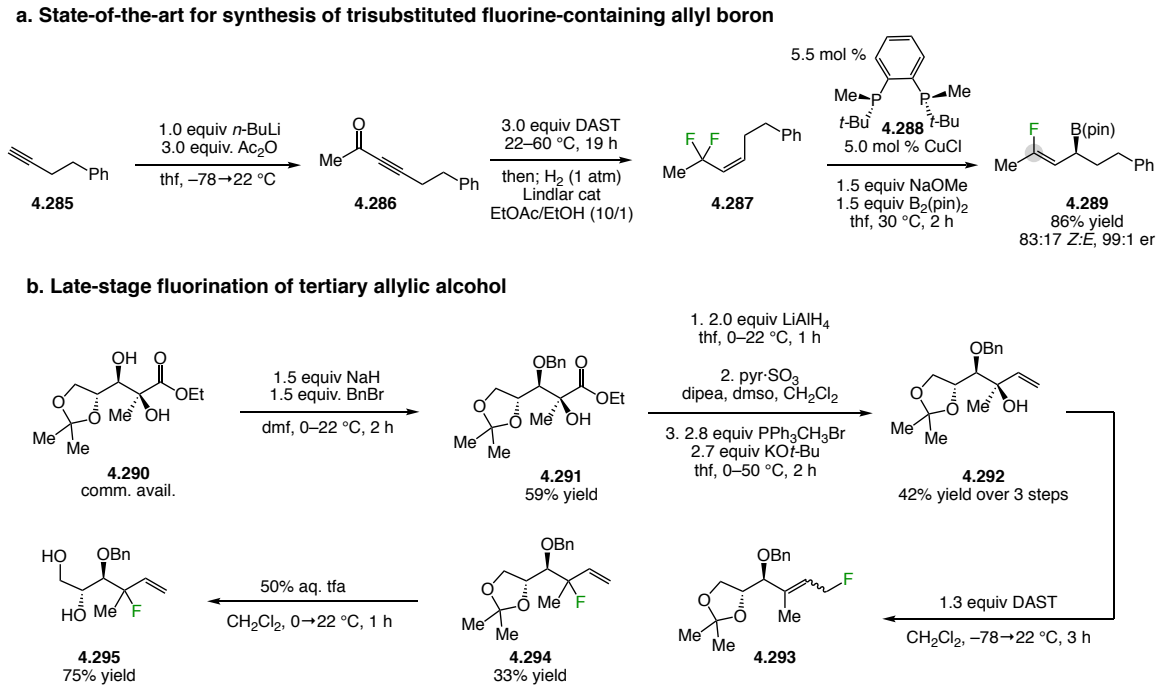
116) Hu, X.-G.; Lawer, A.; Peterson, M. B.; Iranmanesh, H.; Ball, G. E.; Hunter, L. *Org. Lett.* **2016**, *18*, 662–665.

117) Beeson. T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjoersgaard, A.; Jϕrgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703–3706. Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 3706–3710.

118) Dostie, S.; Prévost, M.; Mochirian, P.; Tanveer, K.; Andrella, N.; Rostami, A.; Tambutet, G.; Guindon, Y. *J. Org. Chem.* **2016**, *81*, 10769–10790.

precedent informed us that addition would likely afford the incorrect diastereomer (Felkin-Ahn control).

Scheme 4.46. Synthesis of Quaternary Fluoro-Substituted Stereogenic Center[a]



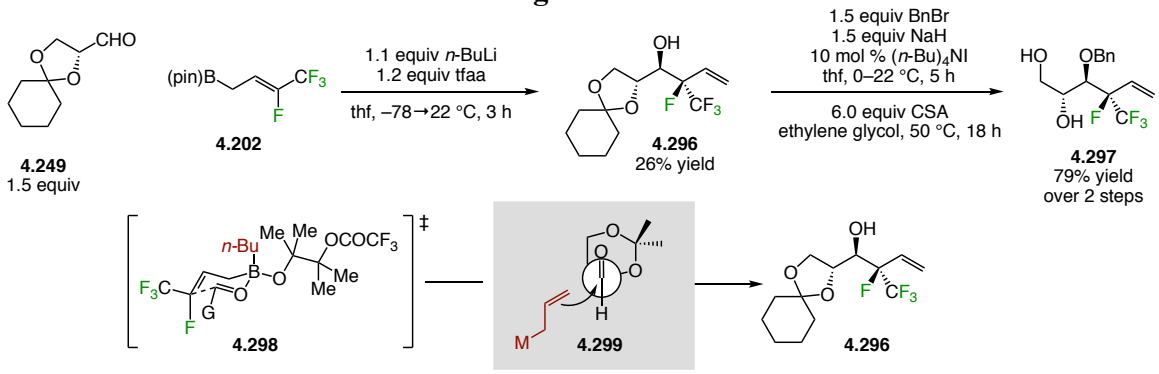
[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

Instead, we opted to commence with commercially available **4.290**, obtained through dihydroxylation of the corresponding trisubstituted olefin,[119] and obtained benzyl ether **4.291** in 59% yield. A three-step sequence, namely reduction of the ester, oxidation and Wittig olefination then furnished allylic alcohol **4.292** in 42% yield. Fluorine was introduced through treatment with DAST, generating regioisomeric allyl fluorides **4.293** and **4.294**, which were separable by silica gel chromatography. Cleavage of the acetal

119) Wang, P.; Chun, B.-K.; Rachakonda, S.; Du, J.; Khan, N.; Shi, J.; Stec, W.; Cleary, D.; Ross, B. S.; Sofia, M. J. *J. Org. Chem.* **2009**, *74*, 6819–6824.

generated **4.294** as a single diastereomer with unknown stereochemistry (see discussion on ambiguity in Section 4.2.5).

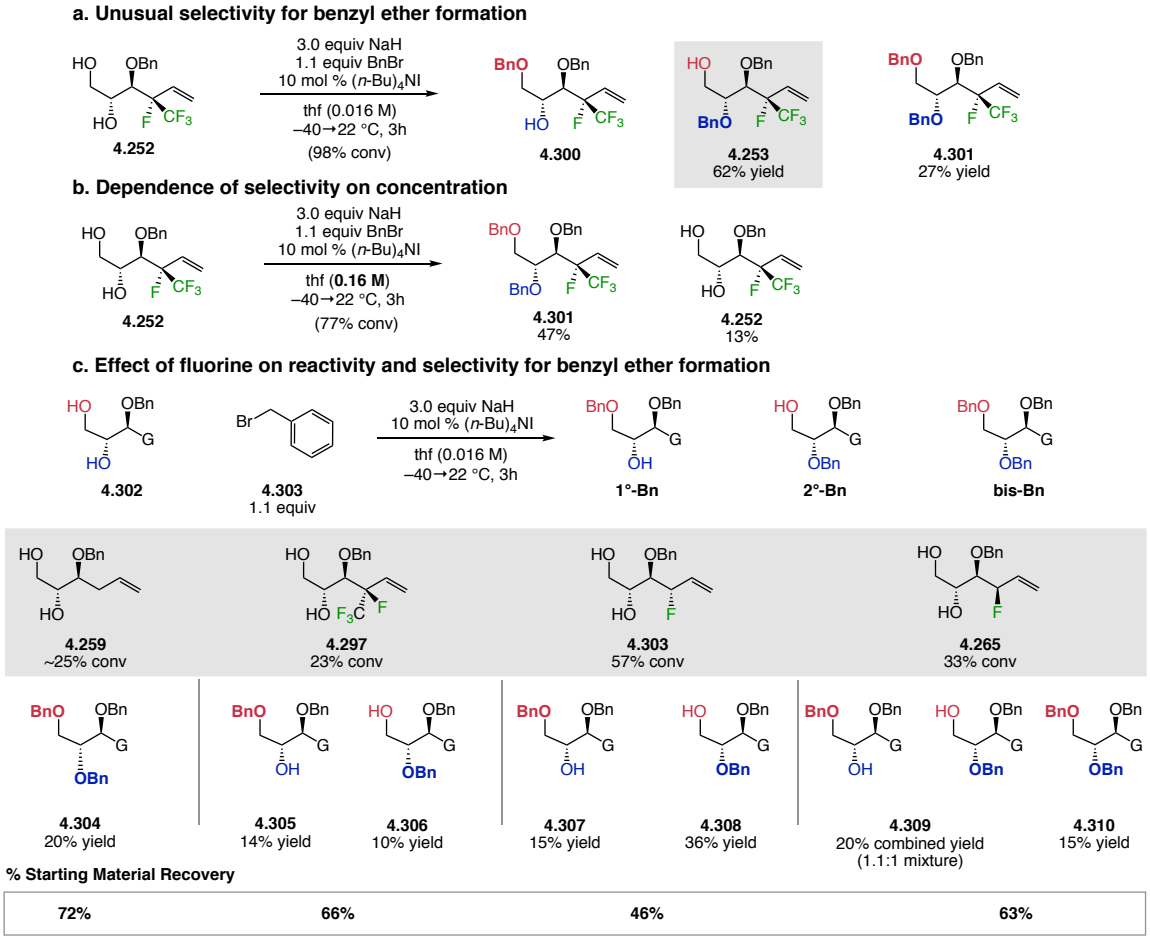
Scheme 4.47. Access to Diastereomeric Fluoro and Trifluoromethyl-Substituted Stereogenic Center[a]



[a]All reactions were performed under an atmosphere of dry N_2. Conv and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified product (±5%). CSA: camphorsulfonic acid; tfaa: trifluoroacetic anhydride. See Experimental Section for details.

To investigate the effect of relative stereochemistry on selectivity, we set out to synthesize **4.297**. An analysis of models for addition revealed that if boronate **4.202** could be converted to a more reactive species, diastereoselective addition to α-alkoxy aldehyde **4.249** would likely generate the Felkin-Ahn product (Scheme 4.47, **4.299)**. Accordingly, treatment with *n*-BuLi and trifluoroacetic anhydride, which probably converts the boronate to a more reactive borinate species (**4.298**), allowed us to isolate **4.296** in 26% yield. The diol was then obtained after alkylation of the secondary alcohol and hydrolysis of the acetal to afford **4.297** in 79% yield.

Scheme 4.48 Benzyl Protection for Fluorinated and Non-Fluorinated Analogs[a]



[a]All reactions were performed under an atmosphere of dry N_2. Conv. and product selectivity ratios (±2%) were determined by analysis of ^1H or ^{19}F NMR spectra of unpurified mixtures, Conv. refers to consumption of diol. Yield of isolated and purified products (±5%). Results are unoptimized and structural determinations tentative. See Experimental Section for details.

With a series of analogs in hand, we set out to examine their reactivity. It is important to note the concentration dependence of the observed selectivity for reactions involving **4.252**. The optimal conditions are reasonably dilute (0.016 M), a factor which we had rationalized should favor reaction with the more accessible primary alcohol. When the concentration was increased by a factor of ten, **4.301** was generated in 47% yield.[120]

120) Reaction in polar media, dmf (0.28 M), generated **4.301** as the major product in 42% yield, accompanied by 35% **4.253** and 10% **4.300**.

To ascertain the effect of incorporation of fluorine, we treated diol **4.259** with a combination of NaH and benzyl bromide, and found that the only product obtained was **4.304** in 20% yield, wherein the primary and secondary alcohol had been converted to the corresponding benzyl ether. The remaining diol was recovered in 72% yield, a notable observation since in the case of **4.252**, the starting material was completely consumed.

We then examined diastereomer **4.297**, finding that reactivity was diminished relative to **4.252**, and the product was afforded as a non-selective mixture of 1° and 2° benzyl ethers accompanied by 66% recovery of starting material. For allylic fluoride **4.303**, where there is a *syn* relationship between the alcohol and fluoro substituent in the stereotriad, 57% of the diol was consumed and a mixture of products were furnished with a 2:1 preference for reaction at secondary alcohol. Transformation of **4.265** was similarly inefficient (33% conv), and the product mixture contained all three possible products, namely 1°, 2° and bis-benzyl ethers.

With this insight, we reasoned that the increased reactivity and selectivity could be the result of an interaction between the sodium alkoxide and the lone pair of one of the fluorine atoms incorporated within the molecule. This is expected to raise the HOMO of the alkoxide (Scheme 4.49) and increase the nucleophilicity of the secondary alcohol due its proximity. The above findings are mechanistically significant because it indicates the stereochemical identity of the quaternary stereogenic center is crucial. It could be that, interaction with an allylic fluorine versus one contained within a trifluoromethyl group, generates a more localized cloud of electron density that is responsible for increased nucleophilicity. Results obtained for diols possessing only an allylic fluoride (**4.265** and **4.30)**, reveal that reactivity is likely a consequence of the trifluoromethyl and fluoro substituents.[121] Studies to gain further insight into such an interaction are underway.

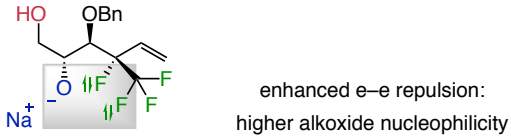
---

121) Steric effects are likely underscored by electronics as reaction with fluoro, methyl analogue **4.295**, afforded 13% conv. and a 1:1 mixture of 1° and 2° ethers. However, the ambiguity of the relative stereochemistry prevents further claims based on these findings.

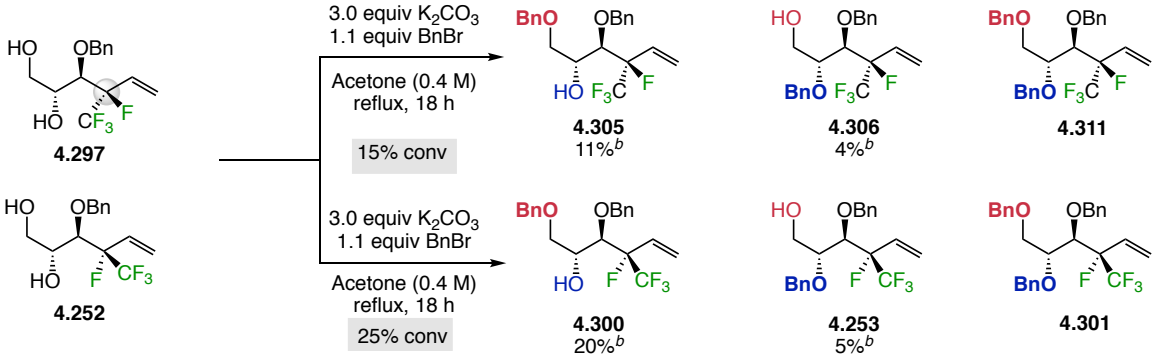
We found further support for the key role a metal alkoxide may play by carrying out benzyl protection under set of conditions wherein an alkoxide is not likely formed (See Scheme 4.49). Although the reaction does not proceed with the same levels of efficiency, we found that for **4.252** and **4.297**, the major product formed resulted from reaction with the less hindered 1° alcohol, although traces of the secondary product were detected as well.

Scheme 4.49 Implication of an Alkoxide-Lone Pair Interaction[a]

a. Rationale for increased reactivity of secondary alcohol



b. Conditions wherein an alkoxide is likely not formed

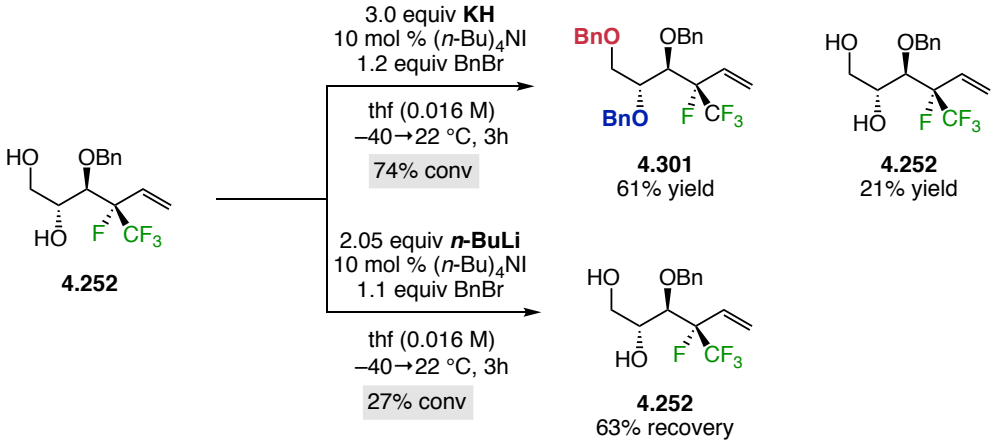


[a]All reactions were performed under an atmosphere of dry N_2. Conv. and product selectivity ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures, Conv. refers to consumption of diol. [b]Spectroscopic yield determined by ^{19}F integration. See Experimental Section for details.

The identity of the counterion effects selectivity and reactivity. When treated with potassium hydride, one product, namely **4.301** was generated in 61% yield, with 21% recovery of starting material. Efforts to generate a lithium-based alkoxide through

treatment of the diol with butyl lithium, did not lead to formation of any benzyl ethers and instead, **4.252** was recovered along with an unknown decomposition product.

Scheme 4.50 Effect of Different Bases on Regioselectivity[a]



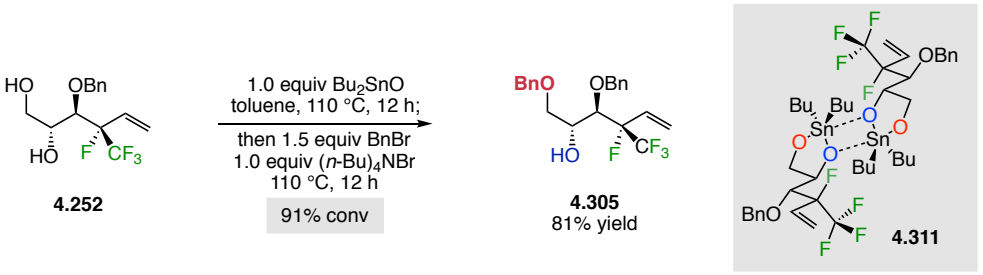
[a]All reactions were performed under an atmosphere of dry N_2. Conv. and product selectivity ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures, Conv. refers to consumption of diol. Yield of isolated and purified products (±5%). See Experimental Section for details.

We were able to identify conditions for selective synthesis of the primary benzyl ether by treating **4.252** with one equivalent of dibutyl tin oxide and benzyl bromide in refluxing toluene.[122] As shown in **4.311**, tin alkoxide species are known to exist as dimeric structures in solution wherein the tin atoms are pentavalent. In these aggregates, one oxygen is situated in an apical position and is dicoordinated (labeled in red) and the other is oriented equatorially and tricoordinated (labeled in blue). Thus, those oxygens not involved in the Sn_2O_2 framework exhibit increased nucleophilic character and are more prone to rupture affording selective reaction at the primary alcohol.[123]

122) Kotkar, S. P.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 6813–6815.

123) David, S.; Hanessian, S. *Tetrahedron*, **1985**, *41*, 643–663. For selective benzoylation, see: Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y.; *J. Org. Chem.* **2000**, *65*, 996–1002.

Scheme 4.51 Conditions for Selective Reaction at the Primary Alcohol[a]

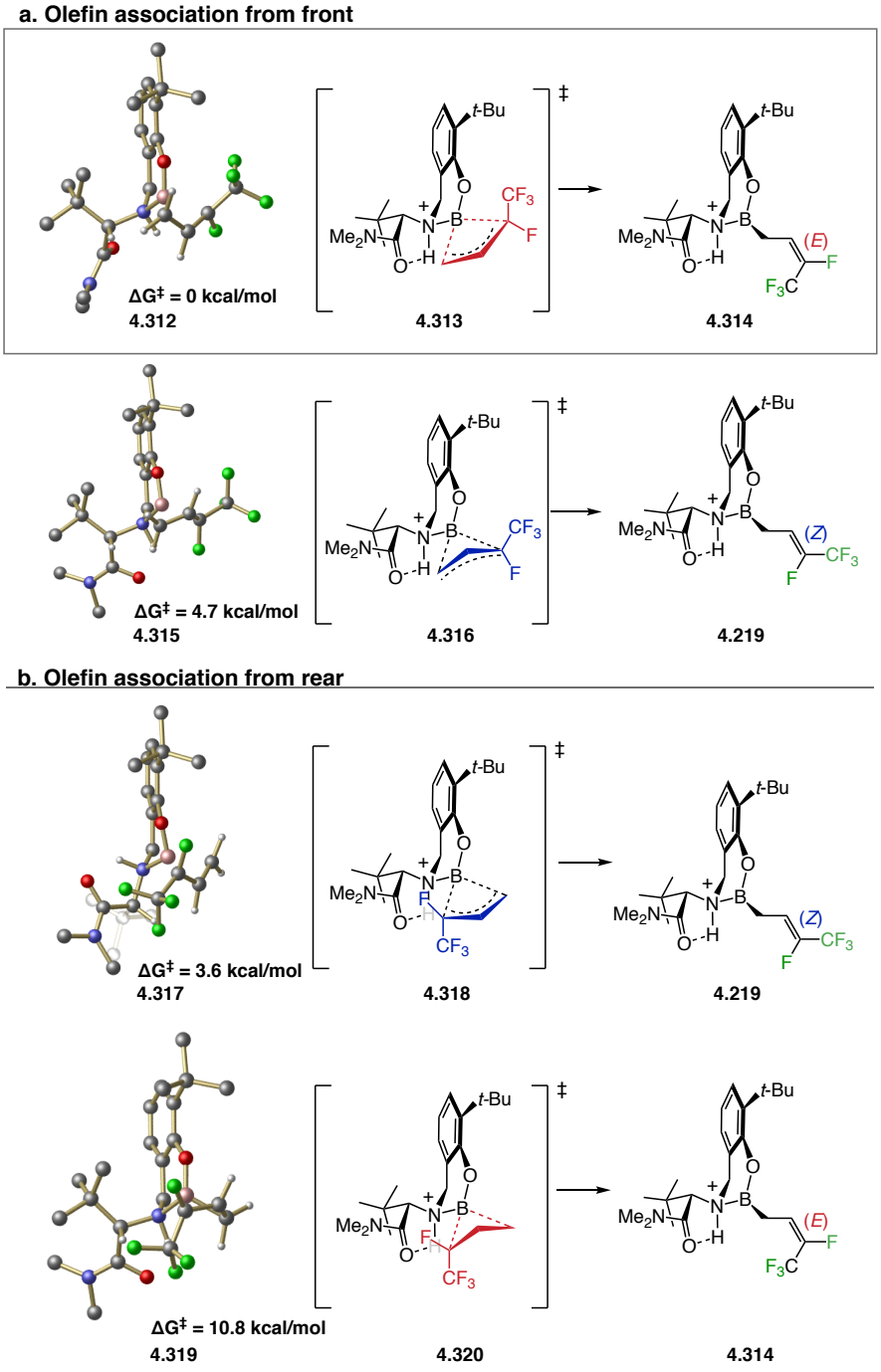


[a]All reactions were performed under an atmosphere of dry N_2. Conv. and product selectivity ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures, Conv. refers to consumption of diol. Yield of isolated and purified products (±5%). See Experimental Section for details.

4.4.2 Mechanism of 1,3-Boryl Shift and Stereochemical Models

As introduced in Section 4.3.1, stereospecific transfer of fluoro-substituted boronates initially generates an aminophenol allyl complex with a stereogenic center at the allylic position. Analysis of molecular models indicated that the most favorable transition state for 1,3-boryl shift would be one wherein the trifluoromethyl group would be oriented away from the catalyst engendering a degree of kinetic selectivity. To gain further insight, we computed possible transition states for isomerization, which revealed that the lowest barrier to rearrangement furnishes an allyl complex containing an *E* olefin as indicated.

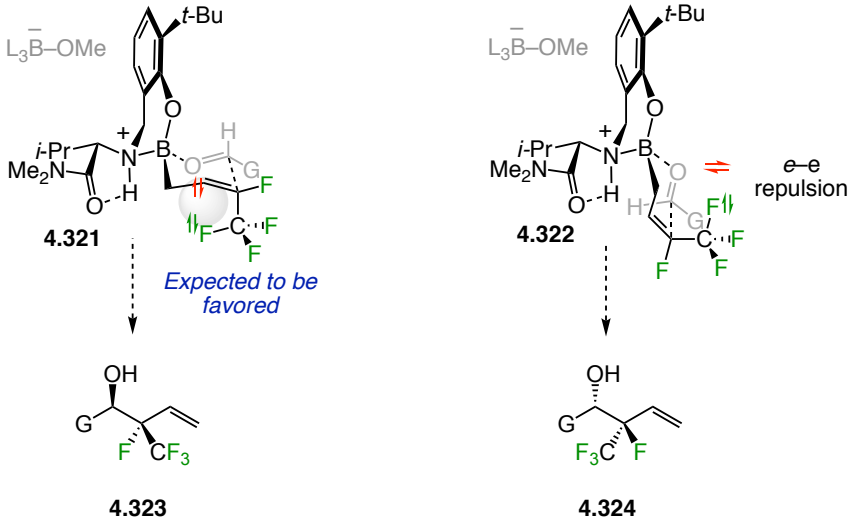
Scheme 4.51 Computationally Modeled Transition States for 1,3–Boryl Shift[a]



[a]Calculations performed at ωB97XD/DEF2TZVPP//ωB97XD/DEF2SVP$_{toluene(SMD)}$ level of theory. See the Experimental Section for details.

However, such a result does not align with the observed stereochemical outcome for the transformation. As shown in Scheme 4.52, two possible transition states for reaction of an aldehyde may be considered. Based on previous models, we would expect addition through **4.321** to be favored due to an alleviation of electron-electron repulsion through interaction with the ammonium. However, this would furnish the opposite enantiomer of the experimentally obtained product. Alternatively, reaction through **4.322,** which predicts the correct enantiomer and diastereomer, suffers from electron-electron repulsion as indicated.

Scheme 4.52. Stereochemical Models Incorrectly Predict Observed Stereoisomer

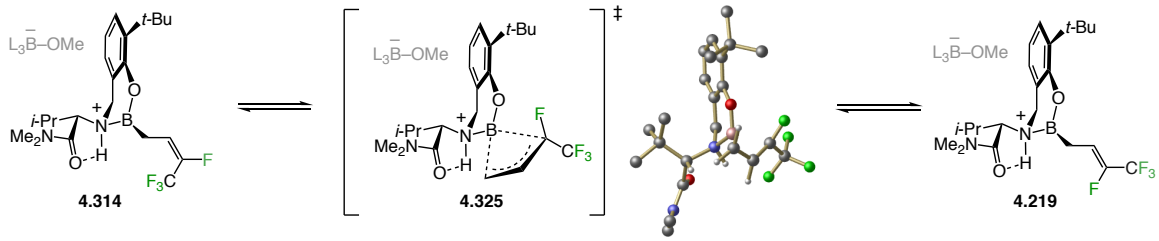


One possible alternative is that hindered *E*-allyl complex **4.314** is unreactive, and instead there is substantial isomerization to *Z*-allyl complex **4.219** proceeding through a transition state resembling boryl shift (Scheme 4.53a). Preliminary calculations indicate that isomerization is favored to proceed through **4.325** by 1.0 kcal/mol affording *Z*-allyl complex **4.219.** It is possible that at 22 °C none of these pathways are accessible, but at 60 °C isomerization of ***E*-4.314** proceeds more readily than addition of the initially generated complex.

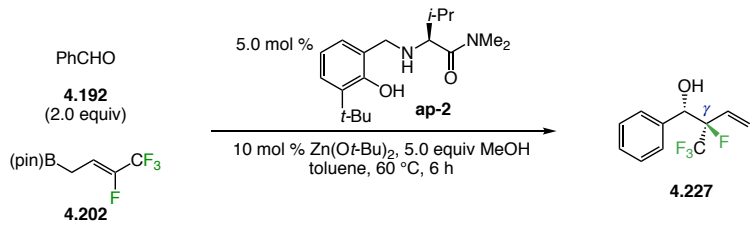
Further support was gleaned by carrying out the reaction with less stereoisomerically pure boronate **4.202**. Addition with an 83:17 *Z*:*E* mixture[124] (vs 95:5) afforded nearly the same diastereo- and enantioselectivity, but with increased yield. This is indicative of possible isomerization to a common intermediate prior to addition to the aldehyde, however, any attempt to detect isomerization of an aminophenol allyl complex were unsuccessful by spectroscopic analysis.

Scheme 4.53. Invoking an Isomerization of the Aminophenol-Allyl Complex[a]

a. Isomerization of aminophenol allyl complex



b. Reaction with less stereoisomerically pure boronate



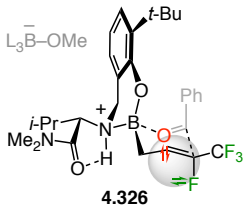
(pin)B, CF3, F	(pin)B, CF3, F
95:5 *Z*:*E*	**83:17 *Z*:*E***
90:10 γ:α	86:14 γ:α
59% yield	67% yield
88:12 dr, 92:8 er	86:14 dr, 94:6 er

[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

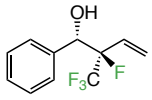
124) *Z*:*E* selectivity may be reduced by performing boryl allylic substitution in more polar media, i.e. pure thf instead of tol/thf (10/1)

Scheme 4.53 Experimental Evidence for Proposed Stereochemical Models[a]

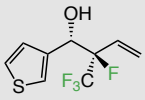
a. Support for pseudo-axial orientation: 5 vs. 6-membered rings



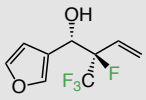
4.326



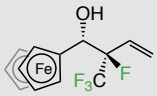
4.227
90:10 γ:α
59% yield (pure γ)
88:12 dr, 92:8 er



4.232
90:10 γ:α
69% yield (pure γ)
92:8 dr, 96:4 er

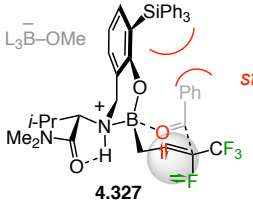


4.233
92:8 γ:α
77% yield (pure γ)
92:8 dr, 96:4 er



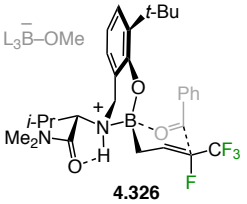
4.231
95:5 γ:α
73% yield (pure γ)
96:4 dr, 95:5 er

b. Effect of ligand substitution on diastereoselectivity

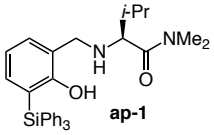


4.327

more steric pressure

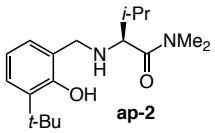


4.326



ap-1

36:74 γ:α,
44% yield (α + γ)
76:24 dr (γ)
93:7 er (γ)



ap-2

90:10 γ:α,
59% yield (pure γ)
88:12 dr (γ)
92:8 er (γ)

[a]All reactions were performed under an atmosphere of dry N_2. Conv. α:γ and dr ratios (±2%) were determined by analysis of ^{19}F NMR spectra of unpurified mixtures. Yield of isolated and purified γ-addition product (±5%). Er values were determined by HPLC analysis (±1%). See Experimental Section for details.

Thus, to account for the observed major isomer, we propose that addition proceeds through **4.326,** wherein the phenyl ring is oriented pseudo-axially. Upon analysis of the data, it is clear that aldehydes possessing five-membered rings (**4.231–233**) tend to be more diastereoselective than the larger six-membered arenes. Furthermore, results obtained from initial evaluation and optimization of aminophenol compounds supports the idea of pseudo-

axial orientation. For additions promoted by the larger $-SiPh_3$ substituted catalyst **ap-1,** observed diastereoselectivity is lower, likely due to increased steric pressure between the substrate and phenyl ring of the large substituent.

4.5 Conclusions

In summary, we have developed a method for synthesis of homoallylic alcohols possessing quaternary centers substituted with a fluoro and trifluoromethyl group in 80:20–98:2 dr and 91:9–96:4 er. Access to these otherwise difficult-to-access products were made possible by merging recent advances in boryl allylic substitution and addition of allyl boronates promoted by aminophenol boron-based catalysts. In doing so, we have demonstrated the first broadly applicable examples of addition of fluorine-containing trisubstituted allyl boronates as well as uncovered factors to favor 1,3-boryl shift. Furthermore, we showcased the synthetic utility of the products obtained through synthesis of the furanoside core of an analogue of Sofosbuvir analogue and discovered an unusual reactivity profile for compounds containing a fluoro- and trifluoromethyl substituted quaternary center.

4.6 Experimental Section

4.6.1 General

Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz), or 600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br s = broad singlet, m = multiplet, app = apparent), coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). ^{19}F NMR spectra were recorded on a Varian Unity INOVA 400 (376 MHz) spectrometer. Chemical shifts are reported in ppm with $C_6H_5CF_3$ as an external standard ($C_6H_5CF_3$: –63.72 ppm). Data are reported as follows: chemical shift, multiplicity, coupling constants (Hz), and integration. Carbons with directly attached boron atoms were not observed in some compounds, most likely due to quadrupolar relaxation.[1] High-resolution mass spectrometry was performed on a JEOL AccuTOF DART (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomeric ratios were determined by high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Chiral Technologies Chiralcel OD-H (4.6 x 250 mm), Chiralcel OJ-H (4.6 x 250 mm), Chiralcel OZ-H (4.6 x 250 mm), Chiralpak AD-H (4.6 x 250 mm), Chiralpak AS-H (4.6 x 250 mm)) in comparison with authentic racemic materials. Specific rotations were measured using either an Atago AP-300 Automated Polarimeter or a Rudolph Research Analytical Autopol IV Polarimeter. Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene was purified through a copper oxide and alumina column. Dimethoxy ethane and tetrahydrofuran were freshly distilled from a sodium and benzophenone ketyl solution. $CDCl_3$ was purchased from Cambridge Isotope Laboratories and store over activated 4Å molecular sieves prior to use. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher Scientific) in air.

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1) Wrackmeyer, B. *Prog. NMR Spectrosc.* **1979**, *12*, 227–259.

4.6.2 Reagents

Acetonitrile (99.9% Extra Dry) was purchased from Acros and used as received.
Aldehydes were purchased from commercial sources. Liquid aldehydes were distilled over CaH_2 prior to use. Crystalline aldehydes were purified by silica gel chromatography.
Allyl bromide was purchased from Aldrich and distilled over CaH_2.
Allyltrimethylsilane was purchased from Aldrich and distilled over CaH_2.
Ammonium chloride was purchased from Acros and used as received.

Benzyl Bromide was purchased from Oakwood and used as received.

Bis(pinacolato)diboron was purchased form Frontier Scientific, Inc. and recrystallized from pentane.

(*R*)-α,α-Bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethyl silyl ether was purchased from Aldrich and used as received.

(*Z*)-1-Bromo-2-fluoroethylene was purchased from Synquest and used as received.

***N*-Butyl Lithium (2.5 M in hexanes)** was purchased from Aldrich and titrated with *N*-Benzylbenzamide prior to each use.
Calcium Hydride was purchased from Strem and used as received.

Camphorsulfonic acid was purchased from Acros and used as received.

Citric acid was purchased from Acros and used as received.

Copper (I) chloride was purchased from Strem and used as received.

Dichloro[1,3-bis(2,6-isopropylphenyl)-2 imidazolidinylidene](benzylidene)(tricyclohexylphosphine)]ruthenium (II) was purchased from Aldrich and used as received.

1,2:5,6-Di-O-cyclohexylidene-D-mannitol was purchased from Aldrich and used as received.

1,2:5,6-Di-O-isopropylidene-D-mannitol was purchased from Aldrich and used as received.

(Diethylamino)sulfur trifluoride was purchased from Oakwood and used as received.

***N,N*-diisopropylethylamine** was purchased from Oakwood and used as received.
***N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC•HCl)** was purchased from Advanced ChemTech and used as received.
4-Dimethylaminopyridine was purchased from Oakwood and used as received.

Dimethyl sulfide was purchased from Aldrich and used as received.

Ethylene glycol was purchased from Oakwood and used as received.

***N*-Fluorobenzenesulfonimide** was purchased from Oakwood and used as received.

Hydrochloric Acid (4.0 M in 1,4-dioxane) was purchased from Aldrich and used as received.
1-Hydroxybenzotriazole hydrate was purchased from Oakwood and used as received.
Lithium Aluminum Hydride was purchased from Aldrich and used as received.

Lithium *tert*-butoxide was purchased from Strem and used as received.

Lithium trimethyl silanolate was purchased from Aldrich and used as received.

Magnesium Sulfate was purchased from Fisher and flame-dried under vacuum prior to use.

Methanol (99.7% Extra Dry) was purchased from Acros and used as received.

3-Methylbut-2-enylboronic acid pinacol ester was prepared according to a literature procedure.[2]

2-C-Methyl-4,5-O-(1-methylethylidene)-D-arabinonic acid ethyl ester was purchased from AK Scientific and used as received.

4-Methylmorpholine *N*-oxide was purchased from Aldrich and used as received.

Methyl sulfoxide (99.7% Extra Dry) was purchased from Acros and used as received.

Methyltriphenylphosphium bromide was purchased from Aldrich and azeotropically dried with benzene prior to use.

4-Nitrobenzoyl chloride was purchased from Sigma-Aldrich and used as received.

3,3,4,4,4-Pentafluorobutene was purchased from Synquest and used as received.

Osmium tetroxide (4 wt % in H_2O) was purchased from Strem and used as received.

1H, 1H, 2H-Perfluorohexene was purchased from Synquest and used as received.

Pinacolborane was purchased from Oakwood and distilled over CaH_2 prior to use.

Potassium Carbonate (granular) was purchased from Fisher and used as received.

Potassium hydride (in paraffin) was purchased from Aldrich and used as received.

Potassium *tert*-butoxide was purchased from Strem and used as received.

Selectfluor was purchased from Oakwood and used as received.

Sodium Hydride (90 wt%) was purchased from Aldrich and used as received.

Sodium periodate was purchased from Alfa Aesar and used as received.

Sulfur trioxide pyridine complex was purchased from Aldrich and used as received.

Tetrabutylammonium iodide was purchased from Oakwood and used as received.

Triethylamine was purchased from Aldrich and distilled from CaH_2 prior to use.

Trifluoroacetic acid was purchased from Oakwood and used as received.

Trifluroacetic anhydride was purchased from Oakwood and distilled over CaH_2 prior to use.

L-Valine Ethyl Ester Hydrochloride was purchased from Aldrich and used as received.

Vinylmagnesium bromide solution (1.0 M in thf) was purchased from Aldrich and used as received.

Zinc dust was purchased from Strem and activated with 1 M HCl prior to use according to a previously established procedure.[3]

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2) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 7092–7100.

3) Lin, M.; Shen, A.; Sun, X.-W.; Xu, M.-H.; Lin, G-Q. *Chem. Eur. J.* **2010**, *15*, 10217–10224.

Zinc *tert*-Butoxide was prepared according to a previously reported procedure.[4]

4.6.3 Ligands

Imidazolinium salts (imid1-4) were synthesized in accordance to a procedure in the literature and the analytical data are fully consistent with those reported previously.[5]

(*R*)-2-((3-(*tert*-Butyl)-2-hydroxybenzyl)amino)-*N*,*N*,3-trimethylbutanamide (*ent*-ap-2): The title compound was synthesized in accordance to a procedure in the literature and the analytical data are fully consistent with those reported previously.[6] $[\alpha]^{20}_{D}$ –22.9 (*c* 0.94, $CHCl_3$).

4.6.4 Preparation of Fluorine-Containing Allyl Boron Reagents through Boryl Allylic Substitution

(*Z*)-4,4,5,5-Tetramethyl-2-(3,4,4,4-tetrafluorobut-2-en-1-yl)-1,3,2-dioxaborolane (4.202): In an N_2-filled glovebox, an oven-dried vial equipped with a magnetic stir bar was charged with **imid-4** (60.1 mg, 0.132 mmol), CuCl (13.0 mg, 0.132 mmol) LiO*t*-Bu (212 mg, 1.32 mmol) and diluted with thf (1.0 mL). The mixture was allowed to stir at 22 °C for 1 h. Bis(pinacolato)diboron (1.22 g, 4.8 mmol) was added to the mixture, and the solution was diluted with toluene (10 mL). The mixture was allowed to stir for 10 minutes at 22 °C and then placed in a –40°C freezer for 30 minutes. A cooled (–40°C) solution of 3,3,4,4,4-pentafluoro-1-butene (1.03 g, 2.40 mmol, 34 wt% in THF) was then added and the vessel was quickly sealed, removed from the glovebox and allowed to stir at 22 °C for 8 hours. The unpurified mixture was concentrated to ~50% of its original volume and passed through a plug of oven dried silica gel (6.0 cm high x 1.0 cm wide) eluting with 50:1 hexanes:Et_2O (solvent passed through columns of activated alumina prior to chromatography). The volatiles were removed and then the flask was fitted with a short path distillation head. The desired allyl boronate was distilled over as a solution in toluene, and the distillate was then concentrated to ~10-20% of its original volume. Dry hexanes (~0.5 mL) was added and the supernatant was divided, loaded onto three short plugs of oven-dried silica gel (5.0 cm high x 1.0 cm wide) and quickly purified by silica gel column chromatography (eluting with hexanes/Et_2O: 50/1) to afford product in 90-95% purity as colorless oil (286 mg, 1.1 mmol, 47%).

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4) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216–221.

5) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490–1493.

6) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216–221.

IR (neat): 2981 (w), 2932 (w), 1458 (w), 1381 (m), 1372 (m), 1139 (s), 843 (m) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 5.73 (1H, dt, J = 33.4, 8.2 Hz), 1.79 (2H, d, J = 8.1 Hz), 1.25 (12H, s); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 145.5 (dq, $J_{C\text{-}F}$ = 254.1, 38.5 Hz), 118.8 (apparent dd, $J_{C\text{-}F}$ = 270.6, 41.9 Hz), 109.7 (m), 84.1, 24.8; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ –72.2 (3F, d, J = 12.0 Hz), –138.3 (1F, m).

Modification for Chromatography-Free Preparation of Allyl Boron

The reaction was set up in an identical manner as described above, except LiOTMS (253.8 mg, 1.32 mmol) was added as the nucleophilic promoter. After 8 hours of reaction, the volatiles were removed by rotary evaporation. The resulting toluene solution was passed through a plug of oven-dried silica gel (8.0 cm high x 6.0 cm wide) eluting with 50:1 hexanes:Et_2O. The volatiles were removed and then the flask was fitted with a short path distillation head. The desired allyl boronate was distilled over as a solution in toluene, the distillate was then concentrated and then passed through a cotton plug topped with 1.0 cm of oven dried silica to filter any remaining impurities. *Note:* If catalytic allyl addition reaction turns dark gray, repeat this filtration with any remaining reagent.

Procedure for Ligand-Free Preparation of Allyl Boron

In an N_2-filled glovebox, an oven-dried vial equipped with a magnetic stir bar was charged with CuCl (13.0 mg, 0.132 mmol) LiO*t*-Bu (212 mg, 1.32 mmol) and Bis(pinacolato)diboron (1.22 g, 4.8 mmol). The solids were then diluted with a pre-prepared mixture of 10 mL toluene and 1.0 mL thf. The mixture was allowed to stir at 22 °C for 10 min, then placed in a –40°C freezer for 30 minutes. A cooled (–40°C) solution of 3,3,4,4,4-pentafluoro-1-butene (1.03 g, 2.40 mmol, 34 wt% in THF) was then added and the vessel was quickly sealed, removed from the glovebox and allowed to stir at 22 °C for 8 hours. The reaction was quenched and purified as described above.

(*Z*)-4,4,5,5-Tetramethyl-2-(3,4,4,5,5,6,6,6-octafluorohex-2-en-1-yl)-1,3,2-dioxaborolane (S-1): The title compound was synthesized analogous to **4.202** and purified by silica gel chromatography to afford **S-1** (259 mg, 0.732 mmol, 61% yield) as colorless oil. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 5.72 (1H, dt, J = 33.6, 8.4 Hz), 1.82 (2H, d, J = 6.5 Hz), 1.25 (12H, s); **^{13}C NMR ($CDCl_3$, 150 MHz):** δ 145.2 (dt, J=254.6, 28.8 Hz), 119.6–116.5 (m), 117.9 (tq, J=285.7, 33.6 Hz), 116.1 (d, J=19.2 Hz), 114.4–114.2 (m), 113.2– 112.4 (m), 112.5–104.8 (m), 84.1, 24.8; **^{19}F NMR (376 MHz, $CDCl_3$)**: –80.9 (td, J = 9.0, 2.5 Hz, 3F), –117.4–119.6 (m, 2F), –127.6 (dd, J = 9.1, 3.4 Hz, 2F), –134.0–134.56 (m, 1F).

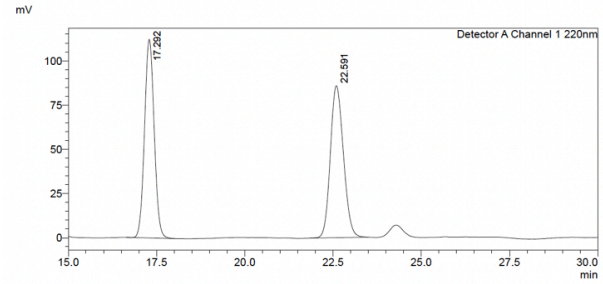
4.6.5 Represenative Procedure for Allyl Addition

In a N_2-filled glovebox, a stock solution of **ap-2** and zinc(II) *tert*-butoxide was prepared. An oven-dried vial (8 mL) equipped with a stir bar was charged with aminophenol (**ap-2**) (6.1 mg, 0.02 mmol), zinc *tert*-butoxide (8.5 mg, 0.04 mmol) and toluene (2.0 mL). The freshly prepared stock solution was allowed to stir for 15 min at 22 °C. In another vial (8 mL), aldehyde (0.2 mmol) was

weighed out. The aminophenol/Zn(O*t*-Bu)$_2$ stock solution was then added by syringe (500 μL) followed by allyl boronate **4.202** (25.4 mg, 0.1 mmol), and the vial walls were rinsed with toluene (500 μL). MeOH (20 μL, 0.5 mmol) was then added and the reaction vessel was sealed with a cap removed from the glovebox. The mixture was placed into a *preheated* oil bath and allowed to stir for 6 h at 60 °C. Upon cooling to 22 °C the reaction was quenched by the addition of MeOH (1.5 mL). The mixture was then allowed to stir for 0.5 h at 22 °C. The volatiles were removed in vacuo and the resulting opaque oil was purified by silica gel chromatography (100:0–5:1 hexanes:Et_2O) to afford the desired homoallylic alcohol.

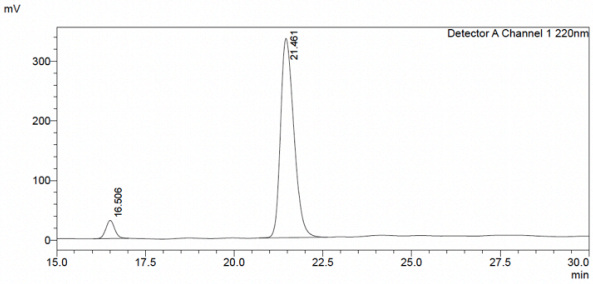
4.6.6 Analytical Data for Addition of Fluoro–Substituted Allyl Boronates to Aldehydes

(1*S*,2*R*)-2-fluoro-1-phenyl-2-(trifluoromethyl)but-3-en-1-ol (4.227). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 5H), 5.89 – 5.66 (m, 1H), 5.58 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.50 (dd, *J* = 11.1, 2.7 Hz, 1H), 5.11 (dd, *J* = 15.8, 4.5 Hz, 1H), 2.42 (ddd, *J* = 4.6, 1.8, 0.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 136.2 (d, *J* = 4.4 Hz), 129.0, 128.3, 127.9, 126.5 (d, *J* = 19.0 Hz), 121.4 (d, *J* = 11.9 Hz), 96.7 (qd, *J* = 28.9 Hz), 94.8 (q, *J* = 28.7 Hz), 74.2 (dd, *J* = 21.3, 5.0 Hz); **HRMS (DART):** Calcd for $C_{11}H_9F_4$ $[M+H–H_2O]^+$: 217.0635; Found: 217.0631; **Specific Rotation:** for a 94:6 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 98:2 hexanes:*i*-PrOH, 1.0 mL/min, 220 nm): t_R: 16.5 min (minor) and 21.5 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	17.292	112139	2139959	49.206
2	22.591	85785	2209063	50.794
Total		197924	4349022	100.000



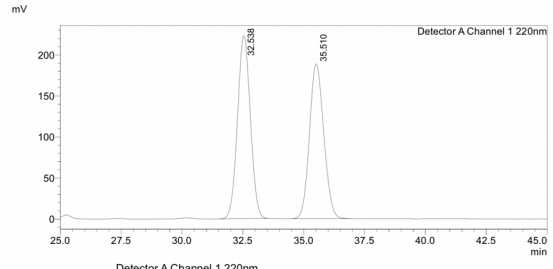
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	16.506	30425	526876	5.652
2	21.461	334214	8795516	94.348
Total		364639	9322392	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	17.292 min	2139959	49.206	1	16.506 min	526876	5.652
2	22.591 min	2209063	50.794	2	21.461 min	8795516	94.348

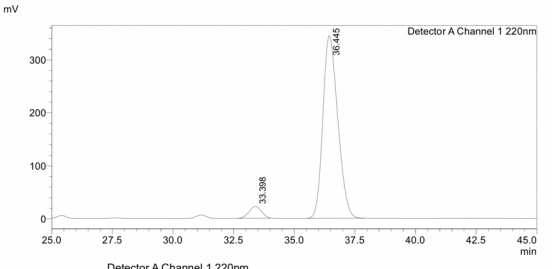
(1*S*,2*R*)-2-fluoro-1-(4-methoxyphenyl)-2-(trifluoromethyl)but-3-en-1-ol (4.228). Following the general procedure for addition, *p*-methoxy benzaldehyde (27.2 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (16.6 mg, 0.063 mmol). **IR (neat):** 3449 (br), 2918 (w), 2842 (w), 1613 (w), 1514 (m), 1250 (m), 1176 (s), 1029 (m), 980 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31–7.23 (m, 2H), 6.92 – 6.82 (m, 2H), 5.74 (dddd, *J* =

21.4, 17.3, 11.2, 0.8 Hz, 1H), 5.57 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.49 (dd, *J* = 11.1, 2.5 Hz, 1H), 5.05 (dd, *J* = 15.7, 4.2 Hz, 1H), 3.80 (s, 2H), 2.39 (dd, *J* = 4.3, 1.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** 159.4, 129.2, 128.3 (d, *J*=4.3 Hz), 126.6 (d, *J*=18.9 Hz), 123.9 (d, *J*=29.1 Hz), 121.3 (d, *J*=11.7 Hz), 113.6, 95.8 (dq *J*=195.8, 28.9 Hz), 73.7 (d, *J*=21.4 Hz), 55.2; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.80 (d, *J*=6.7 Hz, 3F), –182.77 (m, 1F); **HRMS (DART):** Calcd for $C_{12}H_{11}OF_4$ $[M+H-H_2O]^+$: 247.0741, found: 247.0753; **Specific Rotation:** $[\alpha]^{20.0}$ +29.2 (*c* 1.50, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 33.4 min (minor) and 36.4 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	32.538	222819	8199345	51.462
2	35.510	188722	7733464	48.538
Total		411540	15932809	100.000

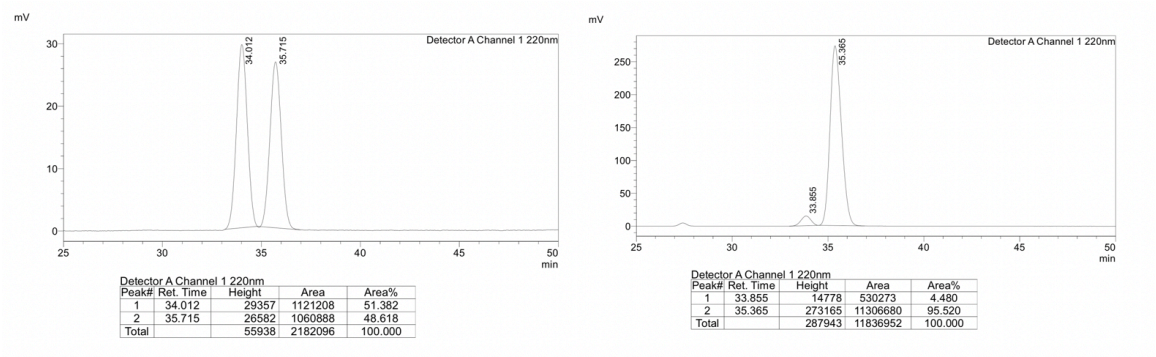


Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	33.398	22323	797569	5.135
2	36.445	344175	14734774	94.865
Total		366497	15532343	100.000

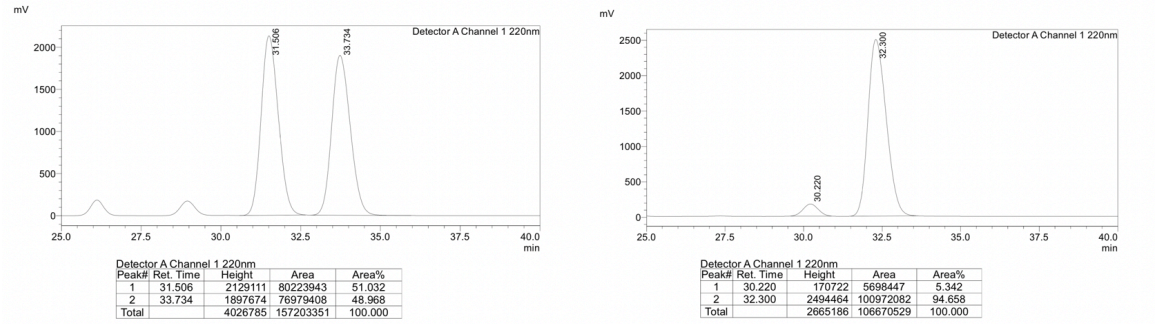
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	32.538 min	8199345	51.462	1	33.398 min	797569	5.135
2	35.510 min	7733464	48.538	2	36.445 min	14734774	94.865

(1*S*,2*R*)-2-Fluoro-1-(4-(methylthio)phenyl)-2-(trifluoromethyl)but-3-en-1-ol (4.229): Following the general procedure for addition, 4-(methylthio)benzaldehyde (30.4 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as a white solid (18.8 mg, 0.067 mmol). **M.p.** 63–65 °C; **IR (neat):** 3414 (br), 2924 (w), 1601 (w), 1497 (w), 1414 (w), 1299 (m), 1285 (m), 1189 (s), 1093 (m), 983 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.29 – 7.16 (m, 4H), 5.73 (ddd, *J* = 21.3, 17.2, 11.1 Hz, 1H), 5.62 – 5.53 (m, 1H), 5.50 (dd, *J* = 11.0, 2.5 Hz, 1H), 5.05 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.47 (s, 3H), 2.45 – 2.41 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 139.7, 132.7 (d, *J*=4.2 Hz), 128.3, 126.4 (d, *J*=19.1 Hz), 125.9, 122.4 (dd, *J*=285.6, 29.1 Hz), 121.5 (d, *J*=11.8 Hz), 95.7 (dq, *J*=194.7, 29.0 Hz), 73.8 (dd, *J*=21.5, 8.8 Hz), 15.4; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.72 (3F, d, *J*=6.8 Hz), –182.75 (1F, m); **HRMS (DART):** Calcd for $C_{12}H_{13}OF_4S$ $[M+H]^+$: 281.0618, found: 281.0620. **Specific Rotation:** $[\alpha]^{20.0}$ +29.9 (*c* 0.47, $CHCl_3$) for 95.5:4.5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 33.9 min (minor) and 35.4 min (major).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	34.012 min	1121208	51.382	1	33.855 min	530273	4.480
2	35.715 min	1060888	48.618	2	35.365 min	11306680	95.520

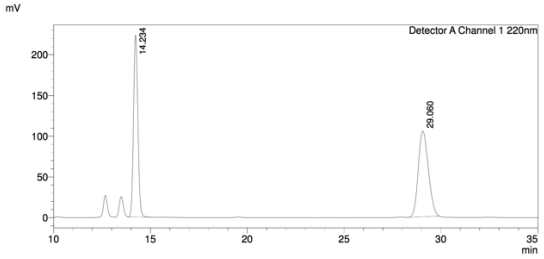
(1*S*,2*R*)-1-(6-Bromonaphthalen-2-yl)-2-fluoro-2-(trifluoromethyl)but-3-en-1-ol (4.230): Following the general procedure for addition, 6-Bromo-2-napthaldehyde (40.7 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as pale yellow solid (18.2 mg, 0.050 mmol). **M.p.** 72–74 °C; **IR (neat):** 3419 (br), 2922 (w), 2850 (w), 1591 (w), 1499 (w), 1338 (m), 1297 (m), 1183 (s), 983 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 1.9 Hz, 1H), 7.79 (s, 1H), 7.72 (dd, *J* = 12.1, 8.7 Hz, 2H), 7.57 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.53 – 7.47 (m, 1H), 5.76 (ddd, *J* = 21.5, 17.2, 11.2 Hz, 1H), 5.58 (d, *J* = 17.2 Hz, 1H), 5.49 (dd, *J* = 11.3, 2.7 Hz, 1H), 5.26 (dd, *J* = 15.7, 4.4 Hz, 1H), 2.54 (dd, *J* = 4.4, 1.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 134.4, 134.1 (d, *J*=4.1 Hz), 131.4, 129.83, 129.79, 129.75, 127.7, 127.3, 126.6 (d,=19.1 Hz), 126.4, 122.5 (dd, *J* =285.6, 29.0 Hz), 121.8 (d, $J_{C\text{-}F}$ = 11.8 Hz), 120.9, 95.9 (dq, *J*=194.7, 29.0 Hz), 74.3 (d, *J*=21.6 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.67 (3F, d, *J*=6.9 Hz), –182.86 (1F, qd, *J*=15.0, 7.3 Hz); **HRMS (DART):** $[M+H-H_2O]^+$ Calcd for $C_{15}H_{10}F_4Br$: 344.9897, found: 344.9904. **Specific Rotation:** $[\alpha]^{20.0}$ +28.0 (*c* 0.87, $CHCl_3$) for a 94.5:5.5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 30.2 min (minor) and 32.3 min (major).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	31.506 min	80223943	51.032	1	30.220 min	5698477	5.342

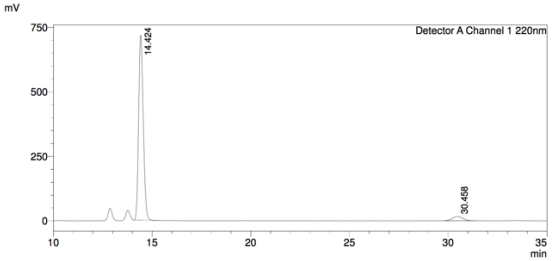
2	33.734 min	76979408	48.968	2	32.300 min	100972082	94.658

(1*S*,2*R*)-2-Fluoro-1-ferrocenyl-2-(trifluoromethyl)but-3-en-1-ol (4.231): Following the general procedure for addition, ferrocenecarboxaldehyde (42.8 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as yellow oil (24.8 mg, 0.073 mmol). **IR (neat):** 3566 (br), 3096 (w), 2923 (w), 1653 (w), 1296 (m), 1182 (s), 999 (m), 981 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.73 (ddd, *J* = 21.1, 17.2, 11.1 Hz, 1H), 5.54 (d, *J* = 17.2 Hz, 1H), 5.45 (dd, *J* = 11.1, 2.6 Hz, 1H), 4.70 (dd, *J* = 15.6, 2.9 Hz, 1H), 4.31 – 4.24 (m, 2H), 4.23 (s, 4H), 4.21 (s, 2H), 2.41 (d, *J* = 2.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 127.0 (dd, *J*=19.1, 0.8 Hz), 122.4 (dd, *J*=285.4, 29.1 Hz), 120.8 (d, *J*=11.9 Hz), 70.4 (d, *J*=22.0 Hz), 70.1 (d, *J*=1.3 Hz), 68.7, 68.0, 65.5 (d, *J* = 1.9 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.89 (d, *J* =12.0 Hz, 3F), –182.19 (m, 1F); **HRMS (DART):** $[M+H-H_2O]^+$ Calcd for $C_{15}H_{13}F_4Fe$: 325.0297, found: 325.0306. **Specific Rotation:** $[\alpha]^{20.0}$ −33.7 (*c* 0.51, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 14.4 min (major) and 30.5 min (minor).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	14.234	223525	3482577	47.795
2	29.060	105405	3803840	52.205
Total		328931	7286417	100.000



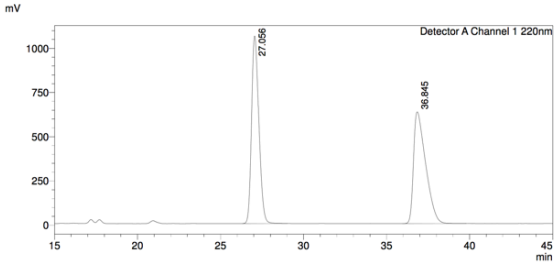
Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	14.424	716419	11720665	94.902
2	30.458	16784	629661	5.098
Total		733202	12350325	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	14.234 min	3482577	47.795	1	14.424 min	11720665	94.902
2	29.060 min	3803840	52.205	2	30.458 min	629661	5.068

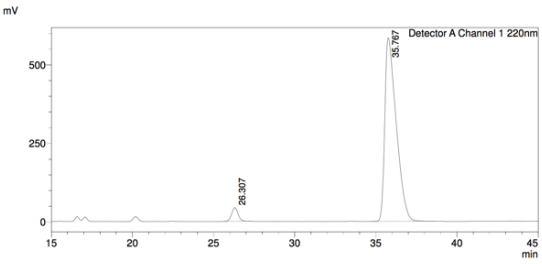
(1*S*,2*R*)-2-Fluoro-1-(thiophen-3-yl)-2-(trifluoromethyl)but-3-en-1-ol (4.232): Following the general procedure for addition, 3-thiophenecarboxaldehyde (22.4 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (16.6 mg, 0.069 mmol). **IR (neat):** 3412 (br), 3110 (w), 2922 (w), 2851 (w), 1417 (w), 1296 (m), 1280 (m), 1181 (s), 1150 (s), 982 (m), 946 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34–7.27 (m, 2H), 7.12–7.06 (m, 1H), 5.77 (ddd, *J* = 21.2, 17.2, 11.1 Hz, 1H), 5.60 (d, *J* = 17.2 Hz, 1H), 5.51 (dd, *J* = 11.2, 2.6 Hz, 1H), 5.21 (dd, *J* = 16.4, 4.7 Hz, 1H), 2.40 (dt, *J* = 4.9, 1.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.2 (d, *J*=4.6 Hz), 126.8 (d, *J*=18.2 Hz), 126.8 (d, *J*=1.4 Hz), 126.0, 124.5, 122.4 (dd, *J*=285.6, 29.2 Hz), 121.4 (d, *J*=11.6 Hz), 95.6 (qd, *J*=194.5, 29.1 Hz), 70.5 (dd, *J* = 22.1, 6.3 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –76.00 (d, *J* = 6.7 Hz, 3F), –183.13 (qd, *J* =15.5, 7.9 Hz, 1F); **HRMS (DART):** $[M+H-H_2O]^+$ Calcd for $C_9H_7F_4S$: 223.0199, found: 223.0209. **Specific Rotation:** $[\alpha]^{20.0}$ +27.1 (*c* 1.03, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity was determined by HPLC analysis in

comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 26.3 min (minor) and 35.8 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	27.056	1059816	32345462	50.413
2	36.845	631418	31815544	49.587
Total		1691234	64161006	100.000

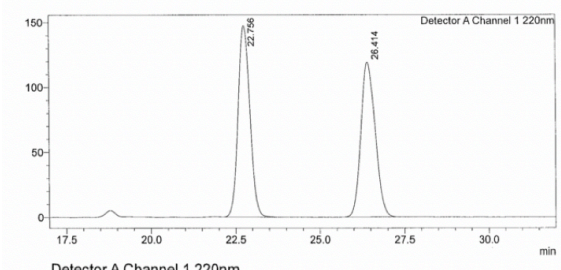


Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	26.307	43639	1232734	4.130
2	35.767	584072	28613636	95.870
Total		627712	29846371	100.000

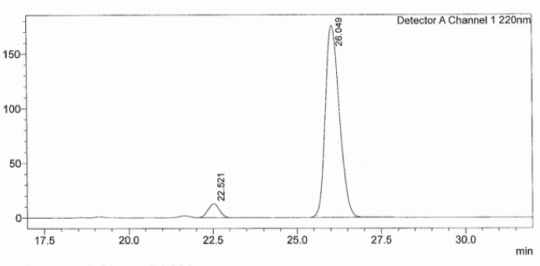
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	27.056 min	32345462	50.413	1	26.307 min	1232734	4.130
2	36.845 min	31815544	49.587	2	35.767 min	28613636	95.870

(1*S*,2*R*)-2-Fluoro-1-(furan-3-yl)-2-(trifluoromethyl)but-3-en-1-ol (4.233): Following the general procedure for addition, 3-furancarboxaldehyde (19.2 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as colorless oil (13.9 mg, 0.077 mmol). **IR (neat):** **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.47 (dt, *J* = 1.5, 0.7 Hz, 1H), 7.40 (t, *J* = 1.7 Hz, 1H), 6.43 (dt, *J* = 1.9, 1.0 Hz, 1H), 5.88–5.71 (m, 1H), 5.65 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.59–5.51 (m, 1H), 5.09 (dd, *J* = 16.7, 5.3 Hz, 1H), 2.25 (dd, *J* = 5.3, 1.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 146.1 (d, *J*=4.2 Hz), 144.0 (d, *J*=3.9 Hz), 129.4 (d, *J*=19.3 Hz), 126.0 (d, *J*=29.3 Hz), 124.2 (d, *J*=11.5 Hz), 124.0, 111.9 (d, *J*=4.7 Hz), 98.3 (apparent dd, *J*=193.7, 29.0 Hz), 70.1 (dd, *J*=22.7, 6.3 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.99 (d, *J* = 6.6 Hz, 3F), –183.61 (qd, *J* = 22.6, 7.2 Hz, 1F); **HRMS (DART):** $[M+H-H_2O]^+$ Calcd for $C_9H_7F_4O$: 207.0428, found: 204.0438. **Specific Rotation:** $[\alpha]^{20.0}$ +29.5 (*c* 0.86, $CHCl_3$) for a 94.5:5.5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm). t_R: 22.5 min (minor) and 26.0 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	22.756	3610206	50.922	147240
2	26.414	3479438	49.078	119112
Total		7089644	100.000	266352



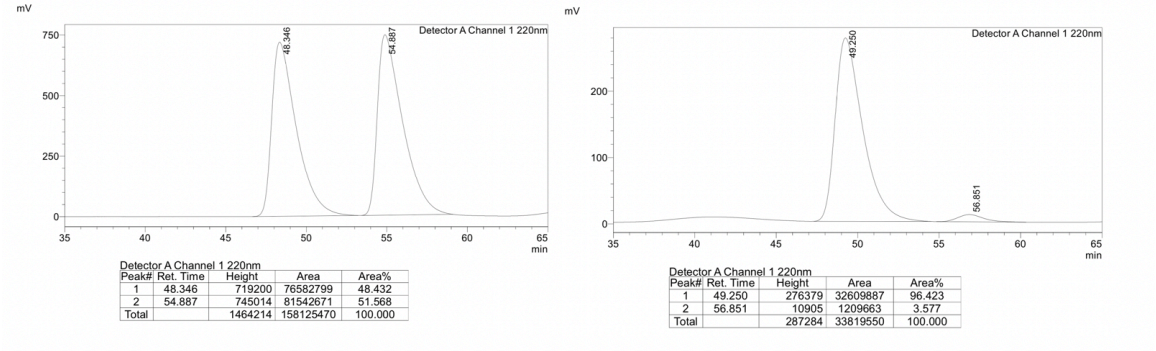
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	22.521	303502	5.618	12871
2	26.049	5098867	94.382	175531
Total		5402369	100.000	188402

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	22.756 min	3610206	50.922	1	22.521 min	303502	5.618

2	26.414 min	3479438	49.078	2	26.049 min	5098867	94.382

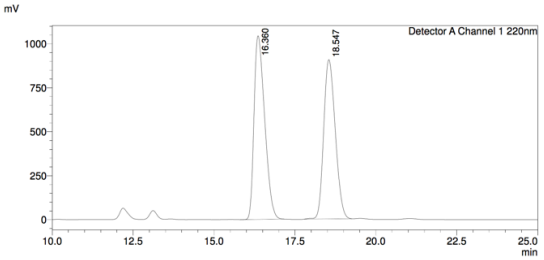
***tert*-Butyl 5-((1*S*,2*R*)-2-fluoro-1-hydroxy-2-(trifluoromethyl)but-3-en-1-yl)-1H-indole-1-carboxylate (4.234):** Following the general procedure for addition, *tert*-butyl 5-formyl-1*H*-indole-1-carboxylate (49.1 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as white solid (20.1 mg, 0.054 mmol). **M.p.** 79–81 °C; **IR (neat):** 3503 (br), 2980 (w), 2926 (w), 2855 (w), 1736 (m), 1507 (w), 1445 (w), 1352 (m), 1184 (s), 1131 (s), 1084 (m), 1023 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.10 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 3.7 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.29 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.55 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.78 (ddd, *J* = 21.6, 17.2, 11.2 Hz, 1H), 5.57 (dd, *J* = 17.3, 0.9 Hz, 1H), 5.48 (dd, *J* = 11.3, 2.7 Hz, 1H), 5.19 (dd, *J* = 15.9, 4.3 Hz, 1H), 2.47 (dd, *J* = 4.4, 1.7 Hz, 1H), 1.66 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 149.8, 135.5, 130.7, 130.6, 126.8 (d, *J*=18.8 Hz), 126.8, 124.2, 122.7 (dd, *J*=285.7, 29.2 Hz), 121.4 (d, *J*=11.8 Hz), 120.7, 115.1, 107.4 (d, *J*=2.9 Hz), 96.1 (dq, *J*=194.6, 28.8 Hz), 84.1, 74.5 (dd, *J* = 21.3, 6.3 Hz), 28.3; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.75 (d, *J* = 6.8 Hz, 3F), –182.74 (m, 1F); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{18}H_{20}F_4NO_3$: 374.1374, found: 374.1381. **Specific Rotation:** $[\alpha]^{20.0}$ +23.0 (*c* 0.57, $CHCl_3$) for a 96.5:3.5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 49.3 min (major) and 56.9 min (minor).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	48.346 min	76582799	48.432	1	49.250 min	32609887	96.423
2	54.887 min	81542671	51.568	2	56.851 min	1209663	3.577

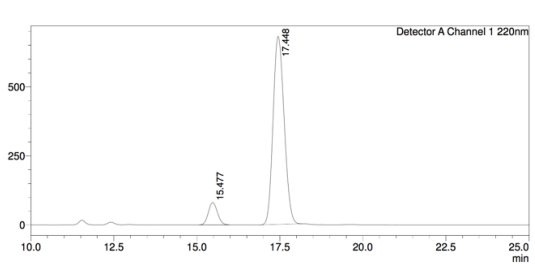
(3*S*,4*R*,*E*)-4-Fluoro-1-phenyl-4-(trifluoromethyl)hexa-1,5-dien-3-ol (4.235): Following the general procedure for addition, cinnamaldehyde (26.4 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as white solid (13.8 mg, 0.053 mmol). **IR (neat):** 3399 (br), 3027 (w), 2923 (w), 1297 (m), 1187 (s), 969 (m), 746 (m), 692 (m). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 – 7.27 (m, 5H), 6.78 (d, *J* = 15.9 Hz, 1H), 6.17 (ddt, *J* = 15.9, 6.7, 1.0 Hz, 1H), 5.89 (ddd, *J* = 21.0, 17.3, 11.0 Hz, 1H), 5.75 (d, *J* = 17.1 Hz, 1H), 5.67 – 5.59 (m, 1H), 4.73 (dt, *J* = 13.5, 6.1 Hz, 1H), 2.15 (dd, *J* = 5.6, 1.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.8 134.7, 128.8, 128.4, 126.7, 126.5, 123.2 (d, J_{C-F} = 6.1 Hz), 122.6 (app dd, J_{C-F} = 283.9, 28.7 Hz), 121.8 (d, *J*= 11.5

Hz), 95.4 (qd, *J*=192.4, 29.2 Hz), 72.8 (d, *J*=22.3 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –76.64 (d, *J* = 7.5 Hz, 3F), –29.19 (ddq, *J* = 21.9, 14.8, 7.6 Hz, 1 F); **HRMS (DART):** $[M+H-H_2O]^+$ Calcd for $C_{13}H_{11}F_4$: 243.0791, found: 243.0801. **Specific Rotation:** $[\alpha]^{20.0}$ +21.3 (*c* 0.56, $CHCl_3$) for a 91:9 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel OZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 15.5 min (minor) and 17.5 min (major).



Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	16.360	1043872	23994723	51.508
2	18.547	905608	22590014	48.492
Total		1949481	46584737	100.000

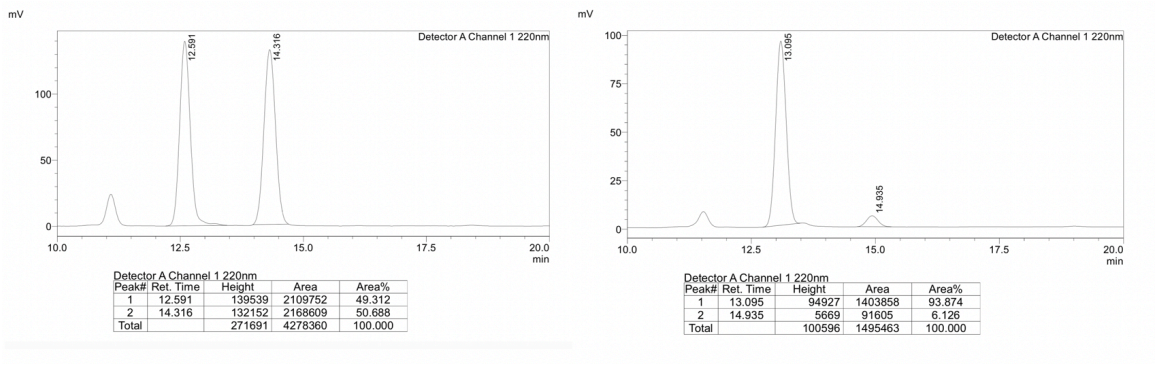


Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	15.477	80585	1528643	8.862
2	17.448	680092	15720715	91.138
Total		760677	17249357	100.000

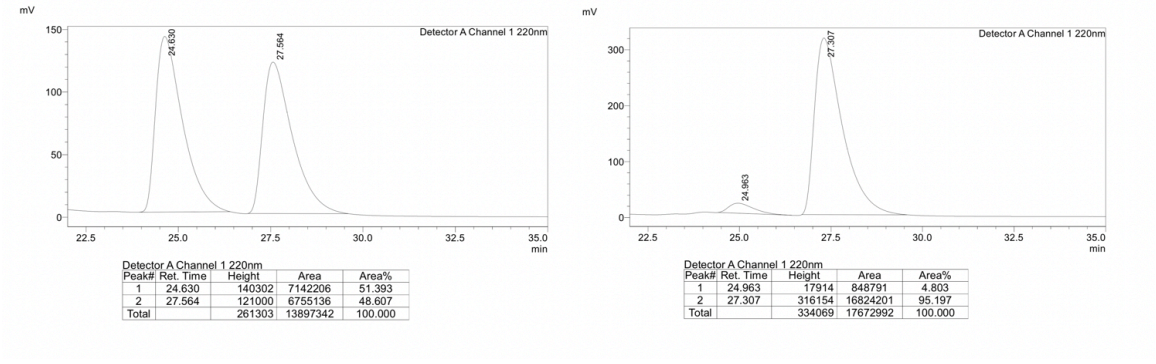
Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	16.360 min	23994723	51.508	1	15.477 min	1528643	8.862
2	18.547 min	22590014	48.492	2	17.488 min	15720715	91.138

(3*S*,4*R*)-4-Fluoro-1-phenyl-4-(trifluoromethyl)hex-5-en-3-ol (4.236): Following the general procedure for addition, hydrocinnamaldehyde (26.8 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as white solid (17.1 mg, 0.065 mmol). **IR (neat):** 3421 (br), 3063 (w), 3029 (w), 2930 (w), 2857 (w), 1472 (w), 1297 (m), 1174 (s), 987 (m), 946 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33–7.27 (2H, m), 7.24–7.18 (3H, m), 5.80 (1H, ddd, *J* = 21.0, 17.5, 10.9 Hz), 5.67 (1H, d, *J* = 17.1 Hz), 5.61–5.55 (1H, m), 4.05–3.91 (1H, m), 2.94 (ddd, *J* = 14.0, 9.4, 4.8 Hz, 1H), 2.68 (ddd, *J* = 13.7, 9.1, 7.6 Hz, 1H), 2.02–1.91 (1H, m), 1.88 (1H, d, *J* = 6.7 Hz), 1.83–1.69 (1H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.9, 128.5 (d, *J*=5.9 Hz), 127.1(d, *J*=5.90 Hz), 126.2, 122.8 (apparent dd, *J*=287.0, 29.4 Hz), 121.2 (d, *J*=12.0 Hz), 96.0 (dq, *J*=190.6, 29.4 Hz), 71.1 (d, *J*=21.3 Hz), 21.2, 14.4; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –76.04 (d, *J* = 6.9 Hz, 3F), –184.55 (m, 1F); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{13}H_{15}OF_4$: 263.1054, found: 263.1057. **Specific Rotation:** $[\alpha]^{20.0}$ +8.2 (*c* 0.38, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 13.1 min (major) and 14.9 min (minor).



Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	12.591 min	2108752	49.312	1	13.095 min	1403858	93.874
2	14.316 min	2168609	50.688	2	14.935 min	91605	6.126

(3*R*,4*S*)-7-(Dibenzylamino)-3-fluoro-3-(trifluoromethyl)hept-1-en-4-ol (4.237) Following the general procedure for addition, 4-(dibenzylamino)butanol (53.5 mg, 0.20 mmol) was transferred to an oven-dried vial and purified by preparative thin layer chromatography to afford the title compound as yellow oil (24.1 mg, 0.061 mmol). **IR (neat):** 3399 (br), 3063 (w), 3029 (w), 2926 (m), 2851 (w), 2801 (w), 1495 (w), 1453 (w), 1296 (m), 986 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36−7.25 (10H, m), 5.83 (1H, ddd, J = 21.0, 17.3, 11.1 Hz), 5.66 (1H, d, J = 16.5 Hz), 5.53 (1H, dd, J = 11.2, 1.8 Hz), 3.83 (1H, dd, J = 17.5, 10.8 Hz), 3.64 (2H, d, J = 13.4 Hz), 3.54 (2H, d, J = 13.4 Hz), 2.50– 2.42 (2H, m), 1.82–1.66 (3H, m), 1.42–1.32 (1H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.0, 129.6, 128.6 (d, J=19.2 Hz), 128.5, 127.4, 123.0 (apparent dd, J=285.8, 29.8 Hz), 120.3 (d, $J_{C\text{-}F}$ = 11.9 Hz), 95.9 (apparent dd, $J_{C\text{-}F}$ = 192.2, 29.1 Hz), 71.9 (d, $J_{C\text{-}F}$ = 21.5 Hz), 58.6, 53.3, 29.6, 23.6; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.57 (d, J = 6.7 Hz, 3F), –185.05 (m, 1F); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{22}H_{26}NOF_4$: 396.1945, found: 396.1933. **Specific Rotation:** $[\alpha]^{20.0}$ +1.6 (*c* 1.30, $CHCl_3$) for 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 24.9 min (minor) and 27.3 min (major).

