Development of Catalyst Systems for Regio- and Enantioselective Transformations of Amine and Ether C–H Bonds

Ahmet Selman Yesilcimen

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

April 2022

Development of Catalyst Systems for Regio- and Enantioselective Transformations of Amine and Ether C–H Bonds

Ahmet Selman Yesilcimen

Advisor: Professor Masayuki Wasa

Abstract

This dissertation describes the development of novel catalyst systems that could promote the regio- and enantioselective transformations of C–H bonds contained in *N*-alkylamines and ethers through Lewis acid-mediated hydride abstraction processes. The progress made in C–H functionalization of *N*-alkylamines and ethers that served as the intellectual foundation of this dissertation research are summarized in Chapter 1. Despite notable advances, the development of broadly applicable, enantioselective, and catalytic protocols to functionalize C–H bonds in *N*-alkylamines and ethers with high regio- and stereo-selectivity was regarded as an unsolved problem when we started this dissertation research. In an effort to overcome these fundamental limitations, we first identified a $B(C_6F_5)_3$/Cu-PyBOX cooperative catalyst system for the enantioselective conversion of α-amino C–H bonds through the generation of an iminium by $(F_5C_6)_3B$-catalyzed hydride abstraction process (Chapter 2). We then envisioned that in situ generated iminium ions could be further deprotonated to furnish an enamine intermediate, which may react with electrophilic species for β–amino C–H functionalization. The design and development of such a catalyst system were discussed in Chapter 3. Finally, we disclose enantioselective Cu–BOX-catalyzed hetero Diels-Alder reactions of enol ethers generated through Ph_3C^+-mediated oxidation of alkyl ethers. (Chapter 4).

Acknowledgement

First and foremost, I would like to express my deep gratitude to my advisor Professor Masayuki Wasa, for his mentorship, guidance, and patience during my doctoral studies. His passion for science and ability to think critically inspired me to become a better version of myself. Additionally, after countless hours of discussions on scientifically stimulating challenges, Dr. Wasa has given me the freedom to attack problems in my own way. He has also been there for me whenever I struggled to find my way out. When I was searching for safe exits, he remained determined and never lowered his standards. I am very fortunate to experience his education; it always encouraged me to aim high and do better. I will always be grateful for this.

I also want to thank Professor Amir H. Hoveyda. He has been a great role model for me in many instances. His youthful enthusiasm, passion for science, and unique philosophy have inspired me to aim higher and be a more creative scientist. I would also like to thank Prof. Hoveyda for the insightful comments and suggestions on our projects and for serving on my dissertation committee.

I am grateful to Professor Marc L. Snapper for serving as my committee member for the oral examination in my second year and for the thesis defense. Thank you for giving me helpful comments and feedback after my second-year oral exam and for spending time reading my dissertation.

I also want to thank Professor James P. Morken for offering his help during my search for my next appointment. I would also like to acknowledge Professor Shih-Yuan Liu for his support in the mechanistic studies.

I have had a great pleasure working next to a group of talented and hardworking people in Wasa Laboratory. I was fortunate to have Dr. Jessica Z. Chan, Dr. Min Cao, Dr. Yejin Chang, Na-Chuan Jiang, Yuyang Zhang, and Bochao Zhang as collaborators. I could not have completed these projects without their hard work and support. I was fortunate to have Jessica, Min, and Yejin next to me during my studies. The standards they have set inspired me to aim higher. They were always kind and supportive. Thank you for all the mentoring and, more importantly offering your friendship.

Finally, I would like to thank my parents and family for their continuous encouragement and tremendous support throughout my studies at Boston College. Without their unconditional love and support, I would never be able to come thus far. Most importantly, I am very fortunate to have my wife, Nadide Hazal Avci, next to me throughout this process. I would not become who I am today were it not for you. Your support turned this dream into a reality. Thank you for believing in me, and I am forever grateful for your love and support.

Table of Contents

Chapter One

Recent Advances in C–H Functionalization of *N*-Alkylamines and Ethers through Hydride Abstraction

N-Alkylamines and ethers that contain stereogenic centers at α-, β-, and/or γ-positions represent the core structure of a myriad of natural products, pharmaceuticals, and polymers.[1] Therefore, methods to rapidly access *N*-alkylamines[2] and ethers[3] with high enantiomeric purity have been extensively investigated.[1–3] Further, enantiomerically enriched *N*-alkylamines are often synthesized through stereoselective transformations of iminium ions (**I**, Scheme 1.1A)[4a] or enamines (**II**, Scheme 1.1B);[4b] conversions of enol ethers (**III**, Scheme 1.1C) can be employed to access chiral ethers.[4c] Despite these notable advances, catalyst systems that directly transform ubiquitous, otherwise stable, and easy-to-handle starting materials into such versatile intermediates en route to the molecules of interest with high enantiopurity, still remain underdeveloped.[4d] To highlight the significance as well as the critical limitations of the state-of-the-art, this section will describe the recent advances in the synthetic methods that involve in situ generation of iminium ion, enamine, and enol ether intermediates.

---

[1] (a) Teruaki, S.; Kuniko, K.; Minoru, S.; Etsuro, K. *Chem. Lett.* **1983,** *12*, 1643−1644. (b) Kennedy, D. J.; Selby, I. A.; Cowe, H. J.; Cox, P. J.; Thomson, R. H. *J. Chem. Soc., Chem. Commun.* **1984,** *3*, 153−155. (c) TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996,** *39*, 2435−2437.

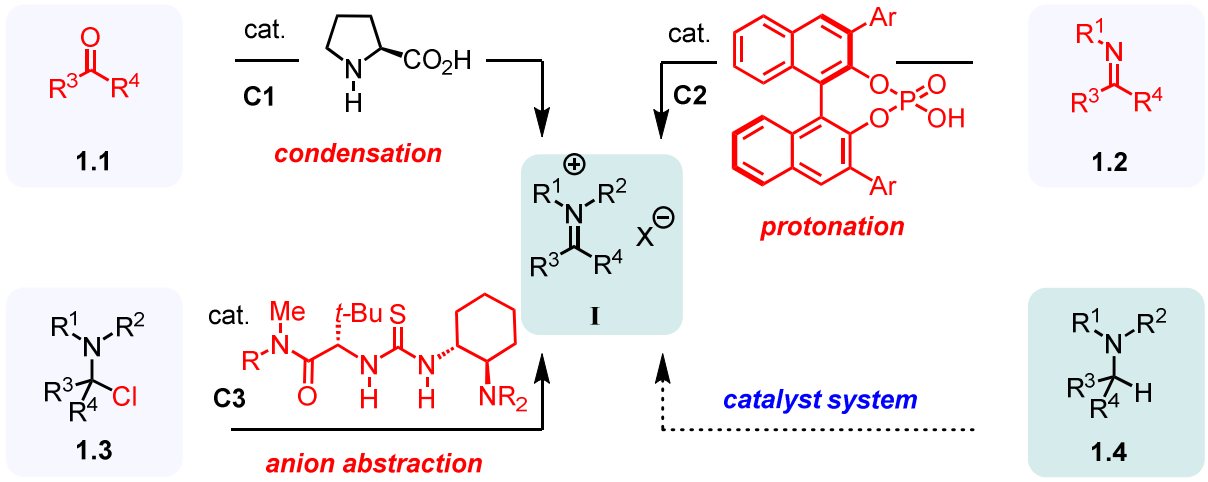
[2] (a) Chiral Amine Synthesis: Methods, Developments and Applications; Nugent, T. C., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2010, p 15−457. (b) Vardanyan, R. in Piperidine-Based Drug Discovery; Vardanyan, R., Ed.; Elsevier: 2017, p 147. (c) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. *Science* **2019**, *363*, eaat0805. (d) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. *Chem. Rev.* **2020**, *120*, 2613–2692. 6

[3] (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in total synthesis: targets, strategies, methods*; Wiley-VCH: Weinheim, 1996. (b)Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953. (c) Cao, B.; Park, H.; Joullie, M. M. *J. Am. Chem. Soc*. **2002**, *124*, 520−521. (d) Tanaka, H.; Sawayama, A. M.; Wandless, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 6864−6865. (f) Worch, J. C.; Prydderch, H.; Jimaja, S.; Bexis, P.; Becker, M. L.; Dove, A. P. *Nat. Rev. Chem.* **2019**, *3*, 514−535.

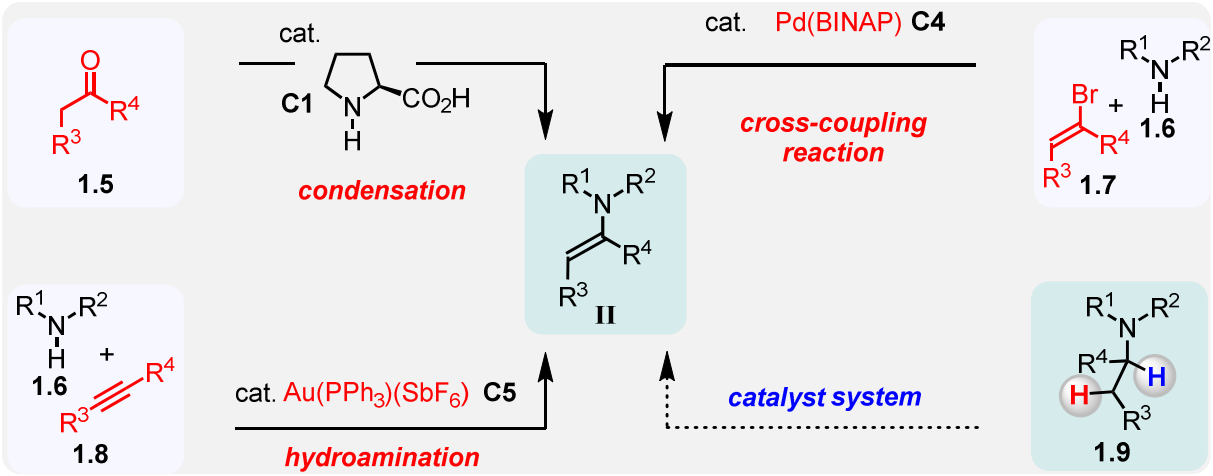
[4] (a)Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568. (b) Hansen, K. B.; Hsiao, Y.; Armstrong III, J. D. *J. Am. Chem. Soc.* **2009**, *131*, 8798−8804. (c) Stavenger, R. A.; Schreiber, S. L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3417−3421. (d) Seidel, D.; Haibach, M. C. Angew. *Chem., Int. Ed.* **2014**, *53*, 5010−5036.

Scheme 1.1. Methods for Generating Iminium Ions, Enamines, and Enol Ethers

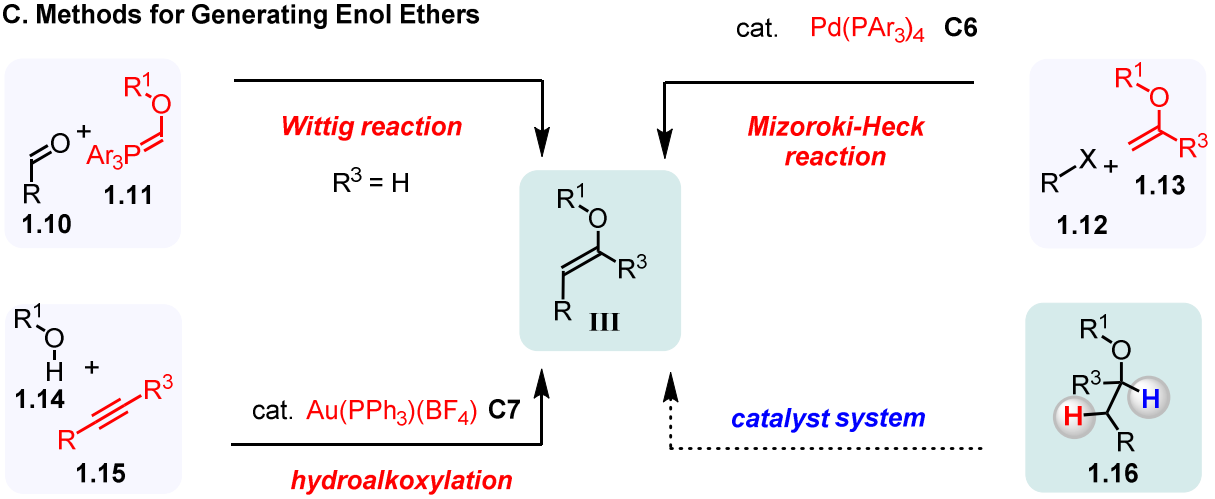
A. Methods for Generating Iminium Ions



B. Methods for Generating Enamines



C. Methods for Generating Enol Ethers



Iminium ions have been widely used as key intermediates for the enantioselective synthesis of *N*-alkylamine-based molecules.[5] Various catalytic systems have been invented to facilitate in situ formation of iminium ions; such methods include, but are not limited to, condensations of primary or secondary amine catalysts with carbonyl molecules (**1.1** → **I**; Scheme 1.1A),[5a] protonation of imines by Brønsted acids (**1.2** → **I**),[4,5b] and anion abstraction from α-(pseudo)haloamines by hydrogen bond donors (**1.3** → **I**).[5c]

Enantiomerically enriched amines containing stereogenic centers at α- and/or β-positions can be achieved through the intermediacy of enamines.[6] Methods to generate such moieties include acid-catalyzed condensation reaction of ketones or aldehydes with secondary amines (**1.5** → **II**, Scheme 1.1B),[6a] cross-coupling reaction of secondary amines with alkenyl bromides (**1.6** + **1.7** → **II**),[7] and hydroamination of alkynes (**1.6** + **1.8** → **II**).[8]

Enol ethers are versatile intermediates that are widely used for the stereoselective synthesis of chiral ether-based compounds.[9] Conventional methods for the synthesis of enol ethers include the Wittig reaction between carbonyl compounds and phosphonium ylides (**1.10** + **1.11** → **III**, Scheme 1.1C),[10] the Mizoroki-Heck coupling of organohalides with structurally simple enol ethers

---

[5] (a) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416−5470. (b) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc*. **2007**, *129*, 6756−6764. (c)) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404−13405. (d) Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; White, M. C. *Nature* **2016**, *537*, 214−219. (e) Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. *Adv. Synth. Catal*. **2021**, *363*, 602−628

[6] (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569. (b) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713−1760. (c) Lin, W.; Zhang, K.-F.; Baudoin, O. *Nat. Catal*. **2019**, *2*, 882−888. (d) Bai, X.-Y.; Zhao, W.; Sun, X.; Li, B.-J. *J. Am. Chem. Soc.* **2019**, *141*, 19870−19878.

[7] Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2004**, *10*, 494−507.

[8] Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 18026−18029.

[9] (a) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc*. **1998**, *120*, 4895−4896. (b) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681−1683 (c) Khan, R. K. M.; O'Brien, R. V.; Torker, S.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2012**, *134*, 12774−12779.

[10] Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem*. **1979**, *44*, 4847−4852.

(**1.12** + **1.13** → **III**),[11] and hydroalkoxylation of alkynes with alcohols (**1.14** + **1.135** → **III**).[12]

Although a wide variety of essential building blocks for biologically active compounds and other molecules of interest have been produced through iminium, enamine, or enol ether intermediates generated through the approaches as shown above, key shortcomings remain unaddressed. Among the most significant limitations of the state-of-the-art is the lack of potent catalyst systems that can generate these reactive and, therefore, often short-lived intermediates from more readily accessible and easy to handle starting materials (e.g., *N*-alkylamines **1.4**, **1.9**, and alkyl ethers **1.16**).[13] As shown in Scheme 1.1, the catalysts used to generate these species are typically weakly to moderately acidic and/or basic catalysts that can only activate highly pre-activated starting materials (i.e., α-haloamines **1.3**, trisubstituted alkenyl bromide **1.7**, enol ethers **1.13**, etc). Preparation and purification of such highly acid- and/or base-sensitive molecules are often cumbersome and wasteful.[14] For instance, conventional methods to synthesize trisubstituted alkenyl bromide **1.7** involve the uneconomical reaction between aldehydes and phosphorus ylides in the presence of stoichiometric quantities of phenyllithium and bromine.[14] If more potent catalysts capable of activating less pre-activated substrates were employed, acid–base complexation, which can occur in the mixture that contains the catalysts, starting materials, and products, may result in the termination of the desired transformation.[13,15] Consequently, previously

[11] Prater, M. B.; Sigman, M. S. *Isr. J. Chem.* **2020**, *60*, 452–460.
[12] Nanda, S. K.; Mallik, R. *Chem. Eur. J.* **2021**, *27*, 15571–15604.
[13] (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924–1942. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704. (c) Allen, A. E.; MacMillan, D. W. *Chem. Sci*. **2012**, *3*, 633–658. (d) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688–701. (e) Shibasaki, M.; Kumagai, N. in *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*, Peters, R., Eds.; Wiley-VCH: New York, 2015; Chapter 1. (f) Lu, X.; Deng, L. in *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*, Peters, R., Eds.; Wiley-VCH: New York, 2015; Chapter 5. (g) Inamdar, S. M.; Shinde, V. S.; Patil, N. T. *Org. Biomol. Chem.,* **2015**, *13*, 8116–8162. (h) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912–14922. (i) 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. (j) Sancheti, S. P.; Urvashi, Shah, M. P.; Patil, N. T. *ACS Catal.* **2020***, 10*, 3462-3489.
[14] Hodgson, D. M.; Arif, T. *J. Am. Chem. Soc*. **2008**, *130*, 16500–16501.
[15] Kumagai, N.; Kanai, M.; Sasai, H. *ACS Catal*. **2016**, *6*, 4699–4709.

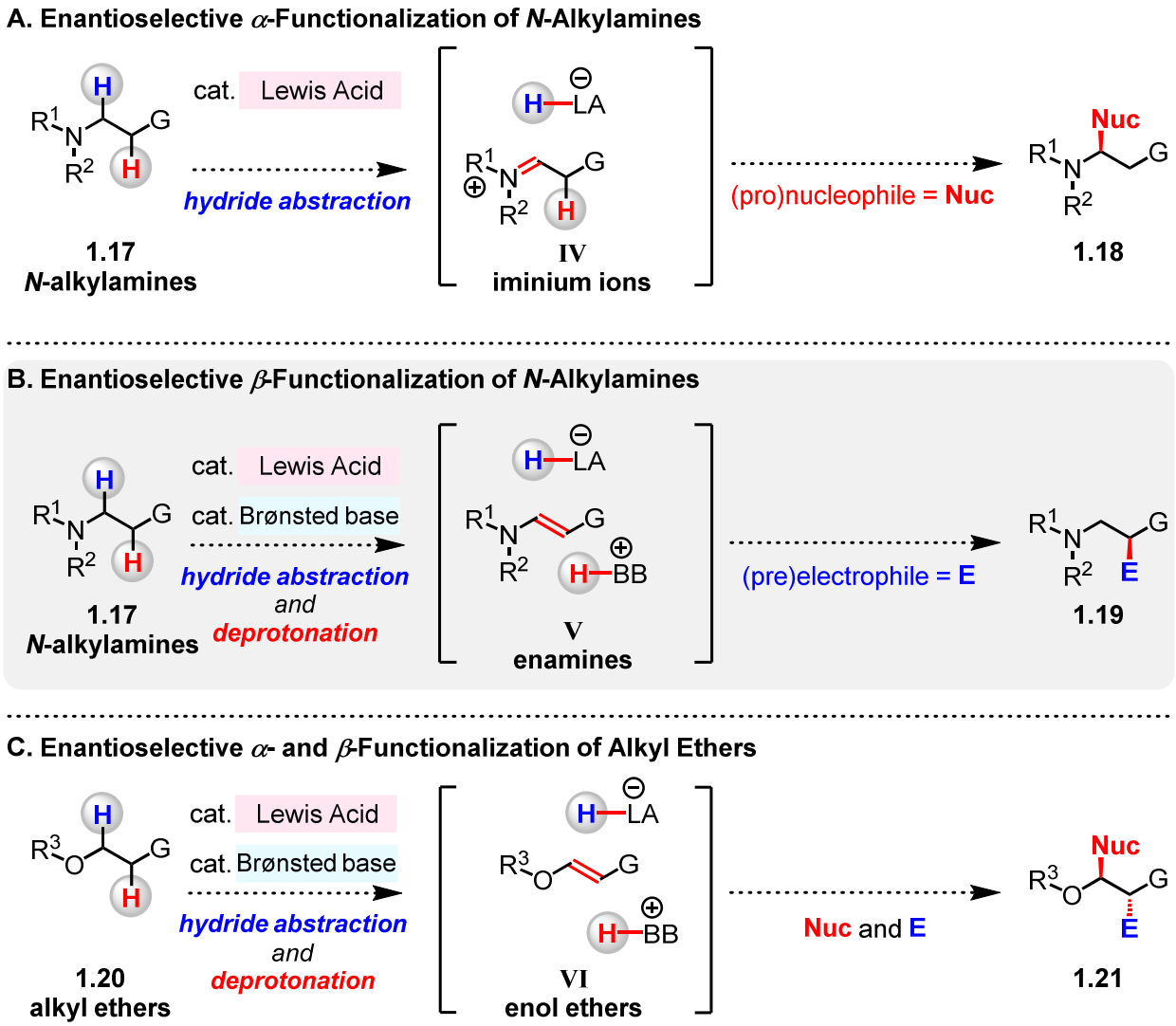
reported methods are primarily confined to enantio- and diastereoselective preparation of synthetically useful building blocks with limited structural complexity.[5,6,9]

The aim of my thesis research is to develop highly efficient catalyst systems that can transform polyfunctional *N*-alkylamines and ethers into the corresponding reactive intermediates en route to the desired amine and ether derivatives in an enantio- and diastereoselective manner. Such catalysts must be able to overcome the aforementioned mutual quenching issue and activate otherwise chemically inert C(sp^3)–H bonds of amines and ethers for the generation of iminiums, enamines, or enol ethers. Specifically, we envisioned processes that involve the use of Lewis acid catalysts that circumvent the formation of stable acid–base adducts with the Lewis basic amine and ether-based compounds due to steric and electronic factors (i.e., "frustrated" Lewis pairs).[16] Such Lewis acids might abstract a hydride from amines and ethers, thereby converting them into iminiums (**1.17** → **IV**; Approach A, Scheme 1.2) and oxocarbeniums, respectively. Enantioselective transformations of iminiums generated in this manner may afford α-substituted amines (**IV** → **1.18**). Alternatively, deprotonation of iminiums or oxocarbeniums by an appropriate Brønsted base can lead to the formation of enamines (**1.17** → **V**; Approach B) or enol ethers (**1.20** → **VI**; Approach C). Stereoselective reactions involving these nucleophilic intermediates could be used to produce various α- and/or β-substituted amines (**V** → **1.19**) or ethers (**VI** → **1.21**). The key advantage of such C–H functionalization strategies is that they enable the transformations of non-isolable intermediates that are generated from ubiquitous and otherwise chemically inert starting materials. Furthermore, we envisioned that, because the sterically hindered catalysts to be developed would not be readily deactivated through their interactions with Lewis basic functional

[16] Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400–6441.

groups, our methods may be applied for late-stage functionalization of polyfunctional and biologically significant amines and ethers.

Scheme 1.2. Enantioselective α- and/or β-Functionalization of *N*-Alkylamines and Alkyl Ethers



The advances in C–H functionalization of *N*-alkylamines and ethers that served as the intellectual foundation of this dissertation research are summarized in the following sections. The selected topics to be highlighted are the following:

1.1. Lewis Acid-Mediated Hydride Abstraction of Amines for the Generation of Iminium Ions and Their Derivatization into Enamines

1.2. $(F_5C_6)_3B$-Catalyzed Transfer Hydrogenation/Dehydrogenation of Amines

1.3. α-Amino C–H Functionalization through Lewis Acid-Catalyzed Conversion of Amines into Iminiums

1.4. Lewis Acid/Brønsted Base-Catalyzed Formation of Enamines for β–Amino C–H Functionalization

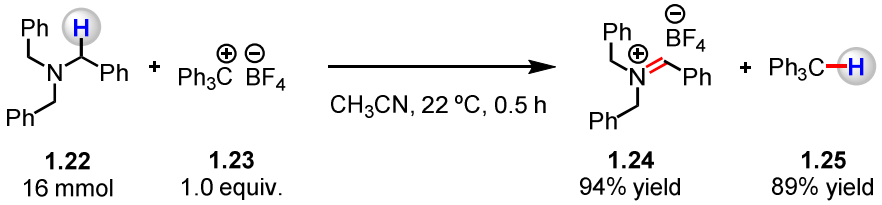
1.5. Lewis Acid-Promoted Generation of Oxocarbenium Ions through Hydride Abstraction from Ethers

1.1. Lewis Acid-Mediated Hydride Abstraction of Amines for the Generation of Iminium Ions and Their Derivatization into Enamines

1.1.1. Carbocation Mediated Hydride Abstraction from *N*-alkylamines

Carbocation-mediated hydride abstraction has previously been established as an enabling strategy to generate iminium ions from *N*-alkylamines.[17] As early as 1966, Broaddus et al. demonstrated that the reaction of tribenzylamine **1.22** and triphenylcarbonium tetrafluoroborate **1.23** affords a tetrafluoroborate salt of iminium **1.24** and triphenylmethane **1.25** in 94% and 89% yield, respectively (Scheme 1.3).[18]

Scheme 1.3. Tritylium-Mediated Hydride Abstraction from Tertiary Amines

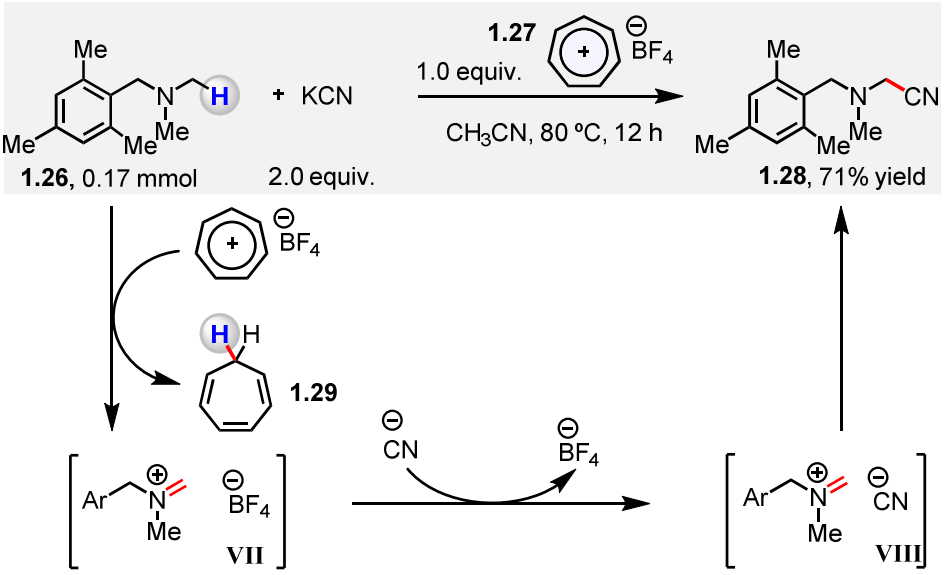


1.22 16 mmol | **1.23** 1.0 equiv. | **1.24** 94% yield | **1.25** 89% yield

The Lambert group achieved the installation of a versatile cyano group at the α-position of *N*-alkylamines through the use of tropylium tetrafluoroborate **1.27** as the hydride acceptor (Scheme 1.4).[19] The proposed mechanism involves tropylium-mediated hydride abstraction from trialkylamine **1.26** to afford iminium tetrafluoroborate **VII**, which reacts with potassium cyanide to generate an ionic complex **VIII**. The subsequent C–CN bond formation then delivers α-cyanoamine **1.28** in 71% yield.

[17]Meerwein, H.; Hederich, J.; Morschel, H.; Wunderlich, K. *Justus Liebigs Ann. Chem*. **1960**, *635*, 1–21.
[18] Damico, R.; Broaddus, C. D. *J. Org. Chem*. **1966**, *31*, 1607–1612.
[19] Allen, J. M.; Lambert, T. H. *J. Am. Chem. Soc*. **2011**, *133*, 1260–1262.

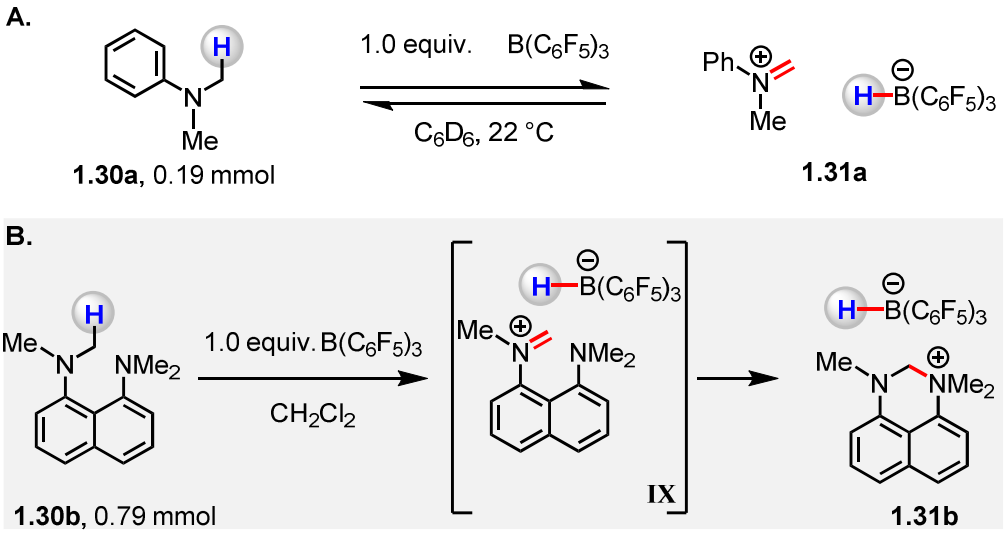
Scheme 1.4. α-Amino C–H Cyanation through Tropylium Ion-Mediated Hydride Abstraction



1.1.2. Organoborane-Mediated Hydride Abstraction from *N*-Alkylamines

Santini and co-workers disclosed $(F_5C_6)_3B$-mediated transformation of *N*,*N*-dimethylaniline **1.30a** into an ion pair comprised of an iminium ion and a borohydride **1.31a** (Scheme 1.5A).[20] In another report, the group of Resconi unveiled that when $B(C_6F_5)_3$ reacts with

Scheme 1.5. $B(C_6F_5)_3$-Mediated Hydride Abstraction from Amine

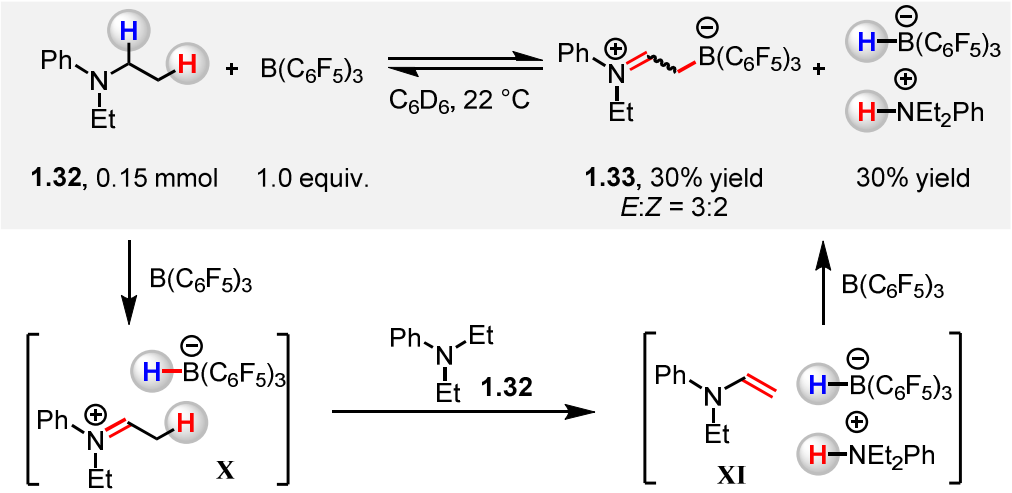


[20] Millot, N.; Santini, C. C.; Fenet, B.; Basset, J. M. *Eur. J. Inorg. Chem.* **2002**, *2002*, 3328–3335.

1,8-bis(dimethylamino)naphthalene **1.30b**, an ammonium/borohydride complex **1.31b** is generated likely through the intermediacy of iminium **IX** (Scheme 1.5B).[21]

The group of Santini reported a $(F_5C_6)_3B$-mediated protocol for the activation of *β*-amino C–H bonds of *N*,*N*-diethylaniline (**1.32**, Scheme 1.6). Enamine intermediate **XI** is proposed to form through $(F_5C_6)_3B$-mediated hydride abstraction, followed by deprotonation of the resulting iminium ion **X**. The ensuing reaction between enamine **XI** and $B(C_6F_5)_3$ affords the zwitterionic product **1.33** together with ammonium ion and borohydride. Thus, the cooperative action of $B(C_6F_5)_3$ and an *N*-alkylamine **1.32** was shown to activate both *α*- and *β*-amino C–H bonds for in situ conversion of amines into enamines.

Scheme 1.6. $B(C_6F_5)_3$-Mediated Enamine Generation through Hydride Abstraction from Amine

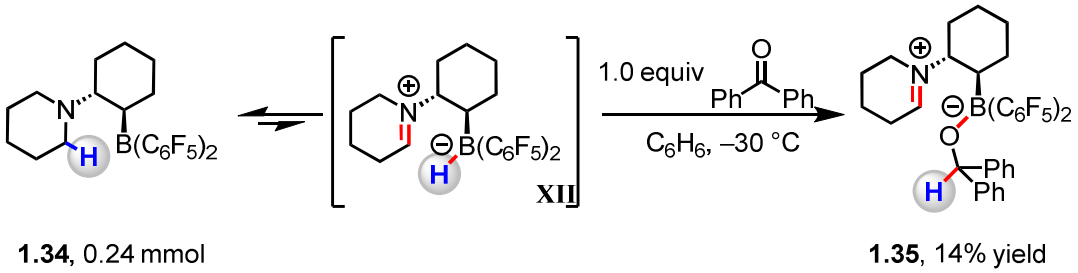


In 2011, Erker and co-workers have reported the reaction involving a cyclohexylene-bridged B/N-based Lewis pair **1.34** (Scheme 1.7).[22] The sterically hindered intramolecular frustrated Lewis pair **1.34** overcomes the undesired acid–base complexation and generates a zwitterion which contains an iminium and a borohydride unit (**XII**) by intramolecular hydride

[21] Di Saverio, A.; Focante, F.; Camurati, I.; Resconi, L.; Beringhelli, T.; D'Alfonso, G.; Donghi, D.; Maggioni, D.; Mercandelli, P.; Sironi, A. *Inorg. Chem.* **2005**, *44*, 5030–5041.
[22] Schwendemann, S.; Frohlich, R.; Kehr, G.; Erker, G. *Chem. Sci.* **2011**, *2*, 1842–1849.

transfer. The subsequent reaction between **XII** and benzophenone afforded **1.35** in 14% yield. This early work established that organoboranes could abstract a hydride from *N*-alkylamines and then transfer it onto an electrophilic entity in an intermolecular manner.

Scheme 1.7. Hydride Abstraction within Intramolecular Frustrated N/B Lewis Pair

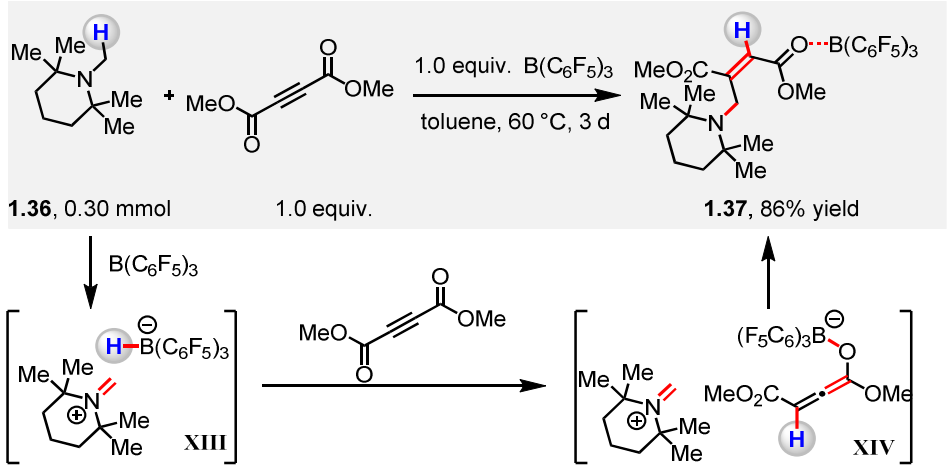


1.34, 0.24 mmol

1.35, 14% yield

Erker and co-workers demonstrated that an intermolecular FLP, which constitutes of pentamethylpiperidine **1.36** and $B(C_6F_5)_3$, engages in organoborane-mediated hydride abstraction from **1.36** to afford an iminium ion and $[(F_5C_6)_3B–H]^-$ (**XIII**, Scheme 1.8).[23] It was illustrated that dimethyl acetylenedicarboxylate undergoes 1,4-borohydride reduction to generate nucleophilic $(F_5C_6)_3B$-enolate **XIV**, which subsequently reacts with the iminium ion to deliver the Mannich-type product **1.37** in 86% yield.

Scheme 1.8. Mannich-Type Reactions of in situ Generated Iminium Ions Mediated by $B(C_6F_5)_3$



1.36, 0.30 mmol

1.0 equiv.

1.37, 86% yield

[23] Chen, G.-Q.; Kehr, G.; Daniliuc, C. G.; Bursch, M.; Grimme, S.; Erker, G. *Chem. Eur. J.* **2017**, *23*, 4723–4729.

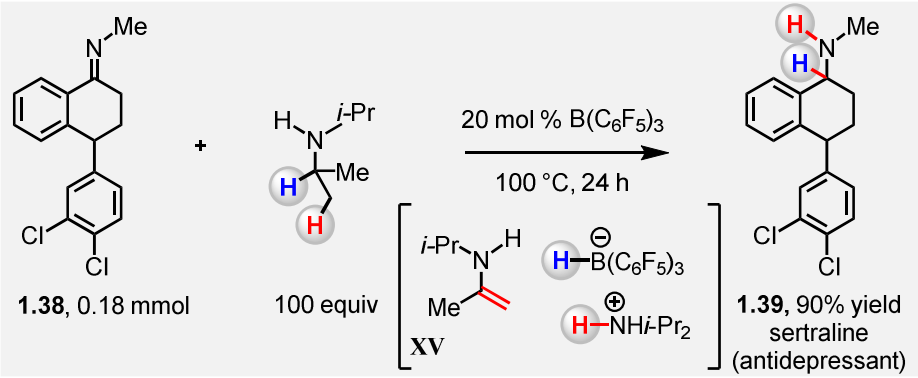
The transformations highlighted in Schemes **1.3** to **1.8** established that highly Lewis acidic carbocations or organoboranes may serve as acceptors of hydride from amines, converting them into iminium ions. However, such processes demand the use of either a stoichiometric or an excess quantities of Lewis acids.

1.2. $(F_5C_6)_3B$-Catalyzed Transfer Hydrogenation/Dehydrogenation of Amines

The unique ability of $B(C_6F_5)_3$ to activate *α*-amino C–H bonds has been exploited for catalytic transfer hydrogenation of imines and dehydrogenation of various *N*-containing heterocycles.

Stephan and co-workers reported a method for transfer hydrogenation of imines utilizing *i*-Pr_2NH as the source of hydride and proton (Scheme 1.9).[24] It was proposed that an ion pair comprised of an iminium ion and an ammonium ion **XV** could be generated from *i*-Pr_2NH through a sequence of $(F_5C_6)_3B$-catalyzed hydride abstraction and deprotonation of the resulting iminium. The ensuing borohydride reduction and protonation of imine **1.38** afford sertraline (**1.39**, antidepressant) in 90% yield.

Scheme 1.9. $(F_5C_6)_3B$-Catalyzed Transfer Hydrogenation

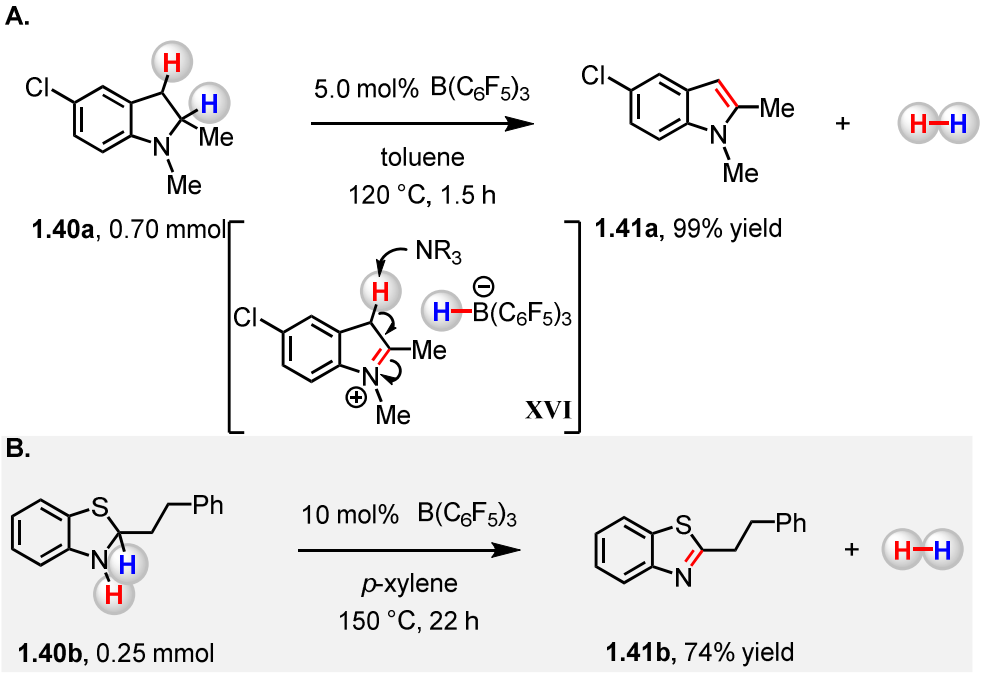


The groups of Grimme and Paradies reported a $(F_5C_6)_3B$-catalyzed metal-free dehydrogenation of saturated *N*-heterocycles to produce different *N*-heteroarenes (Scheme 1.10A).[25] When indoline **1.40a** was treated with 5.0 mol % of $B(C_6F_5)_3$ in toluene at 120 °C, indole **1.41a** was obtained in 99% yield by the release of H_2. It was proposed that $(F_5C_6)_3B$-catalyzed

[24] Farrell, J. M.; Heiden, Z. M.; Stephan, D. W. *Organometallics* **2011**, *30*, 4497–4500.
[25] Maier, A. F. G.; Tussing, S.; Schneider, T.; Flörke, U.; Qu, Z.-W.; Grimme, S.; Paradies, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 12219–12223.

hydride abstraction from **1.40a** generates an ion pair consisting of an iminium ion and a borohydride (**XVI**). The ensuing deprotonation of the iminium ion by a Brønsted base catalyst (i.e., **1.40** or **1.41a**) results in the formation of indole **1.41a**. Upon the release of H_2, $B(C_6F_5)_3$ and the Brønsted base catalyst are regenerated. The Kanai group also reported a similar methodology for the desaturation of *N*-containing heterocycles (Scheme 1.10B).[26] Specifically, the treatment of **1.40b** with 10 mol % of $B(C_6F_5)_3$ at 150 °C results in the formation of benzothiazole **1.41b** in 74% yield.

Scheme 1.10. Dehydrogenation *N*-Heterocycles through $(F_5C_6)_3B$-Catalyzed Hydride Abstraction



These methods demonstrated the proof of concept that a catalytic amount of $B(C_6F_5)_3$ can be employed for the in situ conversion of *N*-alkylamines into iminiums. However, trapping the amine-derived iminium by carbon-based nucleophile for the production of α-substituted amines remained elusive.

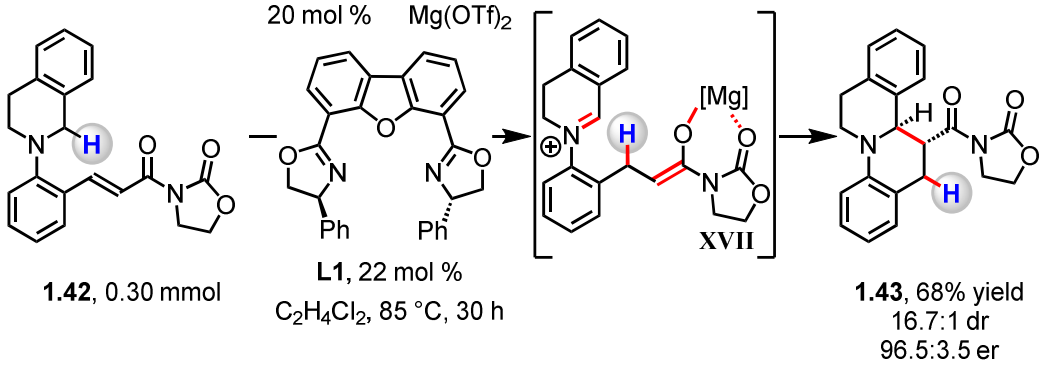
[26] Kojima, M.; Kanai, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 12224–12227.

1.3. α-Amino C–H Functionalization through Lewis Acid-Catalyzed Conversion of Amines into Iminiums

Recently, Lewis acidic organometallic complexes and organoboranes have been employed to facilitate intra- and intermolecular hydride transfer processes to convert amines into iminium ions which are then functionalized with various C- and heteroatom-based nucleophiles.[27]

The group of Seidel investigated the organomagnesium-catalyzed intramolecular hydride shift-ring closure reaction sequences for the synthesis of enantiomerically enriched tetrahydroquinolines (**1.43**, Scheme 1.11).[28] Specifically, the chelation of oxazolidinone **1.42** to [(*S*,*S*)-Ph-DBFox(**L1**)Mg(OTf)$_2$] increases the electrophilicity of the α,β-unsaturated moiety of **1.42** and promotes the intramolecular hydride transfer to generate a zwitterionic intermediate **XVII**. Subsequently, the ring-closing event between the iminium ion and Mg–enolate furnishes tetrahydroquinoline **1.43** in 68% yield and 96.5:3.5 er (16.7:1 dr).

Scheme 1.11. [(*S*,*S*)-Ph-DBFox(**L1**)Mg(OTf)$_2$]-Catalyzed Intramolecular Hydride Shift/Ring Closing Cascade

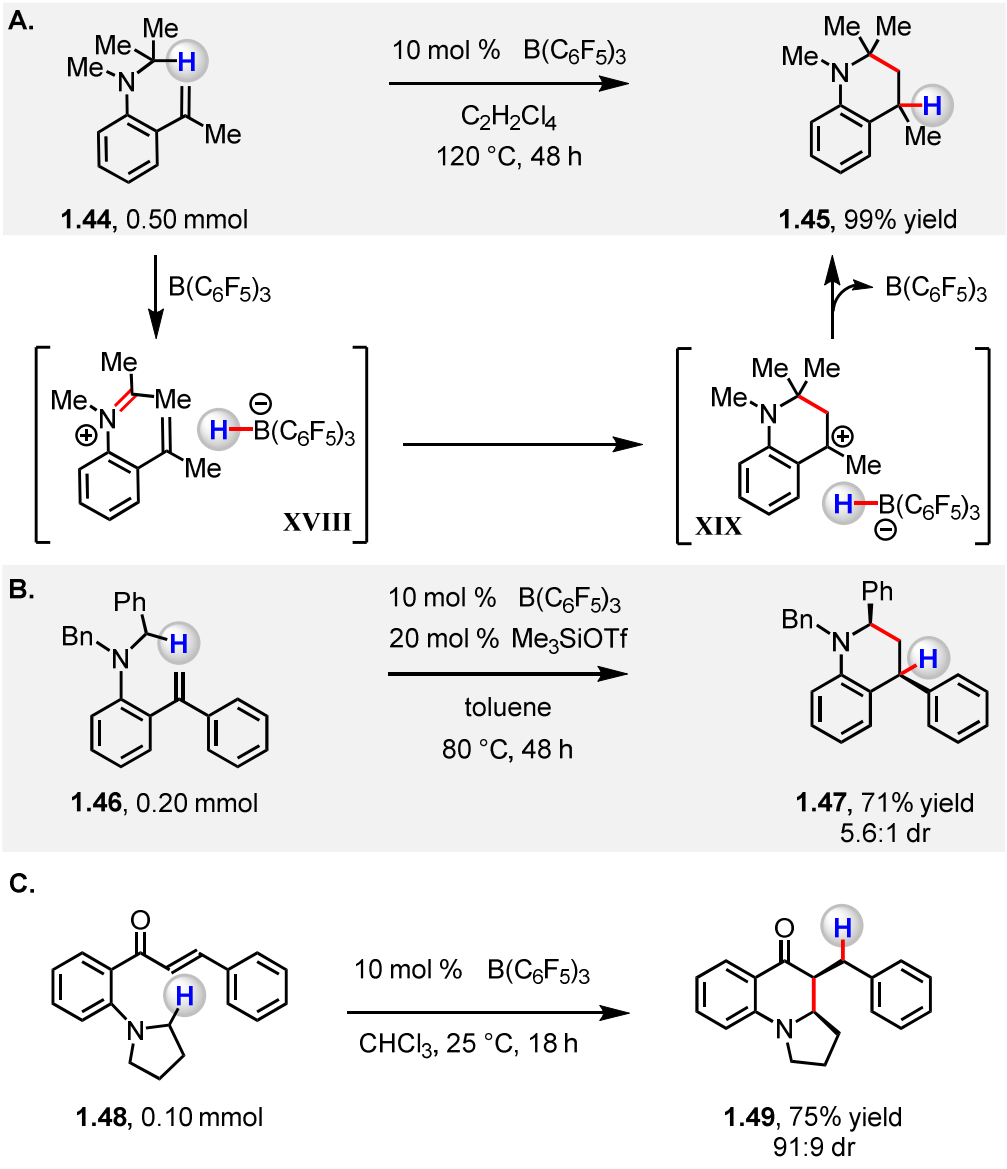


Grimme, Paradies, and co-workers demonstrated the treatment of 2-aminostyrene **1.44**, which contains an electron-rich double bond, with 10 mol % B(C$_6$F$_5$)$_3$ affords **1.45** (Scheme

[27] (a) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5010−5036. (b) Basak, S.; Winfrey, L.; Kustina, B. A.; Melen, R. L.; Morrill, L. C.; Pulis, A. P. *Chem. Soc. Rev.* **2021**, *50*, 3720−3737.
[28] Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226−13227

1.12A).[29] Specifically, $(F_5C_6)_3B$-catalyzed α-amino C–H activation of **1.44** generates an ion pair comprised of an iminium ion and a borohydride **XVIII** which then undergoes electrocyclization reaction to generate carbocation intermediate **XIX**. The subsequent borohydride reduction affords

Scheme 1.12. $(F_5C_6)_3B$-Catalyzed Intramolecular Reactions



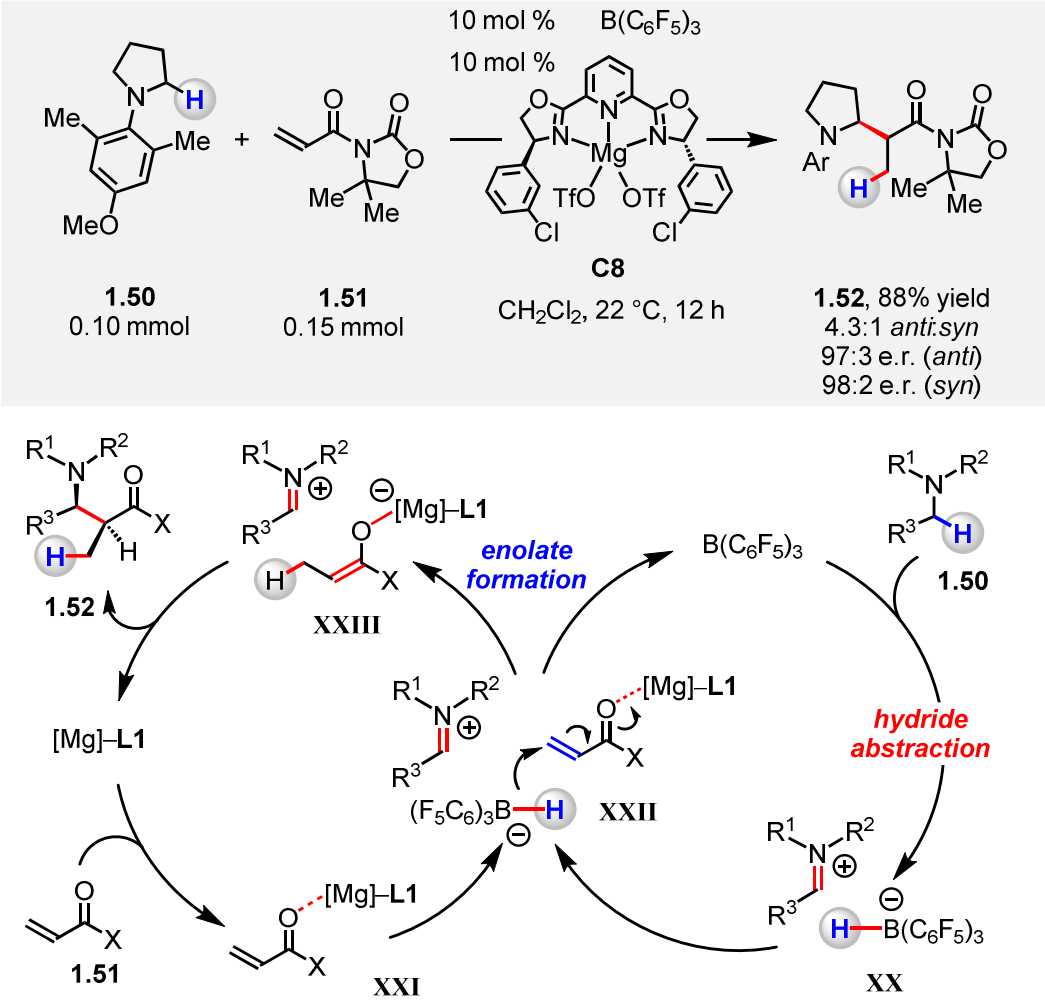
[29] Maier, A. F. G.; Tussing, S.; Zhu, H.; Wicker, G.; Tzvetkova, P.; Flörke, U.; Daniliuc, C. G.; Grimme, S.; Paradies, J. *Chem. Eur. J.* **2018**, *24*, 16287–16291.

1.45 in 99% yield. In related reports by Wang[30] and Paradies,[31] $B(C_6F_5)_3$ was shown to catalyze the intramolecular ring-closing reactions of alkene-tethered amines (e.g., **1.46** → **1.47**, **1.48**→ **1.49**; Schemes 1.12B, 1.12C).

Nonetheless, intermolecular α-functionalization of *N*-alkylamines catalyzed by $B(C_6F_5)_3$ remained unprecedented until the report from our laboratory in 2018, where we developed a method for the enantioselective union of *N*-alkylamines **1.50** and α,β-unsaturated compounds **1.51** to produce β-amino carbonyl compounds **1.52** (Scheme 1.14).[32] This process is promoted through the cooperative action of seemingly competitive Lewis acids, $B(C_6F_5)_3$ and a chiral $(TfO)_2Mg$–PyBOX complex **C8** and is performed under redox-neutral conditions. It was discovered that by proper tuning of various features of structurally and electronically different Lewis acids and substrates, the ability of Lewis acid catalysts to serve as a hydride acceptor from amines (**1.50** → **XX**) or as an activator of α,β-unsaturated compounds (**1.51** → **XXI**) can be adjusted. This might result in a highly enantioselective processes. For instance, the reaction of *N*-alkylamine **1.50** and α,β-unsaturated *N*-acyloxazolidinone **1.51** with 10 mol % of $B(C_6F_5)_3$ and **C8** afforded **1.52** in 88% yield as a 4.3:1 mixture of diastereomers with up to 98:2 er. Mechanistic and computational studies suggested that in situ generated $[H–B(C_6F_5)_3]^-$ through hydride abstraction from amine **1.50** reacts with **C8**-activated α,β-unsaturated compounds to furnish chiral Mg-enolate **XXIII**. The ensuing C–C bond formation between iminium ion and the Mg-enolate **XXIII** would afford the desired product with high stereoselectivity **1.52**.

[30] Tian, J. J.; Zeng, N. N.; Liu, N.; Tu, X. S.; Wang, X.-C. *ACS Catal*. **2019**, *9*, 295–300.
[31] Wicker, G.; Schoch, R.; Paradies, J. *Org. Lett.* **2021**, *23*, 9, 3626–3630.
[32] Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc*. **2018**, *140*, 10593–10601.

Scheme 1.13. Enantioselective α-Amino C–H Functionalization

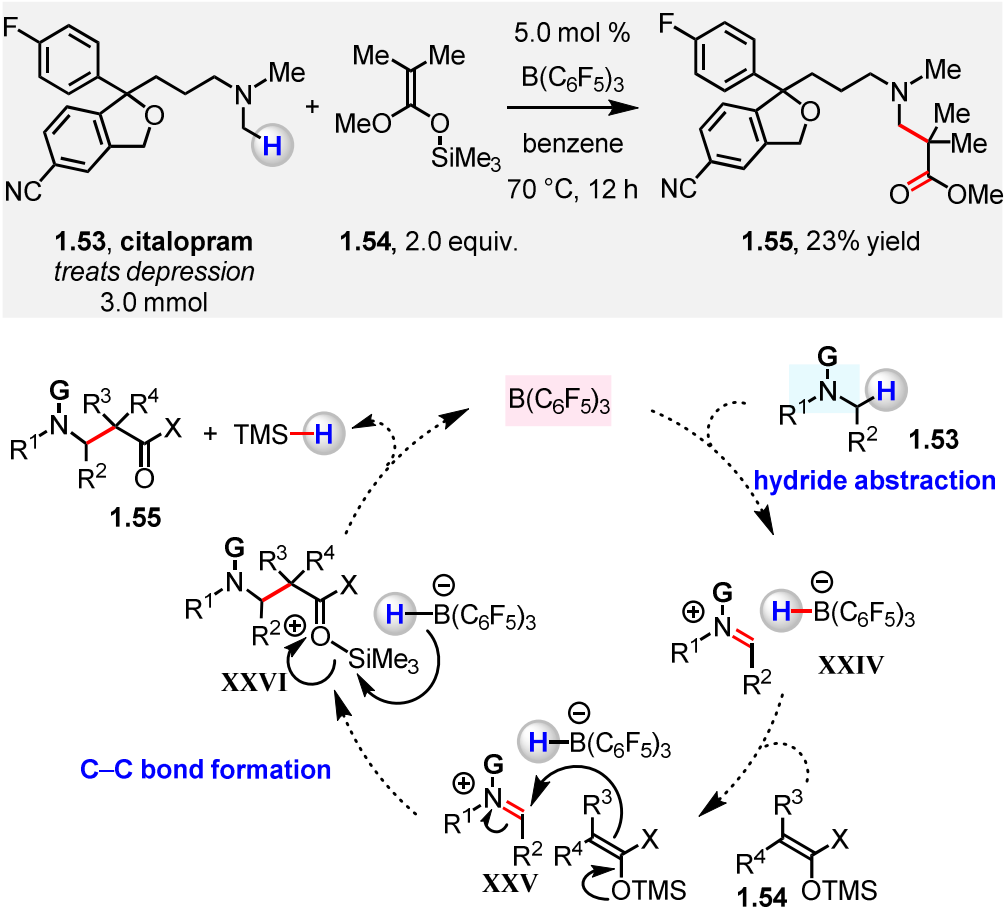


In 2019, Wasa and co-workers disclosed an intermolecular protocol for the reaction of *N*-alkylamines (**1.53**, Scheme 1.14) with silicon enolates (**1.54**) to generate β-amino carbonyl compounds (**1.55**).[33] It was proposed that sterically hindered and strongly Lewis acidic $B(C_6F_5)_3$ overcomes mutual quenching with Brønsted basic motifs and abstract a hydride from α-amino C–H bond of amine substrate **1.53** to form an iminium ion (**XVIV**). The subsequent reaction of the in situ generated iminium with **1.54** forges a C–C bond (via **XV**) to generate intermediate **XVI**.

[33] Chan, J. Z.; Chang, Y.; Wasa, M. *Org. Lett.* **2019**, *21*, 984–988.

β-amino carbonyl product (**1.55**) is obtained upon the release of hydrosilane as the byproduct. This external oxidant-free process has been utilized in the late-stage modification of amine-containing pharmaceuticals. For instance, the reaction of citalopram **1.53** and silyl ketene acetal **1.54** in the presence of 5.0 mol % of $B(C_6F_5)_3$ afforded citalopram-derivative **1.55** in 23% yield.

Scheme 1.14. $(F_5C_6)_3B$-Catalyzed *α*-Amino C–H Functionalization by Silyl Ketene Acetals



In this section, we discussed how the previously developed catalyst systems involving sterically hindered and strongly Lewis acidic organoboranes have the advantage of the in situ generation of iminium ions directly from *N*-alkylamines (vs iminium generation from pre-activated substrates; Scheme 1.1A). Despite that these processes are limited to non-enantioselective intramolecular hydride transfer reactions of a narrow scope of *N*-arylamines, the findings

highlighted by our group in 2018 (Scheme 1.13) provided a rationale for the development of processes that utilizes $B(C_6F_5)_3$ in combination with a chiral co-catalyst for the generation and union of iminiums and nucleophiles derived from a broad scope of polyfunctional *N*-alkylamines and (pro)nucleophiles.

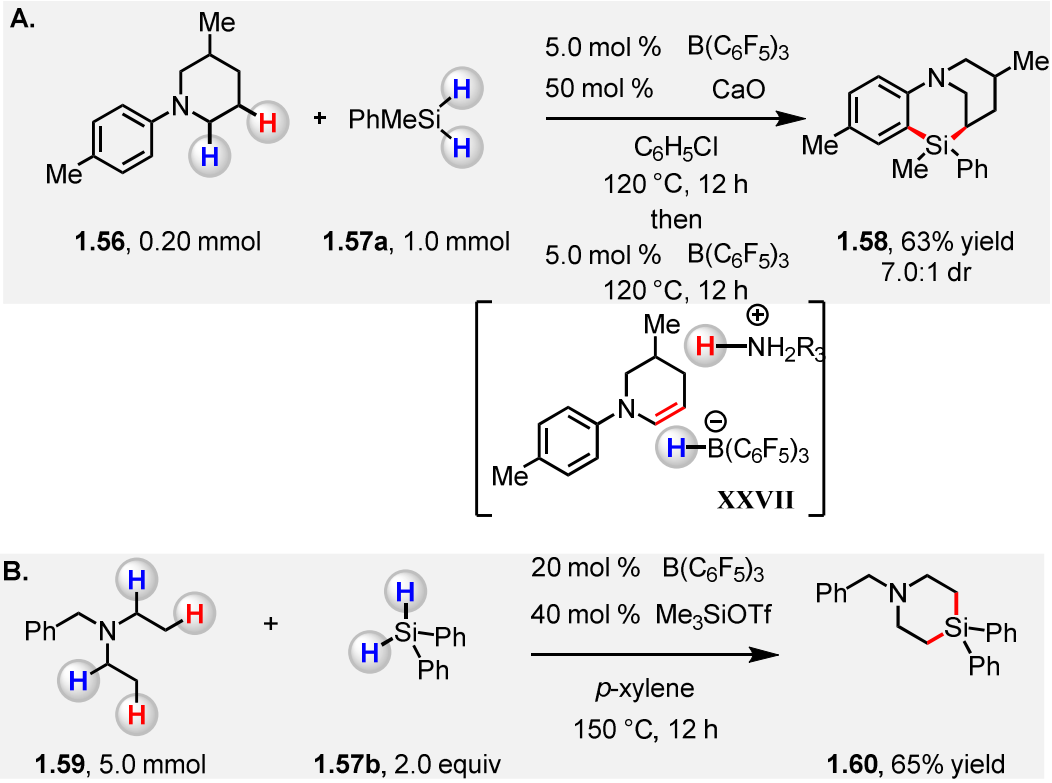
1.4. Lewis Acid/Brønsted Base-Catalyzed Formation of Enamines for β–Amino C–H Functionalization

In this section, the recent progress on organoborane-catalyzed enamine generation through hydride abstraction/deprotonation sequences will be discussed. Although the seminal report by Santini and co-workers demonstrated that the iminium generated by $(F_6C_5)_3B$-mediated hydride abstraction of amine could be deprotonated by an appropriate Brønsted base to form an enamine (Scheme 1.6), catalytic transformations of such species generated in this manner were only reported recently.

The Chang group developed a method for the synthesis of bridged sila-*N*-heterocycle **1.58** through $(F_5C_6)_3B$-catalyzed C−H silylation of *N*-aryl piperidines **1.56** with methylphenylsilane **1.57a** (Scheme 1.15A).[34] The reaction is proposed to proceed through the conversion of **1.56** into an enamine **XXVII** through $(F_6C_5)_3B$-catalyzed hydride abstraction and deprotonation by a suitable Brønsted base (e.g.; **1.56**, **1.58)**. The subsequent hydrosilylation of enamine **XXVII** by methylphenylsilane **1.57** and the ensuing dehydrogenative intramolecular $C(sp^2)$−H silylation affords bridged sila-*N*-heterocycle **1.58** in 63% yield and 7.0:1 dr. In a related work, the group of Oestreich reported a method that can achieve consecutive $C(sp^3)$–H silylation of *N*-alkylamines (**1.59**; Scheme 1.15B).[35] The treatment of *N*-benzyl-*N*-ethylethanamine **1.59** with diphenylsilane **1.57b** in the presence of $B(C_6F_5)_3$ (20 mol %) and TMSOTf (40 mol %) produces 4-silapiperidines (**1.60**), likely through the intermediacy of enamine derived from **1.59**.

[34] Zhang, J.; Park, S.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140*, 13209−13213.
[35] Fang, H.; Xie, K.; Kemper, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2021**, *60*, 8542−8546.

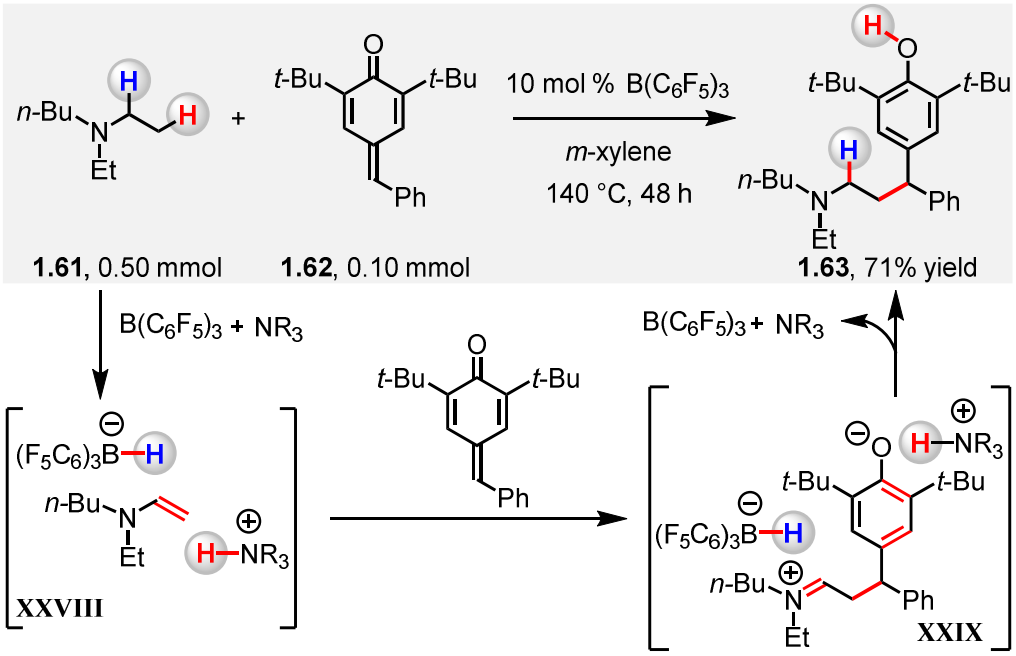
Scheme 1.15. $(F_5C_6)_3B$-Catalyzed *β*-Amino C–H Silylation



In 2019, Ma and co-workers disclosed $(F_5C_6)_3B$-catalyzed intermolecular *β*-alkylation protocol for acyclic *N*-alkylamines (Scheme 1.16).[36] The proposed mechanism involves $(F_5C_6)_3B$-catalyzed hydride abstraction from *N*,*N*-diethylbutan-1-amine **1.61** to form an iminium ion, which then undergoes deprotonation by a Brønsted base (**1.61** or **1.63**) to afford an enamine (**XXVIII**). The subsequent conjugate addition reaction between the in situ generated enamine **XXVIII** and *para*-quinone methide **1.62** results in the formation of zwitterionic intermediate **XXXII** The subsequent protonation and borohydride reduction would deliver the desired product **1.63** and regenerate the catalysts.

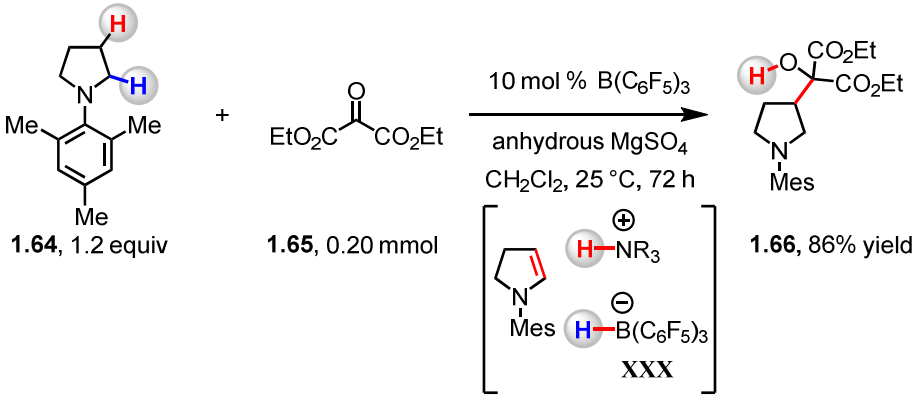
[36] Li, R.; Chen, Y.; Jiang, K.; Wang, F.; Lu, C.; Nie, J.; Chen, Z.; Yang, G.; Chen, Y.-C.; Zhao, Y. Ma, C. *Chem. Commun.* **2019**, *55*, 1217–1220.

Scheme 1.16. $(F_5C_6)_3B$-Catalyzed *β*-Alkylation of *N*-alkylamines



In another related report, the team of Ma disclosed a $(F_5C_6)_3B$-catalyzed protocol for the direct functionalization of *β*-amino C–H bond of *N*-arylpyrrolidine **1.64** with diethyl 2-oxomalonate **1.65** through the in situ generation of enamine **XXX** to afford *β*-functionalized pyrrolidine **1.66** (86% yield, Scheme 1.17).[37]

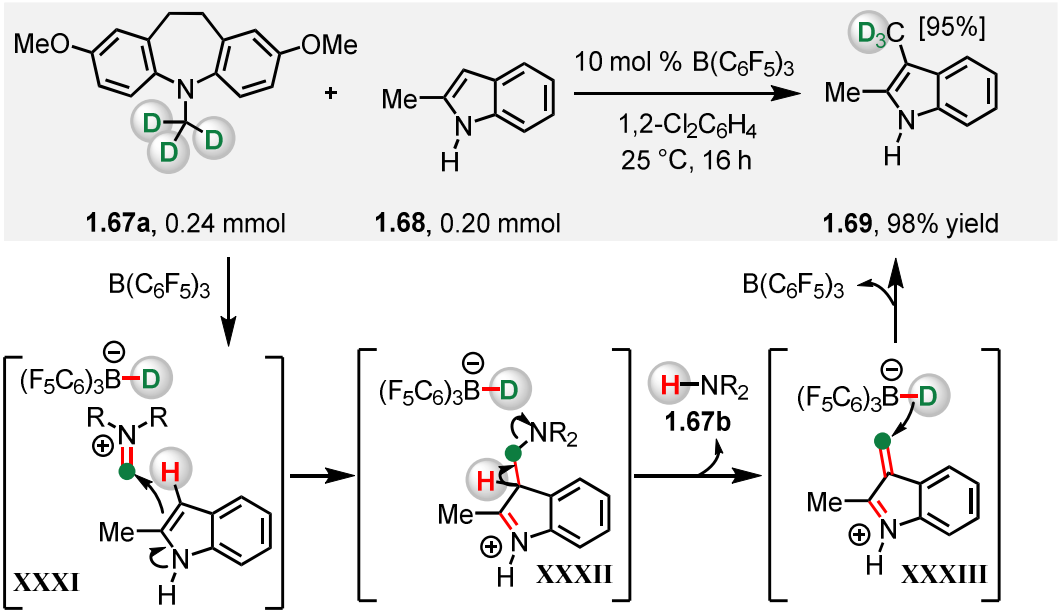
Scheme 1.17. $(F_5C_6)_3B$-Catalyzed *β*-Functionalization of *N*-Aryl Pyrrolidines



[37] Chen, Y.; Wan, H.-L.; Huang, Y.; Liu, S.; Wang, F.; Lu, C.; Nie, J.; Chen, Z.; Yang, G.; Ma, C. *Org. Lett.* **2020**, *22*, 7797–7803.

Pulis et al. achieved the C3 alkylation of indole **1.68** through the use of amine-derived alkylating reagent **1.67a** and $B(C_6F_5)_3$ (Scheme 1.18).[38] By exploiting the unique capability of $B(C_6F_5)_3$ to abstract hydride from amines, the ion pair **XXI** comprised of an iminium ion and a borodeuteride is generated from **1.67a**. Subsequently, C–C bond- forming reaction between

Scheme 1.18. $(F_5C_6)_3B$-Catalyzed C3 Alkylation of Indoles



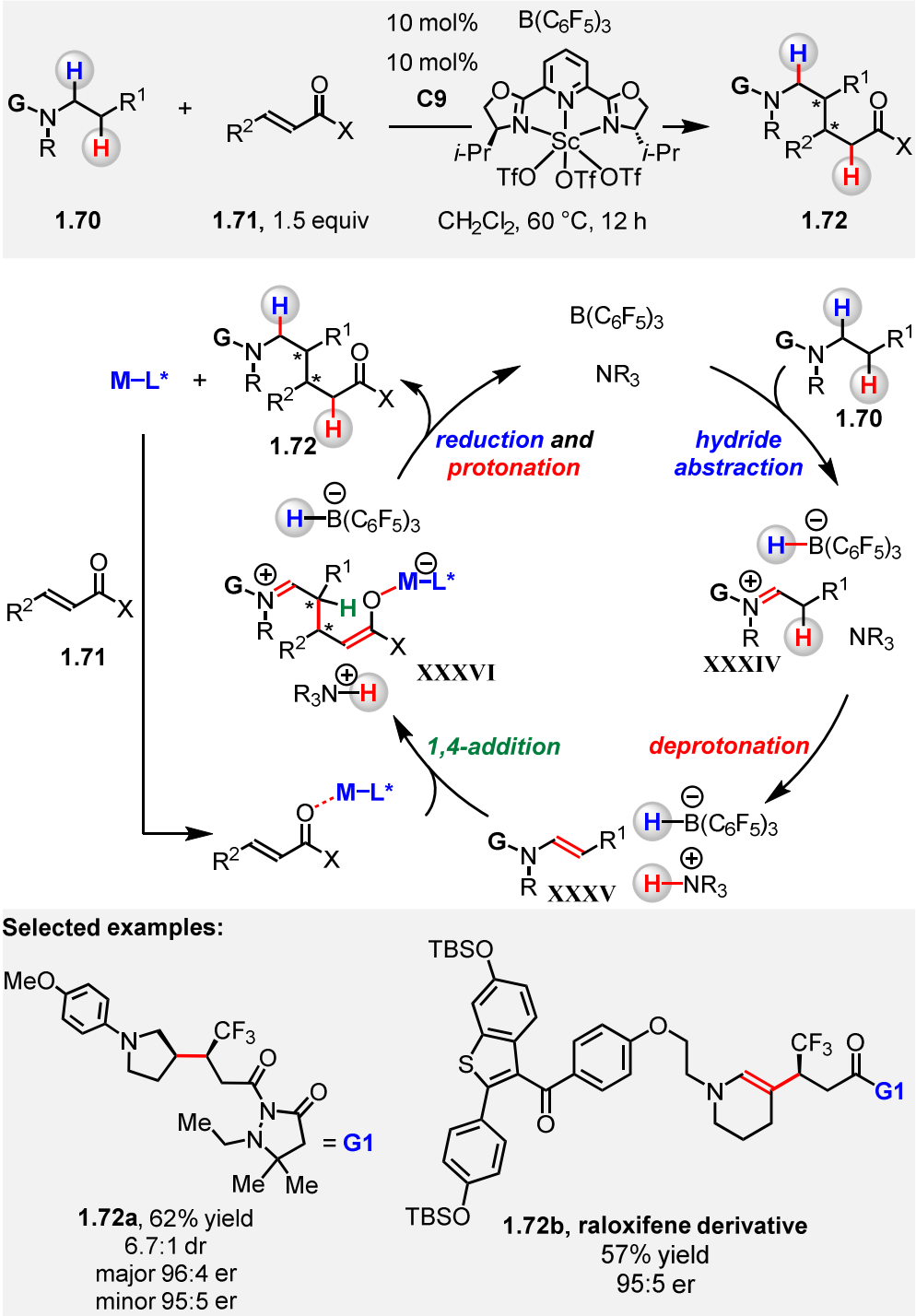
iminium ion **XXXI** and indole **1.68** affords **XXXII**. The ensuing elimination of the amine **1.67b** furnishes a conjugated iminium ion **XXXIII**, which undergoes borodeuteride reduction to afford **1.69** in 98% yield.

In 2021, the Wasa group developed a protocol for stereoselective *β*-C–H functionalization of *N*-alkylamines, including various bioactive amines (Scheme 1.19).[39] This process is promoted by the cooperative function of $B(C_6F_5)_3$, a chiral Sc–PyBOX complex **C9**, and a Brønsted basic *N*-alkylamine (**1.70**). The proposed mechanism involves the formation of enamines from *N*-

[38] Basak, S.; Alvarez-Montoya, A.; Winfrey, L.; Melen, R. L.; Morrill, L. C.; Pulis, A. P. *ACS Catal.* **2020**, *10*, 4835–4840

[39] Chang, Y.; Cao, M.; Chan, J. Z.; Zhao, Y.; Wang, Y.; Wasa, M. *J. Am. Chem. Soc.* **2021**, *143*, 2441–2455.

Scheme 1.19. Enantioselective α-Amino C–H Functionalization



alkylamine **1.70** by sequential $(F_5C_6)_3B$-catalyzed hydride abstraction (**XXXIV**) and Brønsted base-catalyzed deprotonation (**XXXV**). The in situ generated enamine intermediate undergoes

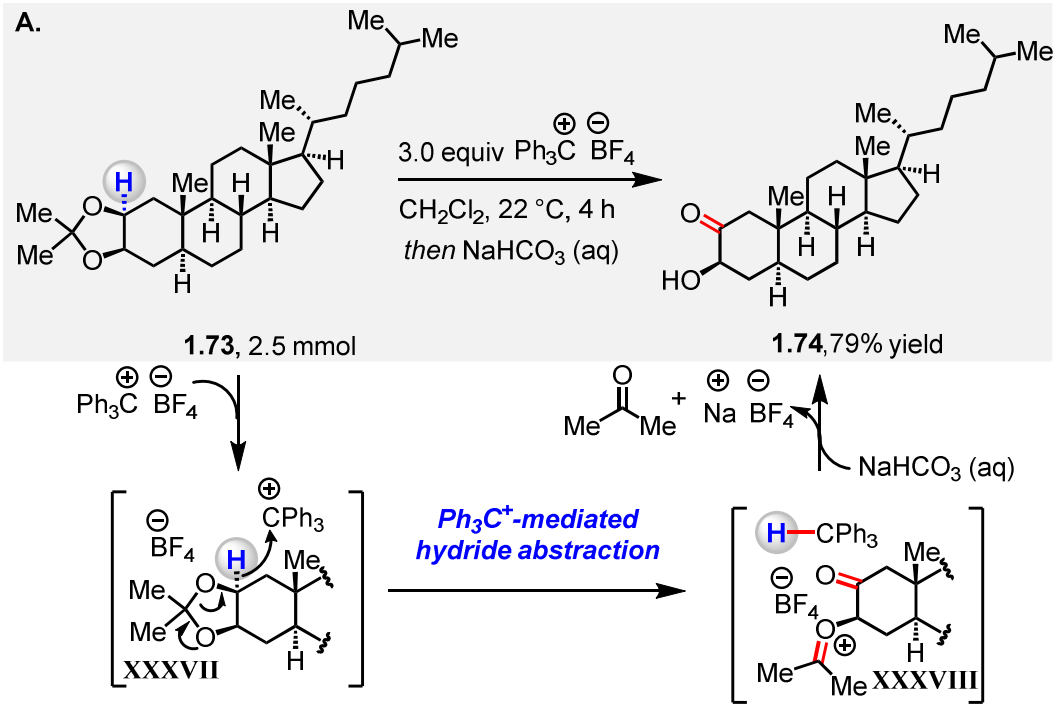
stereoselective C–C bond formation with an α,β-unsaturated compound **1.71** that is activated by **C9** (**XXXVI**). Ensuing borohydride reduction of the resulting iminium ion and protonation of enolate affords β-alkylated amine (**1.72**). It was demonstrated that *N*-aryl pyrrolidine **1.70a** undergoes β-alkylation to afford **1.72a** in 45% yield with up to 96:4 er. The practicality of this methodology was illustrated by the reaction of OTBS-raloxifene **1.70b** (treatment of osteoporosis) with α,β-unsaturated compound **1.71a** affording raloxifene-derivative **1.72b** in 57% yield and 95:5 er. A plausible mechanism for the formation of the unsaturated product might be through the intramolecular deprotonation of iminium ion by the enolate in **XXXVI**.

1.5. Lewis Acid-Promoted Generation of Oxocarbenium Ions through Hydride Abstraction from Ethers

Oxocarbeniums serve as versatile intermediates towards the synthesis of complex ether-based molecules.[40,41,42] Previous studies to be highlighted in this section have shown that such electrophilic species can be generated by Lewis acid-mediated hydride abstraction from *N*-alkyl ethers.

In 1971, Barton and his coworkers reported the use of $[Ph_3C]^+[BF_4]^-$ for the deprotection of an acetal unit within **1.73** (Scheme 1.20A).[40] This process was proposed to proceed through the Ph_3C^+-mediated abstraction of a hydride from **1.73** to produce an oxocarbenium intermediate (**1.73** → **XXXVII** → **XXXVIII**). Ensuing hydrolysis of **XXXVIII** affords *α*-hydroxyl ketone **1.74**.

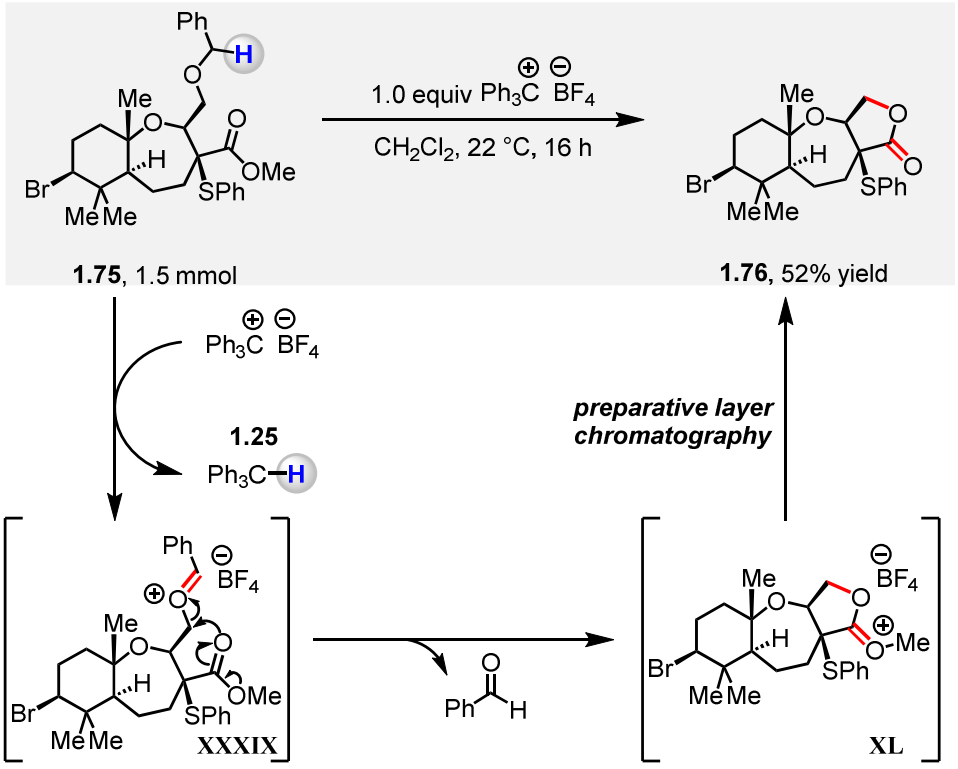
Scheme 1.20. Oxidation of Ethers through Ph_3C^+-Mediated Hydride Abstraction



[40] Barton, D. H. R.; Magnus, P. D.; Smith, G.; Zurr, D. *J. Chem. Soc. (D)*, **1971**, 861–863.
[41] Jung, M. E.; Speltz, L. M. *J. Am. Chem. Soc.* **1976**, *98*, 7882–7884.
[42] Hoye, T. R.; Caruso, A. J.; Dellaria, J. F. Jr.; Kurth, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 6704–6709.

The Hoye group developed a ring-closing reaction of ether to produce a lactone (**1.75** → **1.76**, Scheme 1.21) which serves as an intermediate for the synthesis of Aplysistatin.[42] Authors proposed that Ph_3C^+-mediated hydride abstraction from the benzyl ether unit of **1.75** forms an oxocarbenium intermediate **XXXIX**, which then undergoes cyclization through nucleophilic substitution by the neighboring carbomethoxy group to form **XL**. The lactone **1.76** was furnished in 52% yield upon purification by preparative thin-layer chromatography.

Scheme 1.21. Lactonization Promoted by Ph_3C^+-Mediated Hydride Abstraction from Ethers

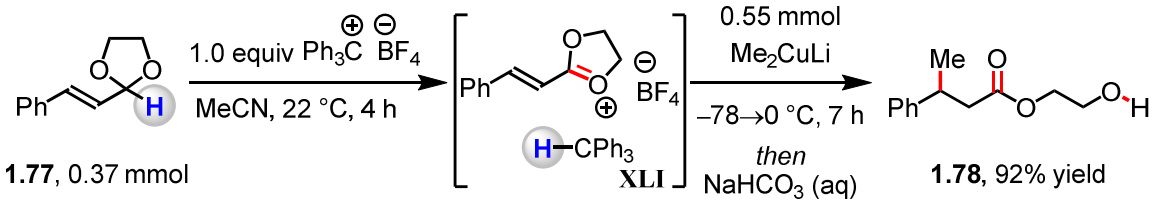


The group of Mukaiyama disclosed a protocol for methylation of α,β-unsaturated acetals (**1.77** → **1.78**; Scheme 1.22).[43] This one-pot, two-step reaction proceeds through Ph_3C^+-mediated hydride abstraction from **1.77** to generate 1,3-dioxolan-2-ylium cation (**XLI**) which then reacts

[43] Mukaiyama, T.; Hayashi, Y.; Hashimoto, Y. *Chem. Lett*. **1986**, *15*, 1627–1630.

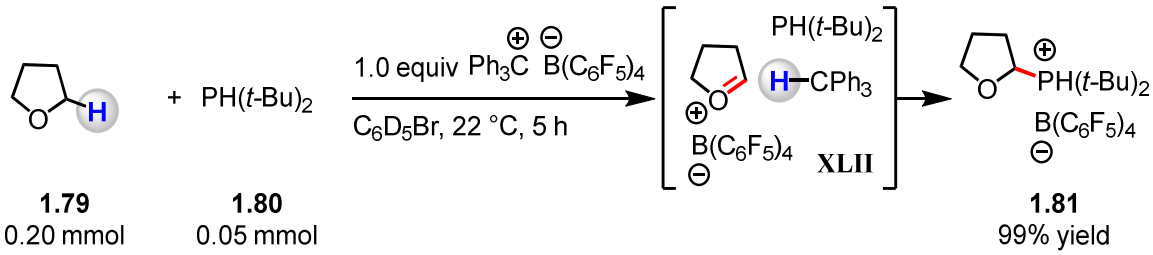
with Me_2CuLi. This is followed by the aqueous base-mediated workup to afford the desired product **1.78** in 92% yield.

Scheme 1.22. Ph_3C^+-Mediated Regioselective Methylation of α,β-Unsaturated Aldehyde Acetals



In a more recent work, Stephan and co-workers unveiled that $[Ph_3C]^+[B(C_6F_5)_4]^-$ mediates a C–P bond-forming reaction between THF **1.79** and $HP(t\text{-}Bu)_2$ **1.80**, giving an ionic complex **1.81** in 99% yield (Scheme 1.23).[44] THF-derived oxocarbenium **XLII** was proposed as a key intermediate in this process.

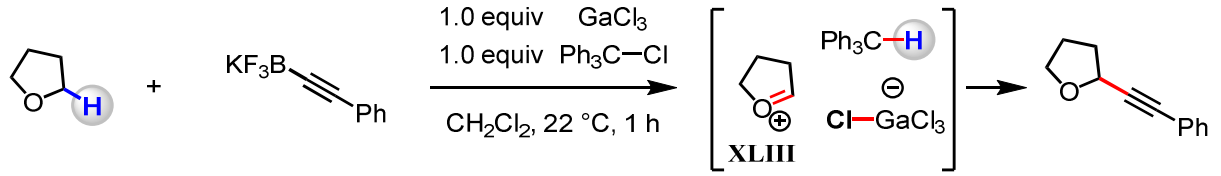
Scheme 1.23. Ph_3C^+-Mediated C–P Bond-Forming Reaction



The Liu group used a combination of Ph_3C–Cl and $GaCl_3$ for in situ generation of Ph_3C^+ which was found to mediate the C–alkynyl bond-forming reaction between various ethers and alkynyl trifluoroborates (e.g., **1.82** + **1.83** → **1.83**4 Scheme 1.24).[45]

[44] Holthausen, M. H.; Mahdi, T.; Schlepphorst, C.; Stephan, D. W *Chem. Commun*. **2014**, *50*, 10038–10040.
[45] Wan, M.; Meng, Z.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed*. **2014**, *53*, 13845–3849.

Scheme 1.24. Ph_3C^+-Mediated Hydride Abstraction for α-Oxy C–H Alkynylation



1.82, 40 equiv **1.83**, 0.2 mmol **1.84**, 92% yield

Despite these notable advances, enantioselective transformations of oxocarbeniums generated by Ph_3C^+-mediated hydride abstraction from ethers stand as a significant challenge due to a paucity of an appropriate catalyst system. Furthermore, the previously reported methods (e.g., Schemes 1.20–1.24) were confined to functionalizations of electronically accessible C–H bond positioned adjacent to the ether substrates' oxygen atom. Catalyst systems for enantio- and diastereoselective transformations of more remote and therefore less electronically accessible ether C–H bonds were unprecedented at the time my dissertation research was started in 2017.

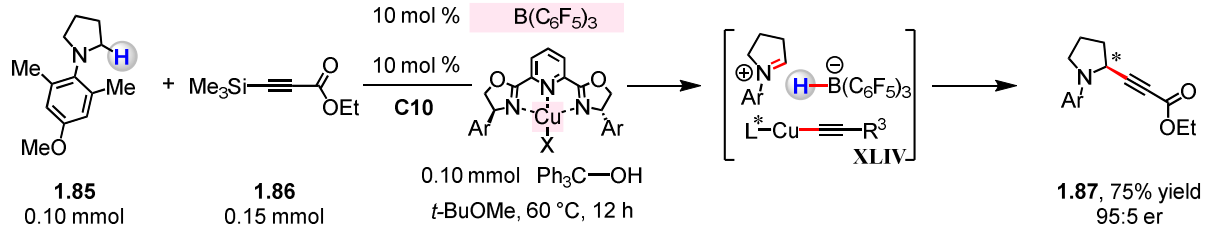
1.6. Specific Aims of the Dissertation Research

As summarized in Chapter 1.1−1.5, significant advances have been made in the transformations of C–H bonds within amines and ethers through their Lewis acid-mediated or Lewis acid-catalyzed conversions into iminiums and oxocarbeniums, respectively. These advances provide a rational basis for the development of methods for the stereoselective synthesis of biologically relevant amine and ether-based molecules, as well as their late-stage functionalization. Accordingly, the central aim of my dissertation research is to develop cooperative catalyst systems that serve two key functions: 1) to convert the polyfunctional amines and ethers into their electrophilic (**1.85** → **XLIV**, Scheme 1.25A) or nucleophilic derivatives (**1.88** → **XLV**, Scheme 1.25B; **1.91** → **XLVI**, Scheme 1.25C), and 2) to perform enantio- and diastereoselective transformations of the resulting intermediates to produce α- and/or β-substituted derivatives (e.g., **1.87, 1.90**, **1.93**).

On the basis of these considerations, the development of a cooperative $B(C_6F_5)_3$/ organocopper **C10** catalyst system for enantioselective conversions of α-amino C−H bonds of various *N*-alkylamines (**1.85**) into C−alkynyl bonds (**1.87**) through the intermediacy of iminium ions (**XLIV**) will be discussed in Chapter 2 (Scheme 1.25A). A novel catalyst system for the β-amino C−H deuteration process of bioactive molecules (**1.88**) that are proceeded through in situ generation enamines (**XLV**) promoted by $B(C_6F_5)_3$ and Brønsted base catalysts will be disclosed in Chapter 3 (Scheme 1.25B). Lastly, the development of organocopper **C11**-catalyzed hetero Diels-Alder reactions of enol ethers (**XLVI**) generated by the Ph_3C^+-mediated oxidation of ethers (**1.91**) with β,γ-unsaturated ketoesters (**1.92**) will be described in Chapter 4 (Scheme 1.25C).

Scheme 1.25. Development of Catalyst Systems for Amine and Ether C–H Functionalization

A. Chapter 2: Direct Conversion of *N*-Alkylamines to *N*-Propargylamines through C–H Activation

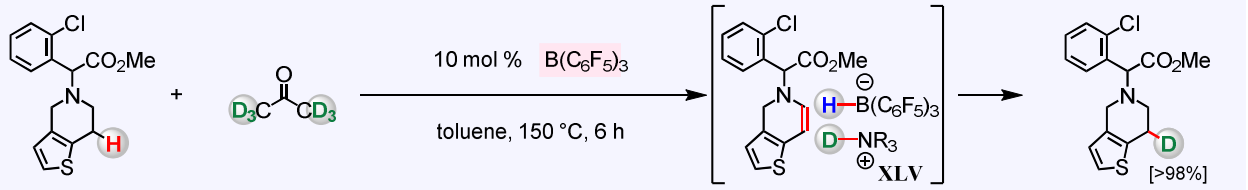


1.85 0.10 mmol

1.86 0.15 mmol

1.87, 75% yield
95:5 er

B. Chapter 3: Catalytic Deuterium Incorporation within Metabolically Stable *β*-Amino C–H Bonds of Drug Molecules

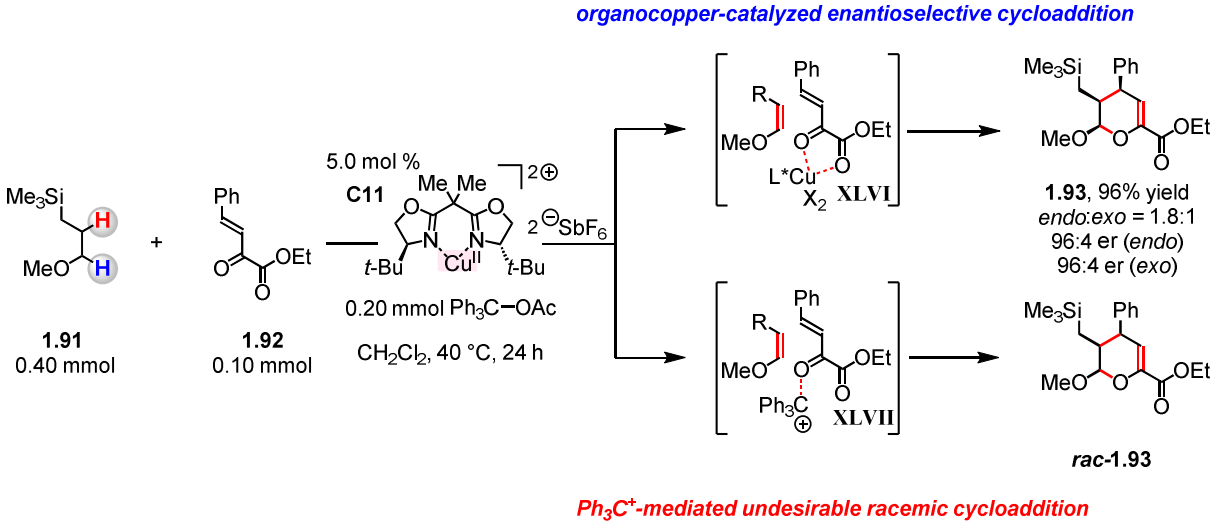


1.88, clopidogrel
0.20 mmol

1.89
2.72 mmol

1.90, 94% yield

C. Chapter 4: Enantioselective Organocopper-Catalyzed Hetero Diels–Alder Reaction through in Situ Oxidation of Ethers into Enol Ethers



1.91 0.40 mmol

1.92 0.10 mmol

To maximize the efficiency of catalyst development, we decided to focus our effort on the identification of effective pairs of untethered and independently operational Lewis acid and/or Lewis base catalysts. The advantage of using such catalysts is that cumbersome tethering of the catalyst units can be circumvented (vs bifunctional catalysts),[13] thereby allowing for rapid evaluation of various catalyst combinations. Specifically, our catalyst design principle is to utilize

a highly potent and achiral Lewis acid catalyst to abstract a hydride from the amine or ether-based starting materials to afford iminiums or oxocarbeniums that can then be deprotonated in the presence of an appropriate Brønsted base. Then, a chiral Lewis acid co-catalyst promotes the stereoselective union of the amine- or ether-derived intermediates with various coupling partners. However, to achieve a highly enantioselective synthesis of amines and ethers, the achiral Lewis acid and the chiral Lewis acid co-catalyst must be able to perform their independent roles without overlapping functions (e.g., **XLVI**, Scheme 1.25C); otherwise, the achiral catalyst could promote racemic transformations of the in situ generated intermediates, thereby resulting in diminished enantioselectivity (e.g., **XLVII**).

Chapter Two

Direct Conversion of *N*-Alkylamines to *N*-Propargylamines through C–H Activation Promoted by Lewis Acid/Organocopper Catalysis: Application to Late-Stage Functionalization of Bioactive Molecules

2.1. Introduction

As described in Chapter 1, the iminium ions are versatile intermediates for enantioselective synthesis of α-substituted amines, moieties that are prevalent in natural products and bioactive compounds (e.g., **2.1**–**2.3**, Scheme 2.1).[46,47] Nonetheless, iminiums are short-lived non-isolable intermediates that are often generated from highly reactive starting materials (e.g., α-chloroamines, imines).[48] An attractive complementary strategy to access the iminiums involves the use of a Lewis acid catalyst to abstract a hydride from the α-position of readily accessible and otherwise chemically inert *N*-alkylamines. However, as highlighted in Chapter 1.3, there is a lack of a generally applicable catalyst system that can perform an enantioselective transformation of *N*-alkylamines into α-substituted amines through the intermediacy of iminiums.

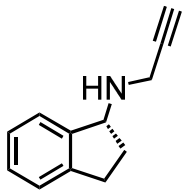
---

[46] (a) Teruaki, S.; Kuniko, K.; Minoru, S.; Etsuro, K. *Chem. Lett.* **1983,** *12*, 1643−1644. (b) Kennedy, D. J.; Selby, I. A.; Cowe, H. J.; Cox, P. J.; Thomson, R. H. *J. Chem. Soc., Chem. Commun.* **1984,** *3*, 153−155. (c) TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996,** *39*, 2435–2437.

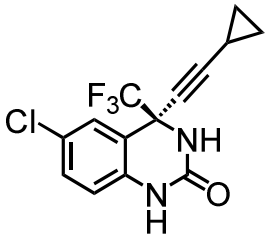
[47] (a) Chiral Amine Synthesis: Methods, Developments and Applications; Nugent, T. C., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2010, p 15−457. (b) Vardanyan, R. in Piperidine-Based Drug Discovery; Vardanyan, R., Ed.; Elsevier: 2017, p 147. (c) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. *Science* **2019**, *363*, eaat0805. (d) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. *Chem. Rev.* **2020**, *120*, 2613–2692.

[48] (a) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416−5470. (b) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc*. **2007**, *129*, 6756−6764. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404−13405. (d) Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; White, M. C. *Nature* **2016**, *537*, 214–219. (e) Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. *Adv. Synth. Catal*. **2021**, *363*, 602−628.

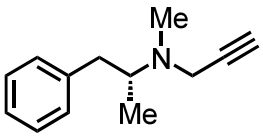
Scheme 2.1. Enantioenriched α-Substituted *N*-Alkylamines



2.1, rasagiline
treats Parkinson's disease



2.2, DPC 961
reverse transcriptase inhibitor



2.3, selegiline
treats Parkinson's disease

A desirable catalyst system overcomes the formation of stable acid−base adducts that could be produced in a reaction mixture of the catalysts, substrates, intermediates, and products.[49] We have previously reported that sterically encumbered and highly Lewis acidic $B(C_6F_5)_3$ circumvents the mutual quenching problem and generates iminiums (**I**, Scheme 2.2A) from a wide range of *N*-alkylamines that includes biologically active molecules such as donepezil **2.4** (used for the treatment of Alzheimer's disease).[50] On the basis of this finding, we envisioned the development of a cooperative catalyst system capable of converting various amine-based molecules (**2.4**) into the corresponding propargyl amine derivatives (**2.4** → **I** → **2.5**). Propargyl amines are prevalent in pharmaceuticals (Scheme 2.1).[51] Therefore, drug derivatives possessing α-alkynyl unit could be

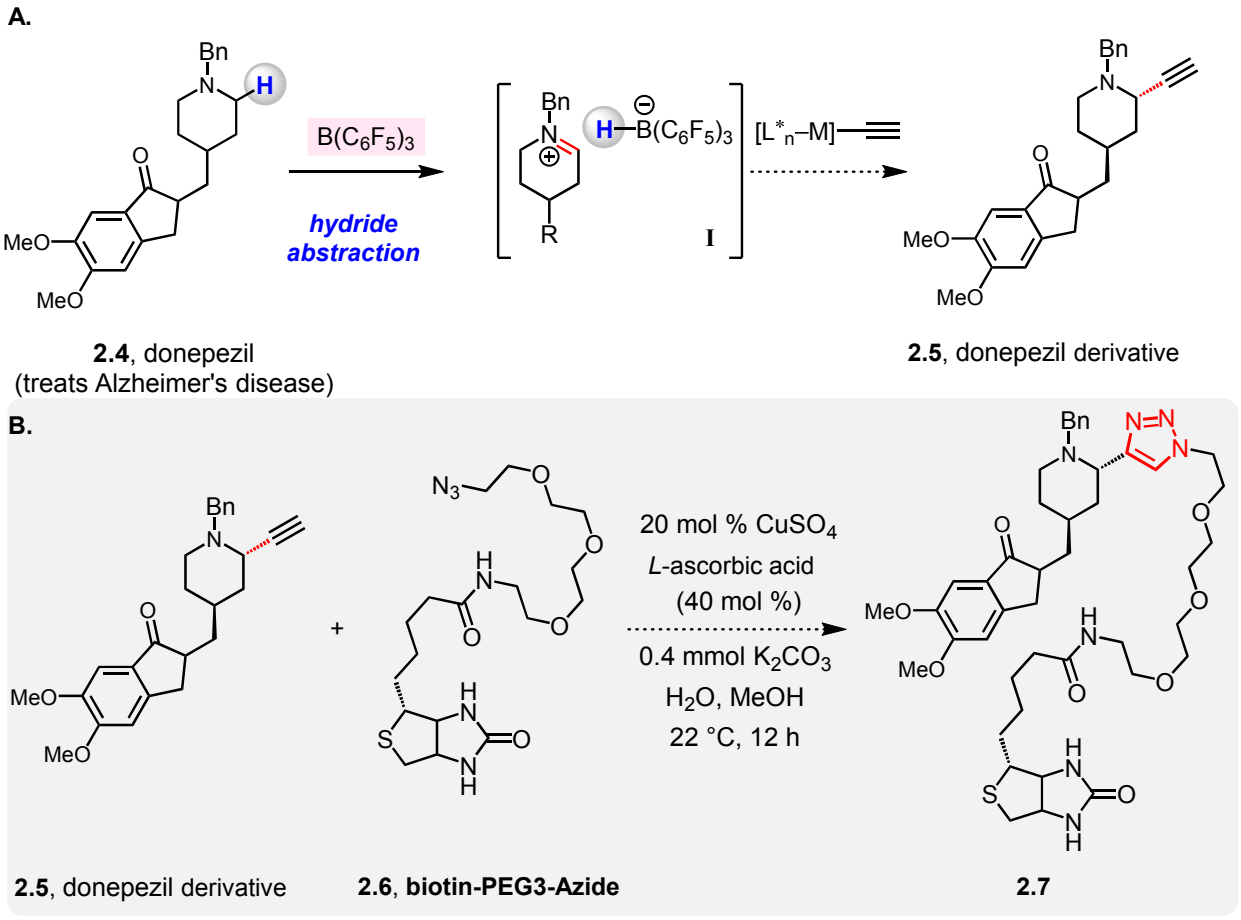
[49] (a) Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem*. **1999**, 527−538. (b) Mömming, C. M.; Otten, E.; Kehr, G.; Fröhlich, R.; Grimme, S.; Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed*. **2009**, *48*, 6643−6646. (c) Ashley, A. E.; Thompson, A. L.; O'Hare, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 9839−9843. (d) Dureen, M. A.; Stephan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 8396−8397. (e) Otten, E.; Neu, R. C.; Stephan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 9918–9919. (f) Voss, T.; Chen, C.; Kehr, G.; Nauha, E.; Erker, G.; Stephan, D. W. *Chem. –Eur. J.* **2010**, *16*, 3005–3008. (g) Ashley, A. E.; O'Hare, D. *Top. Curr. Chem.* **2012**, *334*, 191−218. (h) Voss, T.; Mahdi, T.; Otten, E.; Fröhlich, R.; Kehr, G.; Stephan, D. W.; Erker, G. *Organometallics* **2012**, *31*, 2367–2378. (i) Courtemanche, M. A.; Legare, M. A.; Maron, L.; Fontaine, F. G. *J. Am. Chem. Soc.* **2013**, *135*, 9326–9329. (j) Sajid, M.; Elmer, L. M.; Rosorius, C.; Daniliuc, C. G.; Grimme, S.; Kehr, G.; Erker, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 2243–2246.

[50] (a) Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc*. **2018**, *140*, 10593−10601. (b) Chan, J. Z.; Chang, Y.; Wasa, M. *Org. Lett*. **2019**, *21*, 984−988. (c) Chang, Y.; Yesilcimen, A.; Cao, M.; Zhang, Y.; Zhang, B.; Wasa, M. *J. Am. Chem. Soc.* **2019**, *141*, 14570−14575.

[51] (a) Birks, J.; Flicker, L. Selegiline for Alzheimer's disease. *Cochrane Database of Systematic Reviews*; John Wiley & Sons, Ltd: Chichester, UK, 2003,; Vol. *1*, p CD00044210.1002/14651858.CD000442. (b) Boulton, A. A.; Davis, B. A.; Durden, D. A.; Dyck, L. E.; Juorio, A. V.; Li, X.-M.; Paterson, I. A.; Yu, P. H. *Drug Dev. Res.* **1997**, *42*, 150−156. (c) Arshadi, S.; Vessally, E.; Edjlali, L.; Hosseinzadeh-Khanmiri, R.; Ghorbani-Kalhor, R. *N- Beilstein J. Org. Chem.* **2017**, *13*, 625−638.

utilized as important intermediates for the preparation of their analogs; such propargyl amines may also find applications in bioconjugation (**2.5** + **2.6** → **2.7**; Scheme 2.2B). [52]

Scheme 2.2. Design of Catalyst Systems for Functionalization of α-Amino C(sp^3)–H.



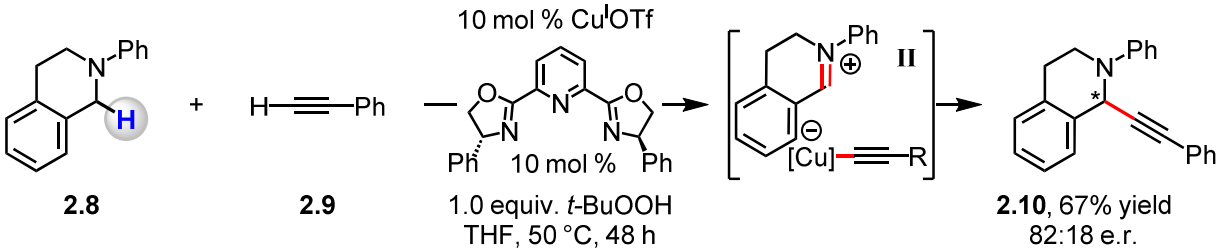
[52] (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *24*, 1128–1137.

2.2 Background

At the time this dissertation research was started in 2017 there was only a limited number of reports in the literature that involves the enantioselective synthesis of propargyl amines through the transformation of α-amino C–H bonds.[53-55]

The seminal report by the Li group disclosed the enantioselective conversions of an α-amino C(sp^3)–H bond contained within 2-phenyl-tetrahydroisoquinoline **2.8** into a C–alkynyl bond (**2.10**, Scheme 2.3).[54] It was proposed that an iminium ion intermediate **II** generated by the oxidation of **2.8** and [Cu]–alkynyl complex derived from the **2.9** undergo an enantioselective C–C bond-forming reaction to afford **2.10** in 67% yield and 82:18 er.

Scheme 2.3. α-Amino C–H Bond Functionalization Promoted by a Cu-based Catalyst and a Stoichiometric Oxidant



The group of Ma reported a N-pinap(**L1**)–Copper-catalyzed enantioselective conversion of α-amino C–H bond of tetrahydroisoquinoline **2.11** into C–alkynyl bond (**2.14**, Scheme 2.4).[55] It was proposed the condensation reaction between tetrahydroisoquinoline **2.11** and benzaldehyde **2.13** generates iminium ion **III**, through in situ iminium ion-isomerization process. The ensuing

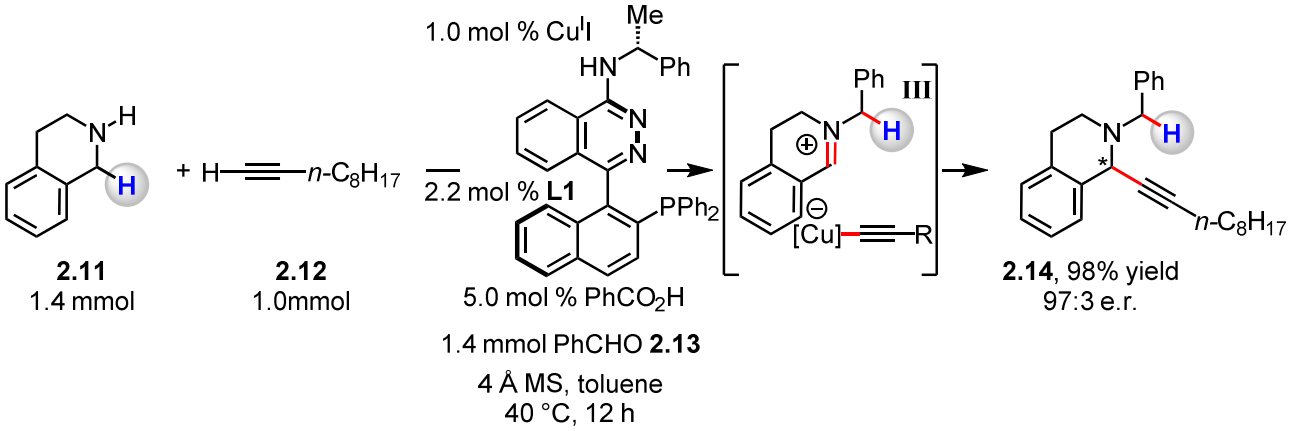
[53] (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc*.**2004**,*126*, 11810−11811. (b) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**,*17*, 590−597. (c) Zhao, C.; Seidel, D. J. Am. Chem. Soc. **2015**, *137*, 4650−4653. (d) Sun, S.; Li, C.; Floreancig, P. E.; Lou, H.; Liu, L. *Org. Lett*. **2015**, *17*, 1684−1687. (e) Xie, Z.; Liu, X.; Liu, L.*Org. Lett.* **2016**, *18*, 2982−2985.

[54] Li, Z.; Li, C.-J. *Org. Lett*. **2004**, *6*, 4997–4999.

[55] Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 277–281.

enantioselective C–alkynyl bond-forming reaction between the iminium intermediate and **2.12**-derived [Cu]–alkynyl affords propargyl amines **2.14** in 98% yield and 97:3 er.

Scheme 2.4. N-pinap**(L1)**-Copper-Catalyzed α-Alkynylation of *N*-Alkylamines



Despite notable advances in the enantioselective synthesis of propargyl amines through the activation of α-amino C–H bonds, there are some key limitations remain to be addressed. Among the most significant limitations of the representative works are:

1) The use of the narrow scope of tetrahydroisoquinoline derivatives that could form stabilized iminium ions as a substrate (Scheme 2.3 and 2.4)
2) Requirement of a stoichiometric amount of strong oxidant (Scheme 2.3)

As a result of these significant limitations, catalytic protocols mentioned above demonstrated to have a poor functional group tolerance and are unsuitable for the late-stage modification of bioactive amines that are diverse in structure and often contain various functional groups that are sensitive to an oxidant. Therefore, we sought to develop a novel catalyst system that is capable of activating and functionalizing α-C–H bonds of a wide array of polyfunctional *N*-alkylamines including bioactive amines.

2.3 Our Approach

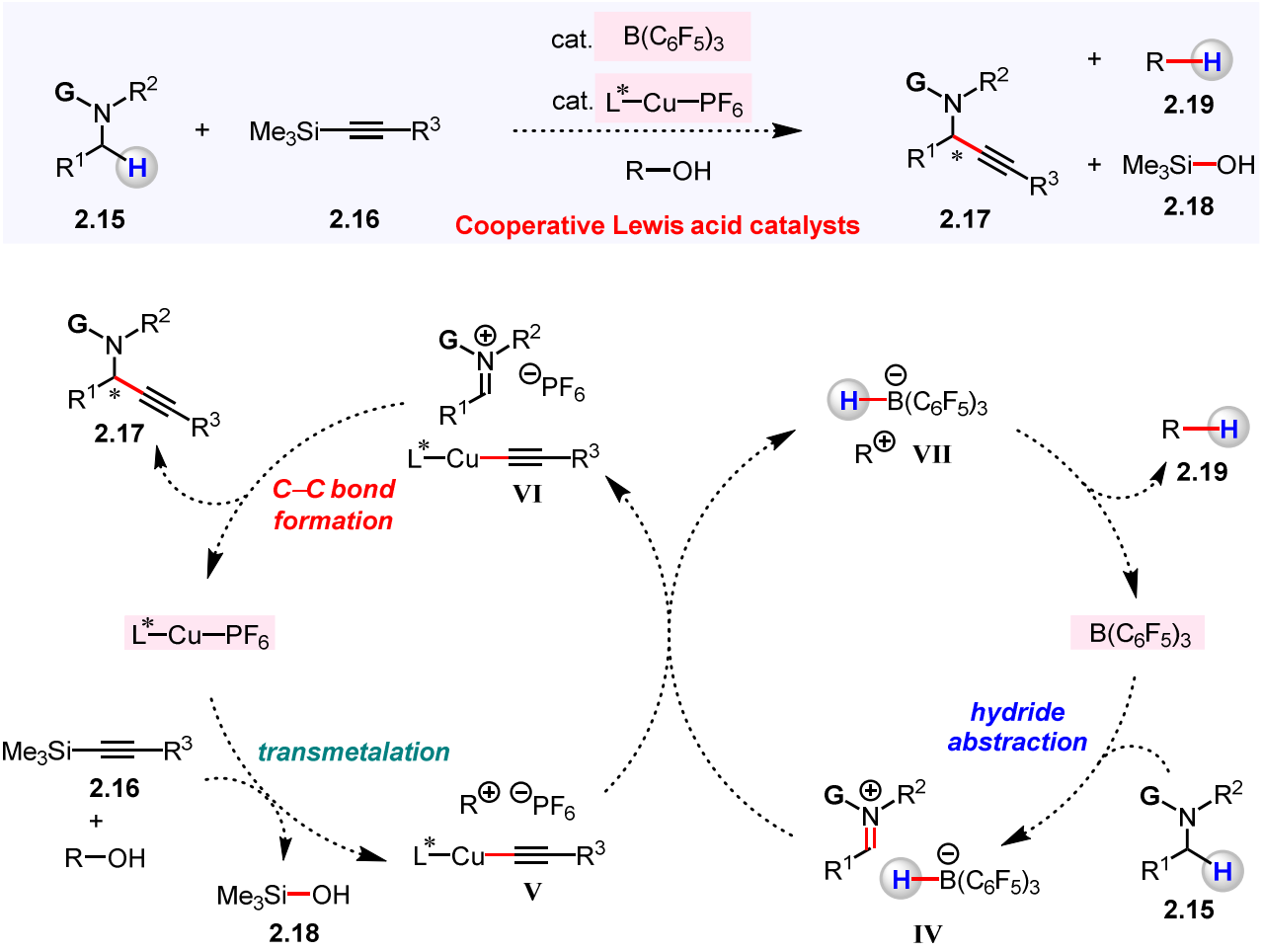
In contemplating ways to design a catalyst system that is applicable for the synthesis and late-stage modification of a broad array of *N*-alkylamines, we envisioned the development of unquenchable catalyst systems that are based on sustainable elements, can be operated under neutral pH, and that do not require the use of strong oxidants. Specifically, we envisioned employing two distinct Lewis acids, namely an organoborane catalyst, which is known to activate C–H bonds contained in *N*-alkylamine **2.15** (Scheme 2.5), and a chiral Cu-based complex that is capable of activating alkynes to generate nucleophilic Cu-alkynyl species from various alkynes (**2.16** → **V**). We proposed that highly Lewis acidic $B(C_6F_5)_3$ might abstract a hydride from amine **2.15** to generate an ion pair of iminium ion and borohydride (**IV**).[56] Meanwhile, an alcohol additive might aid the transmetallation event of the organocopper catalyst with alkynylsilane **2.16** for the formation of L_nCu–alkynyl complex (**V**) and trimethylsilanol **2.18**.[57] The subsequent reaction between in situ generated iminium ion and L_nCu–alkynyl complex (**VI**) would then forge the C–C bond and afford the desired propargylamine **2.17** in an enantioselective fashion. Lastly, R–OH-derived cationic species (**VII**) might react with borohydride to regenerate the $B(C_6F_5)_3$ catalyst and R–H **2.19**; thereby, closing the catalytic cycle. However, in order to promote enantioselective reactions when there are seemingly competitive achiral and chiral Lewis acid catalysts present in

[56] (a) Millot, N.; Santini, C. C.; Fenet, B.; Basset, J. M. *Eur. J. Inorg. Chem.* **2002**, *2002*, 3328–3335. (b) Dureen, M. A.; Brown, C. C.; Stephan, D. W. *Organometallics* **2010**, *29*, 6422–6432. (c) Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc.* **2018**, *140*, 10593–10601. (d) Basak, S.; Winfrey, L.; Kustina, B. A.; Melen, R. L.; Morrill, L. C.; Pulis, A. P. *Chem. Soc. Rev*. **2021**, *50*, 3720–3737.

[57] a) Herron, J. R.; Ball, Z. T. *J. Am. Chem. Soc*. **2008**, *130*, 16486–16487. b) Lee, K.-S.; Hoveyda, A. H. *J. Org. Chem*. **2009**, *74*, 4455–4462. c) Gurung, S. K.; Thapa, S.; Vangala, A. S.; Giri, R. *Org. Lett*. **2013**, *15*, 5378–5381. d) Denmark, S. E.; Tymonko, S. A. *J. Org. Chem*. **2003**, *68*, 9151–9154.

the reaction mixture, the design of the catalyst should enable them to play their own independent role without allowing them to have overlapping functions.

Scheme 2.5. Proposed Catalytic Cycles

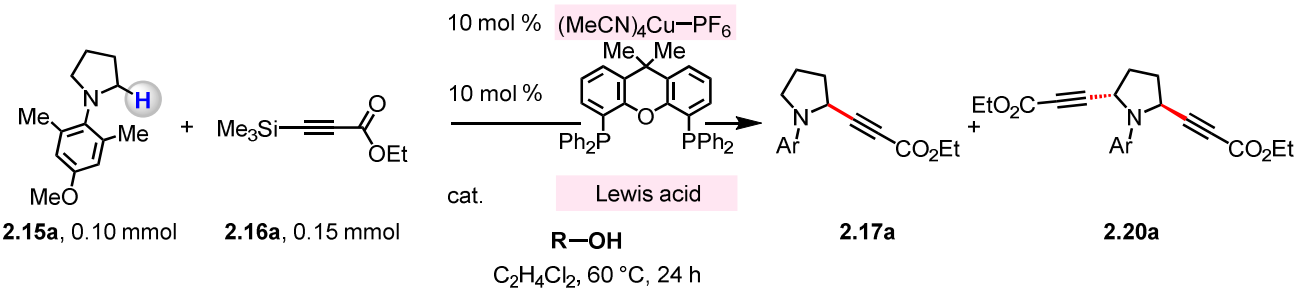


2.3.1. Method Development

To identify an optimal catalyst combination, we probed the ability of $B(C_6F_5)_3$ and various Cu-based organometal complexes to furnish the reaction between 1-(4-methoxy-2,6-dimethylphenyl)pyrrolidine **2.15a** and ethyl 3-(trimethylsilyl)propiolate **2.16a**. We found that the reaction between **2.15a** and **2.16a** in the presence of 10 mol % $B(C_6F_5)_3$, 10 mol % $(MeCN)_4CuPF_6$, and 10 mol % of Xantphos afforded **2.17a** in 7% yield at 60 °C after 24 h (Table 2.1; entry 1). We

then set out to identify a suitable additive that can improve the efficiency of this transformation and discovered that the use of alcohol boosts the efficiency of this process (entries 3−7). We proposed alcohol additive might accelerate the transmetallation step (**2.16** → **VIII**, Figure 2.8) while forming trimethyl silanol **2.18** as a byproduct. Although the addition of *i*-PrOH stopped the reaction (entry 2), the addition of sterically more congested 1-adamantol and *t*-BuOH (2.0 equiv.) led to the formation of **2.15a** in up to 17% yield (entries 3−4). With Ph_3COH (2.0 equiv.) as the additive, we observed the formation of **2.15a** (52% yield) together with **2.20a** (34% yield; entry 5). The ^1H NMR analyses of the unpurified reaction mixture using mesitylene as the internal standard revealed that Ph_3C−H (**2.19a**, 1.2 equiv.) was obtained as a byproduct (i.e., **2.19**, R = Ph_3C; Figure 2.8). Lowering the loading of Ph_3COH (1.0 equiv.) resulted in the formation of **2.15a** (83% yield, entry 6) more predominantly over **2.20a** (15% yield). When less Ph_3COH (1.0 equiv.) was used, and the reaction was performed for only 12 h (vs 24 hours), **2.15a** was obtained in 90% yield almost exclusively (entry 7). The efficiency of this alkynylation process deteriorated when the $B(C_6F_5)_3$ loading was lowered to 5.0 mol % (81% yield, entry 8). The control reactions demonstrated no product was observed in the absence of $B(C_6F_5)_3$ or when the less hindered BF_3 or less Lewis acidic BPh_3 were used (entries 9−11).

Table 2.1. Evaluation of Reaction Parameters



2.15a, 0.10 mmol **2.16a**, 0.15 mmol **2.17a** **2.20a**

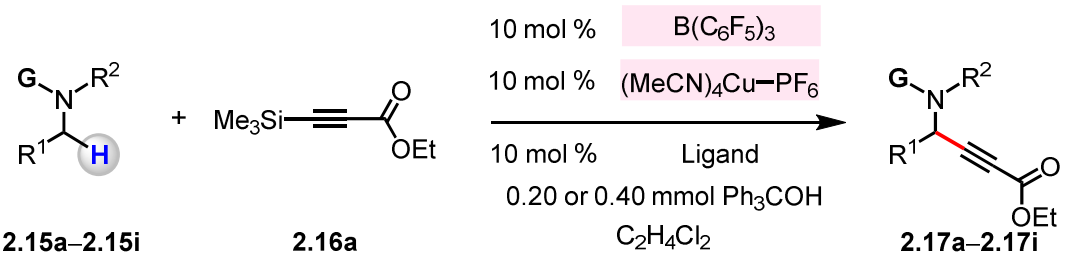
entry	Lewis acid (mol %)		**R–OH** (mmol)	yield (%)	
				2.17a	**2.20a**
1	$B(C_6F_5)_3$	(10)	none	7	0
2	$B(C_6F_5)_3$	(10)	*i*-PrOH (0.20)	0	0
3	$B(C_6F_5)_3$	(10)	1-adamantol (0.20)	10	0
4	$B(C_6F_5)_3$	(10)	*t*-BuOH (0.20)	17	0
5	$B(C_6F_5)_3$	(10)	Ph_3COH (0.20)	52	34
6	$B(C_6F_5)_3$	(10)	Ph_3COH (0.10)	83	15
7[c]	$B(C_6F_5)_3$	(10)	Ph_3COH (0.10)	90	<5
8	$B(C_6F_5)_3$	(5.0)	Ph_3COH (0.10)	81	<5
9	none		Ph_3COH (0.10)	0	0
10	$BF_3•OEt_2$	(10)	Ph_3COH (0.10)	0	0
11	BPh_3	(10)	Ph_3COH (0.10)	0	0

[a] Conditions: Reactions were performed under N_2 atmosphere. *N*-arylpyrrolidine (**2.15a**, 0.10 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.15 mmol), B-based Lewis acid, $(MeCN)_4CuPF_6$ (10 mol %), Xantphos (10 mol %), alcohol additive, $C_2H_4Cl_2$ (0.4 mL), 60 °C, 24 h. [b] Yield values were determined by analysis of the ^1H NMR spectra of unpurified mixtures with mesitylene as the internal standard. [c] Reaction mixture was allowed to stir for 12 h.

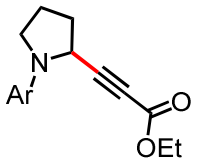
Having found the optimal catalyst system and the reaction conditions for transforming α-amino C–H bonds into C–alkyne bond, we evaluated various substrates and found that a wide range of cyclic and acyclic *N*-alkylamines (**2.15a**–**2.15i**; Table 2.2) are compatible substrates for this transformation to generate the corresponding propargyl amine products (**2.17a**–**2.17i**). When the L_nCu–Xantphos complex was used as the catalysts, an alkyne group was installed to various cyclic amines, including *N*-aryl pyrrolidines (**2.15a**, **2.15b**) and *N*-aryl azepane (**2.15c**) to afford **2.17a**–**2.17c** in 77–90% yield. This alkynylation protocol was applicable for substrates containing

N-methyl sites (**2.15d–2.15i**). The treatment of 4-methoxy-*N*,*N*,2,6-tetramethylaniline **2.15d** with **2.16a** affords **2.17d** in 90% yield. For substrates that possess electronically and sterically disparate α-amino C–H bonds (**2.15e–2.15i**), hydride abstraction efficiently occurred at the sterically most

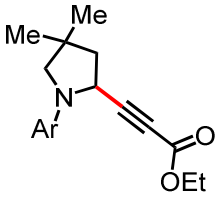
Table 2.2. Incorporation of an Alkyne Unit into Various Cyclic and Acyclic *N*-alkylamines [a,b,c]



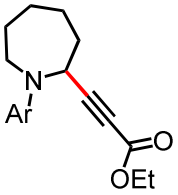
2.15a–2.15i 0.20 mmol | **2.16a** 0.30 mmol | **2.17a–2.17i**



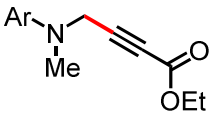
2.17a, 90% yield[a]



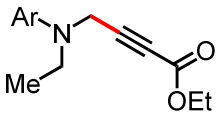
2.17b, 77% yield[a]



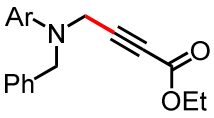
2.17c, 77% yield[a]



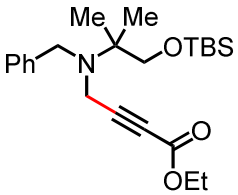
2.17d, 90% yield[a]



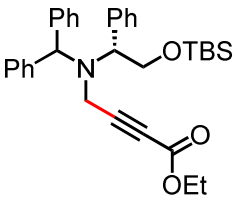
2.17e, 42% yield[a]



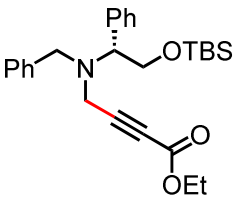
2.17f, 70% yield[a]



2.17g, 76% yield[b]



2.17h, 97% yield[b]



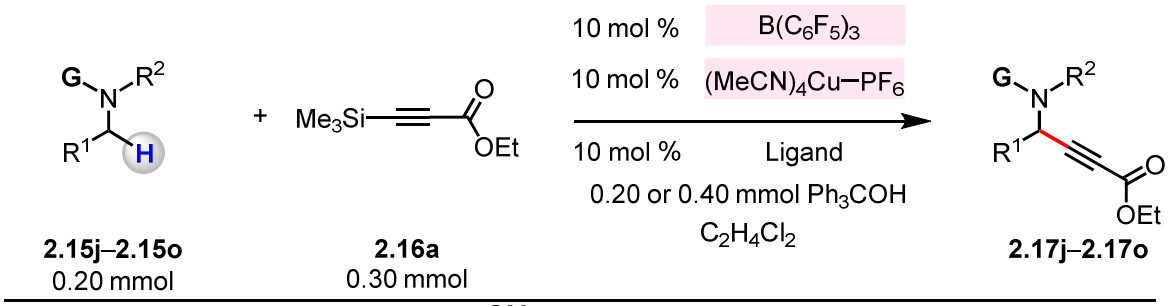
2.17i, 86% yield[b]

[a] Conditions: *N*-alkylamine (**2.15**, 0.20 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.30 mmol), $B(C_6F_5)_3$ (10 mol %), $(MeCN)_4CuPF_6$ (10 mol %), Xantphos (10 mol %), triphenylmethanol (0.20 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2 atmosphere, 60 °C, 12 h. [b] 1,2-Bis(diphenylphosphino)ethane (10 mol %) was used as a ligand, 0.40 mmol of triphenylmethanol was used, and the reaction mixture was allowed to stir at 80 °C for 24 h.

exposed *N*-methyl unit. There was only <10% C–C bond formation at the α-amino C–H bonds of *N*-ethyl and *N*-benzyl groups. It was demonstrated that trialkyl amines (**2.15g**–**2.15i**) are tolerated by this catalyst system when conformationally more flexible and sterically less demanding 1,2-bis-(diphenylphosphino)ethane (vs Xantphos; dppe) was used as the ligand; **2.17g**–**2.17i** was afforded in up to 97% yield. The efficiency of the C–alkyne bond-forming reaction was affected by the size of the *N*-substituents. While more hindered benzhydryl-substituted **2.15h** afforded **2.17h** in 97% yield, the treatment of benzyl-substituted **2.15i** with **2.16a** gave **2.17i** in only 86% yield.

Having found the optimal reaction condition for *N*-alkylamines, we then demonstrated this protocol is pertinent to the late-stage functionalization of bioactive amines (Table 2.3). On top of the *N*-alkylamine units contained in **2.15j–2.15o**, a wide range of Lewis-acid sensitive functional groups including an ester (**2.15k**), an ether (**2.15k**, **2.15l**, **2.15n**), a thienyl (**2.15n**), and an aryl chloride (**2.15o**) were tolerated to afford the desired propargyl amine analogs **2.17j**–**2.17o** in 56–76% yield upon purification by silica gel chromatography. While the α-amino C–H bonds of tertiary amine-containing butenafine (**2.15j**, antifungal) and trimebutine (**2.15k,** antifungal) were promptly transformed into C–alkyne bonds, incorporation of the *N*-benzhydryl unit to secondary amine units of atomoxetine (**2.15l**, treats ADHD), nortriptyline (**2.15m**, antidepressant), duloxetine (**2.15n**, antidepressant), and sertraline (**2.15o**, antidepressant) was crucial for the alkynylation reaction to occur, affording **2.17l**–**2.17o**.

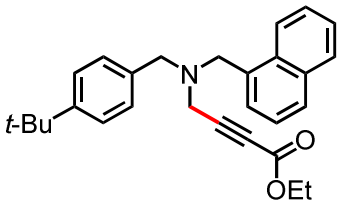
Table 2.3. Late-Stage Functionalization of Various Bioactive *N*-alkylamines[a,b,c]



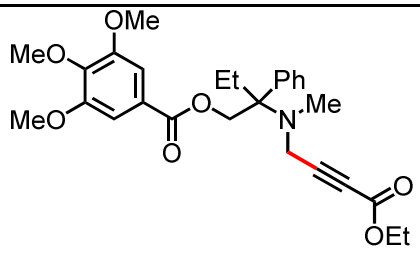
2.15j–2.15o
0.20 mmol

2.16a
0.30 mmol

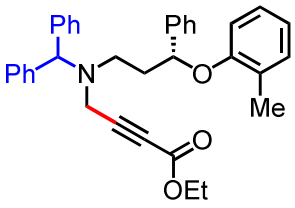
2.17j–2.17o



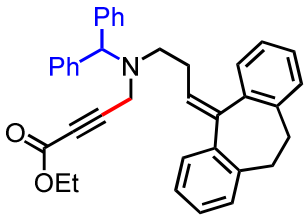
2.17j, 76% yield[b]
butenafine (antifungal) derivative



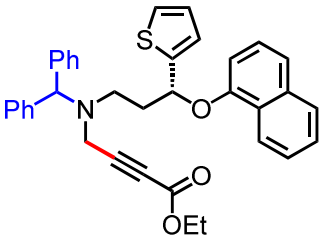
2.17k, 71% yield[b]
trimebutine (antifungal) derivative



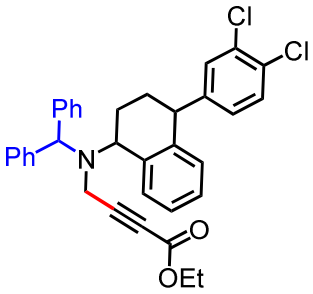
2.17l, 56% yield[b,c]
atomoxetine (treatment of ADHD) derivative



2.17m, 74% yield[b,c]
nortriptyline (antidepressant) derivative



2.17n, 68% yield[b,c]
duloxetine (antidepressant) derivative



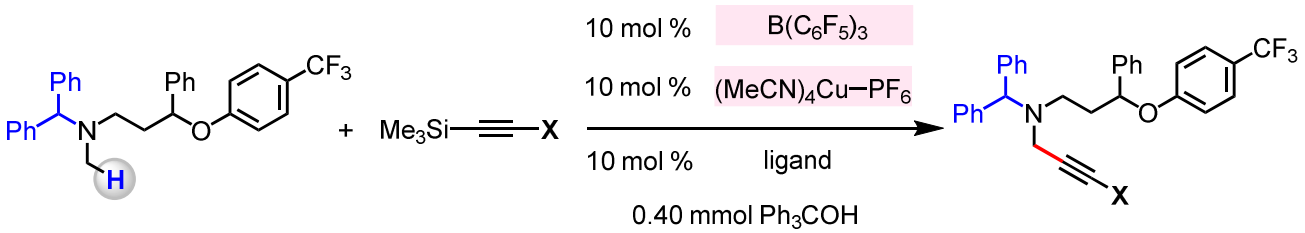
2.17o, 67% yield[b,c]
sertraline (antidepressant) derivative

[a] Conditions: *N*-alkylamine (**2.15**, 0.20 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.30 mmol), $B(C_6F_5)_3$ (10 mol %), $(MeCN)_4CuPF_6$ (10 mol %), Xantphos (10 mol %), triphenylmethanol (0.20 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2 atmosphere, 60 °C, 12 h. [b] 1,2-Bis(diphenylphosphino)ethane (10 mol %) was used as a ligand, 0.40 mmol of triphenylmethanol was used, and the reaction mixture was allowed to stir at 80 °C for 24 h. [c] Blue color indicates protecting groups.

With the identification of a highly efficient catalyst system that can achieve late-stage modification of *N*-containing bioactive molecules, the scope of trimethylsilylacetylenes containing different alkynyl substituents was explored (**2.16a–2.16h**, Table 2.4.). The treatment of *N*-Bzh

fluoxetine **2.15p** with trimethylsilylacetylenyl esters (**2.16a**, **2.16b**) and amide (**2.16c**) provided **2.21a**–**2.21c** in up to 82% yield. An array of trimethylsilylacetylenes, which contains an aromatic substituent, was tested. It was found that phenyl- (**2.16d**), 4-(trifluoromethyl)phenyl- (**2.16e**), 4-chlorophenyl- (**2.16f**) or 3-thiophenyl-substituted (**2.16g**) trimethylsilylacetylenes were suitable substrates to afford **2.21a**–**2.21g** in 74–82% yield. Moreover, 1,2-bis(trimethylsilyl)ethyne **2.16h** was identified as a compatible coupling partner, affording **2.21h** with removable TMS substituent in 87% yield.

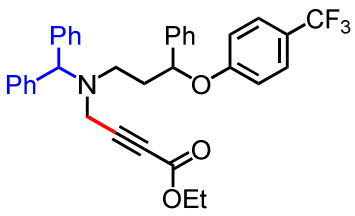
Table 2.4. Reactions of *N*-Bzh Fluoxetine with Triemthylsilylacetylenes



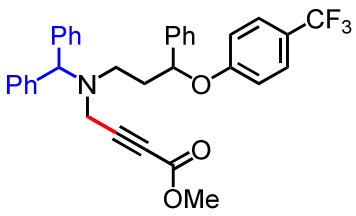
2.15p, 0.20 mmol
***N*-Bzh fluoxetine**

2.16a–2.16h
0.30 mmol

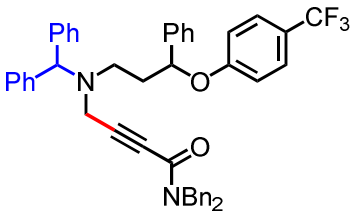
2.21a–2.21h
fluoxetine (antidepressant) derivative



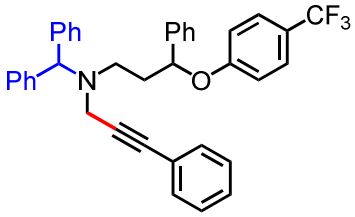
2.21a, 82% yield[a]



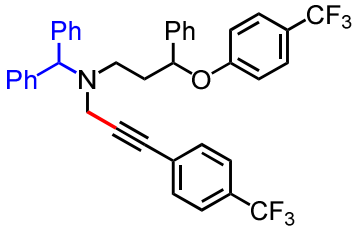
2.21b, 76% yield[a]



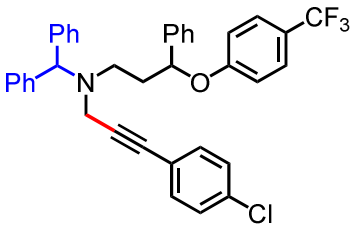
2.21c, 80% yield[b]



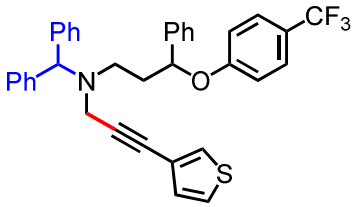
2.21d, 75% yield[b]



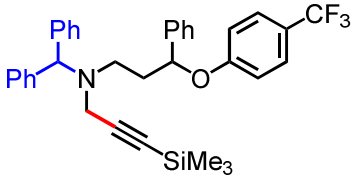
2.21e, 82% yield[b]



2.21f, 80% yield[b]



2.21g, 74% yield[b]



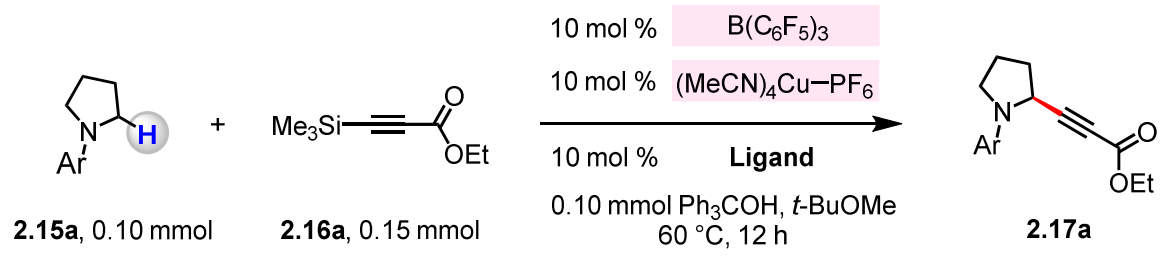
2.21h, 87% yield[b]

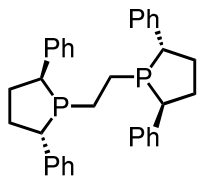
[a] Conditions: *N*-alkylamine (**2.15**, 0.20 mmol), 3-(trimethylsilyl)propiolate (**2.16**, 0.30 mmol), $B(C_6F_5)_3$ (10 mol %), $(MeCN)_4CuPF_6$ (10 mol %), 1,2-bis(diphenylphosphino)ethane (10 mol %), triphenylmethanol (0.40 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2 atmosphere, 80 °C, 24 h. [b] (*S*)-Ph–PyBOX was used as ligand [c] Blue color indicates protecting groups.

2.3.2. Diastereo- and Enantioselective Processes

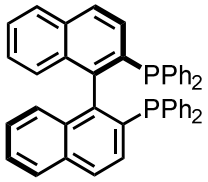
Due to the versatility of enantiomerically enriched propargyl amines as an intermediate for the synthesis and the modification of bioactive molecules, we decided to establish an enantioselective variant of this alkynylation protocol. (Figure 2.1).[53-55] To achieve this goal, we decided to treat *N*-arylpyrrolidine **2.15a**, which is known to undergo $B(C_6F_5)_3$-catalyzed hydride abstraction, with 3-(trimethylsilyl)propiolate **2.16a** in the presence of $B(C_6F_5)_3$, $(MeCN)_4CuPF_6$, and a chiral ligand. Accordingly, we evaluated chiral ligands that are known to coordinate to the Cu-based complex to induce enantioselectivity. Bis-phosphine ligands (**L1**–**L2**; Table 2.5) afforded **2.17a** in up to 70% yield nearly as a racemate (er ≤ 45:55). Next, we explored different bis-oxazoline ligands (**L3**–**L6**) to improve the enantioselectivity of this C–alkyne bond forming reaction. (*S*)-Ph‑PyBOX (**L3**) generated **2.17a** in 84% yield with 82:18 er. The use of sterically more demanding 2,6-bis((*S*)-4-(*m*-tolyl)-4,5-dihydrooxazol-2-yl)pyridine (**L4**) resulted in the formation of **2.17a** in 53% yield with 90:10 er. The efficiency and the enantioselectivity was further improved when conformationally more rigid 2,6-bis((*S*)-4-(3,5-dimethylphenyl)-4,5-dihydrooxazol-2-yl)pyridine (**L5**) was used (75% yield and 95:5 er). However, the efficiency and enantioselectivity did not improve when meta,meta-diethylphenyl-substituted **L6** was used (36% yield, 82:18 er).

Table 2.5. Evaluation of Chiral Ligands

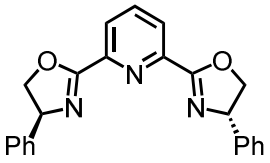




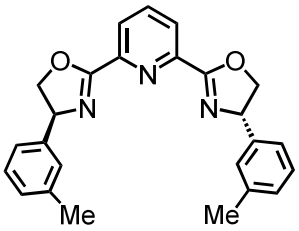
L1
2.17a, 70% yield
45:55 er



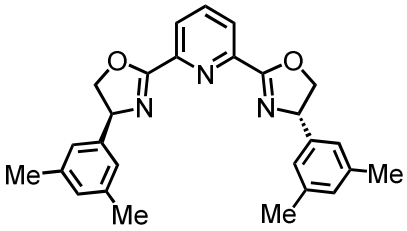
L2
2.17a, 61% yield
49:51 er



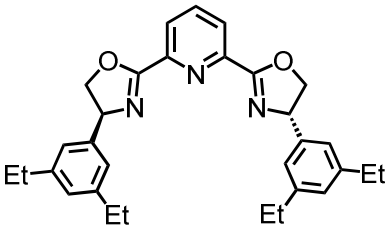
L3
2.17a, 84% yield
82:18 er



L4
2.17a, 53% yield
90:10 er



L5
2.17a, 75% yield
95:5 er

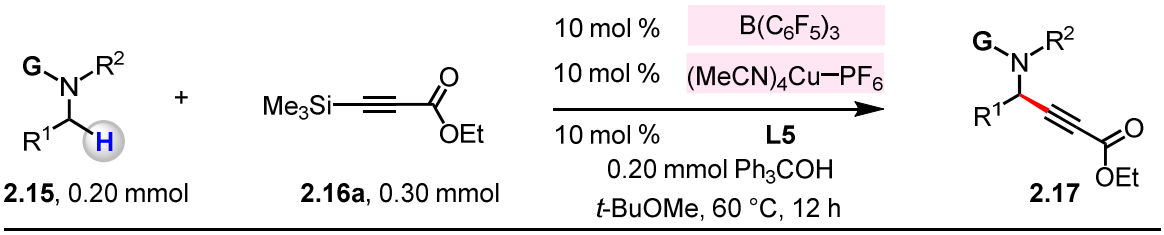


L6
2.17a, 36% yield
82:18 er

Conditions: *N*-arylpyrrolidine (**2.15a**, 0.10 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol %), $(MeCN)_4CuPF_6$ (10 mol %), ligand (10 mol %), triphenylmethanol (0.15 mmol), *t*-BuOMe (0.4 mL), under N_2 atmosphere, 60 °C, 12 h.

The novel enantioselective protocol proved to be readily adaptable to the synthesis of various enantiomerically enriched propargyl amines using $B(C_6F_5)_3$ and $(MeCN)_4CuPF_6$/**L5** as the catalyst combination (Table 2.6). The reactions of 3-(trimethylsilyl)propiolate **2.16a** with an assortment of cyclic *N*-alkylamines (**2.15a–2.15c** and **2.15q–2.15u**)to afford desired products containing *N*-Arylpyrrolidines ((*S*)- **2.17a**, **2.17q**, **2.17b**) as well as *N*-arylazepane (**2.17c**) in 64–75% yield and 83:17–95:5 er. These reactions exclusively gave the desired products, and no more

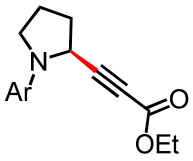
Table 2.6. Diastereo- and Enantioselective Processes



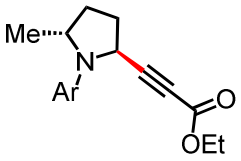
2.15, 0.20 mmol

2.16a, 0.30 mmol

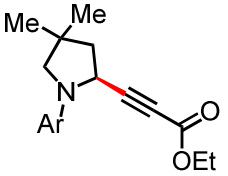
2.17



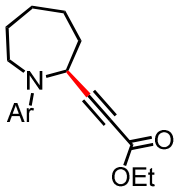
(*S*)-2.17a, 75% yield
95:5 er



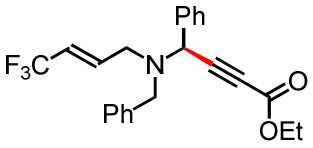
2.17q, 66% yield
6.3:1 *trans:cis*
83:17 er (*trans* isomer)



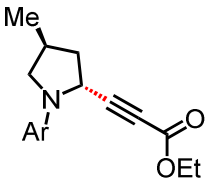
2.17b, 69% yield
93:7 er



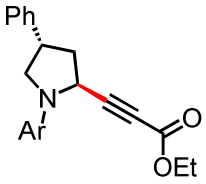
2.17c, 64% yield
95:5 er



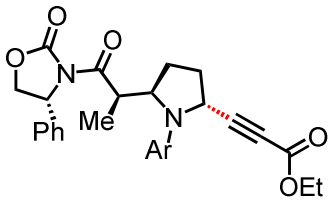
2.17r, 45% yield
84:16 er



2.17s, 64% yield
11.8:1 *trans:cis*
97:3 er (*trans* isomer)



2.17t, 68% yield
10.1:1 *trans:cis*
88:12 er (*trans* isomer)



2.17u, 93% yield
7.7:1 *trans:cis*

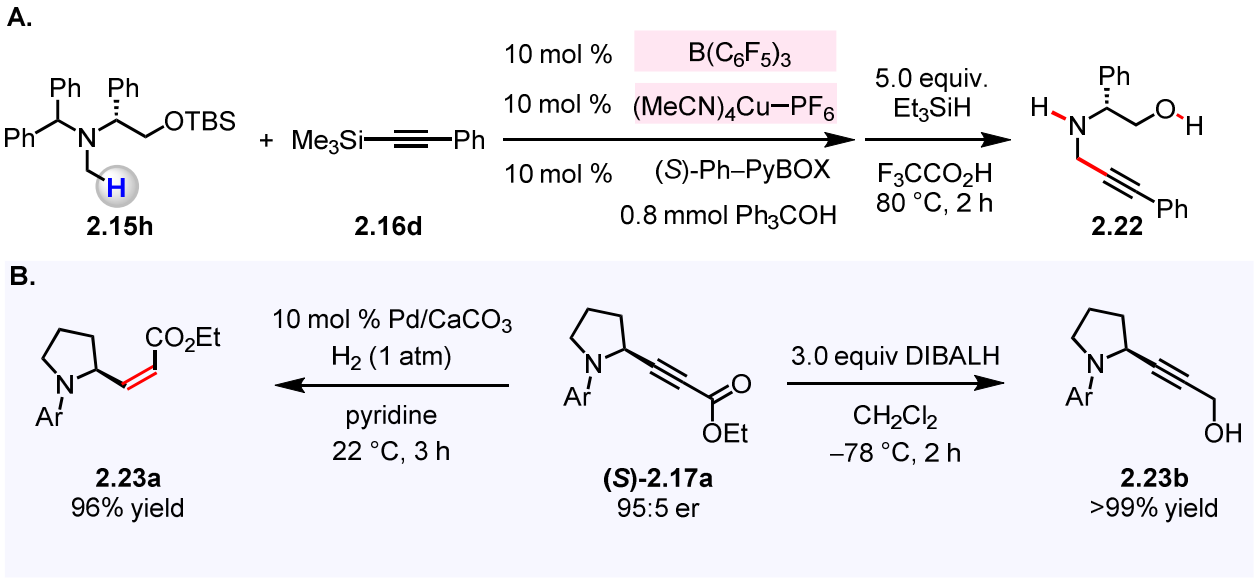
Conditions: *N*-alkylamine (**2.15**, 0.20 mmol), 3-(trimethylsilyl)propiolate (**2.16a,** 0.30 mmol), $B(C_6F_5)_3$ (10 mol %), $(MeCN)_4CuPF_6$ (10 mol %), **L5** (10 mol %), triphenylmethanol (0.20 mmol), *t*-BuOMe (0.4 mL), under N_2 atmosphere, 60 °C, 12 h.

than 5% dialkynyl byproduct formation was detected. Treatment (*E*)-*N,N*-dibenzyl-4,4,4-trifluorobut-2-en-1-amine **2.15r** with 3-(trimethylsilyl)propiolate **2.16a** resulted in the functionalization of benzylic C–H bond, affording **2.17r** in 45% yield with 84:16 er. Moreover, the stereoselective synthesis of polyfunctional pyrrolidines (**2.17s**–**2.17u**; Table 2.6) was achieved using various enantiomerically enriched pyrrolidines as a substrate. The union of (*S*)-3-methyl-

pyrrolidine **2.15s** and (*S*)-3-phenyl pyrrolidine **2.15t** and **2.16a** took place at the sterically less demanding α-amino C–H bonds, affording **2.17s** and **2.17t** in 64% yield (11.8:1 *trans*:*cis*; 97:3 er) and 68% yield (10.1:1 *trans*:*cis*; 88:12 er), respectively. Additionally, β-aminocarbonyl compound **2.15u** underwent stereoselective coupling with **2.16a** to give **2.17u** in 93% yield with 7.7:1 *trans*:*cis* ratio. These diastereoselective processes require the use of an enantiomerically enriched ligand (e.g., **L5**); when an achiral ligand such as Xantphos was used, substantially inferior dr and er were observed.

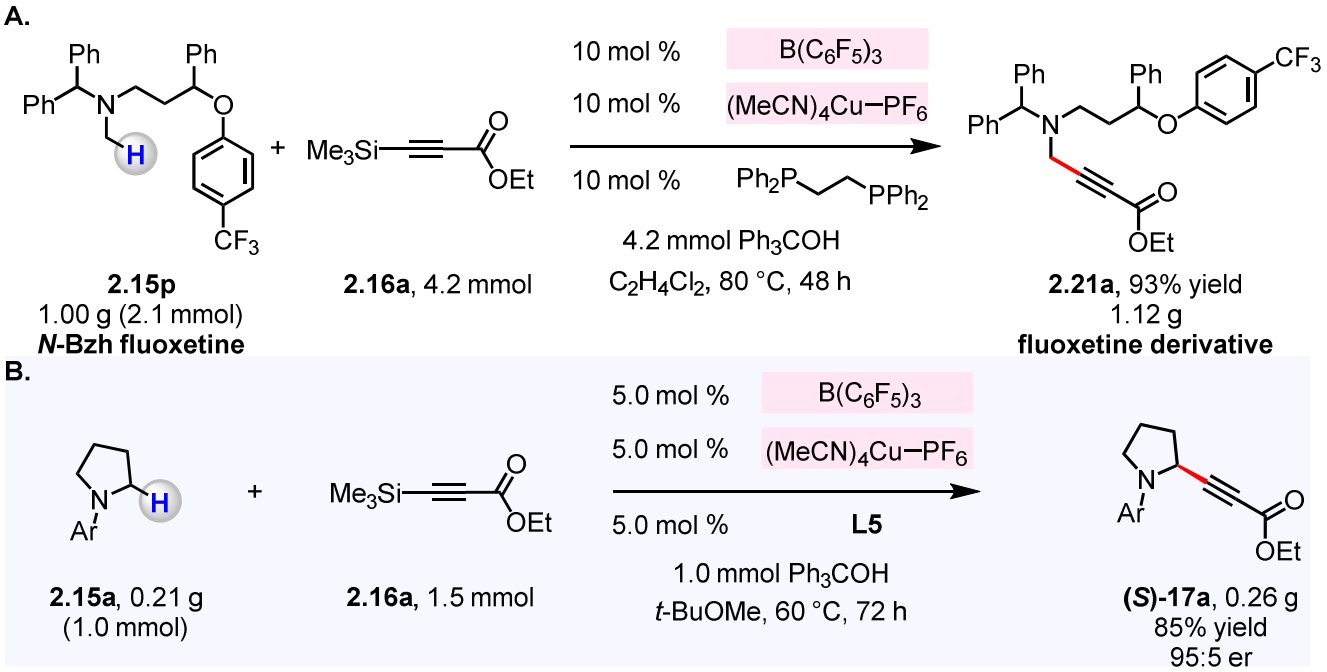
An alkynylation/deprotection cascade was performed for the synthesis of **2.22**; the reaction between **2.15h** and **2.16d** affords the alkynylation product, which is then treated with Et_3SiH and trifluoroacetic acid to remove benzhydryl and TBS groups to furnish **2.22** in 64% yield (Scheme 2.6A). Moreover, upon hydrogenation or reduction of **(*S*)-2.17a**, synthetically versatile *Z*-alkene **2.23a** (96% yield) or propargyl alcohol **2.23b** (>99% yield) could be obtained (Scheme 2.6B).

Scheme 2.6. Modification of Propargyl Amine Products



The catalytic method is amenable to gram-scale operation. For instance, the reaction between 1.0 g (2.1 mmol) of *N*-benzhydryl fluoxetine **2.15p** and **2.16a** with 10 mol % $B(C_6F_5)_3$, 10 mol % Cu-based complex, and 2.0 equivalents of Ph_3COH gave **2.21a** in 93% yield after 48 h (Scheme 2.7A). Next, the scalability of the enantioselective protocol was demonstrated. The treatment of arylpyrrolidine **2.15a** (0.21 g, 1.0 mmol) with **2.16a** in the presence of 5.0 mol % $B(C_6F_5)_3$, 5.0 mol % $(MeCN)_4CuPF_6$/**L5**, and 1.0 equivalent of Ph_3COH afforded **(*S*)-2.17a** in 85% yield (0.26 g) with 95:5 er (Scheme 2.7B).

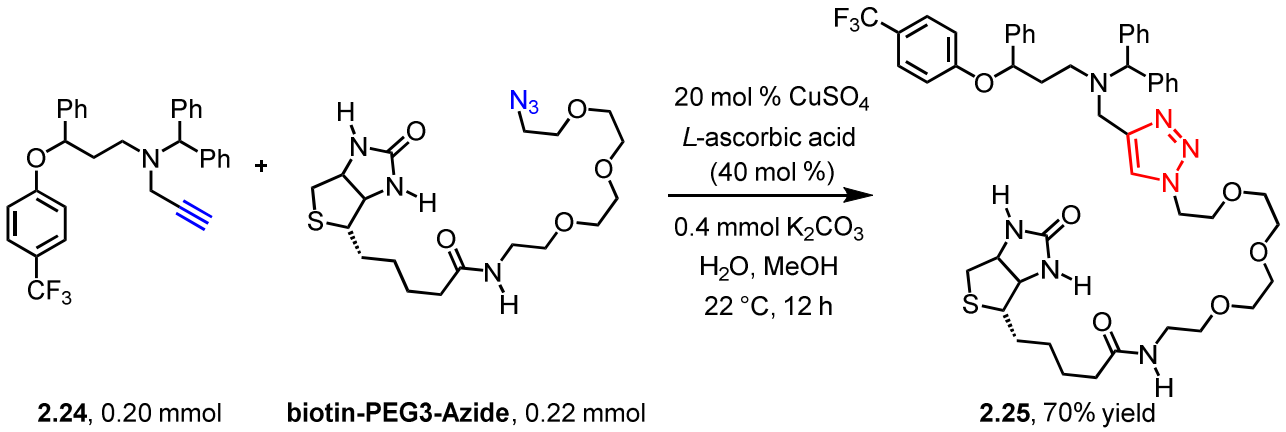
Scheme 2.7. Scale-Up Experiments



Lastly, the versatility of the catalytically installed propargyl unit of fluoxetine derivative **2.21h** was demonstrated in the context of Click reaction. The subjection of **2.21h** with $(n\text{-Bu})_4NF$ afforded terminal alkyne **24** in >95% yield. The subsequent reaction of **24** with biotin-PEG3-azide

in the presence of $CuSO_4$/*L*-ascorbic acid and K_2CO_3 generated the heterocyclic conjugate **25** in 70% yield (Scheme 2.8).[58]

Scheme 2.8. Propargyl Amines as Versatile Handles



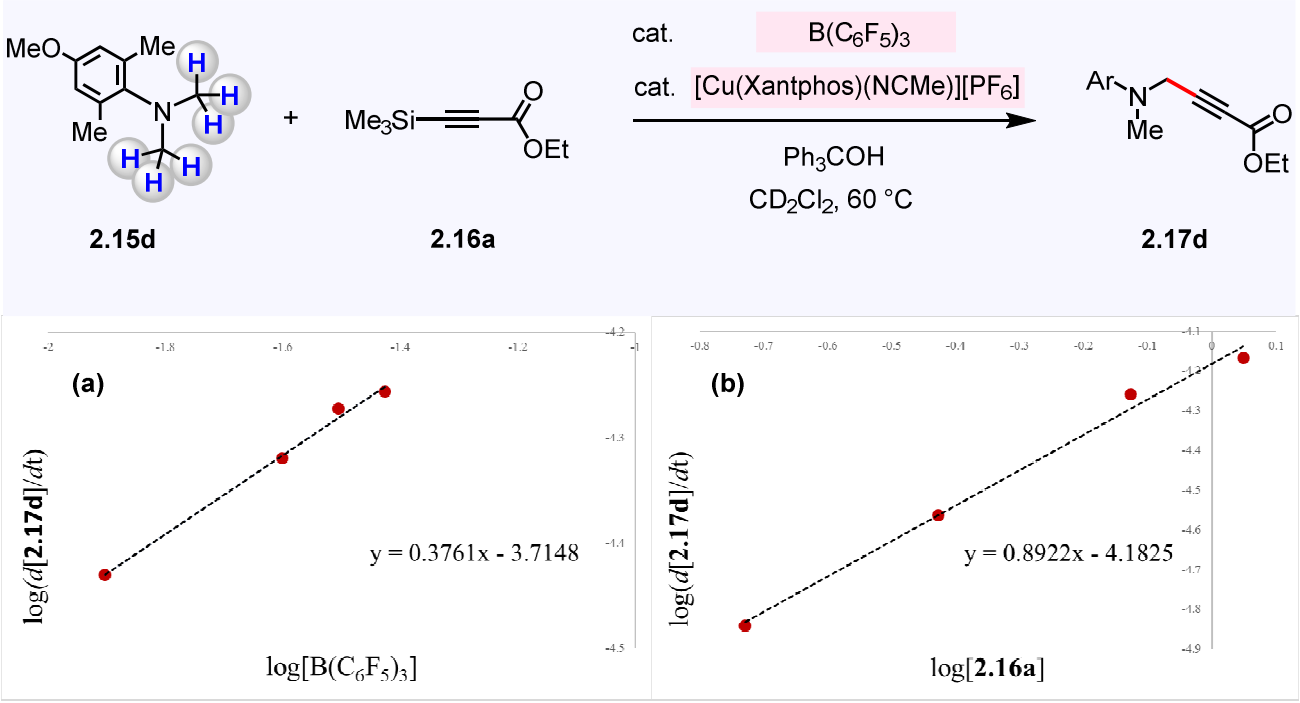
2.24, 0.20 mmol **biotin-PEG3-Azide**, 0.22 mmol **2.25**, 70% yield

2.3.3 Mechanistic Investigations

To gain a better understanding of this catalytic protocol, we designed and performed mechanistic studies. First, we aimed to establish the stoichiometry of the rate-limiting transition structure by carrying out a detailed kinetic analysis. These studies were executed using 4-methoxy-*N*,*N*,2,6-tetramethylaniline **2.15d** with ethyl 3-(trimethylsilyl)propiolate **2.16a** as the model substrates. We found that the reaction has first-order dependence on **2.16a** concentration (Scheme 2.9A) and half-order dependence on the $B(C_6F_5)_3$ concentration (Scheme 2.9B). However, there was no dependency on the concentration of **2.15d**, $(MeCN)_4CuPF_6$/Xantphos complex, and Ph_3COH.[59]

[58] (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *24*, 1128–1137.
[59] Burés, J. *Angew. Chem., Int. Ed*. **2016**, *55*, 2028–2031.

Scheme 2.9. Determination of Reaction Orders

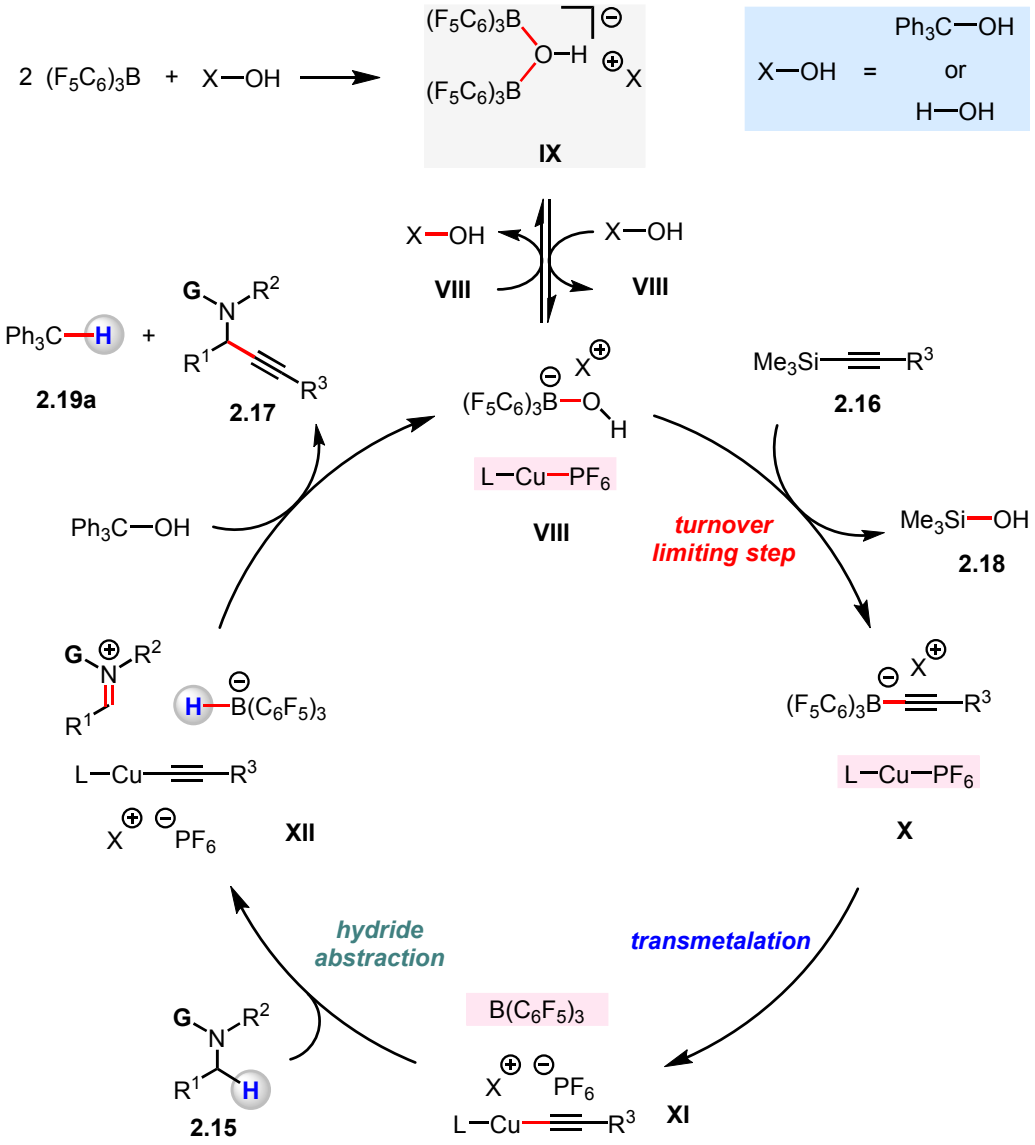


These data suggest the existence of a resting state containing two $B(C_6F_5)_3$ units such as a borate anion $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-$ (**IX**, $[X]^+ = H^+$ and/or Ph_3C^+; Scheme 2.10).[60] The formation of the borate anion **IX** was further confirmed by the analyses of the ^{11}B NMR spectra of the reaction mixture. Subsequently, $[(F_5C_6)_3B\text{–}OH]^-[X]^+$ (**VIII**) could be generated after **IX** reacts with a hydroxy donor (Ph_3COH and/or H_2O). Next, the reaction of **IX** and trimethylsilylacetylene **2.16** is likely the turnover step, affording the $[(F_5C_6)_3B\text{–alkyne}]^-[X]^+$ (**X**). Chemical competency of the intermediate **X** was exhibited by the generation of propargyl amine product **2.17d** (24% yield) through the reaction of preformed $[(F_5C_6)_3B\text{–}C{\equiv}C\text{–}CO_2Et]^-[H\text{–}NR_3]^+$ (0.1 mmol; NR_3 = **2.15d**)[61] and $(MeCN)_4CuPF_6$/Xantphos complex (0.1 mmol).

[60] (a) Strasăk, T.; Sykora, J.; Lamac, M.; Kubista, J.; Horaćek, M.; Gyepes, R.; Pinkas, J. *Organometallics* **2013**, *32*, 4122−4129. (b) Di Saverio, A.; Focante, F.; Camurati, I.; Resconi, L.; Beringhelli, T.; D'Alfonso, G.; Donghi, D.; Maggioni, D.; Mercandelli, P.; Sironi, A. *Inorg. Chem.* **2005**,*44*, 5030−5041.

[61] Dureen, M. A.; Stephan, D. W. *J. Am. Chem. Soc*. **2009**, *131*, 8396–8397.

Scheme 2.10. A Revised Catalytic Cycle Based on the Results of Mechanistic Studies

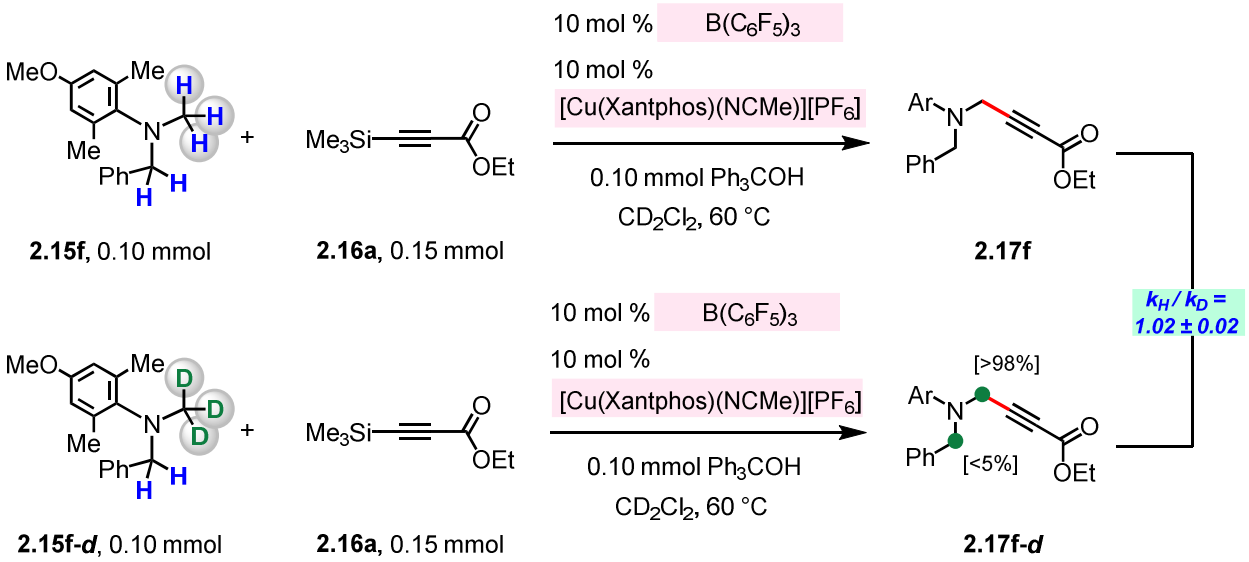


The $[(F_5C_6)_3B\text{–alkynyl}]^-$ $[X]^+$ underwent transmetallation to $(MeCN)_4CuPF_6$/Xantphos complex, generating L_nCu–alkynyl species and free $B(C_6F_5)_3$. Subsequent to transmetallation, $B(C_6F_5)_3$ activates α-amino C–H bonds of **2.15** through hydride abstraction to afford iminium ion (**X** → **XI** → **XII**). The reaction between nucleophilic L_nCu–alkynyl complex and electrophilic iminium ion would forge the C–C bond to give the propargyl amine (**XII** → **2.17**). A hydride

transfer process between borohydride and Ph_3COH derived carbocation would generate Ph_3C–H **2.19a**; thereby, closing the catalytic cycle by regenerating the active catalyst.

We then begin investigating the identity of the $B(C_6F_5)_3$-catalyzed hydride abstraction step (Scheme 2.10, **2.15** → **XII**). The results we obtained from reaction order determination studies indicated that the hydride abstraction step might take place after the turnover-limiting step (Scheme 2.9). We explored other approaches to establish the nature of the hydride abstraction process with greater certainty. A set of kinetic isotope effect (KIE) experiments were conducted (Scheme 2.11). Specifically, 4-methoxy-*N*,*N*,2,6-tetramethylaniline **2.15f** and its isotopologue **2.15f-*d*** were prepared, and their reactions with trimethylsilylacetylene **2.16a** were monitored. The independent rate measurements revealed that there was no considerable KIE ($k_H/k_D = 1.02 \pm 0.02$). Indeed, this KIE value, together with the reaction order studies, further suggests that $B(C_6F_5)_3$-catalyzed hydride abstraction step likely occurs after the turnover-limiting step.

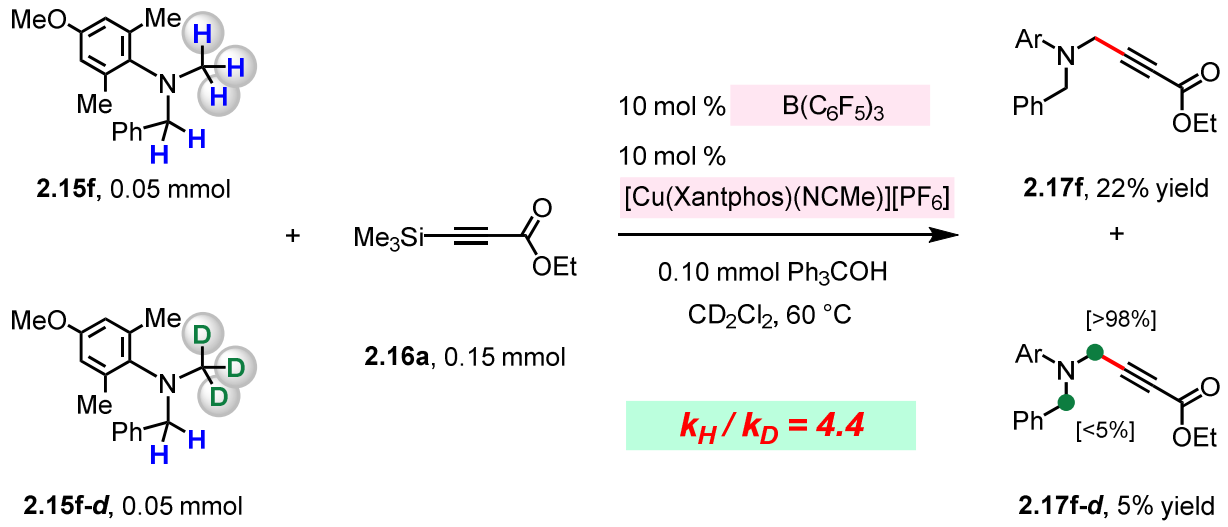
Scheme 2.11. Independent Rate Measurements with Amine Isotopologues



Next, we investigated the reversibility of the $B(C_6F_5)_3$-catalyzed hydride abstraction step with competition rate measurements (Scheme 2.12). A large primary KIE would display the

irreversibility of such a step as this investigation assesses the product distribution that results from a difference in the rate of a C–H bond-breaking step.[62] Under a competition setting, aniline **2.15f** and its isotopologue **2.15f-*d*** were treated with trimethylsilylacetylene **2.16a** as the limiting reagent. The result of this experiment revealed that aniline **2.15f** reacted 4.4 times faster than isotopologue **2.15f-*d***, indicating $B(C_6F_5)_3$-catalyzed hydride abstraction step is irreversible under the C–C bond-forming protocol.

Scheme 2.12. Competition Rate Measurements with Amine Isotopologues

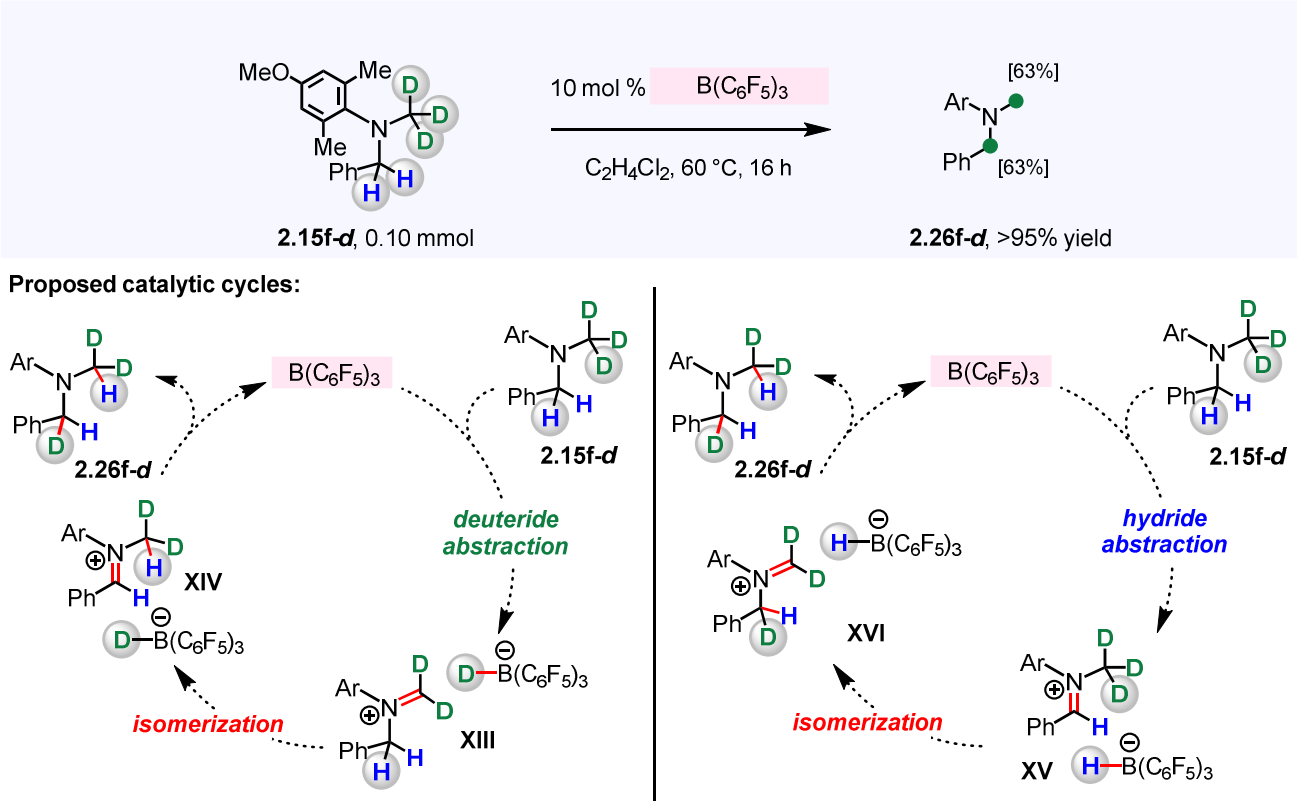


Throughout our investigation, we consistently observed transformations of *N*-methyl C–H bonds preferentially favored compared to that of electronically more accessible *N*-benzyl and *N*-benzhydryl C–H bonds. As an initial step toward determining the basis for this unique selectivity, we endeavored to study the reaction between $B(C_6F_5)_3$ and *N*-benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-d_3)aniline **2.15f-*d*** that contain electronically and sterically disparate C–H bonds. Specifically, we wanted to determine if the *N*-benzyl C–H bonds of **2.15f-*d*** could be activated

[62] (a) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066–3072. (b) Blackmond, D. G. *J. Am. Chem. Soc*. **2015**, *137*, 10852–10866.

under the reaction conditions. To test this idea, we treated **2.15f-*d*** with $B(C_6F_5)_3$ at 60 □ for 16 hours (Scheme 2.13) for the formation of corresponding iminium intermediate $[ArMeN{=}CHPh]^+$ (e.g., **XIV** and **XV**). Confirmed by the ^1H NMR spectrum of isolated and purified **2.26f-*d*,** there was detectable H/D exchange in both *α*-amino positions. Namely, while 37% of *N*-methyl C–D bonds were converted to C–H bonds, 63% of benzylic C–H bonds were transformed to C–D bonds. The resulting mixture of isotopologues suggests that $B(C_6F_5)_3$ can facilitate the formation of C-phenyl iminium ion (**XIV**). We surmised that $B(C_6F_5)_3$ might promote deuteride abstraction at the *N*–CD_3 moiety of **2.15f-*d*** to afford iminium ion **XIII,** which might undergo isomerization to

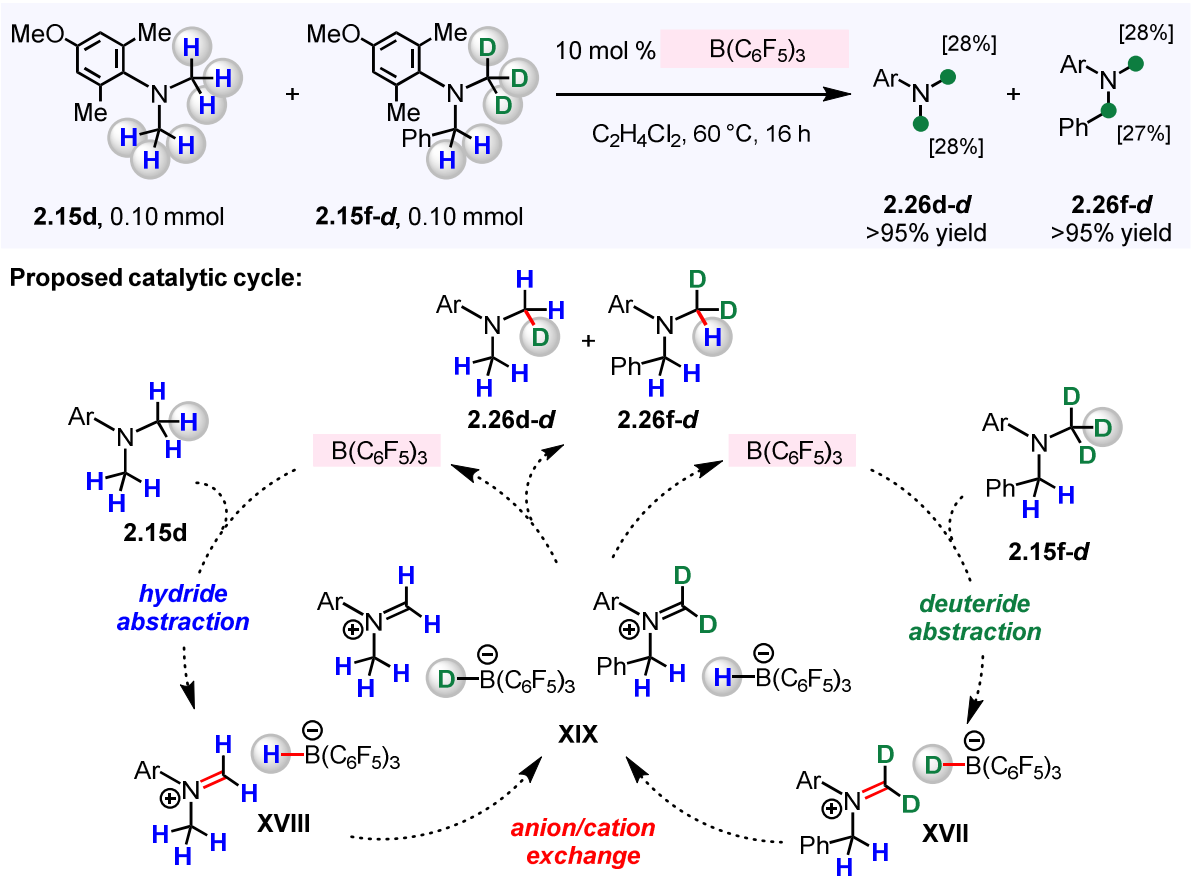
Scheme 2.13. Intermolecular H/D Exchange Experiment



form a more stable intermediate **XIV**.[63] The subsequent reaction between electrophilic iminium and the nucleophilic $[D–B(C_6F_5)_3]^-$ would forge the C–D bond. It is worth noting there might be an alternative process involving benzylic C–H abstraction for H/D exchange to occur. (**2.15f-*d*** → **XV** → **XVI** → **2.26f-*d***).[64]

A third possible scenario might involve the intermolecular H/D exchange for the observed isotope scrambling. To investigate this option, we reacted **2.15d** and **2.15f-*d*** in the presence of 10 mol % $B(C_6F_5)_3$ (Scheme 2.14). Upon completion, products **2.26d-*d*** and **2.26f-*d*** were isolated,

Scheme 2.14. Intramolecular H/D Exchange Experiment



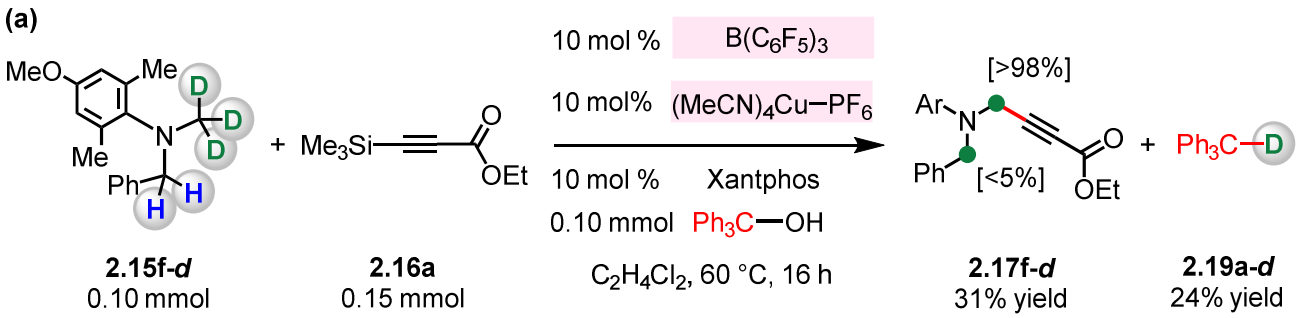
[63] Ma, L.; Paul, A.; Breugst, M.; Seidel, D. *Chem. Eur. J.* **2016**, *22*, 18179–18189.
[64] Farrell, J. M.; Heiden, Z. M.; Stephan, D. W. *Organometallics* **2011**, *30*, 4497–4500.

purified, and further characterized by ^{1}H NMR and HRMS. It was found that while 28% of *N*-methyl C–H bonds in **2.15d** were transformed into C–D bonds, 27% of *N*-benzylic C–H bonds in **2.15f-*d*** were converted to C–D bonds. Based on the results, we proposed in situ generated ion pairs consisting of iminium ions together with $[H–B(C_6F_5)_3]^-$ (**XVIII)** and $[D–B(C_6F_5)_3]^-$ (**XVII**) are sufficiently long-lived, and they could undergo exchange of their anionic and cationic components (**XIX**). The subsequent borohydride or borodeuteride reduction gives **2.26d-*d*** and **2.26f-*d*** (**XIX**).

We then investigated the H/D exchange reaction under the conditions for this catalytic protocol. Specifically, the treatment of 0.10 mmol **2.15f-*d*** with 0.15 mmol of 3-(trimethylsilyl)propiolate **2.16a** and 0.10 mmol Ph_3COH afforded propargylamine product **2.17f-*d*** in 31% yield (Scheme 2.15). The analysis of ^{1}H NMR and HRMS data of **2.17f-*d*** revealed that there is only <5% H/D exchange at the benzylic C–H bonds, and the >98% of C–D at the propargylic position was retained. Moreover, it was found that recovered **2.15f-*d*** did not undergo a H/D exchange reaction. As a result, we hypothesized that under the catalytic C–C bond-forming reaction conditions the in situ generated ion pair of iminium ion and borodeuteride (**XX**) is a highly reactive species and are readily consumed by the L_nCu–alkynyl complex to give propargylamine **2.17f-*d*** (**2.15** $\rightarrow$ **XII** $\rightarrow$ **2.17**, Scheme 2.15). Therefore, the H/D exchange reactions mentioned above do not occur under the standard reaction conditions.

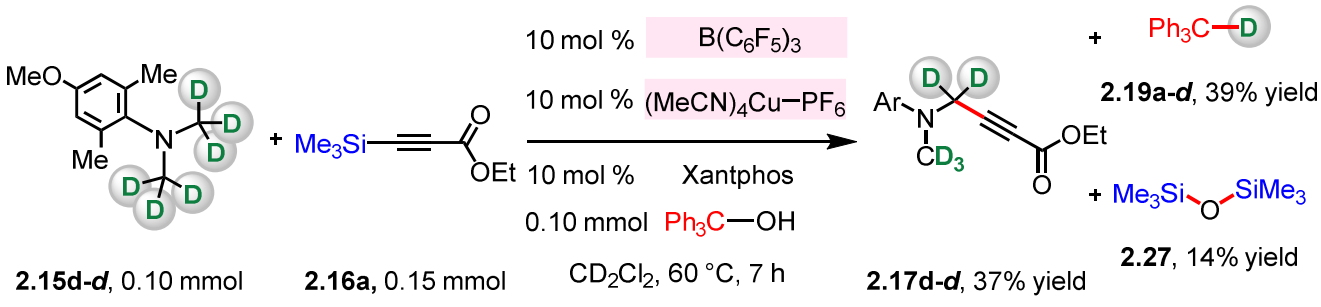
Lastly, the final destinations of deuteride of **2.15d-*d*** and trimethylsilyl group of **2.16a** were traced by analyzing the byproducts of this reaction. The revised catalytic cycle suggests that $Ph_3C–OH$ is responsible for the consumption of both deuteride and the trimethylsilyl group (Scheme 2.10). We proposed while CPh_3^+ ultimately receives the deuteride contained in **2.15d-*d***

Scheme 2.15. Determination of H/D Exchange Under the Standard Reaction Conditions



to afford Ph_3C–D (**2.19a-*d***; Scheme 2.16), the trimethylsilyl group picks up the hydroxy group derived from Ph_3C–OH to generate Me_3Si–OH (**2.18**). To confirm this, we reacted **2.15d-*d*** and **2.16a,** which afforded the propargyl amine **2.17d-*d*** together with other byproducts. Upon purification and the characterization of byproducts by ^1H and ^2H NMR spectroscopy, the formation of Ph_3C–D (**2.19a-*d***; 39% yield) was validated. However, we were not able to detect any Me_3Si–OH **2.18**. Yet, we identified Me_3SiO–$SiMe_3$ as the only byproduct that contains the trimethylsilyl group (**2.27**, 14% yield). We surmised **2.27** is generated by the condensation of Me_3Si–OH (**2.18**), which might be catalyzed by the Lewis acids present in the reaction mixture.[65]

Scheme 2.16. Determination of the Byproducts



[65] Satoh, Y.; Igarashi, M.; Sato, K.; Shimada, S. *ACS Catal.* **2017**, *7*, 1836–1840.

2.4 Conclusion and Future Outlook

In conclusion, we have developed a novel strategy that promotes the regio- and stereo-selective transformations of α-amino C–H bonds for the synthesis of propargyl amines. We demonstrate that cooperative actions of $B(C_6F_5)_3$ and an appropriate Cu-based complex might facilitate the generation of iminium ions from an array of *N*-alkylamines, including bioactive molecules and L_nCu–alkynyl complexes from alkynylsilanes. The subsequent C–C bond-forming step would deliver the synthetically versatile and biologically important propargyl amines. This protocol is demonstrated to tolerate a wide range of Lewis acid-sensitive functional groups, thereby suitable for the late-stage functionalization of bioactive amines. Mechanistic studies provide key insights for the establishment of future processes that can promote the diverse functionalization of bioactive amines. Studies aimed at achieving these objectives are currently underway.

Chapter Three

Catalytic Deuterium Incorporation within Metabolically Stable β-Amino C–H Bonds of Drug Molecules

3.1. Introduction

Pharmaceuticals that are labeled with deuterium (^{2}H) or tritium (^{3}H) are essential diagnostic tools in research aimed at determining their biological outcomes and metabolites.[66,67,68] Biologically active compounds that contain hydrogen isotopes possess practically identical physical properties (e.g., boiling point, melting point, optical rotation, ionization efficiency) relative to their isotopologues.[66b] However, due to their difference in molecular weight, deuterium-labeled compounds can be used as internal standards for quantification of complex matrices while accounting for any potential matrix effects that are originated from the eluent-dependent ionization efficiency of the target molecule.[69] On the other hand, tritium-labeled organic molecules are radioactive and have found unique applications in ligand binding assays.[66a-66c] When tritium decays, it generates helium (^{3}He) and detectable β-particles[70] which are often exploited for

---

[66] (a) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007***, 46,* 7744. (b) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem., Int. Ed.* **2018***, 57,* 1758. (c) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem., Int. Ed.* **2018***, 57,* 3022. (d) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. *J. Med. Chem.* **2019**, *62*, 5276. (e) Kopf, S.; Bourriquen, F.; Li, W.; Neumann, H.; Junge, K.; Beller, M. *Chem. Rev.* **2022**, *122*, 6634.

[67] (a) Penner, N.; Klunk, L. J.; Prakash, C. *Biopharm. Drug Dispos.* **2009**, *30*, 185. (b) Miyoshi, S.; Mitsuoka, K.; Nishimura, S. A. in *Radioisotopes—Applications in Bio-Medical Science,* Singh, N., Ed.; InTech–Open Access Publisher, 2011; Chapter 5. (c) Iglesias, J.; Sleno, L.; Volmer, D. A. *Curr. Drug Metab.* **2012**, *13*, 1213.

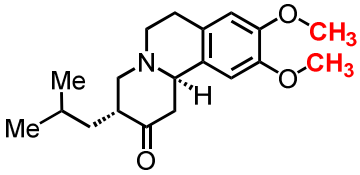
[68] (a) Maltais, F.; Jung, Y. C.; Chen, M.; Tanoury, J.; Perni, R. B.; Mani, N.; Laitinen, L.; Huang, H.; Liao, S.; Gao, H.; Tsao, H.; Block, E.; Ma, C.; Shawgo, R. S.; Town, C.; Brummel, C. L.; Howe, D.; Pazhanisamy, S.; Raybuck, S.; Namchuk, M.; Bennani, Y. L. *J. Med. Chem*. **2009**, *52*, 7993. (b) Allen, P. H.; Hickey, M. J.; Kingston, L. P.; Wilkinson, D. J. *J. Labelled Compd. Rad*. **2010**, *53*, 731. (c) Lockey, W. J. S.; McEwen, A.; Cooke, R. *J. Labelled Compd. Rad.* **2012**, *55*, 235. (d) Elmore, C. S.; Bragg, R. A. *Bioorg. Med. Chem. Lett.* **2015**, *25,* 167.

[69] (a) Stovkis, E.; Rosing, H.; Beijnen, J. H.; *Rapid Commun. Mass Spectrom*. **2005**, *19*, 401 (b) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744. (c) Derdau, V.; Atzrodt, J.; Zimmermann, J.; Kroll, C.; Bruckner, F. *Chem. Eur. J.* **2009**, *15*, 10397.

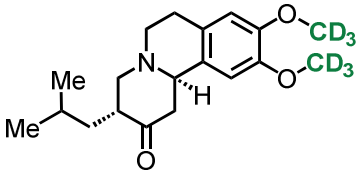
[70] (a) Lappin, G.; Stevens, L. *Expert Opin. Drug Metab. Toxicol*. **2008**, *4*, 1021. (b) Isin, E. M.; Elmore, C. S.; Nilsson, G.; Thompson, R. A.; Weidolf, L. *Chem. Res.Toxicol.* **2012**, *25*, 532. (c) Thompson, R. A.; Isin, E. M.; Li, Y.; Weidolf, L.; Page, K.; Wilson, I.; Swallow, S.; Middleton, B.; Stahl, S.; Foster, A. J.; Dolgos, H.; Weaver, R.; Kenna, J. G. *Chem. Res. Toxicol*. **2012**, *25*, 1616.

studying drugs and their candidates' interactions with the receptors.[71] Another vital incentive to convert the C–H bonds of a drug into C–D bonds is that the deuterated molecule could be more metabolically stable due to the kinetic isotope effect (KIE).[66b] For example, the methoxy groups ($-OCH_3$) of tetrabenazine **3.1**, a drug used for the treatment of chorea associated with Huntington's disease, undergoes cytochrome P450 2D6-mediated oxidation and has a half-life ($t_{1/2}$) of 4.0 h (Scheme **3.1**).[72] However, deutetrabenazine-*d*$_6$ (**3.1-*d*$_6$**), which possesses $-OCD_3$ groups, became the first FDA-approved deuterated drug because its enzymatic oxidation is markedly slower than that of **3.1** ($t_{1/2}$ = 7.6 h). Consequently, the daily dosage **3.1-*d*$_6$** could be reduced to two (versus three dosages required for **3.1**).[72]

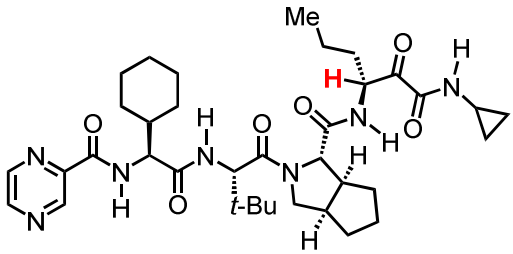
Scheme 3.1. Effects of Deuterium Incorporation on the Properties of the Existing Pharmaceuticals



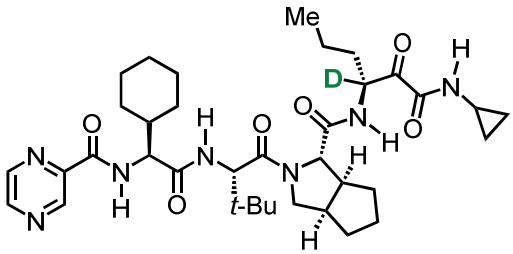
3.1, tetrabenazine
treats chorea
$t_{1/2}$ = 4.0 h
(3 dosages/day)



3.1-*d*$_6$, deutetrabenazine
treats chorea
$t_{1/2}$ = 7.6 h
(2 dosages/day)



3.2, telaprevir
treats hepatitis C
(k_{epi}= 0.020 h^{-1})



3.2-*d*$_1$, telaprevir-*d*$_1$
treats hepatitis C
(k_{epi}= 0.004 h^{-1})

[71] McKinney, M.; Raddatz, R. *Curr. Protoc. Pharmacol*. **2006**, *33*, 131.
[72] Schneider, F.; Bradbury, M.; Baillie, T. A.; Stamler, D.; Hellriegel, E.; Cox, D. S.; Loupe, P. S.; Savola, J.-M.; Rabinovich-Guilatt, L. *Clin. Transl. Sci.* **2020**, *13*, 707.

There are peptide-based drugs, such as telaprevir (**3.2**, hepatitis C protease inhibitor), that often contain base-sensitive α-carbonyl C–H bonds. However, telaprevir-d_1 (**3.2-*d*$_1$**), one of its acidic α-carbonyl C–H bonds is converted into a C–D bond, was found to epimerize at a slower rate (at pH= 7.4: $k_{epi} = 0.020\ h^{-1}$ for **3.2** vs $k_{epi} = 0.004\ h^{-1}$ for **3.2-*d*$_1$**) because of the kinetic isotope effect, resulting in a more efficacious pharmaceutical.[73] As a result, telaprevir-d_1 (**3.2-*d*$_1$**) demonstrated superior plasma stability.

Despite the importance of deuterium- and tritium-labeled bioactive molecules, as described above, the state-of-the-art methods for their preparation often involve cumbersome and wasteful synthesis.[74] A desirable strategy that can circumvent the need for multi-step synthesis for the production of the isotopically labeled compounds is the direct conversion of C–H bonds contained in bioactive molecules into C–D bonds.[1] Despite the recent advances in organometal-catalyzed C–H activation have enabled the direct conversion of C(sp^2)–H into C(sp^2)–D, the isotope exchange reactions at more ubiquitous C(sp^3)–H bonds is a formidable challenge.[66-68]

[73] Maltais, F.; Jung, Y. C.; Chen, M.; Tanoury, J.; Perni, R. B.; Mani, N.; Laitinen, L.; Huang, H.; Liao, S.; Gao, H.; Tsao, H.; Block, E.; Ma, C.; Shawgo, R. S.; Town, C.; Brummel, C. L.; Howe, D.; Pazhanisamy, S.; Raybuck, S.; Namchuk, M.; Bennani, Y. L. *J. Med. Chem*. **2009**, *52*, 7993.

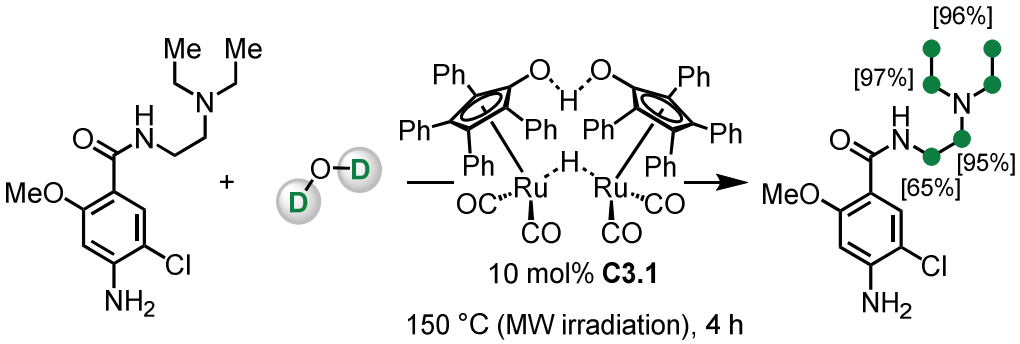
[74] For the multistep synthesis of deuterium-labeled drugs, see: (a) Isin, E. M.; Elmore, C. S.; Nilsson, G. N.; Thompson, R. A.; Weidolf, L. *Chem. Res. Toxicol*. **2012**, *25*, 532. (b) Lockey, W. J. S.; McEwen, A.; Cooke, R. *J. Labelled Comp. Radiopharm*. **2012**, *55*, 235. (c) *Preperation of Compounds Labeled with Tritium and Carbon-14:* Voges, R.; Heys, R.; Moenius, T. Eds.; John Wiley & Sons: Hoboken, 2009. (d) Allen, P. H.; Hickey, M. J.; Kingston, L. P.; Wilkinson, D. J. *J. Labelled Comp. Radiopharm*. **2010**, *53*, 731. (e) Elmore, C. S.; Bragg, R. A. *Bioorg. Med. Chem. Let.* **2015**, *25,* 167. (f) Elmore, C. S. *Annu. Rep. Med. Chem*. **2009**, *44*, 515.

3.2. Background

Bioactive compounds that contain an *N*-alkylamine unit constitute over 50% of the top-selling commercial pharmaceuticals.[75] Therefore, HIE reactions targeting amino C(sp^3)–H bonds of N-based pharmaceuticals could provide a general strategy for the isotopic labeling of a broad array of drugs; the resulting products could be readily utilized as tags or internal standards for the detection and quantification of the drug molecule or its' metabolites.[66a-c]

In order to achieve a highly efficient deuteration protocol for the labeling of amine-containing pharmaceuticals, the Beller group reported the catalytic HIE reaction of α- and β-amino C–H bonds of bioactive tertiary amines (Scheme 3.1).[76] When Ru-based Shvo's catalyst **C3.1** and 1600 equivalent of D_2O **3.4** were reacted with metoclopramide (**3.3**, used for the treatment of heartburn) at 150 °C, α- and β-amino C–H bonds of **3.3** were converted into C–D bonds, affording **3.5** with up to 97% *d*-incorporation.

Scheme 3.2. α- and β-Amino C–H Deuteration Promoted by Shvo's Catalyst



3.3 metoclopramide

3.4, 1600 equiv.

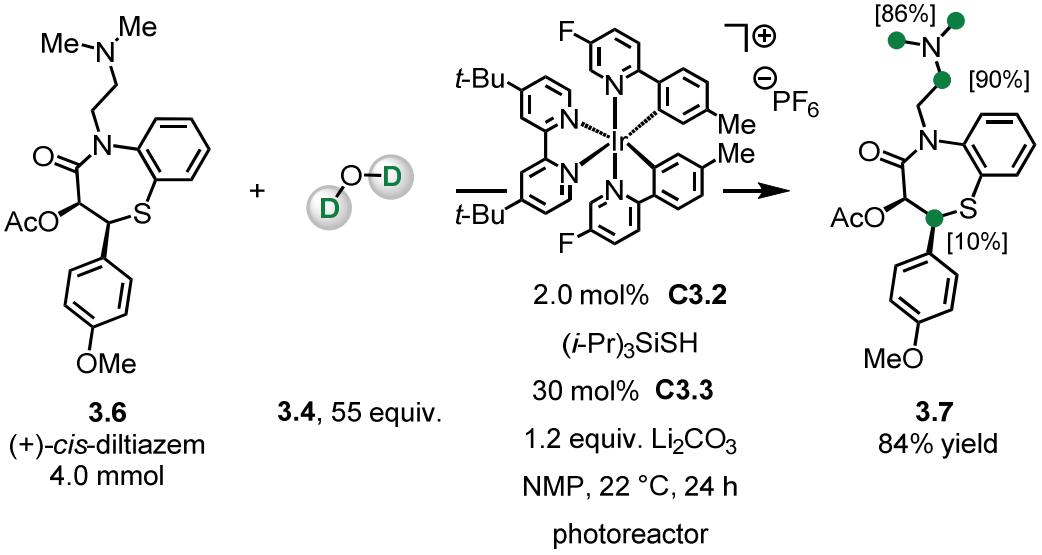
3.5, 83% yield

A method for the C–H deuteration and tritiation of bioactive amines has been developed by the MacMillan group, which employs an Ir-based photoredox catalyst **C3.2** in combination with

[75] McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348.
[76] Neubert, L.; Michalik, D.; Bahn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 12239.

thiol catalyst **C3.3** (Scheme 3.3).[77] With (+)-*cis*-diltiazem (**3.6**, treatment of cardiovascular diseases) deuterated product **3.7** can be obtained in 84% yield under blue LED irradiation. The spectroscopic analyses revealed that while up to 90% of the α-amino C–H bonds were converted into C–D bonds, 10% of the benzylic C–H bond of **3.6** also underwent *d*-incorporation.

Scheme 3.3. Photoredox-Mediated Deuteration and Tritiation of N-Based Drugs



The recent advances in the field of C–H bond functionalization have enabled the development of new HIE technologies that can be utilized for the isotopic labeling of metabolically labile α-amino C–H bonds of various bioactive amines (Scheme 3.2 and 3.3). [78] We envisioned that there may be a great practical significance if a complementary method that selectively converts metabolically stabile β-amino C–H bonds of polyfunctional *N*-alkylamines, including N-based pharmaceuticals, into C–D bonds is developed while using an inexpensive deuterium source and nonprecious metal-based catalysts.

---

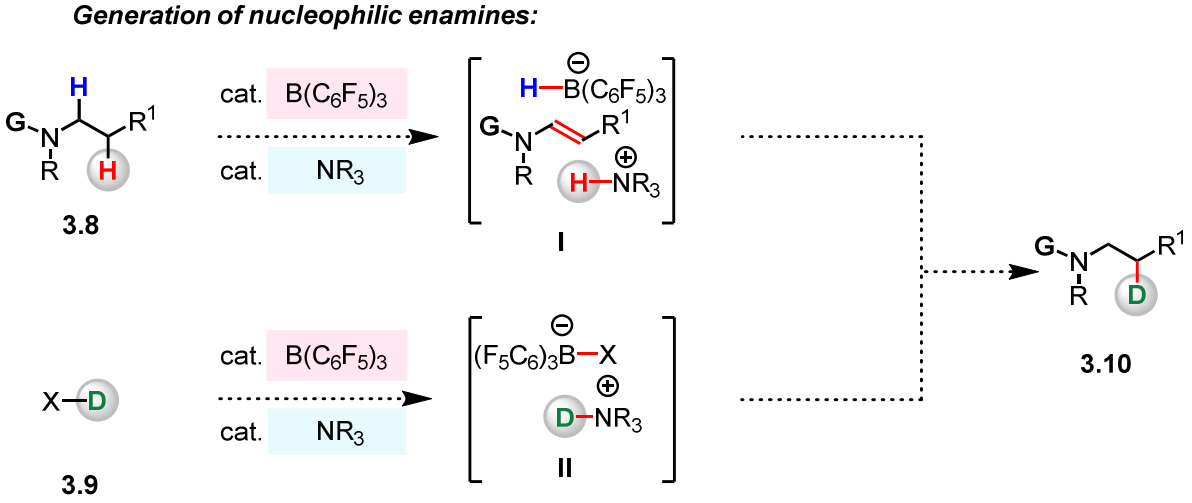
[77] Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C. *Science* **2017**, *358*, 1182.

[78] (a) Markey, S. P. in Principles of Clinical Pharmacology, 2nd ed.; Atkinson, A.J.; Abernethy, D. R.; Daniels, C.E.; Dedrick, R.L.; Markey, S.P. Eds.; Academic Press: Burlington, 2007; Chapter 11. (b) Trager, W. F. in Comprehensive Medicinal Chemistry II, Taylor, J. B.; Triggle, D. J. Eds.; Elsevier, 2007; Volume 5.

3.3. Our Approach

We envisioned the development of a catalyst system that can promote the transformation of β-amino C(sp^3)–H bonds into C–D bonds (Scheme 3.4). Based on previous reactions reported in the field of β-amino C–H activation by $B(C_6F_5)_3$,[79] we envisioned sterically hindered and highly Lewis acidic $B(C_6F_5)_3$ could catalyze the conversion of *N*-alkylamines into enamines (**3.8** → **I**). In the meantime, cooperative action $B(C_6F_5)_3$ and a base co-catalyst furnishes an electrophilic deuterating reagent $[D–NR_3]^+$ through deprotonation of Lewis acid-activated deuterium source (**3.9** →**II**). The ensuing reaction of **I** and **II** affords amines possessing β-amino C(sp^3)–D bonds (**3.10**).

Scheme 3.4. Generation of Enamines and Electrophilic Deuteration Reagent

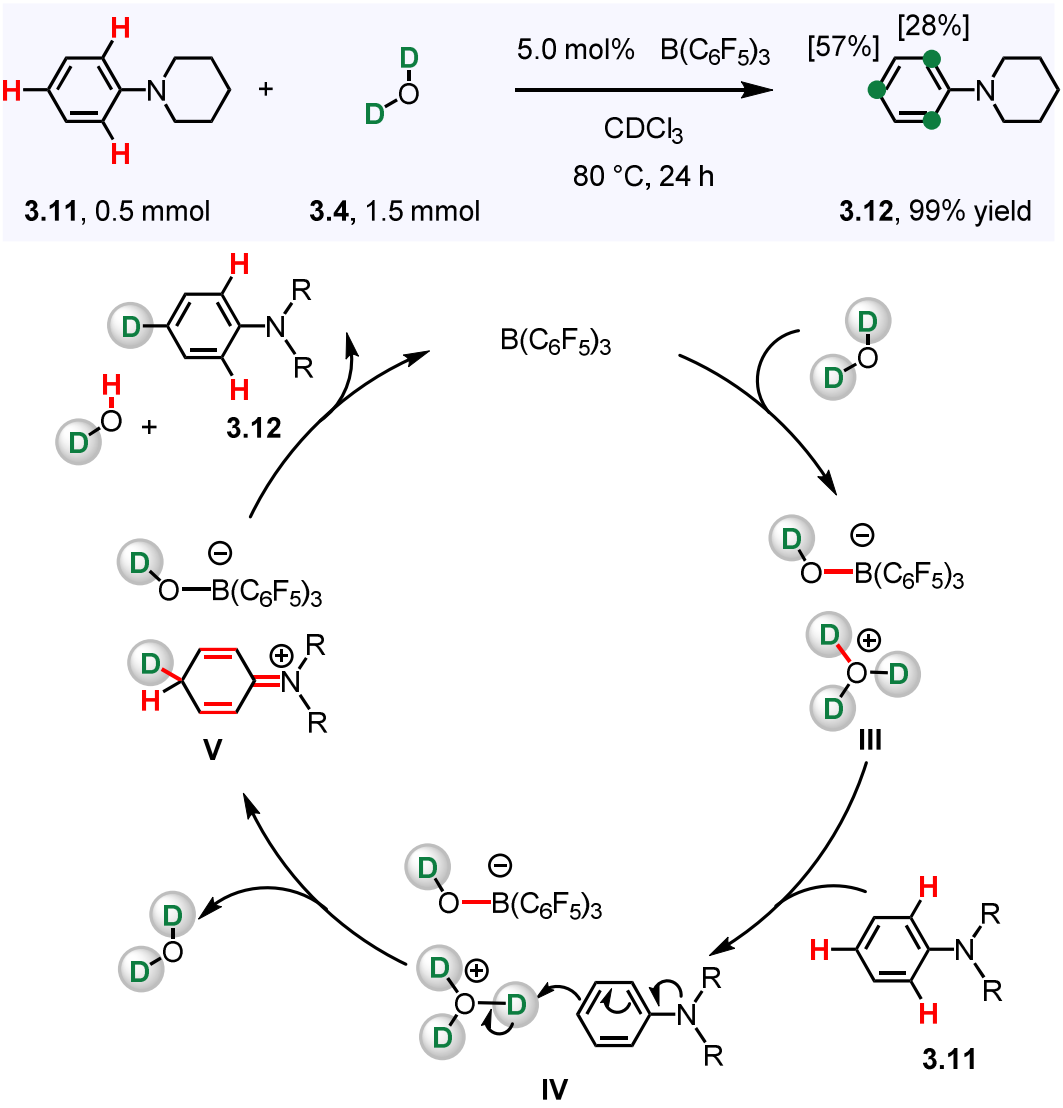


Next, we studied the literature precedents for $(F_5C_6)_3B$-catalyzed electrophilic deuteration reactions. In 2017 the group of Werner reported the conversion of aromatic C–H bonds into C–D

[79] (a) Di Saverio, A.; Focante, F.; Camurati, I.; Resconi, L.; Beringhelli, T.; D'Alfonso, G.; Donghi, D.; Maggioni, D.; Mercandelli, P.; Sironi, A. *Inorg. Chem.* **2005**, *44*, 5030–5041. (b) Farrell, J. M.; Heiden, Z. M.; Stephan, D. W. *Organometallics* **2011**, *30*, 4497–4500. (c) Maier, A. F. G.; Tussing, S.; Schneider, T.; Flörke, U.; Qu, Z.-W.; Grimme, S.; Paradies, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 12219–12223. (c) Kojima, M.; Kanai, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 12224–12227.

bonds using D_2O **3.4** (Scheme 3.15).[80] Using this protocol, ortho- and para- C(sp^2)–H bonds of 1-phenylpiperidine **3.11** underwent deuterium incorporation. The proposed mechanism involves the

Scheme 3.5. $(F_5C_6)_3B$-Catalyzed HIE of Electron-Rich Aromatic C(sp^2)–H



reaction of D_2O and $B(C_6F_5)_3$ to generate an ion pair of $[(C_6F_5)_3B–OD]^-$ and D_3O^+ (**III**). Subsequently, an electrophilic aromatic substitution reaction between aniline **3.11** and D_3O^+ takes

[80] Li, W.; Wang, M.-M.; Hu, Y.; Werner, T. *Org. Lett.* **2017**, *19*, 5768.

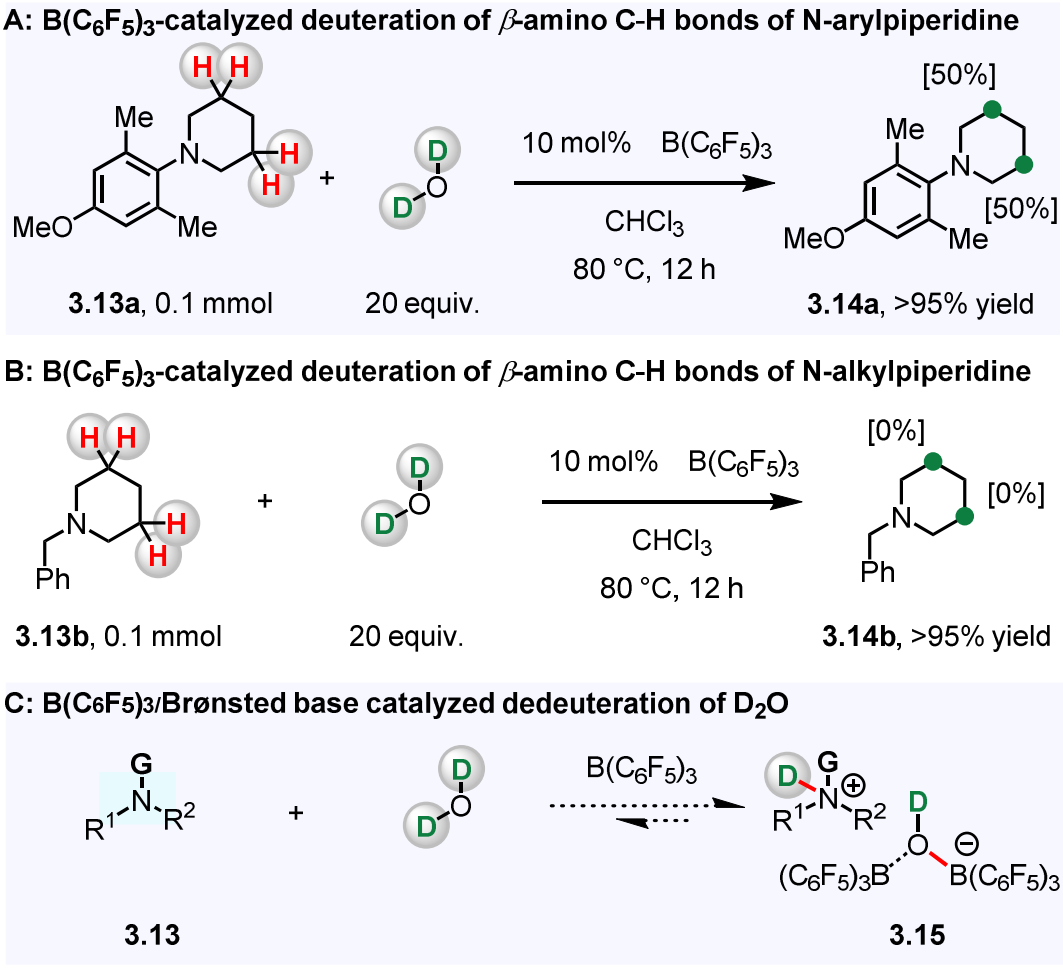
place to afford V. Ensuing deprotonation of **V** by $[(C_6F_5)_3B–OD]^-$ results in the formation of **3.12** and H–OD, while regenerating $B(C_6F_5)_3$ catalyst.

Based on the reactivities described in the aforementioned seminal studies (Schemes 3.5),[80-81] we hypothesized that various *N*-alkylamines **3.13** could be converted into enamines through the cooperative actions of $B(C_6F_5)_3$ and an appropriate Brønsted base catalyst. Furthermore, an electrophilic deuterating agent may be generated in situ by the reaction of $B(C_6F_5)_3$ and D_2O. Our initial studies involving the reaction of 1-(4-methoxy-2,6-dimethylphenyl)piperidine **3.13a** with 10 mol % of $B(C_6F_5)_3$ and 20 equivalents of D_2O in CH_2Cl_2 at 80 °C afforded **3.14a** with 50% *d*-incorporation (Scheme 3.6A). However, with trialkylamines such as 1-benzylpiperidine piperidine **3.13b**, β-amino C–H deuteration did not proceed (Scheme 3.6B). It is known that $B(C_6F_5)_3$ reacts with D_2O in the presence of a trialkylamine to afford an isolable ionic complex $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-[H–NR_3]^+$ (**3.15**, Scheme 3.6C).[81] With more Brønsted basic **3.13b** (vs less basic *N*-arylamine **3.13a**), **3.15** may form more efficiently, thereby inhibiting the desired $(F_5C_6)_3B$-catalyzed iminium formation from **3.13b,** and the subsequent enamine generation.

To overcome catalyst deactivation and promote the catalytic deuteration protocol, we envisioned that less basic *N*-alkylamines could be utilized as the substrate (i.e.; **3.13a**), or alternatively, a less base-sensitive deuterium source may be exploited. Since the specific aim of our approach is to develop a general and broadly applicable deuteration method for bioactive amines, which often contain basic *N*-alkylamine moiety, we started to investigate the suitability of the less acidic deuterium sources.

[81] Di Saverio, A.; Focante, F.; Camurati, I.; Resconi, L.; Beringhelli, T.; D'Alfonso, G.; Donghi, D.; Maggioni, D.; Mercandelli, P.; Sironi, A. *Inorg. Chem*. **2005**, *44*, 5030.

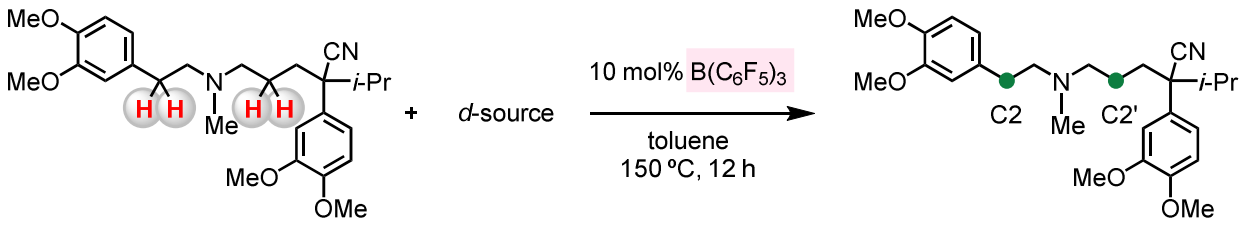
Scheme 3.6. *β*-Amino C–H Deuteration and Potential Catalyst Deactivation



Using verapamil (**3.13c**, calcium channel blocker) as a model substrate, we started to evaluate various alcohols as deuterium sources in the presence of 10 mol % $B(C_6F_5)_3$ (Table 3.1). Treatment of **3.13c** with D_2O, as expected, resulted in the full recovery of the starting material with less than 5% *d*-incorporation (entry 1, Table 3.1). We then probed the ability of deuterated alcohols to serve as a labeling agent. When the transformation was performed with 6.8 equivalent MeOD or isopropanol-d_8, up to 21% of both benzylic C2–H and non-benzylic C2'–H bonds were converted to C–D bonds (entries 2 and 3). In line with the hypothesis, with 6.8 equivalent of sterically more hindered *t*-BuOD, 63% of C2–H bonds and 58% of C2'–H bonds underwent H/D exchange (entry 4). When we increased the amount of *t*-BuOD to 41 equivalents, the deuteration

reaction did not occur (entry 5). This observation suggests that even sterically hindered alcohols can inhibit $B(C_6F_5)_3$ through undesirable acid-base complexation when added in excess quantity. Based on these findings, we surmised that using deuterium sources that is less base-sensitive than D_2O or *d*-alcohol, which contains multiple accessible D atoms per molecule, an efficient HIE reaction within metabolically stable β-amino C–H bonds of drug molecules can be achieved.

Table 3.1. Evaluation of Deuterated Alcohols as the Deuterium Source



3.13c, verapamil
(calcium channel blocker)

3.14c

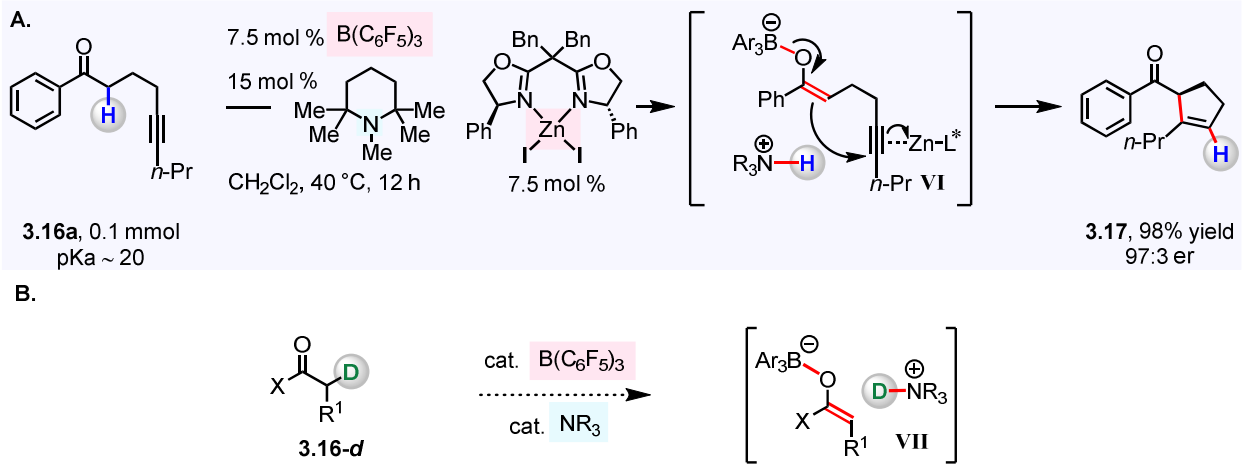
entry	*d*-source	equiv. of *d*-source	*d*-incorporation (%) [C2]	[C4]
1	D_2O	6.8	0	0
2	CH_3OD	6.8	14	20
3	$(CD_3)_2CDOD$	6.8	17	21
4	*t*-BuOD	6.8	63	58
5	*t*-BuOD	40.8	0	0

Our group has previously demonstrated that cooperative Lewis acid and base catalysts can promote Conia-ene-type cycloaddition reaction of monocarbonyl compounds (e.g., **3.16a**) through the deprotonation of less base-sensitive α-carbonyl C–H bonds to in situ generate enolate and ammonium (**VI**; Scheme 3.7a).[82] Based on this finding, we surmised that we could utilize α-

[82] Chang, Y.; Yesilcimen, A.; Cao, M.; Zhang, Y.; Zhang, B.; Chan, J. Z.; Wasa, M. *J. Am. Chem. Soc.* **2019**, *141*, 14570.

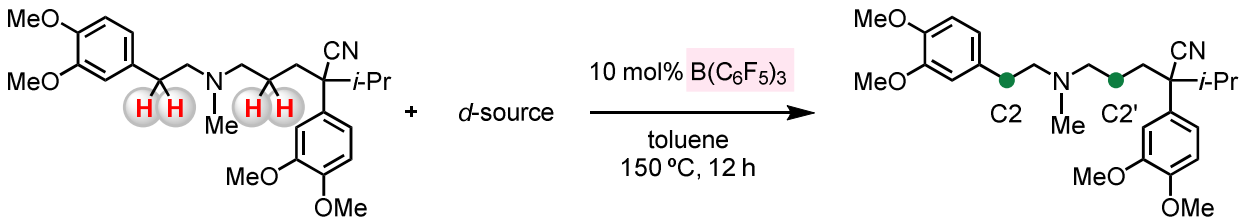
deuterated monocarbonyl compounds **3.16*d***, which have a higher pK_a value than that of D_2O or alcohols, as the deuterium source (Scheme 3.7B). Through the use of $B(C_6F_5)_3$ and *N*-alkylamine, $[R_3N–D]^+$ can be formed in situ and might serve as an electrophilic deuterating reagent (**VII**). Another advantage of this strategy is that by using carbonyl compounds, which can carry multiple α-carbonyl C–D bonds, as the deuterating reagent, we might avoid the use of an excessive amount of deuterium sources and prevent the inhibition of $B(C_6F_5)_3$ through undesirable acid-base complexation with the excess deuterium source.

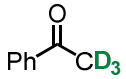
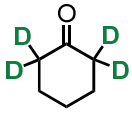
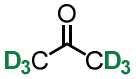
Scheme 3.7. Deuteration of β-Amino C–H Bonds Using Carbonyl Compounds



A series of ketones that contain α-C–D bonds were synthesized and evaluated as deuterium sources for HIE reactions at the β-amino C–H of verapamil (Table 3.2). In line with our hypothesis, when **3.13c** was treated with 6.8 equivalent of acetophenone-d_3 in the presence of 10 mol % $B(C_6F_5)_3$, an improved *d*-incorporation level of up to 79% was observed (entry 1). When cyclohexanone-d_4 was utilized as the deuterium source, **3.14c** was obtained with a lower *d*-incorporation, probably due to its higher pK_a compared to acetophenone (entry 2). Lastly, the use of acetone-d_6, a commercially available and readily accessible reagent containing up to 6 D atom/molecule, resulted in labeling the **3.14c** with >90% of *d*-incorporation (entry 3).

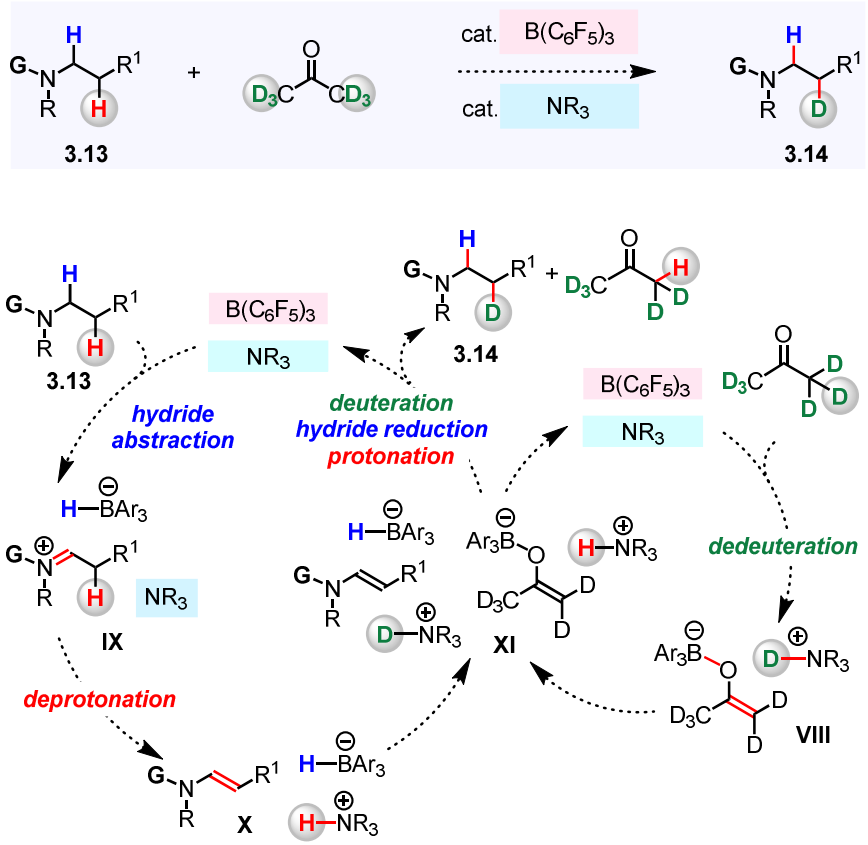
Table 3.2. Evaluation of Ketones as Deuterium Source for *β*-Amino C–H Deuteration of Verapamil



entry	*d*-source	D/molecule	*d*-incorporation (%) [C2]	[C4]
1		3	79	71
2		4	45	50
3		6	90	92

Based on these observations, we proposed an efficient and *β*-selective deuteration of *N*-containing bioactive molecules can be achieved while using *α*-deuterated ketones as the deuterium source. Through the use of $B(C_6F_5)_3$ and Brønsted basic *N*-alkylamine *α*-deuterated ketones can be dedeuterated to generate an ion pair containing a deuterated ammonium ion $[D–NR_3]^+$ (**VIII**, Scheme 3.8). Meanwhile, amine **3.13** can be converted into an iminium ion (**IX**) and then to an enamine (**X**) through $(F_5C_6)_3B$-catalyzed hydride abstraction and base-catalyzed deprotonation. Ensuing deuteration of the enamine by $[D–NR_3]^+$ would generate *β*-deuterated amines (**XI** → **3.14**).

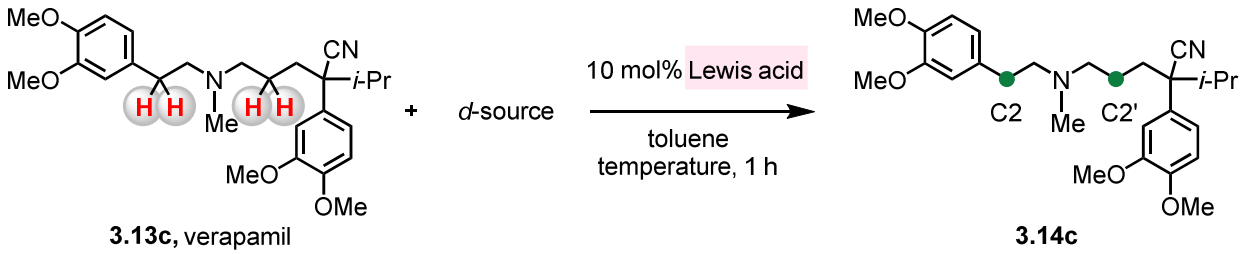
Scheme 3.8. Proposed Mechanism for $(F_5C_6)_3B$-Catalyzed *β*-Amino C–H Deuteration



Having found that acetone-d_6 is the optimal deuterium source, we next evaluated different reaction parameters to further improve reaction efficiency (Table 3.3). It was found that we can observe a high level of *d*-incorporation only after 1 hour (entry 1). 5.0 Mol % of $B(C_6F_5)_3$ was able to catalyze the *β*-selective deuteration of **3.13c**, albeit with a diminished *d*-incorporation level (entry 2). The reaction temperature of 150 °C was found to be critical; when the deuteration protocol was run at 125 °C, and 100 °C deuterium incorporation drastically decreased to ≤35% (entries 3–4). However, by reacting **3.13c** with two batches of 5.0 mol % of $B(C_6F_5)_3$ and acetone-d_6 (6.8 equivalent), we were able to obtain **3.14c** with >95% labeling (entry 5). Conversion of C–H

bonds to C–D bonds was not observed in the absence of $B(C_6F_5)_3$ (entry 6). Moreover, sterically more exposed BF_3, or the less Lewis acidic BPh_3 as the Lewis acid catalyst inhibited the reactivity (entries 7–8). These findings are consistent with the central hypothesis that electronically disparate and sterically hindered Lewis acidic $B(C_6F_5)_3$ and Brønsted basic *N*-alkylamines constitute the most potent pair of catalysts.

Table 3.3. Evaluation of Reaction Parameters[a,b,c]



3.13c, verapamil
(calcium channel blocker)

3.14c

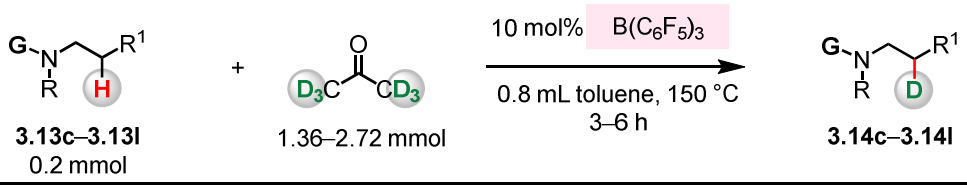
entry	Lewis acid (mol%)	temperature (°C)	*d*-incorporation (%) [C2]	[C4]
1	$B(C_6F_5)_3$ (10)	150	88	92
2	$B(C_6F_5)_3$ (5.0)	150	80	85
3	$B(C_6F_5)_3$ (5.0)	125	21	35
4	$B(C_6F_5)_3$ (5.0)	100	<5	7
5[d]	$B(C_6F_5)_3$ (5.0 x 2)	150	95	>98
6	none	150	0	0
7	BF_3•OEt_2 (5.0)	150	0	0
8	BPh_3 (5.0)	150	0	0

[a] Conditions: verapamil (**3.13c,** 0.1 mmol), acetone-d_6 (0.68 mmol), organoborane, toluene (0.4 mL), under N_2, 1 h. [b] Yield and deuterium incorporation level was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. [c] Green label indicates sites that are beta to N. [d] Conditions: verapamil (**3.13c,** 0.2 mmol), acetone-d_6 (1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 1 h. Isolated and purified **3.14c** was reacted with acetone-d_6 (1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 1 h.

Using the optimized conditions, an array of acyclic amine-containing drug molecules with *β*-amino C−H bonds (**3.13c**−**3.13l**, Table 3.4) were shown to be efficient substrates for this deuteration process. On top of basic *N*-alkyamines moiety (**3.13c**−**3.13l**), other Lewis acid-sensitive functional groups such as cyano (**3.13c**), ether (**3.13c, 3.13d**, **3.13l**), ester (**3.13e**), amide (**3.13f**, **3.13g**, **3.13j**) and ketone (**3.13l**) groups were tolerated to afford the resulting *d*-analogous **3.14c**–**3.14l** in 77 to >95% yield after purification and isolation by silica gel chromatography. Although highly regioselective deuteration of *β*-amino C−H bonds was achieved, drug molecules that contain base-sensitive *α*-carbonyl C–H bonds also underwent efficient HIE reaction based on the analysis of ^{1}H NMR spectra of unpurified mixtures (**3.13g**, **3.13l**). For the substrates that bear electronically and sterically distinct *β*-amino C−H bonds, different levels of *d*-incorporation were observed (**3.13c–3.13e, 3.13h–3.13j**). For instance, for verapamil **3.13c**, deuteration of non-benzylic C2'–H bonds was more efficient in comparison to benzylic C2–H. Moreover, C2'–H bonds on *N*-ethyl groups of clomiphene **3.13d** and dicyclomine **3.13e** underwent more efficient deuteration (90%) than C2–H bonds (15 and 23%).

Although *β*-amino C–H deuteration strategy is tolerant of functional groups commonly present in the bioactive amines, *d*-incorporation was more efficient with substrates bearing protecting groups. For example, lidocaine **3.13f**, which contains base-sensitive amide N–H bond, underwent C−H to C–D exchange to afford **3.14f** with 80% *d*-incorporation. Yet, deuteration of *N*-benzyl-protected lidocaine **3.13g** occurred more efficiently to afford the desired product **3.14g** with 96% deuterium incorporation. Similarly, while cinacalcet **3.13h** containing a secondary amine unit was found to be a compatible substrate, the level of the *d*-incorporation was drastically improved upon *N*-protection with the benzyl group (**3.14i**, 98% *d*-incorporation). On top of C2−H bonds and C2'−H bonds at the *N*-propyl group of ropinirole **3.13j**, *α*-carbonyl C–H bonds

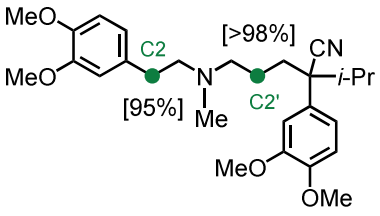
Table 3.4. Deuteration of Acyclic β-Amino C−H Bonds



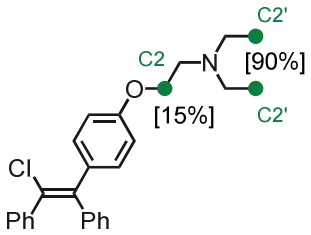
3.13c–3.13l
0.2 mmol

1.36–2.72 mmol

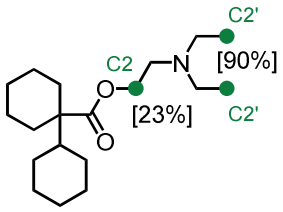
3.14c–3.14l



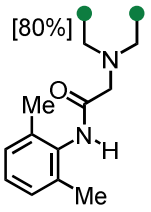
3.14c, verapamil
(calcium channel blocker)
92% yield[d]



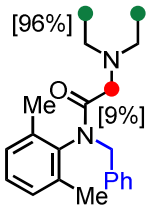
3.14d, clomiphene
(ovulatory stimulant)
>95% yield



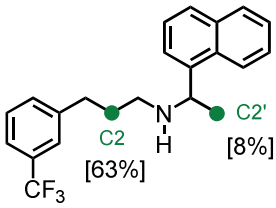
3.14e, dicyclomine
(anticholinergics)
>95% yield



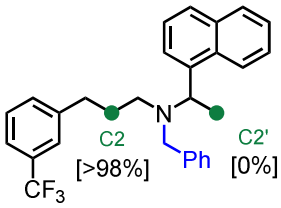
3.14f, lidocaine
(local anesthetic)
>95% yield



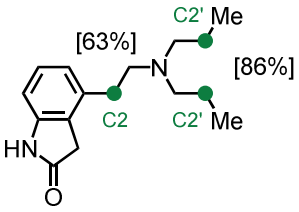
3.14g, *N*-Bn lidocaine
(local anesthetic)
>95% yield[d]



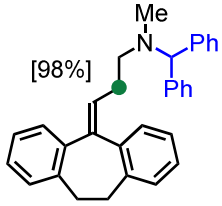
3.14h, cinacalcet
(calcimimetic)
>95% yield



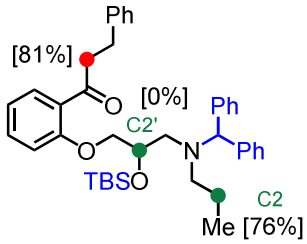
3.14i, *N*-Bn cinacalcet
(calcimimetic)
>95% yield[d]



3.14j, ropinirole
(Parkinson's disease)
77% yield[e]



3.14k, *N*-Bzh nortriptyline
(antidepressant)
>95% yield[d]



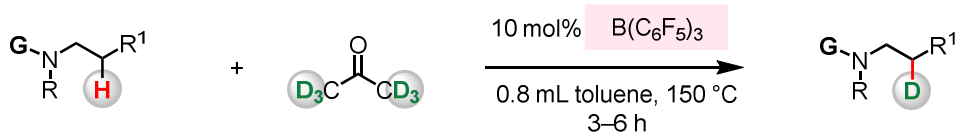
3.14l, *N*-Bzh, *O*-TBS propafenone
(antiarrhythmic agent)
92% yield

[a] Conditions: *N*-alkylamine (**3.13**, 0.2 mmol), acetone-d_6 (1.36 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. [b] Yield of isolated and purified product. Deuterium incorporation level was determined by ^1H NMR analysis of the isolated and purified product. [c] Green label indicates sites that are beta to N. Red label is used for any other sites that undergo deuteration. Blue color indicates protecting groups. [d] Conditions: *N*-alkylamine (**3.13**, 0.2 mmol), acetone-d_6 (1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. After the filtration of the crude reaction mixture through a pad of silica gel and removal of volatiles, acetone-d_6 (1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), and toluene (1.0 mL) were added under N_2, and then heated at 150 °C, 3 h. [e] The reaction was carried out in two batches, using 10 mol% of $B(C_6F_5)_3$ in the first batch, and 5.0 mol% in the second.

transformed into corresponding C–D bonds. Nevertheless, α-carbonyl C–D bonds underwent loss of label through D–H exchange during purification by silica gel column chromatography; **3.14j** was afforded in 77% yield with 63% and 86% *d*-incorporation at C2 and C2' positions, respectively. Protection of secondary alcohol and/or amine units of nortriptyline **3.13k** and propafenone **3.13l** was crucial. Trisubstituted alkene containing *N*-Bzh nortriptyline **3.13k** could undergo hydrogen isotope exchange reaction with no detectable olefin isomerization to afford **3.14k** in nearly quantitative yield with 98% *d*-incorporation. After the installation of *N*-benzhydryl and *O*-TBS groups, 76% of the C–H bonds of propafenone derivative **3.13l** were converted into C–D bonds.

