Trisubstituted Alkenes through Stereoretentive Cross-Metathesis for Natural Product Synthesis

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Abstract

- **Chapter One: Stereoretentive Cross-Metathesis of Trisubstituted Olefins**

The development of stereoretentive olefin metathesis catalysts has solved a long-standing problem in the field, allowing for trisubstituted alkenes to be synthesized in high stereochemical purity and under kinetic control. *E*- as well as *Z*-isomers of trisubstituted alkenyl halides, nitriles, and allylic alcohols can be accessed through cross-metathesis of commercially available and easily accessible alkenes. Through the use of the same strategy, macrocyclic trisubstituted alkenes have been accessed in either isomeric form through stereoretentive ring-closing metathesis of the corresponding diene starting materials. Thus, for the first time, a wide range of *E*- and *Z*-trisubstituted alkenes can be obtained selectively through olefin metathesis, regardless of the underlying thermodynamic preferences.

- **Chapter Two: Development of Catalytic Stereoretentive Cross-Metathesis of Trisubstituted Alkenyl Bromides**

We have introduced a general and widely applicable strategy for the synthesis of *E*- and *Z*-trisubstituted alkenyl bromides through cross-metathesis. The reaction is applicable to terminal, disubstituted, and trisubstituted olefins bearing a variety of functional groups including alkenes with α-, or β-branches. The requisite stereodefined cross-partners, *E*- and *Z*-2-bromo-2-butene are commercially available and can be synthesized with ease in one

step from abundant starting materials. This represents a notable improvement over our previous approach, where the non-halogenated alkene starting material had to be prepared through cross-coupling in high stereochemical purity to ensure high stereoretention in the subsequent cross-metathesis. Catalysts derived from Mo monoaryloxide pyrrolide complexes, some of which are commercially available, are optimal for this transformation. The applicability of the approach is underscored through the formal synthesis of phomactin A with improved overall yield and step count.

- **Chapter Three: Total Synthesis of Ambrein**

We have completed a total synthesis of ambrein, a terpenoid isolated from whale secretion, a much sought perfume ingredient. The approach involved joining two fragments through formation of the central trisubstituted alkene. Our route entailed a sequence of cross-metathesis of alkenyl bromides and cross-coupling, providing access to a previously difficult-to-access trisubstituted olefin with high efficiency and selectivity. One fragment was generated from a readily accessible enantiomerically enriched compound, sclareolide, and the other from inexpensive methylcyclohexenone. The stereogenic center of the latter was established through a NHC-Cu-catalyzed enantioselective allylic substitution, which was followed by differentiation of these alkenes through site-selective epoxidation. The total synthesis is more efficient and offers a more practical route to ambrein.

- **Chapter Four: Stereoretentive Cross-Metathesis of Trisubstituted α,β-Unsaturated Carbonyl Compounds**

We have developed a strategy for the synthesis of *Z*- and *E*-Trisubstituted α,β-unsaturated carbonyl compounds through stereoretentive CM involving commercially available or easily accessible alkene substrates. The method is applicable to a variety of α,β-unsaturated

esters, thioesters, and acyl fluorides. Furthermore, mono-, di-, and trisubstituted alkenes can be used as starting materials. Transformations may be carried out on gram scale and, in some cases, with commercially available Mo catalysts. The utility of the catalytic approach was highlighted through synthesis of previously accessed intermediates more directly and with improved efficiency.

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Acknowledgments

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Chapter One

Stereoretentive Cross-Metathesis of Trisubstituted Olefins

1.1 Introduction

Olefin metathesis has become an indispensable tool for the construction of C–C double bonds in organic synthesis.[1] Whereas early catalysts often required harsh reaction conditions and were only poorly understood, we have seen a remarkable evolution that has led to the highly active and well understood olefin metathesis catalysts of today.[2] Of the many complexes that have been developed over the years, two metals account for the majority of olefin metathesis catalysts employed: Mo[3] and Ru.[4] Although less commonly used alternatives based on W[5], Re,[6] Os,[7] and Fe[8] exist, catalysts incorporating these metals are often less active and only allow for a narrow scope of transformations.

Out of the reaction modes that arise from the ability to exchange methylene units between olefins, ring-closing-metathesis (RCM) and cross-metathesis (CM) are among the

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(1) For select reviews on olefin metathesis, see: (a) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2056. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (c) Fürstner, A. *Angew. Chem.* **2000**, *39*, 3012–3043.

(2) (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (b) Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763–4792.

(3) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633.

(4) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

(5) Schrock, R. R. *Chem. Rev.* **2002**, *102*, 145–179.

(6) Toreki, R.; Schrock, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 2448–2449.

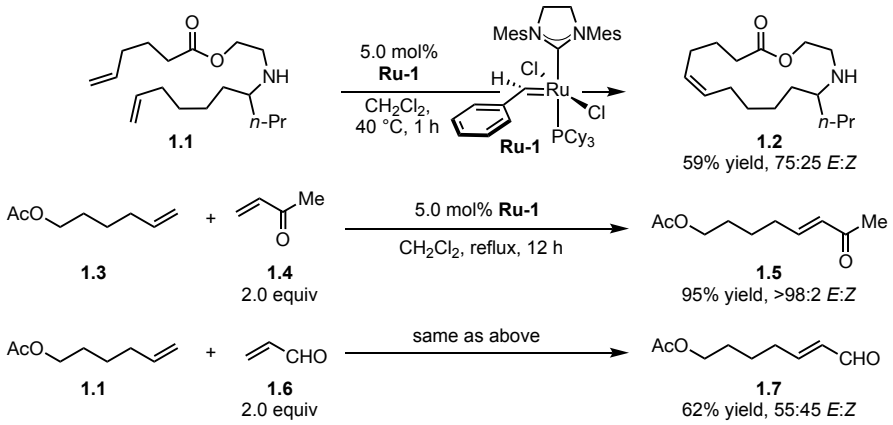
(7) Castarlenas, R.; Esteruelas, M. A.; Oñate, E. *Organometallics* **2005**, *24*, 4343–4346.

(8) (a) Belov, D. S.; Mathivathanan, L.; Beazley, M. J.; Martin, W. B.; Bukhryakov, K. V. *Angew. Chem.* **2021**, *133*, 2970–2974. (b) Takebayashi, S.; Iron, M. A.; Feller, M.; Rivada-Wheelaghan, O.; Leitus, G.; Diskin-Posner, Y.; Shimon, L. J. W.; Avram, L.; Carmieli, R.; Wolf, S. G.; Cohen-Ofri, I.; Sanguramath, R. A.; Shenhar, R.; Eisen, M.; Milstein, D. *Nat. Catal.* **2022**, *5*, 494–502.

most common transformations in organic synthesis. This is in part due to their unique ability to convert simple and easily prepared alkenes into valuable and otherwise difficult-to-access olefins in just one step.

A central challenge in olefin metathesis is controlling the stereochemistry of the newly formed double bond (i.e., *E*:*Z* selectivity). For a long time, the outcome of olefin metathesis reactions was solely dependent on thermodynamic factors (i.e., energetic preference of one product isomer over another) and could not be reversed when the opposite product isomer was desired (e.g., **1.2**, Scheme 1.1.1, epilachnene exhibits a *Z*-olefin, but the *E*-isomer is formed predominantly[9]). As such, olefins bearing certain functional groups could be generated with high efficiency and selectivity for one isomer, but the other isomer was inaccessible (e.g., **1.5**).[10] What is worse, many olefin metathesis reactions afforded isomeric mixtures of products with little to no preference for either isomer (e.g., **1.7**).

Scheme 1.1.1. Olefin-Metathesis Reactions Affording the Thermodynamically Preferred Alkene

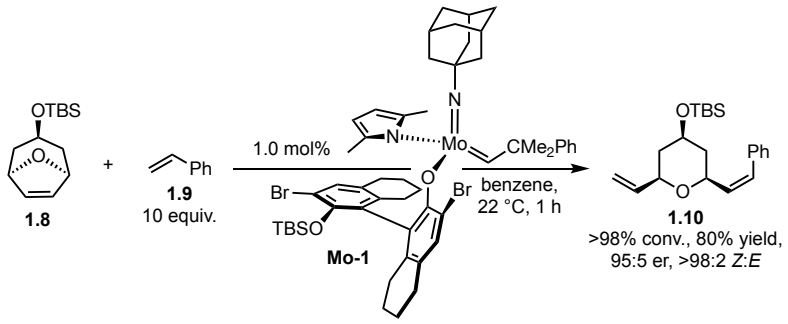


(9) Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 2726–2740.

(10) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

The solution to this long-standing problem presented itself as a side-product of studies aimed at controlling enantioselectivity in olefin metathesis reactions. The complexes that were able to generate the target olefin enantioselectively coincidentally also furnished the *Z*-isomer preferentially. This phenomenon was first observed in the ring-opening cross-metathesis (ROCM) of oxabicycle **1.8** with styrene **1.9**, which surprisingly led to formation of the **1.10** with high preference for the *Z*-isomer (>98:2 *Z*:*E*, Scheme 1.1.2).[11]

Scheme 1.1.2. Enantio- and *Z*-selective Ring-Opening Cross-Metathesis



Following the initial observation, studies with catalysts of similar architecture were used to establish a variety of olefin metathesis reactions that furnished *Z*-alkene products with kinetic preference.[12] This seemingly peculiar behavior can be rationalized by examination of x-ray crystal structures of Mo metallacyclobutane (mcb) complexes, which have been identified as intermediates in the catalytic cycle of olefin metathesis reactions.[13] In the mcb, the imido and aryloxide ligand occupy the apical sites of a trigonal bipyramidal

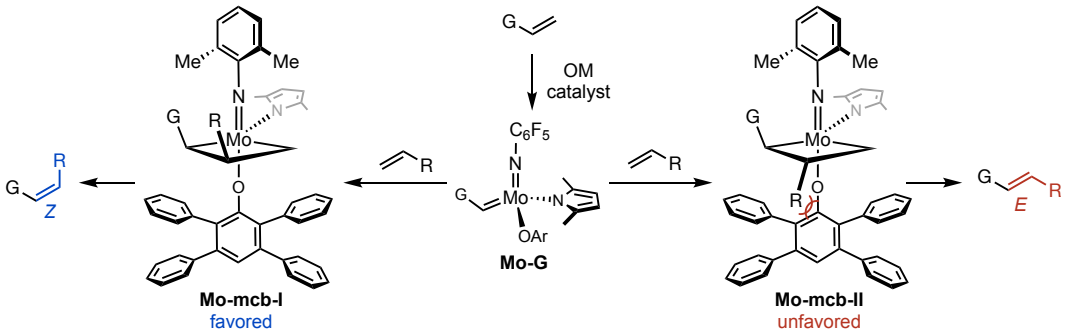
(11) Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

(12) For select examples of olefin metathesis reactions furnishing *Z*-alkenes kinetically, see: (a) Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16630–16631. (b) Meek, S. J.; Obrien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461–466. (c) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88–92.

(13) (a) Schrock, R. R.; DePue, R. T.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423–1435. (b) Schrock, R. R.; DePue, R. T.; Feldman, J.; Yap, K. B.; Yang, D. C.; Davis, W. M.; Park, L.; DiMare, M.; Schofield, M. *Organometallics* **1990**, *9*, 2262–2275.

structure. While the imido ligand is comparatively small and features an almost linear C–N–C bond angle (170.4°),[14] the corresponding aryloxide ligand is comparatively large and bears two or more aryl substituents in close proximity to the metal center. As such, product formation can occur through two different intermediates, depending on the orientation of the olefin upon reaction with the alkylidene (Scheme 1.1.3).

Scheme 1.1.3. Stereochemical Model for *Z*-Selective CM with Terminal Olefins

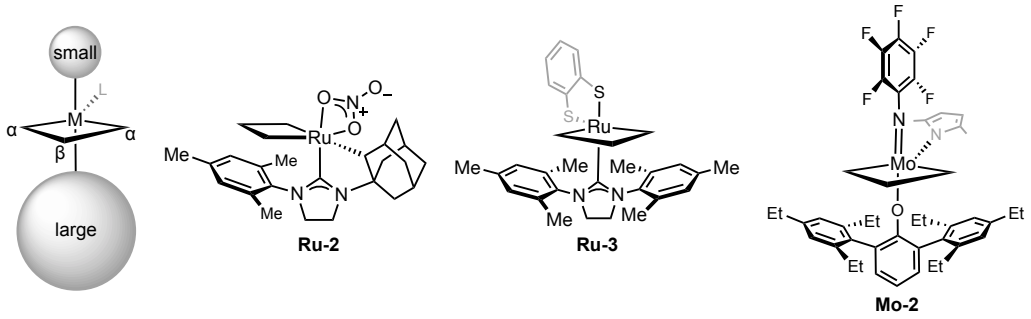


Whereas reaction via **Mo-mcb-I** has the alkene substituent pointing towards the small imido ligand, **Mo-mcb-II** has the substituent oriented towards the large aryloxide. Intermediate **Mo-mcb-II** is higher in energy due to the penalizing steric interactions of the substituent in the β-position of the mcb with the large aryloxide group. Thus, the reaction proceeds predominantly through **Mo-mcb-I**, which, upon cycloreversion, affords the *Z*-alkene product. This design principle has informed the development of many olefin metathesis catalysts, allowing for the synthesis of a wide variety of alkenes in *Z*-configuration. (Scheme 1.1.4).[15]

(14) Marinescu, S. C.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10840–10841.

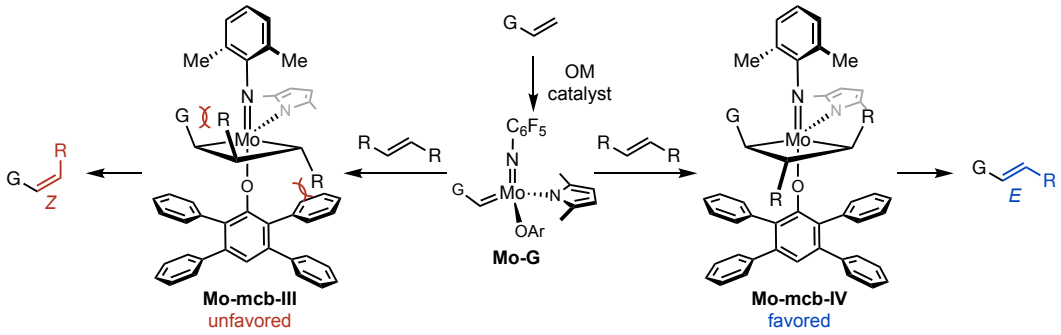
(15) For select examples of Z-selective olefin metathesis catalysts, see: (a) Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527. (b) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 10258–10261. (c) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465.

Scheme 1.1.4. Principle Design Considerations for Controlling *Z*-selectivity in Olefin Metathesis



To achieve a kinetically *E*-selective olefin metathesis reaction, a slightly different approach is required. When stereodefined *E*-olefin starting materials are used in conjunction with more reactive mono- or disubstituted olefins, the corresponding *E*-alkene products are generated stereoretentively.[16]

Scheme 1.1.5 Rationale for Stereoretention in CM with *E*-disubstituted Alkenes



Based on the aforementioned principles, reaction of the active alkylidene complex (**Mo-G**) with an *E*-disubstituted olefin can proceed via two different intermediates (Scheme 1.1.5). Reaction through **Mo-mcb-III** leads to undesirable eclipsing interaction between the α- and β-substituent, as well as unfavorable steric interaction between the other α-substituent and the large aryloxide ligand. Reaction via **Mo-mcb-IV**, on the other hand, avoids both of these energetically unfavorable interactions, instead featuring a β-

(16) (a) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569–575. (b) Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *541*, 380–385.

substituent that is oriented towards the aryloxide ligand. As the β-position is more distal from the metal center, the steric interaction is less severe, and **Mo-mcb-IV** is lower in energy. The consequence is a retention of the alkene configuration throughout the reaction, thus furnishing the desired products in high *E*:*Z* ratio. Transformations that rely on this principle have been adopted for a variety of functional groups and catalysts.[17]

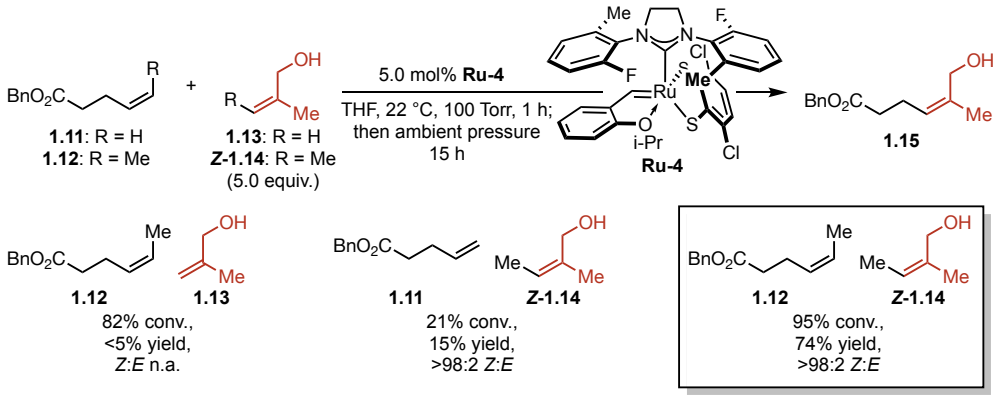
Similar features apply to olefin metathesis reactions that generate trisubstituted olefins. However, only few such cases of stereoretentive trisubstituted olefin metathesis reactions have been reported (vide infra). Part of the challenge is the olefin metathesis of trisubstituted alkenes itself, regardless of the stereochemical outcome. Fundamentally, a trisubstituted alkene can be generated through two different approaches. (1) Olefin metathesis of a mono- or disubstituted olefin on the one hand, and a trisubstituted olefin on the other. In this case, chemoselectivity can be an issue, as less-substituted olefins are usually more prone to undergo olefin metathesis than trisubstituted ones. The consequence is reaction of two identical olefins, which not only generates undesired homo-coupling byproducts, but also keeps the catalyst from reacting with the trisubstituted olefin through non-productive metathesis events. (2) Alternatively, one can consider olefin metathesis of two trisubstituted olefins. Whereas this approach faces less problems with regard to chemoselectivity, it requires a highly substituted mcb intermediate that is likely high in energy and thus requires highly active olefin metathesis catalysts.

(17) Montgomery, T. P.; Ahmed, T. S.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 11024–11036.

1.2 Ru Catechothiolate Catalysts for Cross-Metathesis of Trisubstituted Allylic Alcohols and Ethers

The first instance of a stereoretentive olefin metathesis reaction furnishing trisubstituted alkenes was reported by Hoveyda and co-workers in 2017.[18] A Ru catechothiolate complex[15] with an NHC ligand was identified as the optimal catalyst for the cross-metathesis of trisubstituted allylic alcohols and ethers. Notably, when differently substituted alkenes were investigated as starting materials for this reaction, those with more substituted olefins (**1.12** and ***Z*-1.14**) resulted in a more efficient cross-metathesis, compared to combinations of monosubstituted (**1.11**) or 1,1-disubstituted (**1.13**) alkenes (Scheme 1.2.1). Moreover, when a catalyst lacking the necessary ligand was used (e.g., **Ru-1**), the thermodynamically preferred *E*-isomer product was obtained predominantly (>87:13 *E*:*Z*), regardless of which cross-partner (**1.12**, ***Z*-1.14** or ***E*-1.14**) was used.

Scheme 1.2.1. The Impact of Differently Substituted Alkene Substrates on CM Efficiency

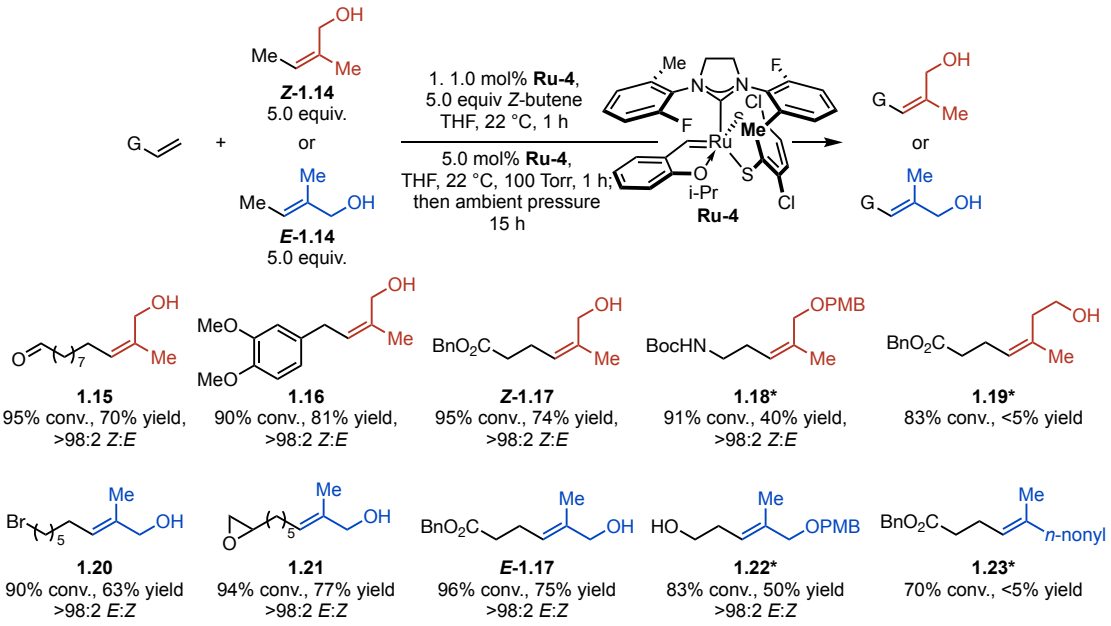


The low conversion in the reaction of **1.11** with ***Z*-1.14** was attributed to catalyst decomposition on account of methylidene formation. The instability of ruthenium

(18) Xu, C.; Liu, Z.; Torker, S.; Shen, X.; Xu, D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 15640–15643.

methylidene complexes and the corresponding decomposition pathways have been the center of several investigations,[19] and is especially pronounced with catechothiolates, such as **Ru-4**.[14,20] Accordingly, the monosubstituted alkene starting materials were converted to the respective 1,2-disubstituted alkenes through cross-metathesis with *Z*-butene, effectively preventing methylidene formation.[21] Through the use of this in situ masking protocol, a wide array of *E*- and *Z*-trisubstituted allylic alcohols and ethers bearing various functional groups could be accessed in 38–81% yield and >98:2 stereoselectivity (Scheme 1.2.2).

Scheme 1.2.2. Cross-Metathesis of *Z*- and *E*-Trisubstituted Allylic Alcohols and Ethers



* a cross-partner different from ***Z*-1.14** or ***E*-1.1.4** with substituents shown in the product was employed

Although the above approach offers efficient access to stereodefined trisubstituted allylic alcohols, it is not applicable to related homoallylic alcohols (e.g., **1.19**) or alkenes

(19) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.

(20) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. *Nature* **2015**, *517*, 181–186.

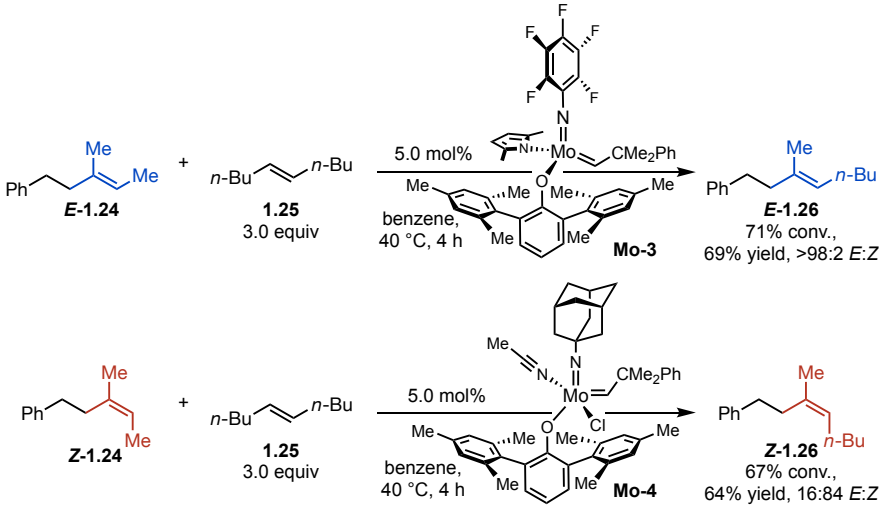
(21) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919–10928.

that lack a proximal hydroxy group (e.g., **1.23**). Evidently, many trisubstituted olefins could not be accessed through the above approach, and a more general method for their synthesis was needed.

1.3 Mo-based Catalysts for Cross-Metathesis of Trisubstituted Alkenyl Halides

Linear trisubstituted alkenes without proximal functional groups are an important subset of olefins found in many natural products and bioactive compounds.[22] Although olefin metathesis is generally an attractive approach for the synthesis of alkenes, up to this point, the available methods either afforded the thermodynamically preferred isomer or was predicated on the presence of an allylic hydroxy group. To develop a more general strategy, Hoveyda and co-workers employed high oxidation state Mo complexes for the synthesis of a variety of trisubstituted olefins.[23]

Scheme 1.3.1. Direct Cross-Metathesis of Alkyl-Substituted Olefins



Nonetheless, the most intuitive approach, direct cross-metathesis of two alkyl-substituted olefins to furnish a trisubstituted alkene is not ideal; often an excess of one

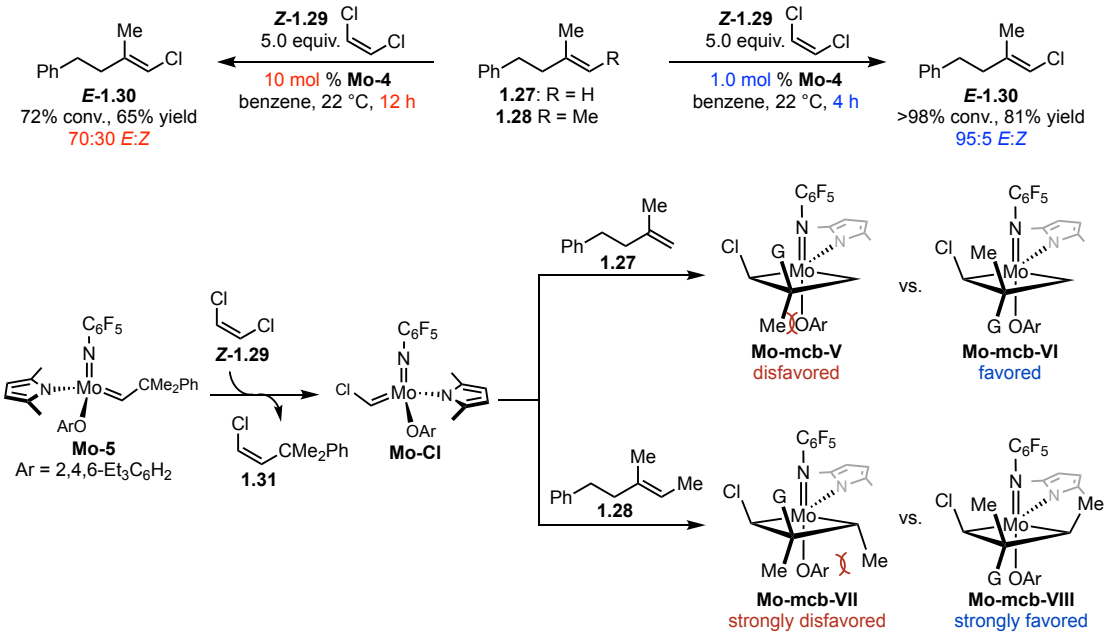
(22) Siau, W.-Y.; Zhang, Y.; Zhao, Y. *Top. Curr. Chem.* **2012**, *327*, 33–58.

(23) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347–354.

reactant is needed for appreciable efficiency, and at times, stereoretentivity is low (Scheme 1.3.1).

An alternative approach would be to generate an alkenyl halide and convert it to a trisubstituted alkene through cross-coupling. Among the advantages of this strategy is that a variety of stereodefined halogenated olefins are commercially available and can therefore be used in excess to ensure high efficiency without wasting compounds that are costly or require multistep routes to prepare. Hoveyda and co-workers therefore sought to develop a cross-metathesis strategy that would allow for the synthesis of trisubstituted alkenyl halides from commercially available halogen-containing alkene building blocks. As some complex molecules incorporate alkenyl halides, this method would also present an attractive way for the synthesis of these motifs in such compounds of interest.[24]

Scheme 1.3.2. Rationale for Lower *E*:*Z* Selectivity with Terminal vs. Trisubstituted Starting Materials

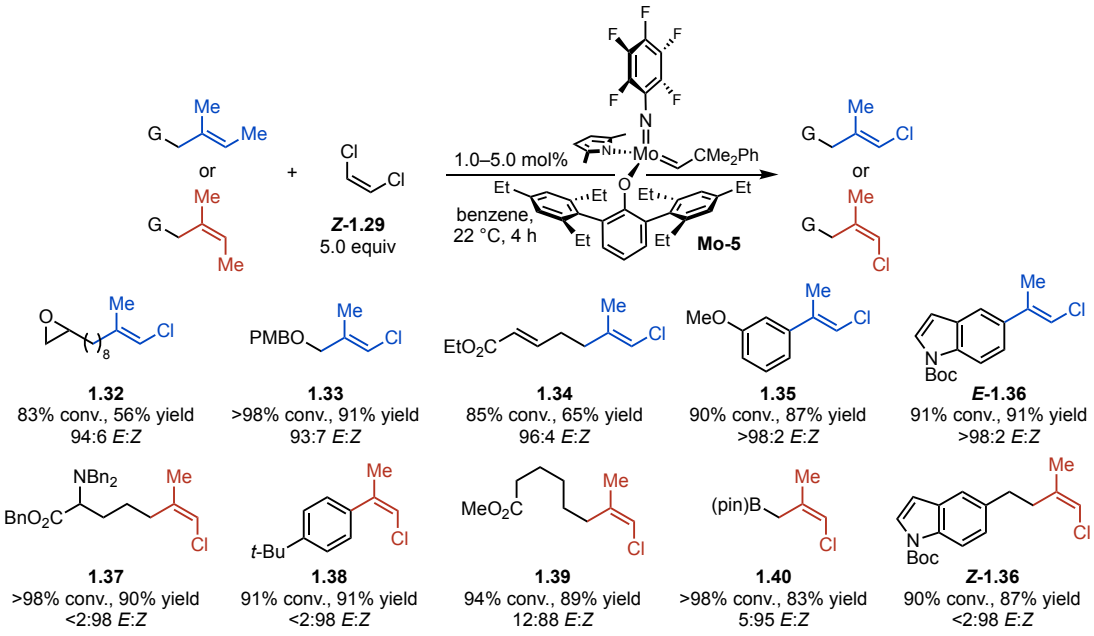


(24) Gribble, G. W. *Mar. Drugs* **2015**, *13*, 4044–4136.

To probe the feasibility of this strategy, two different alkenes, a 1,1-disubstituted (**1.27**) and a *E*-trisubstituted (**1.28**) olefin with otherwise identical substituents, were investigated for the cross-metathesis with ***Z*-1.29** (Scheme 1.3.2). Although one might expect that the reaction of a 1,1-disubstituted olefin should be more facile due to the lower steric strain in the requisite mcb, experiments revealed the opposite trend: reaction with the 1,1-disubstituted olefin required a 10-fold higher catalyst loading (10 mol% vs. 1.0 mol%) and, even then, afforded the target trisubstituted alkenyl chloride in lower yield (65% vs. 81% yield) and diminished *E*:*Z* ratio (70:30 vs. 95:5).

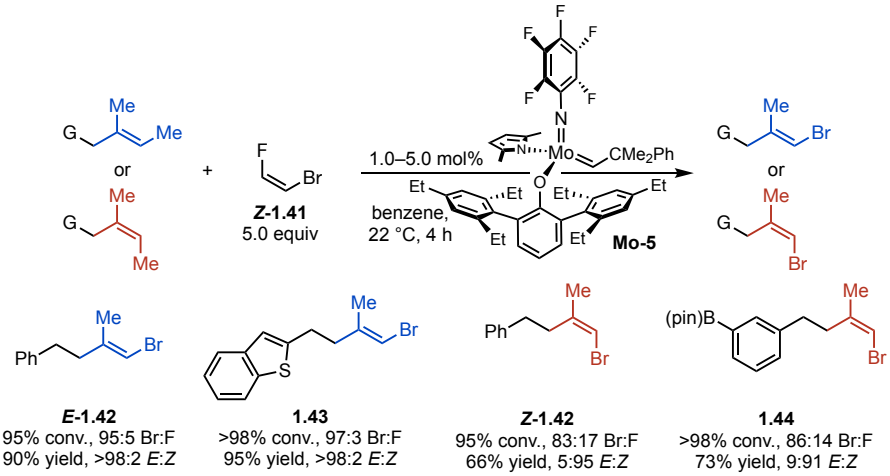
The difference in stereocontrol can be explained through the respective Mo mcb intermediates that lead to product formation. Cross-metathesis with **1.27** can proceed via **Mo-mcb-V** or **Mo-mcb-VI**. The steric interactions of the G-substituent with the aryloxide ligand, favors reaction via **Mo-mcb-V**. At the same time, the penalizing eclipsing interaction with the chloro substituent in the α-position favors reaction through **Mo-mcbVI**. Although the latter is the dominant effect, there are two opposing trends, and as such, a low the *E*-isomer is formed with only little preference. For reaction with **1.28**, however, the additional methyl substituent significantly raises the energy of **Mo-mcb-VII** due to the steric interactions of the α-substituent in the mcb with the aryloxide ligand. Consequently, reaction via **Mo-mcb-VIII** is strongly favored, and the *E*-isomer is formed almost exclusively. Finally, reaction via **Mo-mcb-V** leads to formation of a Mo methylidene complex, which has been shown to be prone to decomposition, thus requiring a much higher catalyst loading to achieve comparable efficiency.

Scheme 1.3.3. *E*- and *Z*-Trisubstituted Alkenyl Chlorides from Stereodefined Alkene Starting Materials



The method is applicable to substrates bearing different functional groups, and the reactions generally proceed with high stereoretentivity (Scheme 1.3.3). Moreover, when ***Z*-1.35** is used instead of ***Z*-1.29**, the corresponding alkenyl bromides can be obtained in similar efficiency and stereoselectivity. Unlike cross-metathesis processes affording disubstituted alkenyl halides,[14,15] in the cases where a trisubstituted olefin is formed, the

Scheme 1.3.4. *E*- and *Z*-Trisubstituted Alkenyl Bromides through Stereoretentive CM

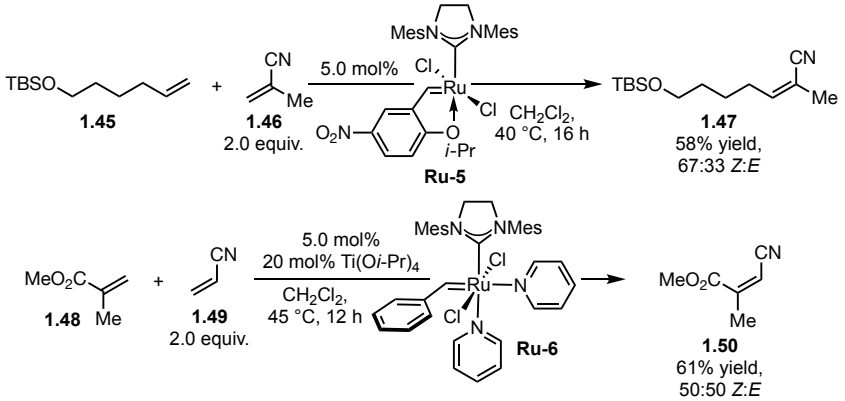


alkenyl bromide is formed preferentially over the alkenyl fluoride due to steric and electronic factors (Scheme 1.3.4).

1.4 E- and Z-Trisubstituted Alkenyl Nitriles Through Cross-Metathesis

Other important motifs are di- and tri-substituted alkenes bearing a cyano substituent. Compounds containing these moieties commonly serve as starting materials for stereoselective transformations (e.g., conjugate additions or catalytic enantioselective hydrogenations).[25] What is more, many medicinally relevant compounds exhibit a cyano group,[26] which is often involved in key binding interactions at the biological target.[27] Despite the plethora of available methods for the synthesis of alkenyl nitriles, only few are applicable to preparation of the corresponding trisubstituted alkenes, and still fewer can be used to obtain the *Z*-isomer selectively.[28]

Scheme 1.4.1. Cross-Metathesis Reactions Affording Trisubstituted Alkenyl Nitriles



(25) (a) Lee, D.; Kim, D.; Yun, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2785–2787. (b) Yan, Q.; Kong, D.; Li, M.; Hou, G.; Zi, G. *J. Am. Chem. Soc.* **2015**, *137*, 10177–10181. (c) Zhang, S.; del Pozo, J.; Romiti, F.; Mu, Y.; Torker, S.; Hoveyda, A. H. *Science* **2019**, *364*, 45–51.

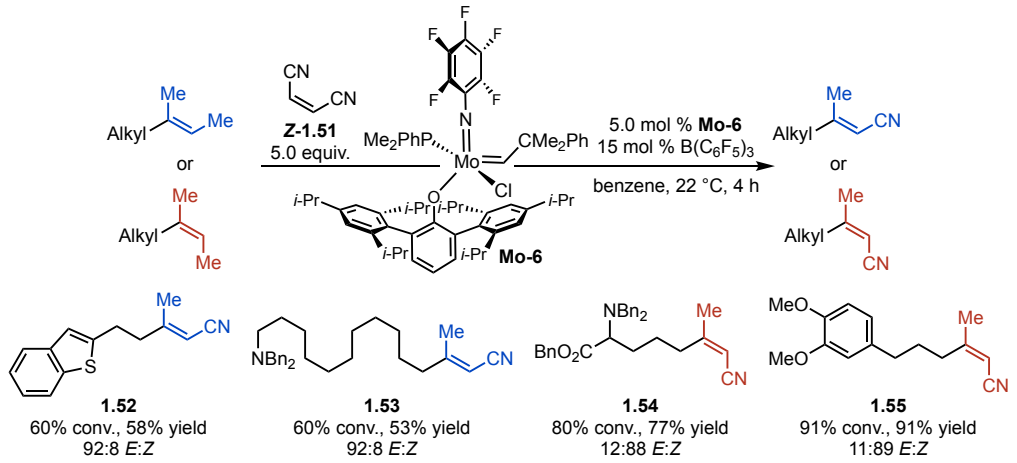
(26) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902–7917.

(27) Janssen, P. A. J.; Lewi, P. J.; Arnold, E.; Daeyaert, F.; de Jonge, M.; Heeres, J.; Koymans, L.; Vinkers, M.; Guillemont, J.; Pasquier, E.; Kukla, M.; Ludovici, D.; Andries, K.; de Béthune, M.-P.; Pauwels, R.; Das, K.; Clark, A. D.; Frenkel, Y. V.; et al. *J. Med. Chem.* **2005**, *48*, 1901–1909.

(28) (a) Pradal, A.; Evano, G. *Chem Commun* **2014**, *50*, 11907–11910. (b) Powell, K. J.; Han, L. C.; Sharma, P.; Moses, J. E. *Org. Lett.* **2014**, *16*, 2158–2161.

Past attempts to access alkenyl nitriles through olefin metathesis were only moderately successful, often affording isomeric product mixtures regardless of which Ru catalyst was employed (Scheme 1.4.1).[29] Part of the challenge in synthesizing alkenyl nitriles through cross-metathesis is the small energy difference between the *Z*- and *E*-isomers,[30] due to the small size and highly polar nature of the cyano group.[31] As a consequence, often undesired mixtures of isomeric products are obtained when the reaction is under thermodynamic control.

Scheme 1.4.2. Synthesis of Alkyl-Substituted *E*- and *Z*-Trisubstituted Alkenyl Nitriles by CM



Hoveyda and co-workers subsequently developed a kinetically controlled synthesis of *E* and *Z* cyano-substituted alkenes through stereoretentive cross-metathesis of easily accessible alkenes with Mo complexes as catalysts.[32] The method is applicable to a wide range of substrates, allowing stereodefined alkene starting materials to be converted to the

(29) (a) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325. (b) Bai, C.-X.; Lu, X.-B.; He, R.; Zhang, W.-Z.; Feng, X.-J. *Org. Biomol. Chem.* **2005**, *3*, 4139.

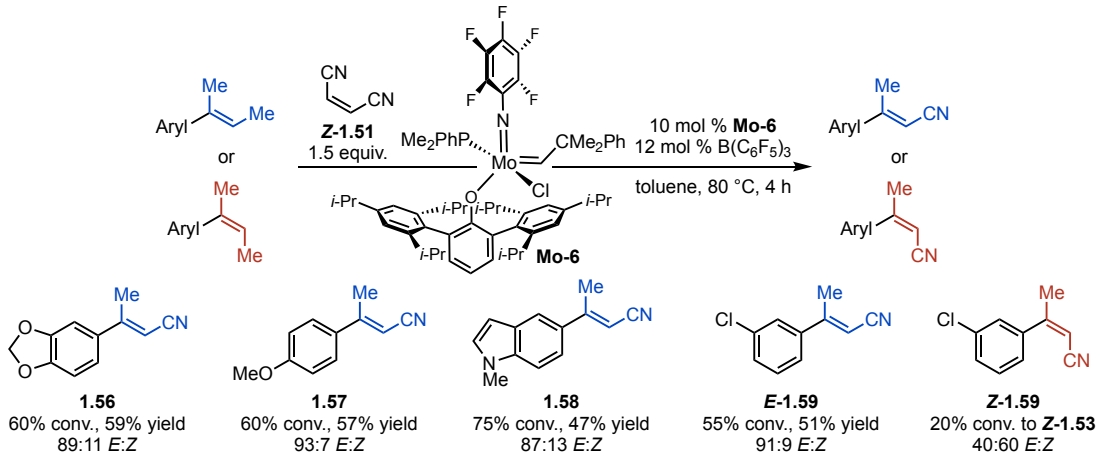
(30) Wiberg, K. B.; Wang, Y.; Petersson, G. A.; Bailey, W. F. *J. Chem. Theory Comput.* **2009**, *5*, 1033–1037.

(31) Allgäuer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2017**, *139*, 13318–13329.

(32) Mu, Y.; Nguyen, T. T.; Koh, M. J.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2019**, *11*, 478–487.

target *E*- or *Z*-trisubstituted alkenyl nitriles (**1.52**–**1.55**) through cross-metathesis with maleonitrile (Scheme 1.4.2).

Scheme 1.4.3. Cross-Metathesis of Aryl-Substituted *E*- and *Z*-Trisubstituted Alkenyl Nitriles



In the case of aryl-substituted alkene starting materials, a higher catalyst loading and increased temperature were required to achieve appreciable product formation (Scheme 1.4.3). However, when the respective *Z*-aryl-substituted alkenes were employed, only minimal conversion (<20% formation of ***Z*-159**) was observed, and the stereochemical purity of the target *Z*-alkenyl nitrile was significantly lower (~60:40 *Z*:*E*).

1.5 Cross-Metathesis of E- and Z-Trisubstituted Chloro Fluoro Alkenes

Fluorine-containing molecules are valuable compounds in medicinal chemistry,[33] material science,[34] and related fields.[35] An important subset thereof are trisubstituted alkenyl fluorides, which can act as secondary amide bond mimics.[36] Whereas naturally occurring amide bonds are twistable and can be cleaved by enzymes, the isosteric fluoro

(33) (a) Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822–5880. (b) Mei, H.; Remete, A. M.; Zou, Y.; Moriwaki, H.; Fustero, S.; Kiss, L.; Soloshonok, V. A.; Han, J. *Chin. Chem. Lett.* **2020**, *31*, 2401–2413.

(34) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.

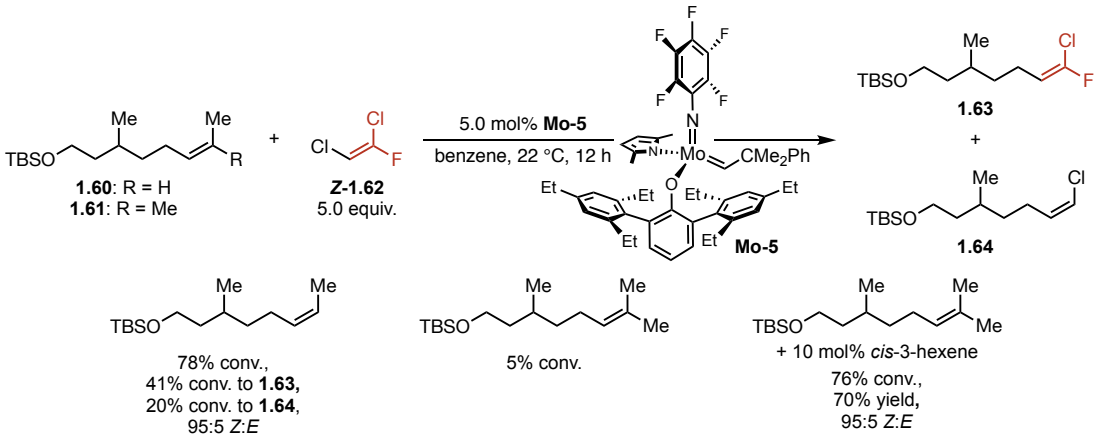
(35) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589.

(36) Oishi, S.; Kamitani, H.; Kodera, Y.; Watanabe, K.; Kobayashi, K.; Narumi, T.; Tomita, K.; Ohno, H.; Naito, T.; Kodama, E.; Matsuoka, M.; Fujii, N. *Org. Biomol. Chem.* **2009**, *7*, 2872–2877.

olefins are stereochemically rigid and stable towards hydrolysis. Therefore, *E*-trisubstituted fluoro olefins are surrogates for amide bonds in the usually unstable *cis*-configuration, which offers the opportunity for studying high-energy peptide analogues.[37]

Although cross-metathesis with fluorine-containing alkenes has been previously reported, the subsequent functionalization is often difficult and a limiting factor for its application.[38] We instead envisioned a strategy that would give access to *E*- and *Z*-trisubstituted olefins that could be easily functionalized, thus allowing a broad variety of alkenyl fluorides to be synthesized. A fluorine-containing motif that is readily amenable for further selective functionalization is a chloro, fluoroalkene.[39] Chloro-substituted olefins are common intermediates in organic syntheses and have been shown to undergo a wide range of functionalizations. Thus, we sought to develop the cross-metathesis of commercially available *E*- or *Z*-1,2-dichloro-1-fluoroethene (***E*-1.62** or ***Z*-1.62**).[40]

Scheme 1.5.1. Cross-Metathesis of ***Z*-1.62** Di- or Trisubstituted Starting Materials



(37) Altman, R. A.; Sharma, K. K.; Rajewski, L. G.; Toren, P. C.; Baltezor, M. J.; Pal, M.; Karad, S. N. *ACS Chem. Neurosci.* **2018**, *9*, 1735–1742.

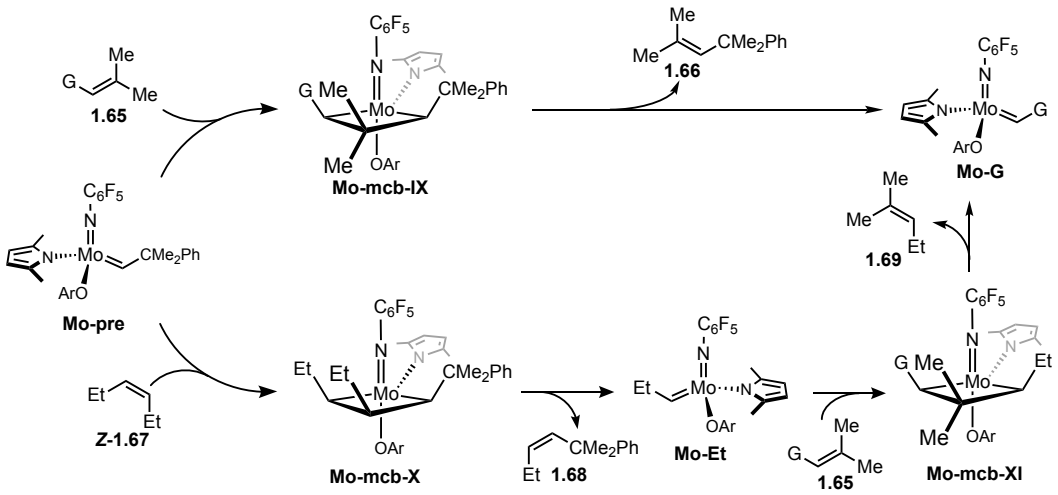
(38) (a) Takahira, Y.; Morizawa, Y. *J. Am. Chem. Soc.* **2015**, *137*, 7031–7034. (b) Nouaille, A.; Pannecoucke, X.; Poisson, T.; Couve-Bonnaire, S. *Adv. Synth. Catal.* **2021**, *363*, 2140–2147.

(39) (a) Chen, C.; Wilcoxen, K.; Strack, N.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 827–830. (b) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405–408.

(40) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463–473.

Cross-metathesis between methyl disubstituted alkene starting material **1.60** and ***Z*-1.62** in the presence of MAP complex **Mo-5** led to 41% formation of the desired product (**1.63**) together with the formation of 20% of the undesired by-product **1.64** (Scheme 1.5.1). When the corresponding trisubstituted alkene **1.61** was investigated, barely any conversion could be detected (5%). However, when a catalytic amount (10 mol%) of a disubstituted olefin (i.e., *cis*-3-hexene) was added, the desired product was isolated in 70% yield and 95:5 *Z*:*E* selectivity. As the use of small olefin additives for catalyst initiation has been reported previously, we reasoned that *cis*-3-hexene likely helped initiate the catalyst precursor into the catalytic cycle (Scheme 1.5.2).[41]

Scheme 1.5.2. Facilitated Catalyst Initiation Through *cis*-3-Hexene

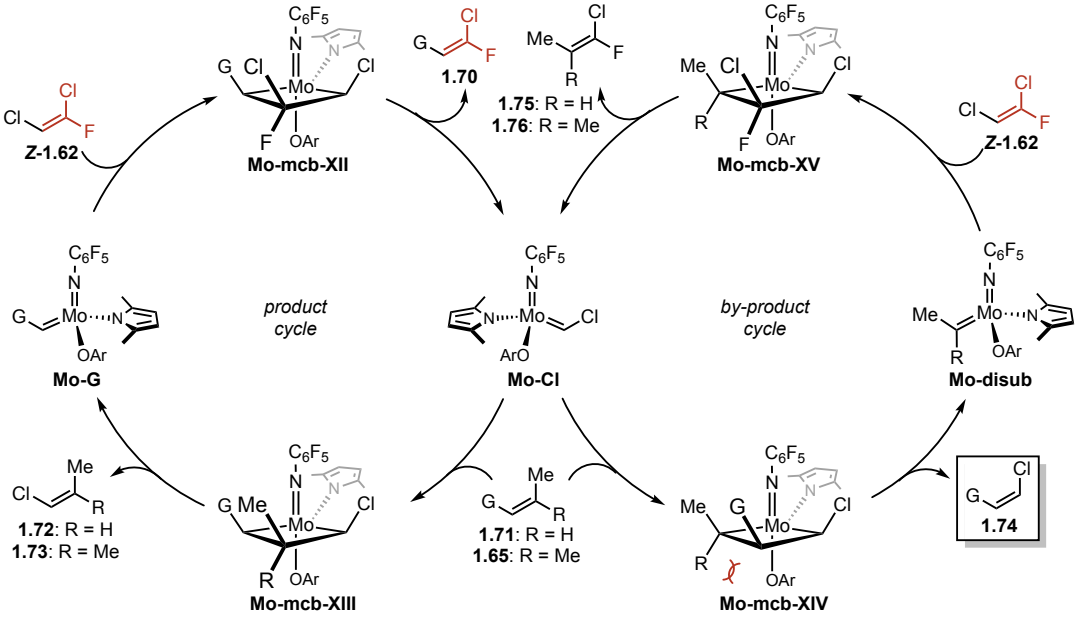


Reaction of the complex **Mo-pre** with starting material **1.65** via **Mo-mcb-IX** is likely slow owing to the steric pressure caused by the dimethylphenyl-substituted Cα. The transformation with *cis*-3-hexene through **Mo-mcb-X** should be considerably faster, and after reaction of **Mo-Et** with **1.65** (via **Mo-mcb-XI)**, the same catalytically active intermediate **Mo-G** is formed. However, as the energy barrier for reaction through **Mo-**

(41) Hoveyda, A. H.; Liu, Z.; Qin, C.; Koengeter, T.; Mu, Y. *Angew. Chem. Int. Ed.* **2020**, *59*, 22324–22348.

mcb-XI is probably lower than for **Mo-mcb-IX** on account of reduced steric repulsion at Cα, catalyst initiation should be more facile through this pathway. It is worth noting that in the case of trisubstituted alkene substrates, only minimal amounts (<5%) of the disubstituted alkenyl chloride side products were generated. This can be explained by considering the requisite mcb intermediate (Scheme 1.5.3).

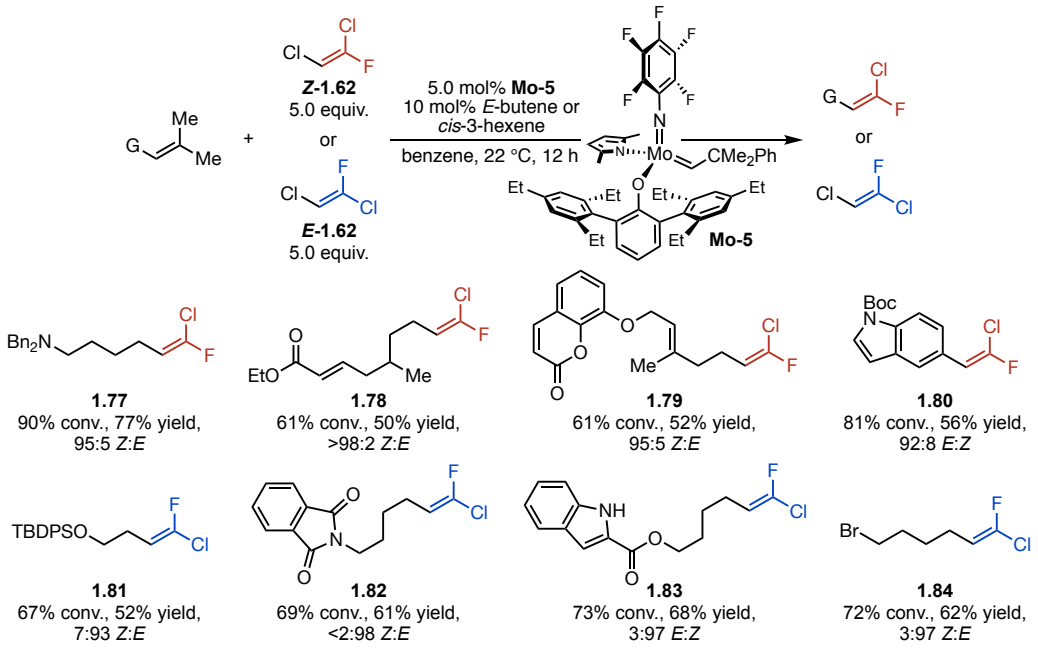
Scheme 1.5.3. Catalytic Cycle for Desired Product (Left) and By-Product Formation (Right)



After initiation into the catalytic cycle, **Mo-G** is formed, which, after reaction with ***Z*-1.62** via **Mo-mcb-XII**, is converted to **1.70** and chloro-alkylidene **Mo-Cl**. The latter species can react with the alkene starting material in two different ways. On the one hand, transformation with the G-group at Cα leads to re-formation of **Mo-G** via **Mo-mcb-XIII,** delivering the desired product. Reaction via **Mo-mcb-XIV**, with the G-group at Cβ, generates by-product **1.74**. Since the latter route is less favorable in the case of trisubstituted alkene **1.65** on account of the attendant steric interaction within the corresponding mcb, minimal side-product was detected. The corresponding disubstituted alkene starting material **1.71**, however, does not suffer from the same unfavorable

interaction. Consequently, reaction through **Mo-mcb-XIV** is less costly, and significant amounts of **1.74** were observed.

Scheme 1.5.4. Select Examples of *Z*- and *E*-Trisubstituted Olefins with a Fluoro-Chloro-Terminus



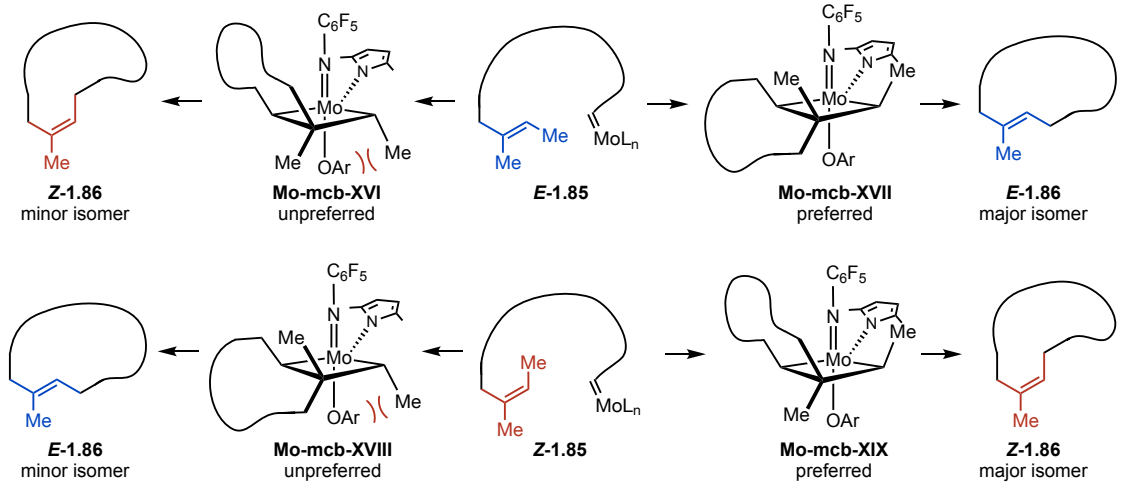
After it was established that trisubstituted olefins are preferable starting materials, the scope of the reaction was investigated. With addition of catalytic amounts of a 1,2-disubstituted olefin and under optimal conditions, a variety of alkyl- and aryl-trisubstituted alkenes were found to be effective substrates (Scheme 1.5.4). Notably, product olefins bearing a fluoro-chloro-terminus were transformed into fluorine-containing α,β-unsaturated enoates, nitriles, boronates, phosphates, halides, and many other functional groups.

1.6 E- and Z-Trisubstituted Alkenes Through Macrocyclic Ring-Closing Metathesis

Many trisubstituted macrocyclic alkenes are biologically active and can be accessed through macrocyclic ring-closing metathesis (MRCM).[42] However, this strategy has major shortcomings. In many cases, isomeric mixtures are generated,[43] or the undesired isomer is formed preferentially.[44] Although protocols to convert one stereoisomer into another exist, the requisite cascade of transformations is often lengthy and leads to low overall yields.[45]

It would be preferable if, similar to disubstituted stereoretentive ring-closing metathesis,[12,16] the corresponding trisubstituted macrocyclic alkenes could be obtained with high stereochemical purity under catalyst-control rather than conformational control. In theory, the same principles that guided stereochemical selectivity in stereoretentive cross-metathesis reactions should be applicable to ring-closing metathesis (Scheme 1.6.1).

Scheme 1.6.1. Stereochemical Model for Stereoretentive Macrocyclic Ring-Closing Metathesis



(42) Yu, M.; Lou, S.; Gonzalez-Bobes, F. *Org. Process Res. Dev.* **2018**, *22*, 918–946.

(43) (a) Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872–8888. (b) Glaus, F.; Altmann, K. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 1937–1940.

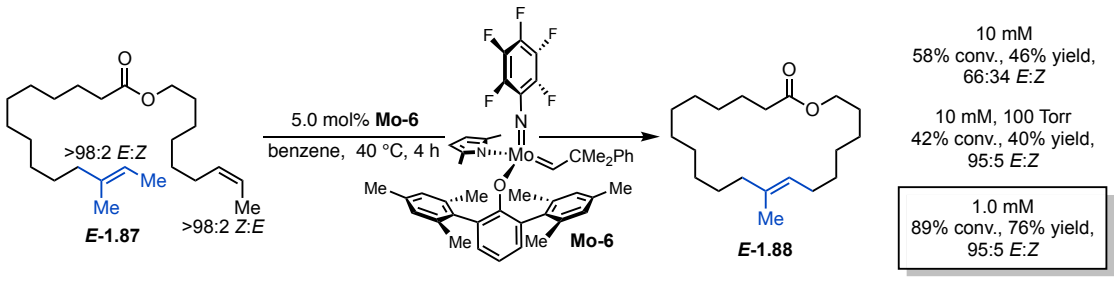
(44) Toelle, N.; Weinstabl, H.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3859–3862.

(45) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949.

Initiation of the Mo catalyst would likely occur with the more reactive disubstituted olefin, furnishing the Mo alkylidenes ***E*-1.85** and ***Z*-1.85**. In the case of a *E*-trisubstituted olefin, the reaction could proceed via **Mo-mcb-XVI** or **Mo-mcb-XVII**. The steric clash between the large aryloxide ligand and the α-methyl substituent in **Mo-mcb-XVI** would disfavor such a pathway, and the process would preferentially proceed via **Mo-mcb-XVII**, affording *E*-trisubstituted macrocyclic alkene ***E*-1.86**.

A related scenario may be envisioned for formation of the *Z*-trisubstituted macrocycle ***Z*-1.86**, namely via **Mo-mcb-XIX** in preference to **Mo-mcb-XVIII**. Nonetheless, there are important differences between cross-metathesis and ring-closing metathesis. Excess of one reactant is often needed for a high conversion in a cross-metathesis reaction, a remedy that does not extend to ring-closing metathesis. Furthermore, ring-closing metathesis reactions are usually carried out at relatively high dilution to encourage cyclization, whereas cross-metathesis processes are typically conducted with minimal solvent to facilitate intermolecular transformation.

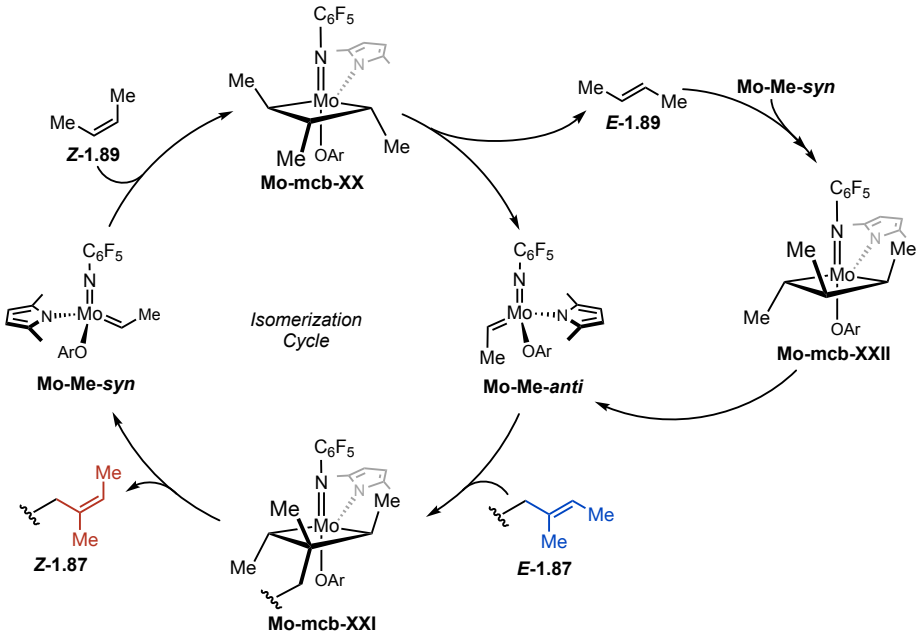
Scheme 1.6.2. Investigation Regarding the Feasibility of Stereoretentive Trisubstituted MRCM



To probe the feasibility of generating macrocyclic trisubstituted alkenes by stereoretentive ring-closing metathesis, Hoveyda and co-workers investigated the reaction of **1.87**, a diene bearing a disubstituted and an *E*-trisubstituted olefin in the presence of

MAP complex **Mo-6** (Scheme 1.6.2).[46] When ***E*-1.87** was subjected to optimal conditions for ring-closing metathesis with **Mo-6**, the desired product **1.88** was isolated in 46% yield and 66:34 *E*:*Z* ratio. Such lack of stereochemical control in a stereoretentive olefin metathesis reaction that generates a trisubstituted alkene was entirely unexpected. Trisubstituted olefins are far less prone to post-metathesis isomerization than their disubstituted counterparts. Thus, it was likely that the trisubstituted olefin substrate that governs the stereochemical outcome of the reaction was isomerized prior to the ring-closing metathesis event. This hypothesis was further corroborated by re-isolation of the diene starting material **1.87**, which, after the reaction, exhibited a diminished *E*:*Z* ratio for the trisubstituted olefin (68:32 *E*:*Z* vs. >98:2 initially). Notably, when the reaction was conducted at lower concentration or under mild vacuum (100 Torr), the level of stereoretention improved dramatically (95:5 and >98:2 *E*:*Z*, respectively). A possible

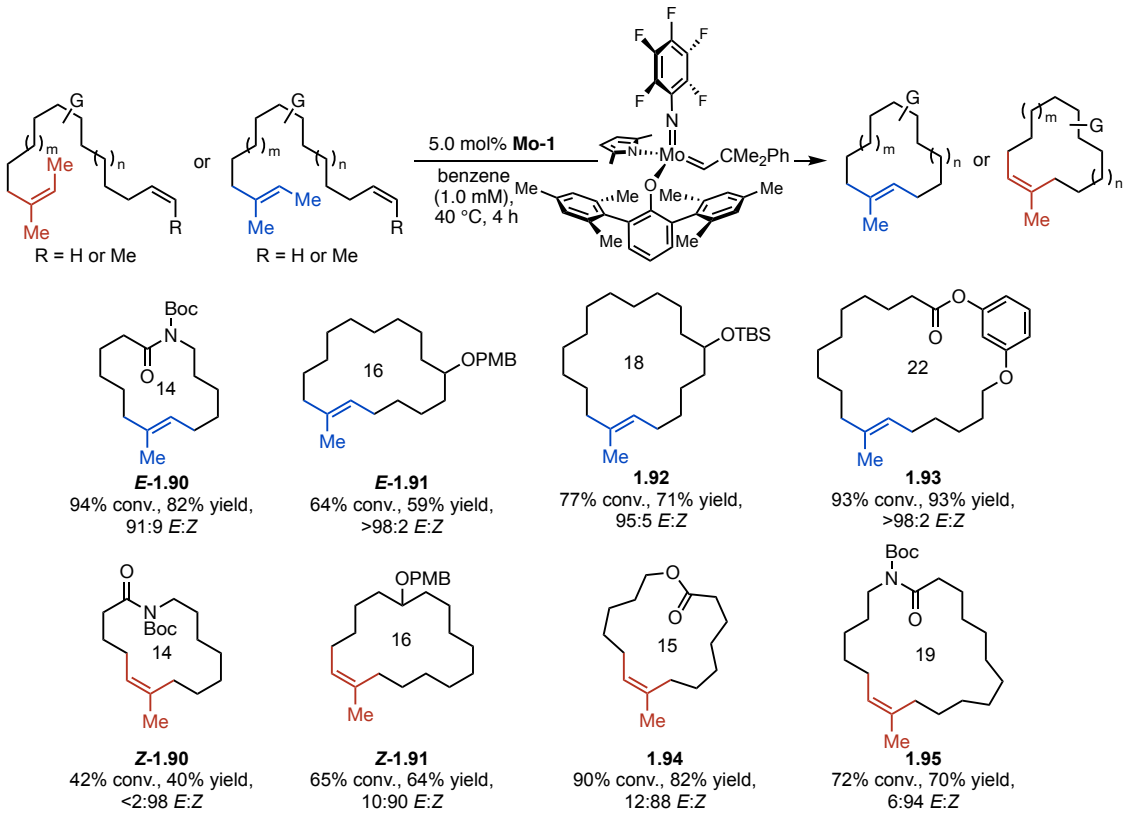
Scheme 1.6.3. Proposed Isomerization Mechanism through Generation of *E*-butene and *Anti*-Alkylidene



(46) Mu, Y.; Hartrampf, F. W. W.; Yu, E. C.; Lounsbury, K. E.; Schrock, R. R.; Romiti, F.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 640–649.

mechanism that accounts for this effect is that *Z*-butene mediates the generation of a Mo *anti*-alkylidene complex (Scheme 1.6.3). Reaction of **Mo-Me-syn** with *Z*-butene (***Z*-1.89**) via **Mo-mcb-XX** (albeit disfavored over the non-productive pathway) leads to generation of *E*-butene (***E*-1.89**) and **Mo-Me-anti**; the *anti*-alkylidene complex can react with the trisubstituted olefin of ***E*-1.87** via **Mo-mcb-XXI**, effectively isomerizing it from ***E*-1.87** to ***Z*-1.87**. Subsequent stereoretentive ring-closing metathesis of ***Z*-1.87** then leads to formation of the undesired *Z*-isomer macrocycle (**1.88**). At the same time, the *E*-butene that was generated in the beginning can also lead to formation of **Mo-Me-*anti***, exacerbating the effect of the initial isomerization. Under more dilute reaction conditions, various *E*- and *Z*-trisubstituted macrocyclic alkenes were synthesized in high stereochemical purity (Scheme 1.6.4).

Scheme 1.6.4. Select Examples of *E*- and *Z*-Trisubstituted Macrocyclic Ring-Closing Metatheses



Carbocyclic alkenes (**1.91** and **1.92**) were accessed in appreciable yield and stereochemical purity, countering the recent claim that macrocyclic ring-closing metathesis of these types of substrates is inherently problematic.[47] More importantly, the method was successfully applied to total synthesis of dolabelide C (66% yield, >98:2 *E*:*Z* for the MRCM step).[48]

1.7 Conclusions

The development of stereoretentive olefin metathesis catalysts has solved a long-standing problem in the field, allowing for trisubstituted alkenes to be synthesized in high stereochemical purity and under kinetic control. *E*- as well as *Z*-isomers of trisubstituted alkenyl halides, nitriles, and allylic alcohols can be accessed through cross-metathesis of commercially available and easily accessible alkenes. Through the use of the same strategy, macrocyclic trisubstituted alkenes have been accessed in either isomeric form through stereoretentive ring-closing metathesis of the corresponding diene starting materials. Thus, for the first time, a wide range of *E*- and *Z*-trisubstituted alkenes can be obtained selectively through olefin metathesis, regardless of the underlying thermodynamic preferences.

(47) Girvin, Z. C.; Andrews, M. K.; Liu, X.; Gellman, S. H. *Science* **2019**, *366*, 1528–1531.
(48) Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155–157.

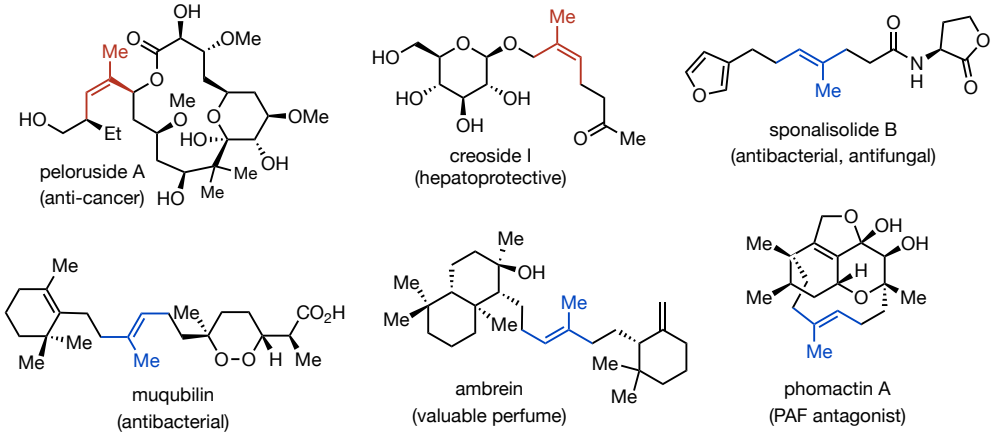
Chapter Two

Development of Catalytic Stereoretentive Cross-Metathesis of Trisubstituted Alkenyl Bromides

2.1 Introduction

Trisubstituted olefins are prevalent in natural products and bioactive molecules. A common motif within this family of compounds are alkenes bearing one methyl and two alkyl substituents, often found naturally occurring polyketides and terpenes.[1] While for the majority of these compounds, the trisubstituted double bond has the *E* stereochemistry, a few contain a *Z*-trisubstituted olefin (Scheme 2.1.1).[2]

Scheme 2.1.1. Select Trisubstituted Olefins in Natural Products and Bioactive Compounds



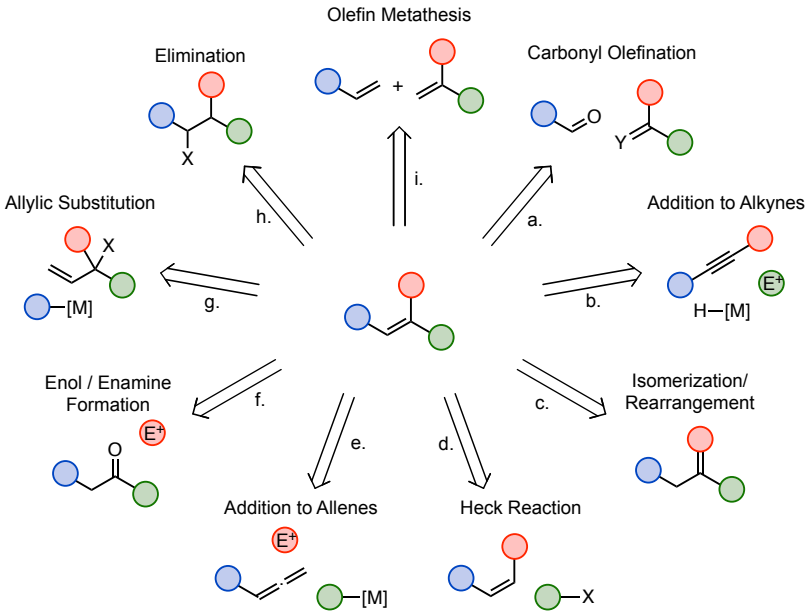
There are a multitude of methods for the synthesis of trisubstituted olefins that involve different starting materials (Scheme 2.1.2). Most afford a mixture of *Z*- and *E*-isomers,

(1) For reviews of polyketide natural products, see: (a) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677–90. (b) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380–416.

(2) For examples of *E*-trisubstituted natural products, see: (a) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445–449. (b) Nakamura, S.; Li, X.; Matsuda, H.; Yoshikawa, M. *Chem. Pharm. Bull.* **2008**, *56*, 536–540.

while others are moderately stereoselective.[3] One of the more common ways to access trisubstituted alkenes is through carbonyl olefination reactions (Scheme 2.1.2.a), with aldehydes or ketones being treated with phosphonium ylides (Wittig and Horner-Wadsworth-Emmons processes),[4] sulfur ylides (Julia),[5] or silanes (Peterson).[6]

Scheme 2.1.2. Possible Disconnections for the Synthesis of Trisubstituted Alkenes



The major drawbacks of these methods are the generation of superstochiometric amounts of waste, substrate-dependent stereoselectivity, and the fact that only one of the two alkene isomers can be accessed. Additionally, strong base is often required to generate the necessary ylide. Not all reagents are commercially available.

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(3) For a review on the stereoselective synthesis of trisubstituted alkenes, see: Faulkner, D. J. *Synthesis* **1971**, *4*, 175–189.

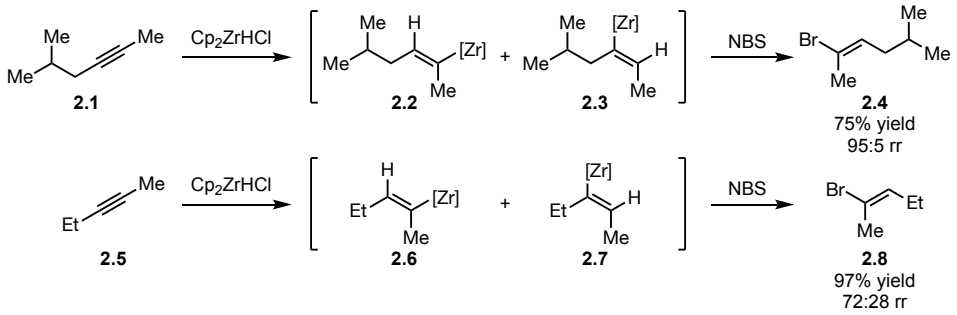
(4) For reviews on the Wittig reaction and related transformations, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (b) Edmonds, M.; Abell, A. In *Modern Carbonyl Olefination*; John Wiley & Sons, Ltd: Weinheim, Germany, 2003, pp 1–17.

(5) For reviews on the Julia reaction, see: (a) Blakemore, P. R. *J. Chem. Soc. Perkin 1* **2002**, *2*, 2563–2585. (b) Kocienski, P. *Phosphorus Sulfur Relat. Elem.* **1985**, *24*, 97–127.

(6) For reviews on the Peterson olefination, see: (a) Kano, N.; Kawashima, T. In *Modern Carbonyl Olefination*; John Wiley & Sons, Ltd: Weinheim, Germany, 2003, pp 18–103. (b) Van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195–200.

Alternatively, trisubstituted alkenes have been prepared through carbometallation or hydrometallation of alkynes (Scheme 2.1.2.b).[7] In the former set, organometallic nucleophiles are added to terminal alkynes, and the resulting alkenylmetal intermediate is trapped with an appropriate electrophile.[8] Hydrometallation of internal alkynes, on the other hand, involves addition of a metal hydride to an internal alkyne. These transformations are often minimally regioselectivity unless the alkyne contains two sterically or electronically differentiated substituents (Scheme 2.1.3).[9]

Scheme 2.1.3. Regioselectivity of Hydrometallation of Internal Alkynes



Another alternative entails conversion of a homopropargylic alcohol (**2.9**) to a silyl ether (**2.10**), followed by directed hydrosilylation to give *E*- or *Z*-trisubstituted cyclic siloxanes (**2.11** or **2.12**), depending on the catalyst used (Scheme 2.1.4).[10] The resulting intermediates may be subjected to cross-coupling conditions to afford *E*- or *Z*-trisubstituted alkenes (**2.13** or **2.14**) in 95:5 to 98:2 stereoselectivity. Still, the latter approach lacks

(7) For reviews on carbometallation reactions, see: (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, *1981*, 841–870. (b) Marek, I.; Minko, Y. In *Metal Catalyzed Cross-Coupling Reactions and More*; Wiley-VCH Verlag GmbH & Co. KGaA, Germany, 2013, pp 763–874.

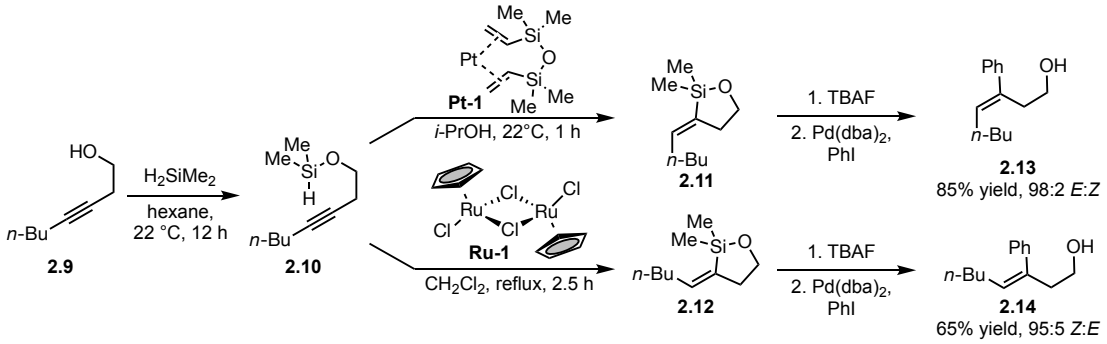
(8) (a) Zhu, C.; Yue, H.; Maity, B.; Atodiresei, I.; Cavallo, L.; Rueping, M. *Nat. Catal.* **2019**, *2*, 678–687. (b) Zhu, C.; Yue, H.; Rueping, M. *Nat. Commun.* **2022**, *13*, 3240.

(9) (a) Schwier, T.; Gevorgyan, V. *Org. Lett.* **2005**, *7*, 5191–5194. (b) Brown, H. C.; Hamaoka, Tsutomu.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456–6457. (c) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679–680.

(10) (a) Denmark, S. E.; Weitao, P. *Org. Lett.* **2001**, *3*, 61–64. (b) Denmark, S. E.; Pan, W. *Org. Lett.* **2002**, *4*, 4163–4166.

generality, as the homopropargylic hydroxy group is not regularly encountered in organic compounds and must be prepared over several steps.

Scheme 2.1.4. Hydrosilylation and Subsequent Cross-Coupling of Homopropargylic Alcohols



There are other, less frequently used, preparative options. Sigmatropic rearrangements, for instance, can be used to generate stereodefined trisubstituted alkenes in moderate stereoselectivity (86:14–93:7 *E*:*Z*); however, elevated temperatures are often needed, and the protocol is only applicable to preparing 1,5-dienes (Scheme 2.1.2.c).[11] A related strategy is the isomerization of disubstituted alkenes to their trisubstituted counterparts.[12] The factor that validates this strategy is that disubstituted alkenes are in many cases easier to synthesize stereoselectively than trisubstituted ones, in part owing to a smaller energy difference between the isomers in a trisubstituted olefin.[13] Although catalytic alkene isomerization is an attractive strategy that has gained interest recently,[14] it remains to be seen if it can be applied to accessing many trisubstituted olefins.

(11) Faulkner, D. J.; Petersen, M. R. *Tetrahedron Lett.* **1969**, *10*, 3243–3246.

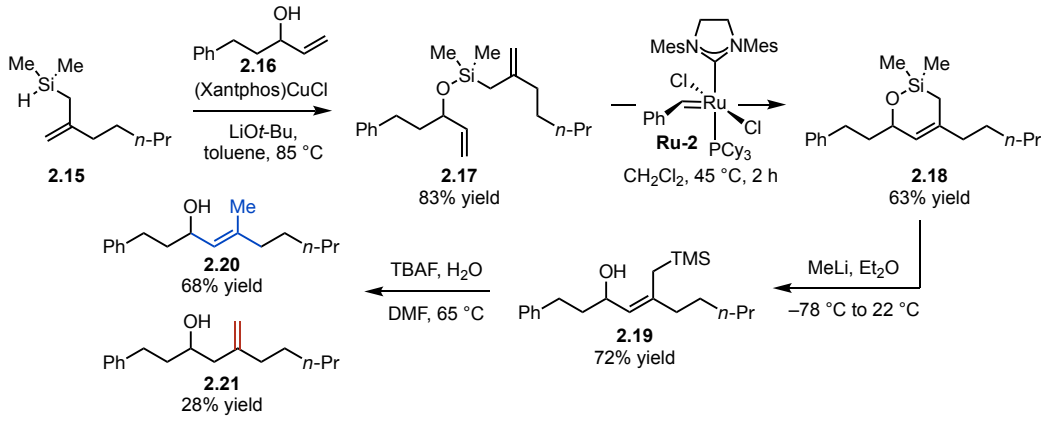
(12) (a) Massad, I.; Sommer, H.; Marek, I. *Angew. Chem. Int. Ed.* **2020**, *59*, 15549–15553. (b) Sherwood, T. C.; Trotta, A. H.; Snyder, S. A. *J. Am. Chem. Soc.* **2014**, *136*, 9743–9753.

(13) Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron Lett.* **1980**, *21*, 1331–1334.

(14) (a) Li, G.; Kuo, J. L.; Han, A.; Abuyuan, J. M.; Young, L. C.; Norton, J. R.; Palmer, J. H. *J. Am. Chem. Soc.* **2016**, *138*, 7698–7704. (b) Kapat, A.; Sperger, T.; Guven, S.; Schoenebeck, F. *Science* **2019**, *363*, 391–396. (c) Zhang, S.; Bedi, D.; Cheng, L.; Unruh, D. K.; Li, G.; Findlater, M. *J. Am. Chem. Soc.* **2020**, *142*, 8910–8917.

Effective control of stereochemistry can be particularly challenging in cases of isolated alkenes with no proximal functional groups. As many synthesis methods rely on such moieties for stereochemical control, they oftentimes must be installed and removed later in additional manipulations, lowering the overall efficiency of the synthesis route.

Scheme 2.1.5. Silyl-Tethered RCM Strategy for Synthesis of Stereodefined Olefins



A prime example is the use of silyl-tethered ring-closing metathesis (RCM) to establish di- and trisubstituted olefins with defined stereochemistry (Scheme 2.1.5).[15] The requisite siloxane **2.17** was prepared through silylation of **2.15** and **2.16**, and the subsequent RCM proceeded with excellent stereoselectivity (>98:2 *Z*:*E*) due to the high strain energy associated with the formation of the non-preferred isomer. Still, the subsequent removal of the silyl group required two steps and led to partial isomerization of the trisubstituted double bond, affording target **2.20** and isomerized **2.21** in an approximately 2:1 mixture. Although the use of transient silyl tethers for the stereoselective generation of alkenes through RCM is precedented,[16,17] the need for silyl group installation and removal, and the

(15) Tiniakos, A. F.; Wittmann, S.; Audic, A.; Prunet, J. *Org. Lett.* **2019**, *21*, 589–592.

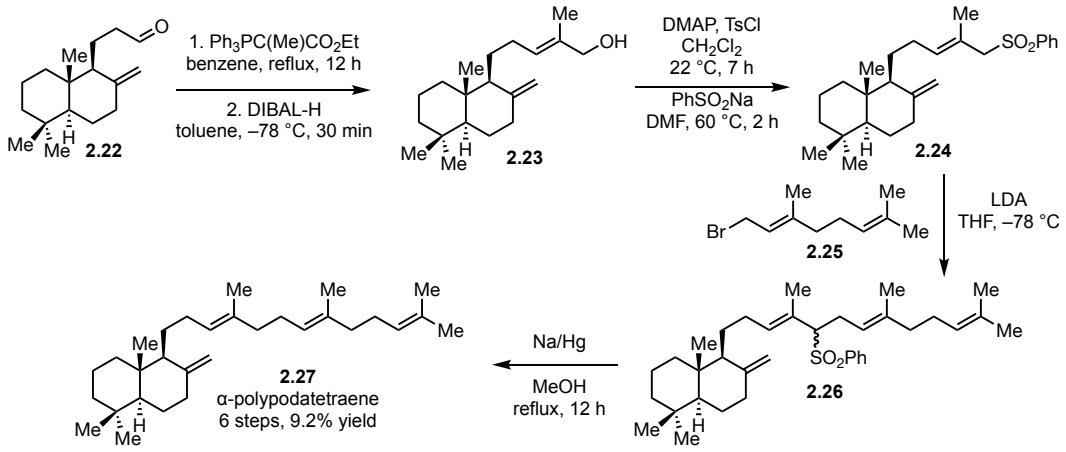
(16) (a) Forbes, M. D. E.; Myers, T. L.; Maynard, H. D.; Schulz, G. R.; Patton, J. T.; Smith, D. W.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978–10980. (b) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757–4760.

(17) For a review on the use of temporary silicon tethers, see: Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, *1997*, 813–854.

fact that only one olefin isomer can be accessed (i.e., the one that is thermodynamically favored) detracts from the applicability of such strategies.

Another instance relates to the use of trisubstituted allylic sulfones, which, after α-deprotonation and subsequent reaction with an electrophile deliver the desired alkene in high stereoisomeric purity (Scheme 2.1.6). The preparation of these sulfones (e.g., **2.24**), however, usually proceeds through a sequence of HWE reaction and numerous functional group manipulations. What is more, subsequent removal of the sulfone (**2.26** → **2.27**) often demands harsh conditions that may not be compatible with other functional groups in the molecule.[18]

Scheme 2.1.6. Synthesis Sequence for Installation and Subsequent Removal of Allyl Sulfone



Direct stereoselective synthesis of these isolated alkenes is thus typically inefficient and minimally stereoselective. Accordingly, development of a more efficient strategy for synthesis of less functionalized trisubstituted alkenes, in either stereoisomeric form, represents a compelling research goal. One attractive approach would entail stereocontrolled formation of a modifiable trisubstituted alkenyl halide that might then be

(18) (a) Rainier, J. D.; Smith, A. B. *Tetrahedron Lett.* **2000**, *41*, 9419–9423. (b) Olson, G. L.; Cheung, H. C.; Morgan, K. D.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3287–3293. (c) Kinoshita, M.; Ohtsuka, M.; Nakamura, D.; Akita, H. *Chem. Pharm. Bull.* **2002**, *50*, 930–934.

converted to a myriad of derivatives through cross-coupling. This strategy is commonly used with alkenyl boronates[19] and halides[20] serving as intermediates. One advantage of this strategy is modularity, allowing for rapid diversification of the intermediate. Favored reactions for the synthesis of trisubstituted alkenyl halides and alkenyl boronates are: carbonyl olefination,[21,22] metal hydride addition to alkynes,[23] boron hydride[24] or copper hydride[25] addition to allenes, Shapiro reactions,[26] Heck reactions,[27] enol tosylation,[28] decarboxylation of α,β-unsaturated carboxylic acids,[29] elimination from dibromoalkanes,[30] or hydrobromination of alkynes.[31] In many cases, however, these reactions do not represent a long-term and broadly applicable solution for the synthesis of trisubstituted alkenes, because often harsh reaction conditions and/ or precious metal catalysts are needed, and only few methods allow access to both olefin isomers.

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(19) For representative examples of alkenyl boronate intermediates in total syntheses, see: (a) Konstantinova, O.; Koskinen, A. *Synthesis* **2019**, *51*, 285–295. (b) Sanchez, A.; Maimone, T. J. *J. Am. Chem. Soc.* **2022**, 7594–7599. (c) Glaus, F.; Altmann, K. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 1937–1940.

(20) For representative examples of alkenyl halides in total syntheses, see: (a) Matsumura, D.; Takarabe, T.; Toda, T.; Hayamizu, T.; Sawamura, K.; Takao, K. I.; Tadano, K. I. *Tetrahedron* **2011**, *67*, 6730–6745. (b) Li, Q.; Pellegrino, J.; Lee, D. J.; Tran, A. A.; Chaires, H. A.; Wang, R.; Park, J. E.; Ji, K.; Chow, D.; Zhang, N.; Brilot, A. F.; Biel, J. T.; van Zundert, G.; Borrelli, K.; Shinabarger, D.; Wolfe, C.; Murray, B.; Jacobson, M. P.; et al. *Nature* **2020**, *586*, 145–150. (c) Yang, J.; Zhang, X. M.; Zhang, F. M.; Wang, S. H.; Tu, Y. Q.; Li, Z.; Wang, X. C.; Wang, H. *Angew. Chem. Int. Ed.* **2020**, *59*, 8471–8475. (d) Okura, K.; Matsuoka, S.; Goto, R.; Inoue, M. *Angew. Chem.* **2010**, *122*, 339–342.

(21) For representative examples of carbonyl olefination reactions affording alkenyl halides, see: (a) Olpp, T.; Brückner, R. *Synthesis* **2004**, 2135–2152. (b) Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833–2838. (c) Hodgson, D. M.; Arif, T. *J. Am. Chem. Soc.* **2008**, *130*, 16500–16501.

(22) For an example of a carbonyl olefination reaction affording an alkenyl boronate, see: Namirembe, S.; Gao, C.; Wexler, R. P.; Morken, J. P. *Org. Lett.* **2019**, *21*, 4392–4394.

(23) Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, *18*, 981–984.

(24) Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett.* **2013**, *15*, 1414–1417.

(25) Sun, Y.; Zhou, Y.; Shi, Y.; Del Pozo, J.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 12087–12099.

(26) Corey, E. J.; Lee, J.; Roberts, B. E. *Tetrahedron Lett.* **1997**, *38*, 8915–8918.

(27) Reid, W. B.; Watson, D. A. *Org. Lett.* **2018**, *20*, 6832–6835.

(28) Nakatsuji, H.; Nishikado, H.; Ueno, K.; Tanabe, Y. *Org. Lett.* **2009**, *11*, 4258–4261.

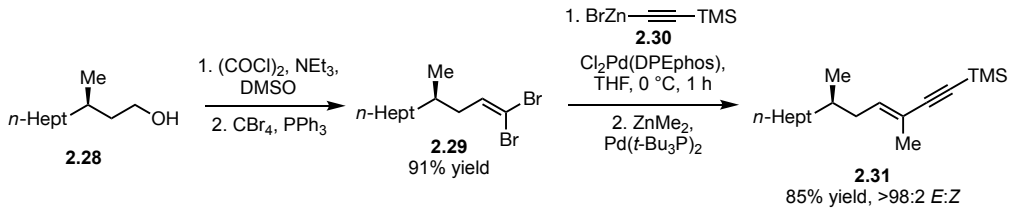
(29) Hunsdiecker, H.; Hunsdiecker, Cl. *Berichte Dtsch. Chem. Ges. B Ser.* **1942**, *75*, 291–297.

(30) Schlosser, M.; Hammer, E. *Helv. Chim. Acta* **1974**, *57*, 2547–2550.

(31) Yu, P.; Bismuto, A.; Morandi, B. *Angew. Chem. Int. Ed.* **2020**, *59*, 2904–2910.

A corollary approach is the stereoselective cross-coupling of 1,1-dihaloalkenes with organometal intermediates.[32] In many cases, palladium- or nickel-based catalysts react preferably with the *trans*-halide substituent, thus leading to a net *trans*-selective functionalization of the trisubstituted dihaloalkene.[33] In an ensuing step, the remaining *cis* halide can be further elaborated into the final all carbon substituted olefin.[34] An application of this strategy may be found in the synthesis of **2.31** by Negishi and co-workers. (Scheme 2.1.7).[35] Swern oxidation and Ramirez olefination allowed for conversion of alcohol **2.28** to alkenyl dibromide **2.29**, which was transformed to the stereodefined enyne **2.31** through a sequence of stereoselective Negishi cross-couplings with high stereoselectivity (>98:2 *E*:*Z*).

Scheme 2.1.7. Ramirez Olefination and Subsequent Stereoselective Cross-Coupling



The aforementioned cross-coupling processes often proceed under comparatively mild conditions and can be used for the stereoselective preparation of trisubstituted olefins in complex molecules. 1,1-Dihaloalkene, however, are commonly prepared through Ramirez olefination[36] of aldehydes under harsh reaction conditions.[37] Moreover, aldehydes are inherently unstable and prone to decomposition. Accordingly, the 1,1-dihaloalkene

(32) For a review on the synthesis and reactions of gem-dihalovinyl intermediates, see: Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344–1462.

(33) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257–1258.

(34) Tan, Z.; Negishi, E. *Angew. Chem.* **2006**, *118*, 776–779.

(35) Shi, J. C.; Zeng, X.; Negishi, E. I. *Org. Lett.* **2003**, *5*, 1825–1828.

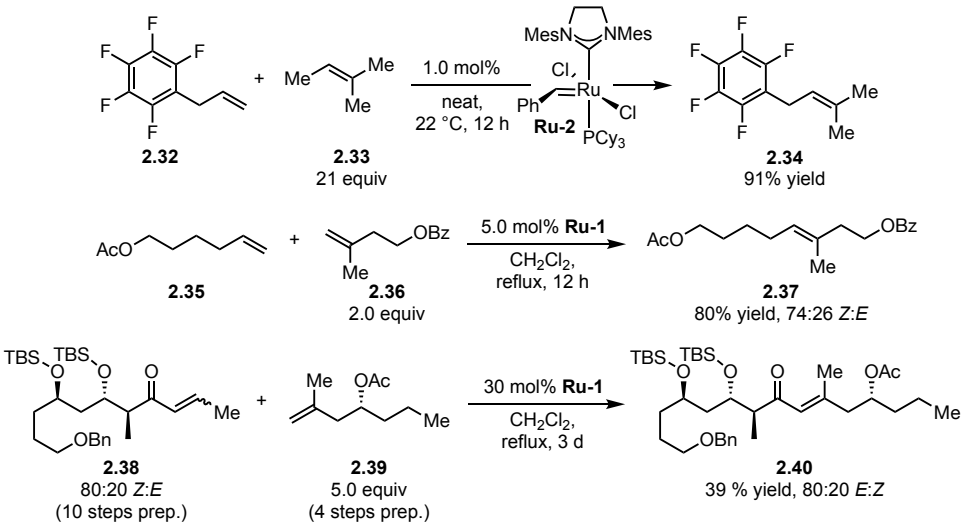
(36) Desai, N. B.; McKelvie, N.; Ramirez, F. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747.

(37) Speziale, A. J.; Ratts, K. W. *J. Am. Chem. Soc.* **1962**, *84*, 854–859.

functional group is often installed in a small fragment of the molecule and then incorporated into the larger, more sensitive structure through cross-coupling.[38]

An alternative strategy to the aforementioned is to access trisubstituted alkenes through olefin-metathesis. However, cross-metathesis of electronically undifferentiated alkenes is often inefficient, leading to statistical mixtures of alkene products. Oftentimes, a large excess of one alkene (e.g., **2.33**) is required to ensure appreciable product formation (Scheme 2.1.8, top).[39] While this may not constitute a problem in the case of commercially available alkenes, it limits the applicability when one or both alkene starting materials have to be prepared over several steps.[40] Moreover, the stereoselectivity of these reactions is moderate to low and often substrate dependent (Scheme 2.1.8, bottom two cases).[41] Thus, here too, it can be beneficial to instead access an alkenyl halide or boronate intermediate,

Scheme 2.1.8. Comparison of Cross-Metatheses Affording Trisubstituted Alkenes



(38) (a) Myers, A. G.; Goldberg, S. D. *Angew. Chem.* **2000**, *112*, 2844–2847. (b) Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381–5383.

(39) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939–1942.

(40) Prunet, J.; Grimaud, L. In *Metathesis in Natural Product Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2010, pp 287–312.

(41) (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753. (b) Braun, M. G.; Vincent, A.; Boumediene, M.; Prunet, J. *J. Org. Chem.* **2011**, *76*, 4921–4929.

and in a second step, convert it to the desired alkene through manipulation of the functional group on the olefin.

Synthesis of stereodefined disubstituted alkenyl halides[42] and boronates[43] can be achieved through catalytic cross-metathesis with high oxidation state Mo and W complexes. Unlike cases where the stereochemical outcome is controlled by thermodynamics,[44] the architecture of these Mo and W complexes allows them to differentiate the two alkene faces based on steric factors, making kinetic control feasible.[45]

Recently, Hoveyda and co-workers reported on the synthesis of stereodefined *E*- and *Z*-trisubstituted alkenyl bromides by cross-metathesis (Scheme 2.1.9).[46] The ability to access both stereoisomers relies on the use of a stereochemically defined trisubstituted alkene (**2.41** or **2.42**; impact on the stereochemistry of **2.43** is negligible), resulting in net retention of the alkene double bond configuration throughout the reaction. *E*-Trisubstituted alkenyl bromides were obtained in high stereochemical purity (e.g., **2.46** or **2.46**; 93:7 to >98:2 *E*:*Z*); the corresponding *Z* isomers exhibited slightly lower stereoretentivity (e.g., **2.48** or **2.49**; 21:79 to 5:95 *E*:*Z*).

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(42) (a) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465. (b) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569–575.

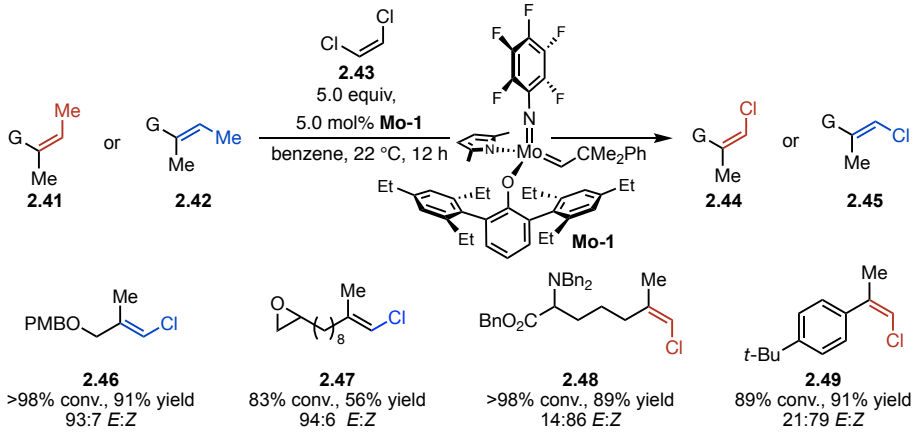
(43) Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.

(44) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733–7736.

(45) For reviews on stereoretentive olefin metathesis, see: (a) Hoveyda, A. H.; Khan, R. K. M.; Torker, S.; Malcolmson, S. J. In *Handbook of Metathesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2015, pp 503–562. (b) Montgomery, T. P.; Ahmed, T. S.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 11024–11036.

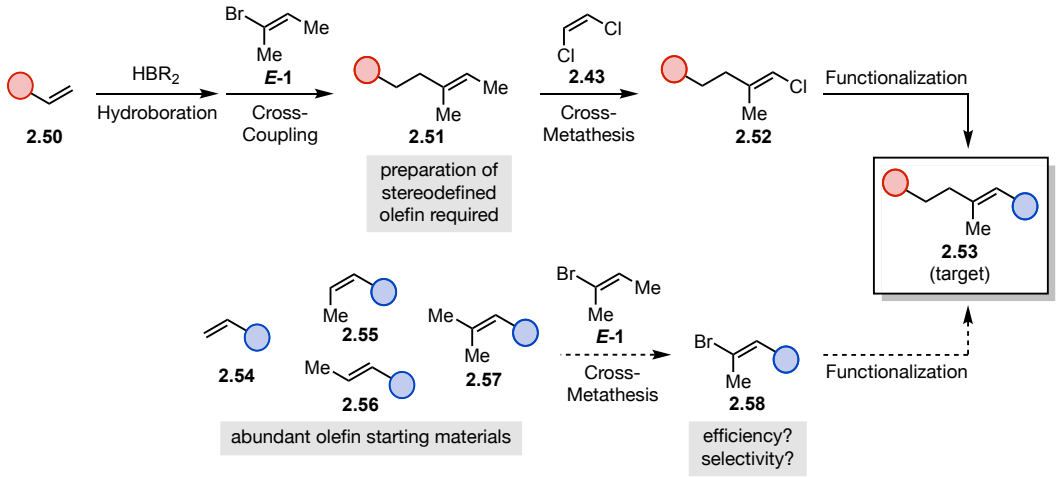
(46) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347–354.

Scheme 2.1.9. Cross-Metathesis of Stereodefined *E*- and *Z*-Trisubstituted Alkenyl Chloride



A major drawback of this approach is the need for a stereodefined all-alkyl trisubstituted alkene starting material (**2.41** or **2.42**). These are generally not commercially available and have to be synthesized through cross-coupling of a stereodefined alkene starting material such as *E*- or *Z*-2-bromo-2-butene (***E*-1** or ***Z*-1**). It would be preferrable if the more abundant terminal (**2.54**), disubstituted (**2.55** or **2.56**), or 1,1-dimethyl trisubstituted alkene starting materials (**2.57**) could be directly subjected to cross-metathesis with a commercially available or easily accessible stereodefined alkene instead (Scheme 2.1.10). This would represent a more concise and stereodivergent approach,

Scheme 2.1.10. Comparison of Synthesis Routes for Stereodefined Trisubstituted Olefins



potentially enabling conversion of a wide range of commercially available starting materials to useful building blocks.

2.2 Development of Stereoretentive Cross-Metathesis of Trisubstituted Alkenyl Bromides

We chose *Z*-2-bromo-2-butene (***Z*-1**) as the starting materials for several reasons. (1) It is commercially available and can be easily prepared in either isomeric from readily available starting materials in high stereoselectivity.[47] (2) Alkenyl bromides have been shown to be versatile intermediates that allow for a variety of functionalization: lithium-halogen exchange,[48] Nozaki-Hiyama-Kishi reactions,[49] Stille reactions,[50] Negishi reactions,[51] Sonogashira reactions,[52] Suzuki reactions affording alkenyl Csp^3 and Csp^2 bonds,[53] as well as conversion to alkenyl iodides[54] and alkenyl boronates.[55] Moreover, alkenyl bromides readily serve as electrophiles in cross-coupling reactions to form alkenyl C–O[56] and C–N[57] bonds. (3) Methyl groups are the most common substituent in trisubstituted olefins occurring in natural products and bioactive compounds.

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(47) (a) Bordwell, F. G.; Landis, P. S. *J. Am. Chem. Soc.* **1957**, *79*, 1593–1597. (b) Cochran, J. C.; Prindle, V.; Young, H. A.; Kumar, M. H.; Tom, S.; Petraco, N. D. K.; Mohoro, C.; Kelley, B. *Synth. React. Inorg. Met.-Org. Chem.* **2002**, *32*, 885–902.

(48) Corey, E. J.; Kania, R. S. *Tetrahedron Lett.* **1998**, *39*, 741–744.

(49) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 3997–4000.

(50) Romo, D.; Choi, N. S.; Li, S.; Buchler, I.; Shi, Z.; Liu, J. O. *J. Am. Chem. Soc.* **2004**, *126*, 10582–10588.

(51) Yin, N.; Wang, G.; Qian, M.; Negishi, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 2916–2920.

(52) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

(53) (a) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1987**, *16*, 25–28. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

(54) Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* **1978**, *7*, 1435–1436.

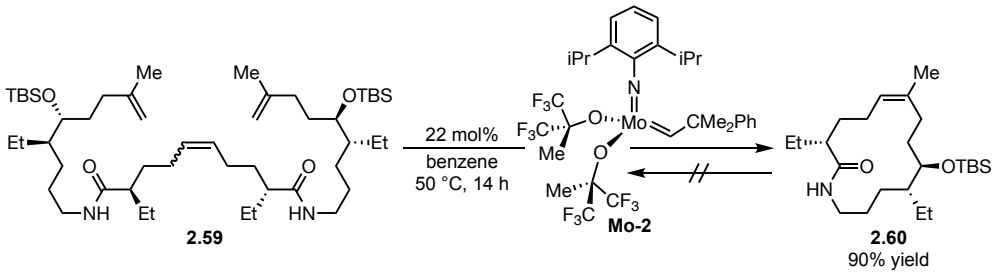
(55) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006.

(56) Ma, D.; Cai, Q.; Xie, X. *Synlett* **2005**, 1767–1770.

(57) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669.

One of the key challenges in cross-metathesis is balancing the reactivity of the alkenes involved in the reaction.[58] Usually, less substituted alkenes react faster. This difference in reactivity can lead to undesired homocoupling (reaction between two identical molecules) byproduct formation, especially when differently substituted alkene starting materials are used. To avoid significant homo-metathesis, it seemed sensible to employ another trisubstituted alkene starting material to match the reactivity of ***Z*-1**. On the other hand, this would imply cross-metathesis between two trisubstituted olefins, which seemed unorthodox at the time, because trisubstituted alkenes (e.g., **2.60**) had been shown to not easily re-enter the catalytic cycle (Scheme 2.2.1).[59]

Scheme 2.2.1. Macrocyclic Ring-Closing Metathesis of **2.59** with **Mo-2**



Seeking to identify suitable catalysts for this transformation, we started our investigations with the recently disclosed Mo monoaryloxide chloride (MAC) complexes.[60] This family of complexes has been shown to exhibit higher reactivity than previously utilized Mo monoaryloxide pyrrolide (MAP), bisaryloxide (BAO), or bisalkoxide complexes (Scheme 2.2.2). It therefore seemed to be the appropriate choice for this challenging transformation. We commenced our studies with the synthesis of TBS-

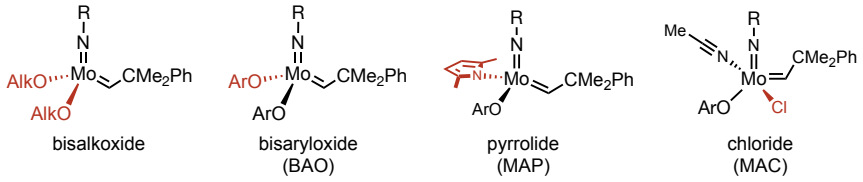
(58) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

(59) (a) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316. (b) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7694–7699.

(60) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80–85.

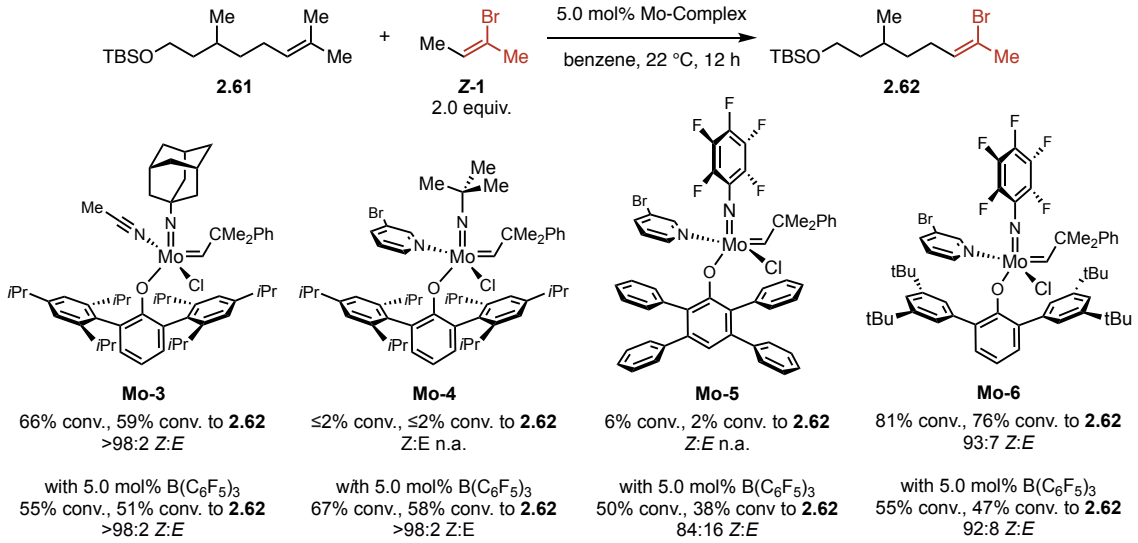
protected citronellol (**2.4**), bearing a 1,1-dimethyl trisubstituted olefin, as our trisubstituted alkene starting material for cross-metathesis with ***Z*-1**.

Scheme 2.2.2. Structural Features of Different High-Oxidation State Mo-Complexes



We were pleased to find that with 2.0 equivalents ***Z*-1**, and 5.0 mol% **Mo-3**, the reaction proceeded to 66% conversion and 59% product formation of **2.62** in >98:2 *Z*:*E* (Scheme 2.2.3). The results were similar with **Mo-4**, with the major difference being that addition of 5.0 mol% of $B(C_6F_5)_3$ was required in the reaction (the Lewis acid is required to irreversibly bind 3-bromopyridine, furnishing the catalytically active 14-electron complex[61]). When the more Lewis acidic C_6F_5-imido complexes (**Mo-5** and **Mo-6**) with less sterically hindered aryloxide ligands were used, **2.62** was generated in up to 76% conversion, albeit with lower stereoselectivity (93:7 *Z*:*E*). Notably, experiments conducted

Scheme 2.2.3. Cross-Metathesis Results with MAC Complexes as Catalysts

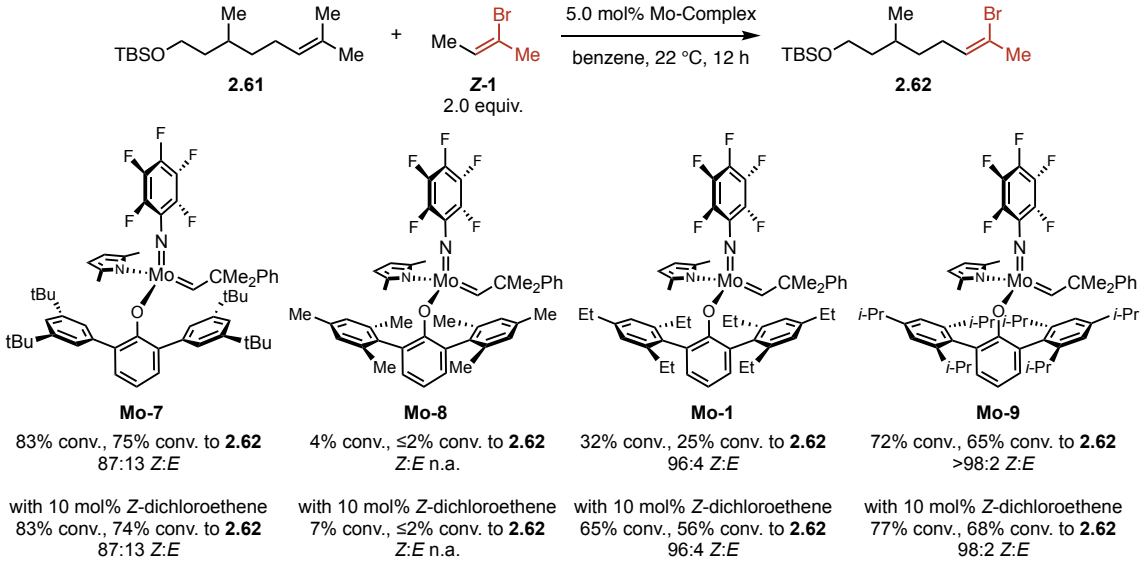


(61) Lam, J. K.; Zhu, C.; Bukhryakov, K. V.; Müller, P.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2016**, *138*, 15774–15783.

with **Mo-6** led to product formation even in the absence of a Lewis acid additive. When the reaction was conducted in solvents other than benzene, a similar trend was observed, but conversion and product formation were lower (toluene: 52% conv., 39% conv. **2.62**; CH_2Cl_2: 22% conv., 12% conv. to **2.62**). Despite attempts to elucidate the root of this unique reactivity, we were not able, at the present time, to offer a plausible rationale for this irregularity.

As reaction efficiency can at times be limited by catalyst longevity rather than reactivity, we decided to screen the more robust monoaryloxide pyrrolide (MAP) complexes (Scheme 2.2.4).

Scheme 2.2.4. Cross-Metathesis Results with MAP Complexes as Catalysts

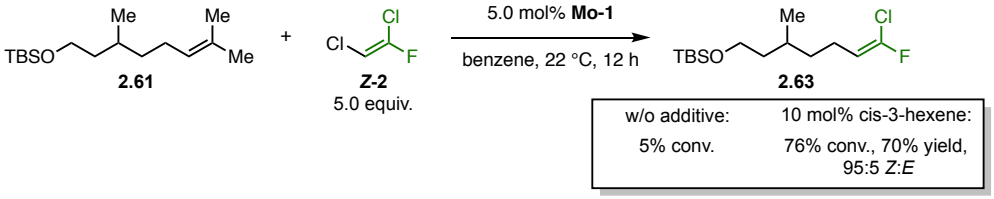


Under otherwise identical conditions, for reactions conducted with **Mo-7**, bearing the same aryloxide ligand as the **Mo-6**, we observed 75% conversion to **2.62** but with reduced stereoselectivity (87:13 *Z*:*E*). Encouraged by this result, we decided to investigate other MAP complexes with more sterically demanding aryloxide ligands. With increasing steric hinderance (**Mo-8** < **Mo-1** < **Mo-9**), we saw an improvement in reaction efficiency and stereoselectivity, with up to 65% formation of **2.62** in >98:2 *Z*:*E* (Scheme 2.2.4). The

higher efficiency and selectivity are likely due to the increased steric hinderance of the aryloxide ligands, which leads to increased stereodifferentiation during metallacyclobutane (mcb) formation and reduced bimolecular decomposition of the catalyst.

To boost reaction efficiency, we investigated the effect of an alkene additive, presumed to accelerate catalyst initiation.[62] However, unlike the reactions involving chloro-fluoro alkenes, addition of 1,2-dichloroethylene enhanced efficiency only marginally. This is in stark contrast to the cross-metathesis involving chloro-fluoro alkenes, where an additive was required to generate appreciable conversion and formation of the desired chloro fluoro olefin **2.63** (Scheme 2.2.5).

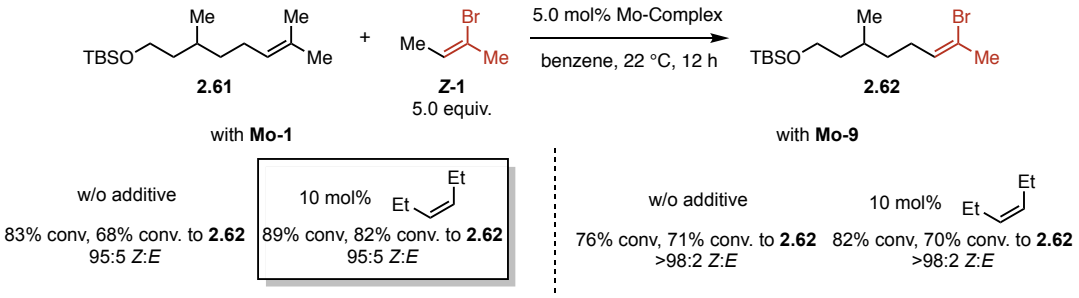
Scheme 2.2.5. Influence of Olefin Additive on Cross-Metathesis of Chloro-Fluoro Alkenes



Although transformations conducted with **Mo-1** and **Mo-9** led to slightly lower conversions than **Mo-6**, we focused our optimization efforts on MAP complexes due to their balance of catalyst efficiency and *Z*:*E* selectivity. When we further investigated disubstituted alkene additives, we determined addition *cis*-3-hexene to be optimal (vs. 1,2-dichloroethylene or bis-allylether). Moreover, we found that product formation could be increased with 5.0 equivalents of ***Z*-1**, resulting in up to 70% (**Mo-1**) and 82% formation of **2.62** (**Mo-9**), respectively (Scheme 2.2.6).

(62) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463–473.

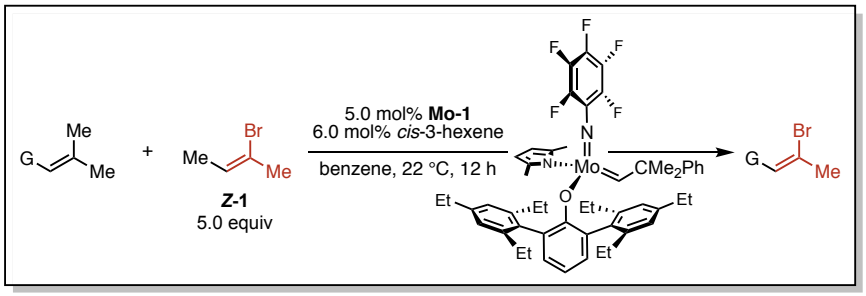
Scheme 2.2.6. Results with MAP complexes, 5.0 equivalents ***Z*-1**, and *cis*-3-hexene

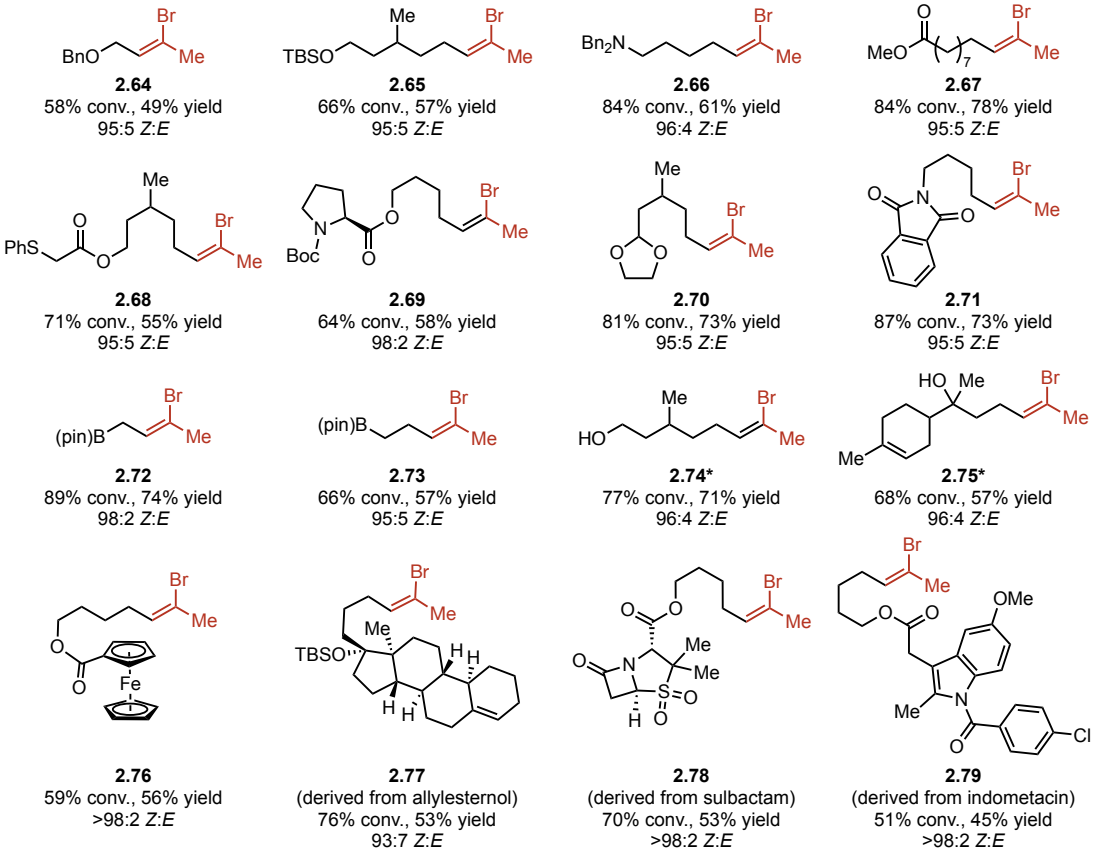


2.3 Synthesis of Z- and E-Trisubstituted Alkenyl Bromides

Next, we aimed to explore the scope of this transformation by employing olefins that bear different functionalities (Scheme 2.3.1).

Scheme 2.3.1. Substrate Scope for CM of Trisubstituted Alkenes with ***Z*-1**





*Traceless masking procedure of hydroxy group with HB(pin) was employed.

We found that a variety of functional groups are tolerated, affording the target *Z*-alkenyl bromides in 49–78% yield and 93:7 to >98:2 *Z*:*E* ratio. The list includes ethers (**2.64**, **2.65**), tertiary amines (**2.66**), esters (**2.67**, **2.68**), amides (**2.69**), acetals (**2.70**), and imides (**2.71**). Moreover, we were delighted to find that allylic (**2.72**) and homoallylic (**2.73**) boronates could be obtained in useful yields and high stereoselectivity (98:2 and 96:4 *Z*:*E*, respectively), as these unsaturated organoboron compounds may be used in

subsequent diastereo- and/or enantioselective transformations.[63] In many instances, Mo complexes are unstable in the presence of protic solvents and compounds that bear hydroxy groups. The issue was addressed by in situ masking these moieties as boronic esters with HB(pin),[64] allowing natural feedstock chemicals bearing free alcohol groups, such as citronellol (**2.74**) and α-bisabolol (**2.75**), to be used directly. Finally, the method is applicable to the late-stage functionalization of drug-derivatives, represented by **2.77** (derived from allylesternol), **2.78** (derived from sulbactam), and **2.79** (derived from indomethacin).

We then turned our attention to the synthesis of the corresponding *E* isomers (Scheme 2.3.2). Under otherwise identical conditions and through the use of ***E*-1** instead of ***Z*-1**, *E*-trisubstituted alkenyl bromides were obtained in 46–80% yield and 89:11 to >98:2 *E*:*Z* ratio. Functional group compatibility was similarly broad, allowing for ethers (**2.80**, **2.81**), aryl-containing substrates (**2.82**–**2.83**), acetals (**2.85**, **2.86**), esters (**2.87**), and imides (**2.88**) to be converted to the desired trisubstituted alkenyl bromides. Allylic (**2.89**) and homoallylic (**2.90**) boronates could be obtained as well. Through in situ protection of the alcohol group, α-bisabolol could be converted to *E* alkenyl bromide **2.91** without the need for a separate protection/ deprotection sequence. Finally, the method is applicable to the late-stage functionalization of complex molecules, such as **2.92** (derived from D-glucose), **2.93** (derived from sulbactam), **2.94** (derived from indomethacin), and **2.95** (derived from allylestrenol) with similar yields and stereoselectivity as for the *Z* isomer.

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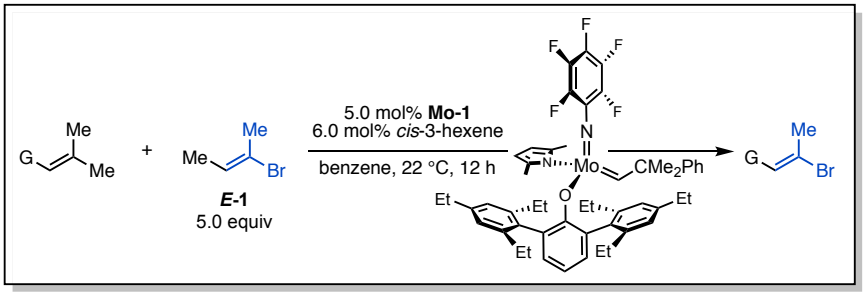
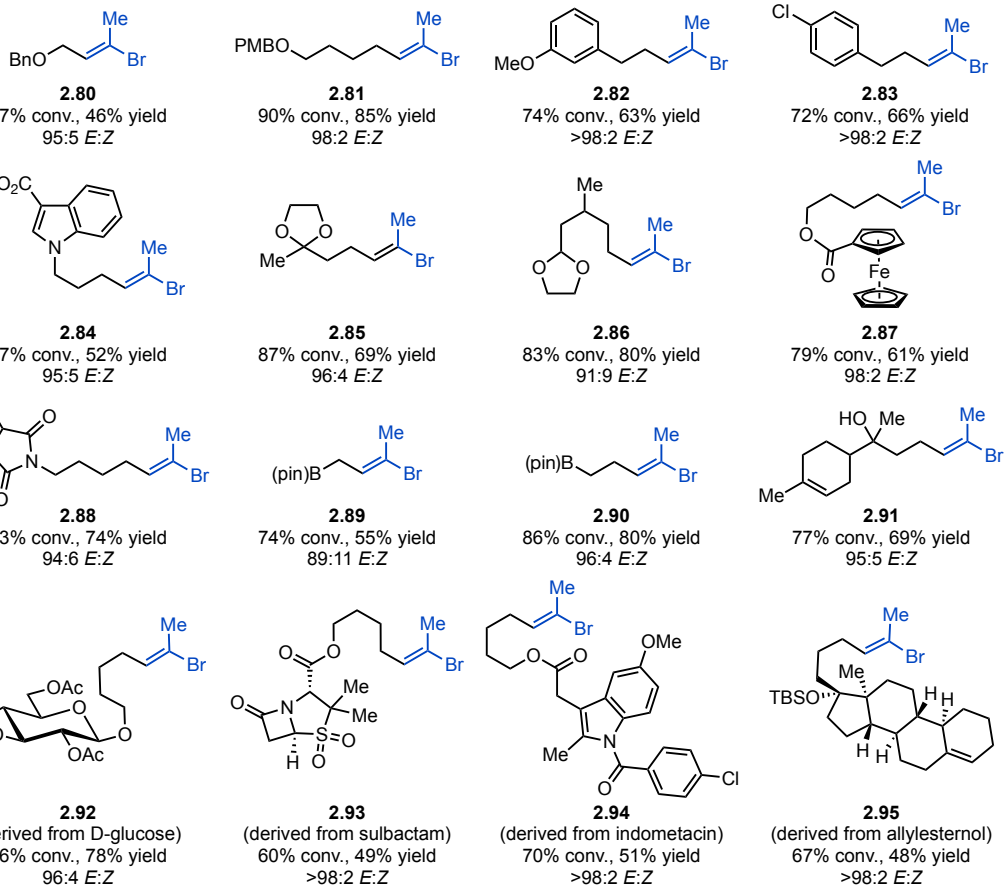
(63) (a) Morrison, R. J.; Van Der Mei, F. W.; Romiti, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2020**, *142*, 436–447. (b) Van Der Mei, F. W.; Qin, C.; Morrison, R. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 9053–9065.

(64) Mu, Y.; Nguyen, T. T.; van der Mei, F. W.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 5365–5370.

Scheme 2.3.2. Substrate Scope for CM of Trisubstituted Alkenes with ***E*-1**





2.80
67% conv., 46% yield
95:5 *E*:*Z*

2.81
90% conv., 85% yield
98:2 *E*:*Z*

2.82
74% conv., 63% yield
>98:2 *E*:*Z*

2.83
72% conv., 66% yield
>98:2 *E*:*Z*

2.84
67% conv., 52% yield
95:5 *E*:*Z*

2.85
87% conv., 69% yield
96:4 *E*:*Z*

2.86
83% conv., 80% yield
91:9 *E*:*Z*

2.87
79% conv., 61% yield
98:2 *E*:*Z*

2.88
83% conv., 74% yield
94:6 *E*:*Z*

2.89
74% conv., 55% yield
89:11 *E*:*Z*

2.90
86% conv., 80% yield
96:4 *E*:*Z*

2.91
77% conv., 69% yield
95:5 *E*:*Z*

2.92
(derived from D-glucose)
86% conv., 78% yield
96:4 *E*:*Z*

2.93
(derived from sulbactam)
60% conv., 49% yield
>98:2 *E*:*Z*

2.94
(derived from indometacin)
70% conv., 51% yield
>98:2 *E*:*Z*

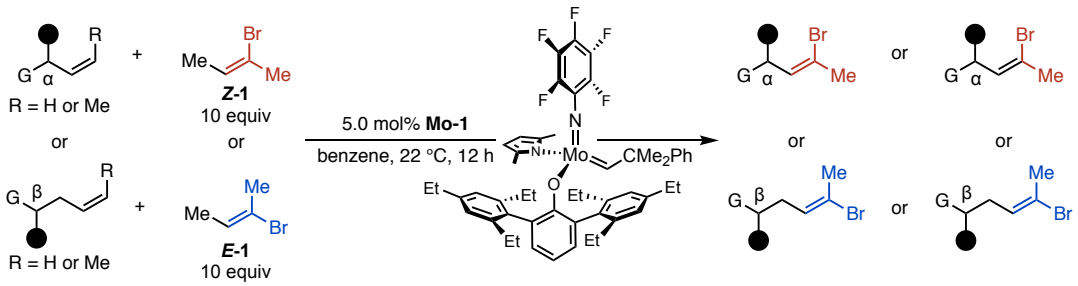
2.95
(derived from allylesternol)
67% conv., 48% yield
>98:2 *E*:*Z*

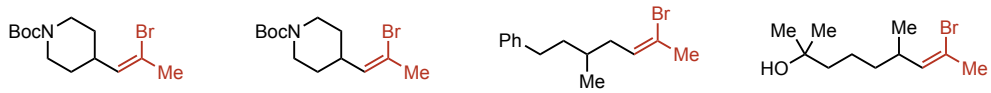
*Traceless masking procedure of hydroxy group with HB(pin) was employed.

A challenging class of substrates for olefin metathesis reactions are α-, and/ or β-branched alkenes, a problem further exacerbated by the inherently lower reactivity of trisubstituted alkenes. These compounds are often afforded in much lower yields compared to their unhindered counterparts, probably on account of the increased steric repulsion in the mcb, leading to a higher energy intermediate.

When trisubstituted alkenes with a sizeable substituent in the α-, or β-position were subjected to our standard reaction conditions, minimal conversion was detected (<10% consumption of starting material, Scheme 2.3.4). To improve the efficiency, we investigated the more reactive terminal and disubstituted variants.

Scheme 2.3.4. Substrate Scope of α-, and/ or β-Branched Alkenyl Bromides



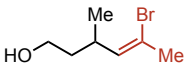


2.96
(from trisubstituted alkene)
<10% conv.

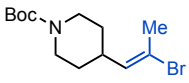
2.96
(from *Z*-alkene)
>98% conv., 60% yield
98:2 *Z*:*E*

2.97
(from *Z*-alkene)
>98% conv., 46% yield
94:6 *Z*:*E*

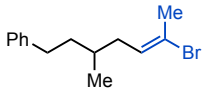
2.98*
(from terminal alkene)
63% conv., 44% yield
>98:2 *Z*:*E*



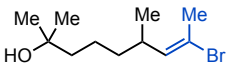
2.99*
(from *Z*-alkene)
95% conv., 43% yield
>98:2 *Z*:*E*



2.100
(from *Z*-alkene)
>98% conv., 38% yield
>98:2 *E*:*Z*



2.101
(from *Z*-alkene)
>98% conv., 46% yield
90:10 *E*:*Z*



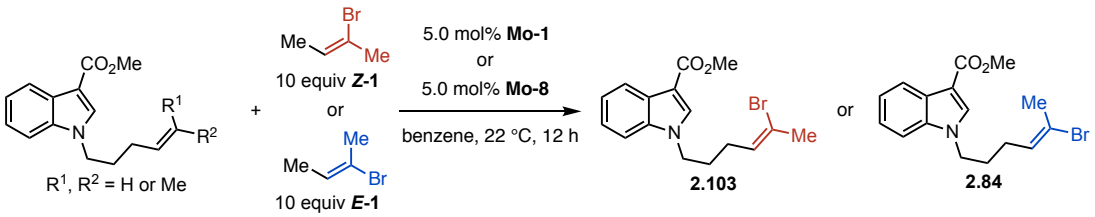
2.102*
(from terminal alkene)
68% conv., 29% yield
96:4 *E*:*Z*

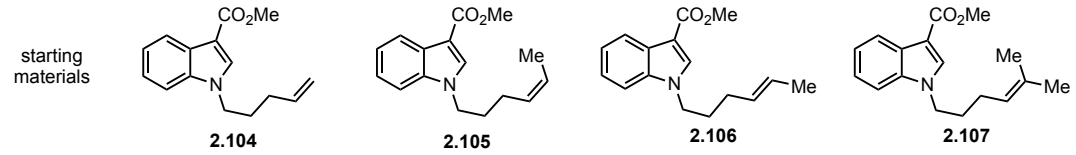
*Traceless masking procedure of hydroxy group with HB(pin) was employed.

Indeed, when the corresponding terminal, or *Z*-methyl-disubstituted alkenes were employed, appreciable amounts of conversion and product formation were observed (29–60% yield and 90:10 to >98:2 stereoselectivity). Examples include *N*-boc-protected piperidines (**2.96** and **2.100**) and β-methyl branched alkenes (**2.97** and **2.101**). As mentioned previously, free hydroxy groups could be masked through in situ masking with HB(pin), allowing for renewable feedstocks such as dihydromyrcenol to be converted to the respective alkenyl bromides (**2.98** and **2.102**).

As disubstituted alkenes were suitable starting materials in the case of sterically encumbered olefins, we wondered if the method might be expanded to unhindered terminal and disubstituted alkenes as well. In order to compare reaction efficiency and selectivity as a function of alkene substitution, we synthesized **3.43**–**3.46** and investigated their cross-metathesis with ***Z*-1** and ***E*-1** (Scheme 2.3.5).

Scheme 2.3.5. Comparison of Differently Substituted Alkene Starting Materials





with ***Z*-1** and **Mo-1**	80% conv., 54% yield >98:2 *Z*:*E*	>98% conv., 80% yield 97:3 *Z*:*E*	>98% conv., 65% yield 96:4 *Z*:*E*	66% conv., 61% yield 98:2 *Z*:*E*
with ***E*-1** and **Mo-8**	90% conv., 58% yield 6:94 *Z*:*E*	>98% conv., 81% yield 5:95 *Z*:*E*	>98% conv., 81% yield 5:95 *Z*:*E*	67% conv., 63% yield 5:95 *Z*:*E*

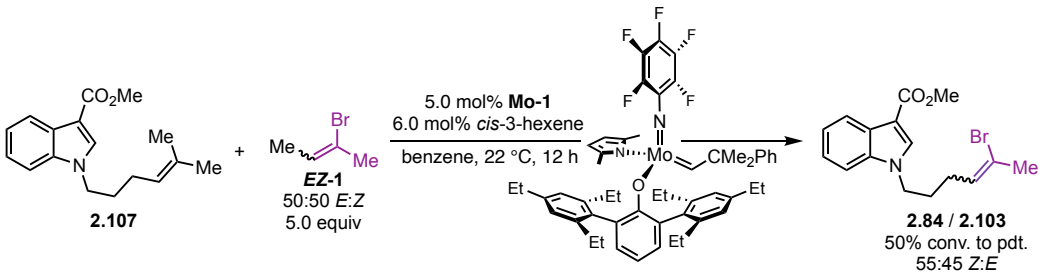
Reactions with *Z*-methyl (**2.105**) or *E*-methyl disubstituted (**2.106**) alkenes proceeded to full conversion, affording the desired *Z*- (**2.103**) or *E*-trisubstituted alkenyl bromides (**2.84**) in 65–81% yield and 95:5 to 97:3 stereoisomeric purity. The discrepancy between overall conversion (i.e., consumption of the non-halogenated alkene) and yield is on account of the formation of homocoupling byproducts. It warrants mention that for the *E*-alkenyl bromides, **Mo-8** was found to be the optimal catalyst. When **Mo-1** was used instead, stereoselectivity was diminished (<81:29 *E*:*Z*) for terminal and methyl-disubstituted alkene starting materials (for further analysis, see below).

When terminal alkene **2.104** was used, the corresponding *Z*- (**2.103**) and *E*-trisubstituted alkenyl bromides (**2.84**) were generated with similar stereoselectivity, albeit

in slightly lower yield. This is probably due to methylidene formation, resulting from the use of a terminal olefin and the associated instability thereof.[65] In the case of trisubstituted alkene **2.107**, no significant homocoupling byproduct was detected (<10%), regardless of the cross-partner isomer (***Z*-1** or ***E*-1**) used. While the yields obtained with trisubstituted alkene starting materials are slightly lower compared to the disubstituted variants, only 5.0 equivalents ***Z*-1** are required (vs. 10 equivalents of ***Z*-1** or ***E*-1** in the case of disubstituted or terminal alkene starting materials). Moreover, in the case of less polar starting materials, separation of homocoupling byproducts and desired product can be an issue.

Next, we sought to investigate whether cross-metathesis with ***Z*-1** or ***E*-1** is more facile. When a cross-metathesis competition experiment was conducted with a 1:1 mixture of ***Z*-1** and ***E*-1** (***EZ*-1**), a 55:45 *Z*:*E* ratio of the corresponding products **2.103** and **2.84** was obtained. Given that at thermodynamic equilibrium, the ratio of ***Z*-1** and ***E*-1** is 86:17 *Z*:*E*,[66] it is likely that the cross-metathesis of both isomers proceeds at comparable rates.

Scheme 2.3.6. Competition of Cross-Metathesis with ***Z*-1** and ***E*-1**

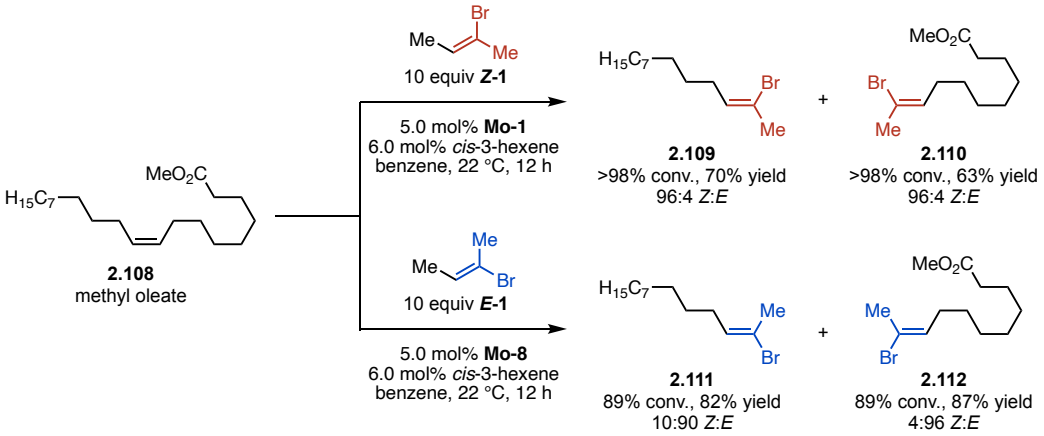


(65) (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633. (b) Hoveyda, A. H.; Liu, Z.; Qin, C.; Koengeter, T.; Mu, Y. *Angew. Chem. Int. Ed.* **2020**, *59*, 22324–22348.

(66) (a) Dreiding, A. S.; Pratt, R. J. *J. Am. Chem. Soc.* **1954**, *76*, 1902–1906. (b) Lepingle, M. *Bull. Chem. Soc.* **1926**, *39*, 741.

We were curious whether disubstituted olefins bearing longer alkyl substituents might be utilized as well. This motif is commonly encountered in fatty acids and esters of variable lengths, which are cheap and abundant renewable feedstock materials.[67] If these

Scheme 2.3.7. Cross-Metathesis of Methyl Oleate with ***Z*-1** or ***E*-1**



could serve as starting materials for the cross-metathesis with ***Z*-1** and ***E*-1**, it would allow for the synthesis of useful building blocks or structural modifications of naturally occurring fatty acids. We thus probed the reaction involving methyl oleate with ***Z*-1** and ***E*-1** under optimal conditions (Scheme 2.3.7).

The cross-metathesis of methyl oleate (**2.108**) and ***Z*-1** proceeded to full conversion, and **2.109** and **2.110** were isolated in 63% and 70% yield, respectively (96:4 *Z*:*E* for both products). When ***E*-1** was used, comparable amounts of conversion and yield were obtained (89% conv., 82–87% yield), but with diminished stereocontrol (80:20 *E*:*Z*), similar to the methyl-disubstituted substrates. Our first hypothesis was that maybe akin to the recently reported macrocyclic ring-closing metatheses (MRCM),[68] the generation of *Z*- or *E*-butene byproducts could be the culprit. However, application of 500 Torr vacuum did not improve

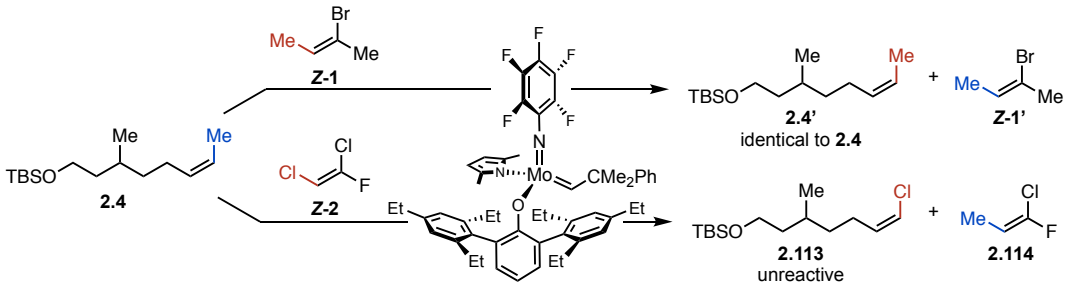
(67) Metzger, J. O. *Eur. J. Lipid Sci. Technol.* **2009**, *111*, 865–876.

(68) Mu, Y.; Hartrampf, F. W. W.; Yu, E. C.; Lounsbury, K. E.; Schrock, R. R.; Romiti, F.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 640–649.

the selectivity substantially (65% conv., 84:16 *E*:*Z*). We therefore turned our attention to a less sterically encumbered catalyst. Under otherwise identical conditions, the use of **Mo-8** resulted in 89% conversion, and **2.111** and **2.112** were isolated in 82% and 87% yield, and 90:10 and 96:4 *E*:*Z*, respectively.

It merits note that unlike reaction with ***Z*-1** or ***E*-1**, the related cross-metathesis affording trisubstituted chloro fluoro alkenes proceeded with considerably lower efficiency when non-trisubstituted alkene starting materials were used.[69] The key difference appears to be the fate of the alkene substituents in the case of cross-metathesis with undesired regiochemistry (Scheme 2.3.8). For the transofrmation with ***Z*-2**, the byproduct is a *Z*-chloro disubstituted olefin (**2.113**) that appears to be less reactive than starting material **2.4**, whereas in the case of reaction with ***Z*-1**, the starting materials (**2.4**, ***Z*-1)** and products (**2.4'**, ***Z*-1'**) are identical (i.e., a non-productive metathesis event).

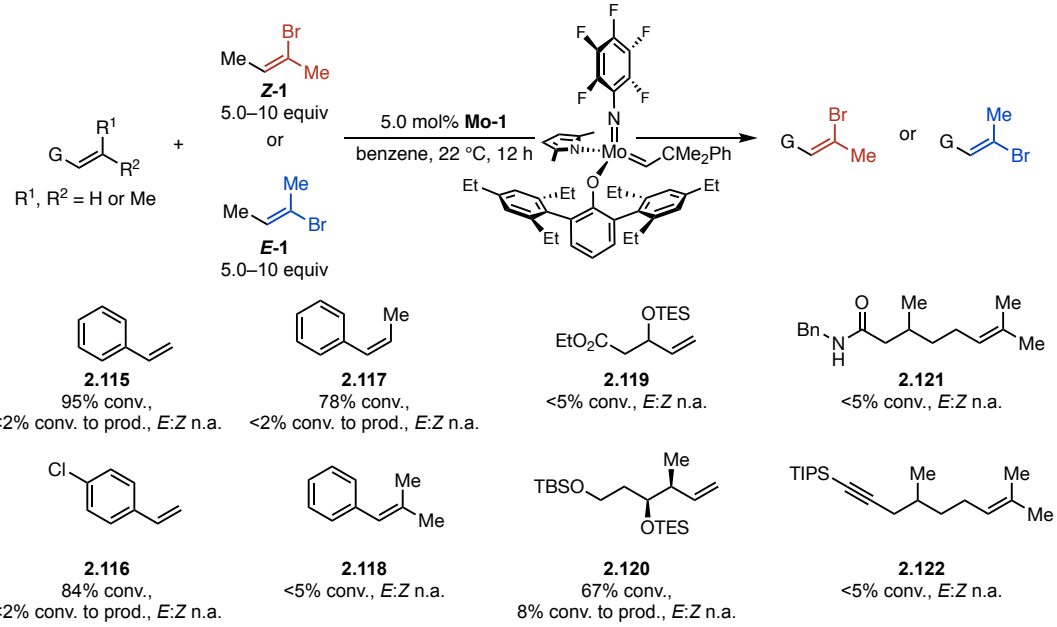
Scheme 2.3.8. Comparison of Cross-Metatheses that Proceed with Undesired Regiochemistry



(69) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463–473.

Throughout, we encountered functional groups and motifs that were not compatible for reactions with ***Z*-1** or ***E*-1** (Scheme 2.3.9). For instance, cross-metathesis with styrene (**2.115**) led to no product formation whatsoever, and only homocoupled byproduct was formed. To minimize homocoupling, we investigated styrenes with electron-withdrawing groups (**2.116**) as well as those bearing a methyl-disubstituted (**2.117**) and a 1,1-dimethyl trisubstituted olefin (**2.118**) instead. Still, even in the case of less reactive **2.116** and disubstituted **2.117**, homocoupling byproducts were formed solely. When trisubstituted

Scheme 2.3.8. Substrates Not Suitable for Cross-Metathesis with Mo Complexes



2.118 was used, there was no conversion, probably because of the increase in steric pressure cause be the trisubstituted alkene, akin to when an α-branched trisubstituted alkene was used (c.f. Scheme 2.3.5).

A similar observation was made in the case of allylic ether **2.119**; there was no consumption of starting material when subjected to previously optimal reaction conditions for α-, or β-branched substrates. Whereas there was some substrate consumption in the reactions with homoallylic ether **2.120**, there was no product formation, again, probably on

account of the steric repulsion stemming from a combination of α- and β-branching. Finally, there was no detectable transformation with secondary amide **2.121** and internal alkyne **2.122** under the standard reaction conditions. While secondary amides,[70] and internal alkynes[71] are tolerated in cross-metatheses with disubstituted olefins, it appears that competitive decomposition pathways dominate when trisubstituted alkenes are involved.

2.4 Formal Synthesis of Phomactin A

Phomactins are a family of terpenoids isolated from the marine fungi and have garnered the attention of researchers due to their pharmacological activity as potent platelet activating factor (PAF) antagonists.[72] The first member of the family, phomactin A (**2.123**), was isolated and characterized in 1991 and has been the subject of several partial and total syntheses.[73] The first total synthesis of phomactin A was accomplished by Pattenden and co-workers in 2002,[74] closely followed by the first non-racemic synthesis by Halcomb *et al.* in 2003.[75] Since then, the research teams of Wulff,[76] Hsung,[77] and Sarpong[78] have each reported alternative routes leading to this natural product.

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(70) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.

(71) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80–85.

(72) For reviews on phomactins, see: (a) Goldring, W. P. D.; Pattenden, G. *Acc. Chem. Res.* **2006**, *39*, 354–361. (b) Ciesielski, J.; Frontier, A. *Org. Prep. Proced. Int.* **2014**, *46*, 214–251.

(73) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463–5464.

(74) Goldring, W. P. D.; Pattenden, G. *Chem. Commun.* **2002**, *11*, 1736–1737.

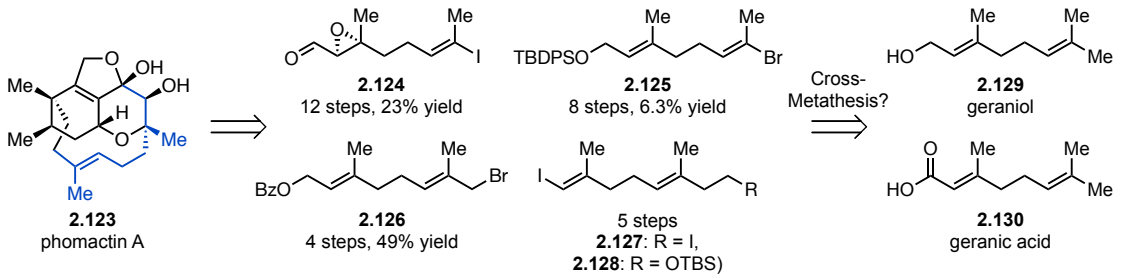
(75) Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712–1713.

(76) Huang, J.; Wu, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 13366–13367.

(77) Tang, Y.; Cole, K. P.; Buchanan, G. S.; Li, G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 1591–1594.

(78) Kuroda, Y.; Nicacio, K. J.; da Silva-Jr, I. A.; Leger, P. R.; Chang, S.; Gubiani, J. R.; Deflon, V. M.; Nagashima, N.; Rode, A.; Blackford, K.; Ferreira, A. G.; Sette, L. D.; Williams, D. E.; Andersen, R. J.; Jancar, S.; Berlinck, R. G. S.; Sarpong, R. *Nat. Chem.* **2018**, *10*, 938–945.

Scheme 2.4.1. Retrosynthesis Analysis of Unsaturated Side Chain of Phomactin A

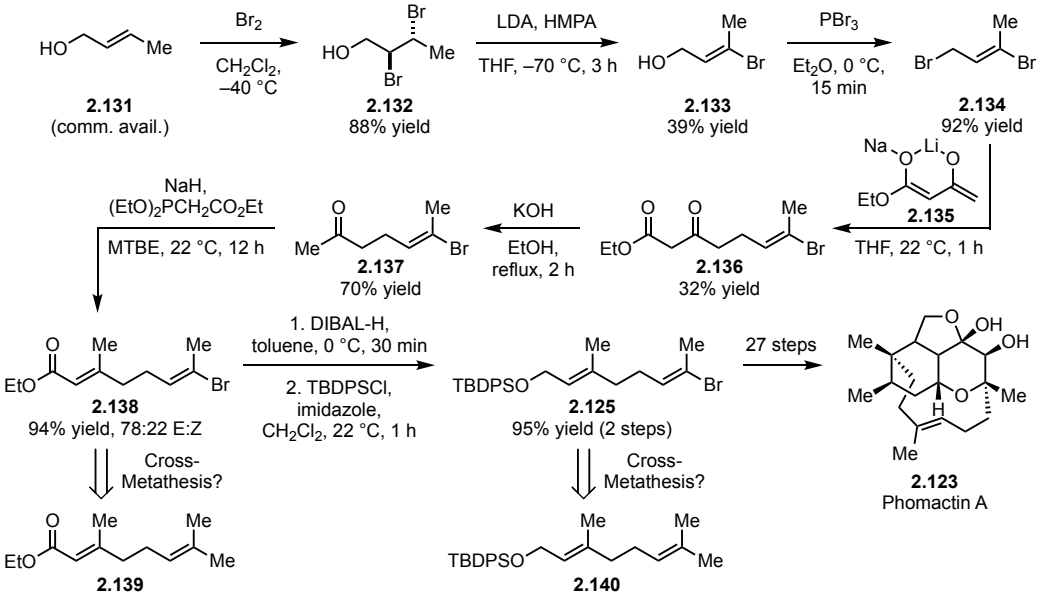


Although each synthesis employs a slightly different intermediate for the construction of the unsaturated side chain (highlighted in blue, Scheme 2.4.1), controlling the olefin stereochemistry proved to be one of the particularly challenging issues. The result was extended sequences of transformations that led to diminution in overall efficiency.

A revealing example may be found in the route disclosed by Hsung and co-workers (Scheme 2.4.2).[79] Their plan was to synthesize the *E*-trisubstituted alkene moiety through incorporation of a side chain that bears the required stereodefined trisubstituted alkene (**2.125**). Preparation of the requisite side chain (**2.125**) required eight steps and was accomplished in 6.3% overall yield. The low overall yield is partly because the stereodefined alkene was generated by an elimination reaction involving dibromide **2.132**, a somewhat nonselective process that necessitates separation of alkenyl bromide isomers.

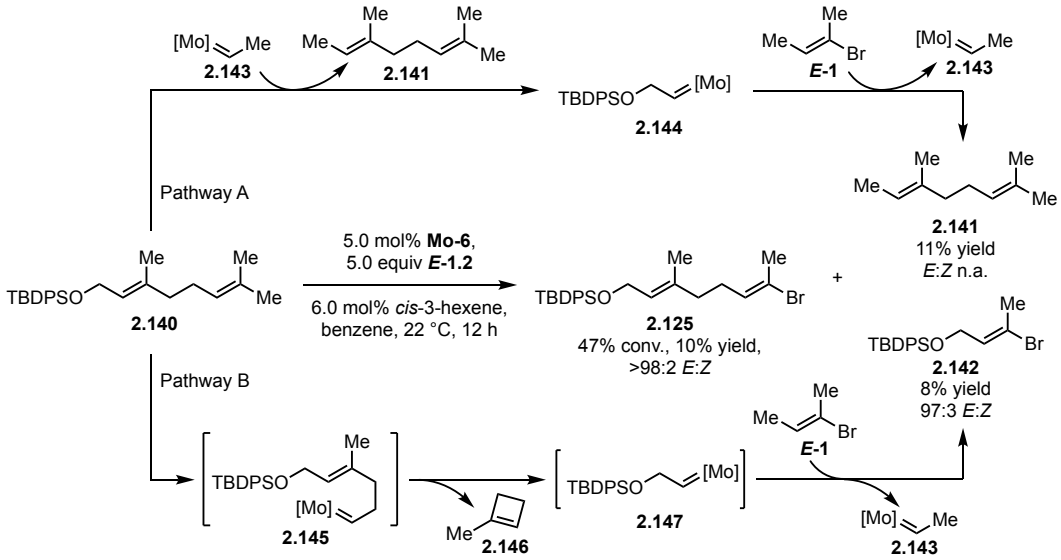
(79) Buchanan, G. S.; Cole, K. P.; Li, G.; Tang, Y.; You, L. F.; Hsung, R. P. *Tetrahedron* **2011**, *67*, 10105–10118.

Scheme 2.4.2. Reported Route for the Synthesis of the Unsaturated Side Chain of Phomactin A



Intermediate **2.125** closely resembles TBDPS-geraniol (**2.140**), with the only difference being that one methyl group has been replaced by a bromine substituent. This led us to ponder the possibility of applying cross-metathesis to preparation of this key intermediate for phomactin A synthesis.

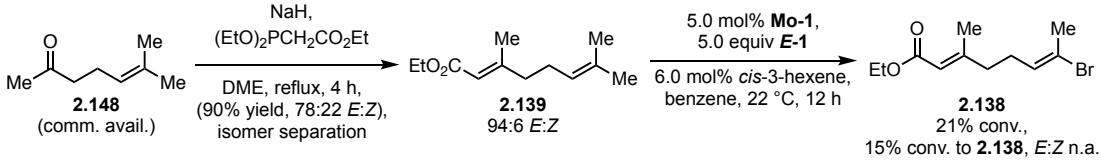
Scheme 2.4.3. Cross-Metathesis of a Silyl-Protected Geraniol and Mechanistic Analysis



When we analyzed the unpurified mixture from the reaction ofbetween **2.140** and ***E*-1**, we observed 47% consumption of **2.140**, but only 17% formation of **2.125** and significant side-product formation (**2.141** and **2.142)**. Two possible pathways might account for the formation of these byproducts (Scheme 2.4.3). Pathway A: Competitive reaction of the undesired double bond with the Mo-ethylidene (**2.143**) (forming **2.141**) followed by cross-metathesis with ***E*-1** (forming **2.142**). This would suggest an inherent lack of chemoselectivity of the Mo-alkylidene. Pathway B: Initiation of Mo-ethylidene **2.143** into the desired dimethyl trisubstituted double bond (forming **2.145**) followed by ring-closing metathesis (forming **4.26**), and subsequent cross-metathesis with ***E*-1** (forming **2.146**). Since **2.141** could be determined to be one of the formed byproducts, and the presence of **2.146** was detected by mass spectrometry, both pathways are likely operative to some degree.

To discourage reaction at the undesired alkene site, we surmised that the introduction of a carbonyl group in the allylic position may electronically deactivate the double bond. Cross-metathesis of **2.139** (synthesized in one step from **2.148** with subsequent separation of isomers through silica gel chromatography) under standard reaction conditions led to 21% conversion and 15% formation of **2.138** (Scheme 2.4.4).

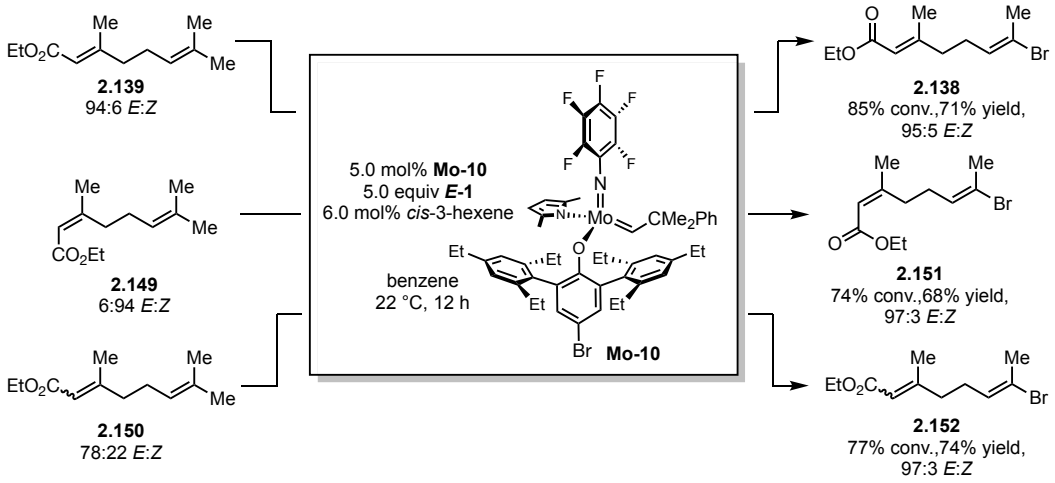
Scheme 2.4.4. Synthesis and Cross-Metathesis of *E*-Ethyl Geranate **2.139**



While the reaction exhibited poor conversion, no olefinic side-product could be detected in the crude reaction mixture. To improve efficiency, we prepared **Mo-10** (a derivative of **Mo-1**), bearing a *para*-bromoaryloxide ligand. These seemingly small

modifications can impact turnover frequency of the corresponding Mo catalyst.[80] Indeed, reactions conducted in the presence of **Mo-10** afforded alkenyl bromides **2.138** and **2.151** in 71% and 68% yield, and 95:5 and 97:3 *E*:*Z*, respectively (Scheme 2.4.5).

Scheme 2.4.5. Cross-Metathesis of *Z* and *E* Ethyl Geranate



In brief, we were able to access the same intermediate (**2.138**) as previously employed in the total synthesis of phomactin A by Hsung *et al*. Using a different disconnection, we were able to reduce the overall steps from seven to two and increase the overall yield to 61% and 70% (c.f. 0.7% previously), depending on which starting material isomer was employed. As for the synthesis of phomactin A, however, the stereochemistry of the enoate starting material bond is inconsequential, rendering the separation of isomers prior to cross-metathesis unnecessary. Cross-metathesis of isomeric mixtures of starting material (**2.150**, 78:22 *E*:*Z*) resulted in comparable yield and stereoselectivity, allowing **2.152** to be isolated in 74% yield and 97:3 *E*:*Z* ratio (with regard to the trisubstituted alkenyl bromide).

(80) Ferreira, M. A. B.; De Jesus Silva, J.; Grosslight, S.; Fedorov, A.; Sigman, M. S.; Copéret, C. *J. Am. Chem. Soc.* **2019**, *141*, 10788–10800.

2.5 Conclusions

We have introduced a general and widely applicable strategy for the synthesis of *E*- and *Z*-trisubstituted alkenyl bromides through cross-metathesis. The reaction is applicable to terminal, disubstituted, and trisubstituted olefins bearing a variety of functional groups including alkenes with α-, or β-branches. The requisite stereodefined cross-partners, *E*- and *Z*-2-bromo-2-butene are commercially available and can be synthesized with ease in one step from abundant starting materials. This represents a notable improvement over our previous approach, where the non-halogenated alkene starting material had to be prepared through cross-coupling in high stereochemical purity to ensure high stereoretention in the subsequent cross-metathesis. Catalysts derived from Mo monoaryloxide pyrrolide complexes, some of which are commercially available, are optimal for this transformation. The applicability of the approach is underscored through the formal synthesis of phomactin A with improved overall yield and step count.

2.6 Experimental Section

2.6.1 General

Unless otherwise noted, transformations were performed with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum line techniques. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz), or 600 (600MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm, C_6D_6: δ 7.16 ppm). Data are reported as follows:

chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, C_6D_6: δ 128.00 ppm). ^{19}F NMR spectra were recorded on a Varian Unity INOVA 400 (376 MHz) spectrometer. ^{31}P NMR spectra were recorded on a Varian Unity INOVA 400 (162 MHz) spectrometer. ^{11}B NMR spectra were recorded on a Varian Unity INOVA 400 (128 MHz) or 500 (160 MHz) spectrometer. High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility. Values for *E*:*Z* ratios of products were determined by ^1H NMR analysis of unpurified mixtures. Enantiomeric ratios were determined by GLC analysis (gas liquid chromatography) with an Agilent chromatograph (Alltech Associated Chiral dex CD-BDM column (30 m x 0.25 mm)) and by high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Regis Technologies Inc (*R*,*R*)-Whelk-O1 (4.6 x 250 mm)) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter. Melting points were determined using a Thomas Hoover Uni-melt capillary melting point apparatus.

2.6.2 Solvents

Solvents (CH_2Cl_2, Et_2O, pentane, benzene and toluene) were purified under a positive pressure of dry argon gas by an Innovative Technologies purification system. Tetrahydrofuran (Sigma-Aldrich) and 1,2-dimethoxyethane (Acros Organics) were purified by distillation from sodium benzophenone ketyl immediately prior to use unless

specified otherwise. All purification procedures of CM products were carried out with reagent grade solvents (purchased from Fisher) under bench-top conditions unless indicated otherwise.

2.6.3 Reagents and Substrates

Starting materials of cross-metathesis reactions are denoted with an apostrophe (’). 1-chloro-4-vinylbenzene (**2.116**, Sigma-Aldrich), (*Z*)-prop-1-en-1-ylbenzene (**2.117**, TCI), *meso*-2,3-Dibromobutane (Sigma Aldrich), 2,6-dimethyloct-7-en-2-ol (**2.98’** and **2.102’**, Sigma-Aldrich), 3,7-dimethyloct-6-en-1-ol (**2.74’**, TCI), 1,2-epoxy-9-decene (TCI), 6-methyl-2-(4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol (**2.75’** and **2.91’**, TCI), 3-methylcyclohex-2-en-1-one (Combi-Blocks), methyl oleate (**2.108**, Sigma-Aldrich), styrene (**2.115**, Sigma-Adlrich), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Oakwood), 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane (Santa Cruz Biotechnology) were distilled over CaH_2 prior to use.

(((3-methylbut-2-en-1-yl)oxy)methyl)benzene (**2.64’** and **2.80’** from 3-methyl-2-butene-1-ol),[81] *tert*-butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane (**2.65‘**, from citronellol),[82] *N*,*N*-dibenzyl-6-methylhept-5-en-1-amine (**2.66’**, from 7-iodo-2-methylhept-2-ene), [83] methyl-11-methyldodec-10-enoate (**2.67’**, from methyl undec-10-enoate), [84] 3,7-dimethyloct-6-en-1-yl 2-(phenylthio)acetate (**2.68’**, from 2-(phenylthio)acetic acid),[85] 1-(*tert*-butyl) 2-(6-methylhept-5-en-1-yl) (*S*)-pyrrolidine-1,2-dicarboxylate (**2.69’**, from

(81) Bourque, L. E.; Cleary, P. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 12602–12603.
(82) Lin, L.; Romano, C.; Mazet, C. *J. Am. Chem. Soc.* **2016**, *138*, 10344–10350.
(83) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 5000–5003.
(84) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939–1942.
(85) Lipshutz, B. H.; Huang, S.; Leong, W. W. Y.; Zhong, G.; Isley, N. A. *J. Am. Chem. Soc.* **2012**, *134*, 19985–19988.

(*tert*-butoxycarbonyl)-*L*-proline), [86] 2-(2,6-dimethylhept-5-en-1-yl)-1,3-dioxolane (**2.70'** and **2.86'**, from citronellal),[87] 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione (**2.71'** and **2.88'**, from phtalimide), [88] 4,4,5,5-Tetramethyl-2-(3-methylbut-2-en-1-yl)-1,3,2-dioxaborolane (**2.72'** and **2.89'**, from prenyl chloride), [89] 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane (**2.73'** and **2.90'**, from 5-chloro-2-methylpent-2-ene),[88] 6-methylhept-5-en-1-yl ferrocenoate (**2.76'** and **2.87'** from ferrocenecarboxylic acid), [90] *tert*-butyldimethyl(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-17-(5-methylhex-4-en-1-yl)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)oxy)silane (**2.77'** and **2.95'**, from allylestrenol),[91] 6-methylhept-5-en-1-yl (2*R*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide (**2.78'** and **2.93'**, from sulbactam),[92] 6-methylhept-5-en-1-yl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (**2.79'** and **2.94'**, from indomethacin),[91] 1-methoxy-4-(((6-methylhept-5-en-1-yl)oxy)methyl)benzene (**2.81'**, from 6-methylhept-5-en-1-ol), [93] 1-methoxy-3-(4-methylpent-3-en-1-yl)benzene (**2.82'**, from 1-methoxy-3-vinylbenzene),[91] 1-chloro-4-(4-methylpent-3-en-1-yl)benzene (**2.83'**, from 1-chloro-4-vinylbenzene),[91] methyl 1-(5-methylhex-4-en-1-yl)-1*H*-indole-3-carboxylate (**2.84'**, from methyl 1*H*-indole-3-carboxylate, [94] 2-methyl-2-(4-methylpent-3-en-1-yl)-1,3-dioxolane (**2.85'**, from

(86) Enholm, J. E.; Low, T.; Cooper, D.; Ghivirija, I. *Tetrahedron* **2012**, *68*, 6920–6927.

(87) Zaghouani, M.; Kunz, C.; Guédon, L.; Blanchard, F.; Nay, B. *Chem. Eur. J.* **2016**, *22*, 15257–15260.

(88) Harned, A. M.; He, H. S.; Toy, P. H.; Flynn, D. L.; Hanson, P. R. *J. Am. Chem. Soc.* **2005**, *127*, 52–53.

(89) Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10642–10645.

(90) Xu, C.; Liu, Z.; Torker, S.; Shen, X.; Xu, D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 15640–15643.

(91) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

(92) Huang, H. M.; Bellotti, P.; Erchinger, J. E.; Paulisch, T. O.; Glorius, F. *J. Am. Chem. Soc.* **2022**, *144*, 1899–1909.

(93) Delcamp, J. H.; Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 8460–8463.

(94) Glaisyer, E. L.; Watt, M. S.; Booker-Milburn, K. I. *Org. Lett.* **2018**, *20*, 5877–5880.

6-methylhept-5-en-2-one),[95] (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-((6-methylhept-5-en-1-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyltriacetate (**2.92'**, from (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-bromotetrahydro-2*H*-pyran-3,4,5-triyl triacetate, [96] *tert*-butyl (*Z*)-4-(prop-1-en-1-yl)piperidine-1-carboxylate (**2.96'** and **2.100'**, from 1-Boc-piperidine-4-carboxaldehyde), [97] (*Z*)-(3-methylhept-5-en-1-yl)benzene (**2.97'** and **2.101'**, from (4-methylpent-4-en-1-yl)benzene),[91] (*Z*)-3-methylhex-4-en-1-ol (**2.99'**, from 3-methyltetrahydrofuran-2-ol), [98] (2-methylprop-1-en-1-yl)benzene (**2.118**, from benzaldehyde),[99] ethyl 3-((triethylsilyl)oxy)pent-4-enoate (**2.119**, from ethyl acetate), [100] (*S*)-7-((*S*)-but-3-en-2-yl)-9,9-diethyl-2,2,3,3-tetramethyl-4,8-dioxa-3,9-disilaundecane (**2.120**, from propane-1,3-diol)[101], *N*-benzyl-3,7-dimethyloct-6-enamide (**2.121**, from 3,7-dimethyloct-6-enoic acid),[102] (4,8-dimethylnon-7-en-1-yn-1-yl)triisopropylsilane (**2.122**, from 3,7-dimethyloct-6-en-1-ol), [103] (*E*)-*tert*-butyl((3,7-dimethylocta-2,6-dien-1-yl)oxy) diphenylsilane (**2.140**, from (*E*)-3,7-dimethylocta-2,6-dien-1-ol), and ethyl (*E*)-3,7-dimethylocta-2,6-dienoate (**2.139**, **2.149**, and **2.150**, from 6-methylhept-5-en-2-one and subsequent chromatographical separation, if necessary)[104] were prepared according to reported procedures.

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(95) Pu, X.; Ma, D. *J. Org. Chem.* **2006**, *71*, 6562–6572.

(96) Marca, E.; Valero-Gonzalez, J.; Delso, I.; Tejero, T.; Hurtado-Guerrero, R.; Merino, P. *Carbohydr. Res.* **2013**, *382*, 9–18.

(97) Reichl, K. D.; Dunn, N. L.; Fastuca, N. J.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, *137*, 5292–5295.

(98) Lacharity, J. J.; Fournier, J.; Lu, P.; Mailyan, A. K.; Herrmann, A. T.; Zakarian, A. *J. Am. Chem. Soc.* **2017**, *139*, 13272–13275.

(99) Pitzer, L.; Sandfort, F.; Strieth-Kalthoff, F.; Glorius, F. *J. Am. Chem. Soc.* **2017**, *139*, 13652–13655.

(100) Kim, T.; Lee, S. I.; Kim, S.; Shim, S. Y.; Ryu, D. H. *Tetrahedron* **2019**, *75*, 130593.

(101) (a) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440–11441. (b) Fürst, R.; Rinner, U. *J. Org. Chem.* **2013**, *78*, 8748–8758.

(102) Brodney, M. A.; Padwa, A. *J. Org. Chem.* **1999**, *64*, 556–565.

(103) Brand, J.; Charpentier, J.; Waser, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9346–9349.

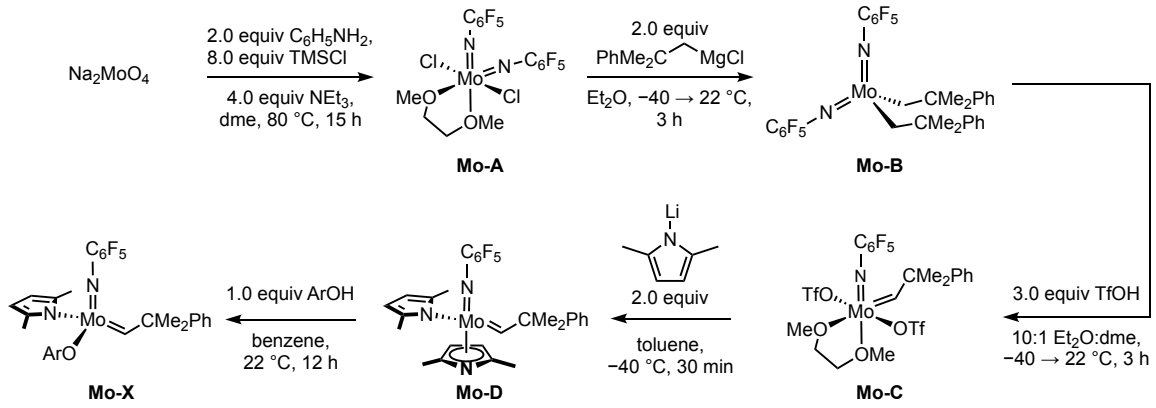
(104) Bhat, B.; Groziak, M. P.; Leonard, N. J. *J. Am. Chem. Soc.* **1990**, *112*, 4891–4897.

Acetobromo-α-D-glucose (Oakwood), 4-allyl-1,2-dimethoxybenzene (Aldrich), ammonium chloride (Fisher), bromine (Fisher), (*E*)-2-bromo-2-butene (Aldrich, Santa Cruz Biotechnology), (*Z*)-2-bromo-2-butene (Aldrich, Santa Cruz Biotechnology), (*tert*-butoxycarbonyl)-*L*-proline (Synthonix), 1-chloro-4-vinylbenzene (Alfa-Aesar), diisobutylaluminum hydride (Sigma-Aldrich), 4-(dimethylamino)pyridine (Oakwood), dimethylformamide (Acros Organics), 3,7-dimethyloct-6-enal (TCI), dimethyl sulfoxide (Acros Organics), D-(+)-glucose (Combi-Blocks), hydrochloric acid (Fisher), imidazole (Oakwood), isopropyltriphenylphosphonium iodide (Sigma-Aldrich), isoindoline-1,3-dione (Fluka), methyl-1*H*-indole-3-carboxylate (Oakwood), (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (Combi-Blocks), 4-phenylbutan-2-one (Sigma-Aldrich), (8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-allyl-13-methyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (Combi-Blocks), 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (AK Scientific), 6-methylhept-5-en-2-one (Oakwood), 1-methoxy-3-vinylbenzene (Sigma-Aldrich), (*Z*)-pent-2-en-1-ol (Aldrich), potassium *tert*-butoxide (Oakwood), potassium sodium tartrate (Acros Organics), sodium bicarbonate (Fisher), sodium hydride (Sigma-Aldrich), sodium hydroxide, tetrakis(triphenylphosphine)palladium (Strem), triethylamine (Sigma-Aldrich), tris(pentafluorophenyl)borane (TCI), triphenylborane (Aldrich), palladium acetate (Strem), 10-undecenoic acid (Sigma-Aldrich) were used as received.