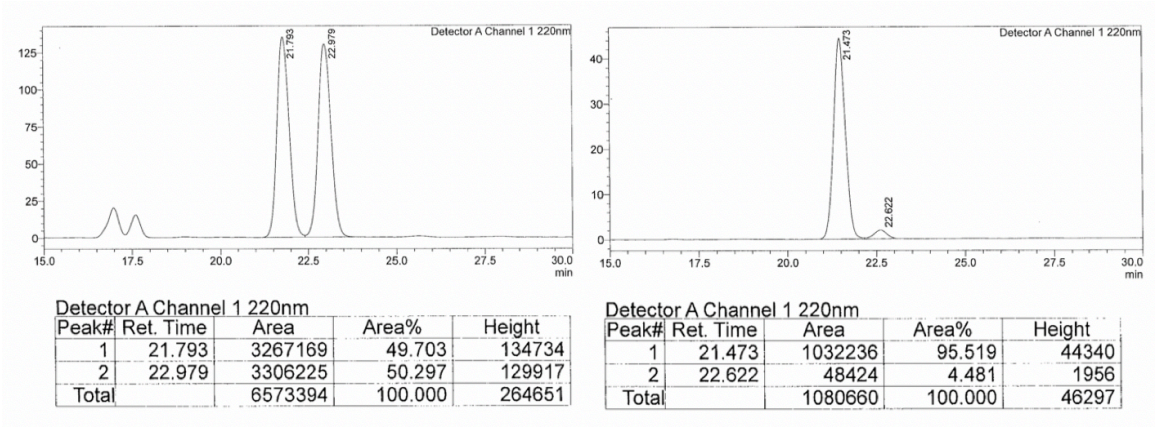


Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %

1	24.630 min	7142206	51.393	1	24.963 min	848791	4.803
2	27.564 min	6755136	48.607	2	27.307 min	16824201	95.197

(3*R*,4*S*,6*S*)-3-Fluoro-6,10-dimethyl-3-(trifluoromethyl)undeca-1,9-dien-4-ol (4.238): Following the general procedure for addition, (+)-citronellal (30.8 mg, 0.20 mmol) was transferred to an oven-dried vial and purified by preparative thin layer chromatography to afford the title compound as yellow oil (19.1 mg, 0.068 mmol). **IR (neat):** 3446 (br), 2961 (w), 2919 (w), 2856 (w), 1457 (w), 1379 (w), 1295 (m), 1180 (s), 986 (m), 943 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.82 (1H, ddd, *J* = 21.0, 17.3, 11.0 Hz), 5.68 (1H, d, *J* = 17.1 Hz), 5.62–5.56 (1H, m), 5.13–5.06 (1H, m), 4.14–4.03 (1H, m), 2.09–1.86 (2H, m), 1.82–1.72 (2H, m), 1.68 (3H, s), 1.60 (3H, s), 1.57–1.40 (2H, m), 1.40–1.31 (1H, m), 1.15–1.04 (1H, m), 0.96 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 131.7, 127.3 (dd, *J*=19.4, 0.8 Hz), 124.6, 122.8 (dq, *J*=285.5, 29.5 Hz), 121.4 (d, *J*=11.8 Hz), 96.2 (qd, *J*=190.3, 29.2 Hz), 70.2 (d, *J*=21.3 Hz), 38.1 (dd, *J*=3.6, 1.5 Hz), 35.4, 29.0, 25.9, 25.3, 20.7, 17.8; **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.87 (d, *J* = 6.8 Hz, 3F), –183.89 (m, 1F); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{14}H_{23}OF_4$: 283.1680, found: 283.1695. **Specific Rotation:** $[\alpha]^{20.0}$ –7.7 (*c* 1.10, $CHCl_3$).

(1*S*,2*R*)-2,3,3,4,4,5,5,5-octafluoro-1-phenyl-2-vinylpentan-1-ol (4.240). Following the general procedure for addition, benzaldehyde (21.2 mg, 0.20 mmol) was transferred to an oven-dried vial to afford the title compound as white solid (18.0 mg, 0.054 mmol). **M.p.** 57–59 °C. **IR (neat):** 3399 (br), 3036 (w), 2922 (w), 1342 (m), 1224 (s), 1192 (s), 1123 (s), 1001 (m), 816 (m), 730 (s), 700 (s), 532 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.35 (5H, m), 5.83 – 5.68 (1H, m), 5.55 (1H, d, *J* = 17.2 Hz), 5.50 (1H, d, *J* = 10.9 Hz), 5.23 (1H, dd, *J* = 14.5, 4.7 Hz), 2.49 (1H, dd, *J* = 4.7, 2.1 Hz); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 136.5 (d, *J* = 3.3 Hz), 129.1, 128.4, 128.3, 126.6 (d, *J*=18.1 Hz), 120.8 (d, *J* = 12.0 Hz), 118.7 (qt, *J* = 290.0, 34.0 Hz), 114.4 (m), 109.7 (m), 96.8 (dt, *J*=196.5, 24.6 Hz), 74.2 (d, *J* = 21.5 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –81.72 (td, *J* = 10.8, 4.0 Hz, 3F), –117.59 (dq, *J* = 292.8, 10.0 Hz, 1F), –120.49 (dq, *J* = 292.8, 11.8 Hz, 1F), –123.46 (ddt, *J* = 288.9, 13.5, 7.0 Hz, 1F), –125.89 (ddd, *J* = 288.9, 27.0, 11.8 Hz, 1F), –183.91 (d, *J* = 27.0 Hz, 1F); **HRMS (DART):** $[M+NH_4]^+$ Calcd for $C_{13}H_{14}NOF_8$: 352.0948, found: 352.0923. **Specific Rotation:** $[\alpha]^{20.0}_D$ +41.2 (*c* 0.6 $CHCl_3$) for a 95:5 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 21.4 min (major) and 22.6 min (minor).



Detector A Channel 1 220nm

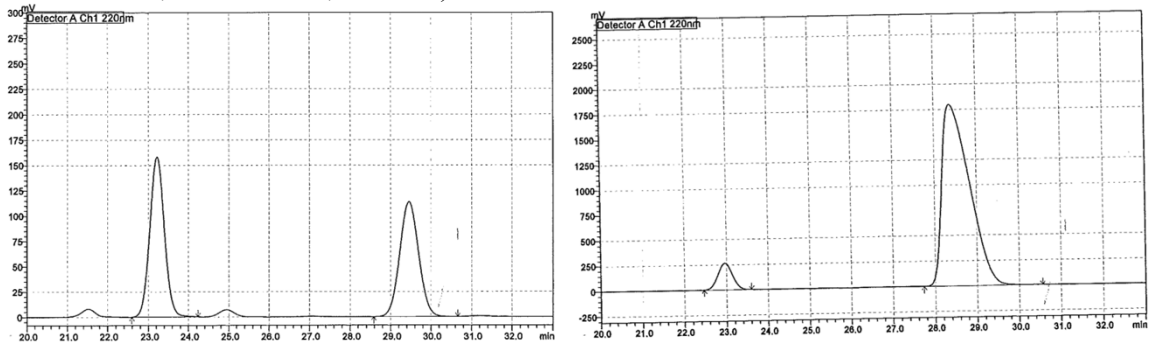
Peak#	Ret. Time	Area	Area%	Height
1	21.793	3267169	49.703	134734
2	22.979	3306225	50.297	129917
Total		6573394	100.000	264651

Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	21.473	1032236	95.519	44340
2	22.622	48424	4.481	1956
Total		1080660	100.000	46297

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	21.793 min	3267169	49.703	1	21.473 min	1032236	95.519
2	22.979 min	3306225	50.297	2	22.622 min	48424	4.481

(1*S*,2*R*)-1-(3-Chlorophenyl)-2-fluoro-2-(trifluoromethyl)but-3-en-1-ol (4.241): Following the general procedure for addition, 3-chlorobenzaldehyde (9.8 mg, 0.1 mmol), allylboronate (25.4 mg, 0.20 mmol) and MeOH (56 μL, 1.4 mmol) were transferred to an oven-dried vial to afford the title compound as colorless oil (13.0 mg, 0.068 mmol). **IR (neat):** **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 – 7.21 (m, 5H), 5.82 – 5.65 (m, 1H), 5.59 (d, *J* = 17.0 Hz, 1H), 5.54 (dd, *J* = 11.3, 2.8 Hz, 1H), 5.08 (dd, *J* = 15.6, 4.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 138.3 (d, *J*= 4.1 Hz), 134.4, 129.6, 129.3, 128.3, 126.4, 126.3, 122.5 (dd, *J* = 284.1, 28.9 Hz), 121.9 (d, *J*= 11.7 Hz), 95.7 (dq, *J*= 194.8, 29.1 Hz), 73.8 (d, *J*= 22.0 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.66 (dd, *J* = 6.8, 2.3 Hz, 3F), –182.94–183.19 (m, 1F); **HRMS (DART):** $[M+H-H_2O]^+$ Calcd for $C_{11}H_8F_4Cl$: 251.0245, found: 251.0254. **Specific Rotation:** $[\alpha]^{20}$ Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 99:1 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm).



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	23.217	4027375	52.071	157954
2	29.452	3707025	47.929	113718
Total		7734399	100.000	271672

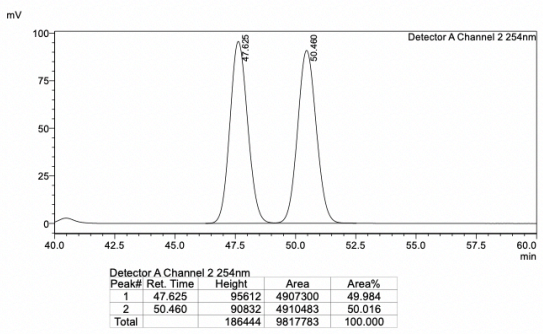
Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%	Height
1	22.960	6428793	7.277	263434
2	28.373	81920250	92.723	1796374
Total		88349043	100.000	2059808

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %

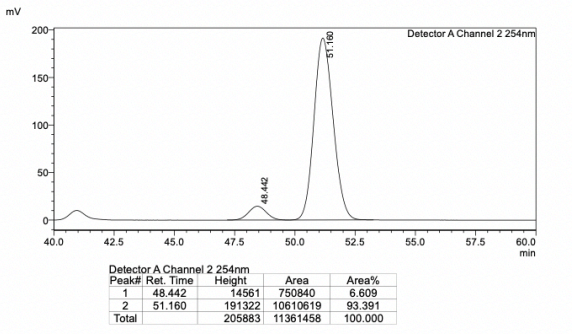
1	23.217 min	4027375	52.071	1	22.960	6428793	7.277
2	29.452 min	3707025	47.929	2	28.373	81920250	92.723

1*S*,2*R*)-2-fluoro-1-(4-nitrophenyl)-2-(trifluoromethyl)but-3-en-1-ol (4.242) Following the general procedure for addition, 4-nitrobenzaldehyde (7.5 mg, 0.1 mmol), allylboronate (25.4 mg, 0.20 mmol) and MeOH (56 μL, 1.4 mmol) were transferred to an oven-dried vial to afford the title compound as white solid (13.0 mg, 0.068 mmol). **IR (neat):** 3440 (br), 2916 (w), 2850 (w), 1604 (m), 1517 (s), 1350 (s), 1184 (s), 1014 (m) 728 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.26 – 8.17 (m, 2H), 7.59 – 7.50 (m, 2H), 5.71 (ddd, *J* = 20.8, 17.1, 10.9 Hz, 1H), 5.62 – 5.52 (m, 2H), 5.31 – 5.17 (m, 1H), 2.64 (dd, *J* = 4.4, 1.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 148.2, 142.9 (d, *J* = 3.9 Hz), 129.0, 125.8 (d, *J* = 18.9 Hz), 123.3, 122.3 (dd, *J* = 285.6, 28.8 Hz), 122.3 (d, *J* = 11.8 Hz), 95.3 (dd, *J*=195.4, 29.5 Hz), 73.4 (d, *J* = 22.2 Hz); **^{19}F NMR (376 MHz, $CDCl_3$):** δ –75.48 (d, *J* = 6.9 Hz), –182.94 (ddd, *J* = 21.8, 14.7, 7.4 Hz); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{11}H_{10}NO_3F_4$: 280.0591, found: 280.0588. **Specific Rotation:** $[\alpha]^{25.0}$ +101 for 93:7 er sample. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AZ-H column, 98:2 hexanes:*i*-PrOH, 0.5 mL/min, 220 nm): t_R: 48.4 min (minor) and 51.2 min (major).



Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	47.625	95612	4907300	49.984
2	50.460	90832	4910483	50.016
Total		186444	9817783	100.000



Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	48.442	14561	750840	6.609
2	51.160	191322	10610619	93.391
Total		205883	11361458	100.000

Peak #	Ret. Time	Area	Area %	Peak #	Ret. Time	Area	Area %
1	47.625 min	4907300	49.984	1	48.442	750840	6.609
2	50.460 min	4910483	50.016	2	51.160	10610619	93.391

4.6.7 Synthesis of Sofosbuvir Analogue

In a N_2-filled glovebox, a stock solution of aminophenol and zinc(II) *tert*-butoxide was prepared. An oven-dried round bottom flask (25 mL) equipped with a stir bar was charged with ***ent*-ap-2** (15.0 mg, 0.05 mmol), Zn(O*t*-Bu)$_2$ (21.0 mg mg, 0.02 mmol) and toluene (7.0 mL). The freshly prepared solution was allowed to stir at 22 °C for 15 min. Then freshly distilled (*R*)-1,4-dioxaspiro[4.5]decane-2-carbaldehyde (**4.249**, 170 mg, 1.0 mmol) and allyl boronate **4.202** (508.1

mg, 2.0 mmol) were added followed by methanol (808 μL, 20 mmol). The vessel was sealed with a septa and electrical and removed from the glovebox. The reaction was then allowed to stir at 60 ºC for 6 h. Upon cooling to 22 °C, the reaction was quenched by the addition of MeOH (10 mL) and allowed to stir for 0.5 h at 22 °C. The reaction mixture was then concentrated and the resulting opaque solid was purified by silica gel column chromatography (30:1 hexanes:Et_2O → 5:1 hexanes:Et_2O), to afford homoallylic alcohol as white solid (262.0 mg, 0.878 mmol, 88% yield).

(1R,2S)-2-Fluoro-1-((R)-1,4-dioxaspiro[4.5]decan-2-yl)-2-(trifluoromethyl)but-3-en-1-ol (4.250): M.p.: 67–69 °C. **IR (neat):** 3451 (br), 2932 (s), 2855 (m), 1307 (m), 1172 (s), 1161 (s), 1143 (s), 1107 (m), 799 (m), 737 (m) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.83 (ddd, *J* = 21.1, 17.3, 11.1 Hz, 1H), 5.67 (d, *J* = 17.3 Hz, 1H), 5.58 (dd, *J* = 11.1, 3.1 Hz, 1H), 4.30 (dt, *J* = 25.9, 3.6 Hz, 1H), 4.22 (td, *J* = 6.8, 3.6 Hz, 1H), 4.03–4.00 (m, 1H), 3.96–3.92 (m, 1H), 2.47 (brs, 1H), 1.67–1.52 (m, 8H), 1.40 (d, *J* = 3.2 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 127.9 (d, *J* = 19.4 Hz), 122.3 (qd, *J* = 285.9, 30.4 Hz), 120.8 (d, *J* = 12.2 Hz), 109.5, 94.5 (dq, *J* = 195.9, 30.4 Hz), 74.4, 70.7 (d, *J* = 19.2 Hz), 63.8 (d, *J* = 6.8 Hz), 36.1, 35.3, 25.2, 24.0, 23.9. **^{19}F NMR (470 MHz, $CDCl_3$):** δ –77.30 (d, *J* = 6.0 Hz, 3F), –192.03 (brs, 1F); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{13}H_{19}O_3F_4$: 299.1270, found: 299.1262. **Specific Rotation:** $[\alpha]^{20.0}$ +12.6 (*c* 1.00, $CHCl_3$).

To a suspension of NaH (95%, 13 mg, 0.51 mmol) in freshly distilled thf (15 ml) was slowly added a solution of **4.250** (100 mg, 0.34 mmol) in thf (5.0 mL) at 0 °C, and the mixture was allowed to stir for 30 minutes. To the solution was then added benzyl bromide (86.6 mg, 0.51 mmol) followed by tetrabutylammonium iodide (TBAI, 12.5 mg, 0.034 mmol). The reaction mixture was gradually warmed to 22 °C and allowed to stir for 5 h, before it was quenched by addition of a saturated aqueous solution of ammonium chloride (10 mL) at 0 °C. The aqueous layer was washed with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with a saturated aqueous solution of sodium chloride, dried over Na_2SO_4 and concentrated under reduced pressure to afford pale yellow oil. To the resulting residue was added ethylene glycol (5.0 ml) and camphorsulfonic acid (CSA, 470 mg, 2.02 mmol) and the solution was allowed to stir at 50 °C for 18h. Upon cooling to 0 °C, the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$. The aqueous layer was washed with ethyl acetate (3 x 10 mL) and the combined organics were washed with a saturated aqueous solution of sodium, dried over Na_2SO_4 and concentrated to afford opaque solid which was purified by silica gel column chromatography (20:1 hexanes: ethyl acetate → 2:1 hexanes: ethyl acetate), to afford **4.252** (81.0 mg, 0.26 mmol, 81% yield), as colorless oil.

(2R,3R,4S)-3-(Benzyloxy)-4-fluoro-4-(trifluoromethyl)hex-5-ene-1,2-diol 4.252: IR (neat): 3384 (br), 2939 (m), 2892 (m), 1307 (m), 1295 (m), 1169 (s), 1067 (s), 1028 (m), 947 (m), 736(s), 697 (m) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.36 (brs, 5H), 5.90 (td, *J* = 20.0, 17.2, 11.2 Hz, 1H), 5.72 (d, *J* = 17.2 Hz, 1H), 5.59 (d, *J* = 11.2 Hz, 1H), 4.79 (m, 2H), 4.08 (d, *J* = 23.2 Hz, 1H), 3.95 (1H, brs), 3.82 (1H, brs), 3.75 (1H, brs), 2.86 (1H, brs), 2.33 (1H, brs). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.2, 128.7, 128.5, 128.3, 127.9 (d, J_{C-F} = 19.4 Hz), 122.7 (qd, *J* = 287.8, 30.3 Hz), 120.8 (d, *J* = 12.1 Hz), 95.4 (dq, *J* = 195.6, 30.3 Hz), 81.37 (dd, *J* = 19.3, 3.1 Hz), 76.47 – 75.46

(m), 63.0 (d, J = 4.5 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ –76.79 (d, J = 6.2 Hz, 3F), –186.43 (brs, 1F); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{14}H_{17}O_3F_4$: 309.1114, found: 309.1102. **Specific Rotation:** $[\alpha]^{20.0}$ + 29.1 (*c* 1.00, $CHCl_3$).

4.6.8 Procedure for Selective Secondary Benzyl Ether Formation and Synthesis of Puranose

In an N_2-filled glovebox, an oven dried vial (8 mL) equipped with a magnetic stir bar was charged with **4.252** (25.0 mg, 0.081 mmol) and diluted with thf (5.0 mL). The solution was cooled to 0 °C and NaH (95%, 5.8 mg, 0.24 mmol) was then added to the solution at 0 °C and the mixture was allowed to stir at 22 °C for 1h. The solution was stored in a –40 °C freezer and then benzyl bromide (17 mg, 0.099 mmol) and tetrabutylammonium iodide (TBAI, 3.0 mg, 0.0081 mmol) were added. The mixture was allowed to stir at 22 °C for 5 h and then quenched at 0 °C by addition of a saturated solution of ammonium chloride (0.1 mL). The mixture was directly loaded onto a plug (4.0 cm high x 1.0 cm wide) of silica gel and eluted with ethyl acetate. The eluent was concentrated under reduced pressure to afford yellow oil that was purified by silica gel column chromatography (50:1 hexanes:EtOAc → 5:1 hexanes:EtOAc), to afford a **4.253** (20.0 mg, 0.050 mmol, 62% yield) as colorless oil.

(2R,3R,4S)-2,3-bis(benzyloxy)-4-fluoro-4-(trifluoromethyl)hex-5-en-1-ol (4.253). IR (neat): 3437 (br), 3063(w), 3030 (w), 2924 (m), 2878 (m), 1454 (m), 1295 (m), 1171 (s), 1072 (s), 995 (m), 736(s), cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.40 – 7.29 (m, 10H), 5.83 (td, J = 20.3, 17.2, 11.0 Hz, 1H), 5.69 (d, J = 17.2 Hz, 1H), 5.52 (d, J = 11.2 Hz, 1H), 4.78 (dd, J = 10.5 Hz, 2H), 4.54 (brs, 2H), 4.10 (d, J = 23.3 Hz, 1H), 3.86 (brs, 1H), 3.77 (brs, 2H), 2.10 (brs). **^{13}C NMR (150 MHz, $CDCl_3$):** δ 137.6, 137.2, 128.7, 128.6, 128.4, 128.2 (d, J = 3.7 Hz), 128.0, 122.6 (qd, J = 285.8, 30.3 Hz), 120.2 (d, J = 12.1 Hz), 95.4 (dq, J= 196.1, 30.3 Hz), 79.6 (d, J = 19.7 Hz), 79.5, 79.0, 75.7, 71.9, 61.1 (d, J = 3.4 Hz). **^{19}F NMR (470 MHz, $CDCl_3$):** δ –76.59 (d, J = 6.2 Hz, 3F), –187.53 (brs, 1F); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{21}H_{23}O_3F_4$: 399.1583 found: 398.1594. **Specific Rotation:** $[\alpha]^{20.0}$ + 16.6 (*c* 1.00, $CHCl_3$).

An oven-dried vial (8 mL) equipped with a stir bar was charged with **4.253** (40 mg, 0.100 mmol) and diluted with thf (1.0 mL) and MeOH (0.2 mL). The solution was allowed to cool to –78 °C and then O_3 was bubbled through the solution (total exposure ~40 minutes) until a blue color persisted. The solution was then purged with a stream of N_2 until it became clear. Dimethyl sulfide (25 mg, 0.40 mmol) was then added and the solution was allowed to warm to 22 °C and left with stirring for 2 hours. The reaction mixture was concentrated under reduced pressure to afford an opaque residue that was purified by silica gel column chromatography (30:1 hexanes:EtOAc → 1:1 hexanes:EtOAc), to afford **4.254** (27.0 mg, 0.067 mmol, 67% yield) as colorless oil.

(2R,3R,4R,5R)-4,5-bis(benzyloxy)-3-fluoro-3-(trifluoromethyl)tetrahydro-2H-pyran-2-ol (4.254): IR (neat): 3401 (br), 3028(w), 2926 (w), 2876 (m), 1721 (w), 1453 (m), 1279 (m), 1191 (s), 1103 (s), 1073(s), 1027 (s), 732 (m) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.39 – 7.28 (m,

10H), 5.42 (d, *J* = 8.1 Hz, 1H), 4.71 (ABq, *J* = 12.0 Hz, 2H), 4.56 (ABq, *J* = 11.3 Hz, 2H), 4.03 (dd, *J* = 28.7, 3.6 Hz, 1H), 3.94 (dd, *J* = 20.0, 15.0 Hz, 2H), 3.78 (brs, 1H), 2.82 (brs, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 137.9, 136.9, 128.6, 128.5, 128.3, 128.1, 122.5, 122.5 (qd, *J*= 286.1, 29.3 Hz), 92.1 (d, *J* = 32.2 Hz), 91.1 (dq, *J* = 198.5, 29.3 Hz), 72.3, 72.0, 71.7 (d, *J* = 16.4 Hz), 71.3, 60.7; **^{19}F NMR (470 MHz, $CDCl_3$):** δ –73.83 (s, 2F), –185.41 (d, *J* = 28.8 Hz,1F); **HRMS (DART):** $[M+NH_4]^+$ Calcd for $C_{20}H_{24}NO_4F_4$: 418.1642 found: 418.1636. **Specific Rotation:** $[\alpha]^{20.0}$ –74.5 (*c* 0.6, $CHCl_3$).

4.6.9 Procedure for Selective Secondary Benzyl Ether Formation and Synthesis of Furanose

Authentic primary benzyl ether **4.300** was prepared according to a procedure by Sudalai.[7] An oven-dried vial (8 mL) equipped with a stir bar was charged with (35.0 mg, 0.114 mmol), Bu_2SnO (28 mg, 0.114 mmol) and toluene (4.0 mL). The suspension was heated to reflux (110 °C) with vigorous stirring for 12 h. After cooling to 22 °C, benzyl bromide (29 mg, 0.170 mmol) and tetrabutylammonium bromide (TBAB, 37.0 mg, 0.114 mmol) were added to the solution. The mixture was allowed to stir at 110 °C for 12 h. Upon cooling to 22 °C, the mixture was diluted with CH_2Cl_2 (5.0 mL) and washed with a saturated aqueous solution of NaHCO3 followed by a 1.0 M aqueous solution of KF. The aqueous layers were back-extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO and concentrated to afford pale yellow oil, which was purified by silica gel column chromatography (30:1 hexanes: ethyl acetate → 5:1 hexanes: ethyl acetate), to afford **4.300** (36.5 mg, 0.092 mmol, 81 % yield) as colorless oil.

(2R,3R,4S)-1,3-Bis(benzyloxy)-4-fluoro-4-(trifluoromethyl)hex-5-en-2-ol (4.300). IR (neat): 3448 (br), 3062(w), 3030 (w), 2920 (m), 2867 (m), 1496 (m), 1273 (m), 1171 (s), 1072 (s), 985 (m), 736(s), 697 (s) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.37–7.29 (m, 10H), 5.89 (ddd, *J* = 20.9, 17.3, 11.2 Hz, 1H), 5.66 (d, *J* = 17.3 Hz, 1H), 5.55 (d, *J* = 11.2 Hz, 1H), 4.74 (m, 2H), 4.57 – 4.49 (m, 2H), 4.14 – 4.07 (m, 1H), 4.06 (dd, *J* = 23.7, 4.0 Hz, 1H), 3.69 (d, *J* = 5.4 Hz, 2H), 2.59 (d, *J* = 3.9 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ 137.8, 137.6, 128.8, 128.6, 128.5, 128.2, 128.1, 128.0 122.6 (qd, *J* = 285.8, 30.6 Hz), 120.5 (d, *J* = 12.1 Hz), 95.6 (dq, *J* = 195.7, 30.3 Hz), 80.3 (d, *J* = 19 Hz), 80.8, 73.6, 70.5, 70.3 (d, *J* = 3.8 Hz). **^{19}F NMR (470 MHz, $CDCl_3$):** δ –75.73 (d, *J* = 6.6 Hz, 3F), –186.86 (brs, 1F); **HRMS (DART):** $[M+H]^+$ Calcd for $C_{21}H_{23}O_3F_4$: 399.1583 found: 398.1576. **Specific Rotation:** $[\alpha]^{20.0}$ 14.0 (*c* 0.50, $CHCl_3$).

An oven dried vial (8 mL) equipped with a stir bar was charged with **4.300** (18 mg, 0.045 mmol) and diluted with CH_2Cl_2 (1.5 mL) and MeOH (0.3 mL). The solution was cooled to –78 °C and O_3 was bubbled (total exposure ~20 minutes) into the reaction mixture until a blue color persisted.

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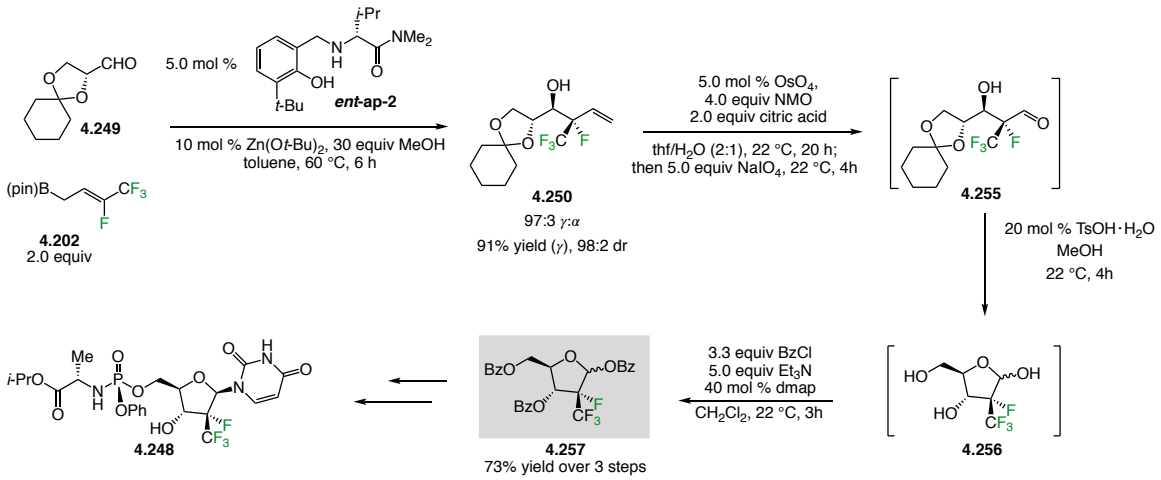
7) Codée, J. D. C.; van den Bos, L. J.; de Jong, A-R.; Dinkelaar, J.; Lodder. G.; Overkleeft, H. S.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*. 38–47.

The mixture was then purged with a stream of N_2 until it became clear. Dimethyl sulfide (11.2 mg, 0.181 mmol) was then added and the mixture was allowed to gradually warm to 22 °C and left with stirring for 3 hours. The mixture was then concentrated to afford an opaque oily residue that was purified by preparative thin layer chromatography (30:1 CH_2Cl_2:EtOAc), to afford an anomeric mixture of **S-2** (12.0 mg, 0.030 mmol, 66% yield) as colorless oil.

(3S,4R,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-3-fluoro-3-(trifluoromethyl) tetrahydrofuran-2-ol (S-2). IR (neat): 3371 (br), 3062(w), 2924 (w), 2867 (m), 1495 (m), 1361 (m), 1191 (s), 1068 (s), 1026(s), 991 (s), 730 (s), 698 (s), 605 (w) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ7.41 – 7.27 (m, 9H), 7.25 – 7.19 (m, 1H), 5.54 (t, *J* = 5.9 Hz, 0.32H, minor anomer), 5.28 (t, *J* = 8.5 Hz, 0.7H, major anomer), 4.78 (m, 1H), 4.61 (ddd, *J* = 21.0, 6.4, 1.3 Hz, 0.7H, major anomer), 4.54 (d, *J* = 12.0 Hz, 0.3H, minor anomer), 4.45 (m, 2H), 4.37 (t, *J* = 11.7 Hz, 1H), 4.31 (dt, *J* = 7.3, 3.4 Hz, 0.3H, minor anomer), 4.27 (m, 0.7H, major anomer), 4.26 – 4.18 (m, 0.3H, minor anomer), 4.08 (d, *J* = 9.1 Hz, 0.7H, major anomer), 3.65 (dt, *J* = 11.1, 2.0 Hz, 0.3H, minor anomer), 3.58 (dt, *J* = 10.5, 1.8 Hz, 0.7H, major anomer), 3.50 (ddd, *J* = 11.2, 4.1, 1.3 Hz, 0.3H, minor anomer), 3.43 (m, 0.3H, minor anomer), 3.12 (dd, *J* = 10.5, 1.7 Hz, 0.7H, major anomer); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 137.8, 137.0, 136.8, 136.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.49, 128.1, 128.0, 127.9, 122.2 (qd, *J* = 281.8, 29.5 Hz), 122.4 (qd, *J* = 281.8, 30.5 Hz), 123.0 (qd, *J* = 281.8, 29.5 Hz), 99.1 (d, *J* = 30.9 Hz), 97.4 (dq, *J* = 200.4, 29.5 Hz), 94.0 (dq, *J* = 208.8, 30.5 Hz), 82.0, 80.0, 75.3 (d, *J* = 15.8 Hz), 74.9 (d, *J* = 15.3 Hz), 73.9, 73.8, 73.7, 67.8, 67.78. **^{19}F NMR (470 MHz, $CDCl_3$):** δ –75.54 (d, *J* = 6.6 Hz, 1.0F), –79.67 (2.6F, d, *J* = 9.5 Hz, 0.8F), –190.21 (dq, *J* = 21.2, 7.7, 7.2 Hz, 0.3F), –195.93 (ddt, *J* = 14.1, 9.2, 4.3 Hz, 0.2F); **HRMS (DART):** $[M+NH_4]^+$ Calcd for $C_{20}H_{24}NO_4F_4$: 418.1642 found: 418.1628. **Specific Rotation:** $[\alpha]^{20.0}$ 60.5 (*c* 0.6, $CHCl_3$).

4.6.10 Procedure for Telescoped Synthesis of Benzoyl-Protected Furanose



To a solution of alkene **4.250** (100 mg, 0.34 mmol), NMO (157 mg, 1.34 mmol) and citric acid (129 mg, 0.67 mmol) in a 2:1 mixture of thf:H_2O (3.3 mL total volume) at 22 °C, was added OsO_4 (4% wt in H_2O, 107 μL, 17.0 μmol) and the resulting solution was allowed to stir at 22 °C for 20 h. $NaIO_4$ (359 mg, 1.68 mmol) was then added to the reaction and the resulting mixture was allowed to stir at 22 °C for 4 h. The reaction was quenched by addition of solid Na_2SO_3 (430 mg) and diluted with CH_2Cl_2 (4.0 mL) and H_2O (4.0 mL). The resulting mixture was allowed to vigorously stir for 30 min, then the two phases were separated and the aqueous phase was back extracted with CH_2Cl_2 (4 × 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde 4.255 was directly subjected to cyclization without further purification.

TsOH•H_2O (13 mg, 67.0 μmol) was added to a solution of aldehyde **4.255** in MeOH (3.0 mL) and the resulting solution was allowed to stir at 22 °C for 5 h. The solution was neutralized (pH = 7) by addition of solid $NaHCO_3$ and then the reaction was concentrated under reduced pressure. The resulting off-white residue was diluted with EtOAc (1 mL) and filtered through Celite® and thoroughly eluted with EtOAc. The filtrate was concentrated under reduced pressure to deliver deoxyribose **4.256**, which was employed directly without further purification.

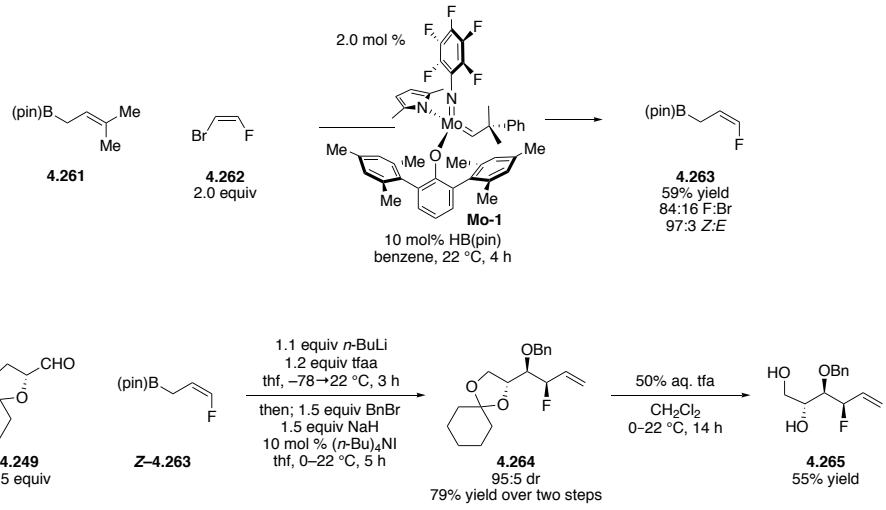
To a solution of deoxyribose **4.256** in CH_2Cl_2 (3.0 mL) were sequentially added Et_3N (234 μL, 1.68 mmol), dmap (16.4 mg, 134 μmol) and benzoyl chloride (129 μL, 1.11 mmol). The resulting solution was allowed to stir at 22 °C for 3 h. The reaction was quenched by addition of 1.0 M aqueous solution of HCl (4.0 mL) and extracted with Et_2O (3 × 4 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (5.0 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford yellow residue that was purified by silica gel chromatography (hexanes:EtOAc = 20:1) afforded benzoylated deoxyribose **4.257** (2:1 anomeric mixture, 130 mg, 0.244 mmol, 73% overall yield) as colorless solid.

IR (neat): 2925 (w), 1739 (s), 1601 (w), 1452 (m), 1261 (s), 1209 (s), 1178 (m), 1106 (m), 1054 (m), 1023 (s), 995 (m), 706 (s) cm^{-1}; **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ 8.15 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.10 (ddd, *J* = 8.5, 6.4, 1.3 Hz, 3H), 8.01 (ddd, *J* = 8.5, 5.9, 1.3 Hz, 3H), 7.87 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.63 (dddt, *J* = 13.9, 8.8, 7.4, 1.4 Hz, 3H), 7.58–7.51 (m, 0.5H), 7.54–7.44 (m, 4H), 7.46–7.36 (m, 4H), 7.19–7.12 (m, 2H), 6.90 (d, *J* = 2.6 Hz, 0.5H minor anomer), 6.68 (d, *J* = 10.9 Hz, 1H, major anomer), 6.40 (dd, *J* = 23.2, 8.0 Hz, 1H, major anomer), 5.92 (dd, *J* = 8.5, 7.0 Hz, 0.5H, minor anomer), 4.89 (ddd, *J* = 7.1, 5.0, 3.8 Hz, 0.5H, minor anomer), 4.82–4.70 (m, 2.5H), 4.60 (dd, *J* = 12.4, 5.0 Hz, 0.5H, minor anomer), 4.52 (dd, *J* = 12.4, 4.1 Hz, 1H, major anomer); **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ 166.0, 165.9, 164.7, 164.6, 164.1, 163.7, 130.2, 130.2, 130.1, 130.1, 129.8, 129.6, 129.2, 129.2, 128.8, 128.7, 128.7, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.11, 128.0, 125.3, –121.9 (qd, *J*= 284.2, 30.1 Hz, minor anomer), 120.9 (qd, *J* = 282.5, 29.7 Hz, major anomer), 97.0 (dq, *J* = 232.1, 33.5 Hz, major anomer), 95.8 (bd, *J* = 34.6 Hz, major anomer), 93.4 (dq, *J* = 219.5, 33.5 Hz, minor anomer), 93.3 (dq, *J* = 15.9, 1.7 Hz, minor anomer), 80.2, 79.2, 68.9 (bd, *J* = 14.2 Hz, major anomer), 68.1 (bd, *J* = 14.2 Hz, minor anomer), 62.8, 62.3; **^{19}F NMR ($CDCl_3$, 471 MHz)**: δ –74.68 (d, *J* = 5.8 Hz, major anomer), –79.21 (d, *J* = 10.4 Hz,

minor anomer), –189.01 (ddt, J = 23.1, 10.9, 6.4 Hz, major anomer), –189.15 (p, J = 9.6 Hz, minor anomer); **HRMS (ESI+)**: Calcd for $C_{27}H_{21}O_7F_4$ $[M+H]^+$: 533.1218, Found: 533.1212

4.6.11 Preparation of Analogues For Benzyl Protection Studies

(2*R*,3*S*)-3-(Benzyloxy)hex-5-ene-1,2-diol was synthesized according to a previously reported procedure.[8] **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ 7.65 – 7.54 (m, 5H), 6.13 (ddt, J = 17.3, 10.3, 7.1 Hz, 1H), 5.46 – 5.33 (m, 2H), 4.93 (d, J = 11.4 Hz, 1H), 4.77 (d, J = 11.3 Hz, 1H), 4.08 – 3.97 (m, 2H), 3.89 (q, J = 5.6 Hz, 1H), 2.73 (dt, J = 13.7, 6.6 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.42 (s, 1H), 1.86 (s, 1H).



(*Z*)-2-(3-Fluoroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.263):

In a N_2-filled glovebox, prenyl–B(pin) (196 mg, 1.0 mmol) and (*Z*)-1-Bromo-2-fluoroethylene (250 mg, mmol) was added to an oven-dried 8 mL vial equipped with a stir bar. Pinacolborane (12.8 mg, 0.1 mmol) was added (gentle release of gas) and the mixture was sealed with a cap and allowed to stir for 10 min (22 °C). A solution of **Mo-1** (16.7 mg, 0.02 mmol) in benzene (0.2 mL) was slowly added to the solution. The vial was capped and the mixture was allowed to stir for 2 h. The vial was removed from the glovebox and the volatiles were carefully evaporated in vacuo. The resulting black oil residue was purified by Kugelrohr distillation (22-35 °C) to afford **4.263** as yellow oil (109.7 mg, 59% yield, 97:3 *Z*:*E*). **IR (neat):** 2977 (m), 1670 (m), 1322 (s), 1141 (s), 970 (m), 846 (m), 753 (m), 689 (m), 539 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.47 (ddt, J = 85.8, 4.6, 1.7 Hz, 1H), 4.84 (dtd, J = 43.0, 8.0, 4.6 Hz, 1H), 1.69 (d, J = 7.9 Hz, 2H), 1.25 (s, 12H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.03, 146.49, 106.27 (d, J = 6.1 Hz), 83.61, 24.90; **^{19}F NMR**

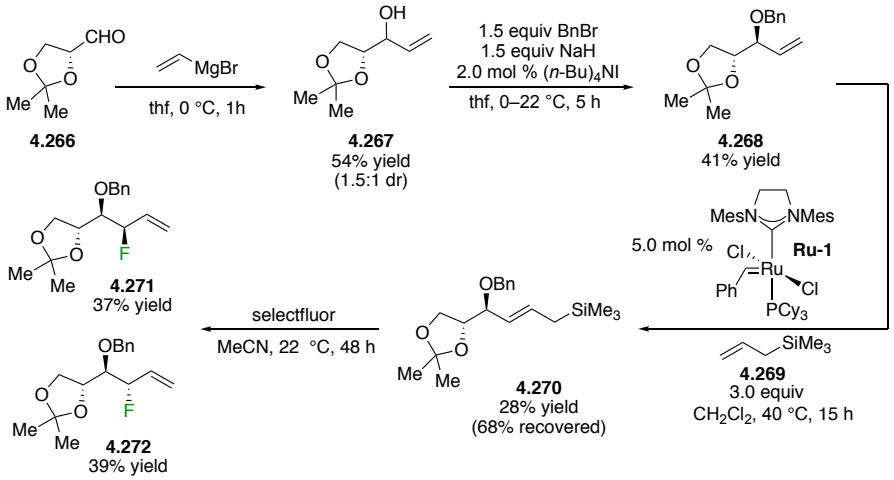
8) Venkataiah, M.; Somaiah, P.; Reddipalli, G.; Fadnavis, N.W. *Tetrahedron: Asymmetry* **2009**, *20*, 2230–2233.

(376 MHz, $CDCl_3$): –131.89 (dd, *J* = 86.4, 42.3 Hz); **HRMS (DART):** Calcd for $C_9H_{17}BO_2F$ $[M+H]^+$: 187.1300; Found: 187.1293.

To a cooled –78 °C solution of **4.263** in freshly distilled thf (4.0 mL) was added *n*-BuLi in hexanes (2.5 M, 0.18 mL) and the solution was allowed to stir for 15 minutes. Freshly distilled trifluoroacetic anhydride (76 μL, 0.54 mmol) was then added in a dropwise manner and the mixture was allowed to stir at –78 °C for an additional 30 minutes. Aldehyde **4.249** (116 mg, 0.675 mmol) was then added as a solution in thf (1.0 mL) and the mixture was allowed to stir at –78 °C for 2 h, then allowed to warm to 22 °C and stir for an additional 2 h. The reaction was quenched by the addition of a 0.5 M solution of NaOH and the layers were separated. The aqueous layer was back-extracted with Et_2O (3 x 5.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford yellow residue which was purified by silica gel chromatography (hexanes:Et_2O 100:0 → 3:1) to afford colorless oil. The obtained alcohol (100 mg, 0.43 mmol) was then diluted in thf (3.0 mL) and benzyl bromide (111.4 mg, 0.65 mmol) and tetrabutylammonium iodide (TBAI, 13.9 mg, 0.043 mmol) were added. The mixture was placed in a –40 °C freezer for 10 minutes then NaH (90%, 15.6 mg, 0.65 mmol) was added in a single portion. The mixture was allowed to stir vigorously for 5 h at 22 °C. The reaction was quenched at 0 ^oC by addition of a saturated solution of ammonium chloride (0.1 mL). Then the mixture was directly loaded onto a plug (6.0 cm high x 5.0 cm wide) of silica gel to remove excess benzyl bromide to afford **4.264** (108.1 mg, 0.355 mmol, 79% yield) as colorless oil.

To a cooled (0 °C) solution of benzyl ether **4.264** in CH_2Cl_2 (3.0 mL) was added a 50% aqueous solution of thf (3.0 mL). The mixture was then allowed to warm to 22 °C and left with stirring for 14 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with a cold solution of saturated aqueous $NaHCO_3$ (3 x 10 mL) followed by brine (1 x 10 mL). The combined organics were then dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford yellow residue which was purified by silica gel chromatography (20:1 hexanes: ethyl acetate → 2:1 hexanes:EtOAc) to afford **4.265** (46.9 mg, 0.195 mmol) as colorless oil.

(2*R*,3*R*,4*R*)-3-(Benzyloxy)-4-fluorohex-5-ene-1,2-diol (4.265). IR (neat): 3424 (br), 2923 (m), 2822 (m), 1454 (m), 1088 (s), 1053 (s), 984 (s), 738 (m), 697 (m) $^{-1}$; **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.41 – 7.31 (m, 5H), 6.02 (dddd, *J* = 17.2, 15.4, 10.7, 6.3 Hz, 1H), 5.49 (ddt, *J* = 17.3, 3.1, 1.4 Hz, 1H), 5.37 (dt, *J* = 10.7, 1.3 Hz, 1H), 5.14 (dddt, *J* = 47.0, 5.9, 4.4, 1.4 Hz, 1H), 4.70 (dd, *J* = 65.2, 11.2 Hz, 2H), 3.82 (m, 1H), 3.75 (m, 2H), 3.68 (ddd, *J* = 20.5, 6.3, 4.3 Hz, 1H), 2.43 (s, 1H), 1.95 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 140.0, 135.6 (d, *J* = 19.8 Hz), 131.6, 130.8, 121.8 (d, *J* = 12.0 Hz), 96.1, 95.0, 83.9 (d, *J* = 19.6 Hz), 77.6, 73.1 (d, *J* = 4.5 Hz), 67.1; **^{19}F NMR ($CDCl_3$, 376 MHz)**: δ –190.37 (dd, *J* = 43.3, 22.2 Hz); **HRMS (DART)**: Calcd for $C_{13}H_{18}O_3F$ $[M+H]^+$: 241.12345, Found: 241.12271; **Specific rotation**: $[\alpha]^{27.3}$ +14.9 (*c* 0.72, $CHCl_3$).



To a cooled (0 °C) solution of aldehyde **4.266** (502.4 mg, 3.86 mmol) in thf (4.0 mL) was added a solution of vinyl magnesium bromide (1.0 M in thf, 6.75 mL, 6.75 mmol) in a dropwise manner. The mixture was allowed to stir at 0 °C for 1 h and then it was quenched by addition of a saturated aqueous solution of ammonium chloride (5.0 mL). The aqueous layer was back-extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **4.267** (332.5 mg, 2.08 mmol) as a mixture of diastereomers in 54% yield. The unpurified allylic alcohol was then diluted in thf (10 mL) and cooled to 0 °C. NaH (60% dispersion in oil, 126 mg, 3.15 mmol) was then added in a single portion and allowed to stir for 30 minutes. Benzyl bromide (540 mg, 3.15 mmol) and tetrabutylammonium iodide (15.5 mg, 0.042 mmol) were then added and the reaction was allowed to warm to 22 °C and stir for 3 h. The reaction was quenched at 0 °C by addition of a saturated solution of ammonium chloride (5.0 mL). The aqueous layer was back-extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford yellow residue as a mixture of diastereomers which was purified by medium pressure liquid chromatography with a Teledyne ISCO Combiflash RF instrument paired with a 24 g RediSep Rf Gold column (catalog number 69-2203-346) and a gradient elution method: 100% hexanes → 30% EtOAc) to furnish **4.268** as colorless oil (215.4 mg, 0.87 mmol, 41% yield) with identical spectra to literature.[9]

Cross-metathesis was performed according to a procedure by Vankar.[10] To a oven-dried 10 mL round bottom flask equipped with a reflux condenser was added a solution of **4.268** (215.4 mg, 0.87 mmol) in CH_2Cl_2 (5.0 mL) and allyl silane **4.269** (297.3 mg, 2.60 mmol) followed by a solution of **Ru-1** (36.9 mg, 0.044 mmol) in CH_2Cl_2 (1.0 mL) under an atmosphere of N_2. The mixture was heated to reflux (45 °C) for 15 h. Upon cooling to 22 °C, the mixture was concentrated

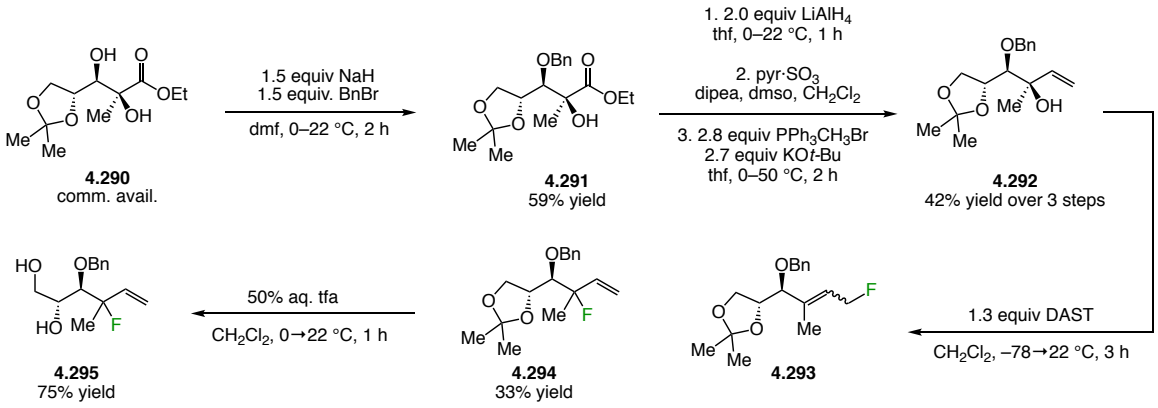
9) Kamal, A.; Reddy, P. V.; Prabhakar, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1120–1124.

10) Dubbu, S.; Bardhan, A.; Chennaiah, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2018**, 6800–6808

to afford dark brown residue which was purified by silica gel chromatography (20:1 hexanes: ethyl acetate → 5:1 hexanes:EtOAc) to afford **4.270** (84.3 mg, 0.25 mmol) as colorless oil.

Fluorination was carried out according to a procedure by Gouverneur *et al.*[11] To a solution of allyl silane **4.270** (84.3 mg, 0.25 mmol) in acetonitrile (3.0 mL) was added selectfluor (88.6 mg, 0.25 mmol) and the mixture was allowed to stir for 48 h at 22 °C. The mixture was then concentrated under reduced pressure to afford a white residue which was purified by medium pressure liquid chromatography with a Teledyne ISCO Combiflash RF instrument paired with a 12 g RediSep Rf Gold column (catalog number 69-2203-345) and a gradient elution method: 100% hexanes → 30% Et_2O) afford **4.272** (27.1 mg, 0.097 mmol) as colorless oil. Unmasking of the diol was performed exactly as described above.

(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-fluorohex-5-ene-1,2-diol (4.272). IR (neat); **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.34 (m, 5H), 6.16 – 6.00 (m, 1H), 5.49 (ddt, *J* = 17.4, 3.8, 1.4 Hz, 1H), 5.41 (dt, *J* = 10.7, 1.3 Hz, 1H), 5.31 – 5.09 (m, 1H), 4.81 (d, *J* = 11.3 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 3.83 – 3.76 (m, 1H), 3.76 – 3.72 (m, 2H), 3.68 (dt, *J* = 8.1, 4.2 Hz, 1H), 2.52 (s, 1H), 1.94 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 137.6, 132.3 (d, *J* = 19.5 Hz), 128.6, 128.2, 128.1, 119.8 (d, *J* = 12.2 Hz), 94.2 (d, *J* = 170.2 Hz), 80.4 (d, *J* = 21.5 Hz), 74.1 (d, *J* = 2.2 Hz), 70.8 (d, *J* = 6.4 Hz), 63.4 (d, *J* = 2.2 Hz); **^{19}F NMR ($CDCl_3$, 376 MHz)**: δ –184.64 (dtd, *J* = 46.6, 14.3, 3.8 Hz); **HRMS (DART)**: Calcd for $C_{13}H_{21}O_3F$ $[M+NH_4]^+$: 258.15000, Found: 258.14953.



Benzyl protection was carried out according to a procedure reported by Lee and Kang *et al.*[12] To a cooled (0 °C) solution of diol **4.290** (2.31 g, 9.3 mmol) and benzyl bromide (1.66 mL, 14 mmol) in dmf (9.0 mL) was added NaH (580 mg, 14 mmol) in three equal portions. The mixture was allowed to stir and warmed to 22 °C over the course of 2 hours. The reaction was then cooled to 0 °C and quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL). The mixture was diluted with ethyl acetate, the organic layer was removed and the aqueous was washed with ethyl acetate (20 mL x 3). The combined organics were washed with brine (50 mL), dried over $MgSO_4$

11) Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891–4893.

12) Yu, G.; Jung, B.; Lim, S.; Lee, H.–S.; Kang, S. H. *Asian J. Org. Chem.* **2016**, *5*, 107–113.

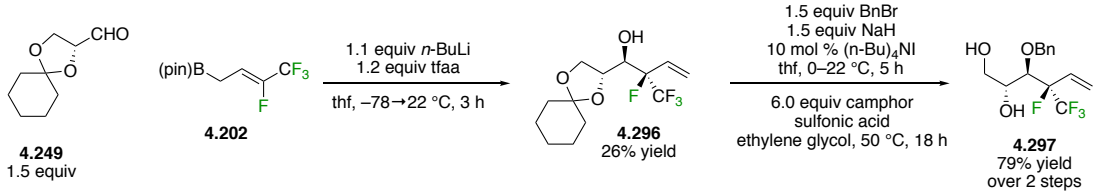
and concentrated under reduced pressure to afford a brown oil which was purified by silica gel chromatography (gradient eluting with 100:0 → 4:1 hexanes:EtOAc) to afford white solid (1.725 g, 5.1 mmol, 55%). To a cooled (0 °C) solution of monobenzyl ether (1.725g, 5.1 mmol) in thf (25 mL) was added $LiAlH_4$ (386 mg, 10.2 mmol) in three equal portions. The mixture was allowed to stir and warmed to 22 °C over the course of 2 hours. The reaction was then cooled to 0 °C and quenched by addition of a saturated aqueous solution of potassium sodium tartrate (Rochelle's salt, 20 mL) and allowed to stir vigorously overnight. The organic layer was removed and the aqueous was washed with CH_2Cl_2 (20 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to afford clear oil which was directly subjected to oxidation and subsequent olefination according to a procedure by Yorimitsu and Oshima *et al*.[13]. To a cooled (0 °C) solution of diol in CH_2Cl_2 (15 mL) was added *N*-Ethyldiisopropylamine (4.52 mL, 26 mmol) and methyl sulfoxide (3.7 mL, 52.5 mmol). Sulfur trioxide pyridine complex (2.47g, 15.5 mmol) was then added in a single portion and allowed to stir for 2 hours. The reaction was quenched by addition of a solution of 1 M HCl (15 mL), and the organic layer was removed. The aqueous layer was washed with CH_2Cl_2 (3 x 15 mL), and the combined organics were then washed with a saturated solution of $NaHCO_3$ (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the corresponding aldehyde as a solution in methyl sulfoxide which was used without further purification. To a solution of methyltriphenylphosphonium bromide (5.0 g, 14.0 mmol) in thf (10 mL) was added potassium *tert*-butoxide (1.51 g, 13.5 mmol) in a single portion, and the resulting yellow mixture was allowed to stir at 22 °C for 30 minutes. A solution of the unpurified aldehyde in thf (10 mL) was then added and the resulting mixture was heated to 50 °C for 2 hours. Upon cooling to 22 °C, the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$. The organic layer was collected, and the aqueous was washed with ethyl acetate (3 x 20 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford a brown oil which was purified by silica gel chromatography (gradient eluting with 100:0 → 3:1 hexanes:Et_2O) to afford **4.292** as colorless oil (611.8 mg, 2.1 mmol, 42% yield over 3 steps).

(1*R*,2*R*)-1-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylbut-3-en-2-ol (4.292): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.25 (m, 5H), 6.06 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.36 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.16 (dd, *J* = 10.8, 1.5 Hz, 1H), 4.93 – 4.54 (m, 2H), 4.29 – 4.20 (m, 1H), 4.03 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.89 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.52 (d, *J* = 5.7 Hz, 1H), 3.04 (s, 1H), 1.44 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.1, 137.0, 128.4, 127.9, 127.2, 112.7, 108.1, 83.9, 76.4, 75.6, 75.3, 26.5, 25.3, 25.2; **HRMS (DART)**: Calcd for $C_{17}H_{23}O_3$ $[M+H-H_2O]^+$: 275.16417, Found: 275.16407; **Specific rotation**: $[\alpha]^{25.8}$ +5.9 (*c* 1.12, $CHCl_3$).

13) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052–2053.

Fluorination was performed in analogy to a procedure by Rapp *et al.*[14] To a cooled (–78 °C) solution of DAST (60 μL, 0.45 mmol) in CH_2Cl_2 (2.0 mL) was added a solution of tertiary alcohol **4.292** (100 mg, 0.34 mmol) in CH_2Cl_2 (2.0 mL) in a dropwise manner. The mixture was kept at –78 °C for 2 h and then allowed to warm to 22 °C and stir for an additional 1 h. The reaction was quenched by pouring the mixture into a saturated solution of $NaHCO_3$ (5.0 mL) containing ice chips. The aqueous layer was back-extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford brown residue which was purified by silica gel chromatography (gradient eluting with 100:0 → 3:1 hexanes:Et_2O) to afford **4.294** (33.0 mg, 0.112 mmol) as colorless oil.

(2*R*,3*R*)-3-(Benzyloxy)-4-fluoro-4-methylhex-5-ene-1,2-diol (4.294): IR (neat): 3387 (br), 2919 (m), 2870 (m), 1454 (m), 1384 (m), 1206 (m), 1098 (s), 1067(s), 977 (s), 737 (m), 699 (m) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.39 – 7.27 (m, 5H), 5.82 (dddt, *J* = 10.3, 6.7, 5.4, 1.2 Hz, 1H), 5.14 – 5.02 (m, 1H), 5.02 – 4.89 (m, 1H), 4.42 (dd, *J* = 101.5, 11.6 Hz, 2H), 3.82 (m, 1H), 3.79 – 3.68 (m, 3H), 2.21 (s, 1H), 2.07 (s, 1H), 1.76 (dd, *J* = 4.1, 1.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.9 (d, *J* = 10.9 Hz), 137.1, 128.6, 128.0, 127.9, 125.1 (d, *J* = 18.6 Hz), 84.8, 78.9 (d, *J* = 213 Hz), 71.0 (d, *J* = 2.4 Hz), 70.3, 61.6, 12.3; **^{19}F NMR (564 MHz, $CDCl_3$):** δ -212.18 (dd, *J* = 52.7, 41.6 Hz); **HRMS (DART)**: Calcd for $C_{13}H_{18}O_3F$ $[M+H–H_2O]^+$: 237.12853, Found: 237.12855; **Specific rotation**: $[\alpha]^{26.8}$ +37.3 (*c* 0.66, $CHCl_3$).



(2*R*,3*R*,4*R*)-3-(Benzyloxy)-4-fluoro-4 (trifluoromethyl)hex-5-ene-1,2-diol (4.297): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.27 (m, 5H), 6.09 (ddd, *J* = 23.3, 17.5, 11.3 Hz, 1H), 5.73 (d, *J* = 17.5 Hz, 1H), 5.60 (dd, *J* = 11.3, 3.2 Hz, 1H), 4.83 – 4.55 (m, 2H), 4.15 (t, *J* = 5.3 Hz, 1H), 3.91 (q, *J* = 4.8 Hz, 1H), 3.85 – 3.72 (m, 2H), 2.49 (s, 1H), 2.03 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 136.9, 128.6, 128.3, 128.1, 127.3 (d, *J* = 17.6 Hz), 122.7 (dd, *J* = 285.7, 28.7 Hz), 120.9 (d, *J* = 12.7 Hz) 94.3 (qd, *J* = 192.6, 29.8 Hz), 79.0 (d, *J* = 23.2 Hz), 75.4, 71.1, 62.8 (d, *J* = 1.6 Hz); **^{19}F NMR (564 MHz, $CDCl_3$):** δ –78.09 (d, *J* = 6.5 Hz), –180.58 (d, *J* = 23.9 Hz); **HRMS (DART)**: Calcd for $C_{14}H_{17}O_3F4$ $[M+H]^+$: 309.11083, Found: 309.11239; **Specific rotation**: $[\alpha]_D^{25.8}$ = +42.8 (*c* 0.71, $CHCl_3$).

14) Rapp, M.; Bilska, M.; Koroniak, H. *J. Fluorine Chem.* **2011**, *132*, 1232–1240.

4.6.12 Crystal Structure Tables

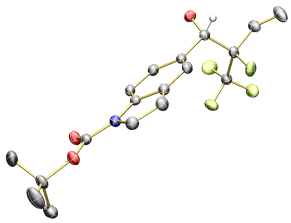


Table 1. Crystal data and structure refinement for **4.294**.

Identification code	C18H19F4NO3	
Empirical formula	C18 H19 F4 N O3	
Formula weight	373.34	
Temperature	100(2) K	
Wavelength	1.54178 ≈	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.2159(2) ≈	α= 90∞.
	b = 16.8180(6) ≈	β= 90∞.
	c = 16.9564(6) ≈	γ = 90∞.
Volume	1772.61(11) ≈^{3}	
Z	4	
Density (calculated)	1.399 Mg/m^3	
Absorption coefficient	1.062 mm^{-1}	
F(000)	776	
Crystal size	0.540 x 0.120 x 0.100 mm^3	
Theta range for data collection	3.702 to 66.556∞.	
Index ranges	-7<=h<=7, -19<=k<=19, -20<=l<=17	
Reflections collected	12650	
Independent reflections	3122 [R(int) = 0.0377]	
Completeness to theta = 66.556∞	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5617	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3122 / 1 / 238	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0306, wR2 = 0.0822	

R indices (all data)	R1 = 0.0320, wR2 = 0.0833
Absolute structure parameter	-0.02(5)
Extinction coefficient	n/a
Largest diff. peak and hole	0.214 and -0.206 e.$\approx^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\approx^2$x 10^3) for **4.234**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	3668(2)	4409(1)	4321(1)	30(1)
F(2)	-157(3)	4860(1)	4875(1)	37(1)
F(3)	-1406(2)	5074(1)	3713(1)	40(1)
F(4)	-441(3)	3892(1)	4061(1)	38(1)
O(1)	1870(3)	6108(1)	3242(1)	25(1)
O(2)	3433(3)	7905(1)	7903(1)	26(1)
O(3)	642(3)	7930(1)	7038(1)	27(1)
N(1)	3717(3)	7234(1)	6781(1)	20(1)
C(1)	4211(5)	4054(2)	2774(2)	42(1)
C(2)	2562(4)	4489(2)	2989(2)	28(1)
C(3)	2335(4)	4820(1)	3806(1)	22(1)
C(4)	3085(3)	5699(1)	3819(1)	20(1)
C(5)	3080(4)	6100(1)	4618(1)	19(1)
C(6)	4827(4)	5997(1)	5111(1)	22(1)
C(7)	4880(4)	6396(1)	5834(1)	21(1)
C(8)	6449(4)	6429(2)	6449(1)	25(1)
C(9)	5730(4)	6929(1)	7007(1)	23(1)
C(10)	3177(4)	6899(1)	6046(1)	19(1)
C(11)	1395(4)	7014(1)	5559(1)	21(1)
C(12)	1383(4)	6607(1)	4846(1)	21(1)
C(13)	72(4)	4667(1)	4120(1)	26(1)
C(14)	2425(4)	7724(1)	7240(1)	21(1)
C(15)	2396(4)	8398(2)	8527(1)	28(1)
C(16)	4171(5)	8455(2)	9138(2)	50(1)
C(17)	1850(6)	9208(2)	8196(2)	41(1)
C(18)	471(5)	7964(2)	8848(2)	40(1)

Table 3. Bond lengths [≈] and angles [∞] for **4.294**.

F(1)-C(3)	1.388(3)
F(2)-C(13)	1.329(3)
F(3)-C(13)	1.338(3)
F(4)-C(13)	1.345(3)
O(1)-C(4)	1.414(3)
O(1)-H(1O)	0.85(2)
O(2)-C(14)	1.323(3)
O(2)-C(15)	1.490(3)
O(3)-C(14)	1.211(3)
N(1)-C(14)	1.389(3)
N(1)-C(9)	1.405(3)
N(1)-C(10)	1.408(3)
C(1)-C(2)	1.311(4)
C(1)-H(1A)	0.9500
C(1)-H(1B)	0.9500
C(2)-C(3)	1.500(3)
C(2)-H(2)	0.9500
C(3)-C(13)	1.526(3)
C(3)-C(4)	1.550(3)
C(4)-C(5)	1.514(3)
C(4)-H(4)	1.0000
C(5)-C(6)	1.381(3)
C(5)-C(12)	1.409(3)
C(6)-C(7)	1.398(3)
C(6)-H(6)	0.9500
C(7)-C(10)	1.402(3)
C(7)-C(8)	1.429(3)
C(8)-C(9)	1.342(3)
C(8)-H(8)	0.9500
C(9)-H(9)	0.9500
C(10)-C(11)	1.395(3)
C(11)-C(12)	1.389(3)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500

C(15)-C(18)	1.504(4)
C(15)-C(17)	1.511(4)
C(15)-C(16)	1.517(4)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800

C(4)-O(1)-H(1O)	110(2)
C(14)-O(2)-C(15)	121.76(19)
C(14)-N(1)-C(9)	125.38(19)
C(14)-N(1)-C(10)	126.50(19)
C(9)-N(1)-C(10)	107.90(19)
C(2)-C(1)-H(1A)	120.0
C(2)-C(1)-H(1B)	120.0
H(1A)-C(1)-H(1B)	120.0
C(1)-C(2)-C(3)	122.5(3)
C(1)-C(2)-H(2)	118.8
C(3)-C(2)-H(2)	118.8
F(1)-C(3)-C(2)	109.88(19)
F(1)-C(3)-C(13)	104.26(18)
C(2)-C(3)-C(13)	110.27(19)
F(1)-C(3)-C(4)	106.67(18)
C(2)-C(3)-C(4)	109.77(19)
C(13)-C(3)-C(4)	115.70(19)
O(1)-C(4)-C(5)	113.59(18)
O(1)-C(4)-C(3)	107.09(18)
C(5)-C(4)-C(3)	115.93(18)
O(1)-C(4)-H(4)	106.5
C(5)-C(4)-H(4)	106.5
C(3)-C(4)-H(4)	106.5

C(6)-C(5)-C(12)	119.9(2)
C(6)-C(5)-C(4)	118.9(2)
C(12)-C(5)-C(4)	121.07(19)
C(5)-C(6)-C(7)	119.2(2)
C(5)-C(6)-H(6)	120.4
C(7)-C(6)-H(6)	120.4
C(6)-C(7)-C(10)	119.8(2)
C(6)-C(7)-C(8)	132.5(2)
C(10)-C(7)-C(8)	107.69(19)
C(9)-C(8)-C(7)	108.2(2)
C(9)-C(8)-H(8)	125.9
C(7)-C(8)-H(8)	125.9
C(8)-C(9)-N(1)	109.5(2)
C(8)-C(9)-H(9)	125.3
N(1)-C(9)-H(9)	125.3
C(11)-C(10)-C(7)	122.0(2)
C(11)-C(10)-N(1)	131.2(2)
C(7)-C(10)-N(1)	106.77(19)
C(12)-C(11)-C(10)	116.9(2)
C(12)-C(11)-H(11)	121.6
C(10)-C(11)-H(11)	121.6
C(11)-C(12)-C(5)	122.1(2)
C(11)-C(12)-H(12)	118.9
C(5)-C(12)-H(12)	118.9
F(2)-C(13)-F(3)	107.3(2)
F(2)-C(13)-F(4)	106.47(18)
F(3)-C(13)-F(4)	107.2(2)
F(2)-C(13)-C(3)	113.2(2)
F(3)-C(13)-C(3)	111.50(18)
F(4)-C(13)-C(3)	110.9(2)
O(3)-C(14)-O(2)	127.4(2)
O(3)-C(14)-N(1)	122.8(2)
O(2)-C(14)-N(1)	109.8(2)
O(2)-C(15)-C(18)	109.3(2)
O(2)-C(15)-C(17)	109.60(19)
C(18)-C(15)-C(17)	113.2(2)

O(2)-C(15)-C(16)	101.9(2)
C(18)-C(15)-C(16)	111.2(2)
C(17)-C(15)-C(16)	111.1(2)
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(15)-C(17)-H(17A)	109.5
C(15)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(15)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(15)-C(18)-H(18A)	109.5
C(15)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(15)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\approx^2$x 10^3) for **4.234**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	33(1)	24(1)	34(1)	1(1)	-7(1)	8(1)
F(2)	45(1)	37(1)	29(1)	-5(1)	17(1)	-10(1)
F(3)	19(1)	51(1)	51(1)	11(1)	2(1)	1(1)
F(4)	41(1)	30(1)	42(1)	-5(1)	12(1)	-13(1)
O(1)	27(1)	25(1)	22(1)	3(1)	-3(1)	-1(1)
O(2)	26(1)	31(1)	21(1)	-7(1)	-2(1)	1(1)
O(3)	25(1)	31(1)	24(1)	-5(1)	-3(1)	7(1)
N(1)	19(1)	21(1)	19(1)	0(1)	0(1)	-1(1)
C(1)	35(1)	41(2)	50(2)	-23(1)	17(1)	-14(1)
C(2)	29(1)	29(1)	26(1)	-6(1)	4(1)	-9(1)
C(3)	22(1)	22(1)	22(1)	0(1)	0(1)	3(1)
C(4)	17(1)	23(1)	21(1)	1(1)	1(1)	0(1)
C(5)	19(1)	17(1)	21(1)	2(1)	3(1)	-2(1)
C(6)	18(1)	21(1)	25(1)	-1(1)	4(1)	3(1)
C(7)	19(1)	21(1)	23(1)	1(1)	2(1)	-1(1)
C(8)	18(1)	29(1)	28(1)	-1(1)	-2(1)	2(1)
C(9)	20(1)	27(1)	23(1)	0(1)	-5(1)	-3(1)
C(10)	20(1)	18(1)	19(1)	2(1)	2(1)	-3(1)
C(11)	21(1)	18(1)	23(1)	0(1)	1(1)	0(1)
C(12)	19(1)	21(1)	22(1)	1(1)	-2(1)	0(1)
C(13)	29(1)	24(1)	26(1)	0(1)	5(1)	-3(1)
C(14)	25(1)	20(1)	19(1)	0(1)	1(1)	-3(1)
C(15)	32(1)	32(1)	18(1)	-7(1)	-1(1)	4(1)
C(16)	46(2)	69(2)	34(2)	-25(1)	-12(1)	11(2)
C(17)	66(2)	26(1)	32(1)	-7(1)	3(1)	3(1)
C(18)	48(2)	42(2)	30(1)	-6(1)	12(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (≈^{2}x 10 ^{3}) for **4.234**.

	x	y	z	U(eq)
H(1O)	2580(50)	6505(15)	3067(17)	29
H(1A)	5320	3938	3142	50
H(1B)	4297	3855	2250	50
H(2)	1470	4600	2612	34
H(4)	4611	5701	3631	24
H(6)	5980	5659	4960	26
H(8)	7772	6147	6461	30
H(9)	6467	7057	7481	28
H(11)	244	7354	5708	25
H(12)	193	6672	4500	25
H(16A)	3670	8772	9587	74
H(16B)	4554	7920	9320	74
H(16C)	5437	8709	8903	74
H(17A)	1169	9531	8607	62
H(17B)	3170	9470	8016	62
H(17C)	858	9147	7751	62
H(18A)	-214	8287	9259	60
H(18B)	-560	7866	8422	60
H(18C)	931	7455	9075	60

Table 6. Torsion angles [∞] for **4.234**.

C(1)-C(2)-C(3)-F(1)	-18.4(3)
C(1)-C(2)-C(3)-C(13)	-132.7(3)
C(1)-C(2)-C(3)-C(4)	98.6(3)
F(1)-C(3)-C(4)-O(1)	174.69(17)
C(2)-C(3)-C(4)-O(1)	55.7(2)
C(13)-C(3)-C(4)-O(1)	-69.9(2)
F(1)-C(3)-C(4)-C(5)	-57.4(2)
C(2)-C(3)-C(4)-C(5)	-176.4(2)
C(13)-C(3)-C(4)-C(5)	58.1(3)
O(1)-C(4)-C(5)-C(6)	-151.6(2)
C(3)-C(4)-C(5)-C(6)	83.7(3)
O(1)-C(4)-C(5)-C(12)	25.0(3)
C(3)-C(4)-C(5)-C(12)	-99.7(2)
C(12)-C(5)-C(6)-C(7)	0.3(3)
C(4)-C(5)-C(6)-C(7)	177.0(2)
C(5)-C(6)-C(7)-C(10)	-0.6(3)
C(5)-C(6)-C(7)-C(8)	-178.0(2)
C(6)-C(7)-C(8)-C(9)	177.6(2)
C(10)-C(7)-C(8)-C(9)	0.0(3)
C(7)-C(8)-C(9)-N(1)	-0.1(3)
C(14)-N(1)-C(9)-C(8)	175.1(2)
C(10)-N(1)-C(9)-C(8)	0.2(2)
C(6)-C(7)-C(10)-C(11)	0.6(3)
C(8)-C(7)-C(10)-C(11)	178.6(2)
C(6)-C(7)-C(10)-N(1)	-177.9(2)
C(8)-C(7)-C(10)-N(1)	0.1(2)
C(14)-N(1)-C(10)-C(11)	6.7(4)
C(9)-N(1)-C(10)-C(11)	-178.5(2)
C(14)-N(1)-C(10)-C(7)	-175.0(2)
C(9)-N(1)-C(10)-C(7)	-0.2(2)
C(7)-C(10)-C(11)-C(12)	-0.3(3)
N(1)-C(10)-C(11)-C(12)	177.8(2)
C(10)-C(11)-C(12)-C(5)	0.0(3)
C(6)-C(5)-C(12)-C(11)	0.0(3)

C(4)-C(5)-C(12)-C(11)	-176.6(2)
F(1)-C(3)-C(13)-F(2)	54.5(2)
C(2)-C(3)-C(13)-F(2)	172.4(2)
C(4)-C(3)-C(13)-F(2)	-62.3(3)
F(1)-C(3)-C(13)-F(3)	175.64(18)
C(2)-C(3)-C(13)-F(3)	-66.5(3)
C(4)-C(3)-C(13)-F(3)	58.9(3)
F(1)-C(3)-C(13)-F(4)	-65.0(2)
C(2)-C(3)-C(13)-F(4)	52.9(3)
C(4)-C(3)-C(13)-F(4)	178.17(19)
C(15)-O(2)-C(14)-O(3)	1.8(4)
C(15)-O(2)-C(14)-N(1)	-177.52(19)
C(9)-N(1)-C(14)-O(3)	-175.3(2)
C(10)-N(1)-C(14)-O(3)	-1.3(4)
C(9)-N(1)-C(14)-O(2)	4.1(3)
C(10)-N(1)-C(14)-O(2)	178.06(19)
C(14)-O(2)-C(15)-C(18)	63.8(3)
C(14)-O(2)-C(15)-C(17)	-60.8(3)
C(14)-O(2)-C(15)-C(16)	-178.5(2)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **4.234** [≈ and ∞].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...O(3)#1	0.85(2)	2.13(3)	2.887(2)	147(3)

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+3/2,-z+1

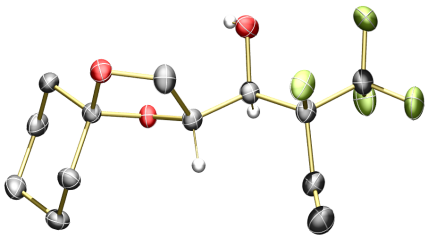


Table 1. Crystal data and structure refinement for **4.250**.

Identification code	C13H18F4O3	
Empirical formula	C13 H18 F4 O3	
Formula weight	298.27	
Temperature	123(2) K	
Wavelength	1.54178 ≈	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.5631(4) ≈	α= 90∞.
	b = 9.3970(5) ≈	β= 91.289(2)∞.
	c = 11.1818(6) ≈	γ = 90∞.
Volume	689.45(7) ≈^{3}	
Z	2	
Density (calculated)	1.437 Mg/m^3	
Absorption coefficient	1.185 mm^{-1}	
F(000)	312	
Crystal size	0.450 x 0.320 x 0.100 mm^3	
Theta range for data collection	3.954 to 67.045∞.	
Index ranges	-7<=h<=7, -11<=k<=11, -13<=l<=13	
Reflections collected	9575	
Independent reflections	2425 [R(int) = 0.0262]	
Completeness to theta = 67.045∞	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7529 and 0.6036	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2425 / 2 / 184	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0229, wR2 = 0.0609	
R indices (all data)	R1 = 0.0230, wR2 = 0.0610	
Absolute structure parameter	0.02(4)	

Extinction coefficient	n/a
Largest diff. peak and hole	0.180 and -0.125 e.$\approx^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\approx^2$x 10^3) for **4.250**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	5314(2)	6521(1)	1505(1)	31(1)
F(2)	5400(2)	4596(2)	-387(1)	43(1)
F(3)	3128(2)	4198(2)	894(1)	48(1)
F(4)	5806(2)	2886(1)	882(1)	43(1)
O(1)	4130(2)	4485(2)	3218(1)	28(1)
O(2)	6120(2)	7125(1)	5381(1)	25(1)
O(3)	7585(2)	5052(1)	4878(1)	21(1)
C(1)	9258(3)	6487(3)	771(2)	40(1)
C(2)	8460(3)	5335(2)	1229(2)	29(1)
C(3)	6283(3)	5213(2)	1616(2)	23(1)
C(4)	6170(3)	4702(2)	2918(2)	21(1)
C(5)	7231(3)	5764(2)	3764(1)	21(1)
C(6)	5951(3)	7057(2)	4101(2)	27(1)
C(7)	7668(2)	6134(2)	5762(1)	20(1)
C(8)	9735(3)	6874(2)	5818(2)	26(1)
C(9)	11394(3)	5853(2)	6265(2)	29(1)
C(10)	10863(3)	5229(2)	7478(2)	33(1)
C(11)	8803(3)	4488(2)	7422(2)	29(1)
C(12)	7130(3)	5492(2)	6960(2)	25(1)
C(13)	5123(3)	4213(2)	749(2)	31(1)

Table 3. Bond lengths [≈] and angles [∞] for **4.250**.