We then investigated the isotopic labeling of cyclic bioactive amines (Table 3.5; **3.13m**–**3.13u**). An assortment of Lewis acid-sensitive heterocycles that are contained in cyclic amines such as piperidine (**3.13m–3.13s**), 1,4-diazepane (**3.13t**), piperazine (**3.13u**), thiophene (**3.13m**, **3.13n**, and **3.13s**), indanone (**3.13o**), benzodioxole (**3.13q**, **3.13r**), as well as benzoimidazole (**3.13t**) are found to be compatible substrates for the β-amino C–H deuteration protocol and underwent efficient H/D exchange (14–98% *d*-incorporation). For bioactive amines that carry base-sensitive α-carbonyl C–H bonds such as clopidogrel **3.13m**, prasugrel **3.13n**, and donepezil **3.13o**, α-carbonyl C–H bonds underwent efficient deuteration together with β-amino C–H bonds to give **3.14k**–**3.14m**. However, the acidic α-keto C–D bond of **3.14k** underwent loss of label during the purification by silica gel chromatography. Sterically congested α-carbonyl C–H bonds in bupivacaine **3.13p** were not transformed into C–D bonds. When both acyclic and cyclic β-amino C–H bonds are present in the *N*-containing pharmaceuticals (**3.13p**, **3.13s**), deuteration of the cyclic C–H bond was more efficient (up to 90%) in comparison to acyclic C–H bonds (up to 29%). For paroxetine, *N*-benzhydryl protection was crucial to obtain **3.14r** with a

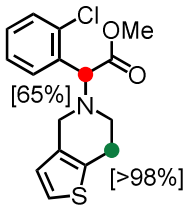
Table 3.5. Deuteration of Cyclic *β*-Amino C−H Bonds



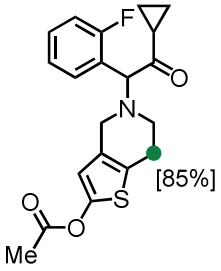
3.13m–3.13u
0.2 mmol

1.36–2.72 mmol

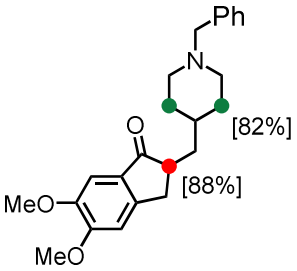
3.14m–3.14u



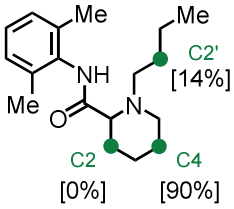
3.14m, clopidogrel (antiaggregant)
94% yield[d]



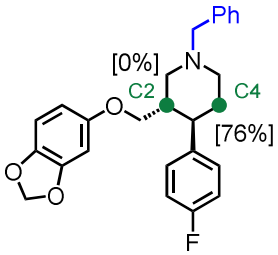
3.14n, prasugrel (antiaggregant)
85% yield[e]



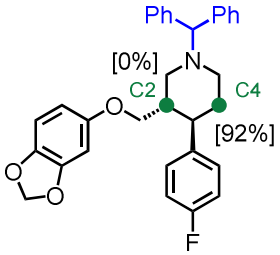
3.14o, donepezil (anti-Alzheimer)
>95% yield



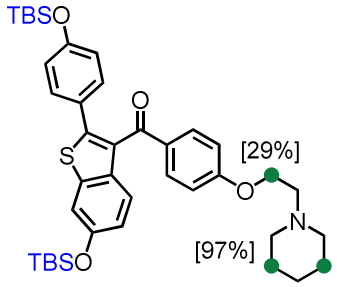
3.14p, bupivacaine (local anesthetic)
>95% yield



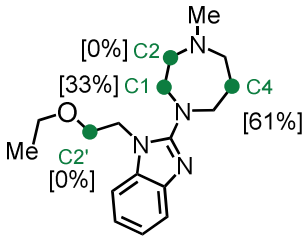
3.14q, *N*-Bn paroxetine
(antidepressant)
>95% yield



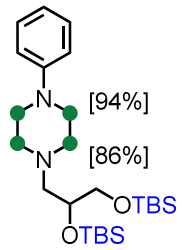
3.14r, *N*-Bzh paroxetine
(antidepressant)
95% yield



3.14s, *O*-TBS raloxifene
(treats osteoporosis)
>95% yield



3.14t, emedastine
(antihistamine)
88% yield



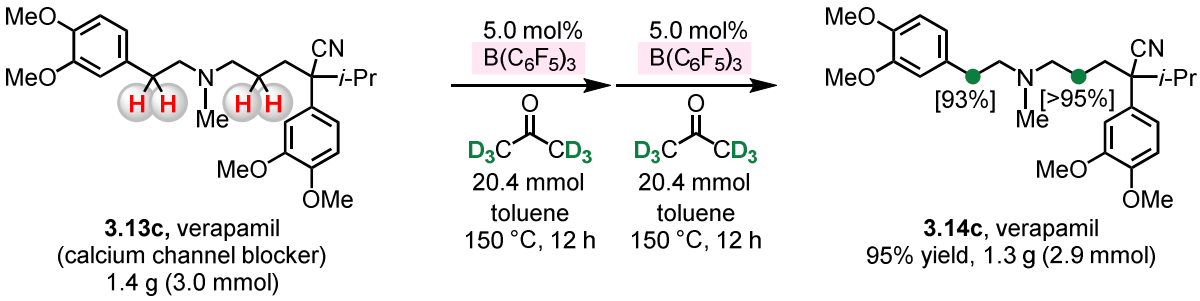
3.14u, *O*-TBS dropropizine
(cough suppressant)
94% yield[d]

[a] Conditions: *N*-alkylamine (**3.13**, 0.2 mmol), acetone-d_6 (1.36 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. [b] Yield of isolated and purified product. Deuterium incorporation level was determined by ^1H NMR analysis of the isolated and purified product. [c] Green label indicates sites that are beta to N. Red label is used for any other sites that undergo deuteration. Blue color indicates protecting groups. [d] Conditions: *N*-alkylamine (**3.13**, 0.2 mmol), acetone-d_6 (1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. After the filtration of the crude reaction mixture through a pad of silica gel and removal of volatiles, acetone-d_6 (1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), and toluene (1.0 mL) were added under N_2, and then heated at 150 °C, 3 h. [e] The reaction was carried out in two batches, using 10 mol% of $B(C_6F_5)_3$ in the first batch, and 5.0 mol% in the second.

higher *d*-incorporation level (92%); less hindered *N*-benzyl-protected **3.13q** was afforded the desired product **3.14q** with only 76% *d*-incorporation. Furthermore, the tertiary C2–H bond remained intact for both **3.13q** and **3.13r**. With emedastine (**3.13t**), deuteration was detected at C1−H (33% *d*-incorporation) and C4−H (61% *d*-incorporation) bonds. All eight distinct C−H bonds of the piperazine ring of *O*-TBS-protected dropropizine (**3.13u**) underwent deuteration to afford **3.14u** (>86% *d*-incorporation).

The protocol is scalable, as demonstrated by the gram scale reaction of verapamil **3.13c** (1.4 g, 3.0 mmol; Scheme 3.9). By treating **3.13c** with 5.0 mol % $B(C_6F_5)_3$, 20.4 mmol of acetone-d_6, followed by filtration through a pad of silica gel and repeating the procedure mentioned above, **3.14c** was obtained in 95% yield (2.9 mmol, 1.3 g) with >93% *d*-incorporation.

Scheme 3.9. Scale-Up Experiment



3.13c, verapamil
(calcium channel blocker)
1.4 g (3.0 mmol)

3.14c, verapamil
95% yield, 1.3 g (2.9 mmol)

3.4. Conclusions and Future Outlook

In brief, we have established an efficient and regioselective HIE protocol that utilizes the cooperative action of $B(C_6F_5)_3$ and *N*-alkylamine for the isotopic labeling of β-amino C–H bonds contained in various bioactive compounds. We have demonstrated that through sequential hydride abstraction and deprotonation of *N*-containing pharmaceuticals, corresponding enamine intermediates can be generated in situ. Subsequent reaction of the enamines with an electrophilic deuterating agent that is in situ generated from readily accessible acetone-d_6 would afford the desired *d*-labeled bioactive amines.

The principles outlined in this chapter provide a new rational basis for the development of processes applicable to the late-stage stereoselective β-amino C–H functionalization of bioactive amines.[83]

[83] Chang, Y.; Cao, M.; Chan, J. Z.; Zhao, Y.; Wang, Y.; Wasa, M. *J. Am. Chem. Soc.* **2021**, *143*, 2441–2455.

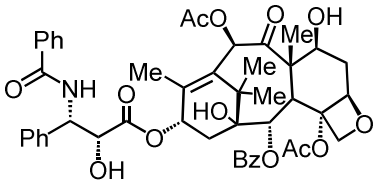
Chapter Four

Enantioselective Organocopper-Catalyzed Hetero Diels–Alder Reactions through in Situ Oxidation of Ethers into Enol Ethers

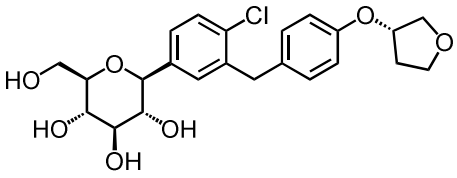
4.1. Introduction

Chiral ethers are essential building blocks of various natural products and pharmaceuticals (Scheme 4.1). While approximately 20% of the FDA-approved drug molecules contain at least one chiral ether unit, ethers with vicinal stereogenic centers represent the most prominent subclass of ether-containing drugs.[84] Such motifs are often synthesized through stereoselective reactions of enol ethers that require cumbersome and wasteful preparation.[85] Moreover, there are only a limited number of enol ethers that are readily available. Therefore, catalyst systems that directly convert ubiquitous, otherwise stable, and easy-to-handle starting materials into such versatile intermediate for the synthesis of chiral ethers with high enantiopurity, still remain underdeveloped

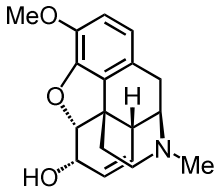
Scheme 4.1. Importance of Bioactive Ethers Containing Vicinal Stereogenic Centers



taxol
chemotherapy medication



empagliflozin
treats diabetes



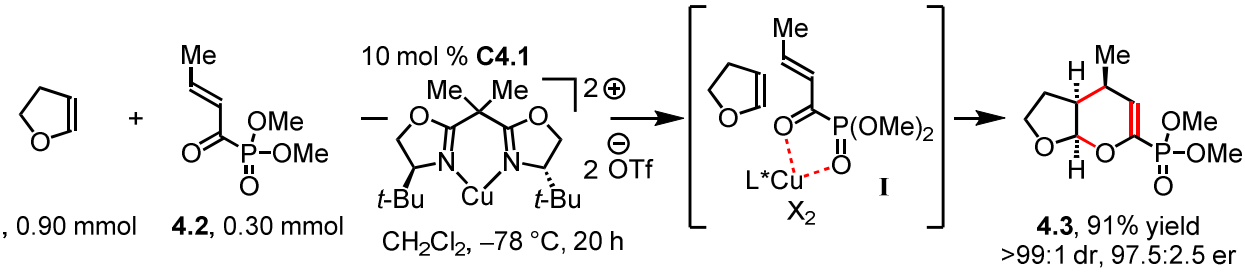
codeine
treats pain

[84] Delost, M. D.; Smith, D. T.; Anderson, B. J.; Njardarson, J. T. *J. Med. Chem*. **2018**, *61*, 10996−11020.
[85] (a) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986-990. (b) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681−1683. (c) Khan, R. K. M.; O'Brien, R. V.; Torker, S.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2012**, *134*, 12774−12779.

4.2. Background

Enantiomerically enriched ethers containing single or vicinal stereogenic centers at the α- and/or β-oxy positions can be synthesized through enantio- and diastereoselective hetero Diels-Alder reactions of enol ethers.[86] One representative example was demonstrated by Evans and co-workers that [(*S*,*S*)-*t*-BuBOX–Cu](OTf)$_2$ complex **C4.1** promotes the efficient and enantioselective inverse electron-demand hetero Diels-Alder reaction of α,β-unsaturated acyl phosphonates **4.2** (Scheme 4.2) and 2,3-dihydrofuran **4.1**, affording dihydropyran **4.3** with vicinal stereogenic centers in 91% yield and 97.5:2.5 er as a single diastereomer.[87]

Scheme 4.2. Enantioselective Synthesis of Ethers through Hetero Diels-Alder Reaction



Although this approach provides a valuable strategy for synthesizing enantiomerically enriched ether molecules, there are key limitations that need to be addressed. Specifically, this protocol requires the use of pre-made enol ethers. However, only a limited number of enol ethers are readily available. Also, methods that allow access to the production of enol ethers often necessitate the preparation and purification of pre-activated starting materials.[88] As a result, the

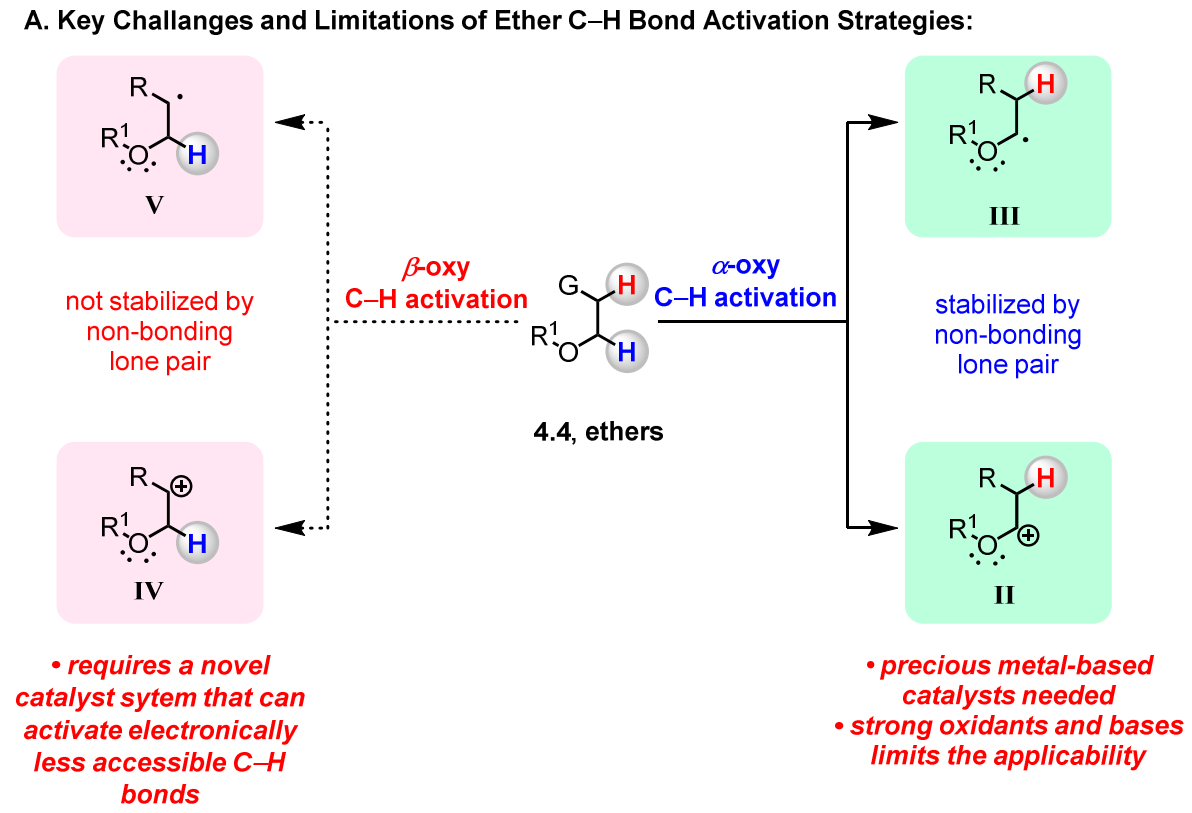
[86] (a) Reymond, S.; Cossy, J. *Chem. Rev*. **2008**, *108*, 5359−5406. (b) Jiang, X.; Wang, R. *Chem. Rev*. **2013**, *113*, 5515−5546. (c) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev*. **2018**, *118*, 2080−2248.
[87] (a) Evans, D. A.; Johnson, J. S *J. Am. Chem. Soc*. **1998**, *120*, 4895−4896. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649.
[88] (a) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem*. **1979**, *44*, 4847–4852. (b) Prater, M. B.; Sigman, M. S. *Isr. J. Chem*. **2020**, *60*, 452–460. (c) Nanda, S. K.; Mallik, R. *Chem. Eur. J*. **2021**, *27*, 15571−15604.

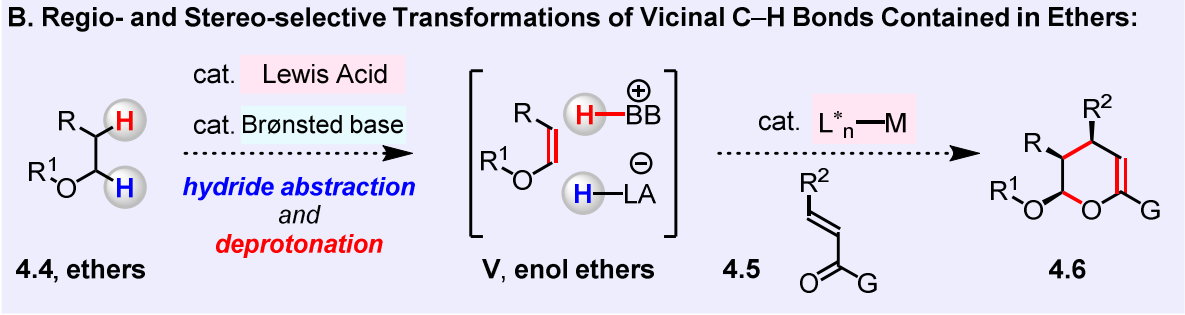
short-lived enol ethers that are unstable to be purified and/or isolated cannot be furnished using such systems.

An enabling strategy for the generation of a broad scope of polyfunctional ethers en route to the synthesis of a broad scope of enantiomerically enriched ethers is the enantioselective C–H activation of a broad scope of significantly more accessible and otherwise stable alkyl ethers (**4.4**, Scheme 4.3).[89] The essential advantage of this approach is that it 1) allows in situ generation of short-lived enol ethers (**4.4** → **V**; Scheme 4.3B) and 2) promotes the enantioselective union of in situ generated enol ethers with suitable coupling partners (**V** → **4.6**) while circumventing purification and isolation. However, these methods often proceed through the intermediacy of positive charge (**II;** Scheme 4.3A) or carboradical (**III**), which are stabilized by the oxygen atom. The carbocation (**IV**) or radical species (**V**) that might be formed by the activation of β-oxy C–H bonds would not be stabilized by the lone pair of the oxygen atom; therefore, they are considered to be less accessible. Therefore, there is an urgent need for the development of a general methodology capable of activating both C1 and C2–H bonds (**4.4** → **V**) contained in various polyfunctional ethers (**4.4**) and promoting their enantioselective union with suitable nucleophiles and electrophiles (**4.5**) while circumventing the use of precious metal-based catalysts, stoichiometric oxidants, and bases (Scheme 4.3B).

[89] (a)Davies, H. M. L.; Yang, J *Adv. Synth. Catal*. **2003**, *345*, 1133−1138. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147−1169. (c)Baudoin, O. *Chem. Soc. Rev*. **2011**, *40*, 4902−4911. (d) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed*. **2014**, *53*, 74−100. (e) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed*. **2014**, *53*, 5010−5036. (f) Cheng, C.; Hartwig, J. F. *Chem. Rev*. **2015**, *115*, 8946−8975. (g) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res*. **2015**, *48*, 1053−1064. (h) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev*. **2017**, *117*, 9247−9301. (i) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G *Chem. Rev*. **2017**, *117*, 9333−9403. (j) Yan, M.; Kawamata, Y.;Baran, P. S. *Chem. Rev*. **2017**, *117*, 13230−13319. (k) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev*. **2017**, *117*, 8754−8786.

Scheme 4.3. Significant Challenges in Ether C–H Activation





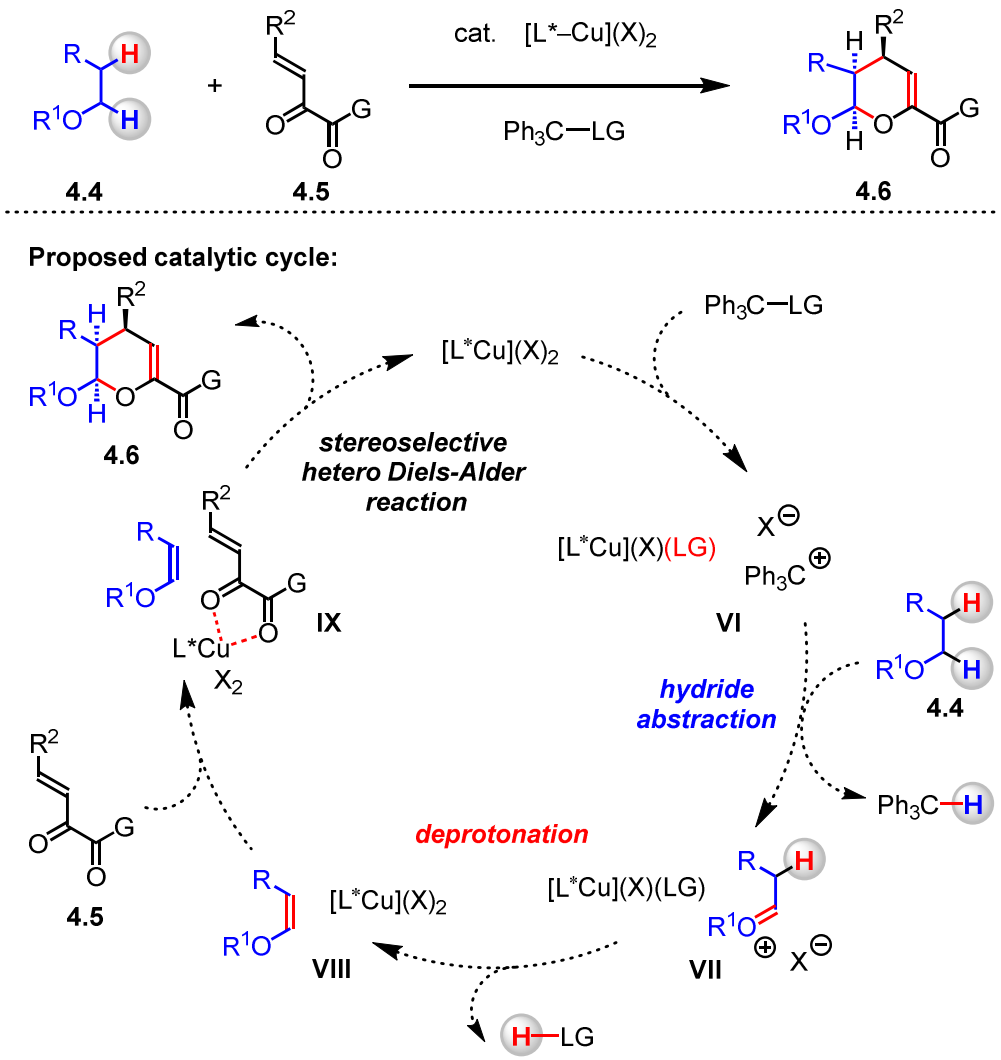
4.3 Our Approach

We contemplated the design of a novel catalyst system that could have multiple roles to functionalize vicinal C–H bonds of various ethers. Initially, it converts the saturated ether molecules into enol ether moieties through a sequential Lewis acid-promoted hydride abstraction and base-promoted deprotonation strategy (Scheme 4.3B).[90] Subsequently, a separate and independently operational, enantiomerically enriched Lewis acid co-catalyst (L^*_n–M) might promote the reaction of enol ethers with suitable dienes (**4.5**) to functionalize both C1 and C2 positions of a wide range of ether molecules to afford 1,2-disubstituted ethers (**4.6**). However, in order to promote enantioselective reactions when there are seemingly competitive achiral (e.g., Lewis acid; Scheme 4.3B) and chiral Lewis acid co-catalysts (L^*_n–M; Scheme 4.3B) in the reaction mixture, the meticulous design of the catalyst system is essential. Specifically, achiral Lewis acids and chiral Lewis acid co-catalysts have to be compatible and play their own independent role without having overlapping functions, which might diminish the stereoselectivity.

While these potential complications in mind, we envisioned that the reaction of ether **4.4**, β,γ-unsaturated ketoesters **4.5** could be promoted by Cu-based complex and Ph_3C–LG, which carries a Lewis-acid sensitive leaving group (LG) to afford the desired dihydro-*2H*-pyrans **4.6** that contain stereogenic centers at the C1, C2, and C3 positions (Scheme 4.4). Particularly, we anticipated Ph_3C^+ (**VI**) could be in situ generated from tritylium precursors (Ph_3C–LG) by its reaction with Cu-based Lewis acid through anion abstraction. After that, an ether molecule **4.4** could undergo hydride abstraction upon its reaction with Ph_3C^+, affording oxocarbenium ion **VII**, which could

[90] (a) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Zurr, D. *J. Chem. Soc. (D)*, **1971**, 861–863. (b) Wan, M.; Meng, Z.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed*. **2014**, *53*, 13845–3849.

Scheme 4.4. Proposed Catalytic Cycle



then undergo deprotonation to generate enol ether **VIII**. Next, the Cu-based complex promotes the stereoselective union of in situ generated enol ether and the *β,γ*-unsaturated ketoesters **4.5** to form a broad array of vicinal stereogenic centers containing dihydro-2*H*-pyrans (**IX** → **4.6**).

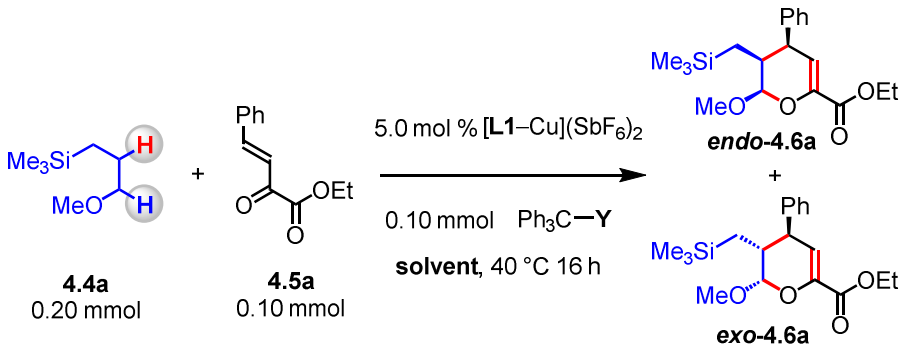
We begin our investigation by searching for a suitable combination of Cu-based complex and tritylium precursor that could utilize the generation and enantioselective transformation of enol ethers (**IX** → **4.6**). As depicted in Chapter 1.5, $[Ph_3C]^+[BF_4]^-$ has been established as a

recipient of hydride from acetals and ethers.[91] Therefore, we initiate our investigation by treating **4.4a** (0.20 mmol) and **4.5a** (0.10 mmol) while using 5.0 mol % [*t*-BuBOX(**L1**)–Cu]$(SbF_6)_2$, which was demonstrated by Evans et al. to be a suitable catalyst to promote the hetero Diels-Alder reaction, and 0.10 mmol $[Ph_3C]^+[BF_4]^-$ at 40 ºC. After 16 hours, we obtained the desired product **4.6a** in 75% yield as a racemate (entry 1; Table 1). It is known in the literature that Ph_3C^+ is a potent Lewis acid that is capable of activating various carbonyl compounds to promote their union with nucleophilic species.[92] Therefore, we hypothesized that if there is a significant excess of Ph_3C^+ in the reaction mixture, on top of its unique capability for generating enol ether **VIII**, it might also promote the non-enantioselective hetero Diels-Alder reaction by activating the carbonyl unit of the diene **4.5**. We removed the Cu-based complex from the reaction mixture and re-ran the reaction to test the hypothesis. In line with our view, $[Ph_3C]^+[BF_4]^-$ was found to mediate the formation of *rac*-**4.6a** in the absence of [*t*-BuBOX(**L1**)–Cu]$(SbF_6)_2$, albeit with lower reaction efficiency of 39% yield (1.3:1 dr; entry 2). This outcome raised a critical design issue about this enantioselective catalytic system due to the overlapping functions of two Lewis acids and their influence on enantioselectivity. Based on these findings, we decided to use tritylium precursors that contains a covalently bound leaving group which requires a Lewis acid activation to furnish Ph_3C^+ in a catalytic quantity. The key advantage of this approach is that it favors the rapid consumption of Ph_3C^+, therefore, enabling the subsequent hetero Diels-Alder to be solely catalyzed by the chiral organocopper. Based on these considerations, we used Ph_3C–Cl then

[91] (a) Barton, D. H. R.; Magnus, P. D.; Smith, M. G.; Streckert, G.; Zurr, D. *J. Chem. Soc. (D)*, **1971**, 861–863. (b) Barton, D. H. R.; Magnus, P. D.; Smith, M. G.; Streckert, G.; Zurr, D. *J. Chem. Soc. Perkin Trans.* **1972**, *1*, 542–552. (c) Jung, M. E.; Speltz, L. M. *J. Am. Chem. Soc.* **1976**, *98*, 7882–7884. (d) Hoye, T. R.; Caruso, A. J.; Dellaria, J. F. Jr.; Kurth, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 6704–6709. (e) Wan, M.; Meng, Z.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed*. **2014**, *53*, 13845–3849. (f) Holthausen, M. H.; Mahdi, T.; Schlepphorst, C.; Hounjet, L. J.; Weigand, J. J.; Stephan, D. W. *Chem. Commun*. **2014**, *50*, 10038–10040.

[92]Lv, J.; Zhang, Q.; Zhong, X.; Luo, S. *J. Am. Chem. Soc*. **2015**, *137*, 15576–15583.

Table 4.1. Evaluation of Reaction Parameters



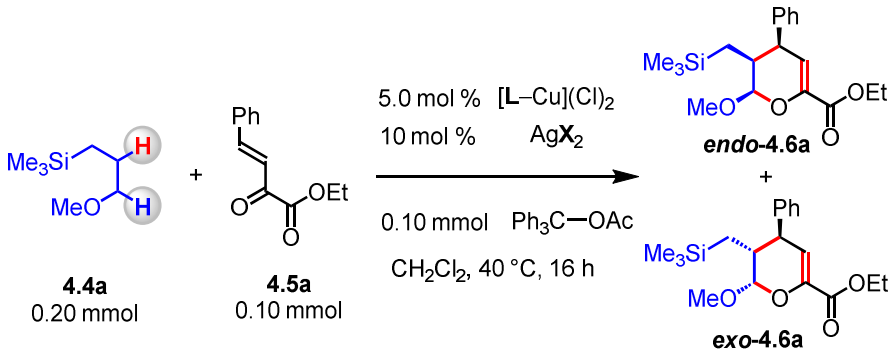
			4.6a			
entry	Ph_3C—**Y**	**solvent**	yield (%)	*endo*:*exo*	er (*endo*)	er (*exo*)
1	$Ph_3C^{\oplus}\,^{\ominus}BF_4$	CH_2Cl_2	75	1.4:1	50:50	51:49
2[a]	$Ph_3C^{\oplus}\,^{\ominus}BF_4$	CH_2Cl_2	39	1.3:1	–	–
3	Ph_3C–Cl	CH_2Cl_2	26	2.0:1	50:50	53:47
4	Ph_3C–OH	CH_2Cl_2	<5	–	–	–
5[b]	Ph_3C–OH	CH_2Cl_2	56	1.7:1	90:10	87:13
6[b]	Ph_3C–OAc	CH_2Cl_2	55	1.5:1	90:10	90:10
7	Ph_3C–OAc	CH_2Cl_2	55	1.8:1	96:4	91:9
8[c]	Ph_3C–OAc	CH_2Cl_2	<5	–	–	–
9	Ph_3C–OAc	C_6H_6	17	1:2.1	96:4	93:7
10	Ph_3C–OAc	toluene	<5	–	–	–
11	Ph_3C–OAc	*t*-BuOMe	<5	–	–	–
12	**none**	CH_2Cl_2	<5	–	–	–

Conditions: Reactions were performed under N_2 atmosphere. [a] (3-methoxypropyl)trimethylsilane (**4.4a**, 0.20 mmol), ethyl (*E*)-2-oxo-4-phenylbut-3-enoate (**4.5a**, 0.10 mmol), [L–Cu]$(Cl)_2$ (5.0 mol %), Ph_3C–Y (0.10 mmol), CH_2Cl_2 (0.6 mL), 40 °C, 16 h. Yield and the ratio of endo and exo products were determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. ND stands for not determined. [b] Reaction was performed at 60 °C. [c] Reaction was performed at 22 °C

Ph_3C–OH, as the tritylium precursor and found that we can obtain **4.6** >40% at 40 ºC (entries 3 and 4). Nevertheless, when the reaction involving Ph_3C–OH, which contains a hard-to-dissociate C–OH bond, was performed at 60 ºC, **4.6a** was generated in 60% yield as a 2.7:1 mixture of ***endo*-4.6a** (90:10 er; entry 5) and exo-**4.6a** (87:13 er). It was found that by using Ph_3C–OAc, which carries a more Lewis acid-sensitive -OAc leaving group, **4.6a** could be obtained in 55% yield and up to 90:10 er when the reaction was run at 60 ºC (1.5:1 dr; entry 6). Moreover, when the reaction temperature decreased to 40 ºC ***endo*-4.6a** was afforded in 35% yield (96:4 er) and ***exo*-4.6a** in 20% yield (96:4 er; entry 7). However, when the reaction temperature was further decreased to 22 ºC, the reaction stopped (<5% yield; entry 8). Next, the reaction was performed in different solvents to improve the reaction efficiency and stereoselectivity. It was found that CH_2Cl_2 is the optimal solvent for this hetero Diels-Alder reaction; aromatic solvents such as benzene (entry 9) and toluene (entry 10) as well as methyl tert-butyl ether (entry 11) gave inferior results. The control experiment demonstrated that there was no product formation in the absence of Ph_3C–OAc (entry 12).

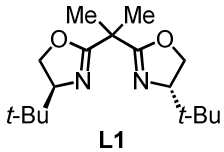
We then evaluated various chiral ligands capable of coordinating to Cu^{II}-complexes to induce enantioselectivity. However, neither [PhBOX(**L2**)–Cu]$(SbF_6)_2$ nor [*t*-BuPyBOX(**L3**)–Cu]$(SbF_6)_2$ could promote the formation of **4.6a** in >40% yield and 76:24 er (entries 1–2; Table 4.2). Moreover, the counterion of the [**L1**–Cu] complex was illustrated to have a great influence over the reaction efficiency and enantioselectivity; while Cl and OTf counterions stopped the reaction (entries 3 and 4), the ClO_4 anion was able to facilitate the formation **4.6a** with substantially low efficiency (13% yield; entry 5). Further optimization of the reaction parameters demonstrated using an excess of **4.6a** is beneficial for improving the reactivities (entry 6); we could generate using an excess of **4.6a** is beneficial for improving the reactivities (entry 6); we could generate

Table 4.2. Evaluation of Organocopper Complexes

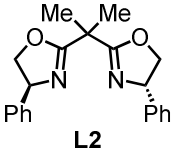


		4.6a			
entry	[L1–Cu](**X**)$_2$	yield (%)	*endo*:*exo*	er (*endo*)	er (*exo*)
1	[**L2**-Cu](**SbF$_6$**)$_2$	40	7.0:1	40:60	76:24
2	[**L3**–Cu](**SbF$_6$**)$_2$	21	2.0:1	49:51	50:50
3	[**L1**–Cu](**Cl**)$_2$	<5	ND	ND	ND
4	[**L1**–Cu](**OTf**)$_2$	<5	ND	ND	ND
5	[**L1**–Cu](**ClO$_4$**)$_2$	13	1.6:1	86:14	88:12
6[b]	[**L1**–Cu](**SbF$_6$**)$_2$	>95	1.8:1	96:4	96:4
7	**none**	<5	–	–	–

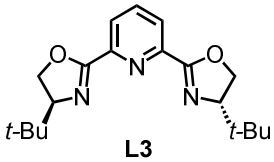
L =



L1



L2



L3

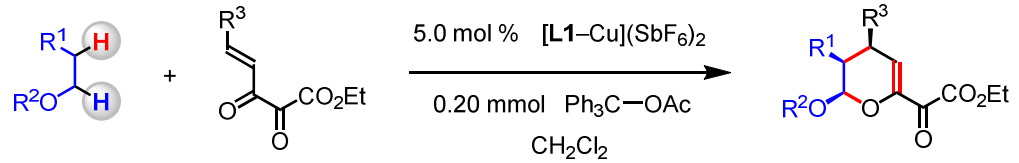
Conditions: Reactions were performed under N_2 atmosphere. [a] (3-methoxypropyl)trimethylsilane (**4.4a**, 0.20 mmol), ethyl (*E*)-2-oxo-4-phenylbut-3-enoate (**4.5a**, 0.10 mmol), [L–Cu](Cl)$_2$ (5.0 mol %), AgX (10 mol %) Ph_3C–OAc (0.10 mmol), CH_2Cl_2 (0.6 mL), 40 °C, 16 h. Yield and the ratio of endo and exo products were determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. ND stands for not determined. [b] **4.4a** (0.40 mmol) and Ph_3C–OAc (0.20 mmol) were used, and the solution was allowed to stir for 24 h.

4.6a nearly in quantitative yield if we increase the equivalency of **4.6a** to 0.40 mmol (vs 0.2 mmol; Table 4.1 entry 7). Control experiments revealed that in the absence of [**L1**–Cu]$(SbF_6)_2$, there was no formation of **4.6a** (entry 7).

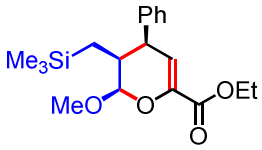
Hetero Diels-Alder products of a wide range of acyclic and cyclic ethers (**4.4a** –**4.4r**) could be obtained with high enantio- and/or diastereoselectivity (**4.6a**–**4.6v**, Tables 4.3–4.4) upon their reaction with an assortment of β,γ-unsaturated ketoesters (**4.5a**, **4.5b**, **4.5s**–**4.5v**). By treating 0.40 mmol **4.4a** and 0.10 mmol **4.5a** with 5.0 mol % of [**L1**–Cu]$(SbF_6)_2$ and 0.20 mmol Ph_3C–OAc, we obtained the **4.6a** in 96% yield as a mixture of diastereomers, favoring ***endo*-4.6a** as the major product (*endo:exo* = 1.8:1; Table 4.3). However, the reaction between **4.4a** and phthalimide-substituted β,γ-unsaturated ketoester **4.5b** resulted in the formation of ***exo*-4.6b** more selectively (48% yield, 95:5 er); ***endo*-4.6b** (was only formed in 23% yield (93:7 er). When we tested the 2-phenethoxyethyl acetate **4.4c,** which is able to form two different enol ethers, the hetero Diels-Alder reaction selectively occurred at the phenethyl site affording **4.6c** in 66% yield and up to 95:5 er. The careful NMR analysis of the crude reaction mixture and the purified products further confirmed the lack of reactivity at the *O*–CH_2CH_2OAc unit of **4.4c** potentially because C–H bonds that are positioned β to -OAc group are inherently less hydridic due to hyperconjugation (σC–H $\rightarrow \sigma^*$C–OAc).[93] It was found that (2-methoxyethyl)trimethylsilane **4.4d** could merge with **4.5a** to provide **4.6d** in 75% yield (*endo:exo* = 8.5:1, 95:5 er). Characterization of the **4.6d** indicated the loss of the trimethylsilyl group, which might occur through a protodesilylation reaction of the product or enol ether intermediate.[94] We were pleased to find that various heteroatom-containing

[93] Kiessling, L. L. *Bioorg. Med. Chem.* **2018**, *26*, 5229–5238.
[94] Yao, W.; Li, R.; Jiang, H.; Han, D. *J. Org. Chem.* **2018**, *83*, 2250–2255.

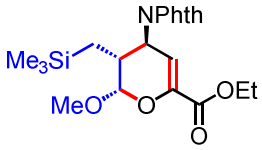
Table 4.3. Enantioselective Hetero Diels-Alder Reactions



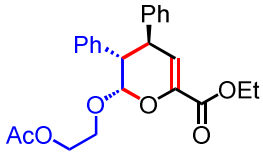
4.4, 0.40 mmol **4.5**, 0.10 mmol **4.6**



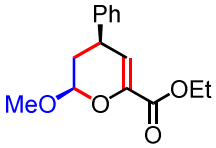
4.6a, 96% yield
endo:*exo* = 1.8:1
96:4 er (*endo*)
96:4 er (*exo*)



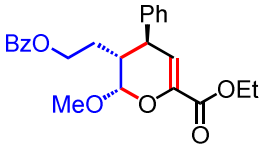
4.6b, 71% yield
endo:*exo* = 1:2.1
93:7 er (*endo*)
95:5 er (*exo*)



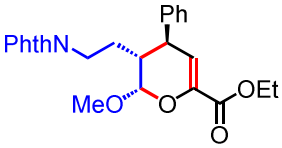
4.6c, 66% yield[c]
endo:*exo* = 1:4.0
81:19 er (*endo*)
95:5 er (*exo*)



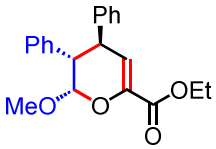
4.6d, 75% yield[c]
endo:*exo* = 8.5:1
95:5 er (*endo*)



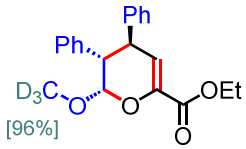
4.6e, 75% yield[c]
endo:*exo* = 1:1.2
96:4 er (*endo*)
83:17 er (*exo*)



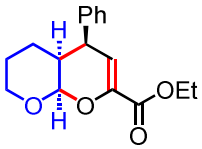
4.6f, 77% yield[c]
endo:*exo* = 1:1.4
92:8 er (*endo*)
85:15 er (*exo*)



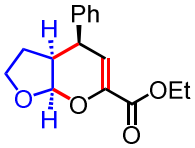
4.6g, 72% yield[c]
endo:*exo* = 1:4.0
95:5 er (*endo*)
95:5 er (*exo*)



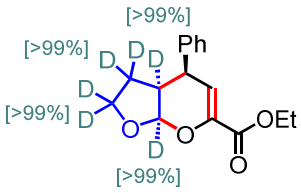
4.6g-*d*$_3$, 68% yield[c]
endo:*exo* = 1:4.0
97:3 er (*endo*)
97:3 er (*exo*)



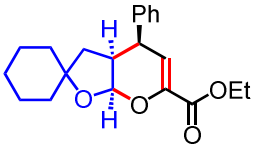
4.6h, 88% yield[c]
endo:*exo* = 2.8:1
94:6 er (*endo*)
79:21 er (*exo*)



4.6i, 88% yield[c]
endo:*exo* = 12:1
95:5 er (*endo*)



4.6i-*d*$_6$, 80% yield[c]
endo:*exo* = 11:1
95:5 er (*endo*)



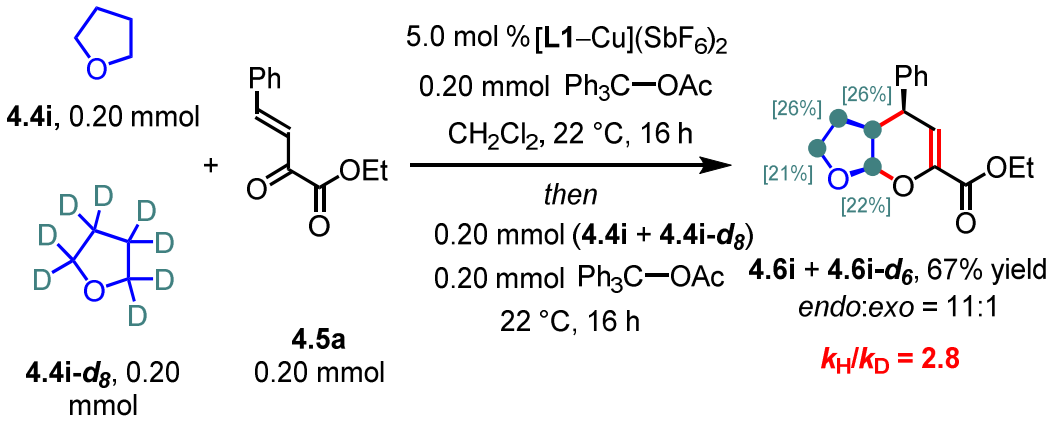
4.6j, 72% yield[c]
endo:*exo* = 10:1
98:2 er (*endo*)

ethers such as benzoate containing **4.4e** and phthalimide containing **4.4f** were tolerated under this catalytic reaction condition to give **4.6e** (1:1.2 *endo*:*exo*; up to 96:4 er) and **4.6f** (1:1.4 *endo*:*exo*; up to 92:8 er) in 75% and 77% yield respectively.

When (2-methoxyethyl)benzene (**4.4g**) was reacted with **4.51**, **4.6g** was obtained in 72% yield as a 1:4.0 mixture of ***endo*-4.6g** (95:5 er) and ***exo*-4.6g** (95:5 er) respectively. Likewise, the reaction of its isotopologue **4.4g -*d*$_3$** resulted in the formation of **4.6g -*d*$_3$** in 68% yield (*endo:exo* =1:4.0, 97:3 er). It was found that there was only 4% erosion of the isotopic label at the OCD_3 unit, indicating the site-selectivity of the Ph_3C^+-mediated hydride abstraction favors the generation of a more stable oxocarbenium intermediate. While the reaction of tetrahydropyran **4.4h** and **4.5a** afforded ***endo*-4.6h** in 65% yield (94:6 er) and ***exo*-4.6h** in 23% yield (79:21 er), the union of tetrahydrofuran **4.4i** and its isotopologue (**4.4i-*d*$_8$**) with **4.5a** provided the **4.6i** and **4.6i-*d*$_6$** in up to 88% yield with higher diasterero- and enantioselectivity (up to *endo:exo* = 12:1, 95:5 er). When sterically more congested oxaspiro[4.4]nonane **4.4j** was tested as a substrate, we were able to obtain ***endo*-4.6j** in 72% yield and 98:2 er.

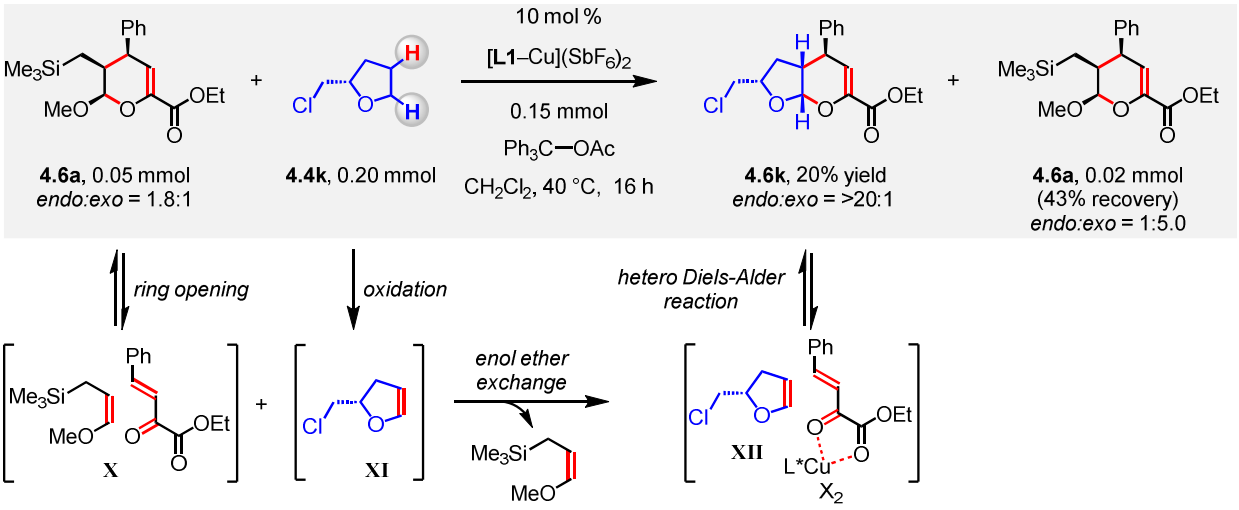
Next, a competition kinetic isotope effect experiment was run to investigate the reversibility of the C–H bond cleavage step mediated by Ph_3C^+ (Scheme 4.5). In particular, the reaction between **4.6i** (0.20 mmol × 2), **4.6i-*d*$_8$** (0.20 mmol × 2), and 0.20 mmol **4.5a** in the presence of 5.0 mol% [**L1**–Cu]$(SbF_6)_2$ and Ph_3C–OAc (0.20 mmol × 2) was performed 32 (16 × 2) hours at 22 ºC affording **4.6i** and **4.6i-*d*$_6$** as a mixture of isotopologues. ^{1}H NMR analysis revealed a k_H/k_D value of 2.8, suggesting that the C–H bond cleavage step is irreversible.

Scheme 4.5. Competition Kinetic Isotope Effect Measurements



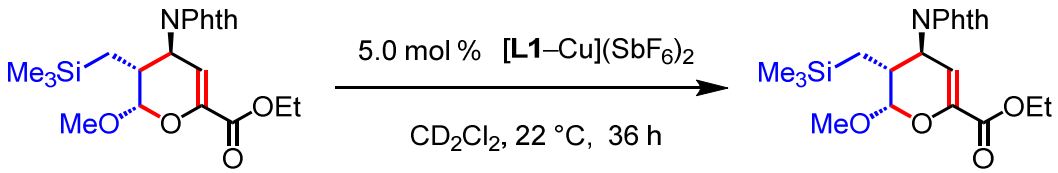
Throughout our studies, organocopper-catalyzed hetero Diels-Alder reactions of acyclic ethers resulted in the formation of corresponding dihydro-*2H*-pyrans with low diastereoselectivity. In order to enhance the diastereoselectivity of this protocol the reversibility of the cycloaddition step was investigated. If this process is reversible, the formation of thermodynamically more stable *exo*-product may be favored. To gain a better understanding on the reversibility of this hetero Diels-Alder reaction, a 1.8:1 *endo*:*exo* mixture of **4.6a** was treated with (*S*)-2-(chloromethyl)tetrahydrofuran **4.4k** in the presence of [**L1**–Cu]$(SbF_6)_2$ and Ph_3COAc (Scheme 4.6). Should this reaction be reversible, the ring-opening of **4.6a** forms a set of enol ether and ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (**X**). In the meantime, the oxidation of **4.4k** could generate enol ether **XI** in situ. The exchange between enol ethers results in the formation of intermediate **XII** which could undergo organocopper-catalyzed hetero Diels-Alder reaction to afford **4.6k**. When the reaction was performed at 40 ºC for 16 hours formation of **4.6k** was observed in 20% yield (*endo*:*exo* = >20:1), thereby implying the reversibility of this reaction. Furthermore, we observed an enhancement in the diastereoselectivity of the recovered **4.6a**, favoring the formation of exo product more predominantly (*endo*:*exo* = 1:5.0).

Scheme 4.6. Determining the Reversibility of Hetero Diels-Alder Reaction



In line with our original hypothesis, the treatment of 2.1:1 mixture of ***exo*-4.6b** and ***endo*-4.6b** with 5.0 mol % [**L1**–Cu]$(SbF_6)_2$ resulted in the formation of thermodynamically more stable ***exo*-4.6b** (93:7 er) as the major product (*endo:exo* = 1:12; Scheme 4.7).

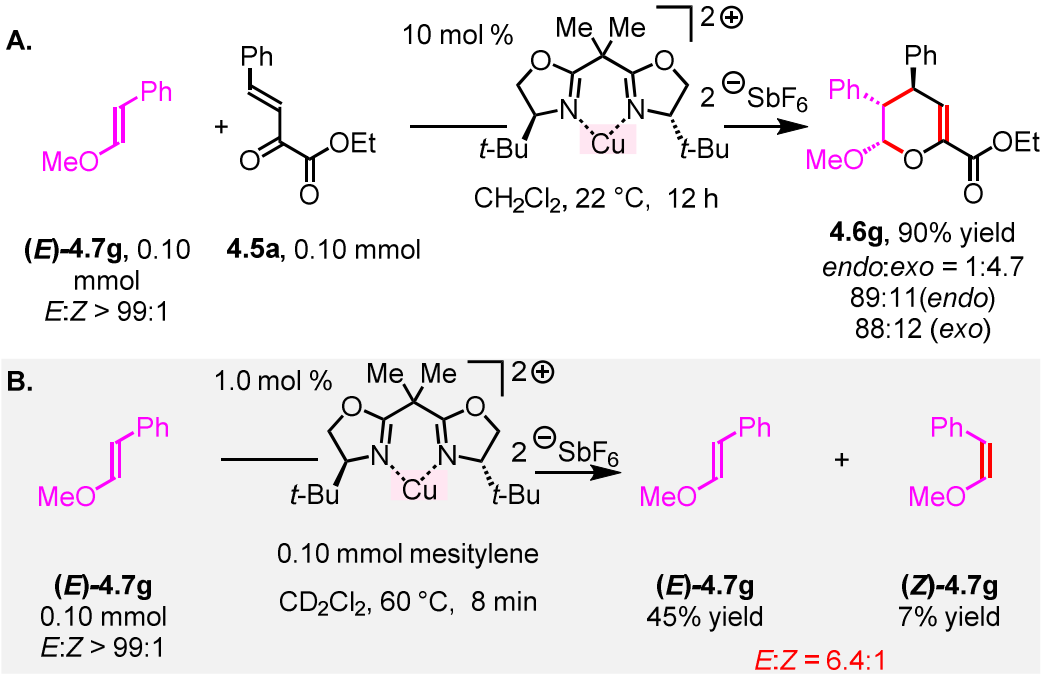
Scheme 4.7. Studies Aimed at Enhancing Diastereoselectivity



We then wanted to determine the configuration of in situ formed enol ethers. Based on the stereochemistry of the products resulting from acyclic ethers, only *Z*-configured enol ethers appear to participate in the hetero Diels-Alder reactions. We performed a control experiment using a preformed *E*-enol ether ((***E*)-4.7g**, Scheme 4.8A) and **4.5a** and found that **4.6g** is formed in 90%

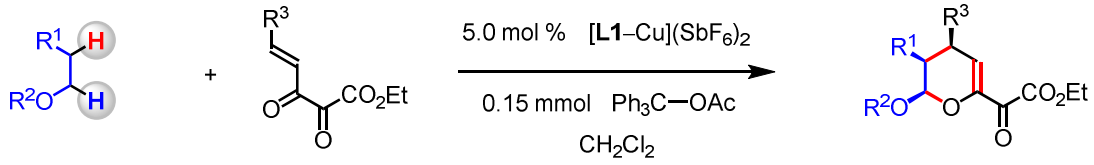
yield (*endo*:*exo* = 1:4.7). In addition, 1.0 mol % of [**L1**–Cu]$(SbF_6)_2$ was able to catalyze the isomerization of **(*E*)-4.7g** solution in CD_2Cl_2 into **(*Z*)-4.7g** at 60 °C (Scheme 4.8B). These results might suggest that the acyclic ethers might be oxidized into a mixture of *E*- and *Z*-configured enol ethers, that can then equilibrate under the reaction conditions.

Scheme 4.8. Studies Aimed at Determining the Configuration of in situ Formed Enol Ethers

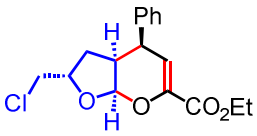


Having found the optimal reaction conditions, we evaluated enantiopure cyclic ethers containing a substituent on its structure and a range of β,γ-unsaturated ketoesters (Table 4.4). We have demonstrated that various Lewis acid-sensitive functional groups, including chloro (**4.4k**), bromo (**4.4l**), acetoxy (**4.4m**), tosyloxy (**4.4n**), alkynyl (**4.4o**), and alkyl (**4.4p**) moieties were tolerated to afford hetero Diels-Alder adducts **4.6k**–**4.6p** in up to 90% yield (*endo:exo* = >20:1–11:1). It was found that the choice of the enantiomer of the ligand is crucial for this diastereoselective process. Specifically, we treated **4.4k** and **4.5a** in the presence of [(*S*,*S*)-**L1**–Cu]$(SbF_6)_2$ or [(*R*,*R*)-**L1**–Cu]$(SbF_6)_2$. While [(*S*,*S*)-**L1**–Cu](SbF_6) give **4.6k** in 90% yield

Table 4.4. Diastereoselective Hetero Diels-Alder Reactions with Enantiopure Ethers

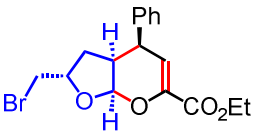


4.4, 0.20 mmol **4.5**, 0.10 mmol **4.6**

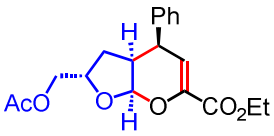


with [(*S*,*S*)-**L1**–Cu](SbF$_6$)$_2$:
4.6k, 90% yield
endo:exo = 11:1

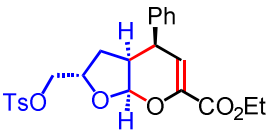
with [(*R*,*R*)-**L1**–Cu](SbF$_6$)$_2$:
***endo*-4.6k**, 13% yield
***exo*-4.6k**, 19% yield
2 other stereoisomers, 23% yield



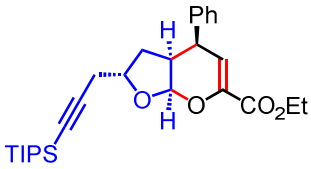
4.6l, 89% yield
endo:exo = 11:1



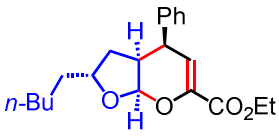
4.6m, 85% yield
endo:exo = 13:1 dr



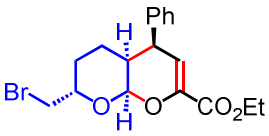
4.6n, 81% yield
endo:exo = 13:1



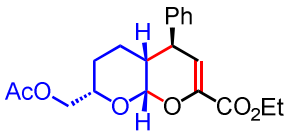
4.6o, 72% yield[c]
endo:exo = >20:1



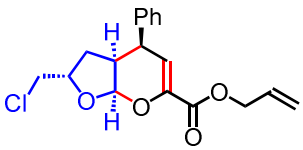
4.6p, 55% yield[c]
endo:exo = 15:1



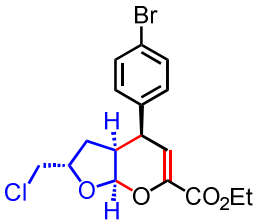
4.6q, 86% yield[c]
endo:exo = 1.7:1



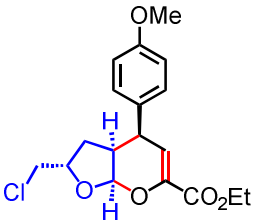
4.6r, 53% yield[c]
endo:exo = 1:2.3



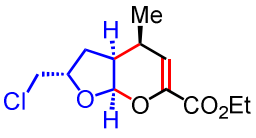
4.6s, 89% yield
endo:exo = 20:1



4.6t, 86% yield
endo:exo = 13:1



4.6u, 89% yield
endo:exo = 9.2:1



4.6v, 58% yield
endo:exo = 7.3:1

(*endo:exo* = 11:1), [(*R*,*R*)-**L1**– Cu]$(SbF_6)_2$ afforded a complex mixture of stereoisomers in 55% overall yield. Tetrahydropyran derivatives (**4.4q**, **4.4r**) required a longer reaction time and a batch-wise addition of Ph_3COAc to afford **4.6q** (*endo:exo* = 1.7:1) and **4.6r** (*endo:exo* = 1:2.3) albeit with lower efficiencies of 86% and 53% yield, respectively. Lastly, an array of β,γ-unsaturated ketoesters was evaluated using **4.4k**. Easily removable allyl acetate moiety bearing **4.5s** afforded the **4.6s** in 89% yield as a single diastereomer. It was demonstrated that both electron-donating and electron-withdrawing groups containing β,γ-unsaturated ketoesters (**4.5t, 4.5u**) readily reacted with **4.4k** to afford **4.6t** and **4.6u** in up to 89% yield and 13:1 dr. We have shown that an aromatic substituent is not required for this reaction. The treatment of ethyl (*E*)-2-oxopent-3-enoate with **4.4v** produced **4.6v** in 58% yield (7.3:1 *endo*:*exo*).

4.4 Conclusion and Future Outlook

We have achieved the dual activation and enantioselective functionalization of C1 and C2–H bonds in an array of acyclic and cyclic ether molecules. The key to success for this regio- and enantioselective C–H functionalization strategy was the design of a catalyst system that is capable of converting ethers containing various Lewis acid-sensitive functional units into corresponding enol ethers and promoting their enantio- and diastereoselective reaction with β,γ-unsaturated ketoesters. By achieving this, we have shown that we could synthesize valuable enantiomerically enriched dihydro-*2H*-pyran derivatives containing stereogenic centers at the C1, C2, and C3 positions.

Although we can achieve chemo- and enantioselective ether C–H bond functionalization, this work highlighted the critical shortcomings of our approach.

1. This protocol requires a stoichiometric amount of hydride acceptor; therefore, it lacks an atom economy.
2. This transformation has a modest functional group tolerance, and Lewis basic units require the installation of protecting groups (e.g., NPhth, OBz)
3. Sequential enol ether generation and the C–C and C–hetero atom bond-forming reactions have a narrow compatible scope (e.g., β,γ-unsaturated ketoesters)

In the upcoming works, the Wasa laboratory will dedicate its effort to solve the limitations as mentioned earlier by developing novel catalyst systems that are:

1. Tolerant of most of the Lewis acid- and Lewis base-sensitive functional groups
2. Generally applicable to a broad scope of substrates, including bioactive molecules containing ethers, amines, thioethers, amides, and alkenes

3. Capable of generating both nucleophilic and electrophilic moieties and promoting their chemo- and enantioselective reactions.

By developing such systems, we would like to showcase the strength of our strategies by applying them to the enantioselective late-stage C–H functionalization reactions.

Appendix A. Experimental Section for Chapter 2

A1. Procedures, Materials and Instrumentation

General experimental procedures. All reactions were performed in standard, dry glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reported concentrations refer to solution volumes at room temperature. Evaporation and concentration *in vacuo* were performed using house vacuum (ca. 40 mm Hg). Column chromatography was performed with SiliaFlash® 60 (40–63 micron) silica gel from Silicycle. Thin layer chromatography (TLC) was used for reaction monitoring and product detection using pre-coated glass plates covered with 0.25 mm silica gel with fluorescent indicator; visualization by UV light (λ_{ex} = 254 nm) or $KMnO_4$ stain.

Materials. Reagents were purchased in reagent grade from commercial suppliers and used without further purification, unless otherwise described. Amines and trimethylsilyl propiolate compounds were prepared according to the procedures reported previously.[1-4] H_2O, in synthetic procedures, refers to distilled water. Tris(pentafluorophenyl)borane, $Cu(MeCN)_4PF_6$, Xantphos, and 1,2-bis(diphenylphosphino)ethane were purchased from TCI and used without further purification. Chiral ligands **L4-7**, **L10**, and **L14-19** were prepared according to the literature procedures.[5-8]

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C {^{1}H} NMR) spectra were recorded at 25 °C (unless stated otherwise) on Inova 600 (600 MHz), Varian Unity/Inova 500 (500 MHz) or Oxford AS400 (400 MHz) spectrometers at the Boston College nuclear magnetic resonance facility. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to 0 ppm. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent. The peak positions are quoted to one decimal place unless they are indistinguishable. The solvent peak was referenced to 77.0 ppm for ^{13}C for $CDCl_3$. Benzotrifluoride was used as an external standard for ^{19}F NMR and referenced to −63.0 ppm. BF_3•OEt_2 was used as an external standard for ^{11}B NMR and referenced to 0 ppm. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz).

Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}).

High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) at the Mass Spectrometry Facility, Boston College. Chiral HPLC analyses were carried using Agilent 1200 series instruments and Shimadzu chromatograph with Daicel CHIRALPAK® columns or Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm).

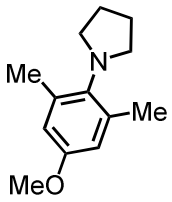
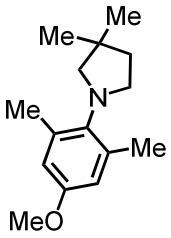
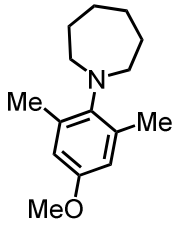
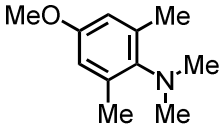
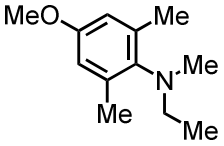
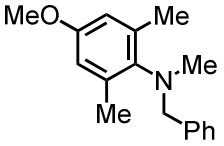
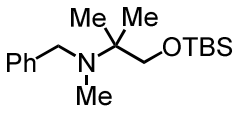
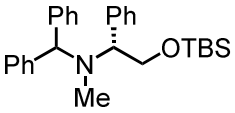
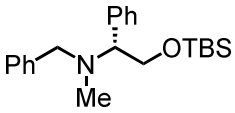
Abbreviations used. Bn = benzyl, COSY = correlated spectroscopy, DART = direct analysis in real time, ESI = electrospray ionization, Et_3N = trimethylamine, EtOAc = ethyl acetate, Et_2O = ethyl ether, HR = high-resolution, HSQC = heteronuclear single quantum coherence, LC = liquid chromatography, MS = mass spectrometry, NOESY = nuclear Overhauser effect spectroscopy, OTf = triflate, PTLC = preparatory thin-layer chromatography, THF = tetrahydrofuran, TLC = thin-layer chromatography, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TOF = time-of-flight.

A2. Experimental Section

A2.1 Substrate Preparation

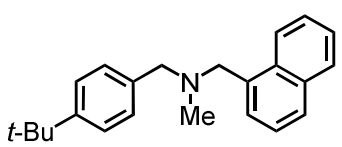
A2.1.1 Preparation of Amine Substrates

Table S1.1A. List of Amine Substrates

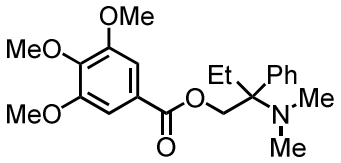
 **2.15a**	 **2.15b**	 **2.15c**
 **2.15d**	 **2.15e**	 **2.15f**
 **2.15g**	 **2.15h**	 **2.15i**

Amines **2.15a**-**2.15f** and **2.15g**-**2.15i** were prepared according to literature procedures.[1] The spectroscopic data for the amine substrates (**2.15g**-**2.15i**) are provided in SI-Section 2.1.

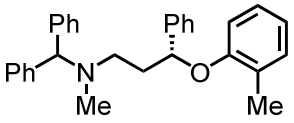
Table S1.1B. List of Amine Substrates



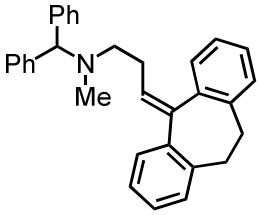
2.15j



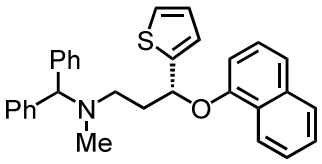
2.15k



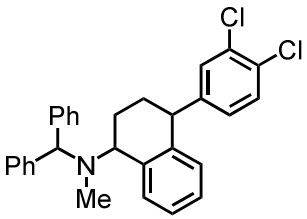
2.15l



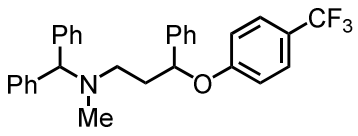
2.15m



2.15n



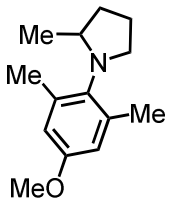
2.15o



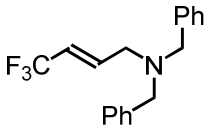
2.15p

Amines **2.15k**-**2.15o** were prepared according to literature procedures.[2] Amines **2.15h** and **1k** were obtained by reacting the commercially available amine hydrochloride salt with NaOH (1.0 M aq.). The spectroscopic data for the amine substrates (**2.15k-2.15o**) are provided in SI-Section 2.1.

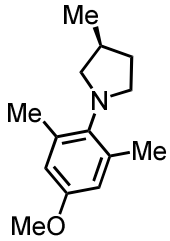
Table S1.1C. List of Amine Substrates



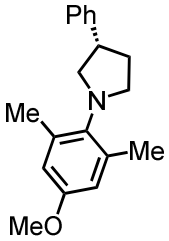
***rac*-2.15q**



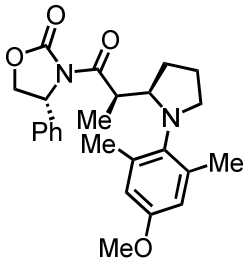
2.15r



(*S*)-2.15s



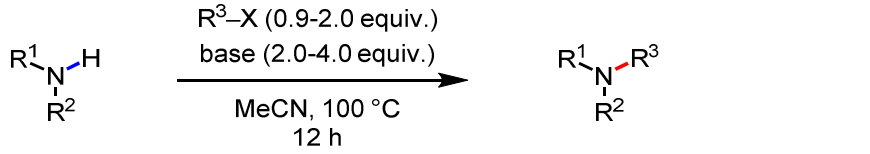
(*S*)-2.15t



(*R,R,R*)-2.15u

Amines listed above were prepared according to literature procedures.[1] The spectroscopic data for the amine substrates (**2.15r**-**2.15t**) are provided in SI-Section 2.1.

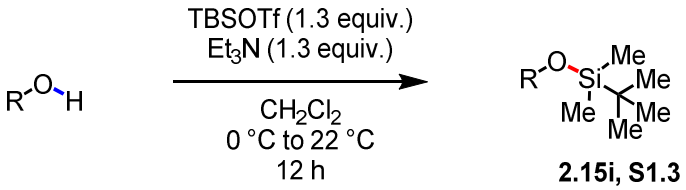
General Procedure for Preparation of Tertiary or Secondary Amines



S1.1, S1.6, 2.15l-2.15p, 2.15s-2.15t

Amines **S1.1**, **S1.6**, **2.15l-2.15p** and **2.15s-2.15t** were prepared by alkylation of the corresponding primary or secondary amines. To a solution of primary or secondary amine (1.0 equiv.) and K_2CO_3 or Et_3N (2.0-4.0 equiv.) in MeCN was added alkyl halide (R^3–X; 0.9-2.0 equiv.). The mixture was allowed to stir at 100 °C for 12 h. Upon completion (determined by TLC), H_2O was added and the organic material was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The desired amine products were obtained after purification by silica gel chromatography.

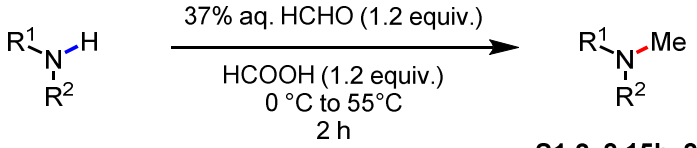
General Procedure for TBS Protection of Alcohols



2.15i, S1.3

Substrates **2.15i** and **S1.3** were prepared by TBS protection of alcohols. To a solution of alcohol in CH_2Cl_2 at 0 °C, Et_3N (1.3 equiv.) and TBSOTf (1.3 equiv.) were added in a dropwise manner. After the addition, the mixture was allowed to warm to 22 °C and stirred for 12 h. Upon completion (determined by TLC), H_2O was added and the organic material was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The desired silyl ether products were obtained after purification by silica gel chromatography.

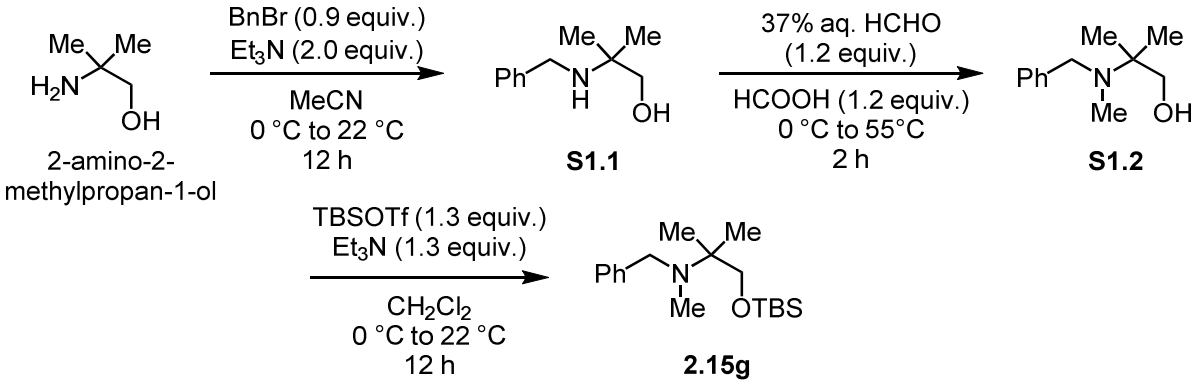
General Procedure for *N*-Methylation of Secondary Amines



S1.2, 2.15h, 2.15i

Substrates **S1.2**, **2.15i**, and **2.15i** were prepared by *N*-methylation of secondary amines. A solution of amine and formaldehyde (37% aq. solution, 1.2 equiv.) was cooled to 0 °C. To the mixture was added formic acid (1.2 equiv.) in a dropwise manner. The mixture was allowed to warm to 55 °C and stirred for 2 h. Upon completion (determined by TLC), the mixture was cooled to 0 °C, NaOH (1.0 M aq. solution) was added until the aqueous layer was alkaline. The organic material was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The desired amine products were obtained after silica gel chromatography.

Procedure for Preparation of *N*-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethylpropan-2-amine (2.15g)



2-(Benzylamino)-2-methylpropan-1-ol (S1.1)

2-(Benzylamino)-2-methylpropan-1-ol was prepared following **General Procedure for Preparation of Secondary Amines** using 2-amino-2-methylpropan-1-ol (69 mmol). The amine product **S1.1** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:1) as a colorless oil (9.0 g, 73% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 3H), 7.26 (d, J = 1.0 Hz, 2H), 3.69 (s, 2H), 3.35 (s, 2H), 1.15 (d, J = 1.0 Hz, 6H).

2-(Benzyl(methyl)amino)-2-methylpropan-1-ol (S1.2)

2-(Benzyl(methyl)amino)-2-methylpropan-1-ol was prepared following **General Procedure for *N*-Methylation of Secondary Amines** using 2-(benzylamino)-2-methylpropan-1-ol (20 mmol). The amine product **S1.2** was obtained after purification by silica gel chromatography (EtOAc:Et_3N:hexanes = 20:1:79) as a colorless oil (2.0 g, 50% yield).

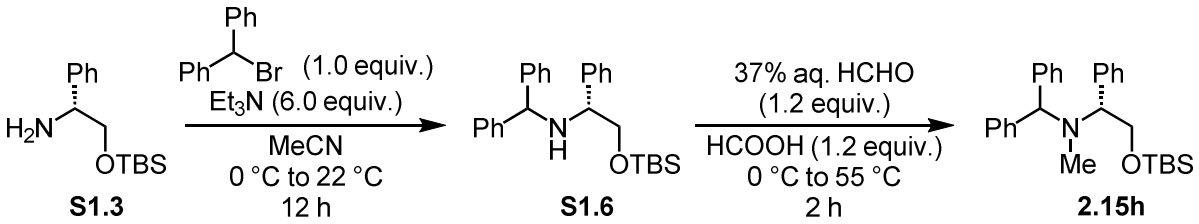
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.8 Hz, 1H), 7.26 – 7.20 (m, 4H), 3.52 (s, 2H), 3.44 (s, 2H), 2.09 (s, 3H), 1.13 (s, 6H).

_N_-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-_N_,2-dimethylpropan-2-amine (2.15g)

_N_-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-_N_,2-dimethylpropan-2-amine was prepared following **General Procedure for TBS Protection of Alcohols** using 2-(benzyl(methyl)amino)-2-methylpropan-1-ol (10 mmol). The amine product **2.15g** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:9) as a colorless oil (3.0 g, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 4H), 7.24 – 7.17 (m, 1H), 3.63 (s, 2H), 3.56 (s, 2H), 2.15 (s, 3H), 1.11 (s, 6H), 0.91 (s, 9H), 0.06 (s, 6H).

Procedure for Preparation of (*R*)-_N_-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-_N_-methyl-1-phenylethan-1-amine (2.15h)



(*R*)-_N_-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (S1.6)

(*R*)-_N_-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine was prepared using **General Procedure for Preparation of Secondary Amines** using (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (46 mmol). The amine product **S1.6** was obtained after purification by silica gel chromatography (Et_3N:hexanes = 1:19) as a colorless oil (9.5 g, 49% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 7H), 7.22 (t, *J* = 6.7 Hz, 6H), 7.19 – 7.10 (m, 2H), 4.62 (s, 1H), 3.68 (dd, *J* = 8.5, 3.7 Hz, 1H), 3.61 (dd, *J* = 9.2, 2.3 Hz, 2H), 0.85 (s, 9H), -0.05 (d, *J* = 11.4 Hz, 6H); $[\alpha]^{25}_D$ = –6.8° (*c* 1.0, CH_2Cl_2).

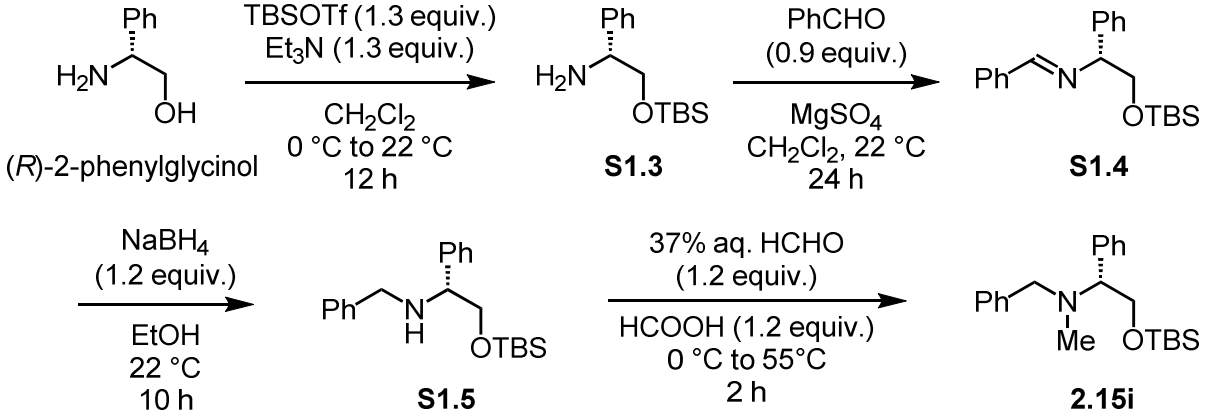
(*R*)-_N_-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-_N_-methyl-1-phenylethan-1-amine (2.15h)

(*R*)-_N_-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-_N_-methyl-1-phenylethan-1-amine was prepared using **General Procedure for _N_-Methylation of Secondary Amines** using (*R*)-_N_-benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (24 mmol). The amine product **2.15h**

was obtained after purification by silica gel chromatography (EtOAc:Et_3N: hexanes 20:1:79) as a colorless oil (10.1 g, 98% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (ddd, *J* = 11.6, 8.2, 1.3 Hz, 4H), 7.34 – 7.29 (m, 6H), 7.25 – 7.19 (m, 4H), 7.17 – 7.12 (m, 1H), 4.80 (s, 1H), 4.06 (dd, *J* = 9.7, 5.9 Hz, 1H), 3.98 – 3.89 (m, 2H), 2.13 (s, 3H), 0.85 (s, 9H), -0.03 (d, *J* = 6.5 Hz, 6H).

Procedure for Preparation of (*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (2.15i)



(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethan-1-amine (S1.3)

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethan-1-amine was prepared following **General Procedure for TBS Protection of Alcohols** using (*R*)-2-amino-2-phenylethan-1-ol (60 mmol). The amine product **S1.3** was obtained after purification by silica gel chromatography (Et_3N:hexanes = 1:19) as a colorless oil (14.0 g, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 4H), 7.19 – 7.13 (m, 1H), 3.98 (dd, *J* = 8.4, 3.9 Hz, 1H), 3.63 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.43 (dd, *J* = 9.8, 8.3 Hz, 1H), 0.81 (s, 9H), -0.07 (d, *J* = 1.6 Hz, 6H).

(*R,E*)-*N*-(2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethyl)-1-phenylmethanimine (S1.4)

To a solution of amine **S1.1** (33 mmol, 1.1 equiv.) and benzaldehyde (30 mmol, 1.0 equiv.) in CH_2Cl_2, was added $MgSO_4$. The mixture was allowed to stir for 24 h at 22 °C. Upon completion (determined by TLC), the unpurified mixture was filtered over a pad of Celite and rinsed with CH_2Cl_2. The organic layer was concentrated *in vacuo*, and the product obtained was directly used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.76 – 7.65 (m, 2H), 7.49 – 7.37 (m, 2H), 7.37 – 7.28 (m, 3H), 7.28 – 7.21 (m, 2H), 7.20 – 7.12 (m, 1H), 4.33 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.86 – 3.68 (m, 2H), 0.73 (s, 9H), -0.10 (s, 3H), -0.16 (s, 3H).

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (S1.5)

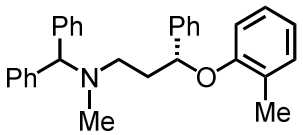
To a solution of imine **S1.4** (30 mmol, 1.0 equiv.) in EtOH, was added $NaBH_4$ (36 mmol, 1.2 equiv.) at 0 °C. The mixture was allowed to stir for 10 h. Upon completion (monitored by TLC), the mixture was diluted with H_2O, and extracted with EtOAc (3 x 20 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The amine product **S1.5** was obtained after purification by silica gel chromatography (Et_3N:hexanes = 1:50) as a colorless oil (10 g, 98% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.24 (ddd, *J* = 7.9, 6.7, 1.6 Hz, 2H), 7.22 – 7.15 (m, 5H), 7.13 (td, *J* = 6.9, 1.7 Hz, 1H), 3.71 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 3.56 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.51 – 3.42 (m, 2H), 0.78 (d, *J* = 1.8 Hz, 9H), -0.06 – -0.12 (m, 6H).

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (2.15i)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine was prepared using **General Procedure for *N*-Methylation of Secondary Amines** using (*R*)-*N*-benzyl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (21 mmol). The amine product **2.15i** was obtained after purification by silica gel chromatography (EtOAc: Et_3N: hexanes 20:1:79) as a colorless oil (6.8 g, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 3H), 7.34 – 7.28 (m, 5H), 7.28 – 7.24 (m, 1H), 7.24 – 7.18 (m, 1H), 4.07 (dd, *J* = 10.4, 6.1 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.70 – 3.56 (m, 2H), 3.45 (d, *J* = 13.5 Hz, 1H), 2.19 (s, 3H), 0.83 (s, 9H), -0.06 (d, *J* = 7.9 Hz, 6H); $[\alpha]^{25}_D$ = 1.6° (*c* 1.0, CH_2Cl_2).

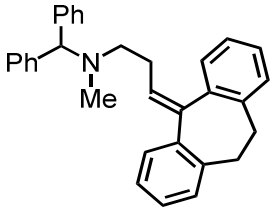


2.15l

(*R*)-*N*-Benzhydryl-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine (2.15l)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using (*R*)-*N*-methyl-3-phenyl-3-(o-tolyloxy)propan-1-amine (1.5 g, 5.9 mmol), (2-bromoethyl)benzene (1.2 equiv.) and K_2CO_3 (1.2 equiv.). The amine product **2.15l** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:19) as a colorless oil (2.0 g, 82%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 4.4 Hz, 6H), 7.23 (t, *J* = 7.3 Hz, 3H), 7.15 (t, *J* = 6.7 Hz, 1H), 7.10 – 7.05 (m, 4H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 5.25 (dd, *J* = 8.9, 3.7 Hz, 1H), 4.33 (s, 1H), 2.72 – 2.65 (m, 1H), 2.48 (ddd, *J* = 12.6, 8.1, 4.5 Hz, 1H), 2.18 (s, 3H), 2.17 – 2.11 (m, 1H), 2.08 – 2.00 (m, 4H).

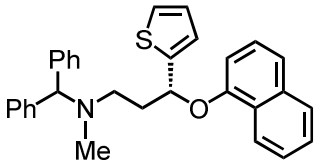


2.15m

***N*-Benzhydryl-3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (2.15m)**

N-Benzhydryl-3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using 3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (4.3 g, 16 mmol), (bromomethylene)dibenzene (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **2.15m** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:19) as a colorless oil (6.5 g, 91%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 5H), 7.23 (s, 4H), 7.19 (d, *J* = 1.0 Hz, 2H), 7.17 – 7.10 (m, 5H), 7.07 (d, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 4.1 Hz, 1H), 5.82 (t, *J* = 7.5 Hz, 1H), 4.31 (s, 1H), 3.30 (s, 2H), 2.94 (s, 1H), 2.72 (s, 1H), 2.46 (s, 2H), 2.31 (d, *J* = 7.4 Hz, 2H), 2.07 (s, 3H).

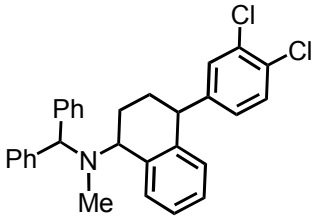


2.15n

(*R*)-*N*-Benzhydryl-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine (2.15n)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using (*R*)-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine (0.9 g, 2.9 mmol), (bromomethylene)dibenzene (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **2.15n** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:4) as a colorless oil (1.2 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.42 – 7.30 (m, 4H), 7.30 – 7.09 (m, 7H), 7.04 – 6.94 (m, 4H), 6.94 – 6.88 (m, 1H), 6.88 – 6.81 (m, 1H), 5.75 (s, 1H), 4.35 (s, 1H), 2.76 – 2.65 (m, 1H), 2.61 – 2.51 (m, 1H), 2.51 – 2.38 (m, 1H), 2.32 – 2.16 (m, 4H).

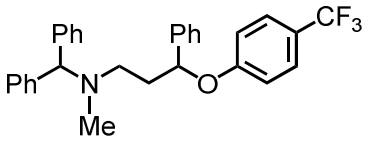


2.15o

***N*-Benzhydryl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (2.15o)**

N-Benzhydryl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using 4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (2.9 g, 6.0 mmol), (bromomethylene)dibenzene (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **2.15o** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:4) as a colorless oil (1.4 g, 49%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 – 8.13 (m, 1H), 7.56 (td, *J* = 7.1, 6.3, 1.5 Hz, 4H), 7.38 – 7.33 (m, 1H), 7.29 (ddt, *J* = 7.9, 4.3, 2.0 Hz, 3H), 7.26 – 7.23 (m, 2H), 7.16 (dtd, *J* = 17.5, 7.2, 1.4 Hz, 3H), 7.08 (d, *J* = 1.9 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.79 (dt, *J* = 8.2, 1.9 Hz, 1H), 4.73 (d, *J* = 1.6 Hz, 1H), 4.08 – 3.99 (m, 2H), 2.04 (d, *J* = 1.7 Hz, 3H), 1.91 (q, *J* = 5.0, 4.5 Hz, 2H), 1.76 – 1.65 (m, 1H), 1.65 – 1.58 (m, 1H).



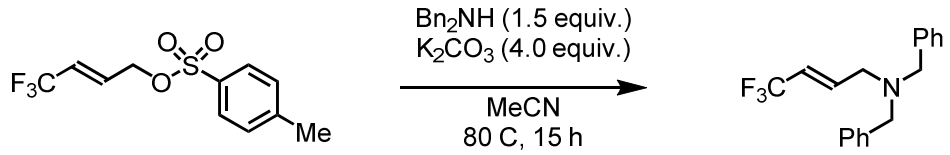
2.15p

***N*-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine (2.15p)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using *N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine (2.8 g, 9.0 mmol), (bromomethylene)dibenzene (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **2.15p** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:9) as a colorless oil (3.0 g, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.29 (dtd, *J* = 7.3, 5.7, 4.7, 1.6 Hz, 6H), 7.23 (td, *J* = 7.5, 1.7 Hz, 3H), 7.19 – 7.14 (m, 1H), 7.12 – 7.07 (m, 3H), 6.84 – 6.79 (m, 2H), 5.34 – 5.29 (m, 1H), 4.35 (s, 1H), 2.71 (dt, *J* = 13.9, 7.5 Hz, 1H), 2.39 (dt, *J* = 12.2, 5.9 Hz, 1H), 2.18 (d, *J* = 1.6 Hz, 3H), 2.13 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.08 – 1.99 (m, 1H); **^{19}F NMR** (564 MHz, $CDCl_3$) δ -61.51.

Procedure for Preparation of (*E*)-*N,N*-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine (2.15r)



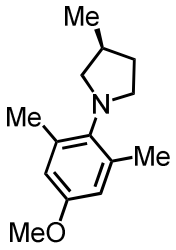
2.15r

(*E*)-*N,N*-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine (2.15r)

(*E*)-*N,N*-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine was prepared following the literature previously reported.[2] To a solution of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (7.0 g, 25 mmol) and K_2CO_3 (13.8 g, 100 mmol) in MeCN (100 mL) was added dibenzylamine (7.4 g, 37.5 mmol). The mixture was then allowed to stir at 80 °C for 15 hours. Upon completion

(determined by TLC), the mixture was filtered and concentrated *in vacuo*. The amine product **2.15r** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:20) as a colorless oil (5.9 g, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 8H), 7.28 – 7.22 (m, 2H), 6.51 – 6.30 (m, 1H), 5.85 (ddt, *J* = 15.8, 6.5, 1.7 Hz, 1H), 3.59 (s, 4H), 3.26 – 3.03 (m, 2H); **^{19}F NMR** (470 MHz, $CDCl_3$) δ -63.97 (d, *J* = 6.1 Hz).

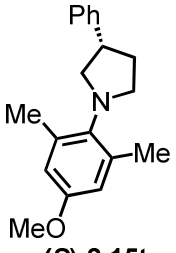


(*S*)-1t

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine ((*S*)-2.15s)

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine was prepared following **General Procedure for Preparation of Tertiary Amines** using 4-methoxy-2,6-dimethylaniline (1.65 g, 10.9 mmol), (*S*)-1,4-dibromo-2-methylbutane (0.9 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **(*S*)-2.15s** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:19) as a colorless oil (1.8 g, 82%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 2H), 3.75 (s, 3H), 3.26 – 3.21 (m, 1H), 3.21 – 3.17 (m, 2H), 2.79 (t, *J* = 7.5 Hz, 1H), 2.39 (dt, *J* = 8.5, 6.8 Hz, 1H), 2.23 (s, 6H), 2.12 – 2.02 (m, 1H), 1.59 (dd, *J* = 11.9, 8.1 Hz, 1H), 1.11 (d, *J* = 6.7 Hz, 3H); $[\alpha]^{25}_D = -19.5°$ (*c* 0.25, CH_2Cl_2).



(*S*)-2.15t

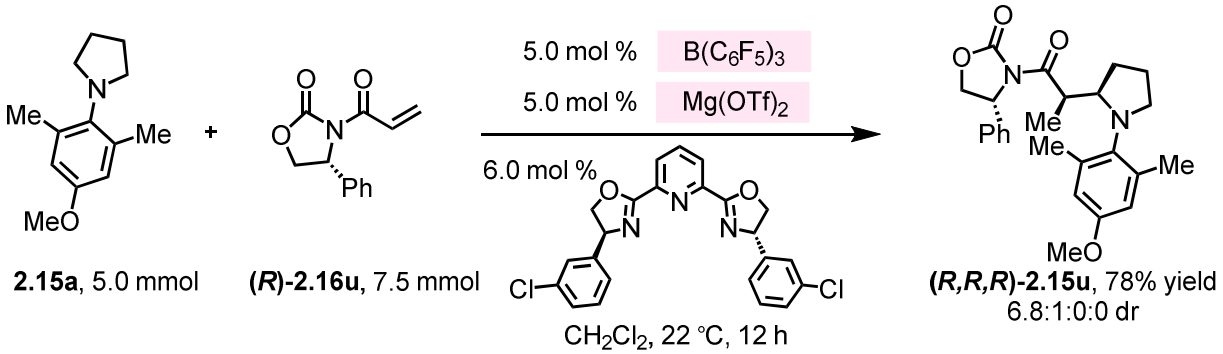
(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-phenylpyrrolidine ((*S*)-2.15t)

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-phenylpyrrolidine was prepared following **General Procedure for Preparation of Tertiary Amines** using 4-methoxy-2,6-dimethylaniline (382 mg,

2.5 mmol), (*S*)-(1,4-dibromobutan-2-yl)benzene (0.9 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **(*S*)-2.15t** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:19) as a colorless oil (549 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 4H), 7.24 – 7.17 (m, 1H), 6.60 (s, 2H), 3.76 (s, 3H), 3.63 – 3.45 (m, 2H), 3.40 (t, *J* = 8.0 Hz, 1H), 3.33 (dd, *J* = 13.9, 7.2 Hz, 2H), 2.49 – 2.33 (m, 1H), 2.30 (s, 6H), 2.24 – 2.06 (m, 1H); $[\alpha]^{25}_D = -20.5°$ (*c* 0.25, CH_2Cl_2).

Procedure for Preparation of (*R*)-3-((*R*)-2-((*R*)-1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propanoyl)-4-phenyloxazolidin-2-one ((*R,R,R*)-2.15u)



(*R*)-3-((*R*)-2-((*R*)-1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propanoyl)-4-phenyloxazolidin-2-one ((*R,R,R*)-2.15u)

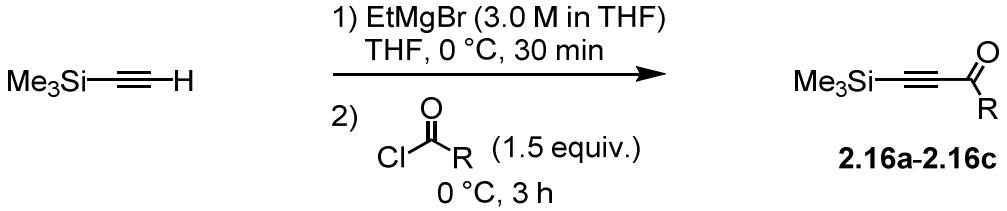
(*R*)-3-((*R*)-2-((*R*)-1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propanoyl)-4-phenyloxazolidin-2-one was prepared according to a literature procedure.[1] To a 35 mL oven-dried sealed tube was added $Mg(OTf)_2$ (0.25 mmol), 2,6-bis((*S*)-4-(3-chlorophenyl)-4,5-dihydrooxazol-2-yl)pyridine (0.30 mmol), CH_2Cl_2 (10 mL) under nitrogen atmosphere. The mixture was allowed to stir for 30 min at 22 °C, then (*R*)-3-acryloyl-4-phenyloxazolidin-2-one **(*R*)-2.16u** (1.3 g, 6.0 mmol), 1-(4-methoxy-2,6-dimethylphenyl)pyrrolidine **2.15a** (1.02 g, 5.0 mmol), $B(C_6F_5)_3$ (0.25 mmol), and CH_2Cl_2 (5.0 mL) were added to the vessel. The mixture was stirred at 22 °C for 48 h. Upon completion, the solvent was removed *in vacuo.* The diastereomeric ratio was determined to be 6.8:1:0:0 by ^{1}H NMR analysis of the unpurified product mixture. Purification by silica gel chromatography (Et_2O:hexanes = 1:4) gave the product as a colorless solid as a mixture of diastereomers (1.63 g, 78% yield). Further purification carried out by silica gel chromatography (Et_2O:hexanes = 1:4) to obtain the major diastereomer **(*R,R,R*)-2.15u** in 1.47 g as a colorless oil.

A2.1.2. Preparation of Trimethylsilyl Propiolate Substrates

Table S1.2. List of Trimethylsilyl Propiolate Compounds

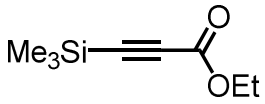
Alkynes **2.16a-2.16c** were prepared according to a literature procedure.[4] Alkyne compounds **2.16d-2.16h** were obtained from commercial sources and used without further purification.

General Procedure for Preparation of 3-(Trimethylsilyl)propiolates



2.16a-2.16c

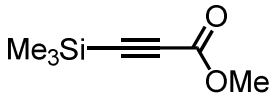
3-(Trimethylsilyl)propiolates **2.16a-2.16c**, were prepared according to a literature procedure.[4] To a solution of ethynyltrimethylsilane (20 mmol) in THF (20 mL) was added ethylmagnesium bromide (3.0 M solution in THF) in a dropwise manner at 0 °C. The mixture was allowed to stir for 30 min. The corresponding chloroformate (30 mmol) in THF (30 mL) was added dropwise and the mixture was allowed to stir at 0 °C for 3 h. Upon completion (determined by TLC), H_2O (50 mL) was added and the organic material was extracted using Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The desired alkyne products were obtained after purification by silica gel chromatography.



2.16a

Ethyl 3-(trimethylsilyl)propiolate (**2.16a**) was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using ethyl chloroformate. The propiolate **2.16a** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:99) as a colorless oil (2.7 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, J = 7.2 Hz, 2H), 1.31 (td, J = 7.1, 0.9 Hz, 3H), 0.25 (s, 9H).

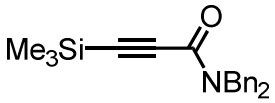


2.16b

Methyl 3-(trimethylsilyl)propiolate (2.16b)

Methyl 3-(trimethylsilyl)propiolate was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using methyl chloroformate. The propiolate **2.16b** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:99) as a colorless oil (2.6 g, 83%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77 (s, 3H), 0.25 (s, 9H).



2.16c

***N,N*-Dibenzyl-3-(trimethylsilyl)propiolamide (2.16c)**

N,N-Dibenzyl-3-(trimethylsilyl)propiolamide was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using *N,N*-dibenzylcarbamoyl chloride. The propiolate **2.16c** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:99) as a colorless oil (3.3 g, 51%).

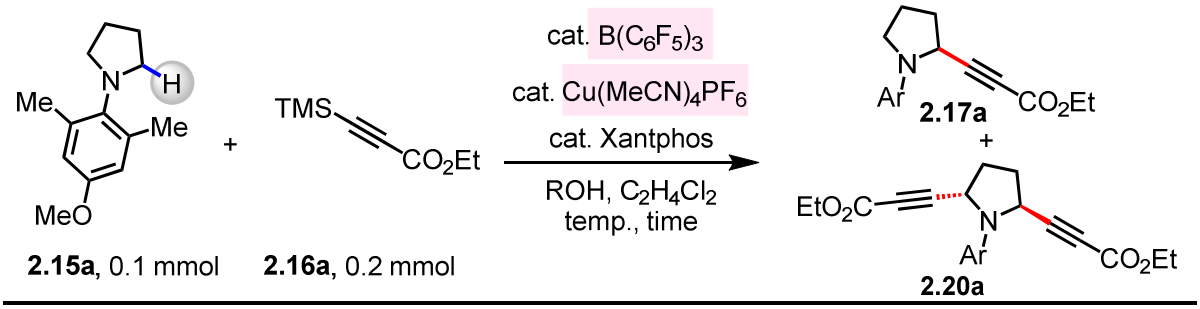
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 10H), 4.67 (s, 2H), 4.50 (s, 2H), 0.21 (s, 9H).

A2.2. Optimization Studies for α-Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Catalysts

Experimental Procedure for Evaluation of Reaction Conditions (see Table S1.3)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), Xantphos (0.01 mmol), and $C_2H_4Cl_2$ (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.2 mmol), alcohol (0.2 mmol), amine **2.15a** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.2 mL) were added to the vessel. The mixture was allowed to stir at 80 or 60 °C for 24 or 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard.

Table S1.3. Evaluation of Alcohol Additive and Reaction Conditions



2.15a, 0.1 mmol **2.16a**, 0.2 mmol

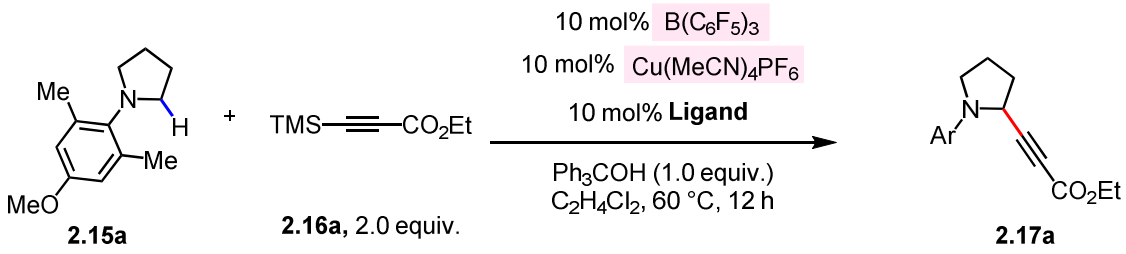
entry	alcohol (equiv.)	Temp. °C	time (h)	yield (%) **2.15a**	yield (%) **2.20a**
1	none	80	24	15	0
2	*i*-PrOH (2.0)	80	24	26	0
3	*t*-BuOH (2.0)	80	24	64	5
4	BnOH (2.0)	80	24	34	0
5	Ph_3COH (2.0)	80	24	52	34
6	1-adamantol (2.0)	80	24	93	<5
7	1-adamantol (2.0)	60	24	6	0
8	Ph_3COH (2.0)	60	24	79	19
9	Ph_3COH (1.0)	60	24	83	15
10	Ph_3COH (1.0)	60	12	90	<5

Conditions: *N*-arylpyrrolidine (**2.15a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), Xantphos (10 mol%), alcohol (0.2 or 0.1 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard.

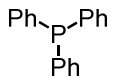
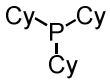
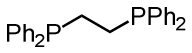
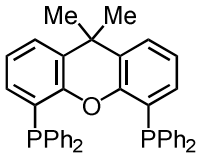
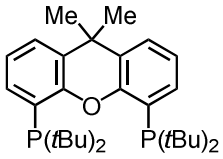
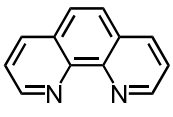
Experimental Procedure for Evaluation of Ligand for 1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine 2.15a (see Table S1.4)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), ligand (0.01 or 0.02 mmol), and $C_2H_4Cl_2$ (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.2 mmol), triphenylmethanol (0.1 mmol), amine **2.15a** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard.

Table S1.4. Evaluation of Ligand for the Reaction of 1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **2.15a** and **2.16a**



2.15a | **2.16a**, 2.0 equiv. | **2.17a**

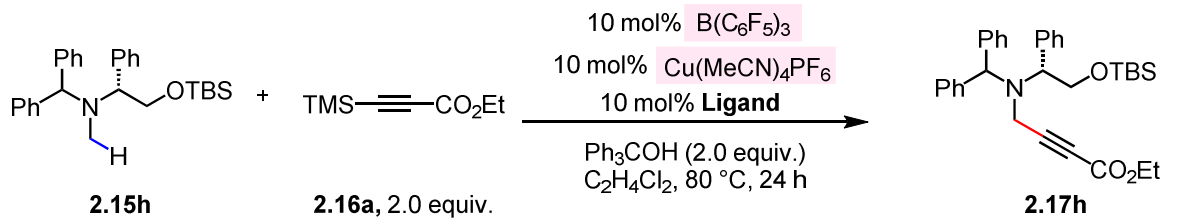
		
SI-L1	**SI-L2**	**SI-L3**
2.17a, 0% yield[a]	**2.17a,** 13% yield[a]	**2.17a**, 43% yield
		
SI-L4	**SI-L5**	**SI-L6**
2.17a, 90% yield	**2.17a,** 0% yield	**2.17a,** 0% yield

Conditions: *N*-arylpyrrolidine (**2.15a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), ligand (10 mol%), triphenylmethanol (0.1 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard. [a]20 mol% ligand was used.

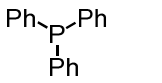
Experimental Procedure for Evaluation of Ligand for (*R*)-*N*-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (2.15h) (see Table S1.5)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), ligand (0.01 or 0.02 mmol), and $C_2H_4Cl_2$ (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.2 mmol), triphenylmethanol (0.1 mmol), amine **2.15h** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard.

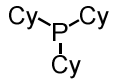
Table S1.5. Evaluation of Ligand for the Reaction of (*R*)-*N*-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (**2.15h**) and **2.16a**



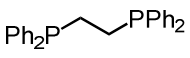
2.15h | **2.16a,** 2.0 equiv. | **2.17h**



SI-L1
2.17h, 45% yield[a]

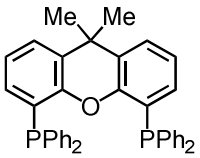


SI-L2
2.17h, 41% yield[a]

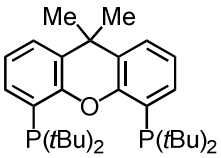


SI-L3
2.17h, 88% yield

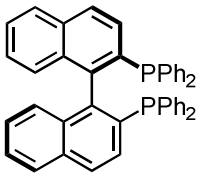
SI-L7
2.17h, 45% yield



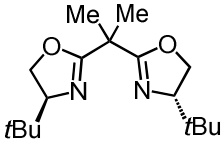
SI-L4
2.17h, 45% yield



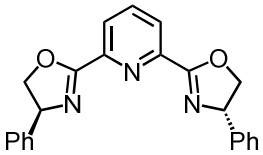
SI-L5
2.17h, 9% yield



L1
2.17h, 45% yield



SI-L8
2.17h, 38% yield



L3
2.17h, 64% yield

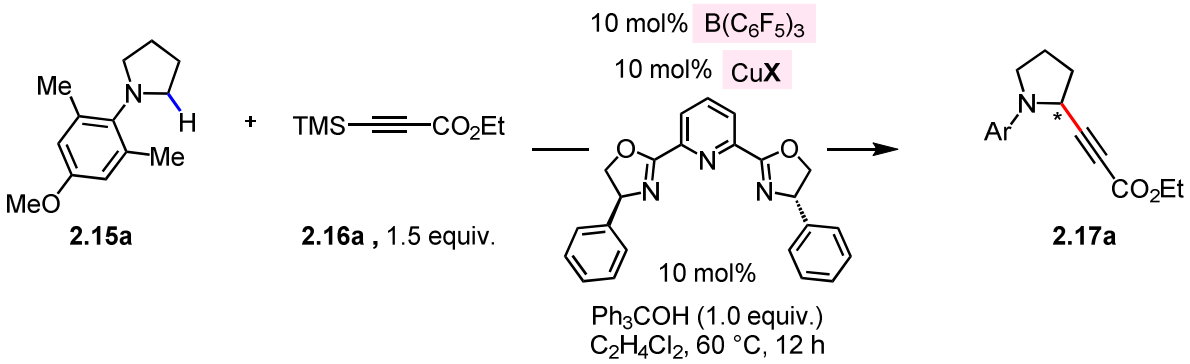
Conditions: *N*-arylpyrrolidine (**2.15h,** 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), ligand (10 mol%), triphenylmethanol (0.2 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2, 80 °C, 24 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. [a]20 mol% ligand was used.

Experimental Procedure for Evaluation of Copper Salt (see Table S1.6)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added CuX (0.01 mmol), (*S*)-Ph-PyBOX (0.01 mmol), and $C_2H_4Cl_2$ (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **2.15a** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^1H NMR analysis of

unpurified reaction mixtures using mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Table S1.6. Evaluation of Copper Salt



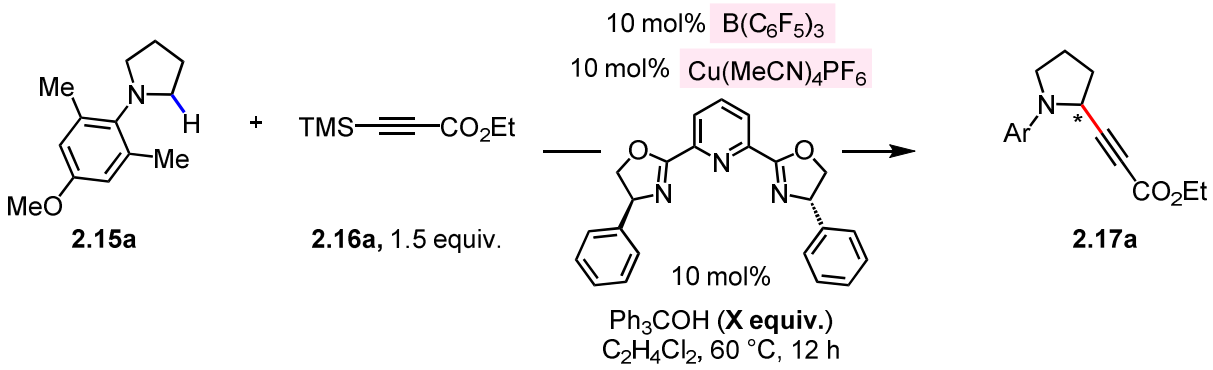
entry	Cu**X**	Yield of **2.17a** (%)	er of **2.17a**
1	CuBr	0	nd
2	CuCl	<3	65:35
3	CuI	0	nd
4	CuOTf·Benzene	13	71:29
5	$Cu(OTf)_2$	14	76:24
6	CuOAc	15	62:38
7	$Cu(OAc)_2$	4	62:38
8	$Cu(MeCN)_4PF_6$	69	81:19

Conditions: *N*-arylpyrrolidine (**2.15a,** 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a,** 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), CuX (10 mol%), (*S*)-PhPyBOX (10 mol%), triphenylmethanol (0.1 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Experimental Procedure for Optimization of Alcohol Additive for the Enantioselective Transformation (see Table S1.7)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), (*S*)-Ph-PyBOX (0.01 mmol), and $C_2H_4Cl_2$ (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 or 0.2 mmol), amine **2.15a** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Table S1.7. Effect of Alcohol Additive for the Enantioselective Transformation



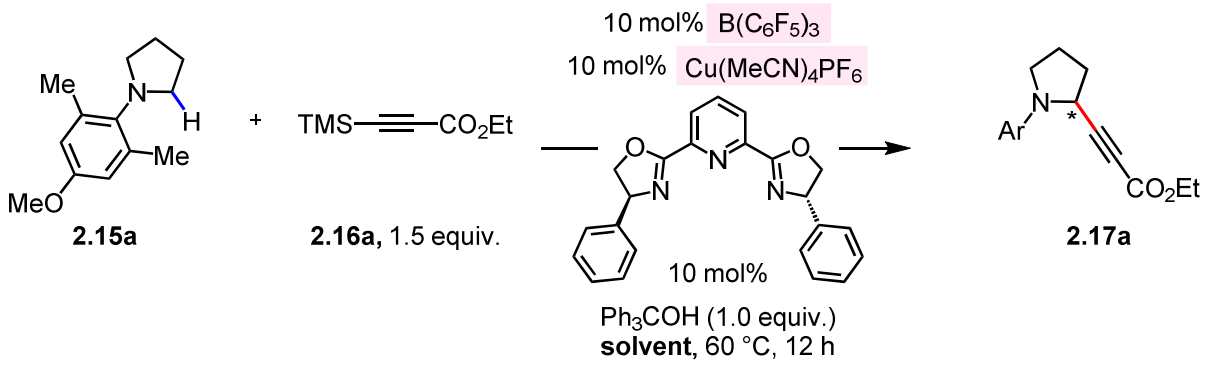
entry	Ph_3COH **(X equiv.)**	Yield of **2.17a** (%)	er of **2.17a**
1	1.0	69	81:19
2	2.0	98	77:23

Conditions: *N*-arylpyrrolidine (**2.15a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), (*S*)-PhPyBOX (10 mol%), triphenylmethanol (0.1 or 0.2 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Experimental Procedure for Evaluation of Solvent (see Table S1.8)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), (*S*)-Ph-PyBOX (0.01 mmol), and solvent (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **2.15a** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and solvent (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Table S1.8. Evaluation of Solvent



2.15a **2.16a,** 1.5 equiv. **2.17a**

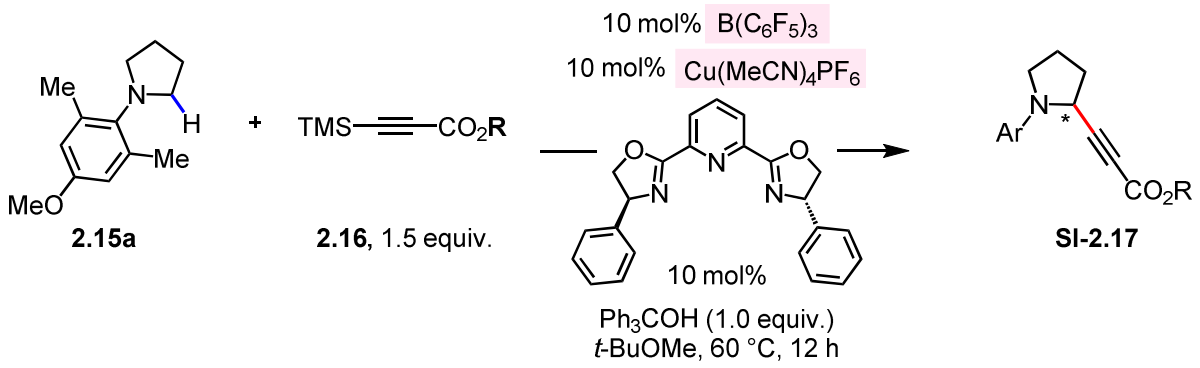
entry	**solvent**	Yield of **2.17a** (%)	er of **2.17a**
1	$CHCl_3$	48	59:14
2	CH_2Cl_2	62	78:22
3	$C_2H_4Cl_2$	69	81:19
4	Benzene	43	80:20
5	Toluene	54	71:29
6	THF	63	83:17
7	Et_2O	28	83:17
8	*t*-BuOMe	84	82:18

Conditions: *N*-arylpyrrolidine (**2.15a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), (*S*)-PhPyBOX (10 mol%), triphenylmethanol (0.1 mmol), solvent (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Experimental Procedure for Evaluation of Alkyne Substrate for the Stereoselective Transformation (see Table S1.9)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), (*S*)-Ph-PyBOX (0.01 mmol), and *t*-BuOMe (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then 3-(trimethylsilyl)propiolate **2.16** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **2.15a** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and *t*-BuOMe (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Table S1.9. Evaluation of Alkyne Substrates



entry	**CO_2R**	Yield of **SI-2.17** (%)	er of **SI-2.17**
1	Me	35	82:18
2	Et	84	82:18
3	*i*-Pr	0	nd
4	*i*-Bu	30	62:38
5	*t*-Bu	0	nd
6	Bn	59	64:36

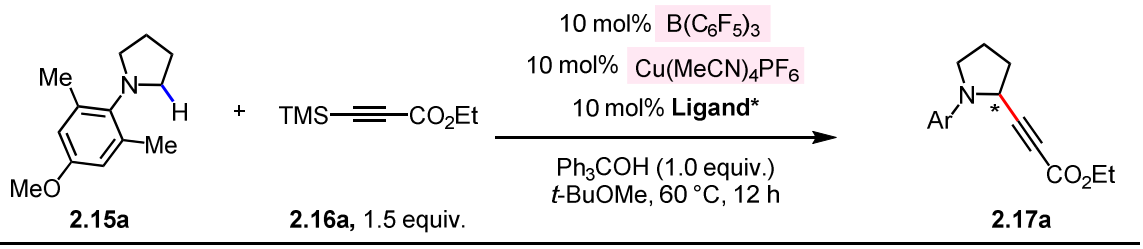
Conditions: *N*-arylpyrrolidine (**2.15a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16,** 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), (*S*)-PhPyBOX (10 mol%), triphenylmethanol (0.1 mmol), *t*-BuOMe (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Experimental Procedure for Evaluation of Chiral Ligands (see Table S1.10)

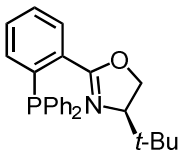
An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), ligand (0.01 mmol), and *t*-BuOMe (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **2.15a** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and *t*-BuOMe (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^{1}H NMR analysis of

unpurified reaction mixtures using mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

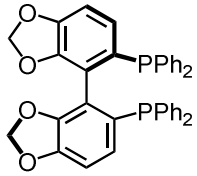
Table S1.10. Evaluation of Chiral Ligands



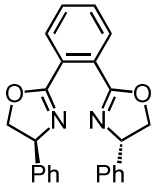
2.15a **2.16a,** 1.5 equiv. **2.17a**



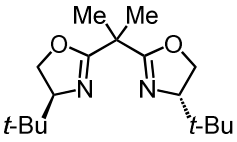
L8
2.17a, 15% yield
41:59 er



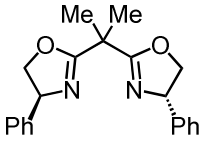
L9
2.17a, 89% yield
49:51 er



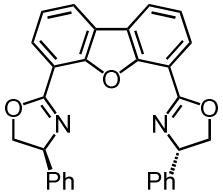
L10
2.17a, 29% yield
66:34 er



L11
2.17a, 81% yield
52:48 er



L12
2.17a, 53% yield
48:52 er



L13
2.17a, 6% yield
72:28 er

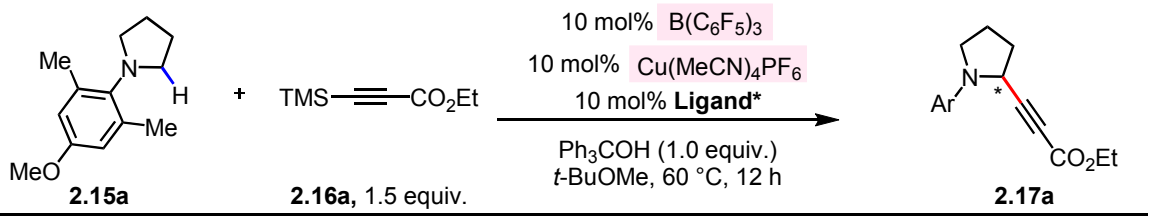
Conditions: *N*-arylpyrrolidine (**2.15a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a,** 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), Ligand (10 mol%), triphenylmethanol (0.1 mmol), *t*-BuOMe (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

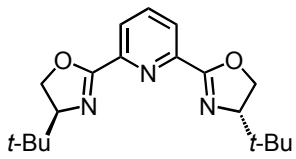
Experimental Procedure for Evaluation of PyBOX Ligands (see Table S1.11)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), ligand (0.01 mmol), and *t*-BuOMe (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **2.15a** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and *t*-BuOMe (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture

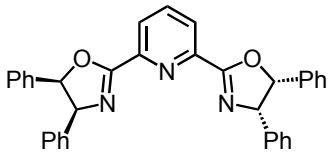
was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

Table S1.11. Evaluation of PyBOX Ligands

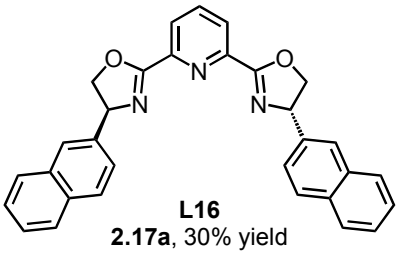




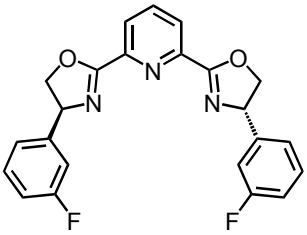
L14
2.17a, 30% yield
54:46 er



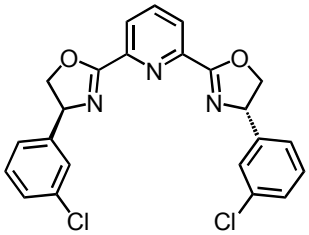
L15
2.17a, 32% yield
89:11 er



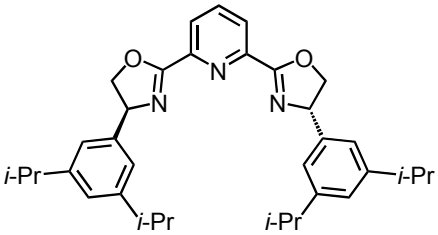
L16
2.17a, 30% yield
90:10 er



L17
2.17a, 31% yield
85:15 er



L18
2.17a, 70% yield
78:22 er



L19
2.17a, 73% yield
68:32 er

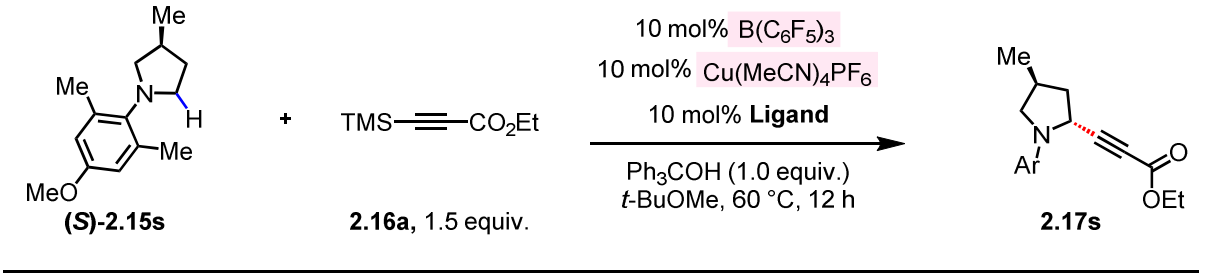
Conditions: *N*-arylpyrrolidine (**2.15a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), Ligand (10 mol%), triphenylmethanol (0.1 mmol), *t*-BuOMe (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

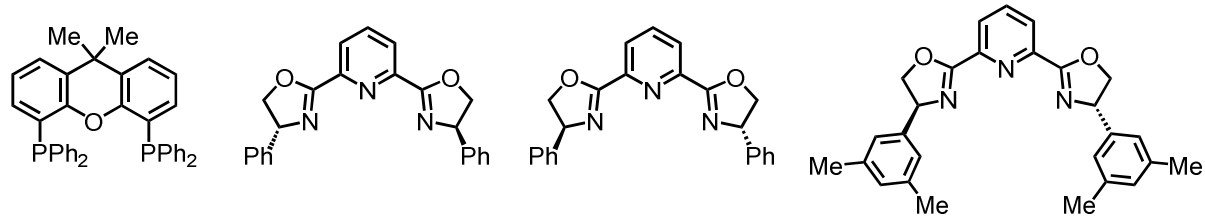
Experimental Procedure for Evaluation of Ligands for Amine (*S*)-2.15s (see Table S1.12)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), ligand (0.01 mmol), and *t*-BuOMe (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **(*S*)-2.15s**

(0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and *t*-BuOMe (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values and *trans:cis* ratios were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard.

Table S12. Evaluation of Ligands for Amine **(*S*)-2.15s**





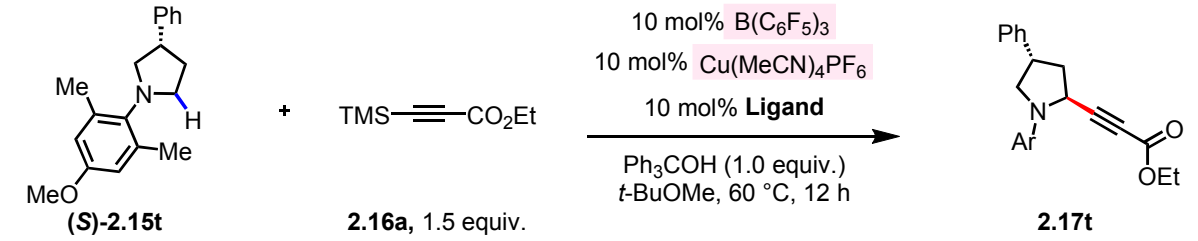
SI-L4	**(*R*)-L3**	**(*S*)-L3**	**L5**
2.17s, 61% yield	**2.17s**, 53% yield	**2.17s,** 34% yield	**2.17s**, 64% yield
1.8:1 *trans:cis*	5.6:1 *trans:cis*	5.8:1 *trans:cis*	11.8:1 *trans:cis*

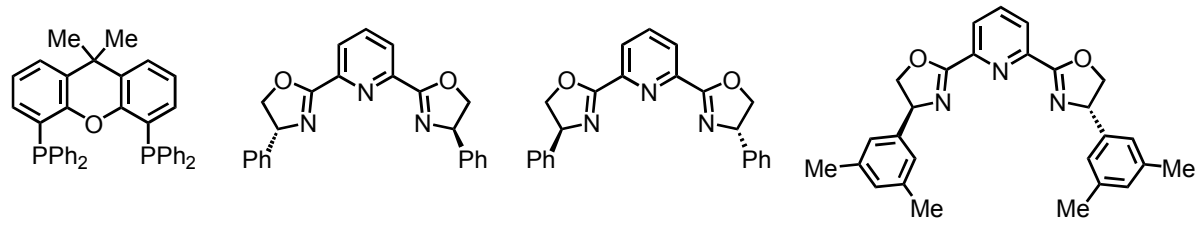
Conditions: *N*-arylpyrrolidine (**(*S*)-2.15s,** 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a,** 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), ligand (10 mol%), triphenylmethanol (0.1 mmol), *t*-BuOMe (0.4 mL), under N_2, 60 °C, 12 h. Yield values and *trans:cis* ratio were determined by ^1H NMR analysis of the unpurified reaction mixtures with mesitylene as the internal standard.

Experimental Procedure for Evaluation of Ligands for the Reaction of Amine (*S*)-2.15t and 2.16a (see Table S1.13)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), ligand (0.01 mmol), and *t*-BuOMe (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **(*S*)-2.15t** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and *t*-BuOMe (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values and *trans:cis* ratios were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard.

Table S1.13. Evaluation of Ligands for Amine **(*S*)-2.15t**





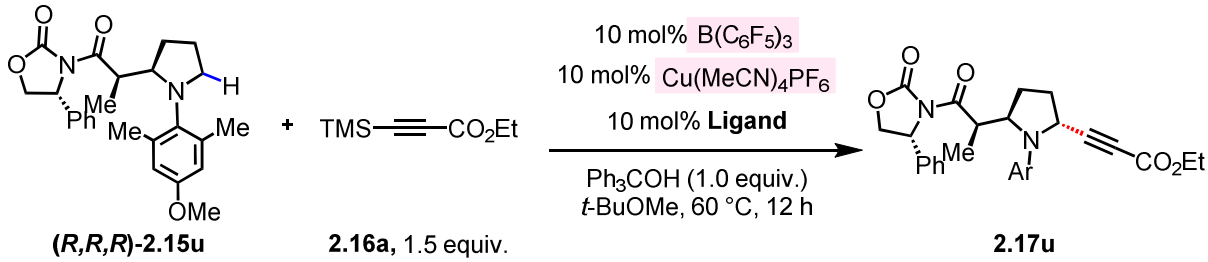
SI-L4	**(*R*)-L3**	**(*S*)-L3**	**L5**
2.17t, 27% yield	**2.17t**, 31% yield	**2.17t**, 35% yield	**2.17t**, 68% yield
2.3:1 *trans:cis*	3.5:1 *trans:cis*	4.2:1 *trans:cis*	10.1:1 *trans:cis*

Conditions: *N*-arylpyrrolidine (**(*S*)-2.15t**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), ligand (10 mol%), triphenylmethanol (0.1 mmol), *t*-BuOMe (0.4 mL), under N_2, 60 °C, 12 h. Yield values and *trans:cis* ratio were determined by ^1H NMR analysis of the unpurified reaction mixtures with mesitylene as the internal standard.

Experimental Procedure for Evaluation of Ligands for the Reaction of Amine (*R,R,R*)-2.15u and 2.16a (see Table S1.14)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), ligand (0.01 mmol), and *t*-BuOMe (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **(*R,R,R*)-2.15u** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and *t*-BuOMe (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Yield values and *trans:cis* ratios were determined by ^{1}H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard.

Table S1.14. Evaluation of Ligands for **(*R,R,R*)-2.15u**



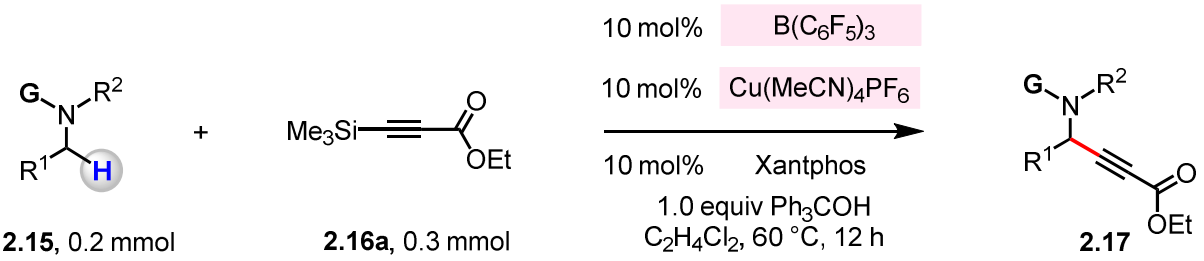
(*R,R,R*)-2.15u | **2.16a,** 1.5 equiv. | **2.17u**

SI-L4	**(*R*)-L3**	**(*S*)-L3**	**L5**
2.17u, 54% yield	**2.17u**, 81% yield	**2.17u**, 49% yield	**2.17u**, 93% yield
5.8:1 *trans:cis*	1.9:1 *trans:cis*	7.2:1 *trans:cis*	7.7:1 *trans:cis*

Conditions: *N*-arylpyrrolidine (**(*R,R,R*)-2.15u**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.16a,** 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), ligand (10 mol%), triphenylmethanol (0.1 mmol), *t*-BuOMe (0.4 mL), under N_2, 60 °C, 12 h. Yield values and *trans:cis* ratio were determined by ^{1}H NMR analysis of the unpurified reaction mixtures with mesitylene as the internal standard.

A2.3 General Procedures for α-C–H Alkynylation of *N*-Alkylamines by $B(C_6F_5)_3$ and Organocopper Complex

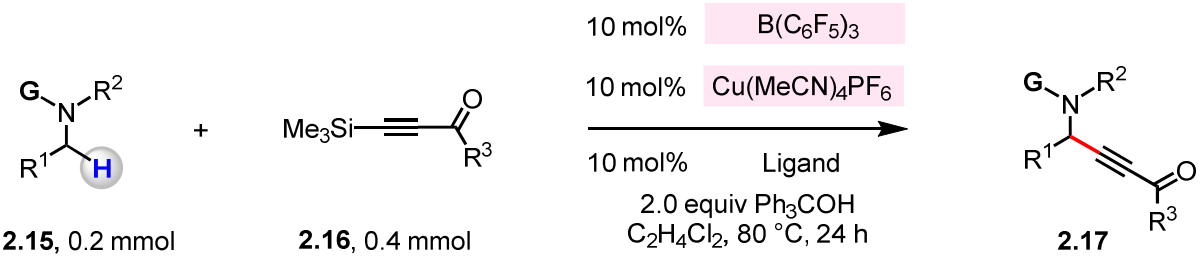
General Procedure A for α-C–H Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Complex



2.15, 0.2 mmol **2.16a**, 0.3 mmol **2.17**

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.02 mmol), Xantphos (0.02 mmol), and $C_2H_4Cl_2$ (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.3 mmol), triphenylmethanol (0.2 mmol), amine **2.15** (0.2 mmol), $B(C_6F_5)_3$ (0.02 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.4 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. The propargylamine product was purified and isolated by silica gel chromatography.

General Procedure B for α-C–H Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Complex

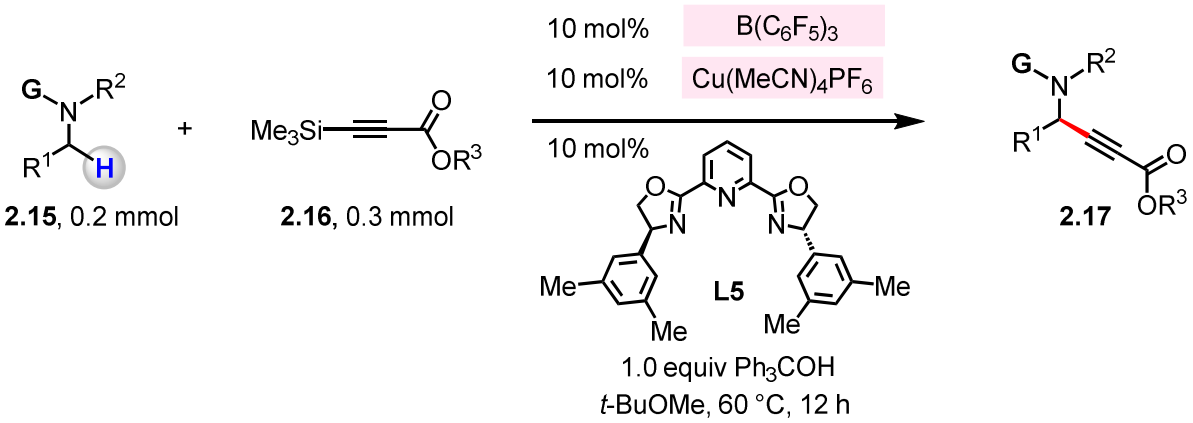


2.15, 0.2 mmol **2.16**, 0.4 mmol **2.17**

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.02 mmol), ligand (1,2-bis(diphenylphosphino)ethane or (*S*)-PhPyBOX, 0.02 mmol), and $C_2H_4Cl_2$ (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then (trimethylsilyl)propiolate **2.16** (0.4 mmol), triphenylmethanol (0.4 mmol), amine **2.15** (0.2 mmol), $B(C_6F_5)_3$ (0.02, 10 mol%), and $C_2H_4Cl_2$ (0.4 mL) were added to

the vessel. The mixture was allowed to stir at 80 °C for 24 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. The propargylamine product was purified and isolated by silica gel column chromatography.

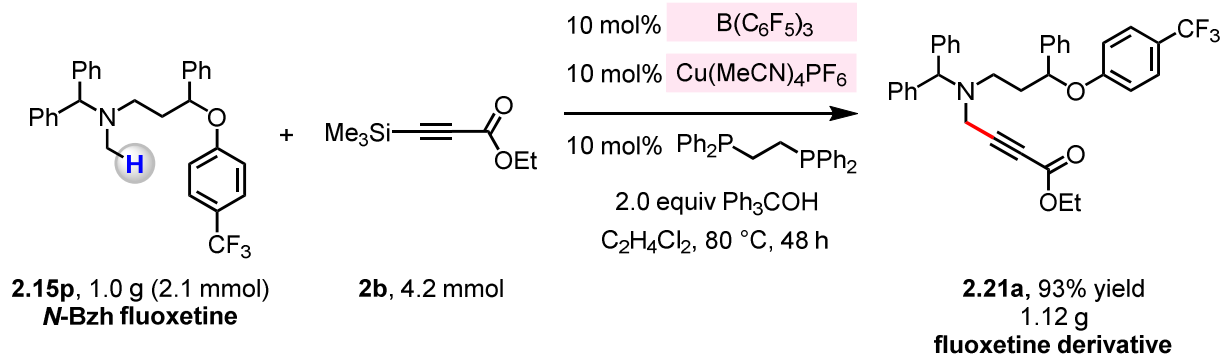
General Procedure C for Stereoselective α-C–H Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Complex



An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.02 mmol), (*S*)-(3,5-dimethylphenyl)PyBOX **L5** (0.02 mmol), and *t*-BuOMe (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then (trimethylsilyl)propiolate **2.16** (0.3 mmol), triphenylmethanol (0.2 mmol), amine **2.15** (0.2 mmol), $B(C_6F_5)_3$ (0.02 mmol, 10 mol%), and solvent (0.4 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with Et_2O. The combined organic material was then concentrated *in vacuo*. The propargylamine product was purified isolated by silica gel chromatography. The er values were determined by HPLC analysis of the isolated product.

A2.4 Procedures for Large Scale Reactions

Procedure for Gram-Scale Synthesis of Alkynylated Fluoxetine Derivative 2.21a



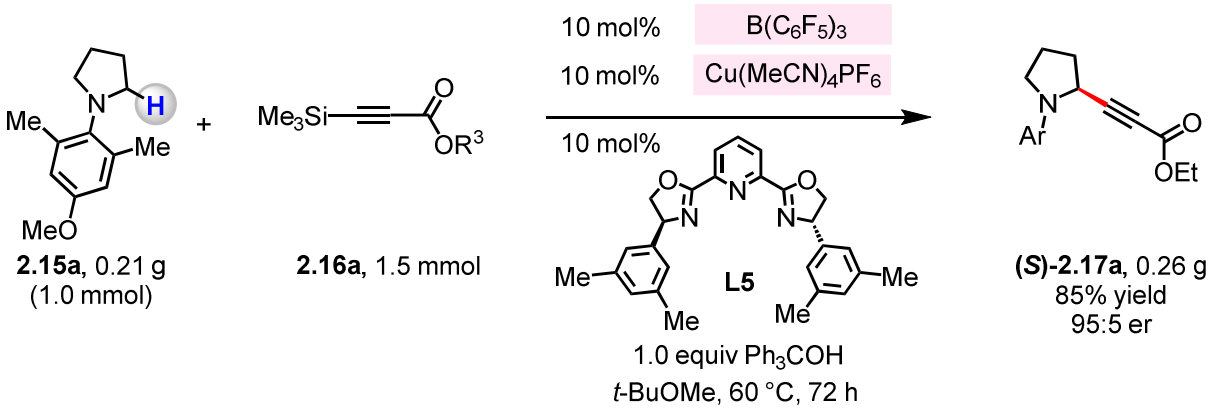
2.15p, 1.0 g (2.1 mmol)
***N*-Bzh fluoxetine**

2b, 4.2 mmol

2.21a, 93% yield
1.12 g
fluoxetine derivative

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (78 mg, 0.21 mmol), 1,2-bis(diphenylphosphino)ethane (84 mg, 0.21 mmol), and $C_2H_4Cl_2$ (4.0 mL) under nitrogen atmosphere. The mixture was allowed to stir for 30 minutes at 22 °C, then (trimethylsilyl)propiolate **2.16a** (715 mg, 4.2 mmol), triphenylmethanol (1.1 g, 4.2 mmol), amine **2.15p** (1.0 g, 2.1 mmol), $B(C_6F_5)_3$ (108 mg, 0.21 mmol), and $C_2H_4Cl_2$ (4.0 mL) were added to the vessel. The mixture was allowed to stir at 80 °C for 48 h. Upon completion, the unpurified reaction mixture was concentrated *in vacuo*. The amine product **2.21a** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:19) as a colorless solid (1.12 g, 1.95 mmol, 93%).

Procedure for Enantioselective α-Alkynylation Reaction in 1.0 mmol Scale



2.15a, 0.21 g
(1.0 mmol)

2.16a, 1.5 mmol

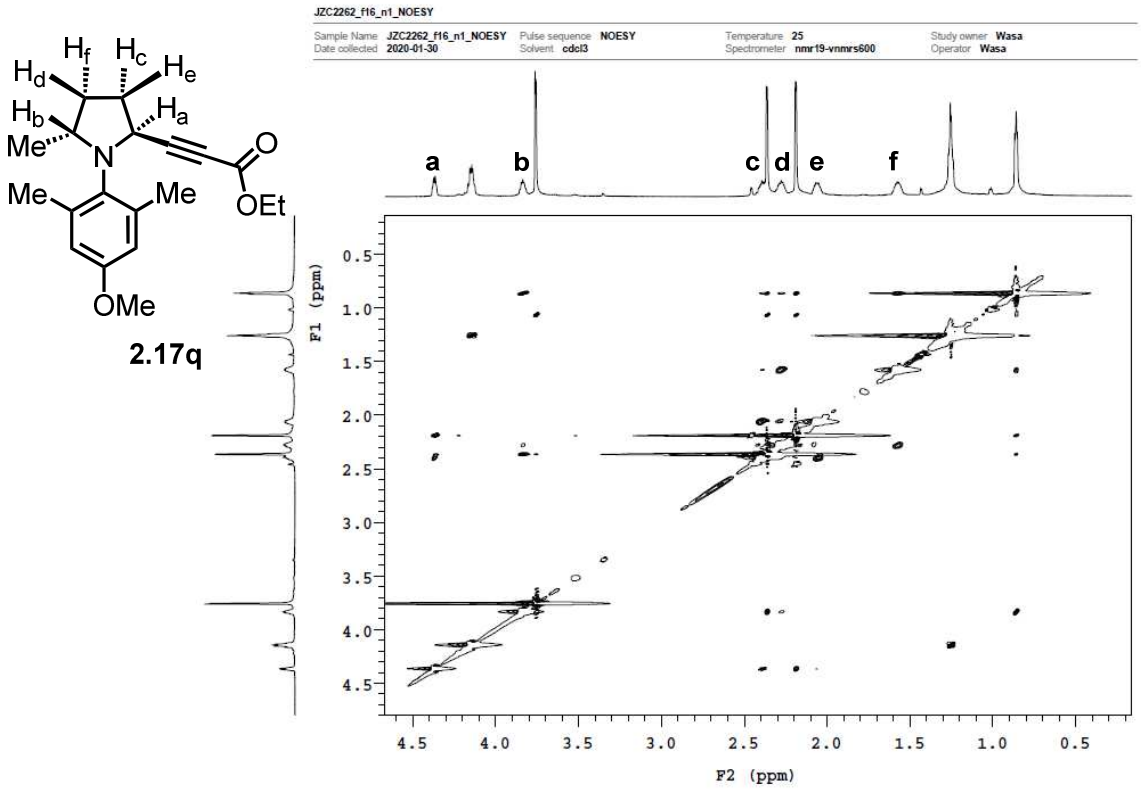
(*S*)-2.17a, 0.26 g
85% yield
95:5 er

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (19 mg, 0.05 mmol), (*S*)-(3,5-dimethylphenyl)PyBOX **L5** (23 mg, 0.05 mmol), and *t*-BuOMe (2.0 mL) under nitrogen atmosphere. The mixture was allowed to stir for

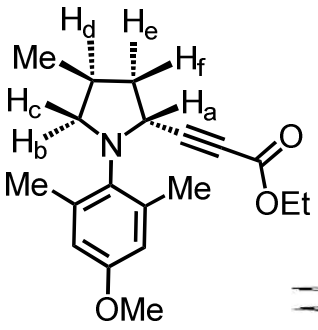
30 minutes at 22 °C, then (trimethylsilyl)propiolate **2.16a** (255 mg, 1.5 mmol), triphenylmethanol (260 mg, 1.0 mmol), amine **2.15a** (205 mg, 1.0 mmol), $B(C_6F_5)_3$ (26 mg, 0.05 mmol), and *t*-BuOMe (2.0 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 72 h. Upon completion, the unpurified reaction mixture was concentrated *in vacuo*. The amine product **(*S*)-2.17a** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:19) as a colorless solid (260 mg, 0.85 mmol, 85%).

A.3. Determination of Relative Configuration

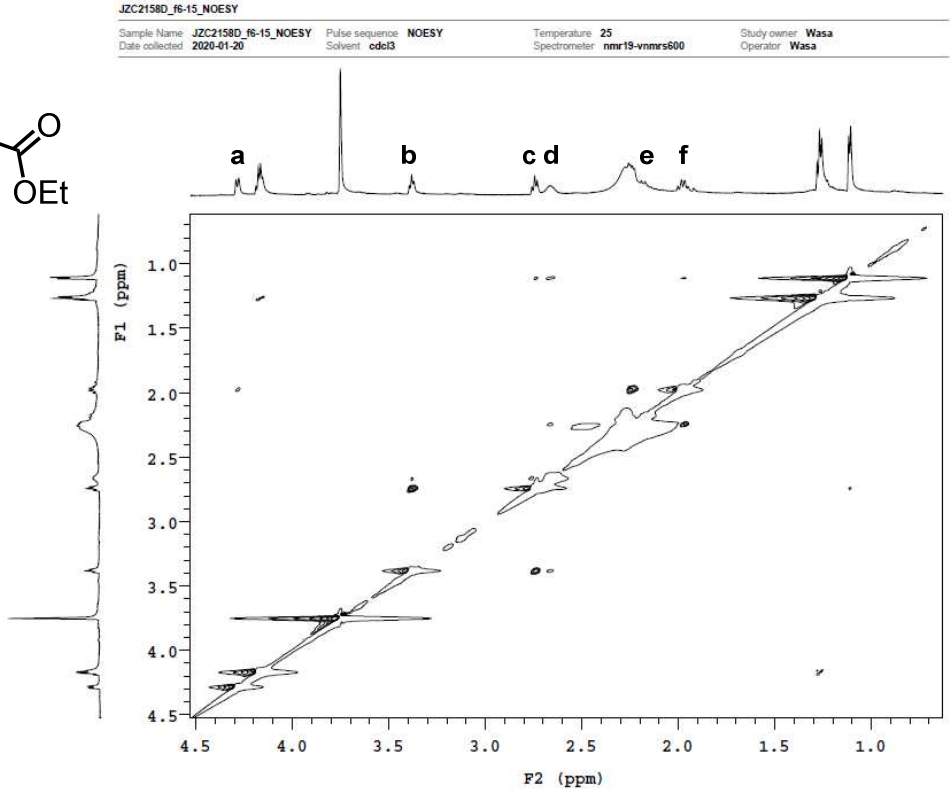
We carried out the following 2D NMR studies in order to determine relative configuration of enantioenriched products **2.17q, 2.17s**, **2.17t**, **2.17u-*trans***, and **2.17u-*cis***.

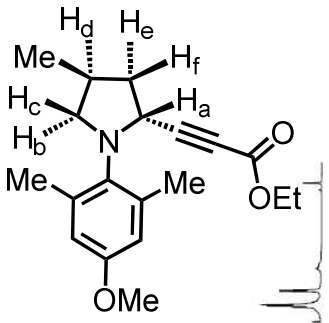


The relative configuration of the major diastereomer of **2.17q** was assigned to be *trans*.

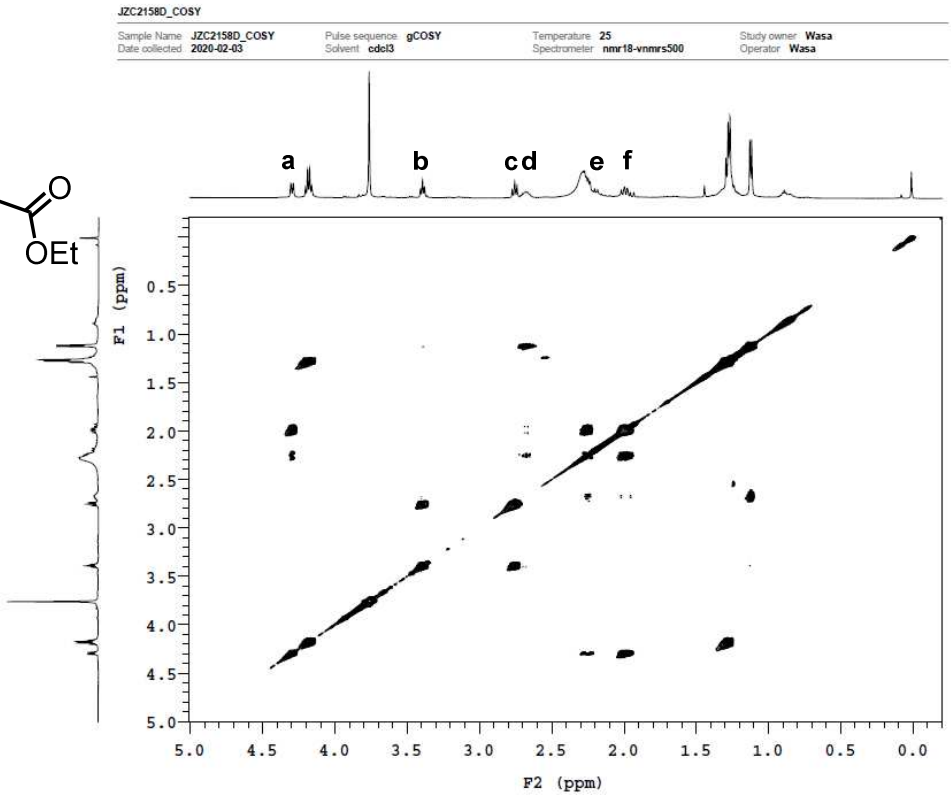

Hd
He
Me
Hf
Hc
Ha
Hb
N
O
Me
Me
OEt
OMe

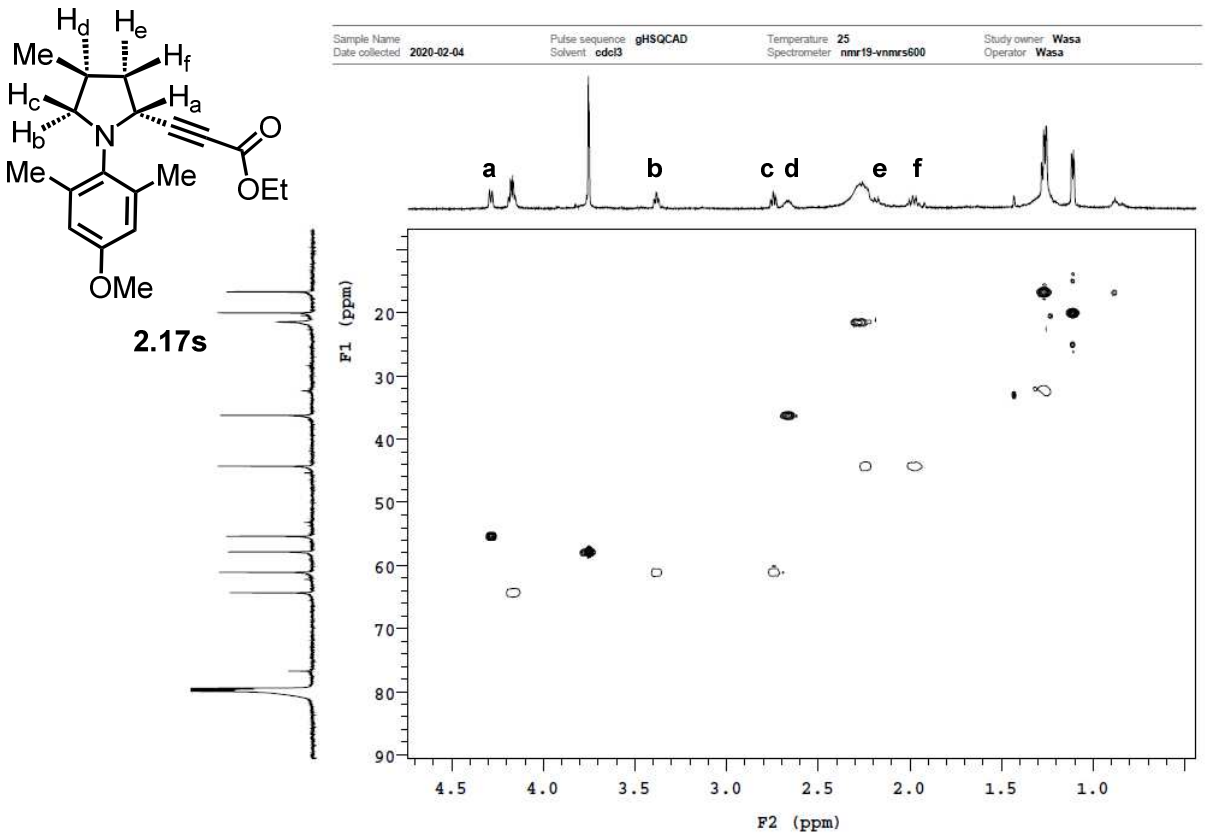
2.17s


JZC2158D_f6-15_NOESY
Sample Name JZC2158D_f6-15_NOESY
Date collected 2020-01-20
Pulse sequence NOESY
Solvent cdcl3
Temperature 25
Spectrometer nmr19-vnmrs600
Study owner Wasa
Operator Wasa
a
b
c d
e
f
F1 (ppm)
F2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5


Hd
He
Me
Hf
Hc
Ha
Hb
N
O
Me
Me
OEt
OMe

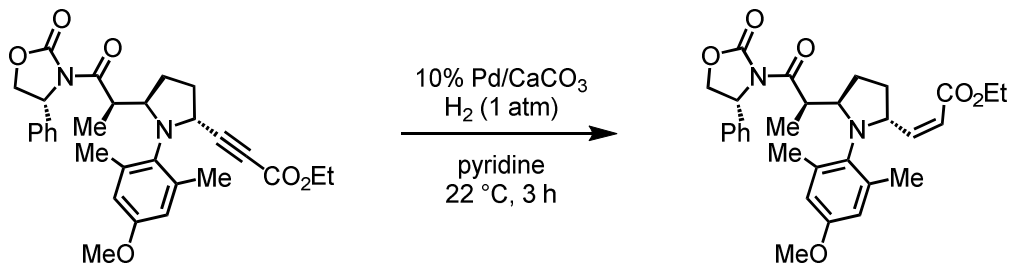
2.17s


JZC2158D_COSY
Sample Name JZC2158D_COSY
Date collected 2020-02-03
Pulse sequence gCOSY
Solvent cdcl3
Temperature 25
Spectrometer nmr18-vnmrs500
Study owner Wasa
Operator Wasa
a
b
cd
e
f
F1 (ppm)
F2 (ppm)



The relative configuration of the major diastereomer of **2.17s** was assigned as *trans*. The relative configuration of **2.17t** was assigned in analogy.

Propargylamine **2.17u-major** was transformed to **15-major** according to the literature procedure.[9]

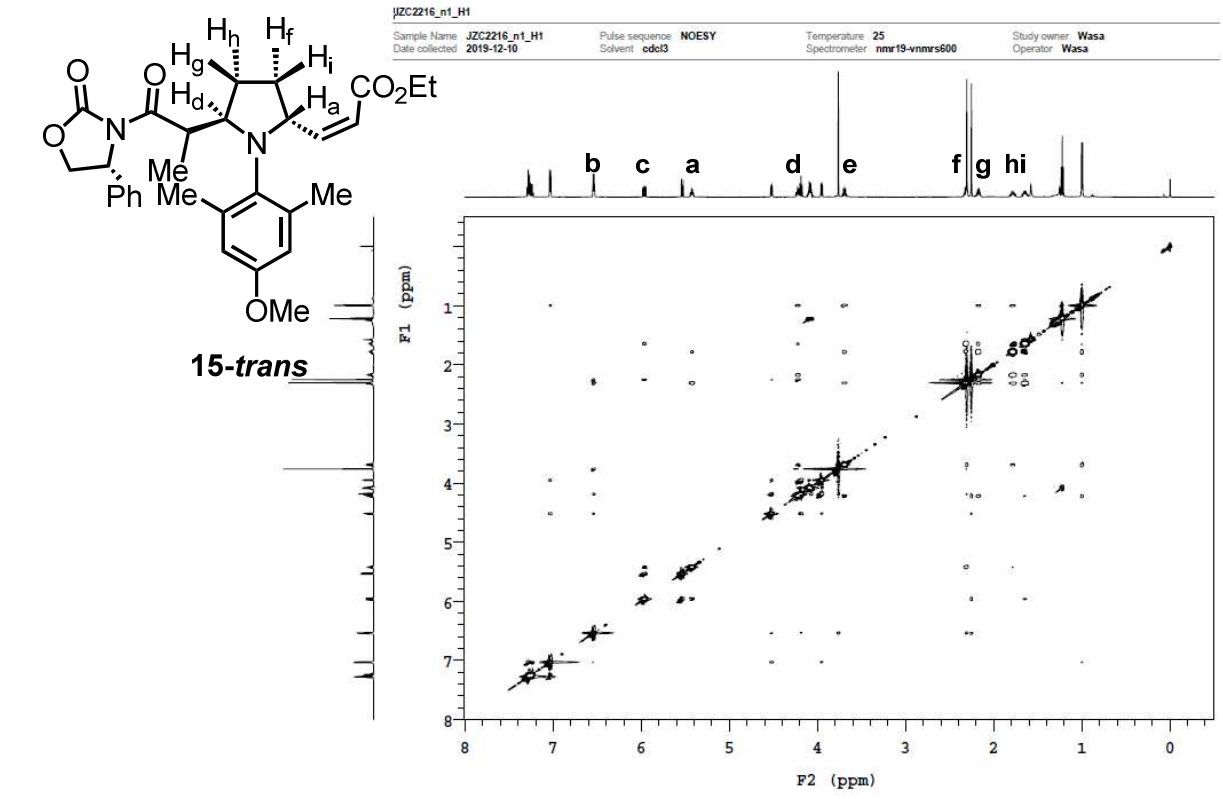


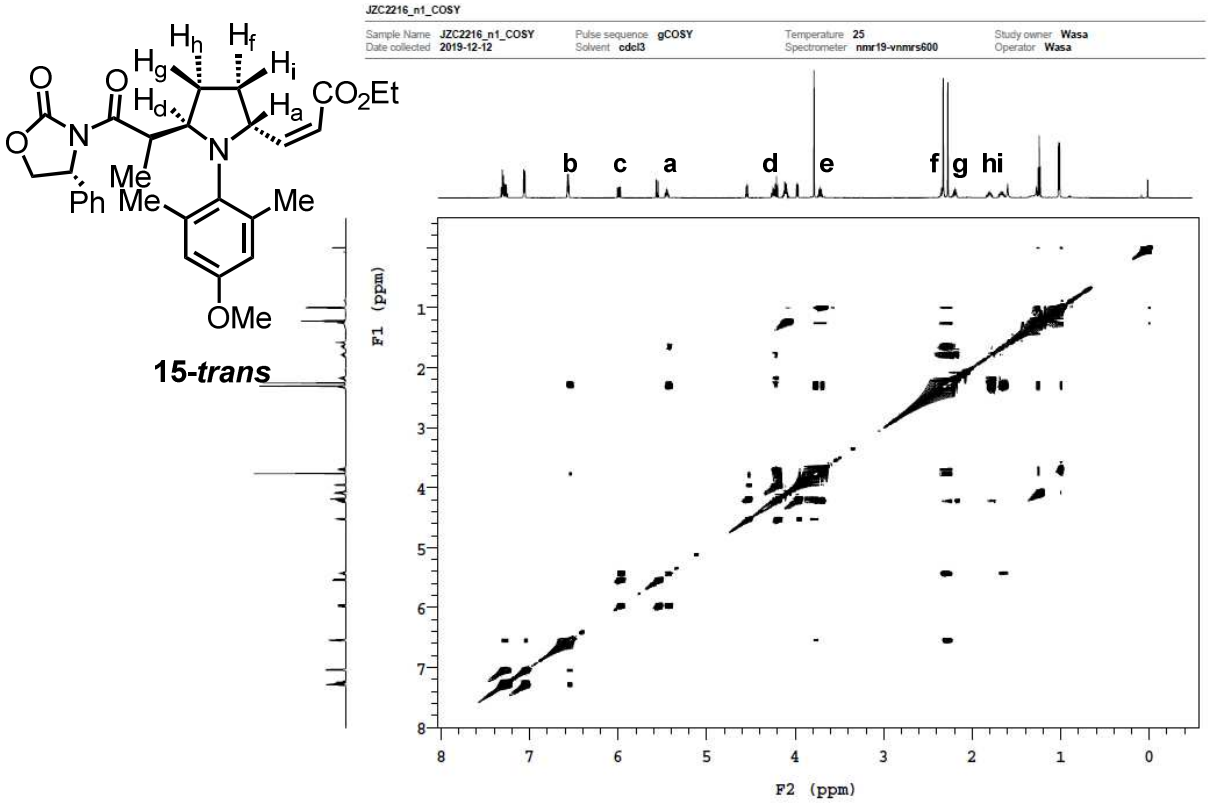
2.17u-major **15-major**, 98% yield

Ethyl (*Z*)-3-((2*R*,5*R*)-1-(4-methoxy-2,6-dimethylphenyl)-5-((*R*)-1-oxo-1-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)propan-2-yl)pyrrolidin-2-yl)acrylate (15-major)

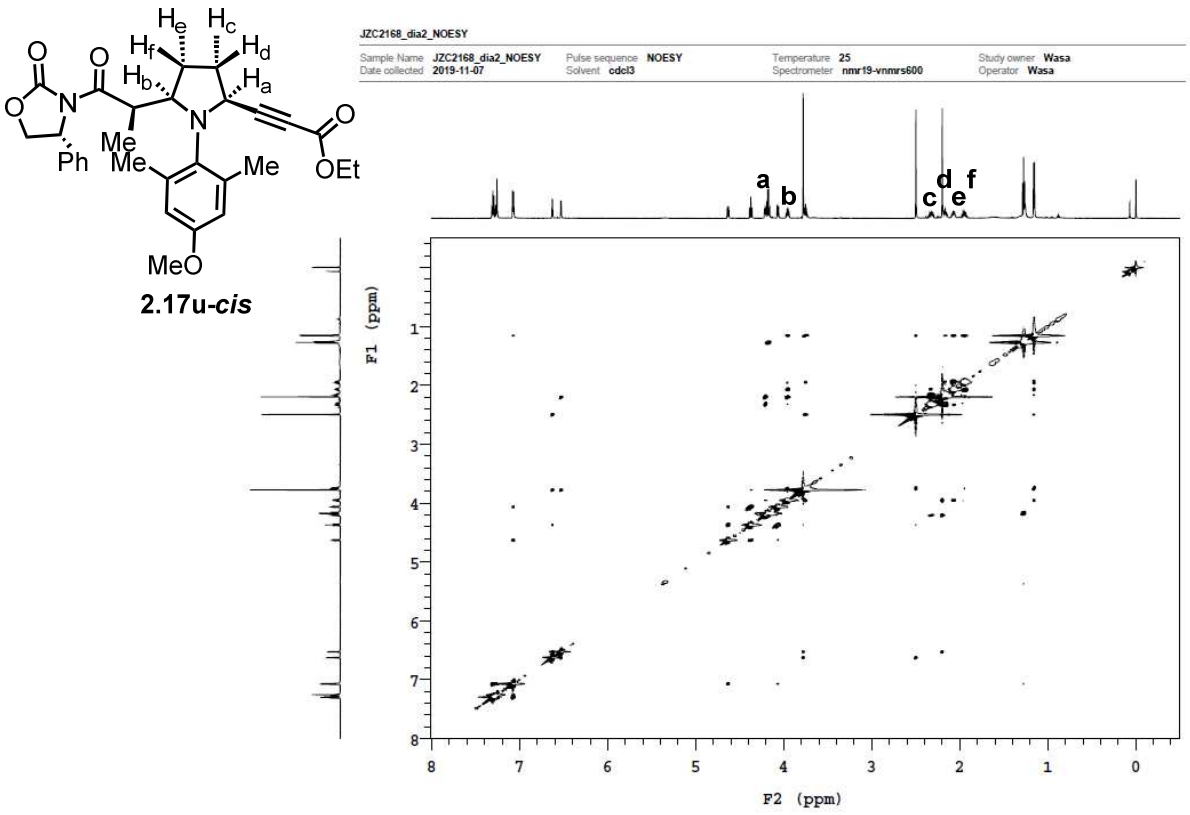
To a solution of **2.17u-major** (26 mg, 0.05 mmol) in pyridine (0.5 mL) was added Pd/$CaCO_3$ (2.6 mg, 10% wt). The mixture was evacuated and filled with hydrogen gas three times. The mixture was allowed to stir under hydrogen atmosphere at 22 °C for 3 h. Upon completion (determined by TLC), the reaction was filtered through a plug of Celite using EtOAc as the eluent. The amine product **15-major** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:4) as a colorless oil (25.5 mg, 0.05 mmol, 98%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 3H), 7.06 – 7.02 (m, 2H), 6.57 – 6.50 (m, 2H), 5.97 (ddd, *J* = 11.6, 8.7, 1.0 Hz, 1H), 5.54 (dt, *J* = 11.7, 1.1 Hz, 1H), 5.43 (td, *J* = 8.9, 5.7 Hz, 1H), 4.52 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.23 (dt, *J* = 9.5, 4.7 Hz, 1H), 4.19 (td, *J* = 8.4, 1.1 Hz, 1H), 4.09 (qdd, *J* = 7.1, 3.8, 1.0 Hz, 2H), 3.95 (ddd, *J* = 8.4, 2.4, 1.1 Hz, 1H), 3.77 (d, *J* = 1.0 Hz, 3H), 3.73 – 3.66 (m, 1H), 2.34 – 2.28 (m, 4H), 2.26 (s, 3H), 2.18 (dt, *J* = 11.8, 6.1 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.65 (tdd, *J* = 12.2, 9.2, 6.5 Hz, 1H), 1.58 (s, 1H), 1.22 (td, *J* = 7.1, 1.0 Hz, 3H), 1.00 (dd, *J* = 6.8, 1.0 Hz, 3H); **IR** (neat) 2957, 2926, 2855, 1778, 1713, 1480, 1411, 1182, 1155, 760, 699 cm^{-1}; $[\alpha]^{25}_D$ = –289.9° (*c* 0.5, CH_2Cl_2).



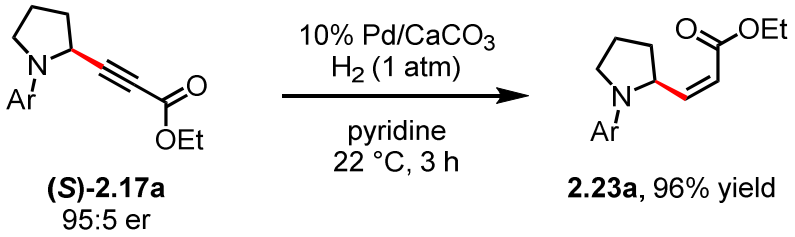


The relative configuration of **15-major** (derivative of **2.17u-major**) was assigned as *trans*.



The relative configuration of the minor diastereomer of **2.17u** was assigned as *cis*.

A4. Determination of Absolute Configuration and Derivatization Experiments



Ethyl (*S,Z*)-3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)acrylate (2.23a)

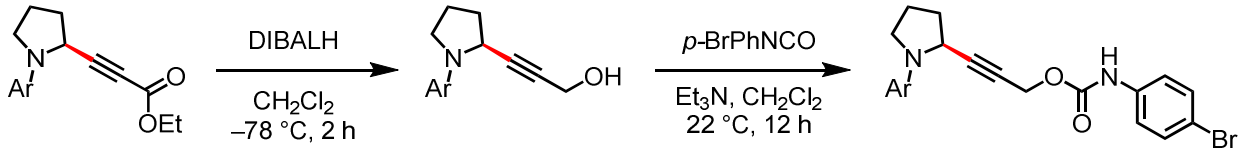
Ethyl (*S,Z*)-3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)acrylate (**2.23a**) was prepared according to the literature procedure.[9]

To a solution of **(*S*)-2.17a** (30.1 mg, 0.1 mmol) in pyridine (0.5 mL) was added Pd/$CaCO_3$ (3.0 mg, 10% wt). The mixture was evacuated and filled with hydrogen gas three times. The reaction was allowed to stir under hydrogen atmosphere at 22 °C for 3 h. Upon completion (determined by TLC), the reaction was filtered through a plug of Celite using EtOAc as the eluent. The amine product **2.23a** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:19) as a colorless oil (29 mg, 0.10 mmol, 96%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.54 (s, 2H), 6.19 (ddd, *J* = 11.7, 8.7, 1.2 Hz, 1H), 5.56 (dt, *J* = 11.6, 1.3 Hz, 1H), 5.26 – 5.16 (m, 1H), 4.06 (qdd, *J* = 7.0, 5.0, 2.3 Hz, 2H), 3.73 (s, 3H), 3.41 – 3.30 (m, 1H), 3.07 (q, *J* = 7.6 Hz, 1H), 2.37 – 2.30 (m, 1H), 2.28 (s, 6H), 2.06 – 1.96 (m, 2H), 1.72 (dt, *J* = 12.1, 6.9 Hz, 1H), 1.20 (td, *J* = 7.2, 1.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.2, 156.6, 154.2, 137.3, 118.8, 59.8, 58.3, 55.1, 51.8, 33.5, 25.5, 19.3, 14.2; **IR** (neat) 2952, 2835, 1715, 1601, 1482, 1317, 1266, 1189, 1154, 1067, 1030, 827 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{18}H_{26}NO_3$ (MH^+): 304.1907; found: 304.1906; $[\alpha]^{25}_D$ = –97.5° (*c* 0.6, CH_2Cl_2).

Determination of Absolute Configuration for 2.17a

We carried out the following studies in order to determine the absolute configuration of enantioenriched products **2.17a**, **2.17b**, and **2.17c**. The absolute configuration of **(*S*)-2.17a** was determined by X-ray crystallographic analysis of **2.23c**. The absolute configuration of **2.17b** and **2.17c** were assigned in analogy.



(*S*)-2.17a 95:5 er

2.23b, >99% yield

2.23c, 71% yield

(*S*)-3-(1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)prop-2-yn-1-ol (2.23b)

(*S*)-3-(1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)prop-2-yn-1-ol (**2.23b**) was prepared according to the literature procedure.[10] A solution of **(*S*)-2.17a** (100 mg, 0.3 mmol) in CH_2Cl_2 (5.0 mL) was cooled to −78 °C. DIBAL-H (0.1 mL, 0.5 mmol) was added dropwise. The mixture was allowed to stir for 2 h at −78 °C. Then, potassium sodium tartarate (saturated aqueous solution, 3.0 mL) was added and stirred. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The amine product **2.23b** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:1) as a colorless oil (85.7 mg, 0.3 mmol, >99% yield).

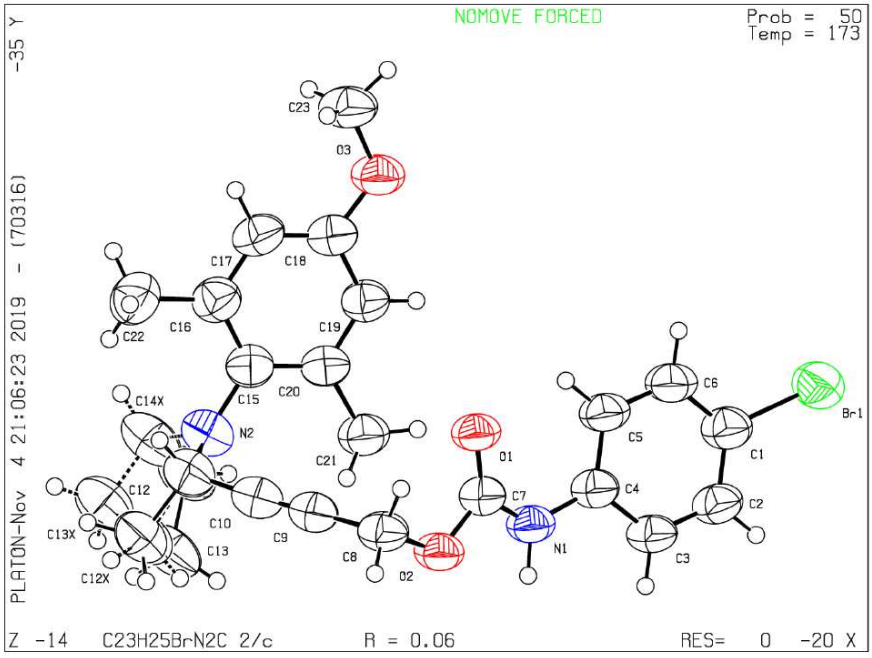
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 2H), 4.22 (ddd, J = 6.7, 4.8, 1.7 Hz, 1H), 4.13 (s, 2H), 3.73 (s, 3H), 3.34 (td, J = 7.6, 4.4 Hz, 1H), 3.06 (q, J = 7.4 Hz, 1H), 2.42 – 2.17 (m, 7H), 2.17 – 2.01 (m, 2H), 1.96 (dtd, J = 11.7, 6.2, 5.8, 3.1 Hz, 1H), 1.70 (d, J = 4.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.8, 136.4, 113.5, 88.6, 79.5, 55.1, 52.1, 51.2, 50.7, 34.4, 25.3, 19.0; **IR** (neat) 3379, 2939, 2834, 1600, 1482, 1273, 1153, 1066, 925, 835, 571 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{22}NO_2$ (MH^+): 260.1645; found: 260.1645.

(*S*)-3-(1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)prop-2-yn-1-yl (4-bromophenyl)carbamate (2.23c)

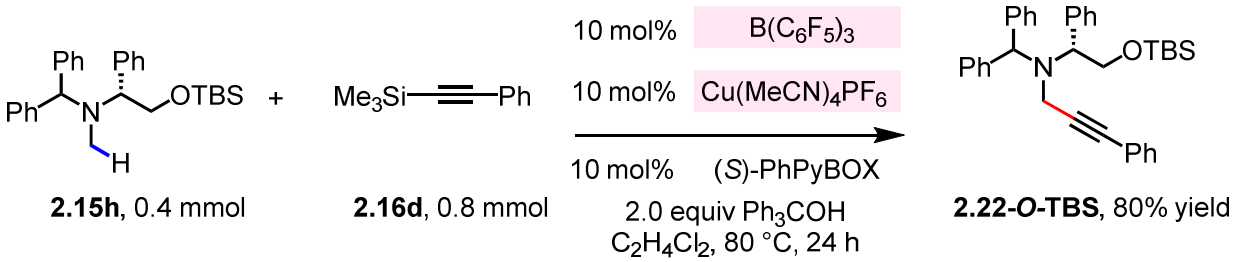
(*S*)-3-(1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)prop-2-yn-1-yl (4-bromophenyl)carbamate was prepared according to the literature procedure.[10] To a solution of **2.23b** (50 mg, 0.2 mmol) in CH_2Cl_2 (1.0 mL), *p*-bromophenyl isocyanate (113 mg, 0.6 mmol) and Et_3N (96 mg, 1.0 mmol) were added. The mixture was allowed to stir at 22 °C for 12 h. Upon

completion (determined by TLC), the mixture was filtered through a short plug of Celite using CH_2Cl_2 as the eluent. The organic layer was concentrated *in vacuo*. The amine product **2.23c** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:1) as a colorless solid (61.3 mg, 71%).

Amine **2.23c** was recrystallized using the vapor-vapor diffusion method, using Et_2O to dissolve the product in an inner vial, and pentane as the precipitant placed in the outer vial in order for slow diffusion to occur into the inner vial. The solution was cooled to 0 °C, whereupon a crystal was obtained for X-ray crystallography. The X-ray crystallographic analysis revealed that the absolute configuration of **2.23c** is (*S*), see SI Section 9 for X-ray crystallographic data. The absolute configuration of **2.17a** is (*S*). The absolute configuration of **2.17b** and **2.17c** were assigned in analogy to **2.17a**.



Procedure for Preparation of Propargylamine 2.22-*O*-TBS



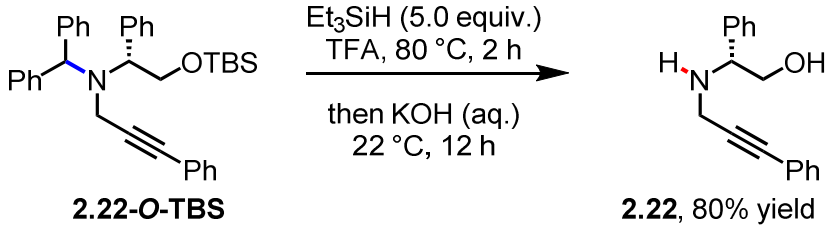
2.15h, 0.4 mmol **2.16d**, 0.8 mmol **2.22-*O*-TBS**, 80% yield

(*R*)-*N*-Benzhydryl-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)-3-phenylprop-2-yn-1-amine (2.22-*O*-TBS)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.04 mmol), (*S*)-PhPyBOX, 0.04 mmol), and $C_2H_4Cl_2$ (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then (trimethylsilyl)propiolate **2.16d** (0.8 mmol), triphenylmethanol (0.8 mmol), amine **2.15h** (0.4 mmol), $B(C_6F_5)_3$ (0.04 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.4 mL) were added to the vessel. The mixture was allowed to stir at 80 °C for 24 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. The propargylamine product was purified and isolated by silica gel chromatography (1:9 CH_2Cl_2:hexanes) to afford **2.22-*O*-TBS** as a colorless oil (170.2 mg, 3.2 mmol, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 6H), 7.47 – 7.33 (m, 12H), 7.33 – 7.24 (m, 2H), 5.40 (s, 1H), 4.38 (dd, J = 10.2, 5.1 Hz, 1H), 4.34 (dd, J = 10.2, 7.3 Hz, 1H), 4.30 (dd, J = 7.2, 5.1 Hz, 1H), 3.75 (d, J = 1.4 Hz, 2H), 0.92 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.6, 142.4, 140.5, 131.5, 128.9, 128.6, 128.5, 128.38, 128.35, 128.07, 128.06, 127.9, 127.7, 127.03, 126.95, 126.9, 123.7, 87.7, 84.4, 69.2, 63.4, 62.8, 37.0, 25.9, 18.2, -5.45, -5.47; **IR** (neat) 3057, 3025, 2924, 2852, 1597, 1488, 1451, 1251, 1095, 835, 813, 744, 699 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{36}H_{42}NOSi$ (MH^+): 532.3030; found: 532.3023; $[\alpha]^{25}_D$ = –25.1° (*c* 1.0, CH_2Cl_2).

Procedure for Deprotection of *N*-Benzhydryl Group



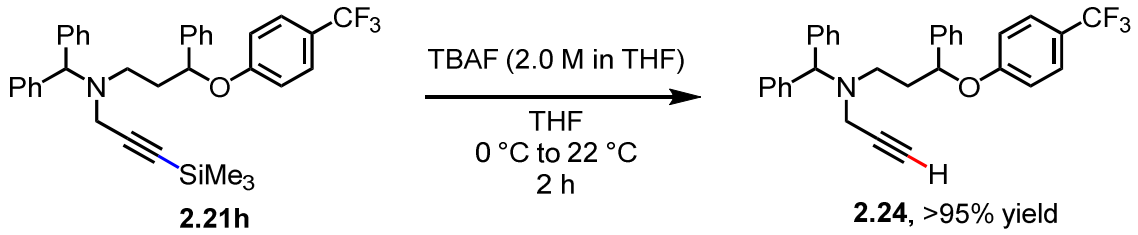
2.22-*O*-TBS **2.22**, 80% yield

(*R*)-2-Phenyl-2-((3-phenylprop-2-yn-1-yl)amino)ethan-1-ol (2.22)

(*R*)-2-Phenyl-2-((3-phenylprop-2-yn-1-yl)amino)ethan-1-ol was prepared according to the literature procedure.[11] To a solution of **2.22-*O*-TBS** (100 mg, 0.2 mmol) in TFA (1.5 mL) was added triethylsilane (0.14 mL, 0.9 mmol). The mixture was allowed to stir at 80 °C for 2 h. The mixture was cooled to 22 °C and KOH (1.0 M, aq.) was added in a dropwise manner until the solution was alkaline. The mixture was allowed to stir at 22 °C for 12 h. CH_2Cl_2 (5 mL) was added and the organic material was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The amine product **2.22** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 8:2) as a colorless solid (36.2 mg, 1.6 mmol, 80%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.38 – 7.33 (m, 4H), 7.32 – 7.26 (m, 4H), 4.06 (dd, J = 8.3, 4.4 Hz, 1H), 3.78 (dd, J = 10.9, 4.4 Hz, 1H), 3.68 – 3.60 (m, 2H), 3.45 (d, J = 17.0 Hz, 1H), 2.42 – 2.12 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.70, 131.63, 128.66, 128.21, 128.03, 127.81, 127.57, 123.09, 87.29, 83.71, 66.79, 63.22, 36.72; **IR** (neat) 3288, 3056, 2914, 2847, 1488, 1451, 1329, 1026, 754, 690, 526 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{17}H_{18}NO$ (MH^+): 252.1383; found: 252.1379; $[\alpha]^{25}_D$ = 199.1° (*c* 1.0, CH_2Cl_2).

Procedure for Removal of Trimethylsilyl Group



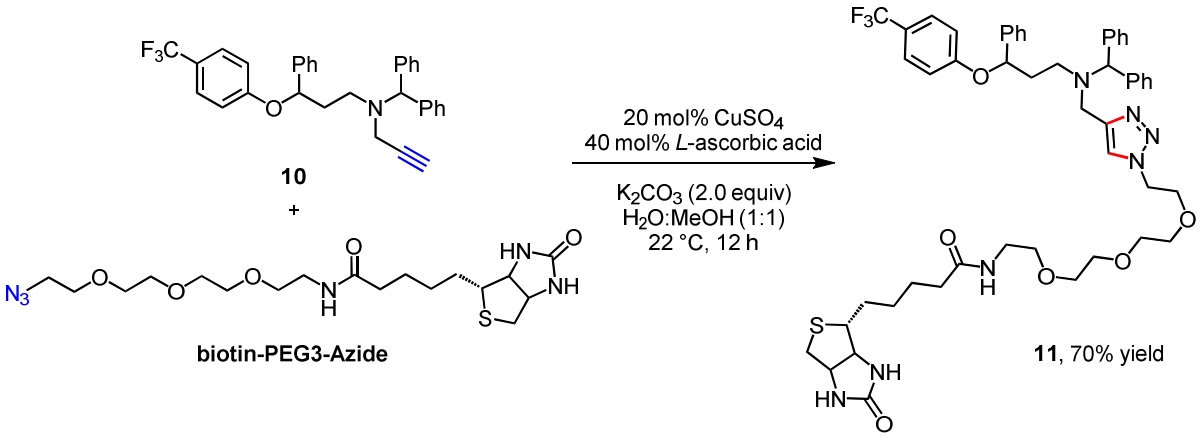
2.21h **2.24**, >95% yield

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-yn-1-amine (2.24)**

To a solution of **2.21h** (228 mg, 0.4 mmol) in THF (10 mL) was added TBAF (1.0 mL, 2.0 M in THF) at 0 °C. The mixture was allowed to stir for 2 h at 22 °C. Upon completion (determined by TLC), the mixture was concentrated *in vacuo*. The amine product **2.24** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:99) as a colorless solid (200 mg, 0.4 mmol, 99% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.4, 3.5 Hz, 4H), 7.34 – 7.30 (m, 2H), 7.28 (d, *J* = 5.9 Hz, 4H), 7.23 (t, *J* = 7.7 Hz, 3H), 7.20 – 7.10 (m, 2H), 7.06 (q, *J* = 7.0, 6.4 Hz, 3H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.26 (d, *J* = 3.8 Hz, 1H), 4.68 (s, 1H), 3.44 (qd, *J* = 17.7, 2.4 Hz, 2H), 2.86 – 2.65 (m, 2H), 2.17 (s, 1H), 2.16 – 1.94 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.6, 143.9, 142.6, 142.5, 141.4, 130.0, 129.4, 128.7, 128.6, 128.52, 128.48, 128.44, 128.38, 128.28, 128.25, 128.00, 127.96, 127.93, 127.92, 127.83, 127.80, 127.7, 127.4, 127.24, 127.15, 127.1, 126.96, 126.92, 126.68, 126.65, 126.63, 126.60, 126.3, 125.8, 125.6, 125.5, 125.4, 123.6, 122.6 (q, *J* = 32.7 Hz), 121.8, 115.7, 78.2, 77.8, 73.5, 72.2, 56.8, 46.4, 39.1, 36.8; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.34; **IR** (neat) ν 3298, 3060, 3025, 2924, 2831, 1700, 1612, 1515, 1491, 1326, 1250, 1110, 1066, 834, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{32}H_{29}NOF_3$ (MH^+): 500.2196; found: 500.2183.

Procedure for Organocopper-Catalyzed Alkyne Azide Click Reaction



***N*-(2-(2-(2-(2-(4-((Benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-((4*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (2.25)**

N-(2-(2-(2-(2-(4-((Benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino) methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-((4*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide was prepared according to the literature procedure.[12]

To a solution of alkyne **2.24** (100 mg, 0.2 mmol) in MeOH (2.0 mL) was added K_2CO_3 (55 mg, 0.4 mmol), $CuSO_4$ (6.4 mg, 0.04 mmol), Biotin-PEG3-azide (98 mg, 0.22 mmol), *L*-ascorbic acid (14.1 mg, 0.08 mmol), and H_2O (2.0 mL). The mixture was then allowed to stir for 12 h. Upon completion (determined by TLC), the mixture was concentrated *in vacuo* to remove the organic solvent. EtOAc (3 x 5 mL) was used to extract the organic material. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The amine product **2.25** was obtained after purification by silica gel chromatography (MeOH:CH_2Cl_2 = 1:99) as a colorless solid (132 mg, 1.4 mmol, 70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 4H), 7.36 – 7.30 (m, 2H), 7.30 – 7.26 (m, 3H), 7.24 (t, *J* = 7.8 Hz, 4H), 7.19 (q, *J* = 7.2, 6.1 Hz, 4H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.64 (s, 1H), 6.57 (s, 1H), 5.63 (s, 1H), 5.23 (dd, *J* = 8.5, 4.2 Hz, 1H), 4.78 (s, 1H), 4.42 (dtt, *J* = 14.3, 10.5, 5.2 Hz, 3H), 4.26 (dd, *J* = 7.8, 4.7 Hz, 1H), 3.94 – 3.74 (m, 4H), 3.54 (d, *J* = 7.2 Hz, 8H), 3.51 (t, *J* = 5.2 Hz, 2H), 3.40 (t, *J* = 5.2 Hz, 2H), 3.10 (td, *J* = 7.3, 4.5 Hz, 1H), 2.85 (dd, *J* = 12.7, 4.9 Hz, 1H), 2.77 – 2.68 (m, 2H), 2.63 (ddd, *J* = 12.9, 7.7, 4.6 Hz, 1H), 2.18 (t, *J* = 7.5 Hz, 2H), 2.12 (dtd, *J* = 14.5, 7.6, 7.0, 3.8 Hz, 2H), 1.78 – 1.56 (m, 4H), 1.46 – 1.34 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$)

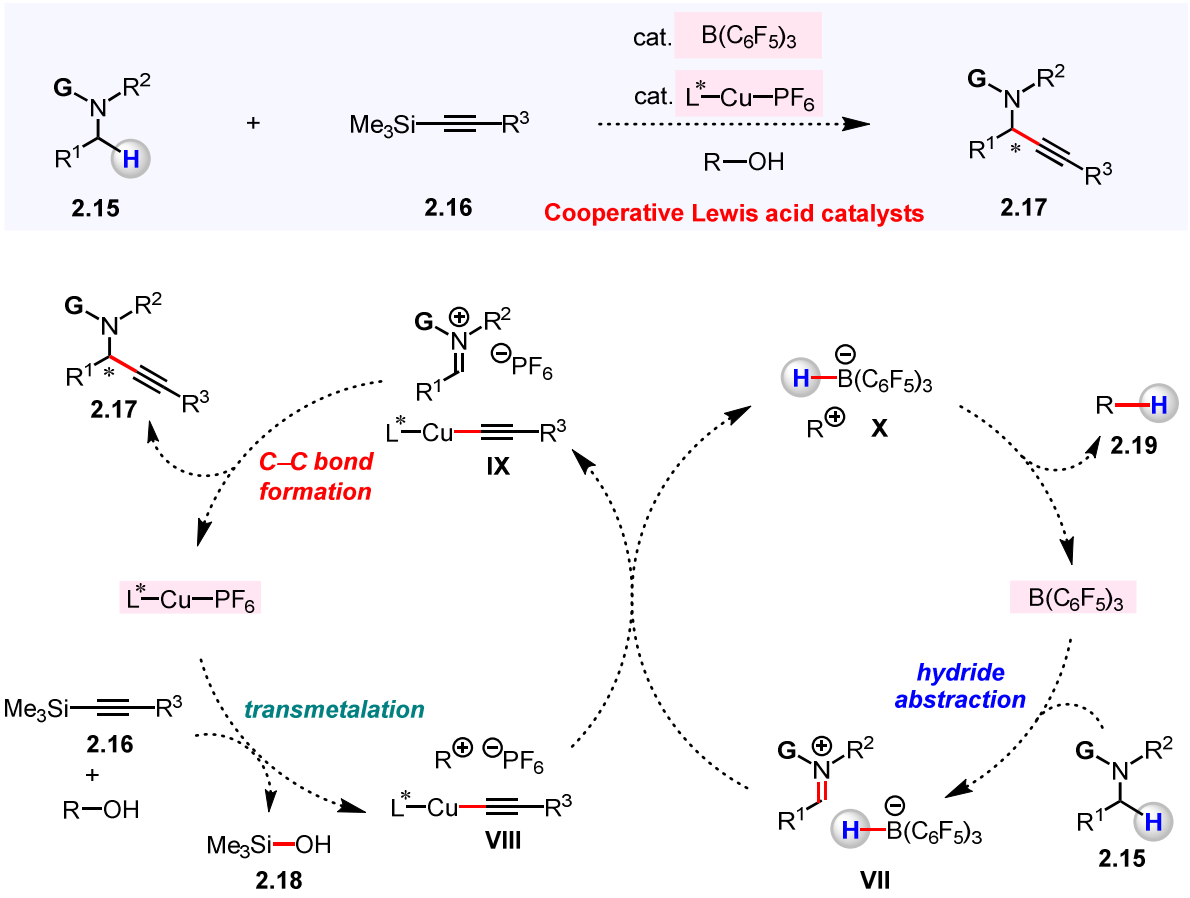
δ 173.2, 164.0, 160.5, 144.8, 142.2, 141.6, 141.30, 128.6, 128.5, 128.4, 128.34, 128.31, 128.26, 128.1, 127.6, 127.07, 127.00, 126.96, 126.62, 126.60, 126.57, 126.55, 125.7, 125.5, 125.3, 123.5, 122.4 (q, J = 32.5 Hz), 121.9, 115.6, 77.8, 77.2, 77.0, 76.9, 76.8, 70.6, 70.5, 70.4, 70.3, 70.0, 69.9, 69.8, 69.5, 65.8, 61.7, 60.1, 55.6, 50.0, 46.1, 44.9, 40.4, 39.1, 36.1, 35.9, 35.9, 30.3, 29.6, 29.6, 28.2, 28.0, 25.5, 15.2; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -61.44; **IR** (neat) 3287, 2921, 2863, 1698, 1612, 1451, 1325, 1250, 1109, 1066, 835, 734, 701 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{50}H_{61}F_3N_7O_6S$ (MH^+): 944.4278; found: 944.4342.

A5. Mechanistic Studies for α-C–H Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Complex

A5.1 Kinetic Experiments for the Coupling of 4-Methoxy-*N*,*N*,2,6-tetramethylaniline and Ethyl 3-(trimethylsilyl)propiolate

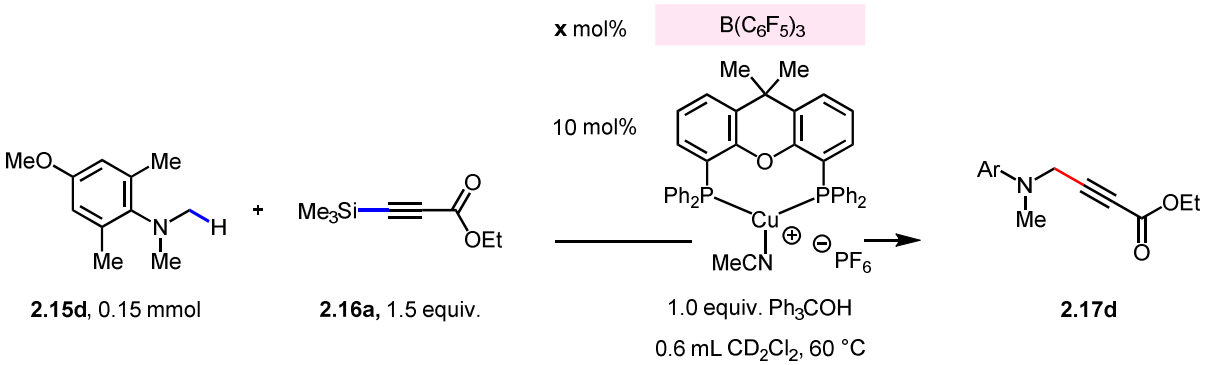
In order to provide evidence for the proposed reaction mechanism, we carried out the following kinetic experiments. We originally proposed (as shown in Figure 1c of the manuscript) that α-alkynylation process is proposed to proceed through $B(C_6F_5)_3$-catalyzed hydride abstraction of the *N*-alkylamine substrate (**2.15**) to afford an iminium ion (**VII**, Scheme S1.1). Subsequently, the organocopper catalyst can activate the alkyne substrate (**2.16**) with the aid of alcohol additive to promote transmetallation (**2.16** → **VIII**), which generates a nucleophilic alkyne that can attack the iminium ion (**IX**) to afford the desired propargylamine **2.17**.

Scheme S1.1. Proposed Catalytic Cycle



A5.1.1 Determination of Reaction Order of $B(C_6F_5)_3$

A kinetic study was conducted following the procedure for time course reaction monitoring by ^1H NMR (using internal standard) while varying the concentration of $B(C_6F_5)_3$ (Figure S1.1). Initial-rate kinetic analysis, which was determined from the data points in the first 400 seconds, demonstrates half-order kinetics of $B(C_6F_5)_3$ in the reaction between 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** and ethyl 3-(trimethylsilyl)propiolate **2.16a** (Figure S1.2).[13]



Procedure for Time Course Reaction Monitoring by *in situ* ^1H NMR

In a nitrogen-filled glove box, previously prepared (Xantphos)Cu(MeCN)PF_6 (41 mg, 0.11 mmol),[14] 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** (197 mg, 1.1 mmol), ethyl 3-(trimethylsilyl)propiolate **2.16a** (281 mg, 1.65 mmol) and mesitylene (132 mg, 1.1 mmol) were weighed in an oven-dried 7.0 mL vial and diluted to 2.2 mL with CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, $B(C_6F_5)_3$ (63.8 mg, 0.125 mmol) was weighed and diluted to 1.0 mL with CD_2Cl_2 (**Stock Solution B**). In 4 oven-dried 7.0 mL vials, were added triphenylmethanol (39 mg, 0.15 mmol). To each oven-dried vial containing triphenylmethanol was added **Stock Solution A** (0.3 mL), **Stock Solution B** (0.06, 0.12, 0.15 and 0.18 mL) and neat CD_2Cl_2 (0.24, 0.18, 0.15 and 0.12 mL) to prepare reaction mixtures (total 0.6 mL) with 0.150 mmol of 4-methoxy-*N,N*,2,6-tetramethylaniline, 0.225 mmol ethyl 3-(trimethylsilyl)propiolate, 0.150 mmol triphenylmethanol, 10.0 mol% (Xantphos)Cu(MeCN)PF_6, and the following amounts of $B(C_6F_5)_3$ (5.00, 10.0, 12.5 and 15.0 mol%). The mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^1H NMR spectra were acquired at 60 °C (preheated) using a pre-acquisition delay in array mode with a spectrum taken every 30 seconds for the length of the experiment. The data were processed using MestReNova and peak integrations were normalized using mesitylene as the internal standard.

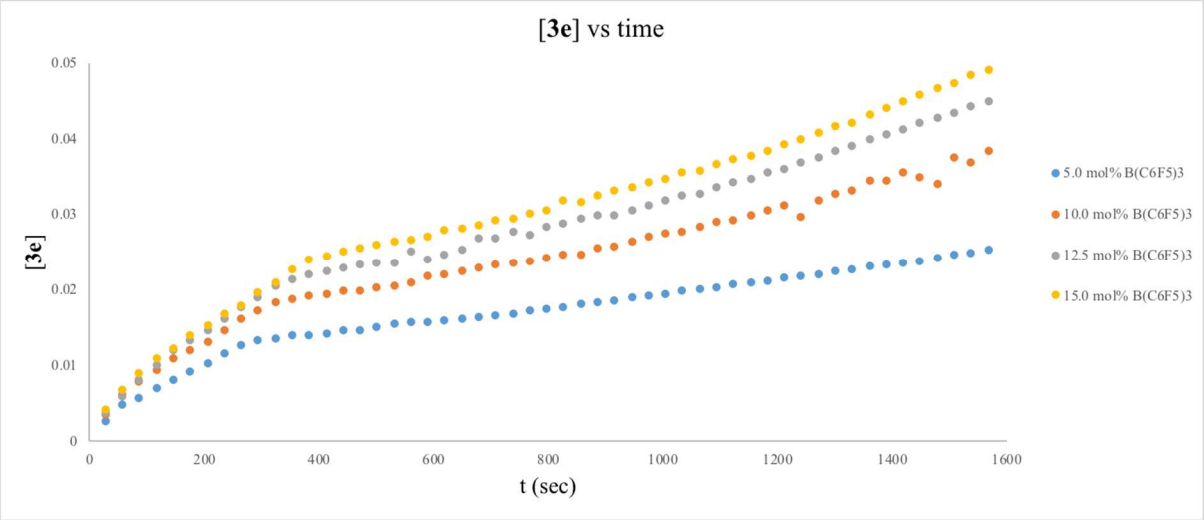


Figure S1. Monitoring the formation of **2.17d** using different concentrations of $B(C_6F_5)_3$.

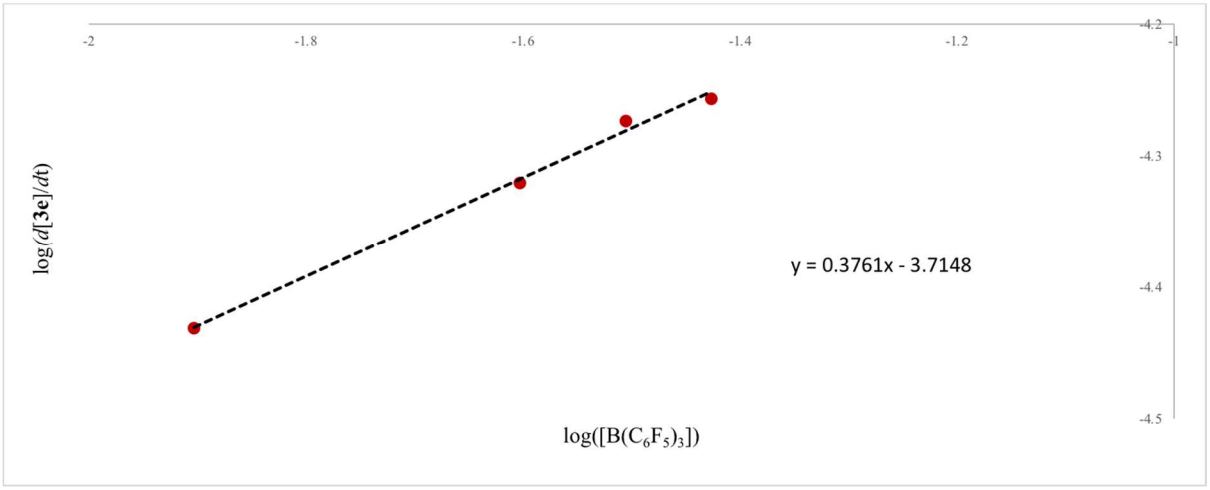
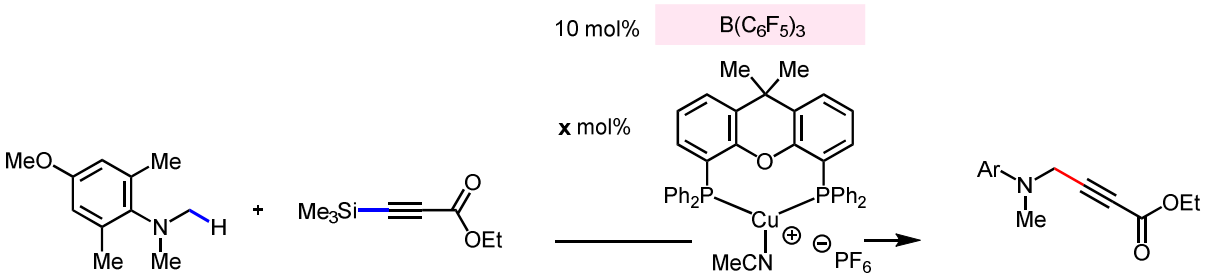


Figure S1.2. Log(rate) *vs* Log[$B(C_6F_5)_3$] plot is employed to determine the reaction order for $B(C_6F_5)_3$**.** The result suggests that there is approximately 0.5-order dependency on the concentration of $B(C_6F_5)_3$.

A5.1.2 Determination of Reaction Order of (Xantphos)Cu(MeCN)PF_6

A kinetic study was conducted following the procedure for time course reaction monitoring by ^{1}H NMR (using internal standard) while varying the concentration of (Xantphos)Cu(MeCN)PF_6 (Figure S3). Initial-rate kinetic analysis, which was determined from the data points in the first 400 seconds, demonstrates zero-order kinetics of (Xantphos)Cu(MeCN)PF_6 in the reaction between 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** and ethyl 3-(trimethylsilyl)propiolate **2.16a** (Figure S1.4).[13]



In a nitrogen-filled glove box, $B(C_6F_5)_3$ (56.3 mg, 0.11 mmol), 4-methoxy-*N,N*,2,6-tetramethylaniline (197 mg, 1.10 mmol), ethyl 3-(trimethylsilyl)propiolate (281 mg, 1.65 mmol) and mesitylene (132 mg, 1.10 mmol) were weighed in an oven-dried 7.0 mL vial and diluted to 2.2 mL with CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, (Xantphos)Cu(MeCN)PF_6 (103.5 mg, 0.125 mmol)[14] was weighed and diluted to 2.00 mL with CD_2Cl_2 (**Stock Solution B**). In 5 oven-dried 7.0 mL vials, were added triphenylmethanol (39 mg, 0.15 mmol). To each oven-dried vial containing triphenylmethanol was added **Stock Solution A** (0.30 mL), **Stock Solution B** (0.06, 0.12, 0.24, 0.30 and 0.36 mL) and neat CD_2Cl_2 (0.30, 0.24, 0.12, 0.06 and 0.00 mL) to prepare reaction mixtures (total 0.62 mL) with 0.150 mmol of 4-methoxy-*N,N*,2,6-tetramethylaniline, 0.225 mmol ethyl 3-(trimethylsilyl)propiolate, 0.15 mmol triphenylmethanol, 10.0 mol% $B(C_6F_5)_3$, and the following amounts of (Xantphos)Cu(MeCN)PF_6 (2.5, 5.0, 10.0, 12.5 and 15.0 mol%). The mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired at 60 °C (preheated) using a pre-acquisition delay in array mode with a spectrum taken every 30 seconds for the length of the experiment. The data were processed using MestReNova and peak integrations were normalized using mesitylene as the internal standard.

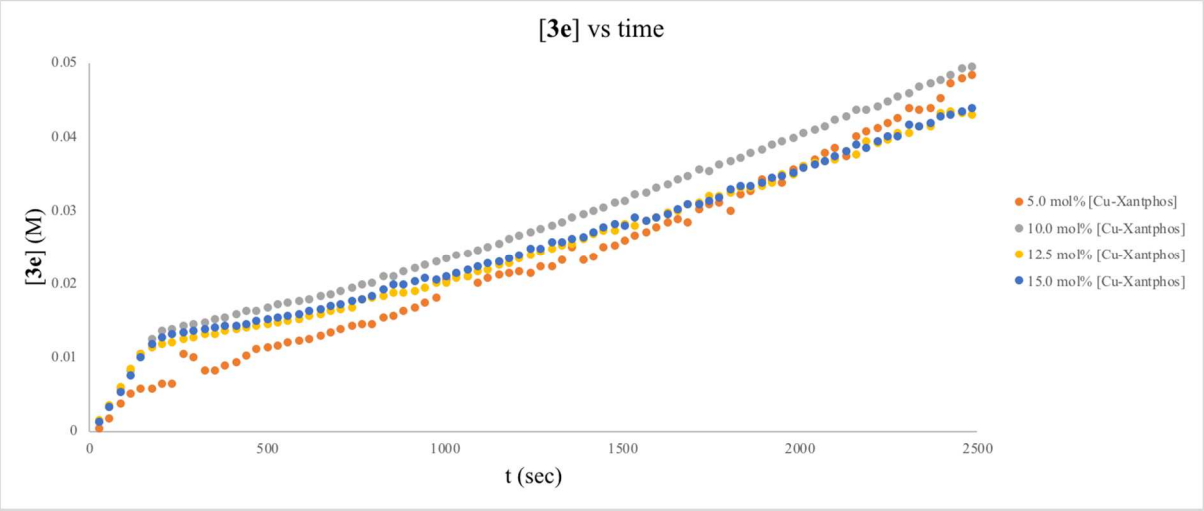


Figure S1.3. Monitoring the formation of **2.17d** using different concentrations of (Xantphos)Cu(MeCN)(PF_6).

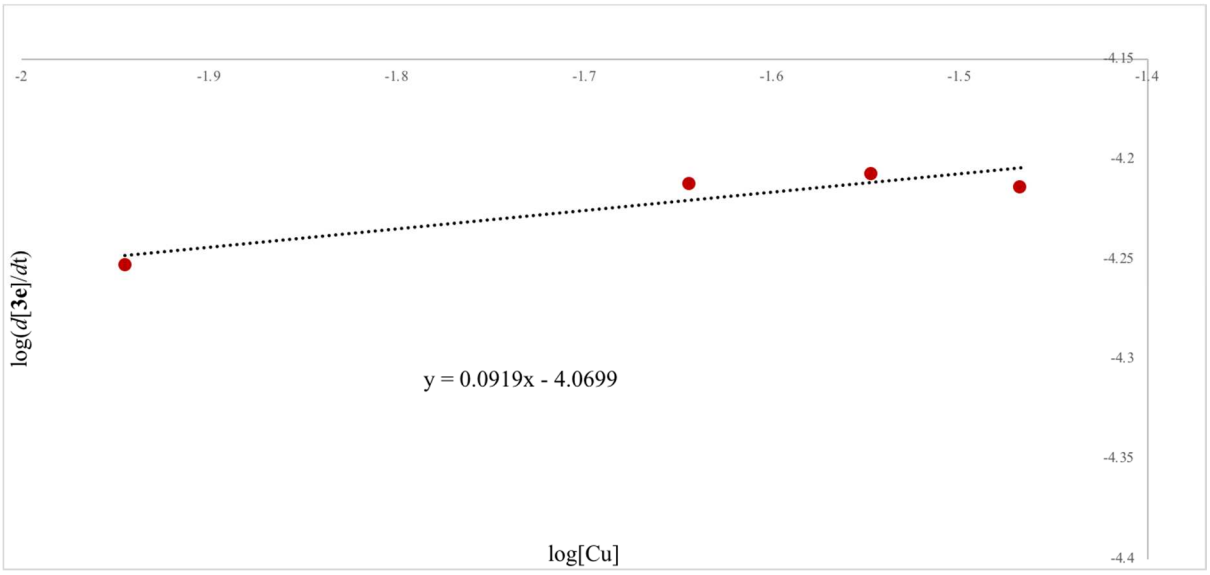
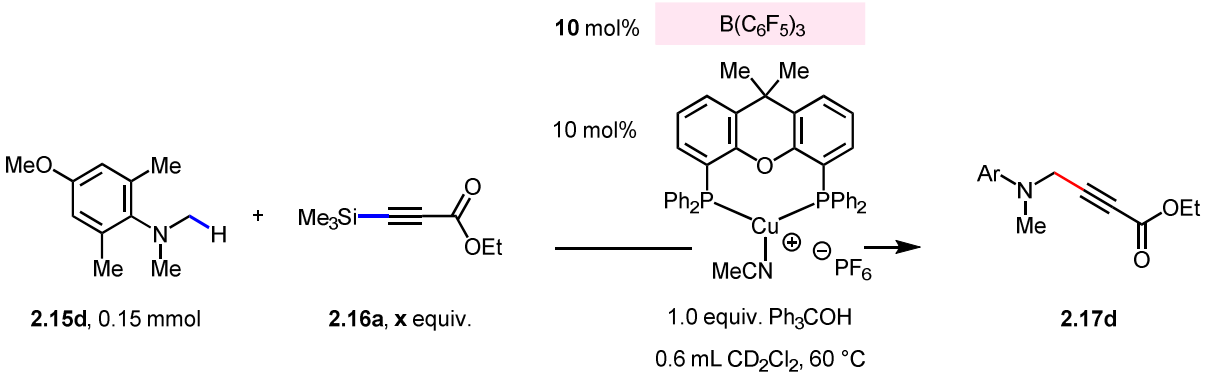


Figure S1.4. Log(rate) *vs* Log[(Xantphos)Cu(MeCN)(PF_6)] plot is employed to determine the initial reaction order for (Xantphos)Cu(MeCN)(PF_6)**.** The result suggests that there is 0-order dependency on the concentration of (Xantphos)Cu(MeCN)(PF_6).

A5.1.3 Determination of Reaction Order of Ethyl 3-(trimethylsilyl)propiolate 2.16a

A kinetic study was conducted following the procedure for time course reaction monitoring by ^{1}H NMR (using internal standard) while varying the concentration of ethyl 3-(trimethylsilyl)propiolate **2.16a** (Figure S1.5). Initial-rate kinetic analysis, which was determined

from the data points in the first 400 seconds, demonstrates zero-order kinetics of ethyl 3-(trimethylsilyl)propiolate in the reaction between 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** and ethyl 3-(trimethylsilyl)propiolate **2.16a** (Figure S1.6).[13]



Procedure for Time Course Reaction Monitoring by *in situ* ^{1}H NMR

In a nitrogen-filled glove box, (Xantphos)Cu(MeCN)PF_6 (103.5 mg, 0.11 mmol),[14] $B(C_6F_5)_3$ (56.3 mg, 0.11 mmol), 4-methoxy-*N,N*,2,6-tetramethylaniline (197 mg, 1.10 mmol), and mesitylene (132 mg, 1.10 mmol) were weighed in an oven-dried 7.0 mL vial and diluted to 2.20 mL with CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, (ethyl 3-(trimethylsilyl)propiolate (623 mg, 3.66 mmol) was weighed and diluted to 1.30 mL with CD_2Cl_2 (**Stock Solution B**). In 5 oven-dried 7.0 mL vials, were added triphenylmethanol (39 mg, 0.15 mmol). To each oven-dried vial containing triphenylmethanol was added **Stock Solution A** (0.30 mL), **Stock Solution B** (0.04, 0.08, 0.12, 0.16 and 0.24 mL) and neat CD_2Cl_2 (0.28, 0.24, 0.18, 0.14 and 0.08 mL) to prepare reaction mixtures (total 0.60 mL) with 0.15 mmol of 4-methoxy-*N,N*,2,6-tetramethylaniline, 0.15 mmol triphenylmethanol, 10.0 mol% $B(C_6F_5)_3$, 10.0 mol% (Xantphos)Cu(MeCN)PF_6 and the following amounts of ethyl 3-(trimethylsilyl)propiolate (0.75, 1.50, 2.25, 3.00 and 4.50 equiv.). The mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired at 60 °C (preheated) using a pre-acquisition delay in array mode with a spectrum taken every 30 seconds for the length of the experiment. The data were processed using MestReNova and peak integrations were normalized using mesitylene as the internal standard.

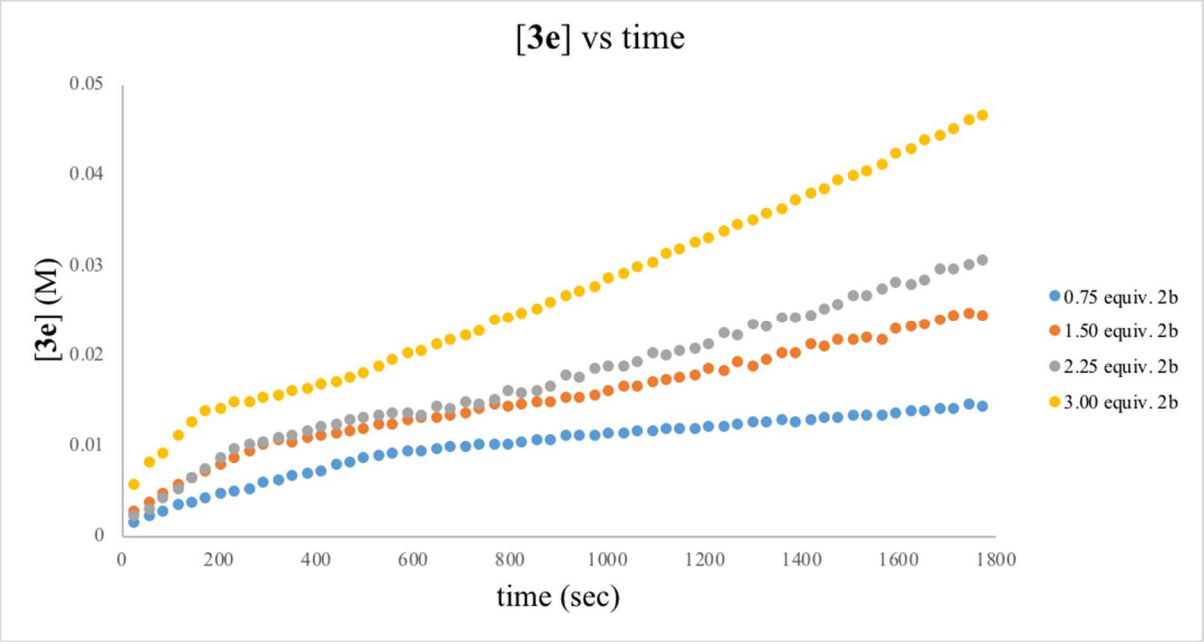


Figure S1.5. Monitoring the formation of **2.17d** using different concentrations of **2.16a**.

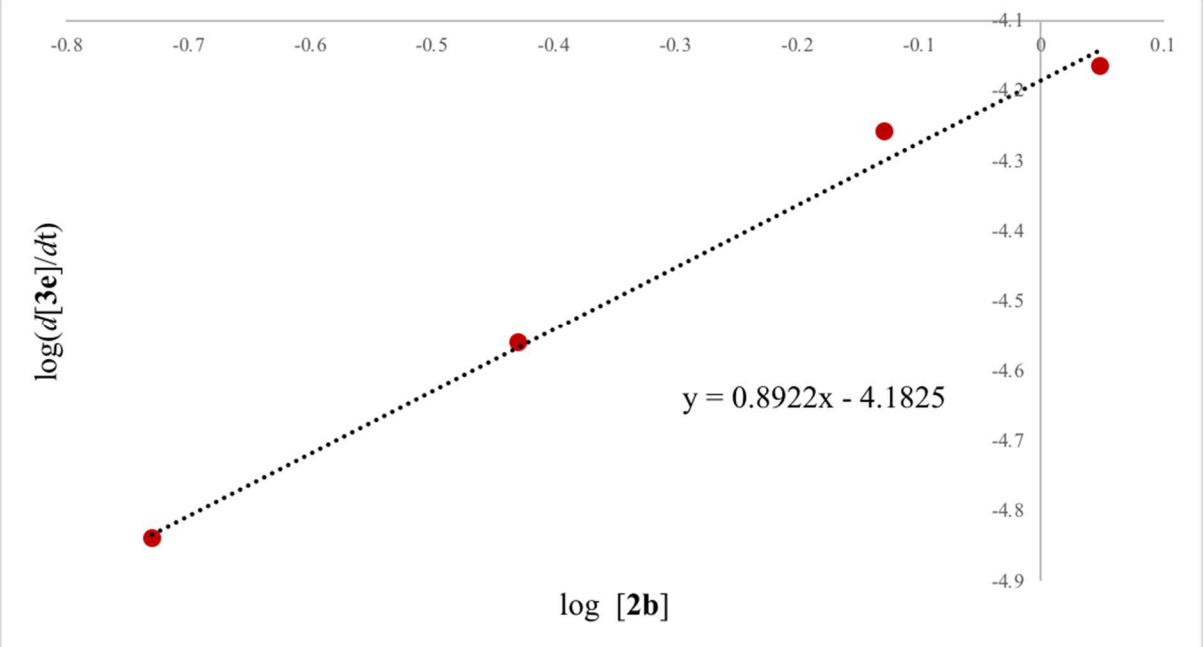
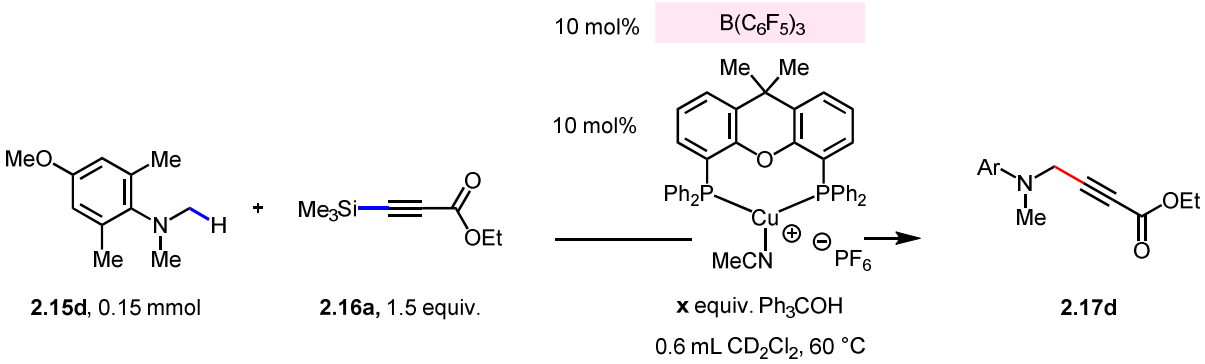


Figure S1.6. Log(rate) *vs* Log[**2.16a**] plot is employed to determine the initial reaction order for **2.16a**. The result suggests that there is 1.0-order dependency on the concentration of **2.16a**.

A5.1.4 Determination of Reaction Order of Ph_3COH

A kinetic study was conducted following the procedure for time course reaction monitoring by ^1H NMR (using internal standard) while varying the concentration of trityl alcohol

(Figure S1.7). Initial-rate kinetic analysis, which was determined from the data points in the first 400 seconds, demonstrates zero-order kinetics of trityl alcohol in the reaction between 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** and ethyl 3-(trimethylsilyl)propiolate **2.16a** (Figure S8).[13]



In a nitrogen-filled glove box, (Xantphos)Cu(MeCN)PF_6 (91.2 mg, 0.11 mmol),[14] $B(C_6F_5)_3$ (56.3 mg, 0.11 mmol), 4-methoxy-*N,N*,2,6-tetramethylaniline (197 mg, 1.1 mmol), ethyl 3-(trimethylsilyl)propiolate (281 mg, 1.65 mmol) and mesitylene (132 mg, 1.1 mmol) were weighed in an oven-dried 7.0 mL vial and diluted to 2.2 mL with CD_2Cl_2 (**Stock Solution A**). In 5 oven-dried 7.0 mL vials, were added triphenylmethanol (19.5 mg, 39.0 mg, 52.0 mg, 64.7 mg and 78.0 mg). To each oven-dried vial containing triphenylmethanol was added **Stock Solution A** (0.3 mL) and neat CD_2Cl_2 (0.3 mL) to prepare reaction mixtures (total 0.6 mL) with 0.15 mmol of 4-methoxy-*N,N*,2,6-tetramethylaniline, 0.22 mmol ethyl 3-(trimethylsilyl)propiolate, 10.0 mol% $B(C_6F_5)_3$, and the following amounts of (Xantphos)Cu(MeCN)PF_6 (10.0 mol%) and triphenylmethanol (0.5, 1.0, 1.3, 1.7 and 2.0 equiv.). The mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired at 60 °C (preheated) using a pre-acquisition delay in array mode with a spectrum taken every 30 seconds for the length of the experiment. The data were processed using MestReNova and peak integrations were normalized using mesitylene as the internal standard.

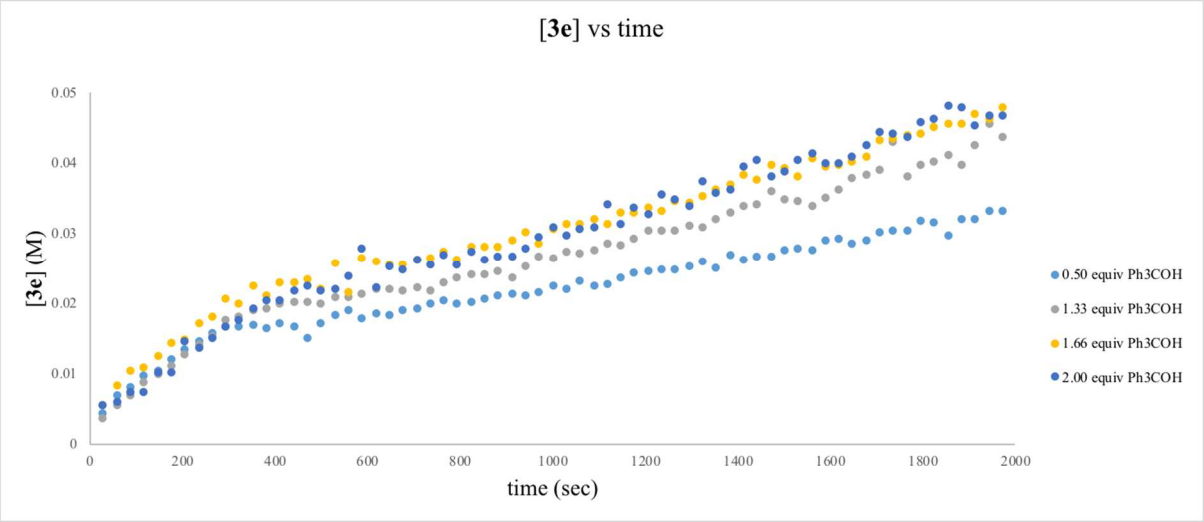


Figure S1.7. Monitoring the formation of **2.17d** using different concentrations of Ph_3COH.

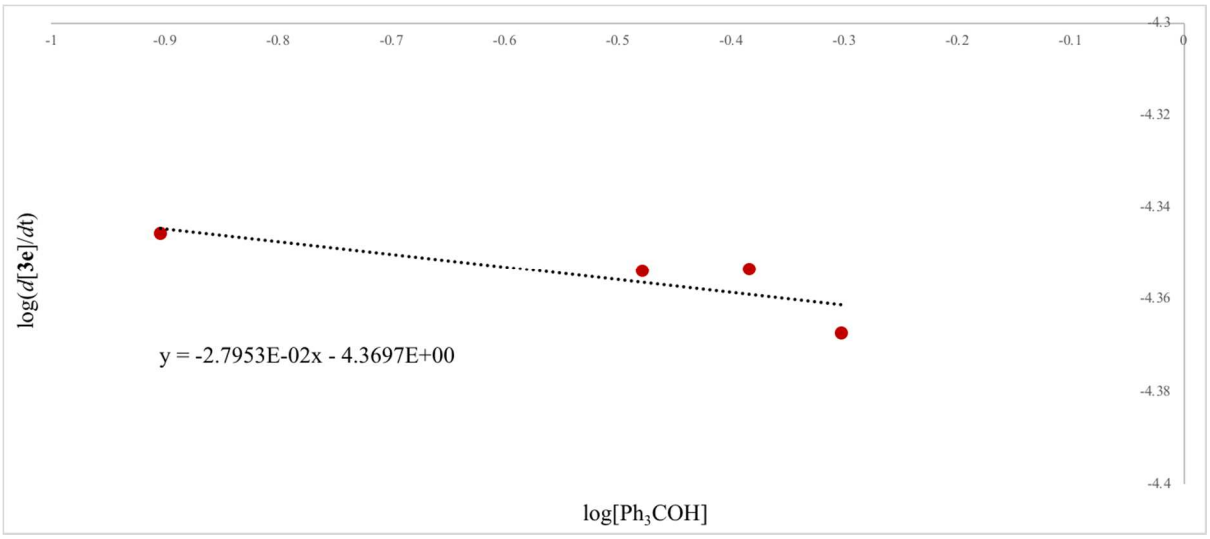
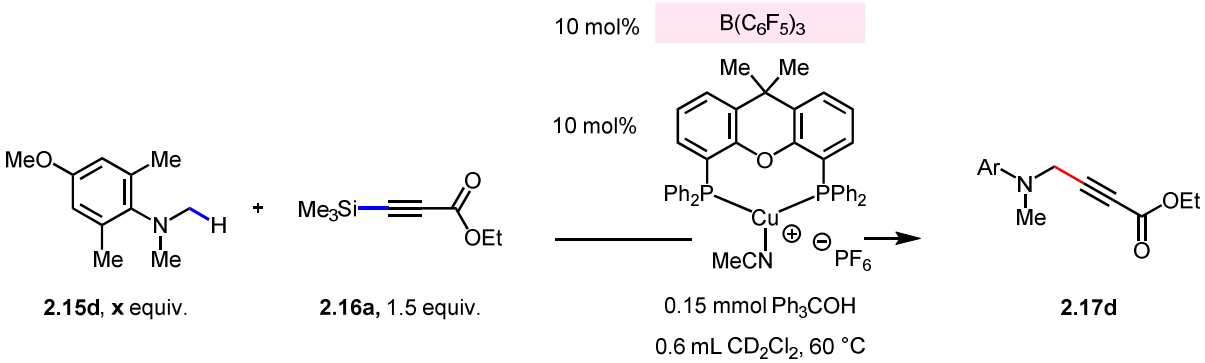


Figure S1.8. Log(rate) *vs* Log[Ph_3COH] plot is employed to determine the initial reaction order for Ph_3COH. The result suggests that there is 0-order dependency on the concentration of Ph_3COH.

A5.1.5 Determination of Reaction Order in Ethyl 4-methoxy-*N,N*,2,6-tetramethylaniline 2.15d

A kinetic study was conducted following the procedure for time course reaction monitoring by ^1H NMR (using internal standard) while varying the concentration of 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** (Figure S1.9). Initial-rate kinetic analysis, which was determined

from the data points in the first 400 seconds, demonstrates zero-order kinetics of 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** (Figure S1.10).[13]



In a nitrogen-filled glove box, $B(C_6F_5)_3$ (56.3 mg, 0.11 mmol), (Xantphos)Cu(MeCN)PF_6 (91.2 mg, 0.11 mmol),[14] ethyl 3-(trimethylsilyl)propiolate (281.0 mg, 1.65 mmol) and mesitylene (132 mg, 1.10 mmol) were weighed in an oven-dried 7.0 mL vial and diluted to 2.20 mL with CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, 4-methoxy-*N,N*,2,6-tetramethylaniline (436.9 mg, 2.44 mmol) was weighed and diluted to 1.30 mL with CD_2Cl_2 (**Stock Solution B**). In 5 oven-dried 7.0 mL vials, were added triphenylmethanol (39 mg, 0.15 mmol). To each oven-dried vial containing triphenylmethanol was added **Stock Solution A** (0.3 mL), **Stock Solution B** (0.04, 0.06, 0.08, 0.16 and 0.24 mL) and neat CD_2Cl_2 (0.28, 0.26, 0.24, 0.16 and 0.08 mL) to prepare reaction mixtures (total 0.62 mL) with 0.225 mmol ethyl 3-(trimethylsilyl)propiolate, 0.15 mmol triphenylmethanol, 10.0 mol% $B(C_6F_5)_3$, 10.0 mol% (Xantphos)Cu(MeCN)PF_6 and the following amounts of 4-methoxy-*N,N*,2,6-tetramethylaniline (0.50, 0.75, 1.00, 2.00 and 3.00 equiv). The mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired at 60 °C (preheated) using a pre-acquisition delay in array mode with a spectrum taken every 30 seconds for the length of the experiment. The data were processed using MestReNova and peak integrations were normalized using mesitylene as the internal standard.

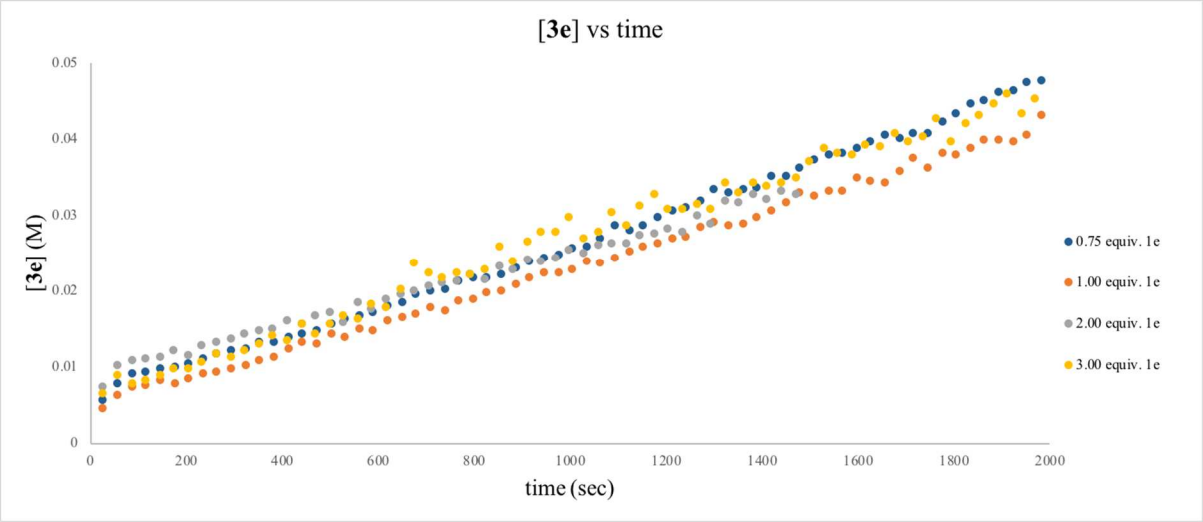


Figure S1.9. Monitoring the formation of **2.17d** using different concentrations of amine **2.15d**.

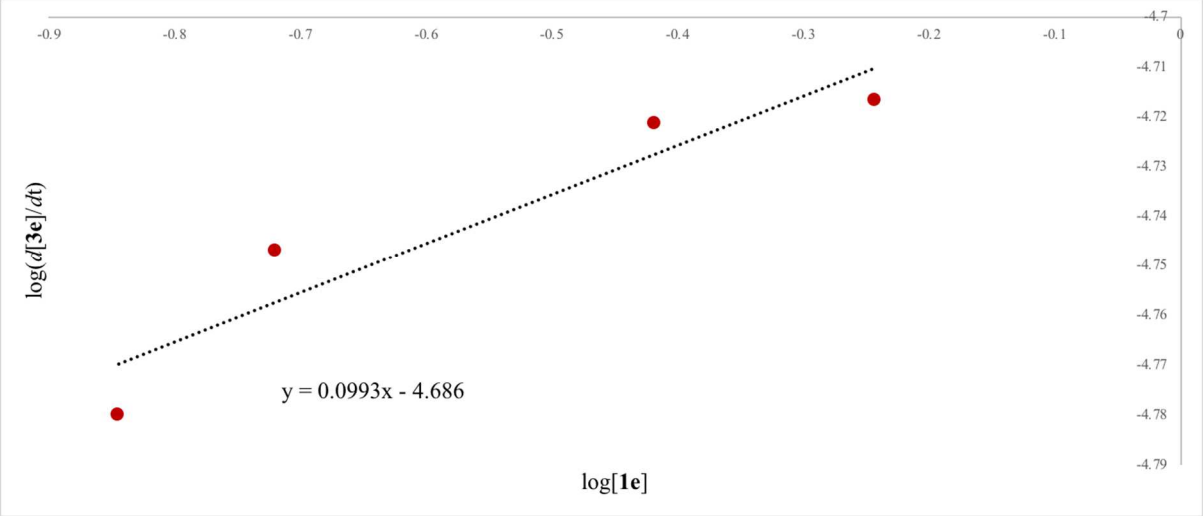
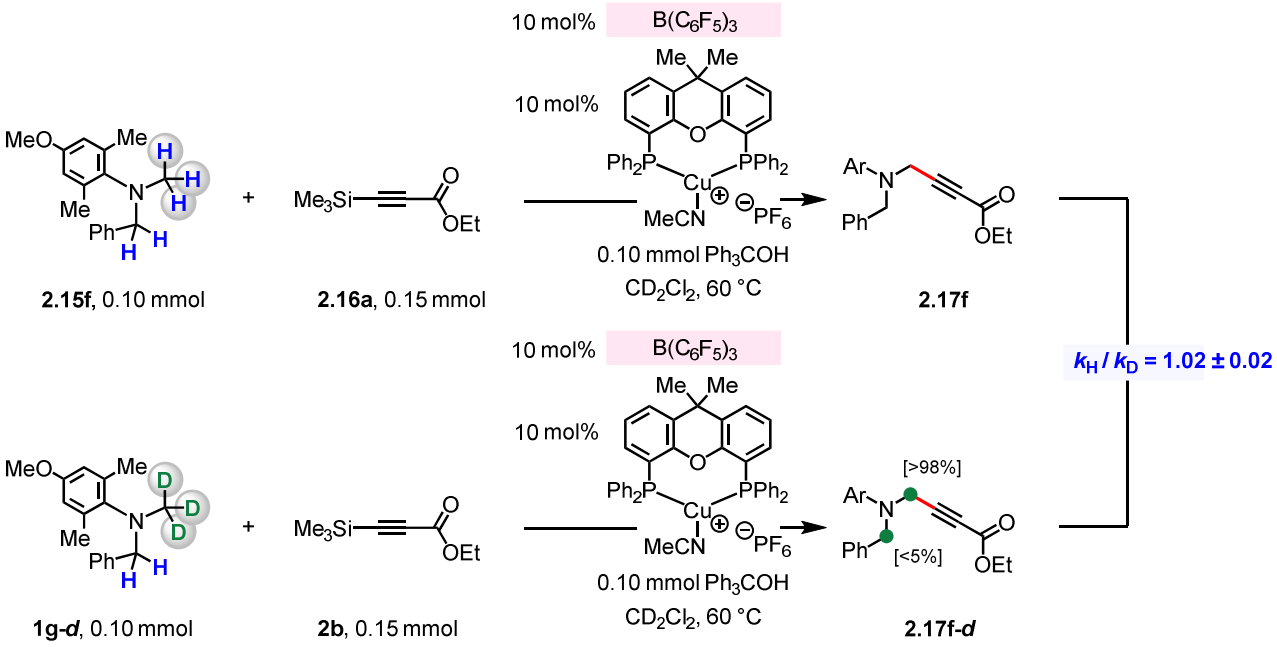


Figure S1.10. Log(rate) *vs* Log[**2.15d**] plot is employed to determine the initial reaction order for amine **2.15d.** The result suggests that there is 0-order dependency on the concentration of **2.15d**.

A5.2 Parallel and Intermolecular Competition Kinetic Isotope Effect Experiments

A5.2.1 Measurements of the Parallel Kinetic Isotope Effect

A parallel kinetic isotope effect study was conducted following the procedure for time course reaction monitoring by ^{1}H NMR (using internal standard). Kinetic analysis based on the initial rates of the product formation (Figure S1.11) demonstrates no kinetic isotope effect (k_H/k_D = 1.02 ± 0.02, average of 2 reactions) in the reaction between *N*-benzyl-4-methoxy-*N*,2,6-trimethylaniline **2.15f** or *N*-benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-d_3)aniline **2.15f-*d*** and ethyl 3-(trimethylsilyl)propiolate **2.16a**.[13,15]



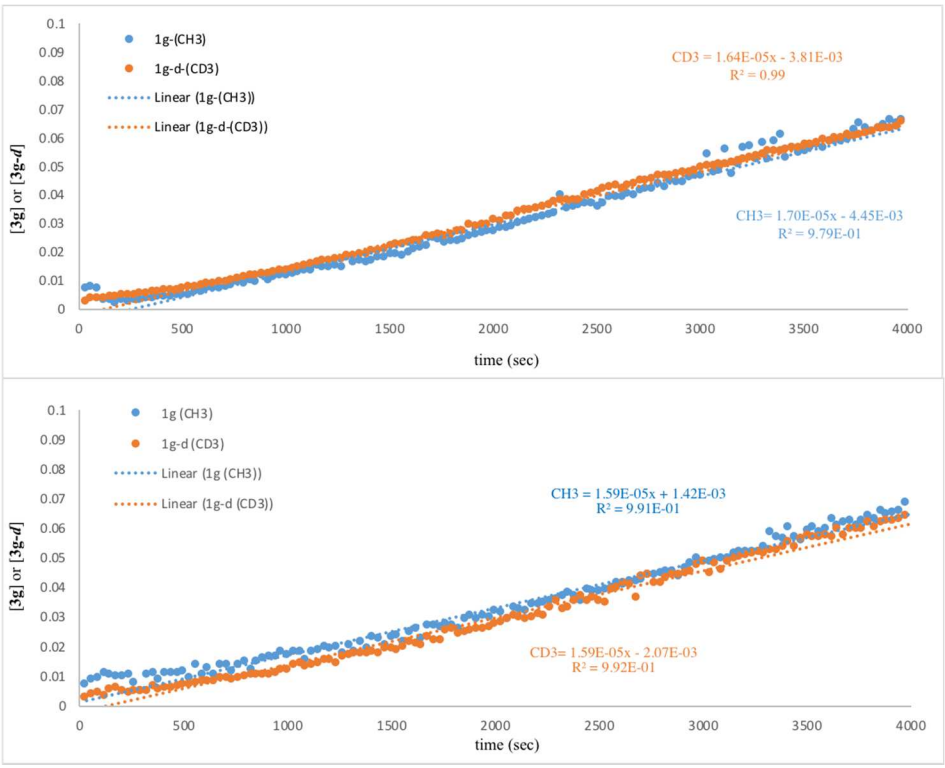


Figure S1.11. Parallel kinetic isotope effect experiments. The rate of the reaction is unaffected when amine **2.15f** or **2.15f-*d*** are employed as both have similar reaction time course plots. From the set of two parallel KIE experiments, the KIE value of 1.02 ± 0.02 was found.

Experimental Procedure for Measuring the Parallel Kinetic Isotope Effect

To an oven-dried 7.0 mL vial were added (Xantphos)Cu(MeCN)PF_6 (0.01 mmol), ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.10 mmol), amine **2.15f** (0.10 mmol) or amine **2.15f-*d*** (0.10 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), mesitylene (0.10 mmol). This mixture was then diluted to 0.40 mL with CD_2Cl_2 and transferred into a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired at 60 °C (preheated) using a pre-acquisition delay in array mode with a spectrum taken every 30 seconds for the length of the experiment. The data were processed using MestReNova and peak integrations were normalized using mesitylene as the internal standard.

A5.2.2 Intermolecular Competition Kinetic Isotope Effect Experiment

An intermolecular competition kinetic isotope effect study was conducted between *N*-benzyl-4-methoxy-*N*,2,6-trimethylaniline **2.15f** and *N*-benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-d_3)aniline **2.15f-*d***. Upon analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy, 27% conversion to both **2.17f** and **2.17f-*d*** was detected where 22% conversion of **2.17f** was detected. This ratio was further verified by studying the ^{2}H NMR spectrum; it revealed that approximately 5% of **2.17f-*d*** is formed.

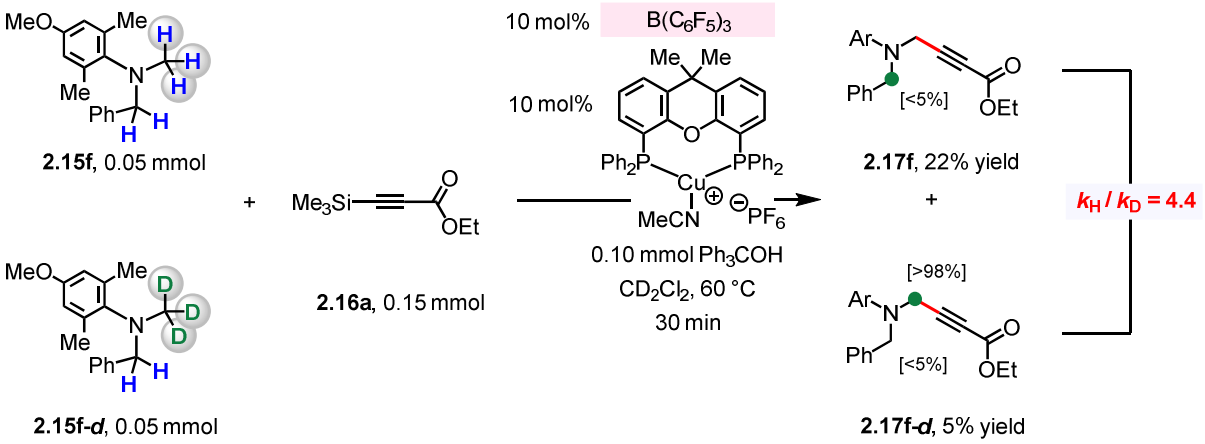


Figure S1.12. Intermolecular Competition Kinetic Isotope Effect Experiment. The result suggests hydride abstraction step is irreversible.

Experimental Procedure for Measuring the Intermolecular Competition Kinetic Isotope Effect

An oven-dried 7.0 mL vial equipped with a magnetic stir bar was used. To the vial were added (Xantphos)Cu(MeCN)PF_6 (0.01 mmol), ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.10 mmol), amine **2.15f** (0.05 mmol), amine **2.15f-*d*** (0.05 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), mesitylene (0.10 mmol), benzene-d_6 (0.05 mmol), and CD_2Cl_2 (0.40 mL). The mixture was then transferred to a J-Young tube and was allowed to heat at 60 °C for 2 h. After 2 h, the mixture was allowed to cool and NMR spectroscopy was obtained. The conversion values were determined by ^{1}H and ^{2}H NMR (Figure S1.13) analysis of the unpurified reaction mixture using mesitylene and benzene-d_6 as internal standards.