2.6.4 Preparation of Organometallic Complexes

Mo-1 and **Mo-7** were prepared according to a previously reported procedure.[42] **Mo-3**, **Mo-4**, **Mo-5**, and **Mo-6**, were prepared according to a previously reported procedure.[70] **Mo-8**

and **Mo-9** were prepared according to a previously reported procedure.[105]



$Mo(NC_6F_5)_2Cl_2(DME)$ (Mo-A): This complex was prepared according to a previously reported procedure.[106] Under N_2 atmosphere, an oven-dried 250 mL round-bottom flask equipped with a magnetic stir bar and a condenser, was charged with $NaMoO_4$ (4.12 g, 20.0 mmol), $C_6F_5NH_2$ (9.16 g, 42.0 mmol), DME (60 mL), Et_3N (14 mL, 100 mmol), and TMSCl (25 mL, 200 mmol). The mixture was allowed to warm to 80 °C and stir for 15 h. Subsequently, the dark red solution was allowed to cool to 22 °C, filtered through a pad of celite, and volatiles were removed in vacuo. The so-obtained dark red oil was suspended in Et_2O, and the mixture was allowed to cool to −40 °C. After 12 h at that temperature, the suspension was filtered to afford **Mo-A** as orange solid (9.31 g, 15.0 mmol, 75% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.05 (s, 4H), 4.01 (s, 6H); **^{19}F NMR (376 MHz, $CDCl_3$):** δ −145.51 (m, 4F), −152.37 (t, J = 20.9 Hz, 2F), −162.04 (m, 4F).

$Mo(NC_6F_5)_2(CH_2CMe_2Ph)_2$ (Mo-B): This complex was prepared according to a previously reported procedure.[107] Under N_2 atmosphere, an oven-dried 250 mL Schlenk

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

(106) Sues, P. E.; John, J. M.; Schrock, R. R.; Müller, P. *Organometallics* **2016**, *35*, 758–761.

(107) Yuan, J.; Schrock, R. R.; Müller, P.; Axtell, J. C.; Dobereiner, G. E. *Organometallics* **2012**, *31*, 4650–4653.

flask equipped with a magnetic stir bar was charged with **Mo-A** (9.31 g, 15.0 mmol) and Et_2O (50 mL). The mixture was allowed to cool to −40 °C, and $PhMe_2CCH_2MgCl$ (60 mL, 30 mmol, 0.50 M) was added. The mixture was allowed to warm to 22 °C and stir for 3 h. Subsequently, the mixture was filtered through a pad of celite, and the volatiles were removed in vacuo. The so-obtained dark red oil was suspended and triturated in hexanes (30 mL), resulting in formation of dark yellow precipitate. The suspension was filtered through a pad of celite, and the filtrate was concentrated to 20 mL, resulting in formation of a red precipitate. The suspension was allowed to cool to −40 °C. After at 12 h at that temperature, the red solid was collected by filtration, washed with cold hexanes, and dried in vacuo to afford **Mo-B** as red solid (5.26 g, 7.26 mmol, 49% yield). **^{1}H NMR (600 Hz, C_6D_6)**: δ 7.26 – 7.21 (m, 4H), 7.09 – 7.03 (m, 4H), 6.93 – 6.87 (m, 2H), 1.94 (s, 4H), 1.36 (s, 12H); **^{19}F NMR (564 Hz, C_6D_6):** δ −149.28 (m, 4F), −159.67 (t, *J* = 21.8 Hz, 2F), −163.85 – −164.54 (m, 4F).

$Mo(NC_6F_5)(CHCMe_2Ph)(DME)(OTf)_2$ (Mo-C): This complex was prepared according to a previously reported procedure.[106] Under N_2 atmosphere, an oven-dried 250 mL round-bottom flask equipped with a magnetic stir bar was charged with **Mo-B** (5.00 g, 6.90 mmol), Et_2O (110 mL), and DME (12.0 mL). The resulting solution was allowed to cool to −40 °C, after which TfOH (3.18 g, 20.7 mmol) was added. The mixture was allowed to warm to 22 °C and stir for 3 h. The resulting yellow solid was collected by filtration, washed with Et_2O (20 mL), and dried in vacuo to afford **Mo-C** as yellow solid (3.03 g, 3.80 mmol, 55% yield). **^{1}H NMR (500 MHz, C_6D_6):** *trans* isomer (major): δ 13.73 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 2H), 6.97 (t, *J* = 7.8 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 3.32 (s, 3H), 3.27 (s, 2H), 3.01 (s, 3H), 2.89 (s, 2H), 1.61 (s, 6H); *cis* isomer (resolved signals only): δ

15.00 (s, 1H), 7.39 (d, J = 7.8 Hz, 2H), 6.89 (t, J = 7.6 Hz, 2H); **^{19}F NMR (564 Hz, C_6D_6):** *trans* isomer (major): δ −76.83 (t, J = 5.4 Hz, 6F), −140.38 – −141.12 (m, 2F), −149.58 (t, J = 21.8 Hz, 1F), −161.43 – −162.08 (m, 2F); *cis* isomer (resolved signals only): δ −76.62 (s, 3F), −77.53 (s, 3F), −143.34 (m, J = 20.9 Hz, 2F), −151.33 (d, J = 21.3 Hz, 1F), −161.19 – −161.63 (m, 2F).

Mo(NC_6F_5)($CHCMe_2Ph$)(Me_2-Pyr)$_2$ (Mo-D): This complex was prepared according to a previously reported procedure.[106] Under N_2 atmosphere, an oven-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with Mo(NC_6F_5)($CHCMe_2Ph$)(DME)$(OTf)_2$ (798 mg, 1.00 mmol) and toluene (50 mL). The resulting suspension was allowed to cool to −40 °C, after which LiMe_2Pyr (222 mg, 2.20 mmol) was added. The mixture was allowed to warm to 22 °C and stir for 30 min. Subsequently, the solution was concentrated to dryness, and the dark red oil was dissolved in CH_2Cl_2 (10.0 mL). The resulting suspension was filtered through a glass Büchner funnel, and the filtrate was concentrated in vacuo. The so-obtained red oil was dissolved in Et_2O (5.0 mL) and allowed to cool to −40 °C. After 12 h at this temperature, the red solid was collected by filtration, washed with cold Et_2O (2.0 mL), and dried in vacuo to afford **Mo-D** as orange solid (397 mg, 0.66 mmol, 66% yield). **^{1}H NMR (500 Hz, C_6D_6):** δ 13.01 (s, 1H), 7.14 – 7.10 (m, 2H), 6.86 – 6.80 (m, 2H), 6.77 – 6.72 (m, 1H), 5.93 (br, 4H), 2.09 (br, 12H), 1.41 (s, 6H); **^{19}F NMR (376 Hz, C_6D_6):** δ −145.41 – −145.91 (m, 2F), −157.29 (t, J = 21.8 Hz, 1F), −163.38 – −163.55 (m, 2F).

2,2'',4,4'',6,6''-Hexaethyl-[1,1':3',1''-terphenyl]-2'-ol (HETO): Under N_2 atmosphere, a 50 mL round-bottom flask equipped with a magnetic stir bar was charged with 2,6-dibromophenol (1.65 g, 6.55 mmol) and THF (10 mL). NaH (315 mg, 13.1 mmol) was

added in portions, and the mixture was allowed to stir for 30 min at 22 °C. The suspension was filtered through a fritted funnel, and the filtrate was transferred to a 150 mL round-bottom flask equipped with a magnetic stir bar. Then, $Pd(OAc)_2$ (120 mg, 0.39 mmol), and a solution of (2,4,6-triethylphenyl)magnesium bromide in THF (0.64 M, 35 mL, 22.4 mmol) was added, and the resultant mixture was allowed to stir under reflux for 12 h. The mixture was allowed to cool to 22 °C, and the reaction was quenched by addition of HCl (2 M, 50 mL). The phases were separated, and the aqueous layer was washed with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and volatiles were removed in vacuo. The so-obtained colorless oil was dissolved in MeOH (20 mL) and transferred to a 50 mL round-bottom flask equipped with a magnetic stir bar. Then, Pd on carbon(10 wt%, 120 mg, 0.11 mmol) was added, and the mixture was sparged with H_2 (1 atm). The resultant suspension was allowed to stir under H_2 atmosphere at for 12 h at 22 °C. Subsequently, the mixture was filtered through celite, and the so-obtained oil was washed with Et_2O (2 x 25 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and volatiles were removed in vacuo. The so-obtained oil was purified through silica gel chromatography (0% → 30% $CHCl_3$ in hexanes), recrystallized (EtOH), and dried in vacuo to afford **5b** as colorless crystals (1.95 g, 4.70 mmol, 72% yield).

IR (neat): 3225 (w), 2960 (s), 2929 (m), 2868 (m), 1605 (w), 1456 (s), 1434 (m), 1320 (m), 1218 (s), 1166 (m), 1086 (m), 1070 (m), 1009 (w), 870 (s), 787 (m), 754 (s); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.10 – 7.06 (m, 1H), 7.04 – 6.99 (m, 2H), 4.54 (s, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.49 – 2.29 (m, 4H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.06 (t, *J* = 7.6 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.4, 144.2, 143.5, 132.3, 132.2, 130.4, 126.5, 126.5, 125.8,

120.1, 28.9, 26.9, 15.5, 15.4; **HRMS [M+H]**$^+$ calcd for $C_{30}H_{39}O$: 415.2995, found: 415.2982; **m.p.** 53−55 °C.

5'-Bromo-2,2'',4,4'',6,6''-hexaethyl-[1,1':3',1''-terphenyl]-2'-ol (BrETO): This compound was synthesized according to a modified procedure by Buchmeiser *et al.*[108] In a 50 mL flask equipped with a magnetic stir bar, (1'r,3's)-2,2'',4,4'',6,6''-hexaethyl-[1,1':3',1''-terphenyl]-2'-ol (415 mg, 1.0 mmol) was dissolved in AcOH (15 mL). Under exclusion of light, a solution of Br_2 in AcOH (1 M, 1.0 mL, 1.0 mmol) was added in a dropwise manner over the course of 5 min, and the resultant mixture was allowed to stir for 2 h at 22 °C. The reaction was quenched by addition of 10 mL of a saturated aqueous solution of Na_2SO_3, and the mixture was washed with Et_2O (3 x 25 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and the volatiles were removed in vacuo. The so-obtained oil was purified through silica gel chromatography (25% $CHCl_3$ in hexanes) and recrystallized (EtOH) to afford **5a** as colorless crystals (424 mg, 0.86 mmol, 86% yield). **IR (neat):** 3489 (br), 2960 (m), 2928 (m), 2865 (w), 1605 (w), 1433 (m), 1310 (w), 1211 (s), 1161 (m), 1102 (m), 1019 (w), 871 (s), 800 (m), 689 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.23 (s, 2H), 7.03 (s, 4H), 4.58 (s, 1H), 2.68 (q, *J* = 7.6 Hz, 4H), 2.50 – 2.31 (m, 8H), 1.29 (t, *J* = 7.6 Hz, 6H), 1.08 (t, *J* = 7.6 Hz, 12H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.8, 144.7, 143.3, 132.7, 130.9, 128.7, 125.9, 112.1, 28.9, 26.9, 15.5, 15.4; **HRMS [M+H]**$^+$ calcd for $C_{30}H_{38}BrO$: 493.2101, found: 493.2090; **m.p.** 110−112 °C.

General procedure for in situ preparation of Mo-10 for catalytic reactions: Under N_2 atmosphere, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with

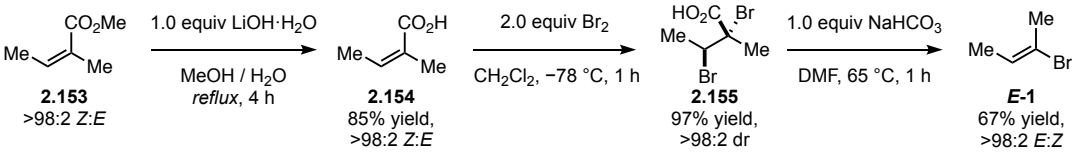
(108) Schowner, R.; Elser, I.; Toth, F.; Robe, E.; Frey, W.; Buchmeiser, M. R. *Chem. Eur. J.* **2018**, *24*, 13336–13347.

Mo-D (29.9 mg, 50.0 μmol), **BrETO** (24.7 mg, 50.0 μmol) and benzene (0.50 mL), resulting in a dark red solution. The vial was sealed, and the mixture was allowed to stir for 2 h at 22 °C, after which the catalyst solution was stored in the freezer (−40 °C) until further use. The diagnostic alkylidene α-proton signal of the *syn*-alkylidene is: **^{1}H NMR (400 MHz, C_6D_6)**: δ 11.29 (1H, s).

2.6.5 Preparation of Z-1 and E-1

***Z*-1** and ***E*-1** were purchased from both Sigma-Aldrich and Santa Cruz Biotechnology. However, the quality of the reagent fluctuated heavily. At times, unknown impurties were encountered in the ^{1}H NMR that when used in a cross-metathesis inhibited the reaction (<5% conv.). Moreover, the stereochemical purity fluctuated as well from >98:2 at best to 60:40 *E*:*Z* or *Z*:*E* at worst. We therefore pursued different routes for the synthesis of ***Z*-1** and ***E*-1** from other commerically available reagents.

(Route A):



(*Z*)-2-Methylbut-2-enoic acid (2.154): This compound was either purchased (TCI America) or synthesized according to a reported procedure by Nicolaou *et al*.[109] A 500 mL flask equipped with a magnetic stir bar was charged with **2.153** (17.1 g, 150 mmol), H_2O (150 mL), and MeOH (150 mL). After addition of $LiOH·H_2O$ (6.29 g, 150 mmol), the mixture was allowed to stir under reflux for 4 h. Subsequently, the reaction was allowed to

(109) Nicolaou, K. C.; Nevalainen, M.; Zak, M.; Bulat, S.; Bella, M.; Safina, B. S. *Angew. Chem. Int. Ed.* **2003**, *42*, 3418–3424.

cool to 22 °C, and the reaction was quenched by addition of HCl (1 M, 150 mL, 150 mmol). The aqueous phase was washed with EtOAc (3 x 100 mL), and the combined organic phases were dried over $MgSO_4$ and filtered. The volatiles were removed in vacuo and the so-obtained off-white solid was recrystallized (EtOH) to afford **2.154** as colorless crystals (12.8 g, 128 mmol, 85% yield, >98:2 *Z*:*E*). **IR (neat):** 2927 (br), 1680 (s), 1636 (m), 1457 (w), 1414 (w), 1256 (m), 1183 (w), 1082 (w), 1043 (w), 908 (m), 732 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 11.23 (br, 1H), 6.23 (qq, *J* = 7.4, 1.8 Hz, 1H), 2.04 (dq, *J* = 7.4, 1.8 Hz, 3H), 1.92 (dq, *J* = 1.8, 3H); *Z* isomer (resolved signals only): δ 7.05 – 6.98 (m, 1H), 2.20 (d, *J* = 7.5 Hz, 3H), 1.84 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.8, 141.3, 127.3, 20.5, 16.2; **HRMS [M+H]$^+$** calcd for $C_5H_9O_2$: 101.0597, found: 101.0600.

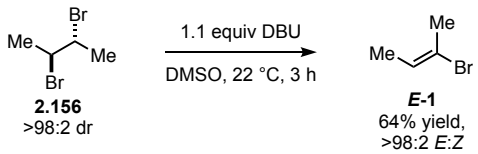
***anti*-2,3-Dibromo-2-methylbutanoic acid (2.155):** This compound was synthesized according to a modified procedure by Cha *et al.*[110] In a 500 mL flask equipped with a magnetic stir bar, **2.154** (12.8 g, 128 mmol) was dissolved in CH_2Cl_2 (250 mL). The mixture was allowed to cool −78 °C, after which Br_2 (13.1 mL, 40.9 mmol) was added in a dropwise manner over the course of 30 min. Upon complete addition, the mixture was allowed to stir for 2 h at this temperature. Subsequently, the reaction was quenched by addition of an aqueous saturated solution of Na_2SO_3 (100 mL). The aqueous phase was washed with CH_2Cl_2 (3 x 75 mL), the combined organic phases were dried over $MgSO_4$ and filtered, and the volatiles were removed in vacuo. The so-obtained off-white paste was recrystallized (CH_2Cl_2) to afford **2.155** as colorless crystals (32.3 g, 124 mmol, 97% yield, 98:2 dr). **IR (neat):** 3331 (br), 2968 (s), 1378 (m), 1302 (w), 1159 (m), 1126 (s), 948 (s), 815 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** major diastereomer: δ 10.95 (br, 1H),

(110) Kim, H.; Lee, S. K.; Lee, D.; Cha, J. K. *Synth. Commun.* **1998**, *28*, 729–735.

4.58 (q, *J* = 6.8 Hz, 1H), 2.06 (s, 3H), 1.88 (d, *J* = 6.8 Hz, 3H); minor diastereomer (resolved signals only): δ 4.84 (q, *J* = 6.8 Hz, 1H), 2.00 (s, 3H), 1.92 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.5, 63.4, 54.3, 26.4, 26.4, 23.0; **HRMS [M+H]$^+$** calcd for $C_5H_9O_2Br_2$: 258.8964, found: 258.8975; **m.p.** 76−78 °C.

(*E*)-2-Bromo-2-butene (*E*-1): This compound was synthesized according to a modified procedure by Cha *et al*.[110] A 100 mL flask equipped with a magnetic stir bar was charged with $NaHCO_3$ (6.17 g, 73.4 mmol) and DMF (30 mL), and the resulting suspension was allowed to heat to 65 °C. Under vigorous stirring, a solution of **2.155** (19.1 g, 73.5 mmol) in DMF (30 mL) was added in a dropwise manner over the course of an hour. After complete addition, the mixture was allowed to stir for 30 min at 65 °C until gas evolution ceased. Distillation of the reaction mixture under ambient pressure afforded cloudy liquid, which was washed with brine (3 x 5 mL) and dried over $MgSO_4$ and filtered subsequently. ***E*-1** was obtained as colorless liquid (6.37 g, 47.2 mmol, 67% yield, 96:4 *E*:*Z*). **IR (neat):** 2978 (w), 2917 (w), 2858 (w), 1654 (w), 1430 (m), 1381 (w), 1120 (s), 1054 (s), 998 (w), 900 (m), 817 (s), 634 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major) δ 5.88 (qq, *J* = 7.1, 1.4 Hz, 1H), 2.20 (dq, *J* = 1.4 Hz, *J* = 1.2 Hz, 3H), 1.61 (dq, *J* = 7.1, 1.2 Hz, 3H); *Z* isomer (resolved signals only): δ 2.27 (dq, *J* = 1.6 Hz, 3H), 1.70 (dq, *J* = 6.5, 1.6 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 126.7, 119.6, 22.9, 15.1; **HRMS [M+H]$^+$** calcd for C_4H_8Br: 134.9804, found: 134.9809.

Route B:



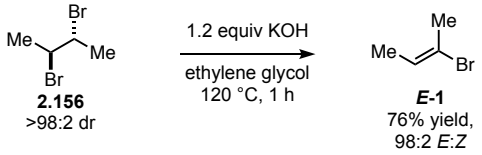
2.156
>98:2 dr

***E*-1**
64% yield,
>98:2 *E*:*Z*

(*E*)-2-Bromo-2-butene (*E*-1): This compound was synthesized according to a modified

procedure by Cochran *et al.*[111] Under light-exclusion, a 100 mL flask equipped with a magnetic stir bar was charged with **2.156** (10.8 g, 50 mmol) and DMSO (35 mL). Then, DBU (8.37 g, 55 mmol) was added in a dropwise manner over the course of 5 min. The mixture was allowed to stir for 2 h at 22 °C. Distillation of the reaction mixture under 300 Torr afforded cloudy liquid, which was washed with H_2O (3 x 5 mL) and dried over 3 Å molecular sieves to afford ***E*-1** as colorless liquid (4.33 g, 32.1 mmol, 64%, >98:2 *E*:*Z*). The analytical data of this compound were consistent with those obtained through Route A.

Route C:



(*E*)-2-Bromo-2-butene (*E*-1): This compound was synthesized according to a modified procedure by Landis *et al.*[112] A 100 mL flask equipped with a magnetic stir bar was charged with **2.156** (10.8 g, 50 mmol) and ethylene glycol (22 mL), and the mixture was allowed to heat to 120 °C. Then, a solution of KOH (3.37 g, 50 mmol) in ethylene glycol (77 mL) was added in a dropwise manner over the course of 20 min. Upon complete addition, the mixture was allowed to stir for 1 h at 120 °C. Distillation of the reaction mixture under ambient pressure afforded cloudy liquid, which was dried over $MgSO_4$ and filtered to afford ***E*-1** as colorless liquid (5.10 g, 37.8 mmol, 76%, 98:2 *E*:*Z*). The analytical data of this compound were consistent with those obtained through route A.

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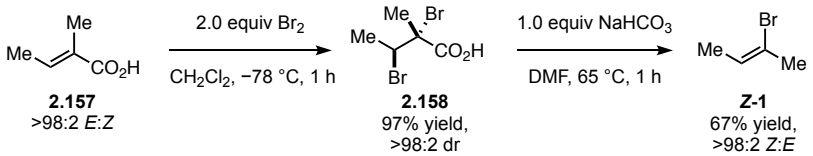
(111) Cochran, J. C.; Prindle, V.; Young, H. A.; Kumar, M. H.; Tom, S.; Petraco, N. D. K.; Mohoro, C.; Kelley, B. *Synth. React. Inorg. Met.-Org. Chem.* **2002**, *32*, 885–902.

(112) Bordwell, F. G.; Landis, P. S. *J. Am. Chem. Soc.* **1957**, *79*, 1593–1597.

Preparation of Z-2-Bromo-2-butene



***syn*-2,3-Dibromo-2-methylbutanoic acid (2.158):** This compound was synthesized according to a modified procedure by Cha *et al*.[110] In a 500 mL flask equipped with a magnetic stir bar, **2.157** (20.0 g, 200 mmol) was dissolved in CH_2Cl_2 (400 mL). The mixture was allowed to cool −78 °C, after which, Br_2 (20.5 mL, 64.09 mmol) was added in a dropwise manner over the course of 30 min. Upon complete addition, the mixture was allowed to stir for another 2 h at the same temperature. Subsequently, the reaction was quenched by addition of an aqueous saturated solution of Na_2SO_3 (150 mL). The aqueous phase was washed with CH_2Cl_2 (3 x 100 mL), the combined organic phases were dried over $MgSO_4$ and filtered, and the volatiles were removed in vacuo. The so-obtained off-white paste was recrystallized (CH_2Cl_2) to afford **2.158** as colorless crystals (32.3 g, 124 mmol, 97% yield, 98:2 dr*)*. **IR (neat):** 2935 (br), 1701 (s), 1443 (w), 1407 (w), 1381 (w), 1265 (m), 1135 (w), 1060 (s), 978 (m), 904 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 12.27 (br, 1H), 4.84 (q, *J* = 6.8 Hz, 1H), 1.99 (s, 3H), 1.91 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 175.9, 61.6, 51.1, 21.2, 21.1; **HRMS $[M+H]^+$** calcd for $C_5H_9O_2Br_2$: 258.8964, found: 258.8973; m.p. 84−86 °C.

(*Z*)-2-Bromo-2-butene (*Z*-1): This compound was synthesized according to a modified procedure by Cha *et al*.[110] A 100 mL flask equipped with a magnetic stir bar was charged with $NaHCO_3$ (8.40 g, 100 mmol) and DMF (40 mL), and the resulting suspension was allowed to heat to 65 °C. Under vigorous stirring, a solution of **2.158** (26.0 g, 100 mmol) in DMF (40 mL) was added in a dropwise manner over the course of 1 h. After complete

addition, the mixture was allowed to stir for 30 min at 65 °C until gas evolution ceased. Subsequent distillation of the reaction mixture under ambient pressure afforded cloudy liquid, which was washed with brine (3 x 5 mL), and dried over $MgSO_4$ and filtered. ***Z*-1** was obtained as colorless liquid (6.37 g, 47.2 mmol, 67% yield, 98:2 *Z*:*E*). **IR (neat):** 2966 (w), 2952 (w), 2917 (w), 1664 (w), 1425 (m), 1283 (s), 1131 (s), 1020 (m), 896 (m), 860 (m), 792 (s), 545 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.67 (qq, *J* = 6.5, 1.6 Hz, 1H), 2.28 (dq, *J* = 1.6 Hz, 3H), 1.71 (dq, *J* = 6.5, 1.6 Hz, 3H); *E* isomer (minor): δ 2.21 (dq, *J* = 1.3 Hz, 3H), 1.62 (dq, *J* = 7.1, 1.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 123.6, 123.6, 28.8, 17.1; **HRMS $[M+H]^+$** calcd for C_4H_8Br: 134.9804, found: 134.9808.

2.6.6 Cross-Metathesis Reactions

(*Z*)-(((3-Bromobut-2-en-1-yl)oxy)methyl)benzene (2.64): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with (((3-methylbut-2-en-1-yl)oxy)methyl)benzene (17.6 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.50 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 µL, 6.0 µmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 58% consumption of (((3-methylbut-2-en-1-yl)oxy)methyl)benzene. The so-obtained brown oil was purified through silica gel chromatography (25% CH_2Cl_2 in hexanes) to afford **2.64** as colorless oil (11.9 mg, 0.049 mmol, 49% yield, 95:5 *Z*:*E*). **IR (neat):** 2918 (w), 2851 (w), 1661 (w), 1452 (w), 1102 (s), 1064 (m), 1027 (w), 735 (s), 697 (s), 572 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.38 – 7.33 (m, 4H), 7.33 – 7.25 (m, 1H), 5.89 (t, *J* = 5.8 Hz, 1H), 4.52 (s, 2H), 4.17 – 4.13 (m, 2H), 2.33 (s, 1H); *E* isomer (resolved signals only): δ 6.09 (t, *J* =

8.2 Hz, 1H), 4.51 (s, 2H), 3.98 (d, J = 7.1 Hz, 2H), 2.26 (t, J = 1.1 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 138.2, 128.6, 128.0, 127.8, 126.3, 124.9, 72.6, 70.0, 29.0; **HRMS $[M+NH_4]^+$** calcd for $C_{11}H_{17}NOBr$: 258.0488, found: 258.0491.

(*Z*)-((7-Bromo-3-methyloct-6-en-1-yl)oxy)(tert-butyl)dimethylsilane (2.65): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with *tert*-butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane (54.1 mg, 0.20 mmol), ***Z*-1** (135 mg, 1.0 mmol), *cis*-3-hexene (12.0 μL of a 1.0 M solution in benzene, 12.0 μmol), and a solution of **Mo-1** in benzene (100 μL of a 0.1 M solution, 10.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 75% consumption of *tert*-butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane. The so-obtained brown oil was purified through silica gel chromatography (pentane) to afford **2.65** as colorless oil (46.6 mg, 0.14 mmol, 69% yield, 96:4 *Z*:*E*). **IR (neat):** 2951 (m), 2924 (m), 2853 (m), 1461 (w), 1253 (m), 1094 (s), 834 (s), 774 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.58 (tq, J = 6.9, 1.4 Hz, 1H), 3.72 – 3.57 (m, 2H), 2.22 – 2.06 (m, 2H), 1.62 – 1.51 (m, 2H), 1.46 – 1.28 (m, 2H), 1.28 – 1.14 (m, 1H), 0.90 – 0.88 (m, 12H), 0.05 (s, 6H); *E* isomer (resolved signals only): δ 5.85 – 5.79 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 129.3, 122.2, 61.5, 39.9, 35.8, 29.2, 29.2, 28.9, 26.1, 19.7, 18.5, −5.1; **HRMS $[M+H]^+$** calcd for $C_{15}H_{32}BrOSi$: 335.1400, found: 335.1389.

(*Z*)-N,N-Dibenzyl-6-bromohept-5-en-1-amine (2.66): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with *N*,*N*-dibenzyl-6-methylhept-5-en-1-amine (61.5 mg, 0.20 mmol), ***Z*-1** (135 mg, 1.0 mmol), *cis*-3-hexene

(12.0 μL of a 1.0 M solution in benzene, 12.0 μmol), and a solution of **Mo-1** in benzene (100 μL of a 0.1 M solution, 10.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 84% consumption of *N*,*N*-dibenzyl-6-methylhept-5-en-1-amine. The so-obtained brown oil was purified through silica gel chromatography (0% → 1% EtOAc in hexanes) to afford **2.66** as colorless oil (45.1 mg, 0.12 mmol, 61% yield, 96:4 *Z*:*E*). **IR (neat):** 2928 (w), 2791 (w), 1492 (m), 1450 (m), 1364 (w), 1125 (w), 1069 (w), 1027 (m), 741 (s), 696 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.39 – 7.35 (m, 4H), 7.34 – 7.28 (m, 4H), 7.25 – 7.20 (m, 2H), 5.54 (tq, *J* = 7.0, 1.4 Hz, 1H), 3.55 (s, 4H), 2.42 (t, *J* = 7.1 Hz, 2H), 2.26 (d, *J* = 1.3 Hz, 3H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.58 – 1.48 (m, 2H), 1.42 – 1.33 (m, 2H); *E* isomer (resolved signals only): δ 5.77 (t, *J* = 6.5, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.2, 129.1, 128.9, 128.3, 126.9, 122.4, 58.5, 53.4, 31.5, 28.9, 26.7, 26.2; **HRMS $[M+H]^+$** calcd for $C_{21}H_{27}NBr$: 372.1321, found: 372.1335.

Methyl-(*Z*)-11-bromododec-10-enoate (2.67): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with methyl-11-methyldodec-10-enoate (45.3 mg, 0.20 mmol), ***Z*-1** (135 mg, 1.0 mmol), *cis*-3-hexene (12.0 μL of a 1.0 M solution in benzene, 12.0 μmol), and a solution of **Mo-1** in benzene (100 μL of a 0.1 M solution, 10.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 84% consumption of methyl-11-methyldodec-10-enoate. The so-obtained brown oil was purified through silica gel chromatography (hexanes) to afford **2.67** as colorless oil (45.4 mg, 0.16 mmol, 78%

yield, 95:5 *Z*:*E*). **IR (neat):** 2923 (m), 2852 (m), 1739 (s), 1361 (w), 1170 (w), 1115 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.59 (tq, *J* = 6.9, 1.3 Hz, 1H), 3.67 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.27 (q, *J* = 1.3 Hz, 3H), 2.15 – 2.08 (m, 2H), 1.66 – 1.57 (m, 2H), 1.40 – 1.33 (m, 2H), 1.33 – 1.25 (m, 8H); *E* isomer (resolved signals only): δ 5.85 – 5.81 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 174.5, 129.3, 122.3, 51.6, 34.3, 31.6, 29.4, 29.3, 29.3, 29.2, 28.9, 28.6, 25.1; **HRMS [M+H]$^+$** calcd for $C_{13}H_{24}BrO_2$: 291.0954, found: 291.0953.

(*Z*)-7-Bromo-3-methyloct-6-en-1-yl 2-(phenylthio)acetate (2.68): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 3,7-dimethyloct-6-en-1-yl 2-(phenylthio)acetate (30.6 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 71% consumption of 3,7-dimethyloct-6-en-1-yl 2-(phenylthio)acetate. The so-obtained brown oil was purified through silica gel chromatography (0% → 20% EtOAc in hexanes) to afford **2.68** as colorless oil (20.5 mg, 0.055 mmol, 55% yield, 95:5 *Z*:*E*). **IR (neat):** 2953 (m), 2916 (m), 1729 (s), 1582 (w), 1480 (w), 1438 (w), 1271 (s), 1130 (s), 738 (s), 689 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.43 – 7.38 (m, 2H), 7.33 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 5.56 (tq, *J* = 6.8, 1.4 Hz, 1H), 4.21 – 4.08 (m, 2H), 3.64 (s, 2H), 2.31 – 2.22 (m, 3H), 2.18 – 2.01 (m, 2H), 1.69 – 1.58 (m, 1H), 1.55 – 1.45 (m, 1H), 1.45 – 1.33 (m, 2H), 1.29 – 1.15 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 3H); *E* isomer (resolved signals only): δ 5.79 (t, *J* = 8.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.9, 135.2, 130.0,

129.2, 128.9, 127.1, 122.6, 64.1, 36.8, 35.5, 35.3, 29.4, 29.1, 28.9, 19.4; **HRMS [M+H]$^+$** calcd for $C_{17}H_{24}BrO_2S$: 371.0675, found: 371.0671.

(*Z*)-2-(6-Bromohept-5-en-1-yl) 1-(*tert*-butyl)-(*S*)-pyrrolidine-1,2-dicarboxylate (2.69): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 1-(*tert*-butyl) 2-(6-methylhept-5-en-1-yl) (*S*)-pyrrolidine-1,2-dicarboxylate (32.5 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 64% consumption of 1-(*tert*-butyl) 2-(6-methylhept-5-en-1-yl) (*S*)-pyrrolidine-1,2-dicarboxylate. The so-obtained brown oil was purified through silica gel chromatography (0% → 20% EtOAc in hexanes) to afford **2.69** as colorless oil (22.7 mg, 0.058 mmol, 58% yield, 98:2 *Z*:*E*). **IR (neat):** 2970 (w), 1743 (m), 1696 (s), 1391 (s), 1364 (m), 1159 (s), 1120 (m), 1086 (w), 771 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.58 (t, *J* = 7.0 Hz, 1H), 4.31 (dd, *J* = 8.7, 3.3 Hz, 0.4H, minor rotamer), 4.21 (dd, *J* = 8.6, 3.9 Hz, 0.6H, major rotamer), 4.19 – 4.05 (m, 2H), 3.58 – 3.48 (m, 1H), 3.48 – 3.42 (m, 0.6H, major rotamer), 3.41 – 3.34 (m, 0.4H, minor rotamer), 2.27 (q, *J* = 1.6 Hz, 3H), 2.24 – 2.19 (m, 1H), 2.19 – 2.11 (m, 2H), 2.00 – 1.89 (m, 2H), 1.89 – 1.81 (m, 1H), 1.70 – 1.61 (m, 2H), 1.48 – 1.40 (m, 11H); *E* isomer (resolved signals only): δ 5.83 – 5.79 (m, 1H); **^{13}C NMR (151 MHz, $CDCl_3$):** major rotamer: δ 173.4, 154.5, 128.6, 123.1, 80.0, 64.9, 59.3, 46.6, 31.1, 30.1, 28.9, 28.6, 28.5, 28.3, 24.9, 24.5, 23.8; minor rotamer (resolved signals only): δ 173.2, 154.5, 128.3, 122.9, 79.8, 59.0, 46.7, 31.2, 24.9; **HRMS [M+H]$^+$** calcd for $C_{17}H_{29}BrNO_4$: 390.1275, found: 390.1274.

(*Z*)-2-(6-Bromo-2-methylhept-5-en-1-yl)-1,3-dioxolane (2.70): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 2-(2,6-dimethylhept-5-en-1-yl)-1,3-dioxolane (19.8 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 81% consumption of 2-(2,6-dimethylhept-5-en-1-yl)-1,3-dioxolane. The so-obtained brown oil was purified through silica gel chromatography (0% → 1% Et_2O in hexanes) to afford **2.70** as colorless oil (19.2 mg, 0.073 mmol, 73% yield, 95:5 *Z*:*E*). **IR (neat):** 2951 (m), 2914 (m), 2874 (m), 1408 (w), 1379 (w), 1124 (s), 1036 (s), 945 (m), 825 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.59 (tq, *J* = 6.8, 1.3 Hz, 1H), 4.92 – 4.88 (m, 1H), 4.02 – 3.91 (m, 2H), 3.89 – 3.79 (m, 2H), 2.30 – 2.22 (m, 3H), 2.22 – 2.08 (m, 1H), 1.75 – 1.61 (m, 2H), 1.55 – 1.42 (m, 2H), 1.31 – 1.21 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H); *E* isomer (resolved signals only): δ 5.82 (t, *J* = 7.6, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 129.1, 122.4, 103.9, 64.9, 64.8, 41.0, 36.0, 29.1, 29.1, 28.9, 19.8; **HRMS [M+H]$^+$** calcd for $C_{11}H_{20}BrO_2$: 263.0641, found: 263.0626.

(*Z*)-2-(6-Bromohept-5-en-1-yl)isoindoline-1,3-dione (2.71): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione (25.7 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the

volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 87% consumption of 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione. The so-obtained brown oil was purified through silica gel chromatography (0% → 20% EtOAc in hexanes) to afford **2.71** as colorless oil (23.5 mg, 0.073 mmol, 73% yield, 95:5 *Z*:*E*). **IR (neat):** 2937 (w), 2856 (w), 1770 (w), 1704 (s), 1434 (w), 1393 (m), 1361 (m), 1170 (w), 1032 (m), 716 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.58 (tq, *J* = 6.9, 1.4 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.26 (q, *J* = 1.3 Hz, 3H), 2.18 (q, *J* = 7.4 Hz, 2H), 1.75 – 1.66 (m, 2H), 1.49 – 1.39 (m, 2H); *E* isomer (resolved signals only): δ 5.81 (t, *J* = 8.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.6, 134.0, 132.3, 128.4, 123.3, 123.0, 38.0, 31.2, 28.9, 28.3, 25.9; **HRMS [M+H]$^+$** calcd for $C_{15}H_{17}BrNO_2$: 322.0437, found: 322.0424.

(*Z*)-2-(3-Bromobut-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.72): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-1-yl)-1,3,2-dioxaborolane (19.6 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.50 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 µL, 6.0 µmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 89% consumption of 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-1-yl)-1,3,2-dioxaborolane. The so-obtained brown oil was purified through silica gel chromatography (0% → 2% Et_2O in hexanes) to afford **2.72** as colorless oil (19.4 mg, 0.074 mmol, 74% yield, 98:2 *Z*:*E*). **IR (neat):** 2975 (w), 2922 (w), 1344 (s), 1324 (s), 1142 (s), 1070 (w), 966 (m), 574 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.74 (tq, *J*

= 7.4, 1.4 Hz, 1H), 2.28 (q, *J* = 1.4 Hz, 3H), 1.77 (d, *J* = 7.4 Hz, 2H), 1.25 (s, 12H); *E* isomer (resolved signals only): δ 5.92 (tq, *J* = 8.2, 1.4 Hz, 1H); **^{11}B NMR (160 MHz, $CDCl_3$):** δ 32.8; **^{13}C NMR (125 MHz, $CDCl_3$):** δ 124.4, 122.8, 83.6, 28.8, 24.9, 15.9; **HRMS [M+H]$^+$** calcd for $C_{10}H_{19}BBrO_2$: 261.0656, found: 261.0652.

(*Z*)-2-(4-Bromopent-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.73): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane (21.0 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 66% consumption of 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane. The so-obtained brown oil was purified through silica gel chromatography with oven-dried silica gel and dry solvents (0% → 1% Et_2O in hexanes) to afford **2.73** as colorless oil (15.6 mg, 0.057 mmol, 57% yield, 95:5 *Z*:*E*). **IR (neat):** 2975 (w), 2922 (w), 1370 (s), 1317 (s), 1213 (m), 1143 (s), 967 (w), 846 (w), 547 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.62 (tq, *J* = 6.6, 1.3 Hz, 1H), 2.28 – 2.18 (m, 5H), 1.25 (s, 12H), 0.91 – 0.83 (m, 2H); *E* isomer (resolved signals only): δ 5.86 – 5.82 (m, 1H); **^{11}B NMR (160 MHz, $CDCl_3$):** 34.6; **^{13}C NMR (125 MHz, $CDCl_3$):** δ 131.0, 121.4, 83.3, 28.9, 26.2, 25.0, 10.3; **HRMS [M+H]$^+$** calcd for $C_{11}H_{21}BBrO_2$: 275.0813, found: 275.0816.

(*Z*)-7-Bromo-3-methyloct-6-en-1-ol (2.74): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 3,7-dimethyloct-6-en-1-ol

(22.2 mg, 0.10 mmol) and HB(pin) (48.0 μL, 0.3 mmol). Under gas evolution, the mixture was allowed to stir for 30 min at 22 °C. Subsequently, the volatiles were removed under vacuum (1 Torr, 30 min), and ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol) were added. The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet MeOH (1 mL), the volatiles were removed in vacuo, Analysis of the unpurified mixture revealed 77% consumption of 3,7-dimethyloct-6-en-1-ol. The so-obtained brown oil was purified through silica gel chromatography (40% EtOAc in hexanes) to afford **2.74** as colorless oil (31.4 mg, 0.14 mmol, 71% yield, 96:4 *Z*:*E*). **IR (neat):** 3335 (br), 2950 (m), 2915 (s), 2869 (m), 1662 (w), 1427 (m), 1376 (m), 1053 (s), 1011 (w), 822 (w), 577 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.58 (tq, *J* = 6.9, 1.3 Hz, 1H), 3.76 – 3.59 (m, 2H), 2.26 (q, *J* = 1.3 Hz, 3H), 2.21 – 2.06 (m, 2H), 1.68 – 1.51 (m, 2H), 1.47 – 1.35 (m, 2H), 1.33 (s, 1H), 1.30 – 1.18 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H); *E* isomer (resolved signals only): δ 5.81 (t, *J* = 6.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 129.1, 122.4, 61.2, 39.9, 35.8, 29.2, 29.2, 28.9, 19.6; **HRMS [M+H]$^+$** calcd for $C_9H_{18}BrO$: 221.0536, found: 221.0538.

(*Z*)-6-Bromo-2-(4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol (2.75): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 6-methyl-2-(4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol (22.2 mg, 0.10 mmol), HB(pin) (48.0 μL, 0.3 mmol), and NEt_3 (0.7 μL, 5.0 μmol). Under gas evolution, the mixture was allowed to stir for 2 h at 70 °C. Subsequently, the volatiles were removed under vacuum (1 Torr, 50 °C, 30 min), and ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol) were added.

The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet MeOH (1 mL), the volatiles were removed in vacuo, Analysis of the unpurified mixture revealed 68% consumption of 6-methyl-2-(4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol. The so-obtained brown oil was purified through silica gel chromatography (0% → 7% EtOAc in hexanes) to afford **2.75** as colorless oil (16.3 mg, 0.057 mmol, 57% yield, 96:4 *Z*:*E*). **IR (neat):** 3429 (br), 2959 (m), 2917 (s), 1662 (w), 1436 (s), 1375 (s), 1249 (s), 1133 (s), 1106 (s), 913 (s), 820 (s), 799 (s), 583 (m), 547 (s), 431 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.63 (t, *J* = 7.1 Hz, 1H), 5.38 (d, *J* = 12.0 Hz, 1H), 2.27 (s, 3H), 2.21 (q, *J* = 7.6 Hz, 2H), 2.10 – 1.73 (m, 5H), 1.65 (s, 3H), 1.61 – 1.50 (m, 3H), 1.35 – 1.20 (m, 3H), 1.13 (d, *J* = 14.0, 3H); *E* isomer (resolved signals only): δ 5.87 – 5.81 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** major diastereomer δ 134.3, 129.0, 122.7, 120.8, 74.3, 43.4, 38.8, 31.2, 28.9, 27.0, 26.2, 24.1, 23.5, 23.4; minor diastereomer (resolved signals only): δ 134.0, 120.6, 74.3, 43.1, 38.1, 31.1, 26.2, 26.0, 24.1, 23.5, 23.4; **HRMS $[M+H-H_2O]^+$** calcd for $C_{14}H_{22}Br$: 269.0899, found: 269.0894.

(*Z*)-6-Bromohept-5-en-1-yl-ferrocencarboxylate (2.76): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 6-methylhept-5-en-1-yl-ferrocencarboxylate (34.0 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 59% consumption of 6-methylhept-5-en-1-yl-ferrocencarboxylate. The so-obtained brown oil was purified

through silica gel chromatography (0% → 2% EtOAc in hexanes) to afford **2.76** as dark red oil (22.4 mg, 0.056 mmol, 56% yield, >98:2 *Z*:*E*). **IR (neat):** 2945 (w), 1707 (s), 1457 (m), 1272 (s), 1133 (s), 1025 (w), 821 (w), 502 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.64 (tq, *J* = 6.9, 1.3 Hz, 1H), 4.81 (t, *J* = 2.0 Hz, 2H), 4.39 (t, *J* = 2.0 Hz, 2H), 4.23 (t, *J* = 6.5 Hz, 2H), 4.21 – 4.19 (m, 5H), 2.29 (d, *J* = 1.3 Hz, 3H), 2.27 – 2.19 (m, 2H), 1.80 – 1.71 (m, 2H), 1.60 – 1.50 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 171.8, 128.5, 123.1, 71.3, 70.3, 69.9, 69.8, 64.1, 31.3, 28.9, 28.6, 25.2; **HRMS [M+H]$^+$** calcd for $C_{18}H_{22}BrFeO_2$: 405.0147, found: 405.0136.

(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-((*Z*)-5-Bromohex-4-en-1-yl)-13-methyl-2,3,6,7,8,9,10,11,12,13,14,15, 16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)oxy)(*tert*-butyl)dimethylsilane (2.77): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with *tert*-butyldimethyl-(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-17-(5-methylhex-4-en-1-yl)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)oxy)silane (47.1 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 µL, 6.0 µmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 76% consumption of *tert*-butyldimethyl-(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-17-(5-methylhex-4-en-1-yl)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)oxy)silane. The so-obtained brown oil was purified through silica gel chromatography (pentane) to afford **2.77** as colorless solid (28.3 mg, 0.053 mmol, 53% yield, 93:7 *Z*:*E*). **IR**

(neat): 2947 (s), 2922 (s), 2852 (s), 1470 (w), 1253 (m), 1188 (w), 1076 (s), 833 (s), 770 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.60 (tq, *J* = 6.8, 1.3 Hz, 1H), 5.40 – 5.35 (m, 1H), 2.28 (d, *J* = 1.3 Hz, 3H), 2.22 – 2.16 (m, 1H), 2.12 – 2.07 (m, 2H), 2.04 – 1.89 (m, 4H), 1.83 – 1.72 (m, 3H), 1.72 – 1.63 (m, 2H), 1.62 – 1.54 (m, 1H), 1.55 – 1.43 (m, 4H), 1.42 – 1.04 (m, 9H), 0.87 (s, 9H), 0.86 – 0.78 (m, 4H), 0.66 – 0.56 (m, 1H), 0.14 – 0.01 (m, 6H); *E* isomer (resolved signals only): δ 5.84 (td, *J* = 7.6, 1.4 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 140.8, 129.2, 122.5, 120.0, 86.6, 50.5, 48.7, 48.0, 42.2, 42.2, 38.7, 35.7, 34.7, 32.1, 32.1, 29.0, 26.3, 26.3, 26.3, 25.7, 24.0, 23.8, 22.3, 18.8, 15.7, −1.3, −1.6; **HRMS [M+H]$^+$** calcd for $C_{30}H_{52}BrOSi$: 535.2965, found: 535.2943; **m.p.** 106−108 °C.

(*Z*)-6-Bromohept-5-en-1-yl-(2*R*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide (2.78): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 6-methylhept-5-en-1-yl (2*R*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide (34.3 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 70% consumption of 6-methylhept-5-en-1-yl (2*R*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide. The so-obtained brown oil was purified through silica gel chromatography (0% → 25% EtOAc in hexanes) to afford **2.78** as yellow oil (21.5 mg, 0.053 mmol, 53% yield, >98:2 *Z*:*E*). **IR (neat):** 2936 (w), 2860 (w); 1792 (s), 1750 (s), 1318 (s), 1288 (m), 1186 (s), 1155 (m), 1117 (s), 1083(m), 950 (w), 709 (w), 550 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.59

(tq, *J* = 6.9, 1.4 Hz, 1H), 4.61 (dd, *J* = 4.2, 2.2 Hz, 1H), 4.38 (s, 1H), 4.22 (t, *J* = 6.7 Hz, 2H), 3.49 (dd, *J* = 16.2, 4.2 Hz, 1H), 3.44 (dd, *J* = 16.2, 2.2 Hz, 1H), 2.28 (d, *J* = 1.2 Hz, 3H), 2.18 (q, *J* = 7.1 Hz, 2H), 1.75 – 1.67 (m, 3H), 1.61 (s, 3H), 1.51 – 1.44 (m, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 170.8, 167.1, 128.0, 123.5, 66.4, 63.4, 62.8, 61.3, 38.5, 31.0, 28.9, 28.0, 24.9, 20.5, 18.8; **HRMS [M+H]$^+$** calcd for $C_{15}H_{23}BrNO_5S$: 408.0475, found: 408.0459.

(*Z*)-6-Bromohept-5-en-1-yl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (2.79): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 6-methylhept-5-en-1-yl 2-(1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetate (46.8 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 µL, 6.0 µmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 51% consumption of 6-methylhept-5-en-1-yl 2-(1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetate. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% EtOAc in hexanes) to afford **2.79** as orange oil (24.2 mg, 0.045 mmol, 45% yield, >98:2 *Z*:*E*). **IR (neat):** 2929 (w), 1731 (s), 1680 (s), 1590 (m), 1476 (m), 1455 (m), 1355 (m), 1314 (s), 1258 (m), 1221 (m), 1164 (m), 1141 (m), 1087 (m), 1066 (m), 1036 (m), 1014 (m), 924 (w), 833 (w), 753 (w), 481 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.69 – 7.63 (m, 2H), 7.50 – 7.43 (m, 2H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.51 (tq, *J* = 6.9, 1.3 Hz, 1H), 4.11 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.66 (s, 2H), 2.39 (s, 3H), 2.25 (d, *J* = 1.3 Hz, 3H), 2.11 (q, *J* = 7.4 Hz, 2H), 1.69 – 1.59 (m,

2H), 1.44 – 1.35 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 171.0, 168.4, 156.2, 139.4, 136.0, 134.1, 131.3, 131.0, 130.8, 129.3, 128.4, 123.1, 115.1, 112.9, 111.8, 101.5, 65.0, 55.8, 31.1, 30.6, 28.9, 28.2, 24.9, 13.5; **HRMS [M+H]$^+$** calcd for $C_{26}H_{28}BrClNO_4$: 532.0885, found: 532.0877.

(*E*)-(((3-Bromobut-2-en-1-yl)oxy)methyl)benzene (2.80): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with (((3-methylbut-2-en-1-yl)oxy)methyl)benzene (17.6 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 67% consumption of (((3-methylbut-2-en-1-yl)oxy)methyl)benzene. The so-obtained brown oil was purified through silica gel chromatography (25% CH_2Cl_2 in hexanes) to afford **2.80** as colorless oil (11.0 mg, 0.046 mmol, 46% yield, 95:5 *E*:*Z*). **IR (neat):** 2918 (w), 2855 (w), 1650 (w), 1495 (w), 1452 (w), 1359 (m), 1116 (s), 1092 (s), 1054 (s), 1027 (m), 736 (m), 670 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 7.40 – 7.27 (m, 5H), 6.10 (tq, *J* = 7.1, 1.3 Hz, 1H), 4.51 (s, 2H), 3.98 (d, *J* = 7.1 Hz, 2H), 2.26 (d, *J* = 1.6 Hz, 3H); *Z* isomer (resolved signals only): δ 5.90 (t, *J* = 6.0 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 138.0, 128.8, 128.6, 128.0, 127.9, 124.7, 72.3, 66.5, 24.0; **HRMS [M+NH_4]$^+$** calcd for $C_{11}H_{17}BrNO$: 258.0488, found: 258.0488.

(*E*)-1-(((6-Bromohept-5-en-1-yl)oxy)methyl)-4-methoxybenzene (2.81): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 1-methoxy-4-(((6-methylhept-5-en-1-yl)oxy)methyl)-benzene (24.8 mg, 0.10 mmol), *E*-2-

bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 90% consumption of 1-methoxy-4-(((6-methylhept-5-en-1-yl)oxy)methyl)-benzene. The so-obtained brown oil was purified through silica gel chromatography (25% EtOAc in hexanes) to afford **2.81** as colorless oil (26.2 mg, 0.084 mmol, 84% yield, 98:2 *E*:*Z*). **IR (neat):** 2932 (w), 2853 (w), 1650 (w), 1510 (s), 1460 (w), 1377 (w), 1243 (s), 1171 (m), 1096 (m), 1034 (m), 818 (m), 636 (w), 515 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 7.29 – 7.23 (m, 2H), 6.91 – 6.85 (m, 2H), 5.83 (tq, *J* = 7.7, 1.2 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.19 (d, *J* = 1.0 Hz, 3H), 2.07 – 1.97 (m, 2H), 1.64 – 1.57 (m, 1H), 1.50 – 1.41 (m, 2H); *Z* isomer (resolved signals only): δ 5.59 (t, *J* = 7.0 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 159.3, 132.2, 130.8, 129.4, 119.5, 113.9, 72.7, 69.9, 55.4, 29.5, 29.3, 25.9, 23.3; **HRMS $[M+H]^+$** calcd for $C_{15}H_{20}BrO_2$: 311.0641, found: 311.0646.

(*E*)-1-(4-Bromopent-3-en-1-yl)-3-methoxybenzene (2.82): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 1-methoxy-3-(4-methylpent-3-en-1-yl)benzene (19.0 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 74% consumption of 1-methoxy-3-(4-methylpent-3-en-1-yl)benzene. The so-obtained brown

oil was purified through silica gel chromatography (0% → 2% EtOAc in hexanes) to afford **2.82** as colorless oil (16.1 mg, 0.063 mmol, 63% yield, >98:2 *E*:*Z*). **IR (neat):** 2933 (w), 2854 (w), 2832 (w); 1599 (s), 1583 (s), 1487 (s), 1452 (m), 1433 (m), 1259 (s), 1164 (m), 1151 (m), 1048 (m), 872 (w), 845 (w), 777 (m) 695 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 7.21 (t, *J* = 7.8 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.73 – 6.71 (m, 1H), 5.88 (tq, *J* = 7.7, 1.4 Hz, 1H), 3.81 (s, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.32 (q, *J* = 7.7 Hz, 2H), 2.14 (d, *J* = 1.0 Hz, 3H); *Z* isomer (resolved signals only): δ 5.64 (tq, *J* = 6.8, 1.3 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 159.8, 142.9, 131.3, 129.5, 121.0, 120.2, 114.4, 111.5, 55.3, 35.4, 31.5, 23.3; **HRMS [M+H]$^+$** calcd for $C_{12}H_{16}BrO$: 255.0379, found: 255.0383.

(*E*)-1-(4-Bromopent-3-en-1-yl)-4-chlorobenzene (2.83): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 1-chloro-4-(4-methylpent-3-en-1-yl)benzene (19.5 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 72% consumption of 1-chloro-4-(4-methylpent-3-en-1-yl)benzene. The so-obtained brown oil was purified through silica gel chromatography (hexanes) to afford **2.83** as colorless oil (17.7 mg, 0.066 mmol, 66% yield, >98:2 *E*:*Z*). **IR (neat):** 2921 (w), 2856 (w), 1649 (w), 1490 (s), 1429 (w), 1405 (w), 1377 (w), 1090 (s), 1060 (m), 1014 (s), 832 (m), 816 (m), 802 (s), 634 (w), 521 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.26 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 5.84 (tq, *J* = 7.7, 1.7 Hz, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.30 (q, *J* = 7.7 Hz, 2H), 2.11 (d, *J* = 1.7 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 139.6, 132.0, 130.8,

129.9, 128.7, 120.5, 34.7, 31.5, 23.3; **HRMS [M−H]$^+$** calcd for $C_{11}H_{11}ClBr$: 256.9727, found: 256.9738.

Methyl (*E*)-1-(5-bromohex-4-en-1-yl)-1*H*-indole-3-carboxylate (2.84): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with methyl 1-(5-methylhex-4-en-1-yl)-1*H*-indole-3-carboxylate (27.1 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 67% consumption of methyl 1-(5-methylhex-4-en-1-yl)-1*H*-indole-3-carboxylate. The so-obtained brown oil was purified through silica gel chromatography (0% → 15% EtOAc in hexanes) to afford **2.84** as colorless oil (17.6 mg, 0.052 mmol, 52% yield, 95:5 *E*:*Z*). **IR (neat):** 2943 (w), 1692 (s), 1531 (s), 1465 (m), 1379 (m), 1265 (m), 1220 (m), 1167 (s), 1167 (m), 1107 (m), 928 (w), 775 (m), 748 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.22 – 8.16 (m, 1H), 7.79 (s, 1H), 7.39 – 7.30 (m, 1H), 7.34 – 7.25 (m, 2H), 5.82 (tq, *J* = 7.2, 1.3 Hz, 1H), 4.18 – 4.12 (m, 2H), 3.92 (s, 3H), 2.14 – 2.09 (m, 3H), 2.06 – 1.93 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.6, 136.6, 134.2, 130.2, 126.9, 123.0, 122.1, 122.0, 121.1, 110.0, 107.3, 51.1, 46.0, 29.0, 26.6, 23.4; **HRMS [M+H]$^+$** calcd for $C_{16}H_{19}BrNO_2$: 336.0594, found: 336.0589.

(*E*)-2-(4-Bromopent-3-en-1-yl)-2-methyl-1,3-dioxolane (2.85): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 2-methyl-2-(4-methylpent-3-en-1-yl)-1,3-dioxolane (34.1 mg, 0.20 mmol), *E*-2-bromo-2-butene (135 mg, 1.0 mmol), *cis*-3-hexene (12.0 μL of a 1.0 M solution in benzene, 12.0 μmol),

and a solution of **Mo-1** in benzene (100 μL of a 0.1 M solution, 10.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 87% consumption of 2-methyl-2-(4-methylpent-3-en-1-yl)-1,3-dioxolane. The so-obtained brown oil was purified through silica gel chromatography (0% → 2% Et_2OAc in hexanes) to afford **2.85** as colorless oil (32.4 mg, 0.14 mmol, 69% yield, 96:4 *E*:*Z*). **IR (neat):** 2978 (w), 2950 (w), 2921 (w), 2876 (w), 1649 (w), 1376 (m), 1252 (m), 1141 (m), 1050 (s), 946 (w), 865 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.84 (tq, *J* = 7.6, 1.4 Hz, 1H), 4.02 – 3.87 (m, 4H), 2.22 (d, *J* = 1.0 Hz, 3H), 2.16 – 2.06 (m, 2H), 1.75 – 1.67 (m, 2H), 1.31 (s, 3H); *Z* isomer (resolved signals only): δ 5.63 (t, *J* = 7.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 131.9, 119.5, 109.6, 64.9, 38.3, 24.4, 24.1, 23.3; **HRMS [M+H]$^+$** calcd for $C_9H_{16}BrO_2$: 235.0328, found: 235.0338.

(*E*)-2-(6-Bromo-2-methylhept-5-en-1-yl)-1,3-dioxolane (2.86): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 2-(2,6-dimethylhept-5-en-1-yl)-1,3-dioxolane (19.8 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 83% consumption of 2-(2,6-dimethylhept-5-en-1-yl)-1,3-dioxolane. The so-obtained brown oil was purified through silica gel chromatography (0% → 2% EtOAc in hexanes) to afford **2.86** as colorless oil (21.0 mg, 0.080 mmol, 80% yield, 91:9 *E*:*Z*). **IR (neat):** 2950 (w), 2916 (w), 2874 (w), 1649 (w), 1457 (w), 1361 (w), 1123 (s), 1060 (m), 1034 (s), 965 (m),

942 (m), 841 (w), 636 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.82 (tq, *J* = 7.6, 1.4 Hz, 1H), 4.92 – 4.86 (m, 1H), 4.03 – 3.89 (m, 2H), 3.90 – 3.77 (m, 2H), 2.20 (d, *J* = 1.0 Hz, 3H), 2.12 – 1.92 (m, 2H), 1.74 – 1.60 (m, 2H), 1.55 – 1.40 (m, 2H), 1.31 – 1.18 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H); *Z* isomer (resolved signals only): δ 5.61 – 5.55 (m, 1H), 2.26 (d, *J* = 1.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 132.3, 119.3, 103.7, 64.9, 64.8, 40.9, 36.6, 29.0, 27.2, 23.3, 19.9; **HRMS [M+H]$^+$** calcd for $C_{11}H_{20}BrO_2$: 263.0641, found: 263.0632.

(*E*)-6-Bromohept-5-en-1-yl-ferrocencarboxylate (2.87): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 6-methylhept-5-en-1-yl-ferrocencarboxylate (34.0 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 79% consumption of 6-methylhept-5-en-1-yl-ferrocencarboxylate. The so-obtained brown oil was purified through silica gel chromatography (0% → 4% EtOAc in hexanes) to afford **2.87** as dark red oil (24.8 mg, 0.061 mmol, 61% yield, 98:2 *E*:*Z*). **IR (neat):** 2926 (w), 1707 (s), 1457 (m), 1373 (w), 1270 (s), 1131 (s), 1105 (m), 1024 (w), 1000 (w), 818 (m), 773 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.87 (tq, *J* = 7.6, 1.5 Hz, 1H), 4.80 (t, *J* = 1.7 Hz, 2H), 4.39 (t, *J* = 1.8 Hz, 2H), 4.21 (t, *J* = 6.6 Hz, 2H), 4.19 (s, 5H), 2.23 (d, *J* = 1.5 Hz, 3H), 2.10 (q, *J* = 7.5 Hz, 2H), 1.77 – 1.70 (m, 2H), 1.54 (p, *J* = 7.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 171.9, 131.9, 131.7, 119.9, 71.6, 71.5, 71.2, 71.0, 70.5, 70.0, 69.7,

69.5, 64.2, 64.0, 63.7, 29.3, 28.5, 25.7; **HRMS [M+H]$^+$** calcd for $C_{18}H_{22}BrFeO_2$: 405.0147, found: 405.0143.

(*E*)-2-(6-Bromohept-5-en-1-yl)isoindoline-1,3-dione (2.88): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione (25.7 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 µL, 6.0 µmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 83% consumption of 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione. The so-obtained brown oil was purified through silica gel chromatography (0% → 20% EtOAc in hexanes) to afford **2.88** as colorless oil (23.7 mg, 0.074 mmol, 74% yield, 94:6 *E*:*Z*). **IR (neat):** 2936 (w), 2856 (w), 1769 (w), 1703 (s), 1465 (w), 1434 (w), 1393 (s), 1368 (s), 1066 (w), 1033 (w), 934 (w), 717 (s), 529 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 7.86 – 7.82 (m, 2H), 7.73 – 7.69 (m, 2H), 5.80 (tq, *J* = 7.7, 1.4 Hz, 1H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.20 (q, *J* = 1.0 Hz, 3H), 2.10 – 2.02 (m, 2H), 1.69 (tt, *J* = 7.9, 6.4 Hz, 2H), 1.43 (tt, *J* = 10.0, 6.4 Hz, 2H); *Z* isomer (resolved signals only): δ 5.58 (td, *J* = 6.9, 1.4 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 168.6, 134.1, 132.3, 131.7, 123.4, 119.9, 37.8, 29.2, 28.1, 26.3, 23.3; **HRMS [M+H]$^+$** calcd for $C_{15}H_{17}BrNO_2$: 322.0437, found: 322.0433.

(*E*)-2-(3-Bromobut-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.89): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-1-yl)-1,3,2-dioxaborolane (39.2 mg, 0.20 mmol), *E*-2-bromo-2-butene (135 mg, 1.0 mmol), *cis*-3-hexene (12 µL of a 1.0 M solution

in benzene, 12 μmol), and a solution of **Mo-1** in benzene (0.1 M, 100 μL, 10 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 74% consumption of 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-1-yl)-1,3,2-dioxaborolane. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% Et_2O in hexanes) to afford **2.89** as colorless oil (28.7 mg, 0.11 mmol, 55% yield, 89:11 *E*:*Z*). **IR (neat**) 2976 (w), 1360 (m), 1325 (s), 1141 (s), 1109 (w), 1057 (w), 967 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.92 (tq, *J* = 8.1, 1.4 Hz, 1H), 2.18 (d, *J* = 1.1 Hz, 3H), 1.63 (d, *J* = 8.0 Hz, 2H), 1.24 (d, *J* = 0.7 Hz, 12H); *Z* isomer (resolved signals only): δ 5.74 (tq, *J* = 7.4, 1.4 Hz, 1H), 2.28 (d, *J* = 1.4 Hz, 3H), 1.77 (d, *J* = 7.4 Hz, 2H), 1.25 (d, *J* = 0.7 Hz, 12H); **^{11}B NMR (128 MHz, $CDCl_3$):** δ 32.73; **^{13}C NMR (100 MHz, $CDCl_3$):** *E* isomer (major): δ 127.1, 118.4, 83.7, 24.9, 23.1; *Z* isomer (resolved signals only): δ 124.4, 83.6, 28.8, 24.9; **HRMS [M+H]$^+$** calcd for $C_{10}H_{19}BBrO_2$: 261.0656, found: 261.0653.

(*E*)-2-(4-Bromopent-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.90): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane (21.0 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 86% consumption of 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane. The so-obtained brown oil was purified

through silica gel chromatography (0% → 20% Et_2O in hexanes) to afford **2.90** as colorless oil (22.1 mg, 0.080 mmol, 80% yield, 96:4 *E*:*Z*). **IR (neat):** 2975 (w), 2923 (w), 1367 (s), 1320 (s), 1241 (m), 1141 (s), 1067 (w), 966 (m), 870 (w), 845 (w), 639 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 5.84 (tq, 7.7, 1.2 Hz, 1H), 2.21 (s, 3H), 2.11 (q, *J* = 7.8 Hz, 2H), 1.24 (s, 12H), 0.86 (t, *J* = 7.5 Hz, 2H); *Z* isomer (resolved signals only): δ 5.62 (t, *J* = 6.7 Hz, 1H); **^{11}B NMR (160 MHz, $CDCl_3$):** δ 33.7; **^{13}C NMR (125 MHz, $CDCl_3$):** δ 134.2, 118.9, 83.3, 25.0, 24.3, 23.3, 11.0; **HRMS [M+H]$^+$** calcd for $C_{11}H_{21}BBrO_2$: 275.0813, found: 275.0818.

(*E*)-6-Bromo-2-(4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol (2.91): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 6-methyl-2-(4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol (22.2 mg, 0.10 mmol), HB(pin) (48.0 µL, 0.3 mmol), and NEt_3 (0.7 µL, 5.0 µmol). Under gas evolution, the mixture was allowed to stir for 2 h at 70 °C. Subsequently, the volatiles were removed under vacuum (1 Torr, 50 °C, 30 min), and *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 µL, 6.0 µmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol) were added. The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet MeOH (1 mL), the volatiles were removed in vacuo, Analysis of the unpurified mixture revealed 77% consumption of 6-methyl-2-(4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol. The so-obtained brown oil was purified through silica gel chromatography (0% → 7% EtOAc in hexanes) to afford **2.91** as colorless oil (19.7 mg, 0.069 mmol, 69% yield, 95:5 *E*:*Z*). **IR (neat):** 3429 (br), 2958 (m), 2918 (s), 1649 (w), 1432 (m), 1376 (s), 1105 (w), 1061 (s), 915 (m), 779 (w), 634 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.84 (t, *J* = 7.6 Hz, 1H), 5.43 – 5.33 (m,

1H), 2.22 (s, 3H), 2.16 – 2.05 (m, 2H), 2.05 – 1.94 (m, 2H), 1.92 – 1.84 (m, 1H), 1.84 – 1.72 (m, 1H), 1.65 (s, 3H), 1.61 – 1.48 (m, 3H), 1.35 – 1.22 (m, 1H), 1.19 – 1.14 (m, 1H), 1.12 (d, J = 9.5 Hz, 3H); *Z* isomer (resolved signals only): δ 5.63 (t, J = 6.7 Hz, 1H), 2.27 (d, J = 1.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** major diastereomer δ 134.1, 132.3, 120.5, 119.4, 74.2, 43.3, 39.4, 31.1, 27.1, 26.2, 24.1, 23.9, 23.5, 23.3; minor diastereomer (resolved signals only): δ 134.4, 132.4, 43.7, 38.6, 31.2, 24.0, 23.5, 23.3; **HRMS $[M+H-H_2O]^+$** calcd for $C_{14}H_{22}Br$: 269.0899, found: 269.0907.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(((*E*)-6-bromohept-5-en-1-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (2.92): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-((6-methylhept-5-en-1-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (45.9 mg, 0.10 mmol) and HB(pin) (48.0 μL, 0.3 mmol). The mixture was allowed to stir for 30 min at 22 °C. Subsequently, the volatiles were removed under vacuum (1 Torr, 30 min), and *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol) were added. The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet MeOH (1 mL), the volatiles were removed in vacuo, Analysis of the unpurified mixture revealed 86% consumption of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-((6-methylhept-5-en-1-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate. The so-obtained brown oil was purified through silica gel chromatography (0% → 30% EtOAc in hexanes) to afford **2.92** as colorless oil (40.7 mg, 0.078 mmol, 78% yield, 96:4 *E*:*Z*). **IR (neat):** 2941 (w), 1743 (s), 1430 (w), 1365 (m), 1211 (s), 1169 (m), 1032 (s), 905 (w), 561 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.80 (tq, J = 7.6, 1.4 Hz, 1H), 5.20 (t, J = 9.5 Hz,

1H), 5.08 (t, *J* = 9.7 Hz, 1H), 4.97 (dd, *J* = 9.6, 8.0 Hz, 1H), 4.48 (d, *J* = 8.0 Hz, 1H), 4.26 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.13 (dd, *J* = 12.3, 2.5 Hz, 1H), 3.87 (dt, *J* = 9.6, 6.2 Hz, 1H), 3.68 (ddd, *J* = 9.9, 4.7, 2.5 Hz, 1H), 3.47 (dt, *J* = 9.6, 6.6 Hz, 1H), 2.20 (d, *J* = 1.0 Hz, 3H), 2.08 (s, 3H), 2.05 – 1.97 (m, 11H), 1.63 – 1.52 (m, 2H), 1.47 – 1.35 (m, 2H); *Z* isomer (resolved signals only): δ 5.57 (tq, *J* = 6.8, 1.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.8, 170.4, 169.5, 169.4, 132.0, 119.7, 100.9, 73.0, 71.9, 71.5, 69.8, 68.6, 62.1, 29.3, 28.9, 25.5, 23.3, 20.9, 20.8, 20.8, 20.7; **HRMS $[M+NH_4]^+$** calcd for $C_{21}H_{35}BrNO_{10}$: 540.1439, found: 540.1431.

(*E*)-6-Bromohept-5-en-1-yl-(2*R*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide (2.93): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 6-methylhept-5-en-1-yl (2*R*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide (34.3 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 µL, 6.0 µmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 60% consumption of 6-methylhept-5-en-1-yl (2*R*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide. The so-obtained brown oil was purified through silica gel chromatography (0% → 25% EtOAc in hexanes) to afford **2.93** as yellow oil (20.2 mg, 0.049 mmol, 49% yield, >98:2 *E*:*Z*). **IR (neat):** 2936 (w), 2860 (w), 1793 (s), 1751 (s), 1319 (m), 1288 (w), 1188 (m), 1118 (s), 1084 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 5.81 (tq, *J* = 7.7, 1.4 Hz, 1H), 4.61 (dd, *J* = 4.2, 2.2 Hz, 1H), 4.38 (s, 1H), 4.25 – 4.16 (m, 2H), 3.53 –

3.41 (m, 2H), 2.21 (d, J = 1.3 Hz, 3H), 2.06 (q, J = 7.4 Hz, 2H), 1.74 – 1.65 (m, 2H), 1.61 (s, 3H), 1.51 – 1.43 (m, 2H), 1.41 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 170.8, 167.1, 131.3, 120.2, 66.3, 63.4, 62.8, 61.3, 38.5, 29.1, 28.0, 25.5, 23.3, 20.5, 18.8; **HRMS [M+H]$^+$** calcd for $C_{15}H_{23}BrNO_5S$: 408.0475, found: 408.0475.

(*E*)-6-Bromohept-5-en-1-yl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (2.94): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 6-methylhept-5-en-1-yl 2-(1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetate (46.8 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 70% consumption of 6-methylhept-5-en-1-yl 2-(1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetate. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% EtOAc in hexanes) to afford **2.94** as orange oil (27.0 mg, 0.051 mmol, 51% yield, >98:2 *E*:*Z*). **IR (neat):** 2922 (m), 2852 (w), 1731 (s), 1680 (s), 1590 (m), 1475 (m), 1435 (m), 1398 (w), 1355 (s), 1312 (s), 1257 (m), 1220 (s), 1163 (m), 1141 (m), 1087 (m), 1066 (s), 1035 (m), 1014 (m), 925 (w), 833 (m), 753 (m), 482 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 7.68 – 7.64 (m, 2H), 7.49 – 7.45 (m, 2H), 6.96 (d, J = 2.5 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 6.67 (dd, J = 9.0, 2.5 Hz, 1H), 5.75 (tq, J = 7.6, 1.4 Hz, 1H), 4.10 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.66 (s, 2H), 2.39 (s, 3H), 2.18 (d, J = 1.0 Hz, 3H), 1.99 (q, J = 7.5 Hz, 2H), 1.66 – 1.59 (m, 2H), 1.42 – 1.34 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 171.0, 168.4, 156.2, 139.4, 136.1, 134.1, 131.7, 131.3, 131.0, 130.8,

129.3, 119.9, 115.1, 112.8, 111.7, 101.6, 64.8, 55.9, 30.6, 29.2, 28.2, 25.5, 23.3, 13.5; **HRMS [M+H]$^+$** calcd for $C_{25}H_{28}BrClNO_4$: 532.0885, found: 532.0861.

(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-((*E*)-5-Bromohex-4-en-1-yl)-13-methyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)oxy)(tert-butyl)dimethylsilane (2.95): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with *tert*-butyldimethyl-(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-17-(5-methylhex-4-en-1-yl)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradeca hydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)oxy)silane (47.1 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 67% consumption of *tert*-butyldimethyl-(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-17-(5-methylhex-4-en-1-yl)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)oxy)silane. The so-obtained brown oil was purified through silica gel chromatography (pentane) to afford **2.95** as colorless solid (25.8 mg, 0.048 mmol, 48% yield, >98:2 *E*:*Z*). **IR (neat):** 2922 (m), 2851 (m), 1470 (w), 1375 (w), 1250 (m), 1187 (w), 1073 (s), 937 (w), 831 (s), 807 (m), 767 (s), 676 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 5.84 (t, *J* = 7.7 Hz, 1H), 5.38 (s, 1H), 2.24 – 2.15 (m, 4H), 2.05 – 1.86 (m, 6H), 1.84 – 1.63 (m, 6H), 1.57 – 1.41 (m, 5H), 1.41 – 1.02 (m, 9H), 0.90 – 0.85 (m, 9H), 0.85 – 0.78 (m, 4H), 0.66 – 0.56 (m, 1H), 0.07 (d, *J* = 10.3 Hz, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 140.8, 132.5, 120.0, 119.4, 86.6, 50.5, 48.7, 48.0, 42.2,

42.2, 38.6, 35.7, 34.7, 32.1, 32.1, 30.7, 29.0, 26.3, 25.7, 24.6, 23.8, 23.4, 22.3, 18.8, 15.7, −1.3, −1.6; **HRMS [M+H]$^+$** calcd for $C_{30}H_{52}BrOSi$: 535.2965, found: 535.2948.

***tert*-Butyl-(*Z*)-4-(2-bromoprop-1-en-1-yl)piperidine-1-carboxylate (2.96):** In a N_2-filled glove-box, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with *tert*-butyl-(*Z*)-4-(prop-1-en-1-yl)piperidine-1-carboxylate (22.5 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% consumption of *tert*-butyl-(*Z*)-4-(prop-1-en-1-yl)piperidine-1-carboxylate. The so-obtained brown oil was purified through silica gel chromatography (0% → 3% Et_2O in hexanes) to afford **2.96** as colorless oil (18.3 mg, 0.060 mmol, 60% yield, >98:2 *Z*:*E*). **IR (neat):** 2971 (w), 2916 (w), 2847 (w), 1687 (s), 1418 (s), 1632 (m), 1315 (w), 1275 (m), 1248 (m), 1221 (m), 1169 (s), 1146 (s), 1085 (m), 1010 (w), 959 (w), 768 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.42 (dq, *J* = 8.5, 1.5 Hz, 1H), 4.05 (br, 2H), 2.77 (t, *J* = 11.9 Hz, 2H), 2.56 – 2.44 (m, 1H), 2.26 (s, 3H), 1.67 (d, *J* = 12.8 Hz, 2H), 1.46 (d, *J* = 1.5 Hz, 9H), 1.31 – 1.19 (m, 2H) **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.0, 132.6, 121.8, 79.5, 43.7, 39.1, 30.9, 28.9, 28.6; **HRMS [M+H]$^+$** calcd for $C_{13}H_{23}BrNO_2$: 304.0907, found: 304.0910.

(*Z*)-(6-Bromo-3-methylhept-5-en-1-yl)benzene (2.97): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with (3,6-dimethylhept-5-en-1-yl)benzene (18.8 mg, 0.10 mmol), ***Z*-1** (67.5 mg, 0.5 mmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 µL, 5.0 µmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and

the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% consumption of (3,6-dimethylhept-5-en-1-yl)benzene. The so-obtained brown oil was purified through silica gel chromatography (hexanes) to afford **2.97** as colorless oil (12.3 mg, 0.046 mmol, 46% yield, 94:6 *Z*:*E*). **IR (neat):** 3023 (w), 2952 (s), 2915 (s), 2868 (s), 1660 (w), 1602 (w), 1427 (m), 1376 (w), 1049 (w), 697 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.61 (tq, *J* = 7.0, 1.4 Hz, 1H), 2.74 – 2.53 (m, 2H), 2.30 – 2.28 (m, 3H), 2.24 – 2.18 (m, 1H), 2.12 – 2.01 (m, 1H), 1.71 – 1.57 (m, 2H), 1.53 – 1.42 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 143.0, 128.5, 128.4, 127.7, 125.8, 123.2, 38.7, 38.6, 33.6, 32.6, 29.1, 19.7; **HRMS [M+H]$^+$** calcd for $C_{14}H_{20}Br$: 267.0743, found: 267.0738.

(*Z*)-8-Bromo-2,6-dimethylnon-7-en-2-ol (2.98): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 2,6-dimethyloct-7-en-2-ol (31.3 mg, 0.20 mmol), HB(pin) (58.0 μL, 0.4 mmol), and NEt_3 (2.8 μL, 0.02 mmol). Under gas evolution, the mixture was allowed to stir for 2 h at 50 °C. Subsequently, the volatiles were removed under vacuum (1 Torr, 30 min), and ***Z*-1** (270 mg, 2.0 mmol), and a solution of **Mo-1** in benzene (0.1 M, 100 μL, 10 μmol) were added. The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet MeOH (1 mL), the volatiles were removed in vacuo, Analysis of the unpurified mixture revealed 63% consumption of 2,6-dimethyloct-7-en-2-ol. The so-obtained brown oil was purified through silica gel chromatography (0% → 25% EtOAc in hexanes) to afford **2.98** as colorless oil (22.1 mg, 0.089 mmol, 44% yield, >98:2 *Z*:*E*). **IR (neat):** 3361 (br), 2963 (s), 2931 (s), 2865 (w), 2846 (w), 1457 (w), 1374 (m), 1262 (w), 1202 (m), 934 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.37 (d, *J* = 9.0 Hz, 1H), 2.61 – 2.47 (m, 1H), 2.26 (d, *J* = 1.3

Hz, 3H), 1.51 – 1.40 (m, 2H), 1.38 – 1.27 (m, 4H), 1.21 (s, 6H), 1.19 (br, 1H), 0.97 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.0, 121.0, 71.2, 44.1, 37.2, 36.4, 29.4, 29.4, 29.1, 22.1, 20.0; **HRMS $[M+NH_4]^+$** calcd for $C_{11}H_{25}NOBr$: 266.1114, found: 266.1113.

(*Z*)-5-bromo-3-methylhex-4-en-1-ol (2.99): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 3-methylpent-4-en-1-ol (11.4 mg, 0.10 mmol), HB(pin) (16 μL, 0.11 mmol). Under gas evolution, the mixture was allowed to stir for 1 h at 22 °C. Subsequently, ***Z*-1** (135 mg, 1.0 mmol), and a solution of **Mo-1** in benzene (50 μL of a 0.1 M solution, 5.0 μmol) were added. The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet MeOH (1 mL), the volatiles were removed in vacuo, Analysis of the unpurified mixture revealed 95% consumption of 3-methylpent-4-en-1-ol. The so-obtained brown oil was purified through silica gel chromatography (0% → 10% EtOAc in hexanes) to afford **2.99** as colorless oil (8.3 mg, 0.043 mmol, 43% yield, >98:2 *Z*:*E*). **IR (neat):** 3330 (br), 2955 (m), 2922 (m), 2867 (m), 1657 (w), 1452 (w), 1427 (m), 1337 (w), 1192 (w), 1048 (s), 1023 (s), 555 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.39 (dq, *J* = 9.0, 1.3 Hz, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.79 – 2.64 (m, 1H), 1.70 – 1.60 (m, 1H), 1.55 – 1.46 (m, 1H), 1.45 (br, 1H), 1.01 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 134.3, 121.6, 61.2, 39.6, 33.5, 28.9, 20.3; **HRMS $[M+NH_4]^+$** calcd for $C_7H_{17}NOBr$: 210.0488, found: 210.0439.

***tert*-Butyl-(*E*)-4-(2-bromoprop-1-en-1-yl)piperidine-1-carboxylate (2.100):** In a N_2-filled glove-box, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with *tert*-butyl (*Z*)-4-(prop-1-en-1-yl)piperidine-1-carboxylate (22.5 mg, 0.10 mmol), *E*-2-

bromo-2-butene (135 mg, 1.0 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% consumption of *tert*-butyl (*Z*)-4-(prop-1-en-1-yl)piperidine-1-carboxylate. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% EtOAc in hexanes) to afford **2.100** as colorless oil (11.6 mg, 0.038 mmol, 38% yield, >98:2 *E*:*Z*). **IR (neat):** 2972 (w), 2923 (w), 2848 (w), 1686 (s), 1419 (s), 1363 (m), 1281 (m), 1225 (m), 1168 (s), 1139 (s), 1053 (w), 939 (w), 768 (w), 655 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.68 (d, *J* = 9.5 Hz, 1H), 4.06 (br, 2H), 2.83 – 2.61 (m, 2H), 2.36 – 2.24 (m, 1H), 2.25 (s, 3H), 1.60 (d, *J* = 12.1 Hz, 2H), 1.45 (d, *J* = 1.8 Hz, 9H), 1.35 – 1.20 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 154.9, 136.0, 119.7, 79.6, 43.5, 37.4, 31.6, 28.6, 23.6; **HRMS [M+H]$^+$** calcd for $C_{13}H_{23}BrNO_2$: 304.0907, found: 304.0907.

(*E*)-(6-Bromo-3-methylhept-5-en-1-yl)benzene (2.101): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with (3,6-dimethylhept-5-en-1-yl)benzene (18.8 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% consumption of (3,6-dimethylhept-5-en-1-yl)benzene. The so-obtained brown oil was purified through silica gel chromatography (hexanes) to afford **2.101** as colorless oil (12.3 mg, 0.046 mmol, 46% yield, 88:12 *E*:*Z*). **IR (neat):** 3023 (w), 2951 (w), 2920 (w), 2851

(w), 1649 (w) 1602 (w), 1494 (w), 1453 (m), 1377 (w), 1059 (w), 744 (w), 697 (s), 637 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 7.31 – 7.26 (m, 1H), 7.22 – 7.15 (m, 3H), 5.85 (tq, *J* = 7.7, 1.1 Hz, 1H), 2.67 (ddd, *J* = 13.7, 10.2, 5.6 Hz, 1H), 2.58 (ddd, *J* = 13.7, 10.2, 6.1 Hz, 1H), 2.21 (s, 3H), 2.11 – 2.01 (m, 1H), 1.97 – 1.87 (m, 1H), 1.70 – 1.62 (m, 1H), 1.62 – 1.54 (m, 1H), 1.53 – 1.41 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H); *Z* isomer (resolved signals only): δ 5.61 (tq, *J* = 6.9, 1.1 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 142.7, 131.0, 128.5, 128.5, 125.9, 119.9, 38.4, 36.9, 33.6, 32.9, 23.5, 19.5; **HRMS $[M+H]^+$** calcd for $C_{14}H_{20}Br$: 267.0743, found: 267.0745.

(*E*)-8-Bromo-2,6-dimethylnon-7-en-2-ol (2.102): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with 2,6-dimethyloct-7-en-2-ol (15.6 mg, 0.10 mmol), HB(pin) (38.4 mg, 0.3 mmol), and NEt_3 (1.4 µL, 0.01 mmol). Under gas evolution, the mixture was allowed to stir for 2 h at 50 °C. Subsequently, the volatiles were removed under vacuum (1 Torr, 30 min), and ***Z*-1** (135 mg, 1.0 mmol), and a solution of **Mo-1** in benzene (0.1 M, 100 µL, 10 µmol) were added. The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet MeOH (1 mL), the volatiles were removed in vacuo, Analysis of the unpurified mixture revealed 37% consumption of 2,6-dimethyloct-7-en-2-ol. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% Et_2O in hexanes) to afford **2.102** as colorless oil (7.3 mg, 0.029 mmol, 29% yield, 96:4 *E*:*Z*). **IR (neat):** 3382 (br), 2962 (s), 2928 (s), 2867 (m), 1649 (w), 1457 (m), 1377 (s), 1190 (w), 1160 (s), 1053 (m), 936 (w), 905 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.63 (dq, *J* = 10.0, 1.4 Hz, 1H), 2.40 – 2.28 (m, 1H), 2.22 (d, *J* = 1.3 Hz, 3H), 1.46 – 1.40 (m, 2H), 1.38 – 1.23 (m, 4H), 1.23 – 1.16 (m, 7H), 0.97 (d, *J* = 6.7 Hz, 3H); *Z* isomer (resolved signals only): 5.37 (d, *J*

= 8.6 Hz, 1H), 2.27 (d, *J* = 2.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.5, 118.4, 71.1, 44.0, 37.7, 35.0, 29.5, 29.4, 23.6, 22.2, 20.8; **HRMS [M+H−H_2O]$^+$** calcd for $C_{11}H_2Br$: 231.0743, found: 231.0752.

Methyl (*E*)-1-(5-bromohex-4-en-1-yl)-1*H*-indole-3-carboxylate (2.84): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with methyl 1-(5-methylhex-4-en-1-yl)-1*H*-indole-3-carboxylate (27.1 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 67% consumption of methyl 1-(5-methylhex-4-en-1-yl)-1*H*-indole-3-carboxylate. The so-obtained brown oil was purified through silica gel chromatography (0% → 15% EtOAc in hexanes) to afford **2.84** as colorless oil (17.6 mg, 0.052 mmol, 52% yield, 95:5 *E*:*Z*). **IR (neat):** 2943 (w), 1692 (s), 1531 (s), 1465 (m), 1379 (m), 1265 (m), 1220 (m), 1167 (s), 1167 (m), 1107 (m), 928 (w), 775 (m), 748 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.22 – 8.16 (m, 1H), 7.79 (s, 1H), 7.39 – 7.30 (m, 1H), 7.34 – 7.25 (m, 2H), 5.82 (tq, *J* = 7.2, 1.3 Hz, 1H), 4.18 – 4.12 (m, 2H), 3.92 (s, 3H), 2.14 – 2.09 (m, 3H), 2.06 – 1.93 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.6, 136.6, 134.2, 130.2, 126.9, 123.0, 122.1, 122.0, 121.1, 110.0, 107.3, 51.1, 46.0, 29.0, 26.6, 23.4; **HRMS [M+H]$^+$** calcd for $C_{16}H_{19}BrNO_2$: 336.0594, found: 336.0589.

(*Z*)-2-Bromoundec-2-ene (2.109): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with methyl oleate (29.7 mg, 0.10 mmol), ***Z*-1** (135 mg, 1.0 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution

of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 84% consumption of methyl oleate. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% Et_2O in hexanes) to afford **2.109** as colorless oil (18.1 mg, 0.063 mmol, 63% yield, 96:4 *Z*:*E*). **IR (neat):** 2952 (s), 2919 (s), 2850 (s), 1458 (m), 1376 (w), 721 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.60 (tq, *J* = 6.8, 1.4 Hz, 1H), 2.27 (d, *J* = 1.4 Hz, 2H), 2.16 – 2.07 (m, 2H), 1.42 – 1.22 (m, 10H), 0.92 – 0.84 (m, 3H); *E* isomer (resolved signals only): δ 5.84 (td, *J* = 7.7, 1.5 Hz, 1H), 2.21 (d, *J* = 1.2 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 129.3, 122.2, 32.0, 31.7, 29.6, 29.4, 29.4, 28.9, 28.6, 22.8, 14.3; **HRMS [M+H]$^+$** calcd for $C_{11}H_{22}Br$: 233.0899, found: 233.0887.

Methyl (*Z*)-10-bromoundec-9-enoate (2.110): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with methyl oleate (29.7 mg, 0.10 mmol), ***Z*-1** (135 mg, 1.0 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% consumption of methyl oleate. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% Et_2O in hexanes) to afford **2.110** as colorless oil (19.2 mg, 0.070 mmol, 70% yield, 96:4 *Z*:*E*). **IR (neat):** 2922 (m), 2852 (m), 1736 (s), 1433 (w), 1360 (w), 1244 (w), 1169 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.59 (tq, *J* = 6.9, 1.5 Hz, 1H), 3.67 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.27 (d, *J* = 1.4 Hz, 3H), 2.15 – 2.07 (m, 2H), 1.61 (q, *J* = 7.2 Hz, 2H), 1.41 – 1.26 (m, 8H); *E* isomer

(resolved signals only): δ 5.82 (t, *J* = 7.6 Hz, 1H), 2.00 (q, *J* = 7.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.5, 129.2, 122.4, 51.6, 34.2, 31.6, 29.2, 29.2, 29.1, 28.9, 28.5, 25.1; **HRMS [M+H]$^+$** calcd for $C_{12}H_{22}BrO_2$: 277.0798, found: 277.0797.

(*E*)-2-Bromoundec-2-ene (2.111): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with methyl oleate (29.7 mg, 0.10 mmol), *E*-2-bromo-2-butene (135 mg, 1.0 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% consumption of methyl oleate. The so-obtained brown oil was purified through silica gel chromatography (hexanes) to afford **2.111** as colorless oil (19.0 mg, 0.082 mmol, 82% yield, 90:10 *E*:*Z*). **IR (neat):** 2953 (m), 2920 (s), 2851 (m), 1650 (w), 1458 (w), 1377 (w), 1064 (w), 964 (w), 721 (w), 636 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.83 (tq, *J* = 7.6, 1.3 Hz, 1H), 2.21 (d, *J* = 1.2 Hz, 3H), 2.00 (q, *J* = 7.3 Hz, 2H), 1.41 – 1.20 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H); *Z* isomer (resolved signals only): δ 5.60 (td, *J* = 6.9, 1.4 Hz, 1H), 2.27 (t, *J* = 1.3 Hz, 3H), 2.12 (q, *J* = 7.5 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 132.7, , 119.2, 32.0, 29.8, 29.5, 29.4, 29.2, 29.2, 23.3, 22.8, 14.3; *Z* isomer (resolved signals only): δ 129.3, 122.2; **HRMS [M+H]$^+$** calcd for $C_{11}H_{22}Br$: 233.0899, found: 233.0894.

Methyl (*E*)-10-bromoundec-9-enoate (2.112): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with methyl oleate (29.7 mg, 0.10 mmol), *E*-2-bromo-2-butene (135 mg, 1.0 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was

sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% consumption of methyl oleate. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% Et_2O in hexanes) to afford **2.112** as colorless oil (24.0 mg, 0.087 mmol, 87% yield, 96:4 *E*:*Z*). **IR (neat):** 2924 (m), 2852 (m), 1736 (s), 1433 (w), 1195 (m), 1169 (m), 1062 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 5.82 (tq, *J* = 7.7, 1.4 Hz, 1H), 3.67 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.20 (d, *J* = 1.0 Hz, 3H), 2.02 – 1.95 (m, 2H), 1.65 – 1.57 (m, 2H), 1.40 – 1.33 (m, 2H), 1.33 – 1.25 (m, 6H); *Z* isomer (resolved signals only): δ 5.58 (t, *J* = 6.9, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 174.4, 132.5, 119.3, 51.6, 34.2, 29.7, 29.2, 29.2, 29.1, 29.0, 25.0, 23.3; **HRMS [M+H]$^+$** calcd for $C_{12}H_{22}BrO_2$: 277.0798, found: 277.0797.

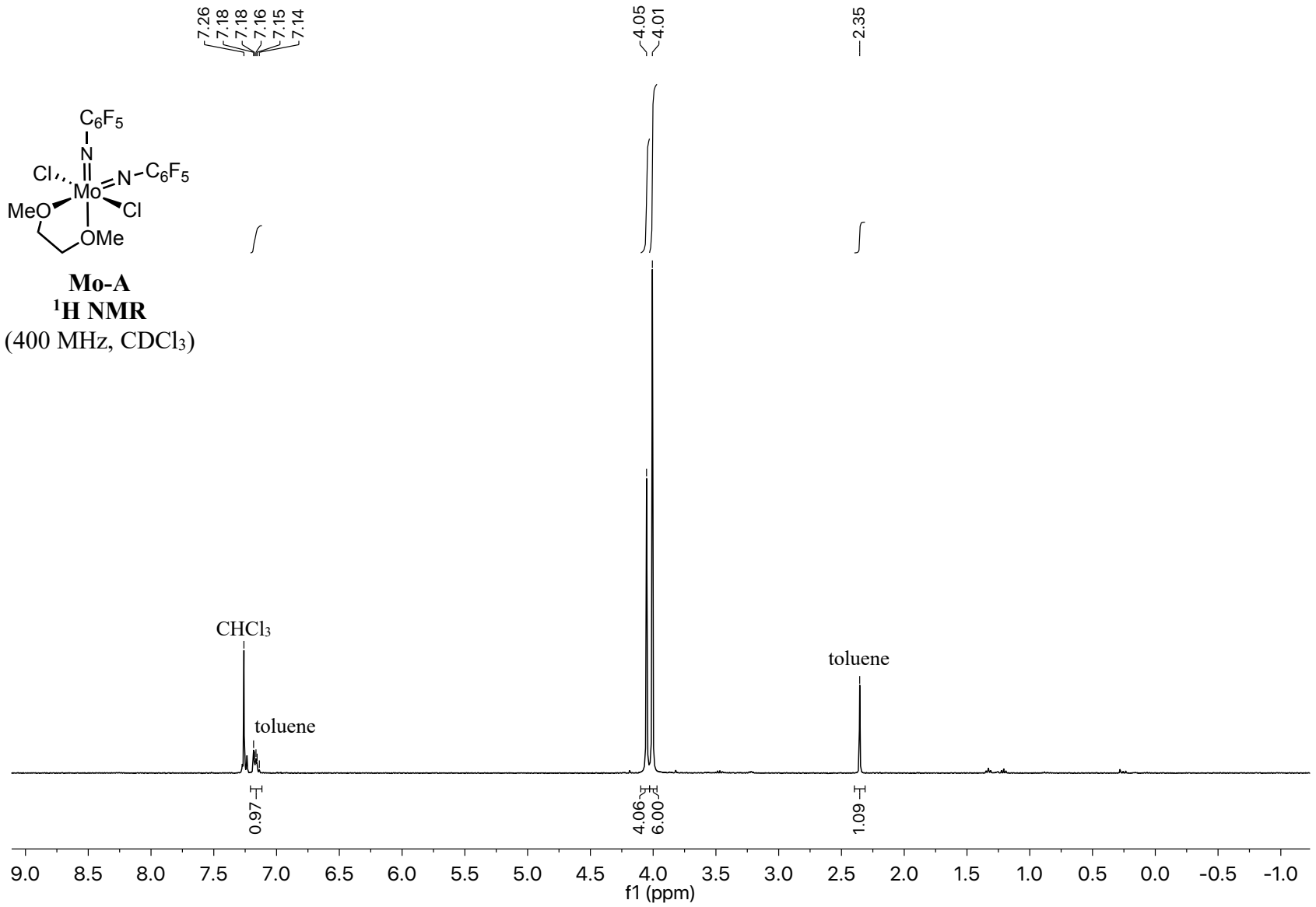
2.6.7 Phomactin A

Ethyl (2*E*,6*E*)-7-bromo-3-methylocta-2,6-dienoate (2.138): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with ethyl (*E*)-3,7-dimethylocta-2,6-dienoate (19.6 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 76% consumption of ethyl (*E*)-3,7-dimethylocta-2,6-dienoate. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% Et_2O in hexanes) to afford **2.138** as colorless oil (20.5 mg, 0.071 mmol, 71% yield, 95:5 *E*:*Z*). **IR (neat):** 2976 (w), 2926 (w), 1713 (s), 1647 (m), 1222 (s); 1146 (s), 1098 (w), 1059 (w); **^{1}H NMR (500 MHz, $CDCl_3$):**

E isomer (major): δ 5.80 (qt, *J* = 3.8, 2.2 Hz, 1H), 5.66 (p, *J* = 1.7, 1.3 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.21 (d, *J* = 1.3 Hz, 3H), 2.20 (s, 2H), 2.19 (s, 2H), 2.15 (d, *J* = 1.3 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 166.8, 158.2, 130.6, 120.4, 116.4, 59.8, 40.0, 27.7, 23.4, 18.9, 14.5; **HRMS [M+H]$^+$** calcd for $C_{11}H_{18}BrO_2$: 261.0485, found: 261.0496.

Ethyl (2*Z*,6*E*)-7-bromo-3-methylocta-2,6-dienoate (2.151): In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with ethyl (*E*)-3,7-dimethylocta-2,6-dienoate (19.6 mg, 0.10 mmol), *E*-2-bromo-2-butene (67.5 mg, 0.5 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-1** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was sealed, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of wet Et_2O (1 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 74% consumption of ethyl (*E*)-3,7-dimethylocta-2,6-dienoate. The so-obtained brown oil was purified through silica gel chromatography (0% → 5% Et_2O in hexanes) to afford **2.151** as colorless oil (17.8 mg, 0.068 mmol, 68% yield, 97:3 *E*:*Z*). **IR (neat):** 2976 (w), 2928 (w), 1710 (s), 1647 (m), 1442 (m), 1376 (w), 1233 (m), 1176 (s), 1143 (s), 1097 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 5.87 (tt, *J* = 7.7, 1.4 Hz, 1H), 5.69 (d, *J* = 1.5 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.70 – 2.63 (m, 2H), 2.23 (d, *J* = 1.4 Hz, 3H), 2.20 (q, *J* = 7.8 Hz, 2H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 166.3, 158.7, 131.3, 120.3, 117.2, 59.7, 32.7, 28.4, 25.5, 23.3, 14.5; **HRMS [M+H]$^+$** calcd for $C_{11}H_{18}BrO_2$: 261.0485, found: 261.0490.

2.6.8 NMR Spectra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7.14
4.05
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N
Cl
N
C6F5
Mo
MeO
Cl
OMe
Mo-A
1H NMR
(400 MHz, CDCl3)
CHCl3
toluene
toluene
0.97
4.06
6.00
1.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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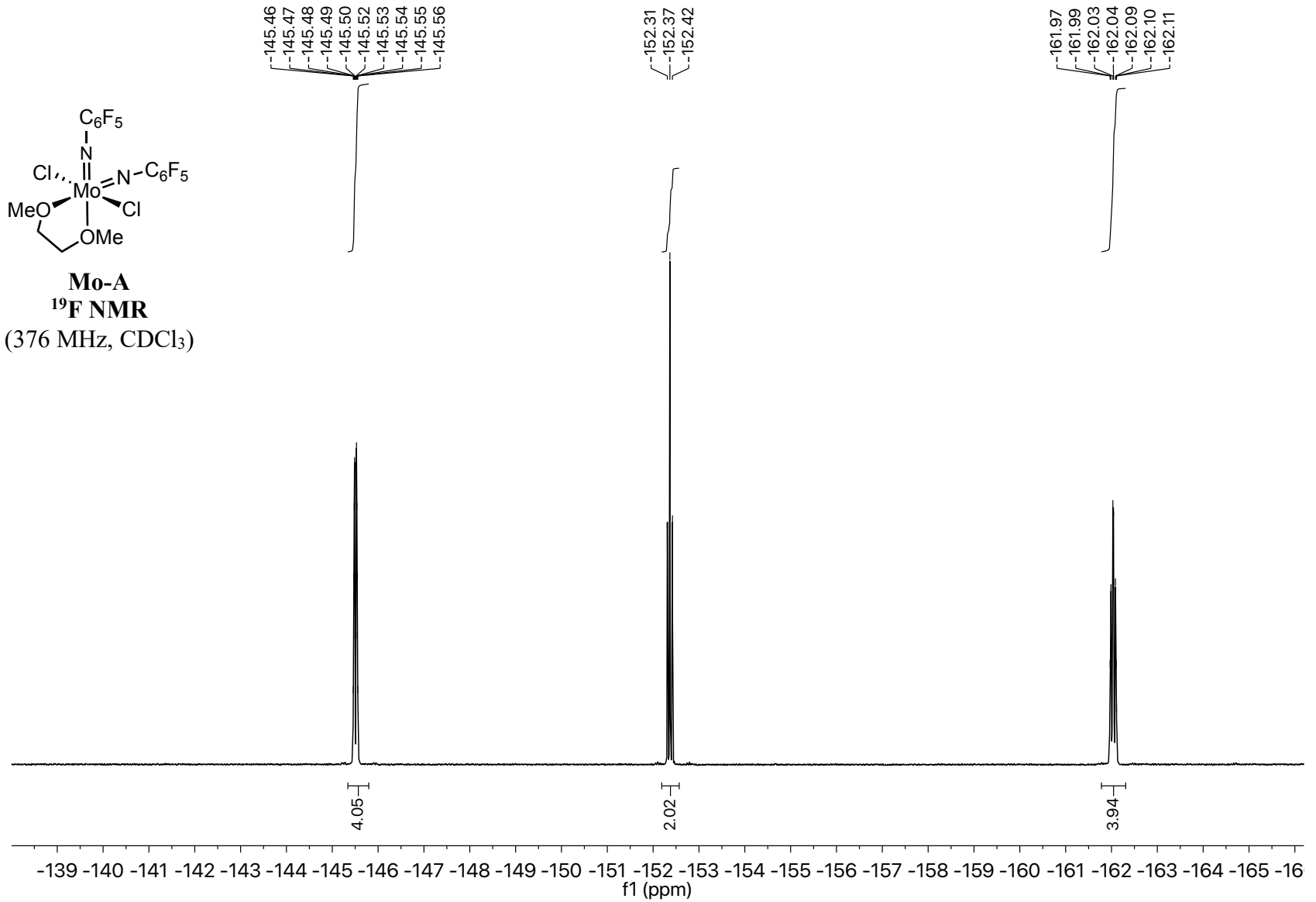
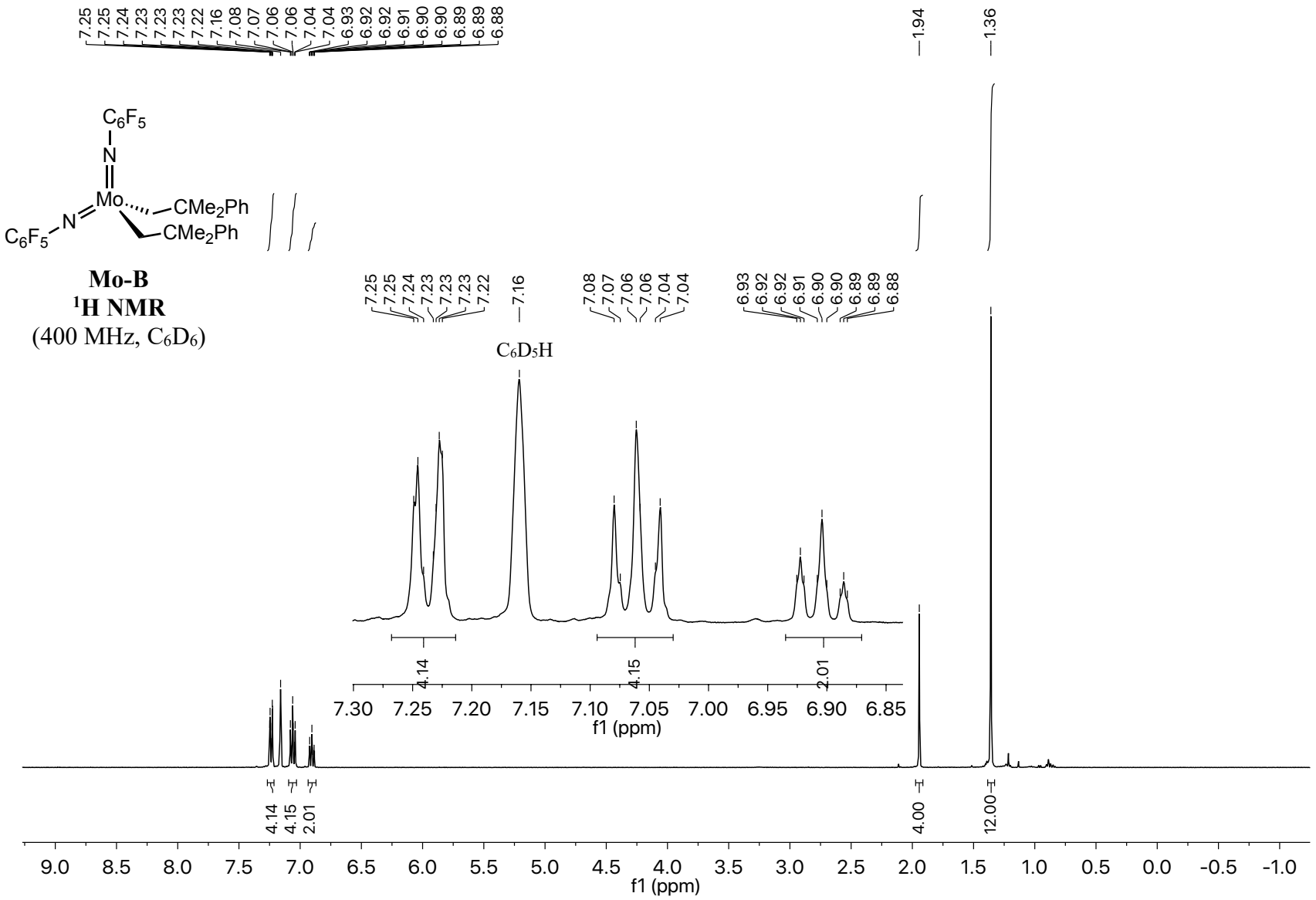
-1.0
f1 (ppm)



Mo-A
^{19}F NMR
(376 MHz, $CDCl_3$)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6.92
6.91
6.90
6.90
6.89
6.89
6.88
1.94
1.36
C6F5
N
Mo
CMe2Ph
CMe2Ph
C6F5
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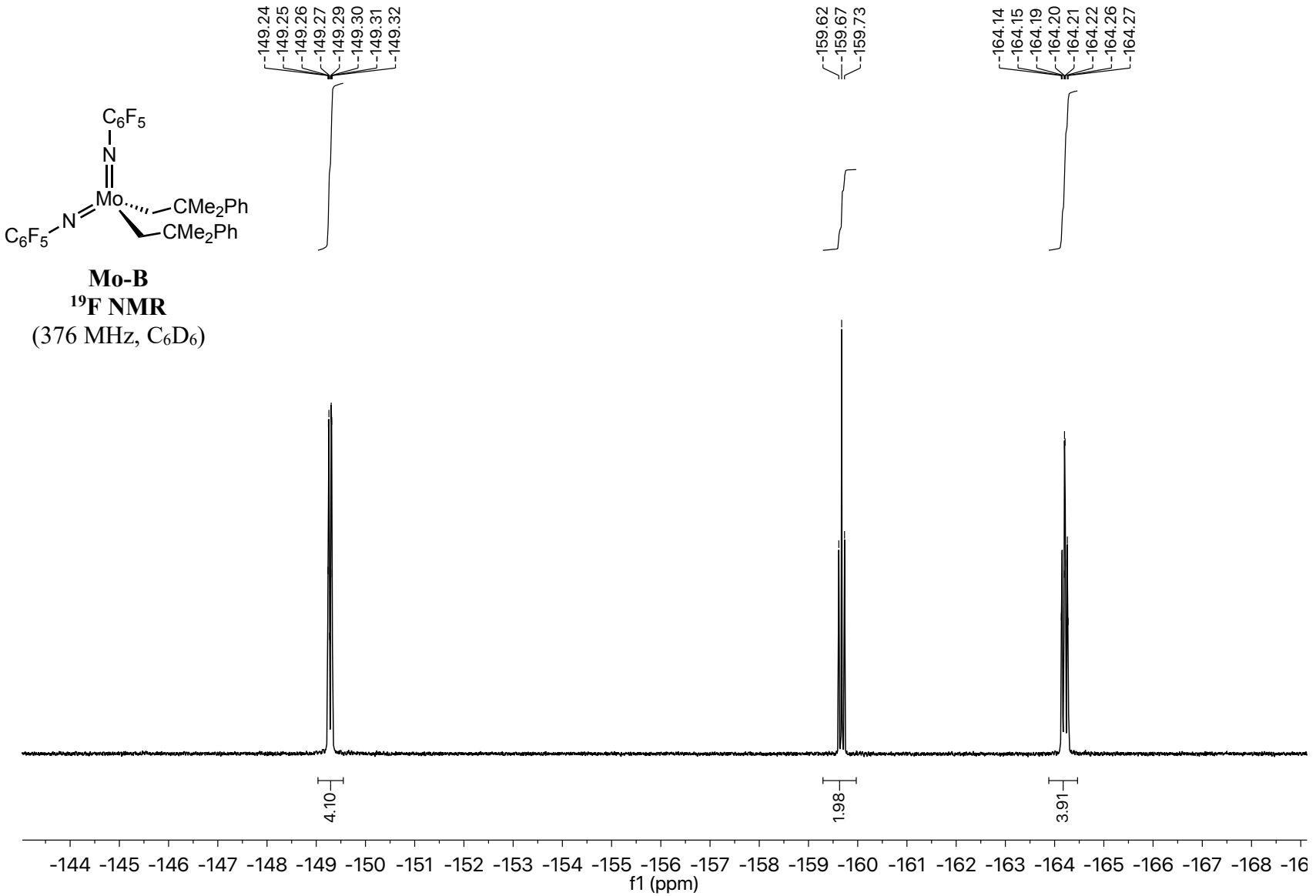
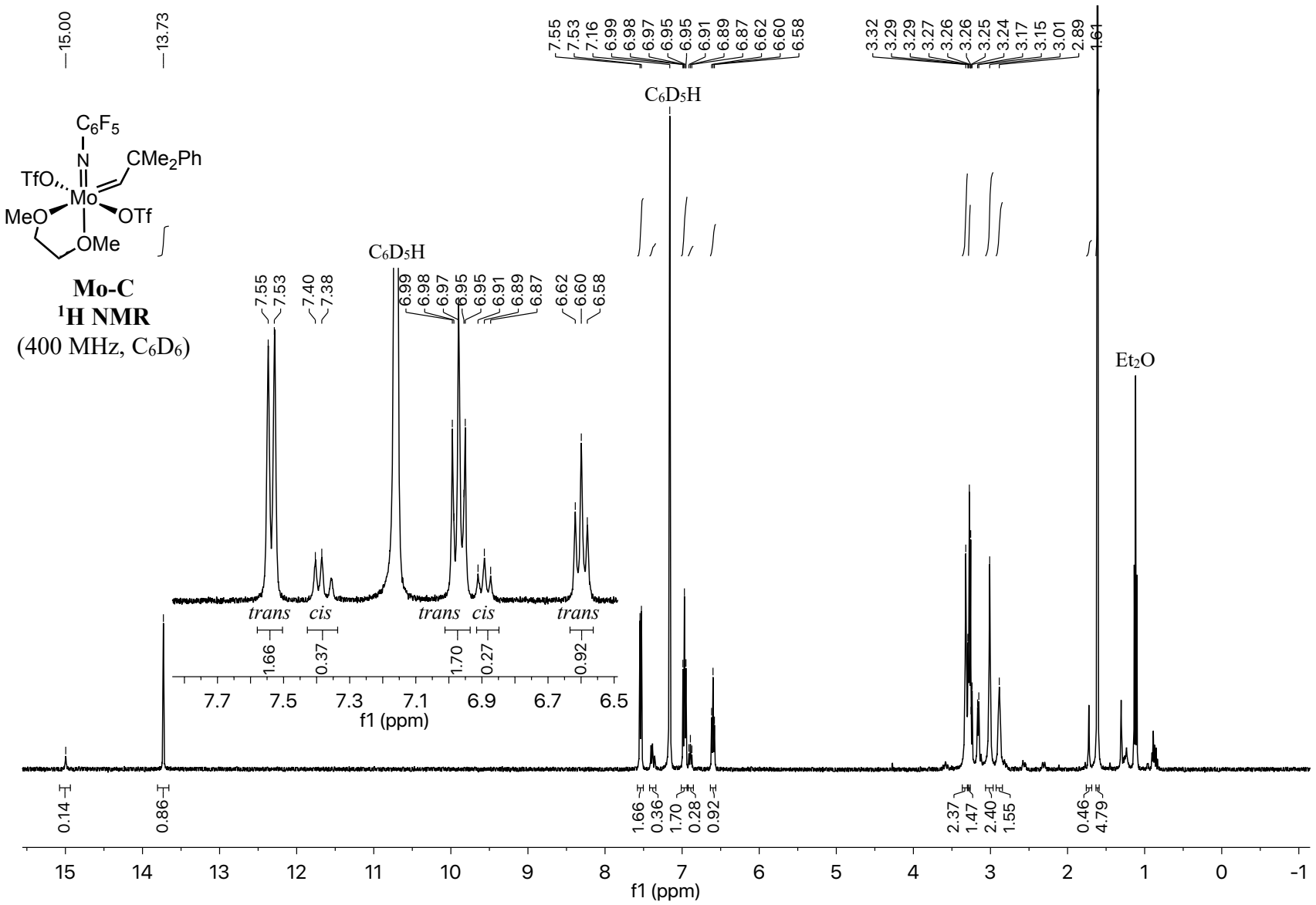
4.15
2.01
4.00
12.00
f1 (ppm)



Mo-B
^{19}F NMR
(376 MHz, C_6D_6)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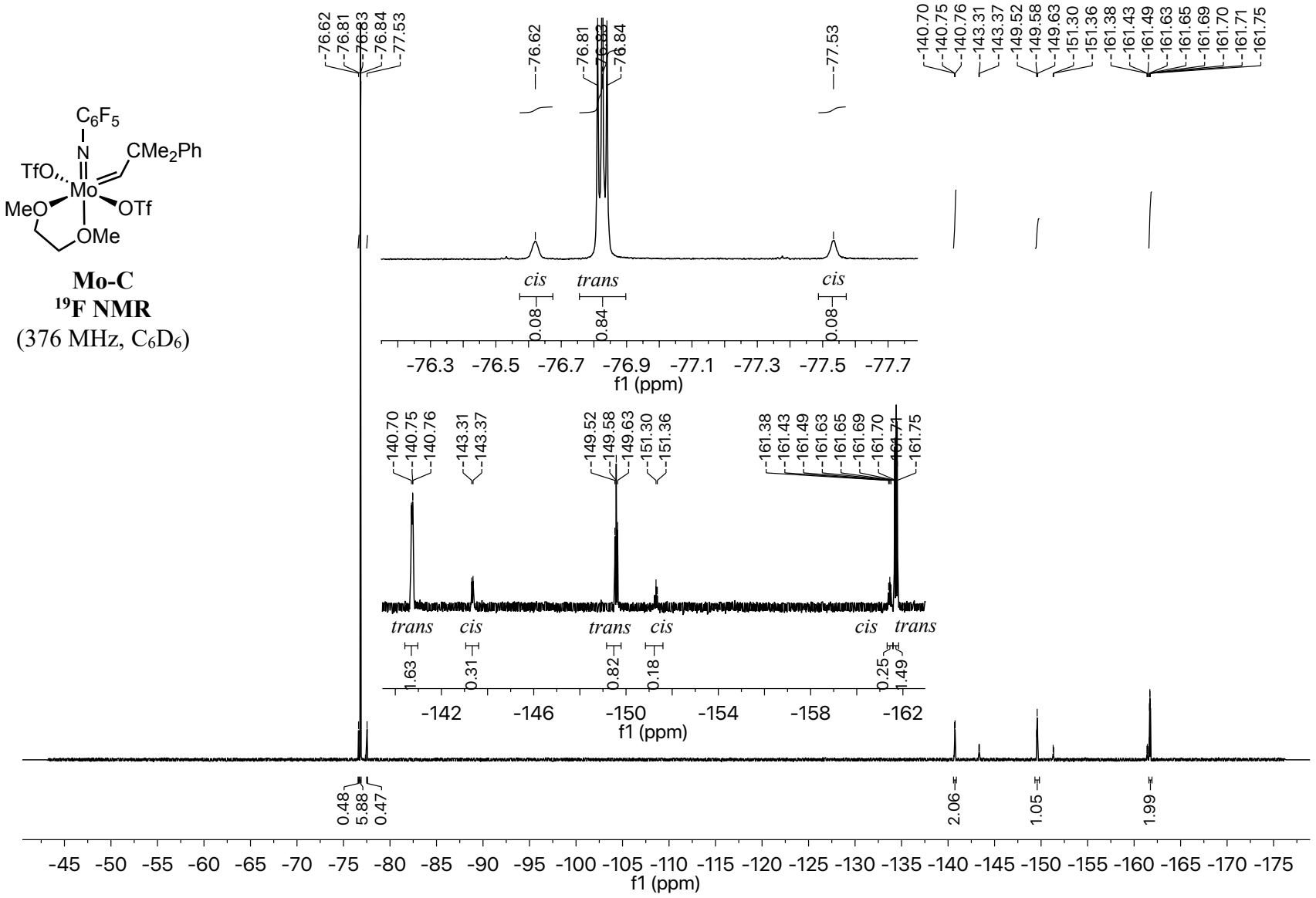
1H NMR
(400 MHz, C6D6)
C6D5H
Et2O
trans
cis
f1 (ppm)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CMe2Ph
TfO
Mo
MeO
OTf
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Mo-C
19F NMR
(376 MHz, C6D6)
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trans
cis
0.08
0.84
0.08
f1 (ppm)
trans
cis
trans
cis
cis
trans
1.63
0.31
0.82
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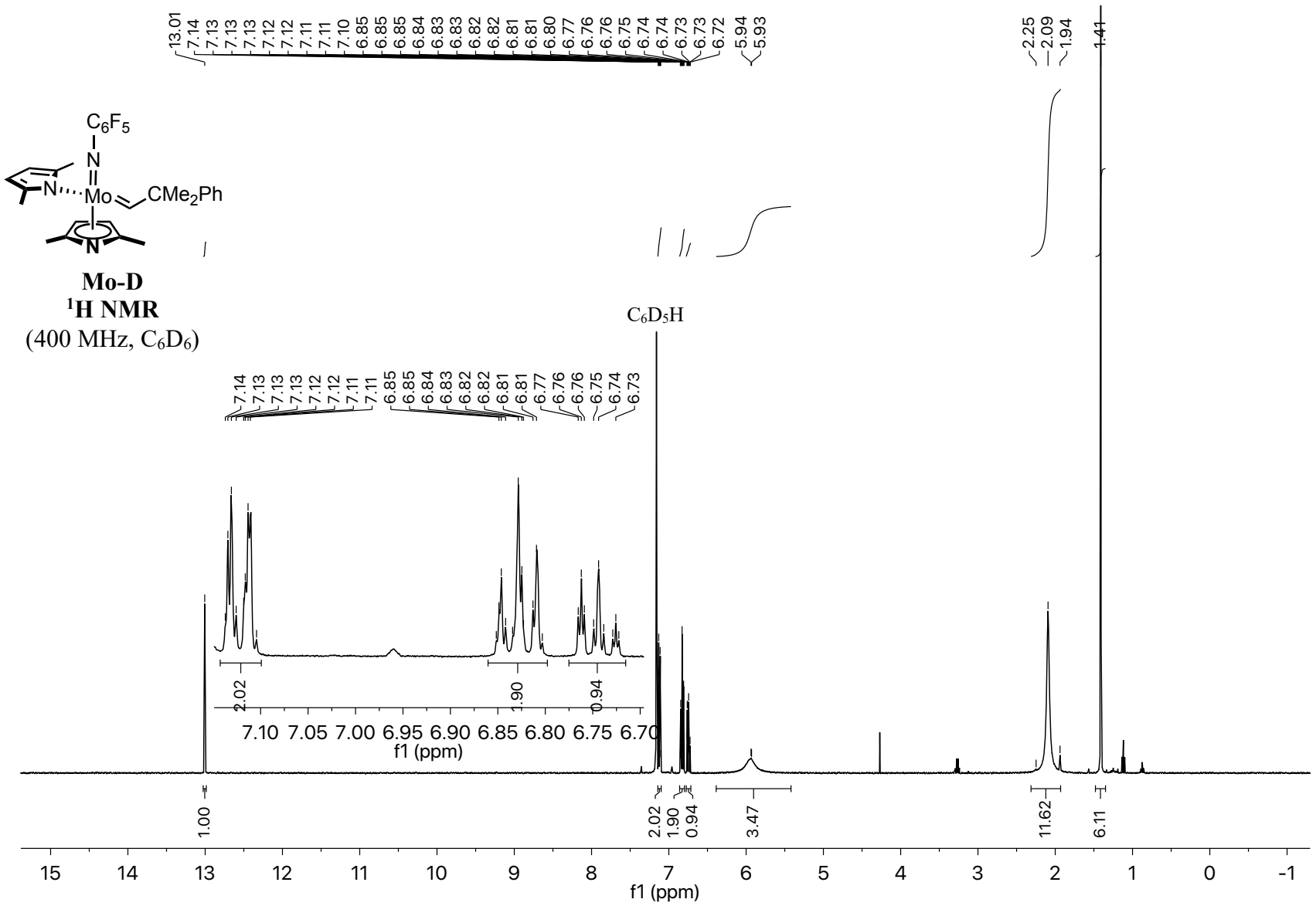
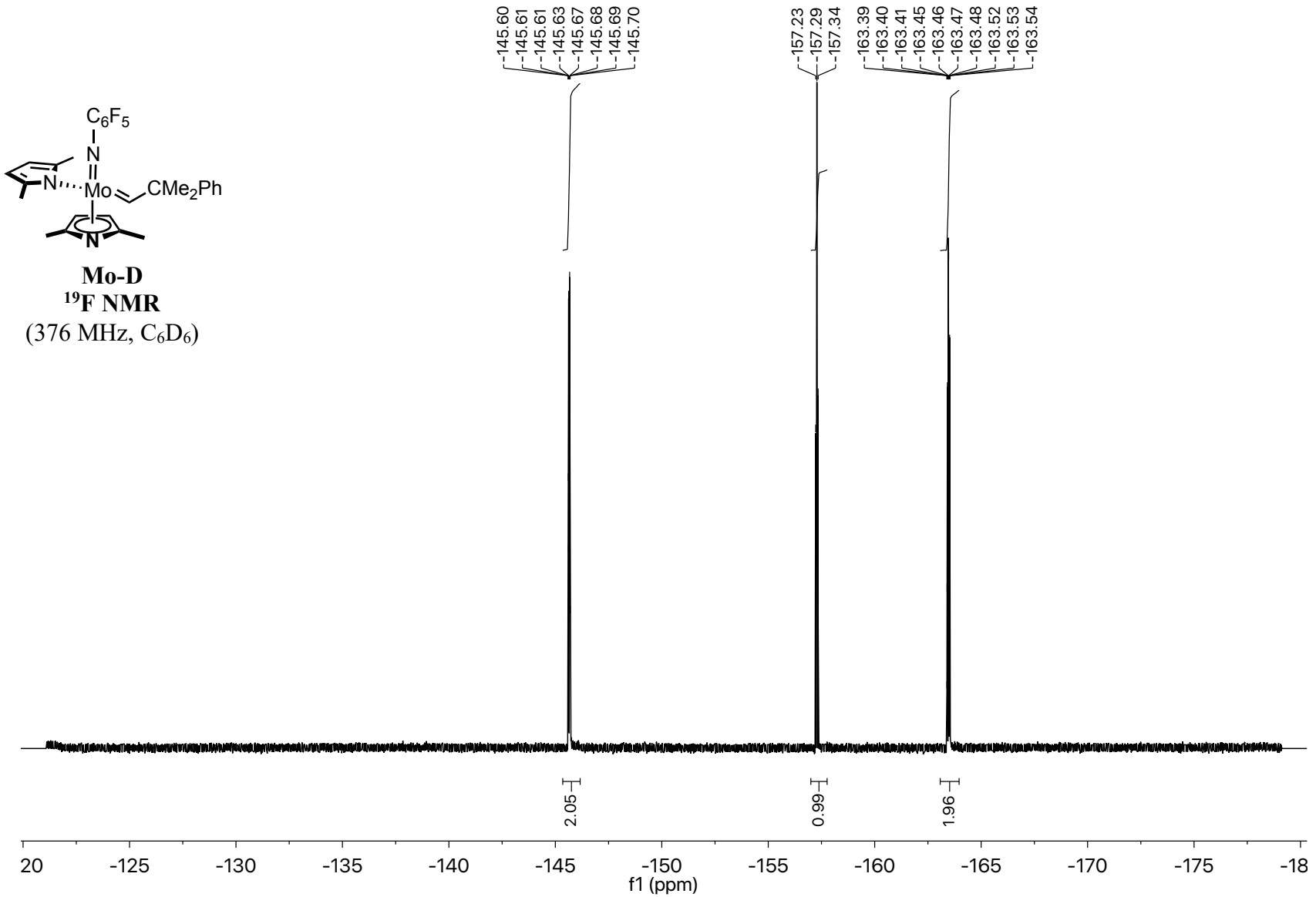
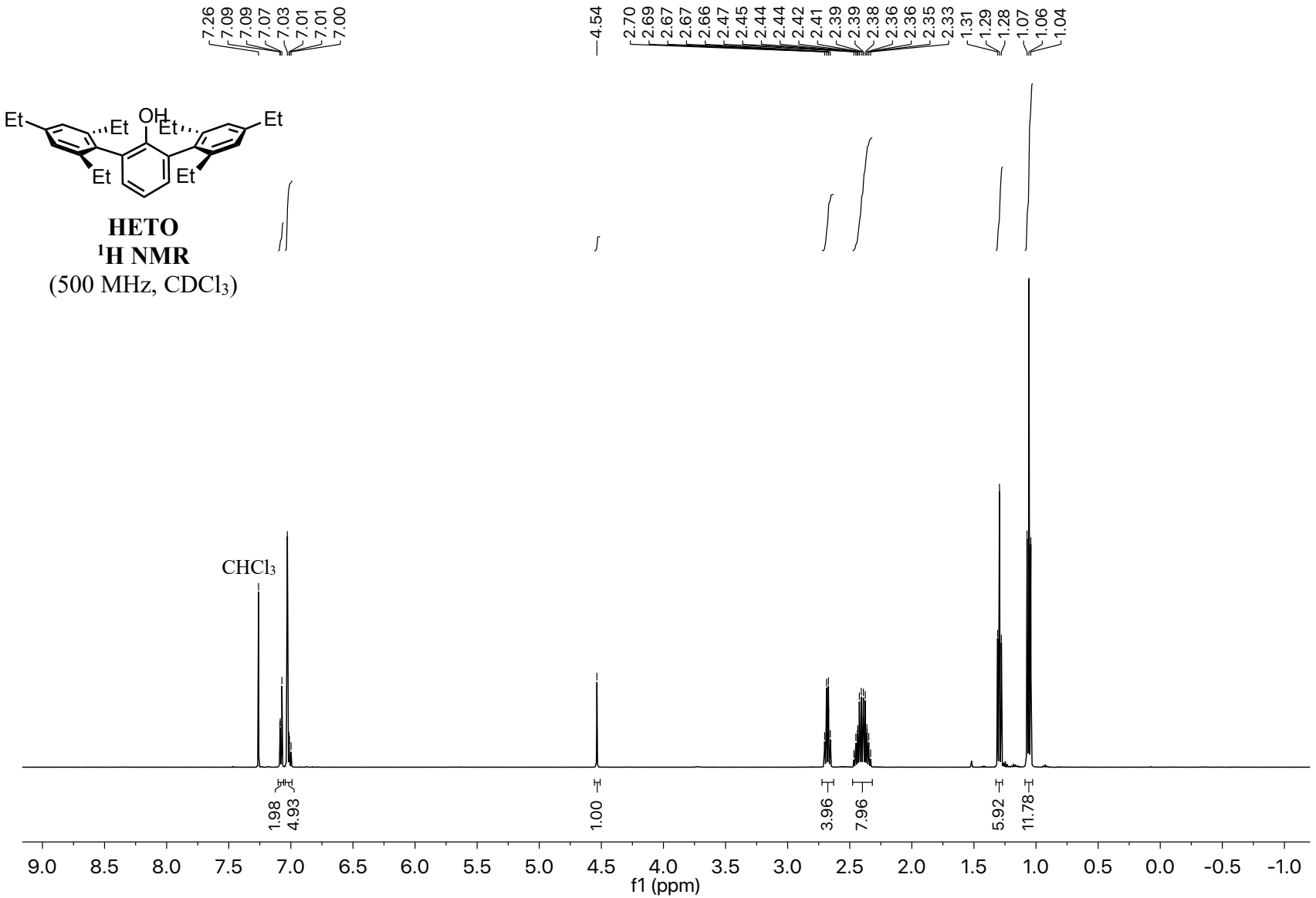
1.05
1.99
f1 (ppm)

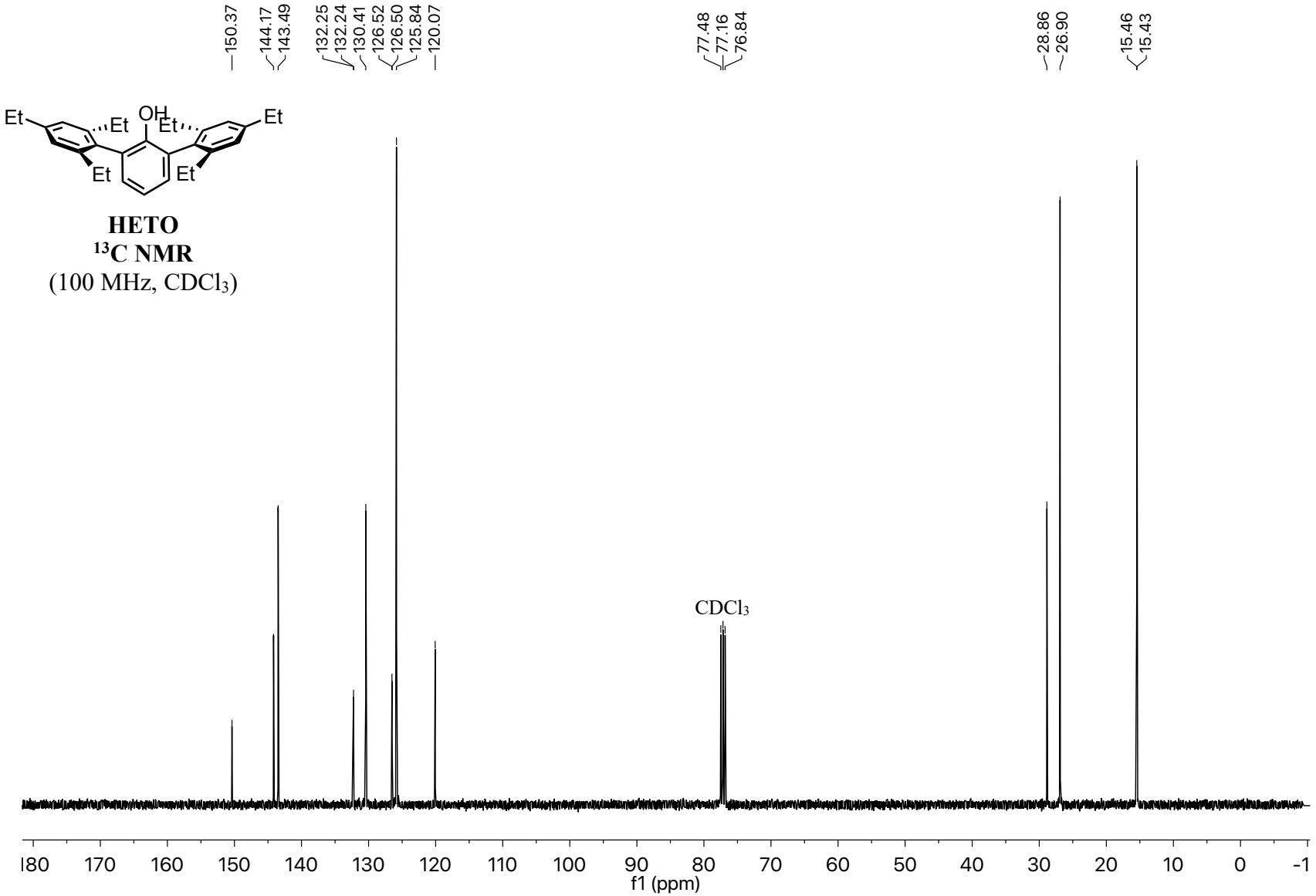

C6F5
N
Mo
CMe2Ph
Mo-D
1H NMR
(400 MHz, C6D6)
C6D5H
f1 (ppm)



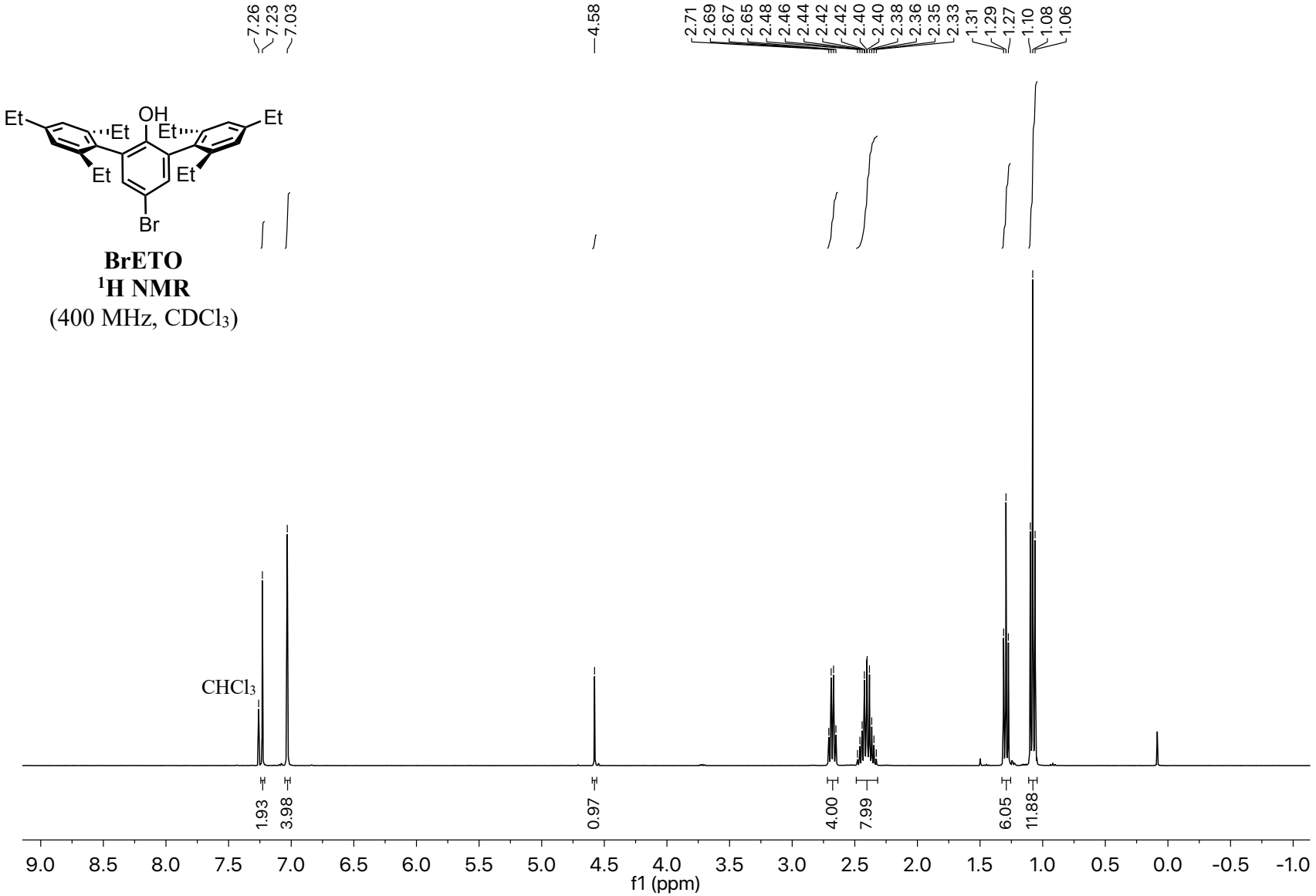
Mo-D
^{19}F NMR
(376 MHz, C_6D_6)



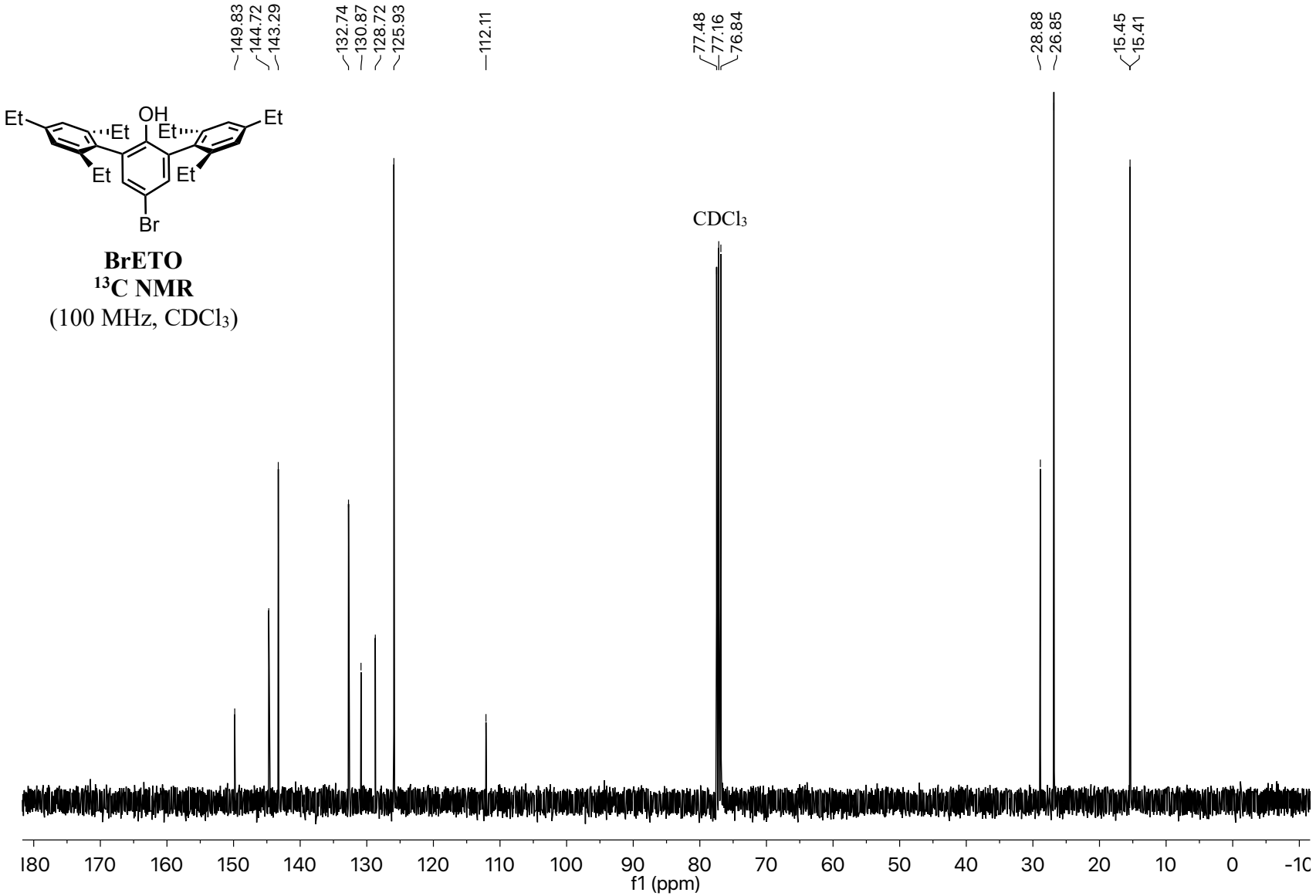
HETO
^{1}H NMR
(500 MHz, $CDCl_3$)

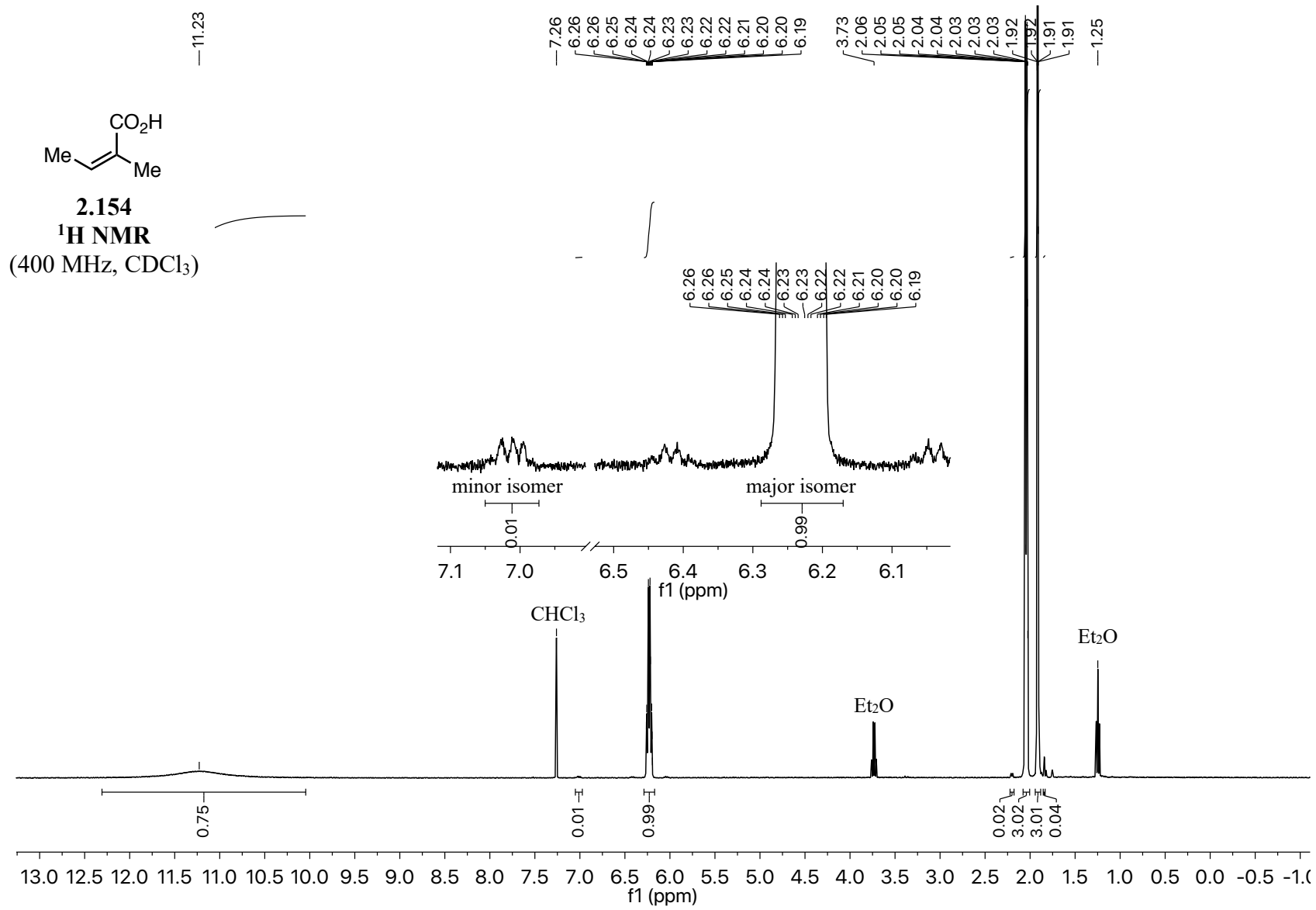


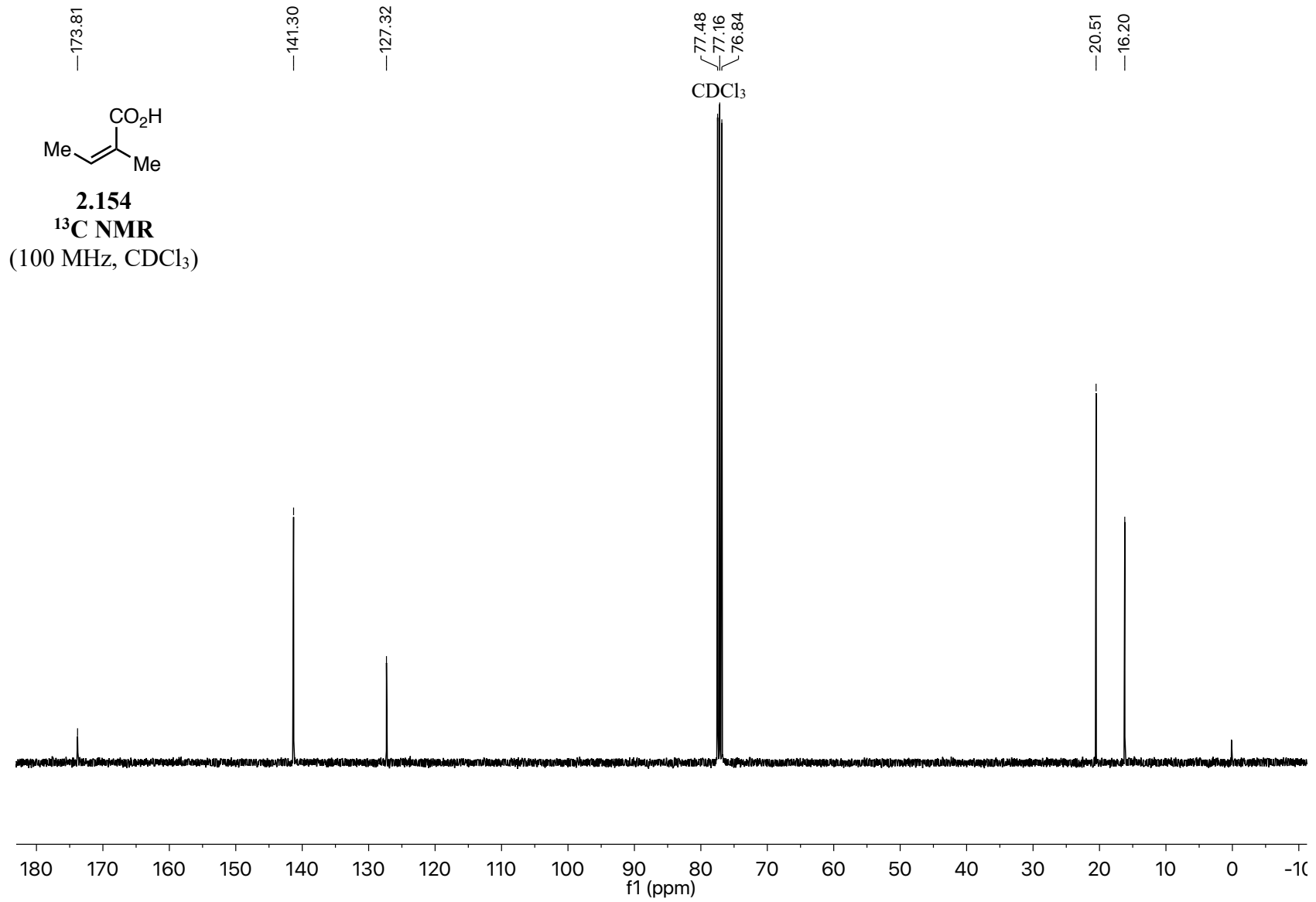
HETO
^{13}C NMR
(100 MHz, $CDCl_3$)



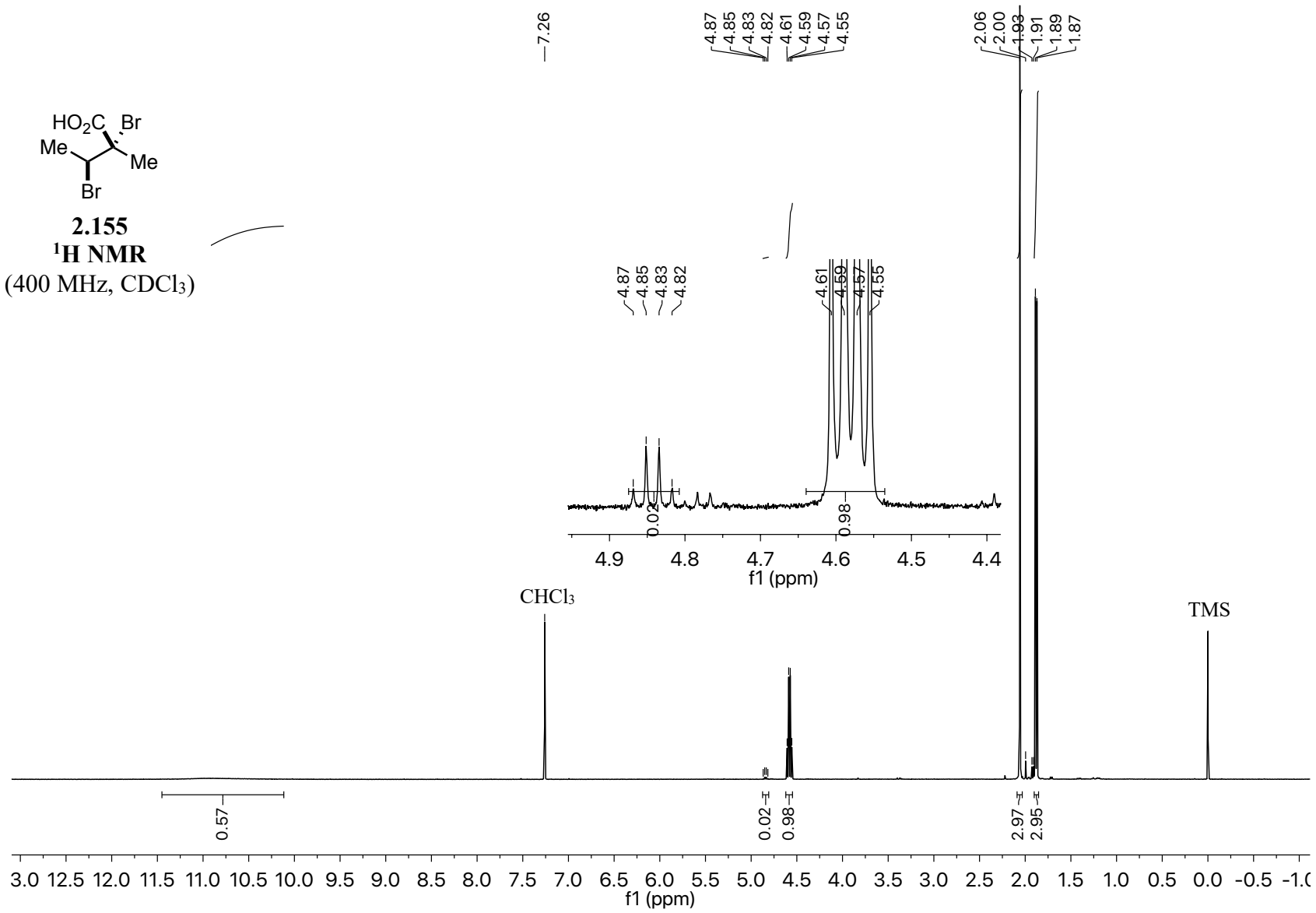
BrETO
^{1}H NMR
(400 MHz, $CDCl_3$)

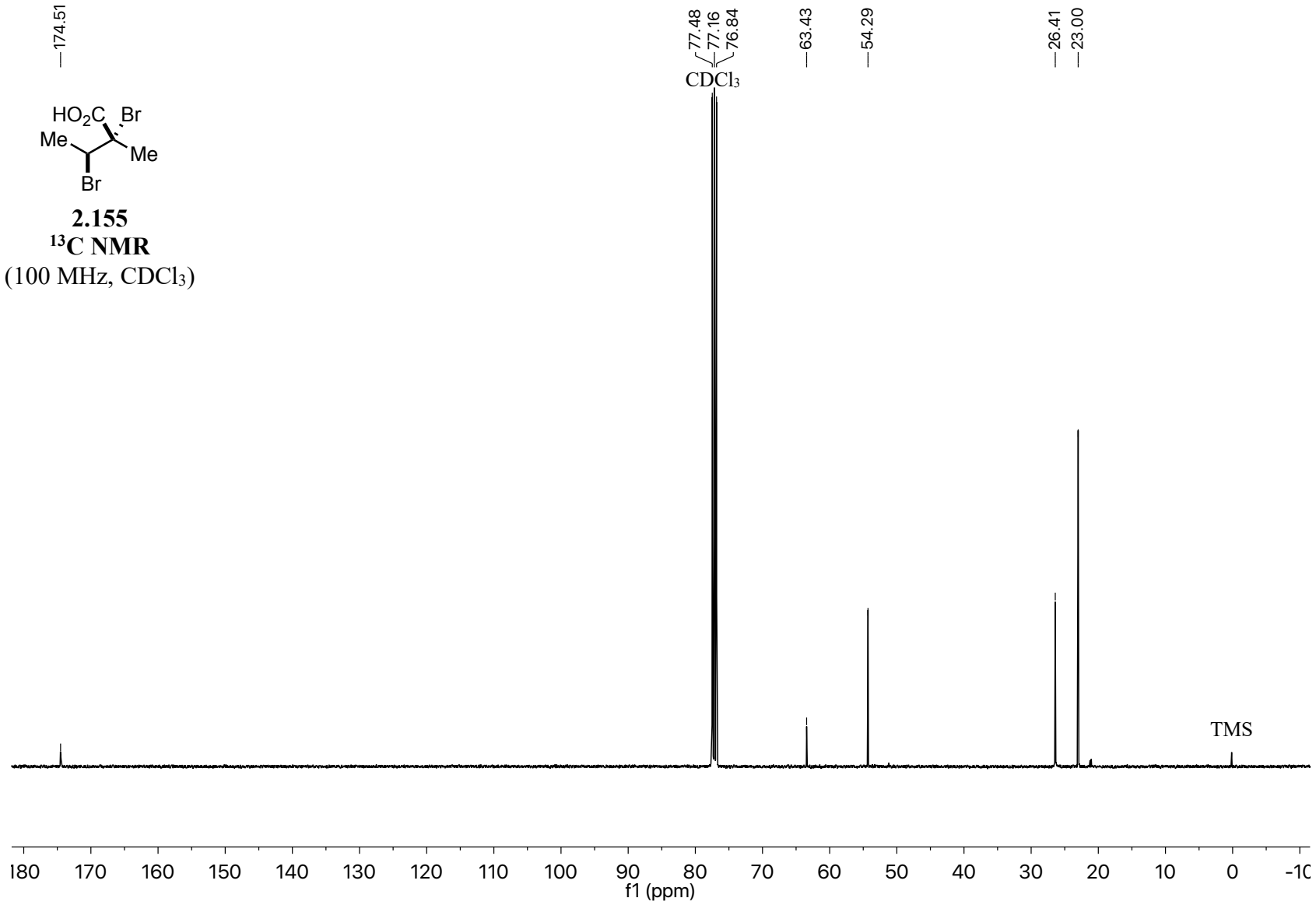

149.83
144.72
143.29
132.74
130.87
128.72
125.93
112.11
77.48
77.16
76.84
28.88
26.85
15.45
15.41
CDCl3
OH
Et
Et
Et
Et
Et
Et
Br
BrETO
13C NMR
(100 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


CO2H
Me
Me
2.154
1H NMR
(400 MHz, CDCl3)
minor isomer
major isomer
CHCl3
Et2O
Et2O
f1 (ppm)

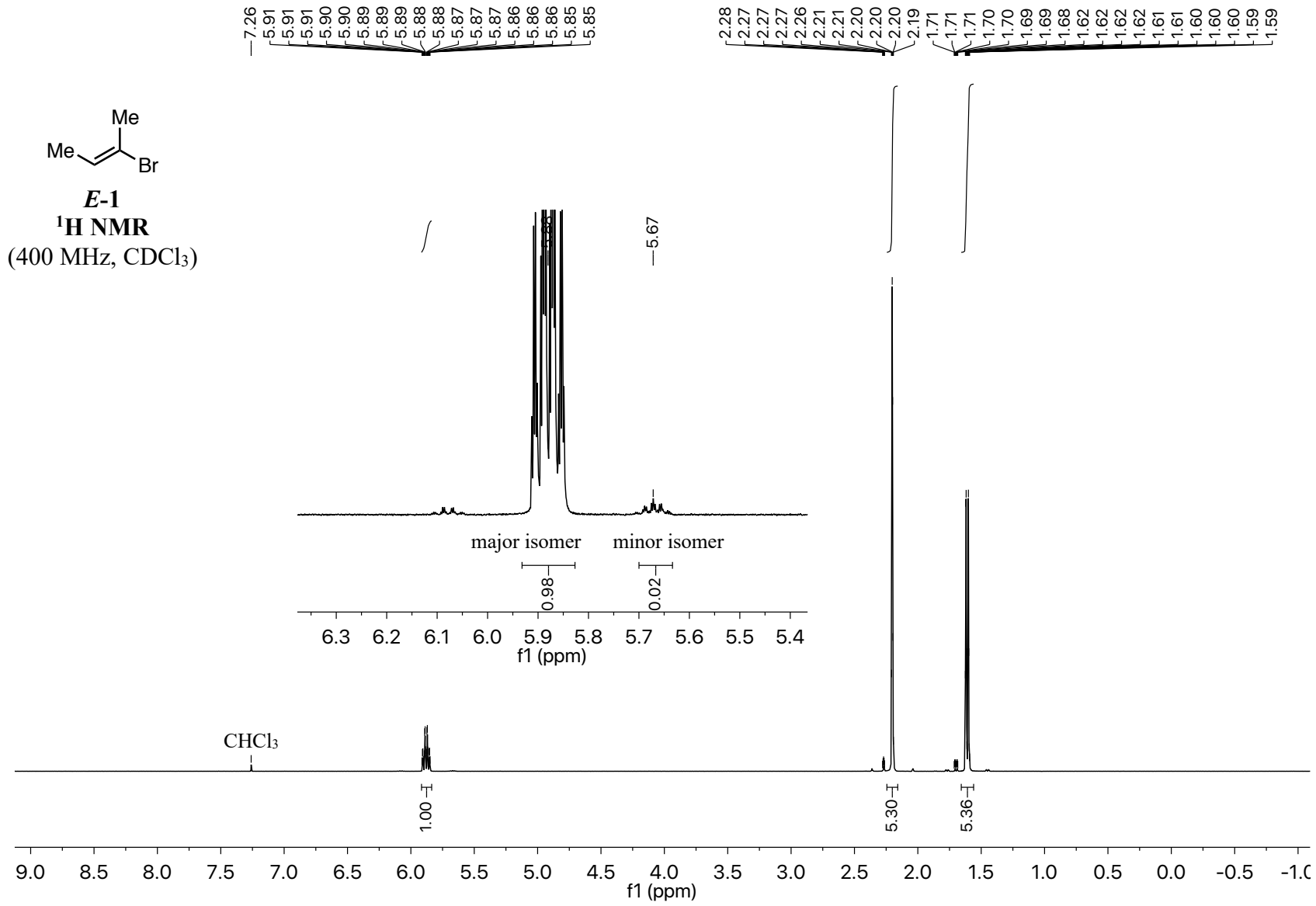


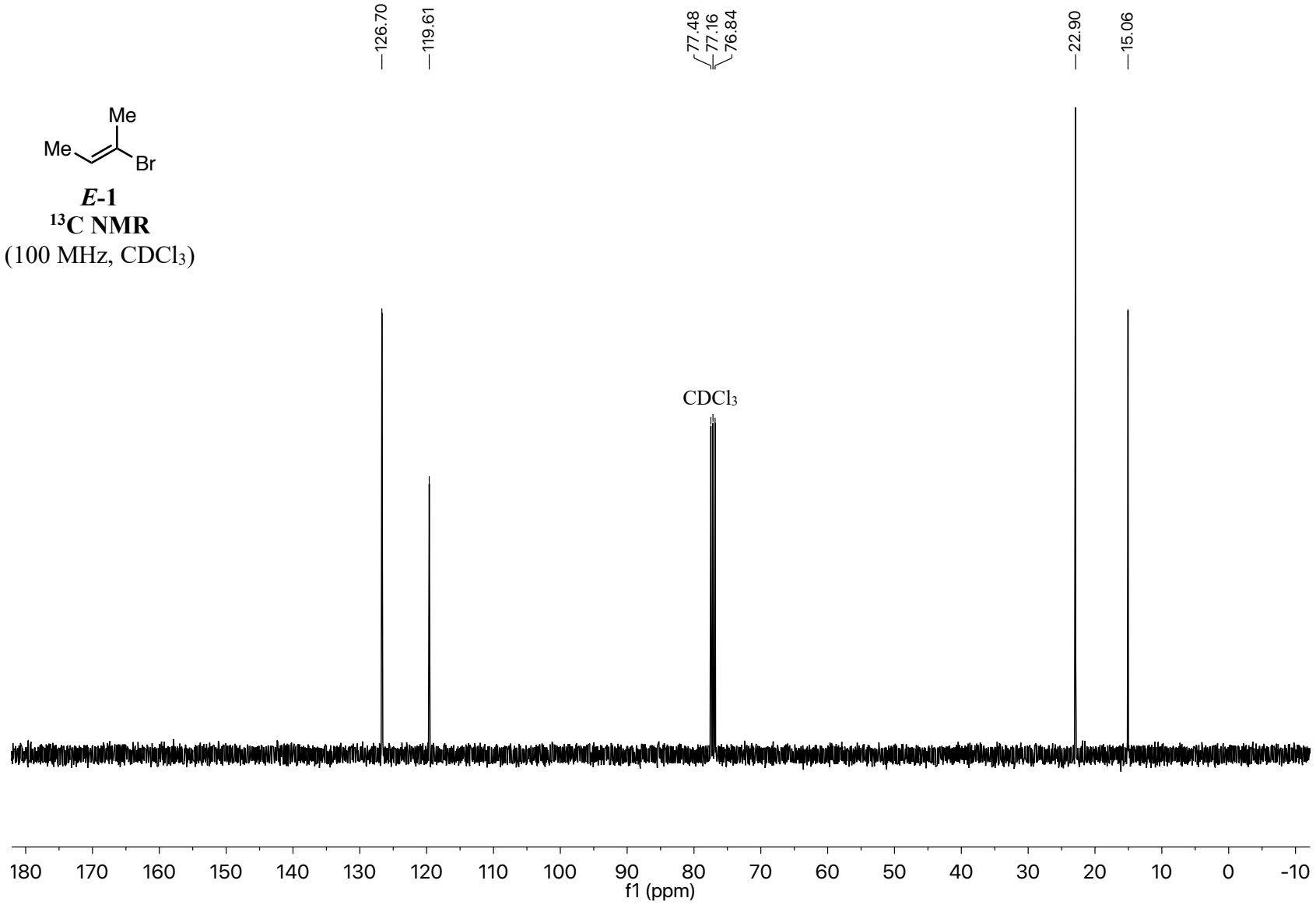
2.154
^{13}C NMR
(100 MHz, $CDCl_3$)


HO2C Br
Me
Me
Br
2.155
1H NMR
(400 MHz, CDCl3)
7.26
4.87
4.85
4.83
4.82
4.61
4.59
4.57
4.55
2.06
2.00
1.93
1.91
1.89
1.87
CHCl3
TMS
0.57
0.02
0.98
2.97
2.95
f1 (ppm)



2.155
^{13}C NMR
(100 MHz, $CDCl_3$)

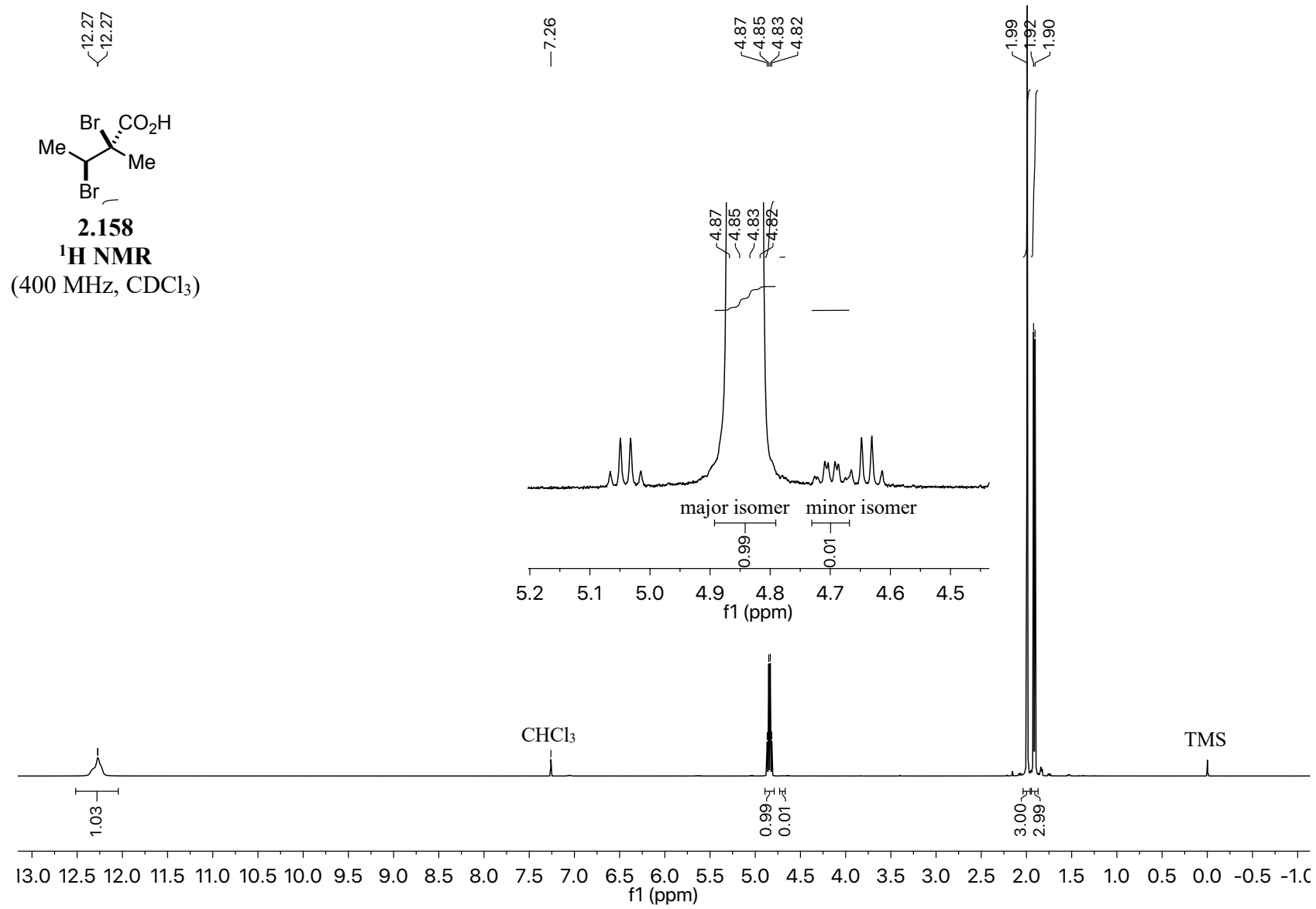

Me
Me
Br
E-1
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
0.98
0.02
CHCl3
1.00
5.30
5.36
f1 (ppm)

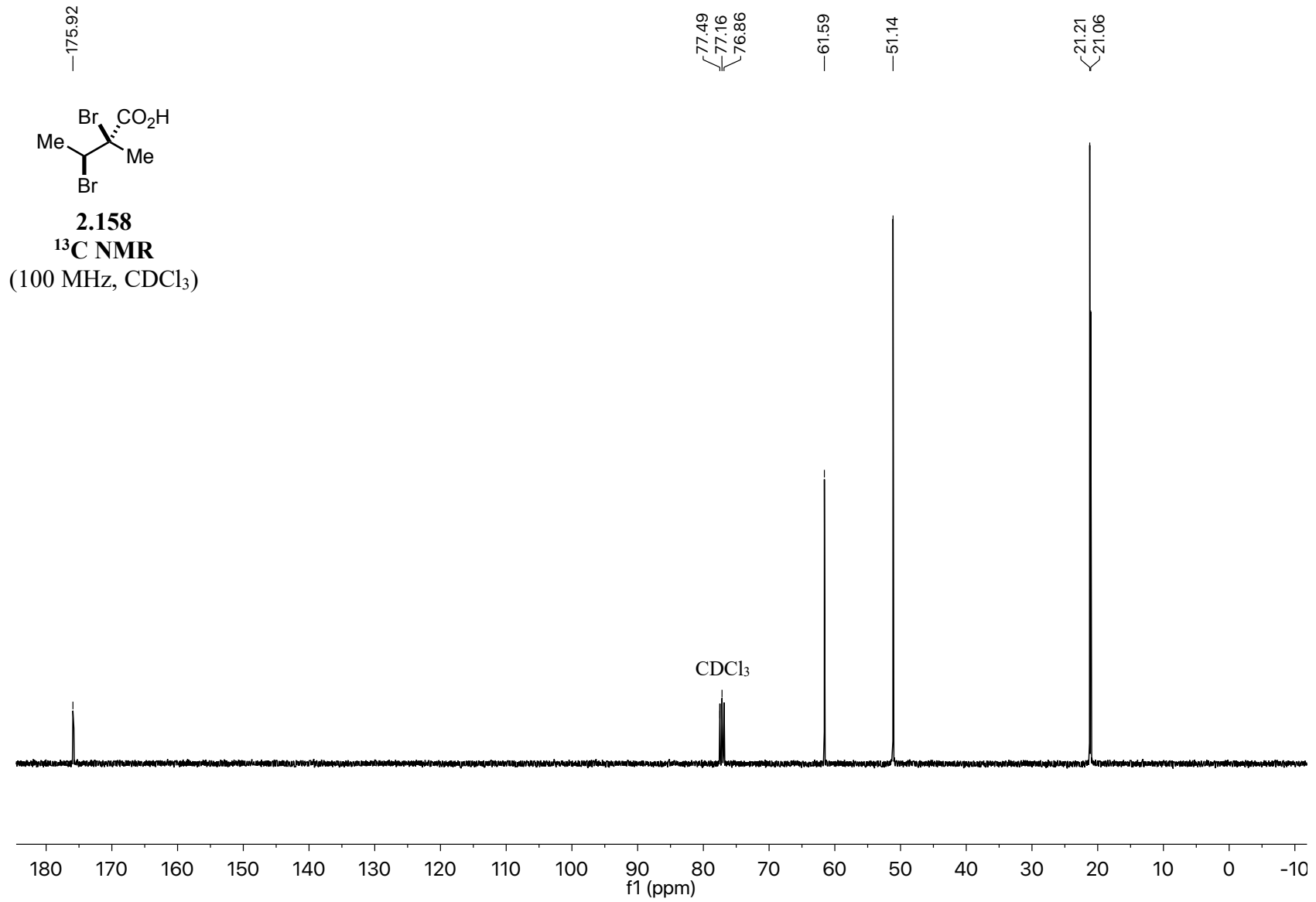


***E*-1**

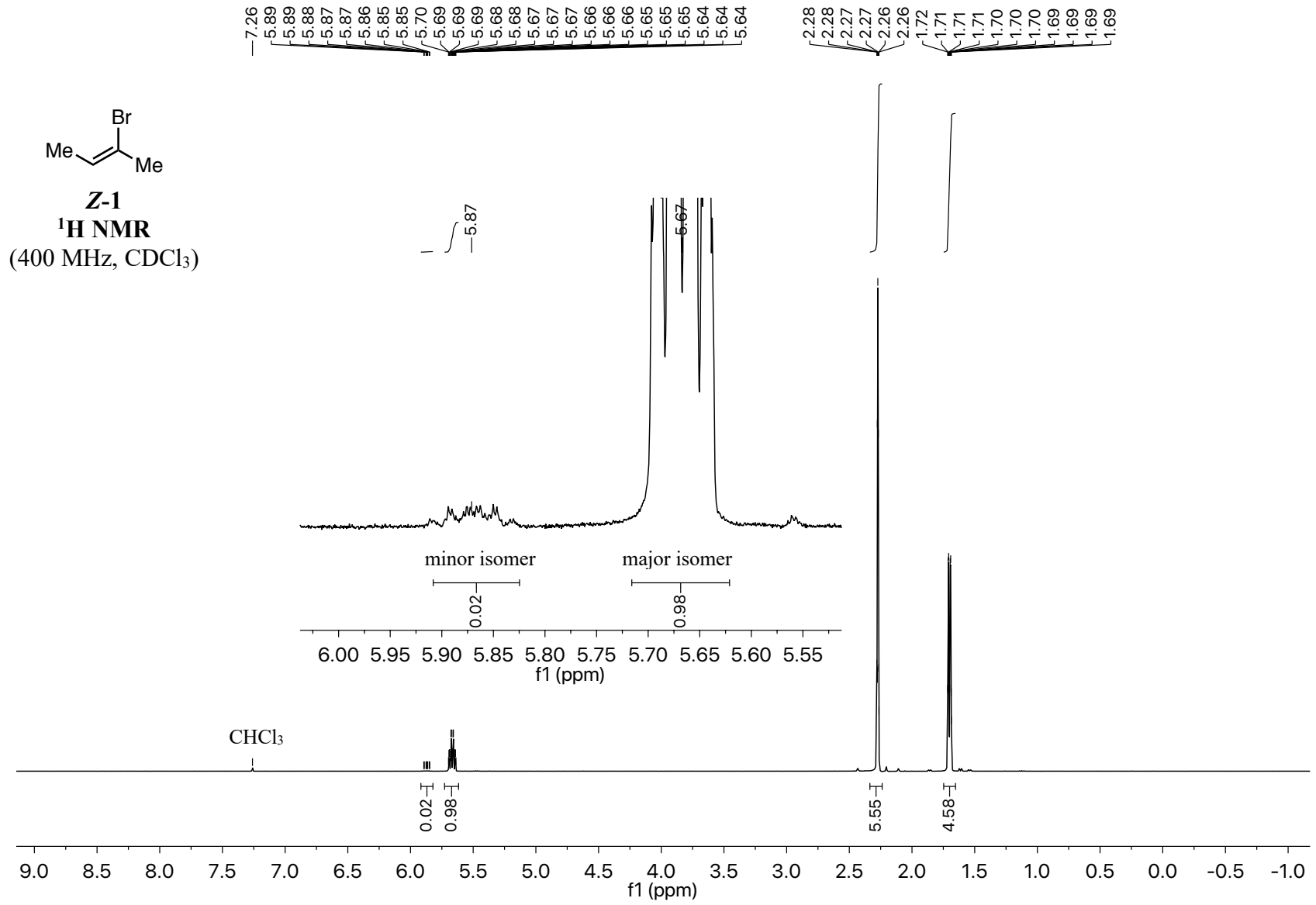
^{13}C NMR

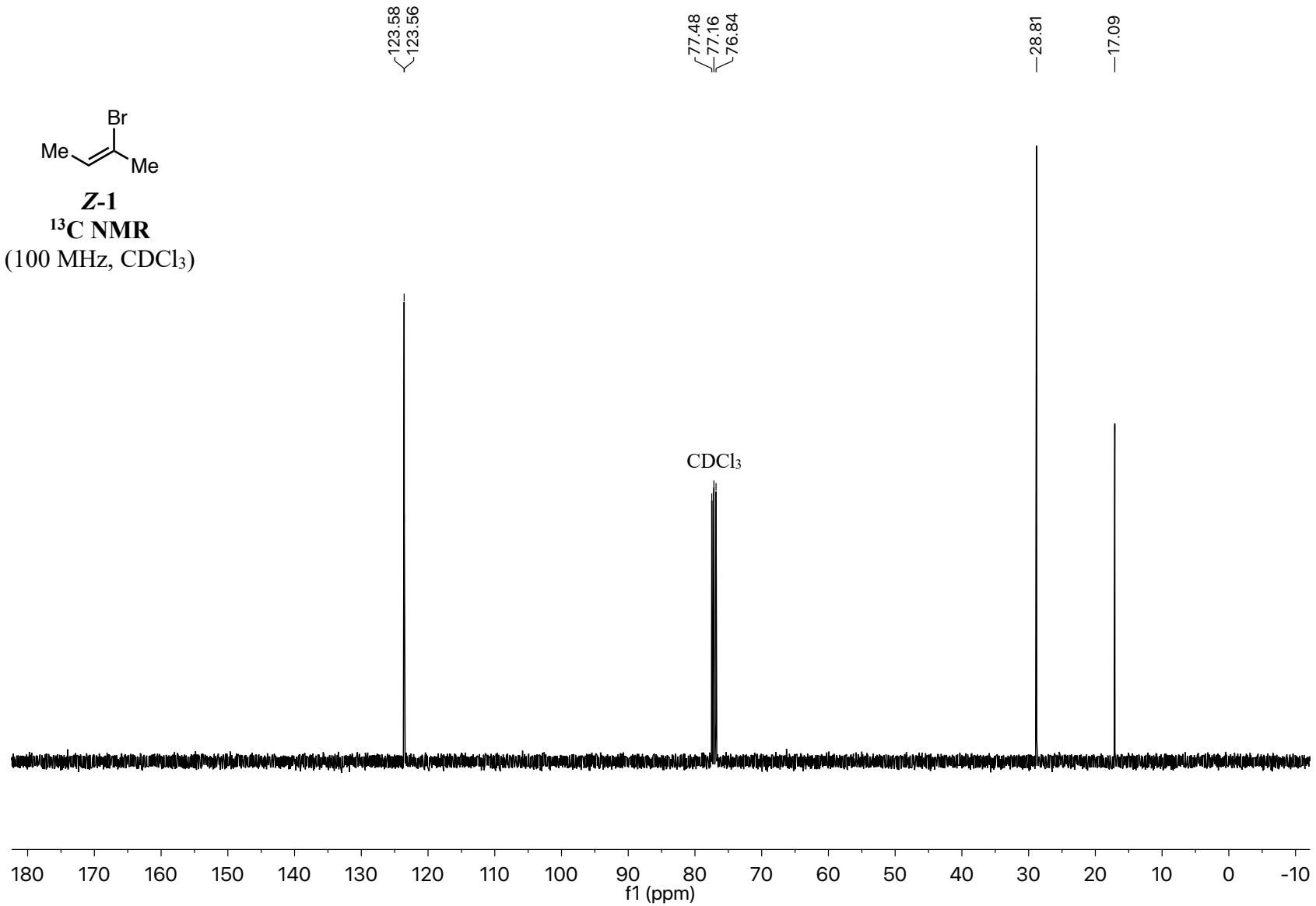
(100 MHz, $CDCl_3$)