F(1)-C(3)	1.389(2)
F(2)-C(13)	1.337(2)
F(3)-C(13)	1.323(2)
F(4)-C(13)	1.332(3)
O(1)-C(4)	1.402(2)
O(1)-H(1O)	0.85(2)
O(2)-C(6)	1.435(2)
O(2)-C(7)	1.436(2)
O(3)-C(7)	1.4188(19)
O(3)-C(5)	1.4290(19)
C(1)-C(2)	1.312(3)
C(1)-H(1A)	0.9500
C(1)-H(1B)	0.9500
C(2)-C(3)	1.506(2)
C(2)-H(2)	0.9500
C(3)-C(4)	1.537(2)
C(3)-C(13)	1.540(2)
C(4)-C(5)	1.532(2)
C(4)-H(4)	1.0000
C(5)-C(6)	1.529(3)
C(5)-H(5)	1.0000
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(12)	1.518(2)
C(7)-C(8)	1.524(2)
C(8)-C(9)	1.526(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.526(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.521(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900

C(11)-C(12)	1.529(2)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900

C(4)-O(1)-H(1O)	106.0(17)
C(6)-O(2)-C(7)	107.80(12)
C(7)-O(3)-C(5)	105.93(12)
C(2)-C(1)-H(1A)	120.0
C(2)-C(1)-H(1B)	120.0
H(1A)-C(1)-H(1B)	120.0
C(1)-C(2)-C(3)	124.35(19)
C(1)-C(2)-H(2)	117.8
C(3)-C(2)-H(2)	117.8
F(1)-C(3)-C(2)	110.03(15)
F(1)-C(3)-C(4)	109.23(13)
C(2)-C(3)-C(4)	111.26(14)
F(1)-C(3)-C(13)	105.37(13)
C(2)-C(3)-C(13)	108.93(14)
C(4)-C(3)-C(13)	111.86(14)
O(1)-C(4)-C(5)	111.76(14)
O(1)-C(4)-C(3)	109.79(13)
C(5)-C(4)-C(3)	110.47(13)
O(1)-C(4)-H(4)	108.2
C(5)-C(4)-H(4)	108.2
C(3)-C(4)-H(4)	108.2
O(3)-C(5)-C(6)	103.70(13)
O(3)-C(5)-C(4)	107.16(13)
C(6)-C(5)-C(4)	115.17(14)
O(3)-C(5)-H(5)	110.2
C(6)-C(5)-H(5)	110.2
C(4)-C(5)-H(5)	110.2
O(2)-C(6)-C(5)	104.51(13)
O(2)-C(6)-H(6A)	110.9
C(5)-C(6)-H(6A)	110.9

O(2)-C(6)-H(6B)	110.9
C(5)-C(6)-H(6B)	110.9
H(6A)-C(6)-H(6B)	108.9
O(3)-C(7)-O(2)	104.03(12)
O(3)-C(7)-C(12)	108.90(13)
O(2)-C(7)-C(12)	110.00(14)
O(3)-C(7)-C(8)	112.05(13)
O(2)-C(7)-C(8)	109.87(13)
C(12)-C(7)-C(8)	111.71(14)
C(7)-C(8)-C(9)	110.77(15)
C(7)-C(8)-H(8A)	109.5
C(9)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
C(9)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	108.1
C(10)-C(9)-C(8)	110.93(15)
C(10)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9A)	109.5
C(10)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	108.0
C(11)-C(10)-C(9)	111.07(14)
C(11)-C(10)-H(10A)	109.4
C(9)-C(10)-H(10A)	109.4
C(11)-C(10)-H(10B)	109.4
C(9)-C(10)-H(10B)	109.4
H(10A)-C(10)-H(10B)	108.0
C(10)-C(11)-C(12)	111.25(16)
C(10)-C(11)-H(11A)	109.4
C(12)-C(11)-H(11A)	109.4
C(10)-C(11)-H(11B)	109.4
C(12)-C(11)-H(11B)	109.4
H(11A)-C(11)-H(11B)	108.0
C(7)-C(12)-C(11)	111.33(14)
C(7)-C(12)-H(12A)	109.4
C(11)-C(12)-H(12A)	109.4

C(7)-C(12)-H(12B)	109.4
C(11)-C(12)-H(12B)	109.4
H(12A)-C(12)-H(12B)	108.0
F(3)-C(13)-F(4)	107.92(18)
F(3)-C(13)-F(2)	106.02(15)
F(4)-C(13)-F(2)	107.78(16)
F(3)-C(13)-C(3)	113.98(16)
F(4)-C(13)-C(3)	109.89(14)
F(2)-C(13)-C(3)	111.00(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\approx^2$x 10^3) for **4.250**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	40(1)	27(1)	26(1)	7(1)	1(1)	11(1)
F(2)	50(1)	59(1)	19(1)	0(1)	-3(1)	-4(1)
F(3)	28(1)	82(1)	34(1)	-12(1)	-4(1)	-10(1)
F(4)	60(1)	32(1)	37(1)	-10(1)	-9(1)	-3(1)
O(1)	26(1)	32(1)	26(1)	9(1)	0(1)	-6(1)
O(2)	24(1)	24(1)	26(1)	-3(1)	-1(1)	6(1)
O(3)	25(1)	18(1)	19(1)	0(1)	-1(1)	2(1)
C(1)	40(1)	48(1)	32(1)	4(1)	6(1)	-8(1)
C(2)	29(1)	35(1)	24(1)	-2(1)	4(1)	0(1)
C(3)	26(1)	22(1)	21(1)	2(1)	0(1)	2(1)
C(4)	23(1)	20(1)	21(1)	2(1)	-1(1)	1(1)
C(5)	24(1)	20(1)	20(1)	3(1)	0(1)	-1(1)
C(6)	36(1)	21(1)	24(1)	3(1)	-3(1)	4(1)
C(7)	20(1)	18(1)	22(1)	-2(1)	0(1)	2(1)
C(8)	22(1)	25(1)	31(1)	-2(1)	0(1)	-3(1)
C(9)	19(1)	34(1)	35(1)	-3(1)	-1(1)	0(1)
C(10)	27(1)	42(1)	28(1)	-4(1)	-6(1)	7(1)
C(11)	30(1)	35(1)	21(1)	4(1)	2(1)	5(1)
C(12)	22(1)	32(1)	22(1)	-3(1)	3(1)	1(1)
C(13)	30(1)	39(1)	23(1)	-2(1)	-1(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (≈^{2}x 10 ^{3}) for **4.250**.

	x	y	z	U(eq)
H(1O)	4140(40)	3830(30)	3740(20)	42
H(1A)	8448	7318	665	47
H(1B)	10644	6491	546	47
H(2)	9312	4523	1323	35
H(4)	6900	3770	2987	26
H(5)	8553	6079	3423	25
H(6A)	6490	7935	3734	33
H(6B)	4513	6930	3836	33
H(8A)	9671	7703	6361	31
H(8B)	10076	7225	5012	31
H(9A)	11552	5073	5679	35
H(9B)	12708	6367	6335	35
H(10A)	11928	4538	7731	39
H(10B)	10834	6000	8081	39
H(11A)	8459	4146	8230	35
H(11B)	8879	3651	6887	35
H(12A)	5832	4962	6874	30
H(12B)	6933	6265	7548	30

Table 6. Torsion angles [∞] for **4.250**.

C(1)-C(2)-C(3)-F(1)	-4.7(3)
C(1)-C(2)-C(3)-C(4)	-125.9(2)
C(1)-C(2)-C(3)-C(13)	110.3(2)
F(1)-C(3)-C(4)-O(1)	63.26(17)
C(2)-C(3)-C(4)-O(1)	-175.07(15)
C(13)-C(3)-C(4)-O(1)	-52.99(19)
F(1)-C(3)-C(4)-C(5)	-60.44(17)
C(2)-C(3)-C(4)-C(5)	61.23(19)
C(13)-C(3)-C(4)-C(5)	-176.69(14)
C(7)-O(3)-C(5)-C(6)	-31.83(16)
C(7)-O(3)-C(5)-C(4)	-154.07(13)
O(1)-C(4)-C(5)-O(3)	73.75(16)
C(3)-C(4)-C(5)-O(3)	-163.69(12)
O(1)-C(4)-C(5)-C(6)	-41.02(19)
C(3)-C(4)-C(5)-C(6)	81.54(17)
C(7)-O(2)-C(6)-C(5)	9.99(17)
O(3)-C(5)-C(6)-O(2)	13.13(17)
C(4)-C(5)-C(6)-O(2)	129.88(15)
C(5)-O(3)-C(7)-O(2)	38.59(15)
C(5)-O(3)-C(7)-C(12)	155.86(13)
C(5)-O(3)-C(7)-C(8)	-80.04(16)
C(6)-O(2)-C(7)-O(3)	-29.75(16)
C(6)-O(2)-C(7)-C(12)	-146.25(14)
C(6)-O(2)-C(7)-C(8)	90.38(16)
O(3)-C(7)-C(8)-C(9)	-66.94(19)
O(2)-C(7)-C(8)-C(9)	177.94(13)
C(12)-C(7)-C(8)-C(9)	55.57(19)
C(7)-C(8)-C(9)-C(10)	-56.2(2)
C(8)-C(9)-C(10)-C(11)	56.5(2)
C(9)-C(10)-C(11)-C(12)	-55.6(2)
O(3)-C(7)-C(12)-C(11)	69.48(18)
O(2)-C(7)-C(12)-C(11)	-177.11(14)
C(8)-C(7)-C(12)-C(11)	-54.82(19)
C(10)-C(11)-C(12)-C(7)	54.7(2)

F(1)-C(3)-C(13)-F(3)	-52.2(2)
C(2)-C(3)-C(13)-F(3)	-170.25(17)
C(4)-C(3)-C(13)-F(3)	66.3(2)
F(1)-C(3)-C(13)-F(4)	-173.49(15)
C(2)-C(3)-C(13)-F(4)	68.5(2)
C(4)-C(3)-C(13)-F(4)	-54.9(2)
F(1)-C(3)-C(13)-F(2)	67.39(18)
C(2)-C(3)-C(13)-F(2)	-50.6(2)
C(4)-C(3)-C(13)-F(2)	-174.04(14)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **4.250** [≈ and ∞].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...O(2)#1	0.85(2)	1.89(2)	2.7222(18)	167(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+1

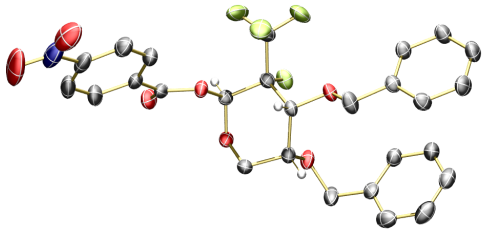


Table 1. Crystal data and structure refinement for **4.254**.

Identification code	C27H23F4NO7	
Empirical formula	C27 H23 F4 N O7	
Formula weight	549.46	
Temperature	173(2) K	
Wavelength	1.54178 ≈	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.6045(2) ≈	α= 90∞.
	b = 14.0158(5) ≈	β= 90∞.
	c = 31.3309(11) ≈	γ = 90∞.
Volume	2461.09(15) ≈^{3}	
Z	4	
Density (calculated)	1.483 Mg/m^3	
Absorption coefficient	1.095 mm^{-1}	
F(000)	1136	
Crystal size	0.380 x 0.180 x 0.120 mm^3	
Theta range for data collection	2.821 to 66.352∞.	
Index ranges	-6<=h<=6, -16<=k<=15, -36<=l<=37	
Reflections collected	30730	
Independent reflections	4292 [R(int) = 0.0315]	
Completeness to theta = 66.352∞	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.6578	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4292 / 0 / 352	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0271, wR2 = 0.0697	
R indices (all data)	R1 = 0.0287, wR2 = 0.0709	
Absolute structure parameter	-0.02(3)	
Extinction coefficient	n/a	

Largest diff. peak and hole	0.145 and -0.241 e.$\approx^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\approx^2$x 10^3) for **4.254**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	13207(2)	5192(1)	4641(1)	36(1)
F(2)	12126(3)	3467(1)	4459(1)	56(1)
F(3)	12231(3)	3514(1)	5141(1)	63(1)
F(4)	8862(3)	3454(1)	4818(1)	53(1)
N(1)	1068(4)	3193(2)	6716(1)	58(1)
O(1)	643(4)	3436(2)	7084(1)	86(1)
O(2)	-132(4)	2630(2)	6511(1)	69(1)
O(3)	10417(3)	5425(1)	6073(1)	41(1)
O(4)	8845(2)	4905(1)	5453(1)	28(1)
O(5)	10549(2)	6340(1)	5229(1)	28(1)
O(6)	10947(3)	6804(1)	4345(1)	34(1)
O(7)	9397(2)	4924(1)	4084(1)	28(1)
C(1)	3156(4)	3629(2)	6505(1)	44(1)
C(2)	3760(4)	3317(2)	6104(1)	41(1)
C(3)	5633(4)	3765(1)	5896(1)	35(1)
C(4)	6857(4)	4503(1)	6094(1)	32(1)
C(5)	6239(5)	4787(2)	6506(1)	44(1)
C(6)	4356(5)	4353(2)	6714(1)	50(1)
C(7)	8889(4)	4993(1)	5887(1)	30(1)
C(8)	10810(3)	5359(1)	5240(1)	26(1)
C(9)	8542(4)	6667(1)	4980(1)	30(1)
C(10)	8854(3)	6385(1)	4515(1)	28(1)
C(11)	9011(3)	5295(1)	4496(1)	24(1)
C(12)	10968(3)	4924(1)	4788(1)	27(1)
C(13)	10499(5)	7607(1)	4071(1)	46(1)
C(14)	9783(4)	7306(1)	3630(1)	33(1)
C(15)	7679(5)	7624(2)	3440(1)	46(1)
C(16)	7067(4)	7321(2)	3030(1)	47(1)
C(17)	8524(4)	6718(2)	2812(1)	40(1)
C(18)	10613(4)	6409(2)	2994(1)	40(1)
C(19)	11232(4)	6695(2)	3400(1)	36(1)

C(20)	7253(4)	4842(2)	3843(1)	37(1)
C(21)	7771(3)	4442(1)	3410(1)	28(1)
C(22)	6122(4)	4590(1)	3088(1)	34(1)
C(23)	6510(4)	4237(2)	2680(1)	38(1)
C(24)	8565(4)	3728(2)	2594(1)	39(1)
C(25)	10213(4)	3565(2)	2914(1)	36(1)
C(26)	9823(3)	3925(1)	3322(1)	31(1)
C(27)	11039(4)	3827(1)	4799(1)	40(1)

Table 3. Bond lengths [≈] and angles [∞] for **4.254**.

F(1)-C(12)	1.389(2)
F(2)-C(27)	1.328(3)
F(3)-C(27)	1.337(3)
F(4)-C(27)	1.328(3)
N(1)-O(2)	1.219(3)
N(1)-O(1)	1.224(3)
N(1)-C(1)	1.477(3)
O(3)-C(7)	1.199(3)
O(4)-C(7)	1.365(2)
O(4)-C(8)	1.437(2)
O(5)-C(8)	1.383(2)
O(5)-C(9)	1.444(2)
O(6)-C(10)	1.416(2)
O(6)-C(13)	1.438(2)
O(7)-C(11)	1.408(2)
O(7)-C(20)	1.423(2)
C(1)-C(2)	1.375(3)
C(1)-C(6)	1.382(4)
C(2)-C(3)	1.385(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.388(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.395(3)
C(4)-C(7)	1.479(3)
C(5)-C(6)	1.380(4)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(8)-C(12)	1.543(2)
C(8)-H(8)	1.0000
C(9)-C(10)	1.518(2)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.531(2)
C(10)-H(10)	1.0000

C(11)-C(12)	1.521(3)
C(11)-H(11)	1.0000
C(12)-C(27)	1.538(3)
C(13)-C(14)	1.500(3)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-C(19)	1.384(3)
C(14)-C(15)	1.394(3)
C(15)-C(16)	1.397(4)
C(15)-H(15)	0.9500
C(16)-C(17)	1.359(3)
C(16)-H(16)	0.9500
C(17)-C(18)	1.373(3)
C(17)-H(17)	0.9500
C(18)-C(19)	1.377(3)
C(18)-H(18)	0.9500
C(19)-H(19)	0.9500
C(20)-C(21)	1.499(3)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-C(22)	1.382(3)
C(21)-C(26)	1.387(3)
C(22)-C(23)	1.388(3)
C(22)-H(22)	0.9500
C(23)-C(24)	1.381(3)
C(23)-H(23)	0.9500
C(24)-C(25)	1.381(3)
C(24)-H(24)	0.9500
C(25)-C(26)	1.393(3)
C(25)-H(25)	0.9500
C(26)-H(26)	0.9500

O(2)-N(1)-O(1)	124.6(3)
O(2)-N(1)-C(1)	117.9(2)
O(1)-N(1)-C(1)	117.4(3)
C(7)-O(4)-C(8)	114.18(14)

C(8)-O(5)-C(9)	114.22(13)
C(10)-O(6)-C(13)	113.90(17)
C(11)-O(7)-C(20)	112.68(14)
C(2)-C(1)-C(6)	123.1(2)
C(2)-C(1)-N(1)	118.3(2)
C(6)-C(1)-N(1)	118.6(2)
C(1)-C(2)-C(3)	118.2(2)
C(1)-C(2)-H(2)	120.9
C(3)-C(2)-H(2)	120.9
C(2)-C(3)-C(4)	120.19(19)
C(2)-C(3)-H(3)	119.9
C(4)-C(3)-H(3)	119.9
C(3)-C(4)-C(5)	120.2(2)
C(3)-C(4)-C(7)	122.07(16)
C(5)-C(4)-C(7)	117.70(18)
C(6)-C(5)-C(4)	120.0(2)
C(6)-C(5)-H(5)	120.0
C(4)-C(5)-H(5)	120.0
C(5)-C(6)-C(1)	118.2(2)
C(5)-C(6)-H(6)	120.9
C(1)-C(6)-H(6)	120.9
O(3)-C(7)-O(4)	122.80(18)
O(3)-C(7)-C(4)	124.83(16)
O(4)-C(7)-C(4)	112.37(16)
O(5)-C(8)-O(4)	111.77(14)
O(5)-C(8)-C(12)	112.18(14)
O(4)-C(8)-C(12)	107.17(13)
O(5)-C(8)-H(8)	108.5
O(4)-C(8)-H(8)	108.5
C(12)-C(8)-H(8)	108.5
O(5)-C(9)-C(10)	110.26(15)
O(5)-C(9)-H(9A)	109.6
C(10)-C(9)-H(9A)	109.6
O(5)-C(9)-H(9B)	109.6
C(10)-C(9)-H(9B)	109.6
H(9A)-C(9)-H(9B)	108.1

O(6)-C(10)-C(9)	110.40(15)
O(6)-C(10)-C(11)	110.56(15)
C(9)-C(10)-C(11)	107.74(14)
O(6)-C(10)-H(10)	109.4
C(9)-C(10)-H(10)	109.4
C(11)-C(10)-H(10)	109.4
O(7)-C(11)-C(12)	108.36(14)
O(7)-C(11)-C(10)	114.43(14)
C(12)-C(11)-C(10)	111.02(15)
O(7)-C(11)-H(11)	107.6
C(12)-C(11)-H(11)	107.6
C(10)-C(11)-H(11)	107.6
F(1)-C(12)-C(11)	111.03(14)
F(1)-C(12)-C(27)	104.72(16)
C(11)-C(12)-C(27)	111.94(16)
F(1)-C(12)-C(8)	104.44(14)
C(11)-C(12)-C(8)	112.04(14)
C(27)-C(12)-C(8)	112.17(15)
O(6)-C(13)-C(14)	112.13(16)
O(6)-C(13)-H(13A)	109.2
C(14)-C(13)-H(13A)	109.2
O(6)-C(13)-H(13B)	109.2
C(14)-C(13)-H(13B)	109.2
H(13A)-C(13)-H(13B)	107.9
C(19)-C(14)-C(15)	118.21(19)
C(19)-C(14)-C(13)	119.8(2)
C(15)-C(14)-C(13)	122.0(2)
C(14)-C(15)-C(16)	120.2(2)
C(14)-C(15)-H(15)	119.9
C(16)-C(15)-H(15)	119.9
C(17)-C(16)-C(15)	120.3(2)
C(17)-C(16)-H(16)	119.9
C(15)-C(16)-H(16)	119.9
C(16)-C(17)-C(18)	120.0(2)
C(16)-C(17)-H(17)	120.0
C(18)-C(17)-H(17)	120.0

C(17)-C(18)-C(19)	120.5(2)
C(17)-C(18)-H(18)	119.8
C(19)-C(18)-H(18)	119.8
C(18)-C(19)-C(14)	120.9(2)
C(18)-C(19)-H(19)	119.6
C(14)-C(19)-H(19)	119.6
O(7)-C(20)-C(21)	110.32(16)
O(7)-C(20)-H(20A)	109.6
C(21)-C(20)-H(20A)	109.6
O(7)-C(20)-H(20B)	109.6
C(21)-C(20)-H(20B)	109.6
H(20A)-C(20)-H(20B)	108.1
C(22)-C(21)-C(26)	119.26(17)
C(22)-C(21)-C(20)	118.36(17)
C(26)-C(21)-C(20)	122.38(17)
C(21)-C(22)-C(23)	120.85(18)
C(21)-C(22)-H(22)	119.6
C(23)-C(22)-H(22)	119.6
C(24)-C(23)-C(22)	119.62(18)
C(24)-C(23)-H(23)	120.2
C(22)-C(23)-H(23)	120.2
C(25)-C(24)-C(23)	120.13(18)
C(25)-C(24)-H(24)	119.9
C(23)-C(24)-H(24)	119.9
C(24)-C(25)-C(26)	120.05(19)
C(24)-C(25)-H(25)	120.0
C(26)-C(25)-H(25)	120.0
C(21)-C(26)-C(25)	120.08(18)
C(21)-C(26)-H(26)	120.0
C(25)-C(26)-H(26)	120.0
F(2)-C(27)-F(4)	107.90(17)
F(2)-C(27)-F(3)	106.85(18)
F(4)-C(27)-F(3)	107.15(19)
F(2)-C(27)-C(12)	111.99(18)
F(4)-C(27)-C(12)	111.73(18)
F(3)-C(27)-C(12)	110.95(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\approx^2$x 10^3) for **4.254**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	21(1)	50(1)	37(1)	-7(1)	3(1)	1(1)
F(2)	74(1)	42(1)	52(1)	-17(1)	-1(1)	23(1)
F(3)	99(1)	37(1)	53(1)	-2(1)	-28(1)	26(1)
F(4)	74(1)	29(1)	55(1)	-1(1)	-3(1)	-15(1)
N(1)	41(1)	80(2)	54(1)	35(1)	16(1)	18(1)
O(1)	64(1)	145(2)	51(1)	30(1)	29(1)	15(2)
O(2)	46(1)	80(1)	83(1)	35(1)	14(1)	4(1)
O(3)	50(1)	42(1)	30(1)	-5(1)	-8(1)	-2(1)
O(4)	35(1)	28(1)	22(1)	2(1)	0(1)	-5(1)
O(5)	35(1)	24(1)	26(1)	-2(1)	-2(1)	-4(1)
O(6)	45(1)	34(1)	25(1)	3(1)	2(1)	-11(1)
O(7)	23(1)	35(1)	25(1)	-8(1)	1(1)	-2(1)
C(1)	41(1)	53(1)	38(1)	23(1)	10(1)	15(1)
C(2)	42(1)	40(1)	40(1)	10(1)	6(1)	2(1)
C(3)	43(1)	34(1)	27(1)	4(1)	5(1)	3(1)
C(4)	42(1)	31(1)	24(1)	6(1)	-1(1)	7(1)
C(5)	56(1)	50(1)	25(1)	-1(1)	0(1)	8(1)
C(6)	57(1)	66(2)	27(1)	9(1)	10(1)	20(1)
C(7)	42(1)	25(1)	22(1)	0(1)	-4(1)	6(1)
C(8)	27(1)	24(1)	27(1)	0(1)	-2(1)	-2(1)
C(9)	36(1)	24(1)	29(1)	-1(1)	2(1)	4(1)
C(10)	31(1)	29(1)	24(1)	1(1)	1(1)	0(1)
C(11)	22(1)	27(1)	22(1)	-3(1)	2(1)	-2(1)
C(12)	23(1)	28(1)	29(1)	-2(1)	2(1)	0(1)
C(13)	81(2)	28(1)	28(1)	2(1)	6(1)	-9(1)
C(14)	43(1)	26(1)	29(1)	6(1)	6(1)	-3(1)
C(15)	47(1)	40(1)	51(1)	10(1)	17(1)	10(1)
C(16)	36(1)	57(1)	48(1)	20(1)	-6(1)	-2(1)
C(17)	49(1)	40(1)	33(1)	7(1)	-6(1)	-9(1)
C(18)	53(1)	40(1)	28(1)	1(1)	0(1)	6(1)
C(19)	37(1)	41(1)	30(1)	3(1)	-2(1)	5(1)

C(20)	24(1)	55(1)	33(1)	-14(1)	-4(1)	2(1)
C(21)	27(1)	28(1)	29(1)	-4(1)	0(1)	-4(1)
C(22)	30(1)	33(1)	37(1)	-5(1)	-4(1)	4(1)
C(23)	41(1)	43(1)	31(1)	-3(1)	-12(1)	2(1)
C(24)	45(1)	44(1)	28(1)	-9(1)	-1(1)	1(1)
C(25)	33(1)	42(1)	34(1)	-8(1)	1(1)	5(1)
C(26)	28(1)	36(1)	29(1)	-4(1)	-3(1)	1(1)
C(27)	54(1)	29(1)	37(1)	-7(1)	-7(1)	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (≈^{2}x 10 ^{3}) for **4.254**.

	x	y	z	U(eq)
H(2)	2915	2809	5972	49
H(3)	6081	3566	5618	42
H(5)	7113	5279	6644	52
H(6)	3898	4547	6993	60
H(8)	12312	5203	5397	31
H(9A)	8408	7369	5002	36
H(9B)	7053	6383	5093	36
H(10)	7438	6604	4348	34
H(11)	7459	5034	4602	29
H(13A)	11957	8004	4054	55
H(13B)	9214	8003	4196	55
H(15)	6657	8049	3590	55
H(16)	5627	7538	2902	56
H(17)	8097	6511	2534	48
H(18)	11639	5995	2840	48
H(19)	12674	6469	3523	43
H(20A)	6501	5478	3814	45
H(20B)	6121	4419	3995	45
H(22)	4706	4938	3147	40
H(23)	5368	4344	2461	46
H(24)	8845	3490	2315	47
H(25)	11613	3206	2855	43
H(26)	10964	3816	3541	37

Table 6. Torsion angles [∞] for **4.254**.

O(2)-N(1)-C(1)-C(2)	-5.6(3)
O(1)-N(1)-C(1)-C(2)	175.6(2)
O(2)-N(1)-C(1)-C(6)	172.1(2)
O(1)-N(1)-C(1)-C(6)	-6.7(3)
C(6)-C(1)-C(2)-C(3)	-1.2(3)
N(1)-C(1)-C(2)-C(3)	176.34(19)
C(1)-C(2)-C(3)-C(4)	0.3(3)
C(2)-C(3)-C(4)-C(5)	1.2(3)
C(2)-C(3)-C(4)-C(7)	179.14(18)
C(3)-C(4)-C(5)-C(6)	-2.0(3)
C(7)-C(4)-C(5)-C(6)	-179.99(19)
C(4)-C(5)-C(6)-C(1)	1.1(3)
C(2)-C(1)-C(6)-C(5)	0.5(3)
N(1)-C(1)-C(6)-C(5)	-177.08(19)
C(8)-O(4)-C(7)-O(3)	1.1(2)
C(8)-O(4)-C(7)-C(4)	-179.15(14)
C(3)-C(4)-C(7)-O(3)	-157.54(19)
C(5)-C(4)-C(7)-O(3)	20.4(3)
C(3)-C(4)-C(7)-O(4)	22.7(2)
C(5)-C(4)-C(7)-O(4)	-159.36(17)
C(9)-O(5)-C(8)-O(4)	-65.08(18)
C(9)-O(5)-C(8)-C(12)	55.32(19)
C(7)-O(4)-C(8)-O(5)	-75.25(18)
C(7)-O(4)-C(8)-C(12)	161.47(14)
C(8)-O(5)-C(9)-C(10)	-62.89(19)
C(13)-O(6)-C(10)-C(9)	-103.98(17)
C(13)-O(6)-C(10)-C(11)	136.90(15)
O(5)-C(9)-C(10)-O(6)	-60.66(18)
O(5)-C(9)-C(10)-C(11)	60.16(19)
C(20)-O(7)-C(11)-C(12)	152.77(16)
C(20)-O(7)-C(11)-C(10)	-82.8(2)
O(6)-C(10)-C(11)-O(7)	-57.0(2)
C(9)-C(10)-C(11)-O(7)	-177.67(15)
O(6)-C(10)-C(11)-C(12)	66.09(18)

C(9)-C(10)-C(11)-C(12)	-54.6(2)
O(7)-C(11)-C(12)-F(1)	58.95(18)
C(10)-C(11)-C(12)-F(1)	-67.51(18)
O(7)-C(11)-C(12)-C(27)	-57.7(2)
C(10)-C(11)-C(12)-C(27)	175.85(16)
O(7)-C(11)-C(12)-C(8)	175.30(13)
C(10)-C(11)-C(12)-C(8)	48.84(19)
O(5)-C(8)-C(12)-F(1)	72.11(17)
O(4)-C(8)-C(12)-F(1)	-164.86(13)
O(5)-C(8)-C(12)-C(11)	-48.2(2)
O(4)-C(8)-C(12)-C(11)	74.88(17)
O(5)-C(8)-C(12)-C(27)	-175.05(17)
O(4)-C(8)-C(12)-C(27)	-52.0(2)
C(10)-O(6)-C(13)-C(14)	-80.2(2)
O(6)-C(13)-C(14)-C(19)	-54.8(3)
O(6)-C(13)-C(14)-C(15)	125.2(2)
C(19)-C(14)-C(15)-C(16)	0.5(3)
C(13)-C(14)-C(15)-C(16)	-179.5(2)
C(14)-C(15)-C(16)-C(17)	-0.3(3)
C(15)-C(16)-C(17)-C(18)	-0.4(3)
C(16)-C(17)-C(18)-C(19)	0.9(3)
C(17)-C(18)-C(19)-C(14)	-0.7(3)
C(15)-C(14)-C(19)-C(18)	0.0(3)
C(13)-C(14)-C(19)-C(18)	-179.97(19)
C(11)-O(7)-C(20)-C(21)	-179.80(15)
O(7)-C(20)-C(21)-C(22)	-159.51(18)
O(7)-C(20)-C(21)-C(26)	21.1(3)
C(26)-C(21)-C(22)-C(23)	-0.6(3)
C(20)-C(21)-C(22)-C(23)	179.92(19)
C(21)-C(22)-C(23)-C(24)	0.2(3)
C(22)-C(23)-C(24)-C(25)	0.6(3)
C(23)-C(24)-C(25)-C(26)	-0.9(3)
C(22)-C(21)-C(26)-C(25)	0.3(3)
C(20)-C(21)-C(26)-C(25)	179.7(2)
C(24)-C(25)-C(26)-C(21)	0.5(3)
F(1)-C(12)-C(27)-F(2)	-41.3(2)

C(11)-C(12)-C(27)-F(2)	79.1(2)
C(8)-C(12)-C(27)-F(2)	-153.95(17)
F(1)-C(12)-C(27)-F(4)	-162.46(15)
C(11)-C(12)-C(27)-F(4)	-42.1(2)
C(8)-C(12)-C(27)-F(4)	84.9(2)
F(1)-C(12)-C(27)-F(3)	78.0(2)
C(11)-C(12)-C(27)-F(3)	-161.59(18)
C(8)-C(12)-C(27)-F(3)	-34.6(3)

Symmetry transformations used to generate equivalent atoms:

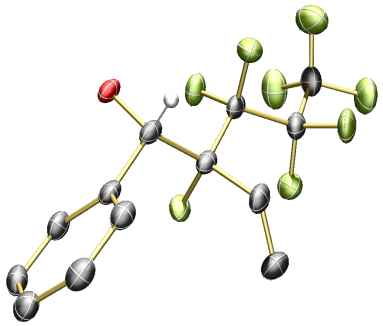


Table 1. Crystal data and structure refinement for **4.240**.

Identification code	C13H10F8O	
Empirical formula	C13 H10 F8 O	
Formula weight	334.21	
Temperature	100(2) K	
Wavelength	1.54178 ≈	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.2086(5) ≈	α= 90∞.
	b = 5.3122(3) ≈	β= 95.195(3)∞.
	c = 20.6191(10) ≈	γ = 90∞.
Volume	1331.75(11) ≈^{3}	
Z	4	
Density (calculated)	1.667 Mg/m^3	
Absorption coefficient	1.641 mm^{-1}	
F(000)	672	
Crystal size	0.550 x 0.080 x 0.060 mm^3	
Theta range for data collection	3.635 to 66.834∞.	
Index ranges	-14<=h<=14, -6<=k<=6, -24<=l<=24	
Reflections collected	16578	
Independent reflections	4694 [R(int) = 0.0636]	
Completeness to theta = 66.834∞	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5346	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4694 / 1 / 399	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0458, wR2 = 0.1100	

R indices (all data)	R1 = 0.0553, wR2 = 0.1159
Absolute structure parameter	-0.05(14)
Extinction coefficient	n/a
Largest diff. peak and hole	0.263 and -0.222 e.$\approx^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\approx^2$x 10^3) for **4.240**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	4926(2)	2488(8)	5358(1)	57(1)
F(2)	6167(2)	194(6)	5865(1)	47(1)
F(3)	6355(2)	4239(7)	5860(1)	50(1)
F(4)	4381(2)	502(6)	6512(1)	38(1)
F(5)	4349(2)	4605(6)	6399(1)	42(1)
F(6)	6632(2)	1424(5)	7093(1)	35(1)
F(7)	6099(2)	5333(5)	7155(1)	37(1)
F(8)	5036(2)	-194(5)	7800(1)	29(1)
O(1)	3382(2)	3120(6)	7477(1)	25(1)
C(1)	5643(4)	2353(11)	5883(2)	39(1)
C(2)	5004(3)	2583(10)	6497(2)	31(1)
C(3)	5738(3)	2939(8)	7144(2)	27(1)
C(4)	5288(3)	2359(8)	7811(2)	23(1)
C(5)	4260(3)	3857(8)	7947(2)	22(1)
C(6)	3941(3)	3438(8)	8637(2)	23(1)
C(7)	3302(3)	1363(9)	8781(2)	26(1)
C(8)	2993(3)	1031(9)	9408(2)	29(1)
C(9)	3331(3)	2744(9)	9894(2)	30(1)
C(10)	3971(3)	4794(9)	9756(2)	31(1)
C(11)	4270(3)	5125(9)	9127(2)	27(1)
C(12)	6219(3)	2872(9)	8326(2)	28(1)
C(13)	6807(3)	1106(11)	8634(2)	37(1)
F(9)	-1167(2)	5467(7)	9305(1)	50(1)
F(10)	313(3)	7690(7)	9376(1)	56(1)
F(11)	383(2)	3728(7)	9172(1)	53(1)
F(12)	-1195(2)	8162(6)	8262(1)	39(1)
F(13)	-807(2)	4266(5)	8036(1)	37(1)
F(14)	813(2)	9701(5)	8200(1)	34(1)
F(15)	1454(2)	5848(6)	8236(1)	34(1)
F(16)	590(2)	4788(5)	7070(1)	28(1)
O(2)	2473(2)	8032(6)	7301(1)	25(1)

C(14)	-192(4)	5798(11)	9061(2)	38(1)
C(15)	-409(3)	6380(9)	8329(2)	29(1)
C(16)	612(3)	7325(9)	7995(2)	25(1)
C(17)	510(3)	7318(8)	7239(2)	24(1)
C(18)	1453(3)	8806(8)	6963(2)	24(1)
C(19)	1464(3)	8430(8)	6232(2)	23(1)
C(20)	976(3)	10186(8)	5796(2)	27(1)
C(21)	1024(3)	9882(9)	5130(2)	30(1)
C(22)	1563(3)	7816(9)	4903(2)	30(1)
C(23)	2048(3)	6055(9)	5331(2)	27(1)
C(24)	1993(3)	6355(9)	5993(2)	27(1)
C(25)	-587(3)	8371(9)	6967(2)	28(1)
C(26)	-1330(3)	7084(11)	6612(2)	38(1)

Table 3. Bond lengths [≈] and angles [∞] for **4.240**.

F(1)-C(1)	1.331(5)
F(2)-C(1)	1.316(6)
F(3)-C(1)	1.330(6)
F(4)-C(2)	1.343(6)
F(5)-C(2)	1.343(5)
F(6)-C(3)	1.368(5)
F(7)-C(3)	1.346(5)
F(8)-C(4)	1.390(5)
O(1)-C(5)	1.433(5)
O(1)-H(1O)	0.8400
C(1)-C(2)	1.550(6)
C(2)-C(3)	1.550(6)
C(3)-C(4)	1.559(6)
C(4)-C(12)	1.508(5)
C(4)-C(5)	1.533(5)
C(5)-C(6)	1.524(5)
C(5)-H(5)	1.0000
C(6)-C(11)	1.383(6)
C(6)-C(7)	1.398(6)
C(7)-C(8)	1.391(6)
C(7)-H(7)	0.9500
C(8)-C(9)	1.387(6)
C(8)-H(8)	0.9500
C(9)-C(10)	1.384(7)
C(9)-H(9)	0.9500
C(10)-C(11)	1.390(6)
C(10)-H(10)	0.9500
C(11)-H(11)	0.9500
C(12)-C(13)	1.310(7)
C(12)-H(12)	0.9500
C(13)-H(13A)	0.9500
C(13)-H(13B)	0.9500
F(9)-C(14)	1.346(5)
F(10)-C(14)	1.319(6)

F(11)-C(14)	1.313(6)
F(12)-C(15)	1.347(5)
F(13)-C(15)	1.345(5)
F(14)-C(16)	1.346(5)
F(15)-C(16)	1.352(5)
F(16)-C(17)	1.394(5)
O(2)-C(18)	1.431(4)
O(2)-H(2O)	0.8400
C(14)-C(15)	1.539(7)
C(15)-C(16)	1.561(6)
C(16)-C(17)	1.552(6)
C(17)-C(25)	1.511(5)
C(17)-C(18)	1.548(6)
C(18)-C(19)	1.521(6)
C(18)-H(18)	1.0000
C(19)-C(24)	1.390(6)
C(19)-C(20)	1.391(6)
C(20)-C(21)	1.390(6)
C(20)-H(20)	0.9500
C(21)-C(22)	1.383(7)
C(21)-H(21)	0.9500
C(22)-C(23)	1.383(6)
C(22)-H(22)	0.9500
C(23)-C(24)	1.382(6)
C(23)-H(23)	0.9500
C(24)-H(24)	0.9500
C(25)-C(26)	1.307(7)
C(25)-H(25)	0.9500
C(26)-H(26A)	0.9500
C(26)-H(26B)	0.9500

C(5)-O(1)-H(1O)	109.5
F(2)-C(1)-F(3)	109.5(3)
F(2)-C(1)-F(1)	108.0(4)
F(3)-C(1)-F(1)	108.3(4)
F(2)-C(1)-C(2)	112.0(4)

F(3)-C(1)-C(2)	110.5(4)
F(1)-C(1)-C(2)	108.5(3)
F(5)-C(2)-F(4)	109.4(3)
F(5)-C(2)-C(1)	106.1(4)
F(4)-C(2)-C(1)	106.4(4)
F(5)-C(2)-C(3)	108.8(4)
F(4)-C(2)-C(3)	111.4(4)
C(1)-C(2)-C(3)	114.7(3)
F(7)-C(3)-F(6)	107.1(3)
F(7)-C(3)-C(2)	107.0(4)
F(6)-C(3)-C(2)	105.4(3)
F(7)-C(3)-C(4)	108.2(3)
F(6)-C(3)-C(4)	107.4(3)
C(2)-C(3)-C(4)	120.9(3)
F(8)-C(4)-C(12)	109.9(3)
F(8)-C(4)-C(5)	109.0(3)
C(12)-C(4)-C(5)	110.9(3)
F(8)-C(4)-C(3)	105.8(3)
C(12)-C(4)-C(3)	106.4(3)
C(5)-C(4)-C(3)	114.7(3)
O(1)-C(5)-C(6)	110.7(3)
O(1)-C(5)-C(4)	108.1(3)
C(6)-C(5)-C(4)	112.1(3)
O(1)-C(5)-H(5)	108.6
C(6)-C(5)-H(5)	108.6
C(4)-C(5)-H(5)	108.6
C(11)-C(6)-C(7)	119.1(4)
C(11)-C(6)-C(5)	120.4(4)
C(7)-C(6)-C(5)	120.6(4)
C(8)-C(7)-C(6)	120.1(4)
C(8)-C(7)-H(7)	119.9
C(6)-C(7)-H(7)	119.9
C(9)-C(8)-C(7)	119.9(4)
C(9)-C(8)-H(8)	120.0
C(7)-C(8)-H(8)	120.0
C(10)-C(9)-C(8)	120.3(4)

C(10)-C(9)-H(9)	119.9
C(8)-C(9)-H(9)	119.9
C(9)-C(10)-C(11)	119.5(4)
C(9)-C(10)-H(10)	120.3
C(11)-C(10)-H(10)	120.3
C(6)-C(11)-C(10)	121.1(4)
C(6)-C(11)-H(11)	119.5
C(10)-C(11)-H(11)	119.5
C(13)-C(12)-C(4)	123.8(4)
C(13)-C(12)-H(12)	118.1
C(4)-C(12)-H(12)	118.1
C(12)-C(13)-H(13A)	120.0
C(12)-C(13)-H(13B)	120.0
H(13A)-C(13)-H(13B)	120.0
C(18)-O(2)-H(2O)	109.5
F(11)-C(14)-F(10)	109.5(4)
F(11)-C(14)-F(9)	107.6(4)
F(10)-C(14)-F(9)	107.8(4)
F(11)-C(14)-C(15)	112.4(4)
F(10)-C(14)-C(15)	111.2(4)
F(9)-C(14)-C(15)	108.3(4)
F(13)-C(15)-F(12)	108.4(3)
F(13)-C(15)-C(14)	107.2(4)
F(12)-C(15)-C(14)	107.4(3)
F(13)-C(15)-C(16)	109.9(3)
F(12)-C(15)-C(16)	108.6(4)
C(14)-C(15)-C(16)	115.1(3)
F(14)-C(16)-F(15)	108.5(3)
F(14)-C(16)-C(17)	108.2(4)
F(15)-C(16)-C(17)	111.0(3)
F(14)-C(16)-C(15)	107.0(3)
F(15)-C(16)-C(15)	105.2(3)
C(17)-C(16)-C(15)	116.6(3)
F(16)-C(17)-C(25)	110.1(3)
F(16)-C(17)-C(18)	109.2(3)
C(25)-C(17)-C(18)	109.8(3)

F(16)-C(17)-C(16)	104.7(3)
C(25)-C(17)-C(16)	111.1(3)
C(18)-C(17)-C(16)	111.9(3)
O(2)-C(18)-C(19)	111.1(3)
O(2)-C(18)-C(17)	108.5(3)
C(19)-C(18)-C(17)	111.8(3)
O(2)-C(18)-H(18)	108.5
C(19)-C(18)-H(18)	108.5
C(17)-C(18)-H(18)	108.5
C(24)-C(19)-C(20)	119.2(4)
C(24)-C(19)-C(18)	120.1(4)
C(20)-C(19)-C(18)	120.7(4)
C(21)-C(20)-C(19)	120.4(4)
C(21)-C(20)-H(20)	119.8
C(19)-C(20)-H(20)	119.8
C(22)-C(21)-C(20)	119.4(4)
C(22)-C(21)-H(21)	120.3
C(20)-C(21)-H(21)	120.3
C(21)-C(22)-C(23)	120.7(4)
C(21)-C(22)-H(22)	119.7
C(23)-C(22)-H(22)	119.7
C(24)-C(23)-C(22)	119.8(4)
C(24)-C(23)-H(23)	120.1
C(22)-C(23)-H(23)	120.1
C(23)-C(24)-C(19)	120.5(4)
C(23)-C(24)-H(24)	119.8
C(19)-C(24)-H(24)	119.8
C(26)-C(25)-C(17)	124.1(4)
C(26)-C(25)-H(25)	117.9
C(17)-C(25)-H(25)	117.9
C(25)-C(26)-H(26A)	120.0
C(25)-C(26)-H(26B)	120.0
H(26A)-C(26)-H(26B)	120.0

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\approx^2$x 10^3) for **4.240**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	41(1)	99(3)	32(1)	3(2)	2(1)	10(2)
F(2)	39(1)	63(2)	40(2)	-10(1)	9(1)	13(2)
F(3)	34(1)	69(2)	50(2)	9(2)	18(1)	-2(2)
F(4)	28(1)	47(2)	38(1)	-9(1)	6(1)	-7(1)
F(5)	25(1)	53(2)	48(2)	13(1)	8(1)	14(1)
F(6)	18(1)	48(2)	40(1)	-4(1)	5(1)	11(1)
F(7)	34(1)	29(2)	49(2)	1(1)	12(1)	-6(1)
F(8)	24(1)	20(1)	42(1)	-2(1)	6(1)	1(1)
O(1)	16(1)	31(2)	28(1)	-2(1)	-3(1)	3(1)
C(1)	28(2)	57(3)	32(2)	-1(2)	6(2)	7(3)
C(2)	19(2)	35(3)	38(2)	5(2)	6(2)	5(2)
C(3)	16(2)	24(3)	40(2)	-1(2)	5(2)	4(2)
C(4)	17(2)	19(2)	32(2)	0(2)	2(2)	0(2)
C(5)	16(2)	23(2)	27(2)	-1(2)	1(1)	1(2)
C(6)	15(2)	23(2)	29(2)	-1(2)	0(2)	3(2)
C(7)	19(2)	27(2)	31(2)	-1(2)	1(2)	-1(2)
C(8)	20(2)	30(2)	37(2)	2(2)	4(2)	-2(2)
C(9)	25(2)	33(3)	32(2)	1(2)	4(2)	1(2)
C(10)	29(2)	32(3)	32(2)	-7(2)	2(2)	1(2)
C(11)	19(2)	26(2)	36(2)	-2(2)	3(2)	-1(2)
C(12)	17(2)	34(3)	34(2)	-3(2)	1(2)	2(2)
C(13)	24(2)	50(3)	37(2)	5(2)	-2(2)	7(2)
F(9)	37(1)	73(2)	44(2)	2(2)	21(1)	-1(2)
F(10)	57(2)	75(3)	36(2)	-14(2)	9(1)	-14(2)
F(11)	51(2)	68(2)	42(2)	17(2)	15(1)	18(2)
F(12)	23(1)	48(2)	47(2)	-3(1)	10(1)	12(1)
F(13)	32(1)	40(2)	40(1)	-5(1)	10(1)	-9(1)
F(14)	31(1)	35(2)	36(1)	-11(1)	5(1)	-3(1)
F(15)	21(1)	48(2)	34(1)	8(1)	4(1)	9(1)
F(16)	25(1)	22(1)	37(1)	-4(1)	8(1)	2(1)
O(2)	14(1)	29(2)	32(2)	-2(1)	-3(1)	0(1)

C(14)	30(2)	47(3)	39(3)	-5(2)	14(2)	0(2)
C(15)	21(2)	30(3)	38(2)	-4(2)	7(2)	4(2)
C(16)	15(2)	26(2)	34(2)	-4(2)	1(2)	4(2)
C(17)	16(2)	20(2)	34(2)	-3(2)	0(2)	1(2)
C(18)	15(2)	24(2)	32(2)	-1(2)	-3(2)	1(2)
C(19)	14(2)	25(2)	29(2)	0(2)	-1(2)	-2(2)
C(20)	19(2)	26(2)	34(2)	0(2)	1(2)	0(2)
C(21)	24(2)	31(2)	35(2)	8(2)	0(2)	-2(2)
C(22)	22(2)	38(3)	30(2)	2(2)	4(2)	-4(2)
C(23)	21(2)	28(2)	35(2)	0(2)	9(2)	1(2)
C(24)	16(2)	30(3)	34(2)	3(2)	1(2)	4(2)
C(25)	18(2)	30(2)	37(2)	1(2)	3(2)	6(2)
C(26)	23(2)	52(3)	39(2)	-5(2)	-4(2)	-1(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (≈^{2}x 10 ^{3}) for **4.240**.

	x	y	z	U(eq)
H(1O)	2964	4355	7390	38
H(5)	4411	5689	7888	27
H(7)	3079	177	8451	31
H(8)	2550	-367	9505	35
H(9)	3123	2510	10322	36
H(10)	4204	5964	10088	37
H(11)	4707	6535	9032	32
H(12)	6390	4576	8433	34
H(13A)	6656	-614	8538	45
H(13B)	7385	1547	8954	45
H(2O)	2909	9259	7335	38
H(18)	1345	10638	7049	29
H(20)	607	11602	5955	32
H(21)	690	11083	4833	36
H(22)	1599	7605	4448	36
H(23)	2418	4644	5171	33
H(24)	2319	5134	6287	32
H(25)	-746	10077	7060	34
H(26A)	-1197	5374	6510	46
H(26B)	-2004	7859	6456	46

Table 6. Torsion angles [∞] for **4.240**.

F(2)-C(1)-C(2)-F(5)	-168.6(4)
F(3)-C(1)-C(2)-F(5)	69.0(4)
F(1)-C(1)-C(2)-F(5)	-49.6(5)
F(2)-C(1)-C(2)-F(4)	-52.2(5)
F(3)-C(1)-C(2)-F(4)	-174.6(4)
F(1)-C(1)-C(2)-F(4)	66.9(5)
F(2)-C(1)-C(2)-C(3)	71.3(5)
F(3)-C(1)-C(2)-C(3)	-51.0(5)
F(1)-C(1)-C(2)-C(3)	-169.6(4)
F(5)-C(2)-C(3)-F(7)	-43.4(4)
F(4)-C(2)-C(3)-F(7)	-164.0(3)
C(1)-C(2)-C(3)-F(7)	75.2(5)
F(5)-C(2)-C(3)-F(6)	-157.2(3)
F(4)-C(2)-C(3)-F(6)	82.2(4)
C(1)-C(2)-C(3)-F(6)	-38.7(5)
F(5)-C(2)-C(3)-C(4)	81.0(5)
F(4)-C(2)-C(3)-C(4)	-39.6(5)
C(1)-C(2)-C(3)-C(4)	-160.5(4)
F(7)-C(3)-C(4)-F(8)	-173.9(3)
F(6)-C(3)-C(4)-F(8)	-58.5(4)
C(2)-C(3)-C(4)-F(8)	62.3(5)
F(7)-C(3)-C(4)-C(12)	-57.0(4)
F(6)-C(3)-C(4)-C(12)	58.3(4)
C(2)-C(3)-C(4)-C(12)	179.2(4)
F(7)-C(3)-C(4)-C(5)	65.9(4)
F(6)-C(3)-C(4)-C(5)	-178.7(3)
C(2)-C(3)-C(4)-C(5)	-57.9(5)
F(8)-C(4)-C(5)-O(1)	-53.9(4)
C(12)-C(4)-C(5)-O(1)	-175.0(3)
C(3)-C(4)-C(5)-O(1)	64.5(4)
F(8)-C(4)-C(5)-C(6)	68.3(4)
C(12)-C(4)-C(5)-C(6)	-52.7(5)
C(3)-C(4)-C(5)-C(6)	-173.2(3)
O(1)-C(5)-C(6)-C(11)	-142.8(4)

C(4)-C(5)-C(6)-C(11)	96.5(5)
O(1)-C(5)-C(6)-C(7)	36.5(5)
C(4)-C(5)-C(6)-C(7)	-84.3(4)
C(11)-C(6)-C(7)-C(8)	0.8(6)
C(5)-C(6)-C(7)-C(8)	-178.4(4)
C(6)-C(7)-C(8)-C(9)	-0.9(6)
C(7)-C(8)-C(9)-C(10)	0.4(6)
C(8)-C(9)-C(10)-C(11)	0.2(6)
C(7)-C(6)-C(11)-C(10)	-0.3(6)
C(5)-C(6)-C(11)-C(10)	178.9(4)
C(9)-C(10)-C(11)-C(6)	-0.2(6)
F(8)-C(4)-C(12)-C(13)	10.2(6)
C(5)-C(4)-C(12)-C(13)	130.8(5)
C(3)-C(4)-C(12)-C(13)	-103.9(5)
F(11)-C(14)-C(15)-F(13)	50.0(5)
F(10)-C(14)-C(15)-F(13)	173.1(3)
F(9)-C(14)-C(15)-F(13)	-68.7(5)
F(11)-C(14)-C(15)-F(12)	166.3(4)
F(10)-C(14)-C(15)-F(12)	-70.6(5)
F(9)-C(14)-C(15)-F(12)	47.7(5)
F(11)-C(14)-C(15)-C(16)	-72.6(5)
F(10)-C(14)-C(15)-C(16)	50.5(5)
F(9)-C(14)-C(15)-C(16)	168.7(4)
F(13)-C(15)-C(16)-F(14)	165.9(3)
F(12)-C(15)-C(16)-F(14)	47.5(4)
C(14)-C(15)-C(16)-F(14)	-73.0(5)
F(13)-C(15)-C(16)-F(15)	-78.8(4)
F(12)-C(15)-C(16)-F(15)	162.8(3)
C(14)-C(15)-C(16)-F(15)	42.3(5)
F(13)-C(15)-C(16)-C(17)	44.6(5)
F(12)-C(15)-C(16)-C(17)	-73.8(5)
C(14)-C(15)-C(16)-C(17)	165.7(4)
F(14)-C(16)-C(17)-F(16)	165.1(3)
F(15)-C(16)-C(17)-F(16)	46.1(4)
C(15)-C(16)-C(17)-F(16)	-74.2(4)
F(14)-C(16)-C(17)-C(25)	-76.0(4)

F(15)-C(16)-C(17)-C(25)	165.0(4)
C(15)-C(16)-C(17)-C(25)	44.6(5)
F(14)-C(16)-C(17)-C(18)	47.0(4)
F(15)-C(16)-C(17)-C(18)	-72.0(5)
C(15)-C(16)-C(17)-C(18)	167.7(3)
F(16)-C(17)-C(18)-O(2)	-67.9(4)
C(25)-C(17)-C(18)-O(2)	171.3(3)
C(16)-C(17)-C(18)-O(2)	47.5(4)
F(16)-C(17)-C(18)-C(19)	54.9(4)
C(25)-C(17)-C(18)-C(19)	-65.9(4)
C(16)-C(17)-C(18)-C(19)	170.3(3)
O(2)-C(18)-C(19)-C(24)	36.7(5)
C(17)-C(18)-C(19)-C(24)	-84.6(4)
O(2)-C(18)-C(19)-C(20)	-141.3(4)
C(17)-C(18)-C(19)-C(20)	97.3(5)
C(24)-C(19)-C(20)-C(21)	-0.5(6)
C(18)-C(19)-C(20)-C(21)	177.6(4)
C(19)-C(20)-C(21)-C(22)	0.0(6)
C(20)-C(21)-C(22)-C(23)	0.2(6)
C(21)-C(22)-C(23)-C(24)	0.2(6)
C(22)-C(23)-C(24)-C(19)	-0.8(6)
C(20)-C(19)-C(24)-C(23)	0.9(6)
C(18)-C(19)-C(24)-C(23)	-177.2(4)
F(16)-C(17)-C(25)-C(26)	-1.5(6)
C(18)-C(17)-C(25)-C(26)	118.7(5)
C(16)-C(17)-C(25)-C(26)	-117.0(5)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **4.240** [≈ and ∞].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...O(2)	0.84	2.05	2.846(4)	158.7
O(2)-H(2O)...O(1)#1	0.84	2.14	2.932(4)	156.1

Symmetry transformations used to generate equivalent atoms:

#1 x,y+1,z

4.6.13 Coordinates for Calculated 1,3-Boryl Shift Transition States

DFT calculations were performed with the Gaussian 09 suite of programs[15] employing the dispersion corrected ωB97XD[16] functional. The DEF2SVP[17] basis set and SMD[18] solvation model (toluene) was used for geometry optimization and frequency calculation. The nature of all stationary points was checked through vibrational analysis. Single point electronic energy (ΔE_{sp}) calculations applying the ωB97XD functional and the DEF2TZVPP basis set in solution with thew SMD solvation model were performed on the geometries obtained with the DEF2SVP basis set. The single point electronic energies (ΔE_{sp}) at the DEF2TZVPP level were corrected by addition of thermal corrections to the Gibbs free energy (ΔG_{corr}) obtained at the corresponding DEF2SVP level.

Structure	E [Hartree]	ΔE [kcal/mol]	G [Hartree]	ΔG [kcal/mol]	ΔG_{corr} [kcal/mol]	Freq cm^{-1}
4.312	-1578.775582	0.00	-1578.867852	0.00	0.00	-360.4541
4.314	-1578.76964	3.73	-1578.8604520	4.64	1.72	-232.4271
4.316	-1578.772677	1.82	-1578.8622340	3.52	2.44	-337.1785
4.317	-1578.850695	9.09	-1578.8506950	10.77	2.08	-323.1222

Structure	E_{sp} [Hartree]	ΔE_{sp} [kcal/mol]	ΔG_{sp} [kcal/mol]
4.312	-1581.1122897	0.00	0.00
4.314	-1581.107638	2.92	4.64

[15] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayshi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyenger, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts. R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, **2009**.

[16] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.

[17] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.

[18] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

4.316	-1581.110556	1.09	3.52
4.317	-1581.098445	8.69	10.77

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ZCF3_alkene_front_TS_wb97xd.log
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charge= 1    multiplicity= 1
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 Cartesian coordinates (Angstroms):
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C    -0.967    -1.926    -2.525
C    -2.140    -2.656    -2.424
C    -2.987    -2.459    -1.335
C    -2.717    -1.528    -0.325
C    -1.543    -0.763    -0.488
C    -0.663    -0.972    -1.553
H    -3.888    -3.067    -1.272
H    -2.394    -3.398    -3.183
H    -0.275    -2.090    -3.354
O    -1.212     0.155     0.473
C     0.596    -0.170    -1.699
C     2.286    -0.341     0.348
B    -0.050     0.920     0.438
C    -0.388     2.620    -0.140
F     0.291     3.074    -1.216
C    -1.865     2.967    -0.249
C     0.367     2.565     1.049
C     3.564    -0.059    -0.468
O     3.500    -0.136    -1.689
N     4.719     0.241     0.166
C     4.898     0.612     1.557
H     5.477    -0.150     2.101
H     3.945     0.752     2.075
H     5.448     1.564     1.609
C     5.922     0.323    -0.651
H     6.791     0.067    -0.030
H     6.062     1.336    -1.061
H     5.856    -0.381    -1.488
N     1.158     0.377    -0.400
H     1.393    -0.726    -2.199
H     0.400     0.726    -2.308
H     1.638     1.214    -0.742
C     2.116    -1.851     0.713
C     3.305    -2.220     1.621
H     3.183    -3.258     1.960
H     3.349    -1.587     2.521
H     4.269    -2.158     1.097
C     0.832    -2.061     1.526
H     0.837    -3.069     1.965
H    -0.070    -1.993     0.909
H     0.748    -1.342     2.356
C     2.130    -2.791    -0.498
H     2.316     0.192     1.305
C    -3.632    -1.393     0.906
C    -4.817    -2.367     0.838
H    -5.467    -2.168    -0.028
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H    -5.433    -2.246     1.742
H    -4.496    -3.419     0.800
C    -4.210     0.029     0.994
H    -4.747     0.296     0.071
H    -3.431     0.778     1.163
H    -4.926     0.093     1.828
C    -2.832    -1.720     2.182
H    -1.999    -1.022     2.333
H    -2.423    -2.742     2.141
H    -3.489    -1.658     3.064
C     0.099     1.625     2.056
H     1.422     2.839     0.902
H    -0.919     1.439     2.409
H     0.901     1.418     2.765
H     1.221    -2.707    -1.106
H     2.173    -3.830    -0.140
H     3.003    -2.623    -1.144
F    -2.490     2.201    -1.132
F    -1.987     4.228    -0.641
F    -2.457     2.836     0.934
YYY
                     1                     2                     3
                     A                     A                     A
 Frequencies --   -360.4541              31.6110               39.6940
 Red. masses --      8.4704               4.7868                4.1167
 Zero-point correction=                          0.558887 (Hartree/Particle)
 Thermal correction to Energy=                   0.590899
 Thermal correction to Enthalpy=                 0.591843
 Thermal correction to Gibbs Free Energy=        0.498529
 Sum of electronic and zero-point Energies=          -1578.807594
 Sum of electronic and thermal Energies=             -1578.775582
 Sum of electronic and thermal Enthalpies=           -1578.774638
 Sum of electronic and thermal Free Energies=        -1578.867952

         Item               Value     Threshold  Converged?
 Maximum Force            0.000001     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1579.36648127', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 312.83193279 kcal/mol
H_corr: 371.38740093 kcal/mol
S_corr: 58.5554674 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.19283935 kcal/mol
S_rot: 10.8103227 kcal/mol
S_vib: 34.55230535 kcal/mol
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redo_ECF3_alkene_front_TS.log
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charge= 1    multiplicity= 1
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 Cartesian coordinates (Angstroms):
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XXX
66

C    -0.743    -1.426    -2.665
C    -1.884    -2.200    -2.804
C    -2.813    -2.262    -1.765
C    -2.655    -1.551    -0.571
C    -1.501    -0.744    -0.478
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C    -0.540    -0.694    -1.494
H    -3.691    -2.891    -1.902
H    -2.055    -2.769    -3.719
H     0.003    -1.389    -3.463
O    -1.300    -0.013     0.658
C     0.701     0.151    -1.368
C     2.209    -0.339     0.651
B    -0.237     0.869     0.772
C    -0.495     2.569     0.469
F     0.691     3.173     0.194
C    -1.587     3.129    -0.416
C    -0.755     2.197     1.830
C     3.460     0.316    -0.073
O     3.284     1.523    -0.275
N     4.661    -0.223    -0.343
C     5.072    -1.606    -0.537
H     4.285    -2.321    -0.320
H     5.937    -1.832     0.105
H     5.375    -1.742    -1.586
C     5.684     0.729    -0.779
H     5.567     0.970    -1.847
H     6.670     0.276    -0.622
H     5.613     1.660    -0.206
N     1.084     0.488     0.048
H     1.556    -0.344    -1.844
H     0.564     1.114    -1.882
H     1.655     1.370    -0.068
C     2.008    -1.853     0.898
C     3.139    -2.264     1.877
H     3.265    -3.356     1.880
H     2.868    -1.964     2.901
H     4.117    -1.812     1.678
C     0.708    -2.111     1.679
H     0.728    -3.141     2.066
H    -0.186    -2.023     1.058
H     0.606    -1.440     2.546
C     1.939    -2.703    -0.387
H     2.329     0.086     1.660
C    -3.685    -1.640     0.570
C    -4.818    -2.616     0.226
H    -5.381    -2.303    -0.666
H    -5.531    -2.654     1.063
H    -4.449    -3.640     0.062
C    -4.318    -0.258     0.816
H    -4.804     0.120    -0.096
H    -3.576     0.483     1.135
H    -5.086    -0.331     1.602
C    -3.011    -2.152     1.858
H    -2.245    -1.459     2.228
H    -2.540    -3.134     1.696
H    -3.766    -2.271     2.651
H    -1.808     2.036     2.085
C     0.209     1.481     2.514
H     0.922    -2.698    -0.799
H     2.189    -3.751    -0.167
H     2.605    -2.361    -1.190
F    -1.285     2.938    -1.698
F    -1.744     4.435    -0.225
F    -2.746     2.527    -0.162
H    -0.083     0.920     3.404
H     1.268     1.728     2.400
YYY
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                     A                    A                    A
 Frequencies --   -232.4271             26.7379              39.1465
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 Thermal correction to Energy=                   0.591594
 Thermal correction to Enthalpy=                 0.592539
 Thermal correction to Gibbs Free Energy=        0.500783
 Sum of electronic and zero-point Energies=          -1578.801050
 Sum of electronic and thermal Energies=             -1578.769640
 Sum of electronic and thermal Enthalpies=           -1578.768696
 Sum of electronic and thermal Free Energies=        -1578.860452

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MP2: no data
Temperature: 298.15
G_corr: 314.24634033 kcal/mol
H_corr: 371.82414789 kcal/mol
S_corr: 57.5775354 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.19283935 kcal/mol
S_rot: 10.8103227 kcal/mol
S_vib: 33.57437335 kcal/mol
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new_ECF3_TS_wb97xd.log
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charge= 1    multiplicity= 1
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 Cartesian coordinates (Angstroms):
----------------------------------------
XXX
66

C     2.466     3.204    -0.062
C     3.789     3.095     0.336
C     4.351     1.835     0.546
C     3.633     0.649     0.366
C     2.292     0.796    -0.046
C     1.707     2.048    -0.259
H     5.391     1.785     0.867
H     4.389     3.992     0.497
H     2.010     4.186    -0.214
O     1.522    -0.320    -0.212
C     0.265     2.180    -0.689
H    -0.399     0.882     0.778
B     0.289    -0.220    -0.849
C    -0.133    -2.031    -1.027
C    -0.387    -1.217    -2.145
F     1.032    -2.666    -0.886
C    -1.233    -2.826    -0.349
N    -0.534     0.984    -0.264
H    -0.152     3.072    -0.222
H     0.173     2.292    -1.776
C    -2.049     0.996    -0.278
C     4.268    -0.735     0.588
C     5.726    -0.614     1.053
H     6.358    -0.100     0.314
H     6.146    -1.621     1.197
H     5.813    -0.084     2.014
C     4.262    -1.519    -0.738
H     4.816    -0.975    -1.519
H     3.244    -1.711    -1.097
```

```
H     4.753    -2.496    -0.599
C     3.494    -1.511     1.671
H     2.456    -1.713     1.378
H     3.484    -0.955     2.621
H     3.985    -2.480     1.855
F    -2.431    -2.428    -0.787
F    -1.102    -4.114    -0.621
F    -1.202    -2.674     0.970
C     0.540    -0.281    -2.620
H     0.162     0.482    -3.301
H     1.604    -0.522    -2.693
H    -1.449    -1.007    -2.306
C    -2.750     2.408    -0.288
C    -2.444     3.172    -1.594
C    -2.416     3.241     0.962
C    -4.277     2.207    -0.280
H    -1.488     3.705    -1.598
H    -3.219     3.937    -1.751
H    -2.474     2.504    -2.469
H    -1.344     3.383     1.153
H    -2.841     2.786     1.868
H    -2.862     4.241     0.855
H    -4.631     1.660    -1.166
H    -4.755     3.197    -0.300
H    -4.633     1.702     0.626
C    -2.358     0.224     1.043
O    -1.505     0.335     1.927
H    -2.393     0.451    -1.165
N    -3.481    -0.487     1.215
C    -4.480    -0.821     0.216
C    -3.716    -1.102     2.515
H    -3.036    -0.676     3.258
H    -3.546    -2.188     2.456
H    -4.758    -0.921     2.818
H    -4.634    -1.908     0.216
H    -4.176    -0.520    -0.789
H    -5.440    -0.337     0.450
YYY
                     1                     2                     3
                     A                     A                     A
 Frequencies --   -337.1785              27.7250              33.5212
 Red. masses --      8.5050               4.7437               3.8180
 Zero-point correction=                          0.561758 (Hartree/Particle)
 Thermal correction to Energy=                   0.592620
 Thermal correction to Enthalpy=                 0.593564
 Thermal correction to Gibbs Free Energy=        0.503063
 Sum of electronic and zero-point Energies=          -1578.803539
 Sum of electronic and thermal Energies=             -1578.772677
 Sum of electronic and thermal Enthalpies=           -1578.771733
 Sum of electronic and thermal Free Energies=        -1578.862234

         Item               Value     Threshold  Converged?
 Maximum Force            0.000000     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1579.36529703', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 315.67706313 kcal/mol
H_corr: 372.46734564 kcal/mol
S_corr: 56.7904194 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.19283935 kcal/mol
S_rot: 10.8061486 kcal/mol
S_vib: 32.7911333 kcal/mol
----------------------------------------
```

ZCF3_TS_wb97xd.log

#P Geom=AllCheck Guess=TCheck SCRF=Check GenChk RwB97XD/def2SVP Freq

charge= 1 multiplicity= 1

 Cartesian coordinates (Angstroms):

XXX
66

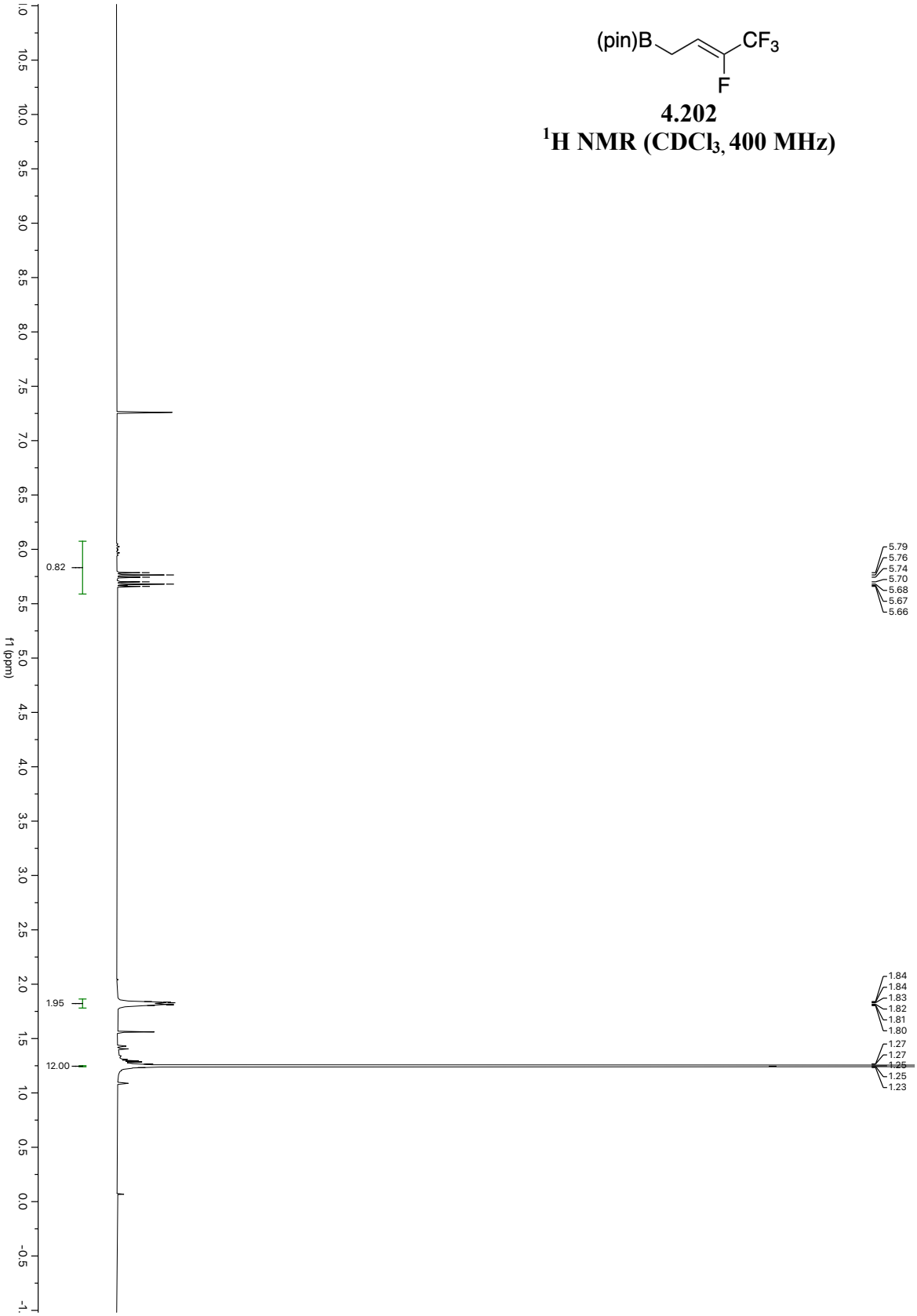
C	-1.666	-2.982	-1.218
C	-2.949	-3.293	-0.796
C	-3.775	-2.293	-0.282
C	-3.367	-0.959	-0.178
C	-2.063	-0.675	-0.631
C	-1.215	-1.665	-1.134
H	-4.774	-2.573	0.049
H	-3.315	-4.320	-0.857
H	-1.002	-3.758	-1.605
O	-1.599	0.604	-0.560
C	0.164	-1.299	-1.605
C	1.697	-0.490	0.277
B	-0.312	0.987	-0.918
C	0.205	2.647	-0.003
C	-0.458	2.743	-1.227
F	-0.482	3.010	1.084
C	1.682	2.954	0.193
C	2.964	-1.000	-0.527
O	3.095	-0.410	-1.609
N	3.931	-1.837	-0.121
C	3.910	-2.903	0.868
H	2.963	-2.974	1.394
H	4.715	-2.756	1.604
H	4.083	-3.862	0.355
C	5.125	-1.861	-0.966
H	4.951	-2.444	-1.884
H	5.943	-2.321	-0.399
H	5.409	-0.842	-1.253
N	0.779	-0.127	-0.879
H	0.848	-2.153	-1.514
H	0.147	-1.015	-2.669
H	1.563	0.148	-1.528
C	1.119	-1.131	1.561
C	2.201	-0.914	2.651
H	1.975	-1.528	3.534
H	2.196	0.138	2.971
H	3.227	-1.137	2.339
C	-0.092	-0.323	2.061
H	-0.326	-0.639	3.088
H	-0.991	-0.495	1.465
H	0.113	0.756	2.093
C	0.672	-2.602	1.405
H	2.077	0.477	0.623
C	-4.287	0.137	0.389
C	-5.642	-0.437	0.824
H	-6.190	-0.891	-0.015
H	-6.269	0.375	1.223
H	-5.539	-1.190	1.620
C	-4.558	1.198	-0.695
H	-5.032	0.743	-1.579
H	-3.638	1.699	-1.022
H	-5.243	1.968	-0.306
C	-3.641	0.793	1.625

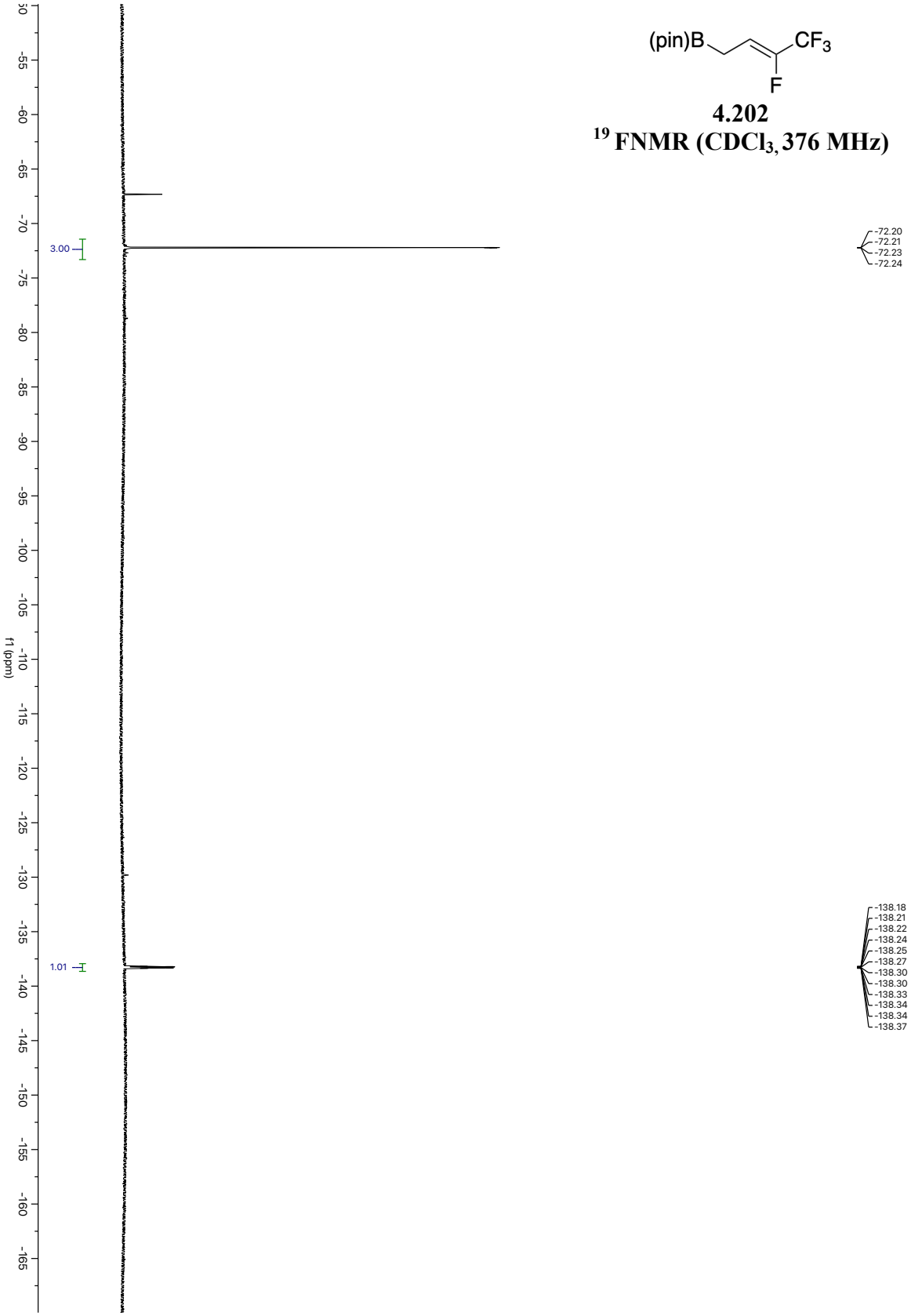
```
H    -2.701     1.305     1.386
H    -3.436     0.044     2.406
H    -4.329     1.538     2.052
F     2.422     2.416    -0.777
F     1.871     4.266     0.179
F     2.122     2.496     1.363
C    -0.099     1.934    -2.339
H    -0.398    -2.662     1.170
H     0.825    -3.156     2.343
H     1.198    -3.144     0.606
H     0.949     1.873    -2.650
H    -0.836     1.883    -3.142
H    -1.516     3.015    -1.125
YYY
                     1                     2                     3
                     A                     A                     A
 Frequencies --   -323.1222              27.3176              49.0144
 Red. masses --      9.0379               3.6607               5.2402
 Zero-point correction=                          0.560580 (Hartree/Particle)
 Thermal correction to Energy=                   0.591715
 Thermal correction to Enthalpy=                 0.592659
 Thermal correction to Gibbs Free Energy=        0.502110
 Sum of electronic and zero-point Energies=          -1578.792225
 Sum of electronic and thermal Energies=             -1578.761090
 Sum of electronic and thermal Enthalpies=           -1578.760146
 Sum of electronic and thermal Free Energies=        -1578.850695