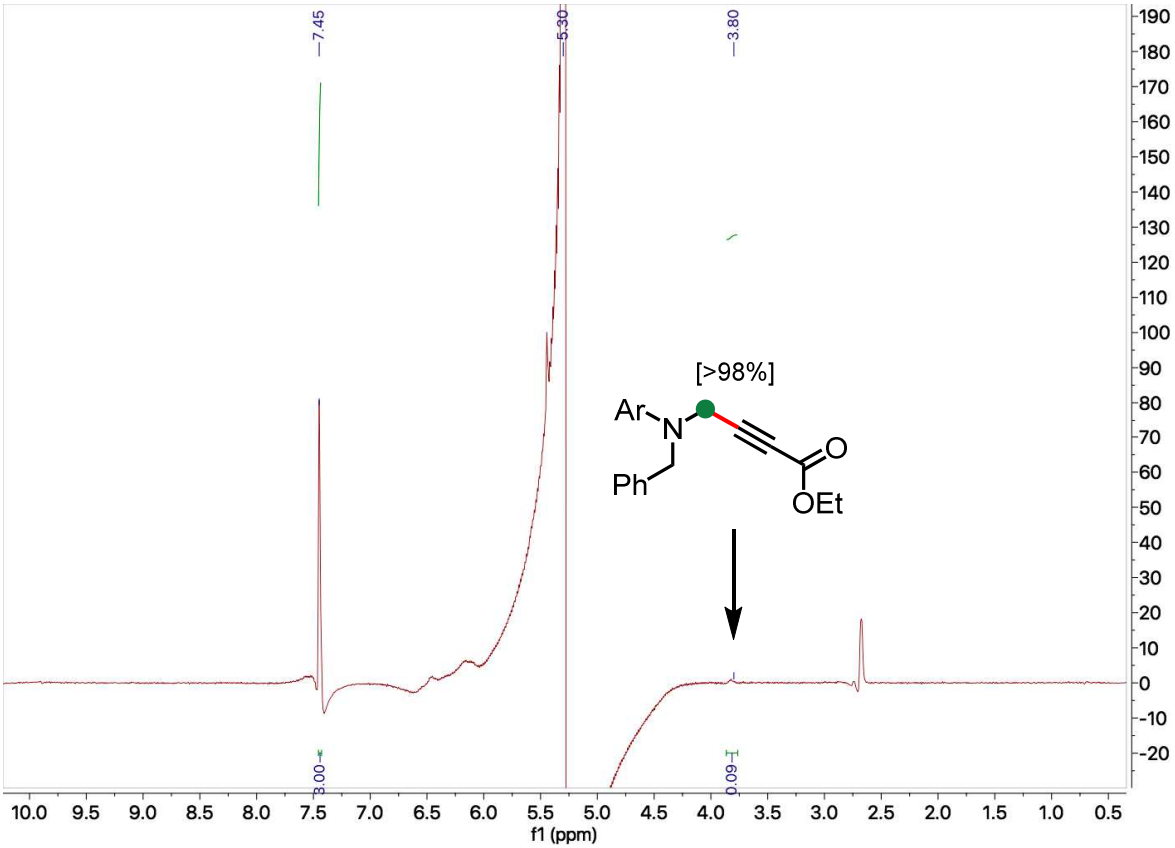


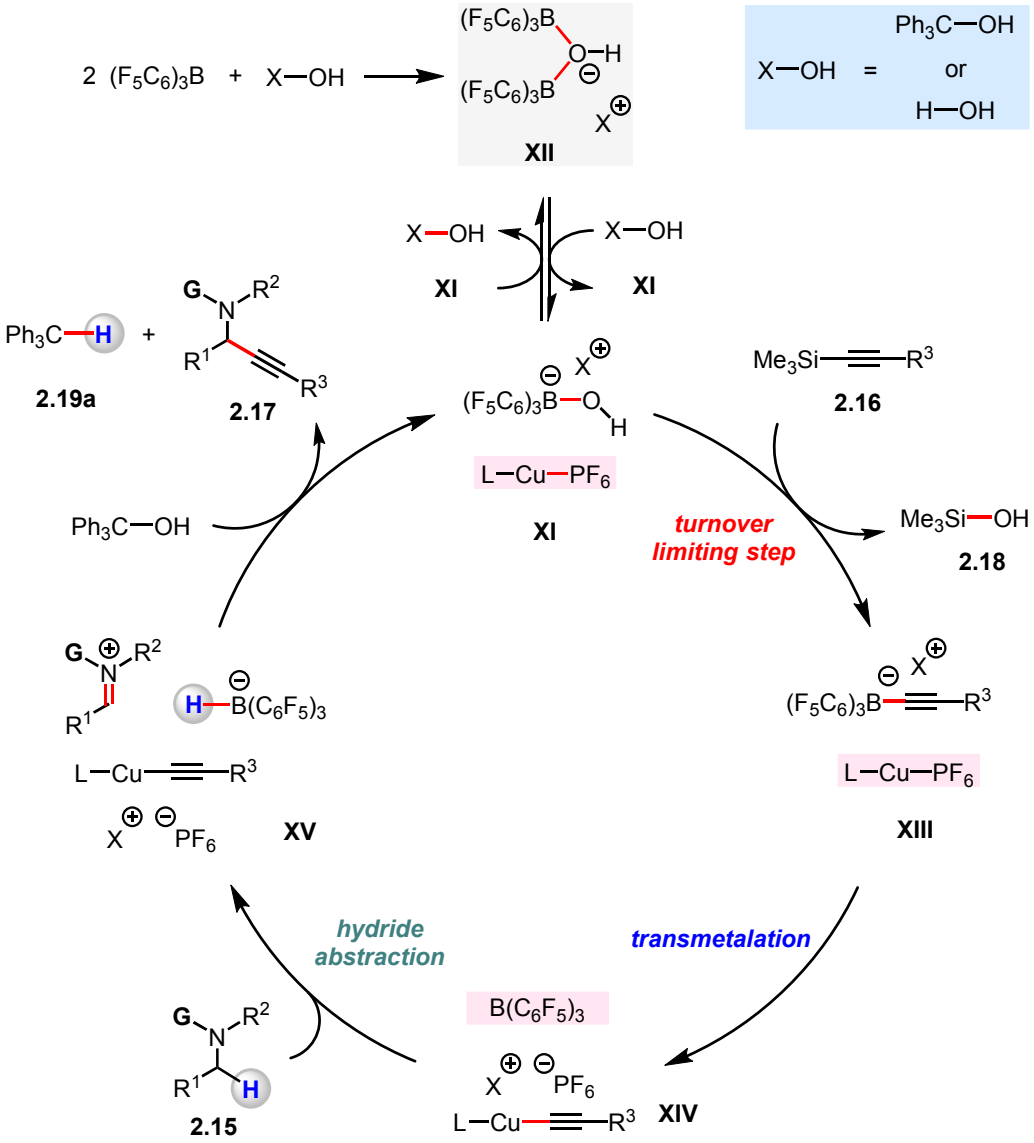
Figure S1.13: ^{2}H NMR spectrum for intermolecular competition kinetic isotope effect study

A5.3 NMR Experiments for Detection of Proposed Intermediates and the Resting State

A5.3.1 Demonstration of Chemical Competency of the Proposed Intermediate XIII

Based on the kinetic studies as described above, we propose that borate anion **IX** (Scheme S1.2) reacts with trimethylsilylacetylene **2.16** to afford $[(F_5C_6)_3B\text{–alkyne}]^-$ $[X]^+$ (**XIII**). To demonstrate the competency of **XIII** as an intermediate to afford the propargylamine product **3**, we prepared a sample of $[(F_5C_6)_3B\text{–}C{\equiv}C\text{–}CO_2Et]^-[H\text{–}NR_3]^+$ (NR_3 = **2.15d**) following a procedure reported previously in the literature.[16]

Scheme S1.2. Proposed Mechanism



Experimental Procedure for the Preparation of $[(F_5C_6)_3B–C\equiv C–CO_2Et]^-[H–2.15d]^+$

An oven-dried 7.0 mL vial equipped with a magnetic stir bar was used. To the vial were added ethyl propiolate (0.10 mmol), amine **2.15d** (0.15 mmol), $B(C_6F_5)_3$ (0.10 mmol, 100 mol%), mesitylene (0.10 mmol), trifluorotoluene (0.10 mmol) and CD_2Cl_2 (0.60 mL) under nitrogen atmosphere. The mixture was then transferred to a J-Young tube and NMR spectroscopy was obtained. Analysis of the ^1H NMR spectra of unpurified mixture with mesitylene as the internal standard revealed that ethyl propiloate was fully consumed (Figure S1.14) and $[(F_5C_6)_3B–C\equiv C–CO_2Et]^-[H–$**2.15d**$]^+$ **(XIII)** was formed (Figure S1.15) which was indicated by a characteristic sharp singlet at -21.5 ppm on ^{11}B NMR (Figure S1.16).[16]

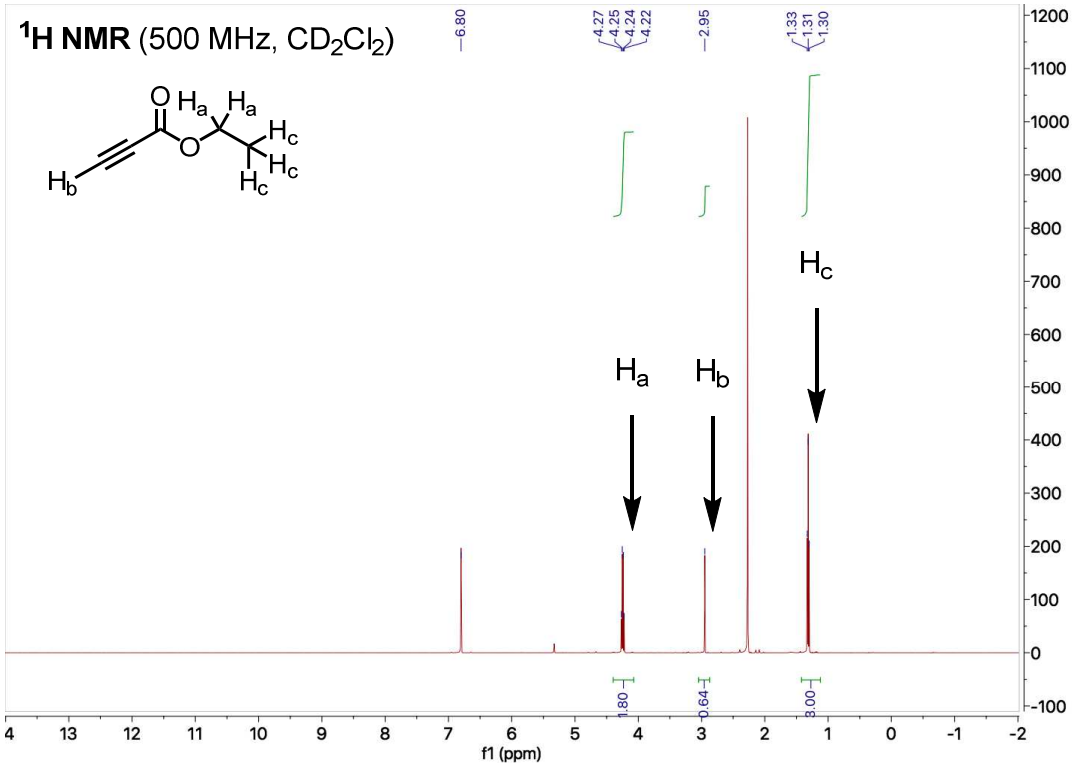


Figure S1.14. ^1H NMR spectrum of ethyl propiolate.

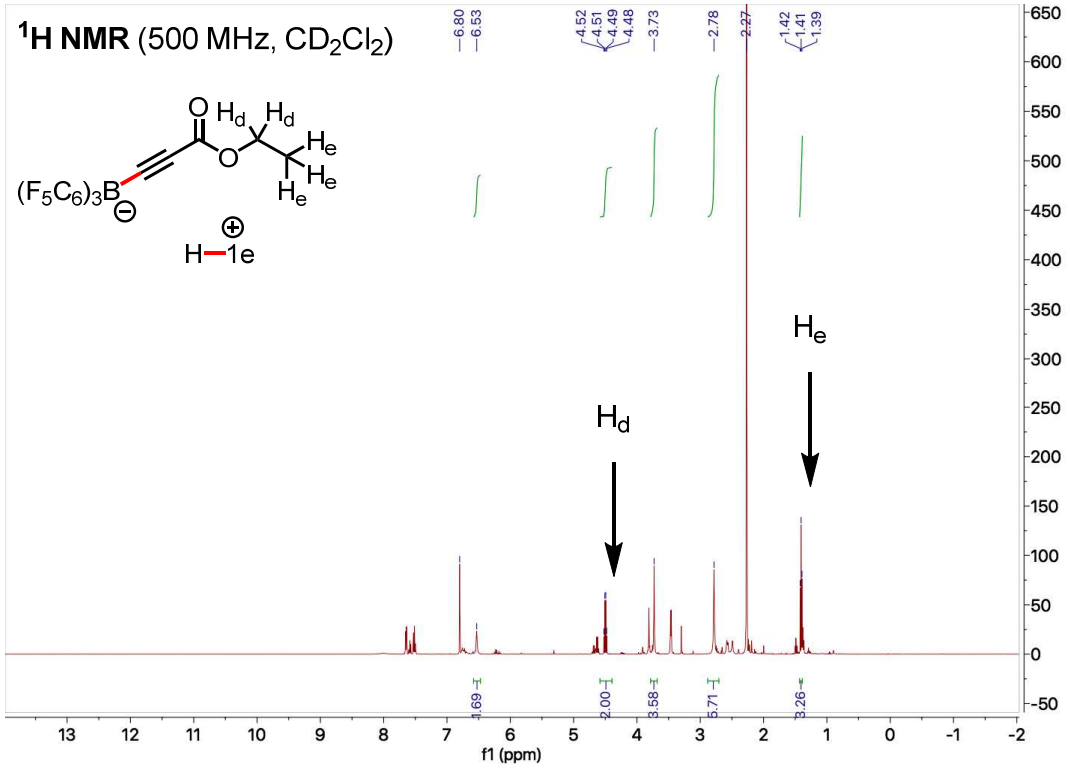


Figure S1.15. ^{1}H NMR spectrum of unpurified reaction mixture of $[(F_5C_6)_3B–C{\equiv}C–CO_2Et]^-[H–2.15d]^+$.

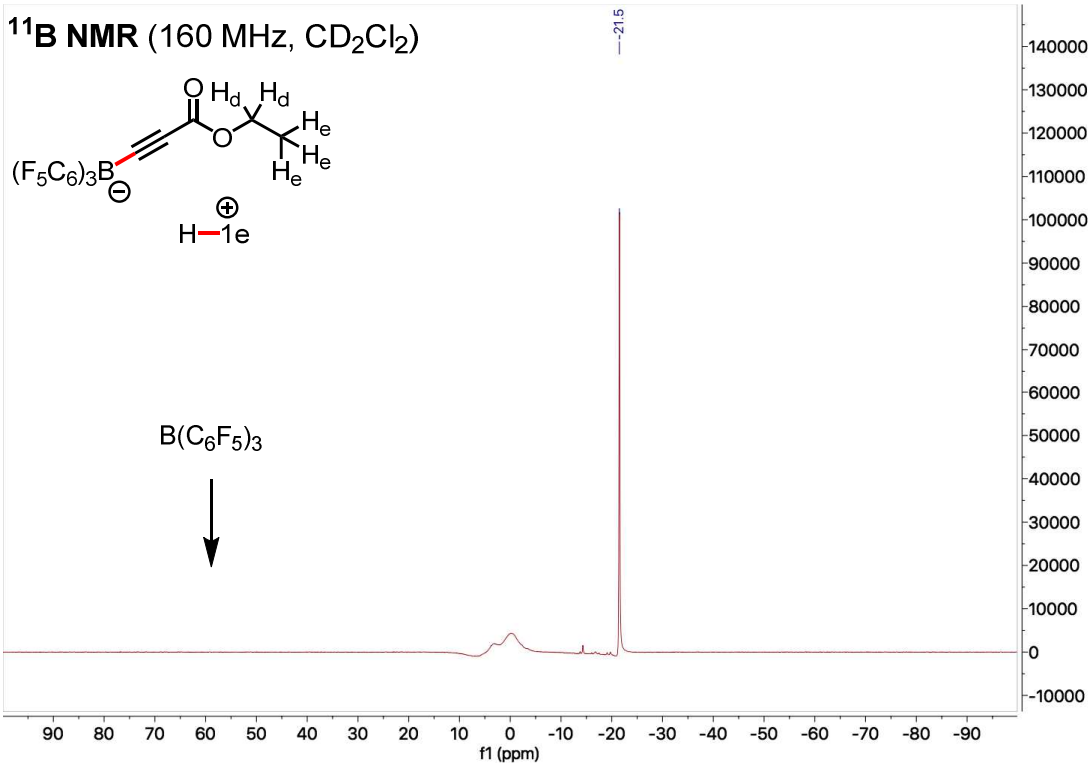


Figure S1.16. ^{11}B NMR spectrum of unpurified reaction mixture of $[(F_5C_6)_3B–C\equiv C–CO_2Et]^-[H–$ **2.15d**$]^+$.

To this unpurified reaction mixture was added (Xantphos)Cu(MeCN)PF_6 (0.10 mmol). The mixture was allowed to stir at 60 °C for 1 h. Then, the mixture was allowed to cool 22 °C and a ^{1}H NMR spectrum was obtained (Figure 1.17). Analysis of the ^{1}H spectrum of unpurified mixtures with mesitylene as the internal standard revealed that **2.17d** was formed in 24% under this reaction conditions, thereby demonstrating competency of the proposed intermediate **XIII** in the alkyne incorporation process.

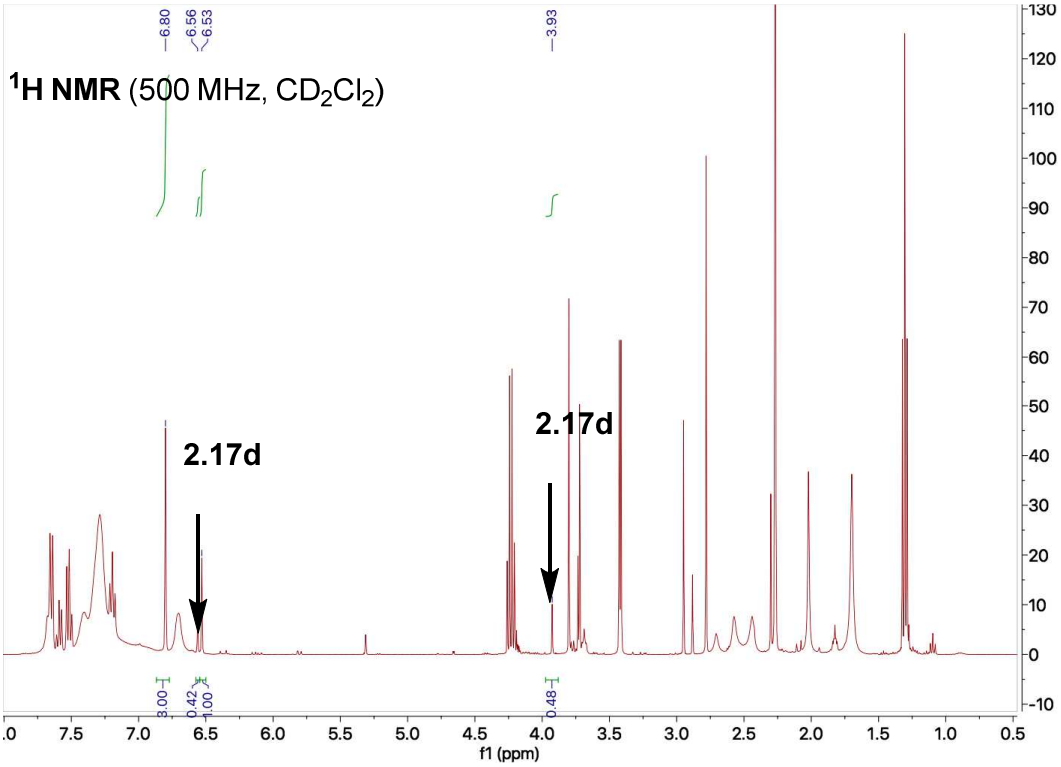
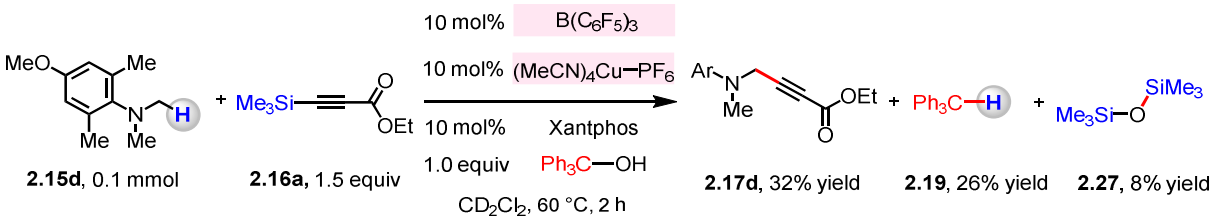


Figure S1.17. ^{1}H NMR spectrum of unpurified reaction mixture of **XIII** and 100 mol % of (Xantphos)Cu(MeCN)PF_6.

A5.3.2 NMR Experiments for Detection of Byproducts

The reaction between 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** and ethyl 3-(trimethylsilyl)propiolate **2.16a** was monitored by ^{1}H NMR spectroscopy (Figure S1.18–S1.20). This study revealed that $Ph_3C–H$ **5** and $Me_3Si–O–SiMe_3$ **14** are the stable byproducts of this α-alkynylation reaction (Scheme S1.2 and S1.3).

Scheme S1.3. Formation of Stable Byproducts **2.19** and **2.27**



Experimental Procedure for the α-Alkynylation of 4-Methoxy-*N,N*,2,6-tetramethylaniline and Ethyl 3-(trimethylsilyl)propiolate

An oven-dried 7.0 mL vial equipped with a magnetic stir bar was used. To the vial were added $Cu(MeCN)_4PF_6$ (0.010 mmol), Xantphos (0.01 mmol), and CD_2Cl_2 (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **2.15d** (0.10 mmol), mesitylene (0.10 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and CD_2Cl_2 (0.20 mL) were added to the vial. The mixture was then transferred to a J-Young tube and was allowed to heat at 60 °C for 1 h. After 1 h, the mixture was allowed to cool and NMR spectroscopy was obtained. Upon analysis of the ^{1}H NMR of the unpurified reaction mixture, triphenylmethane **5** and 1,1,1,3,3,3-hexamethyldisiloxane **2.27** was detected (Figure S1.18).

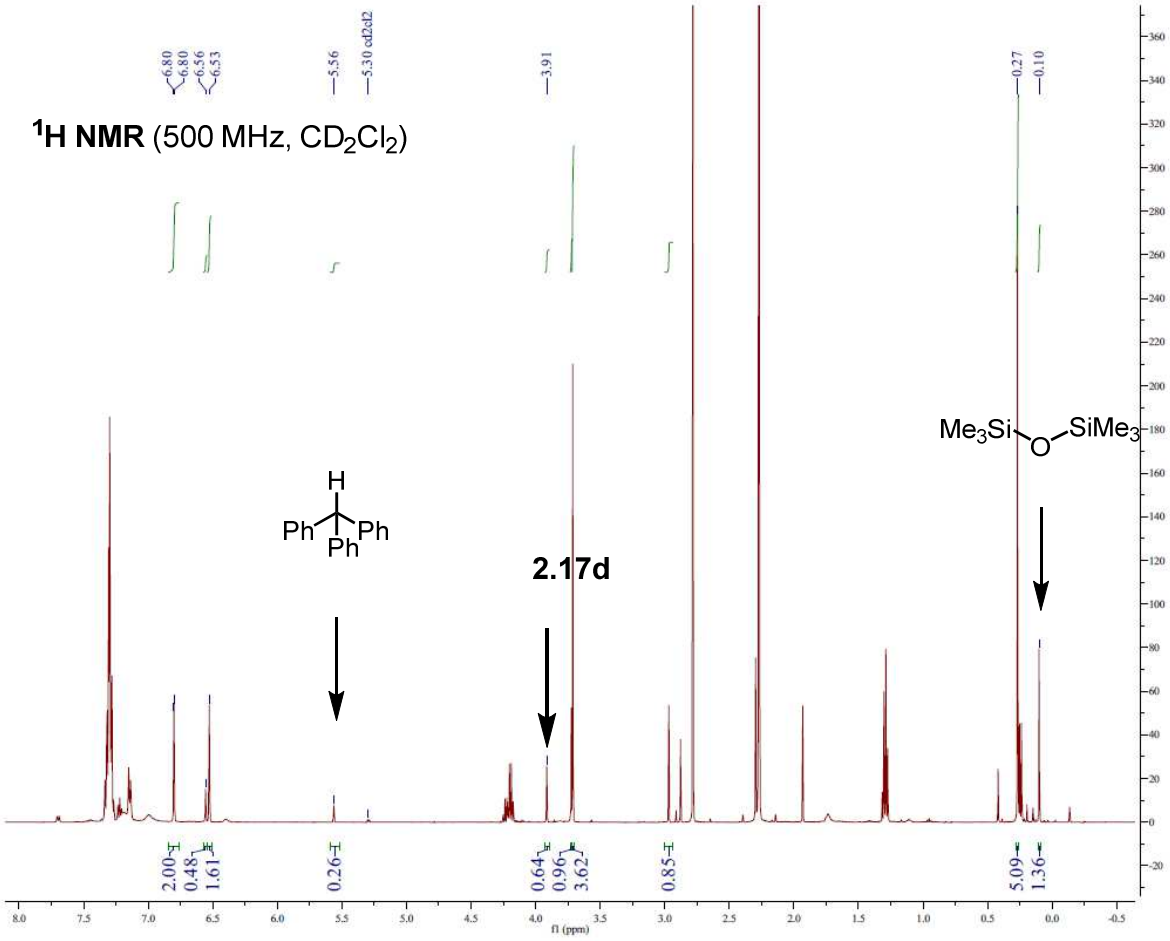


Figure S1.18. ^{1}H NMR spectrum of unpurified reaction mixture of **2.15d** and **2.16a** under α-alkynylation condition.

To this unpurified reaction mixture was added commercially available $Me_3Si–O–SiMe_3$ **2.27** (Figure S1.19).

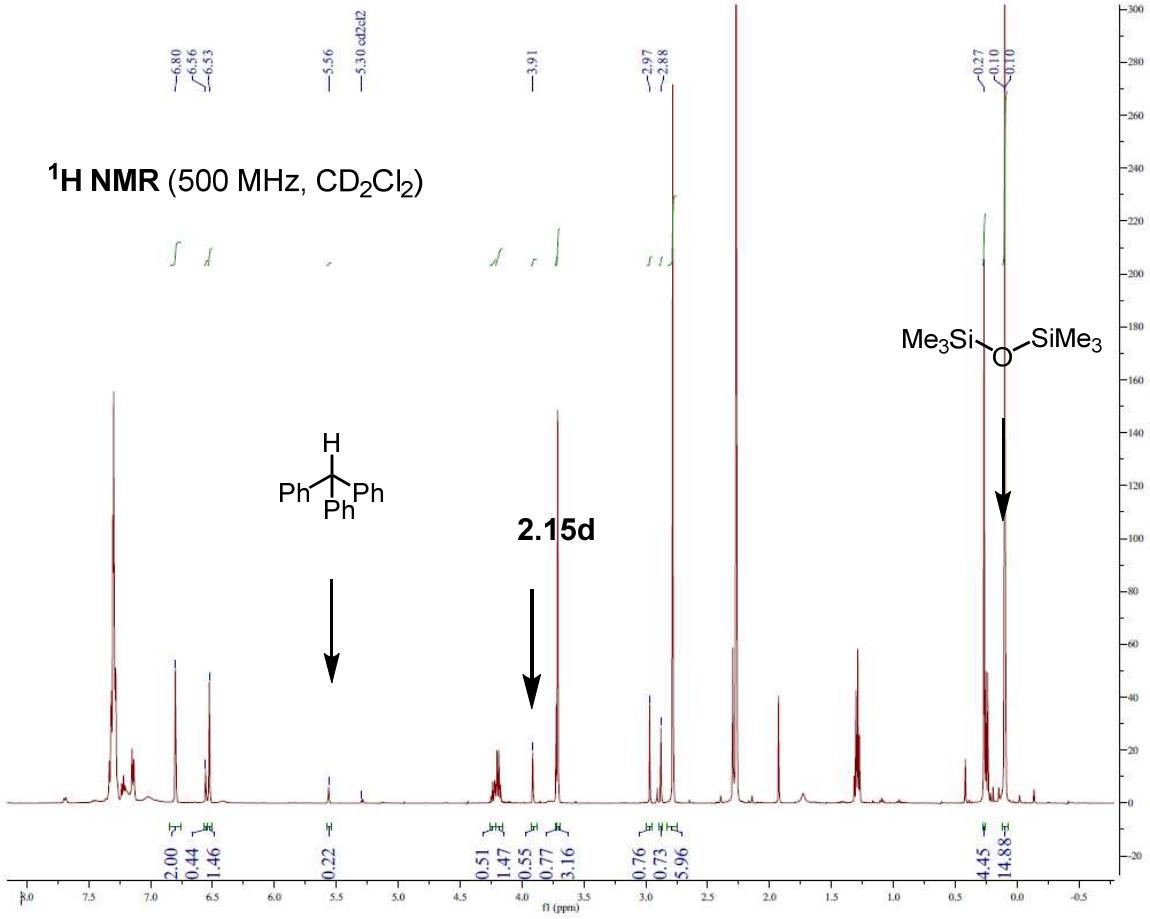


Figure S1.19. ^{1}H NMR spectrum of the unpurified reaction mixture of **2.15d** and **2.16a** under α-alkynylation conditions, where $Me_3Si–O–SiMe_3$ **2.27** was added to the cooled reaction mixture after 1 h.

In order to determine the fate of the hydride of the amine for this alkynylation process, we carried out the transformation between 4-methoxy-2,6-dimethyl-*N,N*-bis(methyl-d_3)aniline **2.15d-*d*** and ethyl 3-(trimethylsilyl)propiolate **2.16a**. Upon analysis of the ^{1}H NMR of the unpurified product mixture, the deuteride was detected on (methanetriyl-*d*)tribenzene **2.19-*d*** (Figure S1.20), which is in agreement with our proposed mechanism. The yield of **2.17d-*d***, **2.19-*d*** and **2.27** were quantified based on the amount of mesitylene added as an internal standard.

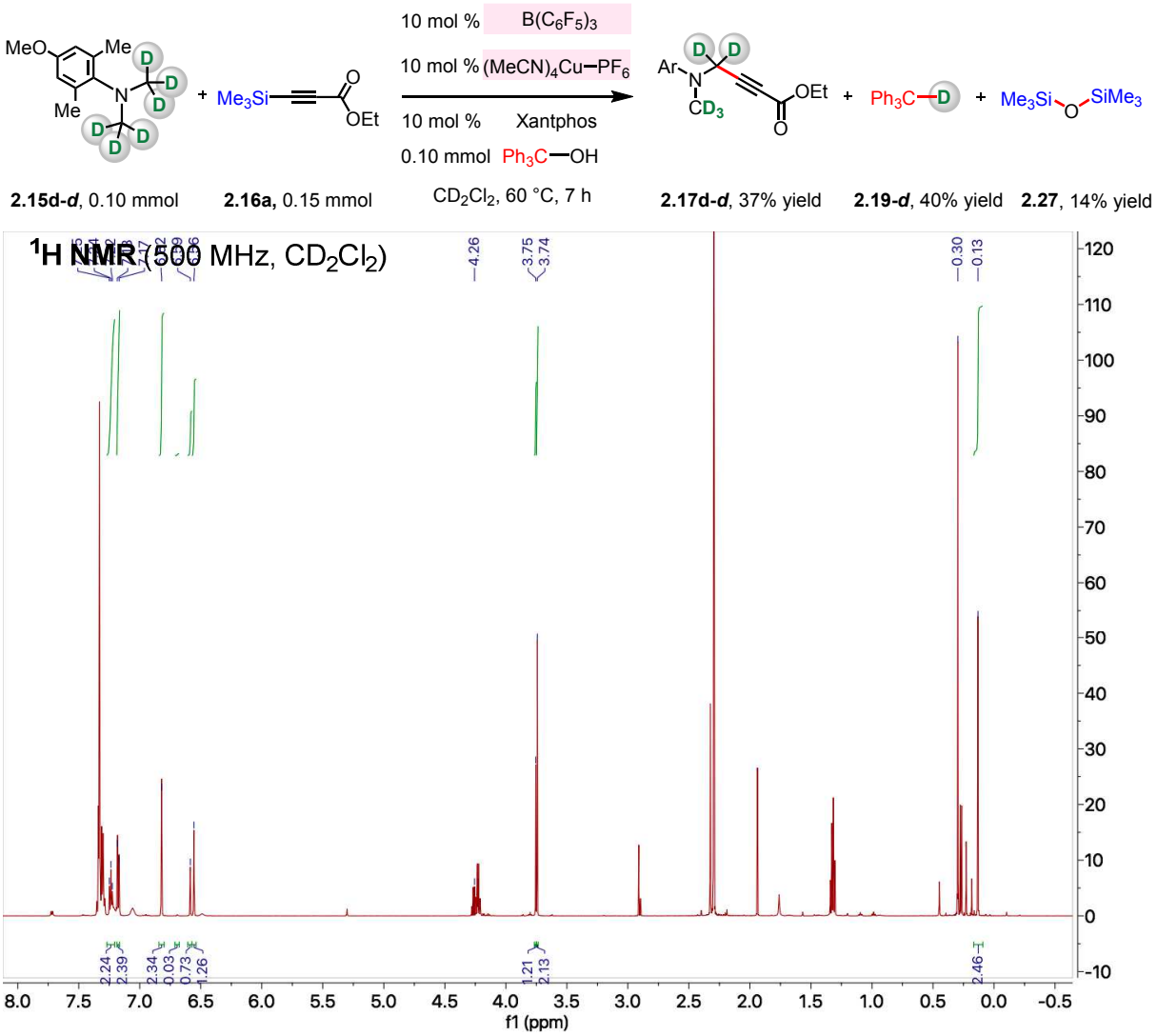


Figure S1.20. ^{1}H NMR spectrum of unpurified reaction mixture of **2.15d-*d*** and **2.16a** under *α*-alkynylation conditions.

5.3.3 NMR Experiments for the Detection of the Resting State Complex Containing $B(C_6F_5)_3$

We embarked on a study to identify the structure of a resting state complex which contains $B(C_6F_5)_3$. Previously, the groups of Pinkas and Resconi have independently reported that a borate anion $[(C_6F_5)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-$ can be formed through the reaction of $B(C_6F_5)_3$ and Ph_3COH,[17] and by reacting $B(C_6F_5)_3$, H_2O and an amine.[18] Since the $B(C_6F_5)_3$/organocopper co-catalyzed transformation of C–H bonds was found to have a *0.5 order dependency* with respect to the

concentration of $B(C_6F_5)_3$, we surmised that $[(C_6F_5)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-$ containing two molecules of $B(C_6F_5)_3$ could be its resting state.

We first acquired the ^1H NMR spectra of a sample containing $B(C_6F_5)_3$ and Ph_3COH in CD_2Cl_2 (Figure S1.21) and compared that to spectra reported by Pinkas[17]; based on this analysis, our spectra was in agreement with the formation of $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-[CPh_3]^+$.

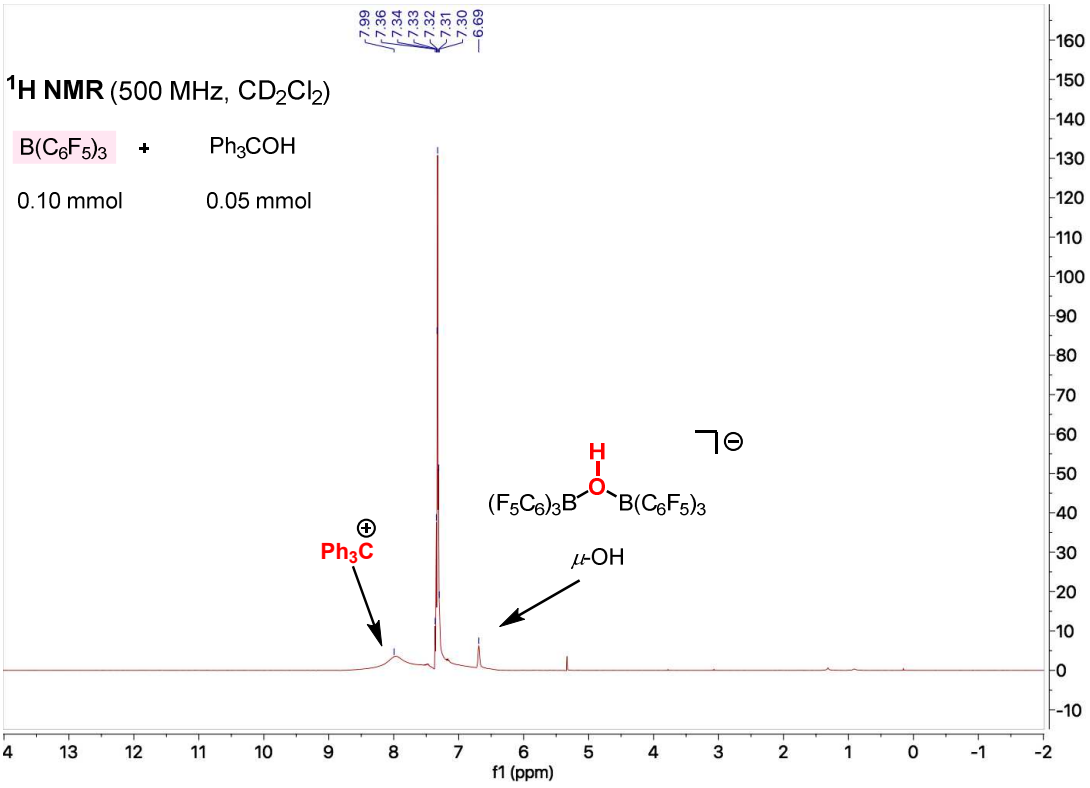


Figure S1.21. ^1H NMR of $B(C_6F_5)_3$ and Ph_3COH in CD_2Cl_2.

Next, we obtained the ^{11}B and/or ^{19}F NMR spectra of:

Figures S1.22–S1.23: the sample containing $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-[CPh_3]^+$ prepared as described above,

and compared those to the spectra we obtained for:

Figures S1.24-25: $B(C_6F_5)_3$ only

Figures S1.26-27: a mixture of $B(C_6F_5)_3$, [Cu(Xantphos)(MeCN)][PF_6], 4-methoxy-*N*,*N*,2,6-tetramethylaniline **2.15d**, 3-(triemthylsilyl)propiolate **2.16a**, Ph_3COH in CD_2Cl_2 at 22 °C, and

Figure S1.28: a mixture of $B(C_6F_5)_3$, [Cu(Xantphos)(MeCN)][PF_6], 4-methoxy-*N*,*N*,2,6-tetramethylaniline **2.15d**, 3-(triemthylsilyl)propiolate **2.16a**, Ph_3COH in CD_2Cl_2 at 60 °C.

The analyses of Figures S1.26–S1.28 revealed that there is no free $B(C_6F_5)_3$ remaining in the mixture (characteristic peak at 58.7 ppm corresponding to $B(C_6F_5)_3$ in Figure 1.24 is not observed in Figure S1.26).

The comparison of ^{19}F NMR spectra for the authentic sample of $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-[CPh_3]^+$ (Figure 1.23) with those acquired for the actual reaction mixture (Figures S1.27 and S1.28) revealed that there are consistent peaks at −135.94, −160.88 and −165.53 ppm.

Furthermore, the comparison of ^{11}B NMR spectrum we acquired for the sample of $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-[CPh_3]^+$ (Figure S1.22) with the one for the mixture (Figure S1.26) also showed that there are common peaks at 0.8 and −3.7 ppm.

These results serve as evidences to support the formation of $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-$ anion under the reaction conditions for $B(C_6F_5)_3$/[Cu(Xantphos)(MeCN)][PF_6] co-catalyzed C–H functionalization.

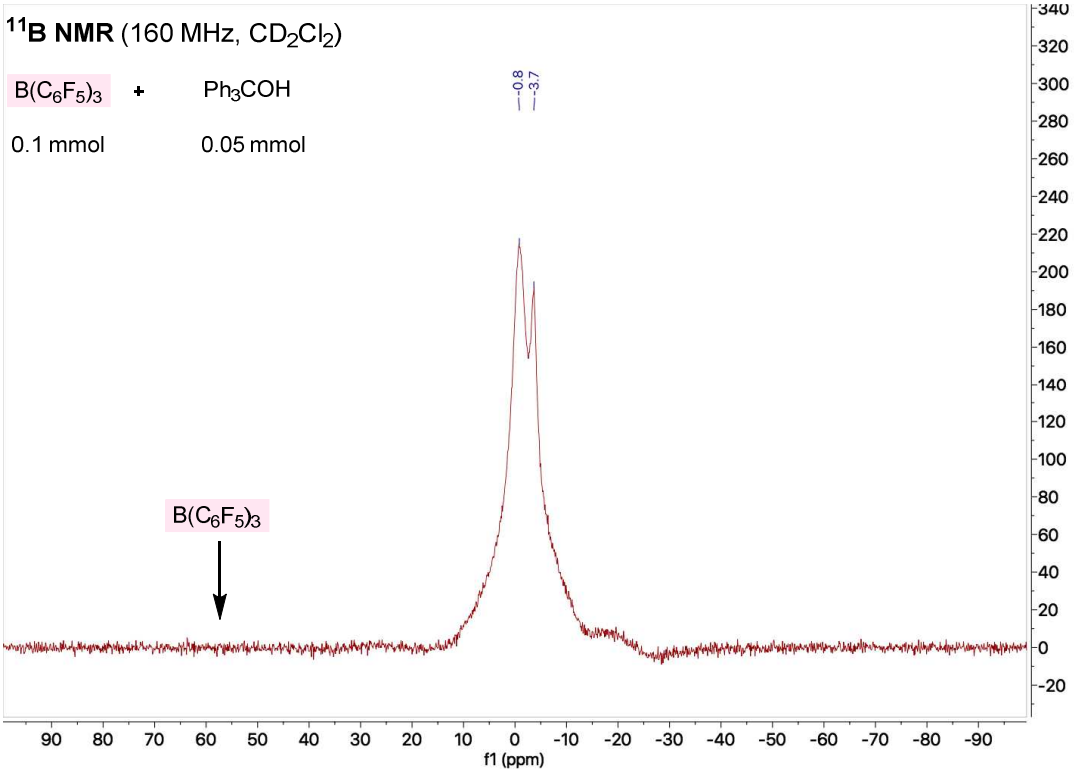


Figure S1.22. ^{11}B NMR spectrum of a sample containing $B(C_6F_5)_3$ and Ph_3COH in CD_2Cl_2

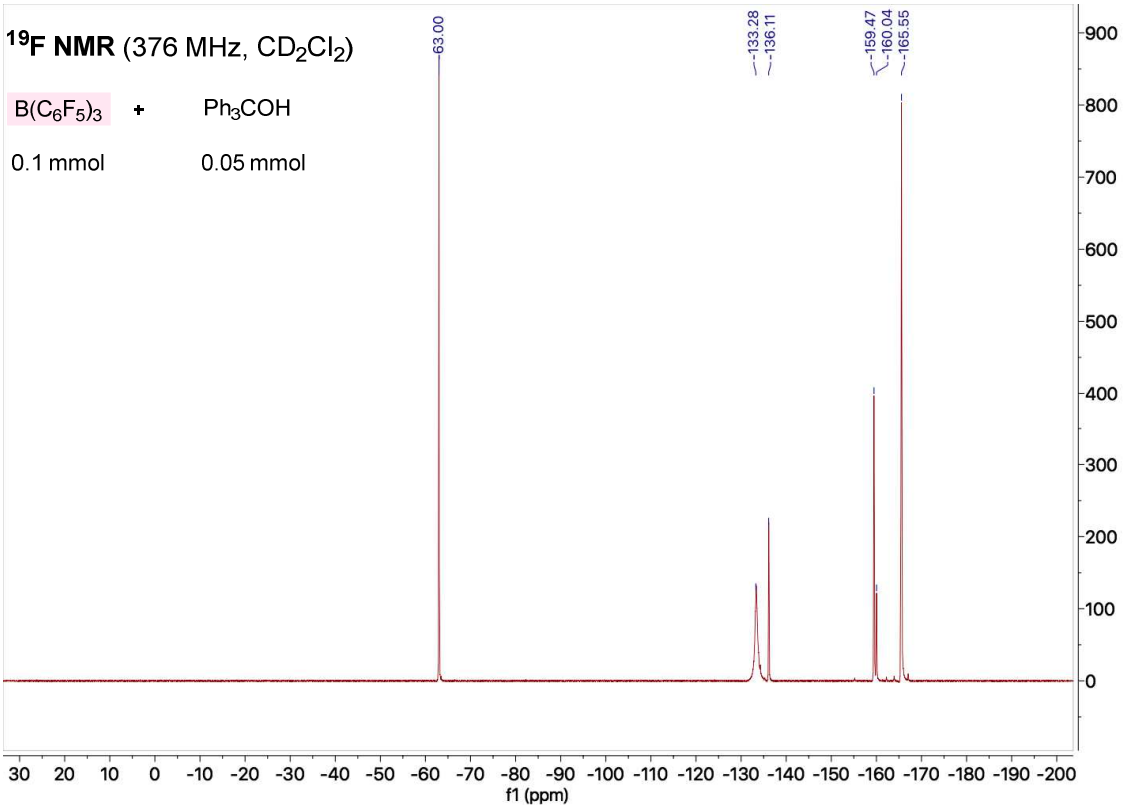


Figure S1.23. ^{19}F NMR spectrum of a sample containing $B(C_6F_5)_3$ and Ph_3COH in CD_2Cl_2.

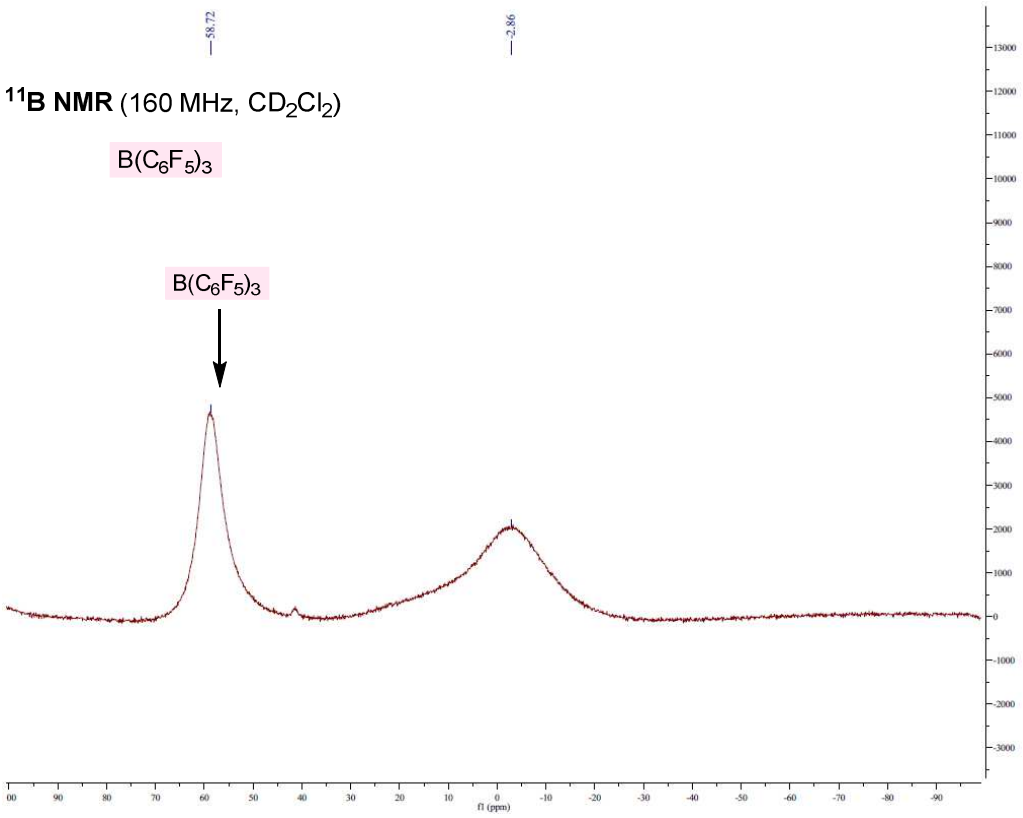


Figure S1.24. ^{11}B NMR spectrum of $B(C_6F_5)_3$ in CD_2Cl_2.

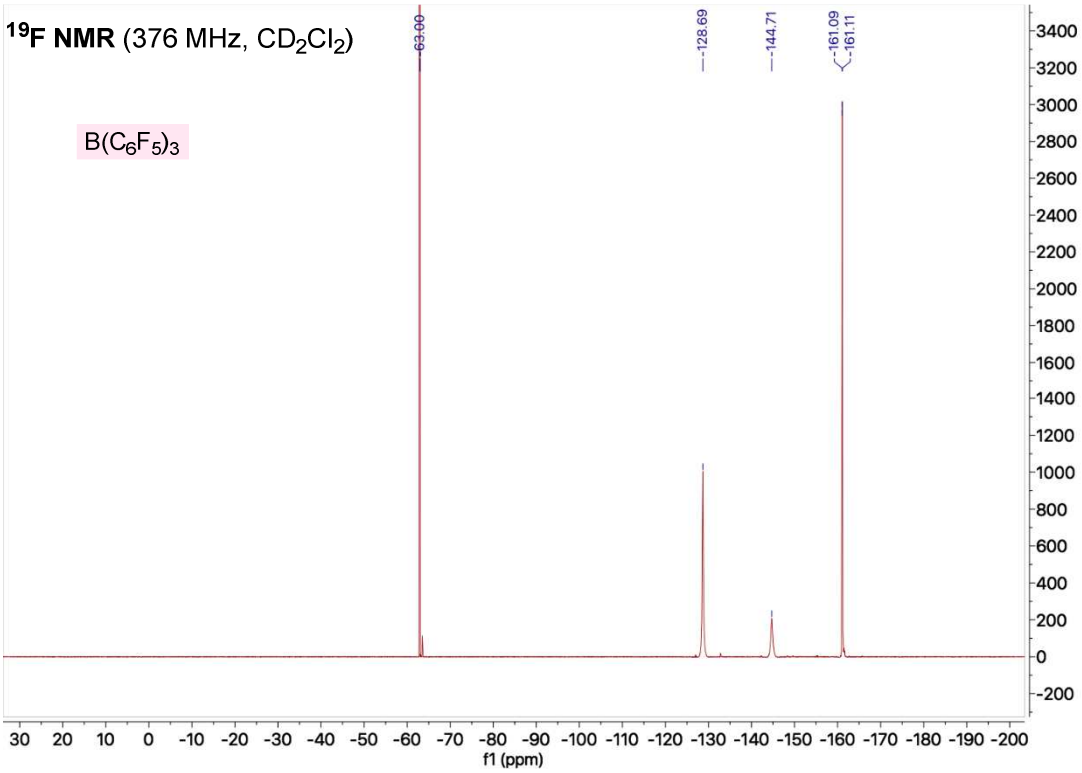


Figure S1.25. ^{19}F NMR spectrum of $B(C_6F_5)_3$ in CD_2Cl_2.

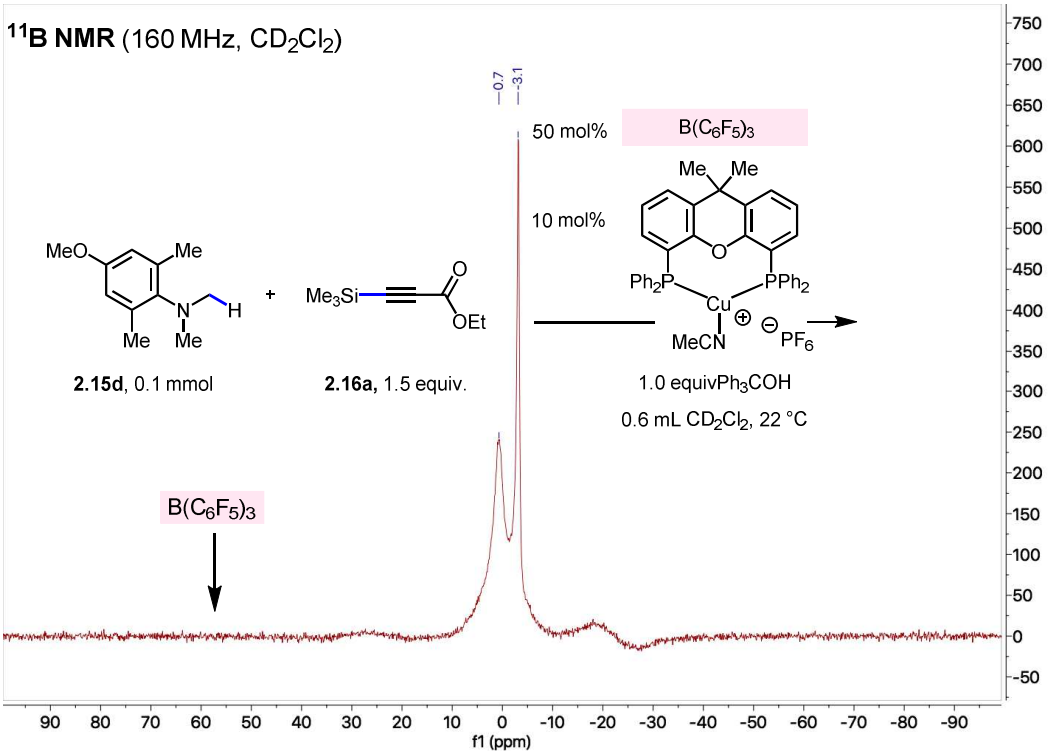


Figure S1.26. ^{11}B NMR spectrum of α-alkynylation reaction between **2.15d** and **2.16a** with 50 mol% $B(C_6F_5)_3$ at 22 °C.

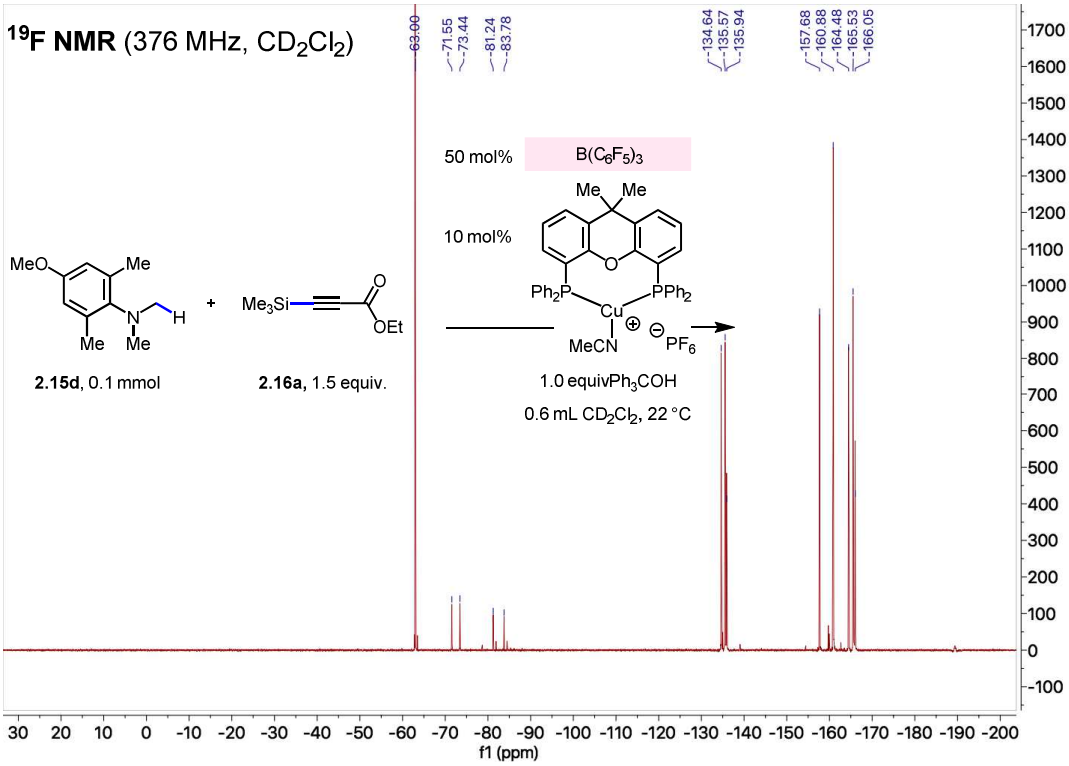


Figure S1.27. ^{19}F NMR spectrum of α-alkynylation reaction of amine **2.15d** with 50 mol% $B(C_6F_5)_3$ at 22 °C.

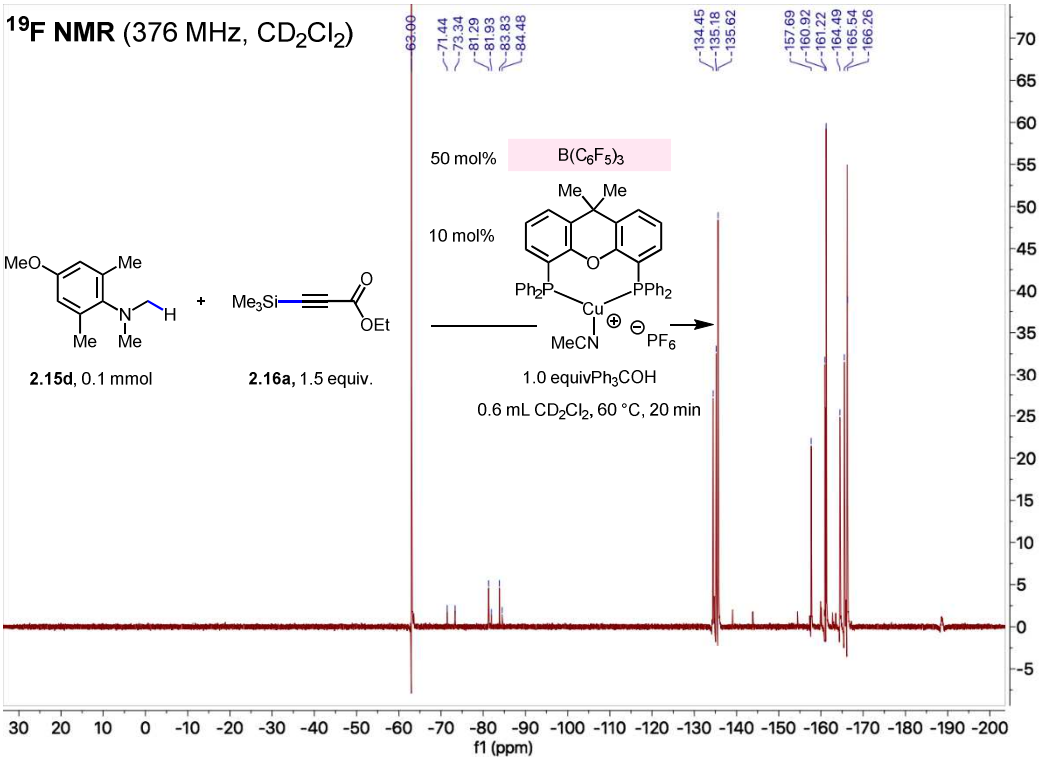


Figure S1.28. ^{19}F NMR spectrum of α-alkynylation reaction between **2.15d** and **2.16a** using 50 mol% $B(C_6F_5)_3$ at 22 °C.

As reported by the group of Resconi, the reaction of $B(C_6F_5)_3$ and H_2O may result in the formation of $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-[H\text{–}NR_3]^+$.[18] To probe if this can occur under our reaction conditions, we acquired the following spectra:

Figures S1.29: ^{11}B spectrum for a mixture of $B(C_6F_5)_3$, H_2O and **2.15d**, and

Figures S1.26: ^{11}B NMR spectra for a mixture of $B(C_6F_5)_3$, [Cu(Xantphos)(MeCN)][PF_6], 4-methoxy-*N*,*N*,2,6-tetramethylaniline **2.15d**, 3-(triemthylsilyl)propiolate **2.16a**, Ph_3COH in CD_2Cl_2 at 22 °C.

Resconi *et al*.[18] reported that ^{11}B NMR spectrum for $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-$ contains a characteristic singlet peak at −1 ppm (298 K). The ^{11}B NMR spectra we acquired (Figures S1.26 and S1.29) both possess a singlet at – 3.7 ppm, therefore suggesting that the formation of $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-$ anion is possible.

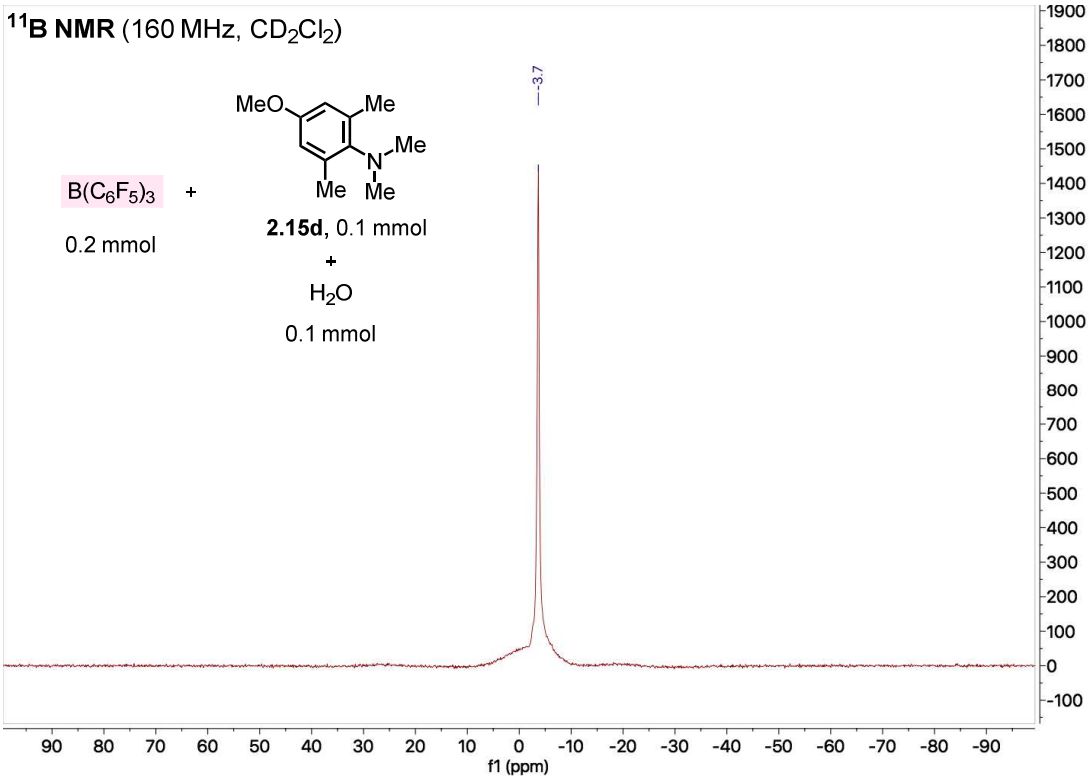


Figure S1.29. ^{11}B NMR spectrum of a sample containing $B(C_6F_5)_3$, H_2O and amine **2.15d** in CD_2Cl_2.

As reported by the group of Basset,[19] a tertiary amine and $B(C_6F_5)_3$ could form an ionic complex containing an iminium ion and $[(F_5C_6)_3B{-}H]^-$. In the ^{11}B NMR spectrum, $[(F_5C_6)_3B{-}H]^-$ has been reported to have a characteristic peak at −23.6 ppm.[19] To probe if the related ion pairs are formed in our system, we prepared the following sample and obtained their ^{1}H, ^{11}B and ^{19}F NMR spectra:

Figures S1.30-S1.32: a reaction mixture containing 0.1 mmol $B(C_6F_5)_3$ and 0.1 mmol of 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** in CD_2Cl_2.

Figure S1.33: 4-methoxy-*N,N*,2,6-tetramethylaniline **2.15d** in CD_2Cl_2 only.

The comparison of the ^{1}H NMR spectra (Figure S1.30 versus Figure S1.33) suggests that, even in the presence of a stoichiometric quantity of $B(C_6F_5)_3$, amine **2.15d** is recovered in full and that the formation of corresponding iminium ion cannot be detected.

The analysis of the ^{11}B NMR spectrum (Figure S1.31) and its comparison to S1.24 (standard spectrum for $B(C_6F_5)_3$ only) indicate that there is free $B(C_6F_5)_3$ (characteristic peak at 59.5 ppm

was observed in both Figures S1.24 and S1.31). In addition, the generation of a small quantity of $B(C_6F_5)_3$•**2.15d** adduct was observed (a characteristic peak at −1.2 ppm was found in S1.31).

In agreement with the observations mentioned above, the ^{19}F NMR spectrum (Figure S1.32) contains peaks corresponding to both free $B(C_6F_5)_3$ and the adduct $B(C_6F_5)_3$•**2.15d**.

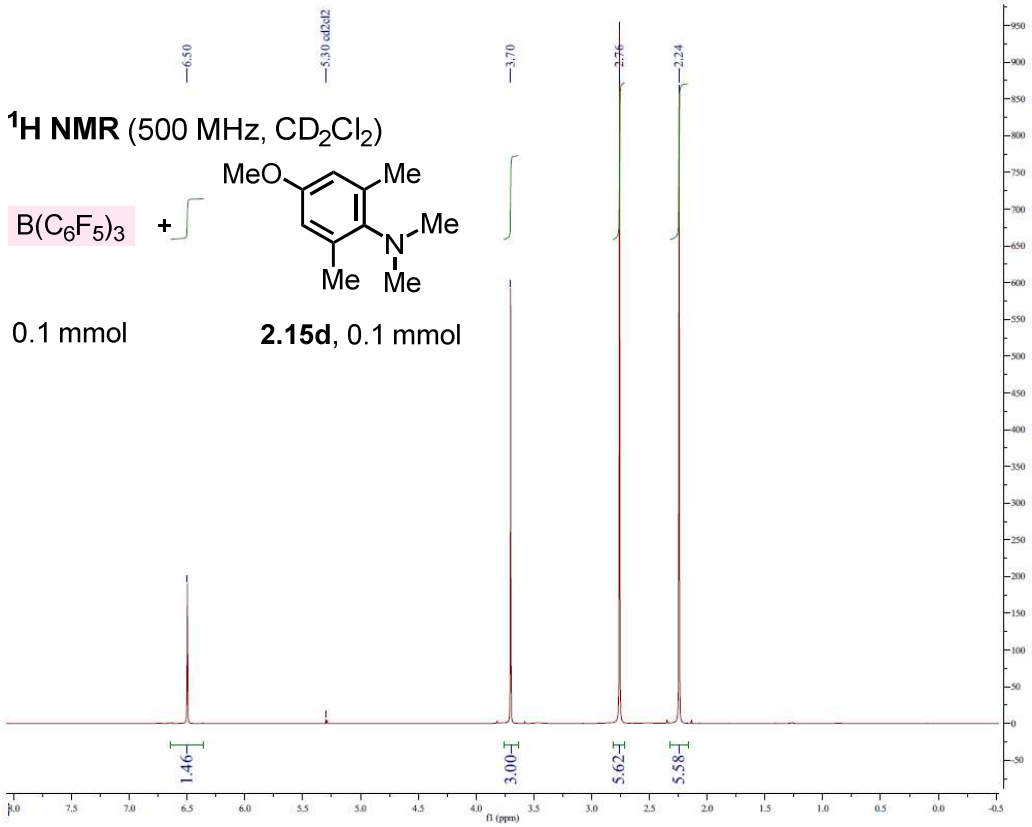


Figure S1.30. ^1H NMR of spectrum of a sample containing $B(C_6F_5)_3$ and amine **2.15d** in CD_2Cl_2.

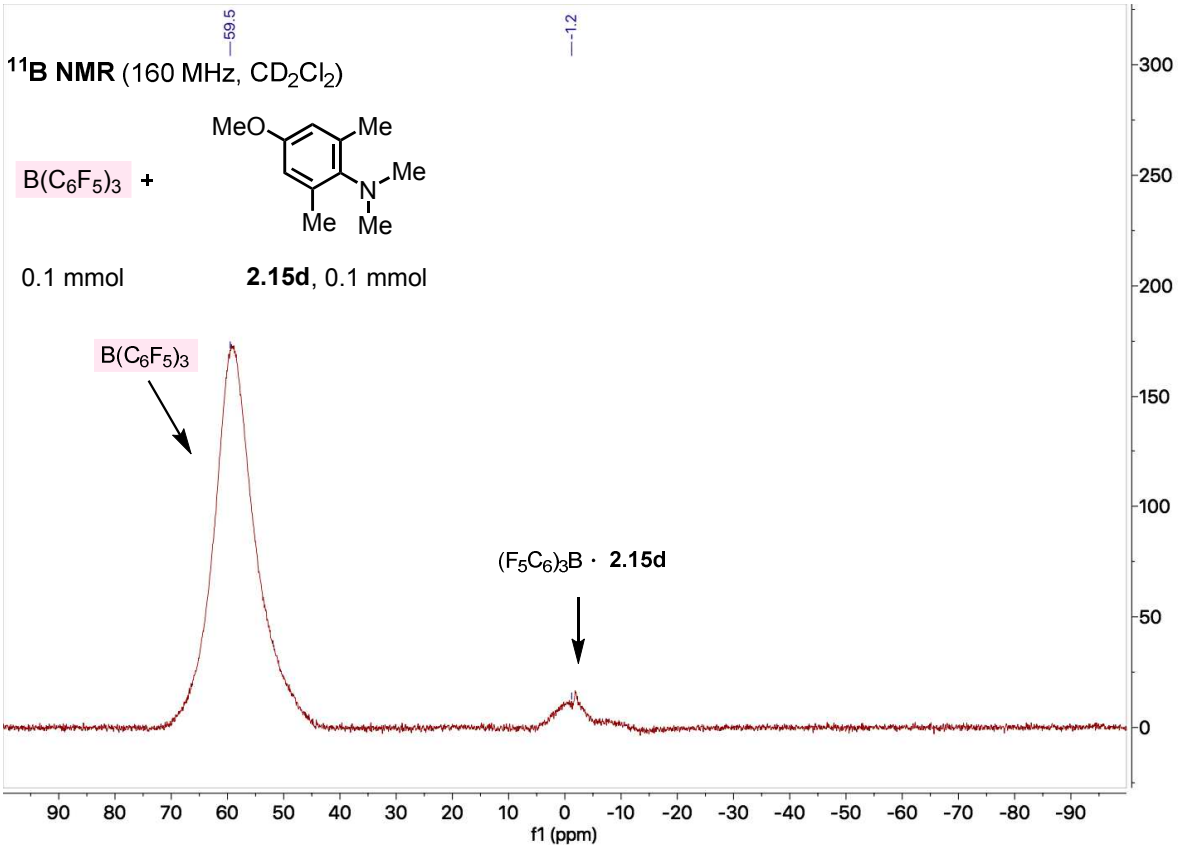


Figure S1.31. ^{11}B NMR spectrum of a sample containing $B(C_6F_5)_3$ and amine **2.15d** in CD_2Cl_2.

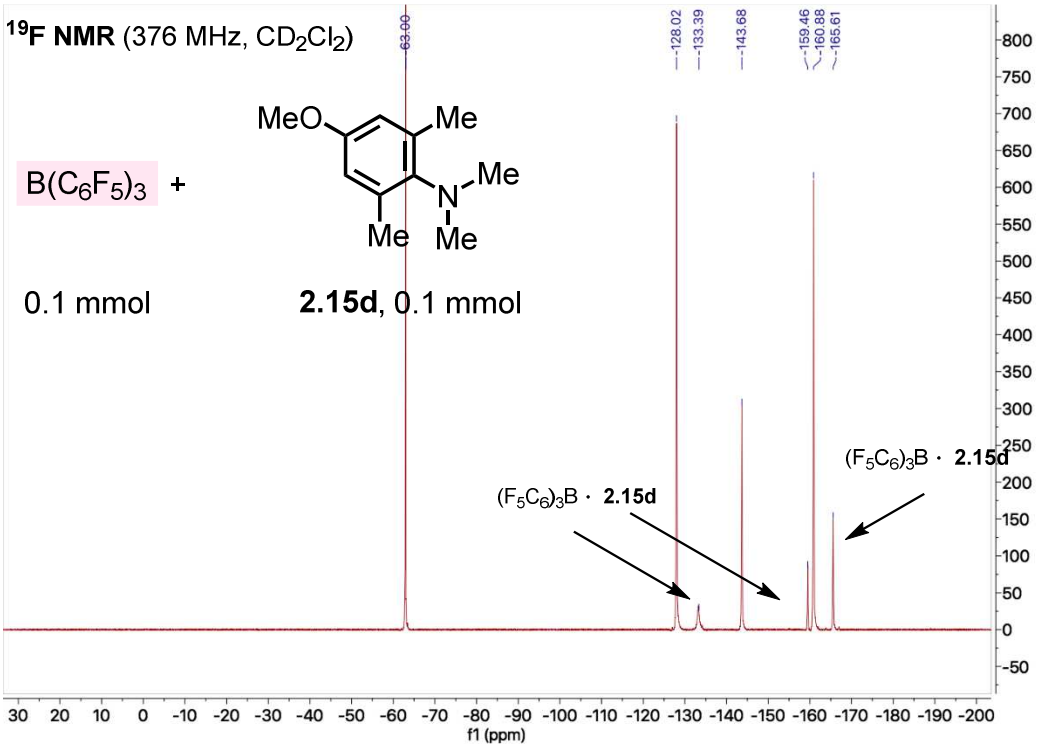


Figure S1.32. ^{19}F NMR spectrum of a sample containing $B(C_6F_5)_3$ and amine **2.15d** in CD_2Cl_2

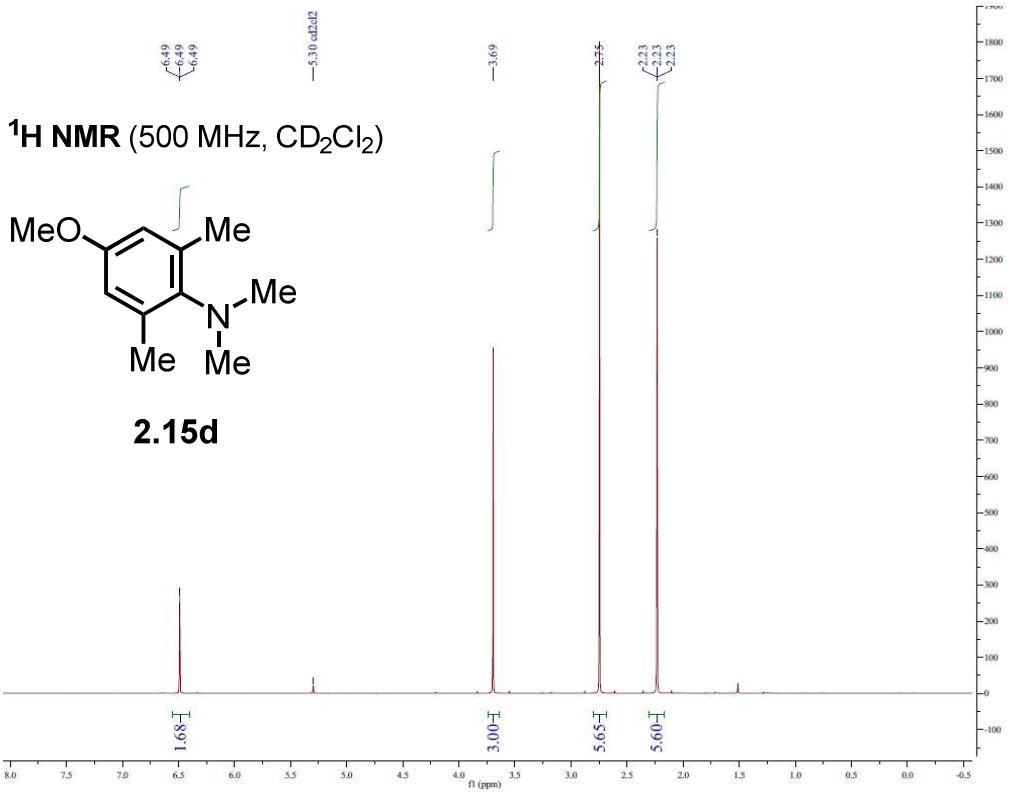


Figure S1.33. ^{1}H NMR spectrum of amine **2.15d** in CD_2Cl_2.

In addition, we attempted to detect a Lewis acid/Lewis base adduct that may form between the carbonyl unit of alkynylsilane **2.16a** and $B(C_6F_5)_3$.[20] The ^{11}B and ^{19}F NMR spectra were obtained for:

Figures S1.34 – S1.35: the sample containing 0.1 mmol of $B(C_6F_5)_3$ and 0.1 mmol of **2.16a**.

It was found through studying the ^{11}B NMR spectrum of the sample (Figure S1.34) that $B(C_6F_5)_3$ forms the adduct with **2.16a** (a characteristic peak was observed at −2.1 ppm), and that $B(C_6F_5)_3$ is consumed.

Furthermore, we detected peaks at −134.14, −157.49 and −164.44 ppm in the ^{19}F NMR spectrum (Figure S1.35) that may correspond to the adduct formed while $B(C_6F_5)_3$ was fully consumed.

In order to determine if the adduct may also be generated in under the standard reaction conditions for catalytic C–H functionalization, ^{19}F NMR spectrum (Figure S1.35) was compared to those obtained for the unpurified reaction mixtures (Figures S1.27–S1.28). In Figures S1.27–S1.28, there were peaks at −134.64, −157.68 and −164.48 ppm (vs those at −134.14, −157.49 and −164.44

ppm found in S1.35), thereby suggesting that the adduct may be present in the unpurified reaction mixture.

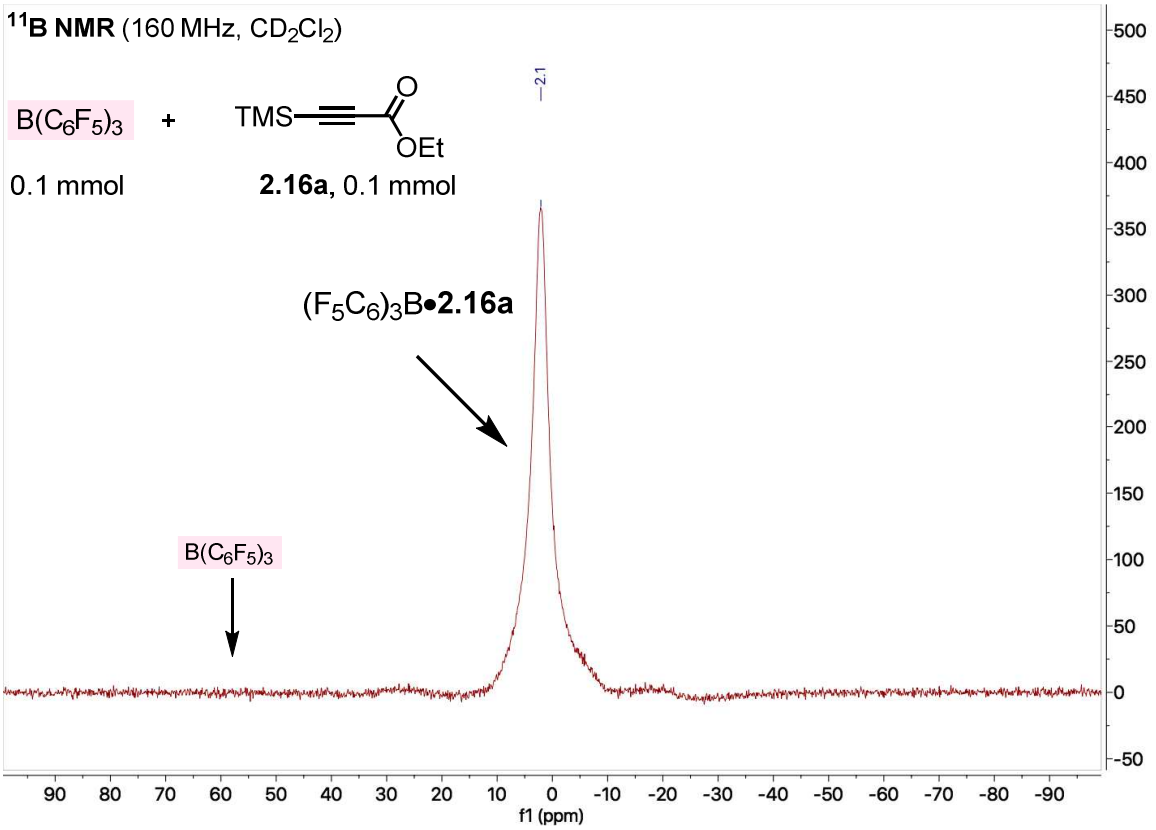


Figure S1.34. ^{11}B NMR spectrum of a sample containing $B(C_6F_5)_3$ and alkyne **2.16a** in CD_2Cl_2.

^{19}F NMR (376 MHz, CD_2Cl_2)

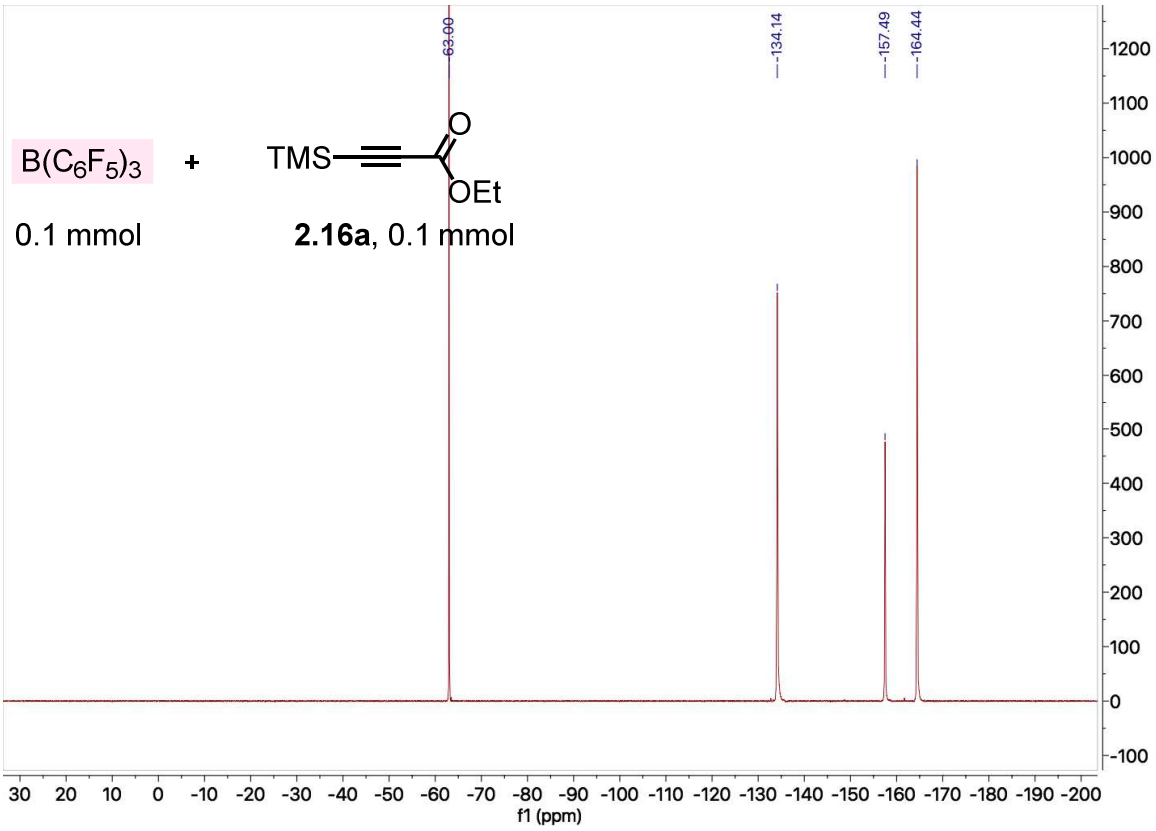
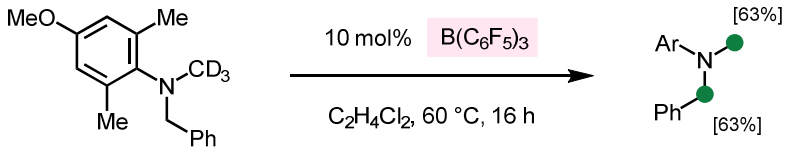


Figure S1.35. ^{19}F NMR spectrum of a sample containing $B(C_6F_5)_3$ and alkyne **2.16a** in CD_2Cl_2.

A5.4. Experiments Involving *N*-Benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-*d*$_3$)aniline

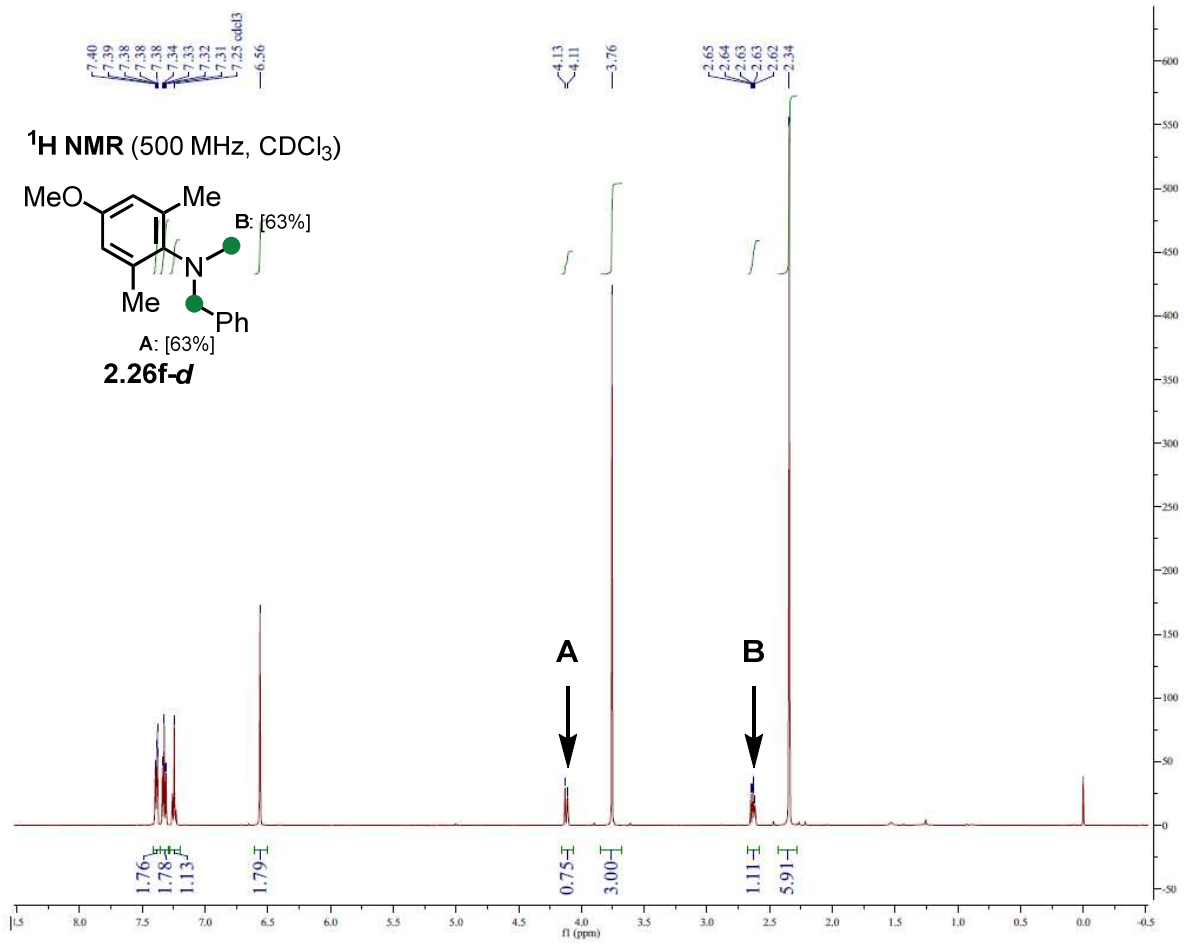


2.15f-*d*, 0.1 mmol

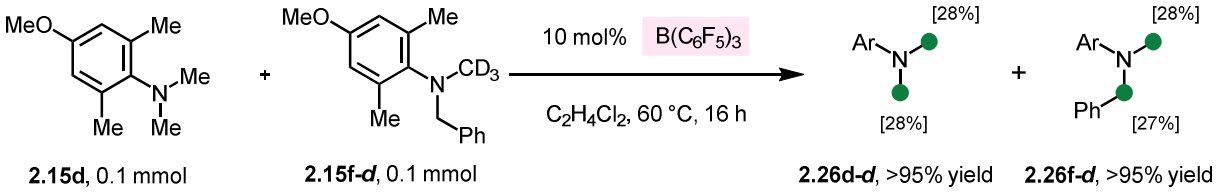
2.26f-*d*, >95% yield

Experimental Procedure for the Isotope Exchange of *N*-Benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-*d*$_3$)aniline

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added amine **2.15f-*d*** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.4 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 16 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. The unpurified mixture was purified by silica gel chromatography (Et_2O:hexanes = 1:19), to afford **2.26f-*d*** as a colorless oil (>95% yield). Deuterium or proton incorporation values were determined based on analysis of the ^{1}H NMR spectrum of the purified product.



Intermolecular Isotope Exchange Experiment Between *N*-Benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-d_3)aniline and 4-Methoxy-*N*,*N*,2,6-tetramethylaniline

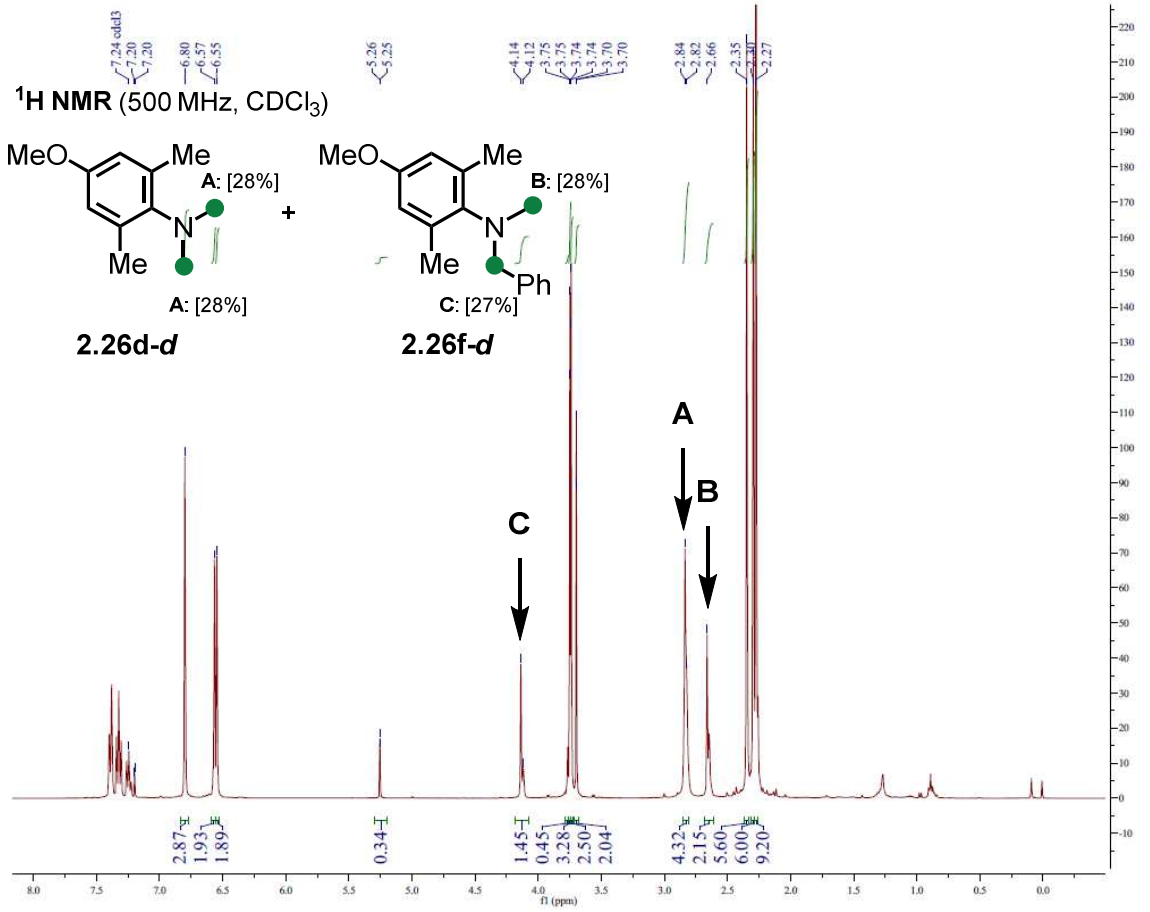


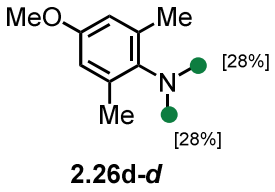
2.15d, 0.1 mmol **2.15f-*d***, 0.1 mmol **2.26d-*d***, >95% yield **2.26f-*d***, >95% yield

Experimental Procedure for the Isotope Exchange Between of *N*-Benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-d_3)aniline and 4-Methoxy-*N*,*N*,2,6-tetramethylaniline

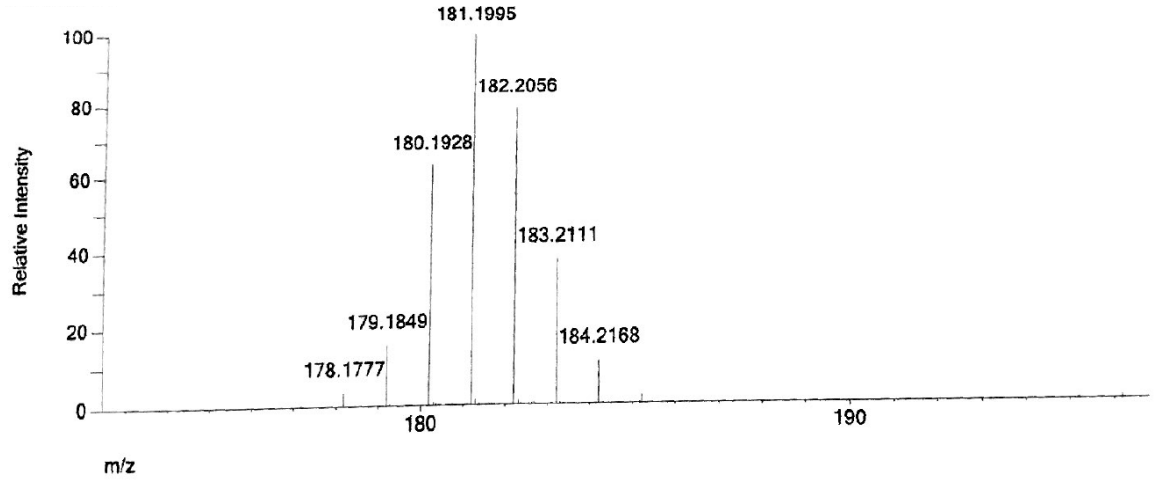
An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added amine **2.15d** (0.1 mmol), amine **2.15f-*d*** (0.1 mmol), $B(C_6F_5)_3$ (0.02 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.4 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 16 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. Deuterium

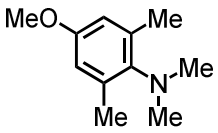
incorporation values were determined based on analysis of the ^{1}H NMR and HRMS spectra of the purified product.



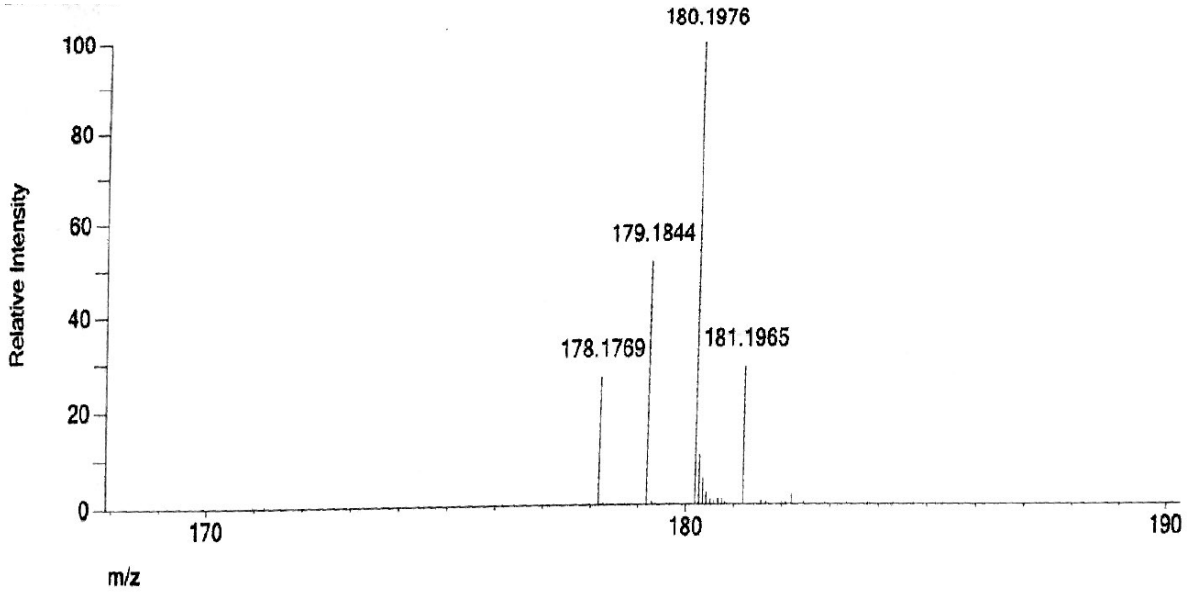


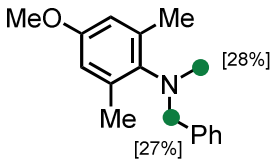
2.26d-*d*



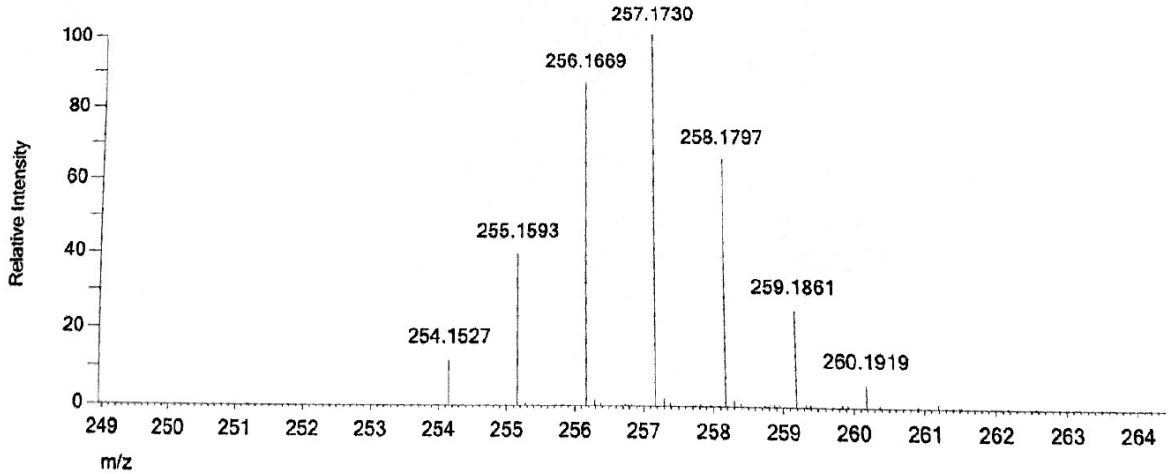

MeO
Me
N
Me
Me
Me

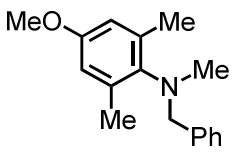
2.15d


180.1976
179.1844
178.1769
181.1965
Relative Intensity
100
80
60
40
20
0
170
180
190
m/z

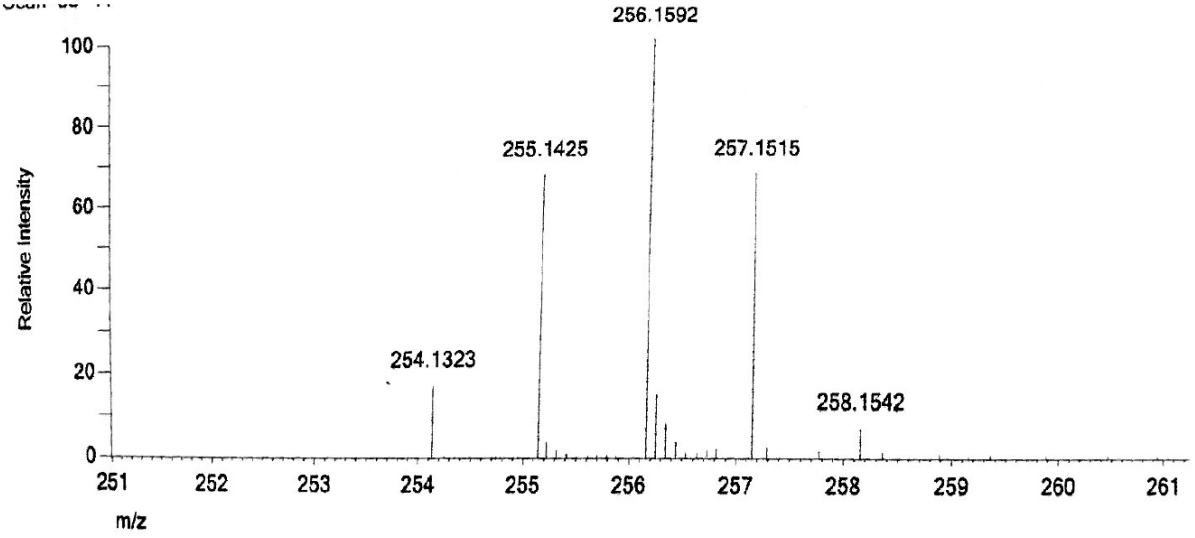

MeO
Me
[28%]
N
Me
Ph
[27%]

2.26f-*d*


257.1730
256.1669
258.1797
255.1593
259.1861
254.1527
260.1919
Relative Intensity
100
80
60
40
20
0
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
m/z

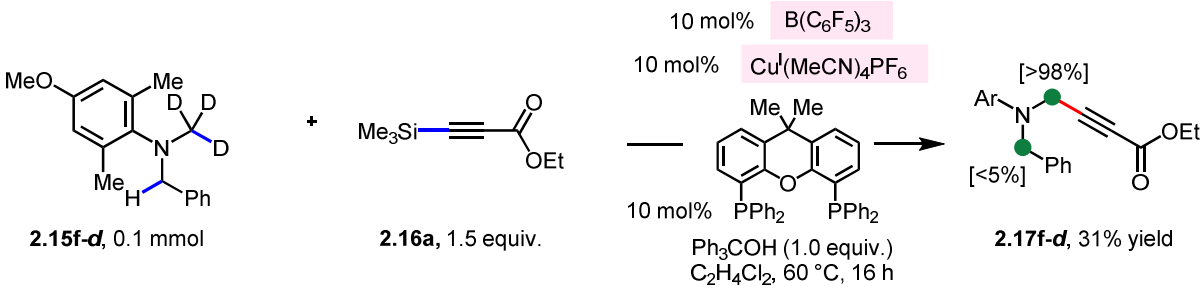


2.15f



Experiments Involving *N*-Benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-*d*$_3$)aniline

We investigated if the H/D exchange reaction may take place under the standard conditions for $B(C_6F_5)_3$ and organocopper co-catalyzed α-amino C–H alkynylation reaction with 0.10 mmol of *N*-benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-*d3*)aniline **2.15f-*d***, 0.15 mmol of 3-(trimethylsilyl)propiolate **2.16a** and 0.10 mmol of Ph_3COH.



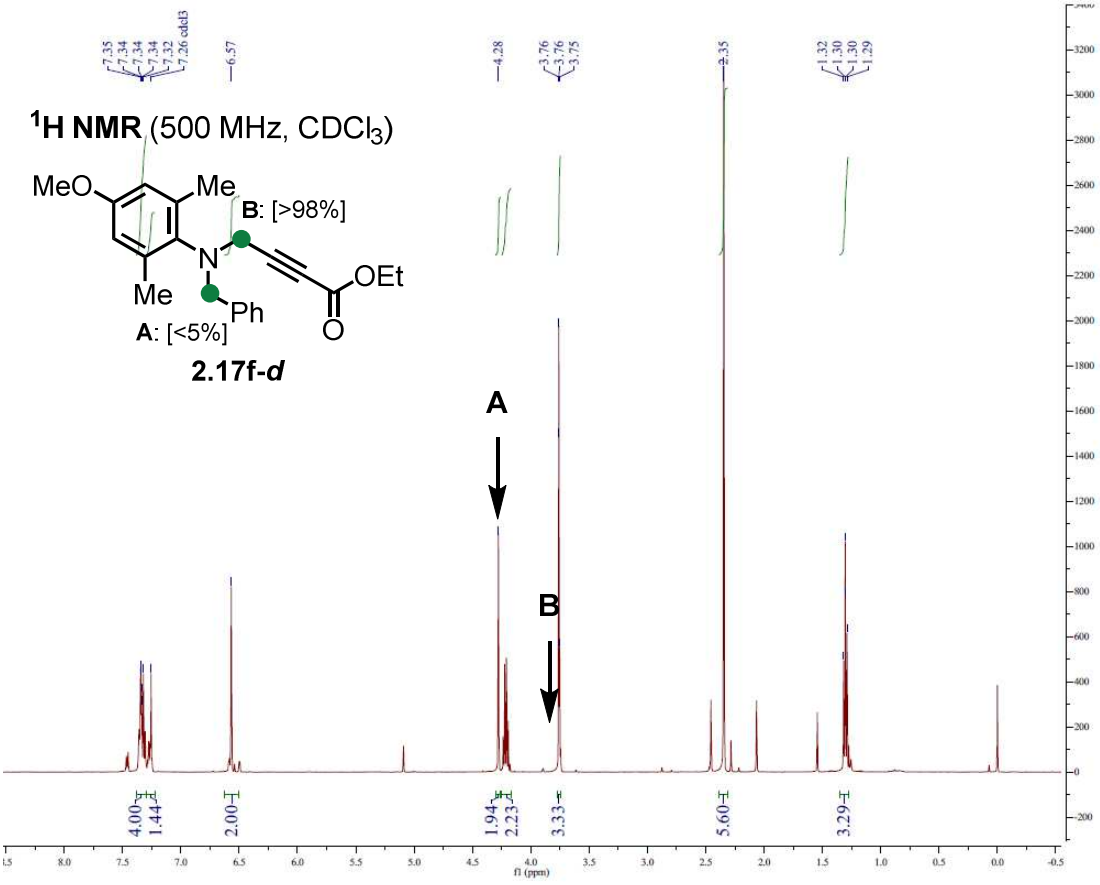
2.15f-*d*, 0.1 mmol **2.16a,** 1.5 equiv. **2.17f-*d***, 31% yield

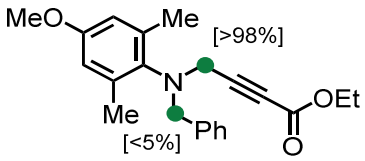
The ^{1}H NMR and HRMS spectrum of the isolated and purified product **2.17f-*d*** showed that there was 19% deuterium incorporation at the benzylic position of **2.17f-*d*.**

Experimental Procedure for the α-Alkynylation of *N*-Benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-*d*$_3$)aniline

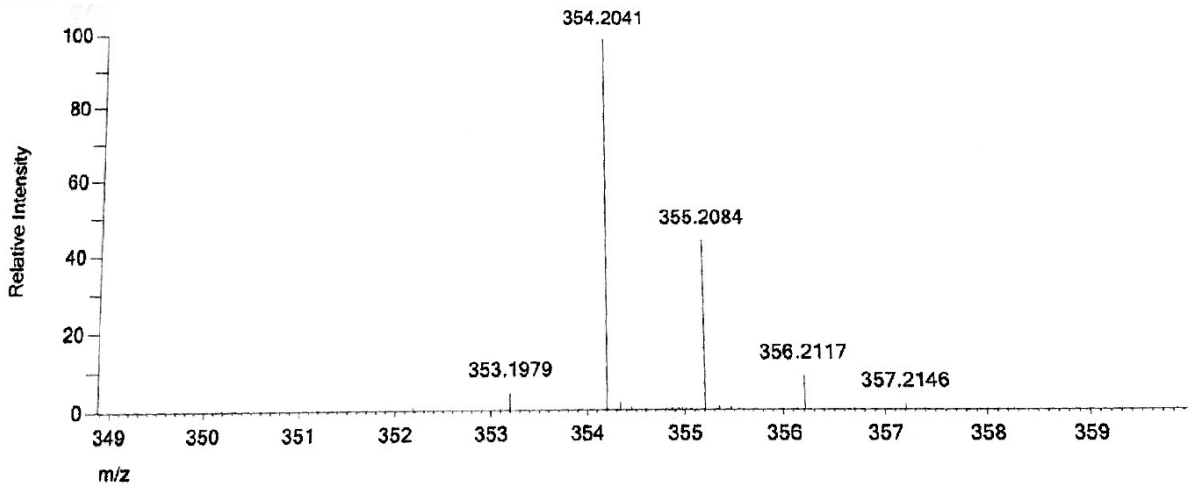
An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.01 mmol), Xantphos (0.01 mmol), and $C_2H_4Cl_2$ (0.2 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.16a** (0.15 mmol), triphenylmethanol (0.1 mmol), amine **2.15f-*d*** (0.1 mmol), $B(C_6F_5)_3$ (0.01 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.2 mL) were added to the vessel. The mixture was allowed to stir at 60 °C for 16 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. The propargylamine product was purified and isolated by silica gel chromatography (Et_2O:hexanes = 1:9), **2.17f-*d*** was obtained as a colorless liquid (12.7 mg, 36%). Deuterium incorporation values were determined based on analysis of the ^1H NMR and HRMS spectra of the purified product.

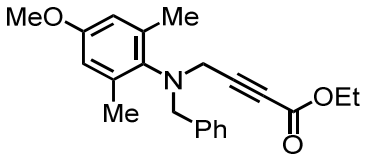
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 6.57 (s, 2H), 4.28 (s, 2H), 4.22 (qd, *J* = 7.1, 0.9 Hz, 2H), 3.76 (s, 3H), 2.35 (s, 6H), 1.30 (dd, *J* = 7.8, 6.9 Hz, 3H).



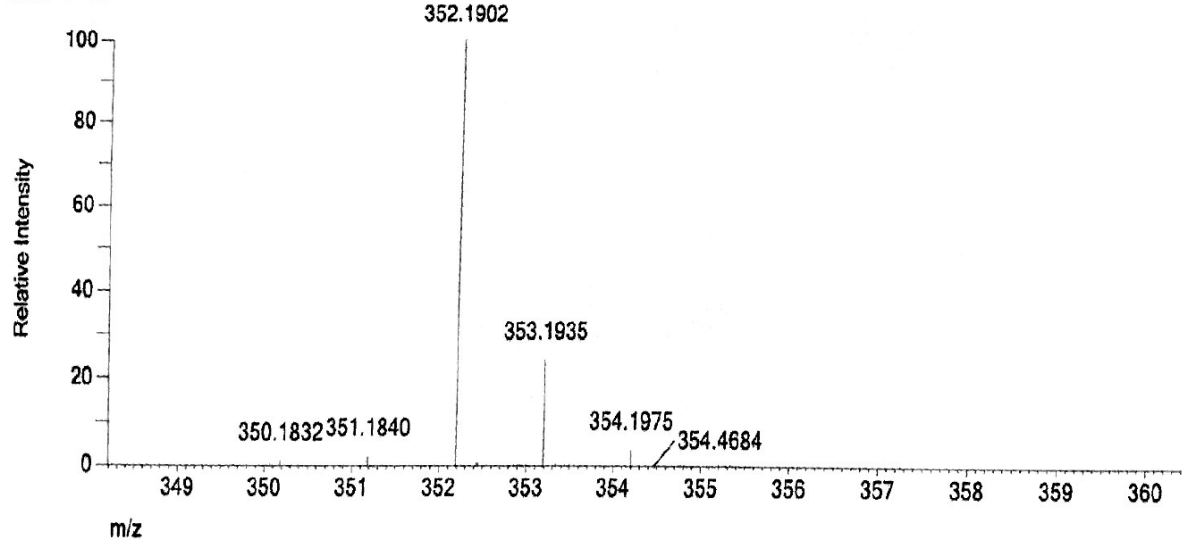

MeO
Me
[>98%]
N
OEt
Me
Ph
[<5%]
O

2.17f-*d*

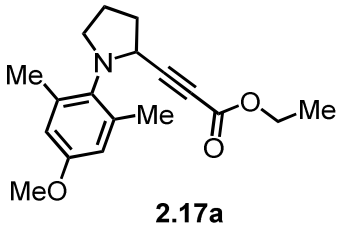

354.2041
355.2084
353.1979
356.2117
357.2146
Relative Intensity
m/z


MeO
Me
N
OEt
Me
Ph
O

2.15f


352.1902
353.1935
350.1832
351.1840
354.1975
354.4684
Relative Intensity
m/z

A6. Analytical Data

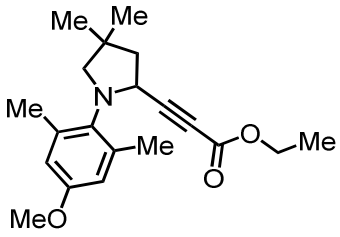


2.17a

Ethyl 3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propiolate (2.17a)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **2.15a** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure A**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17a** was obtained as a colorless liquid (54 mg, 0.18 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.27 (ddd, *J* = 7.8, 3.5, 1.3 Hz, 1H), 4.17 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.75 (s, 3H), 3.43 – 3.31 (m, 1H), 3.09 (q, *J* = 6.9 Hz, 1H), 2.47 – 2.22 (m, 6H), 2.22 – 2.10 (m, 3H), 2.09 – 1.94 (m, 1H), 1.27 (td, *J* = 7.2, 1.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.2, 153.3, 136.6, 113.2, 91.5, 73.9, 63.3, 55.9, 52.3, 51.0, 35.8, 26.7, 18.4, 15.1; **IR** (neat) ν 2967, 2837, 2224, 1707, 1599, 1476, 1366,1244, 1153, 1067, cm^{-1}; **HRMS** (DART) Calcd for $C_{18}H_{24}NO_3$ (MH^+): 302.1751; found: 302.1755.

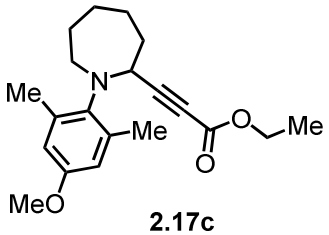


2.17b

Ethyl 3-(1-(4-methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidin-2-yl)propiolate (2.17b)

1-(4-Methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidine **2.15b** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure A**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17b** was obtained as a colorless liquid (51 mg, 0.15 mmol, 77% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 2H), 4.41 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.07 (d, *J* = 7.9 Hz, 1H), 2.95 (d, *J* = 7.8 Hz, 1H), 2.37 (s, 5H), 2.19 (dd, *J* = 12.5, 9.0 Hz, 2H), 1.98 (dd, *J* = 12.5, 3.9 Hz, 1H), 1.37 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 1.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.2, 153.8, 135.4, 113.7, 91.0, 74.3, 64.5, 61.6, 55.2, 51.9, 47.0, 39.1, 27.8, 27.2, 14.0; **IR** (neat) ν 2954, 2864, 2228, 1707, 1601, 1465, 1243, 1094, 1023, 751 cm^{-1}; **HRMS** (DART) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2063; found: 330.2069.

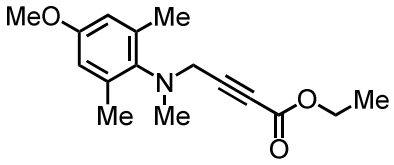


2.17c

Ethyl 3-(1-(4-methoxy-2,6-dimethylphenyl)azepan-2-yl)propiolate (2.17c)

1-(4-Methoxy-2,6-dimethylphenyl)azepane **2.15c** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure A**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17c** was obtained as a colorless liquid (51 mg, 0.15 mmol, 77% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (d, *J* = 13.4 Hz, 2H), 4.18 (d, *J* = 7.1 Hz, 2H), 4.06 (d, *J* = 2.7 Hz, 1H), 3.75 (s, 3H), 3.32 (d, *J* = 9.1 Hz, 1H), 3.08 (d, *J* = 11.1 Hz, 1H), 2.42 (s, 3H), 2.29 (s, 3H), 2.19 (d, *J* = 1.5 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.85 – 1.79 (m, 1H), 1.79 – 1.70 (m, 2H), 1.57 (s, 2H), 1.28 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.4, 153.8, 140.9, 139.7, 137.9, 114.1, 113.6, 90.3, 75.6, 59.4, 55.6, 53.0, 51.3, 34.8, 31.4, 28.9, 25.2, 20.1, 19.6, 14.0; **IR** (neat) ν 2926, 2845, 2221, 1707, 1598, 1474, 1309, 1240, 1065, 853 cm^{-1}; **HRMS** (DART) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2063; found: 330.2061.

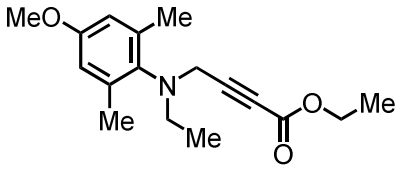


2.17d

Ethyl 4-((4-methoxy-2,6-dimethylphenyl)(methyl)amino)but-2-ynoate (2.17d)

4-Methoxy-*N,N*,2,6-tetramethylaniline **2.15d** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure A**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17d** was obtained as a colorless liquid (50 mg, 0.18 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, 2H), 4.23 (q, *J* = 7.1, 1.5 Hz, 2H), 3.89 (s, 2H), 3.74 (s, 3H), 2.88 (s, 3H), 2.29 (s, 6H), 1.31 (t, *J* = 7.1, 1.5 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.3, 153.6, 140.9, 138.7, 112.8, 86.1, 75.6, 61.8, 55.2, 44.8, 40.1, 19.4, 13.9; **IR** (neat) ν 2933, 2228, 1707, 1598, 1480, 1309, 1244, 1155, 1060, 855 cm^{-1}; **HRMS** (DART) Calcd for $C_{16}H_{22}NO_3$ (MH^+): 276.1594; found: 276.1609.

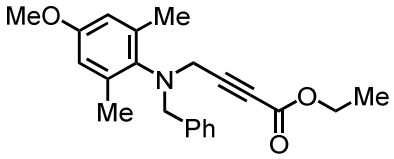


2.17e

Ethyl 4-(ethyl(4-methoxy-2,6-dimethylphenyl)amino)but-2-ynoate (2.17e)

N-Ethyl-4-methoxy-*N*,2,6-trimethylaniline **2.15e** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure A**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17e** was obtained as a colorless liquid (24 mg, 0.84 mmol, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 2H), 3.76 (s, 3H), 3.21 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 6H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.8, 153.7, 139.5, 139.3, 113.6, 86.7, 75.5, 61.8, 55.2, 47.2, 42.9, 19.6, 14.3, 14.0; **IR** (neat) ν 2933, 2230, 1707, 1598, 1490, 1309, 1254, 1120, 1060, 840 cm^{-1}; **HRMS** (DART) Calcd for $C_{17}H_{24}NO_3$ (MH^+): 290.1751; found: 290.1755.

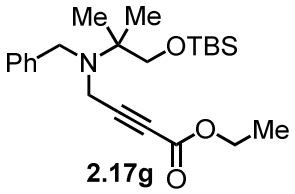


2.17f

Ethyl 4-(benzyl(4-methoxy-2,6-dimethylphenyl)amino)but-2-ynoate (2.17f)

N-Benzyl-4-methoxy-*N*,2,6-trimethylaniline **2.15f** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure A**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17f** was obtained as a colorless liquid (51 mg, 0.14 mmol, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 6.57 (s, 2H), 4.28 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 3.76 (s, 3H), 2.34 (s, 6H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.8, 153.5, 140.6, 139.0, 138.5, 128.9, 128.4, 127.2, 113.4, 85.4, 75.3, 61.8, 58.5, 55.2, 41.5, 19.9, 13.2; **IR** (neat) ν 2927, 2841, 2230, 1708, 1598, 1479, 1312, 1245, 1065, 855 cm^{-1}; **HRMS** (DART) Calcd for $C_{22}H_{26}NO_3$ (MH^+): 352.1907; found: 352.1895.

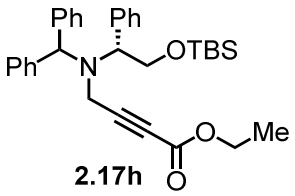


2.17g

Ethyl 4-(benzyl(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)amino)but-2-ynoate (2.17g)

N-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethylpropan-2-amine **2.15g** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17g** was obtained as a colorless liquid (61 mg, 0.15 mmol, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dt, *J* = 6.6, 1.1 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 2H), 3.60 (s, 2H), 3.51 (s, 2H), 1.31 (t, *J* = 7.1, 0.8 Hz, 3H), 1.23 (s, 6H), 0.91 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 140.3, 128.4, 128.2, 126.9, 87.6, 76.7, 69.7, 61.8, 58.6, 51.4, 36.7, 25.9, 22.9, 18.2, 14.1, -5.6; **IR** (neat) ν 2949, 2855, 2221, 1708, 1463, 1364, 1237, 1092, 840, 774 cm^{-1}; **HRMS** (DART) Calcd for $C_{23}H_{38}NO_3Si$ (MH^+): 404.2615; found: 404.2610.

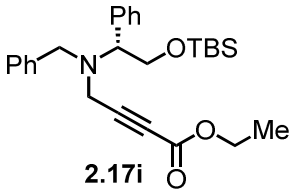


2.17h

Ethyl (*R*)-4-(benzhydryl(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)amino)but-2-ynoate (2.17h)

(*R*)-*N*-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine **2.15h** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17h** was obtained as a colorless liquid (102 mg, 0.19 mmol, 97% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 4H), 7.42 (dt, *J* = 8.1, 1.1 Hz, 2H), 7.35 – 7.14 (m, 9H), 5.23 (s, 1H), 4.24 – 4.06 (m, 5H), 3.55 (s, 2H), 1.31 (t, *J* = 7.1, 3H), 0.82 (s, 9H), -0.04 (d, *J* = 20.0, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.4, 142.0, 141.9, 139.8, 128.7, 128.6, 128.49, 128.47, 128.39, 128.1, 127.24, 127.15, 86.5, 76.6, 69.2, 63.1, 62.9, 61.6, 36.6, 25.9, 18.2, 14.1, -5.55, -5.57; **IR** (neat) ν 3026, 2930, 2855, 2224, 1708, 1456, 1362, 1243,1095, 837 cm^{-1}; **HRMS** (DART) Calcd for $C_{33}H_{42}NO_3Si$ (MH^+): 528.2928; found: 528.2922; $[\alpha]^{25}_D$ = −16.2° (*c* 0.8, CH_2Cl_2).

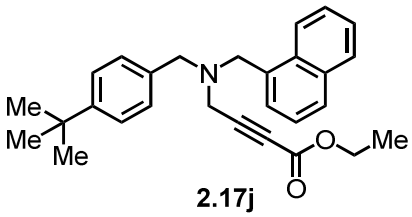


2.17i

Ethyl (*R*)-4-(benzyl(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)amino)but-2-ynoate (2.17i)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine **2.15i** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17i** was obtained as a colorless liquid (78 mg, 1.7 mmol, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.37 – 7.20 (m, 8H), 4.26 (q, *J* = 7.1, 2.1 Hz, 2H), 3.94 (dd, *J* = 7.3, 4.9 Hz, 2H), 3.82 (d, *J* = 2.0 Hz, 1H), 3.74 (d, *J* = 2.1 Hz, 1H), 3.70 – 3.60 (m, 2H), 3.37 – 3.28 (m, 1H), 1.34 (t, *J* = 2.0 Hz, 3H), 0.83 (s, 9H), -0.09 (d, *J* = 5.7, 2.1 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 141.1, 138.8, 128.9, 128.5, 128.30, 128.26, 127.4, 127.1, 84.5, 77.84, 67.6, 65.9, 61.9, 55.1, 39.1, 25.8, 18.2, 14.1, -0.01, -5.67, -5.69; **IR** (neat) ν 2923, 2853, 2222, 1709, 1458, 1365, 1239, 1095, 870, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{27}H_{38}NO_3Si$ (MH^+): 452.2615; found: 452.2612; $[\alpha]^{25}_D$ = 36.7° (*c* 0.2, CH_2Cl_2).

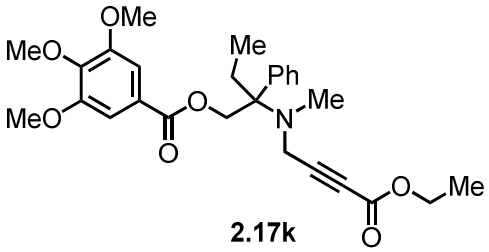


2.17j

Ethyl 4-((4-(*tert*-butyl)phenyl)(naphthalen-1-ylmethyl)amino)but-2-ynoate (2.17j)

4-(*tert*-Butyl)-*N*-methyl-*N*-(naphthalen-1-ylmethyl)aniline **2.15j** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17j**was obtained as a colorless liquid (63 mg, 0.15 mmol, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.4 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.55 – 7.45 (m, 3H), 7.40 (dd, *J* = 8.6, 6.6 Hz, 1H), 7.36 – 7.27 (m, 4H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.15 (s, 2H), 3.78 (s, 2H), 3.35 (s, 2H), 1.37 (t, *J* = 7.1 Hz, 4H), 1.30 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 150.3, 135.1, 133.9, 133.7, 132.5, 128.9, 128.4, 128.3, 127.8, 125.8, 125.7, 125.3, 125.2, 124.9, 83.6, 78.3, 62.0, 57.7, 56.2, 40.9, 34.5, 31.4, 14.1; **IR** (neat) ν 2957, 2825, 2220, 1707, 1597, 1509, 1239, 1107, 1050, 791 cm^{-1}; **HRMS** (DART) Calcd for $C_{28}H_{32}NO_2$ (MH^+): 414.2428; found: 414.2429.

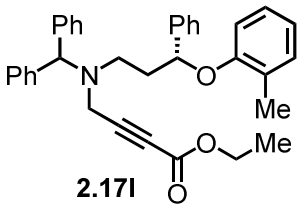


2.17k

2-((4-Ethoxy-4-oxobut-2-yn-1-yl)(methyl)amino)-2-phenylbutyl 3,4,5-trimethoxybenzoate (2.17k)

2-(Dimethylamino)-2-phenylbutyl 3,4,5-trimethoxybenzoate **2.15k** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:2), **2.17k** was obtained as a colorless liquid (69 mg, 0.14 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.40 – 7.33 (m, 2H), 7.29 – 7.22 (m, 1H), 7.18 (d, *J* = 1.4 Hz, 2H), 4.89 (dd, *J* = 12.1, 1.3 Hz, 1H), 4.74 (dd, *J* = 12.0, 1.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 6H), 3.63 (d, *J* = 17.6 Hz, 1H), 3.48 (d, *J* = 17.6 Hz, 1H), 2.63 (s, 3H), 1.95 – 1.78 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 2H), 0.69 (t, *J* = 7.3 Hz, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.8, 153.5, 152.9, 142.3, 141.7, 128.2, 127.3, 126.9, 124.8, 106.8, 86.2, 75.5, 65.7, 64.8, 61.8, 60.8, 56.1, 42.1, 35.8, 30.1, 13.9, 8.5; **IR** (neat) ν 2939, 2231, 1709, 1586, 1498, 1331, 1239, 1123, 1006, 756 cm^{-1}; **HRMS** (DART) Calcd for $C_{27}H_{34}NO_7$ (MH^+): 484.2330; found: 484.2322.

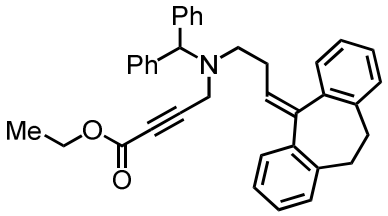


2.17l

Ethyl (*R*)-4-(benzhydryl(3-phenyl-3-(*o*-tolyloxy)propyl)amino)but-2-ynoate (2.17l)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine **2.15l** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17l** was obtained as a colorless liquid (58 mg, .11 mmol, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.35 – 7.13 (m, 10H), 7.07 (qt, *J* = 5.7, 1.3 Hz, 4H), 6.94 (td, *J* = 7.8, 1.8 Hz, 1H), 6.75 (td, *J* = 7.4, 1.1 Hz, 1H), 6.57 – 6.52 (m, 1H), 5.19 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.66 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.50 (m, 2H), 2.86 – 2.77 (m, 2H), 2.13 (dddd, *J* = 19.3, 9.2, 7.5, 5.6 Hz, 1H), 2.02 (s, 3H), 2.02 – 1.95 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.9, 153.4, 142.33, 142.26, 142.24, 130.5, 128.64, 128.57, 128.54, 127.91, 127.88, 127.72, 127.4, 127.20, 127.15, 127.1, 126.4, 125.8, 120.0, 112.3, 83.5, 77.9, 76.9, 72.6, 61.9, 47.3, 39.5, 37.2, 16.3, 14.1; **IR** (neat) ν 3025, 2933, 2831, 2220, 1707, 1594, 1490, 1240, 1049, 749 cm^{-1}; **HRMS** (DART) Calcd for $C_{35}H_{36}NO_3$ (MH^+): 518.2689; found: 518.2691.

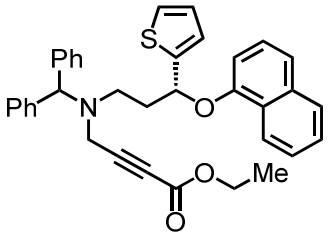


2.17m

Ethyl 4-(benzhydryl(3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)propyl)amino)but-2-ynoate (2.17m)

N-Benzhydryl-3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine **2.15m** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:4), **2.17m** was obtained as a colorless liquid (79 mg, .15 mmol, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 4H), 7.30 – 7.22 (m, 5H), 7.22 – 7.12 (m, 7H), 7.10 – 7.02 (m, 2H), 5.84 (t, *J* = 7.5, 1.5 Hz, 1H), 4.67 (s, 1H), 4.27 (q, *J* = 7.1, 1.5 Hz, 2H), 3.47 – 3.19 (m, 4H), 2.97 (s, 1H), 2.67 (t, *J* = 7.2 Hz, 3H), 2.30 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.1, 1.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.4, 143.8, 142.4, 141.2, 139.9, 139.3, 137.0, 129.9, 128.9, 128.6, 128.51, 128.48, 128.2, 128.0, 127.9, 127.4, 127.1, 126.9, 125.9, 125.8, 83.7, 77.8, 72.3, 61.9, 50.3, 39.3, 33.7, 31.9, 27.6, 14.1; **IR** (neat) ν 3020, 2922, 2836, 2224, 1707, 1484, 1448, 1365, 11243, 751 cm^{-1}; **HRMS** (DART) Calcd for $C_{37}H_{36}NO_2$ (MH^+): 526.2740; found: 526.2751.

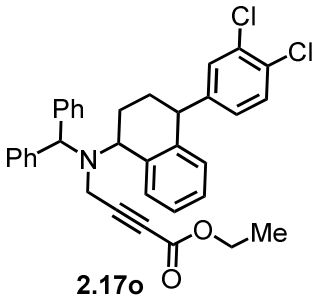


2.17n

Ethyl (*R*)-4-(benzhydryl(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)amino)but-2-ynoate (2.17n)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine **2.15n** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17n** was obtained as a colorless liquid (76 mg, 0.14 mmol, 68% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.40 (dd, *J* = 19.1, 7.8 Hz, 4H), 7.27 (dt, *J* = 25.2, 7.3 Hz, 5H), 7.17 (q, *J* = 5.5 Hz, 2H), 7.01 – 6.91 (m, 4H), 6.89 (t, *J* = 4.4 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.69 (dd, *J* = 8.5, 4.3 Hz, 1H), 4.67 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.59 (d, *J* = 4.6 Hz, 2H), 2.86 (d, *J* = 7.7 Hz, 2H), 2.49 – 2.11 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.4, 153.3, 145.3, 142.3, 141.9, 134.5, 128.7, 128.5, 127.9, 127.7, 127.3, 127.2, 126.9, 126.5, 126.2, 126.1, 125.6, 125.1, 124.6, 124.5, 122.2, 120.5, 106.4, 83.4, 78.1, 73.9, 72.5, 61.9, 53.4, 47.1, 39.7, 37.2, 14.0; **IR** (neat) ν 3055, 2926, 2837, 2220, 1707, 1579, 1453, 1243, 1092, 702 cm^{-1}; **HRMS** (DART) Calcd for $C_{36}H_{34}NO_3S$ (MH^+): 560.2254; found: 560.2239.

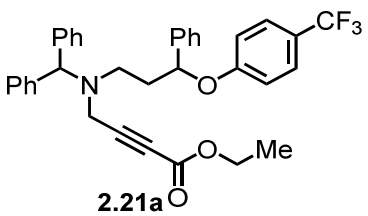


2.17o

Ethyl 4-(benzhydryl(4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)but-2-ynoate (2.17o)

N-Benzhydryl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine **2.15o** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17o** was obtained as a colorless liquid (76 mg, 0.13 mmol, 67% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.1 Hz, 1H), 7.72 – 7.56 (m, 4H), 7.42 – 7.07 (m, 10H), 6.85 (dd, *J* = 69.9, 8.1 Hz, 2H), 5.31 – 5.17 (m, 1H), 4.28 – 4.11 (m, 3H), 4.05 (s, 1H), 3.53 (s, 2H), 2.06 (t, *J* = 12.1 Hz, 1H), 2.00 – 1.75 (m, 3H), 1.27 (t, *J* = 7.1, 3.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.3, 147.2, 142.24, 142.18, 139.1, 138.6, 132.2, 130.7, 130.04, 129.99, 129.87, 128.8, 128.74, 128.70, 128.5, 128.3, 128.2, 128.1, 127.93, 127.91, 127.58, 127.56, 127.45, 127.38, 127.3, 127.2, 127.0, 86.3, 77.5, 69.1, 61.7, 57.8, 43.4, 36.2, 30.3, 17.5, 13.9; **IR** (neat) ν 3023, 2931, 2860, 2221, 1706, 1592, 1459, 1241, 1117, 1052 cm^{-1}; **HRMS** (DART) Calcd for $C_{35}H_{32}NO_2Cl_2$ (MH^+): 568.1805; found: 568.1799.

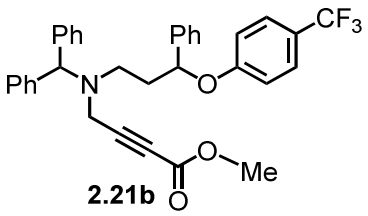


2.21a

Ethyl 4-(benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)but-2-ynoate (2.21a)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.21a** was obtained as a colorless liquid (94 mg, 0.16 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 4H), 7.35 – 7.22 (m, 10H), 7.18 (tt, J = 7.4, 1.5 Hz, 1H), 7.14 – 7.04 (m, 3H), 6.83 – 6.77 (m, 2H), 5.28 – 5.19 (m, 1H), 4.67 (s, 1H), 4.26 (q, J = 7.2, 2.4 Hz, 2H), 3.64 – 3.50 (m, 2H), 2.88 – 2.78 (m, 1H), 2.78 – 2.68 (m, 1H), 2.19 – 2.08 (m, 1H), 2.04 – 1.94 (m, 1H), 1.34 (t, J = 7.2, 2.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.5, 153.4, 142.13, 142.08, 141.2, 128.8, 128.6, 128.5, 127.9, 127.8, 127.3, 127.1, 126.7 (d, J_{CF} = 3.3 Hz), 125.6, 124.4 (d, J_{CF} = 271.1 Hz), 122.7 (q, J_{CF} = 32.7 Hz), 115.7, 83.3, 78.0, 77.7, 72.5, 61.9, 46.9, 39.5, 36.8, 14.0; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.53; **IR** (neat) ν 3028, 2930, 2834, 2221, 1708, 1612, 1513, 1451, 1324, 1246, 1114 cm^{-1}; **HRMS** (DART) Calcd for $C_{35}H_{33}NO_3F_3(MH^+)$: 572.2407; found: 572.2402.

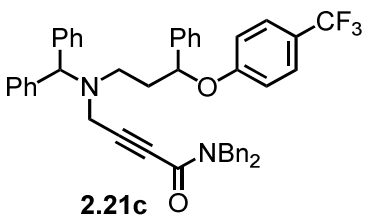


2.21b

Methyl 4-(benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)but-2-ynoate (2.21b)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was added to methyl 3-(trimethylsilyl)propiolate **2.16b** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.21b** was obtained as a colorless liquid (76 mg, 0.14 mmol, 68% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 4H), 7.36 – 7.21 (m, 9H), 7.18 (tt, *J* = 7.1, 1.5 Hz, 1H), 7.12 – 7.05 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.23 (dd, *J* = 9.1, 3.6 Hz, 1H), 4.66 (s, 1H), 3.80 (s, 3H), 3.57 (d, *J* = 10.6 Hz, 2H), 2.88 – 2.67 (m, 2H), 2.20 – 1.95 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.5, 153.8, 142.11, 142.05, 141.2, 128.8, 128.7, 128.6, 127.9, 127.79, 127.75, 127.3, 127.2, 126.7 (d, J_{CF} = 3.8 Hz), 125.6, 124.4 (d, J_{CF} = 271.3 Hz), 122.7 (q, J_{CF} = 32.5 Hz), 115.7, 83.7, 77.7, 72.5, 53.4, 52.7, 46.9, 39.5, 36.8; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.50; **IR** (neat) ν 3028, 2946, 2832, 2226, 1713, 1513, 1445, 1324, 1249, 1114 cm^{-1}; **HRMS** (DART) Calcd for $C_{34}H_{31}NO_3F_3$ (MH^+): 558.2251; found: 558.2246.

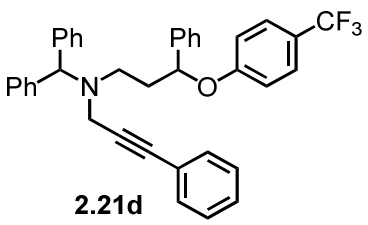


2.21c

4-(Benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)-*N*,*N*-dibenzylbut-2-ynamide (2.21c)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was added to *N,N*-dibenzyl-3-(trimethylsilyl)propiolamide **2.16c** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:4), **2.21c** was obtained as a colorless liquid (116 mg, 0.16 mmol, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 4H), 7.35 (t, *J* = 7.5 Hz, 3H), 7.31 (d, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 4H), 7.23 (t, *J* = 9.3 Hz, 7H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.15 – 7.10 (m, 3H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.16 (dd, *J* = 9.0, 3.7 Hz, 1H), 4.78 – 4.65 (m, 2H), 4.55 (q, *J* = 14.8 Hz, 2H), 4.46 (s, 1H), 3.61 (q, *J* = 18.3 Hz, 2H), 2.75 – 2.57 (m, 2H), 2.13 – 1.90 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.5, 154.7, 142.13, 142.06, 141.1, 136.2, 135.9, 129.0, 128.8, 128.7, 128.6, 128.5, 128.0, 127.8, 127.7, 127.6, 127.24, 127.20, 127.1, 126.6 (d, J_{CF} = 3.0 Hz), 125.6, 124.4 (d, J_{CF} = 271.1 Hz), 122.7 (q, J_{CF} = 32.7 Hz), 115.7, 87.7, 78.9, 77.7, 72.6, 51.3, 46.9, 46.5, 39.6, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.48; **IR** (neat) ν 3028, 2925, 2830, 2221, 1628, 1324, 1245, 1162, 1113, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{47}H_{42}N_2O_2F_3$ (MH^+): 723.3193; found: 723.3167.

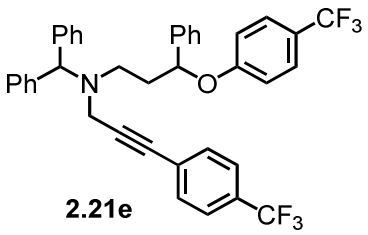


2.21d

***N*-Benzhydryl-3-phenyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-yn-1-amine (2.21d)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was added to trimethyl(phenylethynyl)silane **2.16d** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:49), **2.21d** was obtained as a colorless liquid (86 mg, 0.15 mmol, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.38 (m, 6H), 7.37 – 7.14 (m, 13H), 7.08 (d, J = 6.6 Hz, 3H), 6.81 (d, J = 8.4 Hz, 2H), 5.30 (dd, J = 9.0, 3.8 Hz, 1H), 4.74 (s, 1H), 3.72 – 3.56 (m, 2H), 2.91 – 2.70 (m, 2H), 2.24 – 2.00 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.6, 142.8, 142.7, 141.4, 131.7, 128.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.1, 126.9, 126.6 (d, J_{CF} = 3.1 Hz), 125.7, 124.5 (d, J_{CF} = 271.5 Hz), 123.3, 122.6 (q, J_{CF} = 32.6 Hz), 115.7, 85.9, 84.2, 77.9, 72.6, 46.7, 39.9, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.49; **IR** (neat) ν 3060, 2927, 2829, 2096, 1513, 1491, 1324, 1249, 1162, 1114, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{38}H_{33}NOF_3$ (MH^+): 576.2509; found: 576.2504.

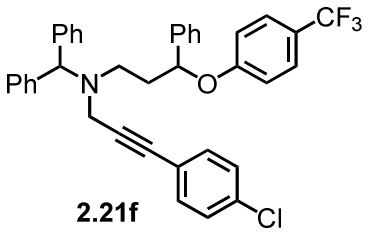


2.21e

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-amine (2.21e)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was added to trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane **2.16e** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.21e** was obtained as a colorless liquid (106 mg, 0.16 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.4, 4.1 Hz, 2H), 7.48 (dd, J = 8.1, 4.1 Hz, 2H), 7.43 (ddd, J = 13.0, 8.0, 4.1 Hz, 4H), 7.35 (tt, J = 4.9, 2.2 Hz, 2H), 7.29 (d, J = 4.8 Hz, 4H), 7.28 – 7.22 (m, 3H), 7.19 (td, J = 7.1, 4.4 Hz, 1H), 7.10 (p, J = 5.2 Hz, 3H), 6.81 (dd, J = 9.0, 4.0 Hz, 2H), 5.30 (dt, J = 8.5, 4.0 Hz, 1H), 4.73 (d, J = 4.2 Hz, 1H), 3.73 – 3.60 (m, 2H), 2.97 – 2.70 (m, 2H), 2.25 – 2.00 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.6, 142.6, 142.5, 141.3, 132.4, 132.2 (d, J_{CF} = 293.4 Hz), 129.8 (q, J_{CF} = 32.6 Hz), 128.8, 128.6, 128.5, 128.0, 127.9, 127.8, 127.2, 127.1, 126.7 (d, J_{CF} = 2.9 Hz), 125.7, 125.2 (d, J_{CF} = 2.8 Hz), 124.2 (d, J_{CF} = 211.0 Hz), 122.7 (q, J_{CF} = 32.5 Hz), 115.7, 87.1, 84.6, 77.9, 72.6, 46.8, 40.0, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.45, -62.75; **IR** (neat) ν 3027, 2931, 2829, 1612, 1513, 1450, 1322, 1249, 1116, 701 cm^{-1}; **HRMS** (DART) Calcd for $C_{39}H_{32}NOF_6$ (MH^+): 644.2383; found: 644.2365.

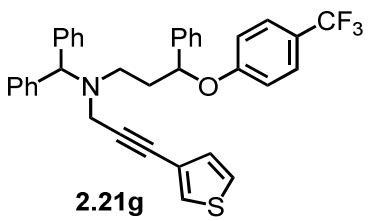


2.21f

***N*-Benzhydryl-3-(4-chlorophenyl)-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) prop-2-yn-1-amine (2.21f)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was added to ((4-chlorophenyl)ethynyl)trimethylsilane **2.16f** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.21f** was obtained as a colorless liquid (98 mg, 0.16 mmol, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 4H), 7.29 (dddd, J = 22.3, 20.6, 9.1, 7.4 Hz, 13H), 7.18 (ddd, J = 7.4, 6.1, 1.4 Hz, 1H), 7.13 – 7.03 (m, 3H), 6.81 (d, J = 8.4 Hz, 2H), 5.29 (dd, J = 9.0, 3.8 Hz, 1H), 4.71 (s, 1H), 3.63 (q, J = 17.7 Hz, 2H), 2.93 – 2.65 (m, 2H), 2.25 – 1.97 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.6, 142.7, 142.5, 141.4, 134.0, 132.9, 128.7, 128.6, 128.53, 128.45, 128.0, 127.9, 127.7, 127.1, 127.0, 126.7 (d, J_{CF} = 2.6 Hz), 125.7, 124.4 (d, J_{CF} = 271.1 Hz), 122.6 (q, J_{CF} = 32.8 Hz), 121.8, 115.7, 85.3, 84.7, 77.9, 72.6, 46.7, 40.0, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.50; **IR** (neat) ν 3055, 2928, 2832, 2223, 1707, 1608, 1488, 1245, 1113, 701 cm^{-1}; **HRMS** (DART) Calcd for $C_{38}H_{32}NOF_3Cl$ (MH^+): 610.2119; found: 610.2125.

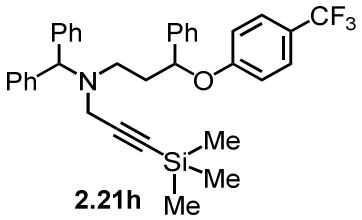


2.21g

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(thiophen-3-yl)prop-2-yn-1-amine (2.21g)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was added to trimethyl(thiophen-3-ylethynyl)silane **2.16g** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:49), **2.21g** was obtained as a colorless liquid (86 mg, 0.15 mmol, 74% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 8.9, 5.0 Hz, 4H), 7.38 (d, *J* = 2.9 Hz, 1H), 7.34 (dd, *J* = 6.2, 3.4 Hz, 2H), 7.29 (t, *J* = 3.4 Hz, 4H), 7.25 (ddq, *J* = 9.9, 7.1, 4.3, 3.5 Hz, 4H), 7.18 (dt, *J* = 7.8, 3.8 Hz, 1H), 7.08 (dt, *J* = 8.8, 4.2 Hz, 4H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 2H), 5.30 (dd, *J* = 9.1, 3.9 Hz, 1H), 4.72 (s, 1H), 3.62 (q, *J* = 17.8 Hz, 2H), 2.80 (ddt, *J* = 50.2, 12.0, 6.5 Hz, 2H), 2.12 (dt, *J* = 55.1, 12.1 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.6, 142.7, 142.6, 141.4, 130.0, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.1, 126.9, 126.7 (d, J_{CF} = 3.6 Hz), 124.7 (d, J_{CF} = 267.9 Hz), 125.7, 122.6 (d, J_{CF} = 32.9 Hz), 122.3, 115.7, 83.8, 80.8, 77.8, 72.5, 46.6, 39.9, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.41; **IR** (neat) ν 3026, 2929, 2829, 2166, 1514, 1450, 1324,1249, 1114, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{36}H_{31}NOF_3S$ (MH^+): 582.2073; found: 582.2074.

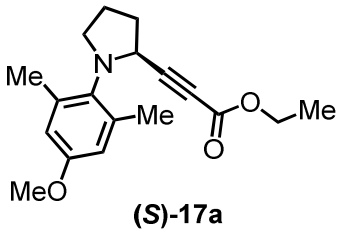


2.21h

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(trimethylsilyl) prop-2-yn-1-amine (2.21h)[21]**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was added to 1,2-bis(trimethylsilyl)ethyne **2.16h** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.21h** was obtained as a colorless liquid (99 mg, 0.17 mmol, 87% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 20.0, 8.2 Hz, 4H), 7.32 – 7.27 (m, 6H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.10 – 7.05 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.25 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.64 (s, 1H), 3.42 (q, *J* = 17.9 Hz, 2H), 2.80 – 2.66 (m, 2H), 2.13 – 1.98 (m, 2H), 0.20 (s, 9H); **^{13}C** NMR;[21] ^{19}F **NMR** (470 MHz, $CDCl_3$) δ -61.50; **IR** (neat) ν 3059, 2951, 2848, 2160, 1612, 1324, 1250, 1116, 840, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{35}H_{37}NOF_3Si(MH^+)$: 572.2591; found: 572.2579.



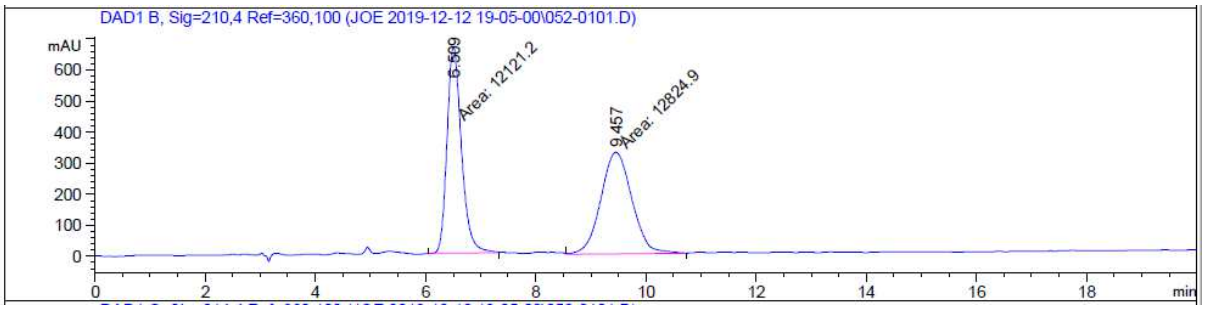
(*S*)-17a

Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propiolate ((*S*)-2.17a)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **2.15a** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure C**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **(*S*)-2.17a** was obtained as a colorless liquid (45 mg, 0.15 mmol, 75% yield). The absolute configuration of **(*S*)-2.17a** was assigned as (*S*) as described in SI Section 4.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.27 (ddd, J = 7.8, 3.5, 1.3 Hz, 1H), 4.17 (qd, J = 7.2, 1.3 Hz, 2H), 3.75 (s, 3H), 3.43 – 3.31 (m, 1H), 3.09 (q, J = 6.9 Hz, 1H), 2.47 – 2.22 (m, 6H), 2.22 – 2.10 (m, 3H), 2.09 – 1.94 (m, 1H), 1.27 (td, J = 7.2, 1.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.2, 153.3, 136.6, 113.2, 91.5, 73.9, 63.3, 55.9, 52.3, 51.0, 35.8, 26.7, 18.4, 15.1; **IR** (neat) ν 2967, 2837, 2224, 1707, 1599, 1476, 1366,1244, 1153, 1067, cm^{-1}; **HRMS** (DART) Calcd for $C_{18}H_{24}NO_3$ (MH^+): 302.1751; found: 302.1755; **Specific Rotation**: $[\alpha]^{25}$ +76.2° (*c* 1.0, CH_2Cl_2); **HPLC** (Chiralcel OJ-H; 95:5 hexanes:isopropanol, 1.0 mL/min; **(*S*)-2.17a:** tr = 6.5 min (major), 9.5 min (minor); 95:5 er.

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   52
Injection Date  : 12/12/2019 7:06:12 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2019-12-12 19-05-00\column4 5%IPA 95% hexane 30min-1.
                  0mL.M (Sequence Method)
Last changed    : 12/12/2019 7:05:05 PM by SYSTEM
Method Info     : Column4 60min-1% iPrOH 99% hexane-1.0mL
```

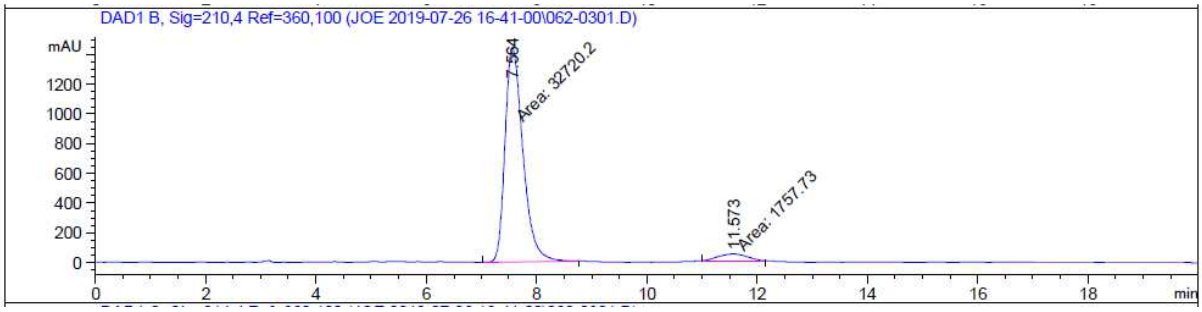


Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.509	MM	0.3045	1.21212e4	663.55304	48.5896
2	9.457	MM	0.6531	1.28249e4	327.28235	51.4104

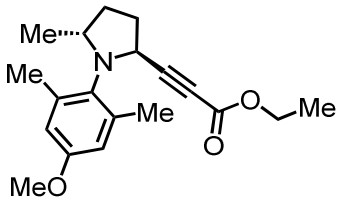
==========

Acq. Operator : SYSTEM Seq. Line : 3
Acq. Instrument : Wasa_LC1 Location : 62
Injection Date : 7/26/2019 5:44:53 PM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\JOE 2019-07-26 16-41-00\column4 5%IPA 95% hexane 30min-1.0mL.M (Sequence Method)
Last changed : 7/26/2019 4:41:04 PM by SYSTEM
Method Info : Column4 60min-1% iPrOH 99% hexane-1.0mL



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.564	MM	0.3774	3.27202e4	1445.16772	94.9019
2	11.573	MM	0.6270	1757.73438	46.72317	5.0981



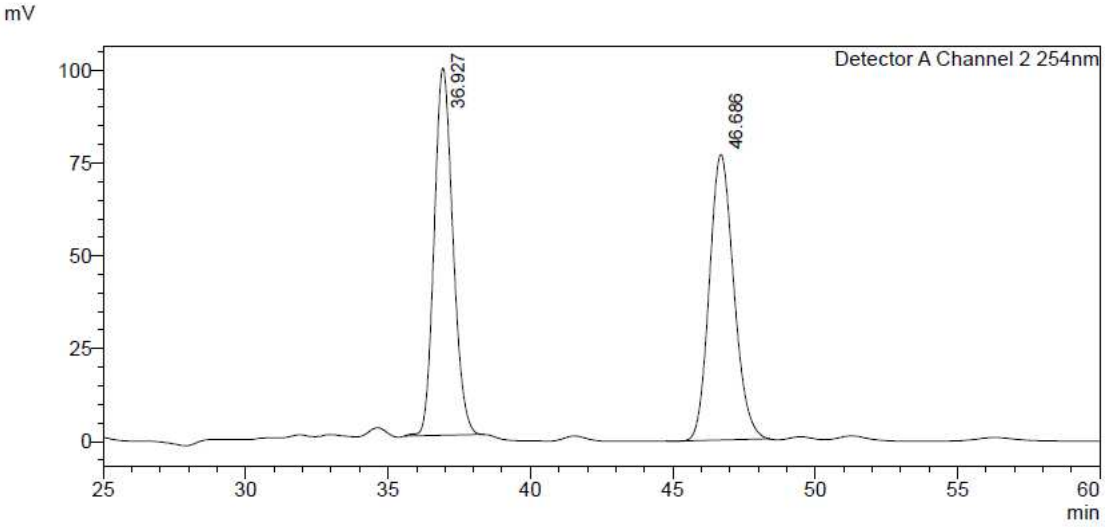
2.17q

Ethyl 3-((2*S*,5*R*)-1-(4-methoxy-2,6-dimethylphenyl)-5-methylpyrrolidin-2-yl)propiolate (2.17q)

1-(4-Methoxy-2,6-dimethylphenyl)-2-methylpyrrolidine ***rac*-2.15q** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure C**. The *trans*:*cis* ratio was determined to be 6.3:1 by ^{1}H NMR analysis of the unpurified reaction mixtures. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17q** was obtained as a yellow oil (42 mg, 0.13 mmol, 66% yield). The relative configuration of **2.17q** was assigned by NOESY analysis as described in SI Section 3.

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (d, *J* = 1.2 Hz, 2H), 4.37 (dd, *J* = 7.7, 4.1 Hz, 1H), 4.15 (qd, *J* = 7.1, 0.8 Hz, 2H), 3.84 (q, *J* = 6.1 Hz, 1H), 3.76 (s, 3H), 2.43 – 2.37 (m, 1H), 2.36 (s, 3H), 2.32 – 2.25 (m, 1H), 2.19 (s, 3H), 2.09 – 2.02 (m, 1H), 1.61 – 1.55 (m, 1H), 1.25 (d, *J* = 0.9 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.8, 153.8, 140.2, 139.7, 133.6, 113.9, 113.2, 91.0, 74.6, 61.7, 55.2, 55.1, 52.2, 33.2, 31.4, 20.3, 19.9, 19.0, 14.0; **IR** (neat) ν 2956, 2222, 1705, 1597, 1471, 1368, 1234, 1152, 1065, 852 cm^{-1}; **HRMS** (DART) Calcd for $C_{19}H_{26}NO_3$ (MH^+): 316.1907; found: 316.1905; **Specific Rotation**: $[\alpha]^{25}$+12.1° (*c* 0.3, CH_2Cl_2); **HPLC** (Chiralpak AD-H; 99.7:0.3 hexanes:isopropanol, 0.3 mL/min; **2.17q:** tr = 36.9 min (minor), 46.7 min (major); 83:17 er.

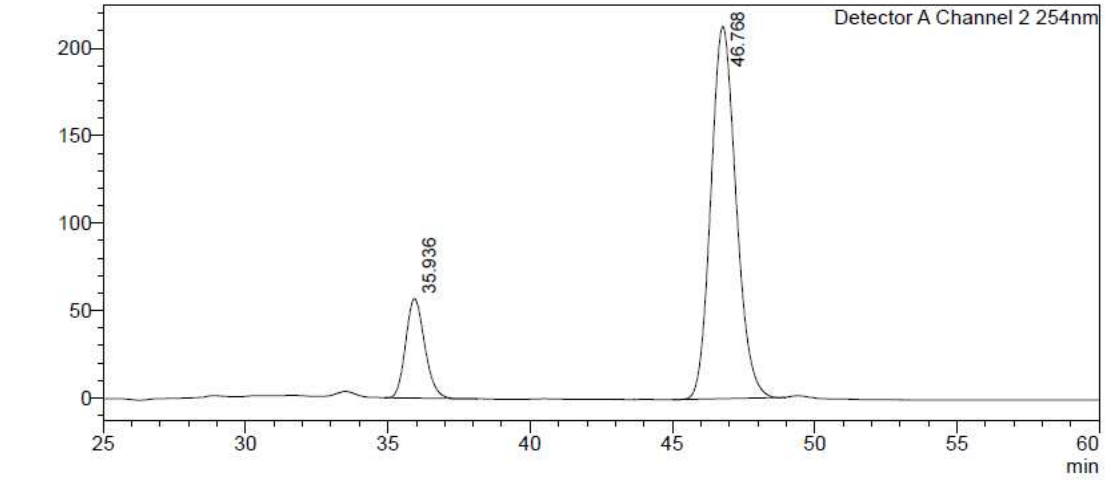
Sample Name	: 8b_rac1_aMe_f6_AD-H_inst4_0.3mL_3		
Sample ID	: 8b_rac1_aMe_f6_AD-H_inst4_0.3mL		
Data Filename	: 8b_rac1_aMe_f6_AD-H_inst4_0.3mL_3.lcd		
Method Filename	: 99.7_0.3_60min_0.3mL.lcm		
Batch Filename	: batch9.lcb		
Vial #	: 1-20	Sample Type	: Unknown
Injection Volume	: 30 uL		
Date Acquired	: 2/13/2020 10:43:40 PM	Acquired by	: System Administrator
Date Processed	: 2/13/2020 11:43:41 PM	Processed by	: System Administrator



Detector A Channel 2 254nm

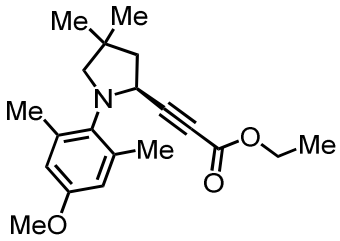
Peak#	Ret. Time	Area	Area%
1	36.927	4524255	49.641
2	46.686	4589671	50.359
Total		9113925	100.000

Sample Name	: 8b_ee2_JZC2264_f9_AD-H_inst4_0.3mL		
Sample ID	: 8b_ee2_JZC2264_f9_AD-H_inst4_0.		
Data Filename	: 8b_ee2_JZC2264_f9_AD-H_inst4_0.3mL.lcd		
Method Filename	: 99.7_0.3_60min_0.3mL.lcm		
Batch Filename	: batch9.lcb		
Vial #	: 1-21	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 2/13/2020 7:34:16 PM	Acquired by	: System Administrator
Date Processed	: 2/13/2020 8:34:17 PM	Processed by	: System Administrator



Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	35.936	2651131	16.814
2	46.768	13116228	83.186
Total		15767359	100.000



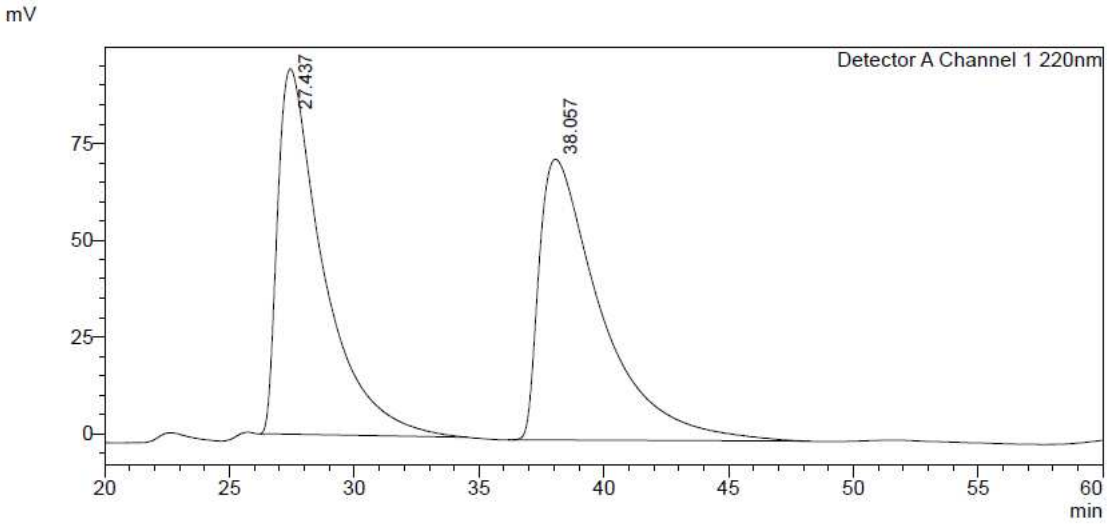
2.17b

Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)-4,4-dimethylpyrrolidin-2-yl)propiolate (2.17b)

1-(4-Methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidine **2.15b** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure C**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17b** was obtained as a yellow oil (45 mg, 0.14 mmol, 69% yield). The absolute configuration of **2.17b** was assigned in analogy to **(*S*)-2.17a** (see: SI Section 4).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 2H), 4.41 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.07 (d, *J* = 7.9 Hz, 1H), 2.95 (d, *J* = 7.8 Hz, 1H), 2.37 (s, 5H), 2.19 (dd, *J* = 12.5, 9.0 Hz, 2H), 1.98 (dd, *J* = 12.5, 3.9 Hz, 1H), 1.37 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 1.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.2, 153.8, 135.4, 113.7, 91.0, 74.3, 64.5, 61.6, 55.2, 51.9, 47.0, 39.1, 27.8, 27.2, 14.0; **IR** (neat) ν 2954, 2864, 2228, 1707, 1601, 1465, 1243, 1094, 1023, 751 cm^{-1}; **HRMS** (DART) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2063; found: 330.2069; **Specific Rotation**: $[\alpha]^{25}$ +20.5° (*c* 0.3, CH_2Cl_2); **HPLC** (Chiralpak AY-3; 99.9:0.1 hexanes:isopropanol, 0.3 mL/min; **2.17b:** tr = 27.4 min (major), 38.1 min (minor); 93:7 er.

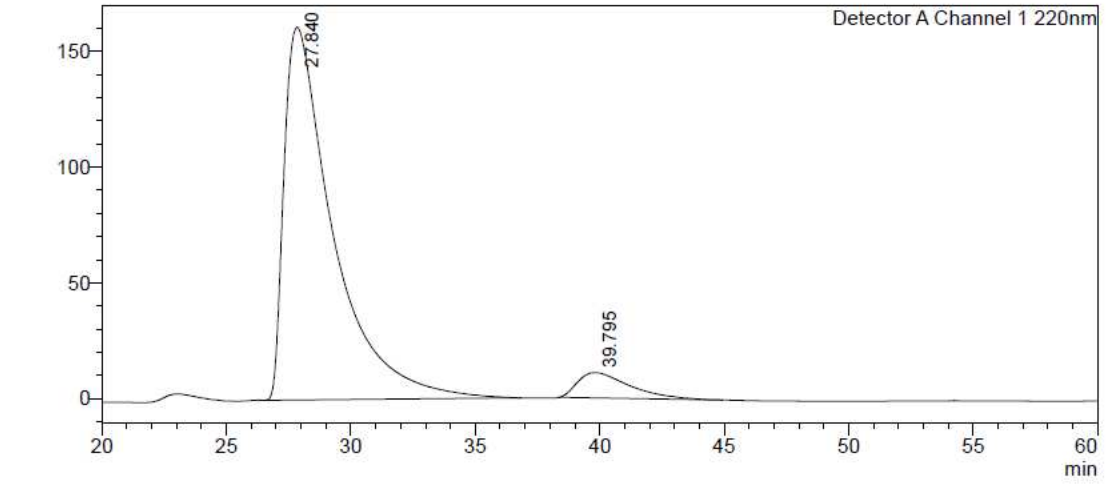
Sample Name	: 8c_rac5_JZC2152A_n2n1_AY-3_2-10		
Sample ID	: 8c_rac5_JZC2152A_n2n1_AY-3_2-10		
Data Filename	: 8c_rac5_JZC2152A_n2n1_AY-3_2-10.lcd		
Method Filename	: 99.9_0.1_60min_0.3mL.lcm		
Batch Filename	: batch8.lcb		
Vial #	: 1-24	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 2/11/2020 2:39:47 AM	Acquired by	: System Administrator
Date Processed	: 2/11/2020 10:17:04 AM	Processed by	: System Administrator



Detector A Channel 1 220nm

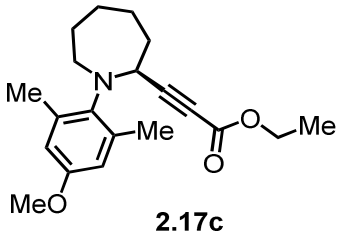
Peak#	Ret. Time	Area	Area%
1	27.437	11999000	48.953
2	38.057	12512111	51.047
Total		24511111	100.000

Sample Name	: 8c_ee4_JZC2101A_AY-3_2-10		
Sample ID	: 8c_ee4_JZC2101A_AY-3_2-10		
Data Filename	: 8c_ee4_JZC2101A_AY-3_2-10.lcd		
Method Filename	: 99.9_0.1_60min_0.3mL.lcm		
Batch Filename	: batch8.lcb		
Vial #	: 1-25	Sample Type	: Unknown
Injection Volume	: 4 uL		
Date Acquired	: 2/11/2020 3:40:02 AM	Acquired by	: System Administrator
Date Processed	: 2/12/2020 4:33:05 PM	Processed by	: System Administrator



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	27.840	22004548	93.243
2	39.795	1594617	6.757
Total		23599165	100.000



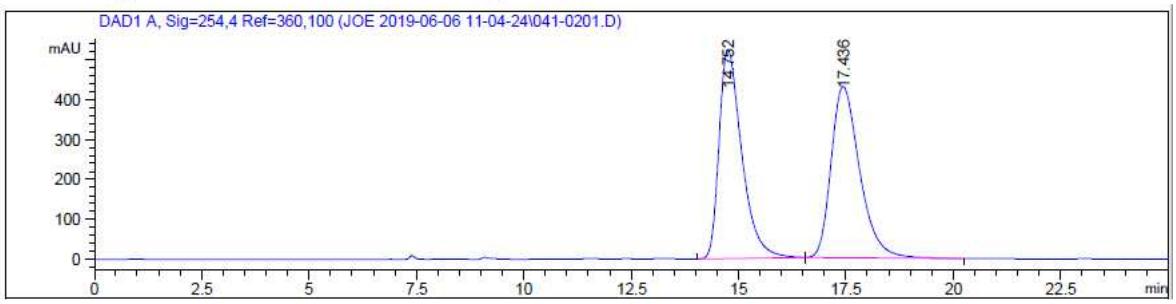
2.17c

Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)azepan-2-yl)propiolate (2.17c)

1-(4-Methoxy-2,6-dimethylphenyl)azepane **2.15c** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure C**. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17c** was obtained as a colorless liquid (42 mg, 0.13 mmol, 64% yield). The absolute configuration of **2.17c** was assigned in analogy to **(*S*)-2.17a** (see: SI Section 4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (d, *J* = 13.4 Hz, 2H), 4.18 (d, *J* = 7.1 Hz, 2H), 4.06 (d, *J* = 2.7 Hz, 1H), 3.75 (s, 3H), 3.32 (d, *J* = 9.1 Hz, 1H), 3.08 (d, *J* = 11.1 Hz, 1H), 2.42 (s, 3H), 2.29 (s, 3H), 2.19 (d, *J* = 1.5 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.85 – 1.79 (m, 1H), 1.79 – 1.70 (m, 2H), 1.57 (s, 2H), 1.28 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.4, 153.8, 140.9, 139.7, 137.9, 114.1, 113.6, 90.3, 75.6, 59.4, 55.6, 53.0, 51.3, 34.8, 31.4, 28.9, 25.2, 20.1, 19.6, 14.0; **IR** (neat) ν 2926, 2845, 2221, 1707, 1598, 1474, 1309, 1240, 1065, 853 cm^{-1}; **HRMS** (DART) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2063; found: 330.2061; **Specific Rotation**: $[\alpha]^{25}$ +30.1° (c 1.0, CH_2Cl_2); **HPLC** (Chiralcel OJ-H; 98.5:1.5 hexanes:isopropanol, 0.5 mL/min; **2.17c:** tr = 14.8 min (major), 17.4 min (minor); 95:5 er.

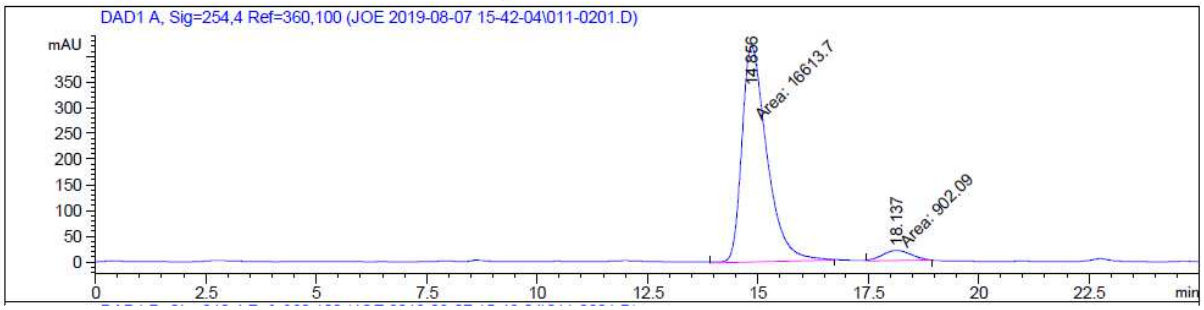
```
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : Wasa_LC1                      Location :   41
Injection Date  : 6/6/2019 11:37:23 AM               Inj :   1
                                               Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2019-06-06 11-04-24\column4 1.5%IPA 98.5% hexane 60min
                  -0.5mL.M
Last changed    : 6/6/2019 11:04:28 AM by SYSTEM
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

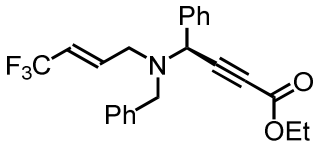
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.752	BB	0.5570	1.92070e4	522.36609	49.2058
2	17.436	BB	0.7122	1.98270e4	428.21890	50.7942

Acq. Operator : SYSTEM
Seq. Line : 2
Acq. Instrument : Wasa_LC1
Location : 11
Injection Date : 8/7/2019 4:14:59 PM
Inj : 1
Inj Volume : 4.000 µl
Acq. Method : C:\Chem32\1\Data\JOE 2019-08-07 15-42-04\column4 1.5%IPA 98.5% hexane 30min -0.5mL.M
Last changed : 8/7/2019 3:42:08 PM by SYSTEM



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.856	MM	0.6745	9.39466e4	2321.40063	95.4662
2	18.137	MM	0.6770	4461.63379	109.84474	4.5338



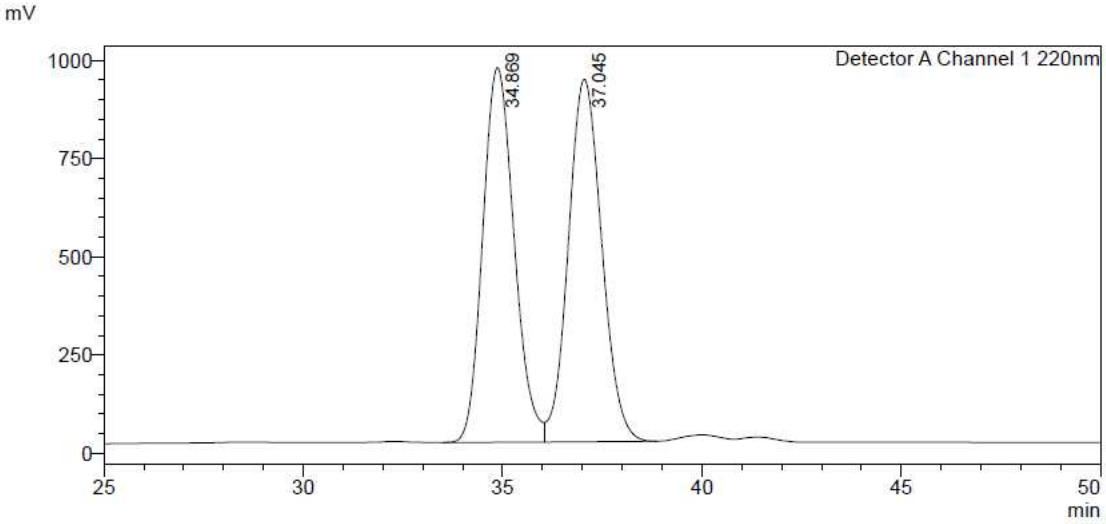
2.17r

Ethyl (*S,E*)-4-(benzyl(4,4,4-trifluorobut-2-en-1-yl)amino)-4-phenylbut-2-ynoate (2.17r)

(*E*)-*N,N*-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine **2.15r** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure C** using (*S*)-PhPyBOX as the ligand. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17r** was obtained as a colorless liquid (36 mg, 0.09 mmol, 45% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dt, *J* = 8.1, 1.1 Hz, 2H), 7.40 – 7.31 (m, 7H), 7.31 – 7.25 (m, 1H), 6.33 (dddd, *J* = 15.8, 7.5, 4.2, 2.1 Hz, 1H), 5.94 – 5.84 (m, 1H), 4.87 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.83 (d, *J* = 13.5 Hz, 1H), 3.54 (d, *J* = 13.5 Hz, 1H), 3.28 (dq, *J* = 15.6, 3.2 Hz, 1H), 3.21 – 3.14 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.4, 138.1, 138.03, 137.99, 137.95, 137.93, 136.5, 128.84, 128.81, 128.68, 128.65, 128.60, 128.57, 128.5, 128.42, 128.36, 128.3, 128.2, 128.0, 127.9, 127.6, 127.21, 127.16, 123.7, 121.9, 120.7, 120.5, 120.3, 120.0, 82.8, 80.5, 62.3, 58.3, 56.3, 55.4, 53.5, 50.6, 14.1; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -64.07, -64.08, -64.08, -64.09, -64.09, -64.10; **IR** (neat) ν 2925, 2222, 1711, 1492, 1450, 1242, 1119, 749, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{23}H_{23}NO_2F_3$ (MH^+): 402.1675; found: 402.1667; **Specific Rotation**: $[\alpha]^{25}$ –45.3° (*c* 1.0, CH_2Cl_2); **HPLC** (Chiralcel AD-H; 99.5:0.5 hexanes:isopropanol, 0.3 mL/min; **2.17r:** tr = 34.9 min (minor), 37.0 min (major); 84:16 er.

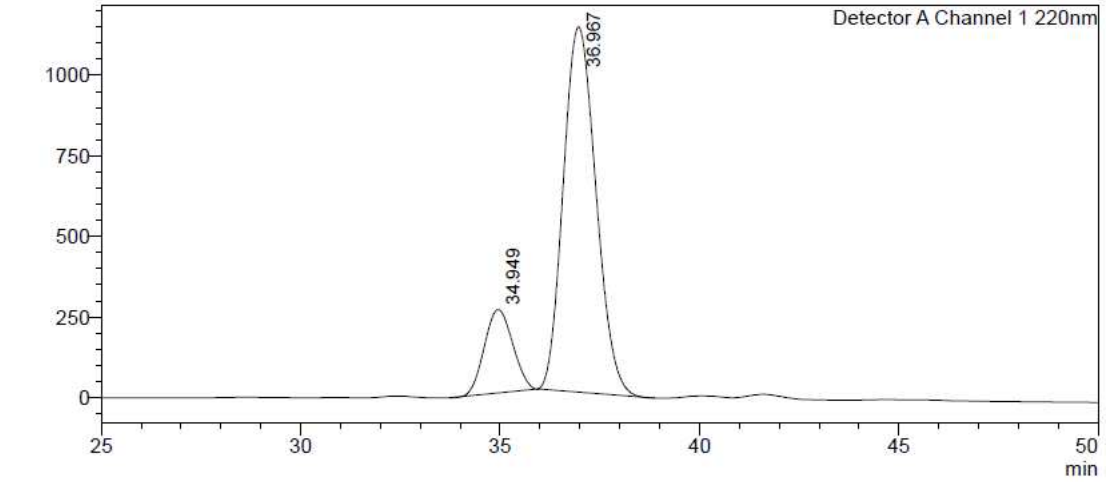
Sample Name	: 8e_rac3_JZC2017H2_AD-H_0.3mL		
Sample ID	: 8e_rac3_JZC2017H2_AD-H_0.3mL		
Data Filename	: 8e_rac3_JZC2017H2_AD-H_0.3mL.lcd		
Method Filename	: 995_05_60min_03mL.lcm		
Batch Filename	: batch9.lcb		
Vial #	: 1-4	Sample Type	: Unknown
Injection Volume	: 4 uL		
Date Acquired	: 2/9/2020 5:43:00 PM	Acquired by	: System Administrator
Date Processed	: 2/10/2020 9:51:53 AM	Processed by	: System Administrator



Detector A Channel 1 220nm

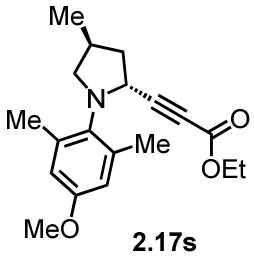
Peak#	Ret. Time	Area	Area%
1	34.869	52257747	49.272
2	37.045	53800949	50.728
Total		106058696	100.000

Sample Name	: 8e_ee3_JZC2187BC_n1n1_AD-H_0.3mL		
Sample ID	: 8e_ee3_JZC2187BC_n1n1_AD-H_0.3m		
Data Filename	: 8e_ee3_JZC2187BC_n1n1_AD-H_0.3mL.lcd		
Method Filename	: 995_05_60min_03mL.lcm		
Batch Filename	: batch9.lcb		
Vial #	: 1-5	Sample Type	: Unknown
Injection Volume	: 4 uL		
Date Acquired	: 2/9/2020 6:43:34 PM	Acquired by	: System Administrator
Date Processed	: 2/10/2020 9:40:28 AM	Processed by	: System Administrator



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	34.949	12756097	16.485
2	36.967	64623088	83.515
Total		77379185	100.000



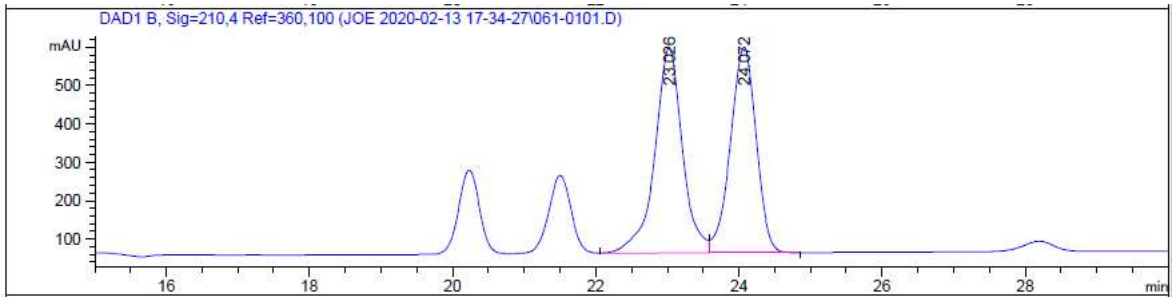
2.17s

Ethyl 3-((2*R*,4*S*)-1-(4-methoxy-2,6-dimethylphenyl)-4-methylpyrrolidin-2-yl)propiolate (2.17s)

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine **(*S*)-2.15s** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure C**. The *trans*:*cis* ratio was determined to be 11.8:1 by ^{1}H NMR analysis of the unpurified reaction mixtures. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17s** was obtained as a colorless liquid (40 mg, 0.13 mmol, 64% yield). The relative configuration of **2.17s** was assigned by NOESY, COSY, and HSQC analysis (see: SI Section 3).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.29 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.17 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.75 (d, *J* = 1.0 Hz, 3H), 3.38 (t, *J* = 7.2 Hz, 1H), 2.74 (dd, *J* = 8.8, 7.8 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.42 – 2.18 (m, 7H), 2.03 – 1.94 (m, 1H), 1.27 (td, *J* = 7.1, 0.9 Hz, 3H), 1.11 (dd, *J* = 6.5, 0.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.1, 153.9, 135.8, 113.6, 91.2, 74.1, 61.7, 58.4, 55.2, 52.7, 41.6, 33.6, 18.8, 17.3, 14.0; **IR** (neat) ν 2954, 2924, 1708, 1601, 1484, 1465, 1244, 1154, 1066 cm^{-1}; **HRMS** (DART) Calcd for $C_{19}H_{26}NO_3$ (MH^+): 316.1907; found: 316.1904; **Specific Rotation**: $[\alpha]^{25}$ +63.0° (*c* 0.2, CH_2Cl_2); **HPLC** (Chiralpak IA; 97.5:2.5 hexanes:isopropanol, 0.2 mL/min; **2.17s:** tr = 23.0 min (major), 24.0 min (minor); 97:3 er.