12.27
12.27
7.26
4.87
4.85
4.83
4.82
1.99
1.92
1.90
Br
CO2H
Me
Me
Br
2.158
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
0.99
0.01
5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5
f1 (ppm)
CHCl3
TMS
1.03
0.99
0.01
3.00
2.99
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)



2.158
^{13}C NMR
(100 MHz, $CDCl_3$)

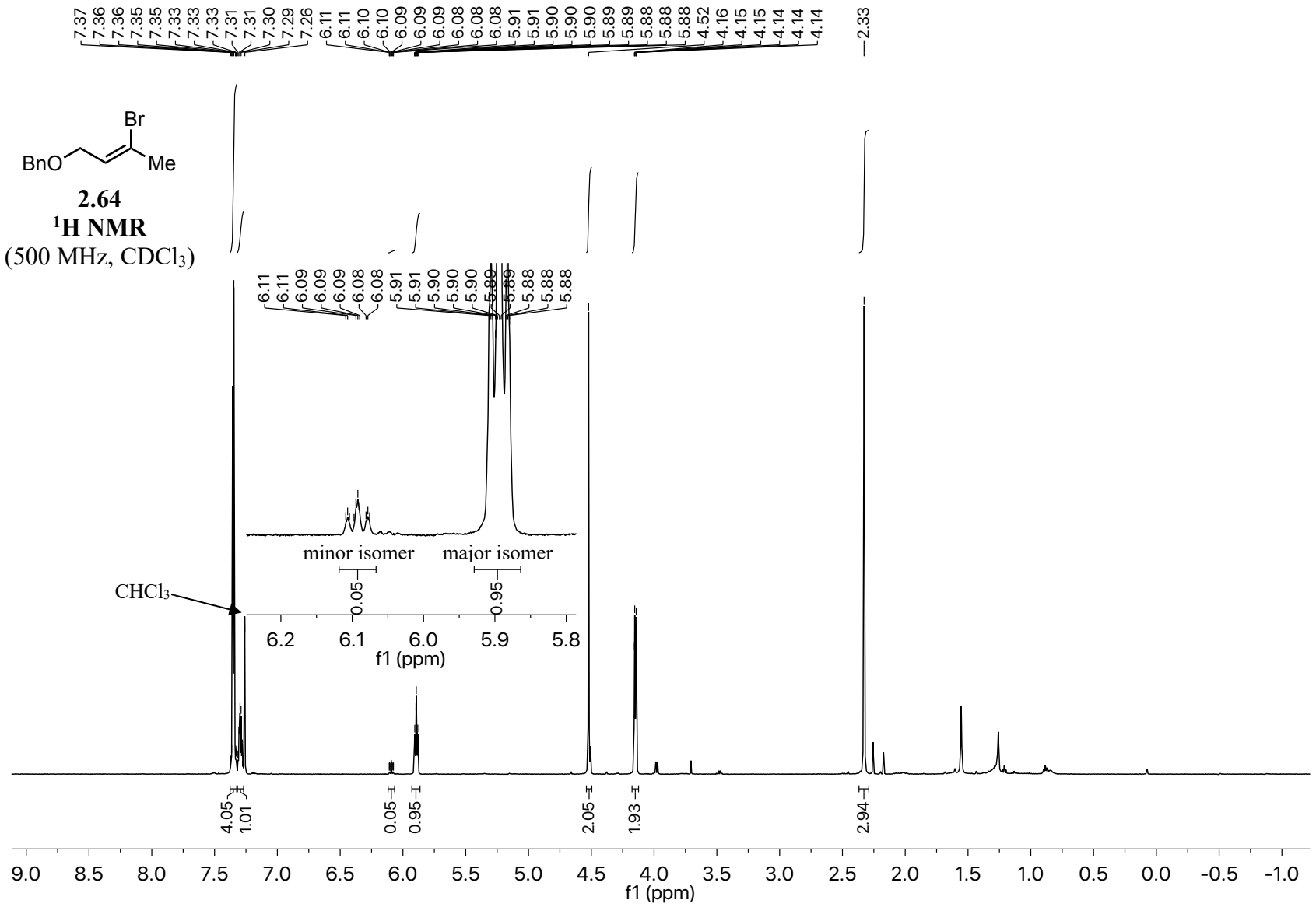

Br
Me
Me
Z-1
1H NMR
(400 MHz, CDCl3)
7.26
5.89
5.89
5.88
5.87
5.87
5.86
5.85
5.85
5.70
5.69
5.69
5.69
5.68
5.68
5.67
5.67
5.67
5.66
5.66
5.66
5.65
5.65
5.65
5.64
5.64
5.64
2.28
2.28
2.27
2.27
2.26
2.26
1.72
1.71
1.71
1.71
1.70
1.70
1.70
1.69
1.69
1.69
1.69
5.87
5.67
minor isomer
major isomer
0.02
0.98
6.00 5.95 5.90 5.85 5.80 5.75 5.70 5.65 5.60 5.55
f1 (ppm)
CHCl3
0.02
0.98
5.55
4.58
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

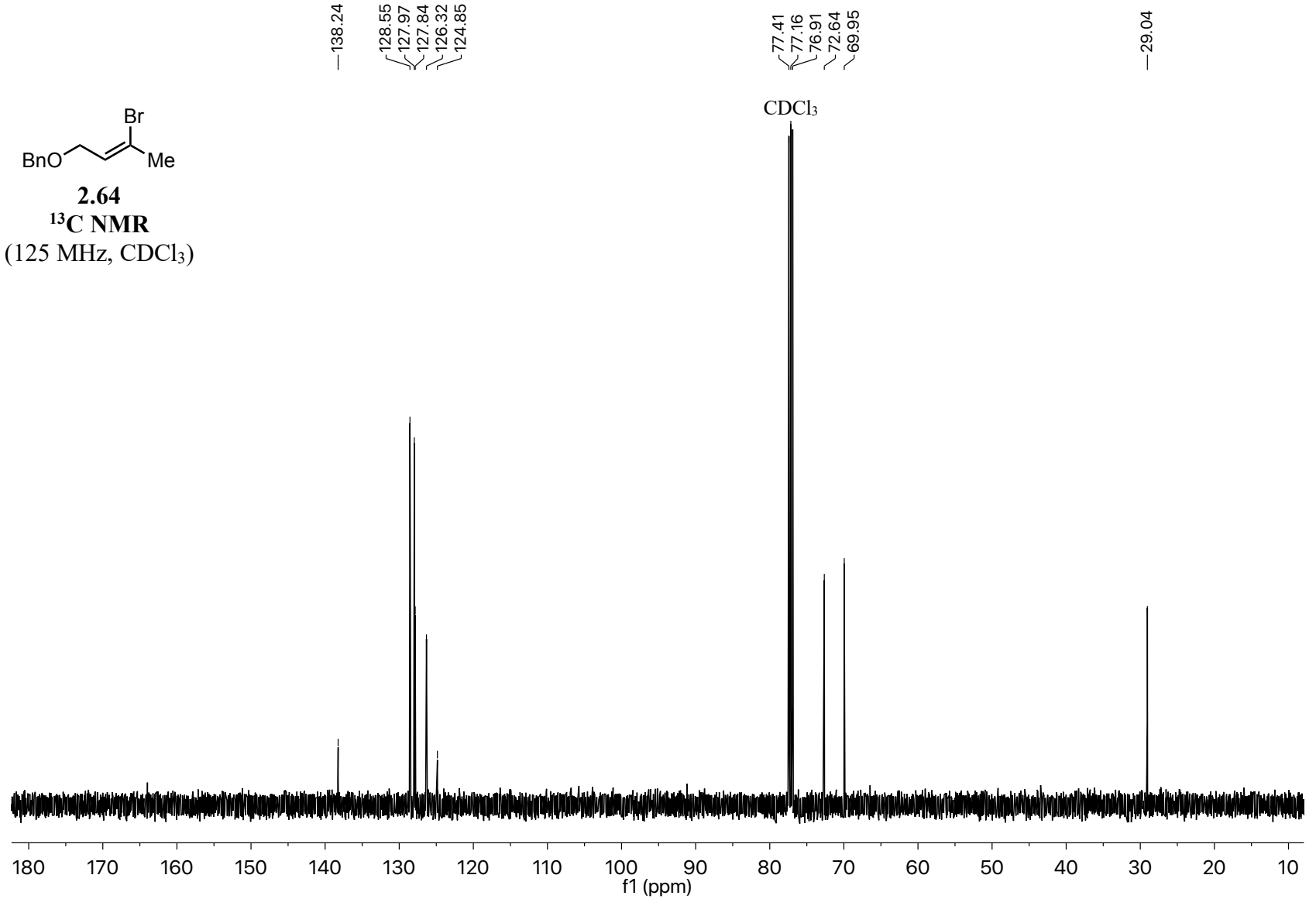


***Z*-1**

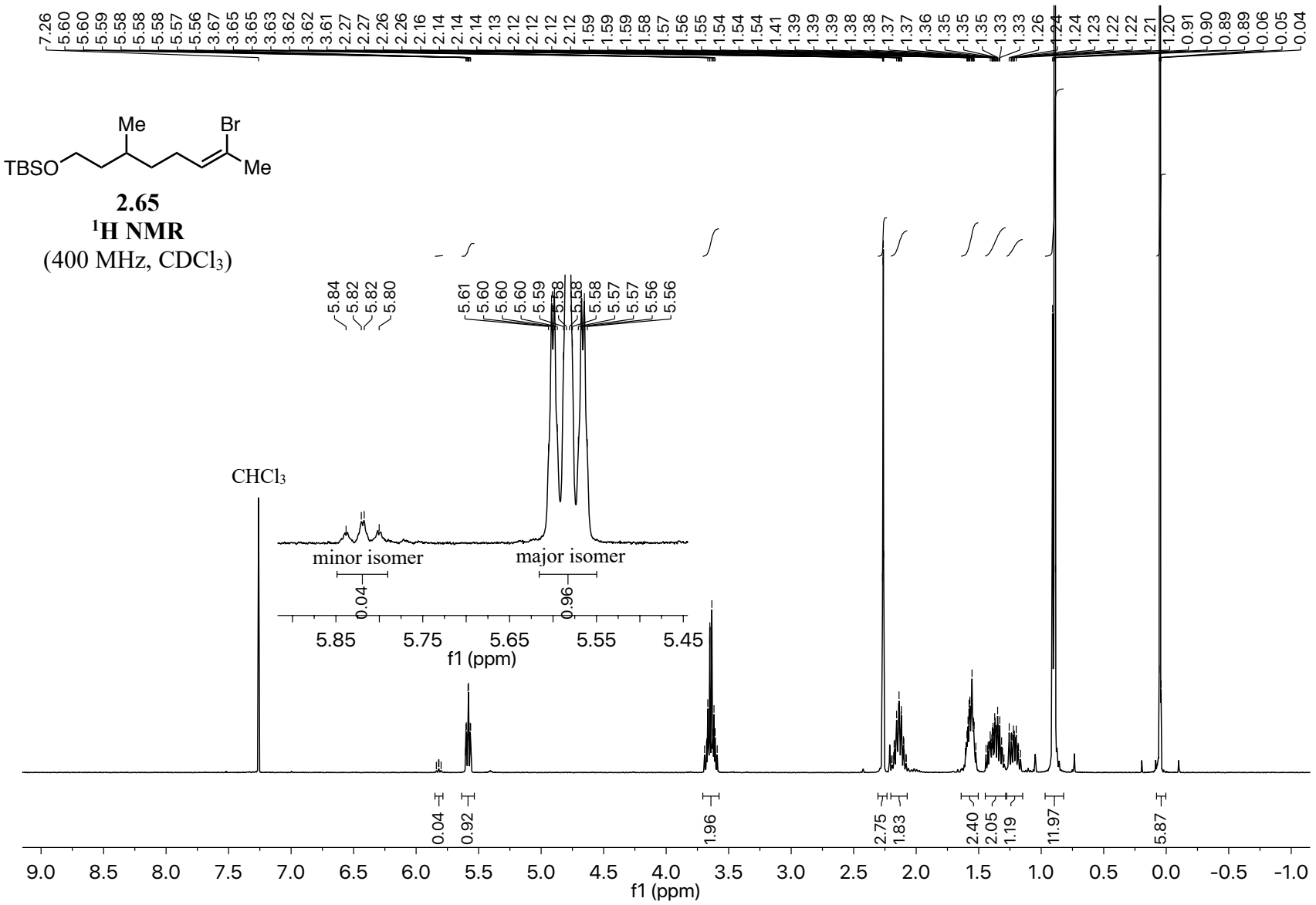
^{13}C NMR

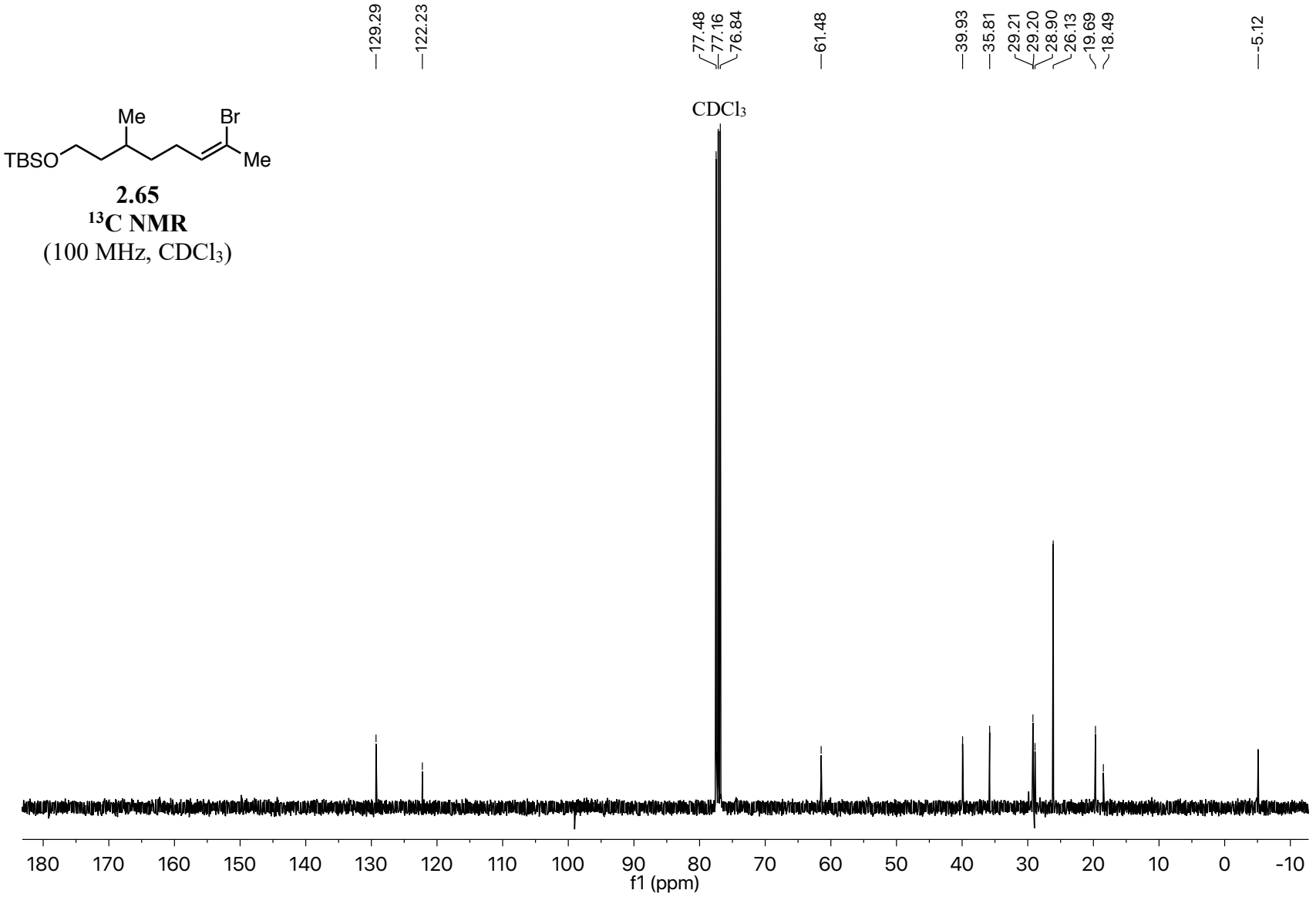
(100 MHz, $CDCl_3$)


Br
BnO
Me
2.64
1H NMR
(500 MHz, CDCl3)
minor isomer
major isomer
0.05
0.95
CHCl3
f1 (ppm)
4.05
1.01
0.05
0.95
2.05
1.93
2.94

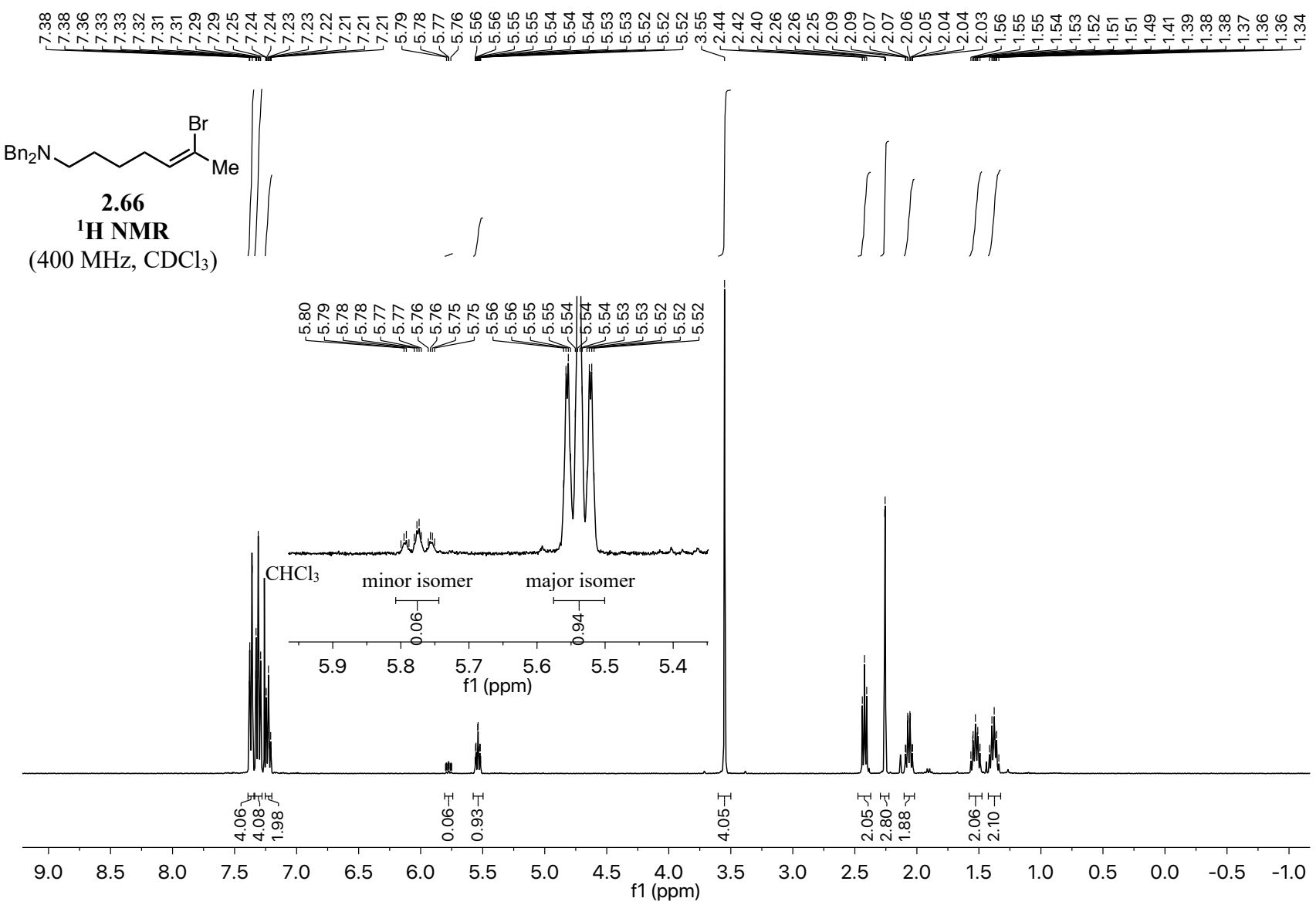


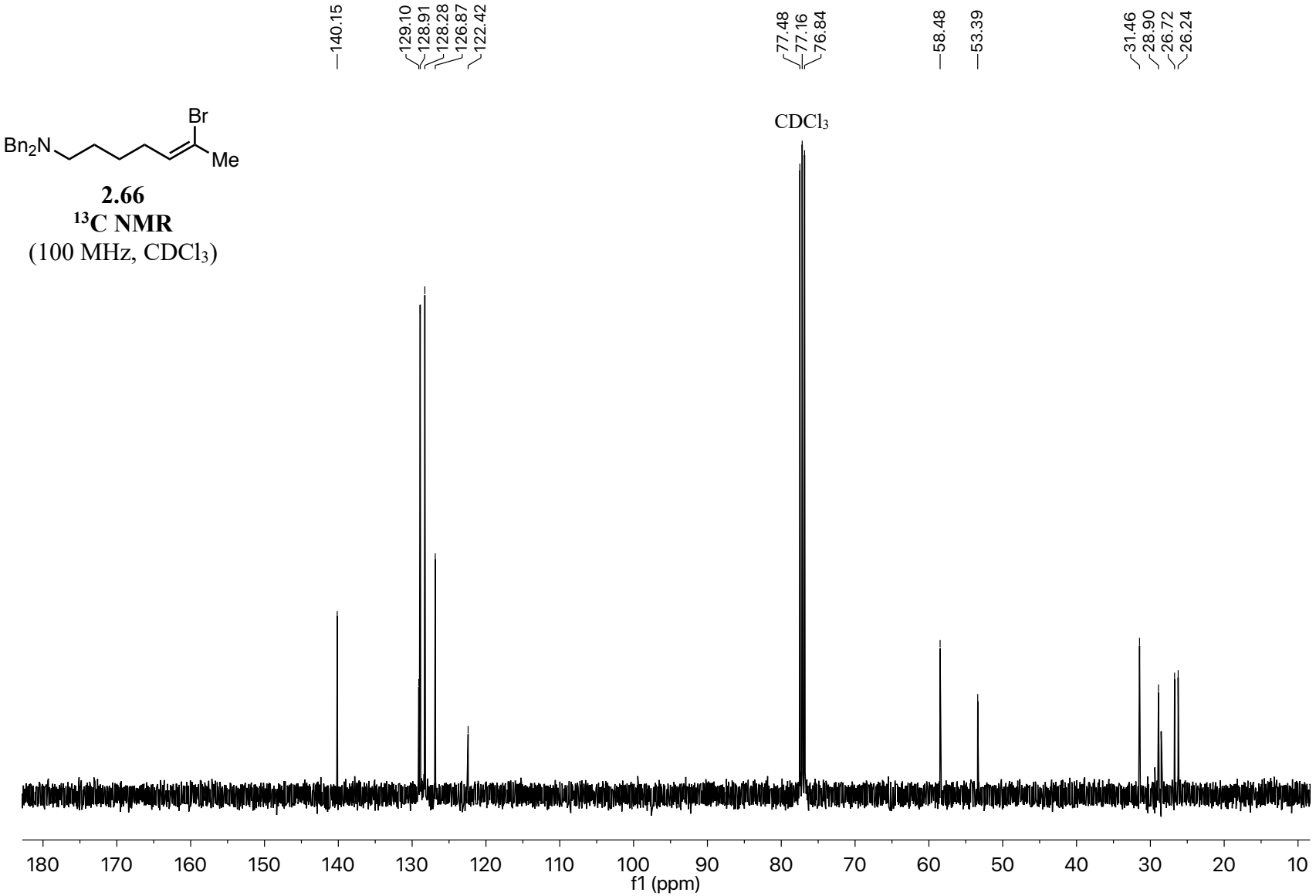
2.64
^{13}C NMR
(125 MHz, $CDCl_3$)


Me
Br
TBSO
Me
2.65
1H NMR
(400 MHz, CDCl3)
CHCl3
minor isomer
major isomer
0.04
0.96
f1 (ppm)
0.04
0.92
1.96
2.75
1.83
2.40
2.05
1.19
11.97
5.87
f1 (ppm)

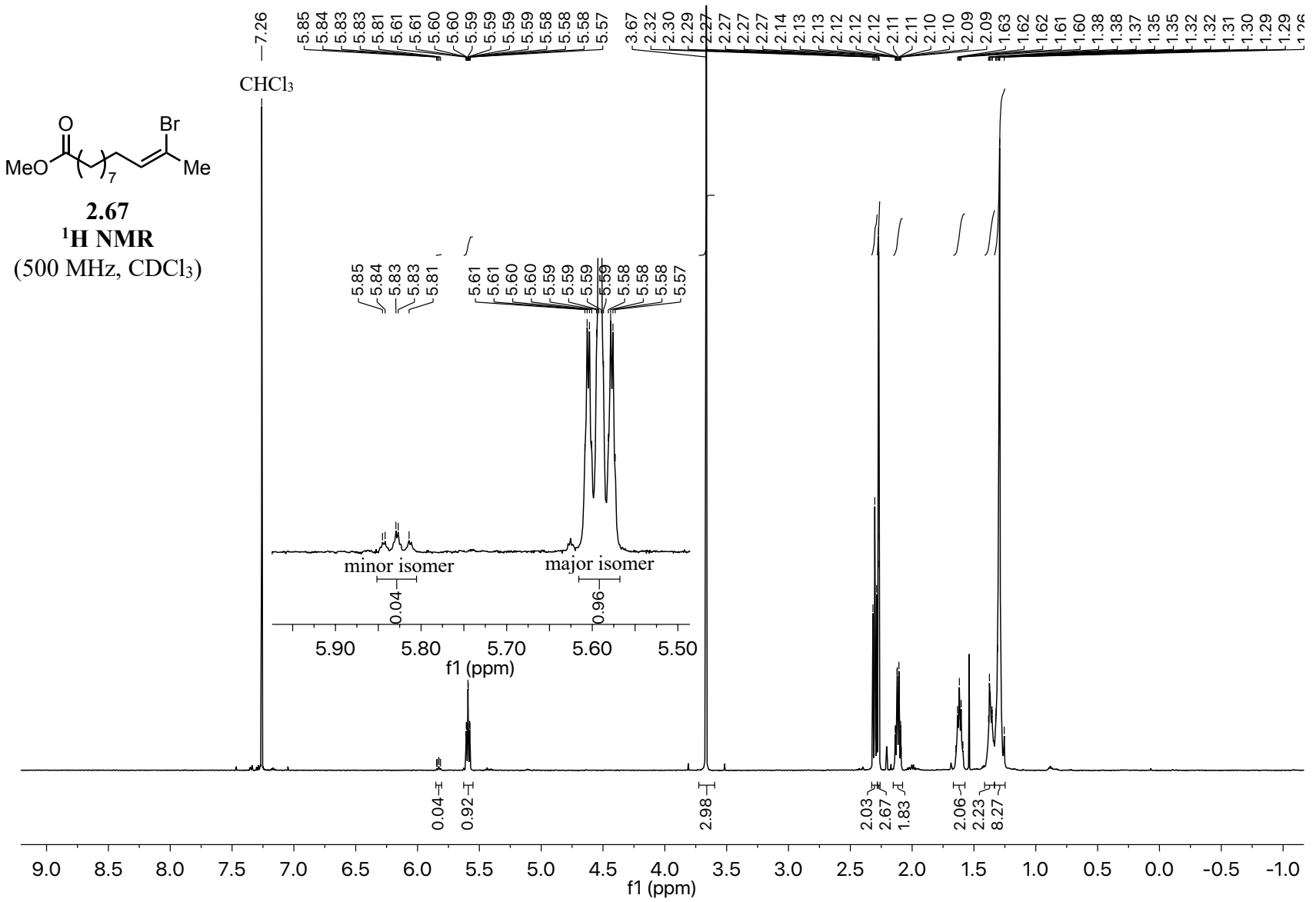


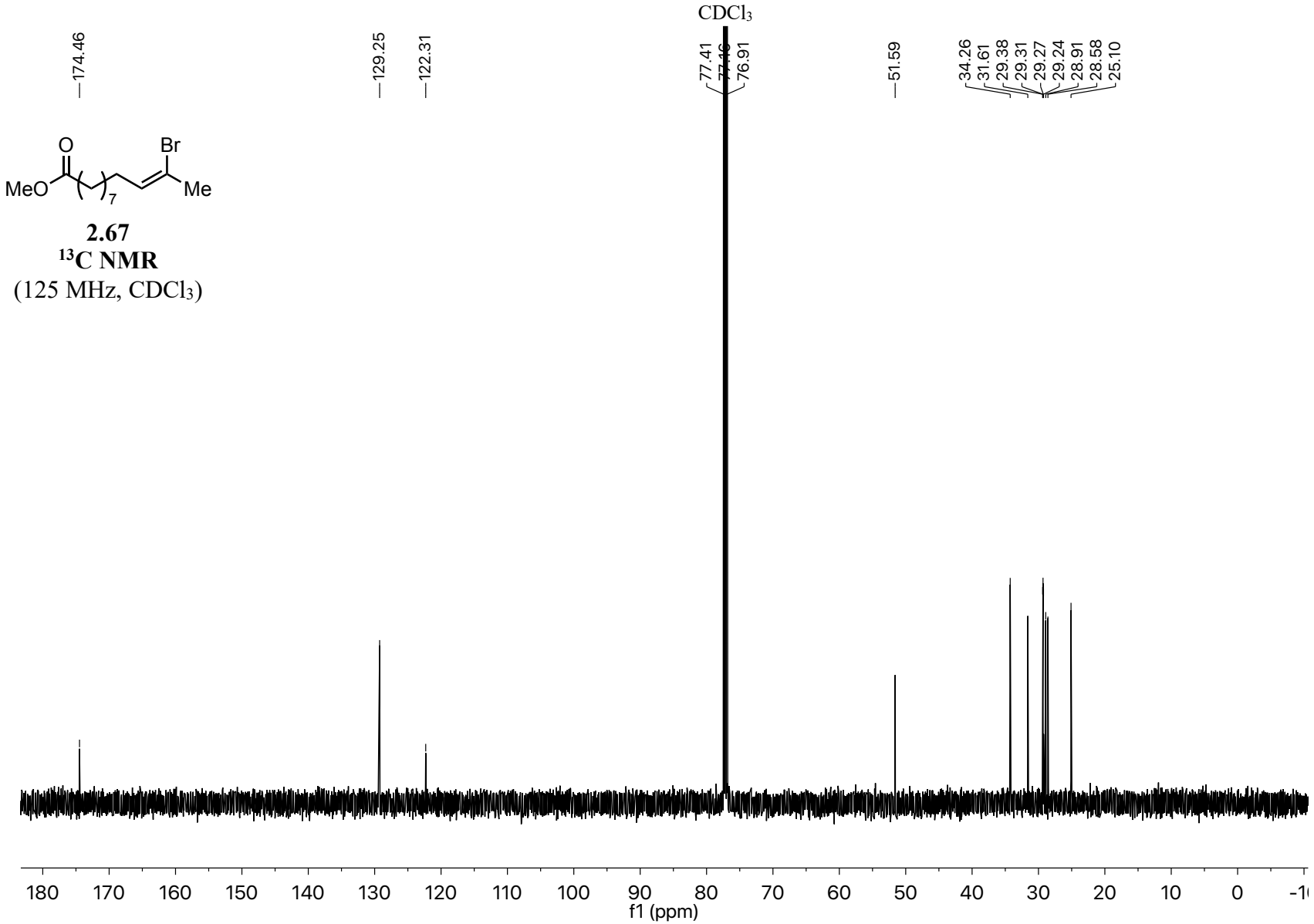
2.65
^{13}C NMR
(100 MHz, $CDCl_3$)


Br
Bn2N
Me
2.66
1H NMR
(400 MHz, CDCl3)
CHCl3
minor isomer
major isomer
0.06
0.94
f1 (ppm)
4.06
4.08
1.98
0.06
0.93
4.05
2.05
2.80
1.88
2.06
2.10
f1 (ppm)

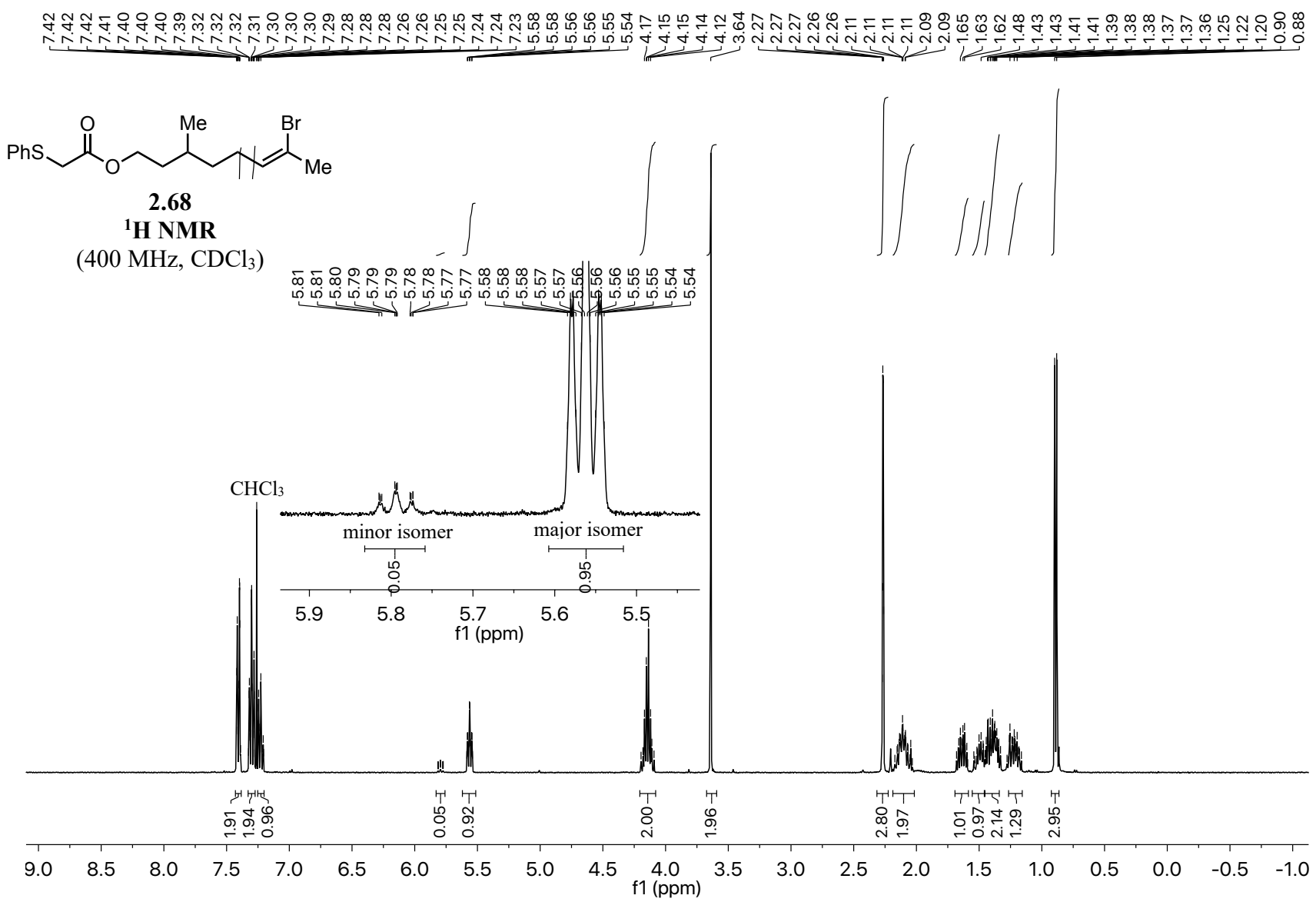


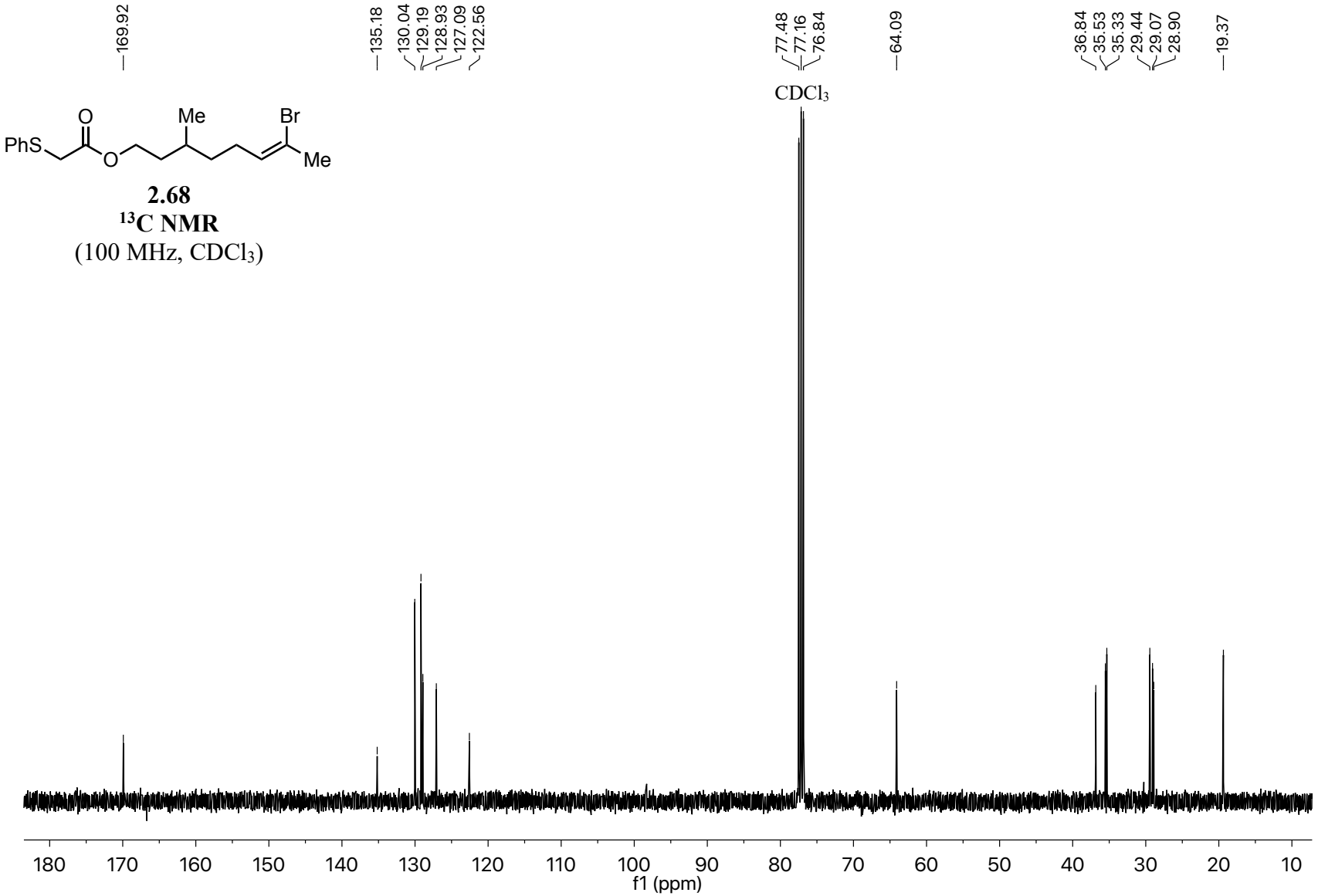
2.66
^{13}C NMR
(100 MHz, $CDCl_3$)


O
Br
MeO
7
Me
2.67
1H NMR
(500 MHz, CDCl3)
CHCl3
minor isomer
major isomer
0.04
0.96
f1 (ppm)
0.04
0.92
2.98
2.03
2.67
1.83
2.06
2.23
8.27
f1 (ppm)

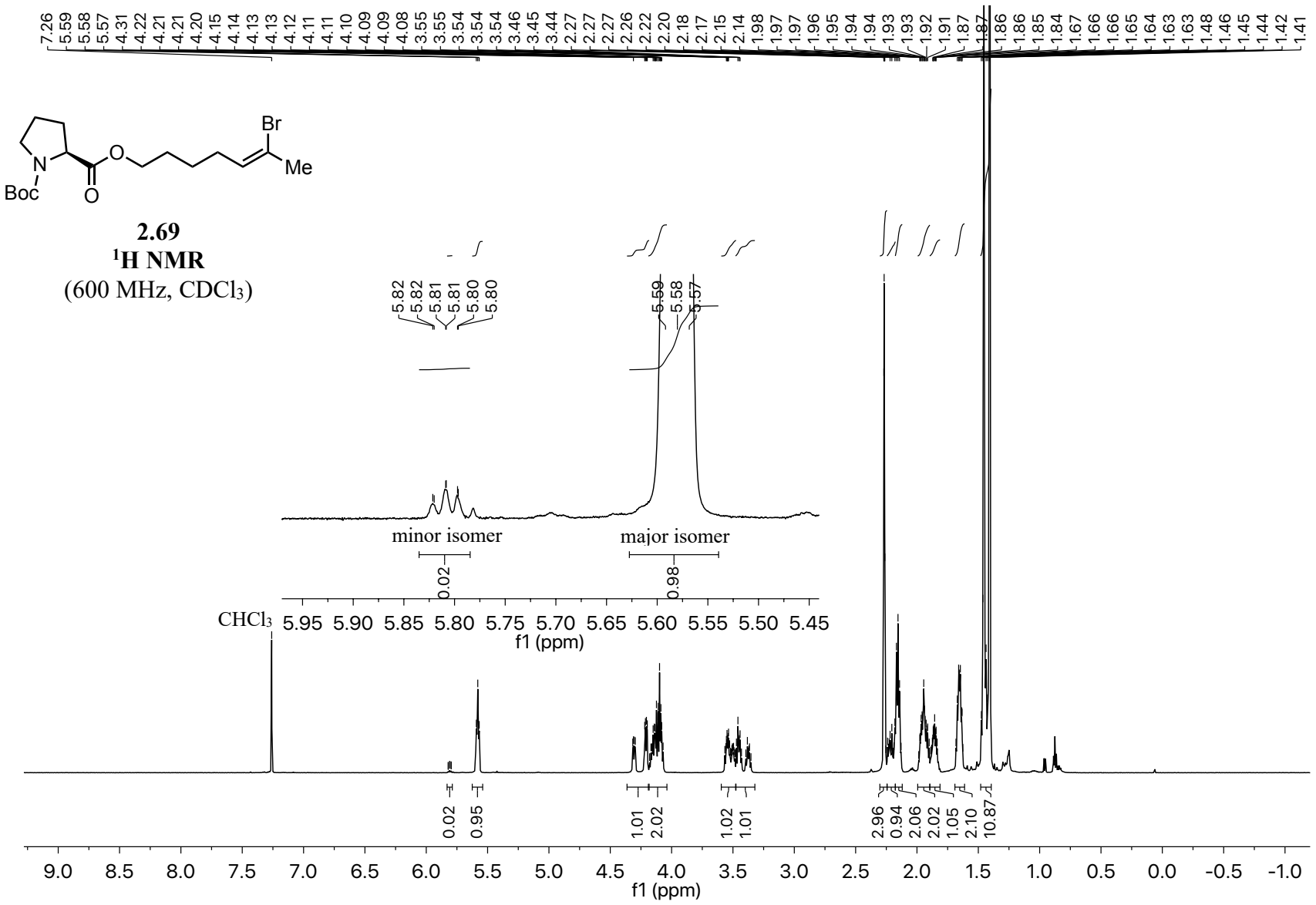


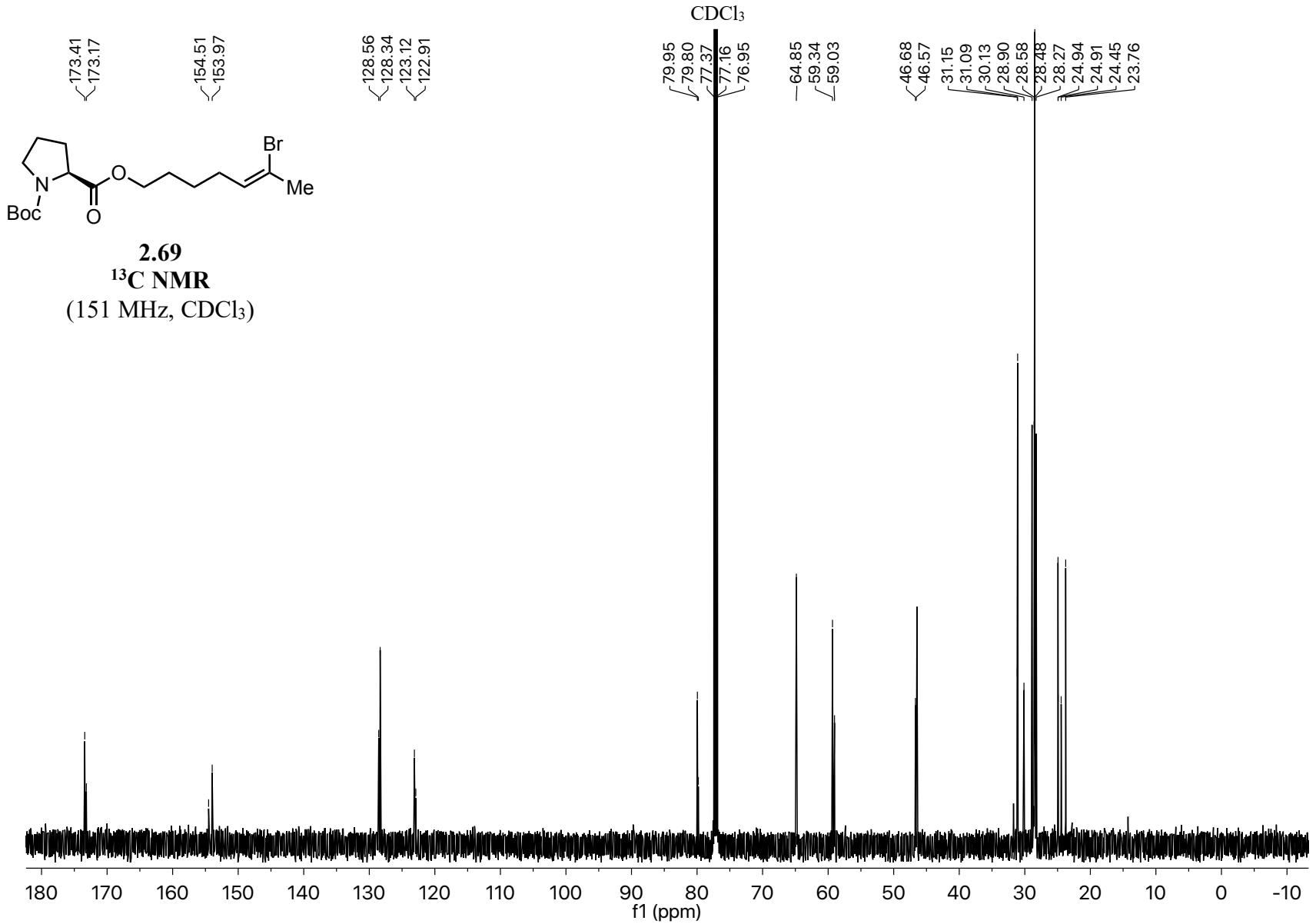
2.67
^{13}C NMR
(125 MHz, $CDCl_3$)


PhS
O
O
Me
Br
Me
2.68
1H NMR
(400 MHz, CDCl3)
CHCl3
minor isomer
major isomer
0.05
0.95
f1 (ppm)
f1 (ppm)

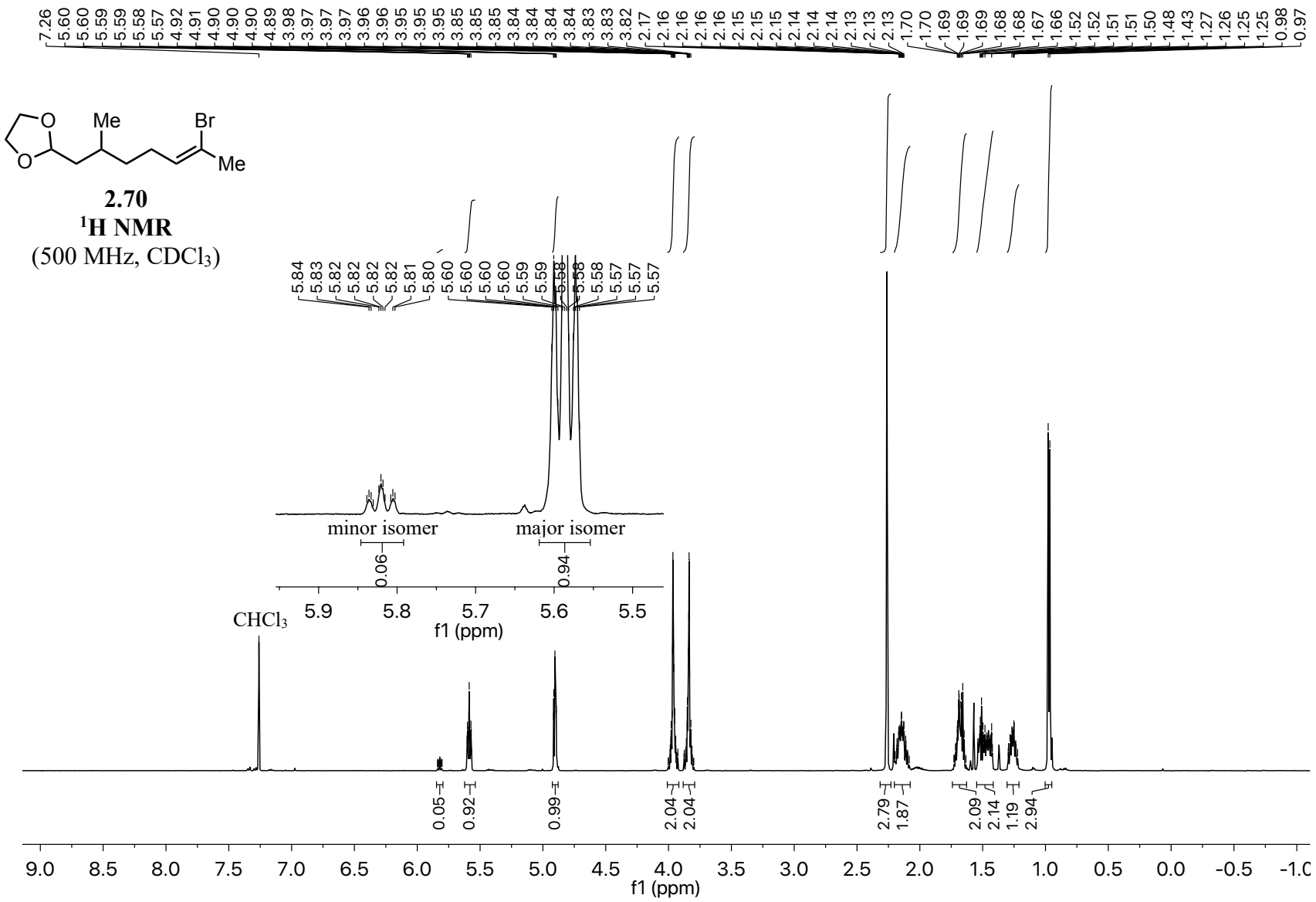


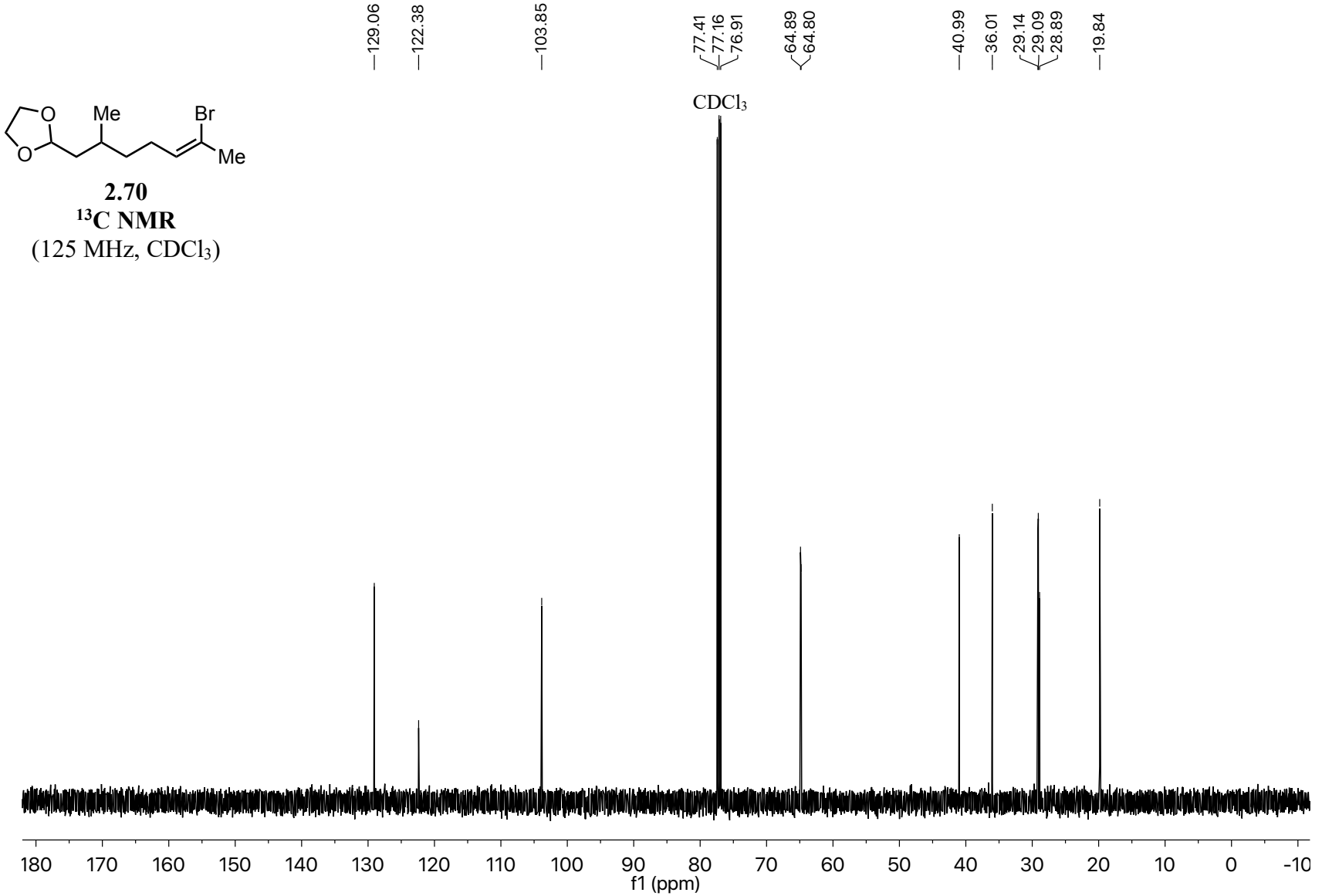
2.68
^{13}C NMR
(100 MHz, $CDCl_3$)


Br
Me
N
Boc
O
O
2.69
1H NMR
(600 MHz, CDCl3)
minor isomer
major isomer
0.02
0.98
CHCl3
f1 (ppm)
0.02
0.95
1.01
2.02
1.02
1.01
2.96
0.94
2.06
2.02
1.05
2.10
10.87

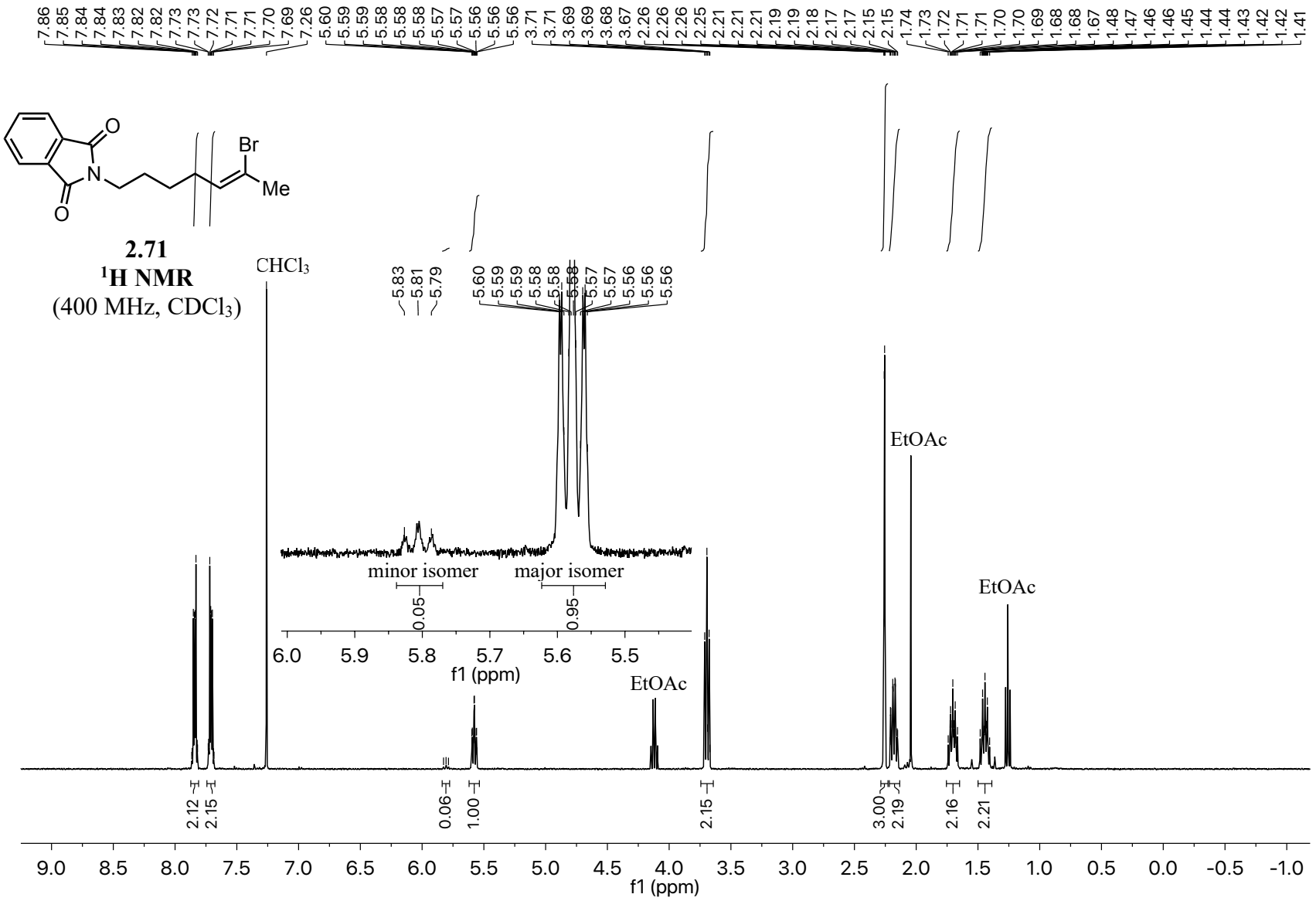


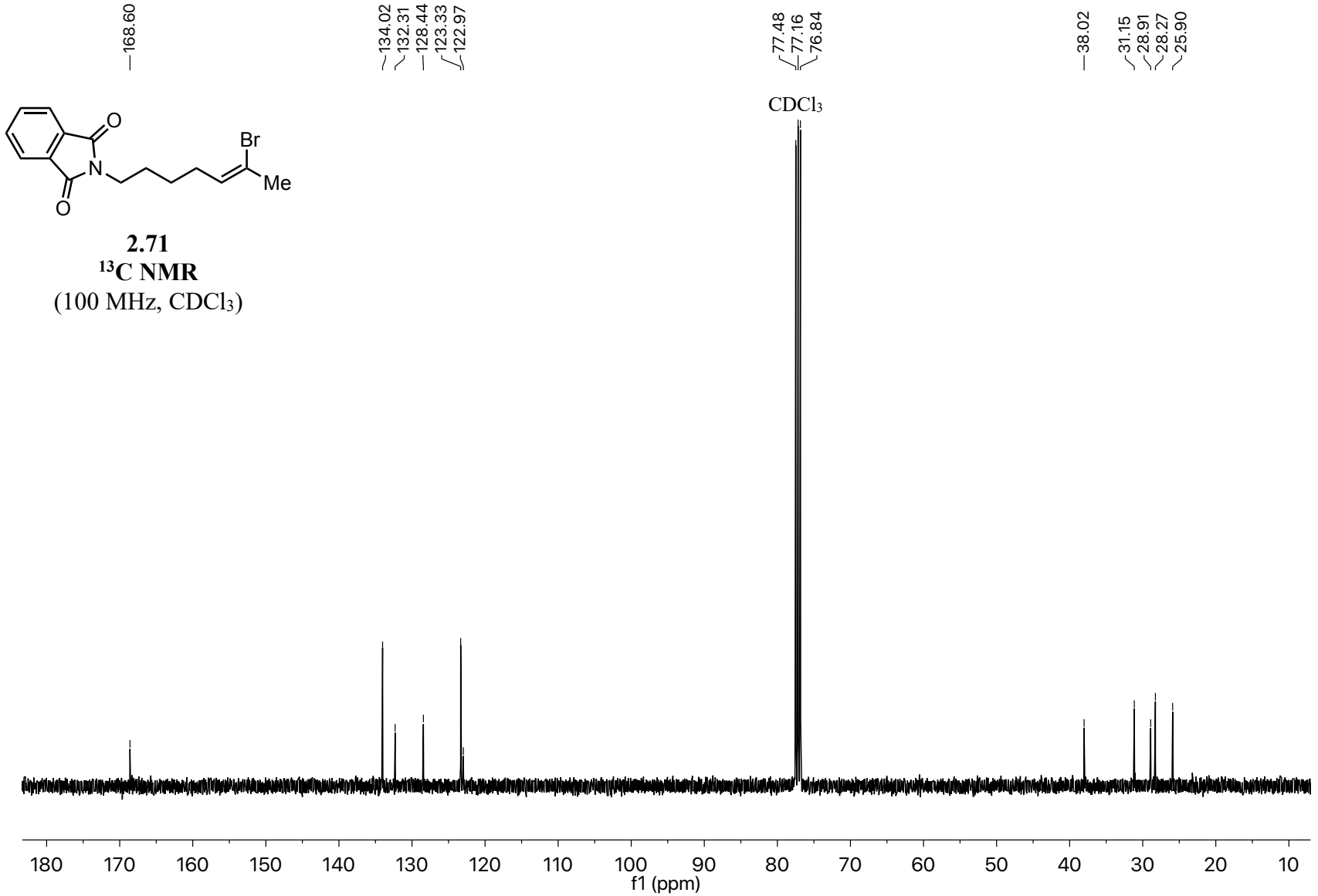
2.69
^{13}C NMR
(151 MHz, $CDCl_3$)


Me
Br
O
O
Me
2.70
1H NMR
(500 MHz, CDCl3)
minor isomer
major isomer
0.06
0.94
CHCl3
f1 (ppm)
0.05
0.92
0.99
2.04
2.04
2.79
1.87
2.09
2.14
1.19
2.94

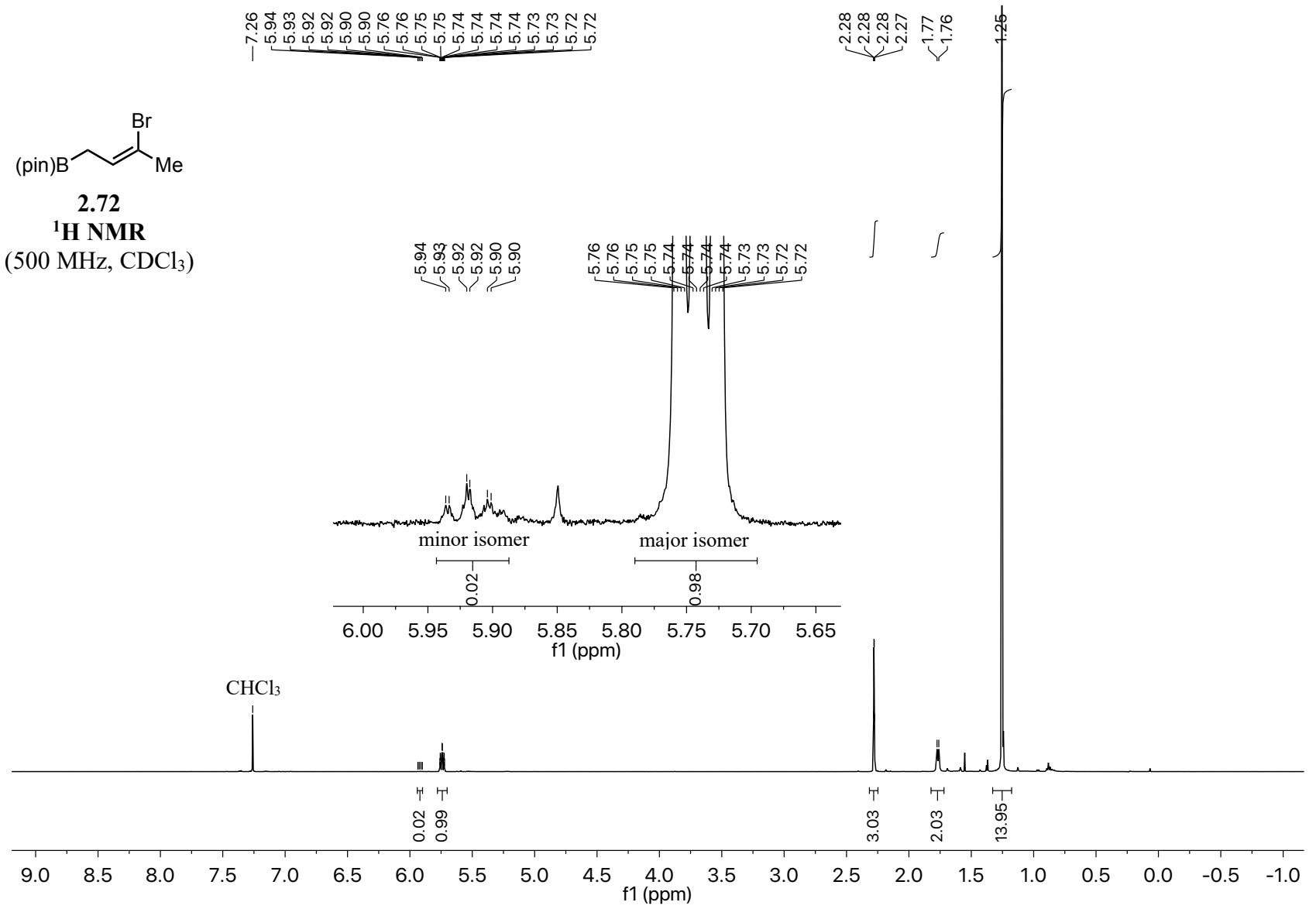


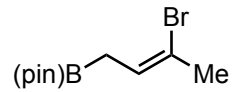
2.70
^{13}C NMR
(125 MHz, $CDCl_3$)


Br
Me
O
O
N
2.71
1H NMR
(400 MHz, CDCl3)
CHCl3
EtOAc
EtOAc
EtOAc
minor isomer
major isomer
0.05
0.95
f1 (ppm)
f1 (ppm)

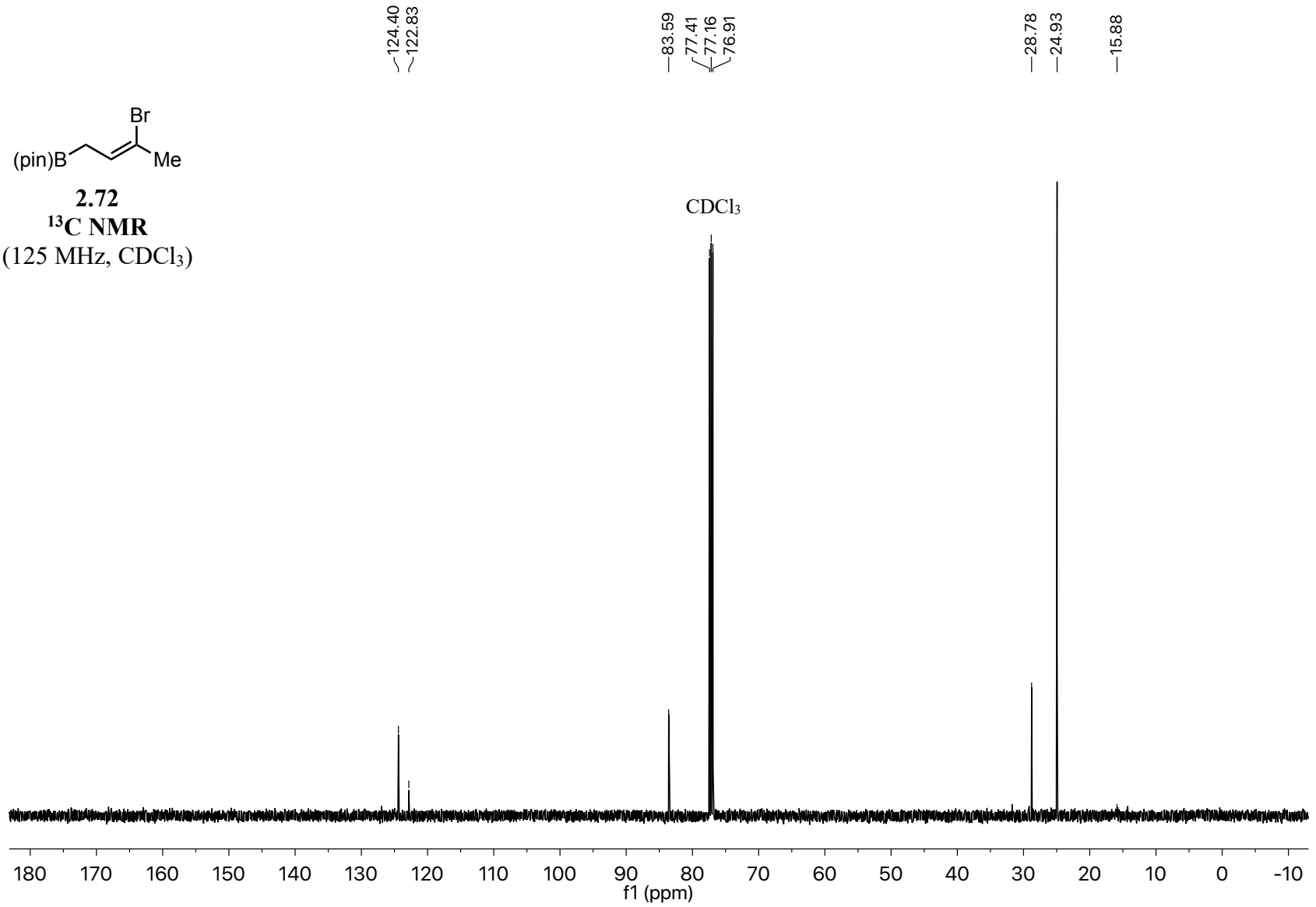


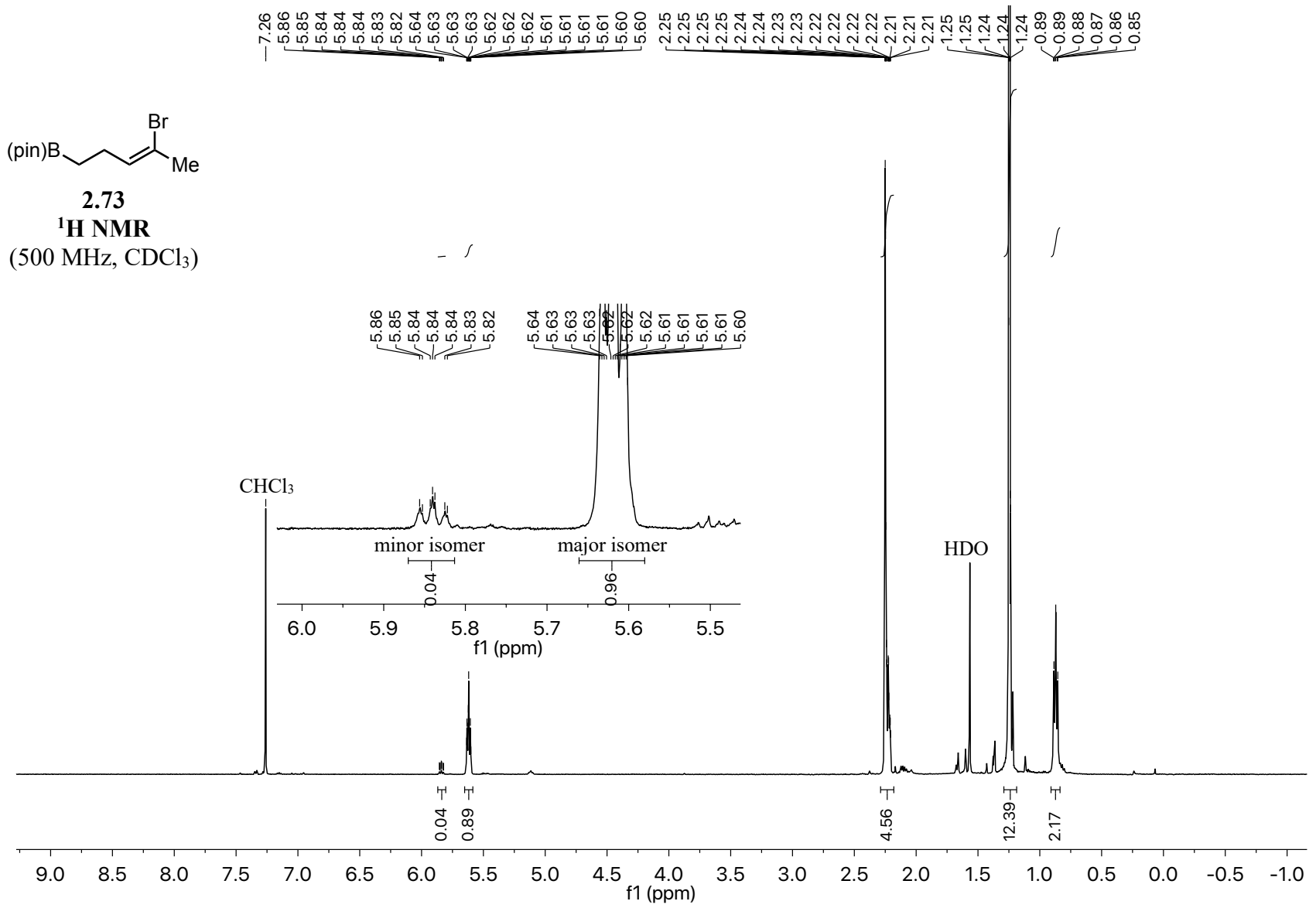
2.71
^{13}C NMR
(100 MHz, $CDCl_3$)

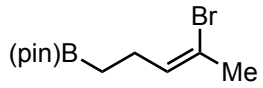

Br
(pin)B
Me
2.72
1H NMR
(500 MHz, CDCl3)
minor isomer
major isomer
0.02
0.98
CHCl3
0.02
0.99
3.03
2.03
13.95
f1 (ppm)



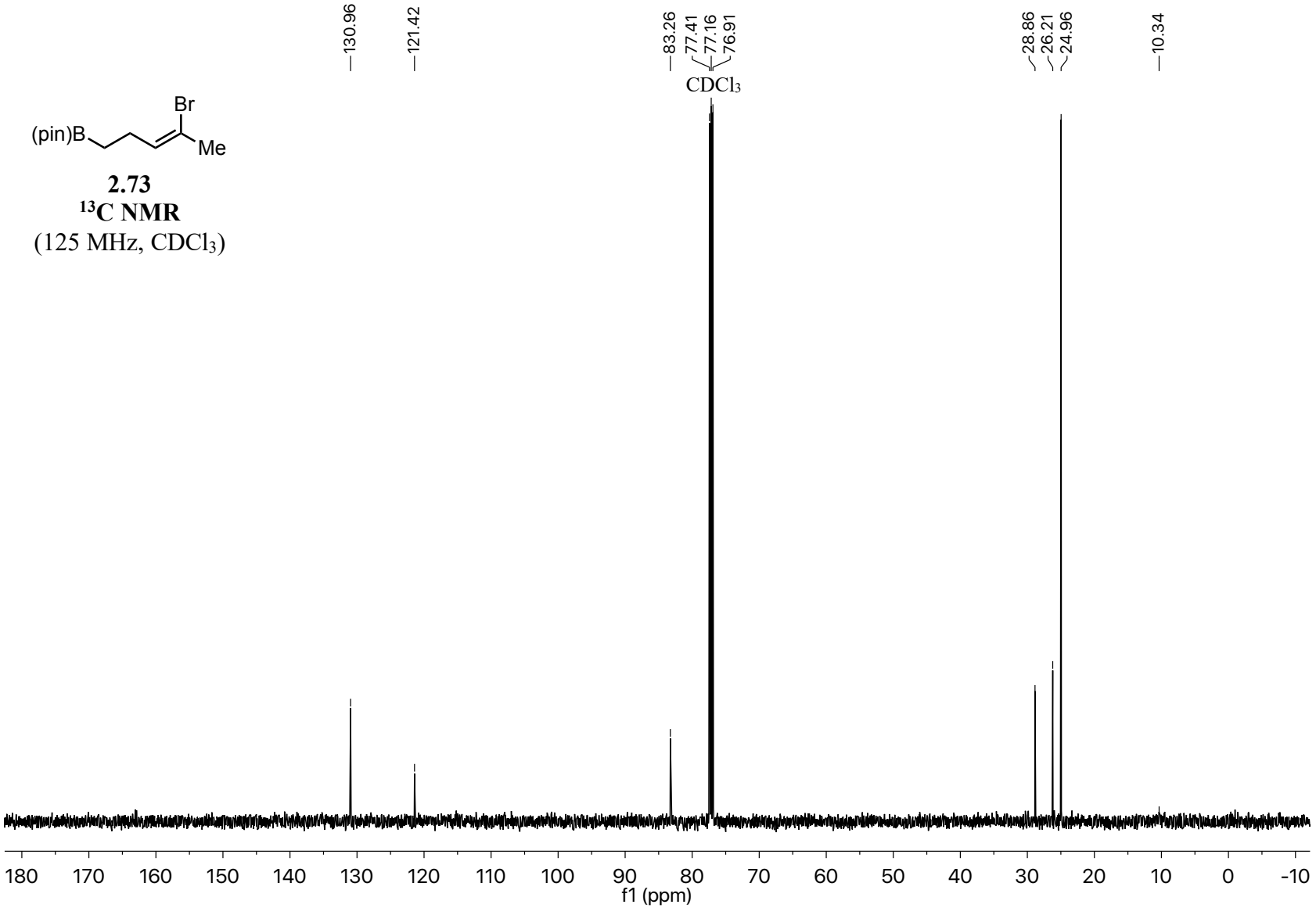
2.72
^{11}B NMR
(160 MHz, $CDCl_3$)


124.40
122.83
83.59
77.41
77.16
76.91
28.78
24.93
15.88
Br
(pin)B
Me
2.72
13C NMR
(125 MHz, CDCl3)
CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

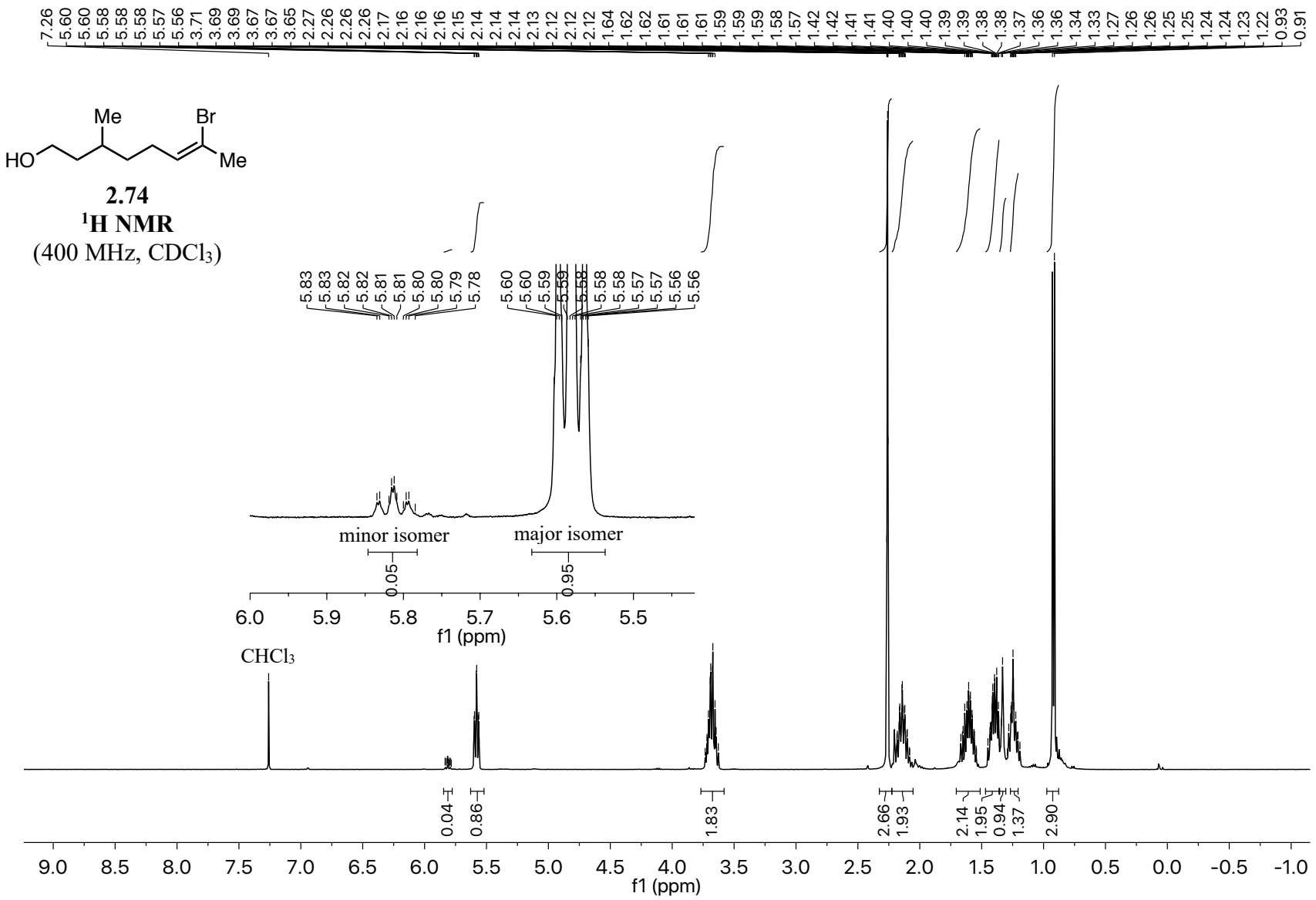

Br
(pin)B
Me
2.73
1H NMR
(500 MHz, CDCl3)
CHCl3
HDO
minor isomer
major isomer
0.04
0.96
f1 (ppm)
0.04
0.89
4.56
12.39
2.17

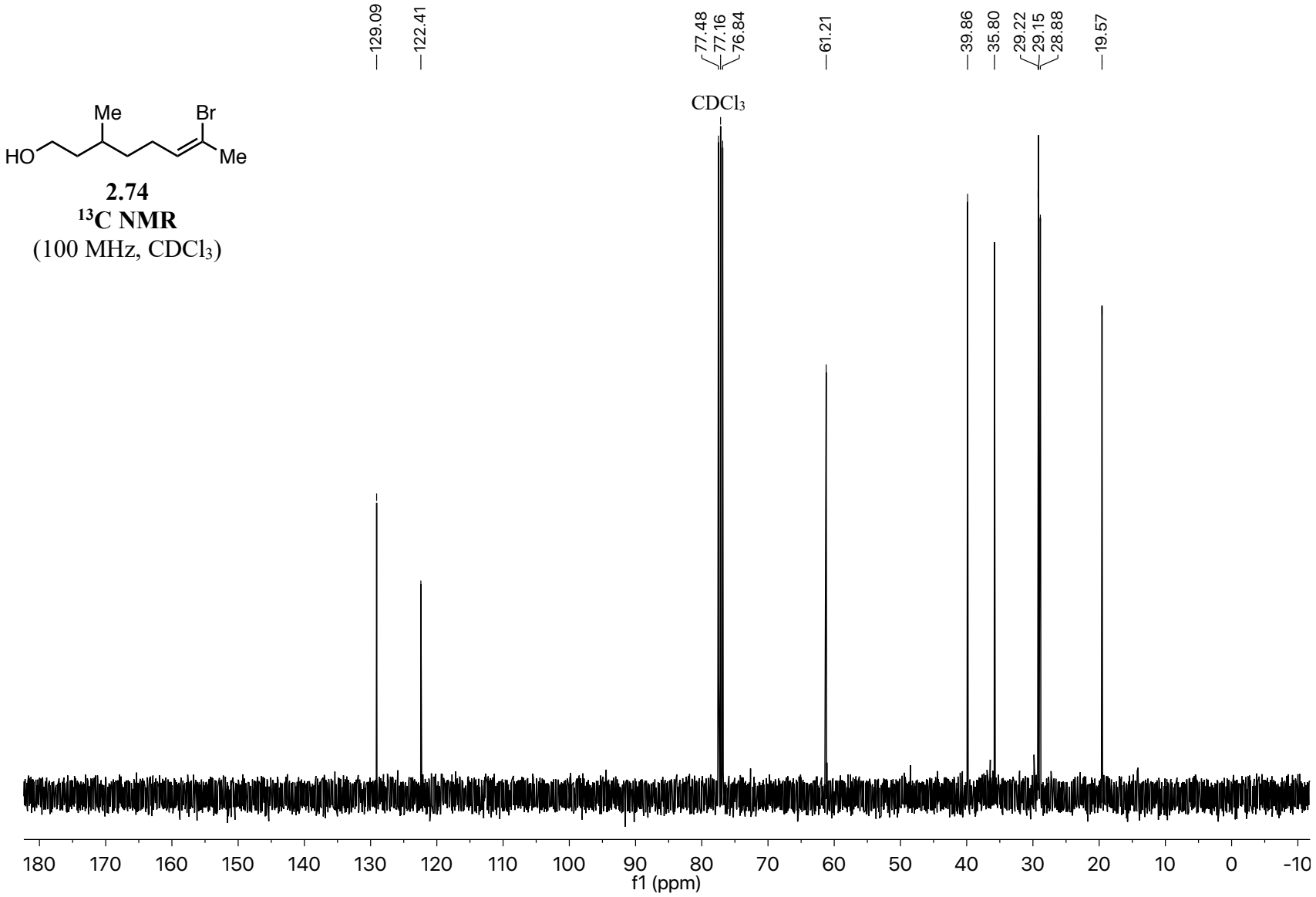


2.73
^{11}B NMR
(160 MHz, $CDCl_3$)

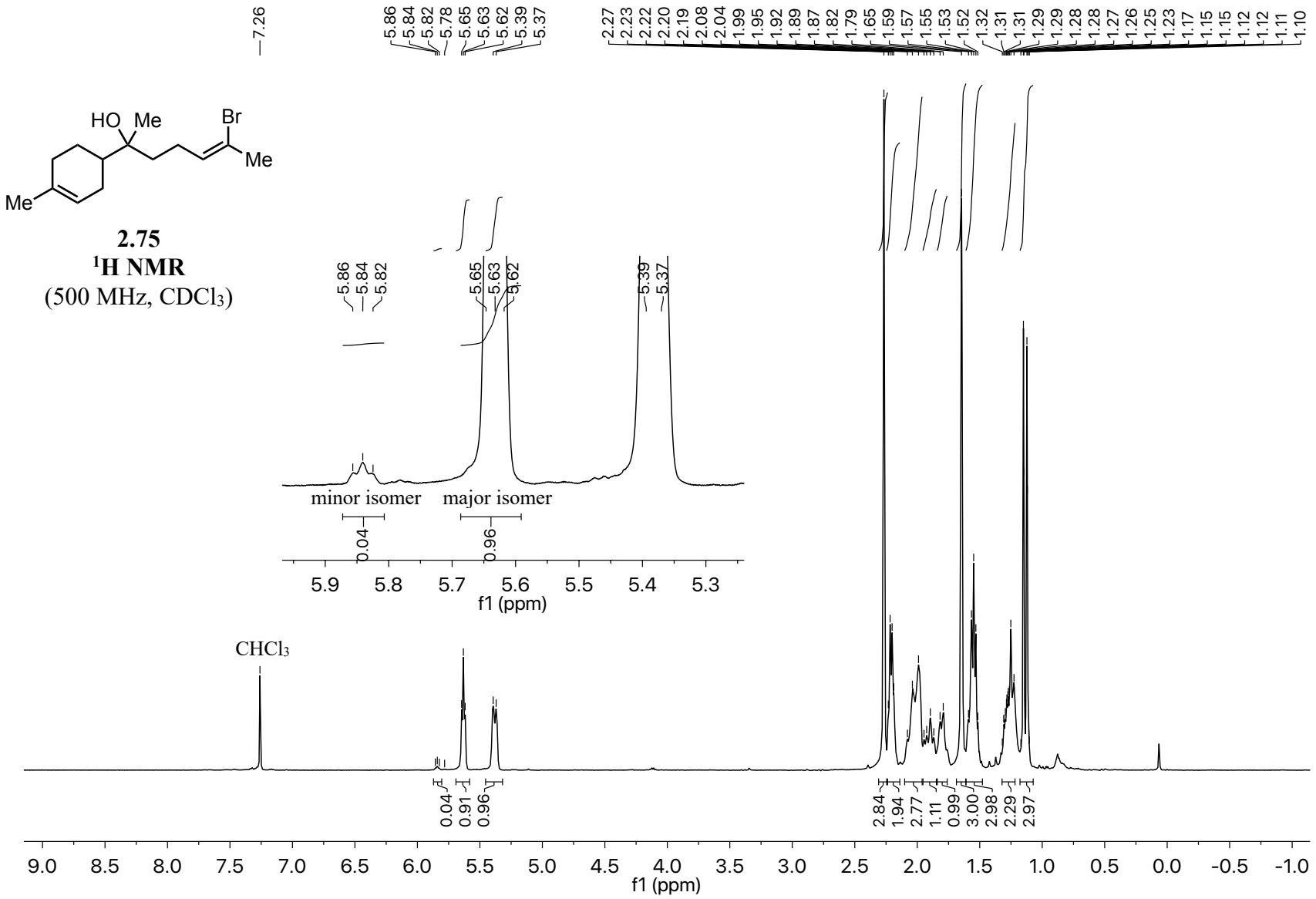


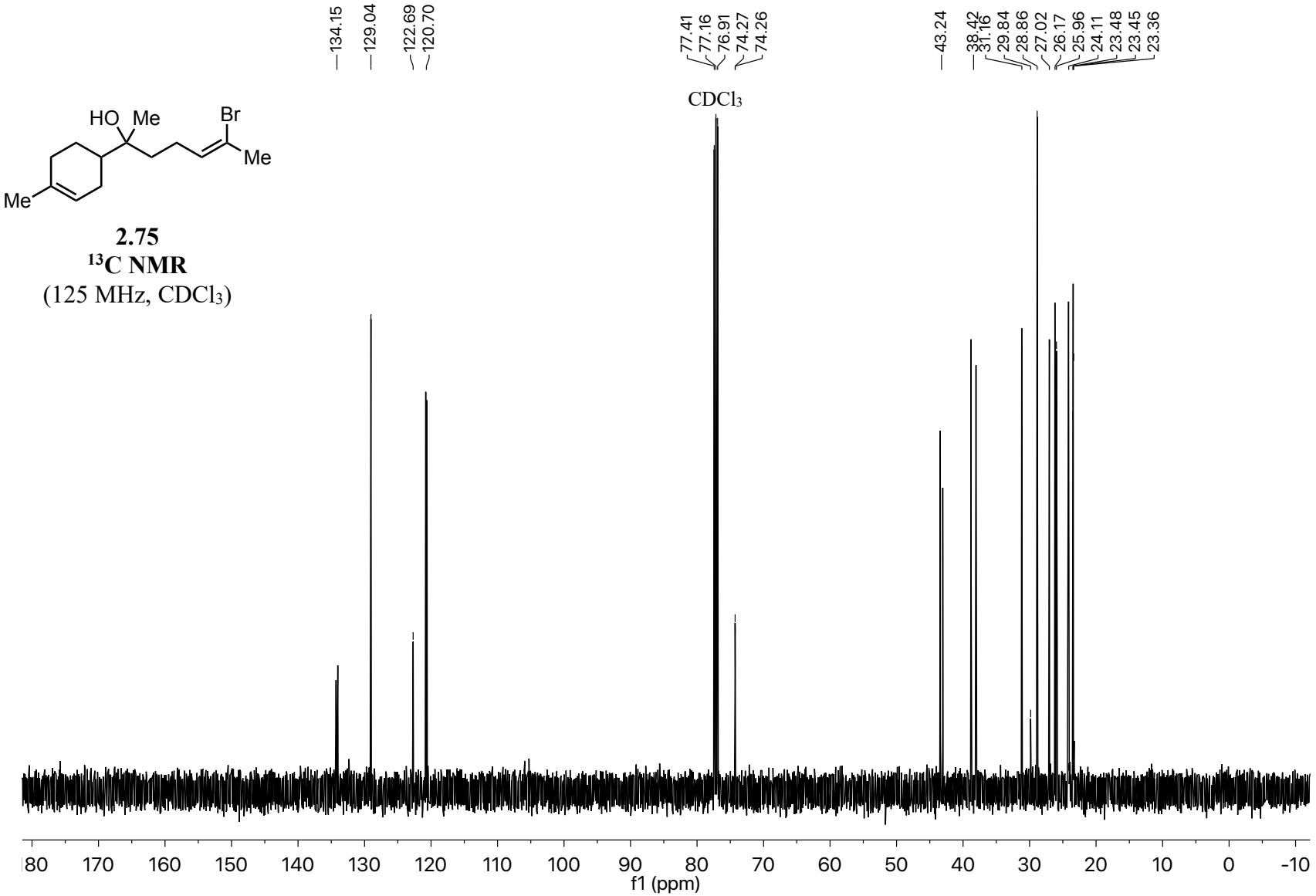
2.73
^{13}C NMR
(125 MHz, $CDCl_3$)


Me
Br
HO
Me
2.74
1H NMR
(400 MHz, CDCl3)
minor isomer
major isomer
0.05
0.95
f1 (ppm)
CHCl3
0.04
0.86
1.83
2.66
1.93
2.14
1.95
0.94
1.37
2.90
f1 (ppm)

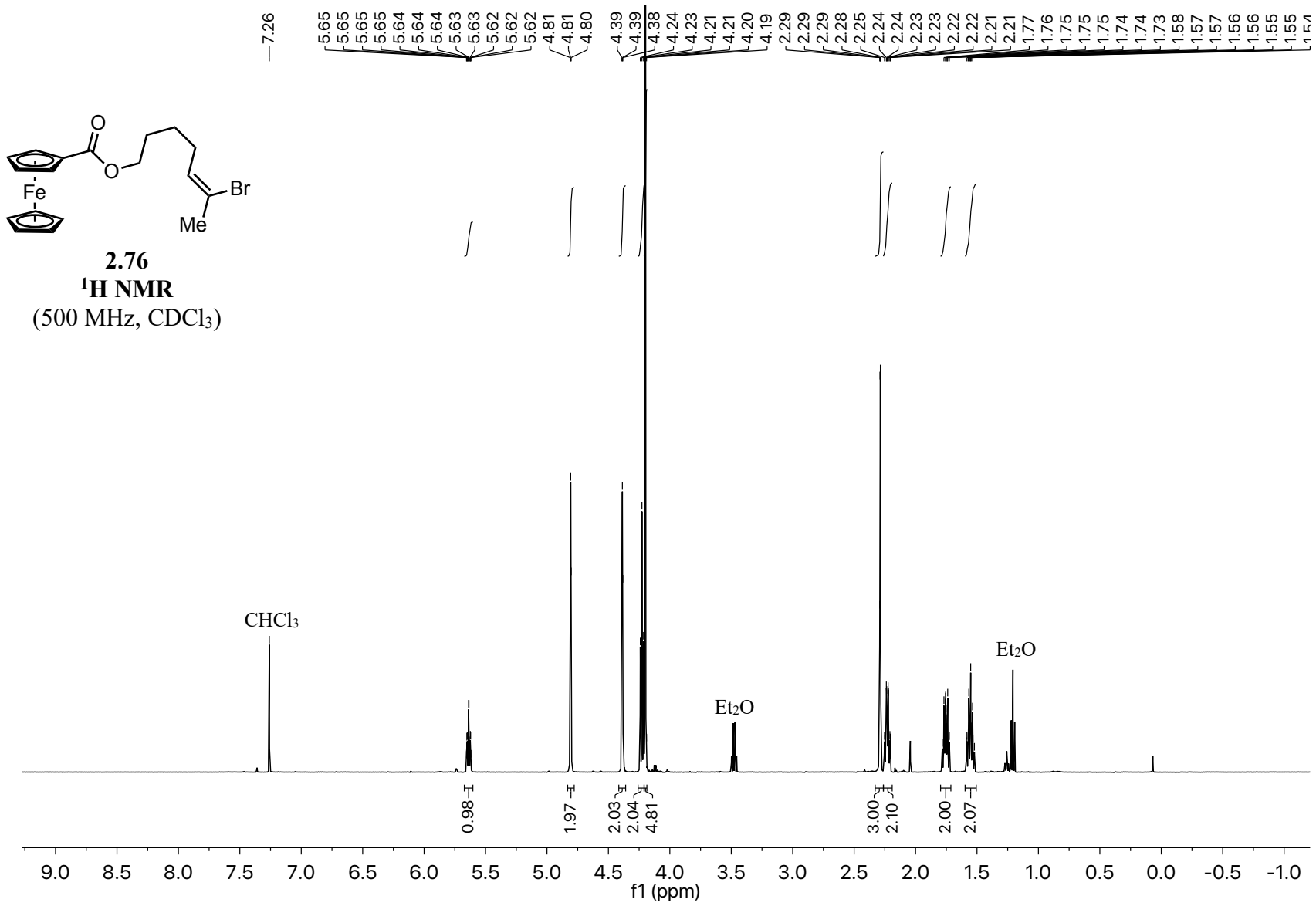


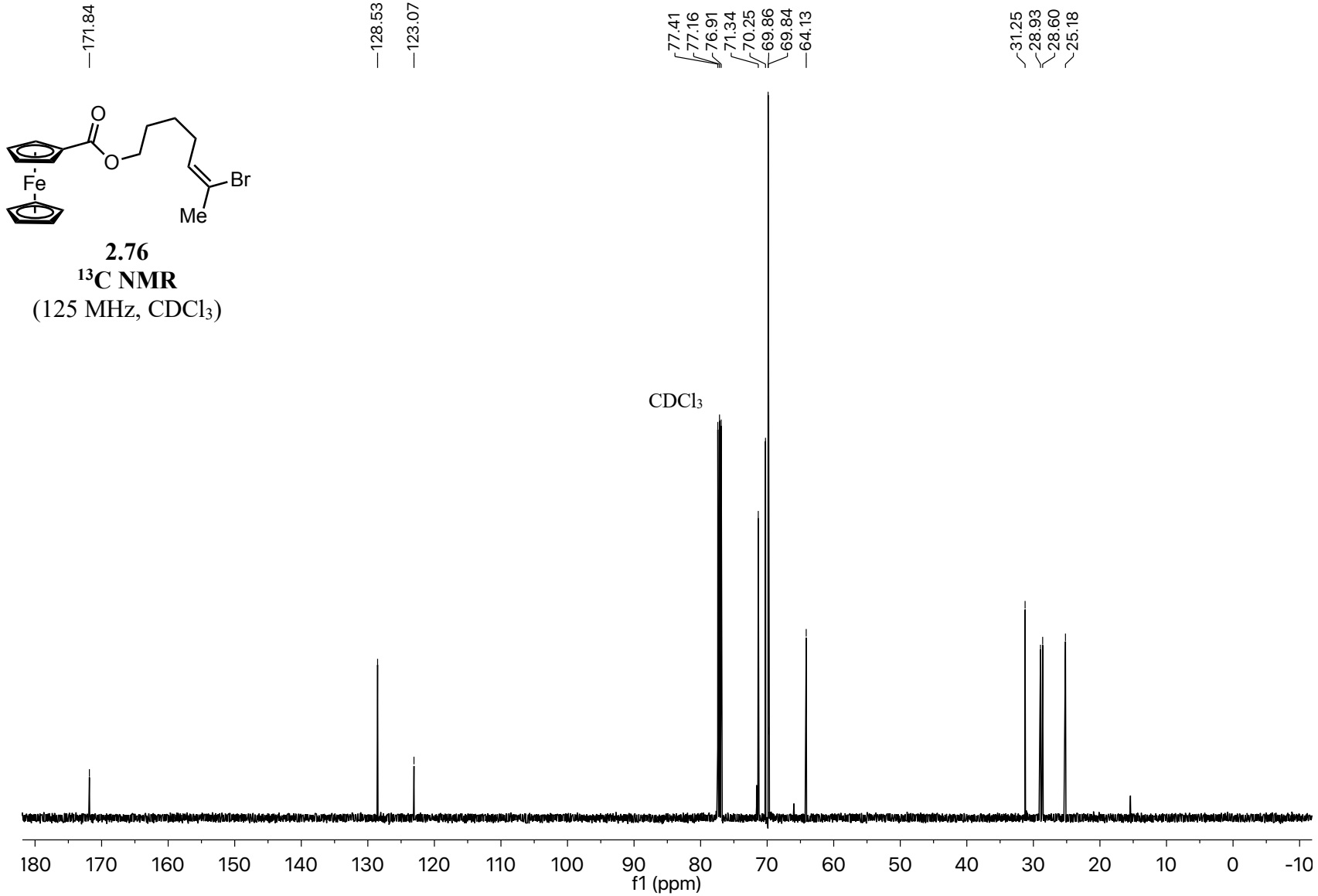
2.74
^{13}C NMR
(100 MHz, $CDCl_3$)


HO
Me
Br
Me
Me
2.75
1H NMR
(500 MHz, CDCl3)
minor isomer
major isomer
0.04
0.96
f1 (ppm)
CHCl3
0.04
0.91
0.96
2.84
1.94
2.77
1.11
0.99
3.00
2.98
2.29
2.97
f1 (ppm)

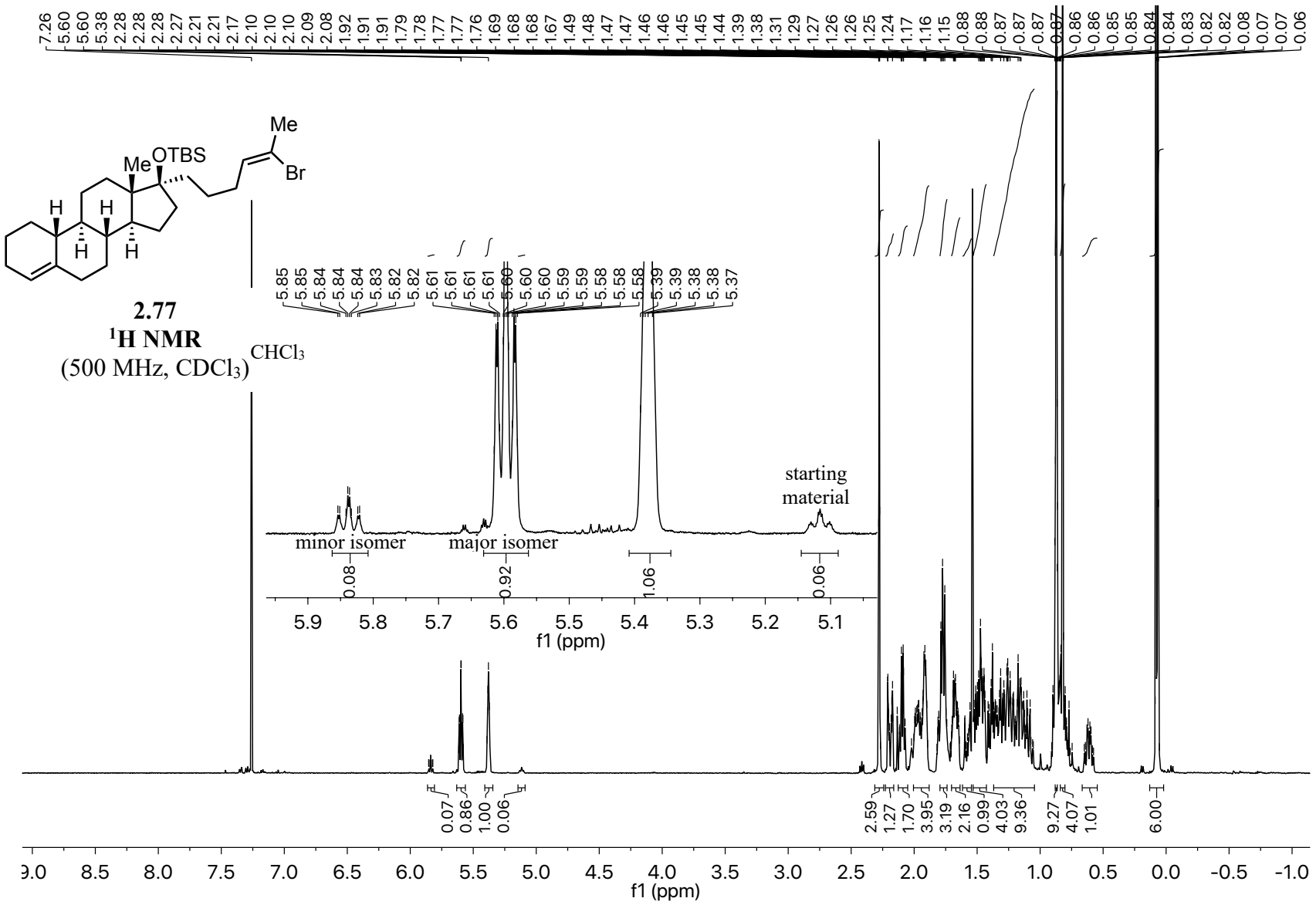


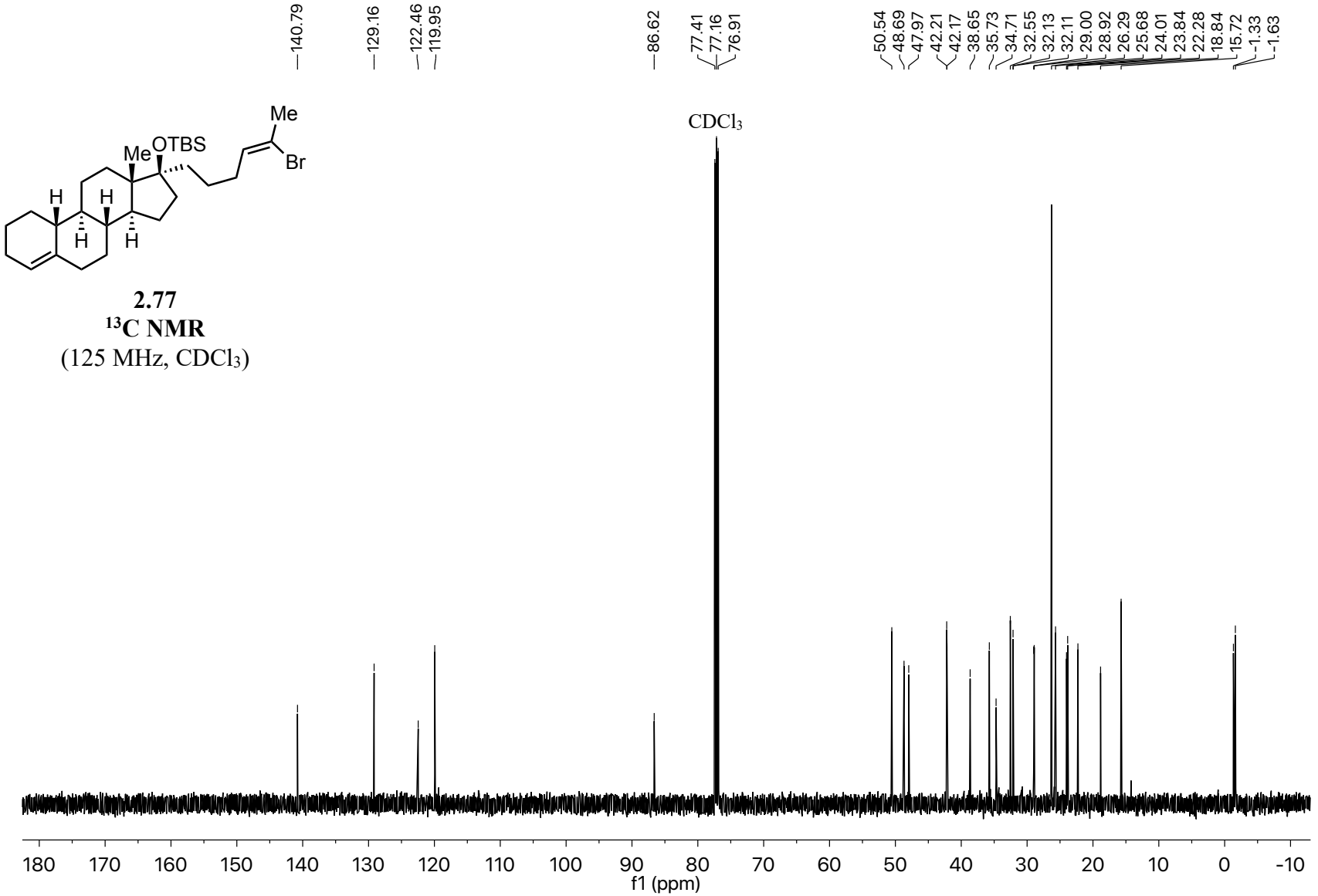
2.75
^{13}C NMR
(125 MHz, $CDCl_3$)


O
O
Fe
Br
Me
2.76
1H NMR
(500 MHz, CDCl3)
CHCl3
Et2O
Et2O
f1 (ppm)

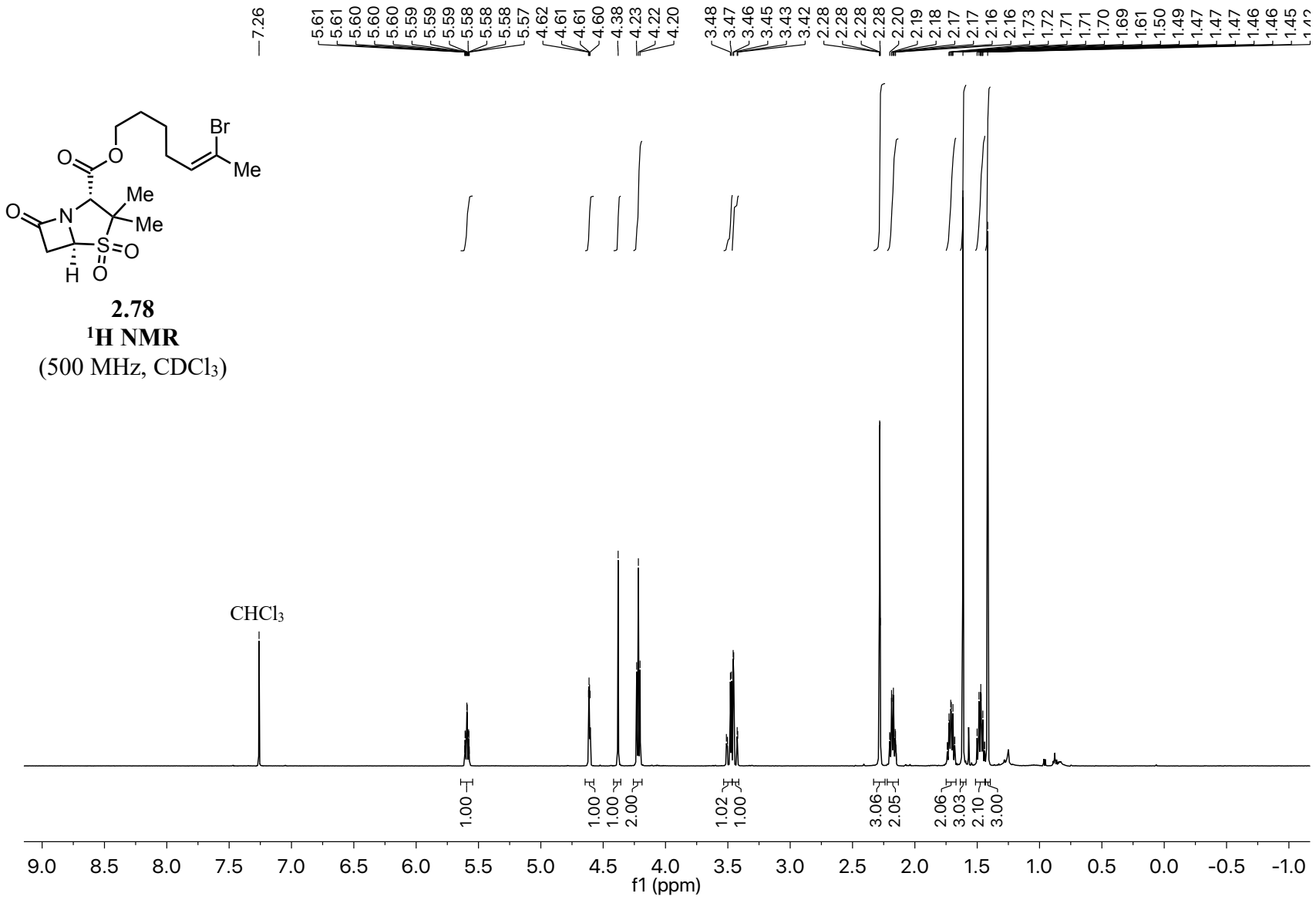


2.76
^{13}C NMR
(125 MHz, $CDCl_3$)

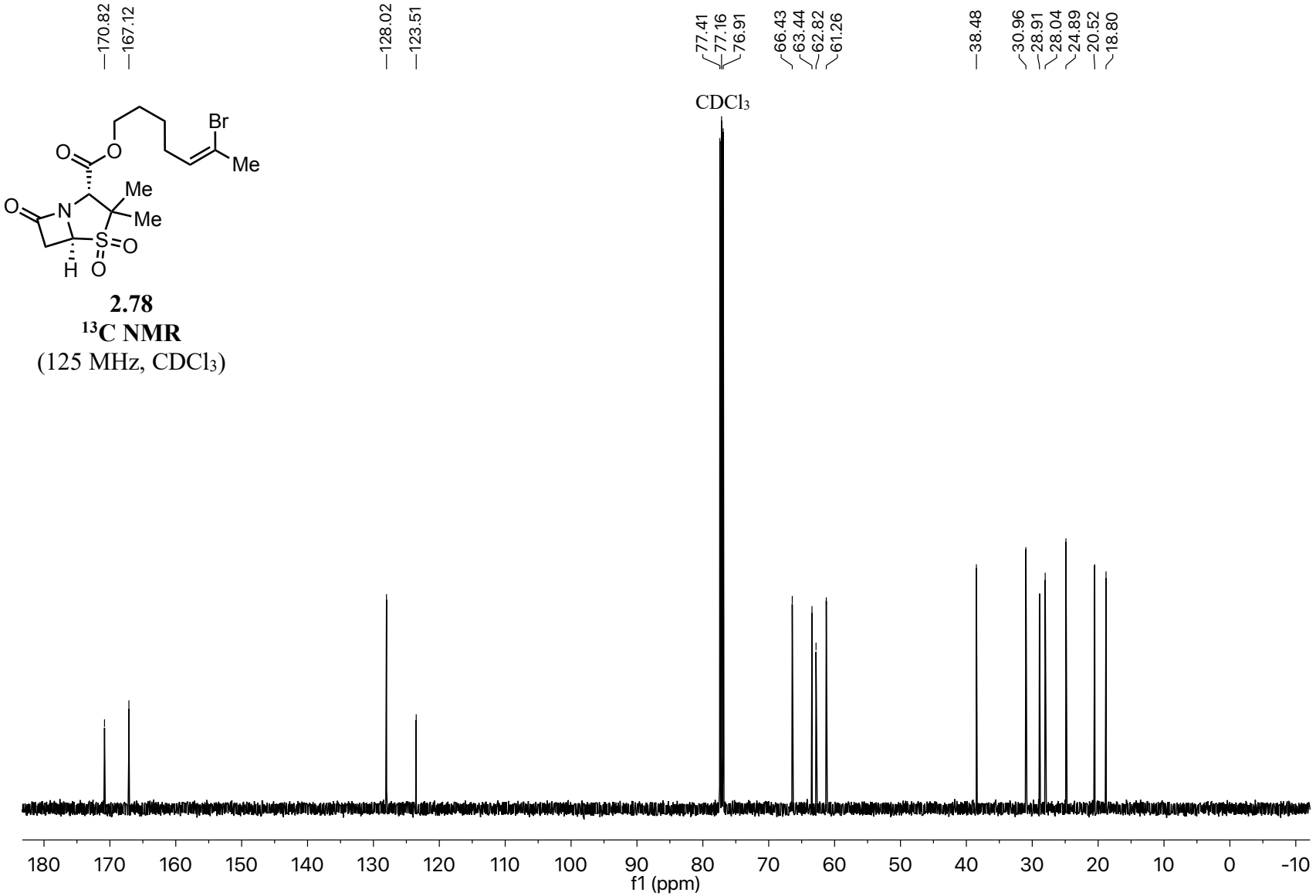

Me
Me
OTBS
Br
H
H
H
H
2.77
1H NMR
(500 MHz, CDCl3)
CHCl3
minor isomer
major isomer
starting material
f1 (ppm)



2.77
^{13}C NMR
(125 MHz, $CDCl_3$)



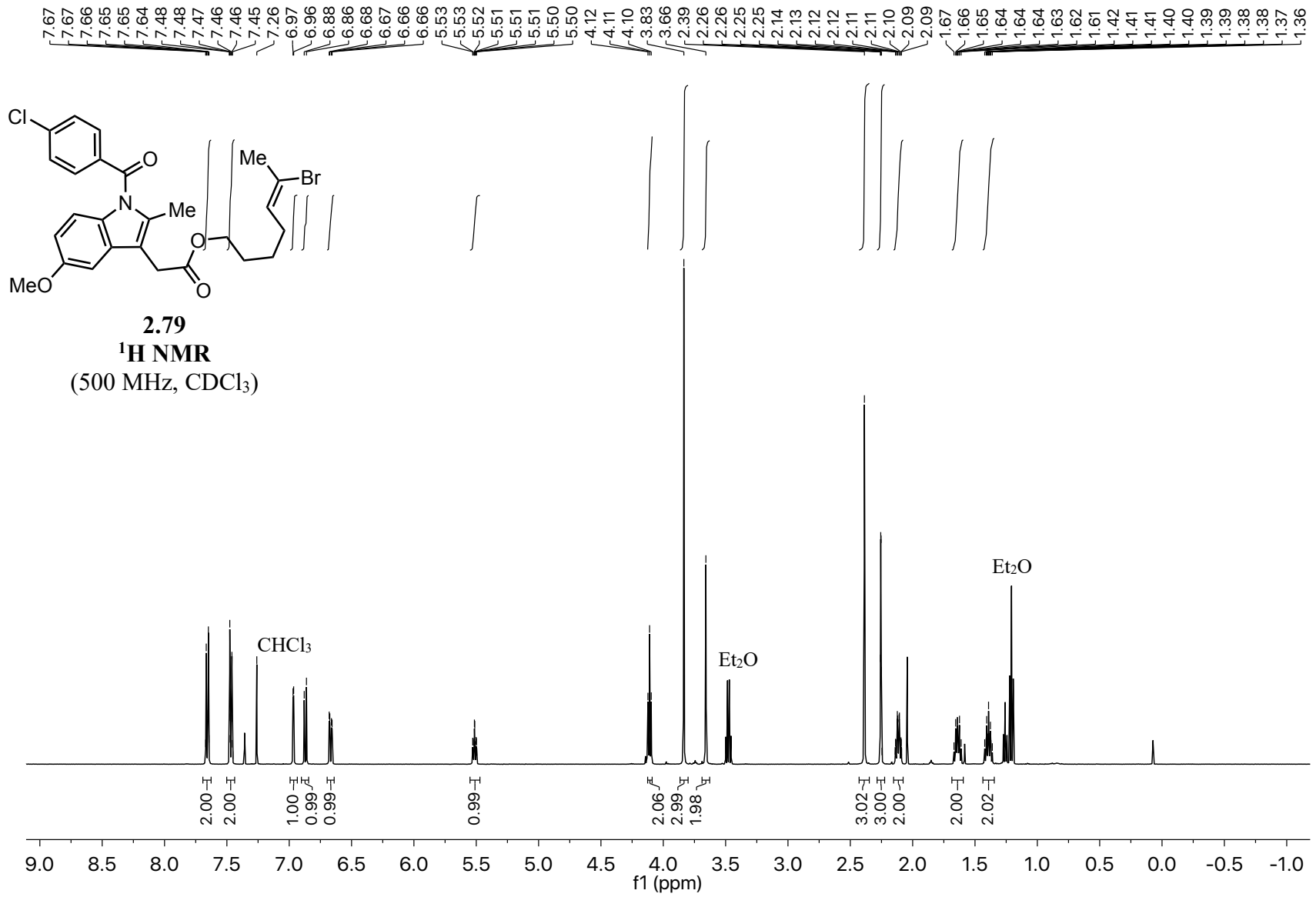
2.78
^{1}H NMR
(500 MHz, $CDCl_3$)

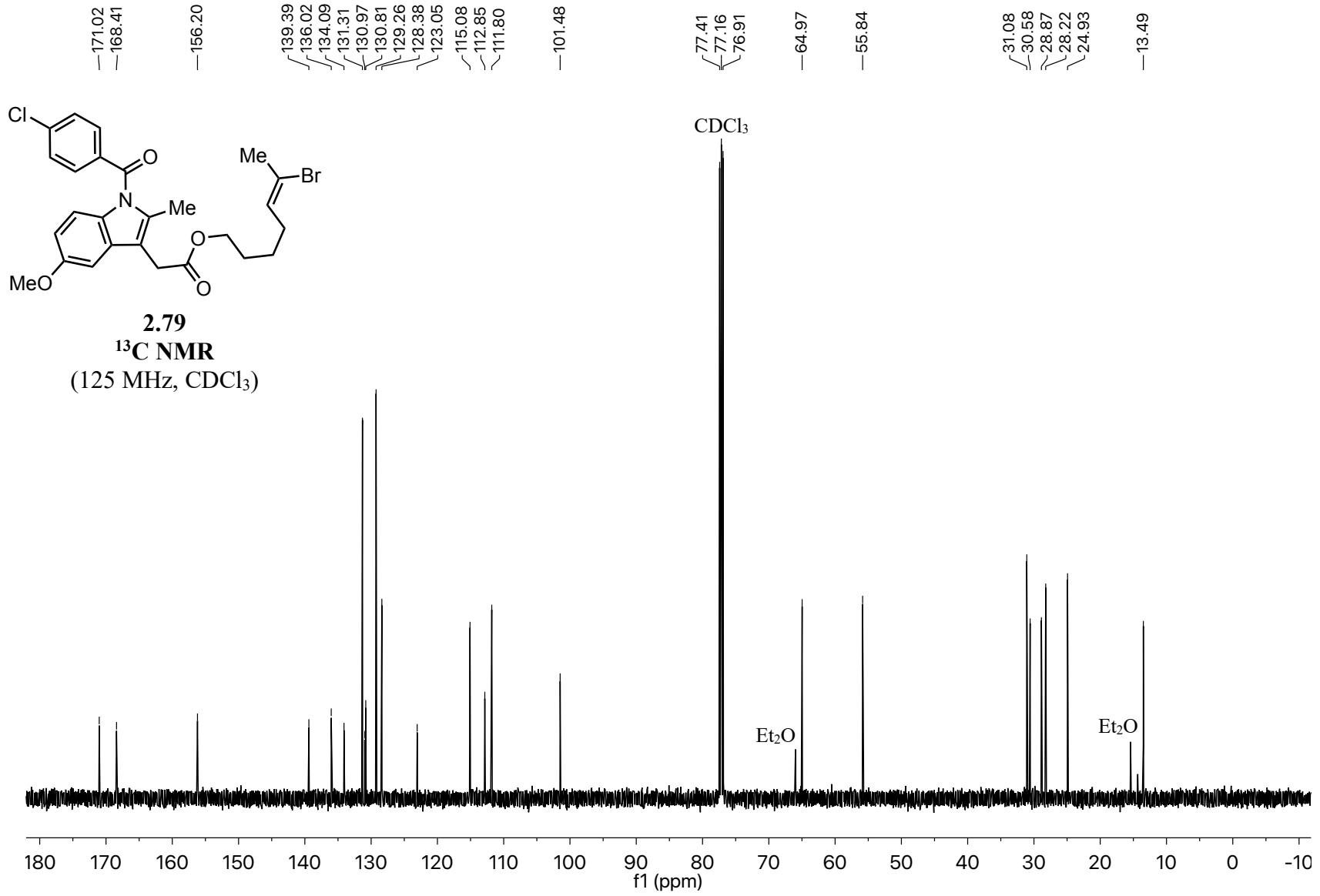


2.78

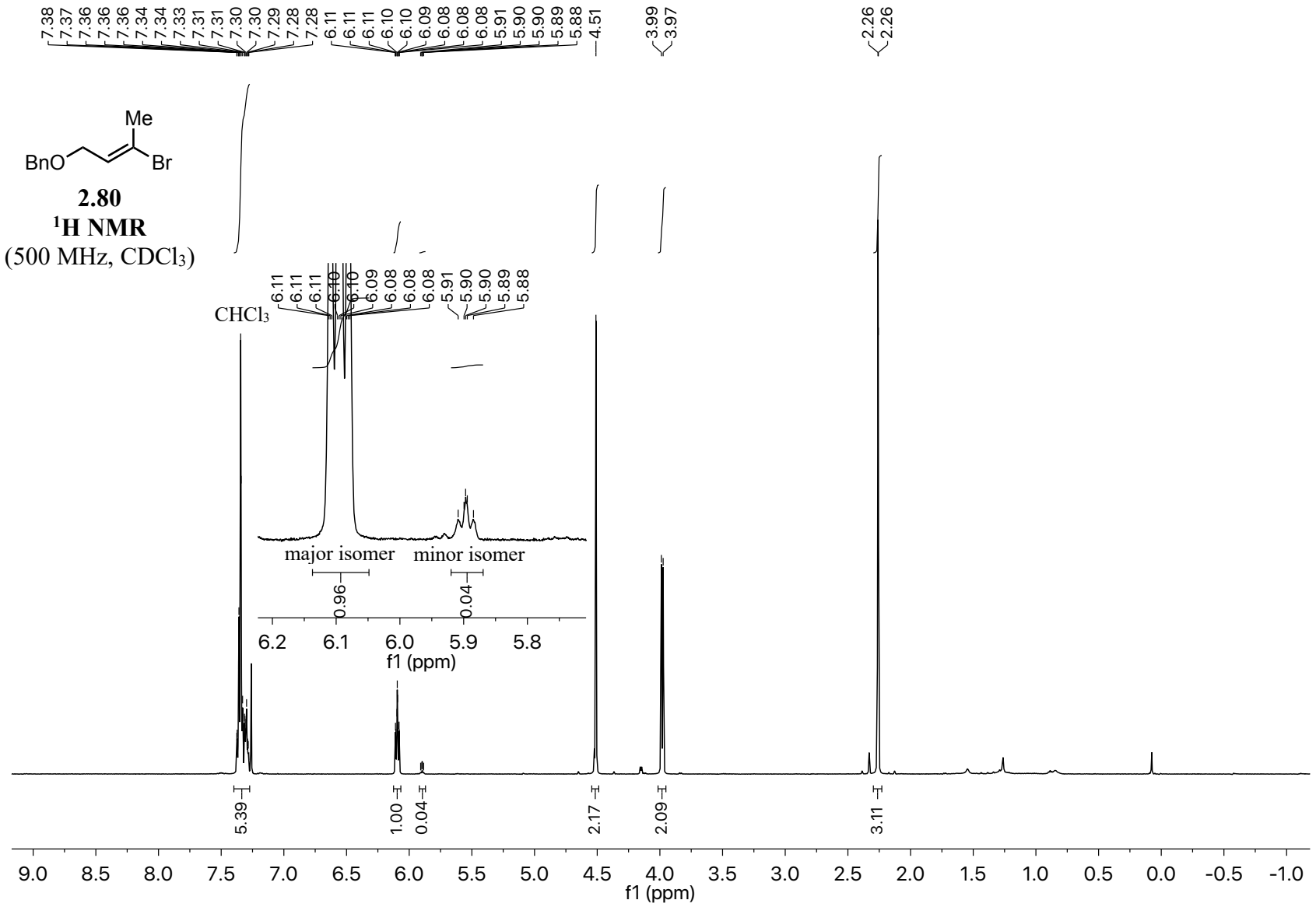
^{13}C NMR

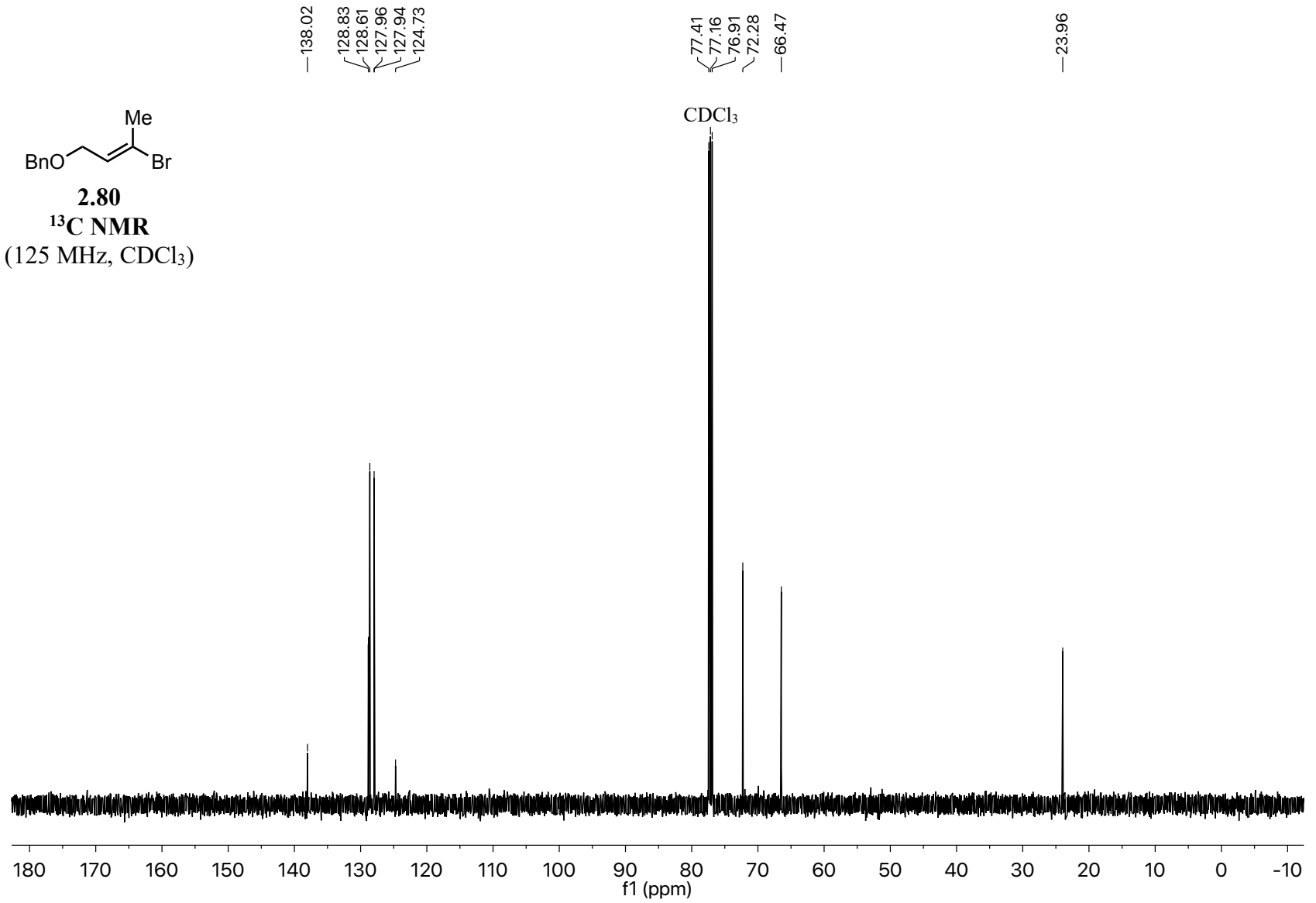
(125 MHz, $CDCl_3$)

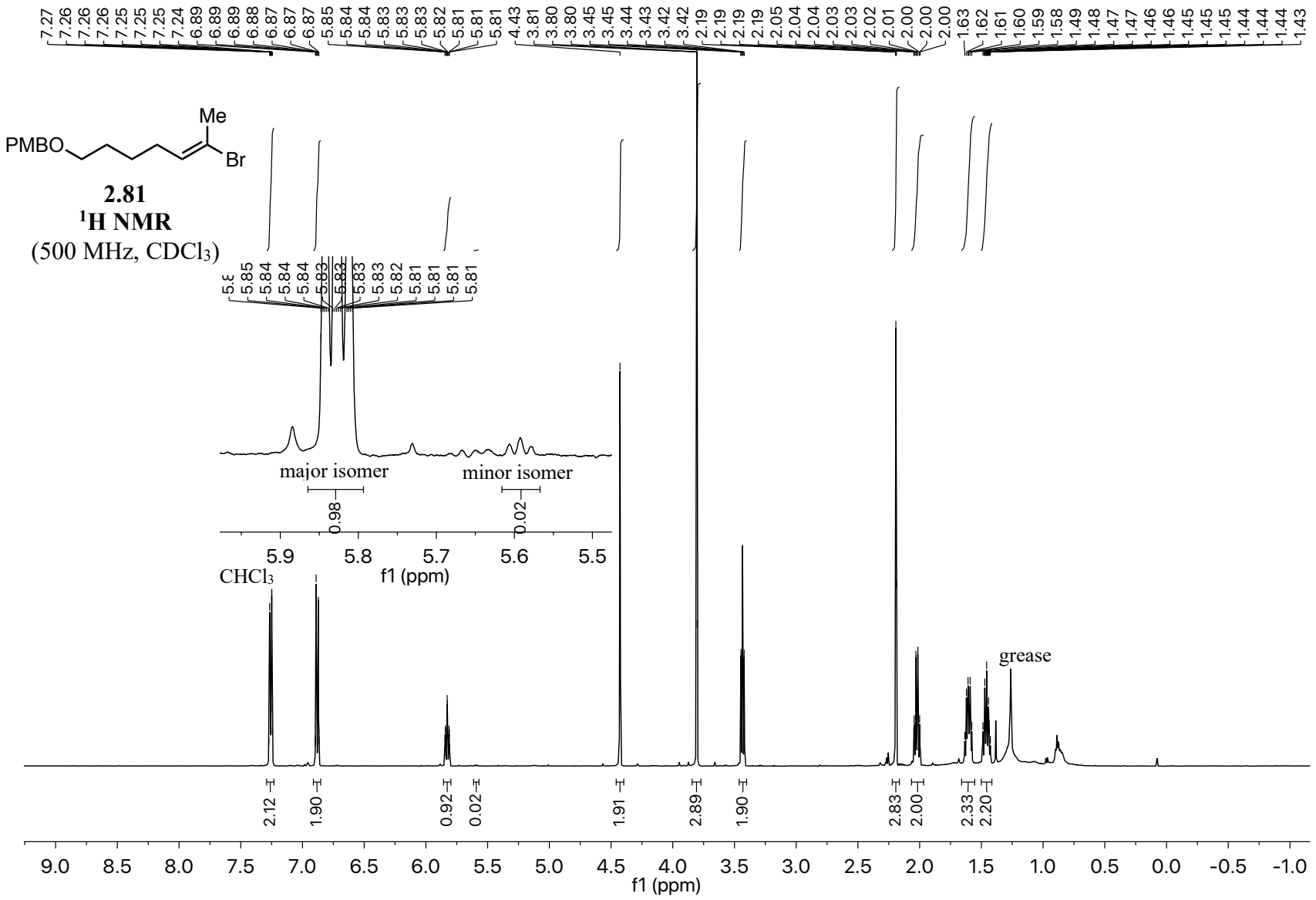

Cl
O
N
Me
Me
Br
O
MeO
O
2.79
1H NMR
(500 MHz, CDCl3)
CHCl3
Et2O
Et2O
f1 (ppm)

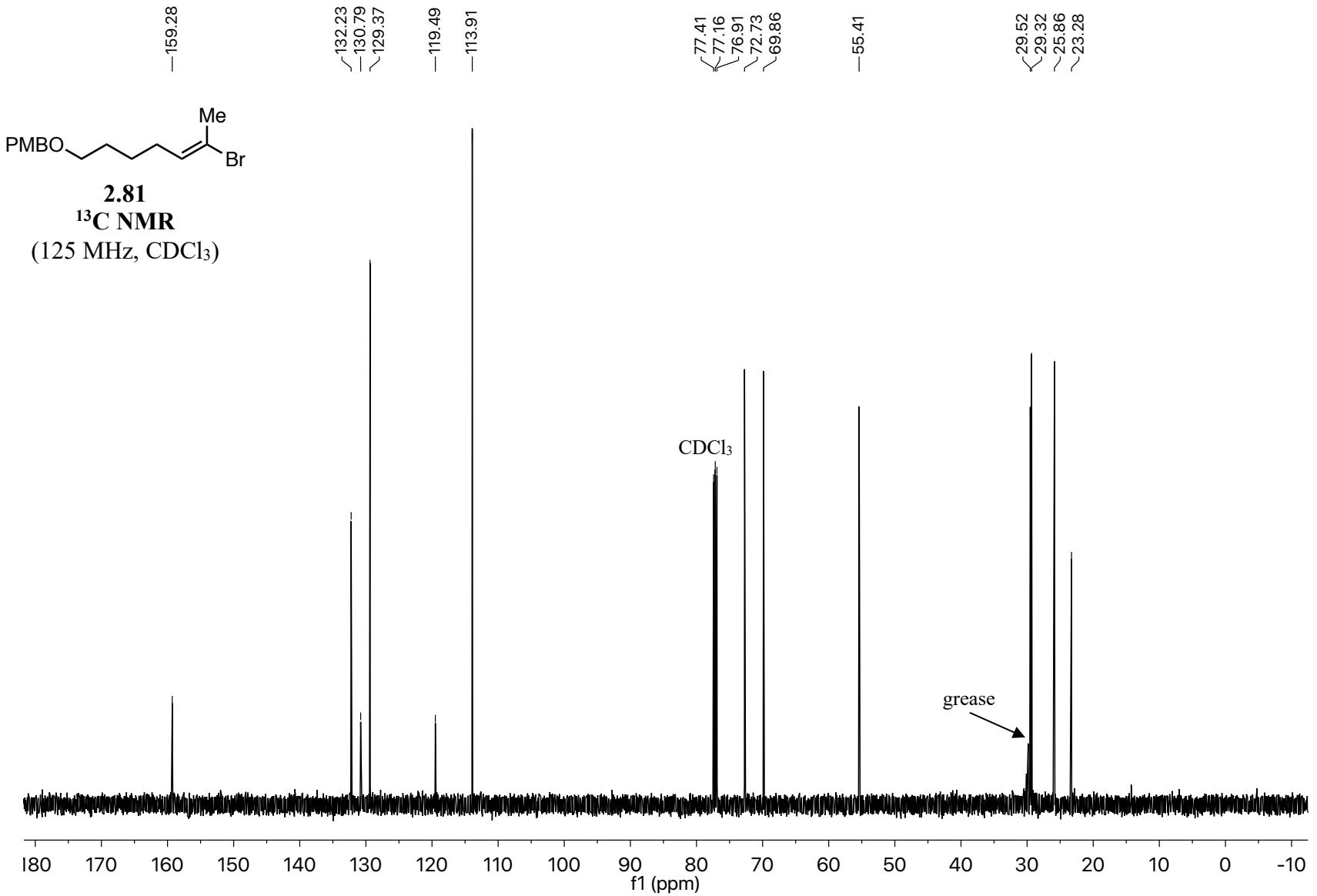


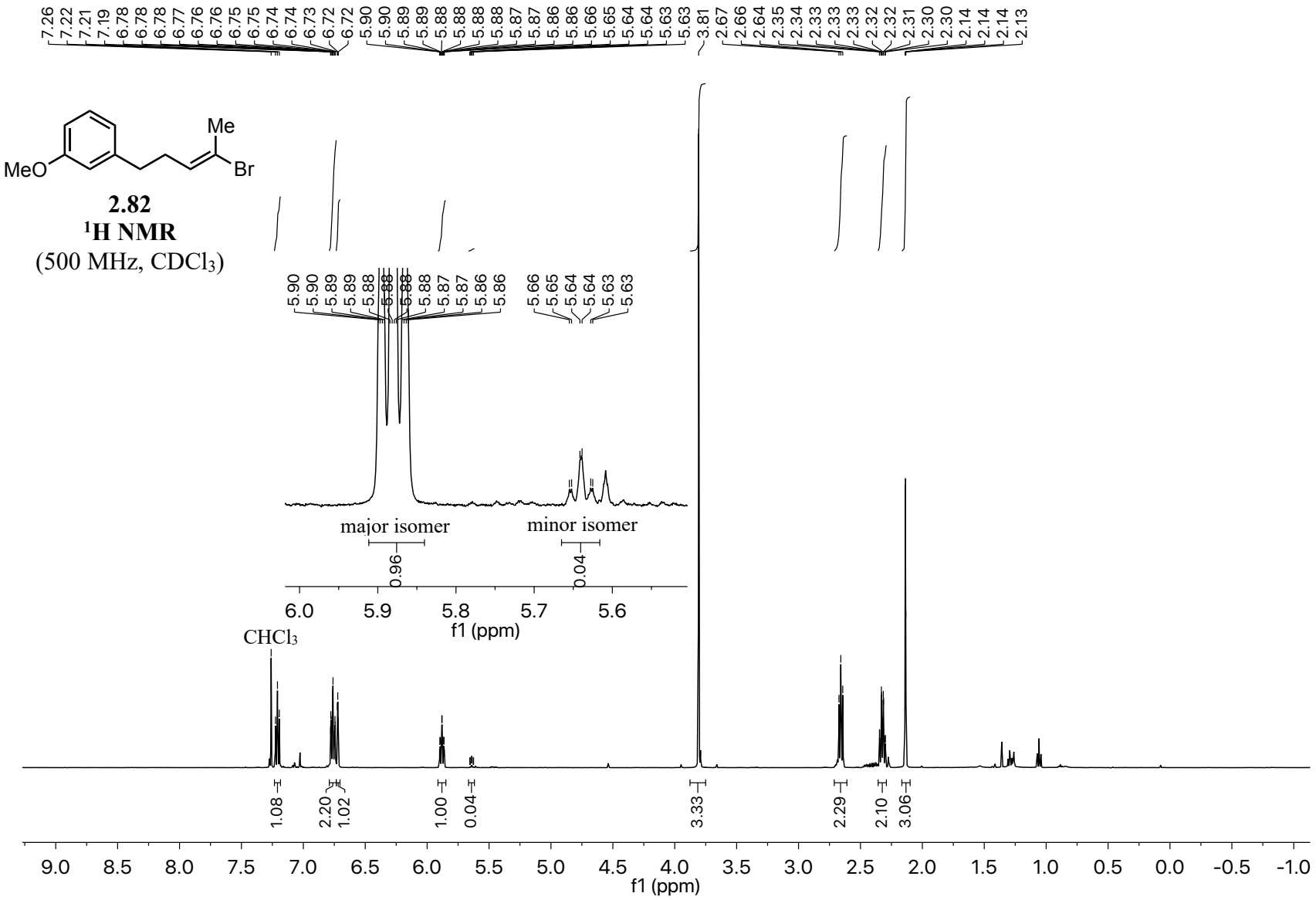
2.79
^{13}C NMR
(125 MHz, $CDCl_3$)


Me
BnO
Br
2.80
1H NMR
(500 MHz, CDCl3)
CHCl3
major isomer
minor isomer
0.96
0.04
f1 (ppm)
5.39
1.00
0.04
2.17
2.09
3.11
f1 (ppm)

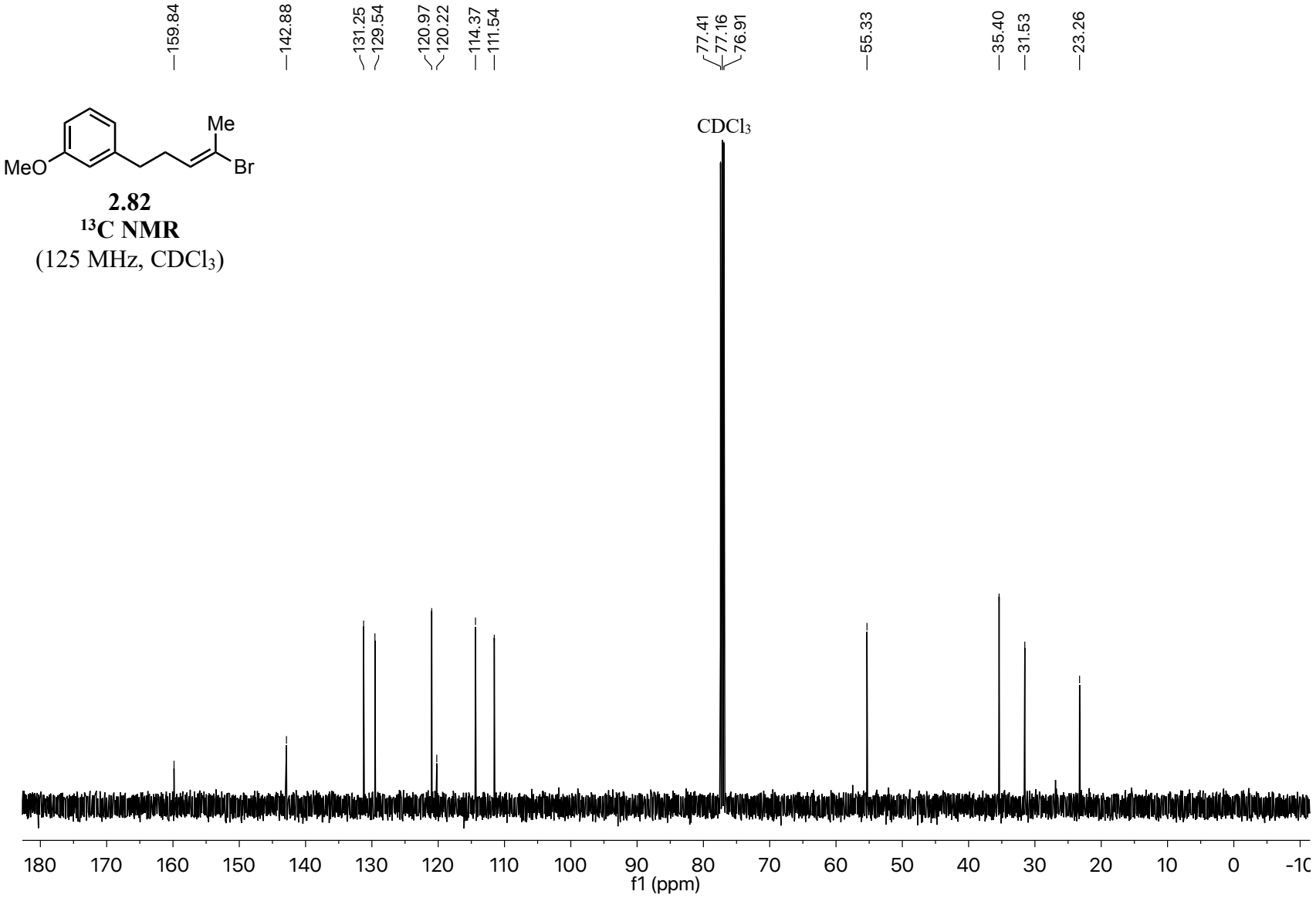

138.02
128.83
128.61
127.96
127.94
124.73
77.41
77.16
76.91
72.28
66.47
23.96
CDCl3
Me
BnO
Br
2.80
13C NMR
(125 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


PMBO
Me
Br
2.81
1H NMR
(500 MHz, CDCl3)
major isomer
minor isomer
0.98
0.02
CHCl3
grease
f1 (ppm)

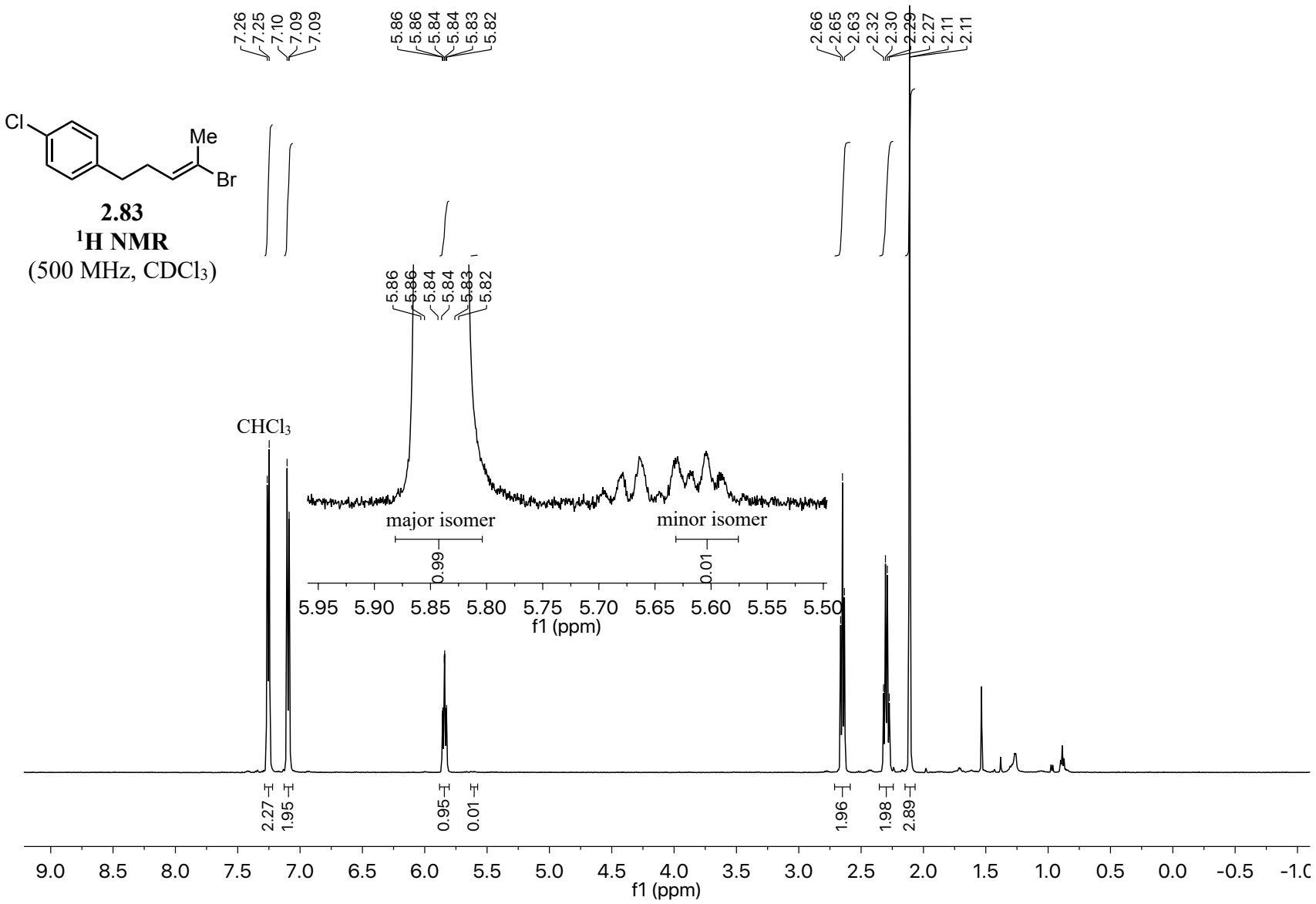

159.28
132.23
130.79
129.37
119.49
113.91
77.41
77.16
76.91
72.73
69.86
55.41
29.52
29.32
25.86
23.28
Me
PMBO
Br
2.81
13C NMR
(125 MHz, CDCl3)
CDCl3
grease
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

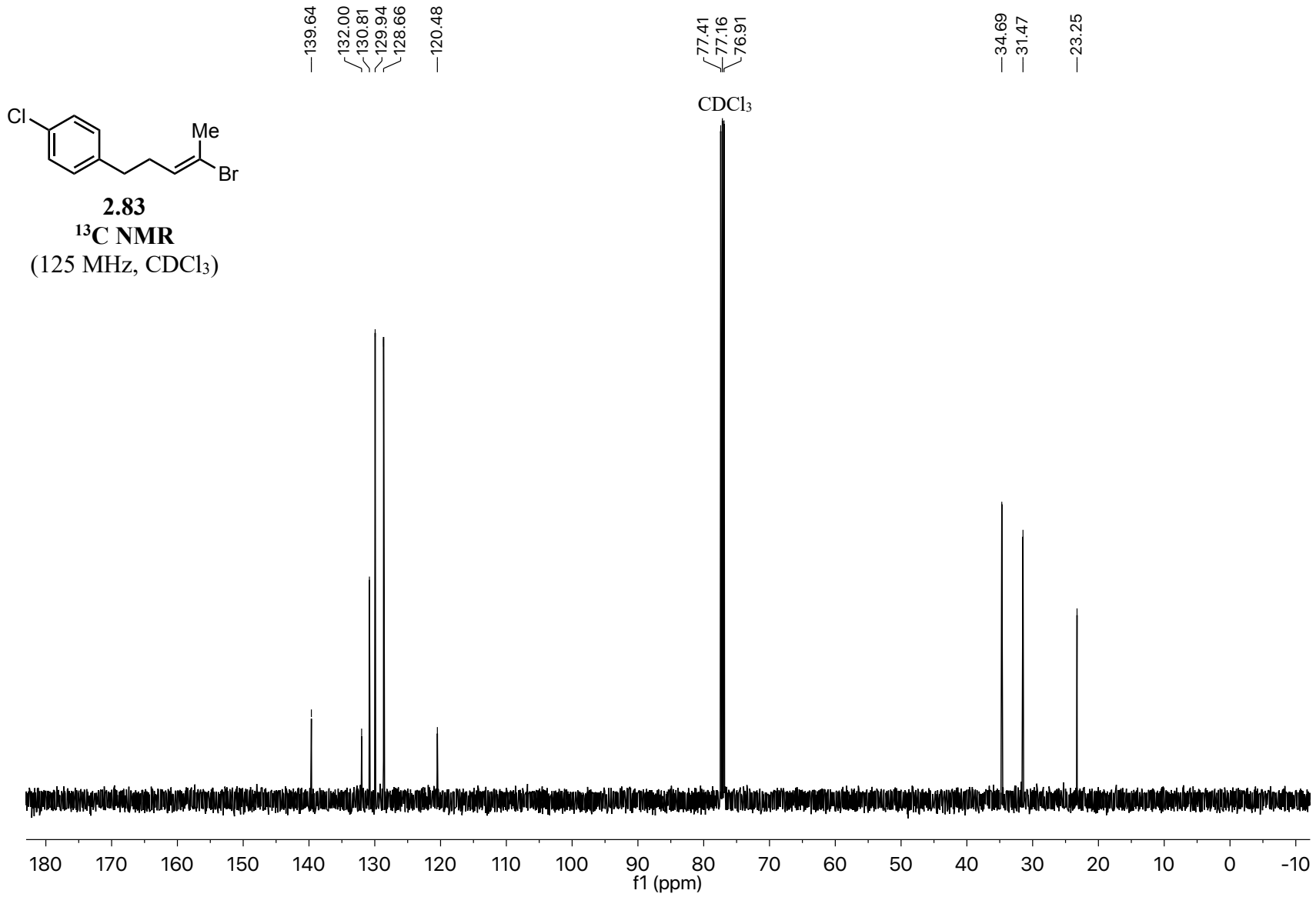


2.82
^{1}H NMR
(500 MHz, $CDCl_3$)

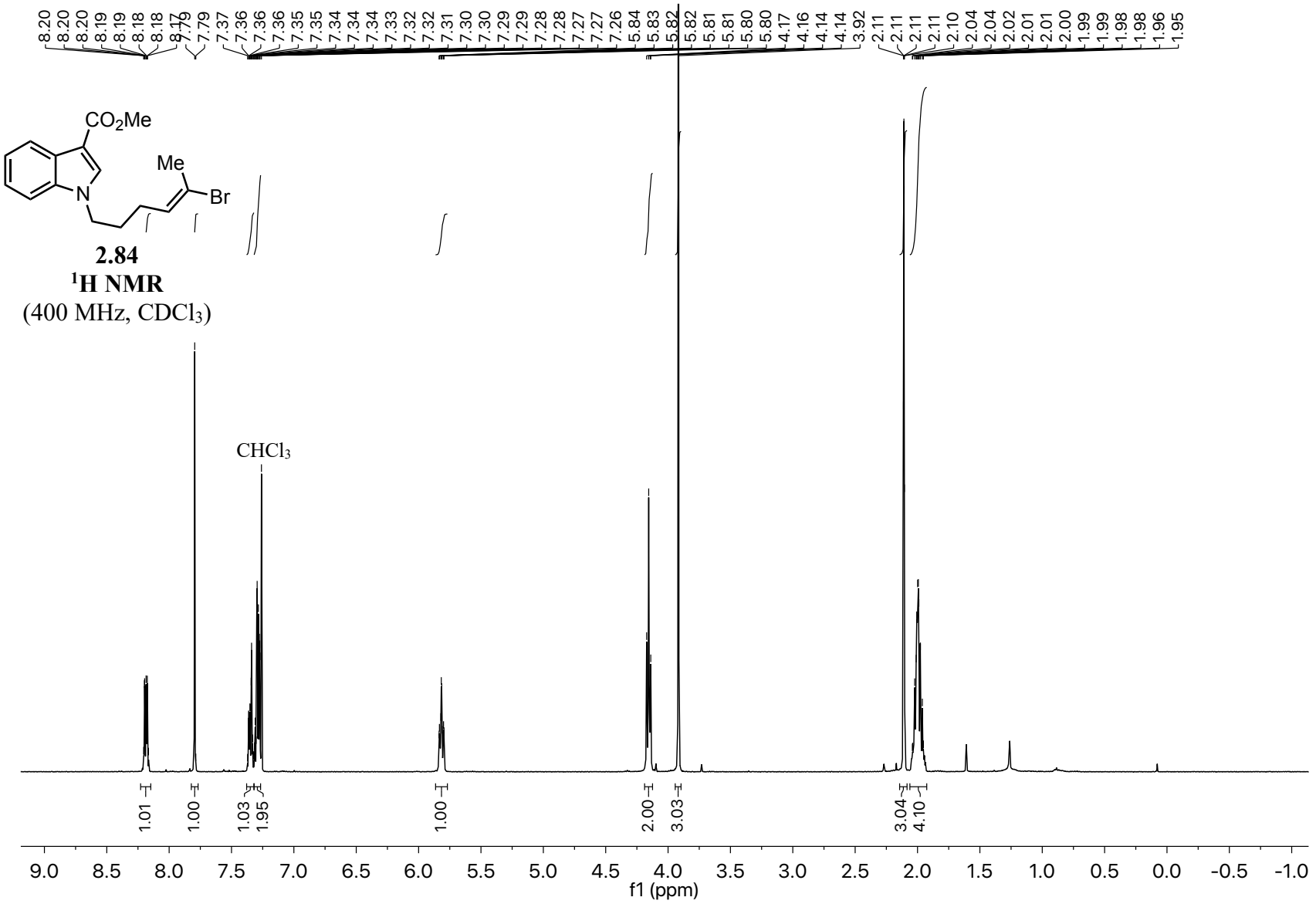


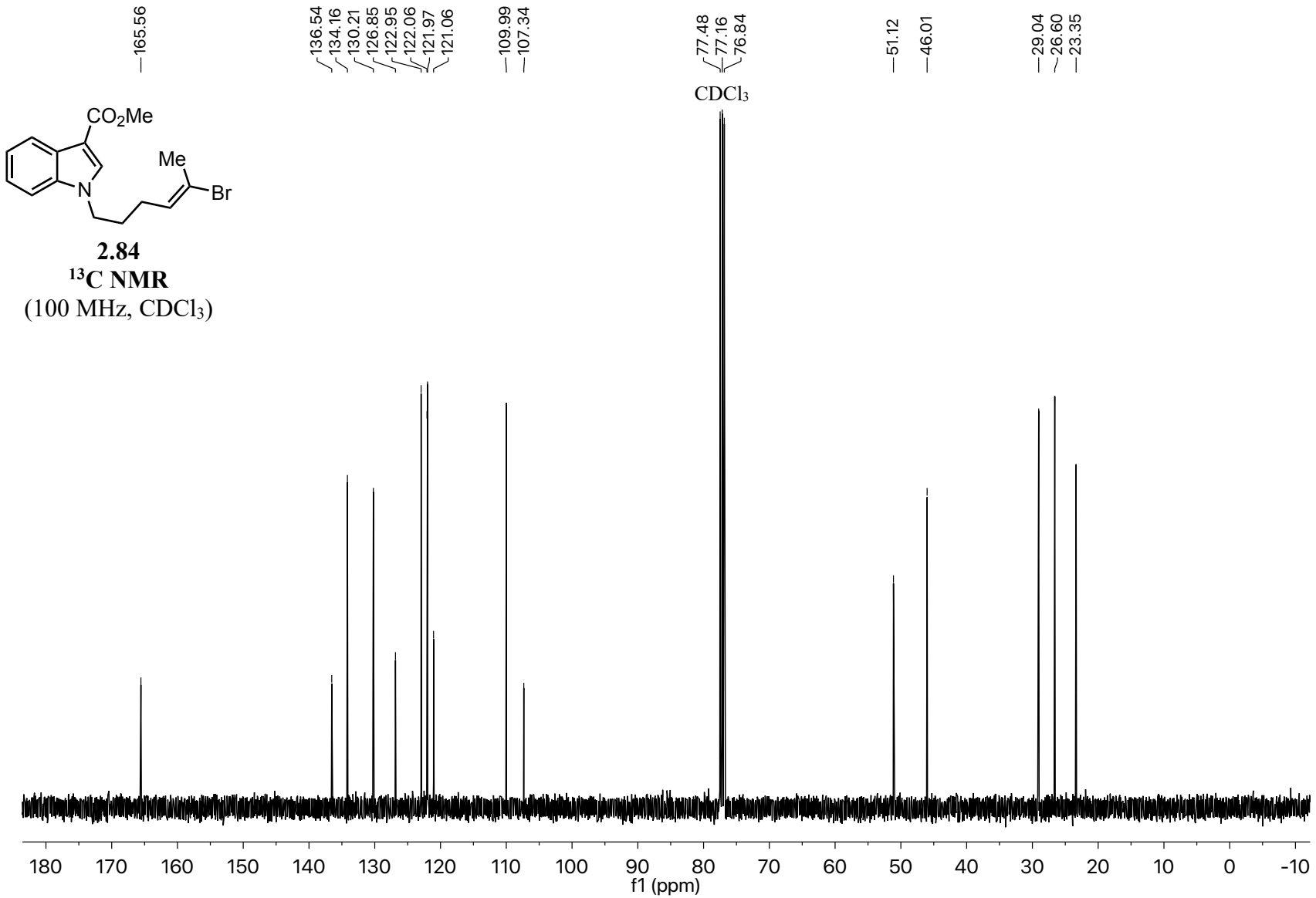
2.82
^{13}C NMR
(125 MHz, $CDCl_3$)


Cl
Me
Br
2.83
1H NMR
(500 MHz, CDCl3)
7.26
7.25
7.10
7.09
7.09
5.86
5.86
5.84
5.84
5.83
5.82
2.66
2.65
2.63
2.32
2.30
2.29
2.27
2.11
2.11
CHCl3
major isomer
minor isomer
0.99
0.01
5.95 5.90 5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50
f1 (ppm)
2.27
1.95
0.95
0.01
1.96
1.98
2.89
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

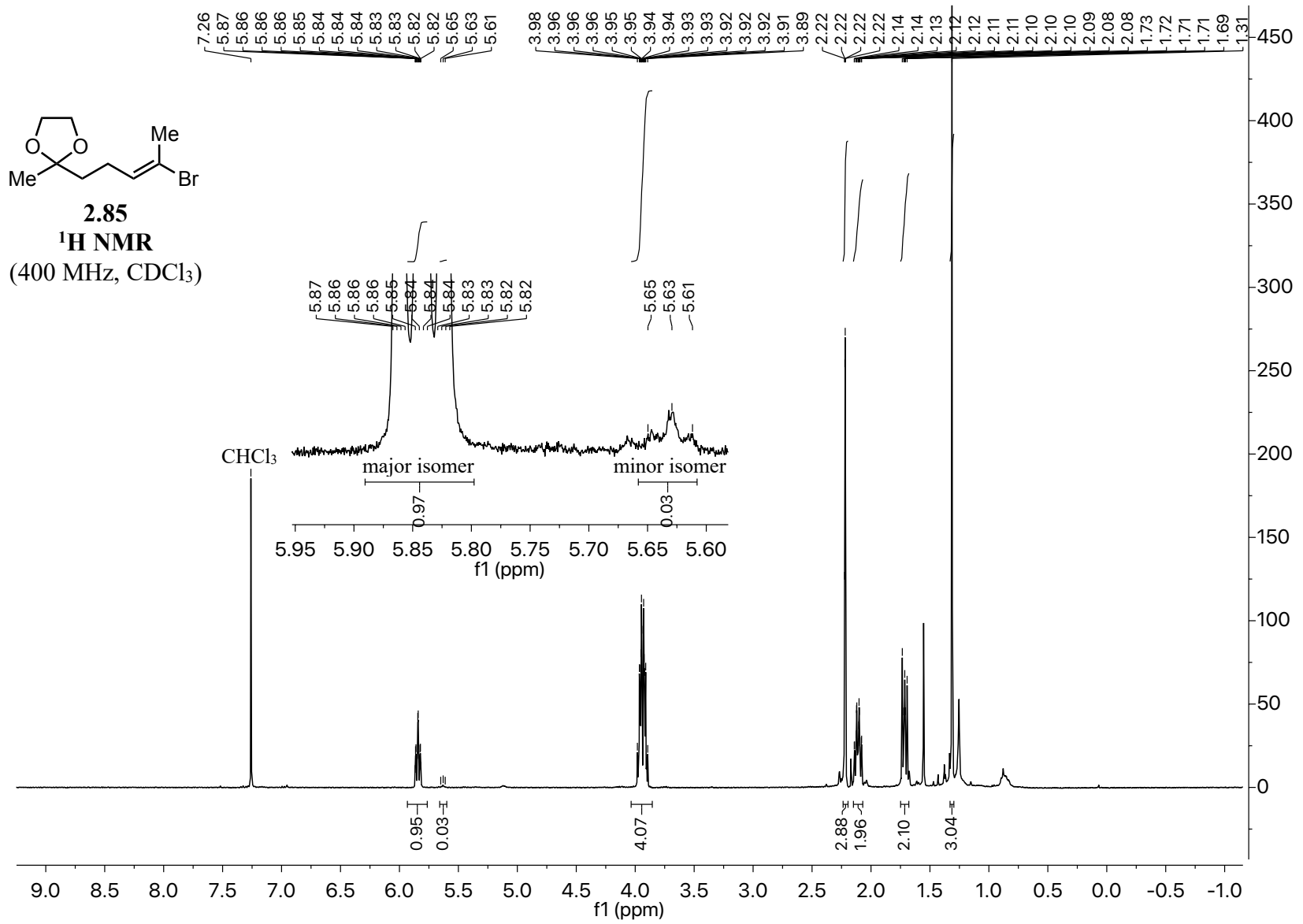


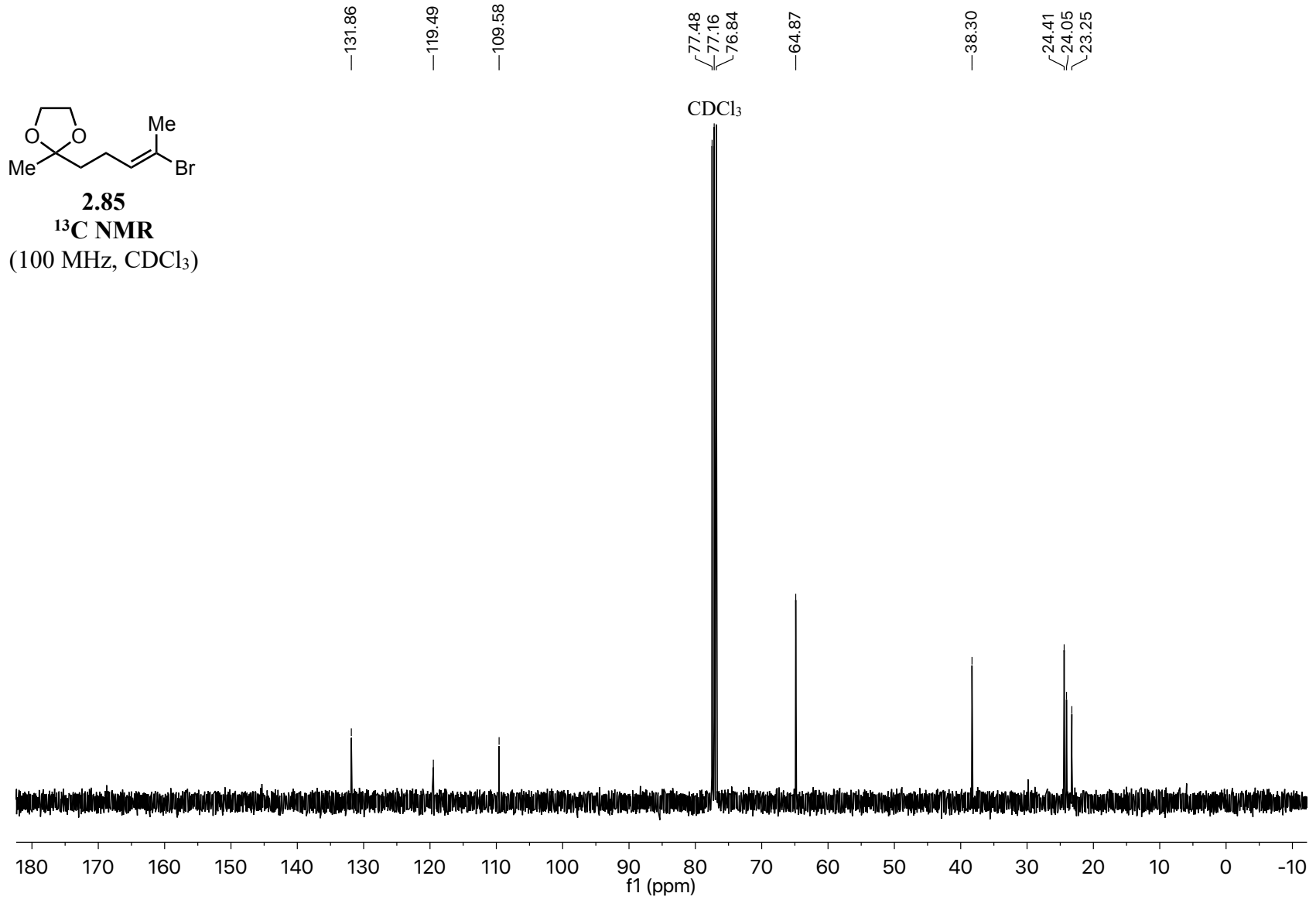
2.83
^{13}C NMR
(125 MHz, $CDCl_3$)