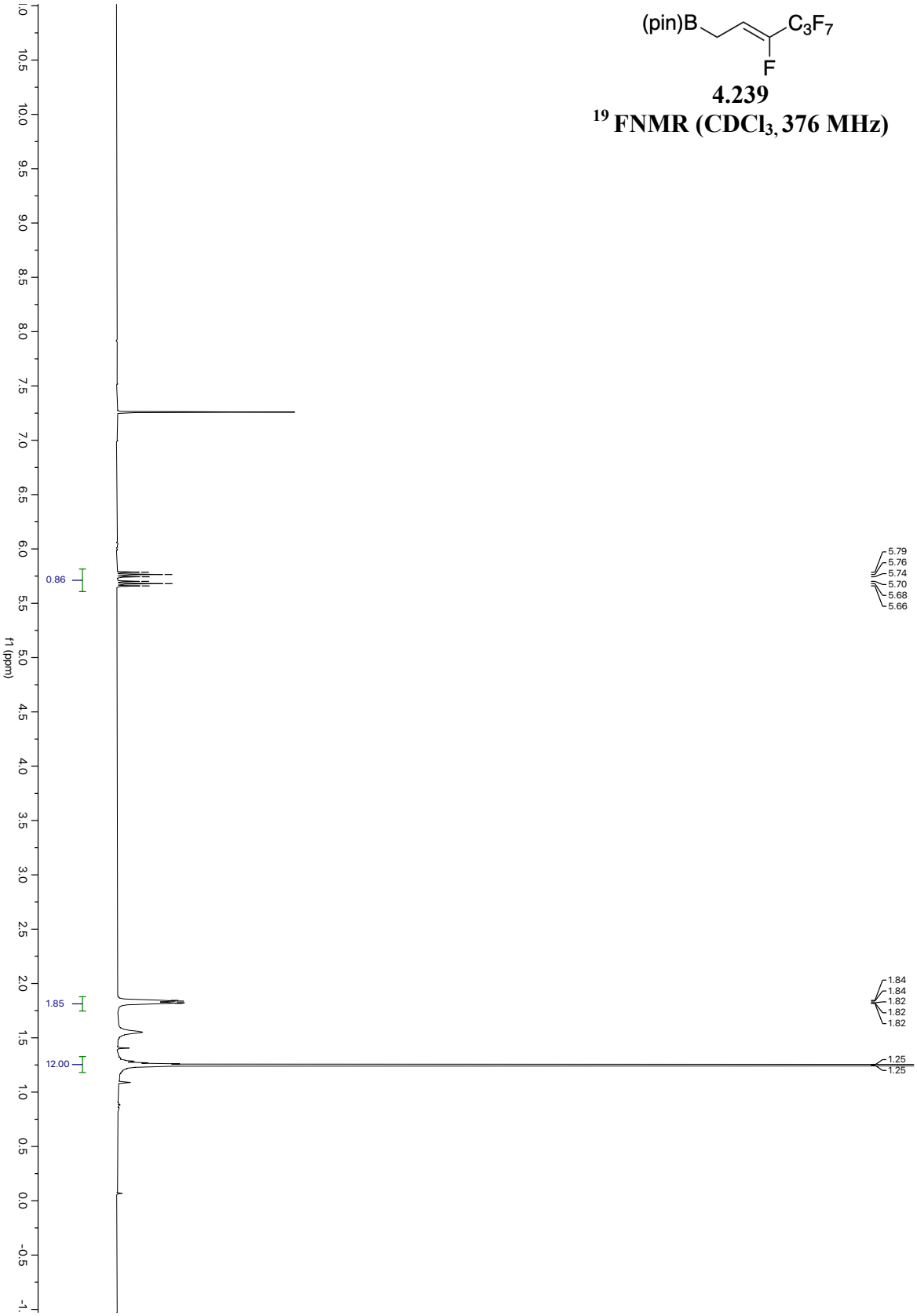
         Item               Value     Threshold  Converged?
 Maximum Force            0.000001     0.000015     YES
 RMS     Force            0.000000     0.000010     YES
SCF: ['SCF', 'Done:', 'E(RwB97XD)', '=', '-1579.35280468', 'A.U.', 'after', '1', 'cycles']
MP2: no data
Temperature: 298.15
G_corr: 315.0790461 kcal/mol
H_corr: 371.89944909 kcal/mol
S_corr: 56.82053255 kcal/mol
S_elec: 0.0 kcal/mol
S_trans: 13.19283935 kcal/mol
S_rot: 10.79303 kcal/mol
S_vib: 32.83436505 kcal/mol
```

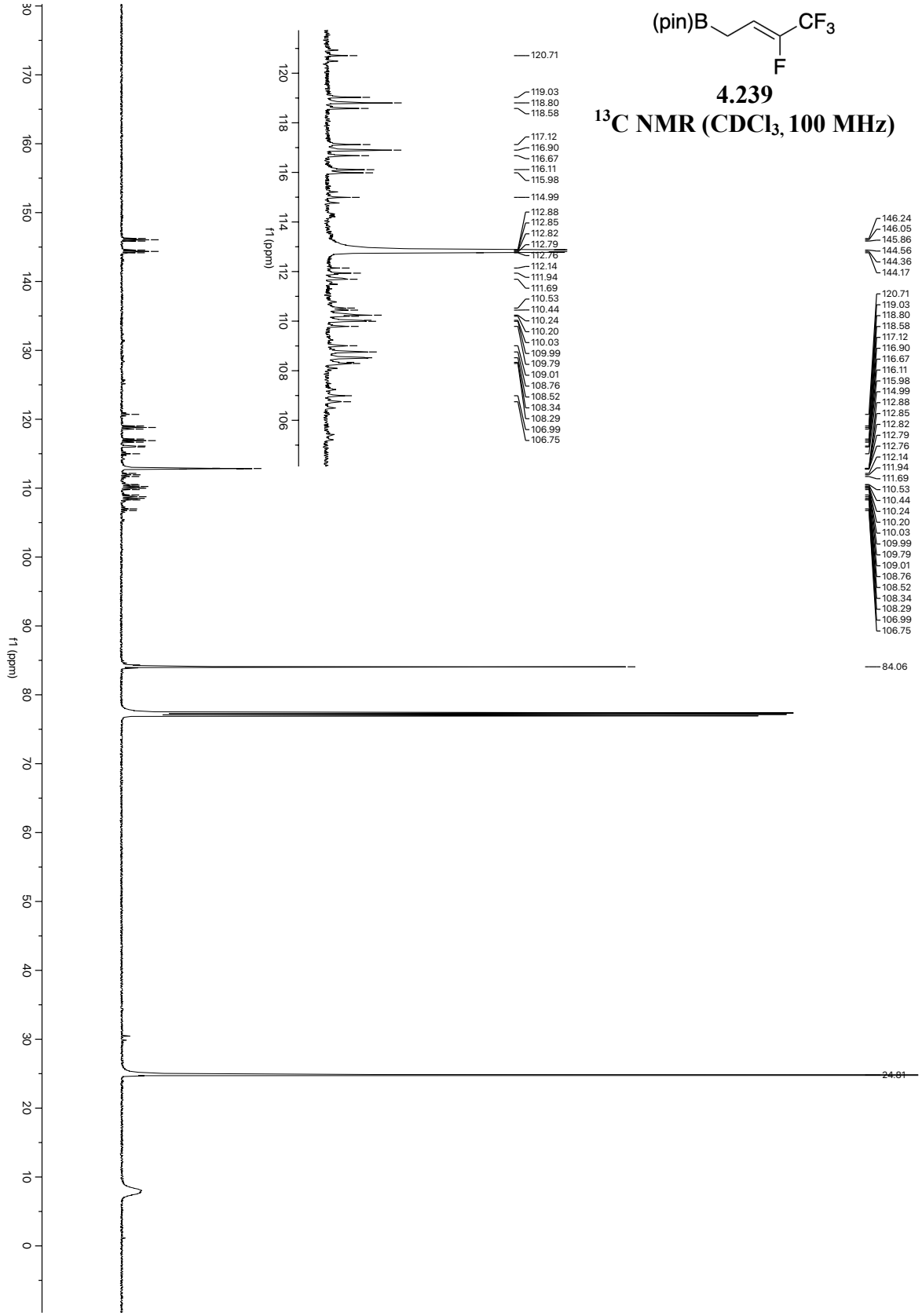
4.6.14 NMR Spectra

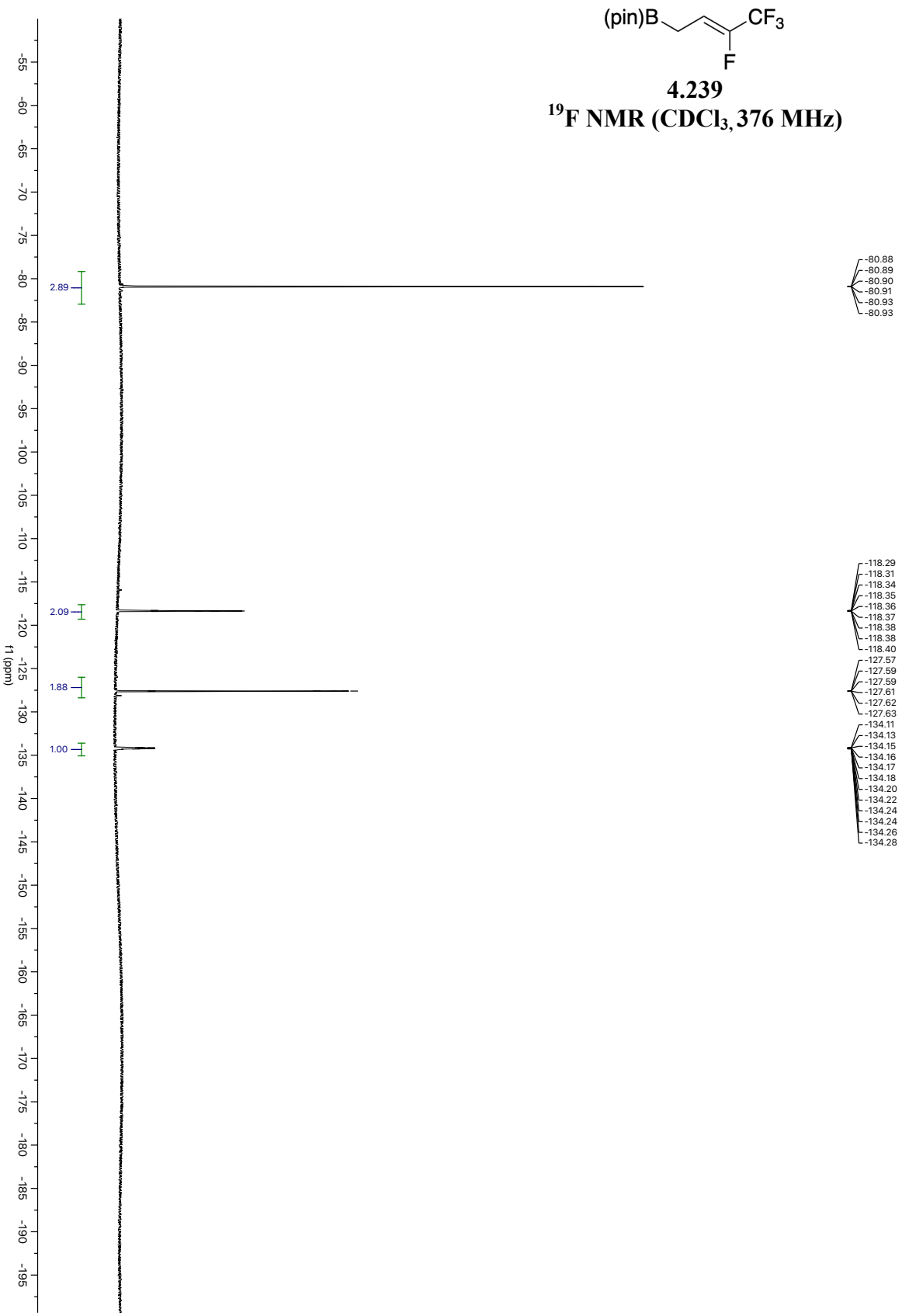
(Appear on the following pages)

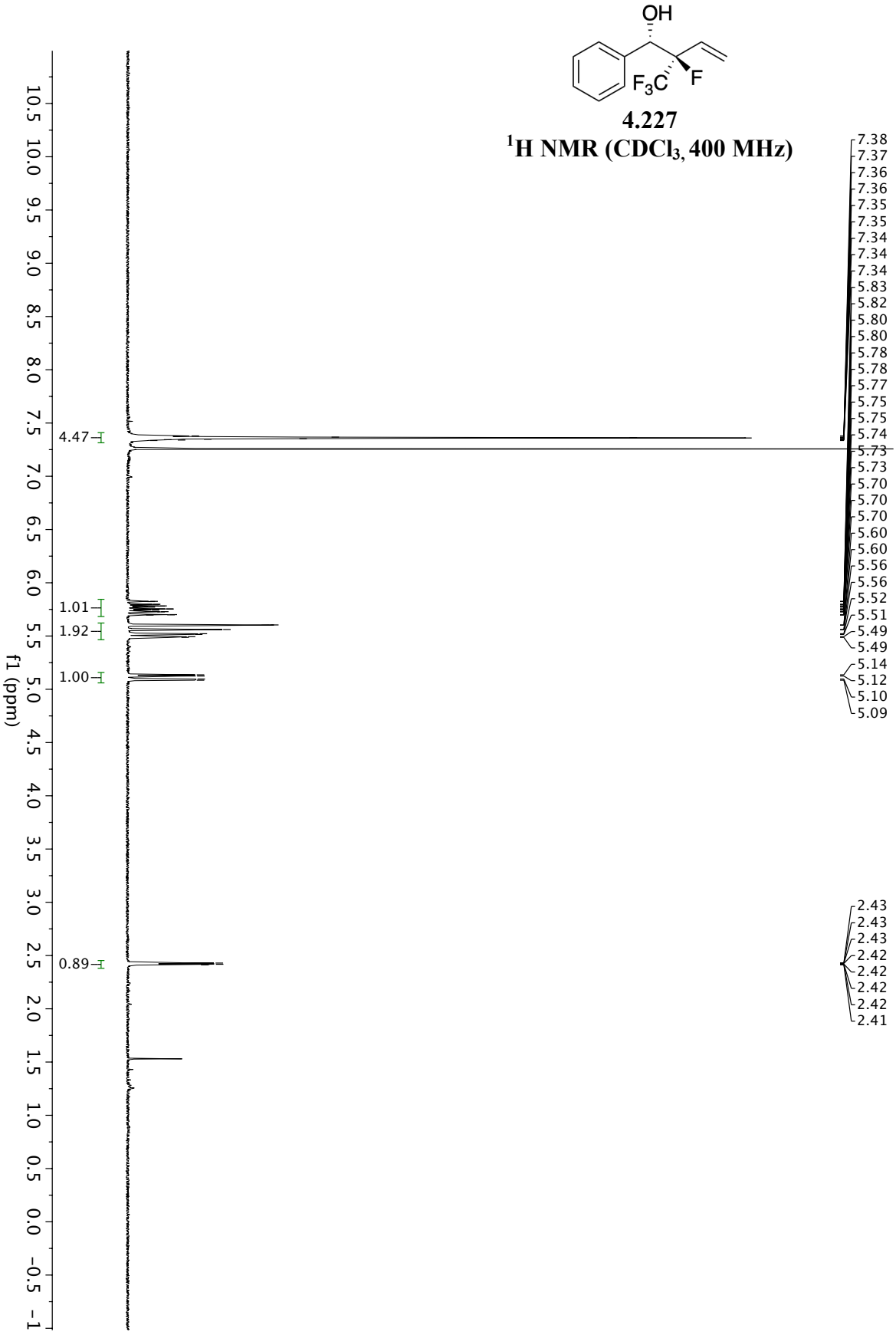

(pin)B
CF3
F
4.202
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.82
1.95
12.00
5.79
5.76
5.74
5.70
5.68
5.67
5.66
1.84
1.84
1.83
1.82
1.81
1.80
1.27
1.27
1.25
1.25
1.23

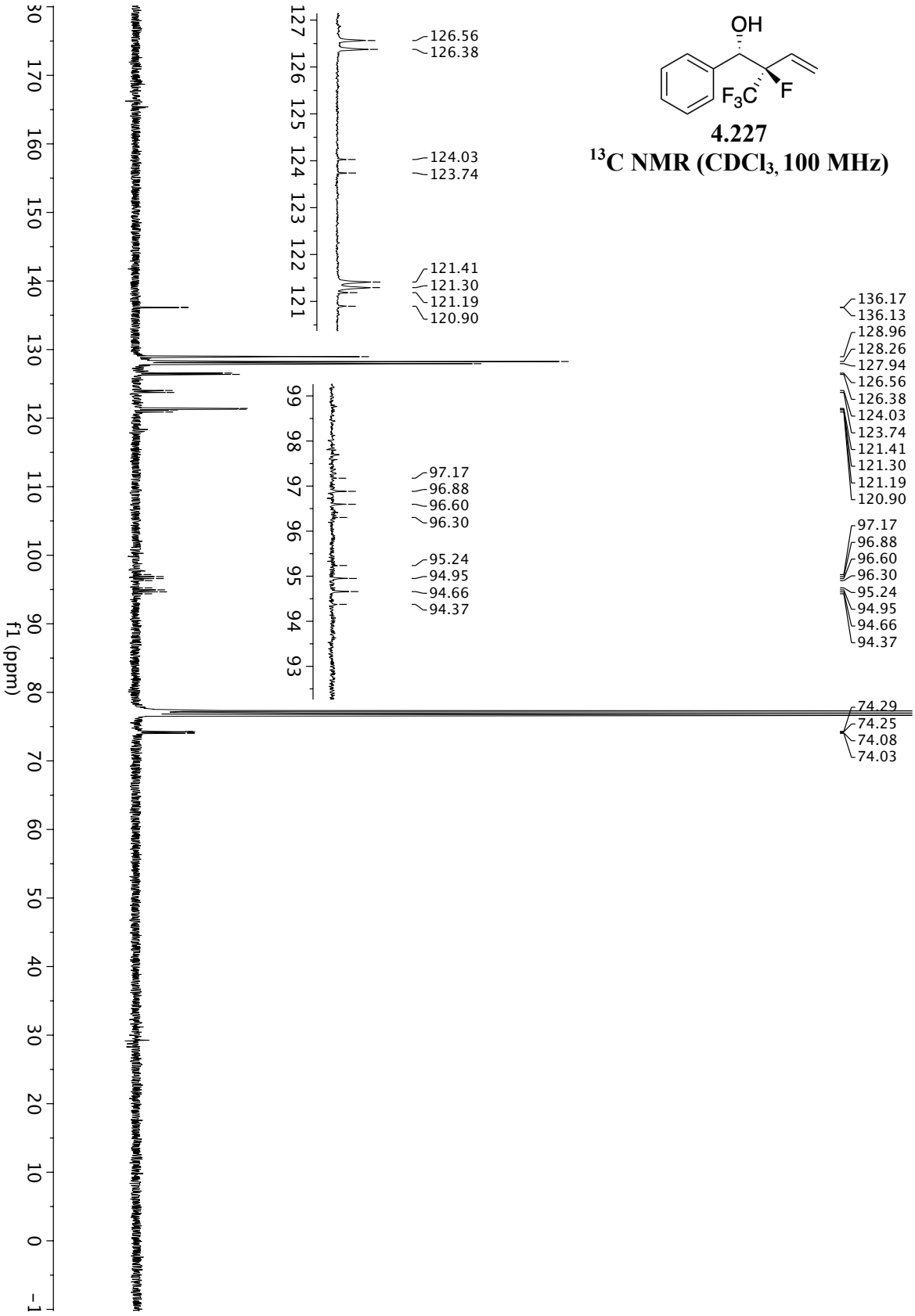

(pin)B
CF3
F
4.202
19 FNMR (CDCl3, 376 MHz)
3.00
1.01
-72.20
-72.21
-72.23
-72.24
-138.18
-138.21
-138.22
-138.24
-138.25
-138.27
-138.30
-138.30
-138.33
-138.34
-138.34
-138.37
f1 (ppm)

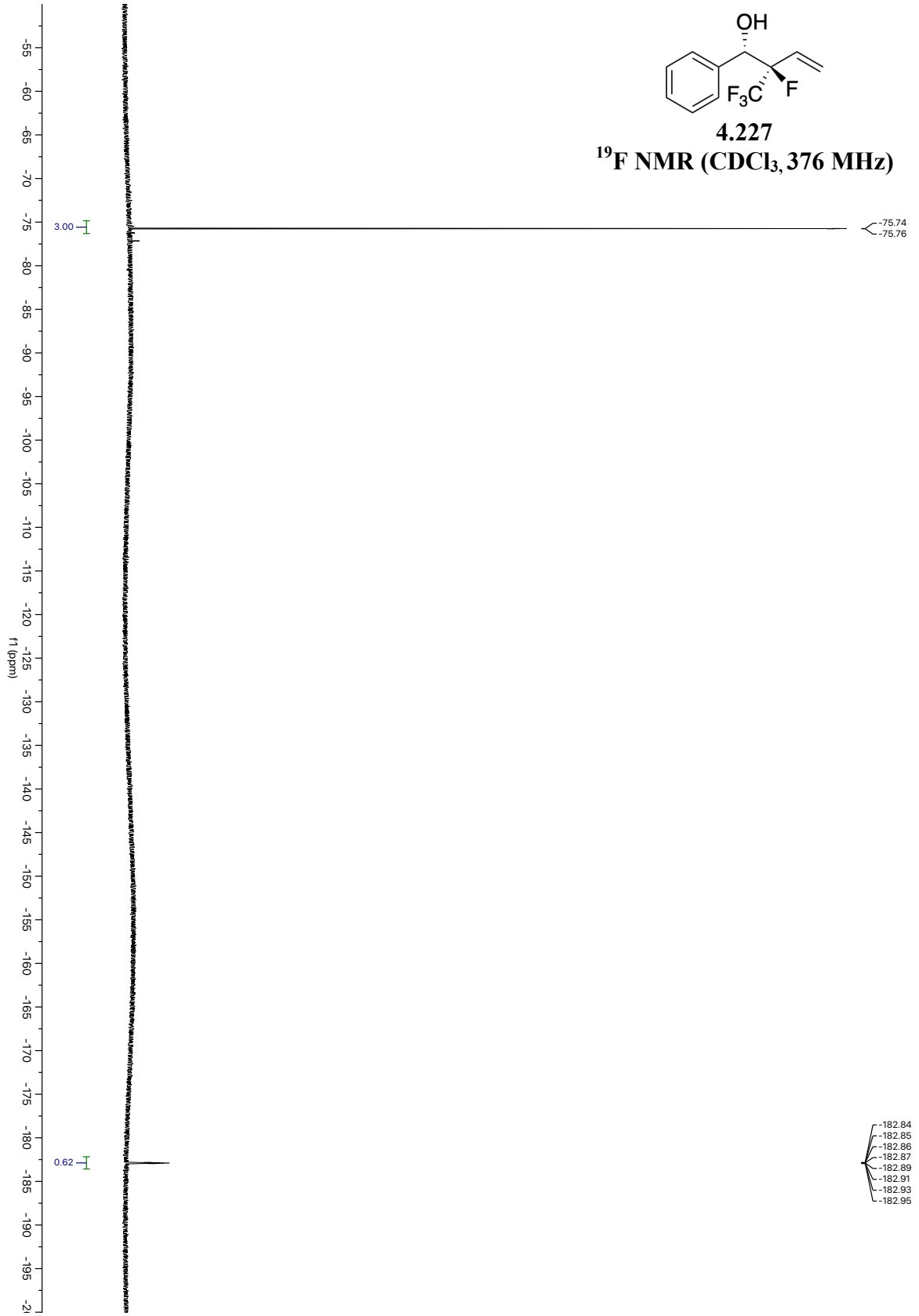

(pin)B
C3F7
F
4.239
19 FNMR (CDCl3, 376 MHz)
f1 (ppm)
0.86
1.85
12.00
5.79
5.76
5.74
5.70
5.68
5.66
1.84
1.84
1.82
1.82
1.82
1.25
1.25

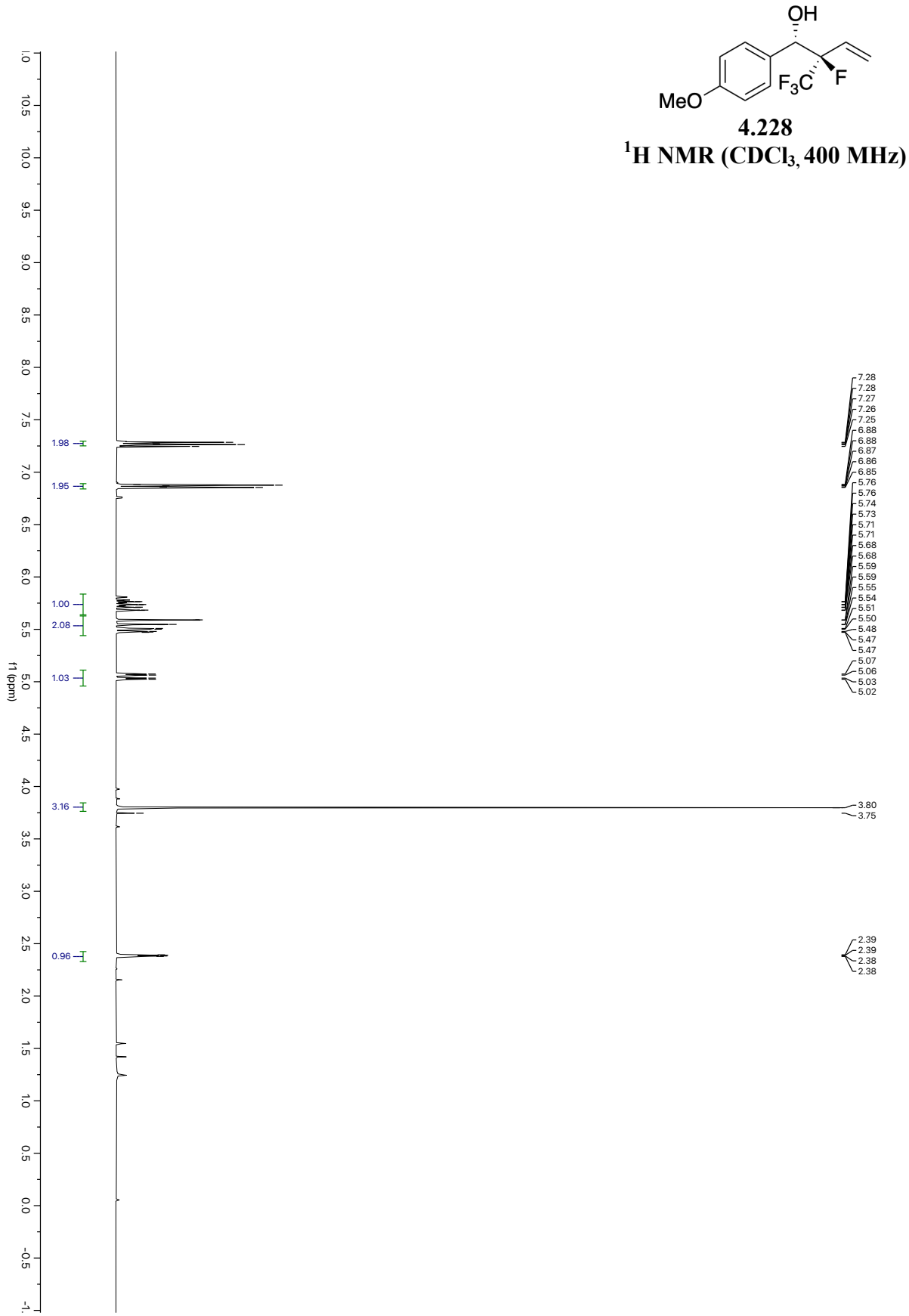

(pin)B
CF3
F
4.239
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
120.71
119.03
118.80
118.58
117.12
116.90
116.67
116.11
115.98
114.99
112.88
112.85
112.82
112.79
112.76
112.14
111.94
111.69
110.53
110.44
110.24
110.20
110.03
109.99
109.79
109.01
108.76
108.52
108.34
108.29
106.99
106.75
146.24
146.05
145.86
144.56
144.36
144.17
84.06
24.81

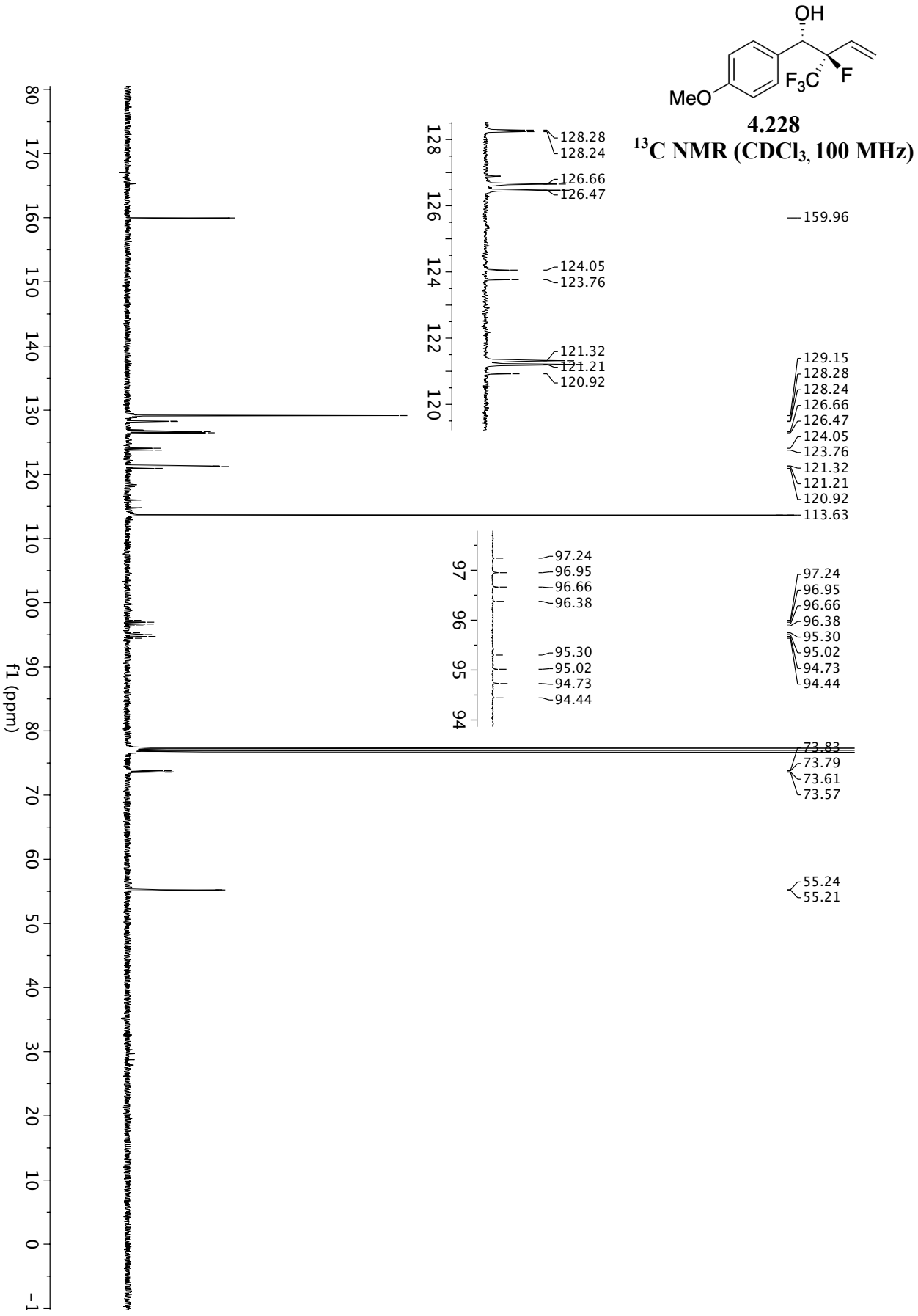

(pin)B
CF3
F
4.239
19F NMR (CDCl3, 376 MHz)
f1 (ppm)
2.89
2.09
1.88
1.00
-80.88
-80.89
-80.90
-80.91
-80.93
-80.93
-118.29
-118.31
-118.34
-118.35
-118.36
-118.37
-118.38
-118.38
-118.40
-127.57
-127.59
-127.59
-127.61
-127.62
-127.63
-134.11
-134.13
-134.15
-134.16
-134.17
-134.18
-134.20
-134.22
-134.24
-134.24
-134.26
-134.28

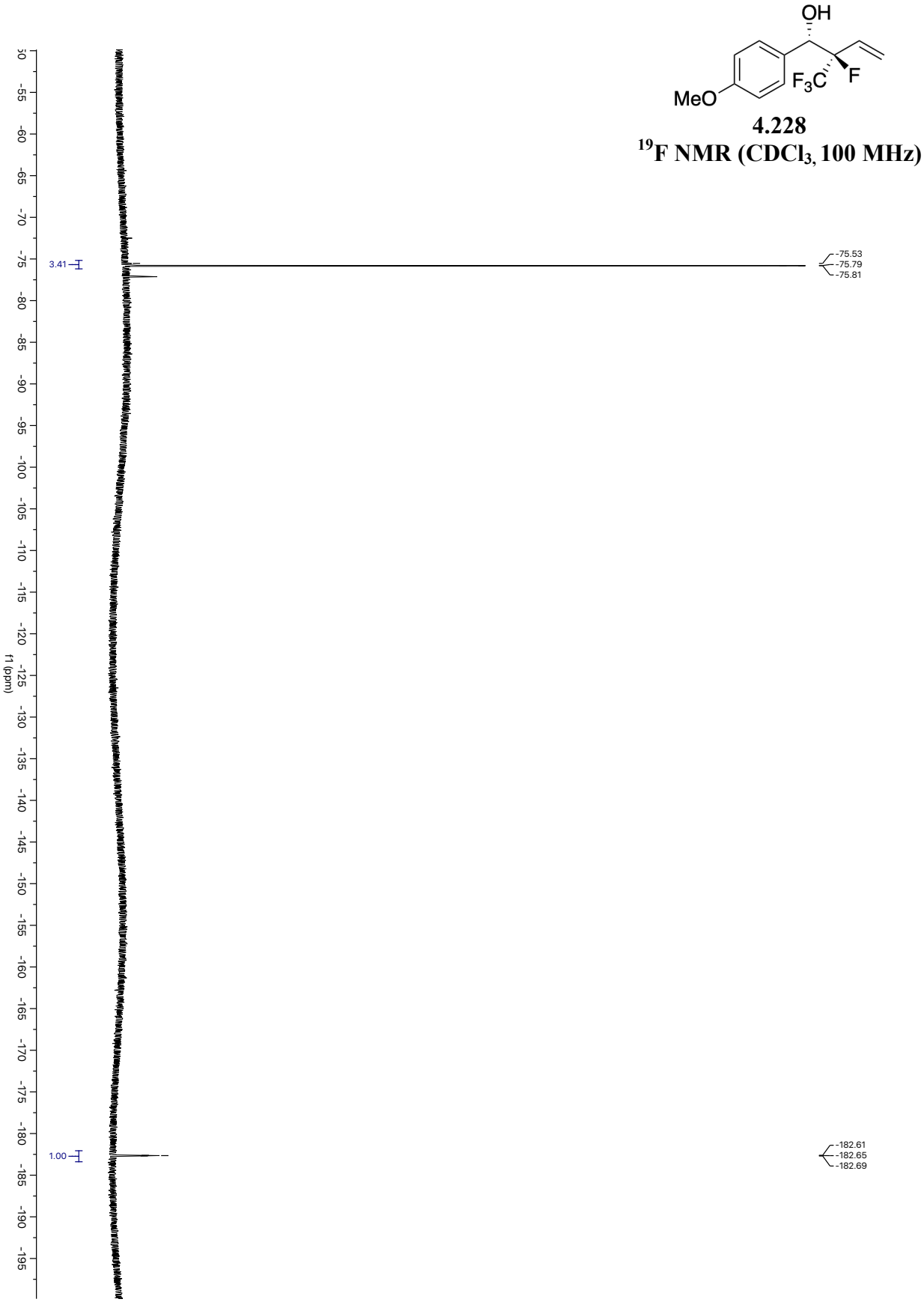

OH
F3C
F
4.227
1H NMR (CDCl3, 400 MHz)
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.34
5.83
5.82
5.80
5.80
5.78
5.78
5.77
5.75
5.75
5.74
5.73
5.73
5.70
5.70
5.70
5.60
5.60
5.56
5.56
5.52
5.51
5.49
5.49
5.14
5.12
5.10
5.09
2.43
2.43
2.43
2.42
2.42
2.42
2.42
2.41
4.47
1.01
1.92
1.00
0.89
f1 (ppm)

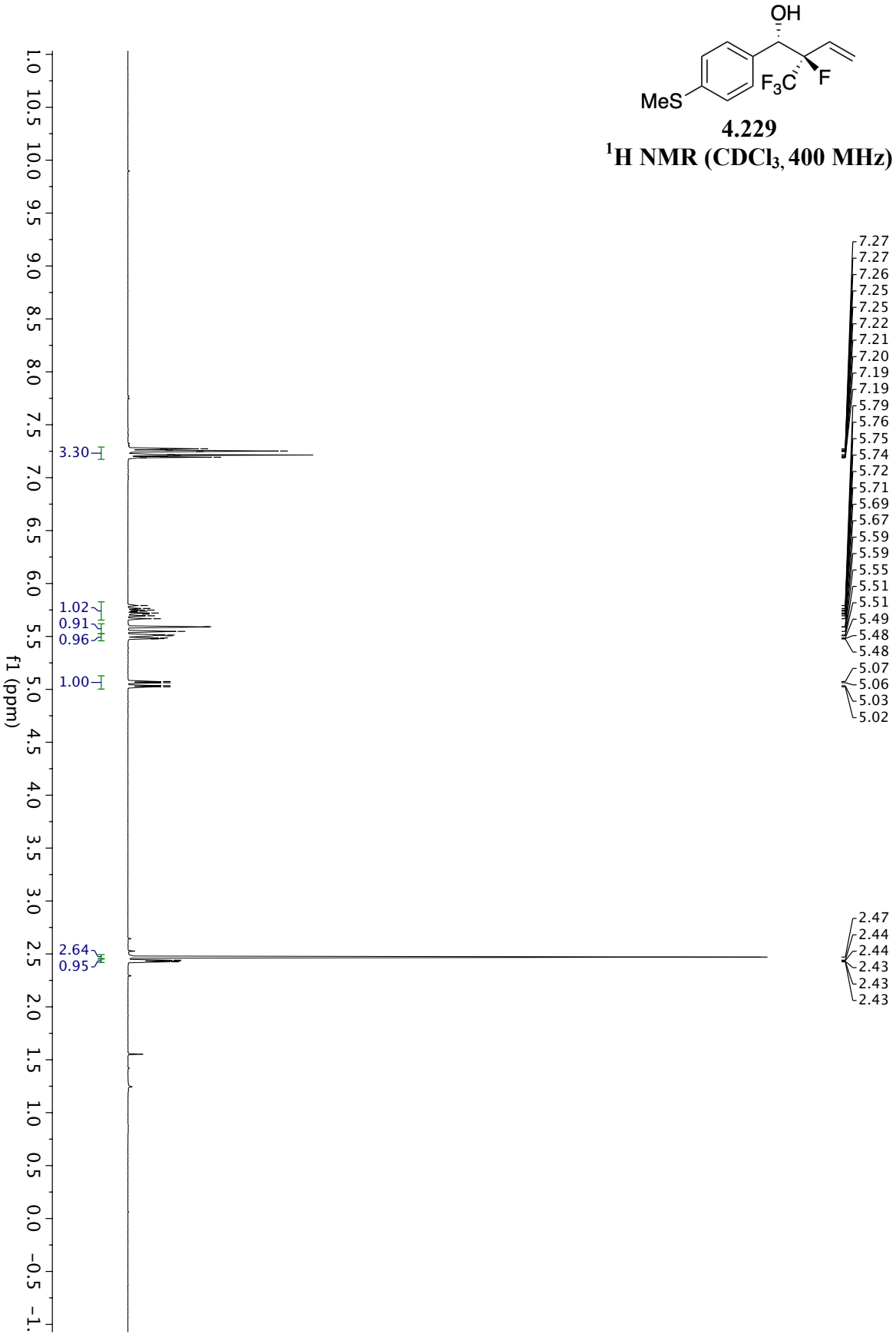

OH
F3C
F
4.227
13C NMR (CDCl3, 100 MHz)
126.56
126.38
124.03
123.74
121.41
121.30
121.19
120.90
97.17
96.88
96.60
96.30
95.24
94.95
94.66
94.37
136.17
136.13
128.96
128.26
127.94
74.29
74.25
74.08
74.03
f1 (ppm)

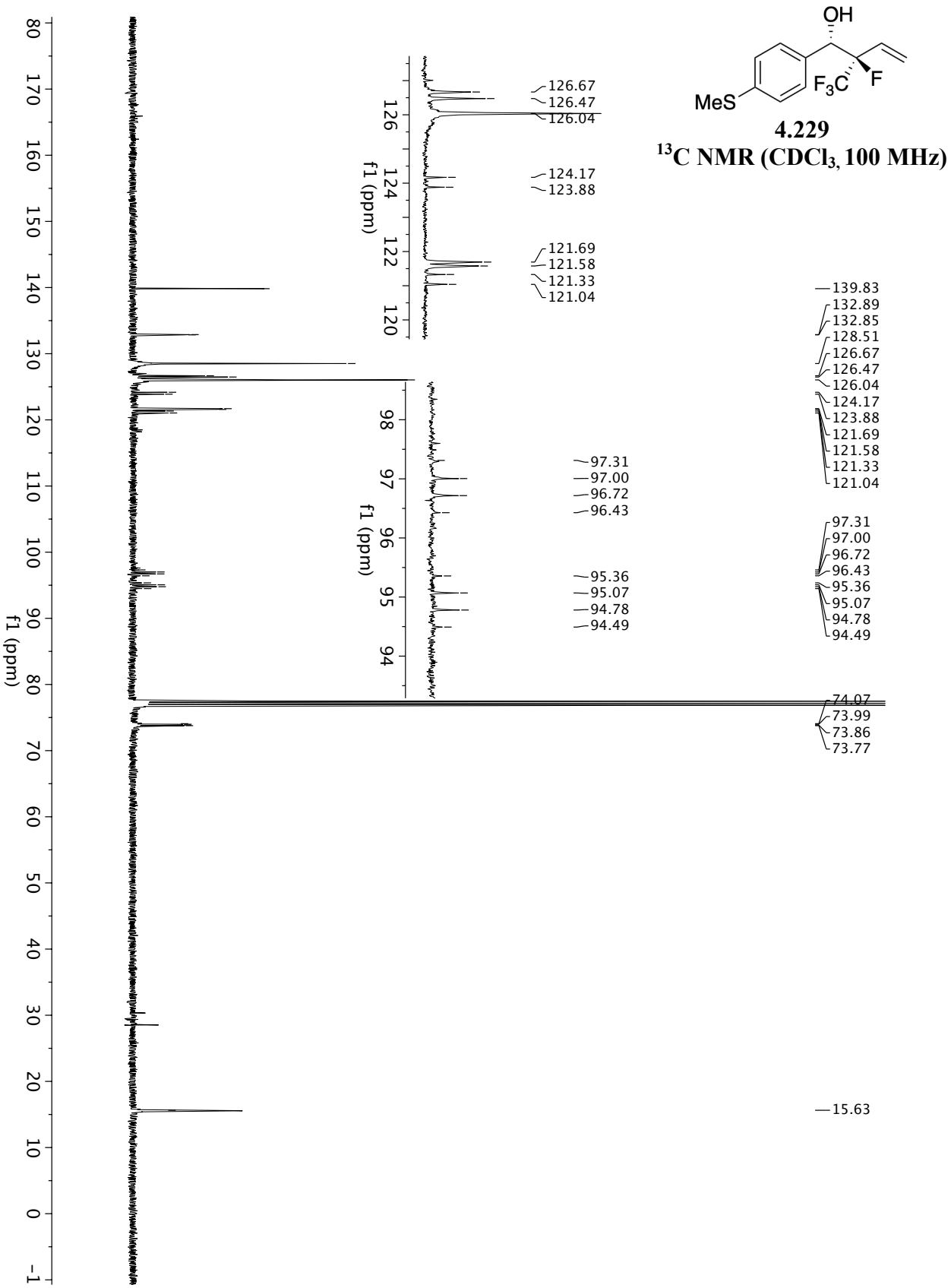

OH
F3C
F
4.227
19F NMR (CDCl3, 376 MHz)
3.00
0.62
-75.74
-75.76
-182.84
-182.85
-182.86
-182.87
-182.89
-182.91
-182.93
-182.95
f1 (ppm)

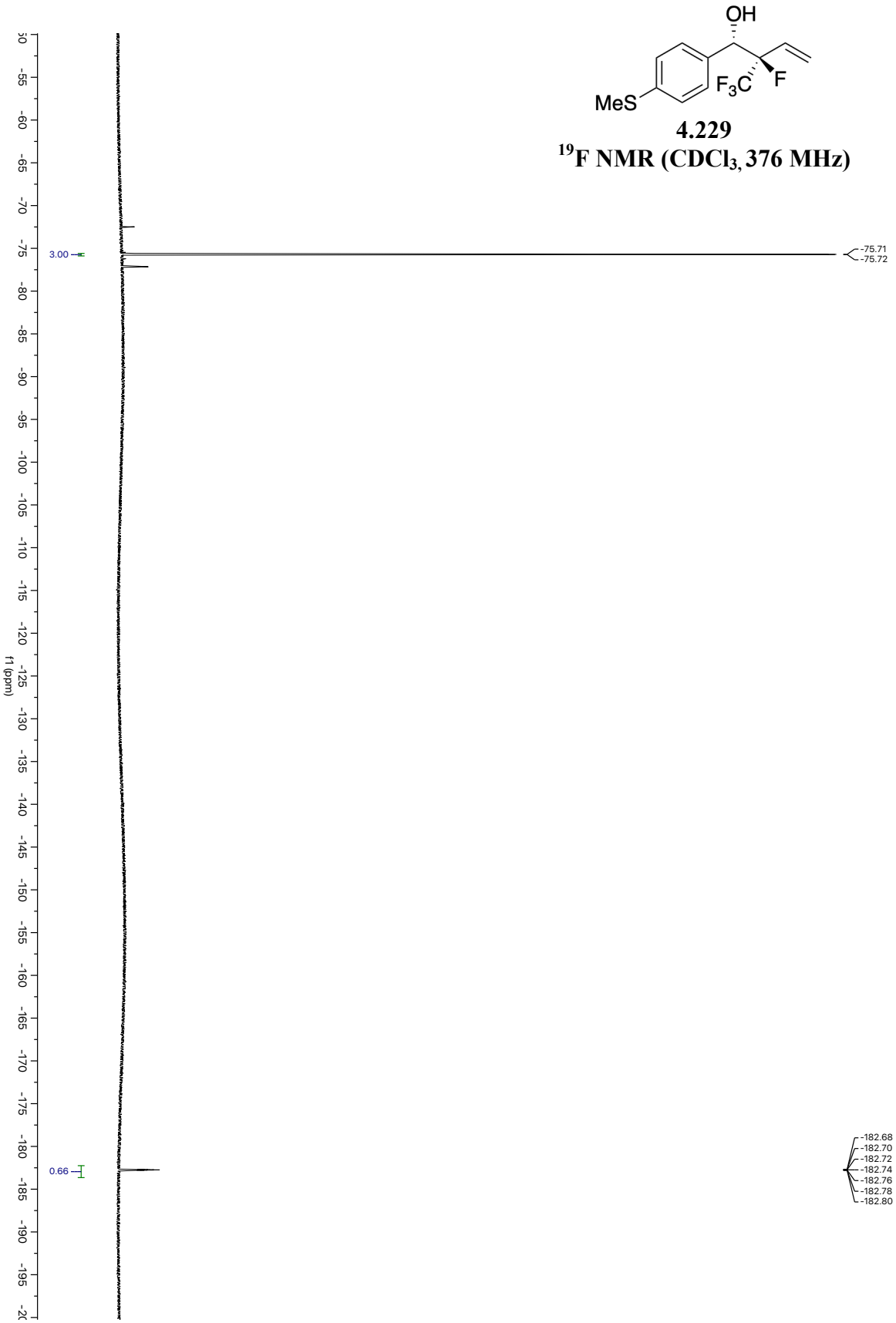

OH
F3C
F
MeO
4.228
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.98
1.95
1.00
2.08
1.03
3.16
0.96
7.28
7.28
7.27
7.26
7.25
6.88
6.88
6.87
6.86
6.85
5.76
5.76
5.74
5.73
5.71
5.71
5.68
5.68
5.59
5.59
5.55
5.54
5.51
5.50
5.48
5.47
5.47
5.07
5.06
5.03
5.02
3.80
3.75
2.39
2.39
2.38
2.38

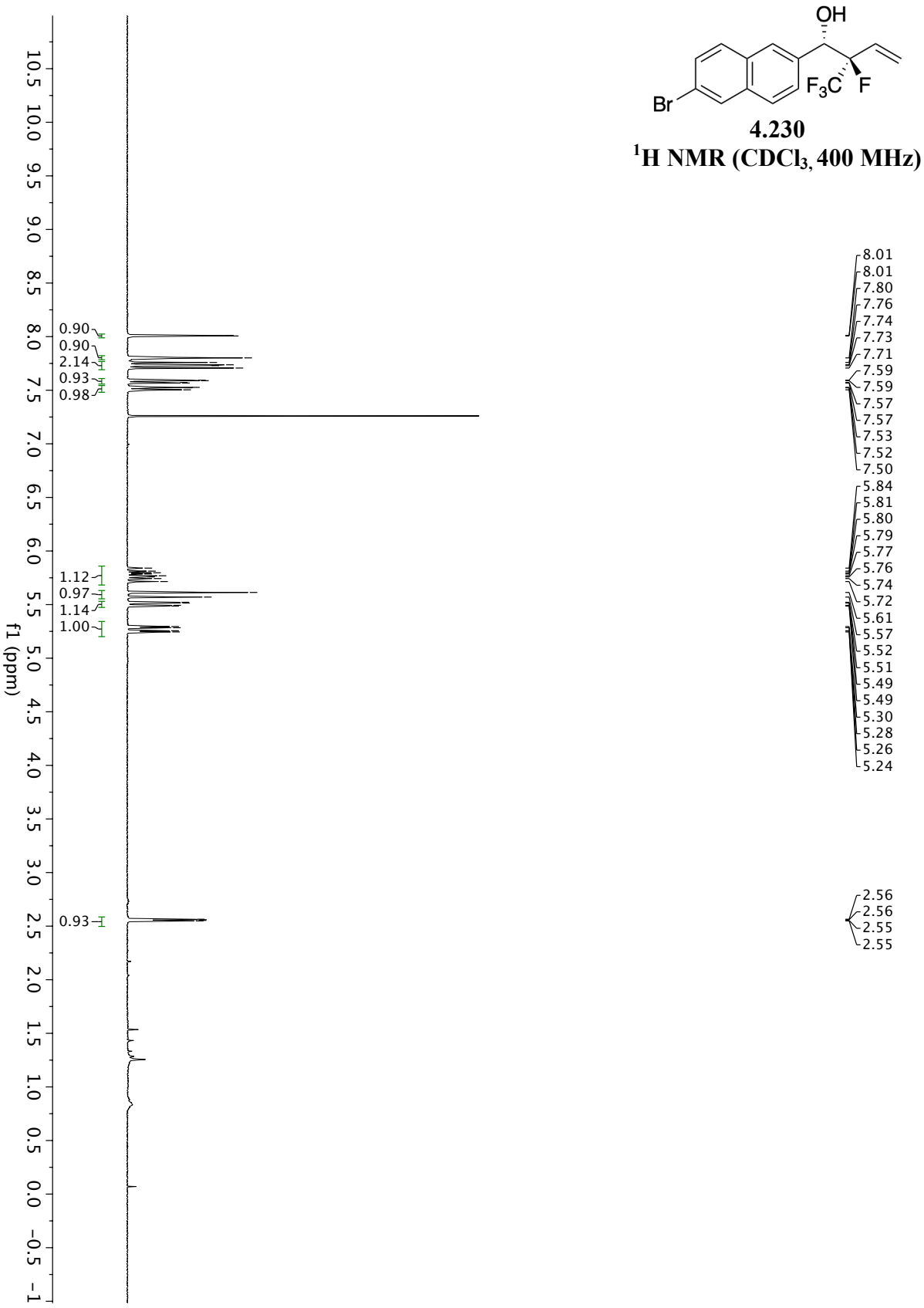

OH
F3C
F
MeO
4.228
13C NMR (CDCl3, 100 MHz)
159.96
129.15
128.28
128.24
126.66
126.47
124.05
123.76
121.32
121.21
120.92
113.63
97.24
96.95
96.66
96.38
95.30
95.02
94.73
94.44
73.83
73.79
73.61
73.57
55.24
55.21
f1 (ppm)

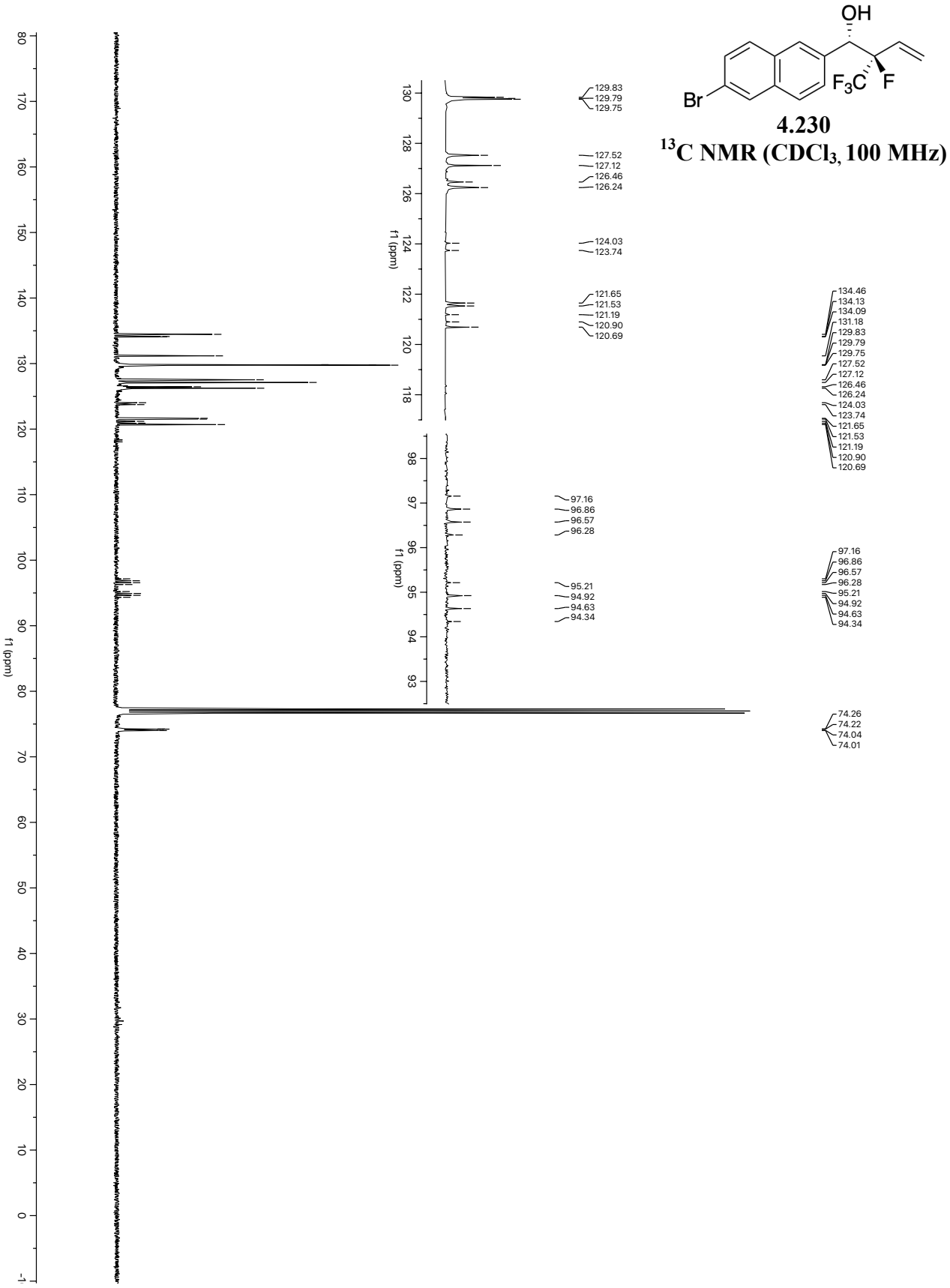

OH
F3C
F
MeO
4.228
19F NMR (CDCl3, 100 MHz)
3.41
1.00
-75.53
-75.79
-75.81
-182.61
-182.65
-182.69
f1 (ppm)

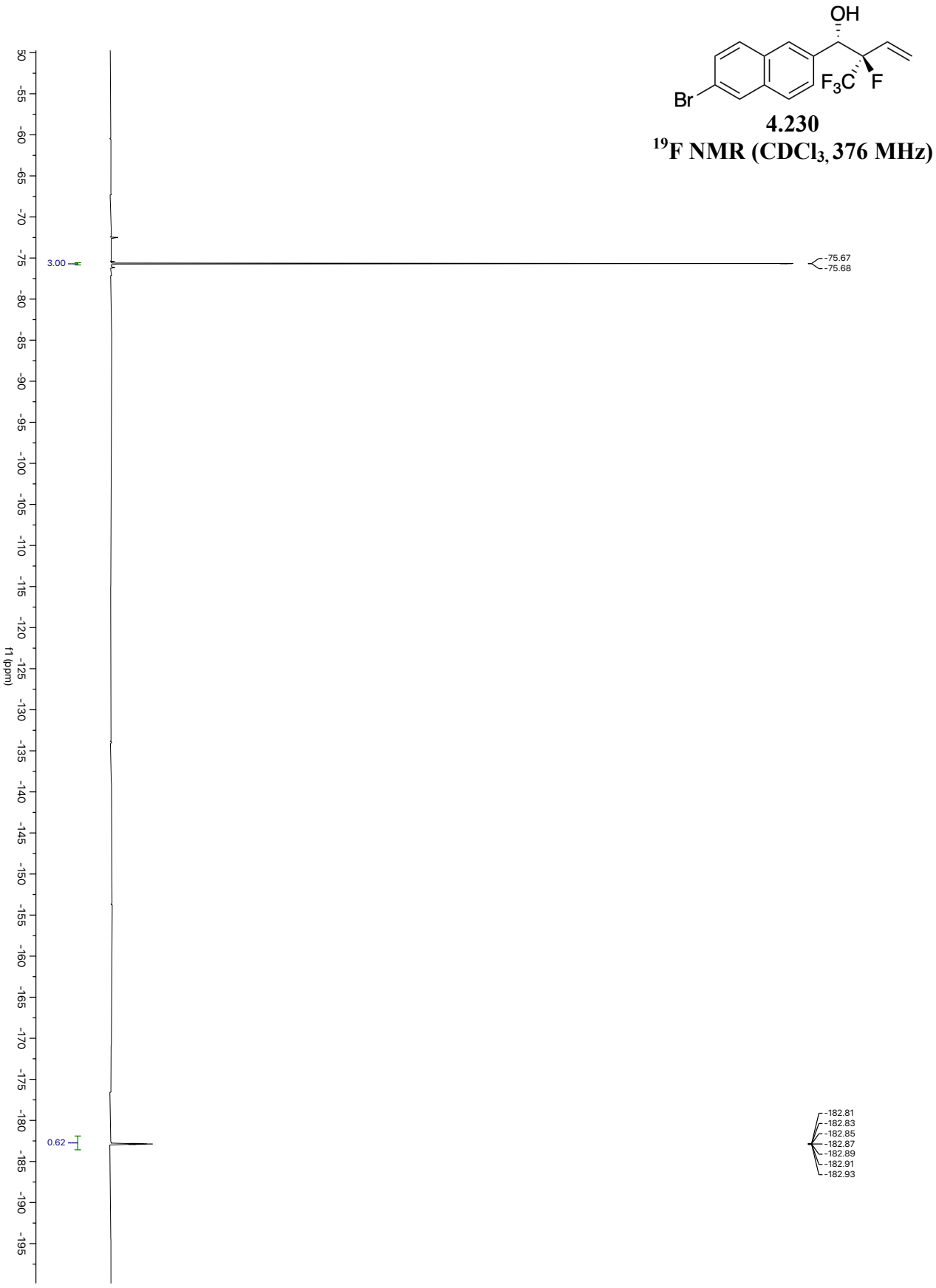

OH
F3C
F
MeS
4.229
1H NMR (CDCl3, 400 MHz)
7.27
7.27
7.26
7.25
7.25
7.22
7.21
7.20
7.19
7.19
5.79
5.76
5.75
5.74
5.72
5.71
5.69
5.67
5.59
5.59
5.55
5.51
5.51
5.49
5.48
5.48
5.07
5.06
5.03
5.02
2.47
2.44
2.44
2.43
2.43
2.43
3.30
1.02
0.91
0.96
1.00
2.64
0.95
f1 (ppm)

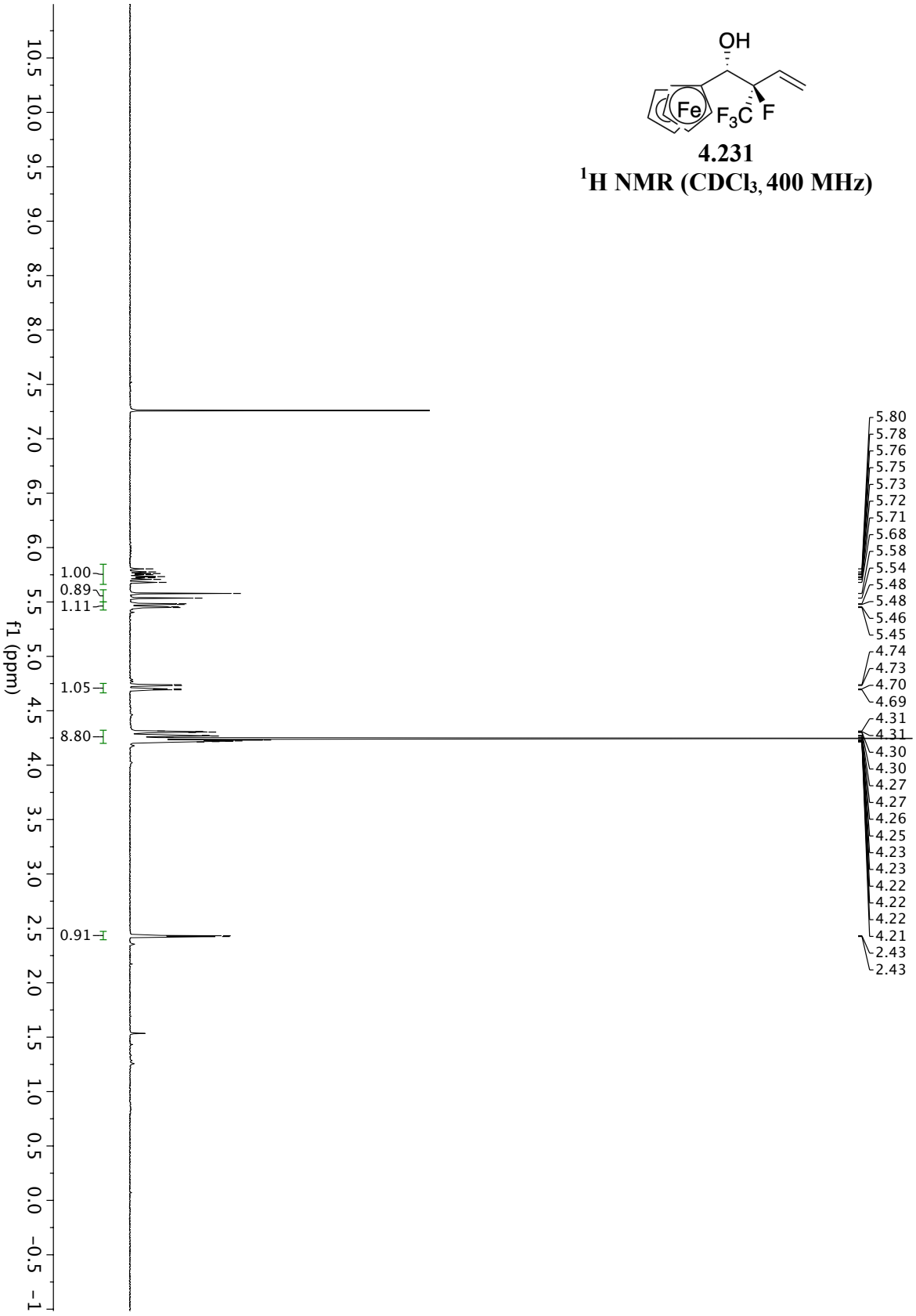

OH
F3C
F
MeS
4.229
13C NMR (CDCl3, 100 MHz)
126.67
126.47
126.04
124.17
123.88
121.69
121.58
121.33
121.04
139.83
132.89
132.85
128.51
126.67
126.47
126.04
124.17
123.88
121.69
121.58
121.33
121.04
97.31
97.00
96.72
96.43
95.36
95.07
94.78
94.49
74.07
73.99
73.86
73.77
15.63
f1 (ppm)

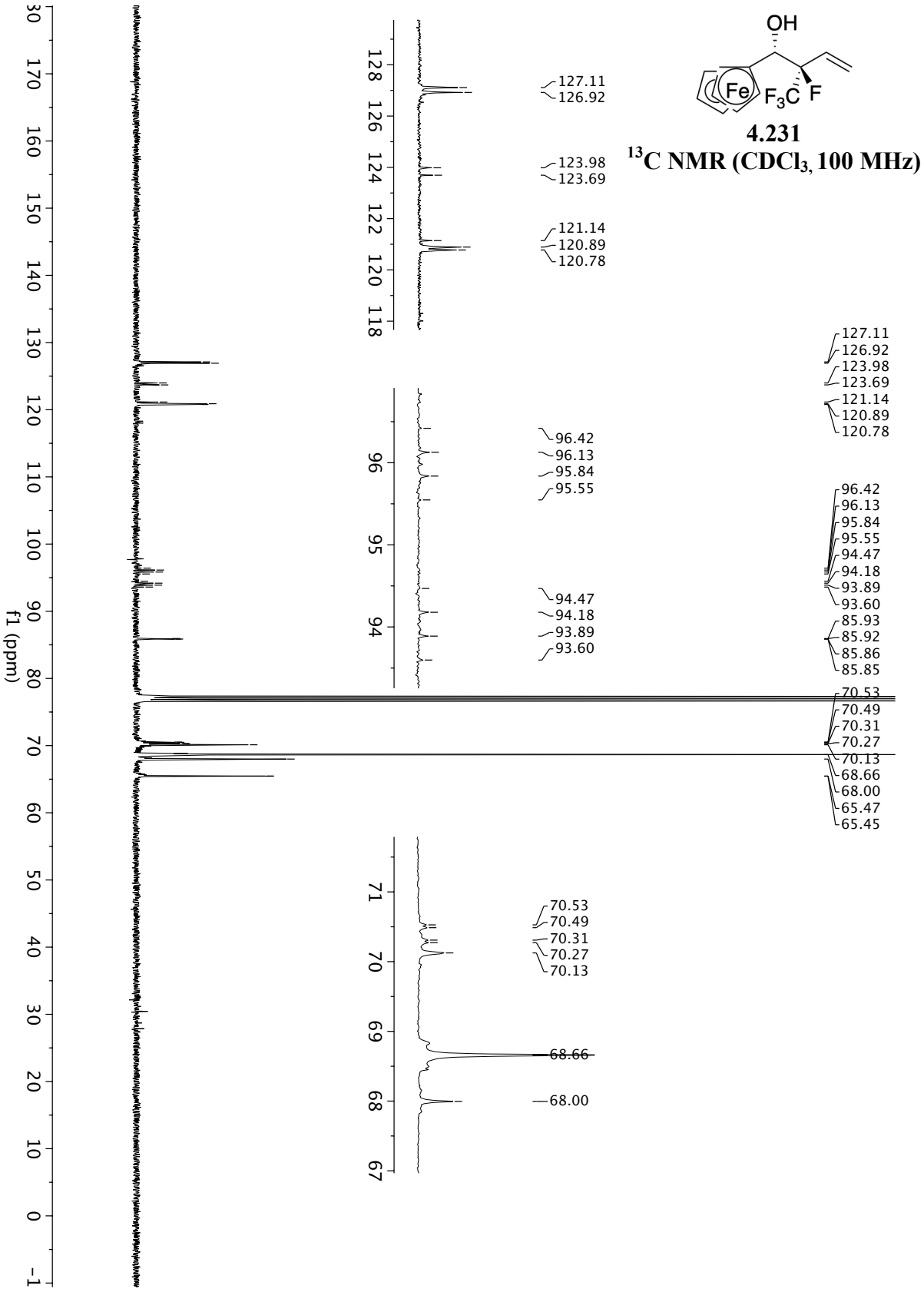

OH
F3C
F
MeS
4.229
19F NMR (CDCl3, 376 MHz)
3.00
0.66
-75.71
-75.72
-182.68
-182.70
-182.72
-182.74
-182.76
-182.78
-182.80
f1 (ppm)

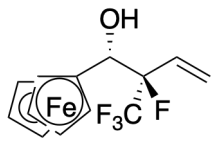

OH
F3C
F
Br
4.230
1H NMR (CDCl3, 400 MHz)
8.01
8.01
7.80
7.76
7.74
7.73
7.71
7.59
7.59
7.57
7.57
7.53
7.52
7.50
5.84
5.81
5.80
5.79
5.77
5.76
5.74
5.72
5.61
5.57
5.52
5.51
5.49
5.49
5.30
5.28
5.26
5.24
2.56
2.56
2.55
2.55
0.90
0.90
2.14
0.93
0.98
1.12
0.97
1.14
1.00
0.93
f1 (ppm)


OH
Br
F3C
F
4.230
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
129.83
129.79
129.75
127.52
127.12
126.46
126.24
124.03
123.74
121.65
121.53
121.19
120.90
120.69
97.16
96.86
96.57
96.28
95.21
94.92
94.63
94.34
74.26
74.22
74.04
74.01
134.46
134.13
134.09
131.18


OH
Br
F3C
F
4.230
19F NMR (CDCl3, 376 MHz)
50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