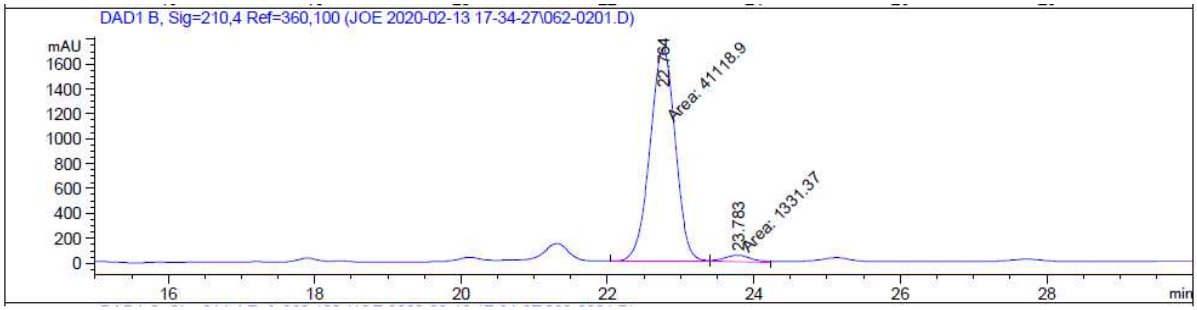
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   61
Injection Date  : 2/13/2020 5:35:45 PM                 Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-02-13 17-34-27\column6 2.5%IPA 97.5% hexane 40min
                  -0.2mL.M
Last changed    : 2/13/2020 5:34:32 PM by SYSTEM
```



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

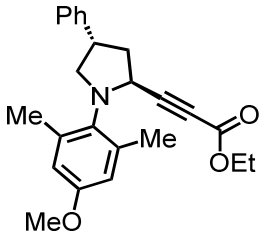
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.026	VV	0.4035	1.44252e4	536.82739	51.7382
2	24.072	VB	0.3885	1.34559e4	536.65869	48.2618

Acq. Operator : SYSTEM Seq. Line : 2
Acq. Instrument : Wasa_LC1 Location : 62
Injection Date : 2/13/2020 6:16:42 PM Inj : 1
Inj Volume : 4.000 µl
Acq. Method : C:\Chem32\1\Data\JOE 2020-02-13 17-34-27\column6 2.5%IPA 97.5% hexane 40min -0.2mL.M
Last changed : 2/13/2020 5:34:32 PM by SYSTEM



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.764	MM	0.3995	4.11189e4	1715.43152	96.8637
2	23.783	MM	0.4273	1331.37109	51.93531	3.1363



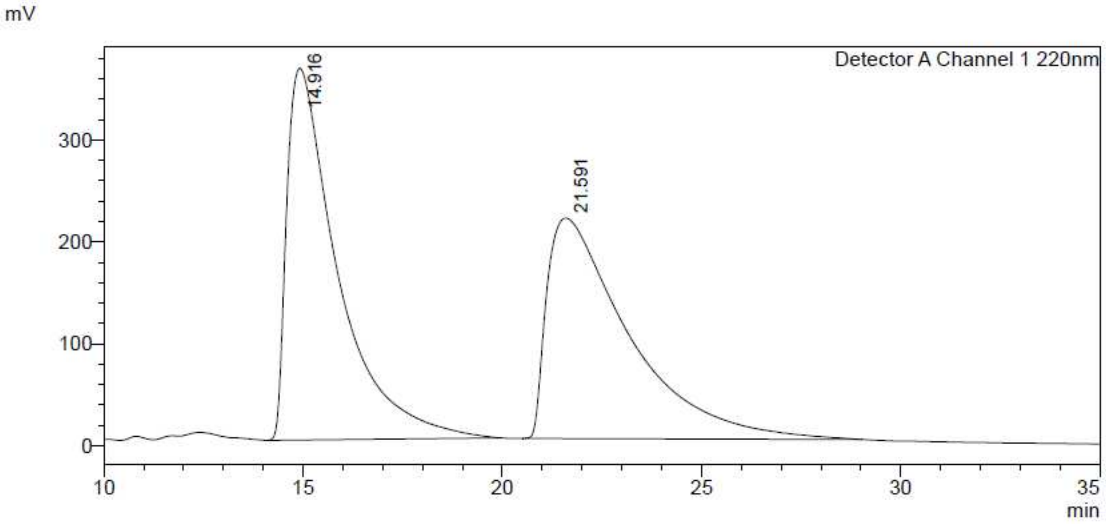
2.17t

Ethyl 3-((2*S*,4*S*)-1-(4-methoxy-2,6-dimethylphenyl)-4-phenylpyrrolidin-2-yl)propiolate (2.17t)

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-phenylpyrrolidine **(*S*)-2.15t** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure C**. The *trans*:*cis* ratio was determined to be 10.1:1 by ^{1}H NMR analysis of the unpurified product mixtures. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **2.17t** was obtained as a colorless liquid (51 mg, 0.14 mmol, 68% yield). The absolute and relative configuration of **2.17t** was assigned in analogy to **2.17s** (see: SI Section 3).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.24 (dt, *J* = 6.8, 1.7 Hz, 1H), 6.61 (s, 2H), 4.44 (dd, *J* = 7.3, 2.8 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.84 (ddd, *J* = 17.7, 10.2, 7.5 Hz, 1H), 3.76 (s, 3H), 3.64 (t, *J* = 7.6 Hz, 1H), 3.25 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.56 – 2.50 (m, 2H), 2.50 – 2.14 (m, 6H), 1.29 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ157.4, 153.9, 141.1, 135.5, 128.6, 127.9, 127.2, 126.7, 113.7, 90.6, 74.4, 61.8, 57.7, 55.2, 52.9, 44.1, 40.5, 18.9, 14.0; **IR** (neat) ν 2196, 2847, 2226, 1701,1601, 1485, 1243, 1153, 1037, 699 cm^{-1}; **HRMS** (DART) Calcd for $C_{24}H_{28}NO_3$ (MH^+): 378.2064; found: 378.2063; **Specific Rotation**: $[\alpha]^{25}$ –25.5° (*c* 0.6, CH_2Cl_2); **HPLC** (Chiralpak AY-3; 99.5:0.5 hexanes:isopropanol, 0.5 mL/min; **2.17t:** tr = 14.9 min (minor), 21.6 min (major); 88:12 er.

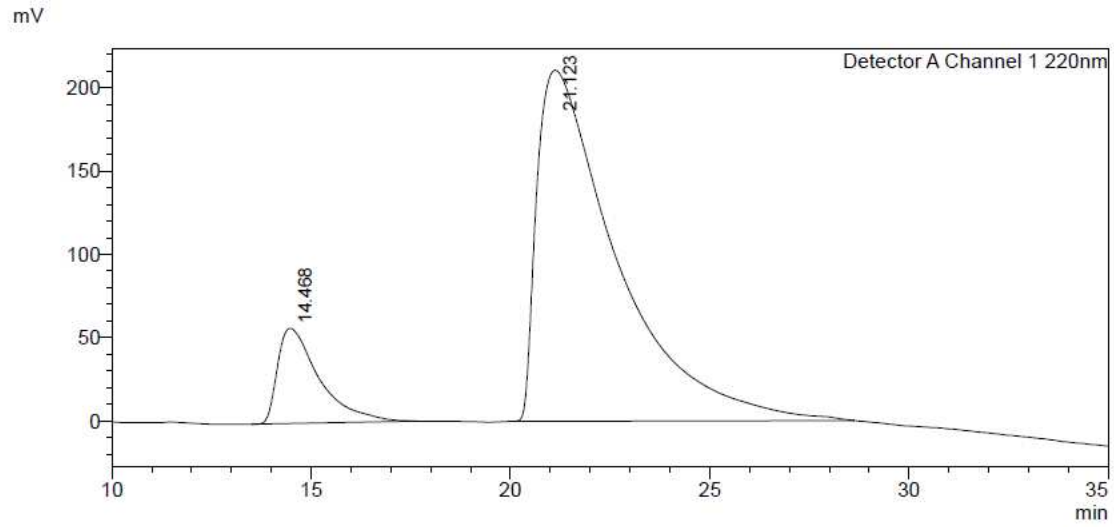
Sample Name	: 8g_rac1_JZC2137C_n1_AY-3_2		
Sample ID	: 8g_rac1_JZC2137C_n1_AY-3_2		
Data Filename	: 8g_rac1_JZC2137C_n1_AY-3_2.lcd		
Method Filename	: 995_05_40min_05mL.lcm		
Batch Filename	: batch8.lcb		
Vial #	: 1-20	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 2/11/2020 12:44:49 PM	Acquired by	: System Administrator
Date Processed	: 2/12/2020 4:14:36 PM	Processed by	: System Administrator



Detector A Channel 1 220nm

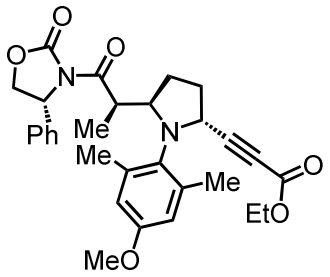
Peak#	Ret. Time	Area	Area%
1	14.916	32360232	51.050
2	21.591	31028467	48.950
Total		63388699	100.000

Sample Name	: 8g_ee2_JZC2194B_AY-3_4		
Sample ID	: 8g_ee2_JZC2194B_AY-3_4		
Data Filename	: 8g_ee2_JZC2194B_AY-3_4.lcd		
Method Filename	: 995_05_40min_05mL.lcm		
Batch Filename	: batch8.lcb		
Vial #	: 1-21	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 2/11/2020 4:21:14 PM	Acquired by	: System Administrator
Date Processed	: 2/12/2020 4:18:29 PM	Processed by	: System Administrator



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	14.468	4143746	12.331
2	21.123	29460297	87.669
Total		33604042	100.000

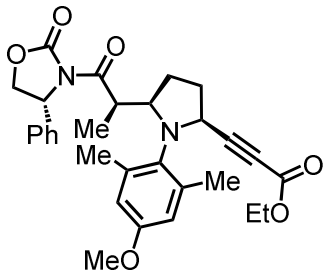


2.17u-*trans*

Ethyl 3-((2*R*,5*R*)-1-(4-methoxy-2,6-dimethylphenyl)-5-((*R*)-1-oxo-1-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)propan-2-yl)pyrrolidin-2-yl)propiolate (2.17u-*trans*)

(*R*)-3-((*R*)-2-((*R*)-1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propanoyl)-4-phenyloxazolidin-2-one **(*R,R,R*)-2.15u** was added to ethyl 3-(trimethylsilyl)propiolate **2.16a** following **General Procedure C**. The *trans*:*cis* ratio was determined to be 7.7:1 by ^{1}H NMR analysis of the unpurified reaction mixtures. After purification by silica gel chromatography (Et_2O:hexanes = 1:4), **2.17u-*trans*** was obtained as a colorless liquid (96 mg, 0.19 mmol, 93% yield). The relative configuration of **2.17u-*trans*** was assigned by NOESY and COSY analysis (see: SI Section 3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 3H), 7.07 – 7.02 (m, 2H), 6.59 (q, *J* = 3.1 Hz, 2H), 4.56 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.47 (t, *J* = 7.0 Hz, 1H), 4.21 (dt, *J* = 12.7, 8.5 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.98 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.79 (s, 3H), 3.71 (dq, *J* = 9.0, 6.9 Hz, 1H), 2.42 (dtd, *J* = 12.3, 7.0, 3.8 Hz, 1H), 2.34 (s, 3H), 2.26 (s, 3H), 2.21 (dtd, *J* = 12.2, 6.3, 3.8 Hz, 1H), 2.11 (ddt, *J* = 12.3, 10.1, 7.0 Hz, 1H), 1.76 (ddt, *J* = 11.9, 9.8, 7.4 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.2, 157.2, 153.6, 153.1, 143.7, 140.6, 139.5, 133.2, 128.9, 128.3, 125.1, 113.8, 112.4, 89.6, 74.8, 69.7, 62.4, 61.7, 57.4, 55.21, 55.20, 52.5, 42.1, 32.2, 30.3, 20.1, 19.5, 15.9, 13.9; **IR** (neat) ν 2960, 2847, 2226, 2172, 1775, 1699, 1597, 1380, 1240, 1039, 699 cm^{-1}; **HRMS** (DART) Calcd for $C_{30}H_{35}N_2O_6$ (MH^+): 519.2489; found: 519. 2475; **Specific Rotation**: $[\alpha]^{25}$ −62.2° (*c* 0.5, CH_2Cl_2).



2.17u-*cis*

Ethyl 3-((2*S*,5*R*)-1-(4-methoxy-2,6-dimethylphenyl)-5-((*R*)-1-oxo-1-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)propan-2-yl)pyrrolidin-2-yl)propiolate (2.17u-*cis*)

The relative configuration of **2.17u-*cis*** was assigned by NOESY analysis (see: SI Section 3). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 3H), 7.08 (dt, *J* = 7.2, 2.3 Hz, 2H), 6.62 (d, *J* = 3.1 Hz, 1H), 6.53 (d, *J* = 3.2 Hz, 1H), 4.63 (dt, *J* = 8.7, 2.9 Hz, 1H), 4.37 (td, *J* = 8.5, 3.0 Hz, 1H), 4.19 (dtt, *J* = 17.6, 7.4, 3.7 Hz, 3H), 4.07 (dt, *J* = 10.5, 2.8 Hz, 1H), 3.95 (q, *J* = 8.7 Hz, 1H), 3.83 – 3.67 (m, 4H), 2.50 (d, *J* = 3.0 Hz, 3H), 2.32 (tt, *J* = 12.3, 4.6 Hz, 1H), 2.25 – 2.12 (m, 4H), 2.07 (dh, *J* = 13.2, 3.5 Hz, 1H), 1.94 (ddd, *J* = 11.9, 7.8, 2.8 Hz, 1H), 1.27 (tt, *J* = 9.0, 4.2 Hz, 4H), 1.15 (dd, *J* = 7.2, 3.0 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.8, 157.5, 153.7, 153.1, 142.8, 140.8, 139.3, 134.7, 129.1, 129.0, 128.4, 125.2, 114.5, 112.8, 90.0, 74.4, 69.9, 63.8, 61.7, 57.4, 55.3, 53.9, 42.0, 32.2, 29.0, 19.9, 19.4, 14.9, 14.0; **IR** (neat) ν 2876, 2848, 2232, 1779, 1704, 1600, 1465, 1382, 1246, 1194, 1066, 1041, 702 cm^{-1}; **HRMS** (DART) Calcd for $C_{30}H_{35}N_2O_6$ (MH^+): 519.2489; found: 519. 2483; **Specific Rotation**: $[\alpha]^{25}$ +108.6° (*c* 0.4, CH_2Cl_2).

A7. References

(1) Shang, M. et al. C–H Functionalization of amines *via* alkene-derived nucleophiles through cooperative action of chiral and achiral Lewis acid catalysts: applications in enantioselective synthesis. *J. Am. Chem. Soc.* **2018**, *140*, 10593−10601.

(2) Chang, Y.; Yesilcimen, A.; Cao, M.; Zhang, Y.; Zhang. B.; Chan, J. Z.; Wasa, M. Catalytic deuterium incorporation within metabolically stable *β*-amino C–H bonds of drug molecules *J. Am. Chem. Soc.* **2019**, *141*, 14570−14575.

(3) Kojima, R.; Akiyama, S.; Ito, H. A copper(I)-catalyzed enantioselective γ-boryl substitution of trifluoromethyl-substituted alkenes: Synthesis of enantioenriched γ,γ-*gem*-difluoroallylboronates. *Angew. Chem., Int. Ed.* **2018**, *57*, 7196−7199.

(4) Kraihanzel, C. S. and Losee, M. L. Ethynylsilanes. III. Syntheses of some 2-organosilicon bicycle[2.2.1]heptadienes and bicycle[2.2.1]hept-2-enes. *J. Org. Chem.* **1968**, *33*, 1983−1986.

(5) Tse, M. D.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem*. *Eur*. *J*. **2006**, *12*, 1855−1874.

(6) Eno, M. S.; Lu, A.; Morken, J. P. Nickel-catalyzed asymmetric Kumada cross-coupling of symmetric cyclic sulfates. *J. Am. Chem. Soc*. **2016**, *138*, 7824−7827.

(7) Lovinger, G. J., Morken, J. P. Ni-catalyzed enantioselective conjunctive coupling with C(sp^3) electrophiles: A radical-ionic mechanistic dichotomy. *J. Am. Chem. Soc.* **2017**, *139*, 17293−17296.

(8) Yoon, T.; MacMillan, D. W. C. Enantioselective Claisen rearrangements: Development of a first generation asymmetric acyl-Claisen reaction. *J. Am. Chem. Soc.* **2001**, *123*, 2911−2912.

(9) Patel, S. K.; Murat, K.; Py, S.; Vallee, Y. Asymmetric total synthesis and stereochemical elucidation of the antitumor agent PM-94128. *Org. Lett.* **2003**, *5*, 4081−4084.

(10) Petrone, D. A.; Isomura, M.; Franzoni, I.; Rossler, S. L.; Carreira, E. M. Allenylic carbonates in enantioselective iridium-catalyzed alkylations. *J. Am. Chem. Soc.* **2018**, *140*, 4697−4704.

(11) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. Synthesis of enantiomerically enriched propargylamines by copper-catalyzed addition of alkynes to enamines. *Chem. Eur. J.* **2003**, *9*, 2797–2811.

(12) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A stepwise Huisgen cycloaddition process: Copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.

(13) Blackmond, D. G. Kinetic profiling of catalytic organic reactions as a mechanistic tool *J. Am. Chem. Soc.* **2015**, *137*, 10852–10866.

(14) Cain, F. M.; Hughes, R. P.; Glueck, D. S.; Golen, J. A.; Moore, C. E.; Rheingold, A. L. Synthesis and structure of intermediates in copper-catalyzed alkylation of diphenylphosphine. *Inorg. Chem*. **2010**, *49*, 7650–7662.

(15) Simmons, E. M.; Hartwig, J. F. On the interpretation of deuterium kinetic isotope effects in C–H bond functionalizations by transition-metal complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066–3072.

(16) Dureen, M. A.; Stephan, D. W. Terminal Alkyne Activation by Frustrated and Classical Lewis Acid/Phosphine Pairs. *J. Am. Chem. Soc.* **2009**, *131*, 8396–8397.

(17) Strašák, T.; Sykora, J.; Lamac, M.; Kubista, J.; Horaćek, M.; Gyepes, R.; Pinkas, J. Reactivity of a Titanocene Pendant Si–H Group toward Alcohols. Unexpected Formation of Siloxanes from the Reaction of Hydrosilanes and Ph_3COH Catalyzed by $B(C_6F_5)_3$. *Organometallics* **2013**, **32**, 4122–4129.

(18) Di Saverio, A.; Focante, F.; Camurati, I.; Resconi, L.; Beringhelli, T.; D'Alfonso, G.; Donghi, D.; Maggioni, D.; Mercandelli, P.; Sironi, A. Oxygen-Bridged Borate Anions from Tris(pentafluorophenyl)borane: Synthesis, NMR Characterization, and Reactivity. *Inorg. Chem*. **2005**, *44*, 5030–5041.

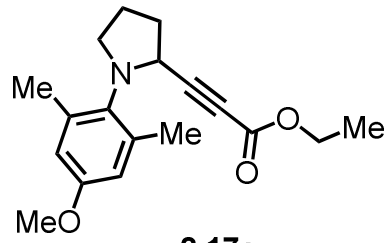
(19) Millot, N.; Santini, C. C.; Fenet, B.; Basset, J. M. Formation and characterization of zwitterionic stereoisomers from the reaction of $B(C_6F_5)_3$ and NEt_2Ph: (*E*)- and (*Z*)-$[EtPhN^+{=}CHCH_2{-}B^-(C_6F_5)_3]$. *Eur. J. Inorg. Chem.* **2002**, *2002*, 3328–3335.

(20) Webb, J. D.; Laberge, V. S.; Geier, S. J.; Stephan, D. W.; Crudden, C. M. Borohydrides from Organic Hydrides: Reactions of Hantzschs Esters with $B(C_6F_5)_3$. *Chem. Eur. J.* **2010**, *16*, 4895–4902.

(21) **2.21h** required longer ^{13}C NMR acquisition during which trimethylsilyl group was fallen off to afford **2.24**. For corresponding ^{13}C NMR, *see: N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-yn-1-amine (p45)

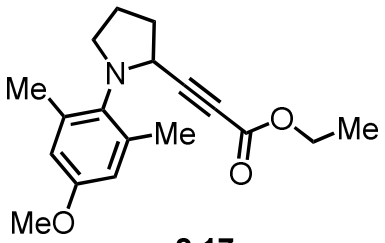
A8. NMR Spectra

^{1}H NMR (500 MHz, $CDCl_3$)



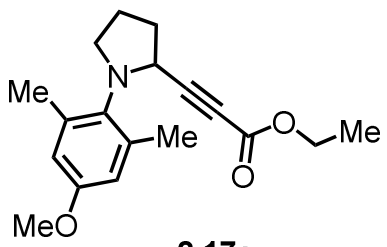
2.17a

^{1}H NMR (500 MHz, $CDCl_3$)



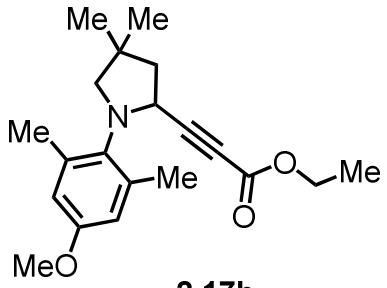
2.17a

^{13}C NMR (151 MHz, $CDCl_3$)



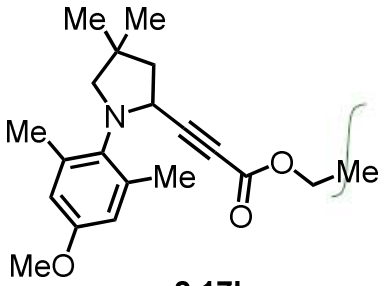
2.17a

^{1}H NMR (600 MHz, $CDCl_3$)



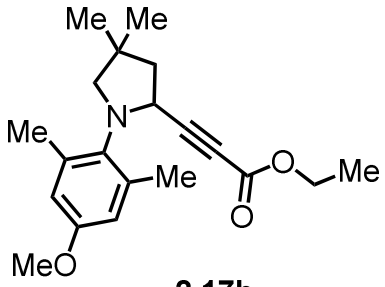
2.17b

^{1}H NMR (600 MHz, $CDCl_3$)



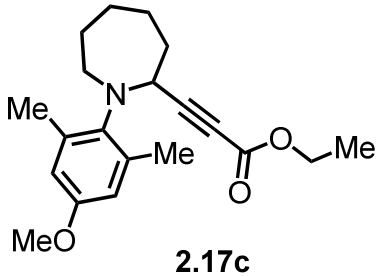
2.17b

^{13}C NMR (151 MHz, $CDCl_3$)



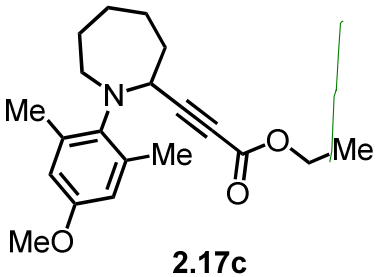
2.17b

^{1}H NMR (500 MHz, $CDCl_3$)



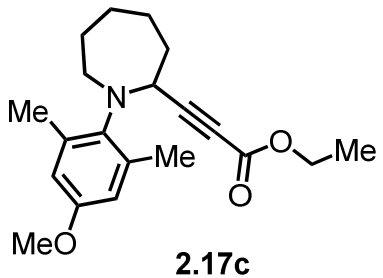
2.17c

^{1}H NMR (500 MHz, $CDCl_3$)



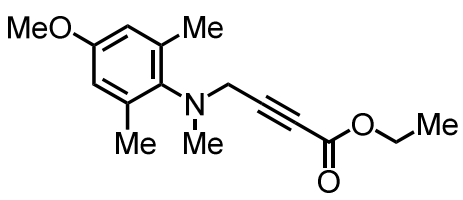
2.17c

^{13}C NMR (151 MHz, $CDCl_3$)



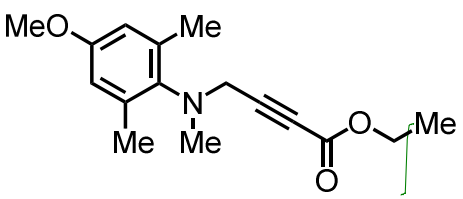
2.17c

^{1}H NMR (500 MHz, $CDCl_3$)



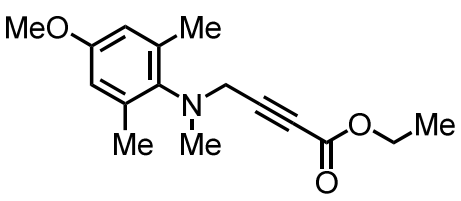
2.17d

^{1}H NMR (500 MHz, $CDCl_3$)



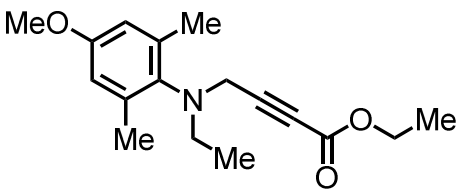
2.17d

^{13}C NMR (151 MHz, $CDCl_3$)



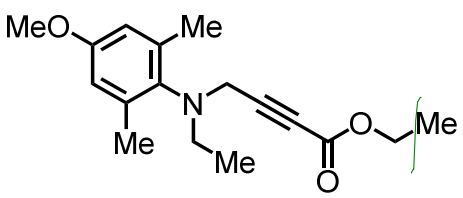
2.17d

^{1}H NMR (500 MHz, $CDCl_3$)



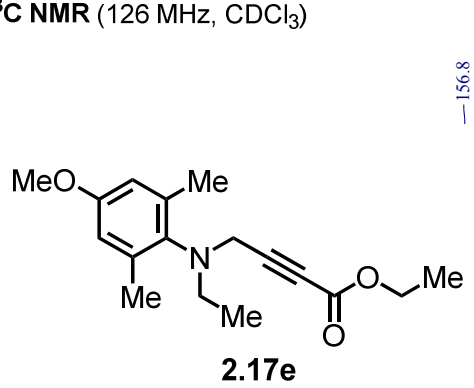
2.17e

^{1}H NMR (500 MHz, $CDCl_3$)



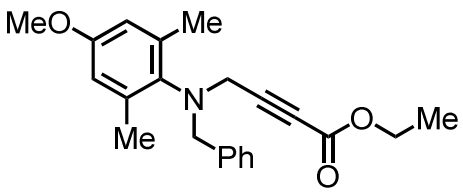
2.17e

^{13}C NMR (126 MHz, $CDCl_3$)



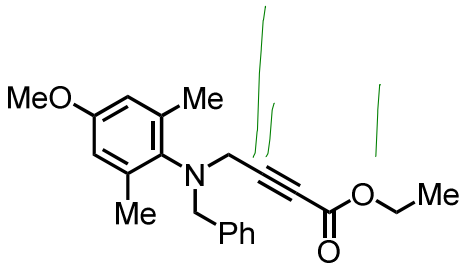
2.17e

^{1}H NMR (500 MHz, $CDCl_3$)



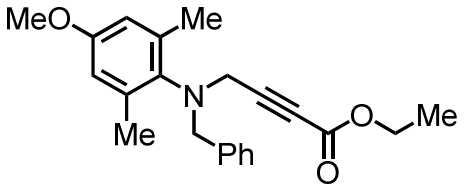
2.17f

^{1}H NMR (500 MHz, $CDCl_3$)



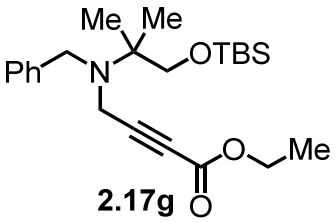
2.17f

^{13}C NMR (151 MHz, $CDCl_3$)



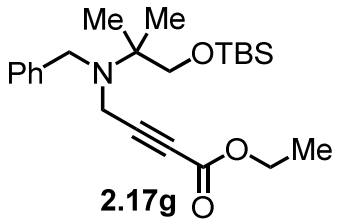
2.17f

^{1}H NMR (500 MHz, $CDCl_3$)



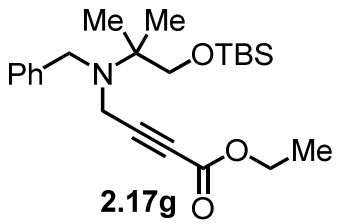
2.17g

^{1}H NMR (500 MHz, $CDCl_3$)



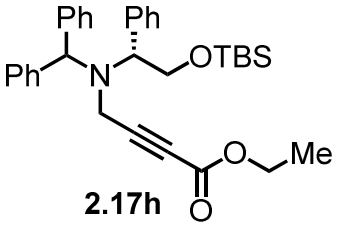
2.17g

^{13}C NMR (126 MHz, $CDCl_3$)



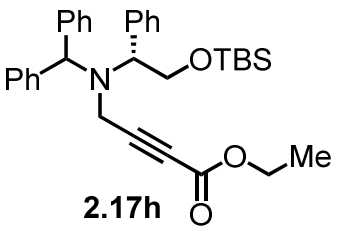
2.17g

^{1}H NMR (600 MHz, $CDCl_3$)



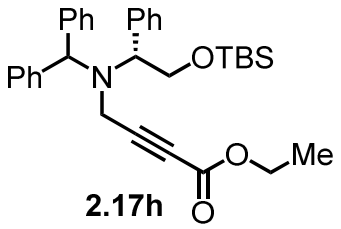
2.17h

^{1}H NMR (600 MHz, $CDCl_3$)



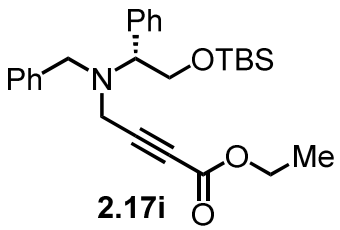
2.17h

^{13}C NMR (151 MHz, $CDCl_3$)



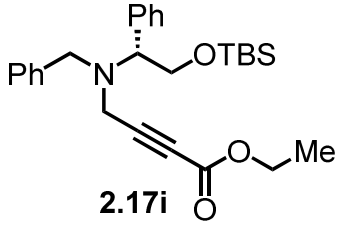
2.17h

^{1}H NMR (500 MHz, $CDCl_3$)



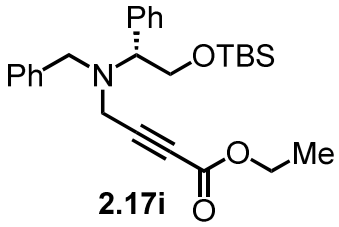
2.17i

^{1}H NMR (500 MHz, $CDCl_3$)



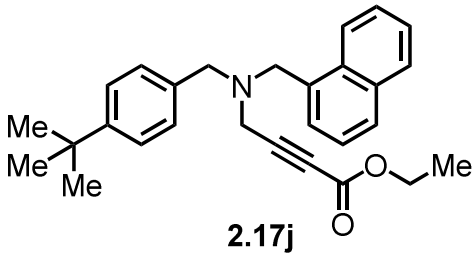
2.17i

^{13}C NMR (126 MHz, $CDCl_3$)



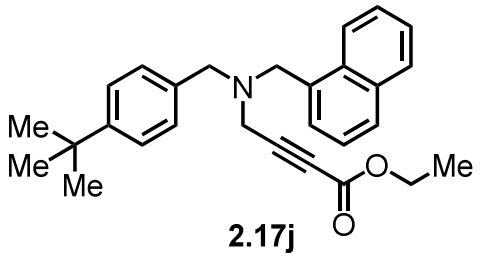
2.17i

^{1}H NMR (500 MHz, $CDCl_3$)



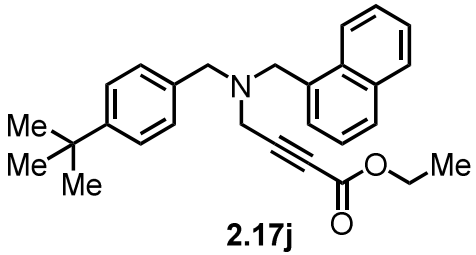
2.17j

^{1}H NMR (500 MHz, $CDCl_3$)



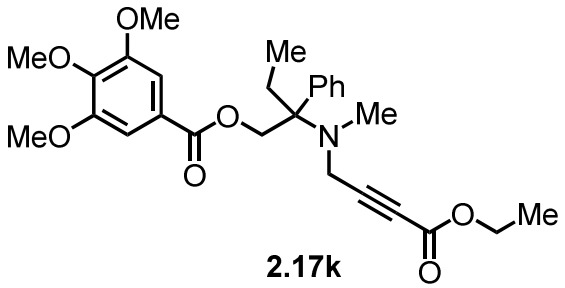
2.17j

^{13}C NMR (126 MHz, $CDCl_3$)



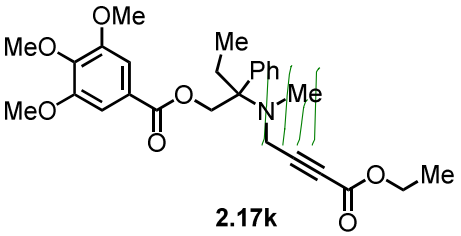
2.17j

^{1}H NMR (500 MHz, $CDCl_3$)



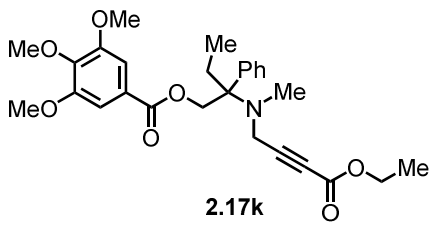
2.17k

^{1}H NMR (500 MHz, $CDCl_3$)



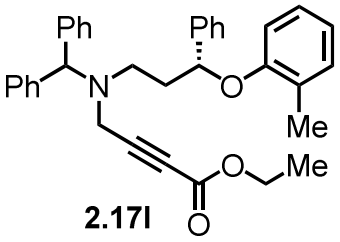
2.17k

^{13}C NMR (126 MHz, $CDCl_3$)



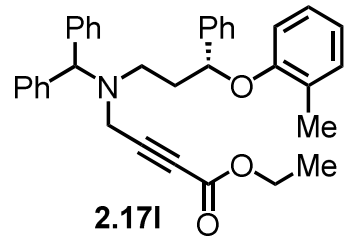
2.17k

^{1}H NMR (500 MHz, $CDCl_3$)



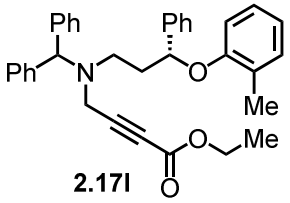
2.17l

^{1}H NMR (500 MHz, $CDCl_3$)



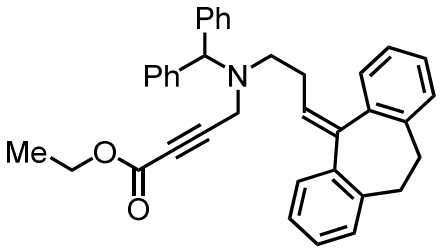
2.17l

^{13}C NMR (126 MHz, $CDCl_3$)

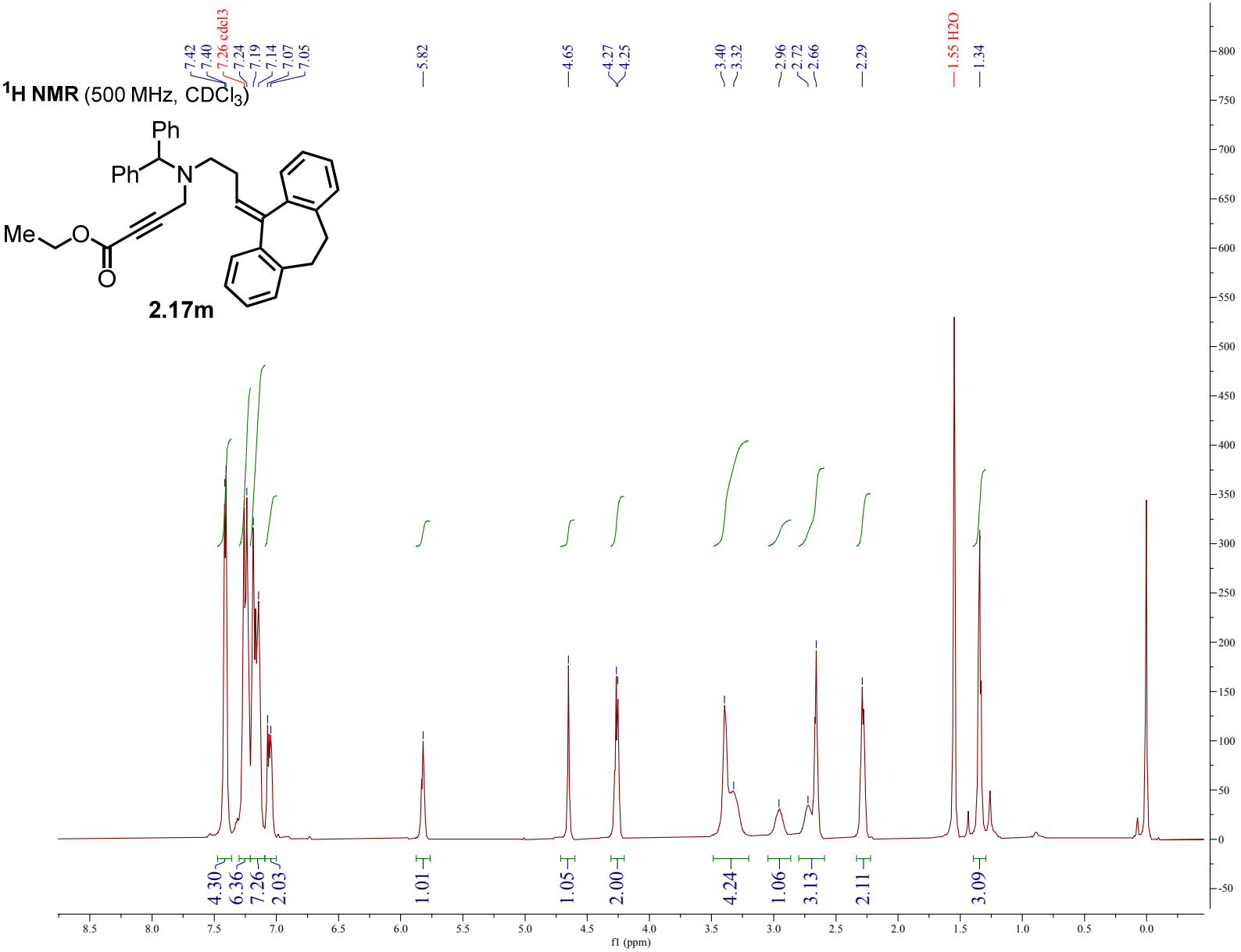


2.17l

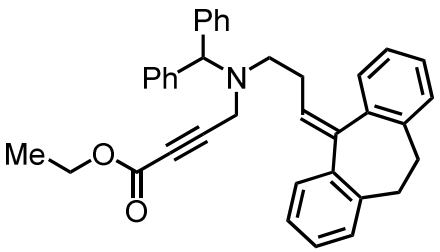
^{1}H NMR (500 MHz, $CDCl_3$)



2.17m

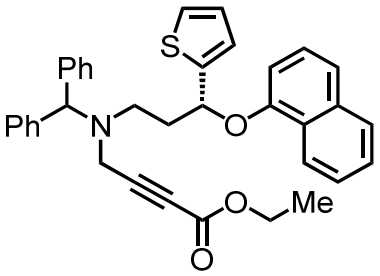

1H NMR (500 MHz, CDCl3)
Ph
Ph
N
Me
O
O
2.17m
7.42
7.40
7.26 cdcl3
7.24
7.19
7.14
7.07
7.05
5.82
4.65
4.27
4.25
3.40
3.32
2.96
2.72
2.66
2.29
1.55 H2O
1.34
4.30
6.36
7.26
2.03
1.01
1.05
2.00
4.24
1.06
3.13
2.11
3.09
f1 (ppm)

^{13}C NMR (126 MHz, $CDCl_3$)



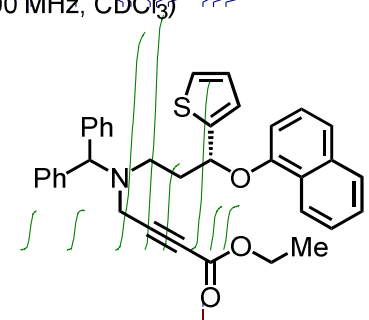
2.17m

^{1}H NMR (600 MHz, $CDCl_3$)



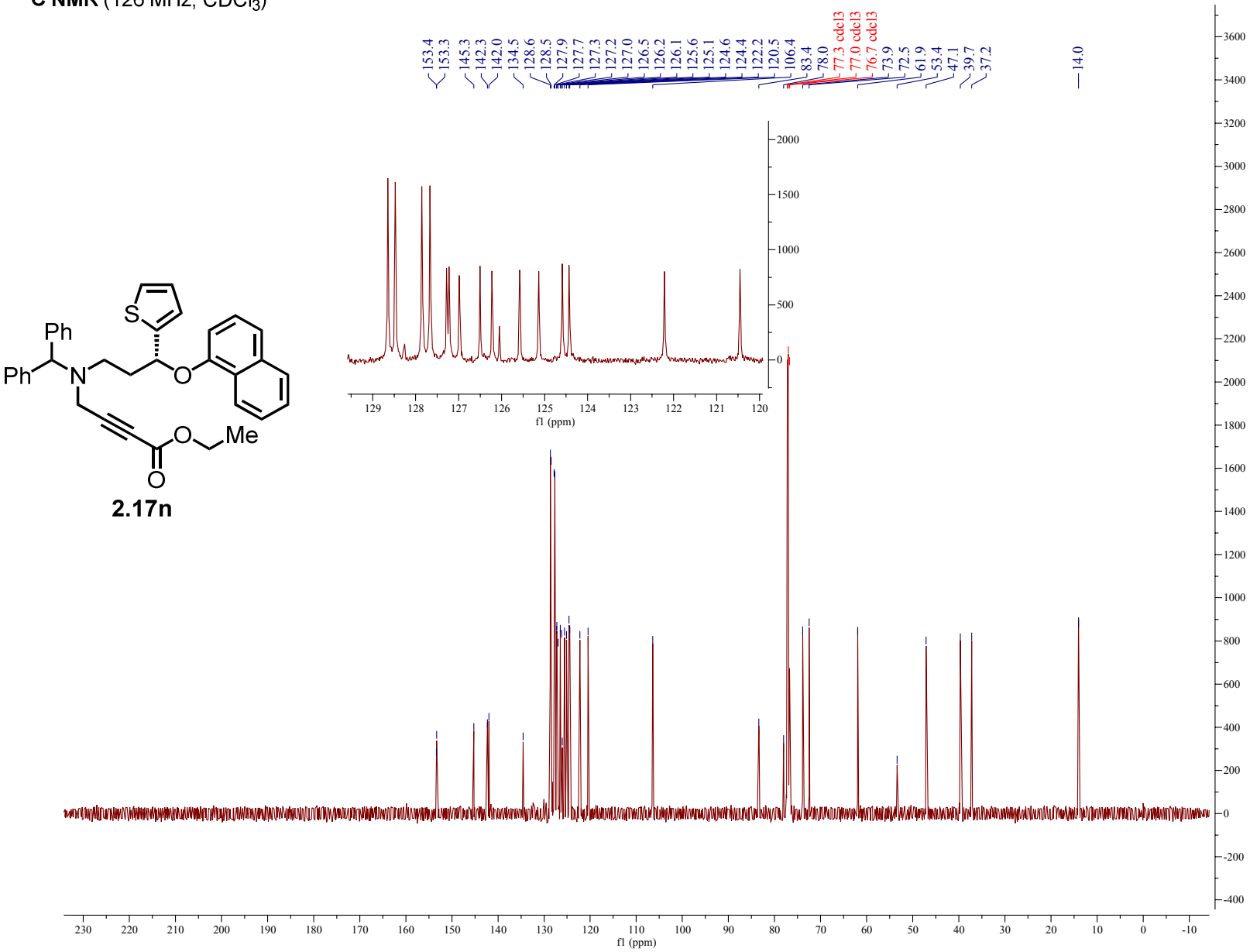
2.17n

^{1}H NMR (600 MHz, $CDCl_3$)



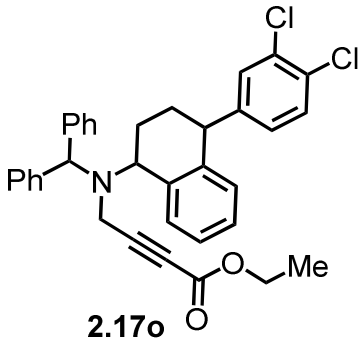
2.17n

^{13}C NMR (126 MHz, $CDCl_3$)

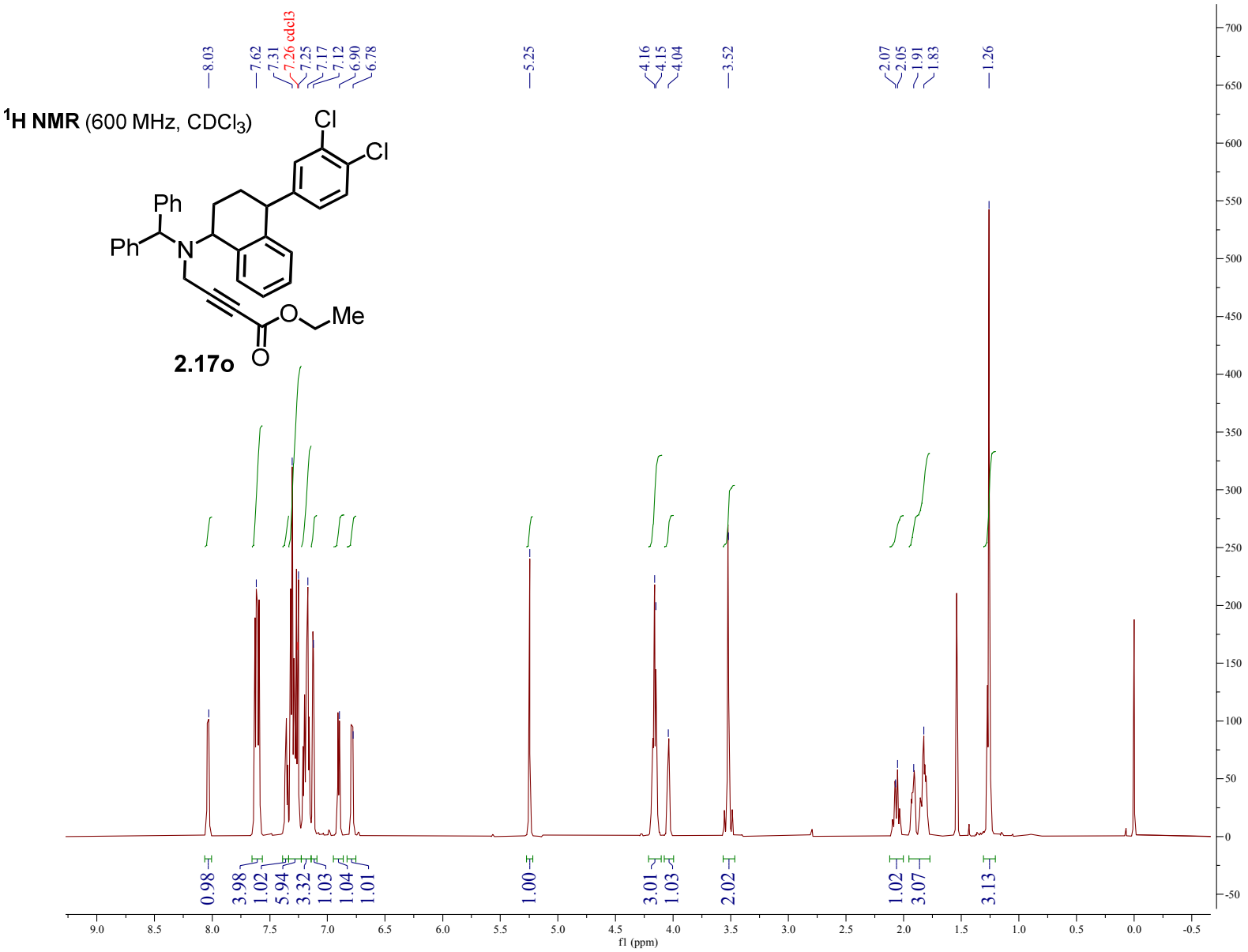


2.17n

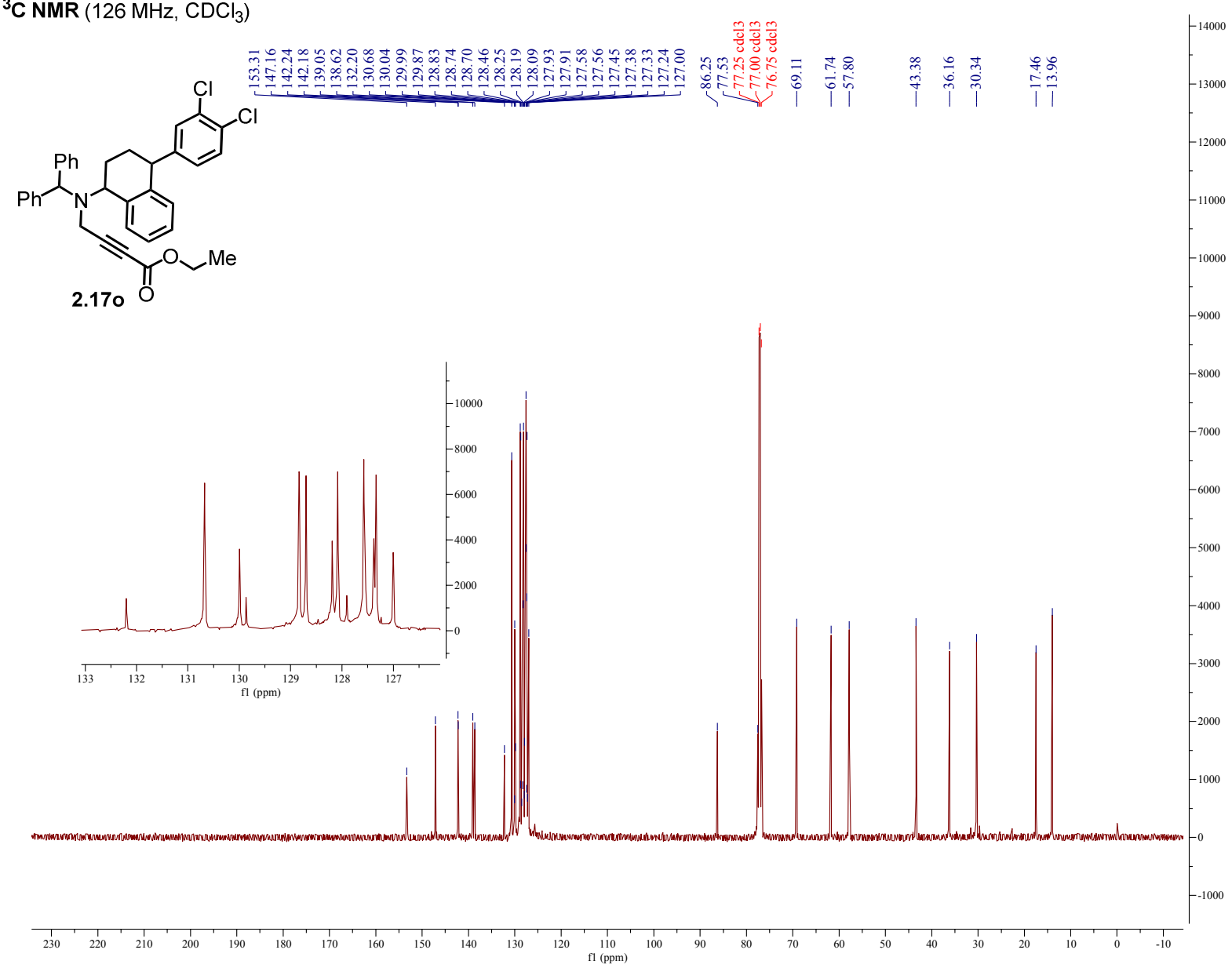
^{1}H NMR (600 MHz, $CDCl_3$)



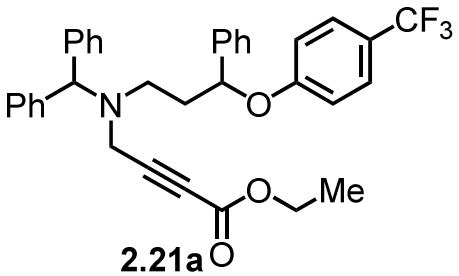
2.17o


1H NMR (600 MHz, CDCl3)
Cl
Cl
Ph
Ph
N
O
Me
O
2.17o
8.03
7.62
7.31
7.26 cdcl3
7.25
7.17
7.12
6.90
6.78
5.25
4.16
4.15
4.04
3.52
2.07
2.05
1.91
1.83
1.26
0.98
3.98
1.02
5.94
3.32
1.03
1.04
1.01
1.00
3.01
1.03
2.02
1.02
3.07
3.13
f1 (ppm)

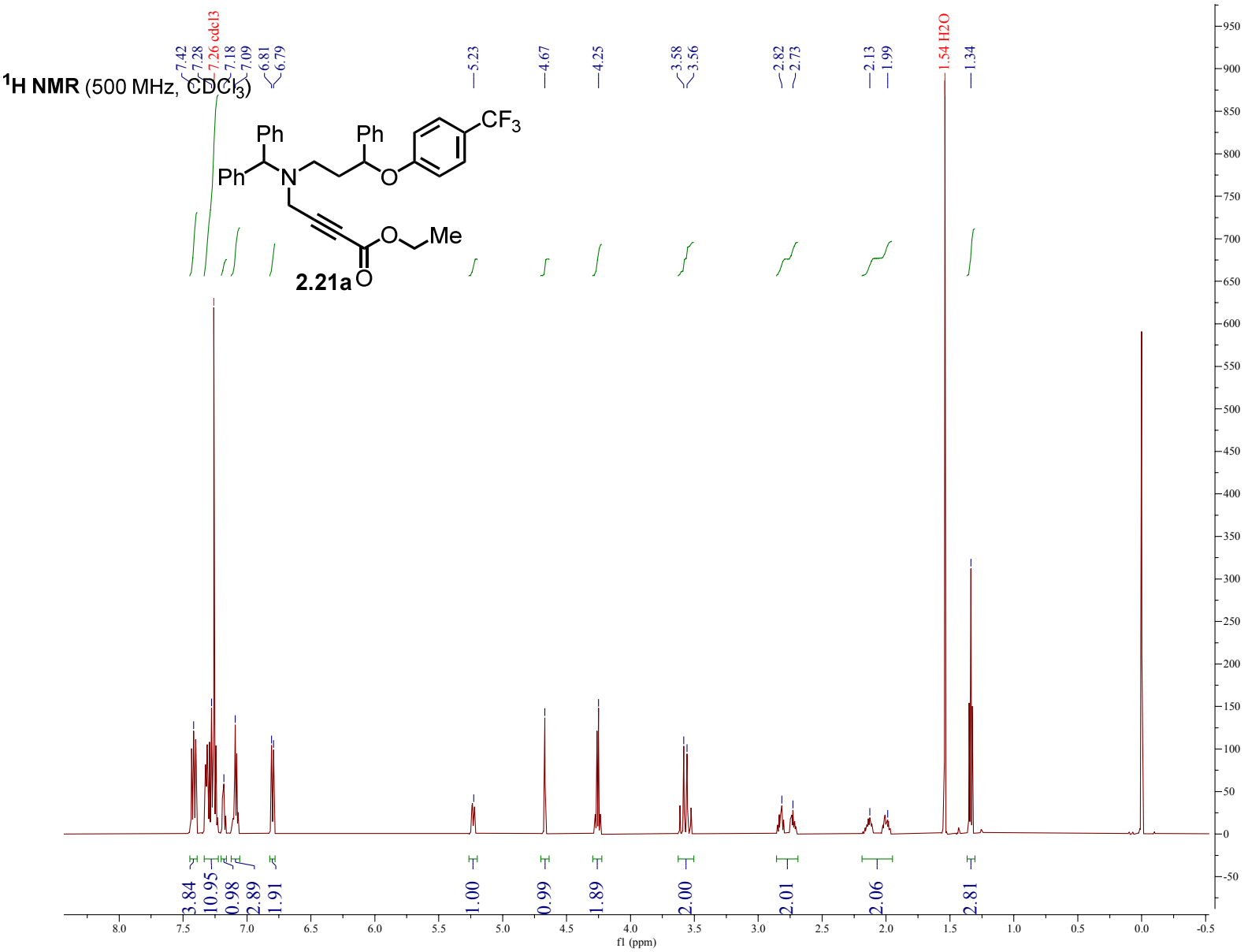
^{13}C NMR (126 MHz, $CDCl_3$)



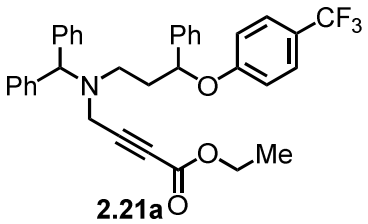
^{1}H NMR (500 MHz, $CDCl_3$)



2.21a

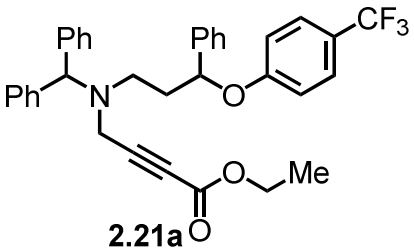

1H NMR (500 MHz, CDCl3)
7.42
7.28
7.26 cdcl3
7.18
7.09
6.81
6.79
5.23
4.67
4.25
3.58
3.56
2.82
2.73
2.13
1.99
1.54 H2O
1.34
Ph
Ph
Ph
N
O
CF3
O
Me
O
2.21a
3.84
10.95
0.98
2.89
1.91
1.00
0.99
1.89
2.00
2.01
2.06
2.81
f1 (ppm)

^{13}C NMR (126 MHz, $CDCl_3$)



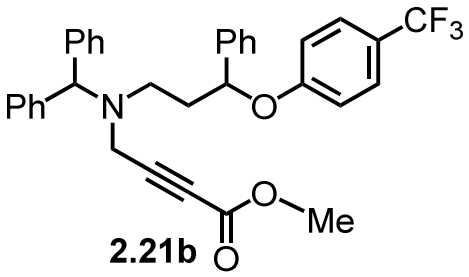
2.21a

^{19}F NMR (470 MHz, $CDCl_3$)



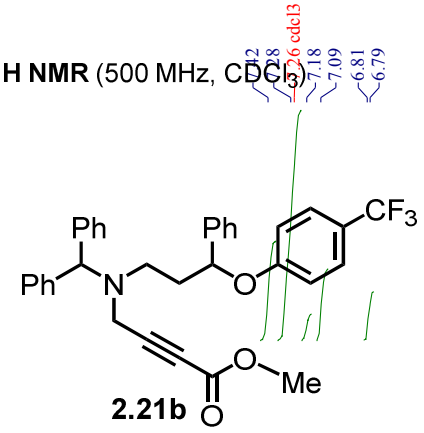
2.21a

^{1}H NMR (500 MHz, $CDCl_3$)



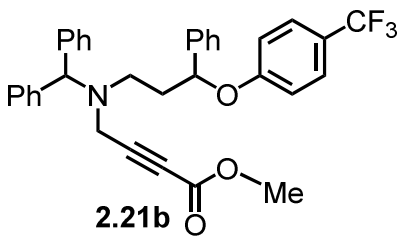
2.21b

^{1}H NMR (500 MHz, $CDCl_3$)



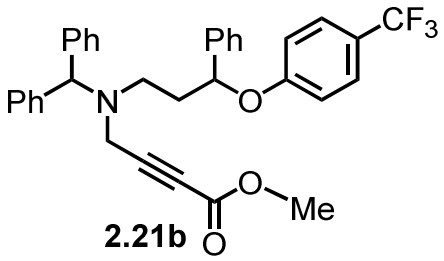
2.21b

^{13}C NMR (126 MHz, $CDCl_3$)



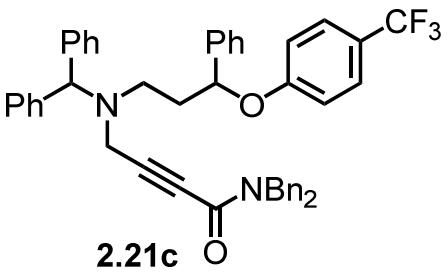
2.21b

^{19}F NMR (470 MHz, $CDCl_3$)

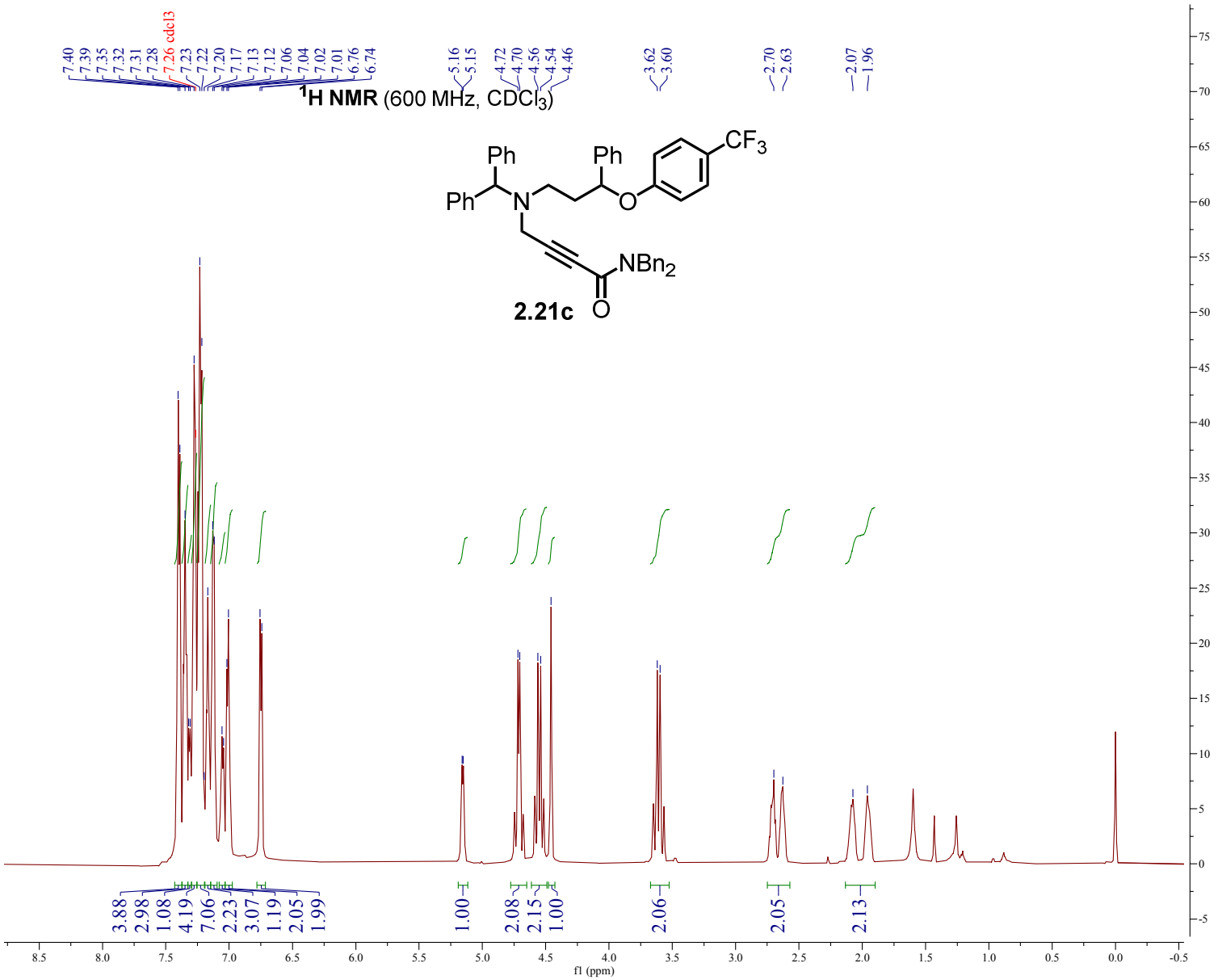


2.21b

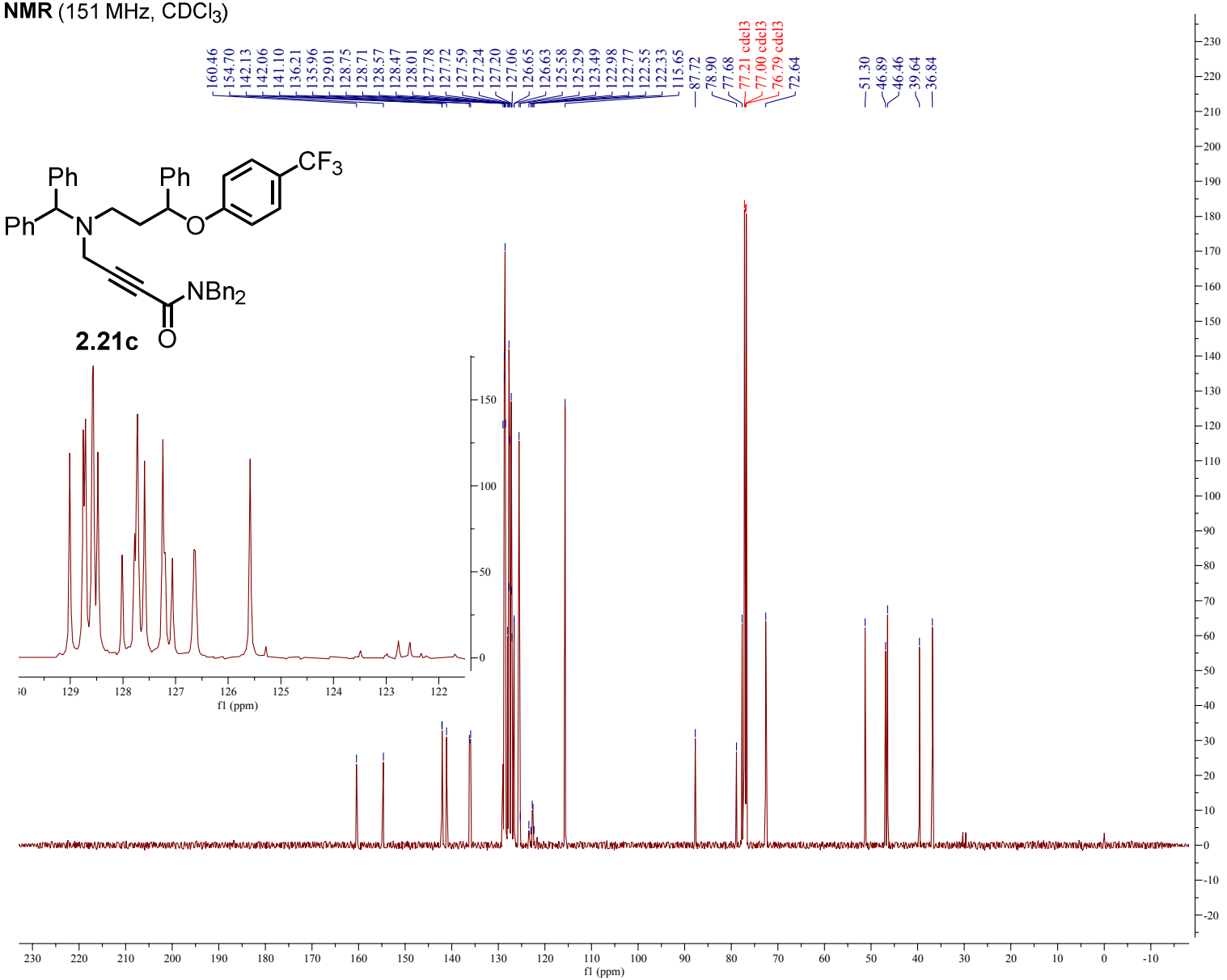
^{1}H NMR (600 MHz, $CDCl_3$)



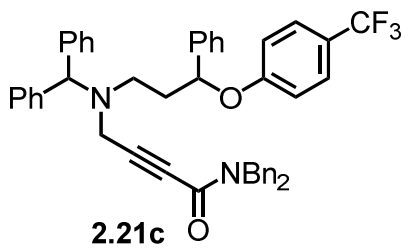
2.21c


7.40
7.39
7.35
7.32
7.31
7.28
7.26 cdcl3
7.23
7.22
7.20
7.17
7.13
7.12
7.06
7.04
7.02
7.01
6.76
6.74
5.16
5.15
4.72
4.70
4.56
4.54
4.46
3.62
3.60
2.70
2.63
2.07
1.96
1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
NBn2
O
2.21c
3.88
2.98
1.08
4.19
7.06
2.23
3.07
1.19
2.05
1.99
1.00
2.08
2.15
1.00
2.06
2.05
2.13
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)

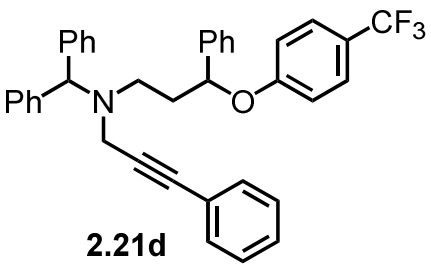


^{19}F NMR (470 MHz, $CDCl_3$)

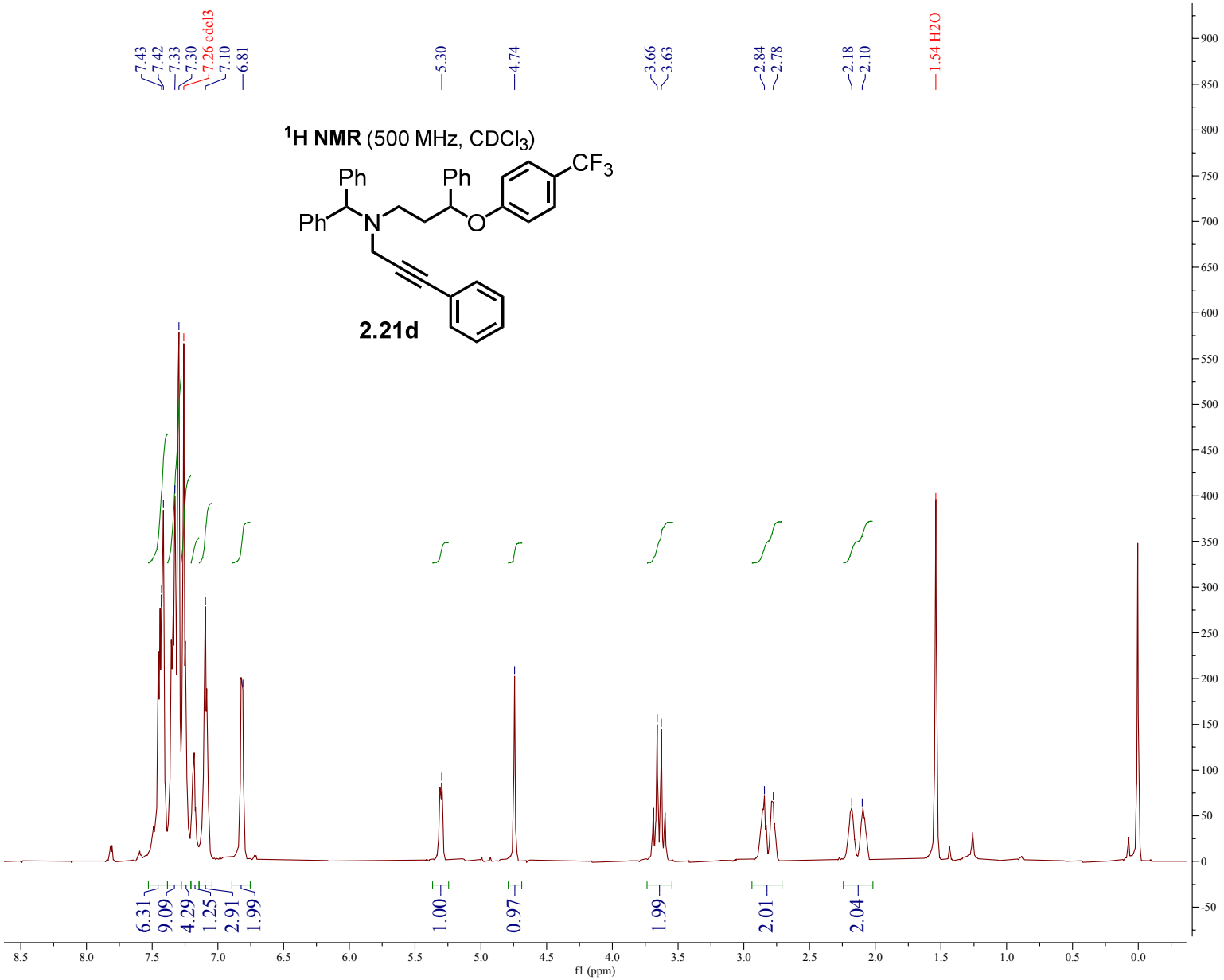


2.21c

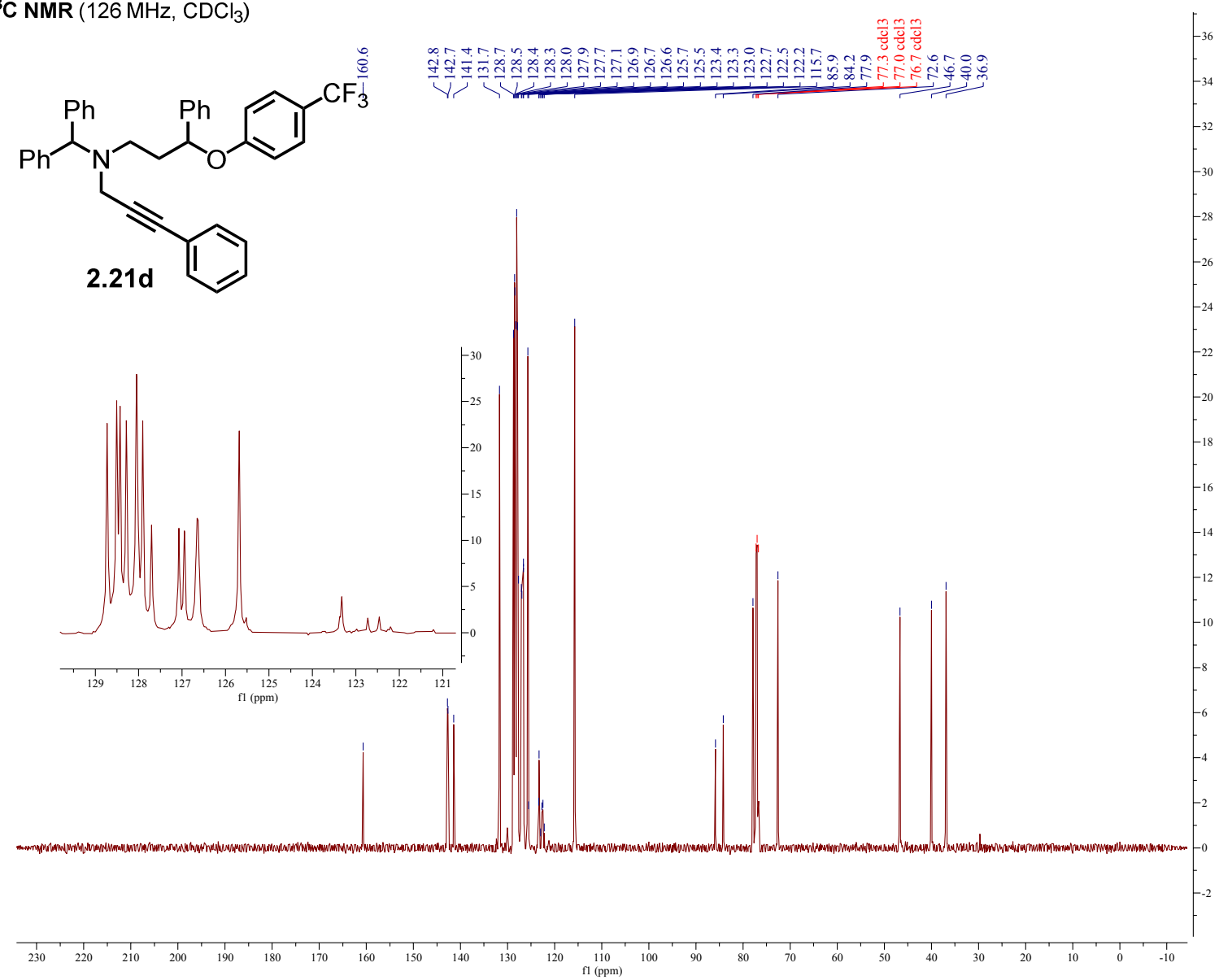
^{1}H NMR (500 MHz, $CDCl_3$)



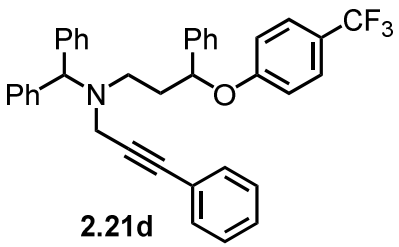
2.21d


7.43
7.42
7.33
7.30
7.26 cdcl3
7.10
6.81
5.30
4.74
3.66
3.63
2.84
2.78
2.18
2.10
1.54 H2O
1H NMR (500 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
2.21d
6.31
9.09
4.29
1.25
2.91
1.99
1.00
0.97
1.99
2.01
2.04
f1 (ppm)

^{13}C NMR (126 MHz, $CDCl_3$)

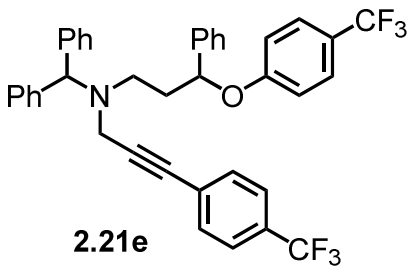


^{19}F NMR (470 MHz, $CDCl_3$)

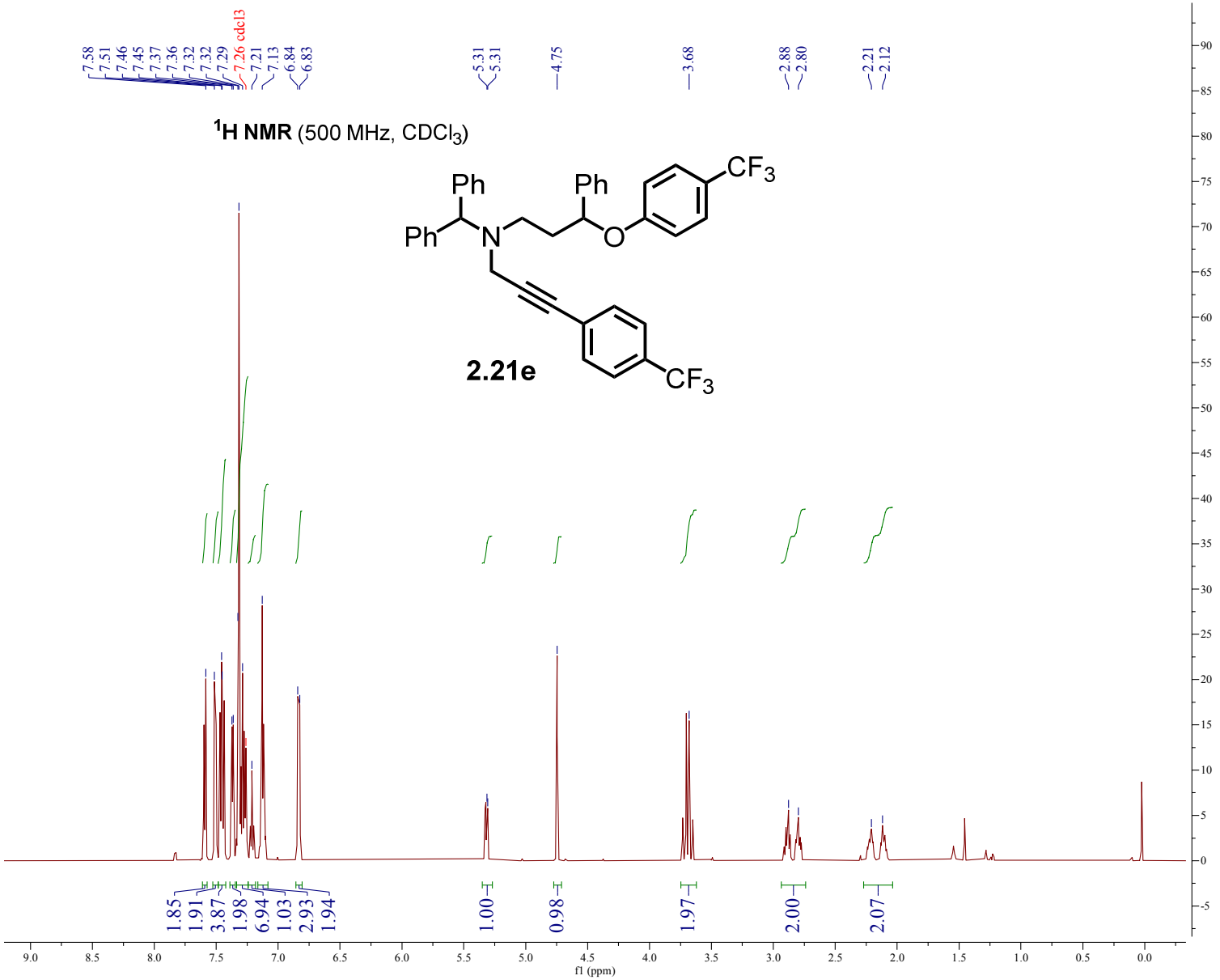


2.21d

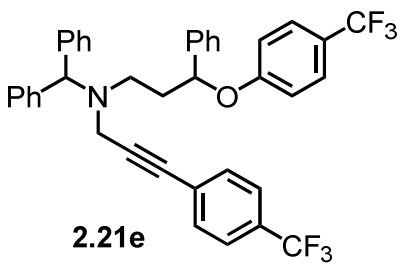
^{1}H NMR (500 MHz, $CDCl_3$)



2.21e

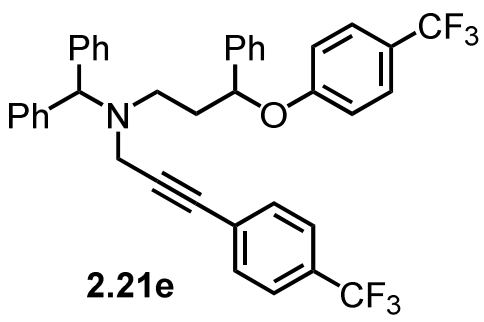

7.58
7.51
7.46
7.45
7.37
7.36
7.32
7.32
7.29
7.26 cdcl3
7.21
7.13
6.84
6.83
5.31
5.31
4.75
3.68
2.88
2.80
2.21
2.12
1H NMR (500 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
CF3
2.21e
1.85
1.91
3.87
1.98
6.94
1.03
2.93
1.94
1.00
0.98
1.97
2.00
2.07
f1 (ppm)

^{13}C NMR (126 MHz, $CDCl_3$)



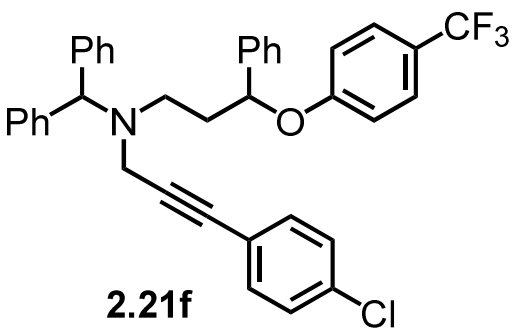
2.21e

^{19}F NMR (470 MHz, $CDCl_3$)

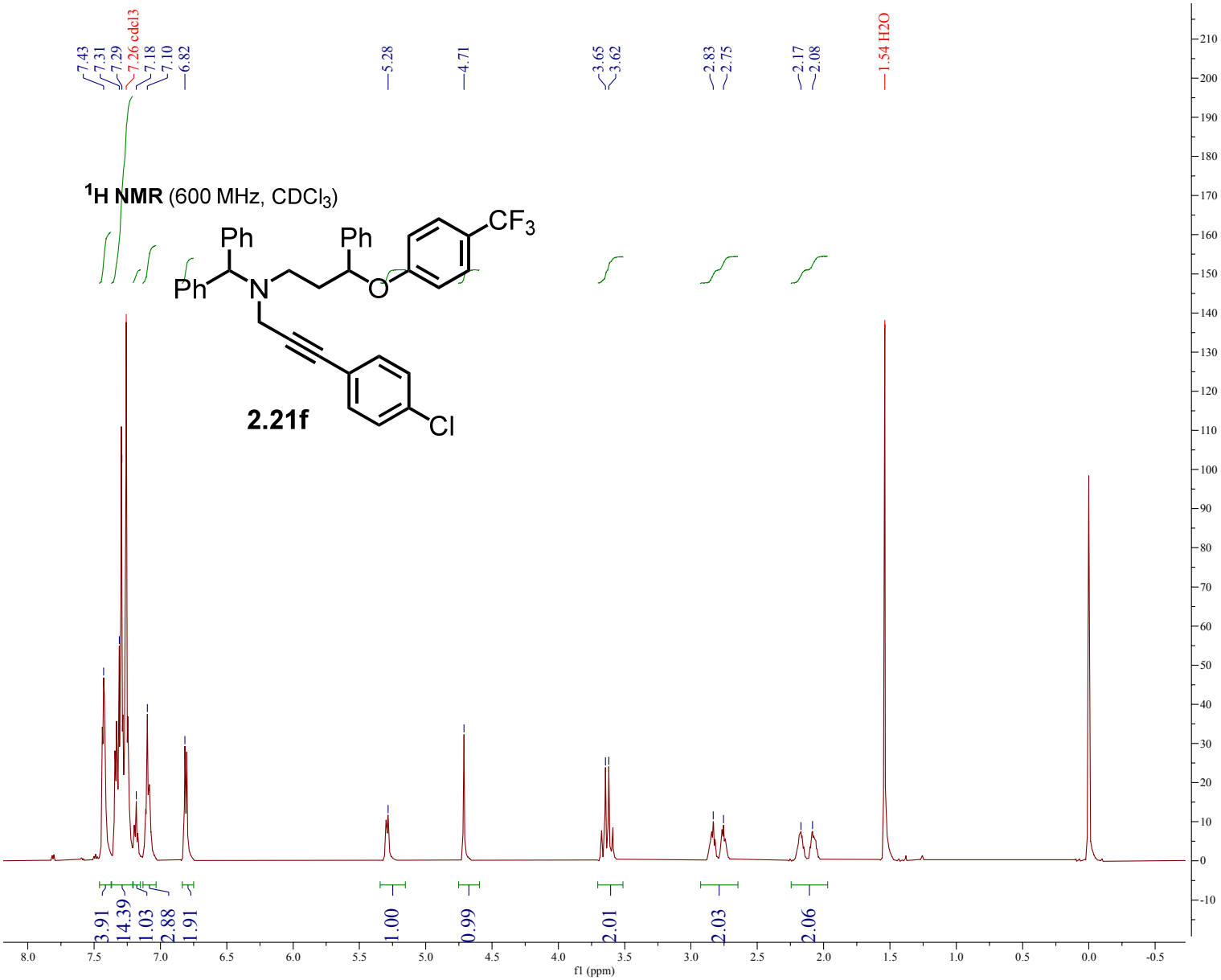


2.21e

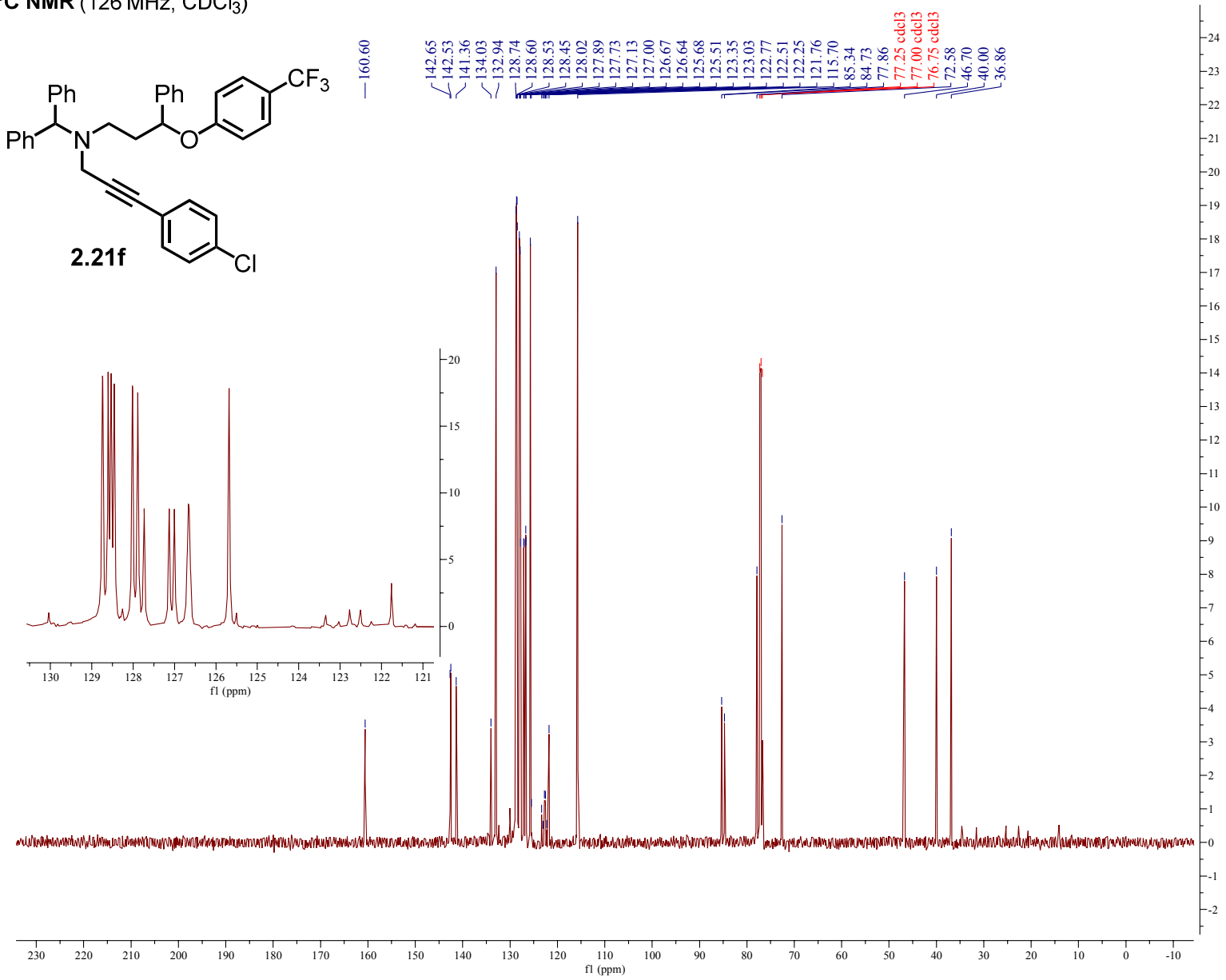
^{1}H NMR (600 MHz, $CDCl_3$)



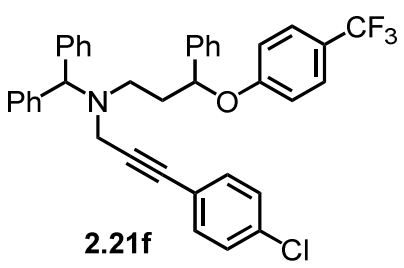
2.21f


7.43
7.31
7.29
7.26 cdcl3
7.18
7.10
6.82
5.28
4.71
3.65
3.62
2.83
2.75
2.17
2.08
1.54 H2O
1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
Cl
2.21f
3.91
14.39
1.03
2.88
1.91
1.00
0.99
2.01
2.03
2.06
f1 (ppm)

^{13}C NMR (126 MHz, $CDCl_3$)

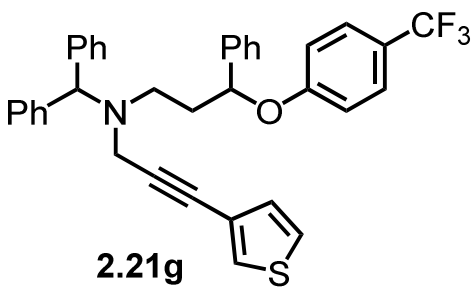


^{19}F NMR (470 MHz, $CDCl_3$)

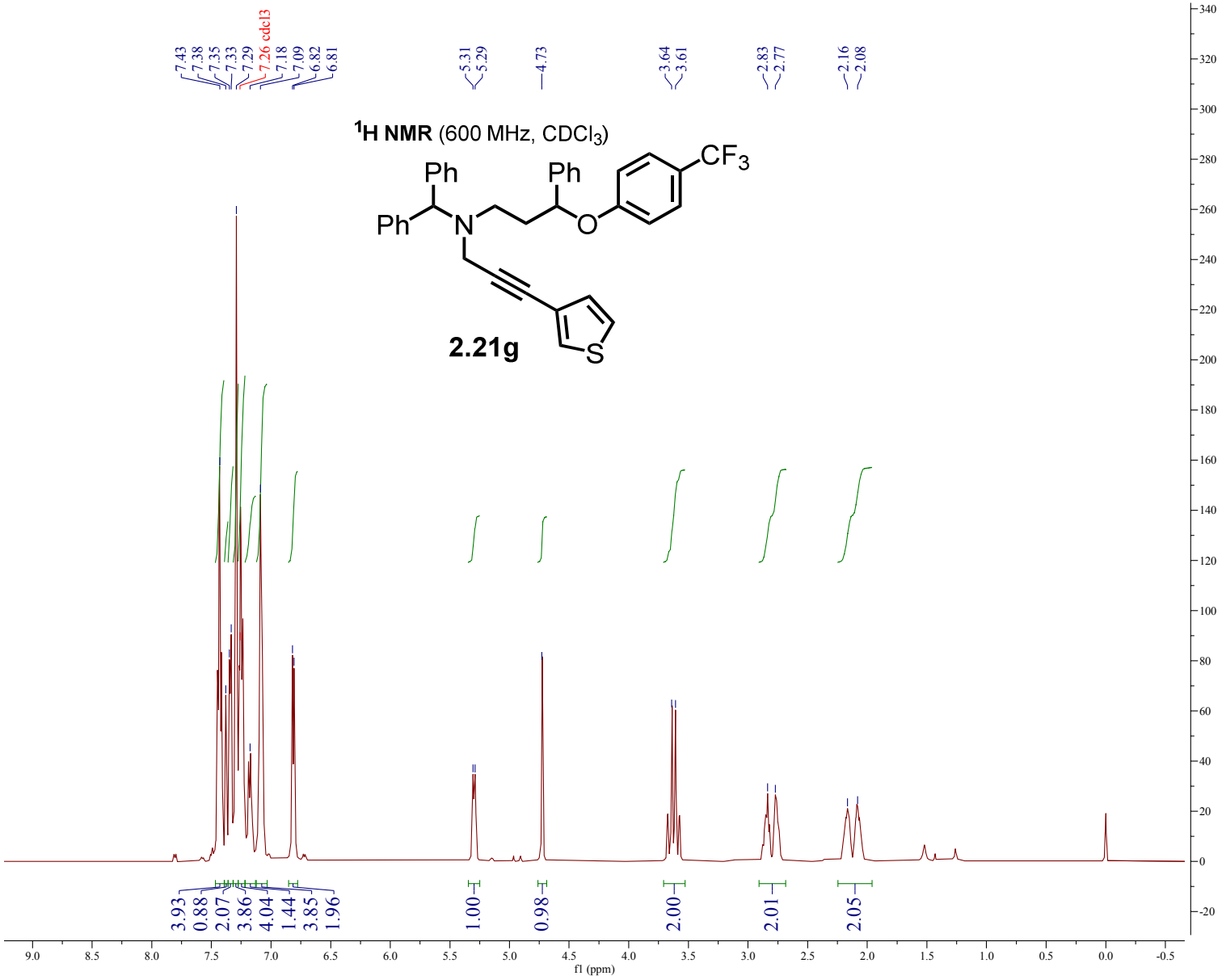


2.21f

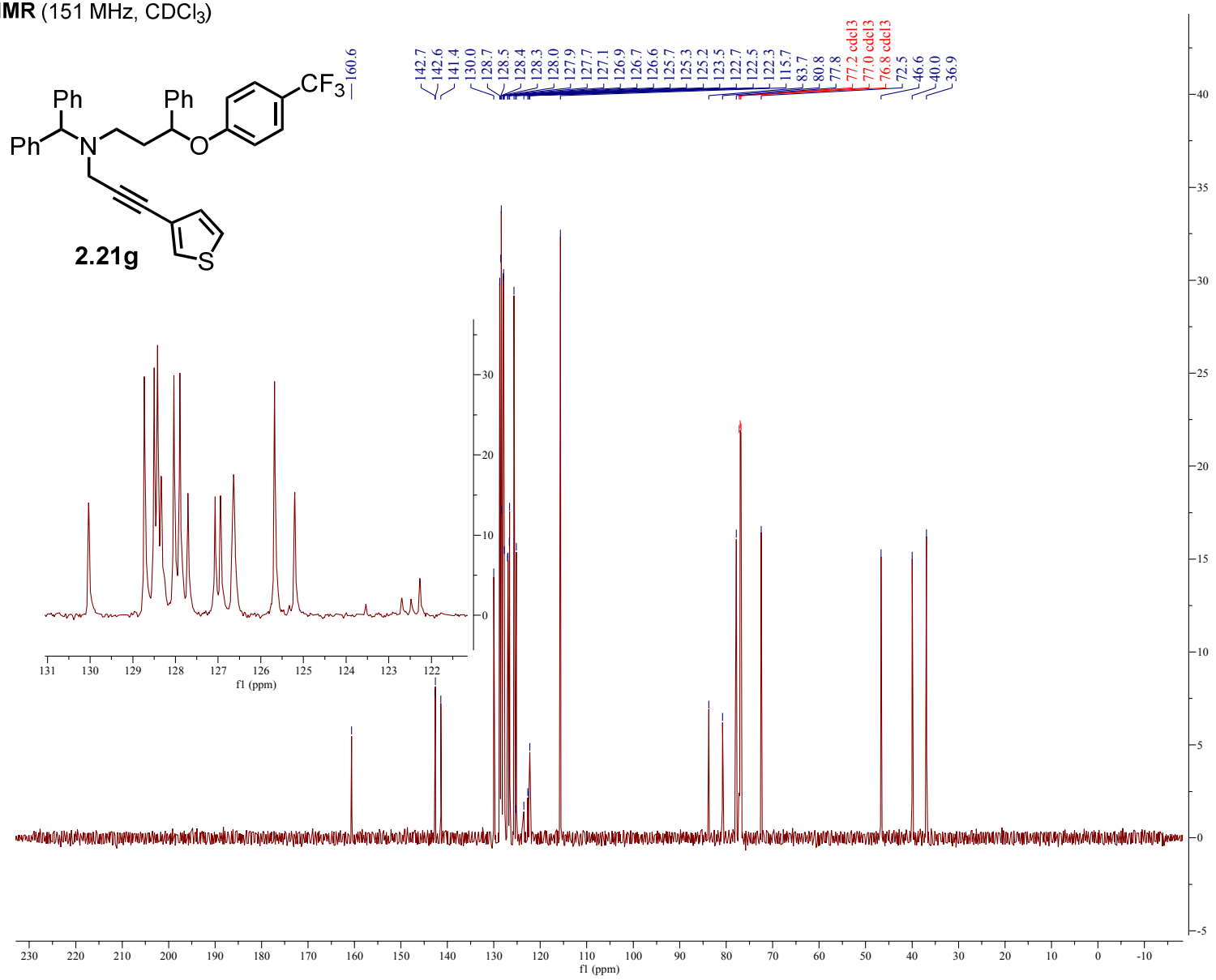
^{1}H NMR (600 MHz, $CDCl_3$)



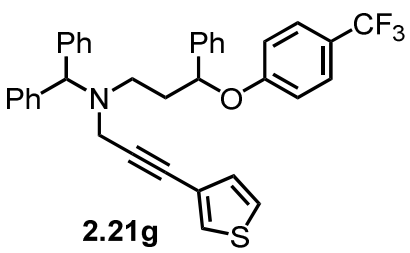
2.21g


7.43
7.38
7.35
7.33
7.29
7.26 cdcl3
7.18
7.09
6.82
6.81
5.31
5.29
4.73
3.64
3.61
2.83
2.77
2.16
2.08
1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
S
2.21g
3.93
0.88
2.07
3.86
4.04
1.44
3.85
1.96
1.00
0.98
2.00
2.01
2.05
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)

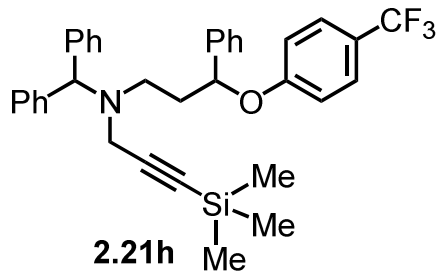


^{19}F NMR (470 MHz, $CDCl_3$)

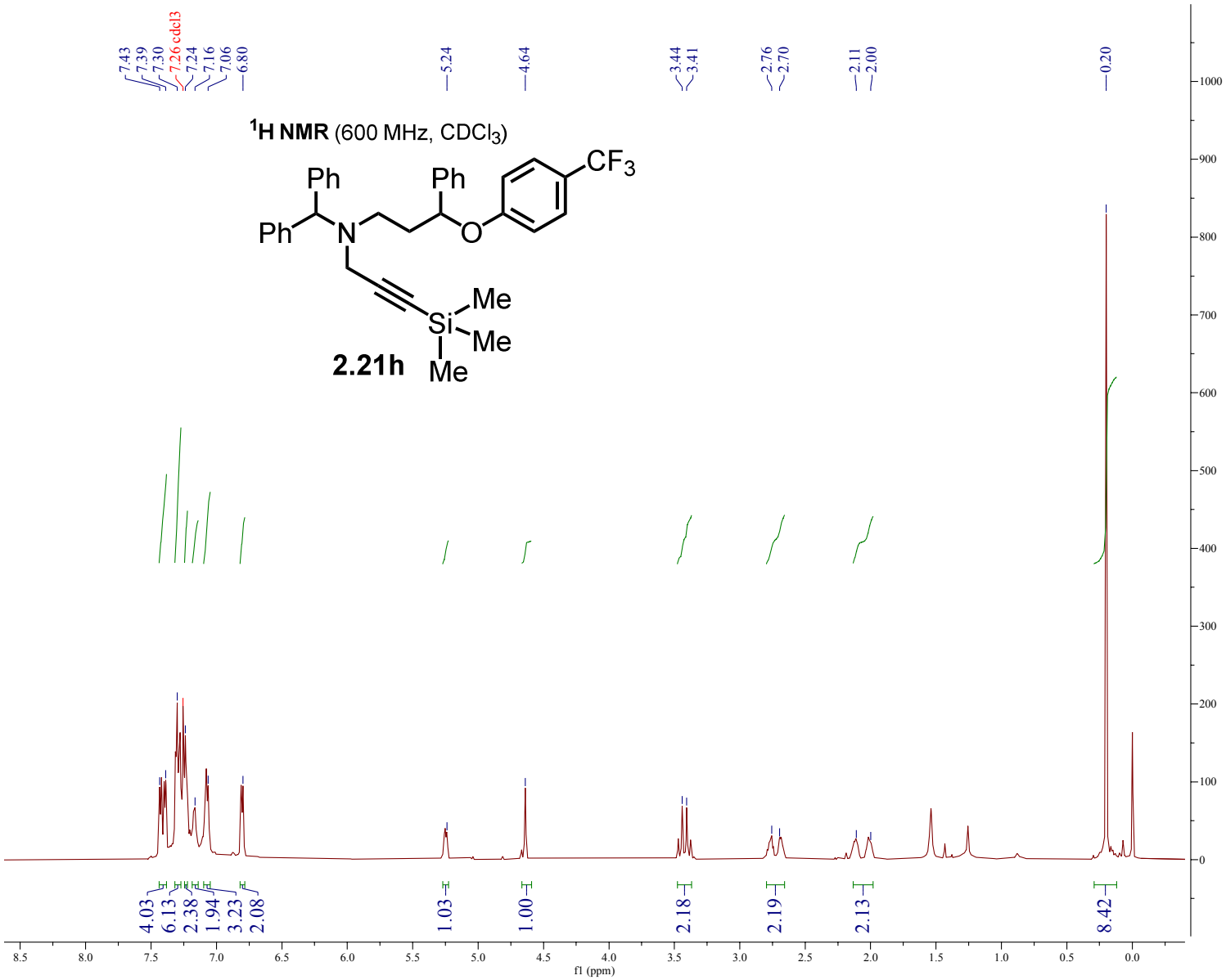


2.21g

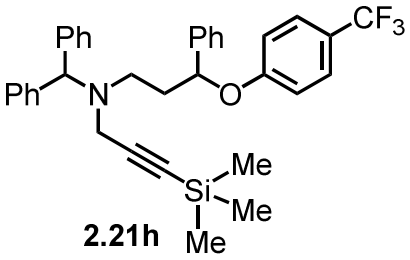
^{1}H NMR (600 MHz, $CDCl_3$)



2.21h

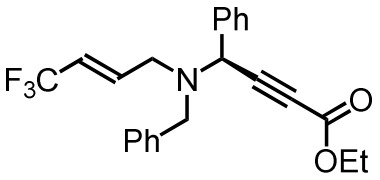

7.43
7.39
7.30
7.26 cdcl3
7.24
7.16
7.06
6.80
5.24
4.64
3.44
3.41
2.76
2.70
2.11
2.00
0.20
1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
Si
Me
Me
Me
2.21h
4.03
6.13
2.38
1.94
3.23
2.08
1.03
1.00
2.18
2.19
2.13
8.42
f1 (ppm)

^{19}F NMR (470 MHz, $CDCl_3$)

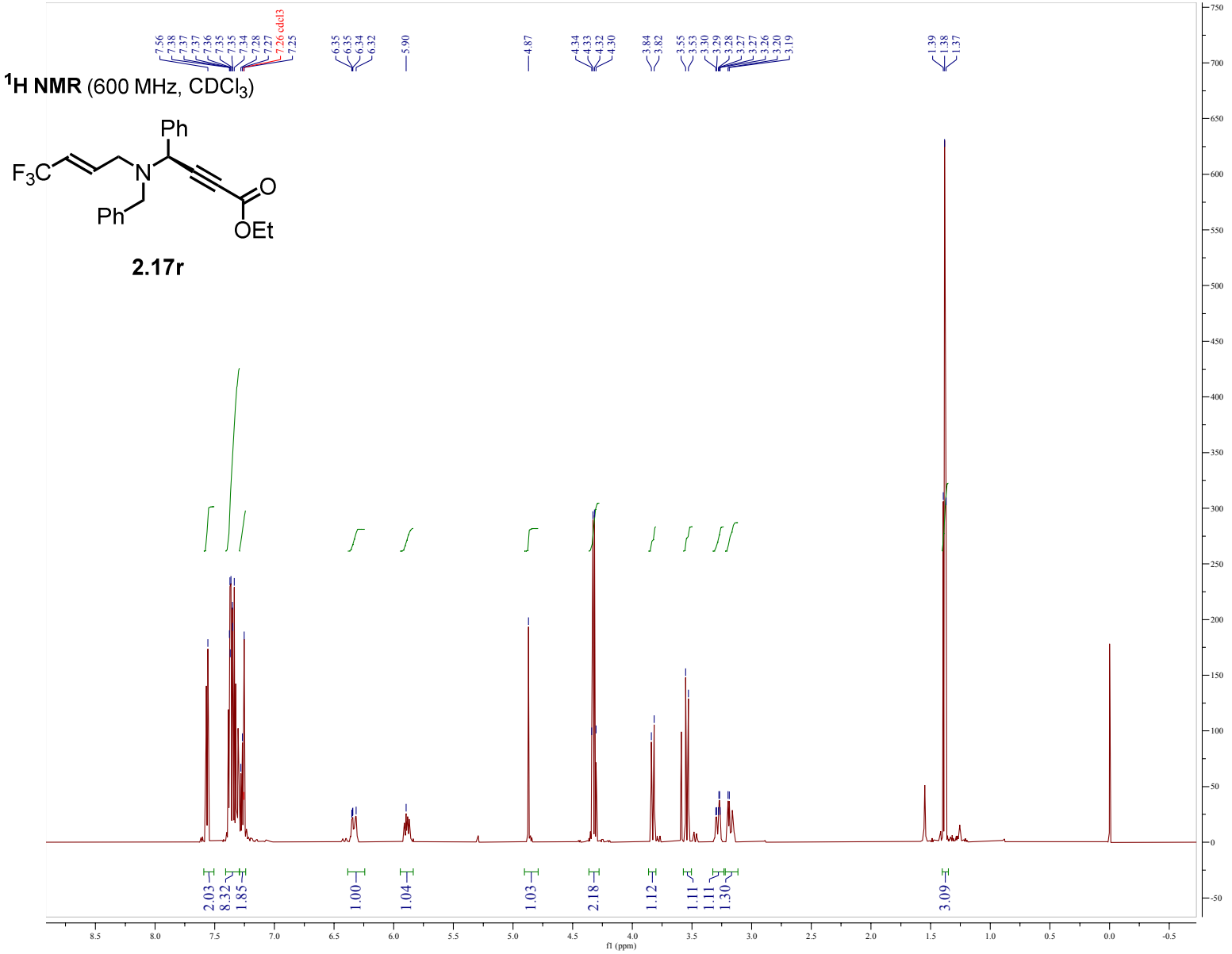


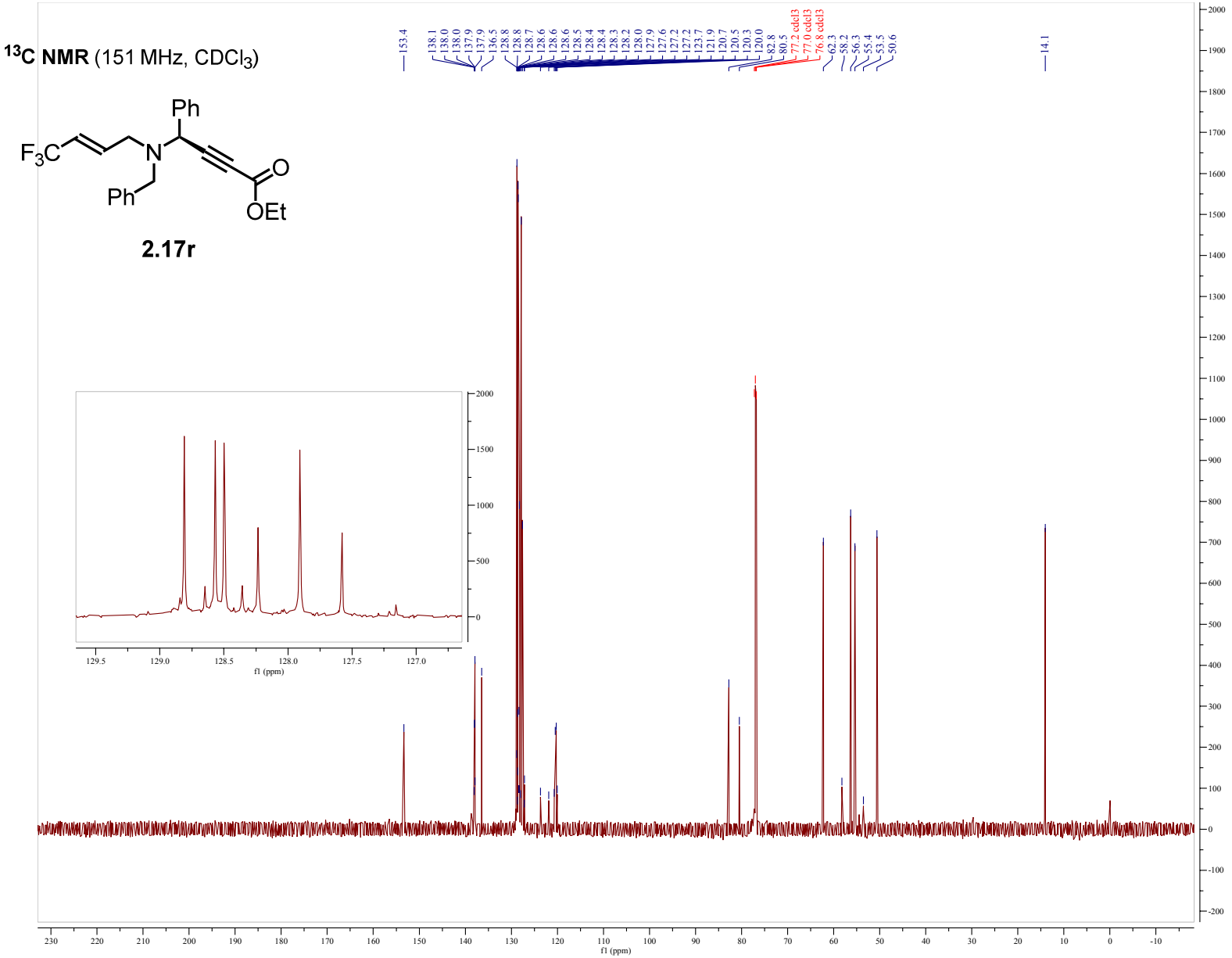
2.21h

^{1}H NMR (600 MHz, $CDCl_3$)

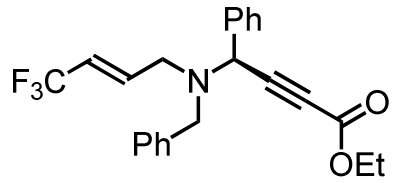


2.17r


1H NMR (600 MHz, CDCl3)
Ph
F3C
N
O
Ph
OEt
2.17r
7.56
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.28
7.27
7.26 cdcl3
7.25
6.35
6.35
6.34
6.32
5.90
4.87
4.34
4.33
4.32
4.30
3.84
3.82
3.55
3.53
3.30
3.29
3.28
3.27
3.27
3.26
3.20
3.19
1.39
1.38
1.37
2.03
8.32
1.85
1.00
1.04
1.03
2.18
1.12
1.11
1.11
1.30
3.09
f1 (ppm)

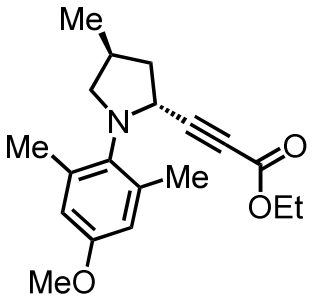

13C NMR (151 MHz, CDCl3)
Ph
F3C
N
O
Ph
OEt
2.17r
153.4
138.1
138.0
138.0
137.9
137.9
136.5
128.8
128.8
128.7
128.6
128.6
128.6
128.5
128.4
128.4
128.3
128.2
128.0
127.9
127.6
127.2
127.2
123.7
121.9
120.7
120.5
120.3
120.0
82.8
80.5
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
62.3
58.2
56.3
55.4
53.5
50.6
14.1
f1 (ppm)

^{19}F NMR (564 MHz, $CDCl_3$)



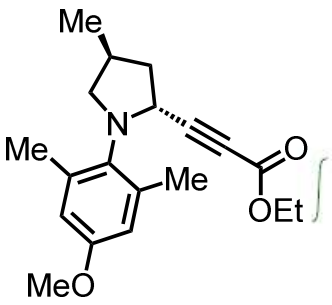
2.17r

^{1}H NMR (600 MHz, $CDCl_3$)



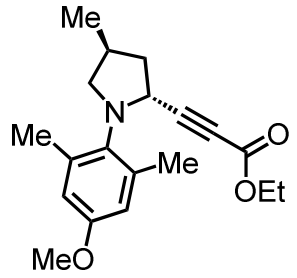
2.17s-*trans*

^{1}H NMR (600 MHz, $CDCl_3$)



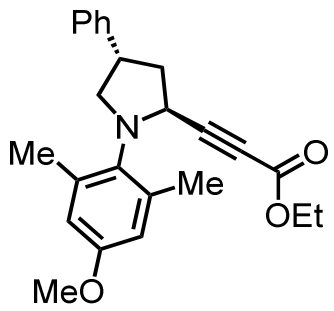
2.17s-*trans*

^{13}C NMR (151 MHz, $CDCl_3$)



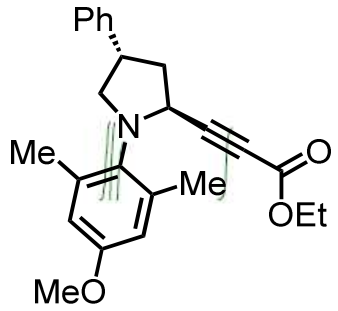
2.17s-*trans*

^{1}H NMR (600 MHz, $CDCl_3$)



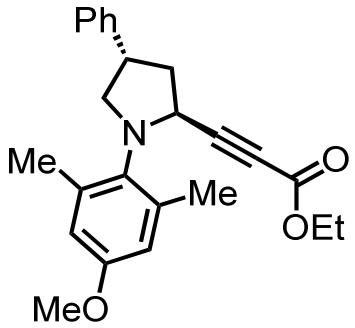
2.17t-*trans*

^{1}H NMR (600 MHz, $CDCl_3$)



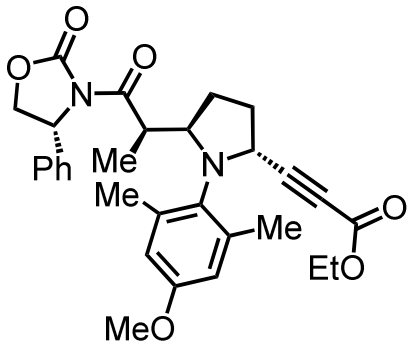
2.17t-*trans*

^{13}C NMR (151 MHz, $CDCl_3$)

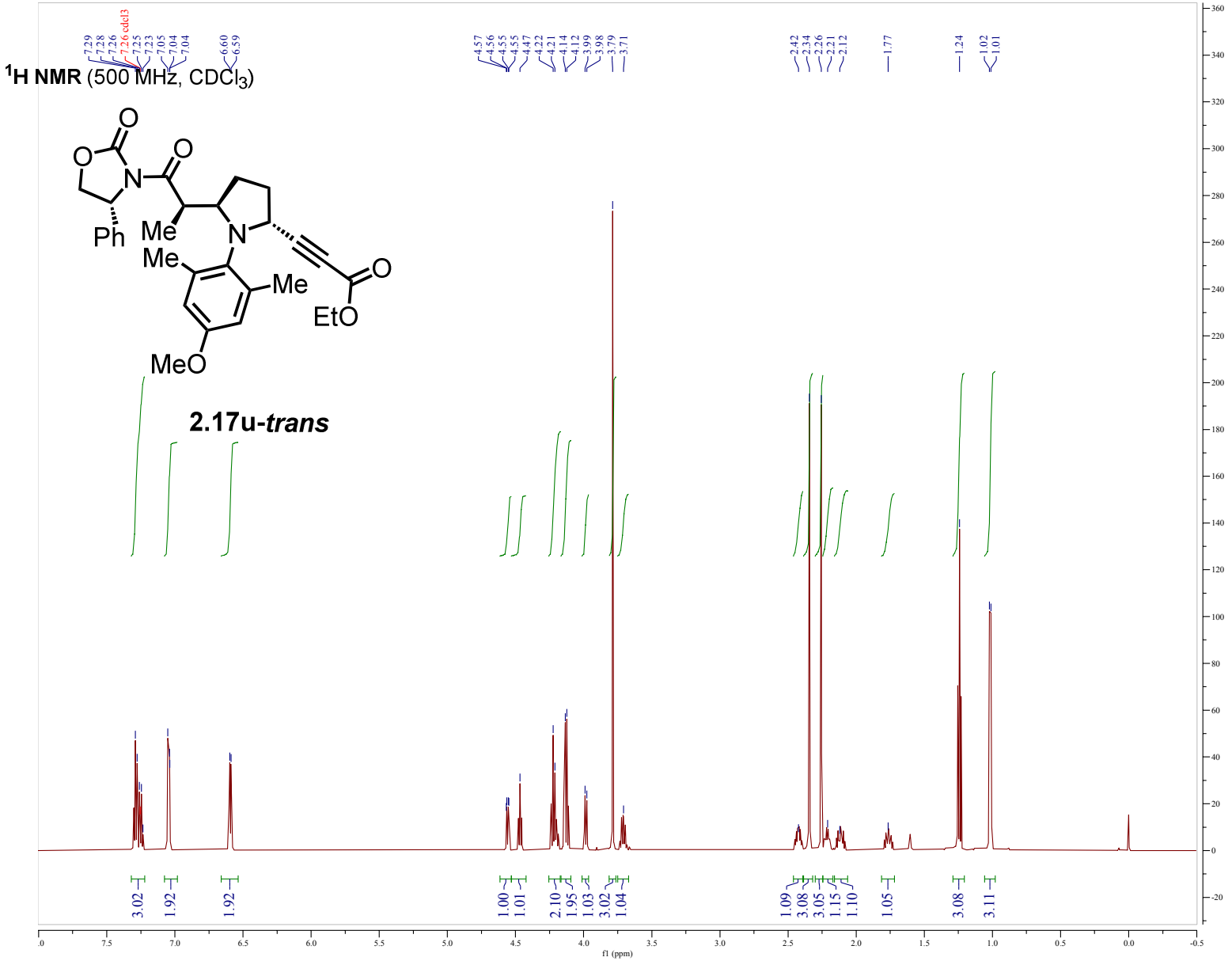


2.17t-*trans*

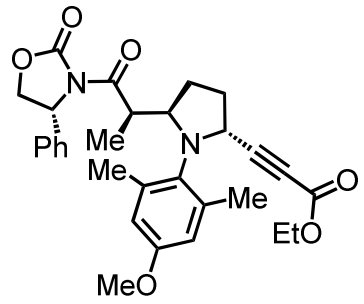
^{1}H NMR (500 MHz, $CDCl_3$)



2.17u-*trans*

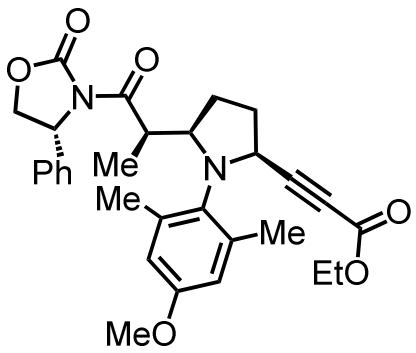

1H NMR (500 MHz, CDCl3)
2.17u-trans
Ph
Me
Me
Me
MeO
EtO
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)

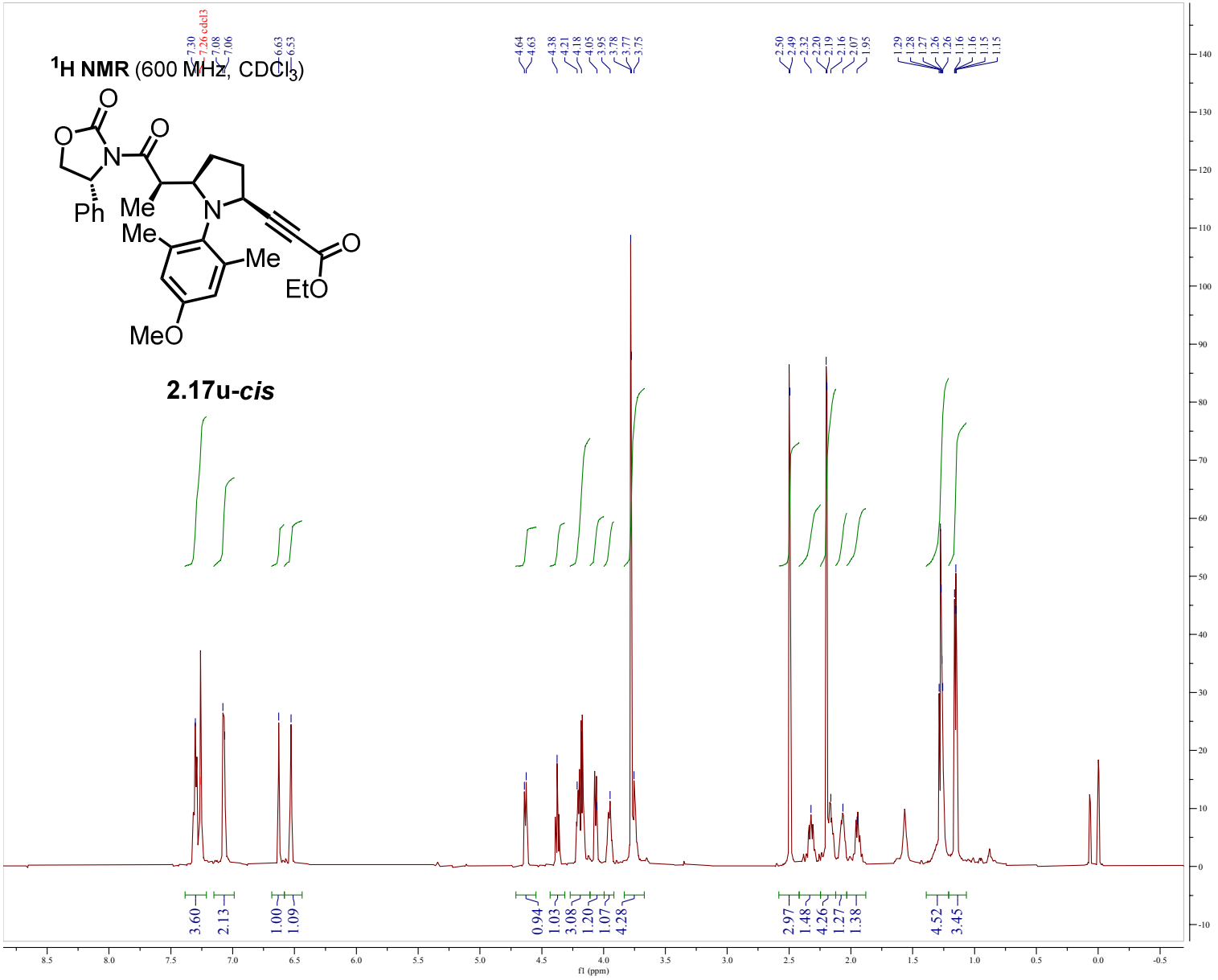


2.17u-*trans*

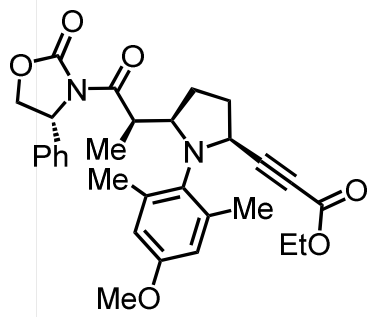
^{1}H NMR (600 MHz, $CDCl_3$)



2.17u-*cis*

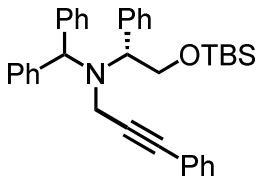

^{1}H NMR (600 MHz, $CDCl_3$)
2.17u-*cis*
Ph
Me
Me
Me
MeO
EtO
7.30
7.26 cdcl3
7.08
7.06
6.63
6.53
4.64
4.63
4.38
4.21
4.18
4.05
3.95
3.78
3.77
3.75
2.50
2.49
2.32
2.20
2.19
2.16
2.07
1.95
1.29
1.28
1.27
1.26
1.26
1.16
1.16
1.15
1.15
3.60
2.13
1.00
1.09
0.94
1.03
3.08
1.20
1.07
4.28
2.97
1.48
4.26
1.27
1.38
4.52
3.45
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)

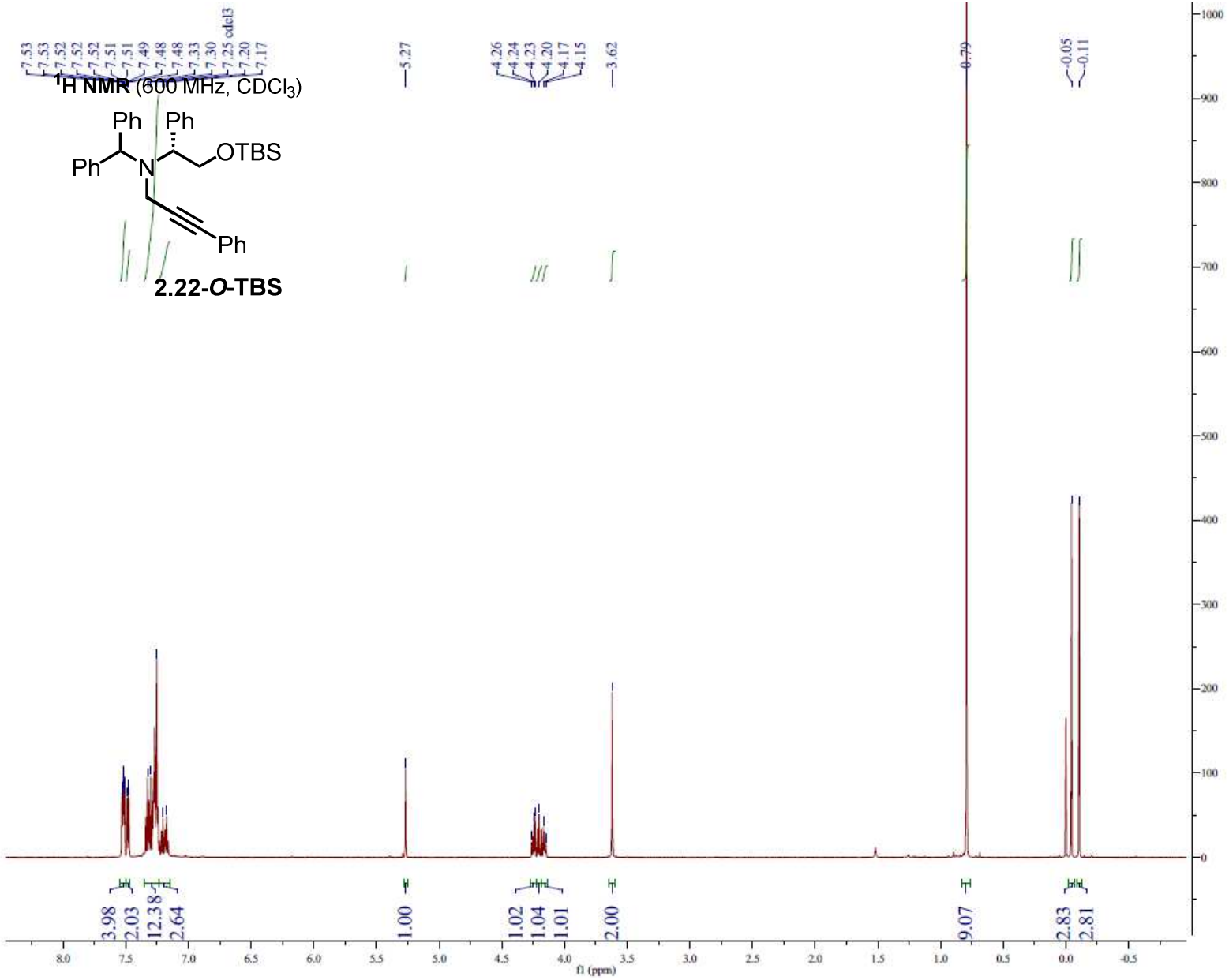


2.17u-*cis*

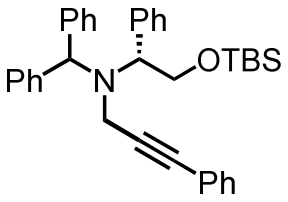
^{1}H NMR (600 MHz, $CDCl_3$)



2.22-*O*-TBS

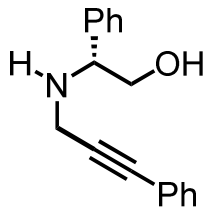

7.53
7.53
7.52
7.52
7.52
7.51
7.51
7.49
7.48
7.48
7.33
7.30
7.25 cdcl3
7.20
7.17
5.27
4.26
4.24
4.23
4.20
4.17
4.15
3.62
0.79
0.05
0.11
1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
OTBS
Ph
2.22-O-TBS
3.98
2.03
12.38
2.64
1.00
1.02
1.04
1.01
2.00
9.07
2.83
2.81
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)

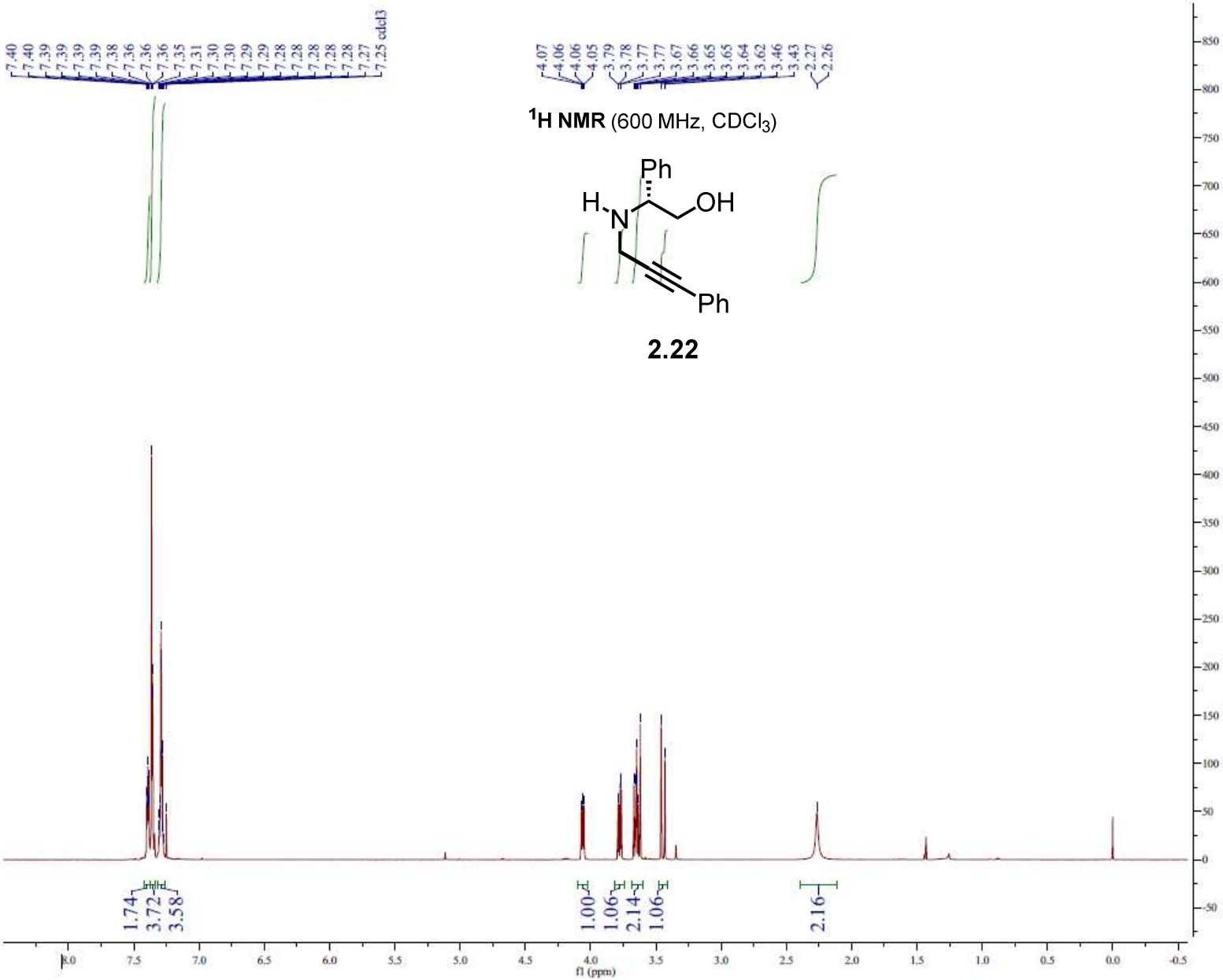


2.22-*O*-TBS

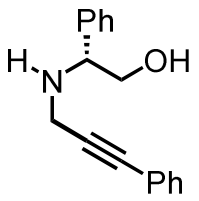
^{1}H NMR (600 MHz, $CDCl_3$)



2.22

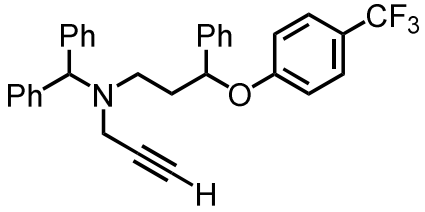

7.40
7.40
7.39
7.39
7.39
7.39
7.38
7.36
7.36
7.36
7.35
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.28
7.28
7.28
7.27
7.25 cdcl3
4.07
4.06
4.06
4.05
3.79
3.78
3.77
3.77
3.67
3.66
3.65
3.65
3.64
3.62
3.46
3.43
2.27
2.26
1H NMR (600 MHz, CDCl3)
Ph
H
N
OH
Ph
2.22
1.74
3.72
3.58
1.00
1.06
2.14
1.06
2.16
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)

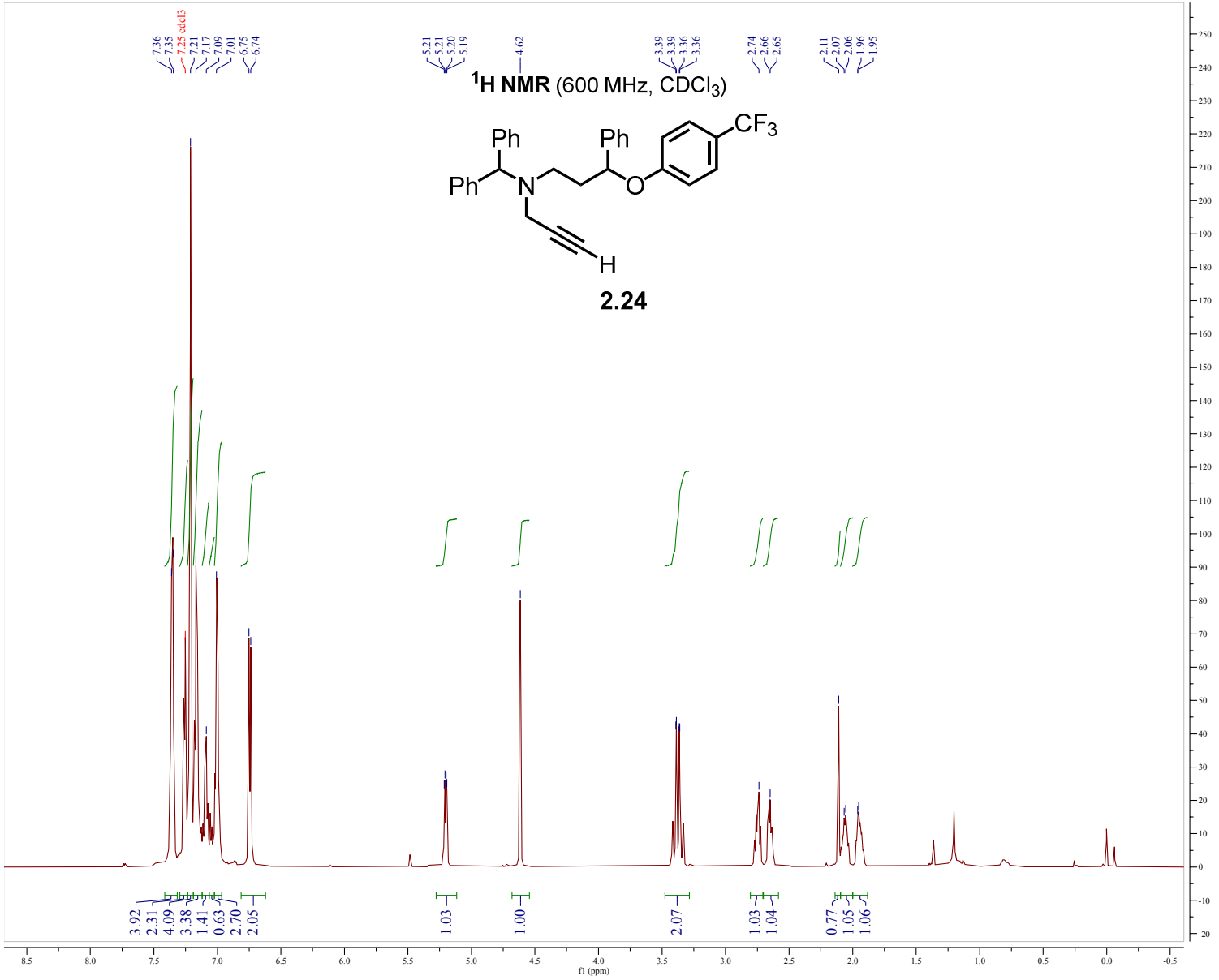


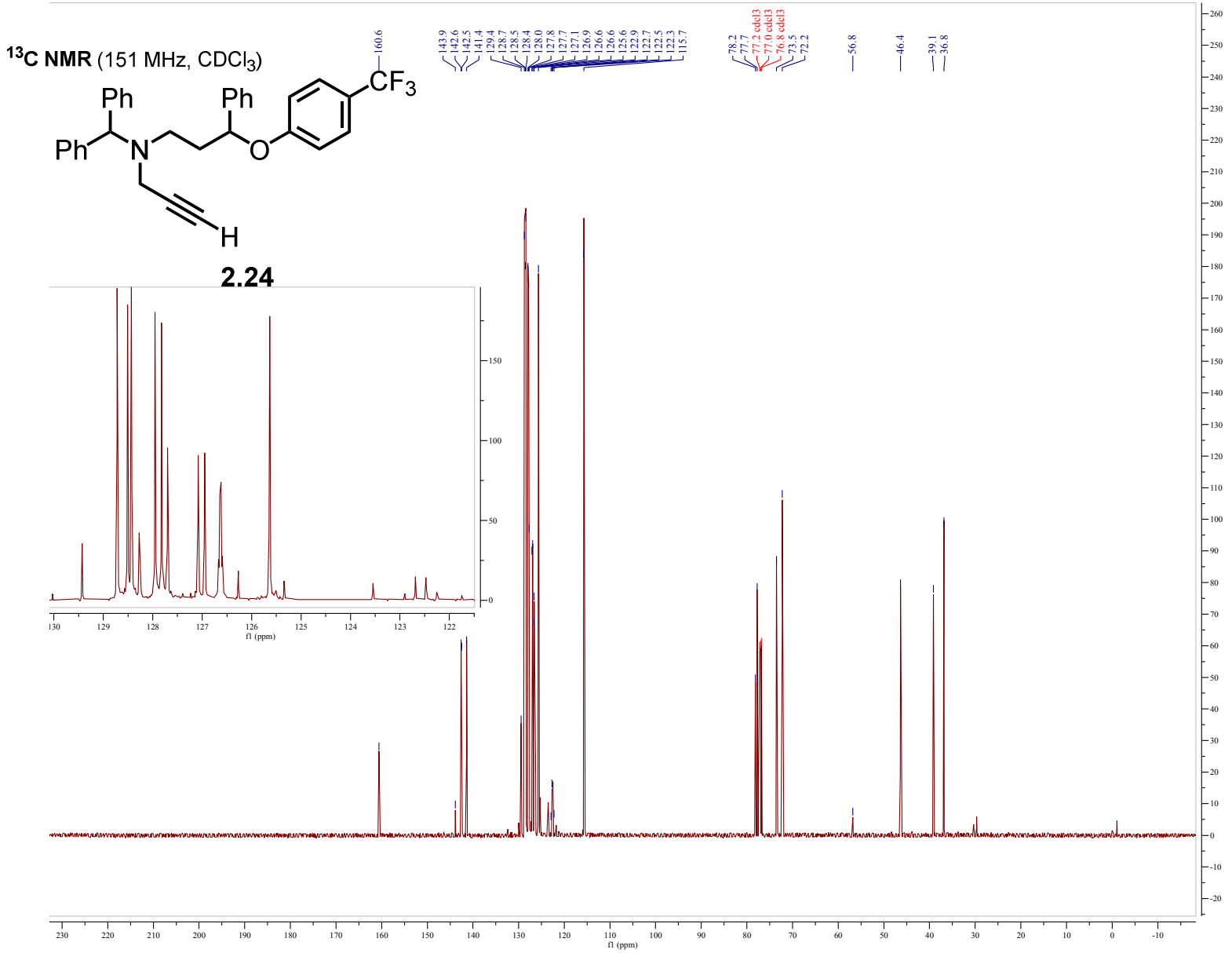
2.22

^{1}H NMR (600 MHz, $CDCl_3$)

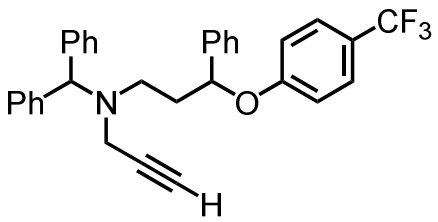


2.24


7.36
7.35
7.25 cdcl3
7.21
7.17
7.09
7.01
6.75
6.74
5.21
5.21
5.20
5.19
4.62
3.39
3.39
3.36
3.36
2.74
2.66
2.65
2.11
2.07
2.06
1.96
1.95
1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
H
2.24
3.92
2.31
4.09
3.38
1.41
0.63
2.70
2.05
1.03
1.00
2.07
1.03
1.04
0.77
1.05
1.06
f1 (ppm)

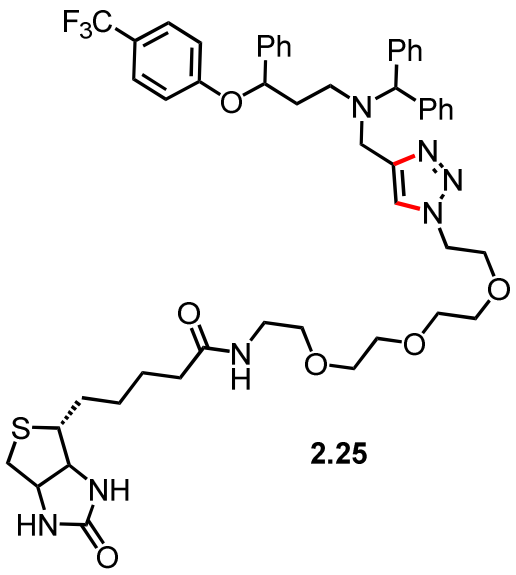

13C NMR (151 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
H
2.24
160.6
143.9
142.6
142.5
141.4
129.4
128.7
128.5
128.4
128.0
127.8
127.7
127.1
126.9
126.6
126.6
125.6
122.9
122.7
122.5
122.3
115.7
78.2
77.7
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
73.5
72.2
56.8
46.4
39.1
36.8
f1 (ppm)

^{19}F NMR (470 MHz, $CDCl_3$)

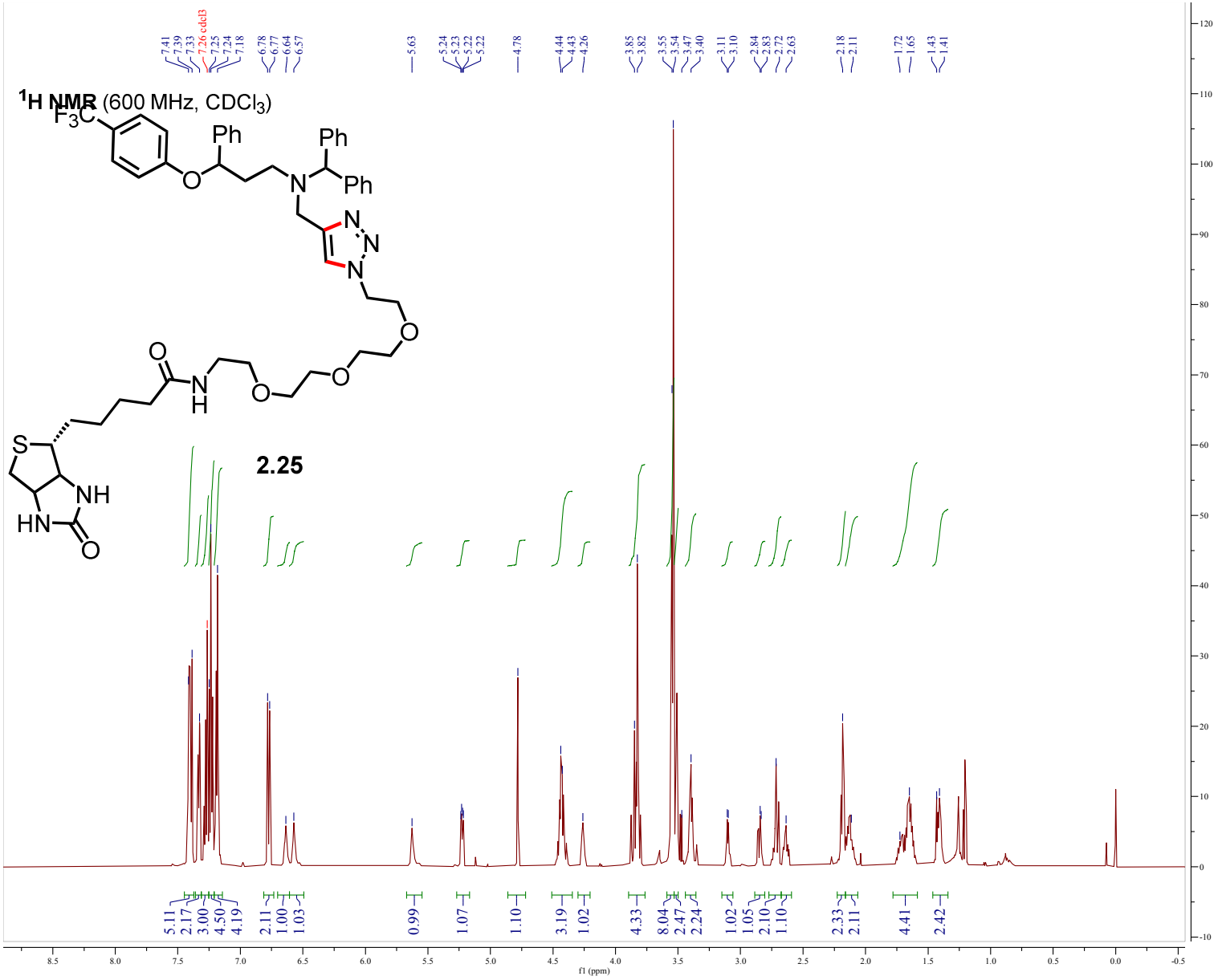


2.24

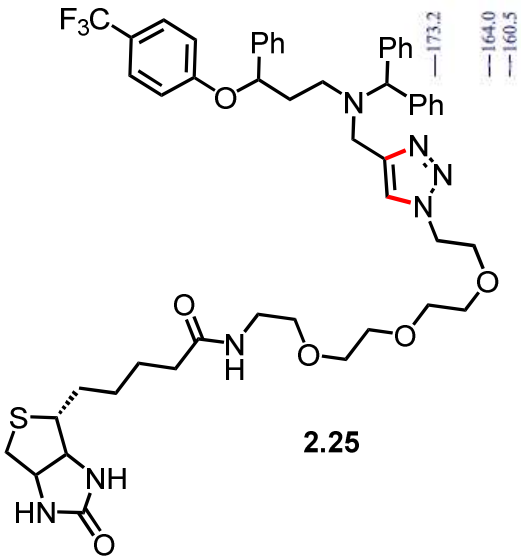
^{1}H NMR (600 MHz, $CDCl_3$)



2.25

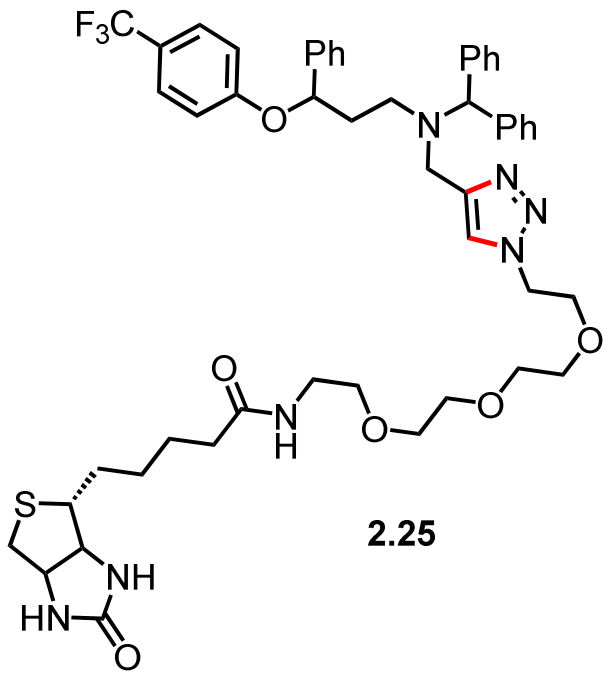

7.41
7.39
7.33
7.26 cdcl3
7.25
7.24
7.18
6.78
6.77
6.64
6.57
5.63
5.24
5.23
5.22
5.22
4.78
4.44
4.43
4.26
3.85
3.82
3.55
3.54
3.47
3.40
3.11
3.10
2.84
2.83
2.72
2.63
2.18
2.11
1.72
1.65
1.43
1.41
1H NMR (600 MHz, CDCl3)
F3C
Ph
Ph
Ph
O
N
N
N
N
O
O
O
O
N
H
S
NH
HN
O
2.25
5.11
2.17
3.00
4.50
4.19
2.11
1.00
1.03
0.99
1.07
1.10
3.19
1.02
4.33
8.04
2.47
2.24
1.02
1.05
2.10
1.10
2.33
2.11
4.41
2.42
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)



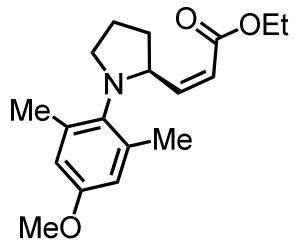
2.25

^{19}F NMR (470 MHz, $CDCl_3$)



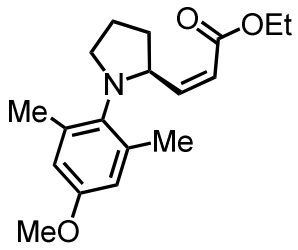
2.25

^{1}H NMR (600 MHz, $CDCl_3$)



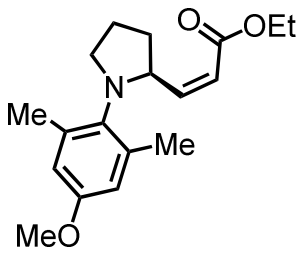
2.23a

^{1}H NMR (600 MHz, $CDCl_3$)



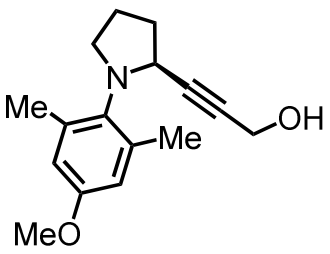
2.23a

^{13}C NMR (151 MHz, $CDCl_3$)



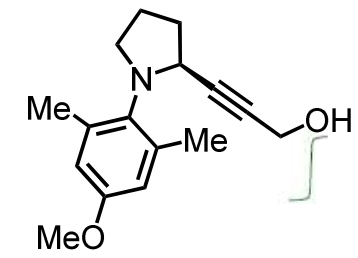
2.23a

^{1}H NMR (600 MHz, $CDCl_3$)



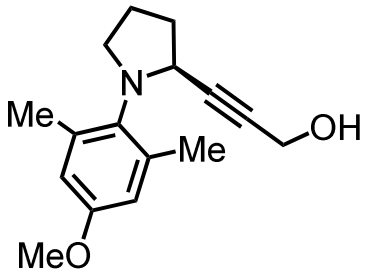
2.23b

^{1}H NMR (600 MHz, $CDCl_3$)



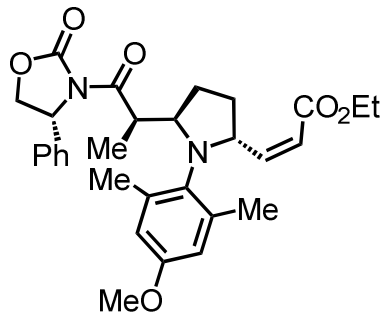
2.23b

^{13}C NMR (126 MHz, $CDCl_3$)

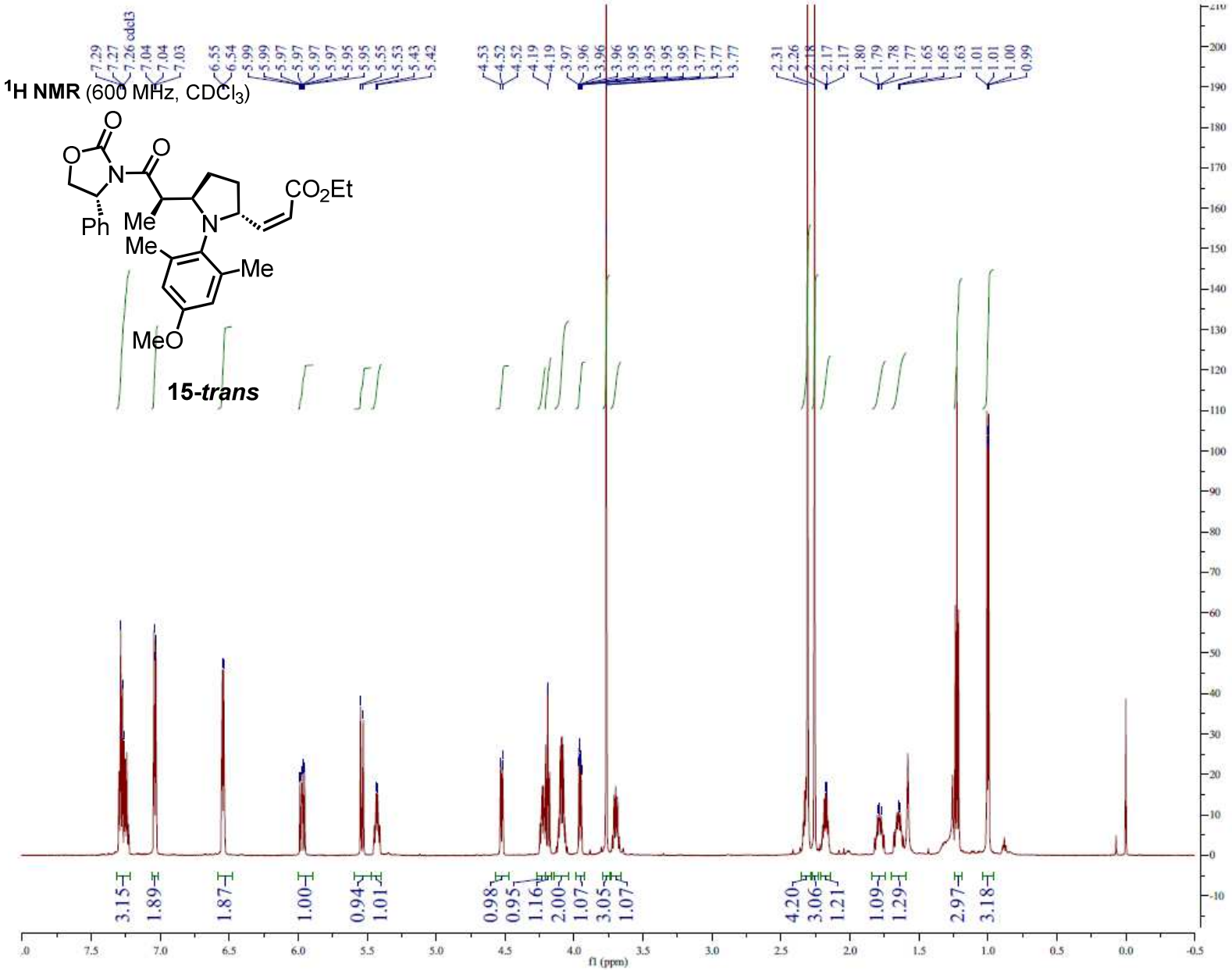


2.23b

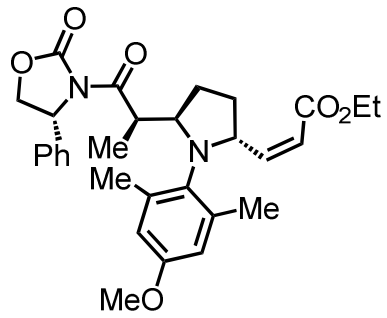
^{1}H NMR (600 MHz, $CDCl_3$)



15-*trans*


1H NMR (600 MHz, CDCl3)
15-trans
Ph
Me
Me
Me
MeO
CO2Et
f1 (ppm)

^{13}C NMR (156 MHz, $CDCl_3$)



15-*trans*

A9. X-Ray Crystallography Data

Table S1.15. Crystal data and structure refinement for $C_{23}H_{25}BrN_2O_3$.

Identification code	$C_{23}H_{25}BrN_2O_3$	
Empirical formula	C23 H25 Br N2 O3	
Formula weight	457.36	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 31.9630(17) Å	α= 90°.
	b = 9.8050(5) Å	β= 112.711(3)°.
	c = 15.0555(8) Å	γ = 90°.
Volume	4352.5(4) $Å^3$	
Z	8	
Density (calculated)	1.396 Mg/m^3	
Absorption coefficient	2.783 mm^{-1}	
F(000)	1888	
Crystal size	0.480 x 0.180 x 0.100 mm^3	
Theta range for data collection	2.997 to 66.526°.	
Index ranges	-37<=h<=34, 0<=k<=11, 0<=l<=17	
Reflections collected	3790	
Independent reflections	3790 [R(int) = 0.1009]	
Completeness to theta = 66.526°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.4332	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3790 / 258 / 278	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0611, wR2 = 0.1753	
R indices (all data)	R1 = 0.0826, wR2 = 0.1919	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.704 and -0.647 $e.Å^{-3}$	

Table S1.16. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for $C_{23}H_{25}BrN_2O_3$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	4645(1)	4818(1)	8410(1)	102(1)
O(1)	2346(1)	5189(2)	7608(2)	72(1)
O(2)	2035(1)	3146(2)	7683(2)	72(1)
O(3)	2085(1)	9312(3)	5196(2)	83(1)
N(1)	2703(1)	3164(3)	7568(3)	70(1)
C(1)	4033(2)	4296(4)	8101(3)	78(1)
C(2)	3927(2)	2965(4)	8208(3)	74(1)
C(3)	3484(1)	2620(4)	8017(3)	69(1)
C(4)	3143(1)	3597(4)	7716(3)	67(1)
C(5)	3255(2)	4934(4)	7597(4)	79(1)
C(6)	3703(2)	5272(4)	7804(4)	85(1)
C(7)	2366(1)	3966(4)	7629(3)	66(1)
C(8)	1644(1)	3829(4)	7738(3)	70(1)
C(9)	1294(2)	4050(4)	6781(3)	70(1)
C(10)	1015(2)	4204(4)	5999(4)	80(1)
N(2)	914(2)	4846(4)	4377(3)	81(1)
C(11)	686(2)	4496(5)	5009(4)	87(1)
C(12)	391(8)	3269(17)	4511(10)	96(2)
C(13)	668(3)	2606(8)	4006(6)	109(2)
C(14)	859(3)	3808(9)	3636(6)	99(2)
C(12X)	430(30)	3200(50)	4500(20)	96(2)
C(13X)	297(7)	3530(20)	3435(13)	99(2)
C(14X)	656(9)	4490(30)	3374(12)	109(2)
C(15)	1209(1)	5996(4)	4559(3)	69(1)
C(16)	1027(2)	7312(5)	4359(3)	76(1)
C(17)	1316(2)	8433(4)	4562(3)	77(1)
C(18)	1776(2)	8273(4)	4965(3)	72(1)
C(19)	1959(1)	6967(4)	5150(3)	68(1)
C(20)	1682(1)	5831(4)	4961(3)	66(1)
C(21)	1900(2)	4441(4)	5148(4)	79(1)

C(22)	518(2)	7512(6)	3924(5)	105(2)
C(23)	1917(2)	10679(5)	5077(4)	93(1)

Table S1.17. Bond lengths [Å] and angles [°] for $C_{23}H_{25}BrN_2O_3$.

Br(1)-C(1)	1.898(5)
O(1)-C(7)	1.200(4)
O(2)-C(7)	1.356(4)
O(2)-C(8)	1.449(5)
O(3)-C(18)	1.367(5)
O(3)-C(23)	1.430(5)
N(1)-C(7)	1.364(5)
N(1)-C(4)	1.404(5)
N(1)-H(1N)	0.93(5)
C(1)-C(6)	1.366(6)
C(1)-C(2)	1.373(6)
C(2)-C(3)	1.373(6)
C(2)-H(2)	0.9500
C(3)-C(4)	1.389(5)
C(3)-H(3)	0.9500
C(4)-C(5)	1.387(5)
C(5)-C(6)	1.384(7)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(8)-C(9)	1.460(7)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.181(6)
C(10)-C(11)	1.482(8)
N(2)-C(15)	1.428(5)
N(2)-C(11)	1.445(6)
N(2)-C(14)	1.470(7)
C(11)-C(12)	1.534(8)
C(11)-H(11)	1.0000

C(12)-C(13)	1.52(2)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.527(10)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.400(6)
C(15)-C(20)	1.403(6)
C(16)-C(17)	1.391(6)
C(16)-C(22)	1.514(7)
C(17)-C(18)	1.366(6)
C(17)-H(17)	0.9500
C(18)-C(19)	1.390(5)
C(19)-C(20)	1.383(5)
C(19)-H(19)	0.9500
C(20)-C(21)	1.508(6)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800

C(7)-O(2)-C(8)	116.1(3)
C(18)-O(3)-C(23)	117.8(4)
C(7)-N(1)-C(4)	125.8(3)
C(7)-N(1)-H(1N)	114(3)
C(4)-N(1)-H(1N)	117(3)
C(6)-C(1)-C(2)	120.7(4)
C(6)-C(1)-Br(1)	118.9(3)
C(2)-C(1)-Br(1)	120.4(3)

C(3)-C(2)-C(1)	119.4(4)
C(3)-C(2)-H(2)	120.3
C(1)-C(2)-H(2)	120.3
C(2)-C(3)-C(4)	120.9(4)
C(2)-C(3)-H(3)	119.6
C(4)-C(3)-H(3)	119.6
C(5)-C(4)-C(3)	119.1(4)
C(5)-C(4)-N(1)	123.8(4)
C(3)-C(4)-N(1)	117.1(3)
C(6)-C(5)-C(4)	119.5(4)
C(6)-C(5)-H(5)	120.2
C(4)-C(5)-H(5)	120.2
C(1)-C(6)-C(5)	120.4(4)
C(1)-C(6)-H(6)	119.8
C(5)-C(6)-H(6)	119.8
O(1)-C(7)-O(2)	124.1(3)
O(1)-C(7)-N(1)	127.5(4)
O(2)-C(7)-N(1)	108.4(3)
O(2)-C(8)-C(9)	111.1(3)
O(2)-C(8)-H(8A)	109.4
C(9)-C(8)-H(8A)	109.4
O(2)-C(8)-H(8B)	109.4
C(9)-C(8)-H(8B)	109.4
H(8A)-C(8)-H(8B)	108.0
C(10)-C(9)-C(8)	178.4(5)
C(9)-C(10)-C(11)	175.3(5)
C(15)-N(2)-C(11)	121.7(4)
C(15)-N(2)-C(14)	124.7(4)
C(11)-N(2)-C(14)	113.1(4)
N(2)-C(11)-C(10)	111.4(4)
N(2)-C(11)-C(12)	103.7(5)
C(10)-C(11)-C(12)	113.8(9)
N(2)-C(11)-H(11)	109.3
C(10)-C(11)-H(11)	109.3
C(12)-C(11)-H(11)	109.3
C(13)-C(12)-C(11)	102.2(10)

C(13)-C(12)-H(12A)	111.3
C(11)-C(12)-H(12A)	111.3
C(13)-C(12)-H(12B)	111.3
C(11)-C(12)-H(12B)	111.3
H(12A)-C(12)-H(12B)	109.2
C(12)-C(13)-C(14)	104.2(7)
C(12)-C(13)-H(13A)	110.9
C(14)-C(13)-H(13A)	110.9
C(12)-C(13)-H(13B)	110.9
C(14)-C(13)-H(13B)	110.9
H(13A)-C(13)-H(13B)	108.9
N(2)-C(14)-C(13)	101.9(5)
N(2)-C(14)-H(14A)	111.4
C(13)-C(14)-H(14A)	111.4
N(2)-C(14)-H(14B)	111.4
C(13)-C(14)-H(14B)	111.4
H(14A)-C(14)-H(14B)	109.3
C(16)-C(15)-C(20)	119.2(4)
C(16)-C(15)-N(2)	119.9(4)
C(20)-C(15)-N(2)	120.9(4)
C(17)-C(16)-C(15)	119.7(4)
C(17)-C(16)-C(22)	120.3(4)
C(15)-C(16)-C(22)	120.0(4)
C(18)-C(17)-C(16)	121.0(4)
C(18)-C(17)-H(17)	119.5
C(16)-C(17)-H(17)	119.5
C(17)-C(18)-O(3)	125.1(4)
C(17)-C(18)-C(19)	119.5(4)
O(3)-C(18)-C(19)	115.4(4)
C(20)-C(19)-C(18)	120.9(4)
C(20)-C(19)-H(19)	119.6
C(18)-C(19)-H(19)	119.6
C(19)-C(20)-C(15)	119.6(4)
C(19)-C(20)-C(21)	118.4(4)
C(15)-C(20)-C(21)	121.9(4)
C(20)-C(21)-H(21A)	109.5

C(20)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(20)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(16)-C(22)-H(22A)	109.5
C(16)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(16)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
O(3)-C(23)-H(23A)	109.5
O(3)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
O(3)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S1.18. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $C_{23}H_{25}BrN_2O_3$. 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}
Br(1)	80(1)	77(1)	152(1)	7(1)	50(1)	-1(1)
O(1)	79(2)	45(1)	97(2)	6(1)	39(2)	3(1)
O(2)	78(2)	47(1)	96(2)	1(1)	41(2)	-1(1)
O(3)	93(2)	52(1)	112(2)	1(1)	47(2)	-1(1)
N(1)	79(2)	45(2)	87(2)	3(1)	35(2)	2(1)
C(1)	83(3)	61(2)	99(3)	5(2)	46(2)	4(2)
C(2)	84(3)	53(2)	93(3)	7(2)	42(2)	11(2)
C(3)	85(2)	46(2)	84(3)	1(2)	41(2)	3(2)
C(4)	77(2)	51(2)	78(3)	3(2)	35(2)	1(2)

C(5)	82(3)	50(2)	111(4)	11(2)	44(3)	6(2)
C(6)	86(3)	52(2)	123(4)	10(2)	46(3)	1(2)
C(7)	74(2)	52(2)	73(2)	2(2)	30(2)	-1(2)
C(8)	84(2)	52(2)	84(3)	-3(2)	44(2)	0(2)
C(9)	79(2)	56(2)	82(3)	-2(2)	39(2)	-6(2)
C(10)	88(3)	63(2)	91(3)	-1(2)	38(2)	-12(2)
N(2)	90(2)	75(2)	83(2)	-8(2)	40(2)	-14(2)
C(11)	85(3)	84(3)	95(3)	1(2)	39(2)	-11(2)
C(12)	89(5)	98(4)	101(3)	-7(3)	37(3)	-25(3)
C(13)	111(5)	95(4)	131(5)	-37(4)	56(4)	-40(4)
C(14)	107(5)	99(4)	101(4)	-33(3)	52(4)	-28(4)
C(12X)	89(5)	98(4)	101(3)	-7(3)	37(3)	-25(3)
C(13X)	107(5)	99(4)	101(4)	-33(3)	52(4)	-28(4)
C(14X)	111(5)	95(4)	131(5)	-37(4)	56(4)	-40(4)
C(15)	77(2)	65(2)	69(2)	2(2)	32(2)	-1(2)
C(16)	78(2)	73(2)	83(3)	8(2)	39(2)	5(2)
C(17)	90(3)	60(2)	90(3)	11(2)	44(2)	14(2)
C(18)	86(2)	57(2)	81(3)	5(2)	39(2)	2(2)
C(19)	77(2)	59(2)	74(3)	0(2)	35(2)	3(2)
C(20)	81(2)	57(2)	67(2)	2(2)	37(2)	1(2)
C(21)	88(3)	58(2)	95(3)	5(2)	39(2)	2(2)
C(22)	81(3)	100(4)	133(4)	26(3)	39(3)	17(3)
C(23)	114(4)	55(2)	120(4)	1(2)	56(3)	2(2)

Table S1.19. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for $C_{23}H_{25}BrN_2O_3$.

	x	y	z	U(eq)
H(1N)	2658(15)	2230(50)	7620(30)	84
H(2)	4157	2289	8411	89
H(3)	3410	1701	8092	83
H(5)	3025	5611	7376	95
H(6)	3782	6190	7738	102
H(8A)	1738	4718	8067	84
H(8B)	1518	3270	8124	84
H(11)	486	5270	5029	104
H(12A)	349	2642	4986	115
H(12B)	90	3564	4045	115
H(13A)	475	2024	3467	131
H(13B)	916	2044	4460	131
H(14A)	1153	3575	3598	118
H(14B)	644	4114	2995	118
H(12C)	626	2389	4691	115
H(12D)	157	3049	4649	115
H(13C)	287	2681	3068	118
H(13D)	-6	3962	3166	118
H(14C)	850	4033	3087	131
H(14D)	516	5309	2989	131
H(17)	1191	9324	4419	93
H(19)	2279	6854	5409	82
H(21A)	1899	4062	4544	119
H(21B)	1731	3836	5406	119
H(21C)	2214	4521	5614	119
H(22A)	409	7687	4438	158
H(22B)	373	6688	3571	158
H(22C)	443	8290	3481	158
H(23A)	1743	10860	4393	140
H(23B)	2172	11317	5324	140

H(23C)	1720	10798	5434	140

Table S1.20. Torsion angles [°] for $C_{23}H_{25}BrN_2O_3$.

C(6)-C(1)-C(2)-C(3)	-0.3(7)
Br(1)-C(1)-C(2)-C(3)	177.4(3)
C(1)-C(2)-C(3)-C(4)	0.2(6)
C(2)-C(3)-C(4)-C(5)	0.8(6)
C(2)-C(3)-C(4)-N(1)	-177.9(4)
C(7)-N(1)-C(4)-C(5)	-24.6(6)
C(7)-N(1)-C(4)-C(3)	154.0(4)
C(3)-C(4)-C(5)-C(6)	-1.6(7)
N(1)-C(4)-C(5)-C(6)	177.0(4)
C(2)-C(1)-C(6)-C(5)	-0.5(8)
Br(1)-C(1)-C(6)-C(5)	-178.2(4)
C(4)-C(5)-C(6)-C(1)	1.5(8)
C(8)-O(2)-C(7)-O(1)	-1.3(5)
C(8)-O(2)-C(7)-N(1)	-179.2(3)
C(4)-N(1)-C(7)-O(1)	17.4(7)
C(4)-N(1)-C(7)-O(2)	-164.8(4)
C(7)-O(2)-C(8)-C(9)	90.8(4)
C(15)-N(2)-C(11)-C(10)	-60.4(6)
C(14)-N(2)-C(11)-C(10)	111.7(6)
C(15)-N(2)-C(11)-C(12)	176.9(11)
C(14)-N(2)-C(11)-C(12)	-11.1(13)
N(2)-C(11)-C(12)-C(13)	30.5(14)
C(10)-C(11)-C(12)-C(13)	-90.7(10)
C(11)-C(12)-C(13)-C(14)	-39.1(14)
C(15)-N(2)-C(14)-C(13)	158.8(6)
C(11)-N(2)-C(14)-C(13)	-13.0(9)
C(12)-C(13)-C(14)-N(2)	32.0(11)
C(11)-N(2)-C(15)-C(16)	-76.4(6)
C(14)-N(2)-C(15)-C(16)	112.5(7)
C(11)-N(2)-C(15)-C(20)	102.0(5)

C(14)-N(2)-C(15)-C(20)	-69.1(7)
C(20)-C(15)-C(16)-C(17)	-0.2(6)
N(2)-C(15)-C(16)-C(17)	178.2(4)
C(20)-C(15)-C(16)-C(22)	179.9(4)
N(2)-C(15)-C(16)-C(22)	-1.7(6)
C(15)-C(16)-C(17)-C(18)	-0.6(7)
C(22)-C(16)-C(17)-C(18)	179.2(5)
C(16)-C(17)-C(18)-O(3)	-179.5(4)
C(16)-C(17)-C(18)-C(19)	1.8(7)
C(23)-O(3)-C(18)-C(17)	5.1(6)
C(23)-O(3)-C(18)-C(19)	-176.2(4)
C(17)-C(18)-C(19)-C(20)	-2.2(6)
O(3)-C(18)-C(19)-C(20)	179.0(4)
C(18)-C(19)-C(20)-C(15)	1.3(6)
C(18)-C(19)-C(20)-C(21)	178.2(4)
C(16)-C(15)-C(20)-C(19)	-0.1(6)
N(2)-C(15)-C(20)-C(19)	-178.5(4)
C(16)-C(15)-C(20)-C(21)	-176.8(4)
N(2)-C(15)-C(20)-C(21)	4.8(6)

Symmetry transformations used to generate equivalent atoms:

Table S1.21. Hydrogen bonds for $C_{23}H_{25}BrN_2O_3$ [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.93(5)	2.03(5)	2.928(4)	160(4)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,y-1/2,-z+3/2

Appendix B. Experimental Section for Chapter 3

General Experimental Procedures

All reactions were performed in standard, oven-dried glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. Stainless steel syringes or cannulas were used to transfer air- and moisture-sensitive liquids. Reported concentrations refer to solution volumes at room temperature. Evaporation and concentration *in vacuo* were performed using a house vacuum (ca. 40 mm Hg). Column chromatography was performed with SiliaFlash® 60 (40–63 micron) silica gel from Silicycle. Thin-layer chromatography (TLC) was used for reaction monitoring and product detection using pre-coated glass plates covered with 0.25 mm silica gel with fluorescent indicator; visualization by UV light (λ_{ex} = 254 nm) or $KMnO_4$ stain.

Materials

Reagents were purchased in reagent grade from commercial suppliers and used without further purification unless otherwise described. Amines were prepared according to the procedures reported previously[1-6]. Tris(pentafluorophenyl)borane was purchased from TCI and used without further purification. Acetone-d_6 was purchased from Cambridge Isotope Laboratory and used without further purification. H_2O, in synthetic procedures, refers to distilled water.

Instrumentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C {^{1}H} NMR) spectra were recorded at 25 °C (unless stated otherwise) on Inova 600 (600 MHz) or Varian Unity/Inova 500 (500 MHz) or Oxford AS400 (400 MHz) spectrometers at the Boston College nuclear magnetic resonance facility. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to 0 ppm. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent. The peak positions are quoted to one decimal place unless they are indistinguishable. The solvent peak was referenced to 77.0 ppm for ^{13}C for $CDCl_3$. Benzotrifluoride was used as an external standard for ^{19}F NMR and referenced to -63.7 ppm. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz).

Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}).

Optical rotations were measured using a 1 mL cell with a 5 cm path length on a Rudolph Research Analytical Autopol IV Polarimeter. Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}). High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) at the Mass Spectrometry Facility, Boston College.

Determination of Deuterium Content

The amount of incorporated deuterium in a sample was quantified by mass spectrometry and by the decrease of ^1H NMR integral intensities at the specified positions compared to the starting material. Integral intensities were calibrated against hydrogen signals that do not undergo H/D-exchange. Mass spectrometry quantification was performed by subtraction of the mean molecular masses of the product and substrate isotopologue clusters in order to eliminate the contribution of the natural isotope abundance to the total mass. The mean molecular masses were calculated as the sum of the relative signal intensities of a given isotopologue multiplied with the corresponding m/z values derived from the mass spectrum.

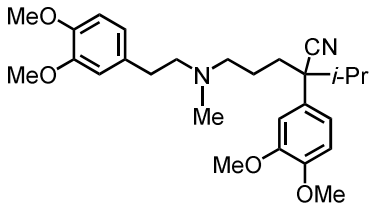
Abbreviations Used

Bn = benzyl, Bzh= benzhydryl, DART = direct analysis in real time, DCM = dichloromethane, Et_3N = trimethylamine, Et_2O = diethyl ether, EtOAc = ethyl acetate, HR = high-resolution, LC = liquid chromatography, MS = mass spectrometry, PTLC = preparative thin layer chromatography, TBS = *tert*-butyldimethylsilyl, Tf = trifluromethanesulfonate, THF = tetrahydrofuran, TOF = time-of-flight.

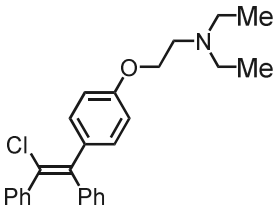
B1. Substrate Preparation

Preparation of Amine Substrates

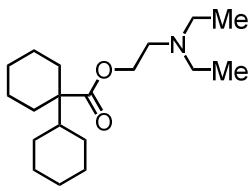
Table S3.1. List of Acyclic Amine Substrates



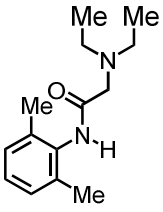
3.13e, verapamil



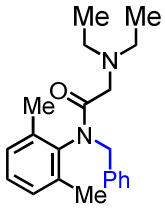
3.13f, clomiphene



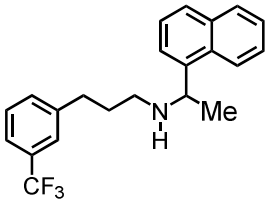
3.13g, dicyclomine



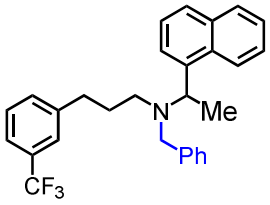
3.13h, lidocaine



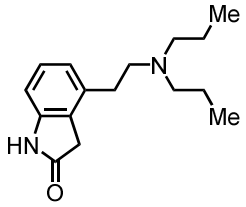
3.13i, *N*-Bn lidocaine



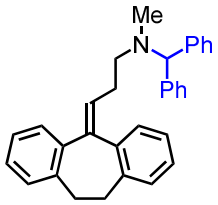
3.13j, cinacalcet



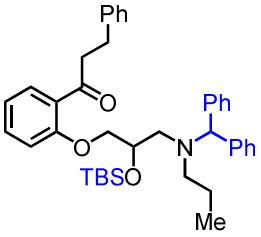
3.13k, *N*-Bn cinacalcet



3.13l, ropinirole



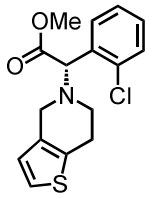
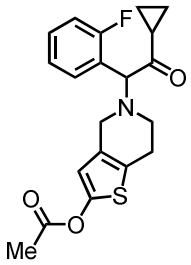
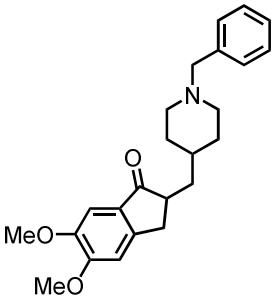
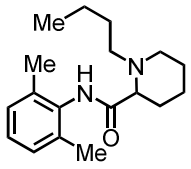
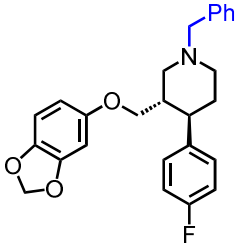
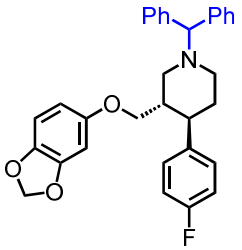
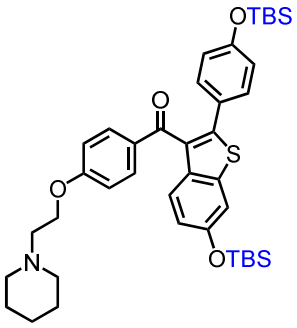
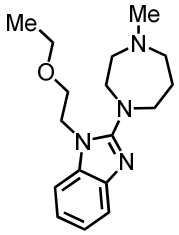
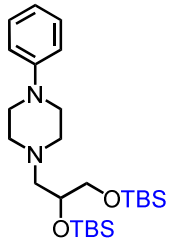
3.13m, *N*-Bzh nortriptyline



3.13n, *N*-Bzh, *O*-TBS propafenone

Amines **3.13c–3.13e**, **3.13h** and **3.13j** were obtained from free-basing commercially available amine salts and used without further purification.[1] Amine **3.13f** was obtained from a commercial source and used without further purification. Amines **3.13g**[2] and **3.13i**, **3.13k**, **3.13l** were prepared according to the literature procedures.[5] The spectroscopic data are provided below.

Table S3.2. List of Cyclic Amine Substrates

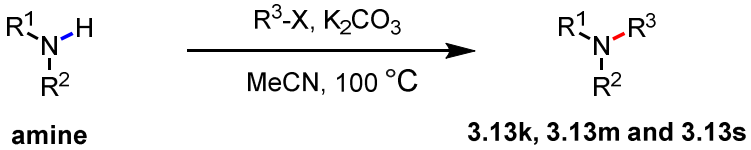
		
3.13o, clopidogrel	**3.13p**, prasugrel	**3.13q**, donepezil
		
3.13r, bupivacaine	**3.13s**, *N*-Bn paroxetine	**3.13t**, *N*-Bzh paroxetine
		
3.13u, *O*-TBS raloxifene	**3.13v**, emedastine	**3.13w**, *O*-TBS dropropizine

Amines **3.13m**–**3.13p** were obtained from commercial sources and used without further purification. Amines **3.13q**[3], **3.13r**[4], **3.13s**[5] and **3.13u**[6] were prepared according to the literature procedures. The spectroscopic data are provided below. Amine **3.13t** was obtained from free-basing commercially available amine salt and used without further purification.[1]

General Procedure for the Free-Basing Amine Salts[1]

To a 250-mL Erlenmeyer flask was added amine salt and DCM. 2 M NaOH (*aq*.) was added dropwise to the stirred solution until pH paper indicated that the aqueous layer is basic. The aqueous layer was extracted with DCM and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting amine was used without further purification.

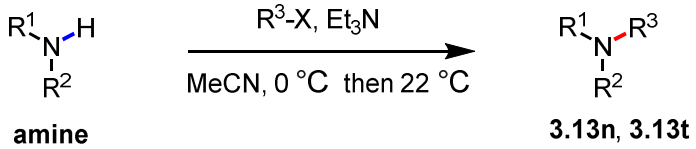
General Procedure A for the Alkylation of Amines[3]



amine **3.13k, 3.13m and 3.13s**

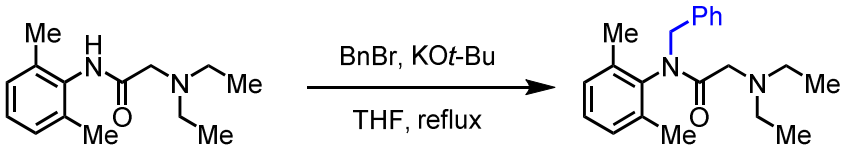
Amines **3.13i**, **3.13k** and **3.13q** were prepared by the alkylation of secondary amines. To a solution of amine (1.0 equiv.) and K_2CO_3 (5.0 equiv.) in MeCN was added alkyl halide (1.5 equiv.). The mixture was then allowed heated to 100 °C for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to silica gel chromatography.

General Procedure B for the Alkylation of Amines[4]



amine **3.13n, 3.13t**

Amines **3.13l** and **3.13r** were prepared by the alkylation of secondary amines. To a solution of amine (1.0 equiv.) and alkyl halide (1.1 equiv.) in MeCN, Et_3N (3.0 equiv.) was added at 0 °C. The mixture was then warmed up to 22 °C and allowed to stir for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to silica gel chromatography.

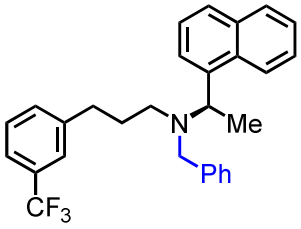


3.13h, **lidocaine** **3.13i**

***N*-Bn lidocaine (3.13g)**

N-Bn lidocaine **3.13g** was prepared following a known procedure.[2] To a solution of lidocaine (**3.13f**, 3.0 g, 12.8 mmol) in THF (45 mL) was added benzyl bromide (1.8 mL, 15.4 mmol). To the mixture, KO*t*-Bu (2.9 g, 25.6 mmol) was then added portionwise and the mixture was allowed to stir at reflux for 48 hours. The mixture was then cooled and concentrated *in vacuo* to remove THF. To the mixture was added H_2O and was extracted with EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was then subjected to silica gel chromatography (MeOH:DCM = 1:99) to afford **3.13g** as a yellow liquid (2.5 g, 60%).

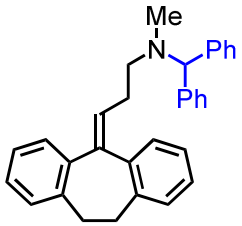
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 5H), 7.12 (d, J = 7.5 Hz, 1H), 7.04 (d, J = 7.5 Hz, 2H), 4.73 (s, 2H), 2.80 (s, 2H), 2.57 (q, J = 7.1 Hz, 4H), 1.87 (s, 6H), 0.91 (t, J = 7.1 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.64, 138.99, 137.10, 136.31, 128.92, 128.18, 127.97, 127.49, 54.60, 51.68, 47.36, 17.83, 11.96; **IR** (neat) 2964, 2926, 1653, 1466, 1453, 1400, 1385, 1258, 1242, 1195, 1078, 773, 743, 699 cm^{-1}.



***N*-Bn cinacalcet (3.13i)**

N-Bn cinacalcet **3.13i** was prepared following a General Procedure A for the Alkylation of Amines using cinacalcet hydrochloride (1.0 g, 2.5 mmol) and benzyl bromide. The unpurified product mixture was then subjected to silica gel chromatography (EtOAc:hexanes = 1:4) to afford **3.13i** as a colorless liquid (0.9 g, 82%).

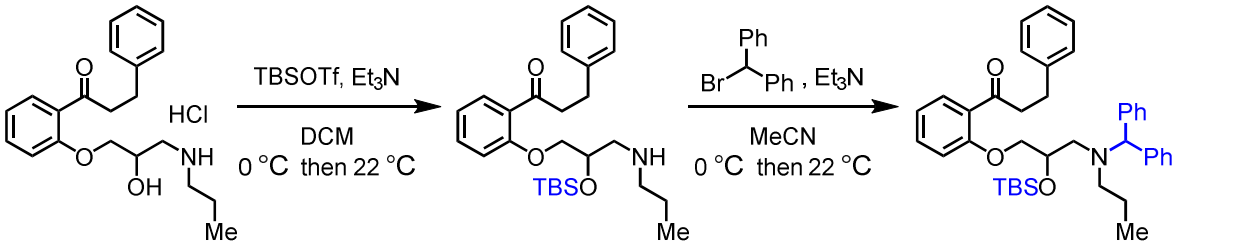
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 6H), 7.12 (s, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 4.75 – 4.62 (m, 1H), 3.72 (d, *J* = 13.8 Hz, 1H), 3.63 (d, *J* = 13.8 Hz, 1H), 2.60 (s, 2H), 2.33 (d, *J* = 14.0 Hz, 1H), 2.26 (d, *J* = 13.9 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.40, 140.62, 140.01, 134.02, 132.14, 131.58, 130.47, 130.22, 128.97, 128.54, 128.43, 128.05, 127.61, 126.74, 125.33, 125.28, 125.00, 124.85, 124.56, 122.30, 56.36, 55.77, 49.79, 33.22, 28.99, 14.33; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -62.40 (d, *J* = 3.0 Hz); **IR** (neat) 2968, 2939, 1492, 1327, 1160, 1120, 1072, 797, 778, 699 cm^{-1}.



***N*-Bzh nortriptyline (3.13k)**

N-Bzh nortriptyline was prepared following a General Procedure A for the Alkylation of Amines using nortriptyline hydrochloride (2.0 g, 6.7 mmol) and (bromomethylene)dibenzene. The unpurified product mixture was then subjected to silica gel chromatography (Et_2O:hexanes = 1:49) to afford **3.13k** as a yellow liquid (2.2 g, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.6 Hz, 4H), 7.23 (dd, *J* = 8.3, 6.9 Hz, 5H), 7.20 – 7.09 (m, 7H), 7.09 – 7.05 (m, 1H), 7.02 (dd, *J* = 5.3, 3.8 Hz, 1H), 5.82 (t, *J* = 7.5 Hz, 1H), 4.31 (s, 1H), 3.30 (s, 2H), 2.94 (s, 1H), 2.71 (s, 1H), 2.46 (d, *J* = 8.7 Hz, 2H), 2.32 (dd, *J* = 15.7, 8.4 Hz, 2H), 2.07 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.20, 143.17, 141.43, 140.13, 139.35, 137.02, 129.92, 129.80, 129.02, 128.51, 128.32, 127.94, 127.26, 126.90, 126.74, 125.93, 125.67, 75.59, 54.98, 40.21, 33.74, 32.01, 27.21; **IR** (neat) 3061, 3020, 1485, 1451, 1278, 1079, 756, 743, 704 cm^{-1}.



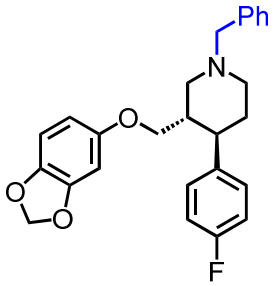
_O_-TBS propafenone

O-TBS propafenone was prepared following the known procedure.[5] To a solution of propafenone HCl (2.0 g, 5.29 mmol) in DCM at 0 °C, imidazole (5.0 equiv.) was added, followed by the dropwise addition of TBSCl (1.3 equiv.). After the addition, the mixture was allowed to warm to 22 °C and stirred for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was then extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to silica gel chromatography (MeOH:DCM = 1:19) to afford *O*-TBS propafenone as a colorless liquid (2.0 g, 83%).

_N_-Bzh, _O_-TBS propafenone (3.13l)

N-Bzh, *O*-TBS propafenone was prepared following the General Procedure B for the Alkylation of Amines using *O*-TBS propafenone (2.0 g, 4.4 mmol) and (bromomethylene)dibenzene. The unpurified product mixture was subjected to silica gel chromatography (Et_2O:hexanes = 1:19) to afford **3.13l** as a colorless liquid (2.2 g, 81%).

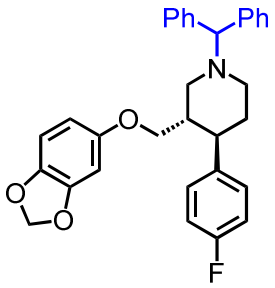
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.5 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.25 (dd, *J* = 25.5, 8.1 Hz, 6H), 7.14 (dt, *J* = 15.4, 7.7 Hz, 9H), 7.03 – 6.92 (m, 2H), 4.82 (s, 1H), 4.18 (dd, *J* = 9.5, 3.8 Hz, 1H), 4.10 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.92 (d, *J* = 4.3 Hz, 1H), 3.36 – 3.16 (m, 1H), 3.08 – 2.99 (m, 1H), 2.98 – 2.84 (m, 2H), 2.79 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.55 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.45 (d, *J* = 6.0 Hz, 2H), 1.43 (d, *J* = 7.4 Hz, 2H), 0.79 (s, 9H), 0.71 (t, *J* = 7.3 Hz, 3H), -0.06 (s, 3H), -0.09 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.22, 158.19, 142.06, 141.67, 141.51, 133.30, 130.45, 128.78, 128.68, 128.44, 128.26, 128.21, 128.15, 128.12, 126.91, 126.88, 125.68, 120.47, 112.33, 71.18, 70.47, 69.93, 54.23, 54.02, 45.40, 30.03, 25.71, 19.40, 17.92, 11.74, -4.67, -4.83; **IR** (neat) 2953, 2926, 1671, 1595, 1578, 1469, 1248, 1110, 838, 752, 698 cm^{-1}.



_N_-Bn paroxetine (3.13q)

_N_-Bn paroxetine was prepared following the General Procedure A for the Alkylation of Amines using paroxetine hydrochloride (3.0 g, 8.2 mmol) and benzyl bromide. The unpurified product was subjected to silica gel chromatography (EtOAc:hexanes = 1:9) to afford **3.13q** as a white solid (2.9 g, 84%).

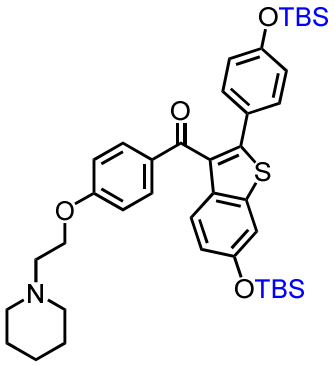
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H), 7.25 (s, 1H), 7.16 (dd, J = 8.6, 5.5 Hz, 2H), 6.96 (t, J = 8.7 Hz, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 2.5 Hz, 1H), 6.10 (dd, J = 8.5, 2.5 Hz, 1H), 5.87 (s, 2H), 3.64 (d, J = 13.1 Hz, 1H), 3.59 – 3.50 (m, 2H), 3.44 (d, J = 6.9 Hz, 1H), 3.04 – 2.96 (m, 1H), 2.55 – 2.42 (m, 1H), 2.27 – 2.14 (m, 1H), 2.12 – 2.01 (m, 2H), 1.90 – 1.73 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.44, 160.50, 154.41, 148.10, 141.51, 139.86, 139.84, 138.27, 129.19, 128.85, 128.79, 128.20, 127.00, 115.40, 115.24, 107.80, 105.60, 101.03, 97.99, 69.65, 63.40, 57.61, 53.83, 44.12, 42.19, 34.39; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -116.71 (d, J = 7.5 Hz); **IR** (neat) 2912, 1602, 1506, 1485, 1221, 1181, 1132, 1036, 933, 831, 781, 738 cm^{-1}.



_N_-Bzh paroxetine (3.13r)

_N_-Bzh paroxetine was prepared following the General Procedure B for the Alkylation of Amines using paroxetine hydrochloride (3.0 g, 8.2 mmol), (bromomethylene)dibenzene. The unpurified product was subjected to silica gel chromatography (Et_2O:hexanes = 1:9) to afford **3.13r** as a white solid (3.5 g, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.35 (m, 4H), 7.28 (t, *J* = 7.5 Hz, 4H), 7.17 (dt, *J* = 8.5, 6.4 Hz, 5H), 6.96 (t, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 8.5 Hz, 1H), 6.21 (d, *J* = 2.5 Hz, 1H), 6.01 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.85 (d, *J* = 0.9 Hz, 2H), 4.37 (s, 1H), 3.50 (dd, *J* = 9.5, 2.9 Hz, 1H), 3.38 (dd, *J* = 9.5, 6.7 Hz, 1H), 3.23 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.08 – 2.89 (m, 1H), 2.47 (dd, *J* = 11.6, 4.2 Hz, 1H), 2.22 (s, 1H), 2.06 – 1.81 (m, 3H), 1.77 (d, *J* = 3.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.46, 160.52, 154.29, 148.07, 142.81, 142.78, 141.51, 140.07, 140.04, 128.90, 128.84, 128.44, 128.43, 128.09, 127.94, 126.89, 115.39, 115.22, 107.78, 105.74, 101.04, 98.13, 76.11, 69.60, 55.96, 52.49, 44.23, 42.49, 34.64; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -116.74 (ddd, *J* = 14.0, 8.9, 5.3 Hz); **IR** (neat) 2912, 1506, 1485, 1466, 1336, 1268, 1222, 1037, 815, 705 cm^{-1}.

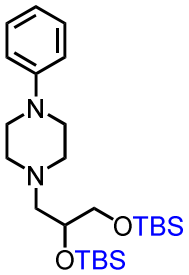


***O*-TBS raloxifene (3.13s)**

O-TBS raloxifene was prepared following the known procedure.[5] To a solution of raloxifene HCl (2.0 g, 3.9 mmol) in DCM at 0 °C, imidazole (5.0 equiv.) was added, followed by the dropwise addition of TBSCl (2.6 equiv.). After the addition, the mixture was allowed to warm to 22 °C and stirred for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was then extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was then subjected to silica gel chromatography (MeOH:DCM = 1:49) to afford **3.13s** as a colorless liquid (2.0 g, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.56 (s, 1H), 7.32 – 7.22 (m, 3H), 6.89 (s, 1H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 2.72 (t, *J* = 6.0 Hz, 2H), 2.47 (s, 4H), 1.58 (p, *J* = 5.6 Hz, 4H), 1.46 – 1.39 (m, 2H), 1.01 (s, 9H), 0.93 (s, 9H), 0.23 (s, 6H), 0.12 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.12, 162.88, 156.08, 153.49, 143.31, 139.86, 134.51, 132.29, 130.60, 130.45, 130.33, 126.79, 123.98, 120.25, 119.24, 114.01, 112.07, 66.14,

57.70, 55.06, 25.92, 25.71, 25.63, 24.13, 18.24, 18.19, -4.36, -4.48; **IR** (neat) 2927, 2891, 1596, 1464, 1255, 1164, 943, 909, 837, 780 cm^{-1}.

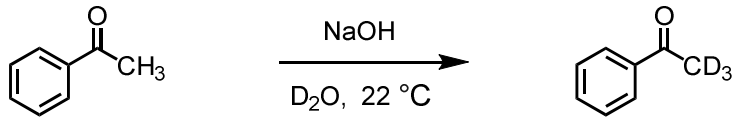


***O*-TBS dropropizine (3.13u)**

O-TBS dropropizine was prepared following the known procedure.[6] To a solution of dropropizine (1.2 g, 5.0 mmol) in DCM at 0 °C, Et_3N (2.6 equiv.) was added, followed by the dropwise addition of TBSOTf (2.6 equiv.). After the addition, the mixture was allowed to warm to 22 °C and stirred for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was then extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was then subjected to silica gel chromatography (MeOH:DCM = 1:99) to afford **3.13u** as a colorless liquid (1.6 g, 69%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.8, 7.2 Hz, 2H), 6.95 – 6.88 (m, 2H), 6.83 (d, *J* = 7.3 Hz, 1H), 3.80 (d, *J* = 5.1 Hz, 1H), 3.61 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.53 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.17 (t, *J* = 5.0 Hz, 4H), 2.72 – 2.64 (m, 2H), 2.64 – 2.57 (m, 2H), 2.50 (dd, *J* = 13.0, 4.8 Hz, 1H), 2.38 (dd, *J* = 13.0, 6.1 Hz, 1H), 0.90 (d, *J* = 5.1 Hz, 18H), 0.09 (d, *J* = 7.5 Hz, 6H), 0.06 (d, *J* = 1.8 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.46, 129.03, 119.44, 115.86, 71.76, 66.18, 61.99, 54.25, 49.15, 25.99, 25.92, 18.37, 18.19, -4.44, -4.49, -5.26, -5.34; **IR** (neat) 2925, 2853, 1598, 1500, 1460, 1229, 1107, 1082, 989, 829, 772 cm^{-1}.

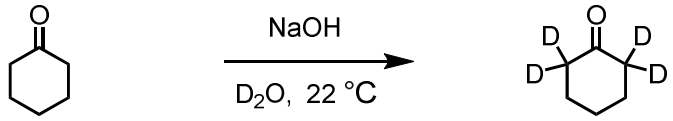
Preparation of α-Deuterated Ketone Substrates



acetophenone **acetophenone-d_3**

Acetophenone-d_3

Acetophenone-d_3 was synthesized following the known procedure.[7] Acetophenone (5.8 g, 48 mmol), NaOH (0.16 g, 4.0 mmol) and D_2O (32 mL) was allowed to stir at 22 °C for 24 hours under nitrogen. The mixture was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The unpurified product mixture was subjected to silica gel chromatography using hexanes as elute to afford the acetophenone-d_3 as colorless liquid (4.9 g, 97%D, 84% yield). The spectroscopic data matched those reported by Zhou.[7]



cyclohexanone **cyclohexa-1-one-2,2,6,6,-d_4**

Cyclohexan-1-one-2,2,6,6-d_4

Cyclohexan-1-one-2,2,6,6-d_4 was synthesized following the known procedure.[7] Cyclohexanone (5.2 mL, 50 mmol), NaOH (0.16 g, 1.0 mmol) and D_2O (32 mL) was allowed to stir at 22 °C for 24 hours under nitrogen. The mixture was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The unpurified product mixture was distilled (40 mmHg, 40 °C) to afford the cyclohexan-1-one-2,2,6,6-d_4 as colorless liquid (4.0 g, 95%D, 78% yield). The spectroscopic data matched those reported by Chang.[8]

B2. Optimization Studies and General Procedures

Evaluation of Reaction Conditions for $B(C_6F_5)_3$-Catalyzed β-Deuteration Involving Verapamil

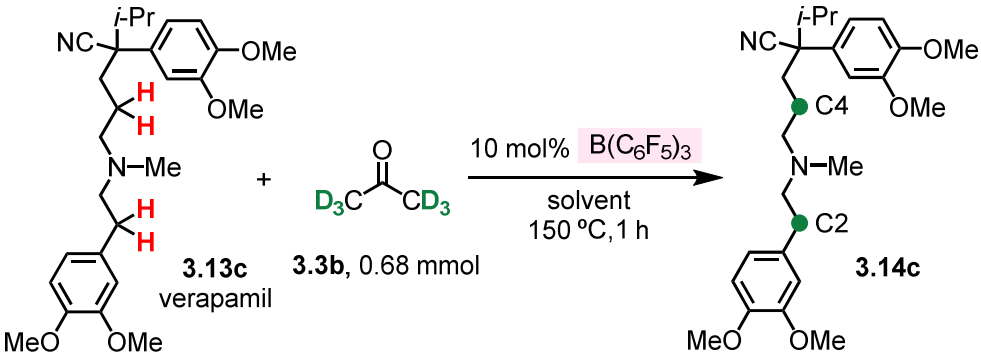
Experimental Procedure for the Evaluation of Reaction Parameters (see Table 1 in the Manuscript)

To a 15 mL oven-dried pressure vessel was added verapamil **3.13c** (0.1 mmol), Lewis acid (5.0 mol% or 10 mol%), Brønsted base (10 mol%), toluene (0.4 mL), and acetone-d_6 **2** (0.68 mmol) under a nitrogen atmosphere. The mixture was allowed to stir for 1 hour at 100 °C, 125 °C, or 150 °C. Upon completion, the mixture was concentrated *in vacuo*. The product yield and deuterium incorporation rate were determined by the ^{1}H NMR analysis of the unpurified product mixtures using mesitylene as the internal standard.

Experimental Procedure for the Evaluation of Solvents (see Table S3.3)

To a 15 mL oven-dried pressure vessel was added verapamil **3.13c** (0.1 mmol), $B(C_6F_5)_3$ (10 mol%), solvent (0.4 mL), and acetone-d_6 **2** (6.8 equiv.) under a nitrogen atmosphere. The mixture was allowed to stir for 1 hour at 150 °C. Upon completion, the mixture was concentrated *in vacuo*. The product yield and deuterium incorporation rate were determined by the ^{1}H NMR analysis of the unpurified product mixtures using mesitylene as the internal standard.

Table S3.3. Evaluation of Solvents Involving Verapamil **3.13c**



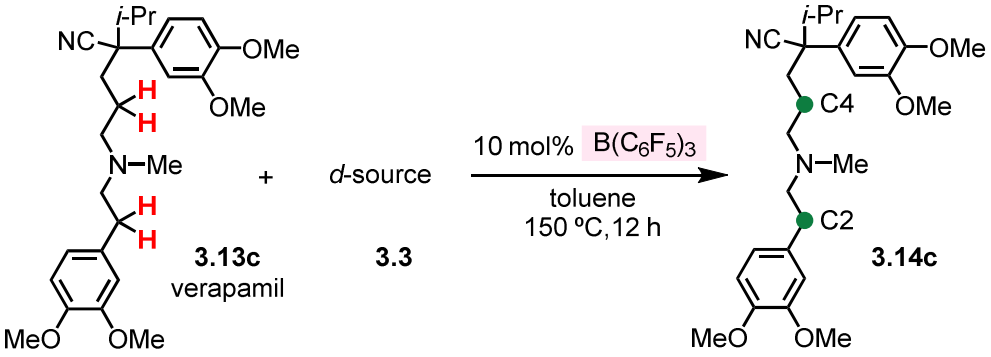
entry	solvent	*d*-incorporation (%)	
		[C2]	[C4]
1	toluene	90	92
2	benzene	84	91
3	$ClCH_2CH_2Cl$	78	90
4	$CHCl_3$	71	85
5	Et_2O	14	24
6	THF	<5	<5

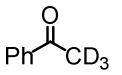
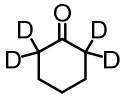
Conditions: verapamil (**3.13c**, 0.1 mmol), $B(C_6F_5)_3$ (10 mol%), solvent (0.4 mL), acetone-d_6 (**3.3b**, 0.68 mmol) under N_2, 150 °C. Yield and deuterium incorporation rate was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

Experimental Procedure for the Evaluation of Deuterium Sources (see Table S3.4)

To a 15 mL oven-dried pressure vessel was added verapamil **3.13c** (0.1 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.4 mL), and deuterium source (6.8 equiv. or 40.8 equiv.) under a nitrogen atmosphere. The mixture was allowed to stir for 12 hours at 150 °C. Upon completion, the mixture was concentrated *in vacuo*. The product yield and deuterium incorporation rate were determined by the ^1H NMR analysis of the unpurified product mixtures using mesitylene as the internal standard.

Table S3.4. Evaluation of Deuterium Sources Involving Verapamil **3.13c**



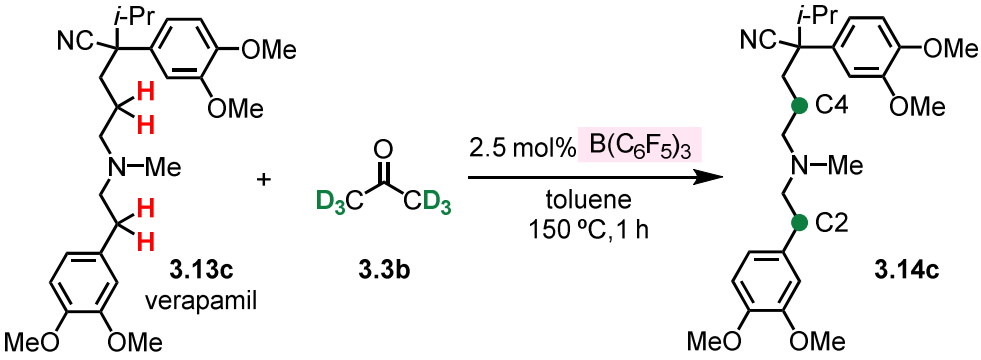
entry	**3.3**	equiv. of **3.3** (D/molecule)	*d*-incorporation (%) [C2]	[C4]
1	acetone-d_6	6.8 (40.8)	90	92
2		6.8 (20.4)	79	71
3		6.8 (27.2)	45	50
4	CH_3OD	6.8 (6.8)	14	20
5	$(CD_3)_2CDOD$	6.8 (6.8)	17	21
6	*t*-BuOD	6.8 (6.8)	63	58
7	*t*-BuOD	40.8 (40.8)	0	0

Conditions: verapamil (**3.13c,** 0.1 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.4 mL), *d*-source (**3.3**) under N_2, 150 ºC. Yield and deuterium incorporation rate was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

Experimental Procedure for the Evaluation of Acetone-d_6 Equivalence (see Table S3.5)

To a 15 mL oven-dried pressure vessel was added verapamil **3.13c** (0.3 mmol), $B(C_6F_5)_3$ (2.5 mol%), toluene (1.2 mL), and acetone-d_6 **2** (2.0-10 equiv.) under a nitrogen atmosphere. The mixture was allowed to stir for 1 hour at 150 °C. Upon completion, the mixture was concentrated *in vacuo*. The product yield and deuterium incorporation rate were determined by the ^{1}H NMR analysis of the unpurified product mixtures using mesitylene as the internal standard.

Table S3.5. Evaluation of Acetone-d_6 Equivalence Involving Verapamil **3.13c**

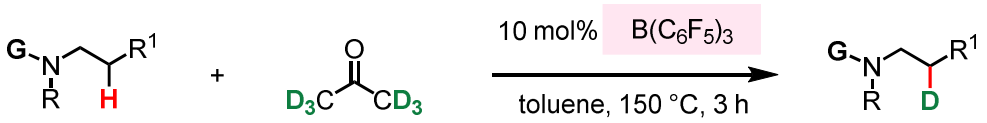


entry	equiv. of **3.3b**	*d*-incorporation (%)	
		[C2]	[C4]
1	2.0	47	60
2	4.0	72	82
3	6.8	80	86
4	10	70	85

Conditions: verapamil (**3.13c**, 0.3 mmol), $B(C_6F_5)_3$ (2.5 mol%), toluene (1.2 mL), acetone-d_6 (**3.3b**) under N_2, 150 °C. Yield and deuterium incorporation rate was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

General Procedures for *β*-Deuteration of *N*-Alkylamines

General Procedure A for the *β*-Deuteration of *N*-Alkylamines



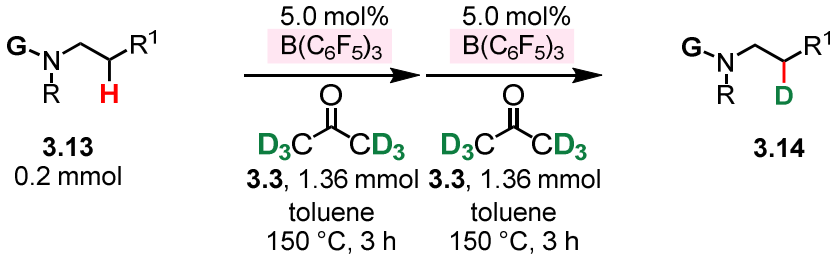
3.13
0.2 mmol

3.3
1.36 mmol

3.14

To a 15 mL oven-dried pressure vessel was added amine **3.13** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), and acetone-d_6 **3.3** (1.36 mmol, 6.8 equiv.) under a nitrogen atmosphere. The mixture was allowed to stir for 3 hours at 150 °C. Upon completion, the mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

General Procedure B for the *β*-Deuteration of *N*-Alkylamines

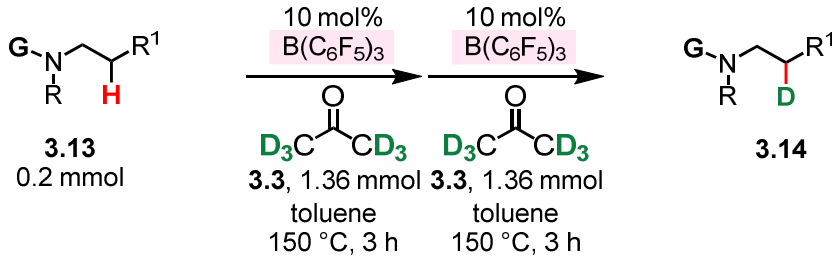


3.13
0.2 mmol

3.14

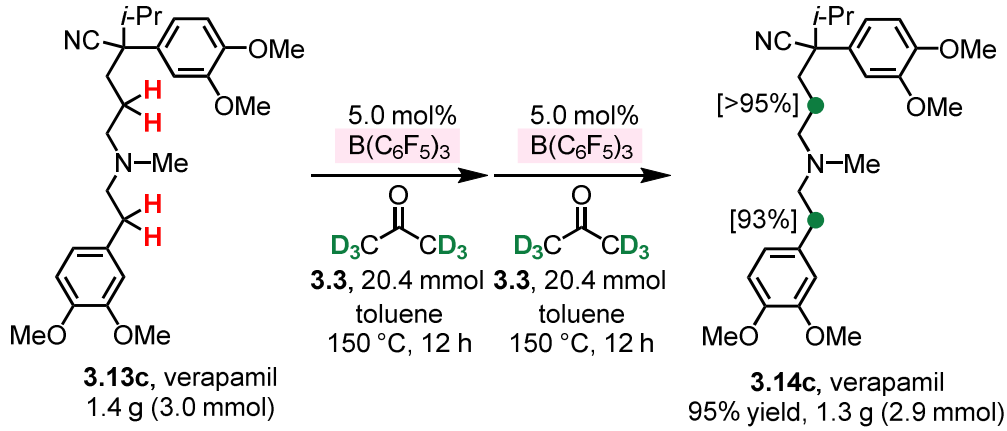
To a 15 mL oven-dried pressure vessel was added amine **3.13** (0.2 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **3.3** (1.36 mmol, 6.8 equiv.) under a nitrogen atmosphere. The mixture was allowed to stir for 3 hours at 150 °C. After the purification by silica gel chromatography and removal of volatiles, $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **2** (1.36 mmol, 6.8 equiv.) were added under a nitrogen atmosphere and was allowed to stir for 3 hours at 150 °C. Upon completion, the mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

General Procedure C for the *β*-Deuteration of *N*-Alkylamines



To a 15 mL oven-dried pressure vessel was added amine **3.13** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), and acetone-d_6 **3.3** (1.36 mmol, 6.8 equiv.) under a nitrogen atmosphere. The mixture was allowed to stir for 3 hours at 150 °C. After the purification by silica gel chromatography and removal of volatiles, $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **3.3** (1.36 mmol, 6.8 equiv.) were added under a nitrogen atmosphere and was allowed to stir for 3 hours at 150 °C. Upon completion, the mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

2.4 Procedure for Scale-Up Reaction

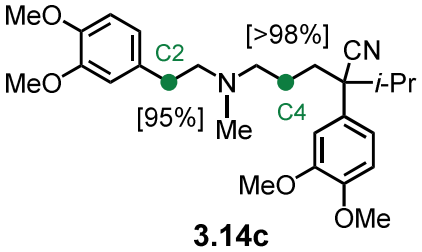


3.13c, verapamil
1.4 g (3.0 mmol)

3.14c, verapamil
95% yield, 1.3 g (2.9 mmol)

To a 100 mL oven-dried Schlenk flask was added amine **3.13c** (3.0 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (12 mL), and acetone-d_6 **3.3** (20.4 mmol, 6.8 equiv.) under a nitrogen atmosphere. The mixture was allowed to stir for 12 hours at 150 °C. After the purification by silica gel chromatography and removal of volatiles, $B(C_6F_5)_3$ (5.0 mol%), toluene (12 mL), and acetone-d_6 **3.3** (20.4 mmol, 6.8 equiv.) were added under a nitrogen atmosphere and was allowed to stir for 12 hours at 150 °C. Upon completion, the mixture was concentrated *in vacuo* and purified by silica gel chromatography (MeOH:DCM = 1:49) to afford **3.14c** as a yellow liquid (1.29 g, 2.85 mmol, 95% yield).

B3. Analytical Data and Spectra



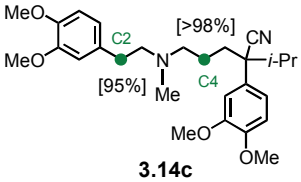
3.14c

Verapamil, 3.14c

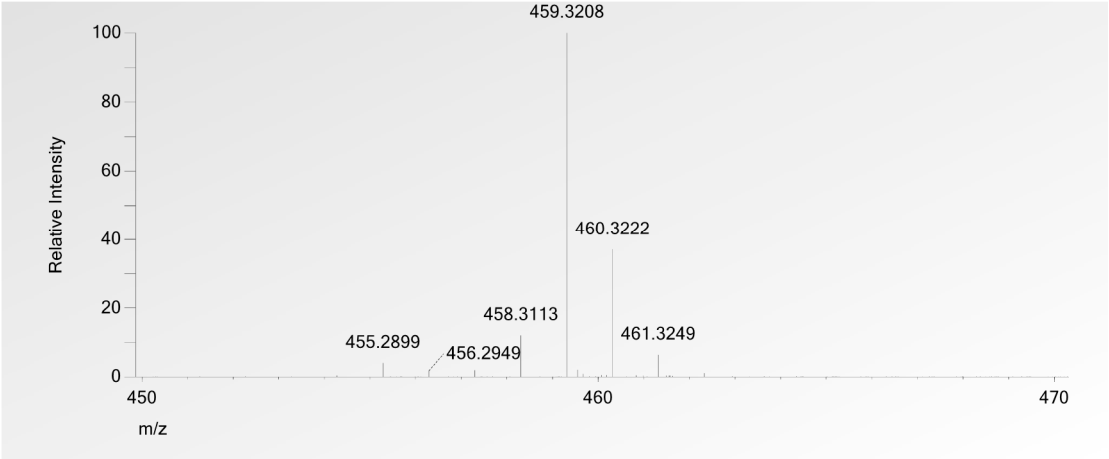
Verapamil **3.13c** was added to acetone-d_6 **2** following the General Procedure B. After purification by silica gel chromatography (MeOH:DCM = 1:49), **3.14c** was obtained as a yellow liquid (84 mg, 0.18 mmol, 92% yield).

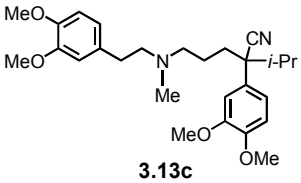
Deuterium incorporation: 3.86 D/molecule (^{1}H NMR), 4.11 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (dd, J = 8.4, 2.2 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.79 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 7.8 Hz, 2H), 3.94 – 3.76 (m, 12H), 2.73 – 2.60 (m, 0.11H, 95%D), 2.56 – 2.46 (m, 2H), 2.44 – 2.29 (m, 2H), 2.20 (s, 3H), 2.15 – 1.99 (m, 2H), 1.84 (d, J = 13.7 Hz, 1H), 1.58 – 1.49 (m, 0.02H, 99%D), 0.79 (d, J = 6.7 Hz, 3.05H, 98%D); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.90, 148.73, 148.18, 147.24, 132.52, 130.47, 121.30, 120.36, 118.55, 111.91, 111.18, 111.01, 109.50, 59.04, 56.53, 55.86, 55.78, 55.73, 55.71, 53.18, 41.72, 37.77, 35.22, 32.14, 22.33, 18.81, 18.46; **IR** (neat) 2933, 1512, 1460, 1411, 1258, 1237, 1162, 1141, 1024, 804, 764 cm^{-1}.

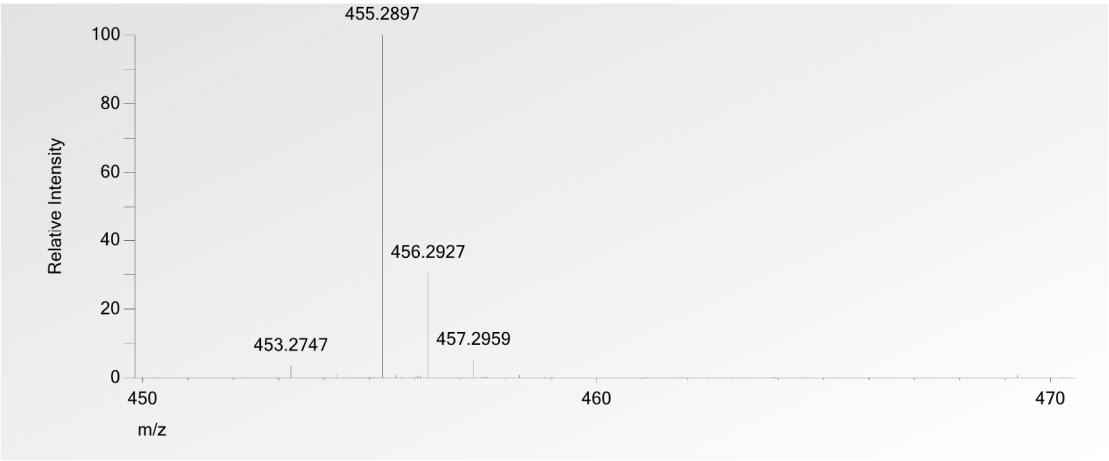

MeO
MeO
C2
[95%]
N
Me
[>98%]
C4
CN
i-Pr
MeO
OMe

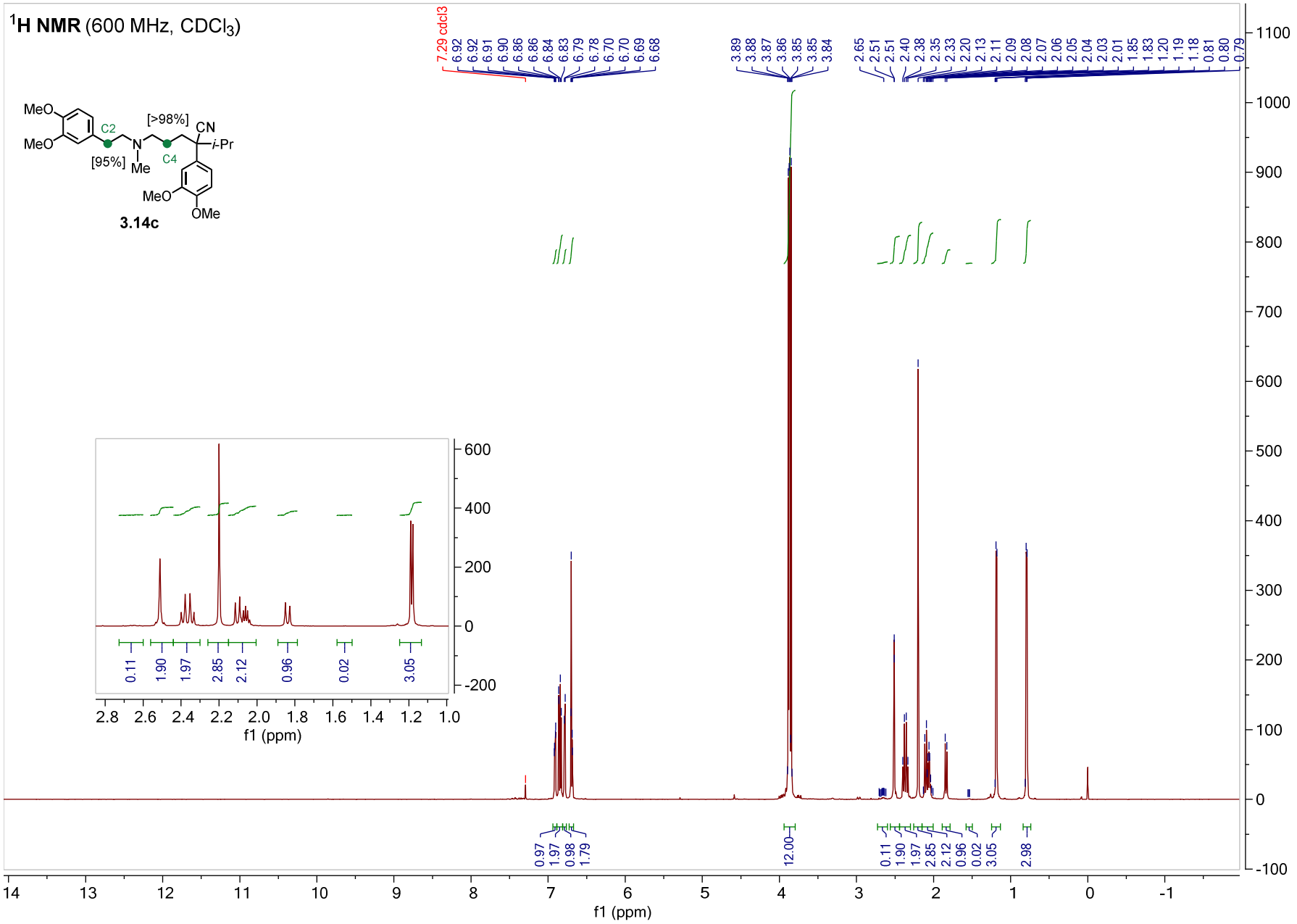
3.14c

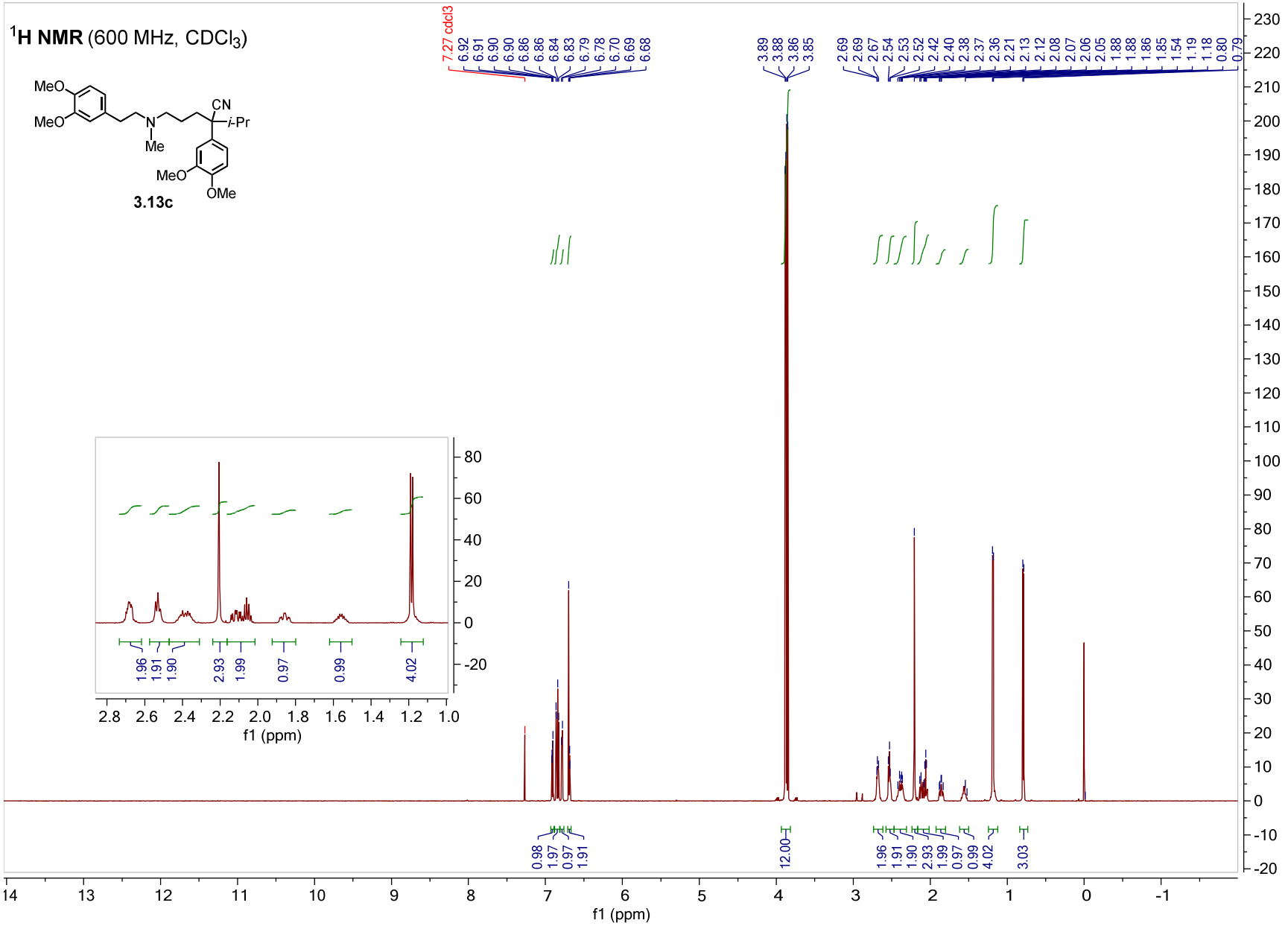

459.3208
100
80
60
40
20
0
Relative Intensity
460.3222
458.3113
461.3249
455.2899
456.2949
450
460
470
m/z


MeO
MeO
N
Me
CN
i-Pr
MeO
OMe

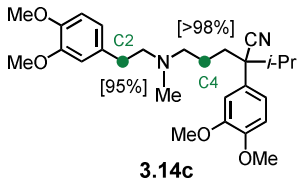
3.13c


455.2897
100
80
60
40
20
0
Relative Intensity
456.2927
453.2747
457.2959
450
460
470
m/z

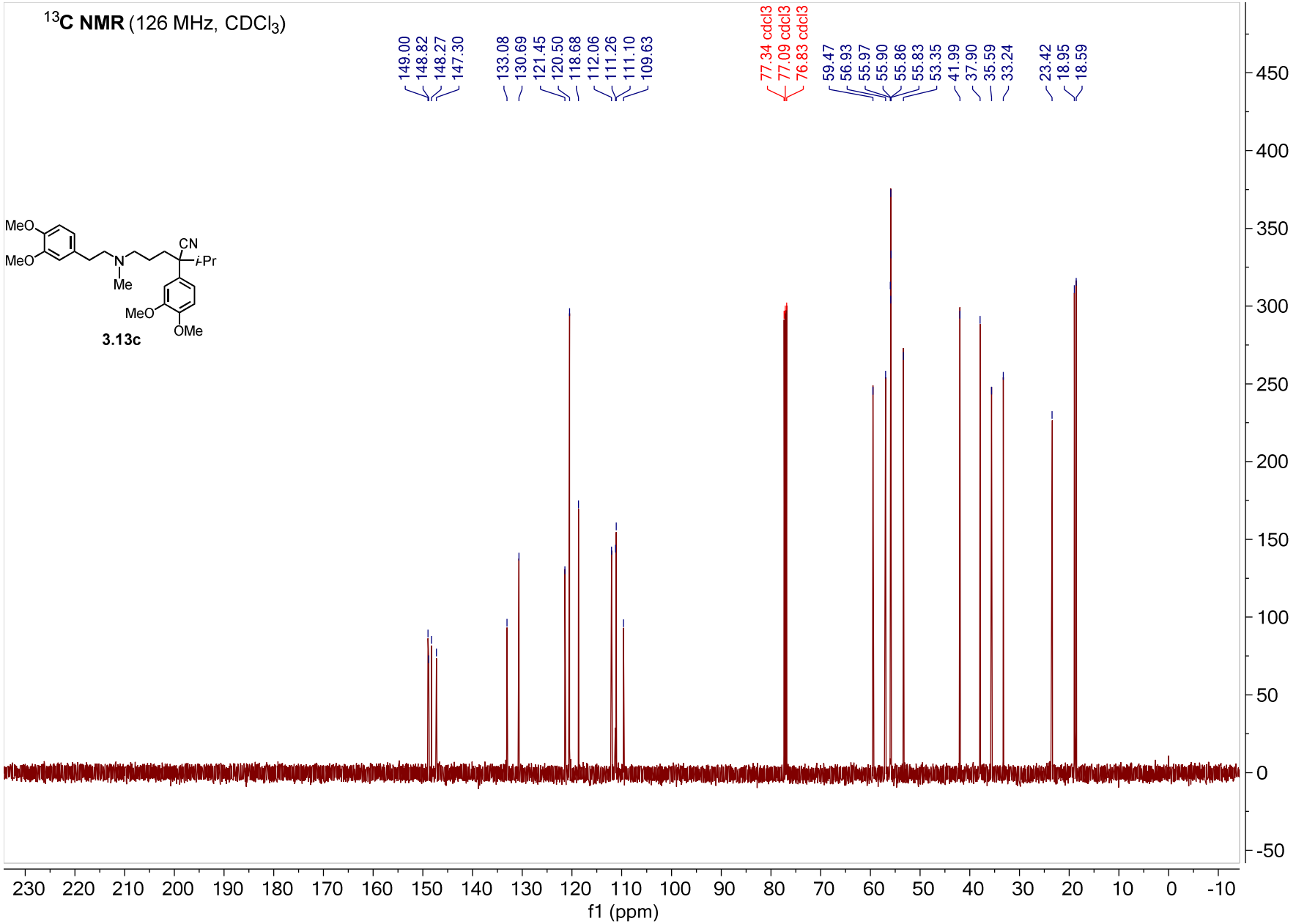

1H NMR (600 MHz, CDCl3)
MeO
MeO
C2
[95%]
N
Me
[>98%]
CN
i-Pr
C4
MeO
OMe
3.14c
7.29 cdcl3
6.92 6.92 6.91 6.90 6.86 6.86 6.84 6.83 6.79 6.78 6.70 6.70 6.69 6.68
3.89 3.88 3.87 3.86 3.85 3.85 3.84
2.65 2.51 2.51 2.40 2.38 2.35 2.33 2.20 2.13 2.11 2.09 2.08 2.07 2.06 2.05 2.04 2.03 2.01 1.85 1.83 1.20 1.19 1.18 0.81 0.80 0.79
0.11 1.90 1.97 2.85 2.12 0.96 0.02 3.05
f1 (ppm)
0.97 1.97 0.98 1.79
12.00
0.11 1.90 1.97 2.85 2.12 0.96 0.02 3.05 2.98
f1 (ppm)

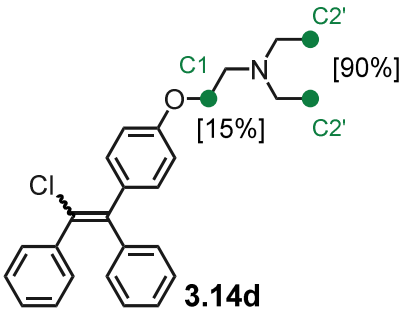

1H NMR (600 MHz, CDCl3)
MeO
MeO
N
Me
CN
i-Pr
MeO
OMe
3.13c
7.27 cdcl3
6.92 6.91 6.90 6.90 6.86 6.86 6.84 6.83 6.79 6.78 6.70 6.69 6.68
3.89 3.88 3.86 3.85
2.69 2.69 2.67 2.54 2.53 2.52 2.42 2.40 2.38 2.37 2.36 2.21 2.13 2.12 2.08 2.07 2.06 2.05 1.88 1.88 1.86 1.85 1.54 1.19 1.18 0.80 0.79
0.98 1.97 0.97 1.91
12.00
1.96 1.91 1.90 2.93 1.99 0.97 0.99 4.02 3.03
f1 (ppm)
1.96 1.91 1.90 2.93 1.99 0.97 0.99 4.02
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)



3.14c


13C NMR (126 MHz, CDCl3)
149.00
148.82
148.27
147.30
133.08
130.69
121.45
120.50
118.68
112.06
111.26
111.10
109.63
77.34 cdcl3
77.09 cdcl3
76.83 cdcl3
59.47
56.93
55.97
55.90
55.86
55.83
53.35
41.99
37.90
35.59
33.24
23.42
18.95
18.59
MeO
MeO
N
Me
CN
i-Pr
MeO
OMe
3.13c
450
400
350
300
250
200
150
100
50
0
-50
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
f1 (ppm)



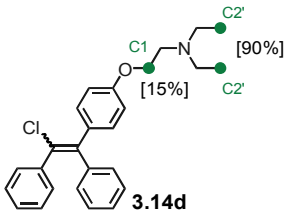
3.14d

Clomiphene, 3.14d

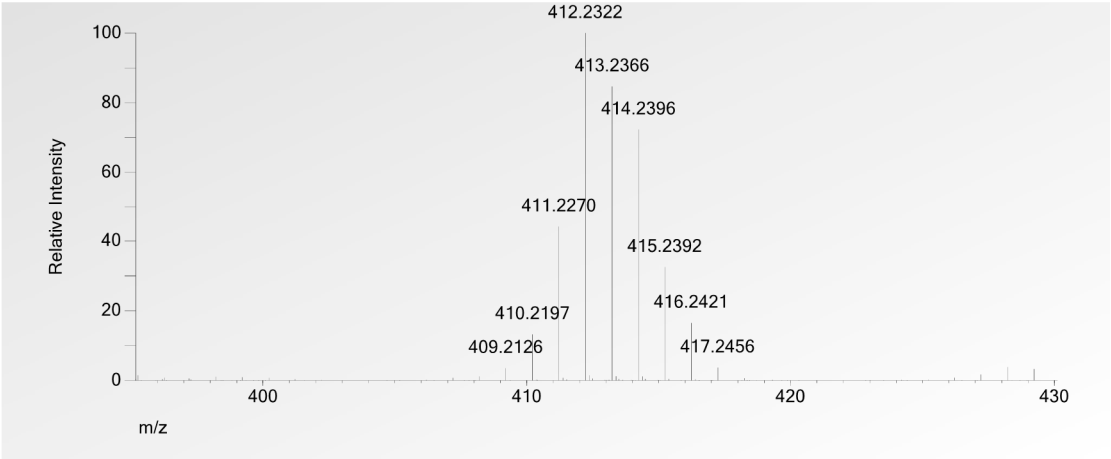
Clomiphene **3.13d** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (MeOH:DCM = 1:19), **3.14d** was obtained as a colorless liquid (78 mg, 0.19 mmol, 96% yield).

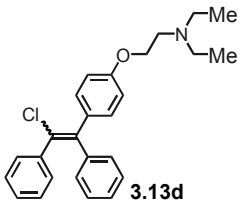
Deuterium incorporation: 5.70 D/molecule (^{1}H NMR), 6.89 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 6H), 7.22 – 7.13 (m, 3H), 7.11 – 6.93 (m, 1H), 6.87 (dd, *J* = 26.9, 8.7 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 4.16 – 3.93 (m, 1.71H, 15%D), 3.00 – 2.81 (m, 2H), 2.67 (d, *J* = 34.3 Hz, 4H), 1.13 – 0.98 (m, 0.61H, 90%D); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.98, 157.63, 142.12, 141.33, 139.87, 139.83, 139.58, 134.33, 133.48, 132.47, 131.79, 131.21, 130.65, 129.97, 129.89, 129.78, 129.67, 129.26, 128.98, 128.05, 127.95, 127.83, 127.42, 126.94, 113.93, 113.85, 66.88, 65.96, 60.29, 51.60, 51.51, 51.43, 51.34, 47.62, 47.56, 10.75; **IR** (neat) 2940, 2806, 1603, 1505, 1244, 1174, 1153, 1029, 758, 745, 695 cm^{-1}.

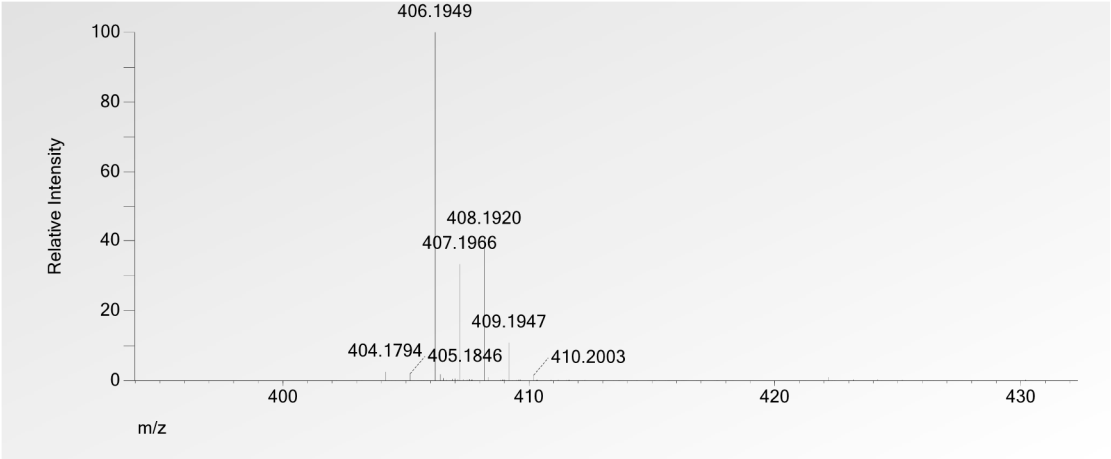

C2'
C1
N
[90%]
O
[15%]
C2'
Cl

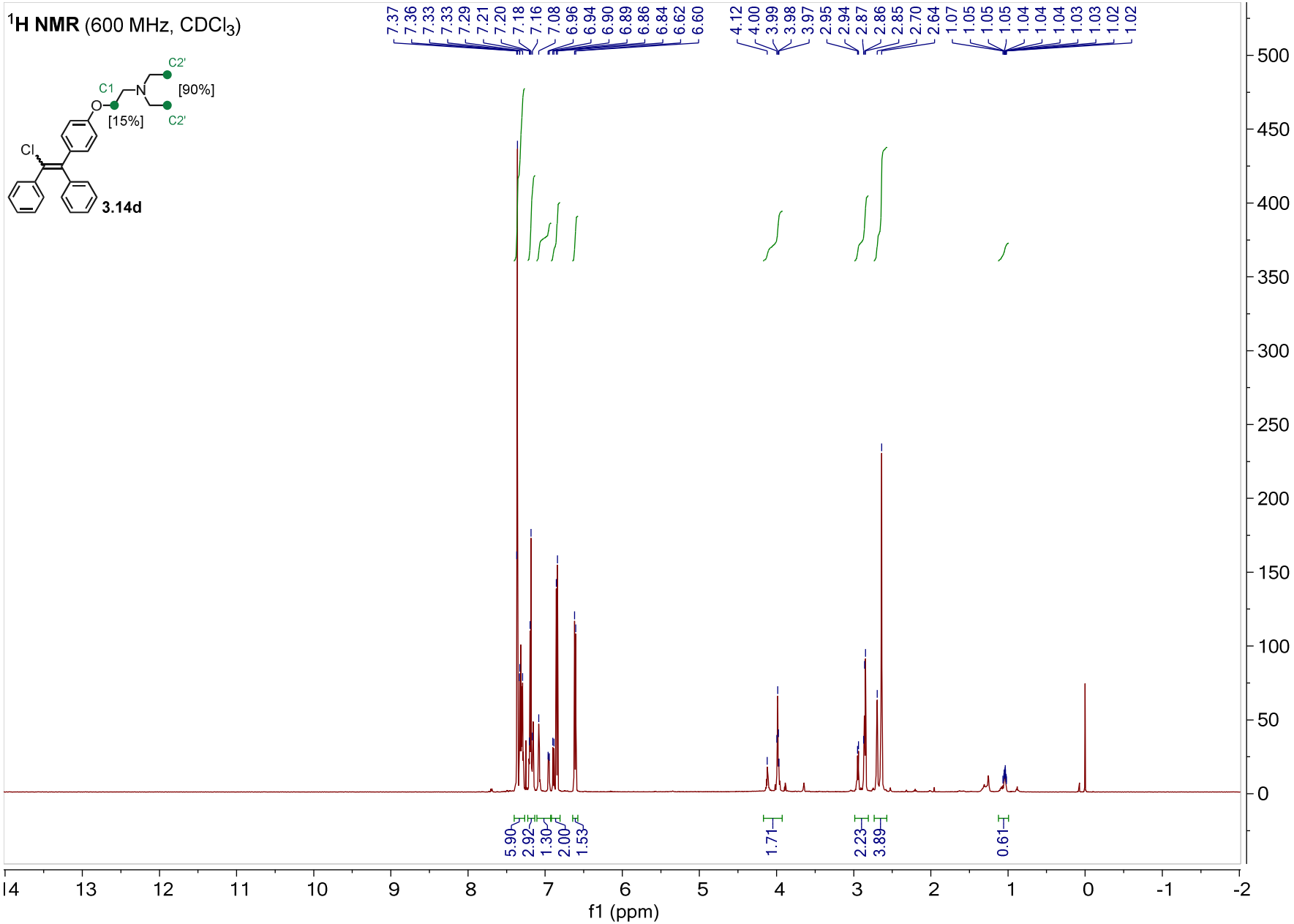
3.14d

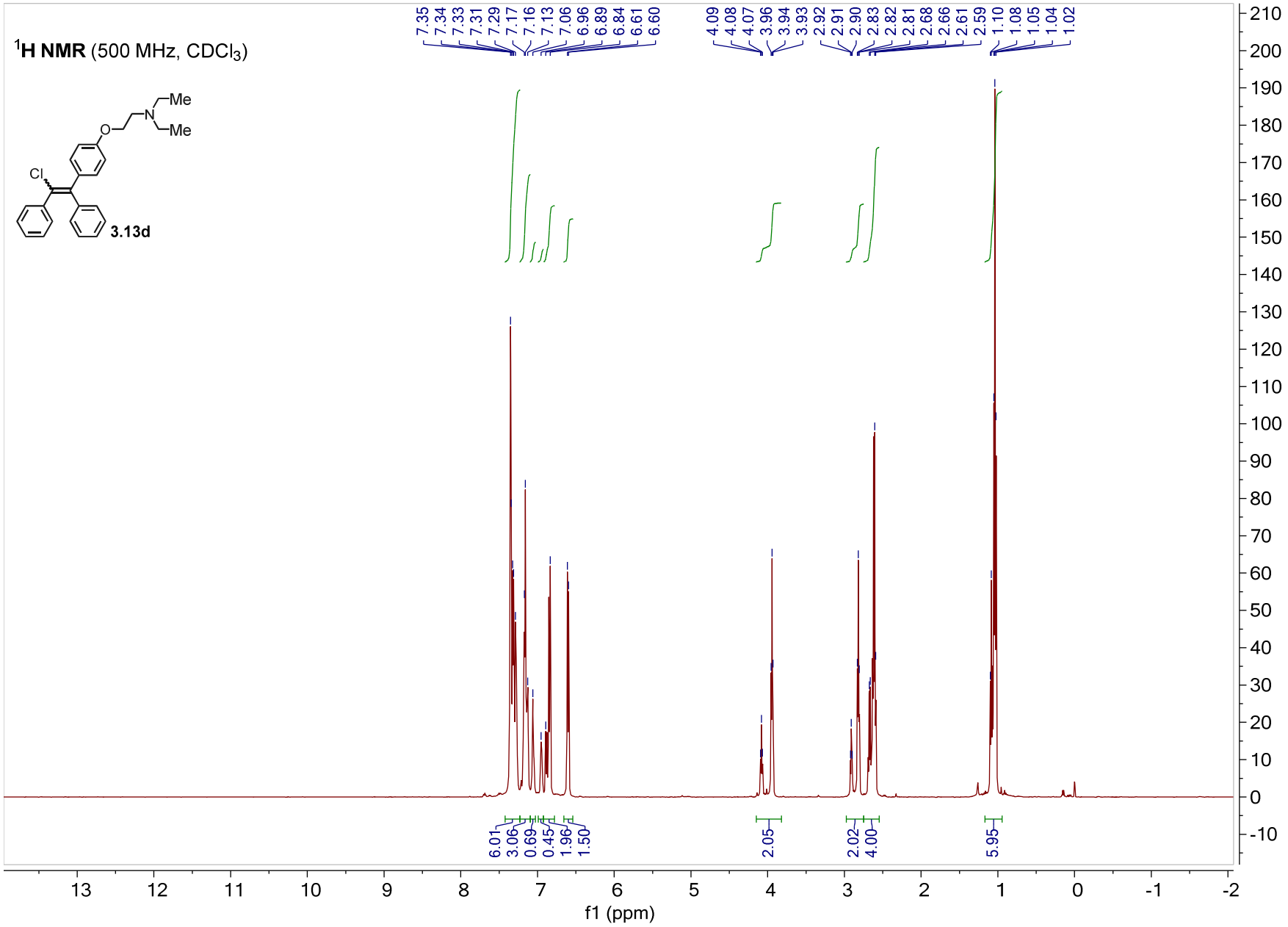

412.2322
413.2366
414.2396
411.2270
415.2392
416.2421
410.2197
409.2126
417.2456
Relative Intensity
m/z
100
80
60
40
20
0
400
410
420
430

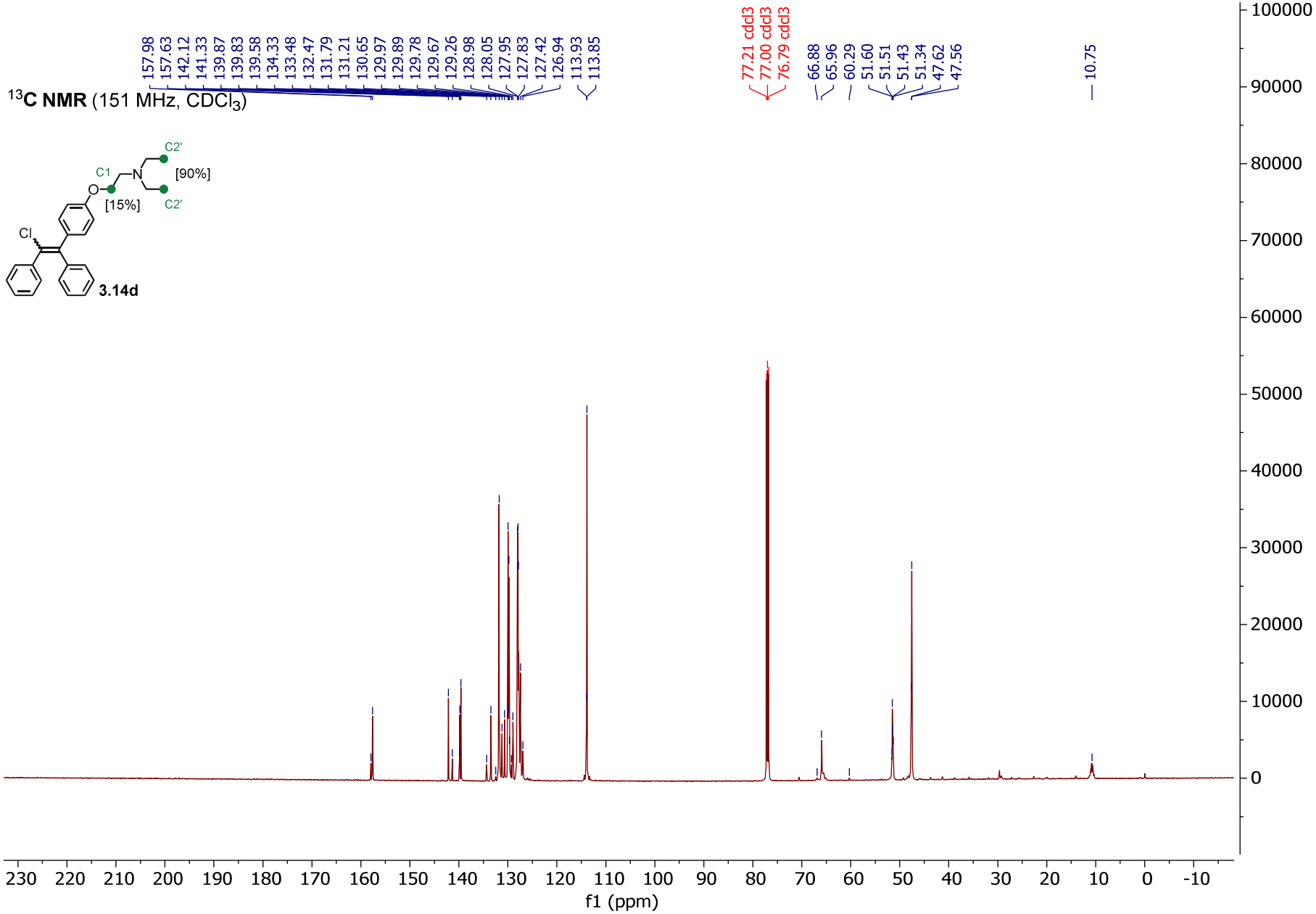

Me
N
Me
O
Cl

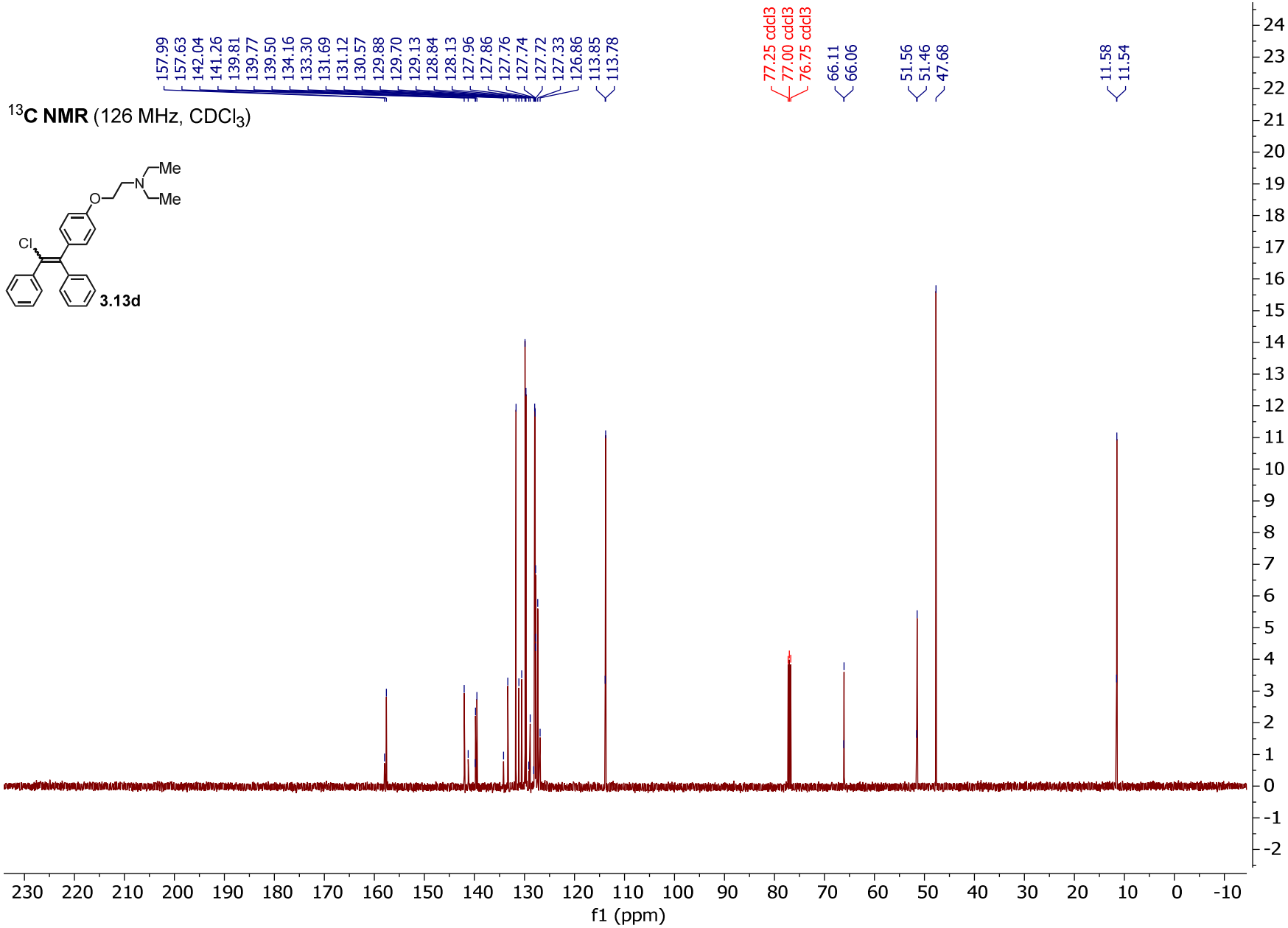
3.13d

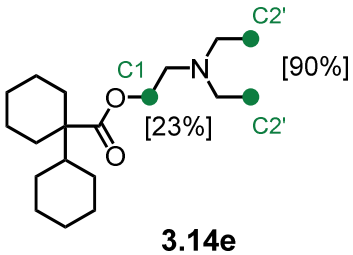

406.1949
408.1920
407.1966
409.1947
404.1794
405.1846
410.2003
Relative Intensity
m/z
100
80
60
40
20
0
400
410
420
430


1H NMR (600 MHz, CDCl3)
C2'
C1
N
[90%]
O
[15%]
C2'
Cl
3.14d
7.37 7.36 7.33 7.33 7.29 7.21 7.20 7.18 7.16 7.08 6.96 6.94 6.90 6.89 6.86 6.84 6.62 6.60
4.12 4.00 3.99 3.98 3.97 2.95 2.94 2.87 2.86 2.85 2.70 2.64 1.07 1.05 1.05 1.05 1.04 1.04 1.04 1.03 1.03 1.02 1.02
5.90 2.92 1.30 2.00 1.53 1.71 2.23 3.89 0.61
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Me
N
Me
O
Cl
3.13d
7.35
7.34
7.33
7.31
7.29
7.17
7.16
7.13
7.06
6.96
6.89
6.84
6.61
6.60
4.09
4.08
4.07
3.96
3.94
3.93
2.92
2.91
2.90
2.83
2.82
2.81
2.68
2.66
2.61
2.59
1.10
1.08
1.05
1.04
1.02
6.01
3.06
0.69
0.45
1.96
1.50
2.05
2.02
4.00
5.95
f1 (ppm)


157.98
157.63
142.12
141.33
139.87
139.83
139.58
134.33
133.48
132.47
131.79
131.21
130.65
129.97
129.89
129.78
129.67
129.26
128.98
128.05
127.95
127.83
127.42
126.94
113.93
113.85
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
66.88
65.96
60.29
51.60
51.51
51.43
51.34
47.62
47.56
10.75
13C NMR (151 MHz, CDCl3)
C2'
C1
N
[90%]
O
[15%]
C2'
Cl
3.14d
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
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
f1 (ppm)


157.99
157.63
142.04
141.26
139.81
139.77
139.50
134.16
133.30
131.69
131.12
130.57
129.88
129.70
129.13
128.84
128.13
127.96
127.86
127.76
127.74
127.72
127.33
126.86
113.85
113.78
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
66.11
66.06
51.56
51.46
47.68
11.58
11.54
13C NMR (126 MHz, CDCl3)
Me
N
Me
O
Cl
3.13d
f1 (ppm)



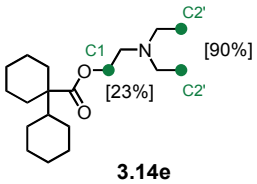
3.14e

Dicyclomine, 3.14e

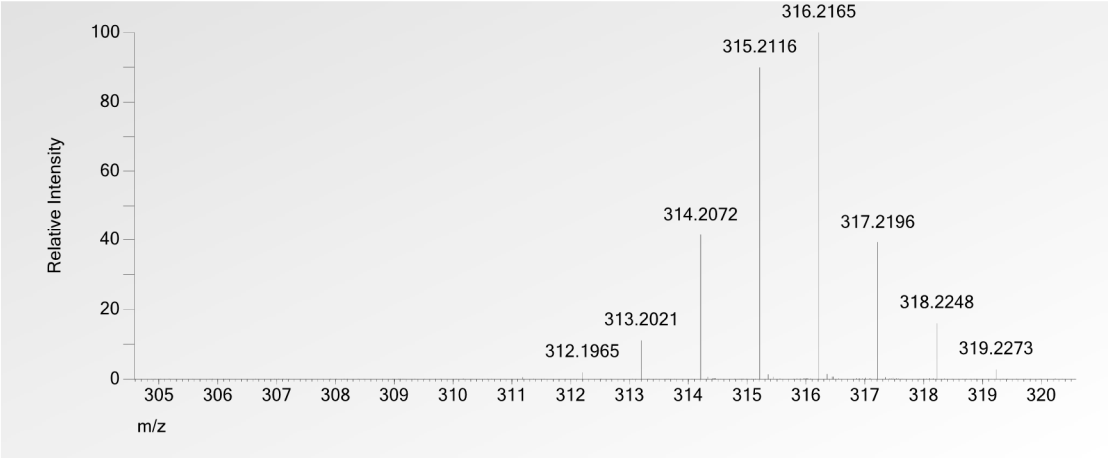
Dicyclomine **3.13e** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (MeOH:DCM = 1:49), **3.14e** was obtained as a colorless liquid (60 mg, 0.19 mmol, 97% yield).

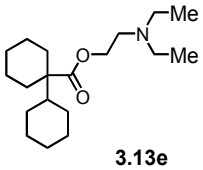
Deuterium incorporation: 5.86 D/molecule (^{1}H NMR), 5.50 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.17 (t, J = 6.3 Hz, 1.55H, 23%D), 2.73 (t, J = 6.5 Hz, 2H), 2.58 (d, J = 7.0 Hz, 4H), 2.06 (d, J = 12.4 Hz, 2H), 1.75 (m, 2H), 1.69 (d, J = 12.9 Hz, 2H), 1.66 – 1.54 (m, 4H), 1.37 – 1.24 (m, 3H), 1.23 – 1.06 (m, 6H), 1.06 – 1.02(m, 0.59H, 90%D), 1.02 – 0.93 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 176.15, 77.21, 77.00, 76.79, 62.02, 51.08, 50.73, 47.30, 46.79, 31.45, 31.40, 27.78, 27.74, 27.03, 26.55, 26.04, 26.00, 23.75, 11.21; **IR** (neat) 2923, 2850, 1720, 1449, 1207, 1194, 1171, 1156, 1125, 1101, 1049 cm^{-1}.

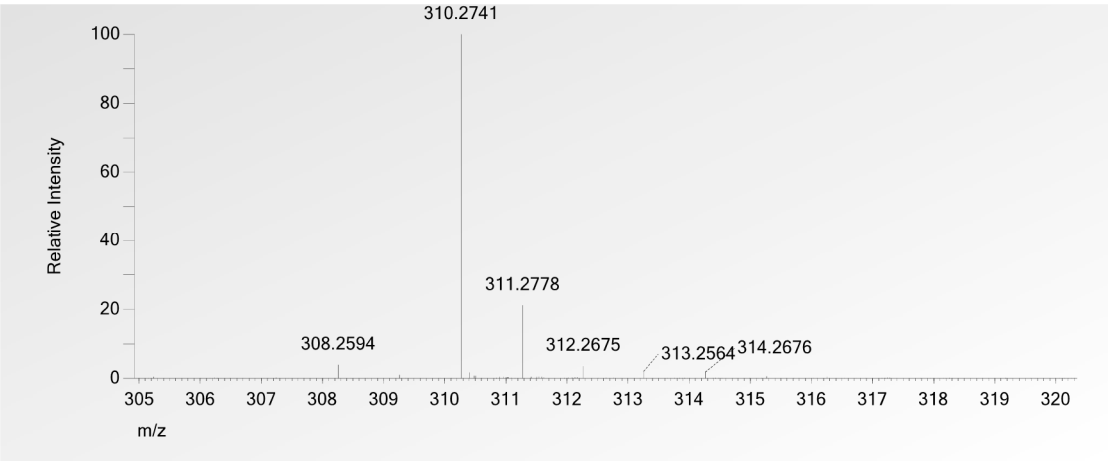

C2'
C1
N
[90%]
O
[23%]
C2'
O

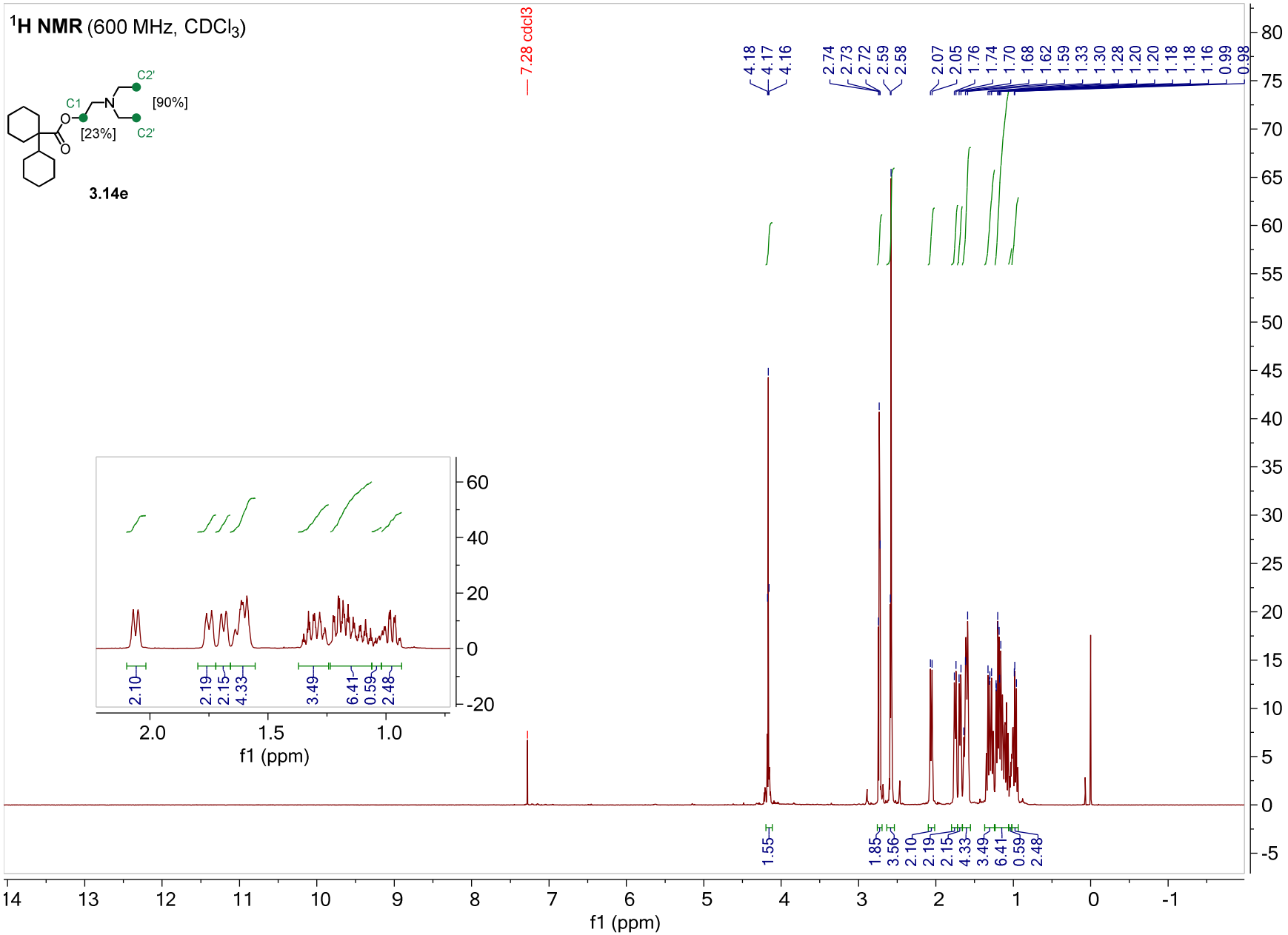
3.14e

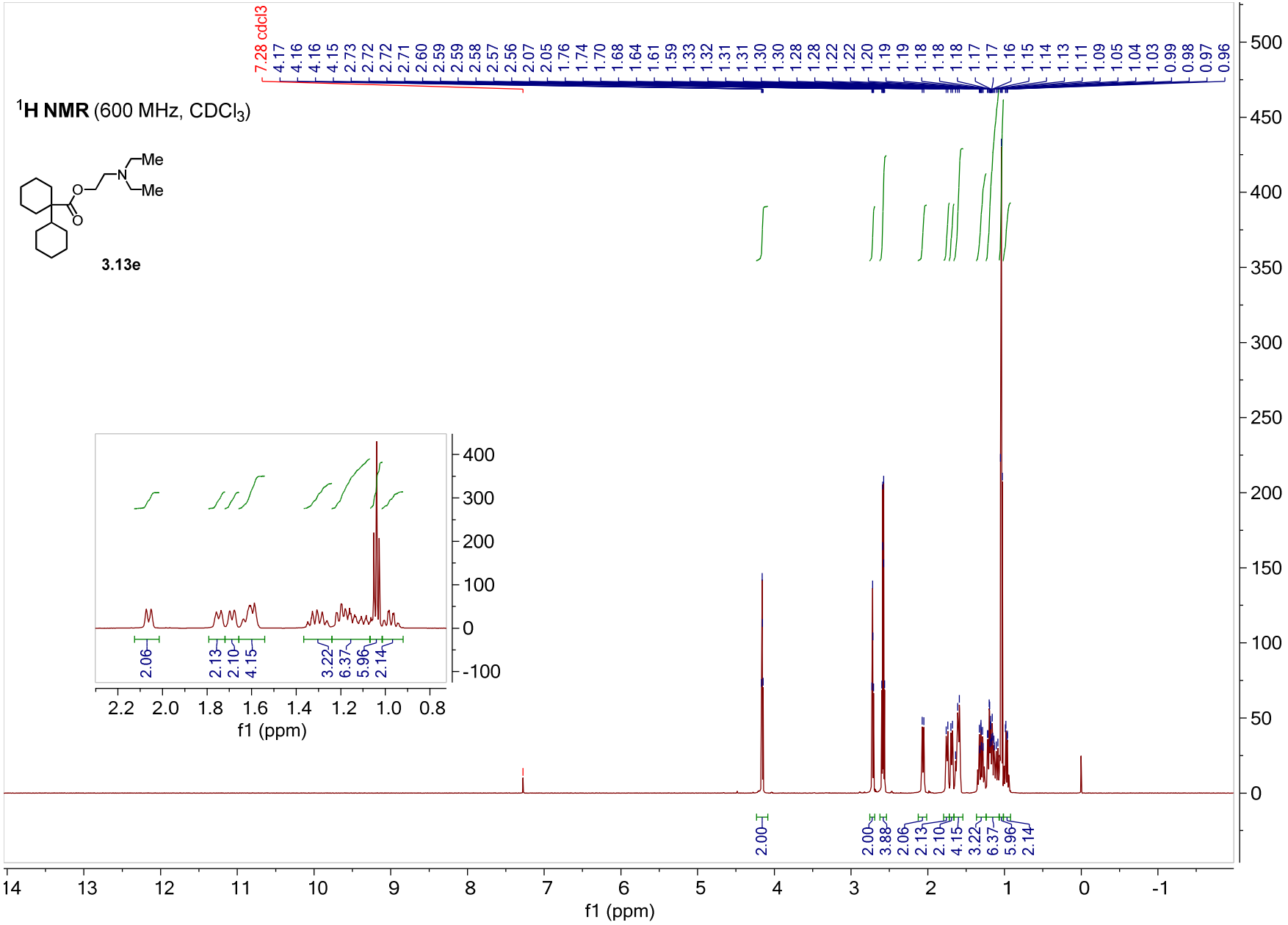

316.2165
315.2116
100
80
60
40
20
0
Relative Intensity
314.2072
317.2196
318.2248
313.2021
319.2273
312.1965
305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320
m/z

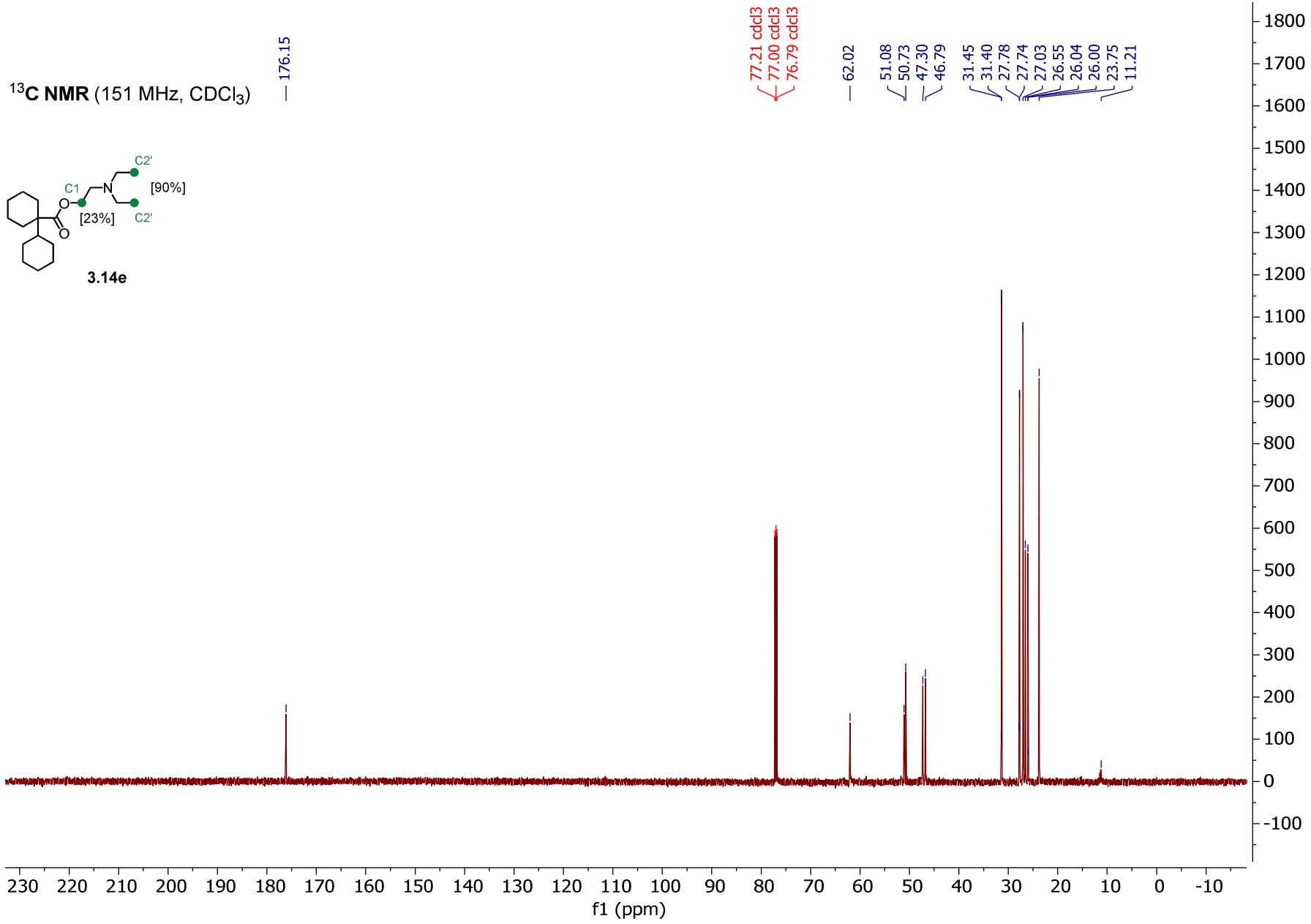

Me
N
Me
O
O

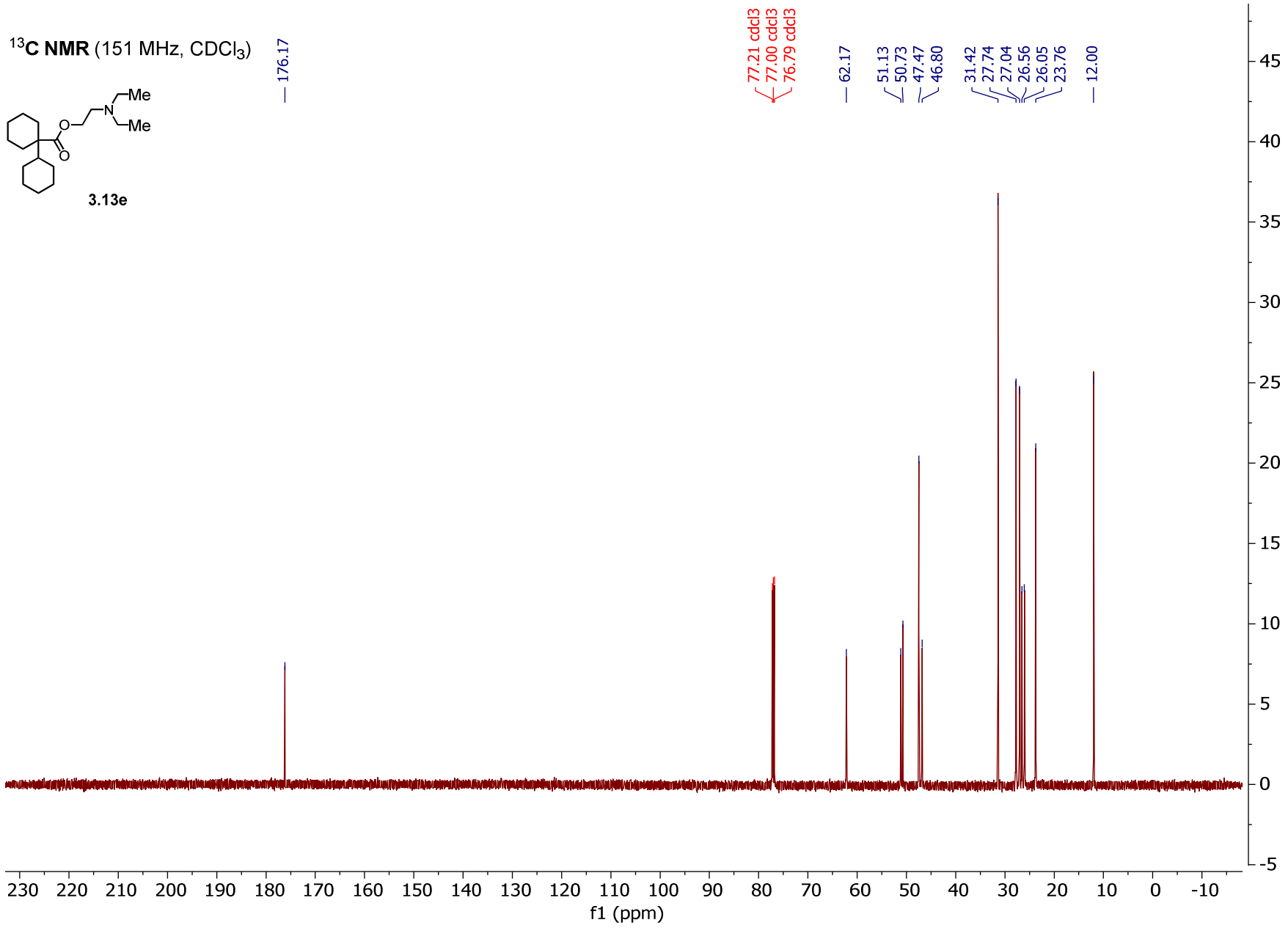
3.13e

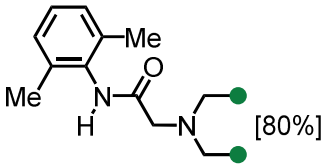

310.2741
100
80
60
40
20
0
Relative Intensity
311.2778
308.2594
312.2675
313.2564
314.2676
305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320
m/z


1H NMR (600 MHz, CDCl3)
C2'
C1
N
[90%]
O
[23%]
C2'
O
3.14e
7.28 cdcl3
4.18
4.17
4.16
2.74
2.73
2.72
2.59
2.58
2.07
2.05
1.76
1.74
1.70
1.68
1.62
1.59
1.33
1.30
1.28
1.20
1.20
1.18
1.18
1.16
0.99
0.98
2.10
2.19
2.15
4.33
3.49
6.41
0.59
2.48
f1 (ppm)
1.55
1.85
3.56
2.10
2.19
2.15
4.33
3.49
6.41
0.59
2.48
f1 (ppm)


7.28 cdcl3
4.17 4.16 4.16 4.15 2.73 2.72 2.72 2.71 2.60 2.59 2.59 2.58 2.57 2.56 2.07 2.05 1.76 1.74 1.70 1.68 1.64 1.61 1.59 1.33 1.32 1.31 1.31 1.30 1.30 1.28 1.28 1.22 1.22 1.20 1.19 1.19 1.18 1.18 1.18 1.17 1.17 1.16 1.15 1.14 1.13 1.11 1.09 1.05 1.04 1.03 0.99 0.98 0.97 0.96
^{1}H NMR (600 MHz, $CDCl_3$)
Me
N
Me
O
O
3.13e
2.06 2.13 2.10 4.15 3.22 6.37 5.96 2.14
2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)
2.00 2.00 3.88 2.06 2.13 2.10 4.15 3.22 6.37 5.96 2.14
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


13C NMR (151 MHz, CDCl3)
176.15
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
62.02
51.08
50.73
47.30
46.79
31.45
31.40
27.78
27.74
27.03
26.55
26.04
26.00
23.75
11.21
C2'
C1
N
[90%]
O
[23%]
C2'
O
3.14e
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Me
N
Me
O
O
3.13e
176.17
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
62.17
51.13
50.73
47.47
46.80
31.42
27.74
27.04
26.56
26.05
23.76
12.00
f1 (ppm)



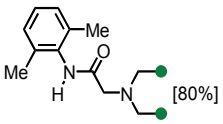
3.14f

Lidocaine, 3.14f

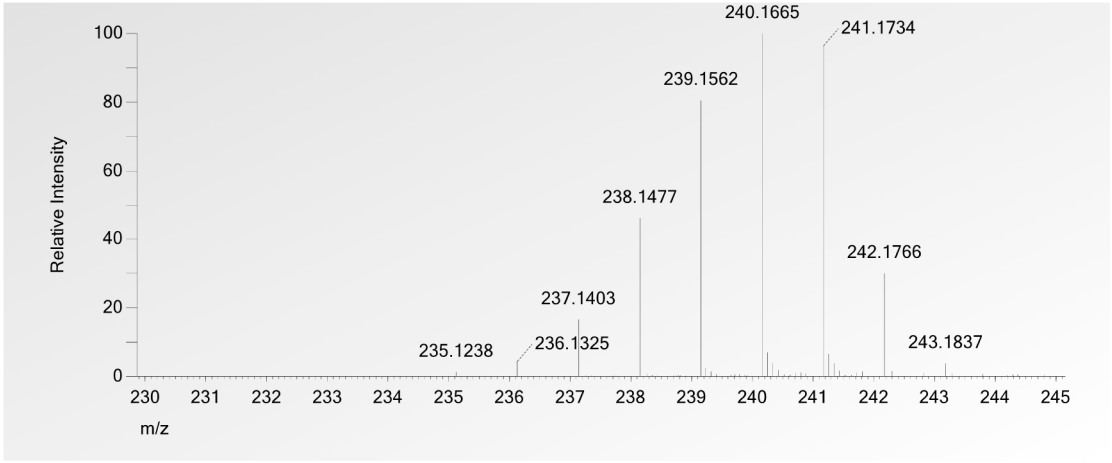
Lidocaine **3.13f** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (MeOH:DCM = 1:49), **3.14f** was obtained as a white solid (46 mg, 0.20 mmol, 99% yield).

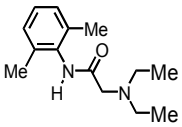
Deuterium incorporation: 4.80 D/molecule (^{1}H NMR), 4.78 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.08 (s, 3H), 3.21 (s, 2H), 2.77 – 2.54 (m, 4H), 2.23 (s, 6H), 1.23 – 1.01 (m, 1.23H, 80%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.09, 134.90, 133.85, 128.04, 126.86, 57.41, 48.82, 48.76, 48.70, 48.64, 18.40, 11.94; **IR** (neat) 3265, 2936, 2818, 2219, 1684, 1491, 1284, 1163, 1051, 767 cm^{-1}.

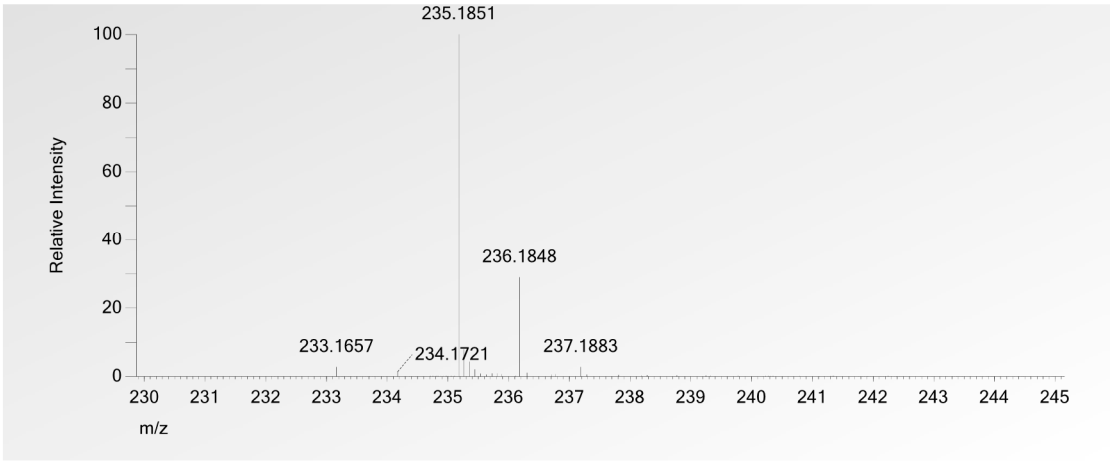

Me
O
Me
N
H
N
[80%]

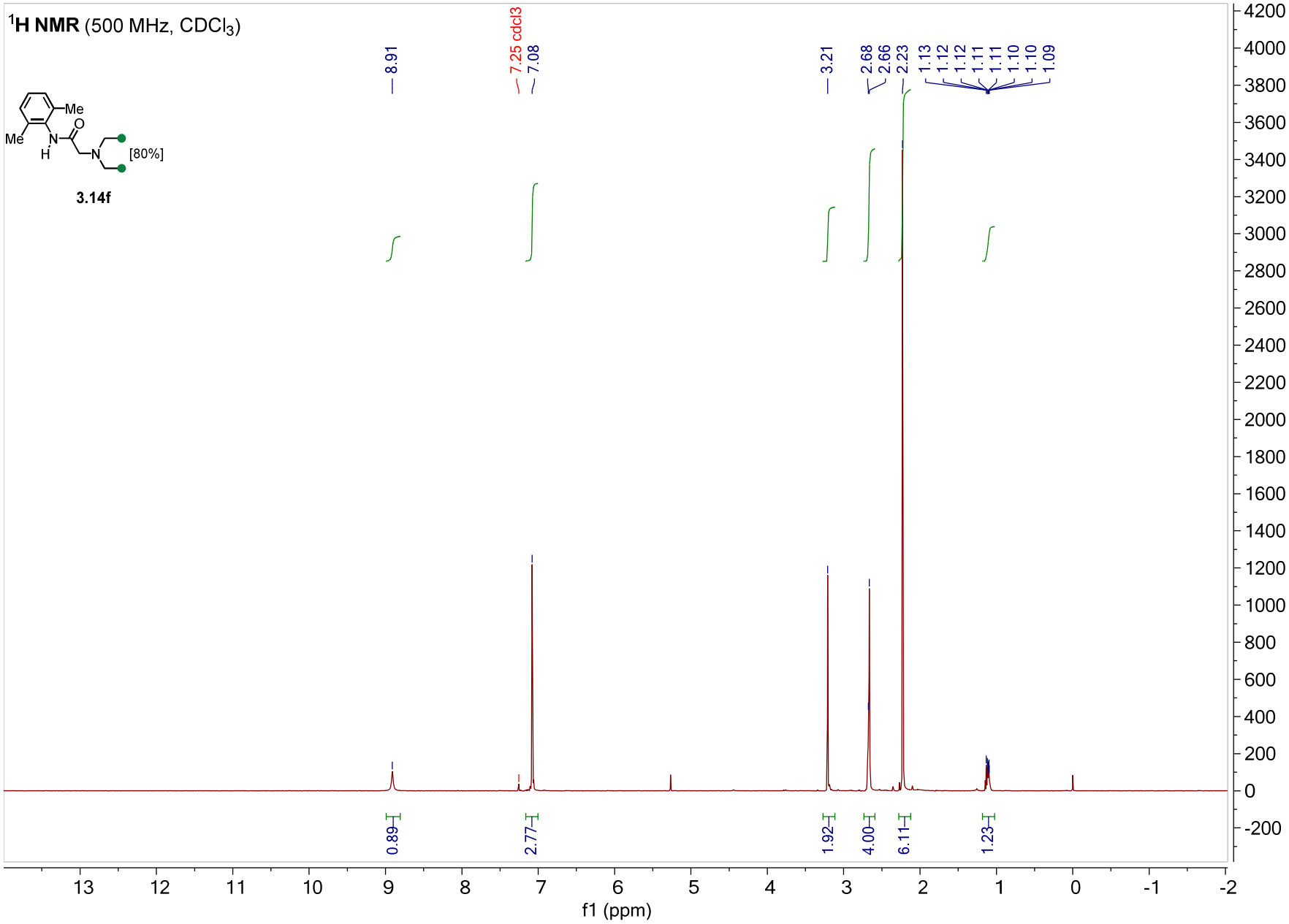
3.14f

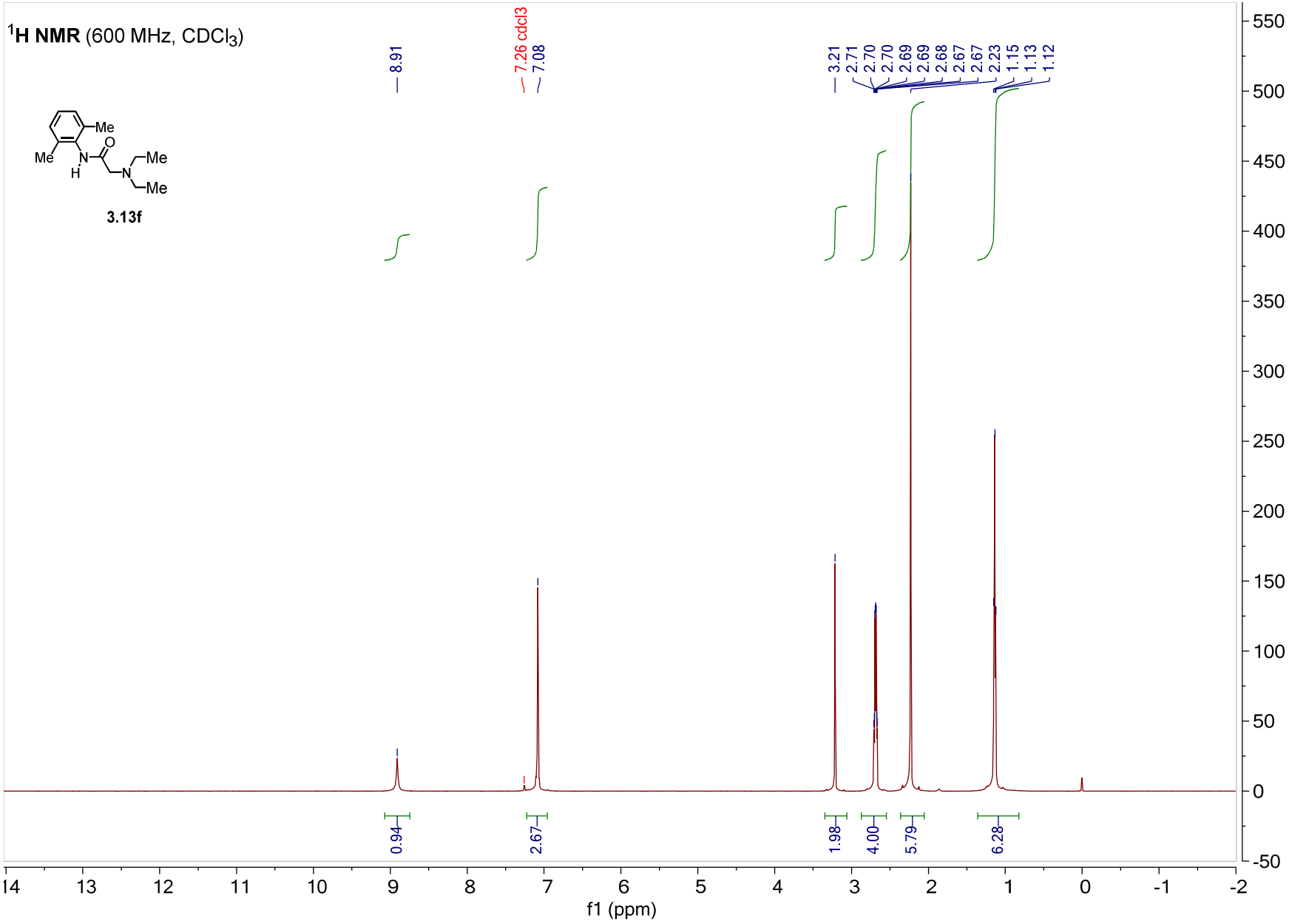

240.1665
241.1734
239.1562
238.1477
242.1766
237.1403
235.1238
236.1325
243.1837
Relative Intensity
m/z

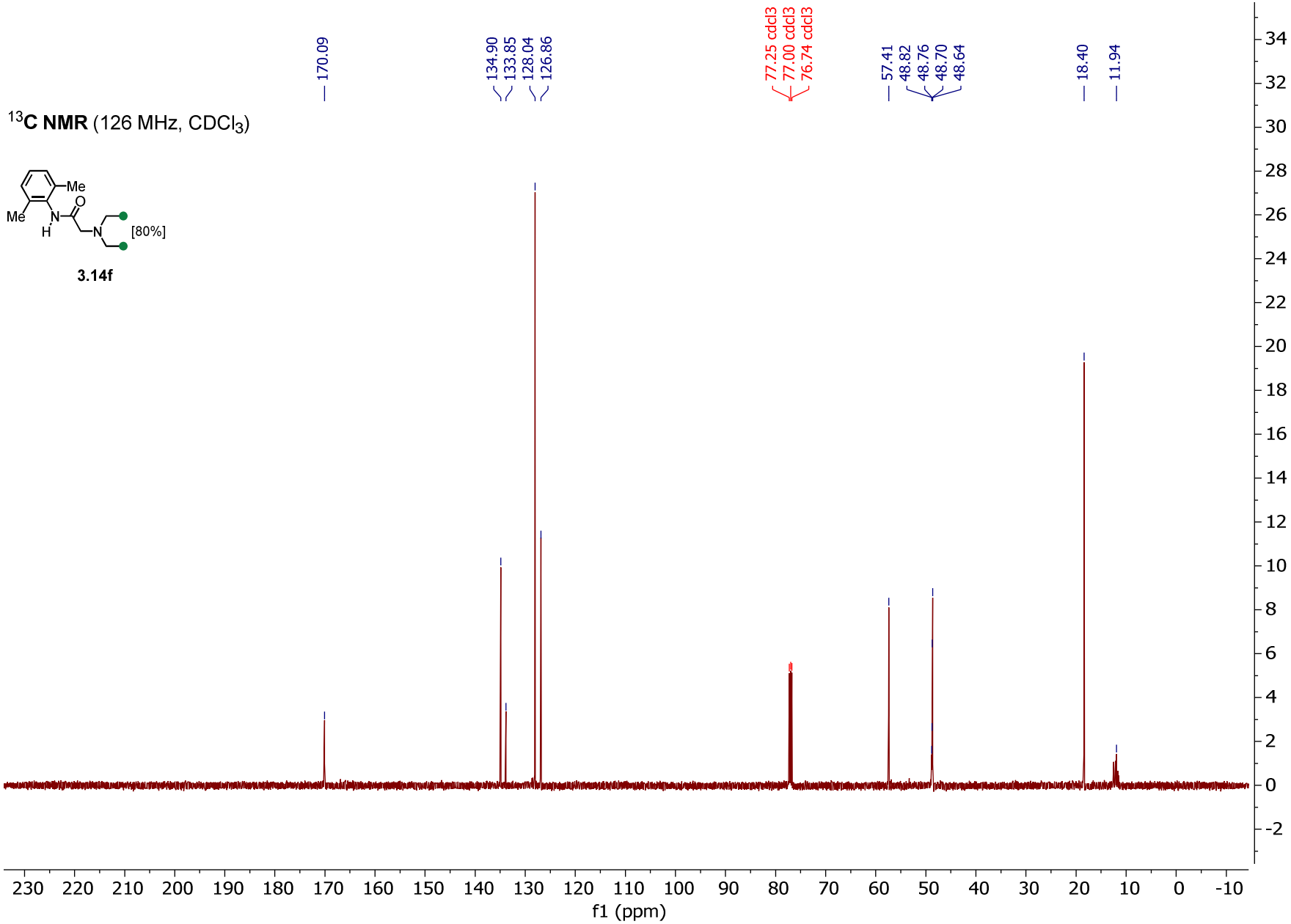

Me
O
Me
N
H
N
Me
Me

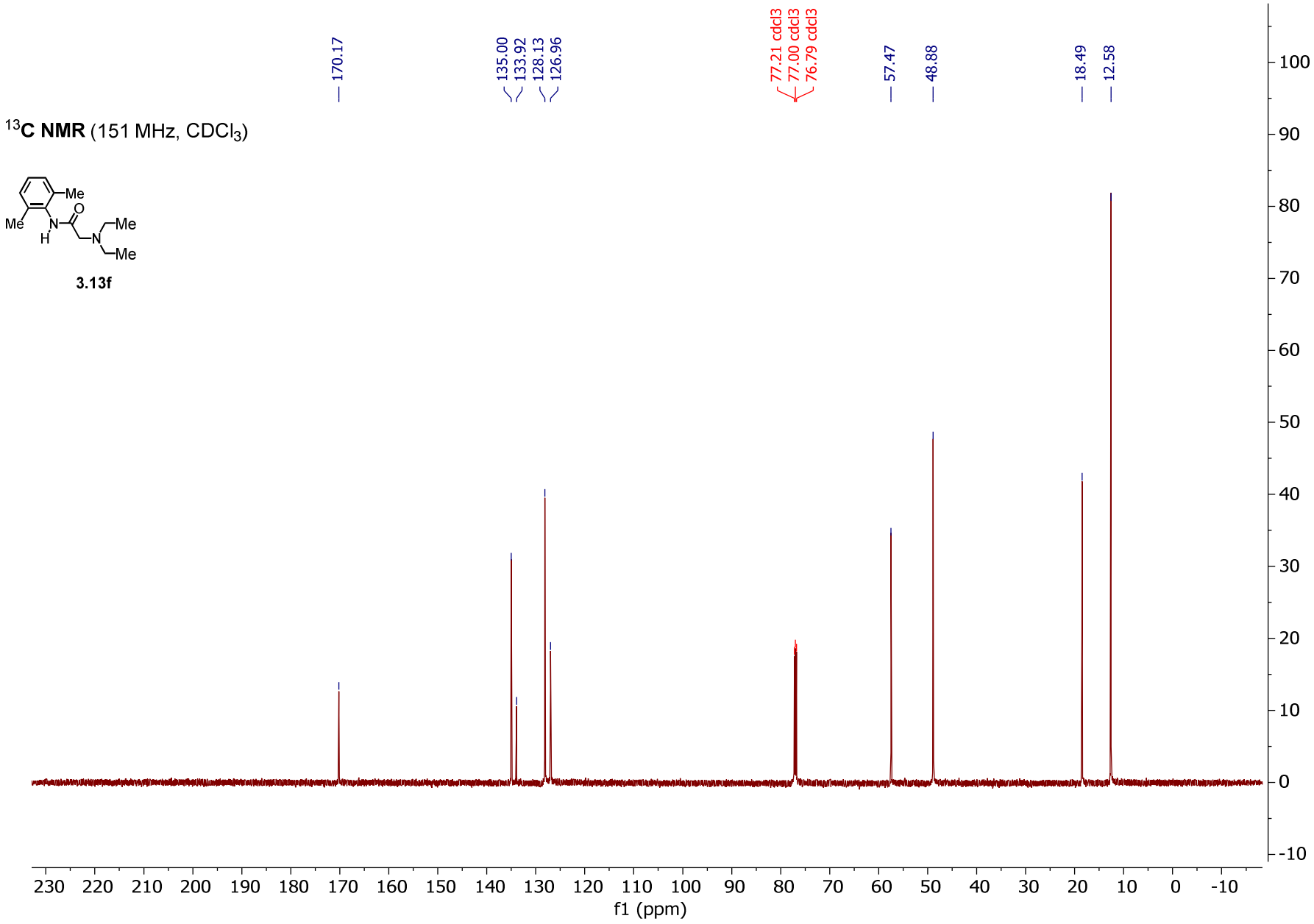
3.13f

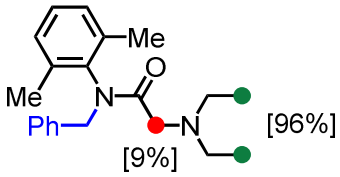

235.1851
236.1848
233.1657
234.1721
237.1883
Relative Intensity
m/z


1H NMR (500 MHz, CDCl3)
Me
Me
N
H
O
N
[80%]
3.14f
8.91
7.25 cdcl3
7.08
3.21
2.68
2.66
2.23
1.13
1.12
1.12
1.11
1.11
1.10
1.10
1.09
0.89
2.77
1.92
4.00
6.11
1.23
f1 (ppm)


1H NMR (600 MHz, CDCl3)
Me
Me
O
N
H
N
Me
Me
3.13f
8.91
7.26 cdcl3
7.08
3.21
2.71
2.70
2.70
2.69
2.69
2.68
2.67
2.67
2.23
1.15
1.13
1.12
0.94
2.67
1.98
4.00
5.79
6.28
f1 (ppm)


13C NMR (126 MHz, CDCl3)
Me
Me
N
H
O
N
[80%]
3.14f
170.09
134.90
133.85
128.04
126.86
77.25 cdcl3
77.00 cdcl3
76.74 cdcl3
57.41
48.82
48.76
48.70
48.64
18.40
11.94
f1 (ppm)


170.17
135.00
133.92
128.13
126.96
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
57.47
48.88
18.49
12.58
13C NMR (151 MHz, CDCl3)
Me
Me
N
H
O
N
Me
Me
3.13f
f1 (ppm)



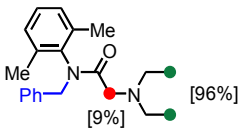
3.14g

***N*-Bn lidocaine, 3.14g**

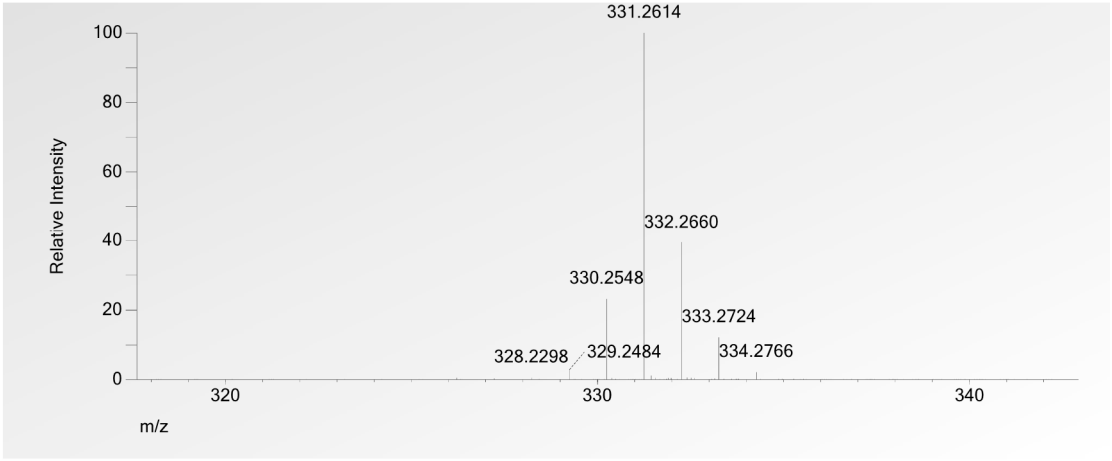
N-Bn lidocaine **3.13g** was added to acetone-d_6 **3.3** following the General Procedure B. After purification by silica gel chromatography (MeOH:DCM = 1:49), **3.14g** was obtained as a yellow liquid (62 mg, 0.19 mmol, 96% yield).

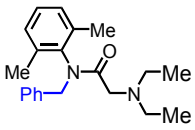
Deuterium incorporation: 6.18 D/molecule (^{1}H NMR), 6.26 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 5H), 7.13 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 2H), 4.73 (s, 1.82H, 9%D), 2.81 (s, 2H), 2.57 (s, 4H), 1.87 (s, 6H), 0.88 (s, 0.22H, 96%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.35, 138.91, 137.06, 136.33, 130.23, 129.03, 128.26, 128.11, 127.60, 54.55, 51.77, 47.30, 17.86, 11.04; **IR** (neat) 2926, 1650, 1460, 1400, 1242, 1141, 1078, 773, 743, 700 cm^{-1}.

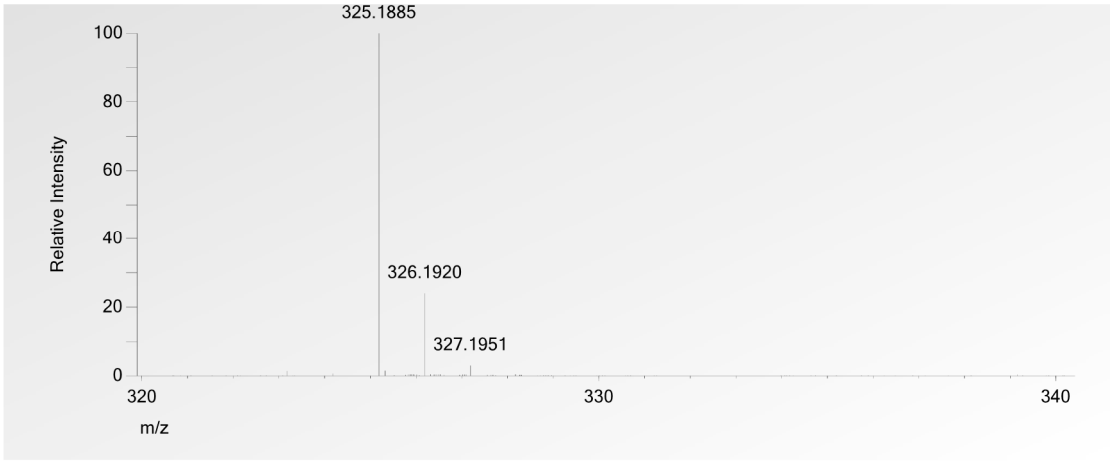

Me
O
Me
N
Ph
N
[96%]
[9%]

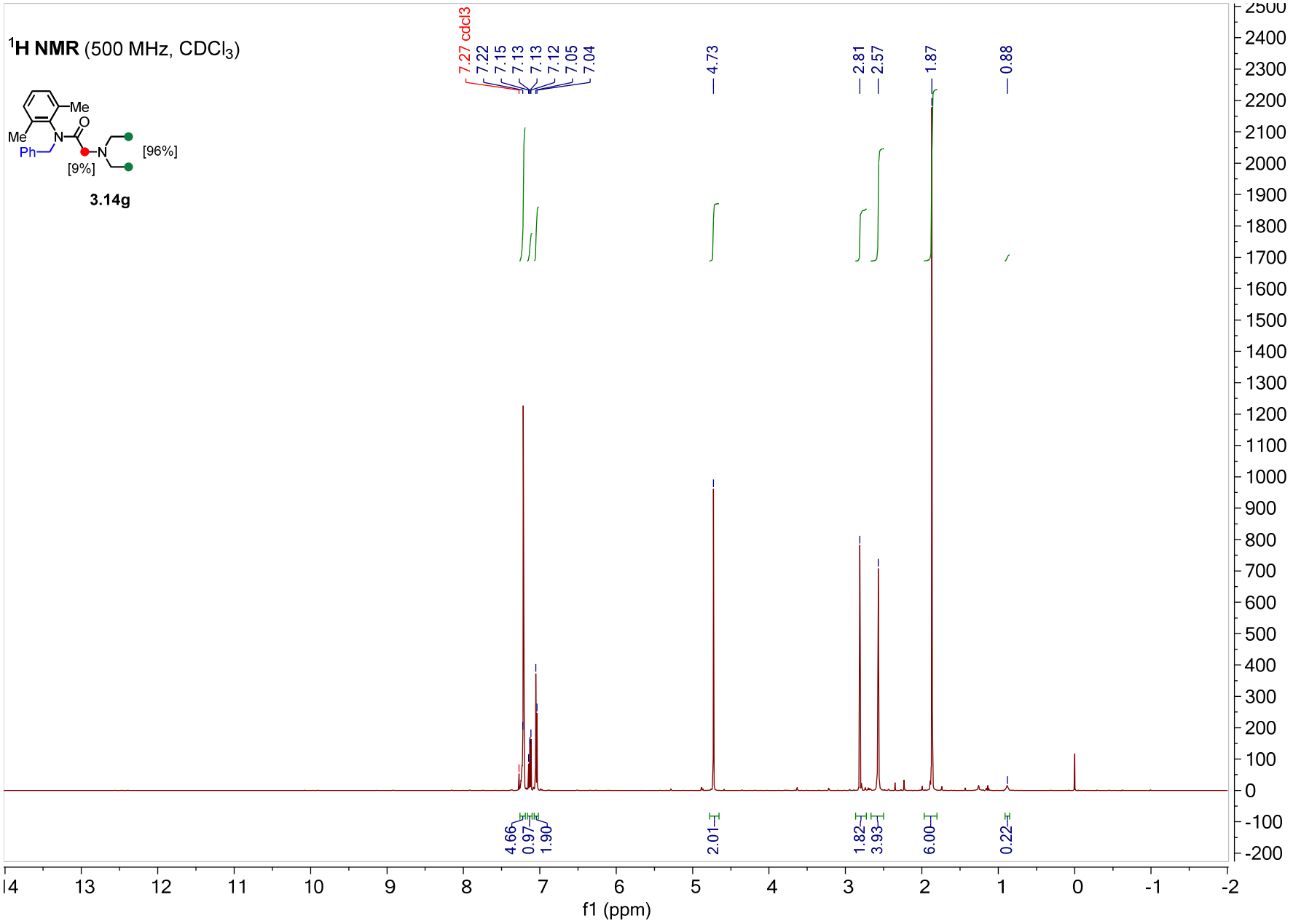
3.14g

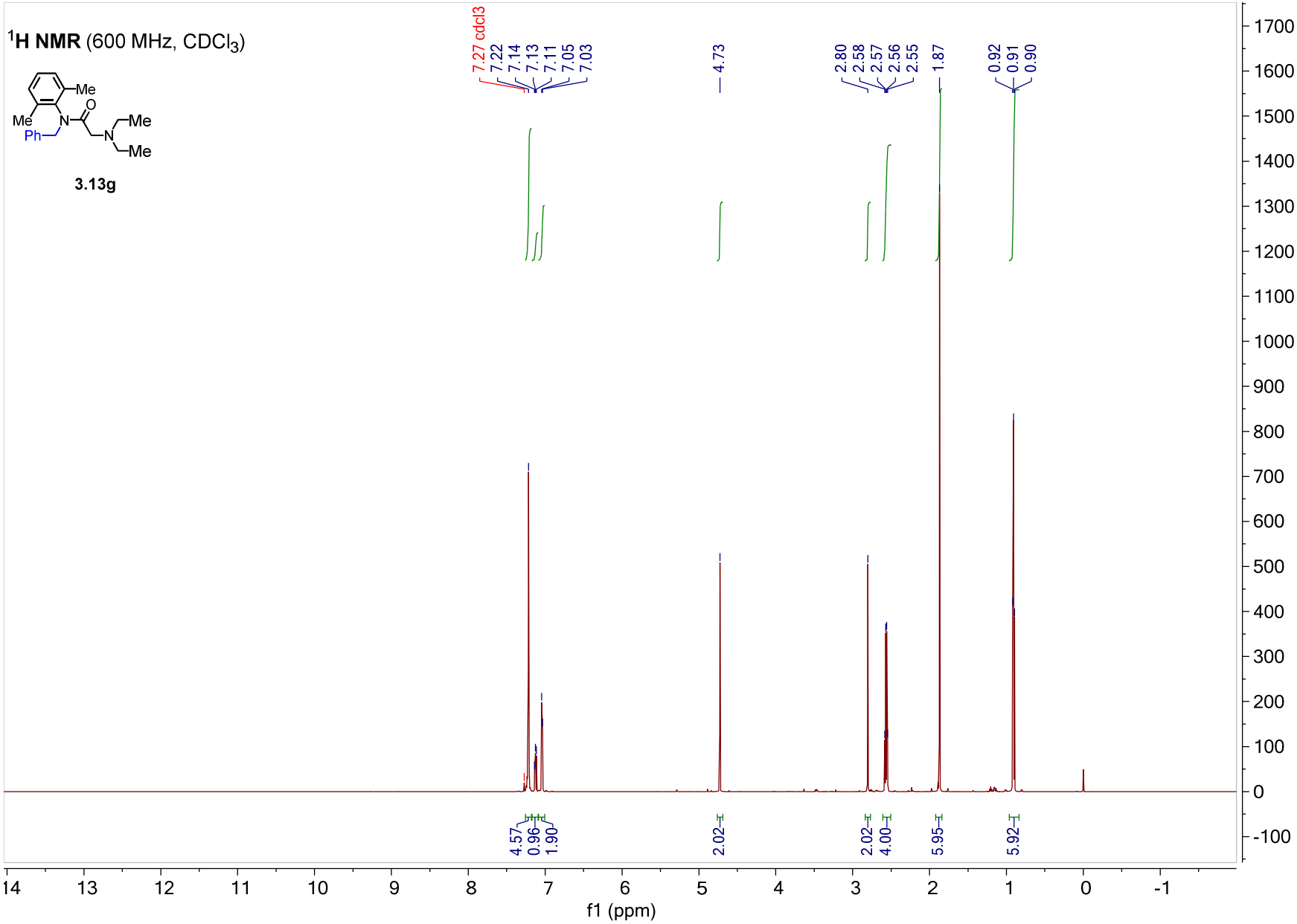

331.2614
100
80
60
40
20
0
Relative Intensity
332.2660
330.2548
333.2724
328.2298
329.2484
334.2766
320
330
340
m/z

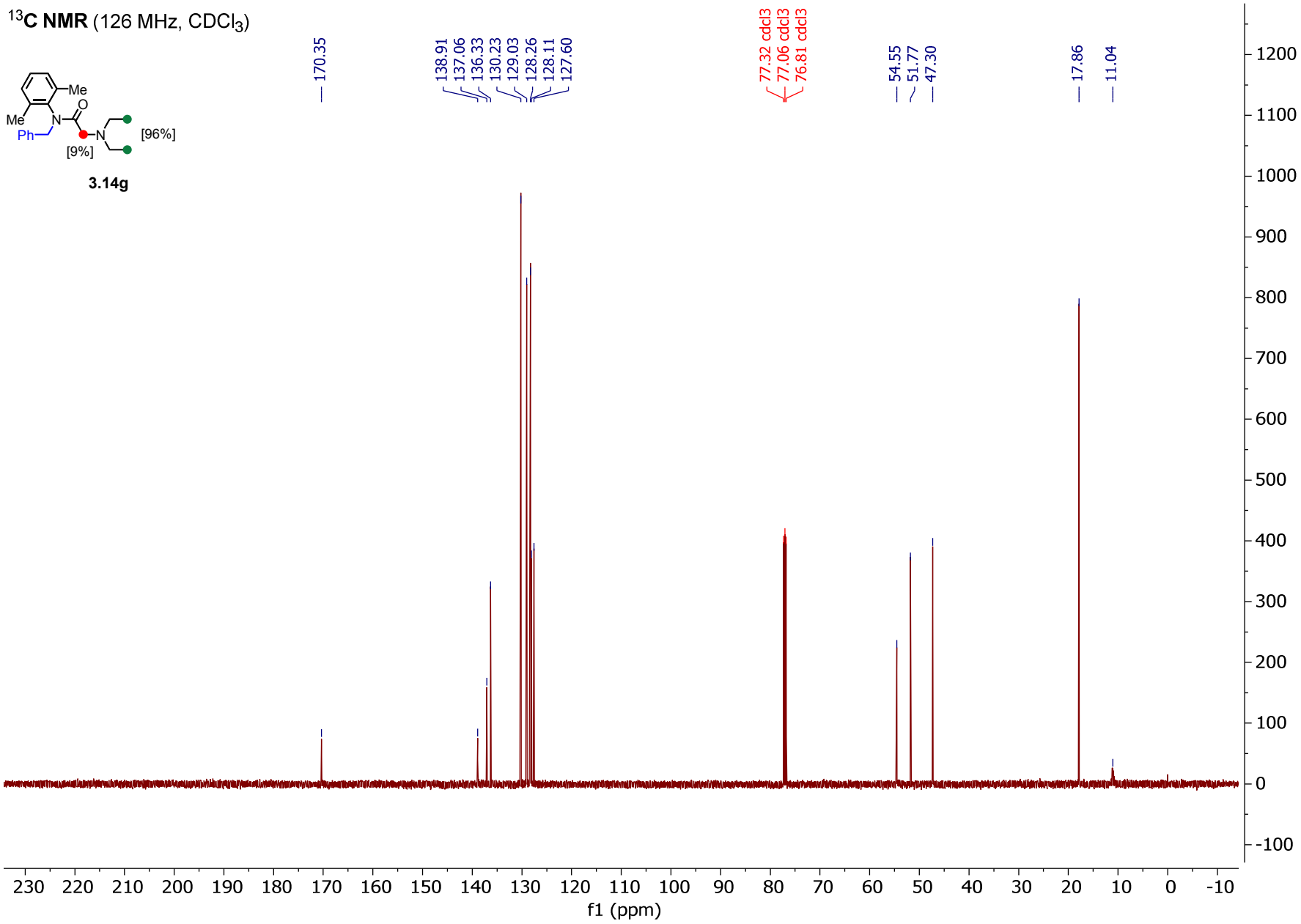

Me
O
Me
N
Me
Ph
N
Me

3.13g

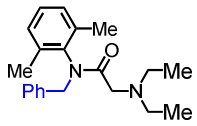

325.1885
100
80
60
40
20
0
Relative Intensity
326.1920
327.1951
320
330
340
m/z


1H NMR (500 MHz, CDCl3)
Me
Me
N
O
Ph
N
[9%]
[96%]
3.14g
7.27 cdcl3
7.22
7.15
7.13
7.13
7.12
7.05
7.04
4.73
2.81
2.57
1.87
0.88
4.66
0.97
1.90
2.01
1.82
3.93
6.00
0.22
f1 (ppm)

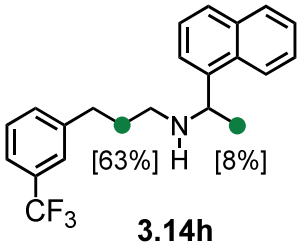

1H NMR (600 MHz, CDCl3)
Me
Me
N
O
Ph
N
Me
Me
3.13g
7.27 cdcl3
7.22
7.14
7.13
7.11
7.05
7.03
4.73
2.80
2.58
2.57
2.56
2.55
1.87
0.92
0.91
0.90
4.57
0.96
1.90
2.02
2.02
4.00
5.95
5.92
f1 (ppm)


13C NMR (126 MHz, CDCl3)
Me
Me
N
O
Ph
N
[96%]
[9%]
3.14g
170.35
138.91
137.06
136.33
130.23
129.03
128.26
128.11
127.60
77.32 cdcl3
77.06 cdcl3
76.81 cdcl3
54.55
51.77
47.30
17.86
11.04
f1 (ppm)

^{13}**C NMR** (151 MHz, $CDCl_3$)



3.13g



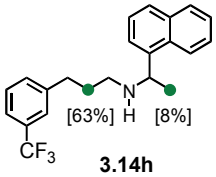
3.14h

Cinacalcet, 3.14h

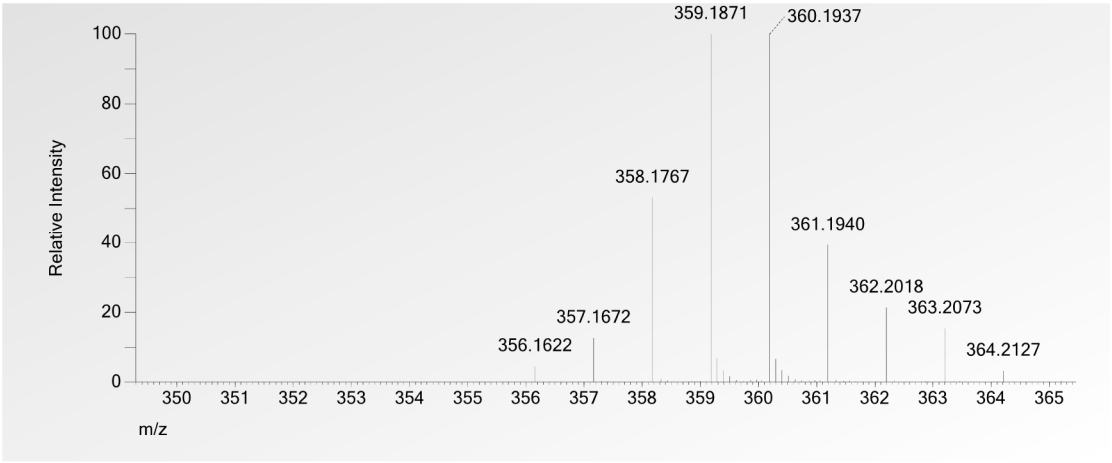
Cinacalcet **3.13h** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (MeOH:DCM = 1:19), **3.14h** was obtained as a yellow liquid (69 mg, 0.19 mmol, 97% yield).

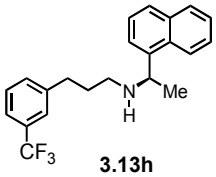
Deuterium incorporation: 1.50 D/molecule (^{1}H NMR), 1.52 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, CD_3OD) δ 8.01 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.40 – 7.26 (m, 5H), 7.20 (dt, J = 16.2, 7.6 Hz, 2H), 4.54 (q, J = 6.5 Hz, 1H), 2.43 (ddd, J = 38.2, 16.0, 8.0 Hz, 4H), 1.75 – 1.57 (m, 0.75H, 63%D), 1.34 (d, J = 6.7 Hz, 2.72H, 8%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.09, 141.08, 134.04, 131.79, 131.78, 131.35, 131.00, 130.74, 130.49, 130.24, 129.04, 129.03, 128.70, 127.28, 125.82, 125.73, 125.41, 125.37, 125.11, 125.08, 125.05, 125.02, 123.24, 122.93, 122.75, 122.71, 122.68, 122.65, 122.62, 53.83, 47.20, 33.33, 31.82, 23.58; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -62.47; **IR** (neat) 2923, 1448, 1326, 1198, 1160, 1119, 1072, 798, 777, 701, 659 cm^{-1}; **Specific Rotation**: $[\alpha]^{25}$ +19.1° (*c* 1.0, CH_2Cl_2; labeled), $[\alpha]^{25}$ +28.3° (*c* 1.0, CH_2Cl_2; unlabeled).

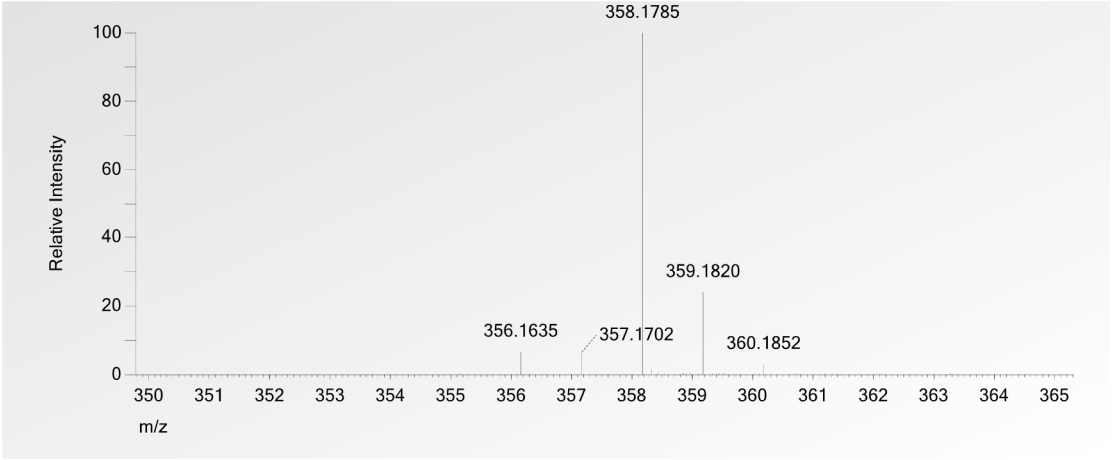

[63%] H [8%]
CF3

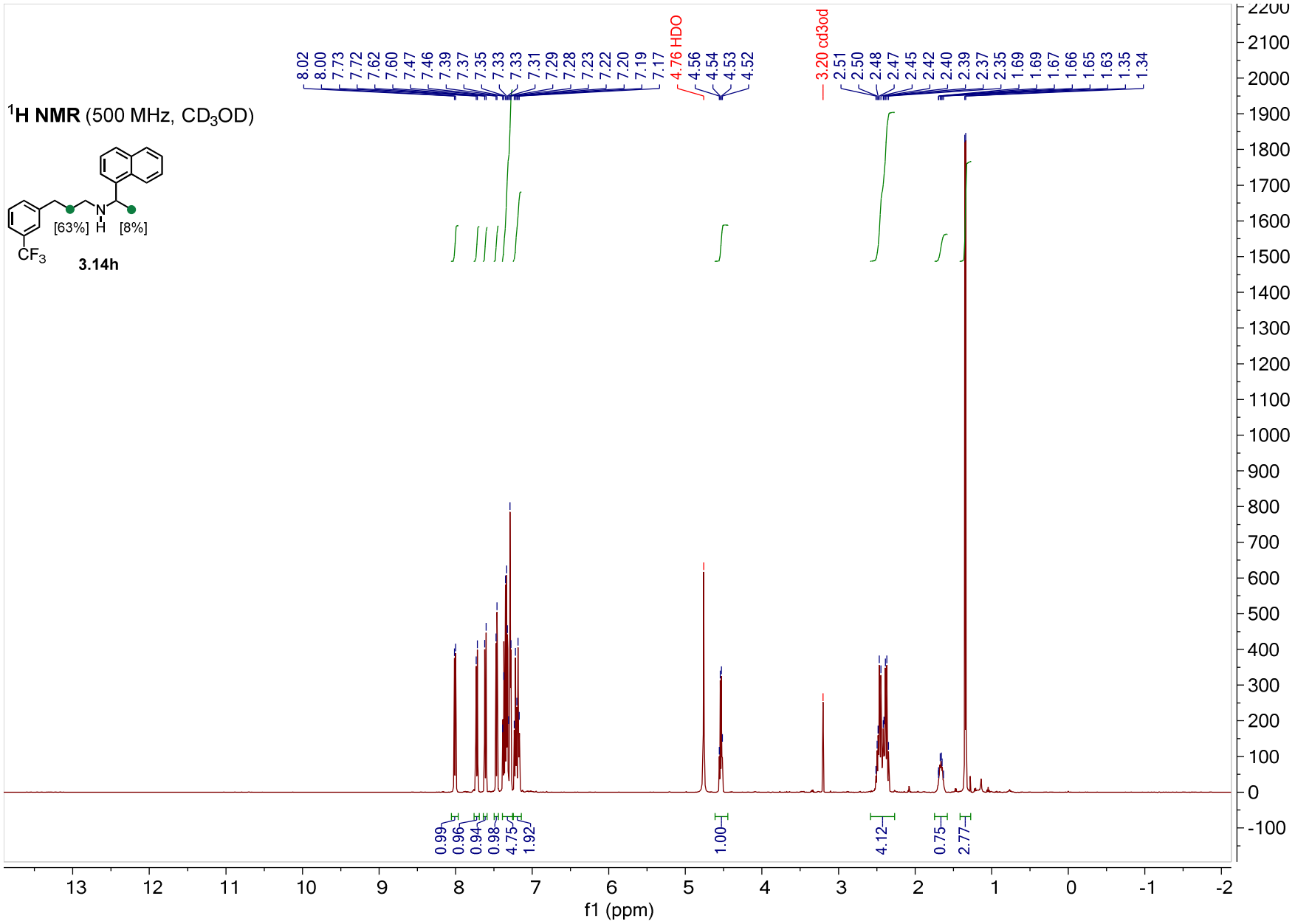
3.14h

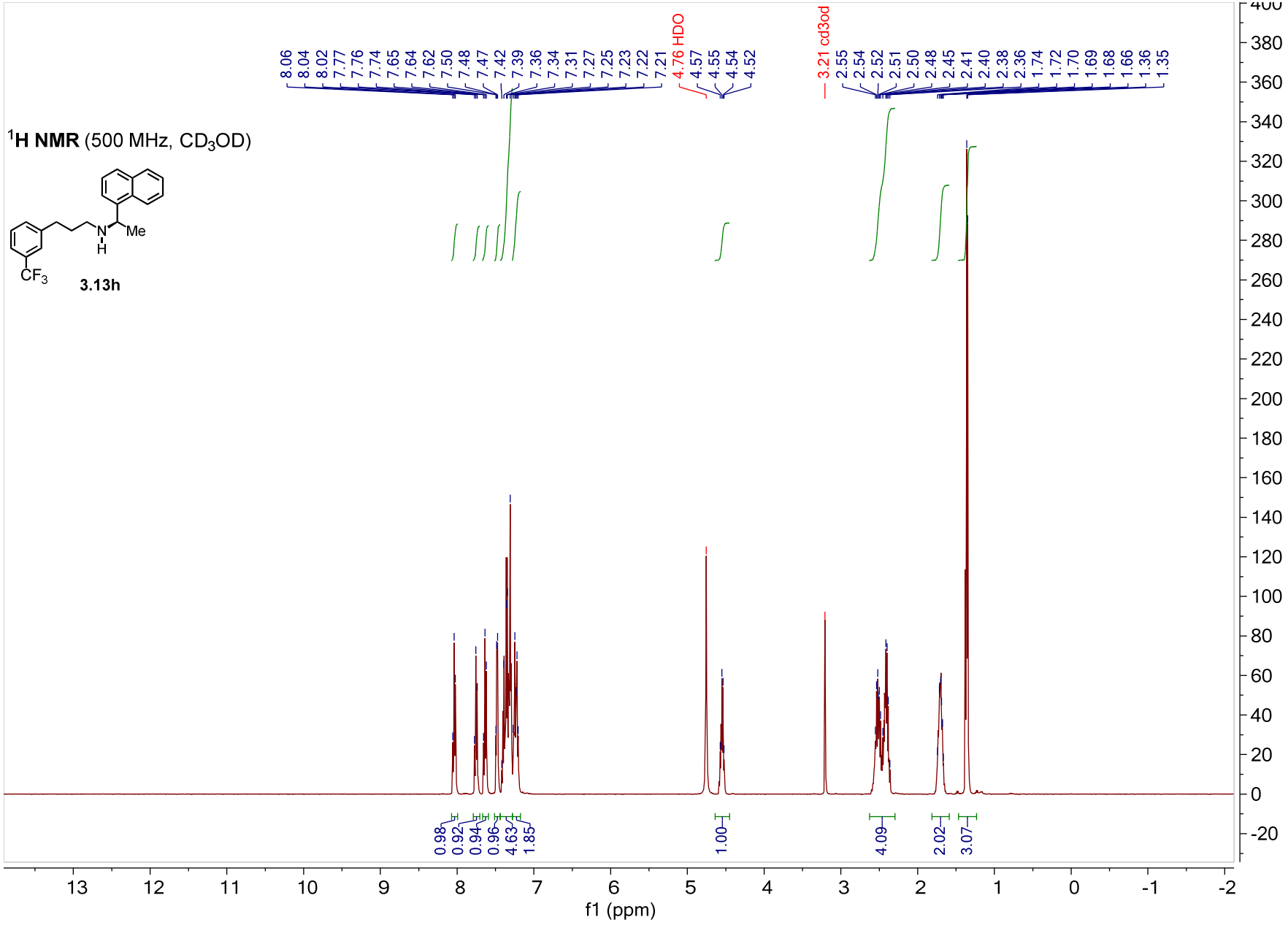

359.1871
360.1937
358.1767
361.1940
362.2018
363.2073
357.1672
356.1622
364.2127
Relative Intensity
m/z

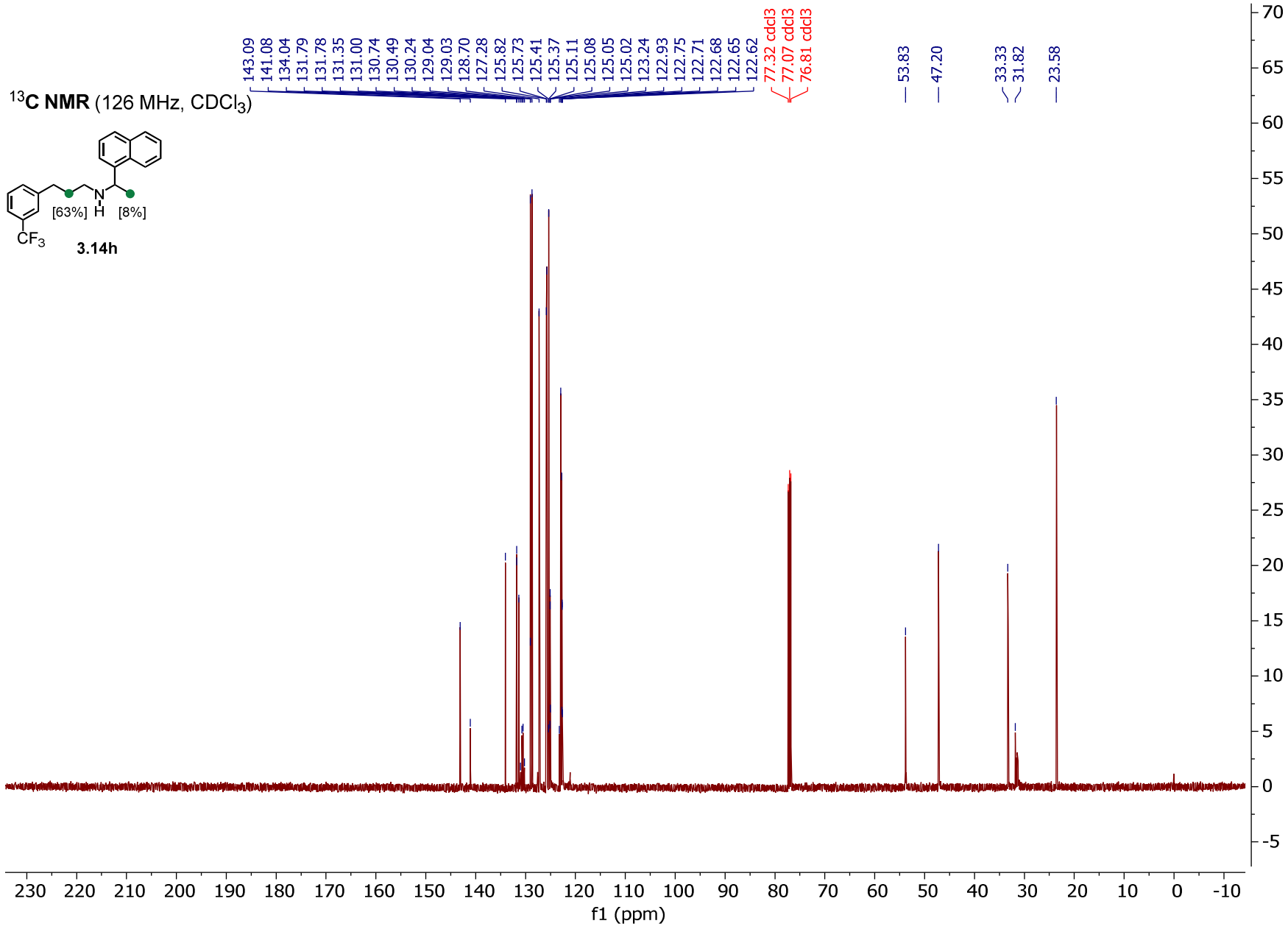

Me
CF3

3.13h

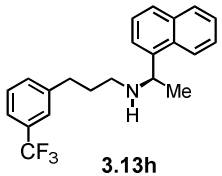

358.1785
359.1820
356.1635
357.1702
360.1852
Relative Intensity
m/z


1H NMR (500 MHz, CD3OD)
[63%] [8%]
CF3
3.14h
8.02 8.00 7.73 7.72 7.62 7.60 7.47 7.46 7.39 7.37 7.35 7.33 7.33 7.31 7.29 7.28 7.23 7.22 7.20 7.19 7.17
4.76 HDO
4.56 4.54 4.53 4.52
3.20 cd3od
2.51 2.50 2.48 2.47 2.45 2.42 2.40 2.39 2.37 2.35 1.69 1.69 1.67 1.66 1.65 1.63 1.35 1.34
0.99 0.96 0.94 0.98 4.75 1.92
1.00
4.12
0.75
2.77
f1 (ppm)

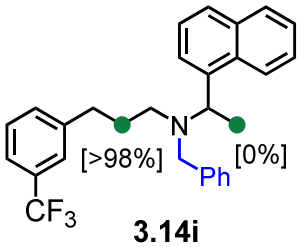

1H NMR (500 MHz, CD3OD)
3.13h
8.06
8.04
8.02
7.77
7.76
7.74
7.65
7.64
7.62
7.50
7.48
7.47
7.42
7.39
7.36
7.34
7.31
7.27
7.25
7.23
7.22
7.21
4.76 HDO
4.57
4.55
4.54
4.52
3.21 cd3od
2.55
2.54
2.52
2.51
2.50
2.48
2.45
2.41
2.40
2.38
2.36
1.74
1.72
1.70
1.69
1.68
1.66
1.36
1.35
0.98
0.92
0.94
0.96
4.63
1.85
1.00
4.09
2.02
3.07
f1 (ppm)


143.09
141.08
134.04
131.79
131.78
131.35
131.00
130.74
130.49
130.24
129.04
129.03
128.70
127.28
125.82
125.73
125.41
125.37
125.11
125.08
125.05
125.02
123.24
122.93
122.75
122.71
122.68
122.65
122.62
77.32 cdcl3
77.07 cdcl3
76.81 cdcl3
53.83
47.20
33.33
31.82
23.58
13C NMR (126 MHz, CDCl3)
[63%]
[8%]
CF3
3.14h
f1 (ppm)

^{13}**C NMR** (126 MHz, $CDCl_3$)



3.13h



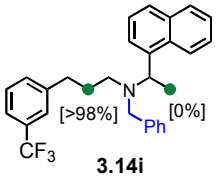
3.14i

***N*-Bn cinacalcet, 3.14i**

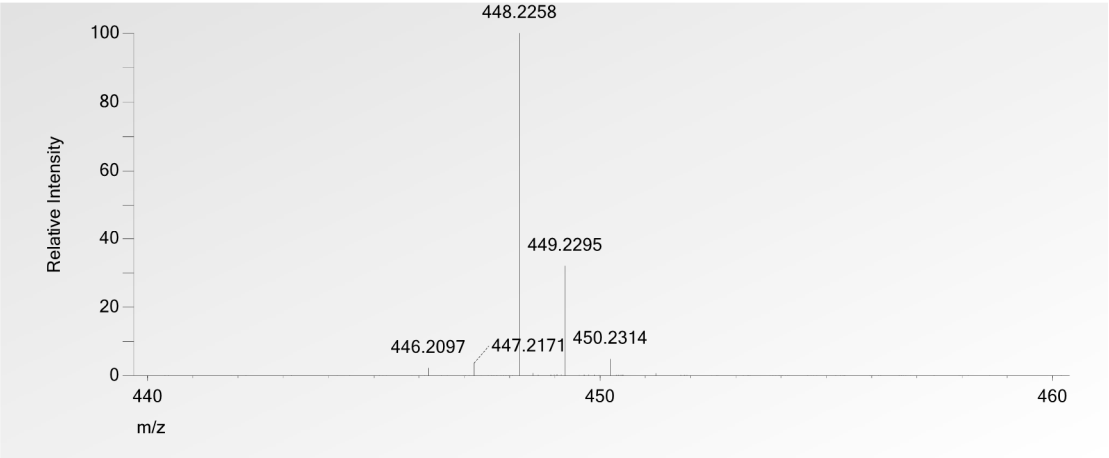
N-Bn cinacalcet **3.13i** was added to acetone-d_6 **3.3** following the General Procedure B. After purification by silica gel chromatography (Et_2O:hexanes = 1:9), **3.14i** was obtained as a yellow liquid (88 mg, 0.20 mmol, 98% yield).

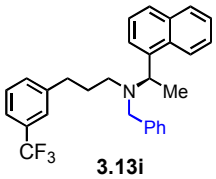
Deuterium incorporation: 1.99 D/molecule (^{1}H NMR), 2.28 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 7.1 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.35 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 7.8 Hz, 6H), 7.12 (s, 1H), 6.96 (d, J = 7.4 Hz, 1H), 4.75 – 4.62 (m, 1H), 3.72 (d, J = 13.8 Hz, 1H), 3.63 (d, J = 13.8 Hz, 1H), 2.60 (s, 2H), 2.33 (d, J = 14.0 Hz, 1H), 2.26 (d, J = 13.9 Hz, 1H), 1.63 (d, J = 6.3 Hz, 0.02H, >98%D), 1.53 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.40, 140.63, 140.03, 134.03, 132.14, 131.59, 131.58, 130.48, 130.23, 128.97, 128.55, 128.44, 128.19, 128.05, 127.61, 126.74, 125.35, 125.33, 125.28, 125.00, 124.89, 124.85, 124.83, 124.80, 124.56, 123.18, 122.36, 122.33, 122.30, 122.27, 56.40, 55.80, 49.66, 33.06, 28.22, 14.36; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -62.49; **IR** (neat) 2858, 1449, 1331, 1197, 1159, 1118, 1097, 797, 778, 733, 699 cm^{-1}; **Specific Rotation**: $[\alpha]^{25}$ –28.5° (*c* 1.0, CH_2Cl_2; labeled), **Specific Rotation**: $[\alpha]^{25}$ –39.2° (*c* 1.0, CH_2Cl_2; unlabeled).