CO2Me
Me
N
Br
2.84
1H NMR
(400 MHz, CDCl3)
CHCl3
1.01
1.00
1.03
1.95
1.00
2.00
3.03
3.04
4.10
f1 (ppm)

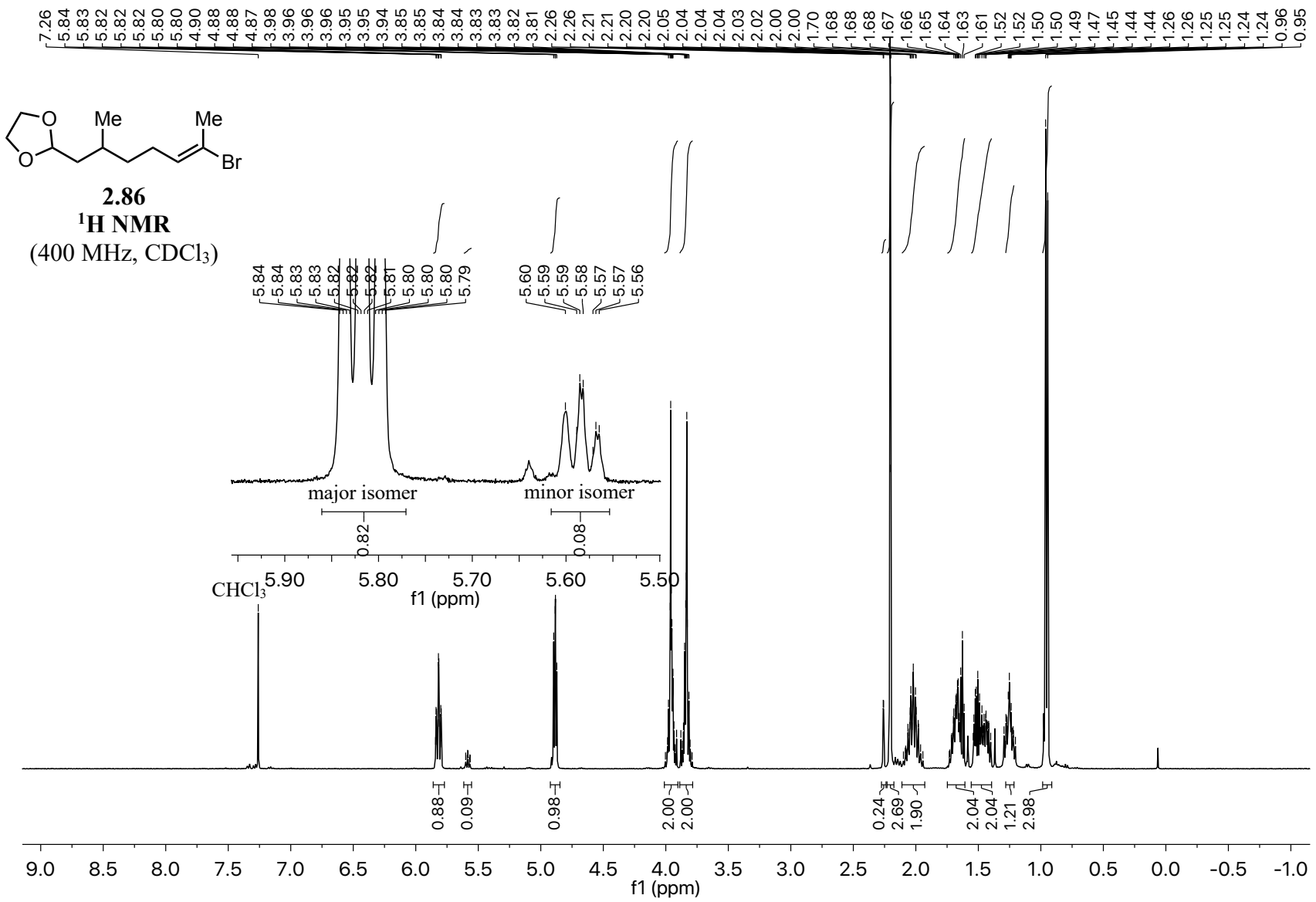


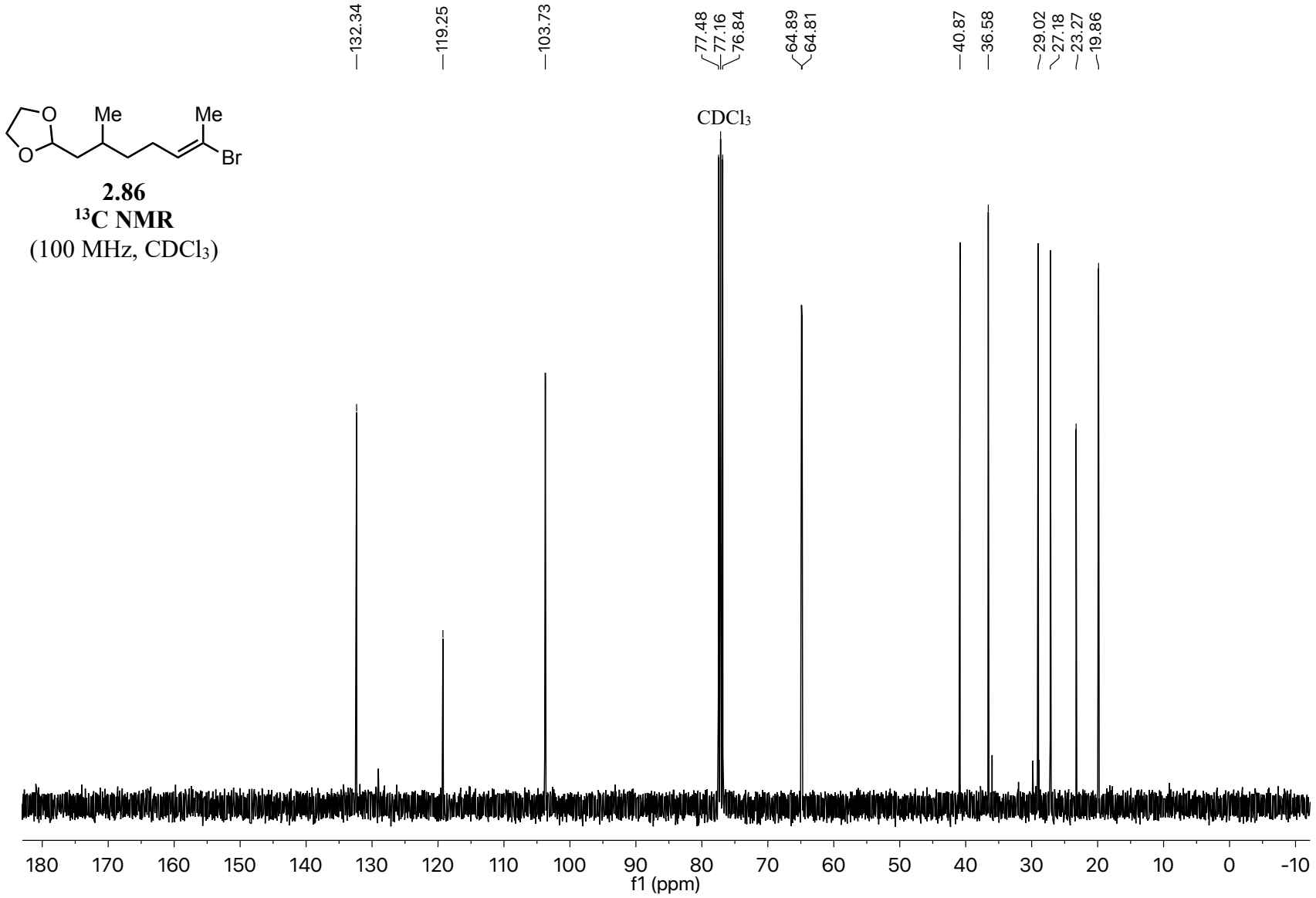
2.84
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
O
O
Me
Br
2.85
1H NMR
(400 MHz, CDCl3)
CHCl3
major isomer
minor isomer
0.97
0.03
f1 (ppm)
0.95
0.03
4.07
2.88
1.96
2.10
3.04

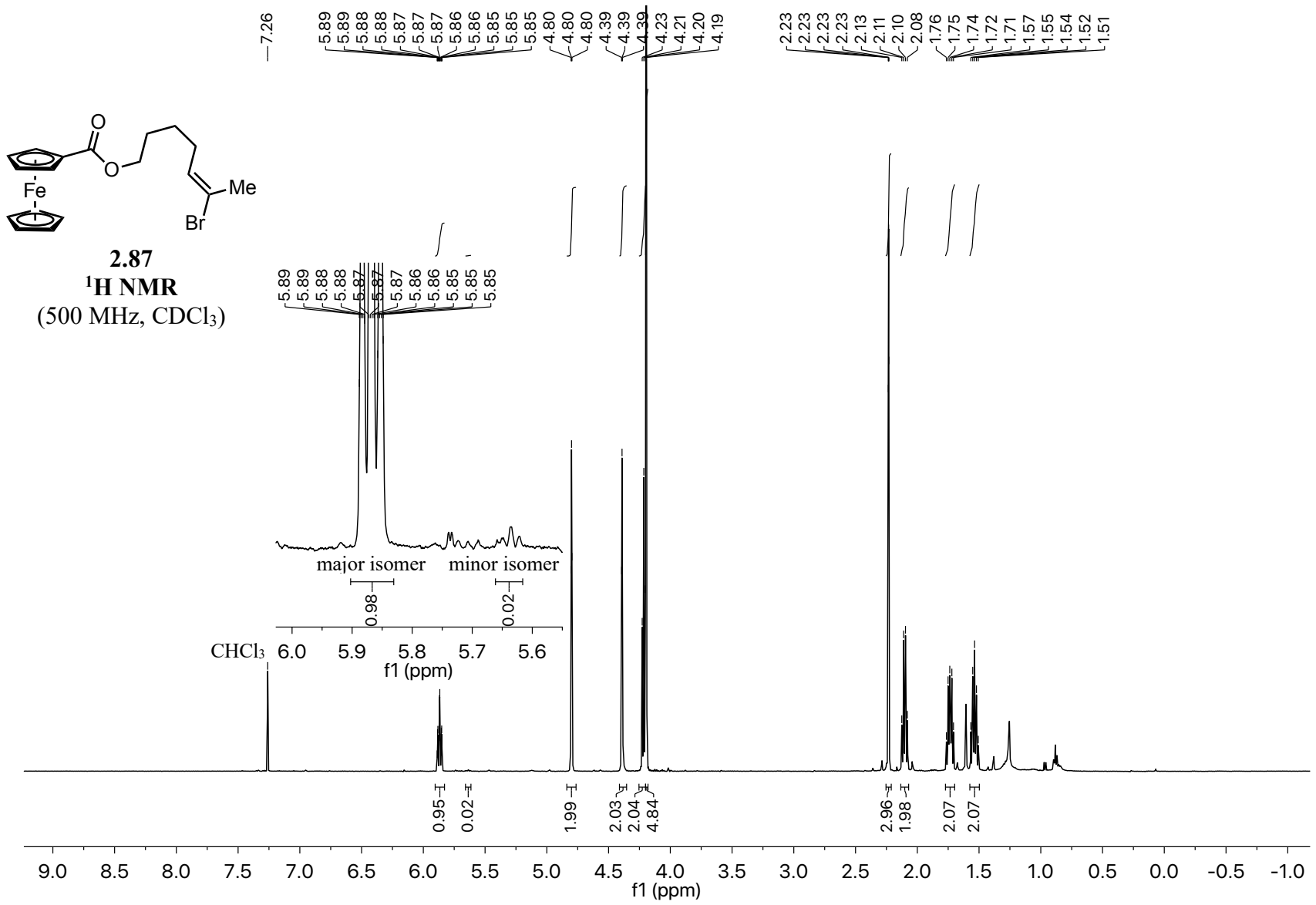


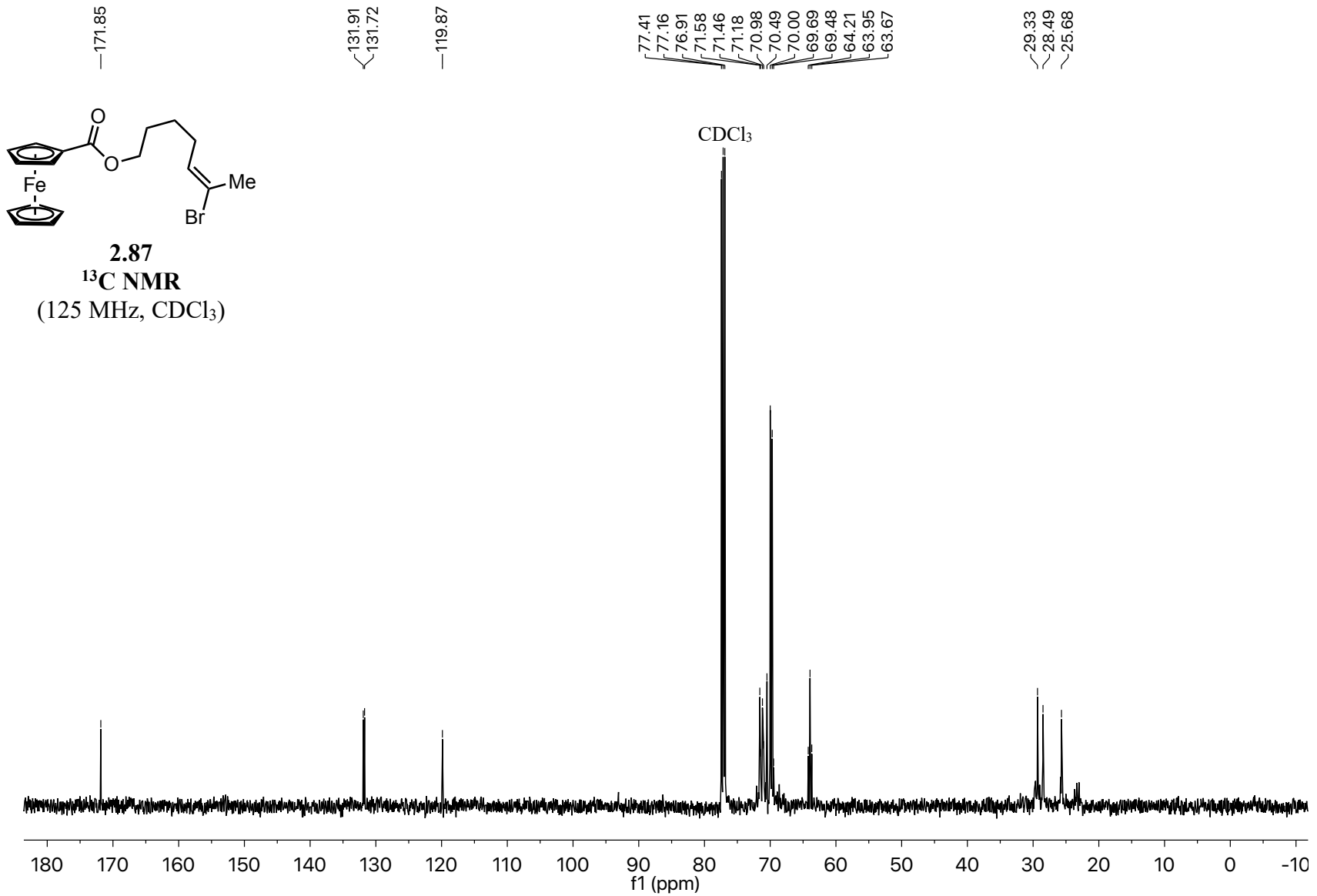
2.85
^{13}C NMR
(100 MHz, $CDCl_3$)


O
Me
Me
O
Br
2.86
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
0.82
0.08
CHCl3
f1 (ppm)
0.88
0.09
0.98
2.00
2.00
0.24
2.69
1.90
2.04
2.04
1.21
2.98

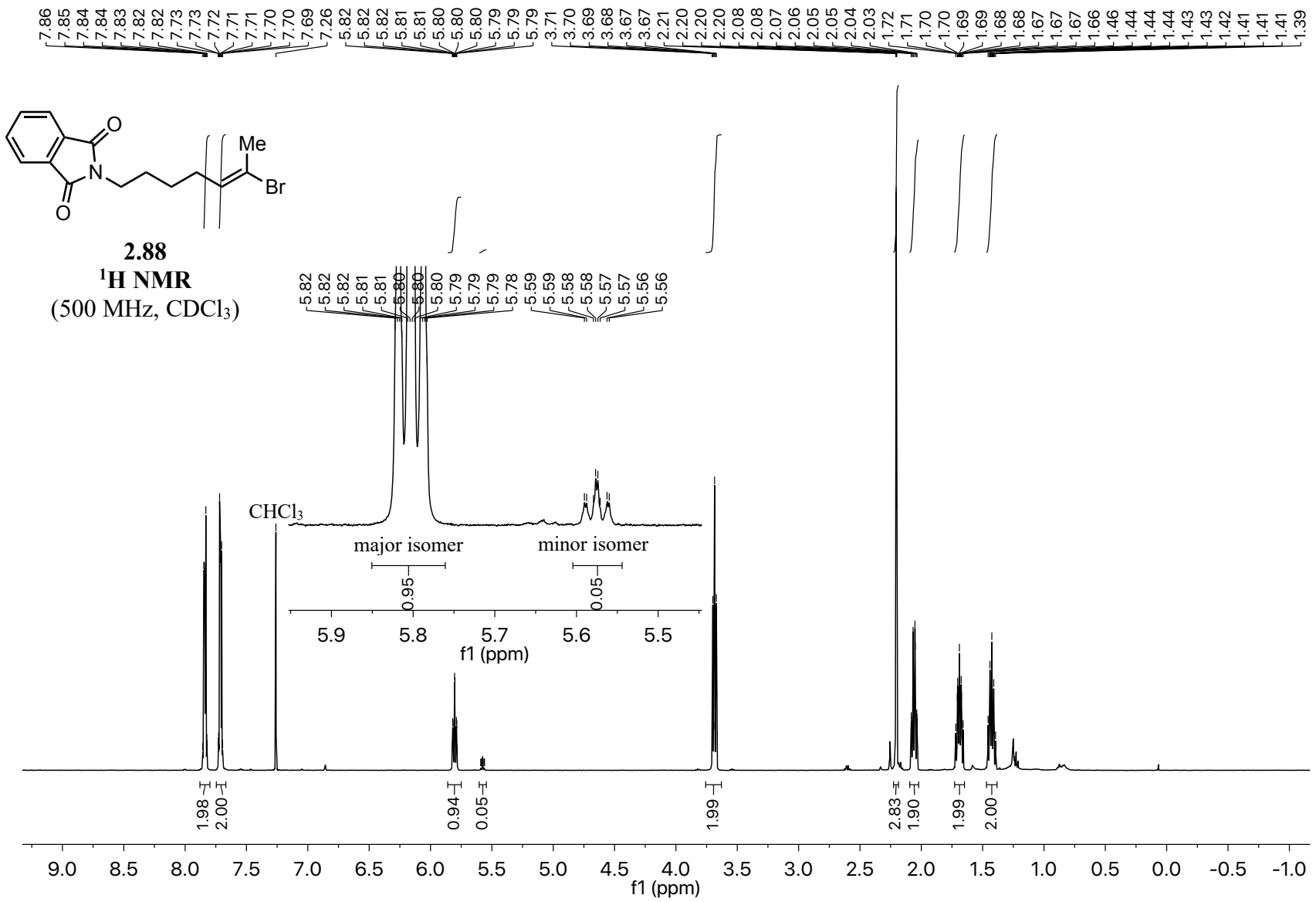


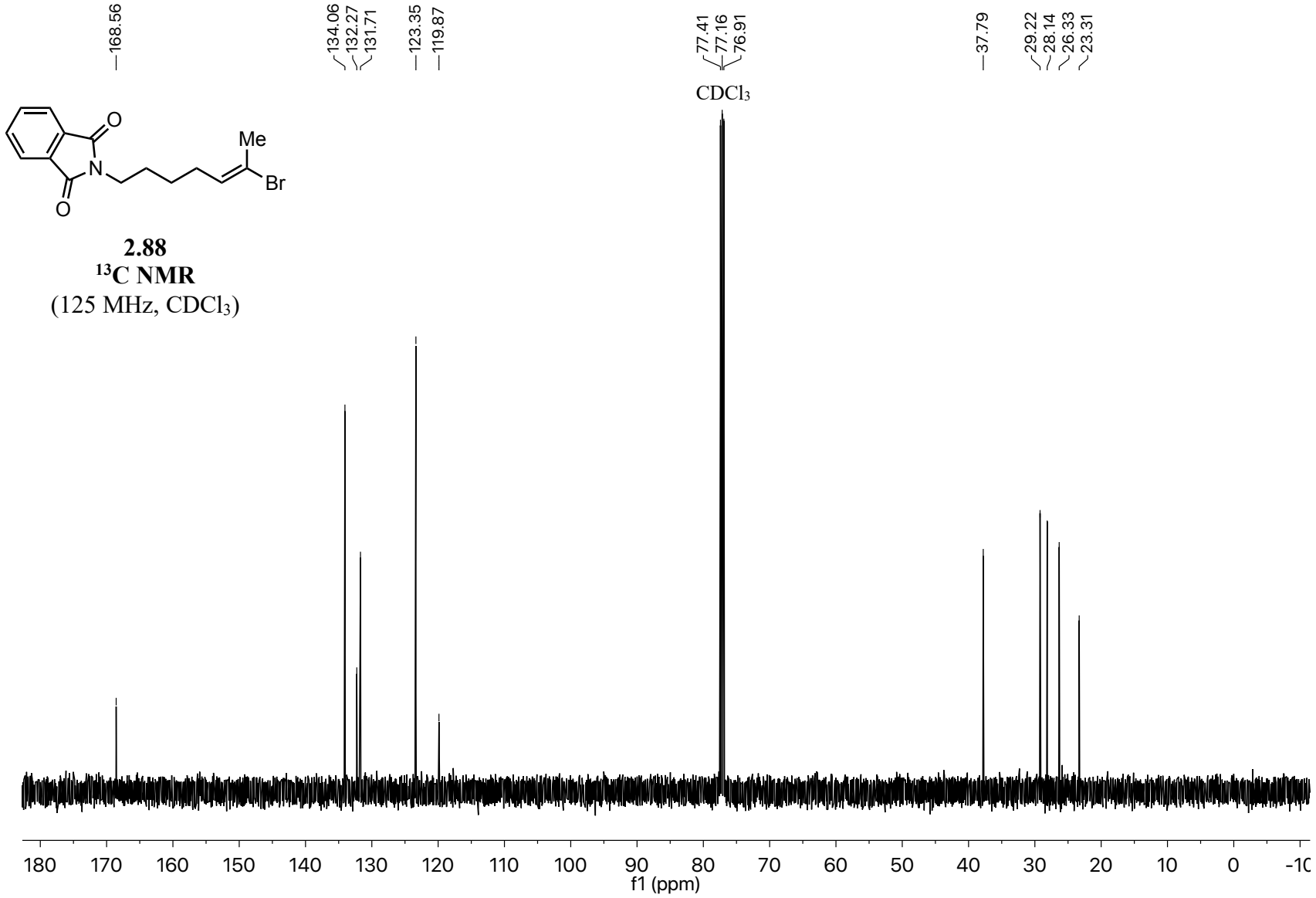
2.86
^{13}C NMR
(100 MHz, $CDCl_3$)


O
O
Fe
Me
Br
2.87
1H NMR
(500 MHz, CDCl3)
major isomer
minor isomer
0.98
0.02
CHCl3
f1 (ppm)
0.95
0.02
1.99
2.03
2.04
4.84
2.96
1.98
2.07
2.07
f1 (ppm)

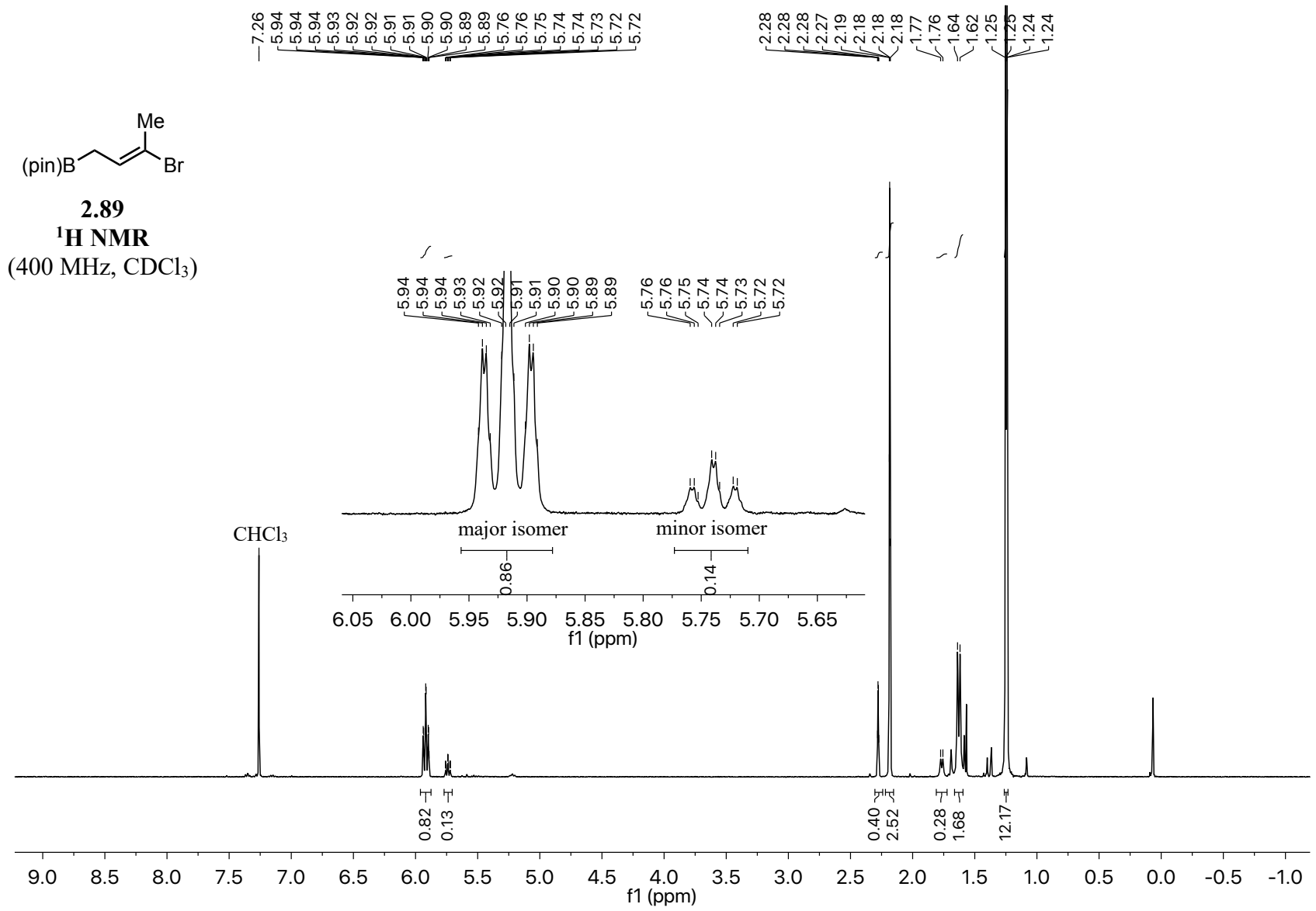


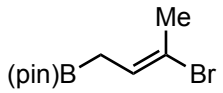
2.87
^{13}C NMR
(125 MHz, $CDCl_3$)


Me
Br
O
N
O
2.88
1H NMR
(500 MHz, CDCl3)
CHCl3
major isomer
minor isomer
0.95
0.05
f1 (ppm)
1.98
2.00
0.94
0.05
1.99
2.83
1.90
1.99
2.00
f1 (ppm)

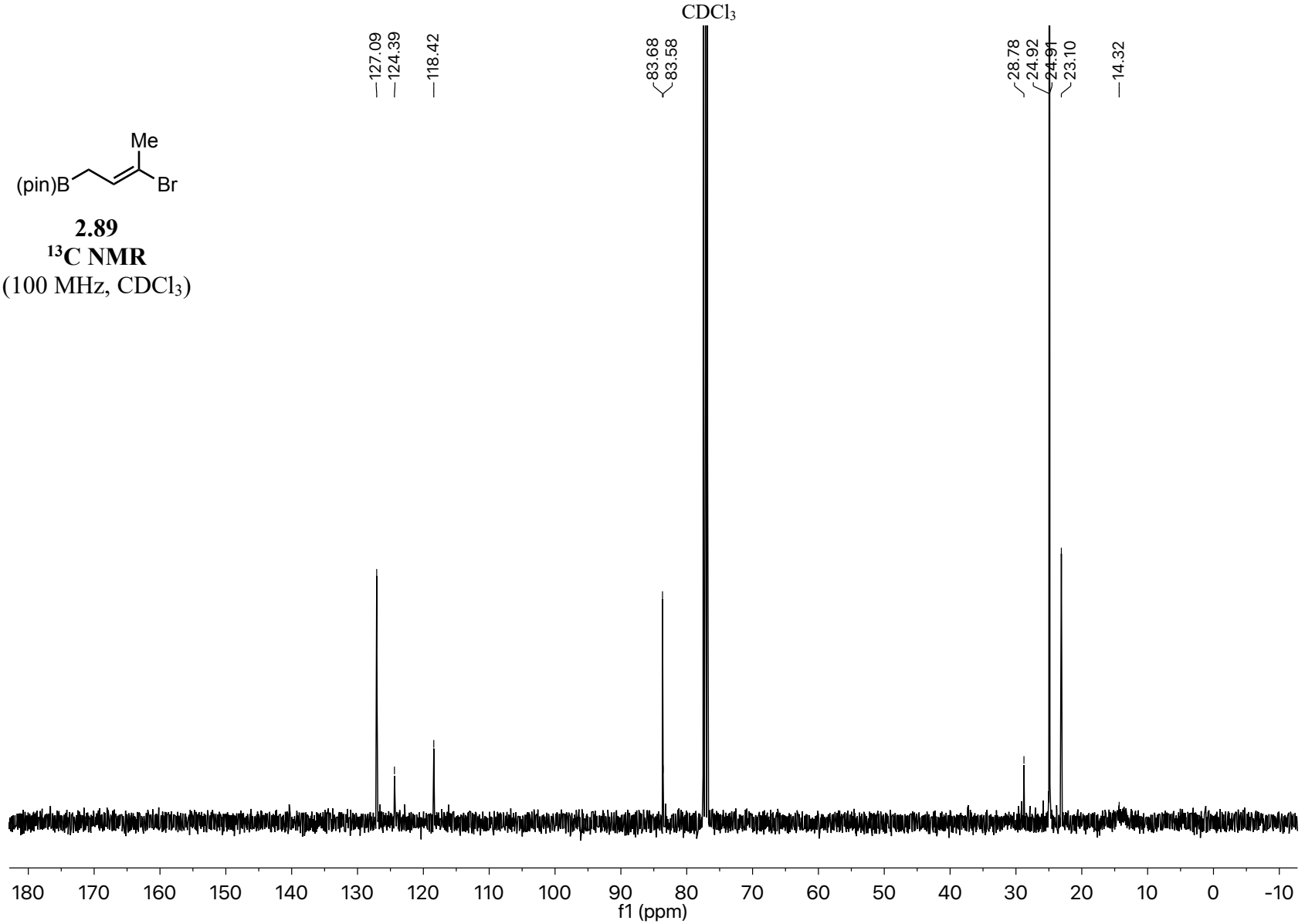


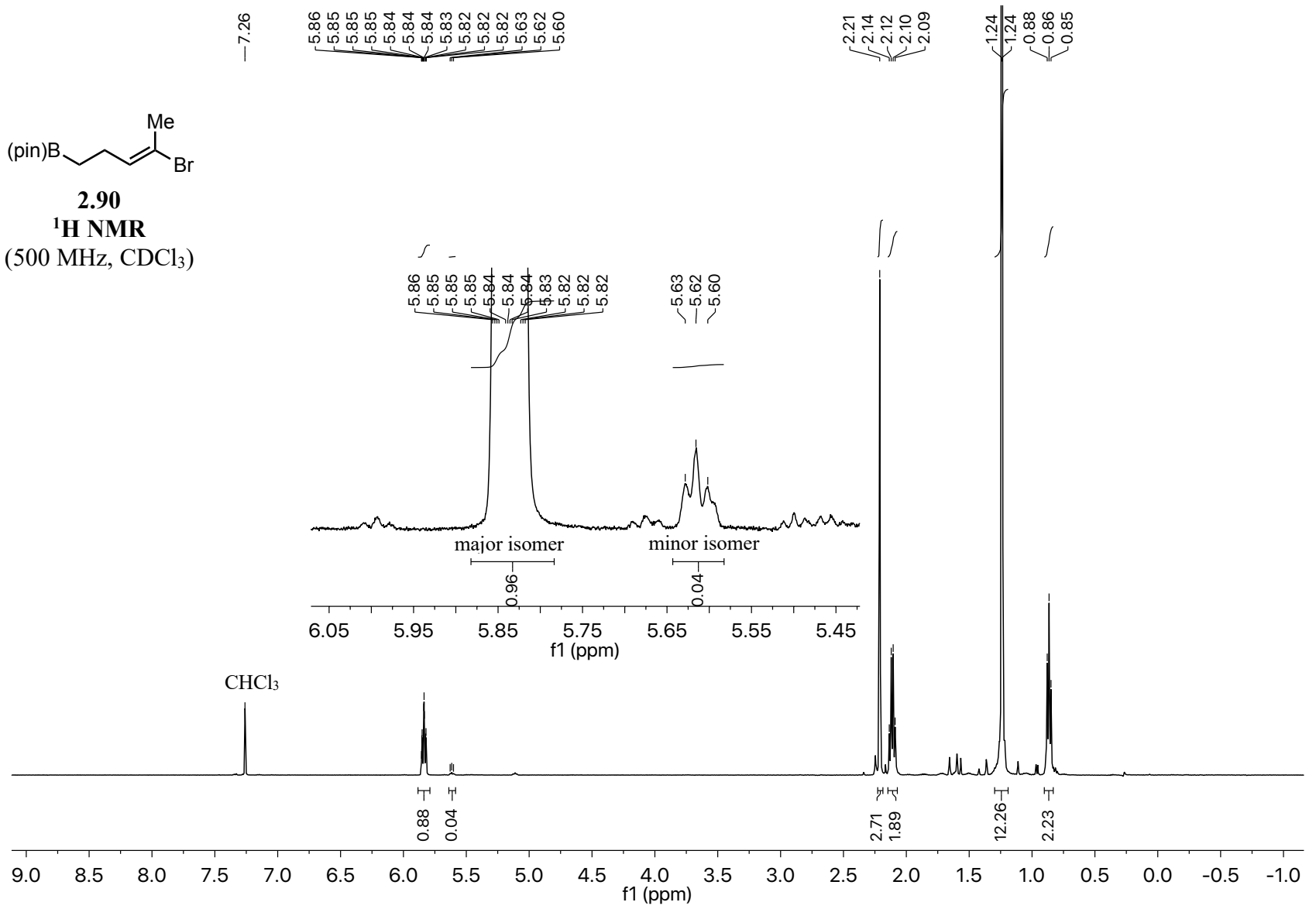
2.88
^{13}C NMR
(125 MHz, $CDCl_3$)

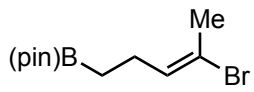

Me
(pin)B
Br
2.89
1H NMR
(400 MHz, CDCl3)
CHCl3
major isomer
minor isomer
0.86
0.14
f1 (ppm)



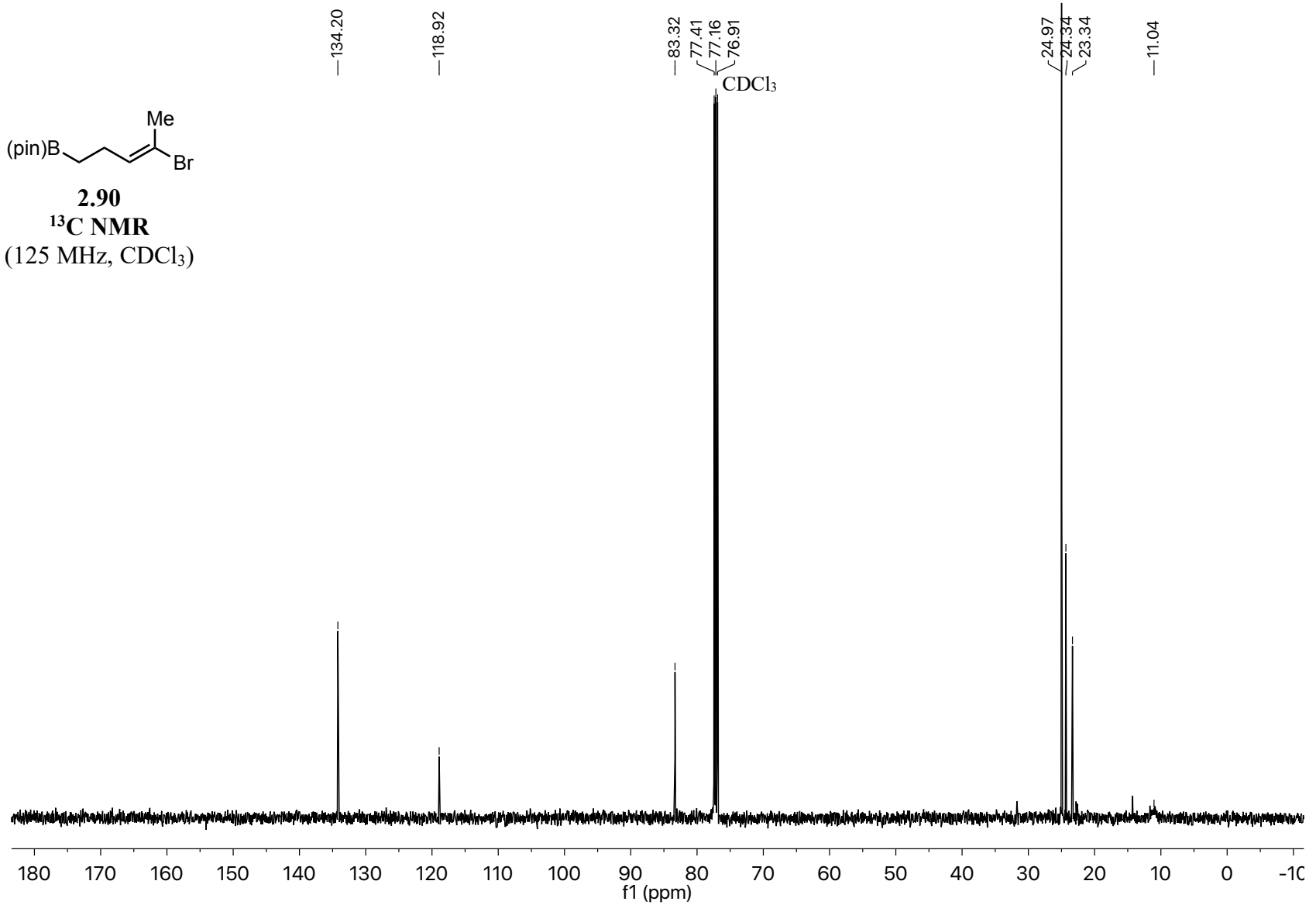
2.89
^{11}B NMR
(128 MHz, $CDCl_3$)

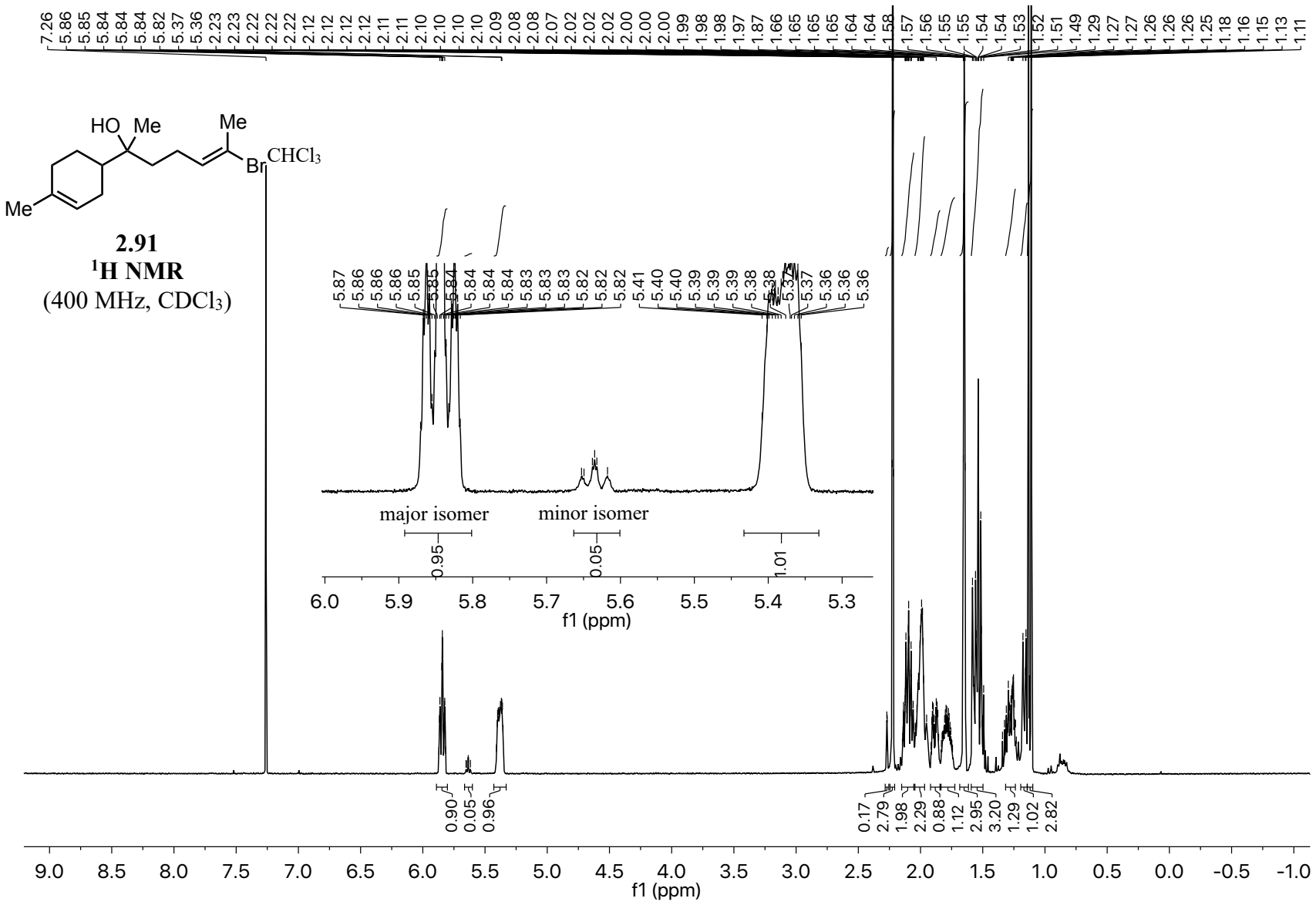

Me
(pin)B
Br
2.89
13C NMR
(100 MHz, CDCl3)
CDCl3
127.09
124.39
118.42
83.68
83.58
28.78
24.92
24.91
23.10
14.32
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
(pin)B
Br
2.90
1H NMR
(500 MHz, CDCl3)
major isomer
minor isomer
0.96
0.04
CHCl3
f1 (ppm)

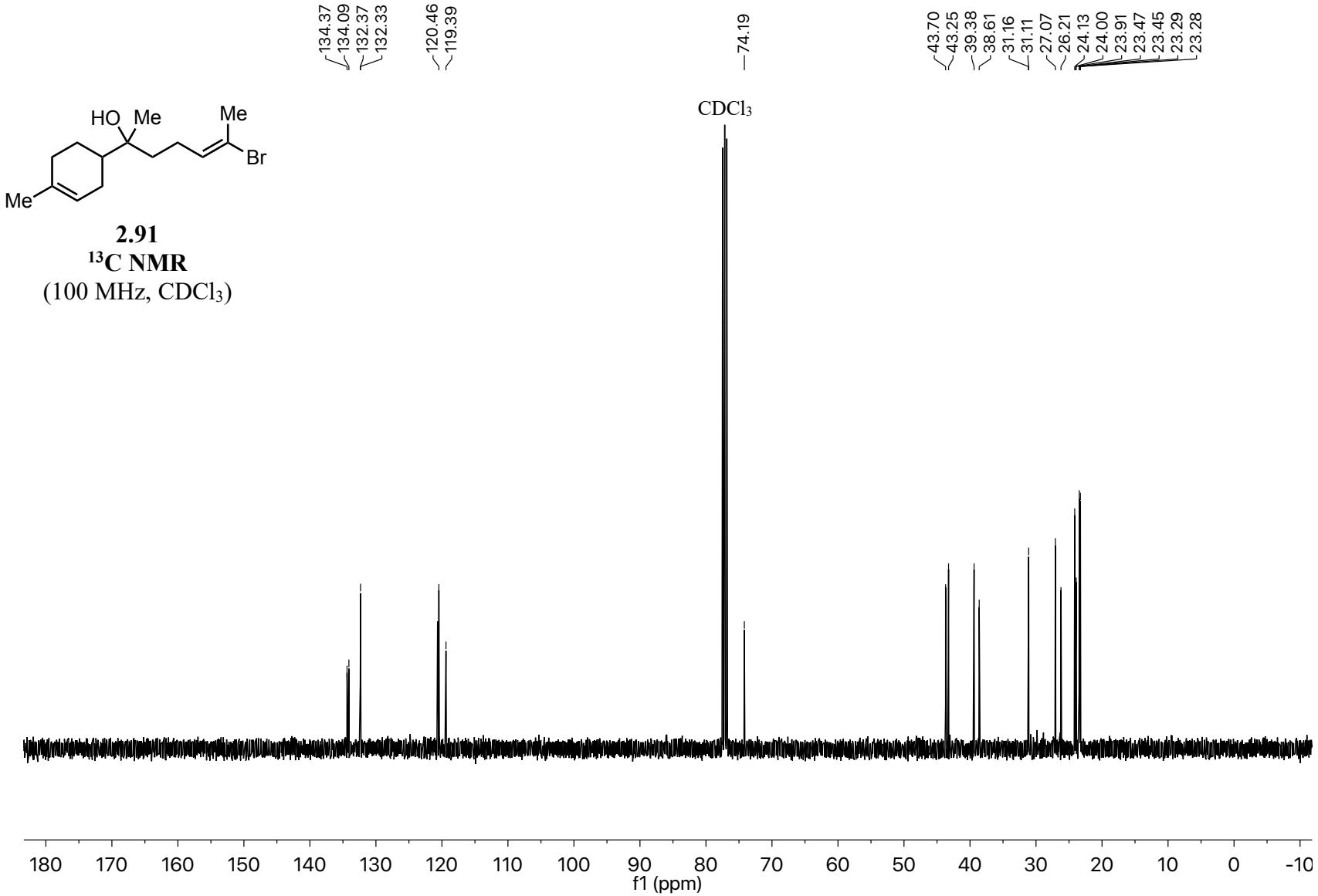


2.90
^{11}B NMR
(160 MHz, $CDCl_3$)

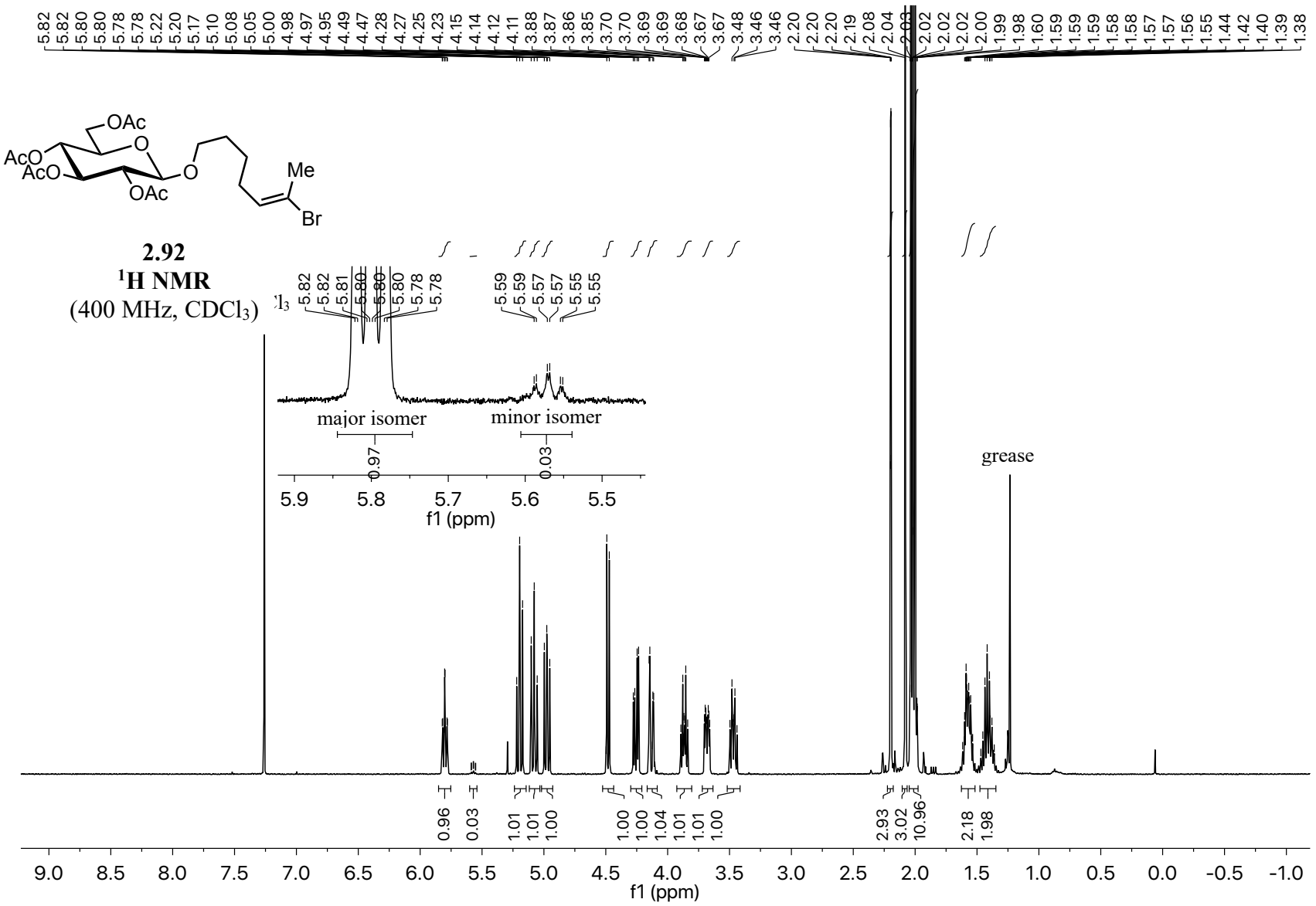

Me
(pin)B
Br
2.90
13C NMR
(125 MHz, CDCl3)
134.20
118.92
83.32
77.41
77.16
76.91
CDCl3
24.97
24.34
23.34
11.04
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

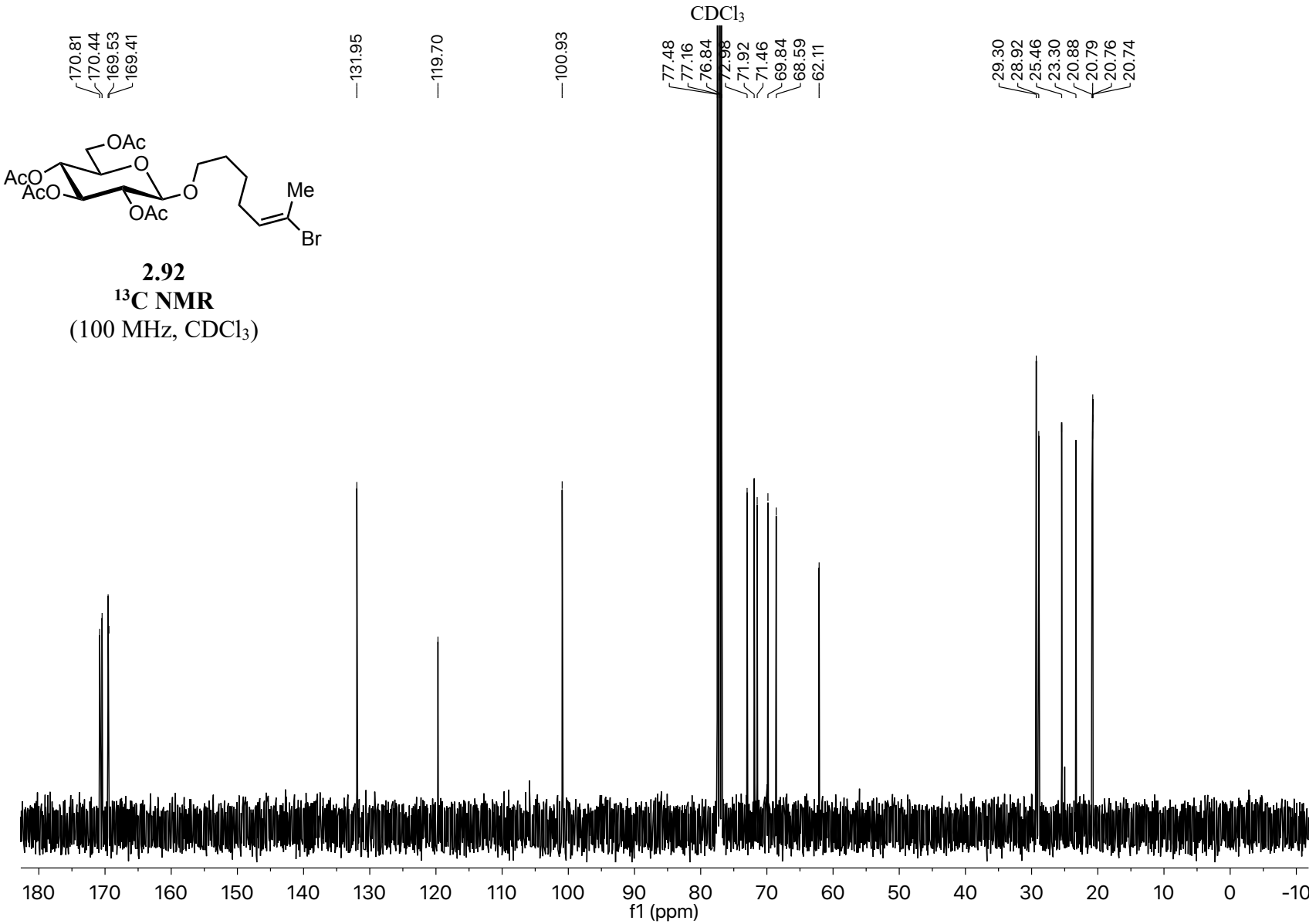


2.91
^{1}H NMR
(400 MHz, $CDCl_3$)

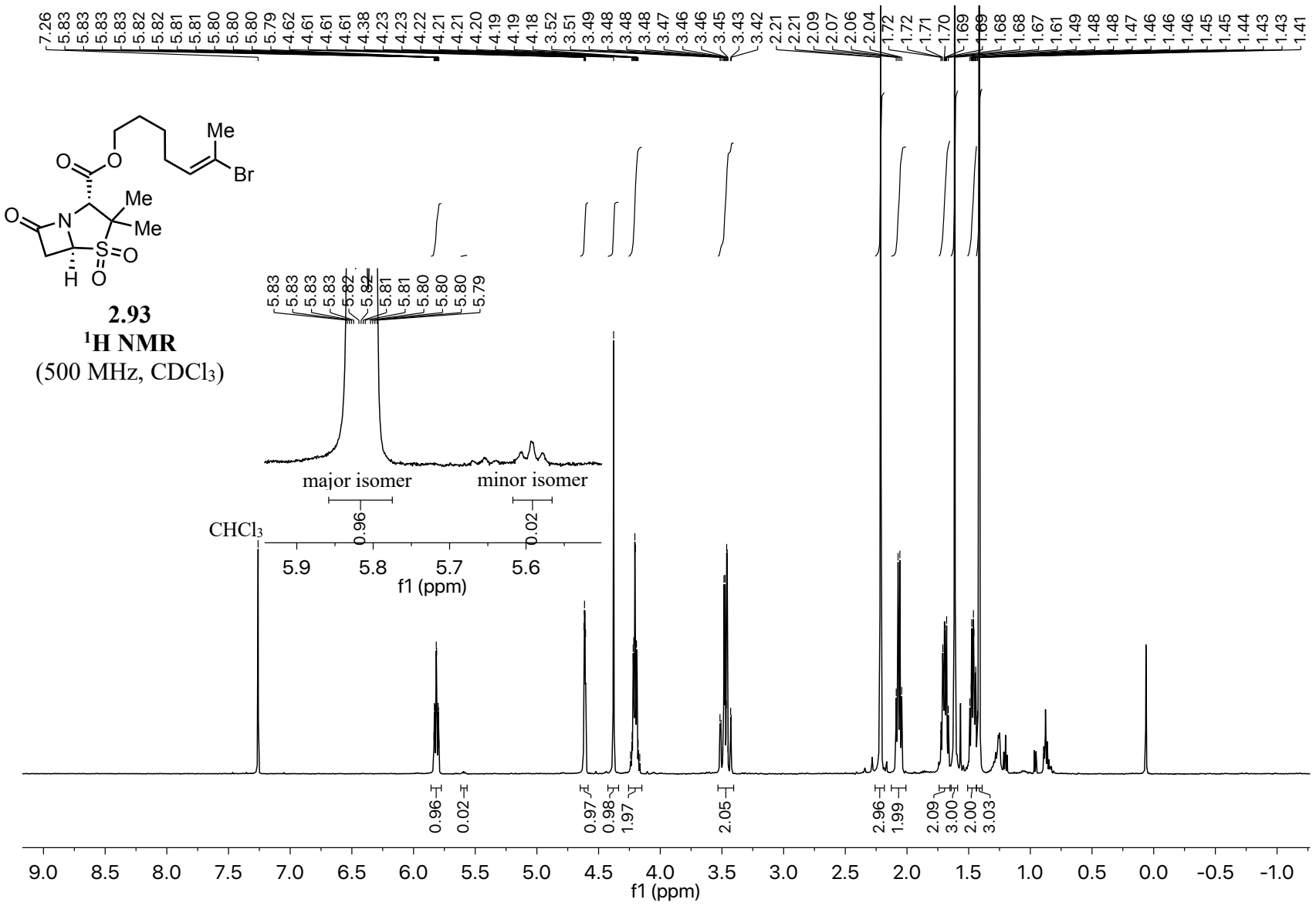


2.91
^{13}C NMR
(100 MHz, $CDCl_3$)

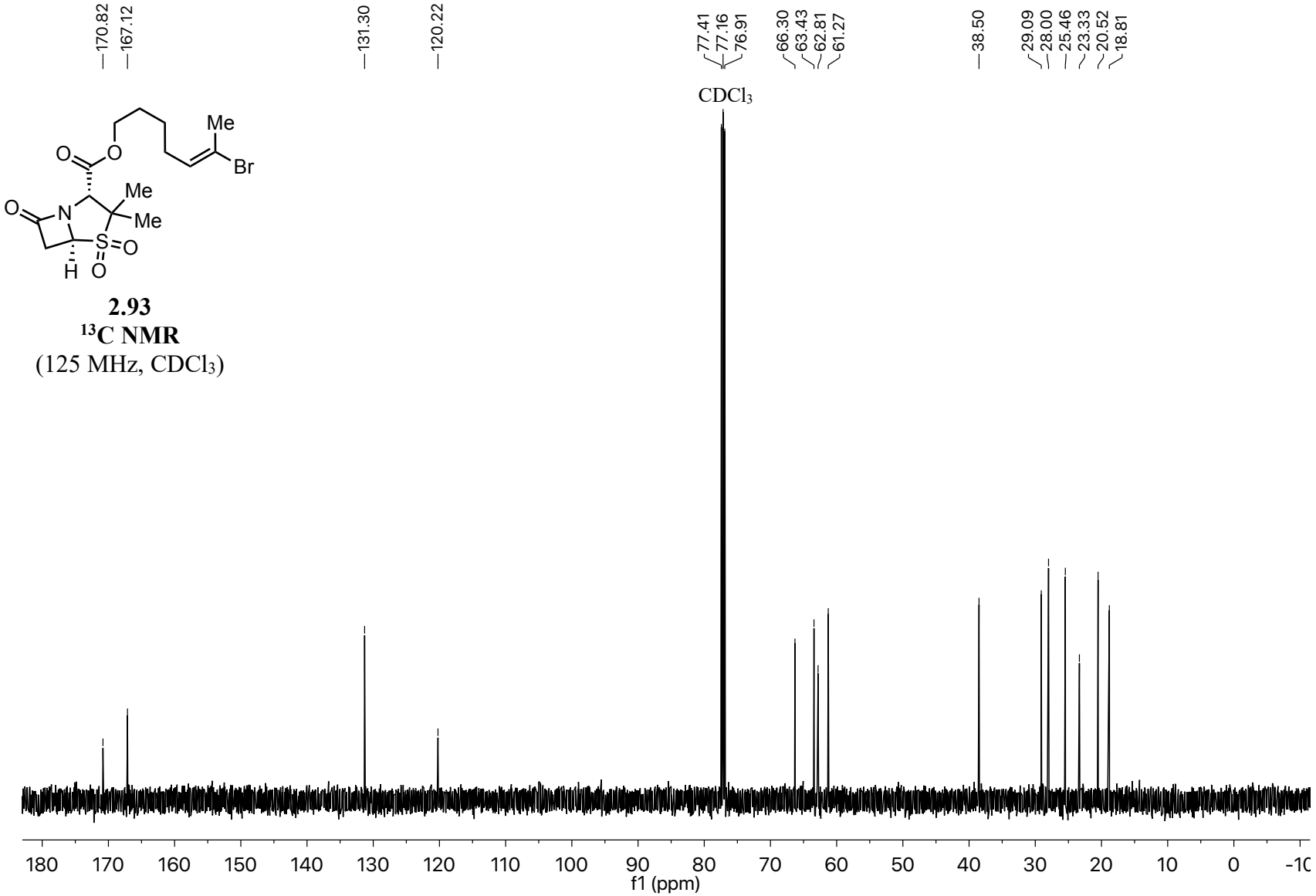

OAc
AcO
AcO
OAc
O
O
Me
Br
2.92
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
0.97
0.03
grease
f1 (ppm)



2.92
^{13}C NMR
(100 MHz, $CDCl_3$)



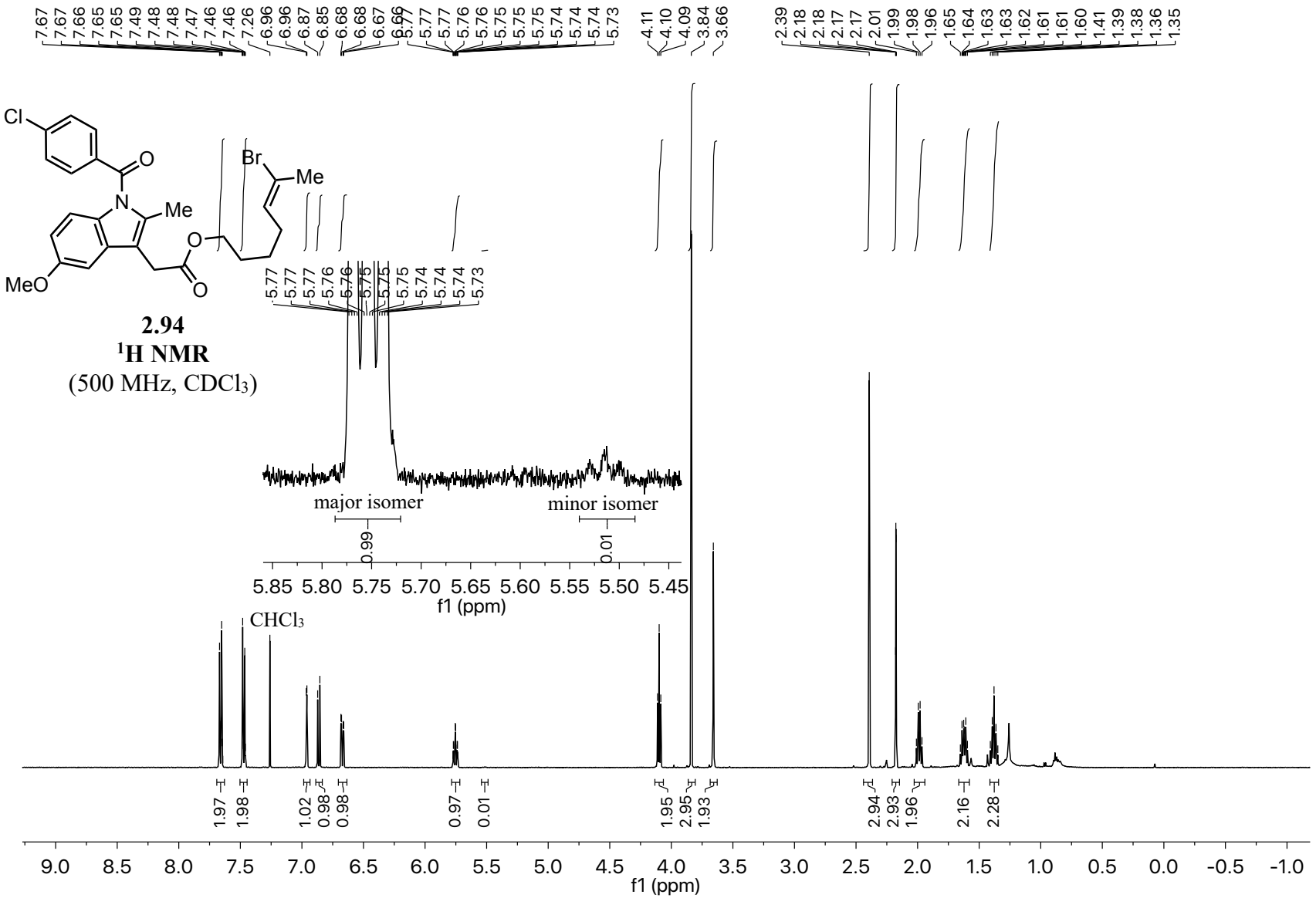
2.93
^{1}H NMR
(500 MHz, $CDCl_3$)

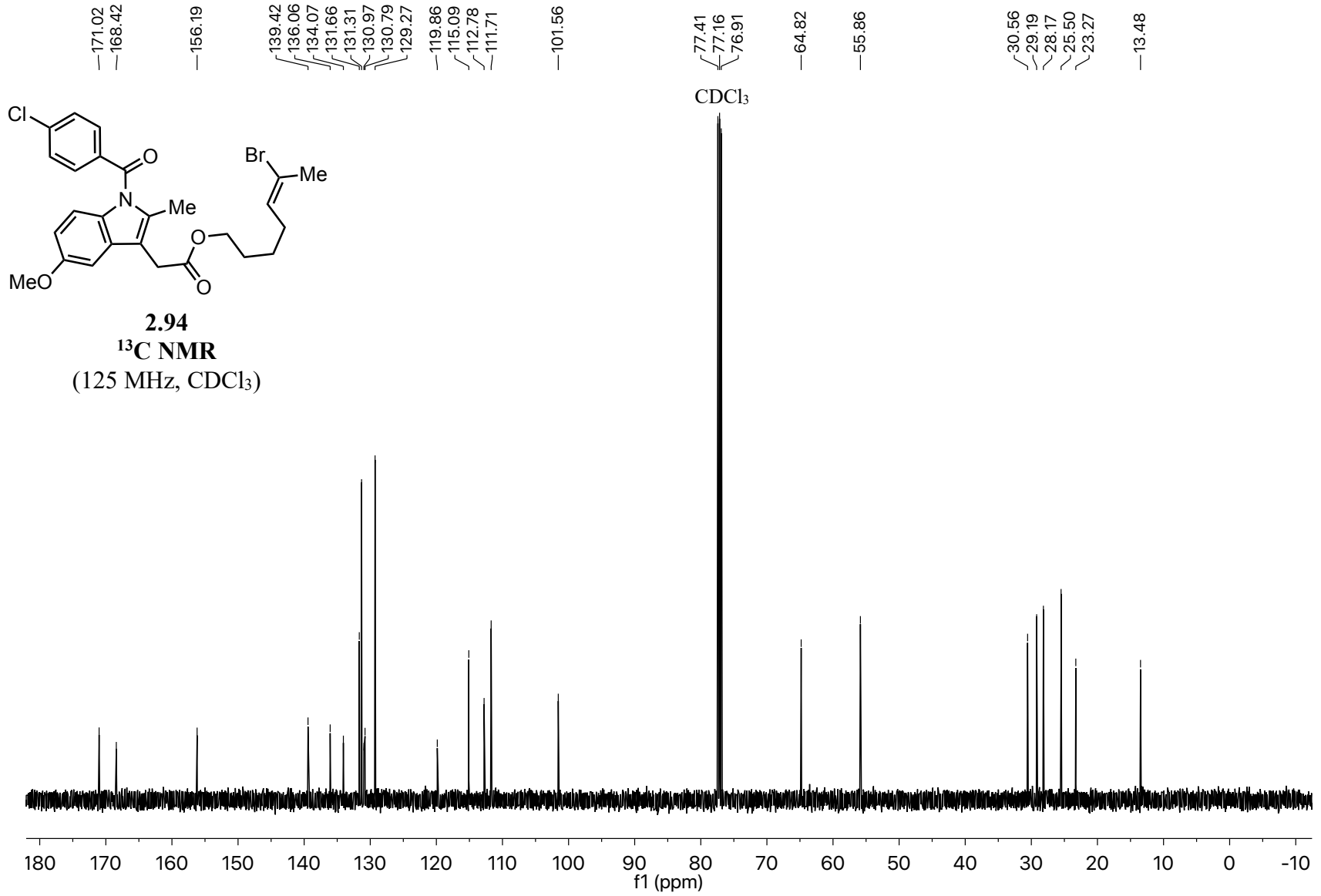


2.93

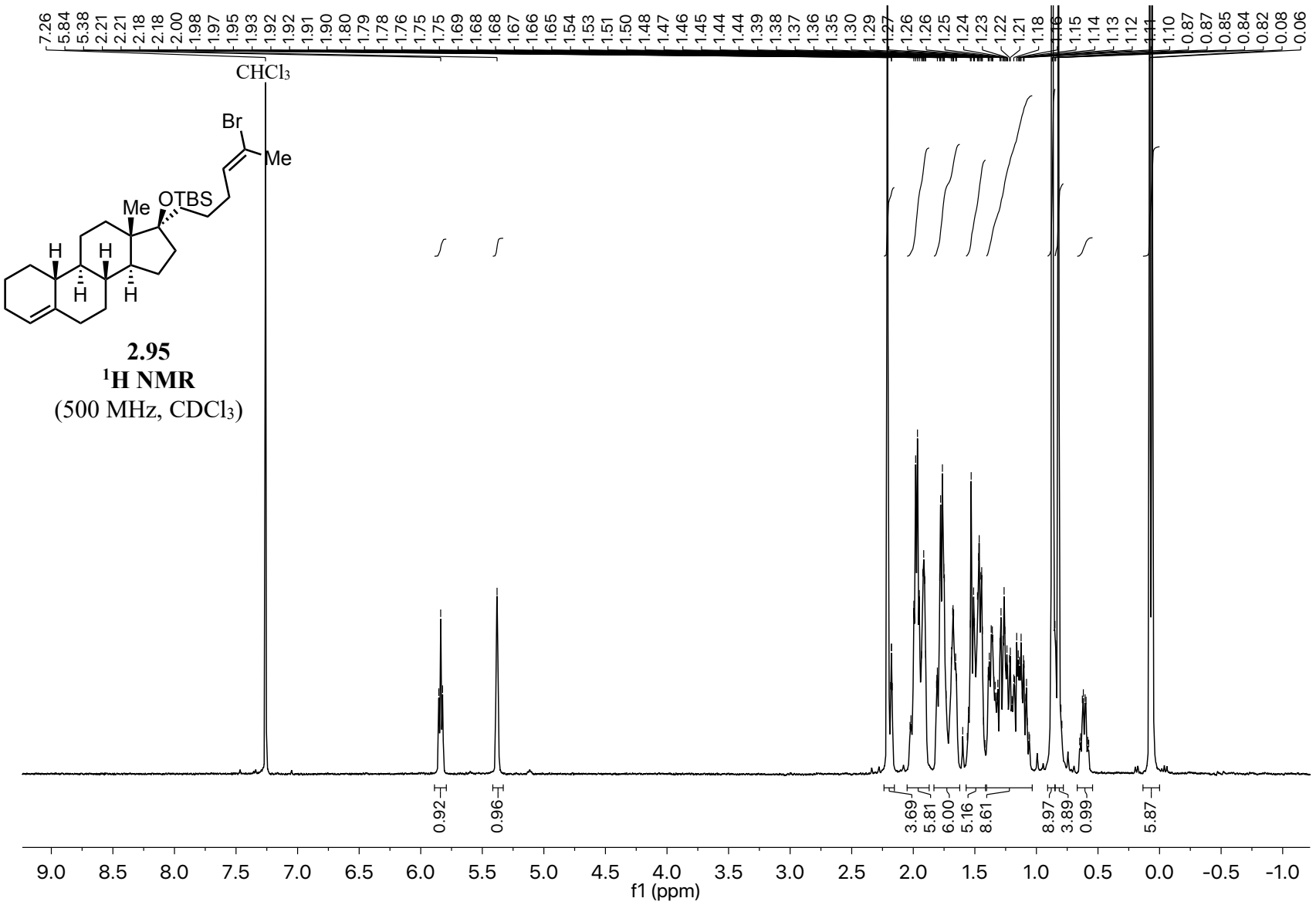
^{13}C NMR

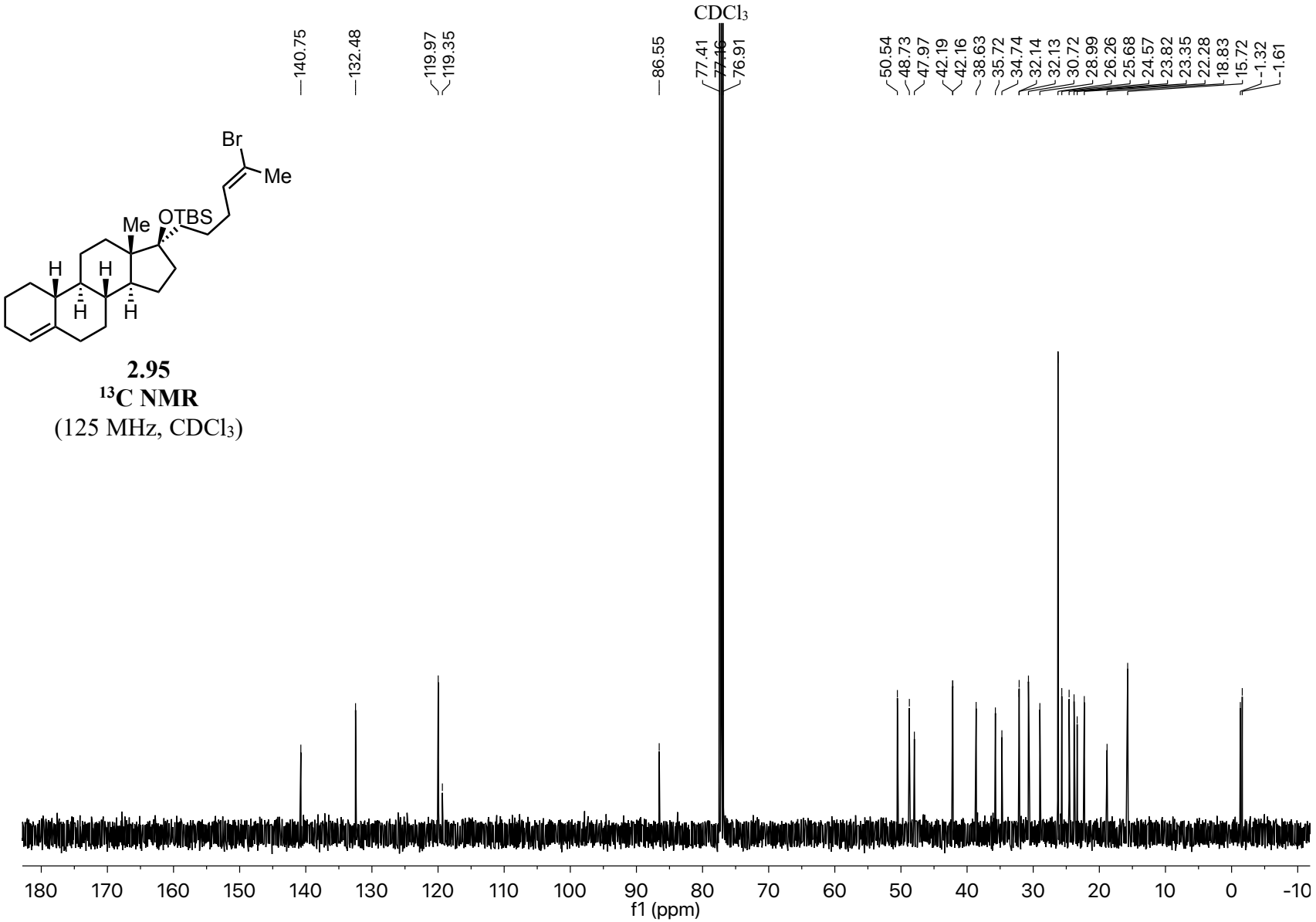
(125 MHz, $CDCl_3$)


Cl
O
N
Me
O
MeO
O
Br
Me
2.94
1H NMR
(500 MHz, CDCl3)
major isomer
minor isomer
0.99
0.01
CHCl3
f1 (ppm)

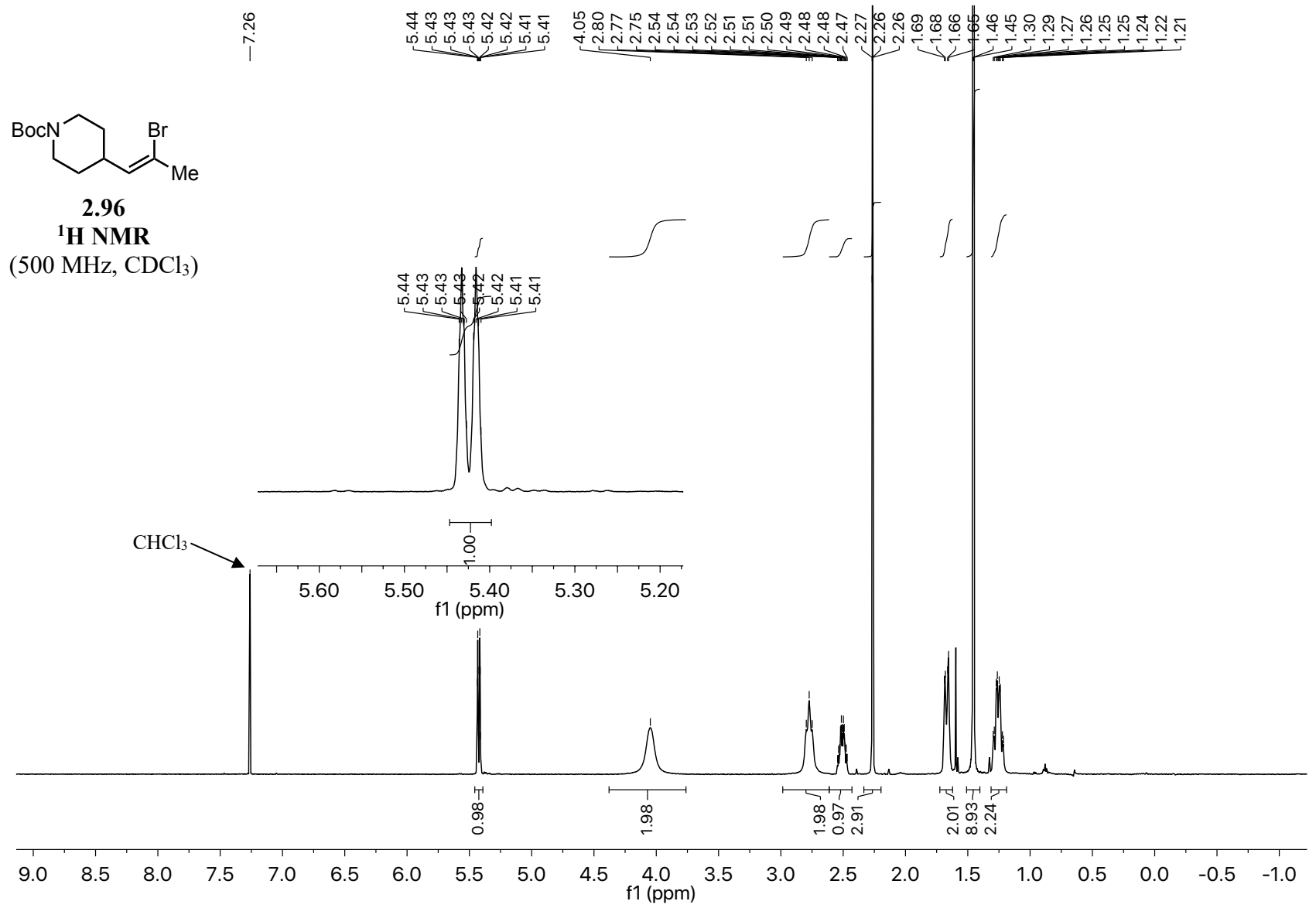


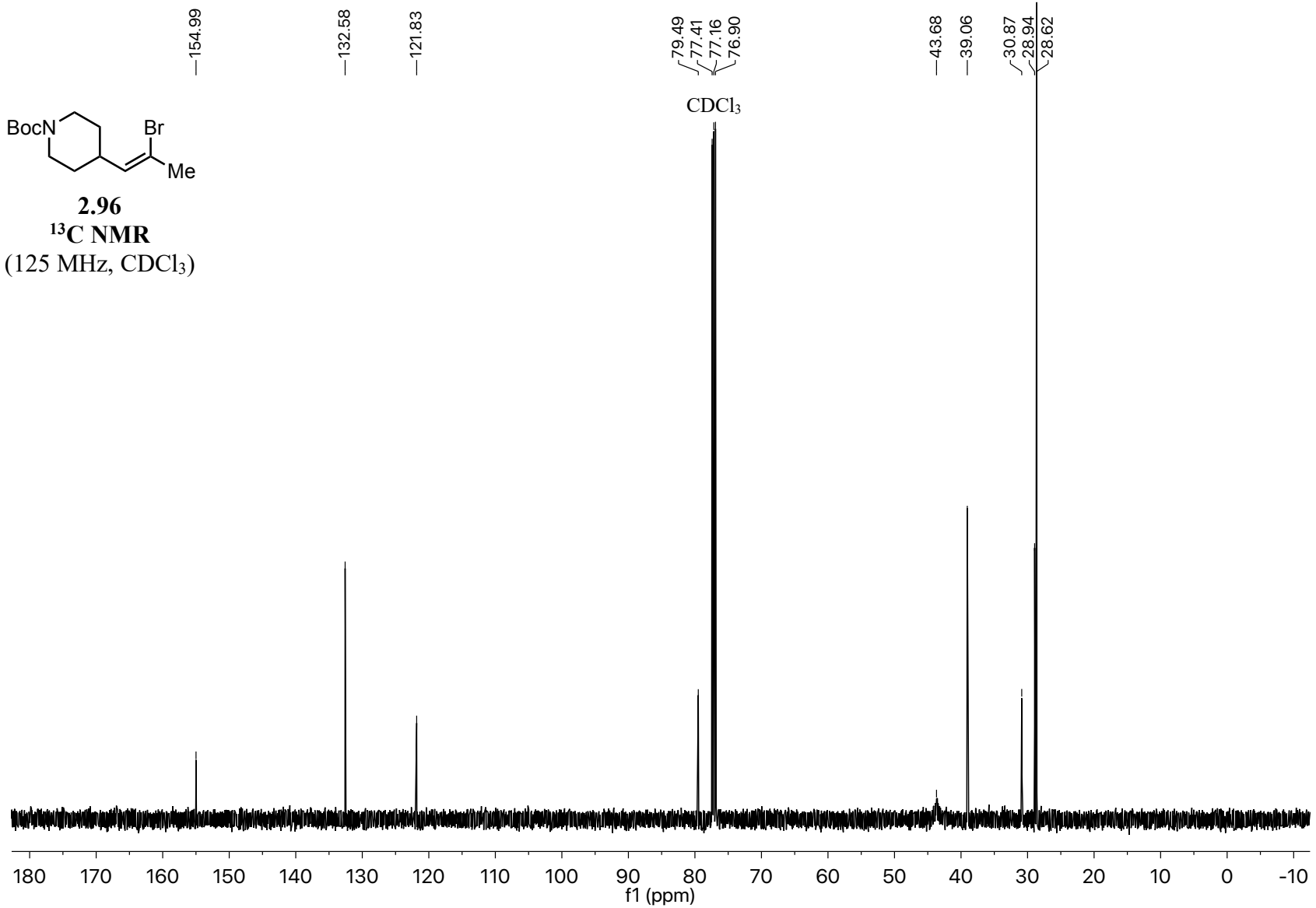
2.94
^{13}C NMR
(125 MHz, $CDCl_3$)


CHCl3
Br
Me
Me
OTBS
H
H
H
H
2.95
1H NMR
(500 MHz, CDCl3)
f1 (ppm)

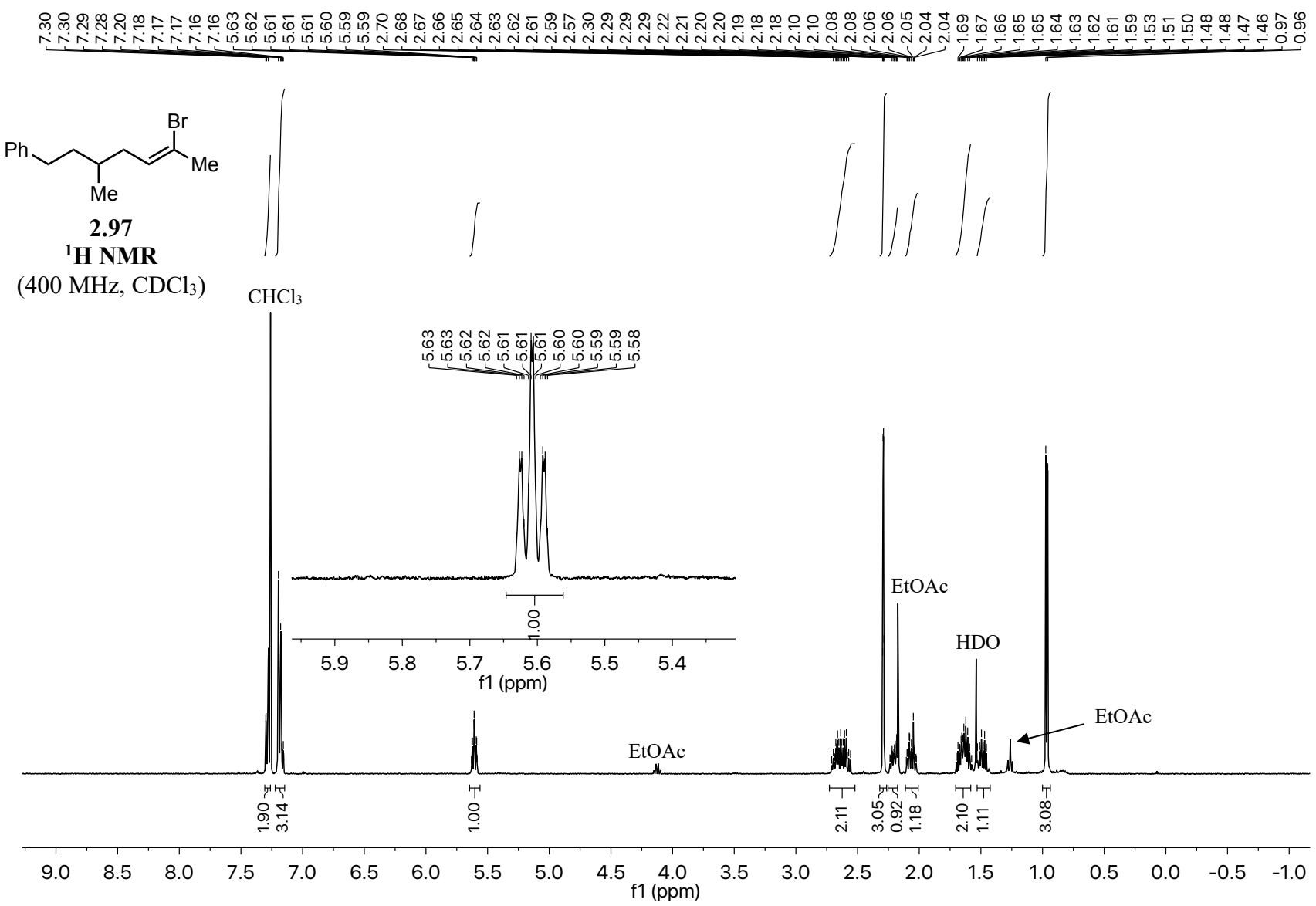


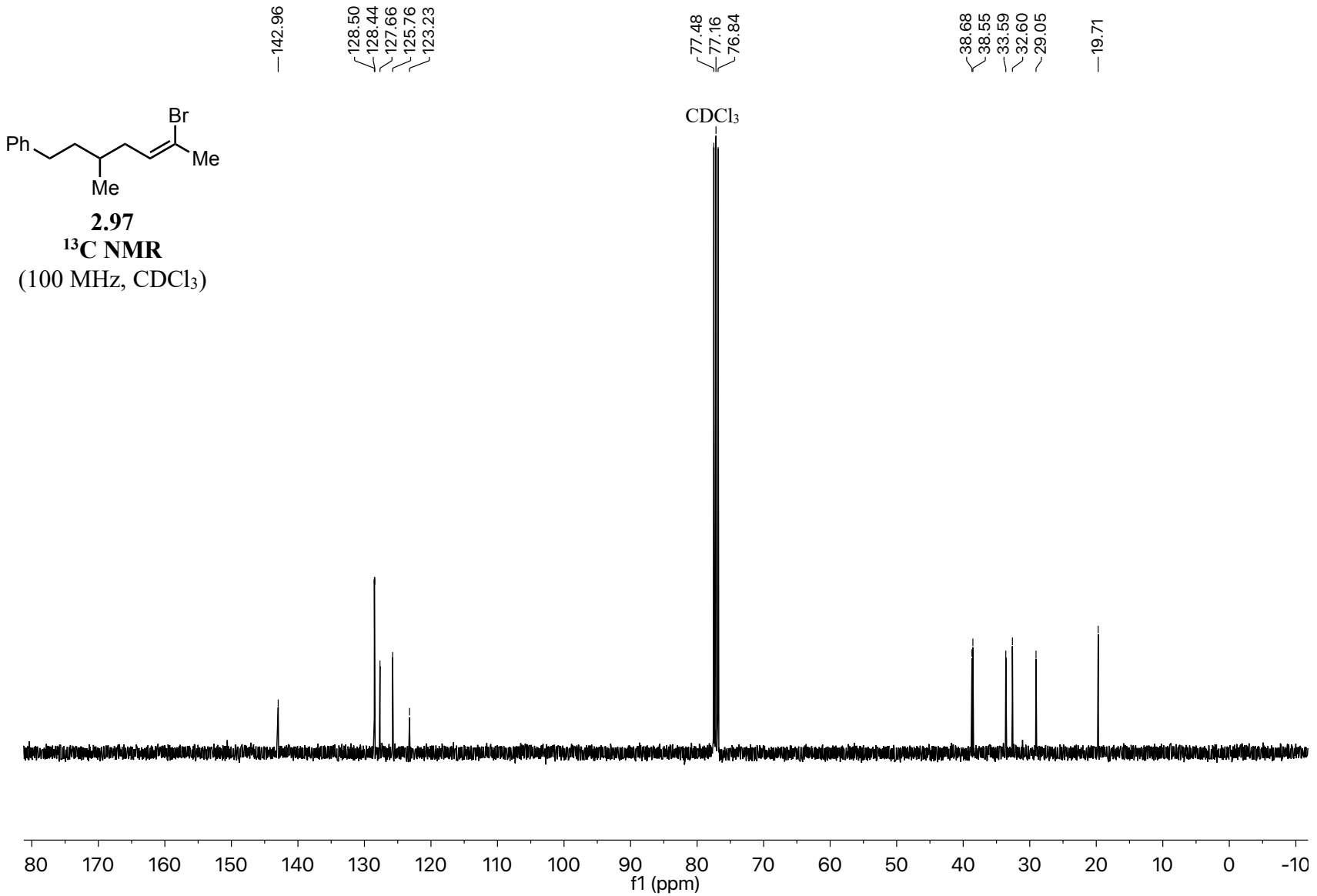
2.95
^{13}C NMR
(125 MHz, $CDCl_3$)


BocN
Br
Me
2.96
1H NMR
(500 MHz, CDCl3)
CHCl3
f1 (ppm)



2.96
^{13}C NMR
(125 MHz, $CDCl_3$)

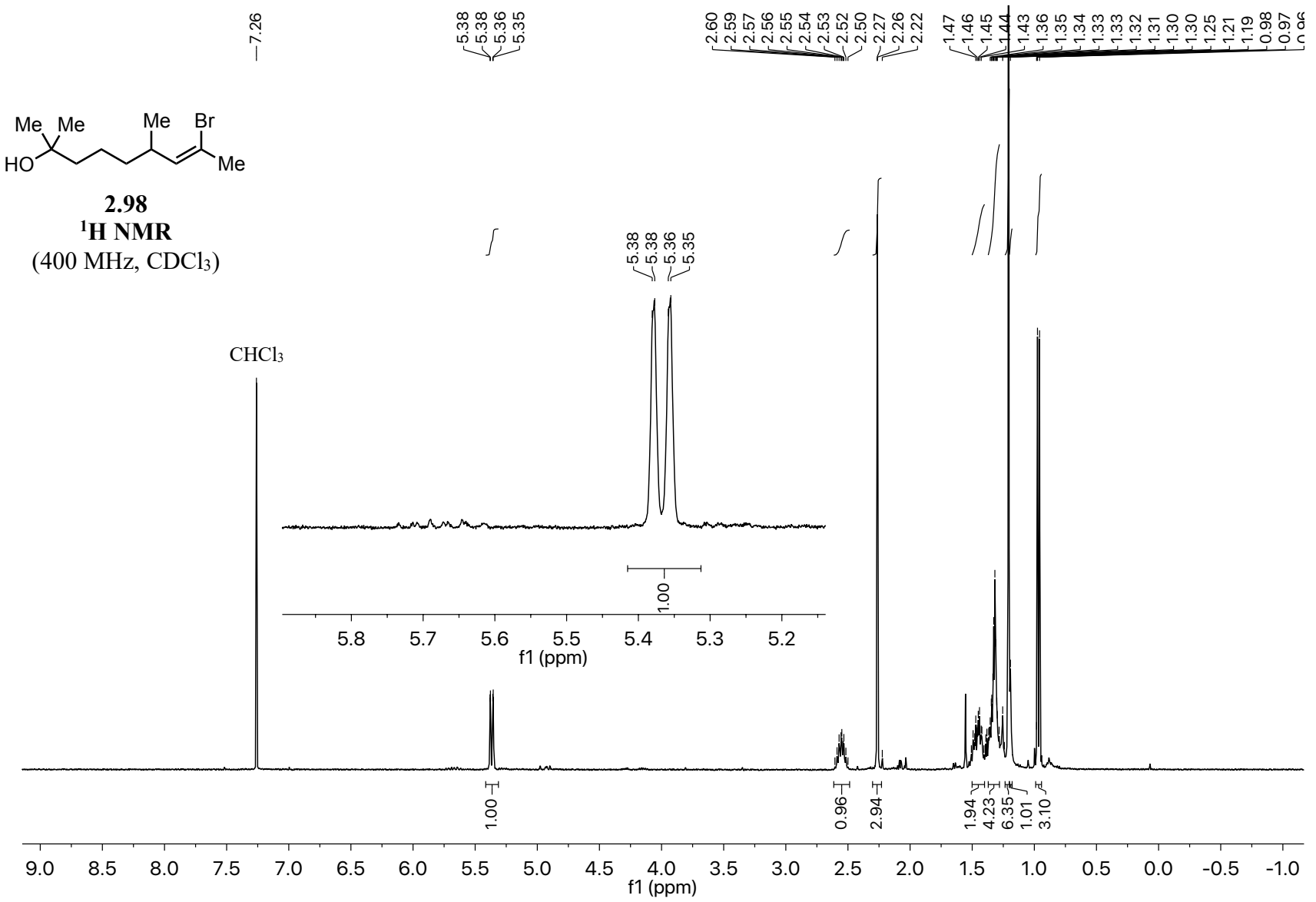

Br
Ph
Me
Me
2.97
1H NMR
(400 MHz, CDCl3)
CHCl3
EtOAc
HDO
EtOAc
EtOAc
f1 (ppm)

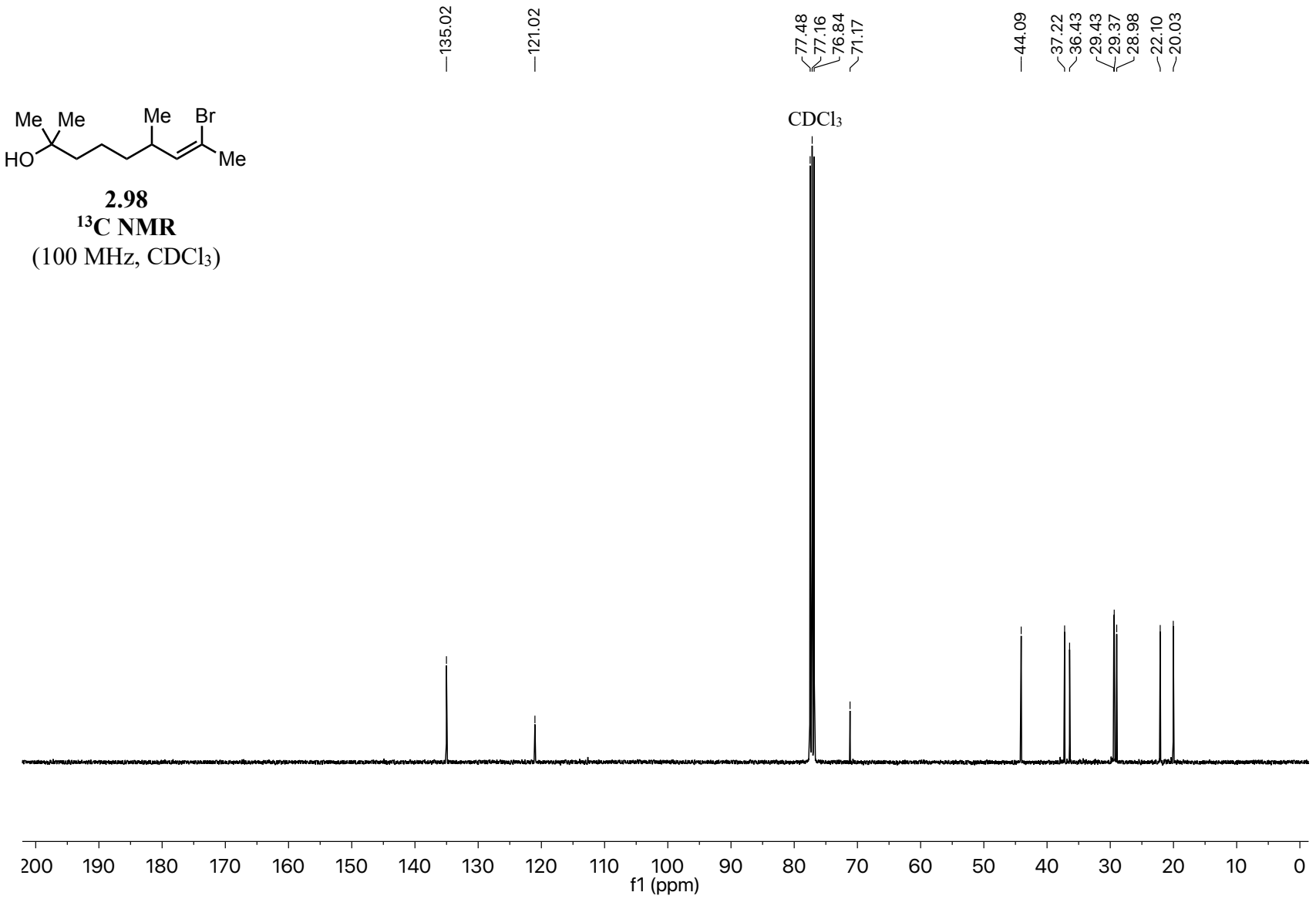


2.97

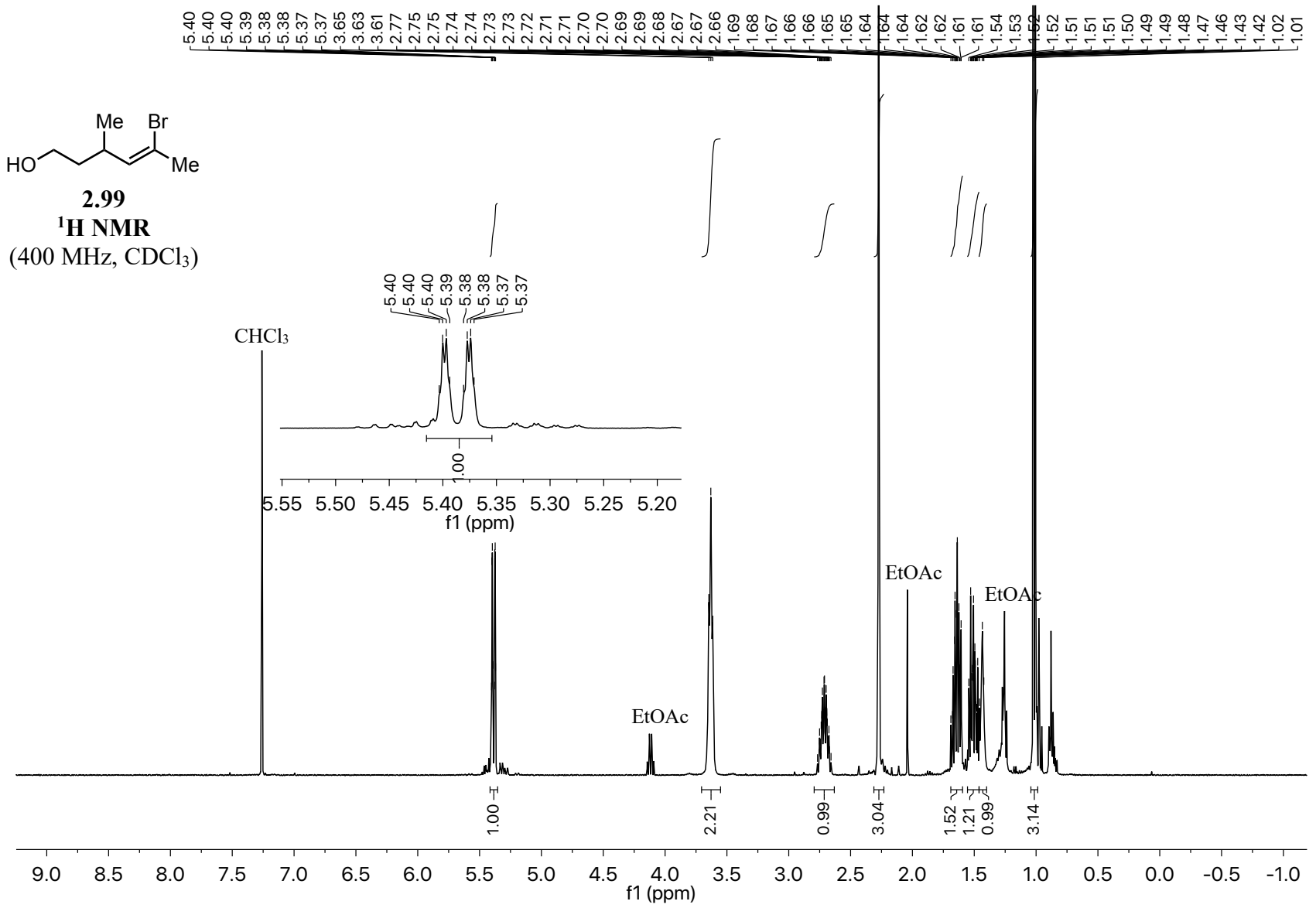
^{13}C NMR

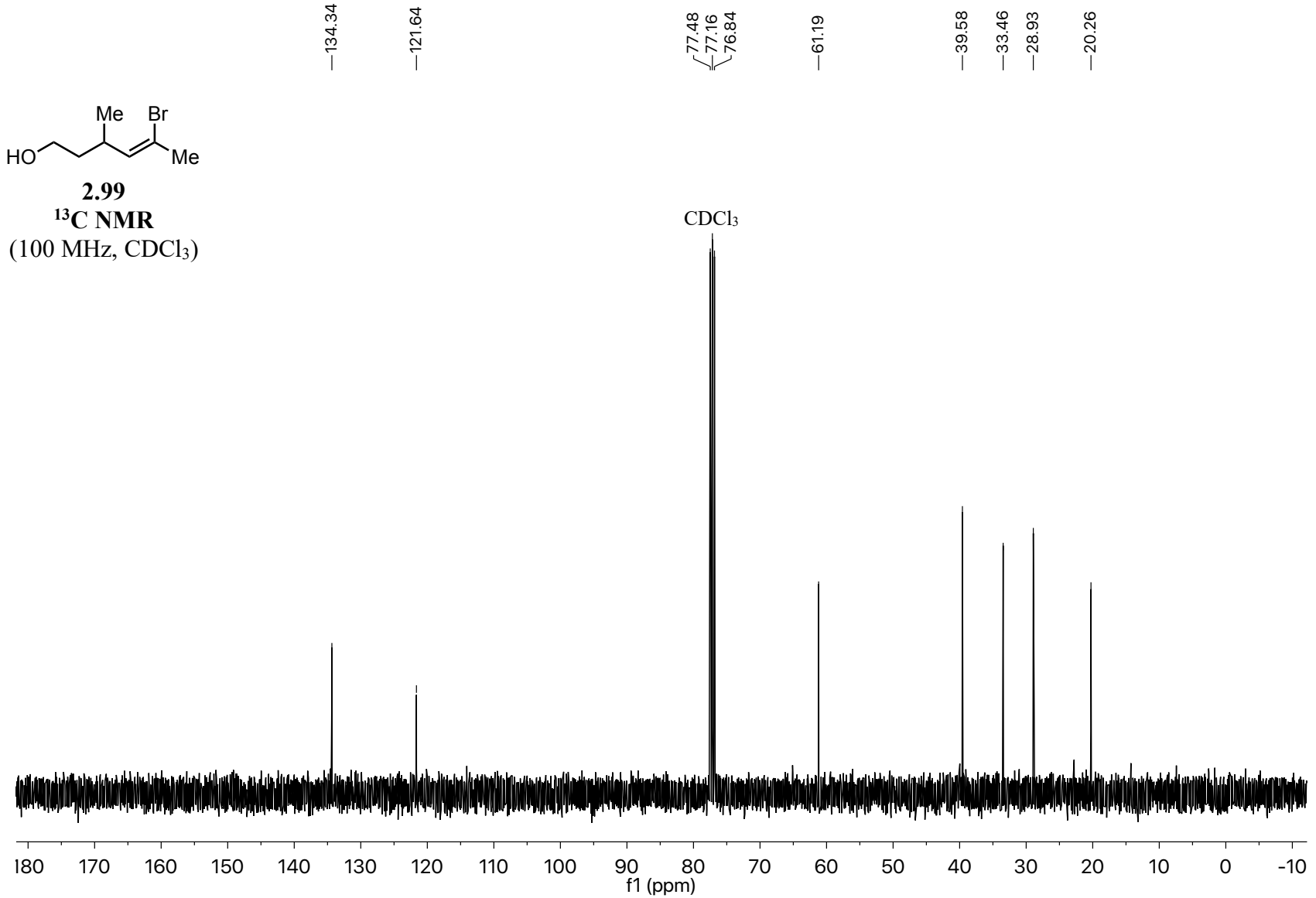
(100 MHz, $CDCl_3$)

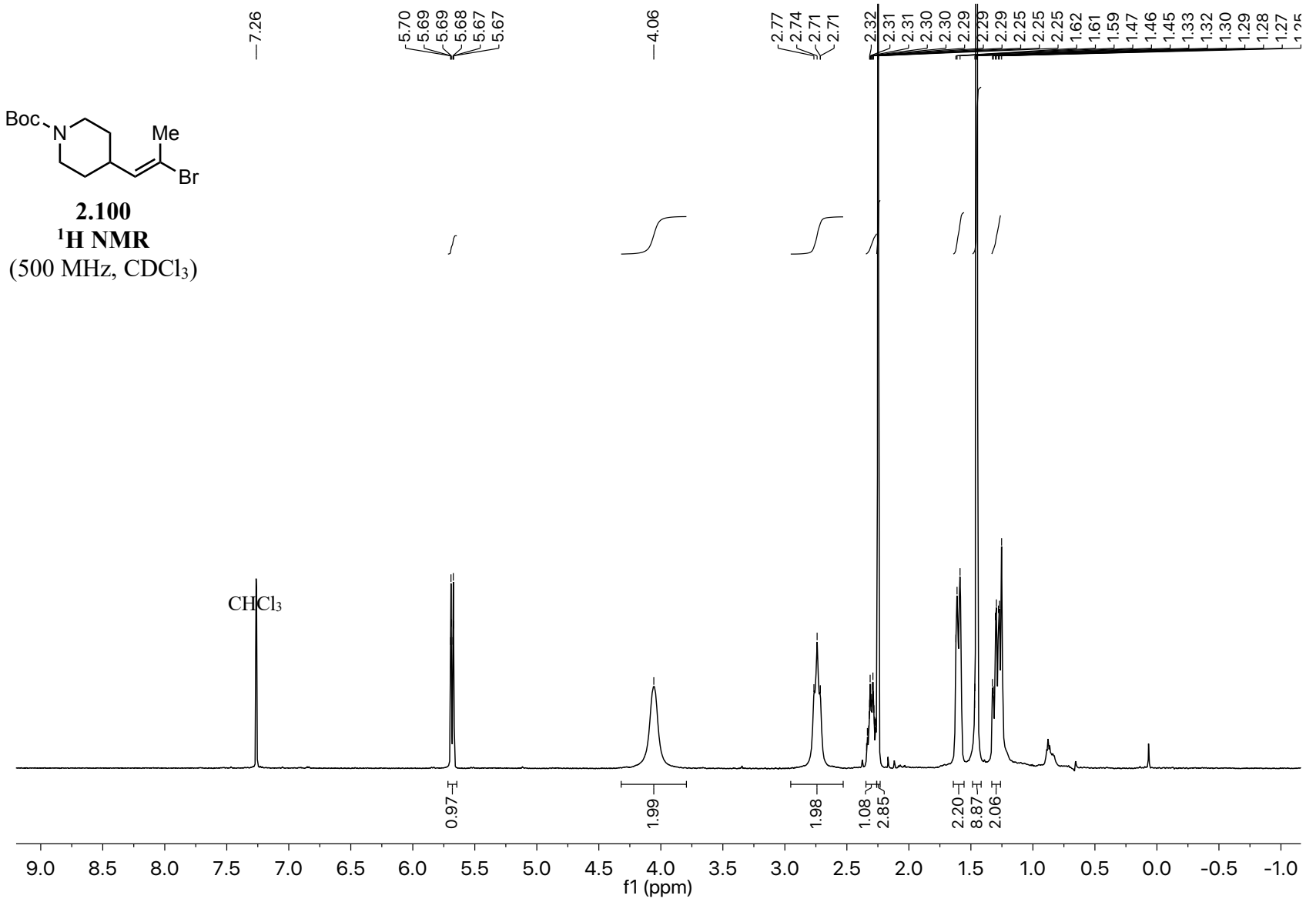

Me
Me
Me
Br
HO
Me
2.98
1H NMR
(400 MHz, CDCl3)
CHCl3
f1 (ppm)

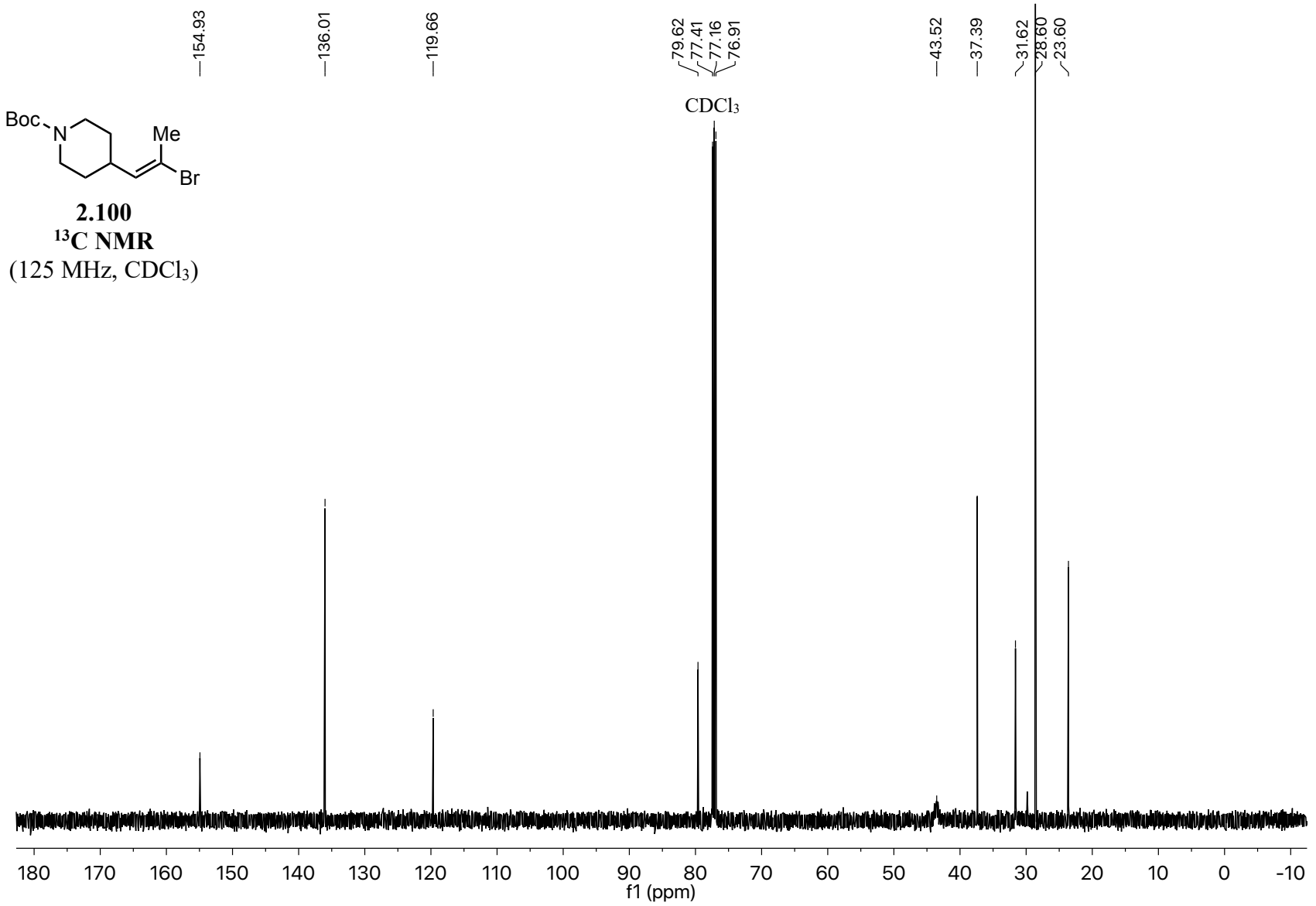


2.98
^{13}C NMR
(100 MHz, $CDCl_3$)

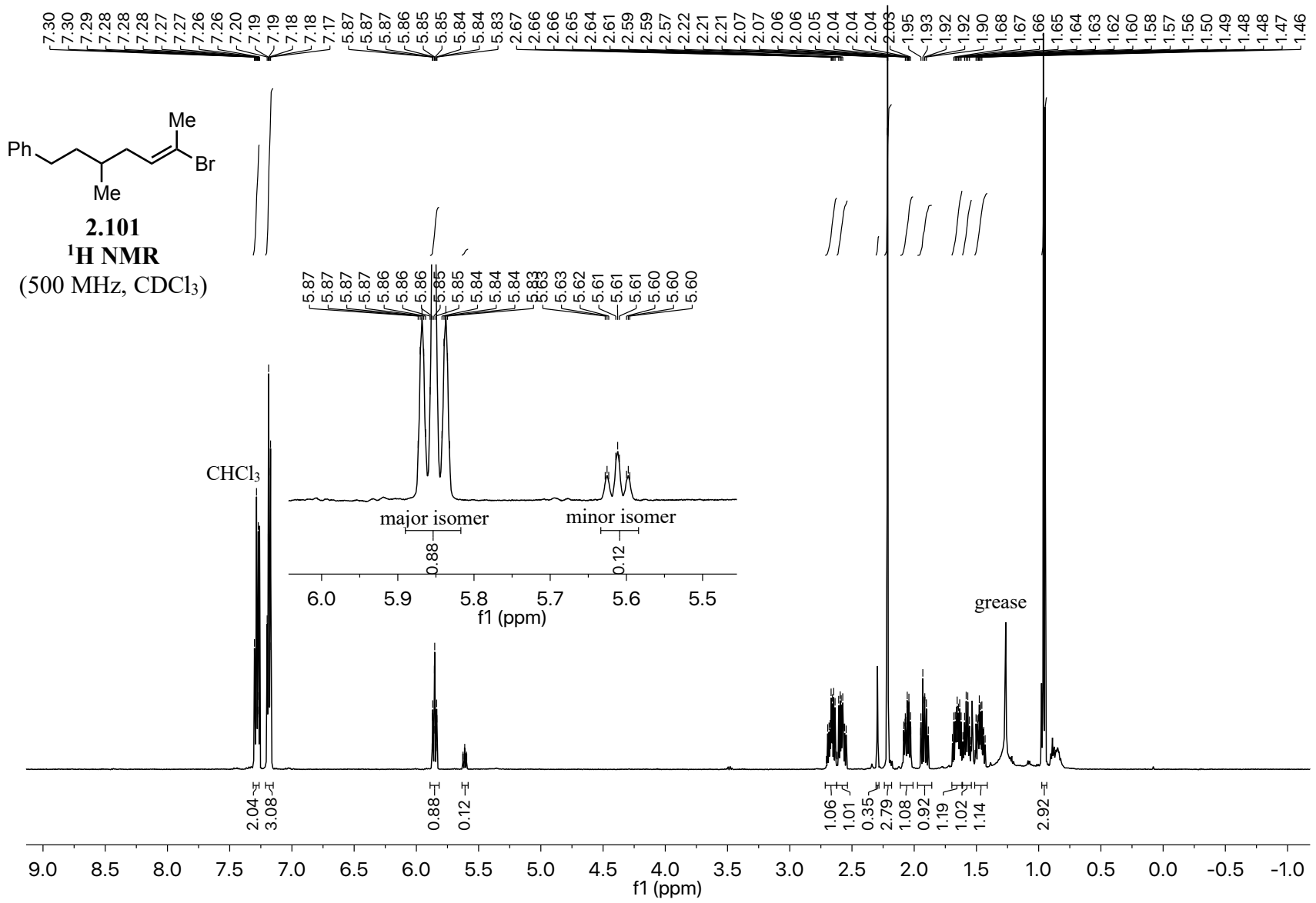

Me
Br
HO
Me
2.99
1H NMR
(400 MHz, CDCl3)
CHCl3
EtOAc
EtOAc
EtOAc
f1 (ppm)
f1 (ppm)

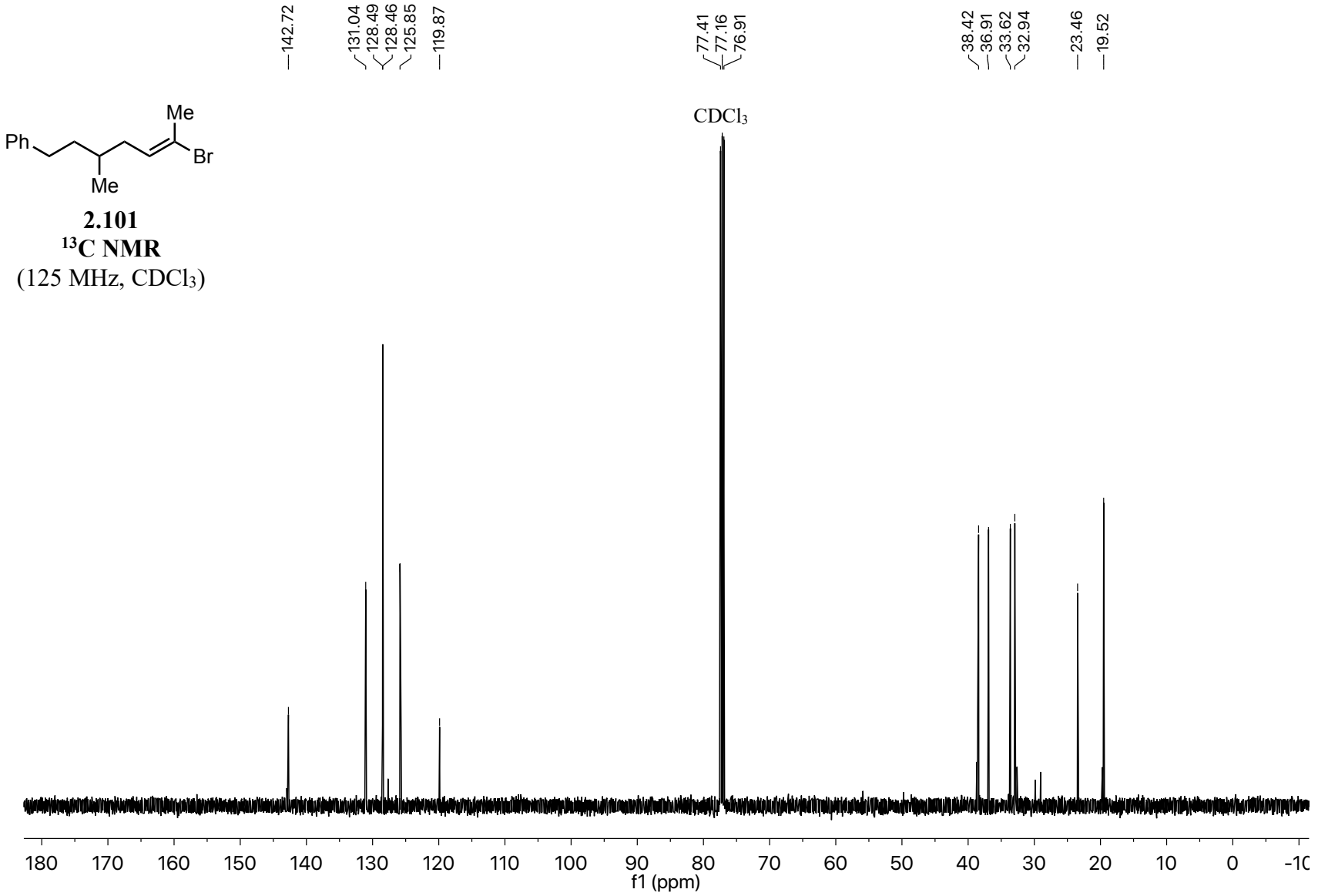

134.34
121.64
77.48
77.16
76.84
61.19
39.58
33.46
28.93
20.26
Me
Br
HO
Me
2.99
13C NMR
(100 MHz, CDCl3)
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Boc
N
Me
Br
2.100
1H NMR
(500 MHz, CDCl3)
7.26
5.70
5.69
5.69
5.68
5.67
5.67
4.06
2.77
2.74
2.71
2.71
2.32
2.31
2.31
2.30
2.30
2.29
2.29
2.29
2.25
2.25
2.25
1.62
1.61
1.59
1.47
1.46
1.45
1.33
1.32
1.30
1.29
1.28
1.27
CHCl3
0.97
1.99
1.98
1.08
2.85
2.20
8.87
2.06
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

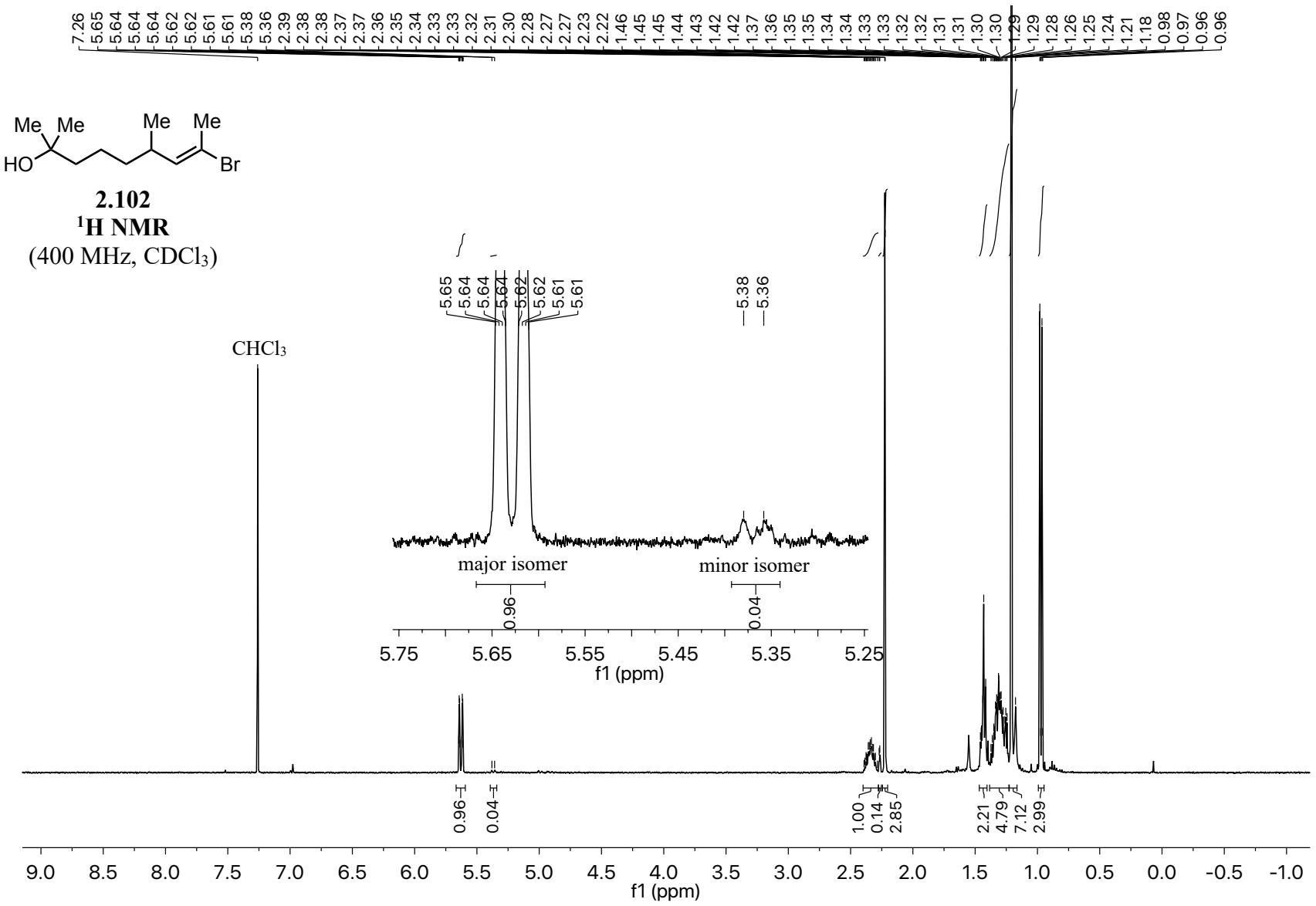


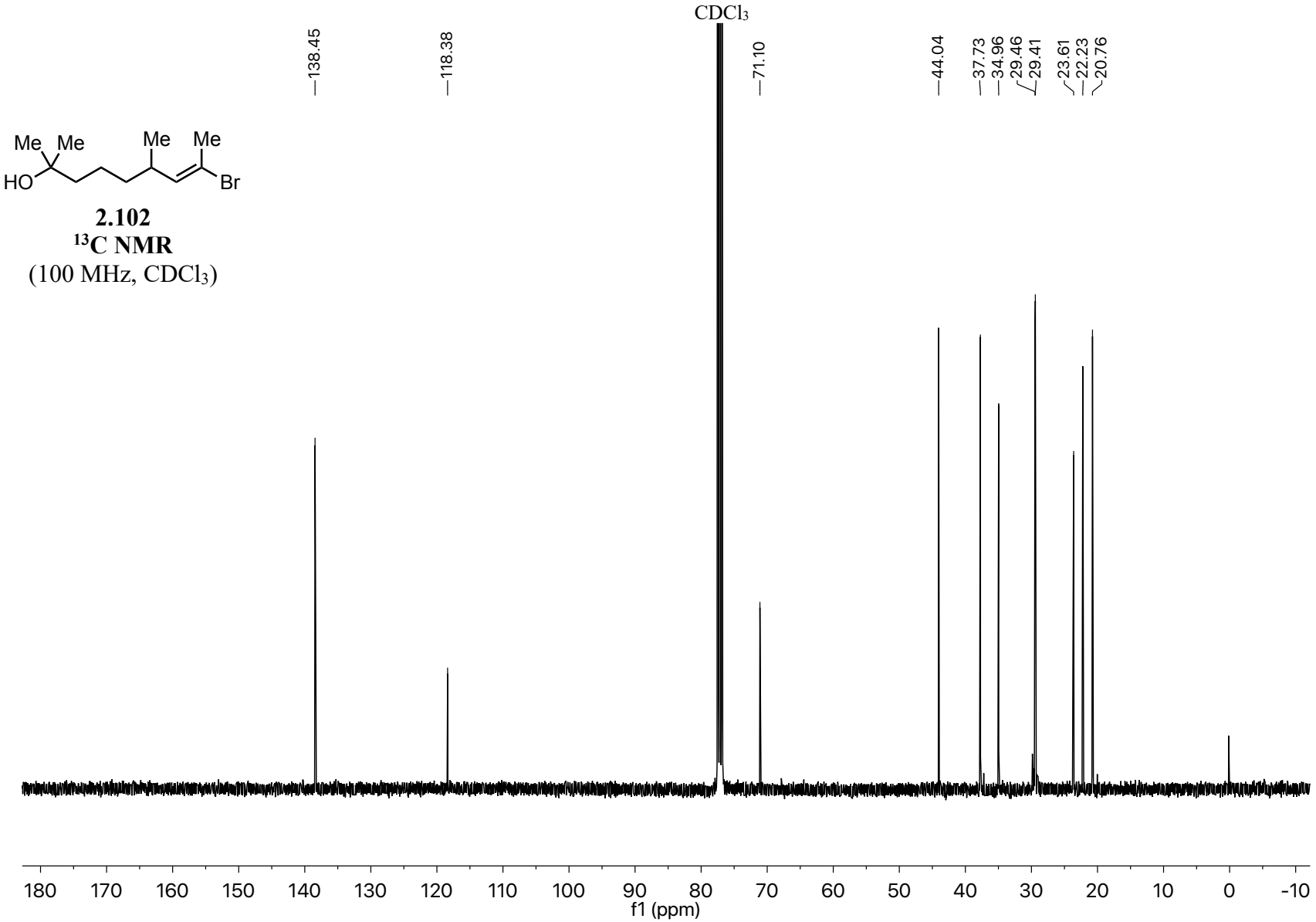
2.100
^{13}C NMR
(125 MHz, $CDCl_3$)


Ph
Me
Me
Br
2.101
1H NMR
(500 MHz, CDCl3)
CHCl3
major isomer
minor isomer
0.88
0.12
grease
f1 (ppm)

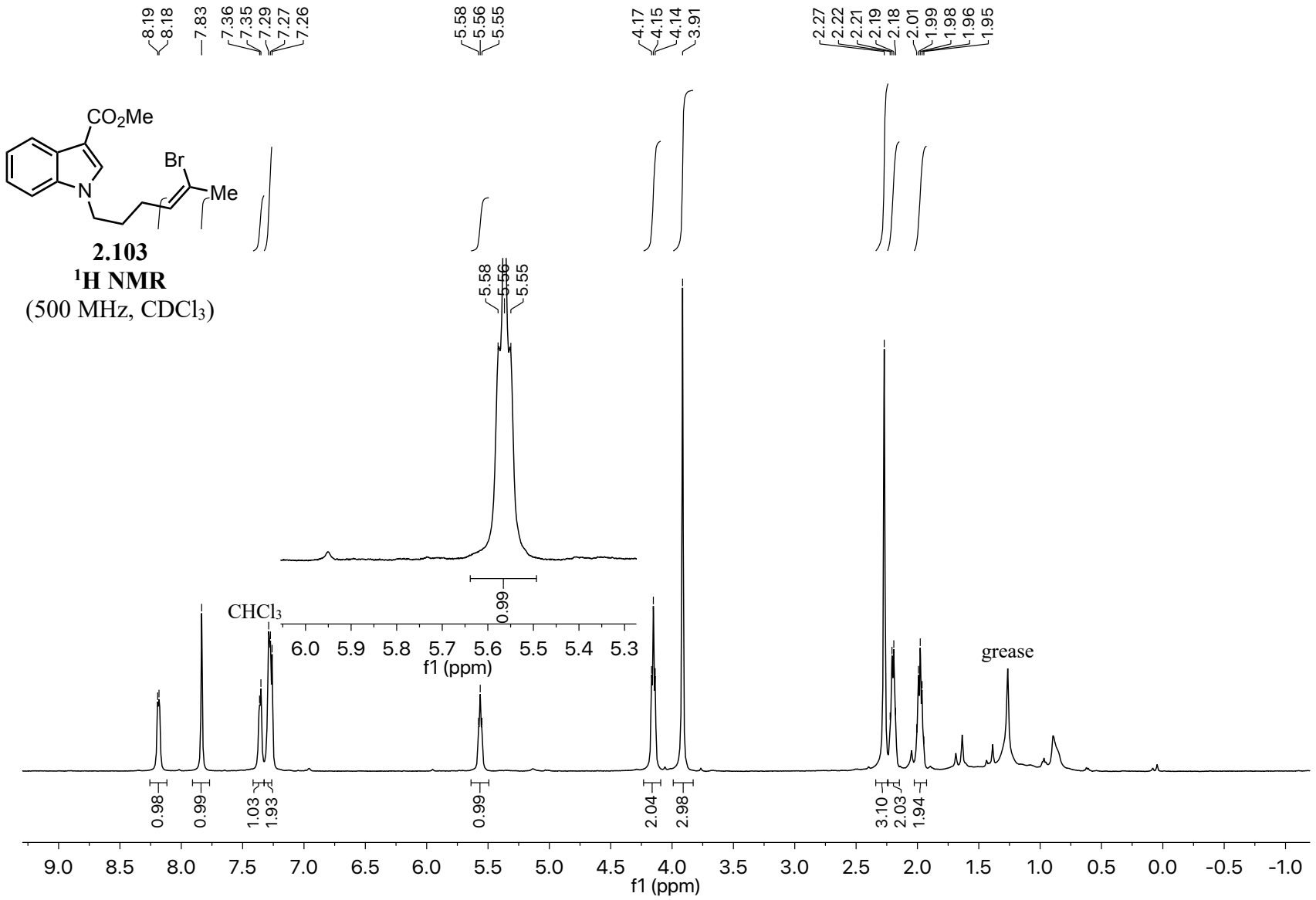


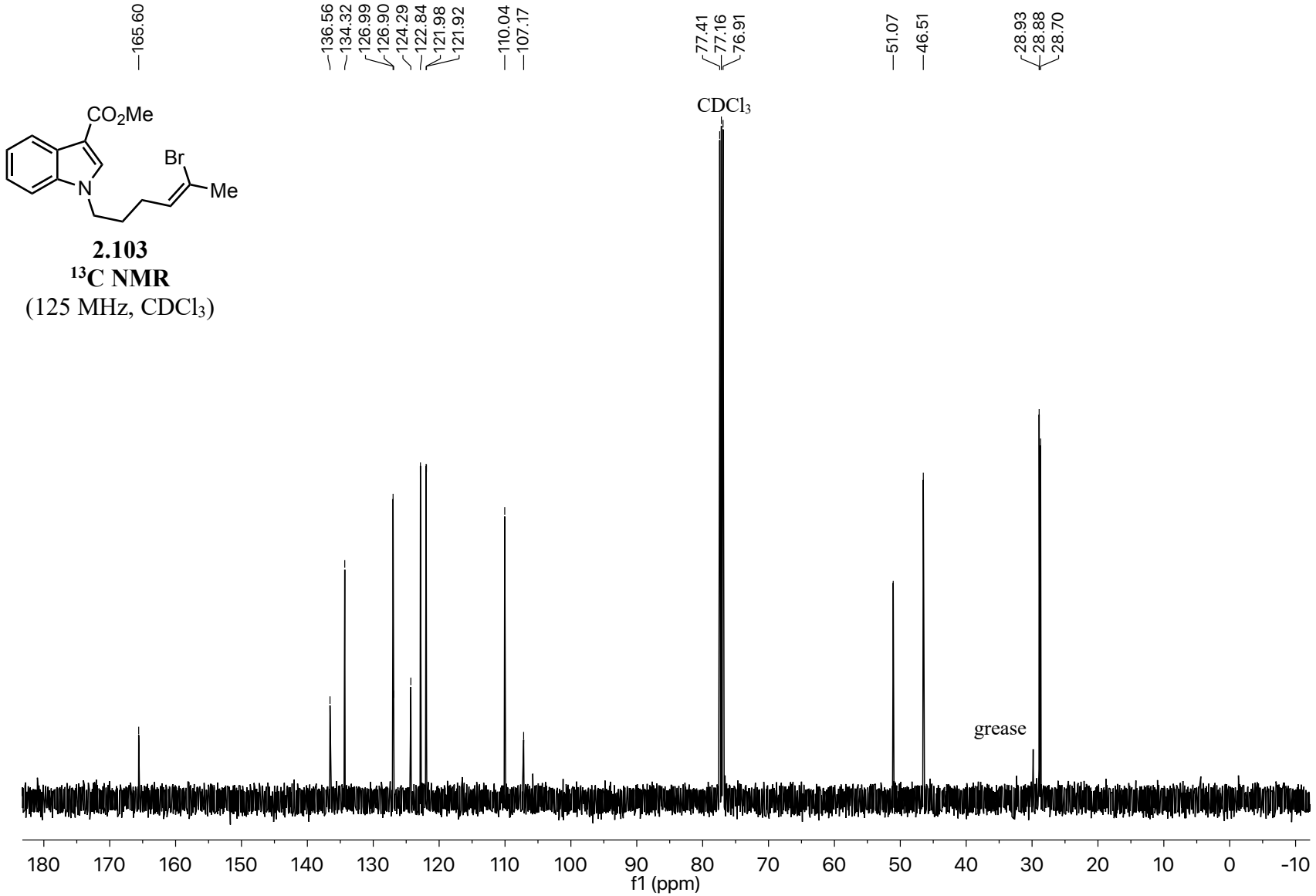
2.101
^{13}C NMR
(125 MHz, $CDCl_3$)


Me Me
Me
Me
HO
Br
2.102
1H NMR
(400 MHz, CDCl3)
CHCl3
major isomer
minor isomer
0.96
0.04
f1 (ppm)
1.00
0.14
2.85
2.21
4.79
7.12
2.99

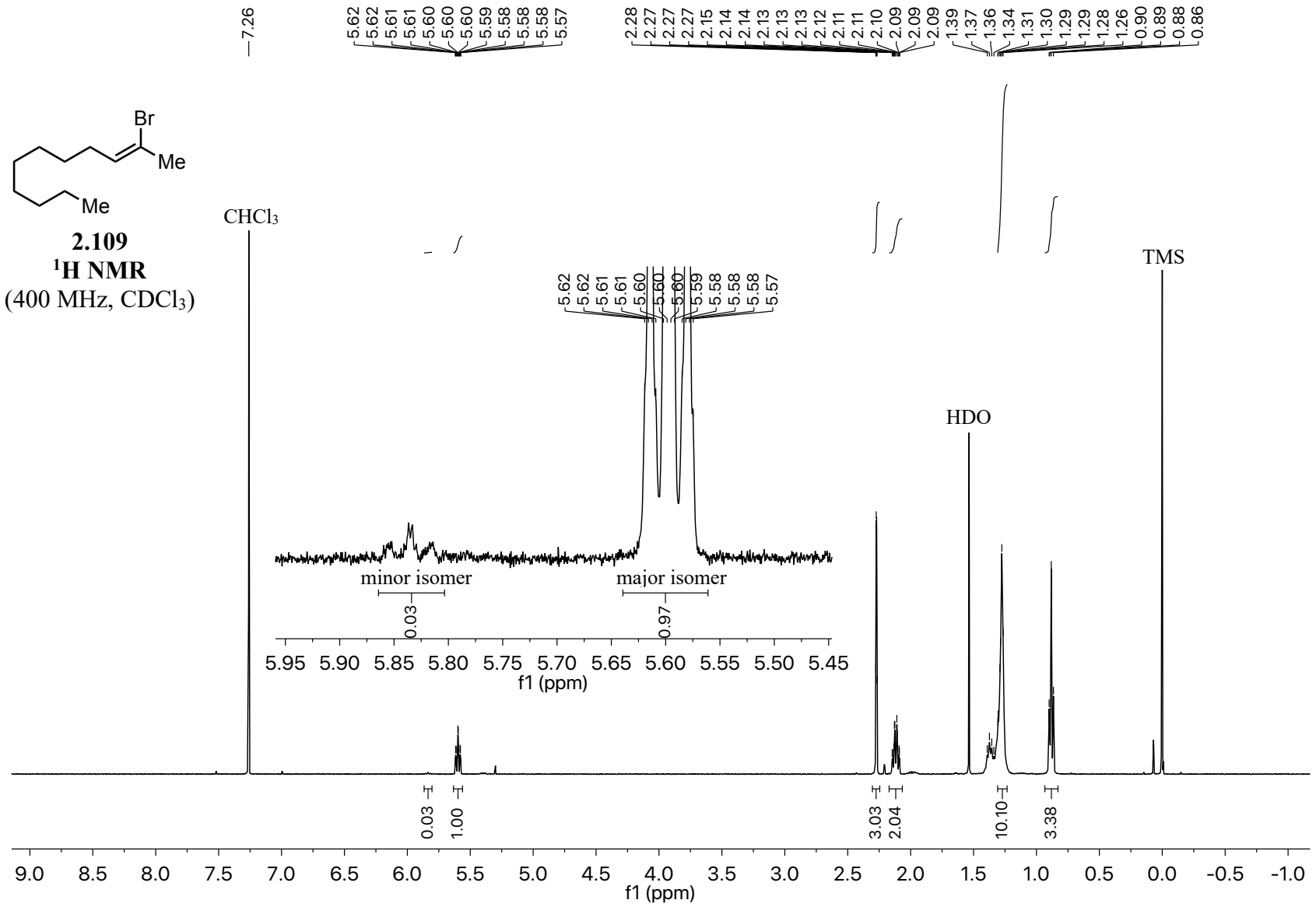


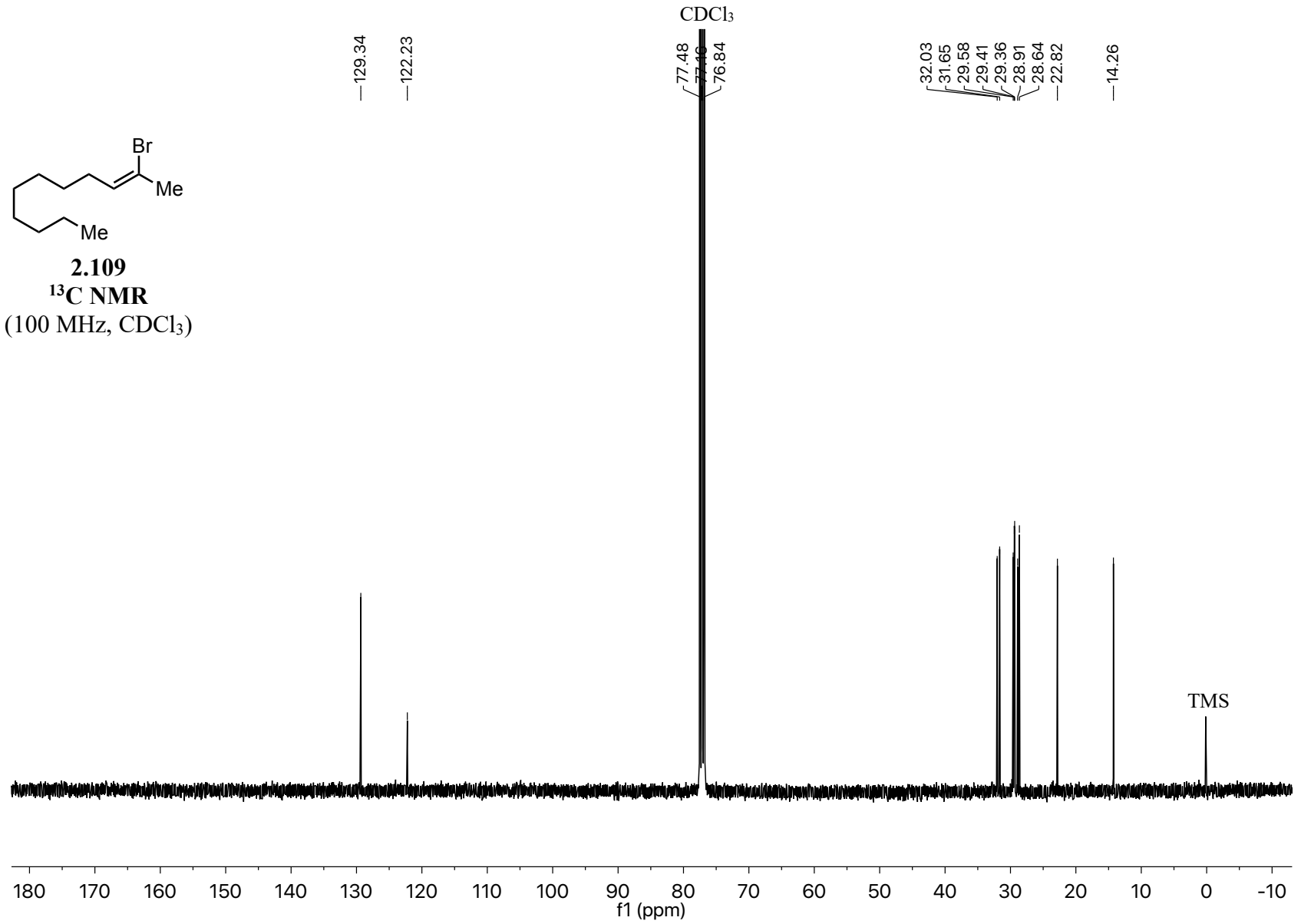
2.102
^{13}C NMR
(100 MHz, $CDCl_3$)


8.19
8.18
7.83
7.36
7.35
7.29
7.27
7.26
5.58
5.56
5.55
4.17
4.15
4.14
3.91
2.27
2.22
2.21
2.19
2.18
2.01
1.99
1.98
1.96
1.95
CO2Me
Br
N
Me
2.103
1H NMR
(500 MHz, CDCl3)
CHCl3
grease
0.98
0.99
1.03
1.93
0.99
2.04
2.98
3.10
2.03
1.94
f1 (ppm)

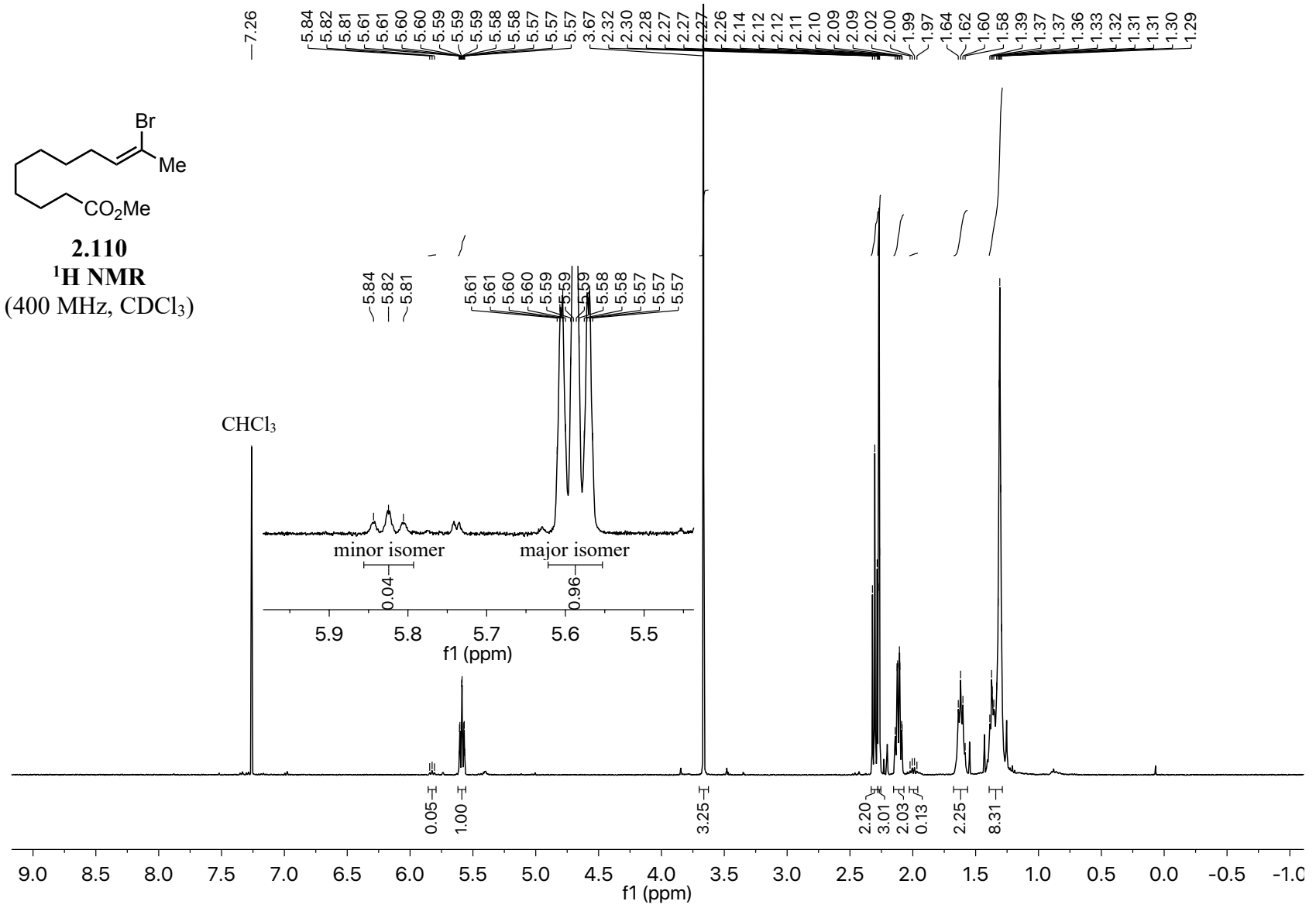


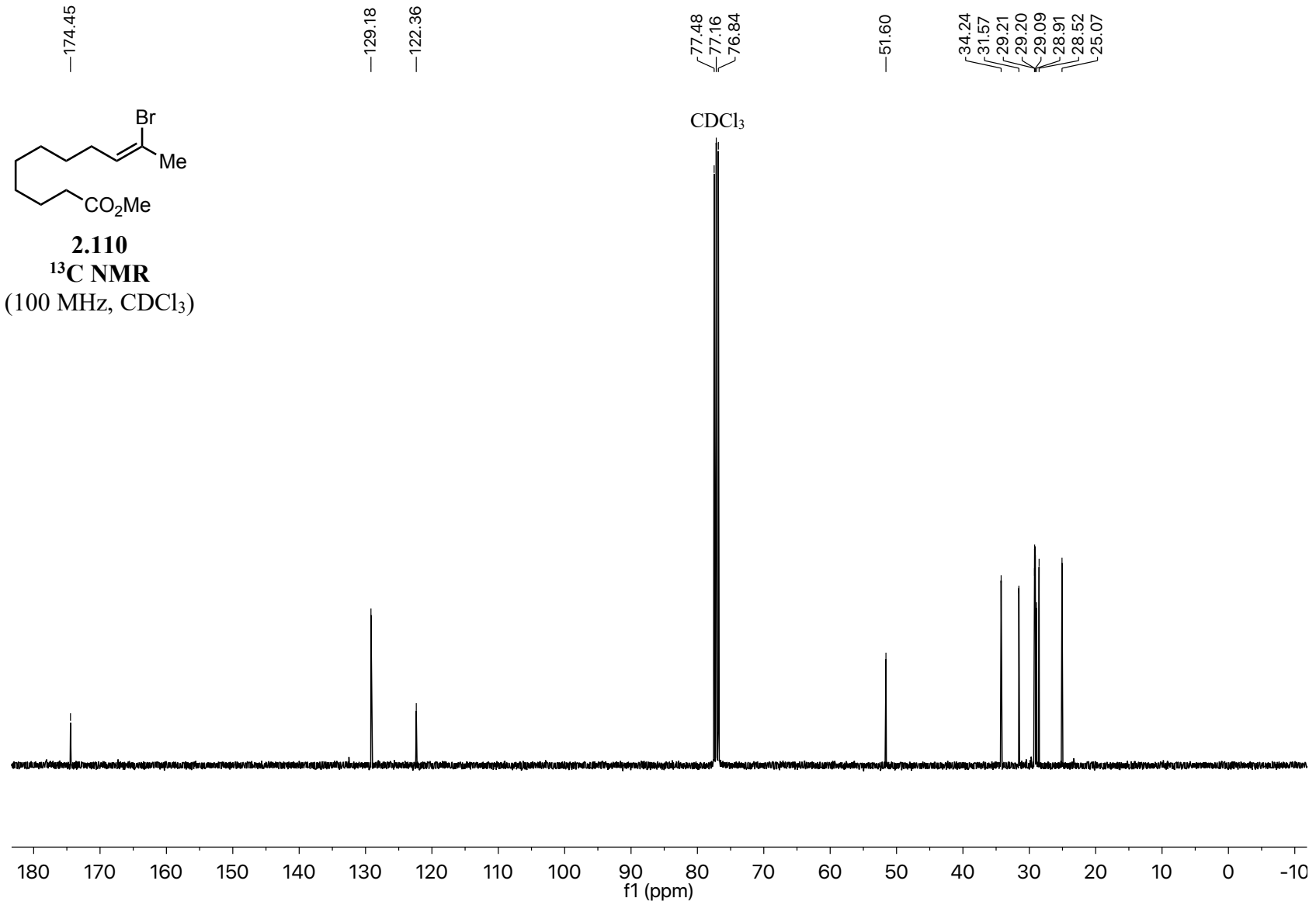
2.103
^{13}C NMR
(125 MHz, $CDCl_3$)


Br
Me
Me
2.109
1H NMR
(400 MHz, CDCl3)
CHCl3
TMS
HDO
minor isomer
major isomer
0.03
0.97
f1 (ppm)
0.03
1.00
3.03
2.04
10.10
3.38
f1 (ppm)

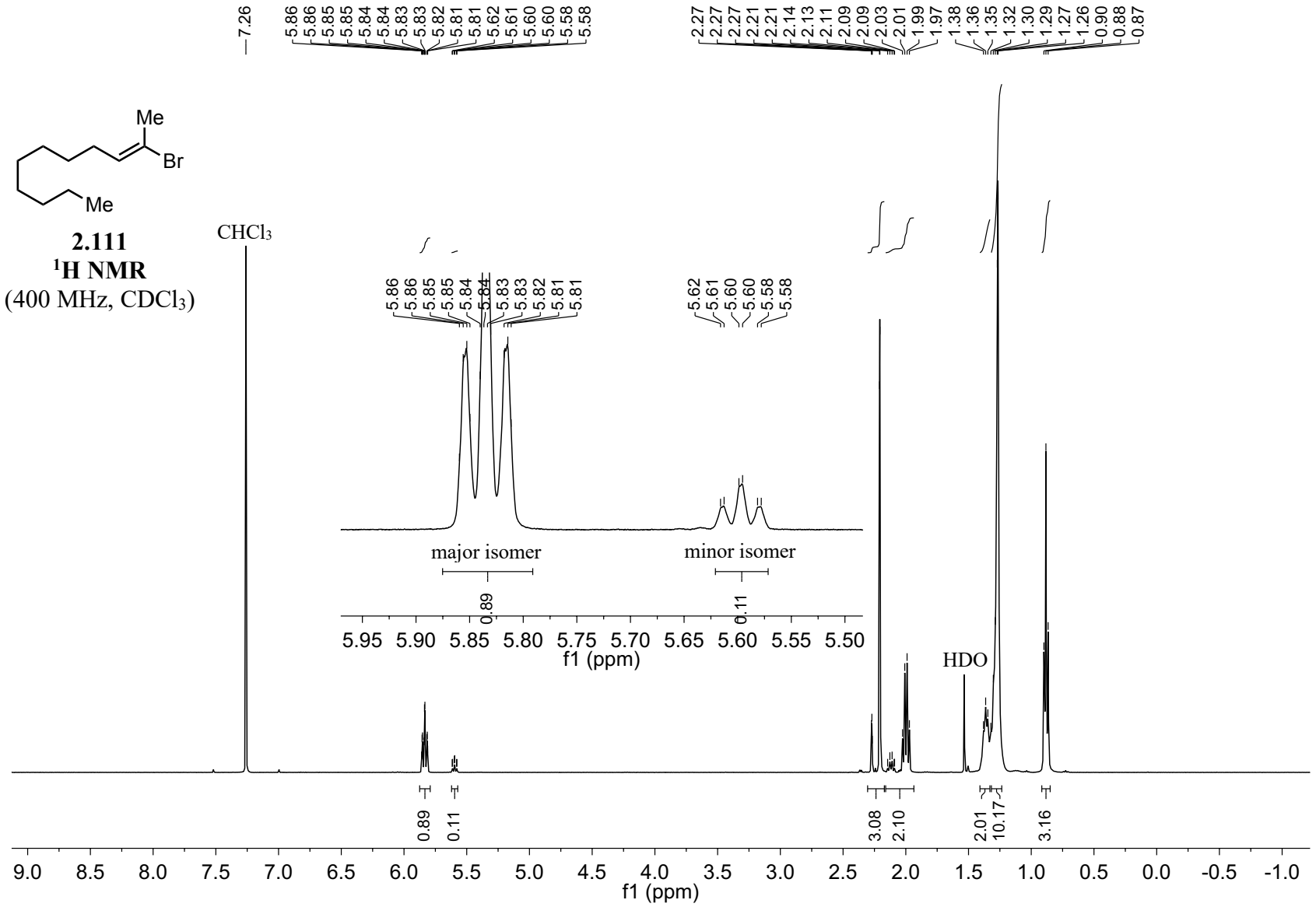


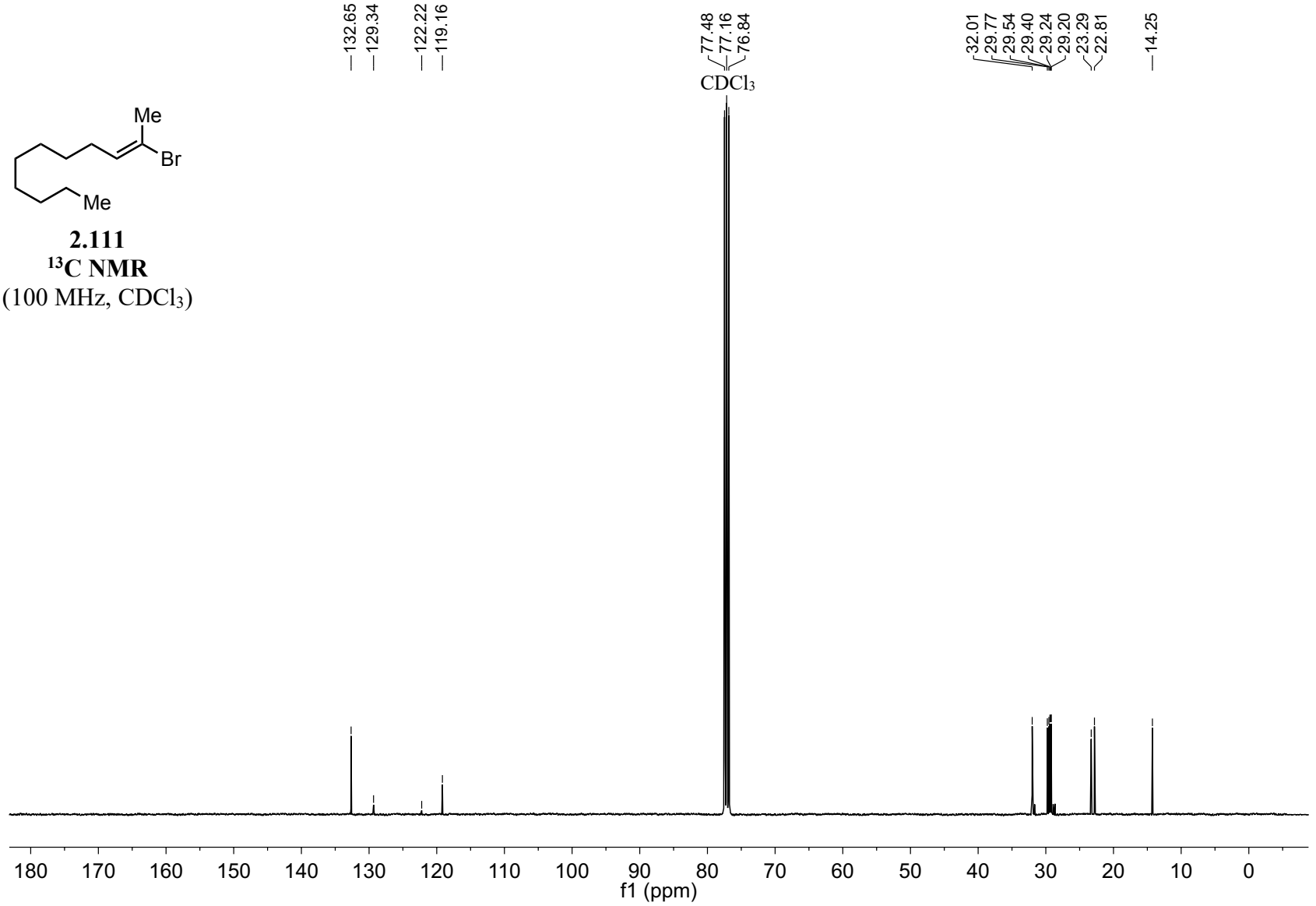
2.109
^{13}C NMR
(100 MHz, $CDCl_3$)


Br
Me
CO2Me
2.110
1H NMR
(400 MHz, CDCl3)
CHCl3
minor isomer
major isomer
0.04
0.96
f1 (ppm)
0.05
1.00
3.25
2.20
3.01
2.03
0.13
2.25
8.31
f1 (ppm)

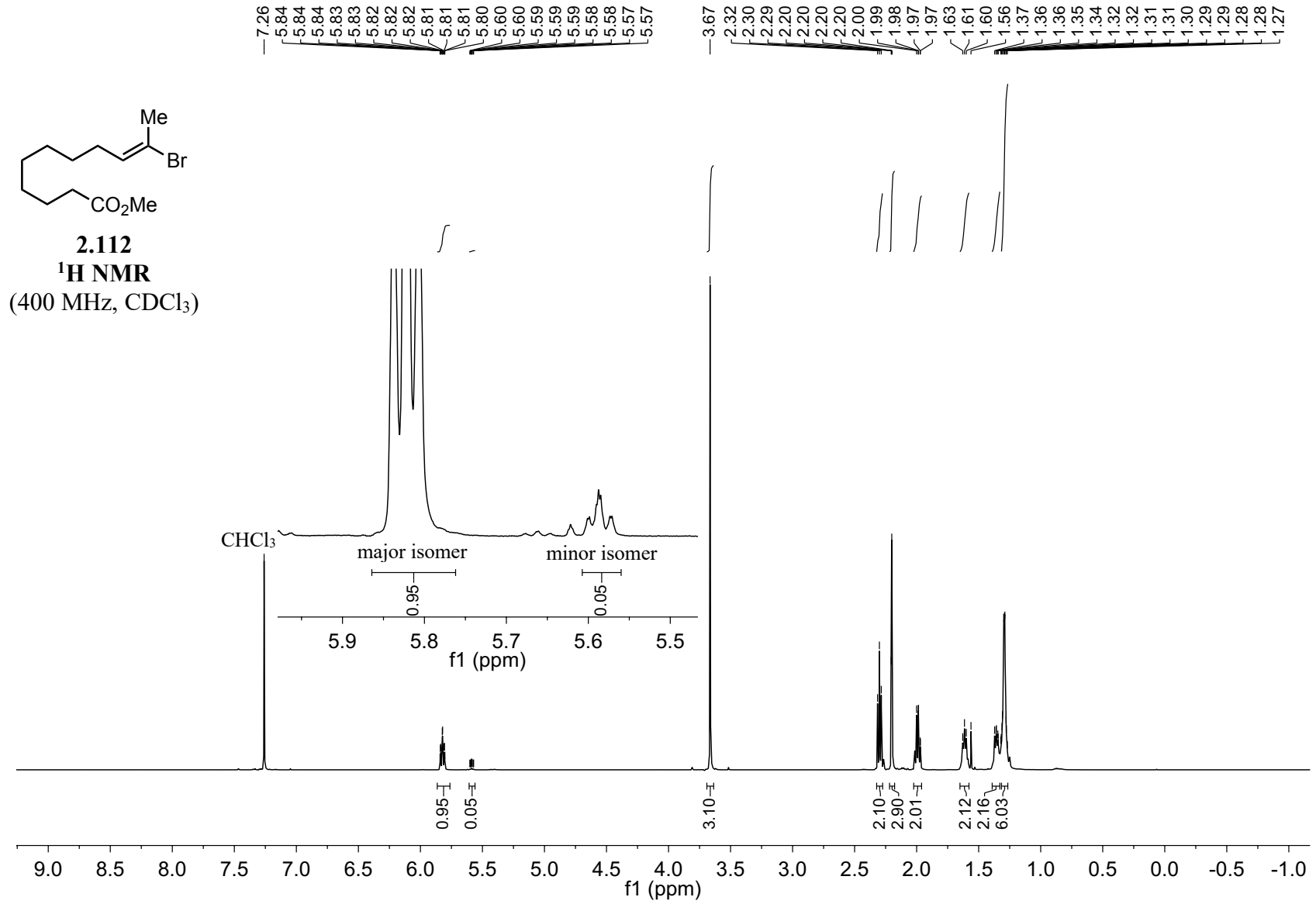


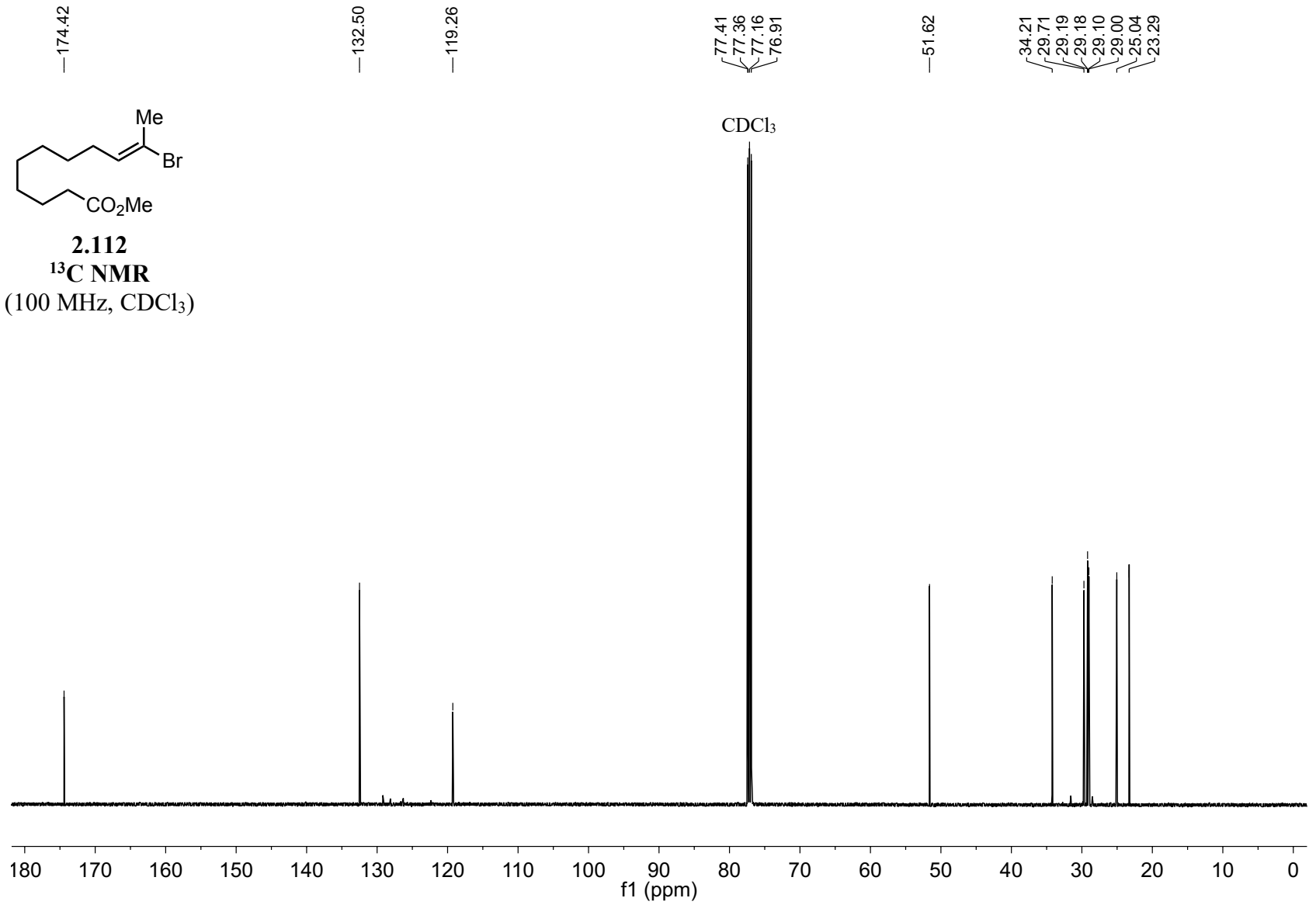
2.110
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
Br
Me
2.111
1H NMR
(400 MHz, CDCl3)
CHCl3
HDO
major isomer
minor isomer
f1 (ppm)

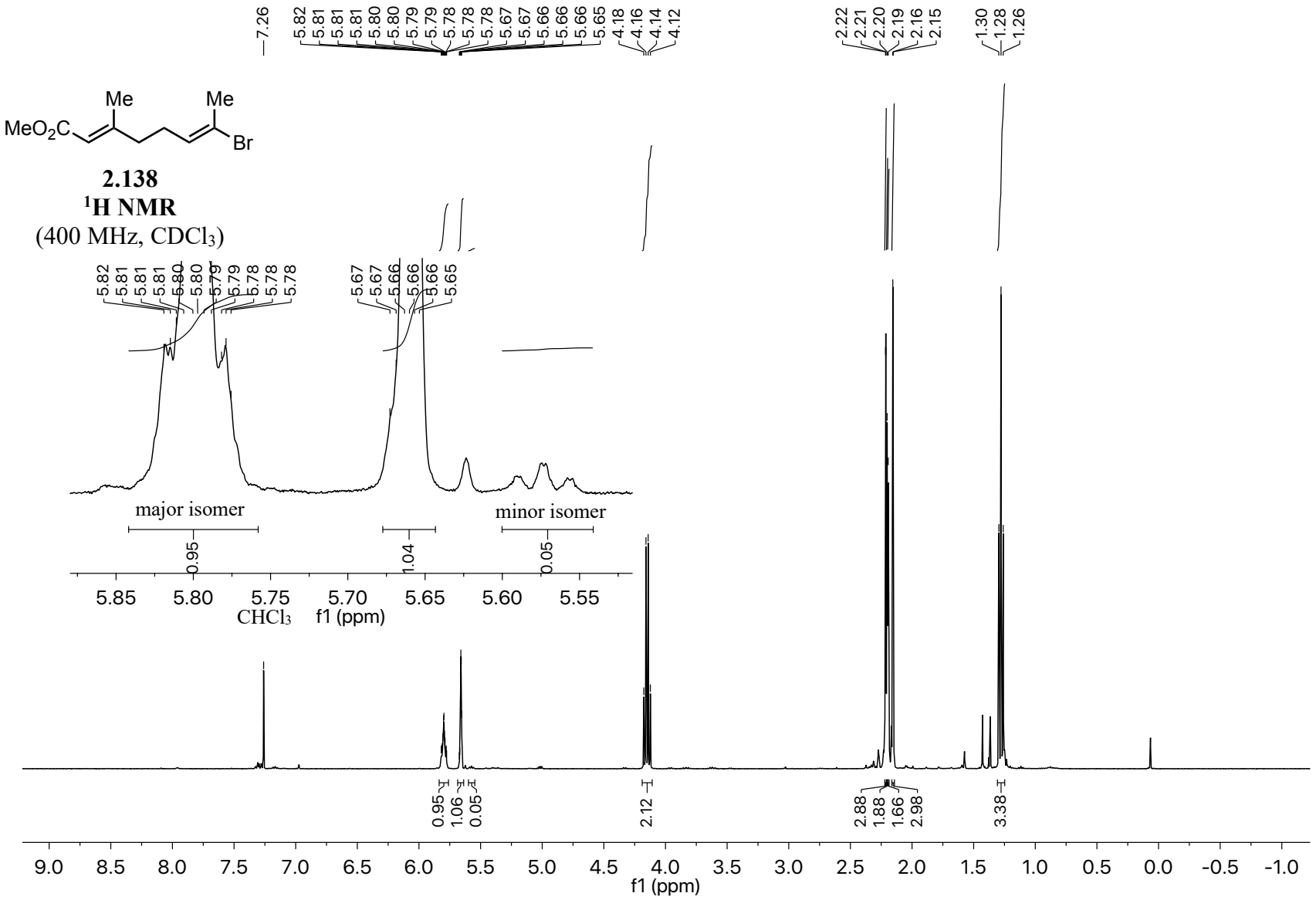


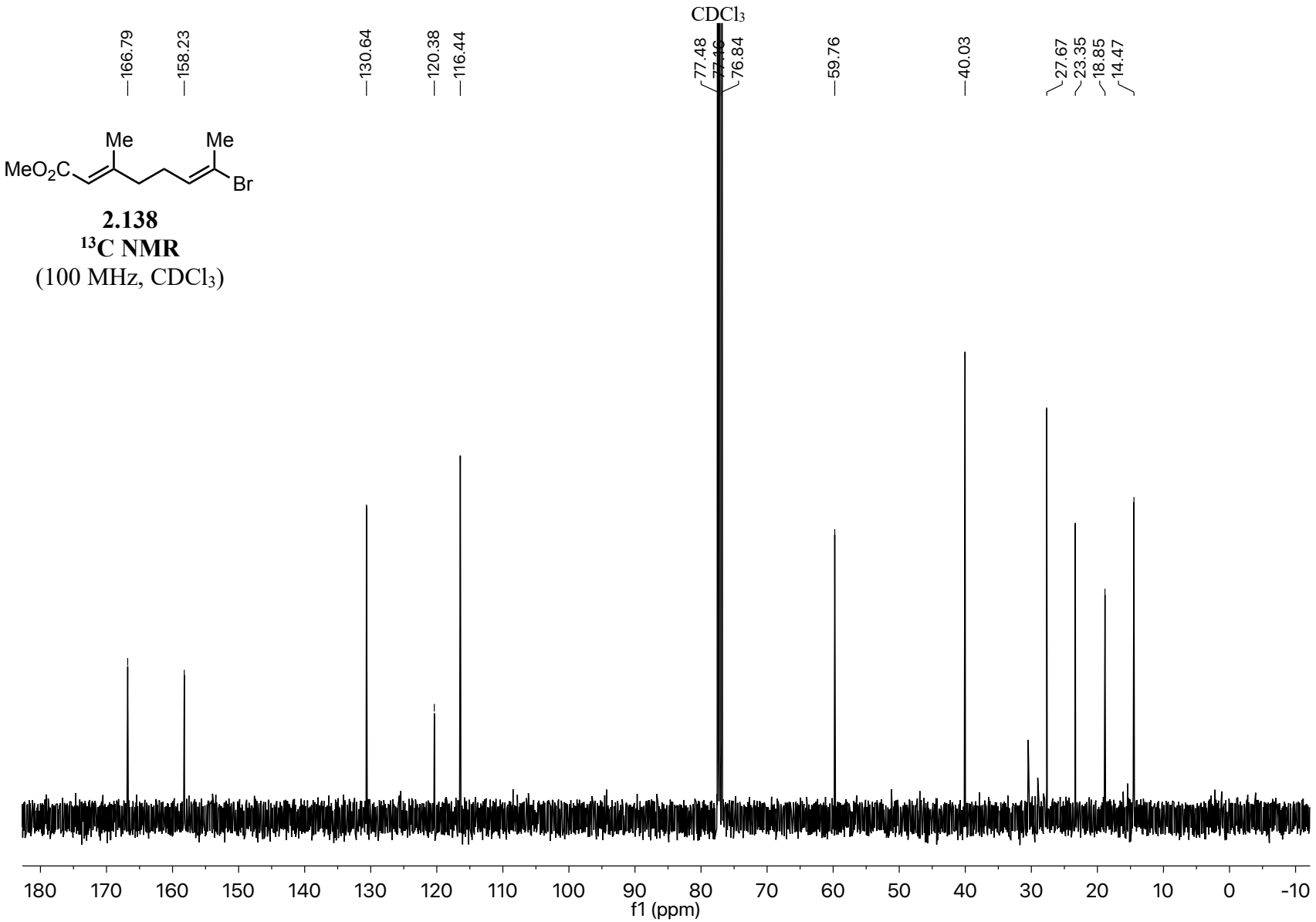
2.111
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
Br
CO2Me
2.112
1H NMR
(400 MHz, CDCl3)
CHCl3
major isomer
minor isomer
0.95
0.05
f1 (ppm)
3.10
2.10
2.90
2.01
2.12
2.16
6.03

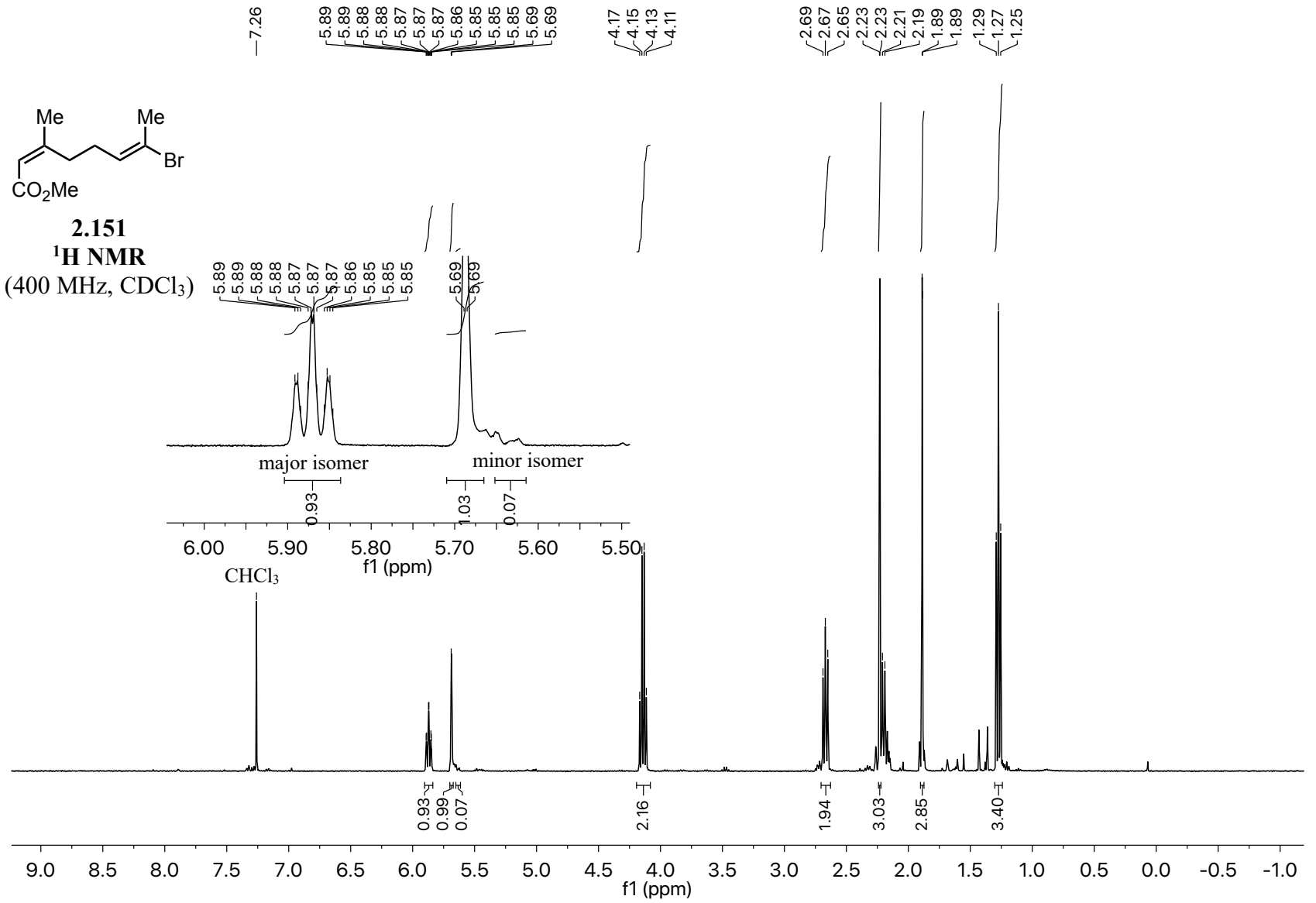


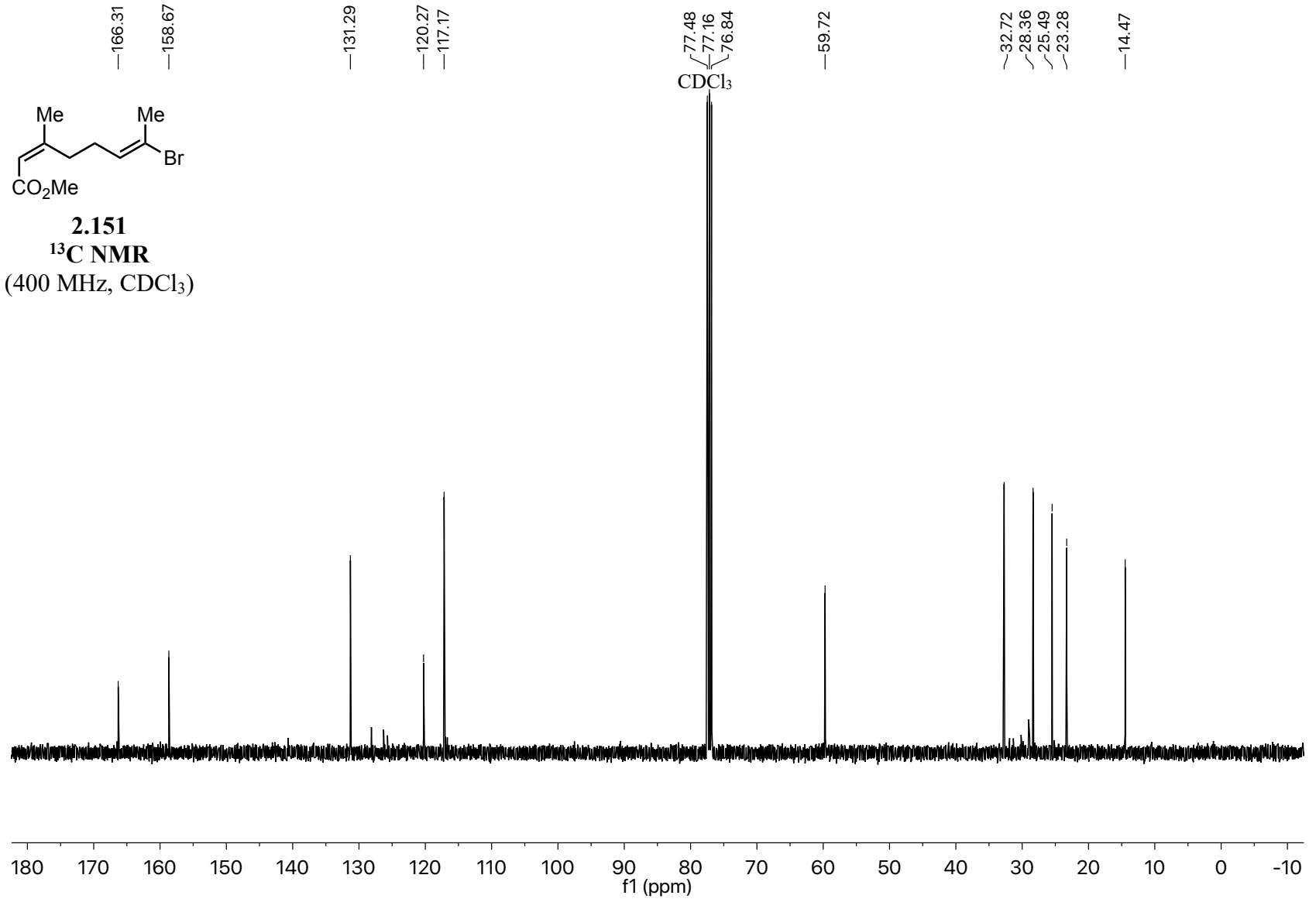
2.112
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
Me
MeO2C
Br
2.138
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
0.95
1.04
0.05
CHCl3
f1 (ppm)
0.95
1.06
0.05
2.12
2.88
1.88
1.66
2.98
3.38
f1 (ppm)



2.138
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
Me
Br
CO2Me
2.151
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
CHCl3
f1 (ppm)



2.151
^{13}C NMR
(400 MHz, $CDCl_3$)

Chapter Three

Total Synthesis of Ambrein

3.1 Introduction

Ambrein is a triterpene alcohol that naturally occurs in ambergris, a waxy secretion found in the digestive system of certain sperm whales (*Physeter macrocephalus*).[1] In air, it rapidly degrades into a multitude of compounds that have a pleasant aroma, rendering it a much sought after ingredient in perfumes.[2] On account of its scarcity and difficulties associated it as well as its poorly understood biosynthesis, ambergris has been and continues to be expensive.[3] As such, there has been a considerable number of initiatives aimed at replacing ambrein with a synthetic analogue, ambrox being the most widely used.[4]

Despite being isolated from ambergris in 1820, ambrein's exact identity remained elusive for more than a century. It was not until the 1940s that studies conducted by Ruzicka and Lederer elucidated the chemical structure.[5] The first total synthesis of ambrein was reported by Mori and co-workers,[6] who based their work on earlier investigations by Oritani and Matsui.[7] The latter team prepared an advanced intermediate, but was not able

(1) For reviews on ambergris and ambrein, see: (a) Oohloff, G. In *Fragr. Chem.*; Academic Press, Inc.: Cambridge, 1982; Clarke, R. *Lat. Am. J. Aquat. Mamm.* **2006**, *5*, 7–21; Schäfer, B. *Chem. Unserer Zeit* **2011**, *45*, 374–388.