f1 (ppm)
3.00
0.62
-75.67
-75.68
-182.81
-182.83
-182.85
-182.87
-182.89
-182.91
-182.93

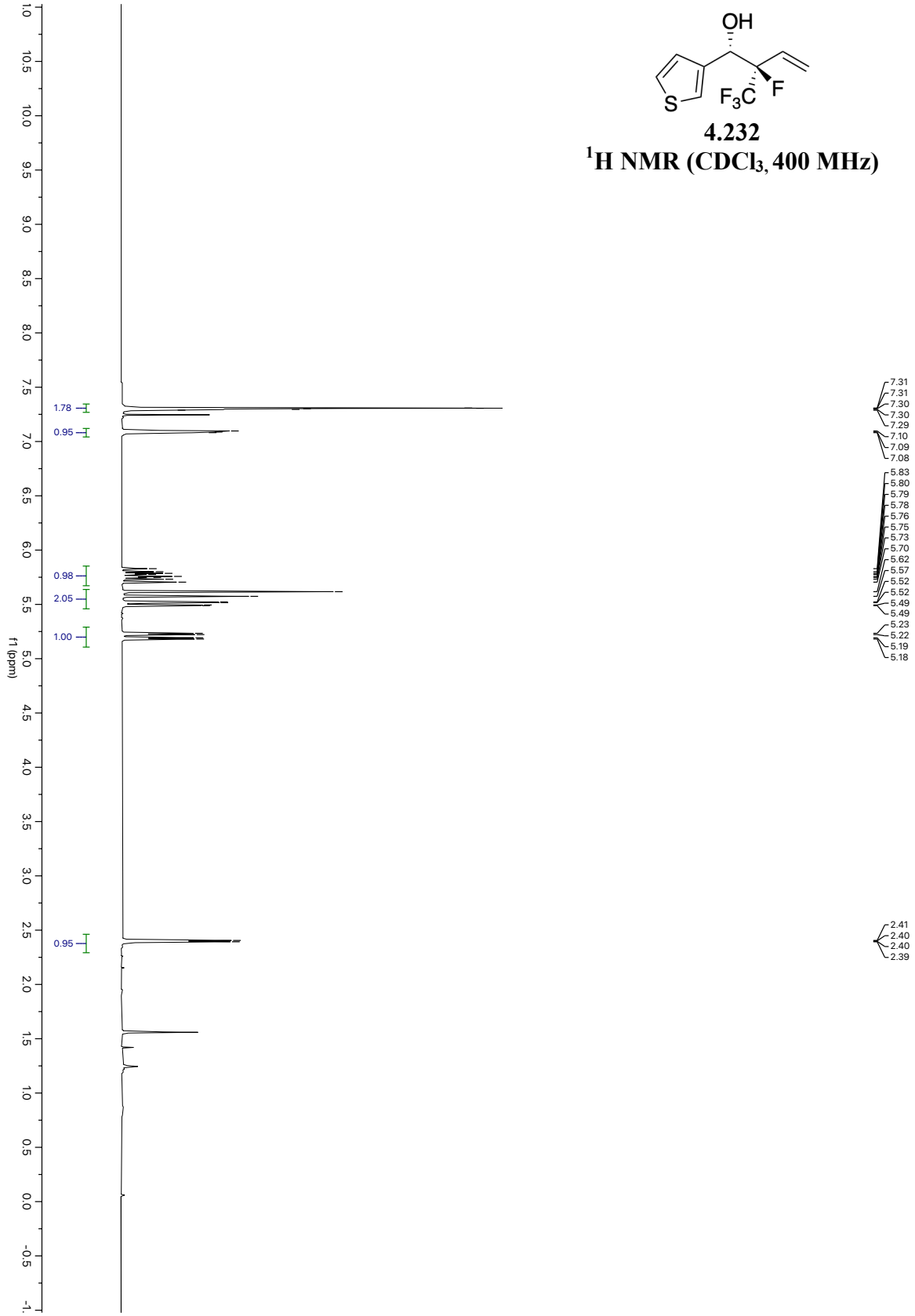

OH
Fe
F3C
F
4.231
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
1.00
0.89
1.11
1.05
8.80
0.91
5.80
5.78
5.76
5.75
5.73
5.72
5.71
5.68
5.58
5.54
5.48
5.48
5.46
5.45
4.74
4.73
4.70
4.69
4.31
4.31
4.30
4.30
4.27
4.27
4.26
4.25
4.23
4.23
4.22
4.22
4.22
4.21
2.43
2.43

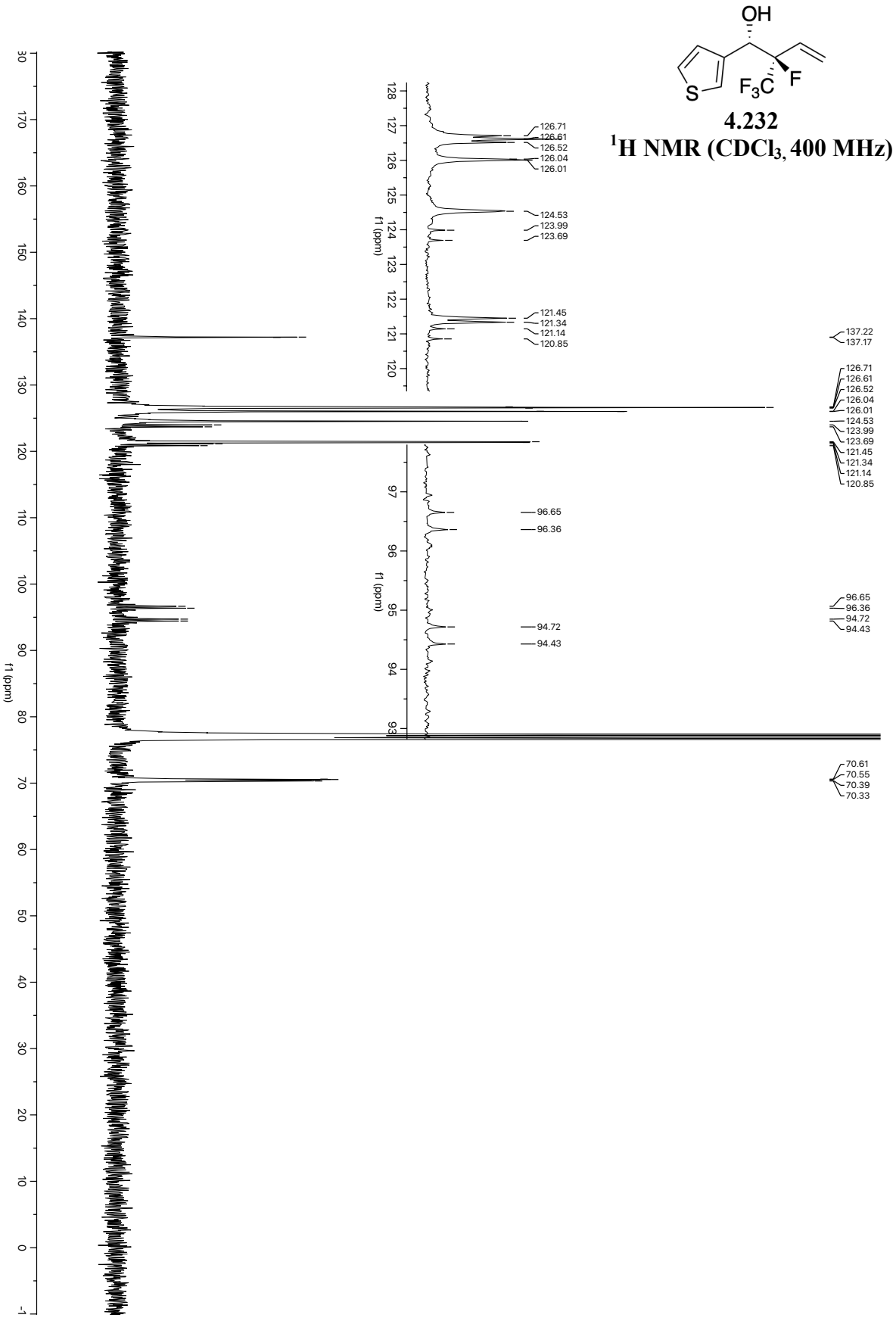

OH
Fe
F3C
F
4.231
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
127.11
126.92
123.98
123.69
121.14
120.89
120.78
96.42
96.13
95.84
95.55
94.47
94.18
93.89
93.60
85.93
85.92
85.86
85.85
70.53
70.49
70.31
70.27
70.13
68.66
68.00
65.47
65.45

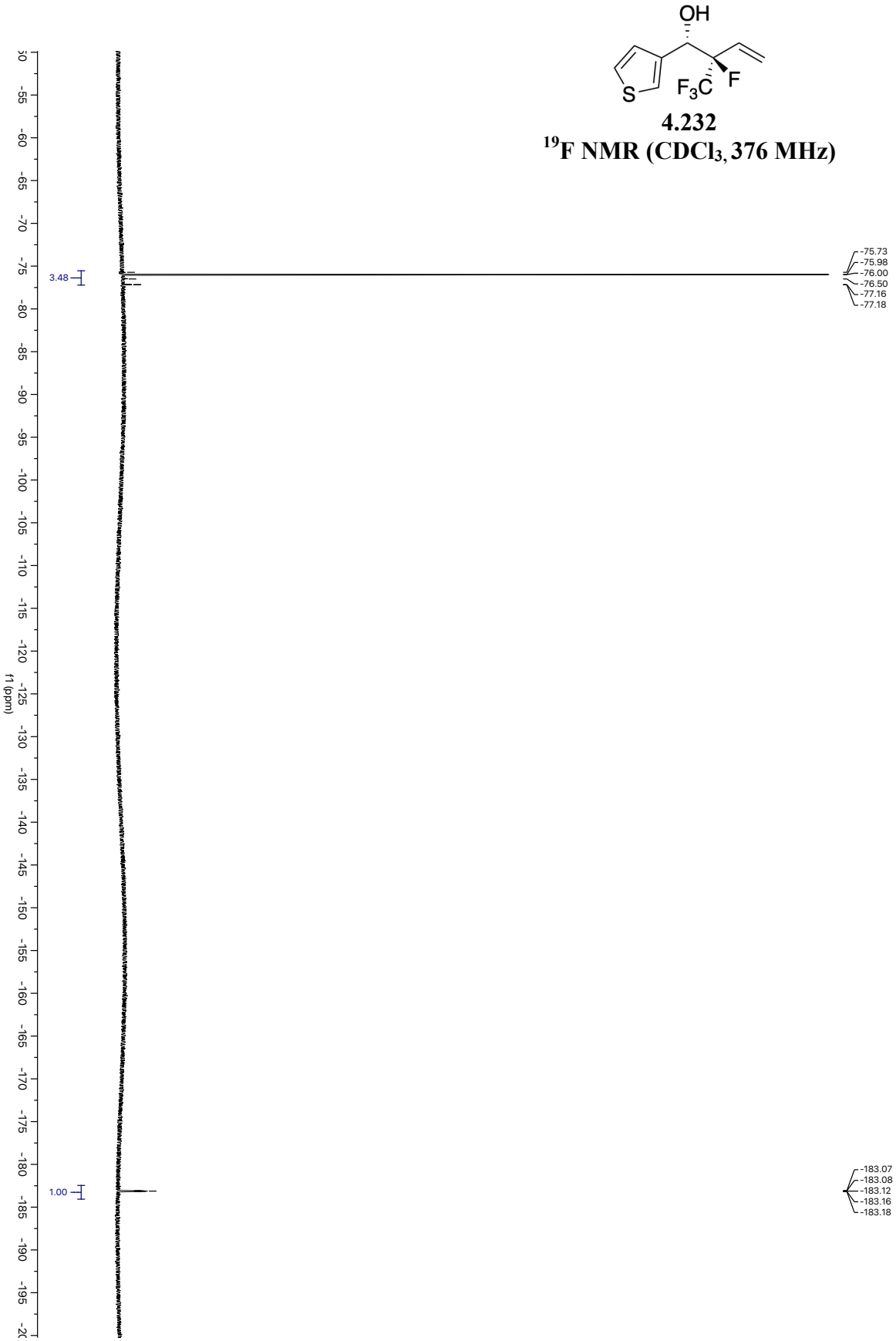


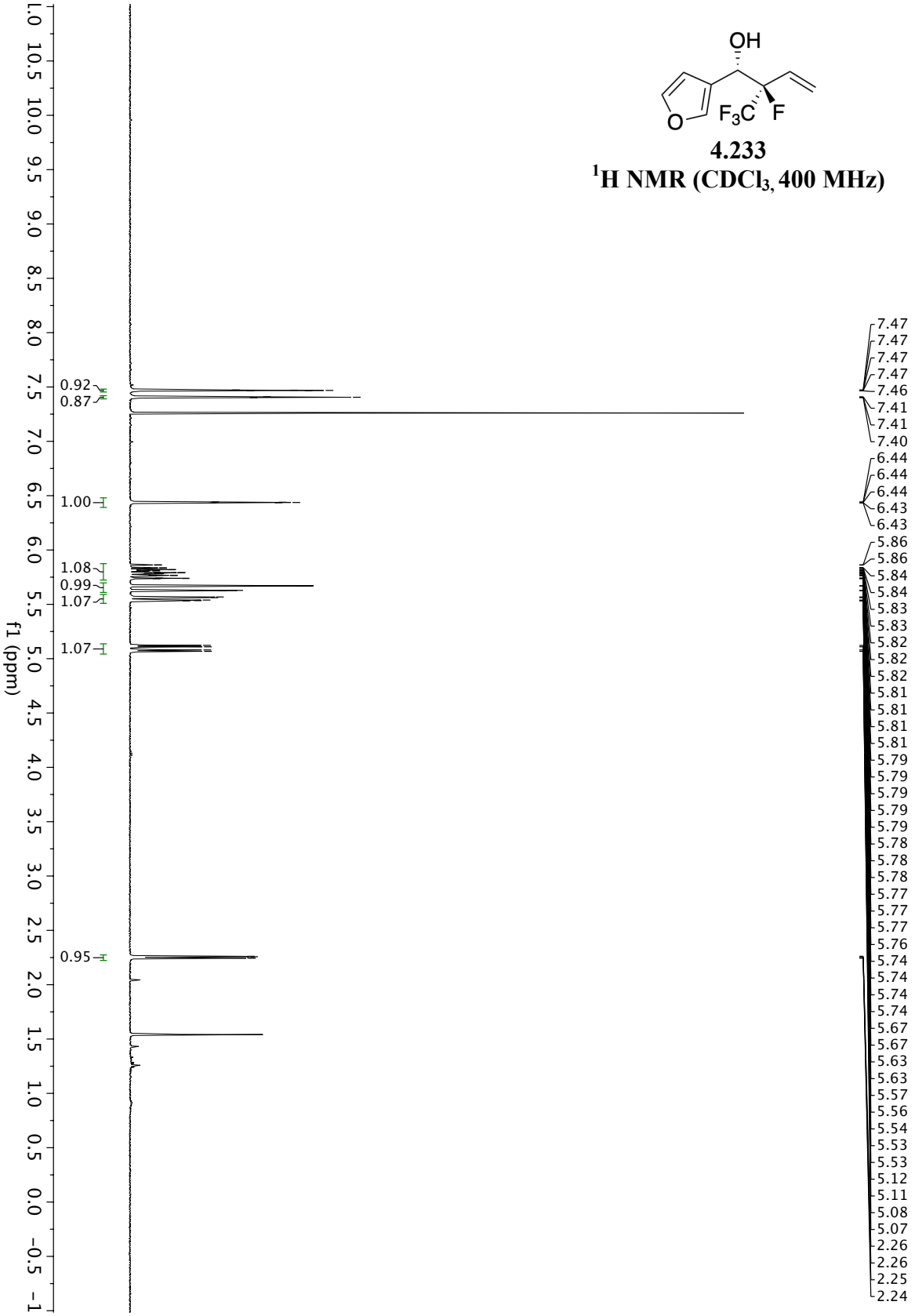
4.231

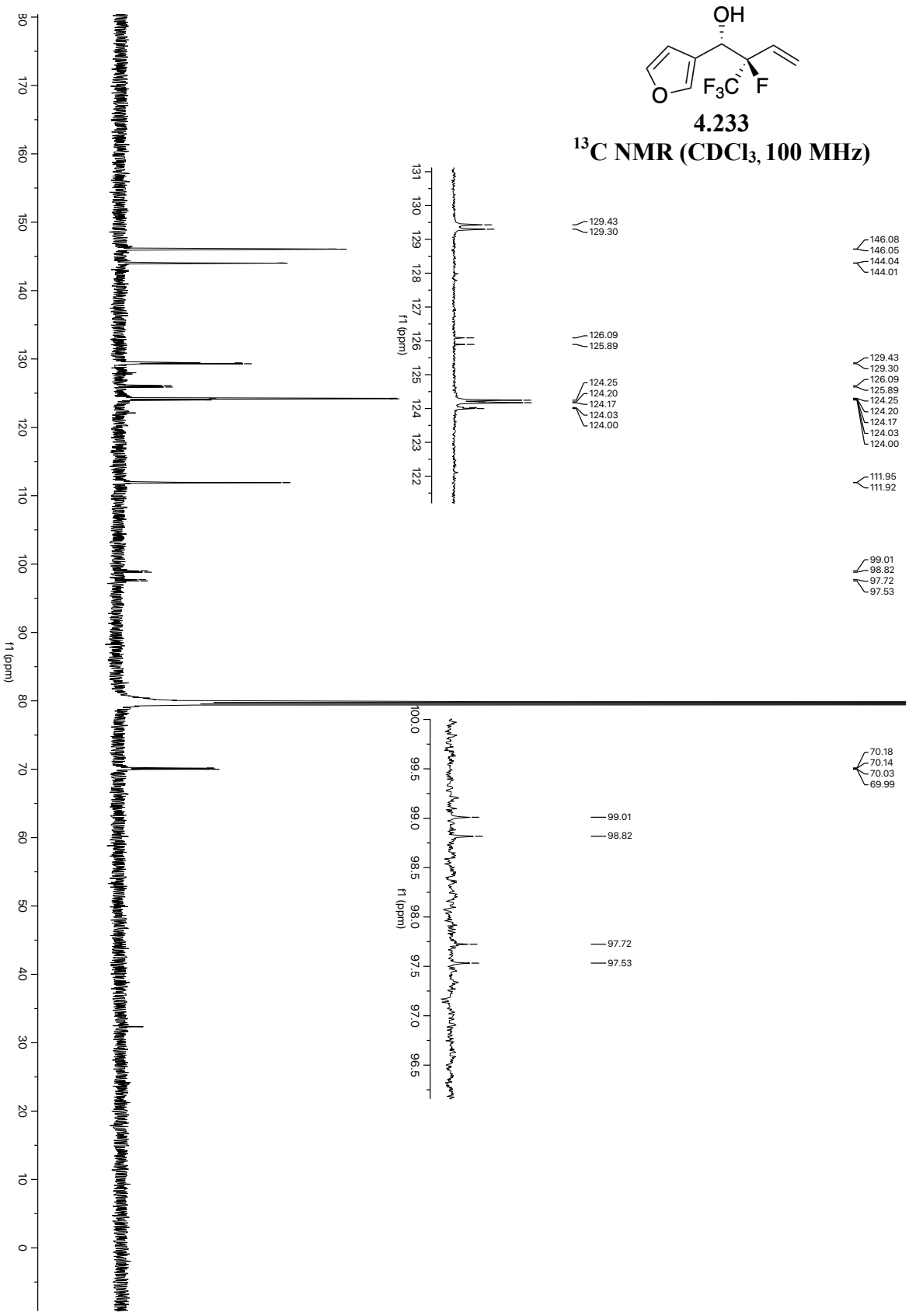
^{1}F NMR ($CDCl_3$, 376 MHz)

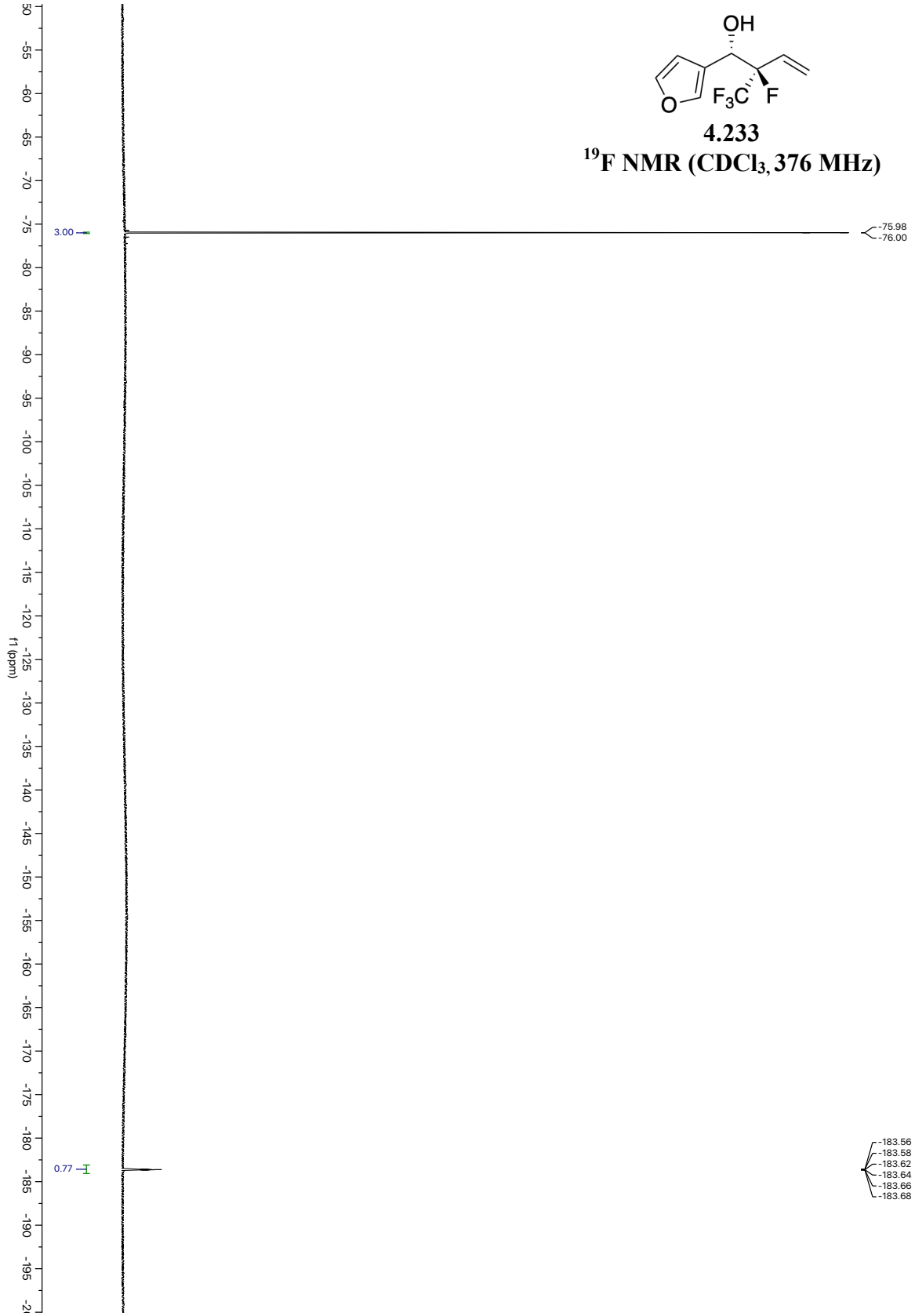

OH
S
F3C
F
4.232
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.78
0.95
0.98
2.05
1.00
0.95
7.31
7.31
7.30
7.30
7.29
7.10
7.09
7.08
5.83
5.80
5.79
5.78
5.76
5.75
5.73
5.70
5.62
5.57
5.52
5.52
5.49
5.49
5.23
5.22
5.19
5.18
2.41
2.40
2.40
2.39

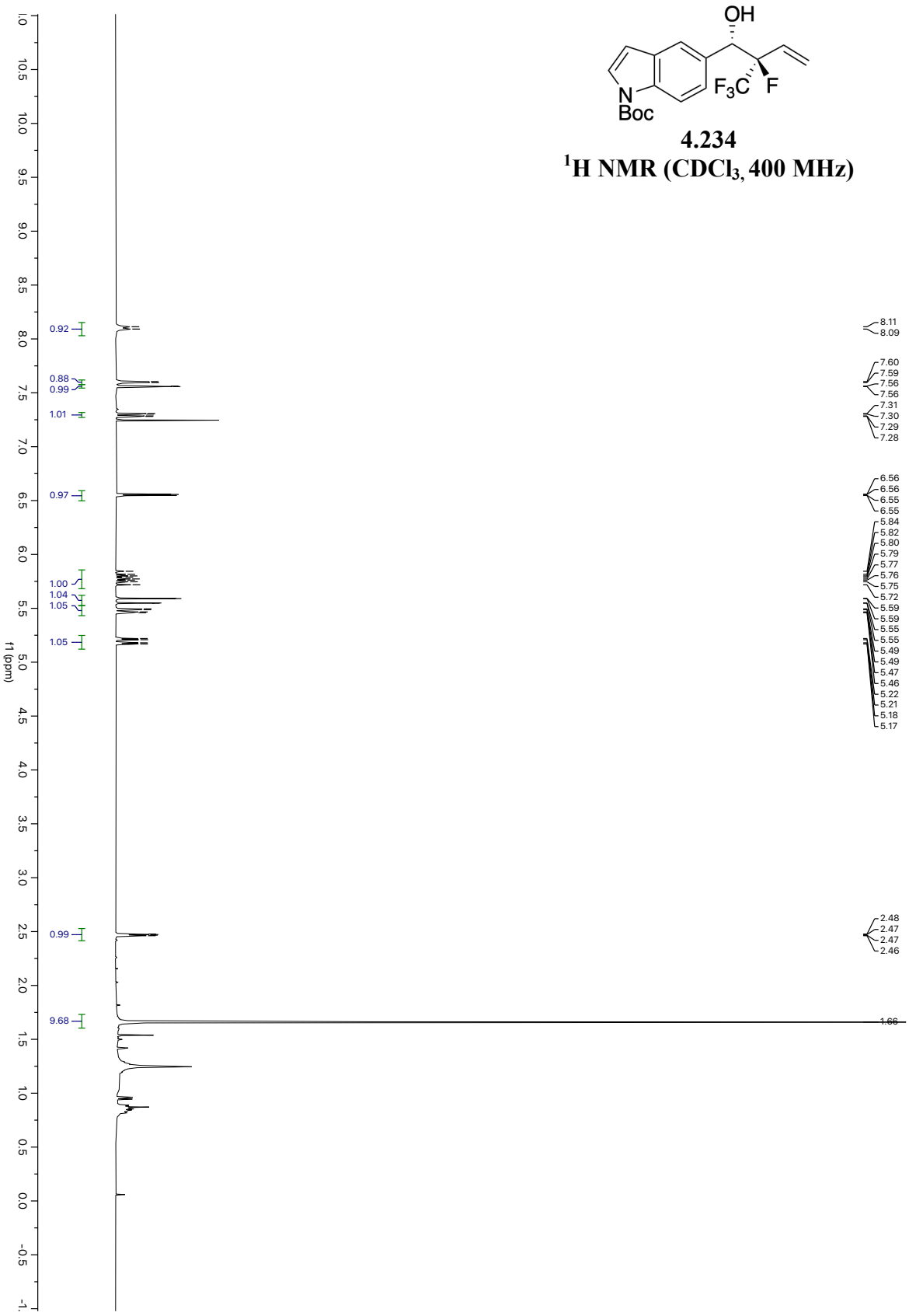

OH
S
F3C
F
4.232
1H NMR (CDCl3, 400 MHz)
126.71
126.61
126.52
126.04
126.01
124.53
123.99
123.69
121.45
121.34
121.14
120.85
137.22
137.17
96.65
96.36
94.72
94.43
70.61
70.55
70.39
70.33
f1 (ppm)


OH
S
F3C
F
4.232
19F NMR (CDCl3, 376 MHz)
-75.73
-75.98
-76.00
-76.50
-77.16
-77.18
3.48
1.00
-183.07
-183.08
-183.12
-183.16
-183.18
f1 (ppm)


OH
F3C
F
O
4.233
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
0.92
0.87
1.00
1.08
0.99
1.07
1.07
0.95
7.47
7.47
7.47
7.47
7.46
7.41
7.41
7.40
6.44
6.44
6.44
6.43
6.43
5.86
5.86
5.84
5.84
5.83
5.83
5.82
5.82
5.82
5.81
5.81
5.81
5.81
5.79
5.79
5.79
5.79
5.79
5.78
5.78
5.78
5.77
5.77
5.77
5.76
5.74
5.74
5.74
5.74
5.67
5.67
5.63
5.63
5.57
5.56
5.54
5.53
5.53
5.12
5.11
5.08
5.07
2.26
2.26
2.25
2.24

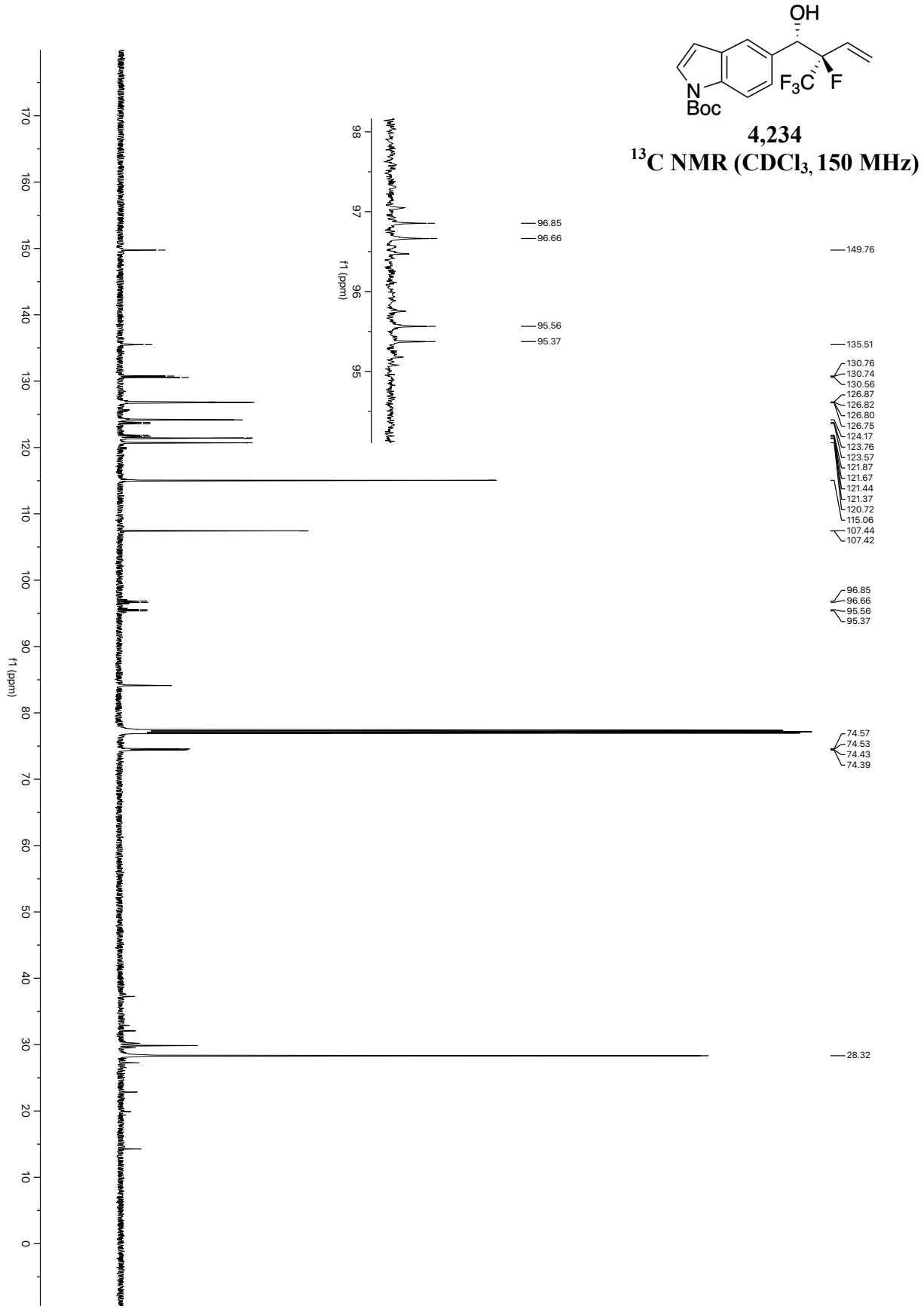

OH
F3C
F
O
4.233
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
129.43
129.30
126.09
125.89
124.25
124.20
124.17
124.03
124.00
146.08
146.05
144.04
144.01
111.95
111.92
99.01
98.82
97.72
97.53
70.18
70.14
70.03
69.99

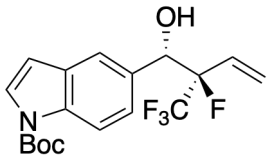

OH
F3C
F
O
4.233
19F NMR (CDCl3, 376 MHz)
3.00
0.77
-75.98
-76.00
-183.56
-183.58
-183.62
-183.64
-183.66
-183.68
f1 (ppm)



4.234

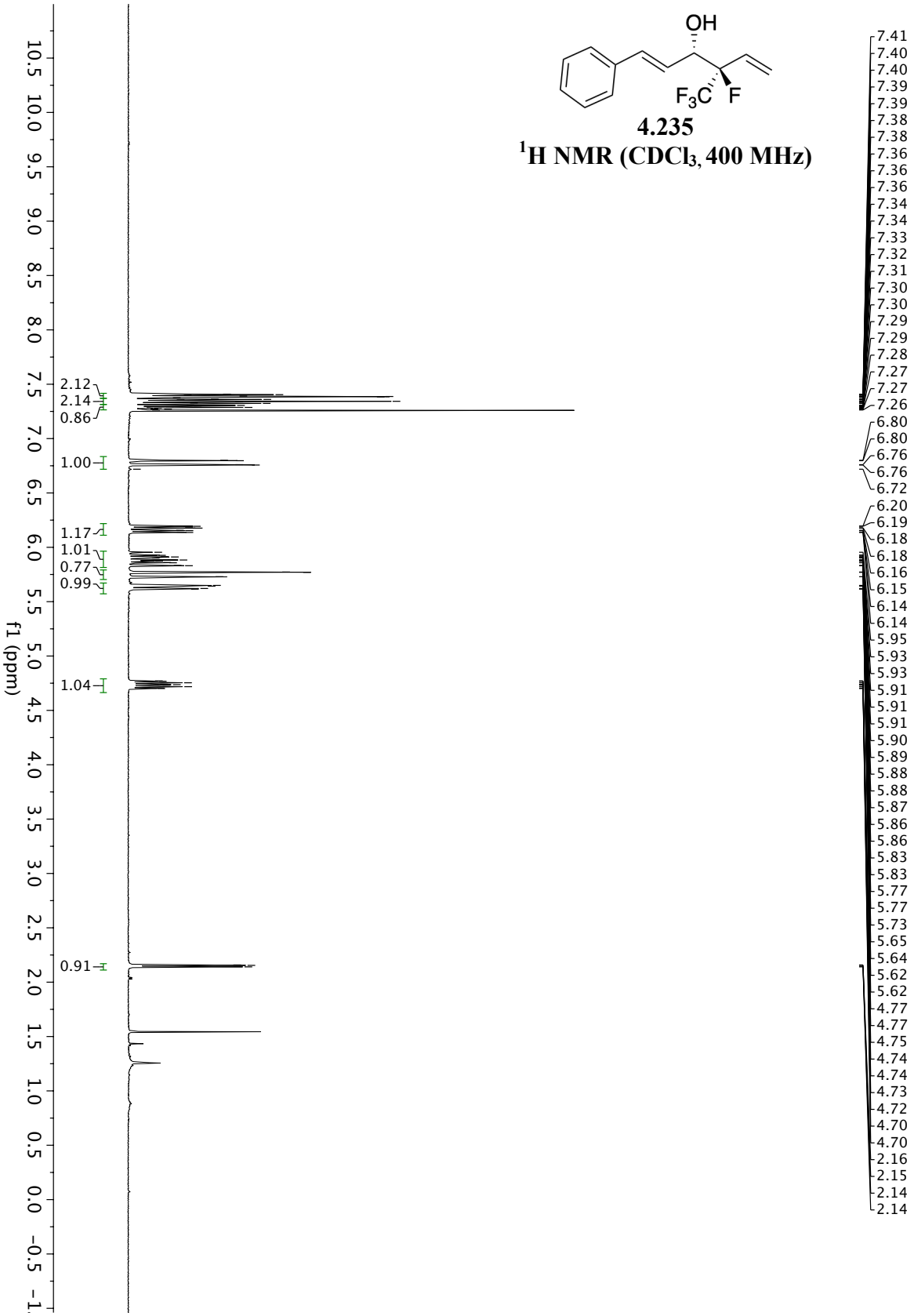
^{1}H NMR ($CDCl_3$, 400 MHz)

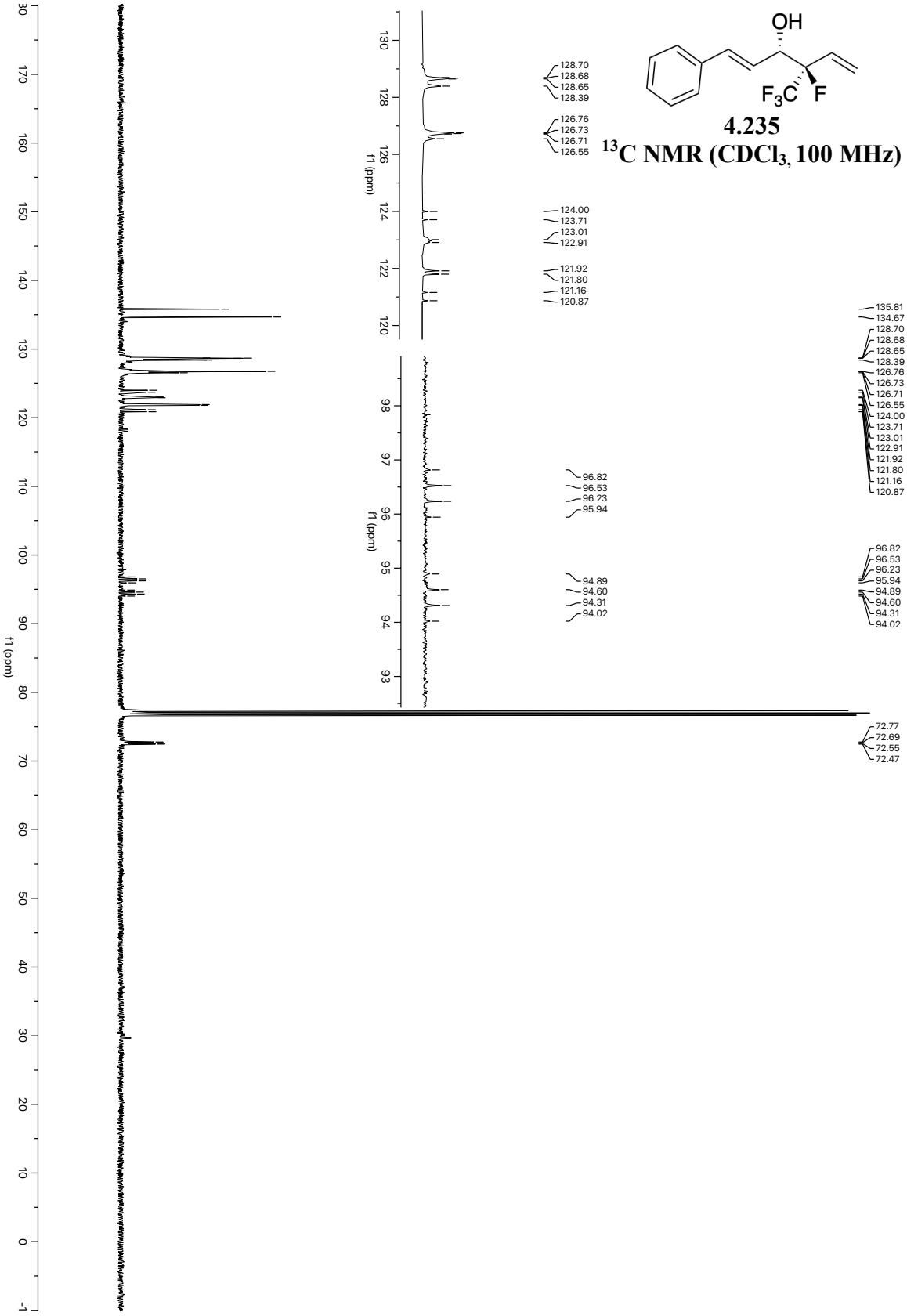

OH
F3C
F
N
Boc
4,234
13C NMR (CDCl3, 150 MHz)
f1 (ppm)
96.85
96.66
95.56
95.37
149.76
135.51
130.76
130.74
130.56
126.87
126.82
126.80
126.75
124.17
123.76
123.57
121.87
121.67
121.44
121.37
120.72
115.06
107.44
107.42
96.85
96.66
95.56
95.37
74.57
74.53
74.43
74.39
28.32

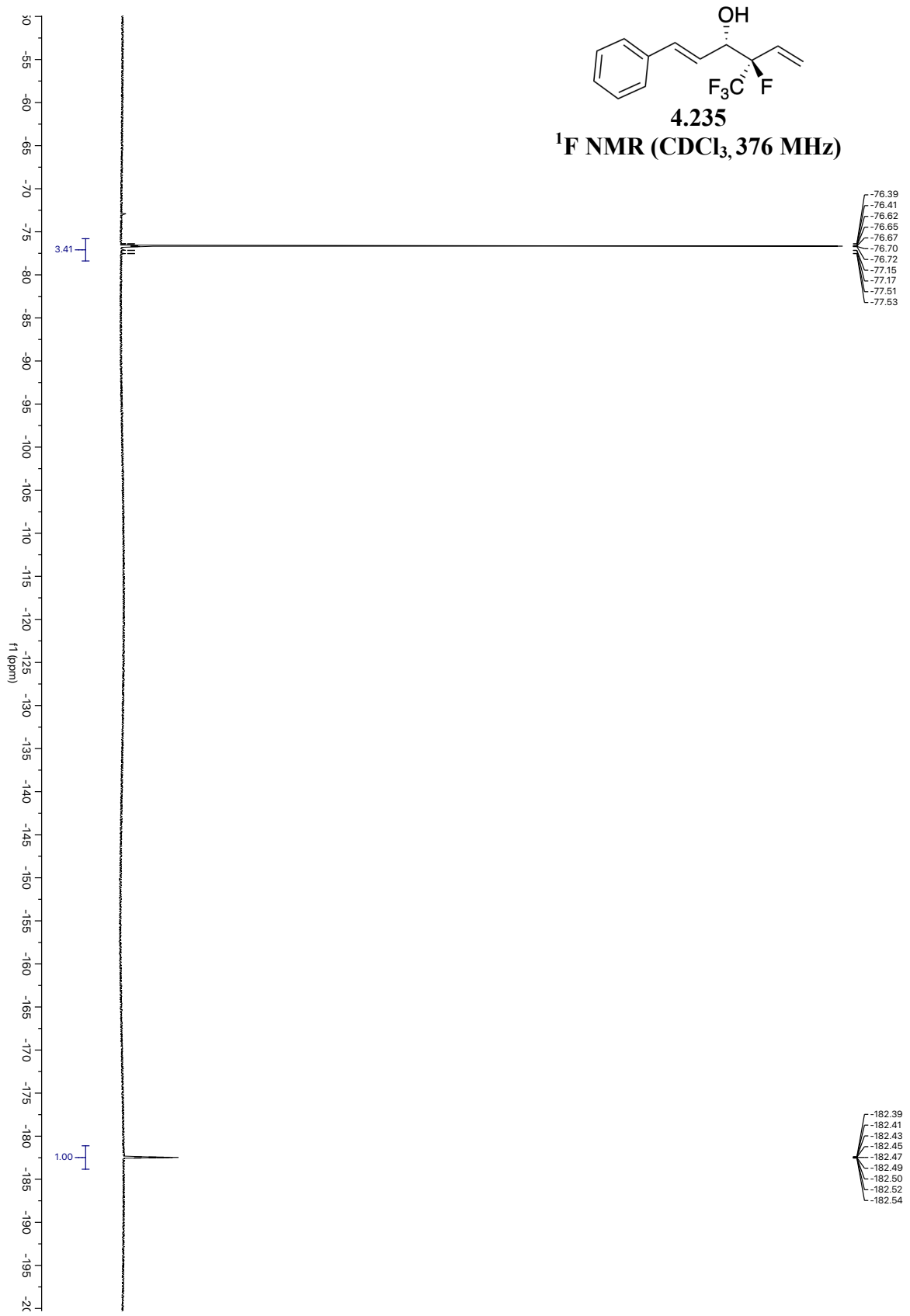


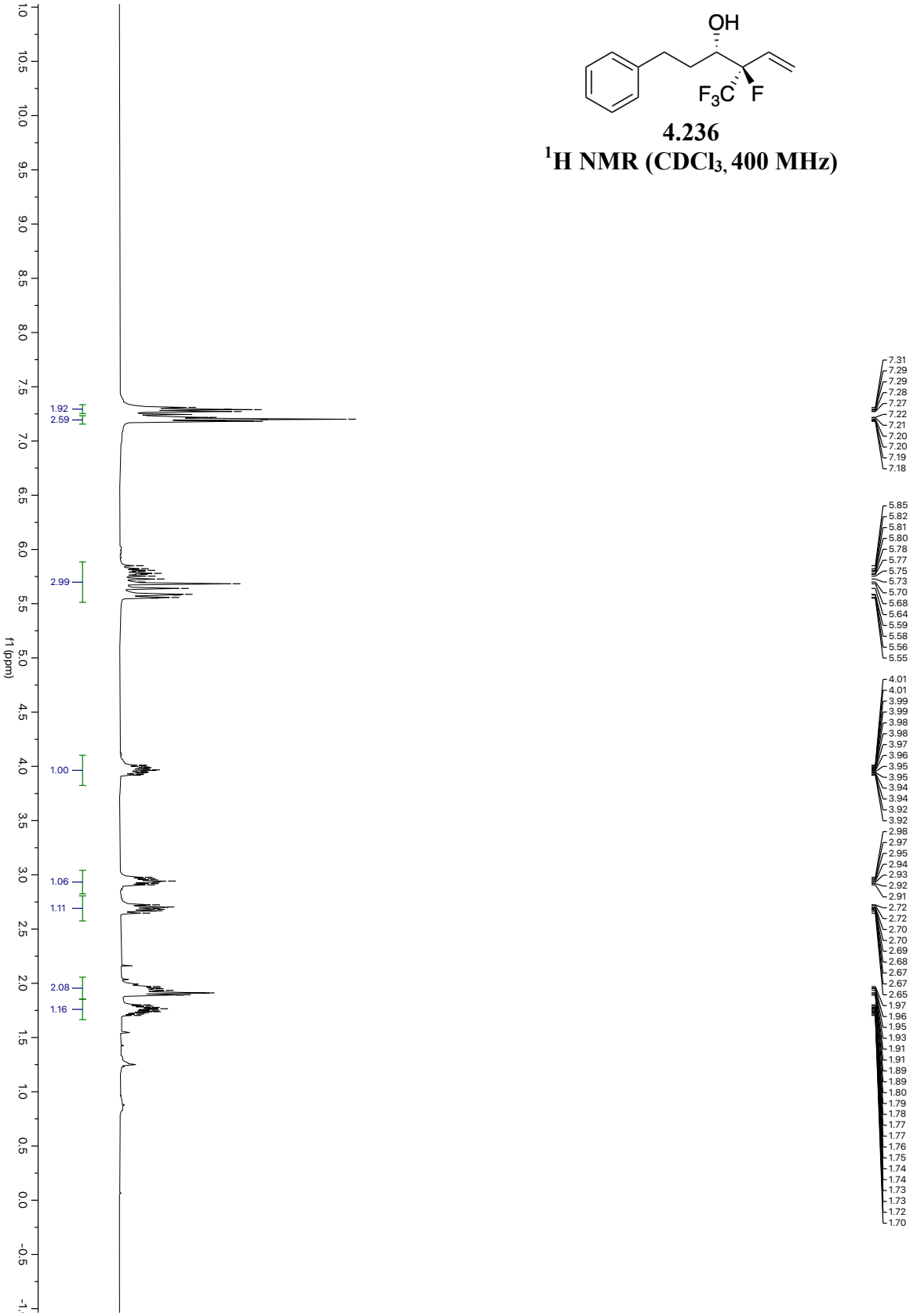
4.234

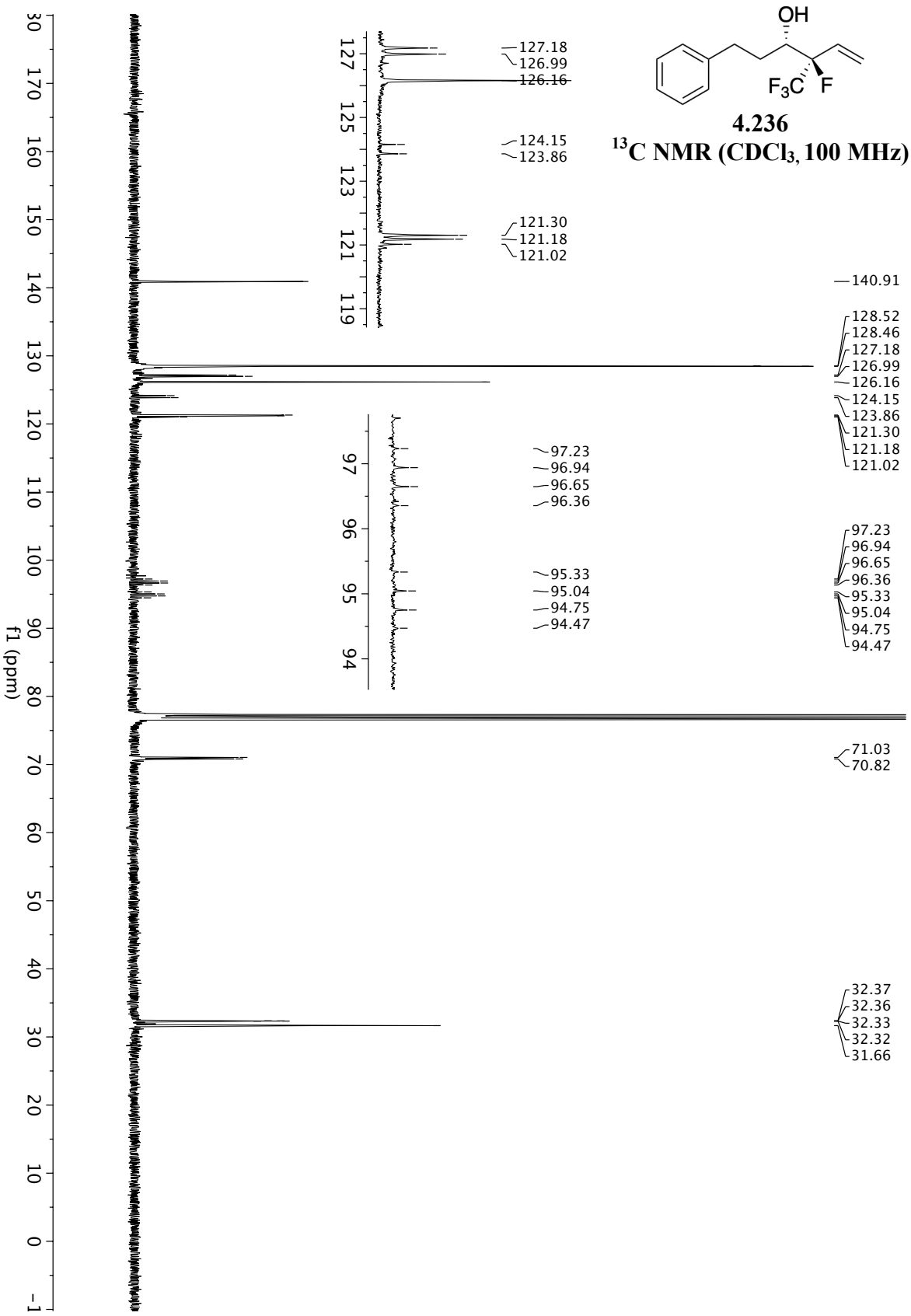
^{19}F NMR ($CDCl_3$, 376 MHz)

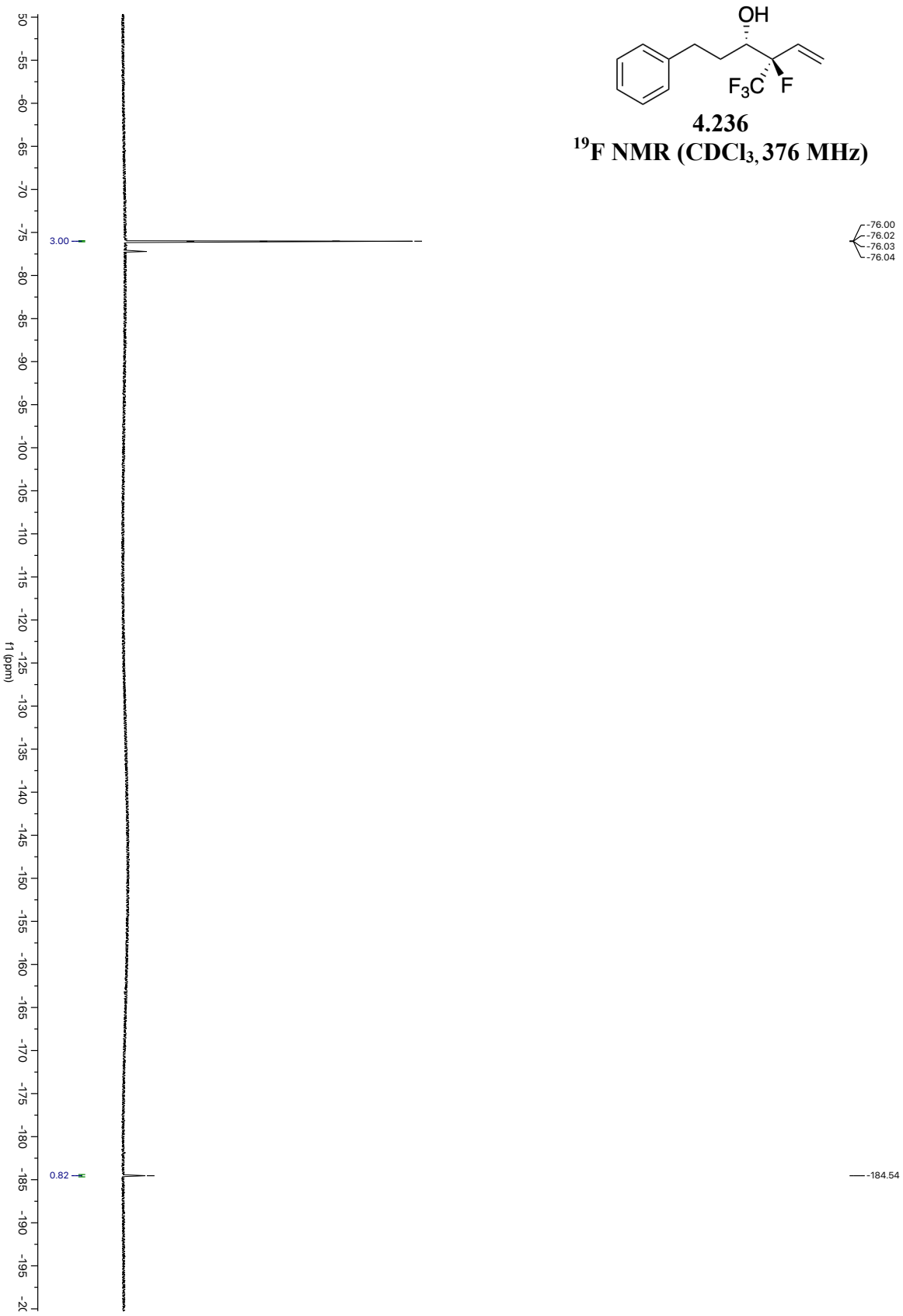

OH
F3C
F
4.235
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.12
2.14
0.86
1.00
1.17
1.01
0.77
0.99
1.04
0.91
7.41
7.40
7.40
7.39
7.39
7.38
7.38
7.36
7.36
7.36
7.34
7.34
7.33
7.32
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.27
7.26
6.80
6.80
6.76
6.76
6.72
6.20
6.19
6.18
6.18
6.16
6.15
6.14
6.14
5.95
5.93
5.93
5.91
5.91
5.91
5.90
5.89
5.88
5.88
5.87
5.86
5.86
5.83
5.83
5.77
5.77
5.73
5.65
5.64
5.62
5.62
4.77
4.77
4.75
4.74
4.74
4.73
4.72
4.70
4.70
2.16
2.15
2.14
2.14

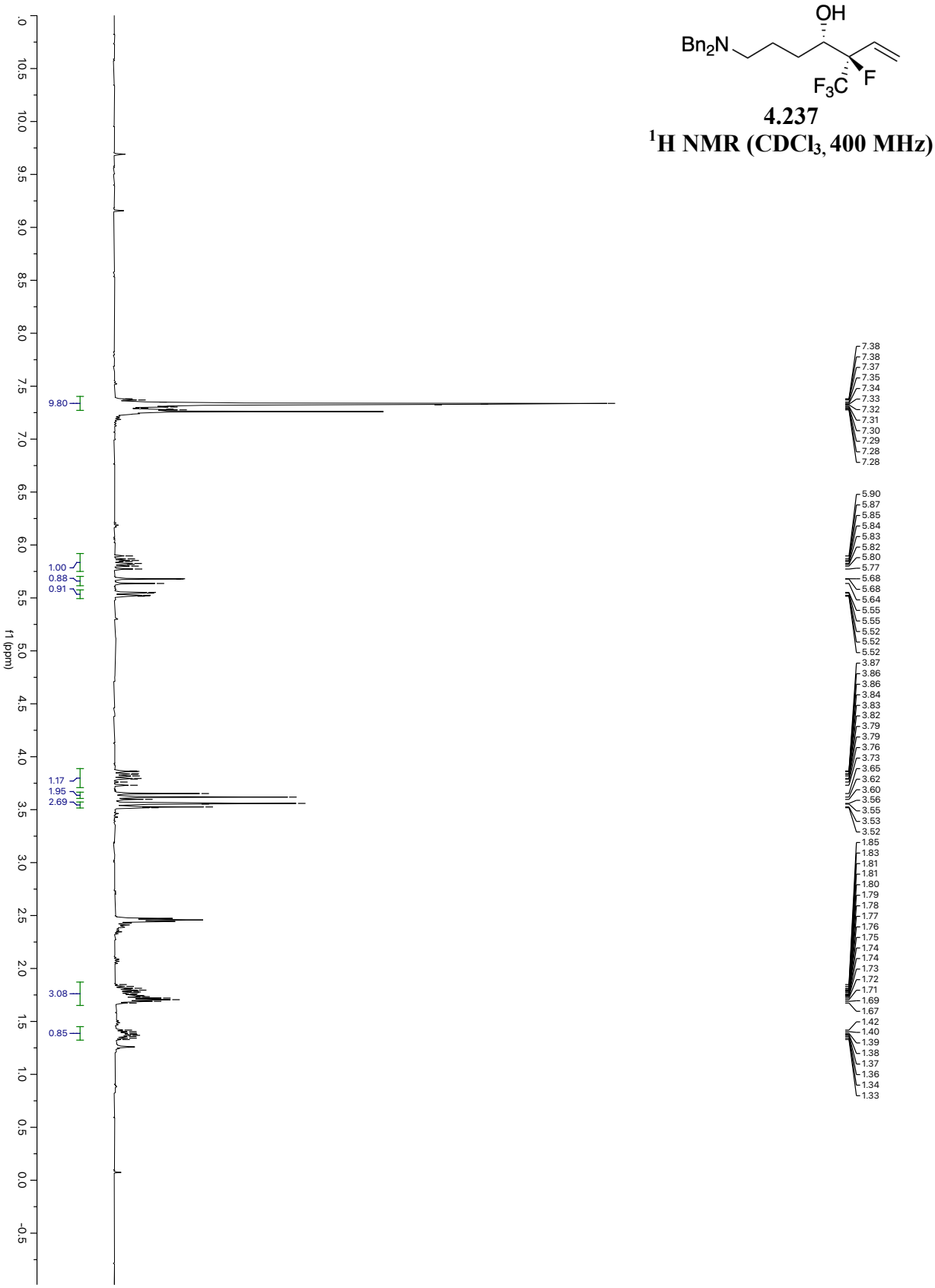

OH
F3C
F
4.235
13C NMR (CDCl3, 100 MHz)
128.70
128.68
128.65
128.39
126.76
126.73
126.71
126.55
124.00
123.71
123.01
122.91
121.92
121.80
121.16
120.87
96.82
96.53
96.23
95.94
94.89
94.60
94.31
94.02
72.77
72.69
72.55
72.47
135.81
134.67
f1 (ppm)


OH
F3C
F
4.235
1F NMR (CDCl3, 376 MHz)
-76.39
-76.41
-76.62
-76.65
-76.67
-76.70
-76.72
-77.15
-77.17
-77.51
-77.53
3.41
1.00
-182.39
-182.41
-182.43
-182.45
-182.47
-182.49
-182.50
-182.52
-182.54
f1 (ppm)


OH
F3C
F
4.236
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.92
2.59
2.99
1.00
1.06
1.11
2.08
1.16
7.31
7.29
7.29
7.28
7.27
7.22
7.21
7.20
7.20
7.19
7.18
5.85
5.82
5.81
5.80
5.78
5.77
5.75
5.73
5.70
5.68
5.64
5.59
5.58
5.56
5.55
4.01
4.01
3.99
3.99
3.98
3.98
3.97
3.96
3.95
3.95
3.94
3.94
3.92
3.92
2.98
2.97
2.95
2.94
2.93
2.92
2.91
2.72
2.72
2.70
2.70
2.69
2.68
2.67
2.67
2.65
1.97
1.96
1.95
1.93
1.91
1.91
1.89
1.89
1.80
1.79
1.78
1.77
1.77
1.76
1.75
1.74
1.74
1.73
1.73
1.72
1.70

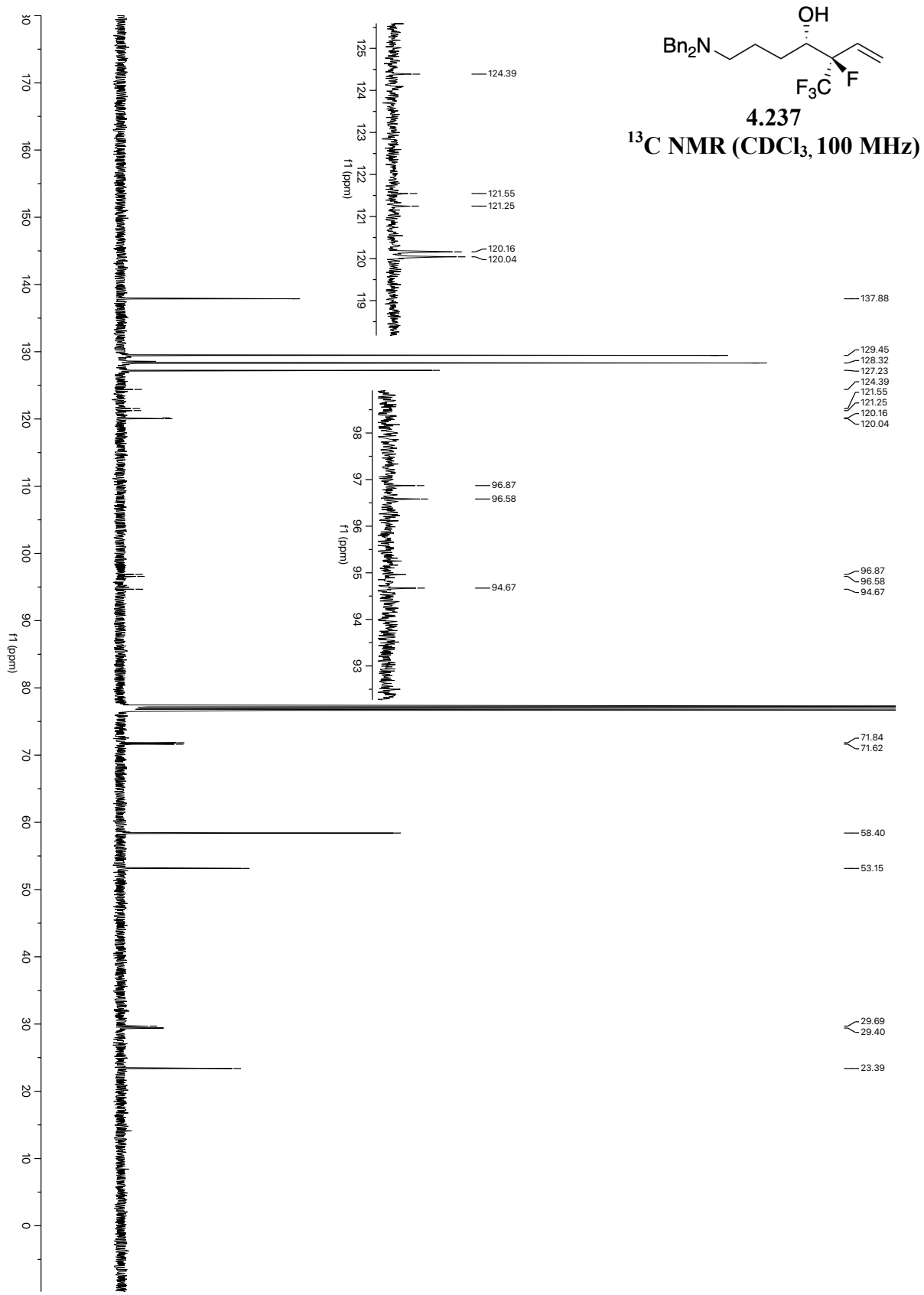

OH
F3C
F
4.236
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
127.18
126.99
126.16
124.15
123.86
121.30
121.18
121.02
140.91
128.52
128.46
127.18
126.99
126.16
124.15
123.86
121.30
121.18
121.02
97.23
96.94
96.65
96.36
95.33
95.04
94.75
94.47
71.03
70.82
32.37
32.36
32.33
32.32
31.66

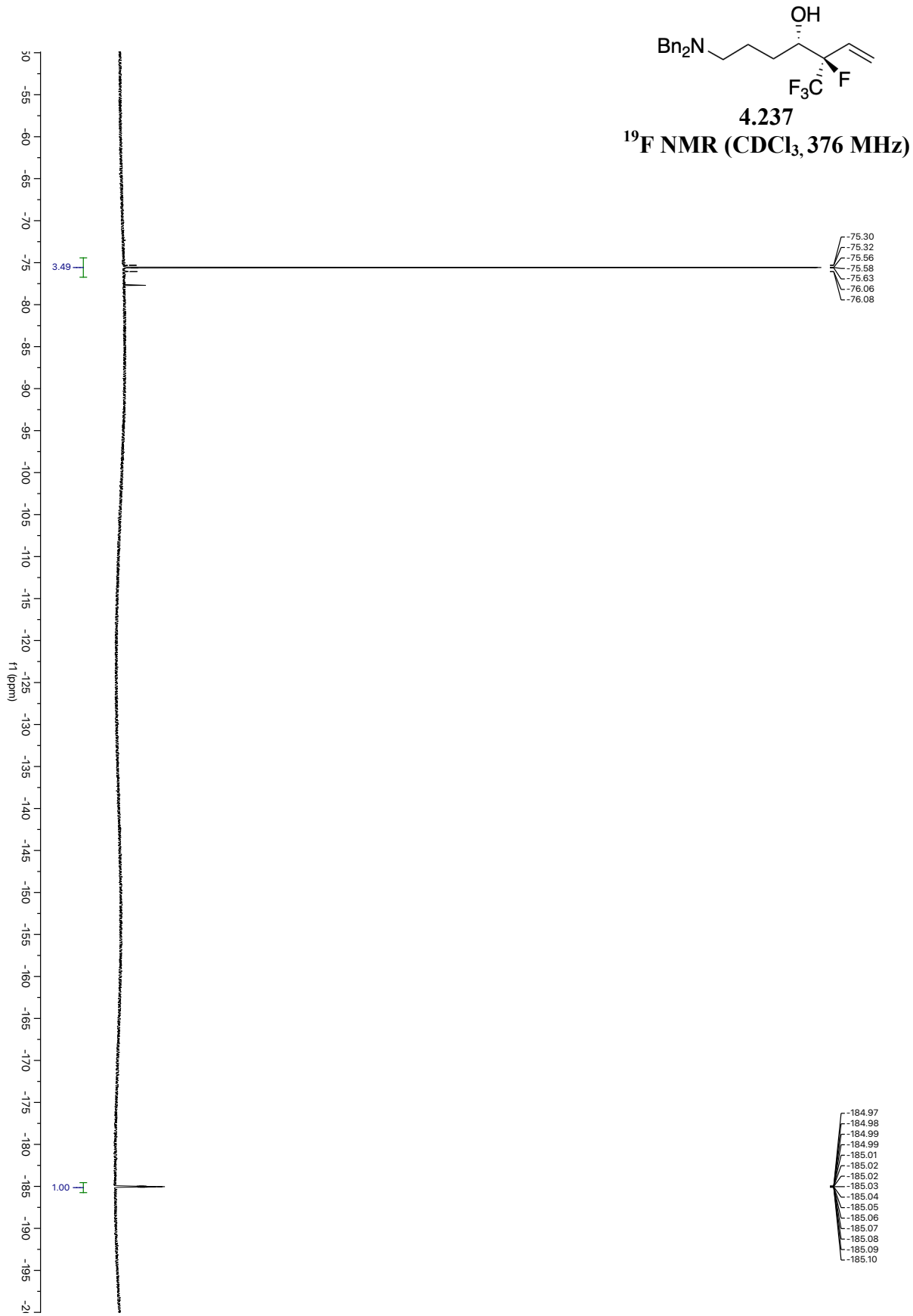

OH
F3C
F
4.236
19F NMR (CDCl3, 376 MHz)
3.00
0.82
-76.00
-76.02
-76.03
-76.04
-184.54
f1 (ppm)

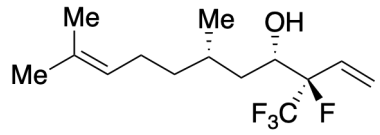


4.237

^{1}H NMR ($CDCl_3$, 400 MHz)

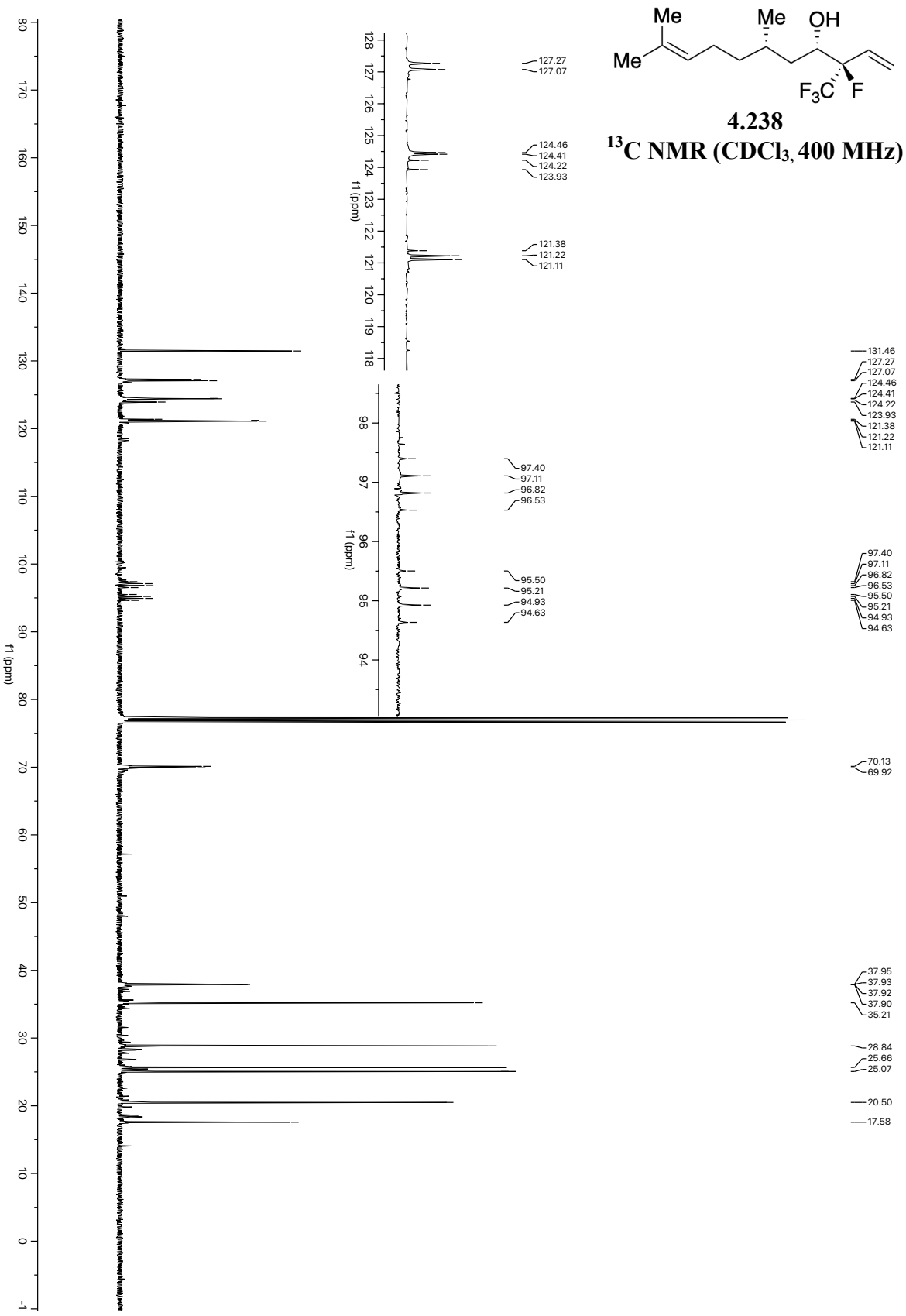

OH