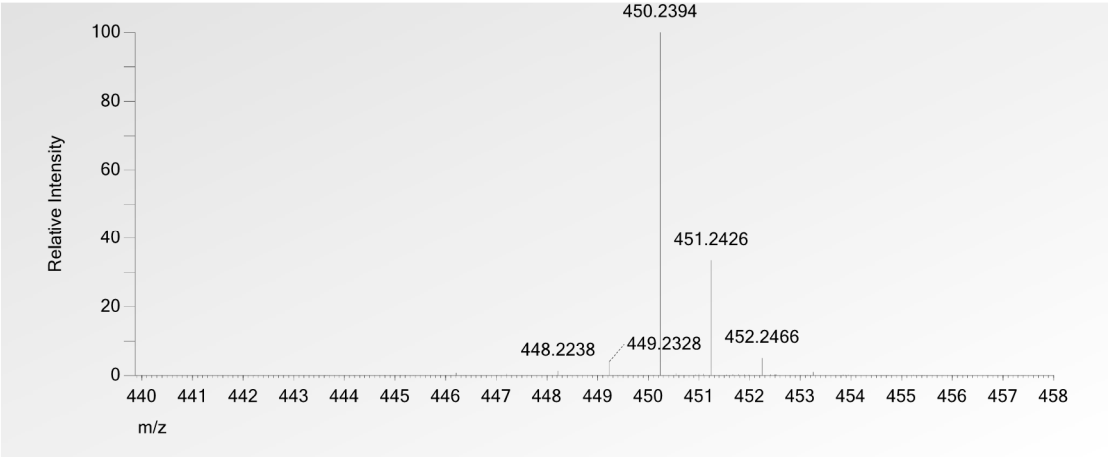

[>98%]
[0%]
N
Ph
CF3

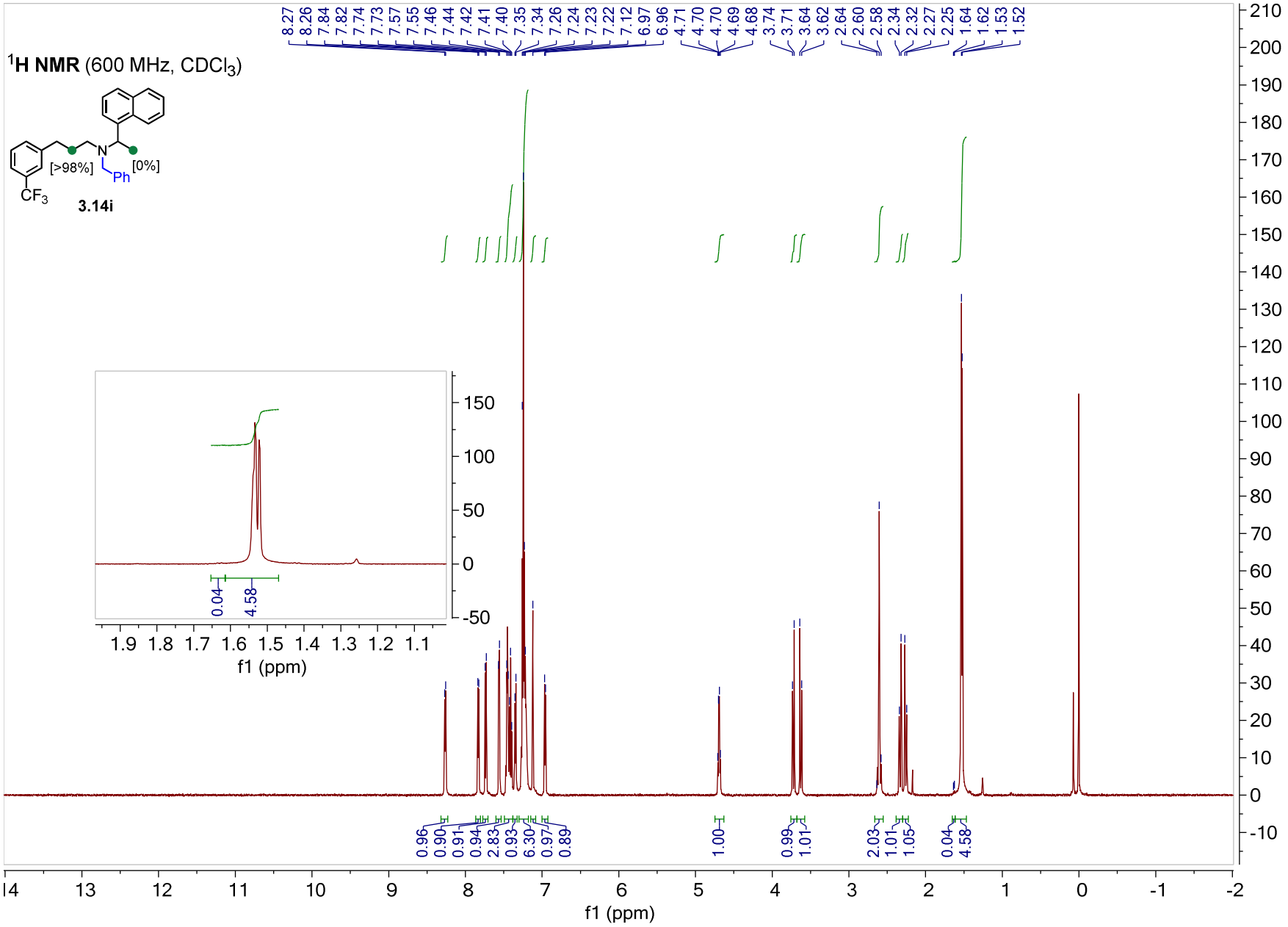
3.14i

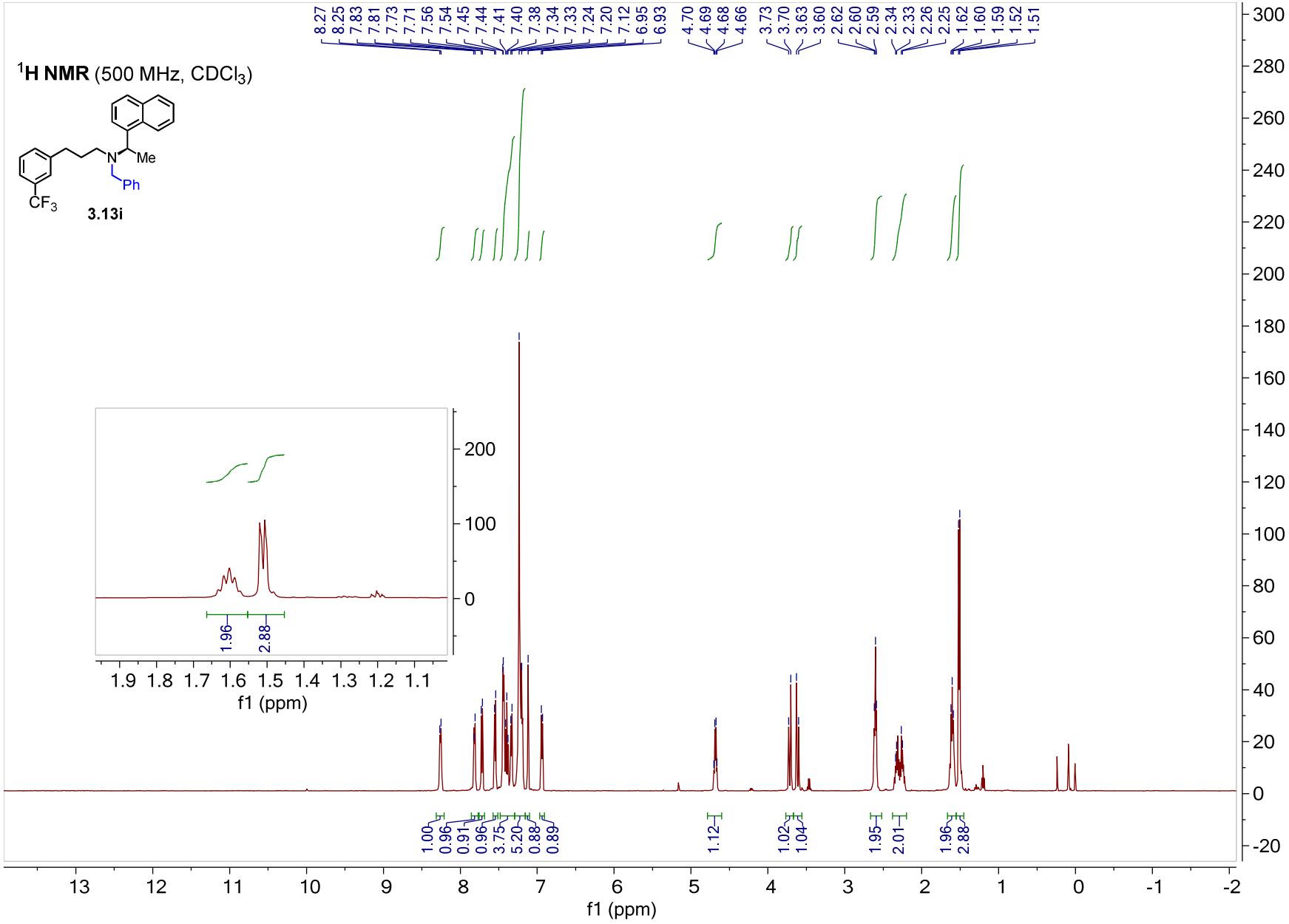

448.2258
449.2295
446.2097
447.2171
450.2314
Relative Intensity
m/z

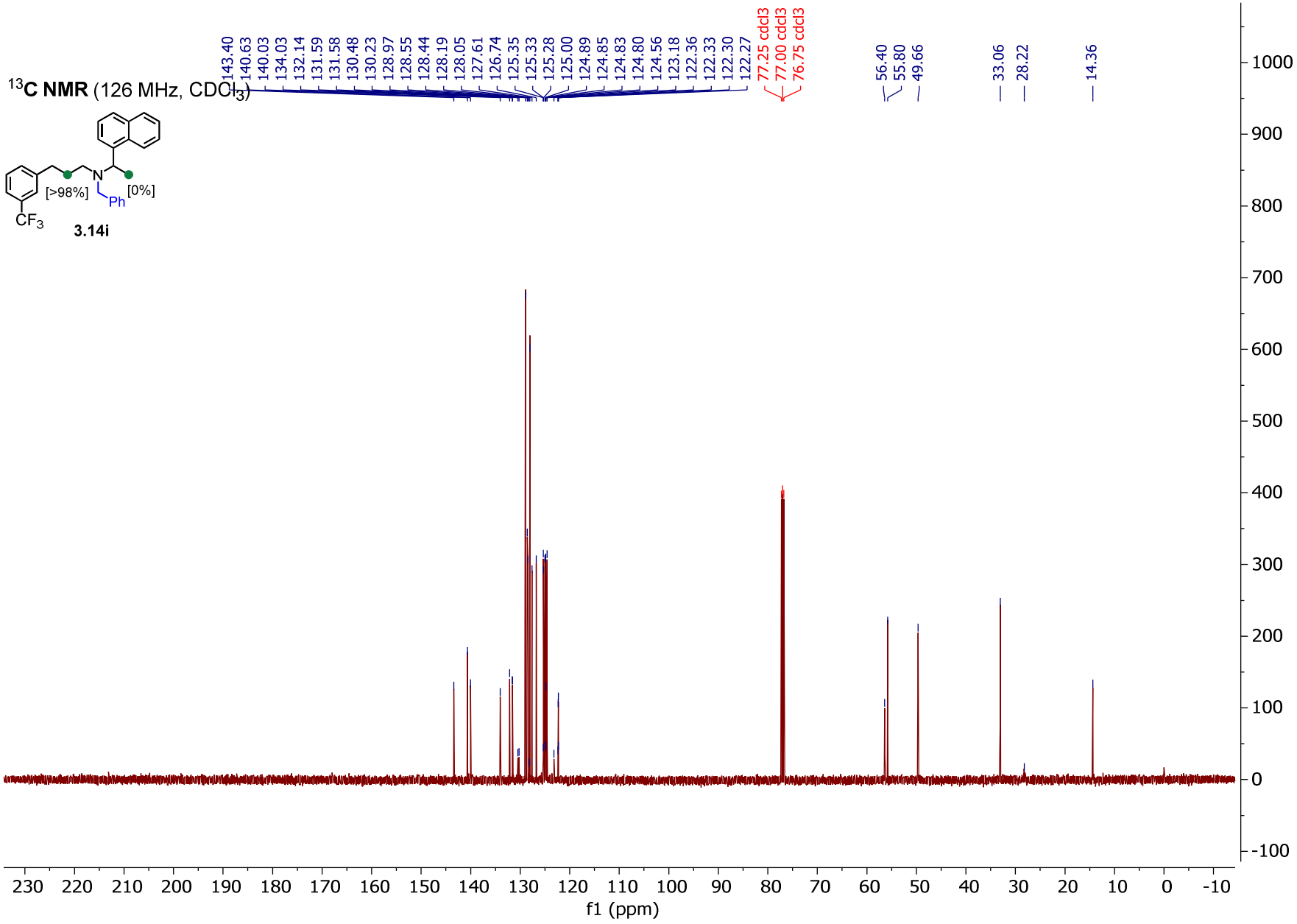

N
Me
Ph
CF3

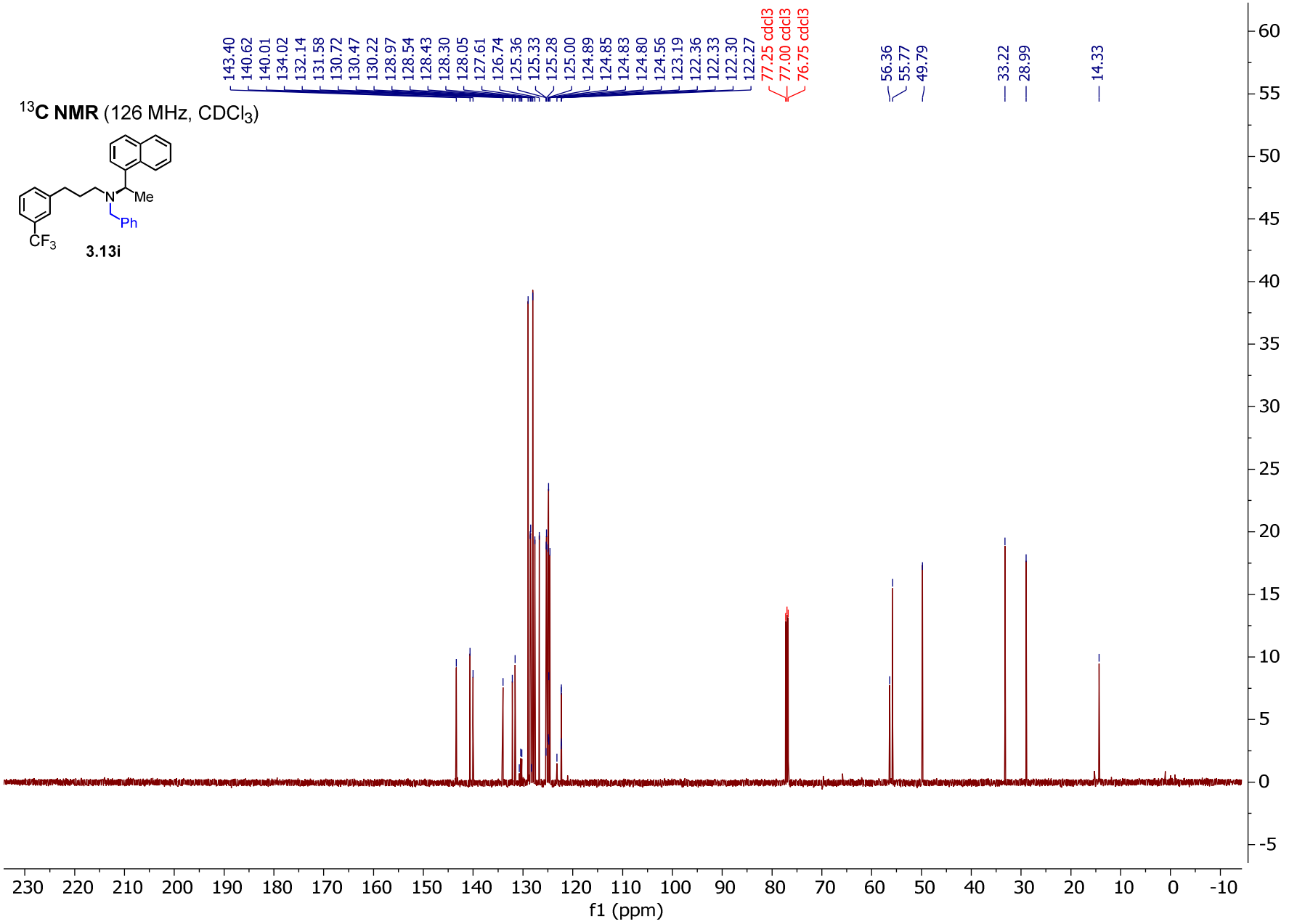
3.13i

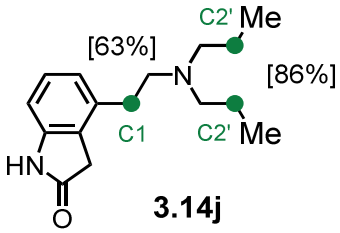

450.2394
451.2426
448.2238
449.2328
452.2466
Relative Intensity
m/z


1H NMR (600 MHz, CDCl3)
[>98%]
[0%]
Ph
CF3
3.14i
f1 (ppm)


^{1}H NMR (500 MHz, CDCl$_3$)
3.13i
8.27 8.25 7.83 7.81 7.73 7.71 7.56 7.54 7.45 7.44 7.41 7.40 7.38 7.34 7.33 7.24 7.20 7.12 6.95 6.93
4.70 4.69 4.68 4.66
3.73 3.70 3.63 3.60
2.62 2.60 2.59
2.34 2.33 2.26 2.25
1.62 1.60 1.59 1.52 1.51
1.96 2.88
f1 (ppm)
1.00 0.96 0.91 0.96 3.75 5.20 0.88 0.89
1.12
1.02 1.04
1.95
2.01
1.96 2.88
f1 (ppm)


13C NMR (126 MHz, CDCl3)
143.40
140.63
140.03
134.03
132.14
131.59
131.58
130.48
130.23
128.97
128.55
128.44
128.19
128.05
127.61
126.74
125.35
125.33
125.28
125.00
124.89
124.85
124.83
124.80
124.56
123.18
122.36
122.33
122.30
122.27
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
56.40
55.80
49.66
33.06
28.22
14.36
[>98%]
[0%]
Ph
CF3
3.14i
f1 (ppm)


143.40
140.62
140.01
134.02
132.14
131.58
130.72
130.47
130.22
128.97
128.54
128.43
128.30
128.05
127.61
126.74
125.36
125.33
125.28
125.00
124.89
124.85
124.83
124.80
124.56
123.19
122.36
122.33
122.30
122.27
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
56.36
55.77
49.79
33.22
28.99
14.33
13C NMR (126 MHz, CDCl3)
N
Me
Ph
CF3
3.13i
f1 (ppm)



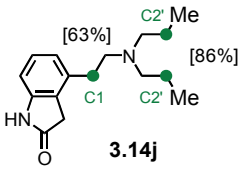
3.14j

Ropinirole, 3.14j

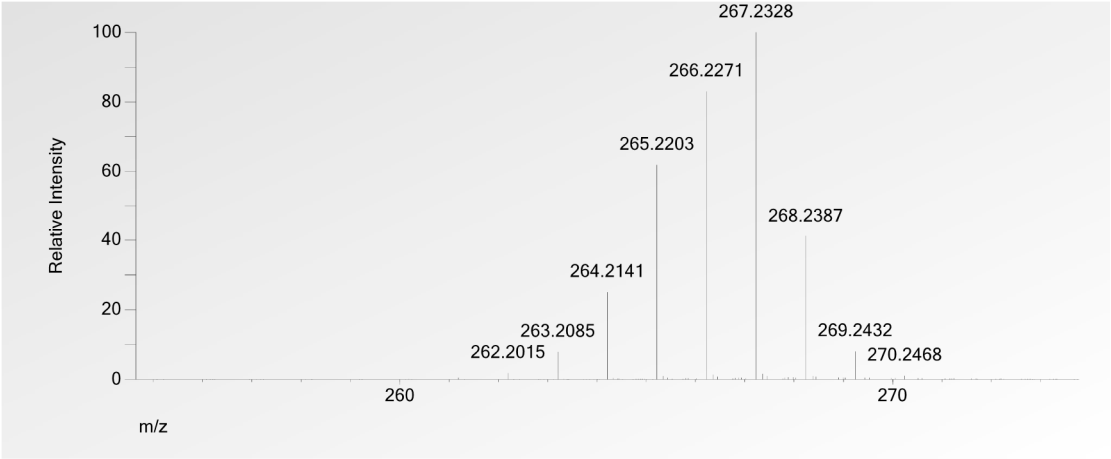
Ropinirole **3.13j** was added to acetone-d_6 **3.3** following the General Procedure C. After purification by silica gel chromatography (MeOH:DCM = 1:24), **3.14j**as obtained as a white solid (40 mg, 0.15 mmol, 77% yield).

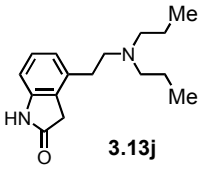
Deuterium incorporation: 4.70 D/molecule (^{1}H NMR), 5.24 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 3.49 (s, 2H), 2.71 (d, *J* = 5.1 Hz, 2.74H, 63%D), 2.50 (s, 4H), 1.55 – 1.44 (m, 0.58H, 86%D), 0.89 (d, *J* = 8.5 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.56, 142.47, 136.77, 128.08, 127.97, 124.01, 122.80, 107.64, 55.90, 55.82, 54.13, 54.07, 54.00, 35.10, 30.52, 19.26, 11.88, 11.77, 11.66; **IR** (neat) 2952, 2928, 2799, 1701, 1615, 1601, 1453, 1254, 762, 719 cm^{-1}.

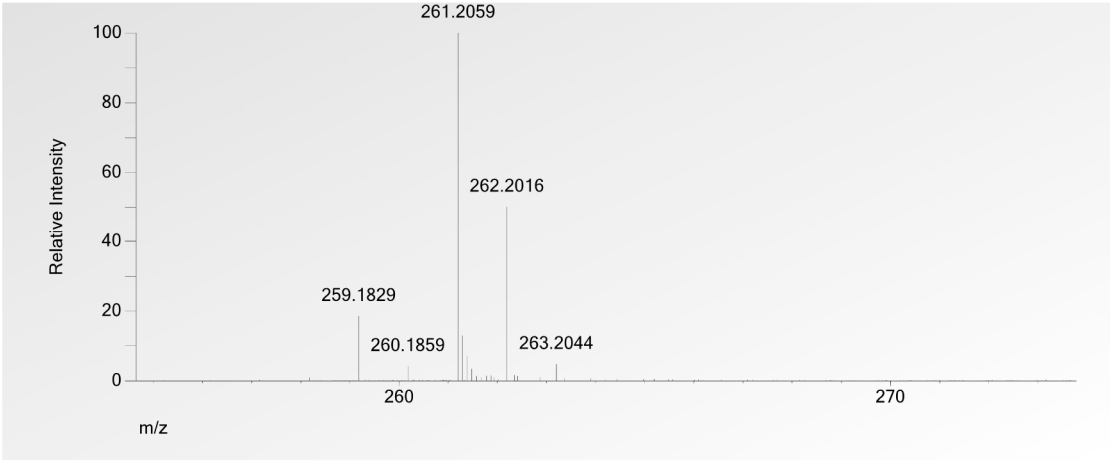

C2' Me
[63%]
N
[86%]
C1
C2' Me
HN
O

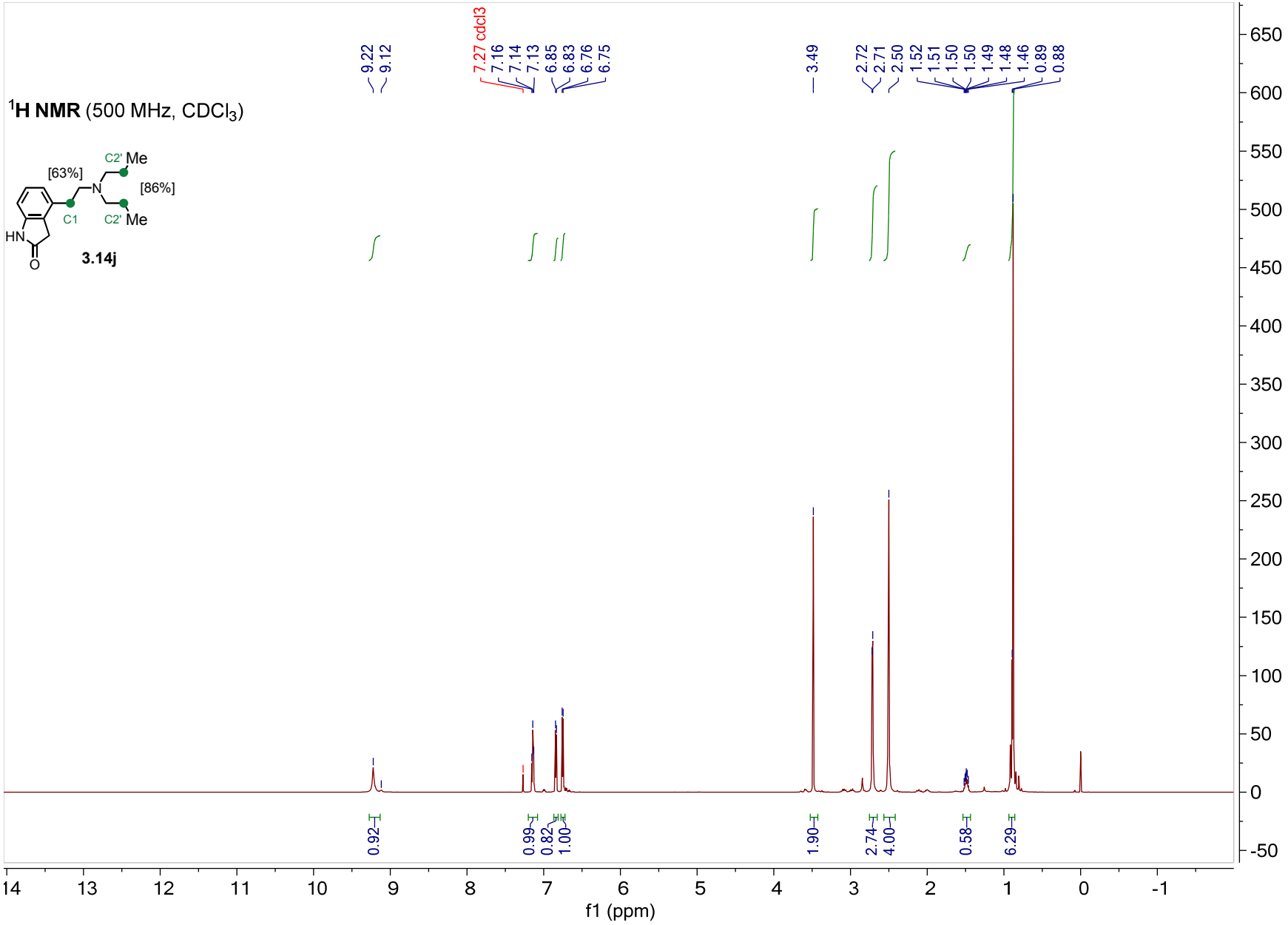
3.14j

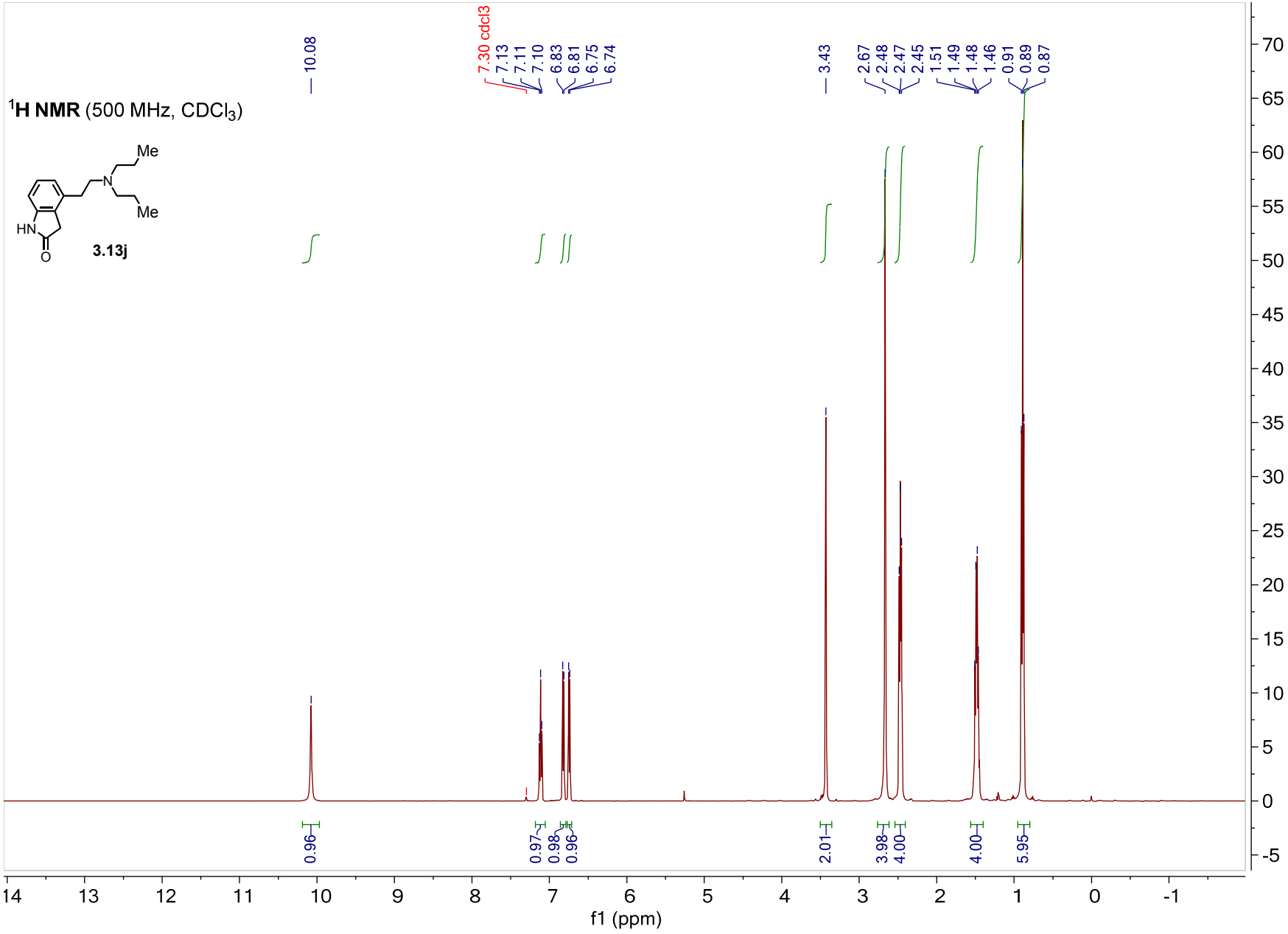

267.2328
266.2271
265.2203
268.2387
264.2141
263.2085
262.2015
269.2432
270.2468
100
80
60
40
20
0
Relative Intensity
260
270
m/z

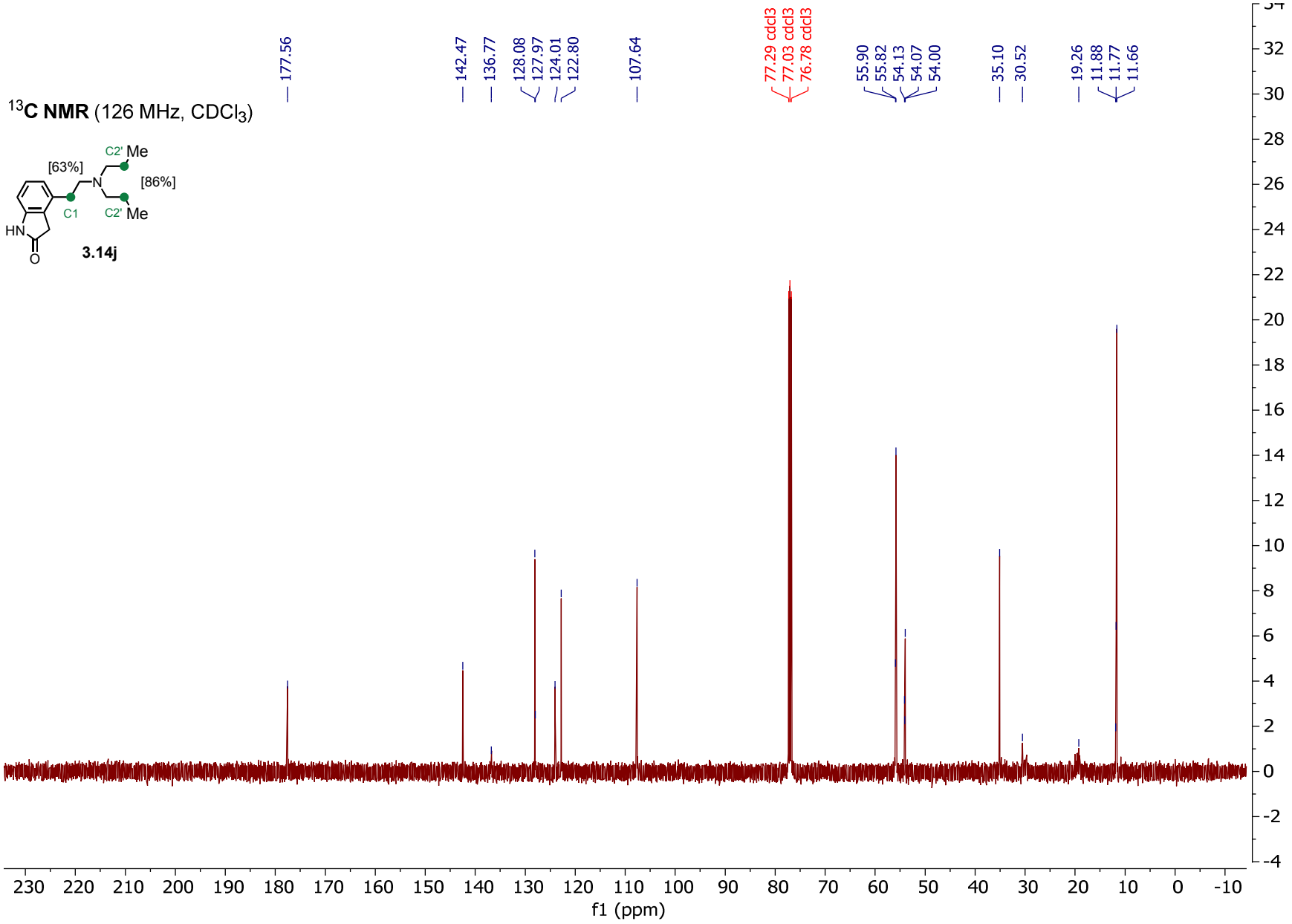

Me
N
Me
HN
O

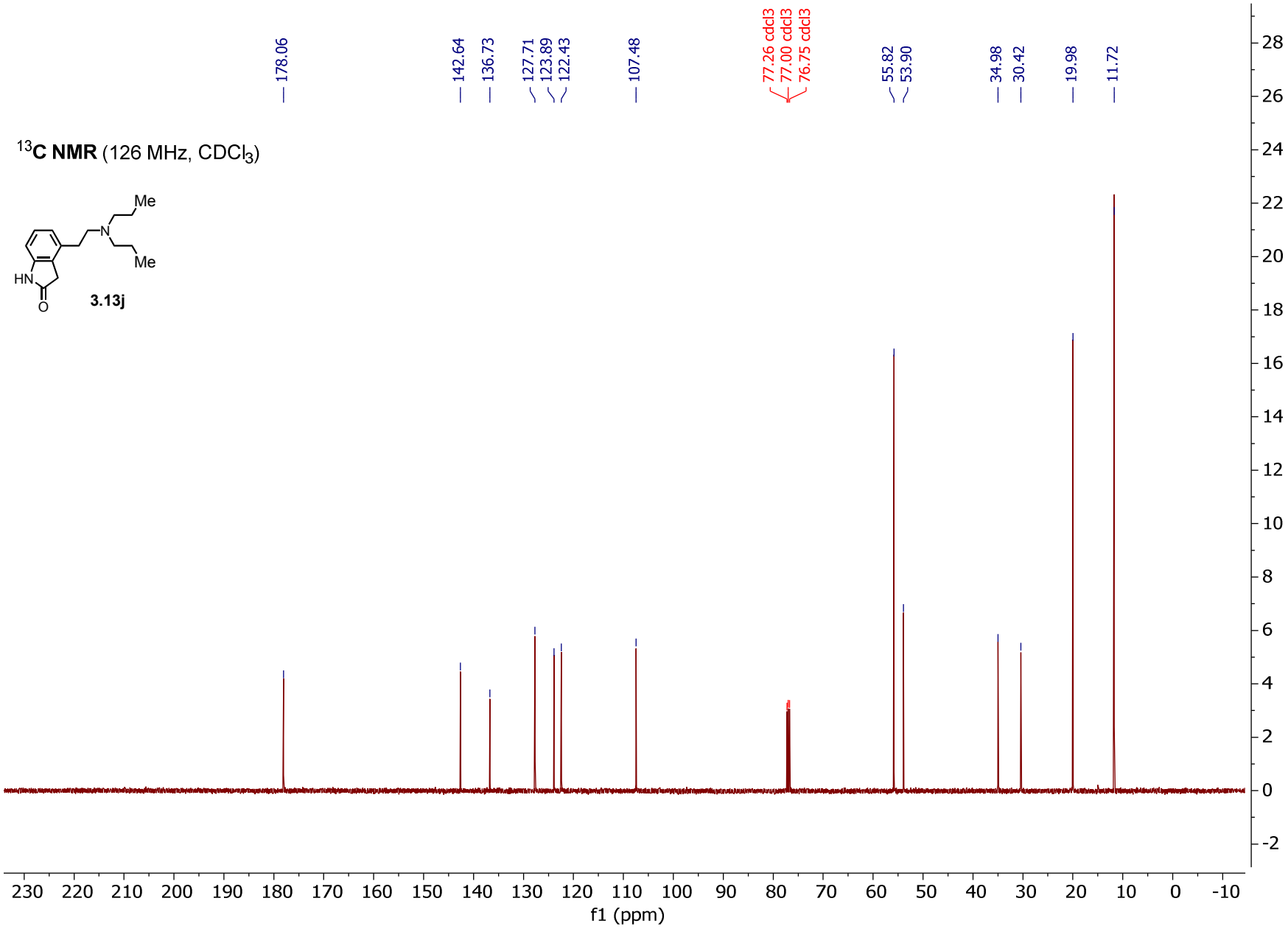
3.13j

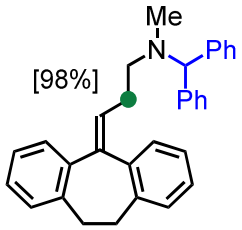

261.2059
262.2016
259.1829
260.1859
263.2044
100
80
60
40
20
0
Relative Intensity
260
270
m/z


1H NMR (500 MHz, CDCl3)
[63%]
[86%]
C2' Me
C2' Me
C1
HN
O
3.14j
9.22
9.12
7.27 cdcl3
7.16
7.14
7.13
6.85
6.83
6.76
6.75
3.49
2.72
2.71
2.50
1.52
1.51
1.50
1.50
1.49
1.48
1.46
0.89
0.88
0.92
0.99
0.82
1.00
1.90
2.74
4.00
0.58
6.29
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
Me
N
Me
HN
O
3.13j
10.08
7.30 cdcl3
7.13
7.11
7.10
6.83
6.81
6.75
6.74
3.43
2.67
2.48
2.47
2.45
1.51
1.49
1.48
1.46
0.91
0.89
0.87
0.96
0.97
0.98
0.96
2.01
3.98
4.00
4.00
5.95
f1 (ppm)


13C NMR (126 MHz, CDCl3)
[63%]
[86%]
C2' Me
C2' Me
C1
HN
O
N
3.14j
177.56
142.47
136.77
128.08
127.97
124.01
122.80
107.64
77.29 cdcl3
77.03 cdcl3
76.78 cdcl3
55.90
55.82
54.13
54.07
54.00
35.10
30.52
19.26
11.88
11.77
11.66
f1 (ppm)


178.06
142.64
136.73
127.71
123.89
122.43
107.48
77.26 cdcl3
77.00 cdcl3
76.75 cdcl3
55.82
53.90
34.98
30.42
19.98
11.72
13C NMR (126 MHz, CDCl3)
Me
N
Me
HN
O
3.13j
f1 (ppm)



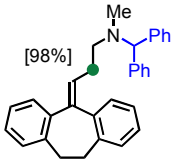
3.14k

***N*-Bzh nortriptyline, 3.14k**

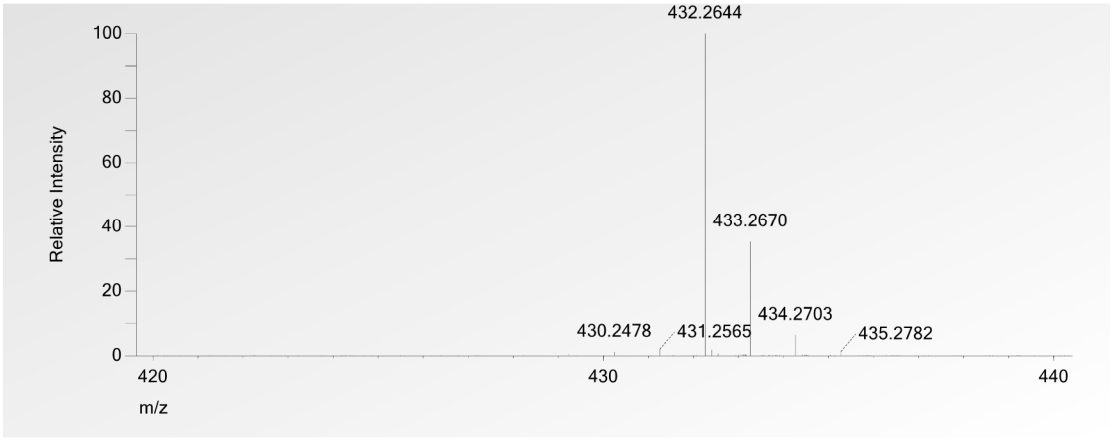
N-Bzh nortriptyline **3.13k** was added to acetone-d_6 **3.3** following the General Procedure B. After purification by silica gel chromatography (Et_2O:hexanes = 1:9), **3.14k** was obtained as a yellow liquid (83 mg, 0.19 mmol, 96% yield).

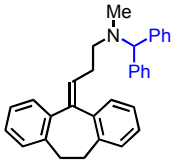
Deuterium incorporation: 1.96 D/molecule (^{1}H NMR), 2.34 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 4H), 7.22 (dd, J = 8.4, 6.8 Hz, 5H), 7.20 – 7.09 (m, 7H), 7.09 – 7.04 (m, 1H), 7.03 (s, 1H), 5.81 (s, 1H), 4.30 (s, 1H), 3.27 (dt, J = 32.1, 23.1 Hz, 2H), 2.94 (s, 1H), 2.71 (s, 1H), 2.44 (d, J = 5.3 Hz, 2H), 2.30 (d, J = 7.5 Hz, 0.04H, 98%D), 2.07 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.25, 141.49, 140.18, 139.40, 137.07, 129.96, 129.76, 128.55, 128.36, 127.99, 127.31, 126.94, 126.78, 125.98, 125.72, 75.65, 54.89, 40.26, 33.79, 32.06; **IR** (neat) 3020, 2784, 1485, 1451, 1265, 1028, 1012, 924, 756, 742, 704 cm^{-1}.

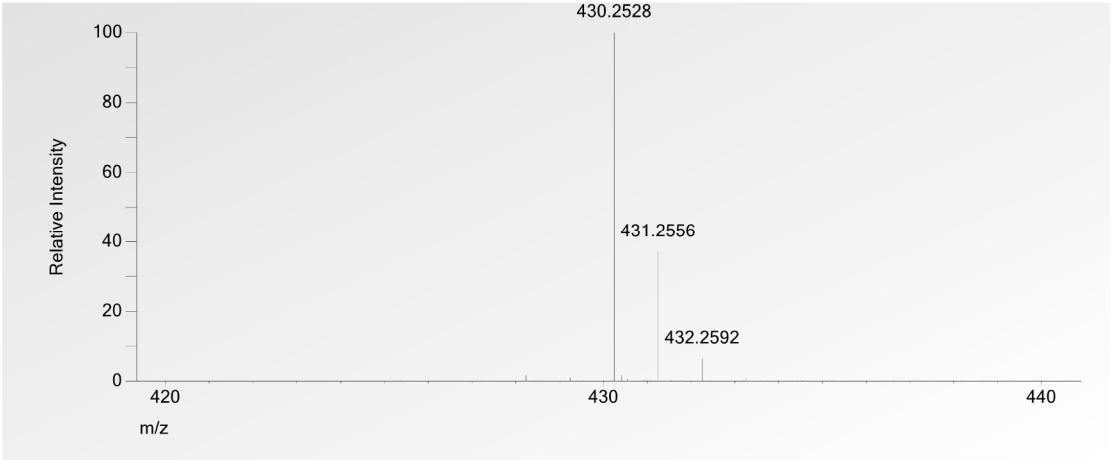

Me
N
Ph
Ph
[98%]

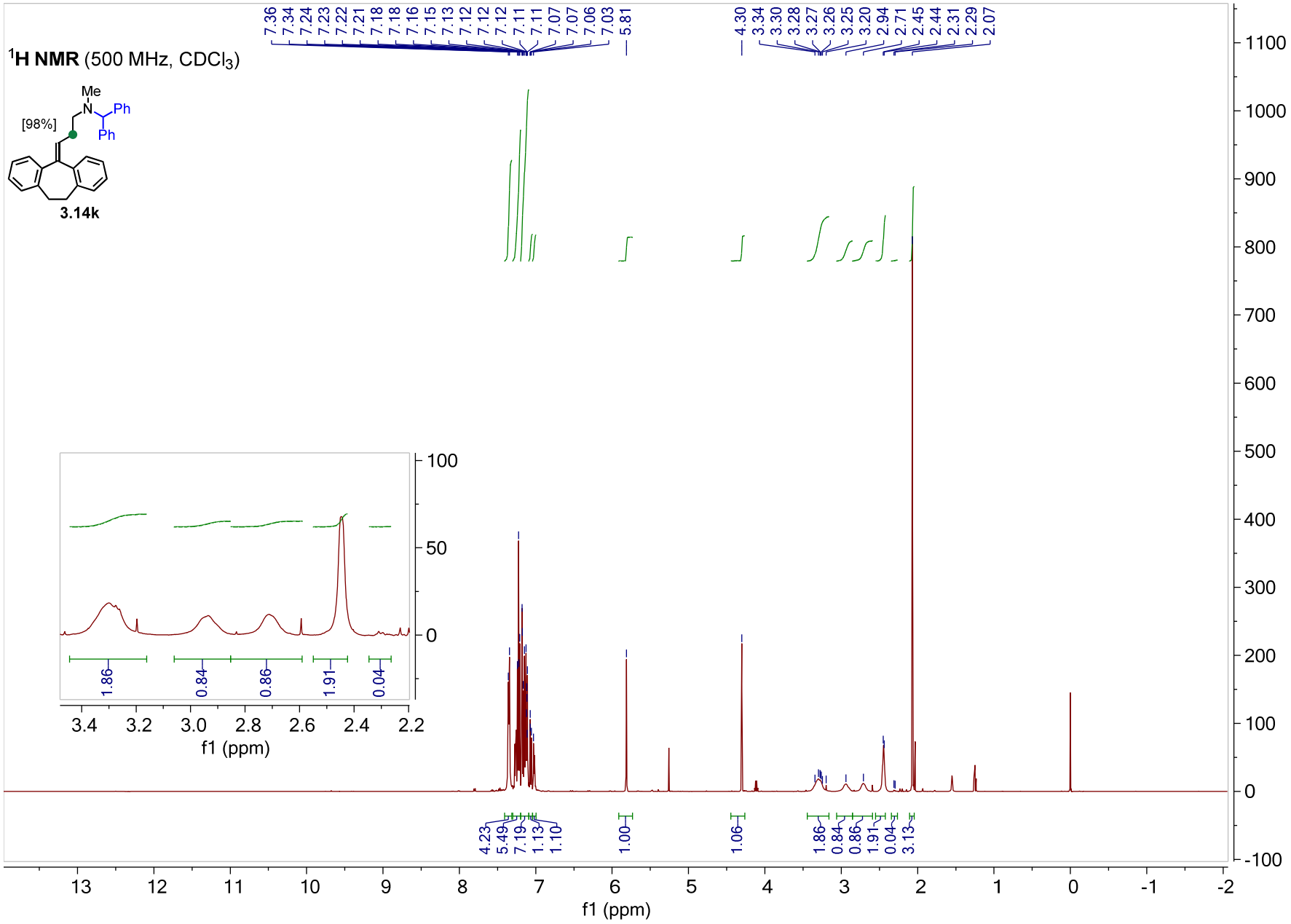
3.14k

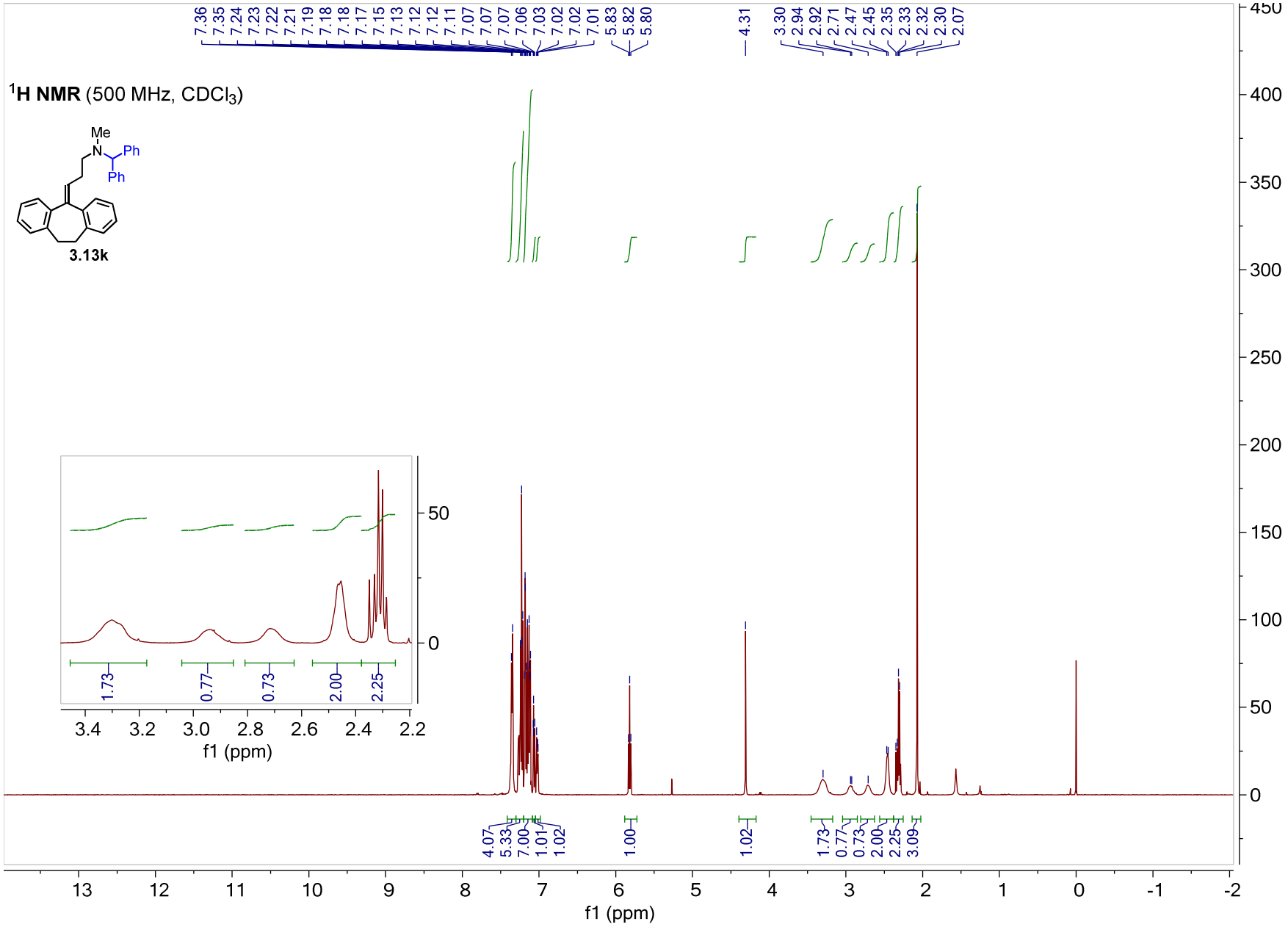

432.2644
433.2670
434.2703
430.2478
431.2565
435.2782
Relative Intensity
100
80
60
40
20
0
420
430
440
m/z

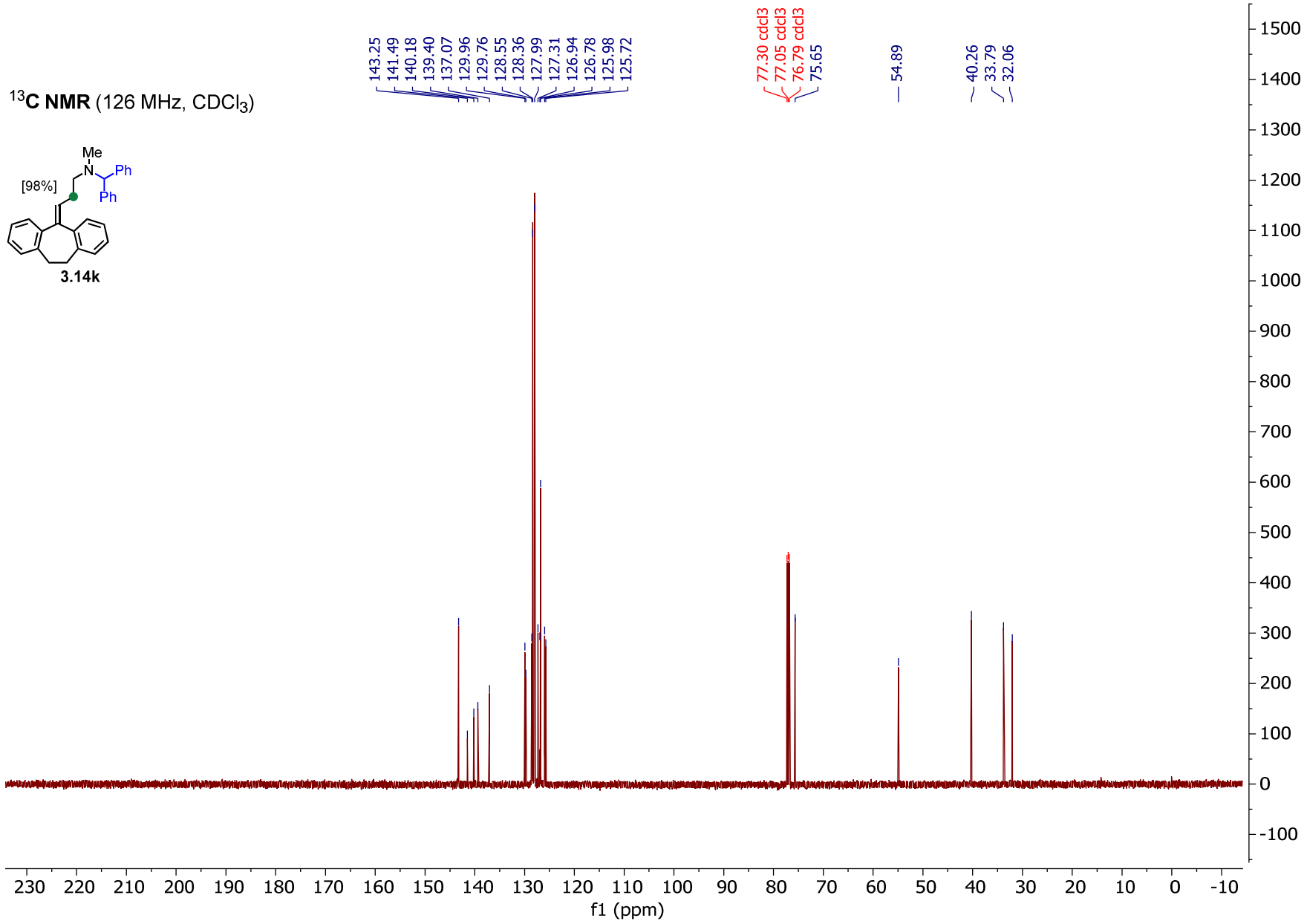

Me
N
Ph
Ph

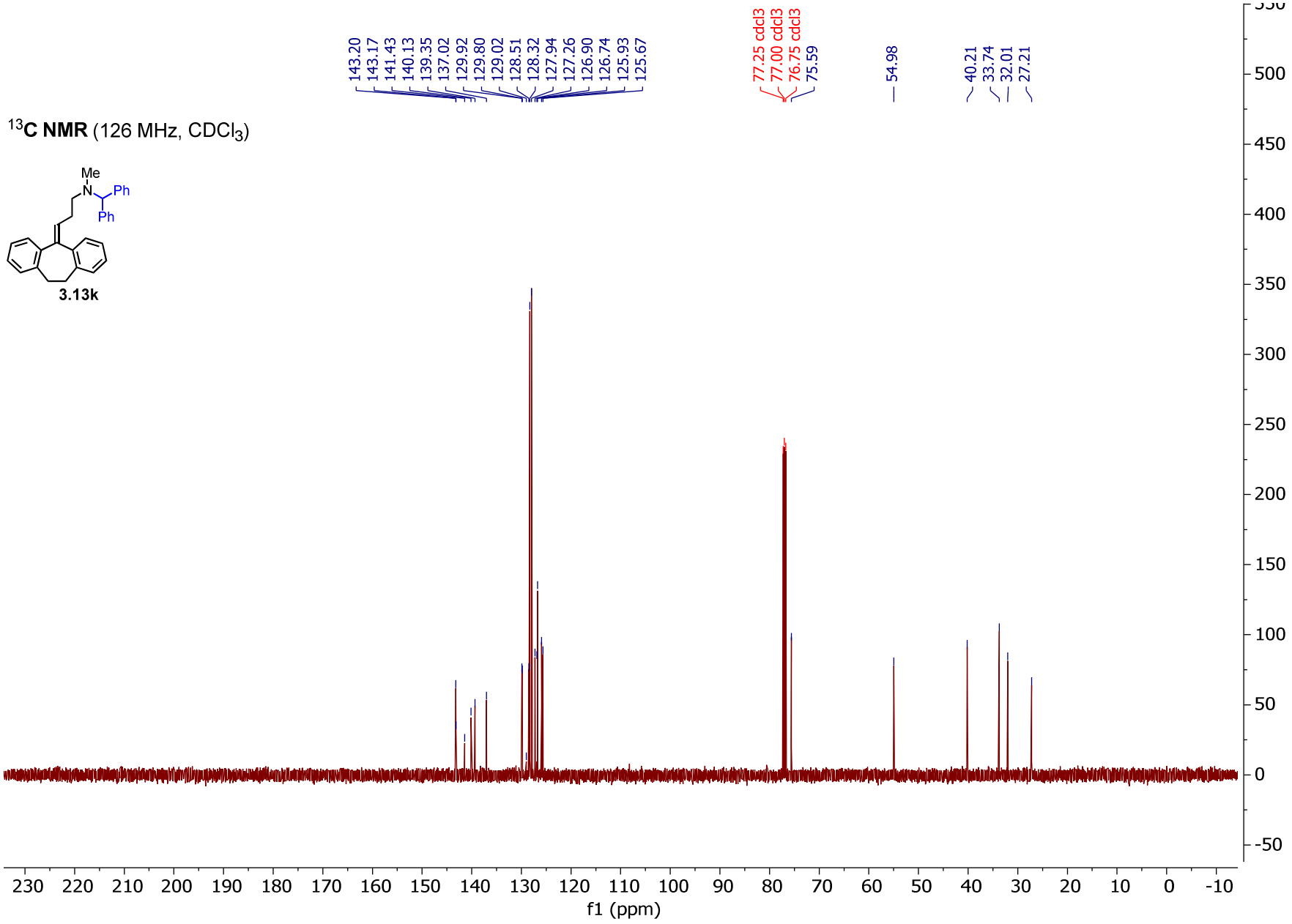
3.13k

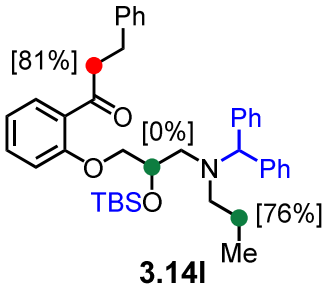

430.2528
431.2556
432.2592
Relative Intensity
100
80
60
40
20
0
420
430
440
m/z


7.36
7.34
7.24
7.23
7.22
7.21
7.18
7.18
7.16
7.15
7.13
7.12
7.12
7.12
7.11
7.11
7.07
7.07
7.06
7.03
5.81
4.30
3.34
3.30
3.28
3.27
3.26
3.25
3.20
2.94
2.71
2.45
2.44
2.31
2.29
2.07
1H NMR (500 MHz, CDCl3)
Me
N
Ph
Ph
[98%]
3.14k
1.86
0.84
0.86
1.91
0.04
f1 (ppm)
4.23
5.49
7.19
1.13
1.10
1.00
1.06
1.86
0.84
0.86
1.91
0.04
3.13
f1 (ppm)


7.36 7.35 7.24 7.23 7.22 7.21 7.19 7.18 7.18 7.17 7.15 7.13 7.12 7.12 7.11 7.07 7.07 7.07 7.06 7.03 7.02 7.02 7.01 5.83 5.82 5.80
4.31
3.30 2.94 2.92 2.71 2.47 2.45 2.35 2.33 2.32 2.30 2.07
^{1}H NMR (500 MHz, $CDCl_3$)
Me
N
Ph
Ph
3.13k
1.73 0.77 0.73 2.00 2.25
f1 (ppm)
4.07 5.33 7.00 1.01 1.02 1.00 1.02 1.73 0.77 0.73 2.00 2.25 3.09
f1 (ppm)


^{13}C NMR (126 MHz, CDCl$_3$)
Me
N
Ph
Ph
[98%]
3.14k
143.25
141.49
140.18
139.40
137.07
129.96
129.76
128.55
128.36
127.99
127.31
126.94
126.78
125.98
125.72
77.30 cdcl3
77.05 cdcl3
76.79 cdcl3
75.65
54.89
40.26
33.79
32.06
f1 (ppm)


143.20
143.17
141.43
140.13
139.35
137.02
129.92
129.80
129.02
128.51
128.32
127.94
127.26
126.90
126.74
125.93
125.67
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
75.59
54.98
40.21
33.74
32.01
27.21
13C NMR (126 MHz, CDCl3)
Me
N
Ph
Ph
3.13k
f1 (ppm)



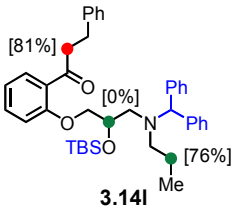
3.14l

***N*-Bzh, *O*-TBS propafenone, 3.14l**

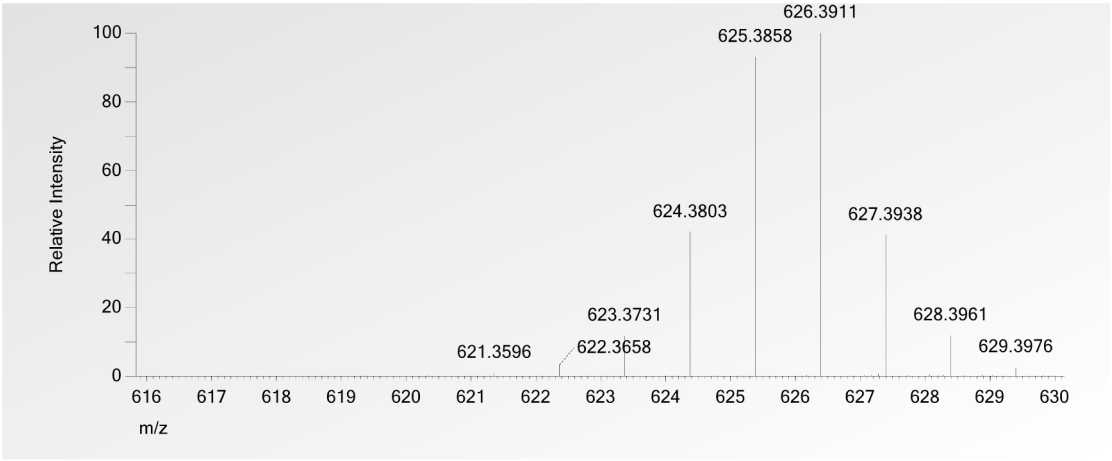
N-Bzh, *O*-TBS propafenone **3.13l** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (Et_2O:hexanes = 1:9), **3.14l** was obtained as a yellow liquid (114 mg, 0.18 mmol, 92% yield).

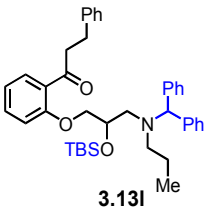
Deuterium incorporation: 3.14 D/molecule (^{1}H NMR), 3.51 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.4 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.27 (d, *J* = 7.1 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 4H), 7.20 – 7.08 (m, 9H), 6.99 (dd, *J* = 15.9, 8.8 Hz, 2H), 4.81 (s, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 4.11 (d, *J* = 3.3 Hz, 1H), 3.92 (dd, *J* = 8.7, 4.3 Hz, 1H), 3.35 – 3.18 (m, 0.19H, 81%D), 3.11 – 2.97 (m, 0.24H, 76%D), 2.91 (d, *J* = 11.4 Hz, 2H), 2.79 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.55 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.51 – 2.38 (m, 2H), 1.50 – 1.35 (m, 0.50H, 76%D), 0.79 (s, 9H), 0.75 – 0.66 (m, 3H), -0.06 (s, 3H), -0.09 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.37, 201.31, 158.22, 142.07, 141.66, 141.53, 133.33, 130.47, 128.78, 128.68, 128.45, 128.35, 128.26, 128.22, 128.16, 128.13, 126.92, 126.89, 125.69, 120.48, 112.34, 71.19, 70.48, 69.93, 54.24, 53.87, 45.04, 29.91, 25.72, 19.04, 17.93, 11.53, -4.66, -4.83; **IR** (neat) 2950, 2926, 1669, 1595, 1470, 1293, 1248, 1113, 833, 747, 699 cm^{-1}.

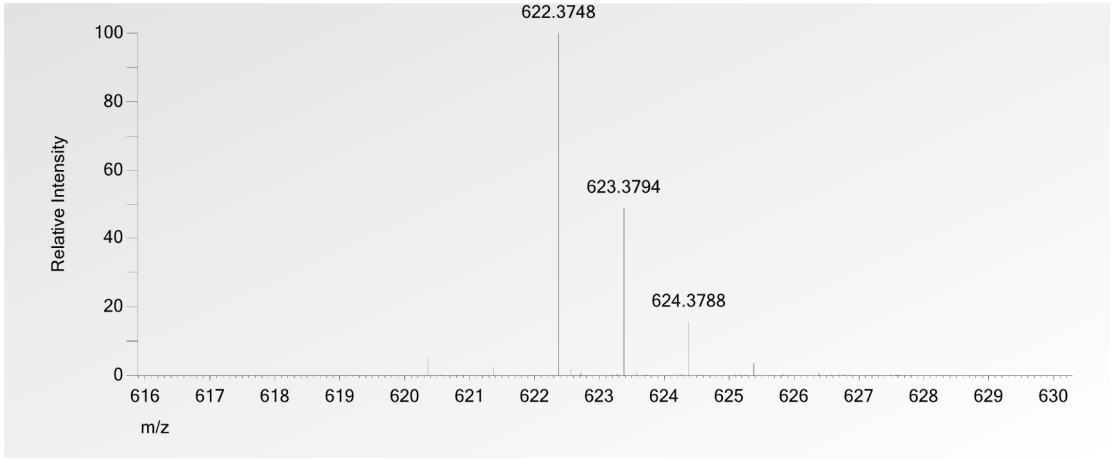

Ph
[81%]
O
[0%]
Ph
Ph
O
N
TBSO
[76%]
Me

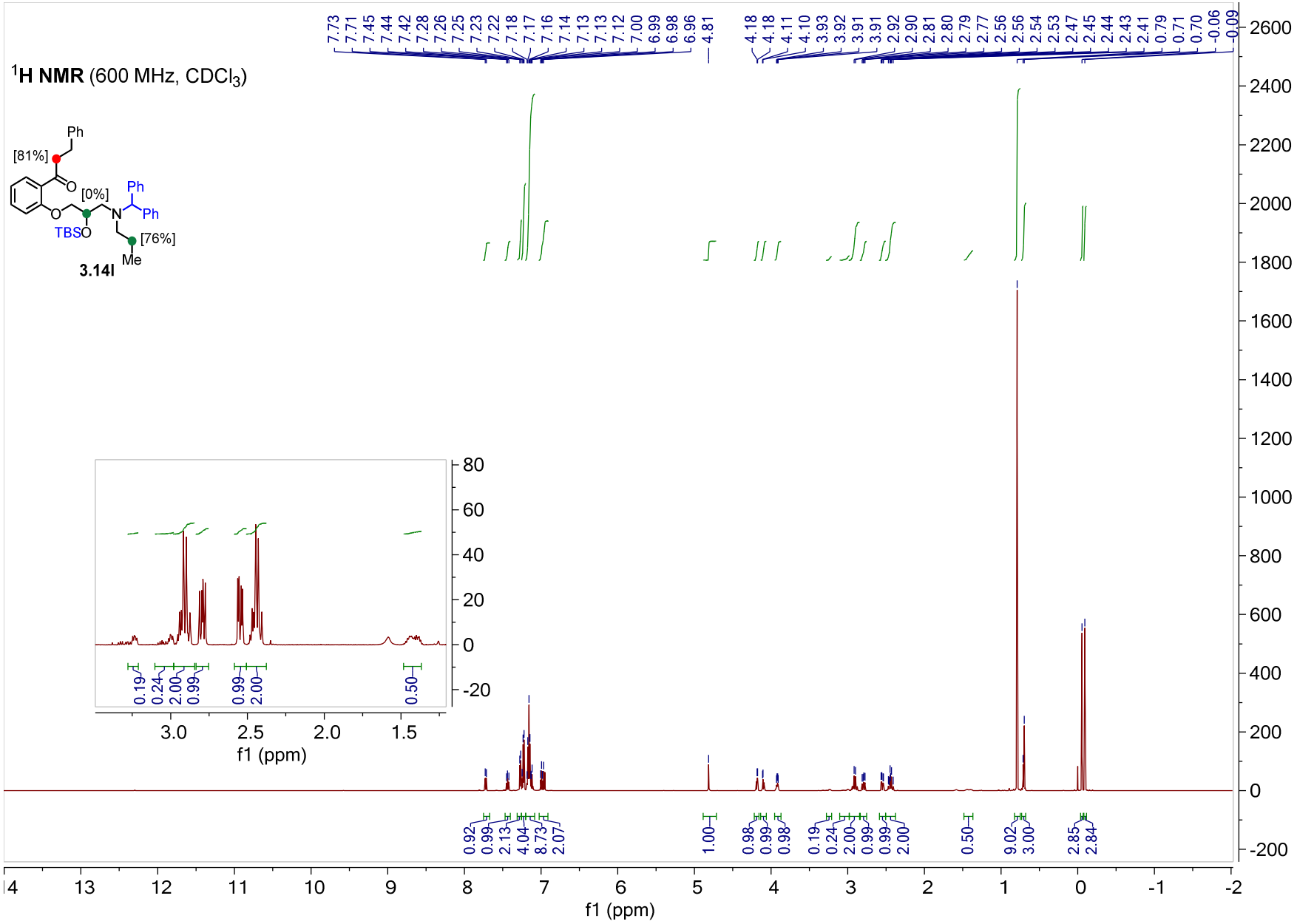
3.14l

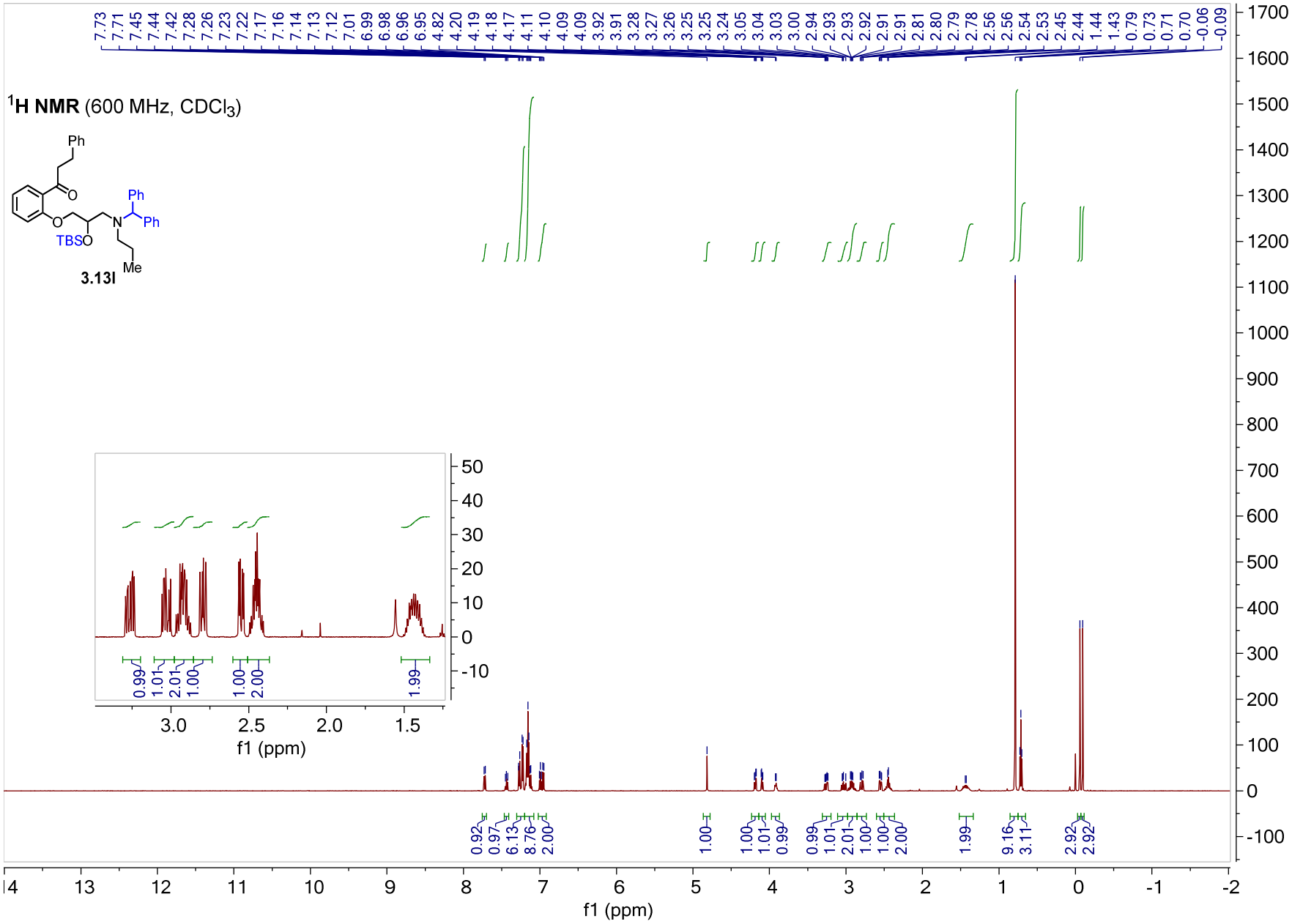

626.3911
625.3858
624.3803
627.3938
623.3731
628.3961
622.3658
621.3596
629.3976
Relative Intensity
m/z

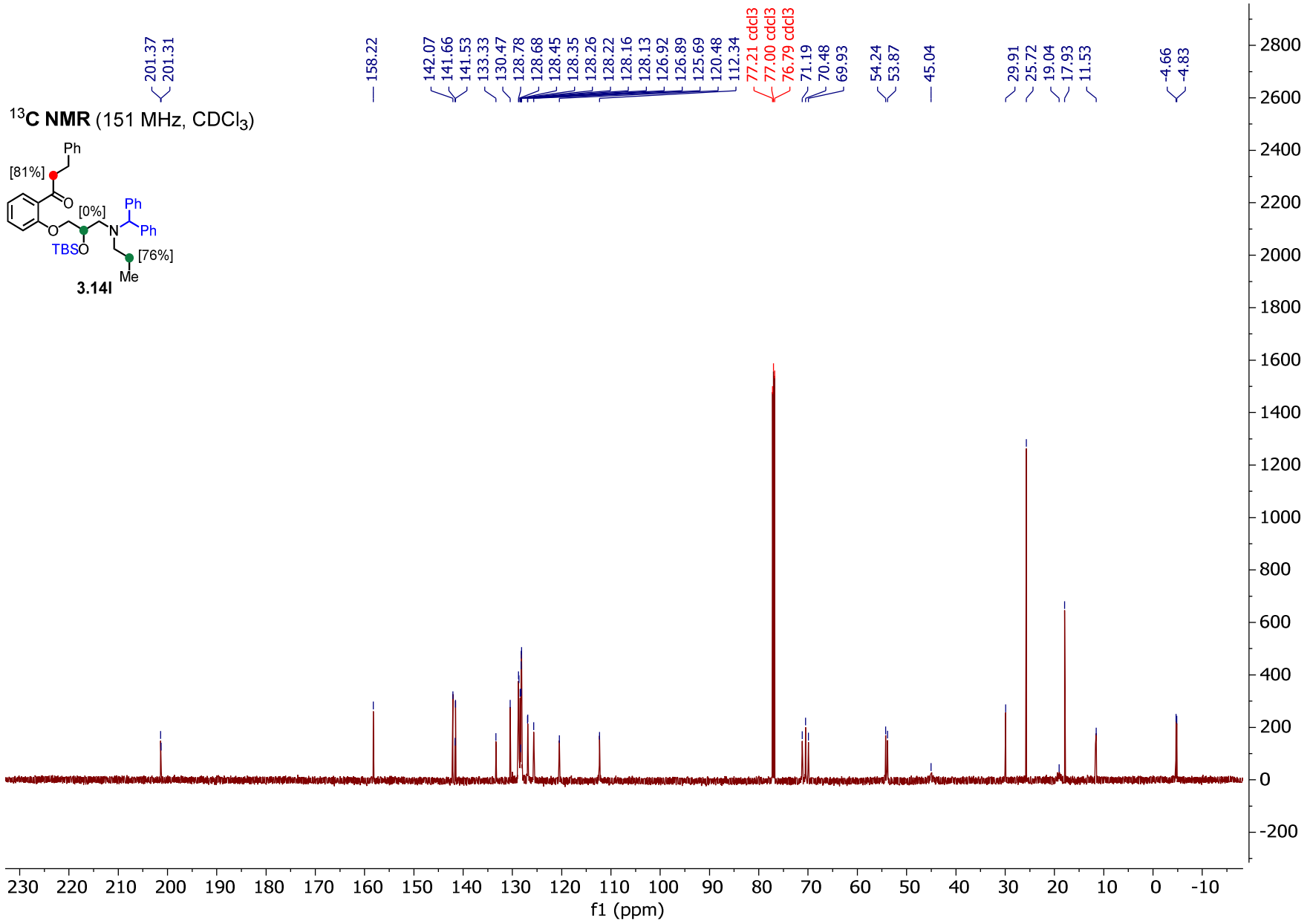

Ph
O
Ph
Ph
O
N
TBSO
Me

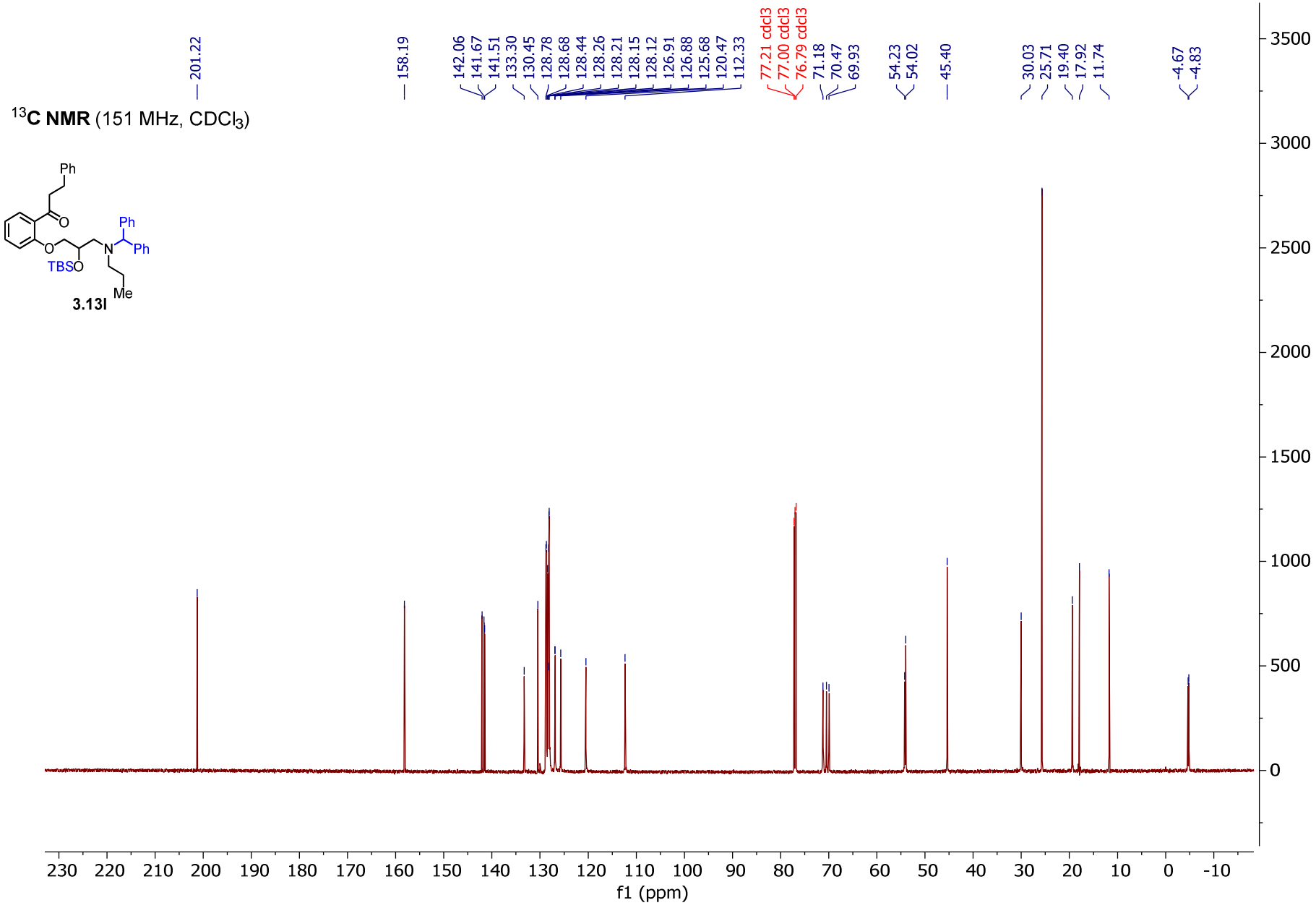
3.13l

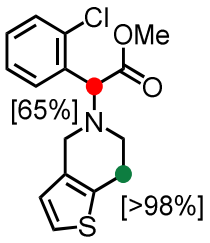

622.3748
623.3794
624.3788
Relative Intensity
m/z


^{1}H NMR (600 MHz, CDCl$_3$)
Ph
[81%]
O
[0%]
Ph
N
Ph
TBSO
[76%]
Me
3.14l
7.73 7.71 7.45 7.44 7.42 7.28 7.26 7.25 7.23 7.22 7.18 7.17 7.16 7.14 7.13 7.13 7.12 7.00 6.99 6.98 6.96 4.81
4.18 4.18 4.11 4.10 3.93 3.92 3.91 3.91 2.92 2.90 2.81 2.80 2.79 2.77 2.56 2.56 2.54 2.53 2.47 2.45 2.44 2.43 2.41 0.79 0.71 0.70 -0.06 -0.09
0.92 0.99 2.13 4.04 8.73 2.07 1.00 0.98 0.99 0.98 0.19 0.24 2.00 0.99 0.99 2.00 0.50 9.02 3.00 2.85 2.84
0.19 0.24 2.00 0.99 0.99 2.00 0.50
f1 (ppm)
f1 (ppm)


1H NMR (600 MHz, CDCl3)
Ph
O
Ph
O
N
Ph
TBSO
Me
3.13l
f1 (ppm)
f1 (ppm)


201.37
201.31
158.22
142.07
141.66
141.53
133.33
130.47
128.78
128.68
128.45
128.35
128.26
128.22
128.16
128.13
126.92
126.89
125.69
120.48
112.34
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
71.19
70.48
69.93
54.24
53.87
45.04
29.91
25.72
19.04
17.93
11.53
-4.66
-4.83
13C NMR (151 MHz, CDCl3)
Ph
[81%]
O
[0%]
Ph
Ph
O
N
TBSO
[76%]
Me
3.14l
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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
f1 (ppm)


201.22
158.19
142.06
141.67
141.51
133.30
130.45
128.78
128.68
128.44
128.26
128.21
128.15
128.12
126.91
126.88
125.68
120.47
112.33
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
71.18
70.47
69.93
54.23
54.02
45.40
30.03
25.71
19.40
17.92
11.74
-4.67
-4.83
13C NMR (151 MHz, CDCl3)
Ph
O
Ph
O
N
Ph
TBSO
Me
3.13l
3500
3000
2500
2000
1500
1000
500
0
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
f1 (ppm)



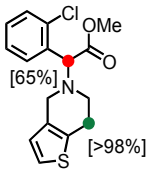
3.14m

Clopidogrel, 3.14m

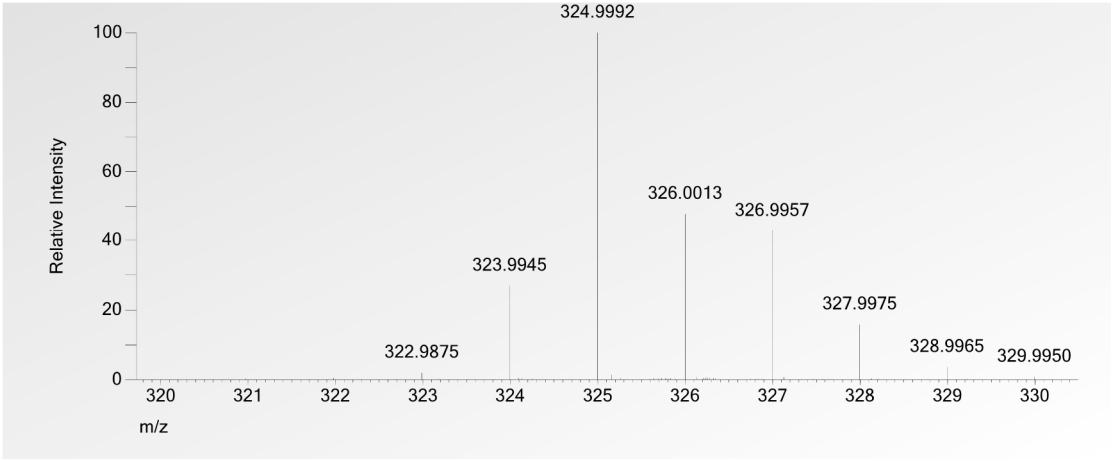
Clopidogrel **3.13m** was added to acetone-d_6 **3.3** following the General Procedure B. After purification by silica gel chromatography (Et_2O:hexanes = 1:9), **3.14m** was obtained as a colorless liquid (61 mg, 0.18 mmol, 94% yield).

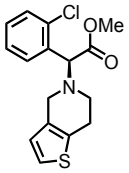
Deuterium incorporation: 2.65 D/molecule (^{1}H NMR), 2.88 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.36 – 7.18 (m, 2H), 7.11 – 7.00 (m, 1H), 6.75 – 6.59 (m, 1H), 4.92 (d, J = 2.0 Hz, 0.35H, 65%D), 3.79 – 3.70 (m, 4H), 3.63 (d, J = 14.2 Hz, 1H), 2.88 (s, 2.00H, >98%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.33, 134.71, 133.82, 133.41, 133.14, 129.99, 129.80, 129.43, 127.15, 125.24, 122.77, 67.92, 52.14, 50.70, 50.65, 48.17, 48.12, 25.07; **IR** (neat) 2947, 1735, 1469, 1431, 1245, 1140, 1105, 1064, 752, 704 cm^{-1}; $[\alpha]^{25}_{D}$ = 0.7° (c = 1.0, CH_2Cl_2 labeled), $[\alpha]^{25}_{D}$ = 15.0° (c = 1.0, CH_2Cl_2 unlabeled).

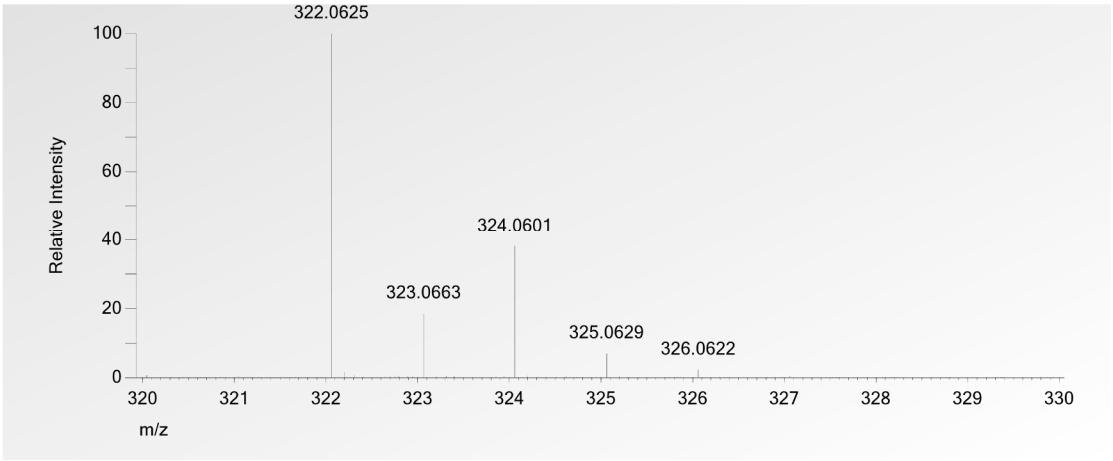

Cl
OMe
O
[65%]
N
S
[>98%]

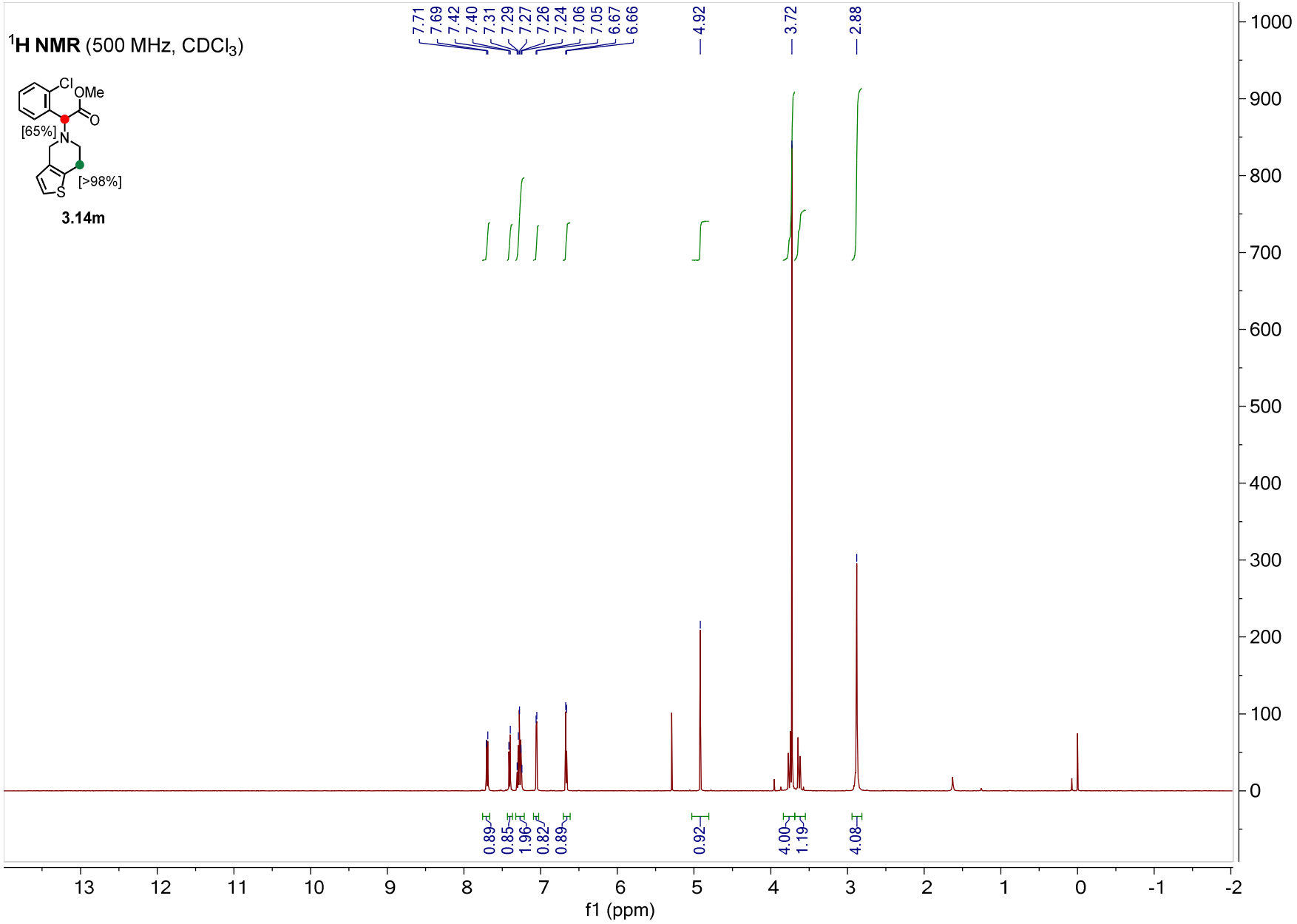
3.14m

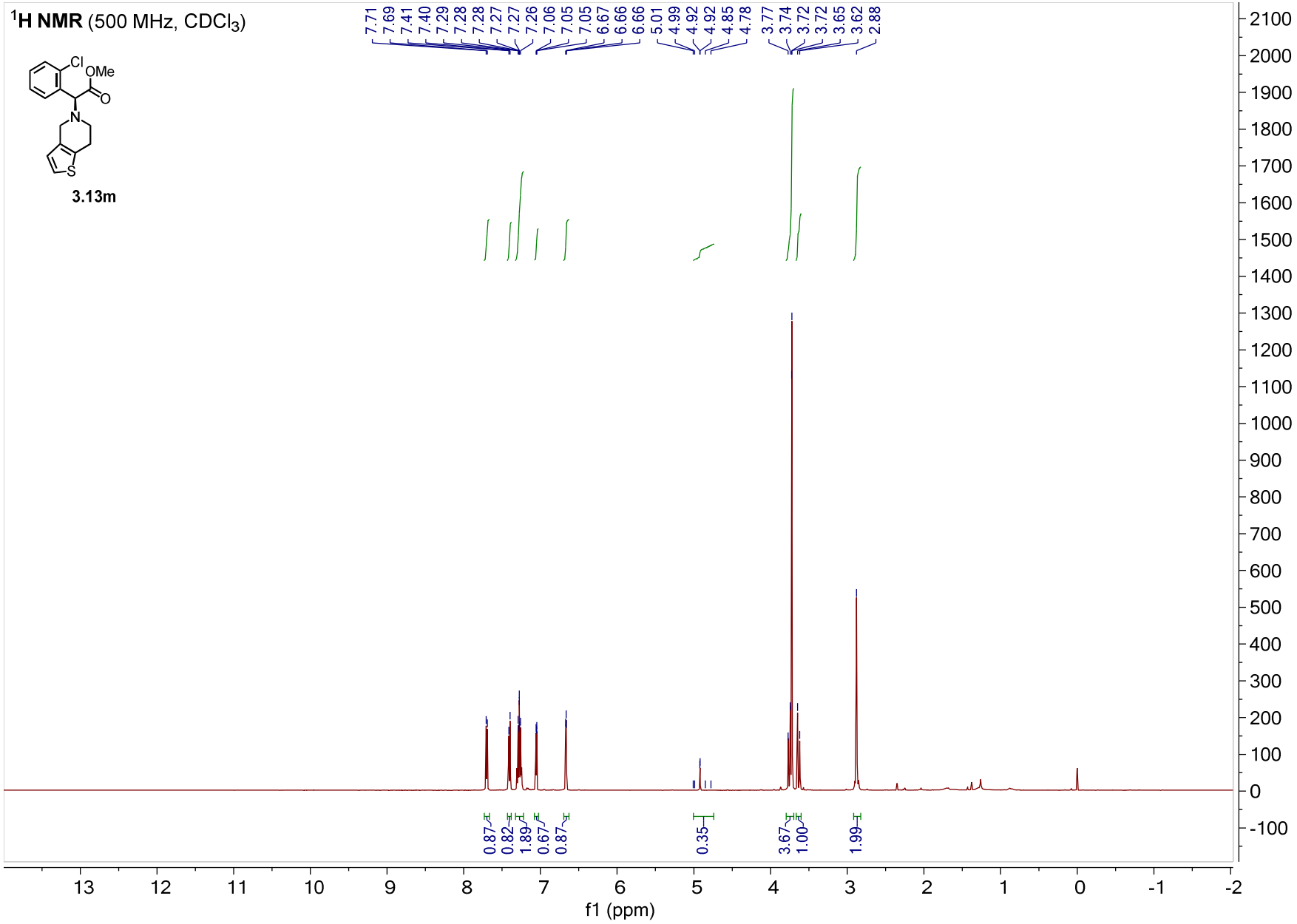

324.9992
326.0013
326.9957
323.9945
327.9975
322.9875
328.9965
329.9950
Relative Intensity
m/z

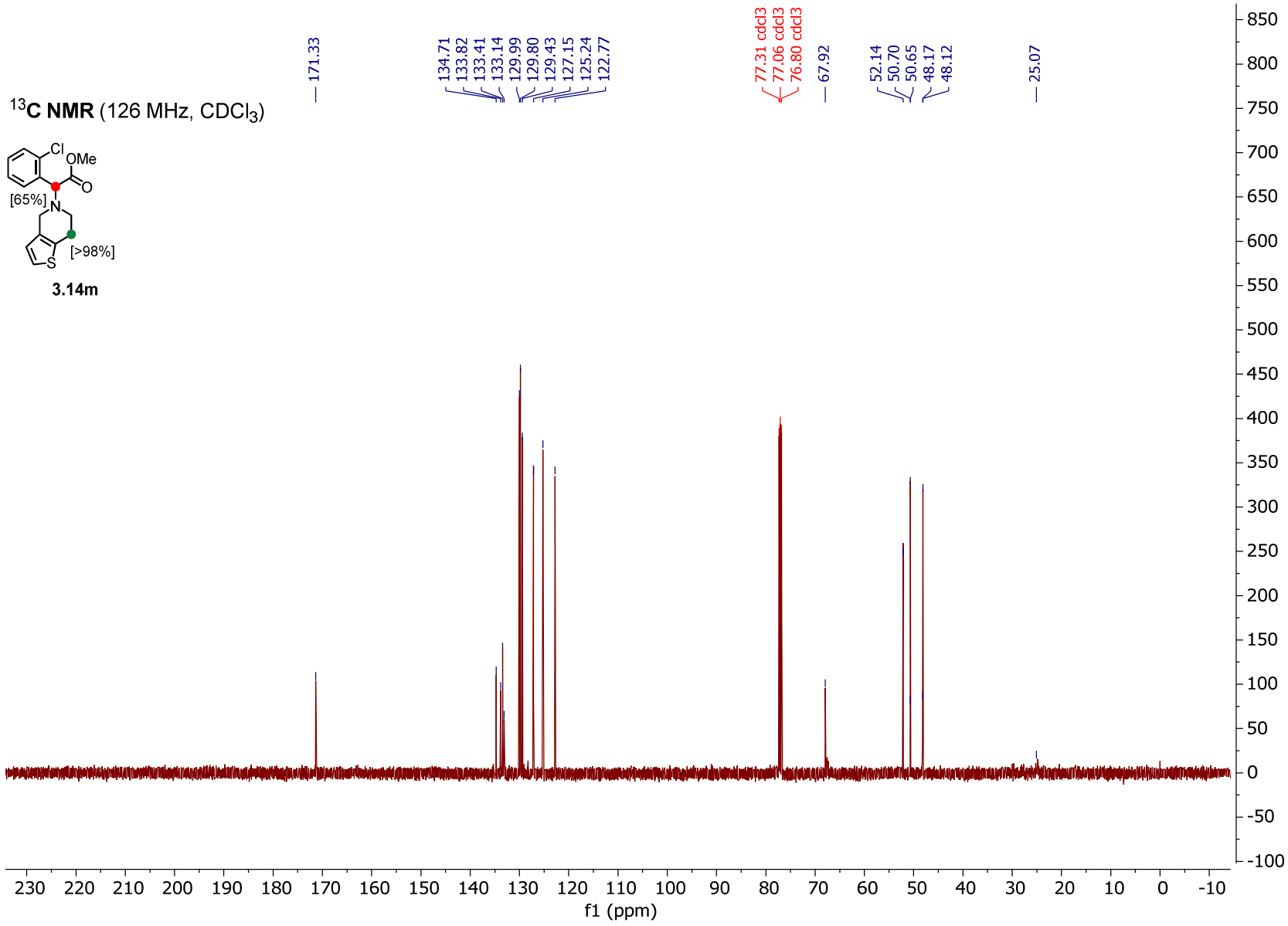

Cl
OMe
O
N
S

3.13m

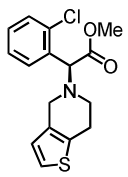

322.0625
324.0601
323.0663
325.0629
326.0622
Relative Intensity
m/z


1H NMR (500 MHz, CDCl3)
Cl
OMe
O
[65%]
N
[>98%]
S
3.14m
7.71
7.69
7.42
7.40
7.31
7.29
7.27
7.26
7.24
7.06
7.05
6.67
6.66
4.92
3.72
2.88
0.89
0.85
1.96
0.82
0.89
0.92
4.00
1.19
4.08
1000
900
800
700
600
500
400
300
200
100
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

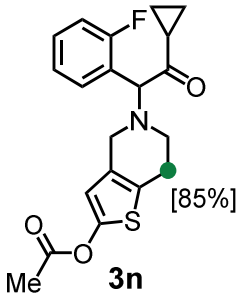

^{1}H NMR (500 MHz, $CDCl_3$)
Cl
OMe
O
N
S
3.13m
7.71
7.69
7.41
7.40
7.29
7.28
7.28
7.27
7.27
7.26
7.06
7.05
7.05
6.67
6.66
6.66
5.01
4.99
4.92
4.92
4.85
4.78
3.77
3.74
3.72
3.72
3.65
3.62
2.88
0.87
0.82
1.89
0.67
0.87
0.35
3.67
1.00
1.99
f1 (ppm)


13C NMR (126 MHz, CDCl3)
Cl
OMe
O
[65%]
N
[>98%]
S
3.14m
171.33
134.71
133.82
133.41
133.14
129.99
129.80
129.43
127.15
125.24
122.77
77.31 cdcl3
77.06 cdcl3
76.80 cdcl3
67.92
52.14
50.70
50.65
48.17
48.12
25.07
f1 (ppm)

^{13}**C NMR** (126 MHz, $CDCl_3$)



3.13m



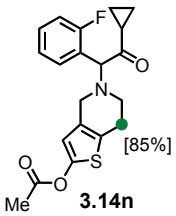
3n

Prasugrel, 3.14n

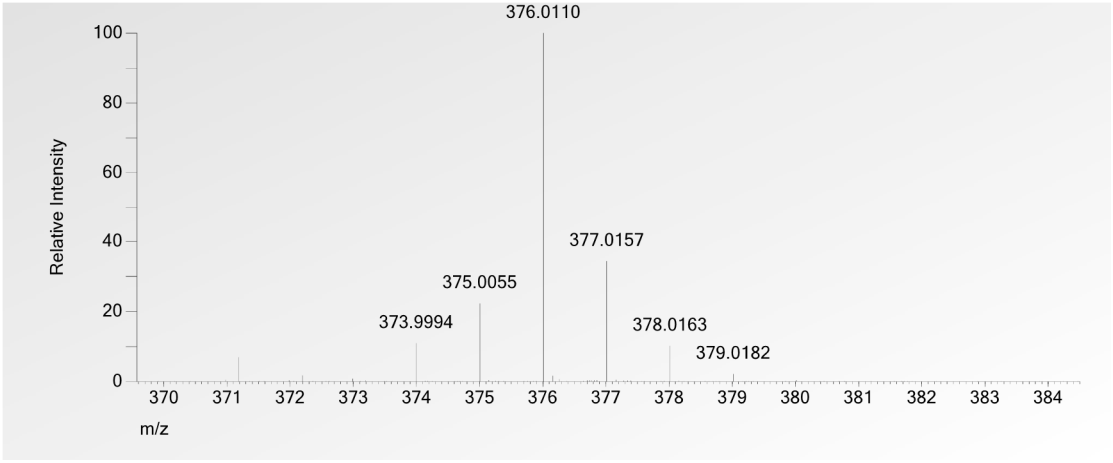
Prasugrel **3.13n** was added to acetone-d_6 **3.3** following the General Procedure C. After purification by silica gel chromatography (Et_2O:hexanes = 1:19), **3.14n** was obtained as a white solid (64 mg, 0.17 mmol, 85% yield).

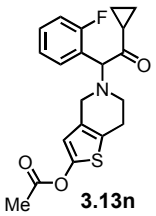
Deuterium incorporation: 1.70 D/molecule (^{1}H NMR), 1.99 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.31 (s, 1H), 7.17 (s, 1H), 7.11 (s, 1H), 6.26 (s, 1H), 4.83 (s, 1H), 3.63 – 3.43 (m, 2H), 2.89 (d, J = 11.5 Hz, 1H), 2.75 (d, J = 11.4 Hz, 1.30H, 85%D), 2.25 (s, 4H), 1.03 (dd, J = 26.7, 2.8 Hz, 2H), 0.85 (d, J = 2.7 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.64, 167.71, 162.11, 160.47, 149.51, 130.55, 129.89, 129.83, 129.45, 125.59, 124.37, 124.35, 122.08, 121.99, 115.86, 115.71, 112.00, 111.96, 71.61, 71.56, 50.50, 50.48, 50.46, 48.26, 25.01, 20.65, 18.30, 12.06, 11.45; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -114.68 – -118.69 (m); **IR** (neat) 1776, 1758, 1698, 1486, 1454, 1369, 1191, 1086, 1037, 1008, 903, 759 cm^{-1}.

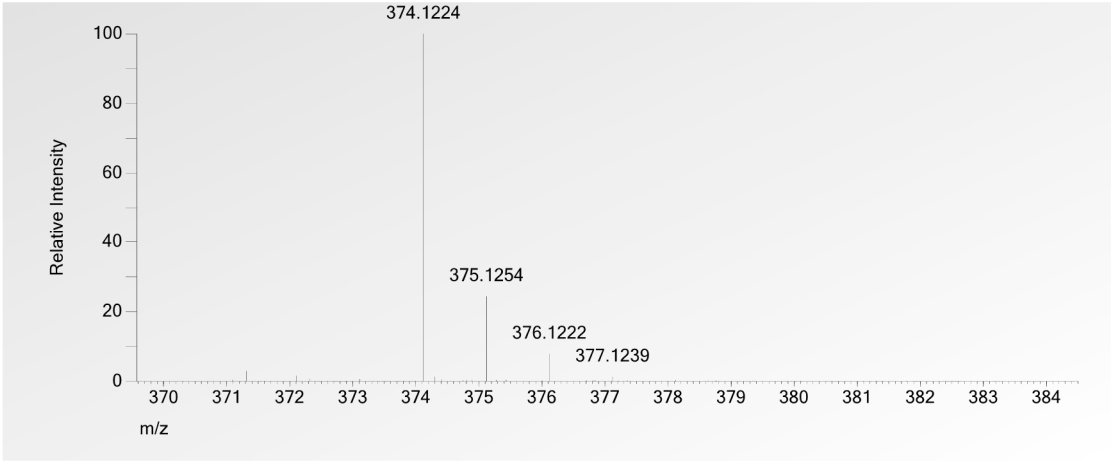

F
O
N
[85%]
S
O
O
Me

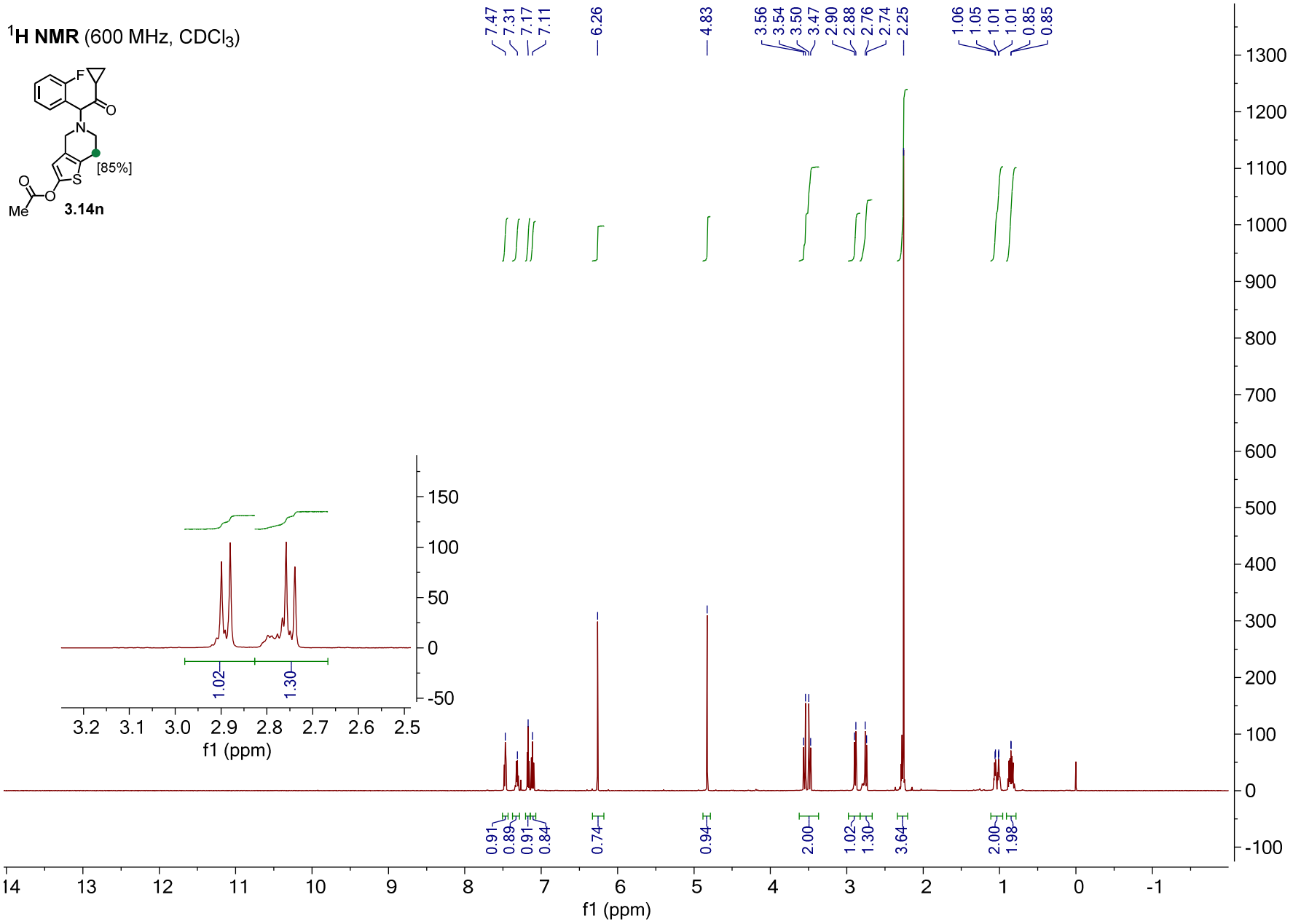
3.14n

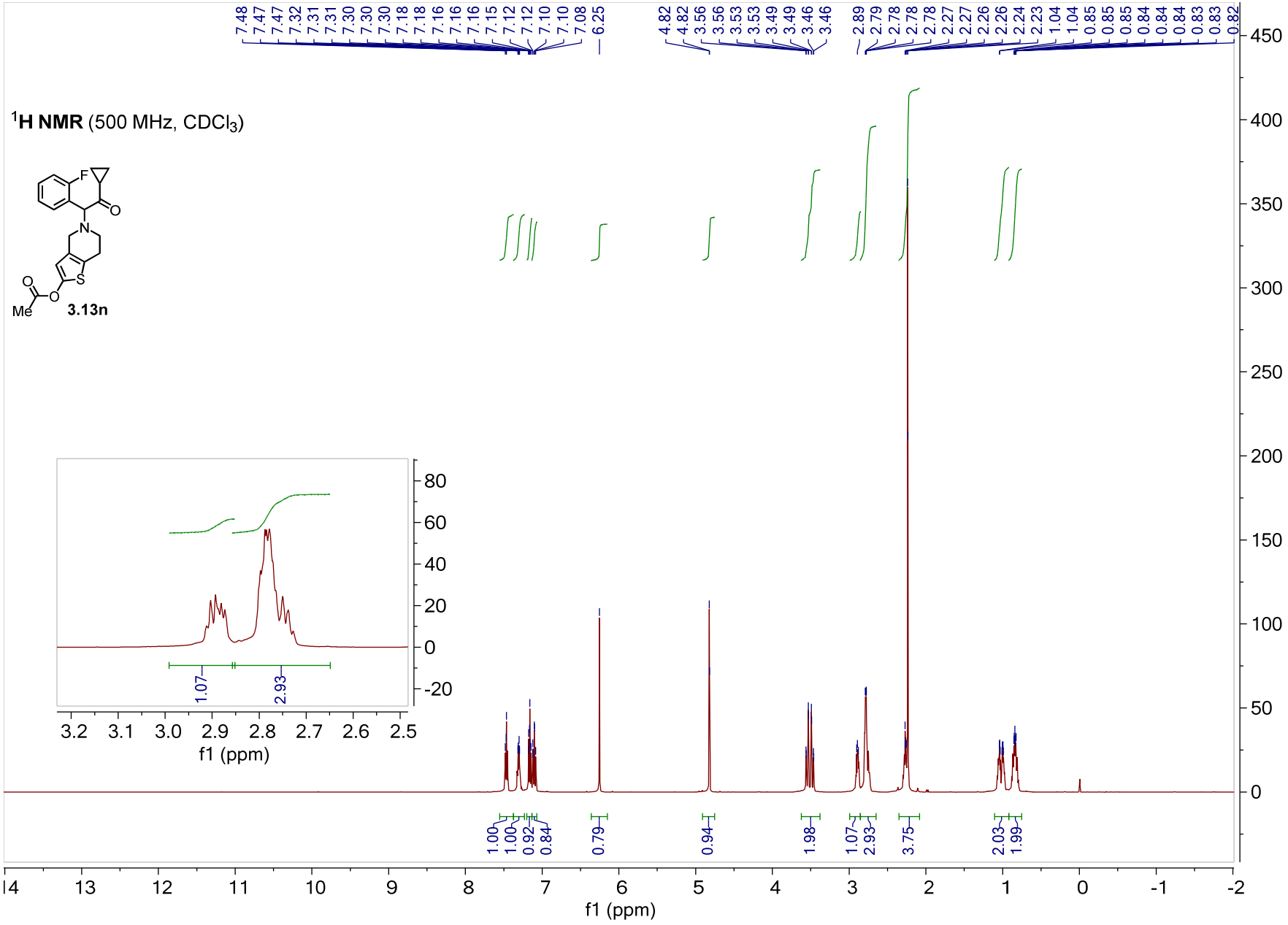

376.0110
377.0157
375.0055
373.9994
378.0163
379.0182
Relative Intensity
m/z
100
80
60
40
20
0
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384

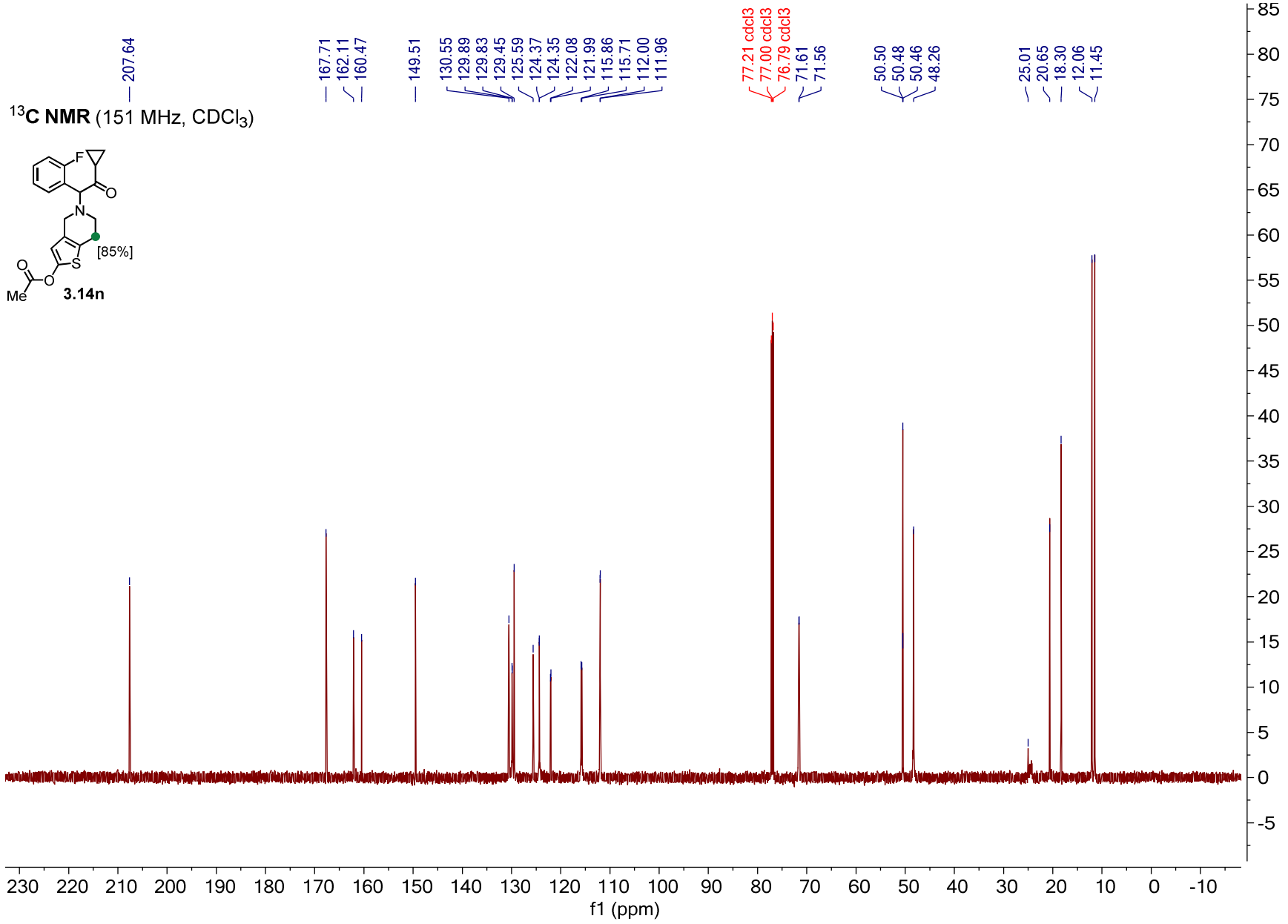

F
O
N
S
O
O
Me

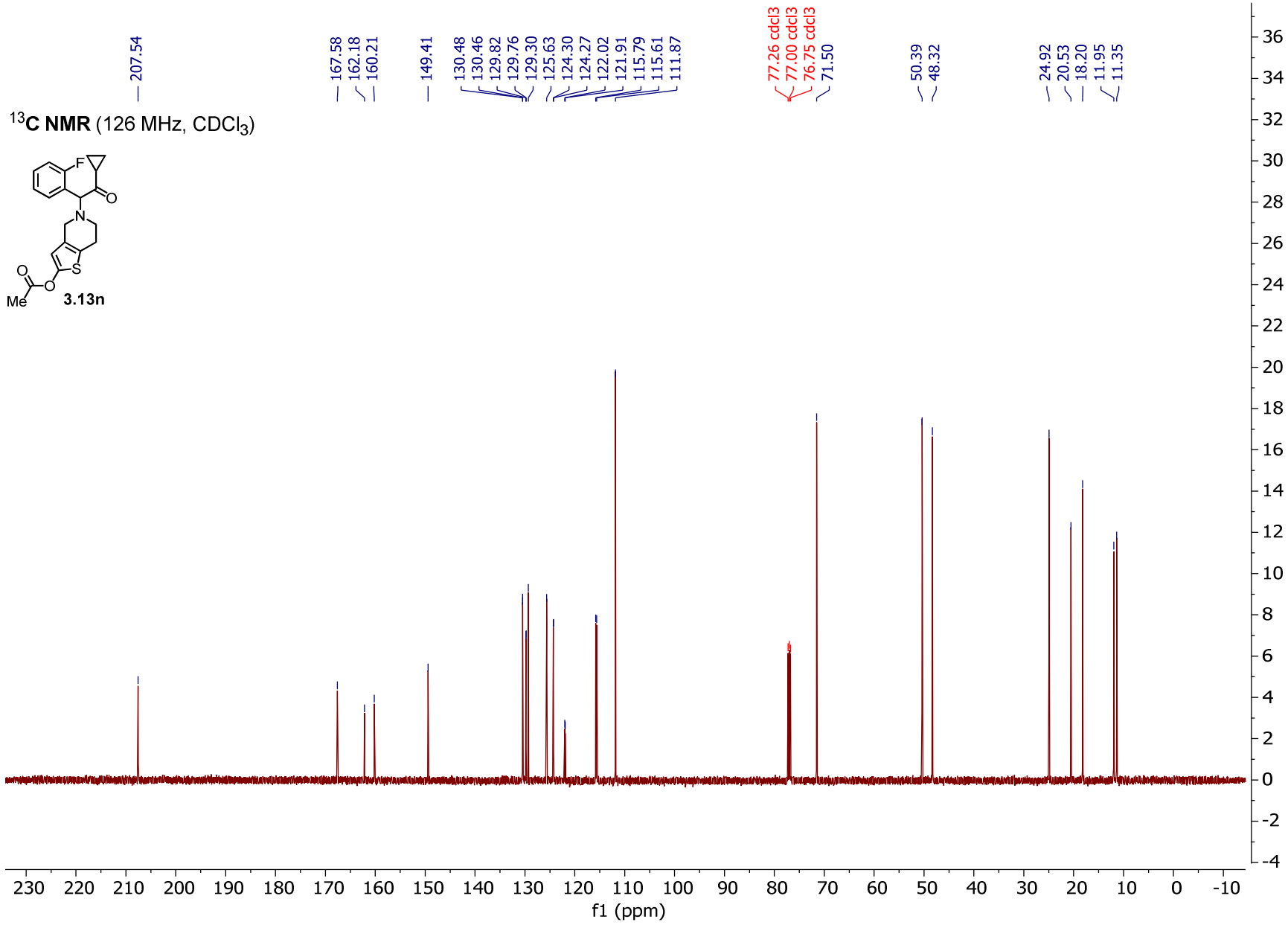
3.13n

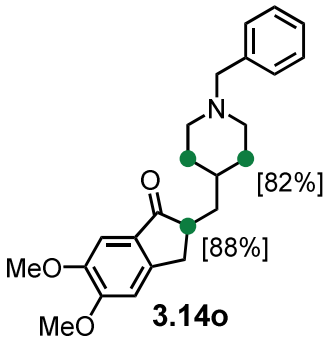

374.1224
375.1254
376.1222
377.1239
Relative Intensity
m/z
100
80
60
40
20
0
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384


1H NMR (600 MHz, CDCl3)
[85%]
3.14n
7.47
7.31
7.17
7.11
6.26
4.83
3.56
3.54
3.50
3.47
2.90
2.88
2.76
2.74
2.25
1.06
1.05
1.01
1.01
0.85
0.85
0.91
0.89
0.91
0.84
0.74
0.94
2.00
1.02
1.30
3.64
2.00
1.98
f1 (ppm)
1.02
1.30
f1 (ppm)


7.48 7.47 7.47 7.32 7.31 7.31 7.30 7.30 7.30 7.18 7.18 7.16 7.16 7.16 7.15 7.12 7.12 7.10 7.10 7.08 6.25
4.82 4.82 3.56 3.56 3.53 3.53 3.49 3.49 3.46 3.46
2.89 2.79 2.78 2.78 2.78 2.27 2.27 2.26 2.26 2.24 2.23 1.04 1.04 0.85 0.85 0.85 0.84 0.84 0.84 0.83 0.83 0.82
1H NMR (500 MHz, CDCl3)
F
O
N
S
O
O
Me
3.13n
1.07
2.93
f1 (ppm)
1.00 1.00 0.92 0.84 0.79 0.94 1.98 1.07 2.93 3.75 2.03 1.99
f1 (ppm)


207.64
167.71
162.11
160.47
149.51
130.55
129.89
129.83
129.45
125.59
124.37
124.35
122.08
121.99
115.86
115.71
112.00
111.96
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
71.61
71.56
50.50
50.48
50.46
48.26
25.01
20.65
18.30
12.06
11.45
13C NMR (151 MHz, CDCl3)
F
O
N
[85%]
S
O
O
Me
3.14n
f1 (ppm)


207.54
167.58
162.18
160.21
149.41
130.48
130.46
129.82
129.76
129.30
125.63
124.30
124.27
122.02
121.91
115.79
115.61
111.87
77.26 cdcl3
77.00 cdcl3
76.75 cdcl3
71.50
50.39
48.32
24.92
20.53
18.20
11.95
11.35
13C NMR (126 MHz, CDCl3)
F
O
N
S
O
O
Me
3.13n
f1 (ppm)



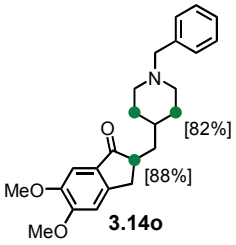
3.14o

Donepezil, 3.14o

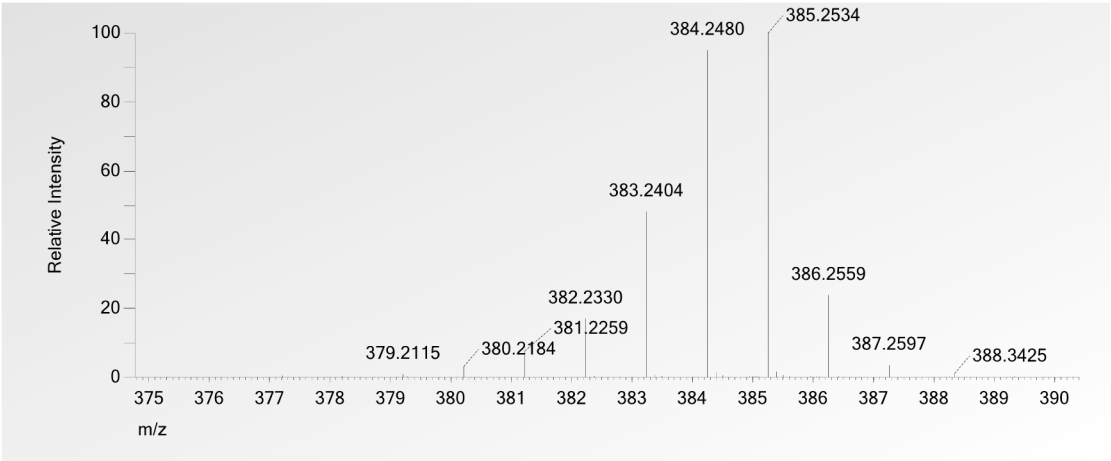
Donepezil **3.13o** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (MeOH:DCM = 1:49), **3.14o** was obtained as a white solid (74 mg, 0.20 mmol, 98% yield).

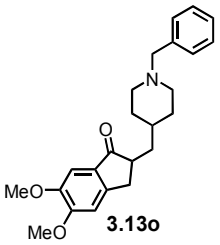
Deuterium incorporation: 5.04 D/molecule (^{1}H NMR), 4.17 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.16 (s, 1H), 6.85 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.67 (s, 2H), 3.24 (d, *J* = 16.9 Hz, 1H), 3.02 (d, *J* = 10.6 Hz, 2H), 2.68 (d, *J* = 16.9 Hz, 1.12H, 88%D), 2.15 (s, 2H), 1.89 (dd, *J* = 13.8, 7.6 Hz, 1H), 1.78−1.70 (m, 0.25H, 88%D), 1.59 (s, 1H), 1.56−1.44 (m, 0.49H, 75%D), 1.43 – 1.32 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.59, 155.48, 149.42, 148.73, 136.16, 129.74, 129.18, 128.37, 127.64, 107.32, 104.31, 62.71, 56.02, 53.12, 45.15, 38.34, 33.33; **IR** (neat) 2913, 1691, 1590, 1499, 1454, 1310, 1269, 1247, 1218, 1114, 727 cm^{-1}.

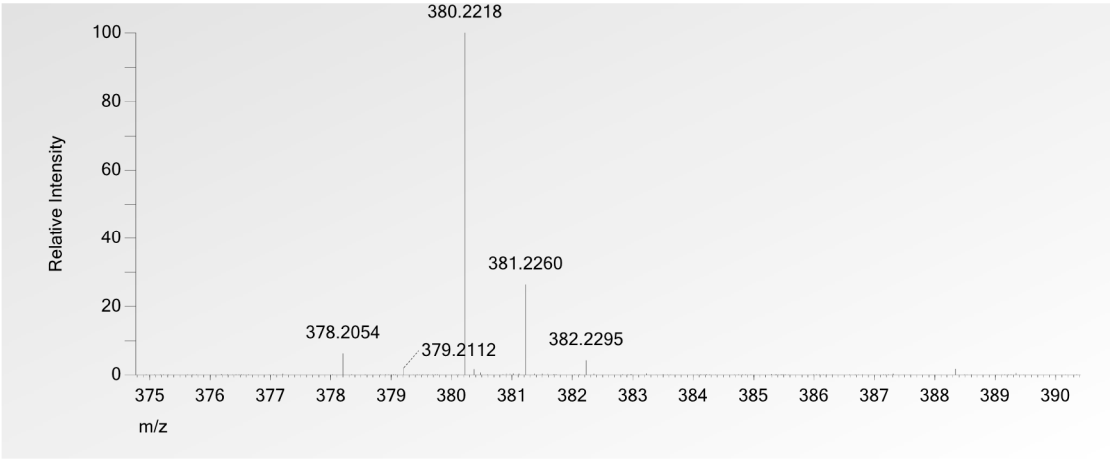

N
O
[82%]
[88%]
MeO
MeO

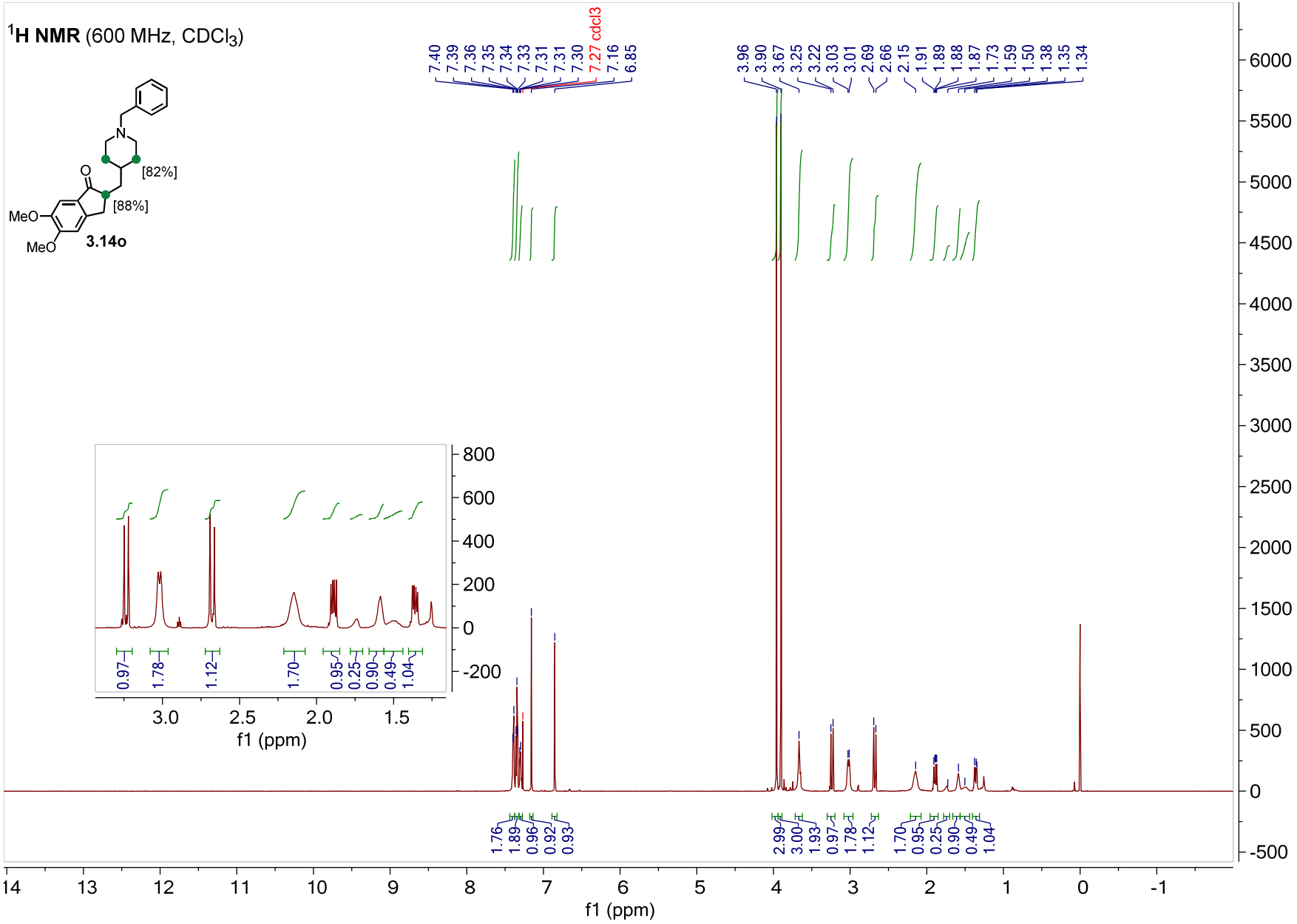
3.14o

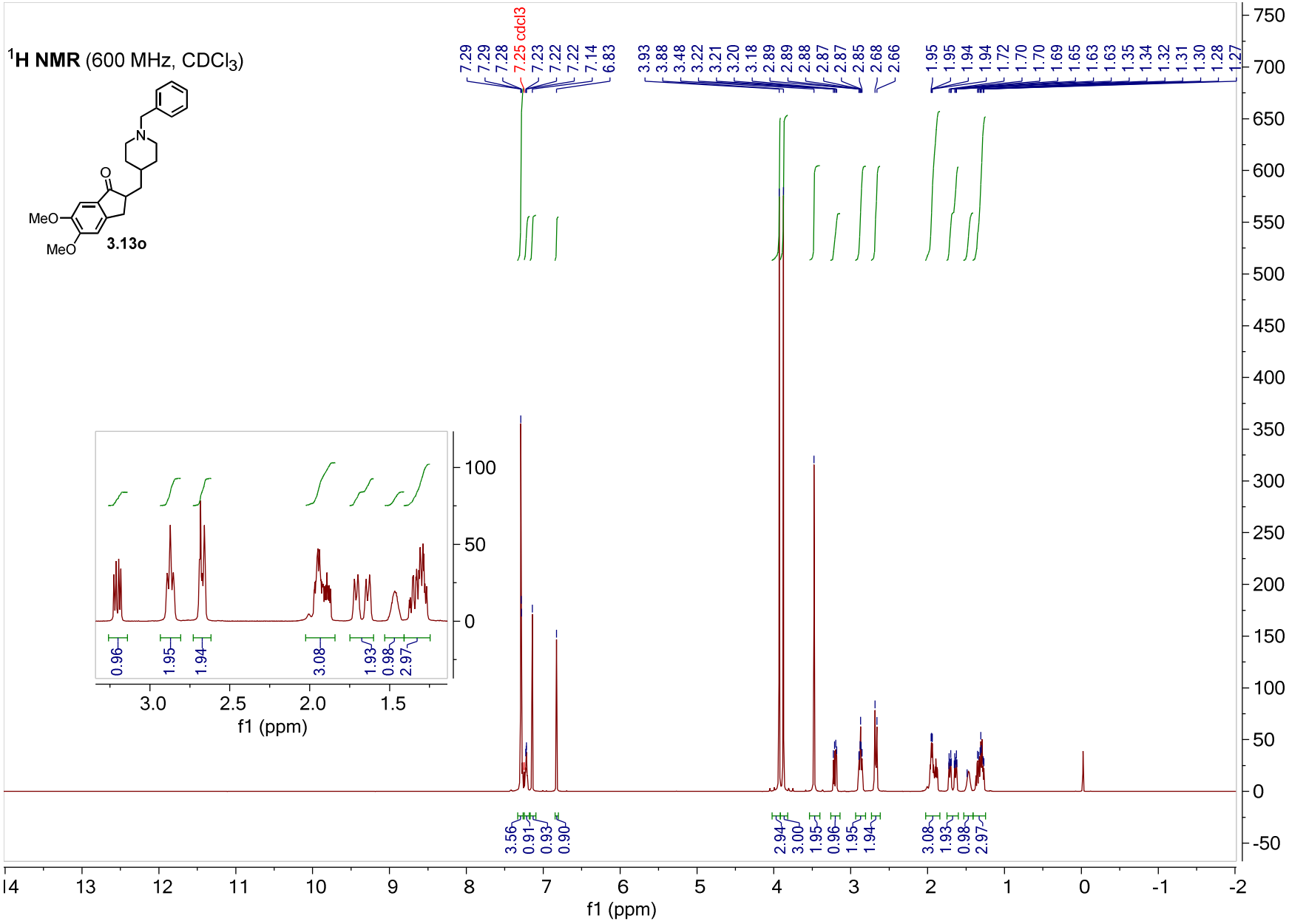

Relative Intensity
m/z
384.2480
385.2534
383.2404
386.2559
382.2330
381.2259
379.2115
380.2184
387.2597
388.3425

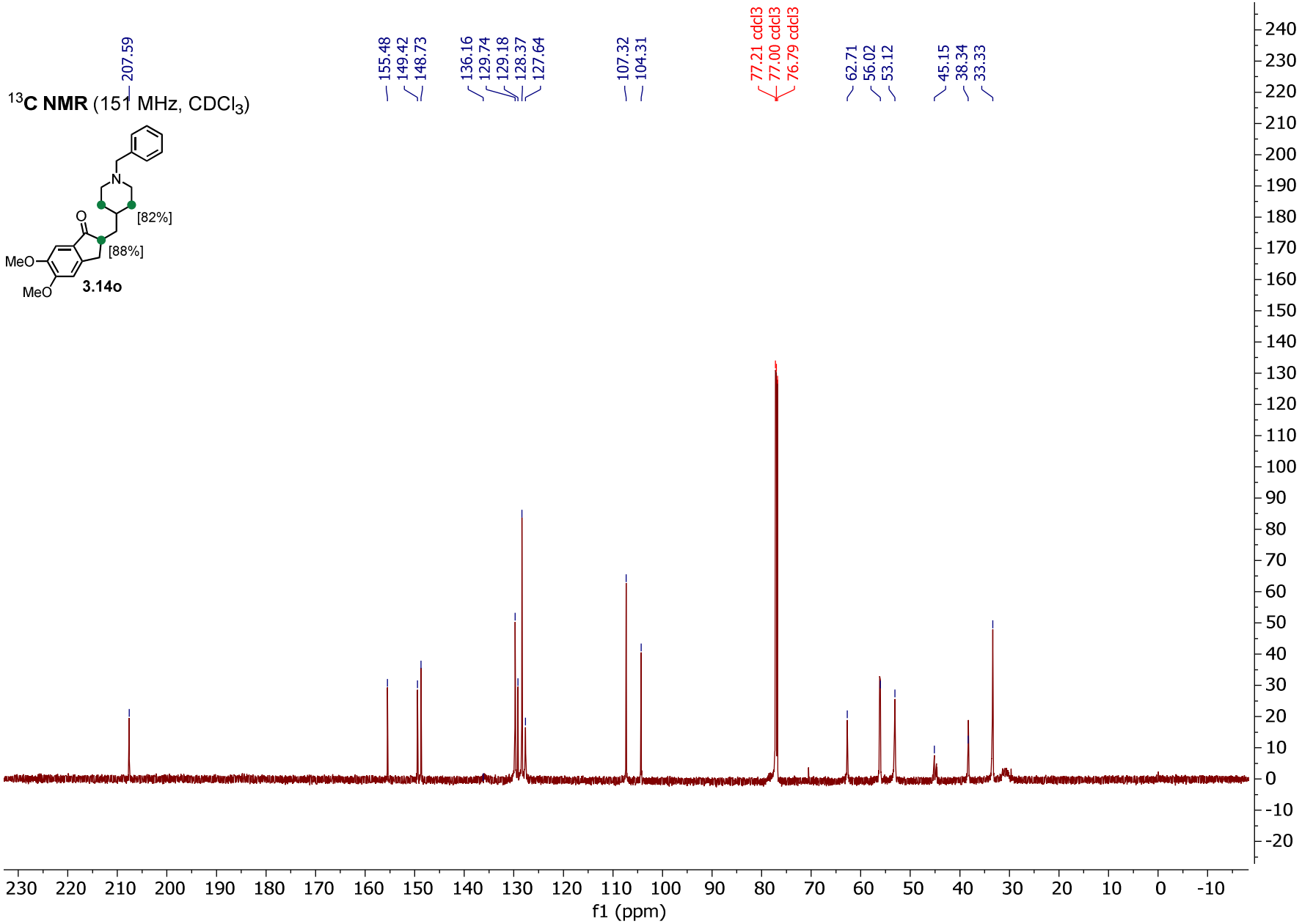

N
O
MeO
MeO

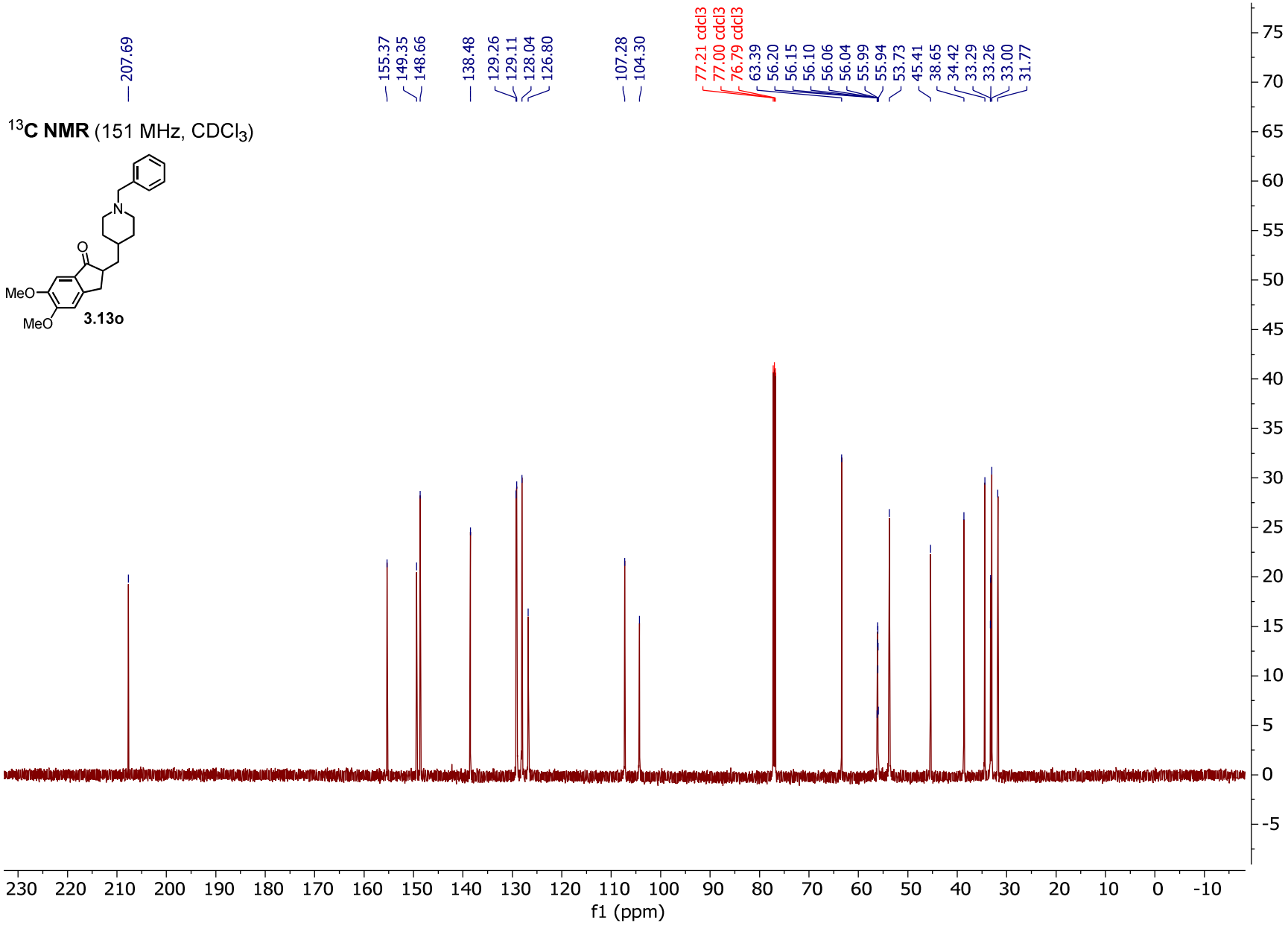
3.13o

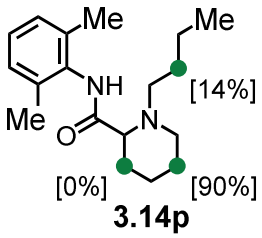

Relative Intensity
m/z
380.2218
381.2260
378.2054
379.2112
382.2295


1H NMR (600 MHz, CDCl3)
[82%]
[88%]
MeO
MeO
3.14o
7.40 7.39 7.36 7.35 7.34 7.33 7.31 7.31 7.30 7.27 cdcl3 7.16 6.85
3.96 3.90 3.67 3.25 3.22 3.03 3.01 2.69 2.66 2.15 1.91 1.89 1.88 1.87 1.73 1.59 1.50 1.38 1.35 1.34
1.76 1.89 0.96 0.92 0.93
2.99 3.00 1.93 0.97 1.78 1.12 1.70 0.95 0.25 0.90 0.49 1.04
0.97 1.78 1.12 1.70 0.95 0.25 0.90 0.49 1.04
f1 (ppm)
f1 (ppm)


1H NMR (600 MHz, CDCl3)
MeO
MeO
O
N
3.13o
7.29 7.29 7.28 7.25 cdcl3 7.23 7.22 7.22 7.14 6.83
3.93 3.88 3.48 3.22 3.21 3.20 3.18 2.89 2.89 2.88 2.87 2.87 2.85 2.68 2.66
1.95 1.95 1.94 1.94 1.72 1.70 1.70 1.69 1.65 1.63 1.63 1.35 1.34 1.32 1.31 1.30 1.28 1.27
0.96 1.95 1.94 3.08 1.93 0.98 2.97
3.56 0.91 0.93 0.90 2.94 3.00 1.95 0.96 1.95 1.94 3.08 1.93 0.98 2.97
f1 (ppm)
f1 (ppm)


^{13}C NMR (151 MHz, $CDCl_3$)
207.59
155.48
149.42
148.73
136.16
129.74
129.18
128.37
127.64
107.32
104.31
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
62.71
56.02
53.12
45.15
38.34
33.33
[82%]
[88%]
MeO
MeO
3.14o
f1 (ppm)


207.69
155.37
149.35
148.66
138.48
129.26
129.11
128.04
126.80
107.28
104.30
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
63.39
56.20
56.15
56.10
56.06
56.04
55.99
55.94
53.73
45.41
38.65
34.42
33.29
33.26
33.00
31.77
13C NMR (151 MHz, CDCl3)
MeO
MeO
O
N
3.13o
f1 (ppm)



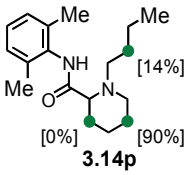
3.14p

Bupivacaine, 3.14p

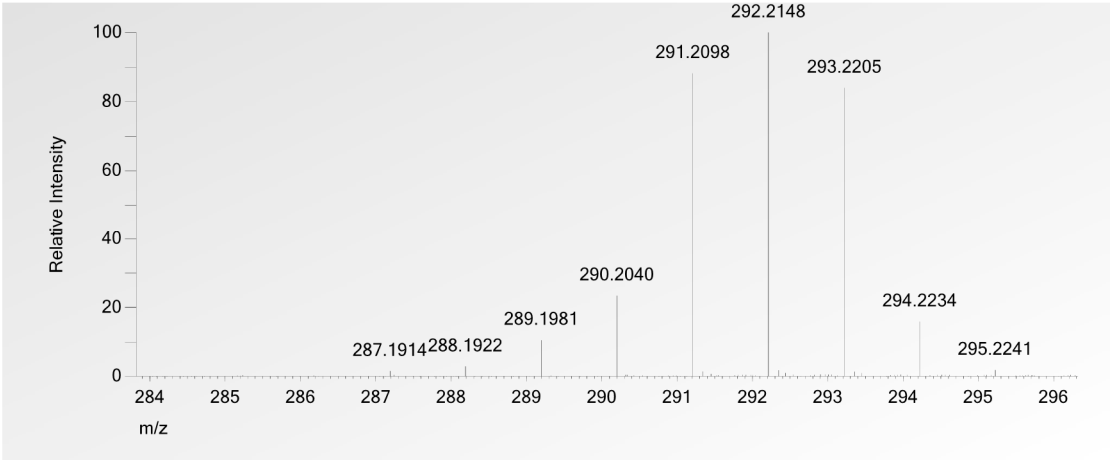
Bupivacaine **3.13p** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (MeOH:DCM = 1:49), **3.14p** was obtained as a white solid (55 mg, 0.19 mmol, 96% yield).

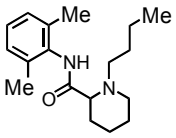
Deuterium incorporation: 2.08 D/molecule (^{1}H NMR), 2.83 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.06 (d, J = 5.5 Hz, 3H), 3.18 (d, J = 11.6 Hz, 1H), 2.92 (d, J = 9.3 Hz, 1H), 2.86 – 2.74 (m, 1H), 2.31 – 2.17 (m, 7H), 2.11 – 2.01 (m, 2H), 1.77 – 1.66 (m, 2.2H, 80%D), 1.65 – 1.54 (m, 0.86H, 14%D), 1.54 – 1.39 (m, 0.85H, 15%D and >98%D), 1.41 – 1.24 (m, 3H), 0.91 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.67, 135.20, 133.57, 128.20, 126.99, 68.28, 57.37, 57.29, 51.48, 51.40, 30.44, 29.45, 23.91, 23.11, 20.55, 20.45, 20.35, 18.60, 13.99; **IR** (neat) 3224, 2952, 2927, 2855, 1650, 1513, 1463, 1228, 1097, 764 cm^{-1}.

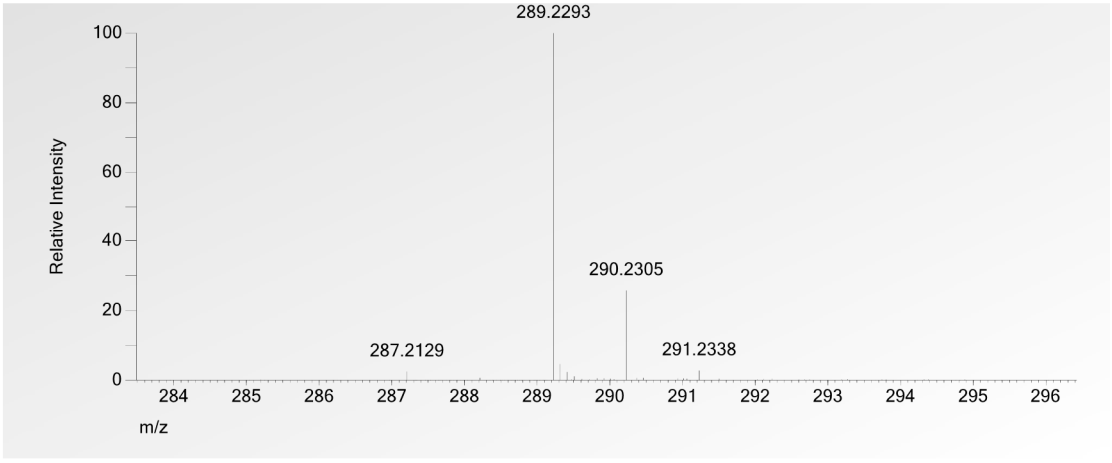

Me
Me
NH
Me
O
N
[14%]
[0%]
[90%]

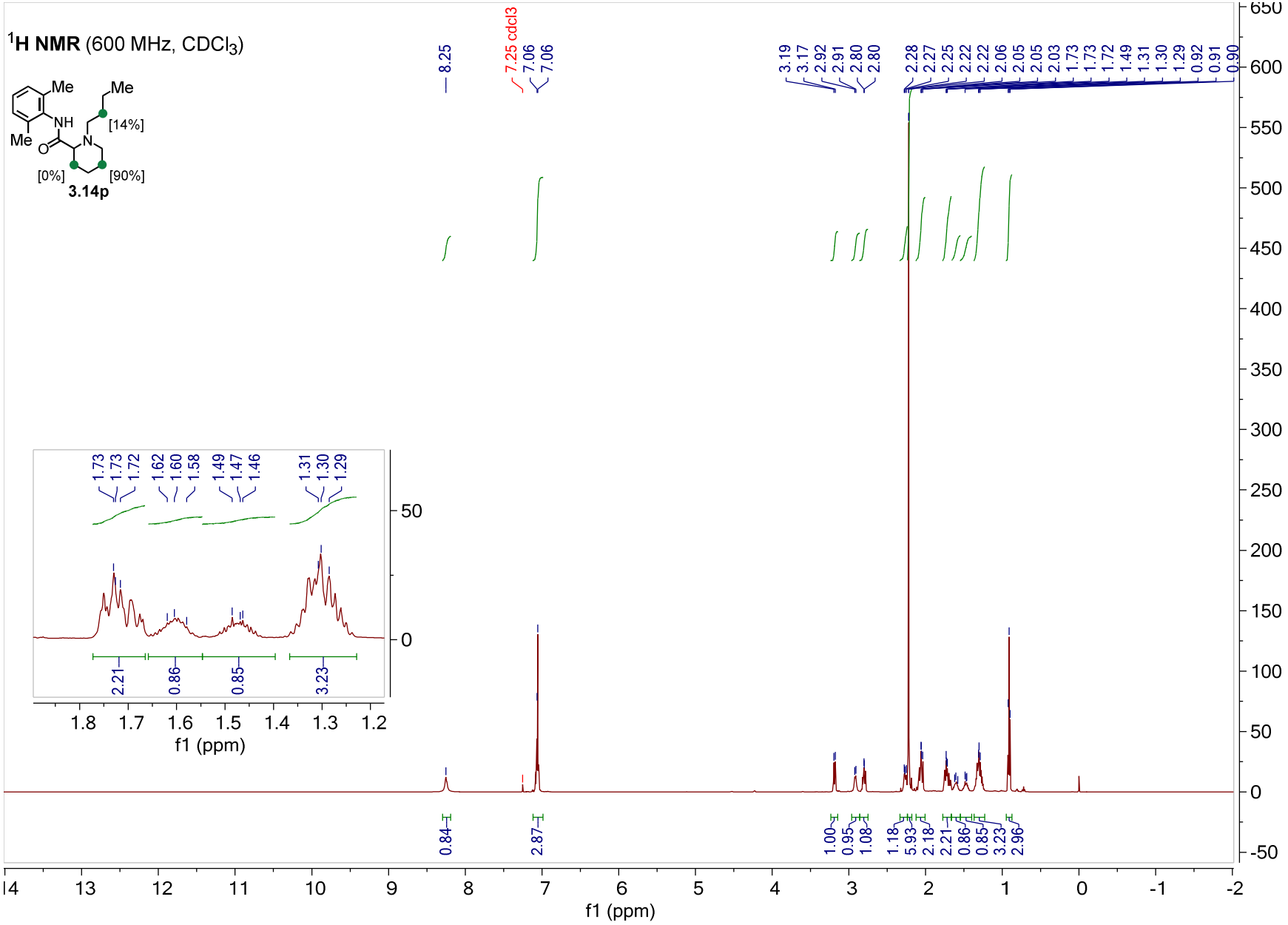
3.14p

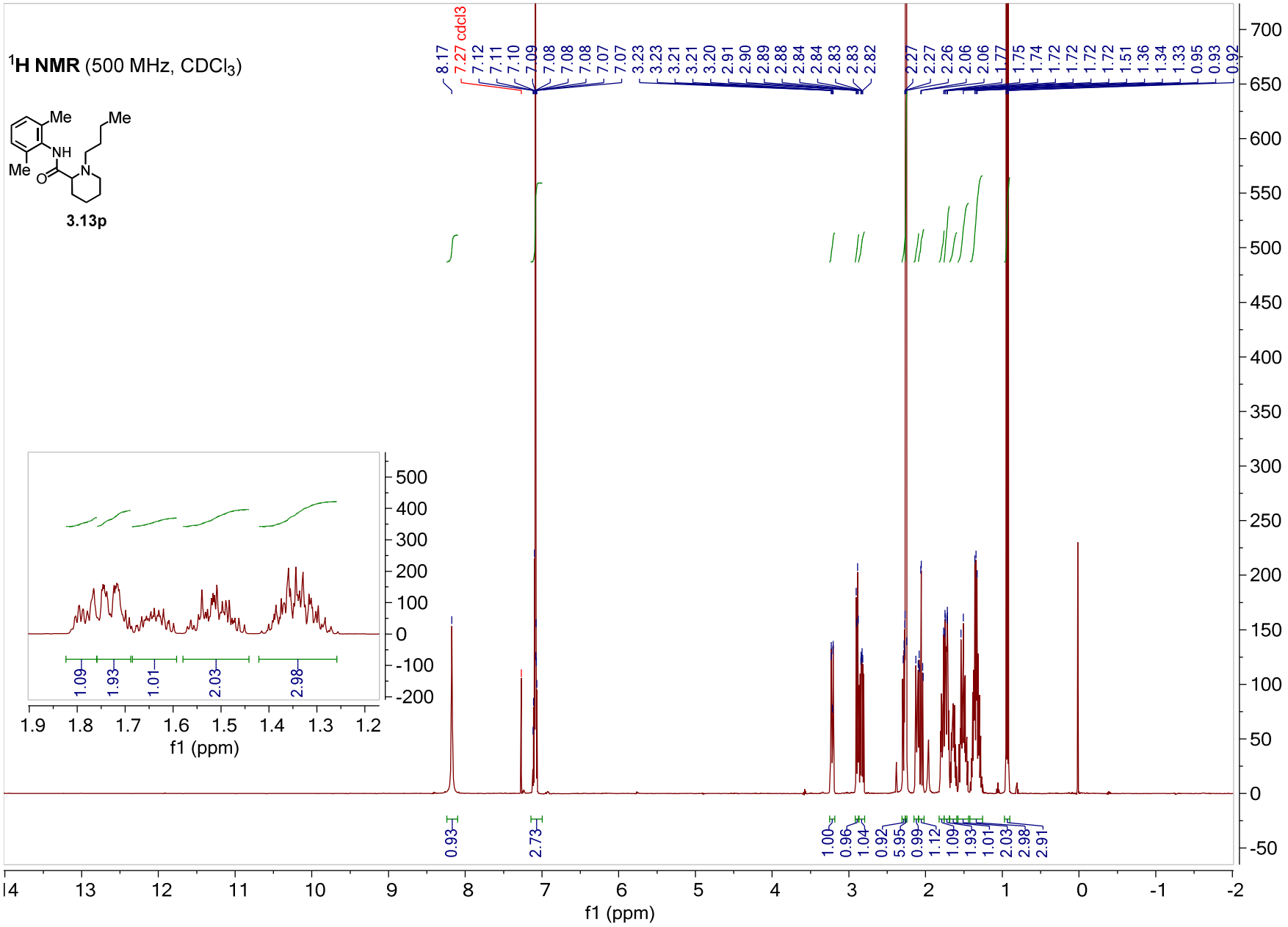

292.2148
291.2098
293.2205
290.2040
294.2234
289.1981
287.1914
288.1922
295.2241
Relative Intensity
m/z

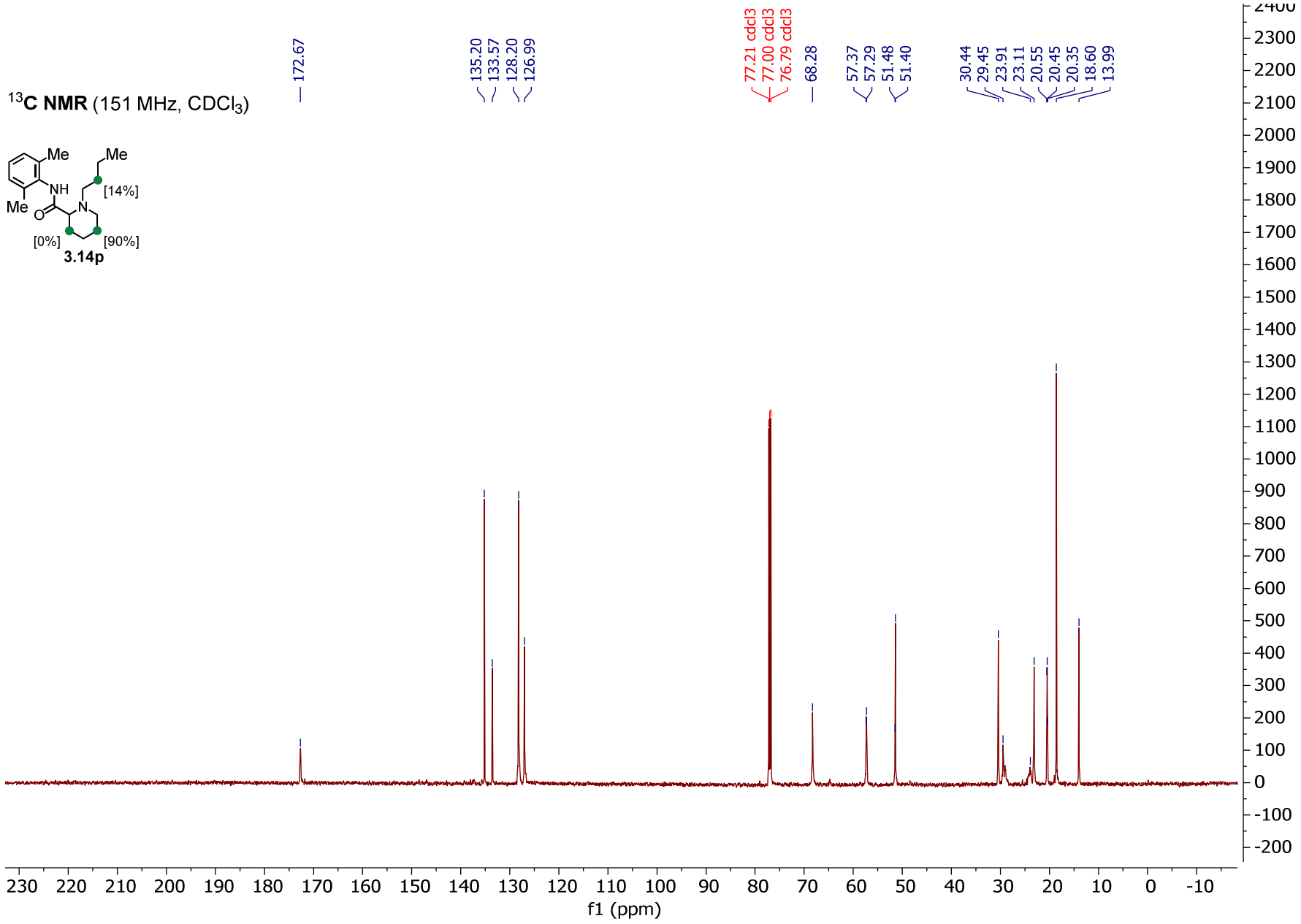

Me
Me
NH
Me
O
N

3.13p

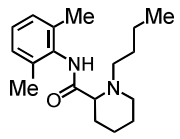

289.2293
290.2305
287.2129
291.2338
Relative Intensity
m/z


1H NMR (600 MHz, CDCl3)
Me
Me
NH
[14%]
Me
O
N
[0%]
[90%]
3.14p
8.25
7.25 cdcl3
7.06
7.06
3.19
3.17
2.92
2.91
2.80
2.80
2.28
2.27
2.25
2.22
2.22
2.06
2.05
2.05
2.03
1.73
1.73
1.72
1.49
1.31
1.30
1.29
0.92
0.91
0.90
1.73
1.73
1.72
1.62
1.60
1.58
1.49
1.47
1.46
1.31
1.30
1.29
2.21
0.86
0.85
3.23
f1 (ppm)
0.84
2.87
1.00
0.95
1.08
1.18
5.93
2.18
2.21
0.86
0.85
3.23
2.96
f1 (ppm)

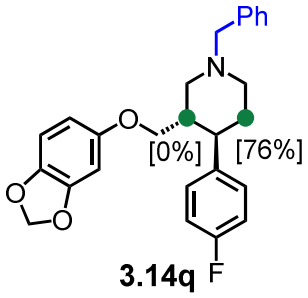

1H NMR (500 MHz, CDCl3)
Me
Me
NH
Me
O
N
3.13p
8.17
7.27 cdcl3
7.12
7.11
7.10
7.09
7.08
7.08
7.08
7.07
7.07
3.23
3.23
3.21
3.21
3.20
2.91
2.90
2.89
2.88
2.84
2.84
2.83
2.83
2.82
2.27
2.27
2.26
2.06
2.06
1.77
1.75
1.74
1.72
1.72
1.72
1.72
1.51
1.36
1.34
1.33
0.95
0.93
0.92
0.93
2.73
1.00
0.96
1.04
0.92
5.95
0.99
1.12
1.09
1.93
1.01
2.03
2.98
2.91
f1 (ppm)
1.09
1.93
1.01
2.03
2.98
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Me
Me
NH
Me
O
N
[14%]
[0%]
[90%]
3.14p
172.67
135.20
133.57
128.20
126.99
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
68.28
57.37
57.29
51.48
51.40
30.44
29.45
23.91
23.11
20.55
20.45
20.35
18.60
13.99
f1 (ppm)

^{13}**C NMR** (126 MHz, $CDCl_3$)



3.13p



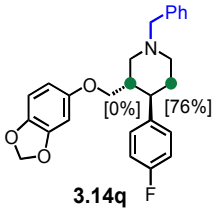
3.14q

***N*-Bn paroxetine, 3.14q**

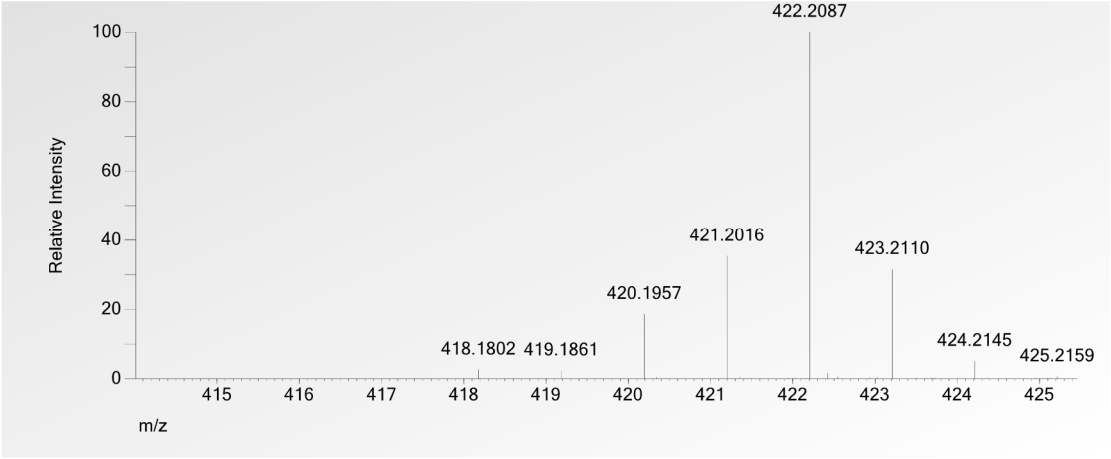
N-Bn paroxetine **3.13q** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (Et_2O:hexanes = 1:9), **3.14q** was obtained as a white solid (82 mg, 0.20 mmol, 98% yield).

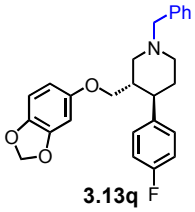
Deuterium incorporation: 1.52 D/molecule (^{1}H NMR), 1.85 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 4H), 7.30 – 7.21 (m, 1H), 7.15 (ddd, *J* = 7.1, 5.3, 2.7 Hz, 2H), 7.04 – 6.87 (m, 2H), 6.61 (dd, *J* = 8.5, 1.6 Hz, 1H), 6.31 (t, *J* = 2.1 Hz, 1H), 6.10 (d, *J* = 8.5 Hz, 1H), 5.86 (d, *J* = 1.7 Hz, 2H), 3.64 (dd, *J* = 13.2, 1.6 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.43 (s, 1H), 3.31 – 3.17 (m, 1H), 2.97 (d, *J* = 11.2 Hz, 1H), 2.46 (d, *J* = 11.1 Hz, 1H), 2.20 (dd, *J* = 7.5, 3.3 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.92 – 1.73 (m, 0.49H, 76%D); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.46, 160.52, 154.44, 148.13, 141.54, 139.88, 139.86, 138.28, 129.22, 128.88, 128.81, 128.23, 127.04, 115.43, 115.26, 107.83, 105.62, 101.06, 98.01, 69.67, 63.43, 57.62, 53.70, 43.96, 42.18, 34.40; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -116.68 (td, J = 8.8, 4.5 Hz); **IR** (neat) 2895, 2799, 1506, 1486, 1466, 1451, 1222, 1181, 1090, 1037, 830, 744, 705 cm^{-1}; **Specific Rotation**: $[\alpha]^{25}$ –27.3° (*c* 1.0, CH_2Cl_2; labeled); **Specific Rotation**: $[\alpha]^{25}$ –44.9° (*c* 1.0, CH_2Cl_2; unlabeled).

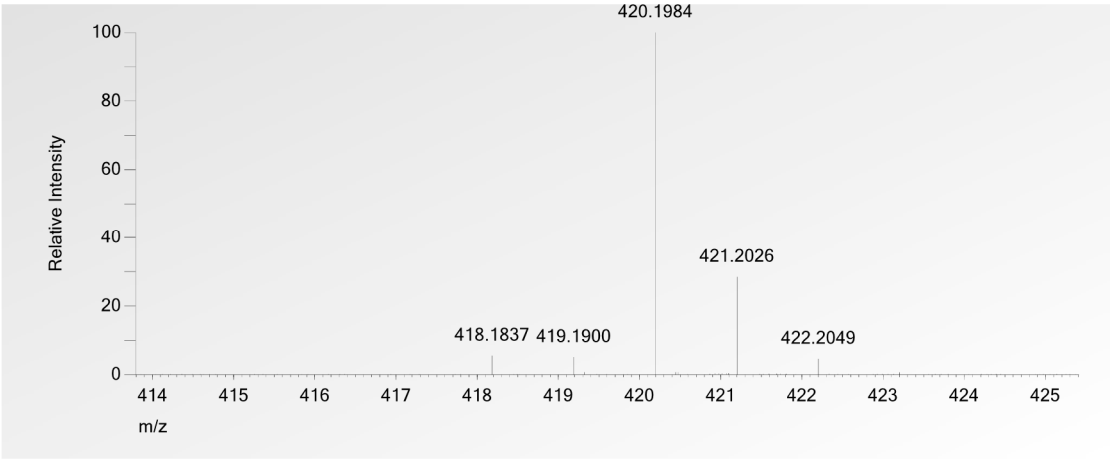

Ph
N
O
[0%]
[76%]
O
O
F

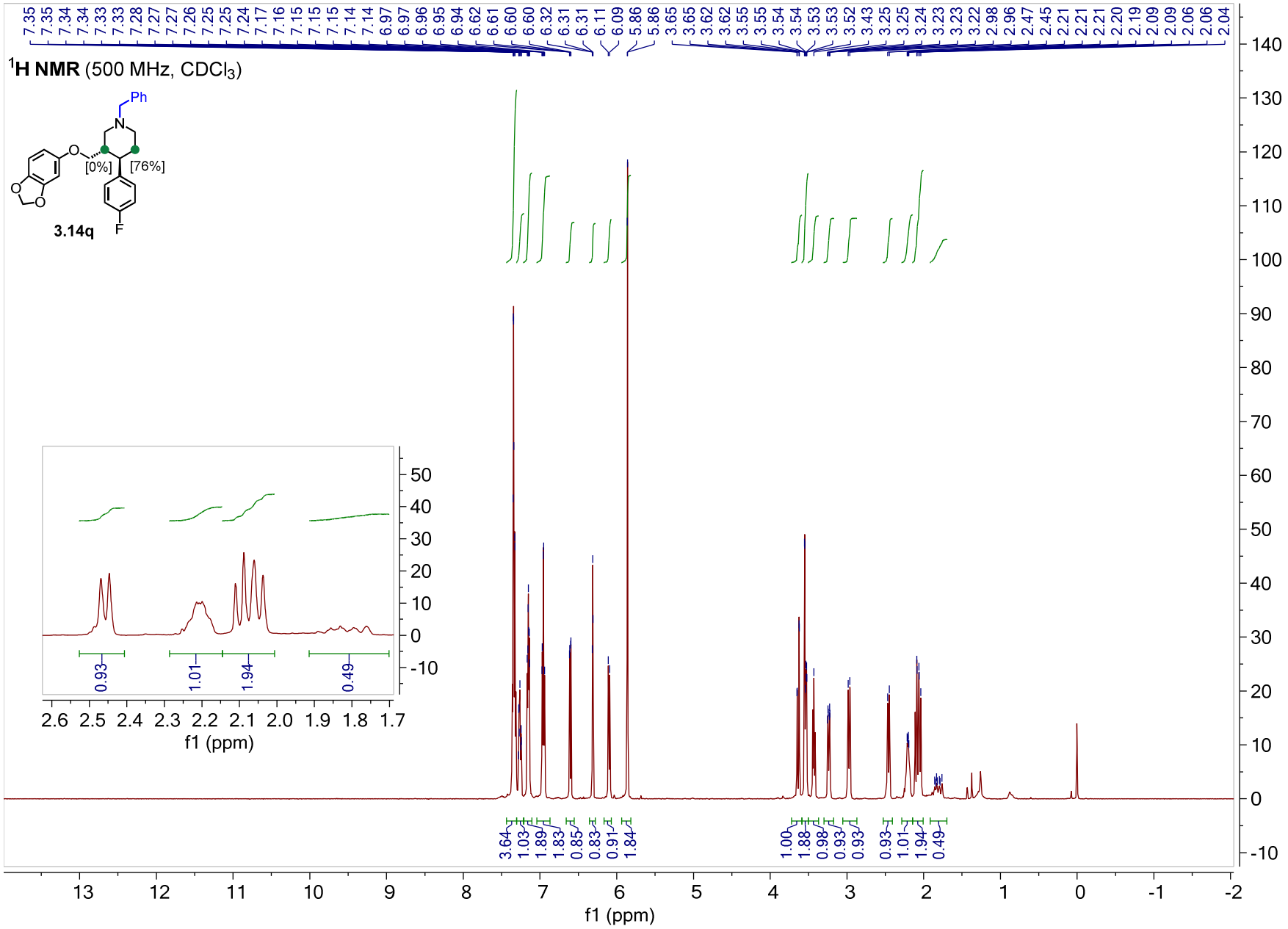
3.14q

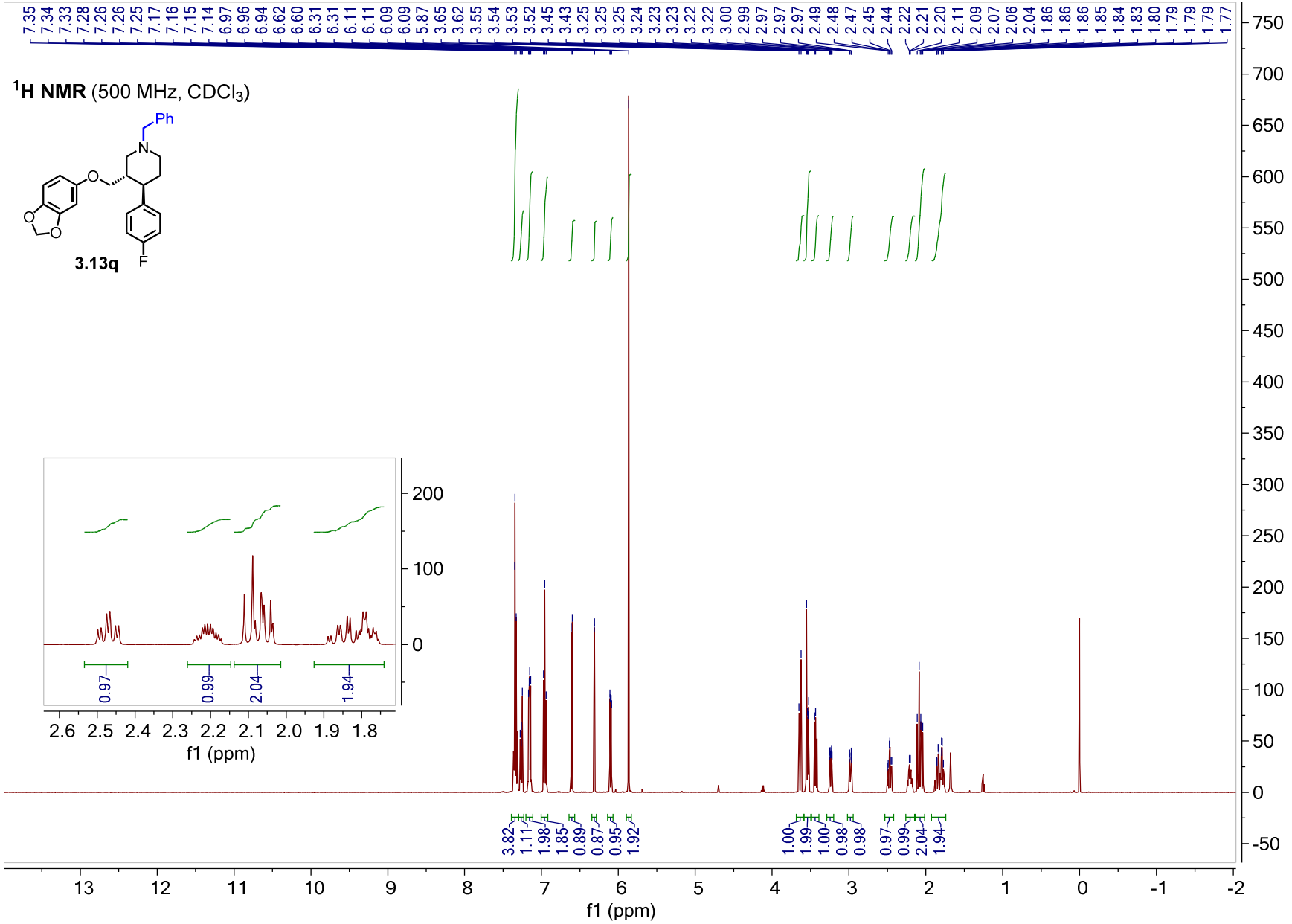

422.2087
100
80
60
40
20
0
Relative Intensity
421.2016
423.2110
420.1957
418.1802
419.1861
424.2145
425.2159
415
416
417
418
419
420
421
422
423
424
425
m/z

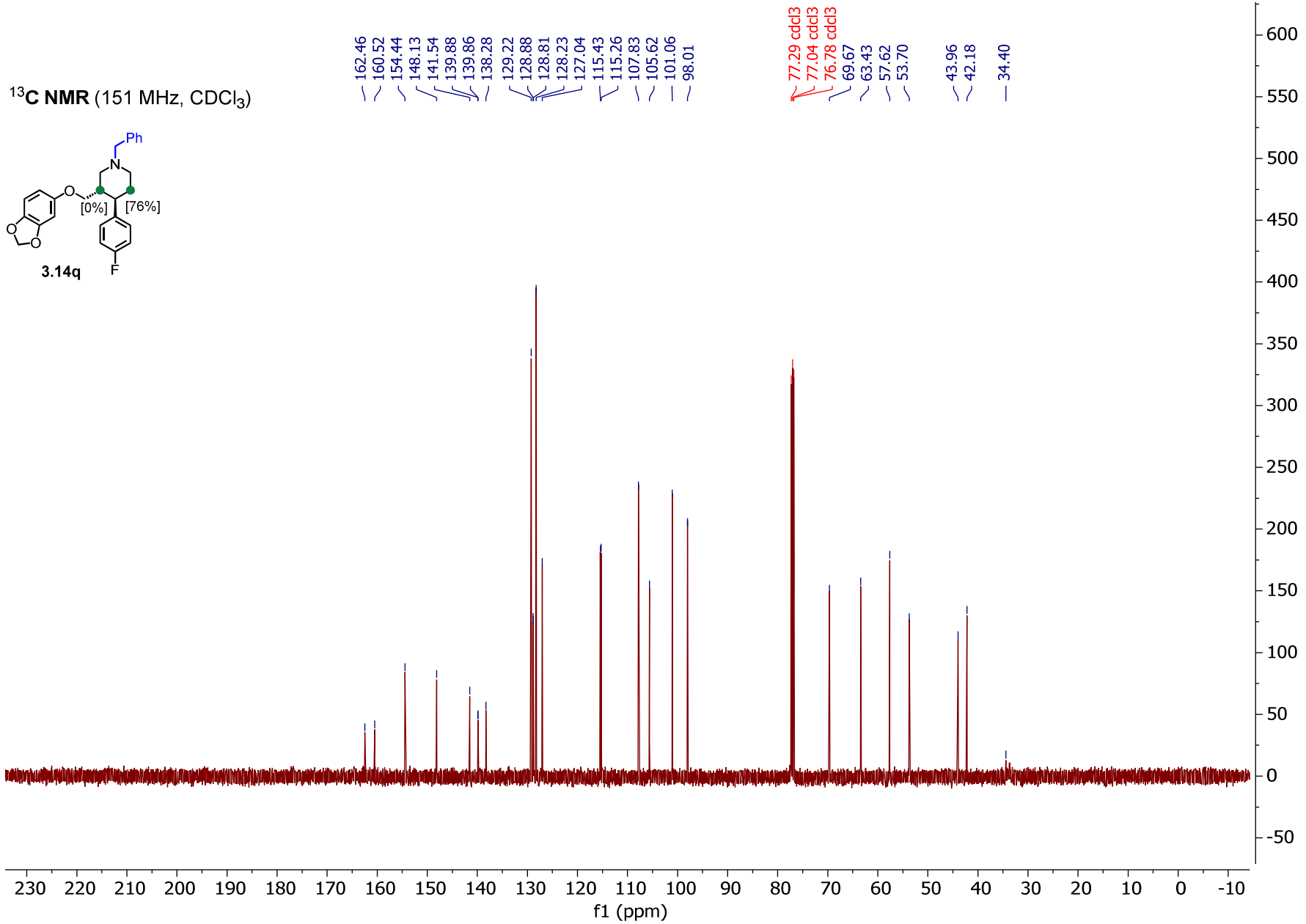

Ph
N
O
O
O
F

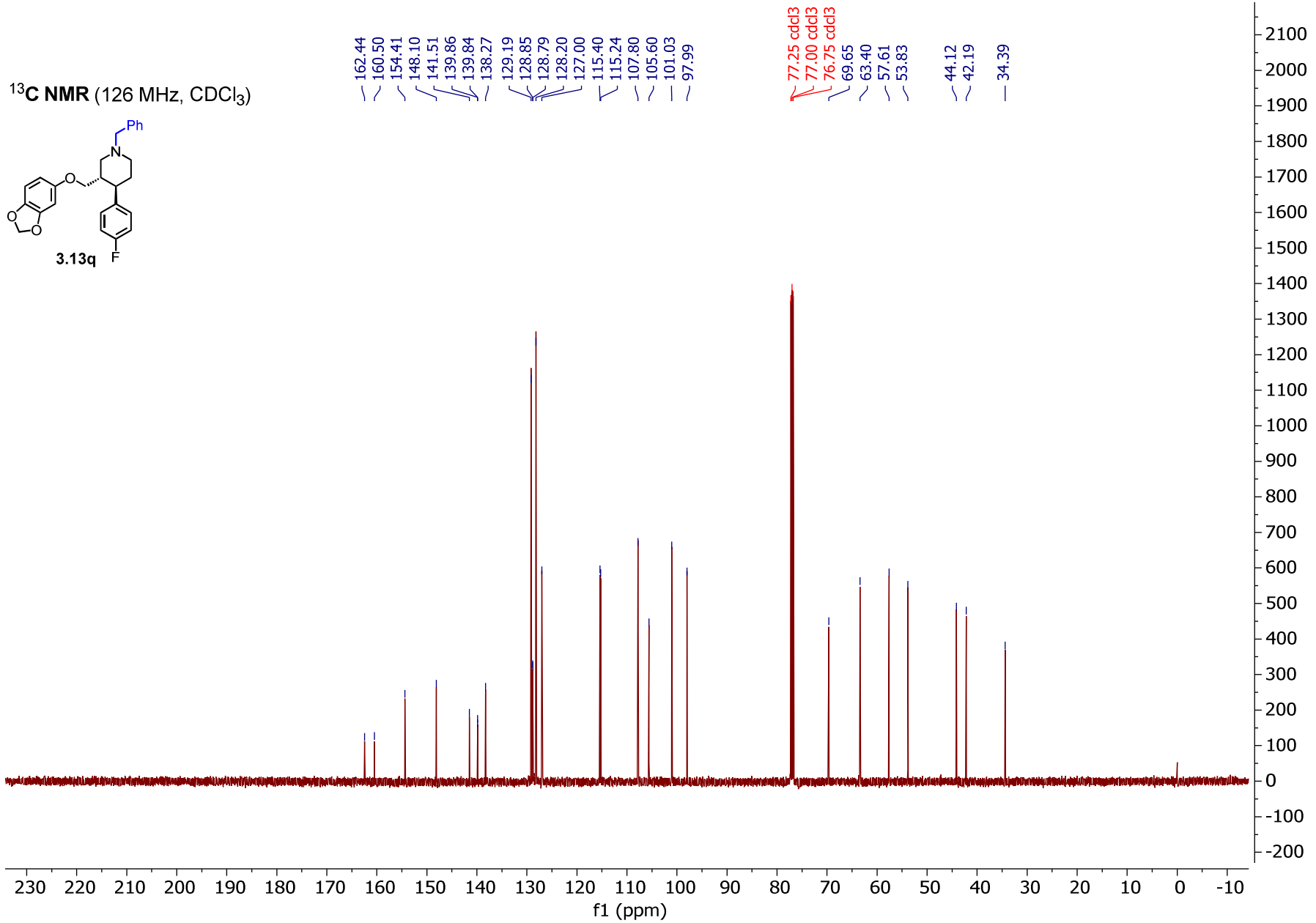
3.13q

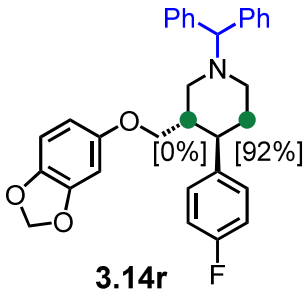

420.1984
100
80
60
40
20
0
Relative Intensity
421.2026
418.1837
419.1900
422.2049
414
415
416
417
418
419
420
421
422
423
424
425
m/z


7.35 7.35 7.34 7.34 7.33 7.33 7.28 7.27 7.27 7.26 7.25 7.25 7.24 7.17 7.16 7.15 7.15 7.15 7.14 7.14 6.97 6.97 6.96 6.95 6.94 6.62 6.61 6.60 6.60 6.32 6.31 6.31 6.11 6.09 5.86 5.86 3.65 3.65 3.62 3.62 3.55 3.55 3.54 3.54 3.53 3.53 3.52 3.43 3.25 3.25 3.24 3.23 3.23 3.22 2.98 2.96 2.47 2.45 2.21 2.21 2.21 2.20 2.19 2.09 2.09 2.06 2.06 2.04
1H NMR (500 MHz, CDCl3)
Ph
N
O
[0%]
[76%]
O
O
F
3.14q
0.93
1.01
1.94
0.49
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7
f1 (ppm)
3.64
1.03
1.89
1.83
0.85
0.83
0.91
1.84
1.00
1.88
0.98
0.93
0.93
0.93
1.01
1.94
0.49
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


7.35 7.34 7.33 7.28 7.26 7.26 7.25 7.17 7.16 7.15 7.14 6.97 6.96 6.94 6.62 6.60 6.31 6.31 6.11 6.11 6.09 6.09 5.87 3.65 3.62 3.55 3.54 3.53 3.52 3.45 3.43 3.25 3.25 3.25 3.24 3.23 3.23 3.22 3.22 3.00 2.99 2.97 2.97 2.97 2.49 2.48 2.47 2.45 2.44 2.22 2.21 2.20 2.11 2.09 2.07 2.06 2.04 1.86 1.86 1.86 1.85 1.84 1.83 1.80 1.79 1.79 1.79 1.77
1H NMR (500 MHz, CDCl3)
Ph
N
O
O
O
F
3.13q
0.97
0.99
2.04
1.94
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
3.82
1.11
1.98
1.85
0.89
0.87
0.95
1.92
1.00
1.99
1.00
0.98
0.98
0.97
0.99
2.04
1.94
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Ph
N
O
O
O
[0%]
[76%]
F
3.14q
162.46
160.52
154.44
148.13
141.54
139.88
139.86
138.28
129.22
128.88
128.81
128.23
127.04
115.43
115.26
107.83
105.62
101.06
98.01
77.29 cdcl3
77.04 cdcl3
76.78 cdcl3
69.67
63.43
57.62
53.70
43.96
42.18
34.40
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
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
f1 (ppm)


13C NMR (126 MHz, CDCl3)
Ph
N
O
O
O
F
3.13q
162.44
160.50
154.41
148.10
141.51
139.86
139.84
138.27
129.19
128.85
128.79
128.20
127.00
115.40
115.24
107.80
105.60
101.03
97.99
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
69.65
63.40
57.61
53.83
44.12
42.19
34.39
f1 (ppm)



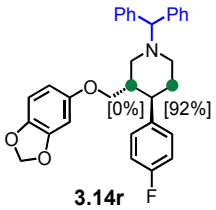
3.14r

***N*-Bzh Paroxetine, 3.14r**

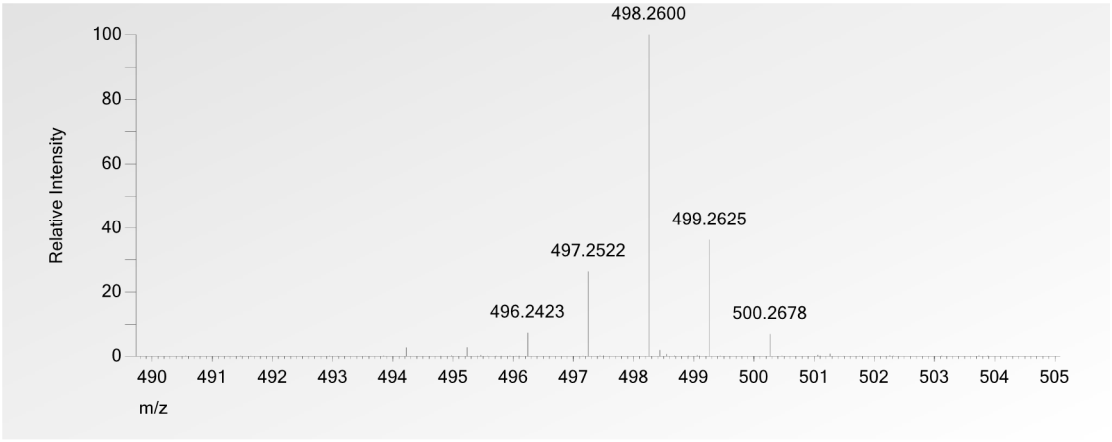
N-Bzh paroxetine **3.13r** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (Et_2O:hexanes = 1:9), **3.14r** was obtained as a colorless liquid (94 mg, 0.19 mmol, 95% yield).

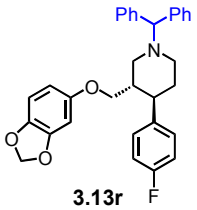
Deuterium incorporation: 1.88 D/molecule (^{1}H NMR), 2.09 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.37 (m, 4H), 7.28 (t, *J* = 7.7 Hz, 4H), 7.23 – 7.08 (m, 4H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.21 (d, *J* = 2.4 Hz, 1H), 6.01 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.84 (s, 2H), 4.36 (s, 1H), 3.49 (d, *J* = 2.9 Hz, 1H), 3.39 (d, *J* = 6.8 Hz, 1H), 3.23 (ddd, *J* = 11.4, 3.6, 2.1 Hz, 1H), 2.97 (s, 1H), 2.47 (d, *J* = 11.2 Hz, 1H), 2.21 (dt, *J* = 7.2, 3.5 Hz, 1H), 1.94 (d, *J* = 11.3 Hz, 2H), 1.89 – 1.84 (m, 0.08H, 92%D), 1.75 – 1.71 (m, 0.08H, 92%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.47, 160.52, 154.30, 148.08, 142.82, 142.79, 141.52, 140.08, 140.05, 128.91, 128.85, 128.45, 128.44, 128.10, 127.95, 126.89, 115.39, 115.22, 107.78, 105.76, 101.04, 98.14, 76.13, 69.61, 55.96, 52.42, 52.35, 44.15, 44.06, 42.47, 33.86; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -116.80 (tt, J = 8.8, 5.2 Hz); **IR** (neat) 2895, 2799, 1506, 1486, 1466, 1222, 1182, 1037, 830, 705 cm^{-1}; **Specific Rotation**: $[\alpha]^{25}$ –36.5 ° (*c* 1.0, CH_2Cl_2; labeled); **Specific Rotation**: $[\alpha]^{25}$ –43.4° (*c* 1.0, CH_2Cl_2; unlabeled).

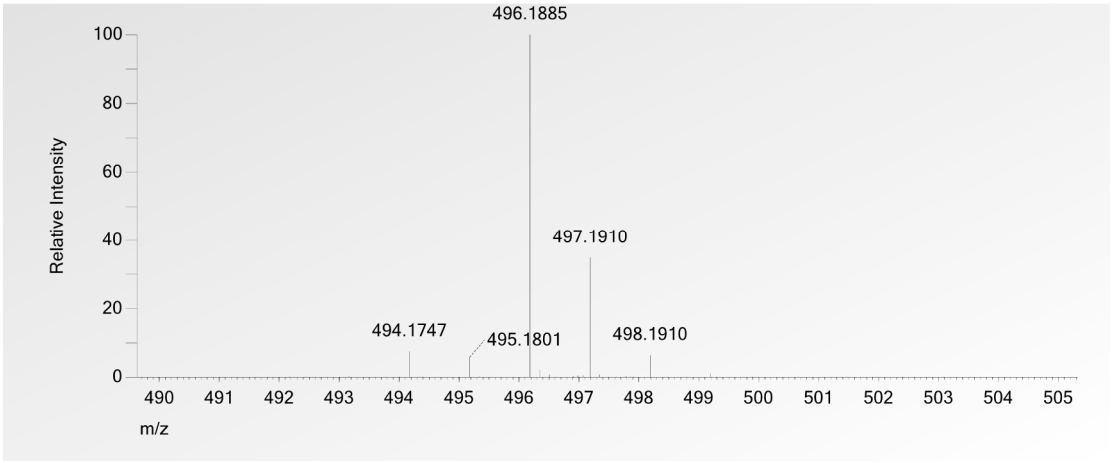

Ph
Ph
N
O
[0%]
[92%]
O
O
F

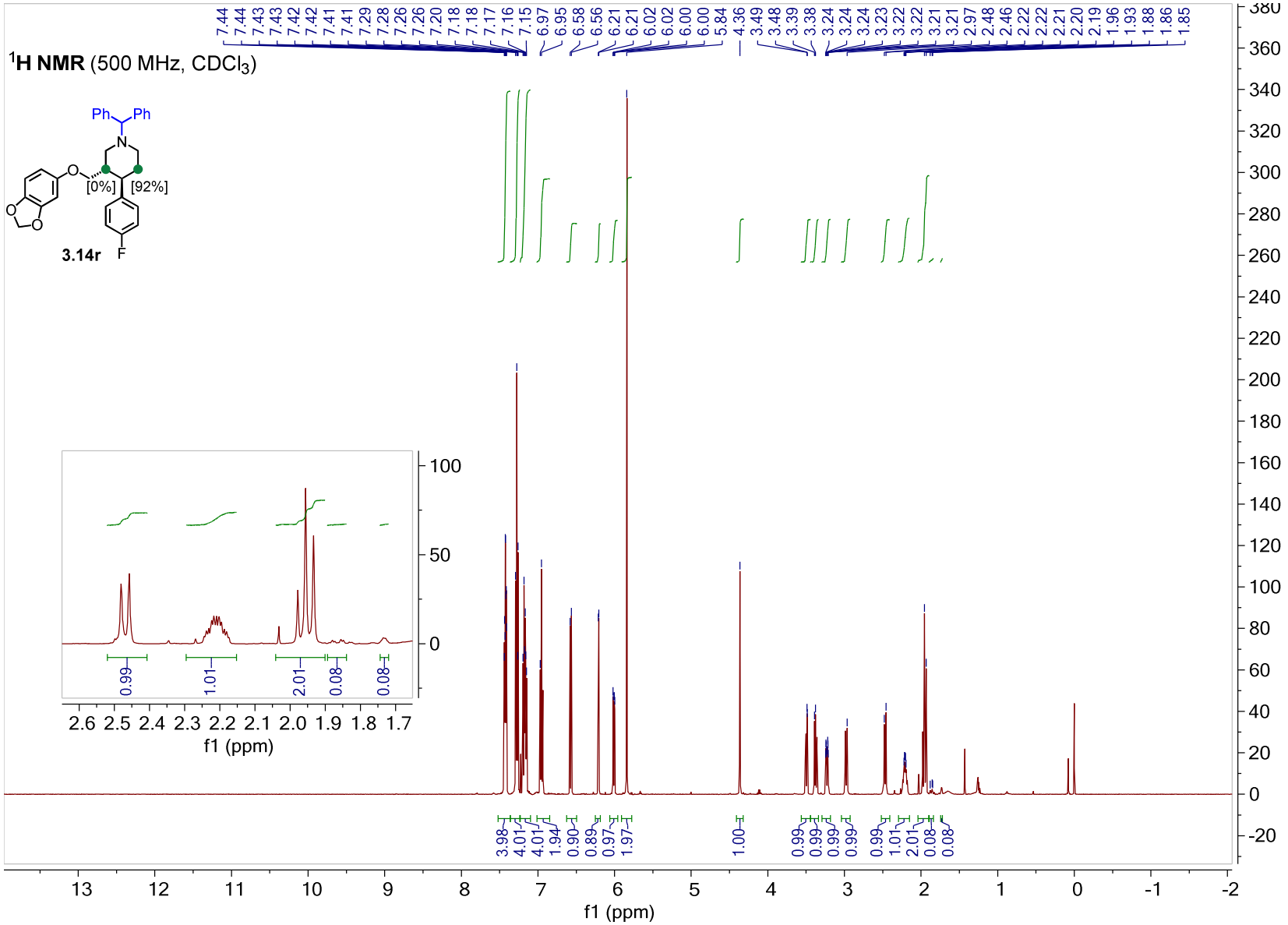
3.14r

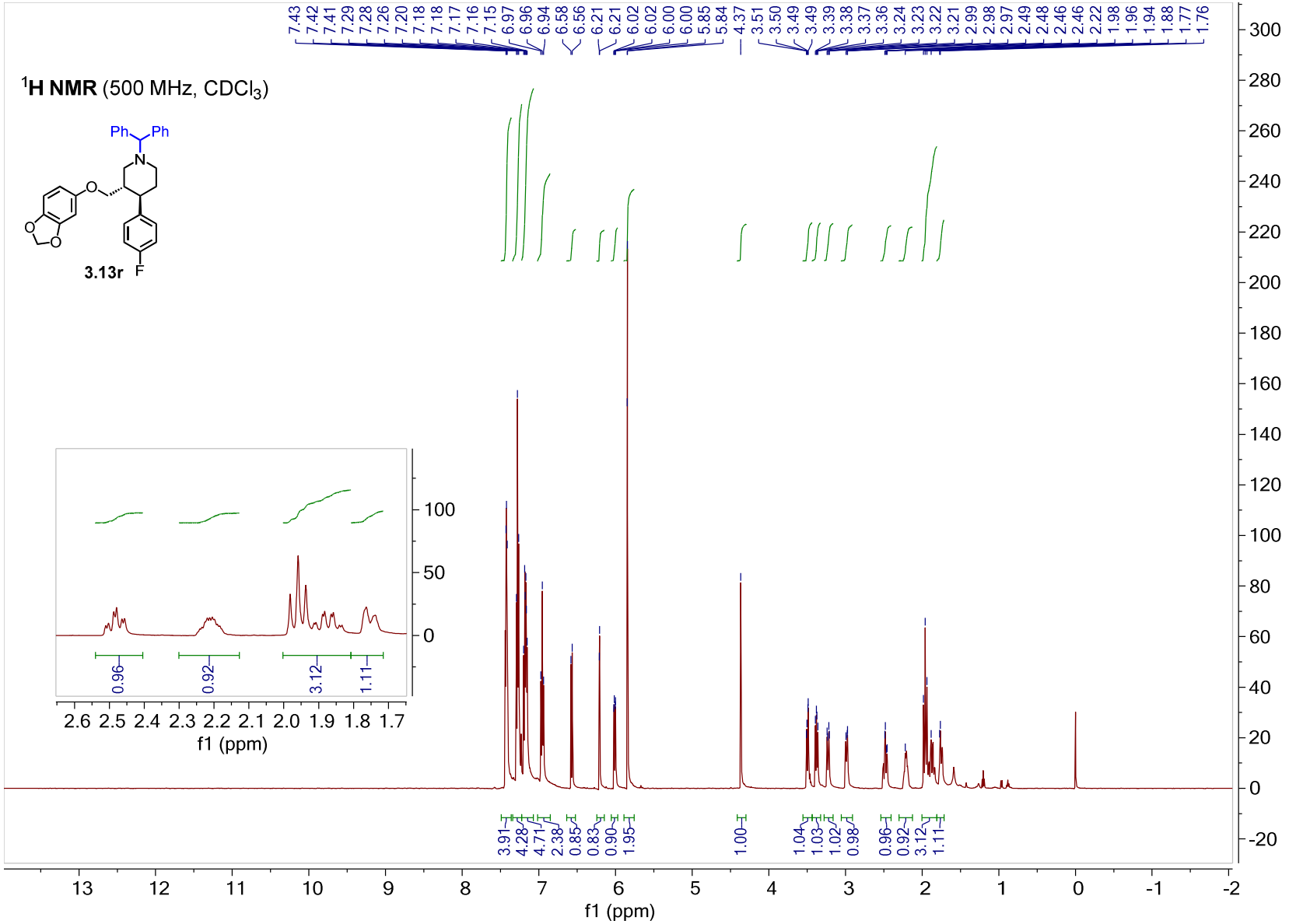

498.2600
100
80
60
40
20
0
Relative Intensity
499.2625
497.2522
496.2423
500.2678
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
m/z


Ph
Ph
N
O
O
O
F

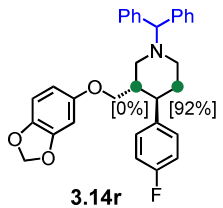
3.13r


496.1885
100
80
60
40
20
0
Relative Intensity
497.1910
494.1747
495.1801
498.1910
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
m/z

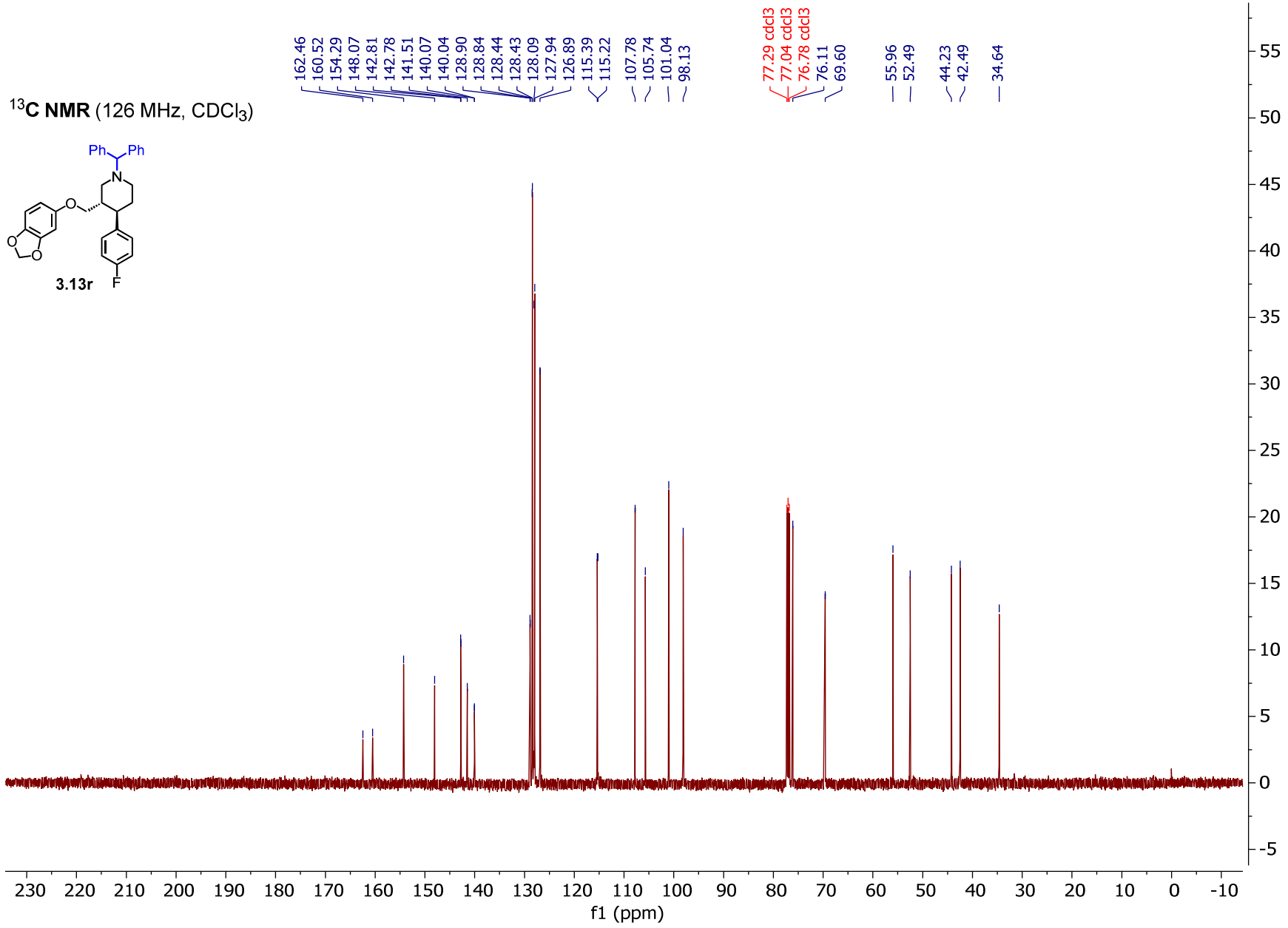

1H NMR (500 MHz, CDCl3)
Ph
Ph
N
O
[0%]
[92%]
O
O
F
3.14r
f1 (ppm)

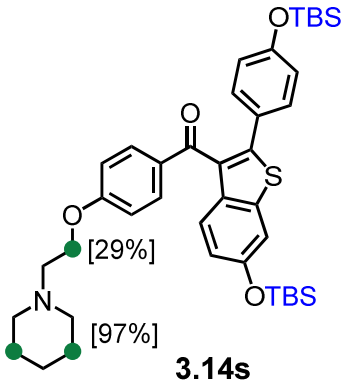

1H NMR (500 MHz, CDCl3)
Ph
Ph
N
O
O
O
F
3.13r
7.43 7.42 7.41 7.29 7.28 7.26 7.20 7.18 7.18 7.17 7.16 7.15 6.97 6.96 6.94 6.58 6.56 6.21 6.21 6.02 6.02 6.00 6.00 5.85 5.84 4.37 3.51 3.50 3.49 3.49 3.39 3.38 3.37 3.36 3.24 3.23 3.22 3.21 2.99 2.98 2.97 2.49 2.48 2.46 2.46 2.22 1.98 1.96 1.94 1.88 1.77 1.76
3.91 4.28 4.71 2.38 0.85 0.83 0.90 1.95 1.00 1.04 1.03 1.02 0.98 0.96 0.92 3.12 1.11
0.96 0.92 3.12 1.11
f1 (ppm)
f1 (ppm)

^{13}**C NMR** (126 MHz, $CDCl_3$)



3.14r


13C NMR (126 MHz, CDCl3)
Ph
Ph
N
O
O
O
F
3.13r
162.46
160.52
154.29
148.07
142.81
142.78
141.51
140.07
140.04
128.90
128.84
128.44
128.43
128.09
127.94
126.89
115.39
115.22
107.78
105.74
101.04
98.13
77.29 cdcl3
77.04 cdcl3
76.78 cdcl3
76.11
69.60
55.96
52.49
44.23
42.49
34.64
f1 (ppm)



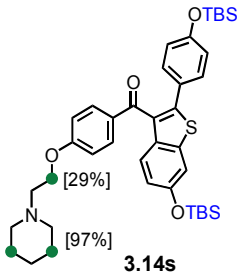
3.14s

***O*-TBS raloxifene, 3.14s**

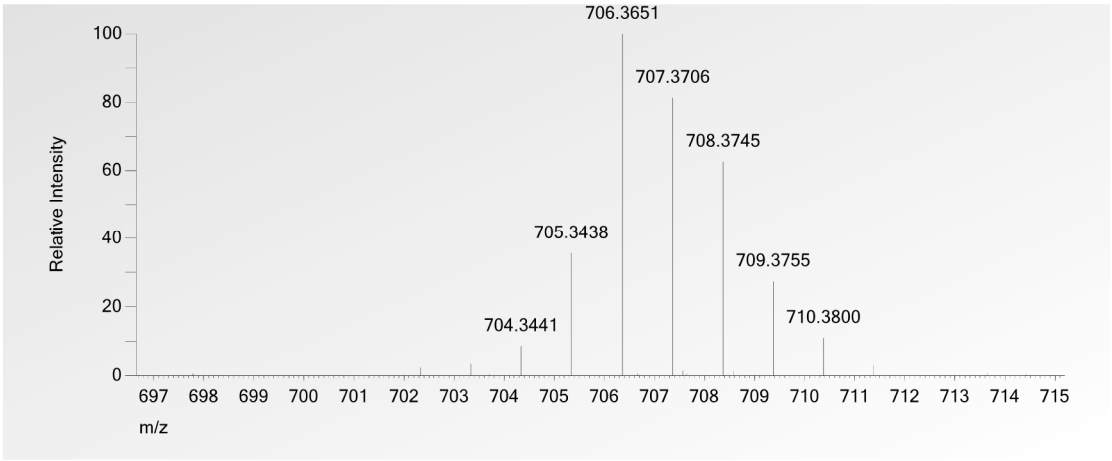
O-TBS raloxifene **3.13s** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (MeOH:DCM = 1:49), **3.14s** was obtained as a yellow liquid (136 mg, 0.19 mmol, 97% yield).

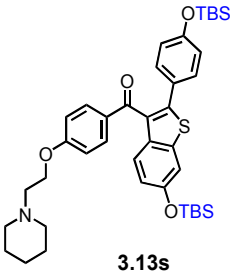
Deuterium incorporation: 4.46 D/molecule (^{1}H NMR), 5.08 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.33 – 7.22 (m, 3H), 6.88 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 4.05 (s, 1.42H, 29%D), 2.77 – 2.70 (m, 2H), 2.46 (s, 4H), 1.62 – 1.51 (m, 0.14H, 97%D), 1.40 (s, 2H), 1.01 (s, 9H), 0.93 (s, 9H), 0.23 (s, 6H), 0.12 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.03, 162.77, 156.01, 153.42, 143.25, 139.79, 134.44, 132.22, 130.52, 130.39, 130.27, 130.24, 126.71, 123.92, 123.90, 120.19, 119.18, 119.16, 113.93, 112.03, 112.00, 65.98, 54.81, 54.81, 25.64, 25.57, 24.97, 23.70, 23.59, 18.17, 18.12, -4.43, -4.54; **IR** (neat) 2927, 1595, 1463, 1252, 1164, 939, 907, 827, 779, 734 cm^{-1}.

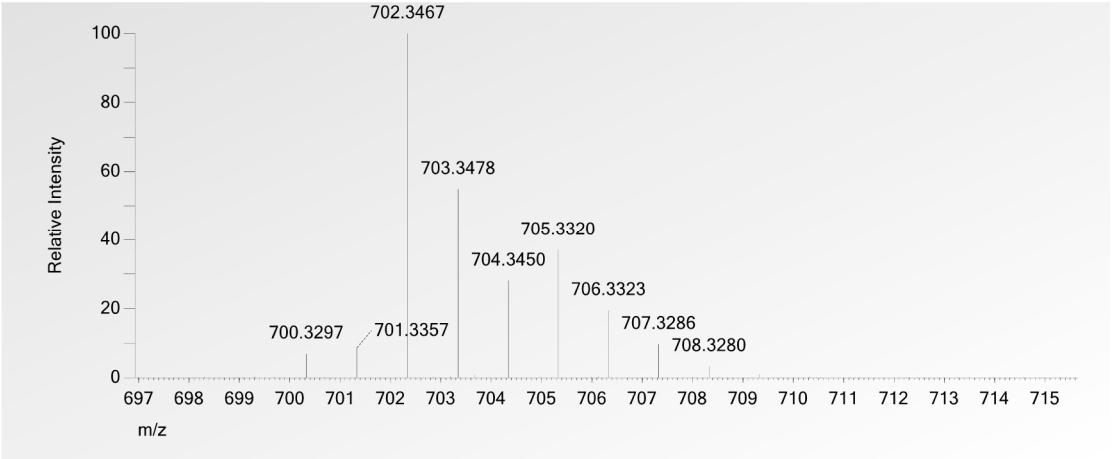

OTBS
O
S
O
[29%]
N
[97%]
OTBS

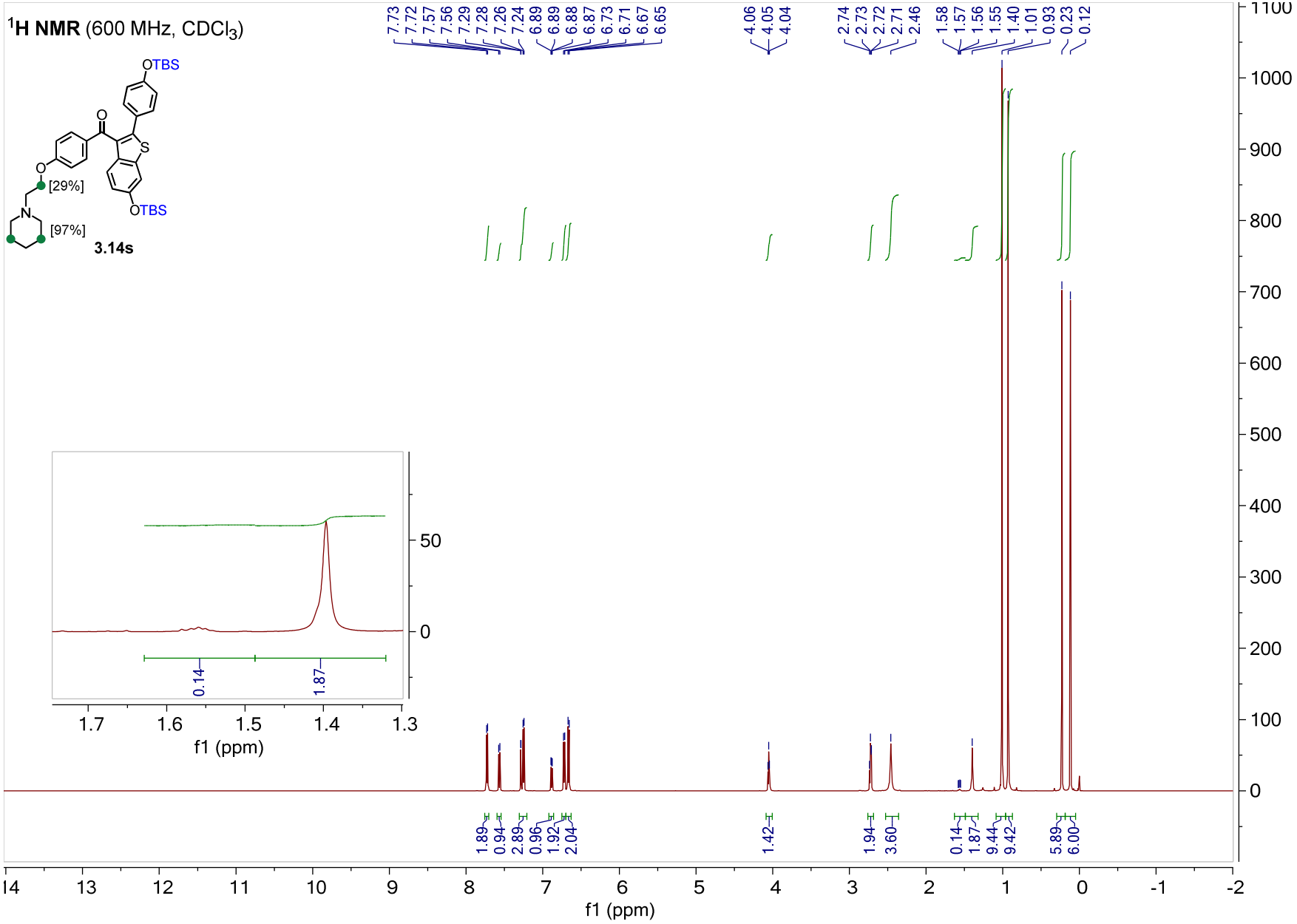
3.14s

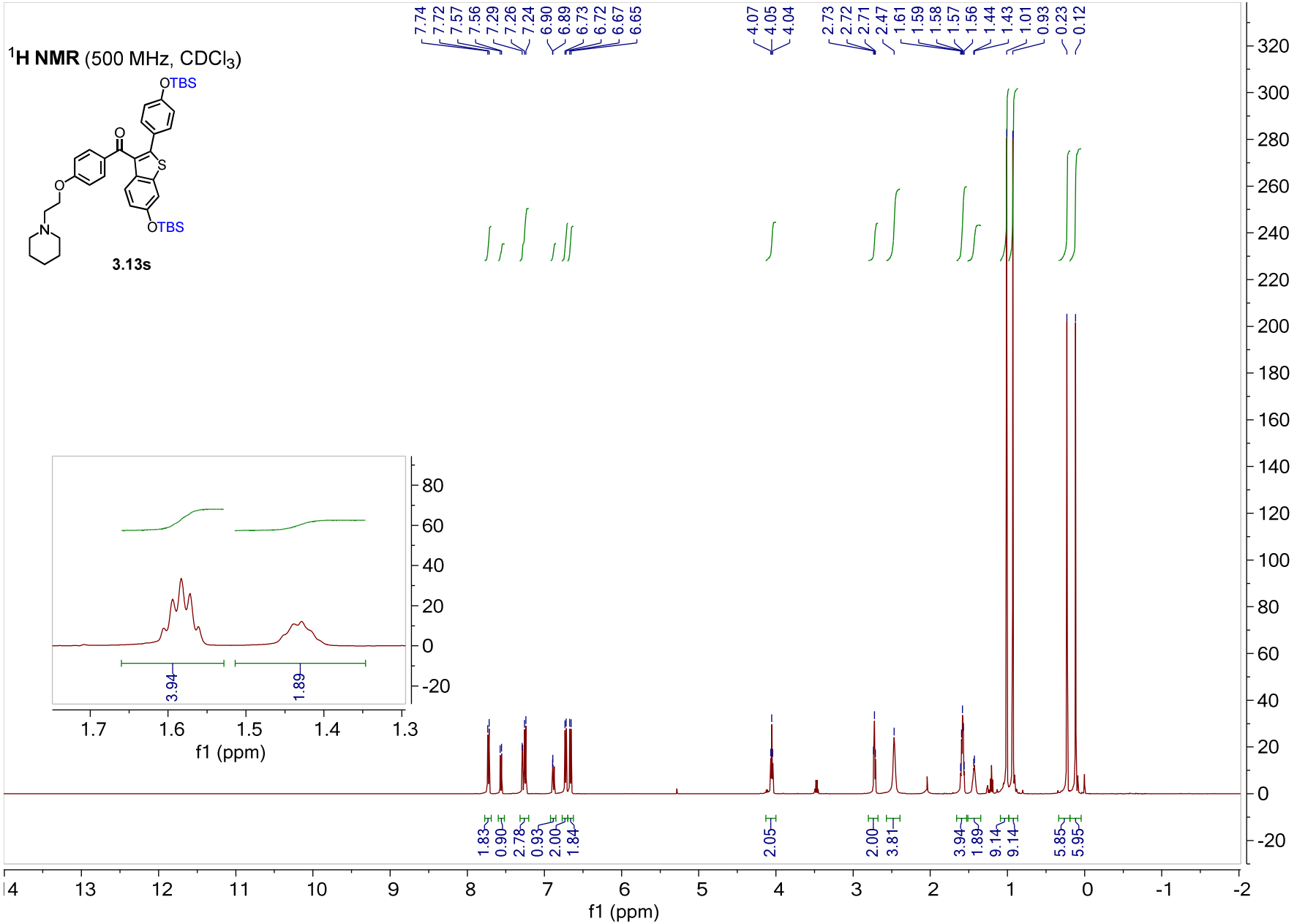

706.3651
707.3706
708.3745
705.3438
709.3755
710.3800
704.3441
Relative Intensity
m/z

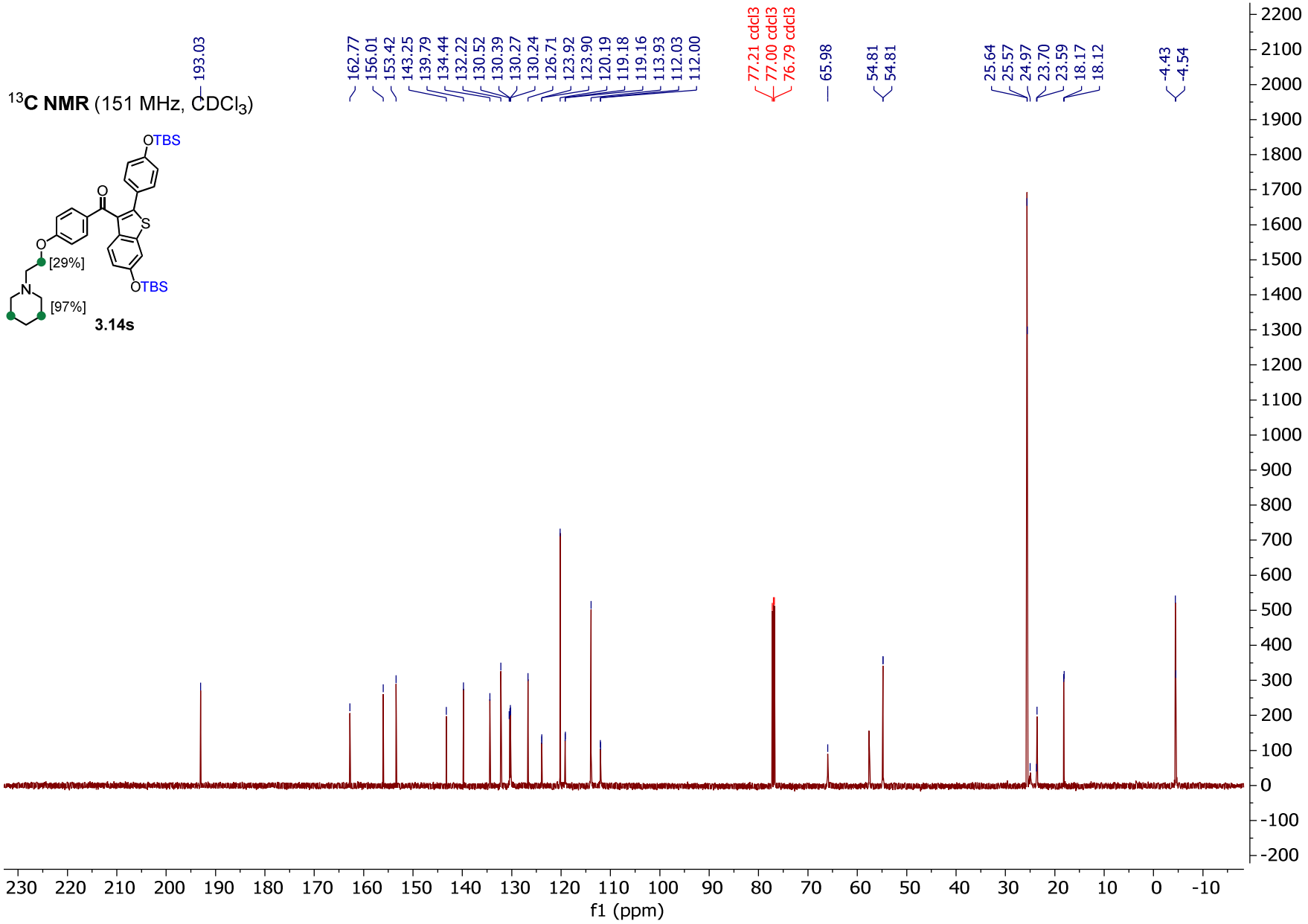

OTBS
O
S
O
N
OTBS

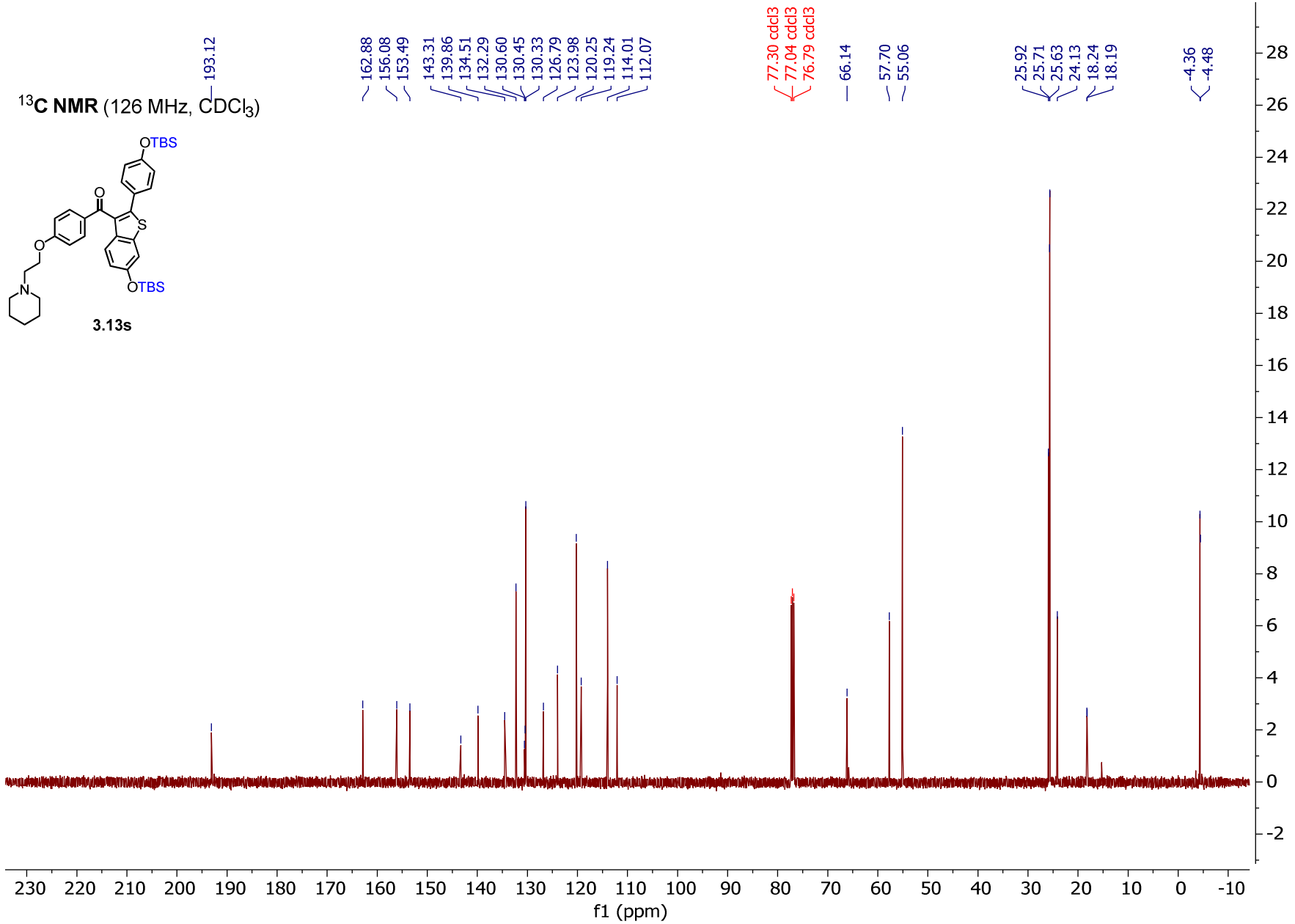
3.13s

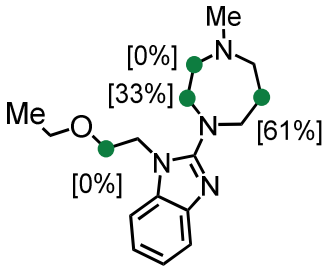

702.3467
703.3478
705.3320
704.3450
706.3323
707.3286
708.3280
700.3297
701.3357
Relative Intensity
m/z


1H NMR (600 MHz, CDCl3)
OTBS
O
S
O
[29%]
N
[97%]
OTBS
3.14s
7.73 7.72 7.57 7.56 7.29 7.28 7.26 7.24 6.89 6.89 6.88 6.87 6.73 6.71 6.67 6.65
4.06 4.05 4.04
2.74 2.73 2.72 2.71 2.46
1.58 1.57 1.56 1.55 1.40 1.01 0.93 0.23 0.12
1.89 0.94 2.89 0.96 1.92 2.04 1.42 1.94 3.60 0.14 1.87 9.44 9.42 5.89 6.00
f1 (ppm)
0.14
1.87
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
OTBS
O
S
O
N
OTBS
3.13s
7.74 7.72 7.57 7.56 7.29 7.26 7.24 6.90 6.89 6.73 6.72 6.67 6.65
4.07 4.05 4.04
2.73 2.72 2.71 2.47 1.61 1.59 1.58 1.57 1.56 1.44 1.43 1.01 0.93 0.23 0.12
1.83 0.90 2.78 0.93 2.00 1.84 2.05 2.00 3.81 3.94 1.89 9.14 9.14 5.85 5.95
3.94
1.89
f1 (ppm)
f1 (ppm)


193.03
162.77
156.01
153.42
143.25
139.79
134.44
132.22
130.52
130.39
130.27
130.24
126.71
123.92
123.90
120.19
119.18
119.16
113.93
112.03
112.00
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
65.98
54.81
54.81
25.64
25.57
24.97
23.70
23.59
18.17
18.12
-4.43
-4.54
13C NMR (151 MHz, CDCl3)
OTBS
O
S
O
[29%]
N
[97%]
OTBS
3.14s
f1 (ppm)


193.12
162.88
156.08
153.49
143.31
139.86
134.51
132.29
130.60
130.45
130.33
126.79
123.98
120.25
119.24
114.01
112.07
77.30 cdcl3
77.04 cdcl3
76.79 cdcl3
66.14
57.70
55.06
25.92
25.71
25.63
24.13
18.24
18.19
-4.36
-4.48
13C NMR (126 MHz, CDCl3)
OTBS
O
S
O
N
OTBS
3.13s
f1 (ppm)



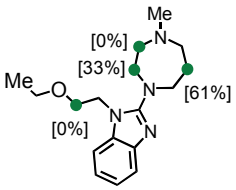
3.14t

Emedastine, 3.14t

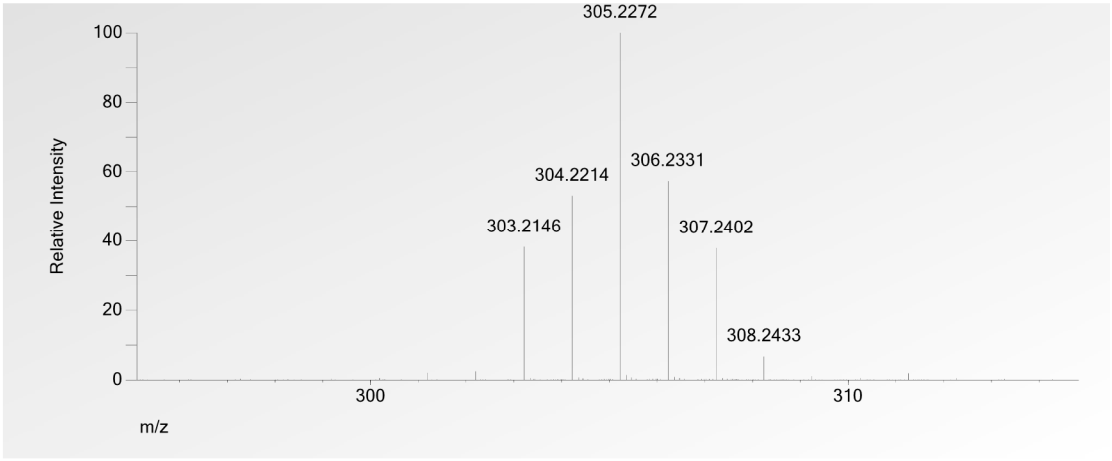
Emedastine **3.13t** was added to acetone-d_6 **3.3** following the General Procedure A. After purification by silica gel chromatography (MeOH:DCM = 1:15), **3.14t** was obtained as a colorless liquid (53 mg, 0.18 mmol, 88% yield).

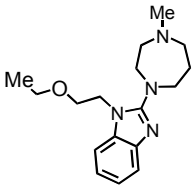
Deuterium incorporation: 1.88 D/molecule (^{1}H NMR), 2.03 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.13 (ddd, *J* = 15.5, 7.6, 1.4 Hz, 2H), 4.19 (t, *J* = 6.0 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.74 – 3.68 (m, 1.33H, 33%D), 3.64 (d, *J* = 6.1 Hz, 2H), 3.46 (q, *J* = 7.0 Hz, 2H), 2.86 – 2.80 (m, 2H), 2.76 (d, *J* = 5.6 Hz, 2H), 2.44 (s, 3H), 2.10 – 1.98 (m, 0.78H, 61%D), 1.15 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.11, 141.68, 135.51, 121.69, 120.66, 117.34, 109.12, 68.20, 66.83, 58.47, 57.30, 52.15, 51.62, 46.73, 44.84, 27.81, 15.05; **IR** (neat) 1522, 1460, 1405, 1375, 1349, 1283, 1115, 1045, 1009, 761, 743.13fm^{-1}.

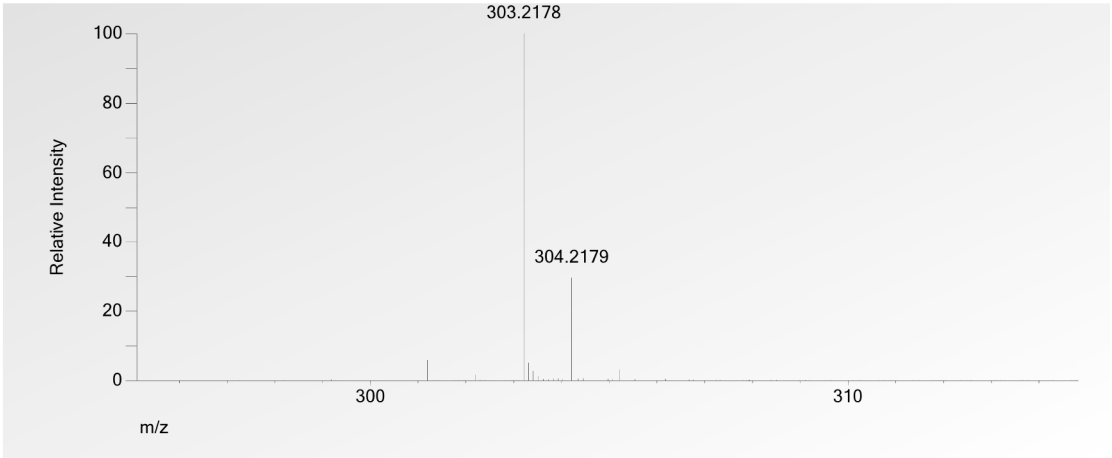

Me
[0%]
[33%]
Me
O
N
N
[61%]
[0%]
N

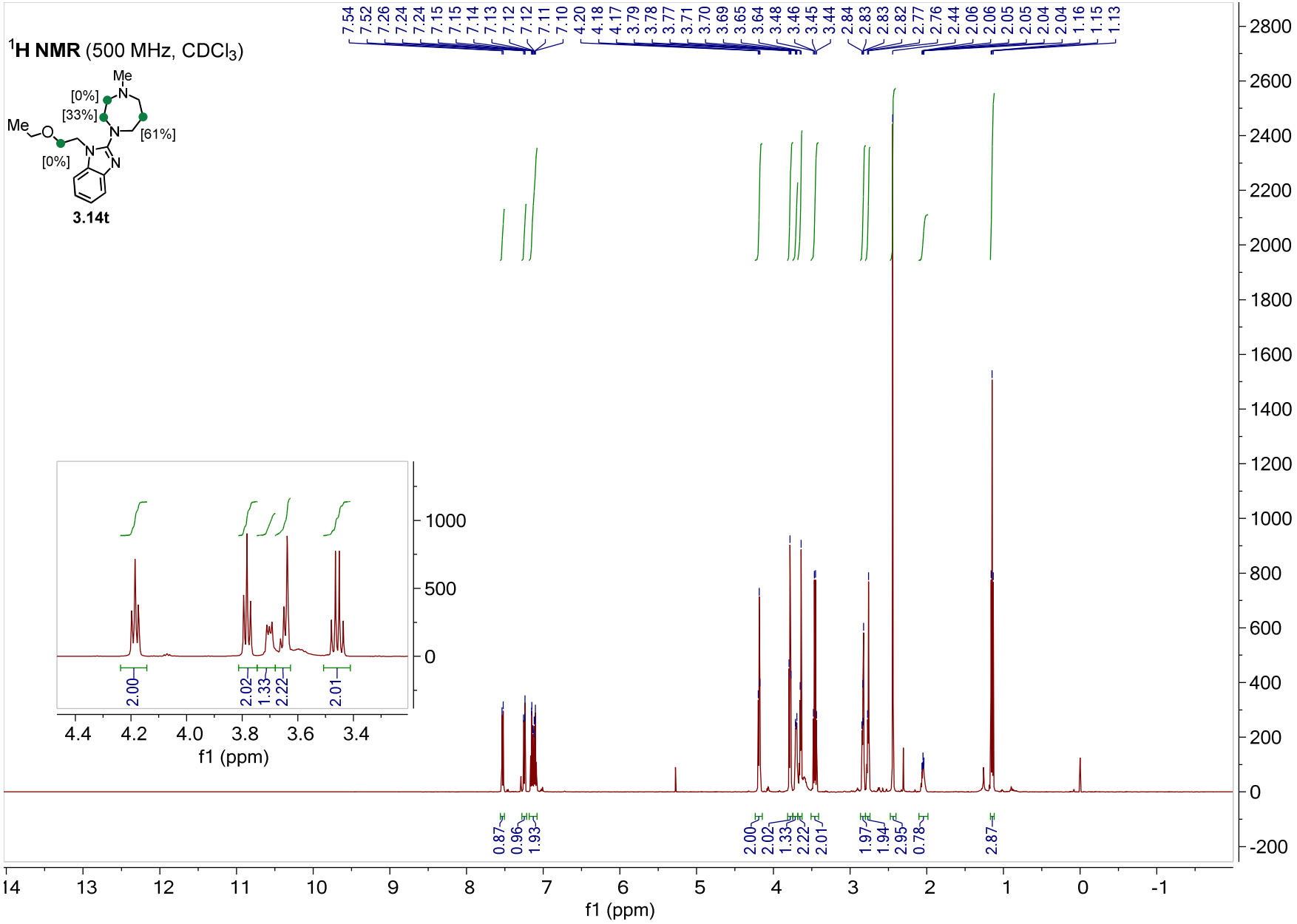
3.14t

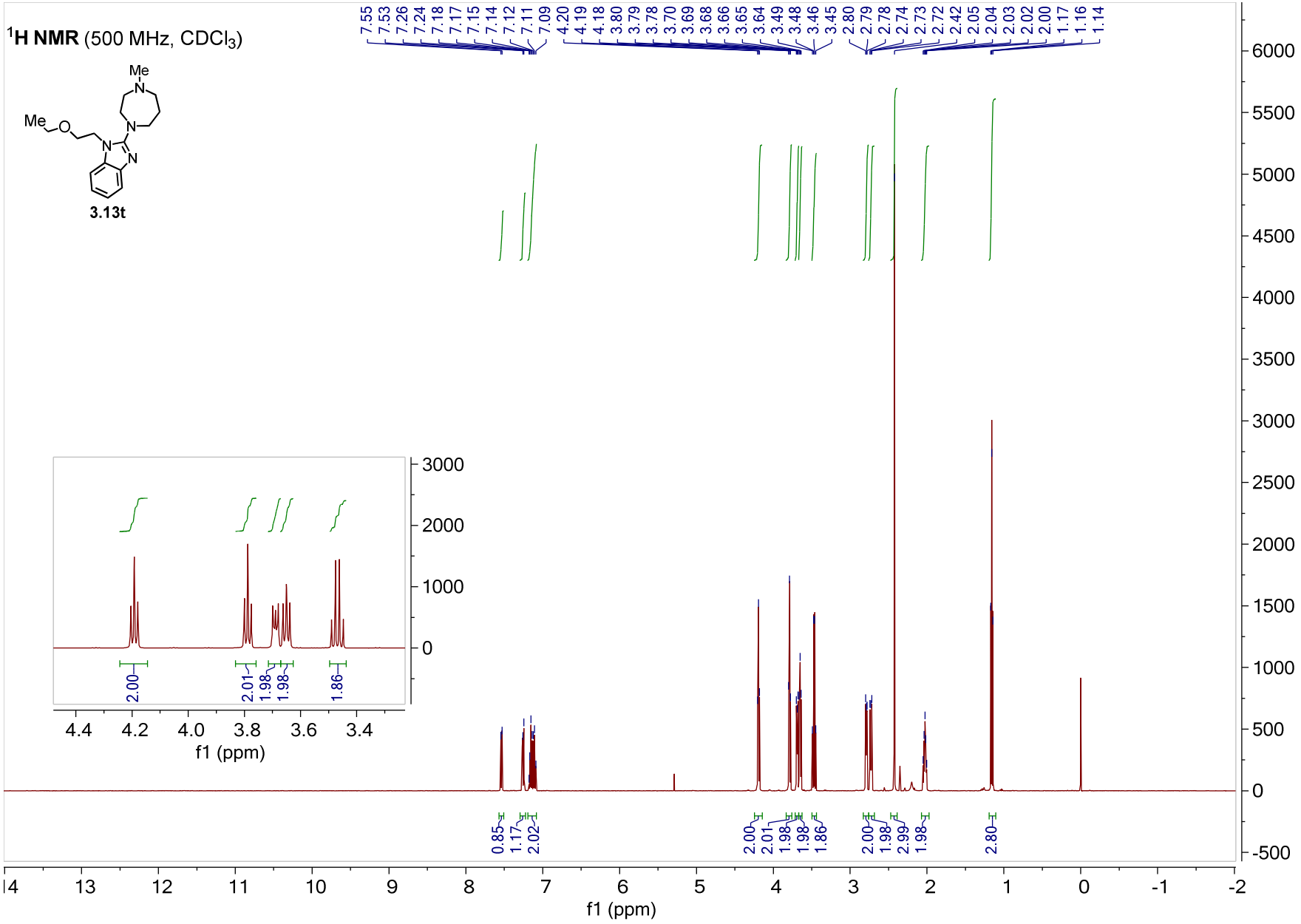

305.2272
100
80
60
40
20
0
Relative Intensity
304.2214
306.2331
303.2146
307.2402
308.2433
300
310
m/z

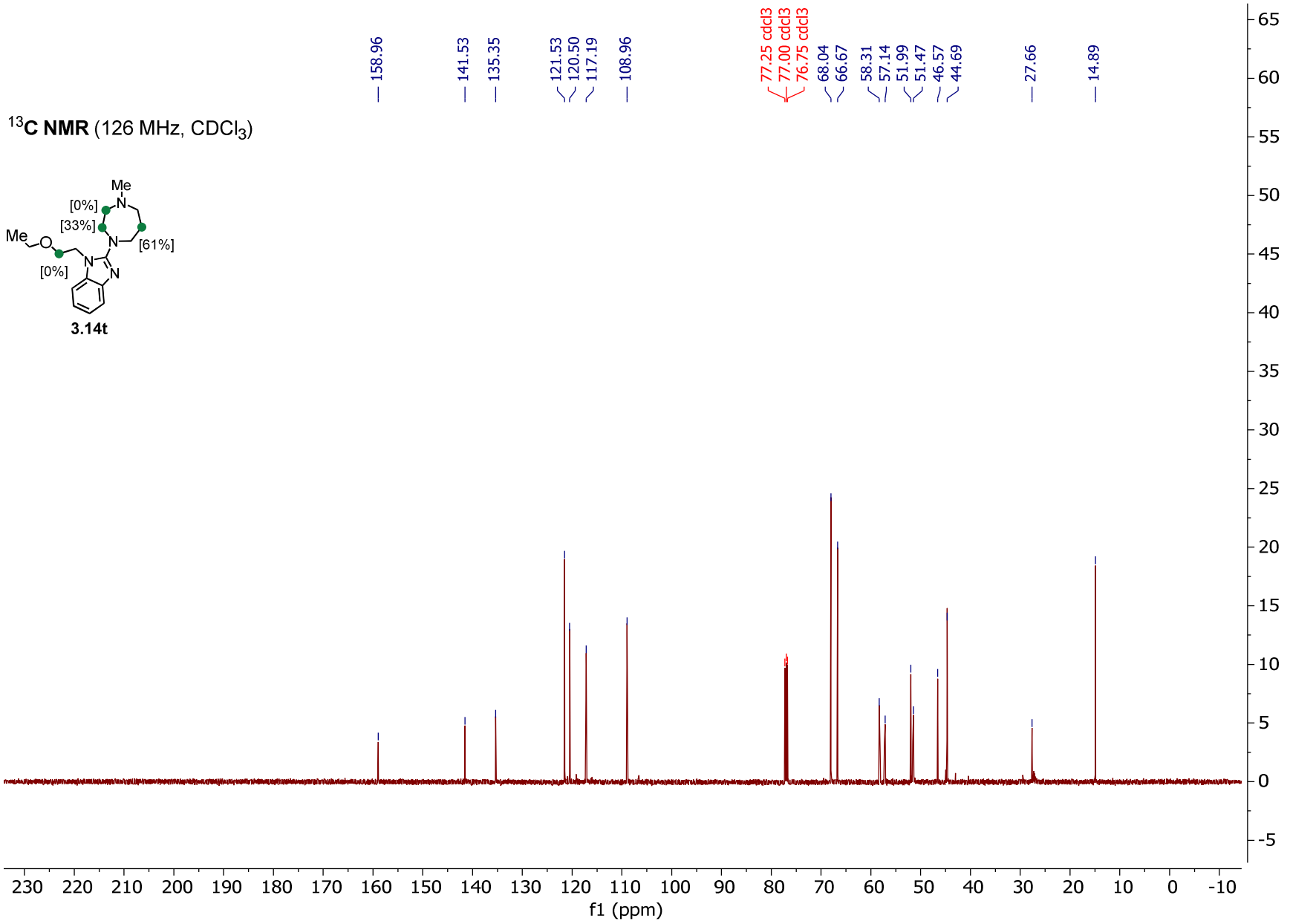

Me
N
Me
O
N
N

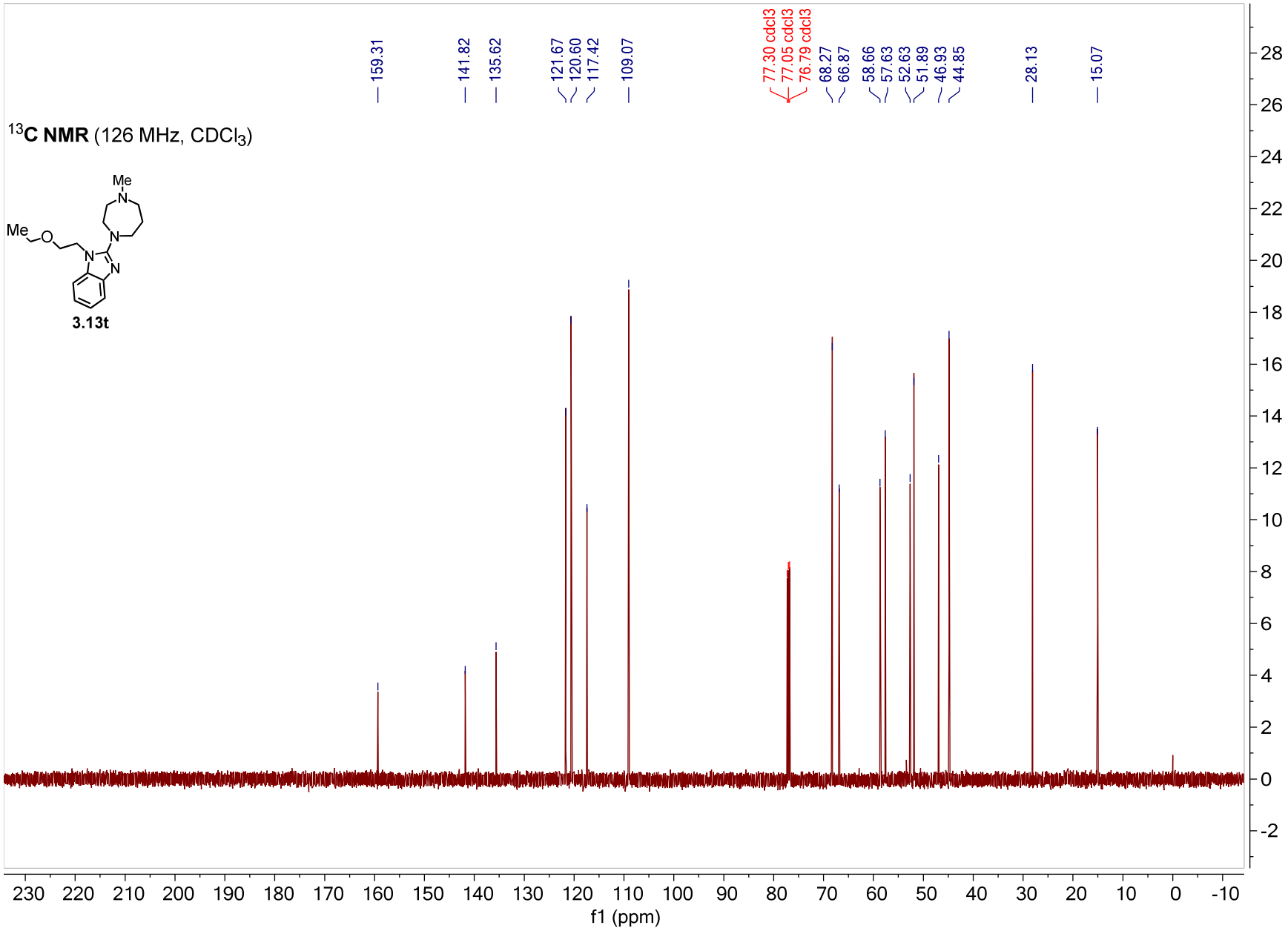
3.13t

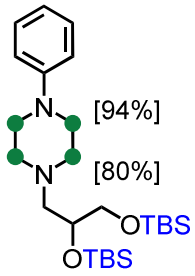

303.2178
100
80
60
40
20
0
Relative Intensity
304.2179
300
310
m/z


1H NMR (500 MHz, CDCl3)
Me
[0%]
[33%]
[61%]
Me
[0%]
3.14t
7.54 7.52 7.26 7.24 7.24 7.15 7.15 7.14 7.13 7.12 7.12 7.11 7.10 4.20 4.18 4.17 3.79 3.78 3.77 3.71 3.70 3.69 3.65 3.64 3.48 3.46 3.45 3.44 2.84 2.83 2.83 2.82 2.77 2.76 2.44 2.06 2.06 2.05 2.04 2.04 1.16 1.15 1.13
2.00 2.02 1.33 2.22 2.01
f1 (ppm)
0.87 0.96 1.93 2.00 2.02 1.33 2.22 2.01 1.97 1.94 2.95 0.78 2.87
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Me
Me
O
N
N
N
N
3.13t
7.55 7.53 7.26 7.24 7.18 7.17 7.15 7.14 7.12 7.11 7.09 4.20 4.19 4.18 3.80 3.79 3.78 3.70 3.69 3.68 3.66 3.65 3.64 3.49 3.48 3.46 3.45 2.80 2.79 2.78 2.74 2.73 2.72 2.42 2.05 2.04 2.03 2.02 2.00 1.17 1.16 1.14
0.85 1.17 2.02 2.00 2.01 1.98 1.98 1.86 2.00 1.98 2.99 1.98 2.80
f1 (ppm)
2.00 2.01 1.98 1.98 1.86
f1 (ppm)


158.96
141.53
135.35
121.53
120.50
117.19
108.96
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
68.04
66.67
58.31
57.14
51.99
51.47
46.57
44.69
27.66
14.89
13C NMR (126 MHz, CDCl3)
Me
[0%]
[33%]
[61%]
Me
[0%]
3.14t
f1 (ppm)


159.31
141.82
135.62
121.67
120.60
117.42
109.07
77.30 cdcl3
77.05 cdcl3
76.79 cdcl3
68.27
66.87
58.66
57.63
52.63
51.89
46.93
44.85
28.13
15.07
13C NMR (126 MHz, CDCl3)
Me
Me
O
N
N
N
N
3.13t
f1 (ppm)



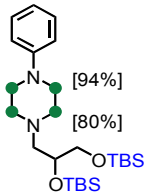
3.14u

***O*-TBS dropropizine, 3.14u**

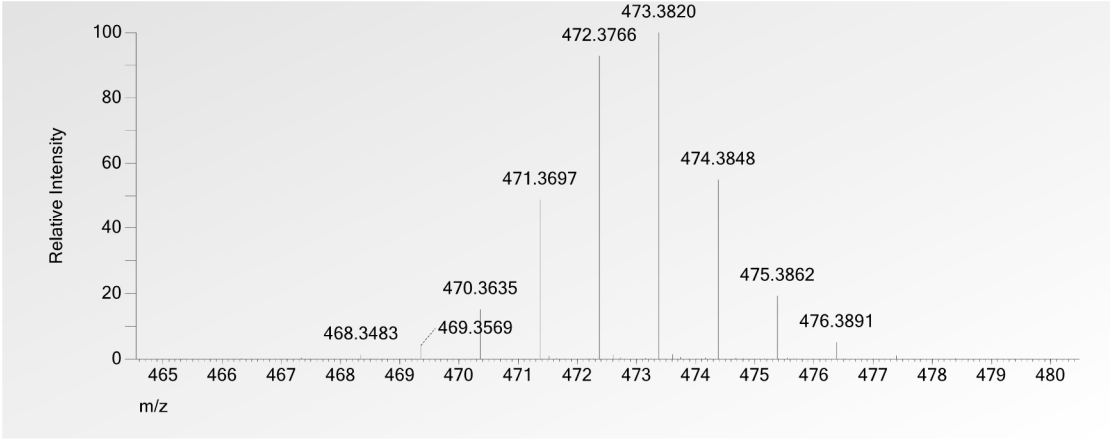
O-TBS dropropizin*e* **3.13u** was added to acetone-d_6 **3.3** following the General Procedure B. After purification by silica gel chromatography (MeOH:DCM = 1:99), **3.14u** was obtained as a yellow liquid (87 mg, 0.19 mmol, 94% yield).

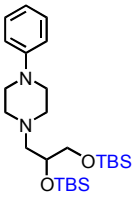
Deuterium incorporation: 6.96 D/molecule (^{1}H NMR), 7.61 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.8, 7.3 Hz, 2H), 6.91 (dt, *J* = 7.8, 1.0 Hz, 2H), 6.83 (s, 1H), 3.80 (dd, *J* = 6.0, 4.9 Hz, 1H), 3.66 – 3.57 (m, 1H), 3.53 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.12 (s, 0.24H, 94%D), 2.62 (s, 0.47H, 77%D), 2.55 (s, 0.34H, 83%D), 2.50 (dd, *J* = 13.0, 4.7 Hz, 1H), 2.37 (dd, *J* = 13.0, 6.1 Hz, 1H), 0.90 (d, *J* = 4.3 Hz, 18H), 0.09 (d, *J* = 6.1 Hz, 6H), 0.06 (d, *J* = 1.6 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.51, 129.08, 119.39, 115.79, 71.87, 66.21, 61.95, 53.18, 48.27, 26.03, 25.95, 18.40, 18.22, -4.41, -4.46, -5.23, -5.31; **IR** (neat) 2925, 2853, 1598, 1499, 1250, 1091, 1003, 830, 810, 773, 753, 689 cm^{-1}.

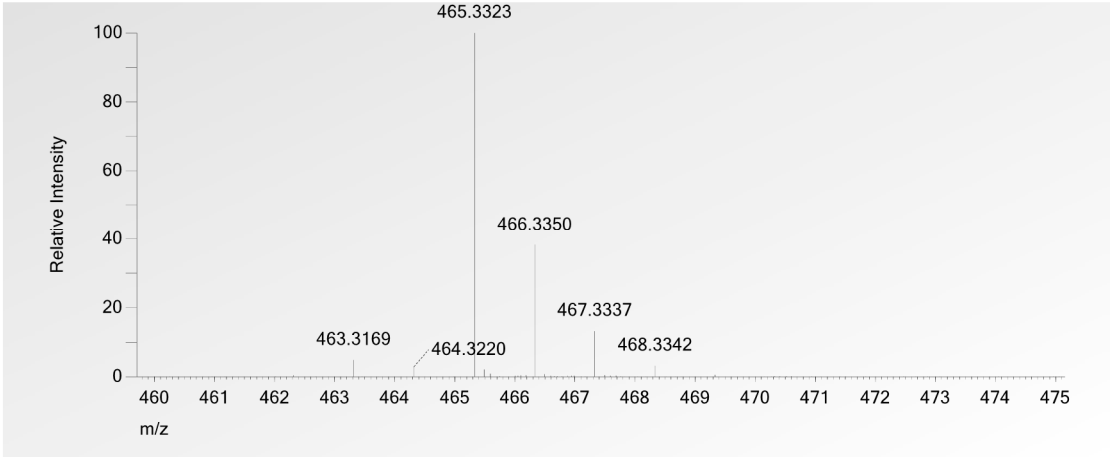

[94%]
[80%]
OTBS
OTBS

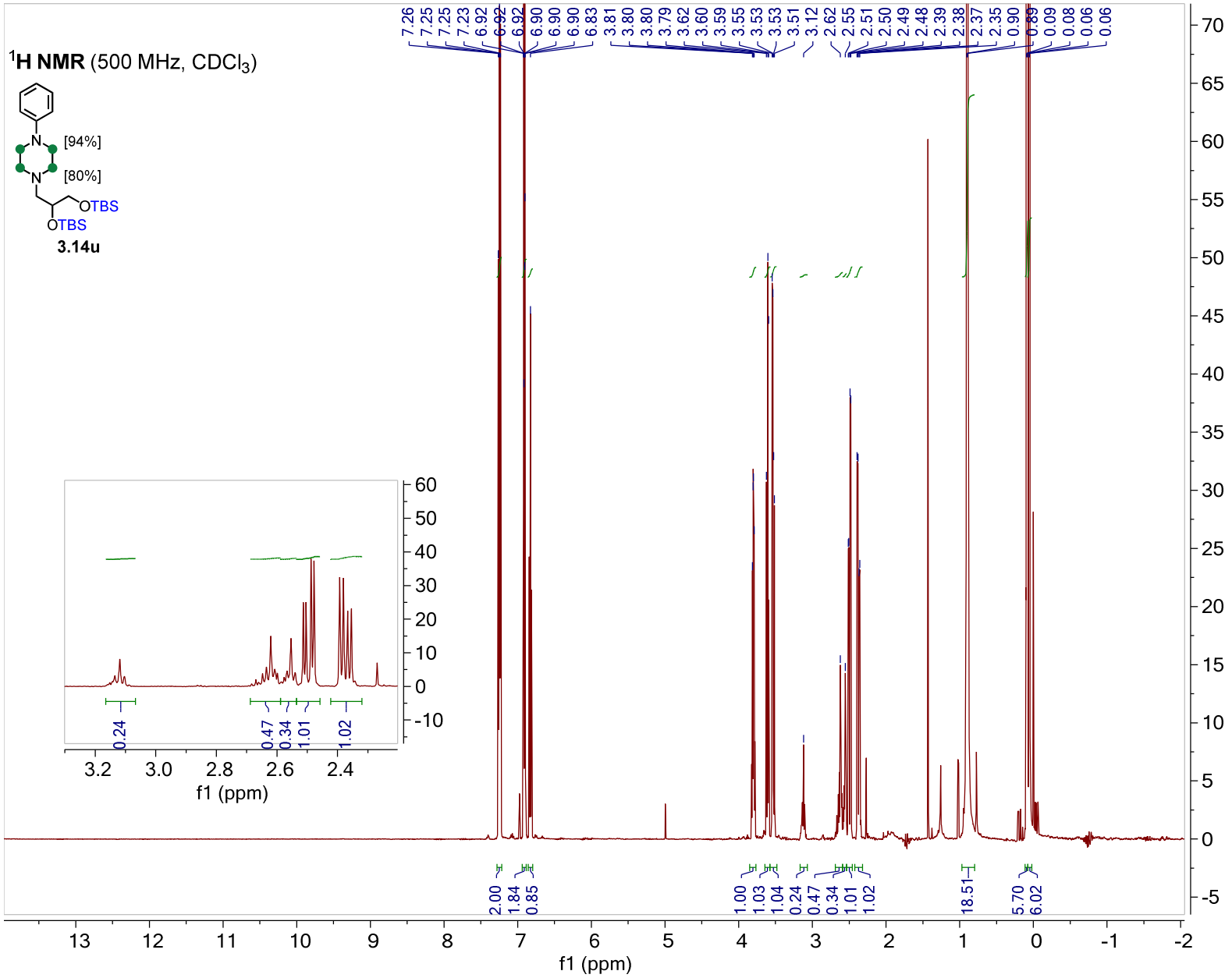
3.14u

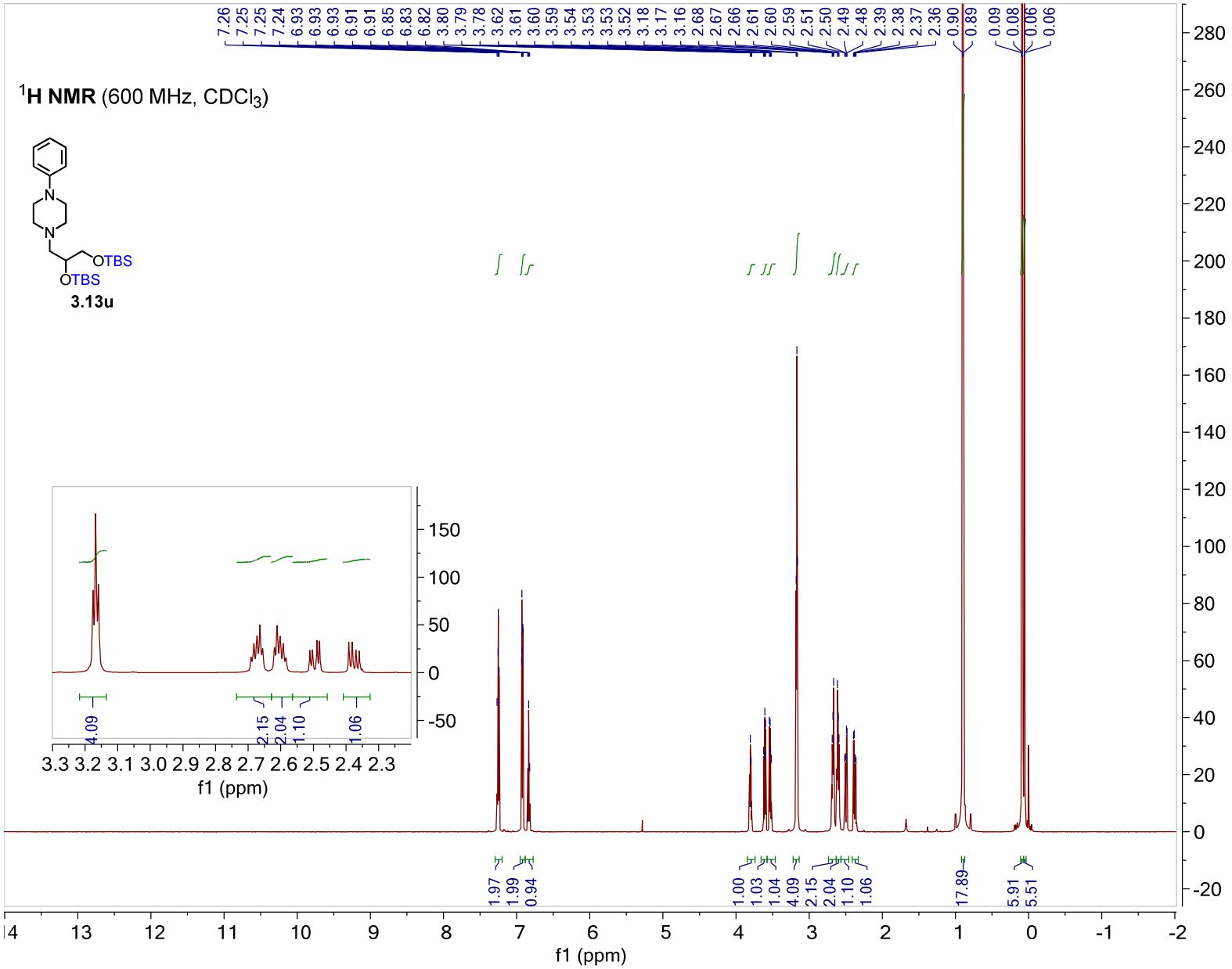

473.3820
472.3766
474.3848
471.3697
475.3862
470.3635
476.3891
468.3483
469.3569
Relative Intensity
m/z

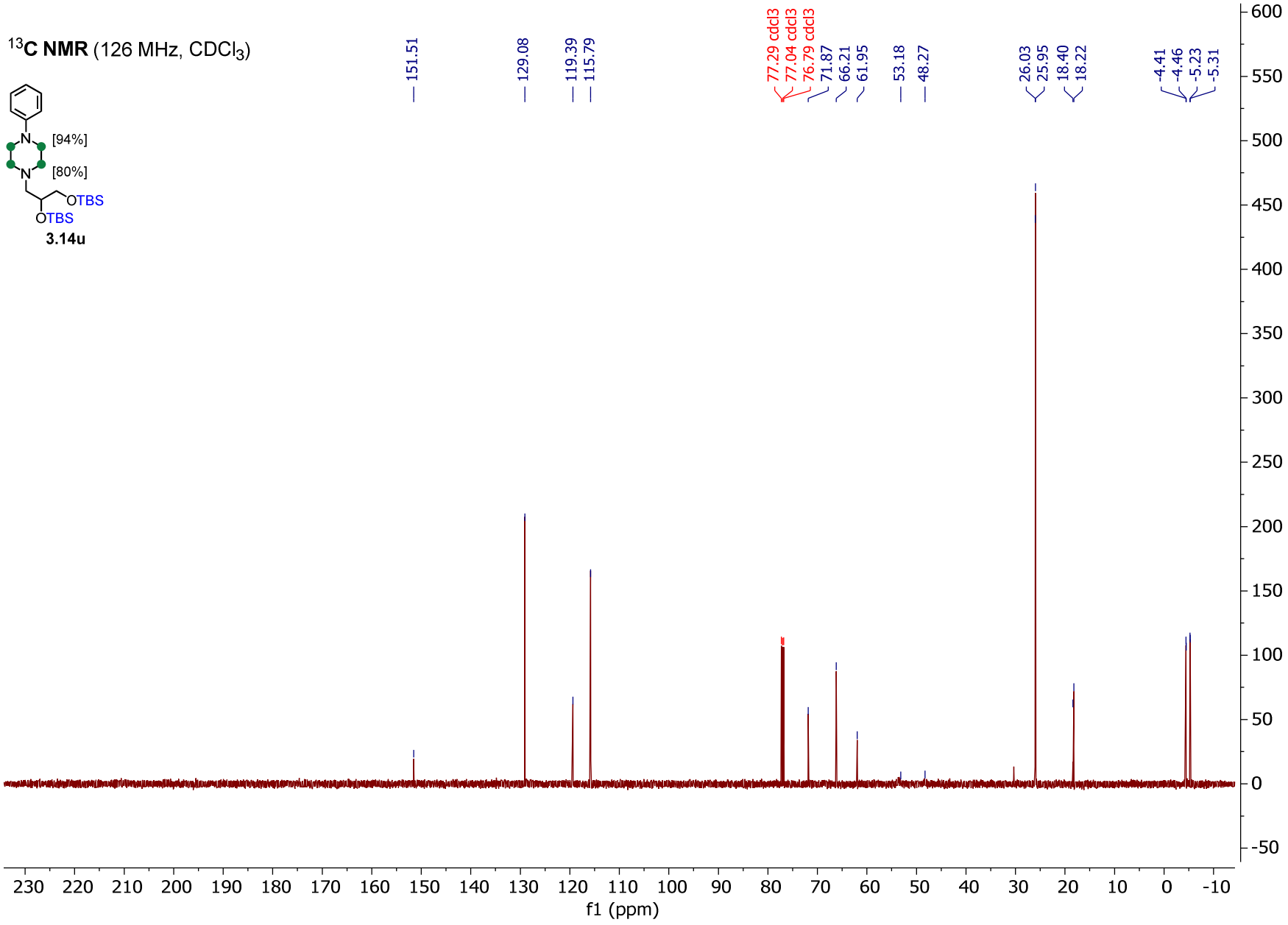

OTBS
OTBS

3.13u

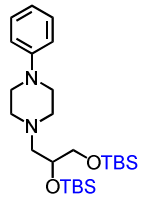

465.3323
466.3350
467.3337
463.3169
464.3220
468.3342
Relative Intensity
m/z


1H NMR (500 MHz, CDCl3)
[94%]
[80%]
OTBS
OTBS
3.14u
f1 (ppm)


1H NMR (600 MHz, CDCl3)
OTBS
OTBS
3.13u
f1 (ppm)


13C NMR (126 MHz, CDCl3)
[94%]
[80%]
OTBS
OTBS
3.14u
151.51
129.08
119.39
115.79
77.29 cdcl3
77.04 cdcl3
76.79 cdcl3
71.87
66.21
61.95
53.18
48.27
26.03
25.95
18.40
18.22
-4.41
-4.46
-5.23
-5.31
f1 (ppm)

^{13}**C NMR** (151 MHz, $CDCl_3$)



3.13u

B4. References

(1) Heinz, C.; Lutz, J. P.; Simmons, E. M.; Miller, M. M.; Ewing, W. R.; Doyle, A. G. Ni-Catalyzed Carbon−Carbon Bond-Forming Reductive Amination. *J. Am. Chem. Soc.* **2018**, *140*, 2292−2300.

(2) Sun, Y-H.; Sun, T-Y.; Wu, Y-D.; Zhang, X.; Rao, Y. A diversity-oriented synthesis of bioactive benzanilides *via* a regioselective C(sp^2)–H hydroxylation strategy. *Chem. Sci.* **2016,** *7*, 2229–2238.

(3) Banwell, M. G.; Coster, M. J.; Harvey, M. J.; Moraes, J. Selective Cleavage of N-Benzyl-Protected Secondary Amines by Triphosgene. *J. Org. Chem.* **2003**, *68*, 613−616.

(4) Park, C. M.; Kim, S. Y.; Park, W. K.; Choi, J. H.; Seong, C. M. Synthesis and SAR of (piperazin-1-yl-phenyl)-arylsulfonamides: A novel series of atypical antipsychotic agents. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 5221−5224.

(5) Liu, L-L.; Yeung, K-S.; Yu, J-Q. Ligand-Promoted Non-Directed C–H Cyanation. *Chem. Eur. J*. **2019**, *25*, 2199–2202.

(6) Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen, E. J. Synthesis of Novel Taxoids. *J. Am. Chem. Soc.***1994**, *116*, 4, 1591−1592.

(7) Lei, C.; Yip, Y. J.; Zhou, J. S. Nickel-Catalyzed Direct Synthesis of Aryl Olefins from Ketones and Organoboron Reagents under Neutral Conditions. *J. Am. Chem. Soc*. **2017**, *139*, 17, 6086−6089.

(8) Chang, D.; Li, T.; Li, L.; Jakowski, J.; Huang, J.; Keum, J. K.; Lee, B.; Bonnesen, P. V.; Zhou, M.; Garashchuk, S.; Sumpter, B. G.; Hong, K. Selectively Deuterated Poly(ε-caprolactone)s: Synthesis and Isotope Effects on the Crystal Structures and Properties. *Macromolecules* **2018**, *51*, 9393−9404.

Appendix C. Experimental Section for Chapter 4

C1. Procedures, Materials and Instrumentation

General Experimental Procedures

All reactions were performed in standard, oven-dried glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. Stainless steel syringes or cannulas were used to transfer air- and moisture-sensitive oils. Reported concentrations refer to solution volumes at 22 ºC. Evaporation and concentration *in vacuo* were performed using house vacuum (ca. 40 mm Hg). Column chromatography was performed with SiliaFlash® 60 (40–63 micron) silica gel from Silicycle. Thin layer chromatography (TLC) was used for reaction monitoring and product detection using pre-coated glass plates covered with 0.25 mm silica gel with fluorescent indicator; visualization by UV light (λ_{ex} = 254 nm) and/or $KMnO_4$ stain.

Materials

Reagents were purchased in reagent grade from commercial suppliers and used without further purification, unless otherwise described. H_2O, in synthetic procedures, refers to distilled water. Chiral BOX ligands were prepared according to the procedures previously reported in the literature.[1]

Instrumentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C {^{1}H} NMR) spectra were recorded at 25°C (unless stated otherwise) on Inova 600 (600 MHz) or Varian Unity/Inova 500 (500 MHz) or Oxford AS400 (400 MHz) spectrometers at the Boston College nuclear magnetic resonance facility. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent. The solvent peak was referenced to 0 ppm for ^{1}H for tetramethylsilane and 77.0 ppm for ^{13}C for $CDCl_3$. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sp = septet, m = multiplet), coupling constants in Hertz (Hz).

Optical rotations were measured using a 1 mL cell with a 5 cm path length on a Rudolph Research Analytical Autopol IV Polarimeter. Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}). High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) or Agilent 6220 TOF-ESI (positive mode) at the Mass Spectrometry Facility, Boston College. Chiral HPLC analyses were carried using Agilent 1200 series instruments with Daicel CHIRALPAK® columns or Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm). Purification of **4.6b** was carried using JAI Next Recycling Preparative HPLC instrument with Daicel CHIRALPAK IA (internal diameter 20 mm, column length 250 mm, particle size 5 μm).

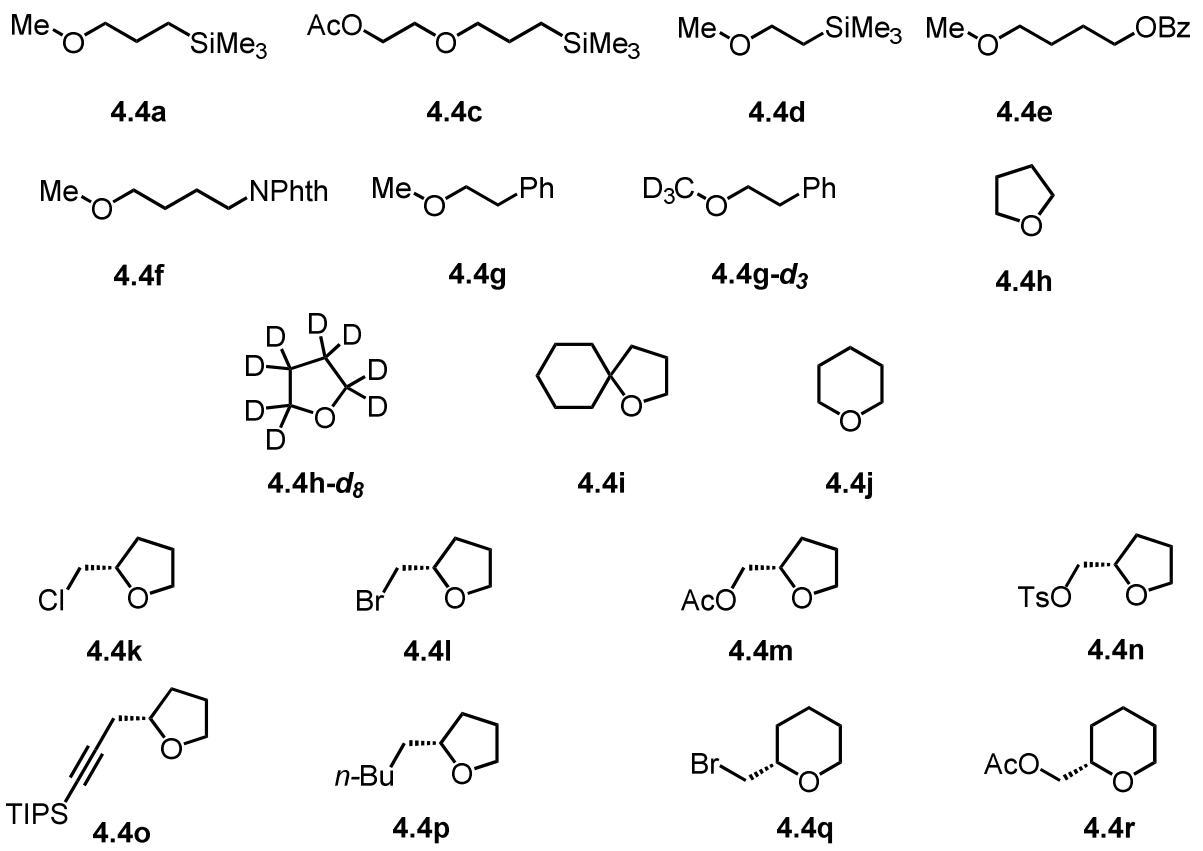
Abbreviations Used

Ac = acetyl, DART = direct analysis in real time, DCC = N,N'-dicyclohexylcarbodiimide, DCM = dichloromethane, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, dr = diastereomeric ratio, er = enantiomeric ratio, ESI = electrospray ionization, Et_2O = diethyl ether, Et_3N = triethylamine, EtOAc = ethyl acetate, H_2O = water, HPLC = high pressure liquid chromatography, HR = high-resolution, HMPA = hexamethylphosphoramide, LC = liquid chromatography, LDA = lithium diisopropylamide MS = mass spectrometry, NA = not applicable, ND = not determined, PTLC = preparative thin layer chromatography, Phth = phthaloyl, TIPS = triisopropylsilyl, Tf = trifluromethanesulfonate, THF = tetrahydrofuran, TOF = time-of-flight, Ts = 4-toluenesulfonyl.

C2. Experimental Section

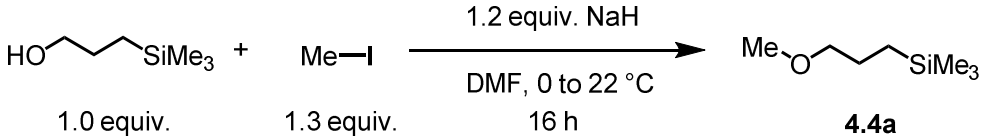
C2.1 Substrate Preparation

Table S4.1. List of Ether Substrates



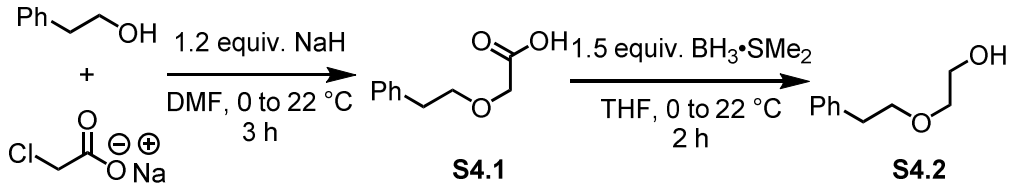
Ethers **4.4h**, **4.4h-*d*$_8$** and **4.4j** were obtained from commercial sources which were used without further purification. Substrates **4.4a**,[2] **4.4c**,[3,4] **4.4d**,[2] **4.4e**,[4] **4.4f**,[5] **4.4g**,[2] **4.4g-*d*$_3$**,[2] **4.4i**,[6] **4.4k**,[7,8] **4.4l**,[9] **4.4m**,[10] **4.4n**,[11] **4.4o**,[12] **4.4p**,[7] **4.4q**[7,9] and **4.4r**[10] were prepared according to the corresponding literature procedures. The spectroscopic data for the newly synthesized molecules **(4.4a**, **4.4c**–**4.4g-*d*$_3$**, **4.4i**, **4.4k**– **4.4r)** are provided below.

Preparation of Ether Substrates[2–11]



(3-Methoxypropyl)trimethylsilane (4.4a)[2]

3-(Trimethylsilyl)propan-1-ol (5.3 g, 40 mmol, 1.0 equiv.) and iodomethane (7.4 g, 52 mmol, 1.3 equiv.) were dissolved in DMF (40 mL) and cooled to 0 ºC under an atmosphere of N_2. Sodium hydride (60% dispersion in mineral oil; 1.9 g, 48 mmol, 1.2 equiv.) was added in one portion. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 16 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the solution was extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (3-Methoxypropyl)trimethylsilane **4.4a** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:40) as a colorless oil (5.6 g, 96% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.36 – 3.31 (m, 5H), 1.62 – 1.51 (m, 2H), 0.52 – 0.45 (m, 2H), –0.01 (s, 9H).

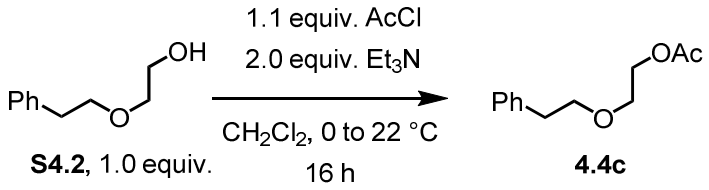


2-Phenethoxyethan-1-ol (S4.2)[3]

2-Phenylethan-1-ol (4.9 g, 40 mmol, 1.0 equiv.) was dissolved in DMF (50 mL) and cooled to 0 ºC under an atmosphere of N_2. Sodium hydride (60% dispersion in mineral oil; 1.9 g, 48 mmol, 1.2 equiv.) was added in one portion. The resulting solution was allowed to stir at 0 ºC for 30 minutes. Then, sodium 2-chloroacetate (4.6 g, 40 mmol, 1.0 equiv.) was added in one portion. The mixture was warmed to 22 ºC and allowed to stir for 1 hour. Then, the reaction temperature was raised to 60 °C and the solution was allowed to stir for another 1 hour. Upon completion (monitored by TLC), the mixture was cooled to 22 °C, and then poured onto water (250 mL). The resulting solution was extracted with Et_2O (2 x 100 mL). The aqueous phase was acidified with concentrated HCl (1 N) to *p*H = *ca*. 1 and extracted with Et_2O (2 x 100 mL). The combined organic fractions were dried over magnesium sulfate and concentrated *in vacuo* to give 2-phenethoxyacetic acid

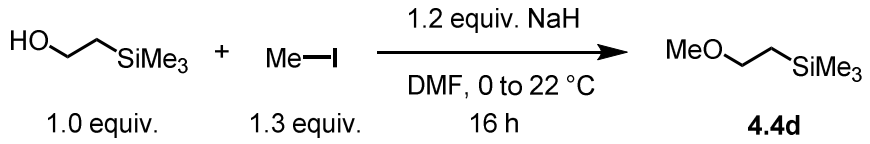
S4.1 as a colorless oil, which was used without further purification in the subsequent step (5.4 g, 75% yield).

2-Phenethoxyacetic acid (**S4.1**, 3.6 g, 20 mmol, 1.0 equiv.) was dissolved in dry THF (40 mL) and cooled to 0 ºC under an atmosphere of N_2. $H_3B{\bullet}SMe_2$ (2.8 g, 30 mmol, 1.5 equiv.) was slowly added over 1 hour. The resulting solution was warmed to 22 ºC and allowed to stir for 2 hours. Upon completion (determined by TLC), MeOH (15 mL) was added dropwise. After the mixture was concentrated *in vacuo*, the resulting crude mixture was dissolved in 200 mL of Et_2O and washed with saturated aqueous solution of $NaHCO_3$ (2 x 100 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 2-phenethoxyethan-1-ol **S4.2** as a colorless oil (2.7 g, 82% yield), which was used without further purification in the subsequent step. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.22 (d, *J* = 7.4 Hz, 3H), 3.70 (s, 4H), 3.55 (s, 2H), 2.90 (t, *J* = 7.1 Hz, 2H).



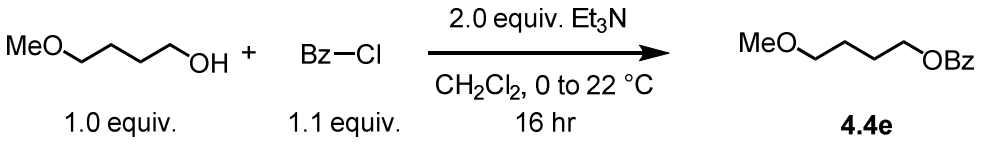
2-Phenethoxyethyl acetate (4.4c)[4]

2-Phenethoxyethan-1-ol (**S4.2**, 1.7 g, 10 mmol, 1.0 equiv.), and Et_3N (2.0 g, 20 mmol, 2.0 equiv.) were dissolved in CH_2Cl_2 (50 mL) and cooled to 0 ºC under an atmosphere of N_2. AcCl (0.86 g, 11 mmol, 1.1 equiv.) was added dropwise. The resulting solution was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the resulting solution was extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. 2-Phenethoxyethyl acetate **4.4c** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:40) as a colorless oil (1.9 g, 92% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.3 Hz, 2H), 7.24 – 7.19 (m, 3H), 4.23 – 4.20 (m, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.69 – 3.62 (m, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.07 (s, 3H).



(2-Methoxypropyl)trimethylsilane (4.4d)[2]

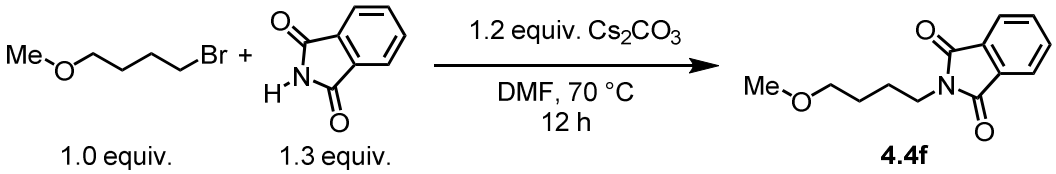
2-(Trimethylsilyl)propan-1-ol (4.7 g, 40 mmol, 1.0 equiv.) and iodomethane (7.4 g, 52 mmol, 1.3 equiv.) were dissolved in DMF (40 mL) and cooled to 0 ºC under an atmosphere of N_2. Sodium hydride (60% dispersion in mineral oil; 1.9 g, 48 mmol, 1.2 equiv.) was added in one portion. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 16 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the resulting solution was extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (2-Methoxypropyl)trimethylsilane **4.4d** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:40) as a colorless oil (4.8 g, 88% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.49 – 3.41 (m, 2H), 3.31 (s, 3H), 0.97 – 0.90 (m, 2H), 0.02 (s, 9H).



4-Methoxybutyl benzoate (4.4e)[4]

4-Methoxybutan-1-ol (4.2 g, 40 mmol, 1.0 equiv.) and Et_3N (8.0 g, 80 mmol, 2.0 equiv.) were dissolved in CH_2Cl_2 (200 mL) and cooled to 0 ºC an atmosphere of N_2. BzCl (6.2 g, 44 mmol, 1.1 equiv.) was added dropwise. The reaction was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the product was then extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. 4-Methoxybutyl benzoate **4.4e** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:10) as a colorless oil (1.9 g, 92% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 7.1 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 4.35 (t, J = 6.5 Hz, 2H), 3.44 (t, J = 6.4 Hz, 2H), 3.35 (s, 3H), 1.88 – 1.82 (m, 2H), 1.77 – 1.71 (m, 2H).



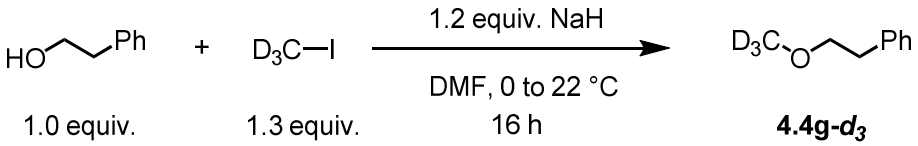
2-(4-Methoxybutyl)isoindoline-1,3-dione (4.4f)[5]

1-Bromo-4-methoxybutane (3.5 g, 21 mmol, 1.0 equiv.), phthalimide (4.0 g, 27 mmol, 1.3 equiv.) and cesium carbonate (8.2 g, 24 mmol, 1.2 equiv.) were dissolved in DMF (30 mL) under an atmosphere of N_2. The resulting solution was allowed to stir at 70 ºC for 12 hours. Upon completion (monitored by TLC), the mixture was cooled to 22 ºC. Then, H_2O (50 mL, pre-cooled to 0 ºC) was added. The resulting solution was allowed to stir for 30 minutes. 2-(4-Methoxybutyl)isoindoline-1,3-dione **4.4f** was obtained as a colorless solid (3.2 g, 65% yield) after it was filtered and washed with cold water. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H), 3.72 (t, *J* = 7.2 Hz, 2H), 3.40 (t, *J* = 6.4 Hz, 2H), 3.31 (s, 3H), 1.79 – 1.73 (m, 2H), 1.65 – 1.59 (m, 2H).

(2-Methoxyethyl)benzene (4.4g)[2]

2-Phenylethan-1-ol (4.9 g, 40 mmol, 1.0 equiv.) and iodomethane (7.4 g, 52 mmol, 1.3 equiv.) were dissolved in DMF (40 mL) and cooled to 0 ºC under an atmosphere of N_2. Sodium hydride (60% dispersion in mineral oil; 1.9 g, 48 mmol, 1.2 equiv.) was added in one portion. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 16 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the resulting solution was extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. **4.4g** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:40) as a colorless oil (5.0 g, 92% yield).

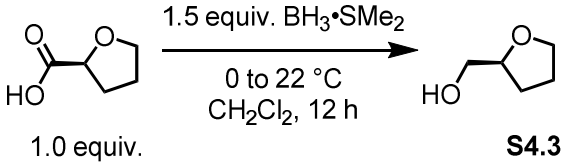
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.21 (dd, *J* = 12.7, 7.1 Hz, 3H), 3.61 (t, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 2.89 (t, *J* = 7.1 Hz, 2H).



(2-(Methoxy-*d*$_3$)ethyl)benzene (4.4g-*d*$_3$)[2]

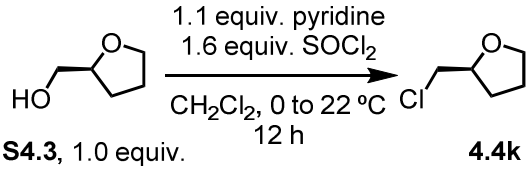
2-Phenylethan-1-ol (4.9 g, 40 mmol, 1.0 equiv.) and iodomethane-d_3 (7.5 g, 52 mmol, 1.3 equiv.) were dissolved in DMF (40 mL) and cooled to 0 ºC under an atmosphere of N_2. Sodium hydride (60% dispersion in mineral oil; 1.9 g, 48 mmol, 1.2 equiv.) was added in one portion. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 16 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the solution was extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. **4.4g-*d*$_3$** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:40) as a colorless oil (5.5 g, 98% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 3.60 (t, J = 7.1 Hz, 2H), 2.89 (t, J = 7.1 Hz, 2H).



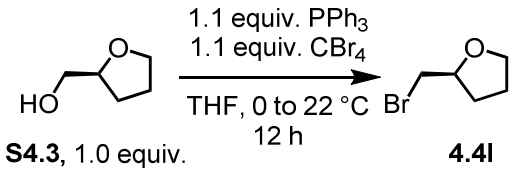
(*S*)-(Tetrahydrofuran-2-yl)methanol (S4.3)[7]

(*S*)-Tetrahydrofuran-2-carboxylic acid (19.7 g, 170 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (150 mL) and cooled to 0 ºC under an atmosphere of N_2. BH_3•SMe_2 (24.2 mL, 255 mmol, 1.5 equiv.) was slowly added over 1 hour. The resulting solution was allowed to stir at 22 ºC for 12 hours. Upon completion (monitored by TLC), 2N aqueous solution of NaOH (300 mL) was added and the solution was extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (*S*)-(Tetrahydrofuran-2-yl)methanol **S4.3** was obtained as a colorless oil (12.2 g, 71% yield), which was used without further purification in the subsequent step. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.04 – 3.99 (m, 1H), 3.90 – 3.84 (m, 1H), 3.82 – 3.77 (m, 1H), 3.70 – 3.65 (m, 1H), 3.53 – 3.47 (m, 1H), 2.05 (t, J = 6.3 Hz, 1H), 1.97 – 1.86 (m, 3H), 1.68 – 1.62 (m, 1H).



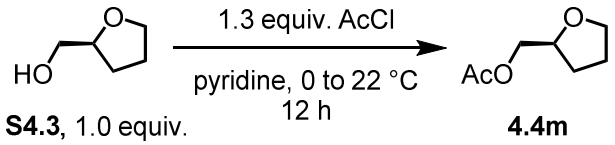
(*S*)-2-(Chloromethyl)tetrahydrofuran (4.4k)[8]

(*S*)-(Tetrahydrofuran-2-yl)methanol (**S4.3**, 4.1 g, 40 mmol, 1.0 equiv.) and pyridine (3.6 mL, 44 mmol, 1.1 equiv.) were dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 ºC under an atmosphere of N_2. $SOCl_2$ (4.6 mL, 64 mmol, 1.6 equiv.) was added dropwise. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the resulting solution was extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (*S*)-2-(Chloromethyl)tetrahydrofuran **4.4k** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:10) as a colorless oil (2.0 g, 42%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.17 – 4.11 (m, 1H), 3.95 – 3.89 (m, 1H), 3.84 – 3.78 (m, 1H), 3.58 – 3.48 (m, 2H), 2.10 – 2.02 (m, 1H), 2.00 – 1.87 (m, 2H), 1.80 – 1.72 (m, 1H). **Specific Rotation: [α]^{25}** – 5.2° (*c* 1.0, CH_2Cl_2).



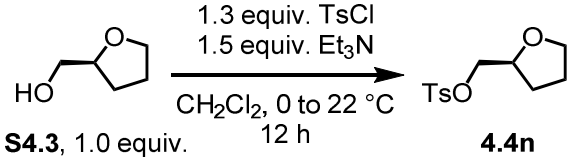
(*S*)-2-(Bromomethyl)tetrahydrofuran (4.4l)[9]

(*S*)-(Tetrahydrofuran-2-yl)methanol (**S4.3**, 1.5 g, 15 mmol, 1.0 equiv.) and CBr_4 (5.6 g, 17 mmol, 1.1 equiv.) were dissolved in dry THF (20 mL) and cooled to 0 ºC under an atmosphere of N_2. PPh_3 (4.5 g, 17 mmol, 1.1 equiv.) was slowly added. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (determined by TLC), the solution was concentrated *in vacuo*, hexane (100 mL) was added and was filtered through a pad of celite. (*S*)-2-(Bromomethyl)tetrahydrofuran **4.4l** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:12) as a yellow oil (1.1 g, 45%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.18 – 4.12 (m, 1H), 3.96 – 3.91 (m, 1H), 3.85 – 3.80 (m, 1H), 3.45 – 3.35 (m, 2H), 2.13 – 2.05 (m, 1H), 2.01 – 1.88 (m, 2H), 1.79 – 1.71 (m, 1H). **Specific Rotation: [α]^{25}** – 9.4° (*c* 1.0, CH_2Cl_2).



(*S*)-(Tetrahydrofuran-2-yl)methyl acetate (4.4m) [10]

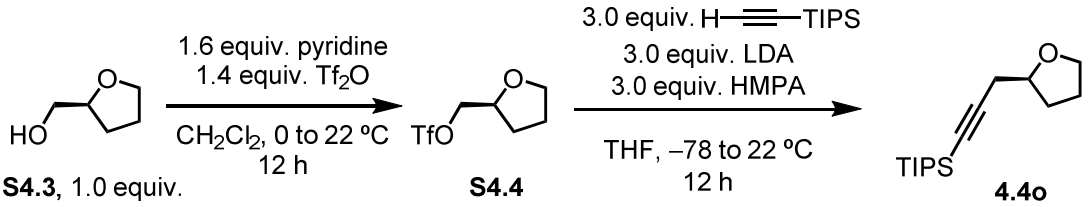
(*S*)-(Tetrahydrofuran-2-yl)methanol (**S4.3**, 3.1 g, 30 mmol, 1.0 equiv.) was dissolved in pyridine (5 mL) and cooled to 0 ºC under an atmosphere of N_2. AcCl (2.8 mL, 39 mmol, 1.3 equiv.) was added dropwise. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the solution was extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (*S*)-(Tetrahydrofuran-2-yl)methyl acetate **4.4m** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:3) as a colorless oil (3.4 g, 71%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.19 – 4.09 (m, 2H), 4.01 – 3.96 (m, 1H), 3.92 – 3.87 (m, 1H), 3.83 – 3.78 (m, 1H), 2.09 (s, 3H), 2.04 – 1.97 (m, 1H), 1.96 – 1.87 (m, 2H), 1.63 – 1.56 (m, 1H). **Specific Rotation: [α]^{25}** +24.0° (*c* 1.0, CH_2Cl_2).



(*S*)-(Tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (4.4n) [11]

(*S*)-(Tetrahydrofuran-2-yl)methanol (**S4.3**, 7.3 g, 72 mmol, 1.0 equiv.) and TsCl (17.9 g, 94 mmol, 1.3 equiv.) were dissolved in dry CH_2Cl_2 (200 mL) and cooled to 0 ºC under an atmosphere of N_2. Triethylamine (14.9 mL, 108 mmol, 1.5 equiv.) was added dropwise. The resulting solution was warmed to 22 ºC and allowed to stir for 16 hours. Upon completion (monitored by TLC), H_2O (100 mL) was added and the solution was extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (*S*)-(Tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate **4.4n** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:3) as a colorless oil (11.0 g, 60%). **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.11 – 4.06 (m, 1H), 4.03 – 3.96 (m, 2H), 3.81 – 3.70

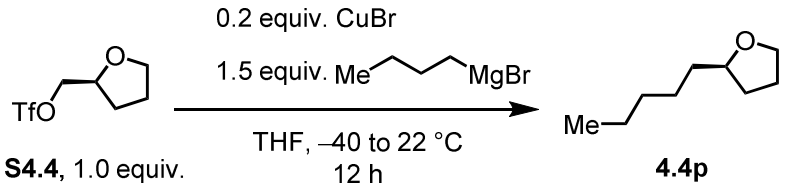
(m, 2H), 2.45 (s, 3H), 2.02 – 1.93 (m, 1H), 1.90 – 1.83 (m, 2H), 1.71 – 1.62 (m, 1H). **Specific Rotation: [α]^{25}** + 17.0° (*c* 1.0, CH_2Cl_2).



(*S*)-Triisopropyl(3-(tetrahydrofuran-2-yl)prop-1-yn-1-yl)silane (4.4o) [12]

(*S*)-(Tetrahydrofuran-2-yl)methanol (**S4.3**, 6.1 g, 60 mmol, 1.0 equiv.) and pyridine (7.7 mL, 96 mmol, 1.6 equiv.) were dissolved in CH_2Cl_2 (250 mL) and cooled to 0 ºC under an atmosphere of N_2. Tf_2O (14.1 mL, 84 mmol, 1.4 equiv.) was added dropwise. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was filtered through a silica gel plug and concentrated *in vacuo* to give **S4.4**, which was used without further purification in the subsequent reaction.

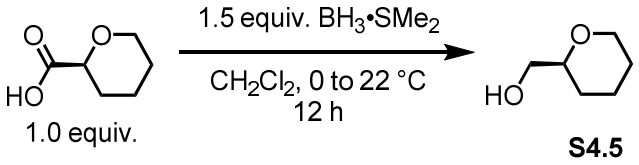
(Triisopropylsilyl)acetylene (11.8 g, 65 mmol, 3.0 equiv.) and hexamethylphosphoramide (11.3 mL, 65 mmol, 3.0 equiv.) were dissolved in dry THF (30 mL) and cooled to −78 ºC under an atmosphere of N_2. Lithium diisopropylamide (65 mL, 1.0 M in THF) was added dropwise. The resulting solution was allowed to stir at −78 ºC for 30 minutes. Next, (*S*)-(tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate (**S4.4**, 5.0 g, 21 mmol, 1.0 equiv.) was added dropwise. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), saturated aqueous solution of NH_4Cl (100 mL) was added and the solution was extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (*S*)-Triisopropyl(3-(tetrahydrofuran-2-yl)prop-1-yn-1-yl)silane **4.4o** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:10) as a colorless oil (2.3 g, 39%). **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 4.07 – 4.02 (m, 1H), 3.93 – 3.87 (m, 1H), 3.79 – 3.74 (m, 1H), 2.58 (dd, *J* = 16.6, 4.3 Hz, 1H), 2.42 (dd, *J* = 16.6, 7.9 Hz, 1H), 2.11 – 2.04 (m, 1H), 1.98 – 1.78 (m, 3H), 1.09 – 1.01 (m, 21H). **Specific Rotation: [α]^{25}** −28.4° (*c* 1.0, CH_2Cl_2).



(*R*)-2-Pentyltetrahydrofuran (4.4p) [7]

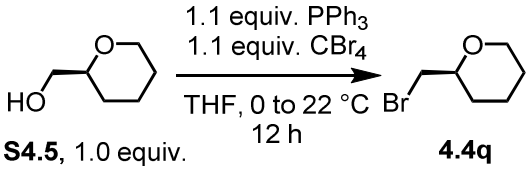
n-BuMgBr (60 mL, 0.5 M in THF, 1.5 equiv.) and CuBr (574 mg, 4.0 mmol, 0.2 equiv.) were cooled to –40 ºC under an atmosphere of N_2. (*S*)-(tetrahydrofuran-2-yl) methyl trifluoromethanesulfonate (**S4.4**, 4.7 g, 20 mmol, 1.0 equiv.) was added dropwise. The resulting solution was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), saturated aqueous solution of NH_4Cl (100 mL) was added and the resulting solution was extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure (100 mbar, 15 °C). The residue was purified by silica gel chromatograp

hy (hexanes), affording the (*R*)-2-pentyltetrahydrofuran **4.4p** (1.6 g, 56%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.88 – 3.83 (m, 1H), 3.80 – 3.75 (m, 1H), 3.73 – 3.68 (m, 1H), 2.00 – 1.93 (m, 1H), 1.91 – 1.80 (m, 2H), 1.61 – 1.53 (m, 1H), 1.48 – 1.36 (m, 3H), 1.35 – 1.25 (m, 5H), 0.91 – 0.87 (m, 3H). **Specific Rotation: [α]^{25}** – 7.4° (*c* 1.0, CH_2Cl_2).



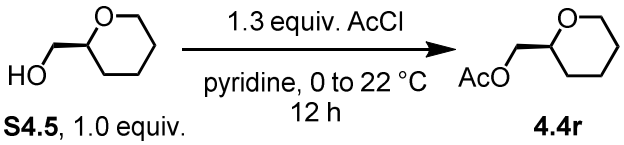
(*S*)-(Tetrahydro-2H-pyran-2-yl)methanol (S4.5) [7]

(*S*)-Tetrahydro-2H-pyran-2-carboxylic acid (5.1 g, 39 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (80 mL) and cooled to 0 ºC under an atmosphere of N_2. BH_3•SMe_2 (5.7 mL, 60 mmol, 1.5 equiv.) was slowly added over 1 hour. The resulting solution was allowed to stir at 22 ºC for 12 hours. Upon completion (monitored by TLC), 2 N aqueous solution of NaOH (100 mL) was added and the mixture was extracted with Et_2O. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (*S*)-(Tetrahydro-2H-pyran-2-yl)methanol **S4.5** was obtained as a colorless oil (3.2 g, 66% yield), which was used without further purification in the subsequent step. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.05 – 3.96 (m, 1H), 3.62 – 3.35 (m, 4H), 2.32 (s, 1H), 1.90 – 1.81 (m, 1H), 1.65 – 1.45 (m, 4H), 1.39 – 1.23 (m, 1H).



(*S*)-2-(Bromomethyl)tetrahydro-2H-pyran (4.4q) [9]

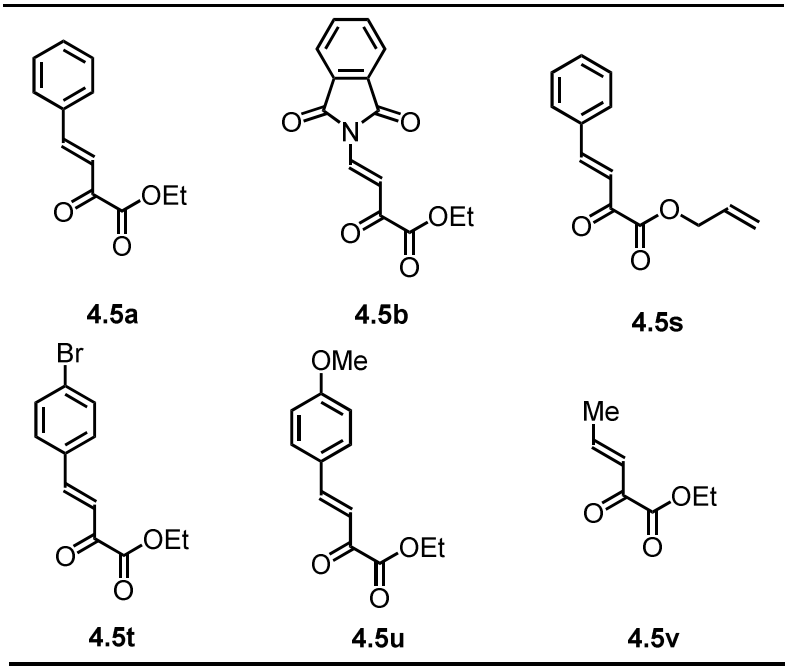
(*S*)-(Tetrahydro-2H-pyran-2-yl)methanol (**S4.5**, 1.5 g, 13 mmol, 1.0 equiv.) and CBr_4 (5.0 g, 15 mmol, 1.1 equiv.) were dissolved in THF (20 mL) and cooled to 0 ºC under an atmosphere of N_2. PPh_3 (3.9 g, 15 mmol, 1.1 equiv.) was slowly added. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 16 hours. Upon completion (determined by TLC), the mixture was concentrated *in vacuo*, hexane (100 mL) was added and mixture was filtered. (*S*)-2-(Bromomethyl)tetrahydro-2H-pyran **4.4q** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:12) as a yellow oil (602 mg, 26%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.07 – 4.02 (m, 1H), 3.53 – 3.44 (m, 2H), 3.38 – 3.32 (m, 2H), 1.91 – 1.85 (m, 1H), 1.76 – 1.71 (m, 1H), 1.63 – 1.47 (m, 3H), 1.39 – 1.31 (m, 1H). **Specific Rotation: [α]^{25}** + 22.6° (*c* 1.0, CH_2Cl_2).



(*S*)-(Tetrahydro-2H-pyran-2-yl)methyl acetate (4.4r) [10]

(*S*)-(Tetrahydro-2H-pyran-2-yl)methanol (**S4.5**, 1.5 g, 13 mmol, 1.0 equiv.) was dissolved in pyridine (5.0 mL) and cooled to 0 ºC under an atmosphere of N_2. AcCl (1.2 mL, 17 mmol, 1.3 equiv.) was added dropwise. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the resulting solution was extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (*S*)-(Tetrahydro-2H-pyran-2-yl)methyl acetate **4.4r** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:3) as a colorless oil (1.3 g, 63%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.10 – 3.98 (m, 3H), 3.57 – 3.52 (m, 1H), 3.48 – 3.42 (m, 1H), 2.09 (s, 3H), 1.90 – 1.85 (m, 1H), 1.64 – 1.46 (m, 4H), 1.38 – 1.29 (m, 1H); **Specific Rotation: [α]^{25}** + 13.0° (*c* 1.0, CH_2Cl_2).

Table S4.2. β,γ-Unsaturated Ketoesters

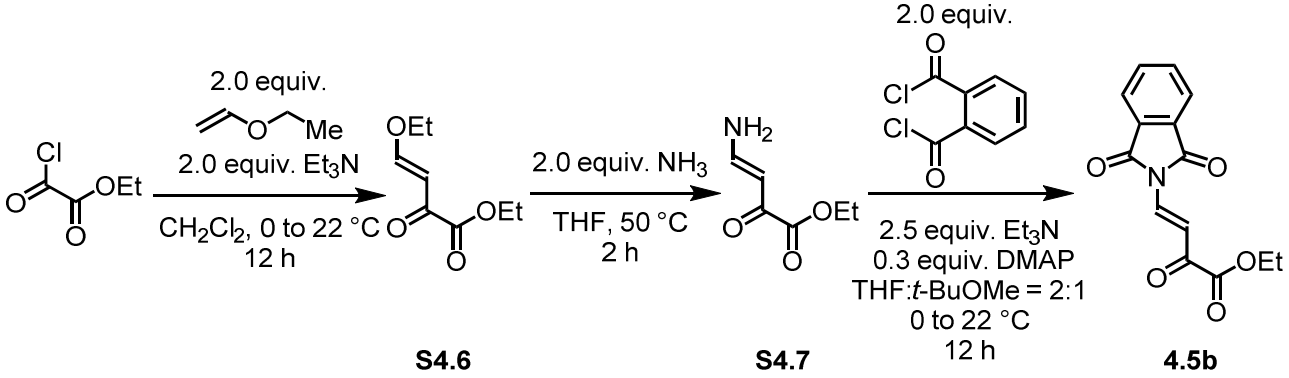


4.5a **4.5b** **4.5s**

4.5t **4.5u** **4.5v**

Substrates **4.5a,**[13] **4.5b,**[14] **4.5s**,[15] **4.5t**,[13] **4.5u**,[13] **4.5v**[13] were prepared according to the procedures previously reported in the literature.

Preparation of ethyl (*E*)-4-(1,3-dioxoisoindolin-2-yl)-2-oxobut-3-enoate(4.5b)[13]



S4.6 **S4.7** **4.5b**

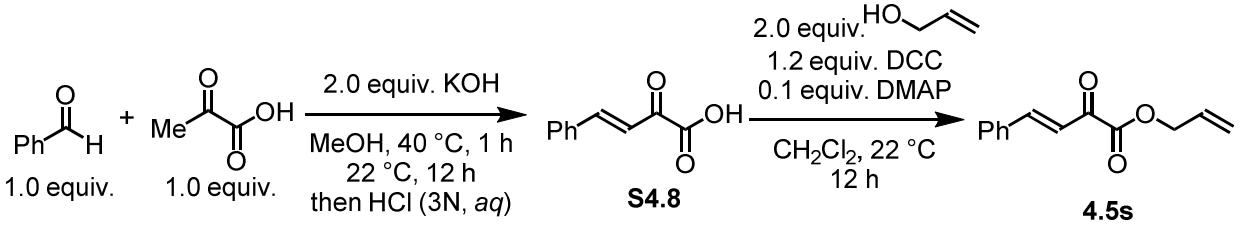
Ethyl 2-chloro-2-oxoacetate (12.3 g, 90 mmol, 1.0 equiv.) and vinyl ethyl ether (13.0 g, 180 mmol, 2.0 equiv.) were dissolved in dry CH_2Cl_2 (100 mL) and cooled to 0 ºC under an atmosphere of N_2. Triethylamine (24.9 mL, 180 mmol, 2.0 equiv.) was added dropwise. The resulting solution was

allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), H_2O (50 mL) was added and the solution was extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Ethyl (*E*)-4-ethoxy-2-oxobut-3-enoate **S4.6** was obtained as a colorless oil (9.6 g, 62% yield), which was used without further purification in the subsequent step.

Ethyl (*E*)-4-ethoxy-2-oxobut-3-enoate (**S4.6**, 1.7 g, 10 mmol, 1.0 equiv.) was dissolved in THF (10 mL) under an atmosphere of N_2. NH_3 (50 mL, 0.4 M in THF) was added. The resulting solution was allowed to stir at 50 °C for 2 hours. Upon completion, the solution was concentrated *in vacuo*. Ethyl (*E*)-4-amino-2-oxobut-3-enoate **S4.7** was obtained as a yellow solid (820 mg, 58% yield) after recrystallization in Et_2O and CH_2Cl_2. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.65 (br, 1H), 7.20 – 7.14 (m, 1H), 5.90 (d, *J* = 7.4 Hz, 1H), 5.77 (br, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

Ethyl (*E*)-4-amino-2-oxobut-3-enoate (**S4.7**, 600 mg, 4.2 mmol, 1.0 equiv.), triethylamine (1.5 mL, 11 mmol, 2.5 equiv.) and DMAP (160 mg, 1.3 mmol, 0.3 equiv.) were dissolved in THF (12 mL) and *t*-BuOMe (6.0 mL) and cooled to 0 ºC under an atmosphere of N_2. Phthaloyl chloride (1.7 g, 8.4 mmol, 2.0 equiv.) was added dropwise. The resulting solution was allowed to stir at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (determined by TLC), H_2O (40 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Ethyl (*E*)-4-(1,3-dioxoisoindolin-2-yl)-2-oxobut-3-enoate **4.5b** was obtained after purification by silica gel chromatography (Et_2O:hexanes = 1:3) as a yellow solid (350 mg, 31% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.13 (d, *J* = 14.8 Hz, 1H), 8.00 – 7.98 (m, 2H), 7.88 – 7.83 (m, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

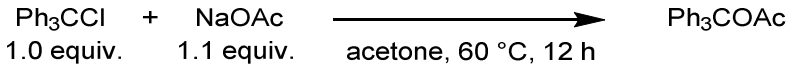
Preparation of allyl (*E*)-2-oxo-4-phenylbut-3-enoate (4.5s)



Benzaldehyde (20.2 mL, 200 mmol, 1.0 equiv.) and pyruvic acid (14.0 mL, 200 mmol, 1.0 equiv.) were dissolved in MeOH (30 mL) and cooled to 0 ºC. Solution of KOH (16.8 g, 300 mmol, 1.5 equiv.) in MeOH (80 mL) was added. The resulting solution was heated to 40 ºC and allowed to stir for 1 hour. Then, the mixture was cooled to 22 ºC and allowed to stir for 12 hours. Upon completion, the solution was filtered through a pad of celite and washed by MeOH and Et_2O to afford potassium (*E*)-2-oxo-4-phenylbut-3-enoate. Obtained potassium salt was dissolved in 3N aqueous solution of HCl (150 mL), and resulting solution was extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. (*E*)-2-oxo-4-phenylbut-3-enoic acid **S4.8** was obtained as a yellow oil, which was used without further purification in the subsequent step (20.2 g, 57%).

(*E*)-2-Oxo-4-phenylbut-3-enoic acid (**S4.8**, 3.5 g, 20 mmol, 1.0 equiv.), DMAP (244 mg, 2.0 mmol, 0.1 equiv.) and allyl alcohol (2.7 mL, 40 mmol, 2.0 equiv.) were dissolved in dry CH_2Cl_2 (40 mL) and cooled to 0 ºC under an atmosphere of N_2. Subsequently, DCC (5.0 g, 24 mmol, 1.2 equiv.) was added in a single portion. The resulting solution was stirred at 0 ºC for 1 hour. Then, the mixture was warmed to 22 ºC and allowed to stir for 12 hours. Upon completion (monitored by TLC), the mixture was filter through a pad of celite and concentrated *in vacuo*. Allyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5s** was obtained after purification by silica gel chromatography (EtOAc:hexanes = 1:10) as a yellow solid (2.1 g, 49%). **^{1}H** NMR (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 16.1 Hz, 1H), 7.65 – 7.62 (m, 2H), 7.48 – 7.40 (m, 3H), 7.36 (d, *J* = 16.0 Hz, 1H), 6.07 – 5.97 (m, 1H), 5.44 (d, *J* = 17.2 Hz, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 4.82 (dd, *J* = 6.0, 1.3 Hz, 2H).

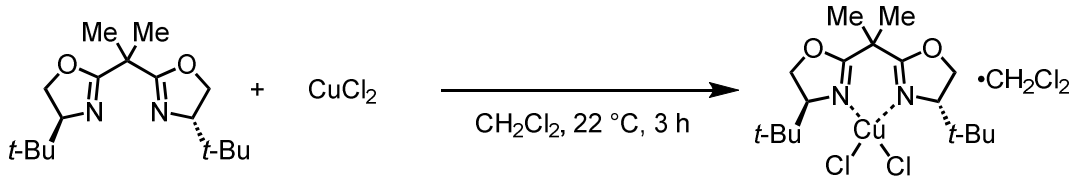
Preparation of Trityl Acetate



Trityl chloride (22.4 g, 80 mmol) and sodium acetate (7.0 g, 85 mmol) were dissolved in dry acetone (200 mL). The resulting reaction mixture was allowed to reflux at 80 °C for 12 hours. Upon completion, reaction mixture was filtered to remove precipitation and concentrated *in vacuo* to obtain crude product. 200 mL dry hexane was added to crude product, resulting solution was sonicating for 10 minutes, filtered to remove insoluble trityl alcohol and concentrated *in vacuo*. Trityl acetate was obtained after keeping at vacuum for overnight as colorless solid (21.2 g, 88%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 – 7.22 (m, 15H), 2.17 (s, 3H).

C2.2 Preparation of Organocopper-Based Complexes

Preparation of [(*S*,*S*)–*t*-BuBOX(L1)–Cu](Cl)$_2$

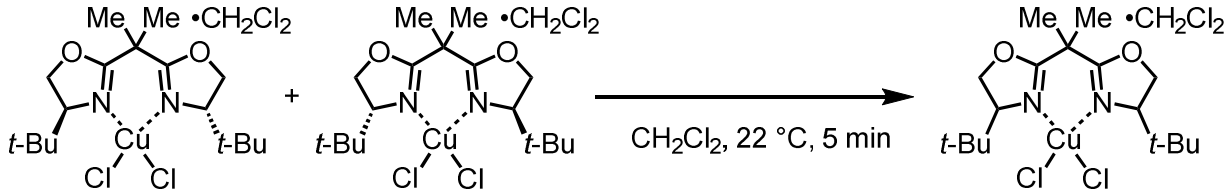


L1, 1.9 mmol 1.9 mmol [**L1**–Cu](Cl)$_2$

Chiral [**L1**–Cu](Cl)$_2$ complex was prepared accordingly the procedure previously reported in the literature.[12] To a 25 mL oven-dried sealed tube was added (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) (**L1**, 559 mg, 1.9 mmol), $CuCl_2$ (255 mg, 1.9 mmol), and CH_2Cl_2 (3 mL) under an atmosphere of N_2. The resulting solution was allowed to stir at 22 °C for 3 hours. Upon completion, the solution was transferred to a syringe fitted with a 0.22 μm PTFE filter and filtered into a Schlenk tube under an atmosphere of N_2. The solvent was removed *in vacuo* to deliver [**L1**–Cu](Cl)$_2$ complex as a green solid (975 mg, 95% yield) which was used without further purification.

IR (neat) 3031, 2967, 1645, 1477, 1389, 1369, 1235, 1127, 966, 944, 726, 604 cm^{-1}; **Specific Rotation: [α]^{25}** – 264.2° (*c* 1.0, CH_2Cl_2).

Preparation of [(±)–L1–Cu](Cl)$_2$



[(*S*,*S*)-**L1**–Cu](Cl)$_2$ [(*R*,*R*)-**L1**–Cu](Cl)$_2$ [(±)-**L1**–Cu](Cl)$_2$

1.0 mmol 1.0 mmol

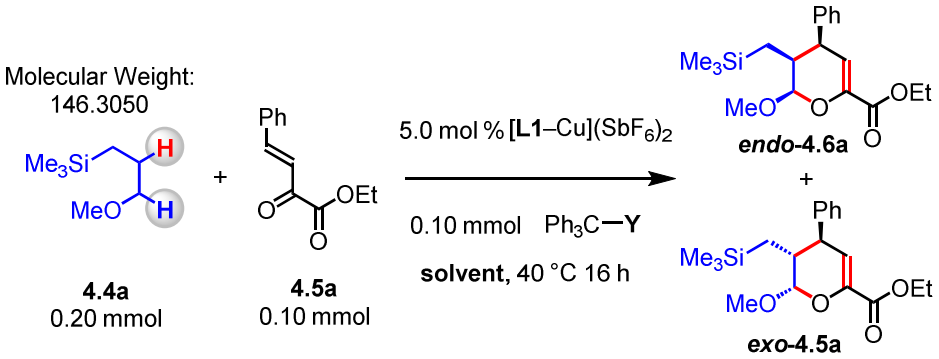
To a 25 mL oven-dried sealed tube was added [(*S*,*S*)–**L1**–Cu](Cl)$_2$ (429 mg, 1.0 mmol), [(*R*,*R*)–**L1**–Cu](Cl)$_2$ (429 mg, 1.0 mmol) and CH_2Cl_2 (3.0 mL) under an atmosphere of N_2. The resulting mixture was allowed to stir at 22 °C for 5 minutes. Upon completion, the solvent was removed *in vacuo* to deliver **[(±)–L1**–Cu](Cl)$_2$ complex as a green solid and used without further purification.

C2.3 Optimization Studies for [L–Cu](X)$_2$-Catalyzed Stereoselective Coupling of Ethers and β,γ-Unsaturated Ketoesters

Experimental Procedure for Evaluation of Reaction Conditions (*see* Table S4.3)

To an oven-dried 7 mL vial equipped with a magnetic stir bar, [**L1**–Cu](Cl)$_2$ (*see:* **Section C2.2** for its preparation; 2.6 mg, 5.0 μmol, 5.0 mol %) and a solvent (0.2 mL) were added under an atmosphere of N_2. To this solution, $AgSbF_6$ (3.4 mg, 10 μmol, 10 mol %) was added and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [**L1**–Cu](SbF$_6$)$_2$. Subsequently, an oven-dried sealed tube equipped with a magnetic stir bar were added ether (**4.4a**, 0.20 mmol, 2.0 equiv.), β,γ-unsaturated ketoester **4.5a** (0.10 mmol, 1.0 equiv.), Ph_3C–Y (0.10 mmol, 1.0 equiv.), [**L1**–Cu](SbF$_6$)$_2$ (0.2 mL of 25 mM solution), and solvent (0.4 mL) under an atmosphere of N_2. The mixture was allowed to stir at 22 °C, 40 °C, or 60 °C for 16 hours (*see:* **Table S4.3**). Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2, and then concentrated *in vacuo*. Yield and dr values were determined by the ^{1}H NMR analysis of the sample prepared as described above using mesitylene as the internal standard.

Table S4.3. Evaluation of Hydride Acceptors, Solvent and Temperature



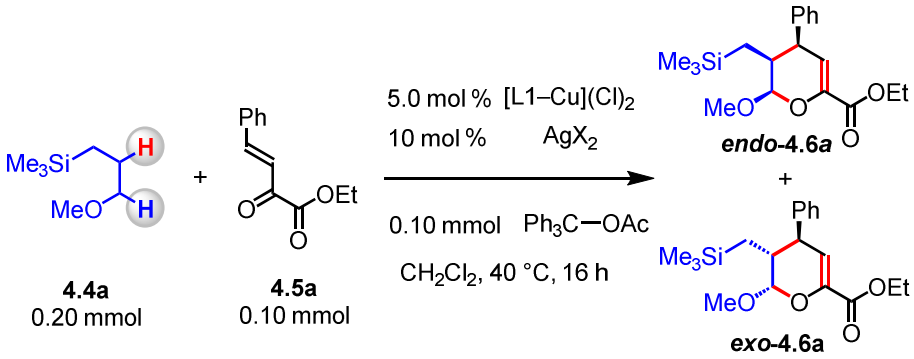
			4.6a			
entry	Ph_3C—**Y**	**solvent**	yield (%)	*endo*:*exo*	er (*endo*)	er (*exo*)
1	$Ph_3C^{\oplus}BF_4^{\ominus}$	CH_2Cl_2	75	1.4:1	50:50	51:49
2[a]	$Ph_3C^{\oplus}BF_4^{\ominus}$	CH_2Cl_2	39	1.3:1	ND	ND
3	Ph_3C–Cl	CH_2Cl_2	26	2.0:1	50:50	53:47
4	Ph_3C–OH	CH_2Cl_2	<5	ND	ND	ND
5[b]	Ph_3C–OH	CH_2Cl_2	56	1.7:1	90:10	87:13
6[b]	Ph_3C–OAc	CH_2Cl_2	55	1.5:1	90:10	90:10
7	Ph_3C–OAc	CH_2Cl_2	55	1.8:1	96:4	91:9
8[c]	Ph_3C–OAc	CH_2Cl_2	<5	ND	ND	ND
9	Ph_3C–OAc	C_6H_6	17	1:2.1	96:4	93:7
10	Ph_3C–OAc	toluene	<5	ND	ND	ND
11	Ph_3C–OAc	*t*-BuOMe	<5	ND	ND	ND

Conditions: [a] no [**L1**–Cu]$(SbF_6)_2$ was added to the reaction. [b] Reaction was performed at 60 °C. [c] Reaction was performed at 22 °C.

Experimental Procedure for Evaluation of Organocopper Complexes (*see* Table S4.4)

To an oven dried 7 mL vial equipped with a magnetic stir bar, [**L1**−Cu](Cl)$_2$ (*see:* **Section C2.2** for its preparation; 2.6 mg, 5.0 μmol, 5.0 mol %) and CH_2Cl_2 (0.2 mL) were added under an atmosphere of N_2. To this solution, Ag-based complexes (AgX_2, 10 μmol, 10 mol %) was added and the resulting solution was allowed to stir at 22 °C for 30 minutes to give the solution of [**L1**−Cu](X)$_2$. Subsequently, to an oven-dried sealed tube equipped with a magnetic stir bar were added ether (**4.4a**, 0.20 mmol, 2.0 equiv.), β,γ-unsaturated ketoester **4.5a** (0.10 mmol, 1.0 equiv.), Ph_3C−OAc (0.10 mmol, 1.0 equiv.), [**L1**−Cu](X)$_2$ (0.2 mL of 25 mM solution), and 0.4 mL CH_2Cl_2 under an atmosphere of N_2. The mixture was allowed to stir at 40 °C for 16 hours. Upon completion, the solution was filtered through a short plug of silica gel and flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. Yield and dr values were determined by the ^{1}H NMR analysis of the sample prepared as described above using mesitylene as the internal standard.

Table S4.4. Evaluation of Organocopper Complexes



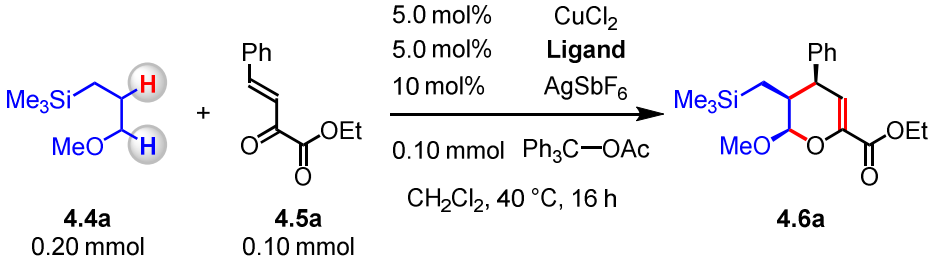
		4.6*a*			
entry	[L1–Cu](**X**)$_2$	yield (%)	*endo*:*exo*	er (*endo*)	er (*exo*)
1	[L1-Cu](**Cl**)$_2$	<5	ND	ND	ND
2	[L1–Cu](**OTf**)$_2$	<5	ND	ND	ND
3	[L1–Cu](**ClO$_4$**)$_2$	13	1.6:1	86:14	88:12
4	[L1–Cu](**SbF$_6$**)$_2$	55	1.8:1	96:4	91:9
4	**none**	0	ND	ND	ND

Experimental Procedure for Evaluation of Ligands for the Organocopper Catalyst (*see* Table S4.5)

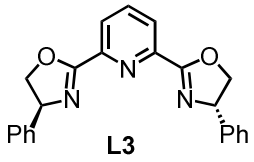
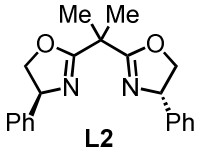
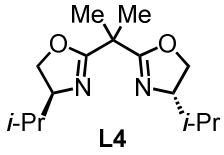
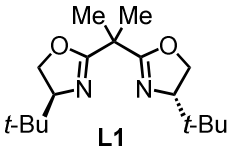
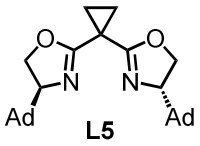
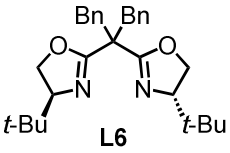
To an oven dried 7 mL vial equipped with a magnetic stir bar, $CuCl_2$ (10 μmol, 5.0 mol %), ligand (10 μmol, 5.0 mol %) and CH_2Cl_2 (0.4 mL) were added under an atmosphere of N_2. The resulting mixture was allowed to stir for 15 minutes at 22 °C. To this solution, $AgSbF_6$ (6.8 mg, 20 μmol, 10 mol %) was added and the resulting mixture was allowed to stir for another 15 minutes to give the solution of [**L**–Cu]$(SbF_6)_2$. Subsequently, to an oven-dried sealed tube equipped with a magnetic stir bar were added ether (**4.4a**, 0.40 mmol, 2.0 equiv.), β,γ-unsaturated ketoester (**4.5a**, 0.20 mmol, 1.0 equiv.), Ph_3C–OAc (0.20 mmol, 1.0 equiv.), [**L1**–Cu]$(SbF_6)_2$ (0.4 mL of 25 mM solution), and 0.8 mL CH_2Cl_2 under an atmosphere of N_2. The mixture was allowed to stir at 40 °C for 16 hours. Upon completion, the solution was filtered through a short plug of silica gel,

flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. Yield and dr values were determined by the ^1H NMR analysis of the sample prepared as described above using mesitylene as the internal standard.

Table S4.5. Evaluation of Ligands for the Organocopper-Catalyzed Enantioselective Hetero Diels-Alder Reaction

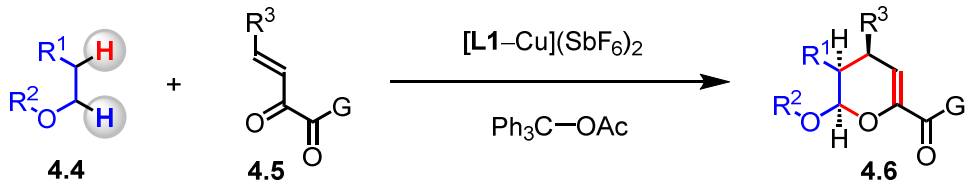


4.4a 0.20 mmol + **4.5a** 0.10 mmol → **4.6a**

 **L3**	 **L2**	 **L4**
4.6a, 21% yield *endo*:*exo* = 2.20:1 49:51 er (*endo*) 50:50 er (*exo*)	**4.6a**, 40% yield *endo*:*exo* = 7.0:1 40:60 er (*endo*) 76:24 er (*exo*)	**4.6a**, 36% yield *endo*:*exo* = 4.1:1 83:17 er (*endo*) 85:15 er (*exo*)
 **L1**	 **L5**	 **L6**
4.6a, 55% yield *endo*:*exo* = 1.8:1 96:4 er (*endo*) 91:9 er (*exo*)	**4.6a**, 60% yield *endo*:*exo* = 1.9:1 95:5 er (*endo*) 90:10 er (*exo*)	**4.6a**, 26% yield *endo*:*exo* = 1.6:1 75:25 er (*endo*) 78:22 er (*exo*)

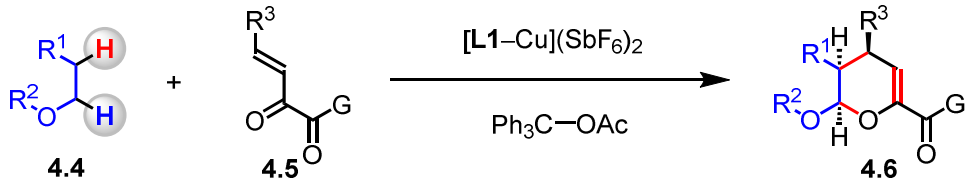
C2.4 General Procedures for the Stereoselective Coupling of Ethers and β,γ-Unsaturated Ketoesters

General Procedure A for [L1–Cu](SbF$_6$)$_2$-Catalyzed Stereoselective Coupling of Ethers and β,γ-Unsaturated Ketoesters



To an oven dried 7 mL vial equipped with a magnetic stir bar, [**L1**–Cu](Cl)$_2$ (*see:* **Section C2.2** for its preparation; 5.0–10 mol %, 5.0–10 μmol) and CH_2Cl_2 (0.2 mL) were added under an atmosphere of N_2. To this solution, $AgSbF_6$ (10–20 mol %, 10–20 μmol) was added and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the CH_2Cl_2 solution of [**L1**–Cu](SbF$_6$)$_2$ (10–20 mol %, 10–20 μmol, 25–50 mM). Subsequently, to an oven-dried sealed tube equipped with a magnetic stir bar were added ether (**4.4**, 0.20–0.40 mmol, 2.0–4.0 equiv.), β,γ-unsaturated ketoester (**4.5**, 0.10 mmol, 1.0 equiv.), trityl acetate (0.10–0.20 mmol, 1.0–2.0 equiv.), 0.4 mL CH_2Cl_2, and [**L1**–Cu](SbF$_6$)$_2$ solution (5.0–10 μmol, 5.0–10 mol %) under an atmosphere of N_2. The resulting solution was allowed to stir at –20 °C, 22 °C, 40 °C or 60 °C for 16–48 hours (*see:* **Section C3** for details). Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2, and then concentrated *in vacuo*.

General Procedure B for [L1–Cu](SbF$_6$)$_2$-Catalyzed Stereoselective Coupling of Ethers and β,γ-Unsaturated Ketoesters

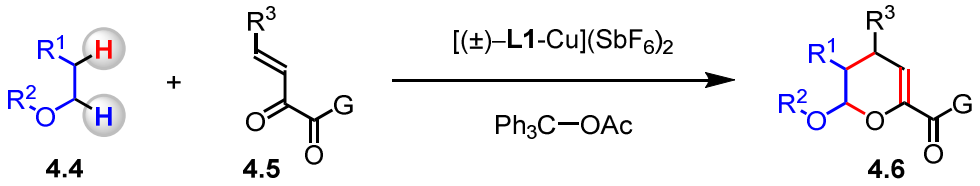


To an oven dried 7 mL vial equipped with a magnetic stir bar, [**L1**–Cu](Cl)$_2$ (*see:* **Section C2.2** for its preparation; 5.0–10 mol %, 5.0–10 μmol) and CH_2Cl_2 (0.2 mL) were added under an atmosphere of N_2. To this solution, $AgSbF_6$ (10–20 mol %, 10–20 μmol) was added and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [**L1**–Cu](SbF$_6$)$_2$ (10–20 mol %, 10–20 μmol, 25–50 mM). Subsequently, to an oven-dried sealed tube equipped with a magnetic stir bar were added ether (**4.4**, 0.20 mmol, 2.0 equiv.), β,γ-unsaturated ketoester (**4.5**, 0.10 mmol, 1.0 equiv.), trityl acetate (0.10 mmol, 1.0 equiv.), [**L1**–Cu](SbF$_6$)$_2$ solution (5.0–10 μmol, 5.0–10 mol %), and 0.4 mL CH_2Cl_2 under an atmosphere of N_2. The mixture was allowed to stir at 22 °C, 40 °C or 60 °C for 16–24 hours (*see:* **Section C3** for details). Then, the solution was allowed to cool 22 °C and a second batch of ether (**4.4**, 0.20 mmol, 2.0 equiv.) and trityl acetate (0.10 mmol, 1.0 equiv.) was added. The mixture was stirred at either 22 °C, 40 °C or 60 °C for another 16–24 hours. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*.

Isolation and Purification of Stereoisomers:

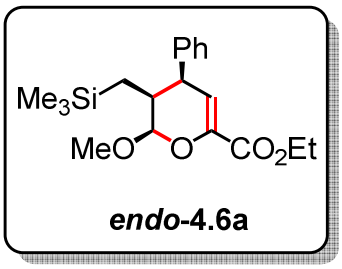
The *endo* and *exo* stereoisomers of **4.6a** and **4.6c–4.6v** were purified by silica gel chromatography. For compounds **4.6a**, **4.6c–4.6f**, **4.6h**, **4.6h-*d*$_6$**, **4.6j**, **4.6k–4.6n**, and **4.6p–4.6v**, further purification was performed by preparative TLC. For the separation of **4.6b**, JAI Next Recycling Preparative HPLC instrument with Daicel CHIRALPAK IA (internal diameter 20 mm, column length 250 mm, particle size 5 μm) was used.

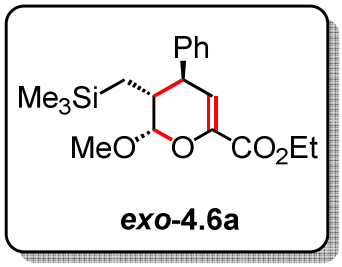
Experiment Procedure to Prepare Racemic Diels-Alder Products



To an oven dried 7 mL vial equipped with a magnetic stir bar, [**(±)–L1**–Cu](Cl)$_2$ (*see:* **Section C2.2** for its preparation; 5.2 mg, 10 μmol, 10 mol %) and CH_2Cl_2 (0.2 mL) were added under an atmosphere of N_2. To this solution, $AgSbF_6$ (6.8 mg, 20 μmol, 20 mol %) was added and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [**L1**–Cu](SbF$_6$)$_2$. Subsequently, to an oven-dried sealed tube equipped with a magnetic stir bar were added ether (**4.4**, 0.40 mmol, 4.0 equiv.), β,γ-unsaturated ketoester (**4.5**, 0.10 mmol, 1.0 equiv.), trityl acetate (0.2 mmol, 1.0–2.0 equiv.), [**(±)–L1**–Cu](SbF$_6$)$_2$ (0.2 mL of 50 mM solution) and 0.4 mL CH_2Cl_2 under an atmosphere of N_2. The mixture was allowed to stir at 60 °C for 24 hours. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2. and then concentrated *in vacuo* and purified by silica gel column chromatography.

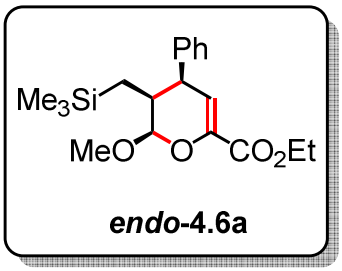
C3. Analytical Data





Ethyl (4*S*)-2-methoxy-4-phenyl-3-((trimethylsilyl)methyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (4.6a)

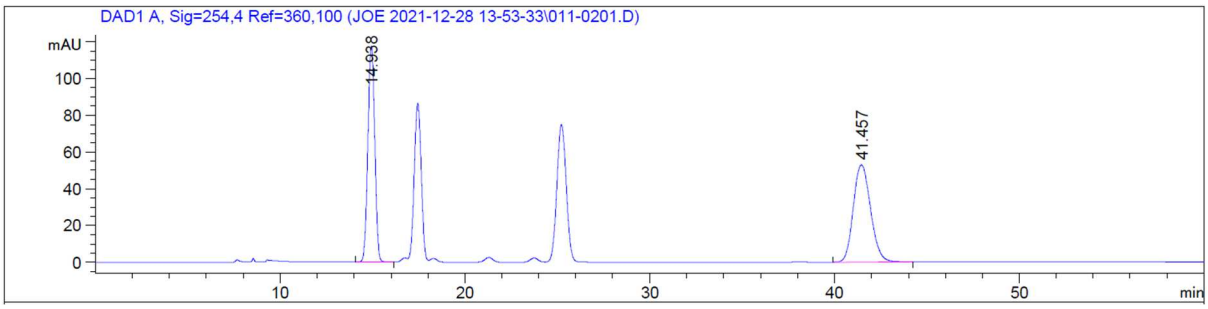
(3-Methoxypropyl)trimethylsilane **4.4a** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 40 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 1.8:1. After purification by silica gel chromatography (hexanes:EtOAc = 9:1), **4.6a** was obtained as a mixture of diastereomers (33.5 mg, 0.10 mmol, 96% yield). Subsequently, purification of diastereomers carried out by PTLC using CH_2Cl_2 as the eluent to separate ***endo*-4.6a and *exo*-4.6a**. The absolute configuration of ***endo*-4.6a** and ***exo*-4.6a** was determined by analogy to that of ***exo*-4.6g** and by 2D NMR experiments (*see:* **Section C5.2** and **C7**).



***endo*-4.6a**. Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.28 – 7.22 (m, 1H), 7.19 (d, *J* = 5.1 Hz, 2H), 6.32 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.96 (d, *J* = 2.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.07 – 4.03 (m, 1H), 3.56 (s, 3H), 2.13 – 2.06 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.35 (dd, *J* = 15.3, 10.6 Hz, 1H), 0.15 (dd, *J* = 15.3, 2.6 Hz, 1H), –0.21 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.7, 140.7, 140.7, 128.7, 128.3, 126.5, 113.5, 102.3, 61.2, 56.2, 38.3, 36.3, 14.3, 11.5, –1.5; **IR** (neat) 1429, 1648, 1366, 1302, 1246, 1189, 1115, 1084, 997, 956, 840, 766, 702 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{19}H_{29}O_4Si$ (MH^+): 349.18296; found: 349.18404; **HPLC** (Chiralpak IC;

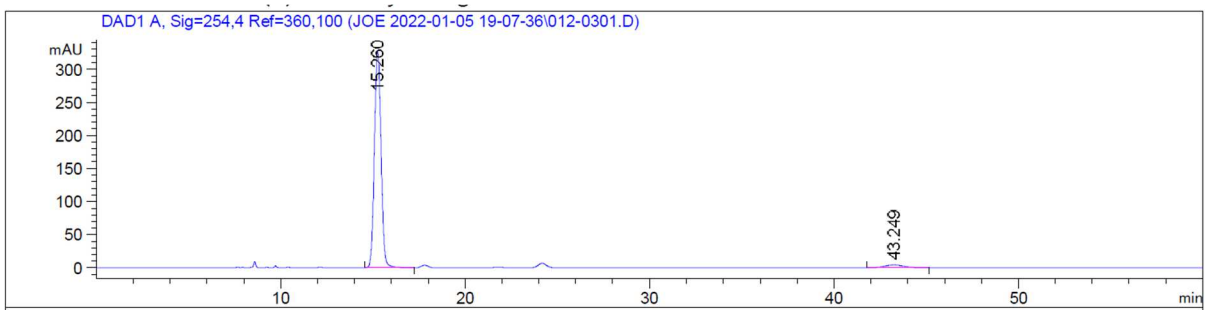
2.0:98.0 isopropanol/; hexanes, 0.4 mL/min; ***endo*-4.6a:** tr = 15.1 min (major), 41.4 min (minor); 96:4 er; **Specific Rotation: $[\alpha]^{25}$** +85.6° (*c* 0.50, CH_2Cl_2).

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                        Location :   11
Injection Date  : 12/28/2021 2:56:43 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2021-12-28 13-53-33\column4 1%IPA 99% hexane 60min-0.
                  4mL.M
Last changed    : 12/28/2021 1:53:41 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2021-12-28 13-53-33\column4 1%IPA 99% hexane 60min-0.
                  4mL.M (Sequence Method)
Last changed    : 1/27/2022 8:19:03 PM by SYSTEM
                  (modified after loading)
Method Info     : Column4 60min-2% iPrOH 99% hexane-0.5mL
```