(2) Ohloff, G.; Schulte-Elte, K. H.; Müller, B. L. *Helv. Chim. Acta* **1977**, *60*, 2763–2766.

(3) Kemp, C. In Floating Gold: A Natural (and Unnatural) History of Ambergris; University of Chicago Press: Chicago, 2012.

(4) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Altarejos, J.; Salido, S.; Ramos, J. M. *Tetrahedron* **1993**, *49*, 10405–10412.

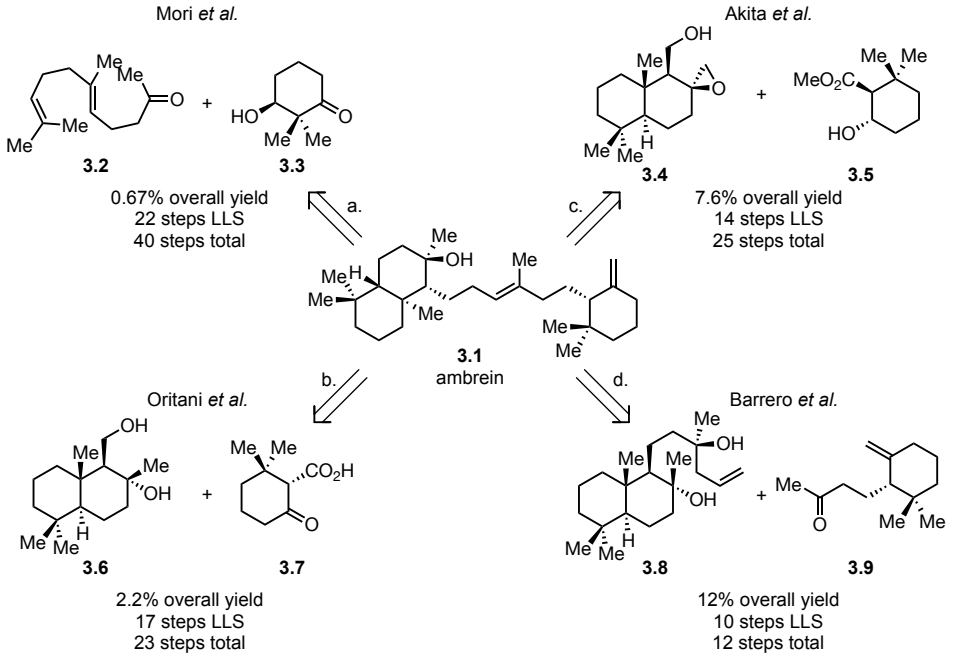
(5) (a) Ruzicka, L.; Lardon, F. *Helv. Chim. Acta* **1946**, *29*, 912–921. (b) Lederer, E.; Marx, F.; Mercier, D.; Pérot, G. *Helv. Chim. Acta* **1946**, *29*, 1354–1365.

(6) Mori, K.; Tamura, H. *Liebigs Ann. Chem.* **1990**, *1990*, 361–368.

(7) Oritani, T.; Matsui, M. *Agric. Biol. Chem.* **1966**, *30*, 759–763.

to obtain the final compound. Mori traced the *trans*-decalin system of ambrein back to geranylacetone (**3.2**), which, after cyclization and separation of enantiomers (resolution), was able to obtain the enantioenriched core (Scheme 3.1.1.a). The other fragment was prepared from hydroxy ketone **3.3**, accessed through stereoselective yeast reduction of a diketone.

Scheme 3.1.1. Ambrein Syntheses and Respective Retrosynthesis Analyses



More than 30 years after Mori's report, Oritani succeeded in synthesizing ambrein from **3.6** and **3.7**, accessed through resolution of racemic mixtures (Scheme 3.1.1.b).[8] The third total synthesis was completed by Akita and co-workers, who again secured the requisite the enantioenriched starting materials (**3.4**, **3.5**) through resolution (Scheme 3.1.1.c).[9] Finally, Barrero *et al.* improved upon the Mori route by accessing two

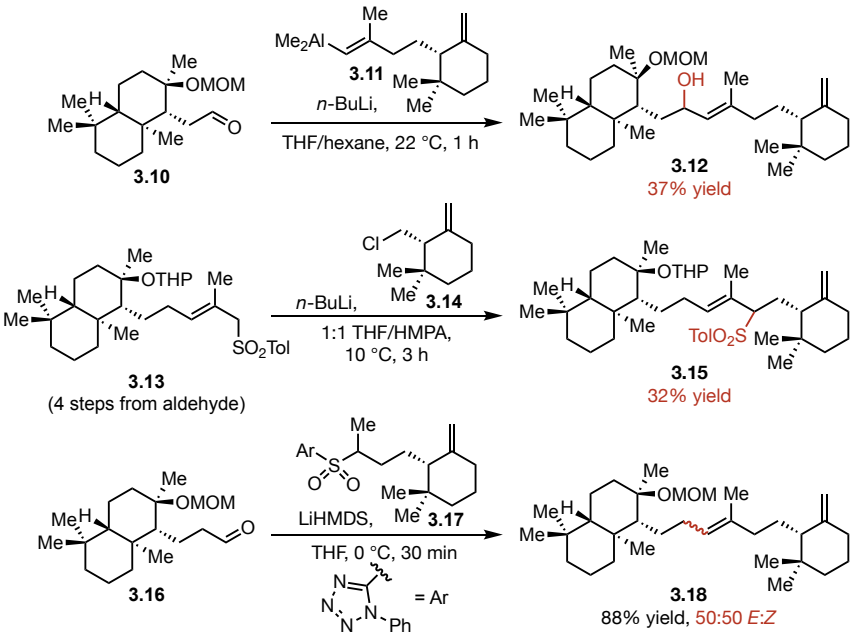
(8) Tanimoto, H.; Oritani, T. *Tetrahedron* **1997**, *53*, 3527–3536.

(9) Fujiwara, N.; Kinoshita, M.; Akita, H. *Tetrahedron Asymmetry* **2006**, *17*, 3037–3045.

intermediates from the chiral pool, namely by using sclareol (**3.8**) and natural product **3.9**, which is not commercially available and was isolated from *Bellardia trixago*.[10]

Additionally, considerable effort has been undertaken toward direct synthesis of ambrein from readily available feedstock through the use of genetically engineered bacteria,[11] yeast,[12] and enzymes.[13] While many of these approaches are highly efficient, they are not applicable to other members of this family of compounds.

Scheme 3.1.2. Synthesis of the Trisubstituted Alkene in Ambrein in Previous Approaches



In the previous syntheses, accessing the trisubstituted alkene proved to be difficult (Scheme 3.1.2). In the first instance (Scheme 3.1.2, top), the requisite double bond was established through carbometallation of a terminal alkyne. Albeit efficient and highly

(10) Castillo, A.; Silva, L.; Briones, D.; Quílez del Moral, J. F.; Barrero, A. F. *Eur. J. Org. Chem.* **2015**, *2015*, 3266–3273.

(11) Ke, D.; Caiyin, Q.; Zhao, F.; Liu, T.; Lu, W. *Biotechnol. Lett.* **2018**, *40*, 399–404.

([12]) Moser, S.; Strohmeier, G. A.; Leitner, E.; Plocek, T. J.; Vanhessche, K.; Pichler, H. *Metab. Eng. Commun.* **2018**, *7*, e00077.

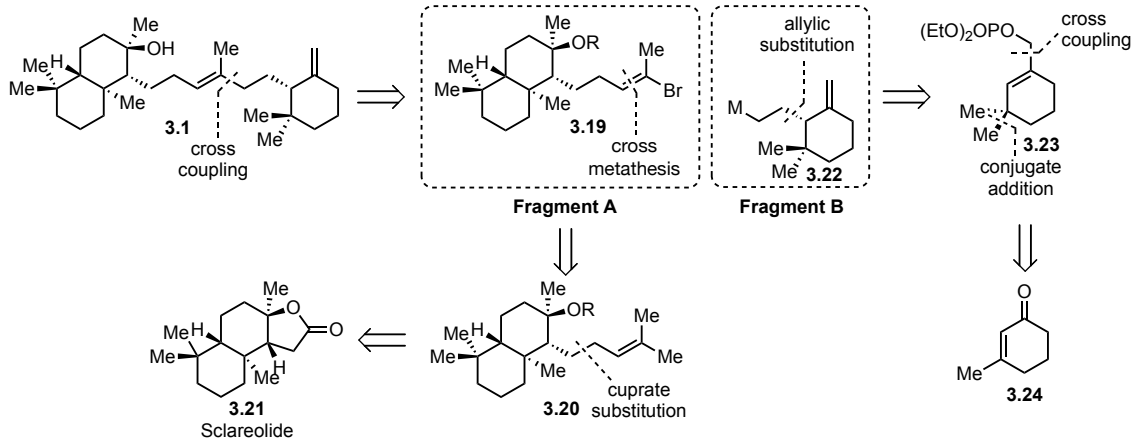
(13) Yamabe, Y.; Kawagoe, Y.; Okuno, K.; Inoue, M.; Chikaoka, K.; Ueda, D.; Tajima, Y.; Yamada, T. K.; Kakihara, Y.; Hara, T.; Sato, T. *Sci. Rep.* **2020**, *10*, 1–12.

stereoselective, the ensuing transformation involving aldehyde **3.10** was low yielding, furnishing **3.12** in 37% yield. Furthermore, removal of the hydroxy group demanded two additional manipulations, causing partial isomerization of the trisubstituted alkene. In the second case (Scheme 3.1.2, middle), the trisubstituted olefin was generated by a HWE process (not shown). α-Deprotonation and trapping with electrophile **3.14** proceeded with high stereoselectivity (>98:2 *E*:*Z*) but the desired product was isolated in 32% yield. Sulfone removal proved to be inefficient as well (36% yield). In the third example (Scheme 3.1.2, bottom), the trisubstituted olefin was synthesized through a Julia reaction involving aldehyde **3.16** and sulfone **3.17**. While the transformation was efficient (88% yield), stereocontrol was minimal, and the 50:50 isomeric mixture had to be separated through silica gel chromatography. Accordingly, the true yield of the desired intermediate that was converted to ambrein was less than 44%.

3.2 Retrosynthesis Analysis

To evaluate the utility of our recent strategies, we decided to explore preparing ambrein's trisubstituted olefin moiety through cross-coupling of an appropriate alkenyl bromide (fragment A, **3.19**; Scheme 3.2.1) and an alkyl nucleophile (fragment B, **3.22**). The necessary alkenyl bromide would be synthesized by cross-metathesis between trisubstituted alkene **3.20**, which, starting from commercially available sclareolide (**3.22**), we would obtain by a Suárez-type and an allylic substitution. We planned to generate fragment B through catalytic enantioselective allylic substitution of allyl phosphate **3.23**, generated by a sequence of conjugate addition/cross-coupling involving methylcyclohexenone (**3.24**).

Scheme 3.2.1. Retrosynthesis Analysis of Ambrein

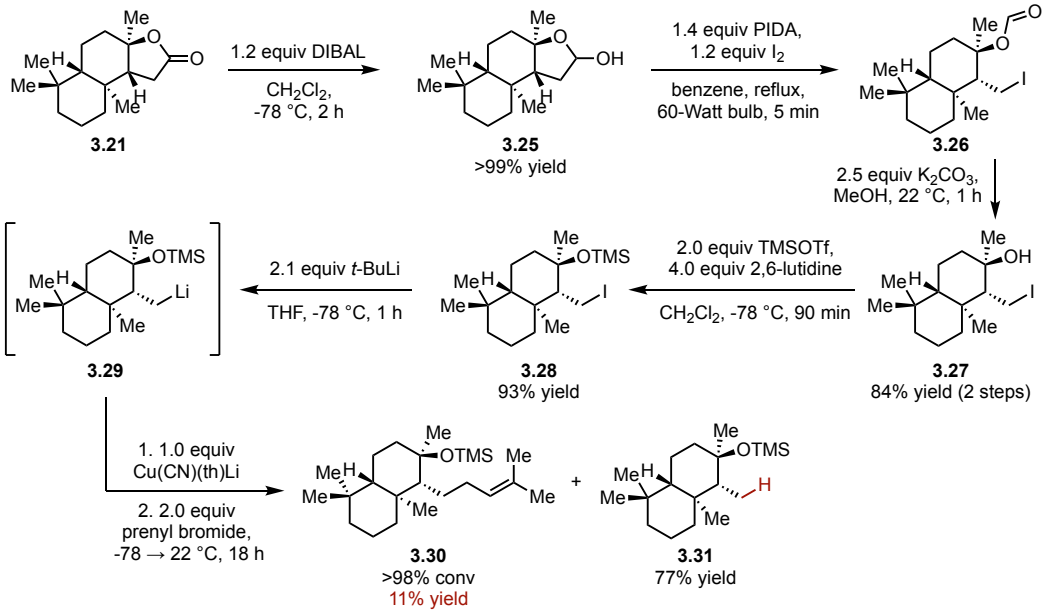


3.3 Synthesis of Fragment A

We began by investigating the transformation of sclareolide (**3.21**) to the requisite cross-metathesis starting material (Scheme 3.3.1). Treatment of **3.21** with DIBAL-H and Suárez cleavage[14] afforded **3.26** (not isolated due to instability), which was converted to **3.27**. Protection of the tertiary alcohol as a silyl ether made it possible to isolate multi-gram quantities of primary iodide **3.28**. Ensuing lithium-halogen exchange transpired as planned, but trapping of alkyl-lithium intermediate **3.29** with prenyl bromide turned out to be inefficient (<10% yield of desired product **3.30**, 77% yield of **3.31**, derived from the protodehalogenated starting material). Various conditions were investigated, and the best set of conditions was determined to involve a thienyl-copper(I) complex, as originally reported by Lipshutz.[15] Still, none of the tested conditions that were tested gave the desired intermediate **3.30** in more than ~10% yield, probably owing to the steric pressure caused by the decalin ring structure.

(14) Sun, Y.; Li, R.; Zhang, W.; Li, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9201–9204.
(15) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945–948.

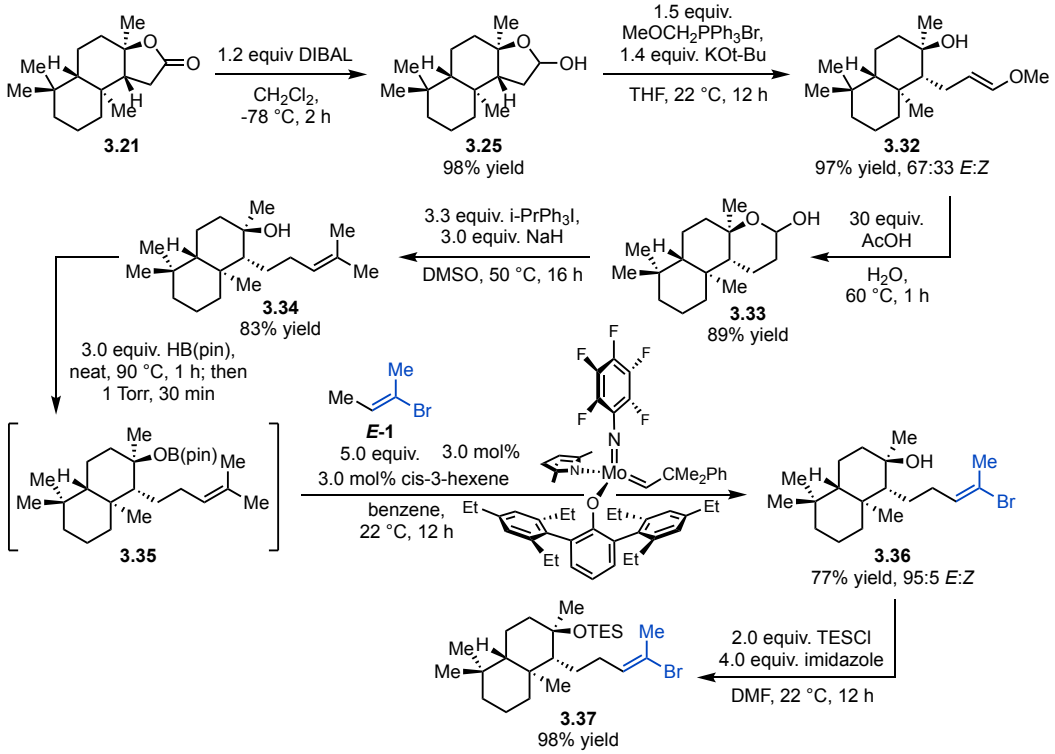
Scheme 3.3.1. The initial Synthesis Route Towards Fragment A of Ambrein



The inefficiency of previously reported routes for synthesis of **3.30** led us to seek an alternative sequence (Scheme 3.3.2). Accordingly, we converted lactol **3.25** to enol ether **3.32**, which after cleavage of the enol ether, was transformed to trisubstituted olefin **3.34** (4 steps, 70% overall yield from sclareolide). Cross-metathesis with ***E*-1** proceeded with high efficiency and stereoretentivity, affording **3.36** in 77% yield and 95:5 *E*:*Z* (by utilizing traceless protection of the tertiary alcohol with HB(pin)[16]). At larger scale, 3.0 mol% catalyst loading sufficed and alkenyl bromide **3.36** was obtained in gram-scale quantities (e.g., 1.27 g). Silyl-protection of the tertiary alcohol furnished **3.37** in 98% yield.

(16) Mu, Y.; Nguyen, T. T.; van der Mei, F. W.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 5365–5370.

Scheme 3.3.2. An Alternative Route for Synthesis of Fragment A of Ambrein



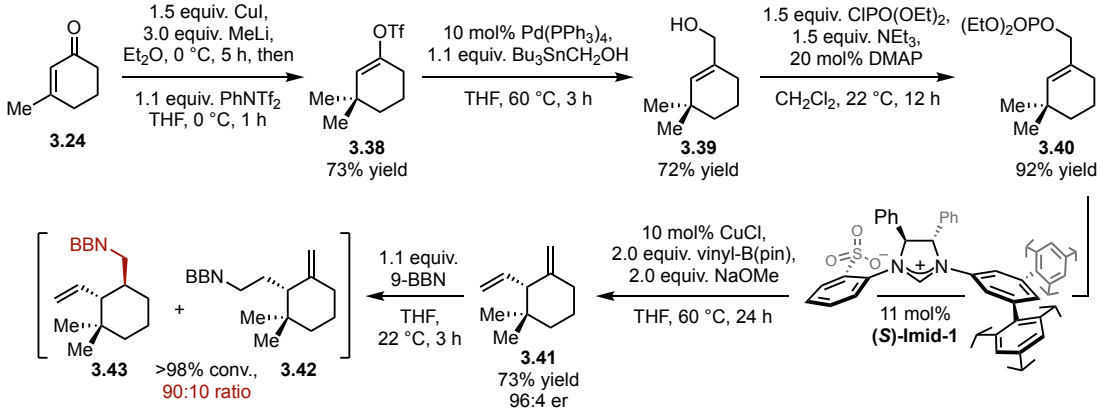
3.4 Towards Synthesis of Fragment B

Synthesis of fragment B began with conjugate methyl addition to **3.24** and trapping of the enolate as an enol triflate (**3.38**, Scheme 3.4.1).[17] Conversion of **3.38** to allylic alcohol **3.39** by Stille coupling (72% yield)[18] was followed by generation of allyl phosphate **3.40** (92% yield). In line with a previously reported protocol,[19] allylic enantioselective substitution afforded skipped diene **3.41** in up to 73% yield and 96:4 er (yields were sensitive to reaction scale on account of the volatility of **3.41**). Installation of a functional group suitable for a Suzuki-type cross-coupling with fragment A turned out to be challenging. When **3.41** was treated with 9-BBN, the exocyclic olefin reacted

(17) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930–8931.
(18) Lu, Z.; Li, H.; Bian, M.; Li, A. *J. Am. Chem. Soc.* **2015**, *137*, 13764–13767.
(19) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 2149–2161.

preferentially, resulting in a 90:10 mixture of **3.43** and **3.42** (undesired vs desired isomer). Attempts to reverse this selectivity trend by slow addition of 9-BBN or conducting the reaction at a lower temperature proved unsuccessful.

Scheme 3.4.1. Synthesis of Fragment B and Unexpected Chemoselectivity of the Hydroboration

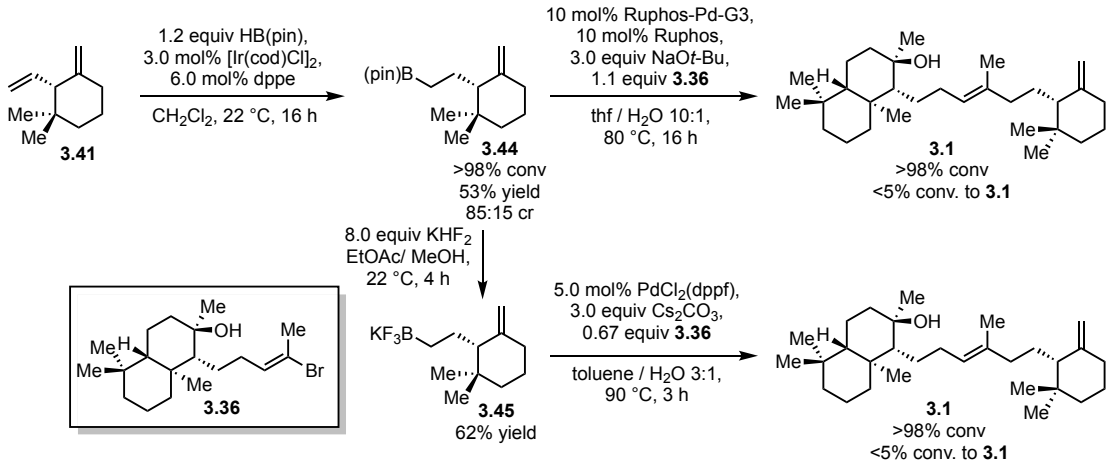


3.5 Functionalization Attempts of Fragment B

At this point, we wondered if the desired selectivity might be achieved if a transition metal catalyzed transformation was used for boron hydride addition (Scheme 3.5.1). As it turned out, use of an Ir-based catalyst allowed us to implement the desired functionalization of the monosubstituted alkene to afford **3.44** as an 85:15 mixture of desired and undesired isomers (formation of the latter likely stems from reaction with the exocyclic olefin). Nonetheless, attempts to cross-couple the alkyl boronate **3.44** with **3.36**, however, proved less than satisfactory (<5% formation of **3.1**), regardless of the catalyst used. As cross-coupling reactions of similar compounds have been reported by Molander,[20] we synthesized potassium trifluoroborate **3.45**, but to no avail (<5% formation of **3.1**). In all cases, significant amounts of side products were formed that we were not able to efficiently separate and characterize.

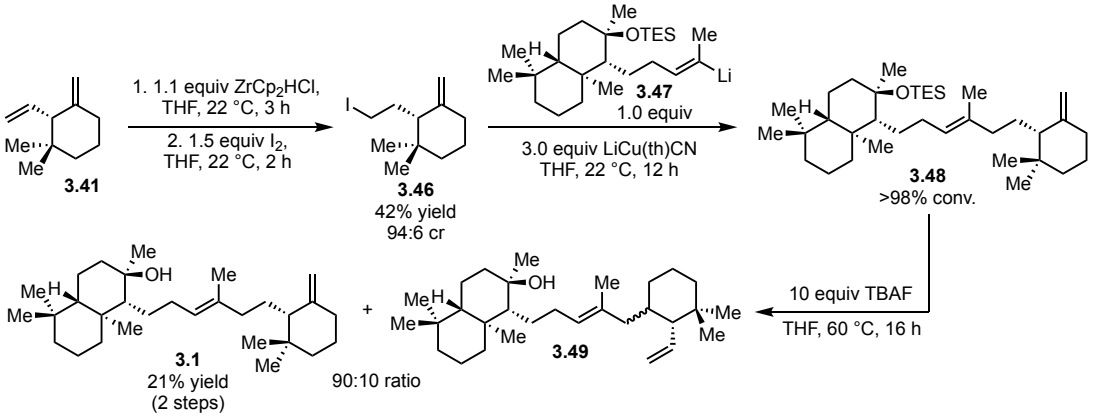
(20) Molander, G. A.; Ham, J.; Seapy, D. G. *Tetrahedron* **2007**, *63*, 768–775.

Scheme 3.5.1. Ir-Catalyzed Boron-Hydride Addition and Subsequent Cross-Coupling Attempts



Our next strategy was to try a different approach (Scheme 3.5.2). Subjection of **3.41** to Schwartz's reagent, followed by oxidation with iodine, afforded primary iodide **3.46** in 42% yield and in a 94:6 ratio, favoring the desired isomer. Copper-mediated cross-coupling of **3.47'**, accessed from lithium-halogen exchange with alkenyl bromide **3.37**, proceeded to full conversion, affording **3.1** in 21% yield, which was isolated after deprotection with TBAF as a 90:10 mixture (**3.1**:**3.49**). The byproduct was found to be the disubstituted olefin, generated during aqueous workup.

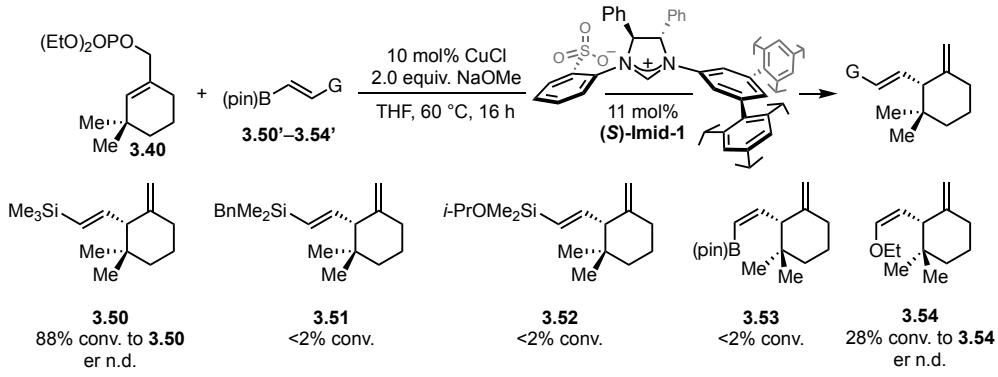
Scheme 3.5.2. Functionalization of **3.41** through Schwartz' Reagent and Subsequent Oxidation



3.6 Enantioselective Allylic Substitution with a Functionalizable Nucleophile

Selective functionalization of the terminal olefin in the presence of the exocyclic double bond in **3.41** turned out to be more complicated than we anticipated. We surmised that the use of an alkenyl boronate nucleophile, one that already contains a readily modifiable moiety, might be a solution. We preapred silyl-, boron-, and ether-substituted alkenyl boronates (**3.50'**–**3.54'**) through boron-hydride addition to the corresponding alkynes,[21] entities that we planned to use as nucleophiles in enantioselective allylic substitution processes (Scheme 3.6.1). We envisioned converting the resulting products to the target alkyl halides through appropriate functional group manipulation.

Scheme 3.6.1. Enantioselective Allylic Substitution with Functionalizable Alkenyl Boronates

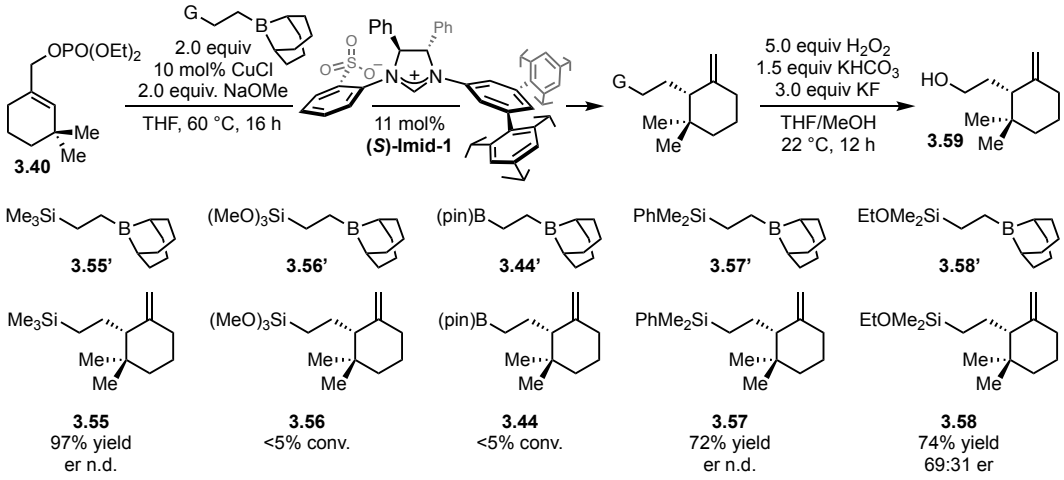


We began by probing allylic substitution with trimethylsilyl-substituted alkenyl boronate **3.50'**. There was no conversion of **3.40** at 22 °C. At 60 °C, on the other hand, there was 88% conversion to **3.50**. Still, functionalization of the organosilane was not feasible as none of the reported conditions would be applicable to an olefin-containing

(21) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127–3128.

substrate.[22] We therefore turned to investigating allylic substitutions with benzyl- or isopropoxy-substituted silanes (**3.51** and **3.52**), for which oxidation procedures are well established. The use of alkenyl boronates **3.51'** and **3.52'** did not lead to any detectable transformation (<2% conv.). The outcome with bis-alkenyl boronate **3.53'** was the same. Reactions with ethoxy-substituted alkenyl boronate **3.54'** afforded 28% of enol ether **3.54**, but subsequent attempts to cleave the enol ether only led to byproduct formation.

Scheme 3.6.2. Enantioselective Allylic Substitution with Functionalizable Alkyl Boronates



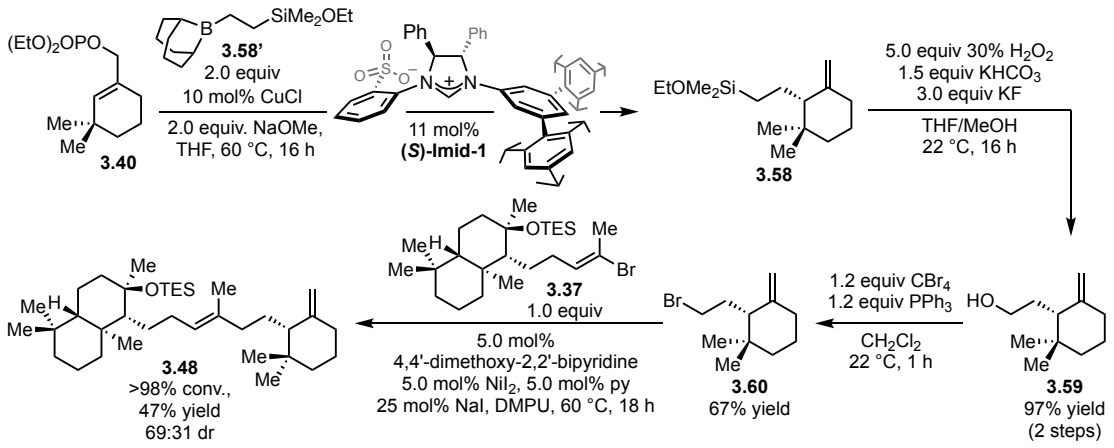
Next, we turned our attention to the respective alkyl boranes for allylic substitution with **3.40** (Scheme 3.6.2). Functionalized alkyl boranes **3.55'**–**3.58'** and **3.44'** were accessed by hydroboration of the appropriate terminal olefins.[23] Transformation with borane **3.55'** allowed us to isolate **3.55** in 97% yield. However, as before, attempts to functionalize the organosilane were futile (<2% conv. to the desired products). Reactions with boranes **3.56'** and **3.44'** did not lead to any product formation, but when the corresponding phenyl- and ethoxy-substituted silanes (**3.57'** and **3.58'**) were used, **3.57** and

(22) (a) Torigoe, T.; Ohmura, T.; Suginome, M. *J. Org. Chem.* **2017**, *82*, 2943–2956. (b) Matsuoka, K.; Komami, N.; Kojima, M.; Mita, T.; Suzuki, K.; Maeda, S.; Yoshino, T.; Matsunaga, S. *J. Am. Chem. Soc.* **2021**, *143*, 103–108. (c) Roy, A.; Oestreich, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 4408–4410.

(23) Soderquist, J. A.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 3571–3578.

3.58 were isolated in 72–74% yield. Oxidation of the phenyl-substituted silane **3.57** with HBF_4 and *m*CPBA[24] led mostly to decomposition. The derived ethoxy-substituted silane **3.58**, however, could be converted to alcohol **3.59** through oxidation with H_2O_2.[25] Stereoselectivity was determined, after oxidation and esterification to the benzoyl ester, to be notably lower than reactions with vinyl–B(pin) (69:31 er for **3.58** vs. 96:4 for vinyl–B(pin)). When **3.58** was subjected reductive cross-coupling conditions to fuse the two fragments,[26] a mixture of diastereomers (69:31 dr) of **3.48** was obtained (Scheme 3.6.3). Despite considerable experimentation, we were unable to separate these diastereomers chromatographically.

Scheme 3.6.3. Enantioselective Allylic Substitution and Subsequent Functionalizations



In view of the fact that enantioselective allylic substitution reactions involving functionalized nucleophiles was either inefficient or minimally selective, we chose to revisit the possibility of utilizing diene intermediate **3.41**.

(24) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc. Chem. Commun.* **1984**, 29.

(25) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org Synth* **1990**, *69*, 96.

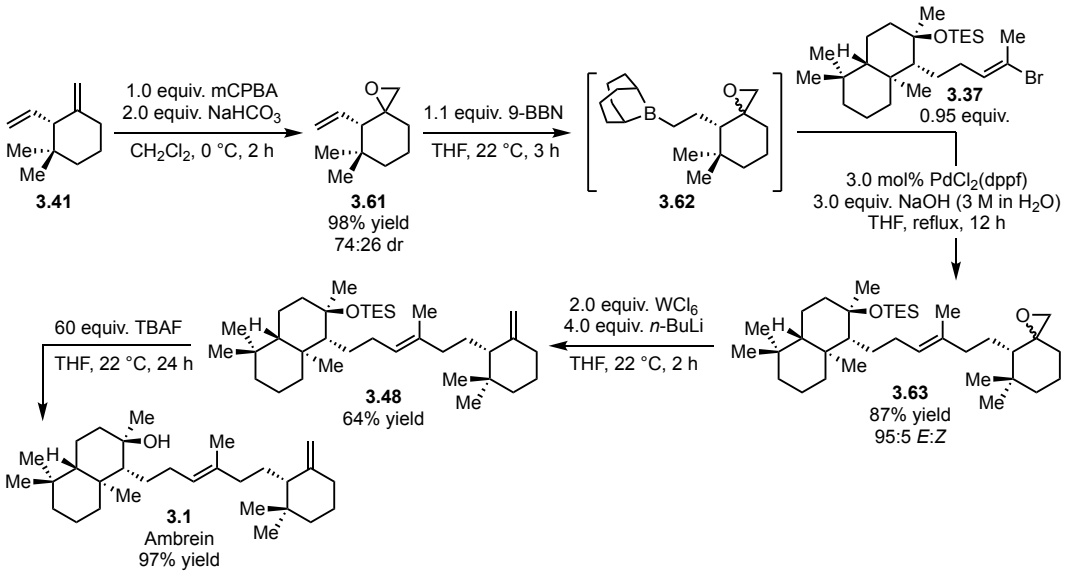
(26) Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159.

3.7 Fragment Coupling After Masking the Problematic Exocyclic Alkene

We reasoned that the exocyclic alkene might be selectively – and temporarily – converted into a functional group that would allow for the unmasking of the alkene at a later stage, thereby unsaturation site during the hydroboration/ cross-coupling sequence. Although a variety of functionalizations of alkenes exist that in principle might be reversed, the vast majority call for conditions that would likely lead to reaction at the monosubstituted olefin as well. The difficulty was finding a reagent or catalyst that would promote selective reaction at the more hindered and more electron rich exocyclic olefin.

It had previously been shown that the reaction rate of epoxidations with peracids, such as *m*CPBA, correlates with the degree of electron density at the olefin.[27] Since the disubstituted exocyclic olefin is probably more electron-rich, we expected selective transformation at this site. In the event, su bjection of **3.41** to one equivalent of *m*CPBA afforded epoxide **3.61** in 98% yield and 74:26 dr (inconsequential to the total synthesis), and without any detectable byproducts from reaction at the monosubstituted alkene

Scheme 3.7.1. Masking of the Exocyclic Alkene and Fusion of the Two Fragments



(27) Kim, C.; Traylor, T. G.; Perrin, C. L. *J. Am. Chem. Soc.* **1998**, *120*, 9513–9516.

(Scheme 3.7.1). We then proceeded with our initially devised sequence of hydroboration and cross-coupling, which led to the formation of the fused target compound **3.63** in 87% yield with complete retention of alkene stereochemistry.

For the subsequent deoxygenation that would revert the epoxide back to the alkene, we investigated several conditions.[28] None generated the alkene **3.48** cleanly and efficiently (<25% yield in all cases). It was only when the conditions by Sharpless were utilized that we were able to isolate **3.48** in 41% yield.[29] By adopting the improved work-up procedure by Baran,[30] we were able to increase the yield to 64%. Silyl deprotection afforded ambrein in 97% yield.

We were thus able to synthesize ambrein in 14 steps overall, with a longest linear sequence of nine steps, and in 28% overall yield. This compared favorably to former routes, the best requiring 25 steps and affording ambrein in 7.6% with a longest linear sequence of 14 steps. While the formal synthesis by Barrero may seem enticing with 12% overall yield over a longest linear sequence of 10 steps, and 12 steps in total, the necessary starting was prepared by oxidative cleavage of a natural product (with OsO_4), which was extracted from *Bellardia trixago* and required a series of purification protocols.

3.8 Conclusions

We have completed a total synthesis of ambrein, a terpenoid isolated from whale secretion, a much-sought perfume ingredient. The approach involved joining two

(28) (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc. Resumed* **1959**, 112. (b) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2005**, *46*, 4107–4110. (c) Mori, T.; Takeuchi, Y.; Hojo, M. *Tetrahedron Lett.* **2020**, *61*, 151518. (d) Nakagiri, T.; Murai, M.; Takai, K. *Org. Lett.* **2015**, *17*, 3346–3349.

(29) Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 6538–6540.

(30) Foo, K.; Usui, I.; Götz, D. C. G.; Werner, E. W.; Holte, D.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 11491–11495.

fragments through formation of the central trisubstituted alkene. Our route entailed a sequence of cross-metathesis of alkenyl bromides and cross-coupling, providing access to a previously difficult-to-access trisubstituted olefin with high efficiency and selectivity. One fragment was generated from a readily accessible enantiomerically enriched compound, sclareolide, and the other from inexpensive methylcyclohexenone. The stereogenic center of the latter was established through a NHC-Cu-catalyzed enantioselective allylic substitution, which was followed by differentiation of these alkenes through site-selective epoxidation. The total synthesis is more efficient and offers a more practical route to ambrein.

3.9 Experimental Section

3.9.1 General

Unless otherwise noted, transformations were performed with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum line techniques. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz), or 600 (600MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm, C_6D_6: δ 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from

tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, C_6D_6: δ 128.00 ppm). ^{19}F NMR spectra were recorded on a Varian Unity INOVA 400 (376 MHz) spectrometer. ^{31}P NMR spectra were recorded on a Varian Unity INOVA 400 (162 MHz) spectrometer. ^{11}B NMR spectra were recorded on a Varian Unity INOVA 400 (128 MHz) or 500 (160 MHz) spectrometer. High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility. Values for *E*:*Z* ratios of products were determined by ^1H NMR analysis of unpurified mixtures. Enantiomeric ratios were determined by GLC analysis (gas liquid chromatography) with an Agilent chromatograph (Alltech Associated Chiral dex CD-BDM column (30 m x 0.25 mm)) and by high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Regis Technologies Inc (*R*,*R*)-Whelk-O1 (4.6 x 250 mm)) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter. Melting points were determined using a Thomas Hoover Uni-melt capillary melting point apparatus.

3.9.2 Solvents

Solvents (CH_2Cl_2, Et_2O, pentane, benzene and toluene) were purified under a positive pressure of dry argon gas by an Innovative Technologies purification system. Tetrahydrofuran (Sigma-Aldrich) and 1,2-dimethoxyethane (Acros Organics) were purified by distillation from sodium benzophenone ketyl immediately prior to use unless specified otherwise. All purification procedures were carried out with reagent grade solvents (purchased from Fisher) under bench-top conditions unless indicated otherwise.

3.9.3 Reagents

Diethyl chlorophosphite (Alfa Aesar), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (Oakwood), 3-methylcyclohex-2-en-1-one (Combi-Blocks), pyridine (Sigma-Aldrich), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Oakwood), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (TCI), were distilled over CaH_2 prior to use. 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Strem) was recrystallized (CH_2Cl_2) prior to use. 3-Chloroperbenozoic acid was purified according to a reported procedure.[31] *n*-Butyllithium and methyllithium were used as received and titrated according to a previously reported procedure prior to use.[32] 9-borabicyclo[3.3.1]nonane[33] and **(*S*)-Imid-1**[34] were prepared according to previously reported procedures. (*E*)-trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)silane (**3.50'**, from ethynyltrimethylsilane), (*E*)-benzyldimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)silane (**3.51'**, from benzyl(ethynyl)dimethylsilane), (*E*)-isopropoxydimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)silane (**3.52'**, from ethynyl (isopropoxy)dimethylsilane), and (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.54'**, from ethoxyethyne) were prepared according to a previously reported procedure.[35] (*E*)-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethene (**3.53'**, from 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane) was prepared according to a previously reported procedure.[36] (2-(9-borabicyclo[3.3.1]nonan-9-yl)ethyl)trimethylsilane (**3.55'**, from trimethyl(vinyl)silane), (2-(9-borabicyclo[3.3.1]nonan-9-

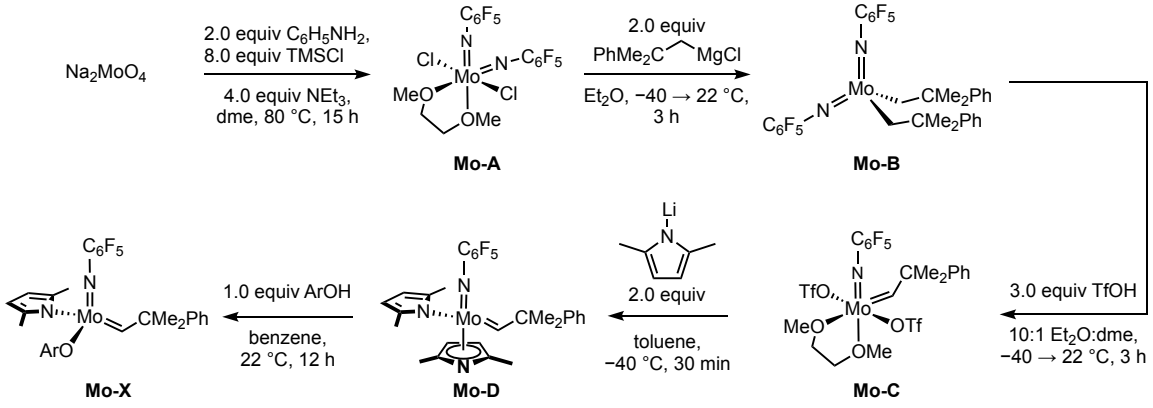
(31) Horn, A.; Kazmaier, U. *Eur. J. Org. Chem.* **2018**, *2018*, 2531–2536.
(32) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281–283.
(33) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5280–5281.
(34) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490–1493.
(35) Yang, C.; Gao, Y.; Bai, S.; Jiang, C.; Qi, X. *J. Am. Chem. Soc.* **2020**, *142*, 11506–11513.
(36) Meng, Y.; Kong, Z.; Morken, J. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 8456–8459.

yl)ethyl)trimethoxysilane (**3.56‘**, from trimethoxy(vinyl)silane), 2-(2-(9-borabicyclo[3.3.1]nonan-9-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.44‘, from 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane), (2-(9-borabicyclo[3.3.1]nonan-9-yl)ethyl)dimethyl(phenyl)silane (**3.57‘**, from dimethyl(phenyl)(vinyl)silane), and (2-(9-borabicyclo[3.3.1]nonan-9-yl)ethyl)(ethoxy)dimethylsilane (**3.58‘**, from ethoxydimethyl(vinyl)silane) were prepared according to a previously reported procedure.[21]

Acetic acid (Oakwood), ammonium chloride (Fisher), bromine (Fisher), (*E*)-2-bromo-2-butene (Aldrich, Santa Cruz Biotechnology), bis(1,5-cyclooctadiene)diiridium(I) dichloride (Strem),1,2-bis(diphenylphosphino)ethane (Strem), (*Z*)-2-bromo-2-butene (Aldrich, Santa Cruz Biotechnology, caesium carbonate (Strem), chlorotriethylsilane (Acros Organics), copper(I) chloride (Strem), (diacetoxyiodo)benzene (Sigma-Aldrich), 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (Ruphos, Sigma-Aldrich), diethylzinc (1 M in hexanes) (Sigma-Aldrich), diisobutylaluminum hydride (Sigma-Aldrich), 4,4'-dimethoxy-2,2'-bipyridine (Sigma-Aldrich), 4-(dimethylamino)pyridine (Oakwood), dimethylformamide (Acros Organics), dimethyl sulfoxide (Acros Organics), hydrochloric acid (Fisher), hydrogen peroxide (30% in H_2O, Fisher Scientific), imidazole (Oakwood), iodine (Alfa Aesar), isopropyltriphenylphosphonium iodide (Sigma-Aldrich), lithium chloride (Oakwood), lithium 2-thienylcyanocuprate (0.25 M solution in THF, Sigma-Aldrich), 2,6-lutidine (Sigma-Aldrich), (methoxymethyl)triphenylphosphonium chloride (Sigma-Aldrich), nickel(II) bis(acetylacetonate) (Strem), nickel(II) iodide (Sigma-Aldrich), *N*-phenyl-bis(trifluoromethanesulfonimide (Oakwood), potassium bicarbonate (Fisher Scientific), potassium bifluoride (Sigma-Aldrich), potassium fluoride

(Strem), potassium *tert*-butoxide (Oakwood), potassium sodium tartrate (Acros Organics), prenyl bromide (TCI), Ruphos-Pd-G3 (Sigma-Aldrich), Schwartz reagent (Oakwood), sclareolide (AK Scientific), sodium bicarbonate (Fisher), sodium hydride (Sigma-Aldrich), sodium iodide (Alfa Aesar), sodium methoxide (Oakwood), tetrabromomethane (Alfa Aesar), tetrabutylammonium fluoride (1 M in THF) (Sigma), tetrakis(triphenylphosphine)palladium (Strem), (tributylstannyl)methanol (Synthonix), triethylamine (Sigma-Aldrich), trimethylsilyl trifluoromethanesulfonate (Sigma-Aldrich), triphenylphosphine (Oakwood), tungsten(VI) chloride (Sigma-Aldrich), and palladium acetate (Strem) were used as received.

3.9.4 Preparation of Organometallic Complexes



Mo(NC$_6$F$_5$)$_2$Cl$_2$(DME) (Mo-A): This complex was prepared according to a previously reported procedure.[37] Under N_2 atmosphere, an oven-dried 250 mL round-bottom flask equipped with a magnetic stir bar and a condenser, was charged with $NaMoO_4$ (4.12 g, 20.0 mmol), $C_6F_5NH_2$ (9.16 g, 42.0 mmol), DME (60 mL), Et_3N (14 mL, 100 mmol), and TMSCl (25 mL, 200 mmol). The mixture was allowed to warm to 80 °C and stir for 15 h. Subsequently, the dark red solution was allowed to cool to 22 °C, filtered through a pad of

(37) Sues, P. E.; John, J. M.; Schrock, R. R.; Müller, P. *Organometallics* **2016**, *35*, 758–761.

celite, and volatiles were removed in vacuo. The so-obtained dark red oil was suspended in Et_2O, and the mixture was allowed to cool to −40 °C. After 12 h at that temperature, the suspension was filtered to afford **Mo-A** as orange solid (9.31 g, 15.0 mmol, 75% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.05 (s, 4H), 4.01 (s, 6H); **^{19}F NMR (376 MHz, $CDCl_3$):** δ −145.51 (m, 4F), −152.37 (t, *J* = 20.9 Hz, 2F), −162.04 (m, 4F).

$Mo(NC_6F_5)_2(CH_2CMe_2Ph)_2$ (Mo-B): This complex was prepared according to a previously reported procedure.[38] Under N_2 atmosphere, an oven-dried 250 mL Schlenk flask equipped with a magnetic stir bar was charged with **Mo-A** (9.31 g, 15.0 mmol) and Et_2O (50 mL). The mixture was allowed to cool to −40 °C, and $PhMe_2CCH_2MgCl$ (60 mL, 30 mmol, 0.50 M) was added. The mixture was allowed to warm to 22 °C and stir for 3 h. Subsequently, the mixture was filtered through a pad of celite, and the volatiles were removed in vacuo. The so-obtained dark red oil was suspended and triturated in hexanes (30 mL), resulting in formation of dark yellow precipitate. The suspension was filtered through a pad of celite, and the filtrate was concentrated to 20 mL, resulting in formation of a red precipitate. The suspension was allowed to cool to −40 °C. After at 12 h at that temperature, the red solid was collected by filtration, washed with cold hexanes, and dried in vacuo to afford **Mo-B** as red solid (5.26 g, 7.26 mmol, 49% yield). **^{1}H NMR (600 Hz, C_6D_6)**: δ 7.26 – 7.21 (m, 4H), 7.09 – 7.03 (m, 4H), 6.93 – 6.87 (m, 2H), 1.94 (s, 4H), 1.36 (s, 12H); **^{19}F NMR (564 Hz, C_6D_6):** δ −149.28 (m, 4F), −159.67 (t, *J* = 21.8 Hz, 2F), −163.85 – −164.54 (m, 4F).

(38) Yuan, J.; Schrock, R. R.; Müller, P.; Axtell, J. C.; Dobereiner, G. E. *Organometallics* **2012**, *31*, 4650–4653.

Mo(NC$_6$F$_5$)(CHCMe$_2$Ph)(DME)(OTf)$_2$ (Mo-C): This complex was prepared according to a previously reported procedure.[37] Under N_2 atmosphere, an oven-dried 250 mL round-bottom flask equipped with a magnetic stir bar was charged with **Mo-B** (5.00 g, 6.90 mmol), Et_2O (110 mL), and DME (12.0 mL). The resulting solution was allowed to cool to −40 °C, after which TfOH (3.18 g, 20.7 mmol) was added. The mixture was allowed to warm to 22 °C and stir for 3 h. The resulting yellow solid was collected by filtration, washed with Et_2O (20 mL), and dried in vacuo to afford **Mo-C** as yellow solid (3.03 g, 3.80 mmol, 55% yield). **^{1}H NMR (500 MHz, C$_6$D$_6$):** *trans* isomer (major): δ 13.73 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 2H), 6.97 (t, *J* = 7.8 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 3.32 (s, 3H), 3.27 (s, 2H), 3.01 (s, 3H), 2.89 (s, 2H), 1.61 (s, 6H); *cis* isomer (resolved signals only): δ 15.00 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 2H), 6.89 (t, *J* = 7.6 Hz, 2H); **^{19}F NMR (564 Hz, C$_6$D$_6$):** *trans* isomer (major): δ −76.83 (t, *J* = 5.4 Hz, 6F), −140.38 – −141.12 (m, 2F), −149.58 (t, *J* = 21.8 Hz, 1F), −161.43 – −162.08 (m, 2F); *cis* isomer (resolved signals only): δ −76.62 (s, 3F), −77.53 (s, 3F), −143.34 (m, *J* = 20.9 Hz, 2F), −151.33 (d, *J* = 21.3 Hz, 1F), −161.19 – −161.63 (m, 2F).

Mo(NC$_6$F$_5$)(CHCMe$_2$Ph)(Me$_2$-Pyr)$_2$ (Mo-D): This complex was prepared according to a previously reported procedure.[37] Under N_2 atmosphere, an oven-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with Mo(NC$_6$F$_5$)(CHCMe$_2$Ph)(DME)(OTf)$_2$ (798 mg, 1.00 mmol) and toluene (50 mL). The resulting suspension was allowed to cool to −40 °C, after which LiMe$_2$Pyr (222 mg, 2.20 mmol) was added. The mixture was allowed to warm to 22 °C and stir for 30 min. Subsequently, the solution was concentrated to dryness, and the dark red oil was dissolved in CH_2Cl_2 (10.0 mL). The resulting suspension was filtered through a glass Büchner funnel,

and the filtrate was concentrated in vacuo. The so-obtained red oil was dissolved in Et_2O (5.0 mL) and allowed to cool to −40 °C. After 12 h at this temperature, the red solid was collected by filtration, washed with cold Et_2O (2.0 mL), and dried in vacuo to afford **Mo-D** as orange solid (397 mg, 0.66 mmol, 66% yield). **^{1}H NMR (500 Hz, C_6D_6):** δ 13.01 (s, 1H), 7.14 – 7.10 (m, 2H), 6.86 – 6.80 (m, 2H), 6.77 – 6.72 (m, 1H), 5.93 (br, 4H), 2.09 (br, 12H), 1.41 (s, 6H); **^{19}F NMR (376 Hz, C_6D_6):** δ −145.41 – −145.91 (m, 2F), −157.29 (t, *J* = 21.8 Hz, 1F), −163.38 – −163.55 (m, 2F).

2,2'',4,4'',6,6''-Hexaethyl-[1,1':3',1''-terphenyl]-2'-ol (HETO): Under N_2 atmosphere, a 50 mL round-bottom flask equipped with a magnetic stir bar was charged with 2,6-dibromophenol (1.65 g, 6.55 mmol) and THF (10 mL). NaH (315 mg, 13.1 mmol) was added in portions, and the mixture was allowed to stir for 30 min at 22 °C. The suspension was filtered through a fritted funnel, and the filtrate was transferred to a 150 mL round-bottom flask equipped with a magnetic stir bar. Then, $Pd(OAc)_2$ (120 mg, 0.39 mmol), and a solution of (2,4,6-triethylphenyl)magnesium bromide in THF (0.64 M, 35 mL, 22.4 mmol) was added, and the resultant mixture was allowed to stir under reflux for 12 h. The mixture was allowed to cool to 22 °C, and the reaction was quenched by addition of HCl (2 M, 50 mL). The phases were separated, and the aqueous layer was washed with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and volatiles were removed in vacuo. The so-obtained colorless oil was dissolved in MeOH (20 mL) and transferred to a 50 mL round-bottom flask equipped with a magnetic stir bar. Then, Pd on carbon(10 wt%, 120 mg, 0.11 mmol) was added, and the mixture was sparged with H_2 (1 atm). The resultant suspension was allowed to stir under H_2 atmosphere at for 12 h at 22 °C. Subsequently, the mixture was filtered through celite, and the so-obtained oil was

washed with Et_2O (2 x 25 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and volatiles were removed in vacuo. The so-obtained oil was purified through silica gel chromatography (0% → 30% $CHCl_3$ in hexanes), recrystallized (EtOH), and dried in vacuo to afford **5b** as colorless crystals (1.95 g, 4.70 mmol, 72% yield). **IR (neat):** 3225 (w), 2960 (s), 2929 (m), 2868 (m), 1605 (w), 1456 (s), 1434 (m), 1320 (m), 1218 (s), 1166 (m), 1086 (m), 1070 (m), 1009 (w), 870 (s), 787 (m), 754 (s); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.10 – 7.06 (m, 1H), 7.04 – 6.99 (m, 2H), 4.54 (s, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.49 – 2.29 (m, 4H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.06 (t, *J* = 7.6 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.4, 144.2, 143.5, 132.3, 132.2, 130.4, 126.5, 126.5, 125.8, 120.1, 28.9, 26.9, 15.5, 15.4; **HRMS [M+H]$^+$** calcd for $C_{30}H_{39}O$: 415.2995, found: 415.2982; **m.p.** 53−55 °C.

General procedure for in situ preparation of Mo-1 for catalytic reactions: Under N_2 atmosphere, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with **Mo-D** (29.9 mg, 50.0 μmol), **HETO** (24.7 mg, 50.0 μmol) and benzene (0.50 mL), resulting in a dark red solution. The vial was sealed, and the mixture was allowed to stir for 2 h at 22 °C, after which the catalyst solution was stored in the freezer (−40 °C) until further use. The diagnostic alkylidene α-proton signal of the *syn*-alkylidene is: **^{1}H NMR (400 MHz, C_6D_6)**: δ 11.29 (1H, s).

3.9.5 Ambrein

(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyldodecahydronaphtho[2,1-*b*]furan-2-ol (3.25): This compound was synthesized according to a previously reported procedure.[39]

(39) Zhao, W.; Li, Z.; Sun, J. *J. Am. Chem. Soc.* **2013**, *135*, 4680–4683.

Under N_2 atmosphere, a 1 L round-bottom flask equipped with a magnetic stir bar was charged with (+)-sclareolide (10.0 g, 40 mmol) and CH_2Cl_2 (400 mL). The mixture was allowed to cool to −78 °C, after which DIBAL-H (8.6 mL, 48 mmol) was added in a dropwise manner over the course of 45 min. After complete addition, the mixture was allowed to stir for another 2 h at this temperature. Subsequently, MeOH (8.0 mL, 200 mmol) was added in a dropwise manner within 10 min, followed by addition of a saturated aqueous solution of sodium potassium tartrate (300 mL). The resultant suspension was allowed to warm to 22 °C and stir vigorously for 5 h. The phases were separated, and the aqueous phase was washed CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, and the volatiles were removed in vacuo. The so-obtained colorless oil was purified by filtration through a short silica gel plug (CH_2Cl_2). **3.25** was isolated as colorless solid (9.89 g, 39.2 mmol, 98% yield). The spectral data of this compound are consistent with those previously reported.

(1*R*,2*R*,4a*S*,8a*S*)-1-(iodomethyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (3.27): This compound was synthesized according to a previously reported procedure.[14] In a Under N_2 atmosphere, a 150 mL round-bottom flask equipped with a magnetic stir bar was charged with **3.25** (2.52 g, 10.0 mmol), I_2 (3.05 g, 12.0 mmol), and (Diacetoxyiodo)benzene (4.51 g, 14.0 mmol). Benzene (100 mL) was added, and the mixture was allowed to stir vigorously in a pre-heated oil bath for 5 min at 100 °C under irradiation of a 60-Watt light bulb. Then, the mixture was allowed to cool to 22 °C, and a saturated aqueous solution of $NaHCO_3$ (50 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) were added. The phases were separated, and the aqueous phase was washed with EtOAc (3 x 50 mL). The combined organic phases were dried over $MgSO_4$,

and volatiles were removed in vacuo. The so-obtained oil was purified through silica gel chromatography (0% → 3% EtOAc in hexanes) to afford **3.26** as colorless oil, which was immediately taken up in MeOH (120 mL). K_2CO_3 (3.46 g, 25.0 mmol) was added, and the resultant suspension was allowed to stir for 2 h at 22 °C. Then, a saturated aqueous solution of NH_4Cl (70 mL) was added, and volatiles were removed in vacuo. EtOAc (75 mL) was added, the phases were separated, and the aqueous layer was washed with EtOAc (2 x 75 mL). The combined organic phases were dried over $MgSO_4$, and volatiles were removed in vacuo. The so-obtained orange oil was purified through silica gel chromatography (0% → 10% EtOAc in hexanes) to afford **3.27** as colorless oil (2.33 g, 6.64 mmol, 66% yield). The spectral data of this compound are consistent with those previously reported.

(((1*R*,2*R*,4a*S*,8a*S*)-1-(iodomethyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-yl)oxy)trimethylsilane (3.28): Under N_2 atmosphere, A 25 mL round-bottom flask equipped with a magnetic stir bar was charged with **3.27** (5.87 g, 16.7 mmol), 2,6-lutidine (7.18 g, 67 mmol), and CH_2Cl_2 (170 mL). Under cooling to 0 °C, TMSOTf (7.45 g, 33.5 mmol) was added, and the mixture was allowed warm to 22 °C. After 3 h, a saturated aqueous solution of NH_4Cl (100 mL) was added. The phases were separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, and the volatiles were removed in vacuo. The so-obtained oil was purified through silica gel chromatography (0% → 5% EtOAc in hexanes) to afford **3.28** a colorless oil (6.55 g, 15.5 mmol, 93% yield). **IR (neat):** 2944 (w), 2921 (w), 2867 (w), 2843 (w), 1458 (m), 1247 (m), 1048 (s), 1066 (m), 877 (m), 834 (s), 750 (m), 642 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.50 (dd, *J* = 10.1, 2.5 Hz, 1H), 3.02 (dd, *J* = 10.1, 4.8 Hz, 1H), 1.91 – 1.79 (m, 2H), 1.68 – 1.44 (m, 4H), 1.41 – 1.23 (m, 3H), 1.23 – 1.14 (m, 2H),

1.11 (d, J = 0.9 Hz, 3H), 0.96 (dd, J = 12.3, 2.2 Hz, 1H), 0.86 (s, 3H), 0.78 (s, 3H), 0.77 (s, 3H), 0.15 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 77.8, 66.2, 56.0, 44.1, 41.9, 40.3, 40.1, 33.5, 33.3, 24.2, 21.6, 20.4, 18.6, 14.9, 3.0, -0.9.

(1*R*,2*R*,4a*S*,8a*S*)-1-(3-Methoxyallyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (3.32): Under N_2 atmosphere, a 500 mL round-bottom flask equipped with a magnetic stir bar was charged with (methoxymethyl)triphenylphosphonium chloride (20.6 g, 60 mmol) and THF (120 mL). The mixture was allowed to cool to 0 °C, after which, potassium *tert*-butoxide (6.28 g, 56 mmol) was added, and the mixture was allowed to stir at this temperature for 1 h. Subsequently, a solution of **3.25** (10.01 g, 40 mmol) in THF (50 mL) was added, and the mixture was allowed to warm to 22 °C and keep stirring for 12 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (100 mL). The phases were separated, and the aqueous layer was washed with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, and the volatiles were removed in vacuo. The so-obtained yellow oil was purified through silica gel chromatography (1% MeOH in $CHCl_3$) to afford **3.32** as colorless oil (10.9 g, 38.9 mmol, 97%, 67:33 *E*:*Z*). **IR (neat):** 3464 (br), 2989 (m), 2921 (s), 2864 (m), 1650 (m), 1458 (m), 1363 (m), 1261 (s), 1126 (m), 1105 (m), 1081 (m), 910 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 6.32 (dt, J = 12.6, 1.3 Hz, 1H), 4.89 – 4.81 (m, 1H), 3.61 (s, 3H), 2.40 – 1.87 (m, 3H), 1.84 (dt, J = 12.2, 3.1 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.67 – 1.51 (m, 2H), 1.49 – 1.31 (m, 3H), 1.30 – 1.20 (m, 2H), 1.21 – 1.17 (m, 2H), 1.12 (dt, J = 13.6, 4.1 Hz, 1H), 0.99 – 0.89 (m, 2H), 0.87 (d, J = 1.4 Hz, 3H), 0.80 (s, 3H), 0.79 (s, 3H); *Z* isomer (resolved signals only): δ 5.84 (dt, J = 6.1, 1.4 Hz, 1H), 4.56 (dt, J = 9.1, 6.3 Hz, 1H), 3.49 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** major isomer: δ 147.0, 106.0, 74.7, 62.5, 59.7, 56.3, 56.1, 44.2, 42.0, 40.2,

39.1, 33.6, 24.5, 21.7, 20.4, 19.5, 18.7, 15.4; minor isomer (resolved signals only): 145.4, 109.8, 74.0, 63.0, 56.3, 43.4, 42.0, 40.1, 38.9, 33.4, 24.5, 23.3, 20.4, 15.3; **HRMS [M+H−H_2O]$^+$** calcd for $C_{18}H_{31}O$: 263.2369, found: 263.2373.

(4a*S*,6a*S*,10a*S*)-4a,7,7,10a-Tetramethyldodecahydro-1*H*-benzo[*f*]chromen-3-ol (3.33): In a 250 mL round-bottom flask equipped with a magnetic stir bar, **3.32** (10.9 g, 38.9 mmol) was dissolved in glacial acetic acid (250 mL). After addition of H_2O (75 mL), the mixture was allowed to stir for 45 min at 60 °C. After cooling to 22 °C, H_2O (75 mL) was added, resulting in precipitation of an off-white solid. The suspension was filtered through a Büchner funnel, and the so-obtained solid was washed with H_2O (3 x 200 mL) and dried under vacuum. Recrystallization (toluene) afforded **3.33** as colorless needles (34.6 mg, 9.22 mmol, 89% yield). **IR (neat):** 3359 (br), 2943 (m), 2915 (m), 2864 (s), 2840 (m), 1457 (m), 1382 (m), 1361 (w), 1121 (s), 1112 (s), 1056 (m), 1042 (m), 867 (w), 608 (br), 527 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.03 – 4.94 (m, 1H), 3.08 (d, *J* = 6.9 Hz, 1H), 2.01 (dq, *J* = 12.5, 2.9 Hz, 1H), 1.80 (dt, *J* = 12.2, 3.3 Hz, 1H), 1.73 – 1.21 (m, 14H), 1.14 (td, *J* = 13.5, 4.2 Hz, 1H), 1.00 – 0.82 (m, 5H), 0.79 (s, 3H), 0.73 (s, 3H); isomer (resolved signals only): δ 5.28 (s, 1H), 2.62 (t, *J* = 2.2 Hz, 1H), 1.94 – 1.85 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 90.8, 76.6, 56.6, 56.3, 42.0, 41.6, 39.2, 36.7, 34.9, 33.3, 33.2, 21.3, 21.0, 19.6, 18.6, 17.8, 15.5; isomer (resolved signals only): δ 92.2, 75.9, 57.8, 56.5, 42.3, 42.1, 39.1, 37.0, 33.3, 32.3, 25.1, 21.3, 19.5, 15.8, 13.6; **HRMS [M+H−H_2O]$^+$** calcd for $C_{17}H_{29}O$: 249.2213, found: 249.2214; **m.p.** 197−199 °C; **Specific rotation**: $[\alpha]_D^{20.0}$ −9.7 (*c* 1.37, $CHCl_3$).

(1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1-(4-methylpent-3-en-1-yl)decahydronaphthalen-2-ol (3.34): Under N_2 atmosphere, in a 1 L round-bottom flask

equipped with a magnetic stir bar, isopropyltriphenylphosphonium iodide (49.4 g, 34.6 mmol) was suspended in DMSO (500 mL). NaH (2.49 g, 104 mmol) was added in portions, and the mixture was allowed to stir for 1 h at 50 °C. Subsequently, **3.33** (9.22 mg, 34.6 mmol) was added in one portion, and the mixture was allowed to stir for 16 h at 50 °C. The reaction was quenched by addition of H_2O (150 mL) and HCl (1 M, 100 mL, 100 mmol). The phases were separated, and the aqueous phase was washed with EtOAc (3 x 150 mL). The combined organic phases were dried over $MgSO_4$, and the volatiles were removed in vacuo. The so-obtained yellow oil was purified through silica gel chromatography (0% → 10% EtOAc in hexanes) to afford **3.34** as colorless solid (8.40 g, 28.7 mmol, 83% yield). **IR (neat):** 3313 (br), 2916 (s), 2860 (m), 1456 (m), 1384 (m), 1155 (w), 1124 (m), 1083 (m), 937 (m), 653 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.20 – 5.14 (m, 1H), 2.05 (q, *J* = 7.9 Hz, 2H), 1.87 (dt, *J* = 11.9, 3.0 Hz, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.68 – 1.53 (m, 6H) , 1.49 – 1.20 (m, 6H), 1.19 – 1.10 (m, 5H), 1.06 – 0.89 (m, 3H), 0.87 (s, 3H), 0.79 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 131.8, 125.5, 74.2, 61.7, 56.3, 44.7, 42.2, 39.9, 39.3, 33.6, 33.4, 31.7, 25.8, 25.7, 24.0, 21.7, 20.7, 18.6, 18.0, 15.6; **HRMS [M+H−H_2O]$^+$** calcd for $C_{20}H_{35}$: 275.2733, found: 275.2734; **m.p.** 86−88 °C; **Specific rotation**: $[\alpha]_D^{20.0}$ −7.1 (*c* 2.83, $CHCl_3$).

(1*R*,2*R*,4a*S*,8a*S*)-1-((*E*)-4-Bromopent-3-en-1-yl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (3.36): In a N_2-filled glovebox, a 6-dram vial equipped with a magnetic stir bar was charged with **3.34** (1.46 g, 5.0 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.92 g, 15 mmol), benzene (0.5 mL), and NEt_3 (7.0 μL, 0.05 mmol), sequentially. The mixture was allowed to stir until gas evolution ceased, after which, the vial was sealed, and the mixture was allowed to stir for 2 h at 90 °C.

Subsequently, the mixture was allowed to cool to 50 °C, and the volatiles were removed in vacuo. Then, ***E*-1** (3.38 g, 25 mmol), *cis*-3-hexene in benzene (1.0 M, 150 μL, 0.15 mmol), and **Mo-1** in benzene (0.1 M, 1.5 mL, 0.15 mmol) were added, the vial was capped, and the mixture was allowed to stir for 12 h at 22 °C. The reaction was quenched by addition of MeOH (5 mL), and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 78% consumption of **3.34**. The so-obtained brown solid was purified through silica gel chromatography (0% → 10% EtOAc in hexanes) to afford **3.36** as colorless solid (1.27 g, 3.56 mmol, 71%, 92:8 *E*:*Z*). **IR (neat):** 3327 (br), 2919 (s), 2851 (m), 1457 (w), 1259 (m), 1096 (m), 906 (m), 733 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.88 (tq, *J* = 7.7, 1.4 Hz, 1H), 2.22 (d, *J* = 1.2 Hz, 3H), 2.20 – 2.01 (m, 2H), 1.87 (dt, *J* = 12.0, 3.1 Hz, 1H), 1.71 – 1.29 (m, 8H), 1.29 – 1.20 (m, 1H), 1.19 – 1.09 (m, 4H), 1.02 (t, *J* = 4.1 Hz, 1H), 1.00 – 0.88 (m, 3H), 0.87 (s, 3H), 0.79 (s, 3H), 0.78 (s, 3H); *Z* isomer (resolved signals only): δ 5.67 (t, *J* = 7.1 Hz, 1H), 2.27 (d, *J* = 1.3 Hz, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 133.1, 119.3, 74.3, 61.4, 56.3, 44.9, 42.1, 39.9, 39.2, 33.5, 33.4, 33.1, 25.1, 24.1, 23.4, 21.6, 20.7, 18.6, 15.5; **HRMS [M+H−H_2O]$^+$** calcd for $C_{19}H_{32}Br$: 339.1682, found: 339.1675; **m.p.** 100−103 °C; **Specific rotation**: $[\alpha]_D^{20.0}$ +4.8 (*c* 1.39, $CHCl_3$).

(((1*R*,2*R*,4a*S*,8a*S*)-1-((*E*)-4-Bromopent-3-en-1-yl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-yl)oxy)triethylsilane (3.37): A 6-dram vial equipped with a magnetic stir bar was charged with **3.36** (750 mg, 2.1 mmol), imidazole (572 mg, 8.4 mmol), and DMF (20 mL). The mixture was allowed to cool to 0 °C, after which TESCl (633 mg, 4.2 mmol) was added in a dropwise manner over the course of 5 min. The mixture was allowed to warm to 22 °C and stir for 12 h. The reaction was

quenched by addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was washed with pentane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, and the volatiles were removed in vacuo. The so-obtained faint yellow oil was purified through silica gel chromatography (pentane) to afford **3.37** as colorless oil (981 mg, 2.08 mmol, >98% yield). **IR (neat):** 2947 (m), 2871 (m), 1456 (w), 1378 (w), 1132 (m), 1099 (s), 1082 (s), 1052 (s), 971 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.85 (t, *J* = 7.6 Hz, 1H), 2.21 (d, *J* = 1.2 Hz, 3H), 2.19 – 1.94 (m, 2H), 1.87 (dt, *J* = 12.1, 3.2 Hz, 1H), 1.71 – 1.31 (m, 7H), 1.29 – 1.05 (m, 7H), 0.98 – 0.88 (m, 11H), 0.86 (d, *J* = 2.2 Hz, 3H), 0.77 (s, 3H), 0.76 (s, 3H), 0.61 – 0.52 (m, 6H); *Z* isomer (resolved signals only): δ 5.63 (t, *J* = 6.9 Hz, 1H), 2.26 (q, *J* = 1.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** *E* isomer (major): δ 133.5, 118.8, 77.5, 62.2, 56.2, 44.5, 42.1, 40.0, 39.1, 35.2, 33.5, 33.3, 25.5, 24.8, 23.4, 21.6, 20.7, 18.6, 15.7, 7.4, 7.2; *Z* isomer (resolved signals only): δ 130.2, 121.4, 28.9, 24.6; **HRMS [M]$^+$** calcd for $C_{25}H_{47}OSiBr$: 470.2574, found: 470.2575; **Specific rotation**: $[\alpha]_D^{20.0}$ +552.3 (*c* 2.12, $CHCl_3$).

3,3-Dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (3.38): This compound was synthesized according to a modified procedure by Ishihara *et al*.[16] Under N_2 atmosphere, a 250 mL flask equipped with a magnetic stir bar was charged with CuI (9.52 g, 50 mmol) and Et_2O (50 mL). The mixture was allowed to cool to 0 °C, after which, a solution of MeLi in Et_2O (1.6 M, 62.5 mL, 100 mmol) was added in a dropwise manner over the course of 10 min. Upon complete addition, the mixture was allowed to stir at this temperature for 30 min. Subsequently, the mixture was allowed to cool to −78 °C, and a solution of freshly distilled **3.24** (5.51 g, 50 mmol) in THF (50 mL) was added in a dropwise manner over the course of 30 min. The resultant mixture was allowed to stir at this temperature for 2 h, then

allowed to warm to 0 °C and stirred at this temperature for another 2 h. At 0 °C, a solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (19.7 g, 55 mmol) in THF (125 mL) was added through a cannula, and the mixture was allowed to stir for 3 h at 0 °C, followed by 12 h at 22 °C. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (100 mL). The phases were separated, and the aqueous phase was washed with hexanes (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, and the volatiles were removed in vacuo. The so-obtained oil was purified through filtration through a short silica gel plug and distillation over CaH_2 (0.5 Torr, 35 °C). **3.38** was obtained as colorless oil (9.57 g, 37.1 mmol, 74% yield). The spectral data of this compound are consistent with those previously reported.

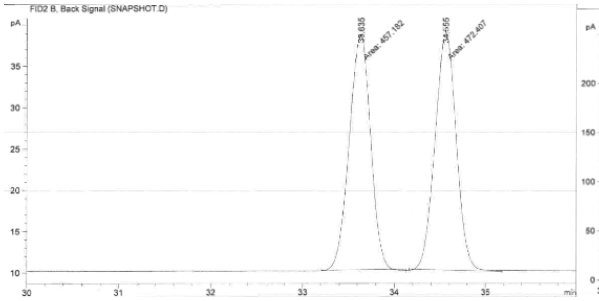
(3,3-Dimethylcyclohex-1-en-1-yl)methanol (3.39): In a N_2-filled glovebox, an oven-dried 6-dram vial equipped with a magnetic stir bar was charged with **3.38** (129 mg, 0.5 mmol), THF (8.0 mL), and LiCl (42 mg, 1.0 mmol), and the mixture was allowed to stir for 5 min. Then, $Pd(PPh_3)_4$ (58.0 mg, 0.05 mmol) and (tributylstannyl)methanol (312 mg, 1.0 mmol) were added, the vial was capped, and the mixture was allowed to stir for 2 h at 65 °C. The reaction was quenched by addition of undistilled Et_2O (5 mL), and the volatiles were removed in vacuo. The so-obtained oil was purified through silica gel chromatography (0% → 10% EtOAc in hexanes) to afford **3.39** as colorless oil (50.3 mg, 0.36 mmol, 72% yield). **IR (neat):** 3310 (br), 2949 (s), 2924 (s), 2860 (s), 1465 (m), 1358 (m), 1203 (w), 1065 (s), 1028 (s), 866 (m), 852 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.38 (t, *J* = 1.6 Hz, 1H), 3.96 (s, 2H), 1.93 (t, *J* = 6.5 Hz, 2H), 1.69 – 1.59 (m, 2H), 1.44 (br, 1H), 1.43 – 1.36 (m, 2H), 0.96 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.3, 133.3, 67.7,

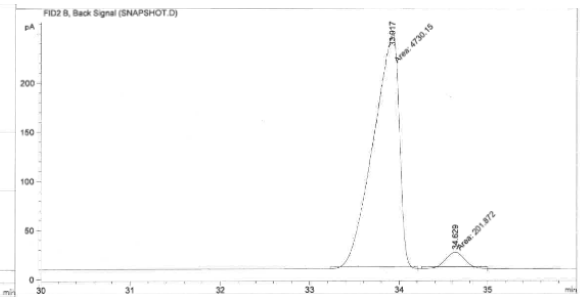
37.3, 31.6, 30.0, 25.8, 19.7, 19.7; **HRMS [M+H−H_2O]$^+$** calcd for C_9H_{15}: 123.1168, found: 123.1170.

(3,3-Dimethylcyclohex-1-en-1-yl)methyl diethyl phosphate (3.40): A 6-dram vial equipped with a magnetic stir bar was charged with **3.39** (106 mg, 0.75 mmol), DMAP (18.3mg, 0.15 mmol), and CH_2Cl_2 (4 mL). The resultant solution was allowed to cool to −10 °C, after which diethyl chlorophosphate (0.16 mL, 1.13 mmol) was added. Upon complete addition, the mixture was allowed to reach 22 °C and stir at this temperature for 12 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL), the phases were separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, and the volatiles were removed in vacuo. The so obtained oil was purified by silica gel chromatography (1% NEt_3 in CH_2Cl_2) to afford **3.40** as colorless oil (191 mg, 0.69 mmol, 92% yield). **IR (neat):** 2930 (w), 2863 (w), 1262 (m), 1024 (s), 969 (s), 730 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.48 (s, 1H), 4.36 (d, *J* = 7.2 Hz, 2H), 4.15 – 4.04 (m, 4H), 1.96 (t, *J* = 6.3 Hz, 2H), 1.69 – 1.60 (m, 2H), 1.43 – 1.37 (m, 2H), 1.33 (td, *J* = 7.1, 1.0 Hz, 6H), 0.96 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 136.8, 131.1 (d, *J* = 6.9 Hz), 72.0 (d, *J* = 5.8 Hz), 63.7 (d, *J* = 5.8 Hz), 37.0, 31.8, 29.7, 25.6, 19.5, 16.3 (d, *J* = 6.9 Hz); **^{31}P NMR (162** MHz, $CDCl_3$) δ −0.74; **HRMS [M+H]$^+$** calcd for $C_{13}H_{26}O_4P$: 277.1563, found: 277.1548.

(*S*)-1,1-Dimethyl-3-methylene-2-vinylcyclohexanes (3.41): In a N_2-filled glovebox, four oven-dried 2-dram vials, each equipped with a magnetic stir bar, were each charged with CuCl (5.0 mg, 0.05 mmol), **(*S*)-Imid-1** (47.3 mg, 0.55 mmol), NaOMe (54.0 mg, 1.0 mmol), and THF (5.0 mL). The resultant suspensions were allowed to stir for 1 h at 22 °C. Subsequently, to each vial vinylB(pin) (154 mg, 1.0 mmol) and **3.40** (138 mg, 0.5 mmol)

were added, and the mixtures were allowed to stir for 24 h at 60 °C. The reaction was quenched by addition of undistilled Et_2O (1 mL), and the reaction mixtures were combined. The combined mixtures were allowed to cool to 0 °C, and volatiles were removed in vacuo. The so-obtained brown oil was purified through silica gel chromatography (pentane) to afford **3.41** as volatile colorless oil (241mg, 1.46 mmol, 73% yield, 96:4 er). **IR (neat):** 2926 (s), 2863 (m), 1643 (w), 912 (m), 890 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.93 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.08 (dd, *J* = 10.2, 2.3 Hz, 1H), 5.02 (dd, *J* = 16.8, 2.1 Hz, 1H), 4.74 (s, 1H), 4.58 (s, 1H), 2.42 (d, *J* = 9.6 Hz, 1H), 2.27 (dt, *J* = 13.3, 5.4 Hz, 1H), 2.10 – 1.97 (m, 1H), 1.61 – 1.53 (m, 2H), 1.52 – 1.44 (m, 1H), 1.37 – 1.25 (m, 2H), 0.90 (s, 3H), 0.81 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.4, 137.8, 116.6, 108.4, 59.2, 39.3, 35.1, 34.8, 29.6, 23.6, 23.4; **HRMS [M+H]$^+$** calcd for $C_{11}H_{19}$: 151.1486, found: 151.1481; Enantiomeric purity of **3.41** was determined by GC analysis in comparison with authentic racemic material; alpha-dex column, 50–150 °C, 10 psi. **Specific rotation**: $[\alpha]_D^{20.0}$ +12.9 (*c* 1.03, $CHCl_3$) for a sample of 96:4 er.





Retention time	Area	Area%
33.635	457.18	49.18
34.555	472.41	50.82

Retention time	Area	Area%
33.917	4730.15	95.91
34.629	201.87	4.09

(*S*)-2-(2-(2,2-dimethyl-6-methylenecyclohexyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.44): Under N_2 atmosphere, a 1-dram vial equipped with a magnetic stir

bar was charged with $[Ir(cod)Cl]_2$ (2.0 mg, 30 μmol), dppe (2.4 mg, 60 μmol), and CH_2Cl_2 (0.36 mL). The mixture was allowed to stir for 5 min at 22 °C. Then, HB(pin) (16.7 mg, 0.12 mmol) and **3.41** (15.0 mg, 0.1 mmol) were added and the mixture was allowed to stir 19 h at 22 °C. Volatiles were removed in vacuo, and the residue was purified through silica gel chromatography (0% → 3% Et_2O in hexanes) to afford **3.44** as colorless oil (14.7 mg, 0.053 mmol, 53% yield, 85:15 cr). **IR (neat):** 2973 (w), 2926 (w), 2864 (w), 1455 (w), 1369 (s), 1315 (s), 1269 (m), 1143 (s), 1109 (w), 967 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** major isomer: δ 4.74 (d, *J* = 2.1 Hz, 1H), 4.53 (d, *J* = 2.6 Hz, 1H), 2.10 – 2.00 (m, 1H), 2.00 – 1.92 (m, 1H), 1.92 – 1.66 (m, 2H), 1.65 – 1.57 (m, 3H), 1.25 – 1.22 (m, 12H), 1.18 – 1.00 (m, 2H), 0.98 – 0.92 (m, 2H), 0.90 (s, 3H), 0.85 (s, 3H); minor isomer (resolved signals only): δ 5.68 – 5.53 (m, 1H), 5.44 – 5.31 (m, 1H), 5.05 – 4.89 (m, 1H); **^{11}B NMR (128 MHz, $CDCl_3$):** δ 34.18; **^{13}C NMR (100 MHz, $CDCl_3$):** major isomer: δ 149.0, 109.4, 82.7, 65.8, 56.5, 34.8, 28.4, 24.9, 24.8, 23.6, 20.4, 15.3; **HRMS [M]$^+$** calcd for $C_{17}H_{31}BO_2$: 279.2490, found: 279.2500.

(*S*)-(2-(2,2-dimethyl-6-methylenecyclohexyl)ethyl)trifluoro-λ4-borane, potassium salt (3.45): In a 10 mL round-bottom flask equipped with a magnetic stir bar, **3.44** (51.3 mg, 0.18 mmol) was dissolved in EtOAc (3 mL) and MeOH (2 mL). Under cooling to 0 °C, a saturated aqueous solution of KHF_2 (1.8 mL, 8.0 mmol) was added dropwise over the course of 5 min. The mixture was allowed to reach 22 °C and stir for 1 h at this temperature. Subsequently, volatiles were removed in vacuo and the residue was dried azeotropically (toluene, 40 mL). The so-obtained colorless powder was dissolved in boiling acetone, filtered, and the residue was washed with hexanes (3 x 20 mL). **3.45** was obtained as colorless solid (28.6 mg, 0.11 mmol, 62% yield). **^{1}H NMR (400 MHz, acetone-d_6):** δ 4.66

(d, J = 2.4 Hz, 1H), 4.51 (d, J = 3.1 Hz, 1H), 2.83 – 2.75 (m, 1H), 1.91 (dt, J = 12.3, 4.6 Hz, 1H), 1.59 (dd, J = 11.4, 3.4 Hz, 1H), 1.54 – 1.44 (m, 5H), 1.34 – 1.25 (m, 2H), 1.24 – 1.13 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H); **^{11}B NMR (128 MHz, acetone-d_6):** δ 4.61; **^{19}F NMR (376 MHz, acetone-d_6):** δ 144.12 (3F); **HRMS [M]$^+$** calcd for $C_{11}H_{19}BF_3K$: 258.1169, found: not detected.

(*S*)-2-(2-iodoethyl)-1,1-dimethyl-3-methylenecyclohexane (3.46): Under N_2 atmosphere, a 1-dram vial equipped with a magnetic stir bar was charged with Cp_2ZrHCl (28.4 mg, 0.11 mmol) and CH_2Cl_2 (200 µL). Then, a solution of **3.41** (15 mg, 0.1 mmol) in CH_2Cl_2 (200 µL) was added, and the mixture was allowed to stir for 3 h at 22 °C. Subsequently, a solution of I_2 (38.1 mg, 0.15 mmol) in THF (400 µL) was added, and the reaction was allowed to stir for 2 h at 22 °C. The reaction was quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (0.5 mL), and the phases were separated. The aqueous layer was washed with CH_2Cl_2 (3 x 1 mL), and the combined organic layers were dried over $MgSO_4$. The so obtained oil was purified by silica gel chromatography (pentane) to afford **3.46** as colorless oil (11.7 mg, 0.042 mmol, 42% yield). The spectral data of this compound are consistent with those previously reported.[40]

(((1*R*,2*R*,4a*S*,8a*S*)-1-((*E*)-6-((*S*)-2,2-dimethyl-6-methylenecyclohexyl)-4-methylhex-3-en-1-yl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-yl)oxy)triethylsilane (3.48): Under N_2 atmosphere, a 1-dram vial equipped with a magnetic stir bar was charged with **3.37** (28.3 mg, 0.06 mmol) and THF (200 µL). Under cooling to –78 °C, a solution of *t*-BuLi (1.65 M in hexanes, 75 µL, 0.12 mmol) was added dropwise over the course of 2 min. The mixture was allowed to stir for 30 min at –78 °C. Then, a solution of lithium 2-

(40) Maier, M. E.; Bayer, A. *Eur. J. Org. Chem.* **2006**, *2006*, 4034–4043.

thienylcyanocuprate (0.25 M in THF, 480 μL, 0.12 mmol) was added, and the solution was allowed to stir for 15 min at –78 °C. Subsequently, a solution of **3.46** (11.1 mg, 0.04 mmol) in THF (200 μL) was added dropwise over the course of 5 min, and the mixture was allowed to reach 22 °C. After 16 h, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (2 mL). The phases were separated, and the aqueous phase was washed with Et_2O (3 x 2 mL). The combined organic phases were dried over $MgSO_4$, and the volatiles were removed in vacuo. The so obtained residue was purified by silica gel chromatography (hexanes) to afford **3.48** as colorless oil (3.6 mg, 8.4 μmol, 21% yield, 90:10 rr). The spectral data of this compound are consistent with those obtained through a later route.

(*S*)-(2-(2,2-dimethyl-6-methylenecyclohexyl)ethyl)trimethylsilane (3.55): In a N_2-filled glovebox, a 2-dram vial equipped with a magnetic stir bar was charged with CuCl (1.0 mg, 0.01 mmol), **(*S*)-Imid-1** (9.5 mg, 0.011 mmol), NaOMe (10.8 mg, 0.2 mmol), and THF (1.0 mL). The suspension was allowed to stir for 1 h at 22 °C. Then, **3.55'** (44.5 mg, 0.2 mmol) and **3.40** (27.6 mg, 0.1 mmol) were added, and the mixture was allowed to stir for 16 h at 60 °C. After cooling to 22 °C, volatiles were removed in vacuo, and the so-obtained residue was purified through silica gel chromatography (hexanes) to afford **3.55** as colorless oil (21.7 mg, 0.097 mmol, 97% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.77 (d, *J* = 2.5 Hz, 1H), 4.51 (d, *J* = 2.6 Hz, 1H), 1.99 (t, *J* = 5.7 Hz, 2H), 1.62 (dd, *J* = 11.3, 3.5 Hz, 1H), 1.57 – 1.40 (m, 4H), 1.24 – 1.15 (m, 1H), 0.92 (s, 3H), 0.84 (s, 3H), 0.50 (ddd, *J* = 14.5, 12.7, 4.2 Hz, 1H), 0.19 (ddd, *J* = 14.5, 12.4, 5.0 Hz, 1H), -0.03 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.4, 109.2, 57.6, 35.2, 31.8, 28.8, 23.9, 22.8, 20.3, 15.0, 14.3, -1.5.

(*S*)-(2-(2,2-dimethyl-6-methylenecyclohexyl)ethyl)dimethyl(phenyl)silane (3.57): In a N_2-filled glovebox, a 2-dram vial equipped with a magnetic stir bar was charged with CuCl (1.0 mg, 0.01 mmol), **(*S*)-Imid-1** (9.5 mg, 0.011 mmol), NaOMe (10.8 mg, 0.2 mmol), and THF (1.0 mL). The suspension was allowed to stir for 1 h at 22 °C. Then, **3.57'** (56.9 mg, 0.2 mmol) and **3.40** (27.6 mg, 0.1 mmol) were added, and the mixture was allowed to stir for 16 h at 60 °C. After cooling to 22 °C, volatiles were removed in vacuo, and the so-obtained residue was purified through silica gel chromatography (hexanes) to afford **3.57** as colorless oil (20.7 mg, 0.072 mmol, 72% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.55 – 7.47 (m, 2H), 7.40 – 7.32 (m, 3H), 4.78 (d, *J* = 2.5 Hz, 1H), 4.51 (d, *J* = 2.6 Hz, 1H), 1.97 (t, *J* = 6.1 Hz, 2H), 1.63 (dd, *J* = 11.3, 3.4 Hz, 1H), 1.54 – 1.48 (m, 2H), 1.46 – 1.27 (m, 3H), 1.18 (dt, *J* = 13.2, 4.7 Hz, 1H), 0.90 (s, 3H), 0.85 – 0.74 (m, 4H), 0.47 (ddd, *J* = 14.8, 12.3, 5.0 Hz, 1H), 0.26 (d, *J* = 1.3 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.2, 139.9, 133.7, 128.9, 128.5, 127.8, 127.8, 109.4, 57.5, 36.3, 35.2, 32.5, 28.7, 23.9, 20.3, 14.0, -2.8, -2.9.

(*S*)-2-(2,2-dimethyl-6-methylenecyclohexyl)ethan-1-ol (3.59): In a N_2-filled glovebox, a 2-dram vial equipped with a magnetic stir bar was charged with CuCl (1.0 mg, 0.01 mmol), **(*S*)-Imid-1** (9.5 mg, 0.011 mmol), NaOMe (10.8 mg, 0.2 mmol), and THF (1.0 mL). The suspension was allowed to stir for 1 h at 22 °C. Then, **3.58'** (50.4 mg, 0.2 mmol) and **3.40** (27.6 mg, 0.1 mmol) were added, and the mixture was allowed to stir for 16 h at 60 °C. After cooling to 22 °C, volatiles were removed in vacuo, and the so-obtained residue was purified through silica gel chromatography (hexanes) to afford **3.58** as colorless oil, which was dissolved a 1:1 mixture of THF:MeOH (0.1 mL). Then, $KHCO_3$ (15.0 mg, 0.15 mmol), KF (17.4 mg, 0.3 mmol), and an aqueous solution of H_2O_2 (30%, 50 μL, 0.5 mmol) were

added. The mixture was allowed to stir for 22 h at 22 °C. The reaction was quenched by addition of an half-saturated aqueous solution of Na_2SO_3 (1 mL). The phases were separated, and the aqueous layer was washed with Et_2O (3 x 1 mL). The combined organic phases were dried over $MgSO_4$, and the volatiles were removed in vacuo. The so-obtained oil was purified through silica gel chromatography (0% → 50% Et_2O in hexanes) to afford **3.59** as colorless oil (16.4 mg, 0.097 mmol, 97% yield). The spectral data of this compound are consistent with those previously reported.[6]

(*S*)-2-(2-bromoethyl)-1,1-dimethyl-3-methylenecyclohexane (3.60): In a N_2-filled glovebox, a 2-dram vial equipped with a magnetic stir bar was charged with **3.59** (16.4 mg, 0.097 mmol) and CH_2Cl_2 (0.5 mL). Under cooling to 0 °C, CBr_4 (38.8 mg, 0.12 mmol), and PPh_3 (30.7 mg, 0.12 mmol) were added, and the mixture was allowed to reach 22 °C. After 3 h, volatiles were removed in vacuo, and the residue was purified through silica gel chromatography (hexanes) to afford **3.60** as colorless oil (15.0 mg, 0.065 mmol, 67% yield). The spectral data of this compound are consistent with those previously reported.[41]

(4*S*)-5,5-Dimethyl-4-vinyl-1-oxaspiro[2.5]octane (3.61): A 50 mL flask equipped with a magnetic stir bar was charged with **3.41** (301 mg, 2.0 mmol) and CH_2Cl_2 (20 mL). The mixture was allowed to cool to 0 °C, after which a mixture of *m*-CPBA (345 mg, 2.0 mmol) and $NaHCO_3$ (336 mg, 4.0 mmol) was added, and the resulting suspension was allowed to stir for 4 h at 0 °C. The reaction was quenched by addition of a saturated aqueous solution of Na_2SO_3 (20 mL), the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with aqueous NaOH (1 M, 1 x 25 mL) and H_2O (1 x 25 mL), dried over $MgSO_4$, and the volatiles were removed

(41) Crombie, B. S.; Smith, C.; Varnavas, C. Z.; Wallace, T. W. *J. Chem. Soc. Perkin 1* **2001**, 206–215.

in vacuo. The biphasic mixture was purified through silica gel chromatography (0% → 4% EtOAc in hexanes) to afford **3.61** as colorless oil (391 mg, 1.83 mmol, 92% yield, 74:26 dr). **IR (neat):** 2921 (s), 2851 (m), 1726 (m), 1455 (w), 1365 (w), 1286 (m), 1255 (m), 1073 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** major isomer: δ 5.71 – 5.60 (m, 1H), 5.13 – 5.08 (m, 1H), 5.08 – 4.99 (m, 1H), 2.61 (d, *J* = 5.1 Hz, 1H), 2.49 (d, *J* = 4.6 Hz, 1H), 1.86 (d, *J* = 9.9 Hz, 1H), 1.83 – 1.69 (m, 1H), 1.69 – 1.55 (m, 2H), 1.55 – 1.43 (m, 2H), 1.35 – 1.23 (m, 2H), 1.01 (s, 3H), 0.86 (s, 3H); minor isomer (resolved signals only): δ 5.11 (dd, *J* = 10.3, 2.4 Hz, 1H), 5.02 (dd, *J* = 17.1, 2.3 Hz, 1H), 2.60 (m, 1H), 2.39 (d, *J* = 5.0 Hz, 1H), 1.96 (d, *J* = 9.8 Hz, 1H), 0.95 (s, 3H), 0.91 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** mixture of major and minor diastereomer: δ 135.0, 134.7, 118.9, 118.8, 59.5, 59.0, 56.7, 55.1, 51.5, 51.0, 39.1, 37.7, 34.9, 33.1, 32.5, 31.7, 30.0, 29.2, 25.4, 23.7, 20.8, 20.3, 14.3; **HRMS [M+H]$^+$** calcd for $C_{11}H_{19}O$: 167.1430, found: 167.1432. **Specific rotation**: $[\alpha]_D^{20.0}$ −30.2 (*c* 0.33, $CHCl_3$).

(((1*R*,2*R*,4a*S*,8a*S*)-1-((*E*)-6-((4*S*)-5,5-Dimethyl-1-oxaspiro[2.5]octan-4-yl)-4-methylhex-3-en-1-yl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-yl)oxy)triethylsilane (3.63): In a N_2-filled glovebox, a 2-dram vial equipped with a magnetic stir bar was charged with **3.61** (33.3 mg, 0.63 mmol) and THF (1.2 mL). The solution was allowed to cool to −50 °C, and a solution of 9-BBN (81.1 mg, 0.67 mmol) in THF (1.8 mL) was added. The mixture was allowed to reach 22 °C and stir at this temperature for 4 h. Subsequently, $PdCl_2$(dppf) (13.8 mg, 0.019 mmol), **3.37** (253 mg, 0.54 mmol), and aqueous NaOH (3 M, 0.63 mL, 1.89 mmol) were added. The resultant suspension was allowed to heat to reflux under vigorous stirring for 12 h. The reaction mixture was allowed to cool to 22°C, and the so-obtained brown suspension was filtered

through a silica gel plug and eluted with hexanes. The volatiles were removed in vacuo and the resultant brown oil was purified through silica gel chromatography (0% → 4% EtOAc in hexanes) to afford **3.63** as colorless oil (262 mg, 0.47 mmol, 87% yield). **IR (neat):** 2933 (s), 2870 (s), 1457 (w), 1364 (w), 1085 (m), 1054 (m), 740 (m), 722 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** major diastereomer: δ 5.17 – 5.09 (m, 1H), 2.62 (d, *J* = 4.7 Hz, 1H), 2.49 (d, *J* = 4.8 Hz, 1H), 2.18 – 1.94 (m, 3H), 1.93 – 1.82 (m, 2H), 1.79 – 1.68 (m, 2H), 1.68 – 0.99 (m, 34H), 0.99 – 0.91 (m, 12H), 0.91 – 0.83 (m, 10H), 0.77 (d, *J* = 2.3 Hz, 6H), 0.57 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 134.4, 126.1, 62.5, 60.1, 56.2, 51.5, 49.8, 44.6, 42.2, 40.0, 40.0, 39.1, 35.7, 34.8, 33.6, 33.4, 32.2, 31.7, 28.8, 26.3, 25.6, 25.4, 24.9, 22.8, 21.6, 20.9, 20.8, 20.7, 18.7, 16.3, 15.8, 14.3, 7.5, 7.4, 7.3; **HRMS $[M+H]^+$** calcd for $C_{36}H_{67}O_2Si$: 559.4905, found: 559.4905; **Specific rotation**: $[\alpha]_D^{20.0}$ +269.9 (*c* 1.03, $CHCl_3$).

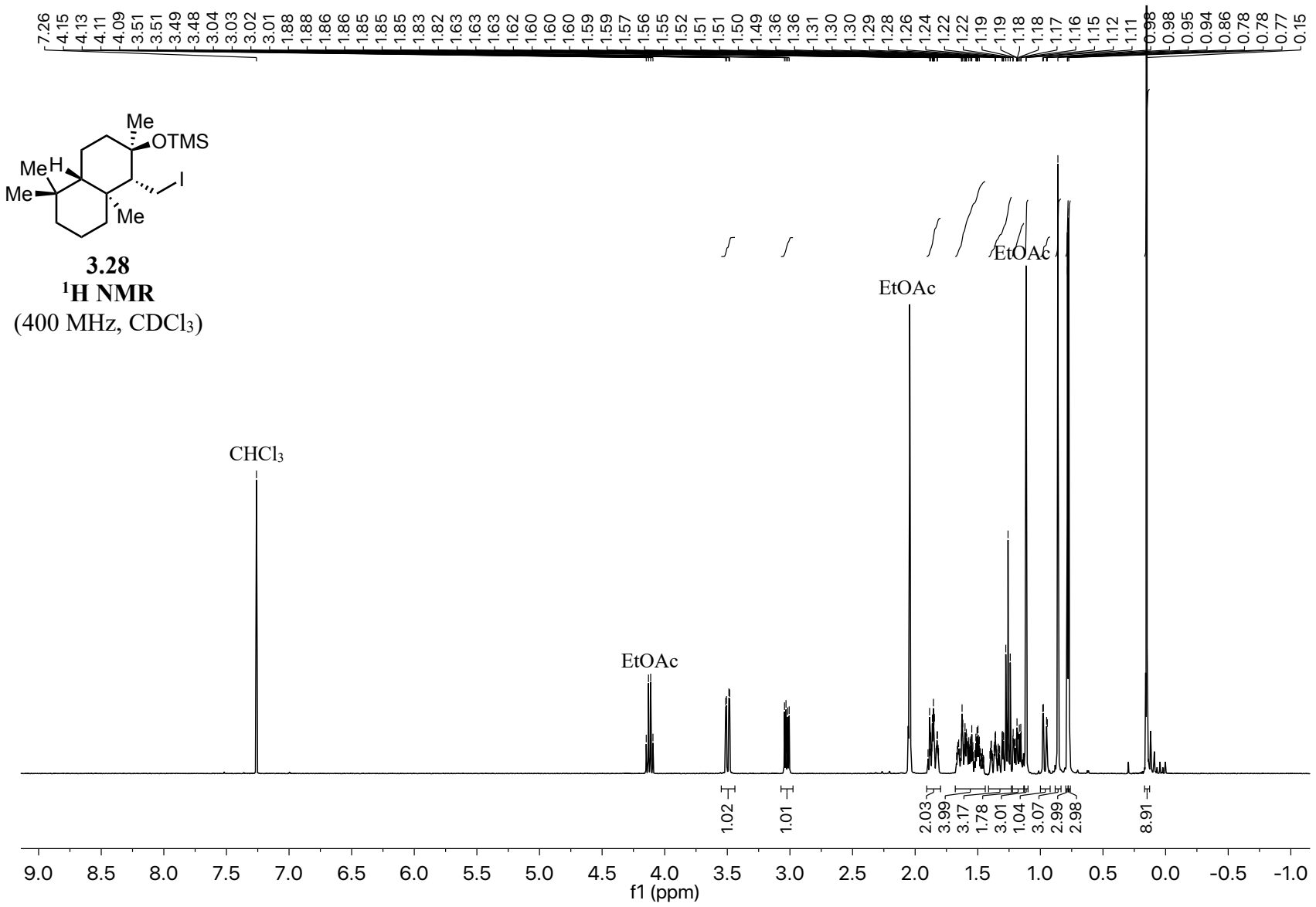
(((1*R*,2*R*,4a*S*,8a*S*)-1-((*E*)-6-((*S*)-2,2-Dimethyl-6-methylenecyclohexyl)-4-methylhex-3-en-1-yl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-yl)oxy)triethylsilane (3.48): A 5-dram vial equipped with a magnetic stir bar was charged with WCl_6 (55.9 mg, 140 μmol) and THF (3.0 mL). The mixture was allowed to cool to −78 °C, after which a solution of *n*-BuLi in hexanes (2.5 M, 115 μL, 280 μmol) was added in a dropwise manner over the course of 1 min. Upon complete addition, the mixture was allowed to reach 22 °C and stir at this temperature for 30 min. Subsequently, the mixture was cooled to 0 °C, and a solution of **3.63** (39.4 mg, 70.5 μmol) in THF (1.0 mL) was added in a dropwise manner over the course of 1 min. The mixture was allowed to reach 22 °C and stir at this temperature for 4 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (1 mL) and a saturated aqueous solution of potassium sodium tartrate (10 mL). The resulting

suspension was allowed to stir for 1 h at 22 °C. The phases were separated and the aqueous layer washed with CH_2Cl_2 (2 x 15 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and the volatiles were removed in vacuo. The so-obtained brown oil was purified through silica gel chromatography (hexanes) to afford **3.48** as colorless oil (24.4 mg, 44.9 μmol, 64% yield). **IR (neat):** 2930 (s), 2868 (s), 1457 (w), 1384 (w), 1155 (m), 1129 (m), 887 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.12 (t, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 2.3 Hz, 1H), 4.54 (d, *J* = 2.5 Hz, 1H), 2.14 – 1.82 (m, 6H), 1.78 – 1.31 (m, 17H), 1.30 – 1.07 (m, 9H), 1.01 – 0.88 (m, 13H), 0.86 (s, 3H), 0.84 (s, 3H), 0.77 (d, *J* = 2.5 Hz, 6H), 0.57 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.6, 134.7, 125.6, 108.9, 77.5, 62.5, 56.2, 53.8, 44.6, 42.2, 40.0, 39.1, 38.4, 36.5, 35.0, 33.6, 33.4, 32.7, 32.2, 28.6, 26.4, 26.3, 25.0, 24.9, 24.9, 23.9, 21.6, 20.8, 18.7, 15.8, 7.4, 7.3; **HRMS $[M+H]^+$** calcd for $C_{36}H_{67}OSi$: 543.4956, found: 543.4930.

Ambrein (3.1): To a 1-dram vial vial equipped with a magnetic stir bar was charged with **3.48** (24.4 mg, 44.9 μmol). A solution of TBAF in THF (1 M , 1 mL, 1.0 mmol) was added, and the mixture was allowed to stir at 22 °C for 24 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous phase was washed with Et_2O (3 x 5 mL), and the combined organic phases were dried over $MgSO_4$ and filtered. The so-obtained yellow oil was purified through silica gel chromatography (5% EtOAc in hexanes) to afford **3.1** as colorless oil (17.6 mg, 41.0 μmol, 91% yield) in 88:12 *E*:*Z* ratio. Upon further purification through preparatory TLC (3% EtOAc in toluene), **3.1** was isolated as colorless solid in (12.0 mg, 27.9 μmol, 62% yield, >98:2 *E*:*Z*). **IR (neat):** 3390 (br), 2923 (s), 2862 (m), 1643 (w), 1459 (w), 1384 (m), 887 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.16 (t, *J* = 7.5 Hz, 1H), 4.75 (s, 1H), 4.53 (s, 1H), 2.06 (q, *J* = 8.0

Hz, 2H), 2.02 – 1.90 (m, 2H), 1.87 (dt, *J* = 11.7, 3.0 Hz, 1H), 1.77 – 1.08 (m, 26H), 1.04 (t, *J* = 4.0 Hz, 1H), 0.99 (dt, *J* = 12.8, 3.7 Hz, 1H), 0.94 (m, 1H), 0.91 (m, 3H), 0.87 (s, 3H), 0.83 (s, 3H), 0.79 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.6, 136.0, 124.8, 109.0, 74.3, 61.7, 56.3, 53.9, 44.7, 42.2, 39.9, 39.3, 38.4, 36.5, 35.1, 33.6, 33.4, 32.7, 31.6, 28.6, 26.4, 25.7, 25.0, 24.0, 23.9, 21.7, 20.8, 18.6, 16.5, 15.6; **HRMS [M+H−H_2O]$^+$** calcd for $C_{30}H_{51}$: 411.3985, found: 411.3984; **Specific rotation**: $[\alpha]_D^{20.0}$ +14.6 (*c* 1.14, $CHCl_3$), lit. $[\alpha]_D^{21}$ +17.2 (*c* 2.00, $CHCl_3$)[7]; **m.p.** 78−80 °C.

3.9.6 NMR Spectra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OTMS
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H
I
Me
Me
3.28
1H NMR
(400 MHz, CDCl3)
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EtOAc
EtOAc
EtOAc
1.02
1.01
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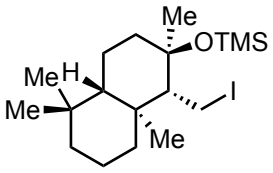
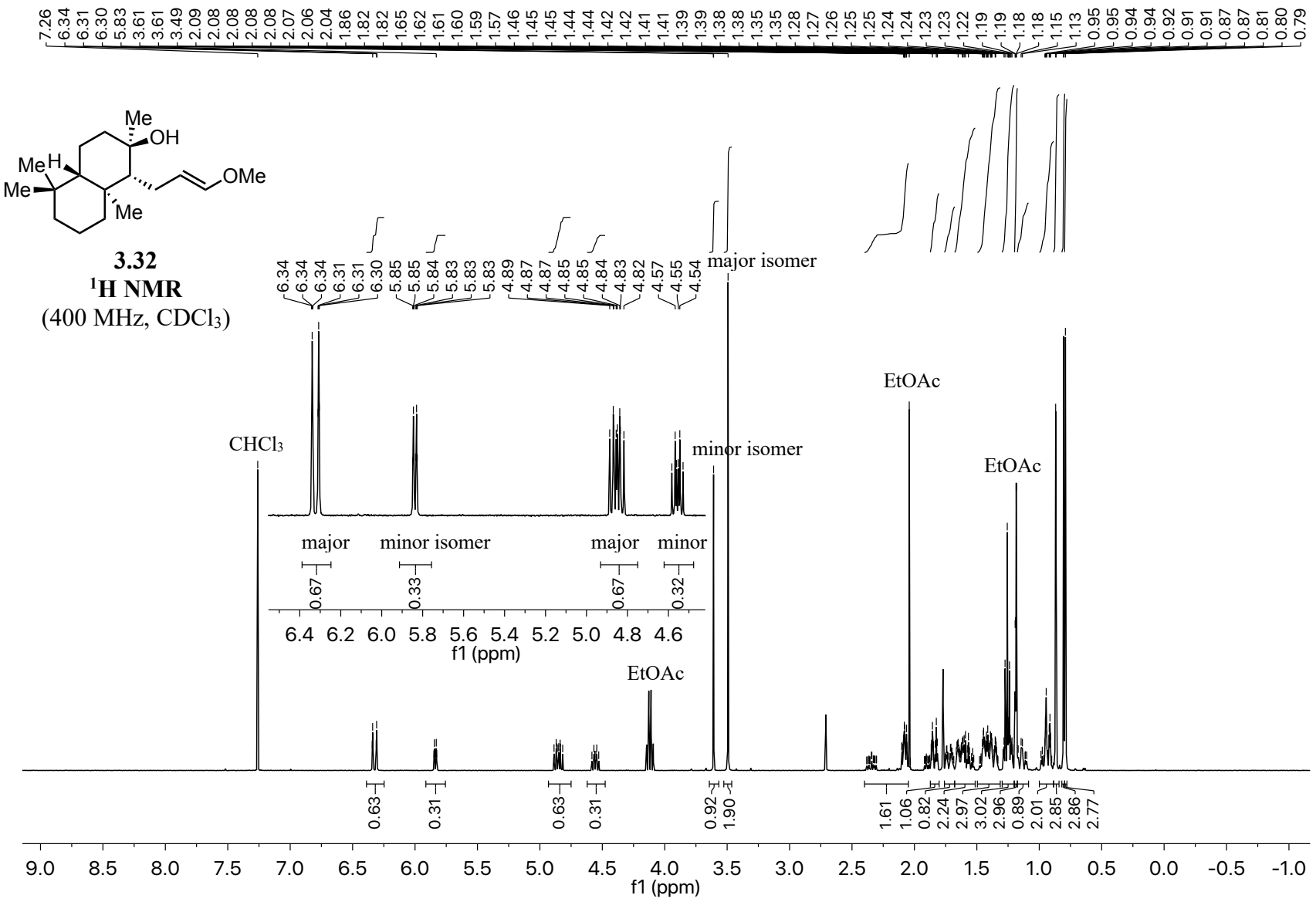
3.17
1.78
3.01
1.04
3.07
2.99
2.98
8.91
f1 (ppm)



3.28
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
OH
MeH
OMe
Me
Me
3.32
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
CHCl3
EtOAc
EtOAc
EtOAc
major
minor isomer
major
minor
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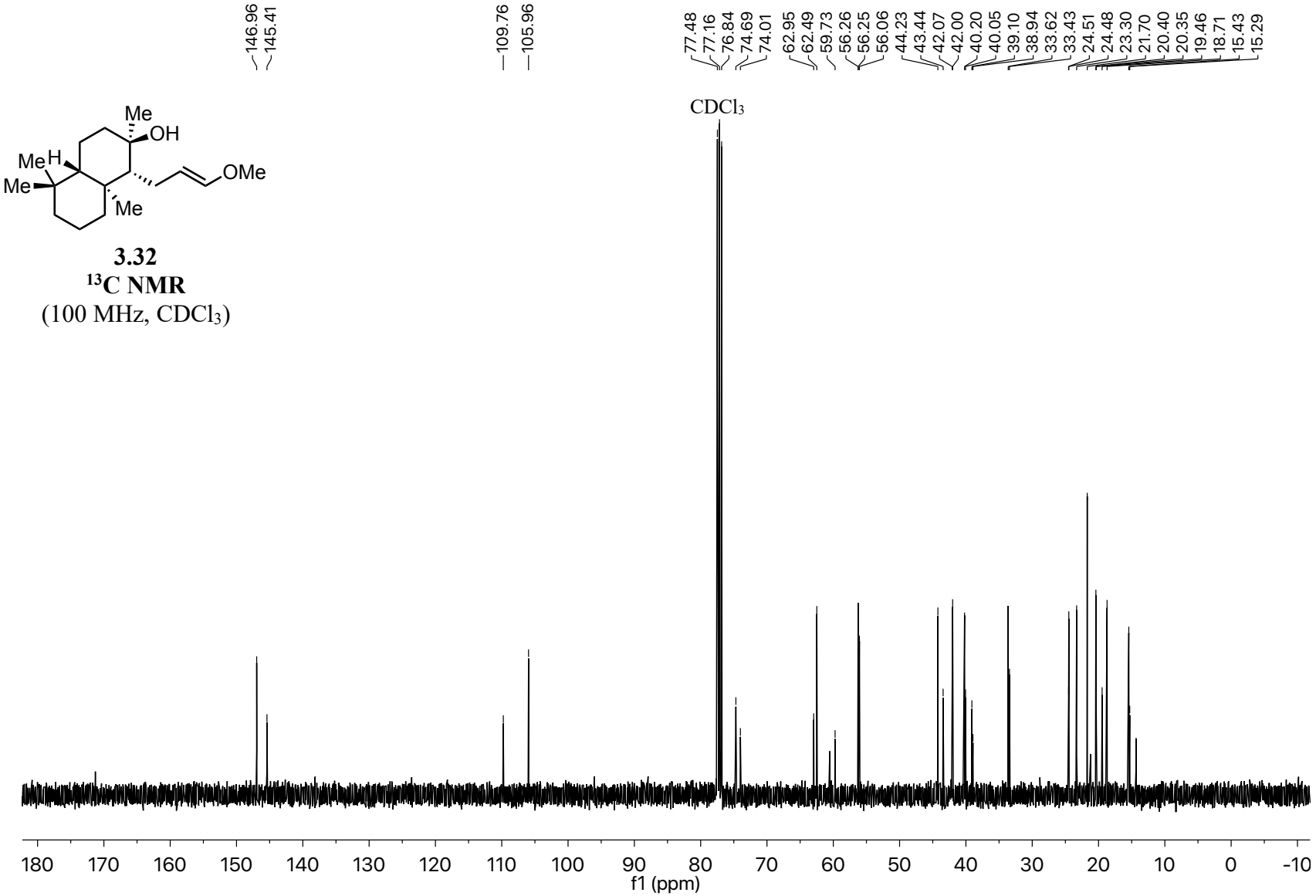
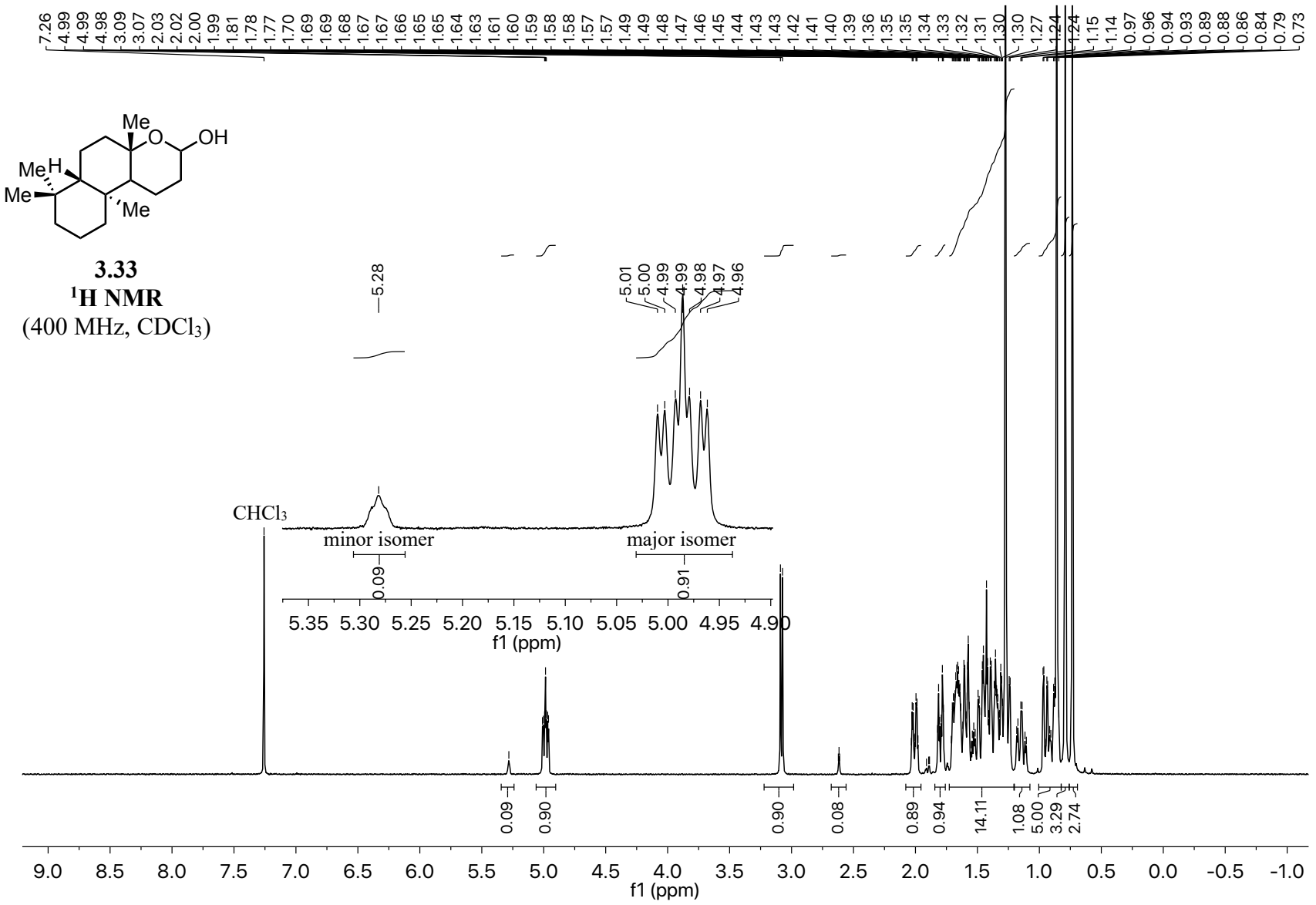
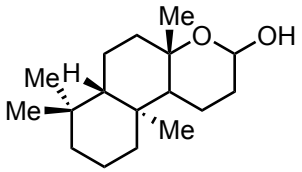
0.33
0.67
0.32
f1 (ppm)
f1 (ppm)

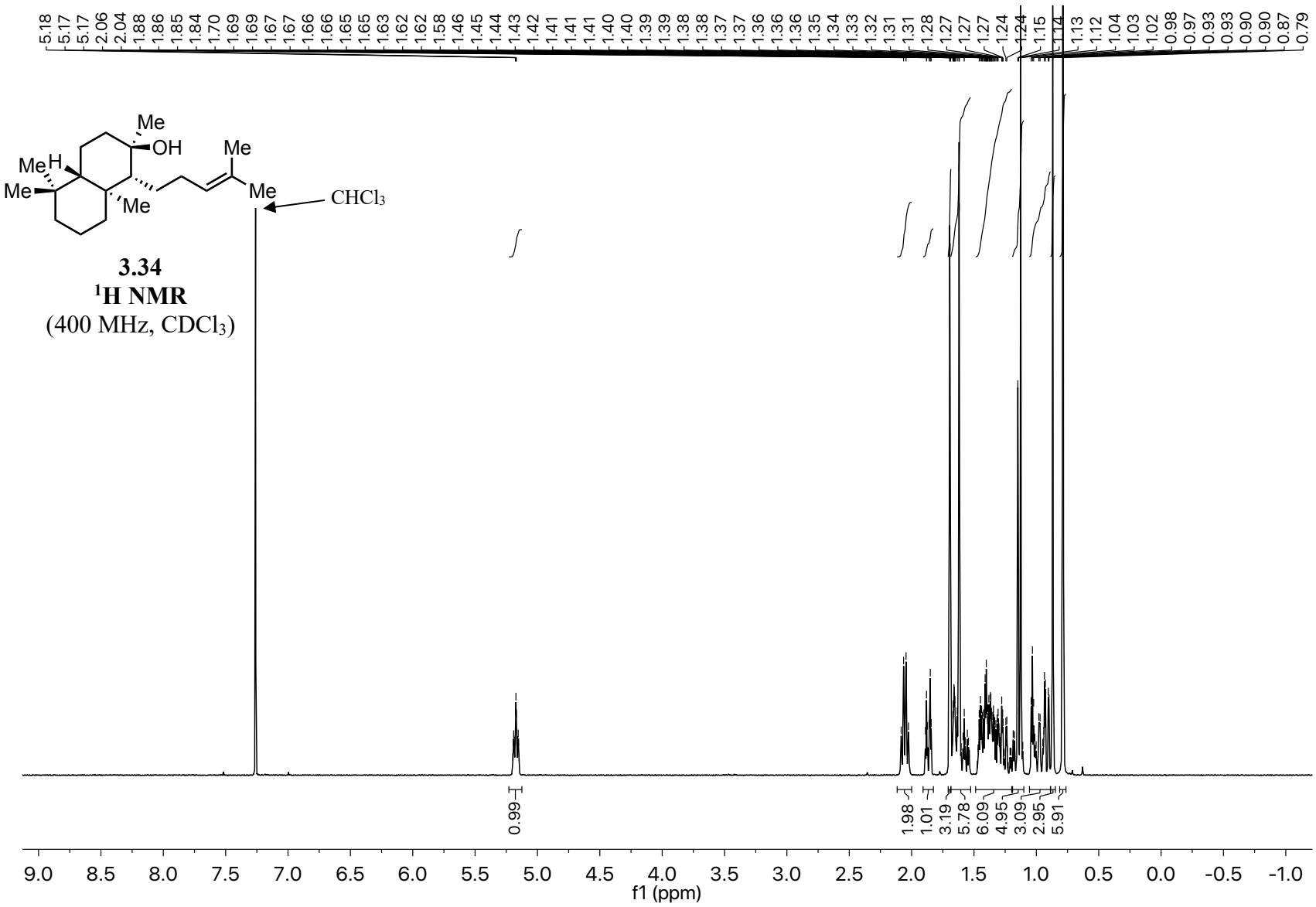


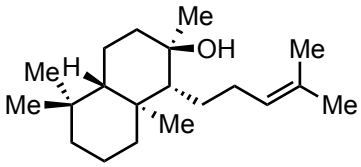
3.32
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
O
OH
Me
H
Me
Me
3.33
1H NMR
(400 MHz, CDCl3)
CHCl3
minor isomer
major isomer
f1 (ppm)
f1 (ppm)

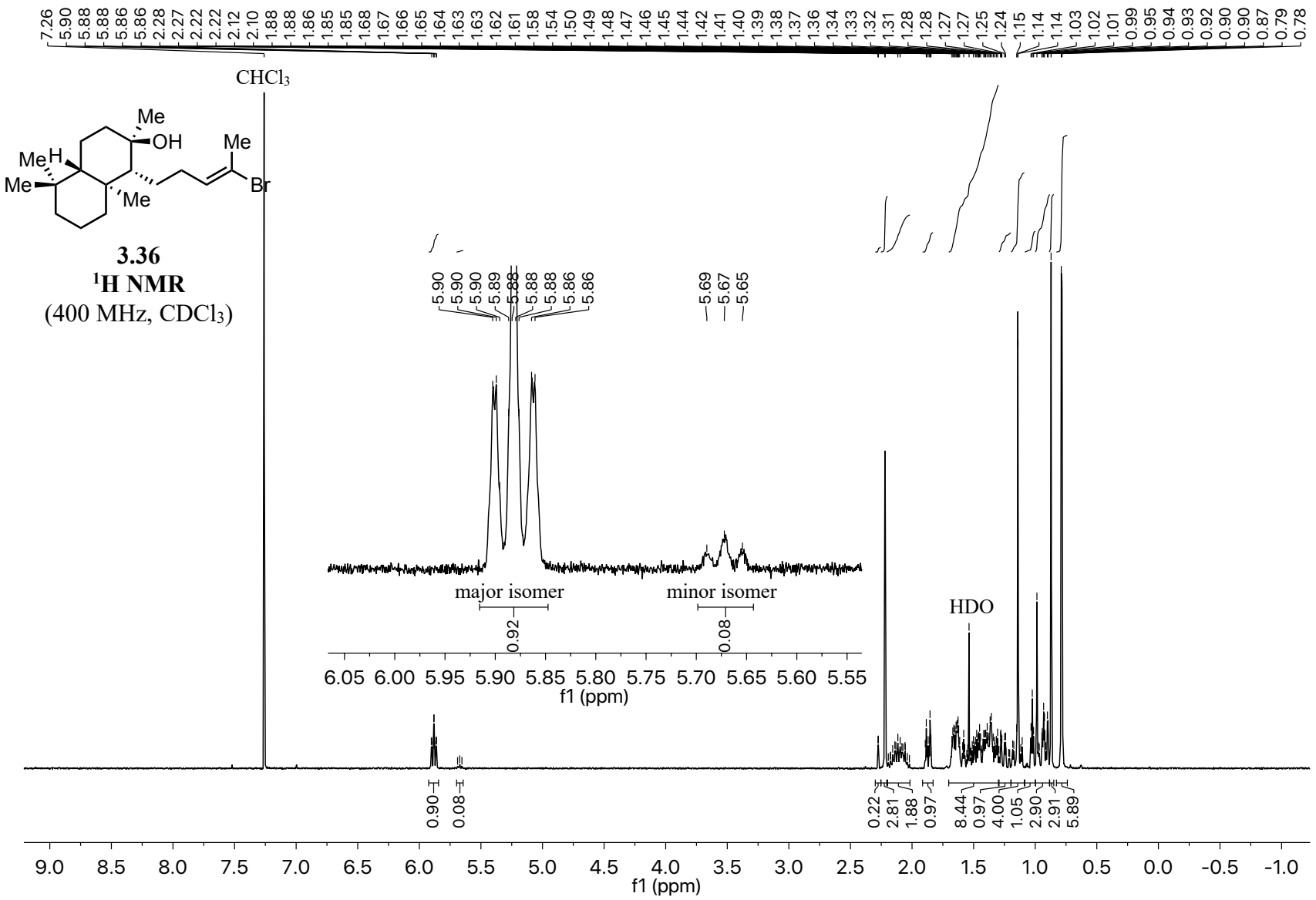


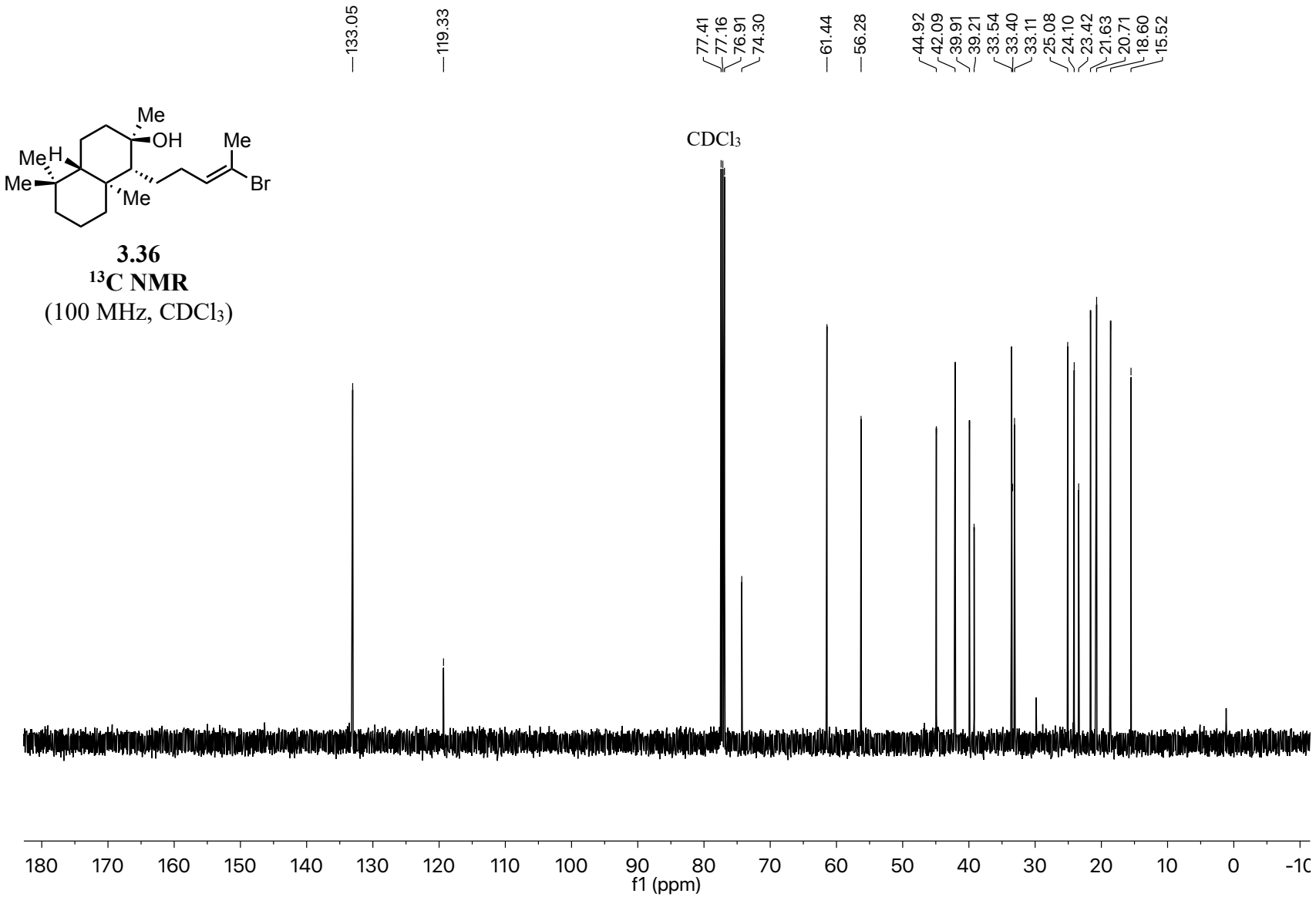
3.33
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
OH
Me
MeH
Me
Me
Me
CHCl3
3.34
1H NMR
(400 MHz, CDCl3)
f1 (ppm)

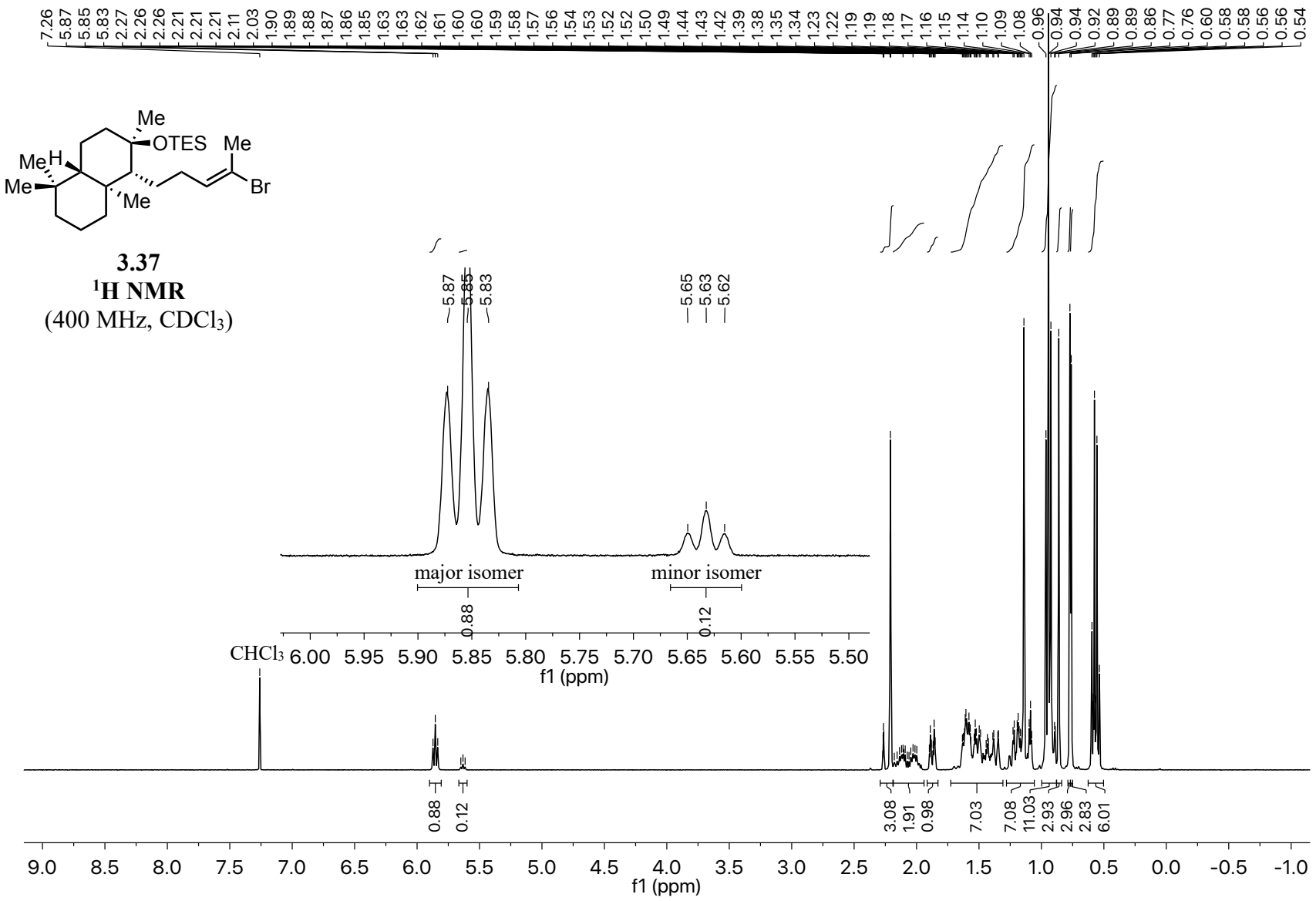


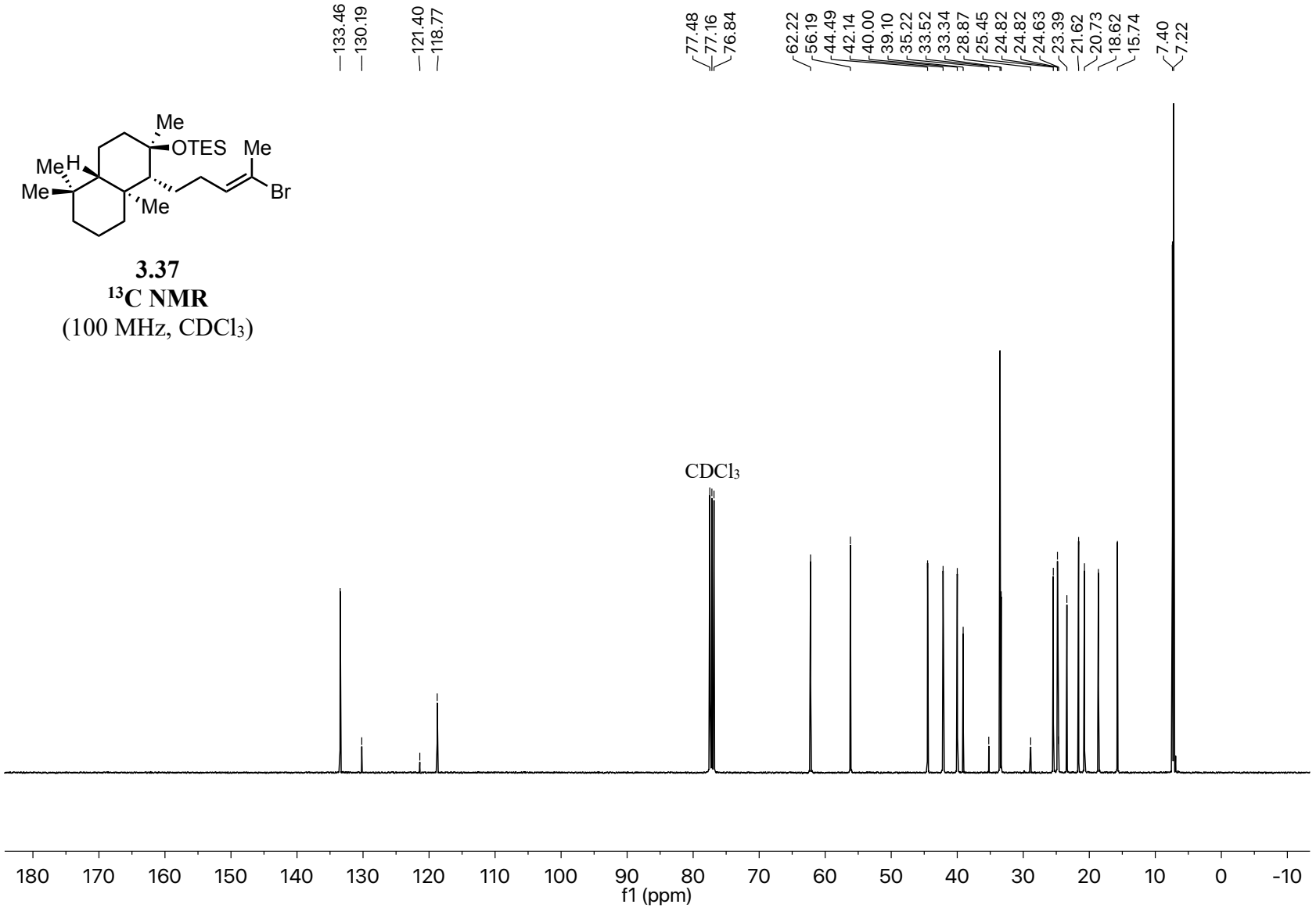
3.34
^{13}C NMR
(100 MHz, $CDCl_3$)


CHCl3
Me
OH
Me
Me
H
Me
Me
Br
3.36
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
0.92
0.08
HDO
f1 (ppm)

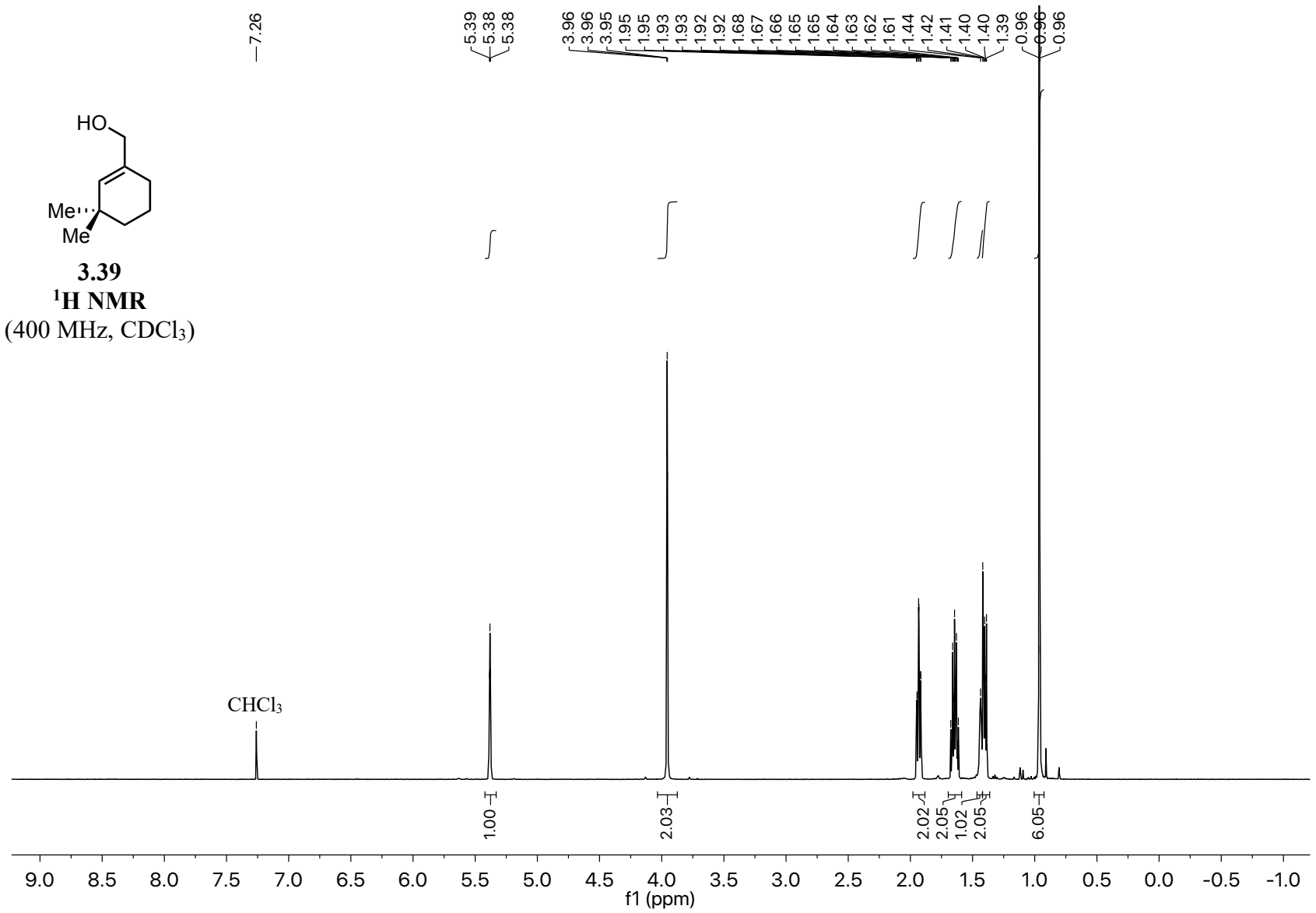


3.36
^{13}C NMR
(100 MHz, $CDCl_3$)

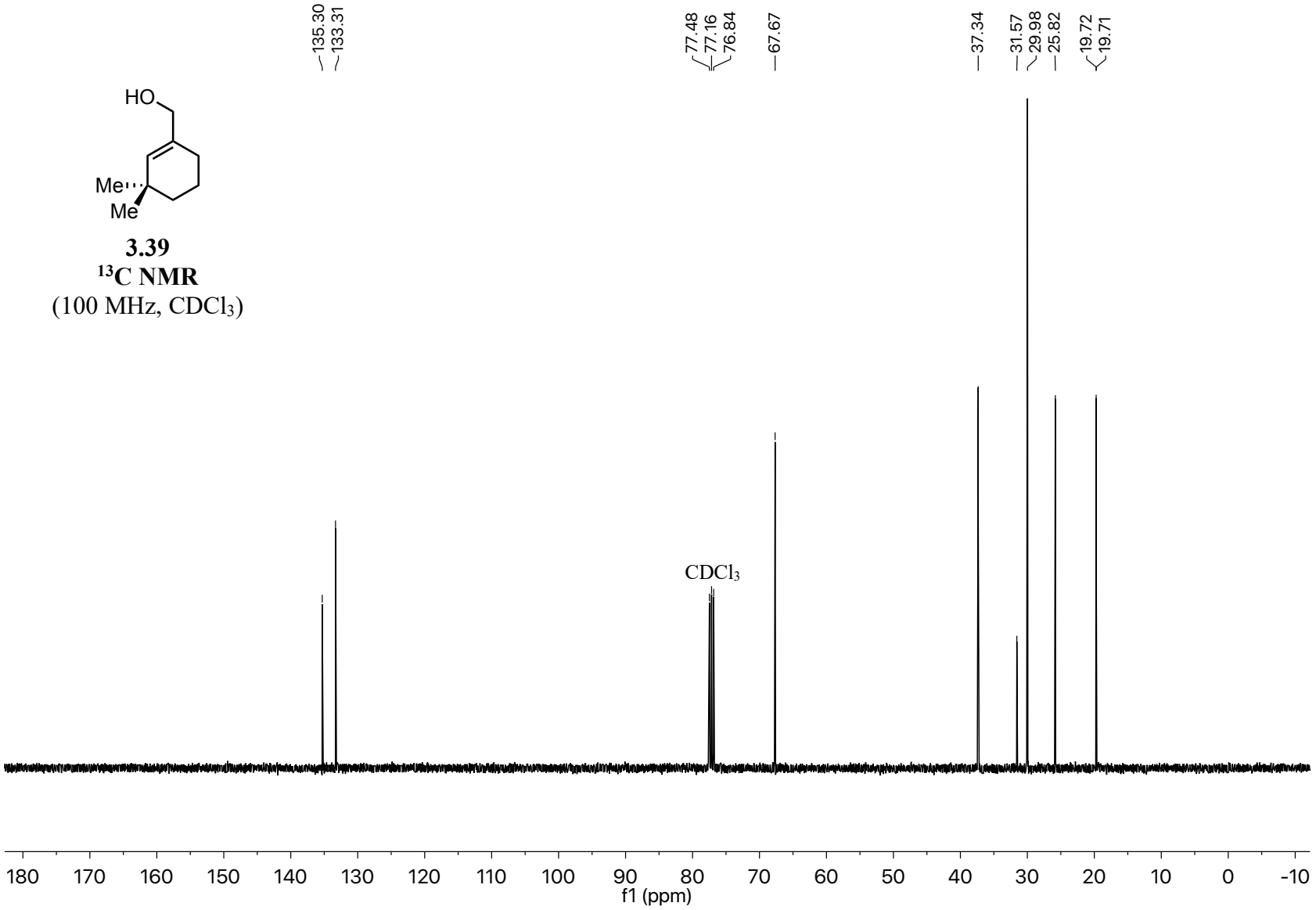

Me
OTES
Me
Me
H
Me
Me
Br
3.37
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
0.88
0.12
CHCl3
f1 (ppm)



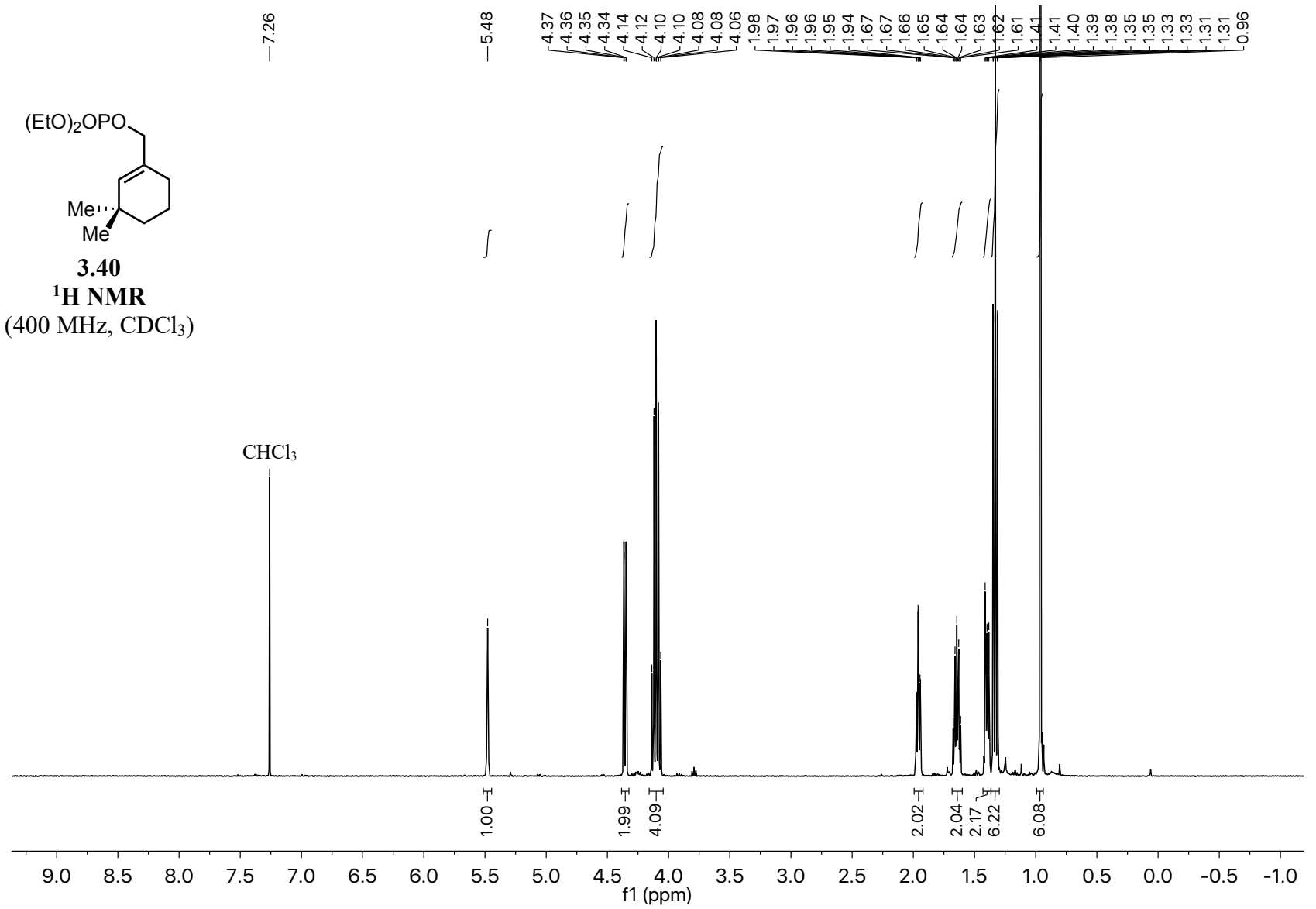
3.37
^{13}C NMR
(100 MHz, $CDCl_3$)

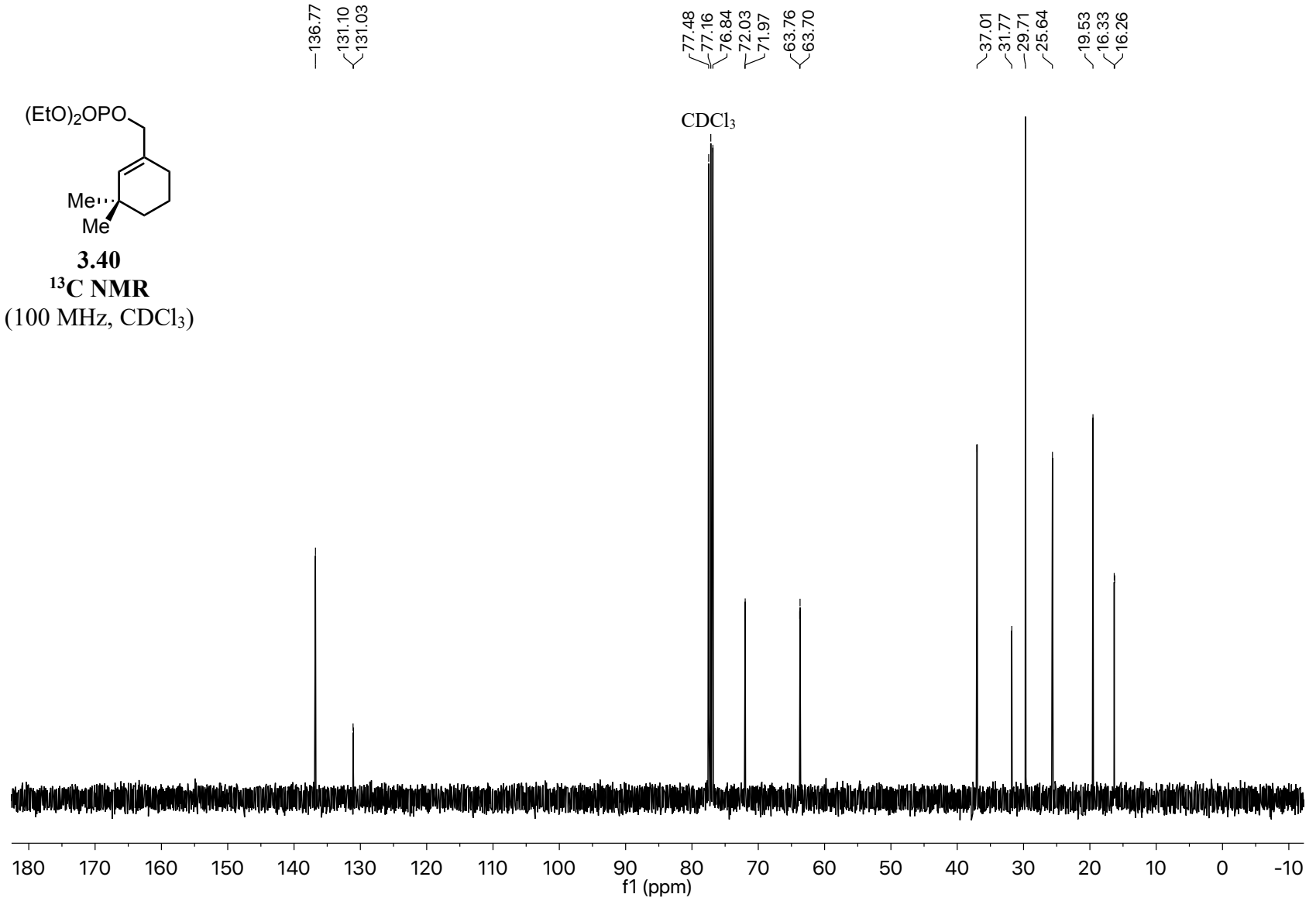


3.39
^{1}H NMR
(400 MHz, $CDCl_3$)



3.39
^{13}C NMR
(100 MHz, $CDCl_3$)

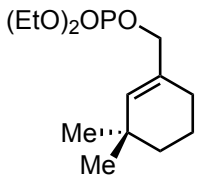

(EtO)2OPO
Me
Me
3.40
1H NMR
(400 MHz, CDCl3)
7.26
5.48
4.37
4.36
4.35
4.34
4.14
4.12
4.10
4.10
4.08
4.08
4.06
1.98
1.97
1.96
1.96
1.95
1.94
1.67
1.67
1.66
1.65
1.64
1.64
1.63
1.62
1.61
1.41
1.41
1.40
1.39
1.38
1.35
1.35
1.33
1.33
1.31
1.31
0.96
CHCl3
1.00
1.99
4.09
2.02
2.04
2.17
6.22
6.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)



3.40

^{13}C NMR

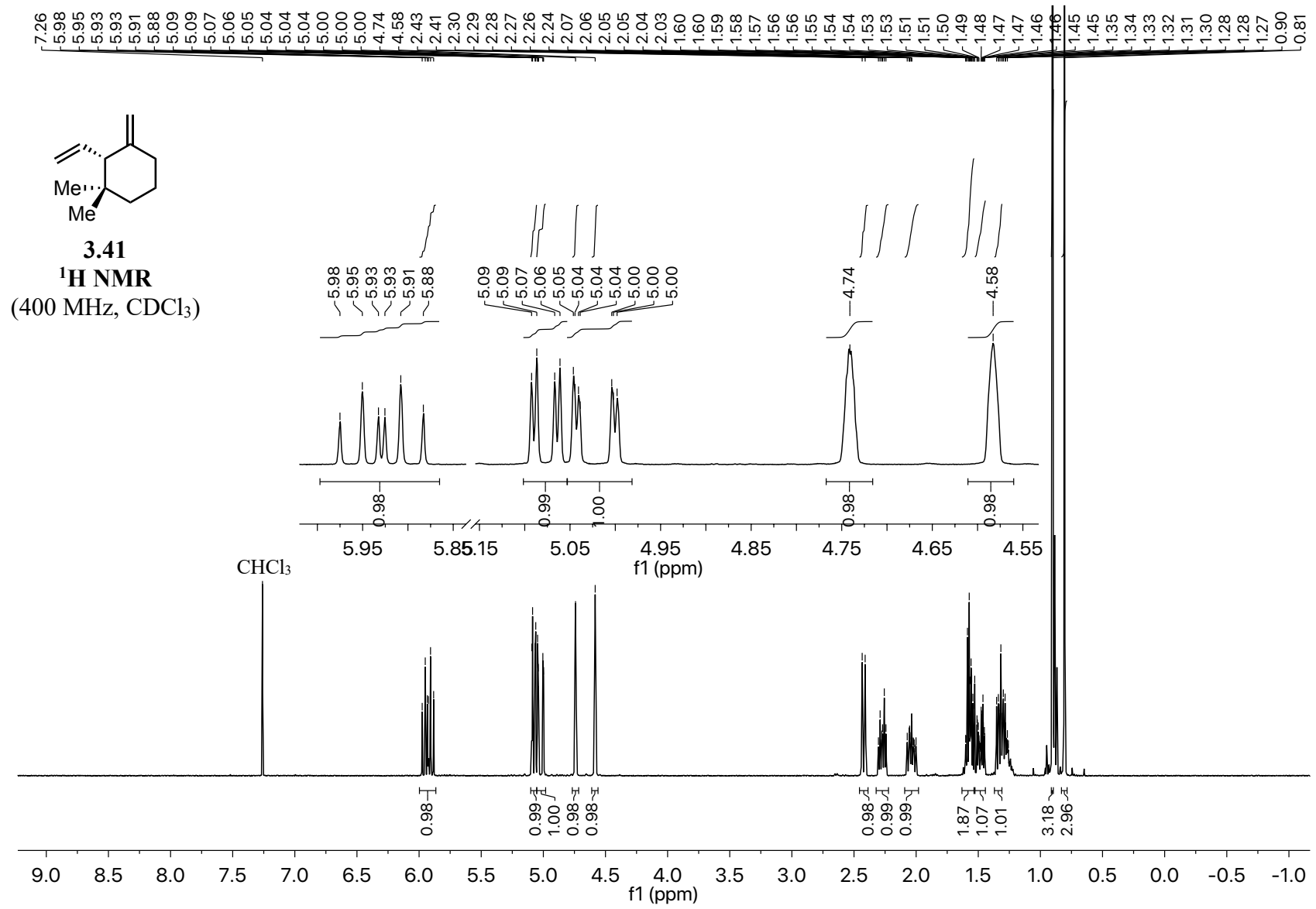
(100 MHz, $CDCl_3$)