Bn2N
F3C
F
4.237
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
124.39
121.55
121.25
120.16
120.04
137.88
129.45
128.32
127.23
96.87
96.58
94.67
71.84
71.62
58.40
53.15
29.69
29.40
23.39

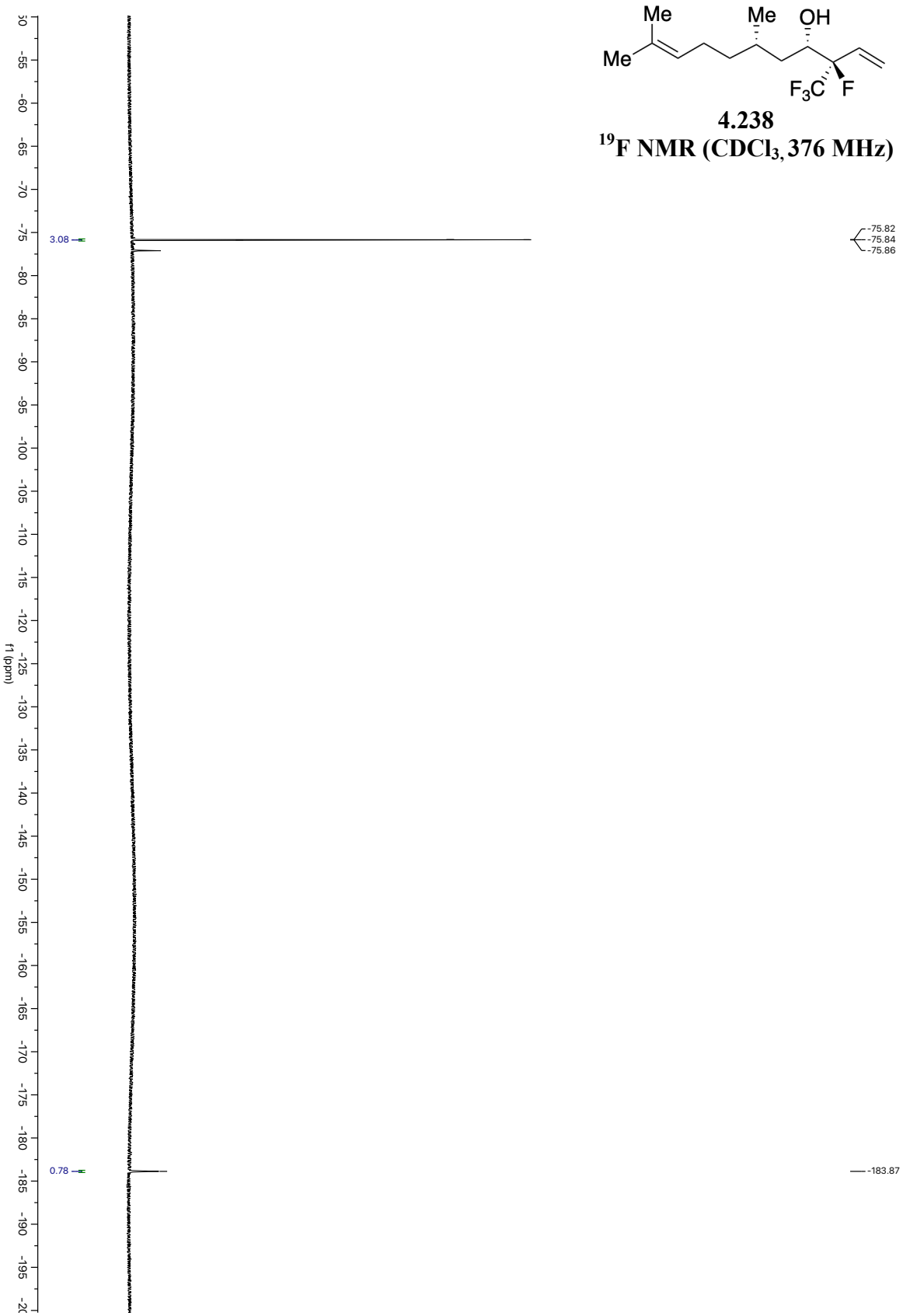

OH
Bn2N
F3C
F
4.237
19F NMR (CDCl3, 376 MHz)
-75.30
-75.32
-75.56
-75.58
-75.63
-76.06
-76.08
3.49
1.00
-184.97
-184.98
-184.99
-184.99
-185.01
-185.02
-185.02
-185.03
-185.04
-185.05
-185.06
-185.07
-185.08
-185.09
-185.10
f1 (ppm)

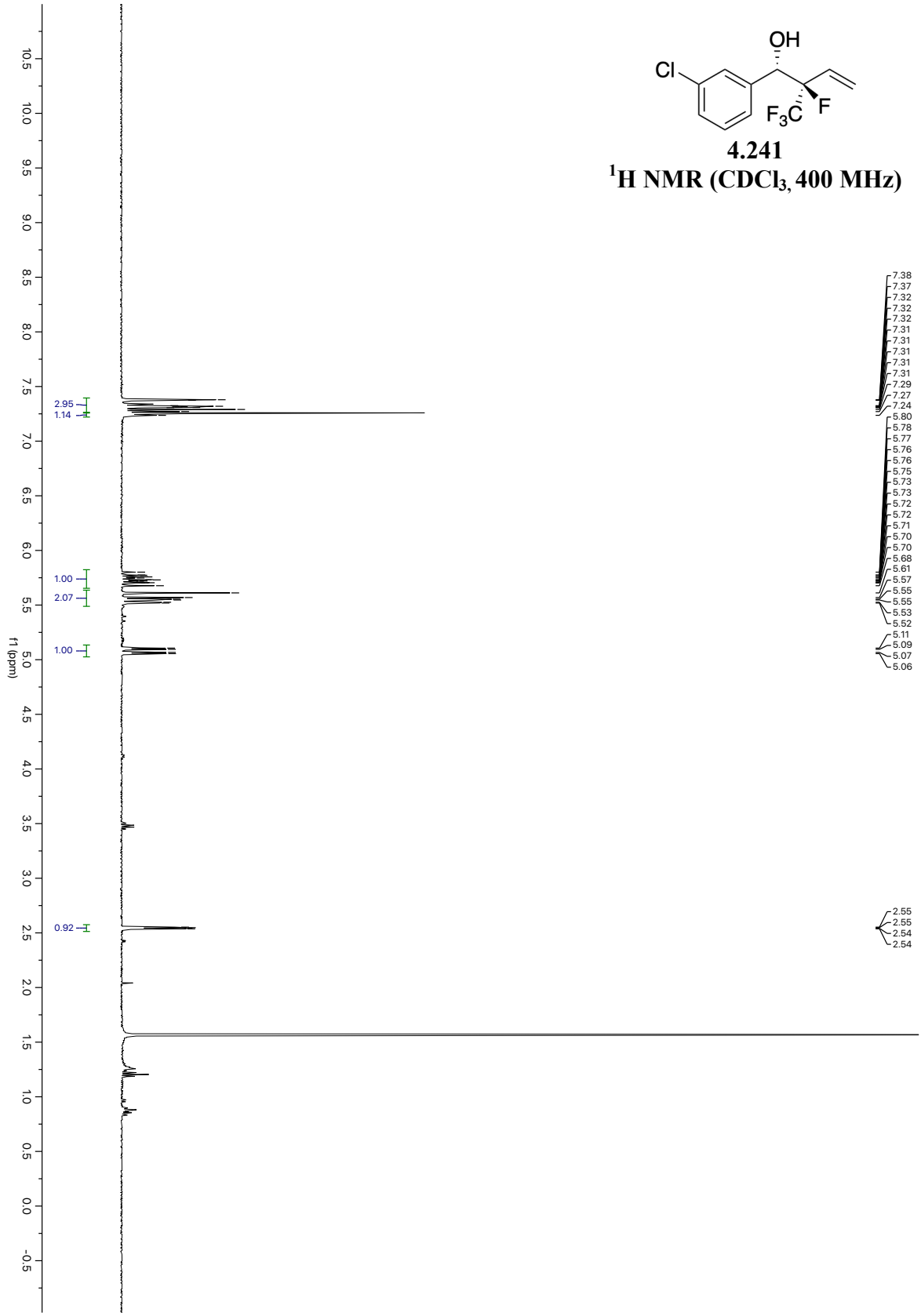


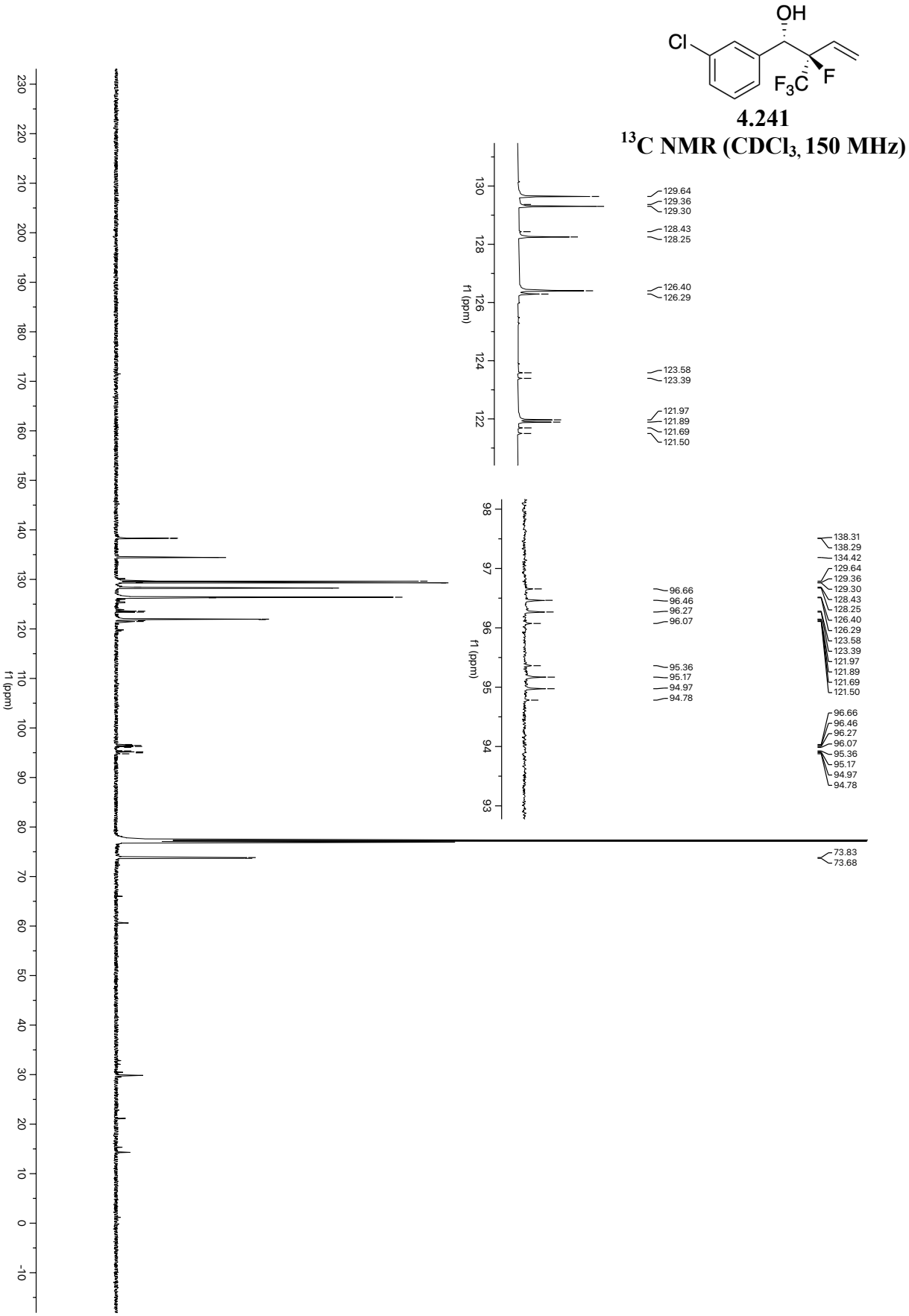
4.238

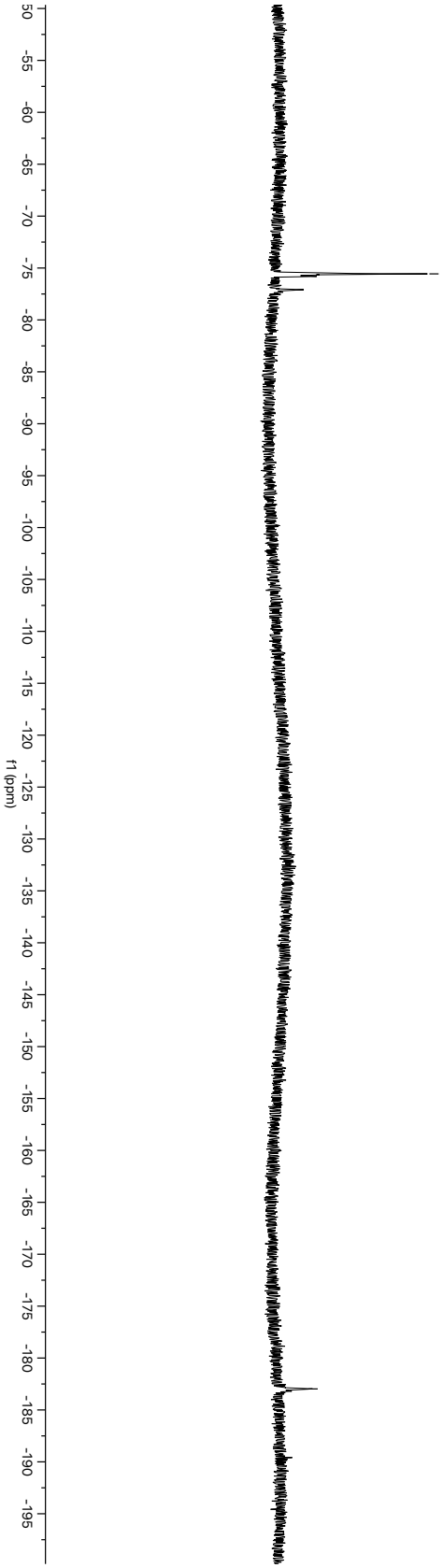
^{1}H NMR ($CDCl_3$, 400 MHz)

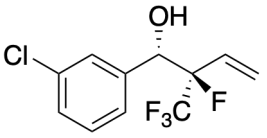

Me
Me
OH
Me
F3C
F
4.238
13C NMR (CDCl3, 400 MHz)
f1 (ppm)
127.27
127.07
124.46
124.41
124.22
123.93
121.38
121.22
121.11
97.40
97.11
96.82
96.53
95.50
95.21
94.93
94.63
131.46
70.13
69.92
37.95
37.93
37.92
37.90
35.21
28.84
25.66
25.07
20.50
17.58


Me
Me
OH
Me
F3C
F
4.238
19F NMR (CDCl3, 376 MHz)
3.08
0.78
-75.82
-75.84
-75.86
-183.87
f1 (ppm)


OH
Cl
F3C
F
4.241
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
2.95
1.14
1.00
2.07
1.00
0.92
7.38
7.37
7.32
7.32
7.32
7.31
7.31
7.31
7.31
7.31
7.29
7.27
7.24
5.80
5.78
5.77
5.76
5.76
5.75
5.73
5.73
5.72
5.72
5.71
5.70
5.70
5.68
5.61
5.57
5.55
5.55
5.53
5.52
5.11
5.09
5.07
5.06
2.55
2.55
2.54
2.54


OH
Cl
F3C
F
4.241
13C NMR (CDCl3, 150 MHz)
f1 (ppm)
129.64
129.36
129.30
128.43
128.25
126.40
126.29
123.58
123.39
121.97
121.89
121.69
121.50
96.66
96.46
96.27
96.07
95.36
95.17
94.97
94.78
138.31
138.29
134.42
73.83
73.68



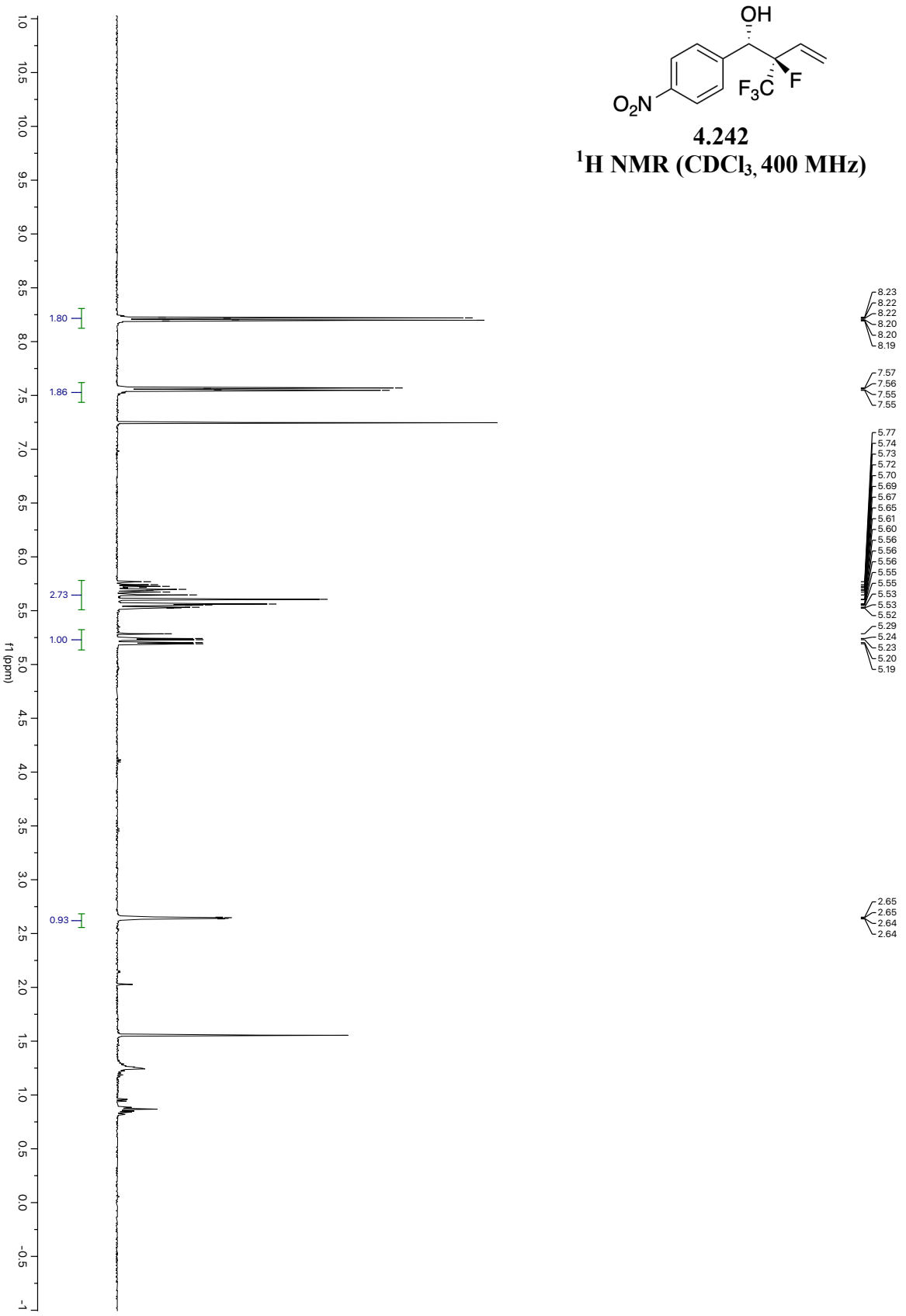


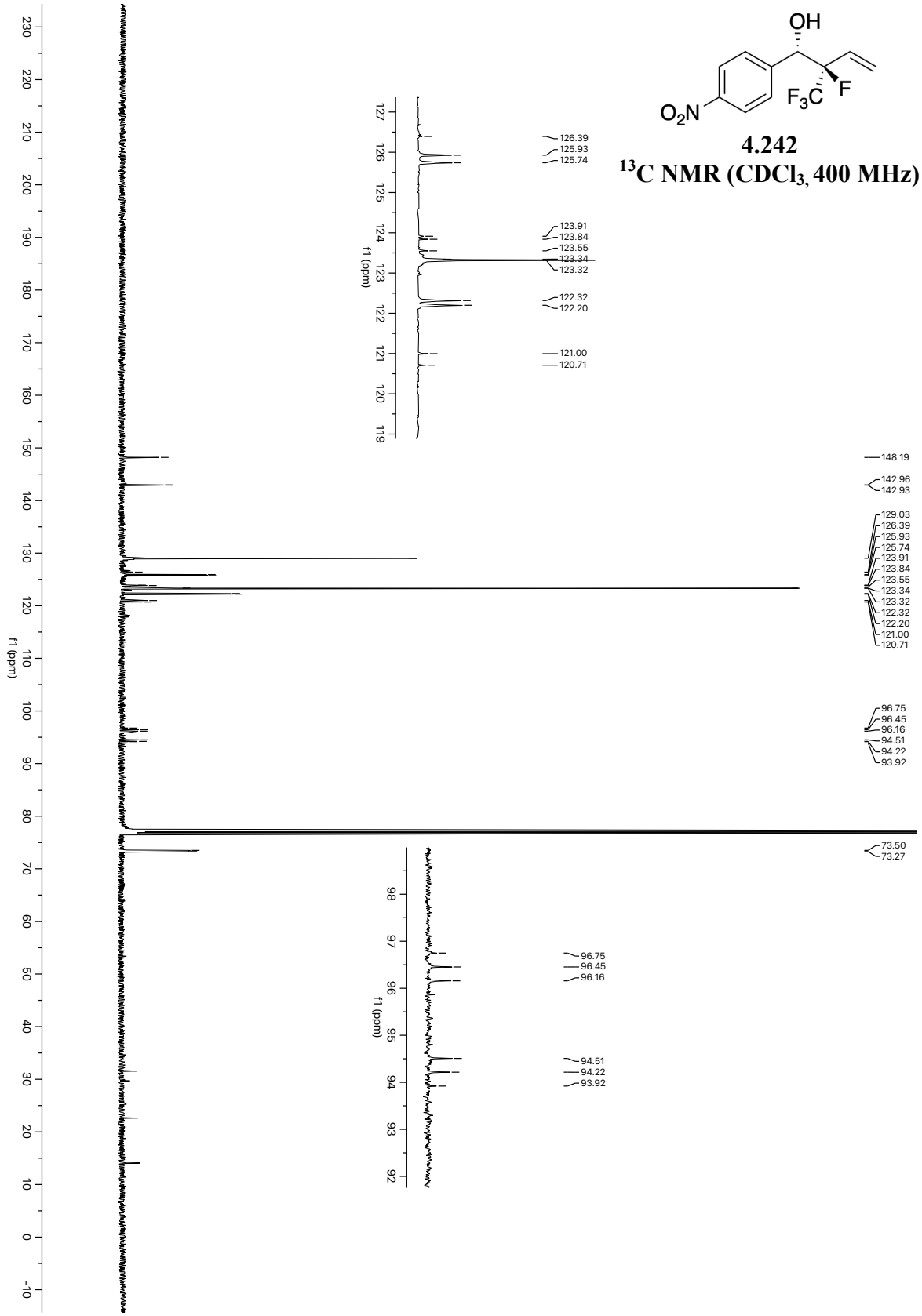
4.241

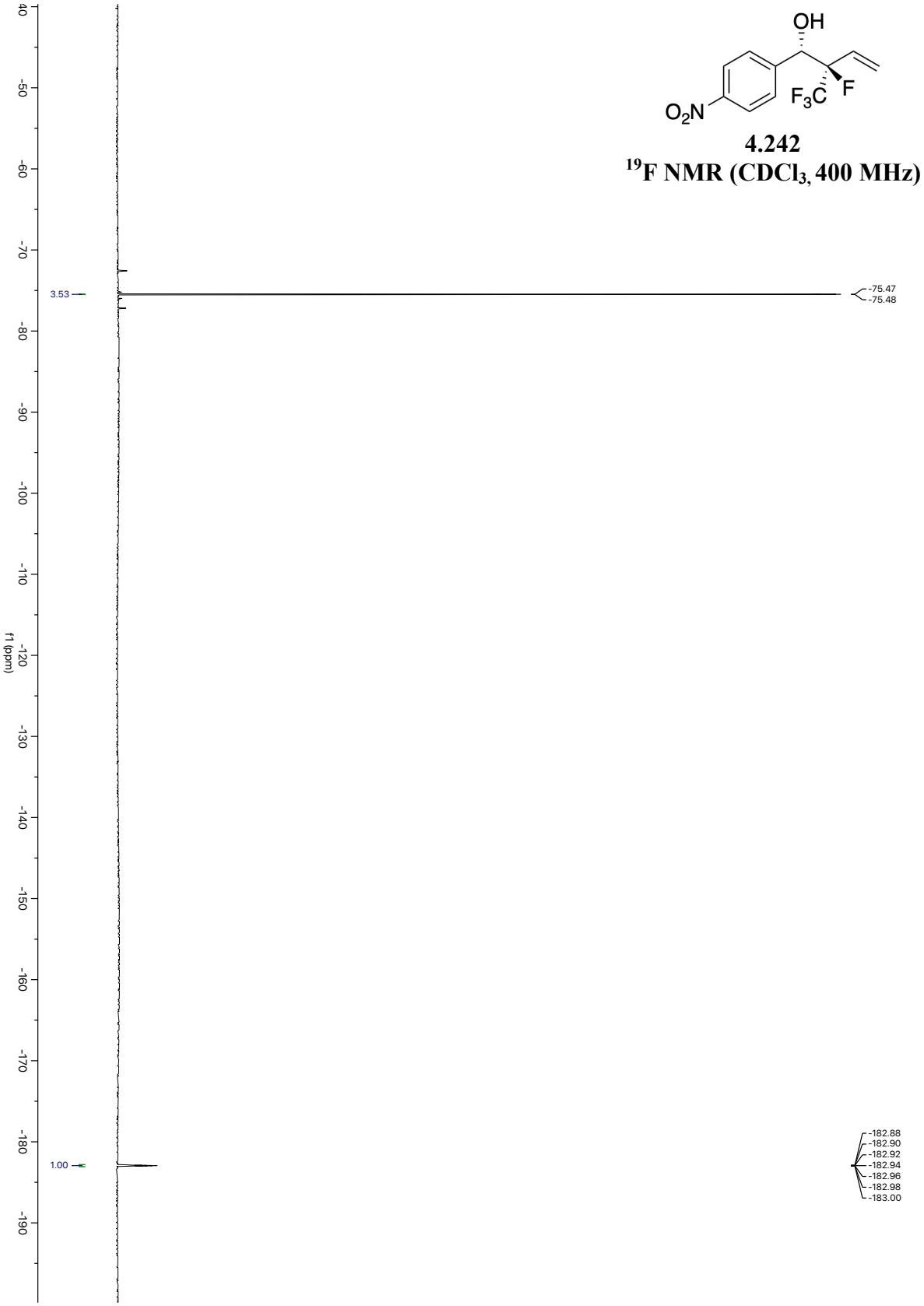
^{19}F NMR ($CDCl_3$, 376 MHz)

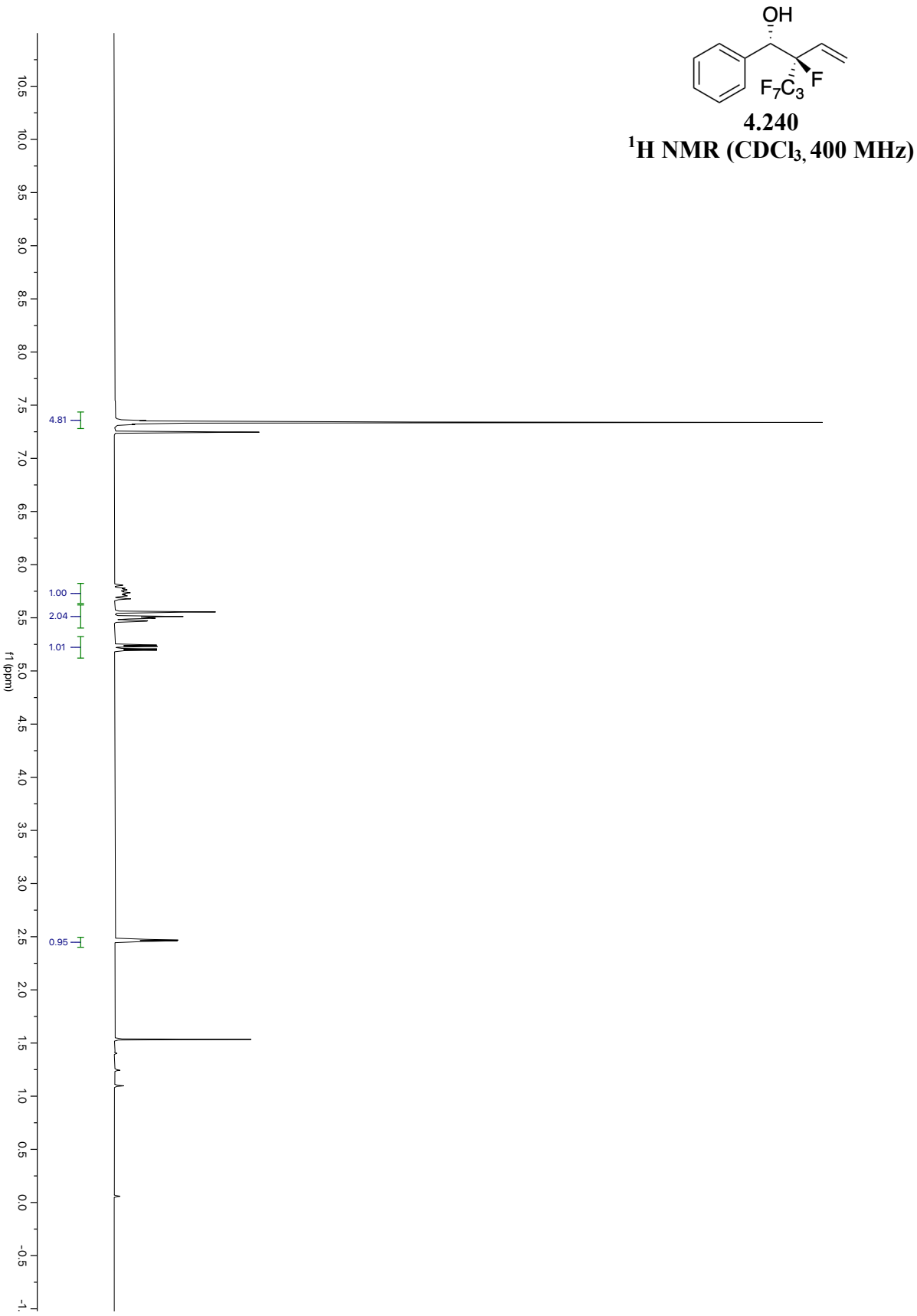
-75.56

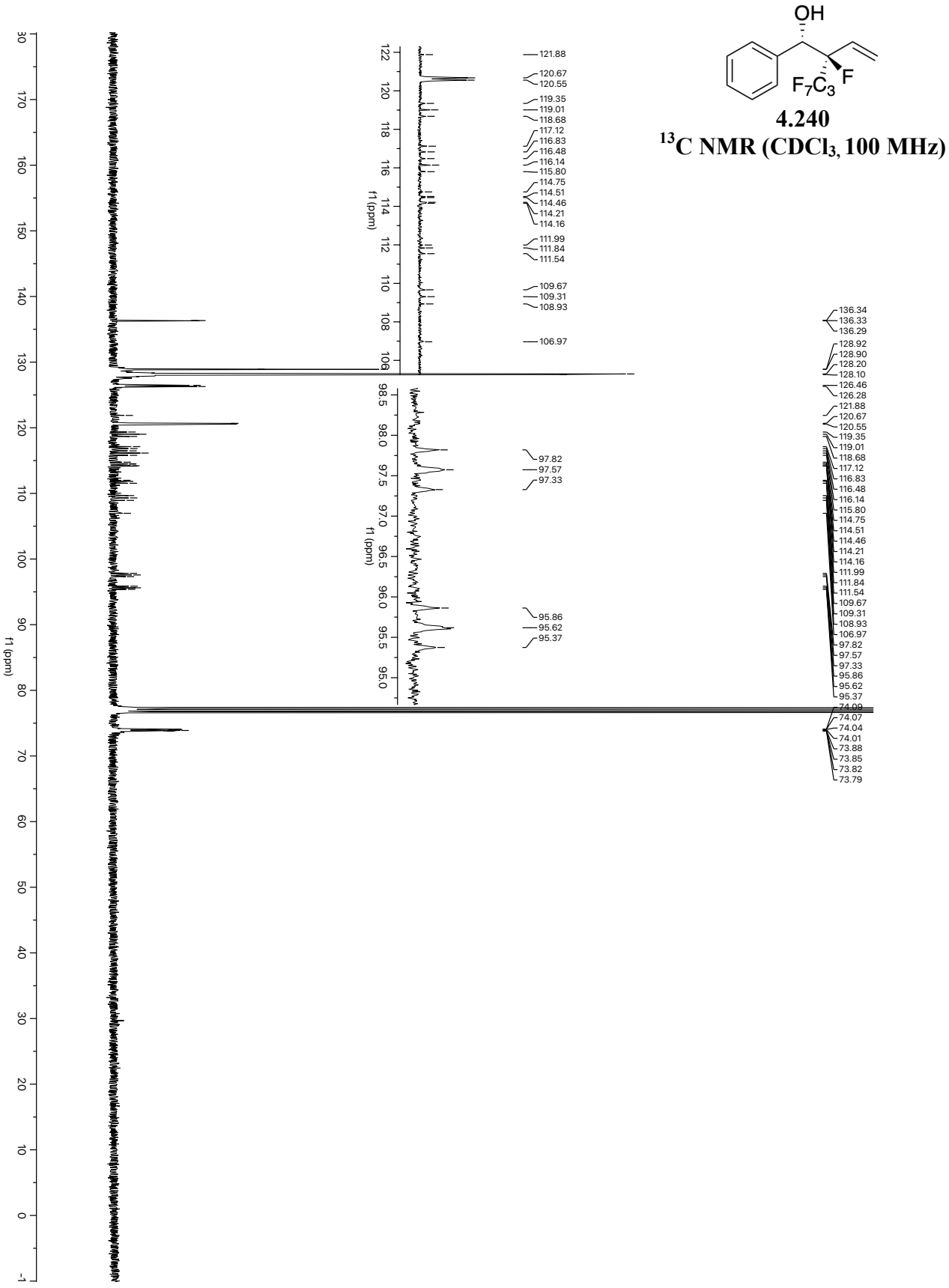
-182.97

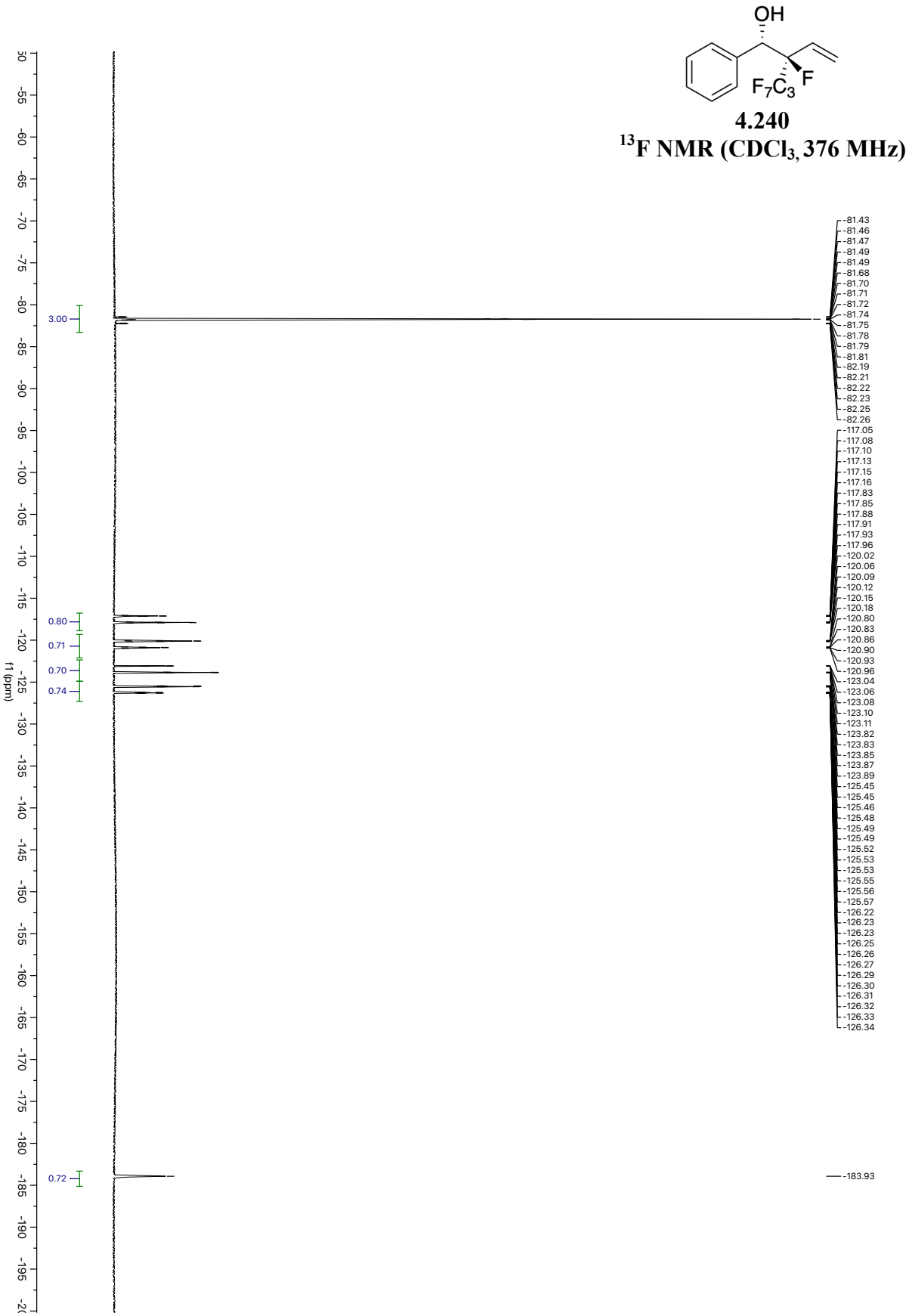

OH
F
F3C
O2N
4.242
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.80
1.86
2.73
1.00
0.93
8.23
8.22
8.22
8.20
8.20
8.19
7.57
7.56
7.55
7.55
5.77
5.74
5.73
5.72
5.70
5.69
5.67
5.65
5.61
5.60
5.56
5.56
5.56
5.55
5.55
5.53
5.53
5.52
5.29
5.24
5.23
5.20
5.19
2.65
2.65
2.64
2.64

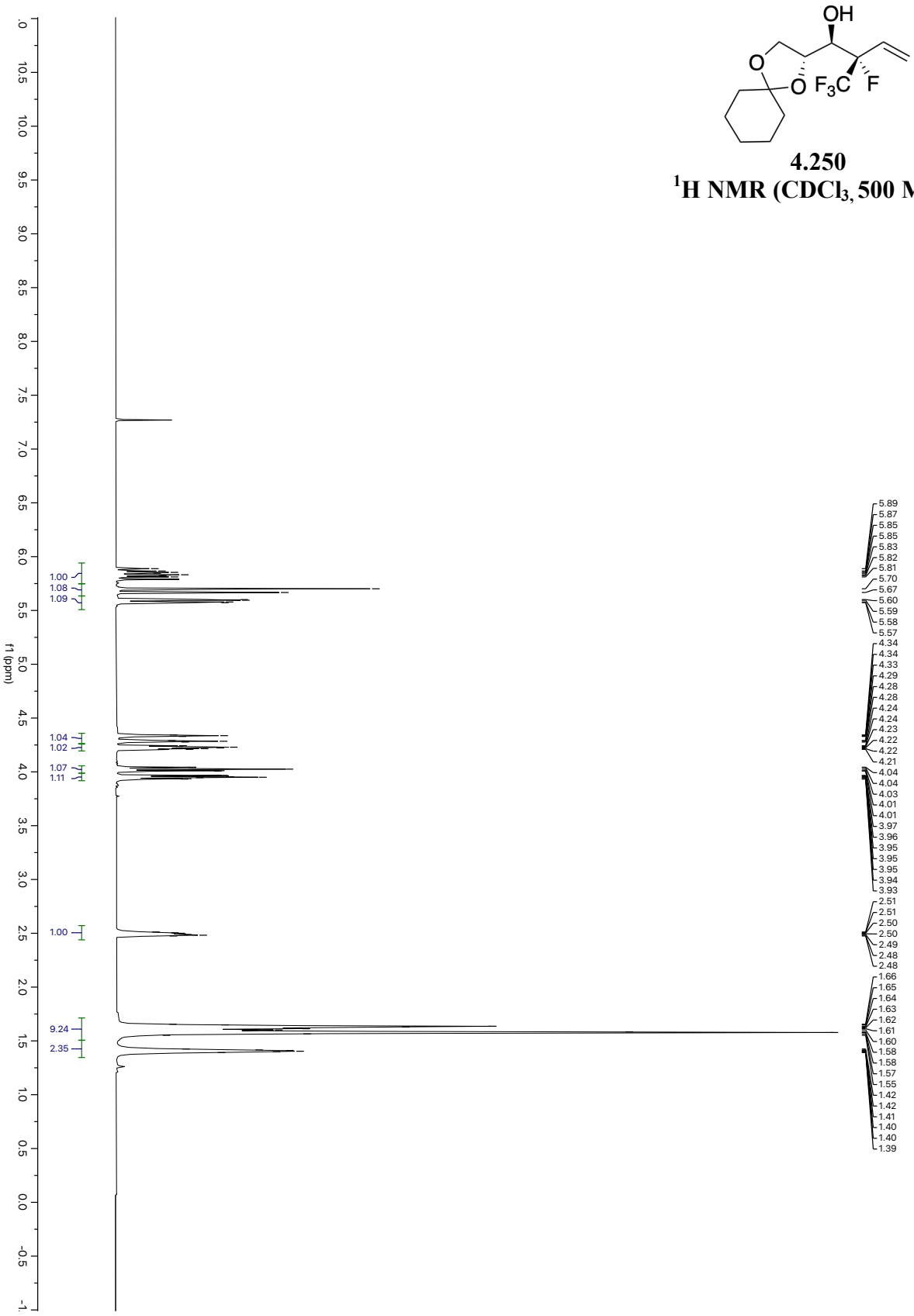

OH
F3C
F
O2N
4.242
13C NMR (CDCl3, 400 MHz)
f1 (ppm)
126.39
125.93
125.74
123.91
123.84
123.55
123.34
123.32
122.32
122.20
121.00
120.71
148.19
142.96
142.93
129.03
126.39
125.93
125.74
123.91
123.84
123.55
123.34
123.32
122.32
122.20
121.00
120.71
96.75
96.45
96.16
94.51
94.22
93.92
73.50
73.27

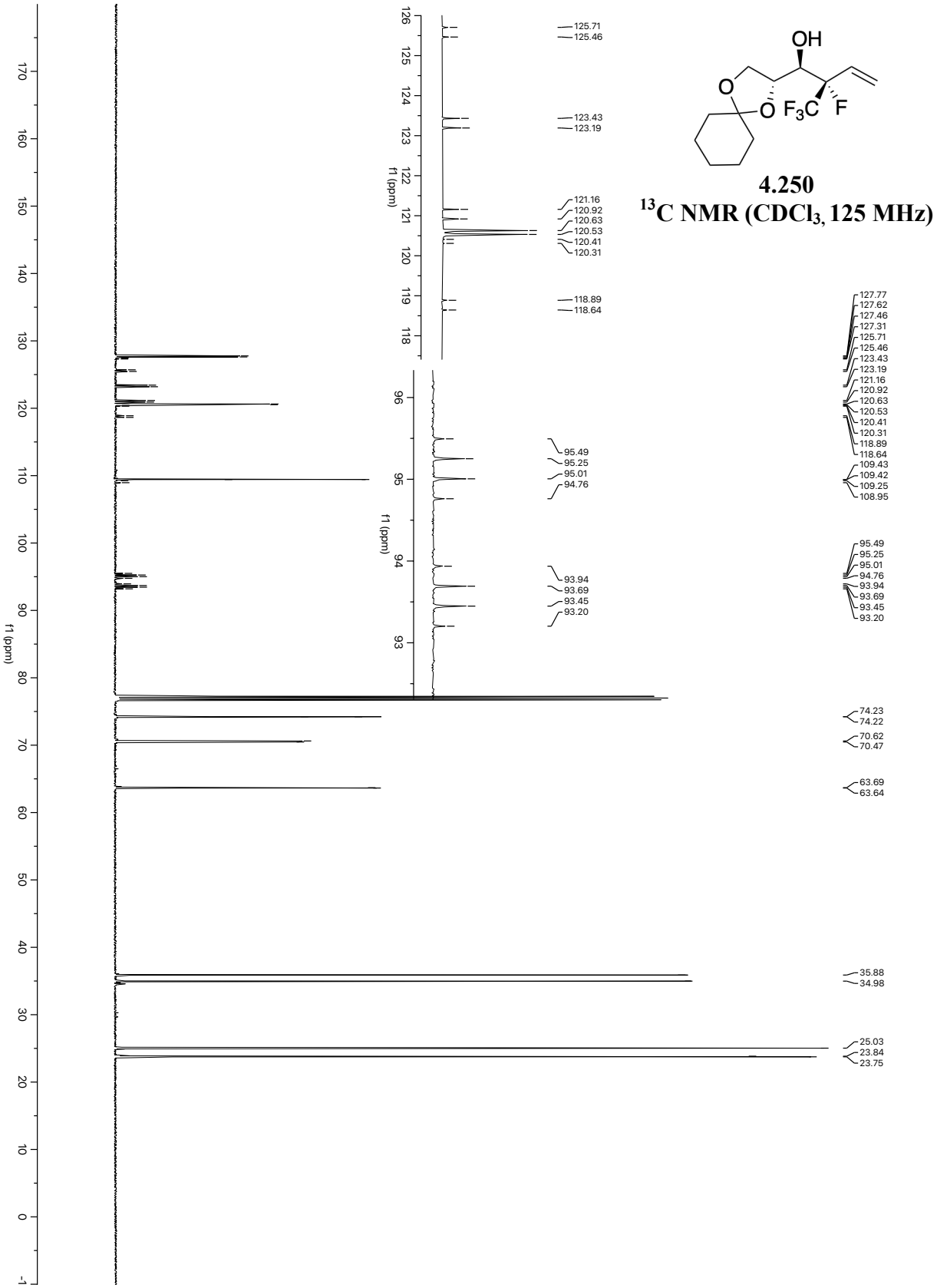

OH
F3C
F
O2N
4.242
19F NMR (CDCl3, 400 MHz)
3.53
1.00
-75.47
-75.48
-182.88
-182.90
-182.92
-182.94
-182.96
-182.98
-183.00
f1 (ppm)
40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

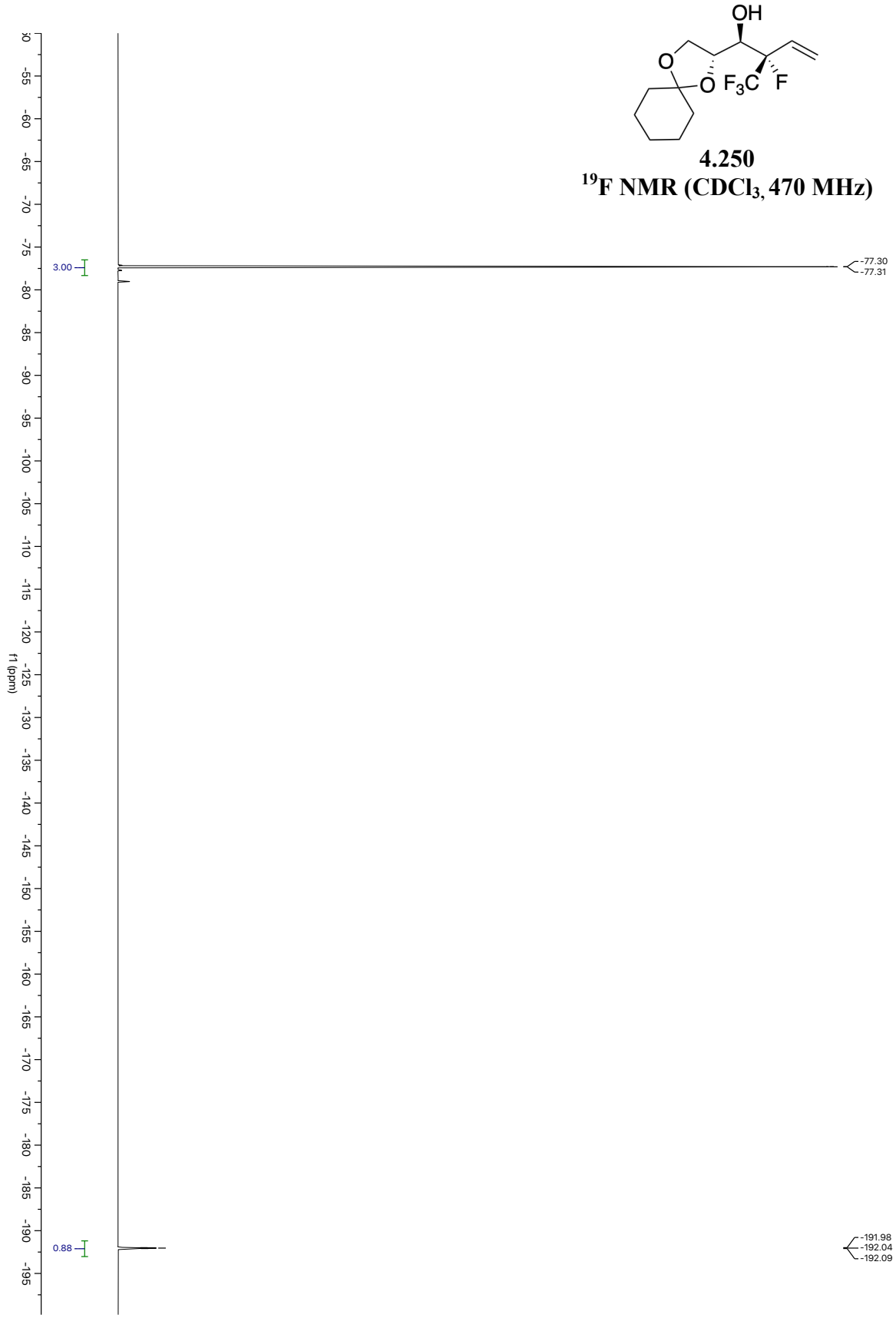

OH
F7C3
F
4.240
1H NMR (CDCl3, 400 MHz)
4.81
1.00
2.04
1.01
0.95
f1 (ppm)

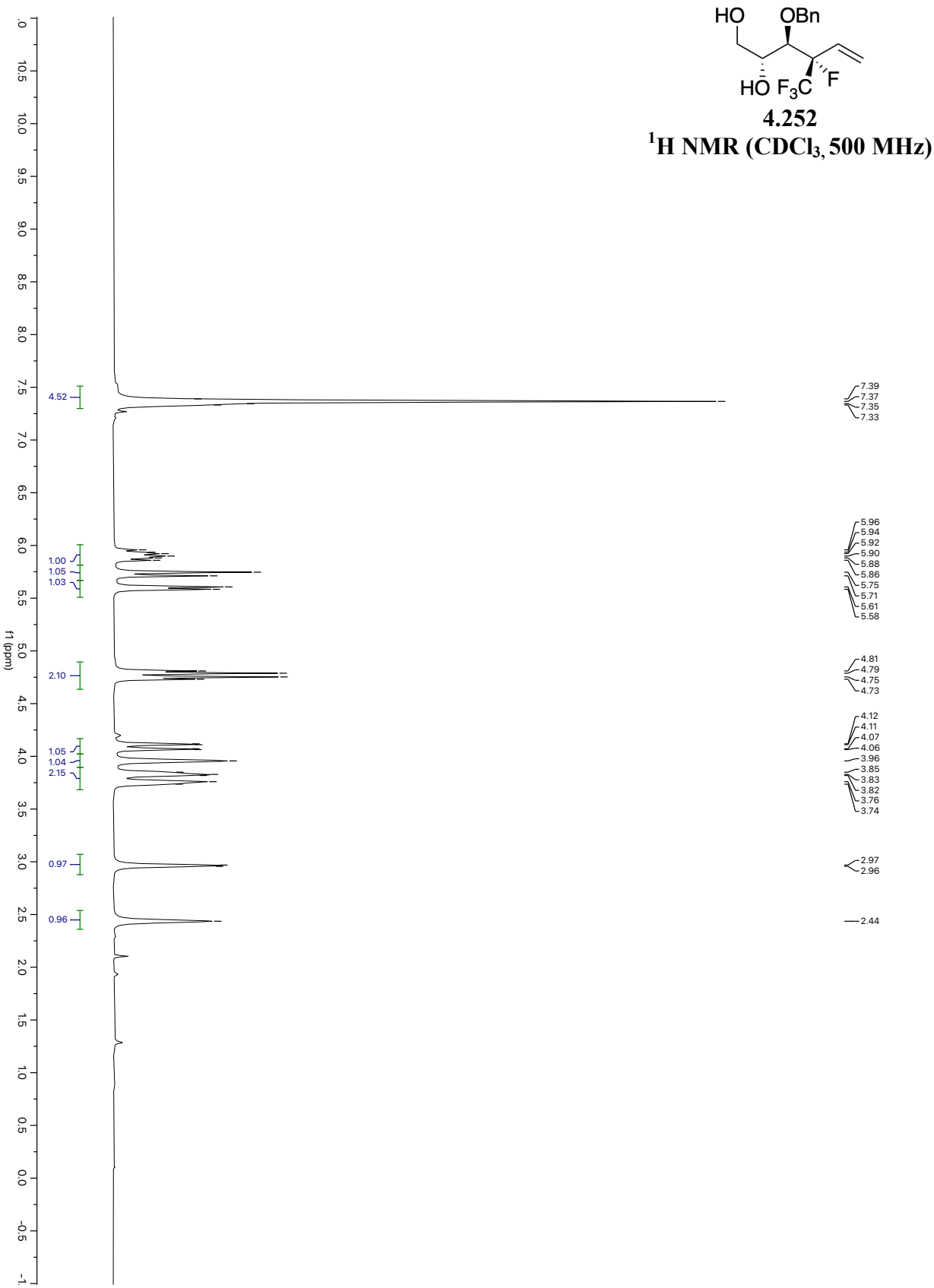

OH
F7C3
F
4.240
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
121.88
120.67
120.55
119.35
119.01
118.68
117.12
116.83
116.48
116.14
115.80
114.75
114.51
114.46
114.21
114.16
111.99
111.84
111.54
109.67
109.31
108.93
106.97
97.82
97.57
97.33
95.86
95.62
95.37
136.34
136.33
136.29
128.92
128.90
128.20
128.10
126.46
126.28
74.09
74.07
74.04
74.01
73.88
73.85
73.82
73.79

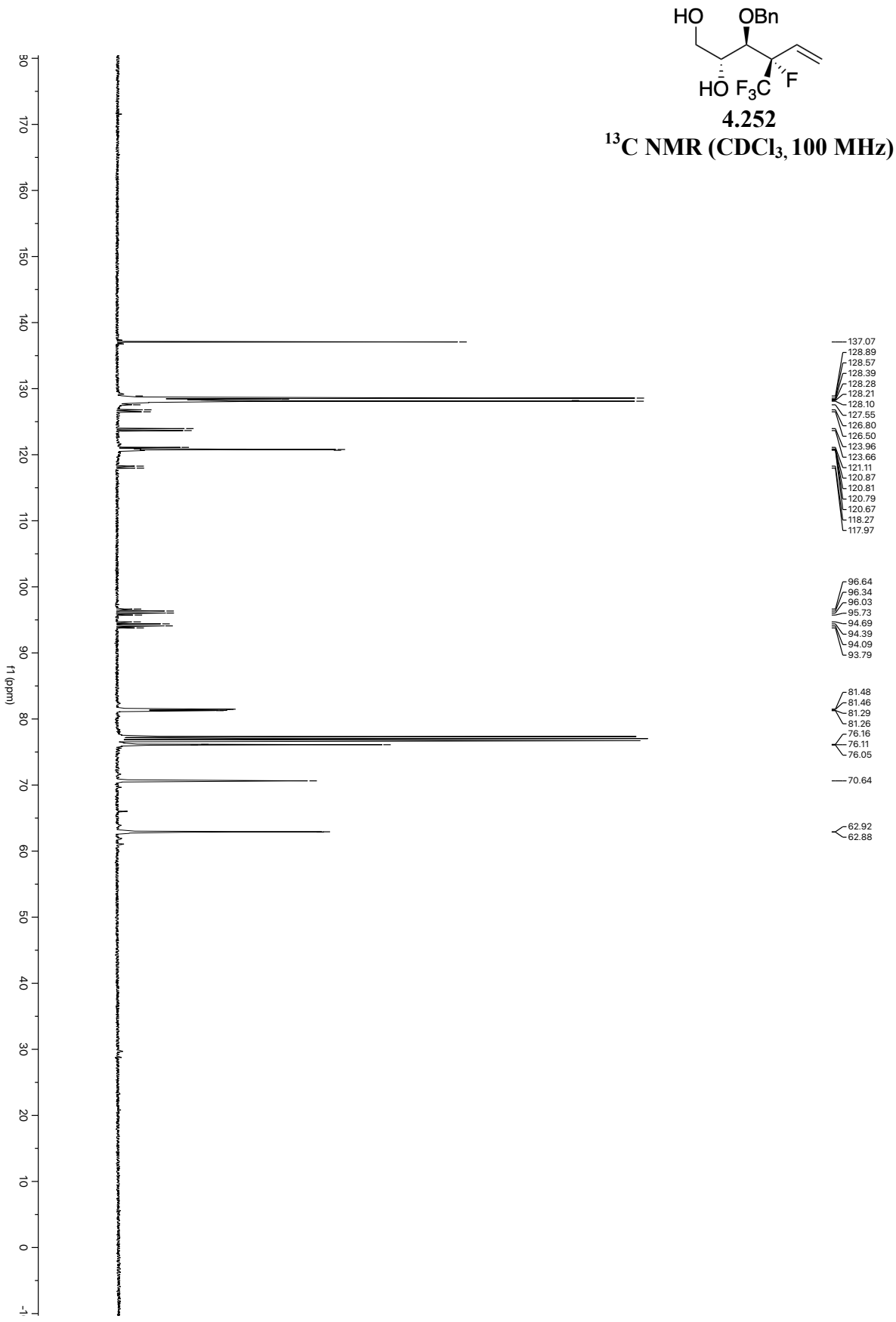

OH
F7C3
F
4.240
13F NMR (CDCl3, 376 MHz)
f1 (ppm)
3.00
0.80
0.71
0.70
0.74
0.72
-81.43
-81.46
-81.47
-81.49
-81.49
-81.68
-81.70
-81.71
-81.72
-81.74
-81.75
-81.78
-81.79
-81.81
-82.19
-82.21
-82.22
-82.23
-82.25
-82.26
-117.05
-117.08
-117.10
-117.13
-117.15
-117.16
-117.83
-117.85
-117.88
-117.91
-117.93
-117.96
-120.02
-120.06
-120.09
-120.12
-120.15
-120.18
-120.80
-120.83
-120.86
-120.90
-120.93
-120.96
-123.04
-123.06
-123.08
-123.10
-123.11
-123.82
-123.83
-123.85
-123.87
-123.89
-125.45
-125.45
-125.46
-125.48
-125.49
-125.49
-125.52
-125.53
-125.53
-125.55
-125.56
-125.57
-126.22
-126.23
-126.23
-126.25
-126.26
-126.27
-126.29
-126.30
-126.31
-126.32
-126.33
-126.34
-183.93

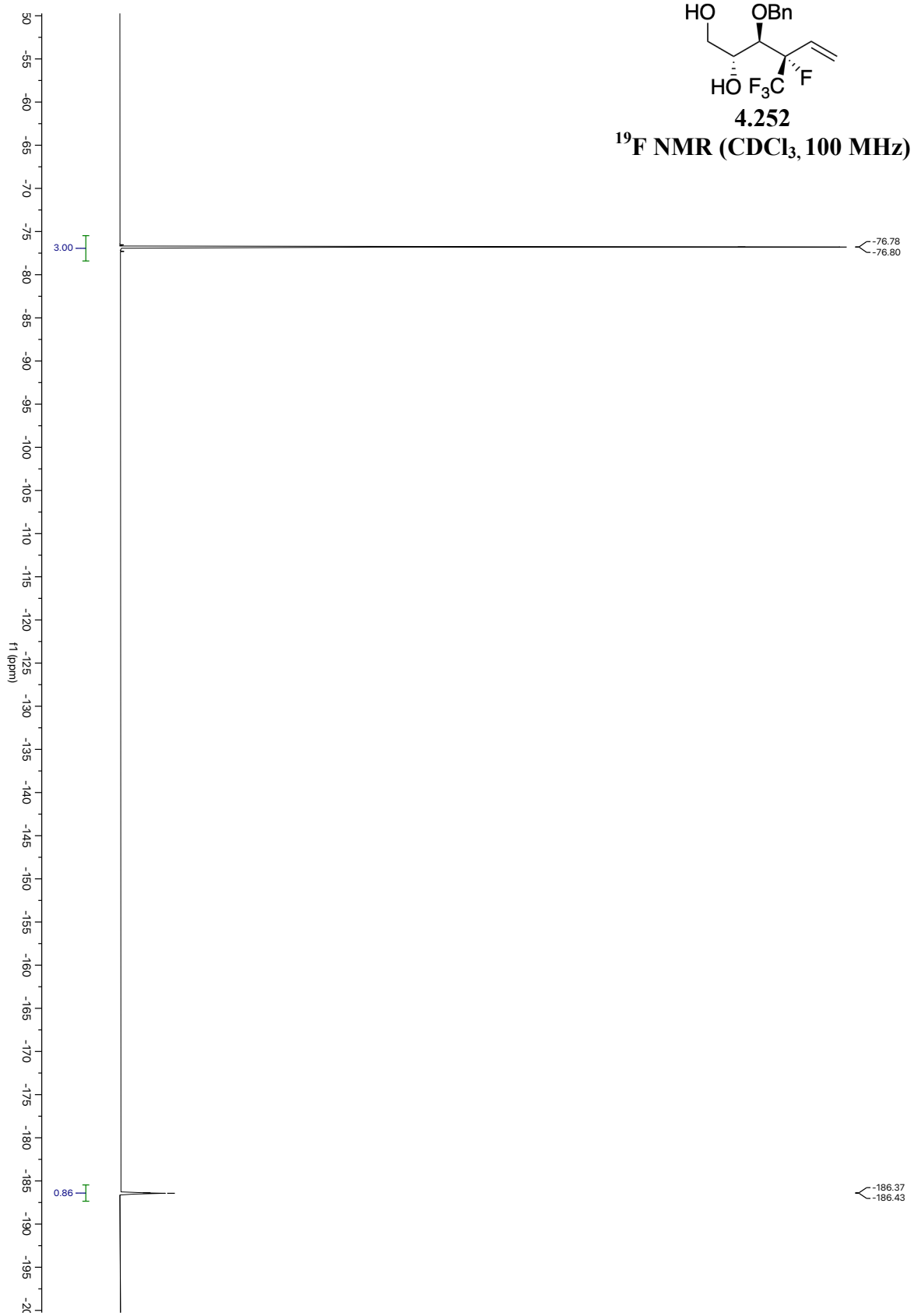

OH
O
O
F3C
F
4.250
1H NMR (CDCl3, 500 MHz)
f1 (ppm)
1.00
1.08
1.09
1.04
1.02
1.07
1.11
1.00
9.24
2.35

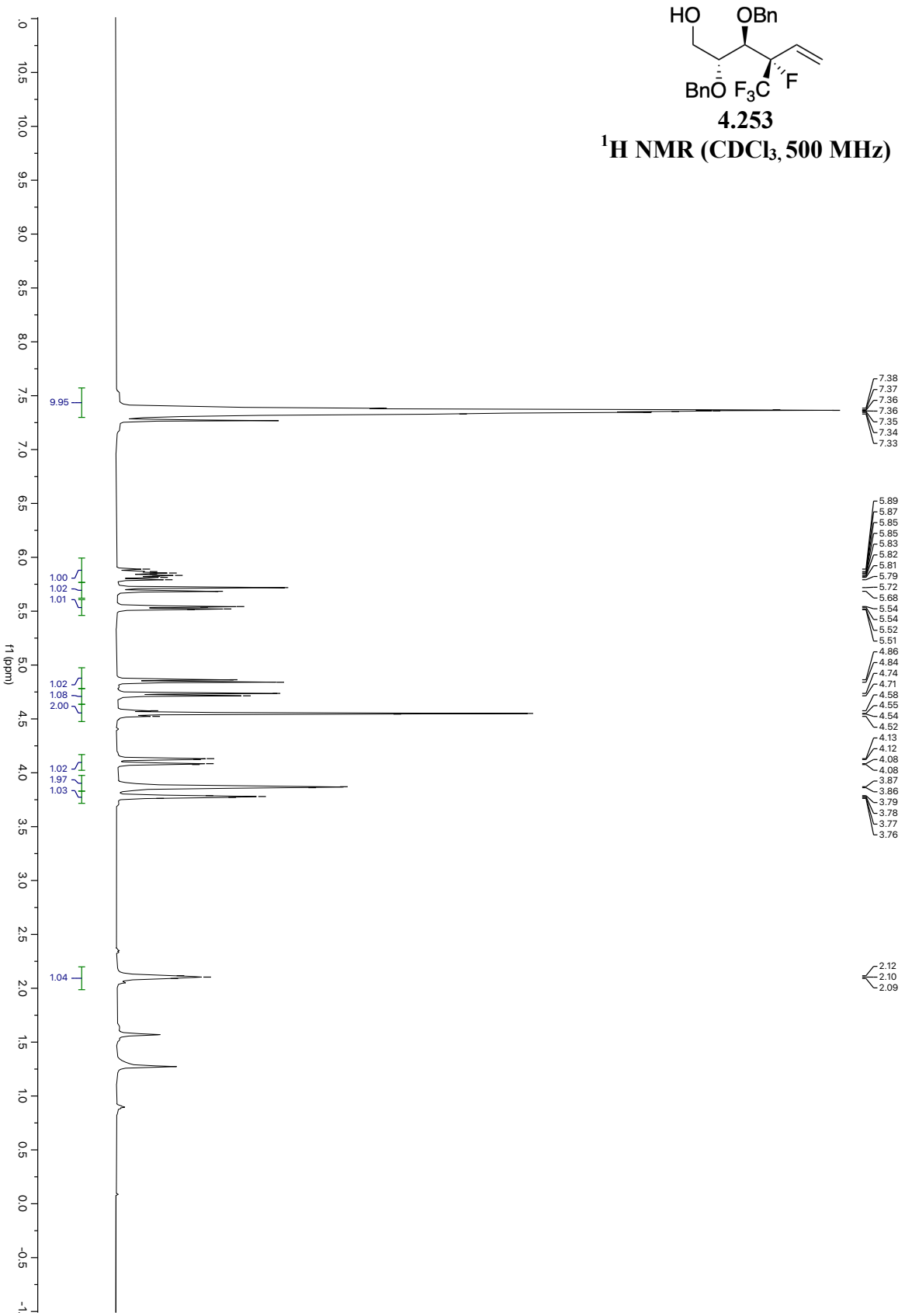

OH
O
O
F3C
F
4.250
13C NMR (CDCl3, 125 MHz)
f1 (ppm)
125.71
125.46
123.43
123.19
121.16
120.92
120.63
120.53
120.41
120.31
118.89
118.64
95.49
95.25
95.01
94.76
93.94
93.69
93.45
93.20
127.77
127.62
127.46
127.31
109.43
109.42
109.25
108.95
74.23
74.22
70.62
70.47
63.69
63.64
35.88
34.98
25.03
23.84
23.75

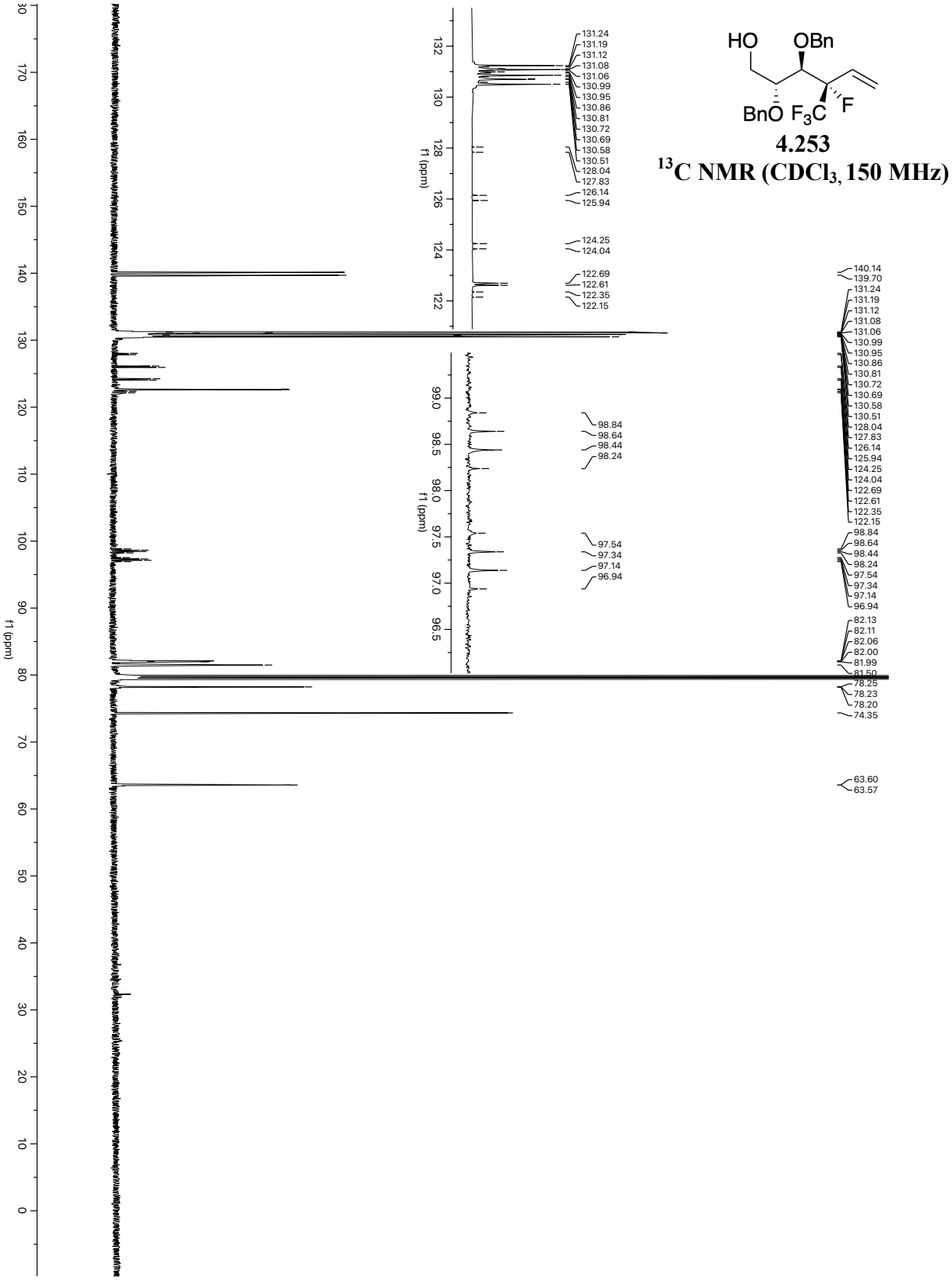

OH
O
O
F3C
F
4.250
19F NMR (CDCl3, 470 MHz)
3.00
0.88
-77.30
-77.31
-191.98
-192.04
-192.09
f1 (ppm)

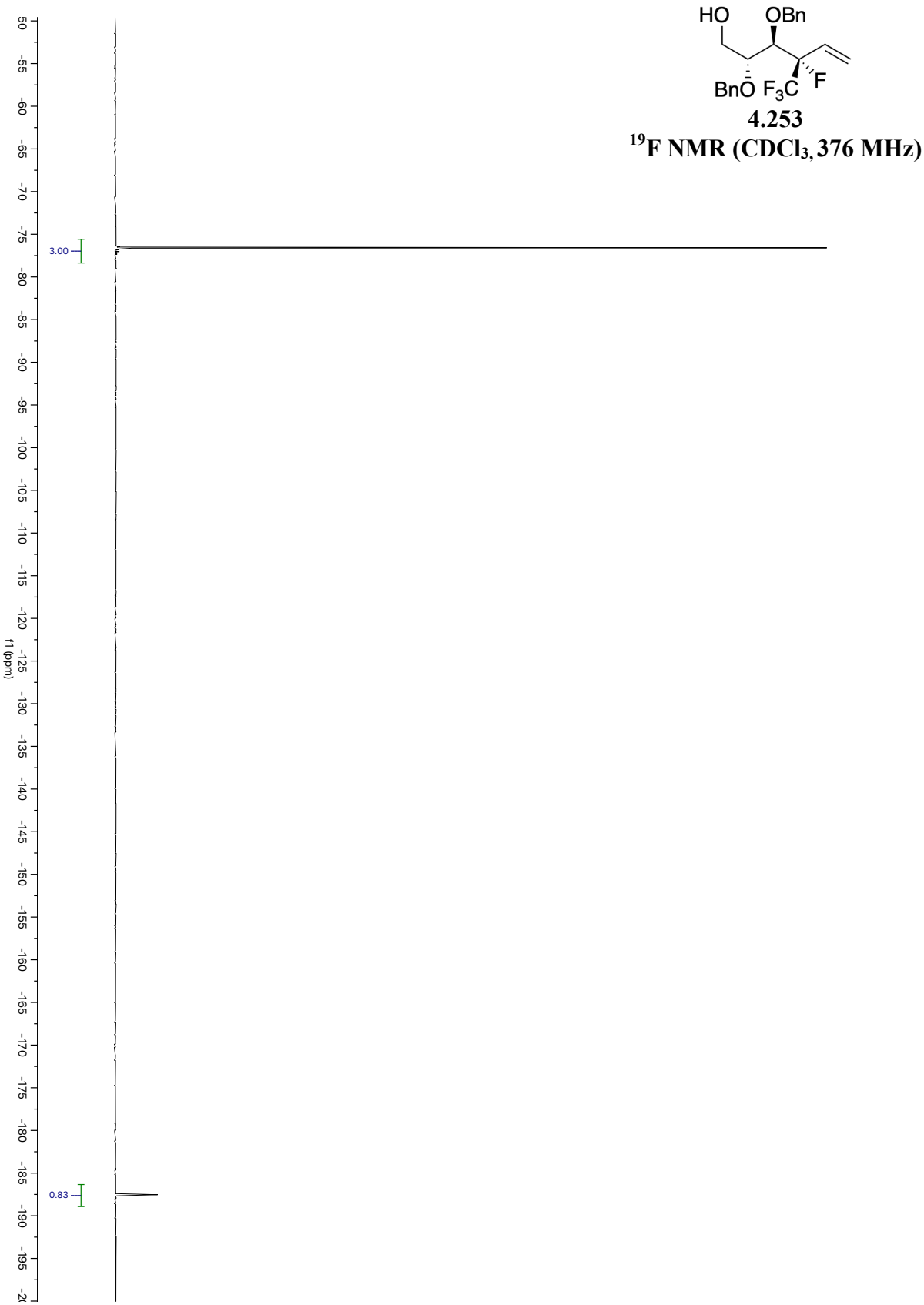

HO
OBn
HO
F3C
F
4.252
1H NMR (CDCl3, 500 MHz)
f1 (ppm)
4.52
1.00
1.05
1.03
2.10
1.05
1.04
2.15
0.97
0.96
7.39
7.37
7.35
7.33
5.96
5.94
5.92
5.90
5.88
5.86
5.75
5.71
5.61
5.58
4.81
4.79
4.75
4.73
4.12
4.11
4.07
4.06
3.96
3.85
3.83
3.82
3.76
3.74
2.97
2.96
2.44

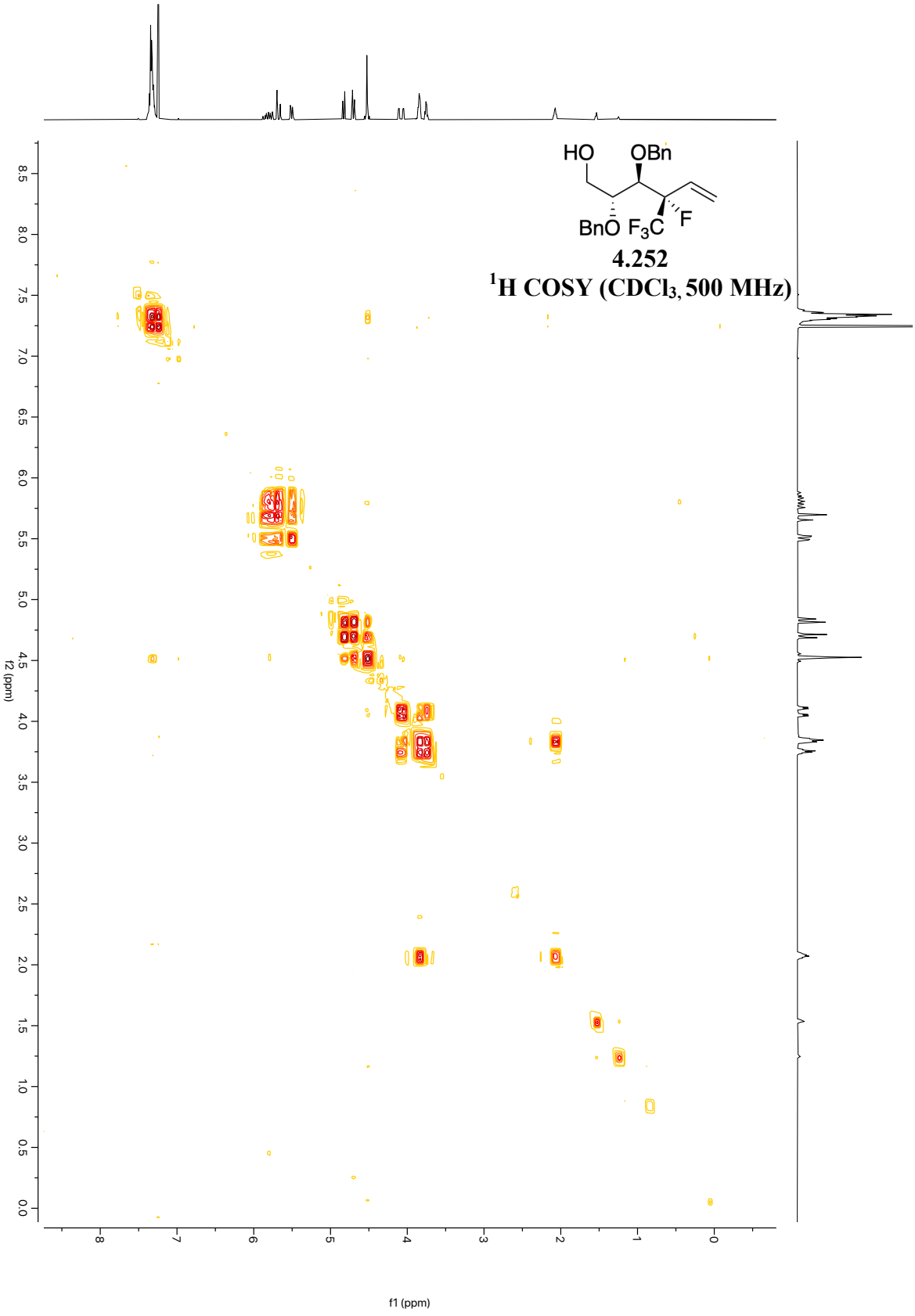

HO
OBn
HO
F3C
F
4.252
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
137.07
128.89
128.57
128.39
128.28