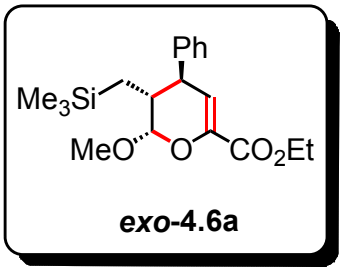

```
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.938 BB    0.4147 3050.60059  117.57490  47.0103
   2  41.457 BB    1.0044 3438.61792   52.89689  52.9897

Totals :                  6489.21851  170.47179
```

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   12
Injection Date  : 1/5/2022 9:11:37 PM                   Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-05 19-07-36\column4 1%IPA 99% hexane 60min-0.
                  4mL.M
Last changed    : 1/5/2022 7:07:43 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-05 19-07-36\column4 1%IPA 99% hexane 60min-0.
                  4mL.M (Sequence Method)
Last changed    : 1/27/2022 7:56:22 PM by SYSTEM
                  (modified after loading)
Method Info     : Column4 60min-2% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.260	BB	0.3925	8206.15332	327.29175	96.5898
2	43.249	BB	0.9504	289.72397	4.28716	3.4102
Totals :				8495.87729	331.57891	

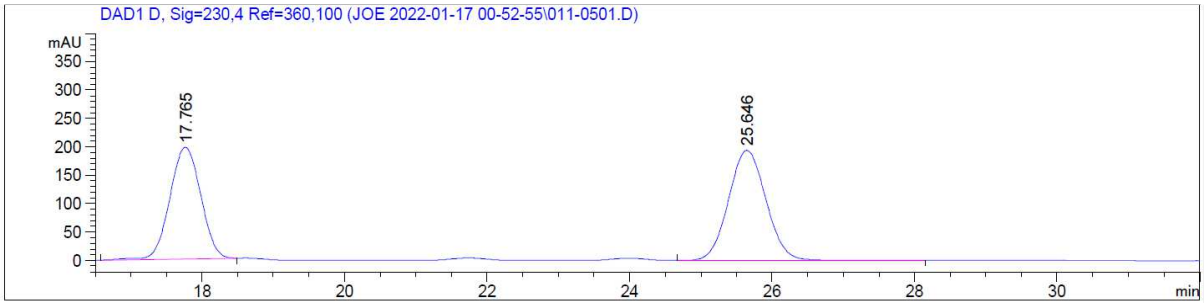


***exo*-4.6a**

***exo*-4.6a.** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.4 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.20 – 7.15 (m, 2H), 6.12 (d, *J* = 2.4 Hz, 1H), 5.09 (d, *J* = 2.2 Hz, 1H), 4.34 – 4.24 (m, 2H), 3.52 (s, 3H), 3.30 (dd, *J* = 11.0, 2.4 Hz, 1H), 2.03 – 1.92 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.65 (dd, *J* = 15.0, 11.2 Hz, 1H), 0.46 (dd, *J* = 15.0, 3.1 Hz, 1H), –0.11 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.9, 142.3, 139.5, 128.7, 128.6, 126.9, 116.6, 101.2, 61.2, 56.1, 43.5, 39.3, 16.0, 14.2, –1.1; **IR** (neat) 2921, 1728, 1649, 1234, 1090, 1058, 1028, 943,

836, 762, 701 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{19}H_{29}O_4Si$ (MH^+): 349.18296; found: 349.18267; **HPLC** (Chiralpak IC; 2.0:98.0 isopropanol/; hexanes, 0.4 mL/min; ***exo*-4.6a:** tr = 17.6 min (major), 25.2 min (minor); 96:4 er); **Specific Rotation: $[\alpha]^{25}$** + 25.6° (*c* 0.50, CH_2Cl_2).

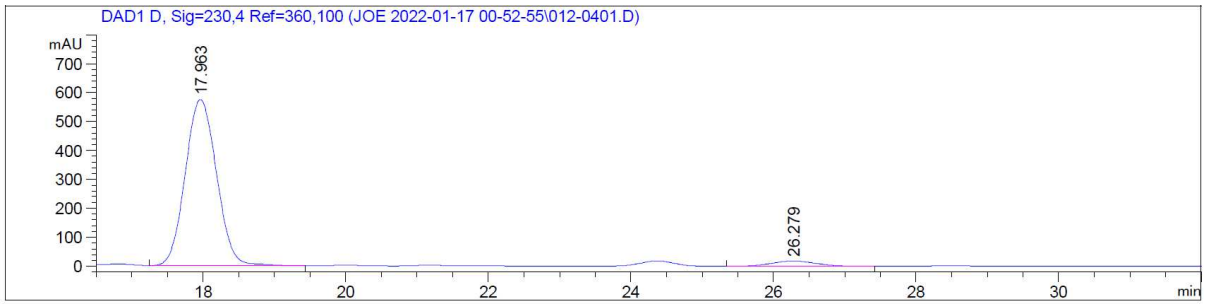
```
Acq. Operator   : SYSTEM                          Seq. Line :   5
Acq. Instrument : Wasa_LC1                        Location :   11
Injection Date  : 1/17/2022 3:58:53 AM                 Inj :   1
                                                Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-17 00-52-55\column4 1%IPA 99% hexane 60min-0.
                  4mL.M
Last changed    : 1/17/2022 12:53:03 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-17 00-52-55\column4 1%IPA 99% hexane 60min-0.
                  4mL.M (Sequence Method)
Last changed    : 1/30/2022 9:05:39 PM by SYSTEM
                  (modified after loading)
Method Info     : Column4 60min-2% iPrOH 99% hexane-0.5mL
```



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

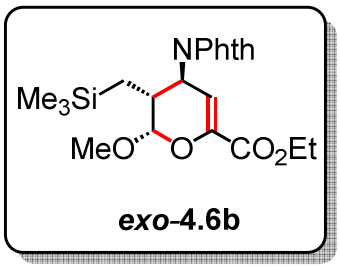
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.765	BB	0.4782	5927.92139	196.38712	45.6025
2	25.646	BB	0.5716	7071.20654	193.84825	54.3975
Totals :				1.29991e4	390.23537	

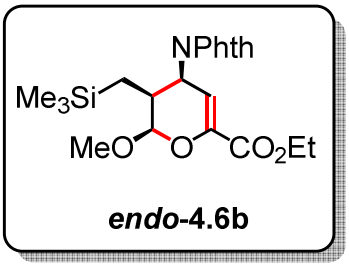
```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                        Location :   12
Injection Date  : 1/17/2022 2:57:56 AM                 Inj :   1
                                                Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-17 00-52-55\column4 1%IPA 99% hexane 60min-0.
                  4mL.M
Last changed    : 1/17/2022 12:53:03 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-17 00-52-55\column4 1%IPA 99% hexane 60min-0.
                  4mL.M (Sequence Method)
Last changed    : 1/30/2022 9:04:39 PM by SYSTEM
                  (modified after loading)
Method Info     : Column4 60min-2% iPrOH 99% hexane-0.5mL
```



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

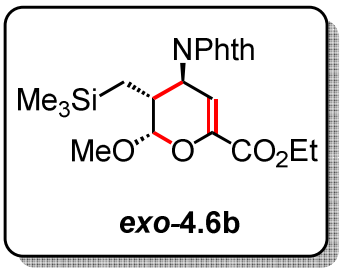
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.963	BB	0.4820	1.75258e4	574.33746	95.8619
2	26.279	BB	0.6588	756.53857	17.90941	4.1381
Totals :				1.82823e4	592.24687	





Ethyl (4*S*)-4-(1,3-dioxoisoindolin-2-yl)-2-methoxy-3-((trimethylsilyl)methyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (4.6b)

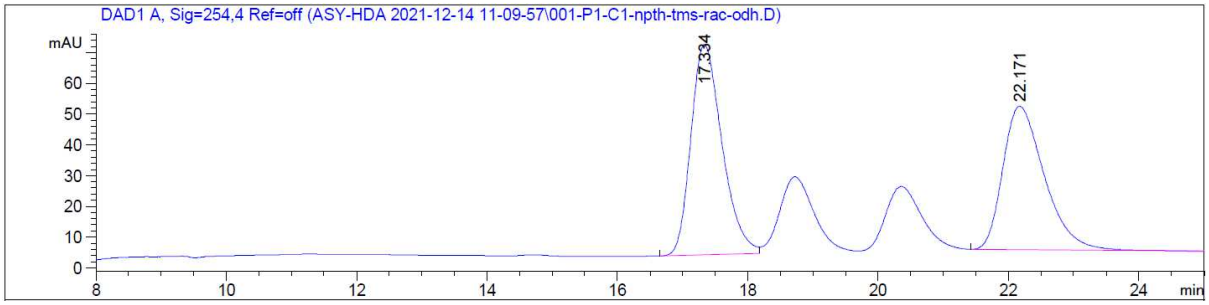
(3-Methoxypropyl)trimethylsilane **4.4a** (0.40 mmol, 4.0 equiv.) was added to ethyl (ethyl (*E*)-4-(1,3-dioxoisoindolin-2-yl)-2-oxobut-3-enoate **4.5b** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 40 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 1:2.1. After purification by silica gel chromatography (hexanes:EtOAc = 3:1), **4.6b** was obtained as a mixture of diastereomers (29.6 mg, 0.07 mmol, 71% yield). Prior to further purification, the enantiomeric ratio was determined. Subsequently, purification of diastereomers carried out by prep-HPLC (Chiralpak IA, internal diameter 20 mm, column length 250 mm, particle size 5 µm; 1.0:99.0 = isopropanol:hexanes, 10 mL/min; tr = 32.5 min (***exo*-4.6b**), 44.3 min (***endo*-25b**). The absolute configuration of ***exo*-4.6b** and ***endo*-4.6b** was determined by analogy to that of ***exo*-4.6g** and by 2D NMR experiments (*see:* **Section C5.2** and **C7**).



***exo*-4.6b**. Colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.99 (d, *J* = 2.3 Hz, 1H), 5.17 (d, *J* = 2.3 Hz, 1H), 4.96 (dd, *J* = 11.2, 2.3 Hz, 1H), 4.26 (dd, *J* = 9.7, 7.1 Hz, 2H), 3.52 (s, 3H), 2.84 (s, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.73 (dd, *J* = 14.9, 11.9 Hz, 1H), 0.44 (dd, *J* = 14.9, 3.1 Hz, 1H), –0.03 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.0, 162.2, 141.4, 134.1, 131.7, 123.4, 111.9, 101.7, 61.3, 56.1, 48.2, 34.2, 15.0, 14.2, –1.0;

IR (neat) 1710, 1381, 1308, 1248, 1190, 1114, 997, 963, 916, 838, 762, 720, 628, 529 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{21}H_{28}NO_6Si$ (MH^+): 418.16804; found: 418.16824; **HPLC** (Chiralpak OD-H; 1.0:99.0 isopropanol:hexanes, 0.6 mL/min; ***exo*-4.6b:** tr = 16.6 min (major), 21.6 min (minor); 95:5 er); **Specific Rotation: $[\alpha]^{25}$** + 119.8° (*c* 1.0, CH_2Cl_2).

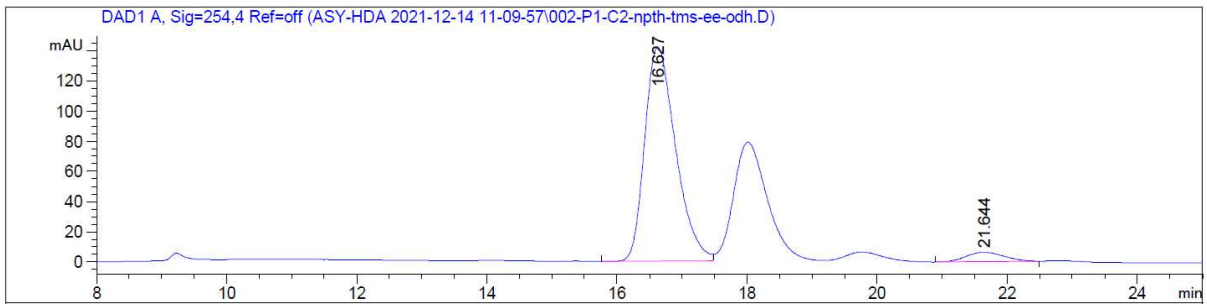
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : HPLC w FC                       Location :   P1-C-01
Injection Date  : 12/14/2021 11:10:55 AM               Inj :   1
                                                 Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\ASY-HDA 2021-12-14 11-09-57\ASY-1.0%-0.6ml-30min.M (
                  Sequence Method)
Last changed    : 12/14/2021 11:09:58 AM by SYSTEM
```



Signal 1: DAD1 A, Sig=254,4 Ref=off

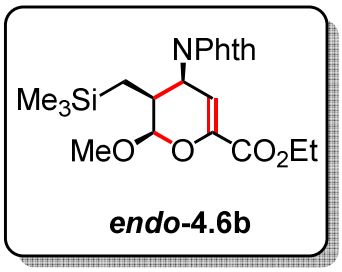
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.334	BV	0.5118	2274.67554	68.43716	52.1797
2	22.171	BB	0.6806	2084.63428	46.71501	47.8203
Totals :				4359.30981	115.15217	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : HPLC w FC                       Location :   P1-C-02
Injection Date  : 12/14/2021 11:41:47 AM               Inj :   1
                                                 Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\ASY-HDA 2021-12-14 11-09-57\ASY-1.0%-0.6ml-30min.M (
                  Sequence Method)
Last changed    : 12/14/2021 11:09:58 AM by SYSTEM
```



Signal 1: DAD1 A, Sig=254,4 Ref=off

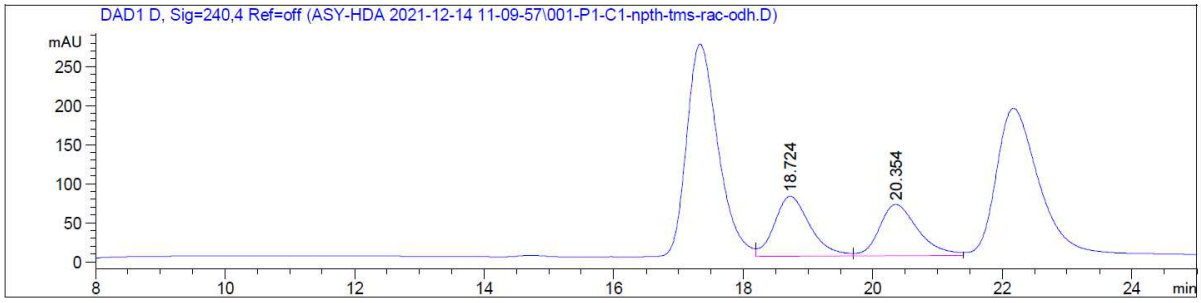
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.627	BV	0.5096	4695.00195	142.06619	94.9493
2	21.644	BB	0.6074	249.74524	6.23406	5.0507
Totals :				4944.74719	148.30025	



***endo*-4.6b**

***endo*-4.6b.** Colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (q, *J* = 5.9 Hz, 2H), 7.75 (q, *J* = 8.5 Hz, 2H), 6.23 (d, *J* = 3.1 Hz, 1H), 5.22 (dd, *J* = 6.2, 3.2 Hz, 1H), 5.06 (d, *J* = 4.1 Hz, 1H), 4.36 – 4.19 (m, 2H), 3.56 (s, 3H), 2.30 (d, *J* = 3.9 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.71 – 0.63 (m, 1H), 0.47 (dd, *J* = 15.3, 3.5 Hz, 1H), –0.06 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.4, 162.1, 141.4, 134.2, 131.6, 123.4, 108.8, 103.0, 61.3, 56.5, 47.1, 36.0, 14.2, 12.4, –1.0; **IR** (neat) 1713, 1385, 1353, 1311, 1249, 1115, 1091, 858, 838, 719 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{21}H_{28}NO_6Si$ (MH^+): 418.16804; found: 418.16824; **HPLC** (Chiralpak OD-H; 1.0:99.0 isopropanol:hexanes, 0.6 mL/min; ***endo*-4.6b:** tr = 18.0 min (major), 19.8 min (minor); 93:7 er); **Specific Rotation:** **[α]^{25}** + 76.4° (*c* 0.50, CH_2Cl_2).

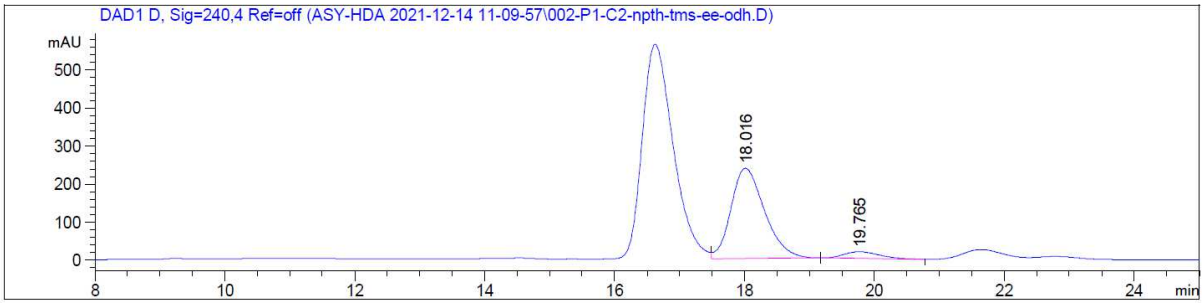
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : HPLC w FC                        Location :   P1-C-01
Injection Date  : 12/14/2021 11:10:55 AM               Inj :   1
                                                 Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\ASY-HDA 2021-12-14 11-09-57\ASY-1.0%-0.6ml-30min.M (
                  Sequence Method)
Last changed    : 12/14/2021 11:09:58 AM by SYSTEM
```



Signal 4: DAD1 D, Sig=240,4 Ref=off

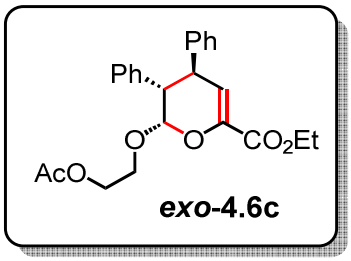
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.724	VV	0.5774	2911.20703	76.59883	51.6840
2	20.354	VV	0.6293	2721.49902	65.70220	48.3160
Totals :				5632.70605	142.30103	

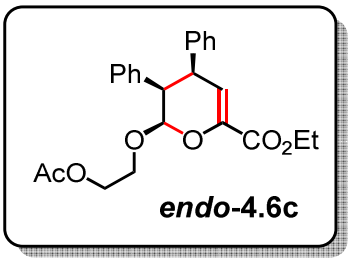
```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : HPLC w FC                        Location :   P1-C-02
Injection Date  : 12/14/2021 11:41:47 AM               Inj :   1
                                                 Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\ASY-HDA 2021-12-14 11-09-57\ASY-1.0%-0.6ml-30min.M (
                  Sequence Method)
Last changed    : 12/14/2021 11:09:58 AM by SYSTEM
```



Signal 4: DAD1 D, Sig=240,4 Ref=off

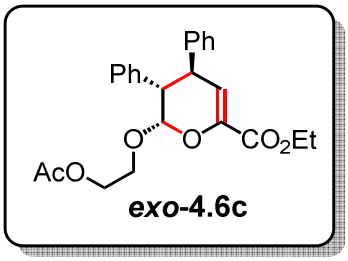
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.016	VB	0.5518	8553.30957	237.73299	92.6136
2	19.765	BB	0.5894	682.16803	17.95048	7.3864
Totals :				9235.47760	255.68346	





Ethyl (4*S*)-2-(2-acetoxyethoxy)-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (4.6c)

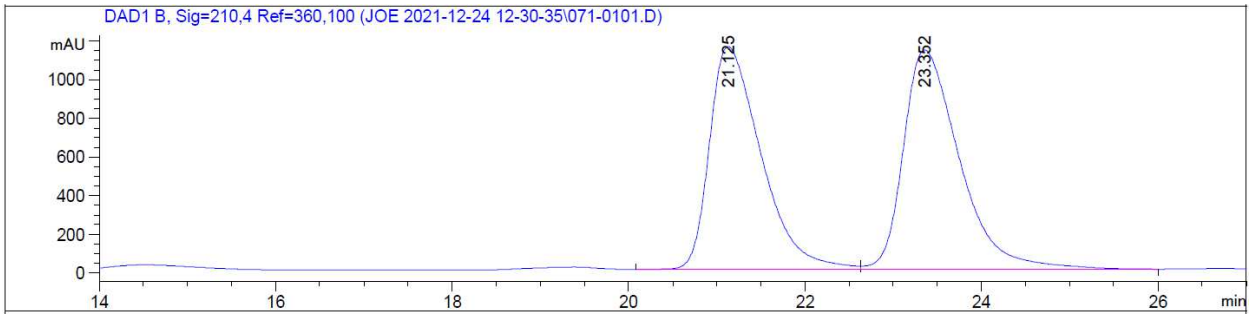
2-Phenethoxyethyl acetate **4.4c** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure A** using using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (10 mol %, 10 μmol, 50 mM, 0.2 mL) and carried out for 48 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 1:4.0. After purification by silica gel chromatography (hexanes:EtOAc = 3:1), **4.6c** was obtained as a mixture of diastereomers (27.1 mg, 0.07 mmol, 66% yield). Subsequently, purification of diastereomers carried out by PTLC using CH_2Cl_2 as the eluent to separate ***exo*-4.6c** and ***endo*-4.6c**. The absolute configuration of ***exo*-4.6c** and ***endo*-4.6c** was determined by analogy to that of ***exo*-4.6g** and by 2D NMR experiments (*see:* **Section C5.2** and **C7**).



***exo*-4.6c**

***exo*-4.6c**. Colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 – 7.07 (m, 8H), 7.00 (d, *J* = 7.1 Hz, 2H), 6.30 (d, *J* = 1.9 Hz, 1H), 5.29 (d, *J* = 1.5 Hz, 1H), 4.37 – 4.18 (m, 4H), 4.05 – 3.96 (m, 2H), 3.81 – 3.73 (m, 1H), 3.11 (dd, *J* = 12.1, 1.4 Hz, 1H), 1.98 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.7, 162.7, 141.2, 139.8, 137.7, 129.4, 128.3, 128.2, 128.0, 127.1, 126.7, 116.8, 100.2, 66.6, 63.0, 61.2, 50.4, 40.8, 20.7, 14.2; **IR** (neat) 1727, 1648, 1452, 1377, 1217, 1133, 1080, 986, 758, 699, 547 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{24}H_{27}O_6$ ($M\text{-}H^+$): 411.18002; found: 418.17978; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.5 mL/min; ***exo*-4.6c:** tr = 23.4 min (major), 21.3 min (minor); 95:5 er); **Specific Rotation: [α]^{25}** –204.7° (*c* 1.0, CH_2Cl_2).

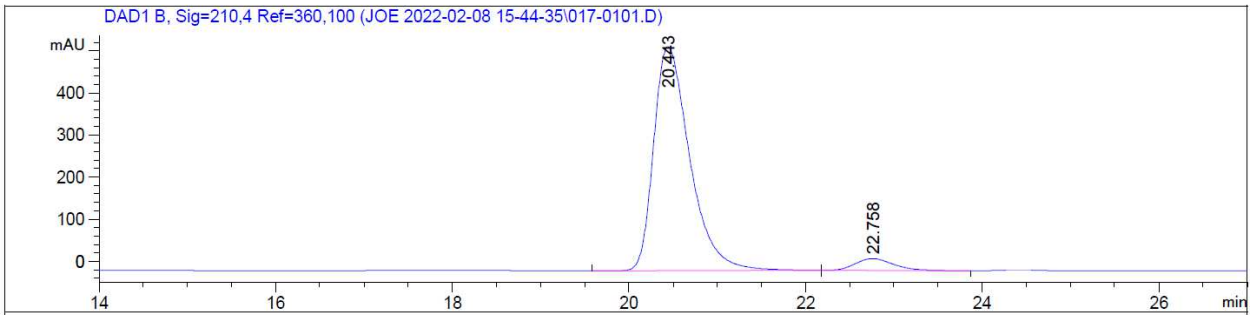
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                        Location :   71
Injection Date  : 12/24/2021 12:32:51 PM               Inj :   1
                                                 Inj Volume : 8.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2021-12-24 12-30-35\column6 1%IPA 99% hexane 60min-0.
                  5mL.M
Last changed    : 12/24/2021 12:30:43 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2021-12-24 12-30-35\column6 1%IPA 99% hexane 60min-0.
                  5mL.M (Sequence Method)
Last changed    : 2/8/2022 7:07:44 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

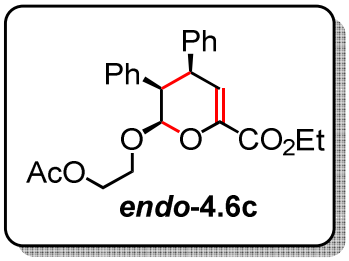
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.125	BV	0.6237	4.68168e4	1153.08875	48.2818
2	23.352	VB	0.6734	5.01489e4	1135.13855	51.7182
Totals :				9.69658e4	2288.22729	

```
Acq. Operator   : SYSTEM                          Seq. Line :  1
Acq. Instrument : Wasa_LC1                         Location :  17
Injection Date  : 2/8/2022 3:46:00 PM                  Inj :  1
                                                 Inj Volume : 2.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-02-08 15-44-35\column6 1%IPA 99% hexane 60min-0.
                  5mL.M
Last changed    : 2/8/2022 3:44:43 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-02-08 15-44-35\column6 1%IPA 99% hexane 60min-0.
                  5mL.M (Sequence Method)
Last changed    : 2/8/2022 6:21:01 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

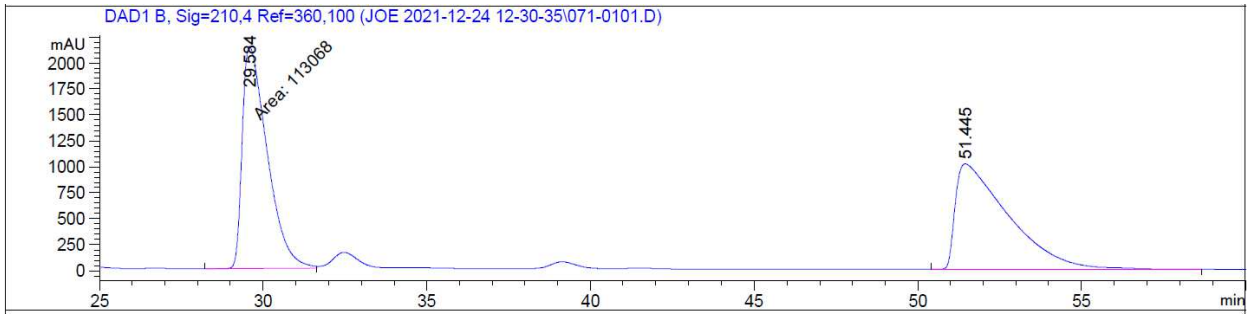
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.443	BB	0.4371	1.50974e4	532.02478	94.5779
2	22.758	BB	0.4666	865.53369	28.47756	5.4221
Totals :				1.59630e4	560.50234	



***endo*-4.6c**

***endo*-4.6c.** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.14 – 7.07 (m, 3H), 7.08 – 7.01 (m, 3H), 6.87 – 6.82 (m, 2H), 6.81 (d, *J* = 7.2 Hz, 2H), 6.39 (d, *J* = 2.7 Hz, 1H), 5.39 (d, *J* = 2.3 Hz, 1H), 4.40 – 4.28 (m, 3H), 4.27 – 4.20 (m, 2H), 4.15 – 4.08 (m, 1H), 3.95 – 3.87 (m, 1H), 3.36 (d, *J* = 7.1 Hz, 1H), 2.06 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.9, 162.5, 141.1, 139.7, 136.4, 129.2, 128.9, 127.9, 127.8, 126.8, 126.5, 114.4, 100.0, 66.1, 63.2, 61.4, 46.6, 39.1, 20.9, 14.2; **IR** (neat) 2924, 1732, 1651, 1452, 1367, 1246, 1087, 977, 761, 700 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{24}H_{27}O_6$ ($M\text{-}H^+$): 411.18002; found: 418.17978; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.5 mL/min; ***endo*-4.6c:** tr = 28.9 min (major), 52.8 min (minor); 81:19 er); **Specific Rotation: [α]^{25}** + 104.7° (*c* 0.50, CH_2Cl_2).

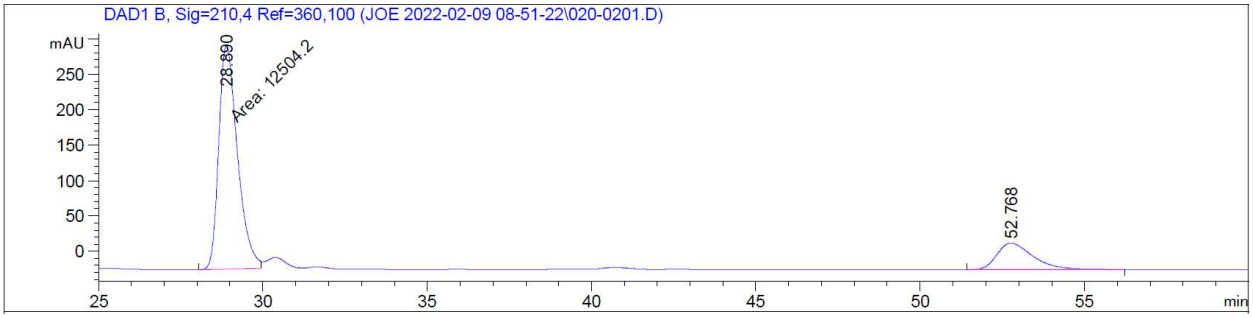
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                        Location :   71
Injection Date  : 12/24/2021 12:32:51 PM               Inj :   1
                                                 Inj Volume : 8.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2021-12-24 12-30-35\column6 1%IPA 99% hexane 60min-0.
                  5mL.M
Last changed    : 12/24/2021 12:30:43 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2021-12-24 12-30-35\column6 1%IPA 99% hexane 60min-0.
                  5mL.M (Sequence Method)
Last changed    : 2/8/2022 7:07:44 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

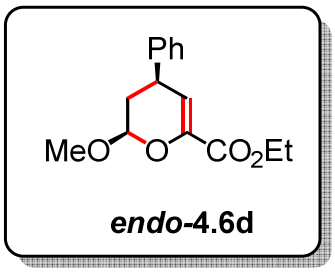
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.584	MF	0.8812	1.13068e5	2138.61548	49.7896
2	51.445	BB	1.5565	1.14024e5	1013.50983	50.2104
Totals :				2.27092e5	3152.12531	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   20
Injection Date  : 2/9/2022 9:24:37 AM                   Inj :   1
                                                  Inj Volume : 2.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-02-09 08-51-22\column6 1%IPA 99% hexane 60min-0.
                  5mL.M
Last changed    : 2/9/2022 8:51:30 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-02-09 08-51-22\column6 1%IPA 99% hexane 60min-0.
                  5mL.M (Sequence Method)
Last changed    : 2/9/2022 10:29:10 AM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

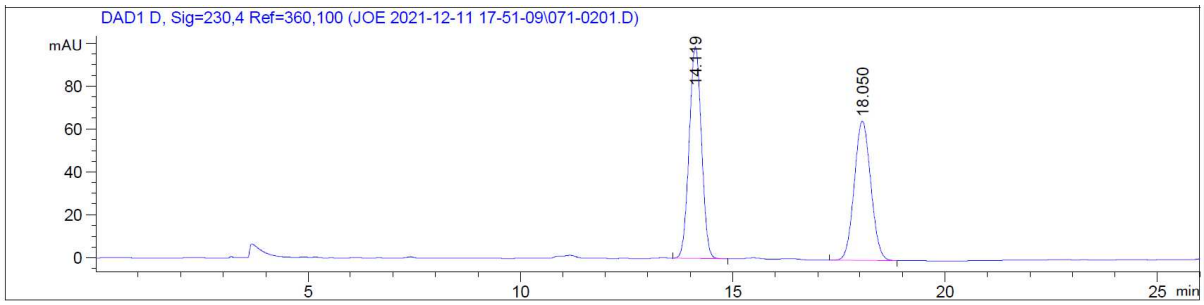
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.890	MF	0.6594	1.25042e4	316.02890	81.4157
2	52.768	BB	1.1437	2854.25684	37.34535	18.5843
Totals :				1.53585e4	353.37425	



Ethyl (2*R*,4*R*)-2-methoxy-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (*endo*-4.6d)

(2-Methoxyethyl)trimethylsilane **4.4d** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure B** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 32 h at 0 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 8.5:1. After purification by silica gel chromatography (hexanes:EtOAc = 9:1), **4.6d** was obtained as a mixture of diastereomers (19.7 mg, 0.08 mmol, 75% yield). Further purification carried out by PTLC using hexanes: EtOAc = 9:1 as the eluent to obtain ***endo*-4.6d** as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.18 (m, 3H), 6.25 – 6.20 (m, 1H), 5.21 (s, 1H), 4.29 (ddd, *J* = 7.1, 3.4, 1.0 Hz, 2H), 3.75 (ddd, *J* = 11.9, 6.2, 2.1 Hz, 1H), 3.56 (s, 3H), 2.23 – 2.15 (m, 1H), 1.89 – 1.79 (m, 1H), 1.36 – 1.28 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.8, 143.2, 140.8, 128.7, 127.6, 126.9, 115.4, 98.4, 61.2, 56.0, 34.7, 34.0, 14.2; **IR** (neat) 2929, 1727, 1646, 1451, 1365, 1269, 1209, 1122, 1087, 1037, 931, 841, 758, 701 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{15}H_{19}O_4$ (MH^+): 263.12779; found: 263.12795; **HPLC** (Chiralpak IC; 1.0:99.0 isopropanol:hexanes, 1.0 mL/min; ***endo*-4.6d:** tr = 14.3 min (major), 18.4 min (minor); 95:5 er); **Specific Rotation: [α]^{25}** + 124.2° (*c* 1.0, CH_2Cl_2).

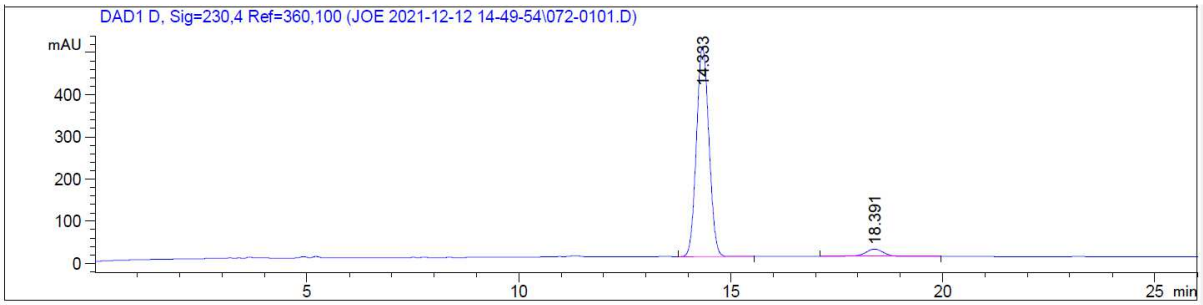
```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                        Location :   71
Injection Date  : 12/11/2021 6:53:35 PM              Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2021-12-11 17-51-09\column4 1%IPA 99% hexane 60min-1.
                  0mL.M (Sequence Method)
Last changed    : 12/11/2021 5:51:17 PM by SYSTEM
Method Info     : Column4 60min-1% iPrOH 99% hexane-1.0mL
```



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

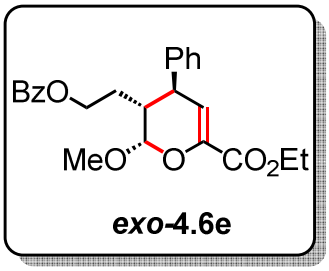
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.119	BB	0.3162	1979.44946	98.58637	52.9995
2	18.050	BB	0.4216	1755.39441	64.89819	47.0005
Totals :				3734.84387	163.48456	

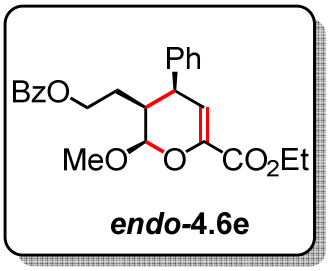
```
================================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                          Location :   72
Injection Date  : 12/12/2021 2:52:05 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2021-12-12 14-49-54\column4 1%IPA 99% hexane 60min-1.
                  0mL.M
Last changed    : 12/12/2021 2:50:01 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2021-12-12 14-49-54\column4 1%IPA 99% hexane 60min-1.
                  0mL.M (Sequence Method)
Last changed    : 12/30/2021 8:05:42 PM by SYSTEM
                  (modified after loading)
Method Info     : Column4 60min-1% iPrOH 99% hexane-1.0mL
```



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

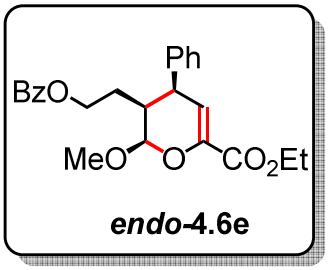
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.333	BB	0.3206	1.02081e4	499.03296	94.9565
2	18.391	BB	0.4703	542.18665	17.45791	5.0435
Totals :				1.07503e4	516.49087	





Ethyl (4*S*)-3-(2-(benzoyloxy)ethyl)-2-methoxy-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (4.6e)

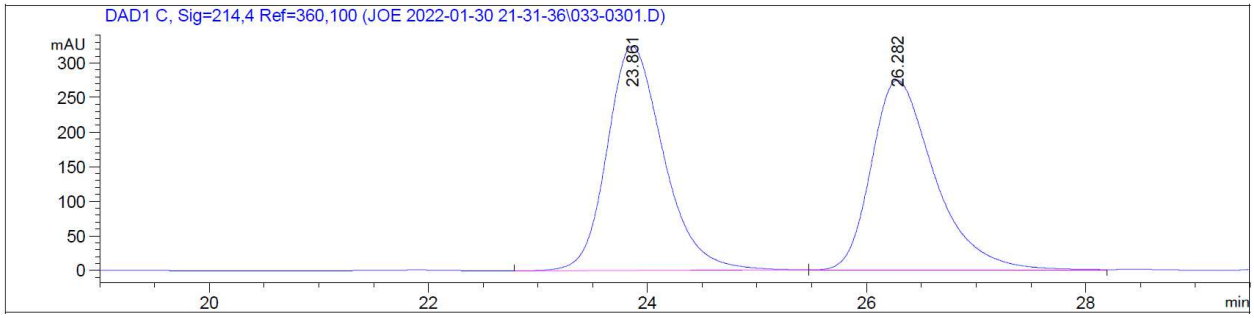
4-Methoxybutyl benzoate **4.4e** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure A** using CH_3Cl solution of [**L1**–Cu]$(SbF_6)_2$ (10 mol %, 10 μmol, 50 mM, 0.2 mL) and using $CHCl_3$ as the solvent and carried out for 48 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 1:1.2. After purification by silica gel chromatography (hexanes:Et_2O = 9:1), **4.6e** was obtained as a mixture of diastereomers (30.8 mg, 0.08 mmol, 75% yield). Further purification carried out by PTLC using hexanes: acetone = 9:1 as the eluent to separate ***endo*-4.6e** and ***exo*-4.6e**. The absolute configuration of ***endo*-4.6e** and ***exo*-4.6e** was determined by analogy to that of ***exo*-4.6g** and by 2D NMR experiments (*see:* **Section C5.2** and **7**).



***endo*-4.6e.** Pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.4 Hz, 2H), 7.57 – 7.51 (m, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.26 (dt, *J* = 14.9, 7.5 Hz, 3H), 6.37 (s, 1H), 5.17 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.13 (d, *J* = 3.7 Hz, 1H), 4.07 – 3.97 (m, 1H), 4.00 – 3.93 (m, 1H), 3.58 (s, 3H), 2.25 (s, 1H), 1.63 – 1.54 (m, 1H), 1.52 – 1.43 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.9, 165.1, 143.6, 142.7, 135.6, 132.7, 132.2, 131.3, 131.1, 131.0, 129.6, 116.0, 103.6, 65.4, 64.0, 58.9, 39.8, 39.8, 27.7, 16.9; **IR** (neat) 2927, 1716, 1648, 1450, 1269, 1091, 1025, 950, 762, 704 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{24}H30NO_6$

($M+NH_4^+$): 428.20676; found: 428.20600; **HPLC** (Chiralpak IA-3; 1.3:98.7 isopropanol:hexanes, mL/min; ***endo*-4.6e:** tr = 23.8 min (major), 26.4 min (minor); 96:4 er); **Specific Rotation: $[\alpha]^{25}$** + 77.8° (*c* 0.33, CH_2Cl_2).

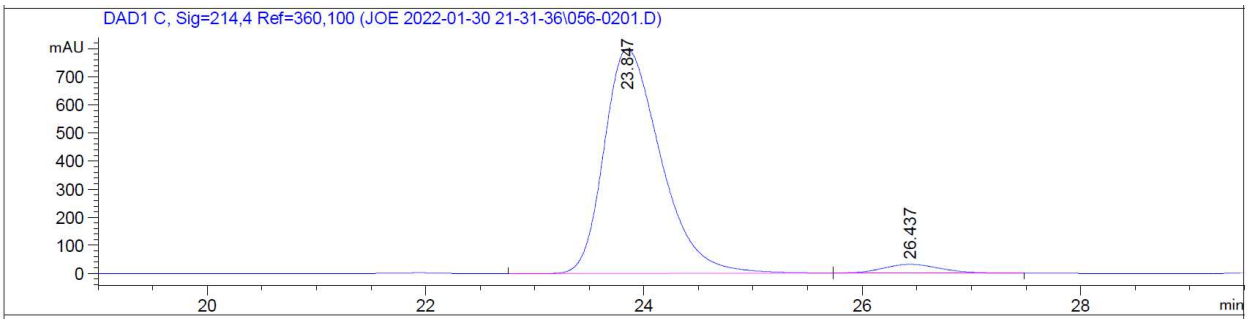
```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                        Location :   33
Injection Date  : 1/31/2022 12:35:46 AM               Inj :   1
                                                Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-30 21-31-36\column6 1.3%IPA 98.7% hexane 90min
                  -0.5mL.M
Last changed    : 1/30/2022 9:31:43 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-30 21-31-36\column6 1.3%IPA 98.7% hexane 90min
                  -0.5mL.M (Sequence Method)
Last changed    : 2/3/2022 6:13:52 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-2.5% iPrOH 99% hexane-0.5mL
```



Signal 3: DAD1 C, Sig=214,4 Ref=360,100

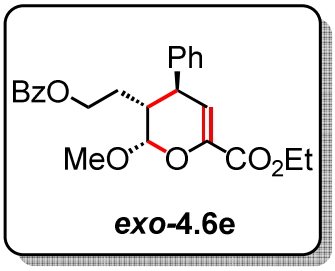
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.861	BB	0.5500	1.16159e4	324.21613	51.4573
2	26.282	BB	0.6064	1.09580e4	274.09985	48.5427
Totals :				2.25739e4	598.31598	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   56
Injection Date  : 1/30/2022 11:04:50 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-30 21-31-36\column6 1.3%IPA 98.7% hexane 90min
                  -0.5mL.M
Last changed    : 1/30/2022 9:31:43 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-30 21-31-36\column6 1.3%IPA 98.7% hexane 90min
                  -0.5mL.M (Sequence Method)
Last changed    : 2/3/2022 6:13:52 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-2.5% iPrOH 99% hexane-0.5mL
```



Signal 3: DAD1 C, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.847	BB	0.5541	2.88187e4	800.23456	96.1733
2	26.437	BB	0.5678	1146.68164	31.42042	3.8267
Totals :				2.99654e4	831.65498	

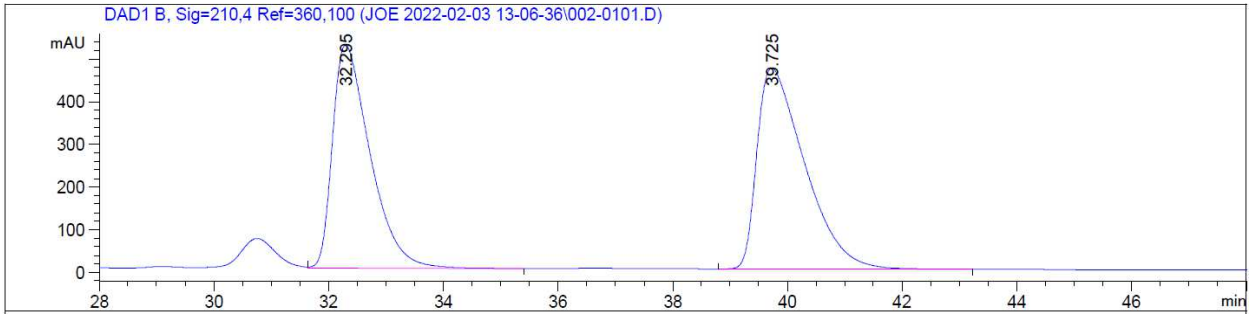


***exo*-4.6e**

***exo*-4.6e.** Pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.37 – 7.27 (m, 2H), 7.26 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.12

(d, J = 2.4 Hz, 1H), 5.23 (d, J = 2.2 Hz, 1H), 4.32 – 4.24 (m, 2H), 4.22 (ddd, J = 11.3, 7.5, 5.6 Hz, 1H), 4.12 (dd, J = 11.7, 5.7 Hz, 1H), 3.52 (s, 3H), 3.41 (dd, J = 11.3, 2.4 Hz, 1H), 2.15 (ddd, J = 9.1, 5.8, 2.0 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.78 – 1.66 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.3, 162.8, 141.8, 139.7, 133.0, 130.0, 129.5, 128.8, 128.5, 128.3, 127.3, 116.1, 99.9, 62.8, 61.2, 56.4, 40.8, 40.1, 28.0, 14.2; **IR** (neat) 2922, 1717, 1451, 1269, 1069, 1026, 945, 761, 711 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{24}H_{30}NO_6$ ($M+NH_4^+$): 428.20676; found: 428.20472; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.5 mL/min; ***exo*-4.6e:** tr = 32.2 min (major), 40.2 min (minor); 83:17 er); **Specific Rotation: [α]^{25}** + 72.4° (*c* 0.30, CH_2Cl_2).

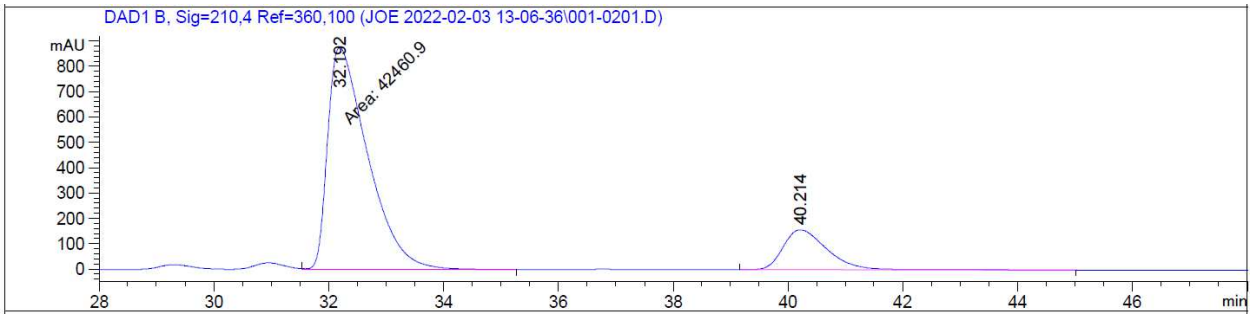
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                          Location :   2
Injection Date  : 2/3/2022 1:08:44 PM                    Inj :   1
                                                 Inj Volume : 2.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-02-03 13-06-36\column6 1%IPA 99% hexane 60min-0.
                  5mL.M
Last changed    : 2/3/2022 1:06:43 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-02-03 13-06-36\column6 1%IPA 99% hexane 60min-0.
                  5mL.M (Sequence Method)
Last changed    : 2/3/2022 6:23:08 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

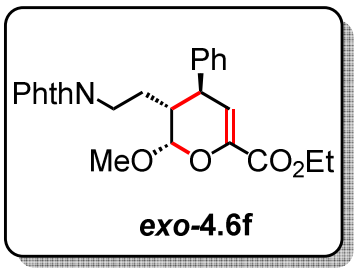
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.295	VB	0.6859	2.37580e4	523.07654	46.6149
2	39.725	BB	0.8699	2.72086e4	471.02768	53.3851
Totals :				5.09666e4	994.10422	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   1
Injection Date  : 2/3/2022 2:09:39 PM                  Inj :   1
                                                 Inj Volume : 2.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-02-03 13-06-36\column6 1%IPA 99% hexane 60min-0.
                  5mL.M
Last changed    : 2/3/2022 1:06:43 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-02-03 13-06-36\column6 1%IPA 99% hexane 60min-0.
                  5mL.M (Sequence Method)
Last changed    : 2/3/2022 6:23:08 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```

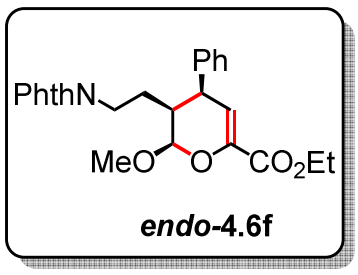


Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.192	FM	0.8063	4.24609e4	877.67993	83.3132
2	40.214	BB	0.8246	8504.51563	158.35249	16.6868
Totals :				5.09654e4	1036.03242	



***exo*-4.6f**

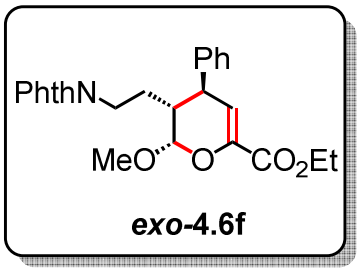


***endo*-4.6f**

Ethyl (4*S*)-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-methoxy-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (4.6f)

2-(4-Methoxybutyl)isoindoline-1,3-dione **4.4f** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.30 mmol, 3.0 equiv.)

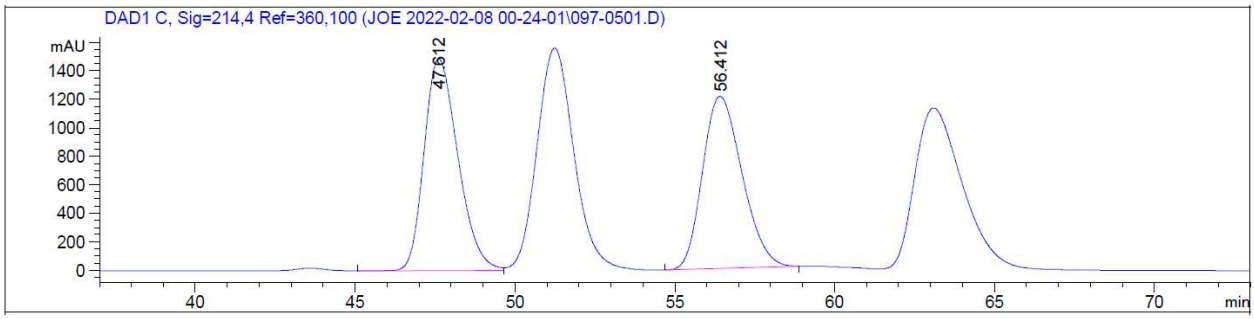
following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (10 mol %, 10 μmol, 50 mM, 0.2 mL) and carried out for 48 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 1:1.4. After purification by silica gel chromatography (hexanes:EtOAc = 3:1), **4.6f** was obtained as a mixture of diastereomers (33.5 mg, 0.08 mmol, 77% yield). Further purification carried out by PTLC using CH_2Cl_2 as the eluent to separate ***exo*-4.6f** and ***endo*-4.6f**. The absolute configuration of ***exo*-4.6f** and ***endo*-4.6f** was determined by analogy to that of ***exo*-4.6g** and by 2D NMR experiments (*see:* **Section C5.2** and **C7**).



***exo*-4.6f**

***exo*-4.6f.** Colorless solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.77 (dd, J = 5.4, 3.1 Hz, 2H), 7.69 (dd, J = 5.5, 3.0 Hz, 2H), 7.23 (t, J = 7.4 Hz, 2H), 7.18 – 7.14 (m, 3H), 6.08 (d, J = 2.5 Hz, 1H), 5.22 (d, J = 2.4 Hz, 1H), 4.26 (dd, J = 7.2, 5.4 Hz, 2H), 3.54 (s, 3H), 3.50 (t, J = 6.9 Hz, 2H), 3.38 (dd, J = 11.3, 2.5 Hz, 1H), 1.99 – 1.94 (m, 1H), 1.81 – 1.75 (m, 1H), 1.74 – 1.67 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.0, 162.8, 141.6, 139.7, 133.8, 132.0, 128.7, 128.4, 127.1, 123.2, 116.0, 100.0, 61.2, 56.5, 40.7, 40.5, 35.8, 27.9, 14.2; **IR** (neat) 1707, 1394, 1368, 1270, 1123, 1096, 1068, 721, 703 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{25}H_{29}N_2O_6$ (MH^+): 453.20201; found: 453.20177; **HPLC** (Chiralpak IC; 10.0:90.0 isopropanol:hexanes, 0.5 mL/min; ***exo*-4.6f:** tr = 47.4 min (major), 56.3 min (minor); 85:15 er); **Specific Rotation: [α]^{25}** + 94.3° (*c* 0.66, CH_2Cl_2).

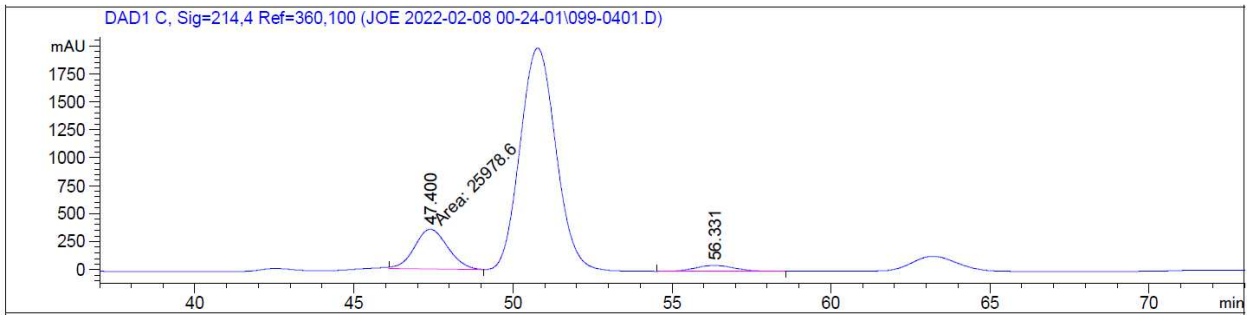
```
Acq. Operator   : SYSTEM                          Seq. Line :   5
Acq. Instrument : Wasa_LC1                        Location :   97
Injection Date  : 2/8/2022 6:30:12 AM                  Inj :   1
                                                Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-02-08 00-24-01\column4 10%IPA 90% hexane 90min-0.
                  5mL.M
Last changed    : 2/8/2022 12:24:09 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-02-08 00-24-01\column4 10%IPA 90% hexane 90min-0.
                  5mL.M (Sequence Method)
Last changed    : 2/8/2022 5:58:01 PM by SYSTEM
                  (modified after loading)
Method Info     : Column4 60min-10% iPrOH 90% hexane-1.0mL
```



Signal 3: DAD1 C, Sig=214,4 Ref=360,100

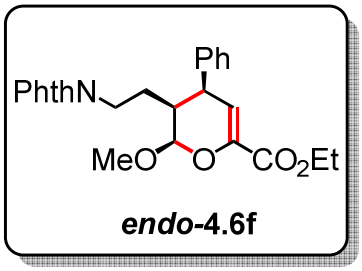
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.612	BV	1.1507	1.09602e5	1489.11267	51.3325
2	56.412	BB	1.3375	1.03912e5	1208.06116	48.6675
Totals :				2.13515e5	2697.17383	

Acq. Operator : SYSTEM
Seq. Line : 4
Acq. Instrument : Wasa_LC1
Location : 99
Injection Date : 2/8/2022 4:59:12 AM
Inj : 1
Inj Volume : 4.000 µl
Acq. Method : C:\Chem32\1\Data\JOE 2022-02-08 00-24-01\column4 10%IPA 90% hexane 90min-0.5mL.M
Last changed : 2/8/2022 12:24:09 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-02-08 00-24-01\column4 10%IPA 90% hexane 90min-0.5mL.M (Sequence Method)
Last changed : 2/8/2022 6:02:02 PM by SYSTEM
(modified after loading)
Method Info : Column4 60min-10% iPrOH 90% hexane-1.0mL



Signal 3: DAD1 C, Sig=214,4 Ref=360,100

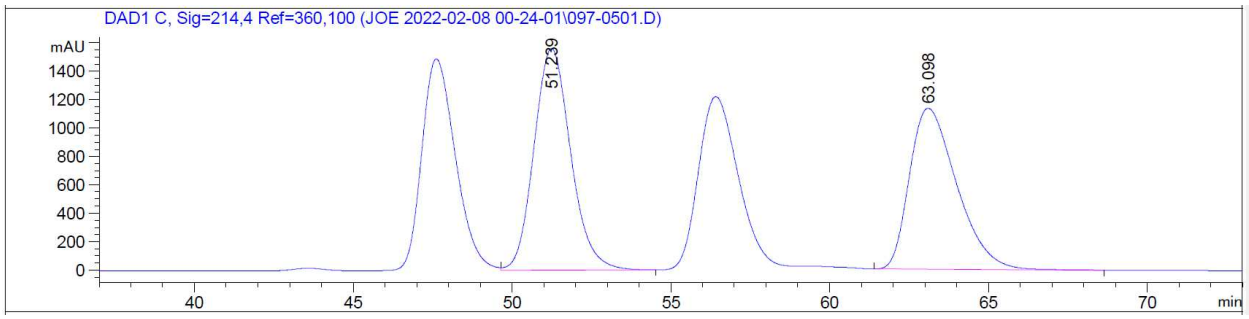
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.400	MM	1.2157	2.59786e4	356.16177	85.1362
2	56.331	BB	1.3003	4535.56836	53.00752	14.8638
Totals :				3.05141e4	409.16929	



***endo*-4.6f**

***endo*-4.6f.** Colorless solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.68 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.24 (d, *J* = 7.4 Hz, 2H), 7.19 – 7.14 (m, 3H), 6.33 (s, 1H), 5.23 (d, *J* = 2.4 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.05 (dd, *J* = 6.2, 2.6 Hz, 1H), 3.59 (s, 3H), 3.42 – 3.37 (m, 1H), 3.32 – 3.26 (m, 1H), 2.09 – 2.02 (m, 1H), 1.49 – 1.43 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.1, 162.5, 141.0, 139.9, 133.8, 132.0, 128.6, 128.4, 126.8, 123.1, 113.4, 101.2, 61.3, 56.3, 38.0, 37.2, 36.2, 25.2, 14.3; **IR** (neat) 1709, 1395, 1365, 1130, 1111, 1088, 1024, 720, 703 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{25}H_{29}N_2O_6$ (MH^+): 453.20201; found: 453.19971; **HPLC** (Chiralpak IC; 10.0:90.0 isopropanol:hexanes, 0.5 mL/min; ***endo*-4.6f:** tr = 14.3 min (major), 18.4 min (minor); 92:8 er); **Specific Rotation: [α]^{25}** + 9.8° (*c* 0.40, CH_2Cl_2).

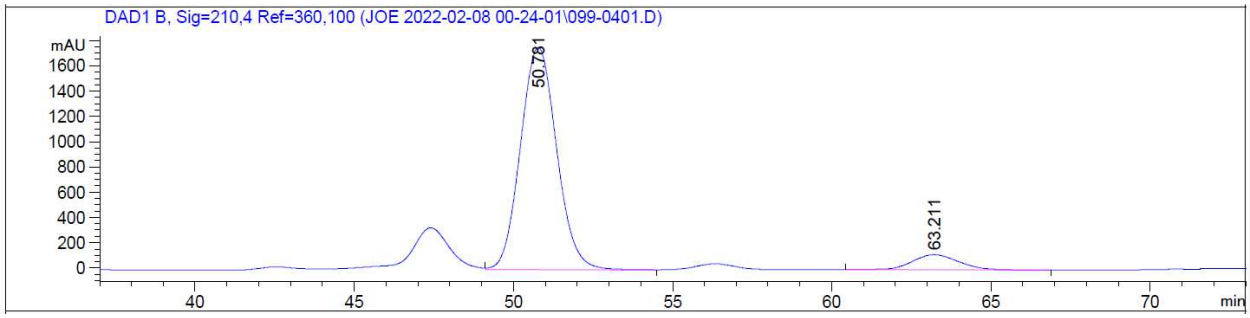
```
Acq. Operator   : SYSTEM                          Seq. Line :   5
Acq. Instrument : Wasa_LC1                        Location :   97
Injection Date  : 2/8/2022 6:30:12 AM                  Inj :   1
                                                Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-02-08 00-24-01\column4 10%IPA 90% hexane 90min-0.
                  5mL.M
Last changed    : 2/8/2022 12:24:09 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-02-08 00-24-01\column4 10%IPA 90% hexane 90min-0.
                  5mL.M (Sequence Method)
Last changed    : 2/8/2022 5:58:01 PM by SYSTEM
                  (modified after loading)
Method Info     : Column4 60min-10% iPrOH 90% hexane-1.0mL
```



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

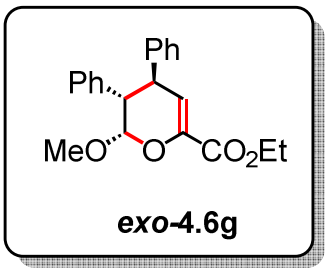
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.240	VB	1.2519	1.10768e5	1374.87354	51.7187
2	63.098	BB	1.5820	1.03406e5	998.71320	48.2813
Totals :				2.14174e5	2373.58673	

Acq. Operator : SYSTEM
Seq. Line : 4
Acq. Instrument : Wasa_LC1
Location : 99
Injection Date : 2/8/2022 4:59:12 AM
Inj : 1
Inj Volume : 4.000 µl
Acq. Method : C:\Chem32\1\Data\JOE 2022-02-08 00-24-01\column4 10%IPA 90% hexane 90min-0.5mL.M
Last changed : 2/8/2022 12:24:09 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-02-08 00-24-01\column4 10%IPA 90% hexane 90min-0.5mL.M (Sequence Method)
Last changed : 2/8/2022 6:02:02 PM by SYSTEM
(modified after loading)
Method Info : Column4 60min-10% iPrOH 90% hexane-1.0mL

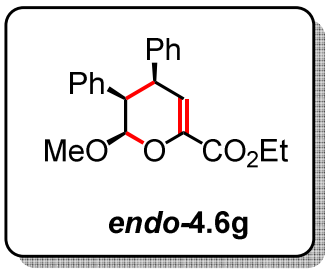


Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.781	VB	1.2320	1.39081e5	1759.84241	92.0273
2	63.211	BB	1.5301	1.20493e4	119.32039	7.9727
Totals :				1.51131e5	1879.16280	



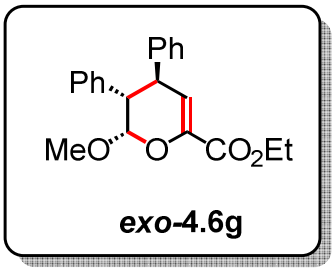
***exo*-4.6g**



***endo*-4.6g**

Ethyl (4*S*)-2-methoxy-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (4.6g)

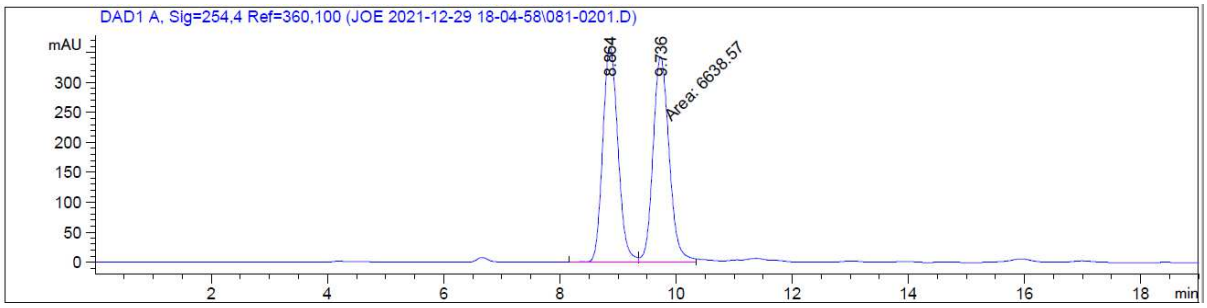
(2-Methoxyethyl)benzene **4.4g** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (10 mol %, 10 μmol, 50 mM, 0.2 mL) and carried out for 32 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 1:4.0. After purification by silica gel chromatography (hexanes:Et_2O = 1:1), **4.6g** was obtained as a mixture of diastereomers (24.4 mg, 0.07 mmol, 72% yield). Further purification carried out by silica gel chromatography using CH_2Cl_2 as the eluent to separate ***exo*-4.6g** and ***endo*-4.6g**. The absolute configuration ***exo*-4.6g** was assigned based on X-ray crystallography data (*see:* **Sections C5.2**, **C7** and **C8**).



***exo*-4.6g**

***exo*-4.6g.** Colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 – 7.07 (m, 8H), 7.05 – 6.96 (m, 2H), 6.29 (d, *J* = 2.3 Hz, 1H), 5.17 (d, *J* = 2.1 Hz, 1H), 4.31 (dd, *J* = 7.0, 5.8 Hz, 2H), 4.00 (dd, *J* = 12.1, 2.3 Hz, 1H), 3.50 (s, 3H), 3.12 (dd, *J* = 12.1, 2.1 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.8, 141.3, 139.9, 137.8, 129.3, 128.3, 128.2, 128.0, 127.0, 126.7, 116.6, 101.4, 61.2, 56.4, 50.4, 40.9, 14.2; **IR** (neat) 1725, 1648, 1452, 1268, 1220, 1122, 1081, 1046, 982, 942, 757, 699, 540 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{21}H_{23}O_4$ (MH^+): 339.15909; found: 339.15919; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.4 mL/min; ***exo*-4.6g:** tr = 9.6 min (major), 8.9 min (minor); 95:5 er); **Specific Rotation: [α]^{25}** + 298.3° (*c* 0.50, CH_2Cl_2).

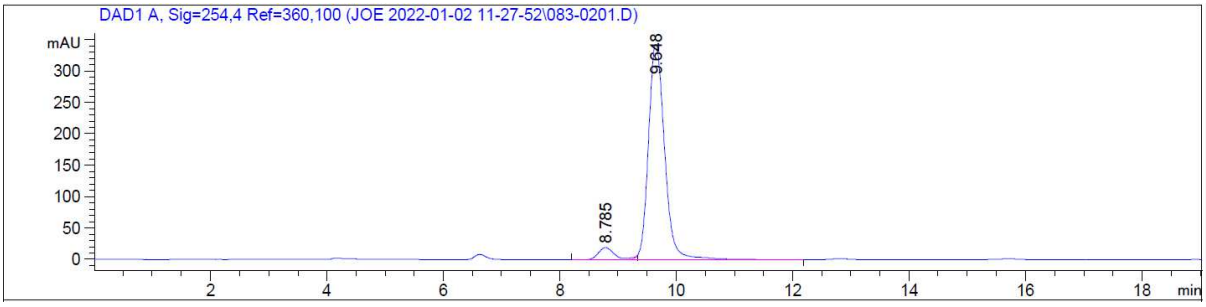
```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                        Location :   81
Injection Date  : 12/29/2021 6:38:05 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-0.
                  5mL.M
Last changed    : 12/29/2021 6:05:05 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 1/2/2022 12:23:29 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 30min-1% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

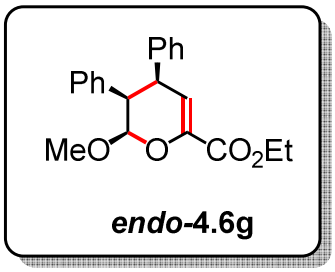
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.864	BV	0.2864	6557.48682	360.25223	49.6928
2	9.736	MF	0.3222	6638.56885	343.40610	50.3072
Totals :				1.31961e4	703.65833	

```
Acq. Operator   : SYSTEM                          Seq. Line :  2
Acq. Instrument : Wasa_LC1                         Location :  83
Injection Date  : 1/2/2022 11:55:18 AM                 Inj :  1
                                                  Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2022-01-02 11-27-52\column6 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 1/2/2022 11:28:00 AM by SYSTEM
Method Info     : Column6 30min-1% iPrOH 99% hexane-0.5mL
```



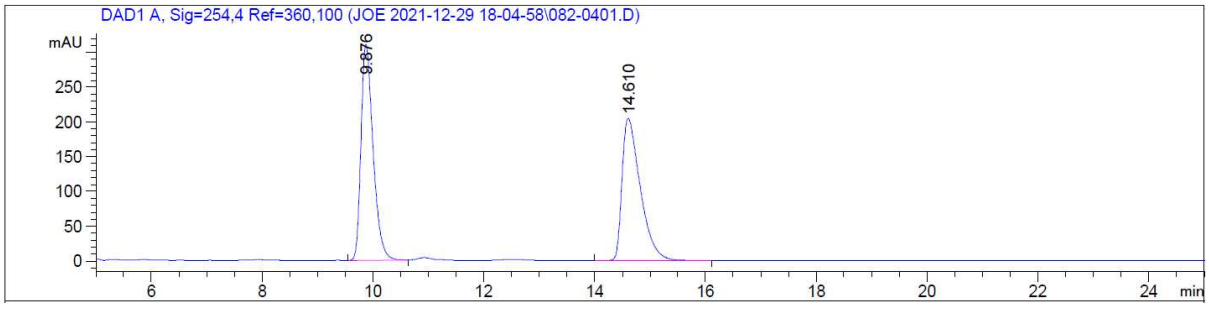
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.785	BV E	0.2968	372.76501	19.34634	5.3204
2	9.648	VB R	0.2995	6633.50732	343.22040	94.6796
Totals :				7006.27234	362.56674	



***endo*-4.6g**. Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.8, 6.2 Hz, 2H), 7.22 – 7.13 (m, 4H), 7.03 – 6.99 (m, 2H), 7.00 – 6.93 (m, 2H), 6.28 (d, *J* = 2.9 Hz, 1H), 5.14 (d, *J* = 7.5 Hz, 1H), 4.31 (dd, *J* = 11.5, 7.2 Hz, 2H), 3.75 (dd, *J* = 9.0, 2.9 Hz, 1H), 3.48 (s, 3H), 3.02 (dd, *J* = 9.1, 7.5 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 162.5, 142.1, 141.3, 139.4, 128.5, 128.3, 128.0, 128.0, 126.9, 126.9, 115.1, 103.9, 61.3, 56.7, 51.9, 46.5, 14.2; **IR** (neat) 1724, 1648, 1452, 1264, 1217, 1126, 1079, 986, 754, 697, 543 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{21}H_{26}NO_4$ ($M+NH_4^+$): 356.18563; found: 356.18543; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.4 mL/min; ***endo*-4.6g**: tr = 14.8 min (major), 9.9 min (minor); 96:4 er); **Specific Rotation: [α]^{25}** + 204.9° (*c* 0.50, CH_2Cl_2).

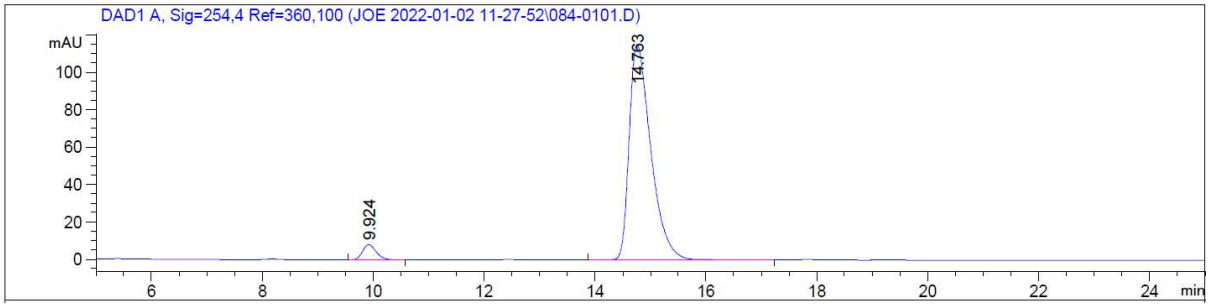
```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                          Location :   82
Injection Date  : 12/29/2021 7:40:03 PM                 Inj :   1
                                                Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-1.
                  0mL.M
Last changed    : 12/29/2021 6:05:05 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-1.
                  0mL.M (Sequence Method)
Last changed    : 1/2/2022 12:24:58 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

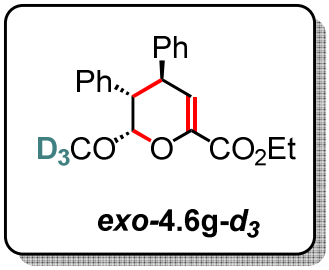
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.876	BB	0.2325	4697.50293	310.50125	50.2214
2	14.610	BB	0.3438	4656.08154	204.35304	49.7786
Totals :				9353.58447	514.85429	

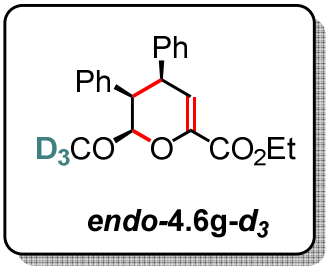
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   84
Injection Date  : 1/2/2022 11:29:18 AM                 Inj :   1
                                                 Inj Volume : 8.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-02 11-27-52\column6 1%IPA 99% hexane 30min-1.
                  0mL.M
Last changed    : 1/2/2022 11:50:23 AM by SYSTEM
                  (modified after loading)
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-02 11-27-52\column6 1%IPA 99% hexane 30min-1.
                  0mL.M (Sequence Method)
Last changed    : 1/2/2022 12:19:40 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

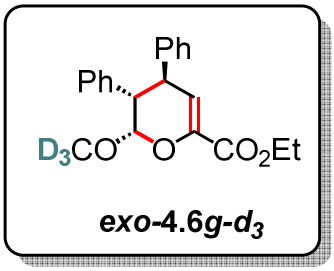
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.924	BB	0.2654	144.31721	8.27965	4.4096
2	14.763	BB	0.4146	3128.49536	115.27300	95.5904
Totals :				3272.81258	123.55266	





Ethyl (4*S*)-2-(methoxy-*d*$_3$)-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (4.6g-*d*$_3$)

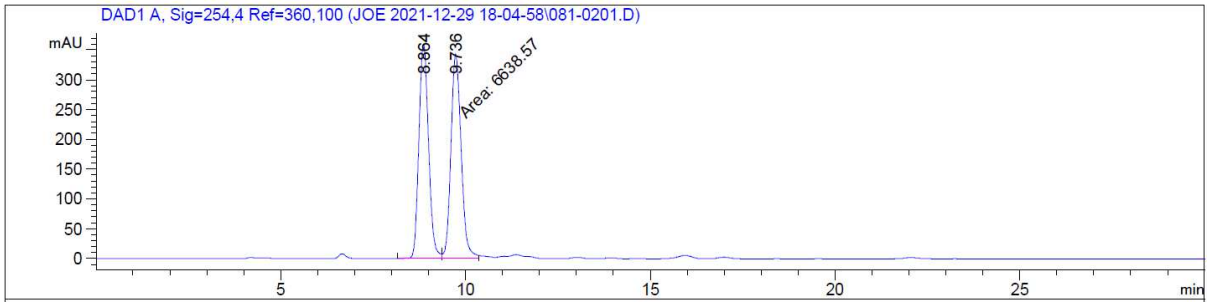
(2-(Methoxy-*d*$_3$)ethyl)benzene **4.4g-*d*$_3$** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (10 mol %, 10 μmol, 50 mM, 0.2 mL) and carried out for 32 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 1:4.0. After purification by silica gel chromatography (hexanes:Et_2O = 1:1), **4.6g-*d*$_3$** was obtained as a mixture of diastereomers (23.2 mg, 0.07 mmol, 68% yield). Further purification carried out by silica gel chromatography using CH_2Cl_2 as the eluent to separate ***exo*-4.6g-*d*$_3$** and ***endo*-4.6g-*d*$_3$**. The absolute configuration of ***exo*-4.6g-*d*$_3$** and ***endo*-4.6g-*d*$_3$** were assigned by analogy to that of ***exo*-** and ***endo*-4.6g** (*see:* **Sections C5.2** and **C7**).



***exo*-4.6g-*d*$_3$.** Colorless solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 4H), 7.17 – 7.12 (m, 3H), 7.11 (d, J = 6.8 Hz, 1H), 7.03 – 6.98 (m, 2H), 6.29 (d, *J* = 2.2 Hz, 1H), 5.17 (d, *J* = 1.9 Hz, 1H), 4.36 – 4.24 (m, 2H), 4.01 (d, *J* = 12.1 Hz, 1H), 3.12 (dd, *J* = 12.1, 2.0 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.8, 141.3, 139.9, 137.8, 129.3, 128.3, 128.2, 128.0, 127.0, 126.7, 116.6, 101.3, 61.2, 50.4, 40.8, 14.2; **IR** (neat) 1723, 1648, 1452, 1265, 1216, 1135, 1083, 1007, 909, 756, 697, 592, 535 cm^{-1}; **HRMS** (AccuTOF) m/z Calcd for $C_{21}H_{20}D_3O_4$ (MH^+): 342.1785; found: 342.1771; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.5 mL/min;

***exo*-4.6g-*d*$_3$**: tr = 9.8 min (major), 9.0 min (minor); 97:3 er); **Specific Rotation: [α]^{25}** + 269.0° (*c* 1.0, CH_2Cl_2).

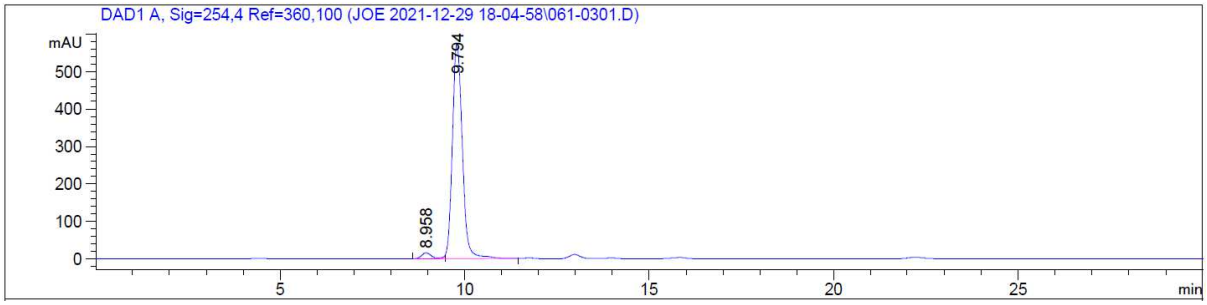
```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                       Location :   81
Injection Date  : 12/29/2021 6:38:05 PM              Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 12/29/2021 6:05:05 PM by SYSTEM
Method Info     : Column6 30min-1% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

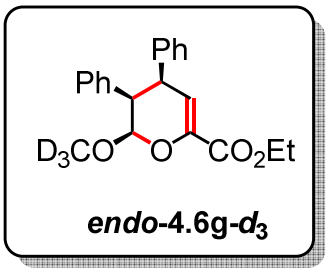
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.864	BV	0.2864	6557.48682	360.25223	49.6928
2	9.736	MF	0.3222	6638.56885	343.40610	50.3072
Totals :				1.31961e4	703.65833	

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                       Location :   61
Injection Date  : 12/29/2021 7:09:02 PM              Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 12/29/2021 6:05:05 PM by SYSTEM
Method Info     : Column6 30min-1% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

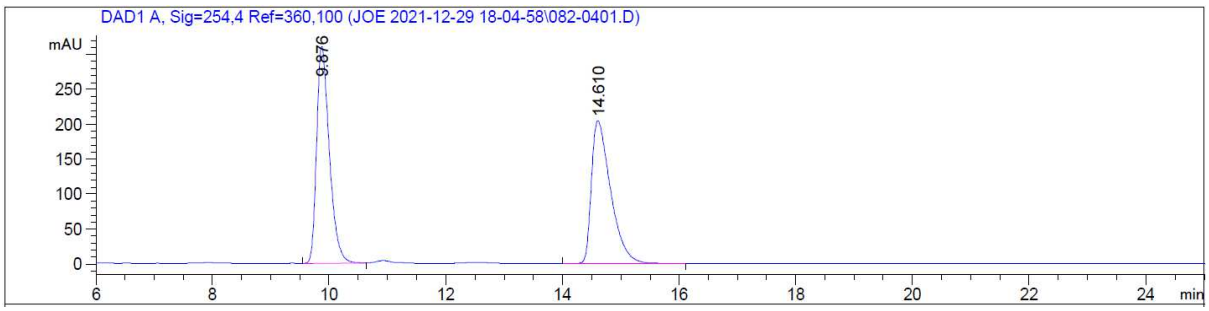
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.958	BV E	0.2845	292.32770	15.89746	2.6403
2	9.794	VB R	0.2933	1.07796e4	573.50244	97.3597
Totals :				1.10720e4	589.39990	



***endo*-4.6g-d_3**

***endo*-4.6g-d_3**. Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 2H), 7.22 – 7.13 (m, 4H), 7.01 (d, *J* = 9.4 Hz, 2H), 6.97 (d, *J* = 10.6 Hz, 2H), 6.28 (d, *J* = 2.1 Hz, 1H), 5.14 (d, *J* = 7.5 Hz, 1H), 4.38 – 4.24 (m, 2H), 3.75 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.02 (t, *J* = 8.3 Hz, 1H), 1.35 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.5, 142.1, 141.4, 139.4, 128.5, 128.3, 128.0, 128.0, 127.0, 126.9, 115.1, 103.8, 61.3, 51.9, 46.5, 14.2; **IR** (neat) 1724, 1649, 1452, 1376, 1272, 1100, 1027, 964, 762, 697, 580 cm^{-1}; **HRMS** (AccuTOF) m/z Calcd for $C_{21}H_{20}D_3O_4$ (MH^+): 342.1785; found: 342.1782. **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 1.0 mL/min; ***endo*-4.6g-d_3**: tr = 15.3 min (major), 10.4 min (minor); 97:3 er); **Specific Rotation: [α]^{25}** + 118.1° (*c* 0.25, CH_2Cl_2).

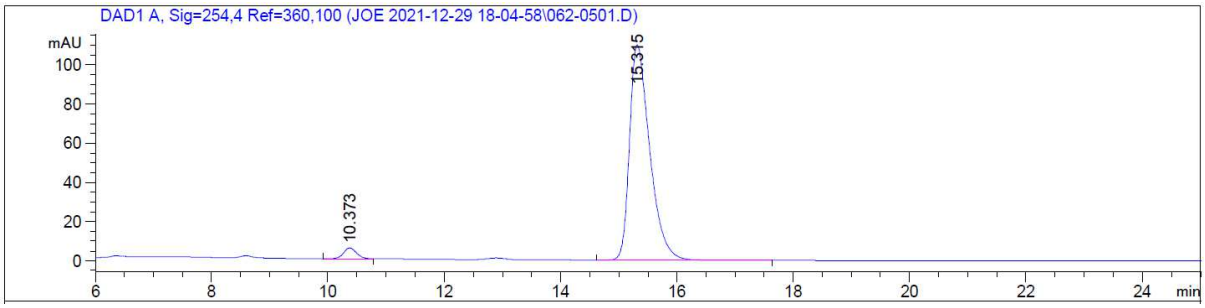
```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                          Location :   82
Injection Date  : 12/29/2021 7:40:03 PM                 Inj :   1
                                                Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-1.
                  0mL.M
Last changed    : 12/29/2021 6:05:05 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-1.
                  0mL.M (Sequence Method)
Last changed    : 12/30/2021 6:31:36 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

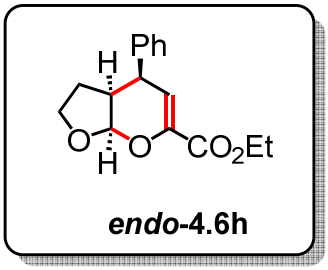
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.876	BB	0.2325	4697.50293	310.50125	50.2214
2	14.610	BB	0.3438	4656.08154	204.35304	49.7786
Totals :				9353.58447	514.85429	

Acq. Operator : SYSTEM
Seq. Line : 5
Acq. Instrument : Wasa_LC1
Location : 62
Injection Date : 12/29/2021 8:11:01 PM
Inj : 1
Inj Volume : 4.000 µl
Acq. Method : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-1.0mL.M
Last changed : 12/29/2021 6:05:05 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2021-12-29 18-04-58\column6 1%IPA 99% hexane 30min-1.0mL.M (Sequence Method)
Last changed : 12/30/2021 6:33:14 PM by SYSTEM
(modified after loading)
Method Info : Column6 60min-1% iPrOH 99% hexane-1.0mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.373	BB	0.2360	86.19542	5.58775	3.1451
2	15.315	BB	0.3658	2654.40723	109.87443	96.8549
Totals :				2740.60265	115.46218	



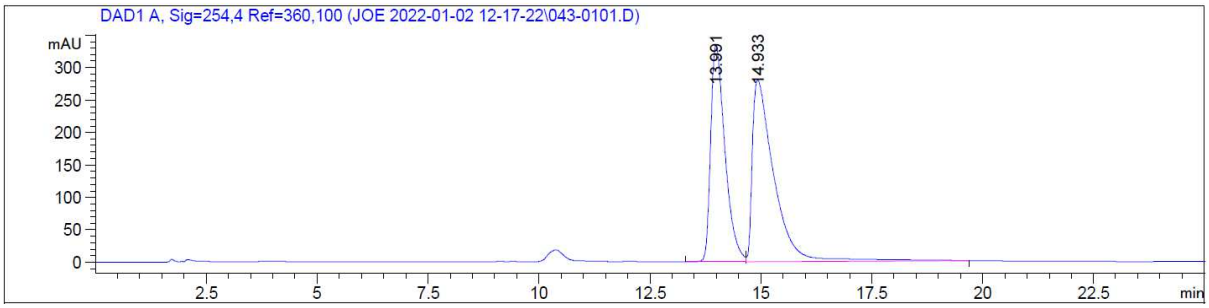
***endo*-4.6h**

Ethyl (3a*S*,4*S*,7a*R*)-4-phenyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (*endo*-4.6h)

Tetrahydrofuran **4.4h** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure B** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 32 h at 22 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 12:1. After purification by silica gel chromatography (hexanes:Et_2O = 2:1), **4.6h** was obtained as a mixture of diastereomers (24.1 mg, 0.09 mmol, 88% yield). Further purification carried out by PTLC using hexanes: Et_2O = 2:1 as the eluent to separate ***endo*-4.6h** as a colorless oil. The absolute configuration of ***endo*-4.6h** was assigned by comparing its optical rotation with the reported molecule.[12] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.23 (d, *J* = 6.0 Hz, 2H), 6.20 – 6.17 (m, 1H), 5.65 (d, *J* = 3.5 Hz, 1H), 4.35 – 4.27 (m, 2H), 4.21 – 4.14 (m, 2H), 3.86 (q, *J* = 9.5, 8.4 Hz, 1H), 2.69 – 2.61 (m, 1H), 1.78 – 1.68 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 4H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.5, 142.7, 141.1, 128.6, 127.6, 127.0, 109.7, 101.2, 68.4, 61.4, 43.9, 38.1, 24.5, 14.2; **IR** (neat) 2977, 1723, 1648, 1450, 1370, 1289, 1237, 1289, 1237,

1128, 1081, 1046, 927, 761, 703 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{17}O_4$ ($M\text{-}H^+$): 273.11214; found: 273.11339; **HPLC** (Chiralpak IA-3; 3.0:97.0 isopropanol:hexanes, 1.0 mL/min; ***endo*-4.6h:** tr = 14.2 min (major), 15.6 min (minor); 95:5 er); **Specific Rotation: $[\alpha]^{25}$** –41.0° (*c* 1.8, CH_2Cl_2).

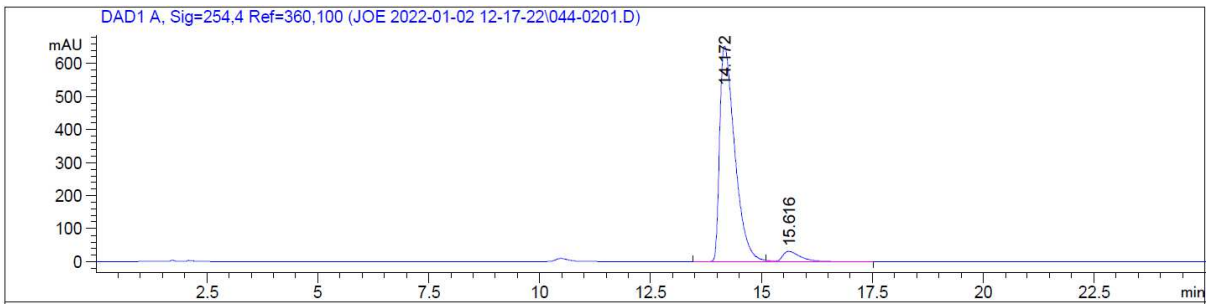
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                       Location :   43
Injection Date  : 1/2/2022 12:18:49 PM               Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2022-01-02 12-17-22\Column6 25min-1% iPrOH 99% hexane-
                  1.0mL.M (Sequence Method)
Last changed    : 1/2/2022 12:17:30 PM by SYSTEM
Method Info     : Column6 25min-1% iPrOH 99% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

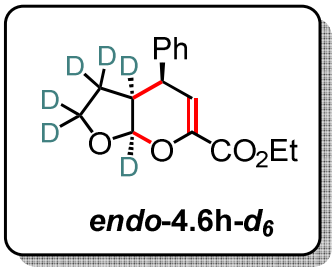
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.991	BV	0.3410	7467.37158	333.80692	44.0352
2	14.933	VB	0.4895	9490.34863	279.92401	55.9648
Totals :				1.69577e4	613.73093	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                       Location :   44
Injection Date  : 1/2/2022 12:44:46 PM               Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2022-01-02 12-17-22\Column6 25min-1% iPrOH 99% hexane-
                  1.0mL.M (Sequence Method)
Last changed    : 1/2/2022 12:17:30 PM by SYSTEM
Method Info     : Column6 25min-1% iPrOH 99% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.172	BV R	0.3604	1.54628e4	652.67261	94.6877
2	15.616	VB E	0.4167	867.51294	31.17502	5.3123
Totals :				1.63303e4	683.84763	



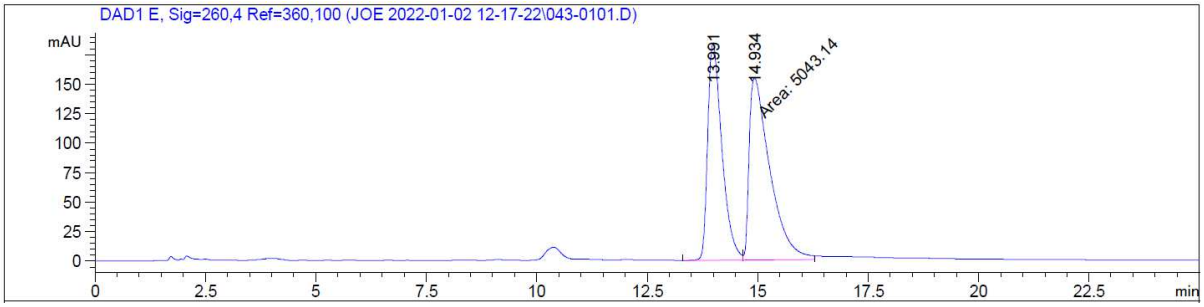
***endo*-4.6h-d_6**

Ethyl (3a*S*,4*S*,7a*R*)-4-phenyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate-2,2,3,3,3a,7a-d_6 (*endo*-4.6h-d_6)

Tetrahydrofuran-d_8 **4.4h-d_8** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure B** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 32 h at 22 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 11:1. After purification by silica gel chromatography (hexanes:Et_2O = 2:1), **4.6h-d_6** was obtained as a mixture of diastereomers (22.4 mg, 0.08 mmol, 80% yield). Further purification carried out by PTLC using hexanes: Et_2O = 1:1 as the eluent to obtain ***endo*-4.6h-d_6** as a colorless oil. The absolute configuration of ***endo*-4.6h-d_6** was determined by analogy to that of ***endo*-4.6h**. **^{1}H NMR**

(500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 1.8 Hz, 2H), 6.18 (d, *J* = 2.7 Hz, 1H), 4.31 (qd, *J* = 7.1, 1.1 Hz, 2H), 4.15 (d, *J* = 2.7 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$**)** δ 162.5, 142.7, 141.1, 128.6, 127.6, 127.0, 109.7, 61.4, 38.0, 14.2; **IR** (neat) 2922, 1724, 1647, 1451, 1370, 1275, 1237, 1197, 1107, 1080, 1050, 1016, 852, 761, 702 cm^{-1}; **HRMS** (AccuTOF) m/z Calcd for $C_{16}H_{13}D_6O_4$ (MH^+): 281.1655; found: 281.1663; **HPLC** (Chiralpak IA-3; 3.0:97.0 isopropanol:hexanes, 1.0 mL/min; ***endo*-4.6h-d_6:** tr = 14.1 min (major), 15.6 min (minor); 95:5 er); **Specific Rotation: [α]^{25}** – 38.9° (*c* 0.50, CH_2Cl_2).

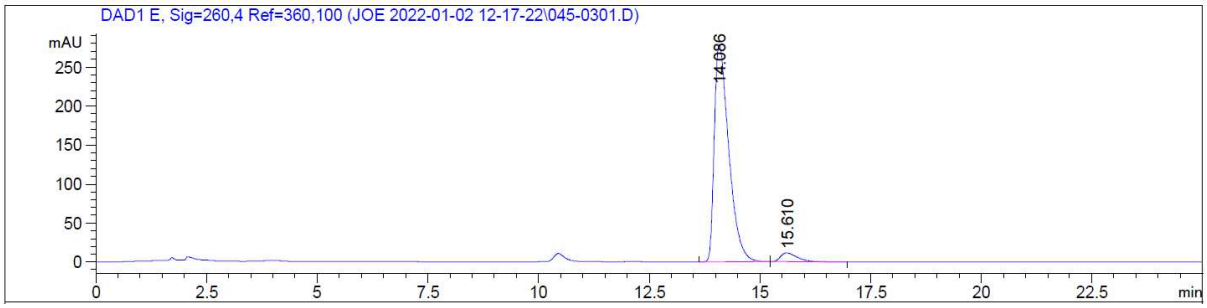
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                       Location :   43
Injection Date  : 1/2/2022 12:18:49 PM                Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2022-01-02 12-17-22\Column6 25min-1% iPrOH 99% hexane-
                  1.0mL.M (Sequence Method)
Last changed    : 1/2/2022 12:17:30 PM by SYSTEM
Method Info     : Column6 25min-1% iPrOH 99% hexane-1.0mL
```



Signal 5: DAD1 E, Sig=260,4 Ref=360,100

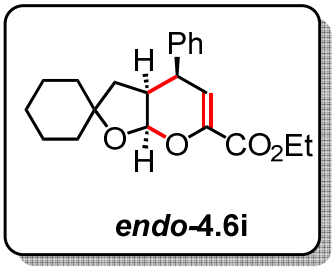
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.991	BV	0.3417	4121.03467	183.68239	44.9690
2	14.934	MF	0.5438	5043.13721	154.55838	55.0310
Totals :				9164.17188	338.24077	

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                       Location :   45
Injection Date  : 1/2/2022 1:10:43 PM                 Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2022-01-02 12-17-22\Column6 25min-1% iPrOH 99% hexane-
                  1.0mL.M (Sequence Method)
Last changed    : 1/2/2022 12:17:30 PM by SYSTEM
Method Info     : Column6 25min-1% iPrOH 99% hexane-1.0mL
```



Signal 5: DAD1 E, Sig=260,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.086	BB	0.3464	6320.27979	278.83862	95.4933
2	15.610	BB	0.4051	298.28085	11.25704	4.5067
Totals :				6618.56064	290.09566	

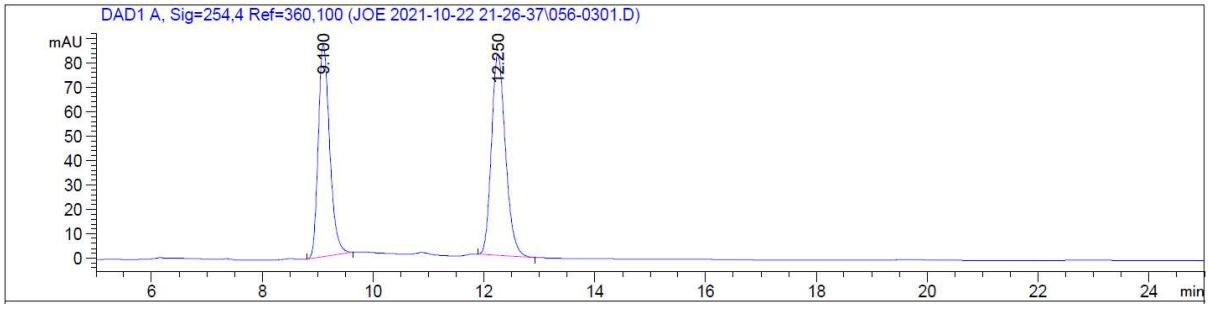


Ethyl (3a'*S*,4'*S*,7a'*R*)-4'-phenyl-3a', 7a'-dihydro-3'*H*, 4'*H*-spiro[cyclohexane-1,2'-furo [2,3-*b*]pyran]-6'-carboxylate (*endo*-4.6i)

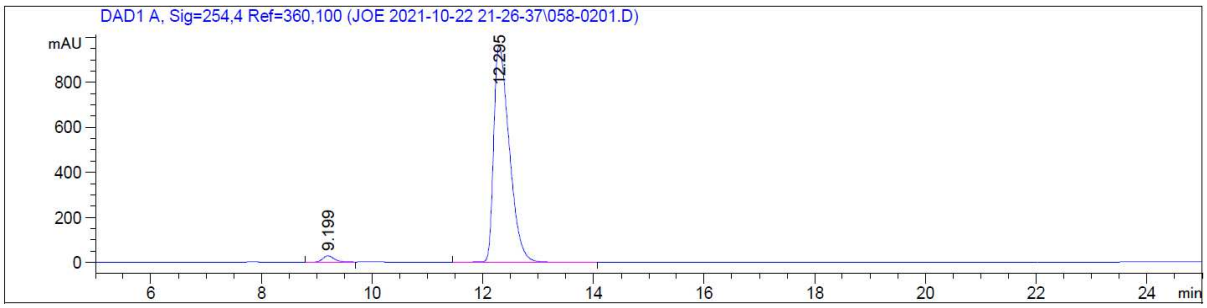
1-Oxaspiro[4.5]decane **4.4i** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure B** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 32 h at –20 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 10:1. After purification by silica gel chromatography (hexanes:Et_2O = 2:1), **4.6i** was obtained as a single diastereomer (24.7 mg, 0.07 mmol, 72%). The absolute configuration of ***endo*-4.6i** was determined by analogy to that of ***endo*-4.6h**. Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.30 – 7.24 (m, 1H), 7.22 (s, 2H), 6.12 (dd, *J* = 2.6, 1.3 Hz, 1H), 5.62 (d, *J* = 3.5 Hz, 1H), 4.35 – 4.22 (m, 2H), 4.08 (dd, *J* = 6.5, 2.6 Hz, 1H), 2.75 (dt, *J* = 6.4, 1.4 Hz, 1H), 1.75 – 1.65

(m, 2H), 1.65 – 1.55 (m, 2H), 1.55 – 1.48 (m, 1H), 1.45 (t, J = 12.5 Hz, 1H), 1.40 – 1.28 (m, 6H), 1.28 – 1.19 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6, 142.9, 141.3, 128.6, 127.6, 126.9, 109.1, 101.3, 86.1, 61.2, 43.4, 40.4, 38.3, 37.3, 34.9, 25.2, 23.8, 23.6, 14.2; **IR** (neat) 2929, 1725, 1648, 1447, 1295, 1224, 1131, 1067, 933, 901, 851, 762, 733, 699 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{21}H_{27}O_4$ (MH^+): 343.19039; found: 343.18855; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 1.0 mL/min; ***endo*-4.6i:** tr = 12.3 min (major), 9.2 min (minor); 98:2 er); **Specific Rotation: [α]^{25}** – 105.9° (*c* 1.0, CH_2Cl_2).

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                        Location :   56
Injection Date  : 10/22/2021 10:29:54 PM              Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2021-10-22 21-26-37\column6 1%IPA 99% hexane 30min-1.
                  0mL.M (Sequence Method)
Last changed    : 10/22/2021 9:26:44 PM by SYSTEM
Method Info     : Column6 60min-1% iPrOH 99% hexane-1.0mL
```

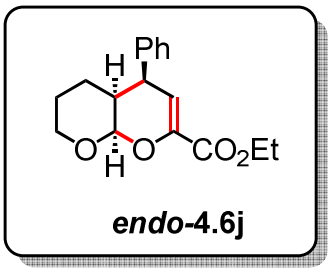



```
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.100 BB    0.2206 1245.06262   87.18157  46.2189
   2  12.250 BB    0.2707 1448.77515   82.56738  53.7811

Totals :                  2693.83777  169.74895

Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                        Location :   58
Injection Date  : 10/22/2021 9:58:57 PM               Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2021-10-22 21-26-37\column6 1%IPA 99% hexane 30min-1.
                  0mL.M (Sequence Method)
Last changed    : 10/22/2021 9:26:44 PM by SYSTEM
Method Info     : Column6 60min-1% iPrOH 99% hexane-1.0mL
```

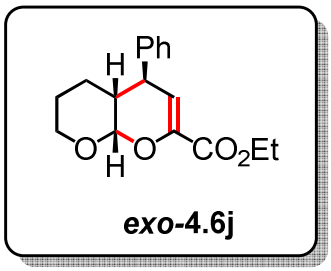


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.199	BB	0.2245	413.20859	28.26831	2.1512
2	12.295	BB	0.2996	1.87948e4	963.27448	97.8488
Totals :				1.92080e4	991.54279	



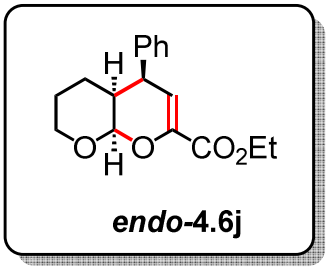
***endo*-4.6j**



***exo*-4.6j**

Ethyl (5*S*)-5-phenyl-3,4,4a,8a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-7-carboxylate (4.6j)

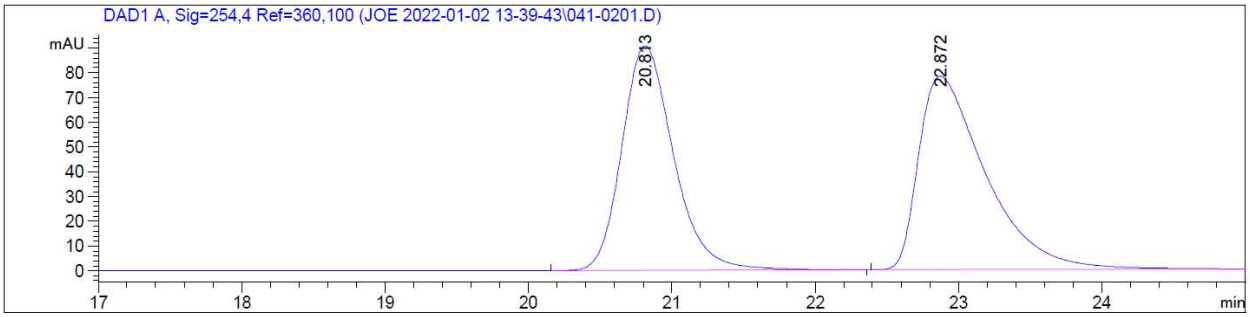
Tetrahydro-2*H*-pyran **4.4j** (0.40 mmol, 4.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure B** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 32 h at 40 °C. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 2.8:1. After purification by silica gel chromatography (hexanes:Et_2O = 2:1), **4.6j** was obtained as a mixture of diastereomers (25.4 mg, 0.09 mmol, 88% yield). Further purification carried out by PTLC using CH_2Cl_2 as the eluent to separate ***endo*-4.6j** and ***exo*-4.6j**. The absolute configuration of ***endo*-4.6j** and ***exo*-4.6j** was determined by analogy to that of ***endo*-4.6h**.