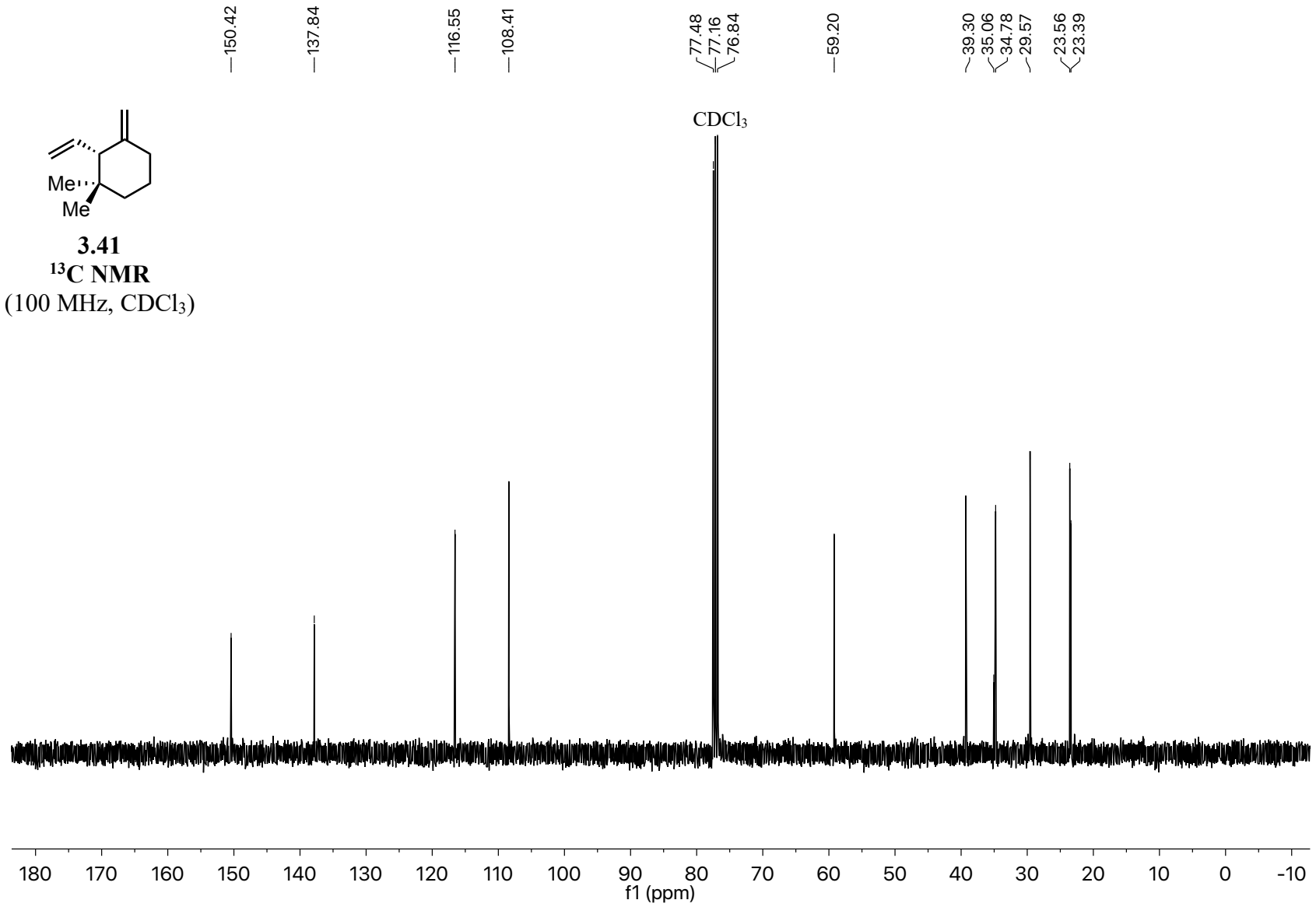
3.40

^{31}P NMR

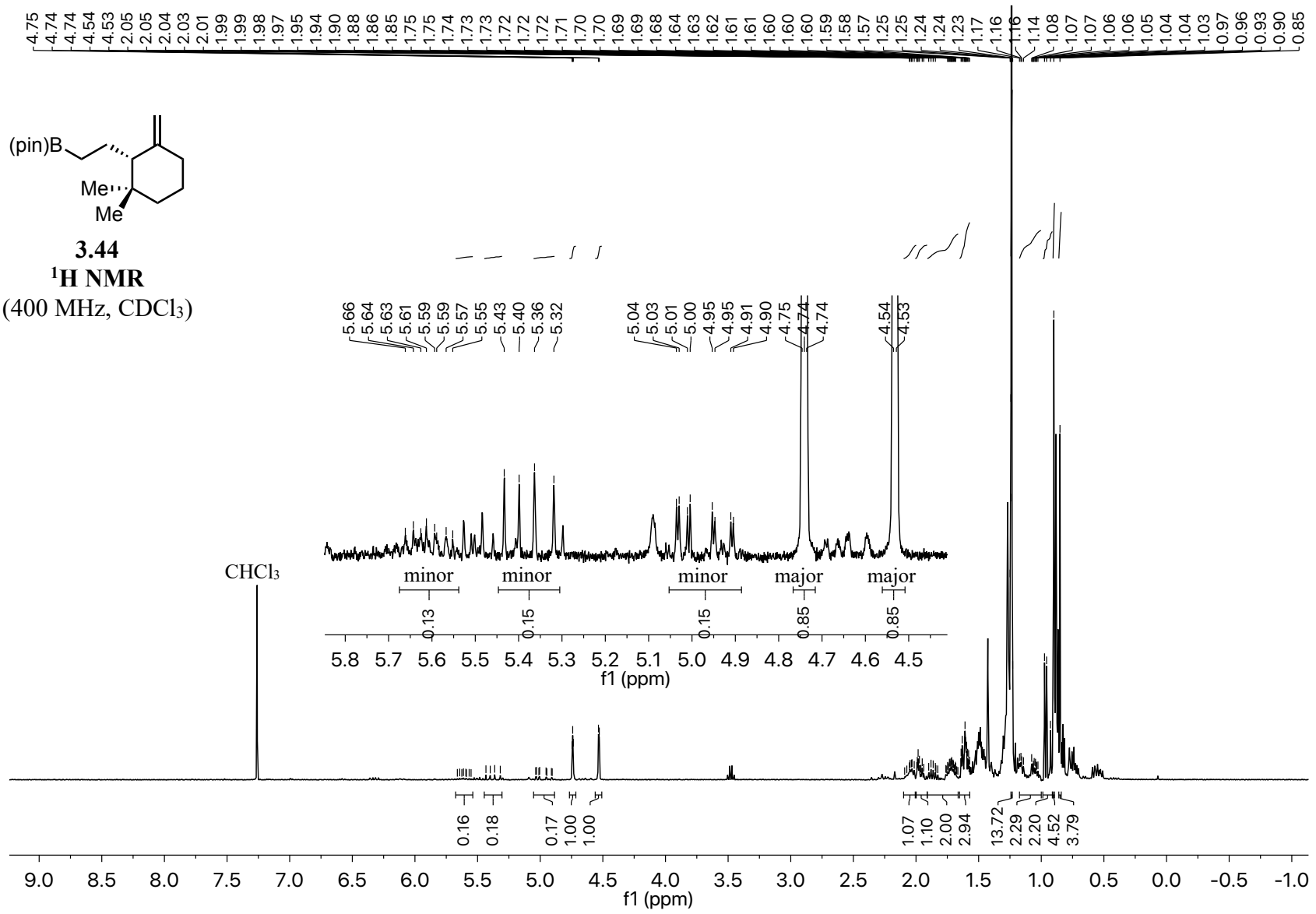
(162 MHz, $CDCl_3$)

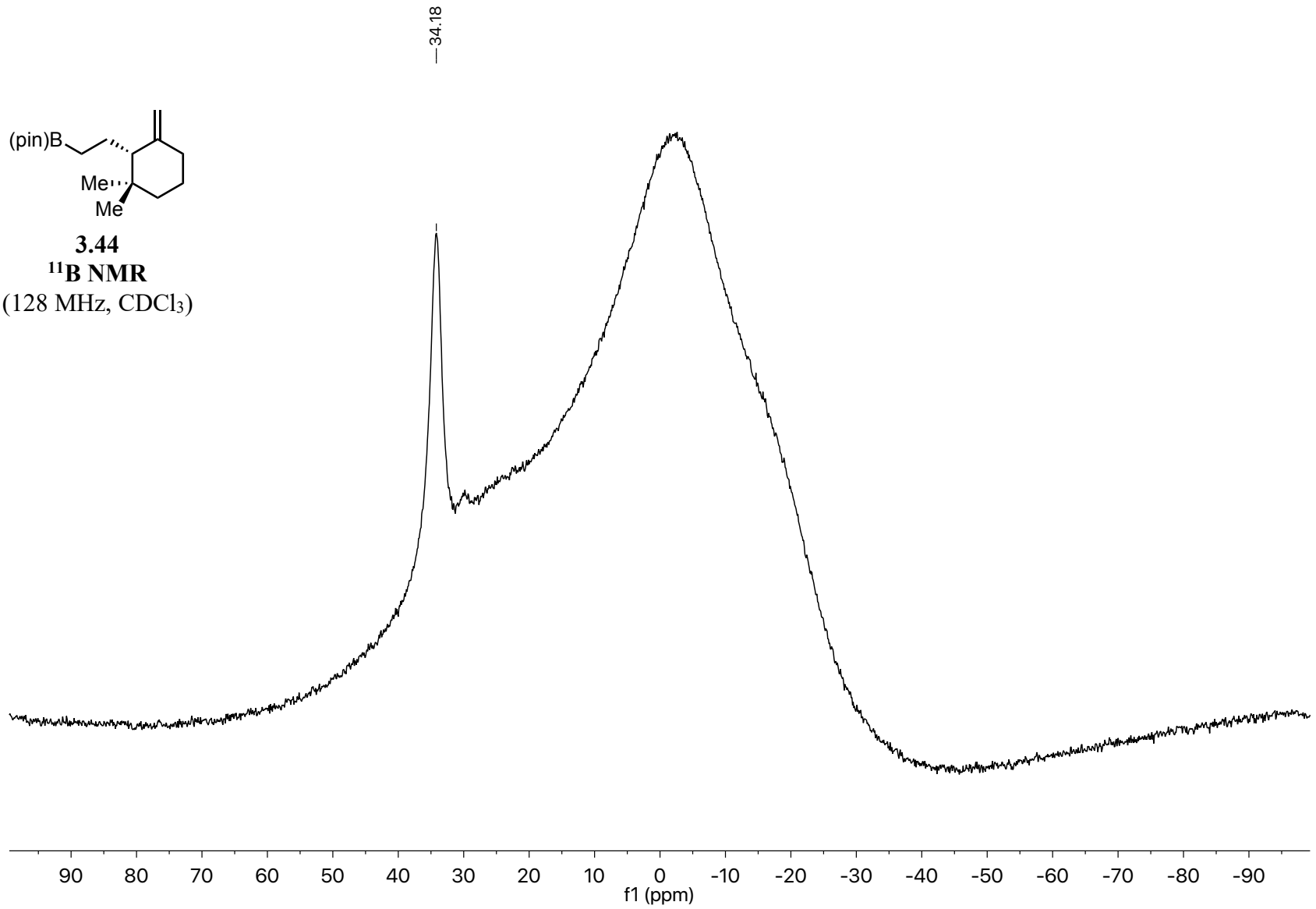


3.41
^{1}H NMR
(400 MHz, $CDCl_3$)

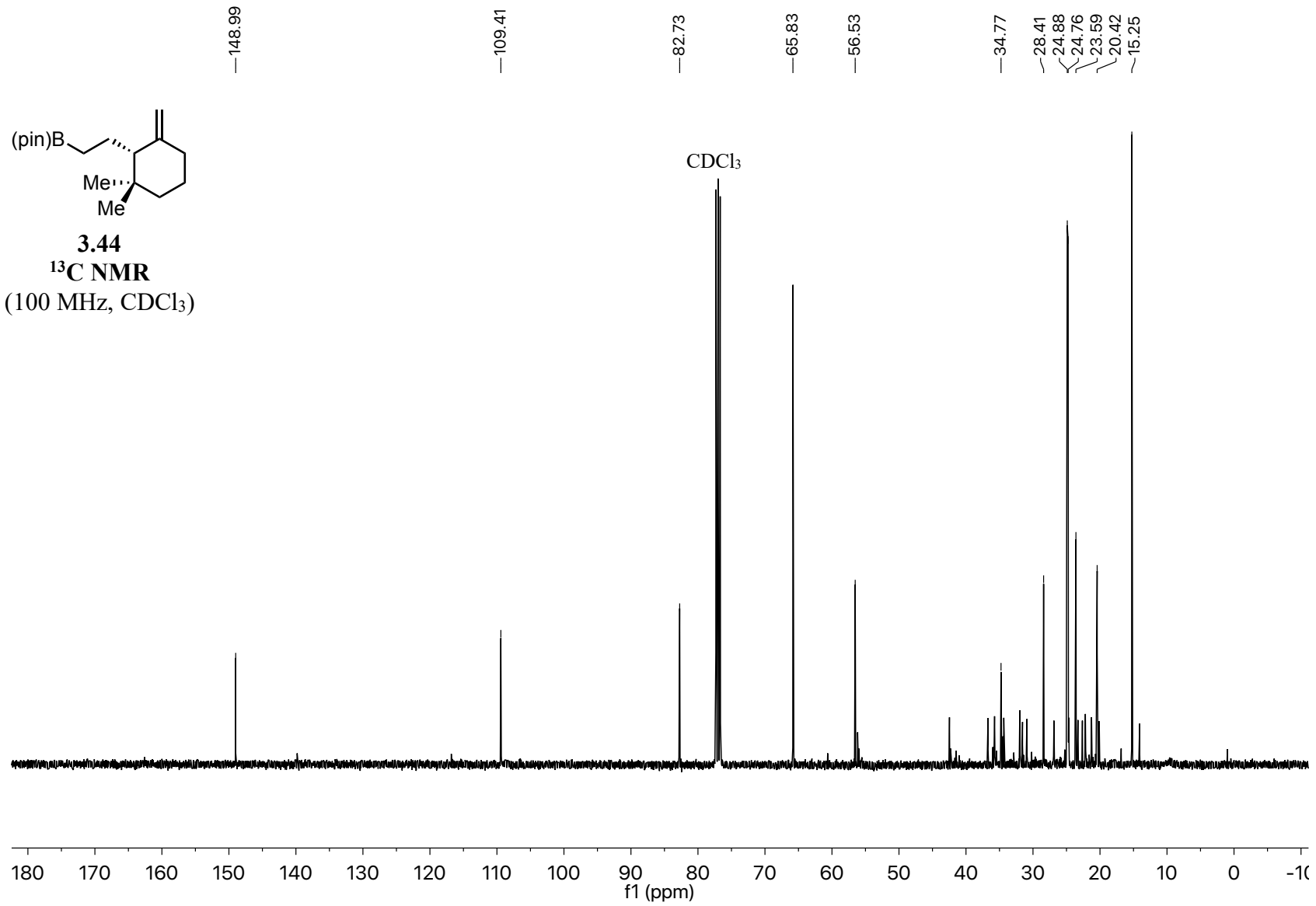


3.41
^{13}C NMR
(100 MHz, $CDCl_3$)

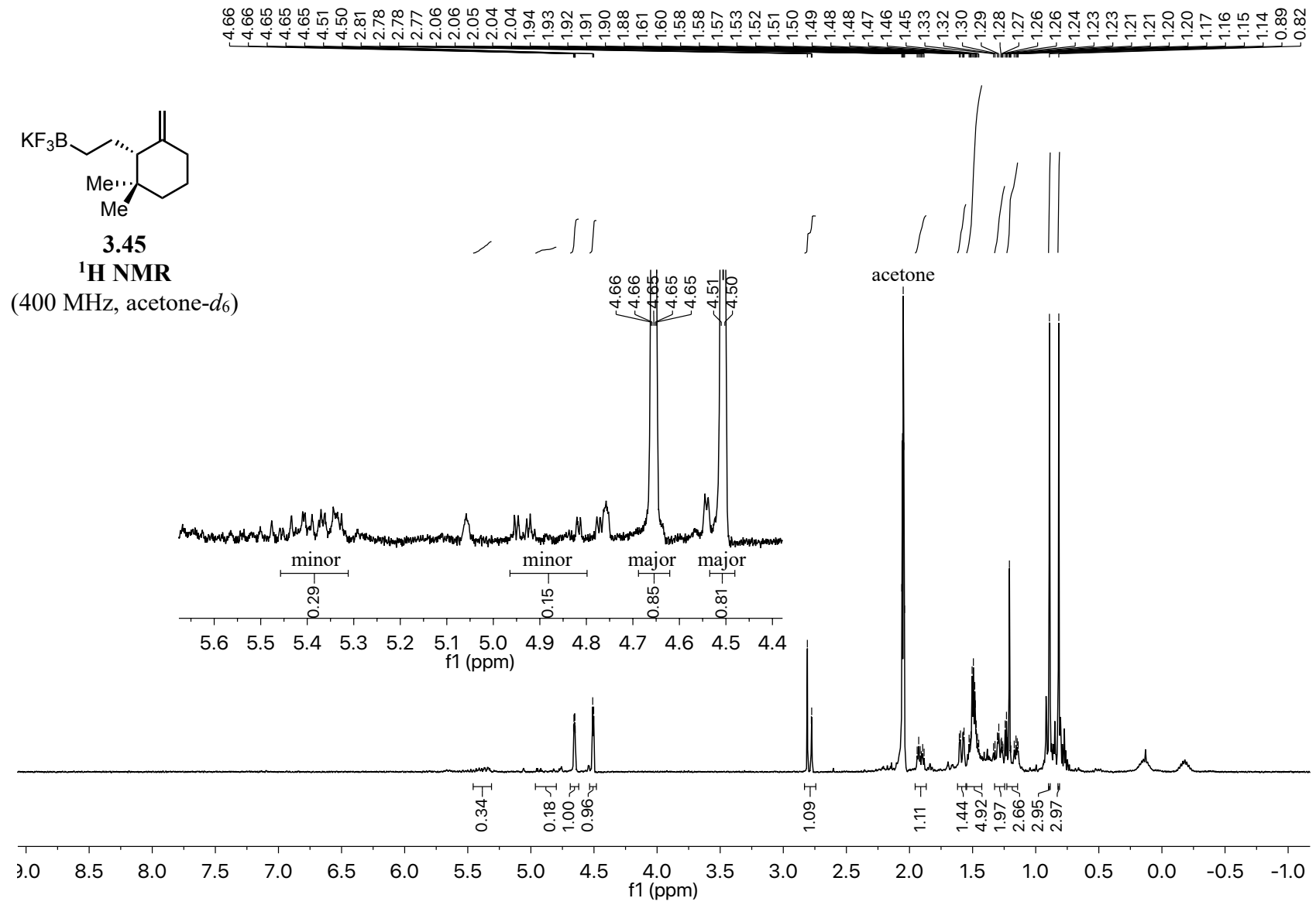

(pin)B
Me
Me
3.44
1H NMR
(400 MHz, CDCl3)
CHCl3
minor
minor
minor
major
major
f1 (ppm)



3.44
^{11}B NMR
(128 MHz, $CDCl_3$)



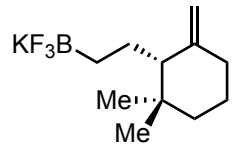
3.44
^{13}C NMR
(100 MHz, $CDCl_3$)



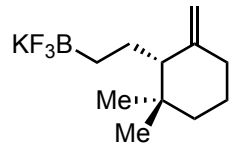
3.45

^{1}H NMR

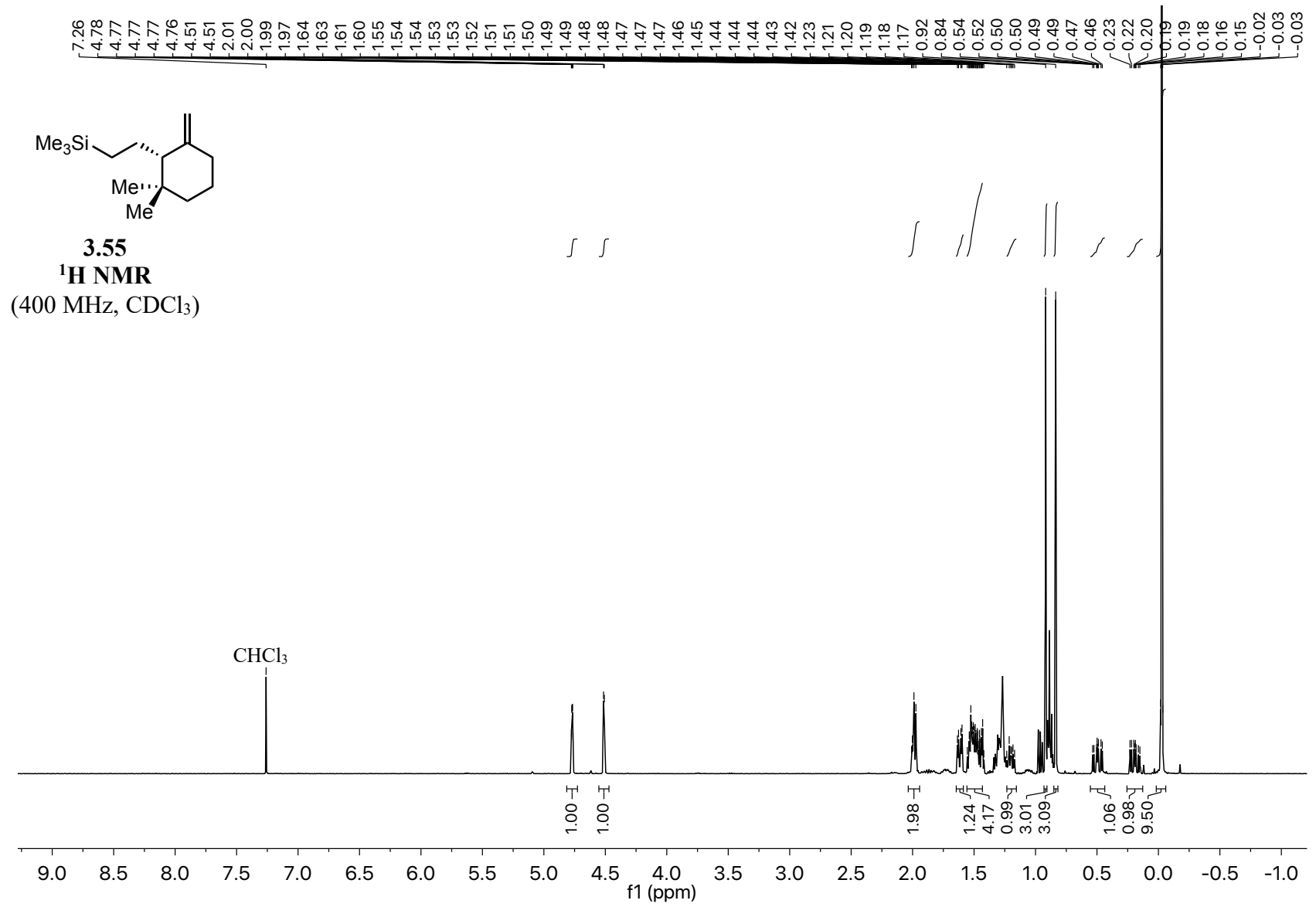
(400 MHz, acetone-d_6)



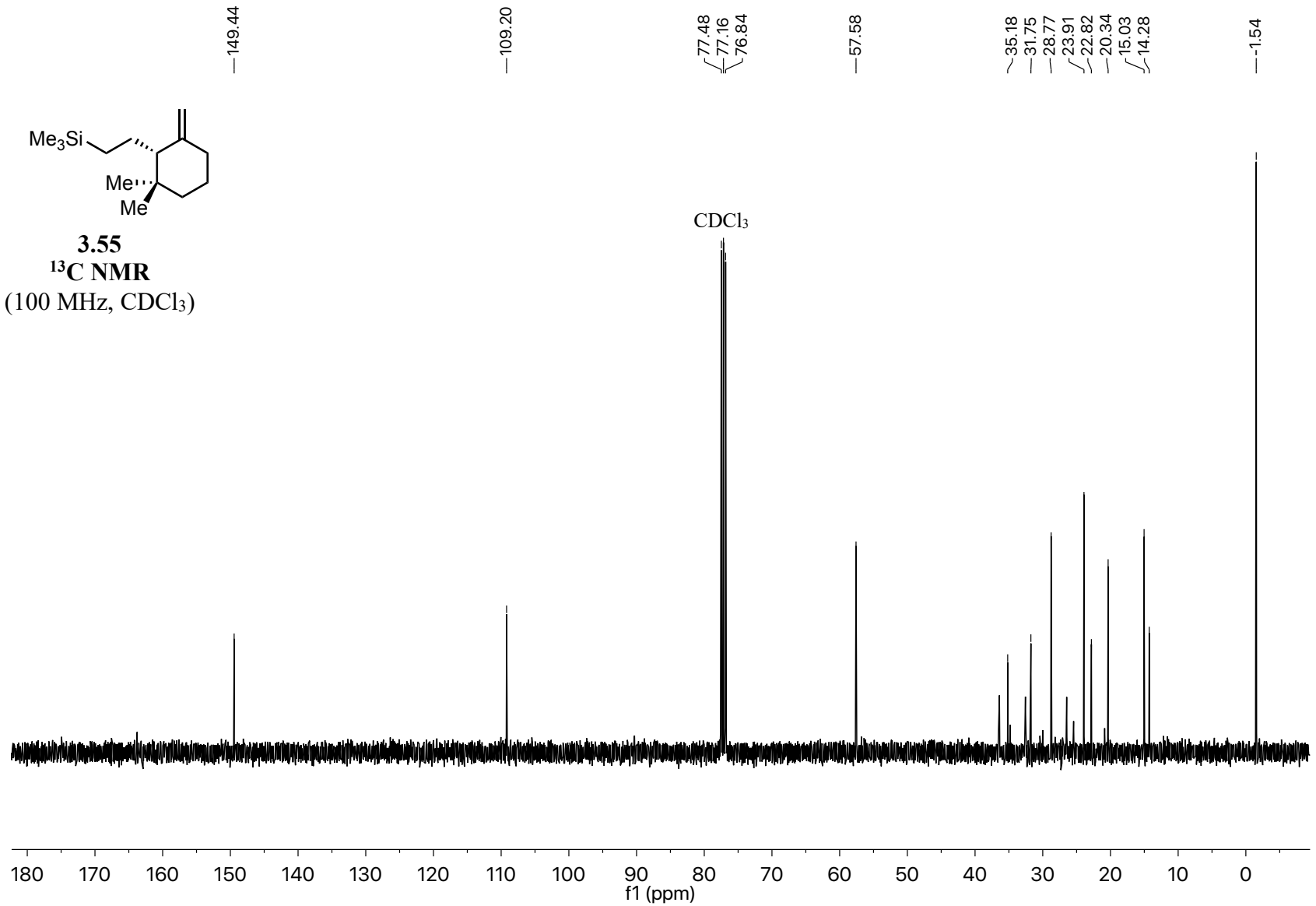
3.45
^{11}B NMR
(128 MHz, acetone-d_6)



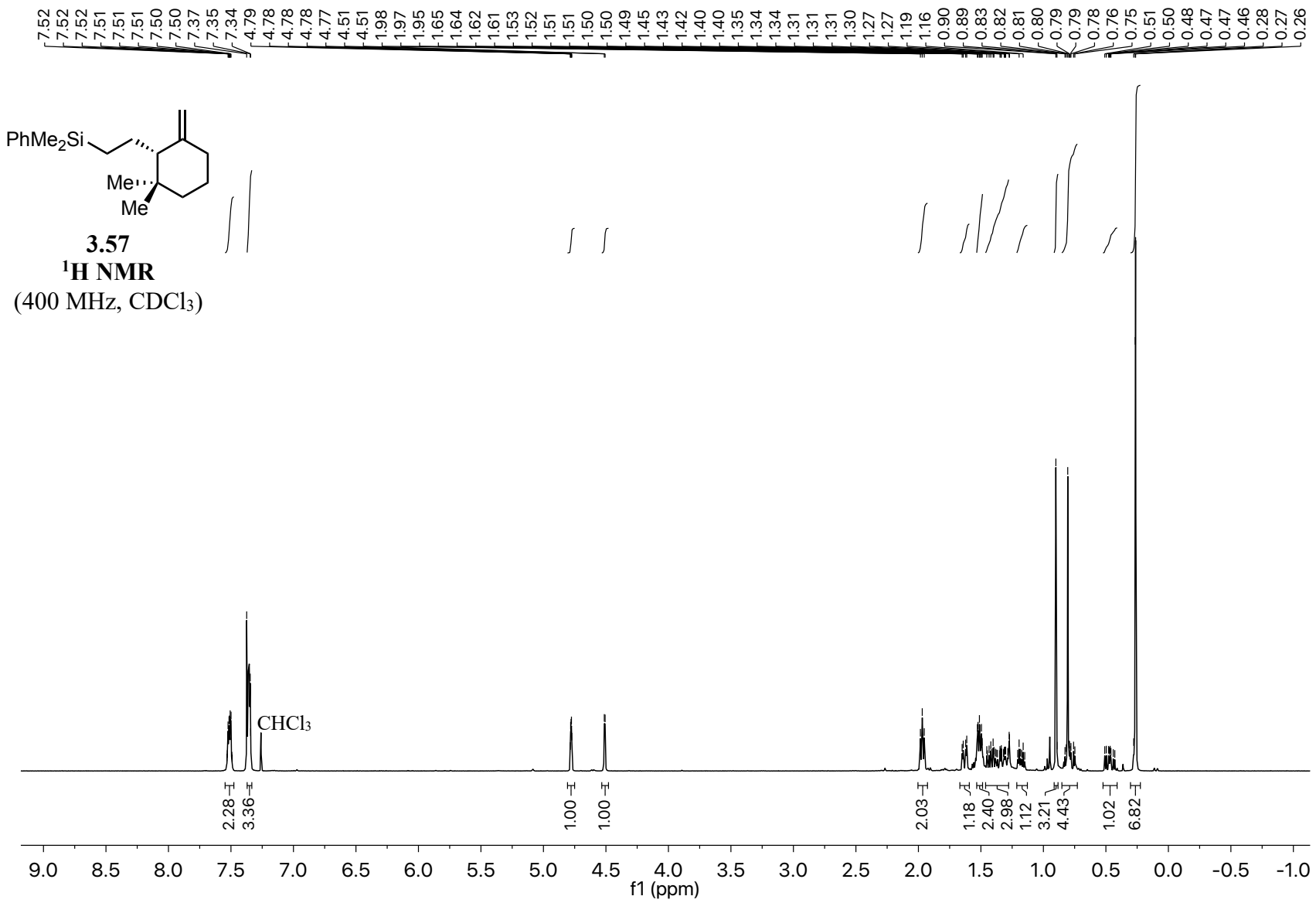
3.45
^{19}F NMR
(376 MHz, acetone-d_6)



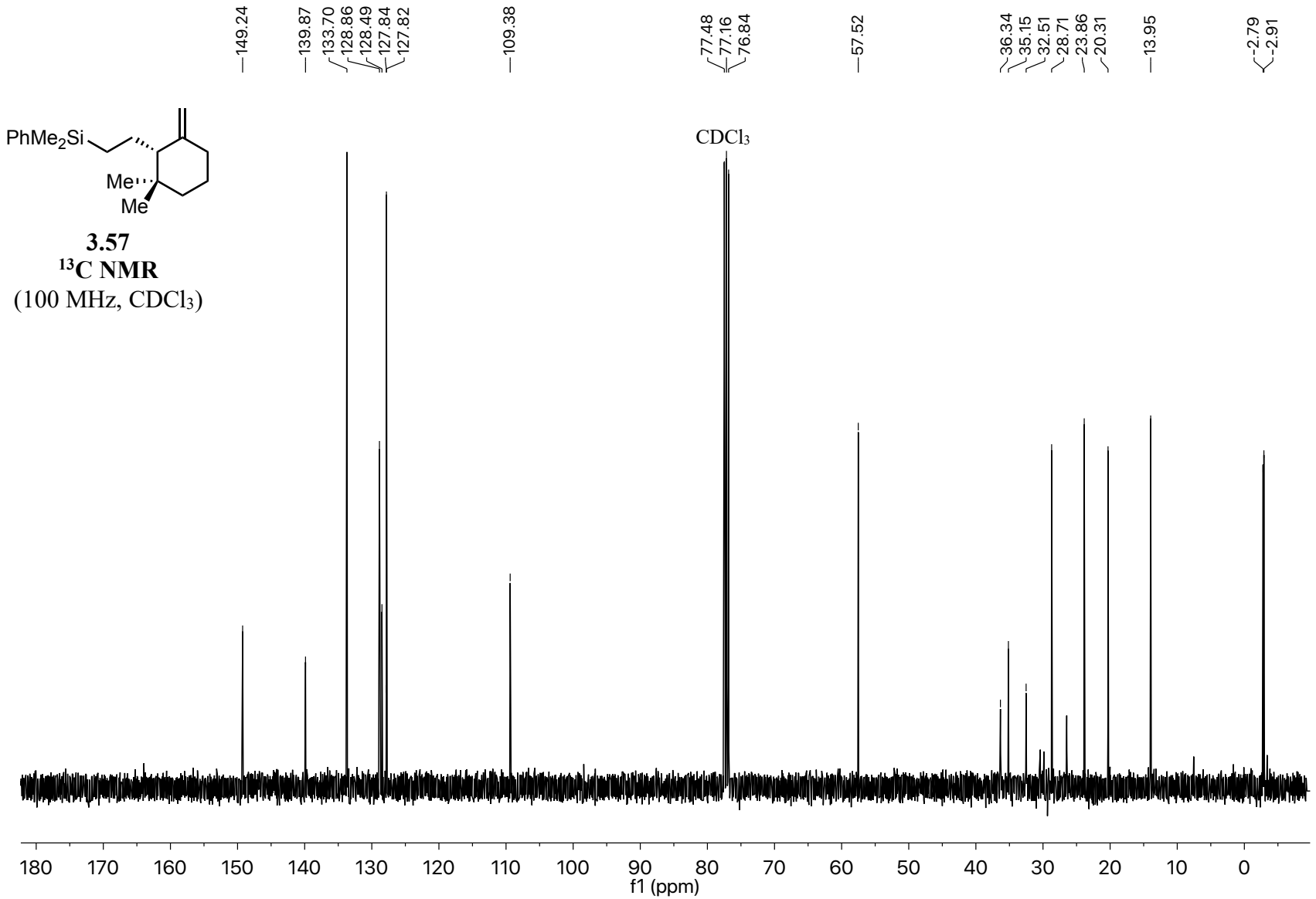
3.55
^{1}H NMR
(400 MHz, $CDCl_3$)



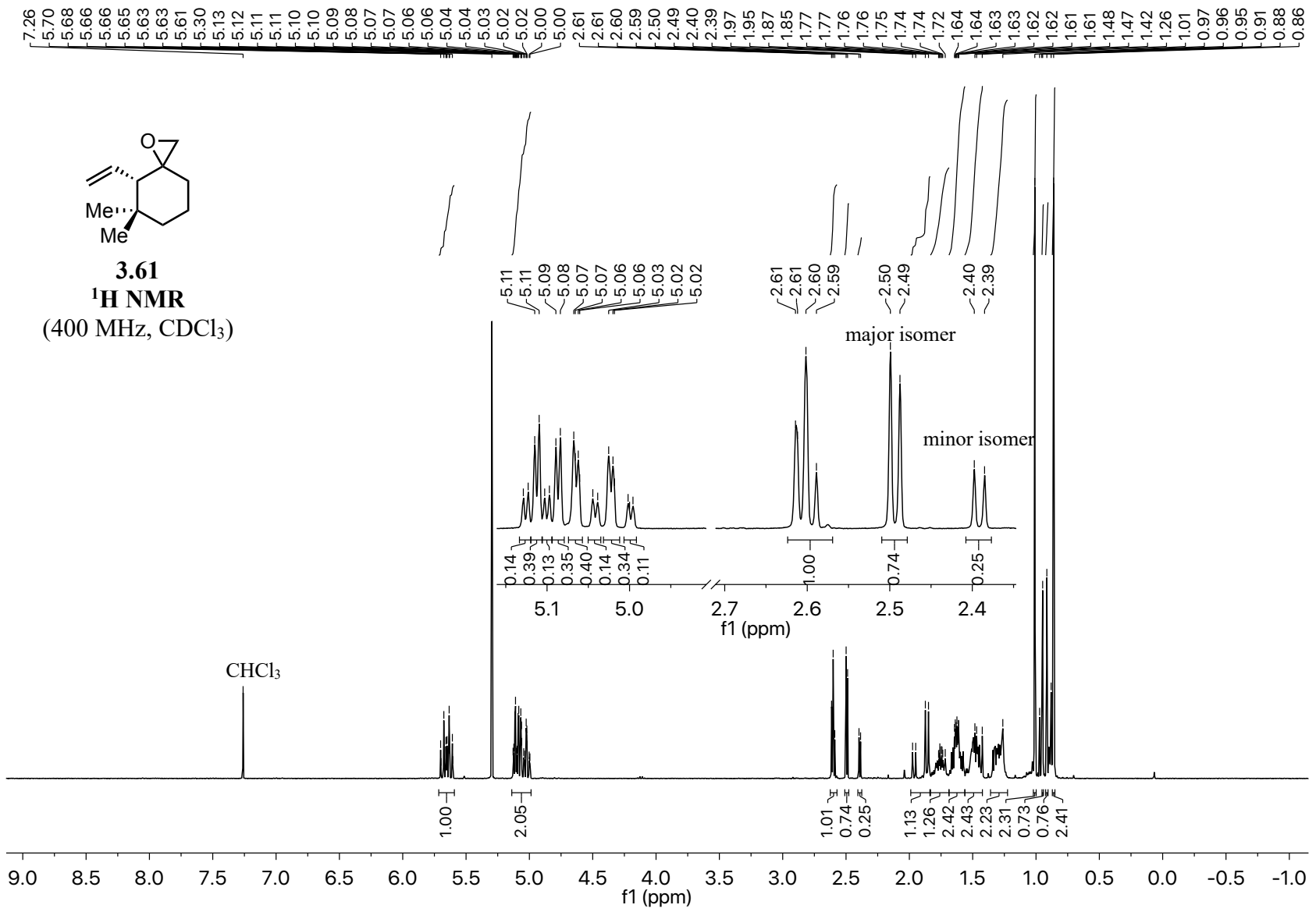
3.55
^{13}C NMR
(100 MHz, $CDCl_3$)

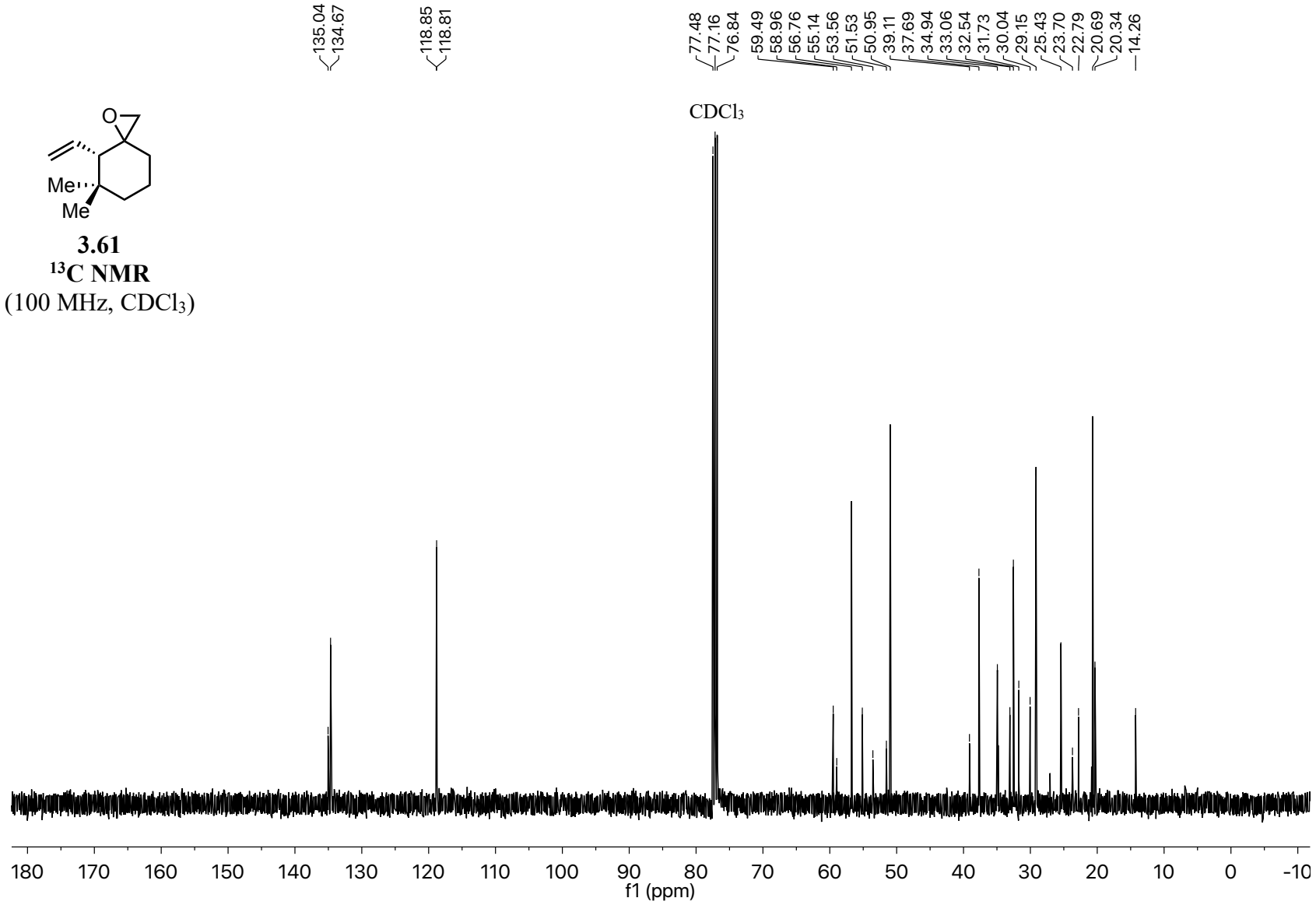


3.57
^{1}H NMR
(400 MHz, $CDCl_3$)

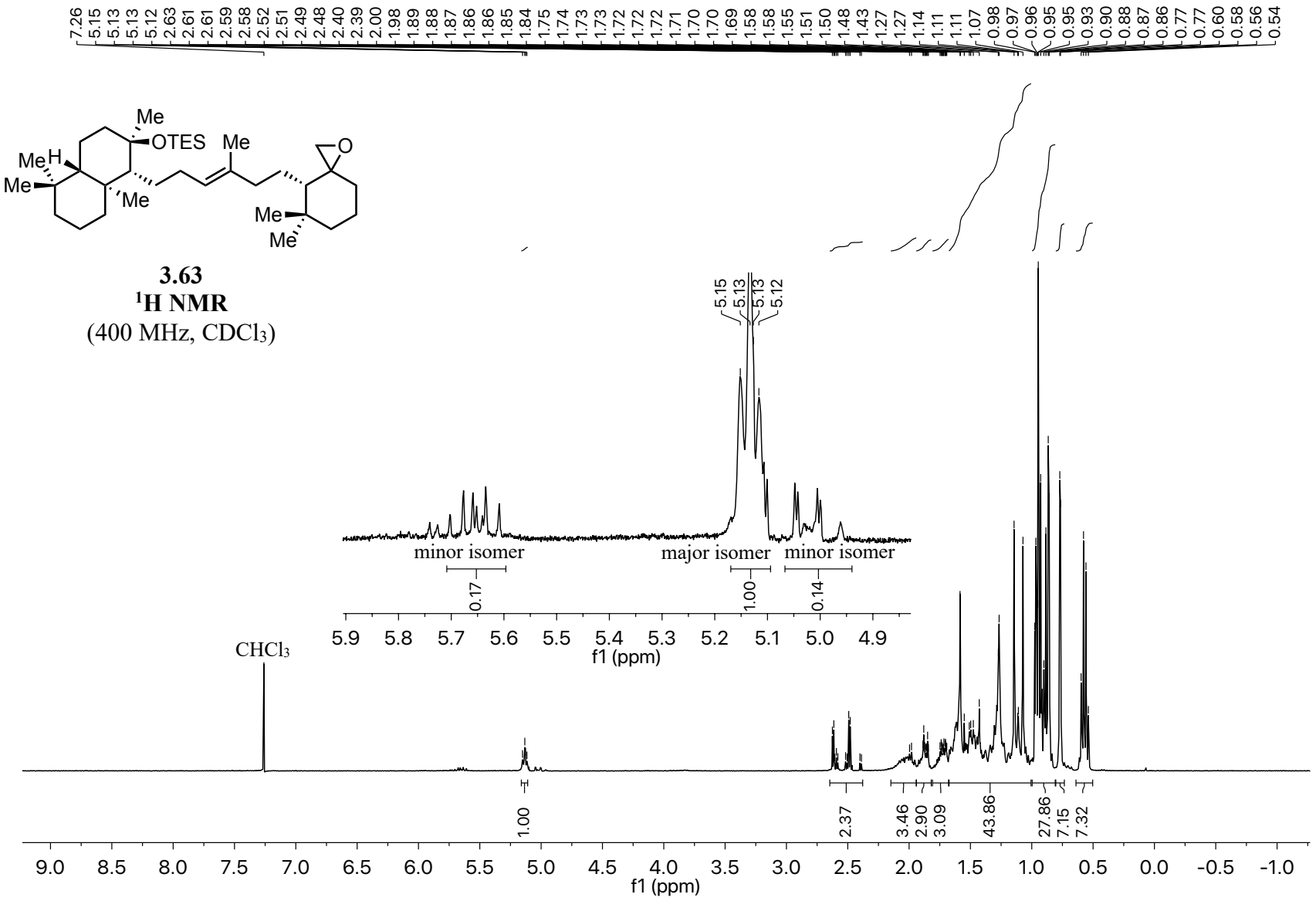


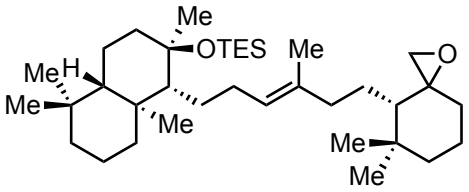
3.57
^{13}C NMR
(100 MHz, $CDCl_3$)


3.61
1H NMR
(400 MHz, CDCl3)
major isomer
minor isomer
CHCl3
f1 (ppm)

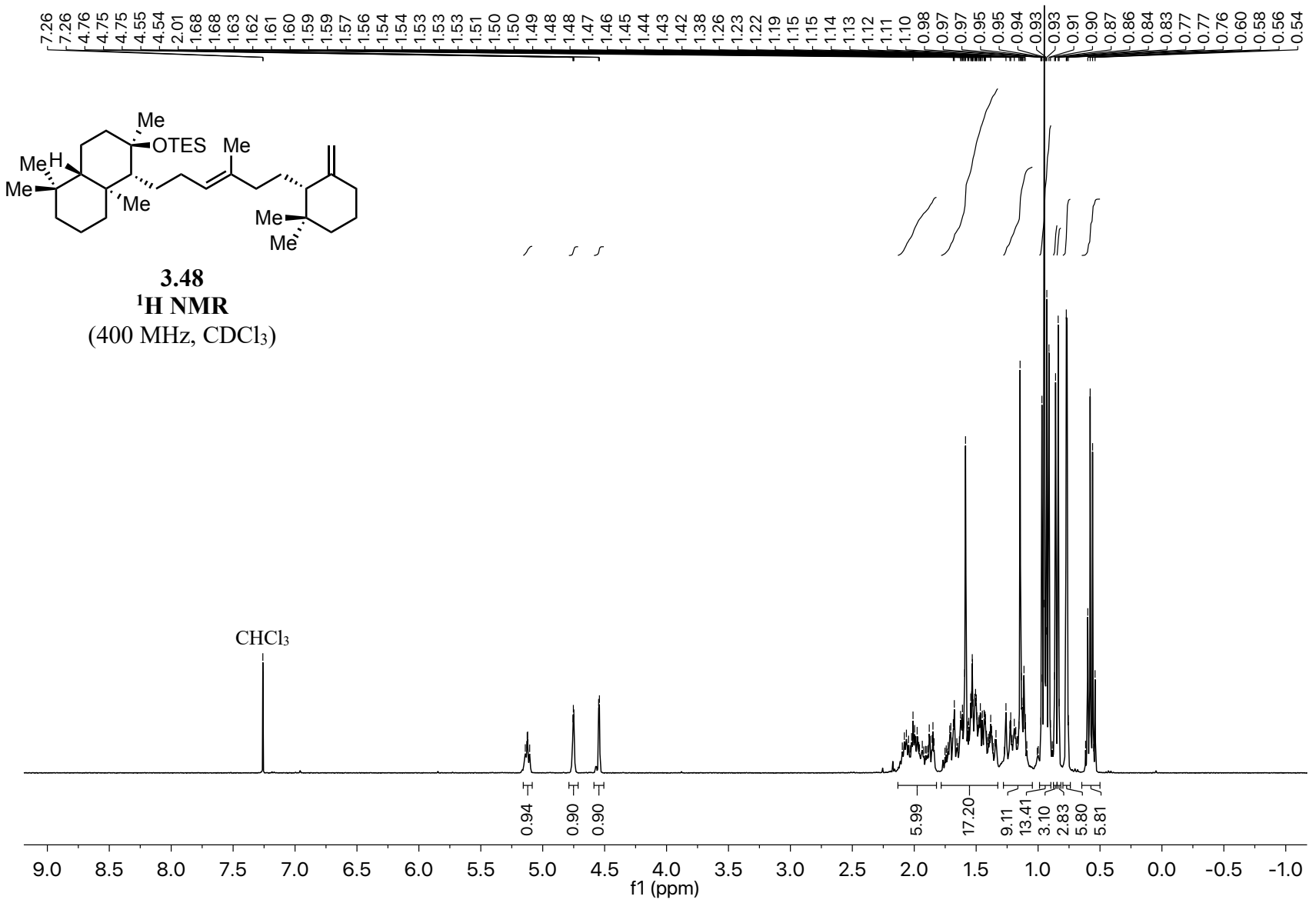


3.61
^{13}C NMR
(100 MHz, $CDCl_3$)

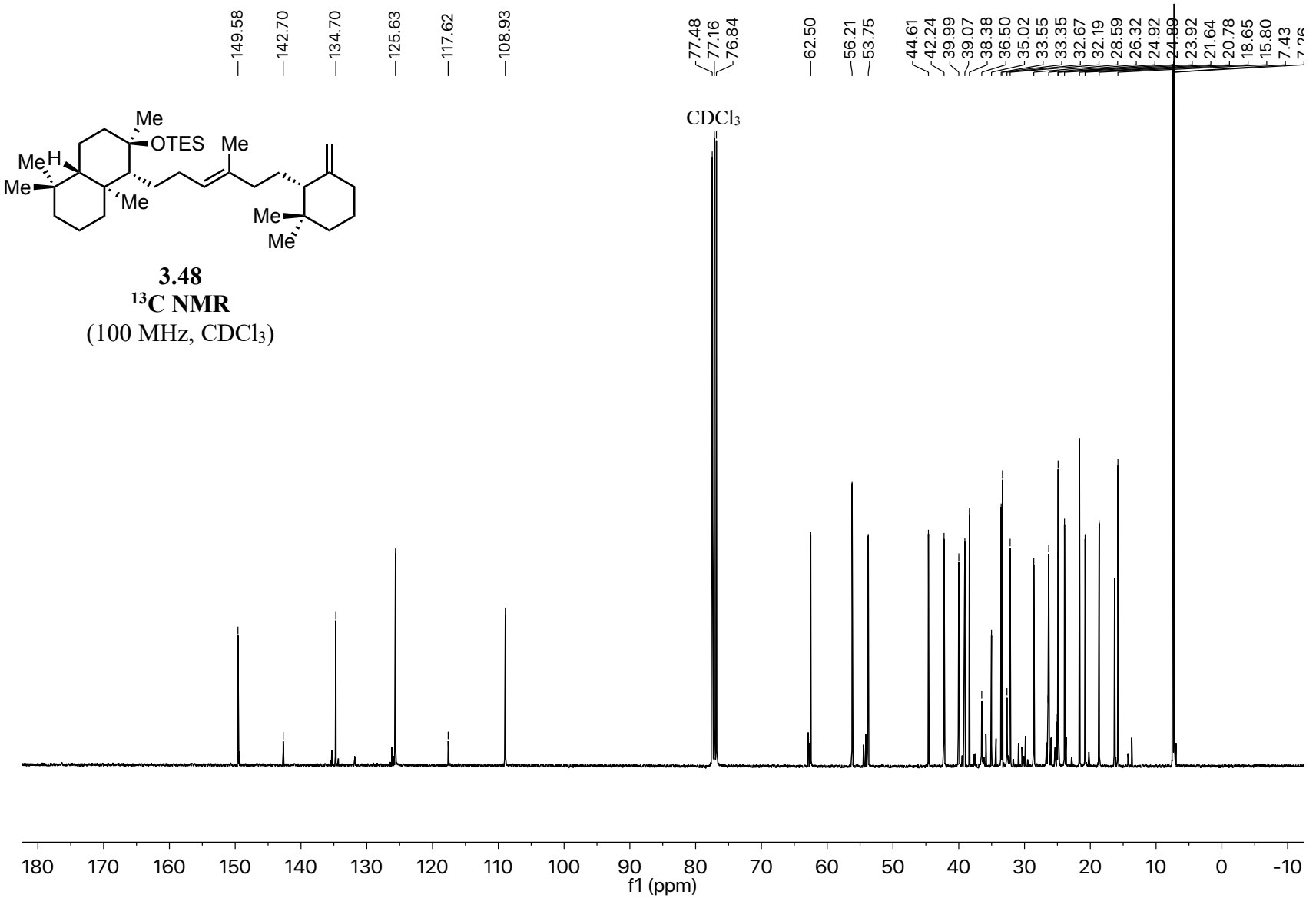

7.26 5.15 5.13 5.13 5.12 2.63 2.61 2.61 2.59 2.58 2.52 2.51 2.49 2.48 2.40 2.39 2.00 1.98 1.89 1.88 1.87 1.86 1.86 1.85 1.84 1.75 1.74 1.73 1.73 1.72 1.72 1.72 1.71 1.70 1.70 1.69 1.58 1.58 1.55 1.51 1.50 1.48 1.43 1.27 1.27 1.14 1.11 1.11 1.07 0.98 0.97 0.96 0.95 0.95 0.93 0.90 0.88 0.87 0.86 0.77 0.77 0.60 0.58 0.56 0.54
Me
OTES
Me
Me
H
Me
Me
Me
O
Me
Me
3.63
1H NMR
(400 MHz, CDCl3)
5.15 5.13 5.13 5.12
minor isomer
major isomer
minor isomer
0.17
1.00
0.14
5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9
f1 (ppm)
CHCl3
1.00
2.37
3.46
2.90
3.09
43.86
27.86
7.15
7.32
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)



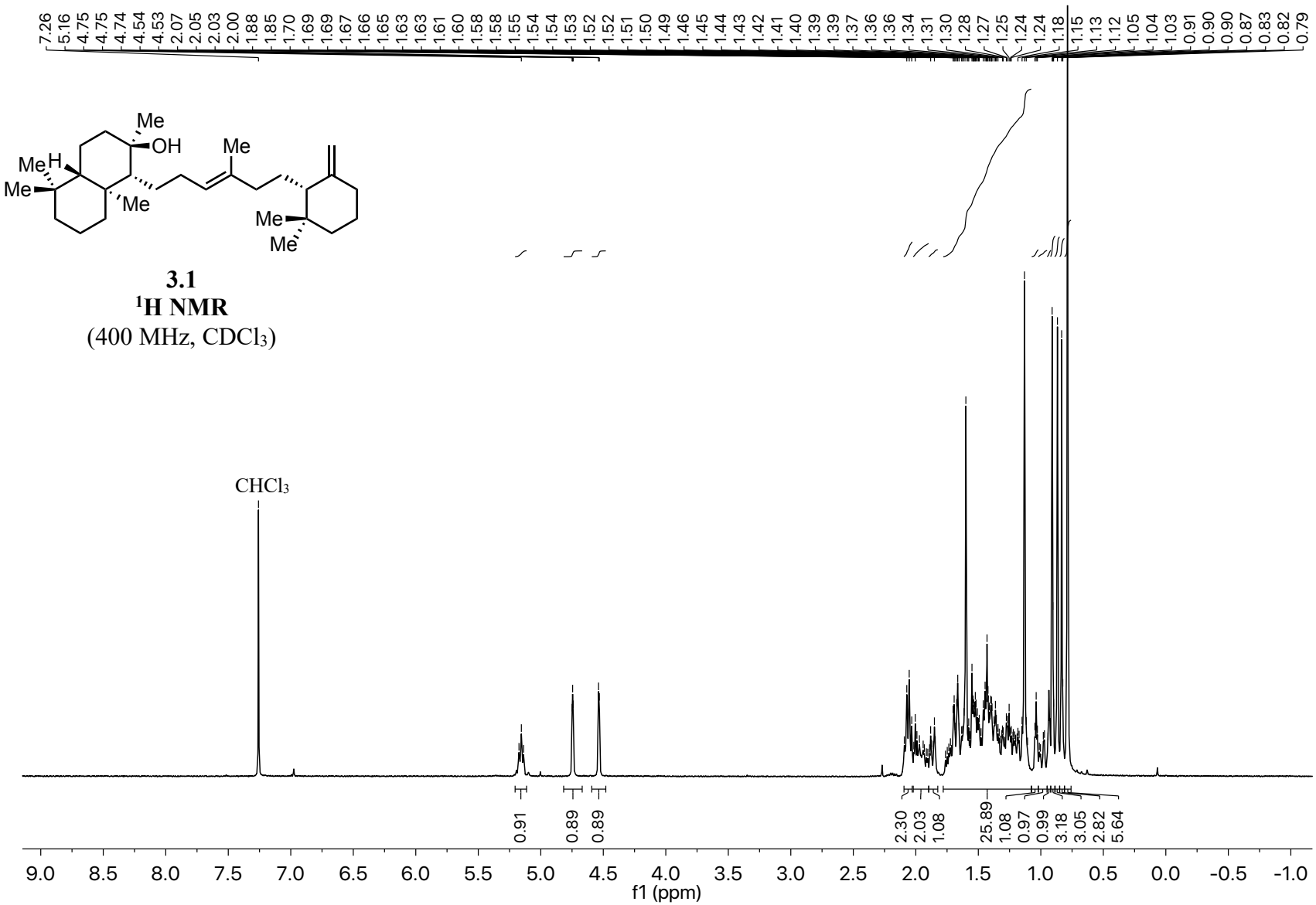
3.63
^{13}C NMR
(100 MHz, $CDCl_3$)



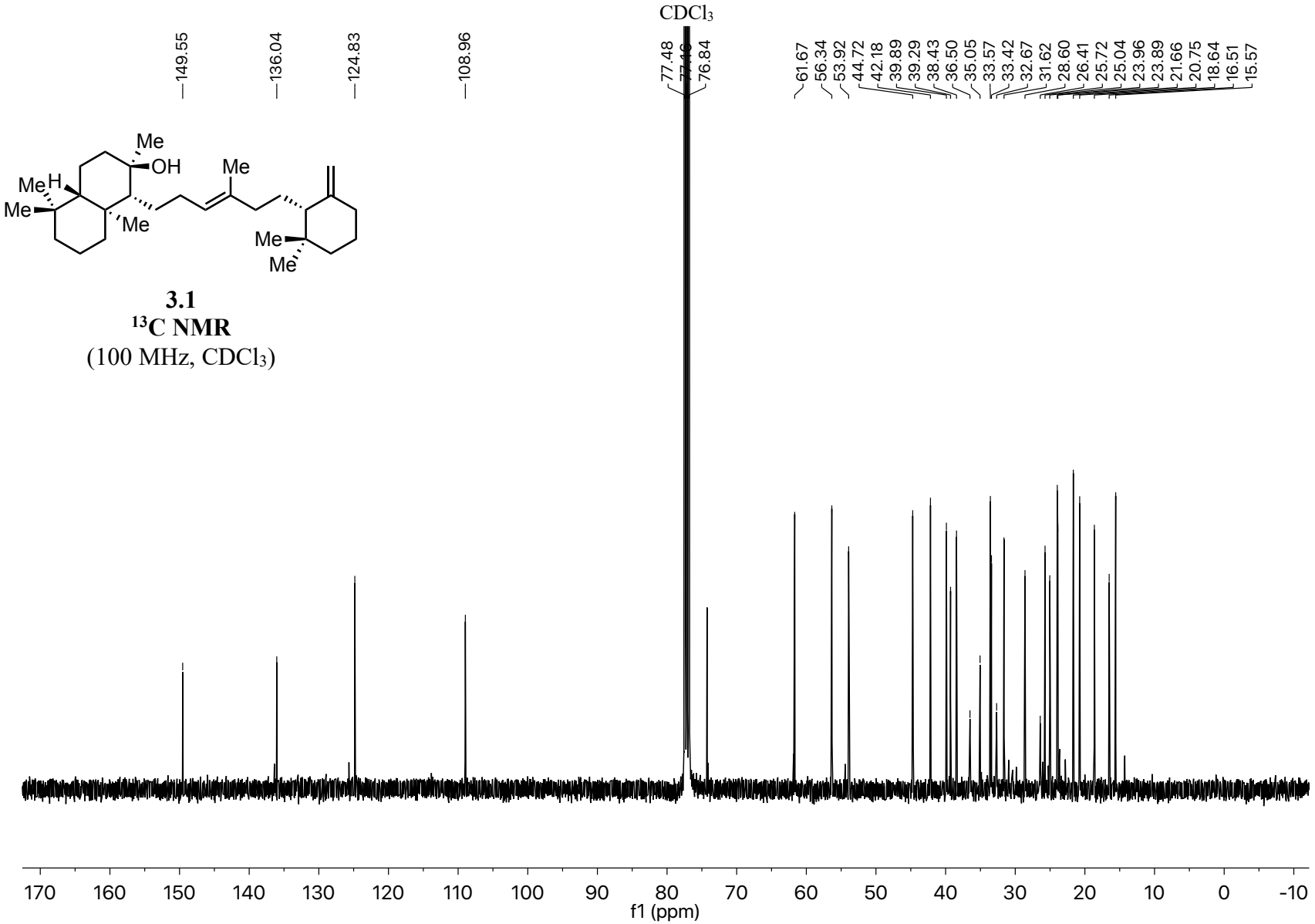
3.48
^{1}H NMR
(400 MHz, $CDCl_3$)



3.48
^{13}C NMR
(100 MHz, $CDCl_3$)



3.1
^{1}H NMR
(400 MHz, $CDCl_3$)



3.1
^{13}C NMR
(100 MHz, $CDCl_3$)

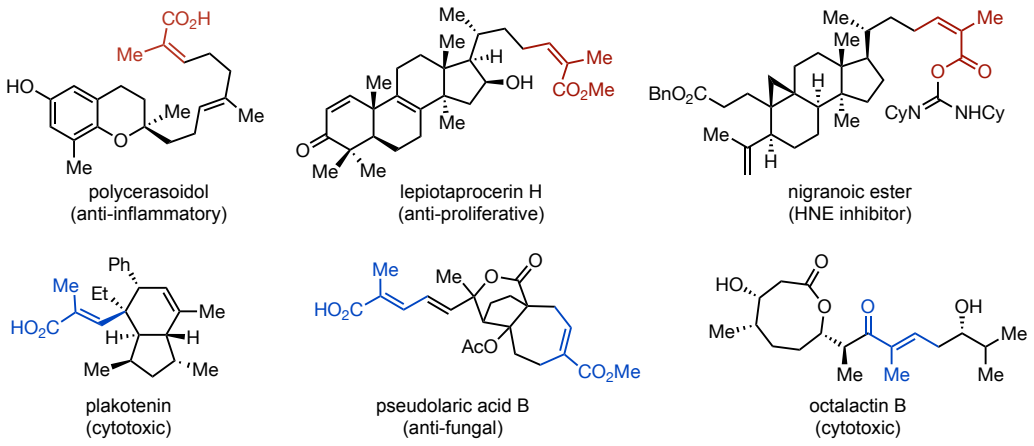
Chapter Four

Stereoretentive Cross-Metathesis of Trisubstituted α,β-Unsaturated Carbonyl Compounds

4.1 Introduction

α,β-Unsaturated acids, esters, and ketones are among the most common functional groups in organic molecules.[1] An important subclass includes those that contain a trisubstituted alkene with a methyl substituent at the α-position. This motif can be found either in as an *E*-trisubstituted alkene[2] or the respective *Z* isomer[3] (Scheme 4.1.1).

Scheme 4.1.1. Select Examples of Trisubstituted α,β-Unsaturated Acids and Esters



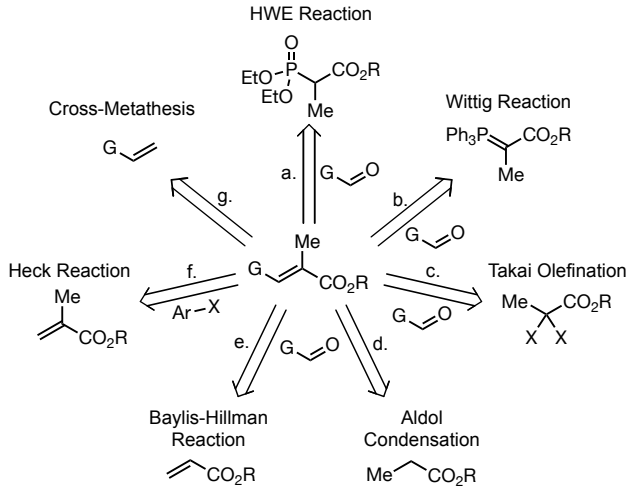
(1) Ertl, P.; Schuhmann, T. *J. Nat. Prod.* **2019**, *82*, 1258–1263.

(2) (a) Kobayashi, J.; Takeuchi, S.; Ishibashi, M.; Shigemori, H.; Sasaki, T. *Tetrahedron Lett.* **1992**, *33*, 2579–2580. (b) Zhou, B.; Ying, B.; Song, G.; Chen, Z.; Han, J.; Yan, Y. *Planta Med.* **1983**, *47*, 35–38. (c) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682–4683.

(3) (a) Zafra-Polo, M. C.; González, M. C.; Tormo, J. R.; Estornell, E.; Cortes, D. *J. Nat. Prod.* **1996**, *59*, 913–916. (b) Chen, H.-P.; Zhao, Z.-Z.; Li, Z.-H.; Huang, Y.; Zhang, S.-B.; Tang, Y.; Yao, J.-N.; Chen, L.; Isaka, M.; Feng, T.; Liu, J.-K. *J. Agric. Food Chem.* **2018**, *66*, 3146–3154. (c) Huang, G.; Feng, L.; Liu, B.; He, Y.; Li, Y.; Chen, Y. *Nat. Prod. Res.* **2015**, *29*, 1650–1656.

Apart from their ubiquity, α,β-unsaturated carbonyl compounds are widely used as starting materials for enantio-, diastereo-, and/or regioselective transformations, such as conjugate addition,[4] hydrogenation,[5] epoxidation,[6] or dihydroxylation.[7] For many reactions, the isomeric purity of the trisubstituted alkene is required for high stereoselectivity, and, consequently, the stereoselective preparation of these compounds is important.

Scheme 4.1.2. Different Way of Accessing *E*-Trisubstituted Enoates



Popular methods for the preparation of *E*-α,β-unsaturated carbonyl compounds include carbonyl olefination processes (Scheme 4.1.2.a–c). Aldehydes (or, less frequently, ketones) are made to react with a phosphonate ester (Horner-Wadsworth-Emmons

(4) For a review on stereoselective conjugate additions to α,β-unsaturated carbonyl compounds, see: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806.

(5) For reviews on stereoselective hydrogenation of α,β-unsaturated carbonyl compounds, see: (a) Lan, X.; Wang, T. *ACS Catal.* **2020**, *10*, 2764–2790. (b) Farrar-Tobar, R. A.; Dell'Acqua, A.; Tin, S.; de Vries, J. G. *Green Chem.* **2020**, *22*, 3323–3357. (c) Shevlin, M.; Friedfeld, M. R.; Sheng, H.; Pierson, N. A.; Hoyt, J. M.; Campeau, L.-C.; Chirik, P. J. *J. Am. Chem. Soc.* **2016**, *138*, 3562–3569.

(6) For a review on stereoselective epoxidation of α,β-unsaturated carbonyl compounds, see: Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215–1225.

(7) For examples of stereoselective dihydroxylation of α,β-unsaturated carbonyl compounds, see: (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Kobayashi, K.; Kobayashi, Y.; Nakamura, M.; Tamura, O.; Kogen, H. *J. Org. Chem.* **2015**, *80*, 1243–1248.

reaction) or an α-phosphorylidene ester (Wittig reaction).[8] Despite their reliability and wide applicability, these methods have several shortcomings, among which are generation of superstochiometric amounts of waste and the need for a strong base, which can be problematic when sensitive functional groups are present. Furthermore, the stereochemical outcome of these transformations is substrate-dependent and can vary according to the reagent involved, resulting in low stereoselectivity or favoring the undesired isomer.[9] Other, less frequently utilized protocols include Takai olefination,[10] aldol condensation,[11] Morita-Baylis-Hillman reaction,[12] Galat reaction,[13] and Heck reaction[14] (Scheme 4.1.2. c–g). Some of these transformations require multiple functional group manipulations, and all, except a Heck process, necessitate the use of an aldehyde.

A general problem is that, while there are strategies for preparation of *E*-trisubstituted α,β-unsaturated carbonyl compounds, there are far fewer options for synthesis of the corresponding *Z* isomers. Akin to synthesis methods for the *E* isomers, reactions of aldehydes with phosphonate esters is the favored way of accessing these compounds. To favor the *Z* isomer, specially designed reagents and conditions are usually needed. One entails the use of phosphonate esters with electron-withdrawing substituents, which facilitate elimination in the oxaphosphetate intermediate and promote *Z* selectivity

(8) Gu, Y.; Tian, S.-K. In *Stereoselective Alkene Synthesis*; Springer Berlin Heidelberg: Berlin, Heidelberg, 2012, pp 197–238.

(9) Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 1735–1741.

(10) Rodríguez-Solla, H.; Concellón, C.; Blanco, E. G.; Sarmiento, J. I.; Díaz, P.; Soengas, R. G. *J. Org. Chem.* **2011**, *76*, 5461–5465.

(11) Ozeki, M.; Egawa, H.; Kuse, A.; Takano, T.; Yasuda, N.; Mizutani, H.; Izumiya, S.; Nakashima, D.; Arimitsu, K.; Miura, T.; Kajimoto, T.; Hosoi, S.; Iwasaki, H.; Kojima, N.; Node, M.; Yamashita, M. *Synthesis* **2015**, *47*, 3392–3402.

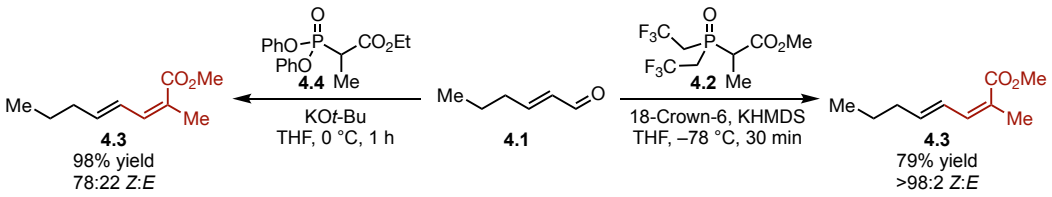
(12) Fernandes, L.; Bortoluzzi, A. J.; Sá, M. M. *Tetrahedron* **2004**, *60*, 9983–9989.

(13) Xavier, T.; Condon, S.; Pichon, C.; Le Gall, E.; Presset, M. *Org. Lett.* **2019**, *21*, 6135–6139.

(14) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526.

(Scheme 4.1.3). [15] Notable examples include polyfluorophosphonate esters (Still-Gennari) [16] and diarylphosphonate reagents (Ando). [17] The downside is the need for expensive 18-crown-6 and cryogenic conditions. Further, stereoselectivity of these reactions can vary widely, depending on the substrate.

Scheme 4.1.3. Methods for Synthesis of *Z*-Trisubstituted Enoates: Ando (left) and Still-Genari (right)



α,β-Unsaturated acids and esters can also be prepared through alkoxycarbonylation of alkenyl halides with carbon monoxide, promoted by palladium-based catalysts (Scheme 4.1.4, top).[18] These transformations are typically completely stereoretentive and therefore require the use of stereoisomerically pure alkenyl halide substrates, which are typically prepared from alkynes or aldehydes and can be accessed only in one isomeric form (for a detailed analysis, see Chapter Two). Alternatively, alkenyl halides may be subjected to a sequence of lithium-halogen exchange and treatment with carbon dioxide (Scheme 4.1.4, bottom). [19] Here again, the issue is the need for strongly basic conditions and a stereochemically pure alkenyl halide.

(15) (a) Ando, K. *J. Org. Chem.* **1999**, *64*, 6815–6821. (b) Motoyoshiya, J.; Kusaura, T.; Kokin, K.; Yokoya, S.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* **2001**, *57*, 1715–1721.

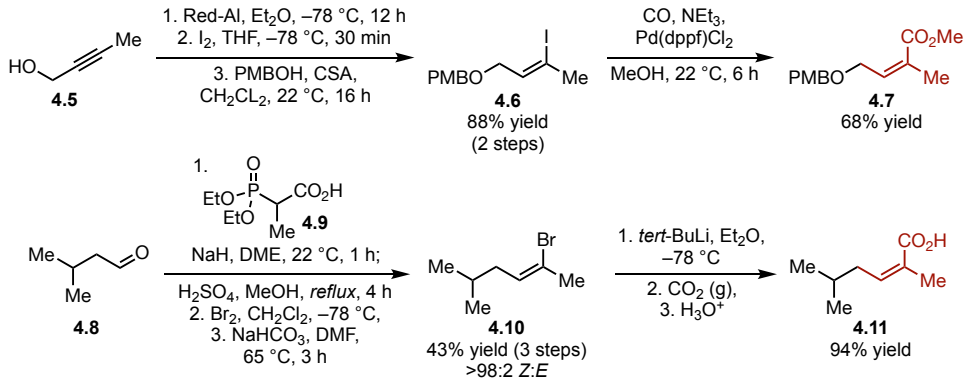
(16) For a review on the Still-Gennari reaction, see: Janicki, I.; Kiełbasiński, P. *Adv. Synth. Catal.* **2020**, *362*, 2552–2596.

(17) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411–8416.

(18) Lautens, M.; Paquin, J.-F. *Org. Lett.* **2003**, *5*, 3391–3394.

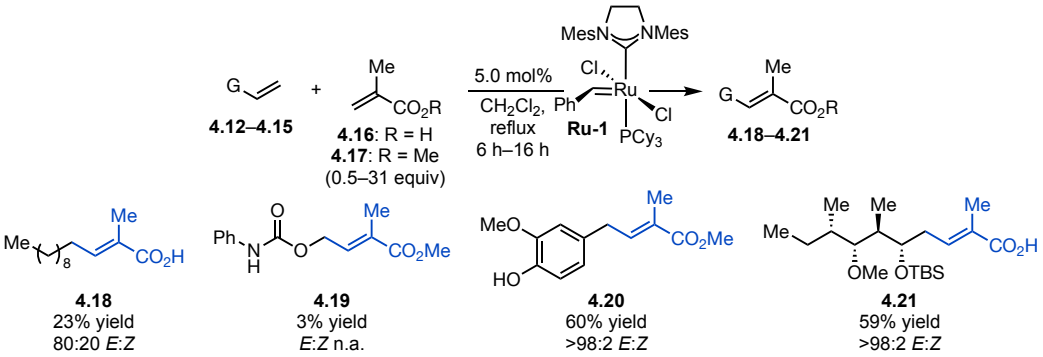
(19) Jeffery, D. W.; Perkins, M. V.; White, J. M. *Org. Lett.* **2005**, *7*, 1581–1584.

Scheme 4.1.4. Synthesis of *Z*-Trisubstituted α,β-Unsaturated Enoates from Alkenyl Halides



The majority of the extant methods rely on aldehyde substrates, often obtained through oxidative cleavage or ozonolysis of alkenes.[20] It would thus be preferrable if an α,β-unsaturated enoate could be directly accessed through catalytic olefin metathesis. There are cross-metathesis (CM) methods available for synthesis of *E*-disubstituted and *E*-trisubstituted α,β-unsaturated acids and esters (Scheme 4.1.5).[21] However, an excess of the often precious and non-purchasable terminal olefin starting material is necessary to maximize efficiency. Moreover, stereoselectivity and efficiency of these processes is strongly substrate-dependent.

Scheme 4.1.5. Synthesis of *E*-Trisubstituted α,β-Unsaturated Enoates through CM

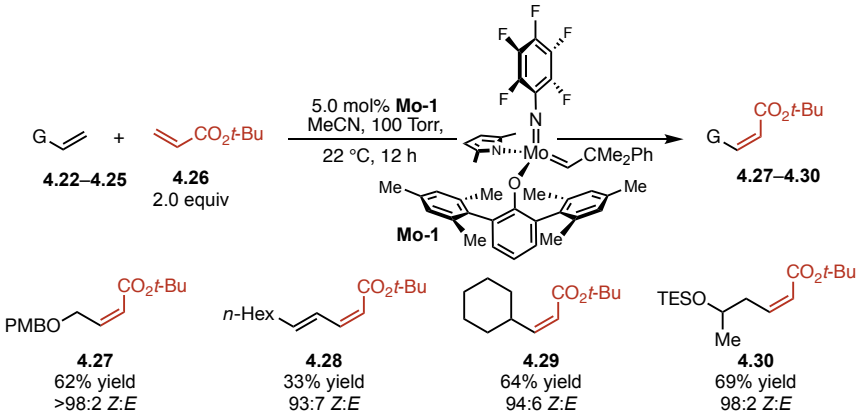


(20) For select examples of oxidative cleavage of alkenes for subsequent HWE reaction, see: (a) Nelson, H. M.; Gordon, J. R.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6699–6703. (b) Wang, X.; Wang, H.; Wu, X.; Yu, T.; Gao, W.; Shi, T.; Peng, X.; He, D.; Wang, Z. *Synlett* **2017**, *28*, 1660–1662. (c) Trost, B. M.; Zhang, G.; Gholami, H.; Zell, D. *J. Am. Chem. Soc.* **2021**, *143*, 12286–12293.

(21) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

In contrast, there are no reports of CM reactions that can be used to generate *Z*-trisubstituted enoates in high stereoisomeric purity. The most relevant case relates to synthesis of *Z*-disubstituted α,β-unsaturated esters through CM involving a Mo complex (Scheme 4.1.6).[22] Although stereoselectivity is high (>93:7 *Z*:*E*), *tert*-butyl esters must be used. We were thus led to ponder the feasibility of accessing *Z*-disubstituted α-methyl enoates by stereoretentive CM, catalyzed by an appropriate Mo complex, and involving a commercially available stereodefined enoate. As such, *Z*- and *E*-product isomers might become more easily accessible.

Scheme 4.1.6. Synthesis of *Z*-Disubstituted α,β-Unsaturated Enoates through CM



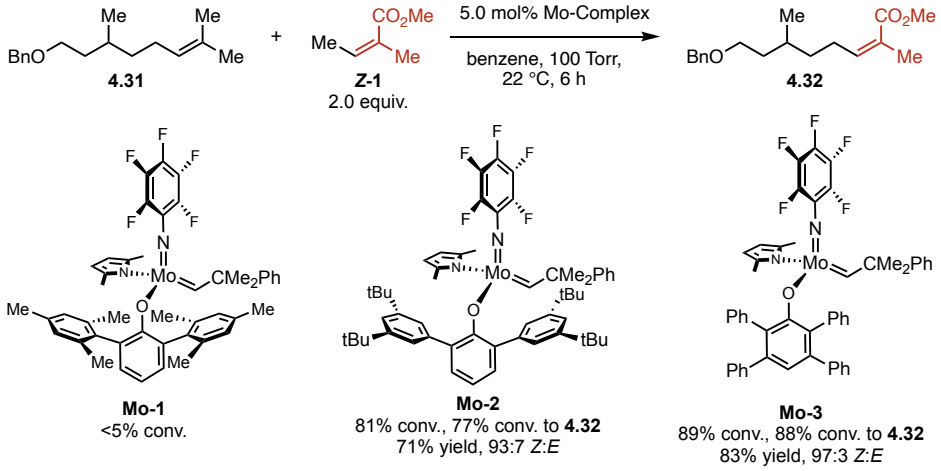
4.2 Catalyst Screening and Optimization Studies

We began with CM between two trisubstituted olefins so as to limit homocoupling Recent studies with chloro-fluoro alkenes had indicated that Mo monoaryloxide pyrrolide (MAP) complexes can be efficient in promoting CM of trisubstituted olefins.[23] We therefore first investigated this catalyst class (Scheme 4.2.1).

(22) Yu, E. C.; Johnson, B. M.; Townsend, E. M.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 13210–13214.

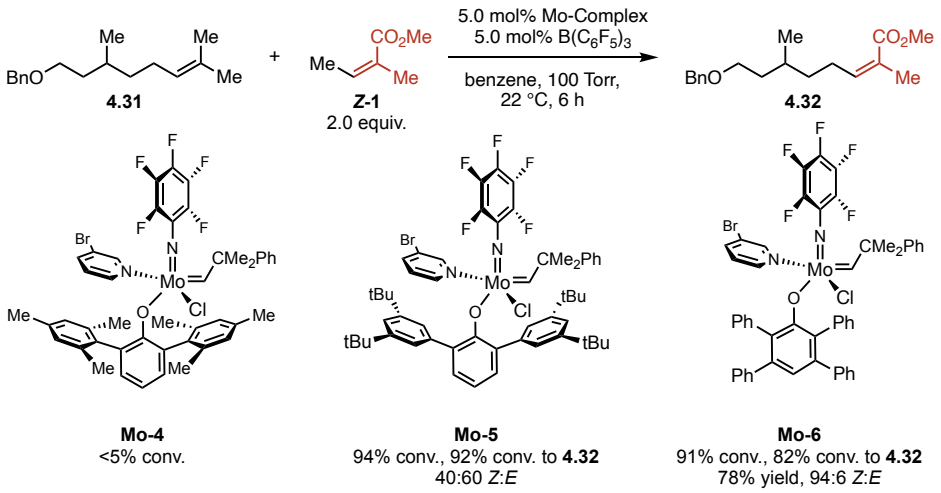
(23) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463–473.

Scheme 4.2.1. CM of Methyl Angelate ***Z*-1** and Benzyl Citronellol **4.31** with MAP Complexes



CM between benzyl-citronellol (**4.31**) and purchasable methyl angelate (***Z*-1**) did not afford any product with complex **Mo-1**. When **Mo-2**, bearing a smaller aryloxide ligand, was used, **4.32** was isolated in 71% yield and 93:7 *Z*:*E* ratio. Following this trend, use of **Mo-3**, a complex with an even smaller aryloxide ligand afforded **4.32** in 83% yield and 97:3 *Z*:*E* ratio.

Scheme 4.2.2. Cross-Metathesis of Methyl Angelate (***Z*-1**) and MAC Complexes



To improve efficiency further, the more reactive Mo monoaryloxide chloride (MAC) complexes were investigated.[24] A similar trend vis-à-vis the aryloxide size was observed here as well. While CM with **Mo-4** did not afford any of the desired product, use of complexes bearing a more diminutive ligand (that is, **Mo-5** and **Mo-6**) led to 92% and 82% conversion to **4.32**, respectively. Nonetheless, CM with **Mo-5** was hardly stereoretentive (40:60 *Z*:*E*). Although reactions with an appropriate MAC complex delivered the desired enoate in high stereoisomeric purity (94:6 *Z*:*E*), conversion to **4.32** was slightly lower compared to when a MAP complex was used (78% vs. 83%, previously).

While preparing **Mo-3**, we noticed an unexpected signal in the alkylidene region of the ^{1}H NMR spectrum. We surmised originate from a Mo bisaryloxide. To probe, when two equivalents of the aryloxide were added, the signal grew in intensity, and we were indeed able to isolate the bisaryloxide species. While less investigated than Mo Mac and particularly Mo MAP systems, related bisaryloxide complexes have previously been used to promote *Z*-selective macrocyclic ring-closing metathesis.[25] However, computational studies by Copéret and Eisenstein have shown that the combination of a strong and a weak σ-donor ligand an effect that is present in a MAP or a MAC system but lost in a bisaryloxide, in a Mo alkylidene is beneficial for the overall efficiency of an olefin metathesis process.[26] This hypothesis was experimentally corroborated by homo-metathesis and ring-opening metathesis polymerization processes disclosed by Schrock

(24) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80–85.

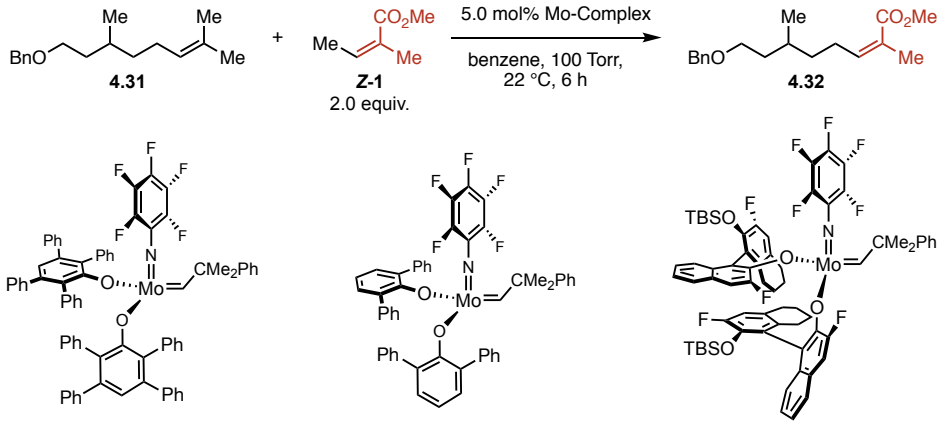
(25) (a) Wang, C.; Haeffner, F.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939–1943. (b) Yu, M.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 215–220.

(26) Poater, A.; Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2007**, *129*, 8207–8216.

and coworkers.[27] Nonetheless, we reasoned that a bisaryloxide complex may be more effective with electron-deficient substrates, because the increased HOMO of the alkylidene might facilitate complexation with ***Z*-1** and the resulting metallacyclobutane (mcb) should be better stabilized on account of diminished *trans* influence).[28]

Among the three bisaryloxide complexes investigated, **Mo-7** emerged as the most effective, affording target **4.32** in 91% yield and 95:5 *Z*:*E* selectivity (Scheme 4.2.3). Whereas **Mo-8** was less efficient and selective (56% conv., 84:16 *Z*:*E*), diminution in stereochemical control was particularly pronounced in the case of **Mo-9** (79% conv., 54:46 *Z*:*E*). The relatively inferior catalyst performance may be attributed lowering of the barrier to rotation around the C–C single bond for the phenyl substituents at the 2- and 6-position of the aryloxide ligand. The absence of the phenyl substituents at the 3- and 5-position, which would restrict rotation, likely decreases the steric pressure caused by the aryloxide ligand, culminating in diminished stereoselectivity.

Scheme 4.2.3. Cross-Metathesis of Methyl Angelate (***Z*-1**) and Bisaryloxide Complexes



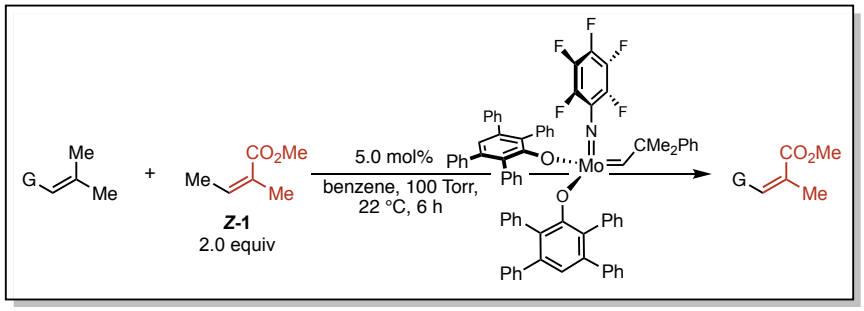
(27) (a) Yuan, J.; Schrock, R. R.; Müller, P.; Axtell, J. C.; Dobereiner, G. E. *Organometallics* **2012**, *31*, 4650–4653. (b) Yuan, J.; Schrock, R. R.; Gerber, L. C. H.; Müller, P.; Smith, S. *Organometallics* **2013**, *32*, 2983–2992. (c) Townsend, E. M.; Hyvl, J.; Forrest, W. P.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *Organometallics* **2014**, *33*, 5334–5341.

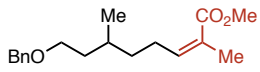
(28) Wang, C.; Haeffner, F.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939–1943.

4.3 Synthesis of Z- and E-Trisubstituted α,β-Unsaturated Esters

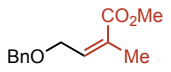
Since Mo bisaryloxide (BAO) **Mo-7** proved to be somewhat superior to Mo MAP complexes, we chose to use it for further study. To evaluate the scope of the method, we investigated reactions with olefins containing different functional groups (Scheme 4.3.1). *Z*-Trisubstituted α,β-unsaturated esters were obtained in 65–91% yield and with 94:6 to >98:2 *Z*:*E* ratio. Examples include ethers (**4.32**–**4.34**), esters (**4.35**–**4.37**), an imide (**4.38**), a tertiary amine (**4.39**), aryl-containing compounds (**4.40**, **4.41**), a homoallylic boronate (**4.42**), and an acetal (**4.43**).

Scheme 4.3.1. Substrate Scope for CM of *Z*-Trisubstituted α,β-Unsaturated Esters

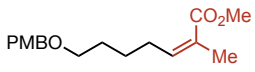




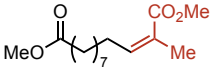
4.32
95% conv., 91% yield,
95:5 *Z*:*E*



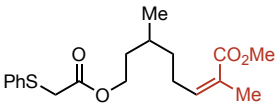
4.33
82% conv., 79% yield,
>98:2 *Z*:*E*



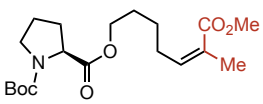
4.34
94% conv., 87% yield,
94:6 *Z*:*E*



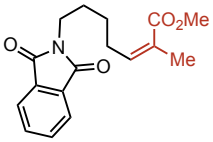
4.35
81% conv., 82% yield,
96:4 *Z*:*E*



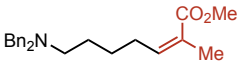
4.36*
89% conv., 86% yield,
>98:2 *Z*:*E*



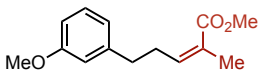
4.37*
89% conv., 85% yield,
97:3 *Z*:*E*



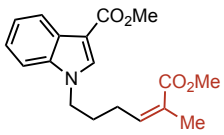
4.38
79% conv., 77% yield,
96:4 *Z*:*E*



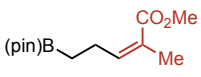
4.39*
89% conv., 85% yield,
96:4 *Z*:*E*



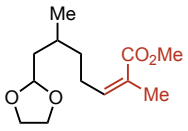
4.40*
69% conv., 65% yield,
>98:2 *Z*:*E*



4.41
87% conv., 81% yield,
98:2 *Z*:*E*



4.42
93% conv., 72% yield,
94:6 *Z*:*E*

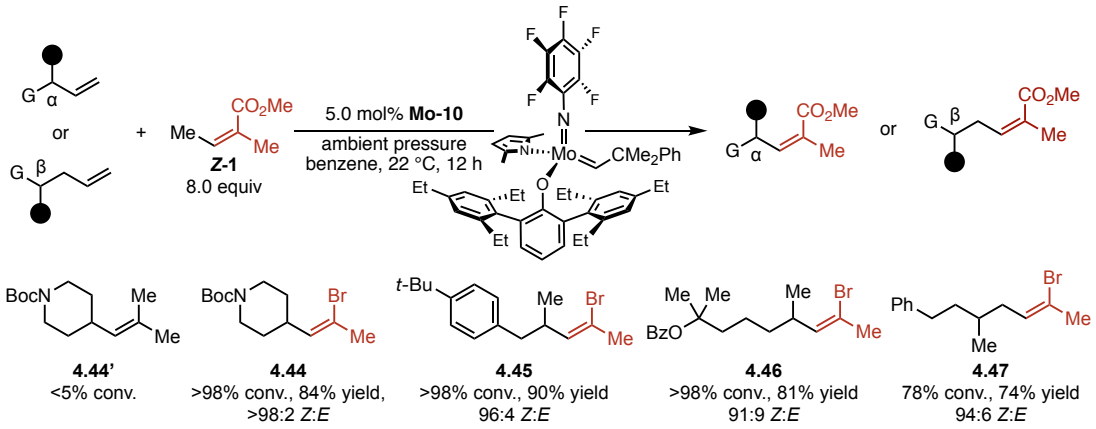


4.43
97% conv., 91% yield,
97:3 *Z*:*E*

*10 mol% cis-3-hexene was added.

CM between a trisubstituted olefin an α- or β-branched alkene proved to be especially problematic, as we were unable to detect any of desired product (**4.44'**, Scheme 4.3.2). Only when a sterically less hindered monosubstituted olefin was used, did CM proceed readily, and instead of **Mo-7**, here it was **Mo-10**, a MAP complex, that was the superior catalyst precursor. Furthermore, larger excess of methyl angelate (***Z*-1**) was needed to ensure appreciable transformation. Accordingly, α- or β-branched *Z*-trisubstituted α,β-unsaturated esters were synthesized in 74–90% yield and in 91:9 to >98:2 *Z*:*E* selectivity (Scheme 4.3.2). This included *N*-Boc-protected piperidine **4.44** as well as α- or β-methyl-branched compounds **4.45**–**4.47**.

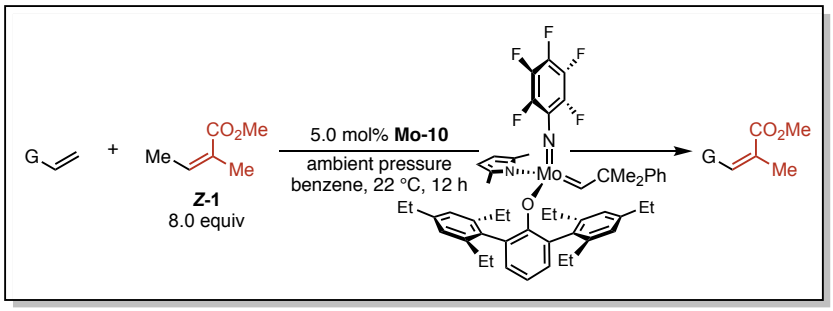
Scheme 4.3.2. CM of α- or β-Branched *Z*-Trisubstituted α,β-Unsaturated Esters

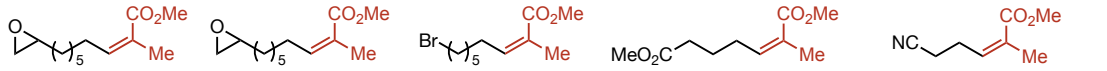


The aforementioned findings led to wonder whether any monosubstituted olefin, including those that are unhindered, might be suitable substrates. Such unsaturated hydrocarbons are abundant and represent an attractive set of CM substrates. As it turned out, CM reactions proved to be efficient, delivering the expected *Z*-enoates in 77–95% yield and in 96:4 *Z*:*E* ratio (Scheme 4.3.3). Moreover, reactions performed with a

commercially available paraffin tablet[29] that contains **Mo-4** (to obviate the need for a glove box), CM was similarly efficient and stereoselective as when the optimal catalyst (**Mo-10**) was employed.

Scheme 4.3.3. CM of α,β-Unsaturated Esters and Terminal Olefin Starting Materials





4.48 >98% conv., 77% yield, 96:4 *Z*:*E*

4.48* 97% conv., 64% yield, 96:4 *Z*:*E*

4.49 >98% conv., 94% yield, 96:4 *Z*:*E*

4.50 >98% conv., 95% yield, 96:4 *Z*:*E*

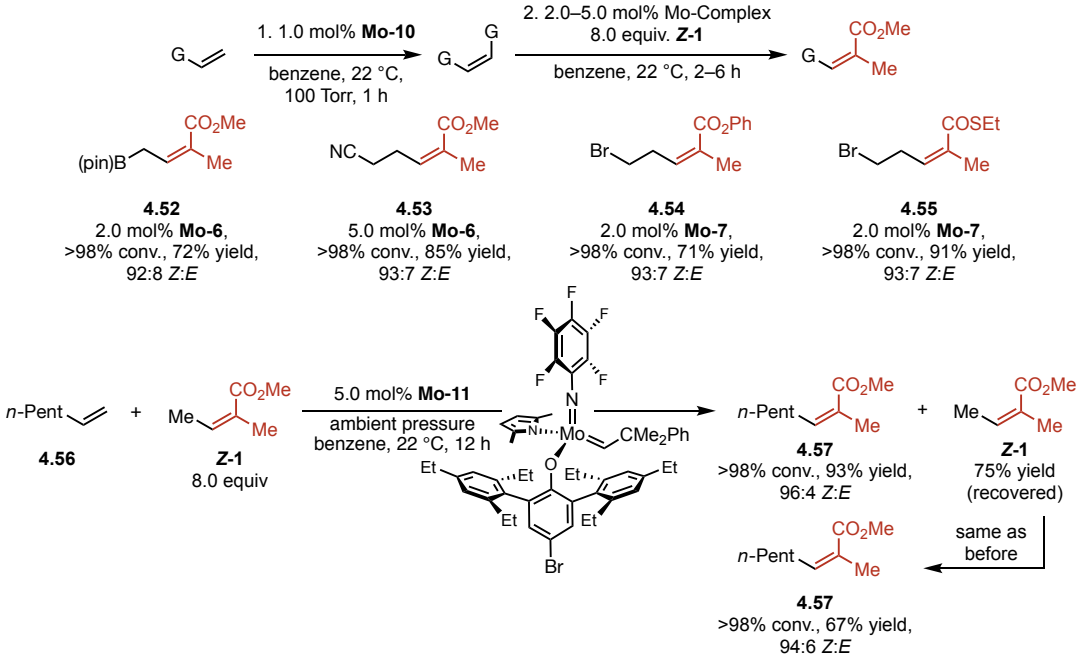
4.51 95% conv., 38% conv. to **4.51**, *Z*:*E* n.a.

*5.0 mol% **Mo-4** in a paraffin tablet used with toluene at 40 °C instead of benzene.

As might be expected, in the case of monosubstituted alkenes that are in a more congested environment, CM efficiency was lower, and homocoupling became the favored pathway. Since a disubstituted alkene in a homocoupled compound should be able to re-enter the catalytic cycle, we devised a two-step procedure for CM of these problematic substrates. The first step consisted of homocoupling of the terminal alkene, and the second step was comprised of addition of the appropriate amount of the enoate reagent (***Z*-1**) and a second batch of a Mo complex. Accordingly, CM of various hindered monosubstituted alkenes could be achieved with reasonable efficiency (Scheme 4.3.4). Although 8.0 equivalents of ***Z*-1** were needed, the unreacted material can be recovered and re-used.

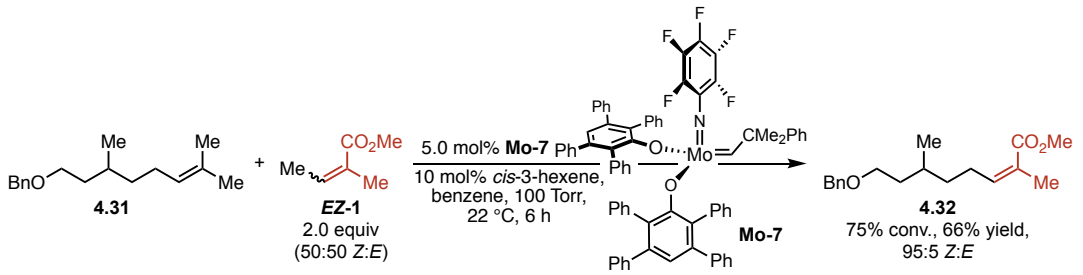
(29) Ondi, L.; Nagy, G. M.; Czirok, J. B.; Bucsai, A.; Frater, G. E. *Org. Process Res. Dev.* **2016**, *20*, 1709–1716.

Scheme 4.3.4. Two-Step CM of Terminal Olefins and Re-Subjection of ***Z*-1** to Standard CM Conditions



CM of **4.56** with ***Z*-1** proceeded to full conversion and the desired α,β-unsaturated esters **4.57** was isolated in 93% yield and 96:4 *Z*:*E* ratio. When excess ***Z*-1** was isolated and resubjected to the same conditions, **4.57** was isolated in slightly lower yield (67% vs. 93%, previously), but with identical isomeric purity (94:6 *Z*:*E*). When an equal isomeric mixture (***EZ*-1**) of the alkene starting material was used, **4.32** was isolated in 66% yield and 95:5 *Z*:*E* ratio, indicating that reaction with ***Z*-1** is faster (Scheme 4.3.5).

Scheme 4.3.5. CM with an Isomeric Mixture of Enoate **1**

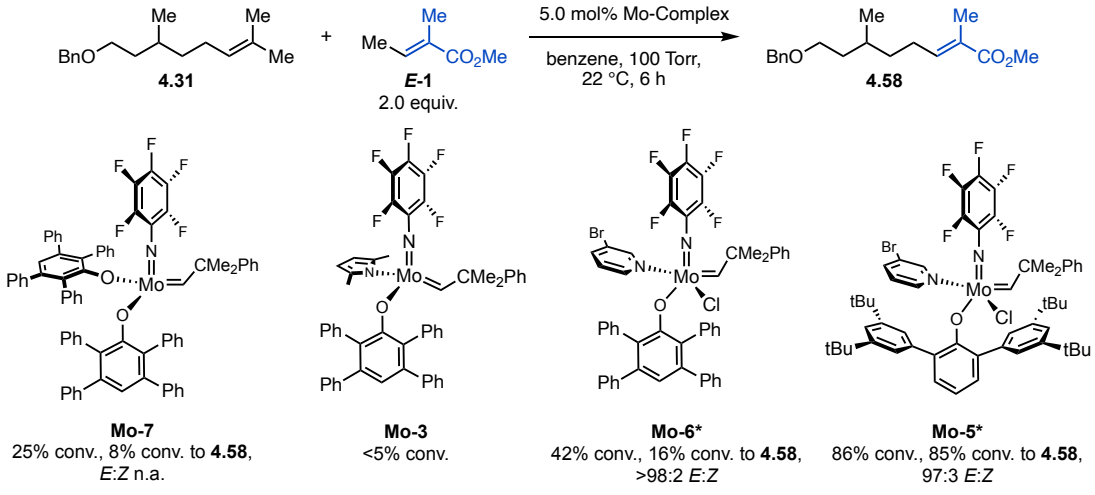


Despite the existing methods for the synthesis for *E*-trisubstituted α,β-unsaturated esters, we sought to establish conditions for an efficient CM with a Mo complex, a

complementary approach. This would allow trisubstituted alkenes to be used as starting materials, of which several are commercially available, and the CM of which cannot be readily promoted by a Ru catalyst.

When the previously identified optimal complex (**Mo-7**) and reaction conditions were used, there was only 8% conversion to **4.58** (Scheme 4.3.6; *E*:*Z* selectivity could not be determined). What is more, MAP complex **Mo-3**, effective in previous cases, did not promote any CM (<5%.). CM in the presence of **Mo-6** proceeded to 42% conversion, 16% of which was to **4.58** (>98:2 *E*:*Z*), a far less efficient transformation compared to when ***Z*-1** was used. Instead, **Mo-5** was found to be comparatively effective, in the presence of which **4.58** was formed in appreciable efficiency and high stereocontrol (85% conv. to **4.58**, 97:3 *E*:*Z*). The greater efficiency of MAC catalysts (vs. MAP and BAO variants) might be on account of steric factors. Product formation requires an mcb wherein the sizeable ester group is oriented towards the larger aryloxide ligand and, consequently, CM with MAC catalysts, which carry a smaller chlorine ligand, end up being more facile.[30]

Scheme 4.3.6. CM of Methyl Tiglate ***E*-1** in the Presence of Various Mo Complexes

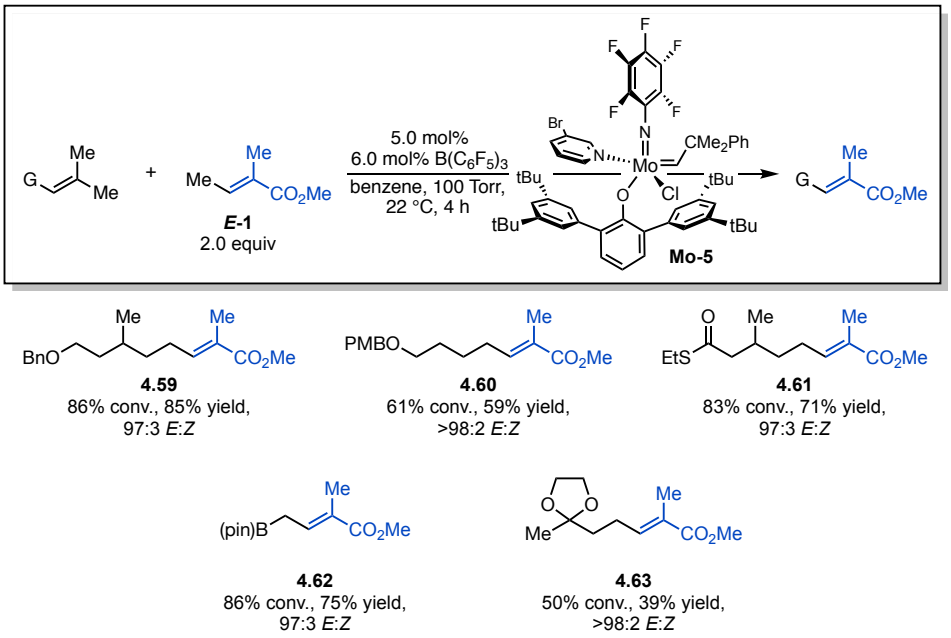


*5.0 mol% $B(C_6F_5)_3$ was added.

(30) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80–85.

With **Mo-5** and $B(C_6F_5)_3$ as the Lewis acid to bind and help dissociate 3-bromopyridine,[31] *E*-trisubstituted α,β-unsaturated esters were obtained in 39–85% yield and 97:3 to >98:2 *E*:*Z* ratio (Scheme 4.3.7). Product containing an ether (**4.59**, **4.60**), a thioesters (**4.61**), an allylic boronate (**4.62**), and an acetal (**4.63**) were thus obtained in high stereochemical purity (>97:3 *E*:*Z*).

Scheme 4.3.7. Substrate Scope for CM of *E*-Trisubstituted α,β-Unsaturated Esters



4.4 Z-Trisubstituted α,β-Unsaturated Aryl, Silyl, Thiol Esters, and Acyl Fluorides

Next, we set out to establish whether the catalytic approach may be extended to preparation of activated esters[32] and fluorides,[33] valuable sets of compounds that can be readily modified in a number of ways. A variety of α,β-unsaturated compounds were

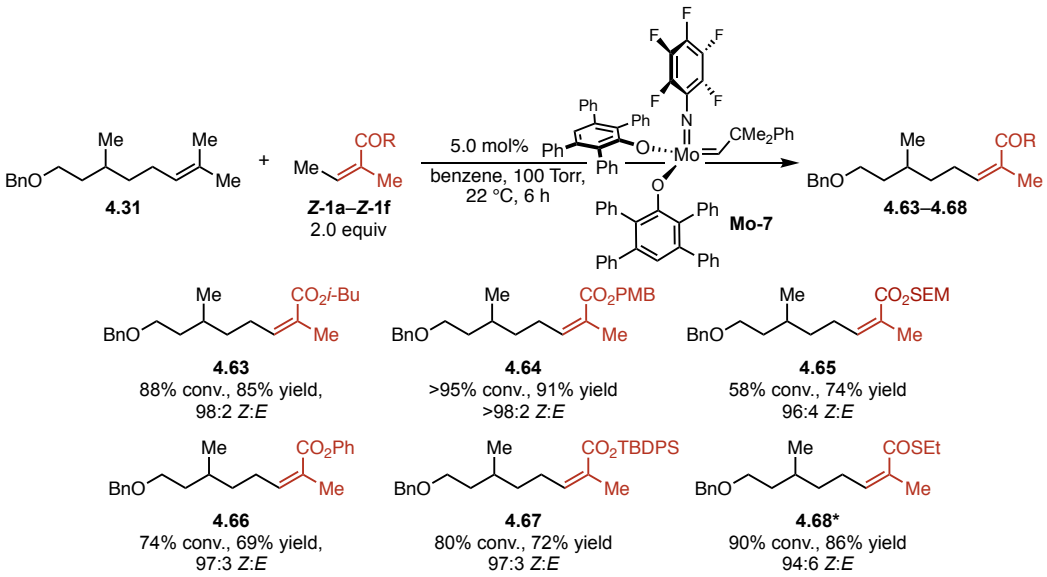
(31) Lam, J. K.; Zhu, C.; Bukhryakov, K. V.; Müller, P.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2016**, *138*, 15774–15783.

(32) Takise, R.; Muto, K.; Yamaguchi, J. *Chem. Soc. Rev.* **2017**, *46*, 5864–5888.

(33) Ogiwara, Y.; Sakai, N. *Angew. Chem. Int. Ed.* **2020**, *59*, 574–594.

purchased or synthesized (in one step from commercially available ***Z*-1**) and subjected to CM conditions with trisubstituted olefin **4.31** (Scheme 4.4.1). Accordingly, we were able to obtain *iso*-butyl- (**4.63**), *p*-methoxybenzyl- (PMB, **4.64**), 2-(trimethylsilyl)ethoxymethyl (SEM, **4.65**), phenyl- (**4.66**), *t*-butyldimethylsilyl- (TBS, **4.67**), and ethylthioester (**4.68**) in 69–91% yield and 96:4 to >98:2 *Z*:*E* ratio.

Scheme 4.4.1. CM of *Z*-Trisubstituted α,β-Unsaturated Aryl, Silyl, and Thiol Esters

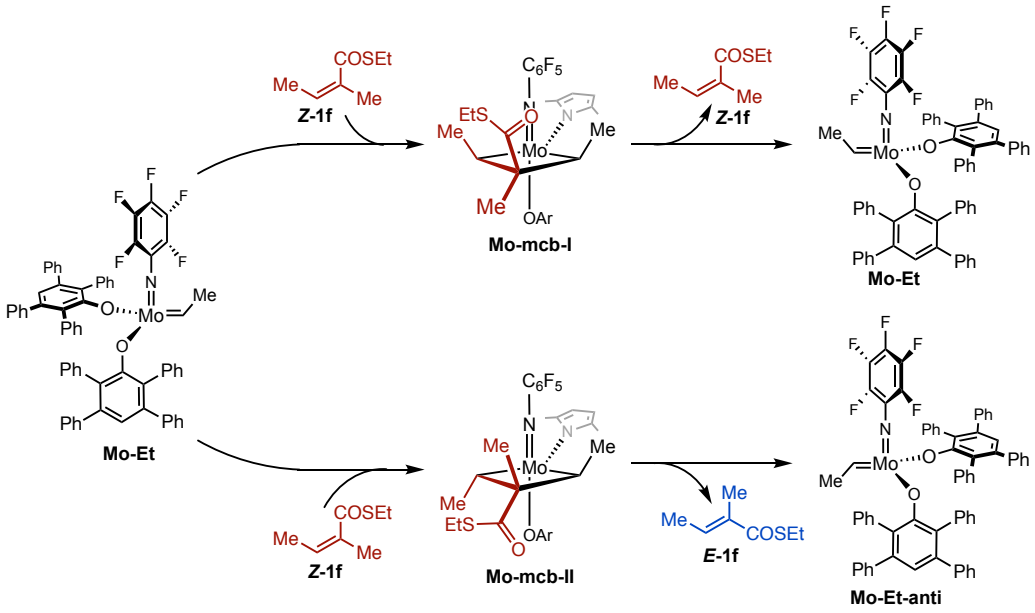


*3 h reaction time instead of 6 h.

Notably, CM involving ethylthioester ***Z*-1f** was less stereoretentive (88:12 *Z*:*E* vs. >96:4 *Z*:*E* for reactions with ***Z*-1a**–***Z*-1e**). When we monitored the *Z*:*E* ratio of ***Z*-1f** during the transformation, we observed a drastic change from >98:2 *Z*:*E* to 48:52 *Z*:*E* after 6 h. This is likely owing to pre-metathesis isomerization of ***Z*-1f** (Scheme 4.4.2). A possible scenario is that intermediate **Mo-Et** reacts with ***Z*-4f**, either via **Mo-mcb-I** or **Mo-mcb-II**. Reaction of the latter is non-productive, as after cycloreversion, ***Z*-1f** and **Mo-Et** are formed again. However, reaction via **Mo-mcb-II** converts ***Z*-1f** into ***E*-1f**, CM of which generates the undesired *E* isomer (***E*-4.68**). Moreover, **Mo-Et-anti** would be generated;

this more reactive *anti*-alkylidene[34] promotes isomerization of ***Z*-1f**. Since, in support of the proposed scenario, the amount of ***E*-1f** increased with time (deduced from analysis of the ^{1}H NMR spectrum), we decided to halt the reaction early and analyze the outcome. Indeed, after 4 h (vs. 6 h), **4.68** was isolated in 86% yield and 94:6 *Z*:*E* ratio.

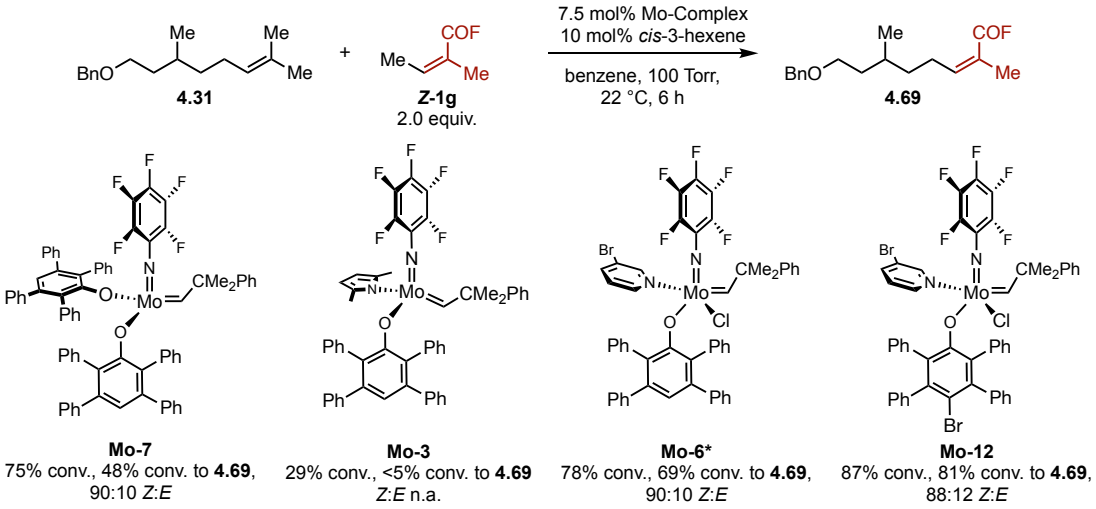
Scheme 4.4.2. Proposed Pre-Metathesis Isomerization Pathway



Study of CM with acyl fluoride ***Z*-1g** was next (Scheme 4.4.3). Under previously optimal reaction conditions and with bisaryloxide complex **Mo-7**, there was 75% conversion, but only 48% conversion of it was to the desired product (21% homocoupling; Scheme 4.4.3). Reactions with **Mo-3**, a MAP complex that contains the same aryloxide as **Mo-7** only led to the formation of homocoupling byproduct (28%).

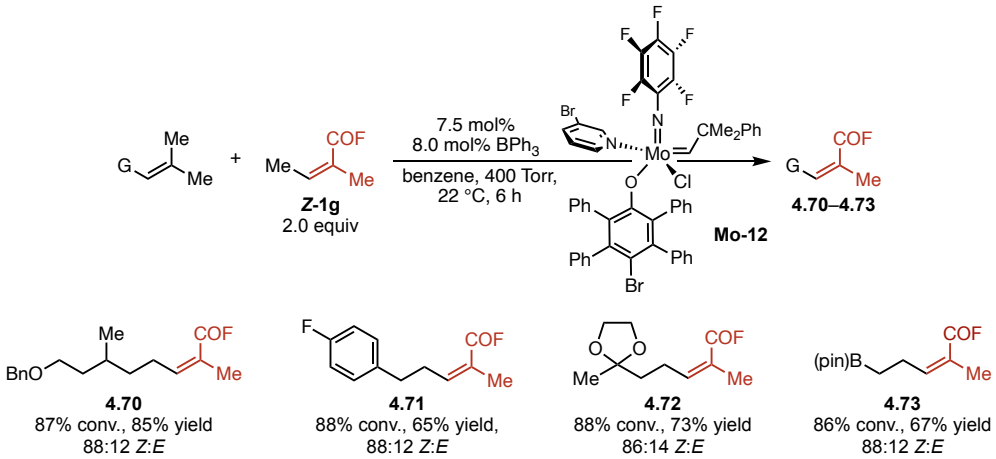
(34) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633.

Scheme 4.4.3. Catalyst Screening for CM of Trisubstituted Acyl Fluoride ***Z*-1g**



When a MAC complex was used, there was considerable decomposition. Through further experiments, we were able to establish that $B(C_6F_5)_3$ promotes decomposition; CM in the presence of less Lewis acidic BPh_3 was much more efficient (78% conv., 90:10 *Z*:*E*) and proceeded with without any detectable decomposition. For further optimization, we investigated MAC complex **Mo-12** (Scheme 4.4.4). As noted previously (see section 2.4), the presence of the bromide substituent can boost efficiency, albeit at the expense of some stereoretention (81% conv. to **4.69**, 88:12 *Z*:*E* vs. 69% conv. to **4.69**, 90:10 *Z*:*E*).

Scheme 4.4.4. Cross-Metathesis of *Z*-Trisubstituted α,β-Unsaturated Acyl Fluorides

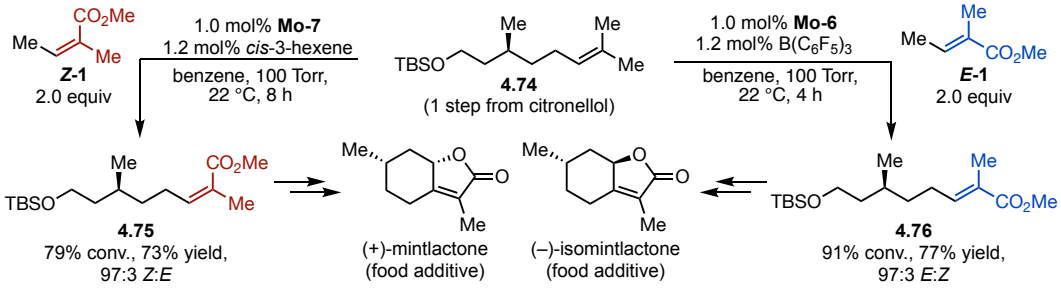


Accordingly, a number of *Z*-trisubstituted α,β-unsaturated acyl fluorides were synthesized in 65–85% yield and 86:14 to 88:12 *Z*:*E* ratio (Scheme 4.4.4).

4.5 Application to Synthesis of Bioactive Compounds

We sought to showcase the utility of the catalytic approach in several ways. One example relates to the synthesis of (+)-mintlactone and (–)-isomintlactone, which was previously accessed through a sequence of dihydroxylation, oxidative cleavage, and HWE or Wittig olefination.[35] Our plan was to access the trisubstituted α,β-unsaturated carboxylic esters directly by a stereoretentive CM involving commercially available and inexpensive citronellol (Scheme 4.5.1). With as little as 1.0 mol% catalyst loading of a MAC or bisaryloxide complex, *Z*- or *E*-trisubstituted α,β-unsaturated methyl ester (**4.75** or **4.76**) were isolated on a gram-scale in 73% and 77% yield, respectively, and in 97:3 stereoisomeric purity. This compares favorably to the 57% and 48% yield obtained over three steps, as described by Wang and co-workers.

Scheme 4.5.1. CM of TBS-Citronellol for Synthesis of Mintlactone and Isomintlactone



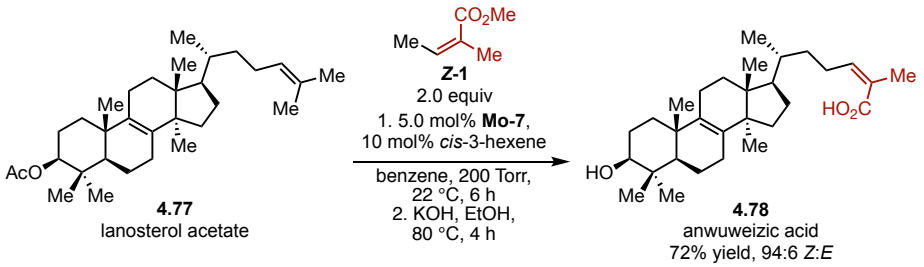
Another example is the synthesis of manwuweizic acid, a naturally occuring triterpenoid with anti-cancer activity against Lewis lung carcinoma cell lines.[36] Liu and coworkers followed a similar strategy for its synthesis as the previous example. Starting

(35) Wang, X.; Wang, H.; Wu, X.; Yu, T.; Gao, W.; Shi, T.; Peng, X.; He, D.; Wang, Z. *Synlett* **2017**, *28*, 1660–1662.

(36) Liu, J.-S.; Huang, M.-F.; Tao, Y. *Can. J. Chem.* **1988**, *66*, 414–415.

from lanosterol, they adopted a 6-step sequence to convert the trisubstituted alkene to an aldehyde for subsequent Wittig reaction and oxidation to the target α,β-unsaturated carboxylic acid intermediate.[37] In contrast, when **4.77** was subjected to the aforementioned CM conditions, anwuweizic acid was isolated **4.78** in 72% yield and 94:6 *Z*:*E* ratio (Scheme 4.5.2). Once again, the direct CM is clearly more efficient compared to the former route, which required six steps and afforded the same compound in 40% overall yield.

Scheme 4.5.2. Synthesis of 3-Epi-Anwuweizic Acid from Lanosterol Acetate Through CM



4.6 Conclusions

We have developed a strategy for the synthesis of *Z*- and *E*-Trisubstituted α,β-unsaturated carbonyl compounds through stereoretentive CM involving commercially available or easily accessible alkene substrates. The method is applicable to a variety of α,β-unsaturated esters, thioesters, and acyl fluorides. Furthermore, mono-, di-, and trisubstituted alkenes can be used as starting materials. Transformations may be carried out on gram scale and, in some cases, with commercially available Mo catalysts. The utility of the catalytic approach was highlighted through synthesis of previously accessed intermediates more directly and with improved efficiency.

(37) Liu, J.-S.; Tao, Y. *Tetrahedron* **1992**, *48*, 6793–6798.

4.7 Experimental Section

4.7.1 General

Unless noted otherwise, reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard glovebox or vacuum-line techniques. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher Scientific or Carlo Erba Reagents) in air. Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, λ_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). NMR spectra were acquired on a Varian Unity INOVA 400 (400 MHz), Varian Unity INOVA 500 (500 MHz), or Varian Unity INOVA 600 (600 MHz) spectrometer (at Merkert Chemistry Department, Boston College), or 400 MHz or 500 MHz Bruker instruments (at Institute of Science Supramolecular Engineering, University of Strasbourg). Chemical shifts for ^1H NMR spectra are reported in ppm with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard ($CDCl_3$: δ 7.26 ppm, CD_2Cl_2: δ 5.32 ppm, C_6D_6: δ 7.16 ppm, DMSO-d_6: δ 2.50 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constant (Hz). Chemical shifts for ^{13}C NMR spectra are reported in ppm with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard ($CDCl_3$: δ 77.16 ppm, CD_2Cl_2: δ 53.84 ppm, C_6D_6: δ 128.06 ppm; DMSO-d_6: δ 39.52 ppm), with complete proton decoupling. Chemical shifts for ^{11}B NMR spectra are reported in ppm with BF_3•Et_2O (10% in $CDCl_3$) as reference. Chemical shifts for ^{19}F NMR spectra are reported in ppm. High-resolution mass spectrometry was performed either on a JEOL AccuTOF DART (positive

mode) at the Mass Spectrometry Facility, Boston College, or on a UHPLC + Ultimate 300 from Thermo equipped with a PDA detector coupled with a Q Exactive extended Mass HRMS from Thermo Fisher Scientific at Institute of Science Supramolecular Engineering, University of Strasbourg.

4.7.2 Solvents

Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and hexanes were purified through a copper oxide column and an alumina column; dichloromethane, diethyl ether, and tetrahydrofuran (THF, Fisher Scientific) were purged with argon and purified by passage through two alumina columns. Dimethoxyethane (DME, Aldrich, extra dry, inhibitor free) was purified by passage through two alumina columns in a glovebox. Alternatively, THF, Et_2O and DME were purified by distillation from sodium benzophenone ketyl immediately prior to use. Benzene was purchased from Aldrich (HPLC grade) and purified by passage through an activated basic alumina column in the glovebox. Acetonitrile (Acros Organics, extra dry), and *N*,*N*-dimethylformamide (DMF, Acros Organics, extra dry) were used directly as received unless otherwise specified.

Solvents for preparation of Mo complexes were stored in a N_2-filled glovebox over 3 Å or 4 Å molecular sieves for at least 48 hours prior to use. Solvents were tested with ketyl radical (if applicable) prior to use.

4.7.3 Reagents and Substrates

Ammonium chloride (Fisher Scientific), benzoyl chloride (TCI), benzyl chloride (Sigma Aldrich), 9-borabicyclo(3.3.1)nonane (Sigma-Aldrich), bromine (Acros), 1-bromo-2-methylprop-1-ene (Sigma-Aldrich), 5-bromo-2-methylpent-2-ene (Alfa Aesar), *tert*-

butyldimethylsilyl chloride (Oakwood), *tert*-butyldiphenylsilyl chloride (Oakwood), caesium carbonate (Strem), (±)-camphorsulfonic acid (Sigma-Aldrich), 1-chloro-3-methylbut-2-ene (TCI), (3,5-di-*tert*-butylphenyl)boronic acid (Ambeed), dicyclohexyl(2′,6′-dimethoxy[1,1′-biphenyl]-2-yl)phosphane (Strem), diethylaminosulfur trifluoride (Oakwood), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Oakwood), 4-(dimethylamino)pyridine (Oakwood), 3,7-dimethyloct-6-enal (TCI), 3,7-dimethyloct-6-en-1-ol (Sigma-Aldrich), 2,6-diphenylphenol (**DPPO**, Sigma-Aldrich), ethanethiol (Acros), ethylene glycol (Oakwood), 4-fluorostyrene (TCI), (*Z*)-hex-3-ene (TCI), hydrochloric acid (Fisher Scientific), imidazole (Oakwood), iodine (Alfa Aesar), isopropyltriphenylphosphonium iodide (Sigma Adlrich), lithium hydroxide monohydrate (Fisher Scientific), lithium carbonate (Fisher Scientific), 2-mesitylmagnesium bromide (1 M in THF, Sigma-Aldrich), 4-methoxybenzyl chloride (TCI), 2-methylbut-2-ene (TCI), (*Z*)-2-methylbut-2-enoic acid (TCI), 3-methylbut-2-en-1-ol (TCI), 6-methyl-5-hepten-2-one (TCI), methyl 10-undecenoate (TCI), methyl 1*H*-indole-3-carboxylate (Oakwood), 2-methyl-2-phenylpropylmagnesium chloride (0.5 M in Et_2O, Sigma Aldrich), methyltriphenylphosphonium iodide (Sigma Aldrich), *N*-(*tert*-butoxycarbonyl)-L-proline (Synthonix), palladium(II) acetate (Strem), palladium(II) bis(acetylacetonate) (Strem), pentafluoroaniline (Oakwood), phenol (TCI), 3-phenylbutanal (Fluorochem), 2-(phenylthio)acetic acid (TCI), phthalimide (Fluka), sodium bicarbonate (Fisher Scientific), sodium chloride (Fisher Scientific), sodium hydride (Strem), sodium molybdate (Strem), sodium sulfate (Fisher Scientific), sodium sulfite (Fisher Scientific), tetrakis(triphenylphosphine)palladium (Strem), 1,3,5-triethylbenzene (TCI), triflic acid (Acros), 2,4,6-triisopropylphenylmagnesium bromide (1 M in THF, Sigma Aldrich),

trimethylsilyl chloride (Oakwood), 2-(trimethylsilyl)ethoxymethyl chloride (TCI), triphenylborane (Sigma Aldrich), tris(pentafluorophenyl)borane (TCI), 10-undecenoic acid (Sigma Aldrich), and 3-vinylanisole (Sigma Aldrich) were purchased and used as received

4-Bromobut-1-ene (TCI), 8-bromooct-1-ene (TCI), 2,5-dimethylpyrrole (TCI), hept-1-ene (TCI), isobutyl angelate (TCI), methyl angelate (TCI), methyl hex-5-enoate (TCI), 2-(oct-7-en-1-yl)oxirane (TCI), pent-4-enenitrile (TCI), triethylamine (Sigma-Aldrich) were distilled over CaH_2 prior to use.

n-Butyllithium and methyllithium were used as received and titrated according to a previously reported procedure prior to use.[38] Bis(pinacolato)diboron (Fluorochem) was recrystallized from *n*-pentane prior to use. Lanosterol (AstaTech) was purified according to a previously reported procedure.[39] Lithium chloride (Oakwood) was dried under vacuum (0.1 Torr) at 200 °C for 5 h prior to use. Pinacolborane (TCI) was distilled under vacuum and stored in a glovebox. 4,4,5,5-Tetramethyl-2-(3-methylbut-2-en-1-yl)-1,3,2-dioxaborolane (Sigma-Aldrich) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Sigma-Aldrich) were pretreated with HB(pin) and NEt_3 and distilled prior to use.

Benzyl 3,7-dimethyl-oct-6-enyl ether (**2a**),[40] methyl 11-methyldodec-10-enoate (**2b**),[41] 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione (**2c**),[41] *p*-methoxybenzyl 6-methylhept-5-en-1-yl ether (**2d**),[42] methyl 1-(5-methylhex-4-en-1-yl)-1*H*-indole-3-carboxylate (**2e**),[43] 2-

(38) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281–283.

(39) (a) Kavtaradze, L. K.; Manley-Harris, M.; Nicholson, B. K. *Steroids* **2004**, *69*, 227–233. (b) Kavtaradze, L. K.; Manley-Harris, M.; Nicholson, B. K. *Steroids* **2004**, *69*, 697–700.

(40) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4873–4875.

(41) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463–473.

(42) Marco, J. L.; Hueso-Rodríguez, J. A. *Tetrahedron Lett.* **1988**, *29*, 2459–2462.

(43) Glaisyer, E. L.; Watt, M. S.; Booker-Milburn, K. I. *Org. Lett.* **2018**, *20*, 5877–5880.

(2,6-dimethylhept-5-en-1-yl)-1,3-dioxolane (**2f**),[44] benzyl 3-methylbut-2-en-1-yl ether (**2g**),[45] 4,4,5,5-tetramethyl-2-(4-methylpent-3-enyl)-1,3,2-dioxaborolane (**2h**),[46] 1-methoxy-3-(4-methylpent-3-en-1-yl)benzene (**2i**),[47] *N*,*N*-dibenzyl-6-methylhept-5-en-1-amine (**2j**),[41] 1-(*tert*-butyl) 2-(6-methylhept-5-en-1-yl) (*S*)-pyrrolidine-1,2-dicarboxylate (**2k**),[48] 3,7-dimethyloct-6-en-1-yl 2-(phenylthio)acetate (**2l**),[41] *tert*-butyldiphenylsilyl 3-methylbut-2-en-1-yl ether (**2m**),[49] (3,6-dimethylhept-5-en-1-yl)benzene (**2n**),[50] (5-methylhex-4-en-2-yl)benzene (**2o**),[51] prenylboronic acid pinacol ester (**2p**),[52] *tert*-butyl 4-vinylpiperidine-1-carboxylate (**2q**),[53] 2,6-dimethyloct-7-en-2-yl benzoate (**2r**),[54] 3-methylpent-4-en-1-yl benzoate (**2s**),[54] 1-(*tert*-butyl)-4-(2-methylbut-3-en-1-yl)benzene (**2t**),[53] and *tert*-butyl((2-methylbut-3-en-1-yl)oxy)diphenylsilane (**2v**)[41] were prepared according to previously reported procedures. Alkene substrates were either distilled over CaH_2 under vacuum or dried by azeotropic distillation (with anhydrous benzene or toluene) prior to use.

(44) Zaghouani, M.; Kunz, C.; Guédon, L.; Blanchard, F.; Nay, B. *Chem. Eur. J.* **2016**, *22*, 15257–15260.

(45) Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. *Science* **2017**, *357*, 575–579.

(46) Aggarwal, V. K.; Ball, L. T.; Carobene, S.; Connelly, R. L.; Hesse, M. J.; Partridge, B. M.; Roth, P.; Thomas, S. P.; Webster, M. P. *Chem. Commun.* **2012**, *48*, 9230.

(47) Bahou, K. A.; Braddock, D. C.; Meyer, A. G.; Savage, G. P.; Shi, Z.; He, T. *J. Org. Chem.* **2020**, *85*, 4906–4917.

(48) Enholm, J. E.; Low, T.; Cooper, D.; Ghivirija, I. *Tetrahedron* **2012**, *68*, 6920–6927.

(49) Nyland II, R. L.; Xiao, Y.; Liu, P.; Freel Meyers, C. L. *J. Am. Chem. Soc.* **2009**, *131*, 17734–17735.

(50) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

(51) Nakahara, A.; Satoh, K.; Kamigaito, M. *Macromolecules* **2009**, *42*, 620–625.

(52) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 7092–7100.

(53) Reichl, K. D.; Dunn, N. L.; Fastuca, N. J.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, *137*, 5292–5295.

(54) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *Nat. Chem.* **2016**, *8*, 144–150.

4.7.4 Preparation of Ligands and Organometallic Complexes

TPPO was prepared according to a previously reported procedure.[55] **BrTPPO** was prepared according to a previously reported procedure.[56]

Mo-1 was prepared according to a previously reported procedure.[57] **Mo-2** was prepared according to a previously reported procedure.[58] **Mo-4** and **Mo-5** were prepared according to a previously reported procedure.[59] **Mo-9** was prepared according to a previously reported procedure.[60]

Mo-10 was prepared according to a previously reported procedure.[42]

$Mo(NC_6F_5)_2Cl_2(DME)$ (Mo-A): This complex was prepared according to a previously reported procedure.[61] Under N_2 atmosphere, an oven-dried 250 mL round-bottom flask equipped with a magnetic stir bar and a condenser, was charged with $NaMoO_4$ (4.12 g, 20.0 mmol), $C_6F_5NH_2$ (9.16 g, 42.0 mmol), DME (60 mL), Et_3N (14 mL, 100 mmol), and TMSCl (25 mL, 200 mmol). The mixture was allowed to warm to 80 °C and stir for 15 h. Subsequently, the dark red solution was allowed to cool to 22 °C, filtered through a pad of celite, and volatiles were removed in vacuo. The so-obtained dark red oil was suspended in Et_2O, and the mixture was allowed to cool to −40 °C. After 12 h at that temperature, the suspension was filtered to afford **Mo-A** as orange solid (9.31 g, 15.0 mmol, 75% yield).

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(55) Maezono, S. M. B.; Poudel, T. N.; Lee, Y. R. *Org. Biomol. Chem.* **2017**, *15*, 2052–2062.

(56) Townsend, E. M.; Kilyanek, S. M.; Schrock, R. R.; Müller, P.; Smith, S. J.; Hoveyda, A. H. *Organometallics* **2013**, *32*, 4612–4617.

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

(58) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569–575.

(59) Mu, Y.; Nguyen, T. T.; Koh, M. J.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2019**, *11*, 478–487.

(60) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937.

(61) Sues, P. E.; John, J. M.; Schrock, R. R.; Müller, P. *Organometallics* **2016**, *35*, 758–761.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05 (s, 4H), 4.01 (s, 6H); **^{19}F NMR (376 MHz, $CDCl_3$):** δ −145.51 (m, 4F), −152.37 (t, *J* = 20.9 Hz, 2F), −162.04 (m, 4F).

$Mo(NC_6F_5)_2(CH_2CMe_2Ph)_2$ (Mo-B): This complex was prepared according to a previously reported procedure.[29] Under N_2 atmosphere, an oven-dried 250 mL Schlenk flask equipped with a magnetic stir bar was charged with **Mo-A** (9.31 g, 15.0 mmol) and Et_2O (50 mL). The mixture was allowed to cool to −40 °C, and $PhMe_2CCH_2MgCl$ (60 mL, 30 mmol, 0.50 M) was added. The mixture was allowed to warm to 22 °C and stir for 3 h. Subsequently, the mixture was filtered through a pad of celite, and the volatiles were removed in vacuo. The so-obtained dark red oil was suspended and triturated in hexanes (30 mL), resulting in formation of dark yellow precipitate. The suspension was filtered through a pad of celite, and the filtrate was concentrated to 20 mL, resulting in formation of a red precipitate. The suspension was allowed to cool to −40 °C. After at 12 h at that temperature, the red solid was collected by filtration, washed with cold hexanes, and dried in vacuo to afford **Mo-B** as red solid (5.26 g, 7.26 mmol, 49% yield). **^{1}H NMR (600 Hz, C_6D_6)**: δ 7.26 – 7.21 (m, 4H), 7.09 – 7.03 (m, 4H), 6.93 – 6.87 (m, 2H), 1.94 (s, 4H), 1.36 (s, 12H); **^{19}F NMR (564 Hz, C_6D_6):** δ −149.28 (m, 4F), −159.67 (t, *J* = 21.8 Hz, 2F), −163.85 – −164.54 (m, 4F).

$Mo(NC_6F_5)(CHCMe_2Ph)(DME)(OTf)_2$ (Mo-C): This complex was prepared according to a previously reported procedure.[29] Under N_2 atmosphere, an oven-dried 250 mL round-bottom flask equipped with a magnetic stir bar was charged with **Mo-B** (5.00 g, 6.90 mmol), Et_2O (110 mL), and DME (12.0 mL). The resulting solution was allowed to cool to −40 °C, after which TfOH (3.18 g, 20.7 mmol) was added. The mixture was allowed to warm to 22 °C and stir for 3 h. The resulting yellow solid was collected by filtration,

washed with Et_2O (20 mL), and dried in vacuo to afford **Mo-C** as yellow solid (3.03 g, 3.80 mmol, 55% yield). **^{1}H NMR (500 MHz, C_6D_6):** *trans* isomer (major): δ 13.73 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 2H), 6.97 (t, *J* = 7.8 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 3.32 (s, 3H), 3.27 (s, 2H), 3.01 (s, 3H), 2.89 (s, 2H), 1.61 (s, 6H); *cis* isomer (resolved signals only): δ 15.00 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 2H), 6.89 (t, *J* = 7.6 Hz, 2H); **^{19}F NMR (564 Hz, C_6D_6):** *trans* isomer (major): δ −76.83 (t, *J* = 5.4 Hz, 6F), −140.38 – −141.12 (m, 2F), −149.58 (t, *J* = 21.8 Hz, 1F), −161.43 – −162.08 (m, 2F); *cis* isomer (resolved signals only): δ −76.62 (s, 3F), −77.53 (s, 3F), −143.34 (m, *J* = 20.9 Hz, 2F), −151.33 (d, *J* = 21.3 Hz, 1F), −161.19 – −161.63 (m, 2F).

Mo(NC_6F_5)(CHCMe$_2$Ph)(Me$_2$-Pyr)$_2$ (Mo-D): This complex was prepared according to a previously reported procedure.[29] Under N_2 atmosphere, an oven-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with Mo(NC_6F_5)(CHCMe$_2$Ph)(DME)$(OTf)_2$ (798 mg, 1.00 mmol) and toluene (50 mL). The resulting suspension was allowed to cool to −40 °C, after which LiMe$_2$Pyr (222 mg, 2.20 mmol) was added. The mixture was allowed to warm to 22 °C and stir for 30 min. Subsequently, the solution was concentrated to dryness, and the dark red oil was dissolved in CH_2Cl_2 (10.0 mL). The resulting suspension was filtered through a glass Büchner funnel, and the filtrate was concentrated in vacuo. The so-obtained red oil was dissolved in Et_2O (5.0 mL) and allowed to cool to −40 °C. After 12 h at this temperature, the red solid was collected by filtration, washed with cold Et_2O (2.0 mL), and dried in vacuo to afford **Mo-D** as orange solid (397 mg, 0.66 mmol, 66% yield). **^{1}H NMR (500 Hz, C_6D_6):** δ 13.01 (s, 1H), 7.14 – 7.10 (m, 2H), 6.86 – 6.80 (m, 2H), 6.77 – 6.72 (m, 1H), 5.93 (br, 4H), 2.09 (br, 12H), 1.41 (s, 6H); **^{19}F NMR (376 Hz, C_6D_6):** δ −145.41 – −145.91 (m, 2F), −157.29 (t, *J*

= 21.8 Hz, 1F), −163.38 – −163.55 (m, 2F).

Mo(NC_6F_5)(CHCMe_2Ph)(TPPO)(Me_2pyr) (Mo-3): In a N_2-filled glovebox, an oven-dried 4 mL screw thread vial equipped with a magnetic stir bar was charged with **Mo-D** (29.9 mg, 0.05 mmol) and toluene (500.0 μL). The mixture was allowed to stir at 22 °C until the solution became homogeneous (~ 1 min). Then, the mixture was allowed to cool to –30 °C for 2 hours, after which **TPPO** (19.9 mg, 0.05 mmol) was added in one portion while the solution was still cold. The mixture was allowed to warm to 22 °C and stir for 8 h. Analysis of aliquot samples by ^{1}H NMR spectroscopy indicated full conversion of Mo(NC_6F_5)(CHCMe_2Ph)(Me_2Pyr)$_2$ to the **Mo-3**. The solution was stored in a freezer (–30 °C) and allowed to warm to room temperature prior to use without further purification. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 11.76 (s, 1H); **^{19}F NMR (564 MHz, $CDCl_3$):** δ –143.96– –144.07 (m, 2F), –157.01– –157.26 (m, 1F), –163.82 (t, *J* = 22.2 Hz, 2F).

Mo(NC_6F_5)(CHCMe_2Ph)(TPPO)Cl(3-Brpy) (Mo-6): In an oven-dried 7 mL screw thread vial, a solution of **Mo-3** (0.200 mmol) was prepared according to the procedure described above. 3-Bromopyridinium chloride (40.9 mg, 0.210 mmol) was added in one portion. The resulting dark red mixture was allowed to stir for 2 h at 22 °C until the color changed to orange, after which it was filtered through a short plug of celite, and the filtrate was concentrated to dryness. The residue was co-evaporated with toluene (~ 2 mL) three times until it became a solid, after which pentane (~4 mL) was added and the mixture was stirred at 22 °C for 30 min. The mixture was allowed to cool to –30 °C in a freezer for 2 hours, and the precipitate was collected by filtration to afford **Mo-6** as light-yellow solid (181.0 mg, 0.181 mmol, 90% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 12.68 (s, 1H); **^{19}F**

NMR (564 MHz, $CDCl_3$): δ –144.09– –144.19 (d, J = 16.8 Hz, 2F), –157.74 (t, J = 21.1 Hz, 1F), –162.63– –162.76 (m, 2F).

Mo(NC_6F_5)($CHCMe_2Ph$)($TPPO)_2$ (Mo-7): In a N_2-filled glovebox, an oven-dried 7 mL screw thread vial equipped with a magnetic stir bar was charged with **Mo-D** (180.0 mg, 0.3 mmol), **TPPO** (239.1mg, 0.6 mmol), and benzene (3.0 mL). The vial was sealed (screw cap and PTFE septum) and the reaction mixture was allowed to stir for 12 hours at 70 °C, after which it was allowed to cool to room temperature. Analysis of the ^1H and ^{19}F NMR spectra of aliquots indicated full conversion. The solution was stored in a freezer (–30 °C) and allowed to warm to room temperature prior to use without further purification.

Mo-7 can be isolated as yellow solid. For that, the above mentioned solution was concentrated to dryness, resulting a dark-brown foam. The residue dissolved in toluene (3 mL) and transferred to an oven-dried 20 mL vial, and the solution was concentrated to dryness. The evaporation process was repeated three times until precipitate formed, after which the residue was suspended in Et_2O/pentane, and the suspension was allowed to cool to –30 °C in a freezer for 12 hours. The solid was collected by filtration (or by removal of supernatant through a syringe) and washed with a small amount of pentane (290.0 mg, 0.253 mmol, 84% yield). **^1H NMR (500 MHz, C_6D_6):** δ 10.55 (s, 1H); **^{19}F NMR (471 MHz, C_6D_6):** δ –144.72– –144.83 (m, 2F), –158.06 (t, J = 21.8 Hz, 1F), –164.39 (td, J = 23.2, 6.0 Hz, 2F).

Mo(NC_6F_5)($CHCMe_2Ph$)($DPPO)_2$ (Mo-8): This complex was prepared in the same fashion as **Mo-7**, except for the use of a **DPPO** instead of **TPPO** as aryloxide ligand.

Mo(NC_6F_5)($CHCMe_2Ph$)(BrTPPO)Cl(3-Brpy) (Mo-11): This complex was prepared in the same fashion as **Mo-6**, except for the use of **BrTPPO** instead of **TPPO** as aryloxide

ligand. **Mo-11** was isolated as light-yellow solid (205.0 mg, 0.190 mmol, 95% yield). **^{1}H NMR** (500 MHz, CD_2Cl_2): δ 12.44 (s, 1H); **^{19}F NMR** (471 MHz, CD_2Cl_2): δ –144.47– –144.62 (m, 2F), –158.36 (t, *J* = 21.2 Hz, 1F), –163.54 (td, *J* = 22.2, 5.9 Hz, 2F).

4.7.5 Cross-Metathesis Reactions

General Procedure A:

In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with alkene substrate (0.10 mmol), ***Z*-1** (22.8 mg, 0.20 mmol), and a solution of **Mo-7** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The mixture was allowed to stir under vacuum (100 Torr) for 6 h at 22 °C. The reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. The so-obtained brown oil was purified through silica gel chromatography to afford the desired product. Consumption of starting material, product formation, and isomeric ratio were determined by analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture.

General Procedure B:

In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with alkene substrate (0.10 mmol), ***Z*-1** (22.8 mg, 0.20 mmol), *cis*-3-hexene in benzene (1.0 M, 6.0 μL, 6.0 μmol), and a solution of **Mo-7** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The mixture was allowed to stir under vacuum (100 Torr) for 6 h at 22 °C. The reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. The so-obtained brown oil was purified through silica gel chromatography to afford the desired product. Consumption of starting material, product formation, and isomeric ratio were determined by analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture.

General Procedure C:

In a N_2-filled glovebox, an oven-dried 4 mL vial equipped with a magnetic stir bar was charged with alkene substrate (0.10 mmol), **Mo-12** (8.1 mg, 7.5 μmol), and benzene (50.0 μL). The mixture was stired manually until the solution became homogeneous (~ 30 sec), after which ***Z*-1g** (30.6 mg, 0.30 mmol) and a solution of BPh_3 (0.1 M in benzene, 80.0 μL, 8.0 μmol) were added subsequently. The mixture was allowed to stir under vacuum (400 Torr) for 2 h at 22 °C. The reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. The so-obtained brown oil was purified through silica gel chromatography to afford the desired product. Consumption of starting material, product formation, and isomeric ratio were determined by analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture.

General Procedure D:

In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with alkene substrate (0.10 mmol), ***Z*-1** (91.3 mg, 0.80 mmol), and a solution of **Mo-10** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The vial was loosely caped, and the mixture was allowed to stir for 6 h at 22 °C under ambient pressure. The reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. The so-obtained brown oil was purified through silica gel chromatography to afford the desired product. Consumption of starting material, product formation, and isomeric ratio were determined by analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture.

General Procedure E:

In a N_2-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with alkene substrate (0.10 mmol), ***E*-1** (0.20 mmol), a solution of **Mo-5** (0.1 M

in benzene, 50.0 μL, 5.0 μmol), and $B(C_6F_5)_3$ (0.1 M in benzene, 60.0 μL, 6.0 μmol). The mixture was allowed to stir under vacuum (100 Torr) for 4 h at 22 °C. The reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. The so-obtained brown oil was purified through silica gel chromatography to afford the desired product. Consumption of starting material, product formation, and isomeric ratio were determined by analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture.

Methyl (*Z*)-8-(benzyloxy)-2,6-dimethyloct-2-enoate (4.32): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 95% conversion, 93% conversion to product, in 95:5 *Z*:*E*. **4.32** was isolated as colorless oil (26.4 mg, 0.091 mmol, 91% yield). **IR (neat):** 2949 (m), 2922 (m), 2853 (w), 1714 (s), 1453 (m), 1433 (m), 1363 (m), 1221 (m), 1196 (m), 1143 (m), 1096 (s), 1077 (m), 735 (m), 697 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.36–7.31 (m, 4H), 7.31–7.26 (m, 1H), 5.92 (tq, *J* = 7.5, 1.5 Hz, 1H), 4.50 (d, *J* = 1.5 Hz, 2H), 3.73 (s, 3H), 3.56–3.45 (m, 2H), 2.56–2.39 (m, 2H), 1.92–1.85 (m, 3H), 1.73–1.57 (m, 2H), 1.49–1.38 (m, 2H), 1.31–1.18 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.6, 143.8, 138.8, 128.5, 127.7, 127.6, 126.8, 73.0, 68.7, 51.3, 36.8, 36.8, 29.8, 27.2, 20.8, 19.6; **HRMS (DART):** Calcd for $C_{18}H_{27}O_3$ $[M+H]^+$: 291.1955, found: 291.1959.

Methyl (*Z*)-4-(benzyloxy)-2-methylbut-2-enoate (4.33): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 82% conversion, 79% conversion to product, in 97:3 *Z*:*E*. **4.33** was isolated as colorless oil (17.0 mg, 0.077 mmol, 77% yield). **IR (neat):** 3027 (w), 2949 (w), 2850 (w), 1714 (s), 1453 (m), 1434 (m), 1356 (w), 1226 (s), 1141 (s), 1106 (m), 1072 (m), 736 (m), 698 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39–7.26 (m, 5H), 6.18 (tq, *J* = 5.0, 1.6 Hz, 1H),

4.53 (s, 2H), 4.51–4.45 (m, 2H), 3.72 (s, 3H), 1.95–1.90 (m, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 167.8, 142.2, 138.3, 128.6, 127.9, 127.8, 127.4, 72.9, 69.0, 51.7, 20.0; **HRMS (DART):** Calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1172, found: 221.1183.

Methyl (*Z*)-7-((4-methoxybenzyl)oxy)-2-methylhept-2-enoate (4.34): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 94% conversion, 93% conversion to product, in 96:4 *Z*:*E*. **4.34** was isolated as colorless oil (25.4 mg, 0.087 mmol, 87% yield). **IR (neat):** 2929 (m), 2854 (m), 1714 (s), 1611 (m), 1511 (s), 1455 (m), 1434 (m), 1363 (m), 1300 (m), 1243 (s), 1214 (m), 1194 (m), 1179 (m), 1138 (m), 1097 (s), 1035 (m), 820 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.28–7.23 (m, 2H), 6.91–6.84 (m, 2H), 5.92 (tq, *J* = 7.3, 1.5 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.44 (t, *J* = 6.5 Hz, 2H), 2.51–2.43 (m, 2H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.66–1.60 (m, 2H), 1.53–1.45 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.6, 159.3, 143.4, 130.9, 129.3, 127.1, 113.9, 72.7, 70.0, 55.4, 51.3, 29.5, 29.4, 26.2, 20.8; **HRMS (DART):** Calcd for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1591, found: 291.1597.

Dimethyl (*Z*)-2-methyldodec-2-enedioate (4.35): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 84% conversion, 80% conversion to product, in 96:4 *Z*:*E*. **4.35** was isolated as colorless oil (21.0 mg, 0.078 mmol, 78% yield). **IR (neat):** 2924 (m), 2852 (m), 1736 (s), 1716 (s), 1455 (w), 1434 (m), 1363 (w), 1227 (m), 1193 (s), 1165 (s), 1124 (m), 1097 (w), 1077 (w) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 5.92 (tq, *J* = 7.5, 1.5 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 2.47–2.39 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.90–1.86 (m, 3H), 1.64–1.55 (m, 2H), 1.43–1.34 (m, 2H), 1.28 (s, 8H); *E* isomer (resolved signals only): 6.77 – 6.72 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 174.4, 168.7, 143.8, 126.8, 51.5, 51.3, 34.2, 34.2,

29.7, 29.5, 29.4, 29.3, 29.2, 25.1, 20.8; **HRMS (DART):** Calcd for $C_{15}H_{27}O_4$ $[M+H]^+$: 271.1904, found: 271.1903.

Methyl (*Z*)-2,6-dimethyl-8-(2-(phenylthio)acetoxy)oct-2-enoate (4.36): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 59% conversion, 53% conversion to product, in 97:3 *Z*:*E*. **4.36** was isolated as colorless oil (29.9 mg, 0.086 mmol, 86% yield). **IR (neat):** 2951 (m), 2921 (m), 2849 (w), 1714 (s), 1455 (m), 1436 (m), 1267 (s), 1222 (m), 1196 (m), 1141 (s), 1077 (w), 739 (m), 689 (m) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.42–7.38 (m, 2H), 7.32–7.27 (m, 2H), 7.25–7.18 (m, 1H), 5.90 (tq, *J* = 7.4, 1.5 Hz, 1H), 4.22–4.02 (m, 2H), 3.73 (s, 3H), 3.63 (s, 2H), 2.56–2.34 (m, 2H), 1.93–1.84 (m, 3H), 1.69–1.57 (m, 1H), 1.56–1.46 (m, 1H), 1.46–1.34 (m, 2H), 1.34–1.16 (m, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 169.9, 168.5, 143.4, 135.2, 130.0, 129.2, 129.2, 127.0, 64.1, 51.3, 36.8, 36.5, 35.3, 29.6, 27.1, 20.8, 19.3; **HRMS (DART):** Calcd for $C_{19}H_{27}O_4S$ $[M+H]^+$: 351.1627, found: 351.1621.

(*Z*)-1-(tert-Butyl) 2-(7-methoxy-6-methyl-7-oxohept-5-en-1-yl) (*S*)-pyrrolidine-1,2-dicarboxylate (4.37): This compound was synthesized following general procedure B. Analysis of the unpurified mixture revealed 89% conversion, 87% conversion to product, in 97:3 *Z*:*E*. **4.37** was isolated as colorless oil (31.5 mg, 0.085 mmol, 85% yield). **IR (neat):** 2971 (w), 2951 (w), 2877 (w), 1742 (m), 1695 (s), 1453 (w), 1389 (s), 1363 (m), 1240 (m), 1157 (s), 1120 (m), 1086 (m), 770 (w) cm^{-1}; **^{1}H NMR (400 MHz, DMSO-d_6, 25 °C):** δ 5.98 (t, *J* = 7.4 Hz, 1H), 4.19–4.11 (m, 1H), 4.11–3.94 (m, 2H), 3.65 (s, 3H), 3.42–3.23 (m, 2H), 2.46–2.34 (m, 2H), 2.28–2.09 (m, 1H), 1.93–1.73 (m, 6H), 1.64–1.51 (m, 2H), 1.50–1.28 (m, 11H); **^{1}H NMR (400 MHz, DMSO-d_6, 85 °C):** δ 5.95 (tq, *J* = 7.4, 1.4 Hz, 1H),

4.22–4.13 (m, 1H), 4.07 (t, J = 6.5 Hz, 2H), 3.68 (s, 3H), 3.43–3.27 (m, 2H), 2.45–2.34 (m, 2H), 2.29–2.13 (m, 1H), 1.91–1.77 (m, 6H), 1.67–1.55 (m, 2H), 1.50–1.40 (m, 2H), 1.38 (s, 9H); **^{13}C NMR (101 MHz, DMSO-d$_6$, 85 °C):** δ 172.9, 168.1, 141.8, 127.6, 79.3, 64.5, 59.2, 51.4, 46.7, 30.5, 28.9, 28.5, 28.3, 25.5, 23.8, 20.5; the signal of the carbonyl carbon of the Boc group was not visible at 85 °C, but was detected at 25 °C as a pair of rotamers (153.4 and 152.9 ppm in DMSO-d_6); **HRMS (DART):** Calcd for $C_{19}H_{32}NO_6$ $[M+H]^+$: 370.2224, found: 370.2218.

Methyl (*Z*)-7-(1,3-dioxoisoindolin-2-yl)-2-methylhept-2-enoate (4.38): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 79% conversion, 76% conversion to product, in 96:4 *Z*:*E*. **4.38** was isolated as colorless oil (22.9 mg, 0.076 mmol, 76% yield). **IR (neat):** 2943 (w), 2856 (w), 1770 (w), 1701 (s), 1434 (w), 1394 (m), 1368 (m), 1220 (m), 1143 (m), 1103 (m), 1037 (m), 876 (w), 719 (m), 529 (w) cm^{-1}; **^{1}H NMR (500 MHz, CDCl$_3$):** δ 7.87–7.80 (m, 2H), 7.74–7.66 (m, 2H), 5.89 (tq, J = 7.5, 1.5 Hz, 1H), 3.71 (s, 3H), 3.68 (t, J = 7.2 Hz, 2H), 2.55–2.43 (m, 2H), 1.91–1.84 (m, 3H), 1.74–1.65 (m, 2H), 1.51–1.40 (m, 2H); **^{13}C NMR (126 MHz, CDCl$_3$):** δ 168.5, 168.5, 142.6, 134.0, 132.3, 127.5, 123.3, 51.3, 38.0, 29.2, 28.4, 26.8, 20.8; **HRMS (DART):** Calcd for $C_{17}H_{20}NO_4$ $[M+H]^+$: 302.1387, found: 302.1383.

Methyl (*Z*)-7-(dibenzylamino)-2-methylhept-2-enoate (4.39): This compound was synthesized following general procedure B. Analysis of the unpurified mixture revealed 89% conversion, 86% conversion to product, in 96:4 *Z*:*E*. **4.39** was isolated as colorless oil (30.0 mg, 0.085 mmol, 85% yield). **IR (neat):** 3020 (w), 2925 (m), 2791 (w), 1714 (s), 1492 (m), 1451 (w), 1433 (w), 1364 (m), 1236 (m), 1213 (m), 1193 (m), 1142 (m), 1107 (w), 1071 (w), 743 (m), 697 (s) cm^{-1}; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.39–7.34 (m, 4H),

7.33–7.28 (m, 4H), 7.25–7.21 (m, 2H), 5.89 (tq, J = 7.3, 1.5 Hz, 1H), 3.71 (s, 3H), 3.56 (s, 4H), 2.46–2.36 (m, 4H), 1.92–1.87 (m, 3H), 1.58–1.50 (m, 2H), 1.44–1.36 (m, 2H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.6, 143.6, 140.1, 128.9, 128.2, 126.9, 126.8, 58.4, 53.4, 51.3, 29.6, 27.2, 26.9, 20.8; **HRMS (DART):** Calcd for $C_{23}H_{30}NO_2$ $[M+H]^+$: 352.2271, found: 352.2268.

Methyl (*Z*)-5-(3-methoxyphenyl)-2-methylpent-2-enoate (4.40): This compound was synthesized following general procedure B. Analysis of the unpurified mixture revealed 69% conversion, 65% conversion to product, in >98:2 *Z*:*E*. **4.40** was isolated as colorless oil (14.7 mg, 0.063 mmol, 63% yield). **IR (neat):** 2947 (m), 2922 (m), 1713 (s), 1599 (m), 1583 (m), 1487 (m), 1453 (m), 1433 (m), 1364 (w), 1256 (s), 1213 (m), 1193 (m), 1164 (m), 1151 (s), 1120 (s), 1051 (w), 1024 (m), 776 (m), 695 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.23–7.18 (m, 1H), 6.83–6.78 (m, 1H), 6.78–6.72 (m, 2H), 5.97 (tq, J = 7.3, 1.6 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 2.83–2.75 (m, 2H), 2.74–2.67 (m, 2H), 1.93–1.85 (m, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.5, 159.8, 143.3, 142.2, 129.4, 127.7, 121.0, 114.4, 111.4, 55.3, 51.4, 35.7, 31.2, 20.8; **HRMS (DART):** Calcd for $C_{14}H_{19}O_3$ $[M+H]^+$: 235.1329, found: 235.1332.

Methyl (*Z*)-1-(6-methoxy-5-methyl-6-oxohex-4-en-1-yl)-1*H*-indole-3-carboxylate (4.41): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 87% conversion, 85% conversion to product, in 98:2 *Z*:*E*. **4.41** was isolated as colorless oil (25.5 mg, 0.081 mmol, 81% yield). **IR (neat):** 2947 (w), 1700 (s), 1533 (m), 1466 (m), 1434 (m), 1396 (w), 1380 (m), 1224 (m), 1192 (m), 1170 (m), 1136 (m), 1118 (w), 1094 (m), 1032 (m), 776 (w), 750 (m) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.23–8.14 (m, 1H), 7.82 (s, 1H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 2H), 5.85

(tq, J = 7.8, 1.6 Hz, 1H), 4.16 (t, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.66 (s, 3H), 2.57–2.47 (m, 2H), 2.03–1.95 (m, 2H), 1.90–1.82 (m, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.2, 165.6, 140.9, 136.6, 134.3, 128.6, 126.9, 122.8, 121.9, 121.9, 110.1, 107.1, 51.4, 51.0, 46.7, 29.5, 27.0, 20.7; **HRMS (DART):** Calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found: 316.1531.

Methyl (*Z*)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate (4.42): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 93% conversion, 77% conversion to product, in 94:6 *Z*:*E*. **4.42** was isolated as colorless oil (18.3 mg, 0.072 mmol, 72% yield). **IR (neat):** 2975 (m), 2949 (w), 2926 (w), 1716 (s), 1455 (w), 1434 (w), 1405 (w), 1369 (s), 1324 (m), 1234 (s), 1192 (m), 1165 (m), 1143 (s), 1114 (m), 1081 (m), 967 (m), 870 (w), 846 (w) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.93 (tq, J = 7.4, 1.6 Hz, 1H), 3.71 (s, 3H), 2.58–2.49 (m, 2H), 1.88–1.85 (m, 3H), 1.22 (s, 12H), 0.95–0.82 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.7, 145.3, 126.1, 83.2, 51.3, 24.9, 24.2, 20.7, 11.4; **^{11}B NMR (160 MHz, $CDCl_3$):** δ 34.70; **HRMS (DART):** Calcd for $C_{13}H_{24}BO_4$ $[M+H]^+$: 255.1762, found: 255.1772.

Methyl (*Z*)-7-(1,3-dioxolan-2-yl)-2,6-dimethylhept-2-enoate (4.43): This compound was synthesized following general procedure A. Analysis of the unpurified mixture revealed 97% conversion, 94% conversion to product, in 97:3 *Z*:*E*. **4.43** was isolated as colorless oil (22.0 mg, 0.091 mmol, 91% yield). **IR (neat):** 2949 (m), 2923 (m), 2879 (w), 1714 (s), 1455 (w), 1433 (w), 1363 (w), 1222 (m), 1195 (m), 1143 (s), 1074 (w), 1036 (m), 945 (w) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.93 (tq, J = 7.5, 1.5 Hz, 1H), 4.90 (dd, J = 5.4, 4.6 Hz, 1H), 4.01–3.91 (m, 2H), 3.89–3.78 (m, 2H), 3.73 (s, 3H), 2.55–2.11 (m, 2H), 1.92–1.85 (m, 3H), 1.77–1.62 (m, 2H), 1.55–1.43 (m, 2H), 1.33–1.22 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.6, 143.5, 126.9, 103.9, 64.9, 64.8, 51.3,

41.0, 37.0, 29.3, 27.1, 20.8, 19.8; **HRMS (DART):** Calcd for $C_{13}H_{23}O_4$ $[M+H]^+$: 243.1590, found: 243.1597.

***tert*-Butyl (*Z*)-4-(3-methoxy-2-methyl-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate (4.44):** This compound was synthesized following general procedure D. Analysis of the unpurified mixture revealed >98% conversion, 86% conversion to product, in >98:2 *Z*:*E*. **4.44** was isolated as colorless oil (23.8 mg, 0.084 mmol, 84% yield). **IR (neat):** 2972 (w), 2927 (w), 2847 (w), 1714 (s), 1689 (m), 1647 (w), 1476 (m), 1419 (m), 1363 (m), 1291 (m), 1262 (m), 1242 (m), 1214 (s), 1168 (s), 1103 (m), 1019 (m), 965 (m), 940 (w), 867 (w), 769 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.68 (dq, *J* = 9.6, 1.5 Hz, 1H), 4.27–3.86 (br, 2H), 3.71 (s, 3H), 3.14–3.04 (m, 1H), 2.89–2.56 (br, 2H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.64 (d, *J* = 12.0 Hz, 2H), 1.43 (s, 9H), 1.27–1.16 (m, 2H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.3, 154.9, 146.7, 126.4, 79.4, 51.4, 43.8, 36.3, 31.7, 28.6, 20.8; **HRMS (DART):** Calcd for $C_{15}H_{26}NO_4$ $[M+H]^+$: 284.1856, found: 284.1857.

Methyl (*Z*)-5-(4-(tert-butyl)phenyl)-2,4-dimethylpent-2-enoate (4.45): This compound was synthesized following general procedure D. Analysis of the unpurified mixture revealed >98% conversion, 87% conversion to product, in 96:4 *Z*:*E*. **4.45** was isolated as colorless oil (23.1 mg, 0.084 mmol, 84% yield). **IR (neat):** 3050 (w), 2959 (m), 2928 (m), 2866 (m), 1716 (s), 1643 (w), 1513 (w), 1456 (m), 1433 (m), 1362 (m), 1267 (m), 1234 (s), 1195 (s), 1154 (m), 1125 (m), 1108 (m), 1024 (w), 803 (w), 562 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.35–7.27 (m, 2H), 7.15–7.05 (m, 2H), 5.78 (dq, *J* = 9.9, 1.4 Hz, 1H), 3.71 (d, *J* = 1.0 Hz, 3H), 3.51–3.39 (m, 1H), 2.68 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.46 (dd, *J* = 13.4, 8.0 Hz, 1H), 1.97–1.82 (m, 3H), 1.31 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.5, 148.7, 148.5, 137.2, 129.0, 125.8, 125.1, 51.3, 42.9, 35.2,

34.5, 31.6, 20.9, 20.0; **HRMS (DART):** Calcd for $C_{18}H_{27}O_2$ $[M+H]^+$: 275.2006, found: 275.2013.

(*Z*)-9-Methoxy-2,6,8-trimethyl-9-oxonon-7-en-2-yl benzoate (4.46): This compound was synthesized following general procedure D. Analysis of the unpurified mixture revealed >98% conversion, 83% conversion to product, in 91:9 *Z*:*E*. **4.46** was isolated as colorless oil (24.6 mg, 0.074 mmol, 74% yield (>98:2 *Z*:*E*)). **IR (neat):** 2947 (m), 2925 (m), 2863 (w), 1711 (s), 1449 (m), 1433 (w), 1366 (m), 1312 (m), 1284 (s), 1246 (m), 1228 (m), 1192 (m), 1173 (m), 1158 (m), 1114 (s), 1069 (w), 1025 (w), 711 (s) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.57–7.47 (m, 1H), 7.47–7.33 (m, 2H), 5.65 (d, *J* = 10.1 Hz, 1H), 3.69 (s, 3H), 3.14 (dq, *J* = 13.3, 7.0, 6.6 Hz, 1H), 1.97–1.77 (m, 5H), 1.55 (d, *J* = 5.3 Hz, 6H), 1.45–1.20 (m, 4H), 0.96 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.7, 165.8, 149.0, 132.5, 132.2, 129.5, 128.3, 125.8, 83.3, 51.3, 41.3, 37.7, 33.3, 26.3, 26.2, 21.9, 20.9, 20.7; **HRMS (DART):** Calcd for $C_{20}H_{29}O_4$ $[M+H]^+$: 333.2060, found: 333.2055.

Methyl (*Z*)-2,5-dimethyl-7-phenylhept-2-enoate (4.47): This compound was synthesized following general procedure B, except **Mo-1** was used instead of **Mo-7**. Analysis of the unpurified mixture revealed 80% conversion, 70% conversion to product, in 95:5 *Z*:*E*. **4.47** was isolated as colorless oil (14.2 mg, 0.058 mmol, 58% yield). **IR (neat):** 2949 (m), 2924 (m), 2854 (w), 1716 (s), 1453 (m), 1433 (w), 1375 (w), 1219 (s), 1191 (m), 1143 (m), 1073 (w), 744 (w), 698 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.31–7.25 (m, 2H), 7.21–7.16 (m, 3H), 5.95 (tq, *J* = 7.6, 1.5 Hz, 1H), 3.73 (s, 3H), 2.67 (ddd, *J* = 13.7, 10.3, 5.6 Hz, 1H), 2.59 (ddd, *J* = 13.7, 10.3, 6.0 Hz, 1H), 2.56–2.49 (m, 1H), 2.40 (dtq, *J* = 15.3, 7.6, 1.4 Hz, 1H), 1.92 (q, *J* = 1.5 Hz, 3H), 1.67 (ddt, *J* = 12.9, 10.0, 5.7 Hz,

1H), 1.65–1.55 (m, 1H), 1.49 (dddd, J = 13.0, 10.2, 7.5, 5.6 Hz, 1H), 0.97 (d, J = 6.6 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.7, 143.0, 142.3, 128.5, 128.4, 127.7, 125.7, 51.3, 38.7, 36.6, 33.6, 33.3, 20.9, 19.7; **HRMS (DART):** Calcd for $C_{16}H_{23}O_2$ $[M+H]^+$: 247.1693 found: 247.1688.

Methyl (*Z*)-2-methyl-9-(oxiran-2-yl)non-2-enoate (4.48): This compound was synthesized following general procedure D. Analysis of the unpurified mixture revealed >98% conversion, 83% conversion to product, in 96:4 *Z*:*E*. **4.48** was isolated as colorless oil (17.5 mg, 0.077 mmol, 77% yield). **IR (neat):** 2923 (m), 2853 (m), 1713 (s), 1644 (w), 1454 (m), 1432 (m), 1364 (m), 1222 (s), 1193 (s), 1133 (s), 1096 (m), 1079 (m), 992 (w), 915 (w), 881 (m), 832 (m), 769 (w), 737 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.91 (tq, J = 7.4, 1.5 Hz, 1H), 3.86–3.58 (m, 3H), 2.93–2.83 (m, 1H), 2.73 (tt, J = 3.9, 1.8 Hz, 1H), 2.50–2.37 (m, 3H), 1.94–1.79 (m, 3H), 1.60–1.21 (m, 10H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.6, 143.7, 126.9, 52.5, 51.3, 47.2, 32.6, 29.6, 29.4, 29.4, 29.3, 26.0, 20.8; **HRMS (DART):** Calcd for $C_{13}H_{23}O_3$ $[M+H]^+$: 227.1642, found: 227.1648.

For a modified procedure with commercially available paraffin pellets, see below: An oven-dried 25 mL Schlenk tube equipped with a stir bar was charged with a paraffin tablet (4.4 wt% in **Mo-1**, contains 10 mg of catalyst, ~5.0 mol %) and 2-(oct-7-en-1-yl)oxirane (37.0 mg, 0.240 mmol). The tube was sealed with a rubber septum, and the vessel put under N_2. ***Z*-1** (0.24 mL, 1.92 mmol) and toluene (0.3 mL) were added, the Schlenk tube was sealed, and the mixture was allowed to stir for 12 h at 40 °C. The reaction was exposed to air, and undistilled acetonitrile was added, which led to precipitation of the paraffin. The resulting slurry was mixed vigorously and then filtered through a short silica gel column. Analysis of the unpurified mixture revealed 97% consumption of 2-(oct-7-en-1-yl)oxirane

and 68% formation of **4.48**. The filtrate was concentrated in vacuo, and the yellow residue was purified by silica gel chromatography to afford **4.48** as colorless oil (33.1 mg, 0.146 mmol, 61% yield, 96:4 *Z*:*E*). The spectral data of this compound are consistent with those obtained through procedure D (see above).

Methyl (*Z*)-9-bromo-2-methylnon-2-enoate (4.49): This compound was synthesized following general procedure D. Analysis of the unpurified mixture revealed >98% conversion, 98% conversion to product, in 96:4 *Z*:*E*. **4.49** was isolated as colorless oil (24.7 mg, 0.094 mmol, 94% yield). **IR (neat):** 2925 (m), 2853 (w), 1713 (s), 1644 (w), 1453 (m), 1432 (m), 1363 (m), 1239 (s), 1213 (s), 1192 (s), 1152 (s), 1110 (m), 1073 (w), 1051 (w), 993 (w), 878 (w), 819 (w), 769 (w), 644 (w), 560 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.92 (tq, *J* = 7.5, 1.5 Hz, 1H), 3.73 (s, 3H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.54–2.35 (m, 2H), 1.94–1.79 (m, 5H), 1.51–1.27 (m, 6H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.6, 143.5, 127.1, 51.4, 34.1, 32.9, 29.6, 29.3, 28.6, 28.1, 20.8; **HRMS (DART):** Calcd for $C_{11}H_{20}O_2Br$ $[M+H]^+$: 263.0641, found: 263.0642.

Dimethyl (*Z*)-2-methyloct-2-enedioate (4.50): This compound was synthesized following general procedure D. Analysis of the unpurified mixture revealed >98% conversion, 98% conversion to product, in 96:4 *Z*:*E*. **4.50** was isolated as colorless oil (20.5 mg, 0.092 mmol, 92% yield). **IR (neat):** 2949 (w), 1736 (s), 1716 (s), 1434 (m), 1365 (w), 1217 (m), 1195 (m), 1165 (m), 1123 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.90 (tq, *J* = 7.5, 1.6 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.54–2.44 (m, 2H), 2.33 (t, *J* = 7.6 Hz, 2H), 1.93–1.86 (m, 3H), 1.75 (tt, *J* = 7.6 Hz, 2H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.1, 168.4, 142.0, 128.0, 51.6, 51.4, 33.6, 29.0, 24.7, 20.8; **HRMS (DART):** Calcd for $C_{11}H_{19}O_4$ $[M+H]^+$: 201.1121, found: 201.1125.

Methyl (*Z*)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (4.52): In a N_2-filled glovebox, an oven-dried 7 mL vial equipped with a magnetic stir bar was charged with 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (33.6 mg, 0.200 mmol) and a solution of **Mo-7** in benzene (0.1 M, 20.0 μL, 2.0 μmol). The mixture was allowed to stir under vacuum (100 Torr) for 1 h at 22 °C. Then, ***Z*-1** (22.8 mg, 0.20 mmol), **Mo-6** (4.0 mg, 4.0 μmol), benzene (40.0 μL), and a solution of BPh_3 in benzene (0.1 M, 60.0 μL, 6.0 μmol) sequentially. The mixture was allowed to stir under vacuum (100 Torr) for 2 h at 22 °C. Subsequently, the reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% conversion, 81% conversion to product, in 92:8 *Z*:*E*. The so-obtained oil was purified through silica gel chromatography (20% CH_2Cl_2 in pentane → 10% Et_2O in pentane) to afford **4.52** as colorless oil (34.5 mg, 0.144 mmol, 72% yield). **IR (neat):** 2978 (w), 1711 (m), 1473 (w), 1455 (m), 1371 (m), 1339 (s), 1321 (s), 1270 (m), 1242 (m), 1198 (m), 1165 (m), 1143 (s), 1105 (m), 1084 (m), 983 (w), 967 (w), 843 (m), 674 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.23 (tq, *J* = 8.3, 1.3 Hz, 1H), 3.71 (s, 3H), 2.09 (d, *J* = 8.4 Hz, 2H), 1.89 (q, *J* = 1.3 Hz, 3H), 1.24 (s, 12H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.6, 140.4, 126.3, 83.4, 51.2, 24.9, 20.6, 15.4; **^{11}B NMR (160 MHz, $CDCl_3$):** δ 32.7; **HRMS (ESI):** Calcd for $C_{12}H_{22}BO_4$ $[M+H]^+$: 241.1606 found: 241.1605.