128.21
128.10
127.55
126.80
126.50
123.96
123.66
121.11
120.87
120.81
120.79
120.67
118.27
117.97
96.64
96.34
96.03
95.73
94.69
94.39
94.09
93.79
81.48
81.46
81.29
81.26
76.16
76.11
76.05
70.64
62.92
62.88

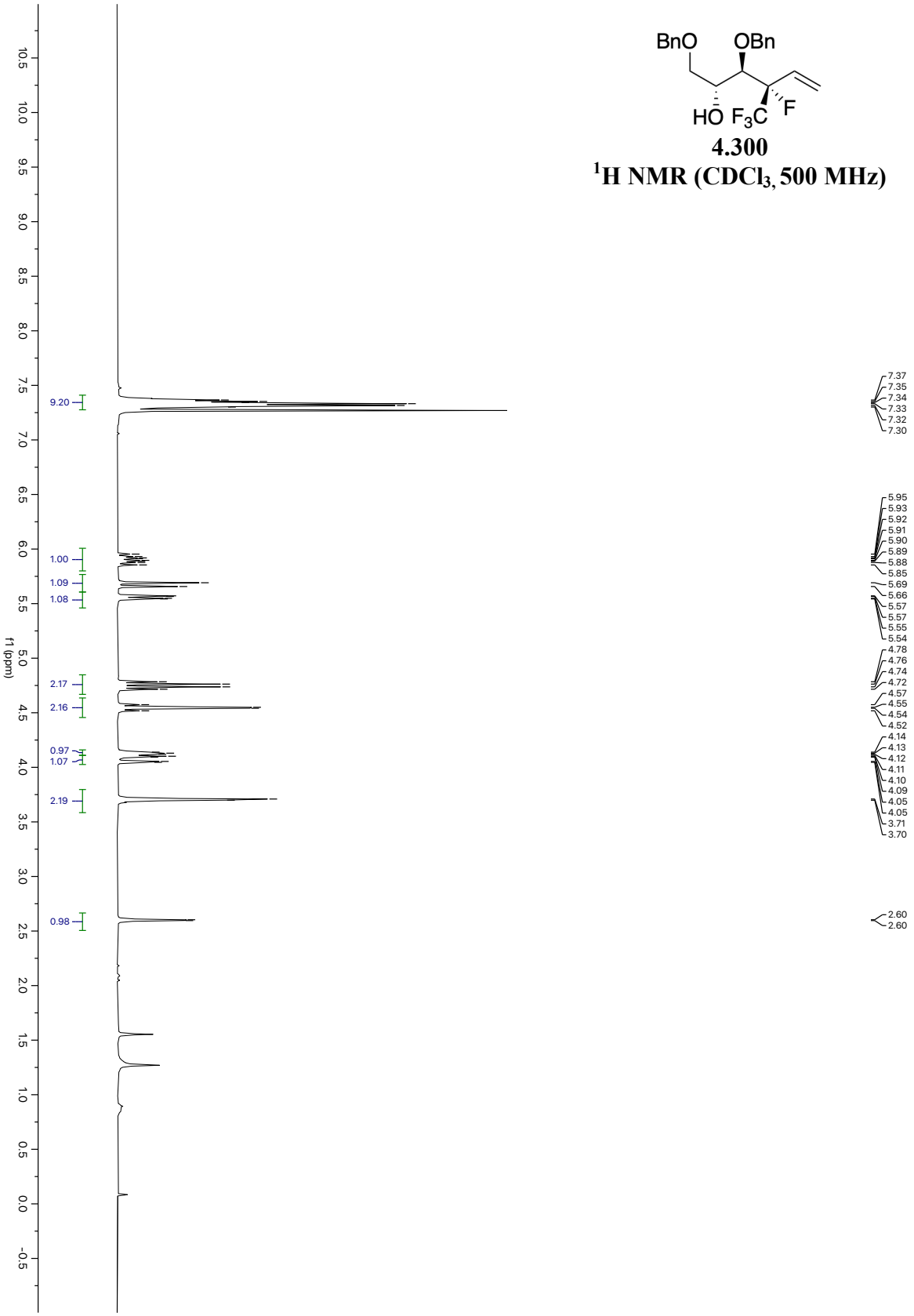

HO
OBn
HO
F3C
F
4.252
19F NMR (CDCl3, 100 MHz)
3.00
-76.78
-76.80
0.86
-186.37
-186.43
f1 (ppm)

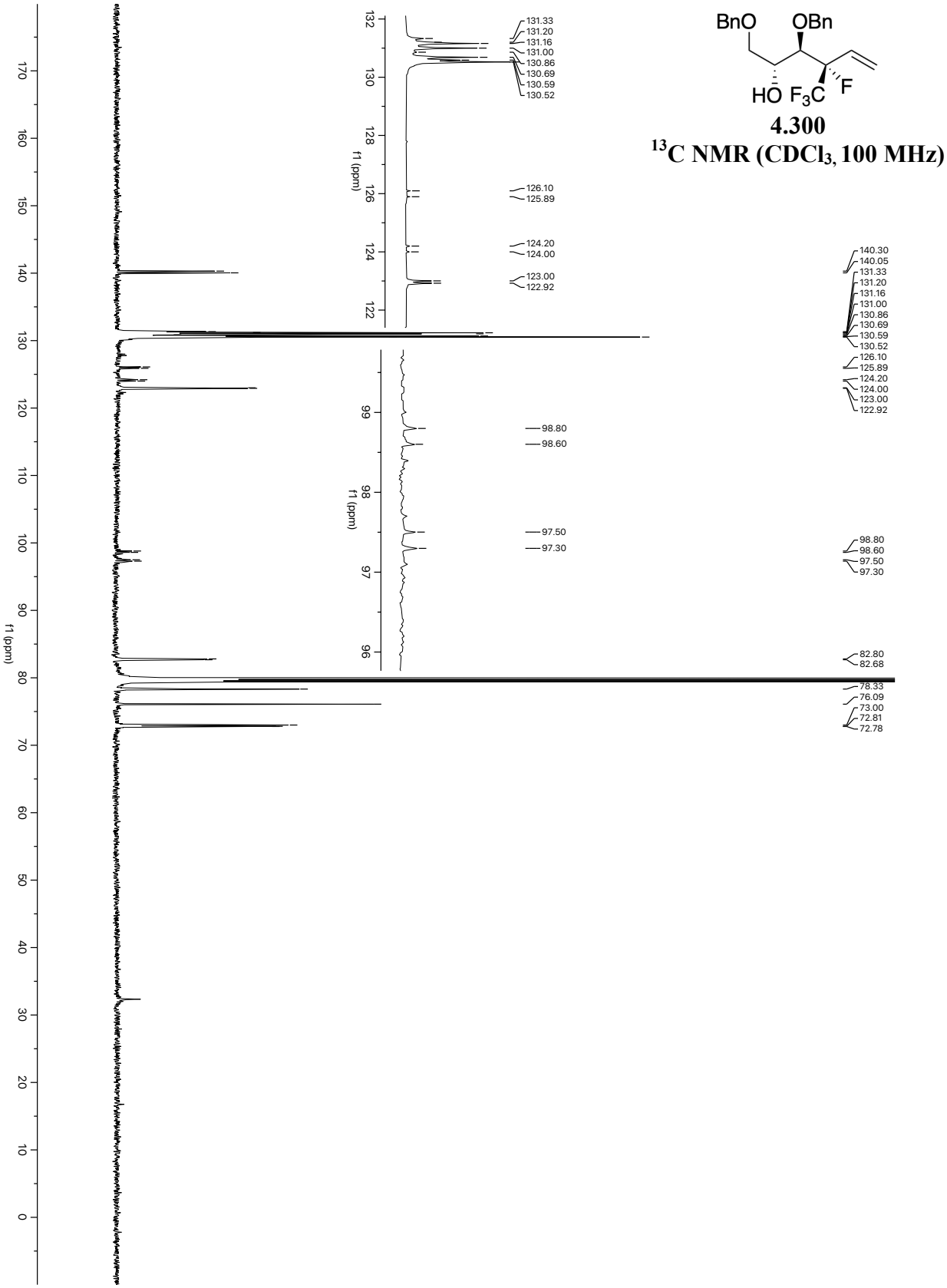

HO
OBn
BnO
F3C
F
4.253
1H NMR (CDCl3, 500 MHz)
f1 (ppm)
9.95
1.00
1.02
1.01
1.02
1.08
2.00
1.02
1.97
1.03
1.04
7.38
7.37
7.36
7.36
7.35
7.34
7.33
5.89
5.87
5.85
5.85
5.83
5.82
5.81
5.79
5.72
5.68
5.54
5.54
5.52
5.51
4.86
4.84
4.74
4.71
4.58
4.55
4.54
4.52
4.13
4.12
4.08
4.08
3.87
3.86
3.79
3.78
3.77
3.76
2.12
2.10
2.09

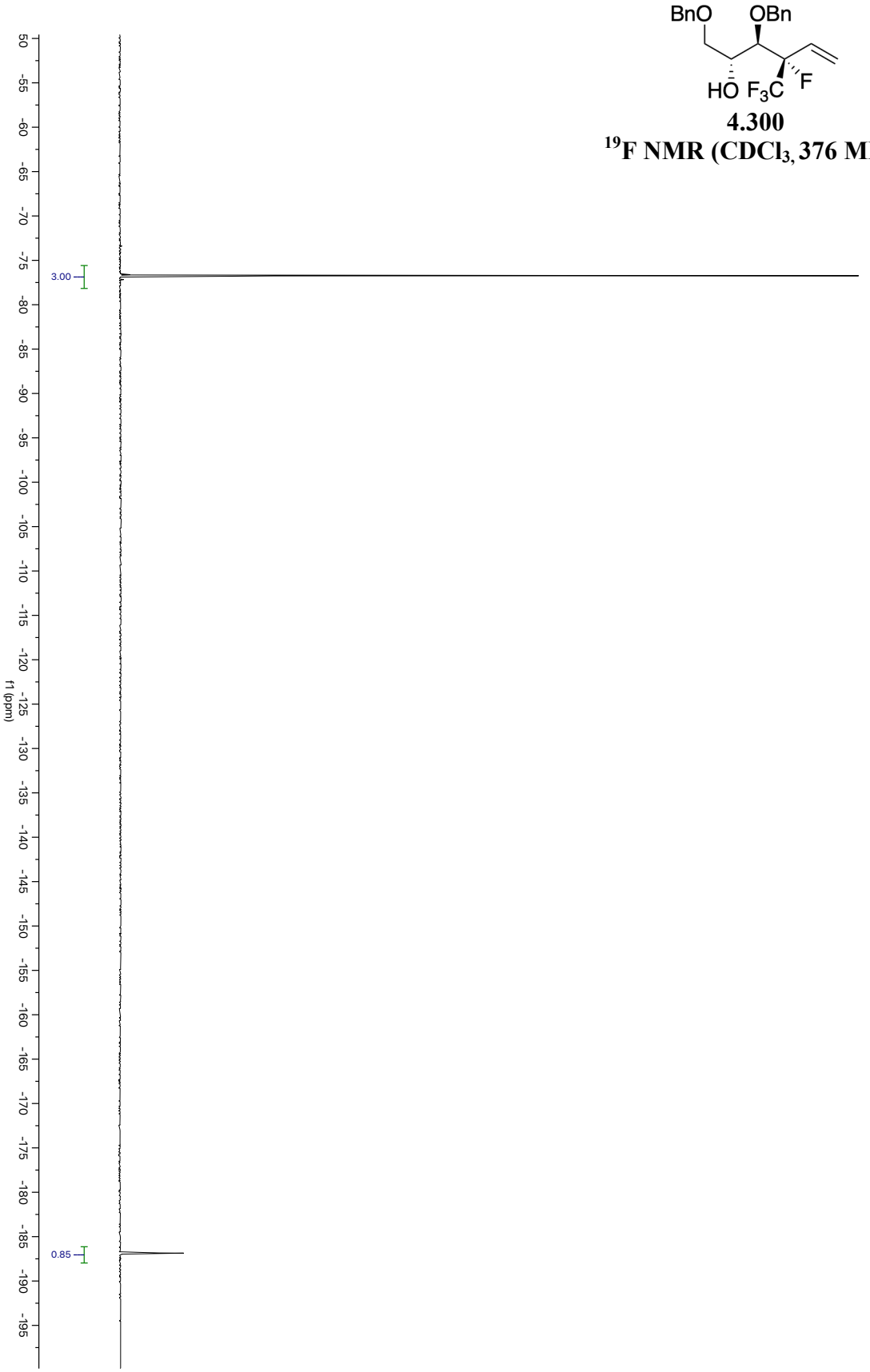

HO
OBn
BnO
F3C
F
4.253
13C NMR (CDCl3, 150 MHz)
f1 (ppm)
131.24
131.19
131.12
131.08
131.06
130.99
130.95
130.86
130.81
130.72
130.69
130.58
130.51
128.04
127.83
126.14
125.94
124.25
124.04
122.69
122.61
122.35
122.15
98.84
98.64
98.44
98.24
97.54
97.34
97.14
96.94
82.13
82.11
82.06
82.00
81.99
81.50
78.25
78.23
78.20
74.35
63.60
63.57
140.14
139.70

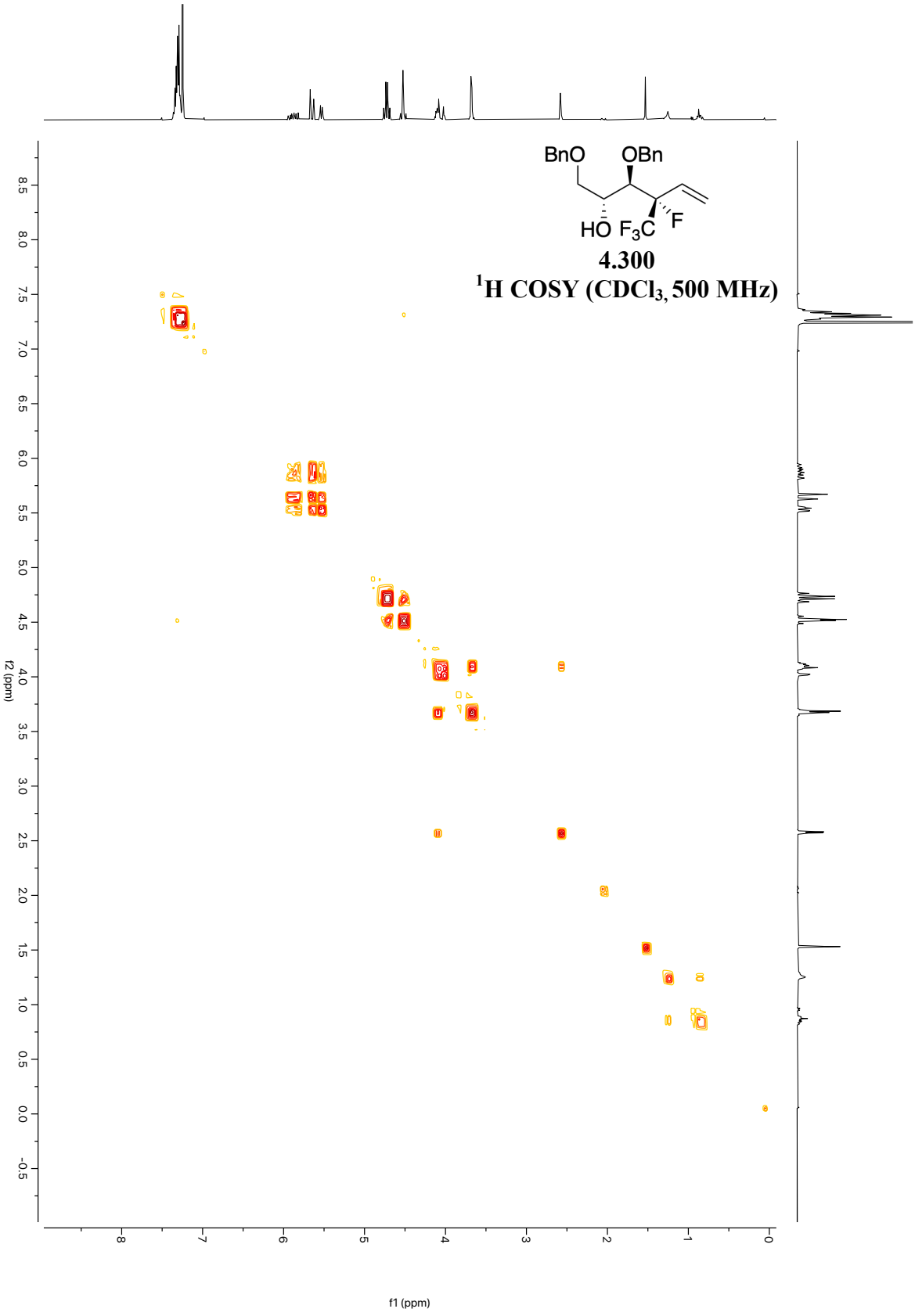

HO
OBn
BnO
F3C
F
4.253
19F NMR (CDCl3, 376 MHz)
3.00
0.83
f1 (ppm)

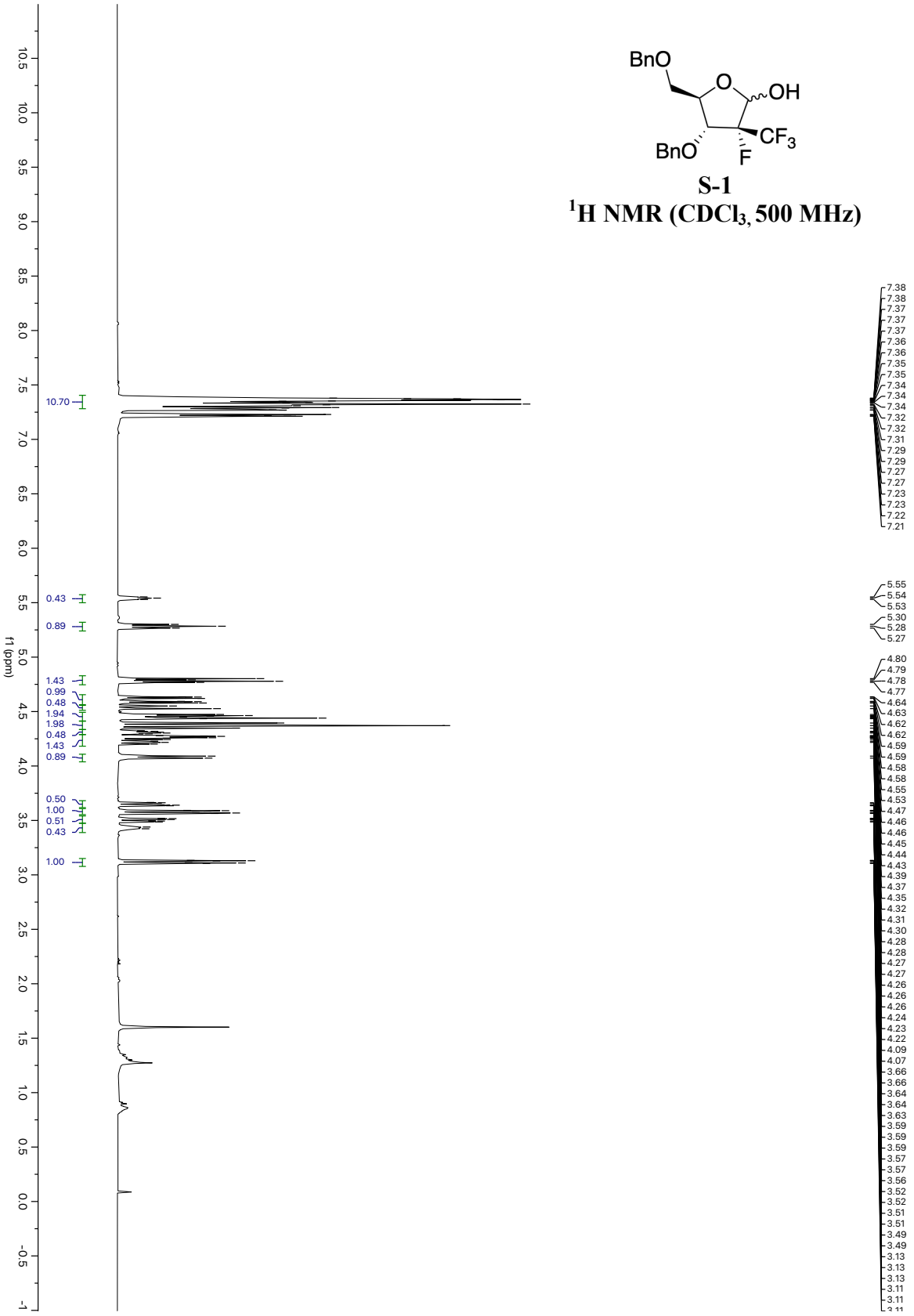

HO
OBn
BnO
F3C
F
4.252
1H COSY (CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)


BnO
OBn
HO
F3C
F
4.300
1H NMR (CDCl3, 500 MHz)
f1 (ppm)
9.20
1.00
1.09
1.08
2.17
2.16
0.97
1.07
2.19
0.98
7.37
7.35
7.34
7.33
7.32
7.30
5.95
5.93
5.92
5.91
5.90
5.89
5.88
5.85
5.69
5.66
5.57
5.57
5.55
5.54
4.78
4.76
4.74
4.72
4.57
4.55
4.54
4.52
4.14
4.13
4.12
4.11
4.10
4.09
4.05
4.05
3.71
3.70
2.60
2.60


BnO
OBn
HO
F3C
F
4.300
13C NMR (CDCl3, 100 MHz)
131.33
131.20
131.16
131.00
130.86
130.69
130.59
130.52
126.10
125.89
124.20
124.00
123.00
122.92
98.80
98.60
97.50
97.30
82.80
82.68
78.33
76.09
73.00
72.81
72.78
f1 (ppm)

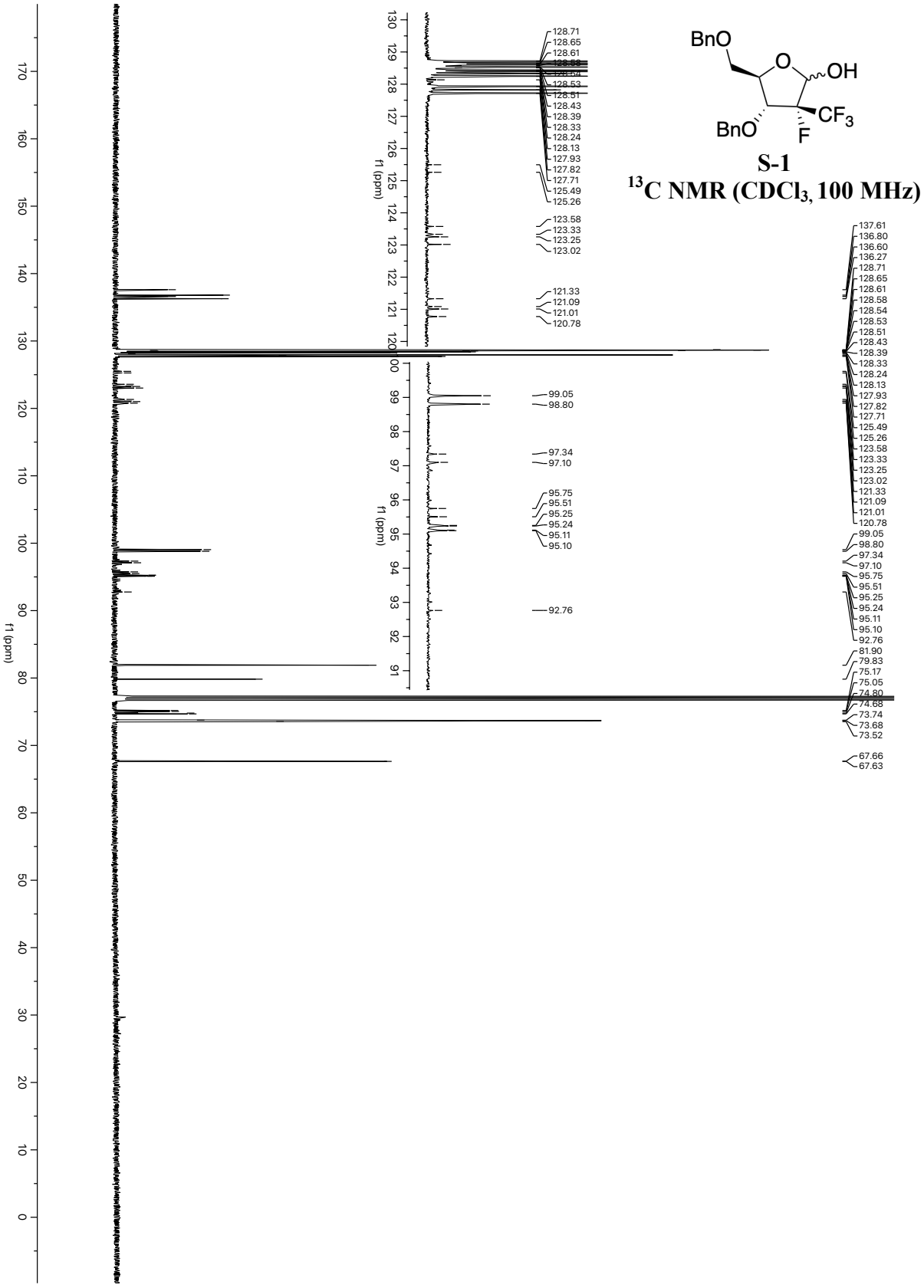

BnO
OBn
HO
F3C
F
4.300
19F NMR (CDCl3, 376 MHz)
3.00
0.85
f1 (ppm)

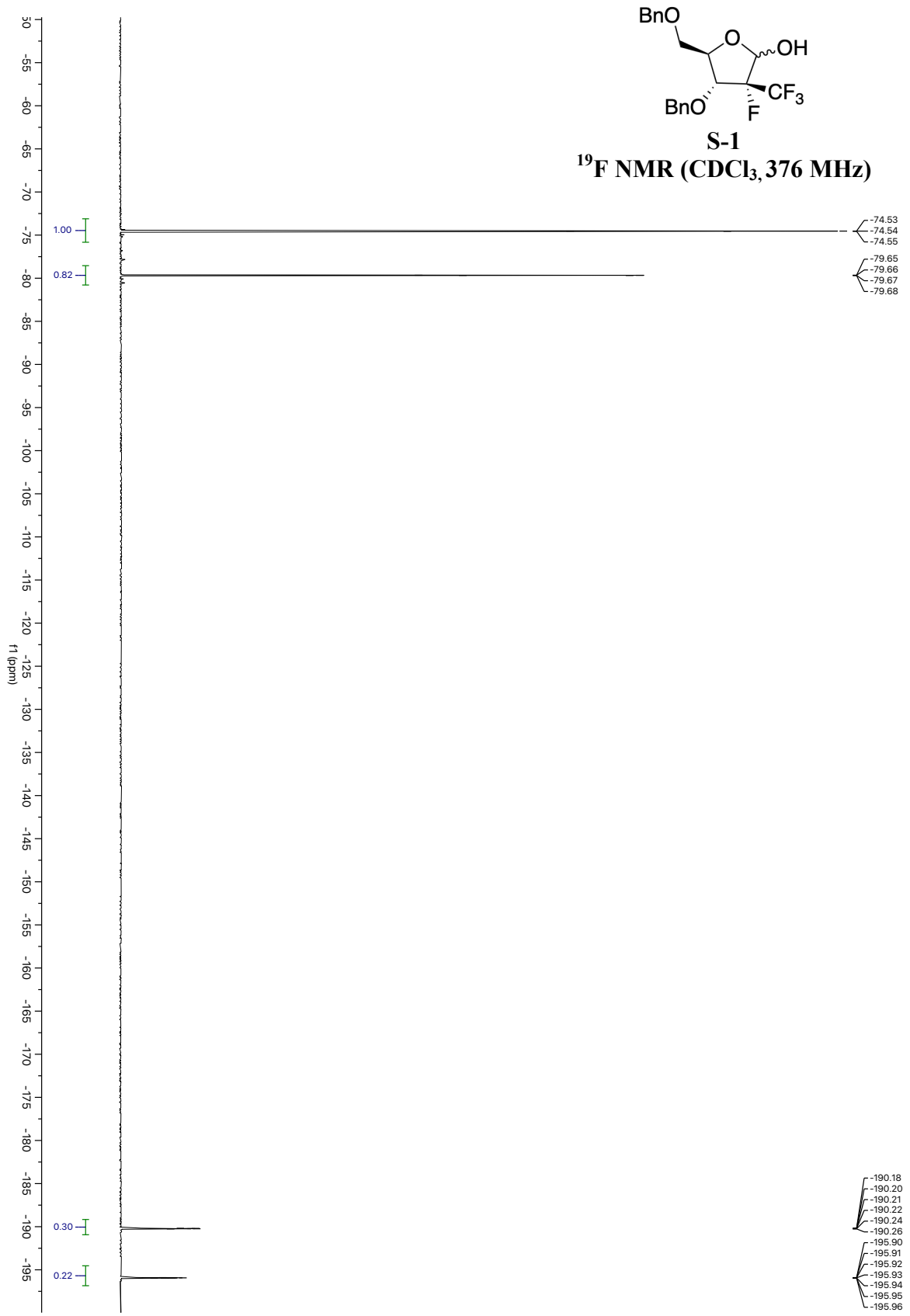

BnO
OBn
HO
F3C
F
4.300
1H COSY (CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

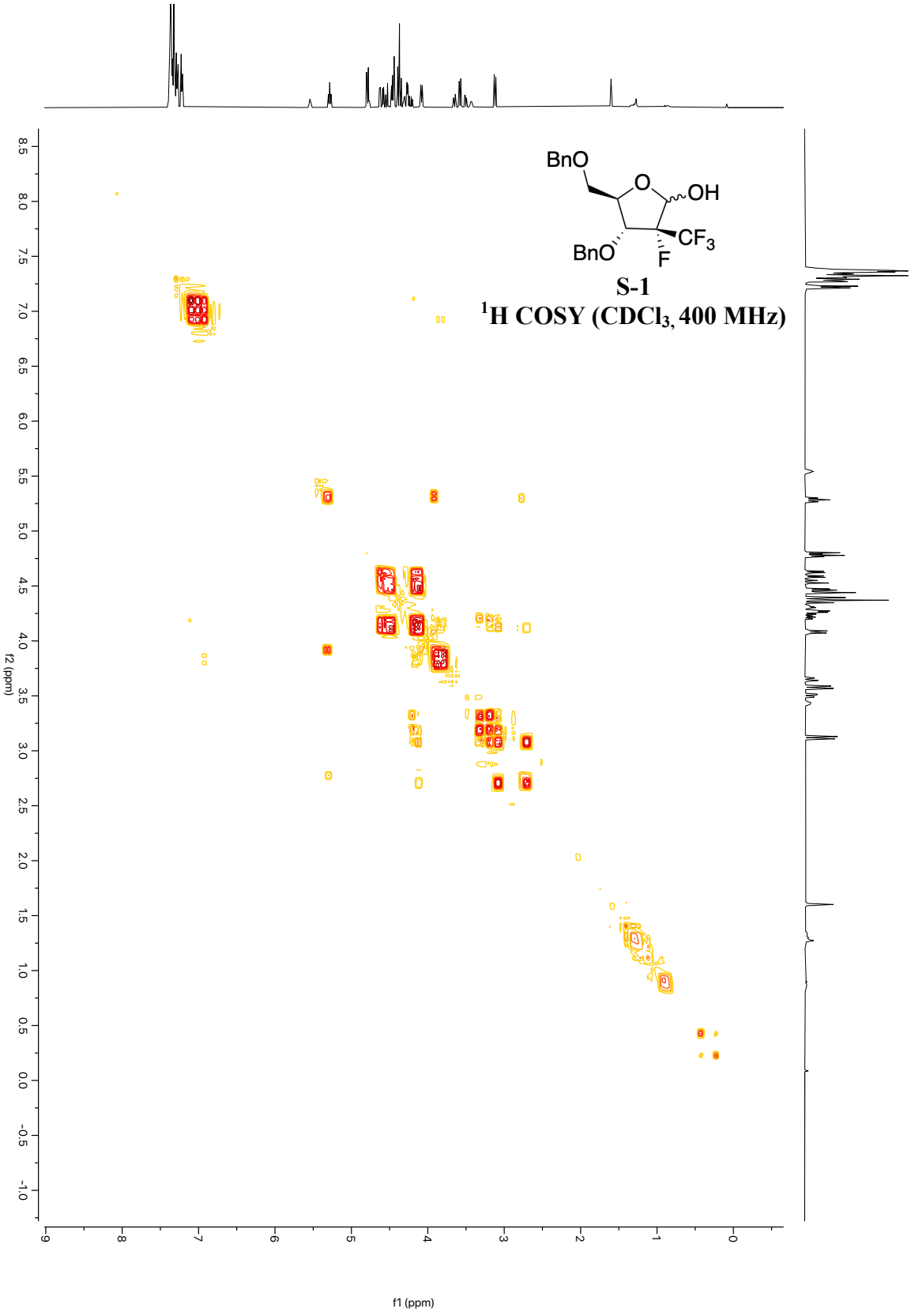


S-1

^{1}H NMR ($CDCl_3$, 500 MHz)

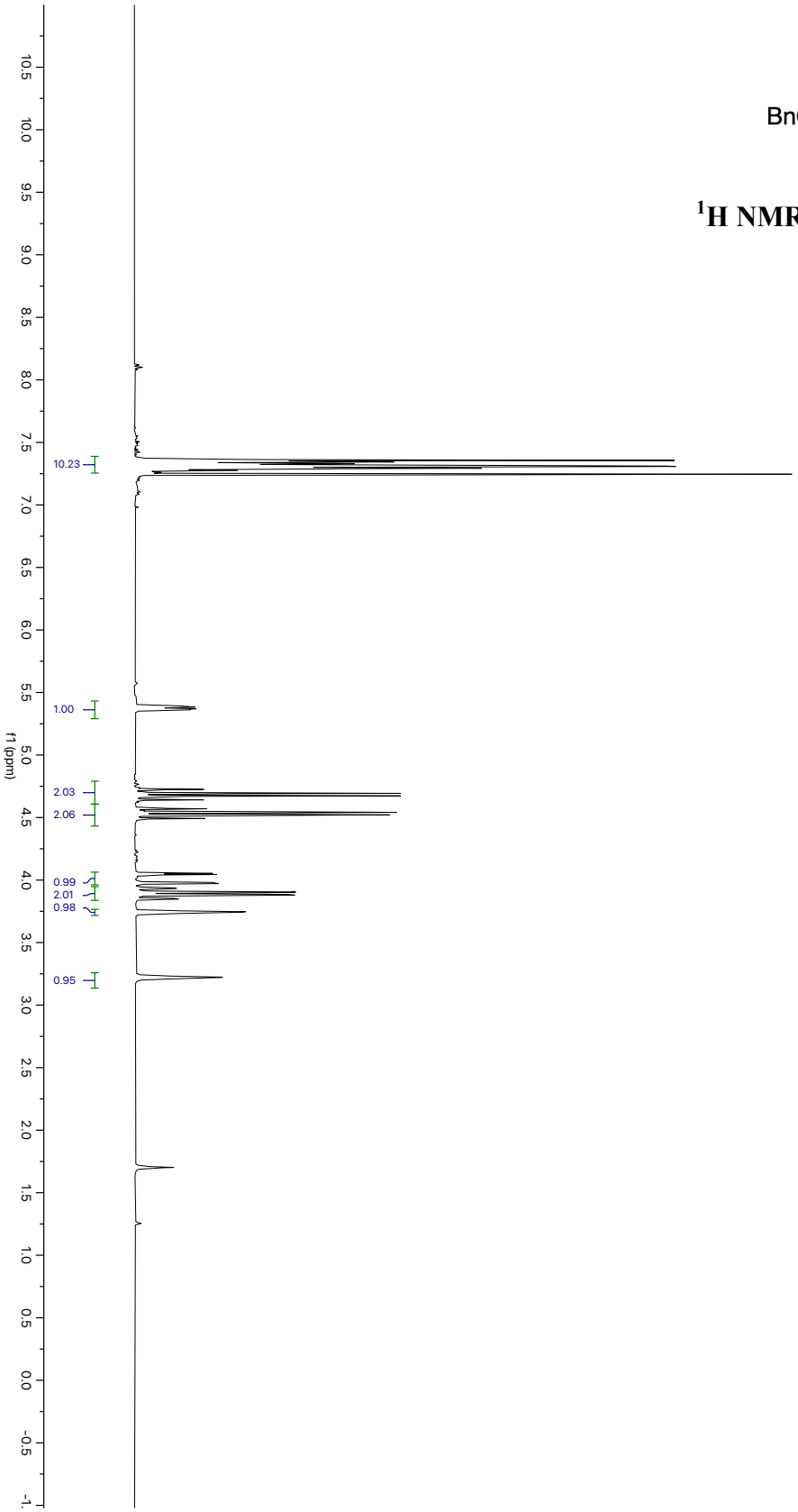

BnO
O
OH
BnO
CF3
F
S-1
13C NMR (CDCl3, 100 MHz)
f1 (ppm)

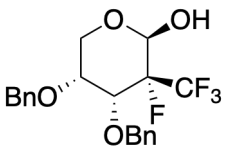

BnO
O
OH
CF3
BnO
F
S-1
19F NMR (CDCl3, 376 MHz)
1.00
0.82
0.30
0.22
-74.53
-74.54
-74.55
-79.65
-79.66
-79.67
-79.68
-190.18
-190.20
-190.21
-190.22
-190.24
-190.26
-195.90
-195.91
-195.92
-195.93
-195.94
-195.95
-195.96
f1 (ppm)



S-1

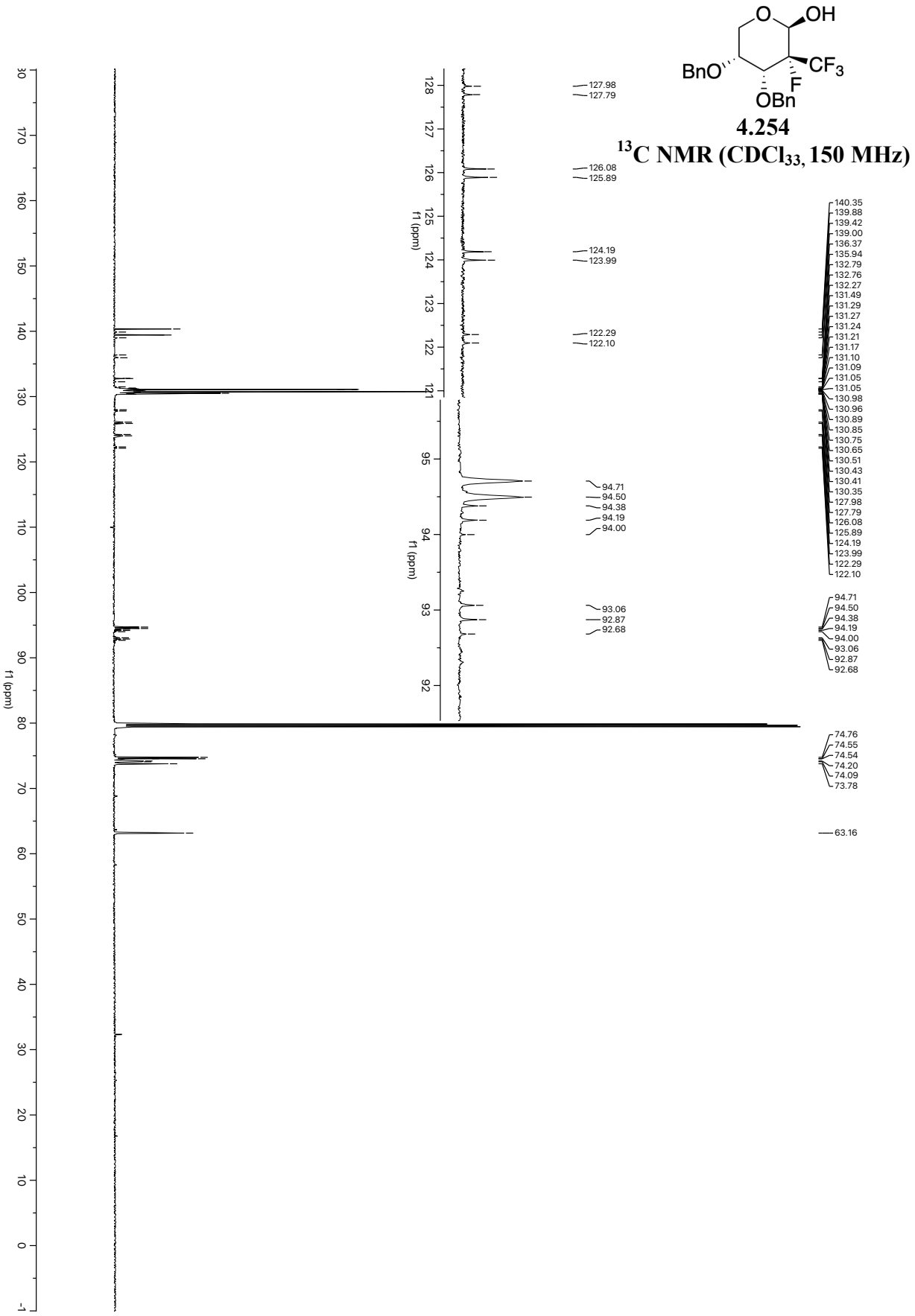
^{1}H COSY ($CDCl_3$, 400 MHz)

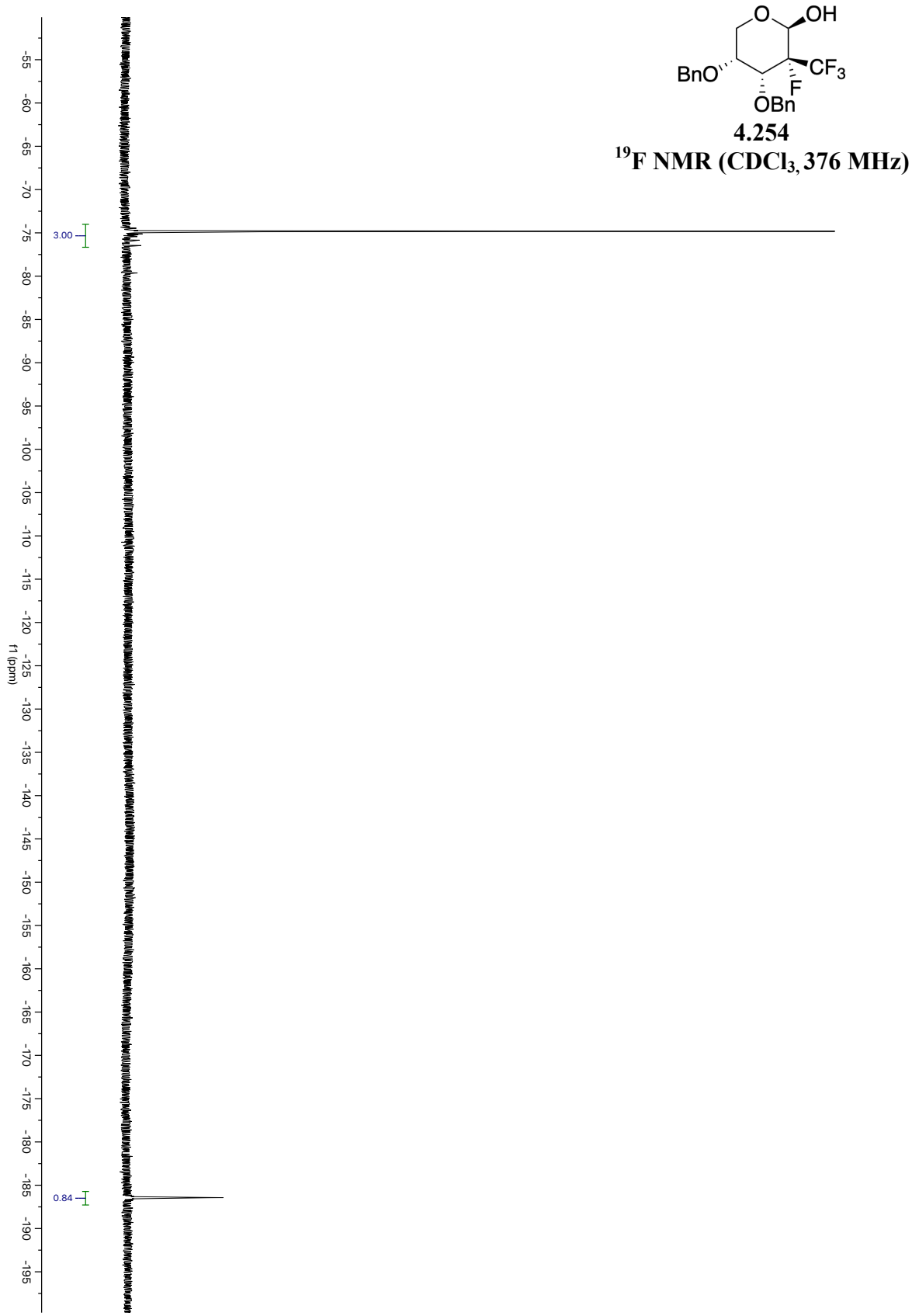


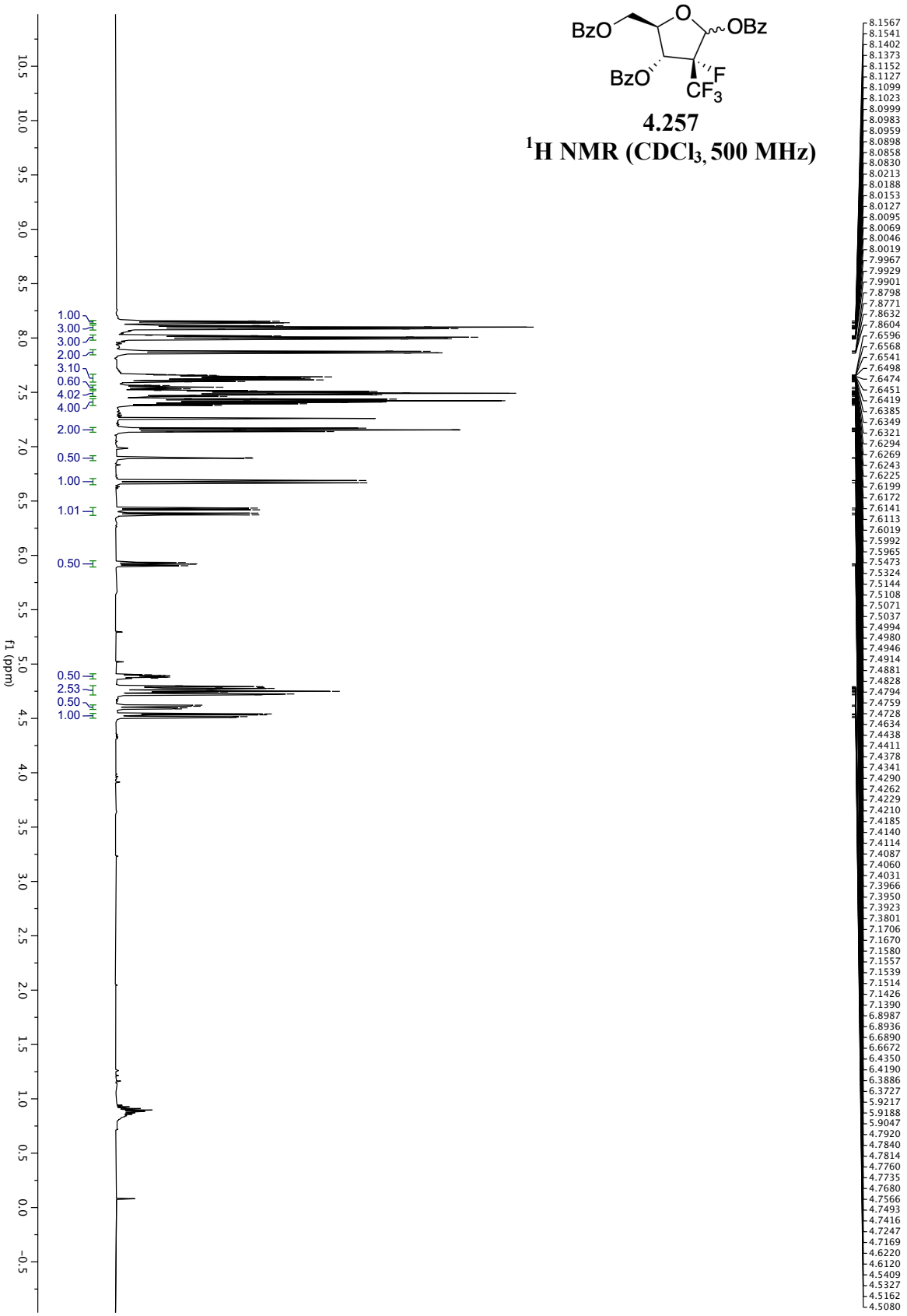


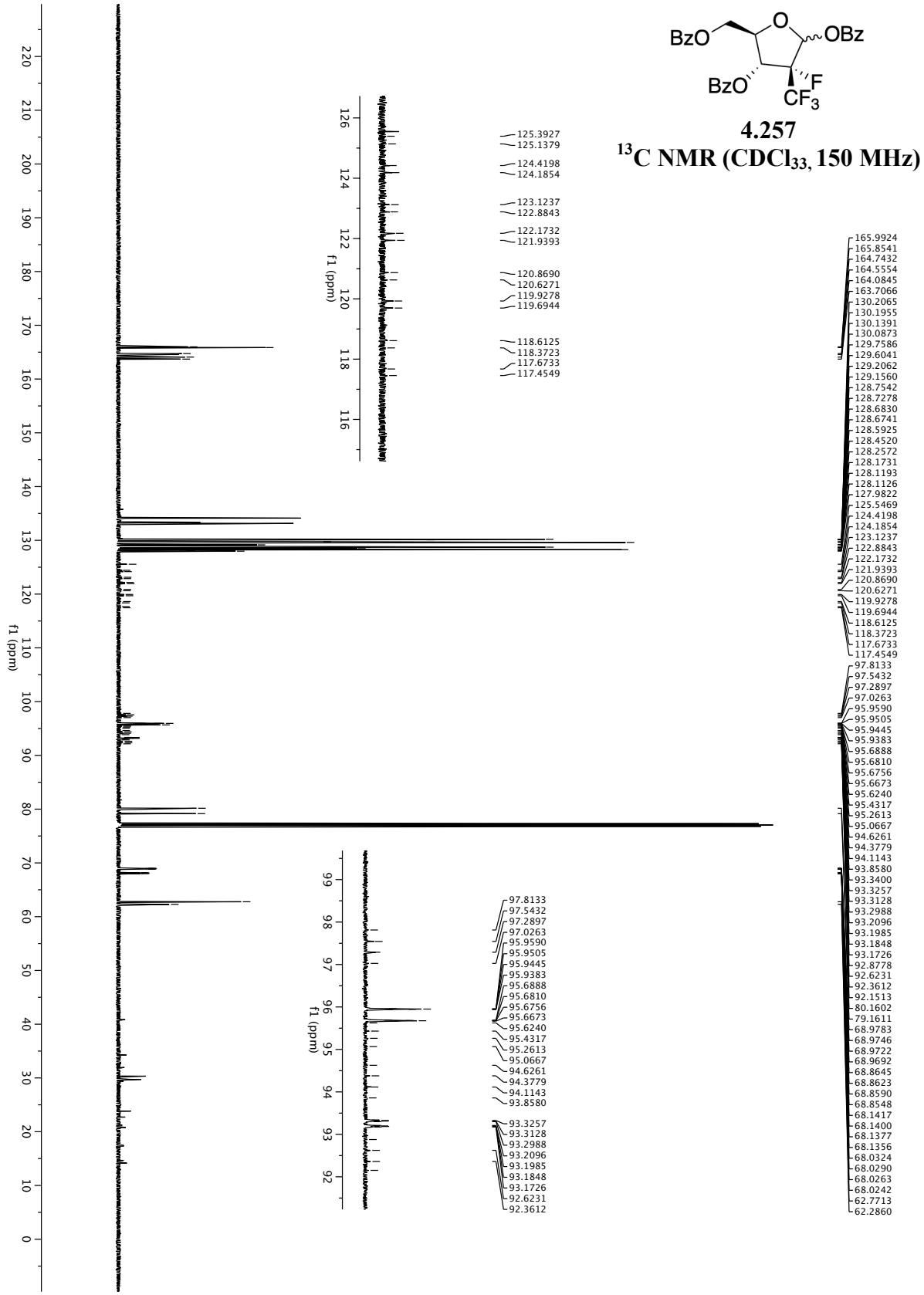
4.254

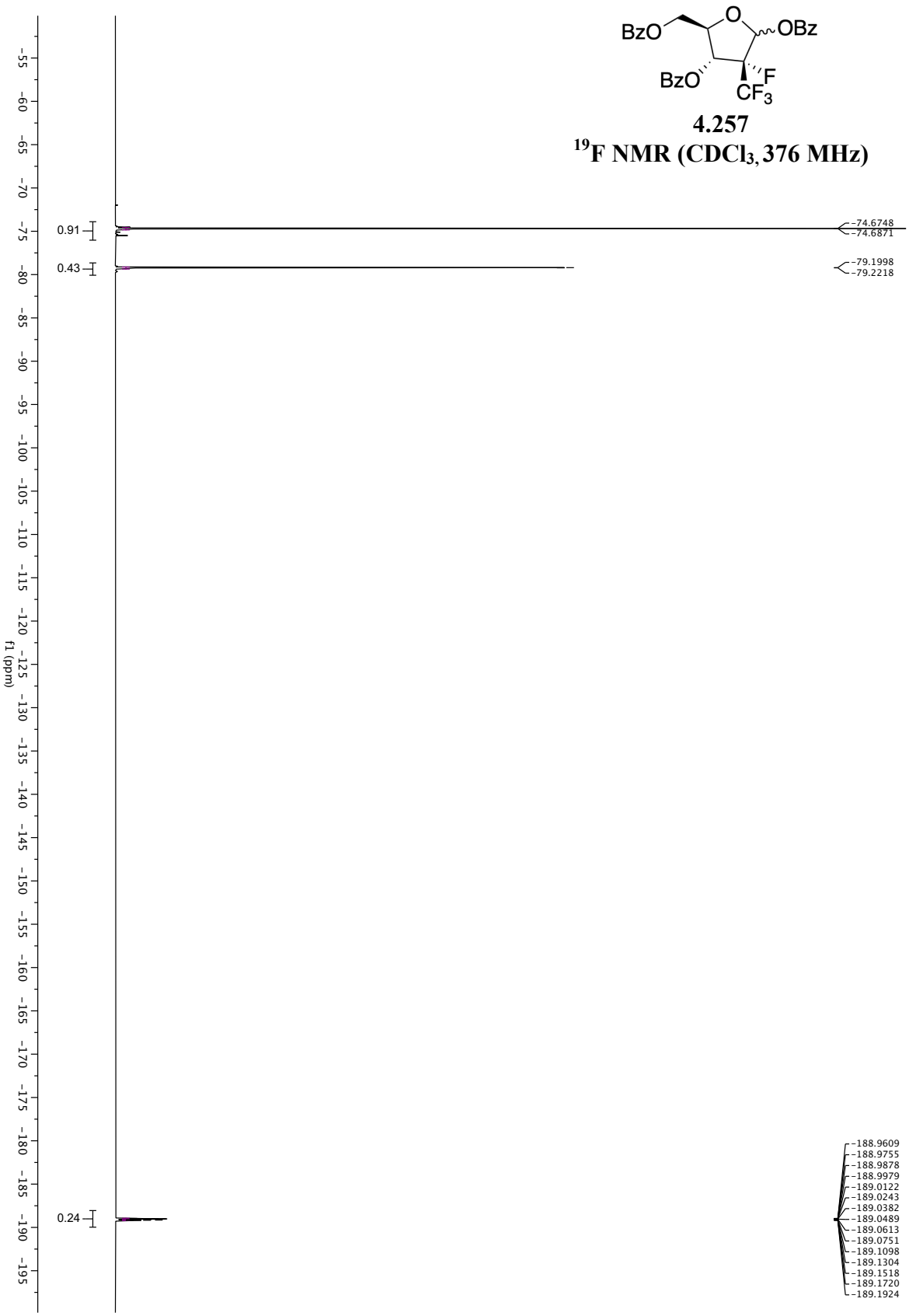
^{1}H NMR ($CDCl_3$, 500 MHz)

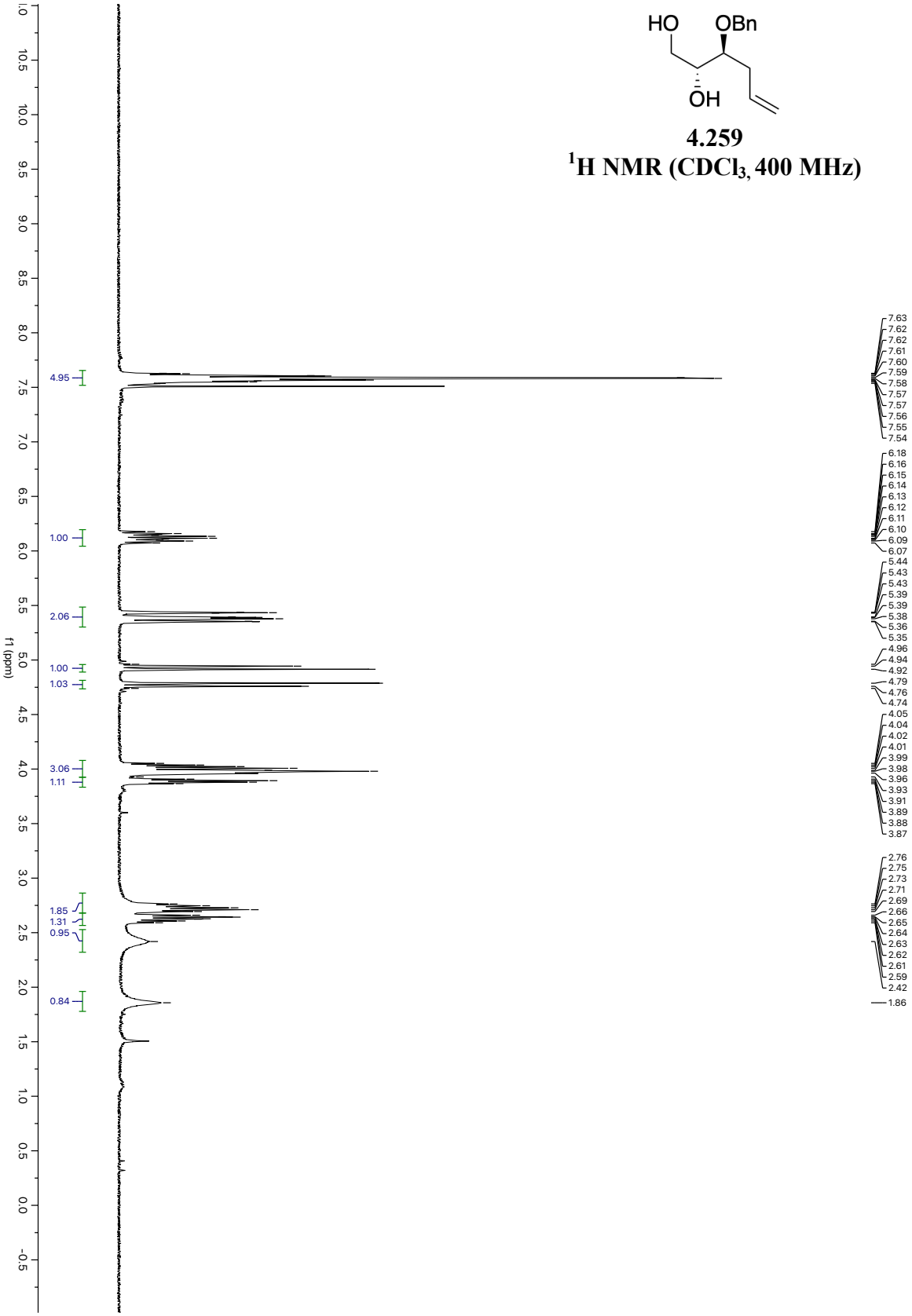

O
OH
BnO
CF3
F
OBn
4.254
13C NMR (CDCl33, 150 MHz)
f1 (ppm)
127.98
127.79
126.08
125.89
124.19
123.99
122.29
122.10
94.71
94.50
94.38
94.19
94.00
93.06
92.87
92.68
140.35
139.88
139.42
139.00
136.37
135.94
132.79
132.76
132.27
131.49
131.29
131.27
131.24
131.21
131.17
131.10
131.09
131.05
131.05
130.98
130.96
130.89
130.85
130.75
130.65
130.51
130.43
130.41
130.35
127.98
127.79
126.08
125.89
124.19
123.99
122.29
122.10
94.71
94.50
94.38
94.19
94.00
93.06
92.87
92.68
74.76
74.55
74.54
74.20
74.09
73.78
63.16

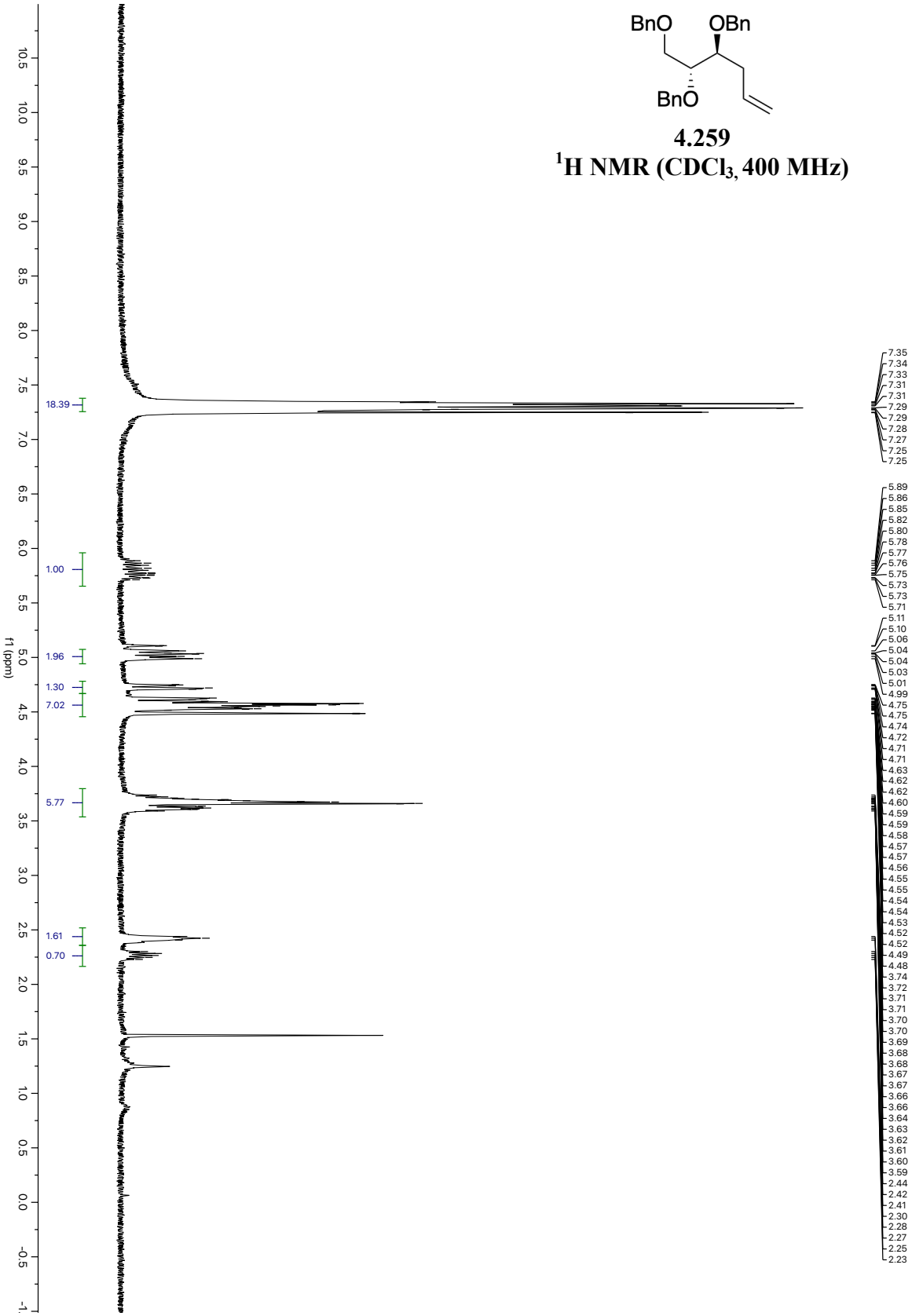

O
OH
BnO
CF3
F
OBn
4.254
19F NMR (CDCl3, 376 MHz)
3.00
0.84
f1 (ppm)
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195

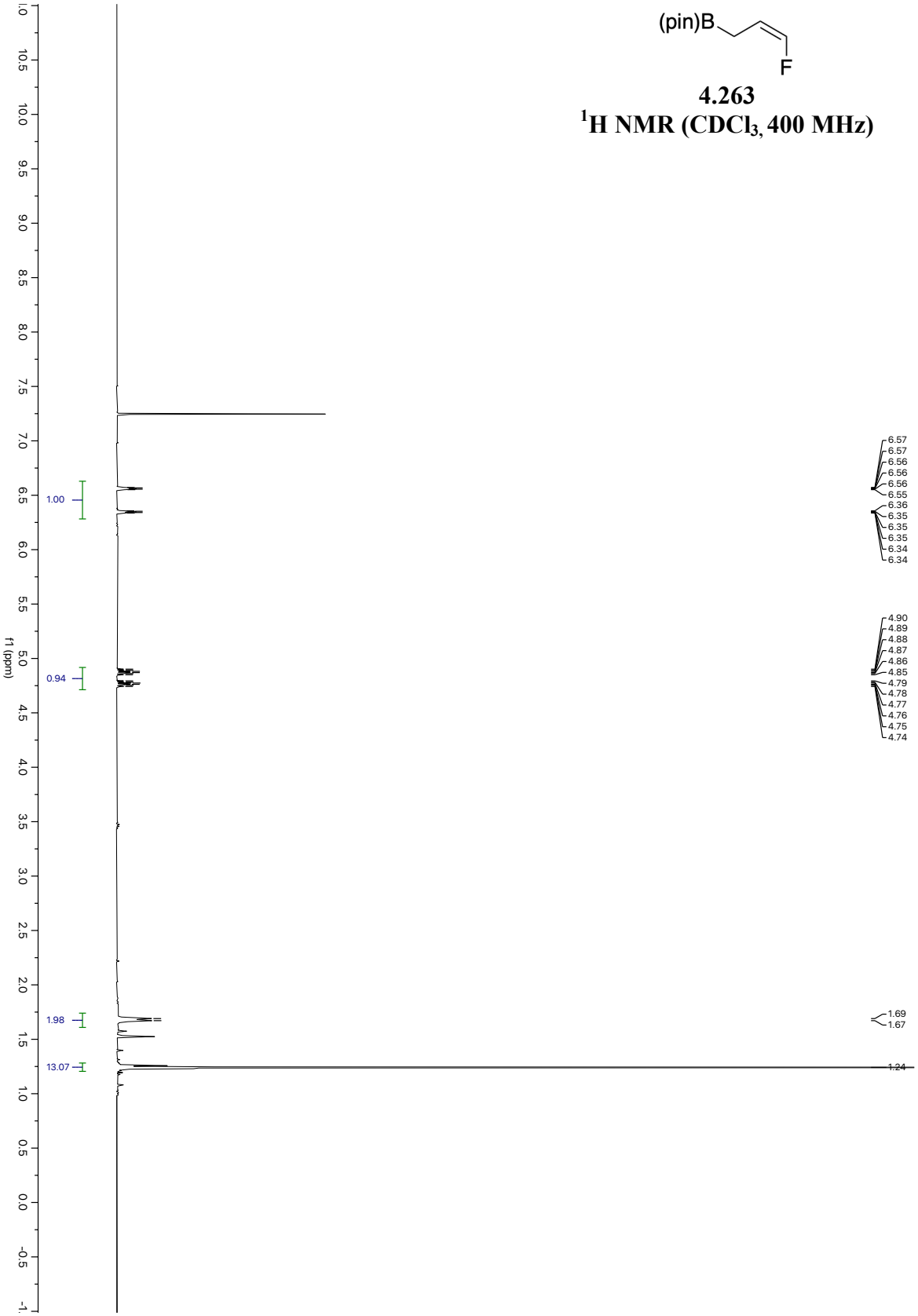

BzO
OBz
BzO
F
CF3
4.257
1H NMR (CDCl3, 500 MHz)
f1 (ppm)
1.00
3.00
3.00
2.00
3.10
0.60
4.02
4.00
2.00
0.50
1.00
1.01
0.50
0.50
2.53
0.50
1.00

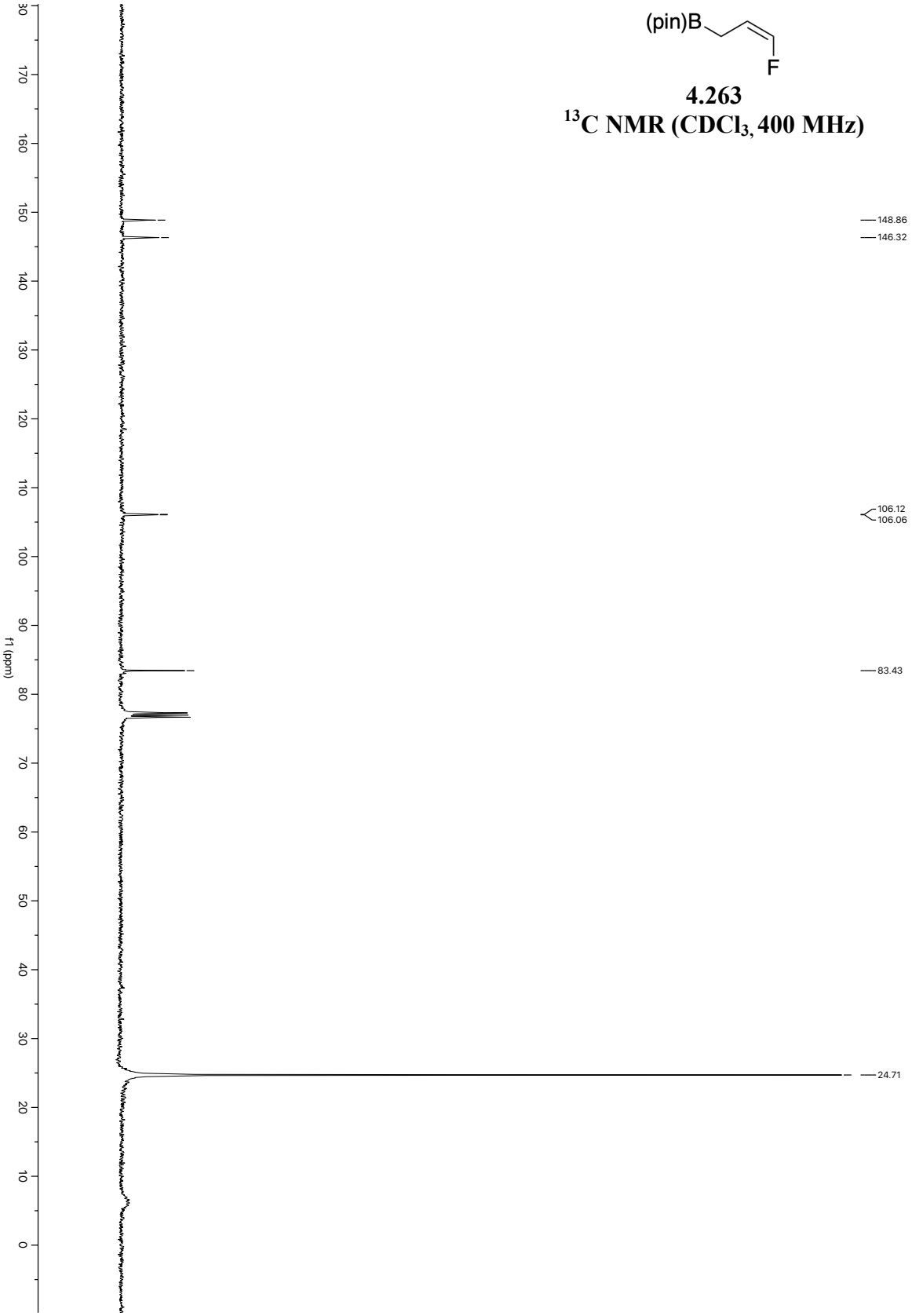

BzO
O
OBz
BzO
F
CF3
4.257
13C NMR (CDCl33, 150 MHz)
f1 (ppm)
125.3927
125.1379
124.4198
124.1854
123.1237
122.8843
122.1732
121.9393
120.8690
120.6271
119.9278
119.6944
118.6125
118.3723
117.6733
117.4549
97.8133
97.5432
97.2897
97.0263
95.9590
95.9505
95.9445
95.9383
95.6888
95.6810
95.6756
95.6673
95.6240
95.4317
95.2613
95.0667
94.6261
94.3779
94.1143
93.8580
93.3257
93.3128
93.2988
93.2096
93.1985
93.1848
93.1726
92.6231
92.3612
165.9924
165.8541
164.7432
164.5554
164.0845
163.7066
130.2065
130.1955
130.1391
130.0873
129.7586
129.6041
129.2062
129.1560
128.7542
128.7278
128.6830
128.6741
128.5925
128.4520
128.2572
128.1731
128.1193
128.1126
127.9822
125.5469
124.4198
124.1854
123.1237
122.8843
122.1732
121.9393
120.8690
120.6271
119.9278
119.6944
118.6125
118.3723
117.6733
117.4549
97.8133
97.5432
97.2897
97.0263
95.9590
95.9505
95.9445
95.9383
95.6888
95.6810
95.6756
95.6673
95.6240
95.4317
95.2613
95.0667
94.6261
94.3779
94.1143
93.8580
93.3400
93.3257
93.3128
93.2988
93.2096
93.1985
93.1848
93.1726
92.8778
92.6231
92.3612
92.1513
80.1602
79.1611
68.9783
68.9746
68.9722
68.9692
68.8645
68.8623
68.8590
68.8548
68.1417
68.1400
68.1377
68.1356
68.0324
68.0290
68.0263
68.0242
62.7713
62.2860


BzO
O
OBz
BzO
F
CF3
4.257
19F NMR (CDCl3, 376 MHz)
0.91
0.43
0.24
-74.6748
-74.6871
-79.1998
-79.2218
-188.9609
-188.9755
-188.9878
-188.9979
-189.0122
-189.0243
-189.0382
-189.0489
-189.0613
-189.0751
-189.1098
-189.1304
-189.1518
-189.1720
-189.1924
f1 (ppm)


HO
OBn
OH
4.259
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.95
1.00
2.06
1.00
1.03
3.06
1.11
1.85
1.31
0.95
0.84
7.63
7.62
7.62
7.61
7.60
7.59
7.58
7.57
7.57
7.56
7.55
7.54
6.18
6.16
6.15
6.14
6.13
6.12
6.11
6.10
6.09
6.07
5.44
5.43
5.43
5.39
5.39
5.38
5.36
5.35
4.96
4.94
4.92
4.79
4.76
4.74
4.05
4.04
4.02
4.01
3.99
3.98
3.96
3.93
3.91
3.89
3.88
3.87
2.76
2.75
2.73
2.71
2.69
2.66
2.65
2.64
2.63
2.62
2.61
2.59
2.42
1.86

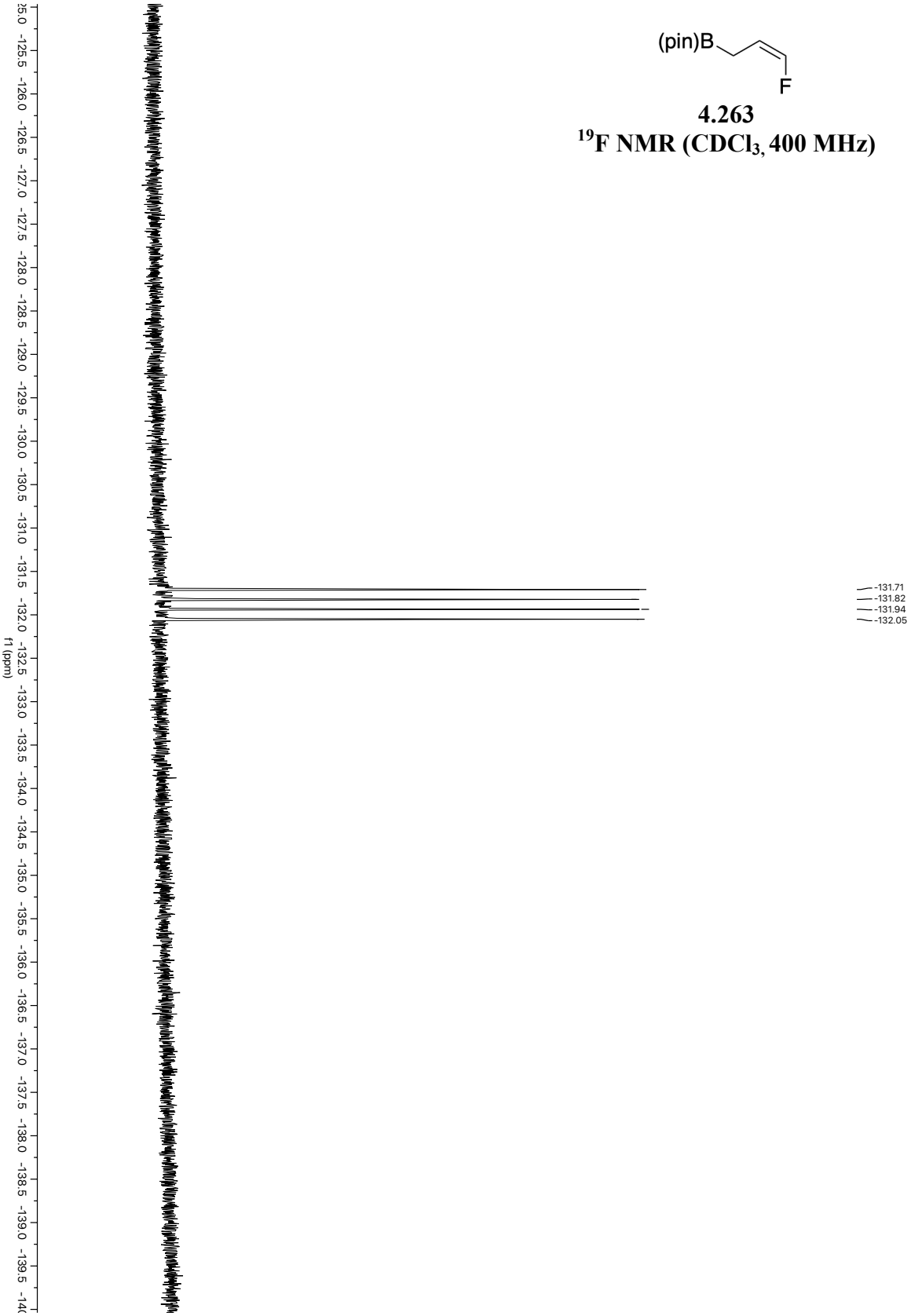

BnO
OBn
BnO
4.259
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
18.39
1.00
1.96
1.30
7.02
5.77
1.61
0.70


(pin)B
F
4.263
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.00
0.94
1.98
13.07
6.57
6.57
6.56
6.56
6.56
6.55
6.36
6.35
6.35
6.35
6.34
6.34
4.90
4.89
4.88
4.87
4.86
4.85
4.79
4.78
4.77
4.76
4.75
4.74
1.69
1.67
1.24



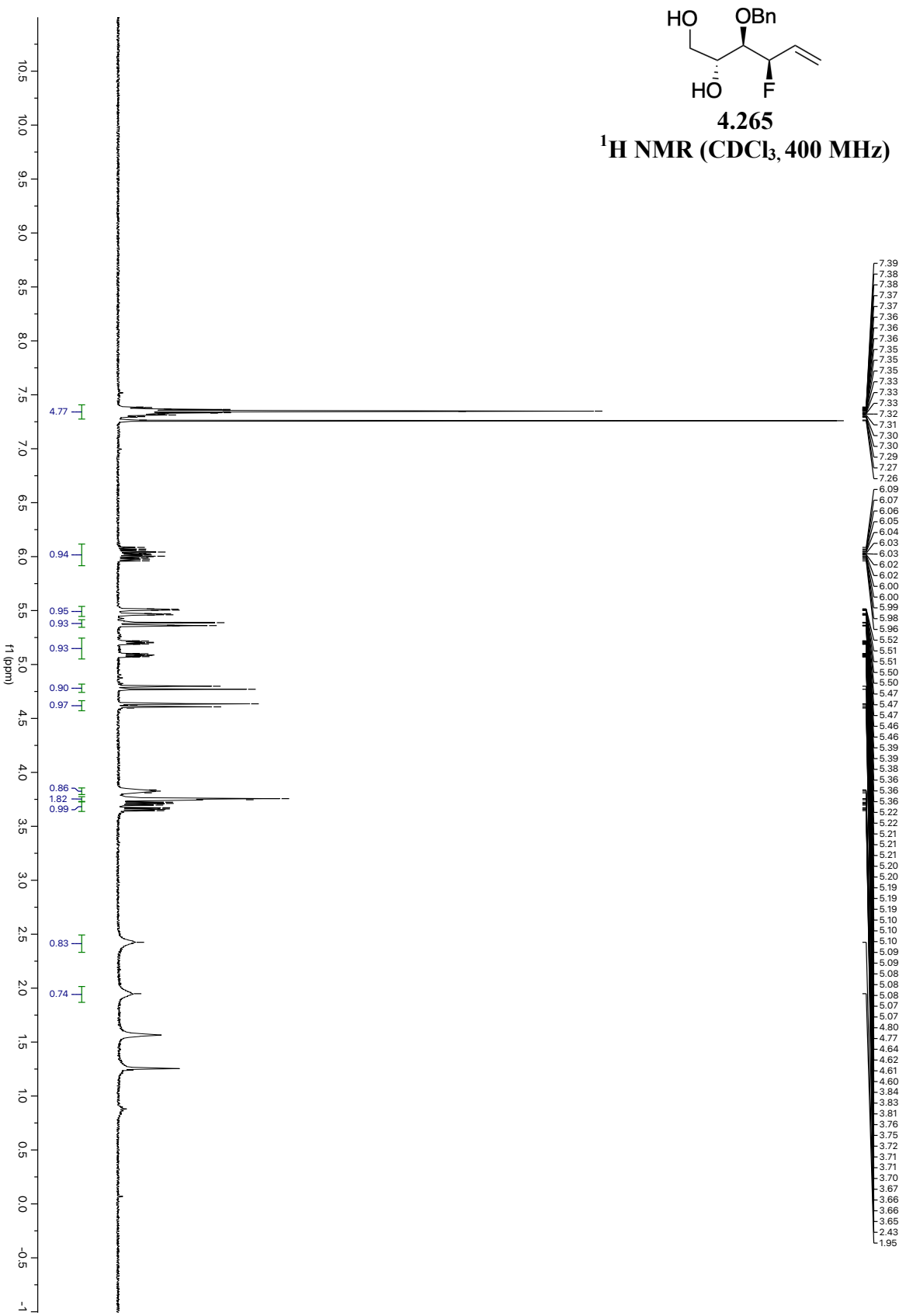
4.263

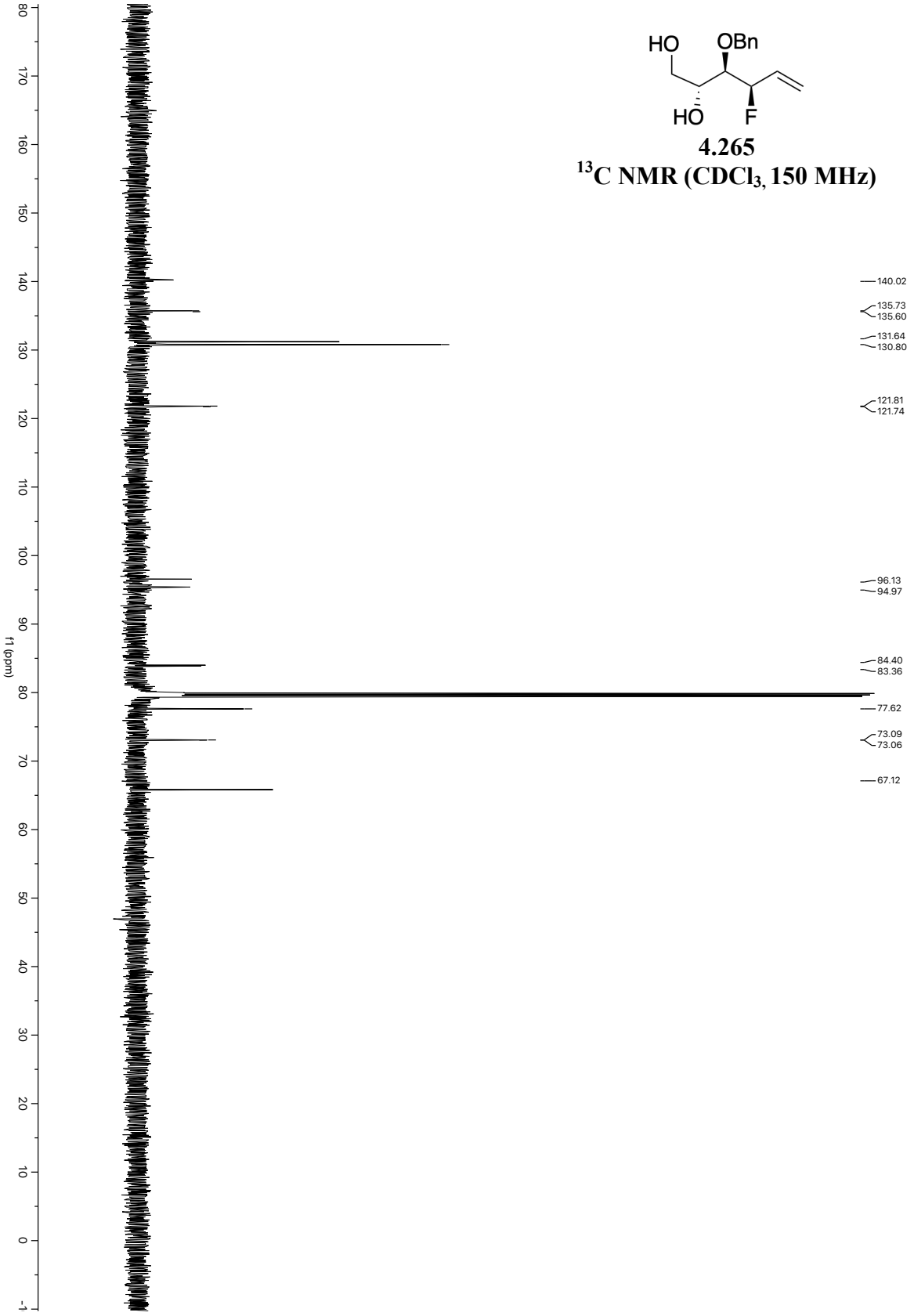
^{13}C NMR ($CDCl_3$, 400 MHz)



4.263

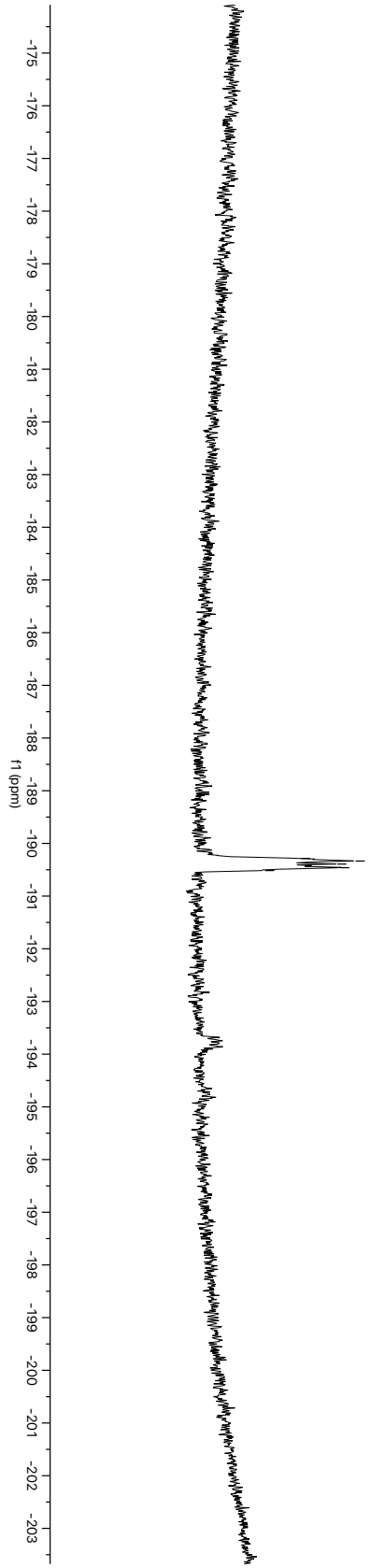
^{19}F NMR ($CDCl_3$, 400 MHz)

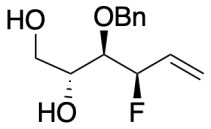

HO
OBn
HO
F
4.265
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.77
0.94
0.95
0.93
0.93
0.90
0.97
0.86
1.82
0.99
0.83
0.74



4.265

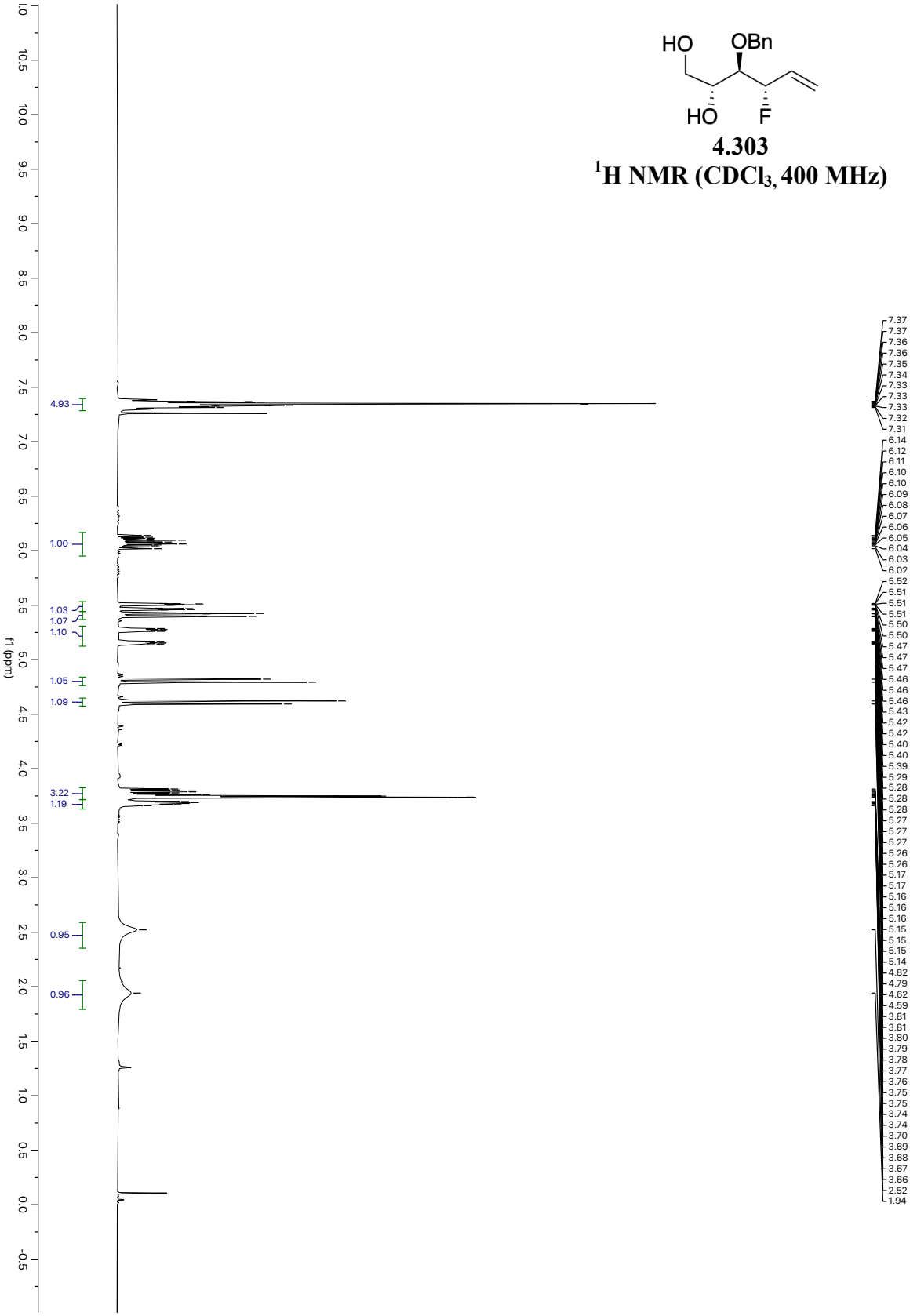
^{13}C NMR ($CDCl_3$, 150 MHz)

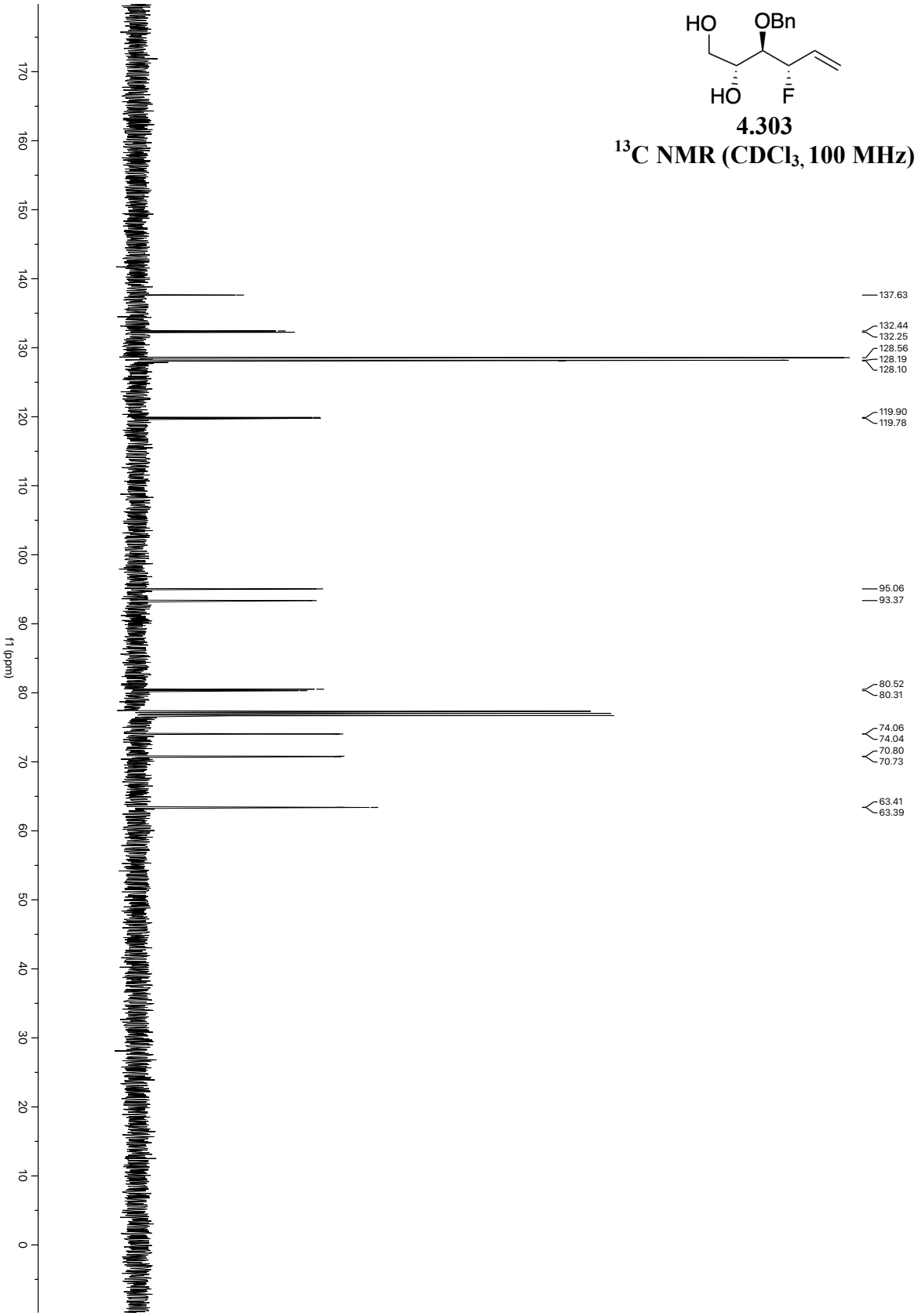




4.265

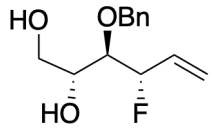
^{19}F NMR ($CDCl_3$, 150 MHz)


HO
OBn
HO
F
4.303
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.93
1.00
1.03
1.07
1.10
1.05
1.09
3.22
1.19
0.95
0.96



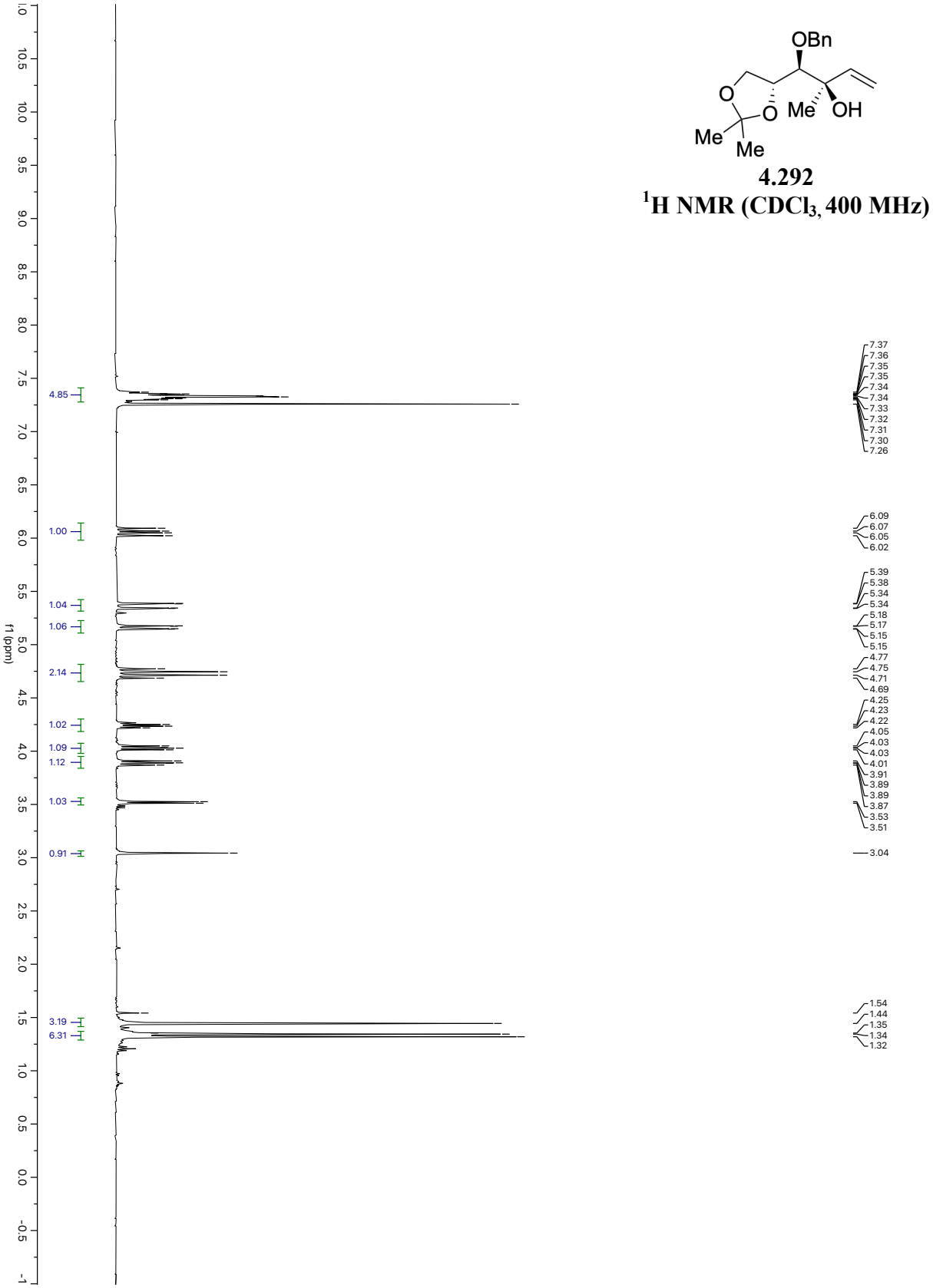
4.303

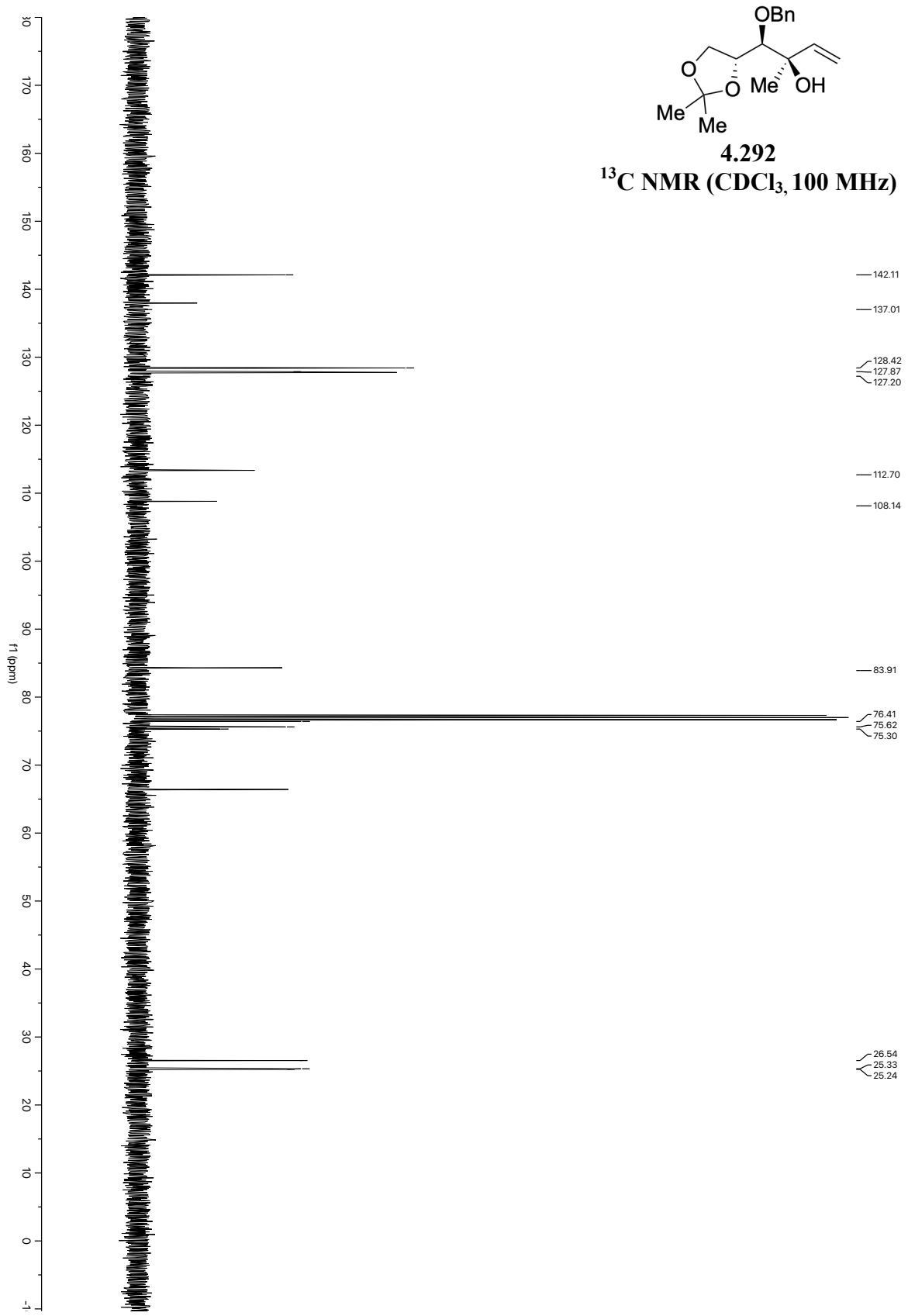
^{13}C NMR ($CDCl_3$, 100 MHz)



5e

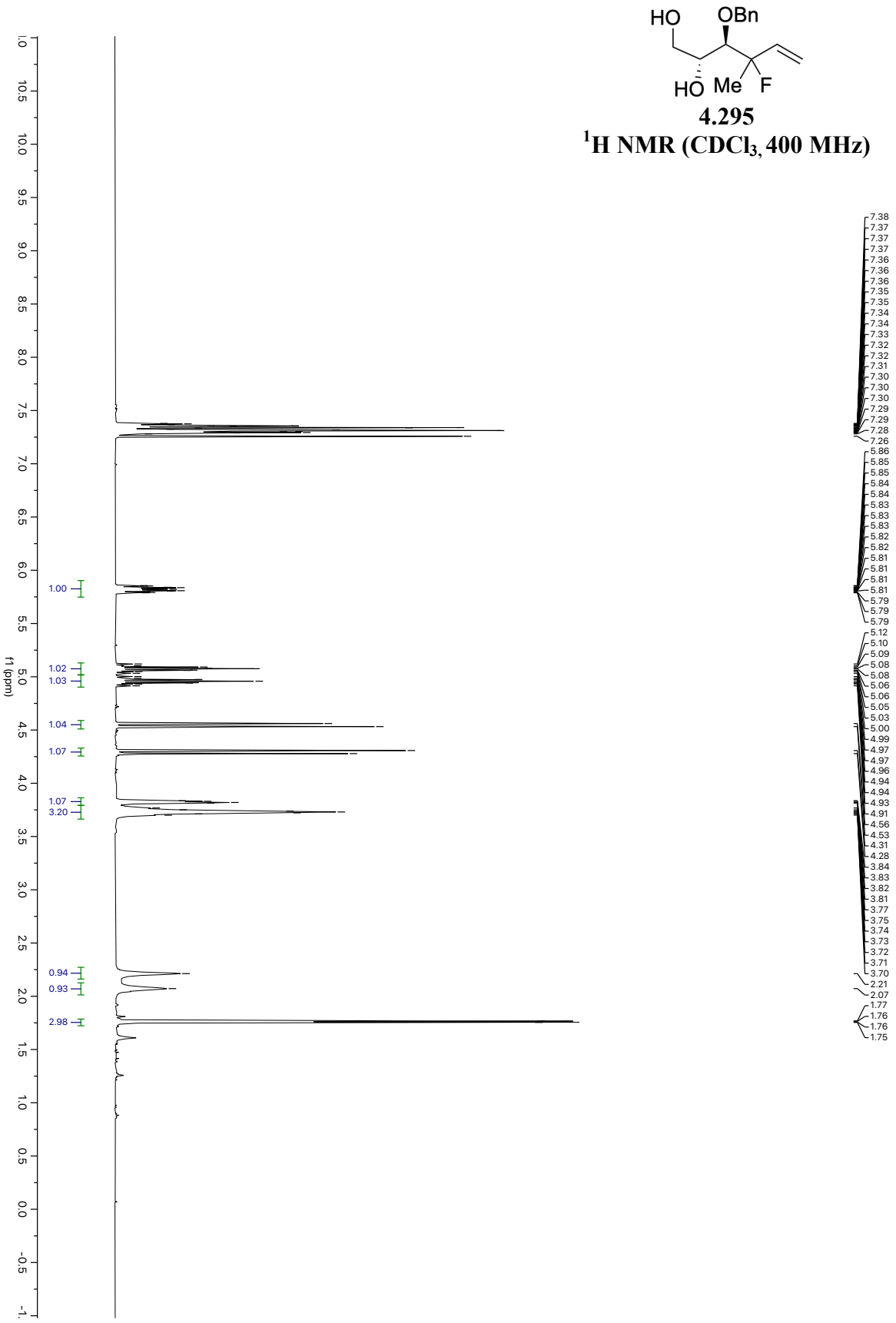
^{19}F NMR ($CDCl_3$, 376 MHz)

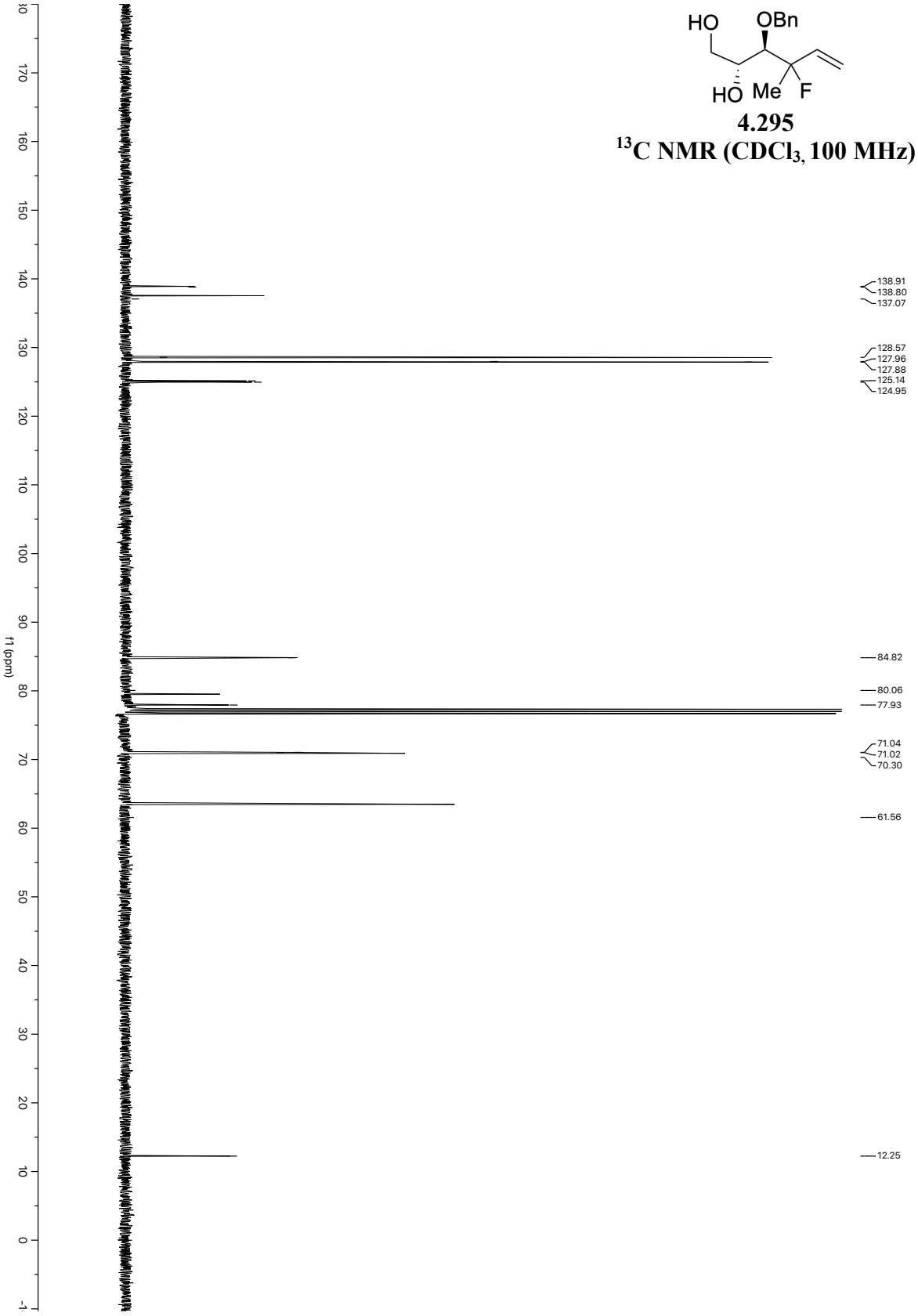

OBn
O
O
Me
OH
Me
Me
4.292
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.85
1.00
1.04
1.06
2.14
1.02
1.09
1.12
1.03
0.91
3.19
6.31
7.37
7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.31
7.30
7.26
6.09
6.07
6.05
6.02
5.39
5.38
5.34
5.34
5.18
5.17
5.15
5.15
4.77
4.75
4.71
4.69
4.25
4.23
4.22
4.05
4.03
4.03
4.01
3.91
3.89
3.89
3.87
3.53
3.51
3.04
1.54
1.44
1.35
1.34
1.32

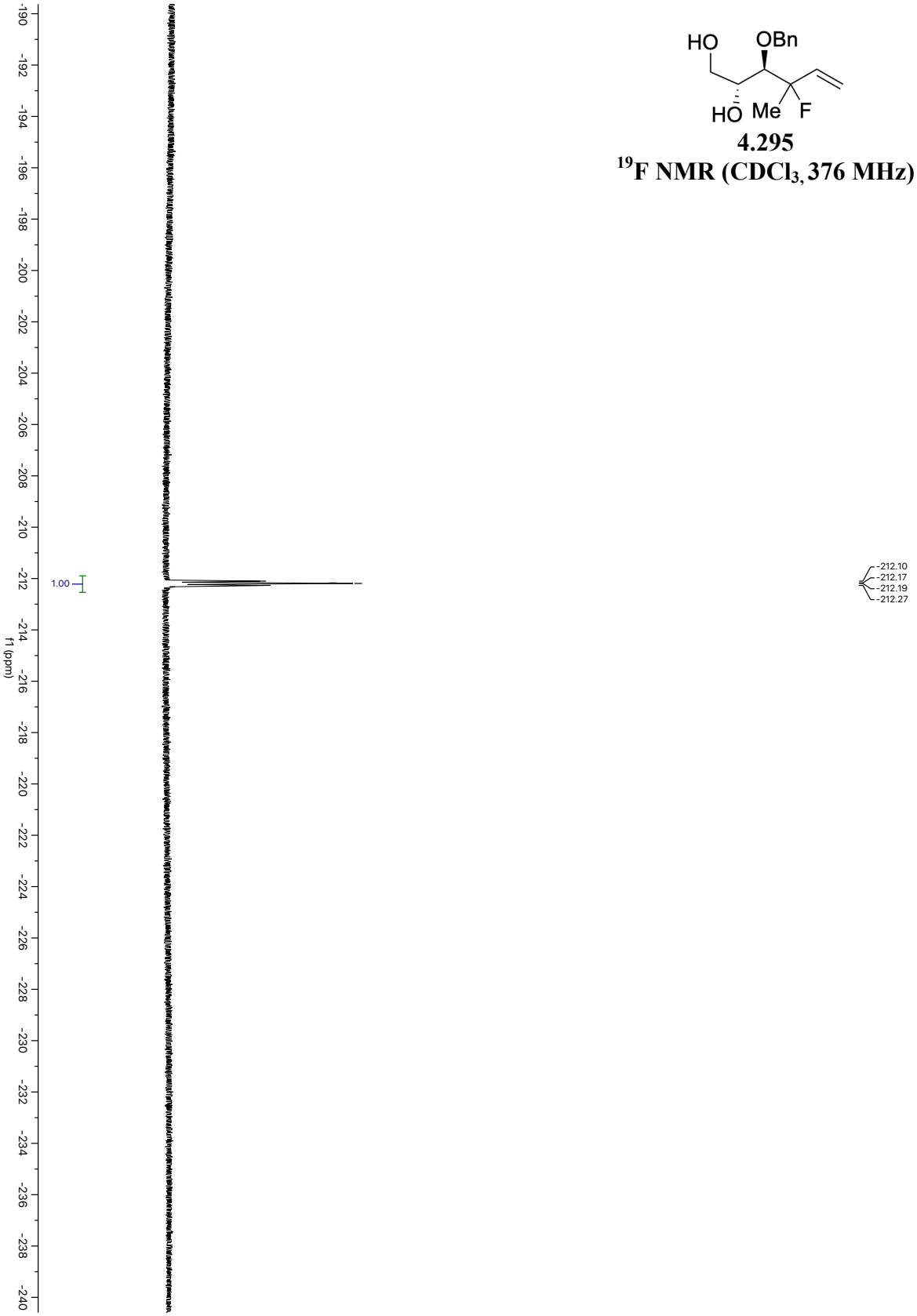


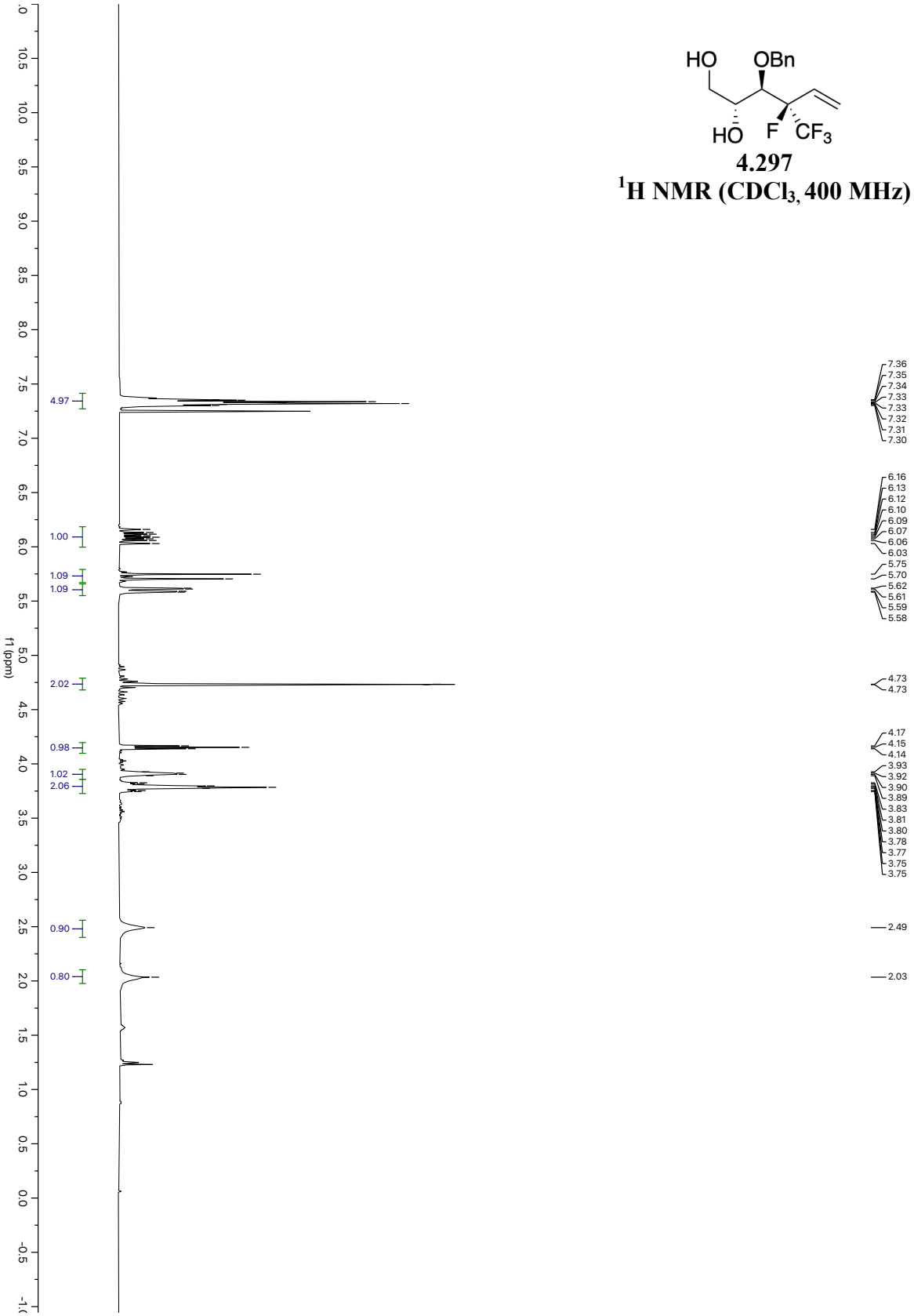
4.292

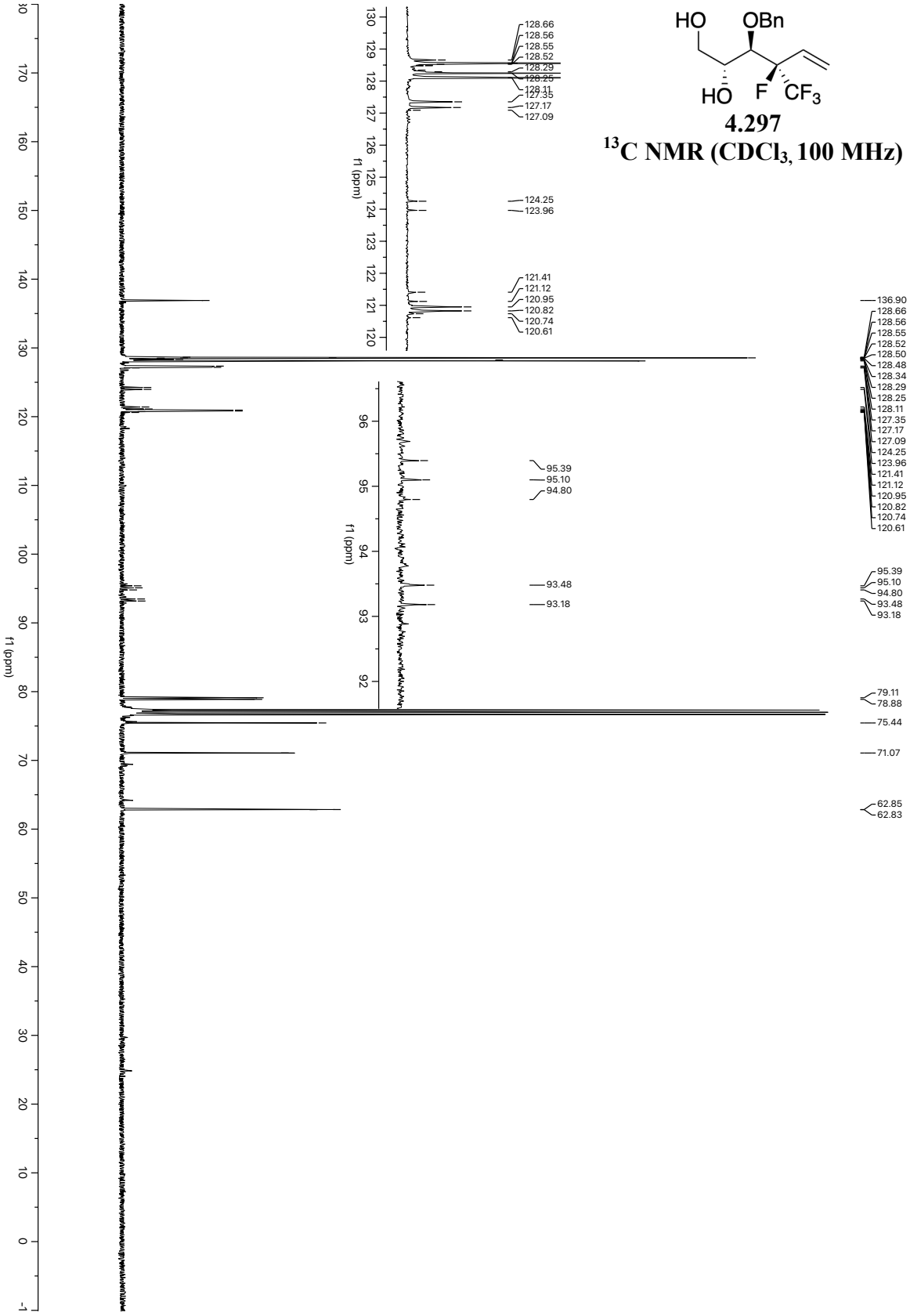
^{13}C NMR ($CDCl_3$, 100 MHz)

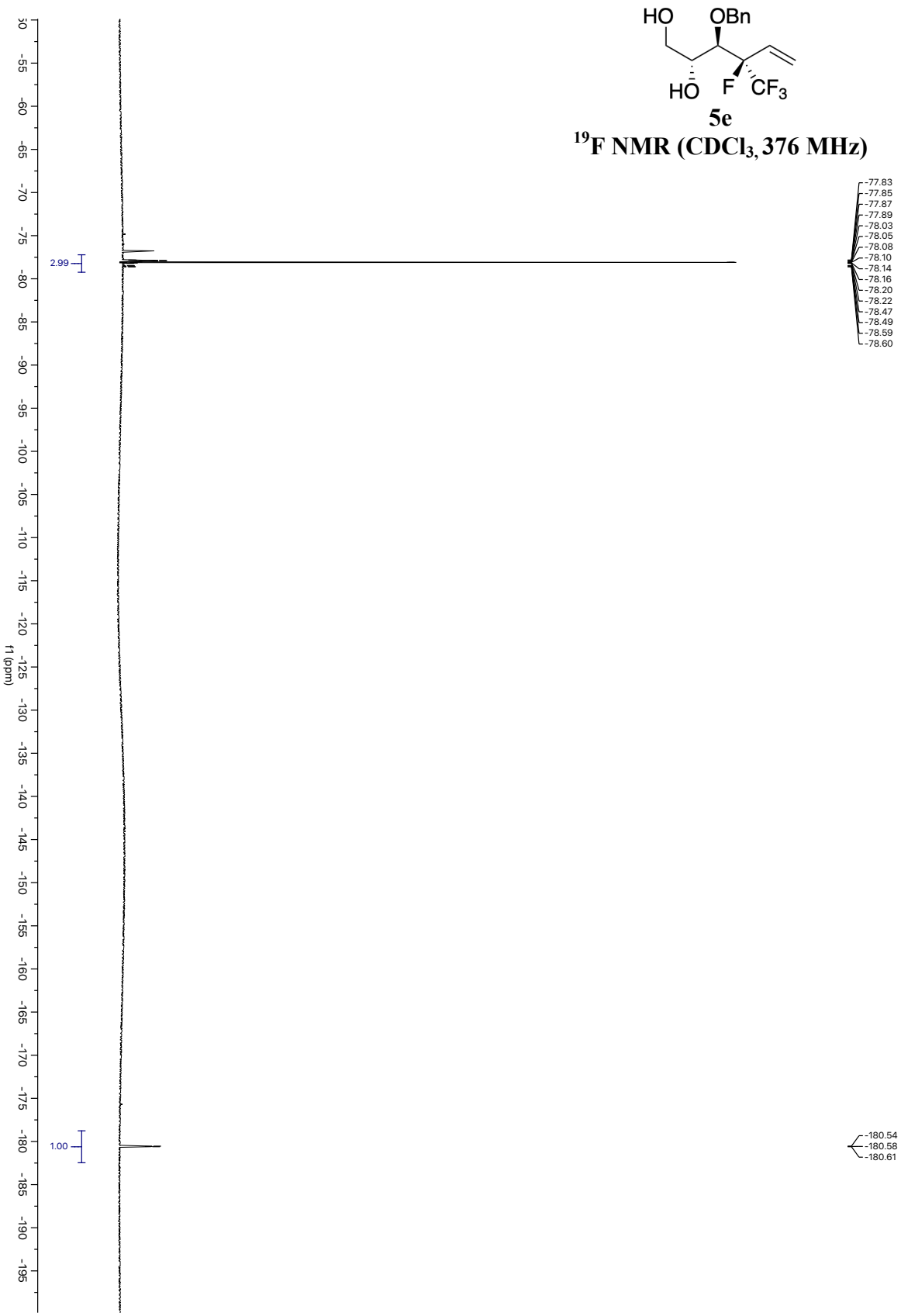

HO
OBn
HO
Me
F
4.295
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
1.00
1.02
1.03
1.04
1.07
1.07
3.20
0.94
0.93
2.98

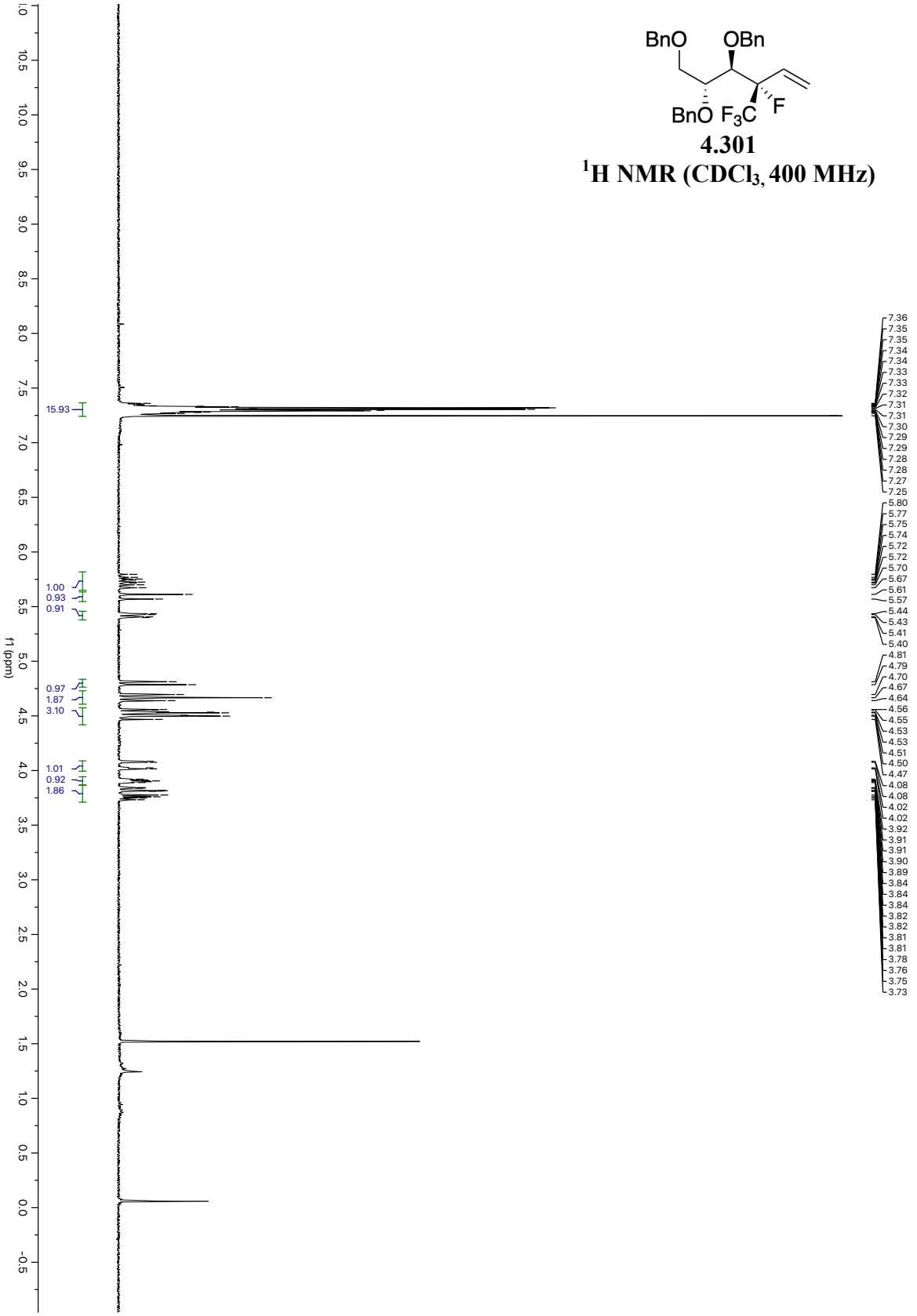

HO
OBn
HO
Me
F
4.295
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
138.91
138.80
137.07
128.57
127.96
127.88
125.14
124.95
84.82
80.06
77.93
71.04
71.02
70.30
61.56
12.25

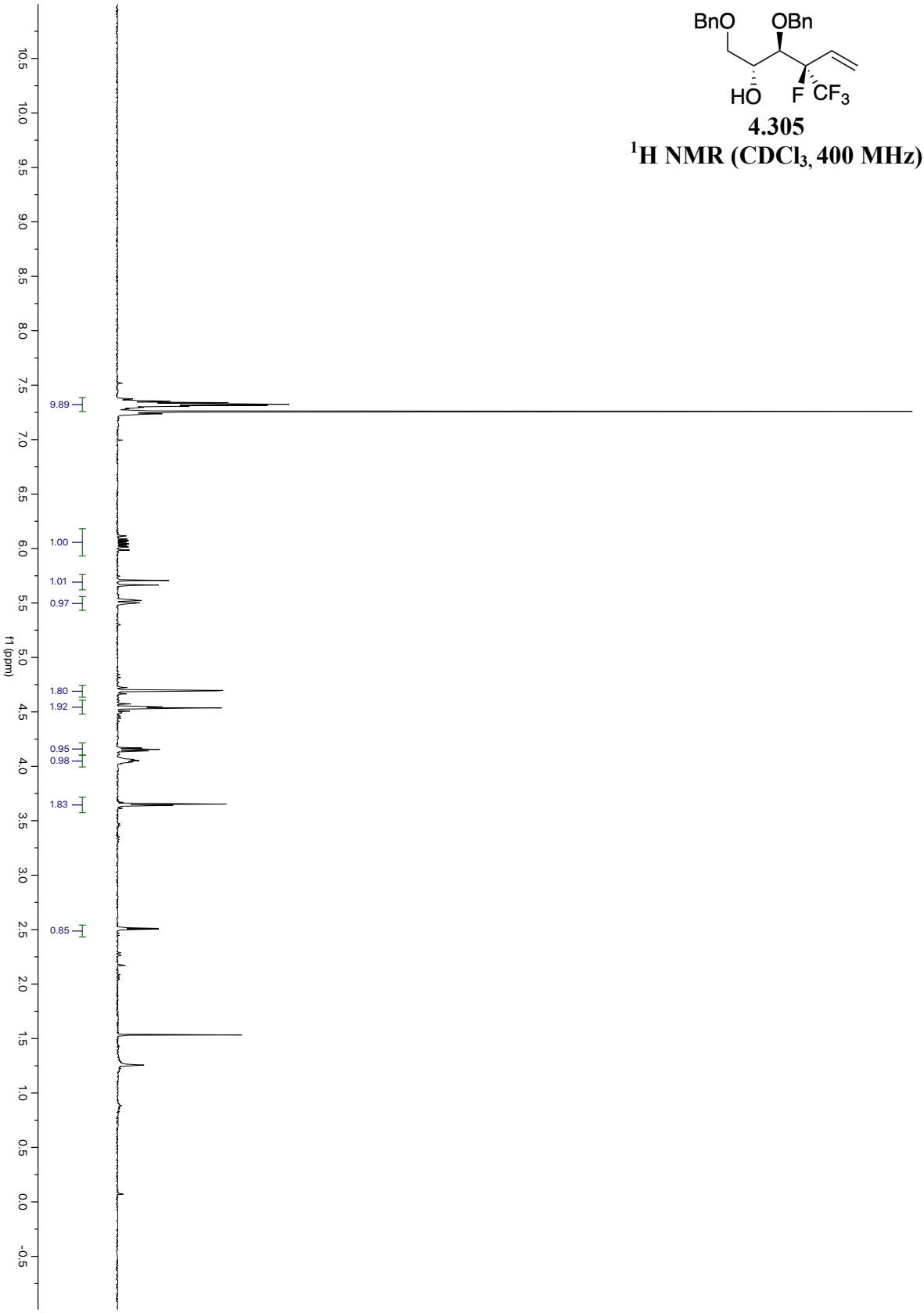

HO
OBn
HO
Me
F
4.295
19F NMR (CDCl3, 376 MHz)
1.00
-212.10
-212.17
-212.19
-212.27
f1 (ppm)
-190
-192
-194
-196
-198
-200
-202
-204
-206
-208
-210
-212
-214
-216
-218
-220
-222
-224
-226
-228
-230
-232
-234
-236
-238
-240

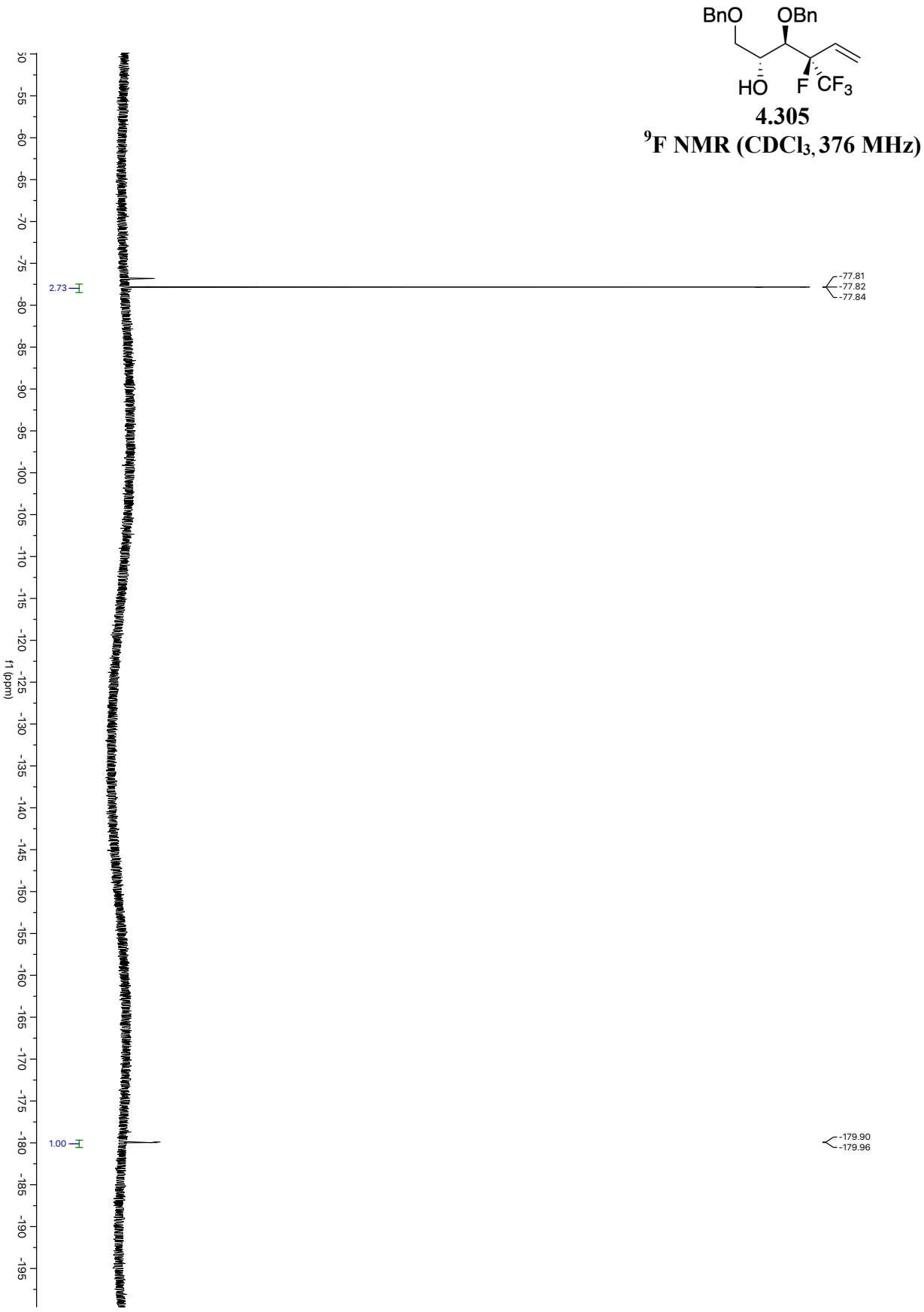

HO
OBn
HO
F
CF3
4.297
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
4.97
1.00
1.09
1.09
2.02
0.98
1.02
2.06
0.90
0.80
7.36
7.35
7.34
7.33
7.33
7.32
7.31
7.30
6.16
6.13
6.12
6.10
6.09
6.07
6.06
6.03
5.75
5.70
5.62
5.61
5.59
5.58
4.73
4.73
4.17
4.15
4.14
3.93
3.92
3.90
3.89
3.83
3.81
3.80
3.78
3.77
3.75
3.75
2.49
2.03

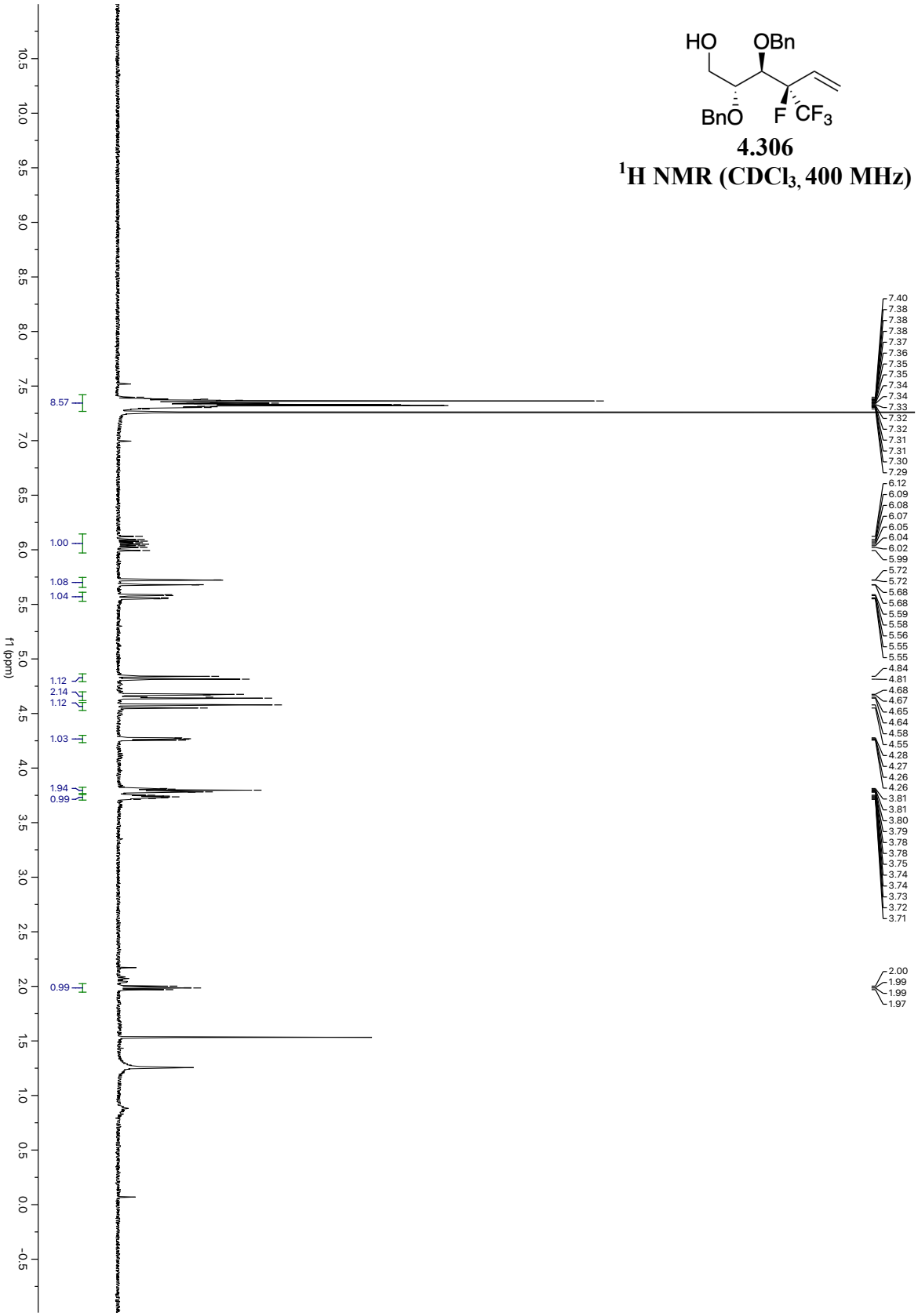

HO
OBn
HO
F
CF3
4.297
13C NMR (CDCl3, 100 MHz)
f1 (ppm)
128.66
128.56
128.55
128.52
128.29
128.25
128.11
127.35
127.17
127.09
124.25
123.96
121.41
121.12
120.95
120.82
120.74
120.61
95.39
95.10
94.80
93.48
93.18
79.11
78.88
75.44
71.07
62.85
62.83


HO
OBn
HO
F
CF3
5e
19F NMR (CDCl3, 376 MHz)
-77.83
-77.85
-77.87
-77.89
-78.03
-78.05
-78.08
-78.10
-78.14
-78.16
-78.20
-78.22
-78.47
-78.49
-78.59
-78.60
2.99
1.00
-180.54
-180.58
-180.61
f1 (ppm)


BnO
OBn
BnO
F3C
F
4.301
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
15.93
1.00
0.93
0.91
0.97
1.87
3.10
1.01
0.92
1.86

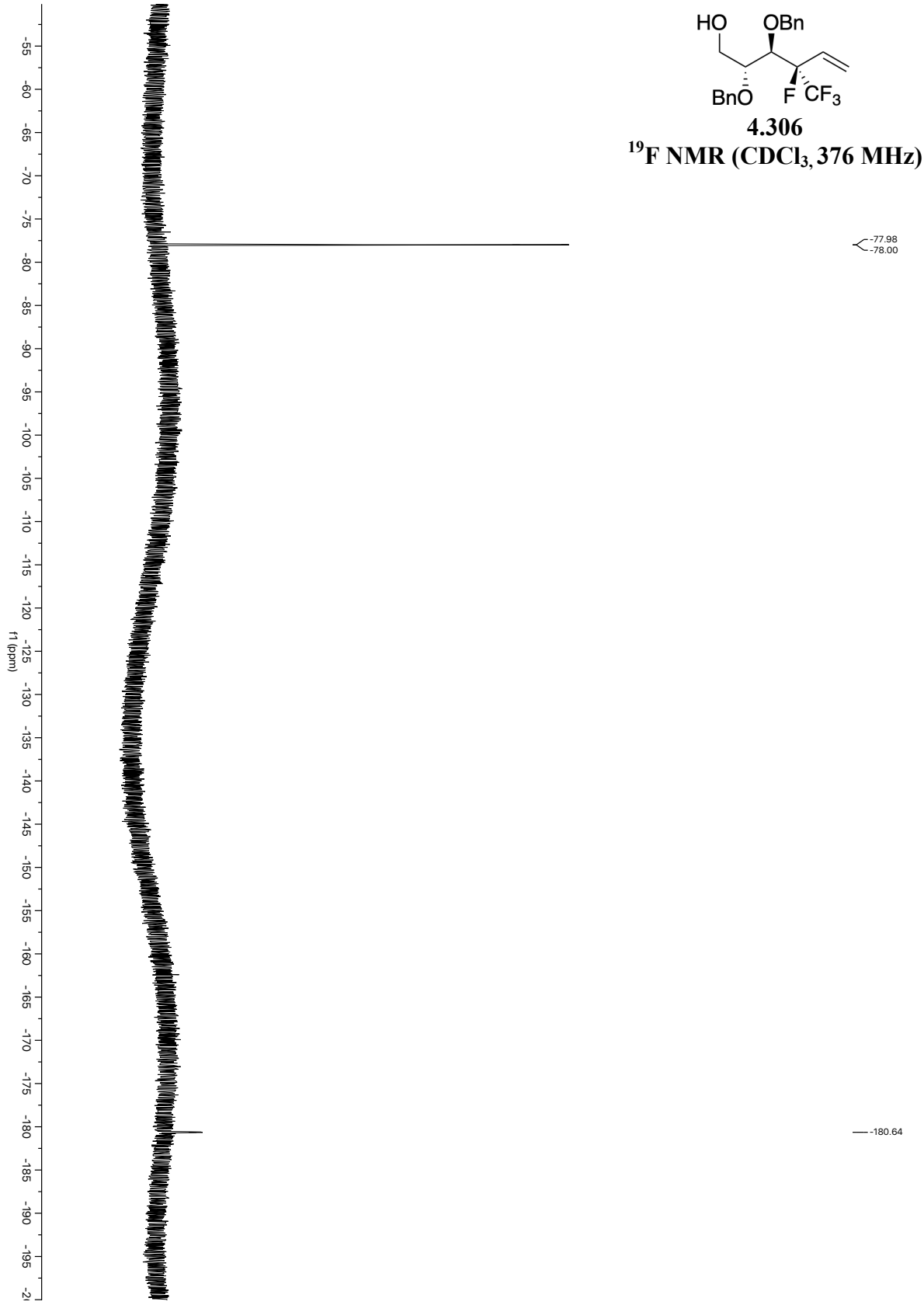

BnO
OBn
HO
F
CF3
4.305
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
9.89
1.00
1.01
0.97
1.80
1.92
0.95
0.98
1.83
0.85


BnO
OBn
HO
F
CF3
4.305
9F NMR (CDCl3, 376 MHz)
-77.81
-77.82
-77.84
2.73
1.00
-179.90
-179.96
f1 (ppm)



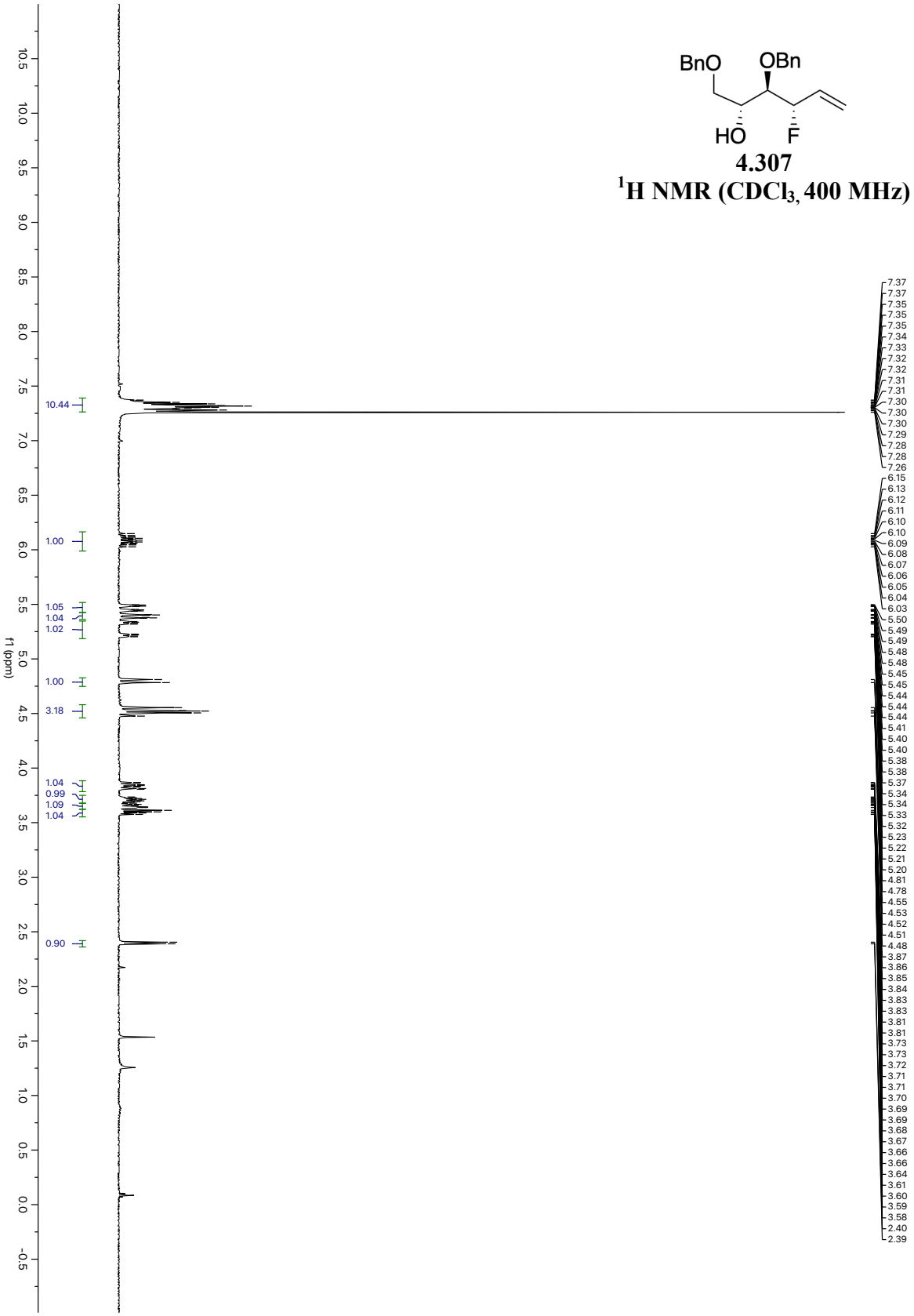
4.306

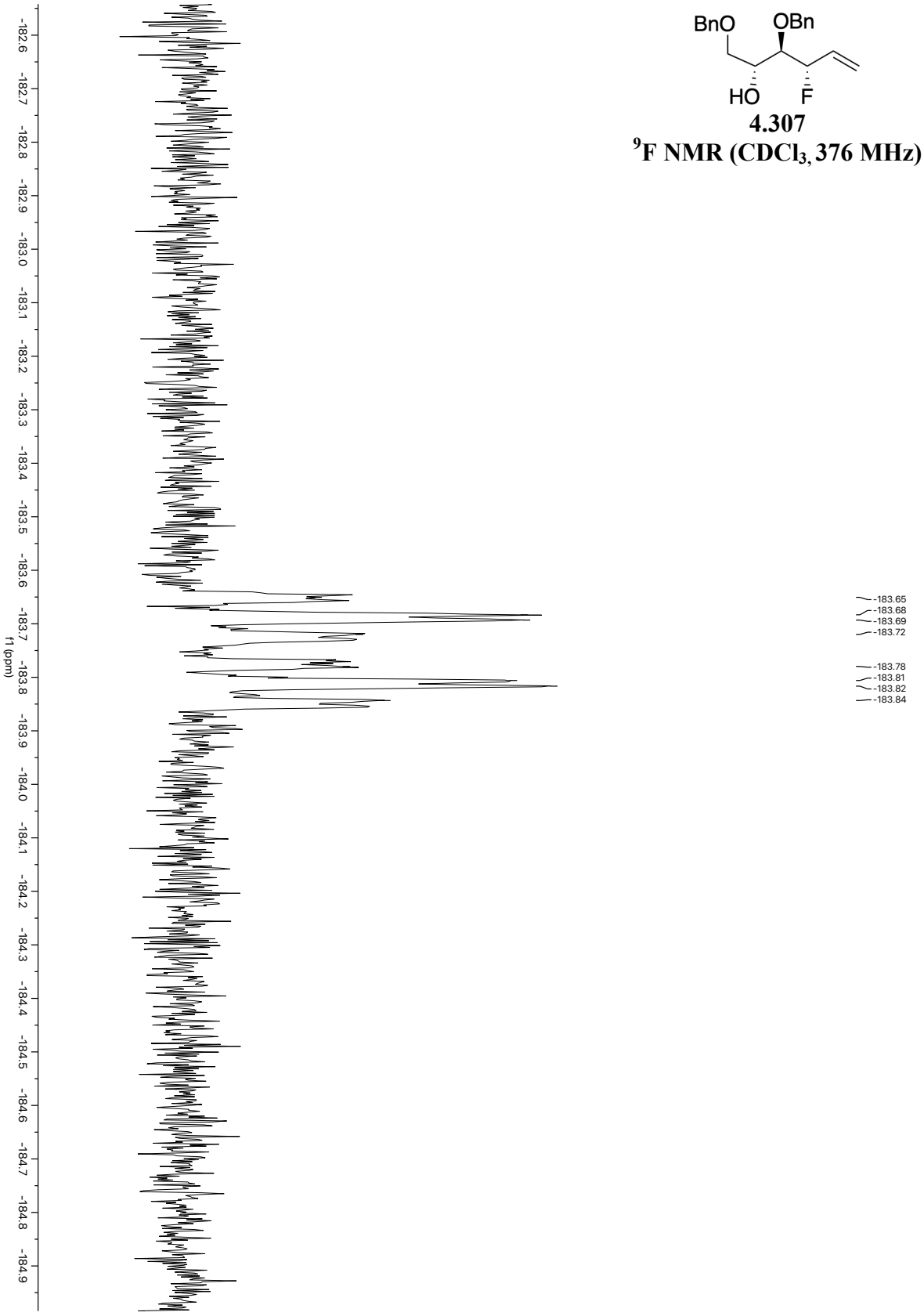
^{1}H NMR ($CDCl_3$, 400 MHz)



4.306

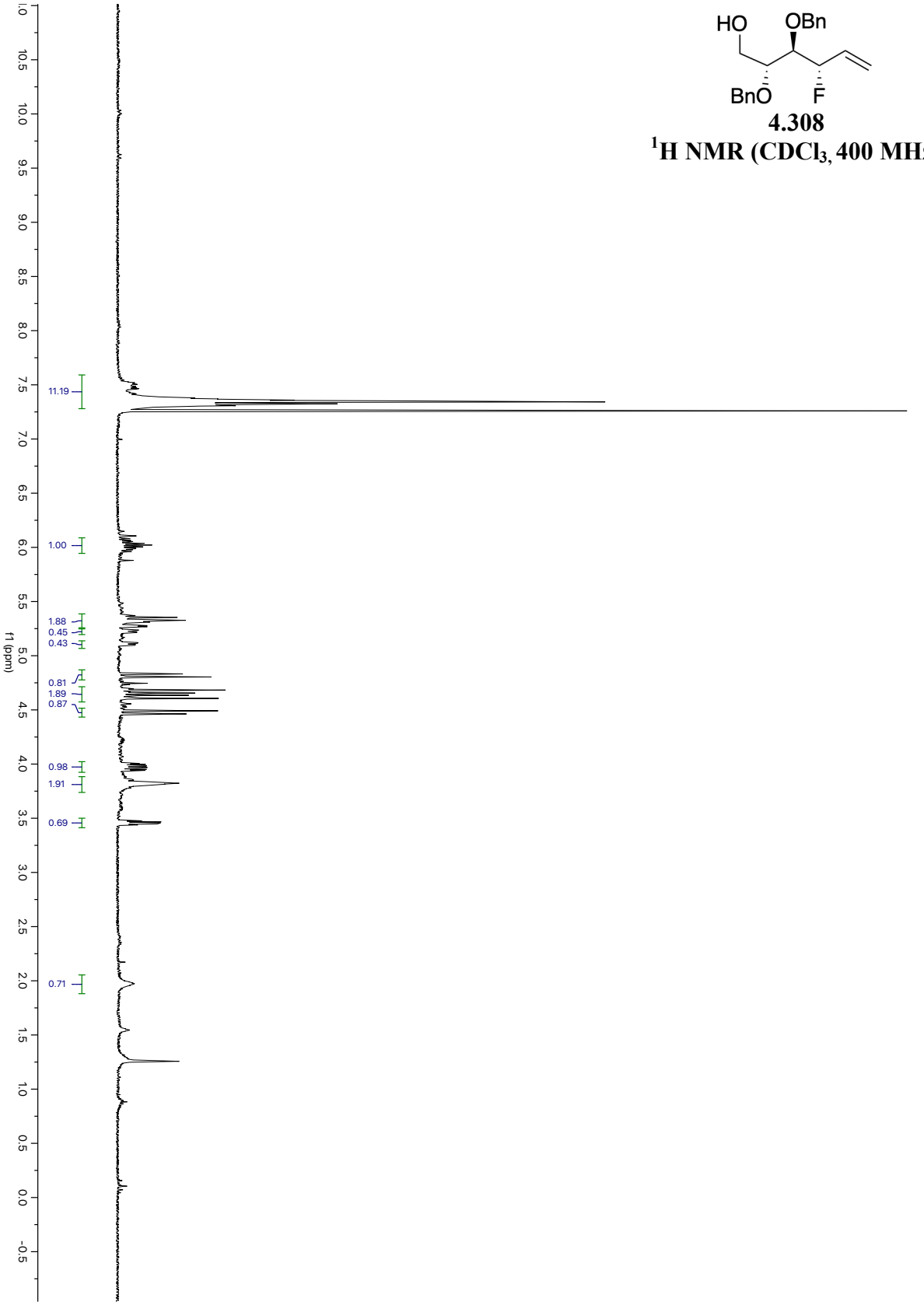
^{19}F NMR ($CDCl_3$, 376 MHz)


BnO
OBn
HO
F
4.307
1H NMR (CDCl3, 400 MHz)
f1 (ppm)
10.44
1.00
1.05
1.04
1.02
1.00
3.18
1.04
0.99
1.09
1.04
0.90



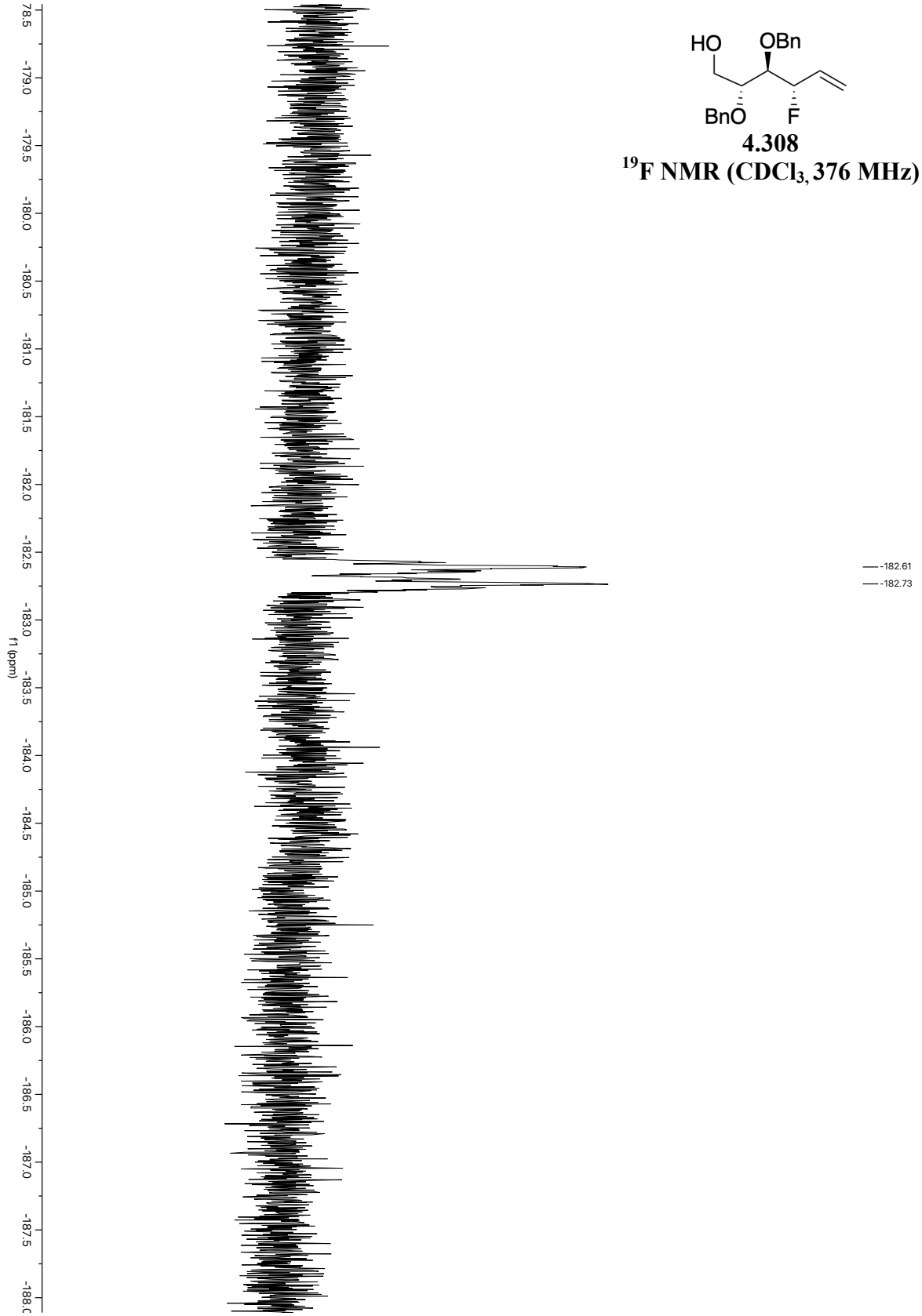
4.307

^{9}F NMR ($CDCl_3$, 376 MHz)



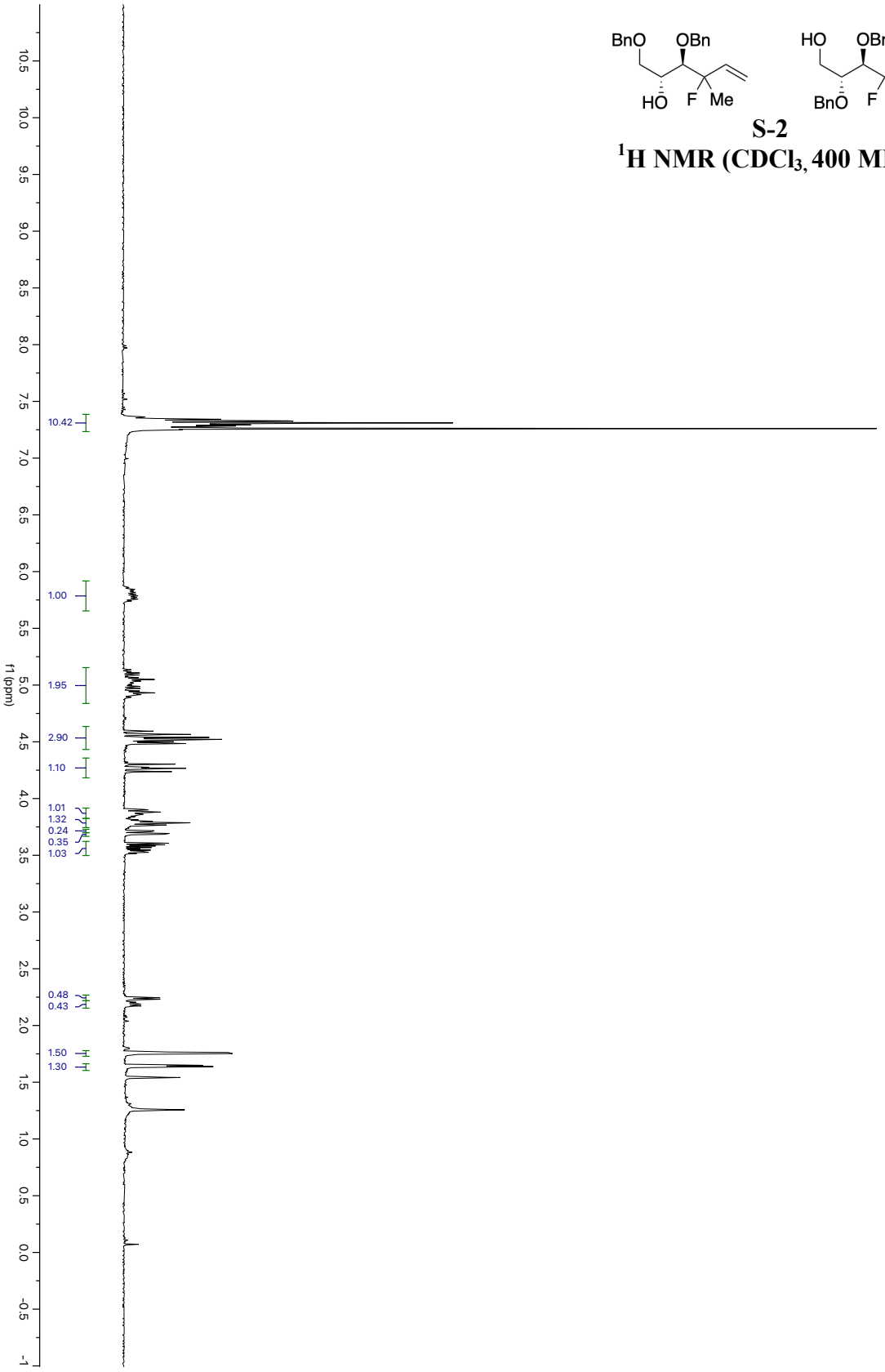
4.308

^{1}H NMR ($CDCl_3$, 400 MHz)



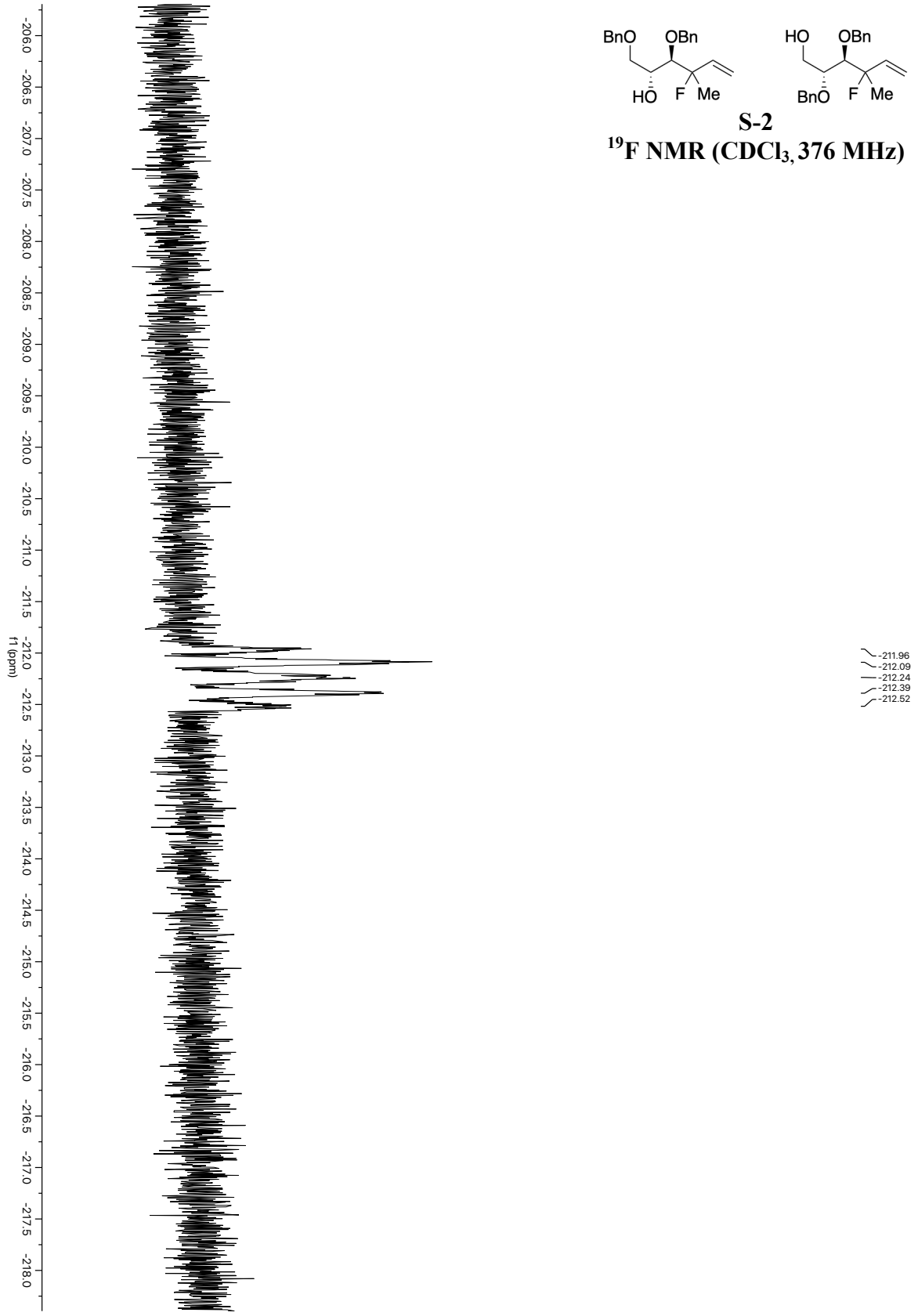
4.308

^{19}F NMR ($CDCl_3$, 376 MHz)



S-2

^{1}H NMR ($CDCl_3$, 400 MHz)



S-2

^{19}F NMR ($CDCl_3$, 376 MHz)