***endo*-4.6j**

***endo*-4.6j.** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 5.9 Hz, 1H), 7.16 (d, *J* = 9.2 Hz, 2H), 6.15 – 6.11 (m, 1H), 5.52 (s, 1H), 4.37 – 4.26 (m, 2H), 4.06 – 3.97 (m, 2H), 3.75 – 3.69 (m, 1H), 2.17 – 2.10 (m, 1H), 1.62 – 1.51 (m, 2H), 1.38 – 1.27 (m, 4H), 0.98 – 0.91 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.3, 143.3, 139.7, 128.4, 128.0, 126.9, 111.0, 98.0, 61.35, 61.30, 42.0, 37.7, 24.7, 19.0, 14.2; **IR** (neat) 2922, 1725, 1647, 1451, 1296, 1242, 1207, 1148, 1078, 988, 912, 860, 762, 703 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{17}H_{24}NO_4$ ($M+NH_4^+$): 306.16998; found: 306.16970; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.5 mL/min; ***endo*-4.6j:** tr = 21.7 min (major), 24.0 min (minor); 94:6 er); **Specific Rotation: [α]^{25}** + 190.1° (*c* 0.25, CH_2Cl_2).

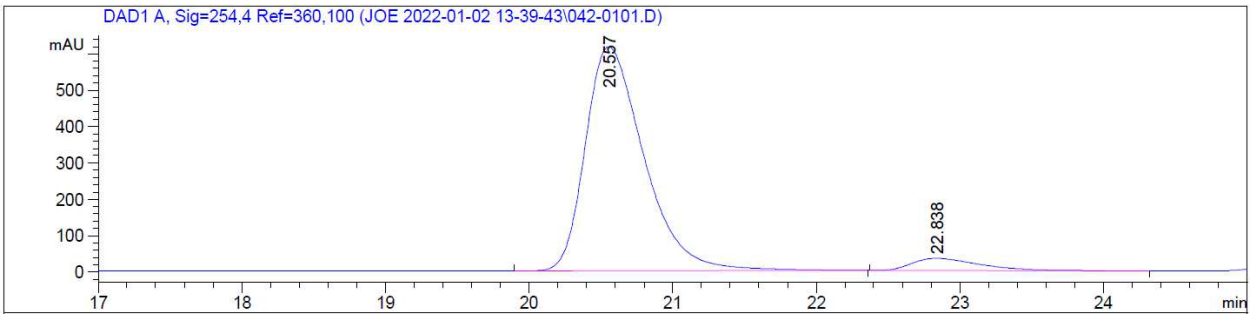
```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                        Location :   41
Injection Date  : 1/2/2022 2:42:51 PM                  Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-02 13-39-43\Column6 60min-1% iPrOH 99% hexane-
                  0.5mL.M
Last changed    : 1/2/2022 1:39:51 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-02 13-39-43\Column6 60min-1% iPrOH 99% hexane-
                  0.5mL.M (Sequence Method)
Last changed    : 2/11/2022 6:26:48 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

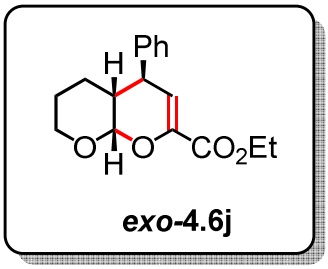
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.813	BB	0.3826	2273.02539	90.63568	47.1732
2	22.872	BB	0.4881	2545.44653	78.13366	52.8268
Totals :				4818.47192	168.76934	

```
Acq. Operator   : SYSTEM                          Seq. Line :  1
Acq. Instrument : Wasa_LC1                         Location :  42
Injection Date  : 1/2/2022 1:41:55 PM                  Inj :  1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2022-01-02 13-39-43\Column6 60min-1% iPrOH 99% hexane-
                  0.5mL.M (Sequence Method)
Last changed    : 1/2/2022 1:39:51 PM by SYSTEM
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

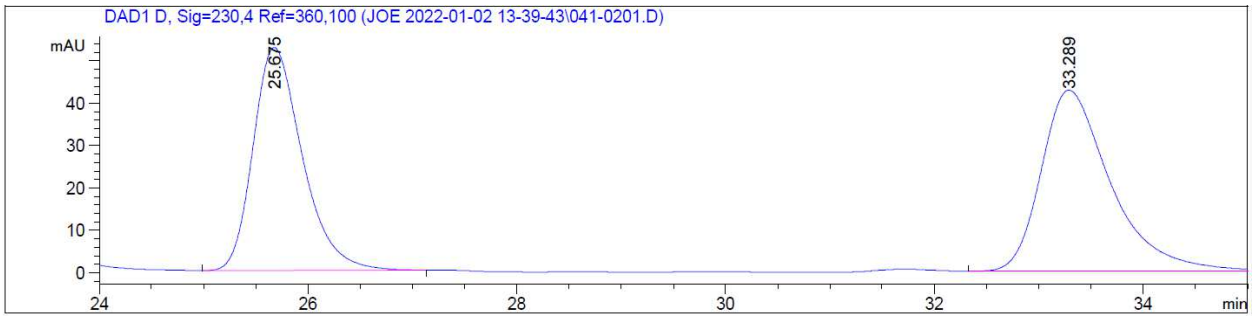
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.557	BB	0.4353	1.74964e4	616.20911	94.0384
2	22.838	BB	0.5060	1109.18567	33.70204	5.9616
Totals :				1.86056e4	649.91115	



***exo*-4.6j**

***exo*-4.6j.** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 (t, 2H), 7.28 – 7.22 (m, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.13 (d, J = 4.1 Hz, 1H), 5.18 (d, J = 2.4 Hz, 1H), 4.36 – 4.24 (m, 2H), 4.10 – 4.02 (m, 1H), 3.73 – 3.66 (m, 1H), 3.46 (t, J = 4.7 Hz, 1H), 2.02 – 1.96 (m, 1H), 1.81 – 1.73 (m, 1H), 1.69 (m, 2H), 1.66 – 1.57 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.4, 143.0, 142.0, 128.7, 128.0, 127.0, 111.2, 95.7, 63.9, 61.3, 41.3, 39.3, 24.4, 23.2, 14.2; **IR** (neat) 2923, 1729, 1648, 1451, 1298, 1229, 1153, 1079, 1042, 934, 763, 702 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{17}H_{24}NO_4$ ($M+NH_4^+$): 306.16998; found: 306.16970; **HPLC** (Chiralpak IA-3; 1.0%:99.0% isopropanol:hexanes, 0.5 mL/min; ***exo*-4.6j:** tr = 25.4 min (major), 33.0 min (minor); 79:21 er); **Specific Rotation: [α]^{25}** + 6.0° (*c* 0.50, CH_2Cl_2).

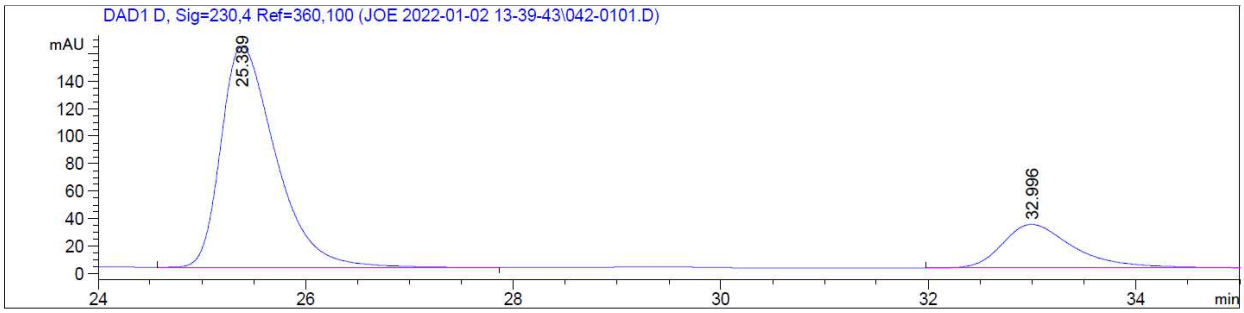
```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                        Location :   41
Injection Date  : 1/2/2022 2:42:51 PM                  Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-02 13-39-43\Column6 60min-1% iPrOH 99% hexane-
                  0.5mL.M
Last changed    : 1/2/2022 1:39:51 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-02 13-39-43\Column6 60min-1% iPrOH 99% hexane-
                  0.5mL.M (Sequence Method)
Last changed    : 2/11/2022 6:26:48 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

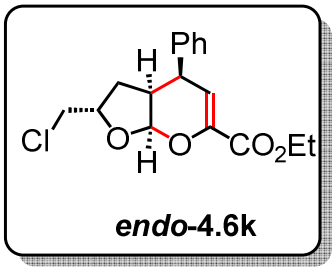
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.675	BB	0.5000	1722.15857	52.59171	46.2203
2	33.289	BB	0.6992	2003.81885	42.72101	53.7797
Totals :				3725.97742	95.31272	

```
Acq. Operator   : SYSTEM                          Seq. Line :  1
Acq. Instrument : Wasa_LC1                         Location :  42
Injection Date  : 1/2/2022 1:41:55 PM                  Inj :  1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2022-01-02 13-39-43\Column6 60min-1% iPrOH 99% hexane-
                  0.5mL.M (Sequence Method)
Last changed    : 1/2/2022 1:39:51 PM by SYSTEM
Method Info     : Column6 60min-1% iPrOH 99% hexane-0.5mL
```



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

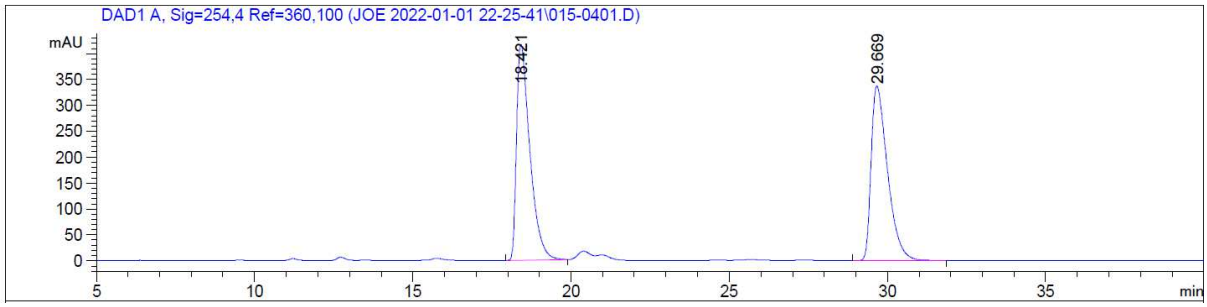
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.389	BB	0.5568	5894.18701	161.11630	79.3987
2	32.996	BB	0.7235	1529.34790	31.77573	20.6013
Totals :				7423.53491	192.89203	



Ethyl (2*S*,3a*S*,4*S*,7a*R*)-2-(chloromethyl)-4-phenyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6k)

(*S*)-2-(Chloromethyl)tetrahydrofuran **4.4k** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate(0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 11:1. After purification by silica gel chromatography (hexanes:Et_2O = 5:1), **4.6k** was obtained as a mixture of diastereomers (29.1 mg, 0.09 mmol, 90% yield). Further purification carried out by PTLC using ethyl ether: hexanes = 1:1 as the eluent to separate ***endo*-4.6k** as a colorless oil. The absolute configuration of ***endo*-4.6k** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 6.9 Hz, 2H), 6.22 – 6.16 (m, 1H), 5.71 (d, *J* = 3.6 Hz, 1H), 4.59 (d, *J* = 6.4 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.14 (dd, *J* = 6.4, 2.4 Hz, 1H), 3.50 (d, *J* = 4.8 Hz, 2H), 2.90 – 2.80 (m, 1H), 1.87 (td, *J* = 12.6, 9.3 Hz, 1H), 1.39 – 1.33 (m, 4H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.3, 143.0, 140.7, 128.7, 127.5, 127.1, 109.6, 101.7, 78.3, 61.4, 46.7, 42.7, 37.9, 27.6, 14.2; **IR** (neat) 1722, 1649, 1451, 1262, 1230, 1126, 1069, 1041, 908, 850, 759, 701 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{17}H_{18}O_4Cl$ ($M-H^+$): 321.08881; found: 321.08851; **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 1.0 mL/min; ***endo*-4.6k:** tr = 18.8 min (minor), 31.3 min (major); >99:1 er;); **Specific Rotation: [α]^{25}** – 83.4° (*c* 1.0, CH_2Cl_2).

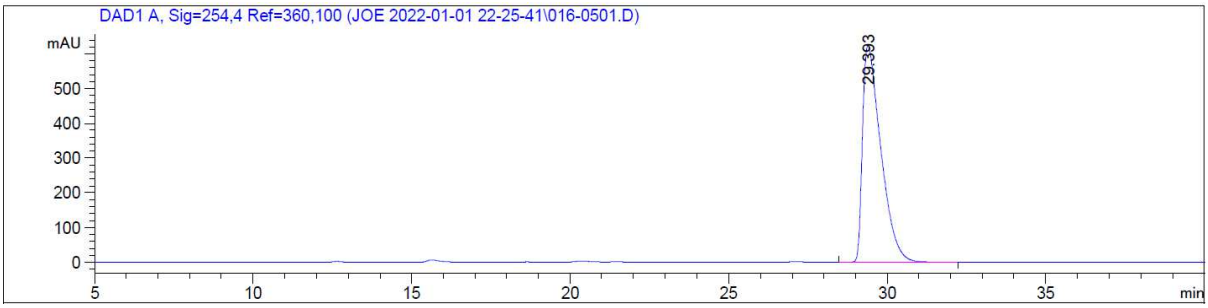
```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                         Location :   15
Injection Date  : 1/2/2022 12:30:46 AM                 Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-01 22-25-41\column6 1%IPA 99% hexane 40min-1.
                  0mL.M
Last changed    : 1/1/2022 10:25:48 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-01 22-25-41\column6 1%IPA 99% hexane 40min-1.
                  0mL.M (Sequence Method)
Last changed    : 1/2/2022 5:10:55 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

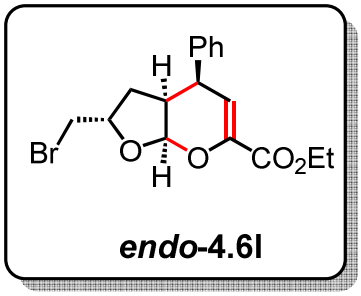
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.421	BB	0.4386	1.21622e4	416.59012	50.1097
2	29.669	BB	0.5471	1.21090e4	337.09290	49.8903
Totals :				2.42712e4	753.68301	

```
Acq. Operator   : SYSTEM                          Seq. Line :   5
Acq. Instrument : Wasa_LC1                         Location :   16
Injection Date  : 1/2/2022 1:11:42 AM                  Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-01-01 22-25-41\column6 1%IPA 99% hexane 40min-1.
                  0mL.M
Last changed    : 1/1/2022 10:25:48 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-01-01 22-25-41\column6 1%IPA 99% hexane 40min-1.
                  0mL.M (Sequence Method)
Last changed    : 1/2/2022 5:12:17 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

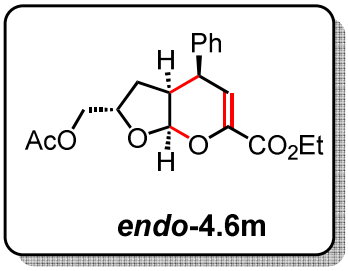
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.393	BB	0.5940	2.50712e4	625.01666	100.0000
Totals :				2.50712e4	625.01666	



***endo*-4.6l**

Ethyl (2*S*,3a*S*,4*S*,7a*R*)-2-(bromomethyl)-4-phenyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6l)

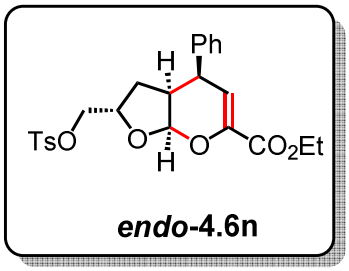
(*S*)-2-(Bromomethyl)tetrahydrofuran **4.4l** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate(0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 11:1. After purification by silica gel chromatography (hexanes:Et_2O = 5:1), **4.6l** was obtained as a mixture of diastereomers (32.7 mg, 0.09 mmol, 89% yield). Further purification carried out by PTLC using ethyl ether:hexanes = 1:1 as the eluent to separate ***endo*-4.6l** as a colorless oil. The absolute configuration of ***endo*-4.6l** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 6.7 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.20 – 6.18 (m, 1H), 5.72 (d, *J* = 3.6 Hz, 1H), 4.62 – 4.56 (m, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.14 (dd, *J* = 6.6, 2.6 Hz, 1H), 3.39 – 3.32 (m, 2H), 2.92 – 2.82 (m, 1H), 1.87 (td, *J* = 12.3, 9.3 Hz, 1H), 1.34 (d, *J* = 23.3 Hz, 4H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.2, 143.0, 140.6, 128.7, 127.5, 127.1, 109.6, 101.8, 78.0, 61.4, 42.6, 37.8, 35.5, 28.6, 14.2; **IR** (neat) 1724, 1649, 1307, 1289, 1262, 1231, 1125, 1090, 1068, 1042, 908, 760, 701 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{17}H_{20}O_4Br$ (MH^+): 367.05395; found: 367.04080; **Specific Rotation: [α]^{25}** – 60.8° (*c* 1.0, CH_2Cl_2).



***endo*-4.6m**

Ethyl (2*S*,3a*S*,4*S*,7a*R*)-2-(acetoxymethyl)-4-phenyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6m)

(*S*)-(Tetrahydrofuran-2-yl)methyl acetate **4.4m** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 13:1. After purification by silica gel chromatography (hexanes:Et_2O = 2:1), **4.6m** was obtained as a mixture of diastereomers (29.5 mg, 0.08 mmol, 85% yield). Further purification carried out by PTLC to separate ***endo*-4.6m** as a yellow oil. The absolute configuration of ***endo*-4.6m** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 6.9 Hz, 2H), 6.18 (dd, *J* = 2.5, 1.3 Hz, 1H), 5.70 (d, *J* = 3.5 Hz, 1H), 4.58 – 4.53 (m, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.15 (dd, *J* = 6.6, 2.6 Hz, 1H), 4.03 – 3.96 (m, 2H), 2.80 – 2.74 (m, 1H), 2.02 (s, 3H), 1.86 (td, *J* = 12.6, 9.5 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.21 – 1.16 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.6, 162.2, 142.9, 140.7, 128.6, 127.4, 127.0, 109.4, 101.5, 76.6, 65.9, 61.3, 42.8, 37.8, 26.7, 20.7, 14.1; **IR (neat)** 1727, 1649, 1366, 1225, 1043, 906, 851, 760, 732, 701, 604 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{19}H_{23}O_6$ (MH^+): 347.14891; found: 347.14881; **Specific Rotation: [α]^{25}** – 20.6° (*c* 1.0, CH_2Cl_2).

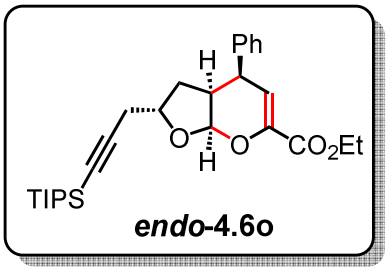


***endo*-4.6n**

Ethyl (2*S*,3a*S*,4*S*,7a*R*)-4-phenyl-2-((tosyloxy)methyl)-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6n)

(*S*)-(Tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate **4.4n** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 13:1. After purification by silica gel chromatography, **4.6n** was obtained as a mixture

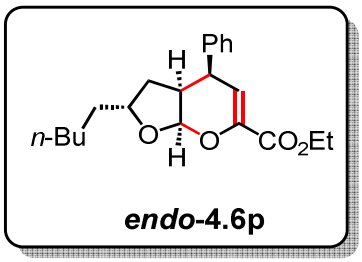
of diastereomers (37.2 mg, 0.08 mmol, 81% yield). Further purification carried out by PTLC using hexanes:ethyl acetate = 2:1 to separate ***endo*-4.6n** as a colorless solid. The absolute configuration of ***endo*-4.6n** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.19 (d, *J* = 7.2 Hz, 2H), 6.16 (dd, *J* = 2.8, 1.3 Hz, 1H), 5.58 (d, *J* = 3.6 Hz, 1H), 4.46 – 4.42 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.09 (dd, *J* = 6.7, 2.7 Hz, 1H), 4.00 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.91 (dd, *J* = 10.7, 3.8 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.43 (s, 3H), 1.79 (td, *J* = 12.6, 9.5 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.24 – 1.19 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.2, 144.9, 142.8, 140.6, 132.5, 129.8, 128.7, 127.8, 127.5, 127.1, 109.6, 101.5, 76.2, 70.9, 61.4, 42.7, 37.8, 26.6, 21.6, 14.2; **IR** (neat) 1723, 1649, 1451, 1359, 1231, 1173, 1056, 958, 811, 734, 701, 662, 553 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{24}H_{27}O_7S$ (MH^+): 459.14720; found: 459.14633; **[α]^{25}** – 21.0° (*c* 1.0, CH_2Cl_2).



Ethyl (2*S*,3a*S*,4*S*,7a*R*)-4-phenyl-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6o)

(*S*)-Triisopropyl(3-(tetrahydrofuran-2-yl)prop-1-yn-1-yl)silane **4.4o** (0.40 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 2.0 equiv.) following the **General Procedure B** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (10 mol %, 10 μmol, 50 mM, 0.2 mL) and carried out for 48 h at 40 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = >20:1. After purification by silica gel chromatography (hexanes:Et_2O = 5:1), ***endo*-4.6o** was obtained as a colorless oil (33.8 mg, 0.07 mmol, 72% yield). The absolute configuration of ***endo*-4.6o** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.3 Hz, 2H), 7.27 – 7.24 (m, 1H), 7.20 (d, *J* = 7.0 Hz, 2H), 6.17 (dd, *J* = 2.7, 1.3 Hz, 1H), 5.67 (d, *J* = 3.5 Hz, 1H), 4.51 – 4.45 (m, 1H), 4.30 (q, *J* = 7.1 Hz, 2H),

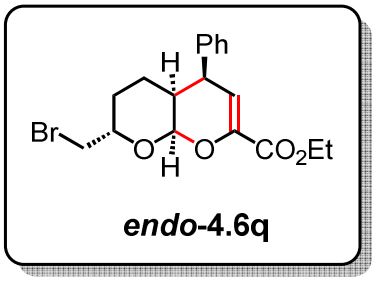
4.11 (dd, J = 6.6, 2.7 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.45 (d, J = 5.6 Hz, 2H), 1.86 (td, J = 12.5, 9.1 Hz, 1H), 1.43 – 1.37 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.02 – 0.94 (m, 21H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.4, 143.0, 140.9, 128.5, 127.5, 126.9, 109.6, 104.3, 101.9, 82.4, 77.3, 61.3, 42.5, 38.0, 28.7, 26.6, 18.5, 14.2, 11.1; **IR** (neat) 2938, 2861, 1726, 1649, 1461, 1365, 1288, 1261, 1230, 1127, 1073, 881, 760, 701, 675 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{28}H_{41}O_4Si$ (MH^+): 469.27686; found: 469.27572; **Specific Rotation: [α]^{25}** – 16.6° (*c* 1.0, CH_2Cl_2).



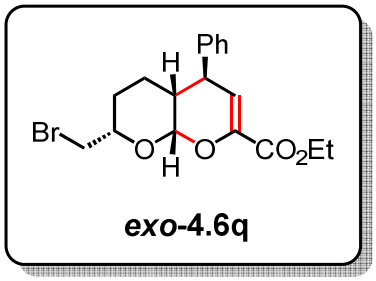
***endo*-4.6p**

Ethyl (2*R*,3a*S*,4*S*,7a*R*)-2-pentyl-4-phenyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6p)

(*R*)-2-Pentyltetrahydrofuran **4.4p** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 48 h at 22 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 15:1. After purification by silica gel chromatography using CH_2Cl_2, ***endo*-4.6p** was obtained as a mixture of diastereomers (19.0 mg, 0.06 mmol, 55% yield). Further purification carried out by PTLC using hexanes:Et_2O = 3:1 to separate ***endo*-4.6p** as a colorless oil. The absolute configuration of ***endo*-4.6p** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 6.9 Hz, 2H), 6.16 (dd, J = 2.6, 1.3 Hz, 1H), 5.65 (d, J = 3.5 Hz, 1H), 4.36 – 4.27 (m, 3H), 4.12 (dd, J = 6.6, 2.6 Hz, 1H), 2.76 – 2.68 (m, 1H), 1.82 (td, J = 12.3, 9.1 Hz, 1H), 1.54 – 1.46 (m, 1H), 1.36 – 1.17 (m, 10H), 1.05 (ddd, J = 12.4, 8.4, 2.7 Hz, 1H), 0.84 (t, J = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.5, 143.2, 141.2, 128.6, 127.6, 126.9, 109.5, 101.6, 79.6, 61.3, 42.7, 38.1, 36.2, 31.7, 29.3, 25.4, 22.5, 14.2, 14.0; **IR** (neat) 2925, 1729, 1649, 1452, 1289, 1260, 1229, 1074, 761, 702 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{21}H_{29}O_4$ (MH^+): 345.20604; found: 345.20577; **Specific Rotation: [α]^{25}** – 27.2° (*c* 0.25, CH_2Cl_2).



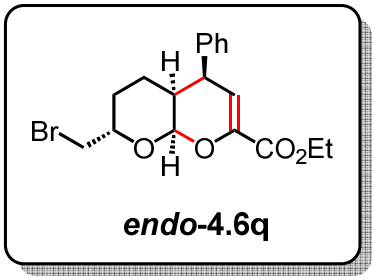
***endo*-4.6q**



***exo*-4.6q**

Ethyl (2*S*,5*S*,)-2-(bromomethyl)-5-phenyl-3,4,4a,8a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-7-carboxylate (4.6q)

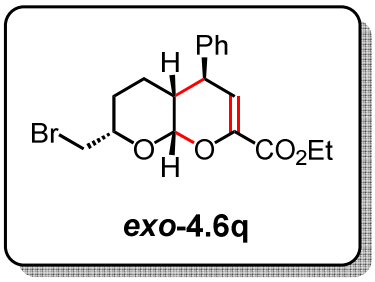
An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added (*S*)-2-(bromomethyl)tetrahydro-2*H*-pyran **4.4q** (0.40 mmol, 4.0 equiv.), ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.), trityl acetate (0.10 mmol, 1.0 equiv.), CH_2Cl_2 solution of [(*R*,*R*)-**L2**–Cu]$(SbF_6)_2$ (10 mol %, 10 μmol, 50 mM, 0.2 mL) and 0.6 mL CH_2Cl_2 under an atmosphere of N_2. The mixture was allowed to stir at 60 °C for 24 hours. Then, the solution was allowed to cool 22 °C and a second batch of trityl acetate (0.10 mmol, 1.0 equiv.) was added. Then, the mixture was stirred at 60 °C for another 24 hours. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 1.7:1. After purification by silica gel chromatography (hexanes:EtOAc = 2:1), **4.6q** was obtained as a mixture of diastereomers (32.8 mg, 0.09 mmol, 86% yield). Further purification carried out by PTLC (hexanes:Et_2O = 1:1) to separate ***endo*-4.6q** and ***exo*-4.6q**. The absolute configuration of ***endo*-4.6q** and ***exo*-4.6q** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra).



***endo*-4.6q**

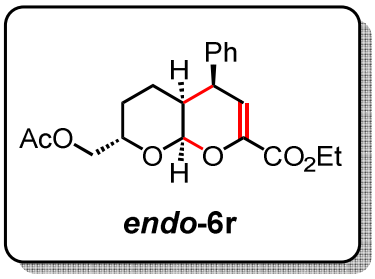
***endo*-4.6q.** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.16 (d, *J* = 6.9 Hz, 2H), 6.14 (s, 1H), 5.57 (s, 1H), 4.36 – 4.26 (m, 2H), 4.4 – 4.19 (m, 1H), 4.06 (dd, *J* = 6.3, 2.4 Hz, 1H), 3.44 (d, *J* = 4.8 Hz, 2H), 2.15 – 2.10 (m, 1H), 1.76 (d, *J* = 9.1 Hz,

1H), 1.44 – 1.39 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.03 – 0.95 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.1, 143.2, 139.6, 128.5, 128.0, 127.0, 111.2, 98.4, 69.3, 61.4, 41.6, 37.1, 35.7, 28.4, 18.6, 14.2; **IR** (neat) 2923, 1723, 1647, 1294, 1243, 1205, 1151, 1091, 1057, 988, 911, 762, 702 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{18}H_{20}O_4Br$ ($M\text{-}H^+$): 379.05395; found: 379.05461; **Specific Rotation: [α]^{25}** −5.2° (*c* 0.50, CH_2Cl_2).

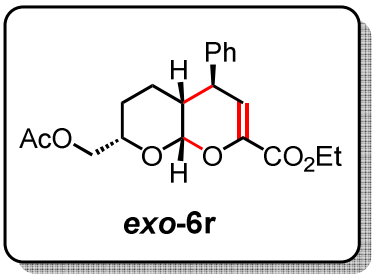


***exo*-4.6q**

***exo*-4.6q.** Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.17 (d, J = 7.6 Hz, 2H), 6.12 (d, J = 5.2 Hz, 1H), 5.23 (s, 1H), 4.36 – 4.27 (m, 2H), 4.21 – 4.17 (m, 1H), 3.43 (d, J = 4.6 Hz, 2H), 3.33 (d, J = 5.3 Hz, 1H), 1.98 (d, J = 12.3 Hz, 1H), 1.89 (dd, J = 12.8, 3.1 Hz, 1H), 1.83 – 1.78 (m, 1H), 1.75 – 1.57 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.2, 143.2, 142.8, 128.7, 127.8, 127.0, 109.3, 94.4, 68.9, 61.4, 44.1, 39.8, 35.7, 28.8, 24.2, 14.2; **IR** (neat) 2927, 1727, 1648, 1451, 1374, 1298, 1276, 1231, 1154, 1089, 1056, 993, 925, 764, 701 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{18}H_{25}NO_4Br$ ($M\text{+}NH_4^+$): 398.09615; found: 398.09655; **Specific Rotation: [α]^{25}** – 128.0° (*c* 0.50, CH_2Cl_2).



***endo*-6r**

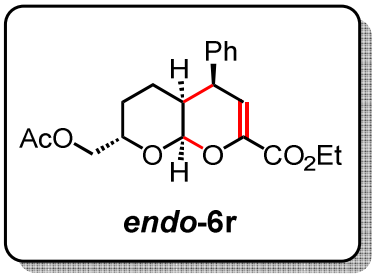


***exo*-6r**

Ethyl (2*S*,5*S*)-2-(acetoxymethyl)-5-phenyl-3,4,4a,8a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-7-carboxylate (4.6r)

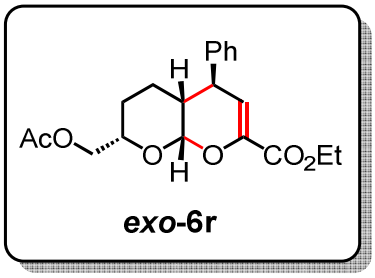
An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added (*S*)-(tetrahydro-2*H*-pyran-2-yl)methyl acetate **4.4r** (0.40 mmol, 4.0 equiv.), ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.), trityl acetate (0.10 mmol, 1.0 equiv.), CH_2Cl_2

solution of [(*R*,*R*)-**L2**–Cu]$(SbF_6)_2$ (10 mol %, 10 μmol, 50 mM, 0.2 mL) and 0.6 mL CH_2Cl_2 under an atmosphere of N_2. The mixture was allowed to stir at 60 °C for 24 hours. The solution was then allowed to cool 22 °C and a second batch of trityl acetate (0.05 mmol, 0.5 equiv.) was added. Subsequently, the mixture was stirred at 60 °C for another 24 hours. Then, the solution was allowed to cool 22 °C and a third batch of trityl acetate (0.05 mmol, 0.5 equiv.) was added. The mixture was stirred at 60 °C for another 24 hours. Then, the solution was allowed to cool 22 °C and the fourth batch of trityl acetate (0.05 mmol, 0.5 equiv.) was added. The mixture was stirred at 60 °C for another 24 hours. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 1:2.3. The combined material was then concentrated *in vacuo* and purified by silica gel silica gel chromatography using hexanes:Et_2O = 2:1 as an eluent to obtain **4.6r** as a mixture of diastereomers (19.1 mg, 0.05 mmo, 53% yield). Further purification carried out by PTLC (hexanes:Et_2O = 2:1) to separate ***endo*-4.6r and *exo*-4.6r**. The absolute configuration of ***endo*-4.6r** and ***exo*-4.6r** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra).



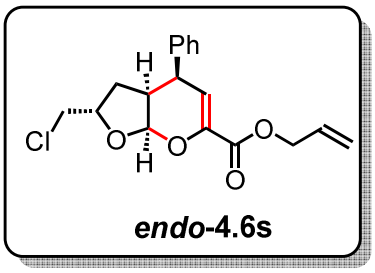
***endo*-6r**

***endo*-4.6r.** Colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.4 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.16 (d, *J* = 7.4 Hz, 2H), 6.13 (s, 1H), 5.57 (s, 1H), 4.35 – 4.22 (m, 3H), 4.15 – 4.04 (m, 3H), 2.15 – 2.06 (m, 4H), 1.61 – 1.55 (m, 1H), 1.43 – 1.32 (m, 5H), 1.02 – 0.95 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.9, 162.2, 143.3, 139.6, 128.5, 128.0, 126.9, 111.1, 98.2, 68.5, 66.4, 61.3, 41.7, 37.2, 26.3, 20.9, 18.6, 14.2; **IR (neat)** 2922, 1731, 1647, 1451, 1364, 1297, 1239, 1153, 1092, 1048, 912, 763, 703 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{20}H_{25}O_6$ (MH^+): 361.16456; found: 361.16372; **Specific Rotation: [α]^{25}** – 9.6° (*c* 0.25, CH_2Cl_2).



***exo*-6r**

***exo*-4.6r.** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.11 (d, *J* = 5.4 Hz, 1H), 5.24 (s, 1H), 4.37 – 4.26 (m, 2H), 4.6 – 4.21 (m, 1H), 4.15 – 4.07 (m, 2H), 3.32 (d, *J* = 5.3 Hz, 1H), 2.07 (s, 3H), 1.98 (d, *J* = 12.2 Hz, 1H), 1.81 – 1.77 (m, 1H), 1.74 – 1.65 (m, 2H), 1.57 – 1.50 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.0, 162.3, 143.3, 142.8, 128.7, 127.8, 127.0, 109.2, 94.2, 68.3, 66.3, 61.4, 44.2, 39.9, 26.8, 24.2, 20.9, 14.2; **IR** (neat) 2925, 1730, 1648, 1365, 1227, 1155, 1089, 1053, 801, 765, 702 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{20}H_{25}O_6$ (MH^+): 361.16456; found: 361.16387; **Specific Rotation: [α]^{25}** – 86.8° (*c* 0.50, CH_2Cl_2).

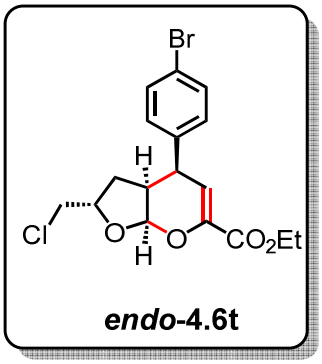


***endo*-4.6s**

Allyl (2*S*,3a*S*,4*S*,7a*R*)-2-(chloromethyl)-4-phenyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6s)

(*S*)-2-(Chloromethyl)tetrahydrofuran **4.4k** (0.20 mmol, 2.0 equiv.) was added to allyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5s** (0.10 mmol, 1.0 equiv.) and trityl acetate(0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 20:1. After purification by silica gel chromatography (hexanes:Et_2O = 5:1), **4.6s** was obtained as a mixture of diastereomers (29.8 mg, 0.09 mmol, 89% yield). Further purification carried out by PTLC using ethyl ether: hexanes = 1:1 as the eluent to separate ***endo*-4.6s** as a colorless oil. The absolute configuration of ***endo*-4.6s** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR**

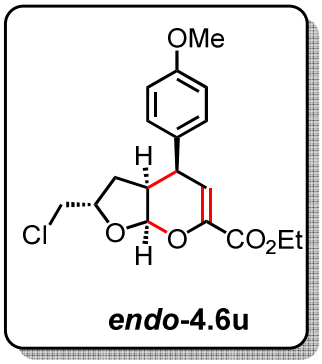
(500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 6.22 (d, *J* = 1.5 Hz, 1H), 6.03 – 5.94 (m, 1H), 5.72 (d, *J* = 3.6 Hz, 1H), 5.38 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.74 (d, *J* = 5.9 Hz, 2H), 4.61 – 4.56 (m, 1H), 4.15 (dd, *J* = 6.6, 2.7 Hz, 1H), 3.50 (d, *J* = 4.8 Hz, 2H), 2.90 – 2.81 (m, 1H), 1.87 (td, *J* = 12.6, 9.2 Hz, 1H), 1.36 (ddd, *J* = 12.9, 8.5, 2.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.9, 142.8, 140.6, 131.8, 128.8, 127.5, 127.1, 118.8, 110.0 101.8, 78.3, 66.0, 46.7, 42.7, 37.9, 27.6; **IR** (neat) 1726, 1648, 1262, 1228, 1126, 1068, 1042, 759, 702 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{18}H_{23}NO_4Cl$ ($M+NH_4^+$): 352.13101; found: 352.13124; **Specific Rotation: [α]^{25}** – 54.4° (*c* 0.50, CH_2Cl_2).



Ethyl (2*S*,3a*S*,4*S*,7a*R*)-4-(4-bromophenyl)-2-(chloromethyl)-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6t)

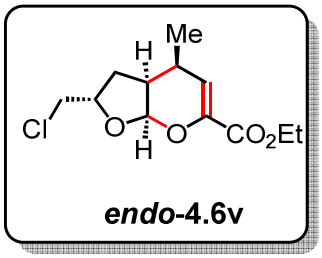
(*S*)-2-(Chloromethyl)tetrahydrofuran **4.4k** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-4-(4-bromophenyl)-2-oxobut-3-enoate **4.5t** (0.10 mmol, 1.0 equiv.) and trityl acetate(0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 13:1. After purification by silica gel chromatography (hexanes:Et_2O = 5:1), **4.6t** was obtained as a mixture of diastereomers (34.6 mg, 0.09 mmol, 86% yield). Further purification carried out by PTLC using Et_2O: hexanes = 1:1 as the eluent to separate ***endo*-4.6t** as a yellow oil. The absolute configuration of ***endo*-4.6t** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.11 (s, 1H), 5.70 (d, *J* = 3.5 Hz, 1H), 4.62 – 4.56 (m, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.10 (dd, *J* = 6.6, 2.7 Hz, 1H), 3.55 – 3.47 (m, 2H), 2.85 – 2.78 (m, 1H), 1.82 (td, *J* = 12.6, 9.3 Hz, 1H), 1.40 – 1.32 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.1, 143.3, 139.7, 131.9, 129.2, 121.0, 108.7, 101.7, 78.2, 61.5, 46.7, 42.5,

37.4, 27.5, 14.2; **IR** (neat) 1724, 1650, 1486, 1366, 1263, 1231, 1070, 1009, 908, 825, 763 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{17}H_{17}O_4ClBr$ ($M\text{-}H^+$): 398.99933; found: 398.99854; **Specific Rotation:** $[\alpha]^{25}$ – 13.2° (*c* 0.50, CH_2Cl_2).



Ethyl (2*S*,3a*S*,4*S*,7a*R*)-2-(chloromethyl)-4-(4-methoxyphenyl)-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6u)

(*S*)-2-(Chloromethyl)tetrahydrofuran **4.4k** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-4-(4-methoxyphenyl)-2-oxobut-3-enoate **4.5u** (0.10 mmol, 1.0 equiv.) and trityl acetate(0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo:exo* = 9.2:1. After purification by silica gel chromatography (hexanes:Et_2O = 5:1), **4.6u** was obtained as a mixture of diastereomers (31.4 mg, 0.09 mmol, 89% yield). Further purification carried out by PTLC using Et_2O: hexanes = 1:1 as the eluent to purify ***endo*-4.6u** as a yellow oil. The absolute configuration of ***endo*-4.6u** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.15 (s, 1H), 5.69 (d, *J* = 3.6 Hz, 1H), 4.60 – 4.55 (m, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.08 (dd, *J* = 6.7, 2.7 Hz, 1H), 3.81 (s, 3H), 3.49 (d, *J* = 4.9 Hz, 2H), 2.84 – 2.78 (m, 1H), 1.86 (td, *J* = 12.6, 9.2 Hz, 1H), 1.40 – 1.36 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.3, 158.6, 142.8, 132.7, 128.5, 114.1, 110.0, 101.7, 78.2, 61.4, 55.2, 46.7, 42.9, 37.1, 27.6, 14.2; **IR** (neat) 2952, 1723, 1649, 1609, 1510, 1461, 1244, 1177, 1036, 831, 749 cm^{-1}. **HRMS** (DART) m/z Calcd for $C_{18}H_{20}O_5Cl$ ($M\text{-}H^+$): 351.09938; found: 351.09932; **Specific Rotation:** $[\alpha]^{25}$ – 29.8° (*c* 1.0, CH_2Cl_2).



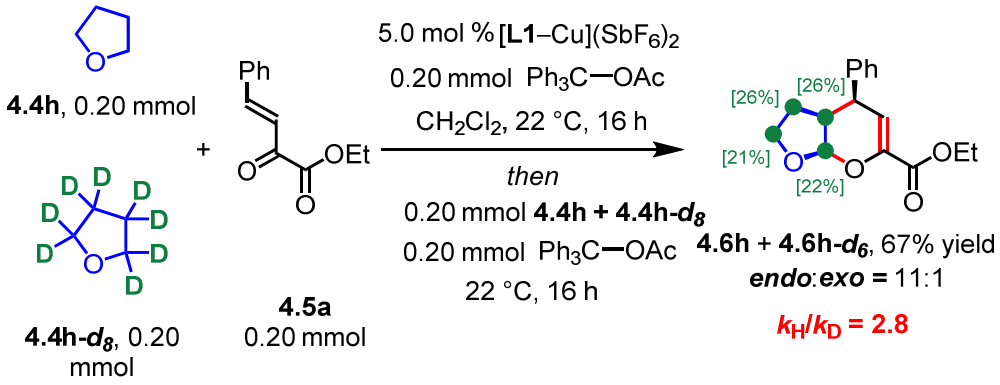
Ethyl (2*S*,3a*S*,4*S*,7a*R*)-2-(chloromethyl)-4-methyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylate (4.6v)

(*S*)-2-(Chloromethyl)tetrahydrofuran **4.4k** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxopent-3-enoate **4.5v** (0.10 mmol, 1.0 equiv.) and trityl acetate (0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. The ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was *endo*:*exo* = 7.3:1. After purification by silica gel chromatography (hexanes:Et_2O = 5:1), **4.6v** was obtained as a mixture of diastereomers (15.2 mg, 0.06mmol, 58% yield). Further purification carried out by PTLC using Et_2O: hexanes = 1:1 as the eluent to separate ***endo*-4.6v** as a colorless oil. The absolute configuration of ***endo*-4.6v** was assigned by 2D NMR experiments (*see:* **Section C7** for NOE spectra). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.80 (s, 1H), 5.57 (d, *J* = 3.7 Hz, 1H), 4.64 – 4.59 (m, 1H), 4.31 – 4.21 (m, 2H), 3.63 – 3.56 (m, 2H), 2.90 – 2.84 (m, 1H), 2.61 – 2.55 (m, 1H), 1.93 – 1.83 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.5, 141.2, 112.6, 101.8, 78.2, 61.3, 46.8, 42.0, 26.7, 26.6, 17.8, 14.2; **IR** (neat) 2959, 1723, 1647, 1292, 1235, 1060, 1015, 858, 760 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{12}H_{18}O_4Cl$ (MH^+): 261.08881; found: 261.08909; **Specific Rotation: [α]^{25}** – 53.6° (*c* 0.25, CH_2Cl_2).

C4 Studies Aimed at Gaining Mechanistic Insights

C4.1 Competition Kinetic Isotope Effect Experiments

In order to determine if the reaction of **4.4h** and **4.5a** proceeds more efficiently than the process involving **4.4h-*d*$_8$,** a competition kinetic isotope effect (KIE) study was conducted.



Experimental Procedure for Measuring the Competition Kinetic Isotope Effect Value

To an oven dried 7 mL vial equipped with a magnetic stir bar, [**L1**–Cu](Cl)$_2$ (*see:* **Section C2.2** for its preparation; 5.2mg, 10 μmol, 5.0 mol %) and CH_2Cl_2 (0.4 mL) were added under an atmosphere of N_2. To this solution, $AgSbF_6$ (6.8 mg, 20 μmol, 10 mol %) was added and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [**L1**–Cu](SbF$_6$)$_2$. Subsequently, to an oven-dried sealed tube equipped with a magnetic stir bar were added **4.4h** (0.20 mmol, 1.0 equiv.), **4.4h-*d*$_8$** (0.20 mmol, 1.0 equiv.), **4.5a** (0.20 mmol, 1.0 equiv.), trityl acetate (0.20 mmol, 1.0 equiv.), [**L1**–Cu](SbF$_6$)$_2$ (0.4 mL of 25 mM solution), and 0.8 mL CH_2Cl_2 under an atmosphere of N_2. The mixture was allowed to stir at 22 °C for 16 hours. Then, a second batch of ethers **4.4h** (0.20 mmol, 1.0 equiv.), **4.4h-*d*$_8$** (0.20 mmol, 1.0 equiv.) and trityl acetate (0.20 mmol, 1.0 equiv.) was added under an atmosphere of N_2. The mixture was stirred at 22 °C for another 16 hours. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. Upon analysis of the sample prepared as described above by ^{1}H NMR spectroscopy, 67% conversion to both **4.6h** and **4.6h-*d*$_6$** were detected where 49.5% of **4.6h** was formed. The combined material was then concentrated *in vacuo* and purified by silica gel chromatography (hexanes:Et_2O = 2:1). A mixture of **4.6h** and **4.6h-*d*$_6$** was obtained (18.4 mg, 67% yield).

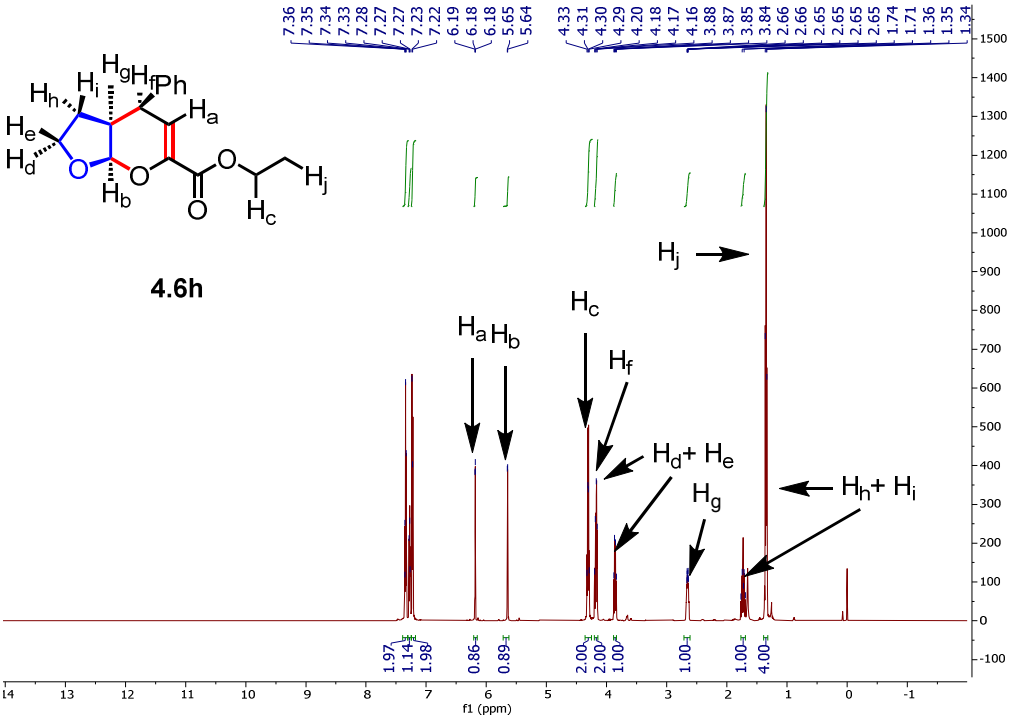


Figure S1: ^{1}H NMR spectrum of **4.6h**

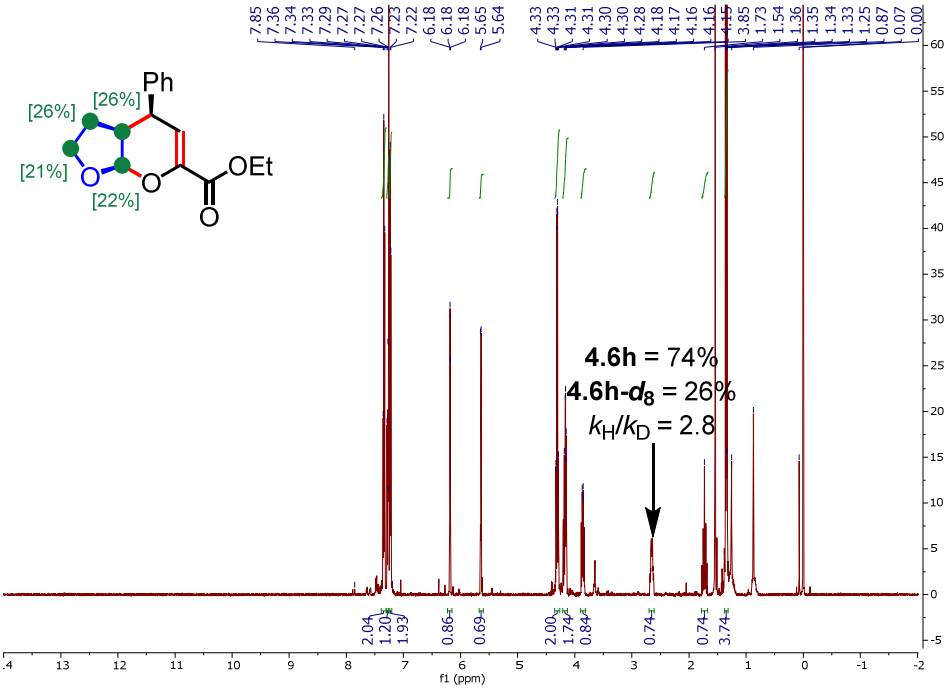


Figure S2: ^{1}H NMR spectrum of the mixture of **4.6h** and **4.6h-*d*$_6$** after competition KIE experiment

C4.2 Studies to Determine the Reversibility of the Hetero Diels-Alder Reaction

To gain a better understanding of the reversibility of the organocopper-catalyzed hetero Diels-Alder reaction, **4.6a** was treated with (*S*)-2-(chloromethyl)tetrahydrofuran **4.4k** in the presence of [**L1**–Cu]$(SbF_6)_2$ and Ph_3COAc. Should this reaction be reversible, the ring-opening of **4.6a** forms a set of enol ether **4.7a** and ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (**S-I**). In the meantime, the oxidation of **4.4k** could generate **4.7l** in situ. The exchange between **4.7a** and **4.7k** results in intermediate **S-II** which could undergo organocopper-catalyzed hetero Diels-Alder reaction to afford **4.6k**, thereby implying the reversibility of this reaction.

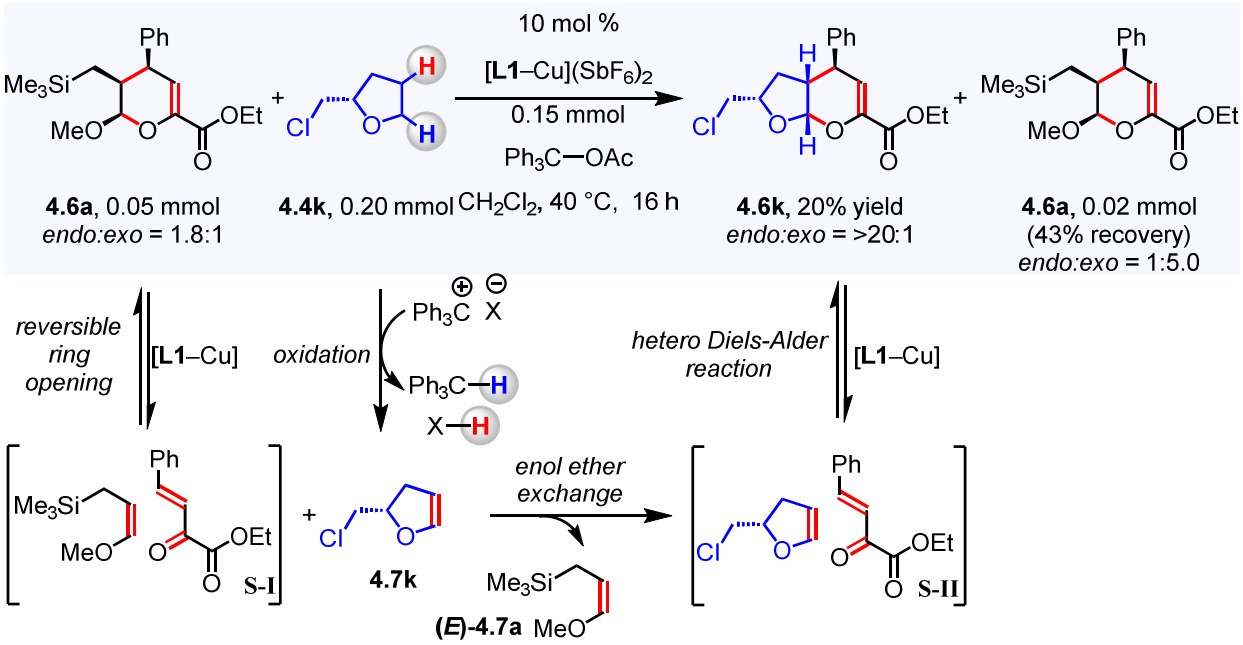


Figure S3: The reaction between **4.6a** and enol ether generated in situ by oxidation of **4.4k**

Procedure for The Reaction Between 4.6a and Enol Ether Generated in situ by Oxidation of 4.4k

To an oven-dried 7 mL vial equipped with a magnetic stir bar, [**L1**−Cu](Cl)$_2$ (*see:* **SI-Section 2.2** for its preparation; 2.6 mg, 5.0 μmol, 10 mol %) and CH_2Cl_2 (0.2 mL) were added under an atmosphere of N_2. To this solution, $AgSbF_6$ (3.4 mg, 10 μmol, 20 mol %) was added, and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [**L1**−Cu](SbF$_6$)$_2$ in CH_2Cl_2. Subsequently, to an oven-dried sealed tube equipped with a magnetic stir bar were added ether **4.4k** (0.20 mmol, 4.0 equiv.), **4.6a** (0.05 mmol, 1.0 equiv.; *endo*:*exo* = 1.8:1), trityl acetate (0.15 mmol, 3.0 equiv.), 0.4 mL CH_2Cl_2, and the solution of [**L1**−Cu](SbF$_6$)$_2$ (5.0 μmol, 10 mol %) in CH_2Cl_2 under an atmosphere of N_2. The resulting solution was allowed to stir at 40 °C for 16 hours. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that **4.6k** was formed in 20% yield (0.02 mmol) while 43% of **4.6a** (0.04 mmol) was recovered (*endo*:*exo* = 1:5.0). Further purification carried out by PTLC (3:1 mixture of hexanes and EtOA was used as the eluent). The formation of **4.6k** and **4.6a** was verified by the ^{1}H NMR analysis of the purified products (See: **SI-Section 3** and **SI-Section 7**).

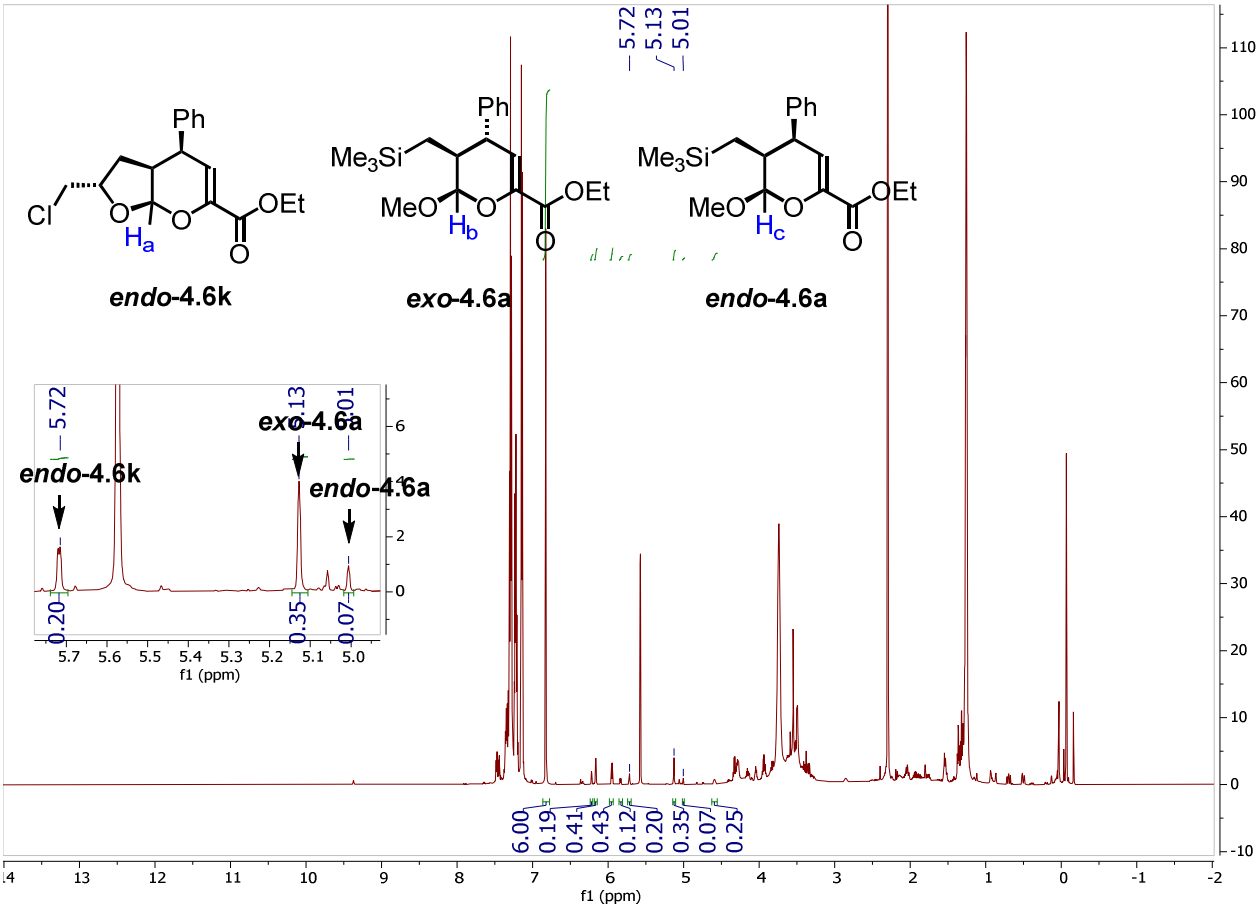
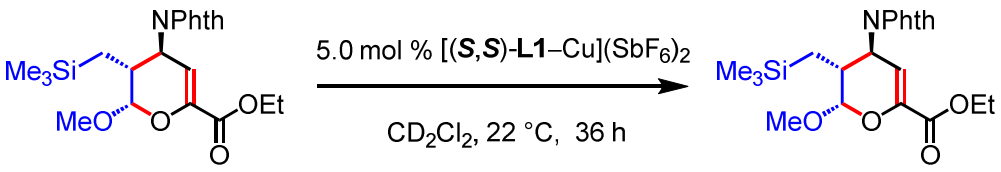


Figure S4: ^{1}H NMR spectrum of crude mixture containing **4.6k** and **4.6a**

C4.3 Studies Aimed at Enhancing the Ratio Between *endo*-4.6b *and exo*-4.6b

Based on the hypothesis that the organocopper catalyzed cycloaddition between the in situ generated enol ethers and β,γ-unsaturated ketoesters is reversible, we carried out studies aimed at converting the 1.2:1 mixture of ***endo*-4.6b** and ***exo*-4.6b**, obtained as described in section **C3**, into the more thermodynamically stable ***exo*-4.6b** predominantly.

C4.3.1 Experiment with [(*S*,*S*)–L1–Cu](SbF$_6$)$_2$

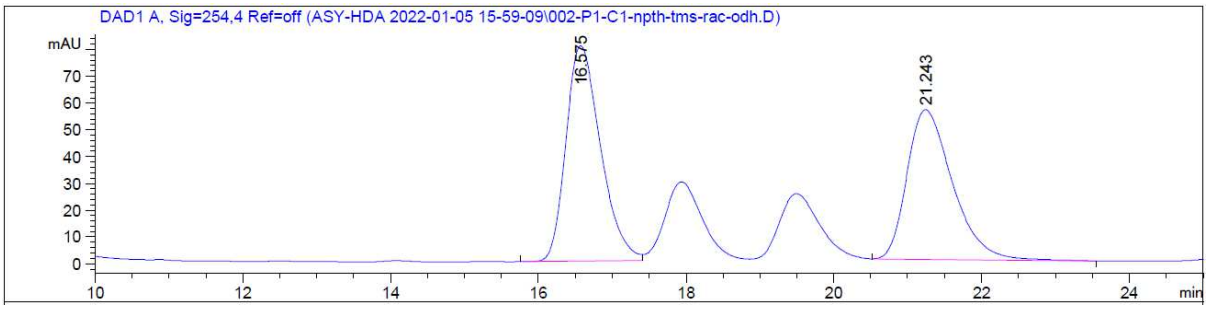


4.6b, 0.10 mmol
endo:exo = 1:2.1
96:4 (***exo***)
95:5 (***endo***)

4.6b, 95% yield
endo:exo = 1:12
93:7 (***exo***)

To a 7 mL oven-dried vial charged with a magnetic stir bar was added [(***S***,***S***)–L1–Cu]$(Cl)_2$ (*see:* **Section C2.2**; 2.6 mg, 5.0 μmol, 5.0 mol %) and CD_2Cl_2 (0.4 mL) under an atmosphere of N_2. To this solution, $AgSbF_6$ (3.4 mg, 10 μmol, 10 mol %) was added and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [(***S***,***S***)–L1–Cu]$(SbF_6)_2$. Subsequently, to a J-Young tube was added [(***S***,***S***)–L1–Cu]$(SbF_6)_2$ (0.4 mL, 5.0 mol %), **4.6b** (41.8 mg, 0.10 mmol), mesitylene (12.0 mg, 0.10 mmol) and diluted to 0.6 mL with CD_2Cl_2. After the J-Young tube was tightly capped with the Teflon plug, the reaction was kept in 22 °C. The mixture was monitored by ^{1}H NMR and after 36 hours (*endo*:*exo* = >1:10 dr) the mixture was filtered through a short plug of silica gel and flashed with 10% methanol in CH_2Cl_2. The resulting solution was then concentrated *in vacuo* and purified by silica gel chromatography (hexanes:EtOAc = 3:1) to afford the **4.6b** in 95% yield (25.7 mg, 0.1 mmol; *endo*:*exo* = 1:12 dr; 93:7 er). **HPLC** (Chiralpak OD-H; 1.0:99.0 isopropanol:hexanes, 0.6 mL/min; ***exo*-4.6b:** tr = 16.3 min (major), 21.1 min (minor); 93:7 er).

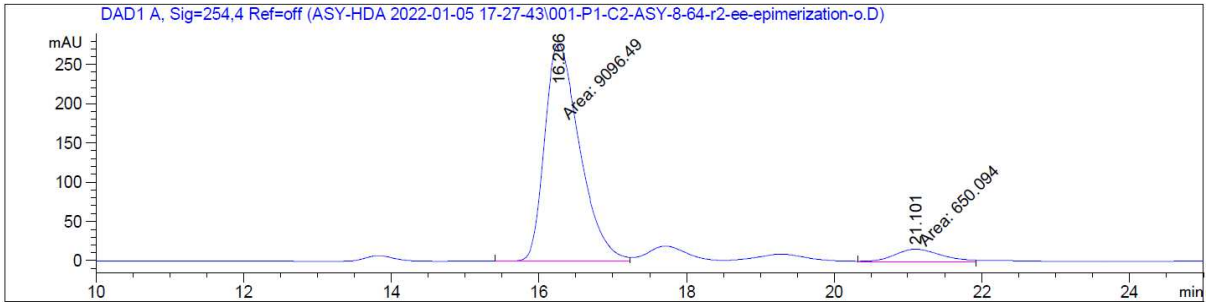
```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : HPLC w FC                        Location :   P1-C-01
Injection Date  : 1/5/2022 4:31:00 PM                   Inj :   1
                                                  Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\ASY-HDA 2022-01-05 15-59-09\ASY-1.0%-0.6ml-30min.M
Last changed    : 1/5/2022 4:40:55 PM by SYSTEM
                  (modified after loading)
Analysis Method : C:\Chem32\1\Data\ASY-HDA 2022-01-05 15-59-09\ASY-1.0%-0.6ml-30min.M (
                  Sequence Method)
Last changed    : 1/5/2022 6:07:29 PM by SYSTEM
                  (modified after loading)
```



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.575	BV	0.4997	2618.79736	80.46603	52.3051
2	21.243	BB	0.6564	2387.97510	55.89736	47.6949
Totals :				5006.77246	136.36340	

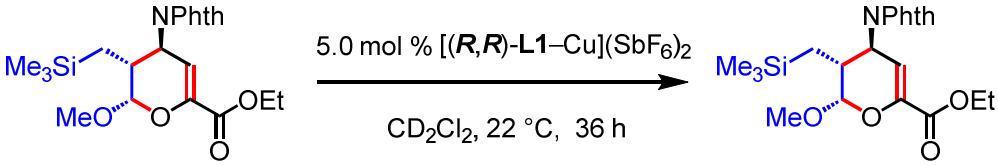
Acq. Operator : SYSTEM
Seq. Line : 1
Acq. Instrument : HPLC w FC
Location : P1-C-02
Injection Date : 1/5/2022 5:28:39 PM
Inj : 1
Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry! Actual Inj Volume : 4.000 µl
Acq. Method : C:\Chem32\1\Data\ASY-HDA 2022-01-05 17-27-43\ASY-1.0%-0.6ml-30min.M
Last changed : 1/5/2022 5:27:45 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\ASY-HDA 2022-01-05 17-27-43\ASY-1.0%-0.6ml-30min.M (Sequence Method)
Last changed : 1/5/2022 6:06:38 PM by SYSTEM (modified after loading)



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.266	MF	0.5486	9096.49121	276.37784	93.3300
2	21.101	MF	0.7048	650.09442	15.37303	6.6700
Totals :				9746.58563	291.75087	

C4.3.2 Experiment with [(*R*,*R*)–L1–Cu](SbF$_6$)$_2$

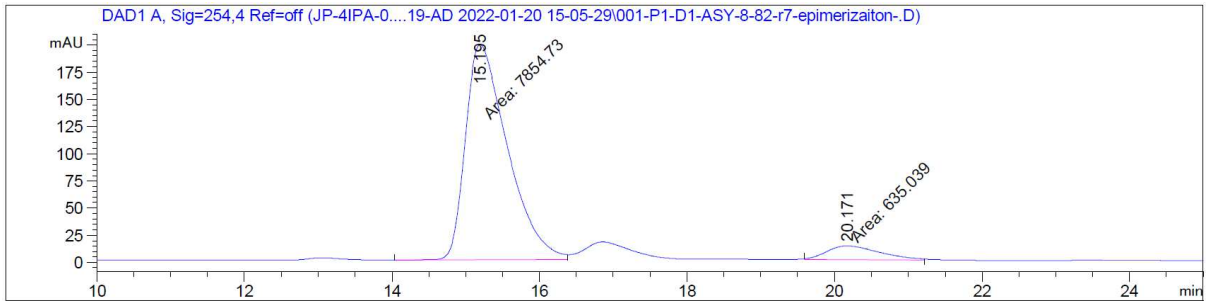


4.6b, 0.10 mmol
endo:exo = 1:2.1
96:4 (***exo***)
95:5 (***endo***)

4.6b, 71% yield
endo:exo = 1:12
93:7 (***exo***)

Reversibility of the cycloaddition reaction was investigated using [(***R***,***R***)–L1–Cu](SbF$_6$)$_2$. Specifically, to a 7 mL oven-dried vial charged with a magnetic stir bar was added [(***R***,***R***)–L1–Cu](Cl)$_2$ (*see:* **Section C2.2;** 2.6 mg, 5.0 mol %, 5.0 μmol) and CD_2Cl_2 (0.4 mL) under an atmosphere of N_2. To this solution, $AgSbF_6$ (3.4 mg, 10 μmol, 10 mol %) was added and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [(***R***,***R***)–L1–Cu](SbF$_6$)$_2$. Subsequently, to a J-Young tube was added [(***R***,***R***)–L1–Cu](SbF$_6$)$_2$ (0.4 mL, 5.0 mol %), **4.6b** (41.8 mg, 0.10 mmol), mesitylene (12.0 mg, 0.10 mmol) and diluted to 0.6 mL with CD_2Cl_2. After the J-Young tube was tightly capped with the Teflon plug, the reaction was kept in 22 °C. The mixture was monitored by ^{1}H NMR and after 36 hours (*endo*:*exo* = >1:10 dr) the solution was filtered through a short plug of silica gel and flashed with 10% methanol in CH_2Cl_2. The resulting solution was then concentrated *in vacuo* and purified by silica gel chromatography (hexanes:EtOAc = 3:1) to afford the **4.6b** in 71% yield (19.2 mg, 0.07 mmol; *endo*:*exo* = 1:12 dr; 93:7 er). **HPLC** (Chiralpak OD-H; 1.0:99.0 isopropanol:hexanes, 0.6 mL/min; ***exo*-4.6b:** tr = 15.1 min (major), 20.1 min (minor); 93:7 er).

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : HPLC w FC                        Location :   P1-D-01
Injection Date  : 1/20/2022 3:06:27 PM                  Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : C:\Chem32\1\Data\JP-4IPA-0.5rate-0219-AD 2022-01-20 15-05-29\ASY-1.0%-0.6ml
                  -60min.M
Last changed    : 1/20/2022 3:05:31 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JP-4IPA-0.5rate-0219-AD 2022-01-20 15-05-29\ASY-1.0%-0.6ml
                  -60min.M (Sequence Method)
Last changed    : 1/25/2022 12:03:33 PM by SYSTEM
```



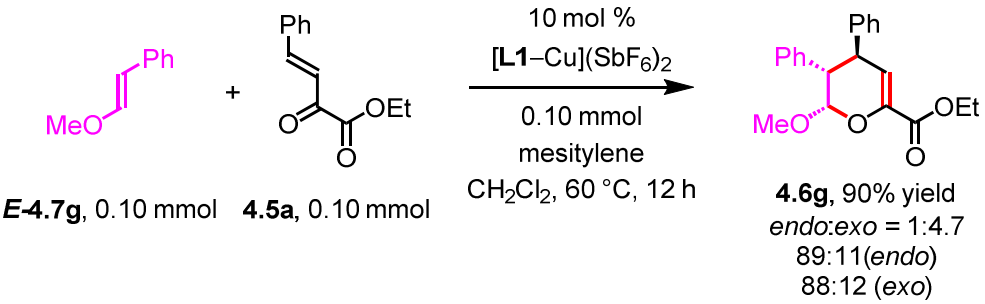
Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.195	MF	0.6602	7854.72852	198.29593	92.5199
2	20.171	FM	0.8295	635.03931	12.75873	7.4801
Totals :				8489.76782	211.05466	

C4.4. Enantioselective Hetero Diels-Alder Reaction with Preformed Enol Ether (*E*)-4.7g

Based on the stereochemistry of the products generated through this protocol, we proposed that only *Z*-enol ethers efficiently participate in the organocopper-catalyzed hetero Diels-Alder reaction. We reasoned this could be due to a selective formation of *Z*-enol ethers (**1**→ **II** → **III**; Figure 1). Alternatively, both *E*- and *Z*-enol ethers are formed, yet they are readily interconvertible under the organocopper-catalyzed hetero Diels-Alder reaction conditions. To test the latter hypothesis, (*E*)-(2-Methoxyvinyl)benzene ((*E*)-**4.7g**) was synthesized according to a known procedure (Figure S8; SI-Section 4.5),[18] and it was subjected to cycloaddition reaction conditions.

Procedure for the Enantioselective Hetero Diels-Alder Reaction with Preformed *E*-Enol Ether



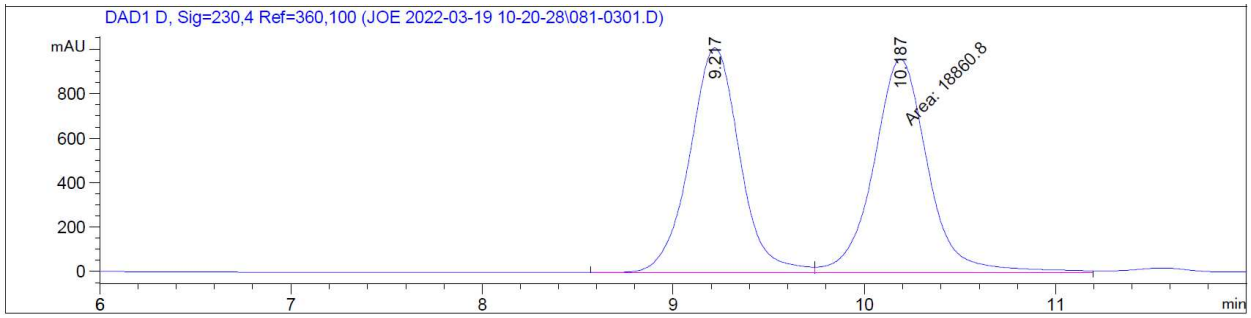
***E*-4.7g**, 0.10 mmol **4.5a**, 0.10 mmol

4.6g, 90% yield
endo:*exo* = 1:4.7
89:11(*endo*)
88:12 (*exo*)

To a 7 mL oven-dried vial charged with a magnetic stir bar was added [(***S***,***S***)–L1–Cu](Cl)$_2$ (*see:* **SI-Section 2.2**; 5.2mg, 10 μmol, 10 mol %) and CH_2Cl_2 (0.4 mL) under an atmosphere of N_2. To this solution, $AgSbF_6$ (6.8 mg, 20 μmol, 20 mol %) was added, and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [(***S***,***S***)–L1–Cu](SbF$_6$)$_2$ in CH_2Cl_2. Subsequently, to an oven-dried sealed tube equipped with a magnetic stir bar were added the solution of [(***S***,***S***)–L1–Cu](SbF$_6$)$_2$ (0.4 mL, 10 mol %) in CH_2Cl_2, (*E*)-(2-methoxyvinyl)benzene **(*E*)-4.7g** (0.10 mmol, 1.0 equiv.), **4.5a** (0.10 mmol, 1.0 equiv.), and diluted to 0.6 mL with CH_2Cl_2. The resulting solution was allowed to stir at 60 °C for 12 hours. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. The ^{1}H NMR analysis of the unpurified product mixture revealed that **4.6g** was obtained in 90% yield (30.4 mg, 0.09 mmol) with the diastereomeric ratio of 1:4.7 (*endo*:*exo*). Further purification carried out by PTLC using CH_2Cl_2 as the eluent to separate the diastereomers. Upon characterization of the pure products (*see:* **SI-Section 3**), it was found that ***exo*-4.6g** and ***endo*-4.6g** (*exo*:*endo* = 1:4.7) were the only products formed under the reaction conditions, suggesting [**L1**–Cu](SbF$_6$)$_2$ is capable of promoting 1) isomerization of (*E*)-(2-methoxyvinyl)benzene (**(*E*)-4.7g**) to (*Z*)-(2-methoxyvinyl)benzene (**(*Z*)-4.7g**), as well as 2) the subsequent hetero Diels-Alder reaction of **(*Z*)-4.7g**.

***exo*-4.6g. HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.5 mL/min; ***exo*-4.6g:** tr = 10.3 min (major), 9.3 min (minor); 89:11 er).

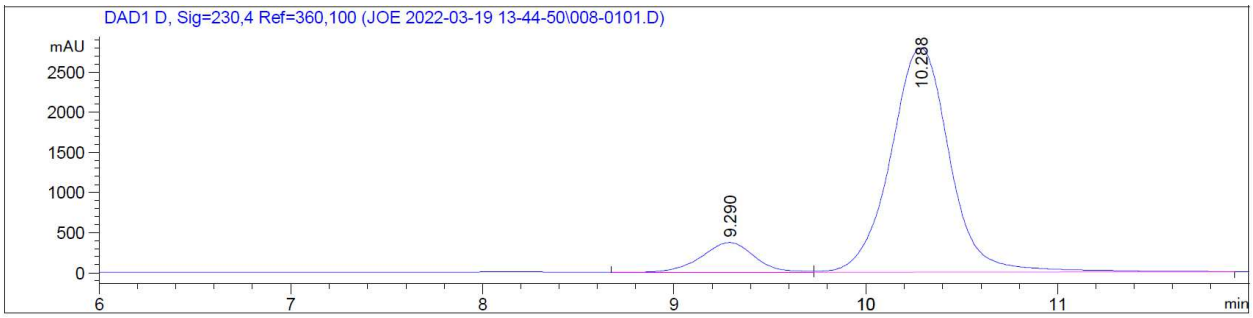
```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   81
Injection Date  : 3/19/2022 12:24:35 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-03-19 10-20-28\column6 1%IPA 99% hexane 30min-0.
                  5mL.M
Last changed    : 3/19/2022 10:20:36 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-03-19 10-20-28\column6 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 3/19/2022 3:10:53 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 30min-1% iPrOH 99% hexane-0.5mL
```



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.217	BV	0.2782	1.83778e4	1010.37805	49.3515
2	10.187	MF	0.3278	1.88608e4	958.88361	50.6485
Totals :				3.72385e4	1969.26166	

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   8
Injection Date  : 3/19/2022 1:47:06 PM                 Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-03-19 13-44-50\column6 1%IPA 99% hexane 30min-0.
                  5mL.M
Last changed    : 3/19/2022 1:44:57 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-03-19 13-44-50\column6 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 3/19/2022 3:09:24 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 30min-1% iPrOH 99% hexane-0.5mL
```

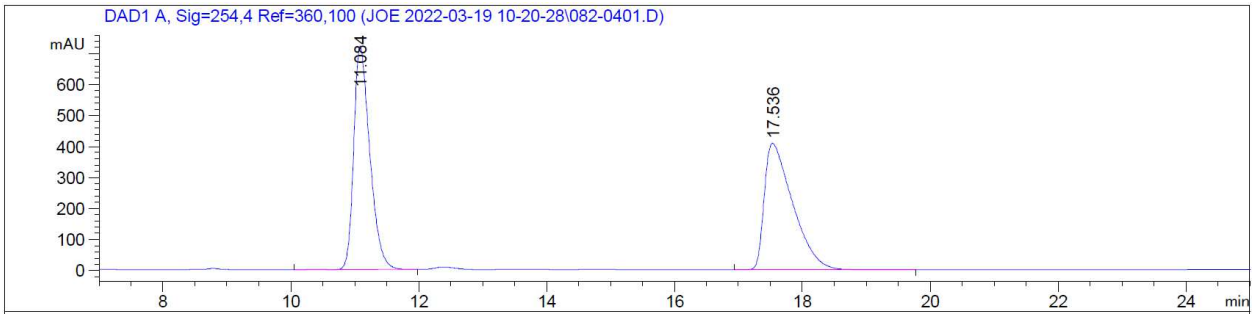


Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.290	BV	0.2952	7137.54102	369.81534	10.6394
2	10.288	VV R	0.3282	5.99482e4	2793.58472	89.3606
Totals :				6.70858e4	3163.40005	

***endo*-4.6g. HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 1.0 mL/min; ***exo*-4.6g:** tr = 15.6 min (major), 10.5 min (minor); 89:11 er).

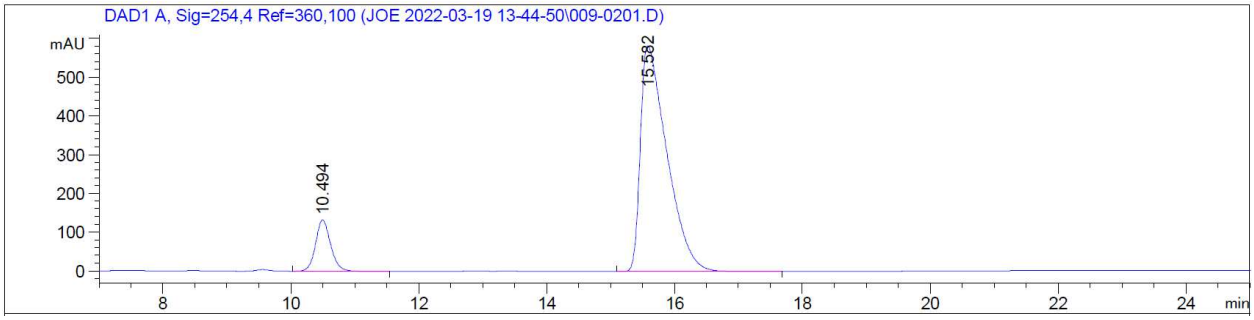
```
Acq. Operator   : SYSTEM                          Seq. Line :  4
Acq. Instrument : Wasa_LC1                        Location :  82
Injection Date  : 3/19/2022 12:55:35 PM               Inj :  1
                                                 Inj Volume : 8.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2022-03-19 10-20-28\column6 1%IPA 99% hexane 30min-1.
                  0mL.M
Last changed    : 3/19/2022 10:20:36 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-03-19 10-20-28\column6 1%IPA 99% hexane 30min-1.
                  0mL.M (Sequence Method)
Last changed    : 3/19/2022 3:07:38 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 60min-1% iPrOH 99% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.084	VB R	0.2643	1.26721e4	721.61609	50.1713
2	17.536	BB	0.4618	1.25856e4	408.11581	49.8287
Totals :				2.52577e4	1129.73190	

Acq. Operator : SYSTEM
Seq. Line : 2
Acq. Instrument : Wasa_LC1
Location : 9
Injection Date : 3/19/2022 2:18:05 PM
Inj : 1
Inj Volume : 8.000 µl
Acq. Method : C:\Chem32\1\Data\JOE 2022-03-19 13-44-50\column6 1%IPA 99% hexane 30min-1.0mL.M
Last changed : 3/19/2022 1:44:57 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2022-03-19 13-44-50\column6 1%IPA 99% hexane 30min-1.0mL.M (Sequence Method)
Last changed : 3/19/2022 3:06:02 PM by SYSTEM (modified after loading)
Method Info : Column6 60min-1% iPrOH 99% hexane-1.0mL



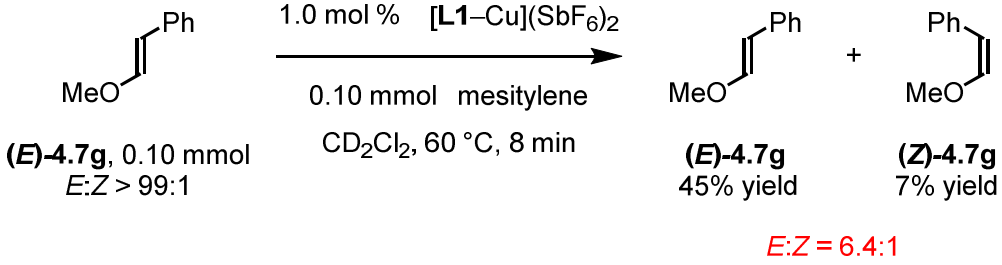
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.494	BB	0.2490	2174.48022	132.79066	11.4787
2	15.582	BB	0.4279	1.67691e4	582.38165	88.5213
Totals :				1.89435e4	715.17232	

C4.5 Isomerization of (*E*)-4.7g into (*Z*)-4.7g

To further confirm that [**L1**–Cu]$(SbF_6)_2$ is capable of promoting the isomerization of (*E*)-(2-methoxyvinyl)benzene (**(*E*)-4.7g**) into *(Z)*-(2-methoxyvinyl)benzene (**(*Z*)-4.7g**) we treated preformed **(*E*)-4.7g** with [**L1**–Cu]$(SbF_6)_2$ and monitored the mixture by the ^{1}H NMR analysis.

Procedure for the Isomerization of (*E*)-4.7g into (*Z*)-4.7g



To a 7 mL oven-dried vial charged with a magnetic stir bar was added [(***S***,***S***)–L1–Cu]$(Cl)_2$ (*see:* **SI-Section 2.2**; 0.5 mg, 1.0 μmol, 1.0 mol %) and CD_2Cl_2 (0.4 mL) under an atmosphere of N_2. To this solution, $AgSbF_6$ (0.7 mg, 2.0 μmol, 2.0 mol %) was added, and the resulting mixture was allowed to stir at 22 °C for 30 minutes to give the solution of [(***S***,***S***)–L1–Cu]$(SbF_6)_2$ in CD_2Cl_2. Subsequently, to a J-Young tube was added the solution of [(***S***,***S***)–L1–Cu]$(SbF_6)_2$ (0.4 mL, 1.0 mol %) in CD_2Cl_2, mesitylene (12 mg, 0.10 mmol), (*E*)-(2-methoxyvinyl)benzene **((*E*)-4.7g)** (0.10 mmol, 1.0 equiv.) and diluted to 0.6 mL with CD_2Cl_2. After that, J-Young tube was tightly capped with the Teflon plug, and the reaction was kept at 60 °C and monitored by ^{1}H NMR. It was found that in eight minutes 7% of **(*E*)-4.7g** (0.01 mmol) was converted into **(*Z*)-4.7g** while 40% **(*E*)-4.7g** (0.04 mmol) was recovered. This might suggest that [**L1**–Cu]$(SbF_6)_2$ is capable of promoting the isomerization of (*E*)-(2-methoxyvinyl)benzene **((*E*)-4.7g)** into *(Z)*-(2-methoxyvinyl)benzene (**(*Z*)-4.7g**).

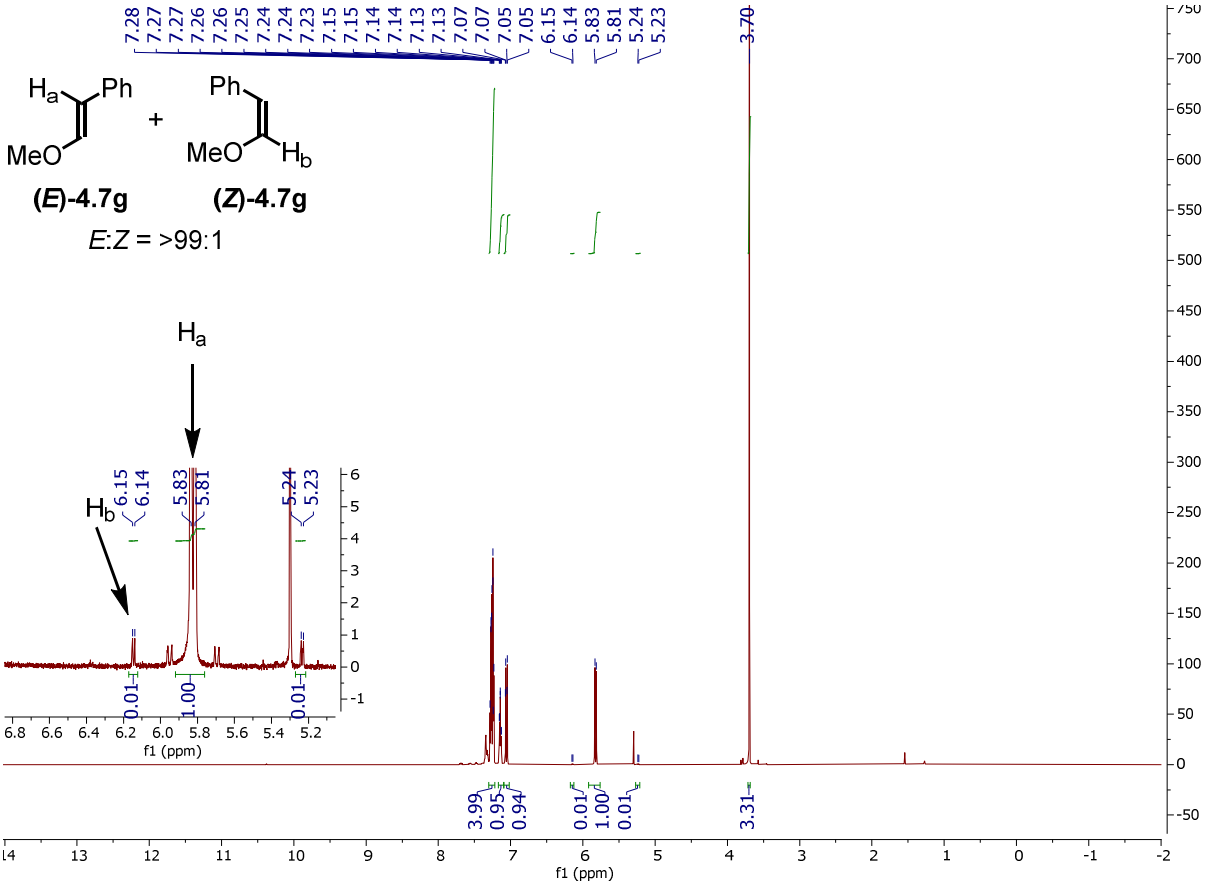


Figure S8: ^{1}H NMR spectrum of (*E*)-(2-methoxyvinyl)benzene (**(*E*)-4.7g**)

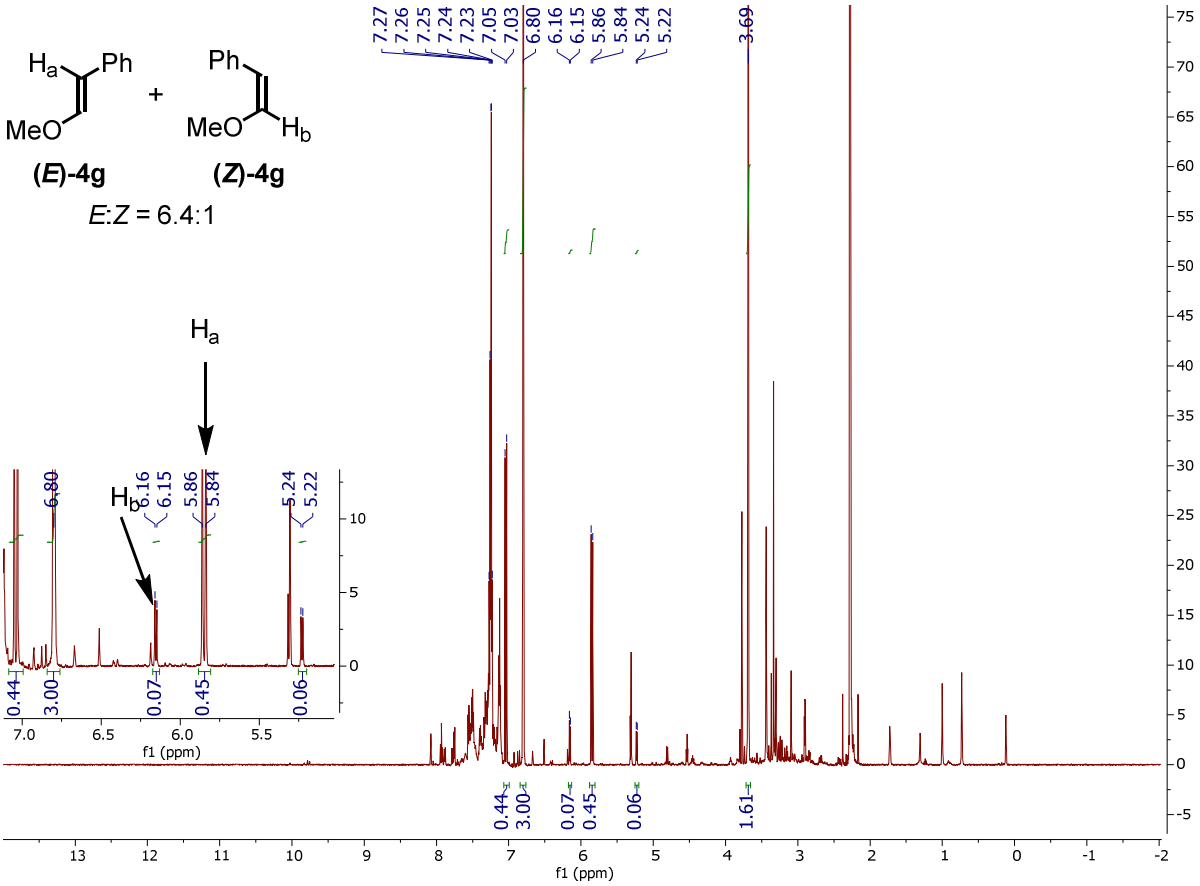
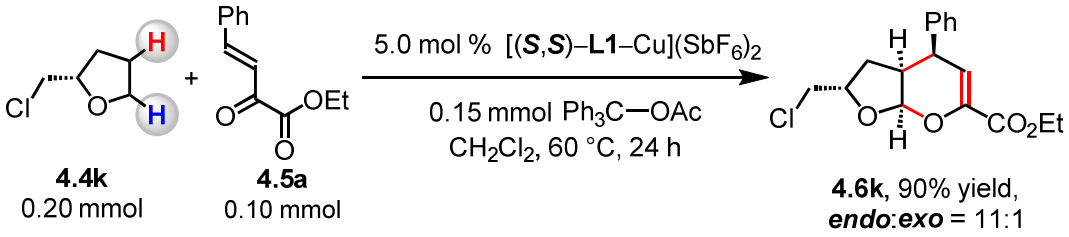


Figure S9: ^{1}H NMR spectrum of J-Young experiment for the isomerization of **(*E*)-4g** into **(*Z*)-4g**

C4.6 Effect of Using (*S*,*S*) or (*R*,*R*) Enantiomers of Ligands on the Diastereoselective Reaction

In order to study the effect of different enantiomers of ligand **L1** on the result of diastereoselective reaction, [(***S***,***S***)–**L1**–Cu](SbF$_6$)$_2$ and [(***R***,***R***)–**L1**–Cu](SbF$_6$)$_2$ were evaluated while ether **4.4k** and β,γ-unsaturated ketoester **4.5a** were used as model substrates.

C4.6.1 Procedure for the Formation of 4.6k Using [(*S*,*S*)–L1–Cu](SbF$_6$)$_2$ as the Catalyst



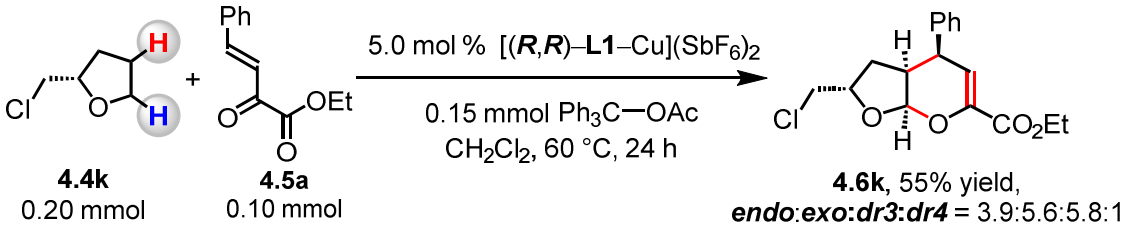
4.4k 0.20 mmol

4.5a 0.10 mmol

4.6k, 90% yield,
endo*:*exo = 11:1

(*S*)-2-(Chloromethyl)tetrahydrofuran **4.4k** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate(0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [**L1**–Cu](SbF$_6$)$_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that ***endo*-4.6k** was obtained in 83% yield (26.7mg, 0.08 mmol) and ***exo*-4.6k** was obtained in 7% yield (2.3 mg, 0.01 mmol).

C4.6.2 Procedure for the Formation of 4.6k Using [(*R*,*R*)–L1–Cu](SbF$_6$)$_2$ as the Catalyst



4.4k 0.20 mmol

4.5a 0.10 mmol

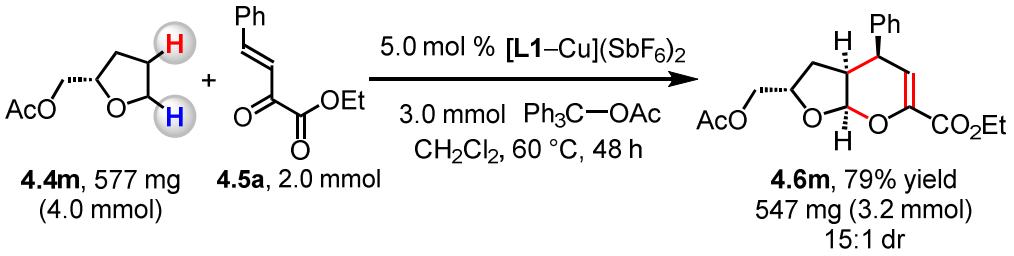
4.6k, 55% yield,
endo*:*exo*:*dr3*:*dr4 = 3.9:5.6:5.8:1

(*S*)-2-(Chloromethyl)tetrahydrofuran **4.4k** (0.20 mmol, 2.0 equiv.) was added to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **4.5a** (0.10 mmol, 1.0 equiv.) and trityl acetate(0.15 mmol, 1.5 equiv.) following the **General Procedure A** using CH_2Cl_2 solution of [(***R***,***R***)–**L1**–Cu](SbF$_6$)$_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and carried out for 24 h at 60 °C. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene

as the internal standard revealed that ***endo*-4.6k** was obtained in 13 % yield (4.2 mg, 0.01 mmol), ***exo*-4.6k** was obtained in 19 % yield (6.1 mg, 0.02 mmol) and two other diastereomers **dr3** and **dr4** were obtained in 20% and 3% yield, respectively.

C5. Procedures for the Large-Scale Reaction and Determination of the Absolute Configuration

C5.1 Procedure for the Large-Scale Reaction

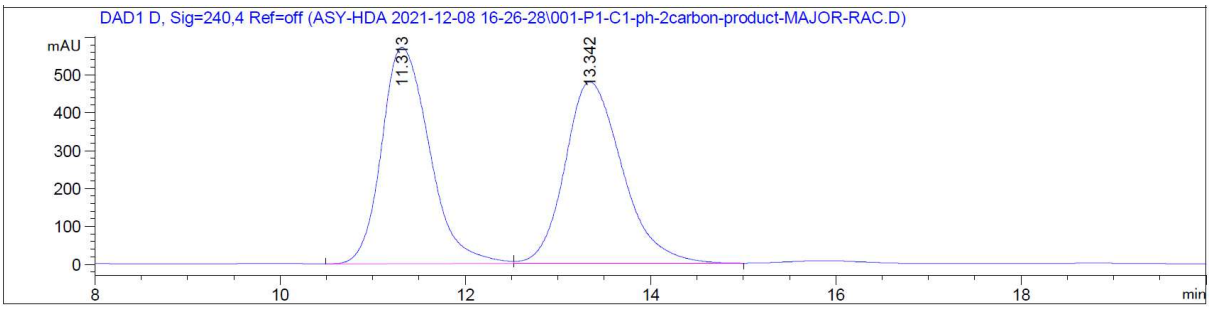


4.4m, 577 mg (4.0 mmol) **4.5a**, 2.0 mmol **4.6m**, 79% yield 547 mg (3.2 mmol) 15:1 dr

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added (*S*)-(tetrahydrofuran-2-yl)methyl acetate **4.4m** (4.0 mmol, 2.0 equiv.), β,γ-unsaturated ketoester **4.5a** (2.0 mmol, 1.0 equiv.), trityl acetate (3.0 mmol, 1.5 equiv.), 5. CH_2Cl_2 solution of [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %, 5.0 μmol, 25 mM, 0.2 mL) and 1.0 mL CH_2Cl_2 under an atmosphere of N_2. The mixture was allowed to stir at 60 °C for 48 hours. Upon completion, the solution was filtered through a short plug of silica gel, flashed with 10% methanol in CH_2Cl_2 and then concentrated *in vacuo*. The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was *endo*:*exo* = 15:1. The combined material was then concentrated *in vacuo* and purified by silica gel chromatography (hexanes:EtOAc = 9:1), **4.6m** was obtained as a yellow oil (547 mg, 1.6 mmol, 79% yield).

C5.2 Determination of the Absolute and Relative Configurations

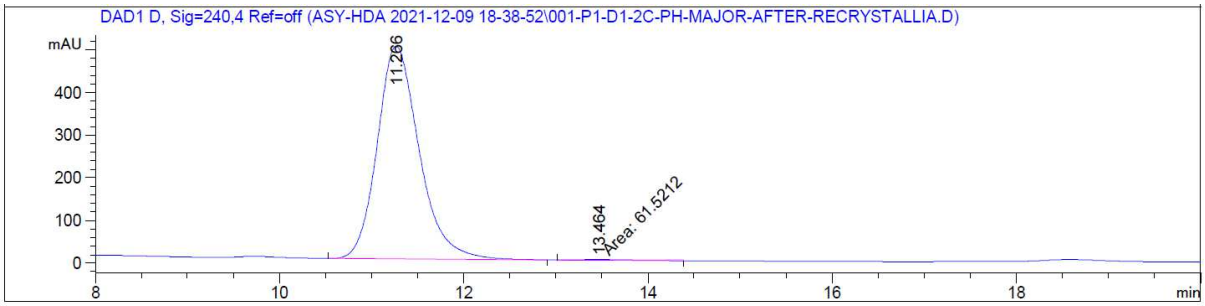
***exo*-4.6g** was recrystallized using the vapor-vapor diffusion method, using *i*-PrOH to dissolve the product in an inner vial, and *n*-hexane as the precipitant placed in the outer vial in order for slow diffusion to occur in the inner vial. The solution was placed at 22 °C, whereupon a crystal was obtained (>99:1 er) for X-ray crystallographic analysis which revealed that the absolute configuration of ***exo*-4.6g** is (*S,S,S*). *see:* **Section C7** for X-ray crystallographic data. **HPLC** (Chiralpak IA-3; 1.0:99.0 isopropanol:hexanes, 0.4 mL/min; ***exo*-4.6g**: tr = 11.3 min (major), 13.5 min (minor); >99:1 er)



Signal 4: DAD1 D, Sig=240,4 Ref=off

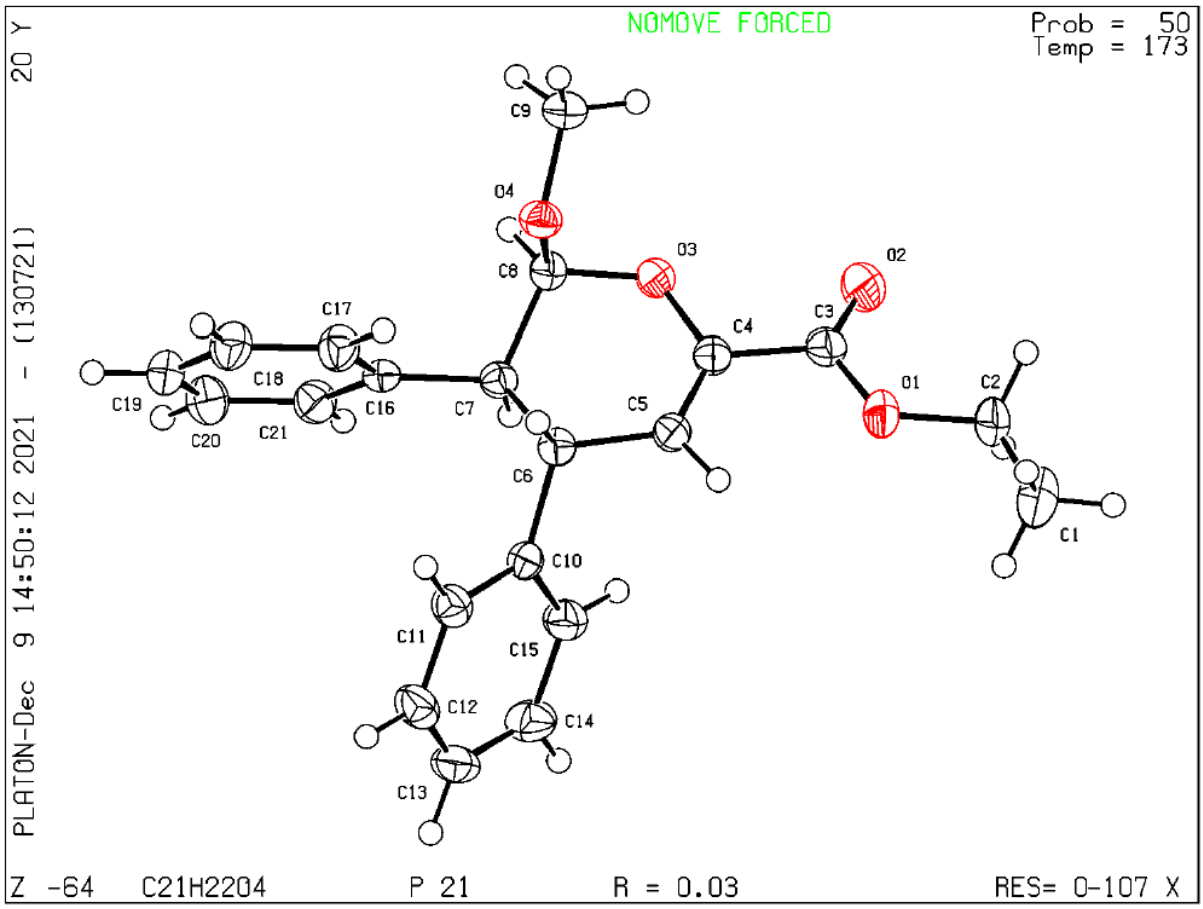
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.313	BV	0.5666	2.05018e4	571.44592	49.8831
2	13.342	VB	0.6653	2.05979e4	479.41052	50.1169
Totals :				4.10997e4	1050.85645	

Acq. Operator : SYSTEM
Seq. Line : 1
Acq. Instrument : HPLC w FC
Location : P1-D-01
Injection Date : 12/9/2021 6:39:49 PM
Inj : 1
Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry! Actual Inj Volume : 4.000 µl
Acq. Method : C:\Chem32\1\Data\ASY-HDA 2021-12-09 18-38-52\ASY-1.0%-0.4ml-25min.M
Last changed : 12/9/2021 6:38:53 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\ASY-HDA 2021-12-09 18-38-52\ASY-1.0%-0.4ml-25min.M (Sequence Method)
Last changed : 1/25/2022 1:14:19 PM by SYSTEM



Signal 4: DAD1 D, Sig=240,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.266	BB	0.4830	1.57659e4	498.48532	99.6113
2	13.464	MM	0.6202	61.52116	1.65318	0.3887
Totals :				1.58274e4	500.13850	



C6. References

(9) Denmark, S. E.; Stiff, C. M. *J. Org. Chem*. **2000**, *65*, 5875–5878.

(10) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2011**, *133*, 13782−13785.

(11) Albello, N.; Geurink, P. P.; van der Toorn, M.; von Oostherhout, A. J. M.; Lugtenburg, J.; van der Marel, G. A.; Kerstjens, H. A. M.; Postma, D. S.; Overkleeft, H. S.; Bischoff, R. *Anal. Chem*. **2008**, *80*, 9171–9180.

(12) Zhang, Q.; Catti, L.; Pleiss, J.; Tiefenbacher, K. *J. Am. Chem. Soc*. **2017**, *139*, 11482−11492.

(13) Richter, F.; Ghazi Z., H.; Jessewitsch, T. L.; Loddenkemper, T.; Kostromine, S. Use of specific open-chain ether isocyanates. Patent WO 2021180709, September 16, 2021.

(14) Canonne, P.; Foscolos, G.; Belanger, D. *J. Org. Chem.* **1980**, *45*, 1828–1835.

(15) Ye. B.; Zhao, J.; Zhao, K.; McKenna, J. M.; Toste, F. D. *J. Am. Chem Soc.* **2018***, 140,* 8350−8356.

(16) Kuang, Y.; Balakrishnan, K.; Gandhi, V.; Peng, X. *J. Am. Chem. Soc*. **2011**, *133*, 19278−19281.

(17) Yeo, W. S.; Min, D. H.; Hsieh, R. W.; Greene, G. L.; Mrksich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5480−5483.

(18) Wang, Z.; Wu, J.; Lamine, W.; Li, B.; Sotiropoulos, J.-M.; Chrostowska, A.; Miqueu, K.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2021**, *60*, 21231−21236.

(19) Ratushnyy, M.; Parasram, M.; Wang, Y.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2018**, *57*, 2712−2715.

(20) Huang, H.; Panek, J. *Org. Lett.* **2001**, *3*, 1693–1696.

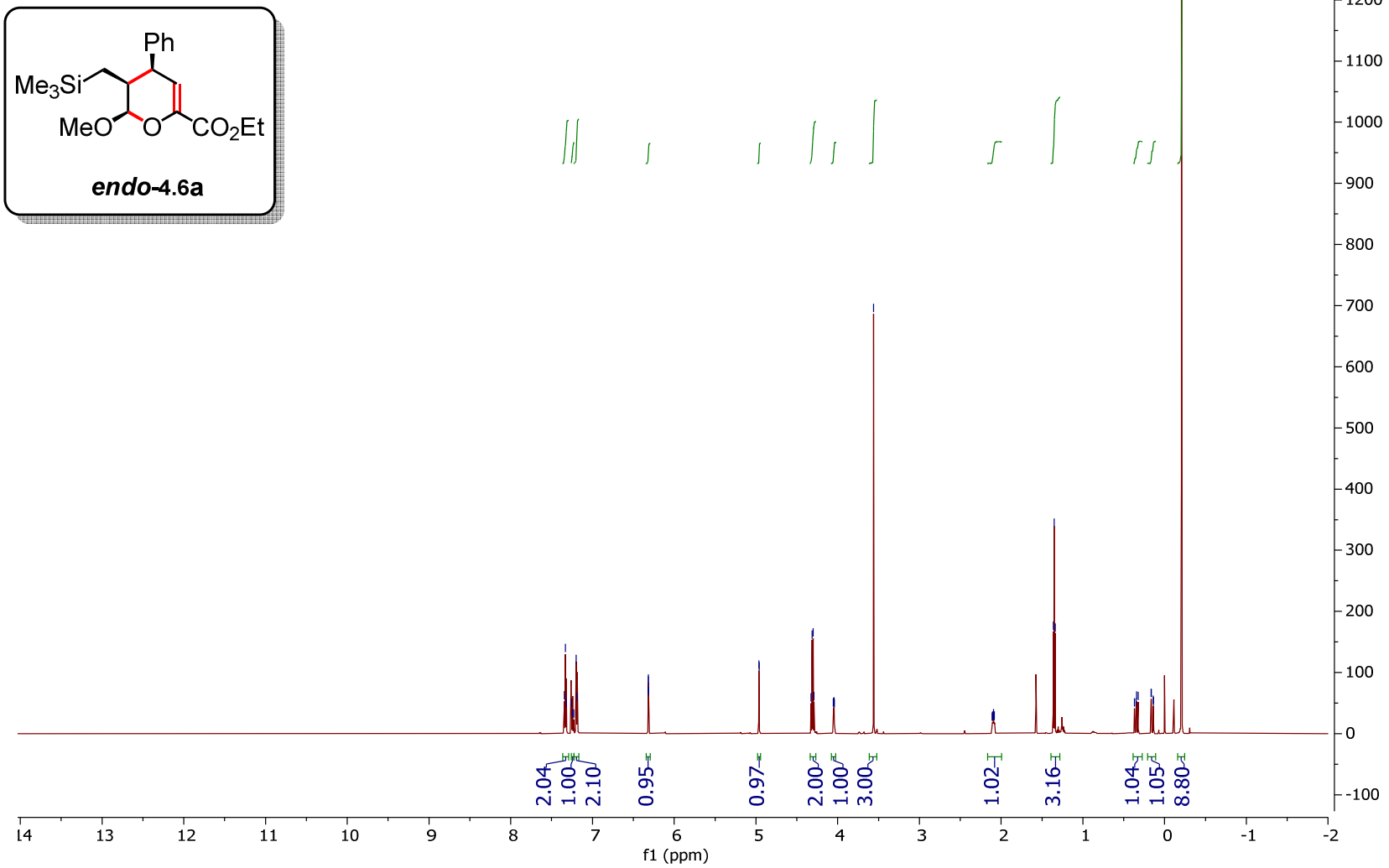
(21) Evans, D. A.; Johnson, J. S.; Olhava E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

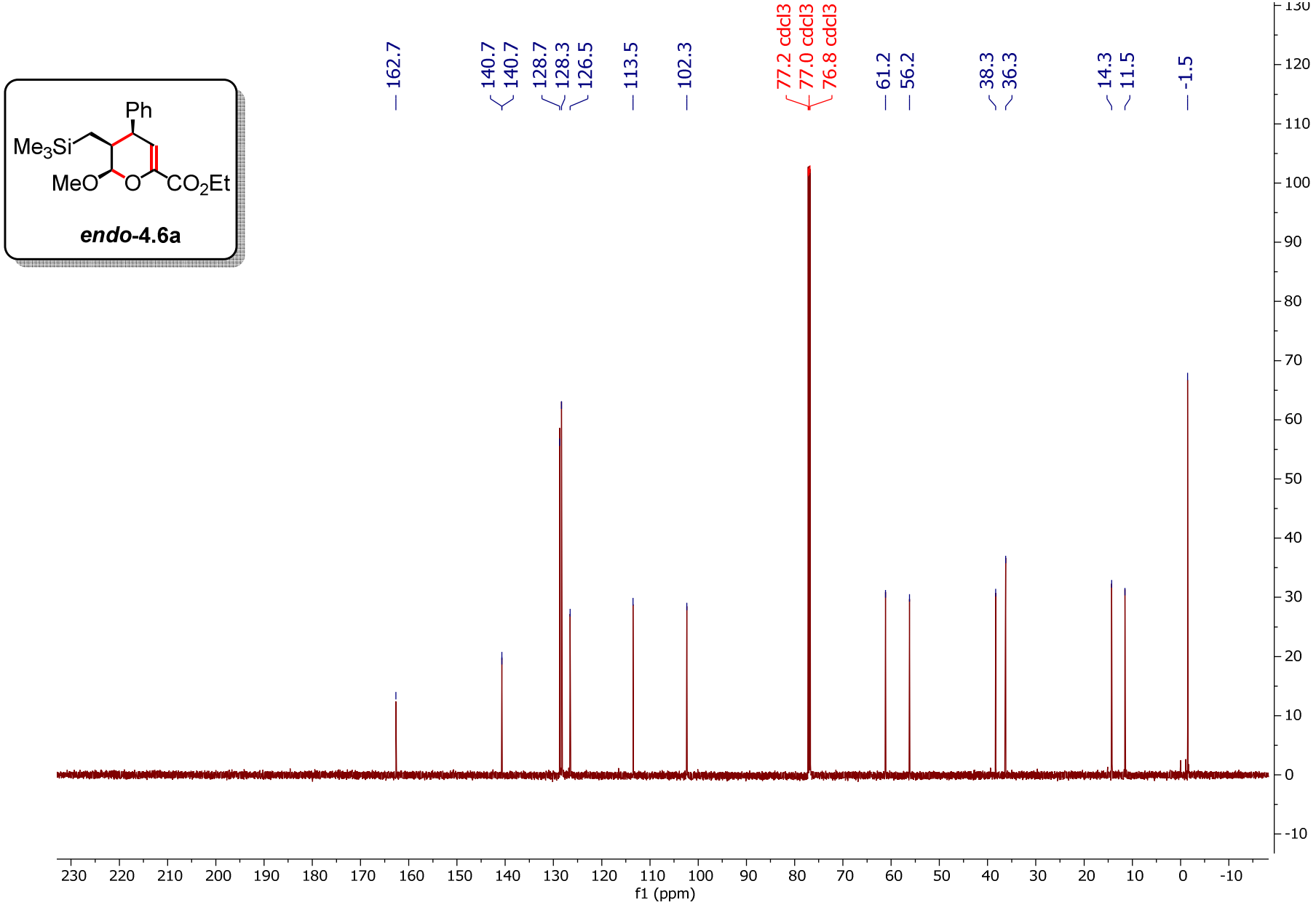
(22) Tietze, L. F.; Bergmann, A.; Brill, G.; Brüggemann, K.; Hartfiel, U.; Voß, E. *Chem. Ber.* **1989**, *122*, 83−94.

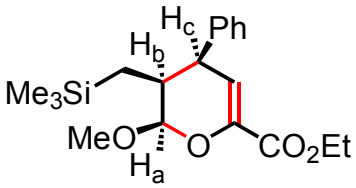
(23) Ji, C.-L.; Hao, W.-J.; Zhang, J.; Geng, F.-Z.; Xu, T.; Tu, S.-J.; Jiang, B. *Org. Lett.* **2019**, *21*, 6494−6498.

(24) McKew, J. C.; Kurth, M. J. J. *Org. Chem.* **1993**, *58*, 4589–4595.

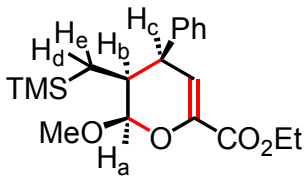
C7. NMR Spectra for New Compounds



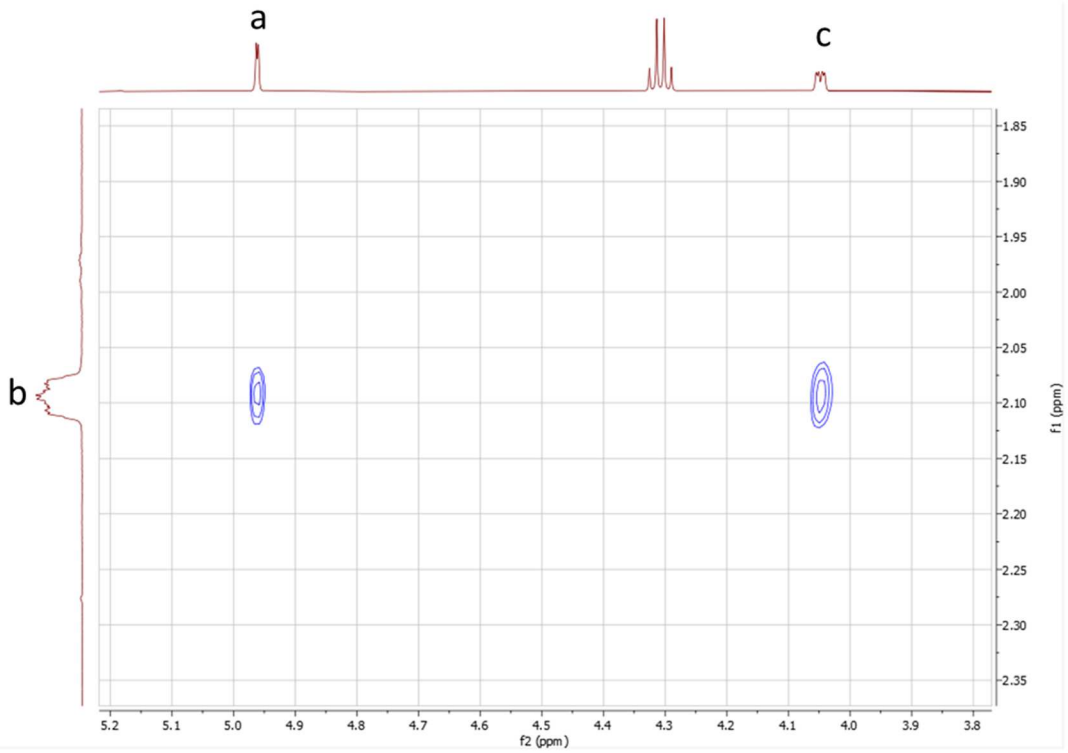

Ph
Me3Si
MeO
O
CO2Et
endo-4.6a
162.7
140.7
140.7
128.7
128.3
126.5
113.5
102.3
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.2
56.2
38.3
36.3
14.3
11.5
-1.5
f1 (ppm)



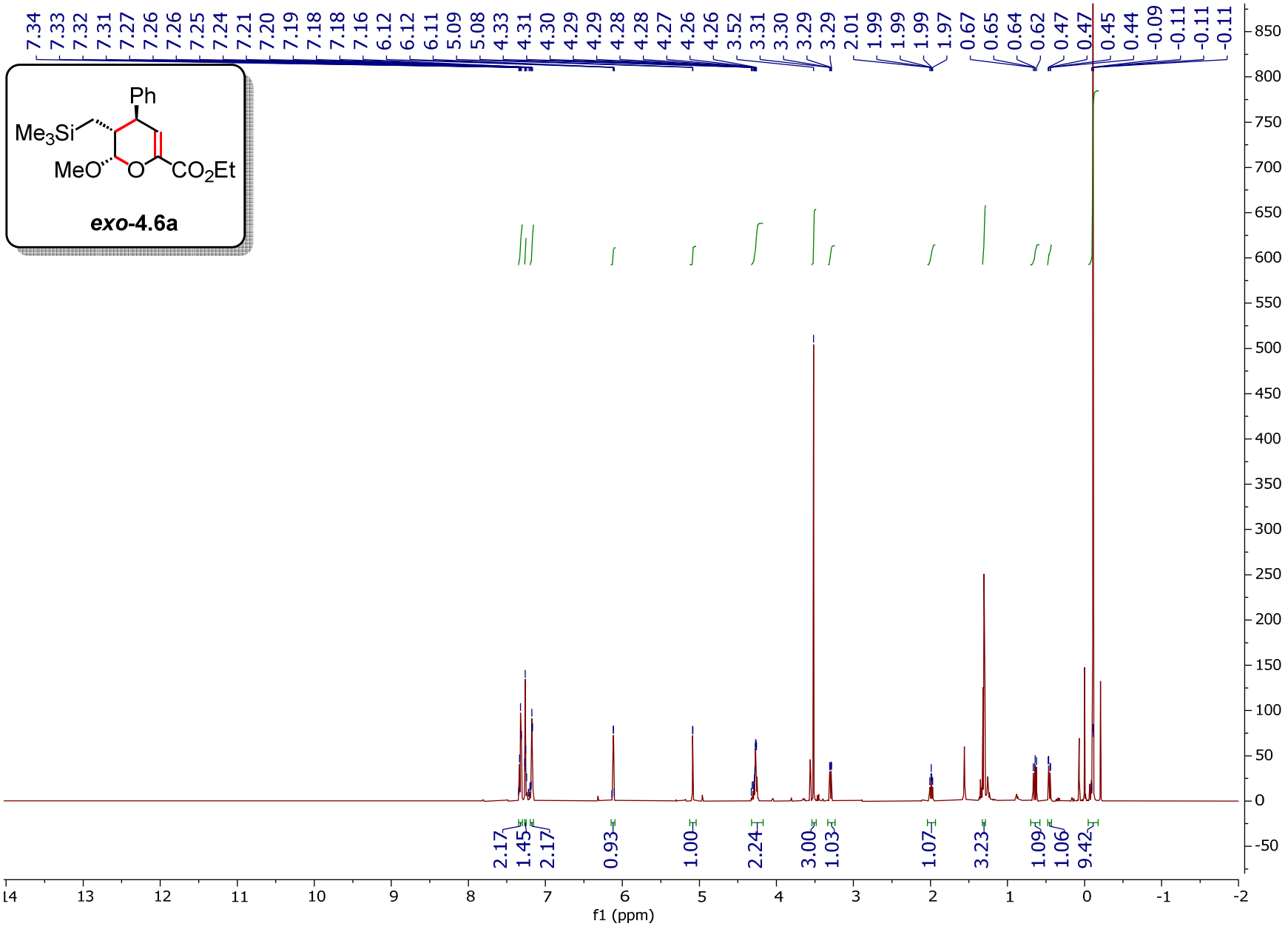
***endo*-4.6a**

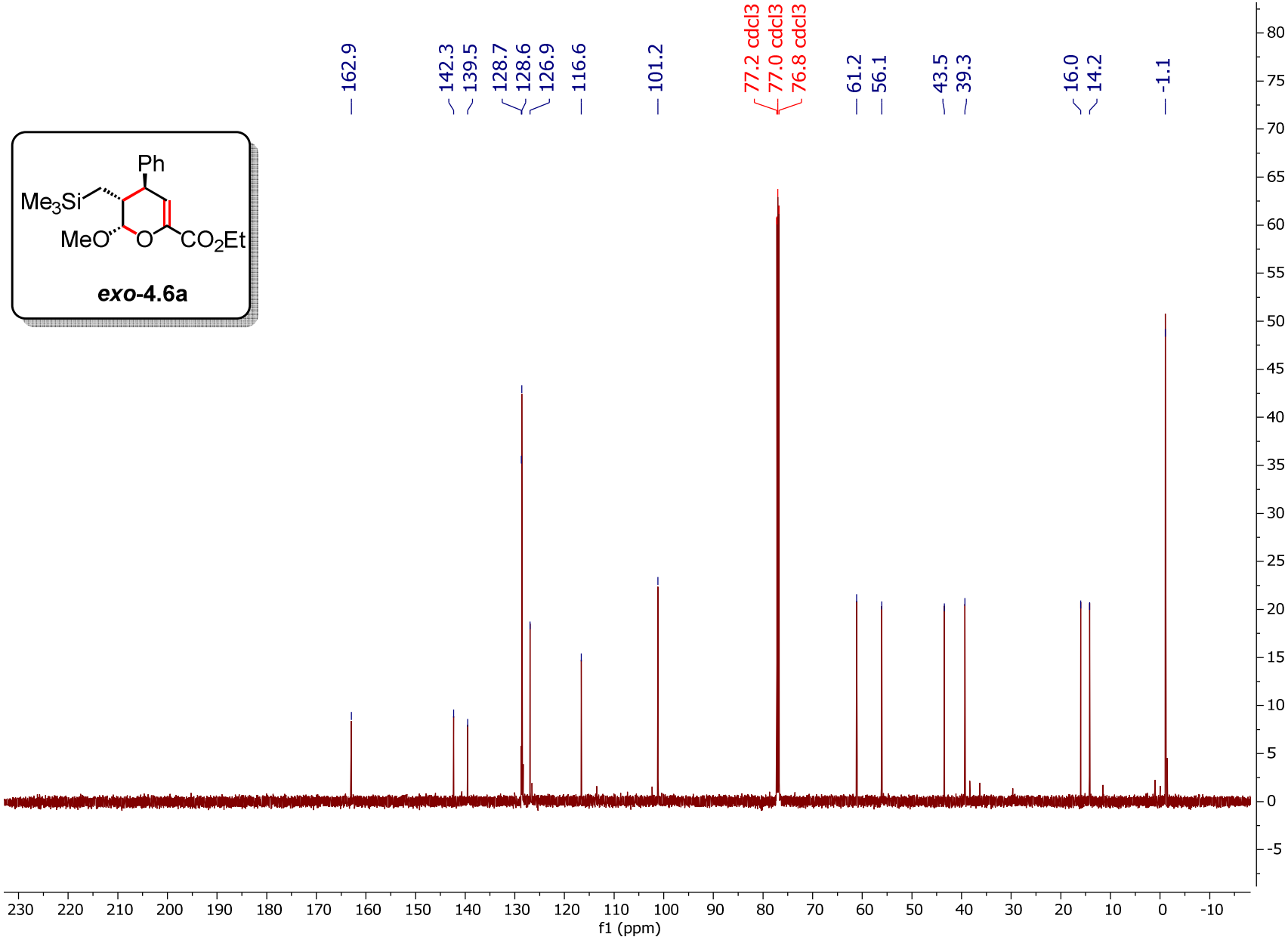


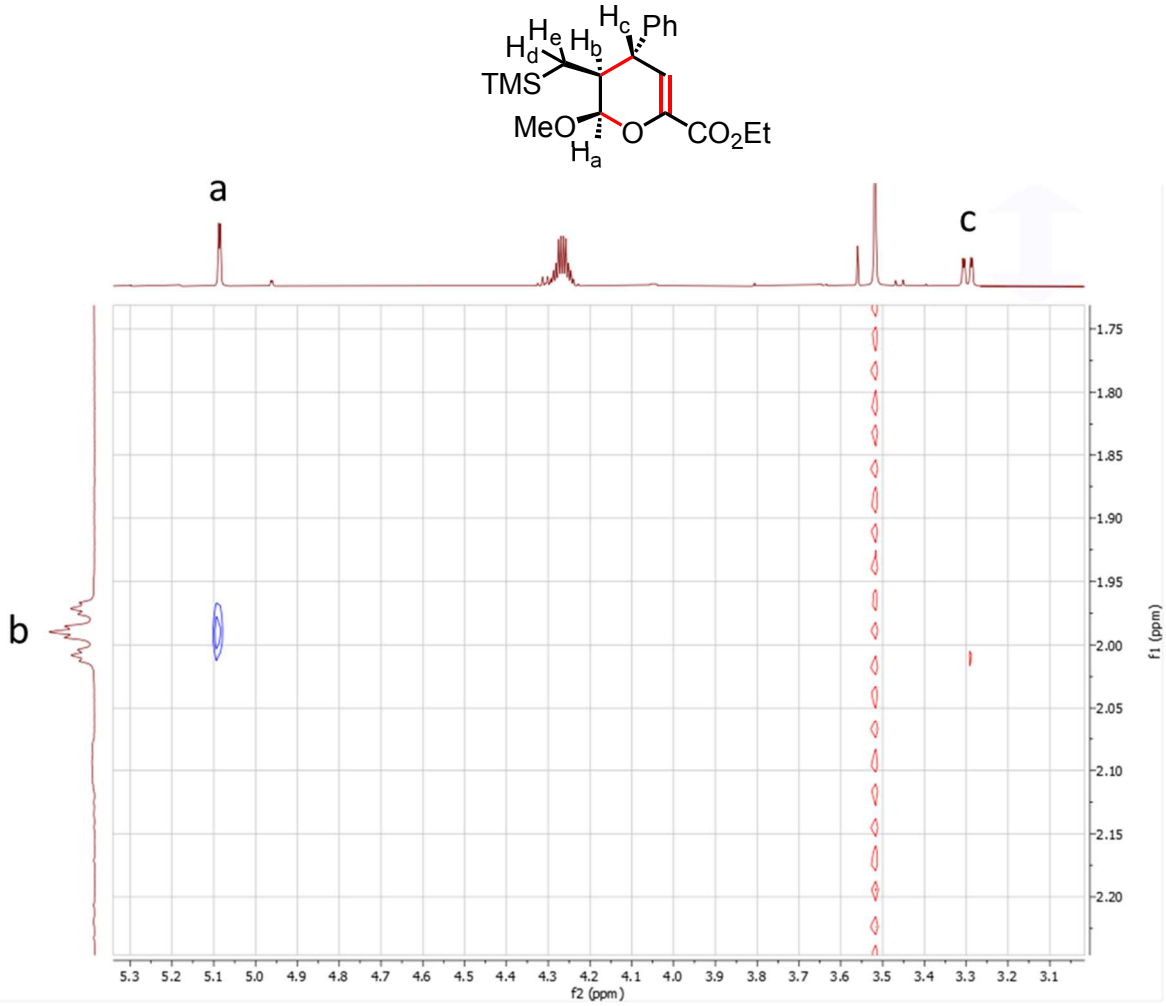
***endo*-4.6a**



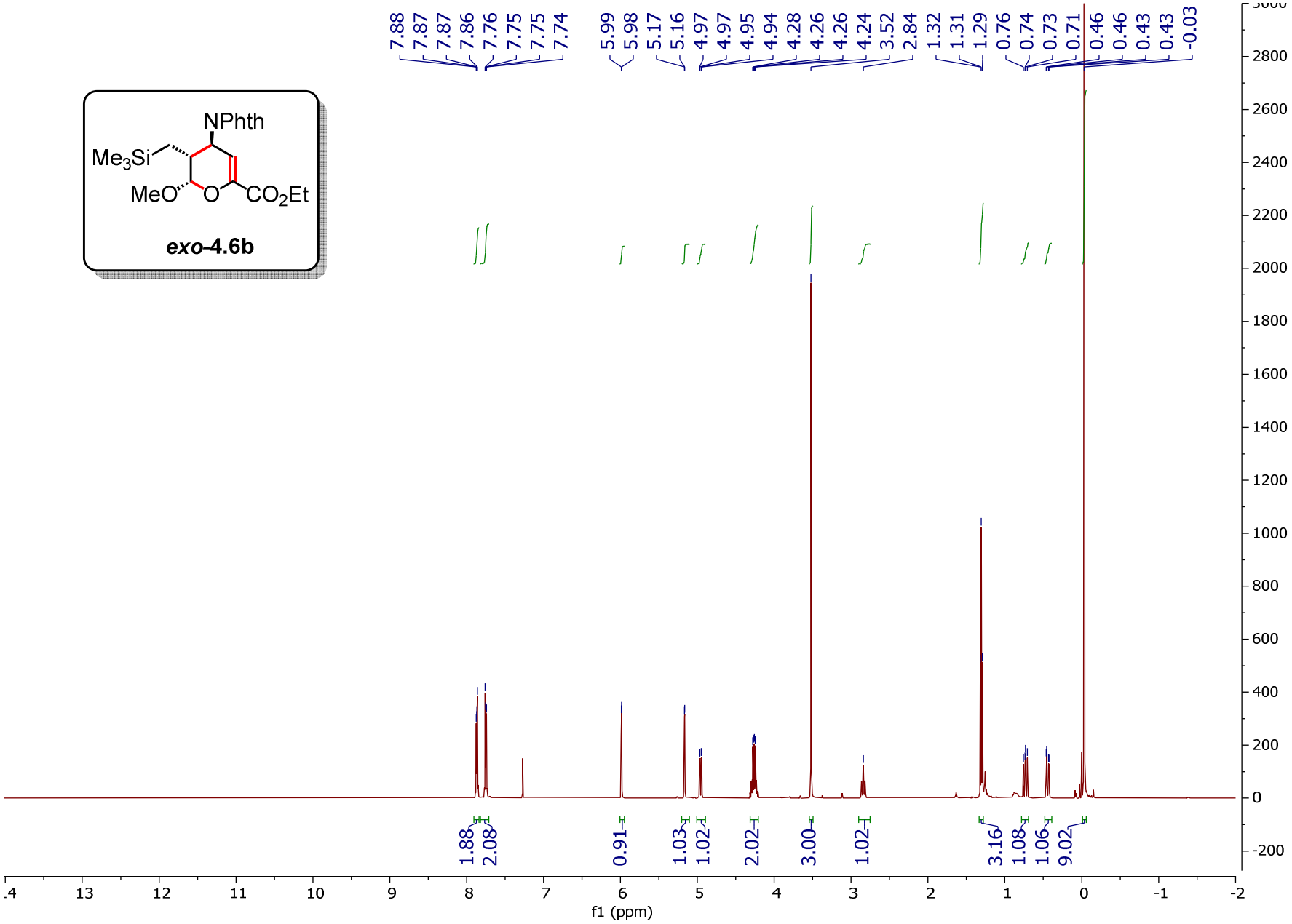
The relative configuration of the major diastereomer of **4.6a** was assigned to be ***end***

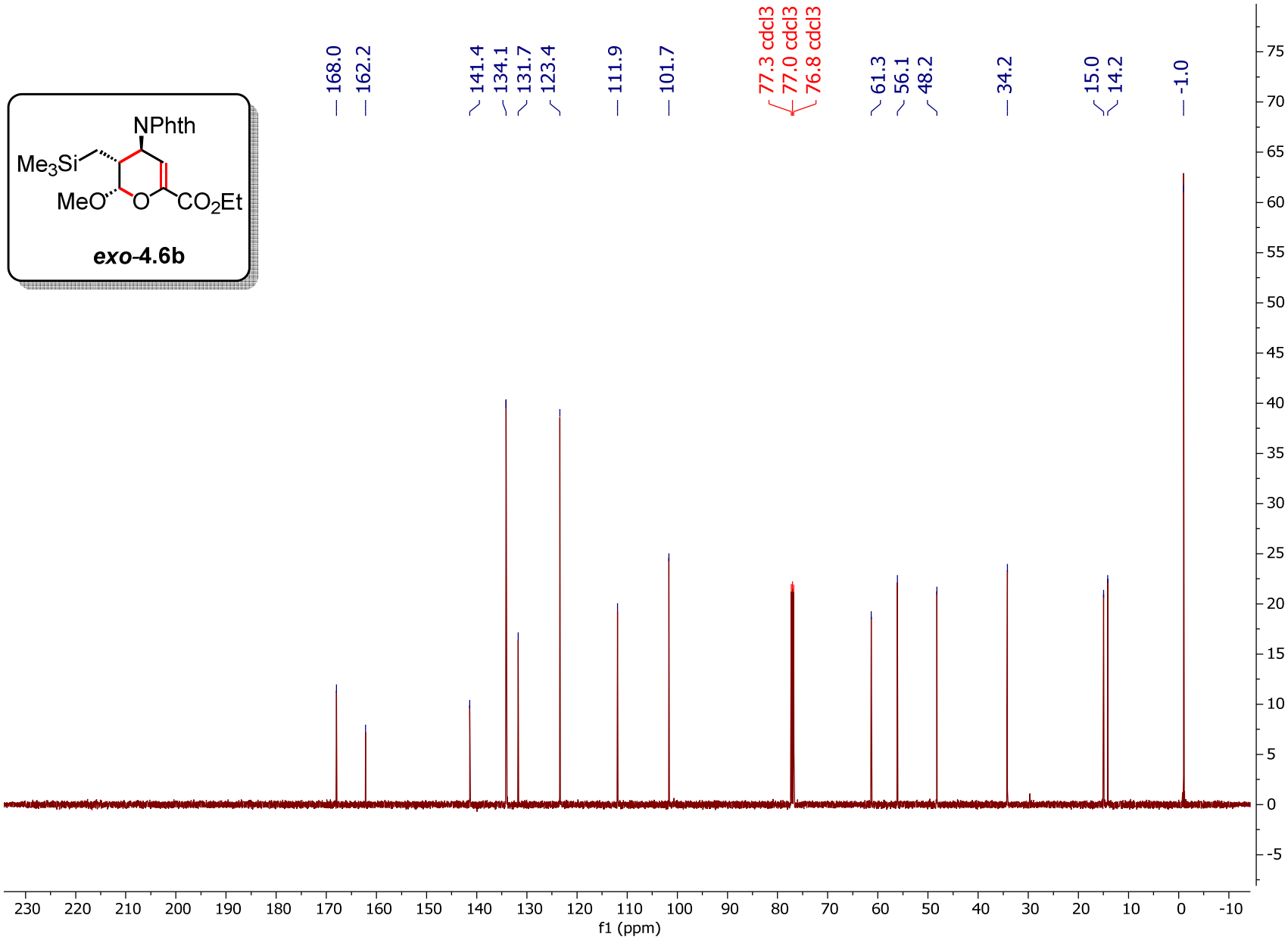

Ph
Me3Si
MeO
O
CO2Et
exo-4.6a
f1 (ppm)

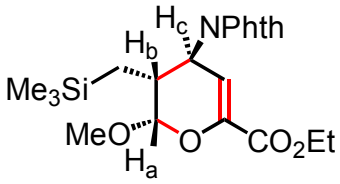

162.9
142.3
139.5
128.7
128.6
126.9
116.6
101.2
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.2
56.1
43.5
39.3
16.0
14.2
-1.1
Ph
Me3Si
MeO
O
CO2Et
exo-4.6a
f1 (ppm)



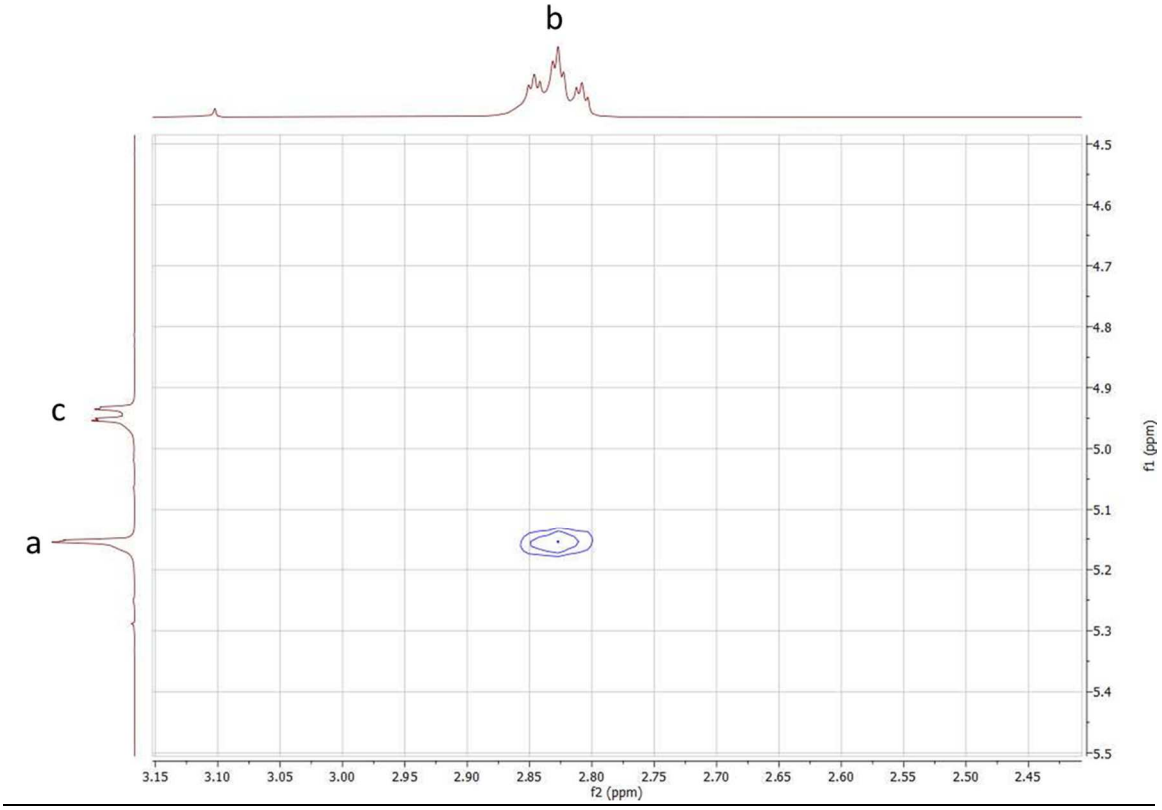
The relative configuration of the minor diastereomer of **4.6a** was assigned to be ***exo***.


NPhth
Me3Si
MeO
O
CO2Et
exo-4.6b
7.88
7.87
7.87
7.86
7.76
7.75
7.75
7.74
5.99
5.98
5.17
5.16
4.97
4.97
4.95
4.94
4.28
4.26
4.26
4.24
3.52
2.84
1.32
1.31
1.29
0.76
0.74
0.73
0.71
0.46
0.46
0.43
0.43
-0.03
1.88
2.08
0.91
1.03
1.02
2.02
3.00
1.02
3.16
1.08
1.06
9.02
f1 (ppm)

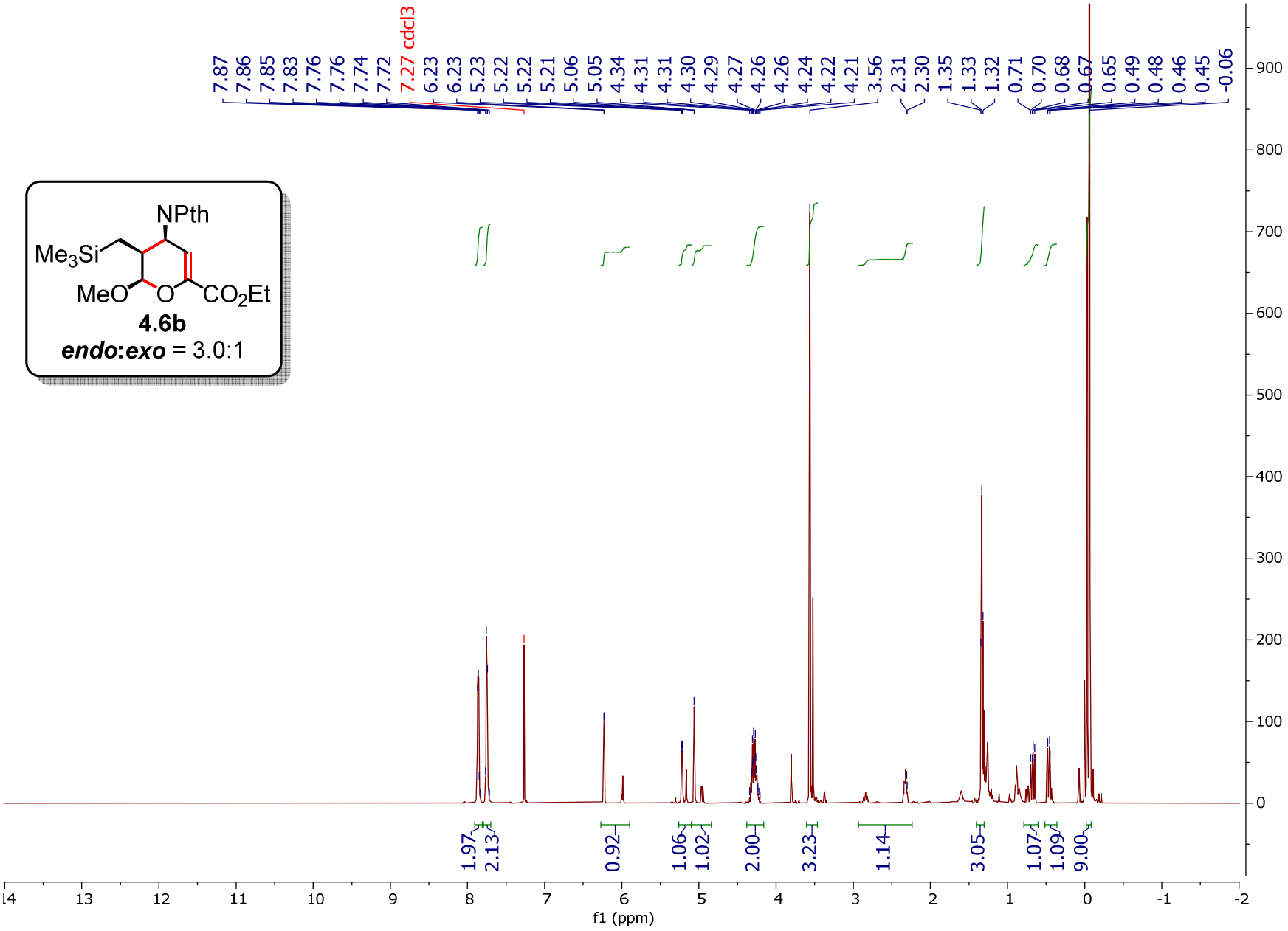

NPhth
Me3Si
MeO
O
CO2Et
exo-4.6b
168.0
162.2
141.4
134.1
131.7
123.4
111.9
101.7
77.3 cdcl3
77.0 cdcl3
76.8 cdcl3
61.3
56.1
48.2
34.2
15.0
14.2
-1.0
f1 (ppm)

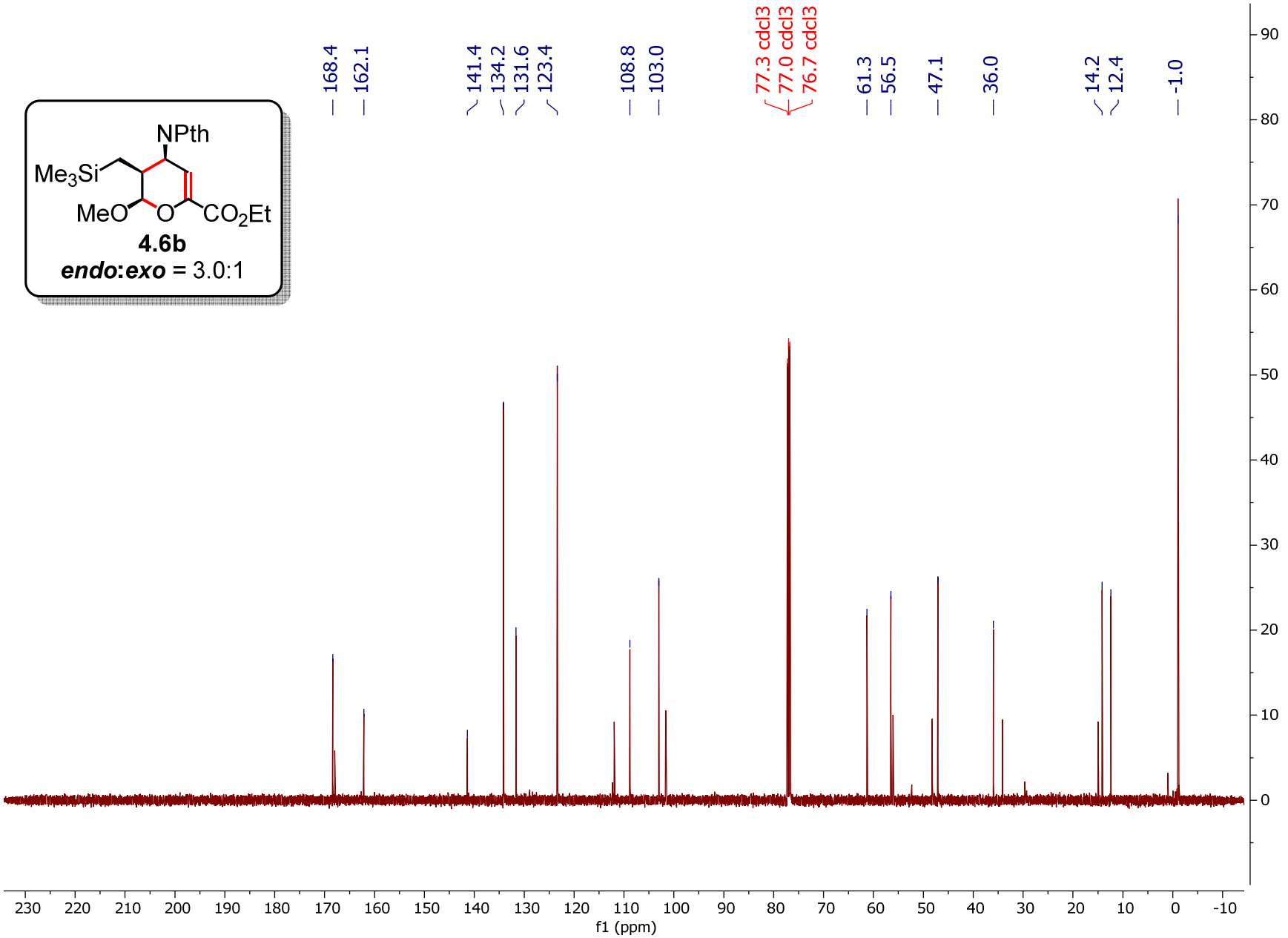


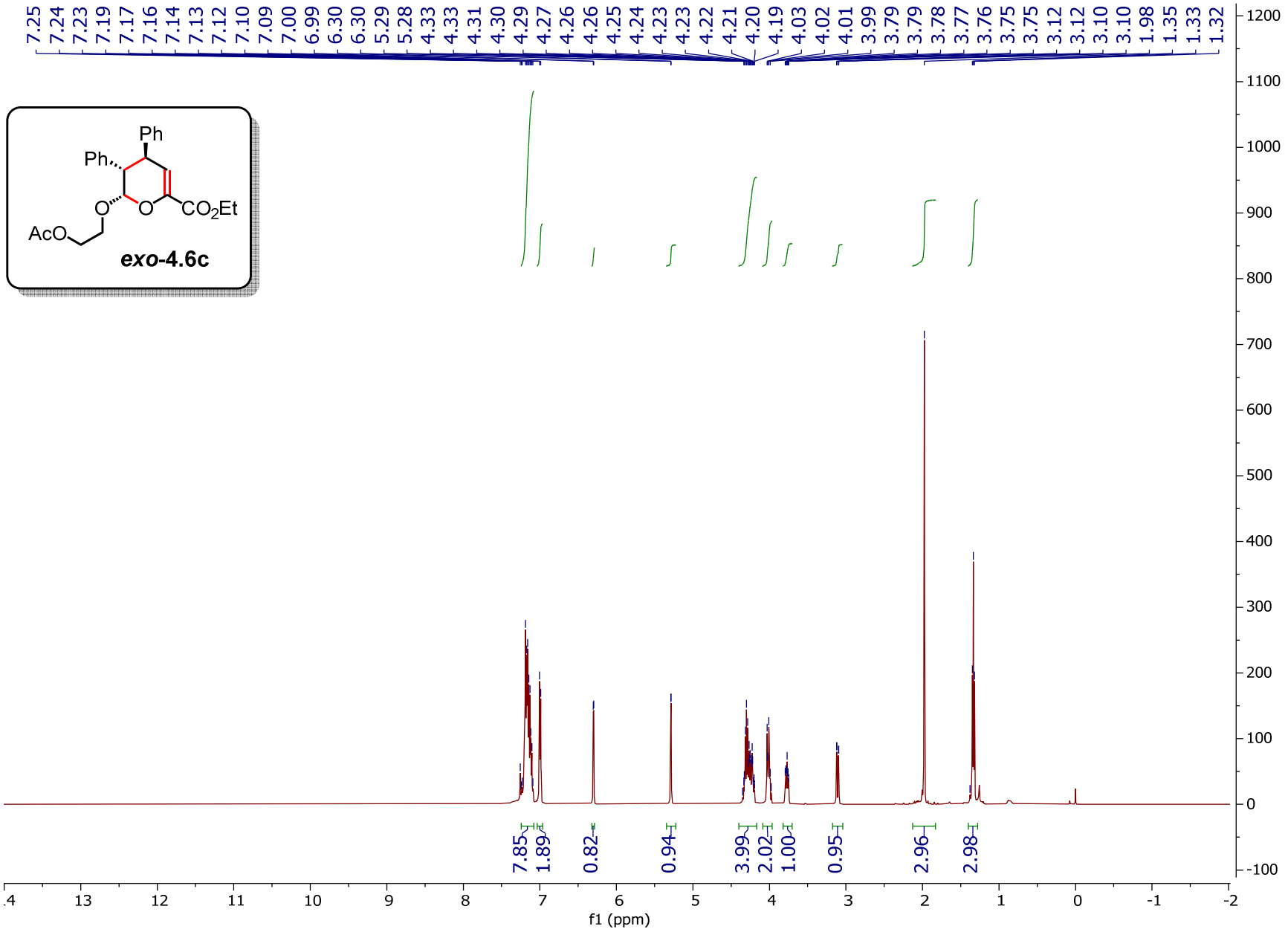
***exo*-4.6b**

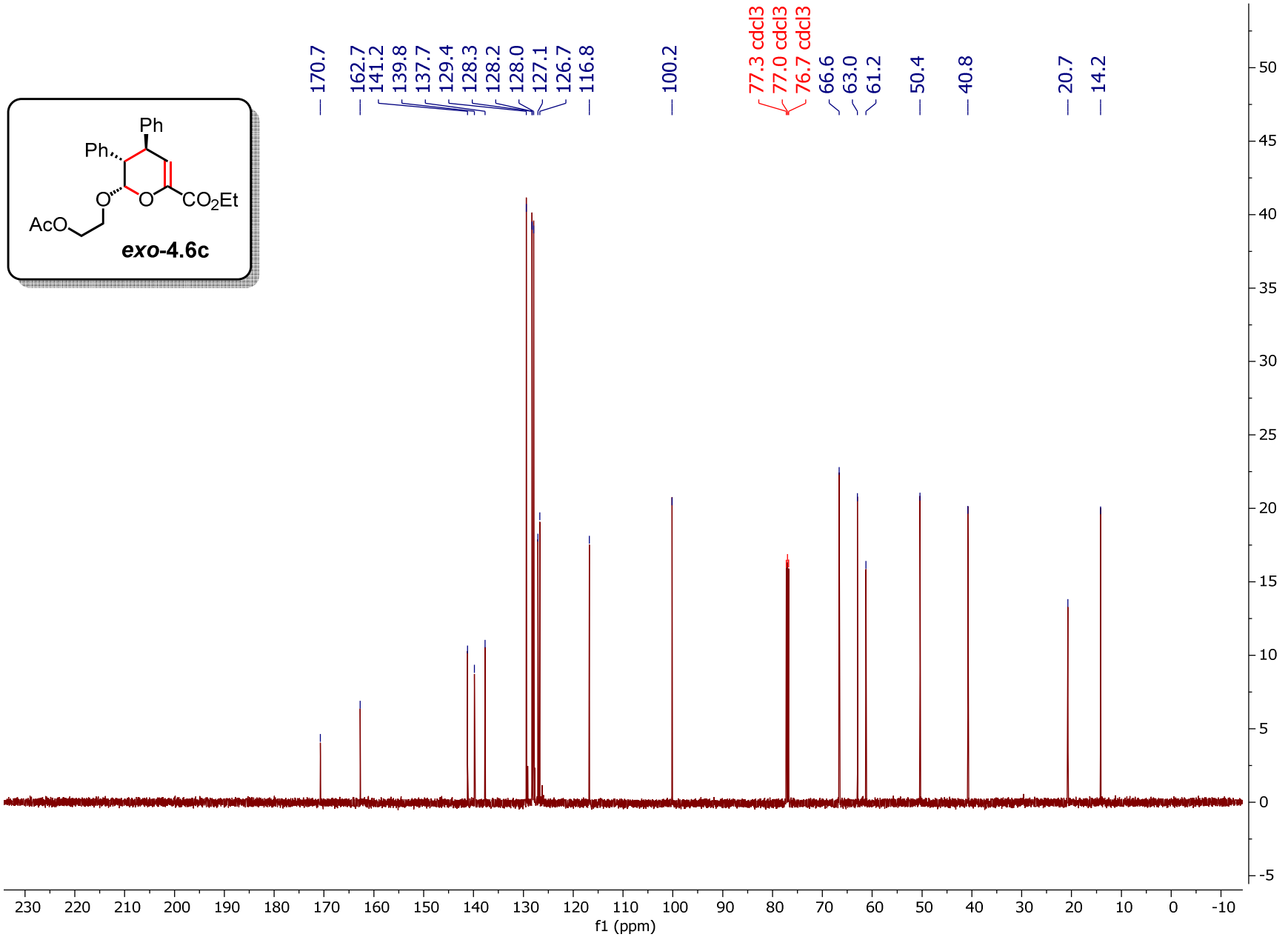


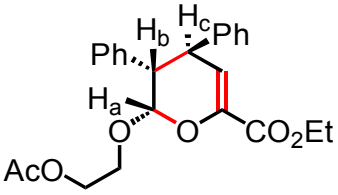
The relative configuration of the major diastereomer of **4.6b** was assigned to be ***exo***


NPth
Me3Si
MeO
O
CO2Et
4.6b
endo:exo = 3.0:1
7.87
7.86
7.85
7.83
7.76
7.76
7.74
7.72
7.27 cdcl3
6.23
6.23
5.23
5.22
5.22
5.21
5.06
5.05
4.34
4.31
4.31
4.30
4.29
4.27
4.26
4.26
4.24
4.22
4.21
3.56
2.31
2.30
1.35
1.33
1.32
0.71
0.70
0.68
0.67
0.65
0.49
0.48
0.46
0.45
-0.06
1.97
2.13
0.92
1.06
1.02
2.00
3.23
1.14
3.05
1.07
1.09
9.00
f1 (ppm)

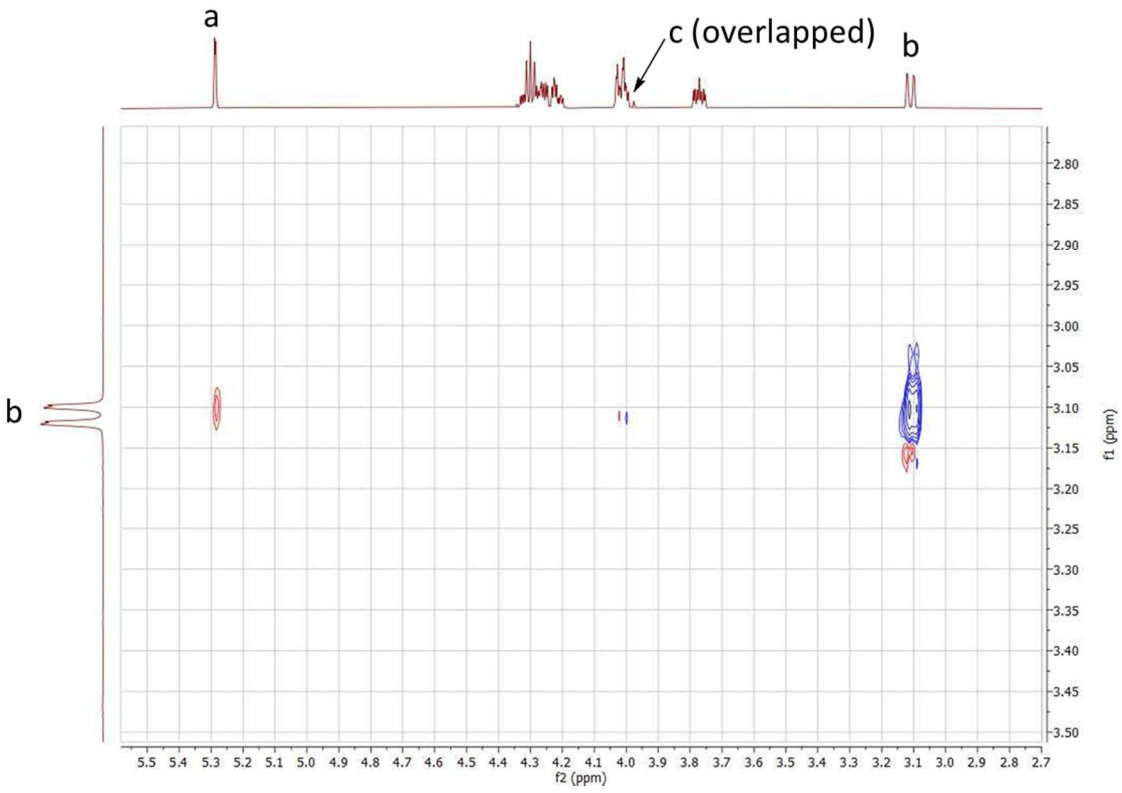

NPth
Me3Si
MeO
O
CO2Et
4.6b
endo:exo = 3.0:1
168.4
162.1
141.4
134.2
131.6
123.4
108.8
103.0
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
61.3
56.5
47.1
36.0
14.2
12.4
-1.0
f1 (ppm)


7.25 7.24 7.23 7.19 7.17 7.16 7.14 7.13 7.12 7.10 7.09 7.00 6.99 6.30 6.30 5.29 5.28 4.33 4.33 4.31 4.30 4.29 4.27 4.26 4.26 4.25 4.24 4.23 4.23 4.22 4.21 4.20 4.19 4.03 4.02 4.01 3.99 3.79 3.79 3.78 3.77 3.76 3.75 3.75 3.12 3.12 3.10 3.10 1.98 1.35 1.33 1.32
Ph
Ph
O
O
CO2Et
AcO
exo-4.6c
7.85 1.89 0.82 0.94 3.99 2.02 1.00 0.95 2.96 2.98
f1 (ppm)

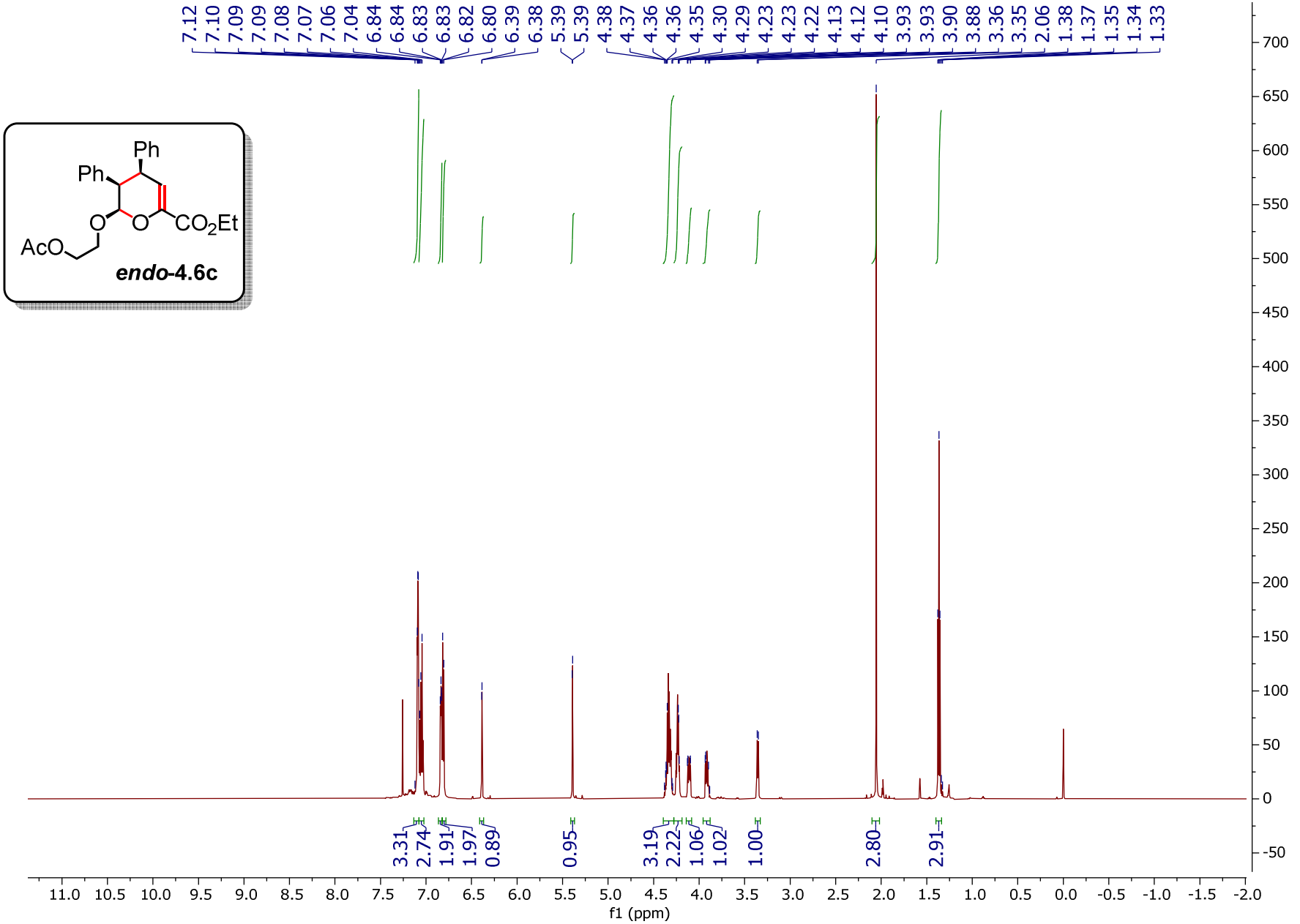

170.7
162.7
141.2
139.8
137.7
129.4
128.3
128.2
128.0
127.1
126.7
116.8
100.2
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
66.6
63.0
61.2
50.4
40.8
20.7
14.2
Ph
Ph
O
O
CO2Et
AcO
exo-4.6c
f1 (ppm)

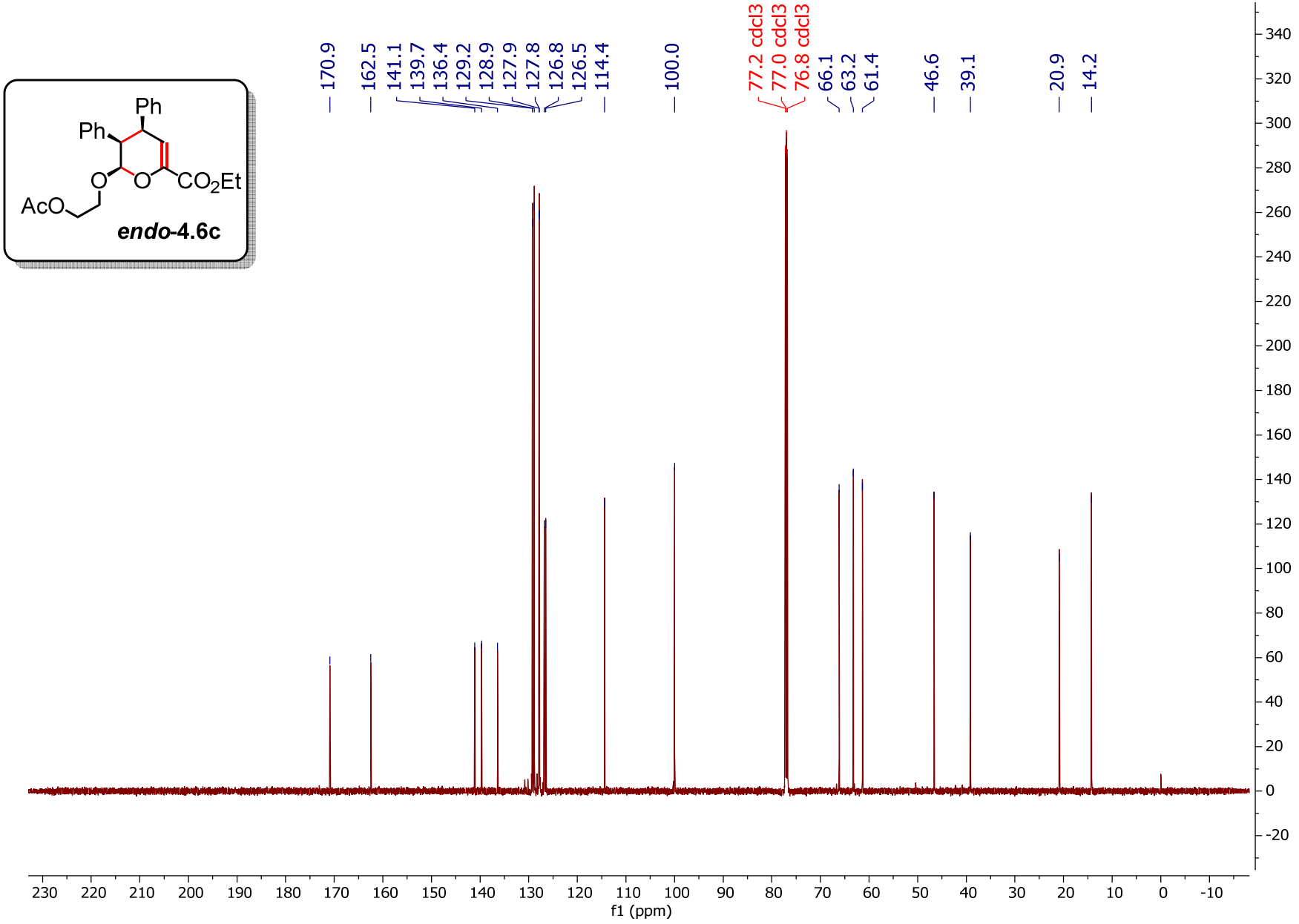


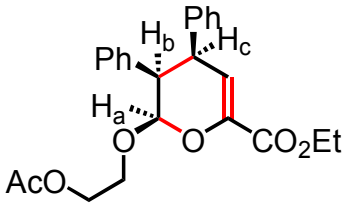
***exo*-4.6c**



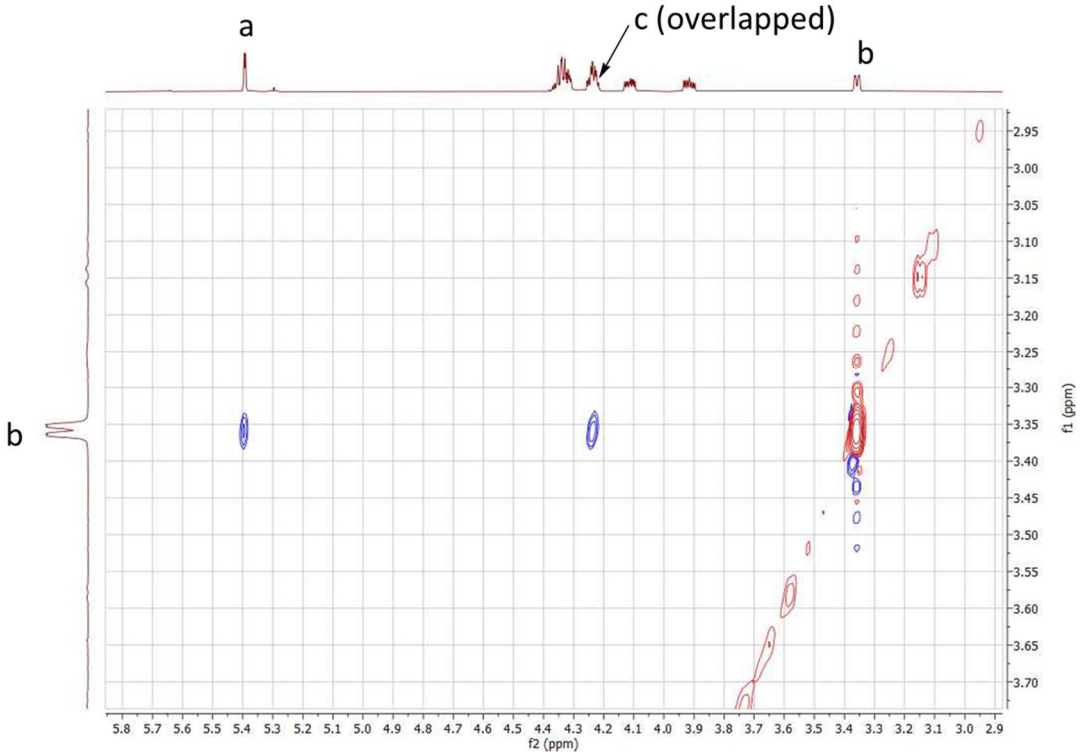
The relative configuration of the major diastereomer of **4.6c** was assigned to be ***exo***.


Ph
Ph
O
O
CO2Et
AcO
endo-4.6c
7.12 7.10 7.09 7.09 7.08 7.07 7.06 7.04 6.84 6.84 6.83 6.83 6.82 6.80 6.39 6.38 5.39 5.39 4.38 4.37 4.36 4.36 4.35 4.30 4.29 4.23 4.23 4.22 4.13 4.12 4.10 3.93 3.93 3.90 3.88 3.36 3.35 2.06 1.38 1.37 1.35 1.34 1.33
3.31 2.74 1.91 1.97 0.89 0.95 3.19 2.22 1.06 1.02 1.00 2.80 2.91
f1 (ppm)

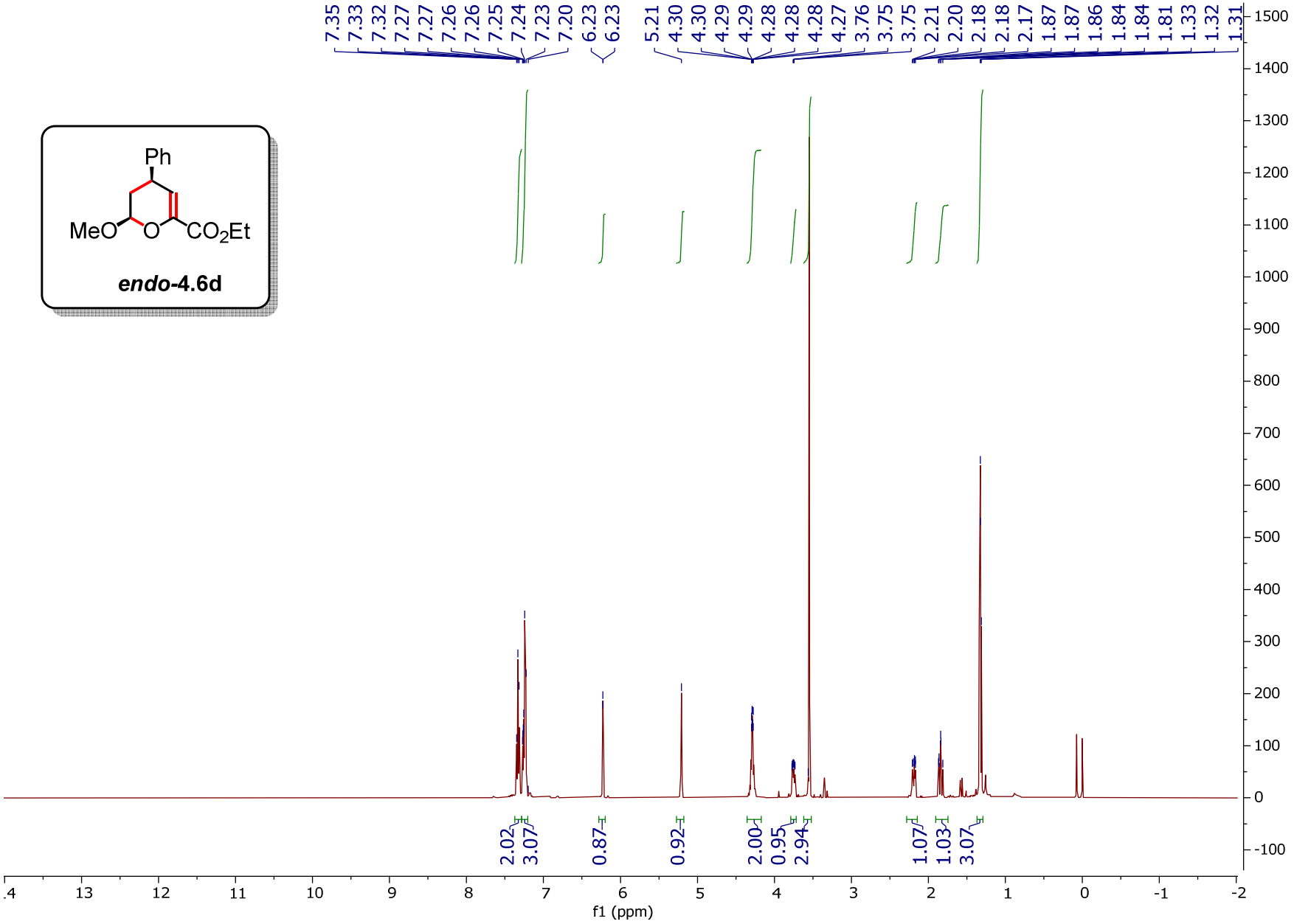

Ph
Ph
O
O
CO2Et
AcO
endo-4.6c
170.9
162.5
141.1
139.7
136.4
129.2
128.9
127.9
127.8
126.8
126.5
114.4
100.0
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
66.1
63.2
61.4
46.6
39.1
20.9
14.2
f1 (ppm)

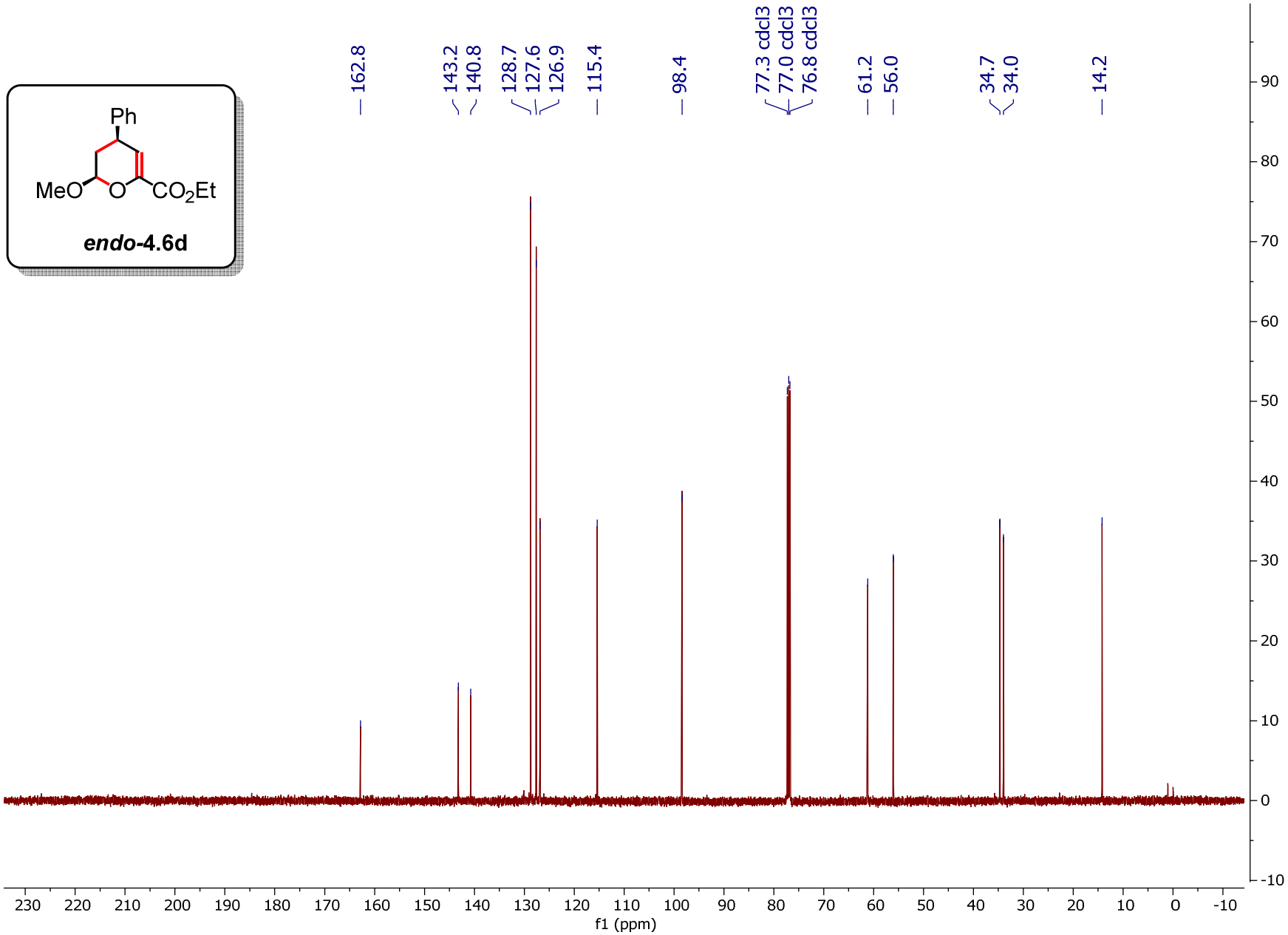


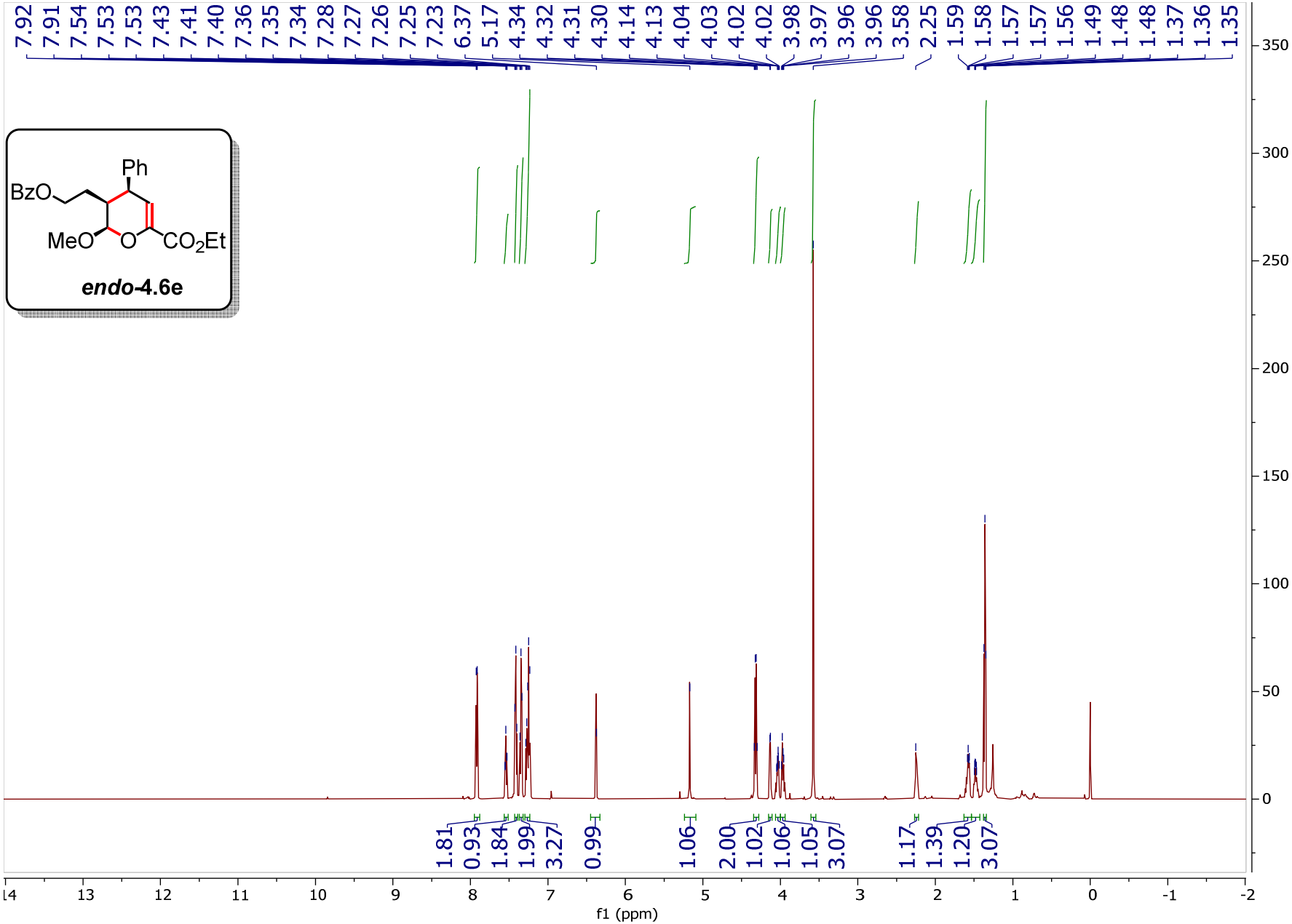
***endo*-4.6c**

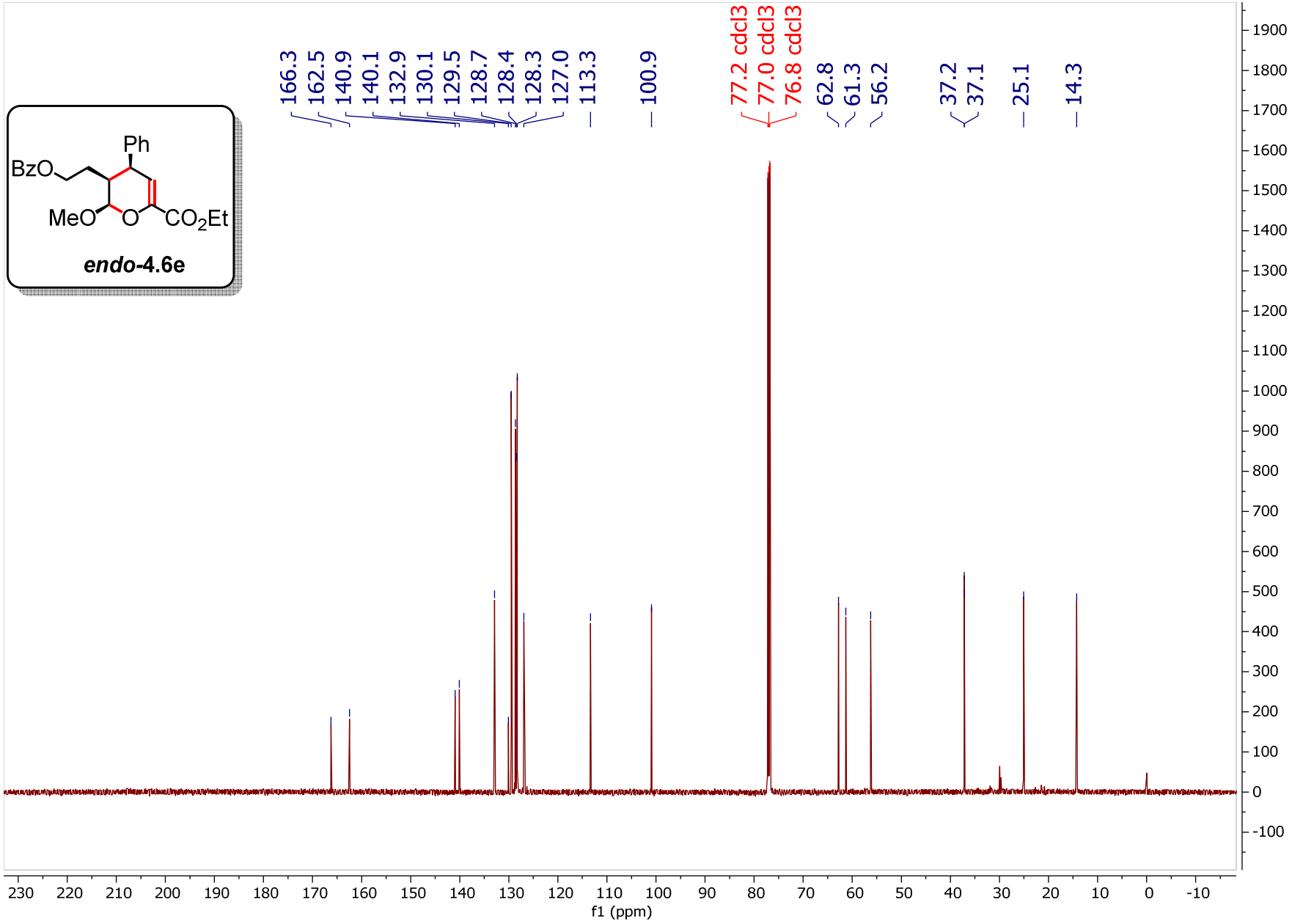


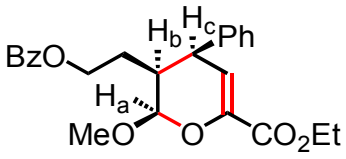
The relative configuration of the minor diastereomer of **4.6c** was assigned to be ***endo***.


Ph
MeO
O
CO2Et
endo-4.6d
7.35 7.33 7.32 7.27 7.27 7.26 7.26 7.25 7.24 7.23 7.20 6.23 6.23
5.21 4.30 4.30 4.29 4.29 4.28 4.28 4.28 4.27 3.76 3.75 3.75 2.21 2.20 2.18 2.18 2.17 1.87 1.87 1.86 1.84 1.84 1.81 1.33 1.32 1.31
2.02 3.07 0.87 0.92 2.00 0.95 2.94 1.07 1.03 3.07
f1 (ppm)

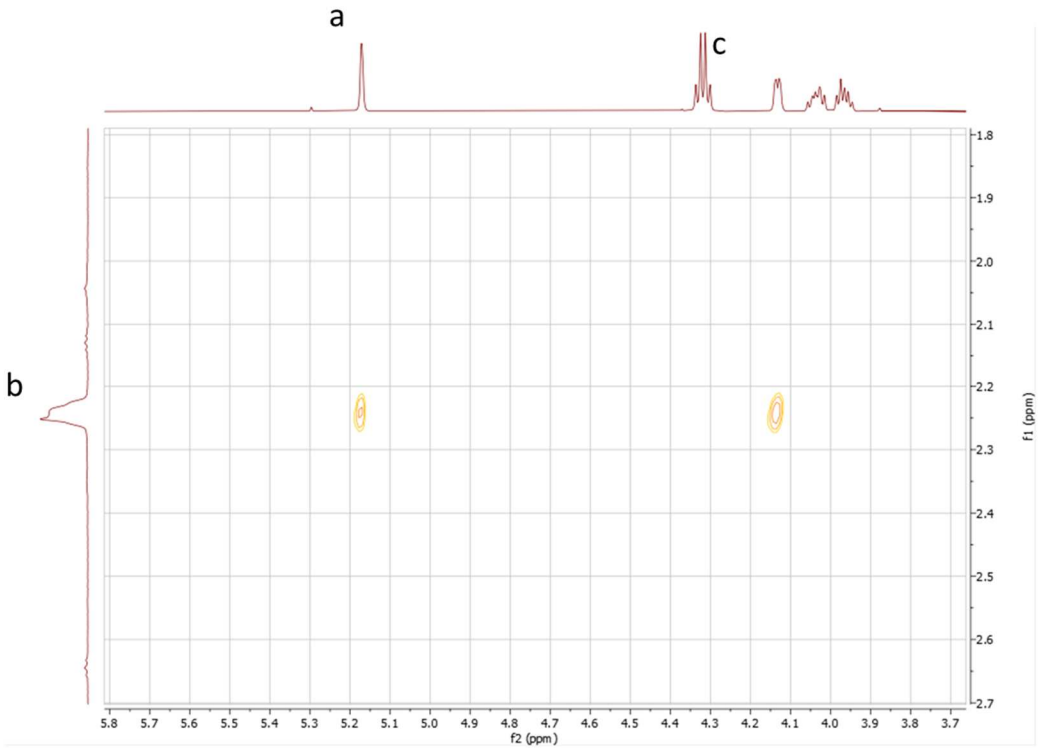

Ph
MeO
O
CO2Et
endo-4.6d
162.8
143.2
140.8
128.7
127.6
126.9
115.4
98.4
77.3 cdcl3
77.0 cdcl3
76.8 cdcl3
61.2
56.0
34.7
34.0
14.2
f1 (ppm)


7.92 7.91 7.54 7.53 7.53 7.43 7.41 7.40 7.36 7.35 7.34 7.28 7.27 7.26 7.25 7.23 6.37 5.17 4.34 4.32 4.31 4.30 4.14 4.13 4.04 4.03 4.02 4.02 3.98 3.97 3.96 3.96 3.58 2.25 1.59 1.58 1.57 1.57 1.56 1.49 1.48 1.48 1.37 1.36 1.35
Ph
BzO
MeO
O
CO2Et
endo-4.6e
1.81 0.93 1.84 1.99 3.27 0.99 1.06 2.00 1.02 1.06 1.05 3.07 1.17 1.39 1.20 3.07
f1 (ppm)

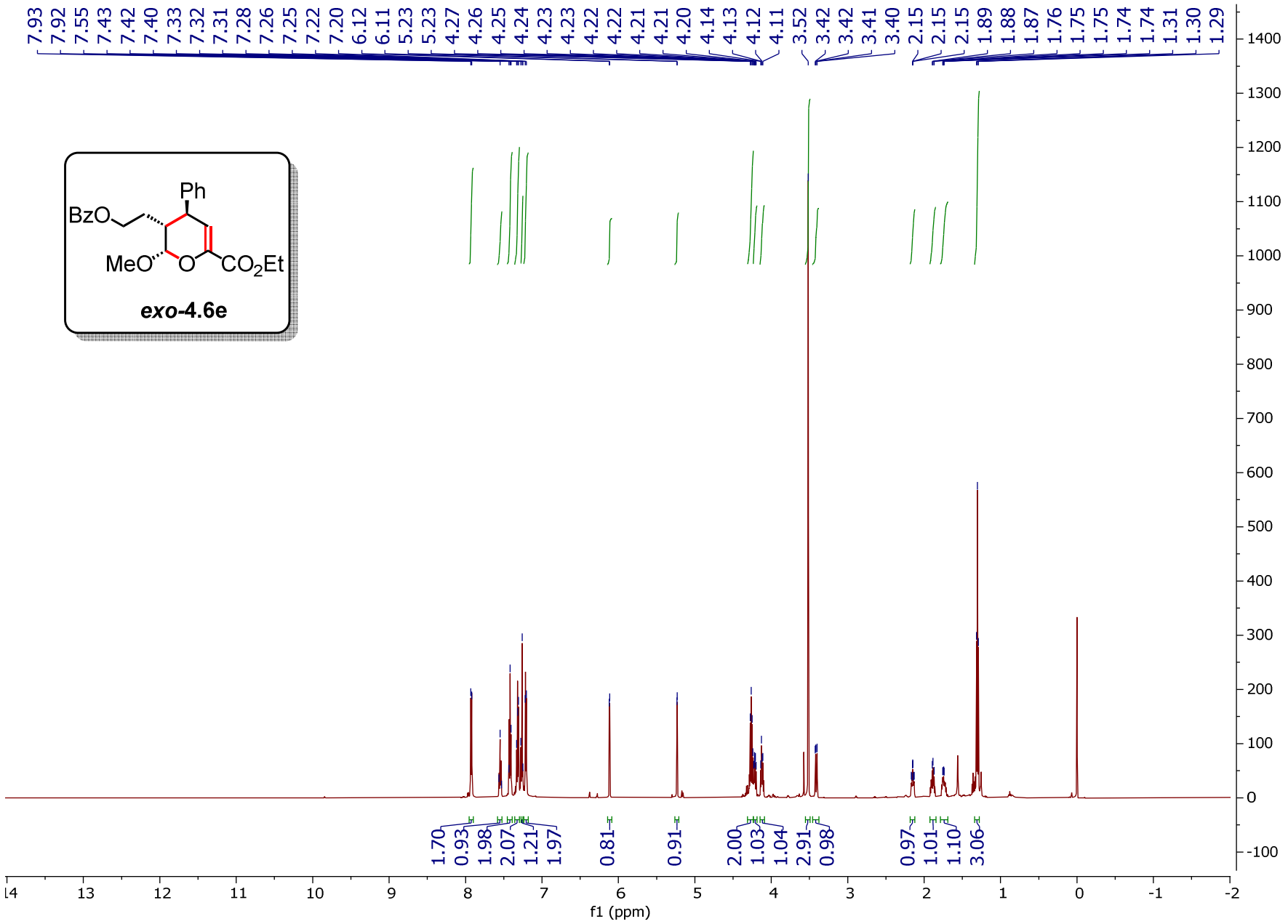

166.3
162.5
140.9
140.1
132.9
130.1
129.5
128.7
128.4
128.3
127.0
113.3
100.9
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
62.8
61.3
56.2
37.2
37.1
25.1
14.3
Ph
BzO
MeO
O
CO2Et
endo-4.6e
f1 (ppm)

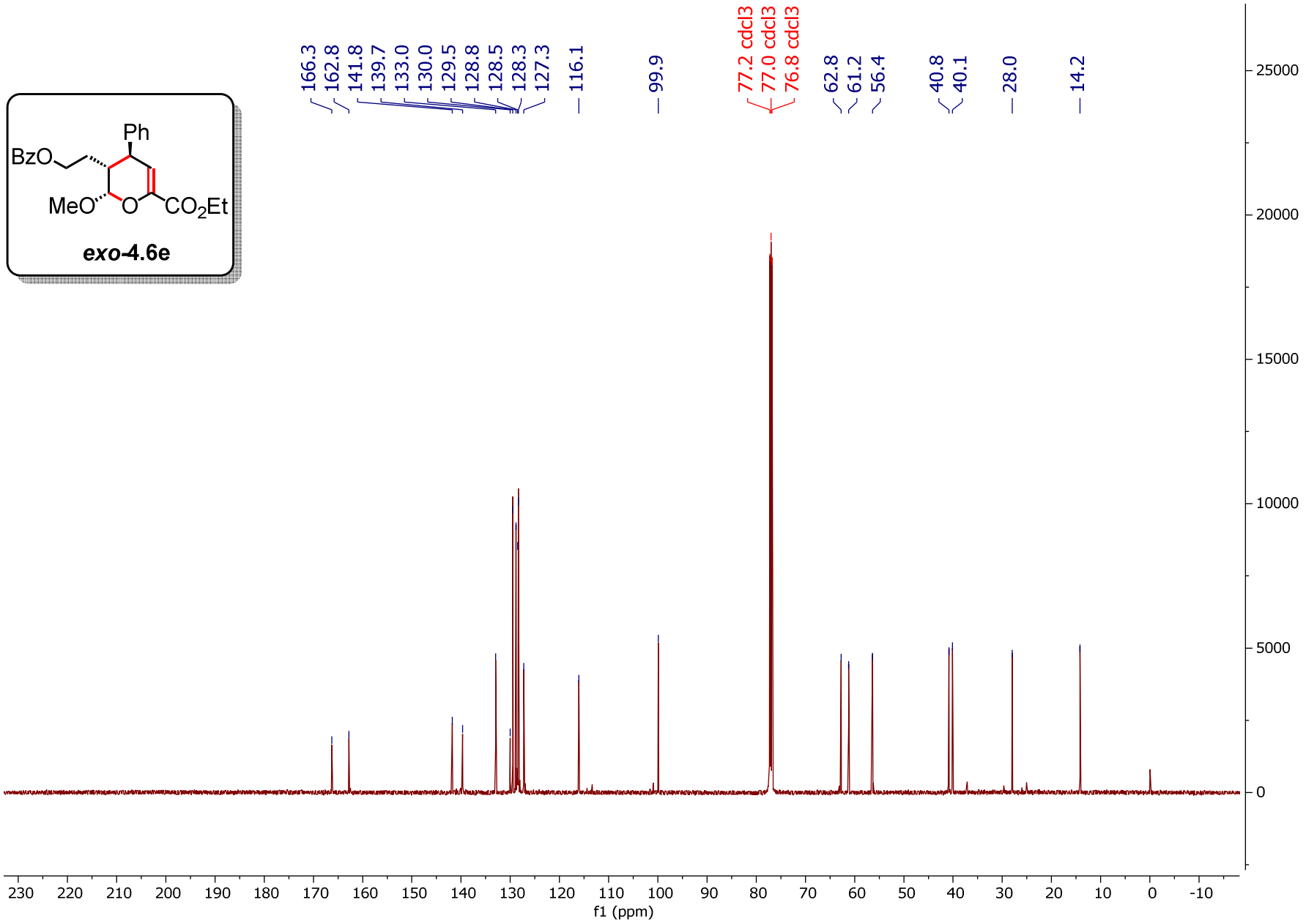


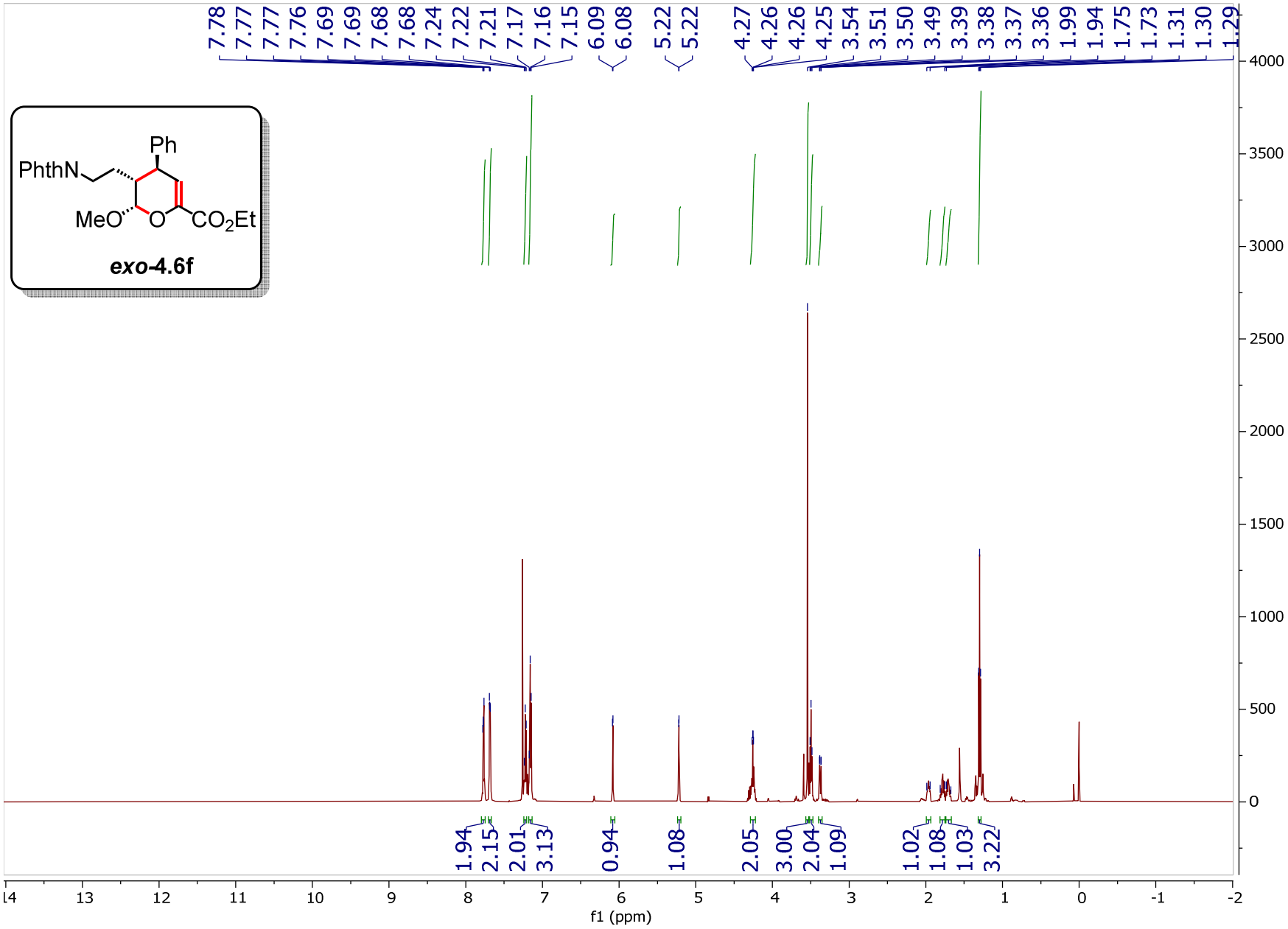
***endo*-4.6e**

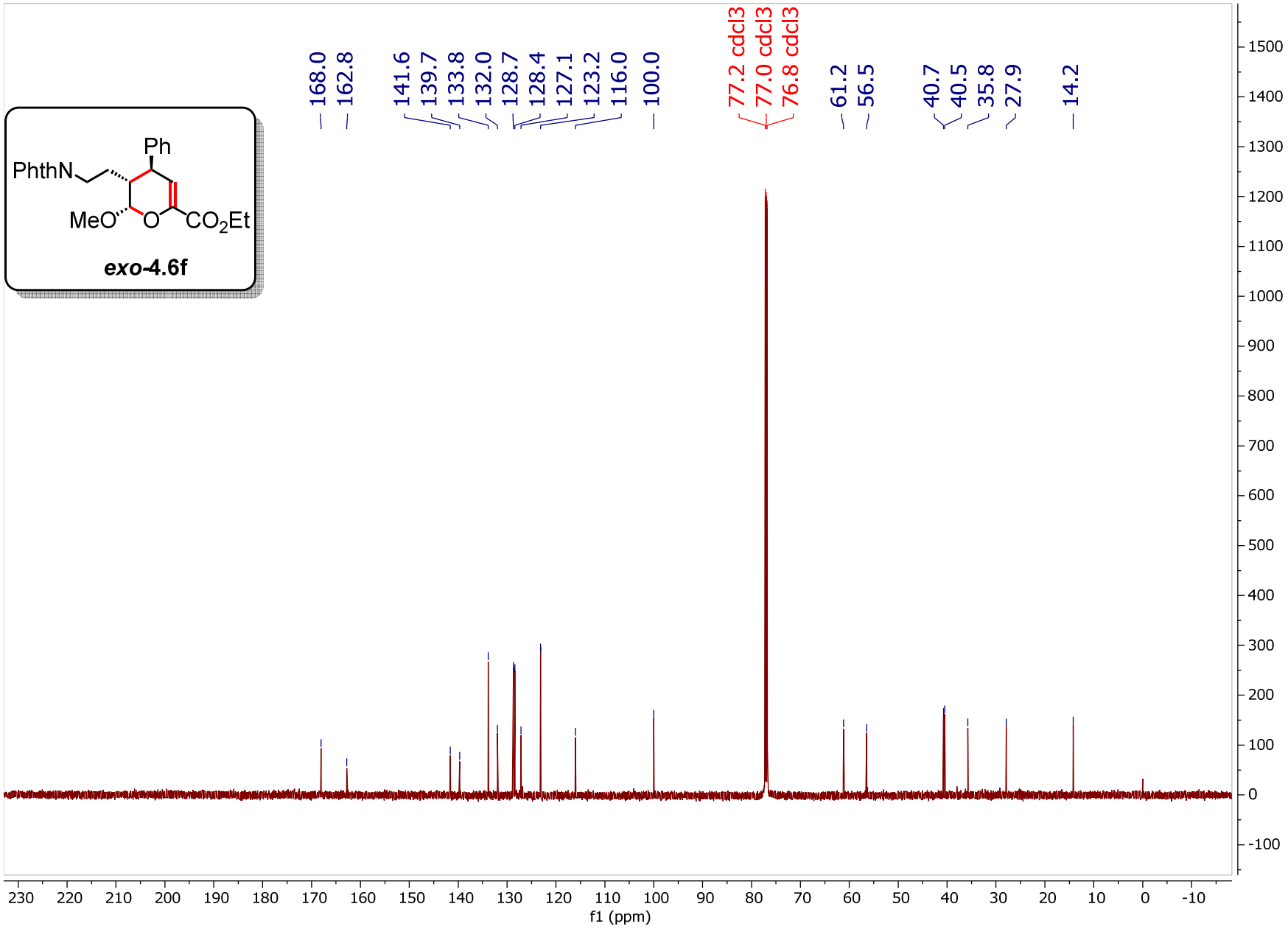


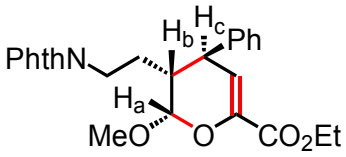
The relative configuration of the minor diastereomer of **4.6e** was assigned to be ***endo***.


7.93 7.92 7.55 7.43 7.42 7.40 7.33 7.32 7.31 7.28 7.26 7.25 7.22 7.20 6.12 6.11 5.23 5.23 4.27 4.26 4.25 4.24 4.23 4.23 4.22 4.22 4.21 4.21 4.20 4.14 4.13 4.12 4.11 3.52 3.42 3.42 3.41 3.40 2.15 2.15 2.15 1.89 1.88 1.87 1.76 1.75 1.75 1.74 1.74 1.31 1.30 1.29
Ph
BzO
MeO
O
CO2Et
exo-4.6e
1.70 0.93 1.98 2.07 1.21 1.97 0.81 0.91 2.00 1.03 1.04 2.91 0.98 0.97 1.01 1.10 3.06
f1 (ppm)

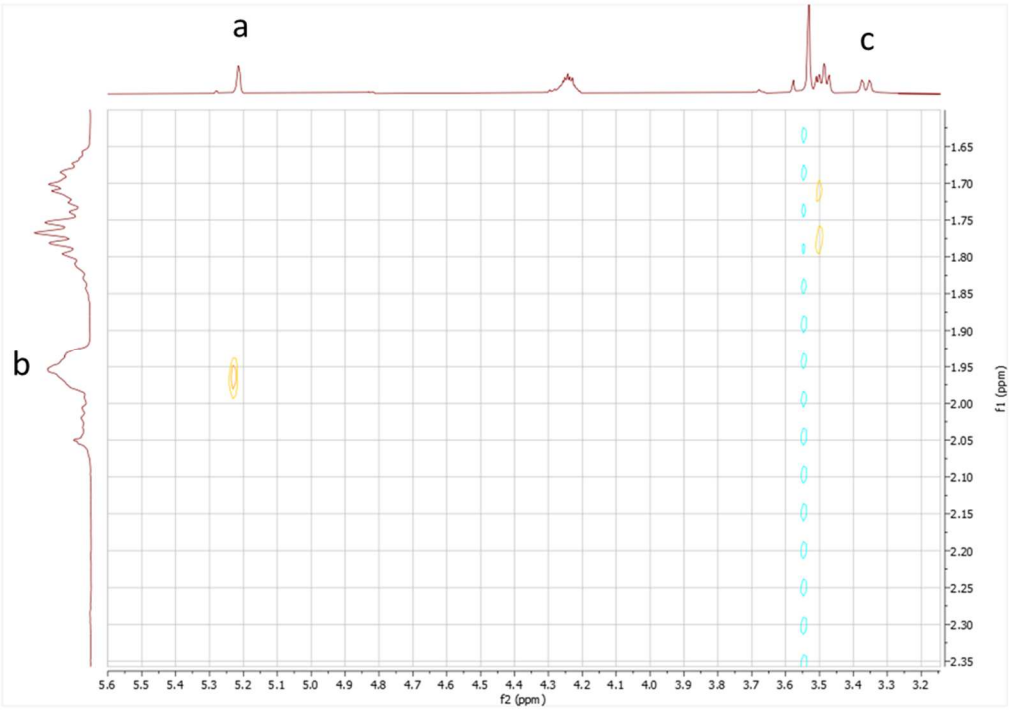

166.3
162.8
141.8
139.7
133.0
130.0
129.5
128.8
128.5
128.3
127.3
116.1
99.9
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
62.8
61.2
56.4
40.8
40.1
28.0
14.2
Ph
BzO
MeO
O
CO2Et
exo-4.6e
25000
20000
15000
10000
5000
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.78
7.77
7.77
7.76
7.69
7.69
7.68
7.68
7.24
7.22
7.21
7.17
7.16
7.15
6.09
6.08
5.22
5.22
4.27
4.26
4.26
4.25
3.54
3.51
3.50
3.49
3.39
3.38
3.37
3.36
1.99
1.94
1.75
1.73
1.31
1.30
1.29
Ph
PhthN
MeO
O
CO2Et
exo-4.6f
1.94
2.15
2.01
3.13
0.94
1.08
2.05
3.00
2.04
1.09
1.02
1.08
1.03
3.22
f1 (ppm)

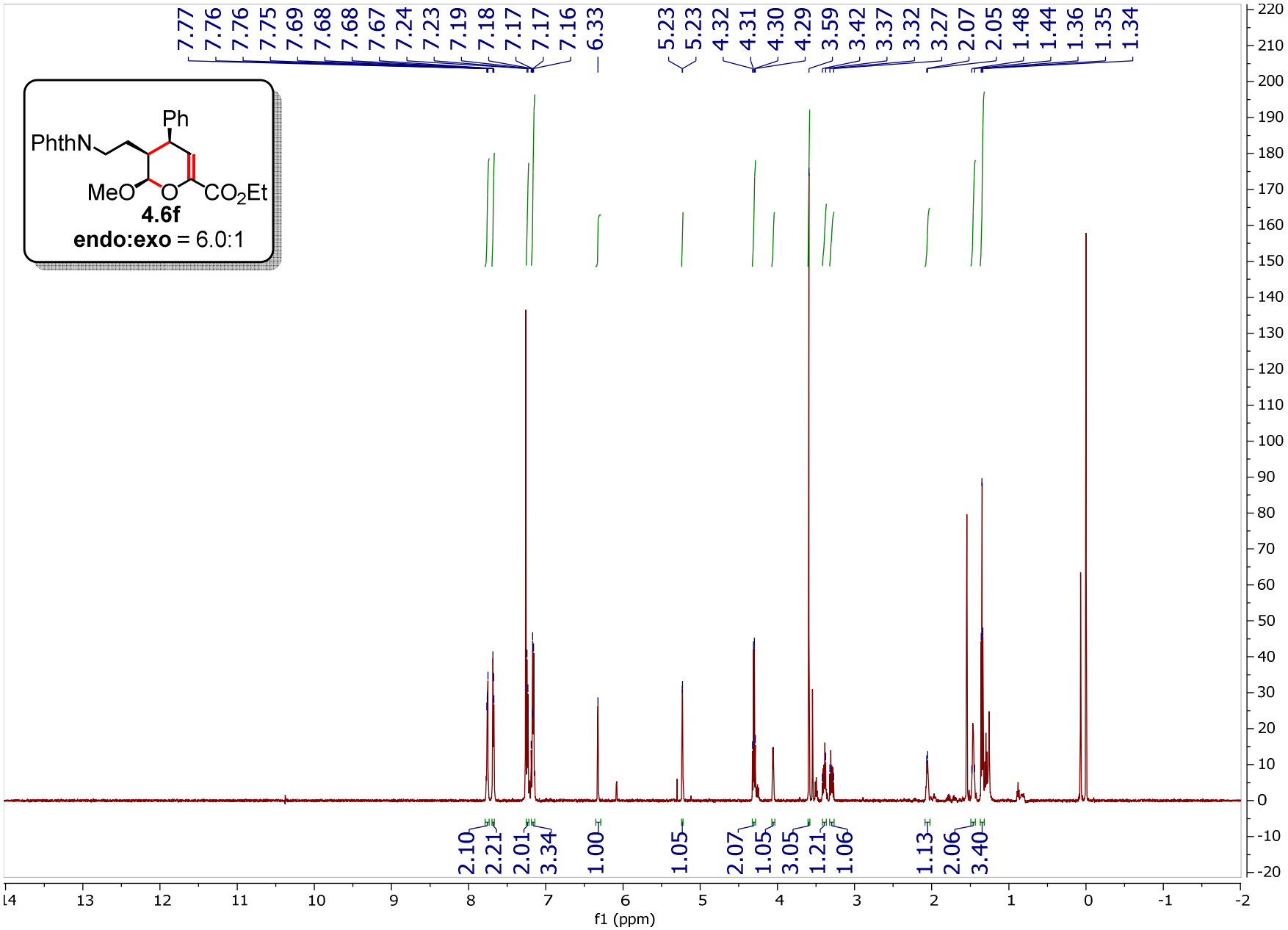

168.0
162.8
141.6
139.7
133.8
132.0
128.7
128.4
127.1
123.2
116.0
100.0
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.2
56.5
40.7
40.5
35.8
27.9
14.2
Ph
PhthN
MeO
O
CO2Et
exo-4.6f
f1 (ppm)

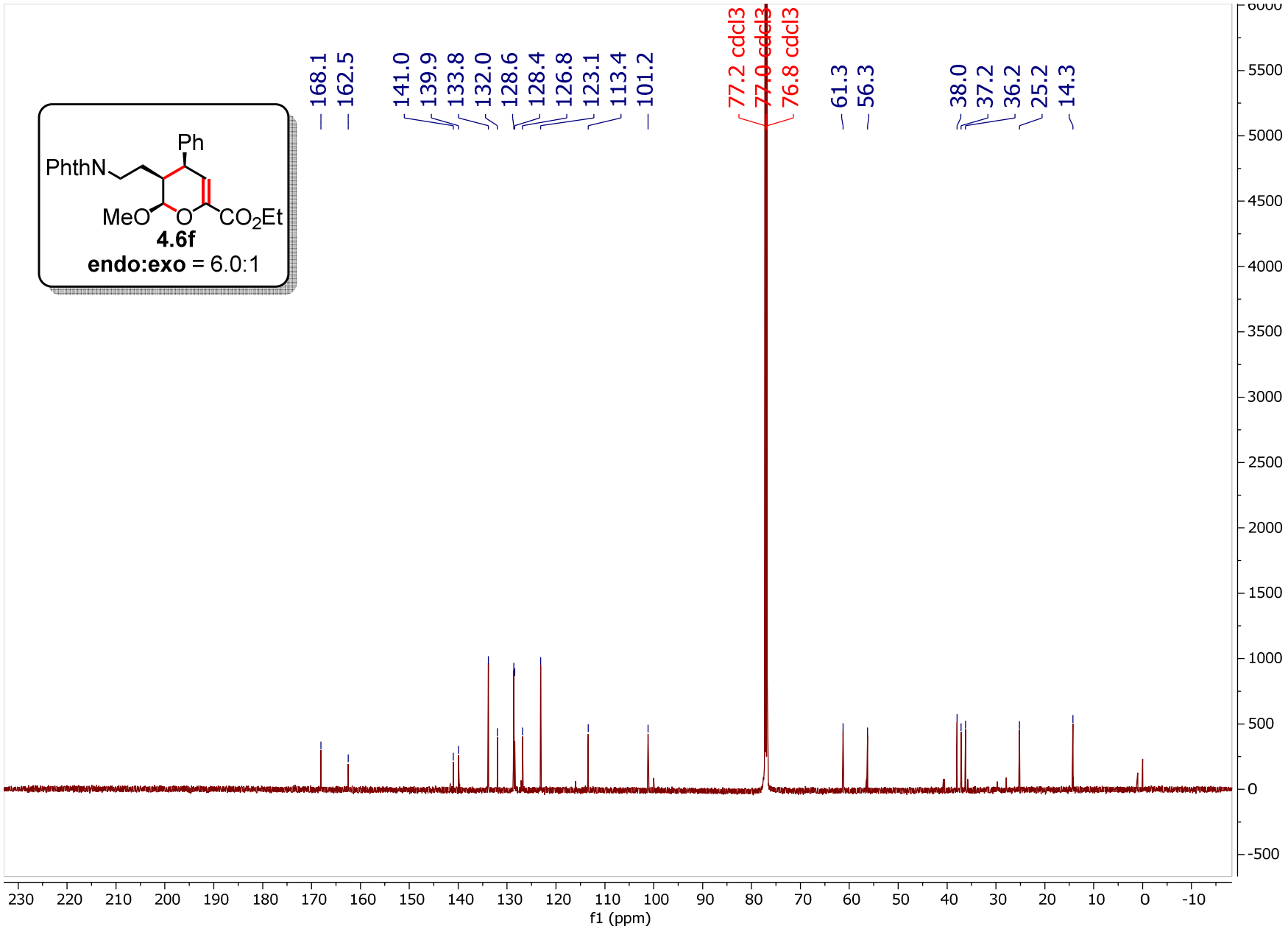


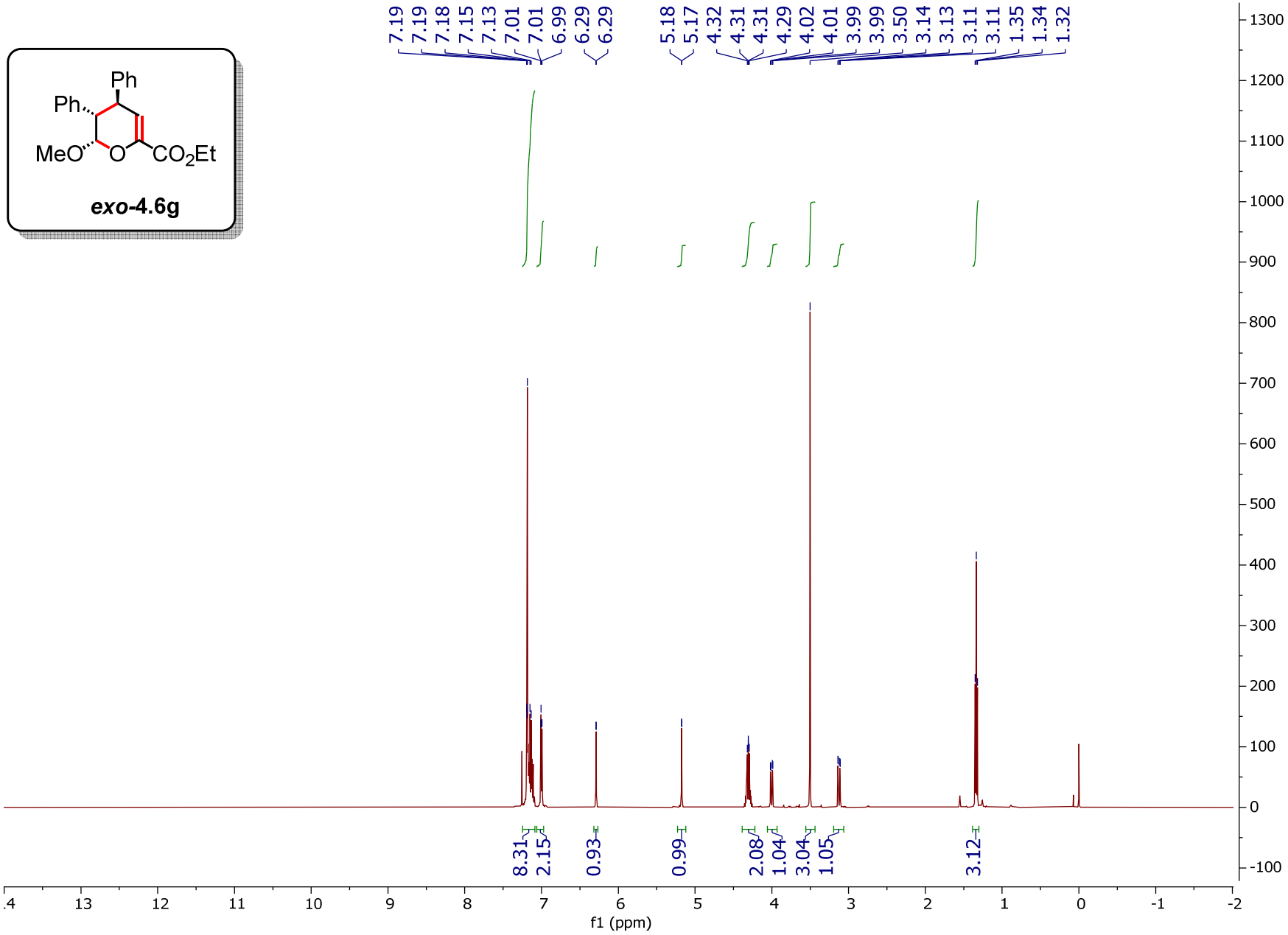
***exo*-4.6f**

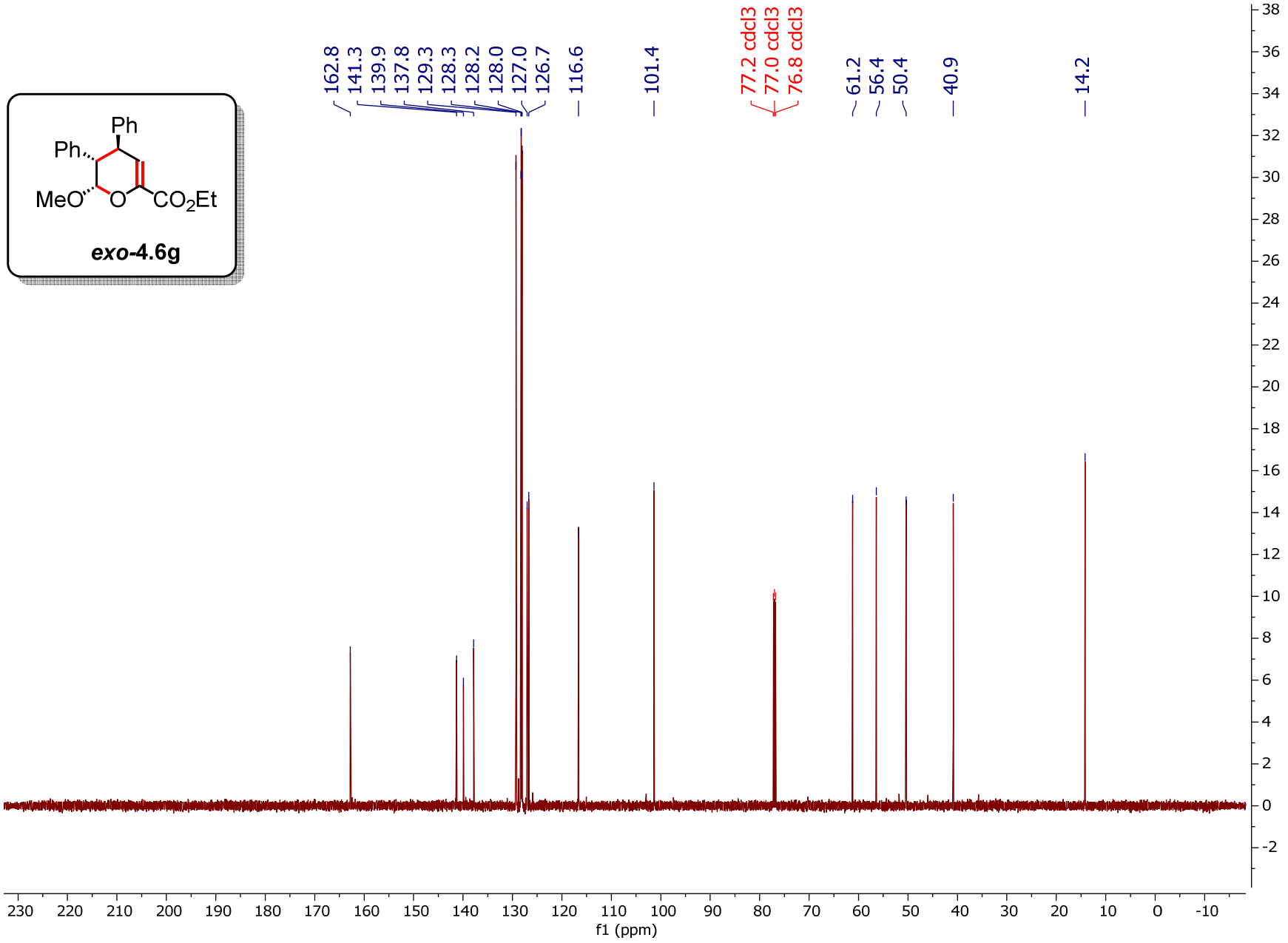


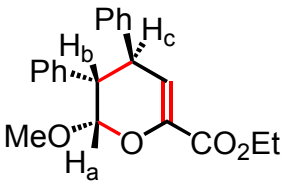
The relative configuration of the major diastereomer of **4.6f** was assigned to be ***exo***.