Methyl (*Z*)-5-cyano-2-methylpent-2-enoate (4.53): In a N_2-filled glovebox, an oven-dried 7 mL vial equipped with a magnetic stir bar was charged with pent-4-enenitrile (16.2 mg, 0.200 mmol) and a solution of **Mo-7** in benzene (0.1 M, 50.0 μL, 5.0 μmol). The mixture was allowed to stir for 8 h at 22 °C , followed by 10 min under vacuum (1 Torr) 22 °C. Then, ***Z*-1** (45.6 mg, 0.400 mmol), **Mo-6** (4.0 mg, 4.0 μmol), benzene (80.0 μL),

and a solution of BPh_3 in benzene (1.0 M, 120.0 μL, 0.120 mmol) sequentially. The mixture was allowed to stir under vacuum (100 Torr) for 4 h at 22 °C. Subsequently, the reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% conversion, 85% conversion to product, in 93:7 *Z*:*E*. The so-obtained oil was purified through silica gel chromatography to afford **4.53** as colorless oil (24.1 mg, 0.157 mmol, 79% yield). **IR (neat):** 2954 (w), 2922 (w), 2849 (w), 2245 (w), 1711 (s), 1649 (w), 1455 (m), 1434 (m), 1368 (w), 1330 (w), 1247 (m), 1218 (m), 1200 (s), 1129 (s), 1090 (w), 1030 (m), 991 (w), 861 (w), 832 (w), 798 (w), 769 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.98 (tq, *J* = 7.6, 1.6 Hz, 1H), 3.75 (s, 3H), 2.81 (qq, *J* = 7.3, 1.3 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 1.94 (q, *J* = 1.4 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 167.7, 137.8, 130.7, 119.3, 51.7, 25.3, 20.7, 17.3; **HRMS (ESI):** Calcd for $C_8H_{12}NO_2$ $[M+H]^+$:154.0863, found:154.0863.

Methyl (*Z*)-5-bromo-2-methylpent-2-enoate (4.54): In a N_2-filled glovebox, an oven-dried 7 mL vial equipped with a magnetic stir bar was charged with 4-bromobut-1-ene (27.0 mg, 0.200 mmol) and a solution of **Mo-1** in benzene (0.1 M, 20.0 μL, 2.0 μmol). The mixture was allowed under vacuum (100 Torr) for 1 h at 22 °C. Then, ***Z*-1c** (70.5 mg, 0.400 mmol) and a solution of **Mo-7** in benzene (0.1 M , 40.0 μL, 4.0 μmol) were added sequentially. The mixture was allowed to stir under vacuum (100 Torr) for 6 h at 22 °C. Subsequently, the reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% conversion, 79% conversion to product, in 95:5 *Z*:*E*. The so-obtained oil was purified through silica gel chromatography to afford **4.54** as colorless oil (38.6 mg (calculated from a 41.6 mg mixture with ***Z*-1c**), 0.143 mmol, 72% yield). **IR (neat):** 3042 (w), 2960 (w), 2925 (w), 1726 (s),

1590 (w), 1492 (m), 1455 (w), 1363 (w), 1265 (w), 1230 (m), 1189 (s), 1160 (s), 1146 (s), 1094 (s), 1072 (s), 1001 (w), 914 (w), 815 (w), 742 (s), 688 (s), 594 (w), 557 (w), 504 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.45–7.34 (m, 2H), 7.27–7.21 (m, 1H), 7.16–7.07 (m, 2H), 6.19 (tq, *J* = 7.1, 1.3 Hz, 1H), 3.49 (t, *J* = 6.6 Hz, 2H), 3.19 – 3.11 (m, 2H), 2.11 (q, *J* = 1.3 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.8, 150.7, 141.8, 129.6, 129.2, 126.0, 121.8, 32.8, 32.4, 20.8; **HRMS (ESI):** Calcd for $C_{12}H_{14}BrO_2$ $[M+H]^+$: 269.0172, found: 269.0159.

***S*-Ethyl (*Z*)-5-bromo-2-methylpent-2-enethioate (4.55):** In a N_2-filled glovebox, an oven-dried 7 mL vial equipped with a magnetic stir bar was charged with 4-bromobut-1-ene (27.0 mg, 0.200 mmol) and a solution of **Mo-1** in benzene (0.1 M, 20.0 μL, 2.0 μmol). The mixture was allowed under vacuum (100 Torr) for 1 h at 22 °C. Then, ***Z*-1d** (57.7 mg, 0.400 mmol), *cis*-3-hexene (1.0 M in benzene, 12.0 μL, 12.0 μmol), and a solution of **Mo-7** in benzene (0.1 M , 40.0 μL, 4.0 μmol) were added sequentially. The mixture was allowed to stir under vacuum (100 Torr) for 4 h at 22 °C. Subsequently, the reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed >98% conversion, 98% conversion to product, in 93:7 *Z*:*E*. The so-obtained oil was purified through silica gel chromatography to afford **4.55** as colorless oil (43.1 mg, 0.182 mmol, 91% yield). **IR (neat):** 2968 (w), 2928 (w), 2872 (w), 1661 (s), 1623 (m), 1449 (m), 1265 (m), 1217 (w), 1127 (w), 1009 (w), 964 (s), 913 (m), 862 (w), 843 (w), 789 (m), 636 (w), 562 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.74 (tq, *J* = 7.2, 1.6 Hz, 1H), 3.43 (t, *J* = 6.7 Hz, 2H), 3.00–2.88 (m, 4H), 2.02 (q, *J* = 1.5 Hz, 3H), 1.28 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** *Z* isomer (major): δ 194.2, 136.4, 134.6, 32.7, 32.5, 23.4, 20.8, 14.7; *E* isomer (minor): δ 193.8, 138.4, 135.9, 31.9,

30.6, 23.5, 14.8, 12.9; **HRMS (ESI):** Calcd for $C_8H_{14}BrOS$ $[M+H]^+$: 236.9943, found: 236.9945.

Ethyl (*Z*)-2-methyloct-2-enoate (4.57):In a N_2-filled glovebox, an oven-dried 20 mL vial equipped with a magnetic stir bar was charged with hept-1-ene (98.2 mg, 1.00 mmol) and ***Z*-1** (913 mg, 8.00 mmol). To this mixture was added a solution of **Mo-11** (0.1 M in benzene, 300.0 μL, 30.0 μmol). The vial was loosely capped, and the reaction mixture was allowed to stir on ambient pressure, for 12 h at 22 °. The vial was removed from the glovebox, and the mixture was transferred to a 10 mL pear-shaped flask. The volatiles were removed carefully at 100 Torr to afford a dark-brown oil. Analysis of the unpurified mixture revealed >98% conversion, 93% conversion to product, in 96:4 *Z*:*E*. Further purified by Kugelrohr distillation afforded ***Z*-1** (10 Torr, 22 °C; 680.0 mg, 5.96 mmol, 75% yield, 96:4 *Z*:*E*) and **4.57** (10 Torr, 22 °C; 158.1 mg, 0.929 mmol, 93% yield, 96:4 *Z*:*E*) as colorless oils. **IR (neat):** 2952 (m), 2923 (m), 2854 (w), 1715 (s), 1645 (w), 1454 (m), 1432 (m), 1364 (w), 1239 (m), 1216 (s), 1196 (m), 1142 (s), 1094 (m), 1076 (m), 995 (w), 879 (w), 812 (w), 770 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.92 (tq, *J* = 7.4, 1.6 Hz, 1H), 3.71 (s, 3H), 2.48–2.38 (m, 2H), 1.91–1.84 (m, 3H), 1.46–1.34 (m, 2H), 1.33–1.21 (m, 4H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ *Z* isomer (major): 168.6, 143.9, 126.8, 51.2, 31.6, 29.7, 29.2, 22.6, 20.8, 14.1; *E* isomer (minor): 168.9, 142.9, 127.5, 51.7, 31.6, 28.7, 28.4, 22.6, 14.1, 12.4. **HRMS (DART):** Calcd for $C_{10}H_{19}O_2$ $[M+H]^+$: 171.1380, found: 171.1391.

Methyl (*E*)-8-(benzyloxy)-2,6-dimethyloct-2-enoate (4.59): This compound was synthesized following general procedure E. Analysis of the unpurified mixture revealed 86% conversion, in 97:3 *E*:*Z*. **4.59** was isolated as colorless oil (24.7 mg, 0.085 mmol, 85%

yield). **IR (neat):** 2948 (m), 2922 (m), 2852 (m), 1711 (s), 1648 (w), 1452 (m), 1433 (m), 1362 (w), 1264 (s), 1194 (m), 1138 (m), 1095 (s), 1026 (w), 737 (m), 697 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.39–7.31 (m, 4H), 7.31–7.26 (m, 1H), 6.75 (tq, *J* = 7.5, 1.4 Hz, 1H), 4.50 (s, 2H), 3.73 (d, *J* = 1.0 Hz, 3H), 3.56–3.45 (m, 2H), 2.26–2.09 (m, 2H), 1.87–1.78 (m, 3H), 1.73–1.55 (m, 2H), 1.53–1.40 (m, 2H), 1.34–1.23 (m, 1H), 0.91 (dd, *J* = 6.7, 1.0 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.8, 142.8, 138.7, 128.5, 127.7, 127.6, 127.5, 73.1, 68.6, 51.8, 36.7, 35.9, 29.8, 26.3, 19.5, 12.5; **HRMS[M+H]$^+$:** Calcd for $C_{18}H_{27}O_3$: 291.1955, found: 291.1943.

Methyl (*E*)-8-(ethylthio)-2,6-dimethyl-8-oxooct-2-enoate (4.61): This compound was synthesized following general procedure E. Analysis of the unpurified mixture revealed 83% conversion, in 97:3 *E*:*Z*. **4.61** was isolated as colorless oil (18.3 mg, 0.071 mmol, 71% yield). **IR (neat):** 2950 (m), 2927 (m), 2871 (w), 1712 (s), 1685 (s), 1648 (w), 1433 (m), 1379 (w), 1351 (w), 1265 (s), 1191 (m), 1141 (m), 1092 (m), 1059 (m), 1010 (m), 969 (w), 938 (w), 744 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.72 (tq, *J* = 7.5, 1.5 Hz, 1H), 3.72 (s, 3H), 2.87 (q, *J* = 7.5 Hz, 2H), 2.52 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.38 (dd, *J* = 14.5, 7.9 Hz, 1H), 2.25–2.11 (m, 2H), 2.10–2.00 (m, 1H), 1.82 (s, 3H), 1.54–1.44 (m, 1H), 1.37–1.28 (m, 1H), 1.24 (td, *J* = 7.4, 1.3 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 199.0, 168.7, 142.0, 127.9, 51.8, 51.2, 35.3, 30.9, 26.2, 23.5, 19.5, 14.9, 12.5; **HRMS[M+H]$^+$:** Calcd for $C_{13}H_{23}O_3S$: 259.1362, found: 259.1372.

Methyl (*E*)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (4.62): This compound was synthesized following general procedure E. Analysis of the unpurified mixture revealed 86% conversion, in 97:3 *E*:*Z*. **4.62** was isolated as colorless oil (18.0 mg, 0.075 mmol, 75% yield). **IR (neat):** 2985 (m), 2944 (w), 2926 (w), 1710 (s),

1453 (w), 1366 (s), 1324 (m), 1235 (s), 1192 (m), 1165 (m), 1143 (s), 1114 (m), 1072 (m), 855 (w) cm-1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.92 (tq, *J* = 8.6, 1.8 Hz, 1H), 3.71 (s, 3H), 1.94–1.76 (m, 5H), 1.24 (s, 12H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.8, 138.7, 127.4, 83.7, 51.7, 24.9, 14.3, 12.3; **^{11}B NMR (160 MHz, $CDCl_3$):** δ 33.37; **HRMS[M+H]$^{+}$:** Calcd for $C_{12}H_{22}BO_4$: 241.1606, found: 241.1608.

Isobutyl (*Z*)-8-(benzyloxy)-2,6-dimethyloct-2-enoate (4.63): This compound was synthesized following general procedure B. Analysis of the unpurified mixture revealed 88% conversion, 87% conversion to product, in 98:2 *Z*:*E*. **4.63** was isolated as colorless oil (28.3 mg, 0.085 mmol, 85% yield). **IR (neat):** 3027 (m), 2955 (m), 2924 (m), 2869 (m), 1713 (s), 1643 (w), 1453 (m), 1377 (m), 1365 (m), 1220 (m), 1192 (m), 1144 (s), 1097 (s), 1075 (m), 1027 (m), 998 (w), 944 (w), 734 (m), 696 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38–7.31 (m, 4H), 7.30–7.24 (m, 1H), 5.91 (tq, *J* = 7.4, 1.5 Hz, 1H), 4.50 (s, 2H), 4.50 (d, *J* = 0.7 Hz, 2H), 3.95–3.90 (m, 2H), 3.56–3.46 (m, 2H), 2.59–2.39 (m, 2H), 2.11–1.92 (m, 1H), 1.92–1.88 (m, 3H), 1.77–1.56 (m, 2H), 1.51–1.38 (m, 2H), 1.32–1.19 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 6H), 0.90 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.3, 143.4, 138.8, 128.5, 127.7, 127.6, 127.2, 73.0, 70.5, 68.7, 36.9, 36.8, 29.9, 27.9, 27.3, 20.9, 19.5, 19.4; **HRMS (DART):** Calcd for $C_{21}H_{33}O_3$ [M+H]$^{+}$: 333.2424, found: 333.2429.

4-Methoxybenzyl (*Z*)-8-(benzyloxy)-2,6-dimethyloct-2-enoate (4.64): This compound was synthesized following general procedure B. Analysis of the unpurified mixture revealed 95% conversion, 93% conversion to product, in >98:2 *Z*:*E*. **4.64** was isolated as colorless oil (36.1 mg, 0.091 mmol, 91% yield). **IR (neat):** 2950 (m), 2922 (m), 2856 (m), 1710 (s), 1612 (m), 1513 (s), 1453 (m), 1359 (w), 1301 (w), 1246 (s), 1174 (m), 1141 (s),

1095 (s), 1075 (m), 1033 (m), 824 (m), 735 (m), 697 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49–7.19 (m, 7H), 6.97–6.81 (m, 2H), 5.92 (t, *J* = 7.6 Hz, 1H), 5.12 (s, 2H), 4.49 (s, 2H), 3.87–3.72 (m, 3H), 3.55–3.43 (m, 2H), 2.55–2.37 (m, 2H), 1.96–1.86 (m, 3H), 1.70–1.52 (m, 2H), 1.50–1.35 (m, 2H), 1.26–1.17 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 168.1, 159.6, 143.8, 138.8, 130.1, 128.5, 128.5, 127.7, 127.6, 126.9, 114.0, 73.0, 68.8, 65.8, 55.4, 36.8, 36.7, 29.8, 27.3, 20.8, 19.5; **HRMS (DART):** Calcd for $C_{25}H_{33}O_4$ $[M+H]^+$: 397.2373, found: 397.2369.

(2-(Trimethylsilyl)ethoxy)methyl (*Z*)-8-(benzyloxy)-2,6-dimethyloct-2-enoate (4.65): This compound was synthesized following general procedure B. Analysis of the unpurified mixture revealed 85% conversion, 83% conversion to product, in 96:4 *Z*:*E*. **4.65** was isolated as colorless oil (30.1 mg, 0.074 mmol, 74% yield). **IR (neat):** 2950 (m), 2922 (m), 2854 (m), 1715 (s), 1453 (w), 1363 (w), 1247 (s), 1196 (w), 1143 (m), 1111 (s), 1069 (s), 939 (m), 858 (s), 835 (s), 734 (w), 696 (m) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.37–7.32 (m, 4H), 7.31–7.24 (m, 1H), 5.97 (t, *J* = 7.4 Hz, 1H), 5.36 (s, 2H), 4.50 (s, 2H), 3.78–3.69 (m, 2H), 3.56–3.45 (m, 2H), 2.60–2.40 (m, 2H), 1.95–1.82 (m, 3H), 1.73–1.59 (m, 2H), 1.50–1.39 (m, 2H), 1.32–1.20 (m, 1H), 1.00–0.95 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.09– ‑0.02 (m, 9H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 167.5, 144.7, 138.8, 128.5, 127.7, 127.6, 126.7, 88.9, 73.0, 68.7, 67.9, 36.8, 36.8, 29.8, 27.3, 20.8, 19.5, 18.2, ‑1.3; **HRMS (DART):** Calcd for $C_{23}H_{42}ONO_4Si$ $[M+NH_4]^+$: 424.2878, found: 424.2879.

Phenyl (*Z*)-8-(benzyloxy)-2,6-dimethyloct-2-enoate (4.66): This compound was synthesized following general procedure B. Analysis of the unpurified mixture revealed 74% conversion, 72% conversion to product, in 97:3 *Z*:*E*. **4.66** was isolated as colorless oil (24.3 mg, 0.069 mmol, 69% yield). **IR (neat):** 3027 (m), 2951 (m), 2922 (m), 2852 (m),

1732 (s), 1642 (w), 1590 (w), 1491 (m), 1453 (m), 1363 (w), 1194 (s), 1161 (m), 1129 (s), 1091 (m), 1070 (m), 1025 (w), 741 (s), 689 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.44–7.37 (m, 2H), 7.37–7.32 (m, 4H), 7.31–7.27 (m, 1H), 7.26–7.22 (m, 1H), 7.16–7.10 (m, 2H), 6.13 (t, *J* = 7.5 Hz, 1H), 4.50 (d, *J* = 1.5 Hz, 2H), 3.58–3.46 (m, 2H), 2.68–2.51 (m, 2H), 2.06 (d, *J* = 1.5 Hz, 3H), 1.76–1.62 (m, 2H), 1.56–1.42 (m, 2H), 1.37–1.25 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 166.3, 150.9, 146.4, 138.8, 129.5, 128.5, 128.5, 126.3, 125.8, 121.9, 73.0, 68.7, 36.8, 36.7, 29.8, 27.5, 20.9, 19.6; **HRMS (DART):** Calcd for $C_{23}H_{29}O_3$ $[M+H]^+$: 353.2111, found: 353.2094.

***tert*-Butyldiphenylsilyl (*Z*)-8-(benzyloxy)-2,6-dimethyloct-2-enoate (4.67):** This compound was synthesized following general procedure B. Analysis of the unpurified mixture revealed 80% conversion, 74% conversion to product, in 97:3 *Z*:*E*. **4.67** was isolated as colorless oil (37.1 mg, 0.072 mmol, 72% yield). **IR (neat):** 2952 (w), 2926 (w), 2855 (w), 1702 (m), 1453 (w), 1426 (m), 1362 (m), 1220 (m), 1190 (m), 1146 (s), 1112 (s), 1074 (m), 820 (m), 737 (s), 696 (s), 608 (m), 504 (s), 487 (m) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.77–7.66 (m, 5H), 7.47–7.25 (m, 10H), 5.98 (t, *J* = 7.3 Hz, 1H), 4.48 (s, 2H), 3.57–3.43 (m, 2H), 2.51 (d, *J* = 8.2 Hz, 2H), 2.03 (s, 3H), 1.72–1.52 (m, 2H), 1.51–1.36 (m, 2H), 1.32–1.19 (m, 1H), 1.16–1.07 (m, 9H), 0.88–0.80 (m, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 167.0, 144.9, 138.8, 135.4, 134.9, 132.3, 130.1, 129.8, 128.5, 128.0, 127.9, 127.8, 127.7, 127.6, 73.0, 68.7, 36.9, 36.8, 29.8, 27.3, 27.1, 26.7, 21.5, 19.5, 19.3; **HRMS (DART):** Calcd for $C_{33}H_{43}O_3Si$ $[M+H]^+$: 515.2976, found: 515.2988.

***S*-Ethyl (*Z*)-8-(benzyloxy)-2,6-dimethyloct-2-enoate (4.68):** This compound was synthesized following general procedure B, except that the reaction was stopped after 4 h. Analysis of the unpurified mixture revealed 90% conversion, 89% conversion to product,

in 94:6 *Z*:*E*. **4.68** was isolated as colorless oil (25.8 mg, 0.081 mmol, 81% yield). **IR (neat):** 2955 (m), 2923 (m), 2852 (m), 1662 (s), 1620 (w), 1451 (m), 1363 (w), 1098 (s), 1040 (w), 1026 (w), 962 (s), 903 (m), 861 (w), 733 (s), 695 (s), 645 (w) cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.38–7.31 (m, 4H), 7.31–7.25 (m, 1H), 5.67 (t, *J* = 7.5 Hz, 1H), 4.50 (s, 2H), 3.58–3.44 (m, 2H), 2.92 (qd, *J* = 7.5, 1.0 Hz, 2H), 2.48–2.30 (m, 2H), 2.02–1.93 (m, 3H), 1.72–1.56 (m, 2H), 1.50–1.38 (m, 2H), 1.32–1.19 (m, 4H), 0.89 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 194.6, 138.9, 138.8, 134.0, 128.5, 127.7, 127.6, 73.0, 68.7, 36.9, 36.8, 29.8, 27.2, 23.3, 20.9, 19.6, 14.8; **HRMS (DART):** Calcd for $C_{19}H_{29}O_2S$ $[M+H]^+$: 321.1883, found: 321.1892.

(*Z*)-8-(Benzyloxy)-2,6-dimethyloct-2-enoyl fluoride (4.70): This compound was synthesized following general procedure C. Analysis of the unpurified mixture revealed 87% conversion, 81% conversion to product, in 88:12 *Z*:*E*. **4.70** was isolated as colorless oil (25.8 mg, 0.081 mmol, 81% yield). **IR (neat):** 2950 (w), 2922 (w), 2884 (w), 1795 (s), 1198 (m), 1124 (m), 1112 (m), 1025 (s) 992 (w), 732 (m), 698 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38–7.32 (m, 4H), 7.31–7.26 (m, 1H), 6.37 – 6.28 (m, 1H), 4.50 (s, 2H), 3.58–3.44 (m, 2H), 2.62–2.43 (m, 2H), 1.94 (q, *J* = 1.4 Hz, 3H), 1.74–1.55 (m, 2H), 1.54–1.36 (m, 2H), 1.34–1.21 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 157.3 (d, *J* = 349.2 Hz), 152.6 (d, *J* = 5.7 Hz), 138.8, 128.5, 127.8, 127.7, 122.3 (d, *J* = 57.2 Hz), 73.1, 68.6, 36.7, 36.3, 29.8, 27.8 (d, *J* = 3.8 Hz), 20.0, 19.5; **^{19}F NMR (376 MHz, $CDCl_3$):** *Z* isomer (major): δ 37.4 (d, *J* = 8.8 Hz); *E* isomer (minor): 14.3 (s). **HRMS (DART):** Calcd for $C_{17}H_{27}NO_2F$ $[M+NH_4]^+$: 296.2020, Found: 296.2021;

(*Z*)-5-(4-Fluorophenyl)-2-methylpent-2-enoyl fluoride (4.71): This compound was synthesized following general procedure C. Analysis of the unpurified mixture revealed

86% conversion, 75% conversion to product, in 88:12 *Z*:*E*. **4.71** was isolated as colorless oil (13.6 mg, 0.065 mmol, 65% yield). **IR (neat):** 2931 (w), 1801 (s), 1644 (w), 1602 (w), 1509 (s), 1455 (w), 1363 (w), 1221 (m), 1158 (w), 1097 (w), 1059 (m), 1018 (m), 824 (m), 748 (m) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.21–7.09 (m, 2H), 7.02–6.89 (m, 2H), 6.39–6.29 (m, 1H), 2.87–2.77 (m, 2H), 2.77–2.69 (m, 2H), 2.00–1.88 (m, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 161.6 (d, *J* = 244.0 Hz), 157.1 (d, *J* = 349.3 Hz), 150.6 (d, *J* = 6.1 Hz), 136.4 (d, *J* = 3.2 Hz), 129.9 (d, *J* = 7.8 Hz), 123.3 (d, *J* = 57.7 Hz), 115.4 (d, *J* = 21.2 Hz), 34.3–34.3 (m), 31.8 (dd, *J* = 3.5, 1.1 Hz), 20.0 (s). **^{19}F NMR (471 MHz, $CDCl_3$):** δ 37.6 (d, *J* = 8.7 Hz), -117.1 (tt, *J* = 9.7, 4.9 Hz). **HRMS (ESI):** Calcd for $C_{12}H_{13}F_2O$ $[M+H]^+$: 211.0929, Found: 211.0935.

(***Z***)**-2-Methyl-5-(2-methyl-1,3-dioxolan-2-yl)pent-2-enoyl fluoride (4.72):** This compound was synthesized following general procedure C. Analysis of the unpurified mixture revealed 88% conversion, 79% conversion to product, in 84:16 *Z*:*E*. **4.72** was isolated as colorless oil (14.7 mg, 0.073 mmol, 73% yield). **IR (neat):** 2984 (w), 2933 (w), 2884 (w), 1794 (s), 1643 (w), 1455 (w), 1375 (m), 1252 (m), 1218 (m), 1135 (m), 1109 (m), 1038 (s), 947 (m), 857 (m), 757 (m), 726 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 6.43 – 6.33 (m, 1H), 4.00–3.87 (m, 4H), 2.68–2.57 (m, 2H), 1.96–1.93 (m, 3H), 1.83–1.78 (m, 2H), 1.33 (s, 3H); *E* isomer (resolved signals only): δ 7.02–6.93 (m, 1H), 2.35 (q, *J* = 7.7 Hz, 2H), 1.92–1.86 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 157.31 (d, *J* = 349.1 Hz), 152.09 (d, *J* = 5.6 Hz), 122.27 (d, *J* = 57.3 Hz), 109.62, 64.87, 38.14, 25.06 (d, *J* = 3.8 Hz), 24.07, 19.96; **^{19}F NMR (471 MHz, $CDCl_3$):** *Z* isomer (major): δ 37.41 (d, *J* = 8.6 Hz); *E* isomer (minor): δ 14.24 (s); **HRMS (ESI):** Calcd for $C_{10}H_{16}O_3F$ $[M+H]^+$: 203.1078, Found: 203.1069.

(*Z*)-2-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoyl fluoride (4.73): This compound was synthesized following general procedure C. Analysis of the unpurified mixture revealed 86% conversion, 80% conversion to product, in 86:14 *Z*:*E*. **4.73** was isolated as colorless oil (16.3 mg, 0.067 mmol, 67% yield). **IR (neat):** 2979 (w), 2928 (w), 1795 (s), 1643 (w), 1457 (w), 1407 (w), 1371 (s), 1325 (s), 1226 (m), 1165 (m), 1141 (s), 1109 (w), 1042 (s), 967 (m), 872 (w), 845 (m), 756 (m), 726 (w), 672 (w), 577 (w) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 6.38 – 6.31 (m, 1H), 2.6 (q, *J* = 7.6 Hz, 2H), 1.9 (dt, *J* = 1.4, 1.3 Hz, 3H), 1.2 (s, 12H), 0.9 (t, *J* = 7.8 Hz, 2H); *E* isomer (minor): δ 7.0 (tq, *J* = 7.6, 1.5 Hz, 1H), 2.3 (q, *J* = 7.7 Hz, 2H), 1.9 (t, *J* = 1.2 Hz, 3H), 1.2 (s, 12H), 1.0 (t, *J* = 7.9 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$):** *Z* isomer (major): δ 157.4 (d, *J* = 349.3 Hz), 154.1 (d, *J* = 5.1 Hz), 121.5 (d, *J* = 56.8 Hz), 83.4 (d, *J* = 0.5 Hz), 24.9 (s), 24.7 (d, *J* = 4.1 Hz), 20.0 (s), 10.8 (br); *E* isomer (resolved signals only): δ 158.7 (d, *J* = 346.6 Hz), 152.1 (s), 122.8 (d, *J* = 51.0 Hz), 83.6 (s); **^{19}F NMR (471 MHz, $CDCl_3$):** *Z* isomer (major): δ 37.3 (d, *J* = 8.5 Hz); *E* isomer (minor): δ 14.0 (s). **^{11}B NMR (160 MHz, $CDCl_3$):** δ 33.9; **HRMS (ESI):** Calcd for $C_{12}H_{21}O_3BF$ $[M+H]^+$: 243.1562, Found: 243.1555.

Methyl (*S*,*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyloct-2-enoate (4.75): In a N_2-filled glovebox, an oven-dried 20 mL vial equipped with a magnetic stir bar was charged with (*S*)-*tert*-butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane (2.00 g, 7.40 mmol), ***Z*-1** (1.69 g, 14.8 mmol), *cis*-3-hexene (1.0 M in benzene, 89.0 μL, 0.089 mmol), and **Mo-7** (0.1 M in benzene, 740.0 μL, 0.074 mmol). The mixture was allowed to stir under vacuum (100 Torr) for 8 h at 22 °C. The reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 78%

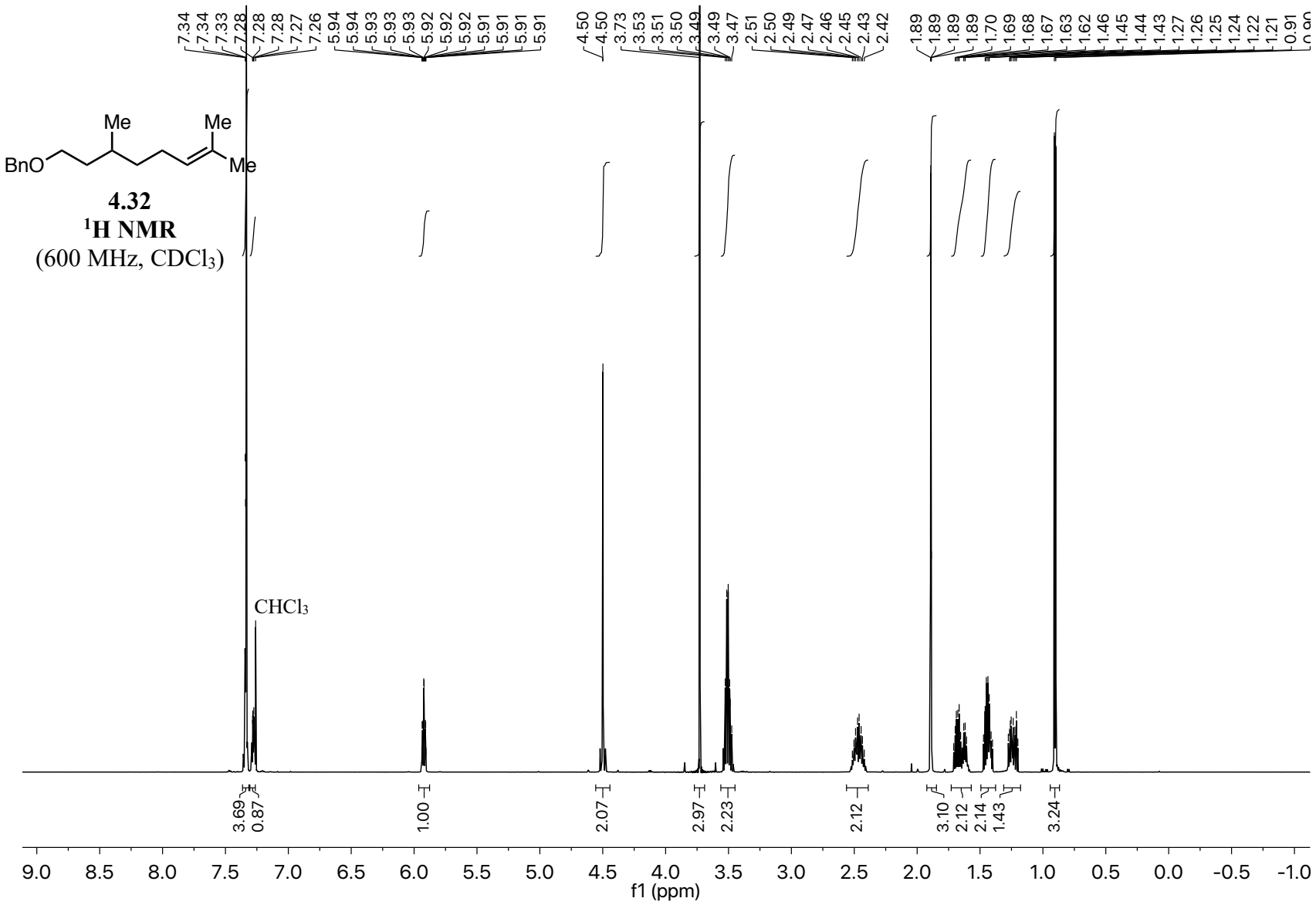
conversion, 76% conversion to product, in 97:3 *Z*:*E*. The so-obtained brown oil was purified through silica gel chromatography to afford **4.75** as colorless oil (1.70 g, 5.40 mmol, 73% yield, >98:2 *Z*:*E*). The spectral data of this compound are consistent with those previously reported.[21]

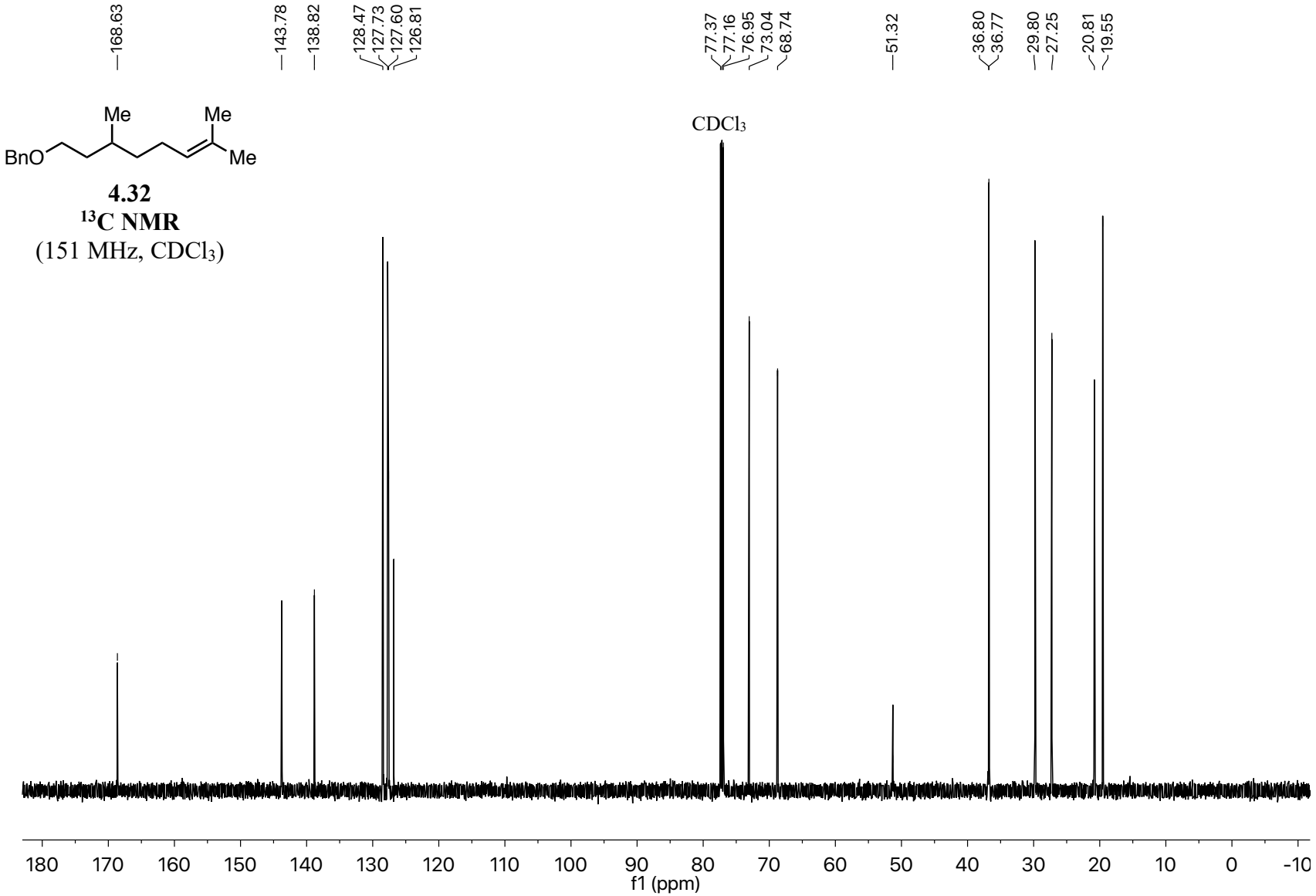
Methyl (*S*,*E*)-8-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyloct-2-enoate (4.76): In a N_2-filled glovebox, an oven-dried 20 mL vial equipped with a magnetic stir bar was charged with (*S*)-*tert*-butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane (2.00 g, 7.40 mmol), ***E*-1** (1.69 g, 14.8 mmol), **Mo-6** (79.4 mg, 0.074 mmol) and benzene (0.75 mL). The mixture was allowed to stir until the solution became homogeneous (~ 30 sec), after which a solution of $B(C_6F_5)_3$ (1.0 M in benzene, 89.0 μL, 0.089 mmol) was added. The mixture was allowed to stir under vacuum (100 Torr) for 4 h at 22 °C. The reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. Analysis of the unpurified mixture revealed 91% conversion, 79% conversion to product, in 97:3 *E*:*Z*. The so-obtained brown oil was purified through silica gel chromatography to afford **4.75** as colorless oil (1.80 g, 5.72 mmol, 77% yield, >98:2 *E*:*Z*). The spectral data of this compound are consistent with those previously reported.[21]

Anwuweizic acid (4.78): In a N_2-filled glovebox, an oven-dried 7 mL vial equipped with a magnetic stir bar was charged **4.77** (23.4 mg, 0.05 mmol), ***Z*-1** (12.5 μL, 0.1 mmol), and benzene (100.0 μL). The mixture was allowed to stir until the solution became homogeneous, after which a solution of *cis*-3-hexene (1.0 M in benzene, 6.0 μL, 6.0 μmol) and **Mo-7** (0.1 M in benzene, 25.0 μL, 2.5 μmol) was added. The mixture was allowed to stir under vacuum (200 Torr) for 6 h at 22 °C. The reaction was quenched by exposing the vial to air, and the volatiles were removed in vacuo. A solution of KOH (5.0 wt% in EtOH,

1.0 mL) was added, and the reaction mixture was allowed to stir for 4 h at 80 °C. The mixture was allowed to cool to 22 °C, and the reaction was quenched by addition of an aqueous solution of HCl (1.0 M, 2.0 mL). The slurry was washed with CH_2Cl_2 (5 x 4 mL), and the combined organic phases were dried over Na_2SO_4. The volatiles were removed in vacuo to afford brown oil, which was purified by silica gel chromatography to afford **4.78** as colorless solid (16.5 mg, 0.0361 mmol, 72% yield, 94:6 *Z*:*E*). The spectral data of this compound are consistent with those previously reported.[36]

4.7.6 NMR Spectra

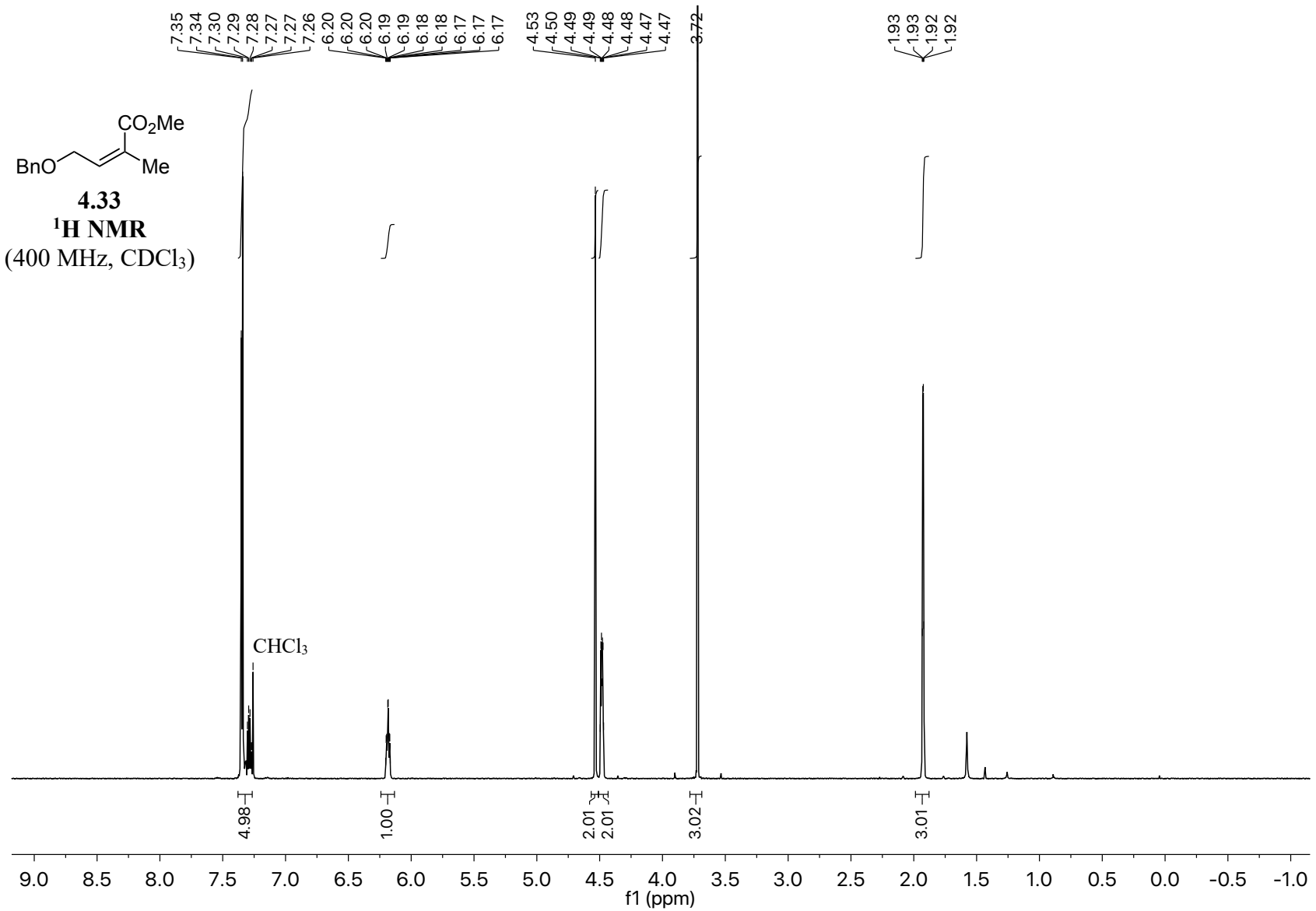

Me
Me
BnO
Me
4.32
1H NMR
(600 MHz, CDCl3)
CHCl3
f1 (ppm)

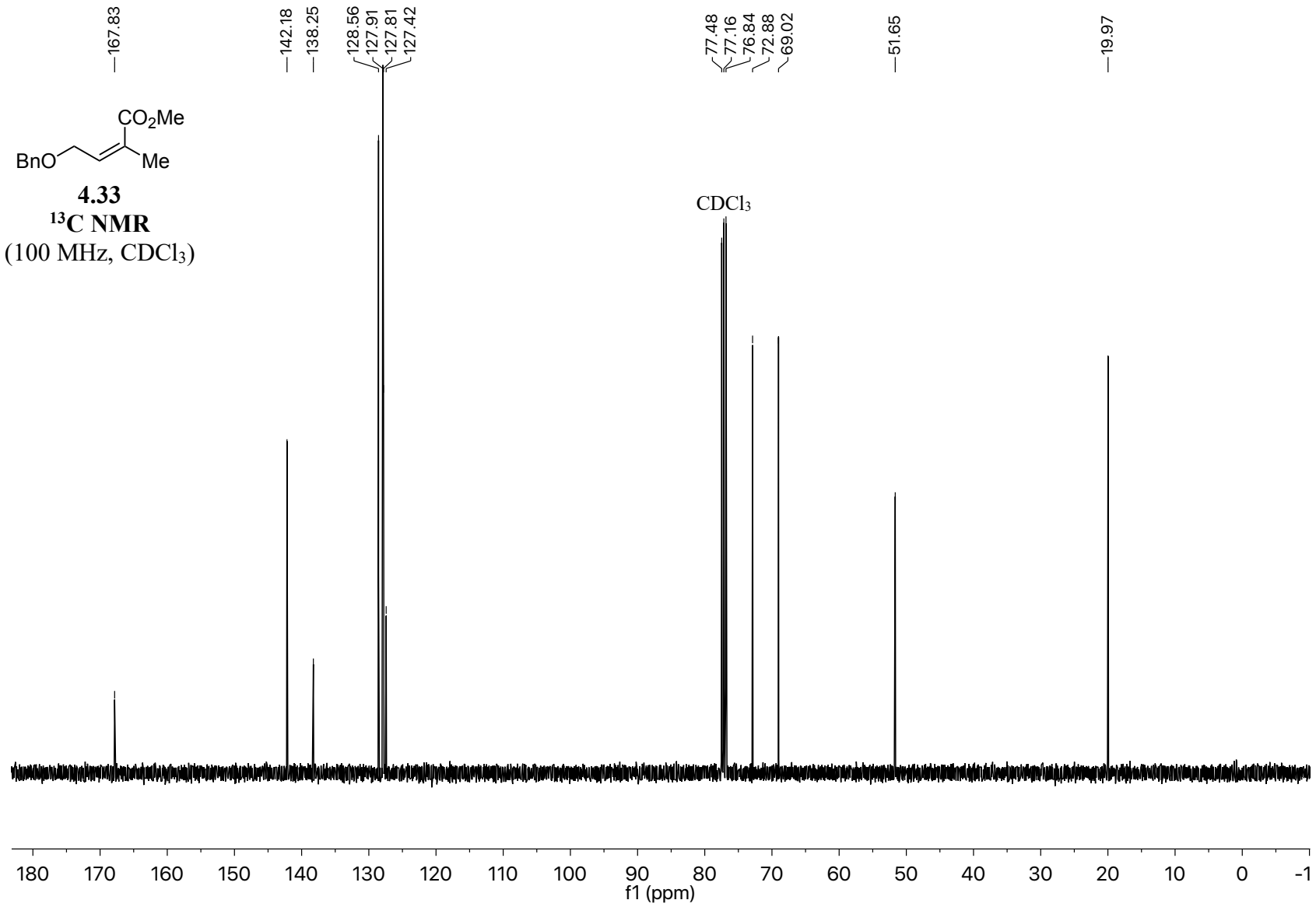


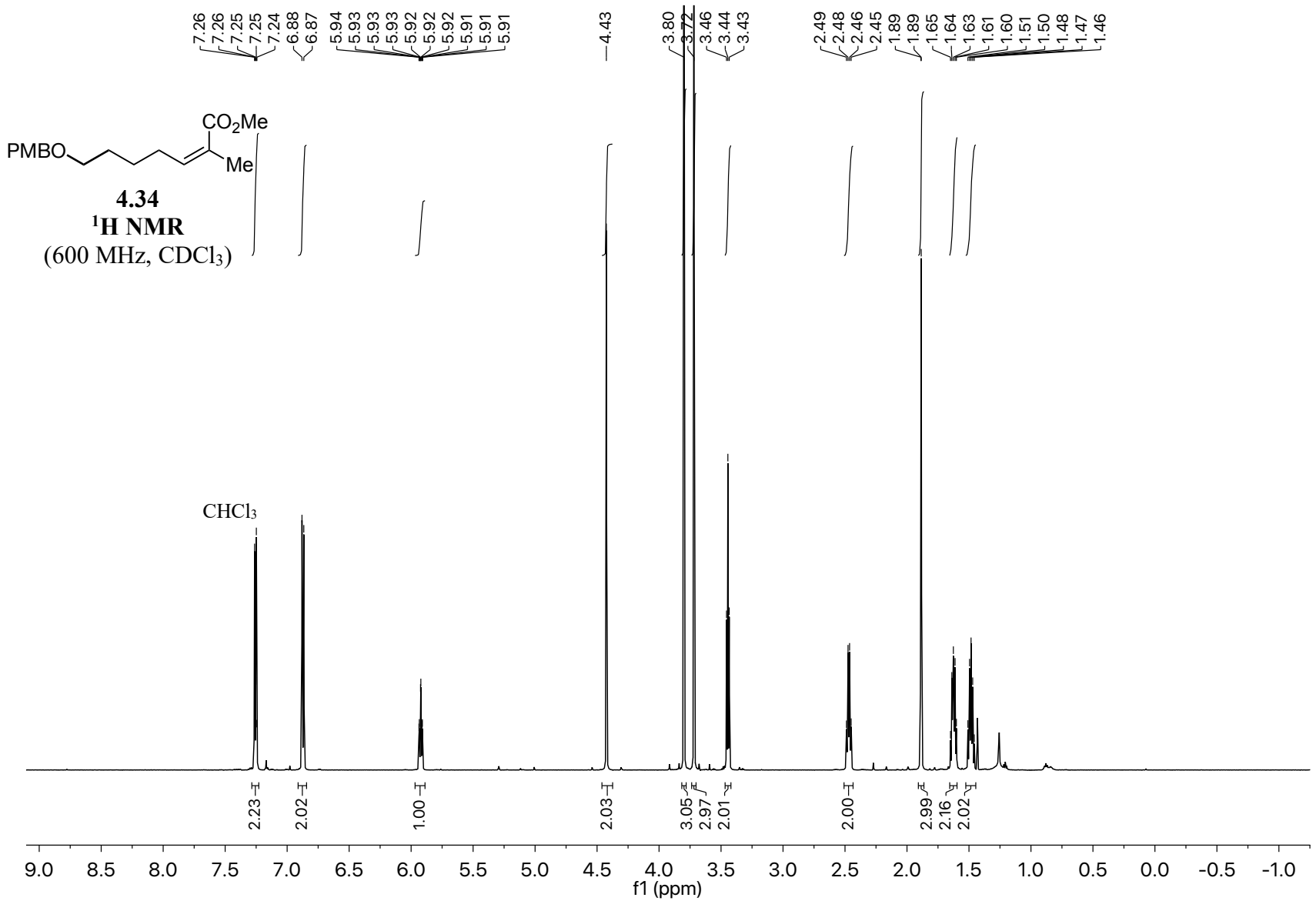
4.32

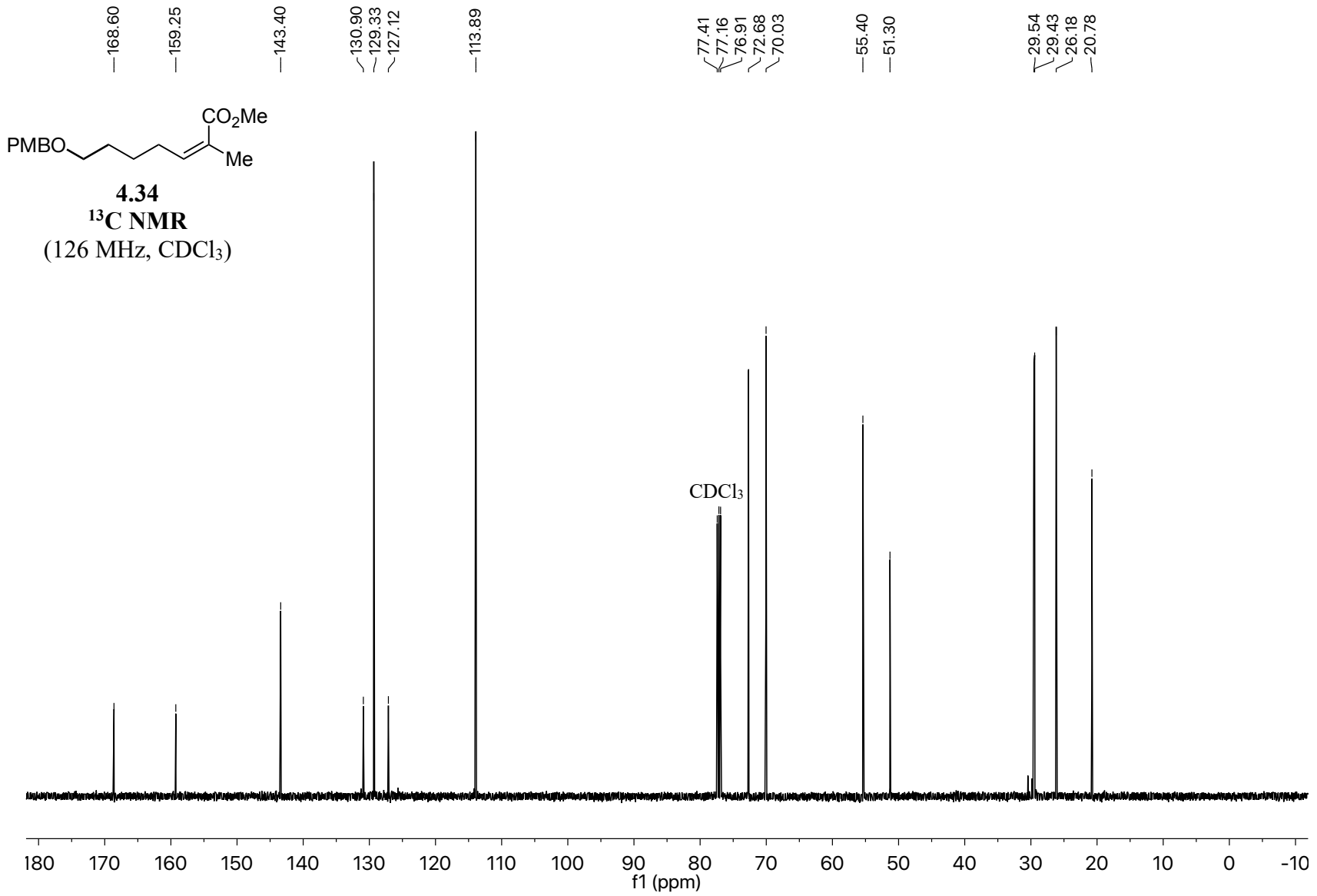
^{13}C NMR

(151 MHz, $CDCl_3$)

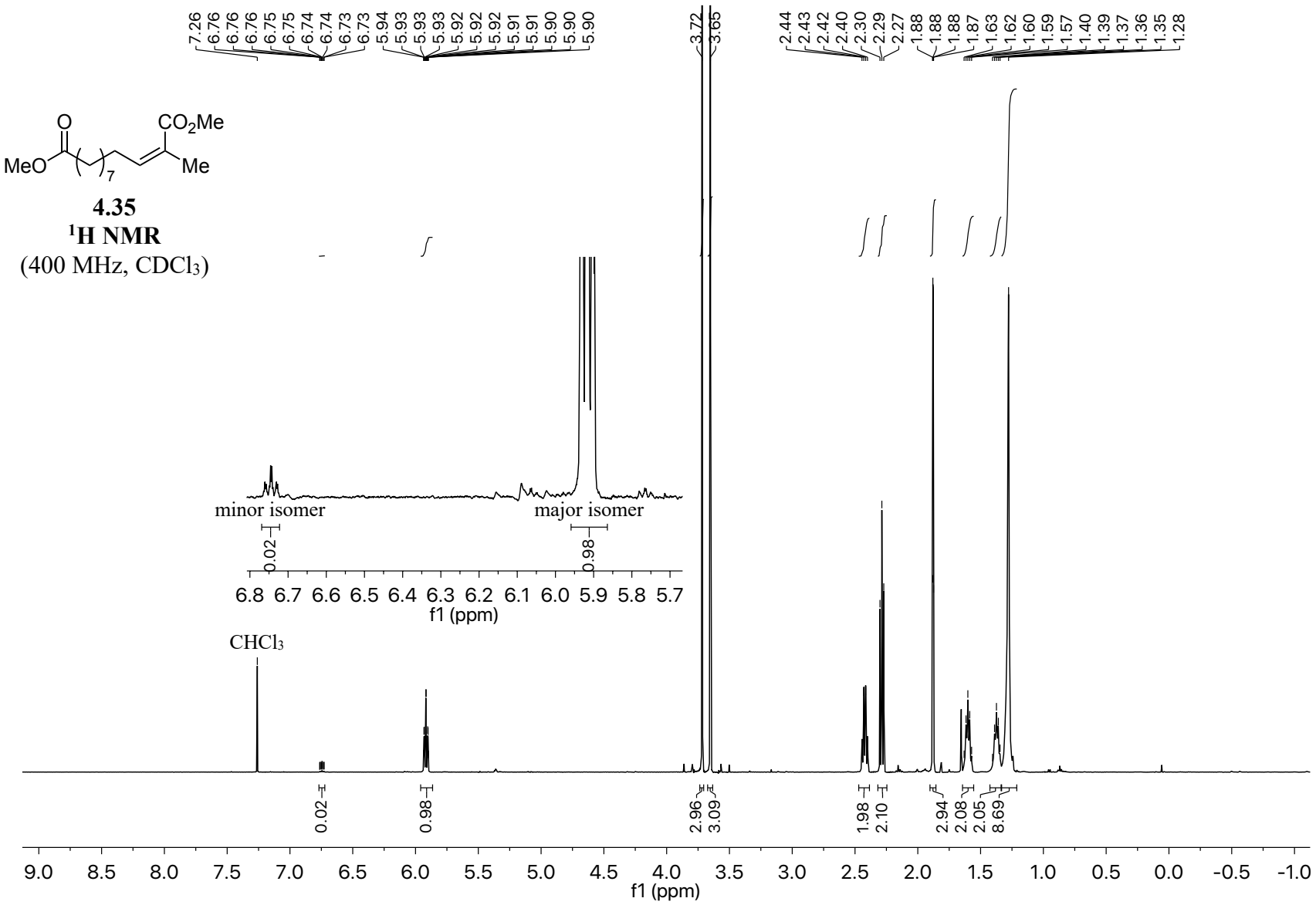

7.35
7.34
7.30
7.29
7.28
7.27
7.27
7.26
6.20
6.20
6.20
6.19
6.19
6.18
6.18
6.17
6.17
6.17
4.53
4.50
4.49
4.49
4.48
4.48
4.47
4.47
3.72
1.93
1.93
1.92
1.92
CO2Me
BnO
Me
4.33
1H NMR
(400 MHz, CDCl3)
CHCl3
4.98
1.00
2.01
2.01
3.02
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

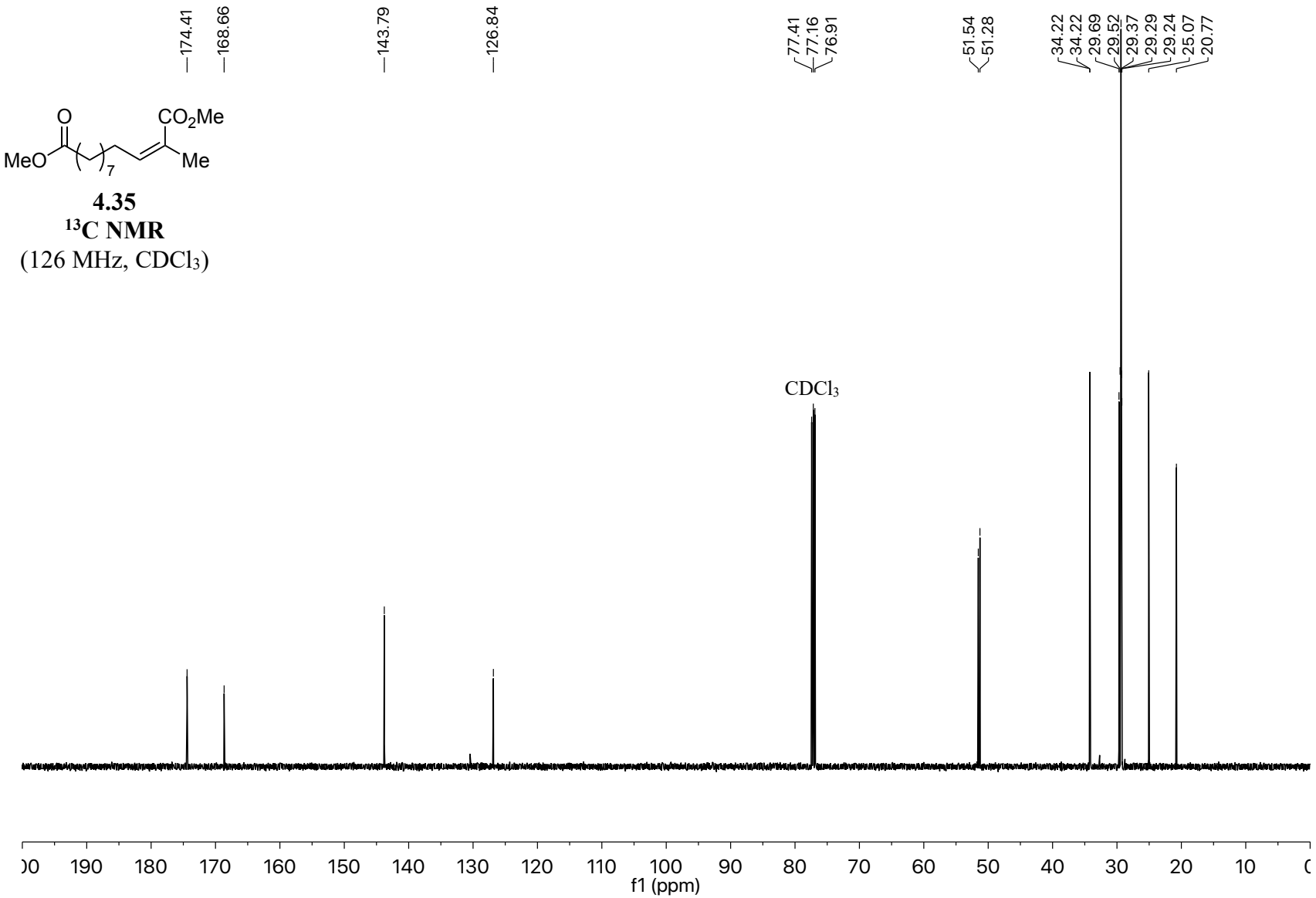

167.83
142.18
138.25
128.56
127.91
127.81
127.42
77.48
77.16
76.84
72.88
69.02
51.65
19.97
CO2Me
BnO
Me
4.33
13C NMR
(100 MHz, CDCl3)
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)


PMBO
CO2Me
Me
4.34
1H NMR
(600 MHz, CDCl3)
CHCl3
f1 (ppm)

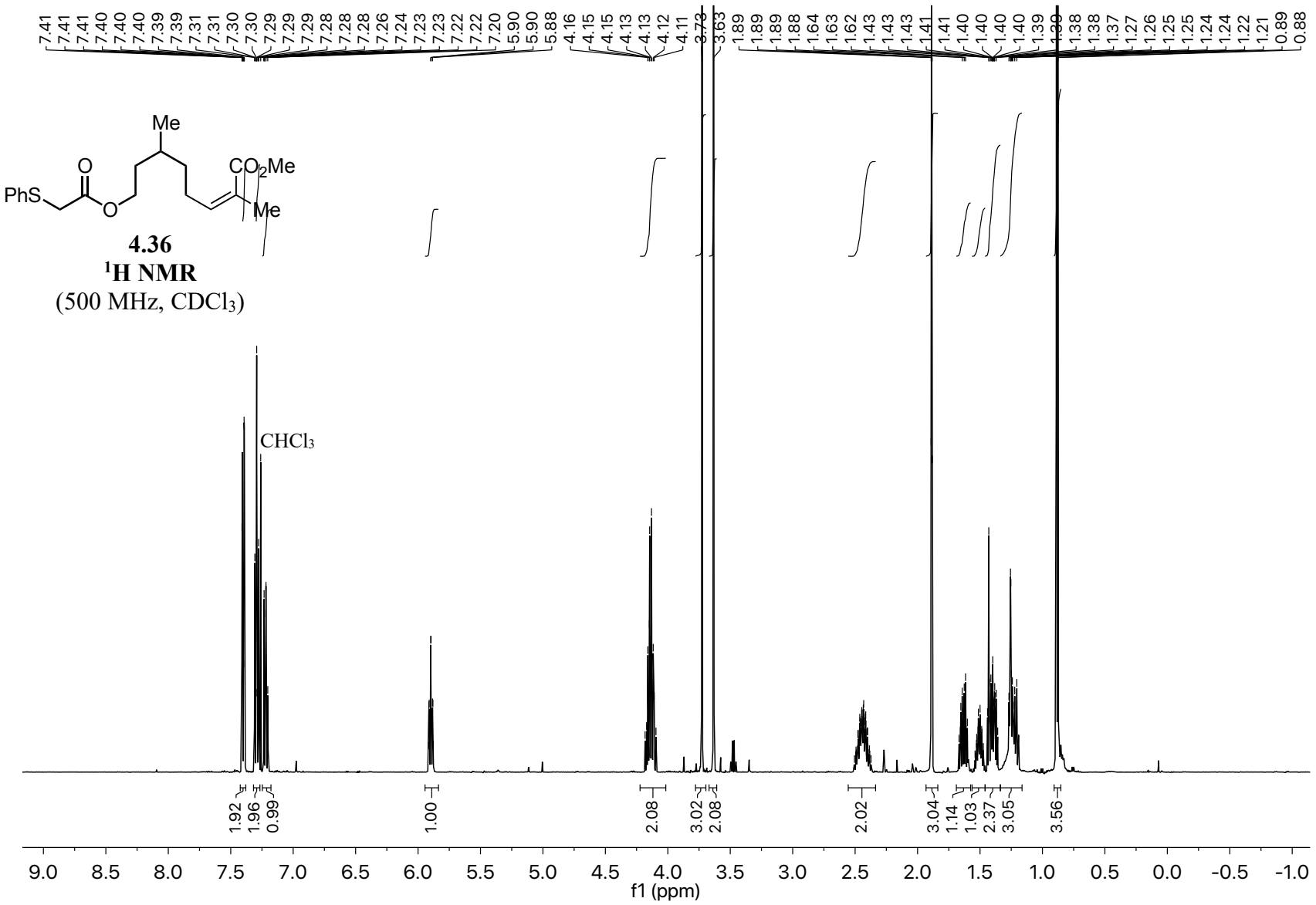


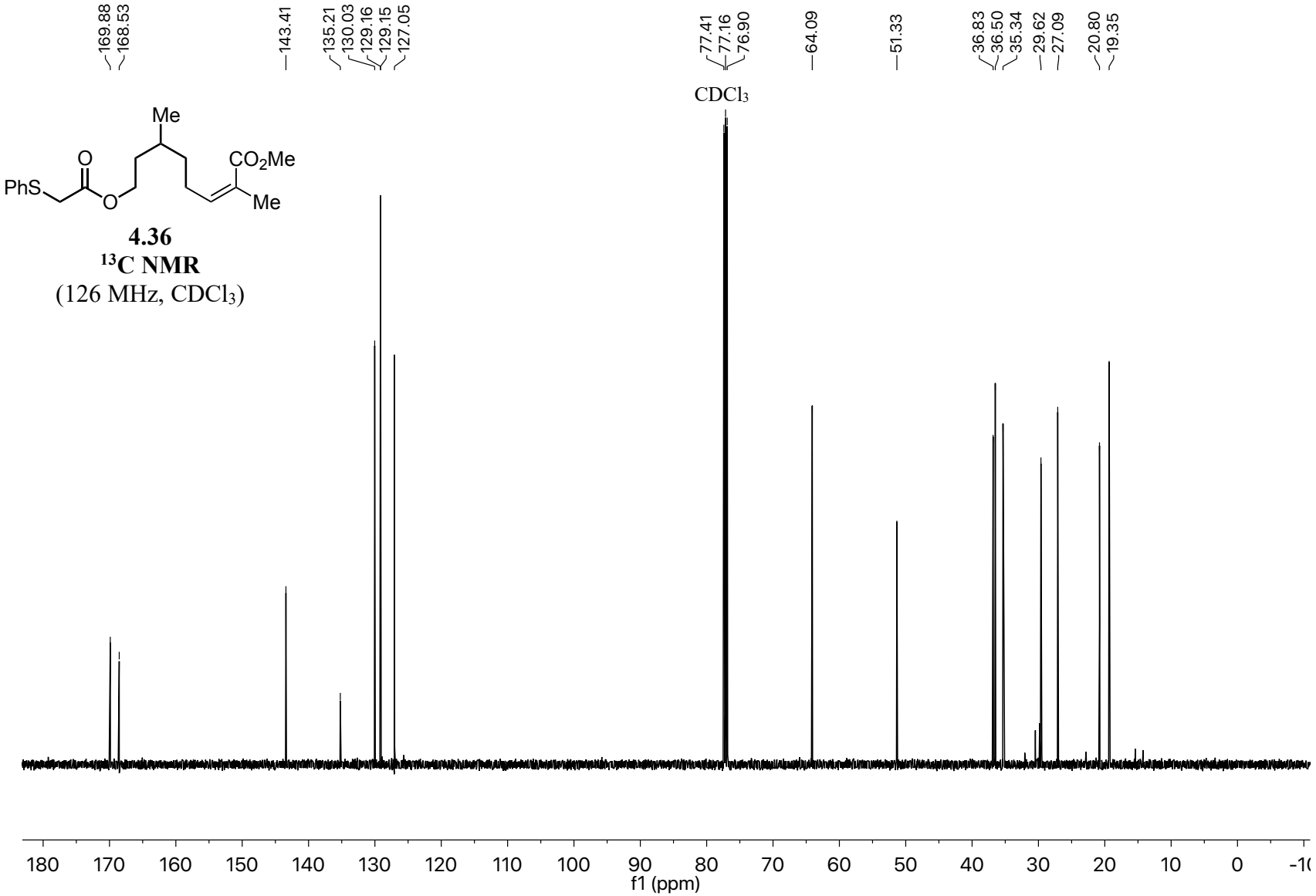
4.34
^{13}C NMR
(126 MHz, $CDCl_3$)


4.35
1H NMR
(400 MHz, CDCl3)
minor isomer
major isomer
CHCl3
f1 (ppm)

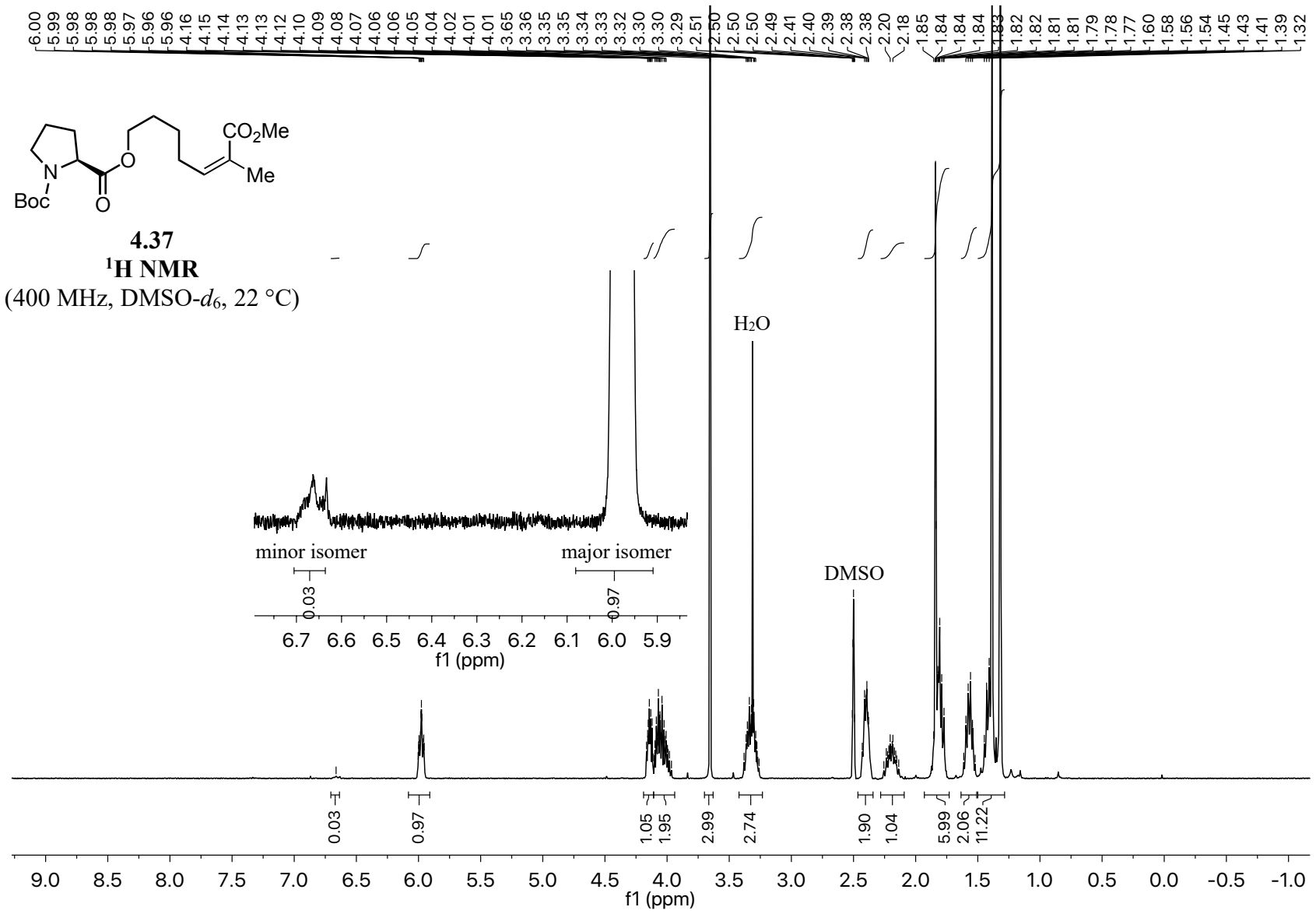


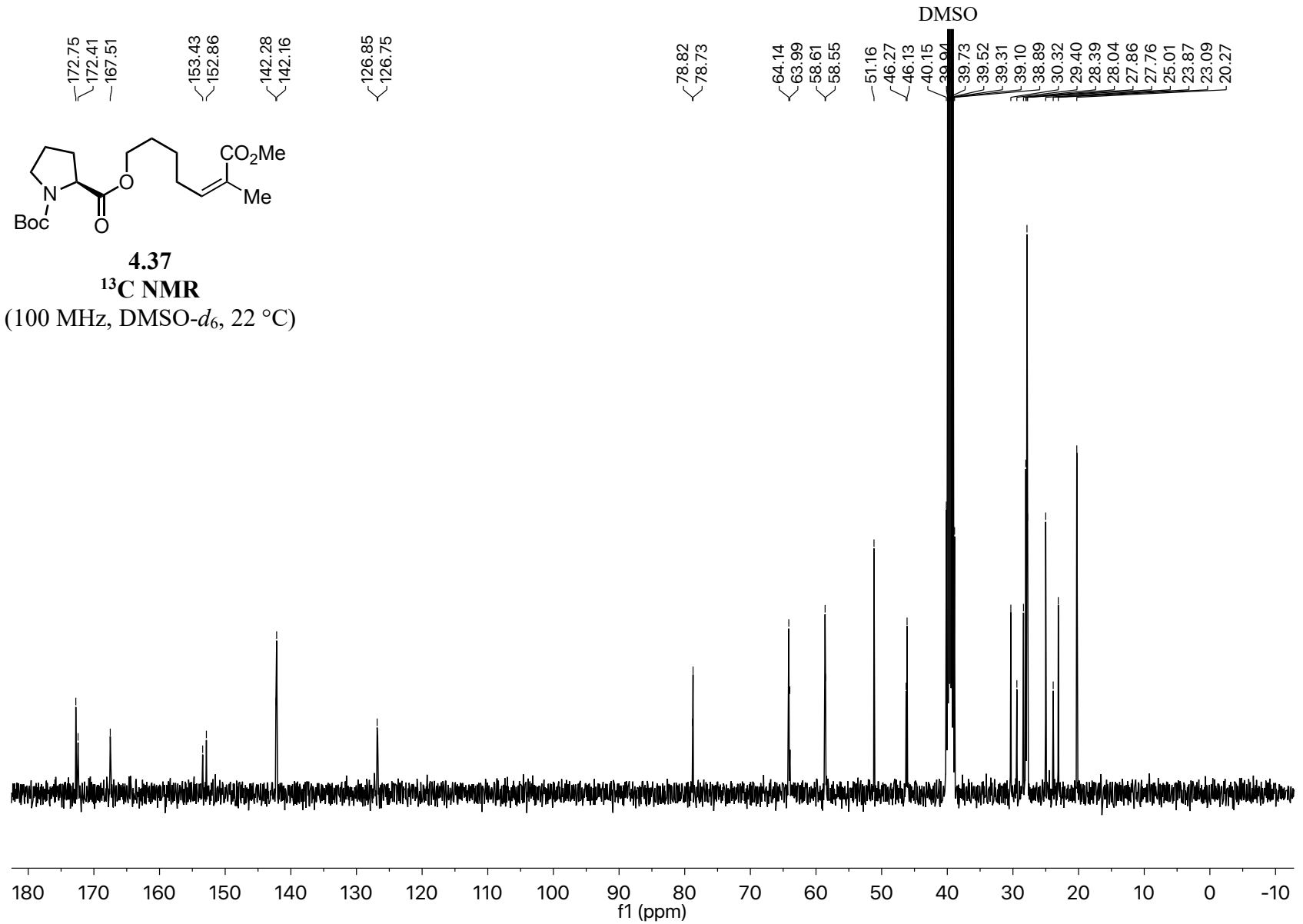
4.35
^{13}C NMR
(126 MHz, $CDCl_3$)


Me
O
CO2Me
PhS
O
Me
4.36
1H NMR
(500 MHz, CDCl3)
CHCl3
f1 (ppm)



4.36
^{13}C NMR
(126 MHz, $CDCl_3$)

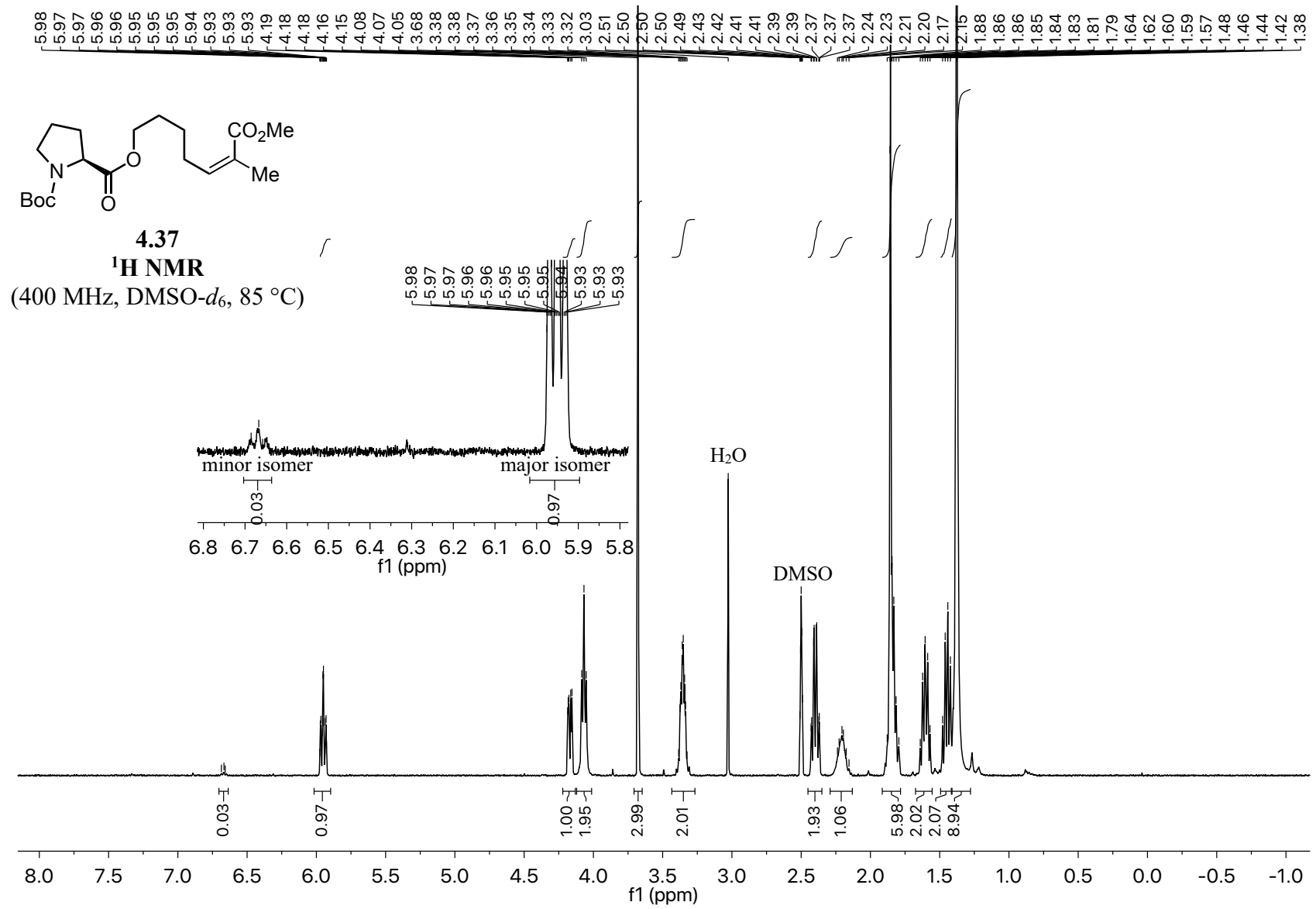

CO2Me
Me
N
Boc
O
O
4.37
1H NMR
(400 MHz, DMSO-d6, 22 °C)
H2O
DMSO
minor isomer
major isomer
0.03
0.97
f1 (ppm)
0.03
0.97
1.05
1.95
2.99
2.74
1.90
1.04
5.99
2.06
11.22
f1 (ppm)

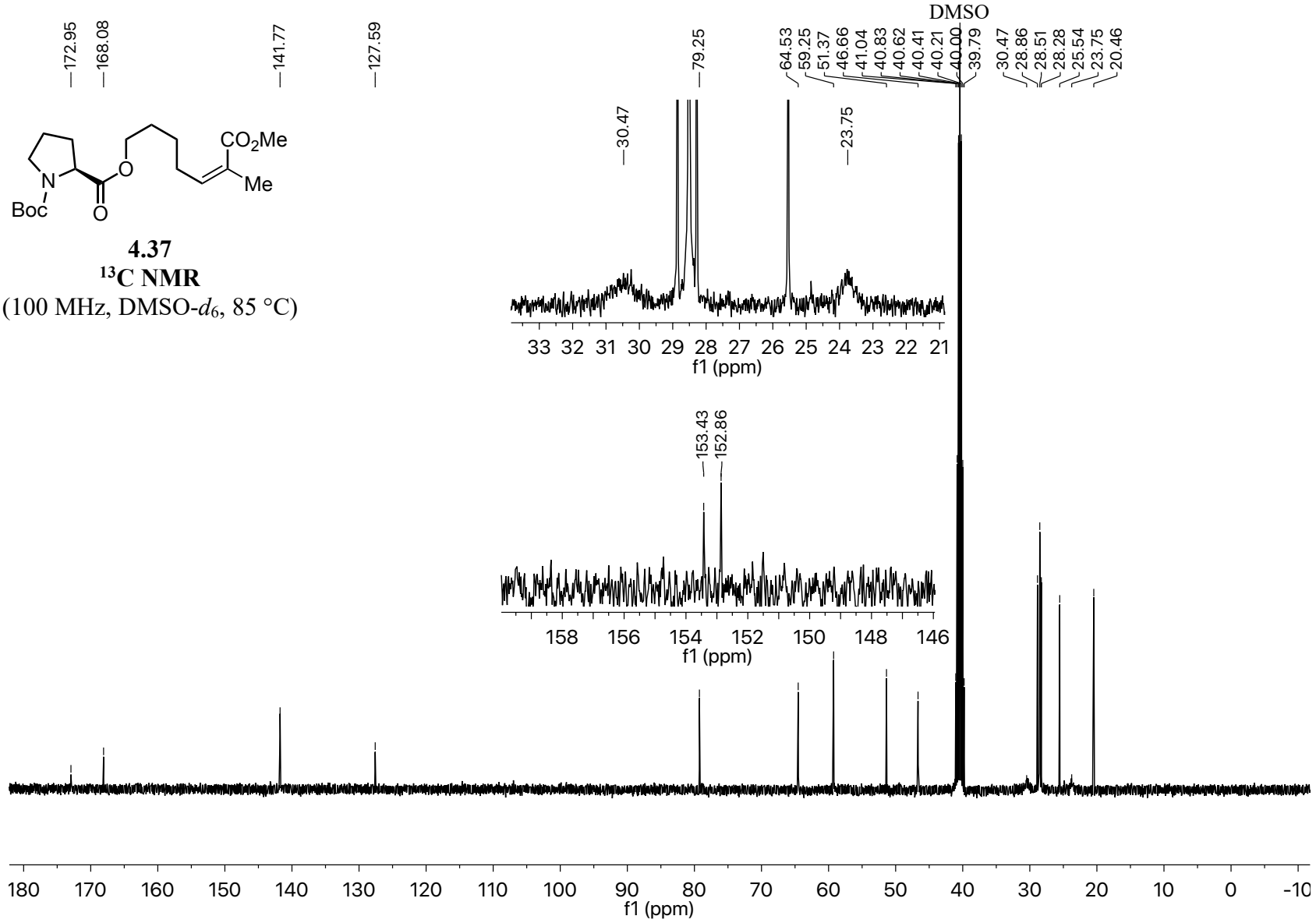


4.37

^{13}C NMR

(100 MHz, DMSO-d_6, 22 °C)

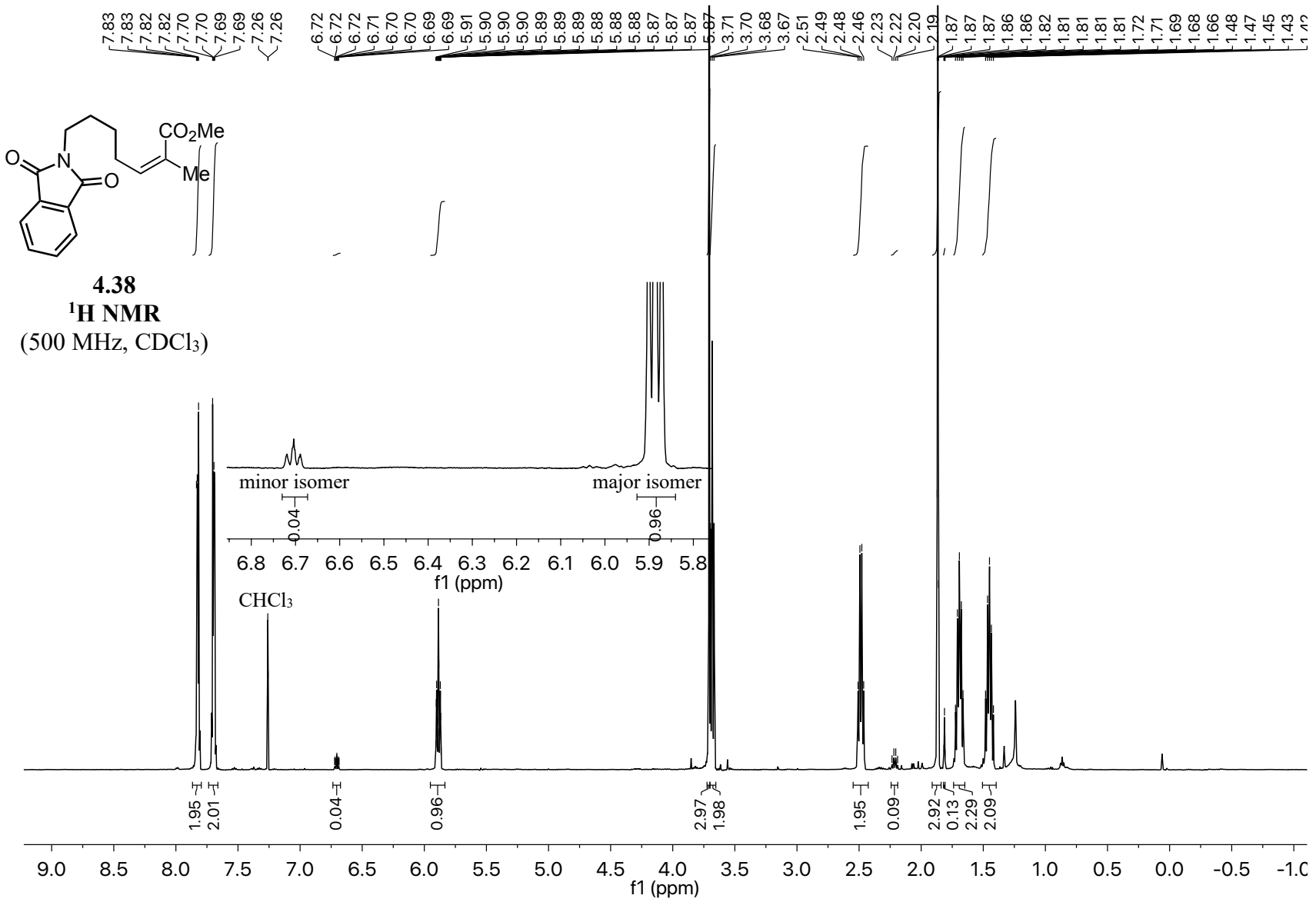

CO2Me
Me
N
Boc
O
O
4.37
1H NMR
(400 MHz, DMSO-d6, 85 °C)
minor isomer
major isomer
0.03
0.97
f1 (ppm)
H2O
DMSO
0.03
0.97
1.00
1.95
2.99
2.01
1.93
1.06
5.98
2.02
2.07
8.94
f1 (ppm)

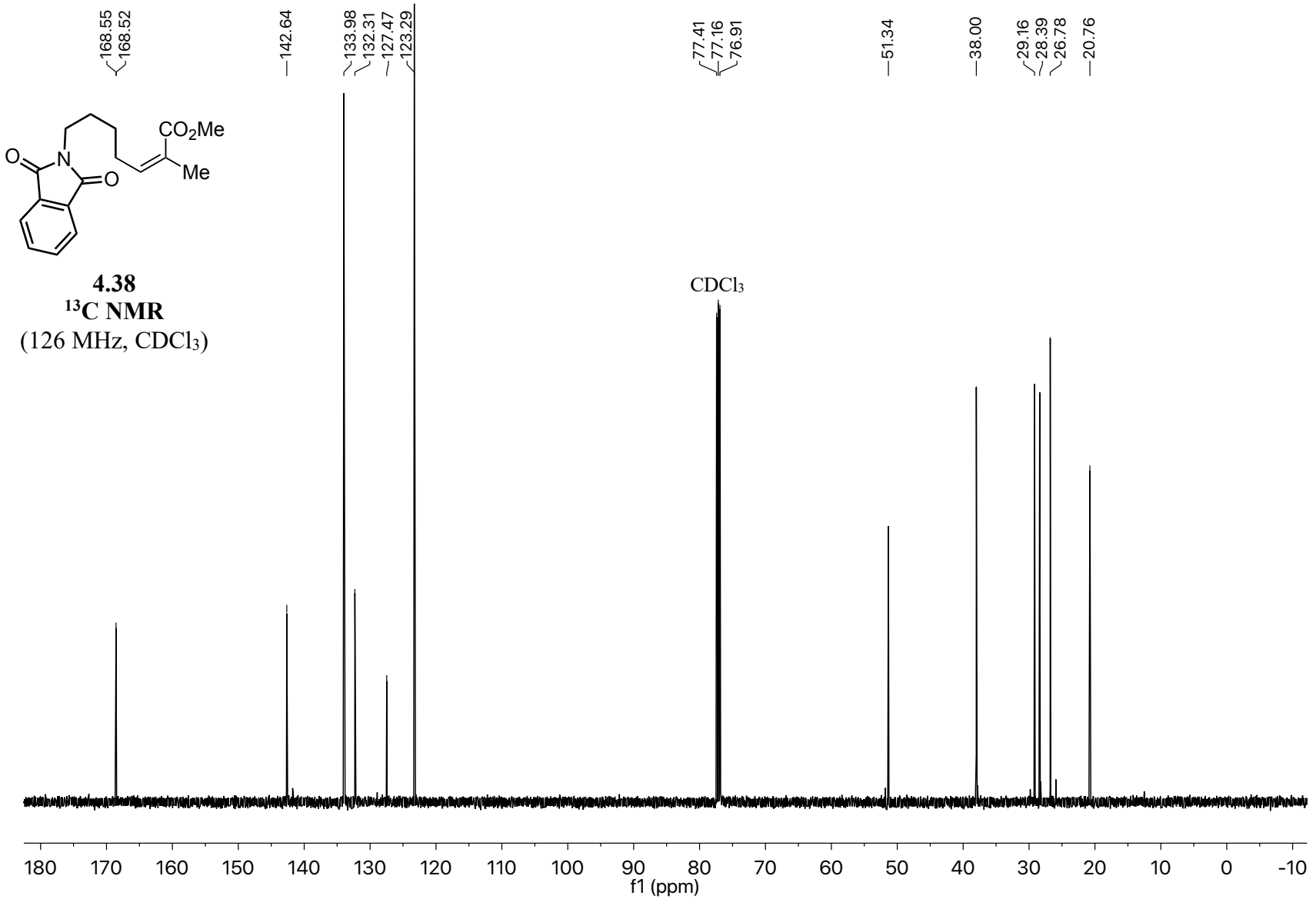


4.37

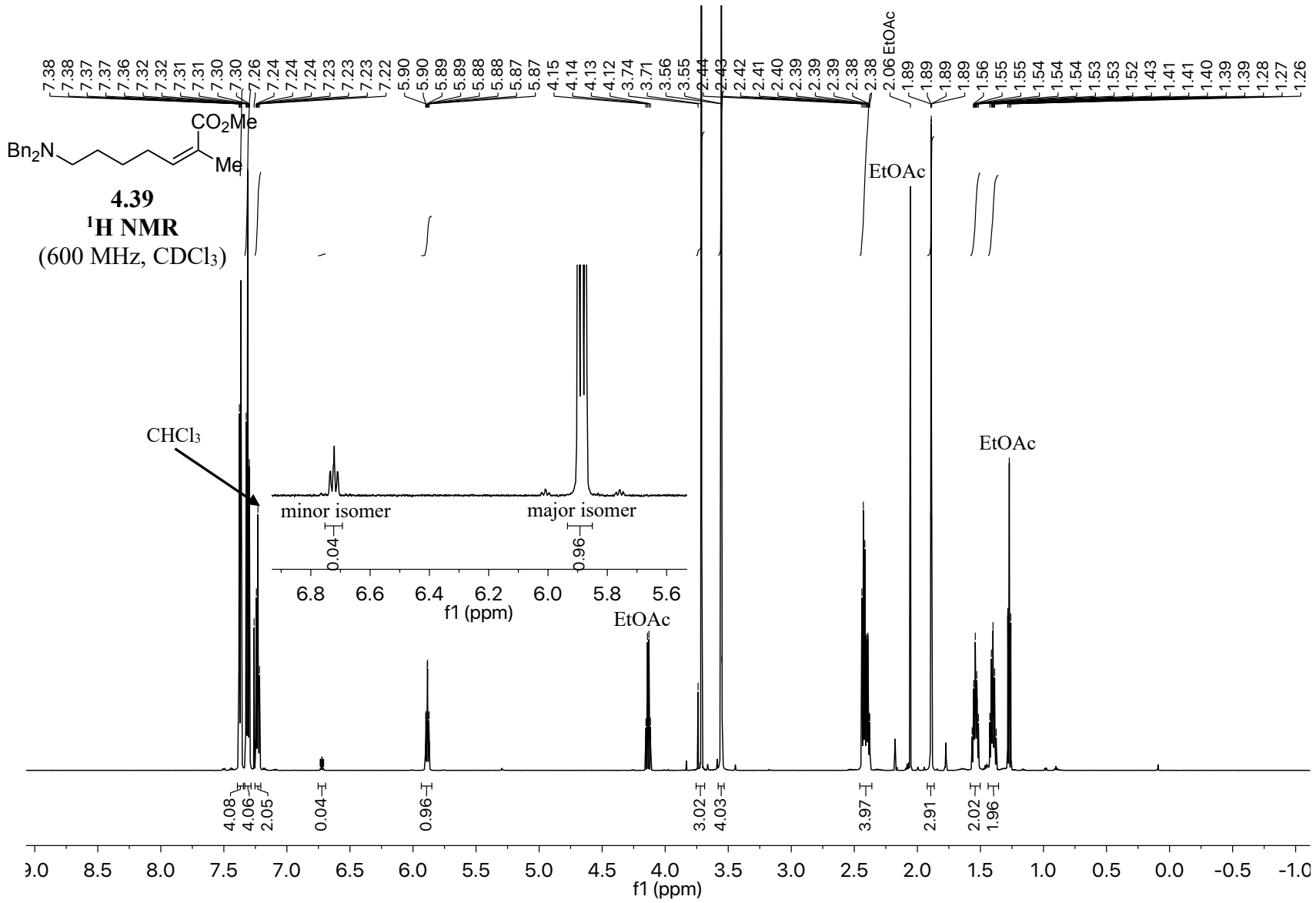
^{13}C NMR

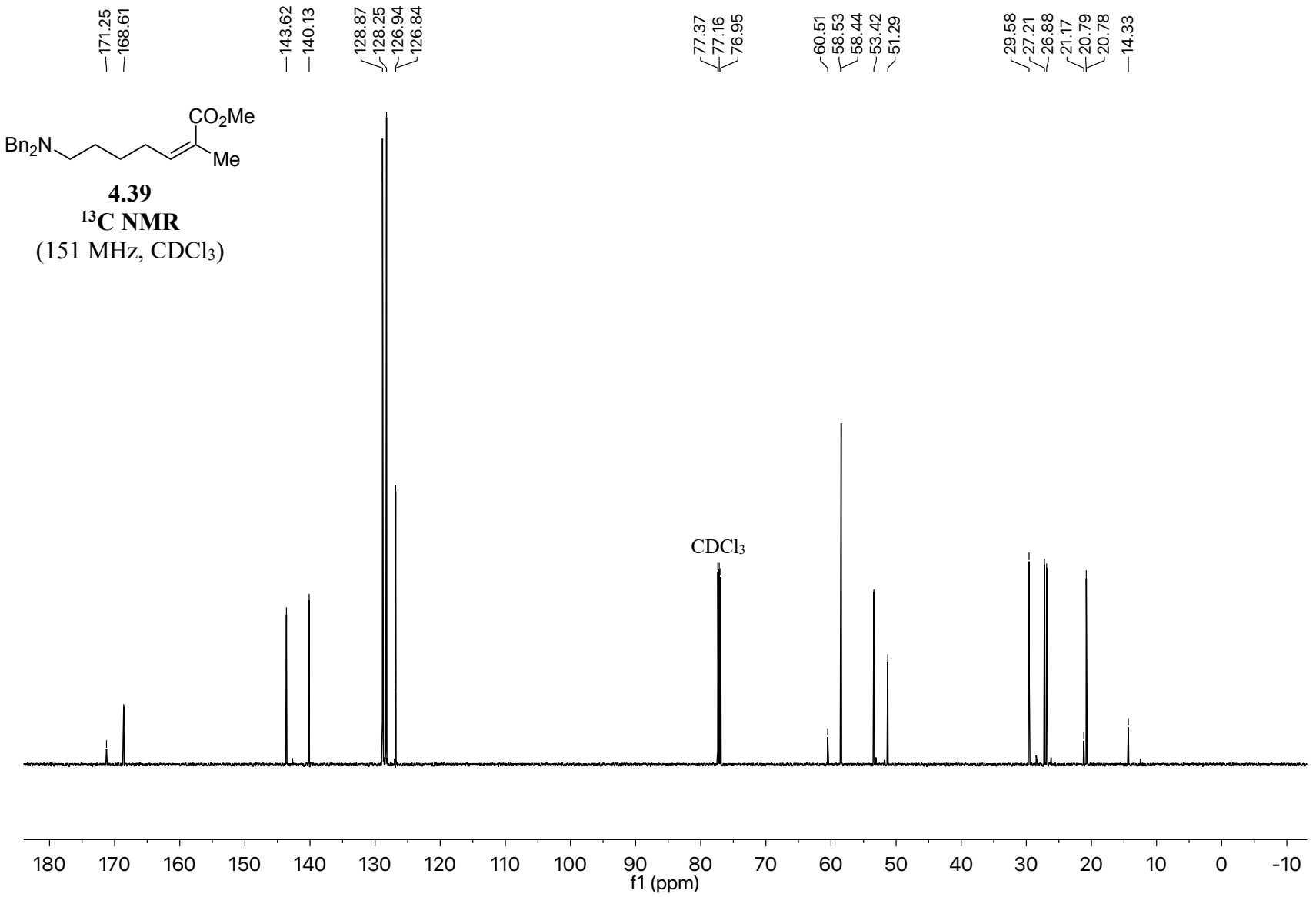
(100 MHz, DMSO-d_6, 85 °C)


CO2Me
Me
O
N
O
4.38
1H NMR
(500 MHz, CDCl3)
minor isomer
major isomer
0.04
0.96
6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8
f1 (ppm)
CHCl3
1.95
2.01
0.04
0.96
2.97
1.98
1.95
0.09
2.92
0.13
2.29
2.09
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

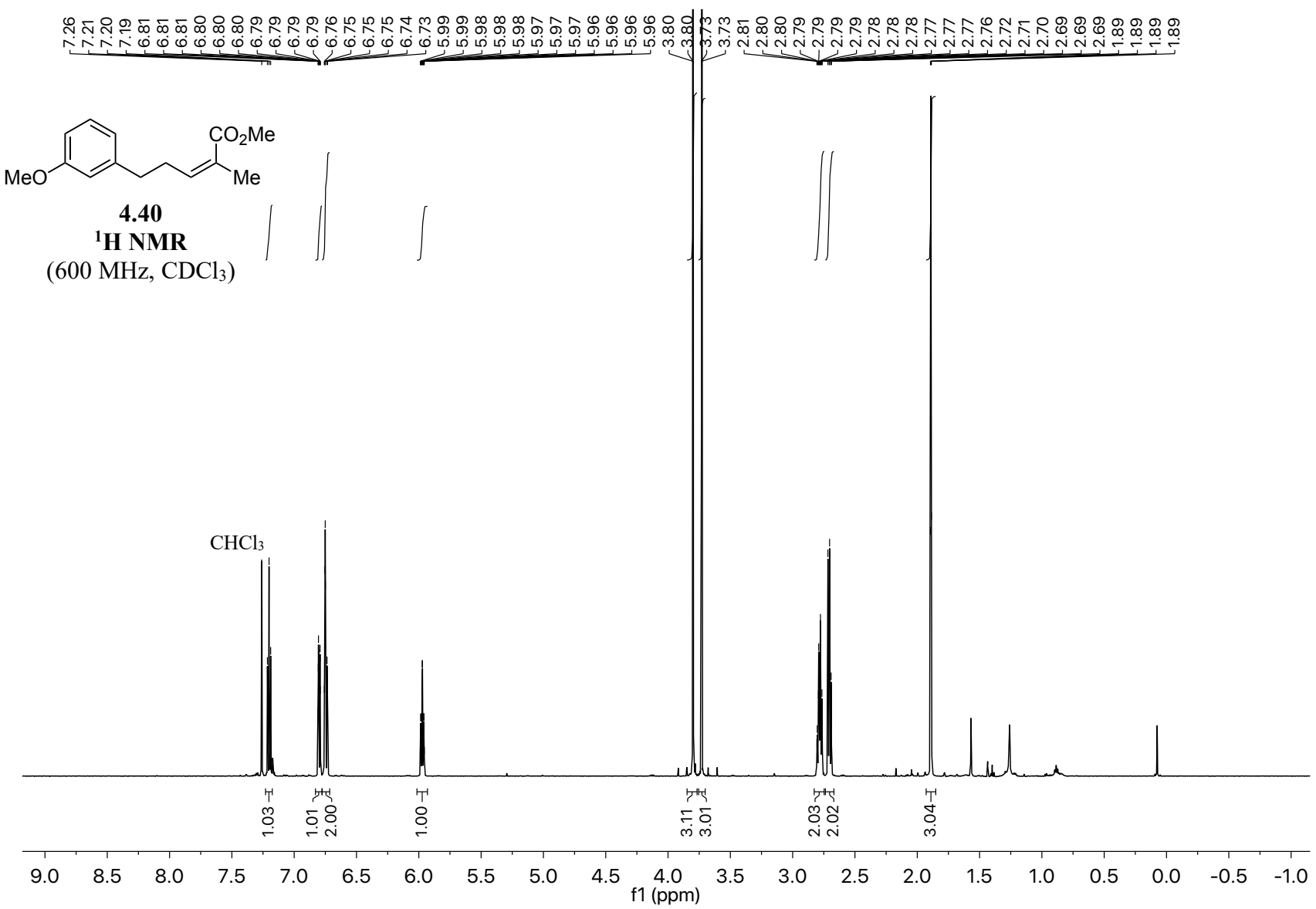


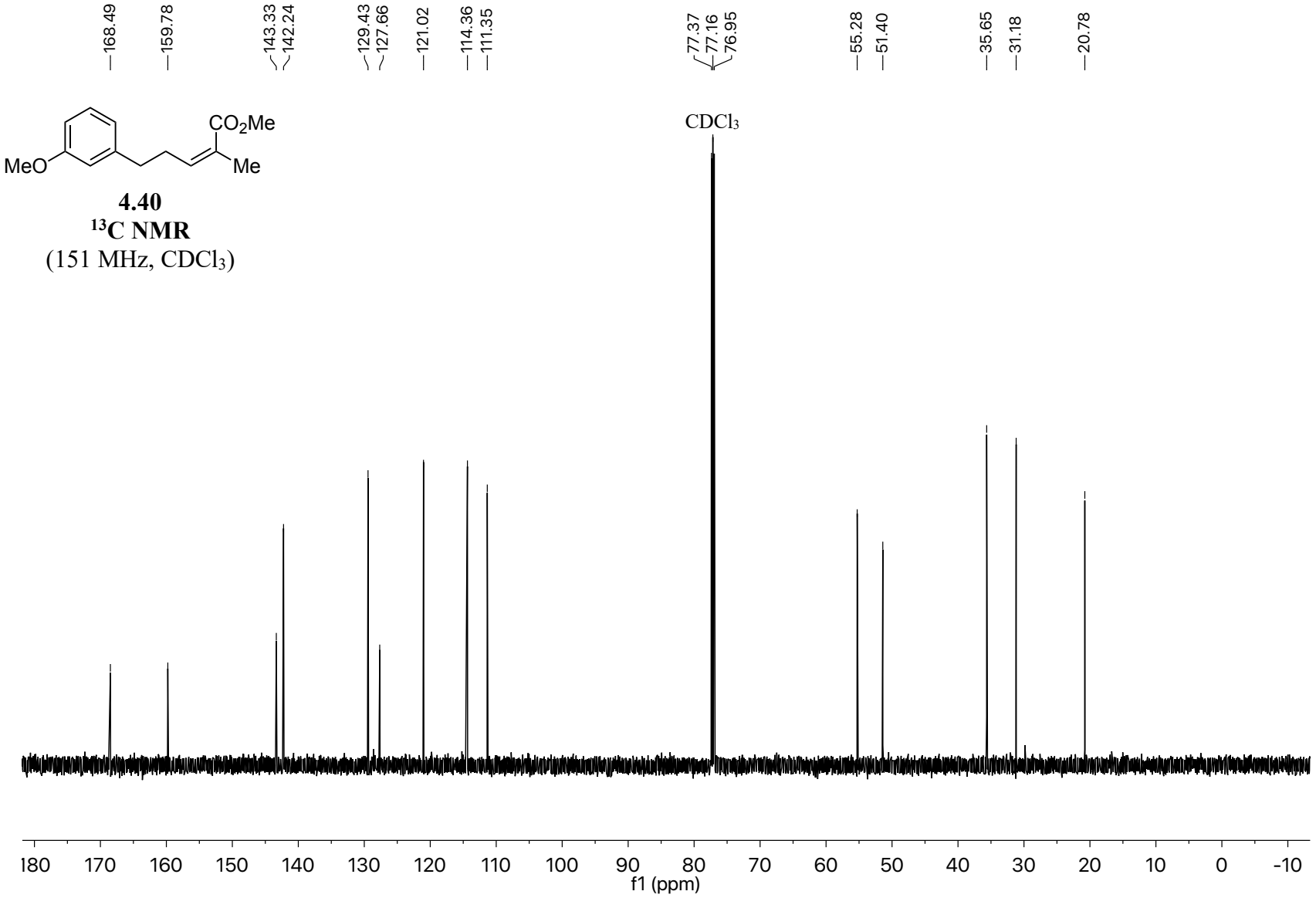
4.38
^{13}C NMR
(126 MHz, $CDCl_3$)


CO2Me
Bn2N
Me
4.39
1H NMR
(600 MHz, CDCl3)
CHCl3
EtOAc
EtOAc
EtOAc
minor isomer
major isomer
0.04
0.96
f1 (ppm)
4.08
4.06
2.05
0.04
0.96
3.02
4.03
3.97
2.91
2.02
1.96
f1 (ppm)

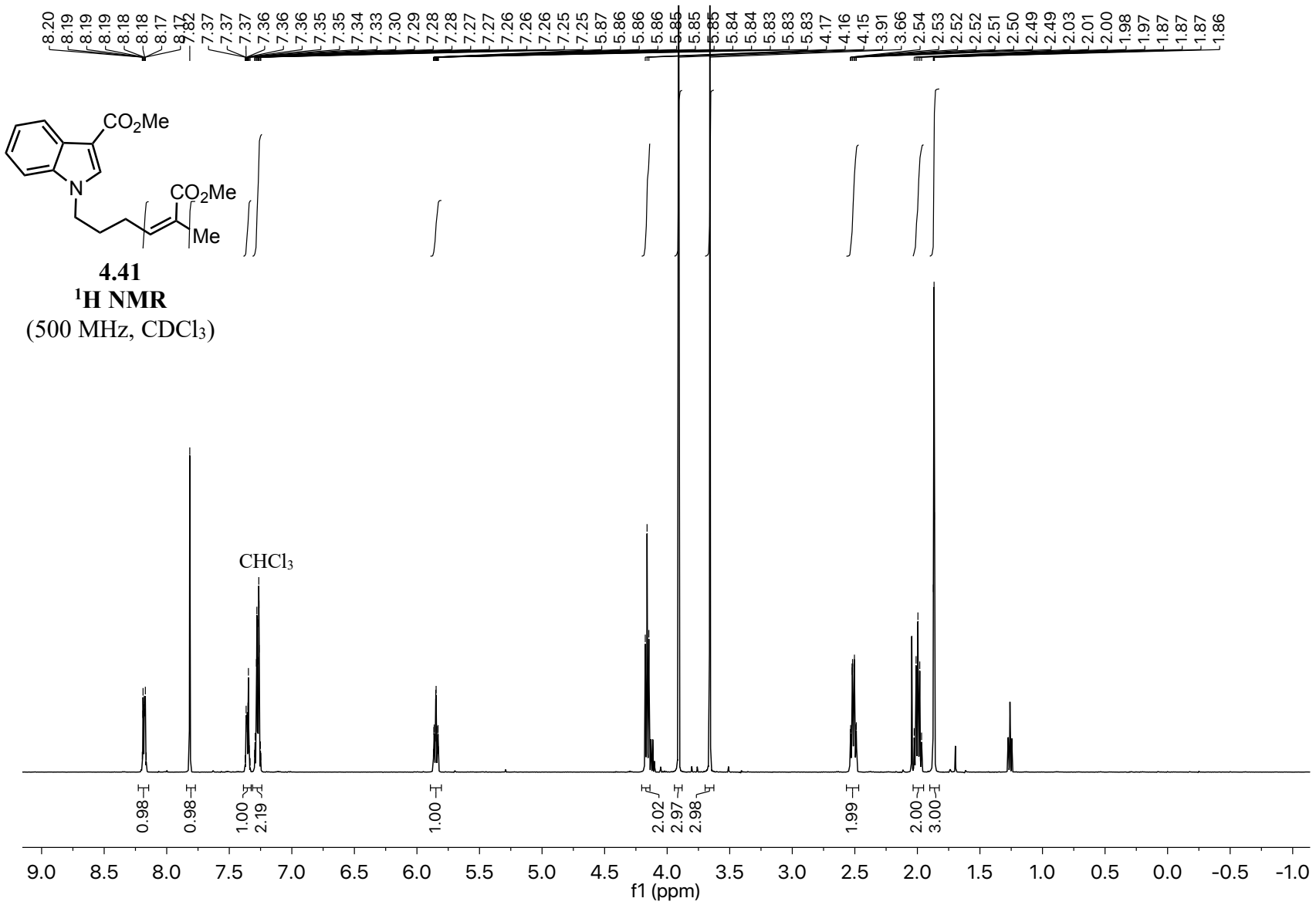


4.39
^{13}C NMR
(151 MHz, $CDCl_3$)

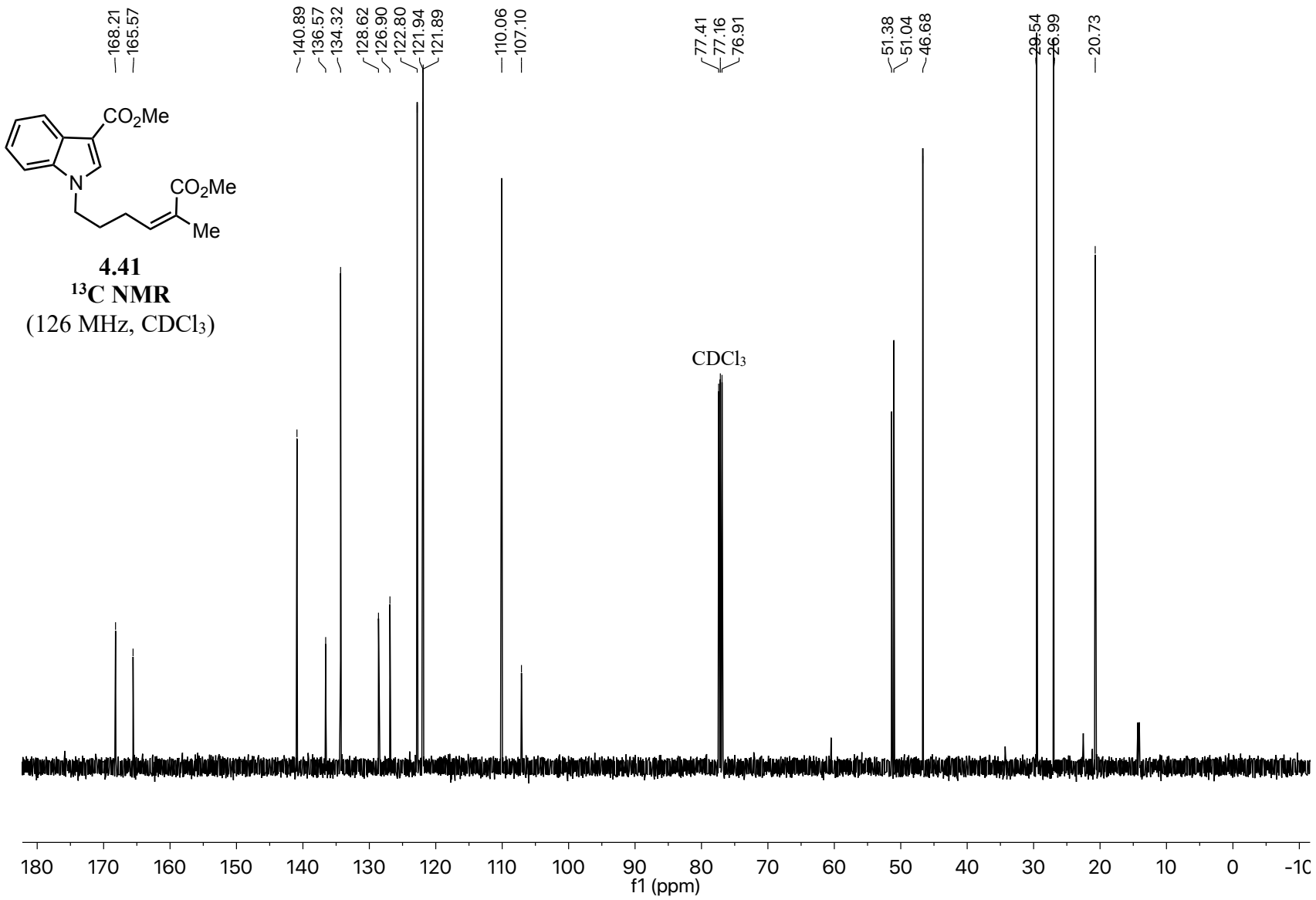

7.26 7.21 7.20 7.19 6.81 6.81 6.81 6.80 6.80 6.80 6.79 6.79 6.79 6.79 6.76 6.75 6.75 6.75 6.74 6.73 5.99 5.99 5.98 5.98 5.98 5.97 5.97 5.96 5.96 5.96 3.80 3.80 3.73 3.73 2.81 2.80 2.80 2.79 2.79 2.79 2.78 2.78 2.78 2.77 2.77 2.77 2.76 2.72 2.71 2.70 2.69 2.69 2.69 1.89 1.89 1.89 1.89
CO2Me
MeO
Me
4.40
1H NMR
(600 MHz, CDCl3)
CHCl3
1.03
1.01
2.00
1.00
3.11
3.01
2.03
2.02
3.04
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)



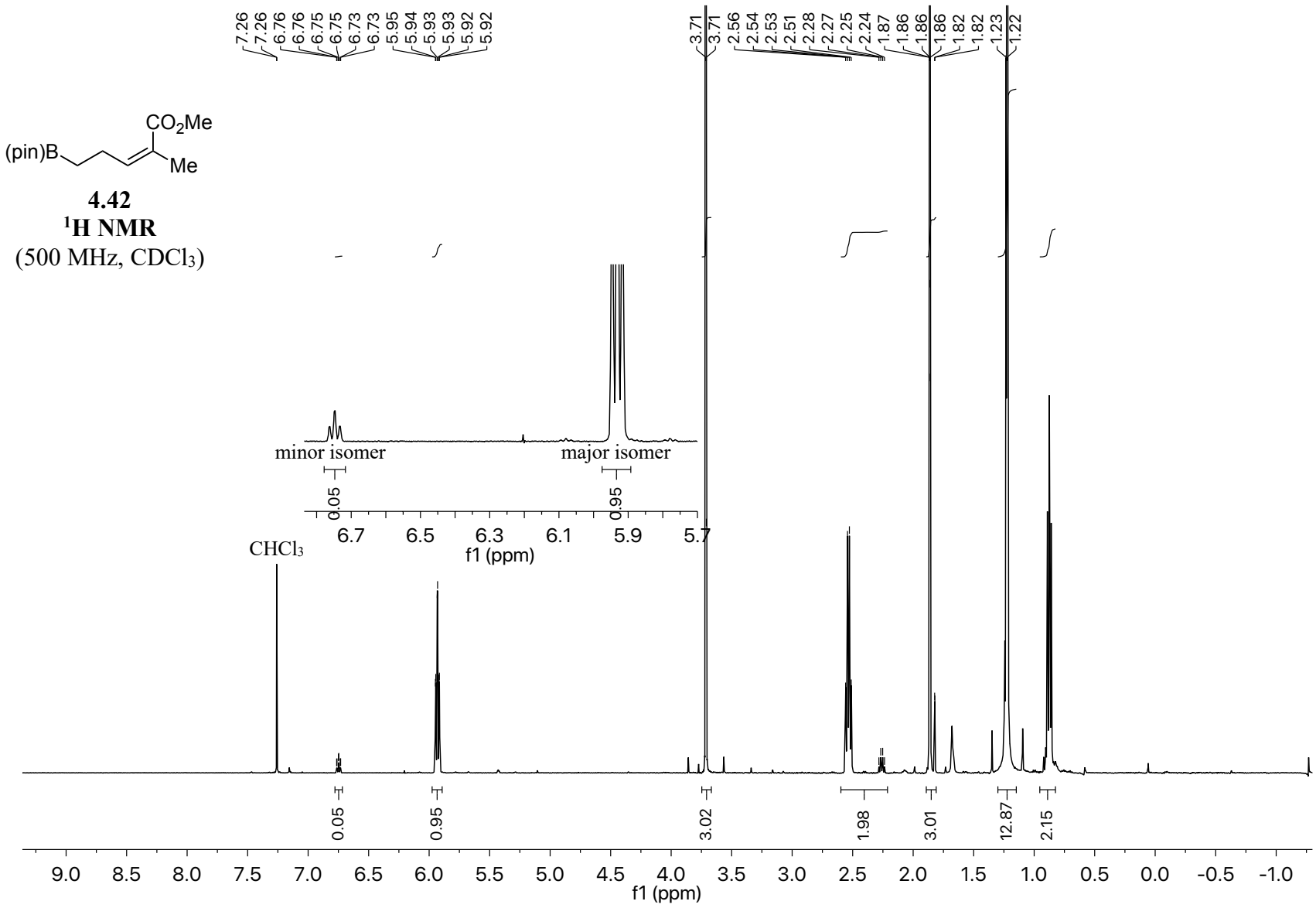
4.40
^{13}C NMR
(151 MHz, $CDCl_3$)

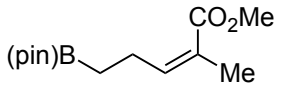


4.41
^{1}H NMR
(500 MHz, $CDCl_3$)

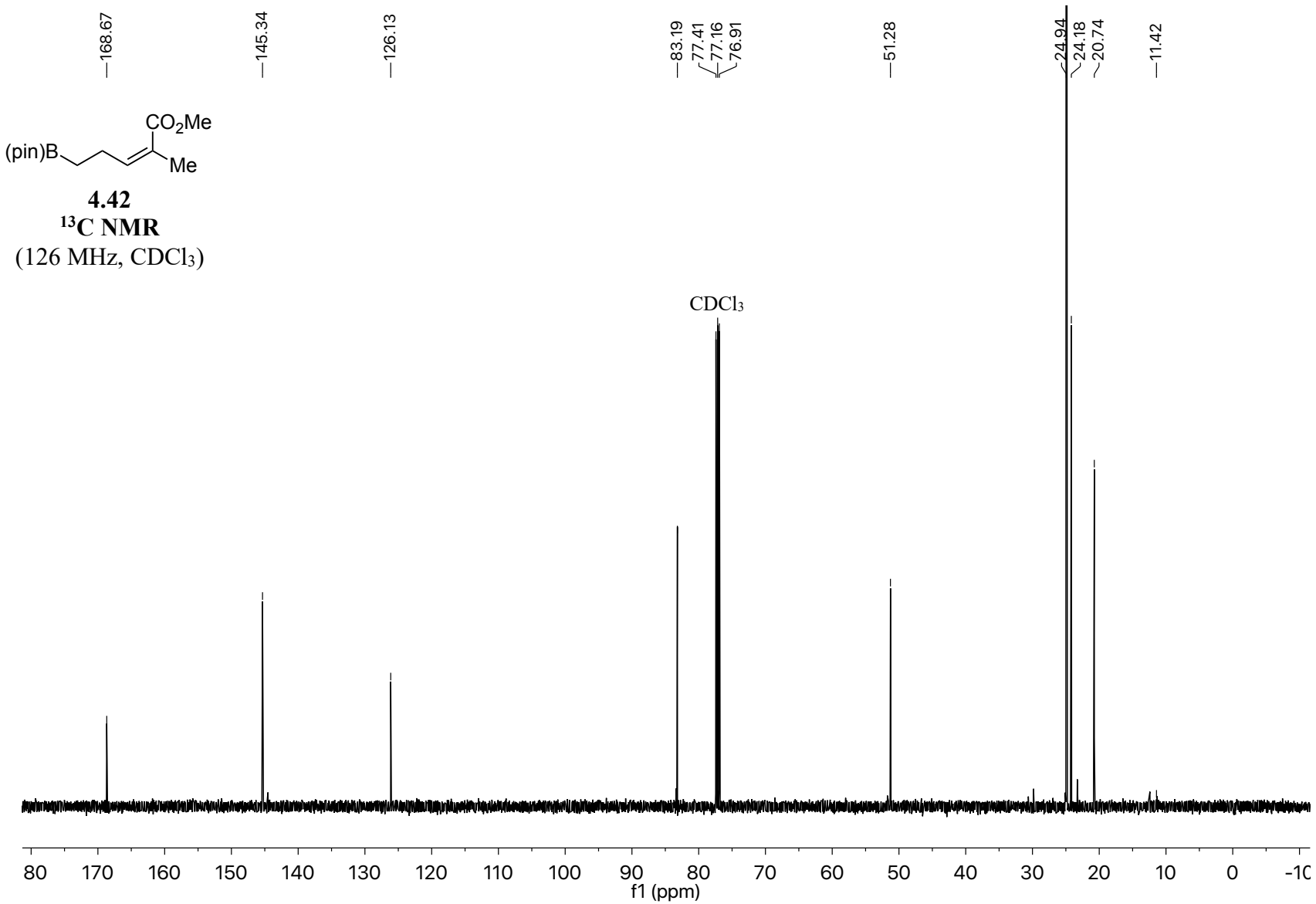


4.41
^{13}C NMR
(126 MHz, $CDCl_3$)

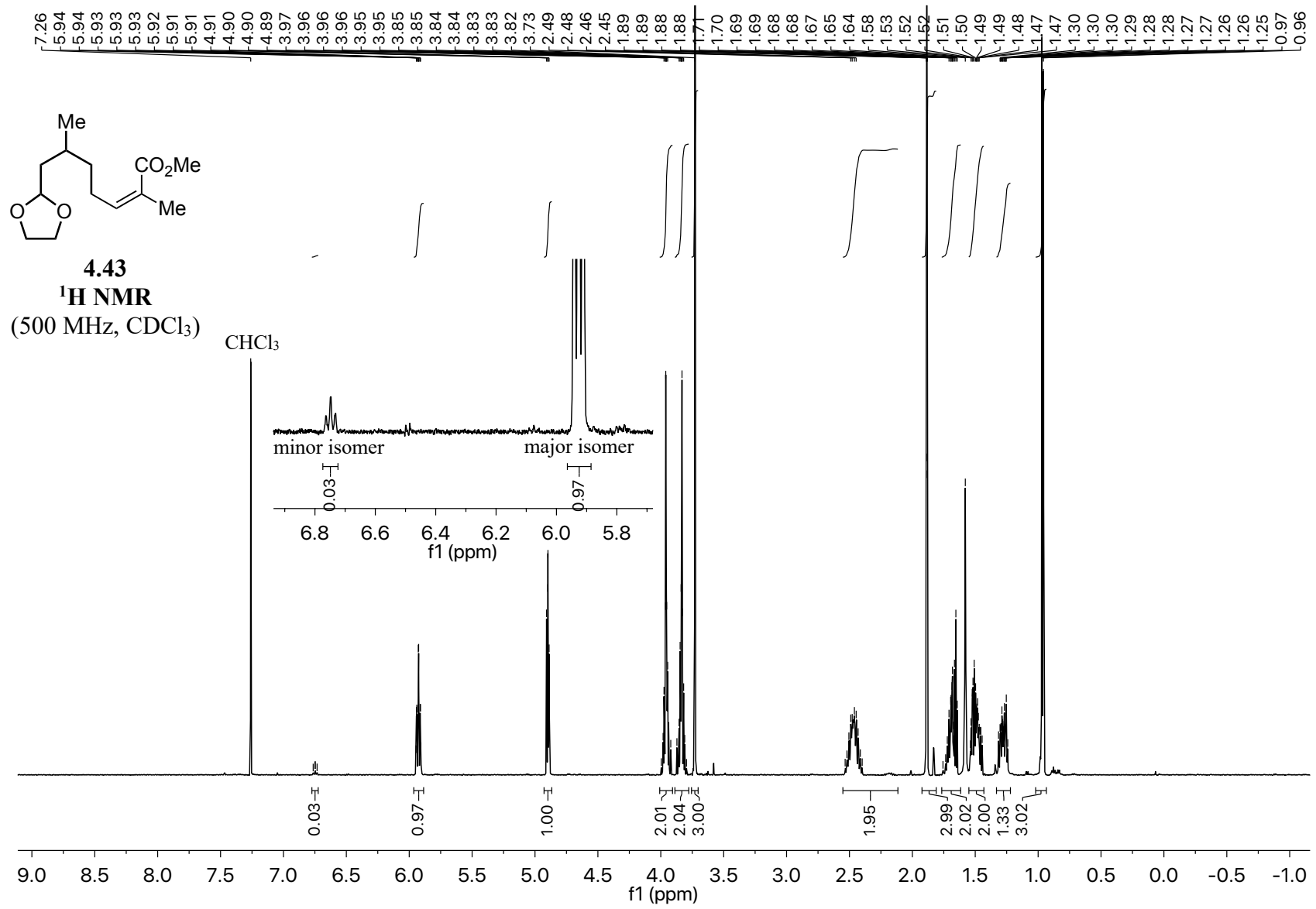

CO2Me
(pin)B
Me
4.42
1H NMR
(500 MHz, CDCl3)
7.26 7.26 6.76 6.76 6.75 6.75 6.73 6.73 5.95 5.94 5.93 5.93 5.92 5.92
3.71 3.71 2.56 2.54 2.53 2.51 2.28 2.27 2.25 2.24 1.87 1.86 1.86 1.86 1.82 1.82 1.23 1.22
minor isomer
major isomer
0.05
0.95
6.7 6.5 6.3 6.1 5.9 5.7
f1 (ppm)
CHCl3
0.05 0.95 3.02 1.98 3.01 12.87 2.15
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

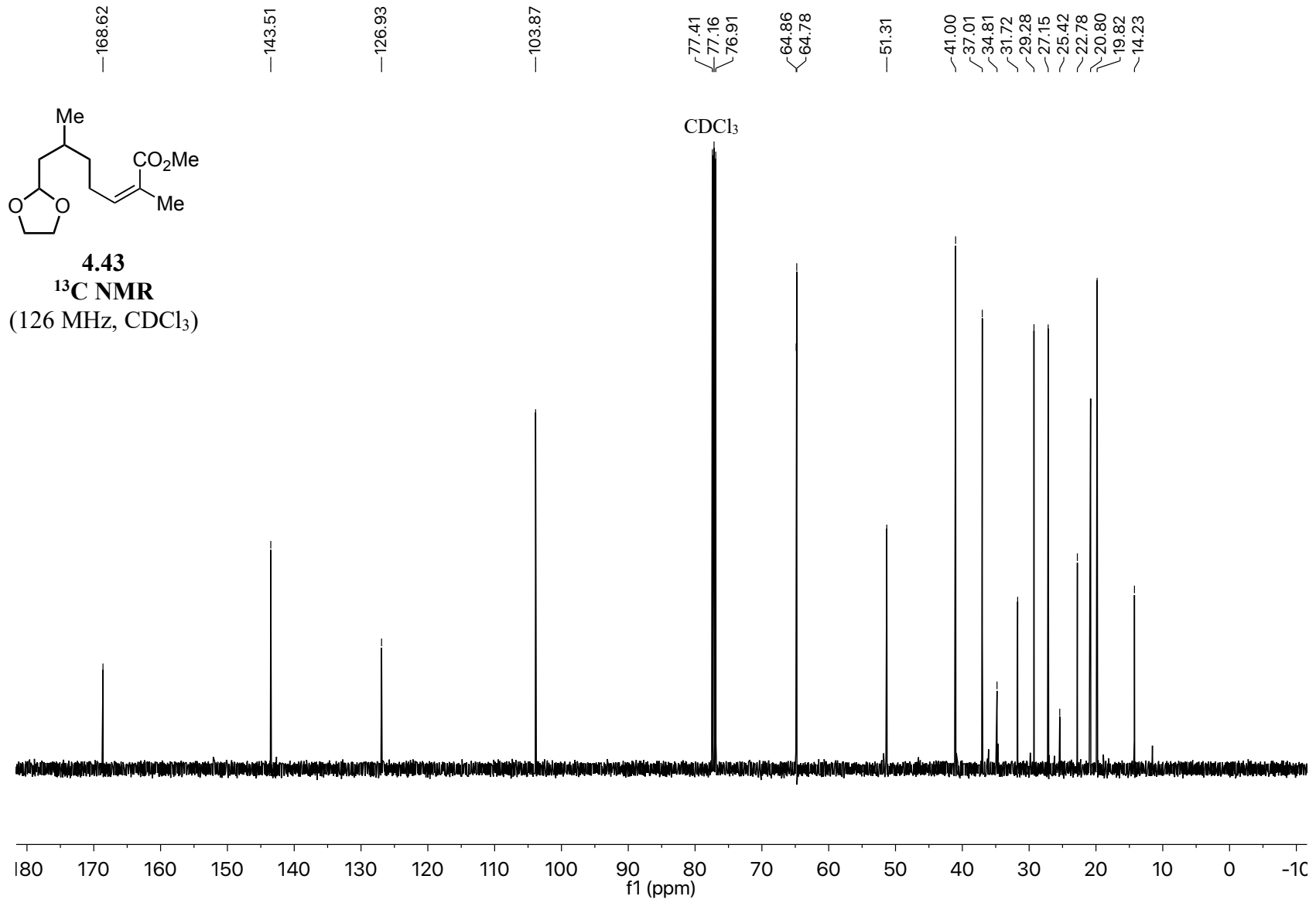


4.42
^{11}B NMR
(160 MHz, $CDCl_3$)

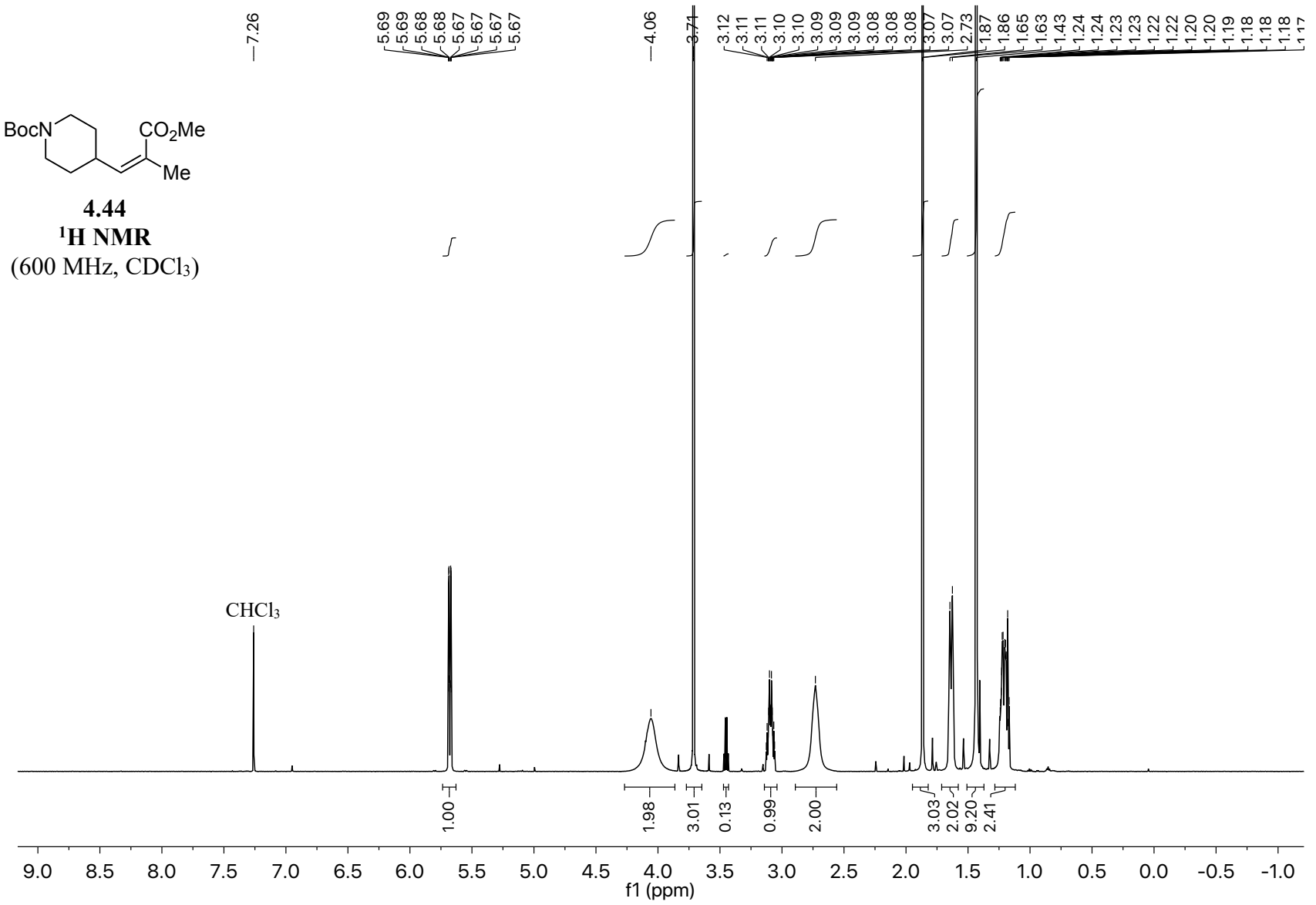


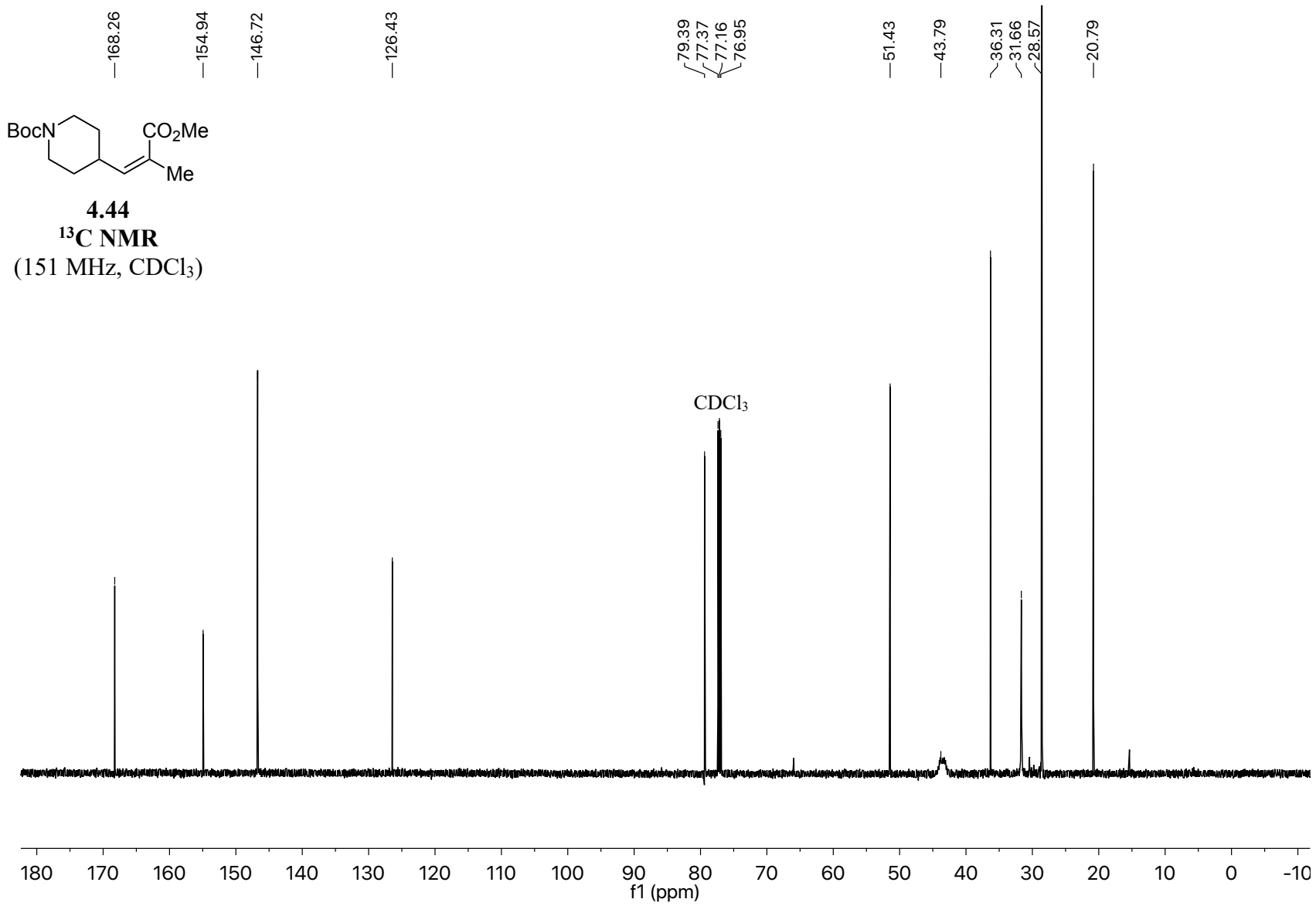
4.42
^{13}C NMR
(126 MHz, $CDCl_3$)


Me
CO2Me
Me
O
O
4.43
1H NMR
(500 MHz, CDCl3)
CHCl3
minor isomer
major isomer
0.03
0.97
6.8
6.6
6.4
6.2
6.0
5.8
f1 (ppm)
0.03
0.97
1.00
2.01
2.04
3.00
1.95
2.99
2.02
2.00
1.33
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

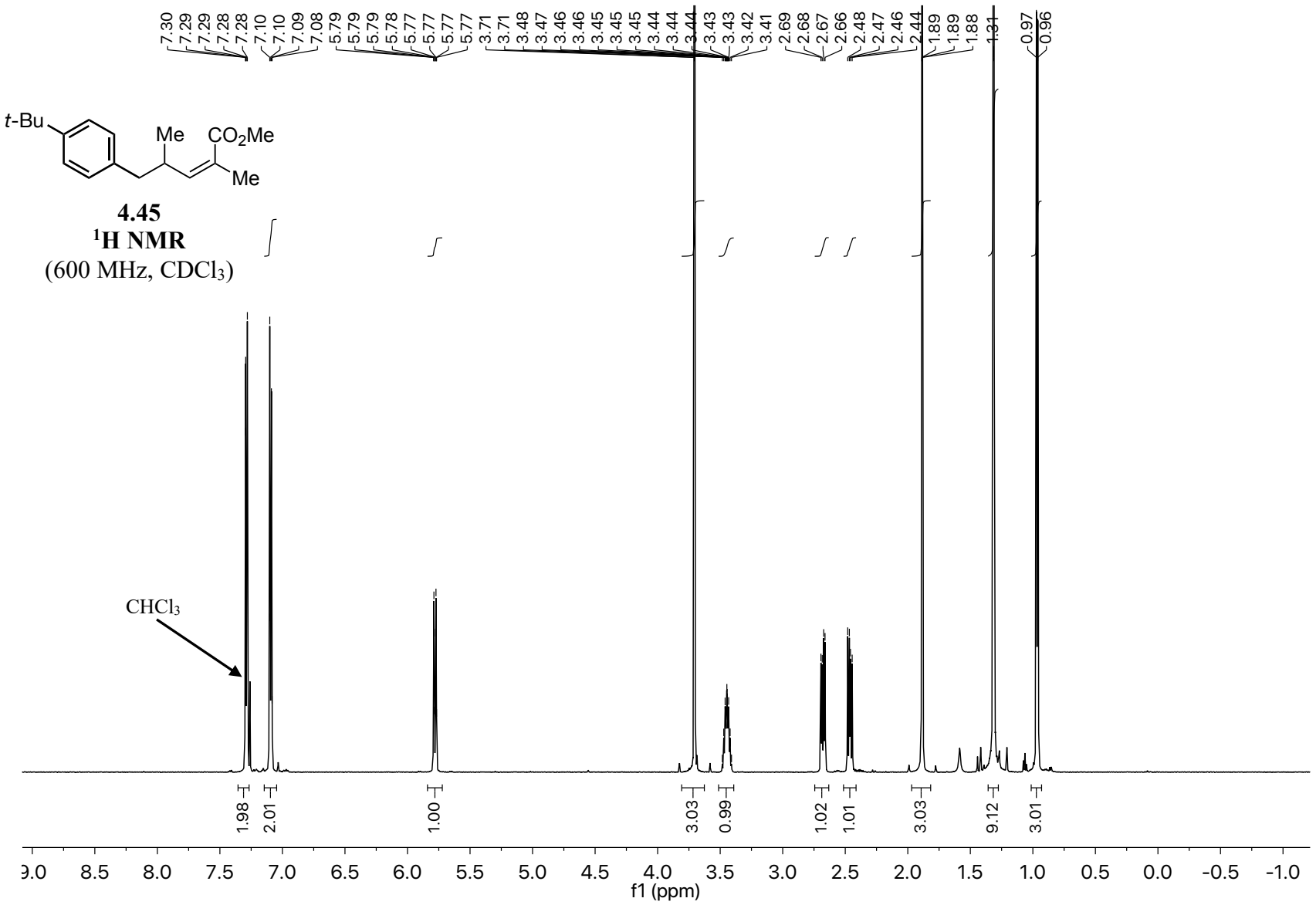


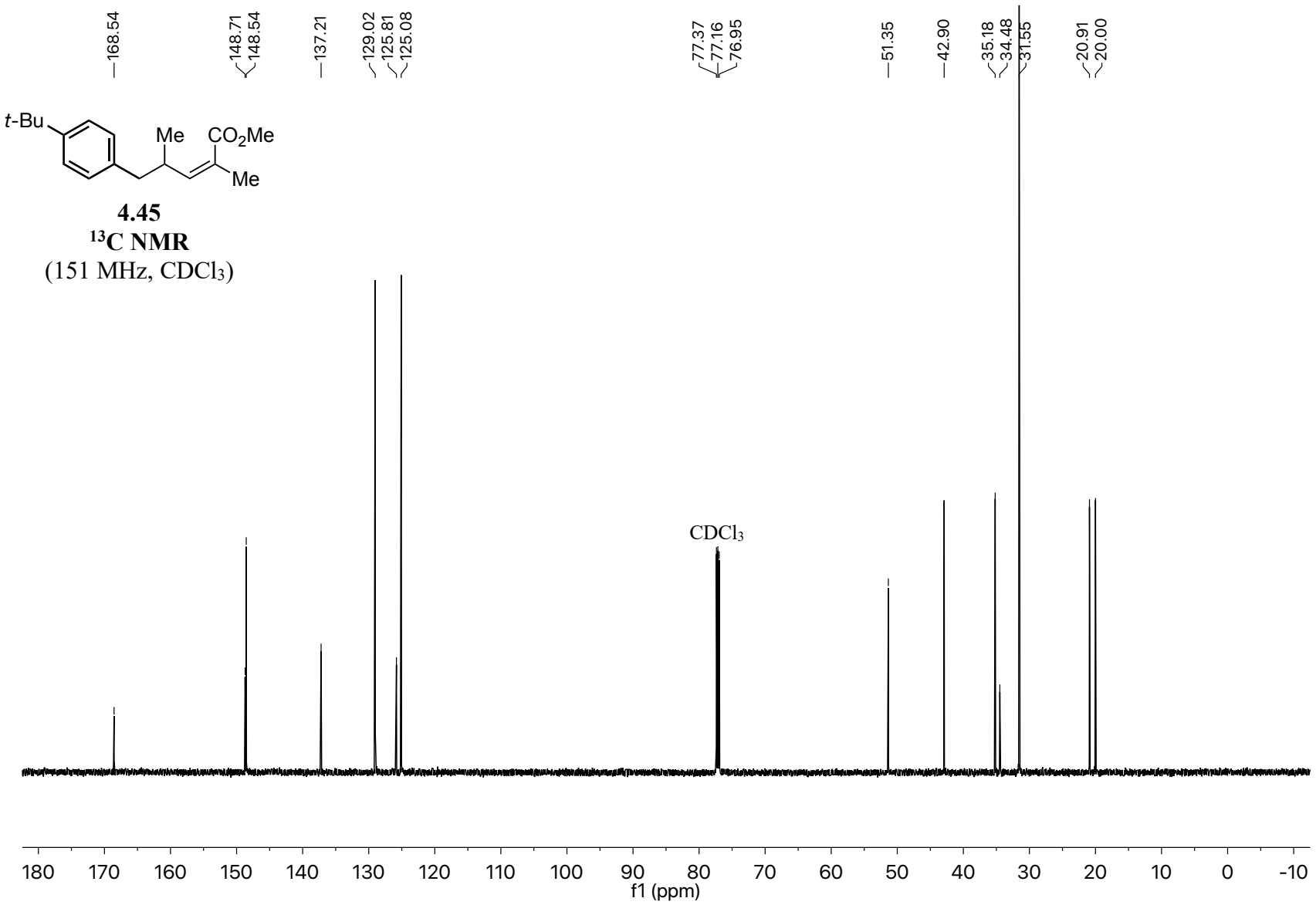
4.43
^{13}C NMR
(126 MHz, $CDCl_3$)


BocN
CO2Me
Me
4.44
1H NMR
(600 MHz, CDCl3)
CHCl3
f1 (ppm)



4.44
^{13}C NMR
(151 MHz, $CDCl_3$)

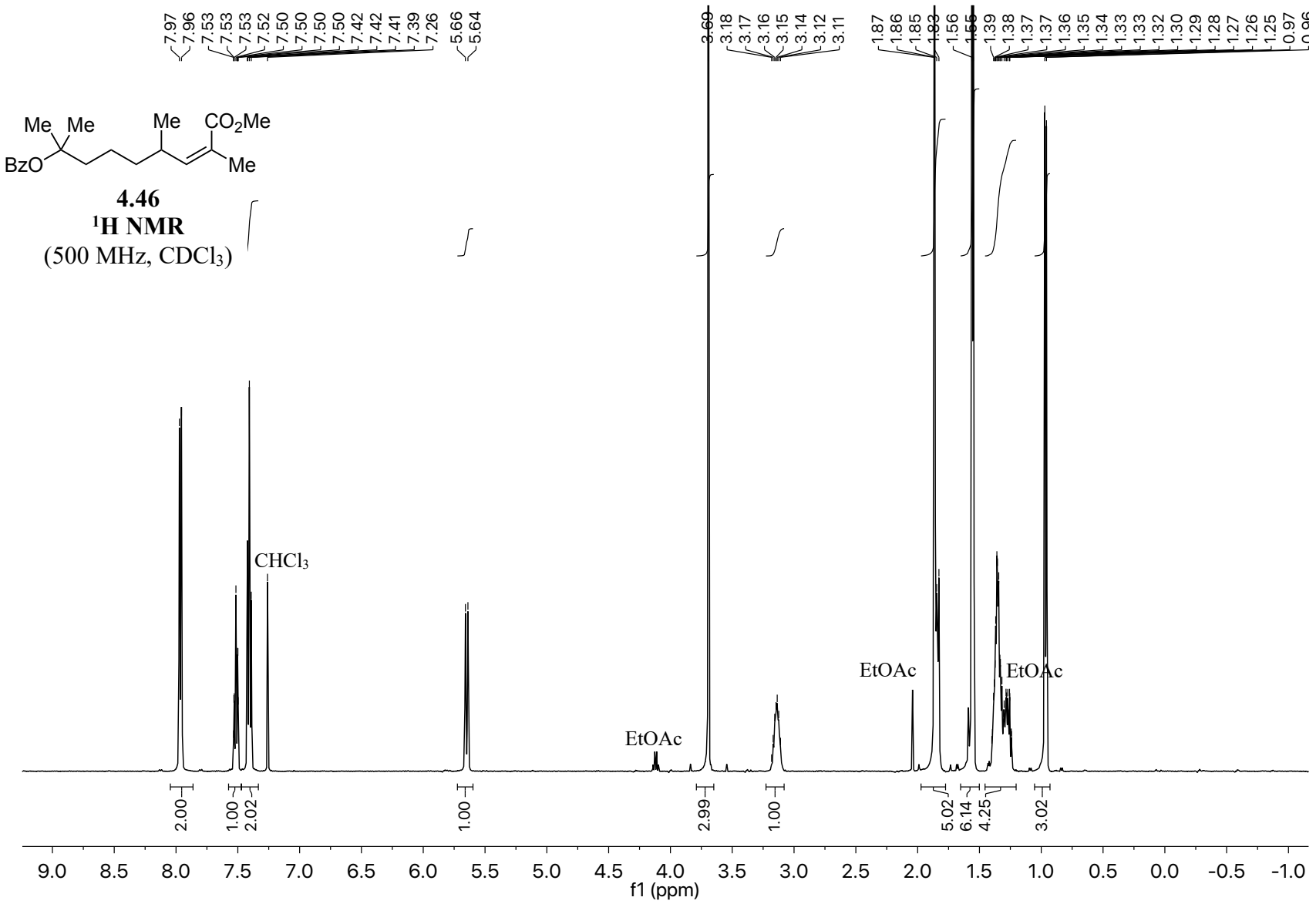

7.30
7.29
7.29
7.28
7.28
7.10
7.10
7.09
7.08
5.79
5.79
5.79
5.78
5.77
5.77
5.77
5.77
3.71
3.71
3.48
3.47
3.46
3.46
3.45
3.45
3.45
3.44
3.44
3.44
3.43
3.43
3.42
3.41
2.69
2.68
2.67
2.66
2.48
2.47
2.46
2.44
1.89
1.89
1.88
1.31
0.97
0.96
t-Bu
Me
CO2Me
Me
4.45
1H NMR
(600 MHz, CDCl3)
CHCl3
1.98
2.01
1.00
3.03
0.99
1.02
1.01
3.03
9.12
3.01
f1 (ppm)

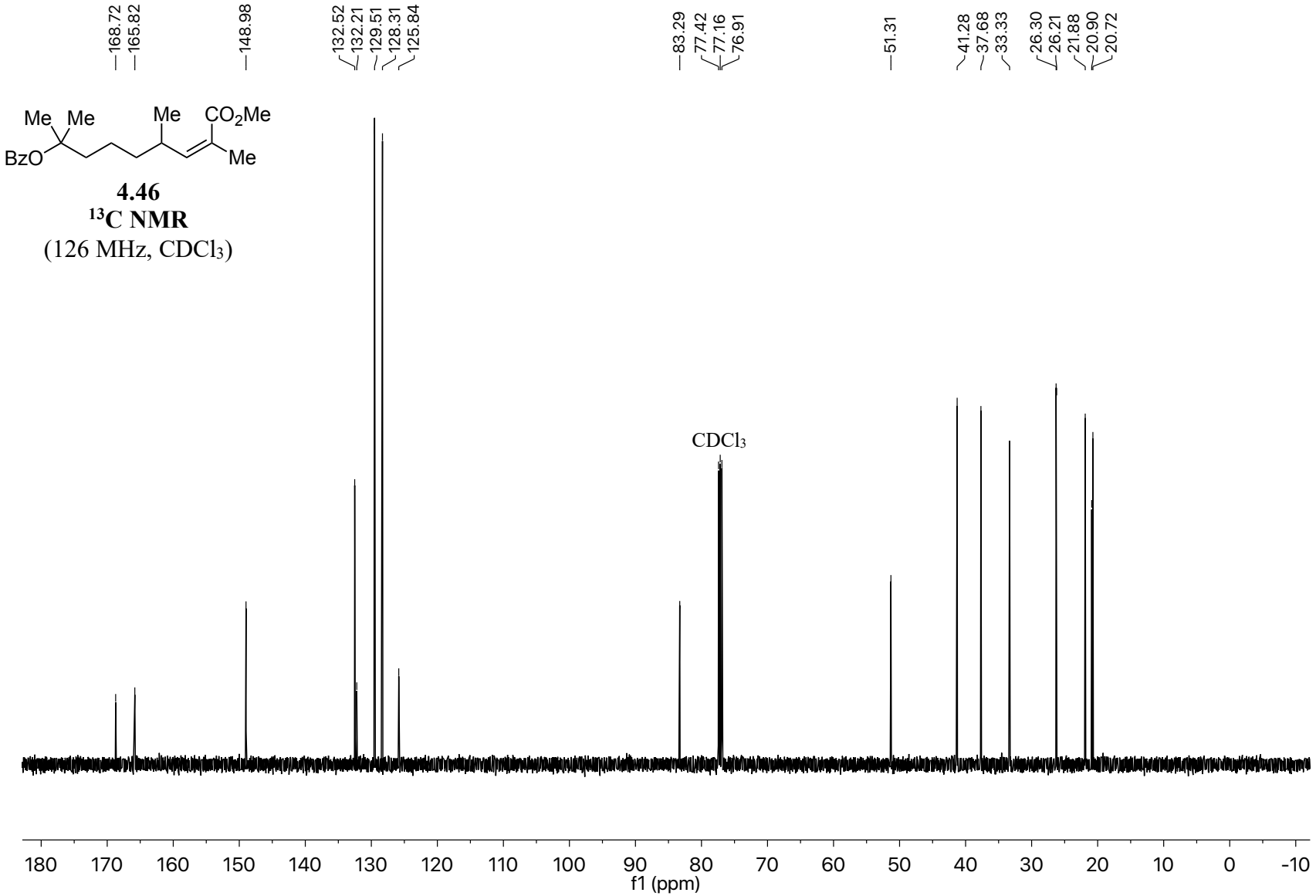


4.45

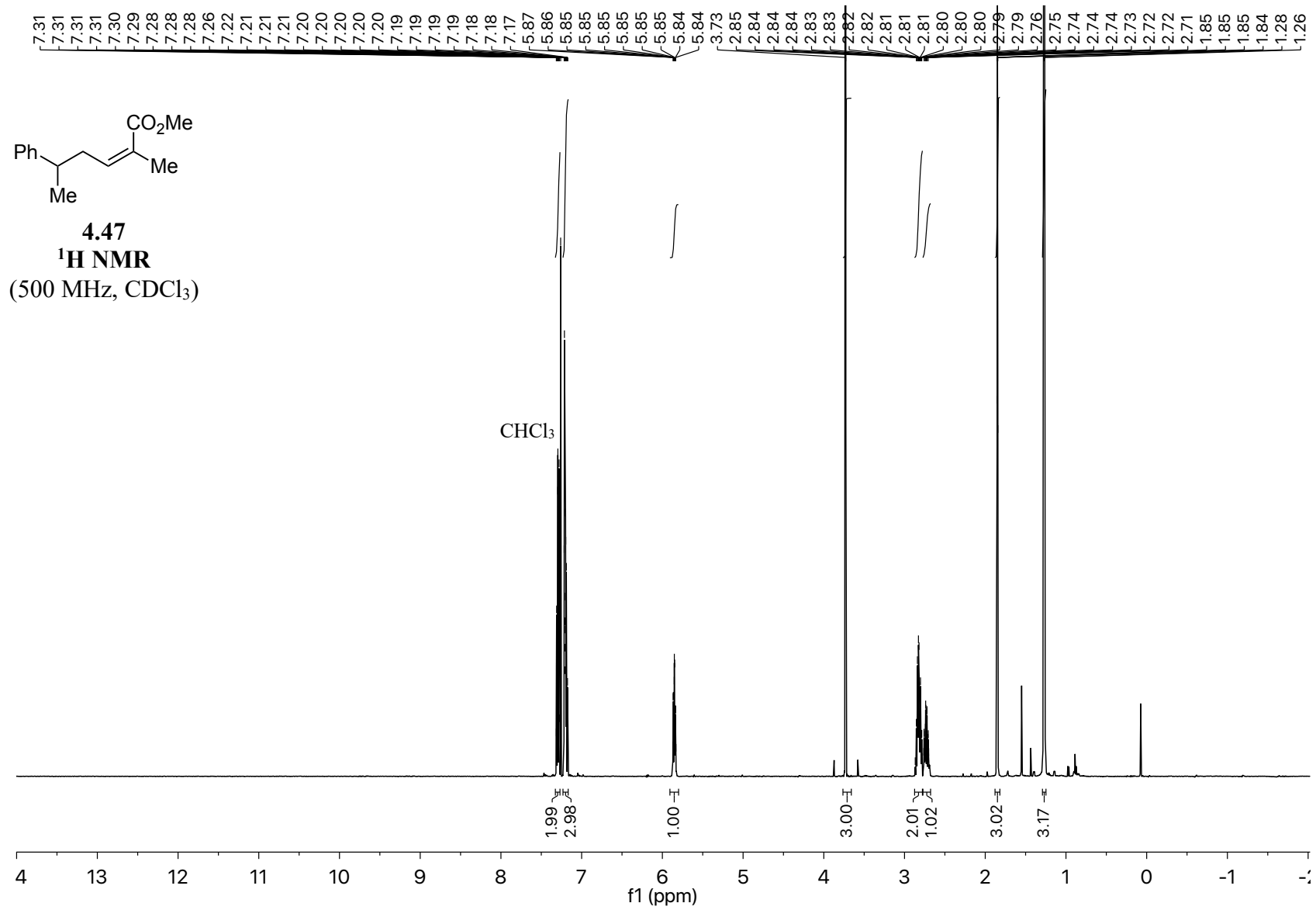
^{13}C NMR

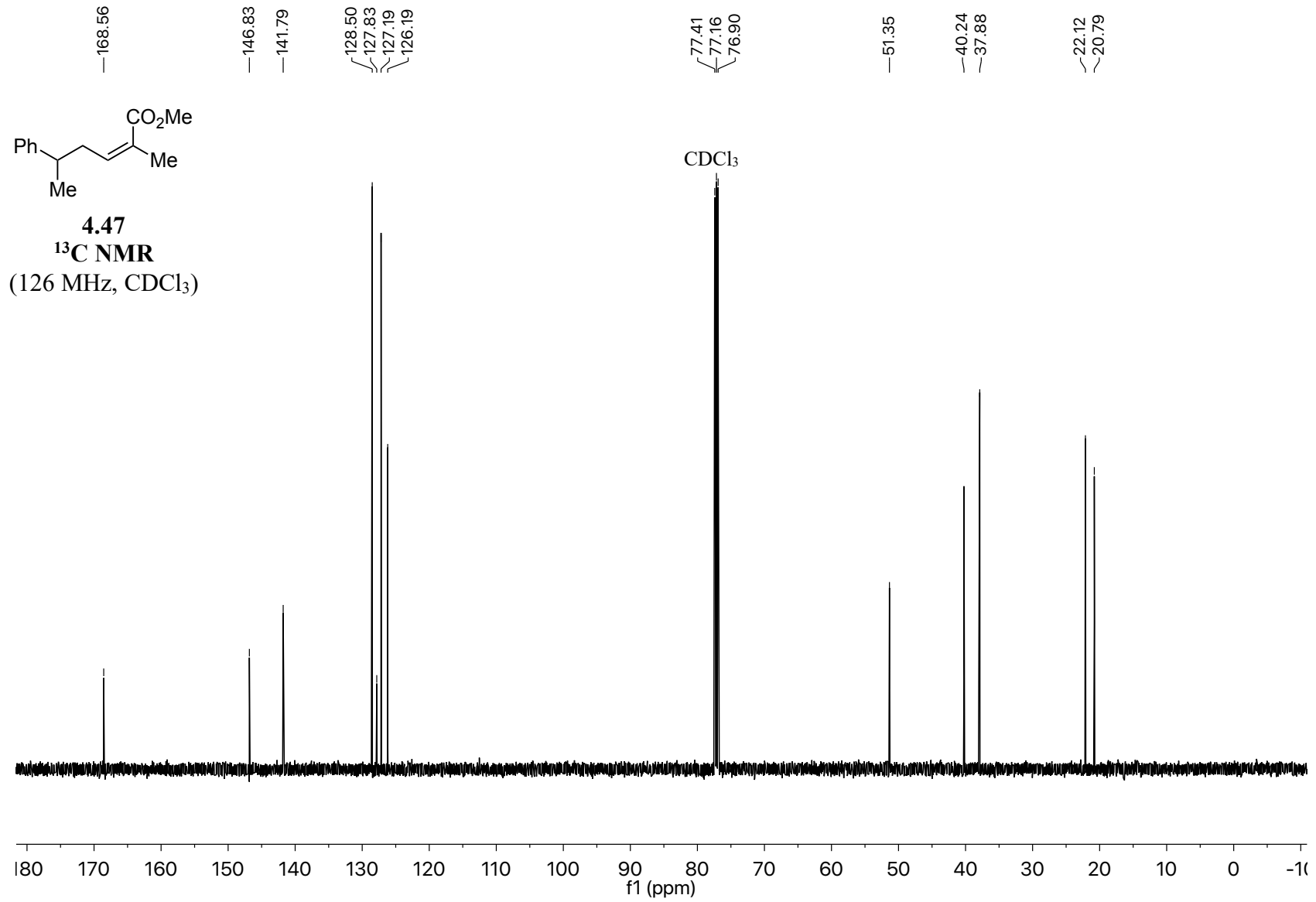
(151 MHz, $CDCl_3$)


Me Me
Me
CO2Me
BzO
Me
4.46
1H NMR
(500 MHz, CDCl3)
CHCl3
EtOAc
EtOAc
EtOAc
2.00
1.00
2.02
1.00
2.99
1.00
5.02
6.14
4.25
3.02
f1 (ppm)

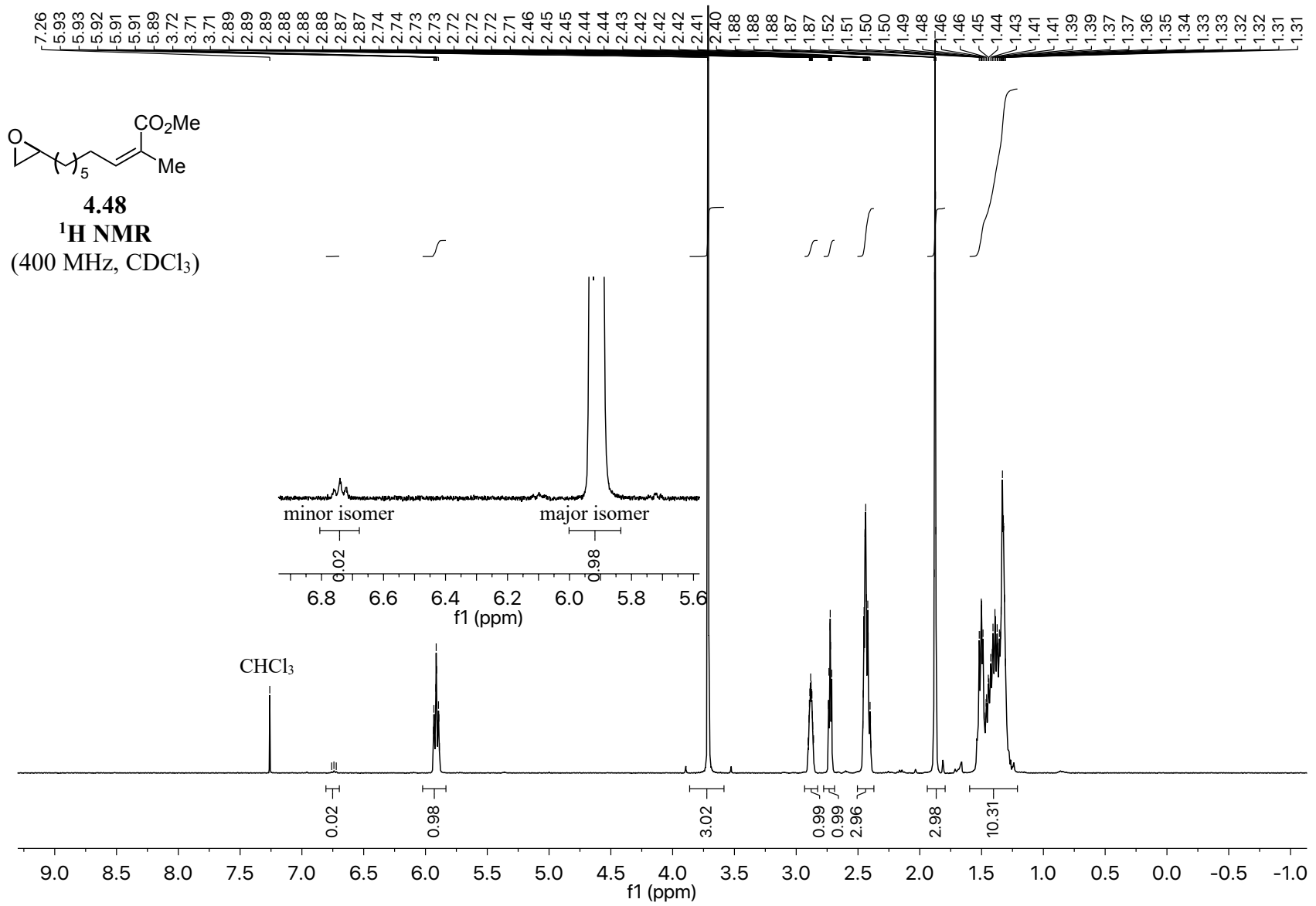


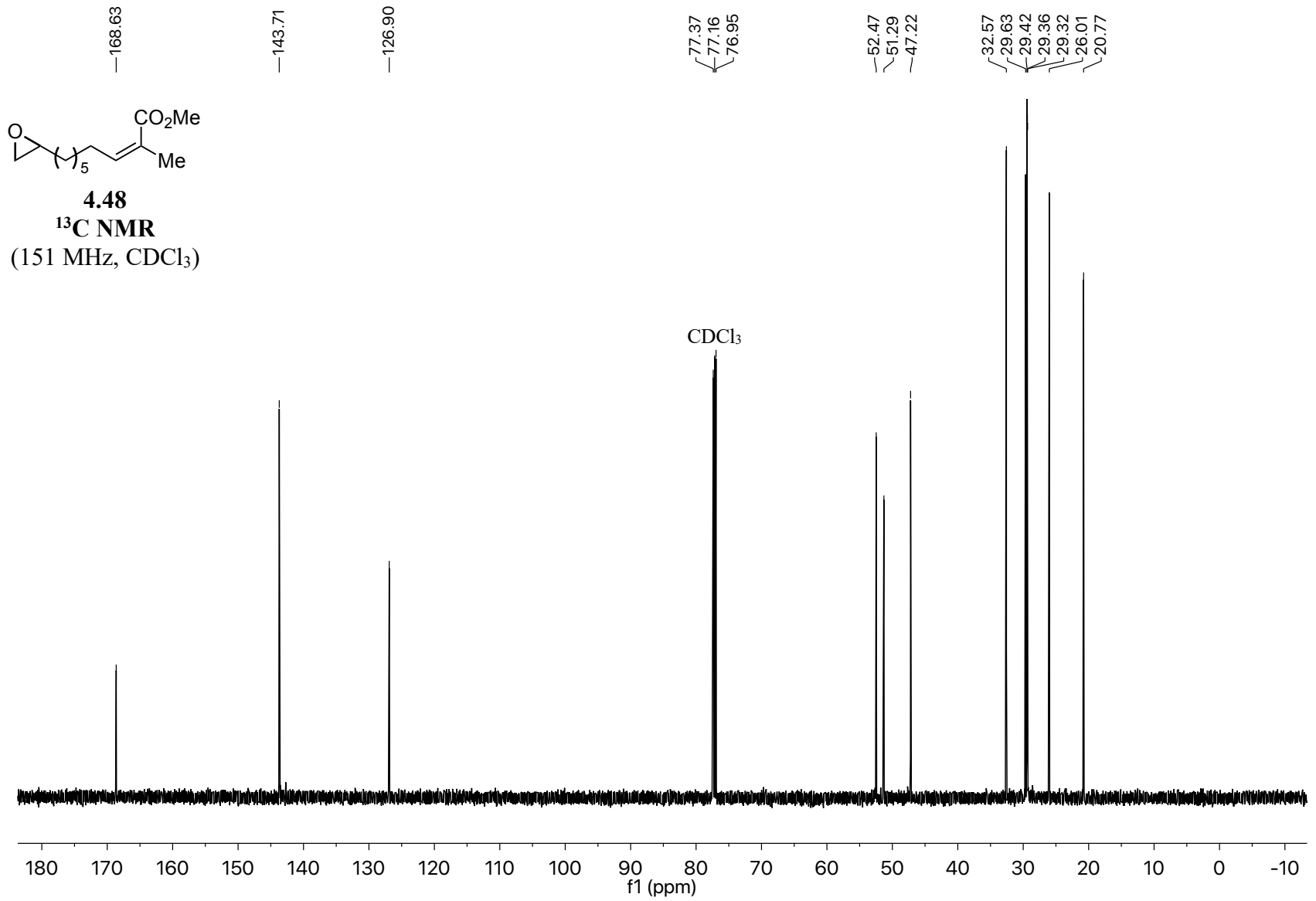
4.46
^{13}C NMR
(126 MHz, $CDCl_3$)


CO2Me
Ph
Me
Me
4.47
1H NMR
(500 MHz, CDCl3)
CHCl3
1.99
2.98
1.00
3.00
2.01
1.02
3.02
3.17
f1 (ppm)

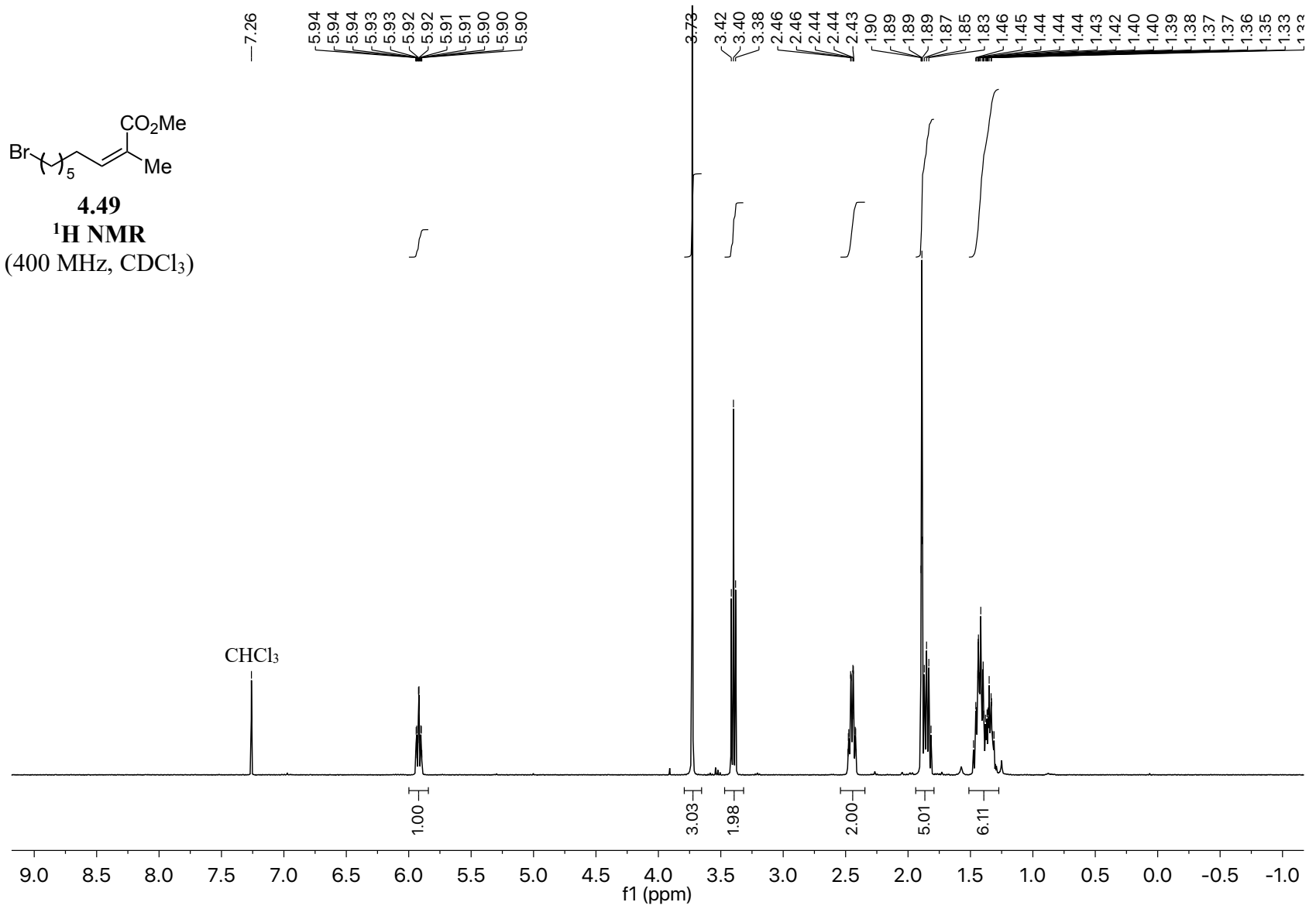


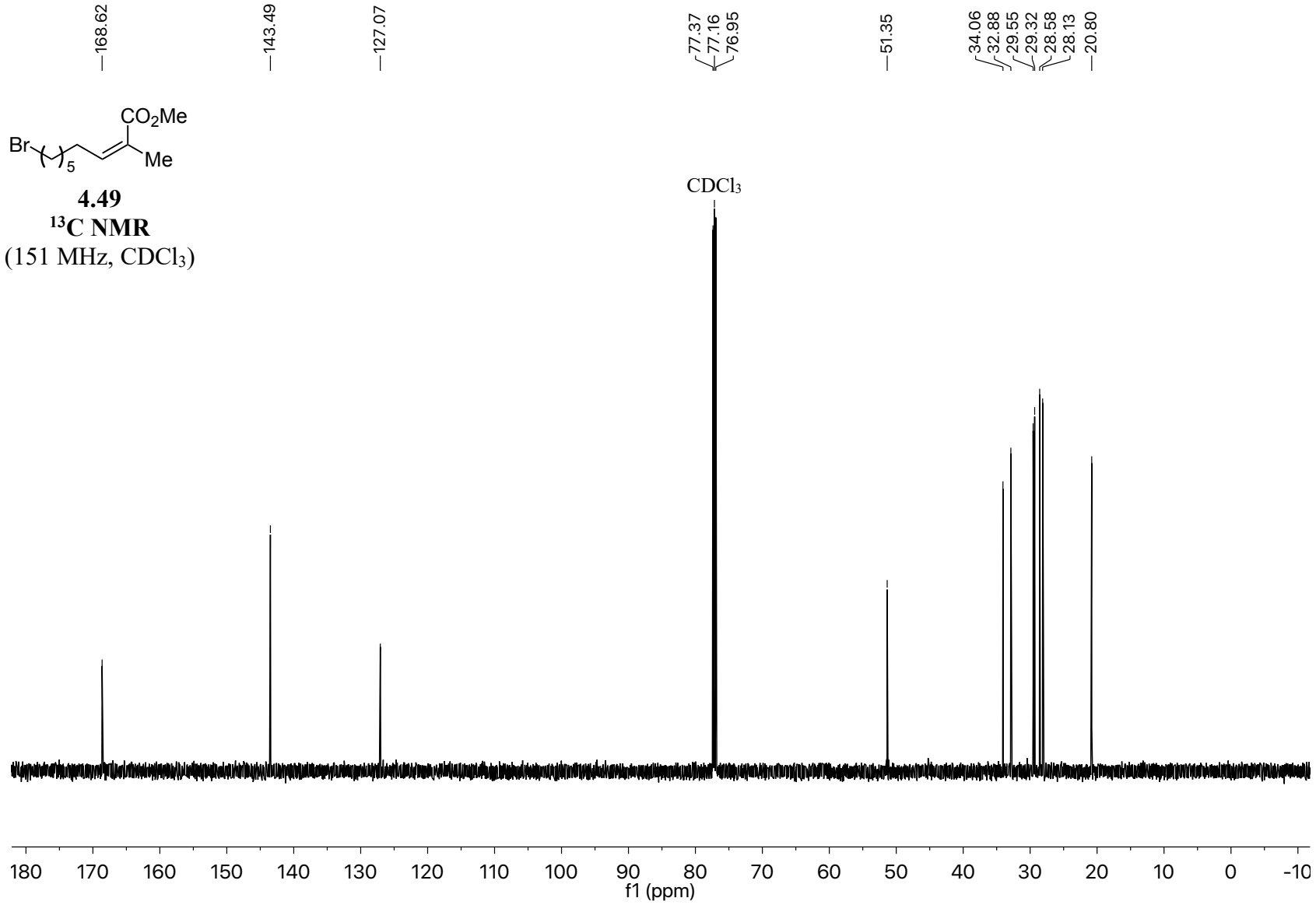
4.47
^{13}C NMR
(126 MHz, $CDCl_3$)


CO2Me
Me
5
4.48
1H NMR
(400 MHz, CDCl3)
minor isomer
major isomer
0.02
0.98
f1 (ppm)
CHCl3
0.02
0.98
3.02
0.99
0.99
2.96
2.98
10.31
f1 (ppm)

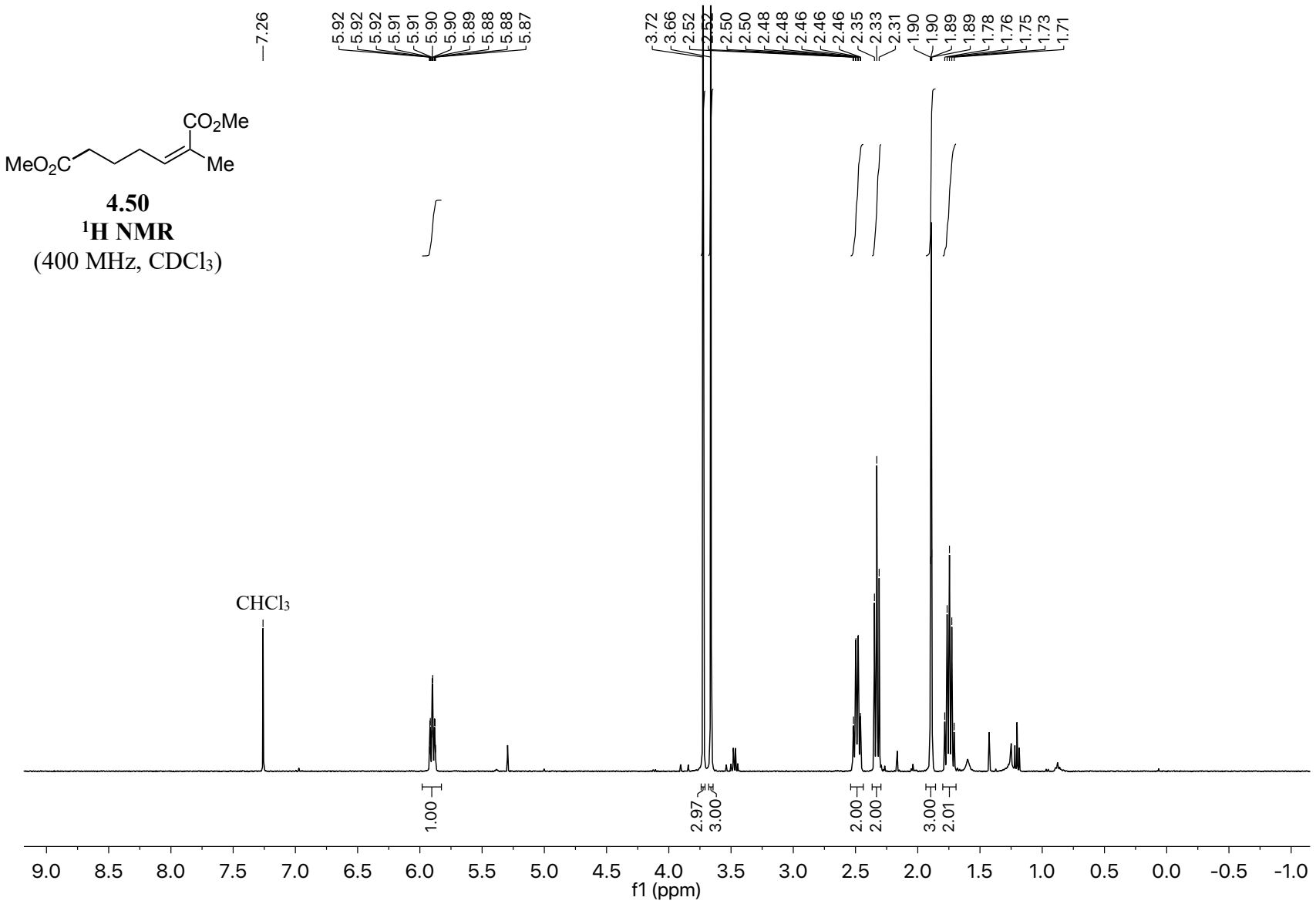


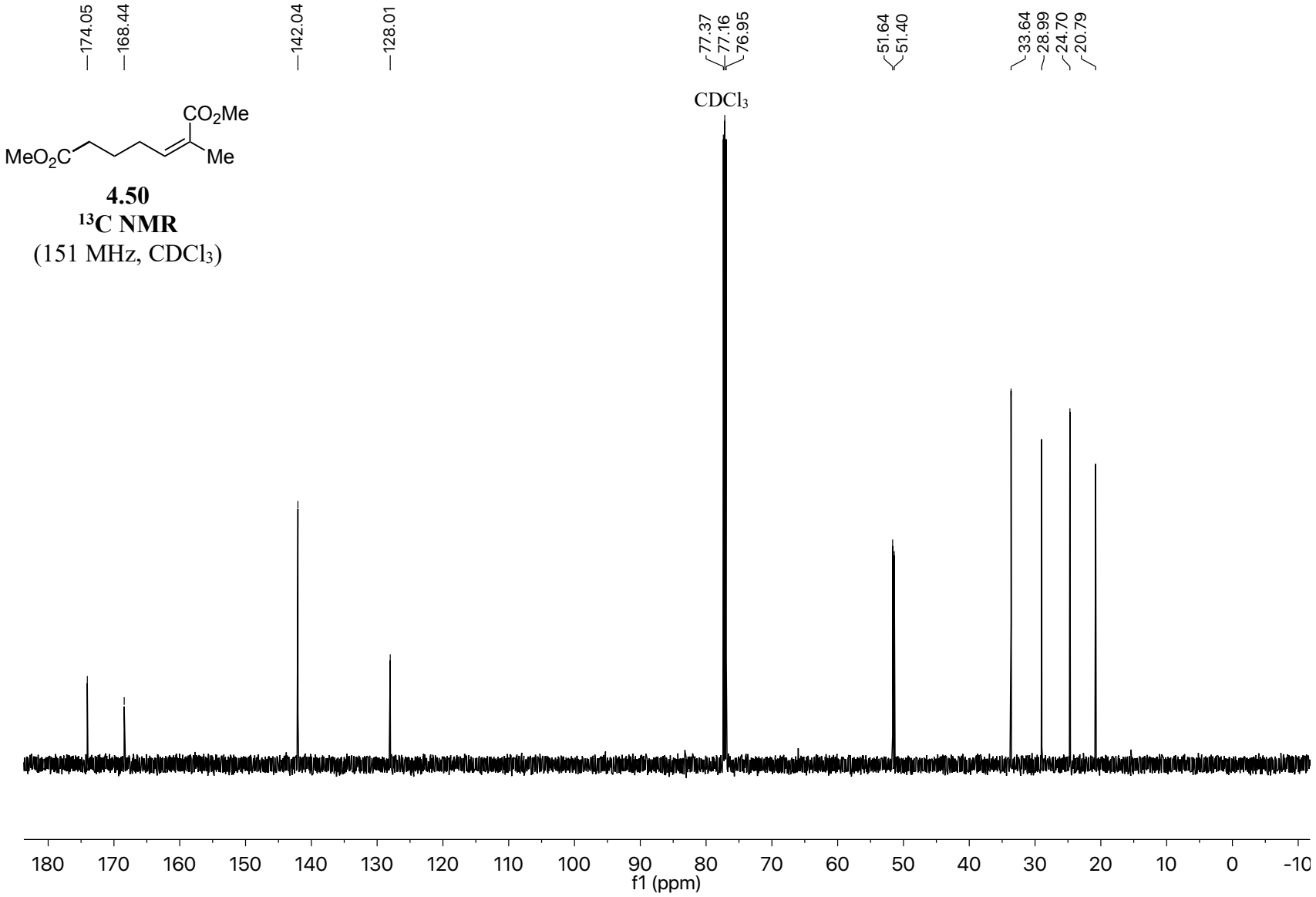
4.48
^{13}C NMR
(151 MHz, $CDCl_3$)


CO2Me
Br
5
Me
4.49
1H NMR
(400 MHz, CDCl3)
7.26
5.94
5.94
5.94
5.93
5.93
5.92
5.92
5.91
5.91
5.90
5.90
5.90
3.73
3.42
3.40
3.38
2.46
2.46
2.44
2.44
2.43
1.90
1.89
1.89
1.89
1.87
1.85
1.83
1.46
1.45
1.44
1.44
1.44
1.43
1.42
1.40
1.40
1.39
1.38
1.37
1.37
1.36
1.35
1.33
CHCl3
1.00
3.03
1.98
2.00
5.01
6.11
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

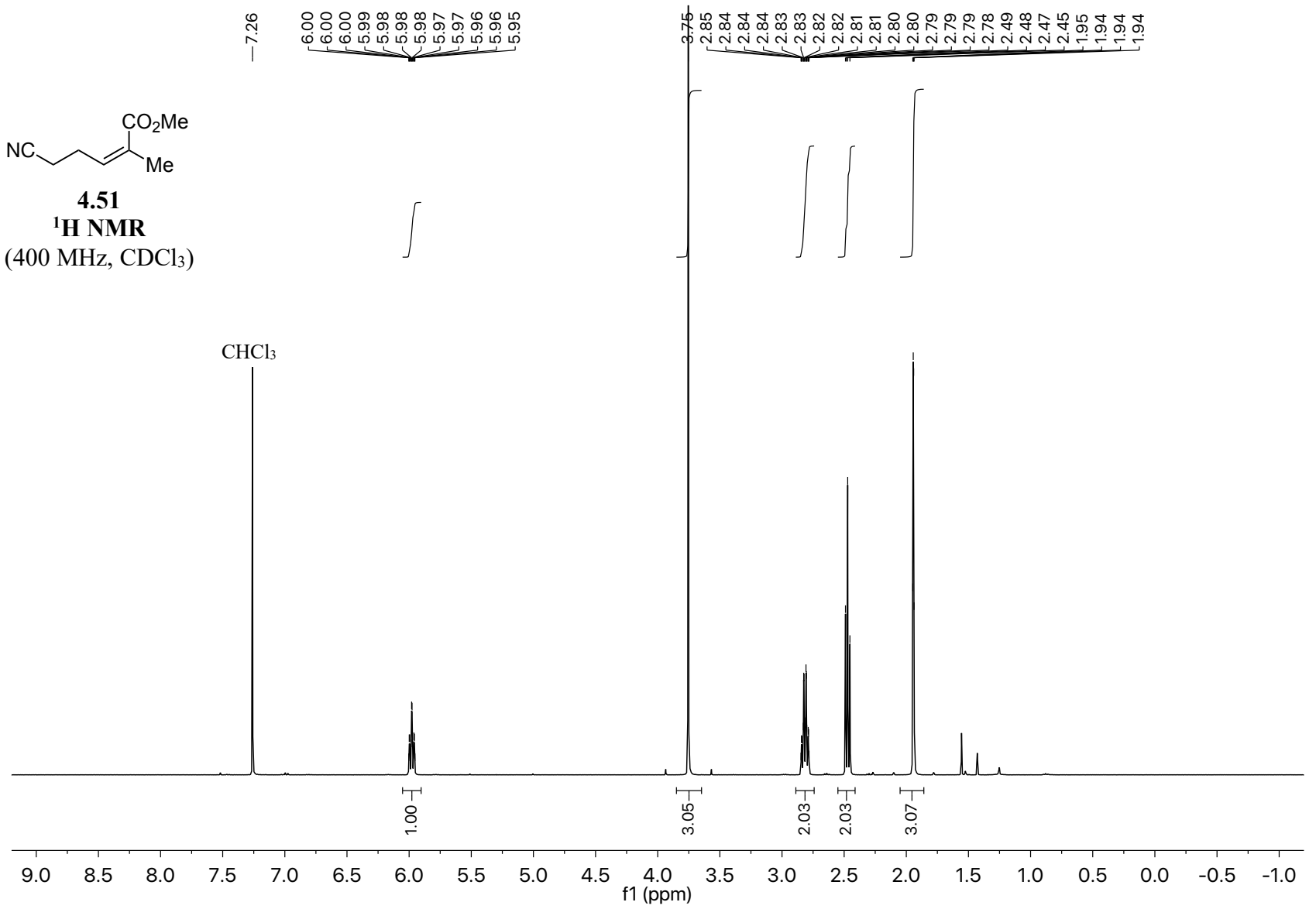


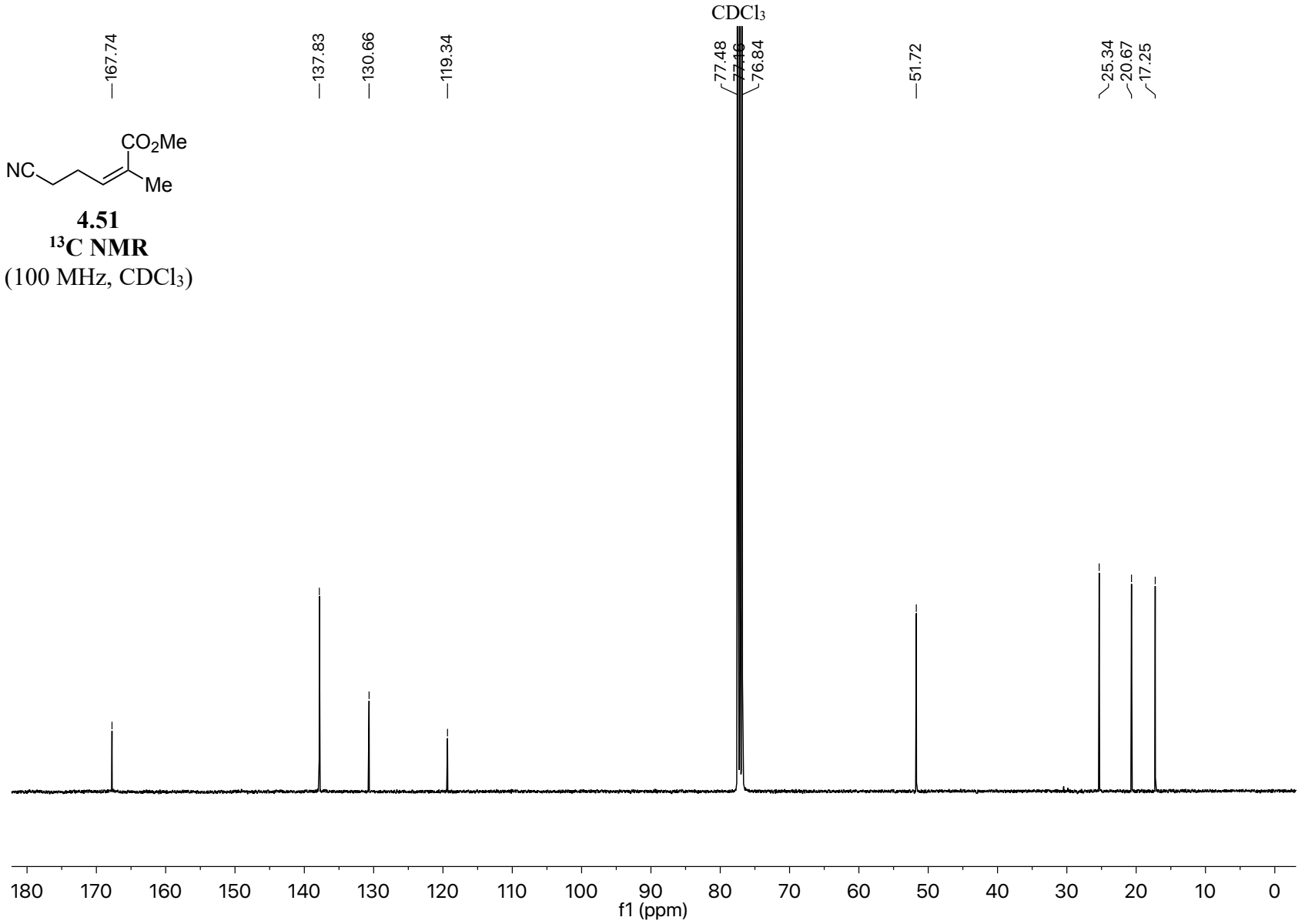
4.49
^{13}C NMR
(151 MHz, $CDCl_3$)


CO2Me
MeO2C
Me
4.50
1H NMR
(400 MHz, CDCl3)
7.26
5.92
5.92
5.92
5.91
5.91
5.90
5.90
5.89
5.88
5.88
5.87
3.72
3.66
2.52
2.52
2.50
2.50
2.48
2.48
2.46
2.46
2.46
2.35
2.33
2.31
1.90
1.90
1.89
1.89
1.78
1.76
1.75
1.73
1.71
CHCl3
1.00
2.97
3.00
2.00
2.00
3.00
2.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

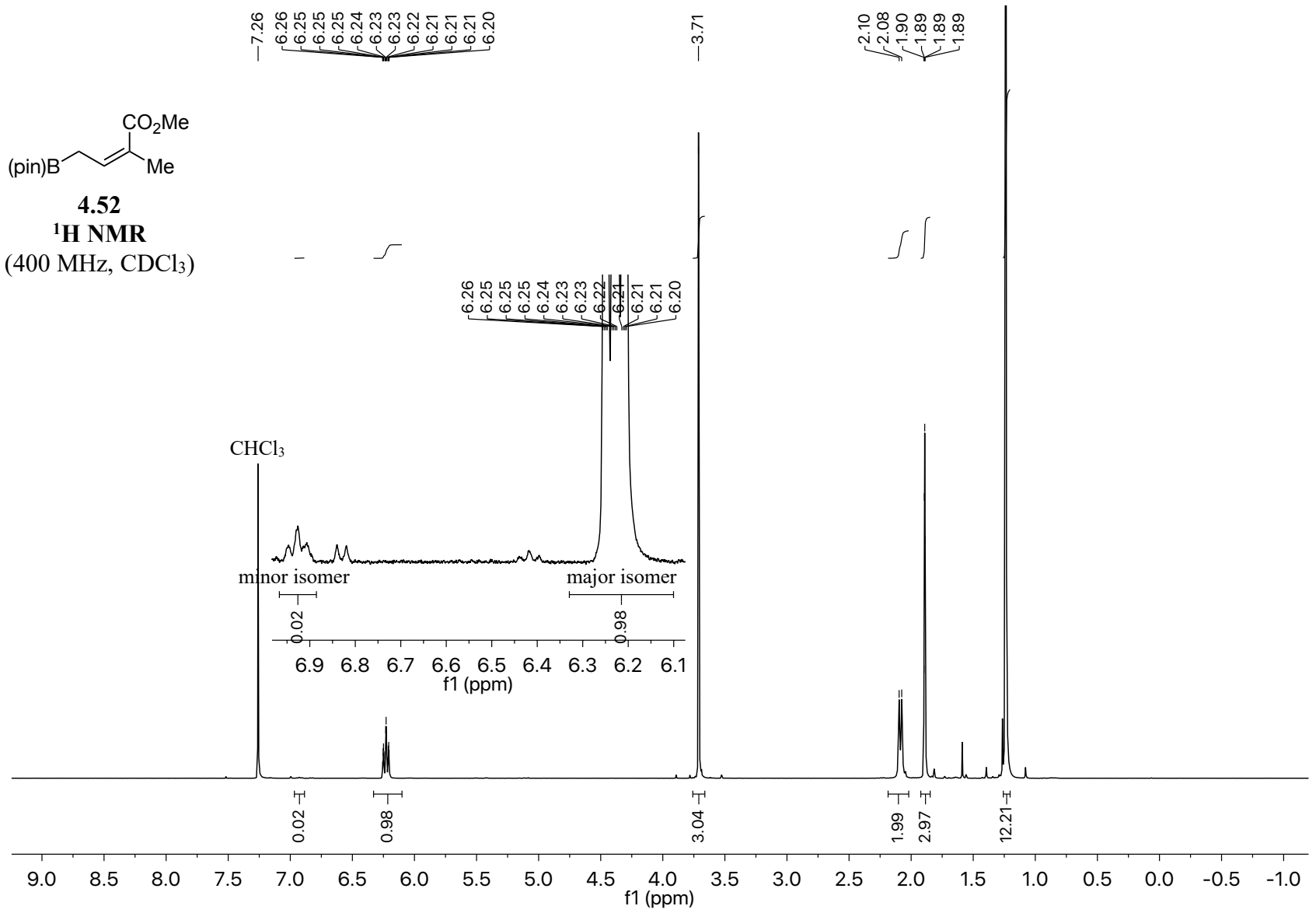


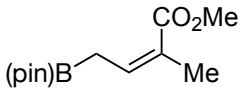
4.50
^{13}C NMR
(151 MHz, $CDCl_3$)


CO2Me
NC
Me
4.51
1H NMR
(400 MHz, CDCl3)
CHCl3
7.26
6.00
6.00
6.00
5.99
5.98
5.98
5.98
5.97
5.97
5.96
5.96
5.95
3.75
2.85
2.84
2.84
2.84
2.83
2.83
2.82
2.82
2.81
2.81
2.80
2.80
2.79
2.79
2.79
2.78
2.49
2.48
2.47
2.45
1.95
1.94
1.94
1.94
1.00
3.05
2.03
2.03
3.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

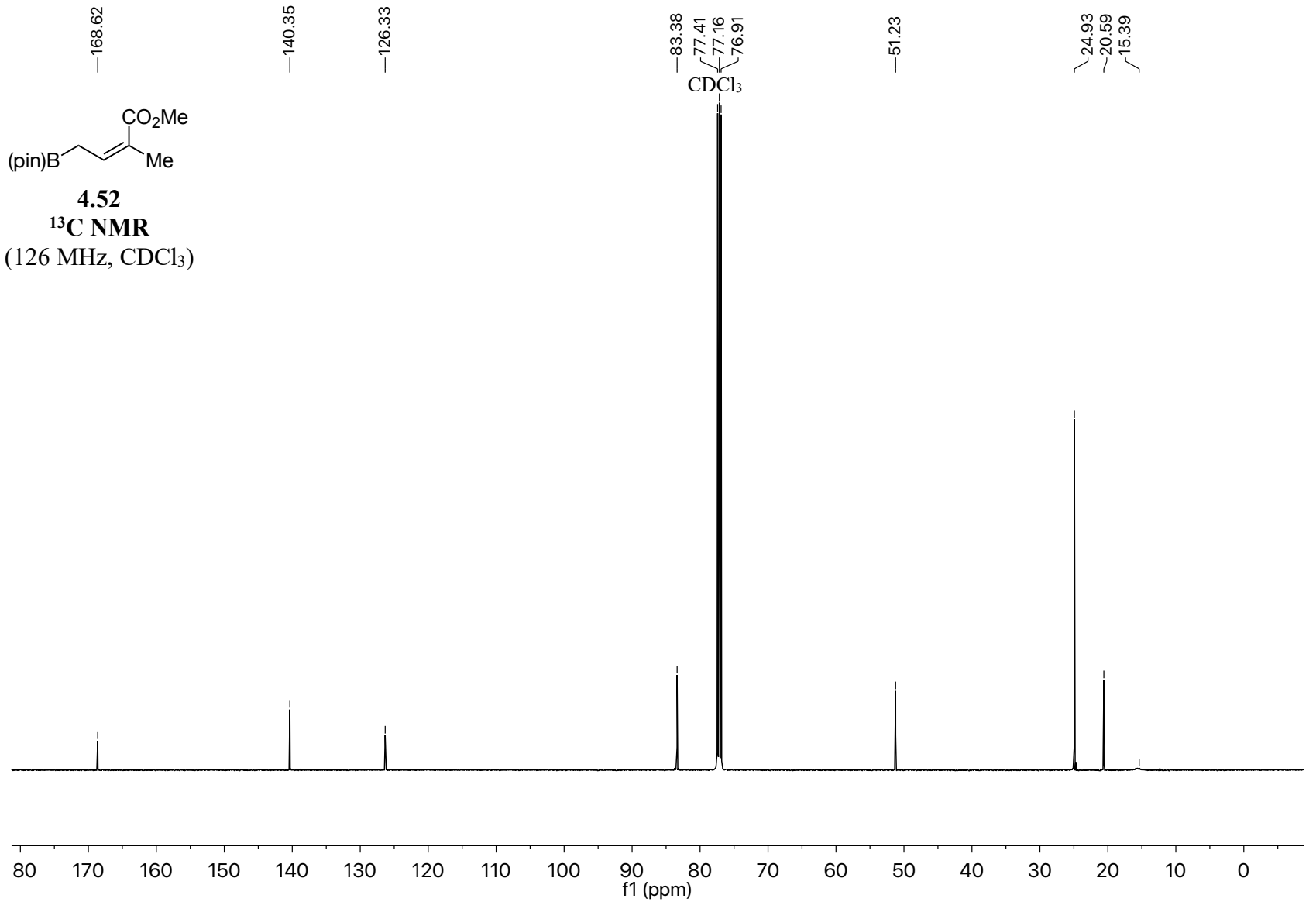


4.51
^{13}C NMR
(100 MHz, $CDCl_3$)

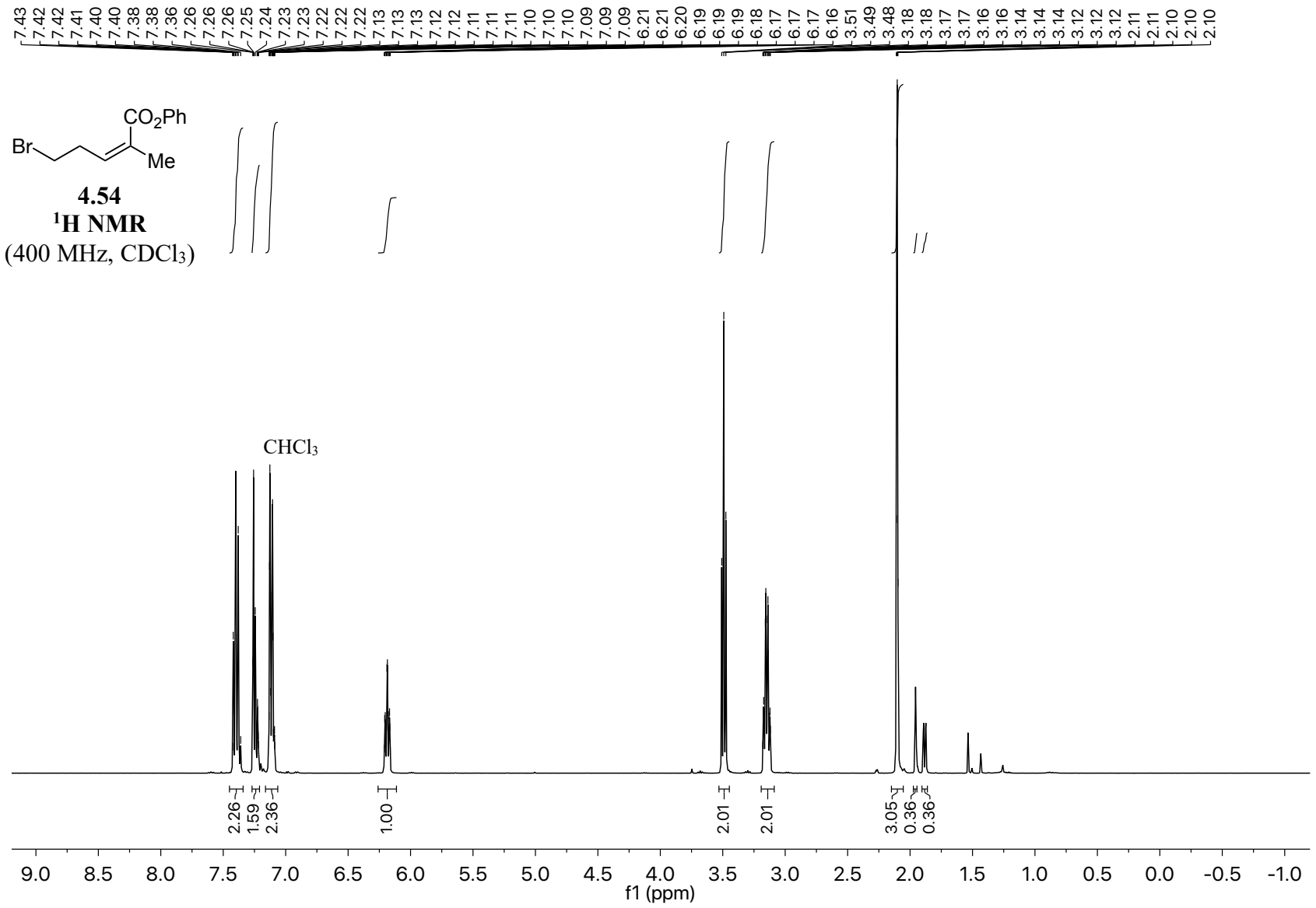

CO2Me
(pin)B
Me
4.52
1H NMR
(400 MHz, CDCl3)
7.26
6.26
6.25
6.25
6.25
6.24
6.23
6.23
6.22
6.21
6.21
6.20
3.71
2.10
2.08
1.90
1.89
1.89
1.89
CHCl3
minor isomer
major isomer
0.02
0.98
f1 (ppm)
0.02
0.98
3.04
1.99
2.97
12.21
f1 (ppm)

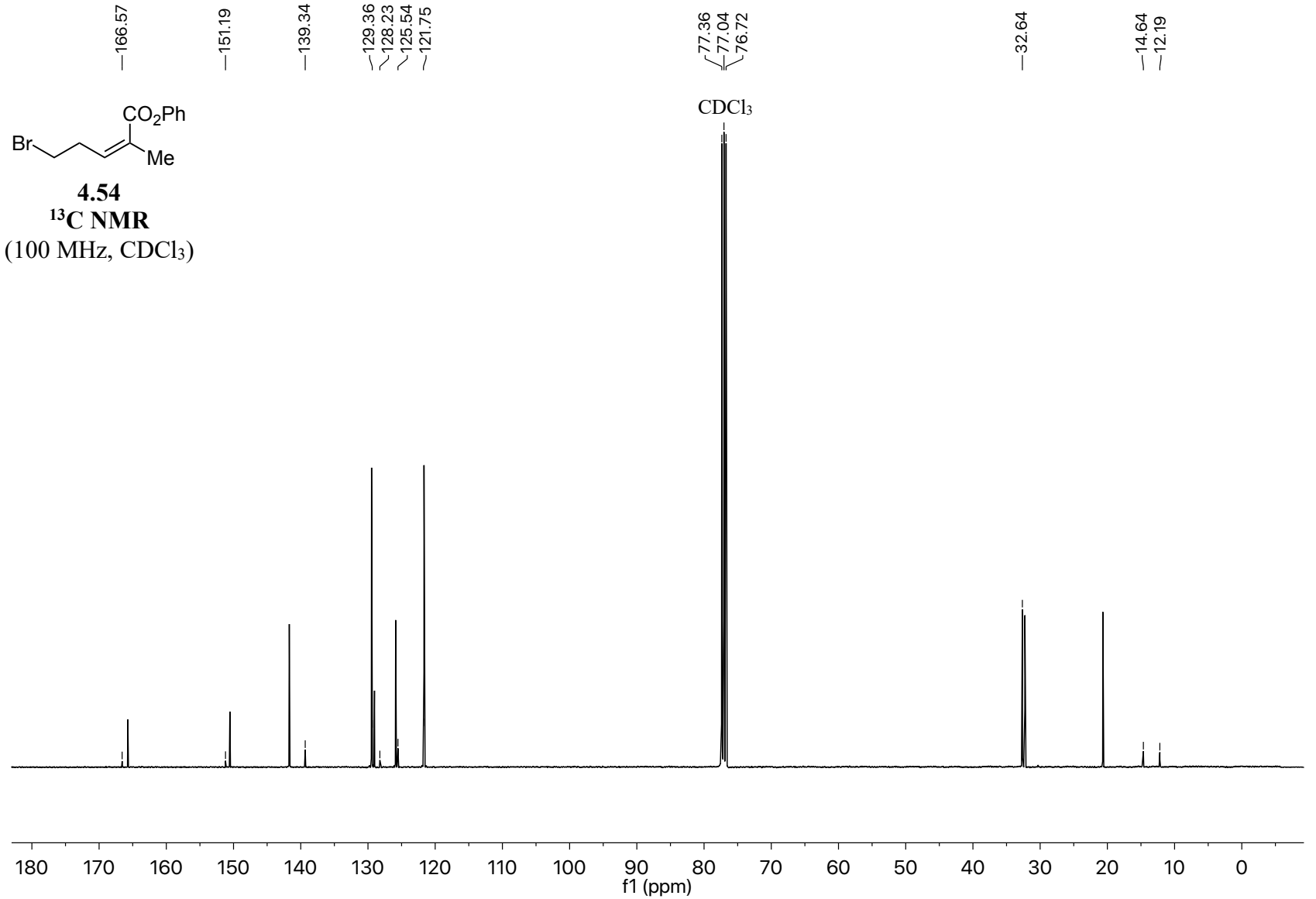


4.52
^{11}B NMR
(160 MHz, $CDCl_3$)

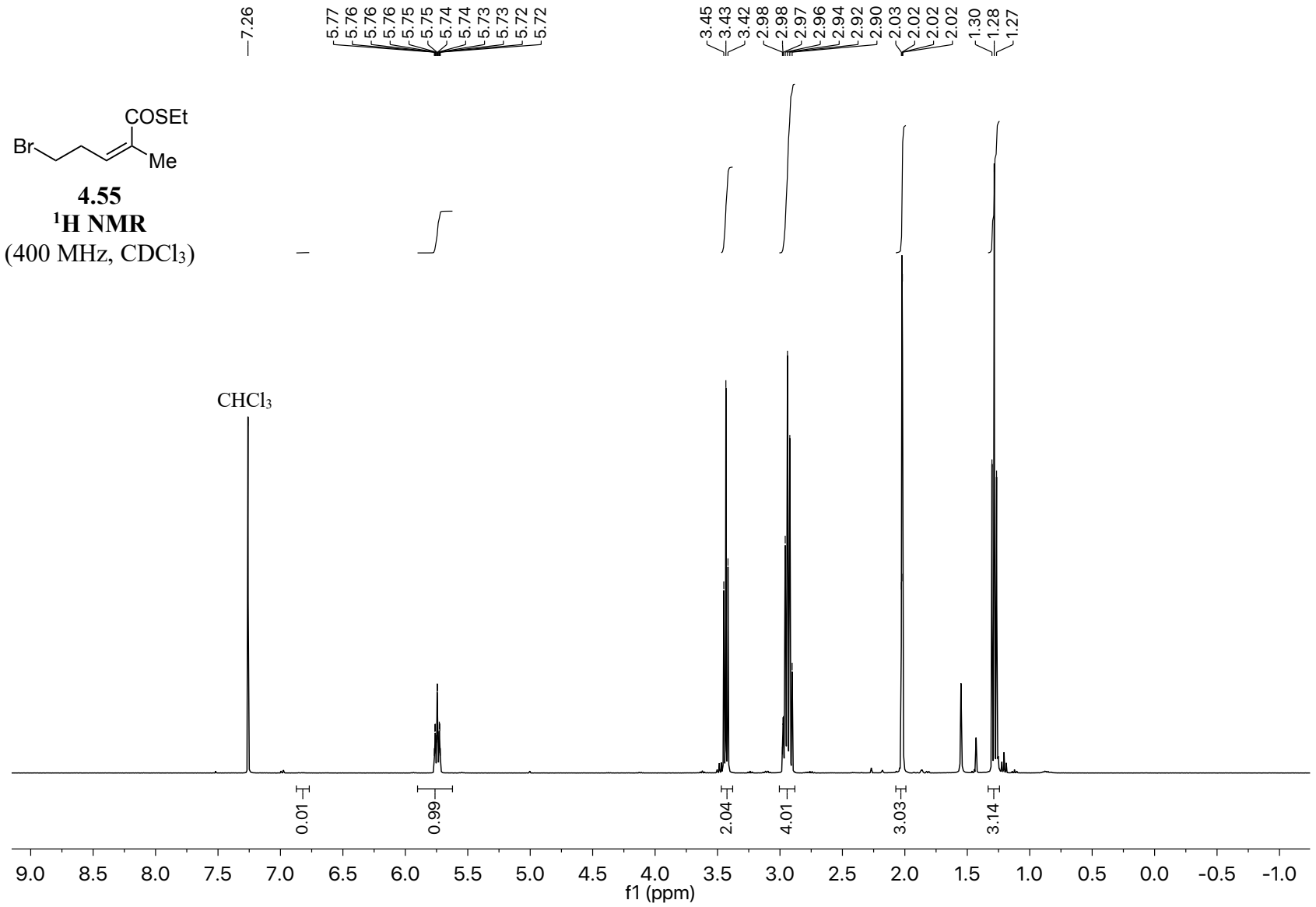


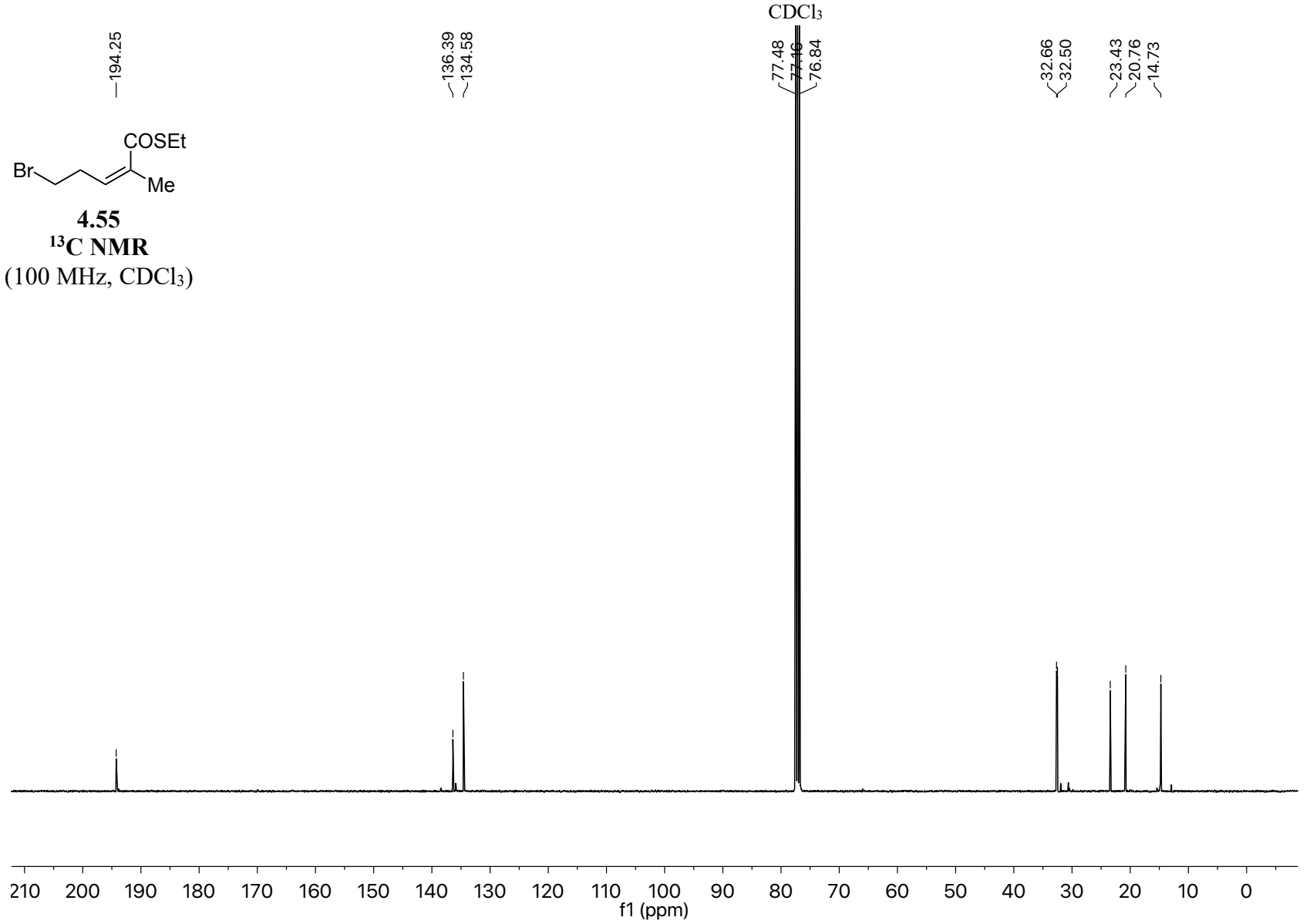
4.52
^{13}C NMR
(126 MHz, $CDCl_3$)


7.43 7.42 7.42 7.41 7.40 7.40 7.38 7.38 7.36 7.26 7.26 7.26 7.25 7.24 7.23 7.23 7.22 7.22 7.22 7.13 7.13 7.13 7.12 7.12 7.11 7.11 7.11 7.10 7.10 7.10 7.09 7.09 7.09 6.21 6.21 6.20 6.19 6.19 6.19 6.18 6.17 6.17 6.17 6.16 3.51 3.49 3.48 3.18 3.18 3.17 3.17 3.16 3.16 3.14 3.14 3.12 3.12 3.12 2.11 2.11 2.10 2.10 2.10
CO2Ph
Br
Me
4.54
1H NMR
(400 MHz, CDCl3)
CHCl3
2.26
1.59
2.36
1.00
2.01
2.01
3.05
0.36
0.36
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

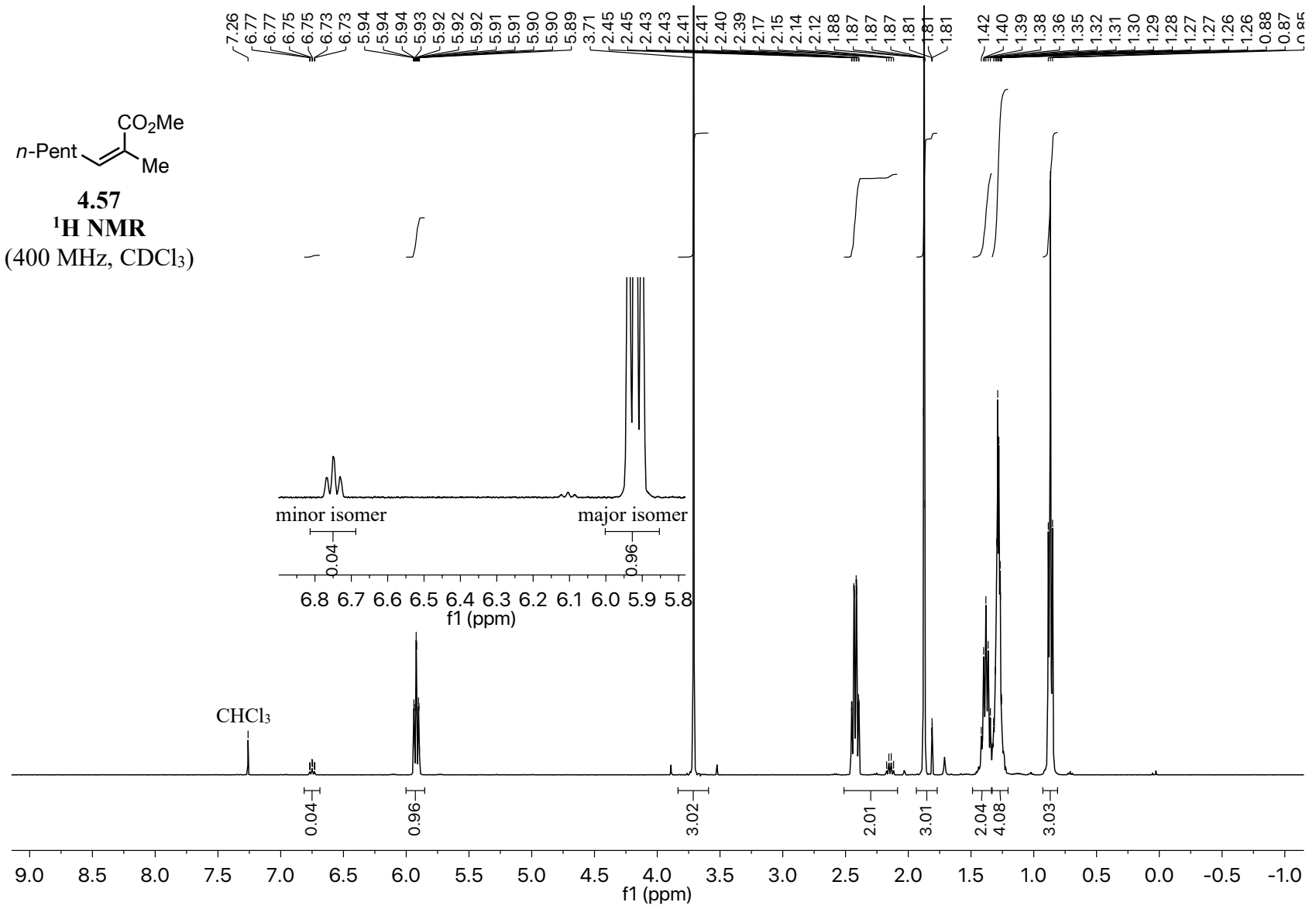


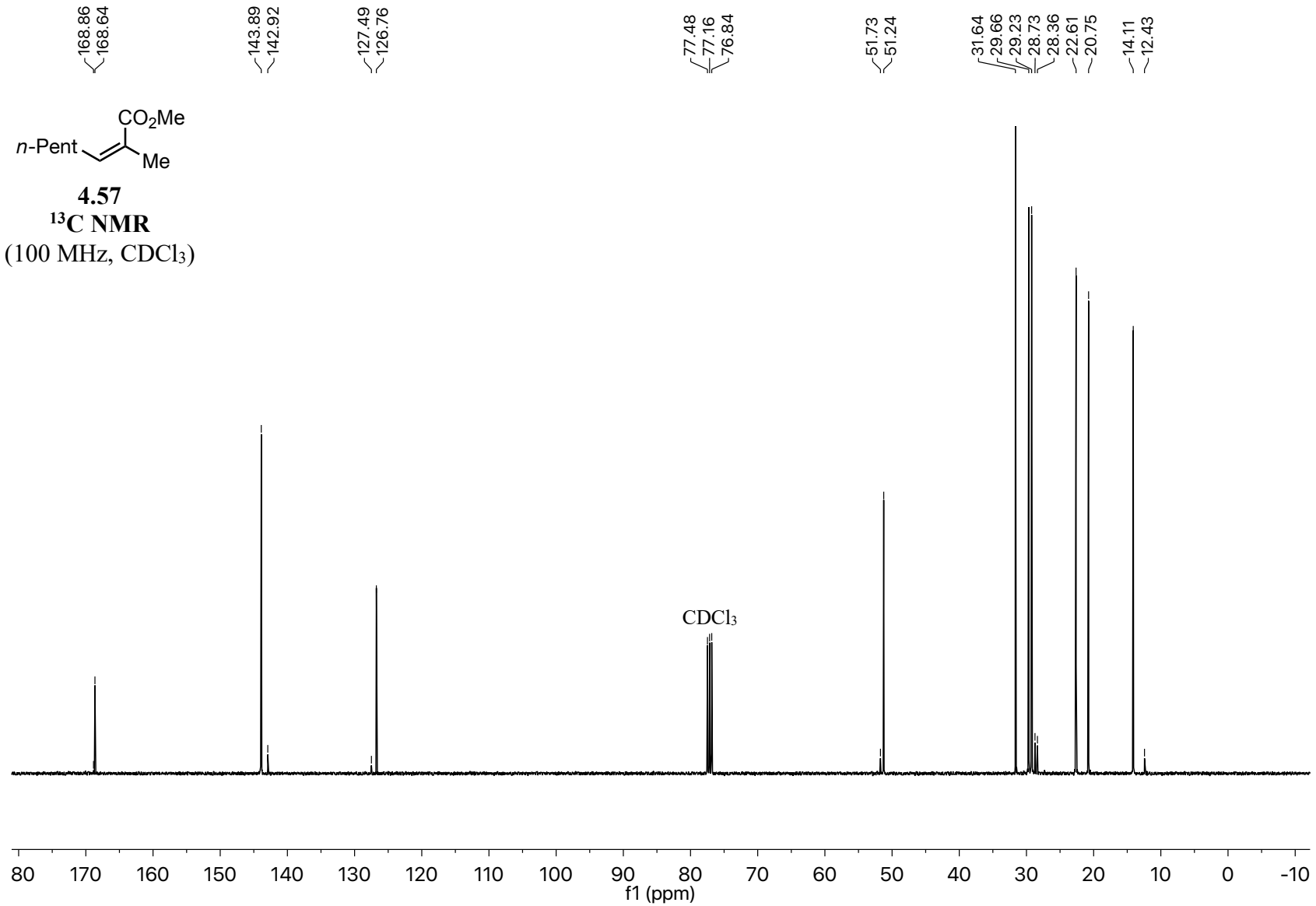
4.54
^{13}C NMR
(100 MHz, $CDCl_3$)


COSEt
Br
Me
4.55
1H NMR
(400 MHz, CDCl3)
7.26
5.77
5.76
5.76
5.76
5.75
5.75
5.74
5.74
5.73
5.73
5.72
5.72
3.45
3.43
3.42
2.98
2.98
2.97
2.96
2.94
2.92
2.90
2.03
2.02
2.02
2.02
1.30
1.28
1.27
CHCl3
0.01
0.99
2.04
4.01
3.03
3.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

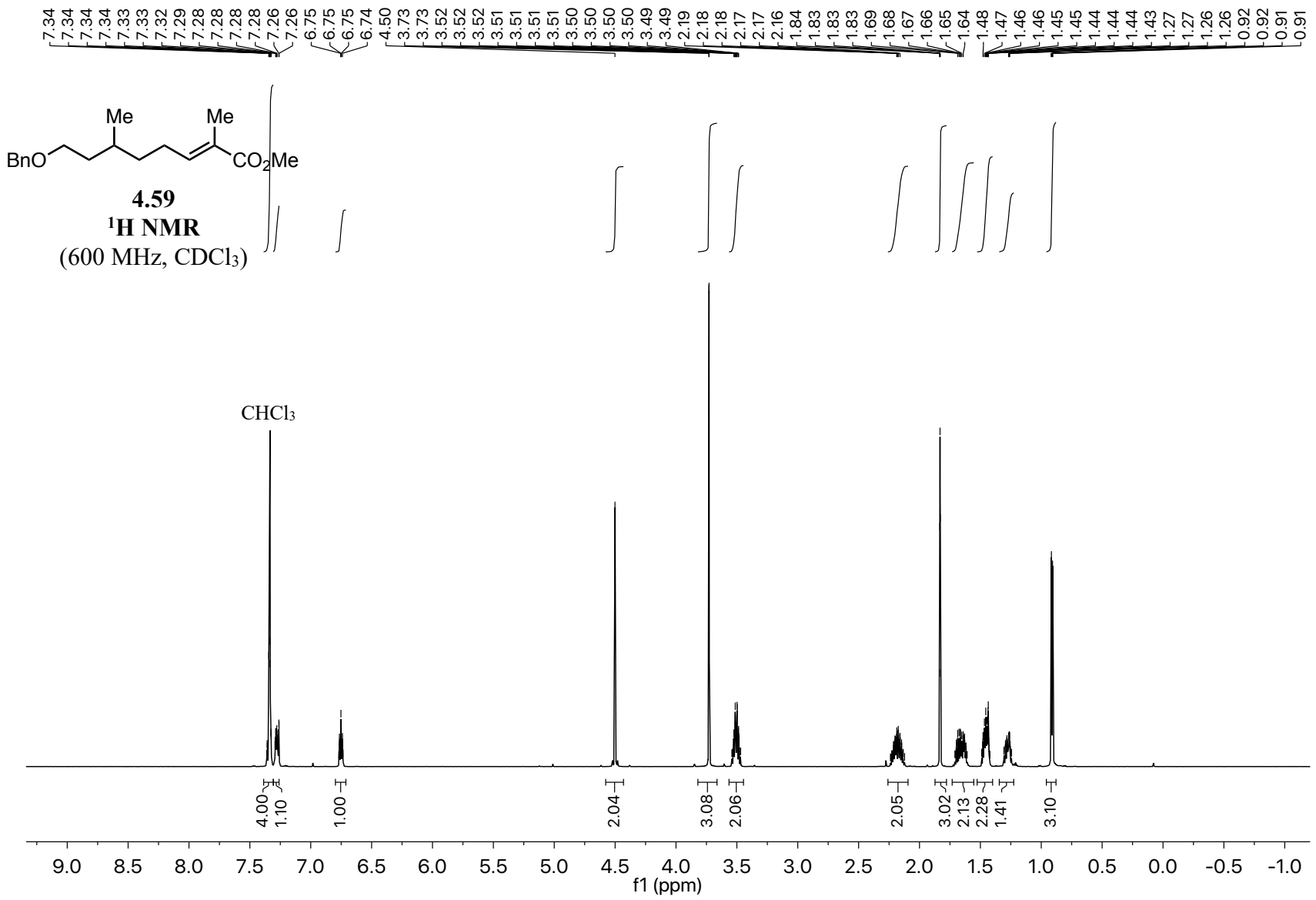


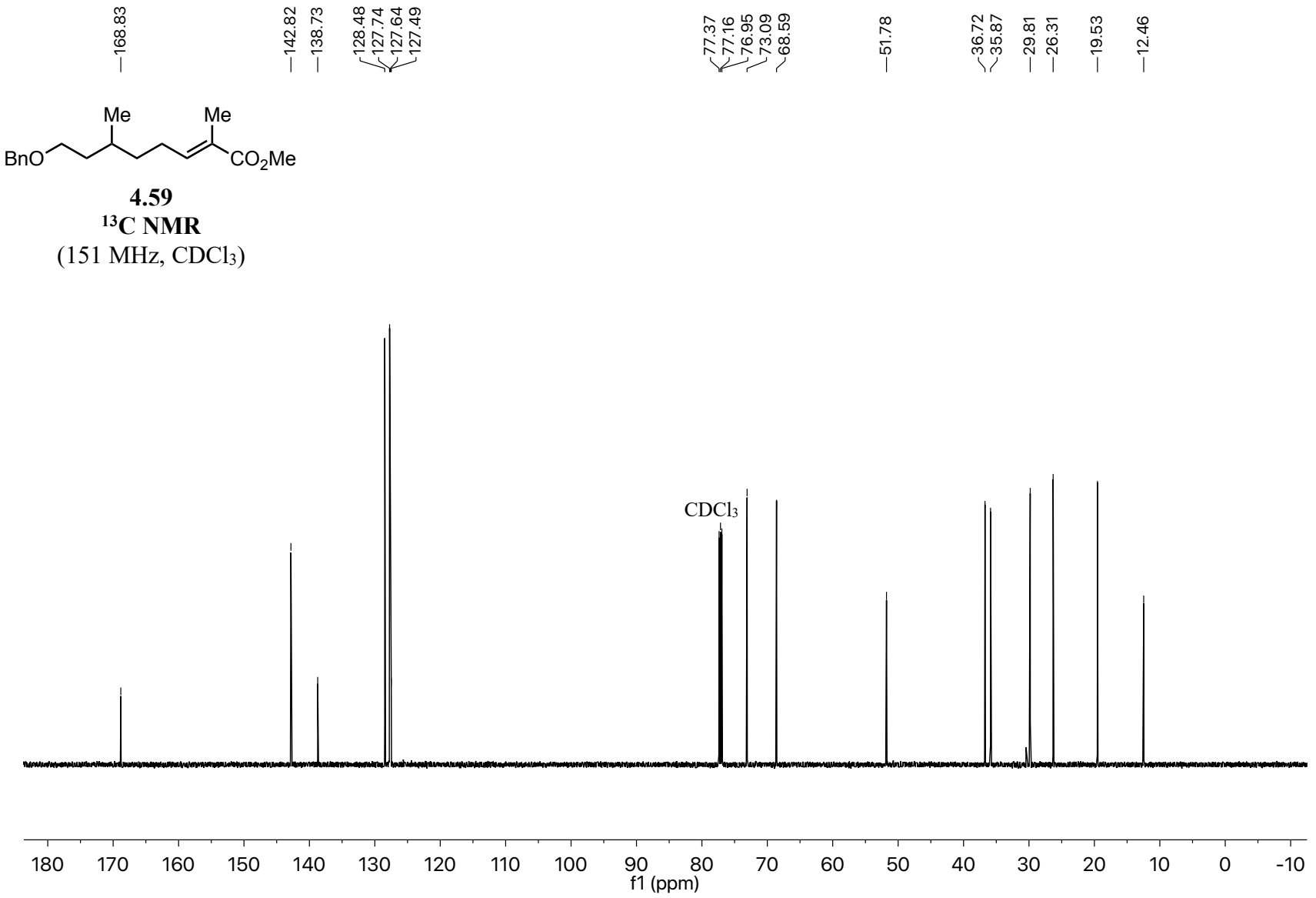
4.55
^{13}C NMR
(100 MHz, $CDCl_3$)


CO2Me
n-Pent
Me
4.57
1H NMR
(400 MHz, CDCl3)
minor isomer
major isomer
0.04
0.96
f1 (ppm)
CHCl3
0.04
0.96
3.02
2.01
3.01
2.04
4.08
3.03
f1 (ppm)

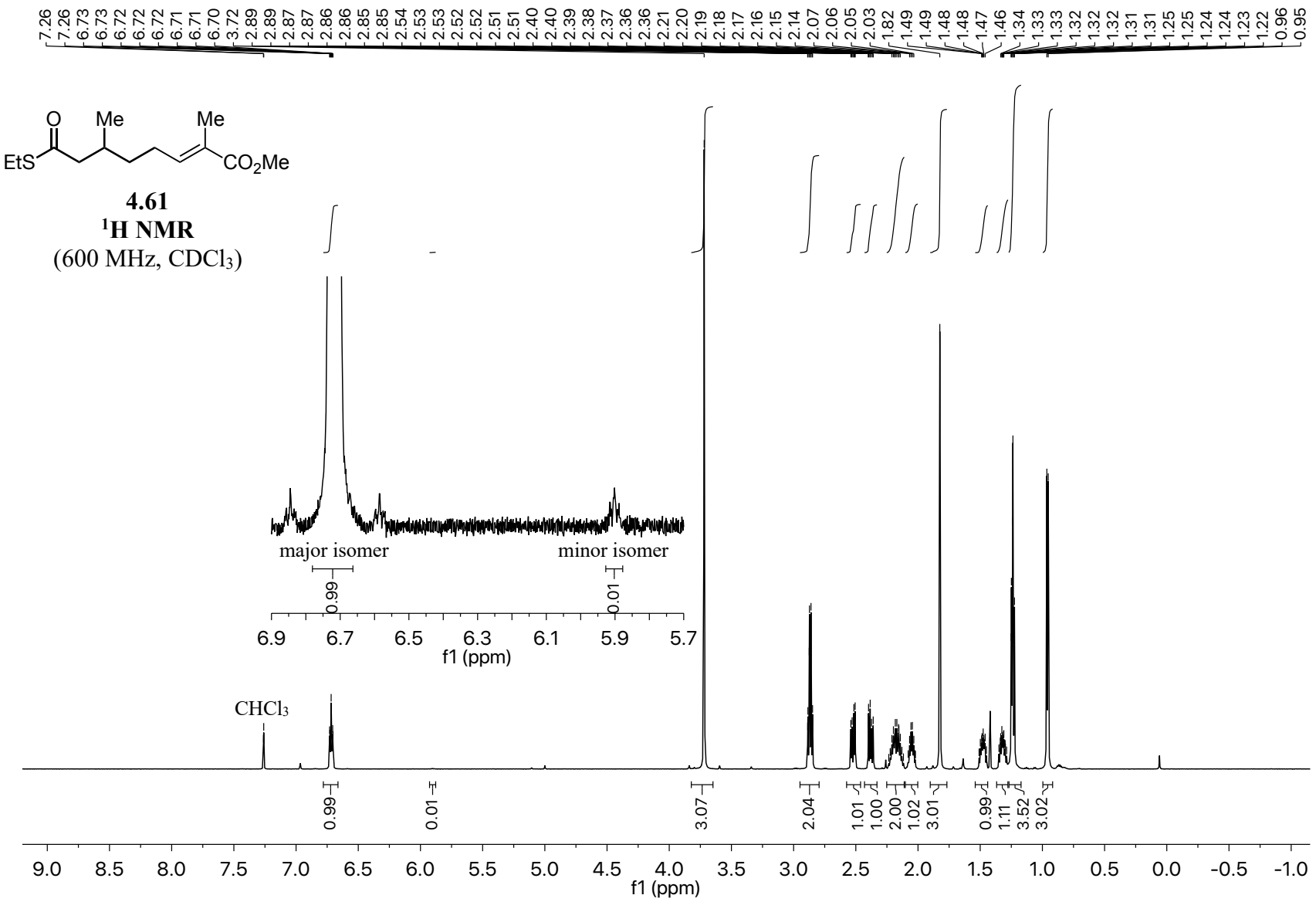


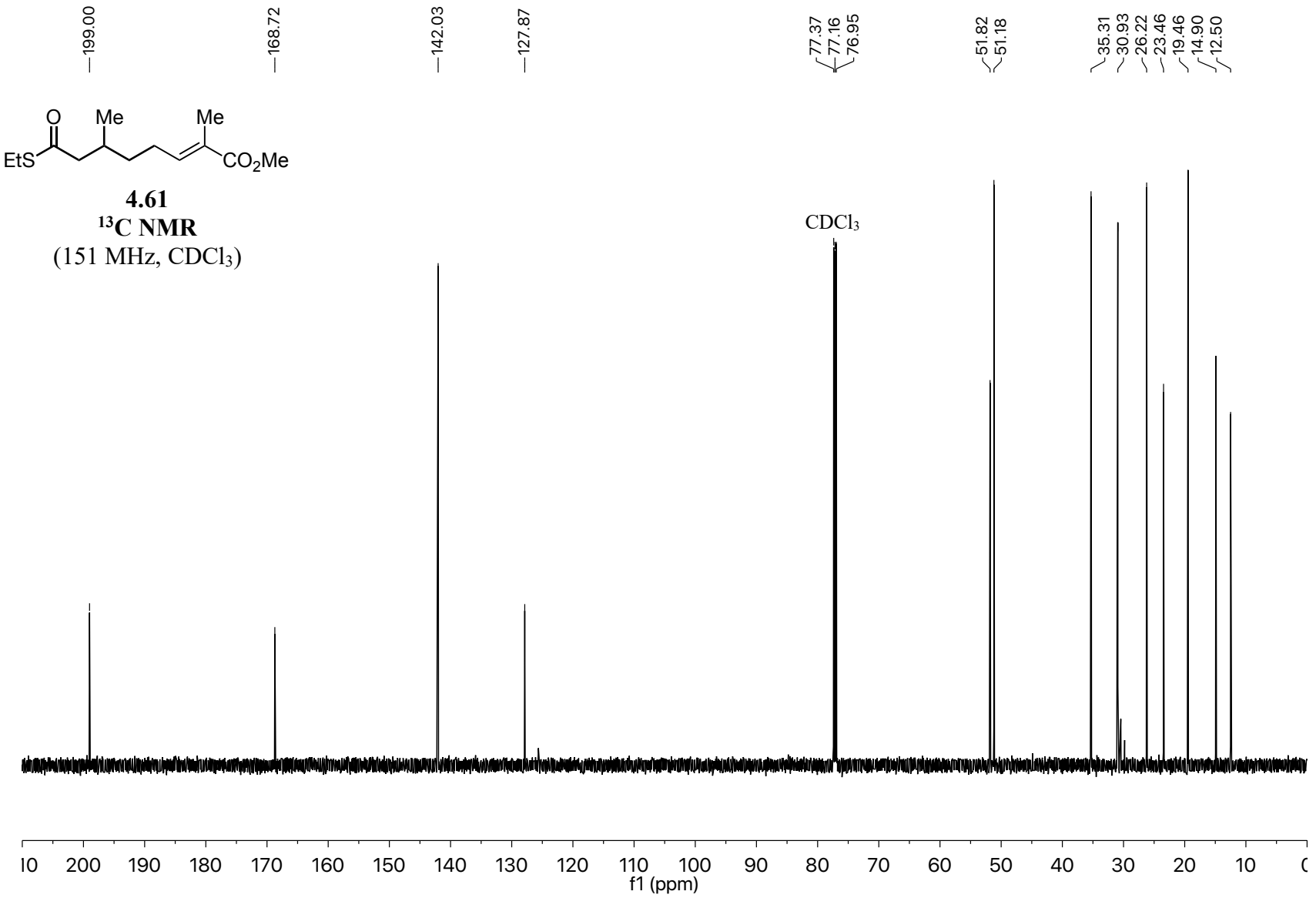
4.57
^{13}C NMR
(100 MHz, $CDCl_3$)


Me
Me
BnO
CO2Me
4.59
1H NMR
(600 MHz, CDCl3)
CHCl3
f1 (ppm)

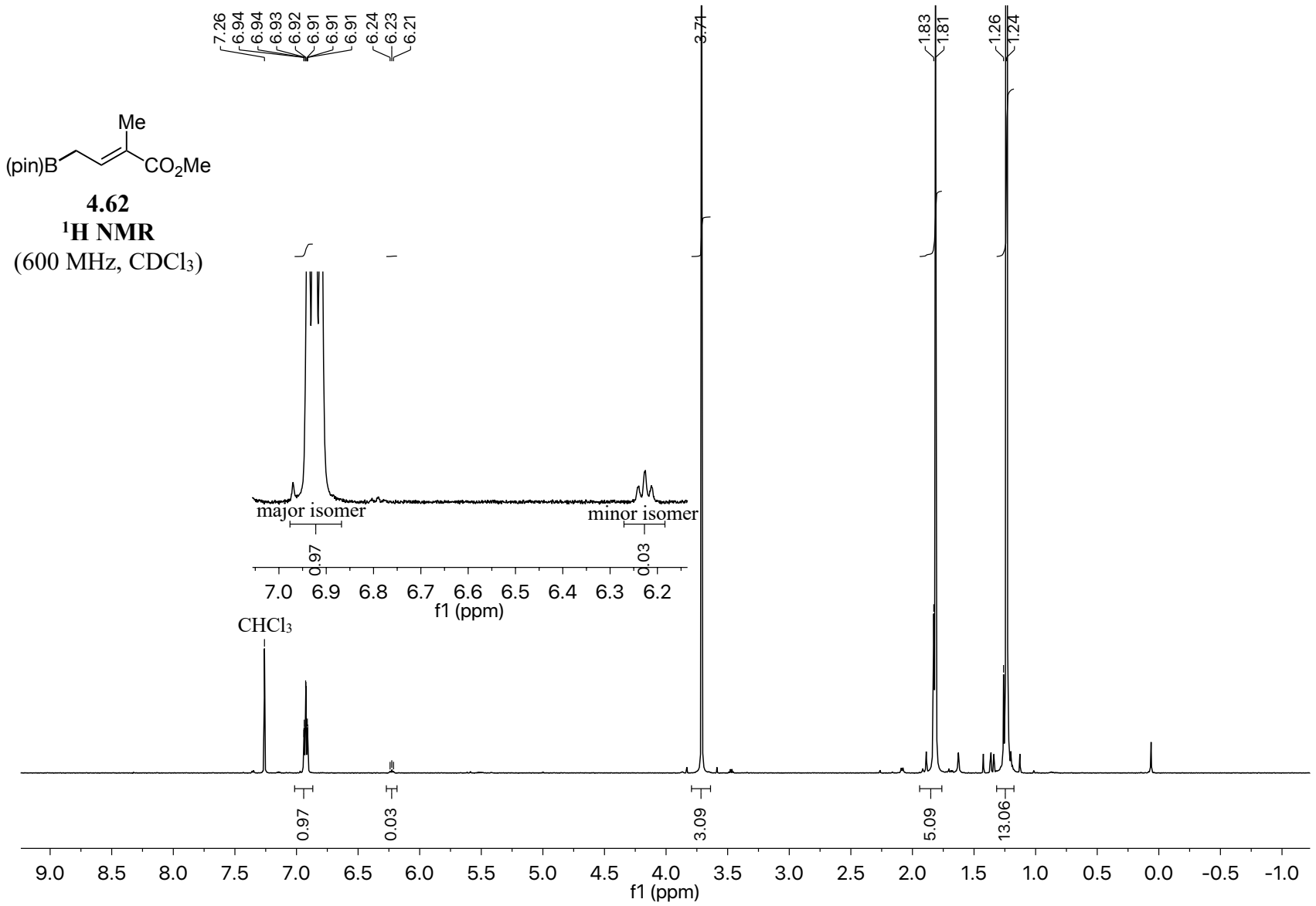


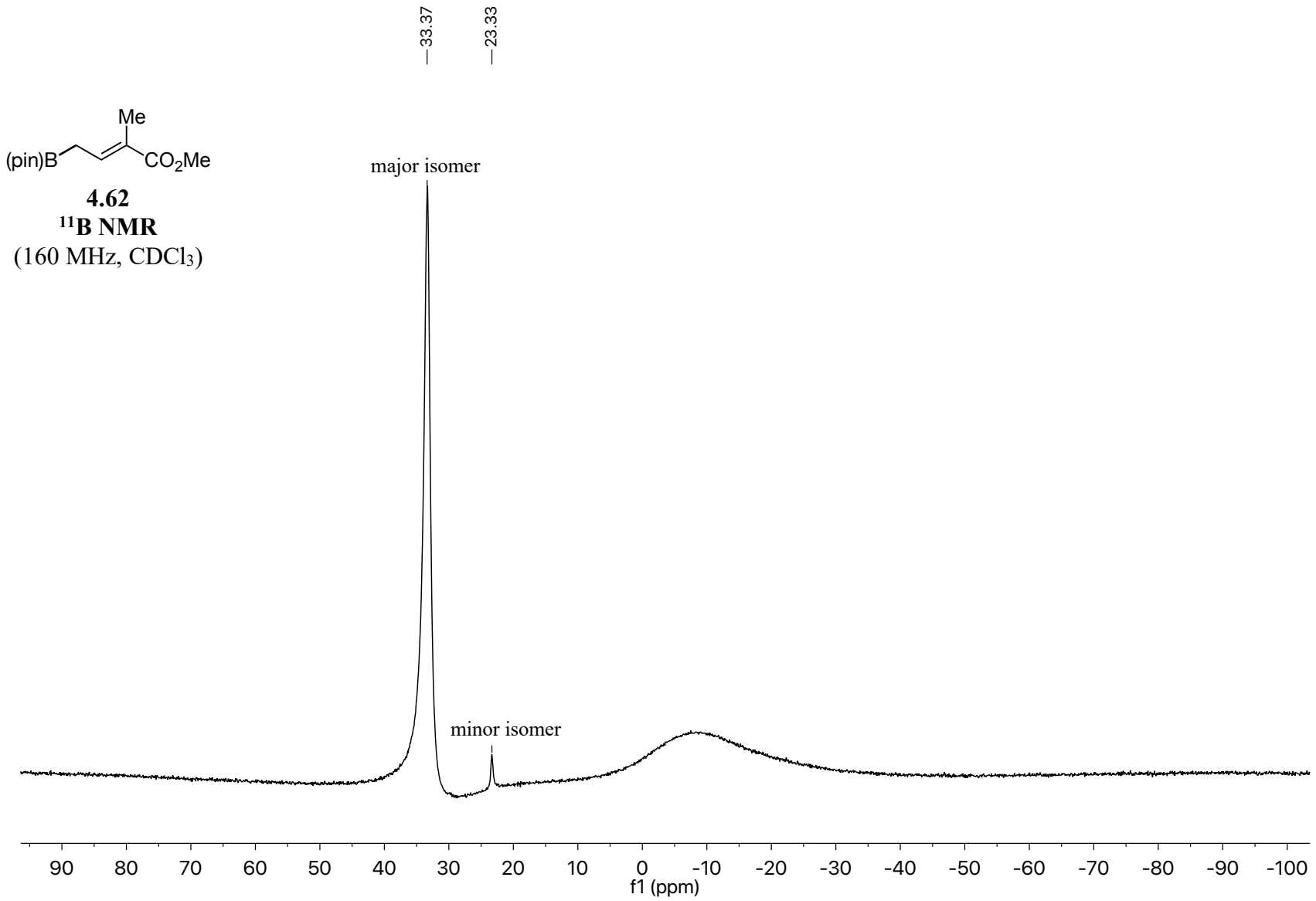
4.59
^{13}C NMR
(151 MHz, $CDCl_3$)


7.26 7.26 6.73 6.73 6.72 6.72 6.72 6.71 6.71 6.70 3.72 2.89 2.89 2.87 2.87 2.86 2.86 2.85 2.85 2.54 2.53 2.53 2.52 2.52 2.51 2.51 2.40 2.40 2.39 2.38 2.37 2.36 2.36 2.21 2.20 2.19 2.18 2.17 2.16 2.15 2.14 2.07 2.06 2.05 2.03 1.82 1.49 1.49 1.48 1.48 1.47 1.46 1.34 1.33 1.33 1.32 1.32 1.32 1.31 1.31 1.25 1.25 1.24 1.24 1.23 1.22 0.96 0.95
O
Me
Me
EtS
CO2Me
4.61
1H NMR
(600 MHz, CDCl3)
major isomer
minor isomer
0.99
0.01
6.9 6.7 6.5 6.3 6.1 5.9 5.7
f1 (ppm)
CHCl3
0.99 0.01 3.07 2.04 1.01 1.00 2.00 1.02 3.01 0.99 1.11 3.52 3.02
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

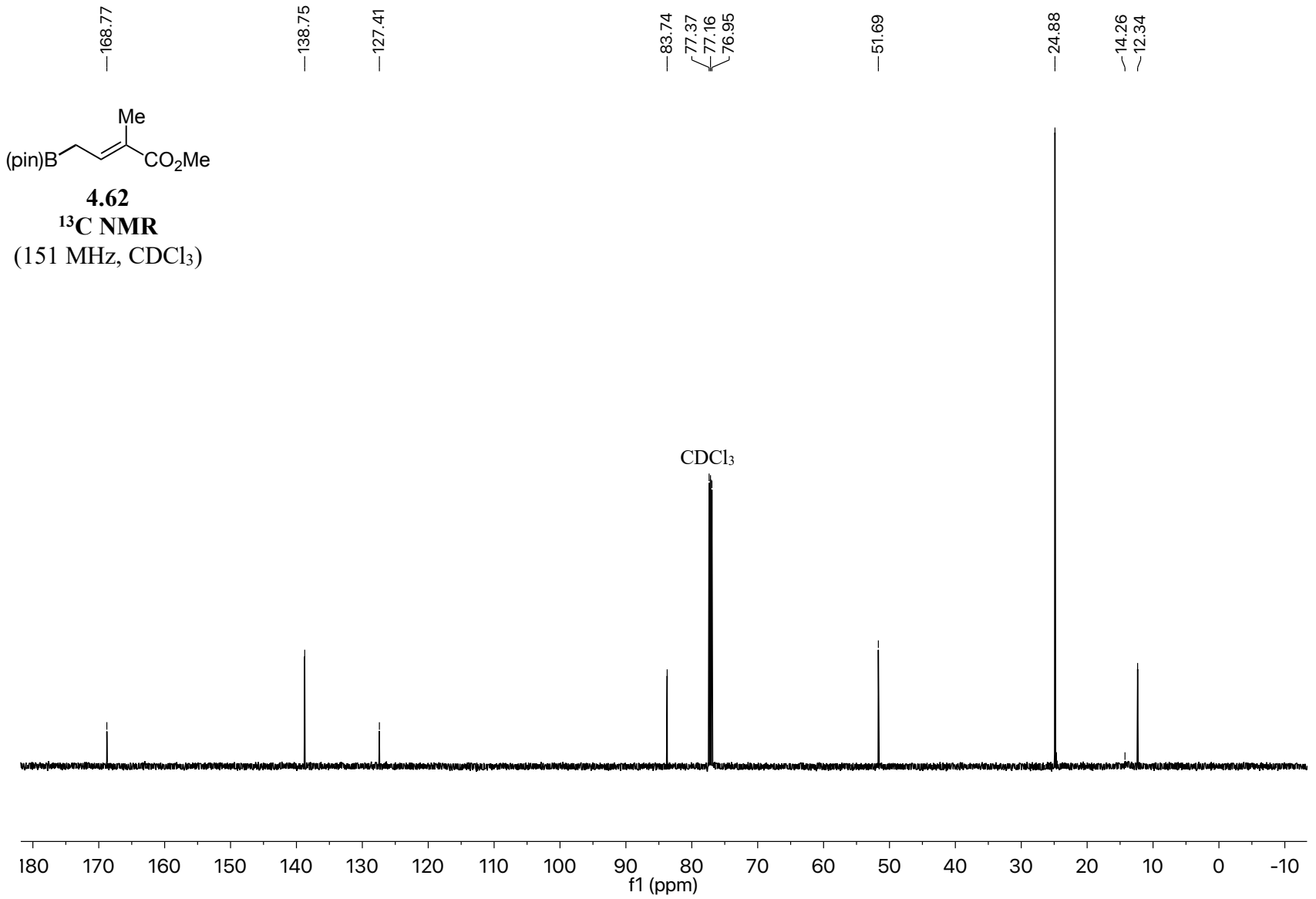


4.61
^{13}C NMR
(151 MHz, $CDCl_3$)

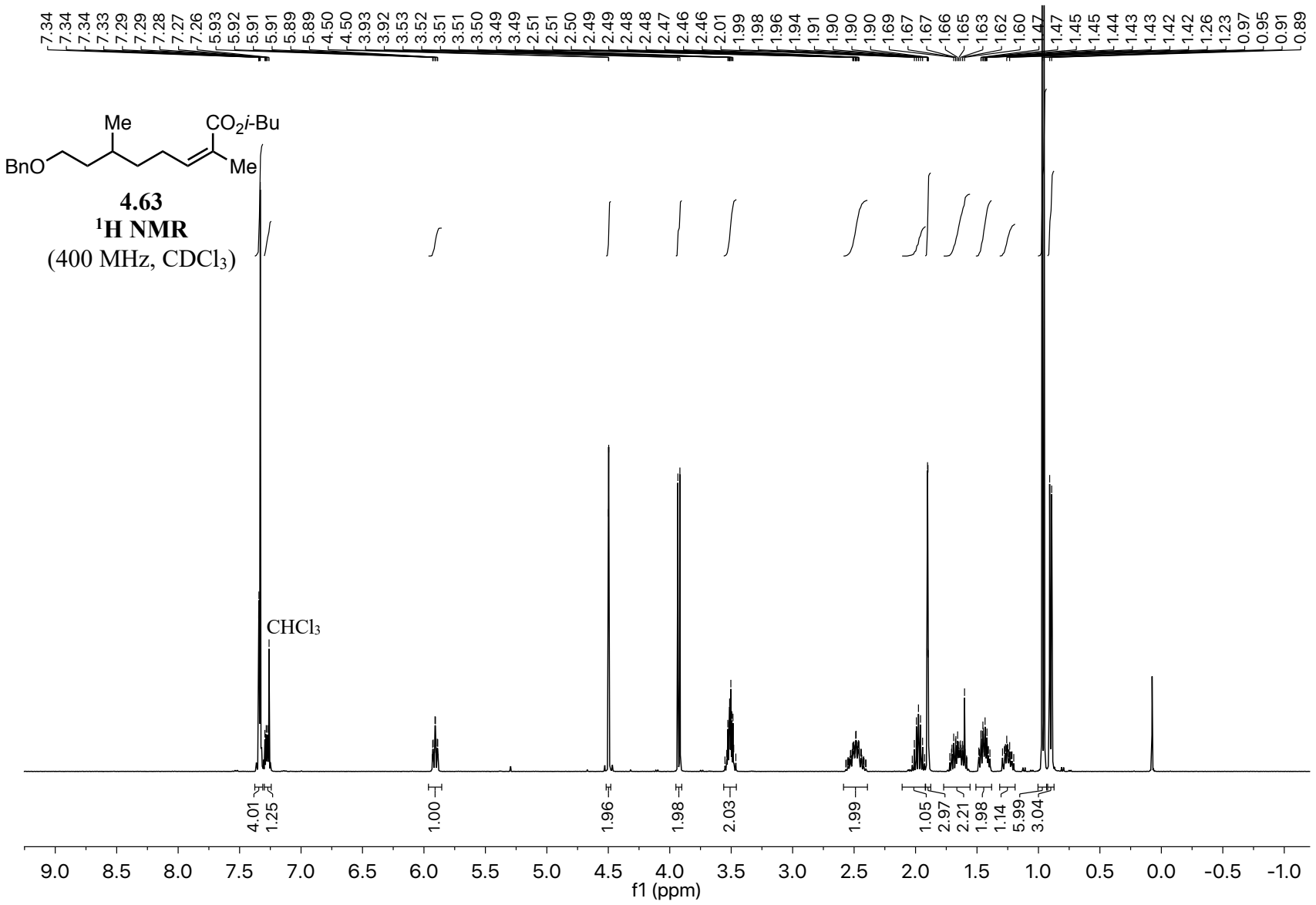

Me
(pin)B
CO2Me
4.62
1H NMR
(600 MHz, CDCl3)
major isomer
minor isomer
CHCl3
f1 (ppm)

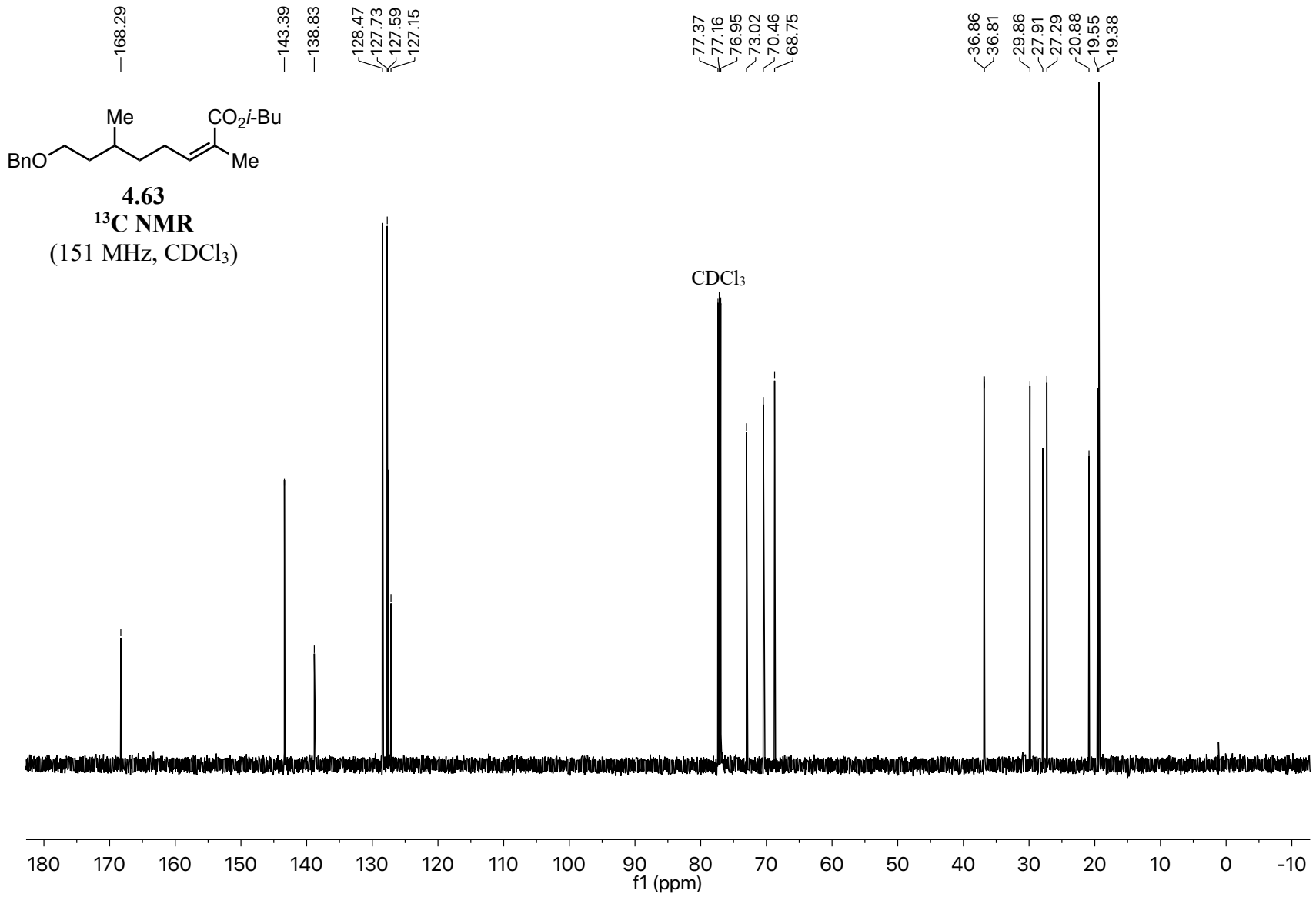


4.62
^{11}B NMR
(160 MHz, $CDCl_3$)

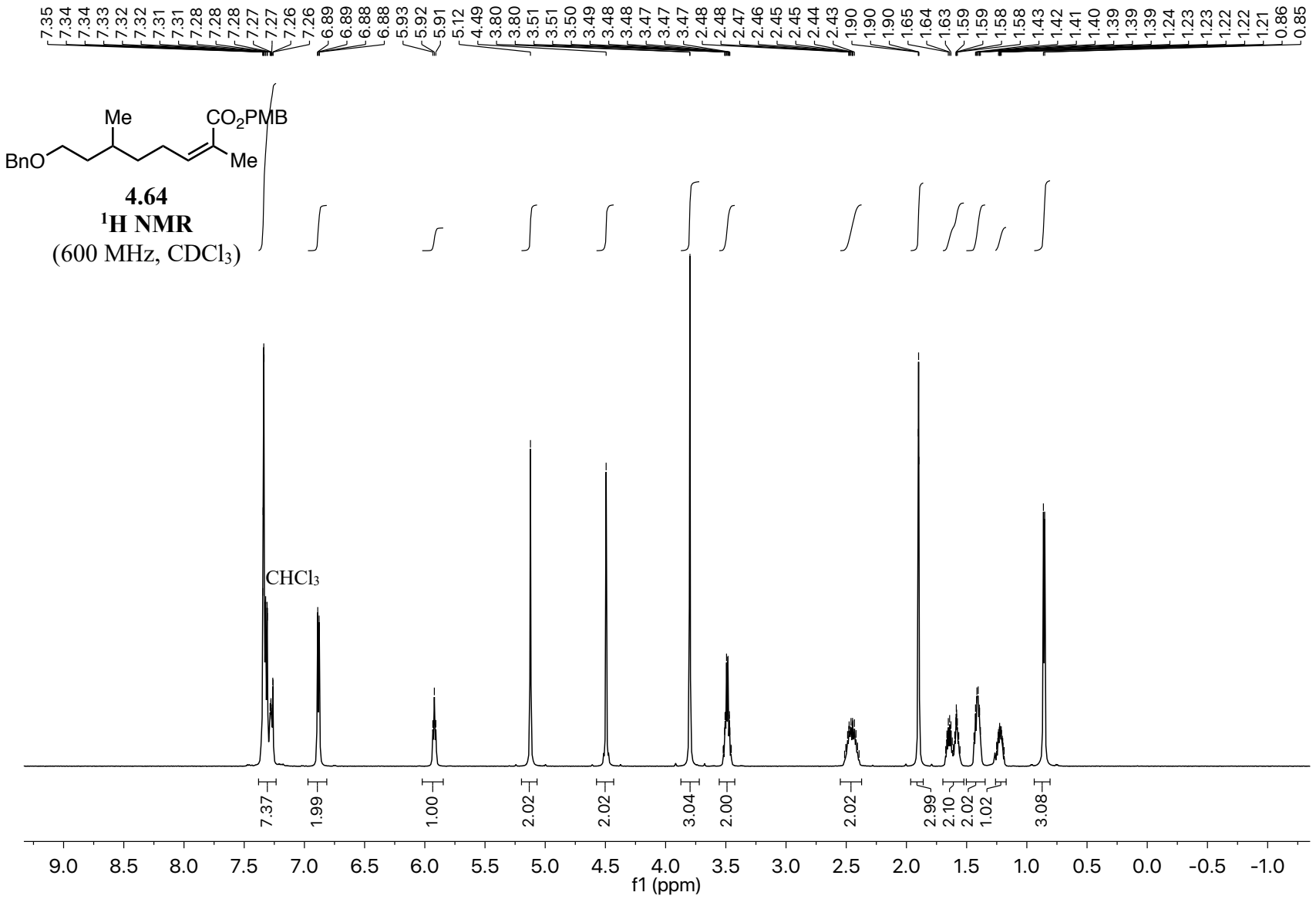


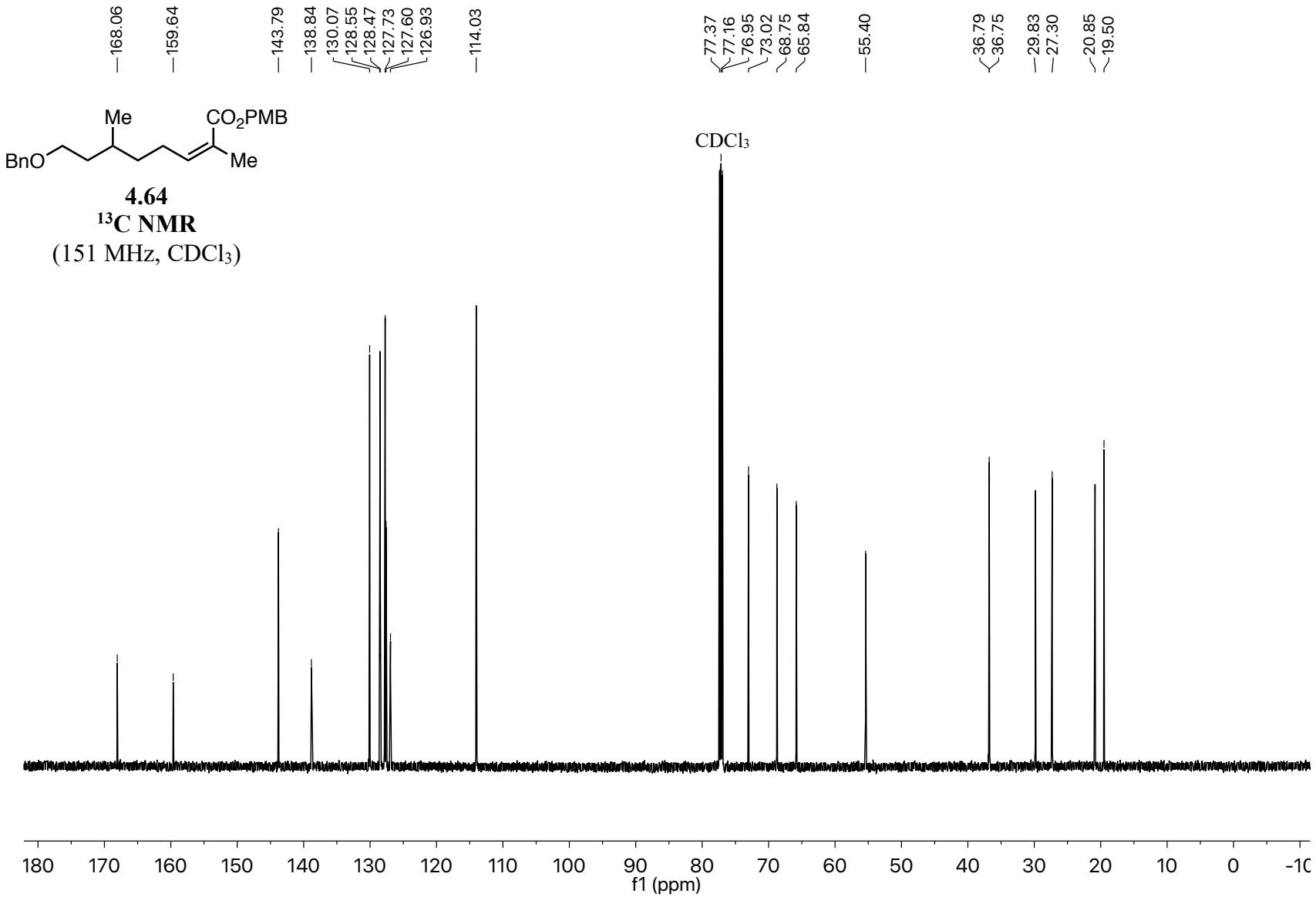
4.62
^{13}C NMR
(151 MHz, $CDCl_3$)


Me
CO2i-Bu
BnO
Me
4.63
1H NMR
(400 MHz, CDCl3)
CHCl3
f1 (ppm)

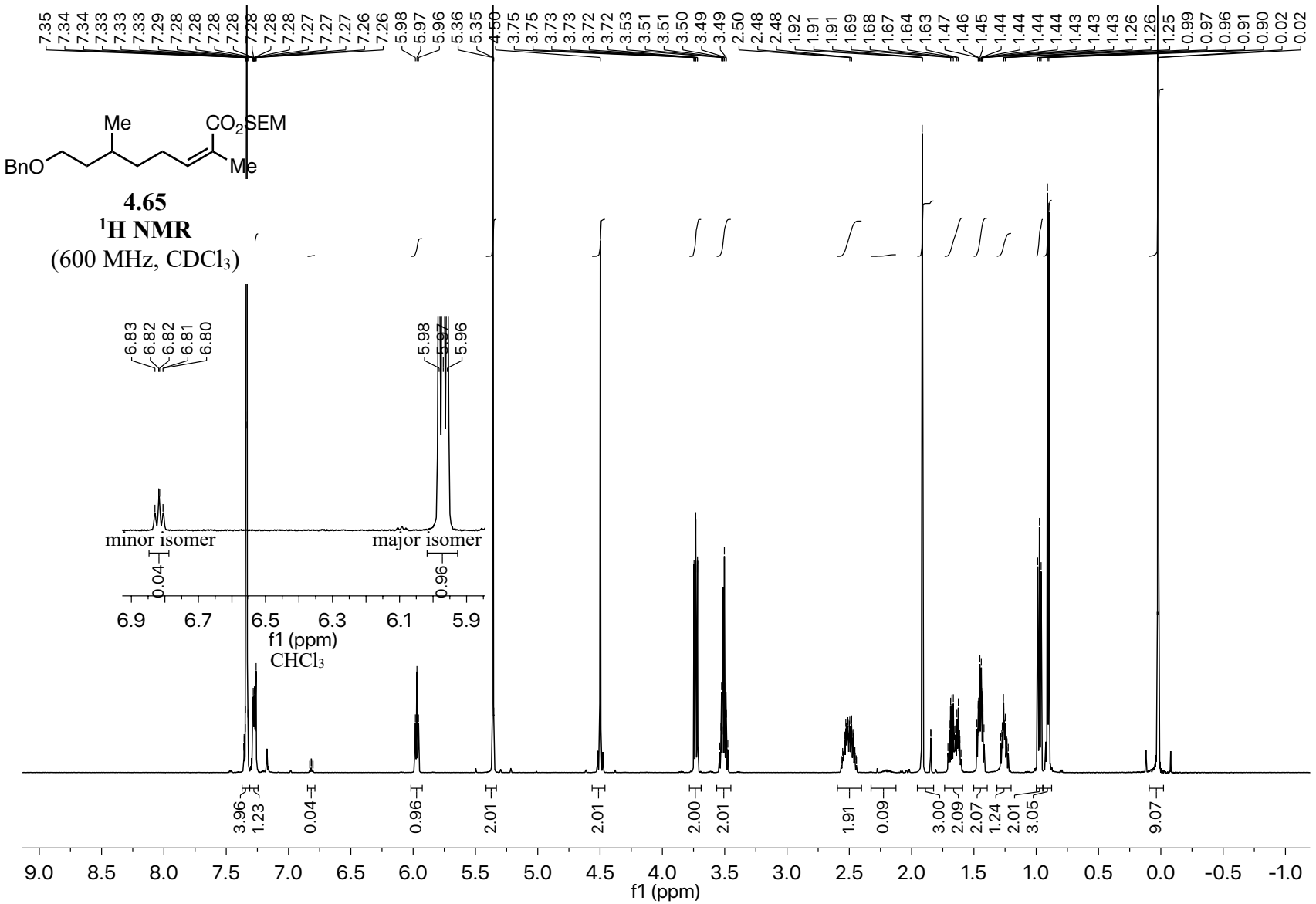


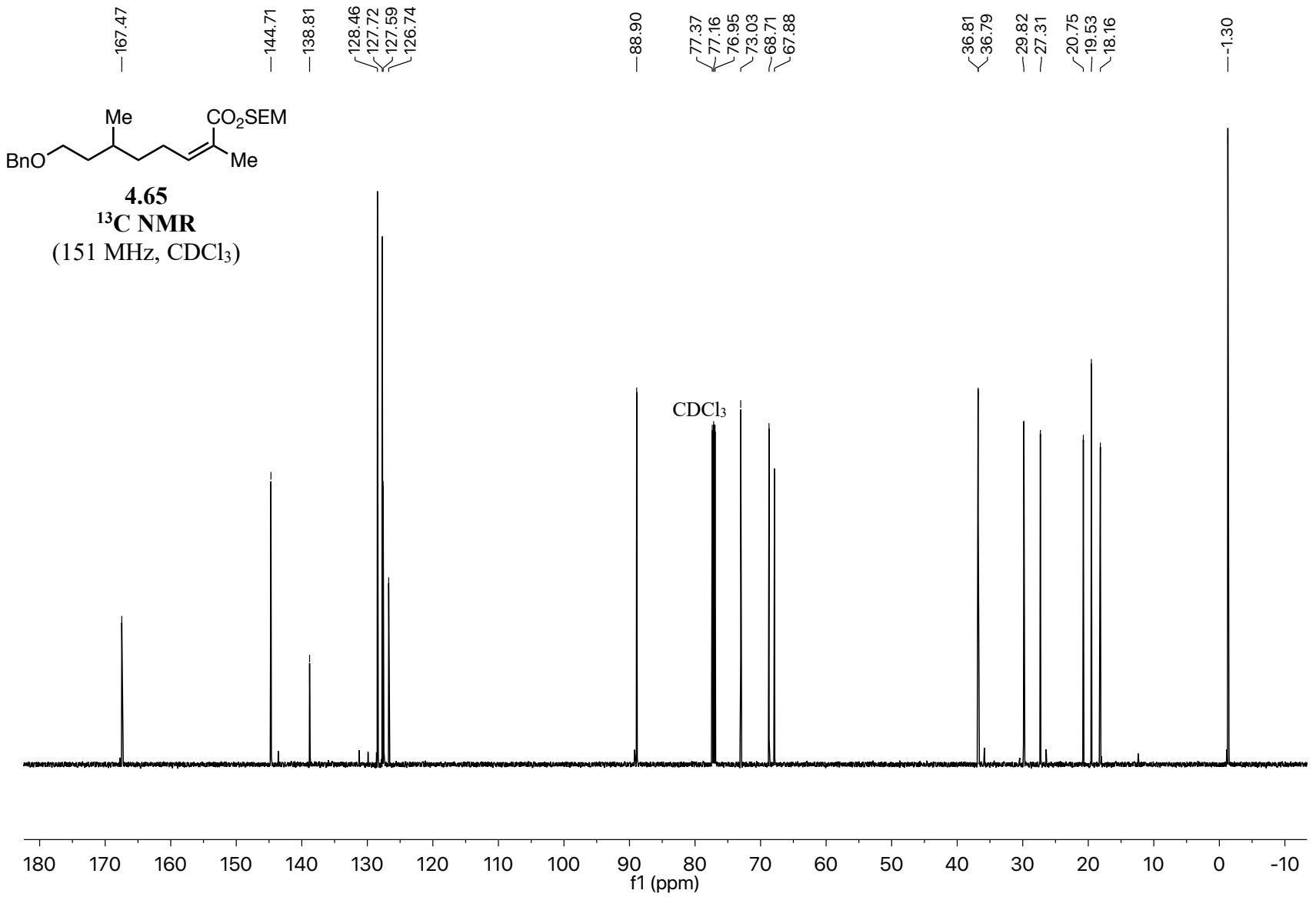
4.63
^{13}C NMR
(151 MHz, $CDCl_3$)


7.35 7.34 7.34 7.33 7.32 7.32 7.31 7.31 7.28 7.28 7.28 7.27 7.27 7.26 7.26
6.89 6.89 6.88 6.88
5.93 5.92 5.91
5.12 4.49 3.80 3.80 3.51 3.51 3.50 3.49 3.48 3.48 3.47 3.47 3.47 2.48 2.48 2.47 2.46 2.45 2.45 2.44 2.43 1.90 1.90 1.90 1.65 1.64 1.63 1.59 1.59 1.58 1.58 1.43 1.42 1.41 1.40 1.39 1.39 1.39 1.24 1.23 1.23 1.22 1.22 1.21 0.86 0.85
Me
CO2PMB
BnO
Me
4.64
1H NMR
(600 MHz, CDCl3)
CHCl3
7.37
1.99
1.00
2.02
2.02
3.04
2.00
2.02
2.99
2.10
2.02
1.02
3.08
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

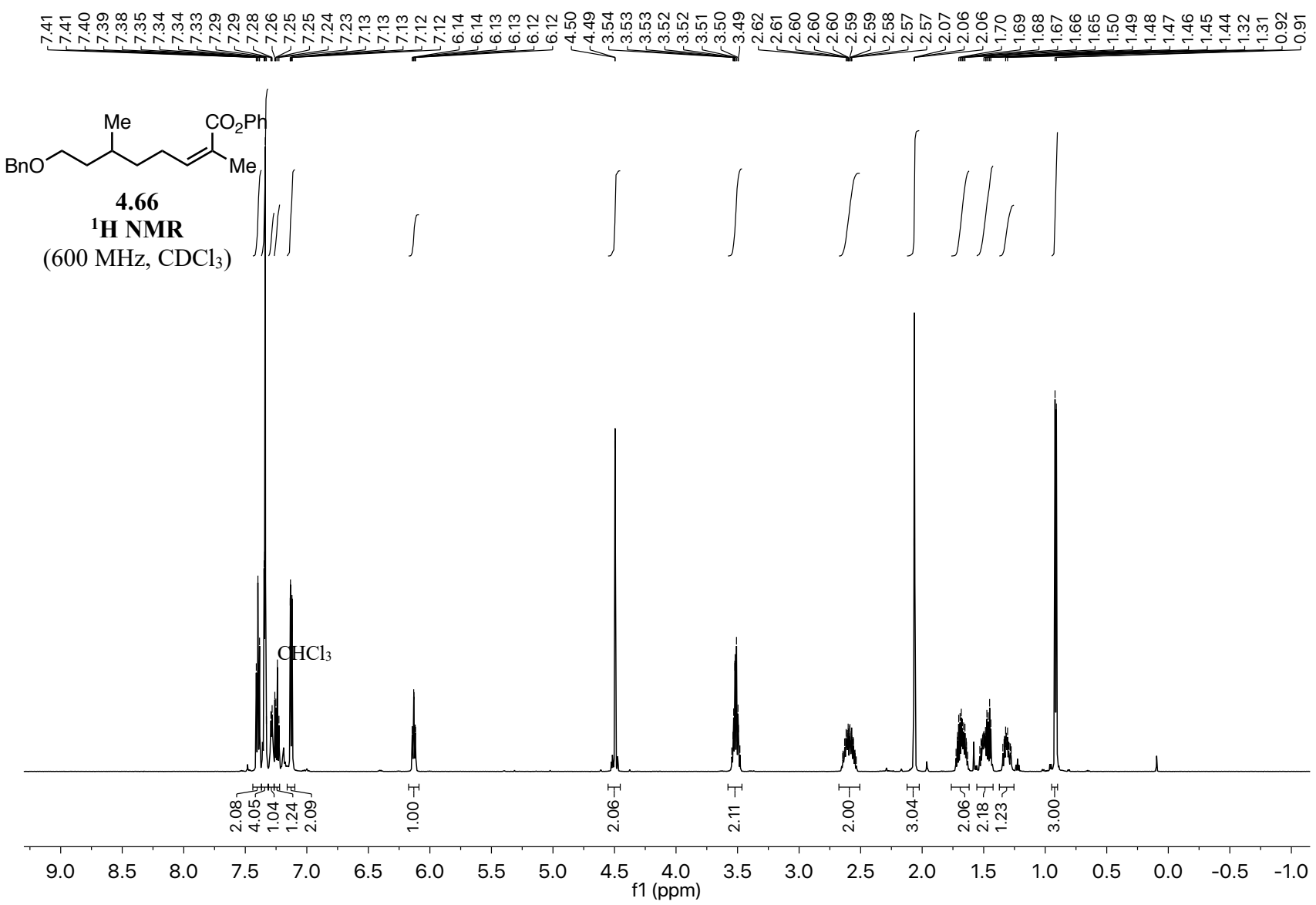


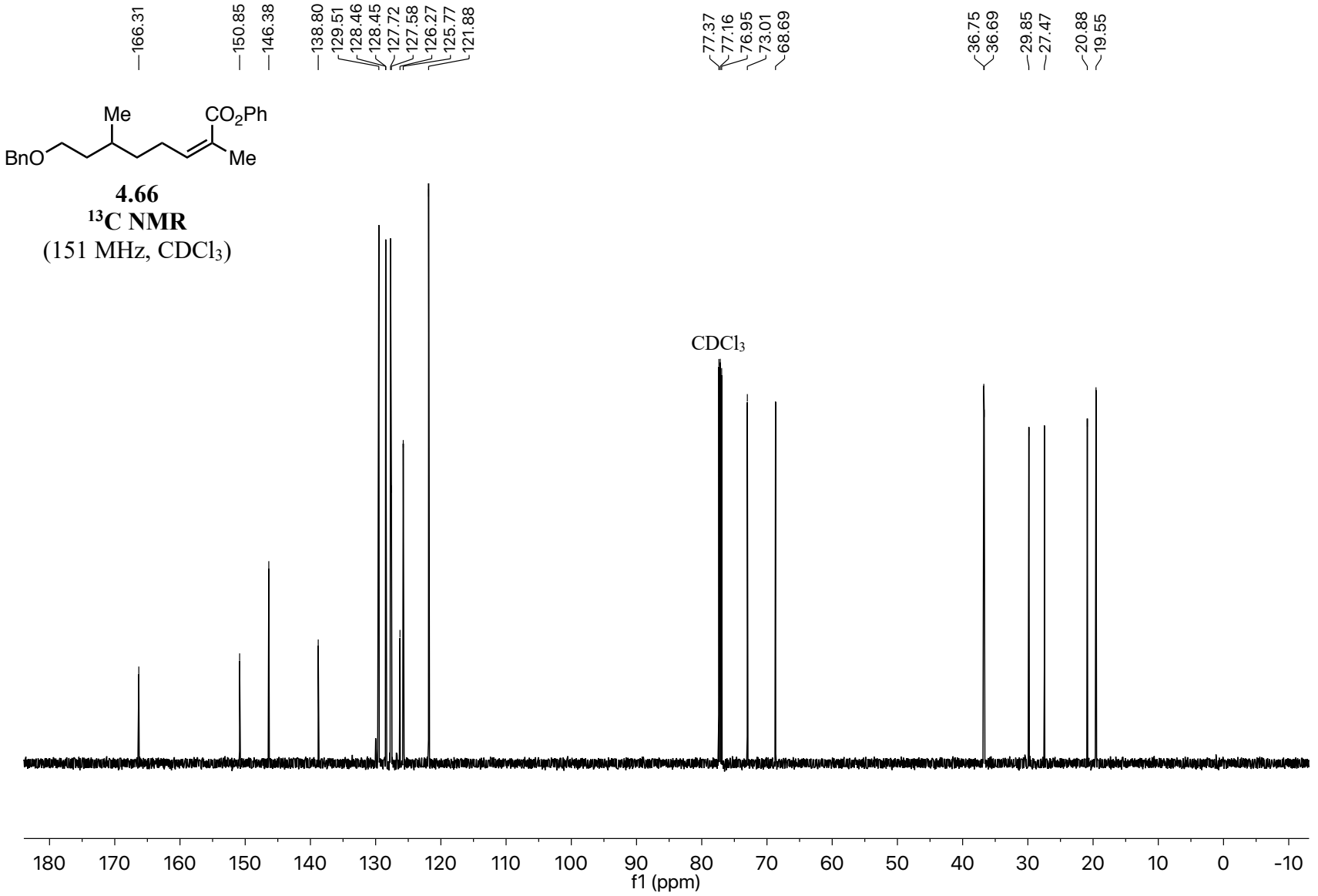
4.64
^{13}C NMR
(151 MHz, $CDCl_3$)


Me
CO2SEM
BnO
Me
4.65
1H NMR
(600 MHz, CDCl3)
minor isomer
major isomer
0.04
0.96
f1 (ppm)
CHCl3
3.96
1.23
0.04
0.96
2.01
2.01
2.00
2.01
1.91
0.09
3.00
2.09
2.07
1.24
2.01
3.05
9.07
f1 (ppm)

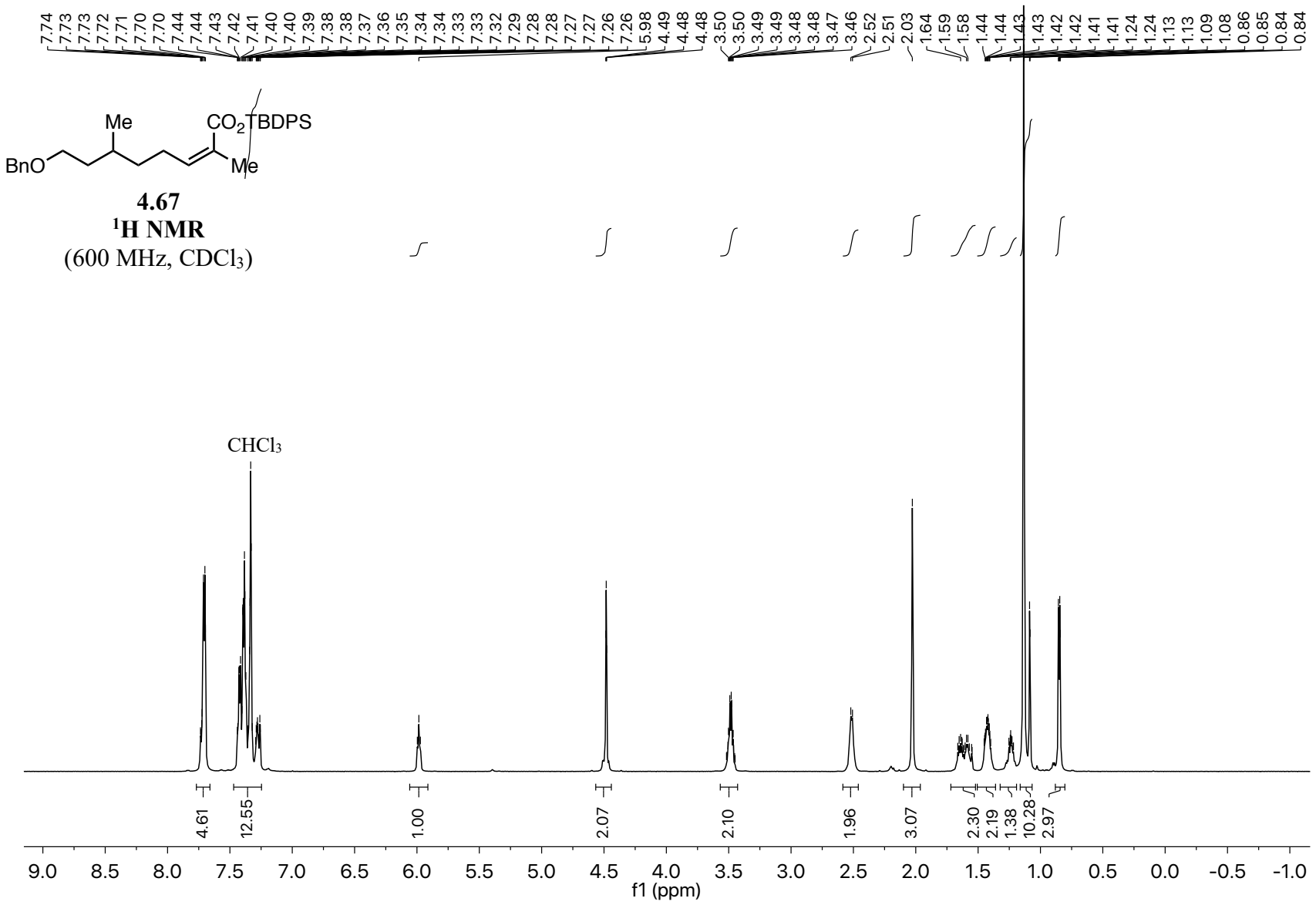


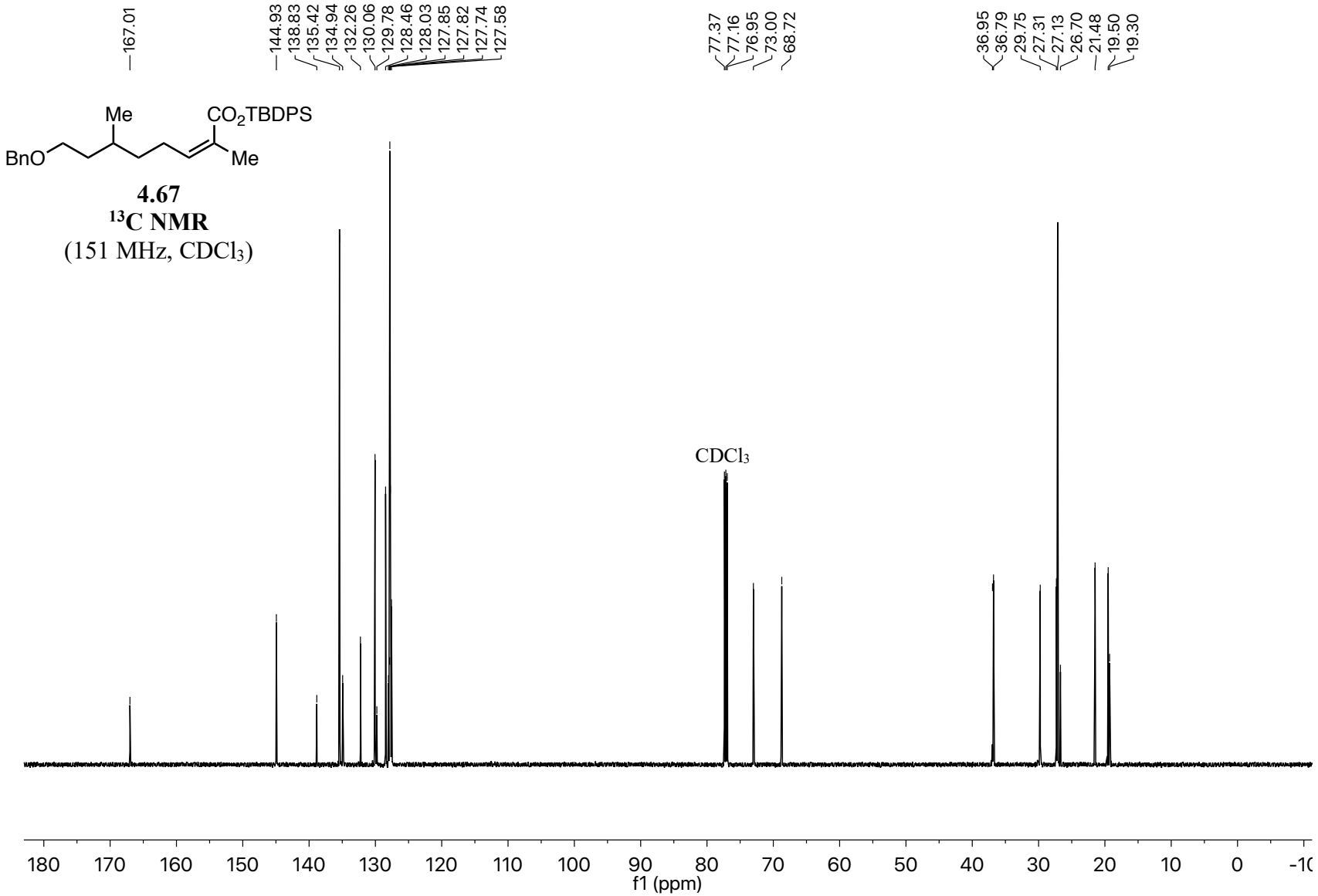
4.65
^{13}C NMR
(151 MHz, $CDCl_3$)

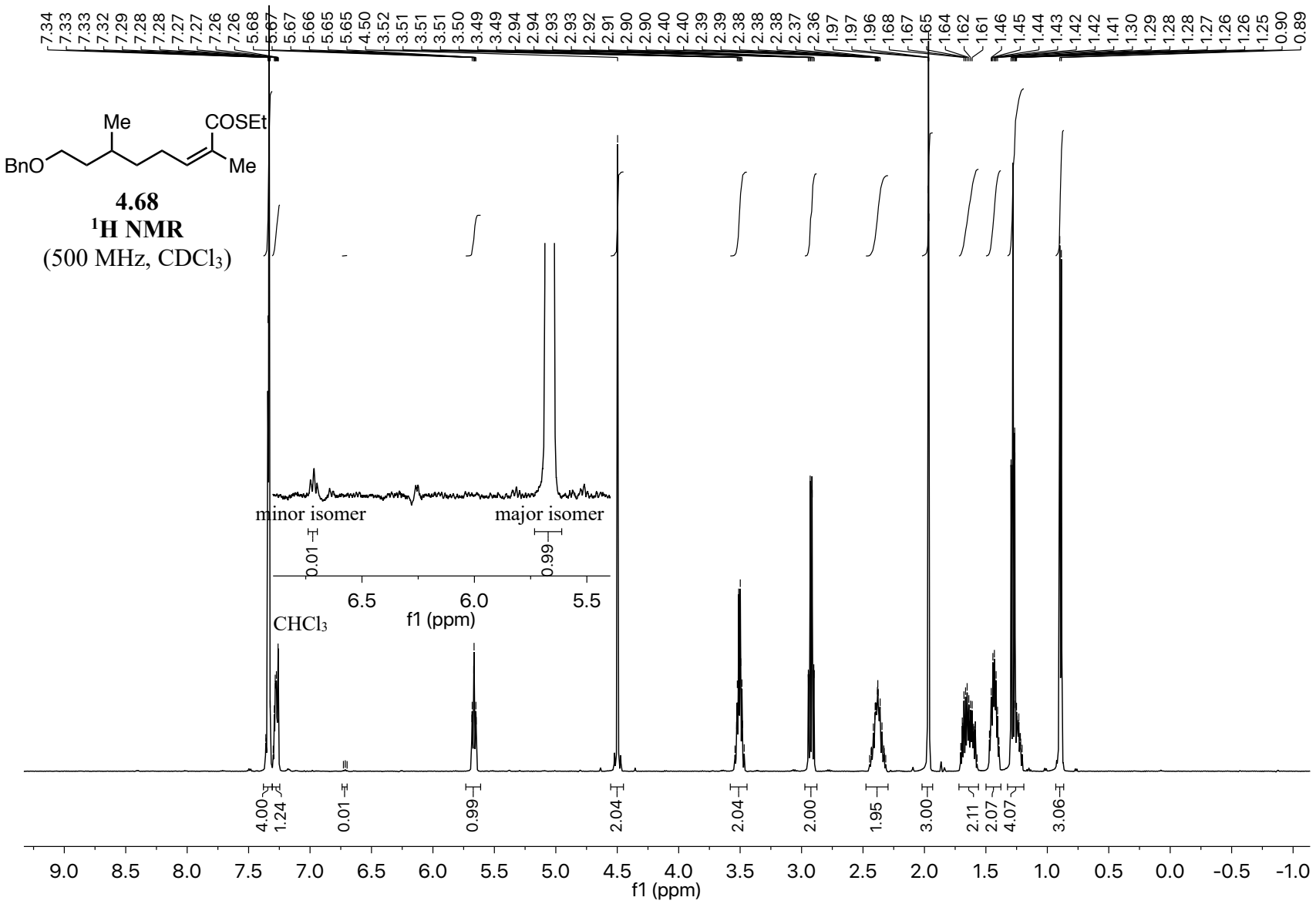

Me
CO2Ph
BnO
Me
4.66
1H NMR
(600 MHz, CDCl3)
CHCl3
f1 (ppm)

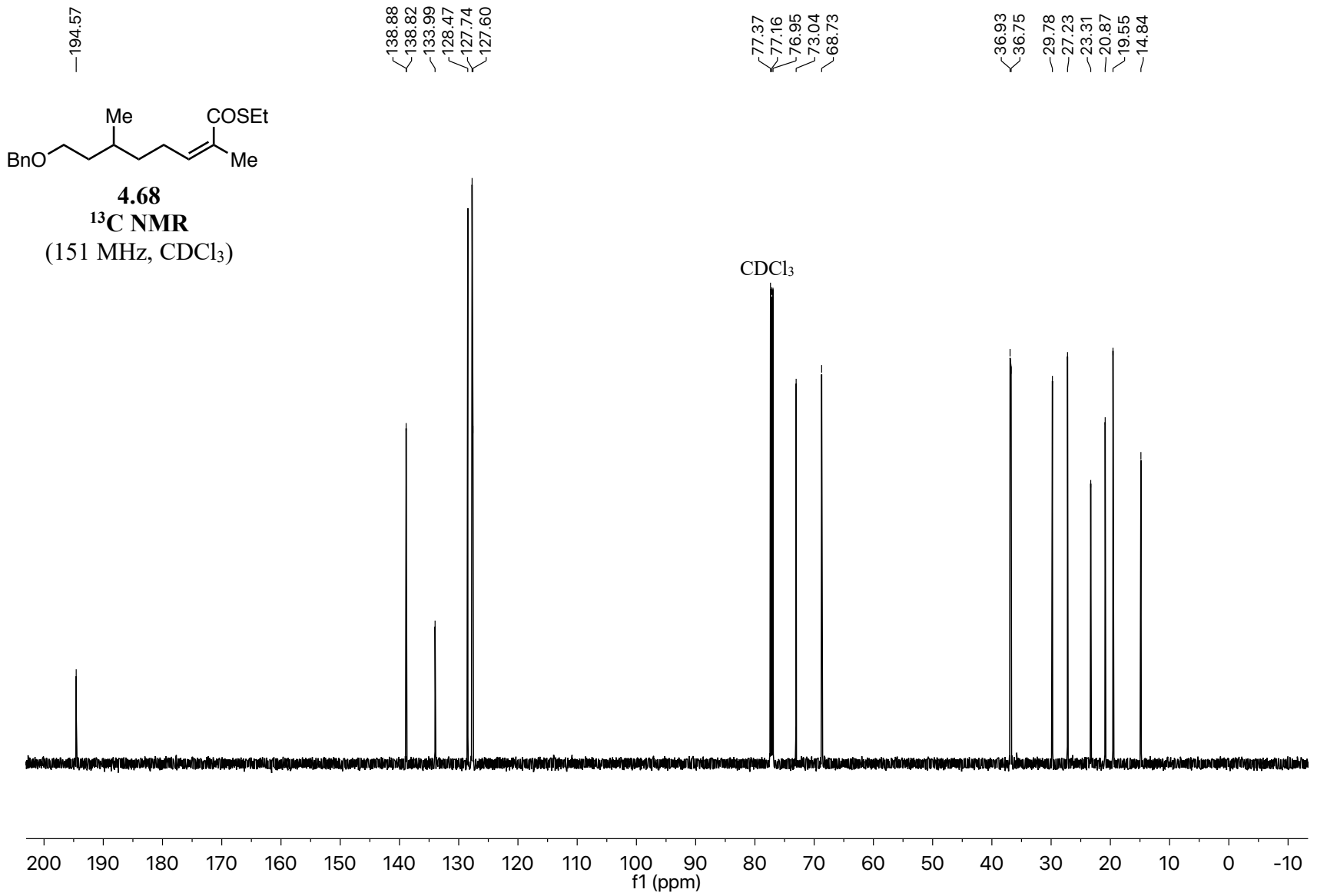


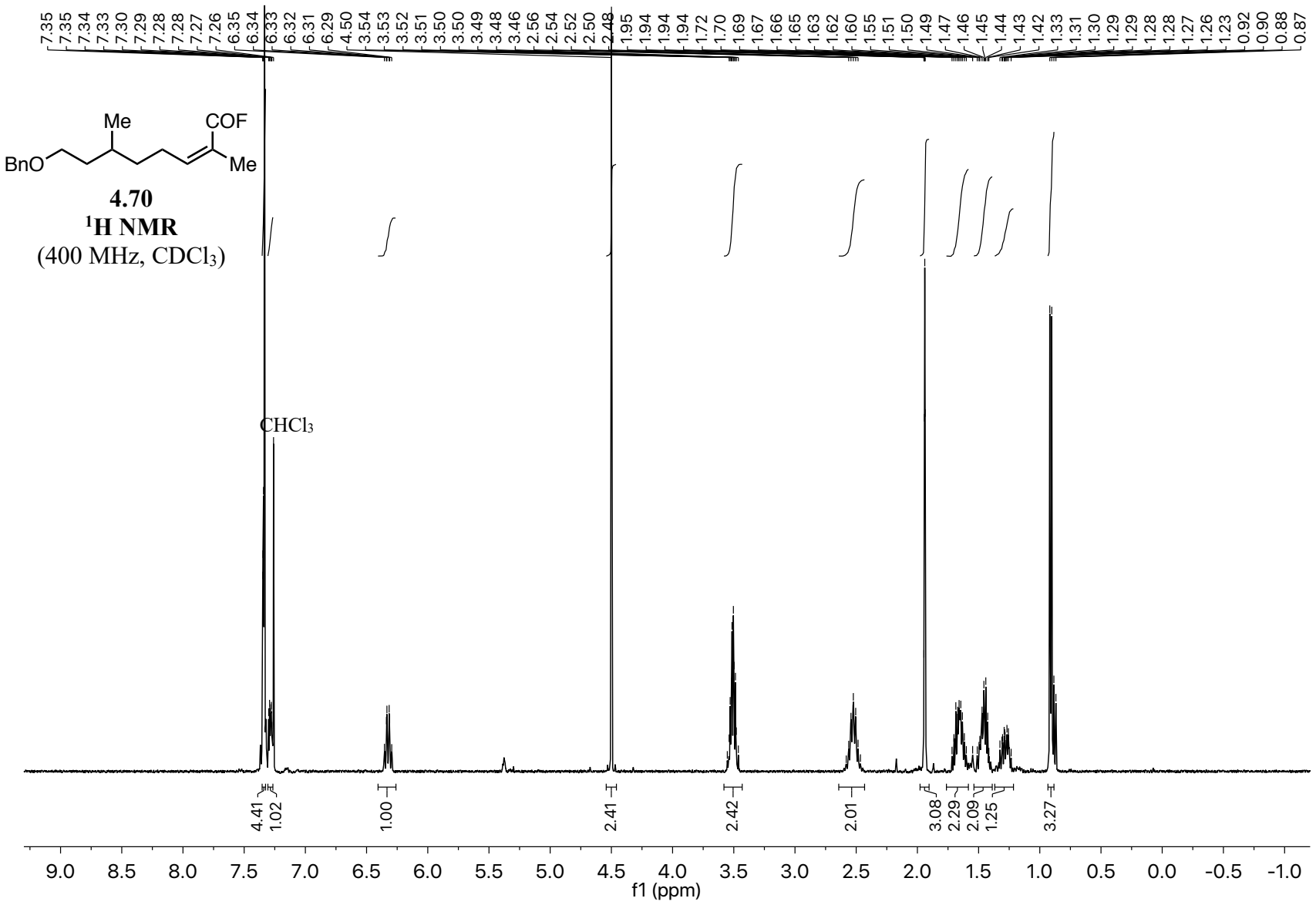
4.66
^{13}C NMR
(151 MHz, $CDCl_3$)

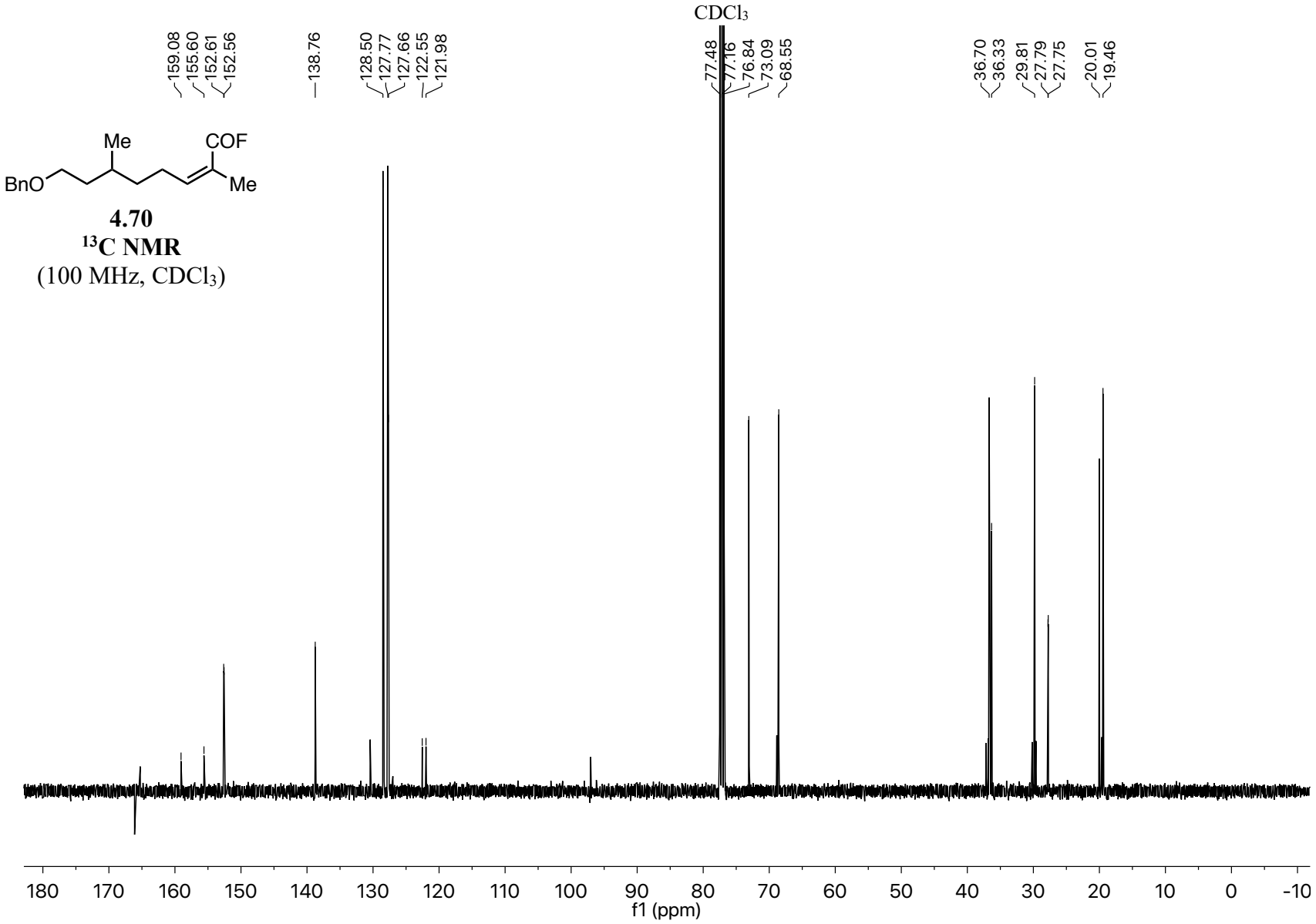

Me
CO2TBDPS
BnO
Me
4.67
1H NMR
(600 MHz, CDCl3)
CHCl3
f1 (ppm)

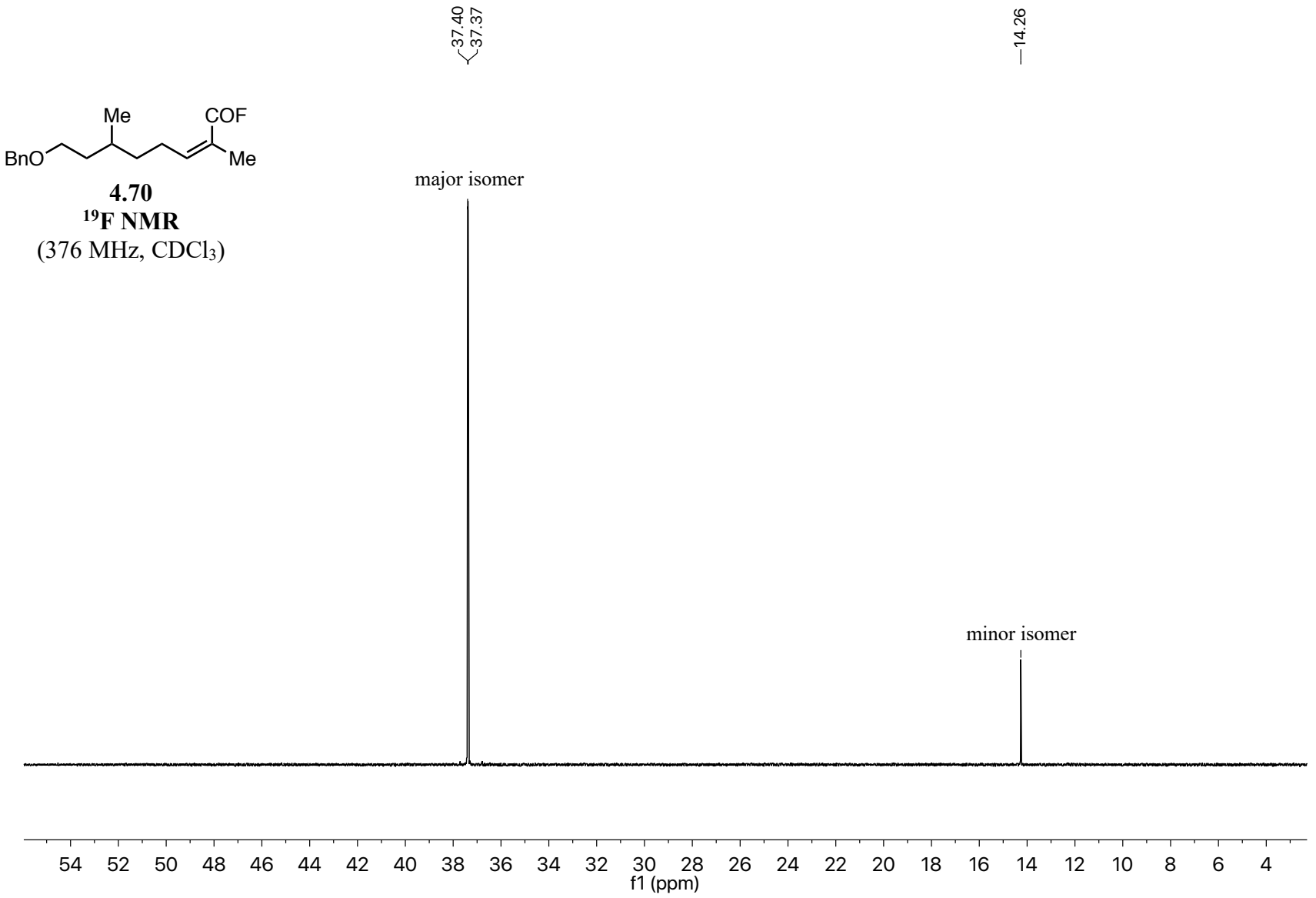

167.01
144.93
138.83
135.42
134.94
132.26
130.06
129.78
128.46
128.03
127.85
127.82
127.74
127.58
77.37
77.16
76.95
73.00
68.72
36.95
36.79
29.75
27.31
27.13
26.70
21.48
19.50
19.30
Me
CO2TBDPS
BnO
Me
4.67
13C NMR
(151 MHz, CDCl3)
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

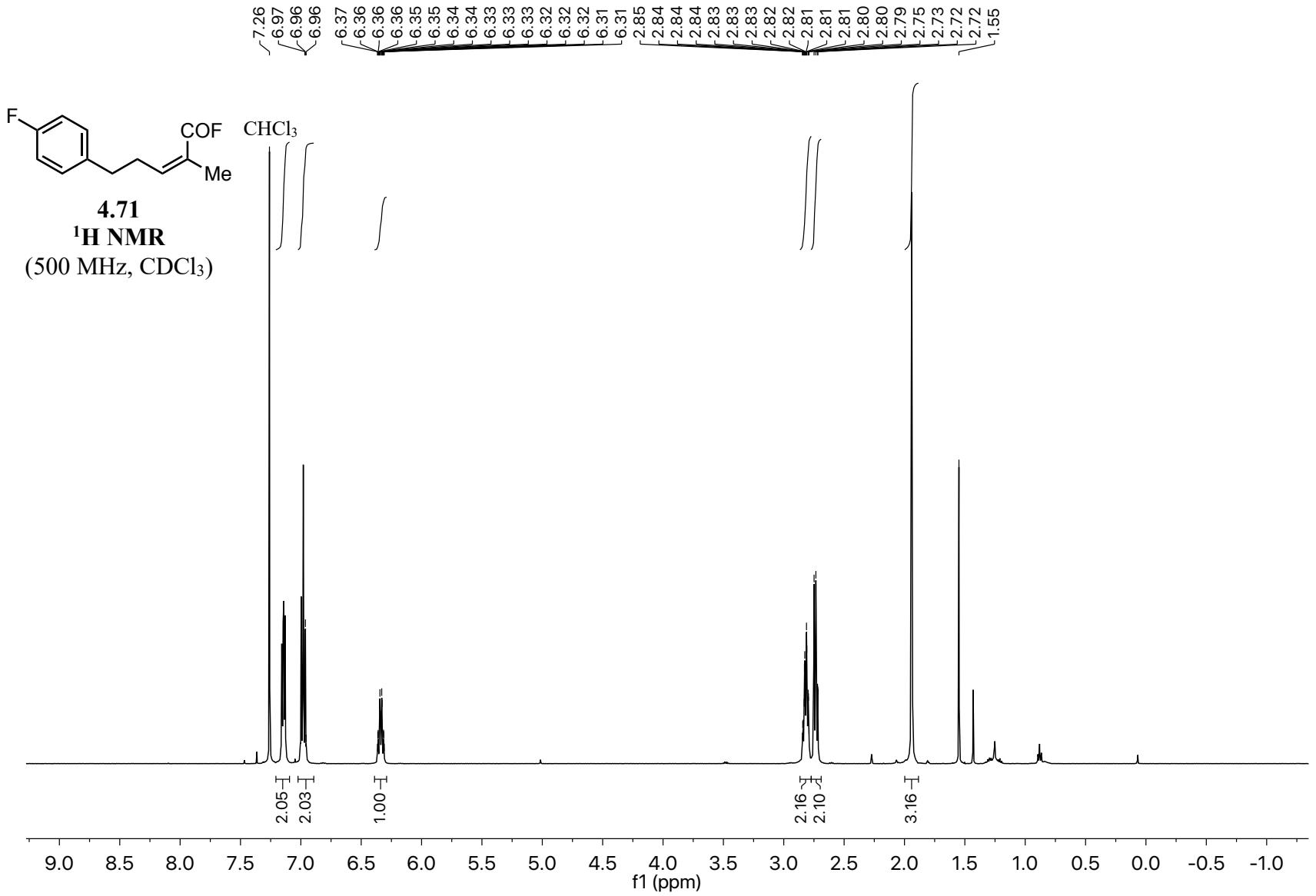

Me
COSEt
BnO
Me
4.68
1H NMR
(500 MHz, CDCl3)
minor isomer
major isomer
0.01
0.99
6.5
6.0
5.5
f1 (ppm)
CHCl3
4.00
1.24
0.01
0.99
2.04
2.04
2.00
1.95
3.00
2.11
2.07
4.07
3.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

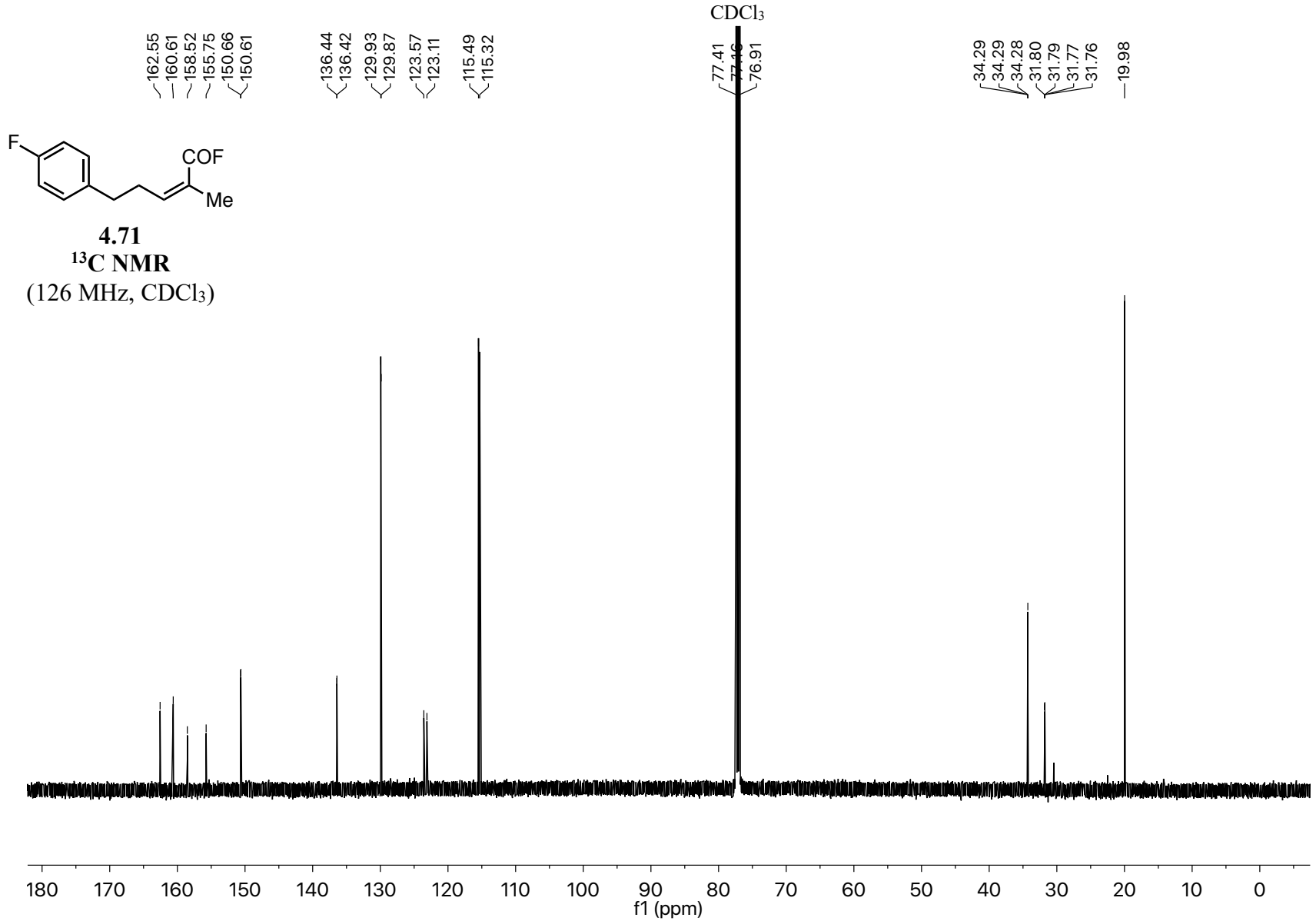

194.57
138.88
138.82
133.99
128.47
127.74
127.60
77.37
77.16
76.95
73.04
68.73
36.93
36.75
29.78
27.23
23.31
20.87
19.55
14.84
Me
COSEt
BnO
Me
4.68
13C NMR
(151 MHz, CDCl3)
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
COF
BnO
Me
4.70
1H NMR
(400 MHz, CDCl3)
CHCl3
f1 (ppm)

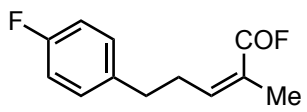

CDCl3
159.08
155.60
152.61
152.56
138.76
128.50
127.77
127.66
122.55
121.98
77.48
77.16
76.84
73.09
68.55
36.70
36.33
29.81
27.79
27.75
20.01
19.46
Me
COF
BnO
Me
4.70
13C NMR
(100 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Me
COF
BnO
Me
4.70
19F NMR
(376 MHz, CDCl3)
37.40
37.37
14.26
major isomer
minor isomer
54 52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4
f1 (ppm)

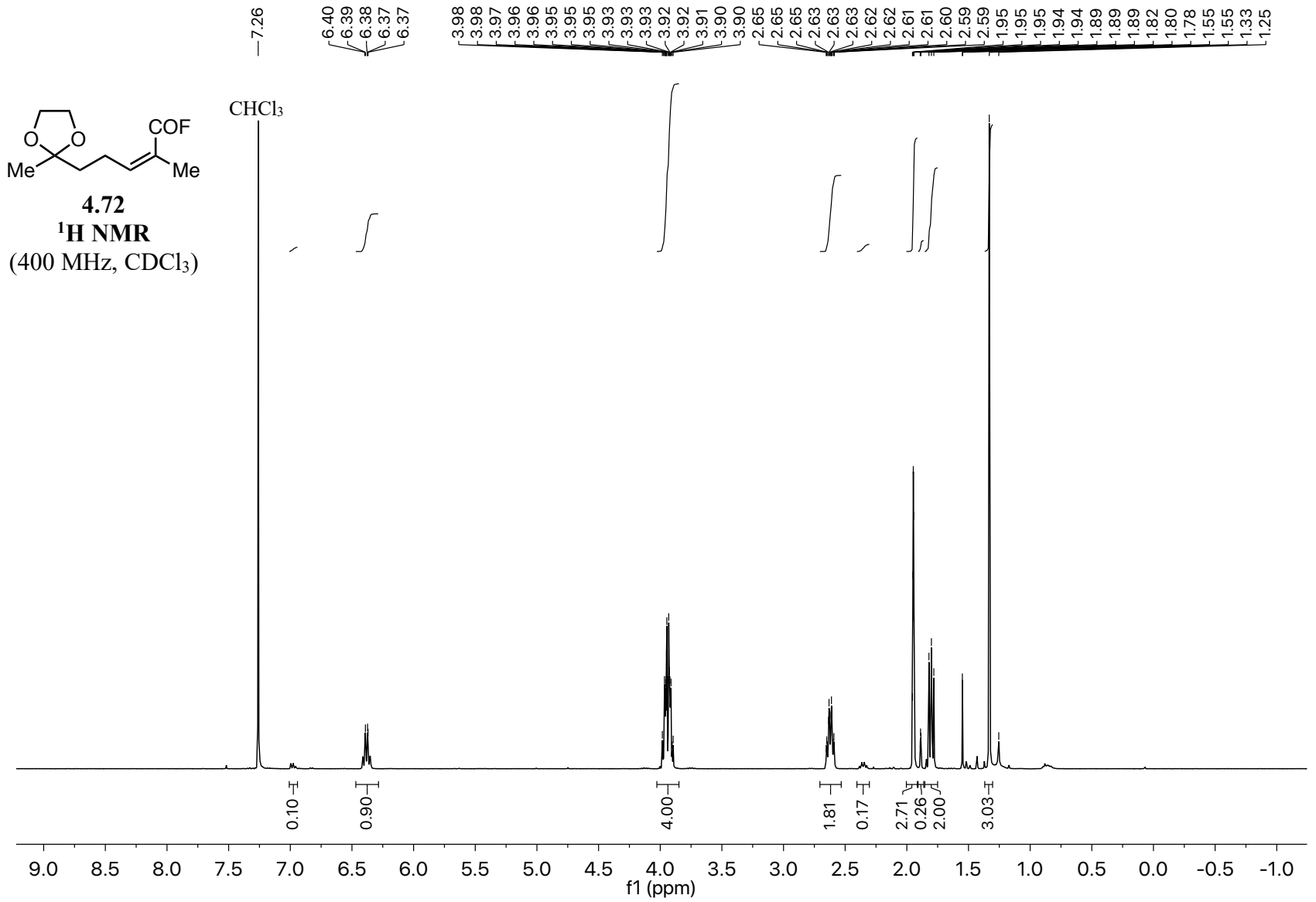

7.26
6.97
6.96
6.96
6.37
6.36
6.36
6.36
6.35
6.35
6.34
6.34
6.33
6.33
6.33
6.32
6.32
6.32
6.31
6.31
2.85
2.84
2.84
2.84
2.83
2.83
2.83
2.82
2.82
2.81
2.81
2.81
2.80
2.80
2.79
2.75
2.73
2.72
2.72
1.55
F
COF
Me
CHCl3
4.71
1H NMR
(500 MHz, CDCl3)
2.05
2.03
1.00
2.16
2.10
3.16
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

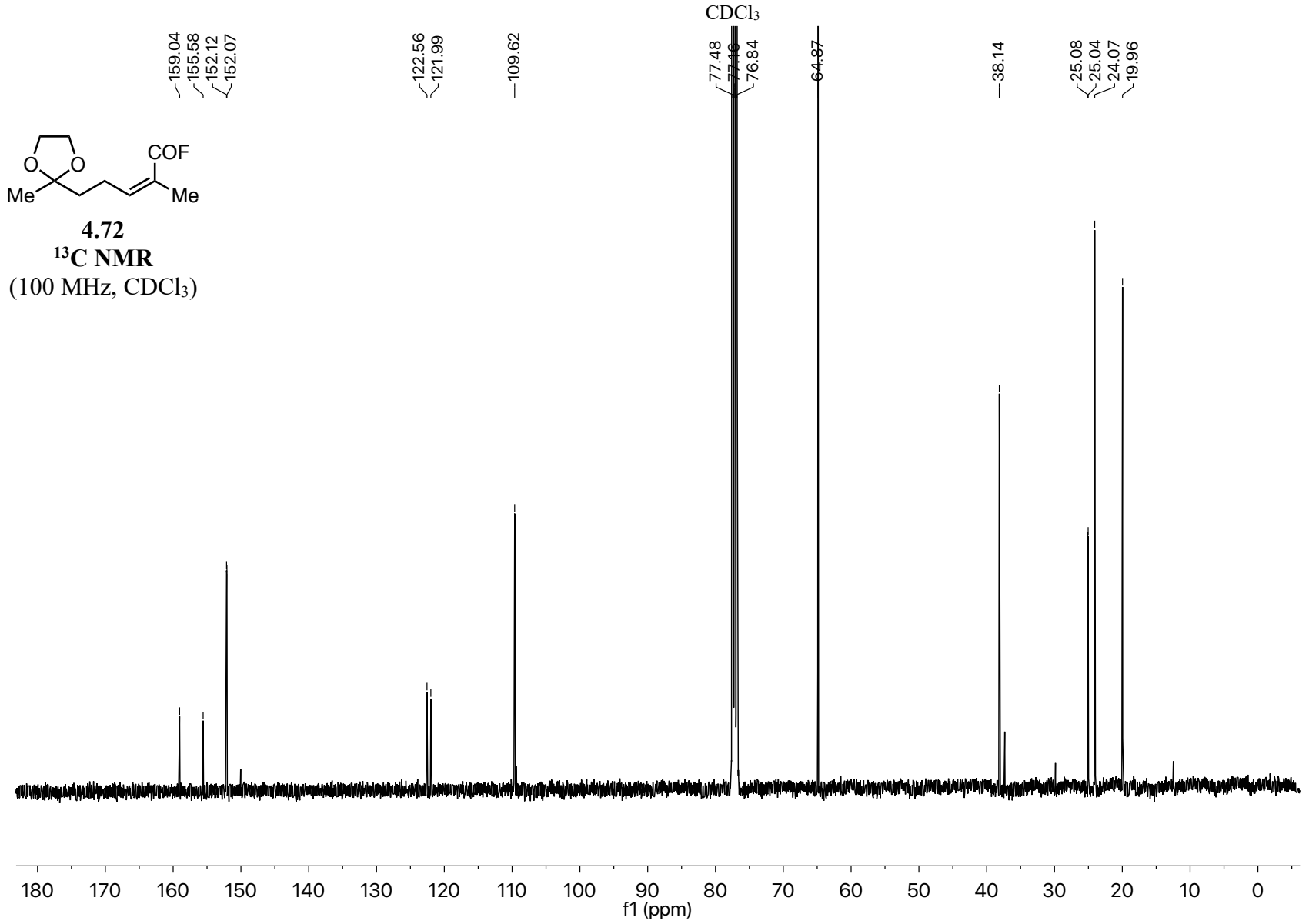


4.71
^{13}C NMR
(126 MHz, $CDCl_3$)

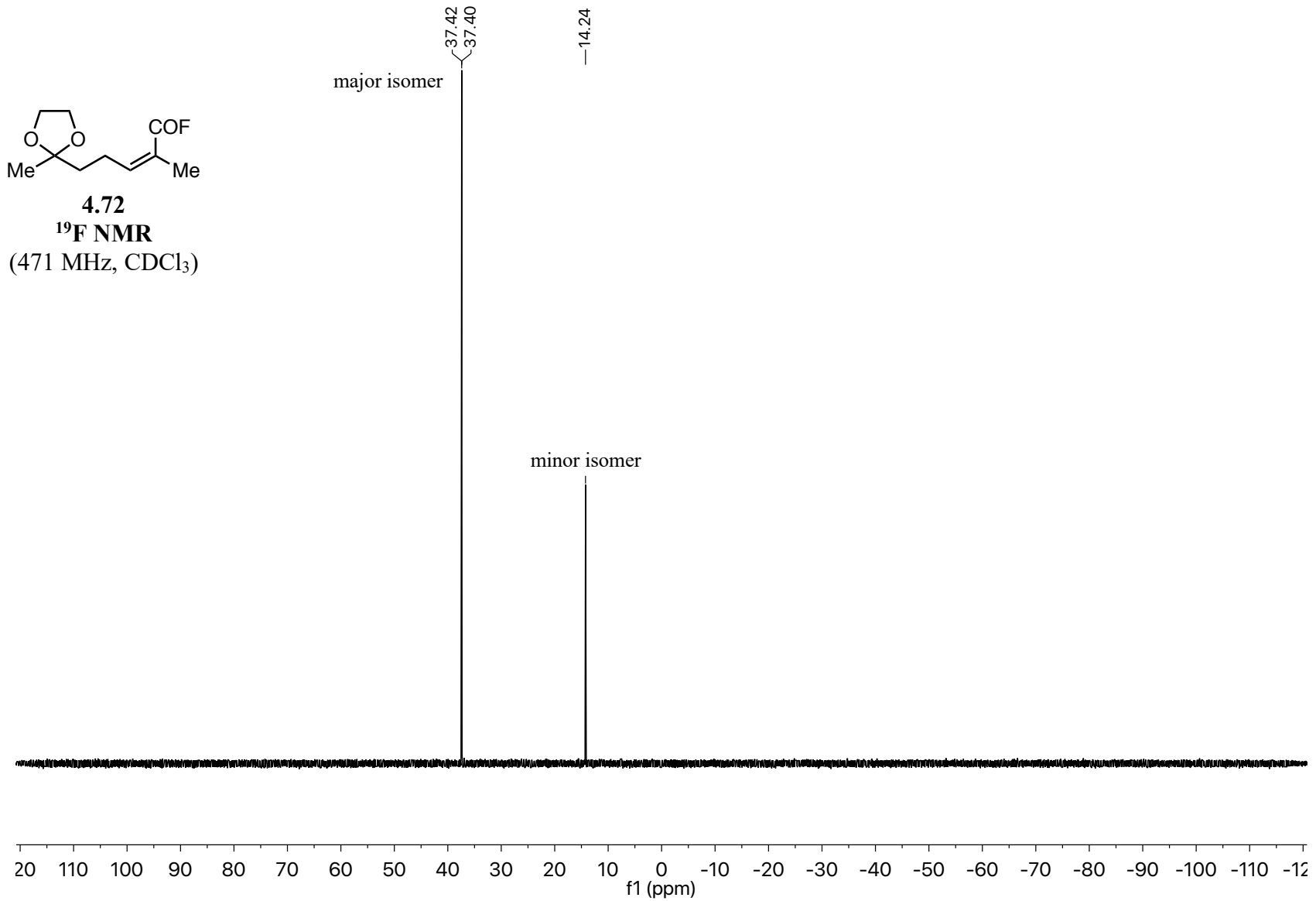


4.71
^{19}F NMR
(471 MHz, $CDCl_3$)

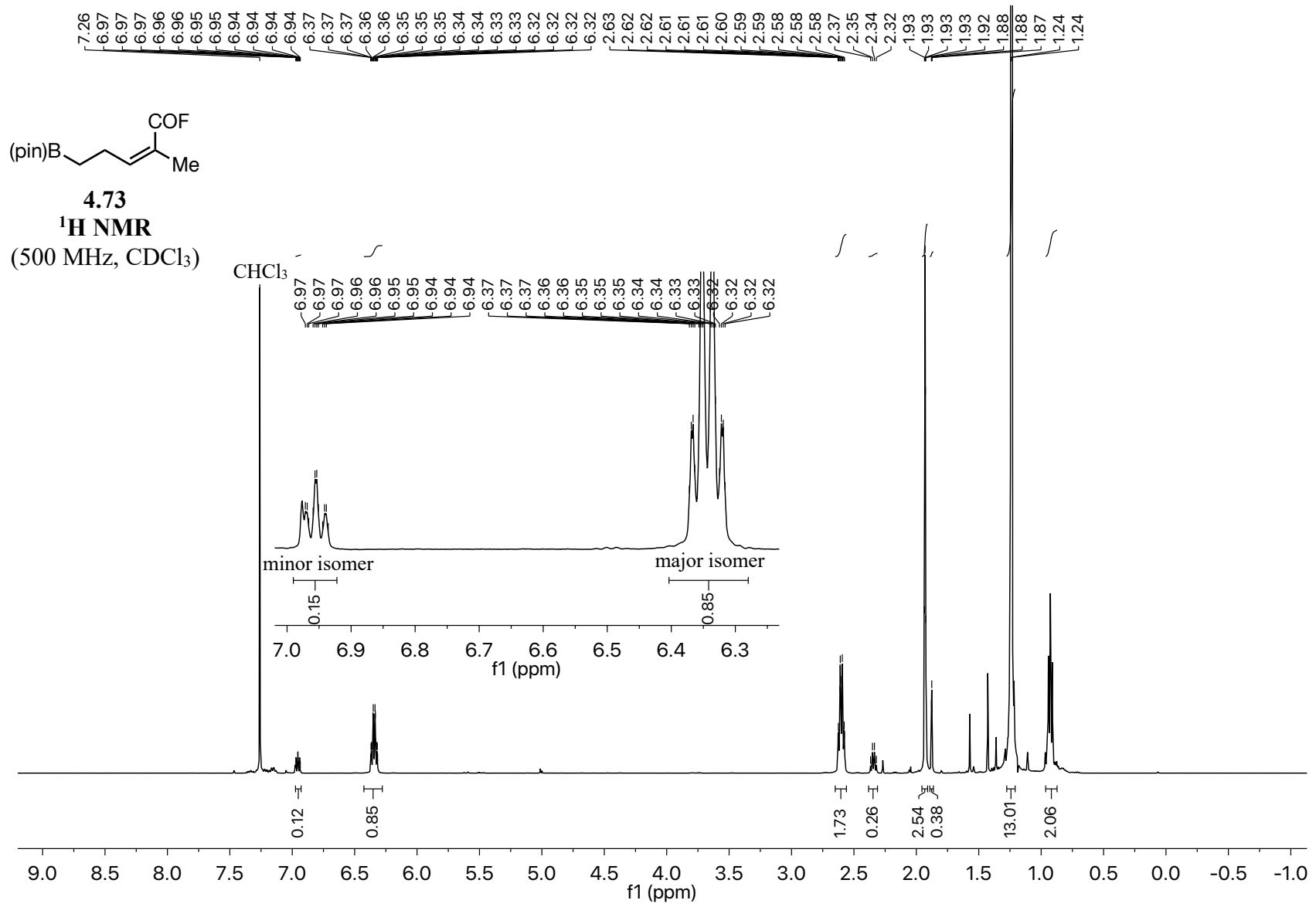

7.26
6.40
6.39
6.38
6.37
6.37
3.98
3.98
3.97
3.96
3.96
3.95
3.95
3.95
3.93
3.93
3.93
3.92
3.92
3.91
3.90
3.90
2.65
2.65
2.65
2.63
2.63
2.63
2.62
2.62
2.61
2.61
2.60
2.59
2.59
1.95
1.95
1.95
1.94
1.94
1.89
1.89
1.89
1.82
1.80
1.78
1.55
1.55
1.33
1.25
CHCl3
O
O
COF
Me
Me
4.72
1H NMR
(400 MHz, CDCl3)
0.10
0.90
4.00
1.81
0.17
2.71
0.26
2.00
3.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

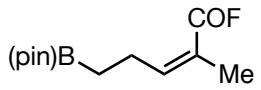


4.72
^{13}C NMR
(100 MHz, $CDCl_3$)

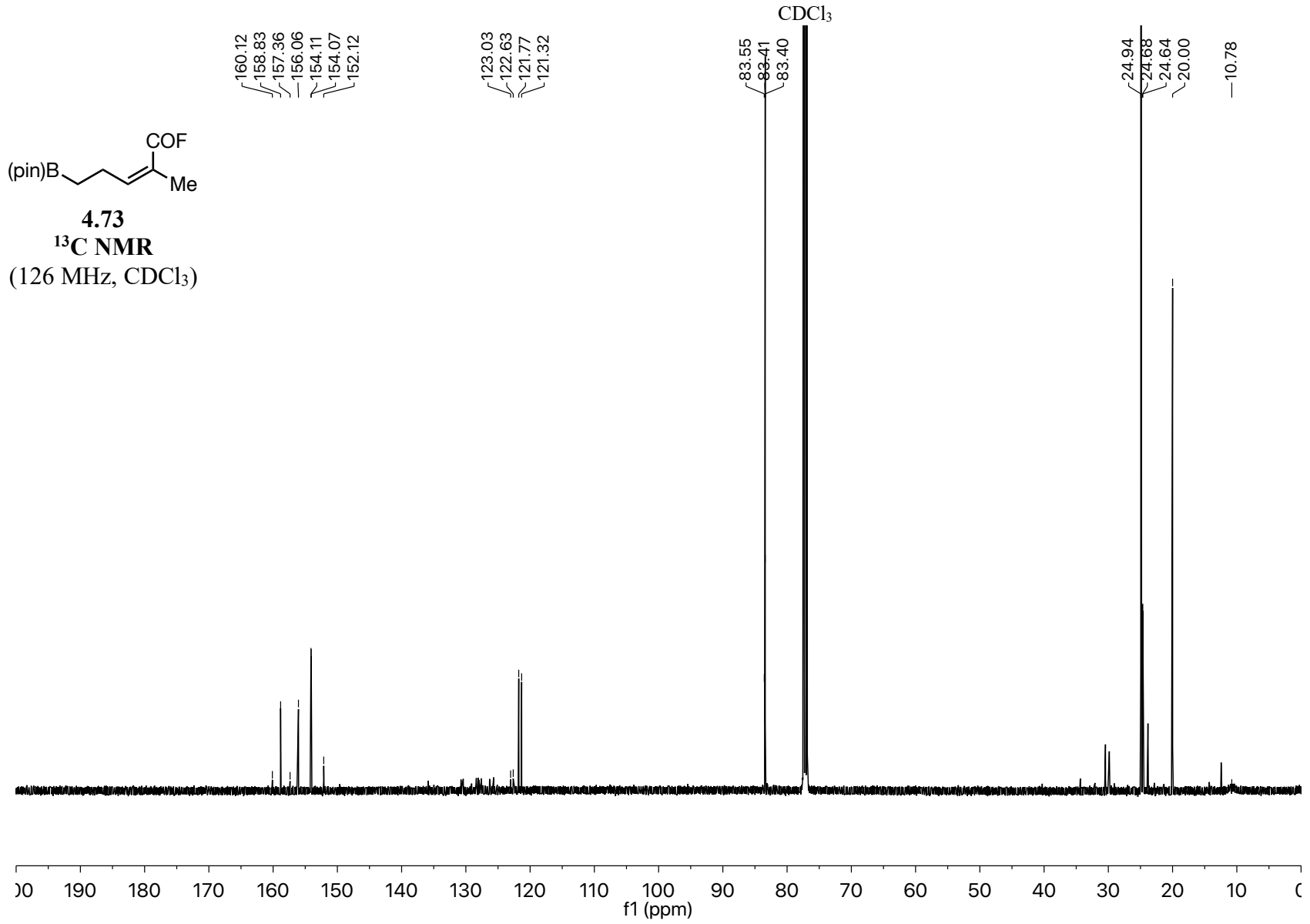


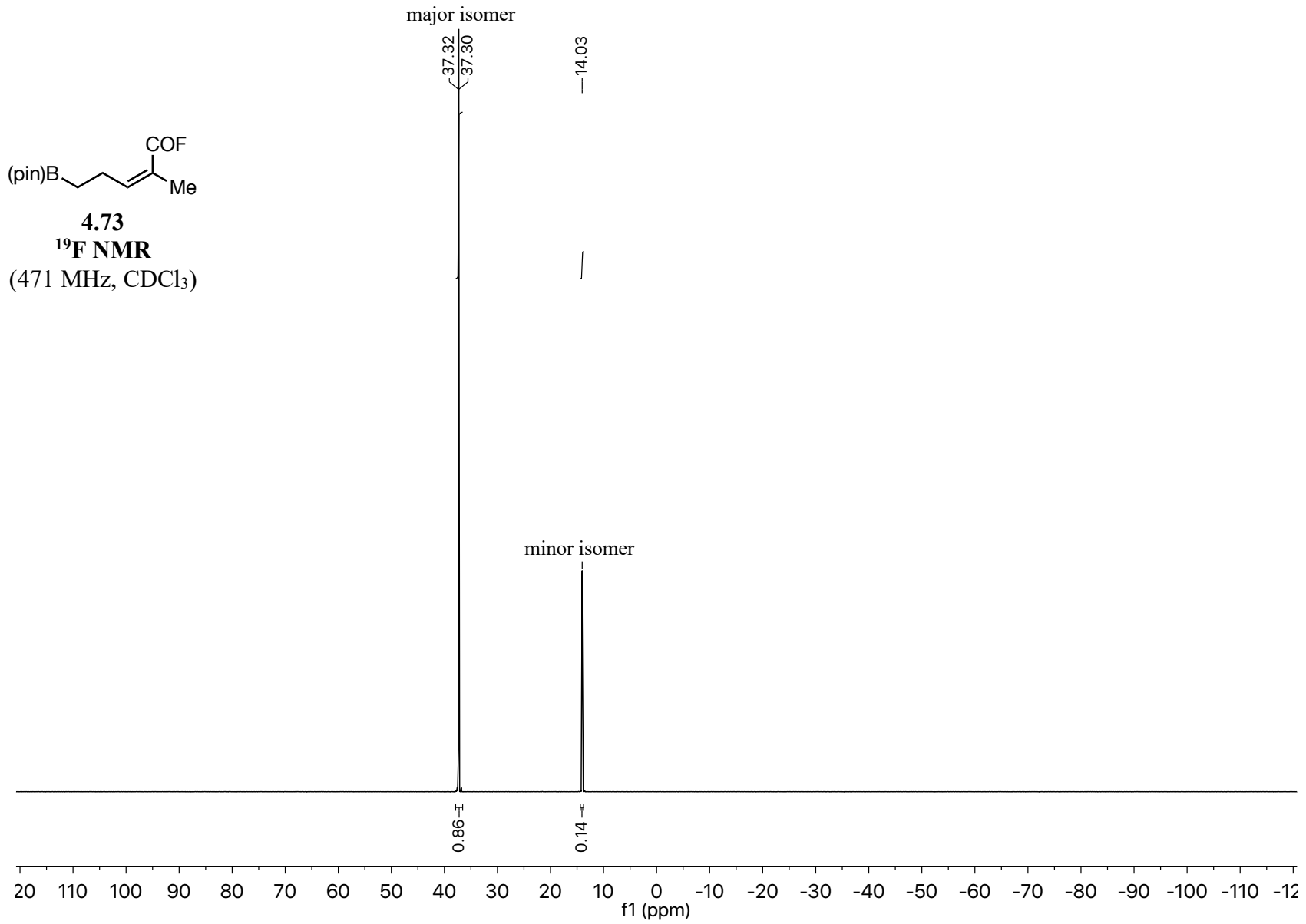
4.72
^{19}F NMR
(471 MHz, $CDCl_3$)


COF
(pin)B
Me
4.73
1H NMR
(500 MHz, CDCl3)
CHCl3
minor isomer
major isomer
0.15
0.85
f1 (ppm)
0.12
0.85
1.73
0.26
2.54
0.38
13.01
2.06
f1 (ppm)



4.73
^{11}B NMR
(160 MHz, $CDCl_3$)


COF
(pin)B
Me
4.73
13C NMR
(126 MHz, CDCl3)
CDCl3
160.12
158.83
157.36
156.06
154.11
154.07
152.12
123.03
122.63
121.77
121.32
83.55
83.41
83.40
24.94
24.68
24.64
20.00
10.78
f1 (ppm)



4.73
^{19}F NMR
(471 MHz, $CDCl_3$)