7.77 7.76 7.76 7.75 7.69 7.68 7.68 7.67 7.24 7.23 7.19 7.18 7.17 7.17 7.16 6.33
5.23 5.23 4.32 4.31 4.30 4.29 3.59 3.42 3.37 3.32 3.27 2.07 2.05 1.48 1.44 1.36 1.35 1.34
Ph
PhthN
MeO
O
CO2Et
4.6f
endo:exo = 6.0:1
2.10 2.21 2.01 3.34 1.00 1.05 2.07 1.05 3.05 1.21 1.06 1.13 2.06 3.40
f1 (ppm)

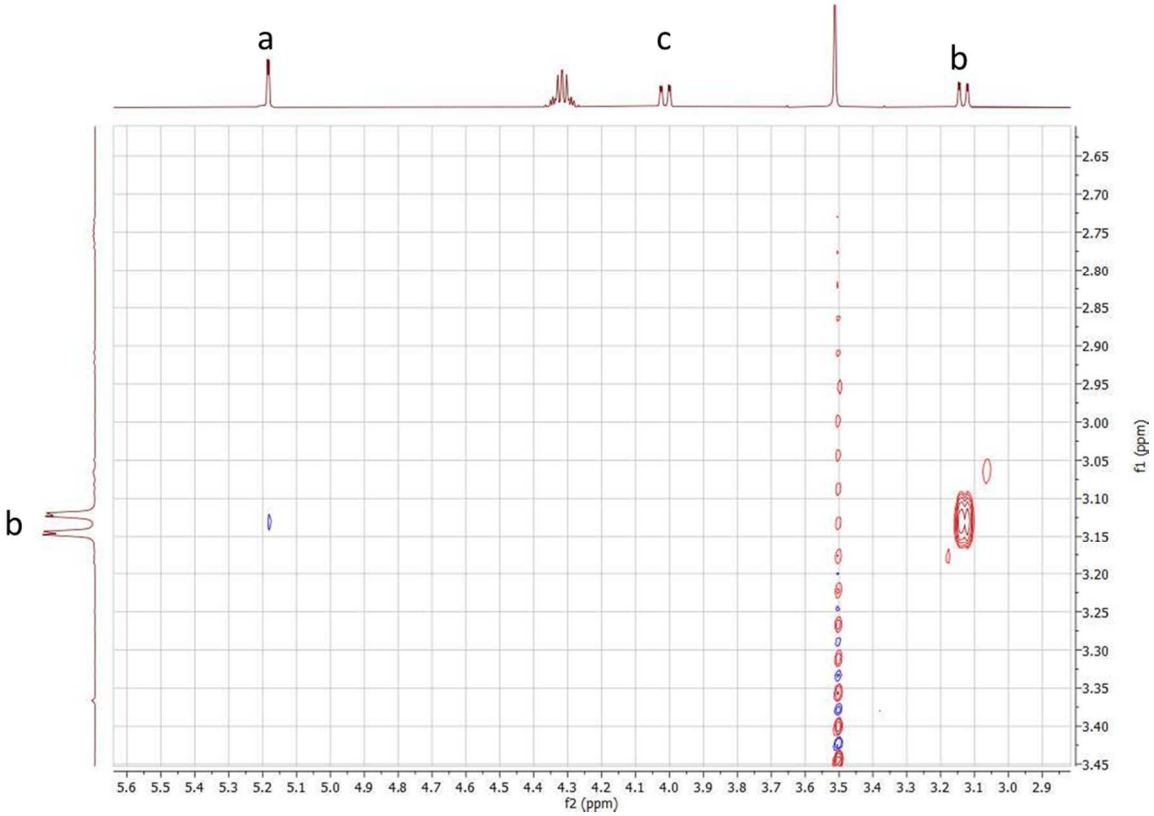

168.1
162.5
141.0
139.9
133.8
132.0
128.6
128.4
126.8
123.1
113.4
101.2
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.3
56.3
38.0
37.2
36.2
25.2
14.3
Ph
PhthN
MeO
O
CO2Et
4.6f
endo:exo = 6.0:1
f1 (ppm)


Ph
Ph
MeO
O
CO2Et
exo-4.6g
7.19
7.19
7.18
7.15
7.13
7.01
7.01
6.99
6.29
6.29
5.18
5.17
4.32
4.31
4.31
4.29
4.02
4.01
3.99
3.99
3.50
3.14
3.13
3.11
3.11
1.35
1.34
1.32
8.31
2.15
0.93
0.99
2.08
1.04
3.04
1.05
3.12
f1 (ppm)

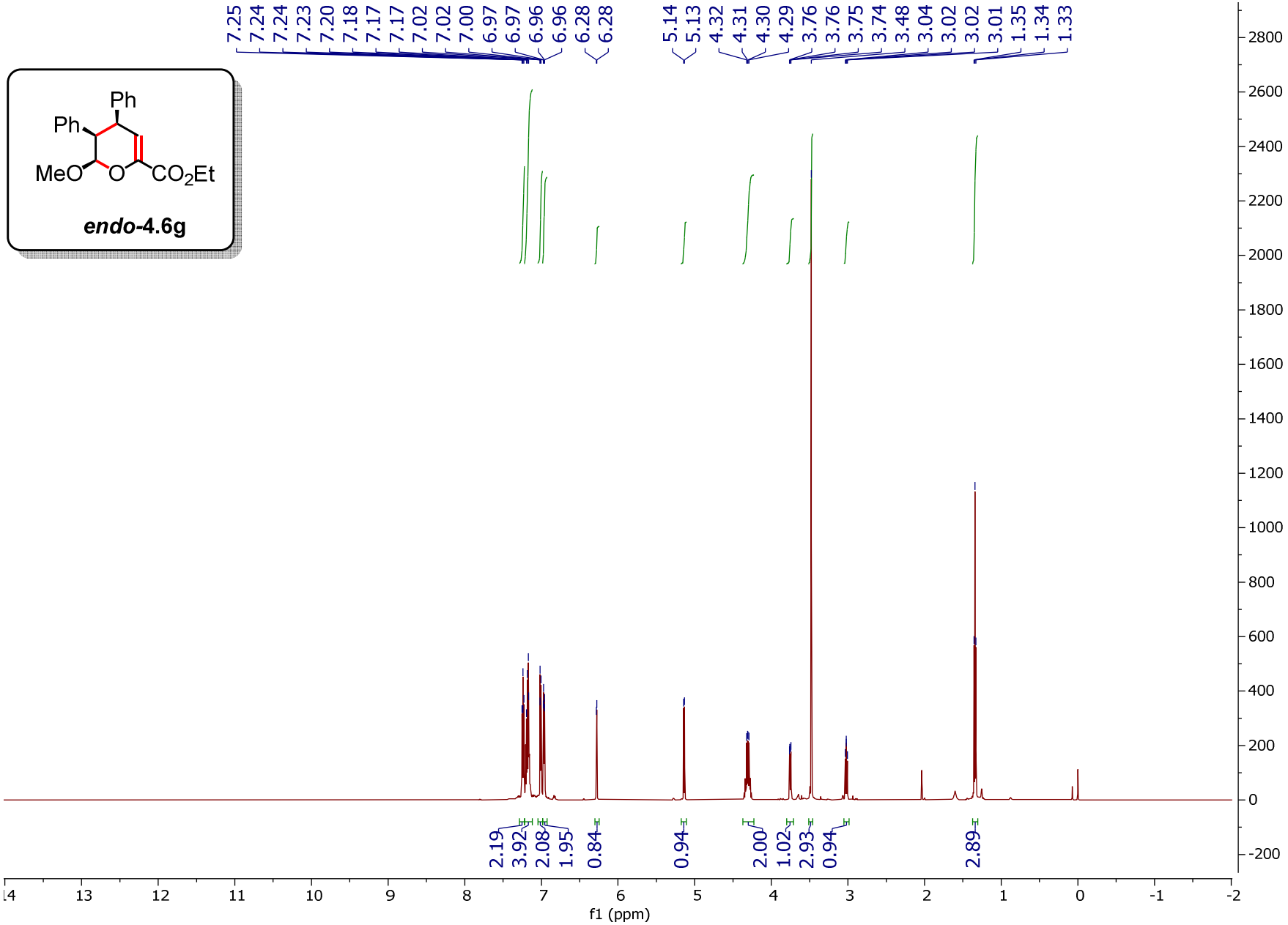

Ph
Ph
MeO
O
CO2Et
exo-4.6g
162.8
141.3
139.9
137.8
129.3
128.3
128.2
128.0
127.0
126.7
116.6
101.4
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.2
56.4
50.4
40.9
14.2
f1 (ppm)

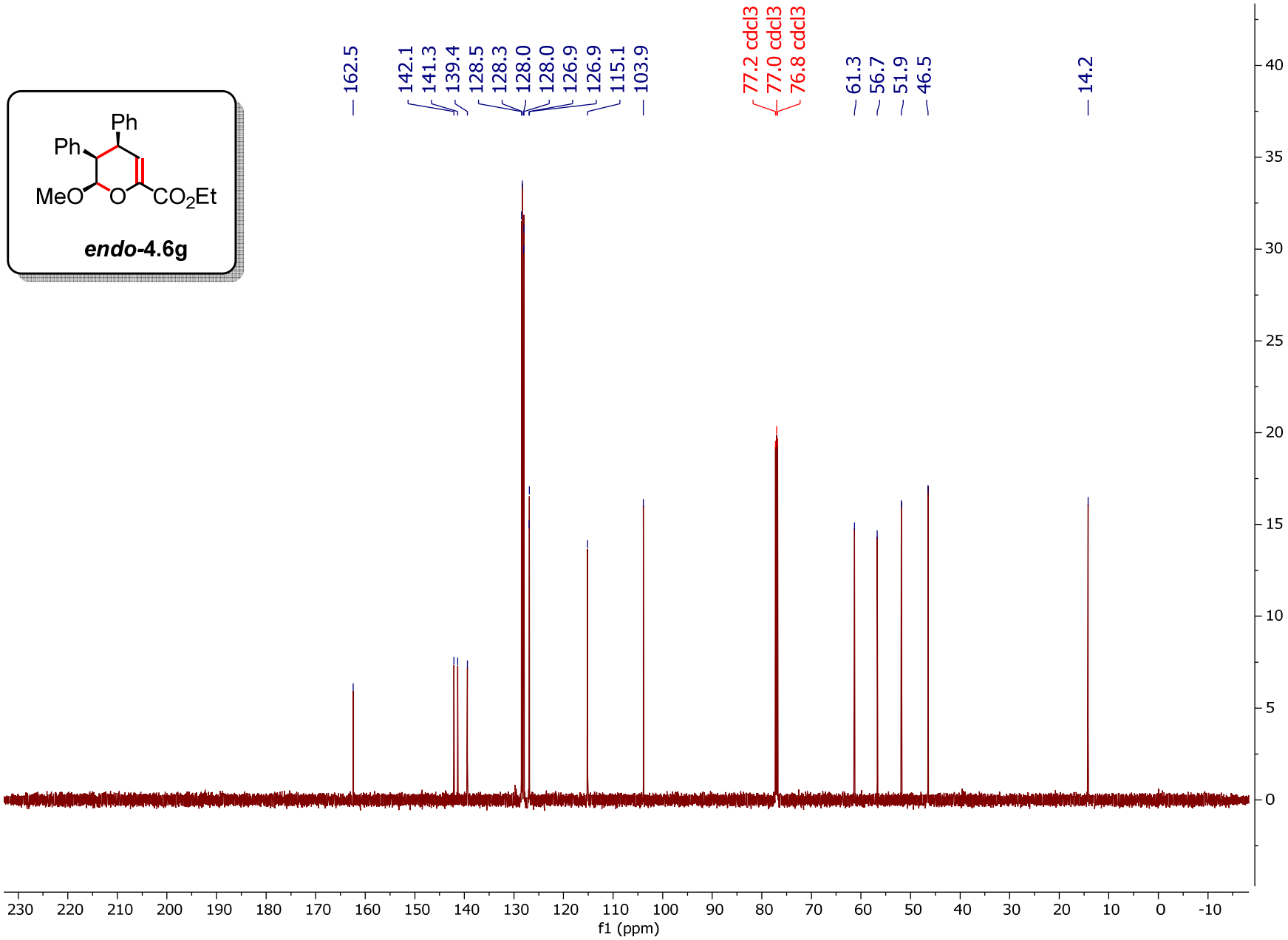


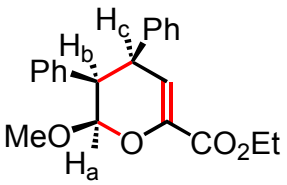
***exo*-4.6g**



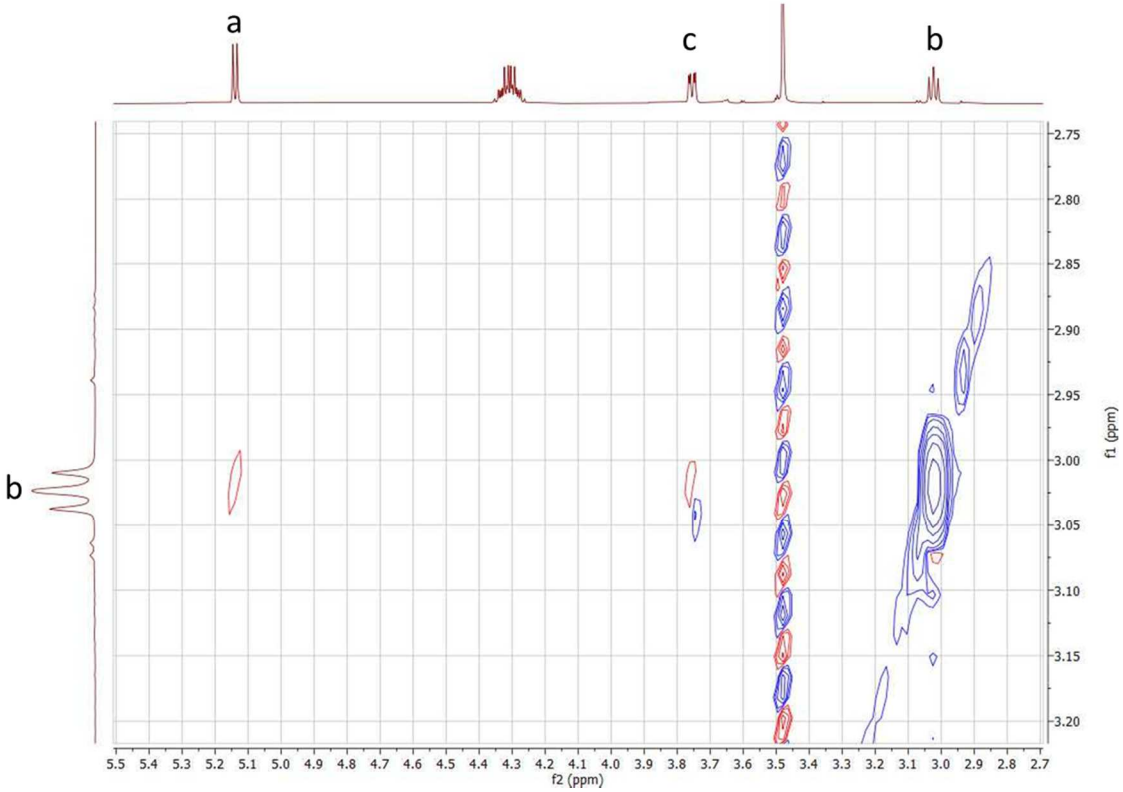
The relative configuration of the major diastereomer of **4.6g** was assigned to be ***exo***. (*see:* **Section C8** for X-ray structure)


Ph
Ph
MeO
O
CO2Et
endo-4.6g
7.25 7.24 7.24 7.23 7.20 7.18 7.17 7.17 7.02 7.02 7.00 6.97 6.97 6.96 6.96 6.28 6.28
5.14 5.13 4.32 4.31 4.30 4.29 3.76 3.76 3.75 3.74 3.48 3.04 3.02 3.02 3.01 1.35 1.34 1.33
2.19 3.92 2.08 1.95 0.84 0.94 2.00 1.02 2.93 0.94 2.89
f1 (ppm)

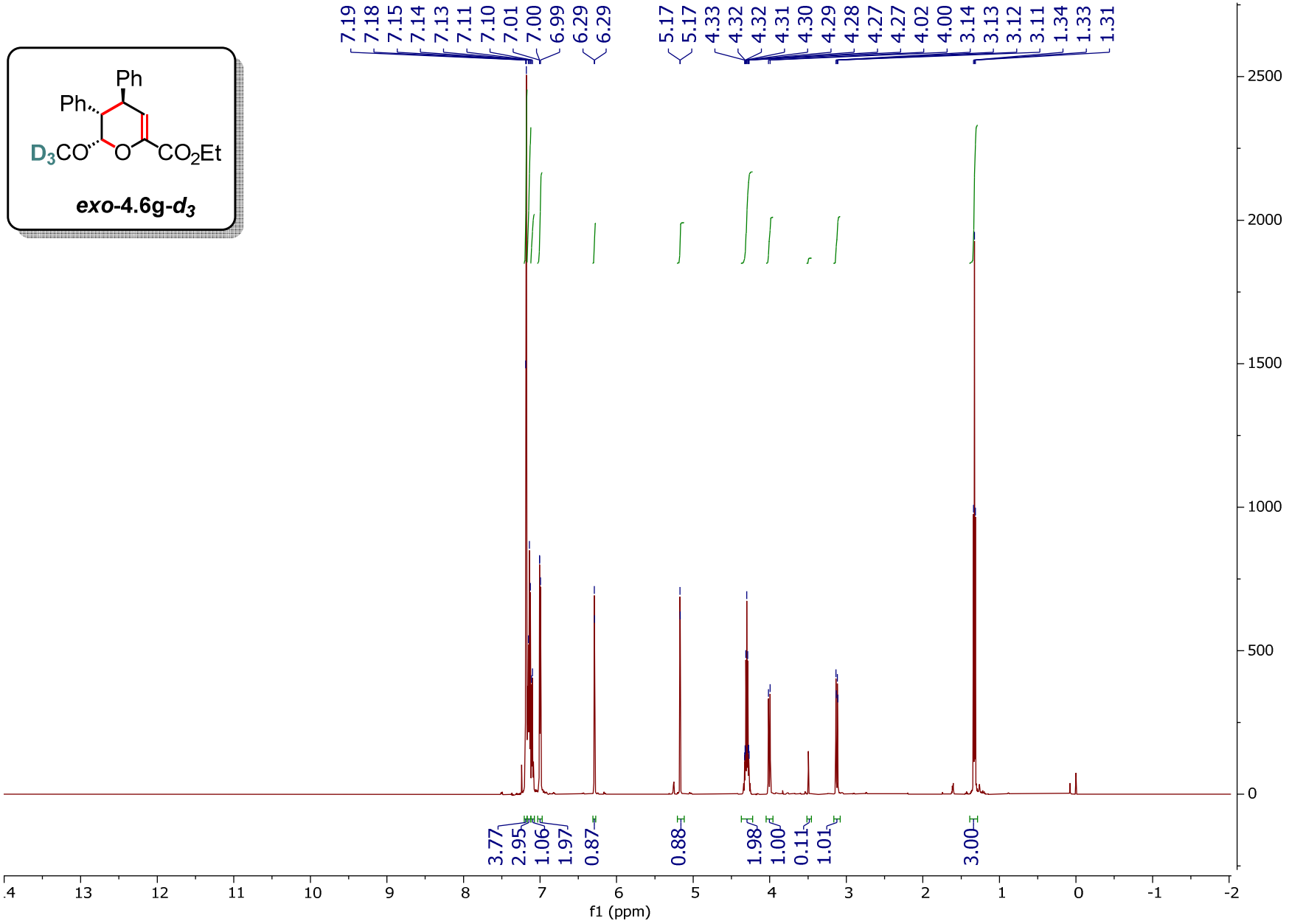

Ph
Ph
MeO
O
CO2Et
endo-4.6g
162.5
142.1
141.3
139.4
128.5
128.3
128.0
128.0
126.9
126.9
115.1
103.9
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.3
56.7
51.9
46.5
14.2
f1 (ppm)

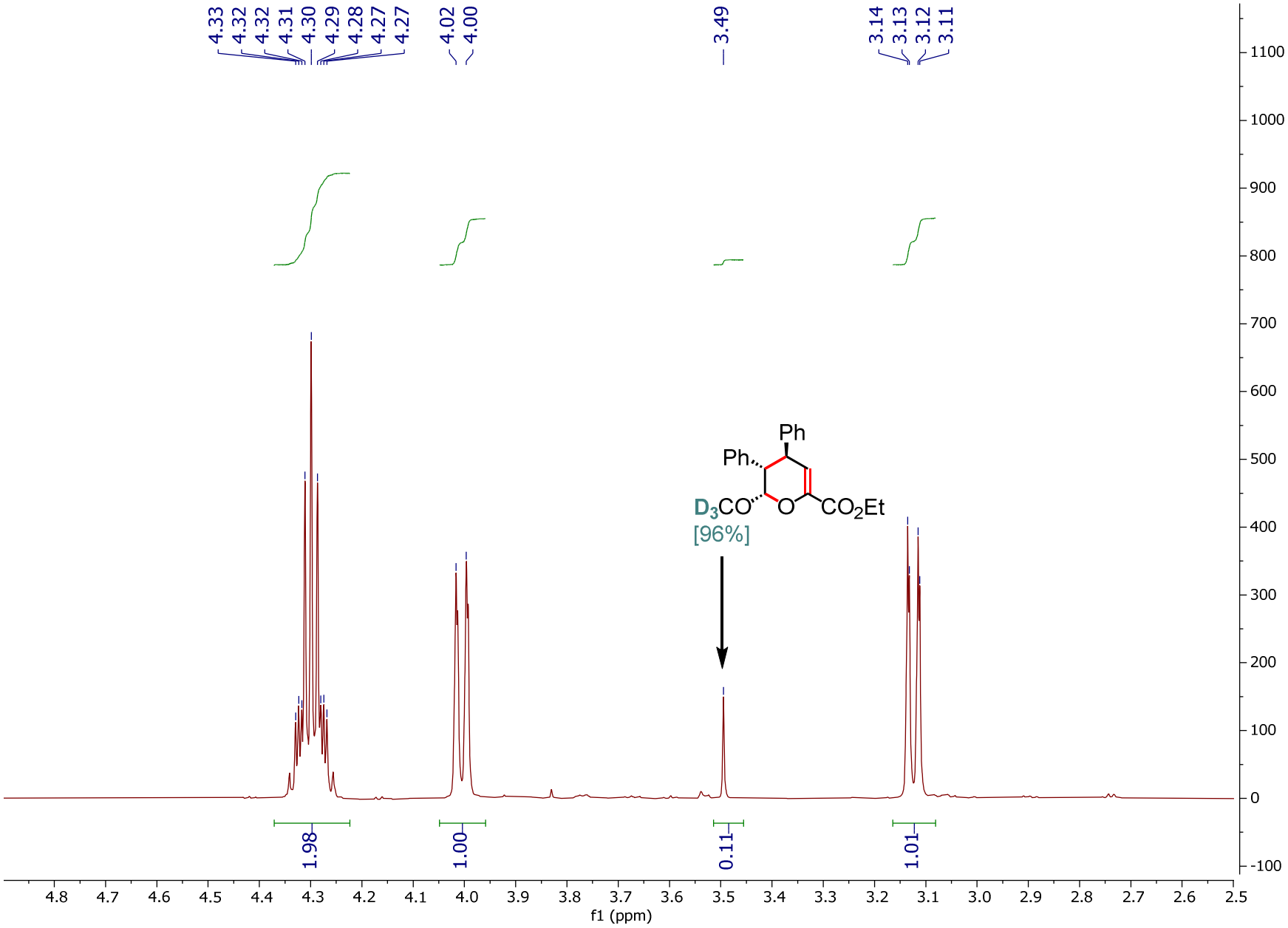


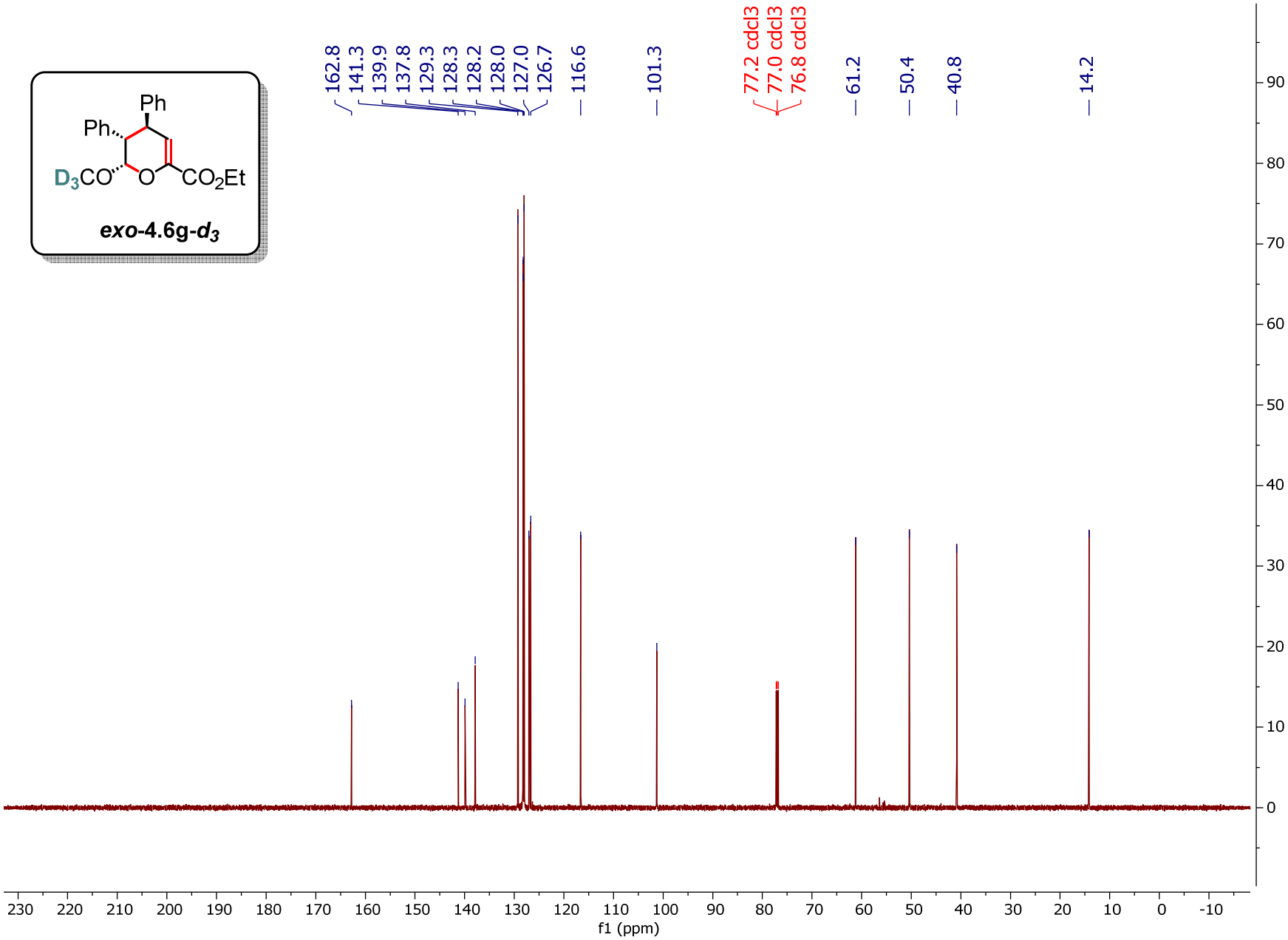
***endo*-4.6g**

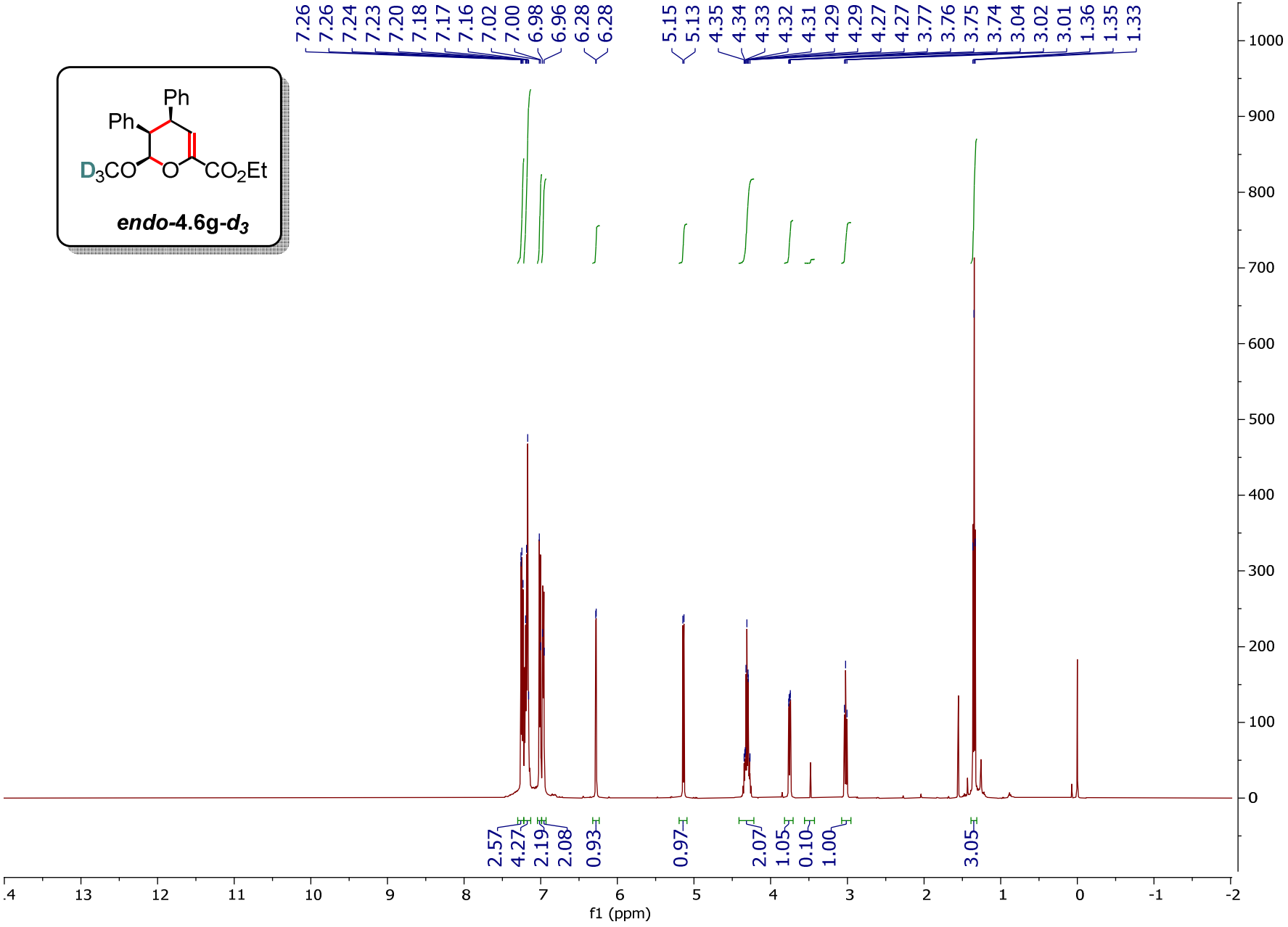


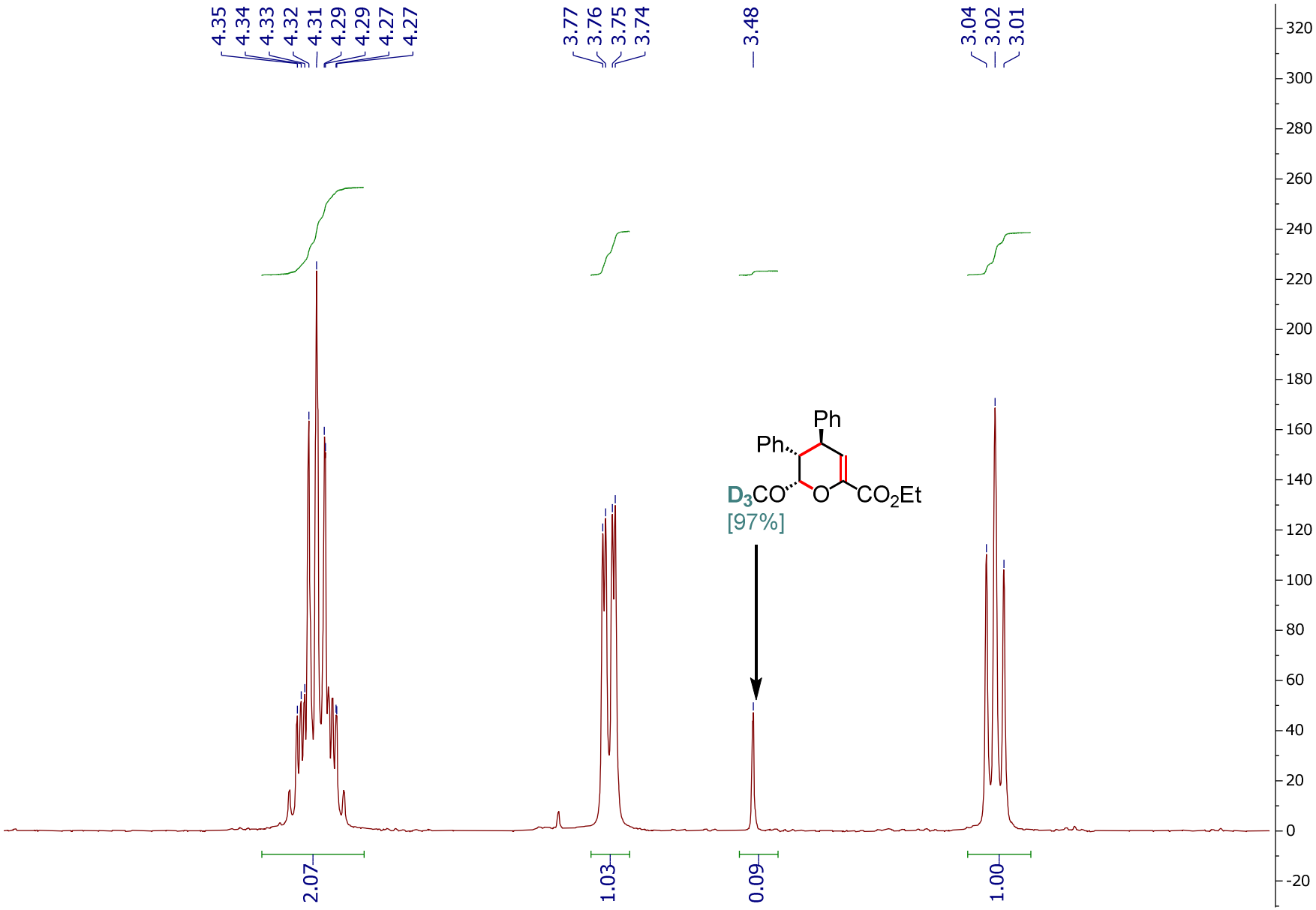
The relative configuration of the minor diastereomer of **4.6g** was assigned to be ***endo***.

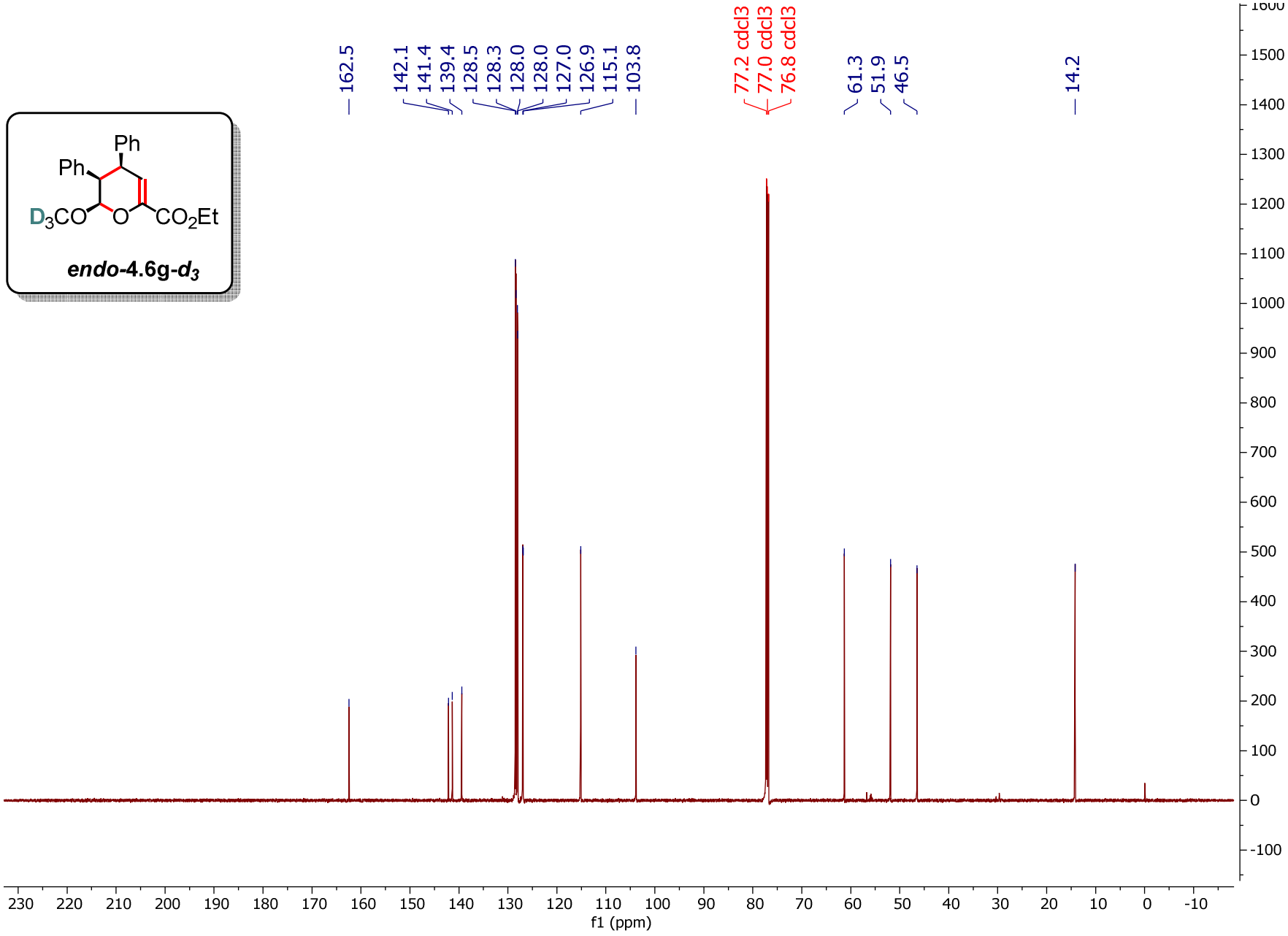

Ph
Ph
D3CO
O
CO2Et
exo-4.6g-d3
7.19
7.18
7.15
7.14
7.13
7.11
7.10
7.01
7.00
6.99
6.29
6.29
5.17
5.17
4.33
4.32
4.32
4.31
4.30
4.29
4.28
4.27
4.27
4.02
4.00
3.14
3.13
3.12
3.11
1.34
1.33
1.31
3.77
2.95
1.06
1.97
0.87
0.88
1.98
1.00
0.11
1.01
3.00
2500
2000
1500
1000
500
0
f1 (ppm)

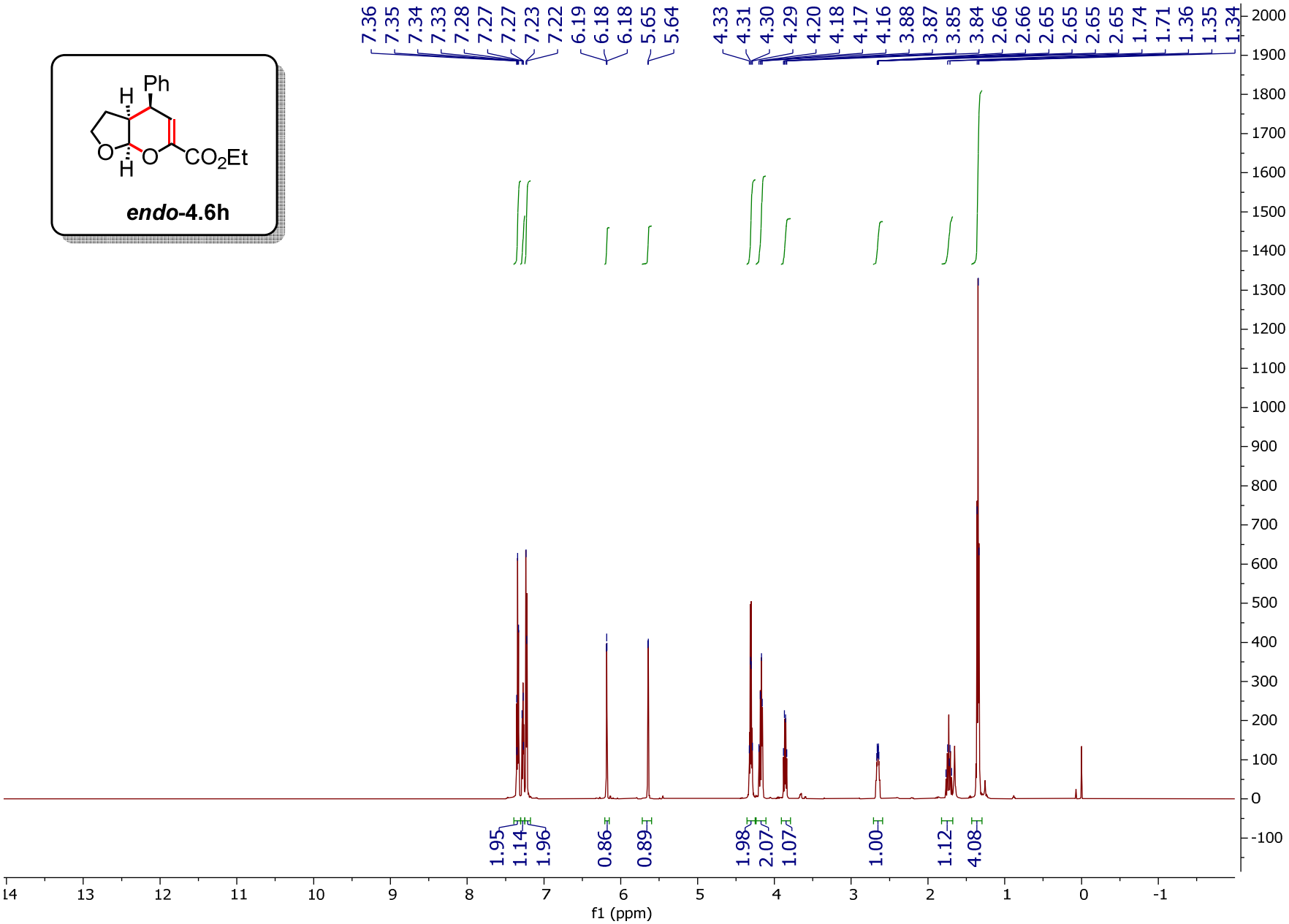

4.33
4.32
4.32
4.31
4.30
4.29
4.28
4.27
4.27
4.02
4.00
3.49
3.14
3.13
3.12
3.11
Ph
Ph
D3CO
O
CO2Et
[96%]
1.98
1.00
0.11
1.01
f1 (ppm)

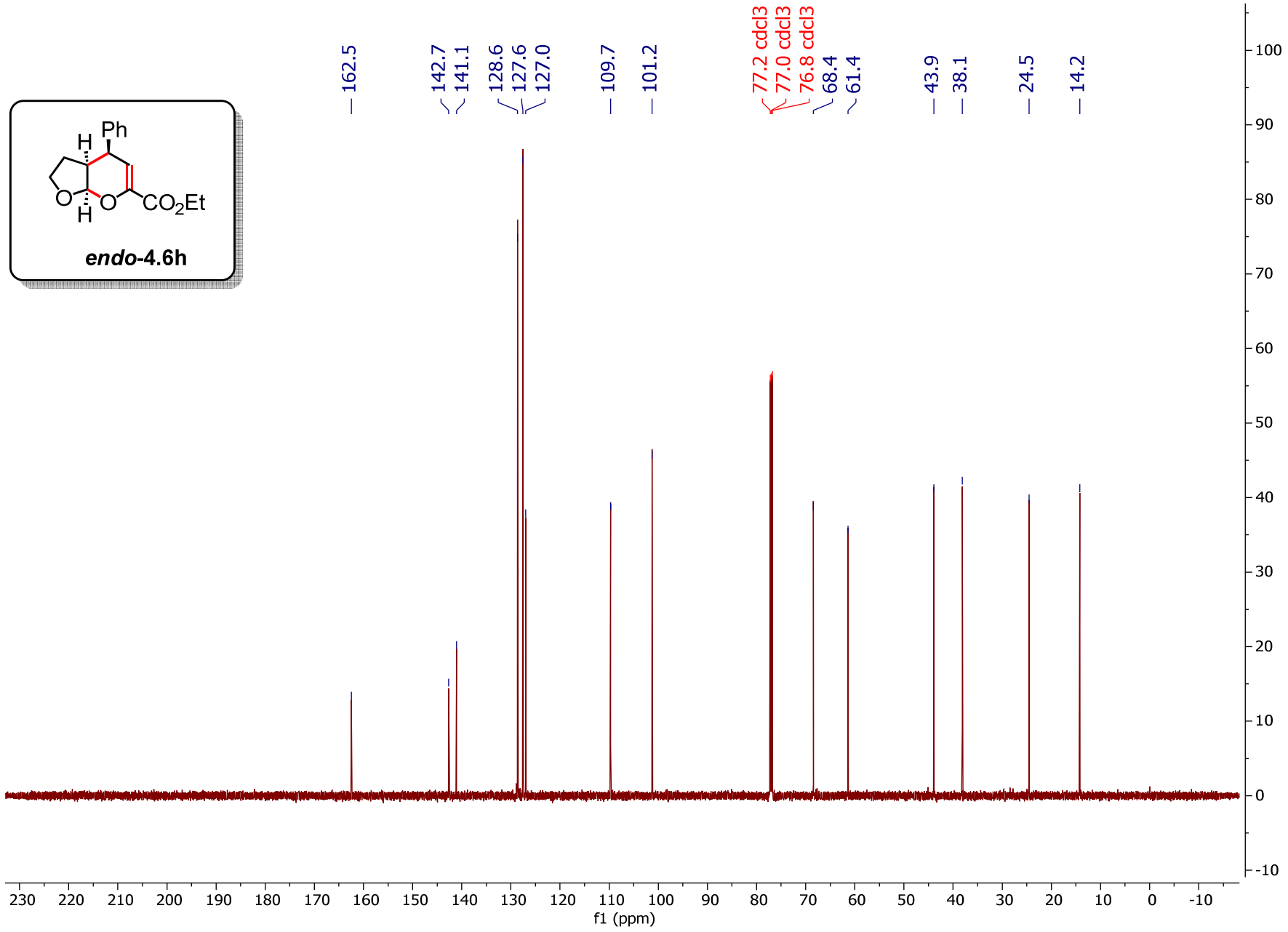

Ph
Ph
D3CO
O
CO2Et
exo-4.6g-d3
162.8
141.3
139.9
137.8
129.3
128.3
128.2
128.0
127.0
126.7
116.6
101.3
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.2
50.4
40.8
14.2
f1 (ppm)

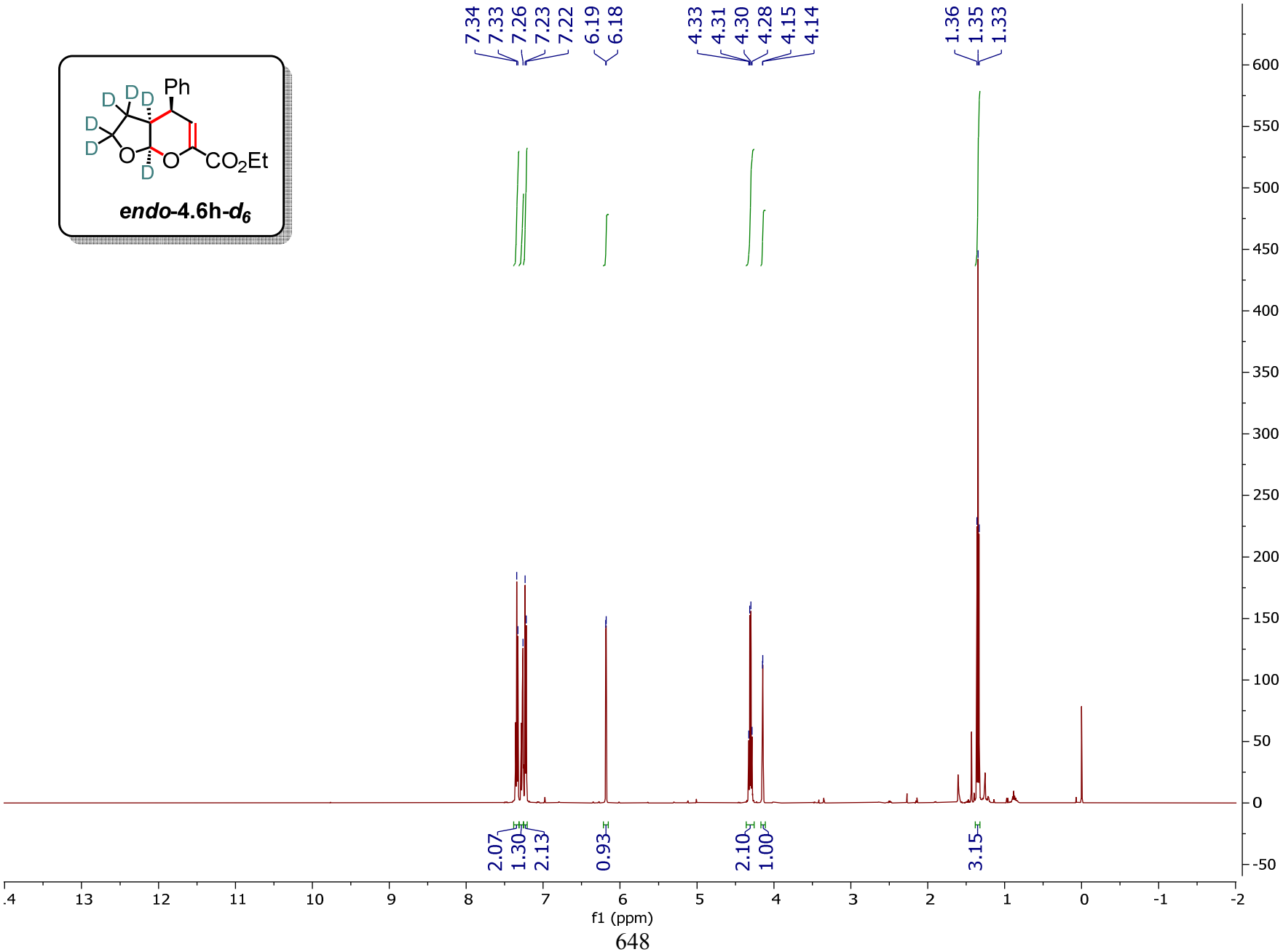

Ph
Ph
D3CO
O
CO2Et
endo-4.6g-d3
7.26 7.26 7.24 7.23 7.20 7.18 7.17 7.16 7.02 7.00 6.98 6.96 6.28 6.28
5.15 5.13 4.35 4.34 4.33 4.32 4.31 4.29 4.29 4.27 4.27 3.77 3.76 3.75 3.74 3.04 3.02 3.01 1.36 1.35 1.33
2.57 4.27 2.19 2.08 0.93 0.97 2.07 1.05 0.10 1.00 3.05
f1 (ppm)

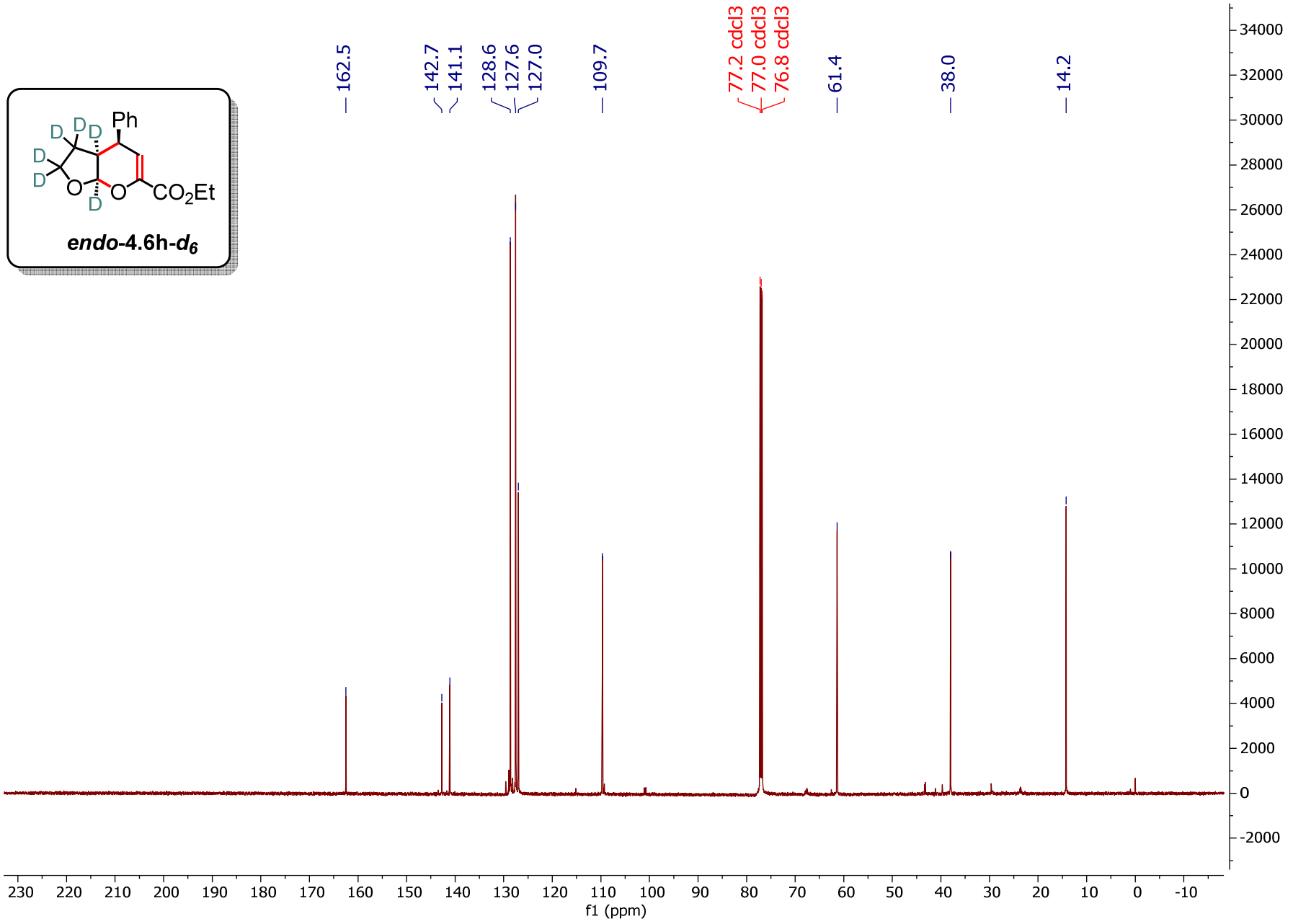

4.35
4.34
4.33
4.32
4.31
4.29
4.29
4.27
4.27
3.77
3.76
3.75
3.74
3.48
3.04
3.02
3.01
Ph
Ph
D3CO
O
CO2Et
[97%]
2.07
1.03
0.09
1.00
f1 (ppm)

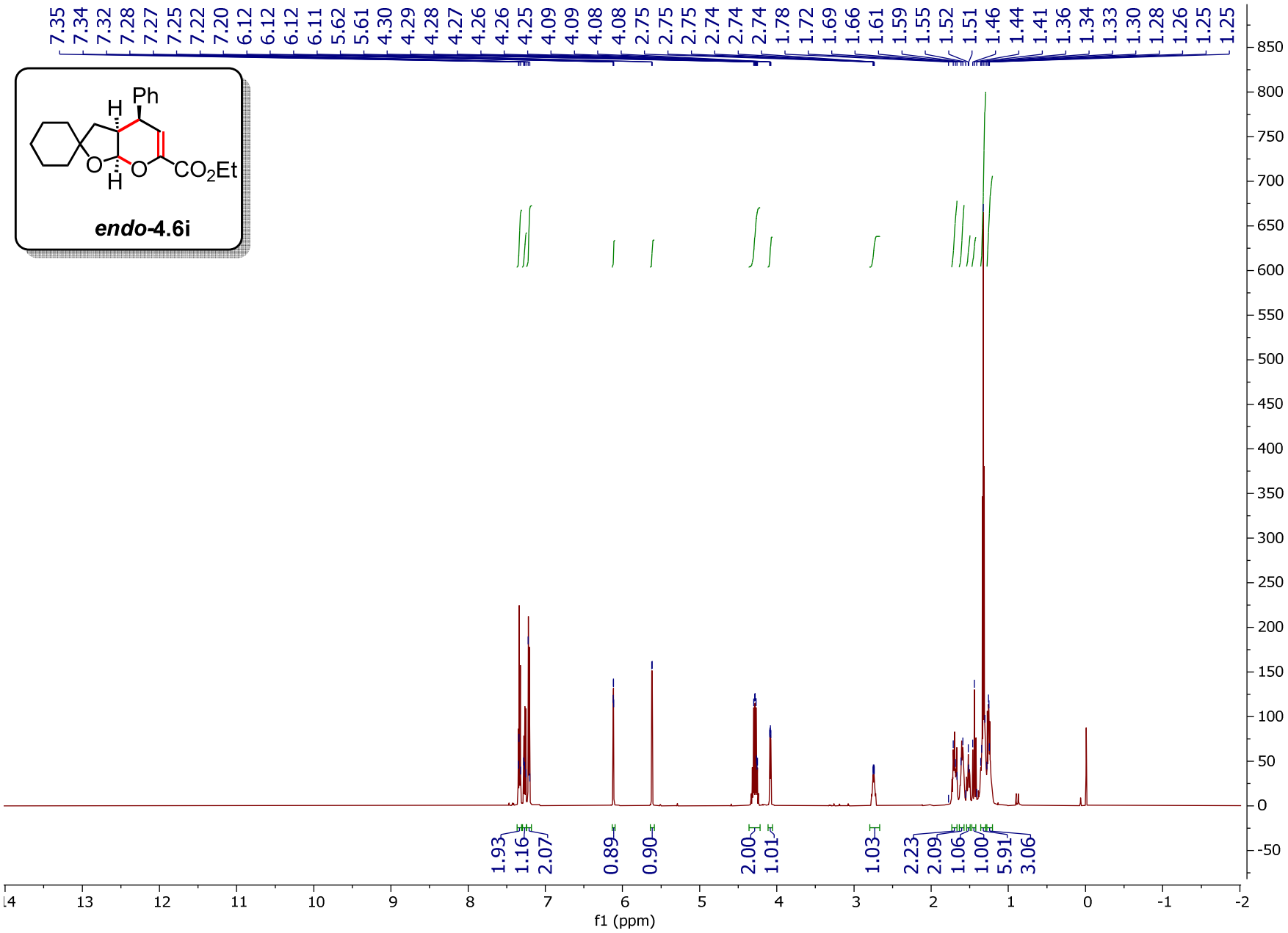

Ph
Ph
D3CO
O
CO2Et
endo-4.6g-d3
162.5
142.1
141.4
139.4
128.5
128.3
128.0
128.0
127.0
126.9
115.1
103.8
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.3
51.9
46.5
14.2
f1 (ppm)

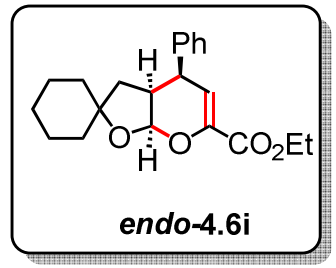

Ph
H
O
O
H
CO2Et
endo-4.6h
7.36 7.35 7.34 7.33 7.28 7.27 7.27 7.23 7.22 6.19 6.18 6.18 5.65 5.64
4.33 4.31 4.30 4.29 4.20 4.18 4.17 4.16 3.88 3.87 3.85 3.84 2.66 2.66 2.65 2.65 2.65 2.65 1.74 1.71 1.36 1.35 1.34
1.95 1.14 1.96 0.86 0.89 1.98 2.07 1.07 1.00 1.12 4.08
f1 (ppm)


Ph
H
O
O
H
CO2Et
endo-4.6h
162.5
142.7
141.1
128.6
127.6
127.0
109.7
101.2
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
68.4
61.4
43.9
38.1
24.5
14.2
f1 (ppm)


Ph
D
D
D
D
D
O
O
CO2Et
endo-4.6h-d6
7.34
7.33
7.26
7.23
7.22
6.19
6.18
4.33
4.31
4.30
4.28
4.15
4.14
1.36
1.35
1.33
2.07
1.30
2.13
0.93
2.10
1.00
3.15
f1 (ppm)

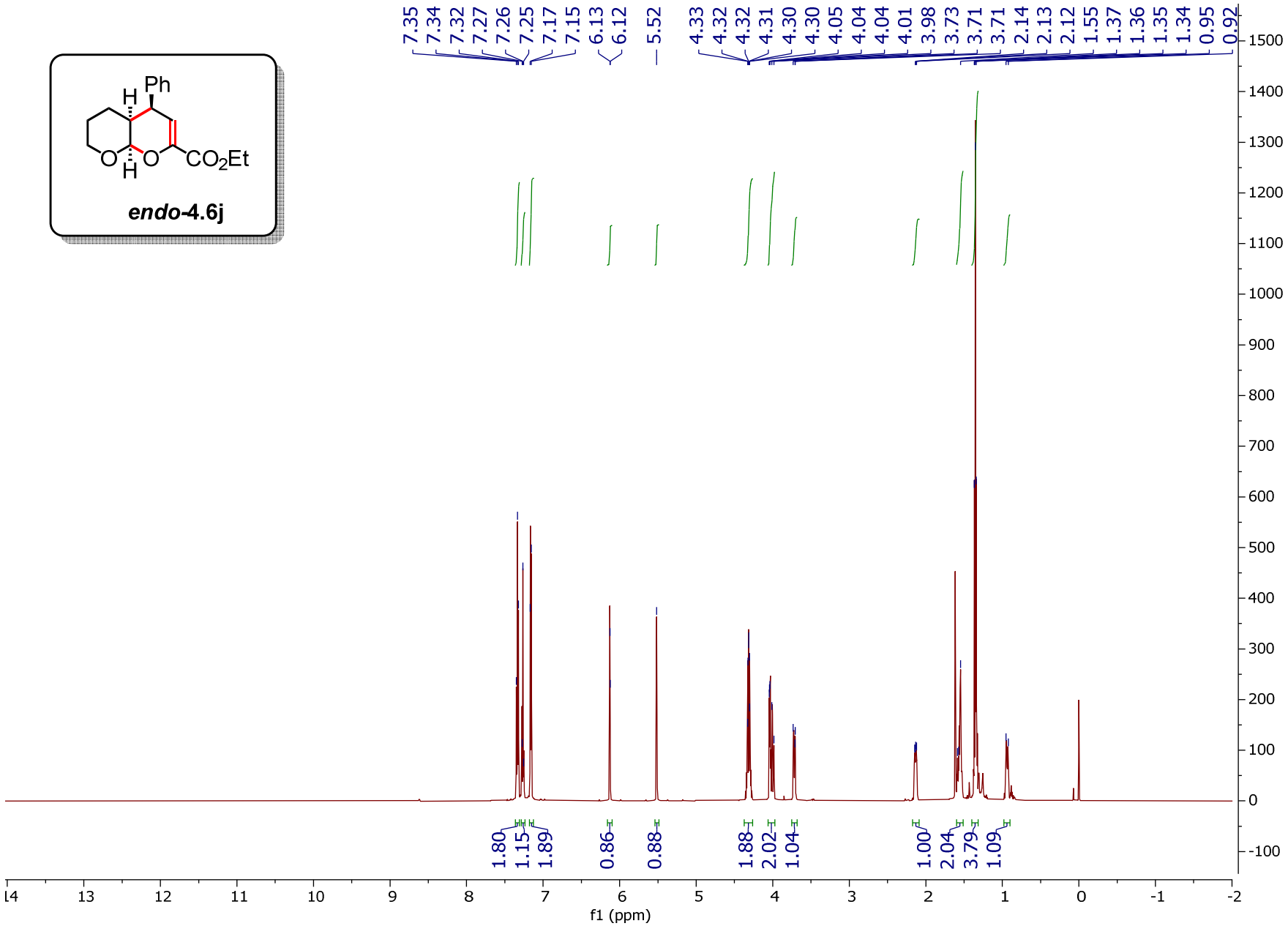

Ph
D
D
D
D
D
O
O
CO2Et
endo-4.6h-d6
162.5
142.7
141.1
128.6
127.6
127.0
109.7
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.4
38.0
14.2
f1 (ppm)

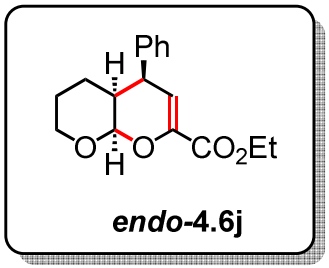

Ph
H
O
O
H
CO2Et
endo-4.6i
7.35 7.34 7.32 7.28 7.27 7.25 7.22 7.20 6.12 6.12 6.12 6.11 5.62 5.61 4.30 4.29 4.28 4.27 4.26 4.26 4.25 4.09 4.09 4.08 4.08 2.75 2.75 2.75 2.74 2.74 2.74 1.78 1.72 1.69 1.66 1.61 1.59 1.55 1.52 1.51 1.46 1.44 1.41 1.36 1.34 1.33 1.30 1.28 1.26 1.25 1.25
1.93 1.16 2.07 0.89 0.90 2.00 1.01 1.03 2.23 2.09 1.06 1.00 5.91 3.06
f1 (ppm)


Ph
H
O
O
H
CO2Et

***endo*-4.6i**

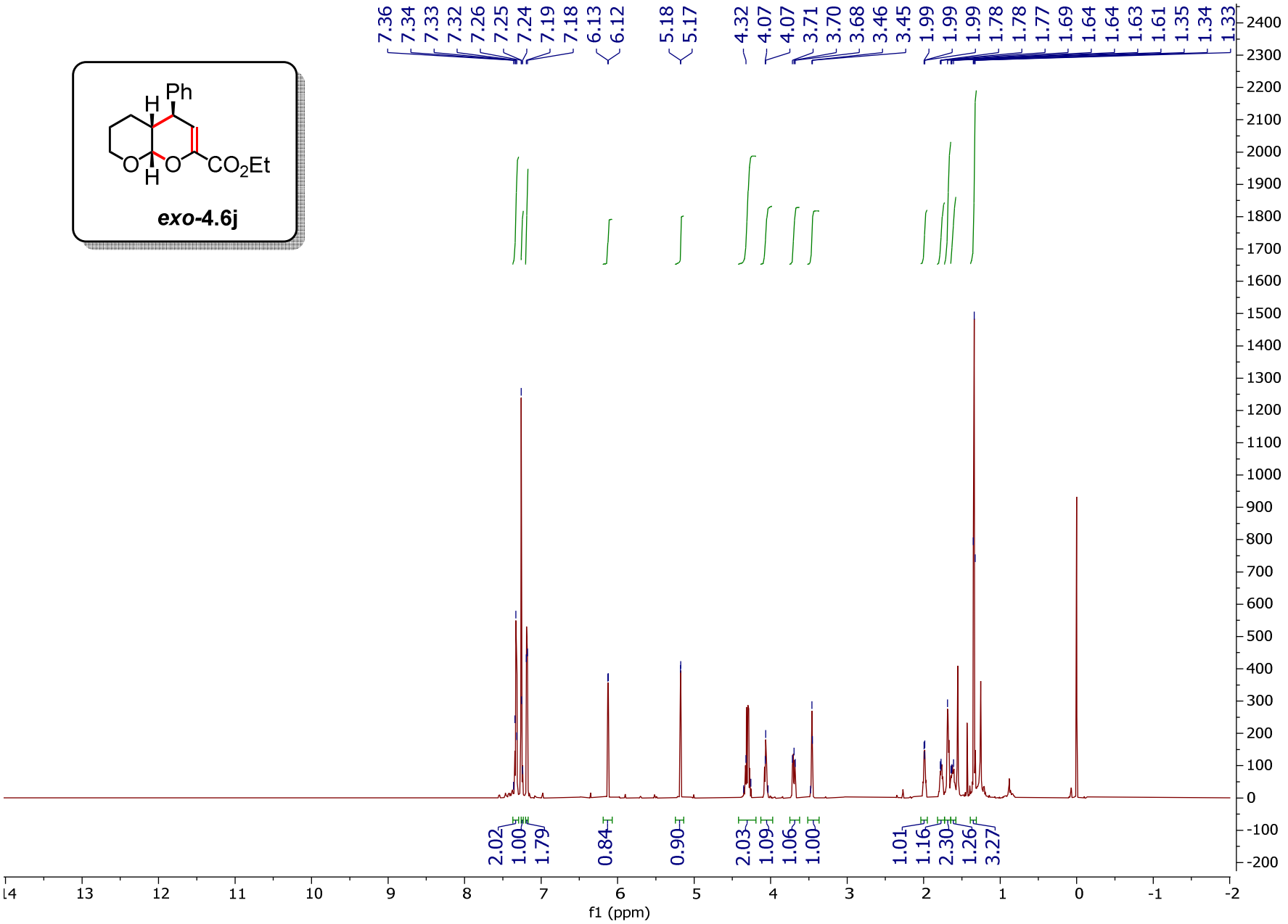
162.6
142.9
141.3
128.6
127.6
126.9
109.1
101.3
86.1
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
61.2
43.4
40.4
38.3
37.3
34.9
25.2
23.8
23.6
14.2
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

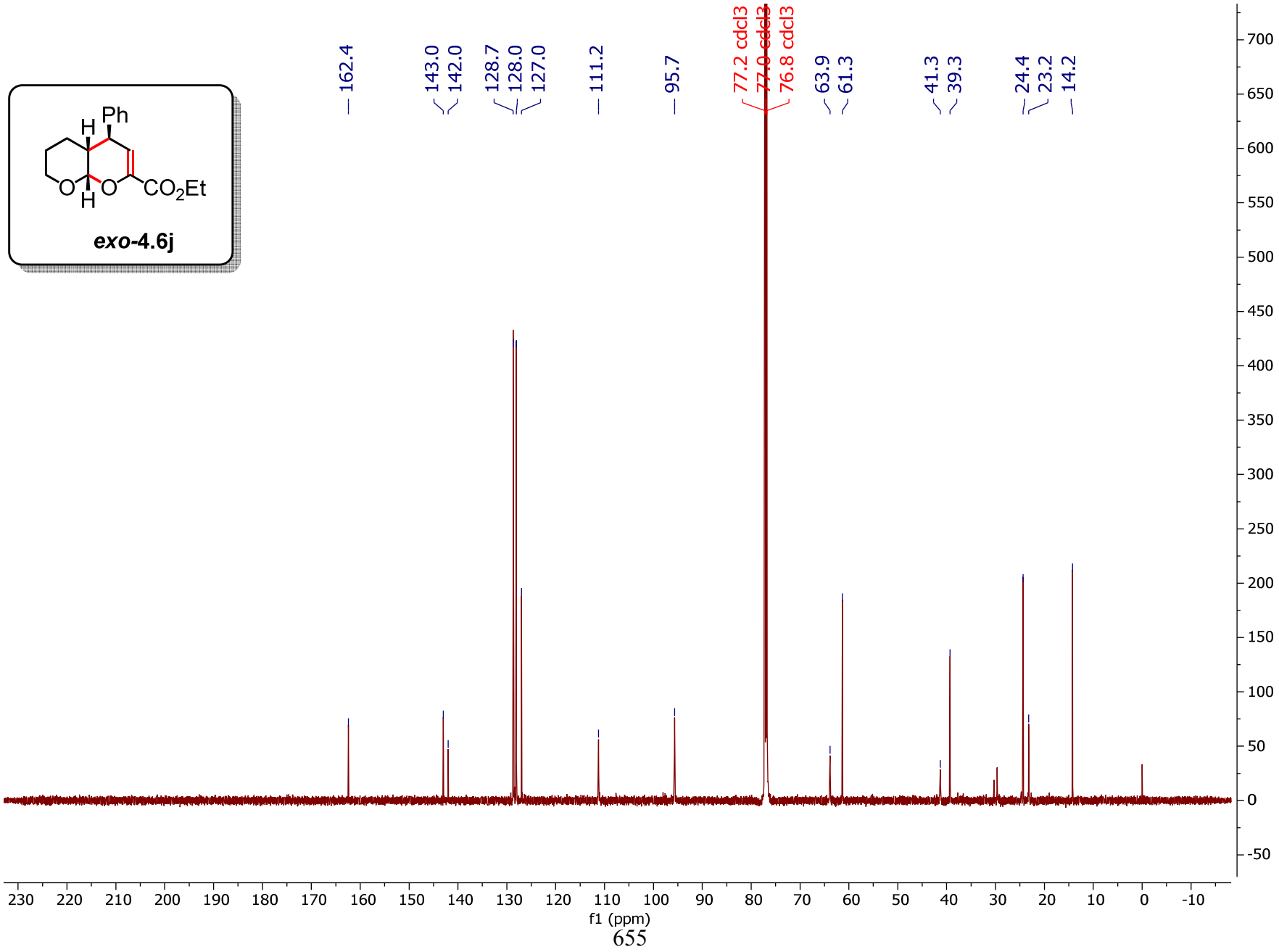

Ph
H
O
O
H
CO2Et
endo-4.6j
7.35 7.34 7.32 7.27 7.26 7.25 7.17 7.15 6.13 6.12 5.52 4.33 4.32 4.32 4.31 4.30 4.30 4.05 4.04 4.04 4.01 3.98 3.73 3.71 3.71 2.14 2.13 2.12 1.55 1.37 1.36 1.35 1.34 0.95 0.92
1.80 1.15 1.89 0.86 0.88 1.88 2.02 1.04 1.00 2.04 3.79 1.09
f1 (ppm)

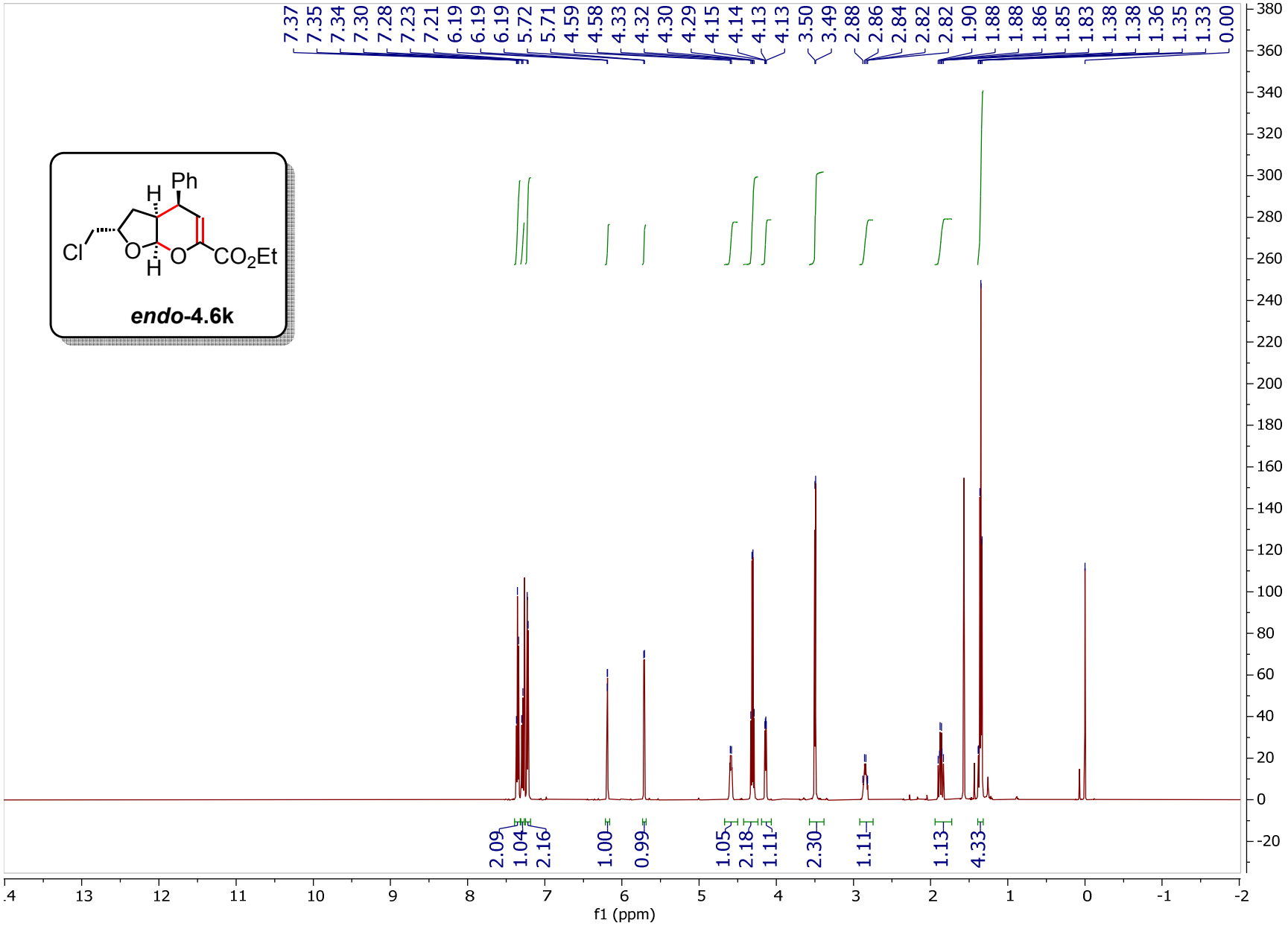

H
Ph
O
H
O
CO2Et

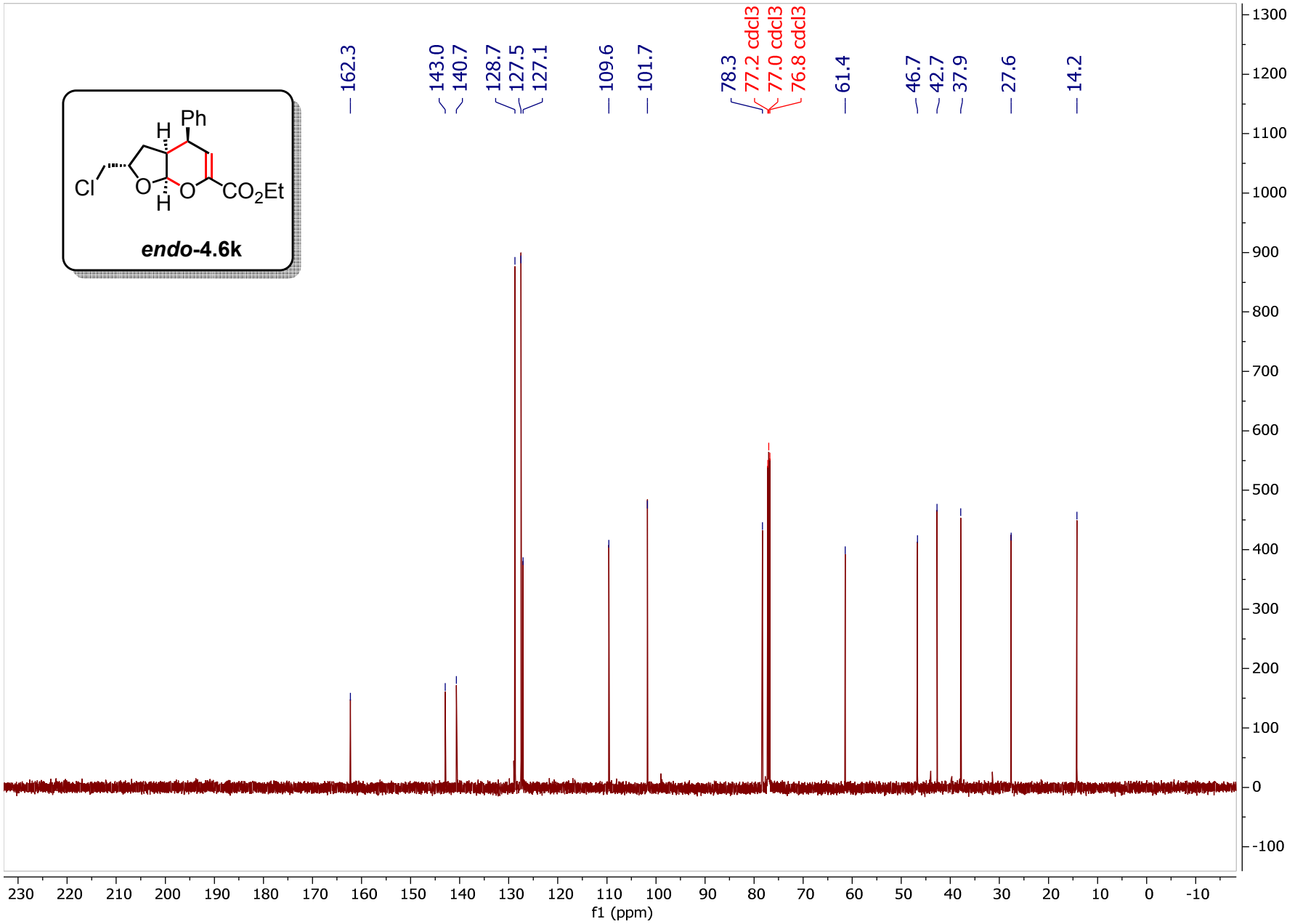
***endo*-4.6j**

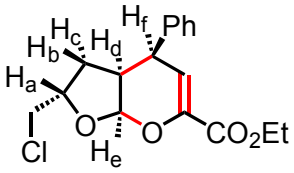
162.3
143.3
139.7
128.4
128.0
126.9
111.0
98.0
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.3
61.3
42.0
37.7
24.7
19.0
14.2
f1 (ppm)


Ph
H
O
O
H
CO2Et
exo-4.6j
7.36
7.34
7.33
7.32
7.26
7.25
7.24
7.19
7.18
6.13
6.12
5.18
5.17
4.32
4.07
4.07
3.71
3.70
3.68
3.46
3.45
1.99
1.99
1.99
1.78
1.78
1.77
1.69
1.64
1.64
1.63
1.61
1.35
1.34
1.33
2.02
1.00
1.79
0.84
0.90
2.03
1.09
1.06
1.00
1.01
1.16
2.30
1.26
3.27
f1 (ppm)

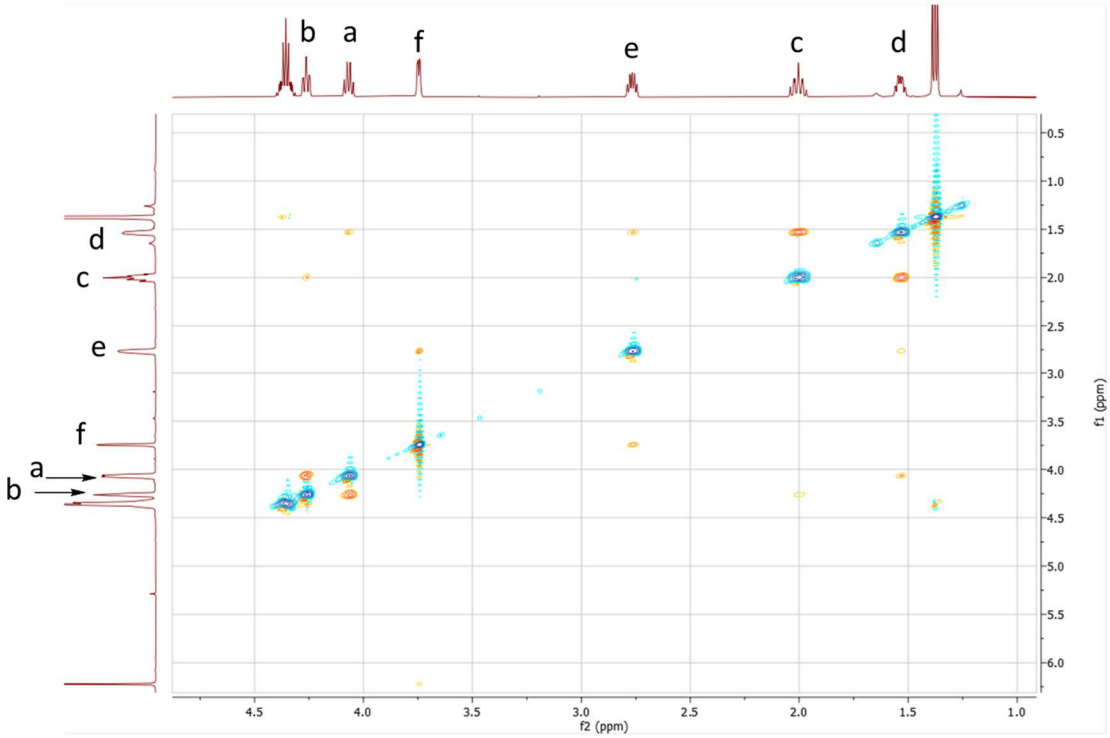

Ph
H
O
H
O
CO2Et
exo-4.6j
162.4
143.0
142.0
128.7
128.0
127.0
111.2
95.7
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
63.9
61.3
41.3
39.3
24.4
23.2
14.2
f1 (ppm)


7.37
7.35
7.34
7.30
7.28
7.23
7.21
6.19
6.19
6.19
5.72
5.71
4.59
4.58
4.33
4.32
4.30
4.29
4.15
4.14
4.13
4.13
3.50
3.49
2.88
2.86
2.84
2.82
2.82
1.90
1.88
1.88
1.86
1.85
1.83
1.38
1.38
1.36
1.35
1.33
0.00
Ph
H
Cl
O
O
H
CO2Et
endo-4.6k
2.09
1.04
2.16
1.00
0.99
1.05
2.18
1.11
2.30
1.11
1.13
4.33
f1 (ppm)

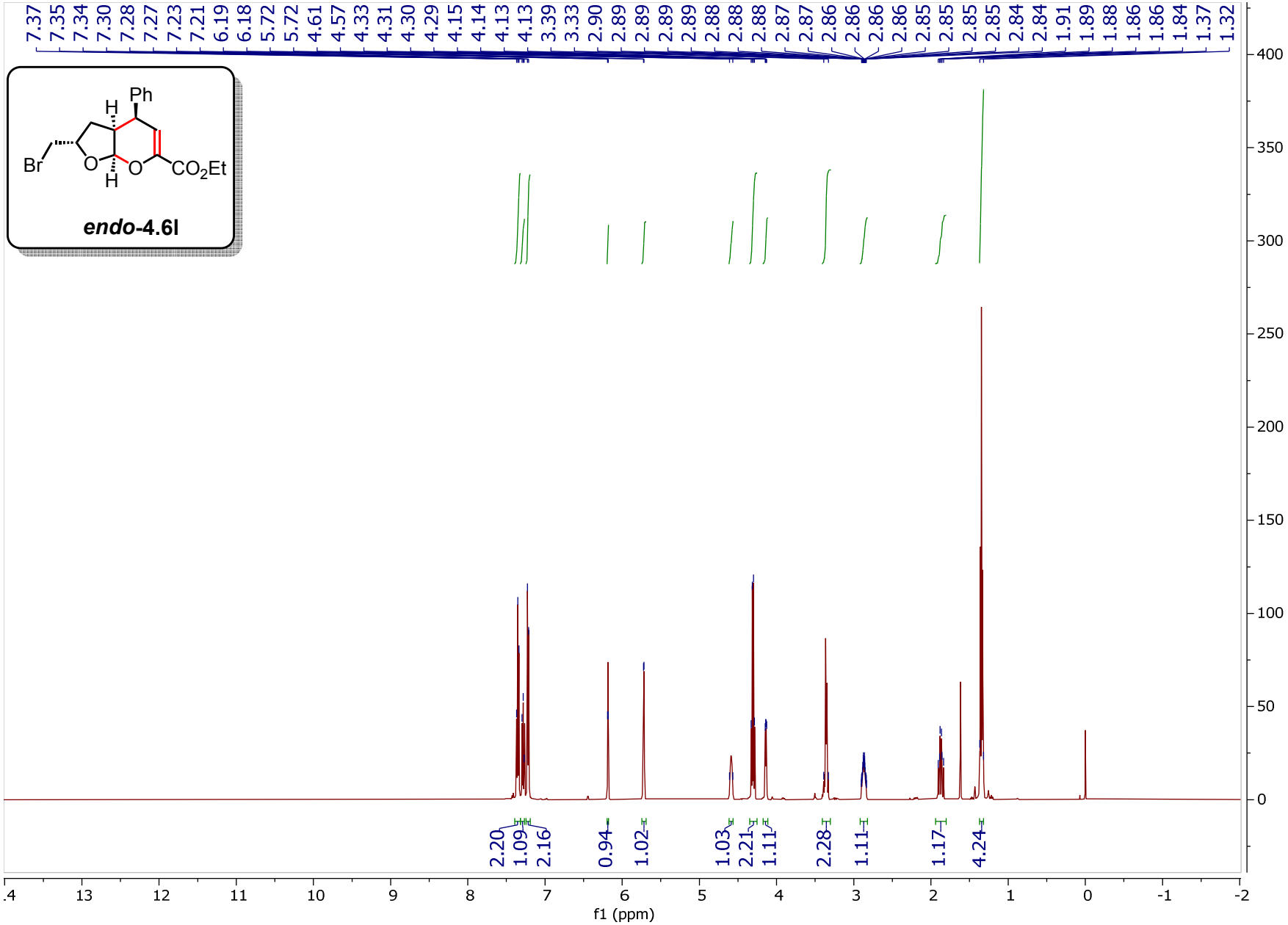

Ph
H
Cl
O
H
O
CO2Et
endo-4.6k
162.3
143.0
140.7
128.7
127.5
127.1
109.6
101.7
78.3
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.4
46.7
42.7
37.9
27.6
14.2
f1 (ppm)

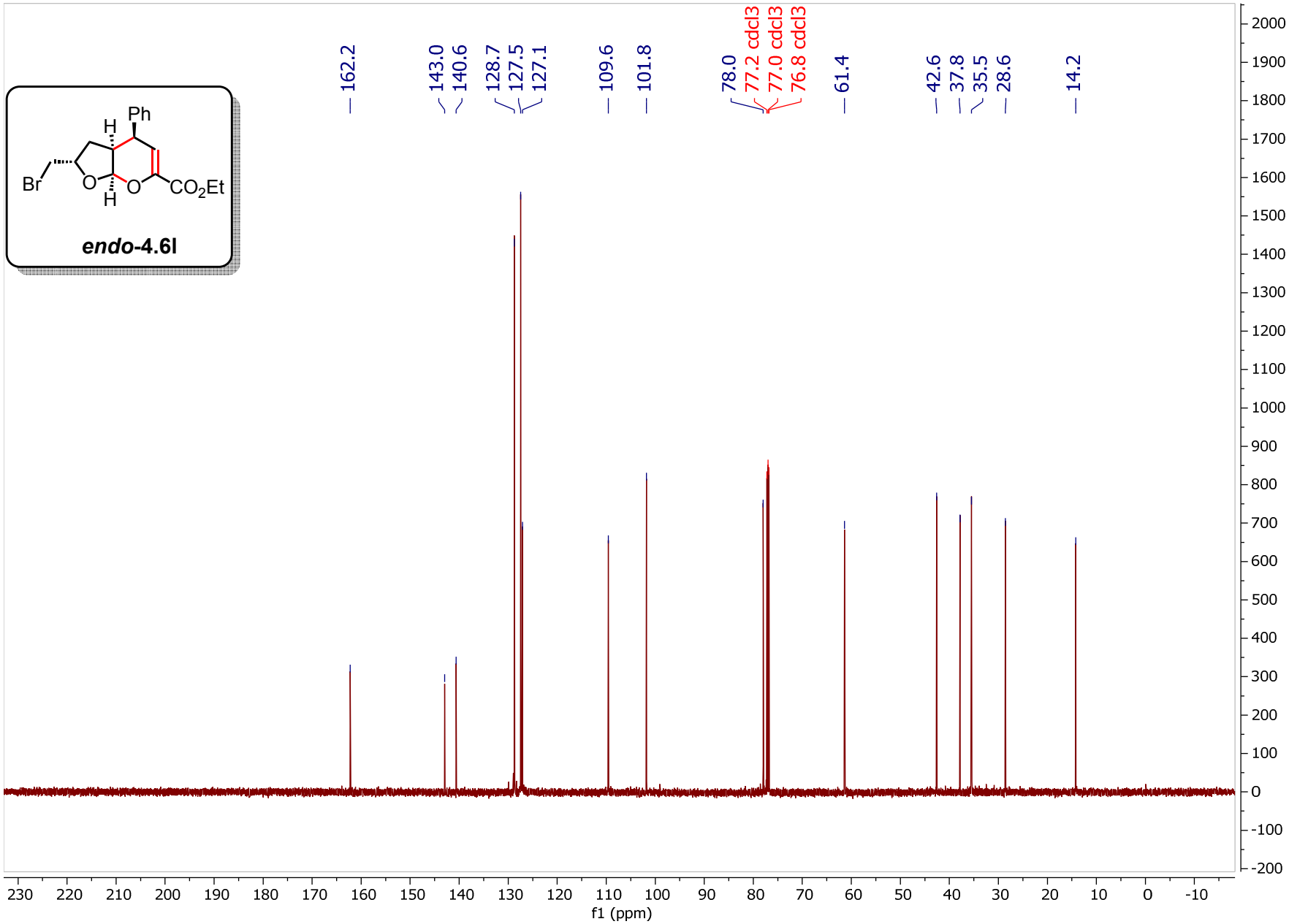


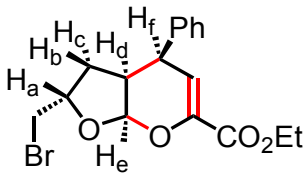
***endo*-4.6k**



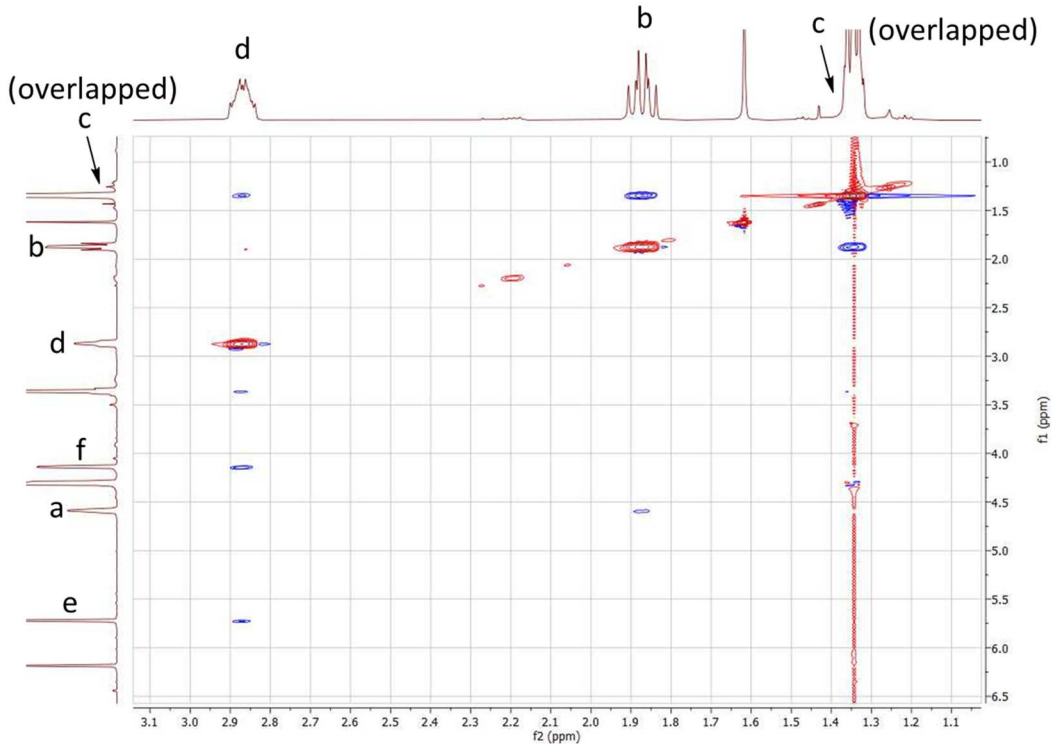
The configuration of the major diastereomer of **4.6k** was assigned to be ***endo***.


7.37 7.35 7.34 7.30 7.28 7.27 7.23 7.21 6.19 6.18 5.72 5.72 4.61 4.57 4.33 4.31 4.30 4.29 4.15 4.14 4.13 4.13 3.39 3.33 2.90 2.89 2.89 2.89 2.89 2.88 2.88 2.88 2.87 2.87 2.86 2.86 2.86 2.86 2.85 2.85 2.85 2.85 2.84 2.84 1.91 1.89 1.88 1.86 1.86 1.84 1.37 1.32
Ph
H
Br
O
O
H
CO2Et
endo-4.6l
400
350
300
250
200
150
100
50
0
2.20 1.09 2.16 0.94 1.02 1.03 2.21 1.11 2.28 1.11 1.17 4.24
.4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

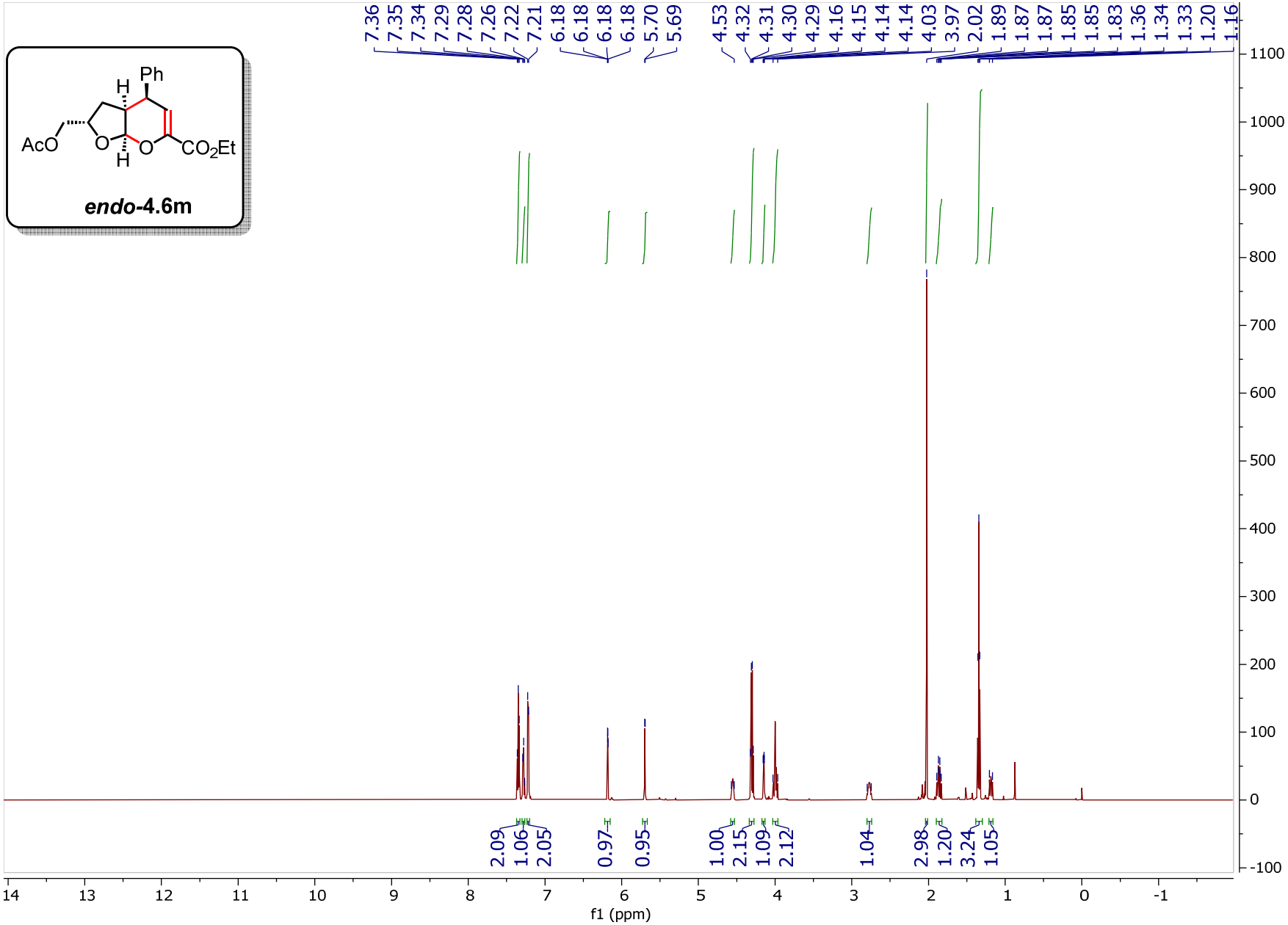

162.2
143.0
140.6
128.7
127.5
127.1
109.6
101.8
78.0
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.4
42.6
37.8
35.5
28.6
14.2
Ph
H
Br
O
O
H
CO2Et
endo-4.6l
f1 (ppm)

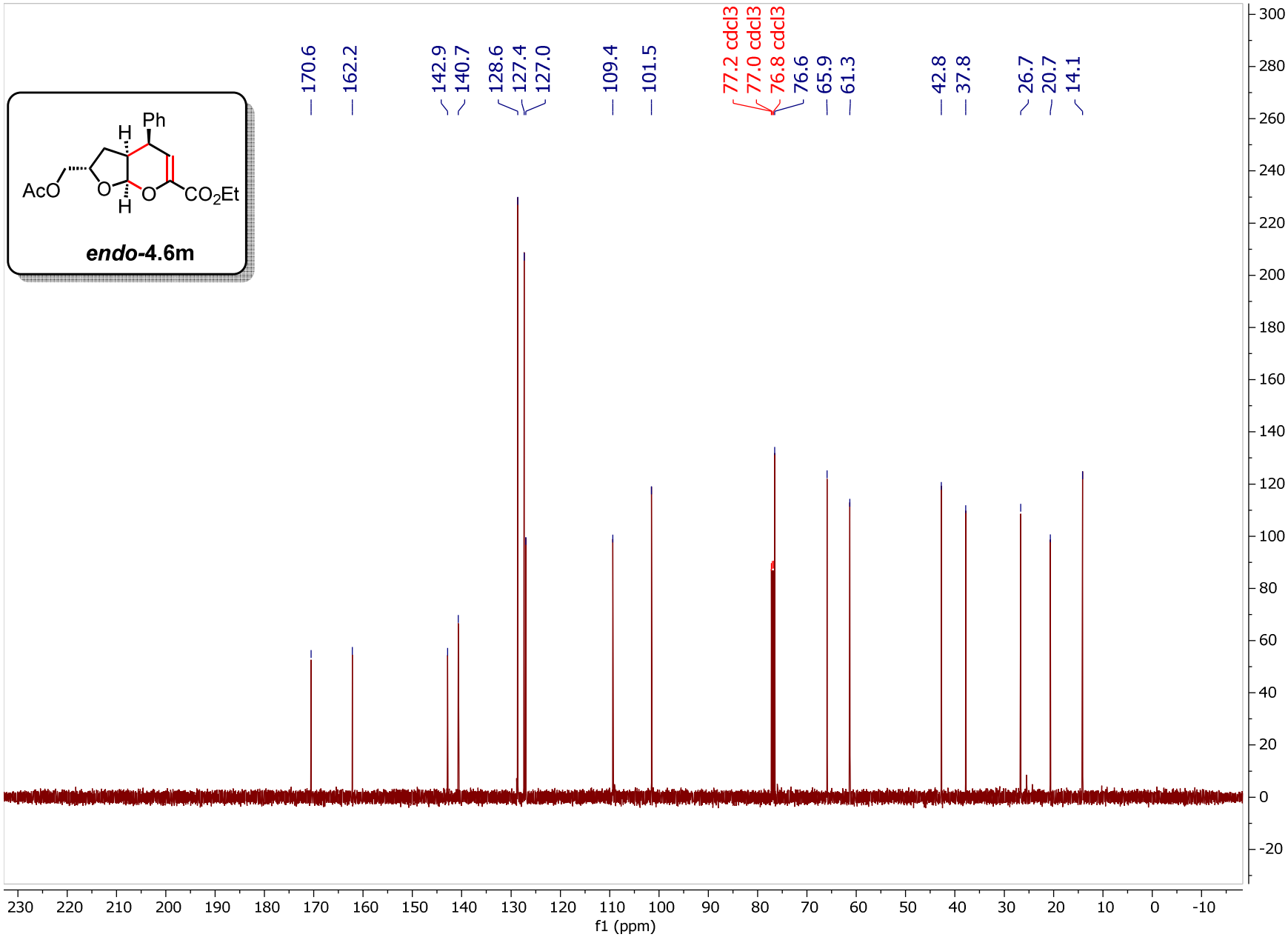


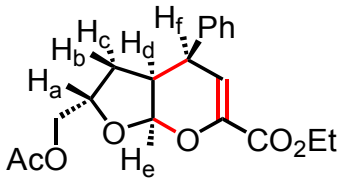
***endo*-4.6l**



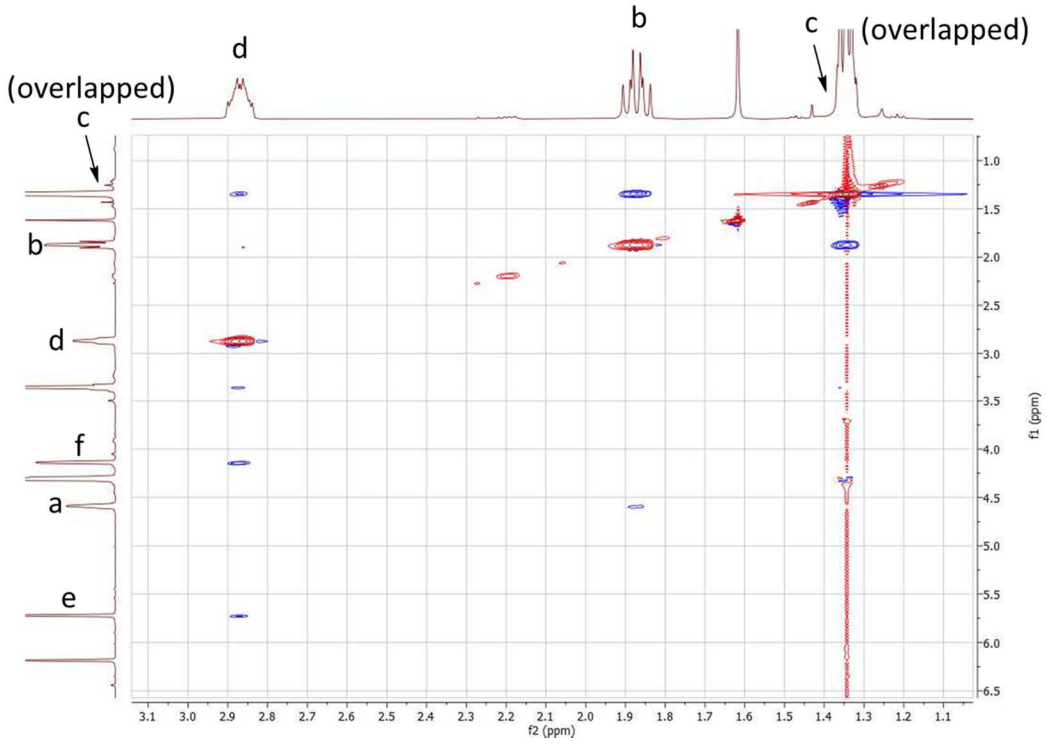
The configuration of the major diastereomer of **4.6l** was assigned to be ***endo***.


Ph
H
AcO
O
O
H
CO2Et
endo-4.6m
7.36
7.35
7.34
7.29
7.28
7.26
7.22
7.21
6.18
6.18
6.18
6.18
5.70
5.69
4.53
4.32
4.31
4.30
4.29
4.16
4.15
4.14
4.14
4.03
3.97
2.02
1.89
1.87
1.87
1.85
1.85
1.83
1.36
1.34
1.33
1.20
1.16
2.09
1.06
2.05
0.97
0.95
1.00
2.15
1.09
2.12
1.04
2.98
1.20
3.24
1.05
f1 (ppm)

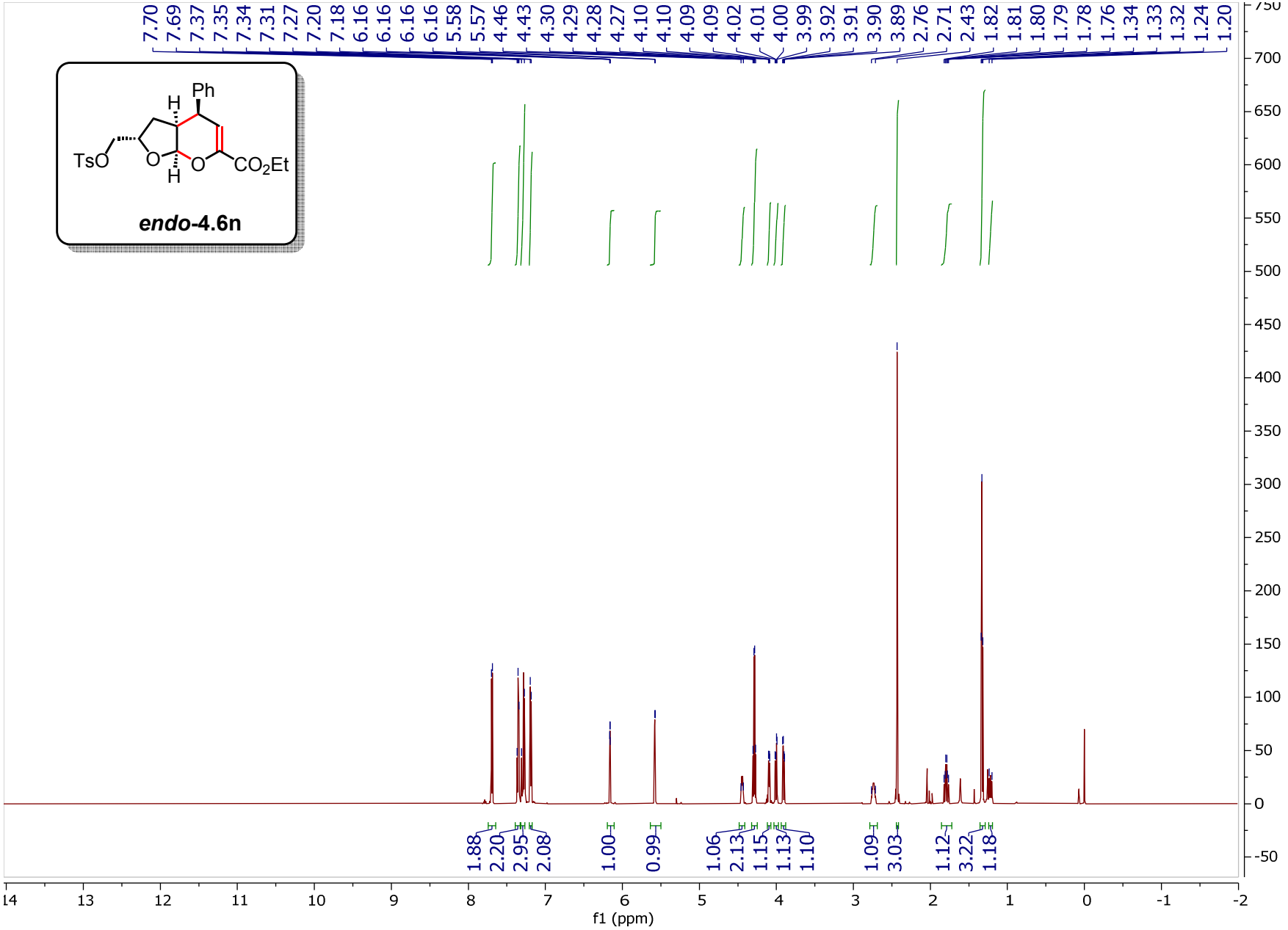

170.6
162.2
142.9
140.7
128.6
127.4
127.0
109.4
101.5
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
76.6
65.9
61.3
42.8
37.8
26.7
20.7
14.1
Ph
H
AcO
O
O
H
CO2Et
endo-4.6m
f1 (ppm)

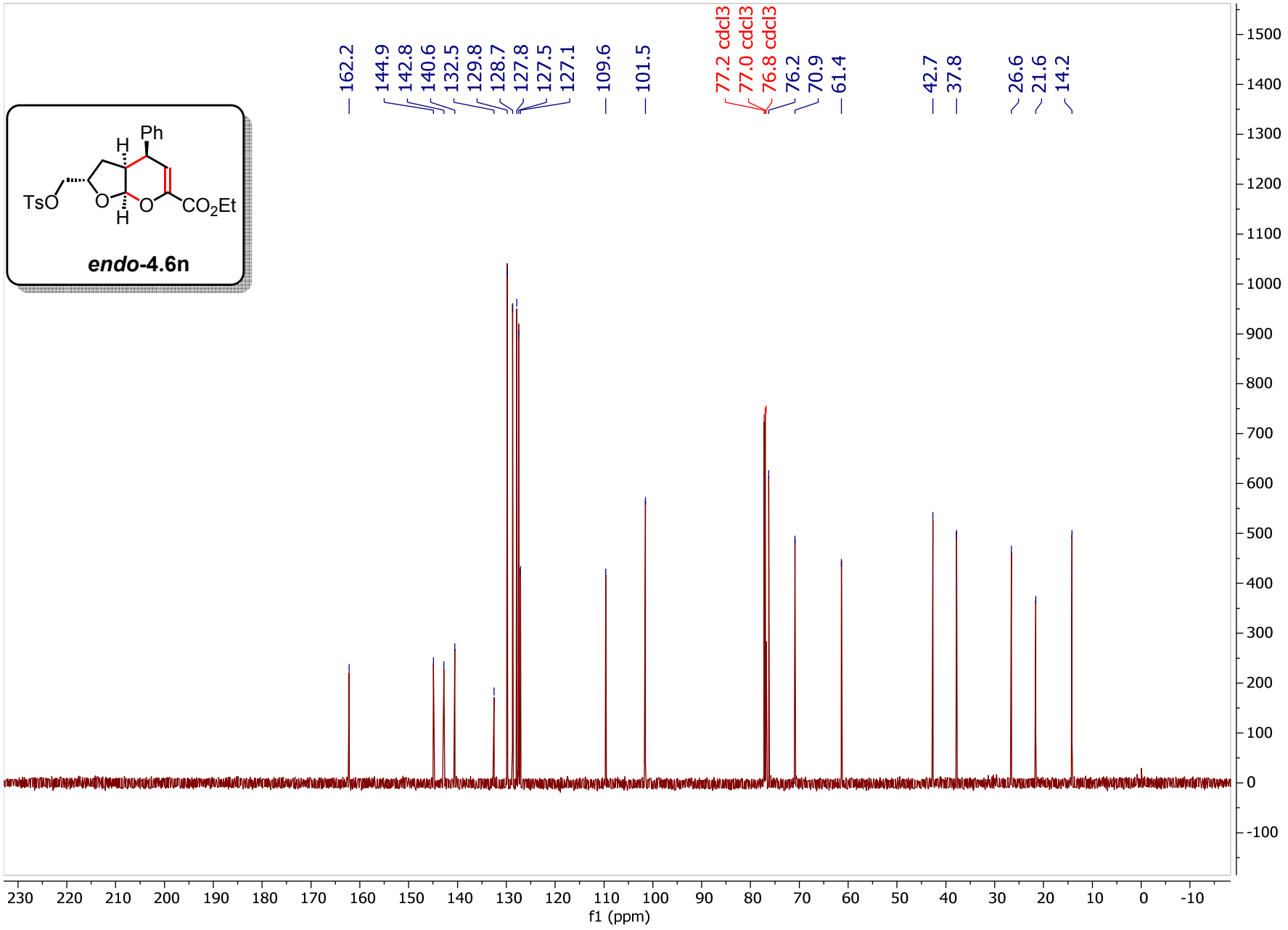


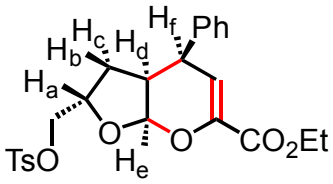
***endo*-4.6m**



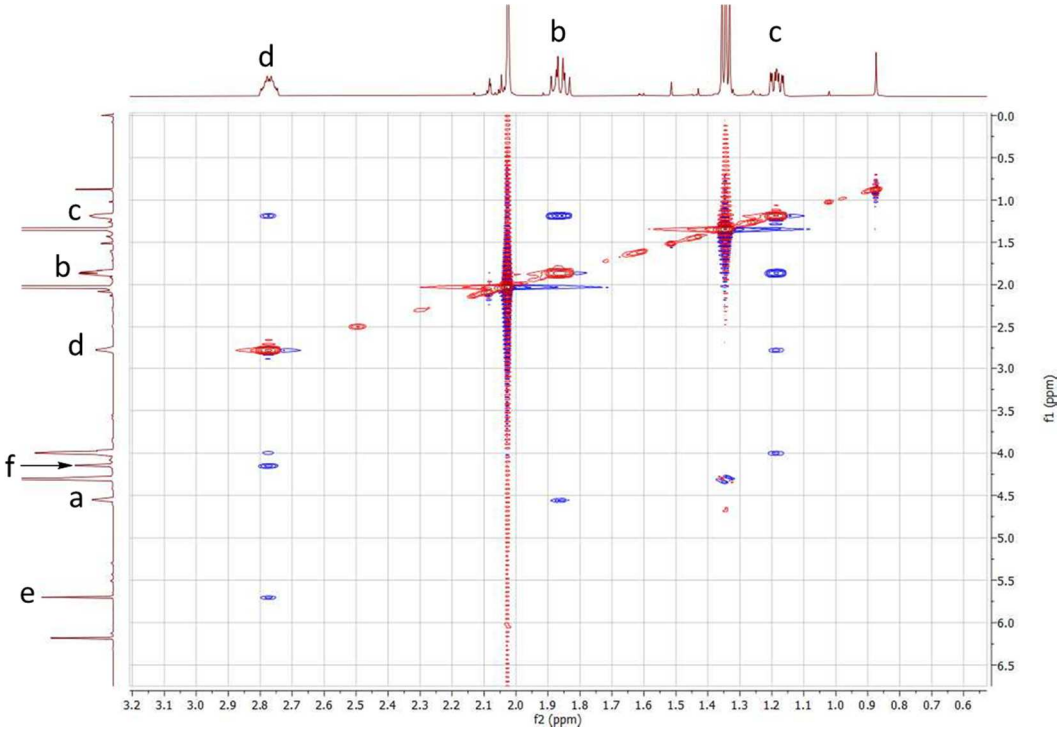
The configuration of the major diastereomer of **4.6m** was assigned to be ***endo***.


7.70 7.69 7.37 7.35 7.34 7.31 7.27 7.20 7.18 6.16 6.16 6.16 6.16 5.58 5.57 4.46 4.43 4.30 4.29 4.28 4.27 4.10 4.10 4.09 4.09 4.02 4.01 4.00 3.99 3.92 3.91 3.90 3.89 2.76 2.71 2.43 1.82 1.81 1.80 1.79 1.78 1.76 1.34 1.33 1.32 1.24 1.20
Ph
H
TsO
O
O
CO2Et
H
endo-4.6n
1.88 2.20 2.95 2.08 1.00 0.99 1.06 2.13 1.15 1.13 1.10 1.09 3.03 1.12 3.22 1.18
f1 (ppm)

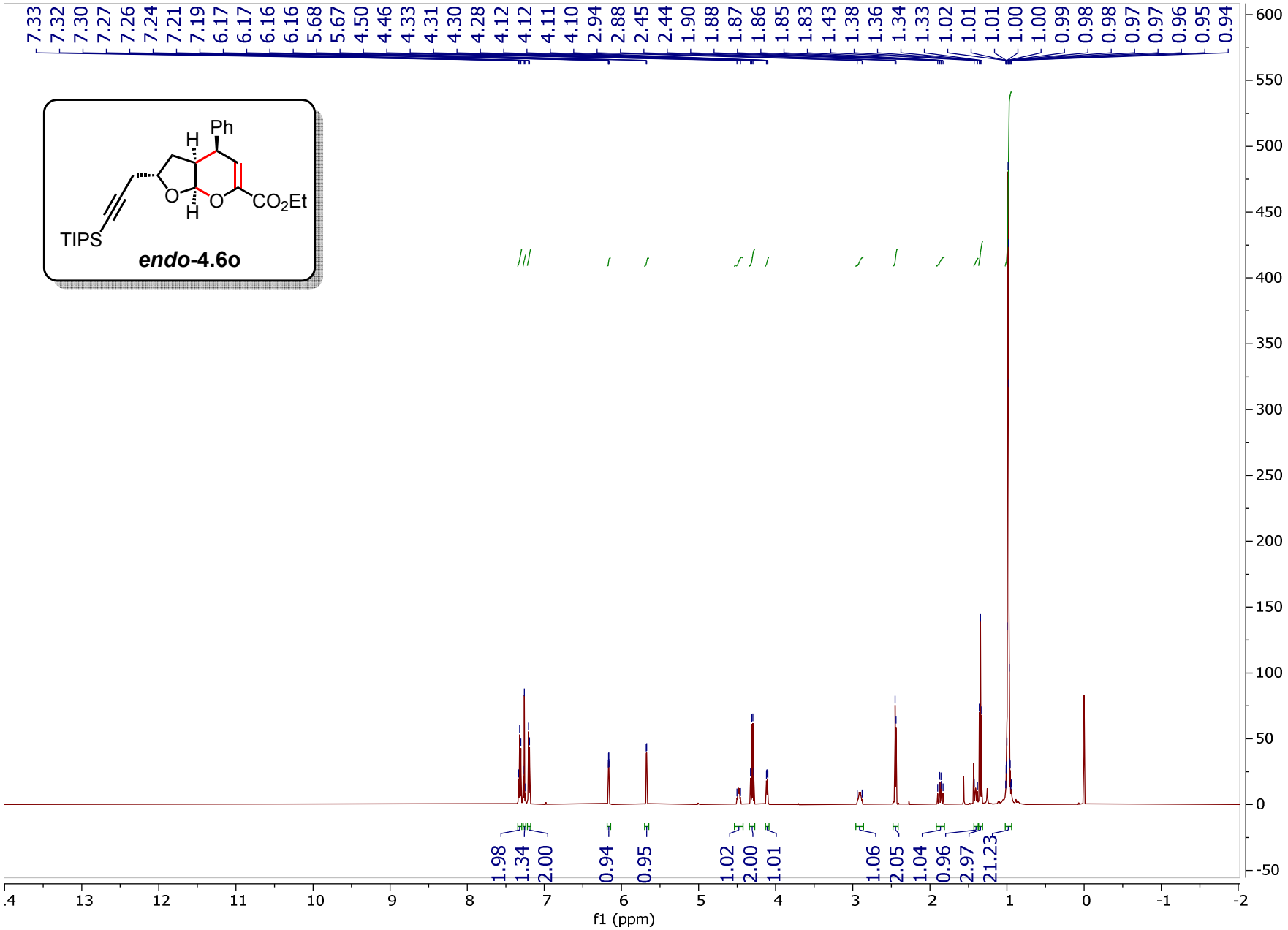

162.2
144.9
142.8
140.6
132.5
129.8
128.7
127.8
127.5
127.1
109.6
101.5
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
76.2
70.9
61.4
42.7
37.8
26.6
21.6
14.2
Ph
H
TsO
O
O
H
CO2Et
endo-4.6n
f1 (ppm)

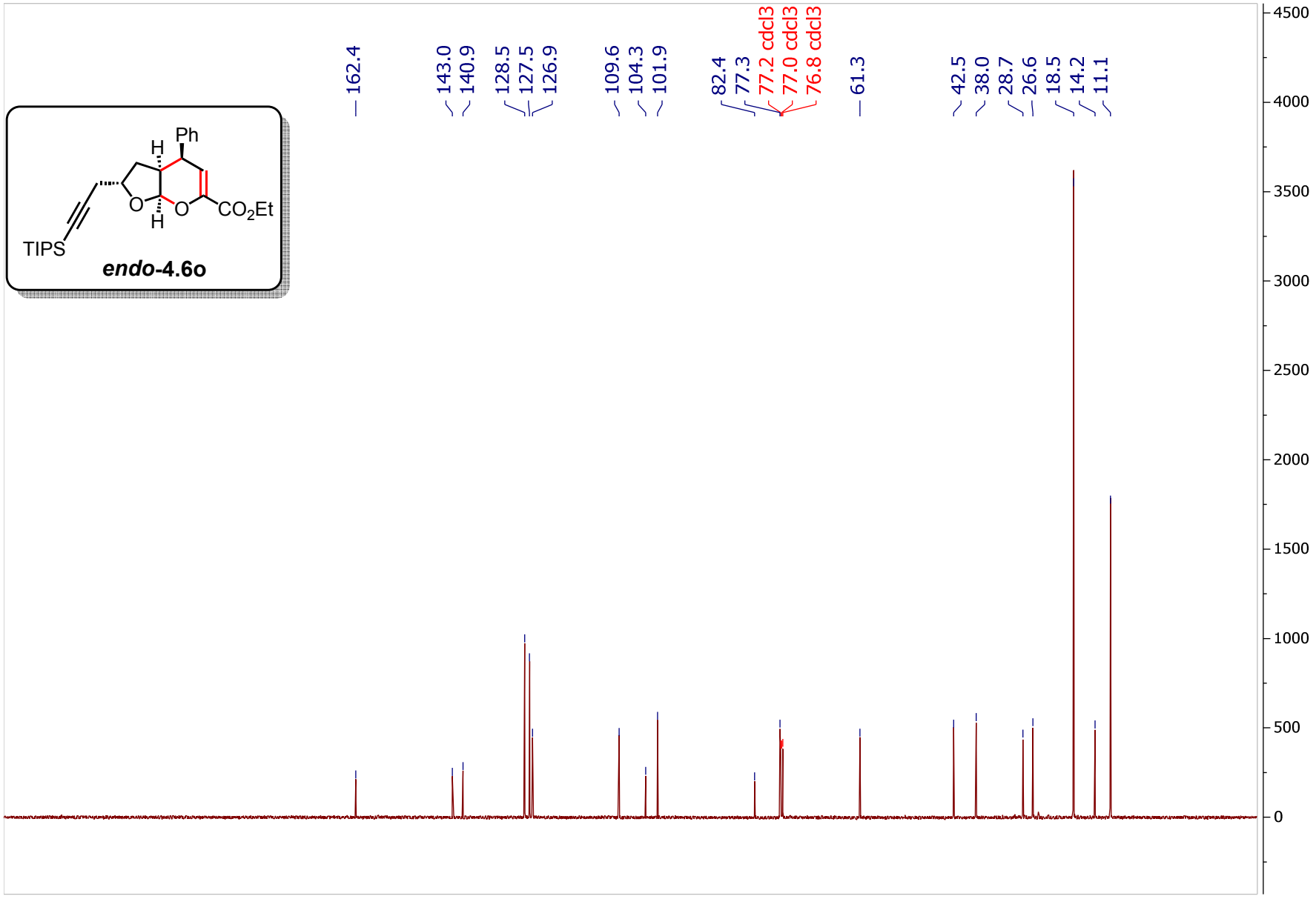


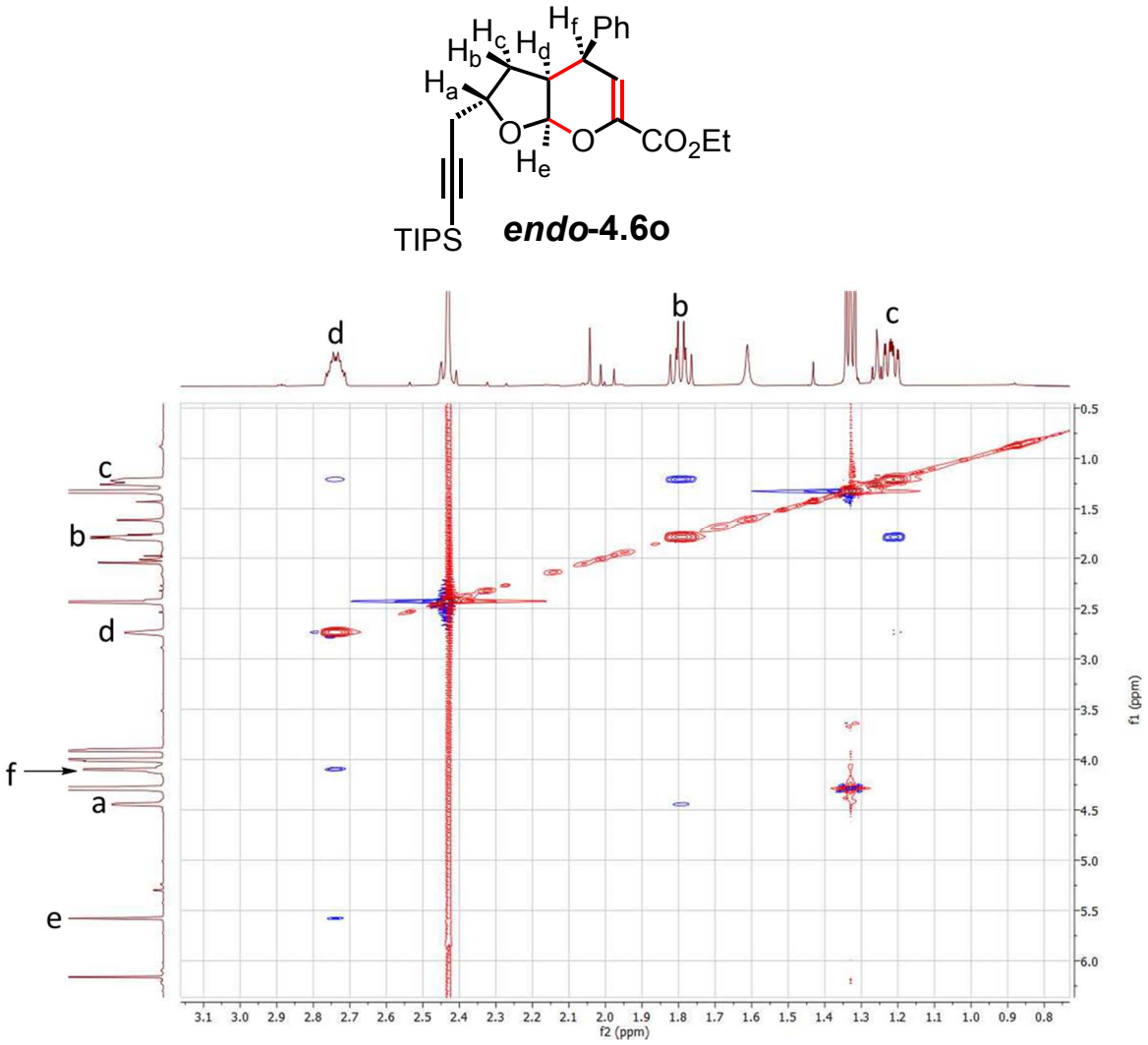
***endo*-4.6n**



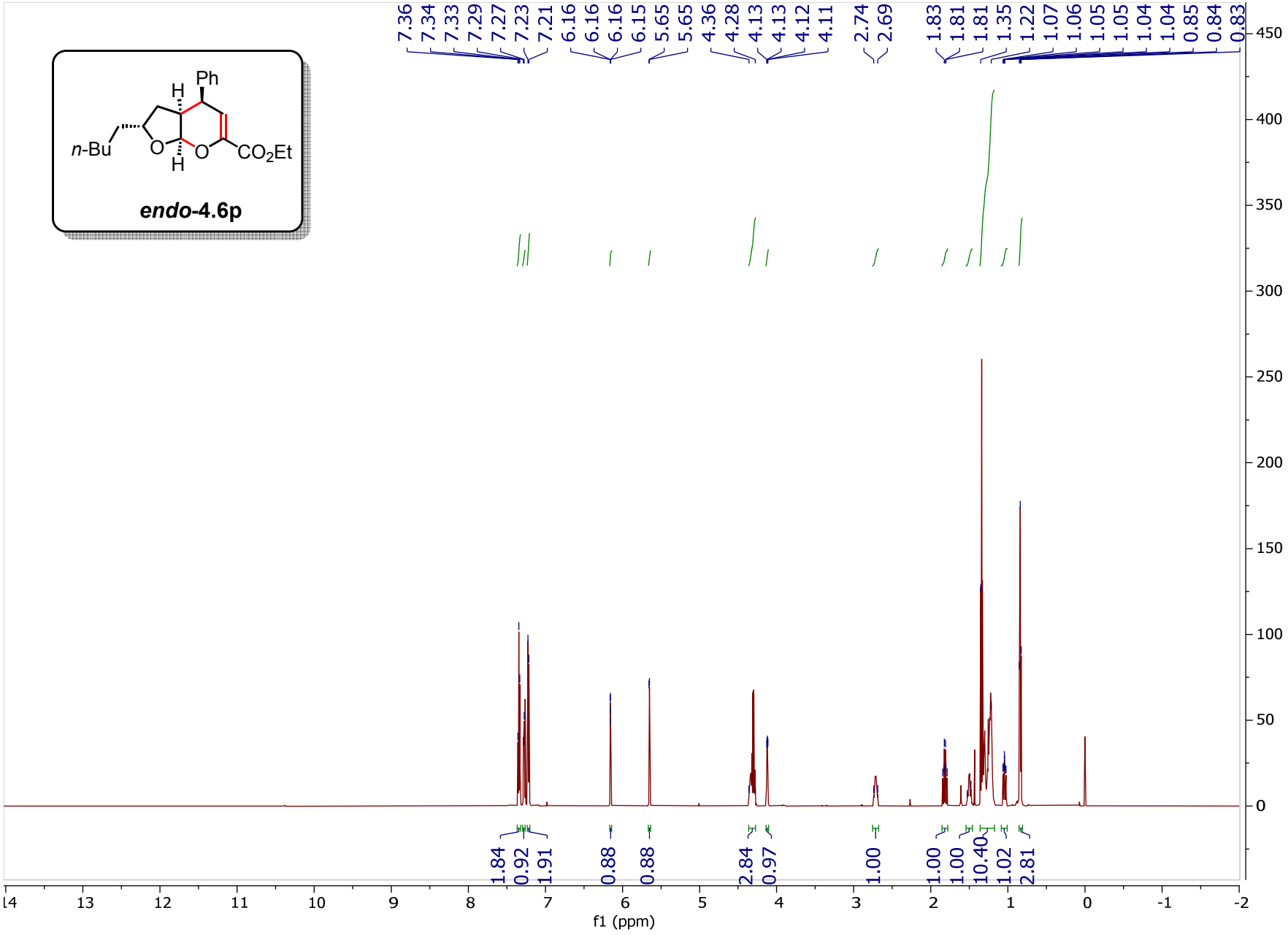
The configuration of the major diastereomer of **4.6n** was assigned to be ***endo***.

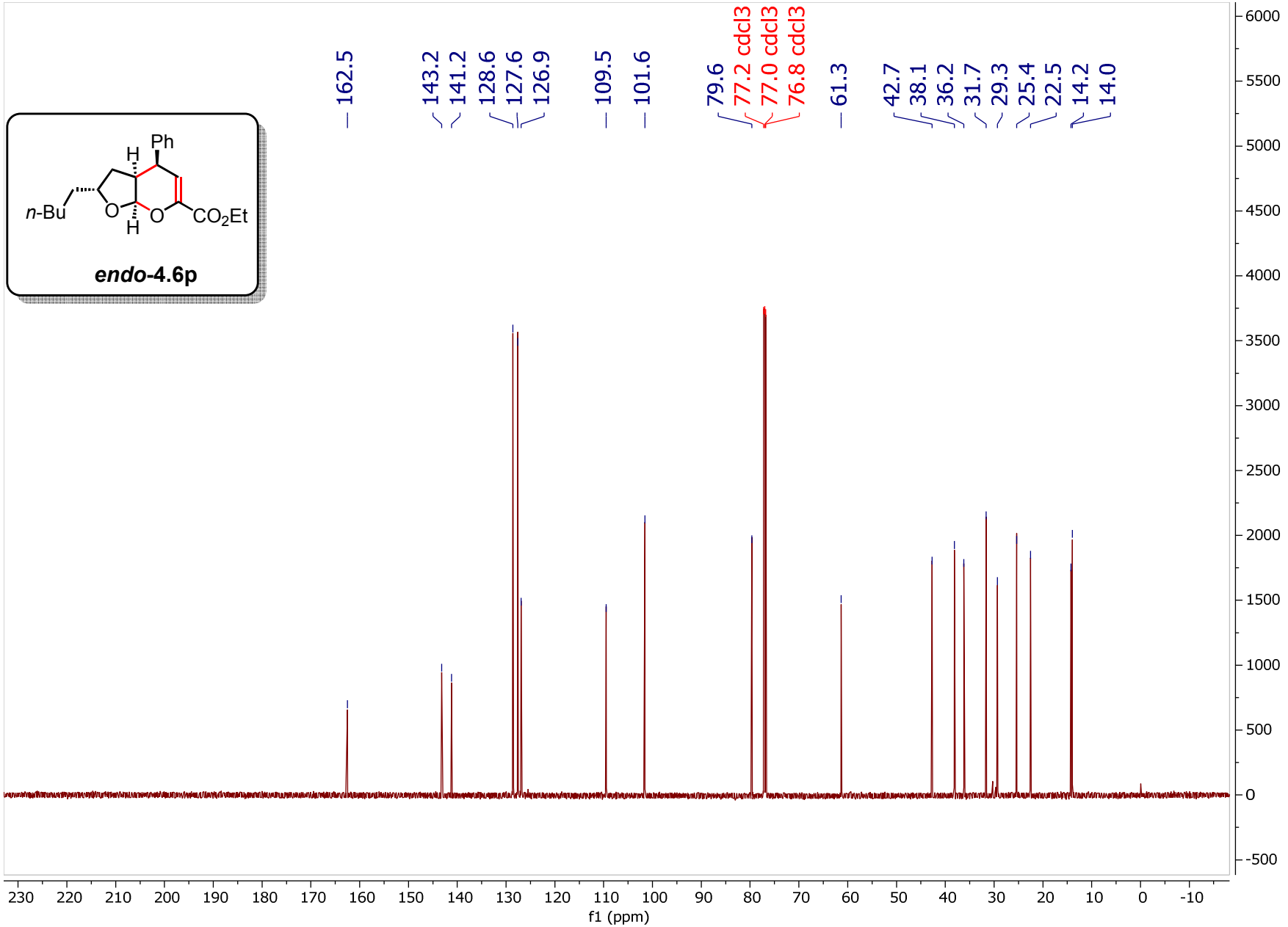

7.33 7.32 7.30 7.27 7.26 7.24 7.21 7.19 6.17 6.17 6.16 6.16 5.68 5.67 4.50 4.46 4.33 4.31 4.30 4.28 4.12 4.12 4.11 4.10 2.94 2.88 2.45 2.44 1.90 1.88 1.87 1.86 1.85 1.83 1.43 1.38 1.36 1.34 1.33 1.02 1.01 1.01 1.00 1.00 0.99 0.98 0.98 0.97 0.97 0.96 0.95 0.94
Ph
H
O
O
H
CO2Et
TIPS
endo-4.6o
1.98 1.34 2.00 0.94 0.95 1.02 2.00 1.01 1.06 2.05 1.04 0.96 2.97 21.23
f1 (ppm)

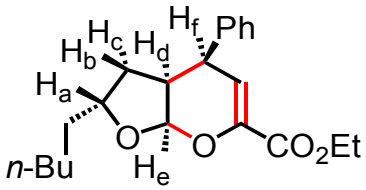

162.4
143.0
140.9
128.5
127.5
126.9
109.6
104.3
101.9
82.4
77.3
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.3
42.5
38.0
28.7
26.6
18.5
14.2
11.1
Ph
H
O
O
H
CO2Et
TIPS
endo-4.6o
4500
4000
3500
3000
2500
2000
1500
1000
500
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



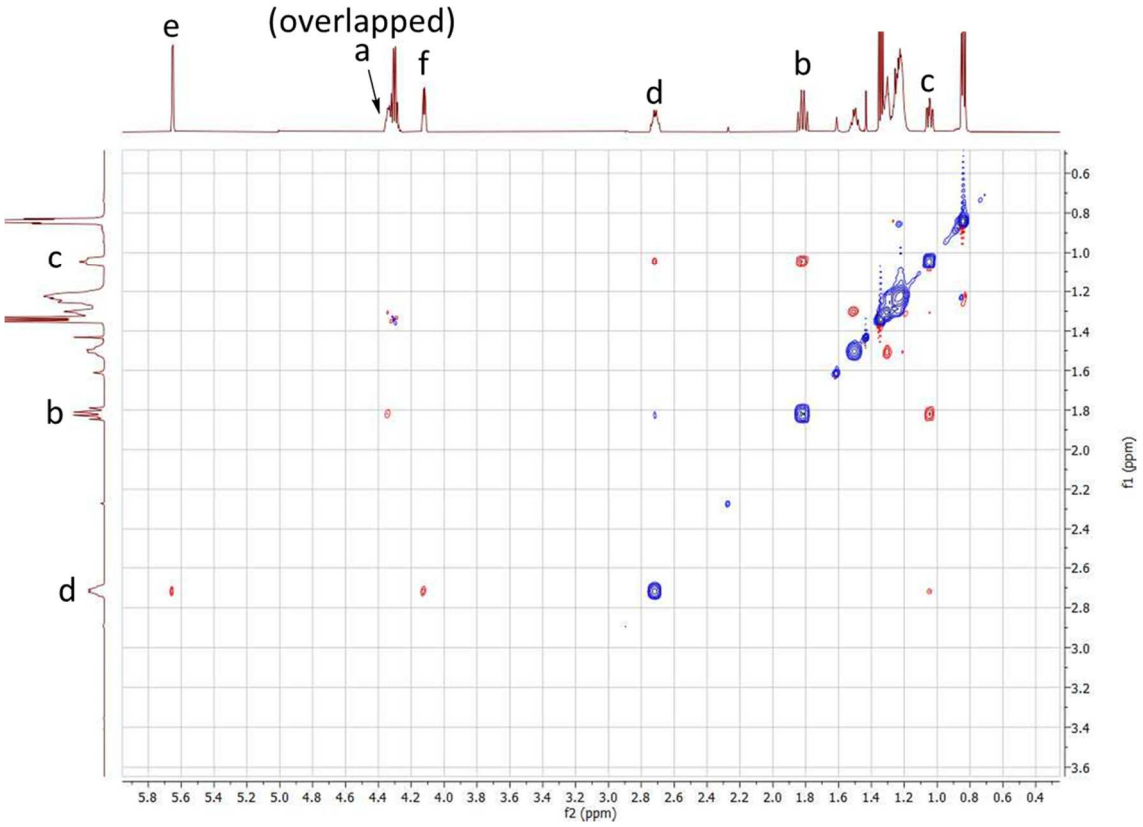
The configuration of the major diastereomer of **4.6o** was assigned to be ***endo***.


Ph
H
n-Bu
O
O
H
CO2Et
endo-4.6p
7.36
7.34
7.33
7.29
7.27
7.23
7.21
6.16
6.16
6.16
6.15
5.65
5.65
4.36
4.28
4.13
4.13
4.12
4.11
2.74
2.69
1.83
1.81
1.81
1.35
1.22
1.07
1.06
1.05
1.05
1.04
1.04
0.85
0.84
0.83
1.84
0.92
1.91
0.88
0.88
2.84
0.97
1.00
1.00
1.00
10.40
1.02
2.81
f1 (ppm)

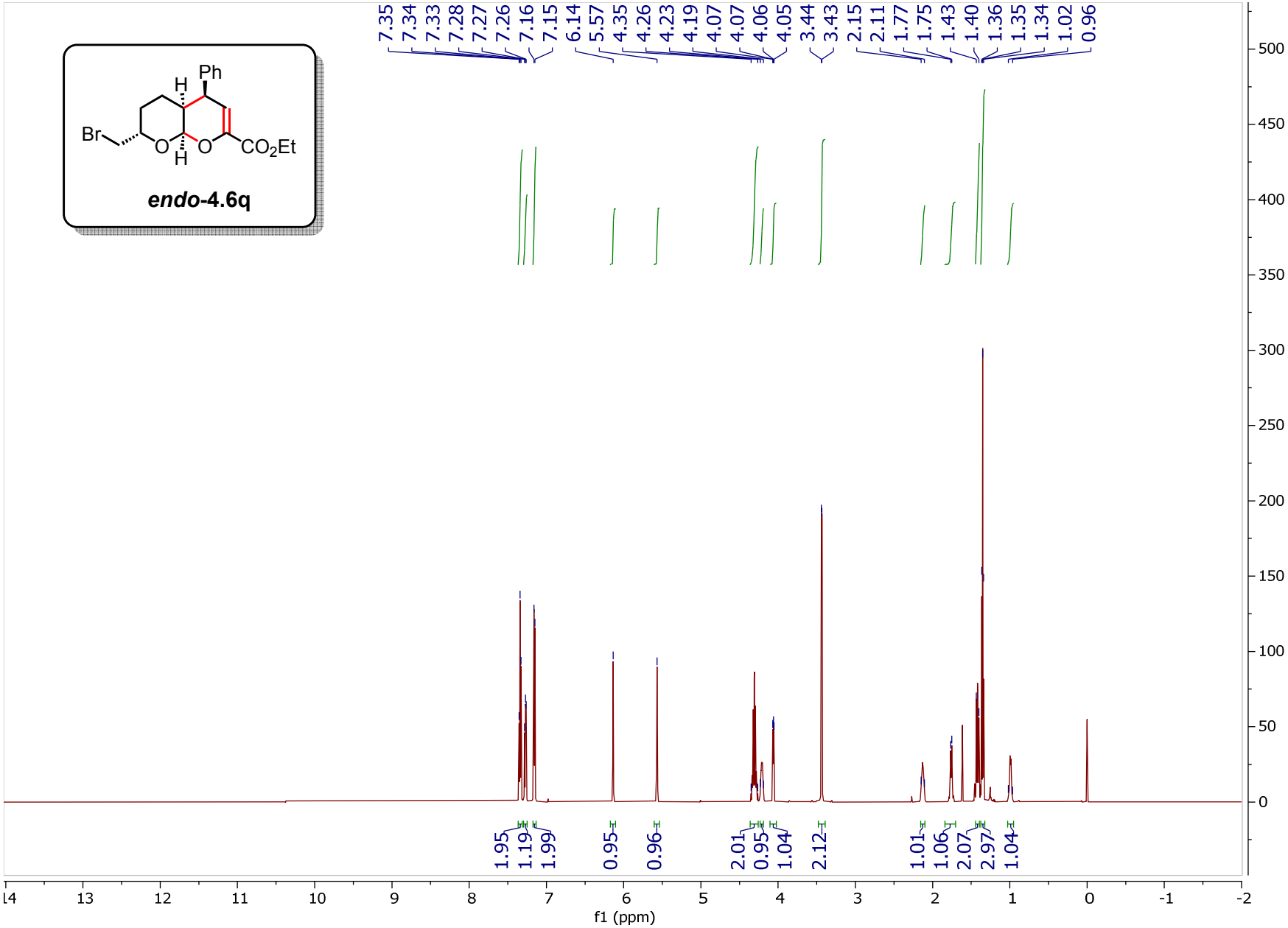

162.5
143.2
141.2
128.6
127.6
126.9
109.5
101.6
79.6
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.3
42.7
38.1
36.2
31.7
29.3
25.4
22.5
14.2
14.0
Ph
H
n-Bu
O
O
H
CO2Et
endo-4.6p
f1 (ppm)

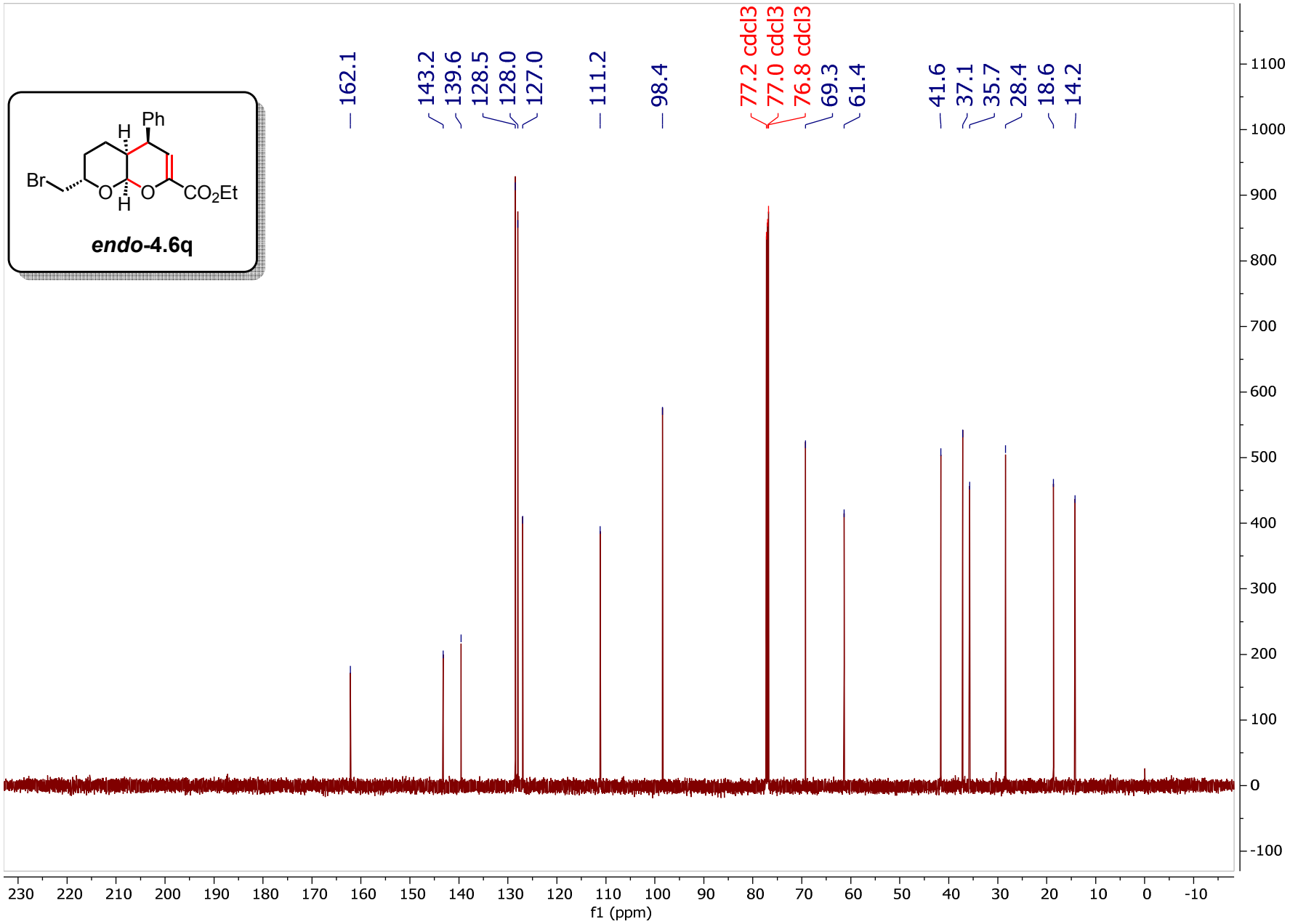


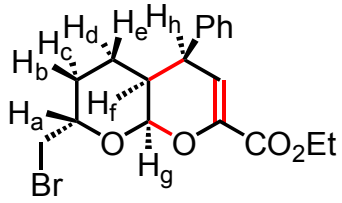
***endo*-4.6p**



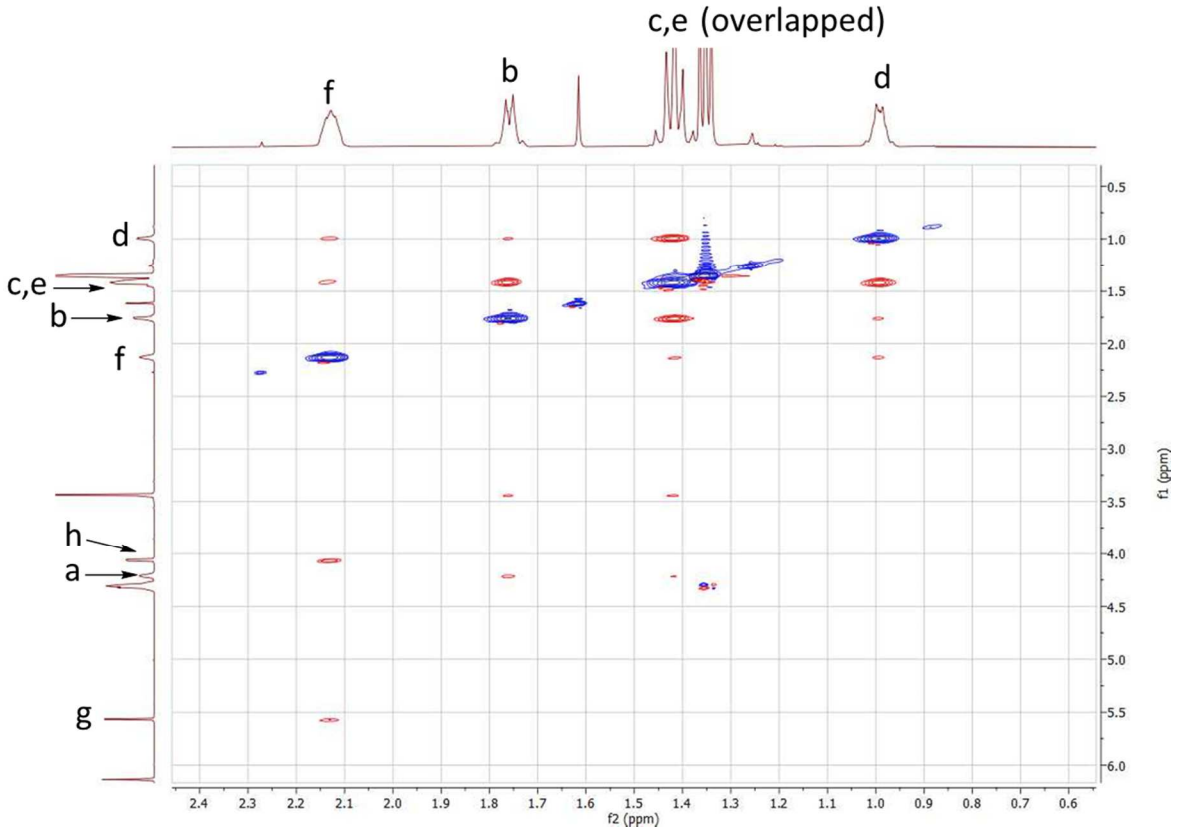
The configuration of the major diastereomer of **4.6p** was assigned to be ***endo***.


Ph
H
Br
O
O
H
CO2Et
endo-4.6q
7.35
7.34
7.33
7.28
7.27
7.26
7.16
7.15
6.14
5.57
4.35
4.26
4.23
4.19
4.07
4.07
4.06
4.05
3.44
3.43
2.15
2.11
1.77
1.75
1.43
1.40
1.36
1.35
1.34
1.02
0.96
1.95
1.19
1.99
0.95
0.96
2.01
0.95
1.04
2.12
1.01
1.06
2.07
2.97
1.04
f1 (ppm)

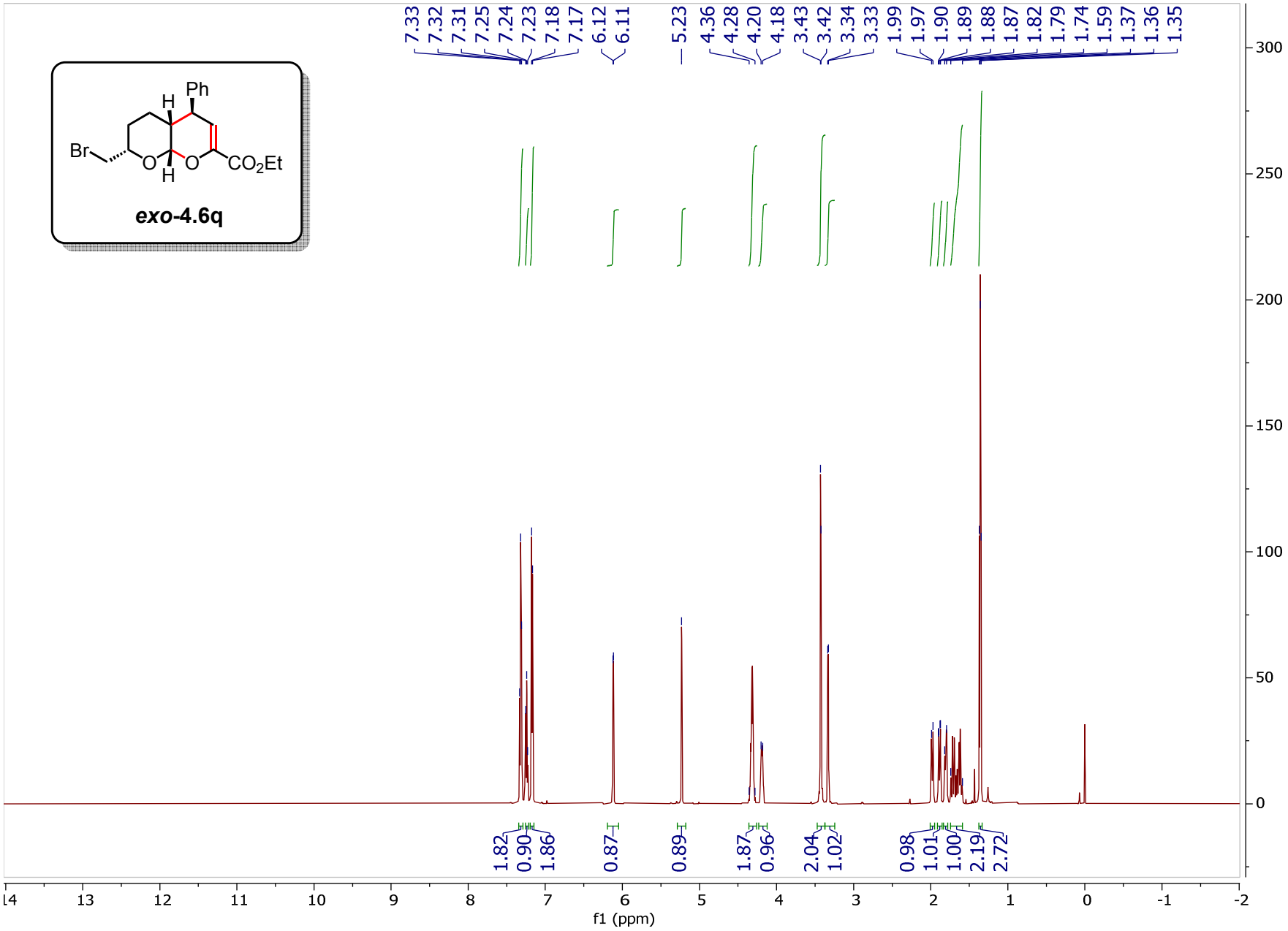

Ph
H
Br
O
H
O
CO2Et
endo-4.6q
162.1
143.2
139.6
128.5
128.0
127.0
111.2
98.4
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
69.3
61.4
41.6
37.1
35.7
28.4
18.6
14.2
f1 (ppm)

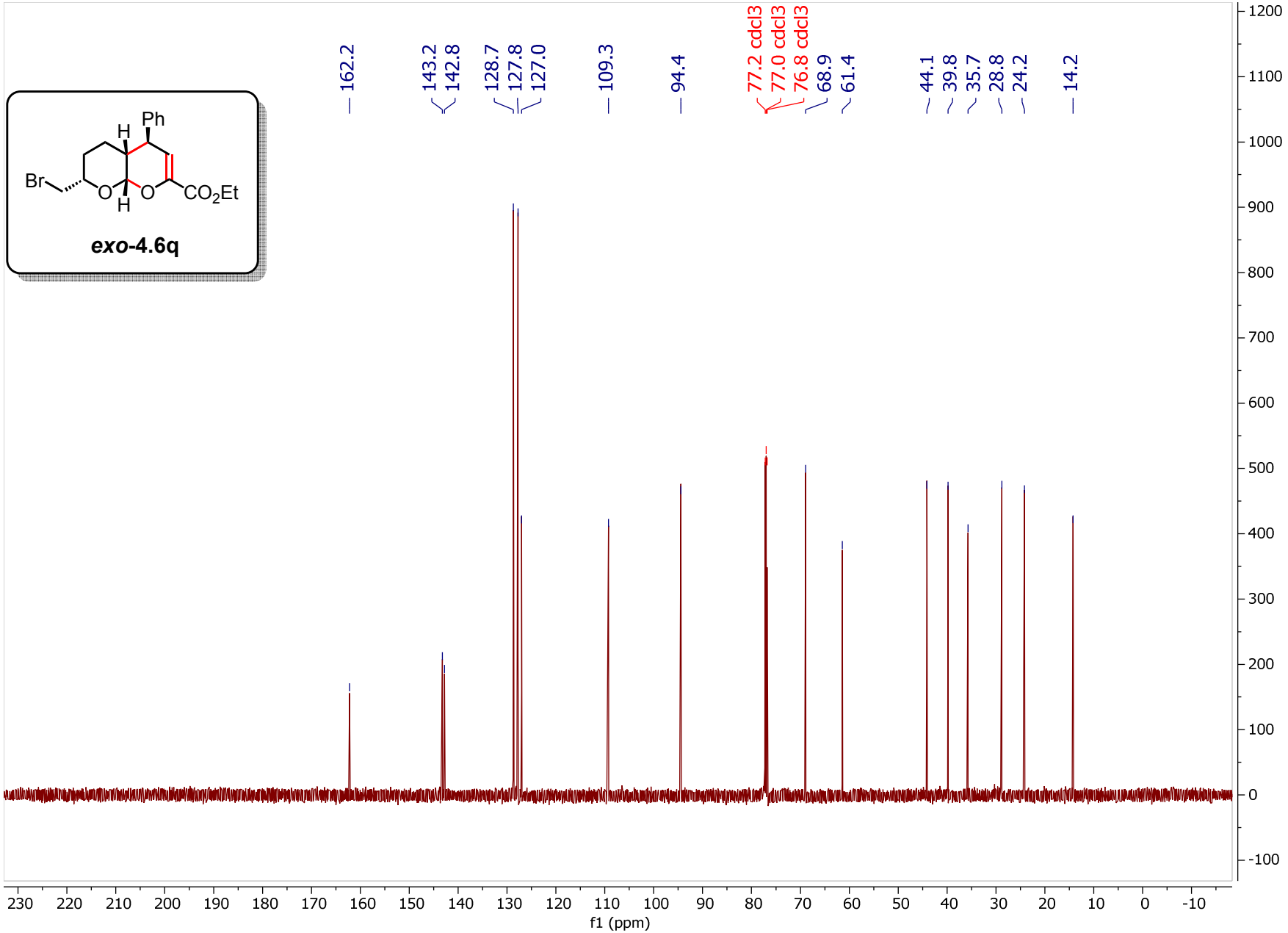


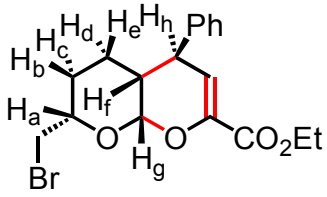
***endo*-4.6q**



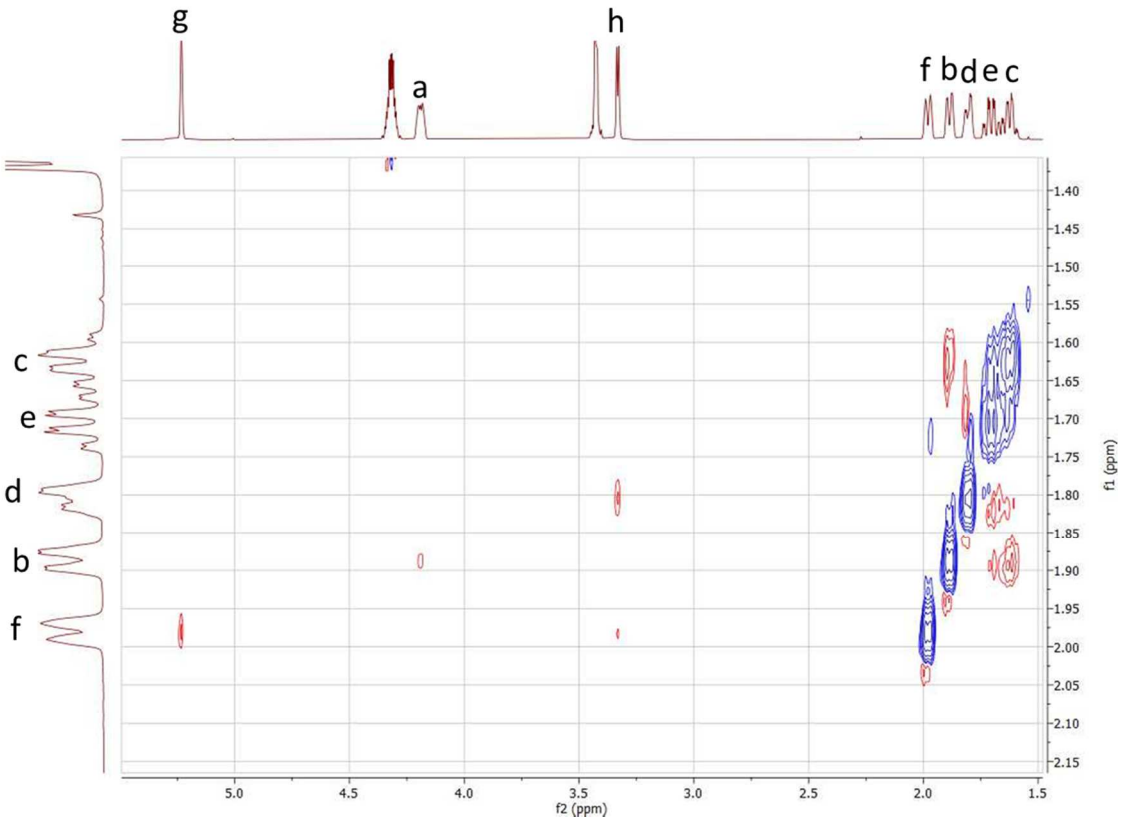
The configuration of the major diastereomer of **4.6q** was assigned to be ***endo***.


Ph
H
Br
O
O
H
CO2Et
exo-4.6q
7.33
7.32
7.31
7.25
7.24
7.23
7.18
7.17
6.12
6.11
5.23
4.36
4.28
4.20
4.18
3.43
3.42
3.34
3.33
1.99
1.97
1.90
1.89
1.88
1.87
1.82
1.79
1.74
1.59
1.37
1.36
1.35
1.82
0.90
1.86
0.87
0.89
1.87
0.96
2.04
1.02
0.98
1.01
1.00
2.19
2.72
f1 (ppm)

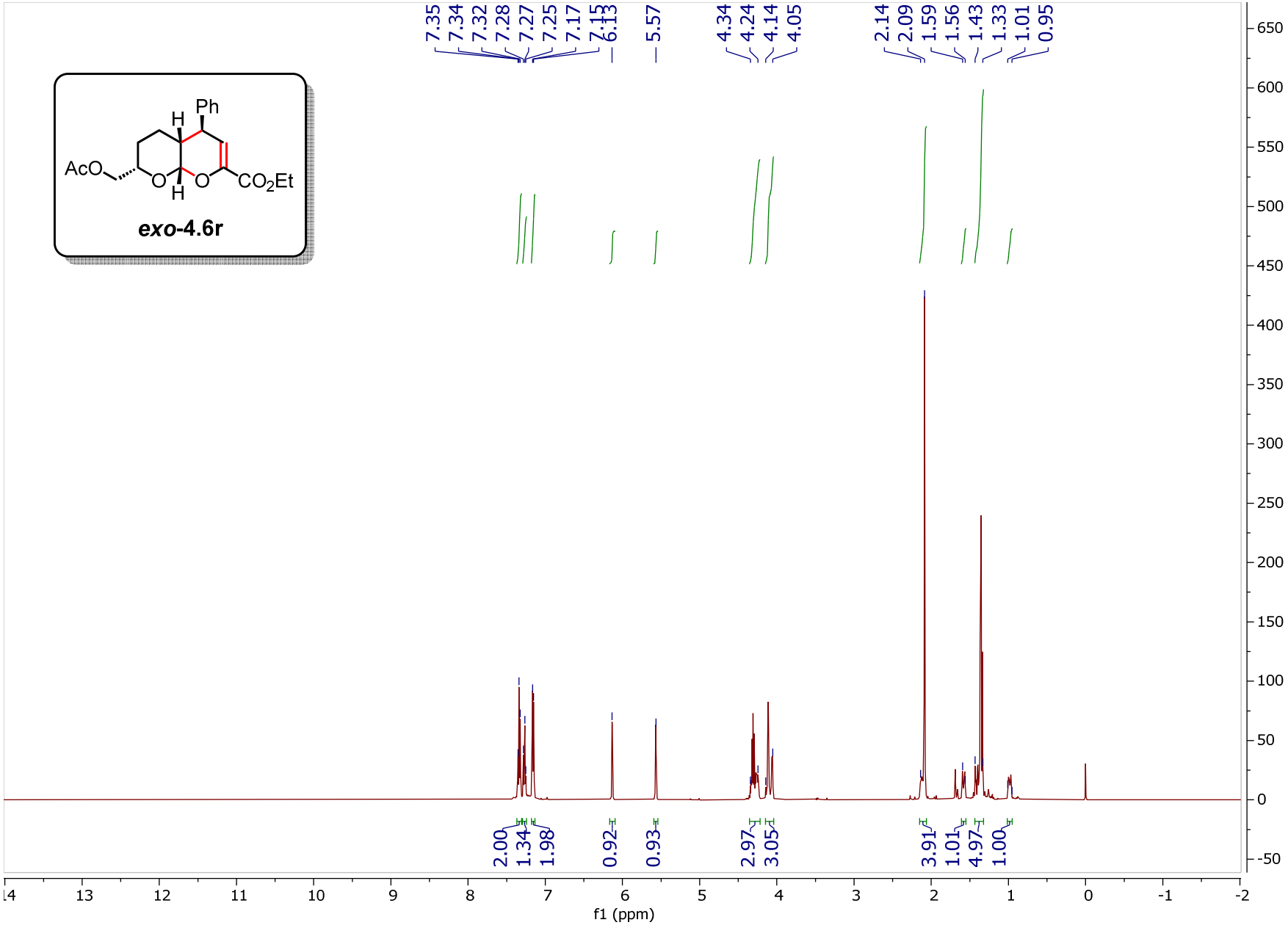

Ph
H
Br
O
O
H
CO2Et
exo-4.6q
162.2
143.2
142.8
128.7
127.8
127.0
109.3
94.4
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
68.9
61.4
44.1
39.8
35.7
28.8
24.2
14.2
f1 (ppm)

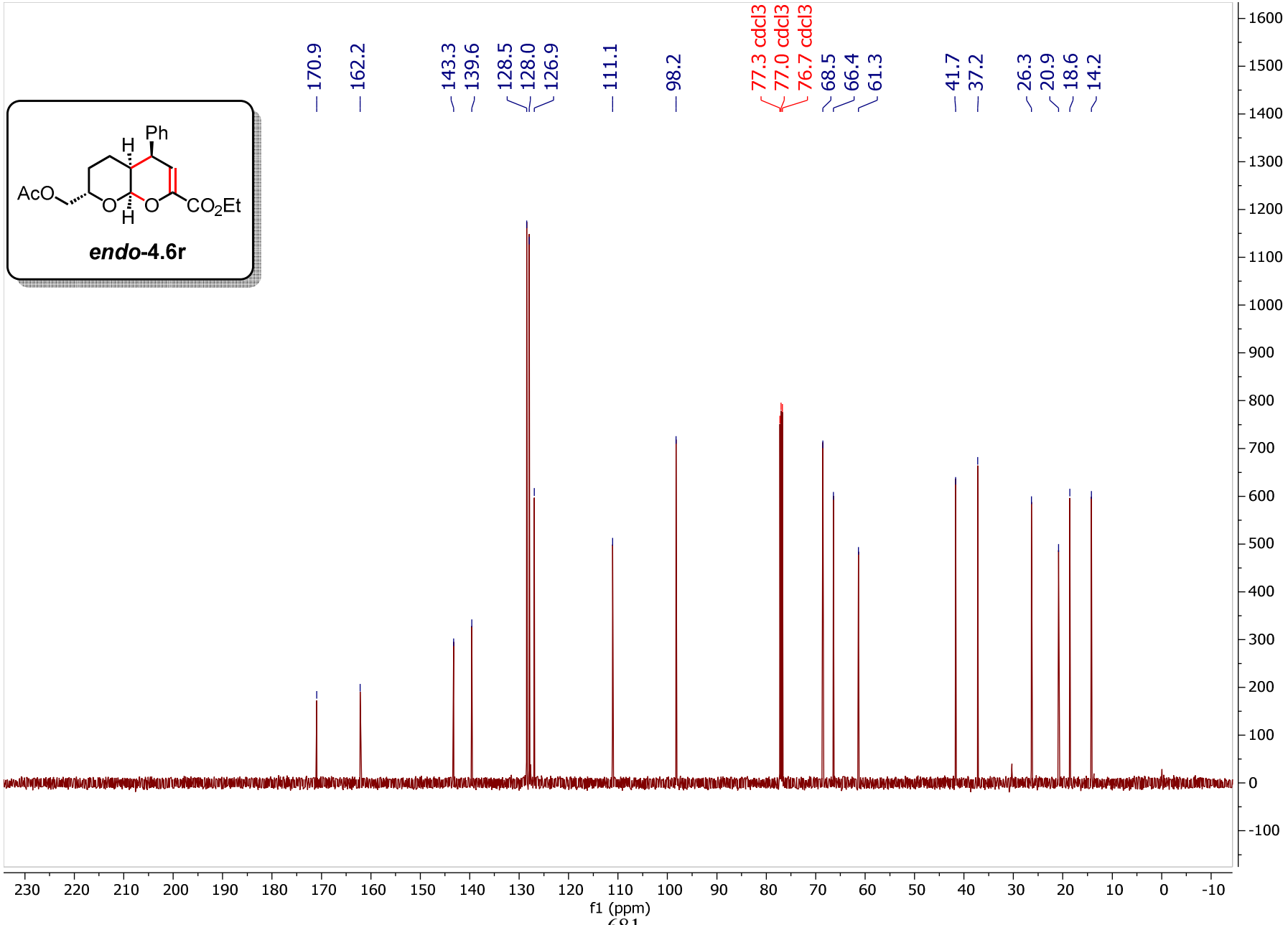


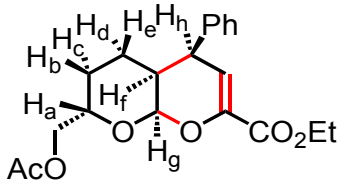
***exo*-4.6q**



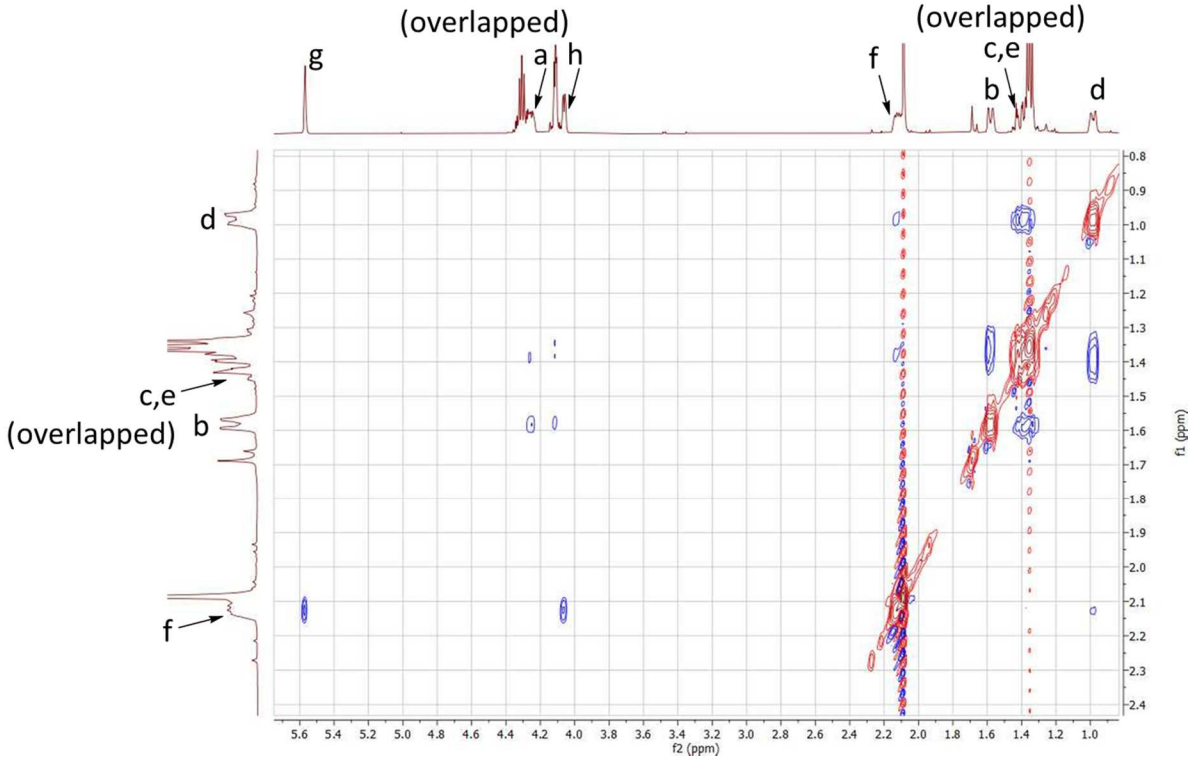
The configuration of the minor diastereomer of **4.6q** was assigned to be ***exo***.


7.35
7.34
7.32
7.28
7.27
7.25
7.17
7.15
7.13
5.57
4.34
4.24
4.14
4.05
2.14
2.09
1.59
1.56
1.43
1.33
1.01
0.95
Ph
H
AcO
O
O
H
CO2Et
exo-4.6r
2.00
1.34
1.98
0.92
0.93
2.97
3.05
3.91
1.01
4.97
1.00
f1 (ppm)

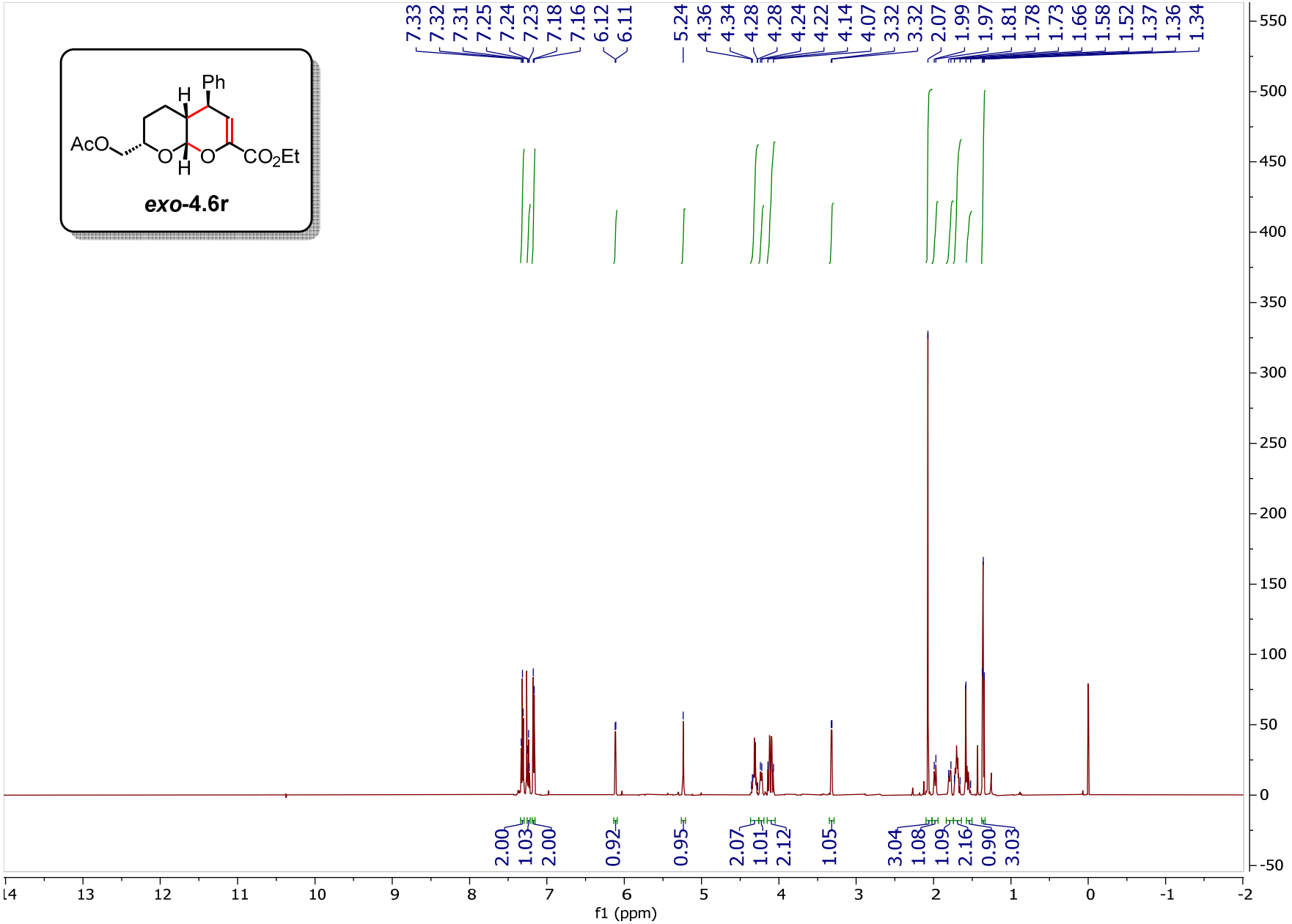

170.9
162.2
143.3
139.6
128.5
128.0
126.9
111.1
98.2
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
68.5
66.4
61.3
41.7
37.2
26.3
20.9
18.6
14.2
Ph
H
AcO
O
O
H
CO2Et
endo-4.6r
f1 (ppm)

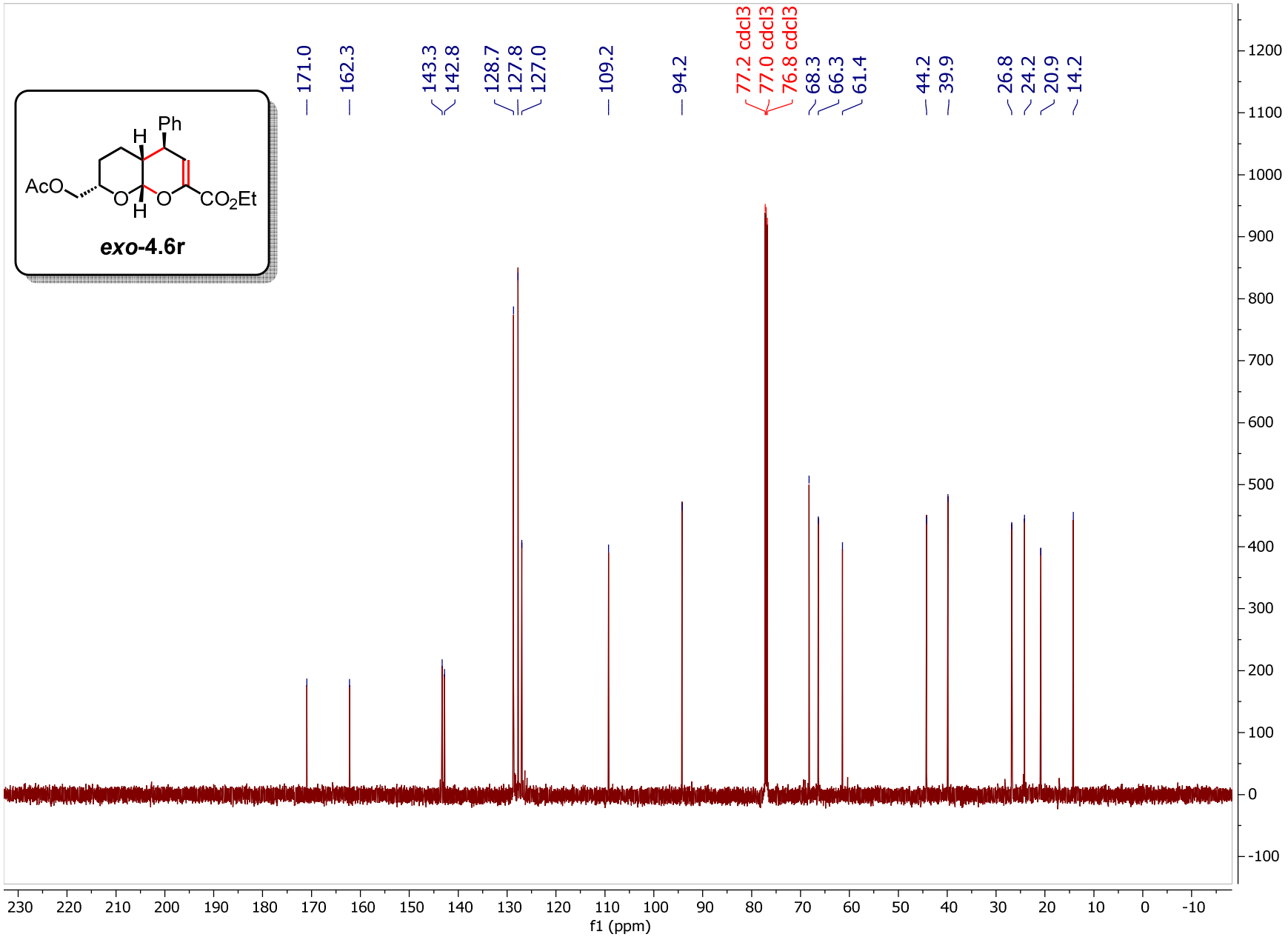


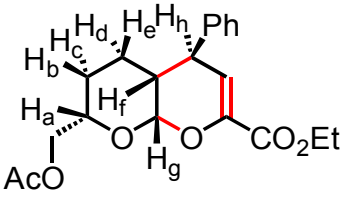
***endo*-4.6r**



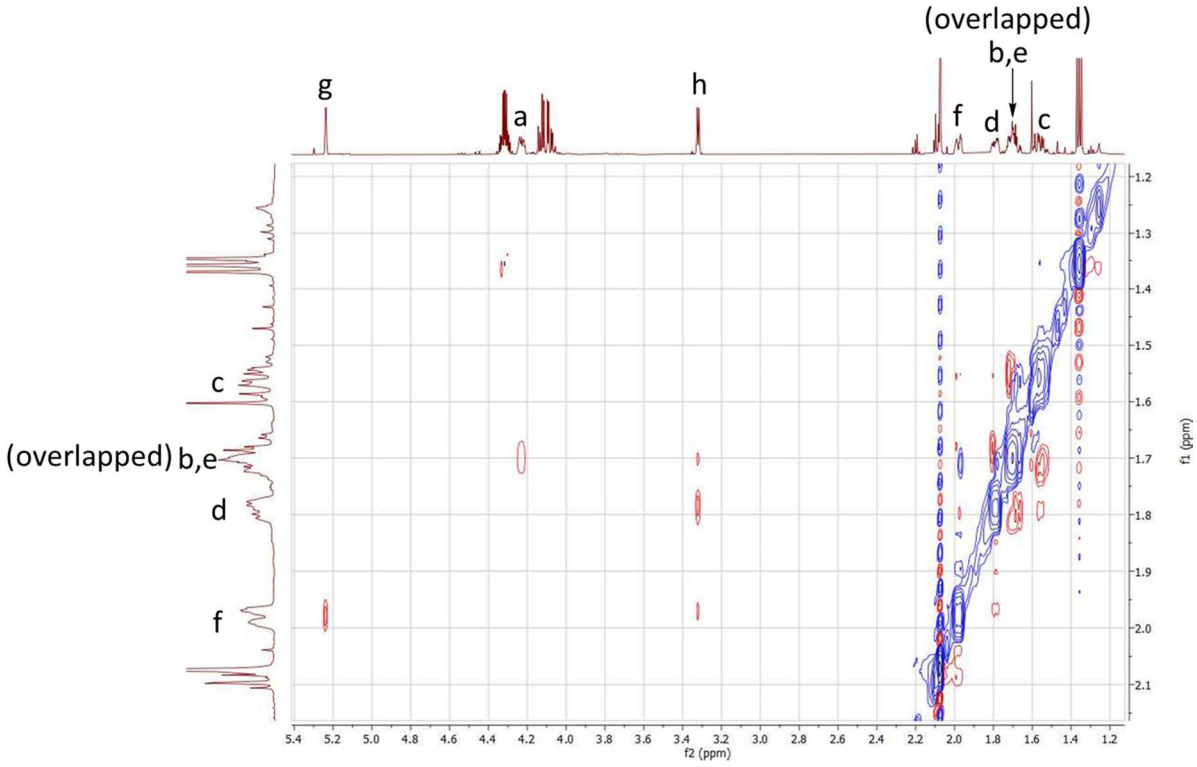
The configuration of the minor diastereomer of **4.6r** was assigned to be ***endo***.


Ph
H
AcO
O
O
H
CO2Et
exo-4.6r
7.33
7.32
7.31
7.25
7.24
7.23
7.18
7.16
6.12
6.11
5.24
4.36
4.34
4.28
4.28
4.24
4.22
4.14
4.07
3.32
3.32
2.07
1.99
1.97
1.81
1.78
1.73
1.66
1.58
1.52
1.37
1.36
1.34
2.00
1.03
2.00
0.92
0.95
2.07
1.01
2.12
1.05
3.04
1.08
1.09
2.16
0.90
3.03
f1 (ppm)

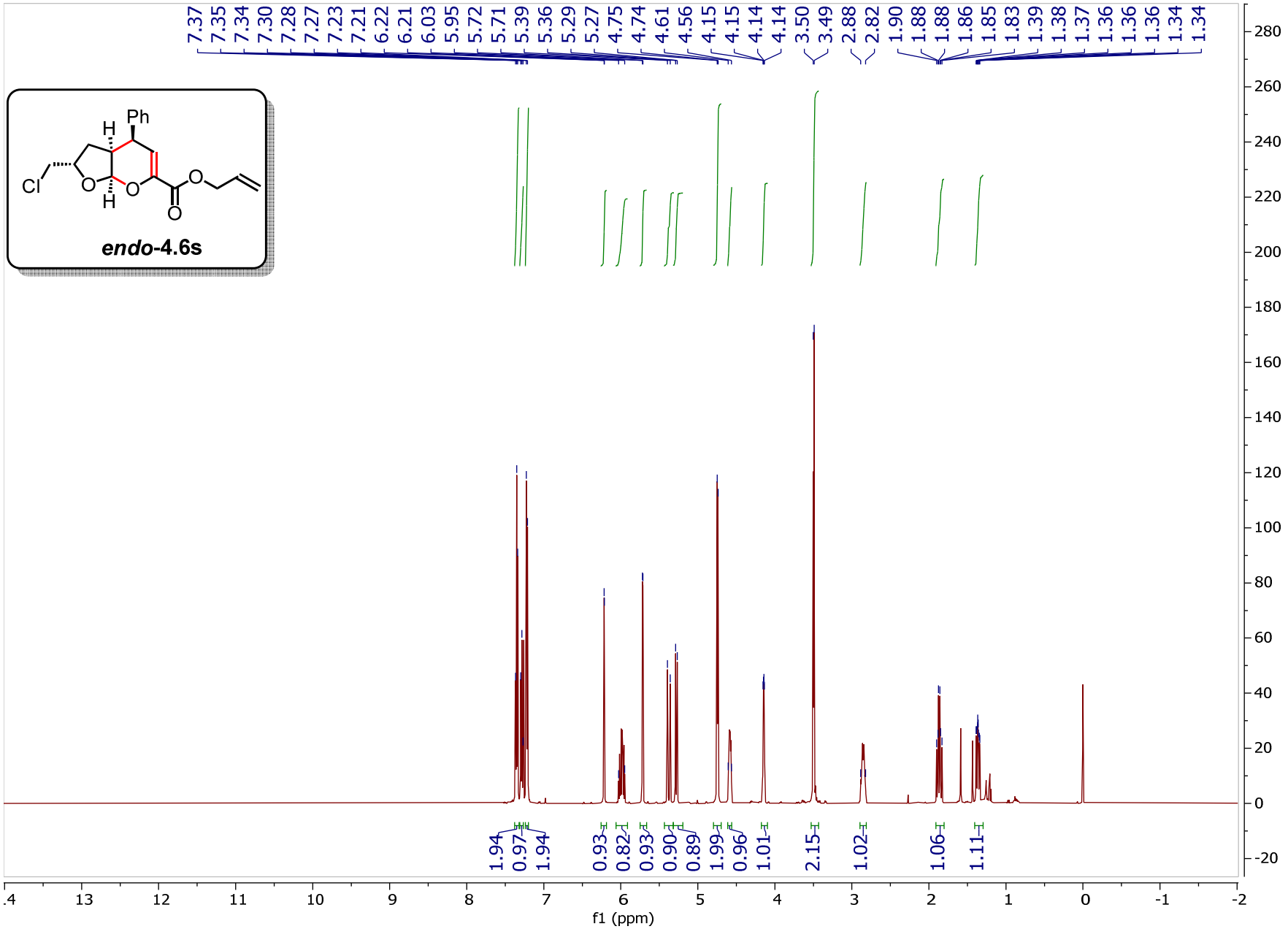

171.0
162.3
143.3
142.8
128.7
127.8
127.0
109.2
94.2
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
68.3
66.3
61.4
44.2
39.9
26.8
24.2
20.9
14.2
Ph
H
AcO
O
O
CO2Et
H
exo-4.6r
f1 (ppm)

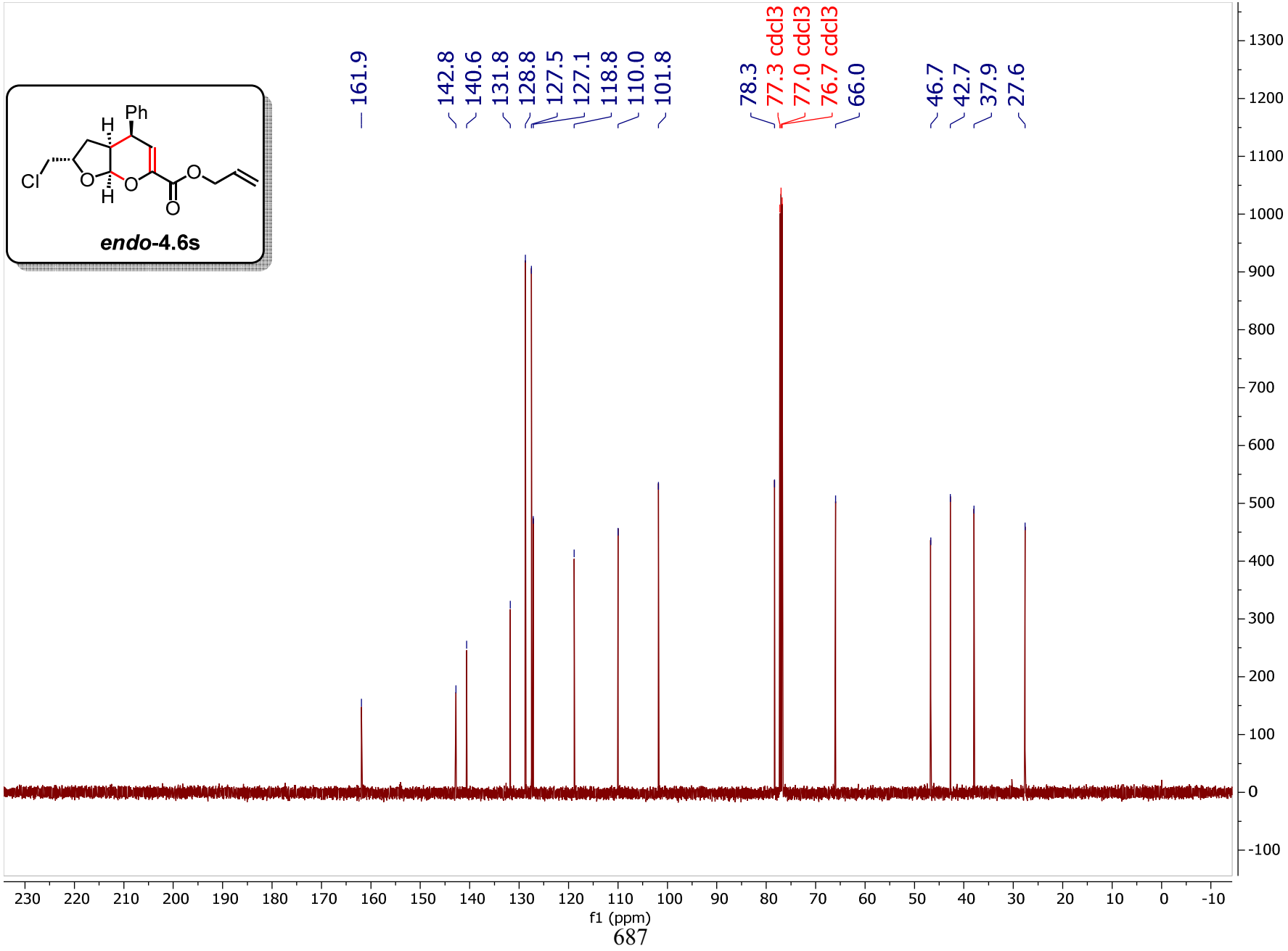


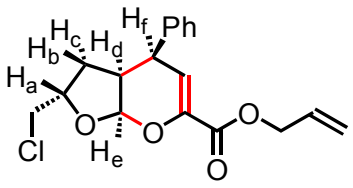
***exo*-4.6r**



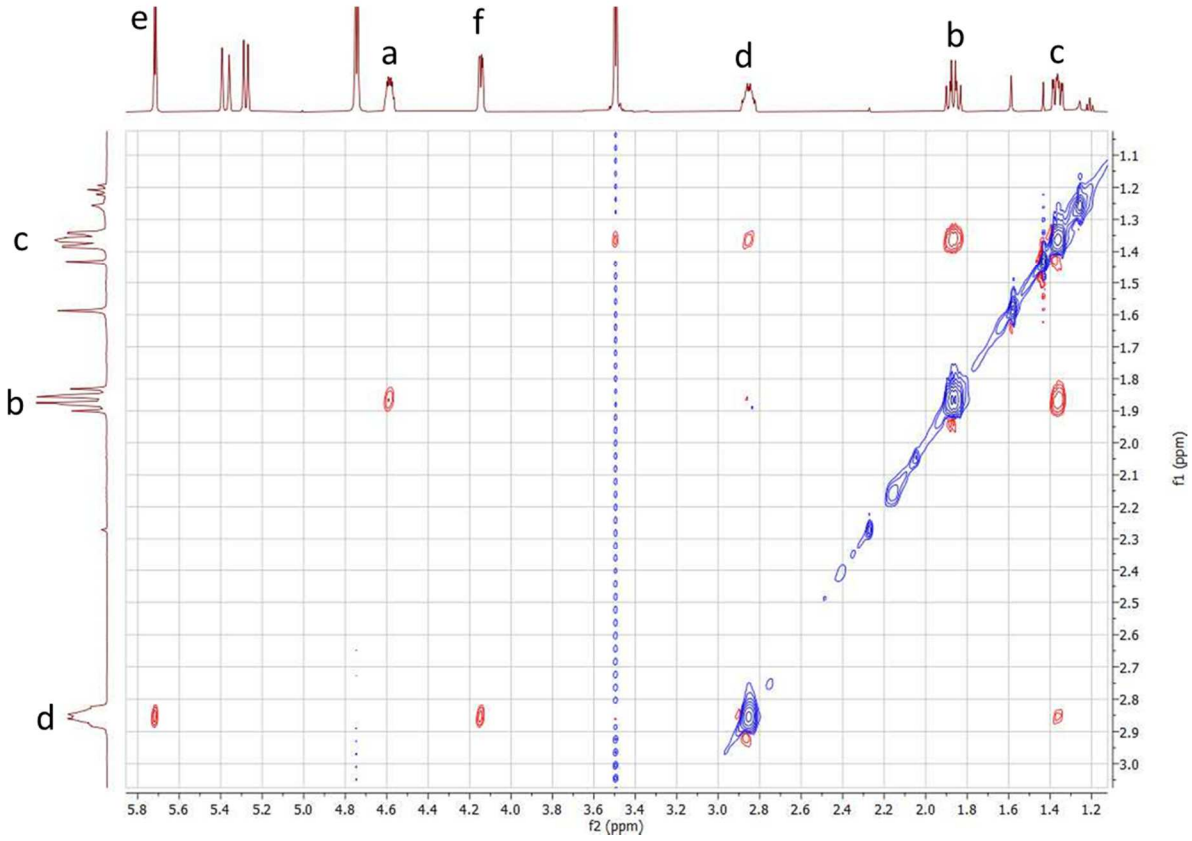
The configuration of the major diastereomer of **4.6r** was assigned to be ***exo***.


7.37 7.35 7.34 7.30 7.28 7.27 7.23 7.21 6.22 6.21 6.03 5.95 5.72 5.71 5.39 5.36 5.29 5.27 4.75 4.74 4.61 4.56 4.15 4.15 4.14 4.14 3.50 3.49 2.88 2.82 1.90 1.88 1.88 1.86 1.85 1.83 1.39 1.38 1.37 1.36 1.36 1.36 1.34 1.34
Ph
H
Cl
O
O
H
O
O
O
endo-4.6s
1.94 0.97 1.94 0.93 0.82 0.93 0.90 0.89 1.99 0.96 1.01 2.15 1.02 1.06 1.11
f1 (ppm)

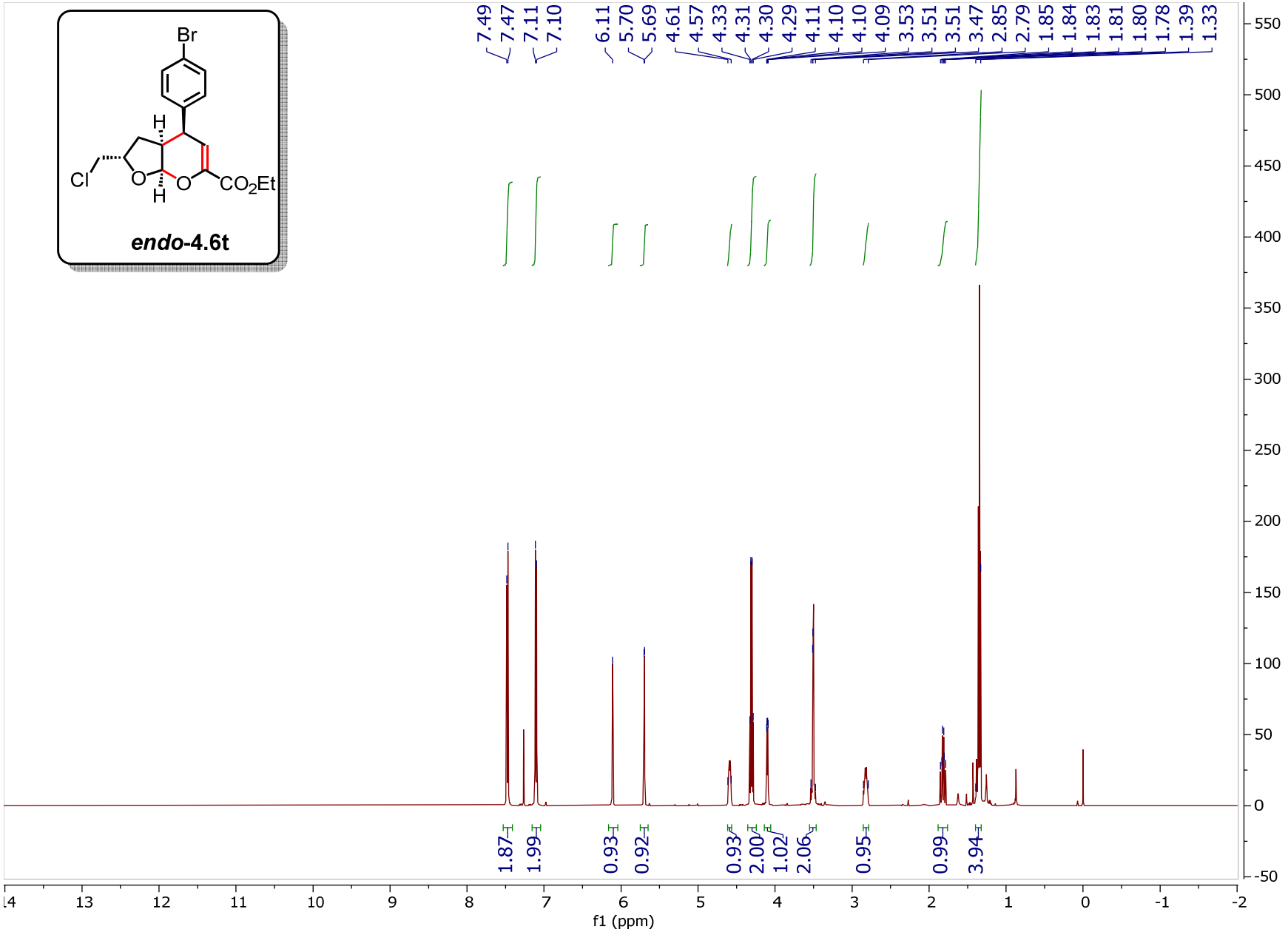

endo-4.6s
161.9
142.8
140.6
131.8
128.8
127.5
127.1
118.8
110.0
101.8
78.3
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
66.0
46.7
42.7
37.9
27.6
f1 (ppm)

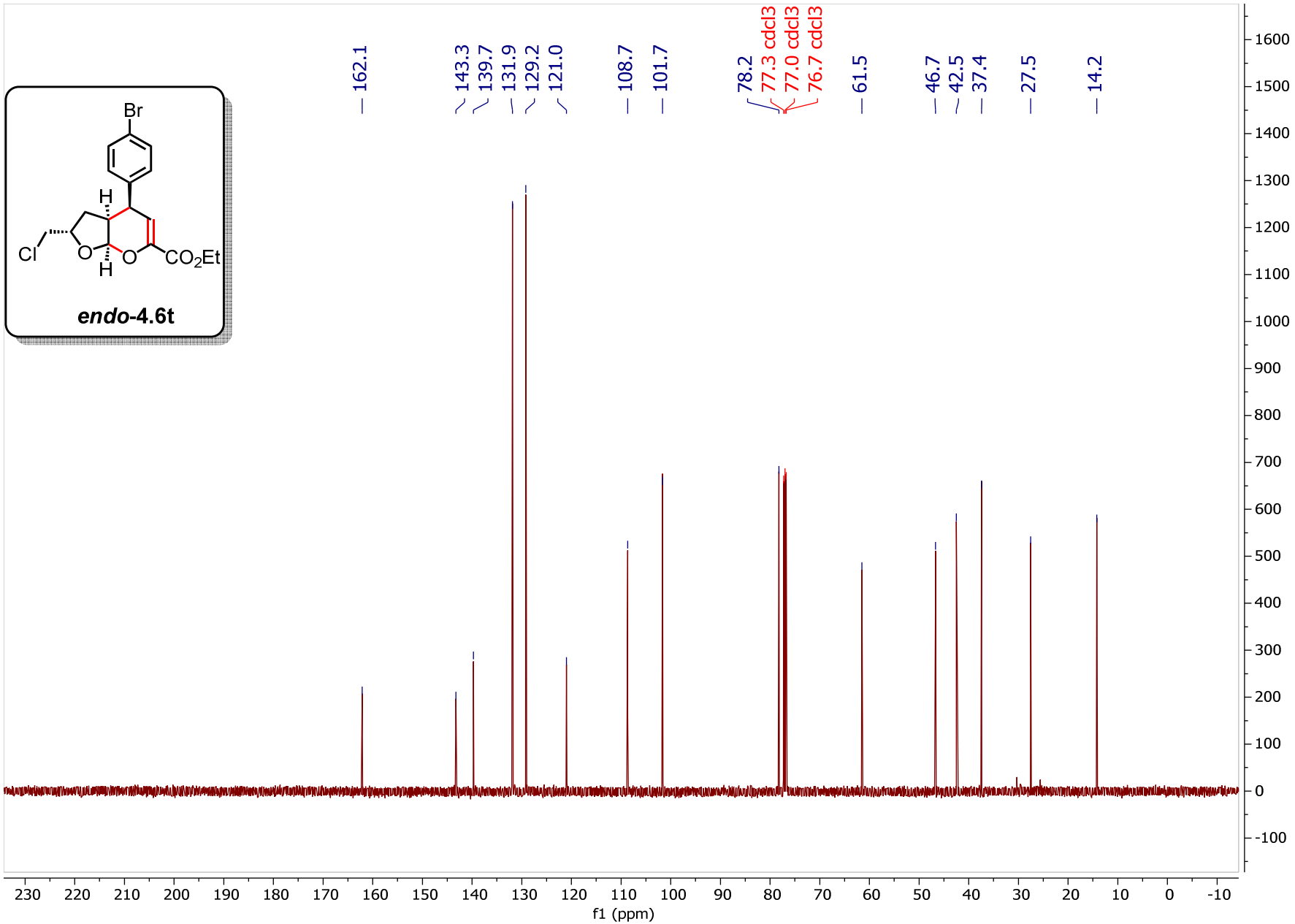


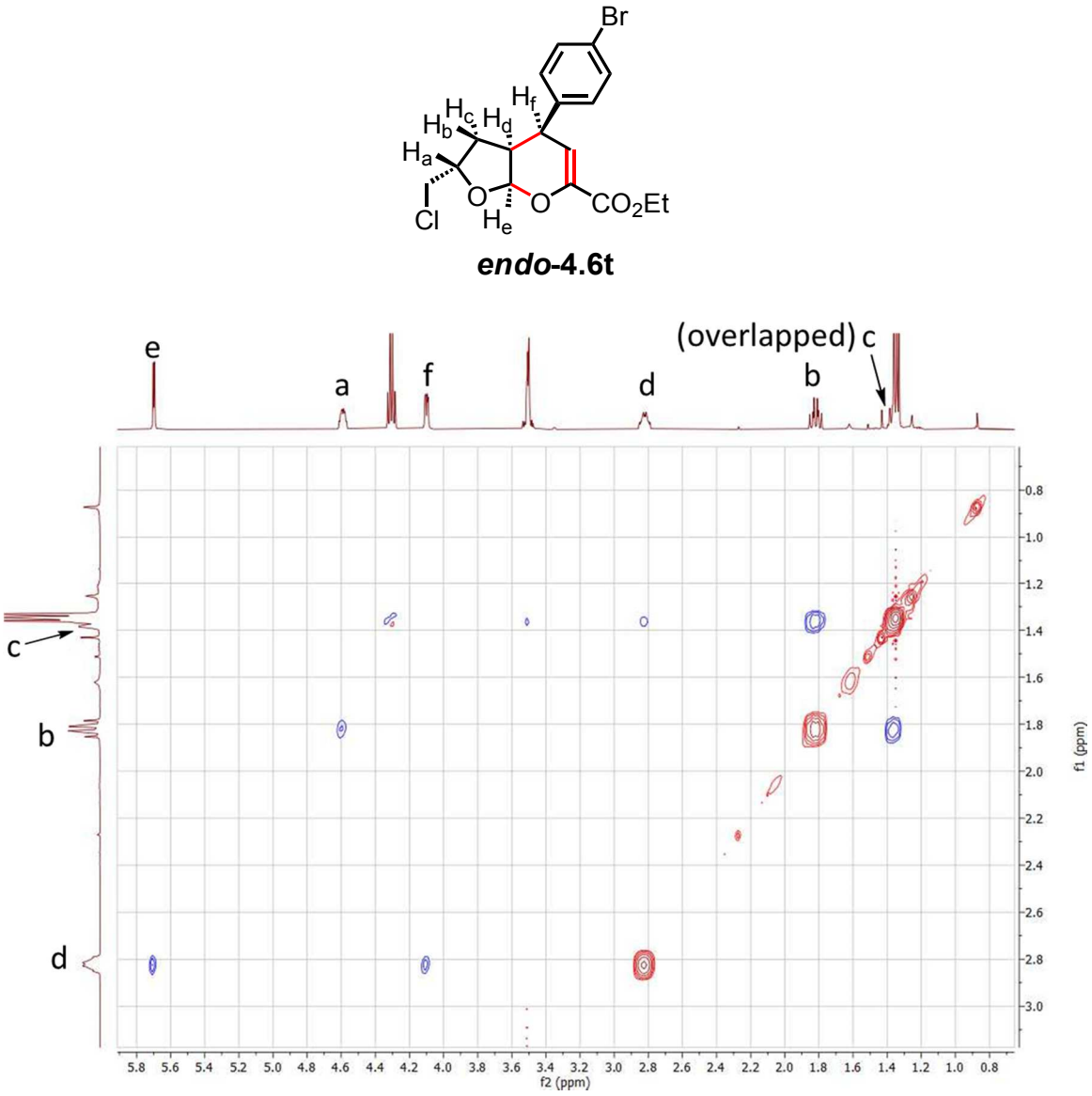
***endo*-4.6s**



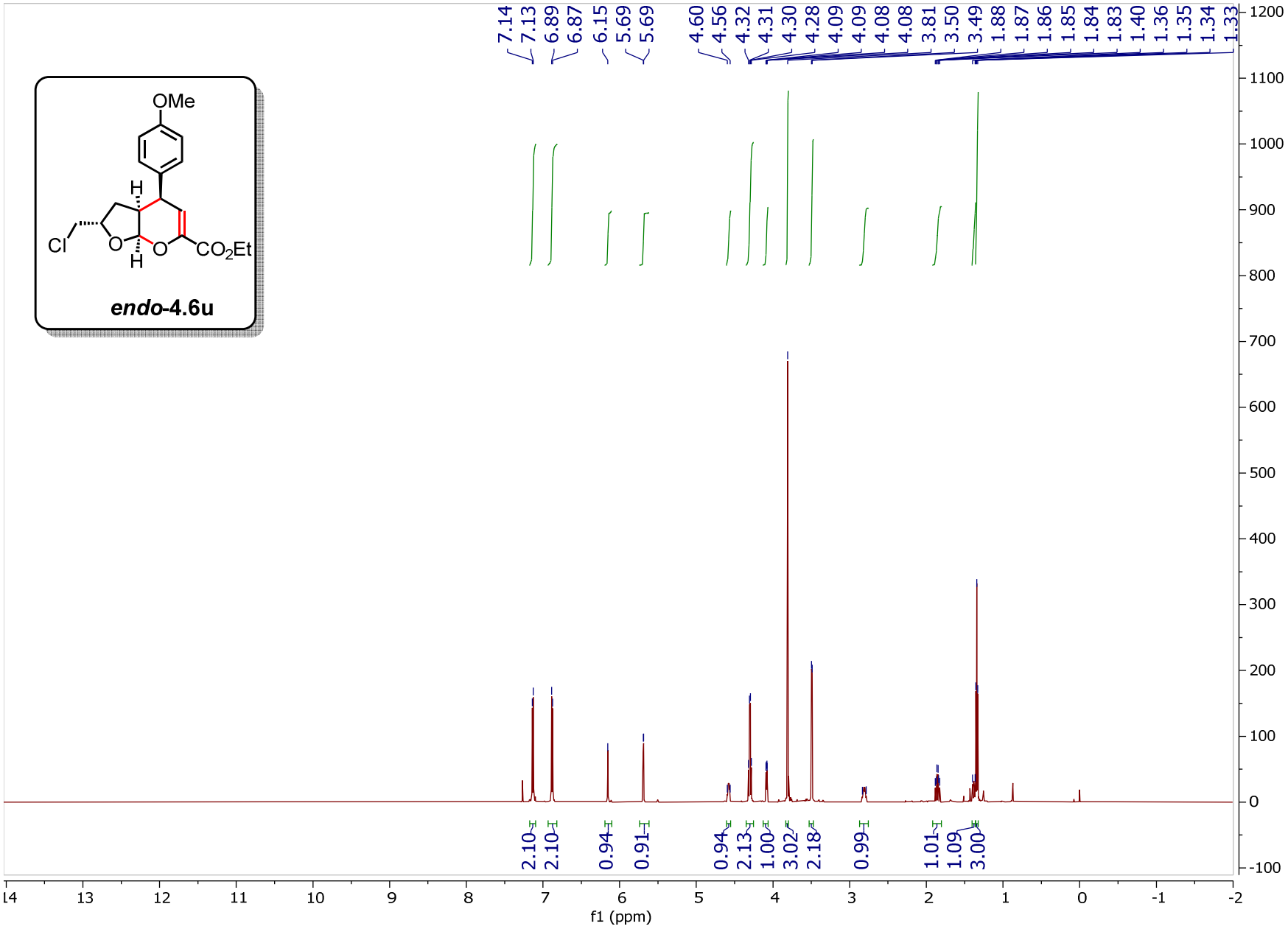
The configuration of the major diastereomer of **4.6s** was assigned to be ***endo***.

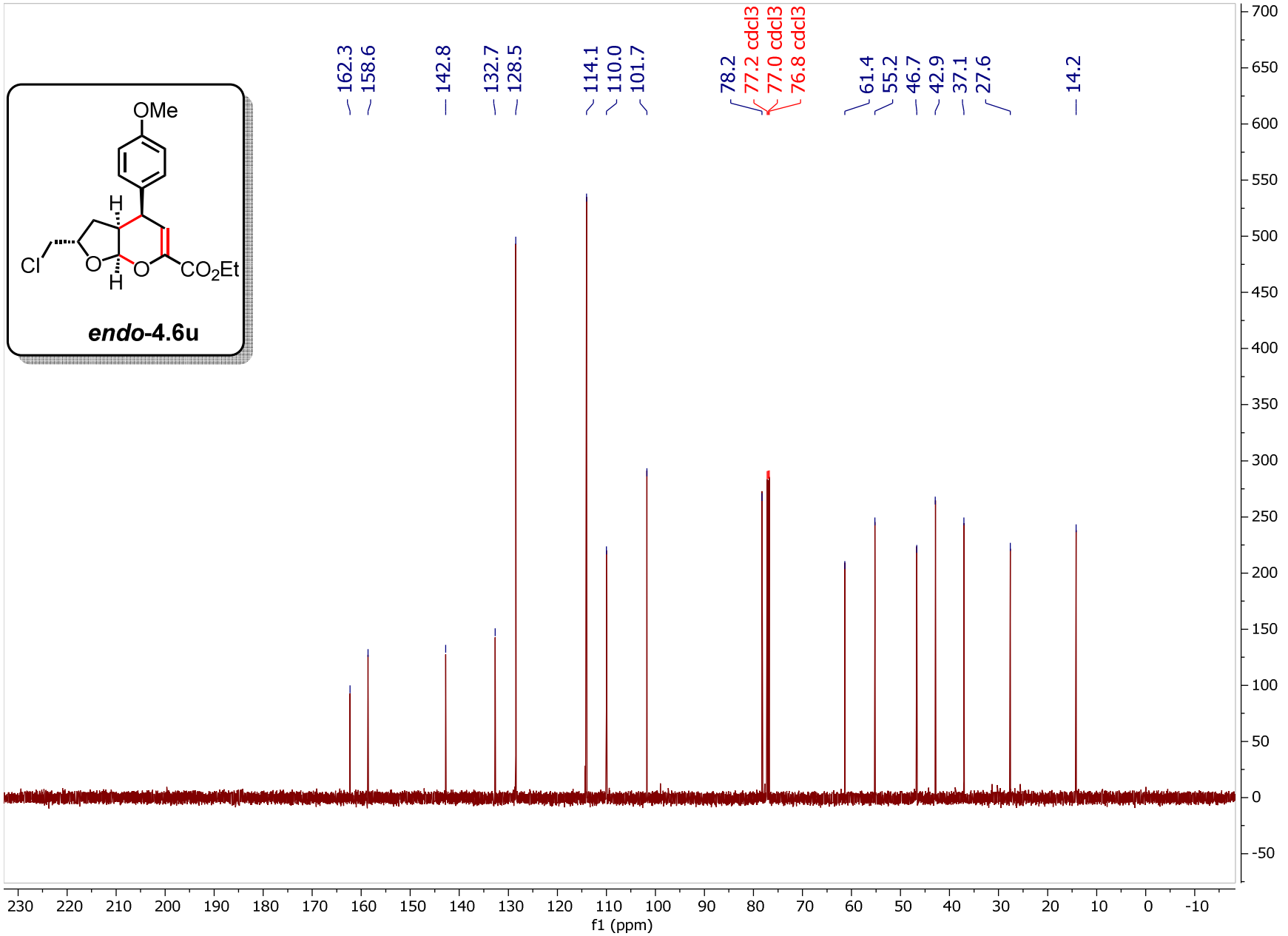

Br
H
Cl
O
O
CO2Et
H
endo-4.6t
7.49
7.47
7.11
7.10
6.11
5.70
5.69
4.61
4.57
4.33
4.31
4.30
4.29
4.11
4.10
4.10
4.09
3.53
3.51
3.51
3.47
2.85
2.79
1.85
1.84
1.83
1.81
1.80
1.78
1.39
1.33
1.87
1.99
0.93
0.92
0.93
2.00
1.02
2.06
0.95
0.99
3.94
f1 (ppm)

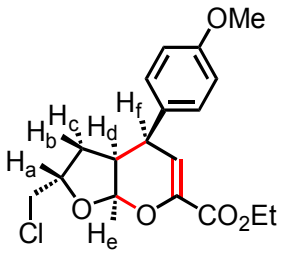

Br
H
Cl
O
O
H
CO2Et
endo-4.6t
162.1
143.3
139.7
131.9
129.2
121.0
108.7
101.7
78.2
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
61.5
46.7
42.5
37.4
27.5
14.2
f1 (ppm)



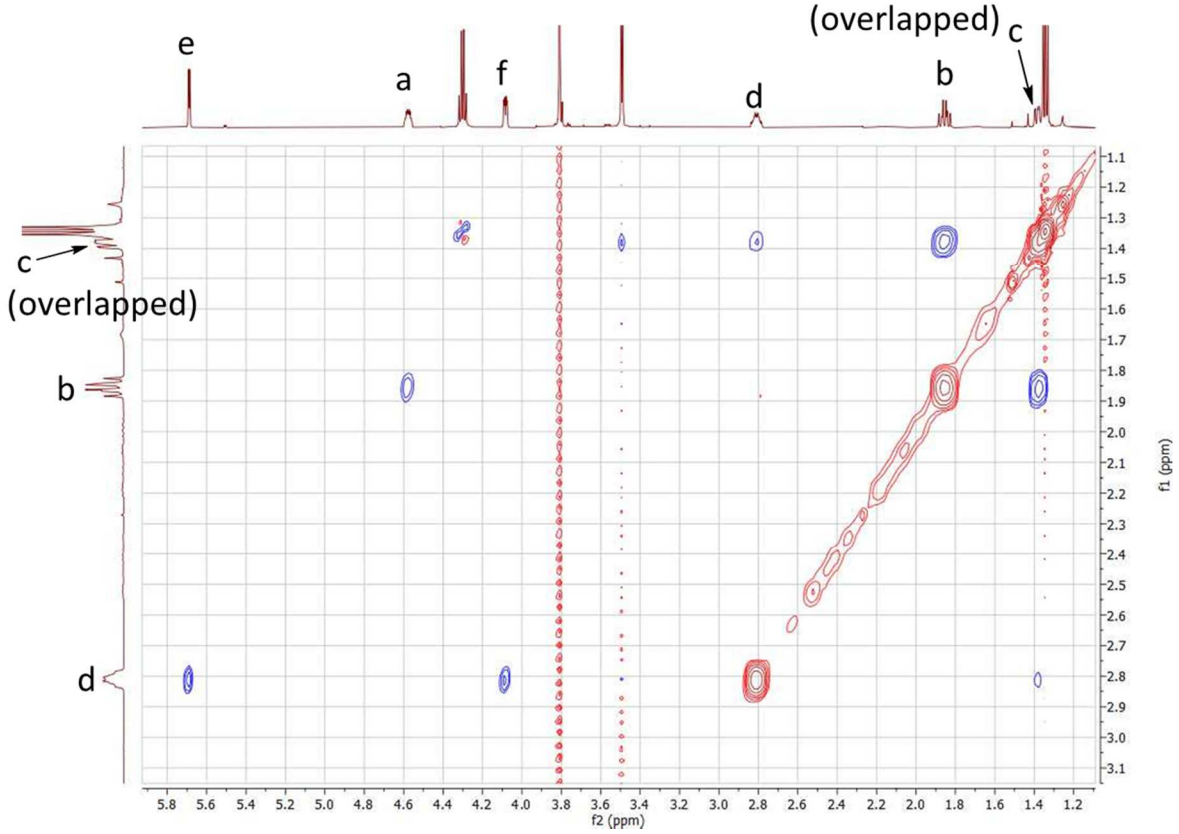
The configuration of the major diastereomer of **4.6t** was assigned to be ***endo***.


OMe
H
Cl
O
O
CO2Et
H
endo-4.6u
7.14
7.13
6.89
6.87
6.15
5.69
5.69
4.60
4.56
4.32
4.31
4.30
4.28
4.09
4.09
4.08
4.08
3.81
3.50
3.49
1.88
1.87
1.86
1.85
1.84
1.83
1.40
1.36
1.35
1.34
1.33
2.10
2.10
0.94
0.91
0.94
2.13
1.00
3.02
2.18
0.99
1.01
1.09
3.00
f1 (ppm)

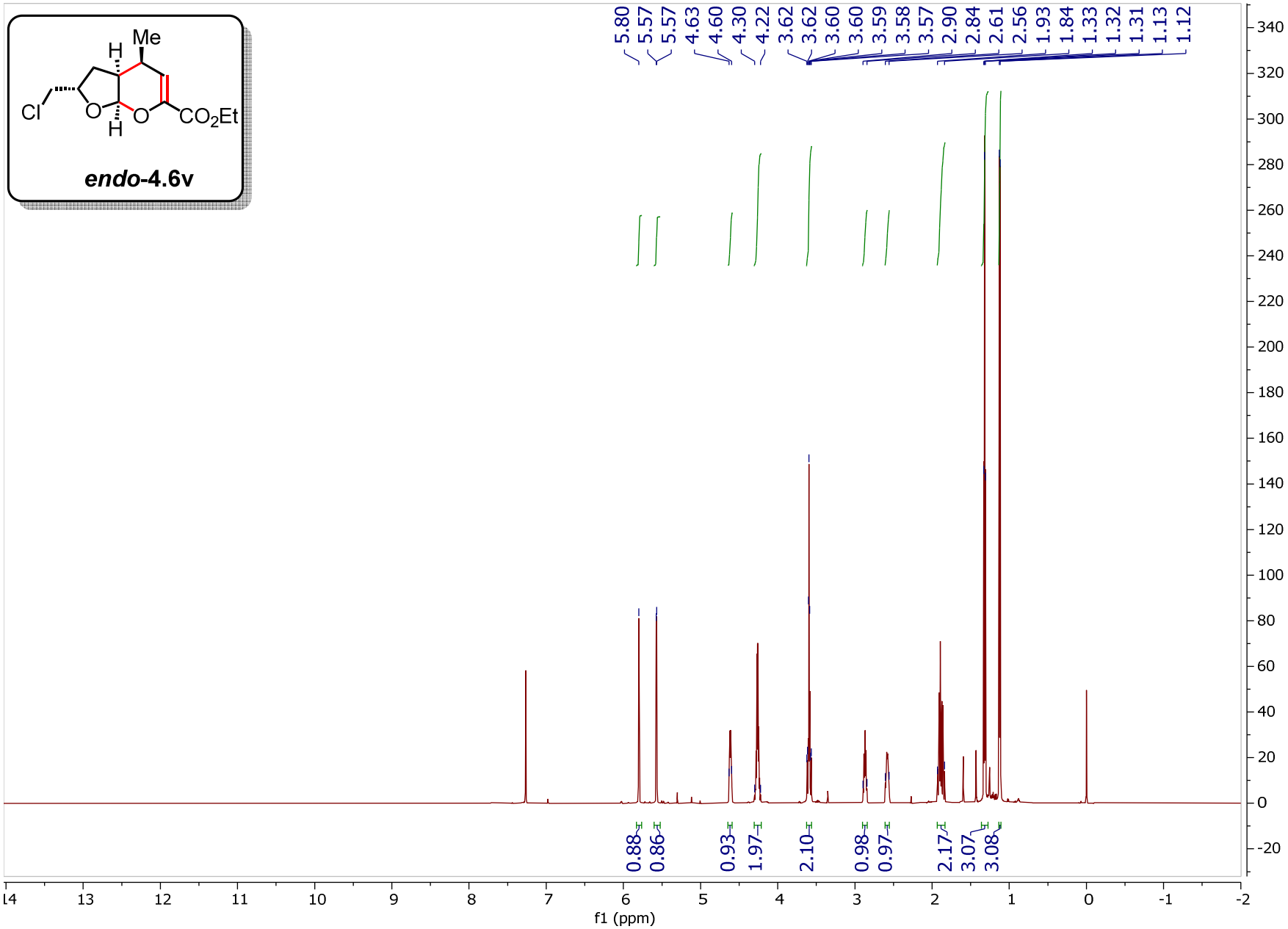

OMe
H
Cl
O
O
H
O
CO2Et
endo-4.6u
162.3
158.6
142.8
132.7
128.5
114.1
110.0
101.7
78.2
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.4
55.2
46.7
42.9
37.1
27.6
14.2
f1 (ppm)

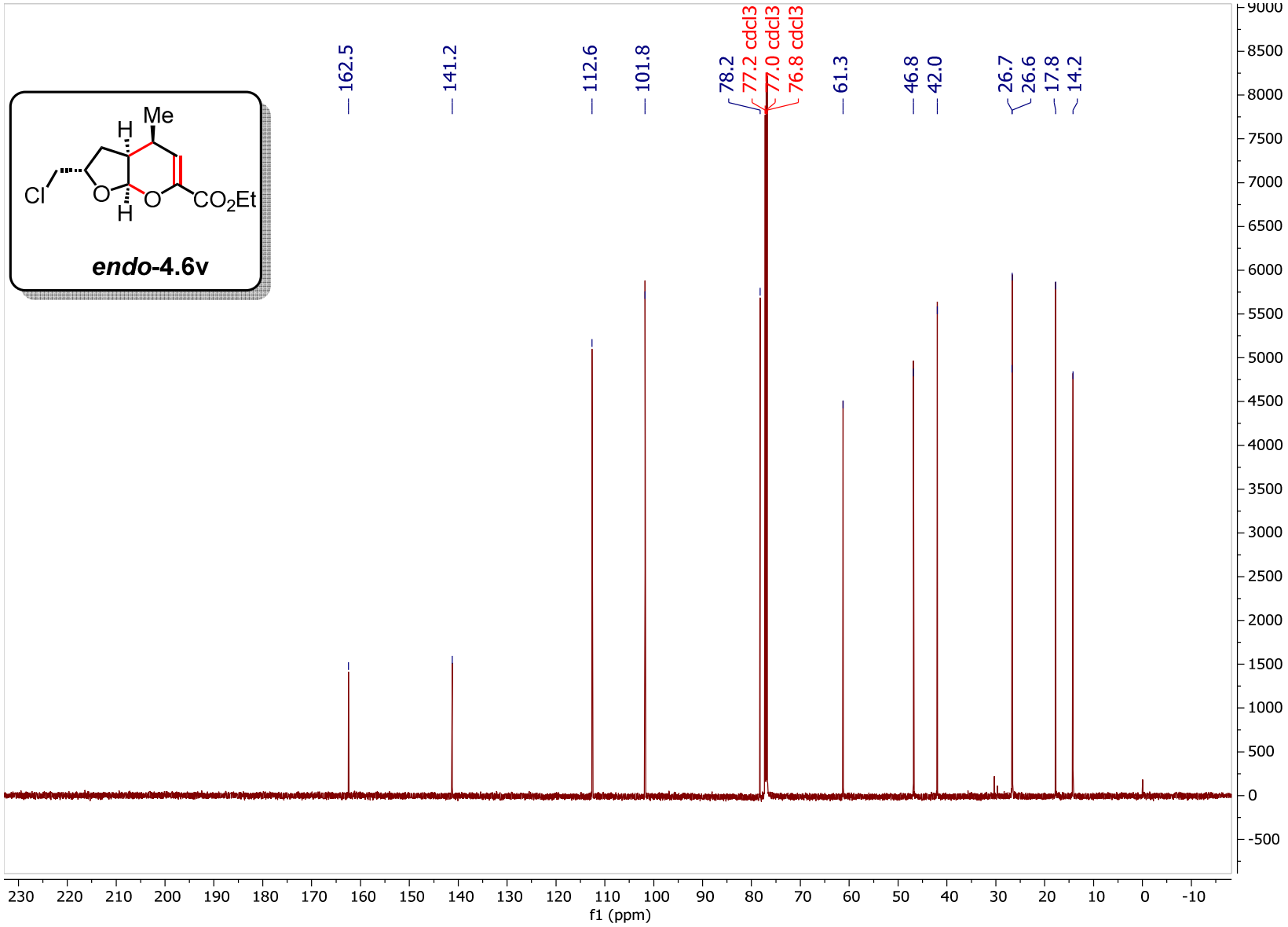


***endo*-4.6u**



The configuration of the major diastereomer of **4.6u** was assigned to be ***endo***.


Me
H
Cl
O
O
H
CO2Et
endo-4.6v
5.80
5.57
5.57
4.63
4.60
4.30
4.22
3.62
3.62
3.60
3.60
3.59
3.58
3.57
2.90
2.84
2.61
2.56
1.93
1.84
1.33
1.32
1.31
1.13
1.12
0.88
0.86
0.93
1.97
2.10
0.98
0.97
2.17
3.07
3.08
f1 (ppm)


Me
H
Cl
O
O
H
O
CO2Et
endo-4.6v
162.5
141.2
112.6
101.8
78.2
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
61.3
46.8
42.0
26.7
26.6
17.8
14.2
f1 (ppm)

C8. X-Ray Crystallography Data of *exo*-4.6g

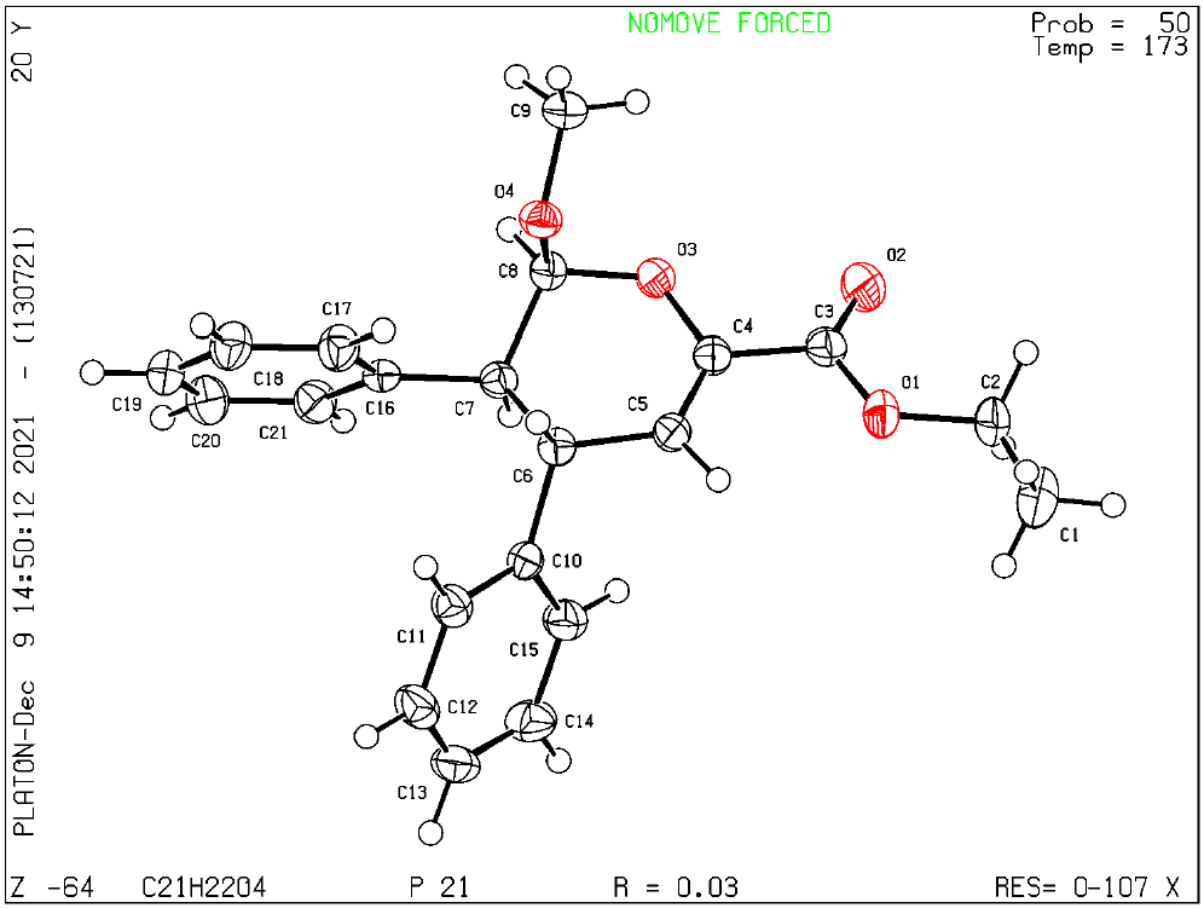


Table 1. Crystal data and structure refinement for $C_{21}H_{22}O_4$.

Identification code	$C_{21}H_{22}O_4$
Empirical formula	$C_{21}H_{22}O_4$
Formula weight	338.38
Temperature	173(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic

Space group P21

Unit cell dimensions a = 8.5311(6) Å □= 90°.

b = 10.6486(8) Å □= 96.612(3)°.

c = 9.7523(7) Å □ = 90°.

Volume 880.05(11) Å3

Z 2

Density (calculated) 1.277 Mg/m3

Absorption coefficient 0.709 mm-1

F(000) 360

Crystal size 0.480 x 0.160 x 0.100 mm3

Theta range for data collection 4.564 to 66.423°.

Index ranges-10<=h<=9, -12<=k<=12, -11<=l<=11

Reflections collected 15529

Independent reflections 3048 [R(int) = 0.0261]

Completeness to theta = 66.423° 99.5 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.7528 and 0.6711

Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	3048 / 1 / 226
Goodness-of-fit on F2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0282, wR2 = 0.0716
R indices (all data)	R1 = 0.0289, wR2 = 0.0729
Absolute structure parameter	0.05(7)
Extinction coefficient	n/a
Largest diff. peak and hole	0.117 and -0.156 e.Å-3

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103)

for $C_{21}H_{22}O_4$. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	10535(2)	5146(2)	8043(1)	36(1)

O(2)	11337(2)	3173(2)	7705(2)	44(1)
O(3)	10020(2)	3252(1)	5048(1)	28(1)
O(4)	10447(2)	4178(1)	2962(1)	28(1)
C(1)	10999(3)	6366(3)	10093(2)	46(1)
C(2)	11194(3)	5085(2)	9487(2)	40(1)
C(3)	10638(2)	4103(2)	7294(2)	29(1)
C(4)	9766(2)	4248(2)	5888(2)	25(1)
C(5)	8806(2)	5211(2)	5532(2)	25(1)
C(6)	7815(2)	5304(2)	4165(2)	24(1)
C(7)	7779(2)	3999(2)	3466(2)	24(1)
C(8)	9430(2)	3421(2)	3614(2)	26(1)
C(9)	11915(2)	3571(2)	2805(2)	34(1)
C(10)	6141(2)	5713(2)	4324(2)	25(1)
C(11)	5341(2)	6554(2)	3410(2)	30(1)
C(12)	3768(3)	6833(2)	3496(2)	36(1)
C(13)	2978(2)	6287(2)	4498(2)	37(1)
C(14)	3775(2)	5473(2)	5436(2)	40(1)

C(15)	5344(2)	5186(2)	5351(2)	33(1)
C(16)	7003(2)	3999(2)	1987(2)	24(1)
C(17)	7457(2)	4837(2)	1013(2)	32(1)
C(18)	6714(3)	4829(2)	-334(2)	36(1)
C(19)	5500(2)	3999(2)	-712(2)	37(1)
C(20)	5039(3)	3165(2)	241(2)	39(1)
C(21)	5787(2)	3167(2)	1588(2)	32(1)

Table 3. Bond lengths [Å] and angles [°] for $C_{21}H_{22}O_4$.

O(1)-C(3)	1.338(3)
O(1)-C(2)	1.457(2)
O(2)-C(3)	1.201(3)
O(3)-C(4)	1.373(2)
O(3)-C(8)	1.442(2)
O(4)-C(8)	1.390(2)

O(4)-C(9) 1.433(2)

C(1)-C(2) 1.504(4)

C(1)-H(1A) 0.9800

C(1)-H(1B) 0.9800

C(1)-H(1C) 0.9800

C(2)-H(4.24a) 0.9900

C(2)-H(2B) 0.9900

C(3)-C(4) 1.490(3)

C(4)-C(5) 1.333(3)

C(5)-C(6) 1.497(2)

C(5)-H(5A) 0.9500

C(6)-C(10) 1.518(2)

C(6)-C(7) 1.547(3)

C(6)-H(6A) 1.0000

C(7)-C(16) 1.516(2)

C(7)-C(8) 1.529(2)

C(7)-H(7A) 1.0000

C(8)-H(8A) 1.0000

C(9)-H(9A) 0.9800

C(9)-H(9B) 0.9800

C(9)-H(9C) 0.9800

C(10)-C(11) 1.386(3)

C(10)-C(15) 1.391(3)

C(11)-C(12) 1.387(3)

C(11)-H(11A) 0.9500

C(12)-C(13) 1.378(3)

C(12)-H(12A) 0.9500

C(13)-C(14) 1.381(3)

C(13)-H(13A) 0.9500

C(14)-C(15) 1.385(3)

C(14)-H(14A) 0.9500

C(15)-H(15A) 0.9500

C(16)-C(21) 1.385(3)

C(16)-C(17) 1.391(3)

C(17)-C(18)	1.391(3)
C(17)-H(17A)	0.9500
C(18)-C(19)	1.380(3)
C(18)-H(18A)	0.9500
C(19)-C(20)	1.375(3)
C(19)-H(19A)	0.9500
C(20)-C(21)	1.393(3)
C(20)-H(20A)	0.9500
C(21)-H(21A)	0.9500

C(3)-O(1)-C(2)	116.61(17)
C(4)-O(3)-C(8)	114.92(14)
C(8)-O(4)-C(9)	112.73(15)
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
O(1)-C(2)-C(1)	106.93(19)
O(1)-C(2)-H(2A)	110.3
C(1)-C(2)-H(2A)	110.3
O(1)-C(2)-H(2B)	110.3
C(1)-C(2)-H(2B)	110.3
H(2A)-C(2)-H(2B)	108.6
O(2)-C(3)-O(1)	124.34(18)
O(2)-C(3)-C(4)	124.63(19)
O(1)-C(3)-C(4)	111.03(17)
C(5)-C(4)-O(3)	124.98(17)
C(5)-C(4)-C(3)	123.07(17)
O(3)-C(4)-C(3)	111.89(16)
C(4)-C(5)-C(6)	123.34(17)
C(4)-C(5)-H(5A)	118.3
C(6)-C(5)-H(5A)	118.3

C(5)-C(6)-C(10) 111.70(14)

C(5)-C(6)-C(7) 108.30(15)

C(10)-C(6)-C(7) 109.40(14)

C(5)-C(6)-H(6A) 109.1

C(10)-C(6)-H(6A) 109.1

C(7)-C(6)-H(6A) 109.1

C(16)-C(7)-C(8) 112.77(14)

C(16)-C(7)-C(6) 113.80(15)

C(8)-C(7)-C(6) 110.41(15)

C(16)-C(7)-H(7A) 106.4

C(8)-C(7)-H(7A) 106.4

C(6)-C(7)-H(7A) 106.4

O(4)-C(8)-O(3) 110.43(14)

O(4)-C(8)-C(7) 109.86(15)

O(3)-C(8)-C(7) 110.92(14)

O(4)-C(8)-H(8A) 108.5

O(3)-C(8)-H(8A) 108.5

C(7)-C(8)-H(8A) 108.5

O(4)-C(9)-H(9A) 109.5

O(4)-C(9)-H(9B) 109.5

H(9A)-C(9)-H(9B) 109.5

O(4)-C(9)-H(9C) 109.5

H(9A)-C(9)-H(9C) 109.5

H(9B)-C(9)-H(9C) 109.5

C(11)-C(10)-C(15) 118.57(17)

C(11)-C(10)-C(6) 121.27(17)

C(15)-C(10)-C(6) 120.04(17)

C(10)-C(11)-C(12) 120.49(19)

C(10)-C(11)-H(11A) 119.8

C(12)-C(11)-H(11A) 119.8

C(13)-C(12)-C(11) 120.5(2)

C(13)-C(12)-H(12A) 119.7

C(11)-C(12)-H(12A) 119.7

C(12)-C(13)-C(14) 119.42(19)

C(12)-C(13)-H(13A) 120.3

C(14)-C(13)-H(13A) 120.3

C(13)-C(14)-C(15)120.3(2)

C(13)-C(14)-H(14A) 119.9

C(15)-C(14)-H(14A) 119.9

C(14)-C(15)-C(10)120.7(2)

C(14)-C(15)-H(15A) 119.7

C(10)-C(15)-H(15A) 119.7

C(21)-C(16)-C(17)118.47(17)

C(21)-C(16)-C(7) 119.86(17)

C(17)-C(16)-C(7) 121.65(16)

C(16)-C(17)-C(18)120.61(18)

C(16)-C(17)-H(17A) 119.7

C(18)-C(17)-H(17A) 119.7

C(19)-C(18)-C(17)120.1(2)

C(19)-C(18)-H(18A) 119.9

C(17)-C(18)-H(18A) 119.9

C(20)-C(19)-C(18)119.88(19)

C(20)-C(19)-H(19A) 120.1

C(18)-C(19)-H(19A) 120.1

C(19)-C(20)-C(21)120.0(2)

C(19)-C(20)-H(20A) 120.0

C(21)-C(20)-H(20A) 120.0

C(16)-C(21)-C(20)120.9(2)

C(16)-C(21)-H(21A) 119.6

C(20)-C(21)-H(21A) 119.6

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å2x 103) for $C_{21}H_{22}O_4$. The anisotropic

displacement factor exponent takes the form: -2□2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	38(1)	43(1)	24(1)	-1(1)	-5(1)	4(1)
O(2)	48(1)	48(1)	33(1)	5(1)	-3(1)	17(1)
O(3)	28(1)	28(1)	26(1)	2(1)	1(1)	4(1)
O(4)	24(1)	32(1)	30(1)	2(1)	6(1)	2(1)
C(1)	53(1)	56(2)	28(1)	-2(1)	1(1)	-17(1)
C(2)	38(1)	60(2)	22(1)	0(1)	-4(1)	5(1)
C(3)	23(1)	37(1)	28(1)	1(1)	6(1)	0(1)
C(4)	23(1)	28(1)	24(1)	1(1)	4(1)	-3(1)
C(5)	23(1)	27(1)	25(1)	-2(1)	4(1)	-3(1)
C(6)	24(1)	24(1)	24(1)	1(1)	3(1)	-2(1)
C(7)	21(1)	26(1)	24(1)	1(1)	4(1)	-2(1)
C(8)	26(1)	28(1)	23(1)	0(1)	2(1)	1(1)
C(9)	26(1)	42(1)	34(1)	-2(1)	7(1)	4(1)

C(10) 24(1) 24(1) 25(1) -4(1) 1(1) 0(1)

C(11) 30(1) 28(1) 31(1) 1(1) 0(1) 1(1)

C(12) 31(1) 29(1) 44(1) -3(1) -5(1) 6(1)

C(13) 25(1) 36(1) 50(1) -14(1)4(1) 4(1)

C(14) 32(1) 49(1) 42(1) -2(1) 14(1) -1(1)

C(15) 30(1) 40(1) 31(1) 3(1) 6(1) 4(1)

C(16) 22(1) 26(1) 26(1) -3(1) 4(1) 4(1)

C(17) 32(1) 37(1) 28(1) 1(1) 4(1) -5(1)

C(18) 42(1) 42(1) 26(1) 4(1) 4(1) 3(1)

C(19) 36(1) 47(1) 26(1) -6(1) -2(1) 6(1)

C(20) 34(1) 43(1) 38(1) -7(1) -2(1) -5(1)

C(21) 30(1) 33(1) 32(1) -2(1) 4(1) -3(1)

Table 5. Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2x 10 3)

for $C_{21}H_{22}O_4$.

	x	y	z	U(eq)
H(1A)	11430	6363	11069	69
H(1B)	11563	6987	9594	69
H(1C)	9875	6582	10012	69
H(2A)	12325	4854	9562	49
H(2B)	10630	4447	9983	49
H(5A)	8749	5872	6178	30
H(6A)	8303	5925	3573	29
H(7A)	7118	3447	3998	28
H(8A)	9369	2580	3155	31
H(9A)	12585	4142	2342	51
H(9B)	12449	3347	3716	51
H(9C)	11714	2809	2249	51

H(11A)	5875	6943	2720	36
H(12A)	3229	7405	2859	43
H(13A)	1895	6469	4544	45
H(14A)	3245	5108	6143	48
H(15A)	5882	4624	6000	40
H(17A)	8282	5420	1269	39
H(18A)	7045	5397	-996	44
H(19A)	4982	4004	-1628	44
H(20A)	4210	2586	-20	47
H(21A)	5460	2591	2242	38

Table 6. Torsion angles [°] for $C_{21}H_{22}O_4$.

C(3)-O(1)-C(2)-C(1)	177.84(17)
C(2)-O(1)-C(3)-O(2)	-6.0(3)
C(2)-O(1)-C(3)-C(4)	173.69(15)

C(8)-O(3)-C(4)-C(5)	12.5(2)
C(8)-O(3)-C(4)-C(3)	-170.22(14)
O(2)-C(3)-C(4)-C(5)	169.38(19)
O(1)-C(3)-C(4)-C(5)	-10.3(2)
O(2)-C(3)-C(4)-O(3)	-7.9(3)
O(1)-C(3)-C(4)-O(3)	172.39(15)
O(3)-C(4)-C(5)-C(6)	2.7(3)
C(3)-C(4)-C(5)-C(6)	-174.27(16)
C(4)-C(5)-C(6)-C(10)	134.91(18)
C(4)-C(5)-C(6)-C(7)	14.4(2)
C(5)-C(6)-C(7)-C(16)	-171.98(14)
C(10)-C(6)-C(7)-C(16)	66.06(19)
C(5)-C(6)-C(7)-C(8)	-43.99(18)
C(10)-C(6)-C(7)-C(8)	-165.95(15)
C(9)-O(4)-C(8)-O(3)	69.77(19)
C(9)-O(4)-C(8)-C(7)	-167.57(15)
C(4)-O(3)-C(8)-O(4)	78.30(18)

C(4)-O(3)-C(8)-C(7)	-43.7(2)
C(16)-C(7)-C(8)-O(4)	66.96(19)
C(6)-C(7)-C(8)-O(4)	-61.59(18)
C(16)-C(7)-C(8)-O(3)	-170.67(15)
C(6)-C(7)-C(8)-O(3)	60.78(19)
C(5)-C(6)-C(10)-C(11)	140.03(19)
C(7)-C(6)-C(10)-C(11)	-100.1(2)
C(5)-C(6)-C(10)-C(15)	-43.9(2)
C(7)-C(6)-C(10)-C(15)	76.0(2)
C(15)-C(10)-C(11)-C(12)	-1.9(3)
C(6)-C(10)-C(11)-C(12)	174.24(18)
C(10)-C(11)-C(12)-C(13)	0.6(3)
C(11)-C(12)-C(13)-C(14)	1.1(3)
C(12)-C(13)-C(14)-C(15)	-1.4(3)
C(13)-C(14)-C(15)-C(10)	0.1(3)
C(11)-C(10)-C(15)-C(14)	1.6(3)
C(6)-C(10)-C(15)-C(14)	-174.6(2)

C(8)-C(7)-C(16)-C(21) 106.57(19)

C(6)-C(7)-C(16)-C(21) -126.66(18)

C(8)-C(7)-C(16)-C(17) -74.8(2)

C(6)-C(7)-C(16)-C(17) 52.0(2)

C(21)-C(16)-C(17)-C(18) -0.6(3)

C(7)-C(16)-C(17)-C(18) -179.25(18)

C(16)-C(17)-C(18)-C(19) 1.0(3)

C(17)-C(18)-C(19)-C(20) -1.0(3)

C(18)-C(19)-C(20)-C(21) 0.7(3)

C(17)-C(16)-C(21)-C(20) 0.2(3)

C(7)-C(16)-C(21)-C(20) 178.93(18)

C(19)-C(20)-C(21)-C(16) -0.3(3)

Symmetry transformations used to generate equivalent atoms: