# New Strategies for the Development of Catalytic Regio- and Enantioselective Allylic Substitution and Conjugate Addition Reactions

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# New Strategies for the Development of Catalytic Regio- and Enantioselective Allylic Substitution and Conjugate Addition Reactions

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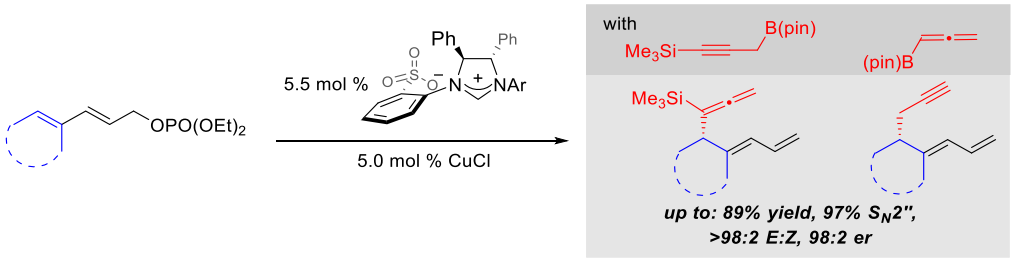
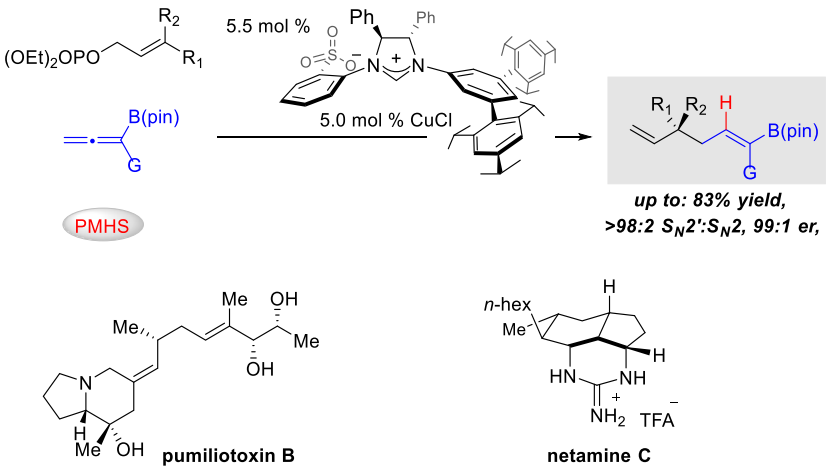
## Abstract

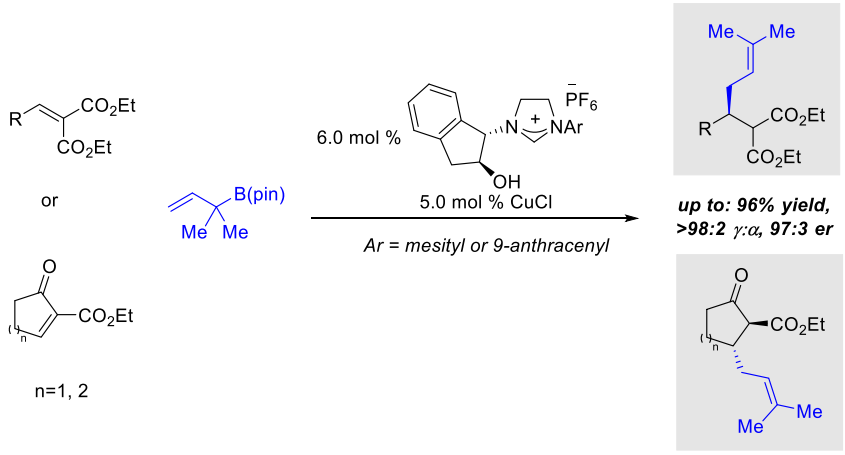
**Chapter 1. Catalytic $S_N2$"-Selective and Enantioselective Substitution Reactions.** The first broadly applicable strategy for $S_N2$"-selective and enantioselective catalytic allylic substitution will be presented. It will be shown that transformations can be promoted by 5.0 mol% of a sulfonate-containing NHC–Cu complex (NHC = N-heterocyclic carbene), and may be carried out by the use of a commercially available allenyl–B(pin) (pin = pinacolato) or a readily accessible silyl protected propargyl–B(pin). Products bearing a 1,3-diene, a silyl allenyl or a propargyl moiety were obtained in high efficiency and selectivities. Also provided is insight regarding several of the unique mechanistic attributes of the catalytic process, obtained on the basis of kinetic isotope effect measurements and DFT studies. These investigations indicated that cationic π-allyl–Cu complexes are the likely intermediates, clarifying the role of the *s-cis* and *s-trans* conformers of the intermediate organocopper species and their impact on *E:Z* selectivity and enantioselectivity. It will also be shown we were able to highlight the utility of the approach by chemoselective functionalization of various product types, through which the propargyl, allenyl, or 1,3-dienyl sites within the products can be converted catalytically and chemoselectively to several synthetically useful derivatives.




**Chapter 2. NHC–Copper–Hydride-Catalyzed Enantioselective Processes with Allenyl Boronates and its Application in Natural Product Synthesis.** Here, the development of a catalytic process that delivers otherwise difficult-to-access organoboron compound will be detailed. These processes involve the combination of a hydride, an allenyl–B(pin) and an allylic phosphate. As will be discussed, two unique selectivity problems were solved: avoiding rapid Cu–H reduction of an allylic phosphate, while promoting its addition to an allenylboronate as opposed to the commonly observed Cu–B exchange. We were able to underscore the considerable utility of the approach by applications to preparation of the linear fragment of pumiliotoxin B (myotonic, cardiotonic) and the first enantioselective synthesis of netamine C (anti-tumor), which also served to confirm its stereochemical identity.



**Chapter 3. Catalytic Enantioselective Prenyl Conjugate Addition Reactions.** In this final section, studies leading to the development of the first class of catalytic enantioselective strategies for prenyl conjugate additions will be detailed. At the core of these investigations was finding ways to overcome two problems. One challenge originated from the fact that highly activated allylmetal species often deliver product with low enantioselectivity. The other was that regioselectivity was difficult to control owing to a strong preference for γ-selective additions. As will be described, we were able to address these difficulties by the use of a hydroxy NHC–copper complex and 3,3-dimethyl allyl–B(pin) as a reagent. In the end, we were able to use acyclic as well as cyclic enoates as substrates. The results of DFT studies that provide insight regarding varying selectivity profiles with different chiral ligands will be discussed as well.



# Table of Contents

# CHAPTER 1

# Catalytic $S_N2$" -Selective and Enantioselective Substitution Reactions

## 1.1 Introduction

Catalytic enantioselective allylic substitution is widely used in organic synthesis for the transformation of an alkenyl substrate to a new unsaturated compound bearing an allylic stereogenic center. The majority of $S_N2$'-selective reactions only allow for the addition of a methyl or a simple alkyl group.[1] Recently, strategies for the incorporation of readily modifiable functional groups such as alkenyl,[2] allyl,[3]

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(1) For reviews regarding catalytic enantioselective allylic substitution (EAS) reactions with "hard" organometallic compounds, see: (a) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun*. **2004**, 1779−1785. (b) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435−4439. (c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824−2852. (d) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796−2823. (e) Baslé, O.; Denicourt-Nowicki, A.; Crévisy, C.; Mauduit, M. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A., Krause, N., Woodward, S., Eds.; Wiley-VCH, 2014; pp 85−125. (f) Calvo, B. C.; Buter, J.; Minnaard, A. J. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A., Krause, N., Woodward, S., Eds.; Wiley−VCH, 2014; pp 373−447.

(2) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446−447. (b) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419−423. (c) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 14315−14320. (d) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed*. **2012**, *51*, 6613−6617. (e) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 2149−2161. (f) Yap, C.; Lenagh-Snow, G. M. J.; Karad, S. N.; Lewis, W.; Diorazio, L. J.; Lam, H. W. *Angew. Chem., Int. Ed*. **2017**, *56*, 8216−8220.

(3) (a) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686−10688. (b) Le, H.; Kyne, R. E.; Brozek, L. A.; Morken, J. P. *Org. Lett.* **2013**, *15*, 1432−1435. (c) Hornillos, V.; Peréz, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2013**, *135*, 2140−2143. (d) Ardolino, M. J.; Morken, J. P. *J.*

alkynyl,[4] or a propargyl[5] moieties have been introduced. However, in cases with an extended π-system, regioselectivity can become an issue. Regioselective addition of a nucleophile to the alkene further from the leaving group is commonly referred to as $S_N2$"-selective substitution.[6] Although the development of enantioselective $S_N2$'-selective allylic substitution has been the subject of countless studies in the past few decades, there are no reported methods for broadly applicable catalytic enantioselective $S_N2$"-selective substitution.

Inspired by a recently developed enantioselective 1,6-conjugate addition method,[7] we envisioned that it might be possible to apply the key event in such transformations, namely, 3,3'-reductive elimination, to allylic substitution to promote $S_N2$" selectivity. We therefore set out to design and develop a catalytic process through which a dienyl phosphate and an allenyl–B(pin) would react in the presence of catalytic amount of copper complex to form **1.1** and subsequent 3,3'-reductive elimination would afford the propargyl $S_N2$"-selective substitution product enantioselectively (Scheme 1.1). The propargyl and the 1,3-dienyl groups would render the expected products of considerable utility especially when containing a stereochemically defined trisubstituted alkene, and orthogonal

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*Am. Chem. Soc.* **2014**, *136*, 7092−7100. (e) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367−374. (f) Yasuda, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 10816−10820.

(4) (a) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778−4781. (b) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694−7699. (c) Harada, A.; Makida, Y.; Sato, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 13932−13939. (d) Cui, X.-Y.; Ge, Y.; Tan, S. M.; Jiang, H.; Tan, D.; Lu, Y.; Lee, R.; Tan, C.-T. *J. Am. Chem. Soc*. **2018**, *140*, 8448−8455.

(5) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948−8964.

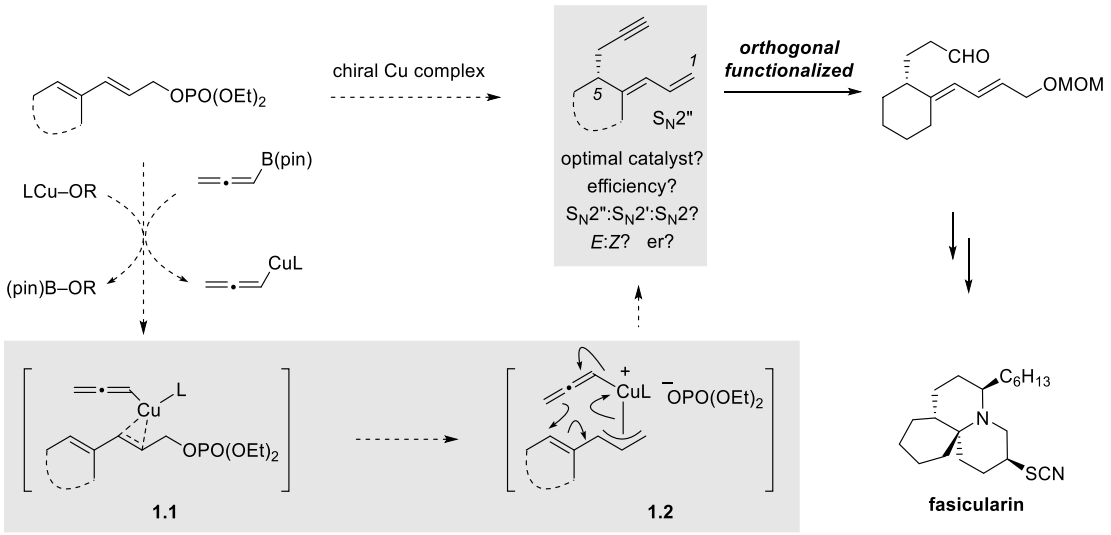
(6) Tissot, M.; Li, H.; Alexakis, A. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A., Krause, N., Woodward, S., Eds.; Wiley−VCH, 2014; pp 69−84.

(7) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. *Nature* **2016**, *537*, 387−393.

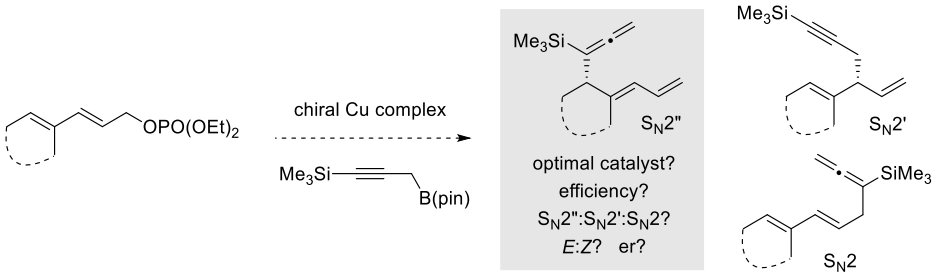
functionalization of either moiety would generate otherwise difficult-to-access and versatile products (Scheme 1.1). For instance, an intermediate used for the total synthesis of natural product fasicularin might then be prepared by utilizing such a strategy. Similarly, use of a readily accessible propargyl boronic ester [8] would furnish the allenyl $S_N2$"-selective substitution product.

***Scheme 1.1.*** Concept and Application of $S_N2$" Allylic Substitution

**a. Addition of a propargyl group through $S_N2$" allylic substitution:**




**b. Addition of a allenyl group through $S_N2$" allylic substitution:**



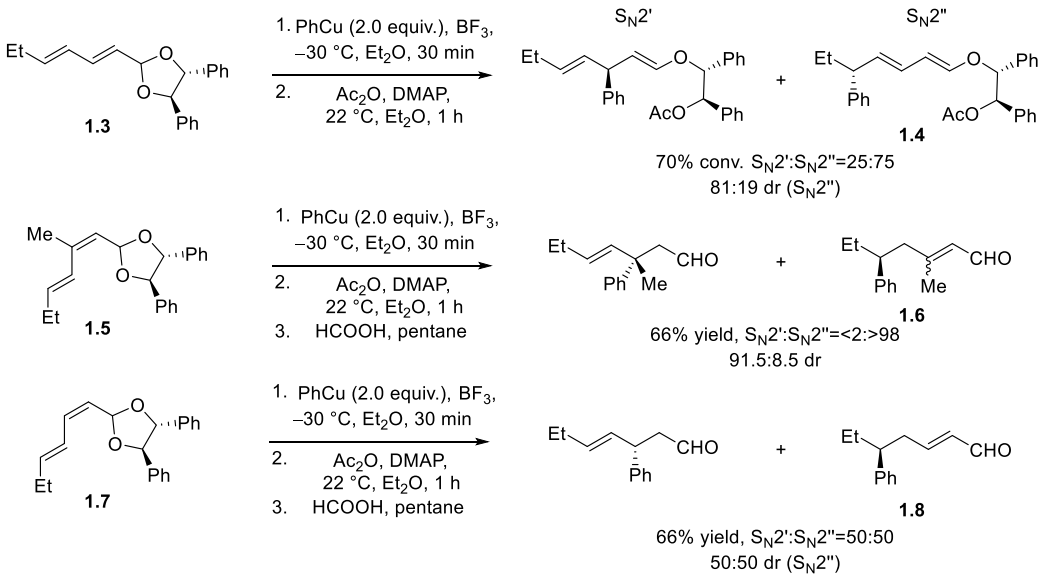

## 1.2 Background

### 1.2.1 Organocopper mediated enantiospecific $S_N2$"-selective substitution reactions

(8) Fandrick, D. R.; Reeves, J. T.; Song J. J. International Patent WO 2010/141328 A2.

Methods for stereoselective $S_N2$”-selective allylic substitution are rare. The first example was reported by Mangeney group in 1996 (Scheme 1.2);[9] a chiral auxiliary was used to induce diastereoselectivity for the addition of PhCu to diene **1.3**, affording **1.4** in 81:19 er. Regio- and enantioselectivity proved to be substrate-dependent. In the case of an *E, Z*-diene with a Me group at the $S_N2$’ addition site (**1.5**), the $S_N2$”-addition product was formed exclusively. In the absence of such a substituent (**1.7**) there was little or no regio- and enantioselectivity.

***Scheme 1.2.*** Diastereoselective $S_N2$"-Selective Substitution Reactions



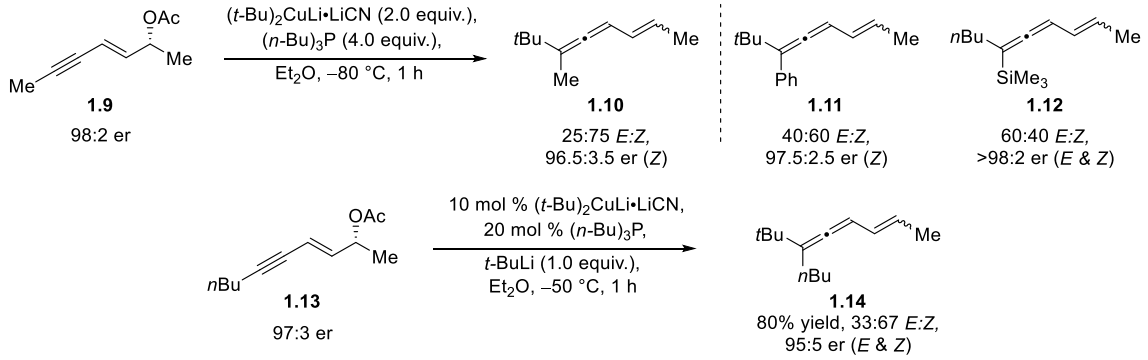

Krause et al. have shown that enantiomerically enriched enynes may be used as substrates for $S_N2$” substitution to generate alkenylallene compounds.[10] Although the stereogenic center is somewhat distal from the site of C–C bond formation, the desired products were obtained in 95:5 to >98:2 er (Scheme 1.3). Alkyl-, aryl-, and silyl-substituted

(9) Rakotoarisoa, H.; Perez, R. H.; Mangeney, P.; Alexakis, A. *Organometallics* **1996**, *15*, 1958–1959.

(10) Krause, N.; Purpura, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4355−4356; for a related example, see: Purpura, M.; Krause, N. *Eur. J. Org. Chem*. **1999**, 267–275.

enynes proved to be suitable substrates, albeit with low *E:Z* ratios. The presence of (*n*--Bu)$_3$P as an additive was found to be central to high enantioselectivity; without which products were formed with considerably lower enantioselectivity (e.g., **1.12** in 64:36 er for the *Z* isomer). A catalytic variant was introduced as well: with 10 mol % *t*-butylcuprate complex and 20 mol % (*n*-Bu)$_3$P, **1.14** was generated in 80% yield and 95:5 er (Scheme 1.3).

***Scheme 1.3.*** Enantiospecific $S_N2$"-Selective Substitution Reactions with Enynes




### 1.2.2 Catalytic $S_N2$"-selective substitutions promoted by Pd-based complexes

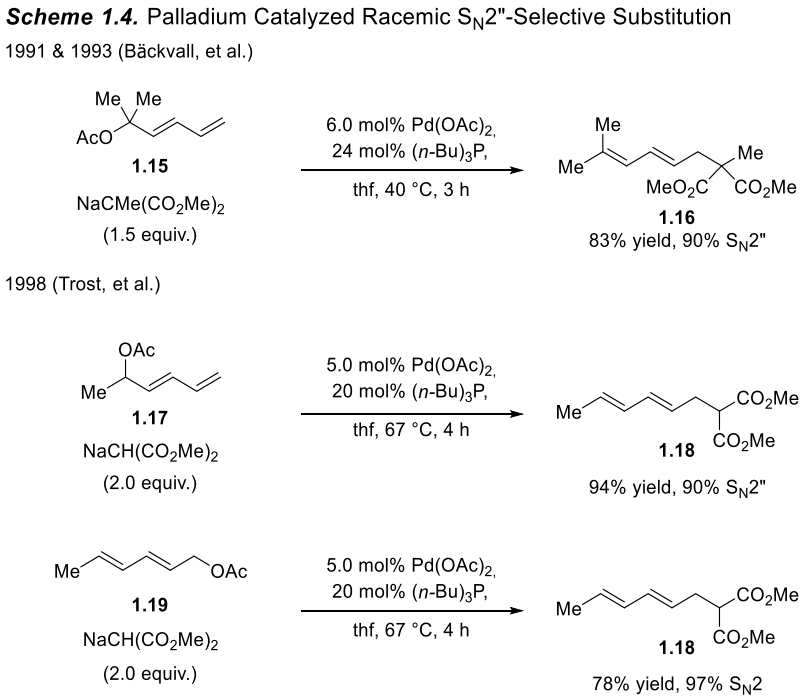
Palladium-based catalysts have been shown to be effective in promoting $S_N2$" substitution. Early examples were disclosed by the Bäckvall[11] and Trost groups,[12] mainly involving non-enantioselective transformations with the regioselectivity being largely a function of substrate substitution pattern. Bond formation took place preferentially at the least substituted position probably due to steric factors (Scheme 1.4). Reaction between dienyl allylic acetate **1.15** and diethyl methylmalonate sodium salt afforded **1.16** in 90% $S_N2$" selectivity; the presence of (*n*-Bu)$_3$P led to an increase in regioselectivity (vs 60%

(11) (a) Andersson, P. G.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 5349–5353. (b) Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc*. **1993**, *115*, 6609–6613.

(12) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc*. **1998**, *120*, 70–79. For a related example, see: Trost, B. M.; Urch, C. J.; Hung, M.-H. *Tetrahedron Lett.* **1986**, *27*, 4949–4952.

$S_N2$" with $PPh_3$ at 20 °C) presumably because its Lewis basicity causes a diminution in the π-allyl–Pd complex's electrophilicity so that this intermediate is converted to the thermodynamically more stable isomer prior to C–C bond formation. The fact that reactions with branched dienyl acetate **1.17** and linear dienyl acetate **1.19** afford the same product, namely, **1.18** ($S_N2$" for **1.17**, $S_N2$ for **1.19**), suggests that the regioselectivity is largely controlled by steric factors.

***Scheme 1.4.*** Palladium Catalyzed Racemic $S_N2$"-Selective Substitution

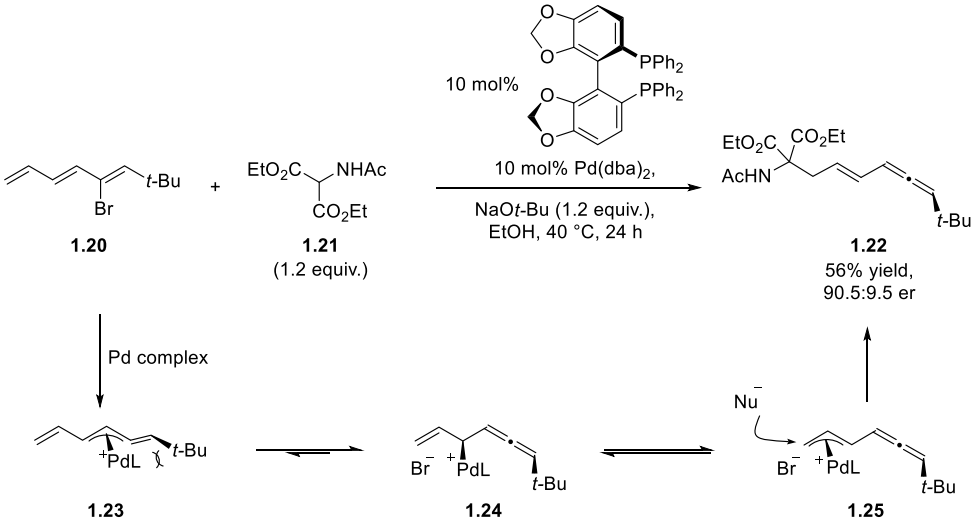



Later in 2006, Ogasawara and Takahashi reported a protocol for $S_N2$" substitution involving a trienylbromide, an aminomalonate and a Pd-based catalyst. Similar to previous cases, bond formation took place at the least hindered carbon, affording the $S_N2$" addition products (Scheme 1.5). A single enantioselective variant was included as well, involving Pd-segphos as the catalyst and affording the alkenylallene **1.22** in 90.5:9.5 er.[13] The

(13) Ogasawara, M.; Fan, L.; Ge, Y.; Takahashi, T. *Org. Lett.* **2006**, *8*, 5409–5412

proposed rationale for the observed regioselectivity is that upon oxidative addition, π-allyl complex **1.23** is generated, in which there is considerable steric pressure between the transition metal complex and *t*-Bu group of the starting material. Thus, it was suggested that **1.23** favors isomerization to **1.24** and then **1.25**, which undergoes nucleophilic addition at the least substituted site to afford **1.22**.

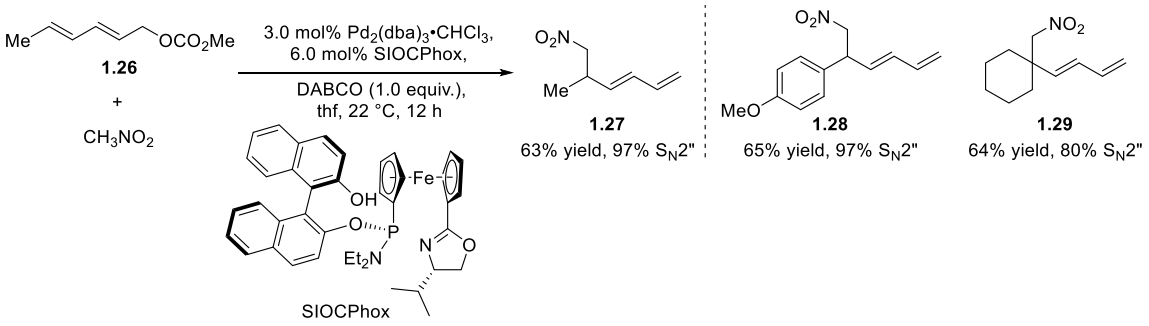
***Scheme 1.5.*** The Only Example of Catalytic Enantioselective $S_N2$"-Selective Substitution




In 2014, Hou and co-workers outlined a more broadly applicable $S_N2$"-selective substitution, albeit one that is non-enantioselective.[14] Nitromethane was used as the nucleophile precursor in these highly regioselective processes. Alkyl- and aryl-substituted dienyl carbonates were shown to be suitable substrates, regardless of the electronic attributes of the aryl substituents (Scheme 1.6). Even in the case where a quaternary carbon is generated, $S_N2$" substitution product was formed with 80% regioselectivity (**1.29**). However, attempts at developing an enantioselective version were unsuccessful.

(14) Yang, X.-F.; Li, X.-H.; Ding, C.-H.; Xu, C.-F.; Dai, L.-X.; Hou X.-L. *Chem. Commun.,* **2014**, *50*, 484–486

***Scheme 1.6.*** $S_N2$"-Selective Substitution with Nitromethane



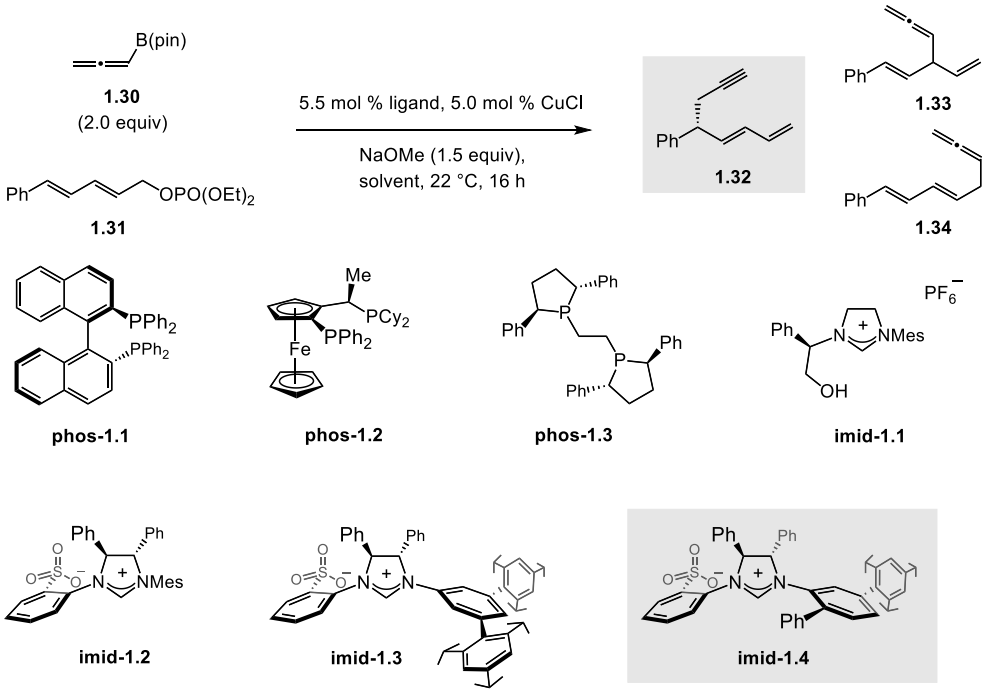

## 1.3 Catalytic $S_N2$"-Selective and Enantioselective Substitutions Involving an Allenyl–B(pin) Compound

As discussed above, in the majority of the existing $S_N2$" substitution methods high regioselectivity is based on steric factors and in only one instance was the product generated with appreciable enantiomeric purity.[13] We reasoned that the development of a broadly applicable method for $S_N2$"-selective substitution would not only be of value in chemical synthesis, it would pose a previously unexplored strategy, namely, a 3,3'-reductive elimination event. This crucial step would be dissimilar to 1,6-conjugate addition[7] in that C–C bond formation would be occurring within an intermediate that no longer carries an electron-withdrawing moiety. As a consequence, one would have to contend with a conformationally more flexible and electronically less activated π system. Such flexibility means that an *s-cis* or an *s-trans* conformer might be involved in the transformation, posing key questions regarding their relative rates of interconversion and reaction, factors that impact *E:Z* selectivity and enantioselectivity.

### 1.3.1 Identification of an effective catalyst

To explore feasibility, we chose to examine the reaction of allenyl–B(pin) **1.30** with dienyl phosphate **1.31** in the presence of 5.5 mol % of a ligand and 5.0 mol % CuCl in thf at 22 °C (Table 1.1). Without a ligand (entry 1), the reaction was efficient and highly $S_N2$"-

***Table 1.1.*** Examination of Different Types of Cu-based Complexes[a]




| entry | ligand | solvent | conv (%)[b] | $S_N2$":$S_N2$':$S_N2$ (**1.32**:**1.33**:**1.34**)[b] | *E*:*Z* (**1.32**)[b] | yield (**1.32**,%)[c] | er[d] |
|---|---|---|---|---|---|---|---|
| 1 | – | thf | >95 | 95:<2:5 | 81:19 | 71 | – |
| 2 | **phos-1.1** | thf | 87 | 88:<2:12 | 79:21 | 55 | 50:50 |
| 3 | **phos-1.2** | thf | >95 | 92:<2:8 | 81:19 | 65 | 50:50 |
| 4 | **phos-1.3** | thf | 79 | 93:<2:7 | 83:17 | 58 | 50:50 |
| 5 | **imid-1.1** | thf | >95 | 90:<2:10 | 80:20 | 82 | 50:50 |
| 6 | **imid-1.2** | thf | >98 | 80:18:2 | 86:14 | 76 | 39:61 |
| 7 | **imid-1.3** | thf | >95 | 86:10:4 | 93:7 | 69 | 85:15 |
| 8 | **imid-1.4** | thf | >95 | 74:19:7 | 85:15 | 72 | 73:27 |
| 9 | **imid-1.3** | $CH_2Cl_2$ | >98 | 93:4:3 | 95:5 | 75 | 85:15 |
| 10 | **imid-1.4** | $CH_2Cl_2$ | >98 | 88:7:5 | 90:10 | 75 | 90:10 |

[a]Performed under $N_2$ atm. [b]Conversion and $S_N2$":$S_N2$':$S_N2$ ratios were determined by analysis of $^1$H NMR spectra of unpurified mixtures; conv (±2%) refers to disappearance of the **1.31**. [c]Yields are for isolated and purified **1.32** (*E* and *Z* isomers; ±5%). [d]Enantioselectivity was determined by HPLC analysis (±1%).

selective, affording $S_N2$" product **1.32** in 71% yield and 95% regioselectivity, but the *E:Z* ratio was only 81:19.

Next, we examined a number of different chiral bisphosphine ligands. The transformation carried out with **phos-1.1**, **phos-1.2** and **phos-1.3** were similarly efficient and regioselective (88–93% $S_N2$") as when there was no ligand present, and the product was generated in up to 83:17 *E:Z* ratio and in the racemic form (entry 2–4).

Imidazolinium salts were then tested, and to our surprise, the reaction with **imid-1.1**, optimal for enantioselective 1,6-conjugate additions with the same allenyl–B(pin) compound,[7] afforded **1.32** in 80:20 *E:Z* selectivity and in the racemic form (entry 5). A minor degree of enantioselectivity was detected only when sulfonate-containing imidazolinium salt **imid-1.2** was employed (39:61 er, entry 6). Furthermore, an improvement in *E:Z* ratio (86:14) was observed, which came at the expense of regioselectivity (80% $S_N2$"). A sulfonate-containing imidazolinium salt (**imid-1.3**) bearing a 3,5-disubsituted N-aryl unit, proven to be optimal in a number of previous studies,[4,5,15] was then investigated (entry 7), leading to observed modest increase in $S_N2$" selectivity, along with significant increase in *E:Z* selectivity (93:7) and enantioselectivity (85:15 er). When **imid-1.4**, which contains a 2,5-disubstituted N-aryl moiety, was used, all selectivity profiles suffered (74% $S_N2$", 85:15 *E:Z* and 73:27 er). Due to the promising results obtained with **imid-1.3** and **imid-1.4**, we evaluated their performance in a less polar and

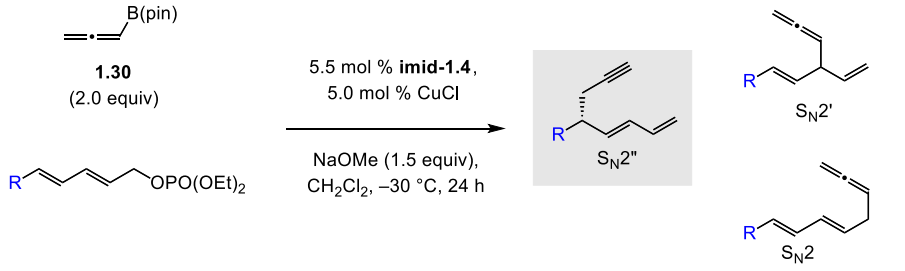
(15) (a) Shi, Y.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 3455−3458. (b) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 2149−2161. (c) Xu, G.; Zhao, H.; Fu, B.; Cang, A.; Zhang, G.; Zhang, Q.; Xiong, T.; Zhang, Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 13130−13134. (d) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H. *Nat. Chem.* **2017**, *9*, 1269−1275.

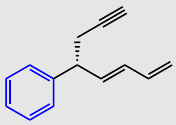
non-coordinating solvent ($CH_2Cl_2$, entries 9–10). Accordingly, we discovered that **imid-1.4** is the most selective and efficient chiral ligand (88% $S_N2$", 90:10 *E:Z*, 90:10 er).

### 1.3.2 Further optimization and exploration of the method's scope

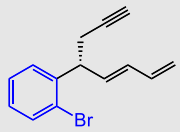
We were able to improve selectivity by decreasing the reaction temperature to –30 °C. Under these conditions, **1.32** was isolated in 71% yield, 96% $S_N2$" selectivity, 92:8 er, and 94:6 *E:Z* selectivity (Scheme 1.7). Transformation with dienyl phosphates bearing an *ortho*-, a *meta*-, or a *para*-substituted aryl halide delivered the desired products in ≥90%

***Scheme 1.7.*** $S_N2$"-Selective and Enantioselective Substitutions with Dialkenyl Phosphates that contain Only Disubstituted Alkenes[a]

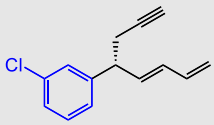


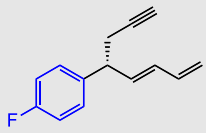
**1.32**
92% conv,
$S_N2$":$S_N2$':$S_N2$ = 96:4:<2,
71% yield ($S_N2$"),
94:6 *E*:*Z*, 92:8 er



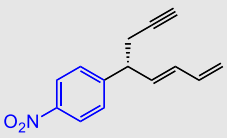

**1.35**
84% conv,
$S_N2$":$S_N2$':$S_N2$ = 94:6:<2,
73% yield ($S_N2$"),
91:9 *E*:*Z*, 89:11 er



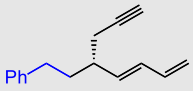

**1.36**
90% conv,
$S_N2$":$S_N2$':$S_N2$ = 94:4:2,
76% yield ($S_N2$"),
92:8 *E*:*Z*, 89:11 er




**1.37**
80% conv,
$S_N2$":$S_N2$':$S_N2$= 90:6:4,
69% yield ($S_N2$"),
92:8 *E*:*Z*, 91:9 er




**1.38**[b]
83% conv,
$S_N2$":$S_N2$':$S_N2$= 86:8:6,
54% yield ($S_N2$"),
93:7 *E*:*Z*, 91:9 er



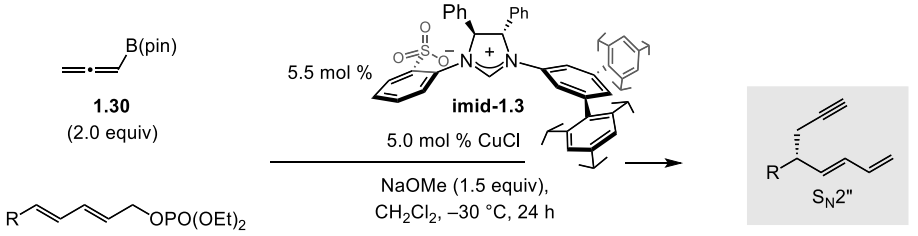

**1.39**
78% conv,
$S_N2$":$S_N2$':$S_N2$ = 96:<2:4,
51% yield ($S_N2$"),
94:6 *E*:*Z*, 86:14 er

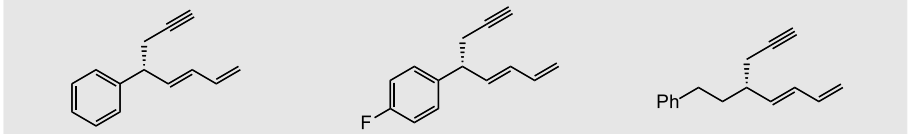
[a]Reactions were carried out under $N_2$ atm. Conversion was determined by analysis of $^1$H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%) and correspond to *E* and *Z* olefin mixtures. Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more. [b]Performed with 7.5 mol % **imid-1.4** and 7.5 mol% CuCl.

$S_N2$" selectivity and 89:11–91:9 er (**1.35–1.36**). Particularly noteworthy is that reaction with a dienyl phosphate containing a sizeable *ortho*-bromo-substituted aryl moiety afforded **1.35** with 94% regioselectivity. *para*-Nitro-substituted aryl dienyl phosphate underwent $S_N2$" substitution to generate **1.38** with comparable efficiency and selectivity, but required higher catalyst loading (7.5 mol % for >80% conv). The reaction of alkyl-substituted **1.39** was similarly regio- and stereoselective, but efficiency was lower (51% yield) probably owing to diminished substrate electrophilicity.

In most instances where a comparative experiment was carried out with **imid-1.3**, the reactions were less enantioselective; however, yield, *E:Z* selectivity and regioselectivity were at times higher (e.g., **1.32** was generated in 82% yield, 97:3 *E:Z*, >98% $S_N2$" selectivity and 89:11 er with **imid-1.3** vs 71% yield, 94:6 *E:Z*, 96% $S_N2$" selectivity and 92:8 er with **imid-1.4**; Scheme 1.8).

***Scheme 1.8.*** $S_N2$"-Selective and Enantioselective Substitutions Promoted by **imid-1.3**[a]



**1.32**
>95% conv,
$S_N2$":$S_N2$':$S_N2$ = >98:<2:<2,
82% yield ($S_N2$"),
97:3 *E*:*Z*, 89:11 er




**1.37**
89% conv,
$S_N2$":$S_N2$':$S_N2$ = 98:2:<2,
81% yield ($S_N2$"),
95:5 *E*:*Z*, 89:11 er




**1.39**
79% conv,
$S_N2$":$S_N2$':$S_N2$ = 95:5:<2,
50% yield ($S_N2$")
95:5 *E*:*Z*, 80:20 er

[a]Reactions were carried out under $N_2$ atm. Conversion was determined by analysis of $^1$H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%) and correspond to *E* and *Z* olefin mixtures. Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more.

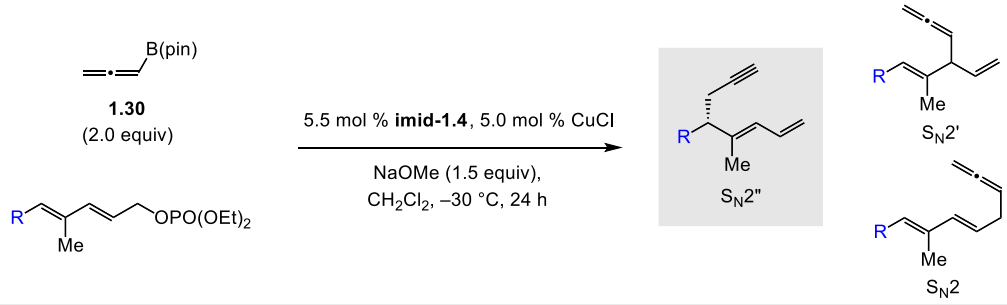
While the reactions were highly $S_N2$”-selective and *E:Z* ratios were >90:10, enantioselectivities were moderate (86:14 er) for the alkyl-substituted case that was studied. This led us to investigate the processes where C–C bond formation takes place at a trisubstituted olefin. We reasoned that the additional substituent could increase the energy difference between the competing transition states and improve enantioselectivity. Moreover, the products would contain a stereochemically defined trisubstituted olefin, a moiety difficult to access by alternative catalytic methods and applicable to synthesis of an intermediate en route to natural product fasicularin.[16,17]

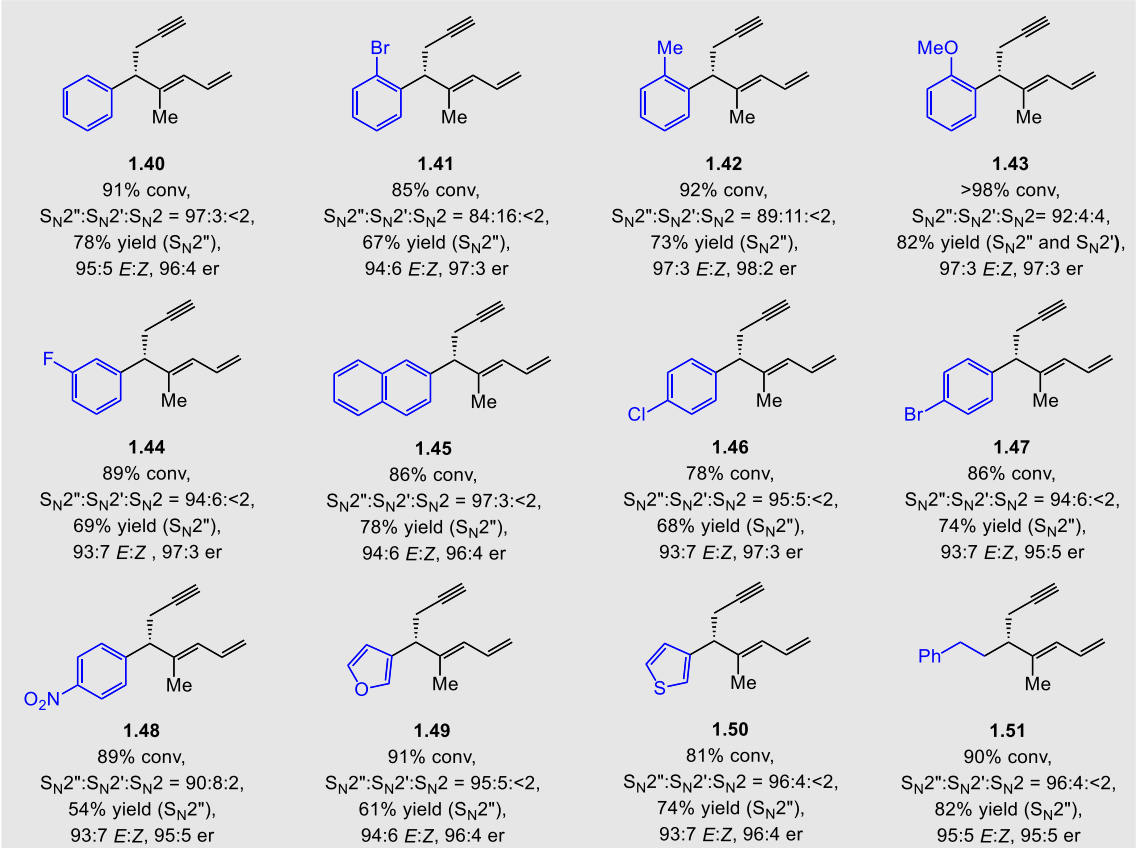
Reactions with the more substituted dienyl phosphates were effective and proceeded from 78% to >98% conversion under the same conditions previously used. As before, $S_N2$” selectivity was high (84–97%, Scheme 1.9). Furthermore, the $S_N2$” products were isolated in higher *E* selectivity (93:7–97:3 vs 91:9–94:6 in Scheme 1.7) and er (95:5–98:2 vs 86:14–92:8 in Scheme 1.7). An assortment of aryl-substituted dienyl phosphates, regardless of the position and electronic attributes of their substituents, heteroaryl containing substrates, reacted efficiently and selectively (**1.40–1.50**, Scheme 1.9). Aliphatic dienyl phosphate, which gave **1.39** in 51% yield and 86:14 er previously, were converted to **1.51** in 82% yield and 95:5 er.

(16) For reviews on stereoselective synthesis of trisubstituted alkenes, see: (a) Negishi, E.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, *Acc. Chem. Res*. **2008**, *41*, 1474−1485. (b) Siau, W.-Y.; Zhang, Y.; Zhao, Y. *Top. Curr. Chem*. **2012**, *327*, 33−58.

(17) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592.

***Scheme 1.9.*** $S_N2$"- and Enantioselective Substitutions with Dialkenyl Phosphates that Contain a Trisubstituted Alkene[a]




**1.40**
91% conv,
$S_N2$":$S_N2$':$S_N2$ = 97:3:<2,
78% yield ($S_N2$"),
95:5 *E*:*Z*, 96:4 er

**1.41**
85% conv,
$S_N2$":$S_N2$':$S_N2$ = 84:16:<2,
67% yield ($S_N2$"),
94:6 *E*:*Z*, 97:3 er

**1.42**
92% conv,
$S_N2$":$S_N2$':$S_N2$ = 89:11:<2,
73% yield ($S_N2$"),
97:3 *E*:*Z*, 98:2 er

**1.43**
>98% conv,
$S_N2$":$S_N2$':$S_N2$= 92:4:4,
82% yield ($S_N2$" and $S_N2$'),
97:3 *E*:*Z*, 97:3 er

**1.44**
89% conv,
$S_N2$":$S_N2$':$S_N2$ = 94:6:<2,
69% yield ($S_N2$"),
93:7 *E*:*Z* , 97:3 er

**1.45**
86% conv,
$S_N2$":$S_N2$':$S_N2$ = 97:3:<2,
78% yield ($S_N2$"),
94:6 *E*:*Z*, 96:4 er

**1.46**
78% conv,
$S_N2$":$S_N2$':$S_N2$ = 95:5:<2,
68% yield ($S_N2$"),
93:7 *E*:*Z*, 97:3 er

**1.47**
86% conv,
$S_N2$":$S_N2$':$S_N2$ = 94:6:<2,
74% yield ($S_N2$"),
93:7 *E*:*Z*, 95:5 er

**1.48**
89% conv,
$S_N2$":$S_N2$':$S_N2$ = 90:8:2,
54% yield ($S_N2$"),
93:7 *E*:*Z*, 95:5 er

**1.49**
91% conv,
$S_N2$":$S_N2$':$S_N2$ = 95:5:<2,
61% yield ($S_N2$"),
94:6 *E*:*Z*, 96:4 er

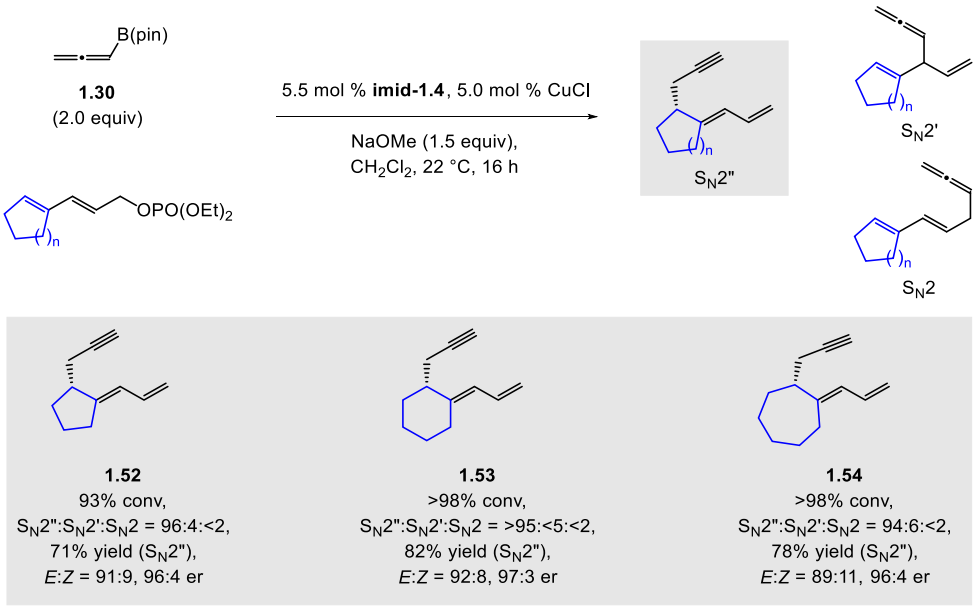
**1.50**
81% conv,
$S_N2$":$S_N2$':$S_N2$ = 96:4:<2,
74% yield ($S_N2$"),
93:7 *E*:*Z*, 96:4 er

**1.51**
90% conv,
$S_N2$":$S_N2$':$S_N2$ = 96:4:<2,
82% yield ($S_N2$"),
95:5 *E*:*Z*, 95:5 er

[a]Reactions were carried out under $N_2$ atm. Conversion was determined by analysis of $^1$H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicateor more.

Cyclic dienyl phosphates were suitable substrates (Scheme 1.10). Products containing an exocyclic trisubstituted alkene were obtained in 71–82% yield and in 96:4–97:3 er. Nonetheless, *E* selectivity was slightly lower (89:11–92:8 *E*:*Z*), which could be improved by decreasing the reaction temperature, albeit with a lower yield (at –30 °C for 24 h: **1.53** in 61% yield, >95:<5:<2 $S_N2$":$S_N2$':$S_N2$ selectivity, 94:6 *E*:*Z*, and 98:2 er).

***Scheme 1.10.*** $S_N2$"-Selective and Enantioselective Substitutions with Allenyl–B(pin) and Involving Cyclic Substrate[a]s

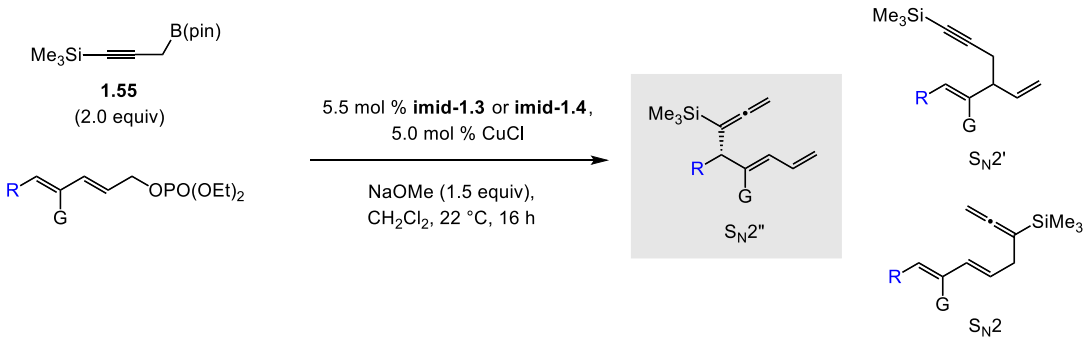



[a]Reactions were carried out under $N_2$ atm. Conversion was determined by analysis of $^1$H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicateor more.

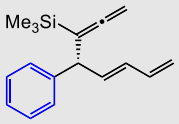
## 1.4 Catalytic $S_N2''$-Selective and Enantioselective Substitutions with a Propargyl–B(pin) Reagent

Similar to propargyl groups, allenyl groups may be easily modified, and the corresponding $S_N2$"-selective processes would generate compounds that would be of notable utility in chemical synthesis. In this set of reactions, a propargyl–Cu species must be generated to engage in 3,3'-reductive elimination. Through the use of silyl-substituted propargyl boronate compound **1.55**, $S_N2$"-selective substitution proceeded to >98% conversion, affording the desired products in high er and with exceptional *E:Z* selectivity

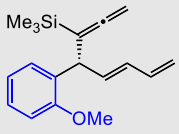
***Scheme 1.11.*** $S_N2$"-Selective and Enantioselective Substitution Leading to Transfer of a Silyl-Substituted Allenyl Moiety[a]



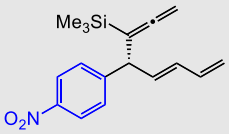

**a. Products bearing a 1,3-diene with a 1,2-disubstituted alkene:**



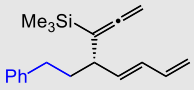

**1.56**
(wth **imid-1.4**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 82:14:4,
74% yield ($S_N2$"+$S_N2$),
>98:2 *E*:*Z*, 95:5 er




**1.57**
(with **imid-1.4**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 82:14:4,
76% yield ($S_N2$"),
98:2 *E*:*Z*, 97:3 er

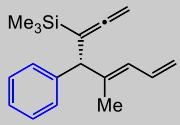



**1.58**
(with **imid-1.4**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 69:19:12,
53% yield ($S_N2$"),
>98:2 *E*:*Z*, 94:6 er

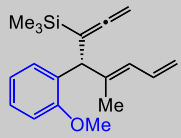



**1.59**
(with **imid-1.4**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 81:17:2,
74% yield ($S_N2$"+$S_N2$),
>98:2 *E*:*Z*, 96:4 er

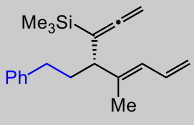
**b. Products bearing a 1,3-diene with a trisubstituted alkene:**



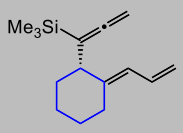

**1.60**
(with **imid-1.3**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 94:6:<2,
87% yield ($S_N2$"),
>98:2 *E*:*Z*, 95:5 er




**1.61**
(with **imid-1.3**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 91:5:4,
54% yield ($S_N2$"),
>98:2 *E*:*Z*, 95:5 er

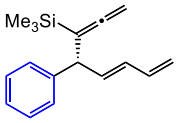



**1.62**
(with **imid-1.4**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 81:17:2,
80% yield ($S_N2$"+$S_N2$),
>98:2 *E*:*Z*, 96:4 er

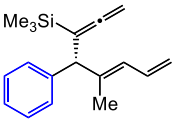



**1.63**
(with **imid-1.4**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 96:4:<2,
89% yield ($S_N2$"),
>98:2 *E*:*Z*, 98:2 er

**c. The impact of catalyst structure on selectivity:**




**1.56**
(with **imid-1.3**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 94:4:2,
92% yield ($S_N2$"+$S_N2$),
>98:2 *E*:*Z*, 87:13 er




**1.60**
(with **imid-1.4**):
>98% conv,
$S_N2$":$S_N2$':$S_N2$ = 83:13:4,
78% yield ($S_N2$"+$S_N2$),
>98:2 *E*:*Z*, 97:3 er

[a]Reactions were carried out under $N_2$ atm. Conversion was determined by analysis of $^1$H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more.

(Scheme 1.11). The lower observed $S_N2$" ratios likely arise from steric repulsion between the trimethylsilyl and dienyl phosphate groups. As before, a variety of aryl-, alkyl- and

cyclic dienyl phopshates react to deliver the desired products in high efficiency and stereoselectivity (Scheme 1.11). Compared to reactions with allenyl–B(pin) (Scheme 1.7–1.10), substrates that contain only disubstituted alkenes were more enantioselective. Transformation with **imid-1.3** afforded product in higher $S_N2$" selectivity but enantioselectivity was lower. For example, **1.56** was generated with 94% $S_N2$" selectivity and in 87:13 er when **imid-1.3** was used (vs 82% $S_N2$" and 95:5 er with **imid-1.4**; the reaction with **1.55** did not proceed at −30 °C). In cases where yield is more critical than enantiomeric purity, **imid-1.3** is a more effective catalyst precursor. Such ligand effect is more straightforward with substrates containing a trisubstituted olefin. As indicated in Scheme 1.11c, **1.60** was isolated in similar er for reactions promoted by **imid-1.3** and **imid-1.4** (95:5 vs 97:3 er, respectively), but the $S_N2$" selectivity was significantly higher in the former case (94% vs 83%).

## 1.5 Mechanistic Studies

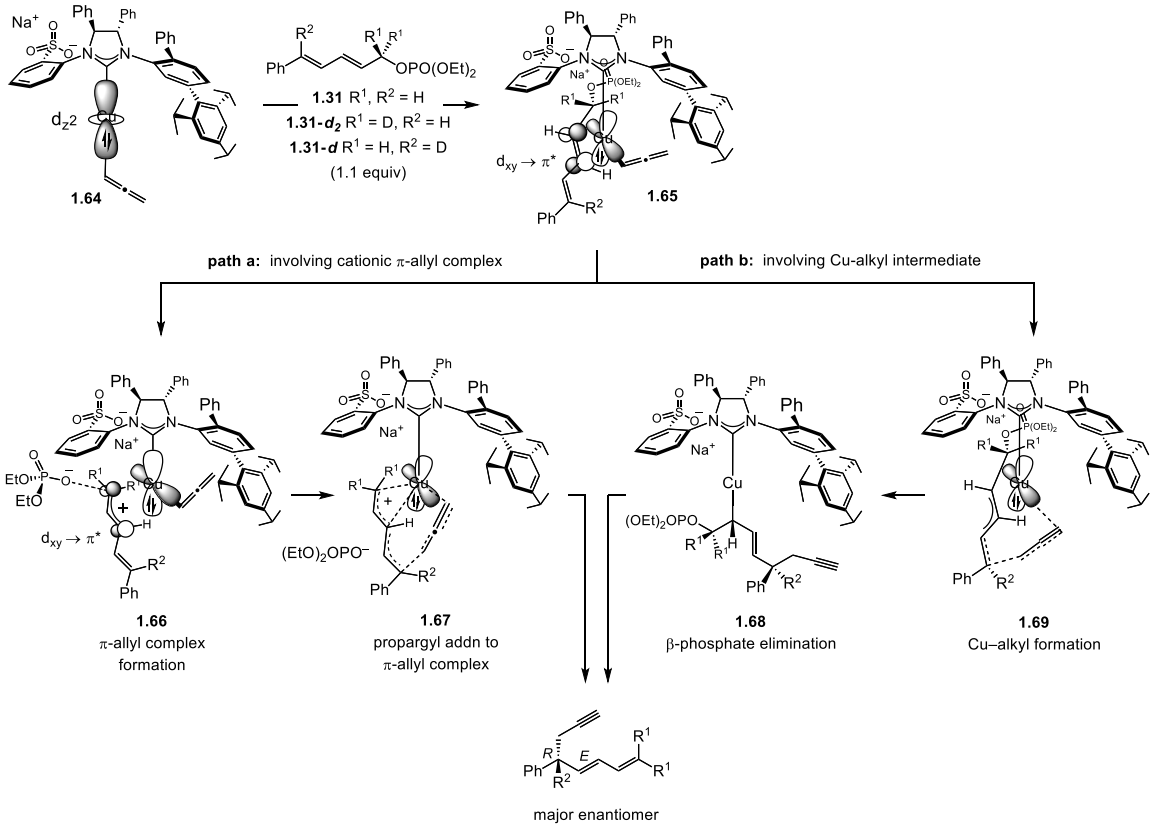
Sulfonate-containing NHC–Cu complexes have been demonstrated on numerous occasions to be especially effective in promoting $S_N2$' and enantioselective allylic substitution reactions. Most likely, this is because these catalysts have the ability to form a metal bridge with their sulfonate moiety and the electrophile's phosphate unit.[5] Nonetheless, the $S_N2$"-selective processes are mechanistically distinct because of the presence of an extend π system, which is able to interconvert between *s-cis* and *s-trans* conformations. The relative rate of interconversion and relative reactivity of these latter isomers compared to C–C bond formation can impact *E:Z* selectivity and enantioselectivity. What is more, because of the involvement of a more reactive dienyl

phosphate (versus a simple allyl phosphate), it is possible that the stereochemistry-determining step is different from $S_N2$'-selective allylic substitutions. Mindful of the above-mentioned issues, we set out to investigate the key mechanistic features of catalytic $S_N2$"-selective transformations.

### 1.5.1 Identifying the stereochemistry-determining step

Two pathways may be proposed, both involving *anti* displacement of the leaving group, a process commonly invoked in allylic substitution (Scheme 1.12).[18] One route (path a) would entail the formation of π-allyl complex **1.66** by oxidative addition, followed

***Scheme 1.12.*** Mechanistic Analysis on the Basis of Deuterium-Labeling Experiments

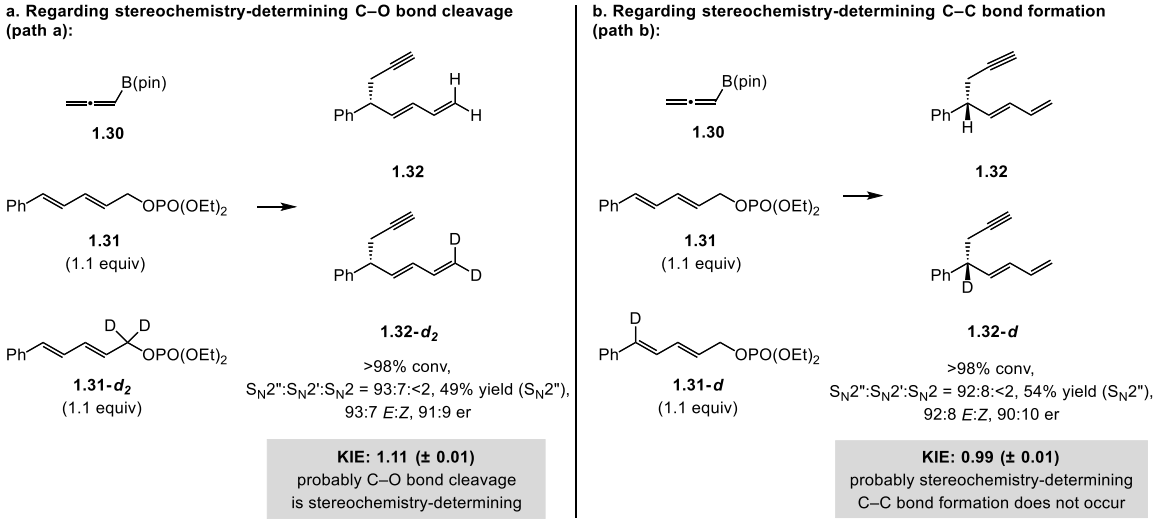



(18) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339−2372.

by a 3,3'-reductive elimination[19] (**1.67**) to form a C–C bond. Alternatively, C–C bond formation may take place first through a migratory insertion prior to elimination of the phosphate moiety from an alkyl–Cu complex (path b).

Competition experiments involving equal amounts of a representative deuterium-labeled (e.g., **1.31-*d*$_2$**, **1.31-*d***) and non-labeled substrate (**1.31**) were carried out to identify the more likely scenario. A secondary kinetic isotope effect of 1.11 ± 0.01 was observed when **1.31-*d*$_2$** was used (Scheme 1.13a), suggesting a $sp^3 \rightarrow sp^2$ hybridization change at the carbon bearing the phosphate group during the turnover-limiting step. In contrast, we observed no secondary kinetic isotope effect (0.99 ± 0.01) with **1.31-*d*** (Scheme 1.13b), implying that C–C bond formation is probably not the turnover-limiting step. Thus, path a is more likely the way these transformations proceed.

***Scheme 1.13.*** Kinetic Isotope Effect Measurements[a]

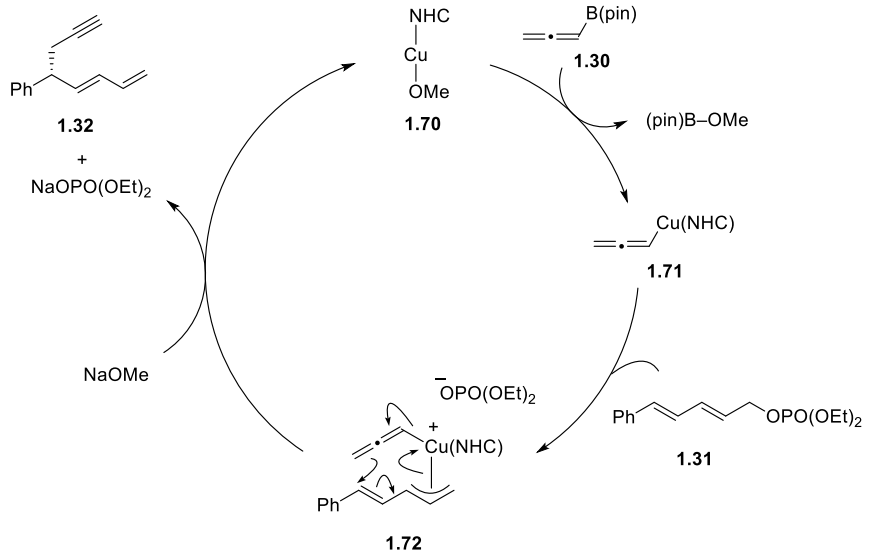



[a]Conditions: 5.5 mol% **imid-1.4**, 5.0 mol% CuCl, 1.5 equiv NaOMe, $CH_2Cl_2$, –30 °C, 24 h.

(19) (a) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620–3628; (b) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686−10688; (c) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716−9719; (d) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778−16781; (e) Ardolino, M.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 7092−7100.

A catalytic cycle has been proposed. First, NHC–Cu complex **1.70** reacts with **1.30** to form allenyl–Cu **1.71**, which undergoes oxidative addition (stereochemistry-determining step) on dienylphosphate **1.31** to generate π-allyl–Cu complex **1.72**. The ensuing 3,3'-reductive elimination affords the desired product **1.32** and regenerate NHC–Cu complex **1.70.**

***Scheme 1.14.*** Proposed Catalytic Cycle

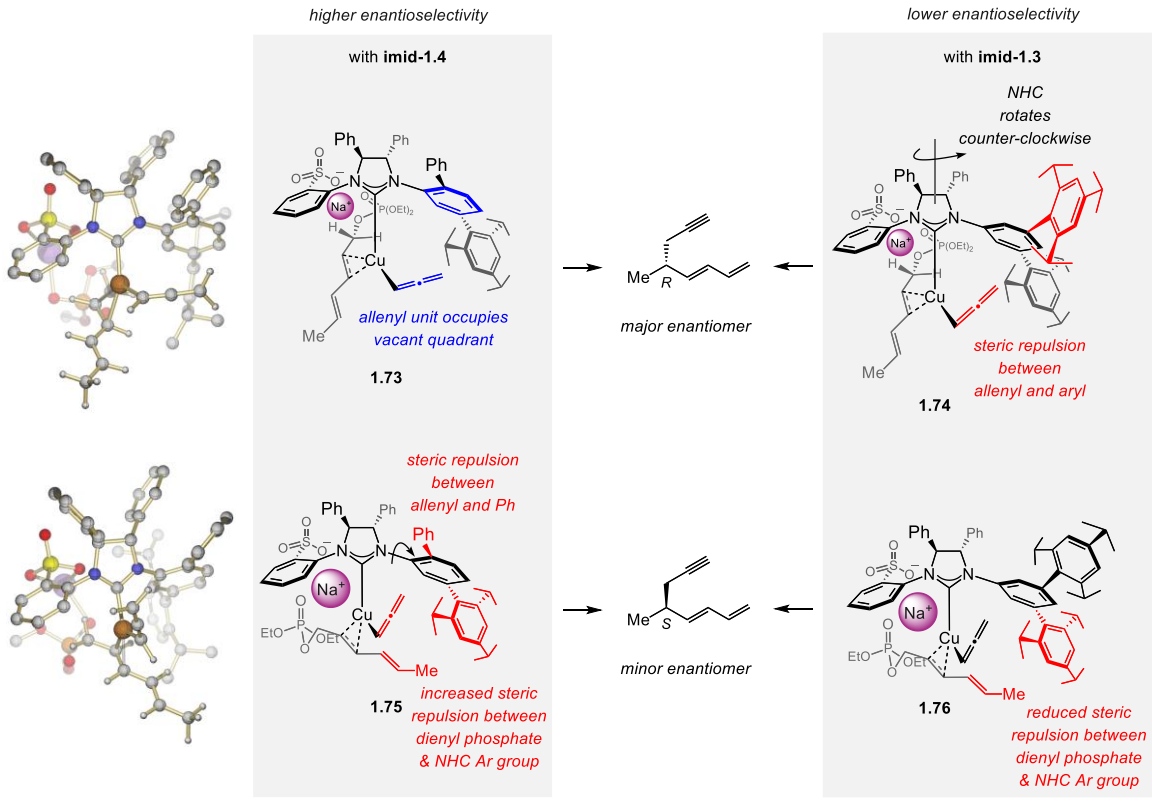



### 1.5.2 Regarding the enantioselectivity variations

We carried out DFT calculations to find a way to explain why the reactions were more enantioselective with the Cu-based complex derived from imidazolinium salt **imid-1.4** compared to when **imid-1.3** was used. Comparison of the transition states leading to the *E* isomer of the major enantiomer in processes involving **imid-1.4** (cf. **1.73**) and **imid-1.3** (cf. **1.74**) revealed that the Cu-complex possess distinct conformational preferences (Scheme 1.15). In these transition states, the dienyl phosphate approaches the allenyl–Cu complex such that the phosphate moiety can establish a sodium cation bridge with the NHC ligand's sulfonate group.[5] In the mode of addition represented by **1.73,** the lowest energy

conformer, the allenyl moiety may reside within the vacant quadrant below the N-aryl ring as there is no *meta* substituent in the Cu complex derived from **imid-1.4**. On the other hand, the proximity of a triisopropylphenyl moiety and the allenyl group in **1.74** would engender steric pressure, which can be reduced by counterclockwise rotation around the Cu–$C^{NHC}$ bond. These factors impact the relative energies of the transition state leading to the minor

***Scheme 1.15.*** Mechanistic Model: Origin of Enantioselectivity[a]

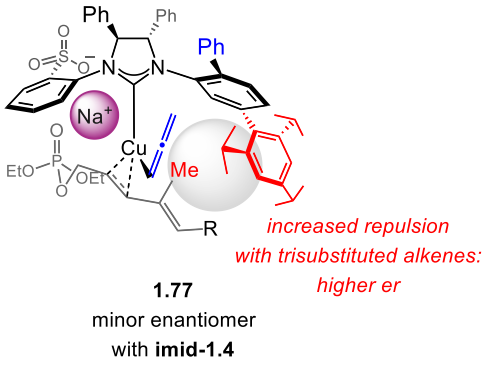



[a]DFT at the MN15/Def2-TZVPP//M06L/Def2-SVP level.

enantiomer (**1.75** and **1.76**). In **1.75,** rotation around the N–$C^{Ar}$ bond decreases the steric strain caused by the propinquity of the ligand's *ortho*-phenyl substituent and the allenyl moiety. Nevertheless, this rotation would place the *meta*-triisopropylphenyl group more proximal to the tail end of the dienyl phosphate, exacerbating an unfavorable interaction. As a result, **1.75** is higher in energy, which leads to higher er with **imid-1.4**. In the mode of reaction represented by **1.76**, the aforementioned counterclockwise rotation would allow

the triisopropylphenyl group in the rear to move further away from the dienyl phosphate, diminishing the steric repulsion and therefore a greater amount of the minor enantiomer is formed.

The DFT model offers an explanation for the enantioselectivity trend regarding the dienyl phosphate containing a trisubstituted alkene as well. In **1.77**, the intermediate leading to the minor enantiomer, greater repulsion between the additional substituent and the NHC ligand is observed, which increases the energy difference and the er values (cf. Scheme 1.7 and Scheme 1.9).




**1.77**
minor enantiomer
with **imid-1.4**

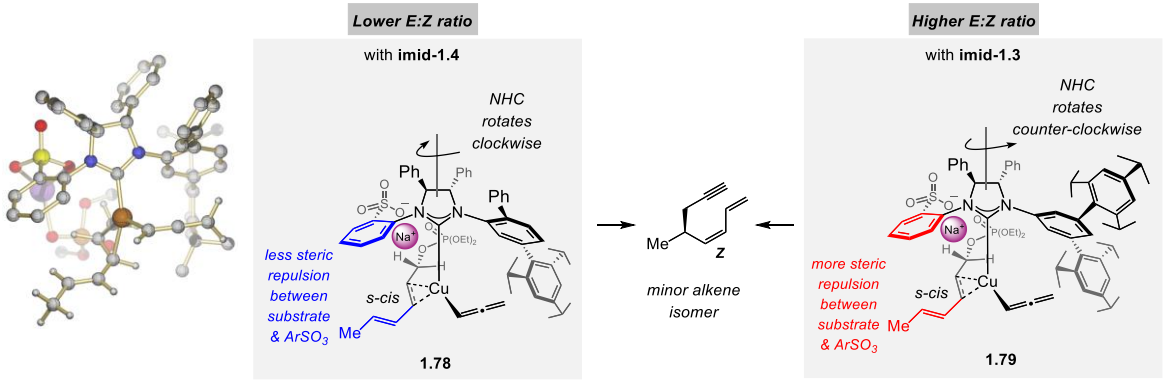
### 1.5.3 Regarding the *E* selectivity variations

Apart from the origin of enantioselectivity, we wished to find out why the catalyst derived from **imid-1.3** generates products with higher *E:Z* ratios (95:5 vs 90:10 for **imid-1.3** and **imid-1.4**, respectively). We focused on the geometry of the extended π-system in the transition state for oxidative addition, in which the *s-cis* conformation delivers *Z* isomer and *s-trans* gives *E* isomer.

The conformational mobility of the NHC ligands discussed above (i.e., counterclockwise rotation around the Cu–$C^{NHC}$ bonds; see Scheme 1.15) offers a plausible rationale regarding why *E* selectivities are higher with the NHC–Cu complex derived from **imid-1.3**. Due to the lack of a *meta* substituent, the *s-cis* transition state derived from **imid-**

**1.4** (cf. **1.78**) can rotate clockwise to relieve steric repulsion between the substrate and the sulfonate NAr ring without experiencing significant steric pressure between the allenyl group and the NHC ligand. Whereas in the case of the *s-cis* conformer corresponding to **imid-1.3**, the counterclockwise rotation of the NHC ligand positions the dienyl phosphate in closer proximity with the sulfonate NAr ring, causing a stronger repulsion and thus raising the energy of **1.79**. Therefore, a smaller amount of the *Z*-alkene is generated and the *E:Z* ratio is higher when **imid-1.3** is used as ligand precursor.

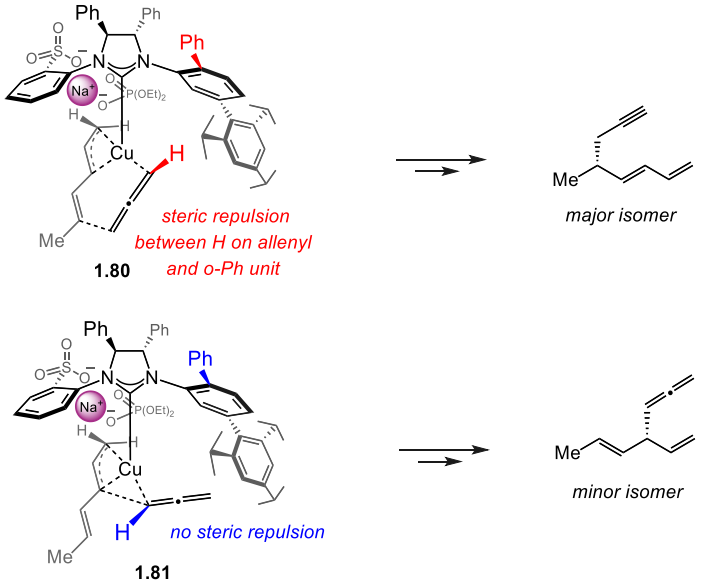
***Scheme 1.16.*** Mechanistic Model: Differences in *E* Selectivity as a Function of NHC Ligand




### 1.5.4 Regarding the $S_N2$"/$S_N2$' selectivity variations

Another noteworthy observation was that catalyst derived from **imid-1.3** generally afforded products in higher $S_N2$" selectivity compared to when **imid-1.4** was utilized (93:4 vs 88:7 for **1.32** with **imid-1.3** and **imid-1.4** respectively). This trend may be attributed to the different conformations of the transition states in the C–C bond formation step. With the catalyst derived from **imid-1.4**, the reaction leads to a transition state where the allenyl moiety is situated in a position that engenders steric repulsion between the nucleophile's C–H and the *ortho*-phenyl moiety of the NHC ligand (**1.80**), generating greater amounts of the $S_N2$' isomer. In the case of **imid-1.3**, such repulsion does not exist due to the lack of an *ortho* substituent, leading to higher $S_N2$" selectivity.

***Scheme 1.17.*** Mechanistic Model: Variations in $S_N2$"/$S_N2$' Selectivity



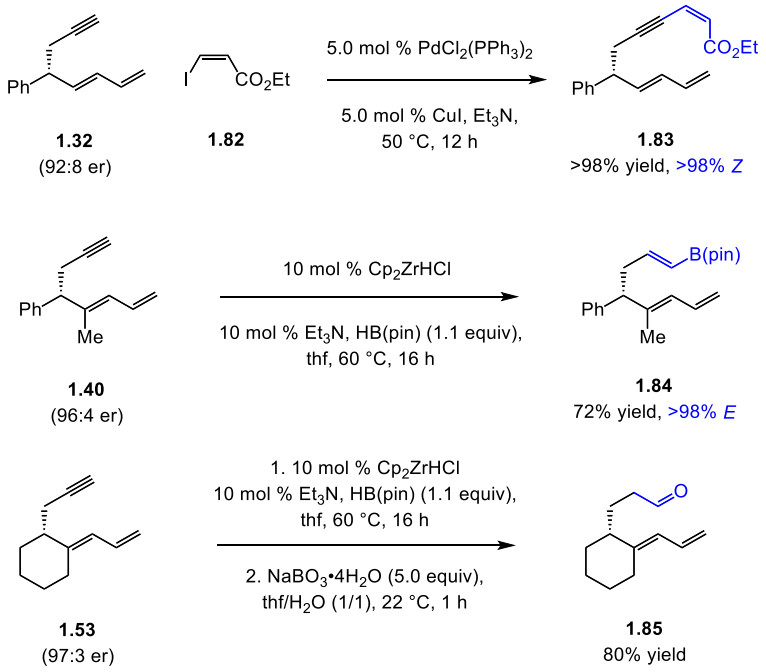

## 1.6 Utility in Chemical Synthesis

An advantage of the method is that it delivers products bearing a 1,3-diene and a terminal alkyne or a silyl-substituted allene, which can be easily functionalized with chemo- and stereoselectivity.

Sonogashira coupling[20] of **1.32** to *Z*-alkenyl iodide **1.82** afforded enyne **1.83** efficiently and with complete retention of stereochemical identity (Scheme 1.18). Similarly, with a Zr-based complex, boron–hydride addition to **1.40** takes place exclusively at the alkyne (vs diene), affording **1.84** in 72% yield and >98:2 *E:Z* selectivity. The same process was applied to cyclic product **1.53**, the subsequent oxidative work-up furnished aldehyde **1.85** in 80% yield.

(20) For a recent review on the Sonogashira coupling process, see: Thomas, A. M.; Sujatha, A.; Anilkumar, G. *RSC Adv.* **2014**, *4*, 21688−21698.

***Scheme 1.18.*** Chemo- and Stereoselective Functionalization of Propargyl Addition Products[a]




[a]Reactions were carried out under $N_2$ atm. Conversion was determined by analysis of $^1$H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more.

The transformations shown in Scheme 1.19 outline the types of chemoselective modifications that can be applied to silyl-allenyl products. Catalyzed by a phosphine-copper complex derived from **phos-1.4**,[21] proto-boryl addition of **1.56** occurred selectively on the 1,3-diene to afford **1.86** in 83% yield and 96:4 *Z:E* selectivity. When a Pd-based complex was used,[22] boron–hydride addition took place only at the silyl-allene, furnishing a stereochemically defined tetrasubstituted olefin, which can be further functionalized through chemoselective catalytic cross-coupling.[23] In contrast to previous related studies where alkenes serve as a directing group,[22] here a diene provides the same function. An

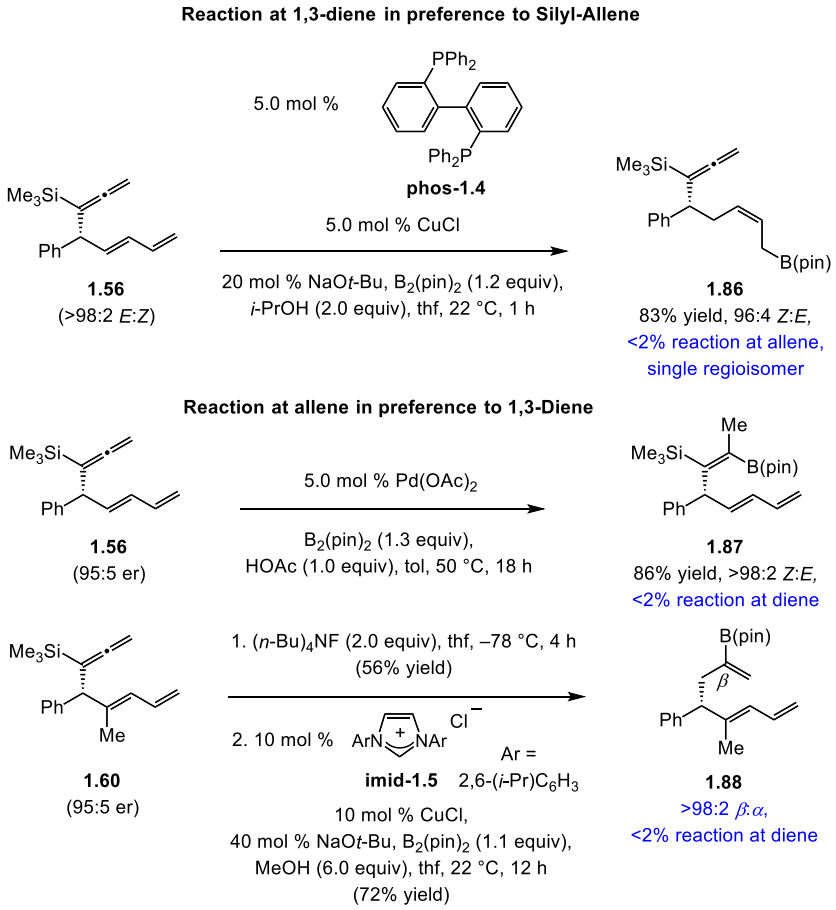
(21) (a) Yuan, W.; Song, L.; Ma, S *Angew. Chem., Int. Ed.* **2016**, *55*, 3140−3143. (b) Song, L.; Yuan, W.; Ma, S. *Org. Chem. Front.* **2017**, *4*, 1261−1265.

(22) Zhu, C.; Yang, B.; Qiu, Y.; Bäckvall, J.-E. *Chem. - Eur. J.* **2016**, *22*, 2939−2943.

(23) Jiao, J.; Hyodo, K.; Hu, H.; Nakajima, K.; Nishihara, Y. *J. Org. Chem.* **2014**, *79*, 285−295.

NHC–Cu complex catalyzed proto-boryl addition of the desilylated allene to afford **1.88** in 72% yield and >98% β selectivity.

***Scheme 1.19.*** Chemo- and Stereoselective Functionalization of Silyl-Allenyl Addition Products[a]



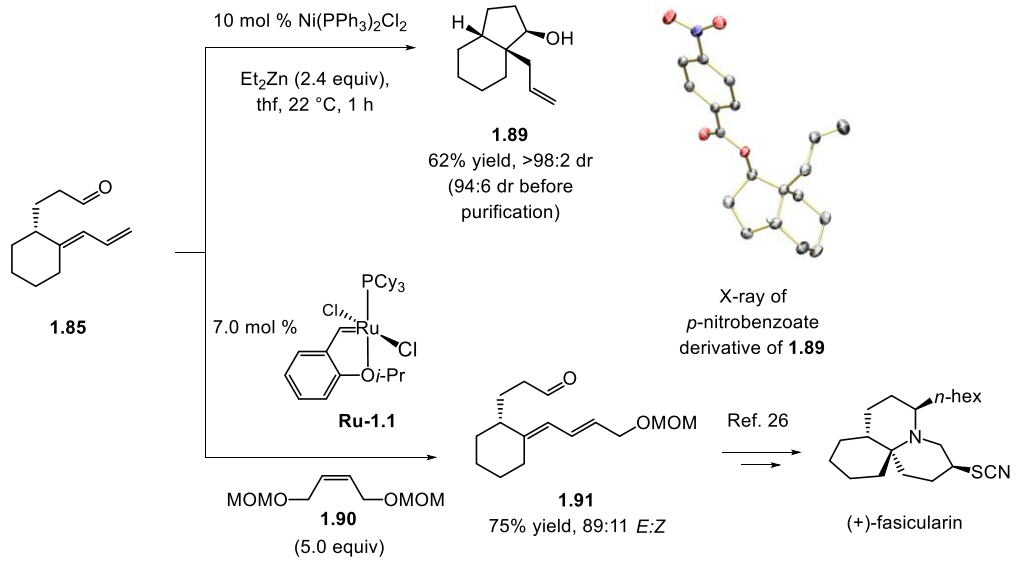

[a]Reactions were carried out under $N_2$ atm. Conversion was determined by analysis of $^1$H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more.

The utility of $S_N2$" substitution was further highlighted by phosphine-Ni-catalyzed cyclization[24] of **1.85** to afford bicyclic compound **1.86** with high diastereoselectivity. The X-ray structure of the *p*-nitrobenzoate derivative confirmed the absolute and relative stereochemistry of **1.89.** Starting from the same aldehyde **1.85**, dienyl aldehyde **1.91** was

(24) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181−2183.

synthesized through cross-metathesis in 75% yield and 89:11 *E:Z* ratio. This compound is an intermediate that has previously been used in total synthesis of bioactive natural product fasicularin in the racemic form.

***Scheme 1.20.*** Application to Synthesis of Enantiomerically Enriched Polycyclic Structures[a]




[a]Reactions were carried out under $N_2$ atm. Conversion, diastereoselectivity and *E/Z* ratio was determined by analysis of $^1$H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more.

## 1.7 Conclusions

The studies described above represent the first examples of catalytic $S_N2$”-selective and enantioselective substitutions that allow for incorporation of easily modifiable propargyl or allenyl moieties. While there is only a single report corresponding to $S_N2$’-selective enantioselective allylic substitution of an allenyl unit[25] and one dealing with incorporation of a silyl-protected propargyl moiety[5], to the best of our knowledge, none involve the addition of an unprotected propargyl group or a silyl-allenyl group. The

(25) Jung, B.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2012,** *134*, 1490–1493.

aforementioned investigations illustrated that these versatile functional groups can be modified easily to access a variety of useful and otherwise difficult-to-access compounds in high enantiomeric purity.

DFT studies in combination with deuterium labeling experiments were used to elucidate that in $S_N2$" substitution, a π-allyl–Cu intermediate is likely formed prior to the C–C bond formation. The stereochemical models account for the high regio- and stereoselectivity and provide insight regarding some of the unique properties of the sulfonate-containing NHC bearing a 2,5-disubtituted NAr moiety.

## 1.8 Experimentals

- **General**

Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, $\lambda_{max}$ in $cm^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). $^1H$ NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), Varian Unity INOVA 500 (500 MHz) or Varian Unity INOVA 600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm, Benzene-$d_6$: δ 7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), and integration. $^{13}C$ NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer, Varian Unity INOVA 500 (125 MHz) or or Varian Unity INOVA 600 (150 MHz) 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). High-resolution mass

spectrometry was performed on a JEOL AccuTOF DART (positive mode), or ESI (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by GC analysis (Alltech Associated Chiraldex B-DM (30 m x 0.25 mm), Chiraldex G-TA (30 m x 0.25 mm)) or HPLC analysis (Chiral Technologies Chiralpak AZ–H (4.6 x 250 mm), Chiralcel OD–H (4.6 x 250 mm), Chiralpak AD–H (4.6 x 250 mm), Chiralcel OJ–H (4.6 x 250 mm), Chiralcel OZ–H (4.6 x 250 mm), and Chiralcel OZ–3 (4.6 x 150 mm) in comparison with authentic racemic materials. Specific rotations were measured on an ATAGO® AP-300 Automatic Polarimeter or a Rudolph Research Analytical Autopol IV Polarimeter. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry $N_2$ in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and hexanes were purified through a copper oxide and alumina column; $CH_2Cl_2$ and $Et_2O$ were purged with Ar and purified by passage through two alumina columns. Tetrahydrofuran (Fisher Scientific, Inc.) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher Scientific, Inc.) in air.

- **Reagents**

**Acetic acid:** was purchased from Fisher Scientific and used as received.

**(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (Au-I):** was purchased from Strem and used as received.

**Allenylboronic acid pinacol ester (1.30):** was purchased from Aldrich and used as received.

**Aluminium chloride:** was purchased from Aldrich and used as received.

**(*R*)-(+)-(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine) (phos-1.1):** was purchased from Strem and used as received.

**2,2'-Bis(diphenylphosphino)-1,1'-biphenyl (phos-1.4):** was purchased from Alfa Aesar and used as received.

**Bis(pinacolato)diboron [$B_2(pin)_2$]:** was purchased from Frontier Scientific, Inc. and recrystallized from hexanes.

**(−)-1,2-Bis((2*R*, 5*R*)-2,5-diphenylphospholano)ethane (phos-1.3):** was purchased from Strem and used as received.

**Bis(triphenylphosphine)nickel(II) chloride [$Ni(PPh_3)_2Cl_2$]:** was purchased from Strem and used as received.

**Bis(triphenylphosphine)palladium(II) dichloride [$PdCl_2(PPh_3)_2$]:** was purchased from Strem and used as received.

**Copper (I) chloride (CuCl):** was purchased from Strem and used as received.

**Copper (I) iodide (CuI):** was purchased from Strem and used as received.

**Dess–Martin periodinane (DMP):** was purchased from Oakwood and used as received.

**Dichloro(2-isopropoxyphenylmethylene) (tricyclohexylphosphine)ruthenium(II) (Ru-1.1):** was purchased from Materia Inc. and used as received.

**Diethyl chlorophosphate:** was purchased from Aldrich and used as received.

**(*R*)-1-[(*S*$_P$)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (phos-1.2):** was purchased from Strem and used as received.

**Diethylzinc ($Et_2Zn$):** was purchased neat from Aldrich and used after diluted to a 1.5 M toluene solution.

**Diisobutylaluminum hydride (dibal–H):** was purchased neat from Aldrich and used as received.

**4-Dimethylaminopyridine (DMAP):** was purchased neat from Oakwood and used as received.

**Imid-1.1** were prepared according to previously reported procedures.[26]

**Imid-1.2** were prepared according to previously reported procedures.[25]

**Imid-1.3** were prepared according to previously reported procedures.[27]

**Imid-1.4** were prepared according to previously reported procedures.[28]

**Isopropanol:** was purchased from Aldrich and purified by distillation from Na (Aldrich) prior to use.

**Lithum aluminium deuteride:** was purchased from EMD Chemicals Inc. and used as received.

**Methanol** was purchased from Acros and purified by distillation from Na (Aldrich) prior to use.

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(26) Meng, F.; McGrath, K. P.; Hoveyda, A. H., *Nature* **2014,** *513*, 367–374.

(27) Jung, B.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2012,** *134*, 1490–1493.

(28) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2015,** *137*, 8948–8964.

**4-Nitrobenzoyl chloride:** was purchased from Aldrich and used as received.

**Palladium(II) acetate [$Pd(OAc)_2$]:** was purchased from Strem and used as received.

**Palladium on carbon (10 wt%):** was purchased from Aldrich and used as received.

**Sodium bicarbonate ($NaHCO_3$):** was purchased from Fisher Scientific and used as received.

**Sodium *t*-butoxide (NaO*t*-Bu):** was purchased from Strem and used as received.

**Sodium perborate tetrahydrate** (**$NaBO_3 \cdot 4H_2O$**): was purchased from Aldrich and used as received.

**Sodium methoxide (NaOMe):** was purchased from Strem and used as received.

**Tetrabutylammonium fluoride solution (TBAF, 1.0 M in thf)**: was purchased from Aldrich and dried with 4 Å MS for 48 h before use.

**(*Z*)-2,4,9,11-Tetraoxadodec-6-ene (1.87):** were prepared according to previously reported procedures.[29]

**4,4,5,5-Tetramethyl-1,3,2-dioxaborolane [HB(pin)]:** was purchased from Oakwood Chemical and used as received.

**Triethyl phosphonoacetate:** was purchased from Oakwood and used as received.

**Trimethyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-yn-1-yl)silane (1.55):** were prepared according to previously reported procedures.[30]

**Triethylamine:** was purchased from Fisher Scientific, Inc. and distilled over $CaH_2$ prior to use.

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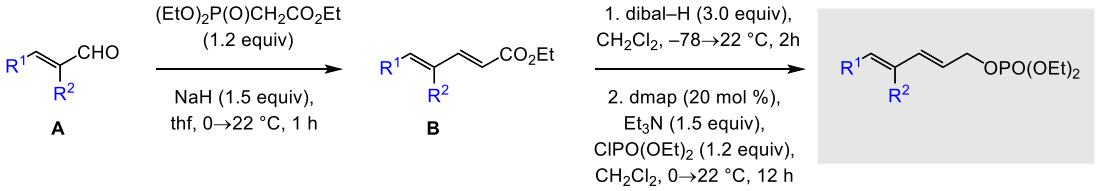
(29) Parsons, S. R.; Hooper, J. F.; Willis, M. C. *Org. Lett.* **2011,** *13*, 998−1000.

(30) Fandrick, D. R.; Reeves, J. T.; Song J. J. International Patent WO 2010/141328 A2

**Zirconocene chloride hydride (Schwartz' reagent):** was purchased from Aldrich and used as received.

- **Synthesis of Dienyl Allylic Phosphates**




**Procedure:**[31] To a stirred solution of NaH (1.80 g, 45.0 mmol, 60% in mineral oil) in thf (50 mL) was added triethyl phosphonoacetate (7.10 mL, 36.0 mmol) dropwise at 0 °C. After 30 min, aldehyde **A**[32] (3.96 g, 30.0 mmol for $R_1$=Ph, $R_2$=H) was added to the mixture slowly at 0 °C. The mixture was allowed to warm to 22 °C and stir for 1 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (50 mL) and diluted with $Et_2O$ (50 mL). The organic layer was separated and the aqueous layer was washed with $Et_2O$ (50 mL x 3). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The resulting yellow oil was passed through a plug of silica gel (20:1 hexanes:ethyl acetate) to afford 6.06 g of **B** ($R_1$=Ph, $R_2$=H) as pale yellow oil (30.0 mmol, >98% yield).

To a solution of **B** (2.02 g 10.0 mmol) in $CH_2Cl_2$ (20 mL) was added diisobutylaluminium hydride (5.30 mL, 30.0 mmol) dropwise at –78 °C. The mixture was allowed to warm to 22 °C and stir for 2 h. At this point, the reaction was quenched by slowly addition of a mixture of ice and saturated potassium sodium tartrate tetrahydrate,

(31) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H., *Angew. Chem. Int. Ed.* **2007,** *46*, 4554–4558.

(32) a) Fan, X.; Lv, H.; Guan, Y. H.; Zhu, H. B.; Cui, X. M.; Guo, K., *Chem. Commun.* **2014,** *50*, 4119–4122. b) Kim, E.; Park, S.; Chang, S. *Chem. Eur. J.* **2018**, *24*, 5765–5769.

and the mixture was allowed to stir for 1 h. The organic layer was separated and the aqueous layer was washed with $CH_2Cl_2$ (30 mL x 3). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo to afford the corresponding alcohol as pale yellow oil (1.41 g, 8.8 mmol for $R_1$=Ph, $R_2$=H). The alcohol was dissolved in $CH_2Cl_2$ (15 mL) and 4-dimethylaminopyridine (219.6 mg, 1.8 mmol), triethylamine (1.85 mL, 13.2 mmol) was added. After which the solution was allowed to cool to 0 °C, diethyl chlorophosphate (1.52 mL, 10.5 mmol) was added dropwise and the resulting mixture was allowed to stir for 12 h. The reaction was then quenched by the addition of a saturated solution of aqueous $NaHCO_3$ and diluted by the addition of $CH_2Cl_2$ (30 mL). The organic layer was separated and the aqueous layer was washed with $CH_2Cl_2$ (30 mL x 3). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The resulting yellow oil was purified by silica gel chromatography (5:1:0.3→3:1:0.2 hexanes:ethyl acetate:$Et_3N$) to afford **3a** ($R_1$=Ph, $R_2$=H) as yellow oil (2.19 g, 30.0 mmol, 84% yield).

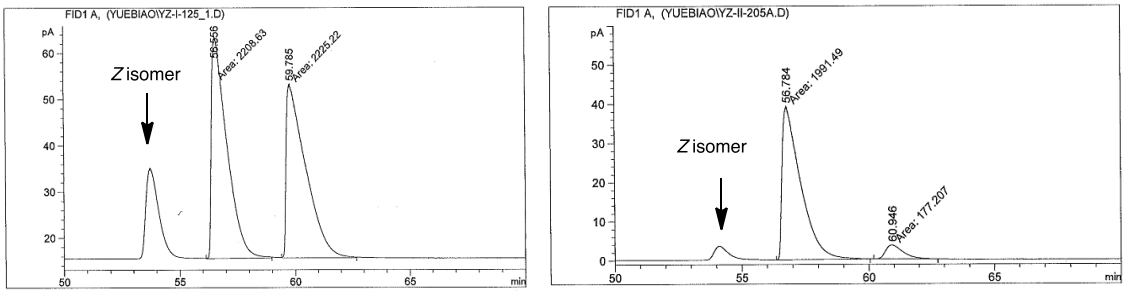
- **Procedure for Catalytic $S_N2$"- and Enantioselective Propargyl Substitution**

An oven-dried 1-dram vial equipped with a stir bar was charged with imidazolinium salt **imid-1.4** (4.0 mg, 5.5 μmol), NaOMe (8.1 mg, 150 μmol), and CuCl (0.5 mg, 5.0 μmol) in a $N_2$-filled glove box. The vial was sealed with a cap (phenolic open top cap with a red PFTE/white silicon septum) and electrical tape, and removed from the glove box. $CH_2Cl_2$ (0.5 mL) was added and the mixture was allowed to stir for 1 h under $N_2$ at 22 °C (the mixture turned pale blue-green). Allenyl–B(pin) compound **1.30** (35.9 μL, 0.20 mmol) was then added by syringe, and the resulting mixture was allowed to stir at 22 °C for 30 min. At this point, allylic phosphate **1.31** (29.6 mg, 0.10 mmol) was added (at −78 °C), and the mixture was allowed to stir at −30 °C for 24 h, after which it was passed through a short

plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$ (3.0 mL). The organic layer was concentrated in vacuo, affording yellow oil residue, which was purified by silica gel chromatography (hexanes, $R_f$ = 0.30) to afford **1.32** as colorless oil (12.9 mg, 0.071 mmol, 71% yield).

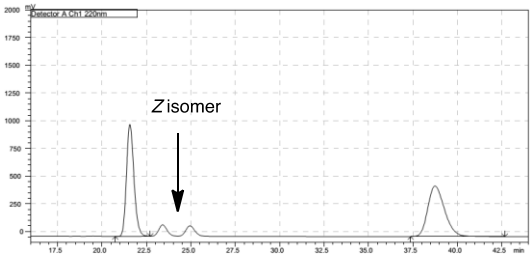
- **Characterization Data for Products with a Disubstituted Alkene**

**(*R*,*E*)-Octa-5,7-dien-1-yn-4-ylbenzene (1.32): IR (neat):** 3298 (m), 3062 (w), 2971 (w), 2911 (w), 2119 (w), 1650 (w), 1602 (w), 1494 (m), 1453 (w), 1431 (w), 1004 (s), 952 (w), 904 (m), 758 (m), 699 (s), 639 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.37–7.29 (m, 2H), 7.27–7.21 (m, 3H), 6.35 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.12 (dd, *J* = 15.3, 10.2 Hz, 1H), 5.94 (dd, *J* = 15.3, 7.2 Hz, 1H), 5.16 (d, *J* = 17.0 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 3.60 (q, *J* = 7.2 Hz, 1H), 2.68–2.57 (m, 2H), 1.98 (t, *J* = 2.6 Hz, 1H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 142.7, 136.9, 136.0, 131.7, 128.7, 127.8, 126.9, 116.7, 82.5, 70.2, 47.4, 25.6; **HRMS (DART):** Calcd for $C_{14}H_{15}$ $[M+H]^+$: 183.1174; Found: 183.1180. Specific rotation: $[\alpha]_D^{20}$ –34.7 (*c* 0.59, $CHCl_3$) for a 92:8 er sample. Enantiomeric purity of **1.32** was determined by GC analysis in comparison with authentic racemic material; CDB/DM column, 100 °C, 15 psi.



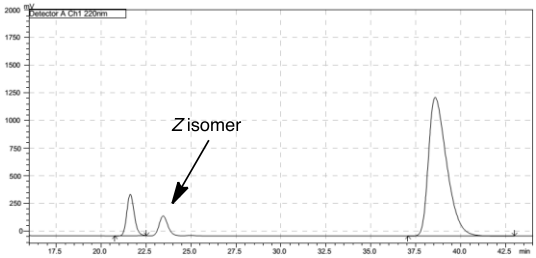

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 56.558 | 2165.83 | 49.830 | 56.784 | 1991.49 | 91.829 |
| 59.776 | 2180.58 | 50.170 | 60.946 | 177.207 | 8.171 |

**(*R*,*E*)-1-Bromo-2-(octa-5,7-dien-1-yn-4-yl)benzene (1.35): IR (neat):** 3299 (m), 3060 (w), 3015 (w), 2912 (w), 2120 (w), 1649 (w), 1602 (w), 1567 (w), 1469 (m), 1437 (m), 1275 (w), 1024 (m), 1003 (s), 952 (m), 905 (m), 753 (s), 727 (m), 638(s) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.57 (d, *J* = 8.1 Hz, 1H), 7.31–7.26 (m, 2H), 7.11–7.08 (m, 1H), 6.35 (dt, *J* = 16.8, 10.2 Hz, 1H), 6.16 (dd, *J* = 15.3, 10.2 Hz, 1H), 5.92 (dd, *J* = 15.3, 7.0 Hz, 1H), 5.17 (d, *J* = 16.8 Hz, 1H), 5.07 (d, *J* = 10.2 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 1H), 2.68–2.59 (m, 2H), 1.98 (t, *J* = 2.6 Hz, 1H); **$^{13}$C NMR (150 MHz, $CDCl_3$):** δ 141.7, 136.8, 134.3, 133.2, 132.4, 128.9, 128.4, 127.7, 124.7, 117.1, 81.9, 70.4, 45.5, 24.4; **HRMS (DART):** Calcd for $C_{14}H_{14}Br$ $[M+H]^+$: 261.0279; Found: 261.0271. Specific rotation: $[\alpha]_D^{20}$ +24.8 (*c* 0.66, $CHCl_3$) for a 89:11 er sample. Enantiomeric purity of **1.35** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.3 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 21.566 | 29659291 | 49.737 |
| 2 | 38.744 | 29973418 | 50.263 |
| Total | | 59632709 | 100.000 |

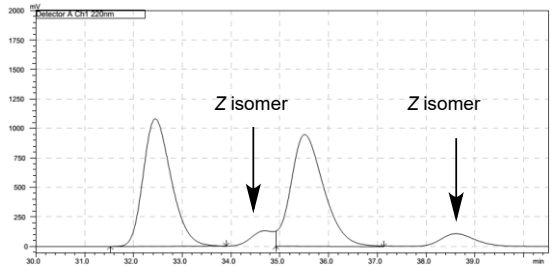



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 21.621 | 10812101 | 10.945 |
| 2 | 38.570 | 87975614 | 89.055 |
| Total | | 98787715 | 100.000 |

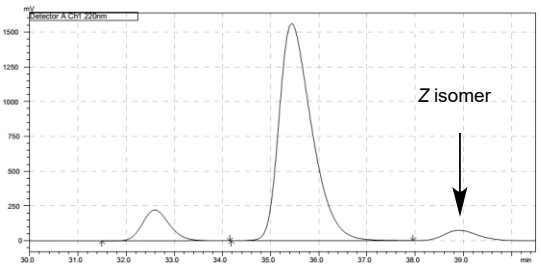
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 21.566 | 29659291 | 49.737 | 21.620 | 5793436 | 10.945 |
| 38.744 | 29973418 | 50.263 | 38.759 | 43667104 | 89.055 |

**(*R*,*E*)-1-Chloro-3-(octa-5,7-dien-1-yn-4-yl)benzene (1.36): IR(neat):** 3301 (m), 3085 (w), 3014 (w), 2972 (w), 2120 (w), 1810 (w), 1650 (m), 1596 (m), 1476 (m), 1430 (m), 1081 (m), 1003 (s), 952 (m), 905 (m), 879 (m), 784 (s), 695 (m), 639 (s) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.31–7.24 (m, 3H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.38 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.14 (dd, *J* = 15.3, 10.2 Hz, 1H), 5.92 (dd, *J* = 15.3, 7.3 Hz, 1H), 5.21 (d, *J* = 17.0 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 3.60 (q, *J* = 7.3 Hz, 1H), 2.69–2.59 (m, 2H), 2.02 (t, *J* = 2.6 Hz, 1H); **$^{13}$C NMR (150 MHz, $CDCl_3$):** δ 144.7, 136.7, 135.1, 134.4, 132.2, 129.9, 128.0, 127.1, 126.0, 117.2, 81.9, 70.5, 47.0, 25.5; **HRMS (DART):** Calcd for $C_{14}H_{14}Cl$ $[M+H]^+$: 217.0784; Found: 217.0791. Specific rotation: $[\alpha]_D^{20}$ –25.3 (*c* 0.69, $CHCl_3$) for a 89:11 er sample. Enantiomeric purity of **1.36** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.3 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 32.446 | 42988263 | 49.199 |
| 2 | 35.509 | 44387300 | 50.801 |
| Total | | 87375564 | 100.000 |



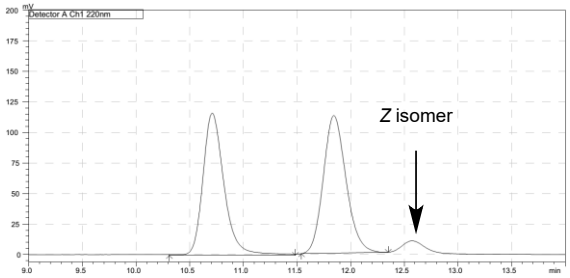

Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 32.594 | 8659646 | 10.583 |
| 2 | 35.436 | 73163913 | 89.417 |
| Total | | 81823559 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 32.446 | 42988263 | 49.199 | 32.594 | 8659646 | 10.583 |
| 35.509 | 44387300 | 50.801 | 35.436 | 73163913 | 89.417 |

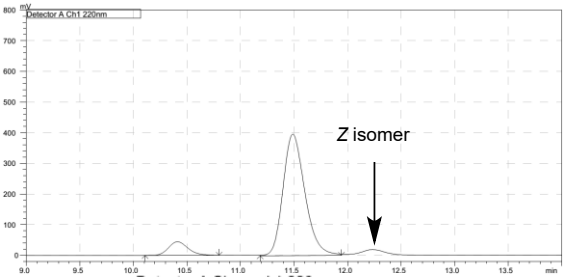
**(*R*,*E*)-1-Fluoro-4-(octa-5,7-dien-1-yn-4-yl)benzene (1.37): IR(neat):** 3304 (m), 3088 (w), 3040 (w), 2973 (w), 2119 (w), 1649 (w), 1603 (m), 1509 (s), 1432 (w), 1225 (m), 1159 (m), 1098 (w), 1005 (m), 953 (w), 906 (m), 831 (m), 640 (m) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.22–7.17 (m, 2H), 7.04–6.98 (m, 2H), 6.34 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.09

(dd, $J$ = 15.3, 10.2 Hz, 1H), 5.90 (dd, $J$ = 15.3, 7.2 Hz, 1H), 5.16 (d, $J$ = 17.0 Hz, 1H), 5.06 (d, $J$ = 10.2 Hz, 1H), 3.58 (q, $J$ = 7.2 Hz, 1H), 2.65–2.54 (m, 2H), 1.97 (t, $J$ = 2.6 Hz, 1H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 161.8 (d, $J_{CF}$ = 244.9 Hz), 138.3 (d, $J_{CF}$ = 3.1 Hz), 136.8, 135.8, 131.8 129.3 (d, $J_{CF}$ = 7.8 Hz), 117.0, 115.4 (d, $J_{CF}$ = 21.2 Hz), 82.2, 70.4, 46.5, 25.7; **$^{19}$F NMR (376 MHz, $CDCl_3$):** δ -116.2–-116.3 (m); **HRMS (DART):** Calcd for $C_{14}H_{14}F$ $[M+H]^+$: 201.108; Found: 201.108. Specific rotation: $[\alpha]_D^{20}$ –25.3 (*c* 0.69, $CHCl_3$) for a 89:11 er sample. Enantiomeric purity of **1.37** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.8 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.710 | 1605087 | 49.086 |
| 2 | 11.843 | 1664866 | 50.914 |
| Total | | 3269953 | 100.000 |



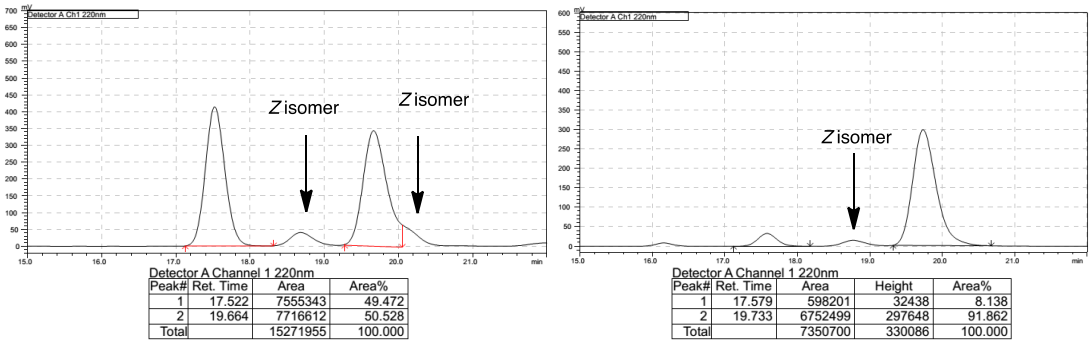

Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.411 | 558019 | 9.004 |
| 2 | 11.488 | 5639269 | 90.996 |
| Total | | 6197288 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 10.710 | 1605087 | 49.086 | 10.411 | 558019 | 9.004 |
| 11.843 | 1664866 | 50.914 | 11.488 | 5639268 | 90.996 |

**(*R*,*E*)-1-Nitro-4-(octa-5,7-dien-1-yn-4-yl)benzene (1.38): IR(neat):** 3297 (m), 3083 (w), 2919 (w), 2121 (w), 1604 (m), 1517 (s), 1432 (w), 1346 (s), 1110 (w), 1005 (m), 953 (w), 909 (w), 855 (m), 754 (w), 700 (w), 644 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.19 (d, $J$ = 8.8 Hz, 2H), 7.41 (d, $J$ = 8.8 Hz, 2H), 6.34 (dt, $J$ = 17.0, 10.2 Hz, 1H), 6.11 (dd, $J$ = 15.3, 10.2 Hz, 1H), 5.88 (ddd, $J$ = 15.3, 7.3, 0.7 Hz, 1H), 5.19 (d, $J$ = 17.0 Hz, 1H), 5.10 (d, $J$ = 10.2 Hz, 1H), 3.71 (q, $J$ = 7.3 Hz, 1H), 2.85–2.54 (m, 2H), 1.98 (t, $J$ = 2.6 Hz, 1H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 150.1, 147.1, 136.3, 134.0, 132.8, 128.8, 123.9, 117.9,

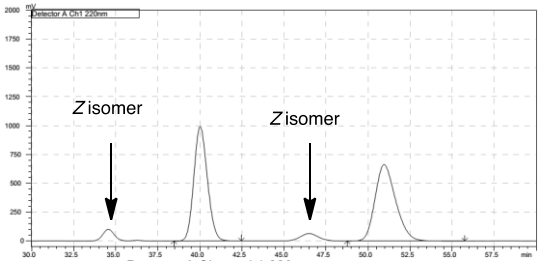
81.3, 71.0, 47.1, 25.3; **HRMS (DART):** Calcd for $C_{14}H_{14}O_2N$ $[M+H]^+$: 228.1025; Found: 228.1022. Specific rotation: $[\alpha]_D^{20}$ –46.0 (*c* 0.35, $CHCl_3$) for a 91:9 er sample. Enantiomeric purity of **1.38** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel AZ-H, 99.5% hexanes, 0.5% isopropanol, 0.8 mL/min, 220 nm.




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 17.522 | 7555343 | 49.472 | 17.579 | 598201 | 8.138 |
| 19.664 | 7716612 | 50.528 | 19.722 | 6752499 | 91.862 |

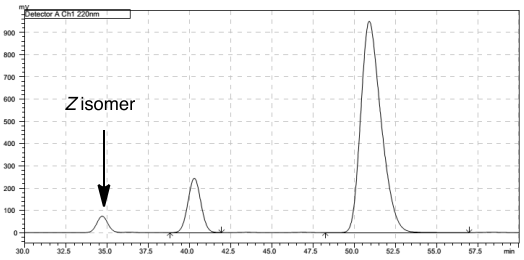
**(*R*,*E*)-(3-(Prop-2-yn-1-yl)hepta-4,6-dien-1-yl)benzene (1.39): IR(neat):** 3301 (m), 3085 (w), 3026 (m), 2923 (m), 2857 (m), 2118 (w), 1651 (w), 1603 (m), 1496 (m), 1454 (m), 1429 (m), 1004 (s), 953 (m), 902 (m), 747 (m), 699 (s), 638 (s) $cm^{-1}$**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.38–7.33 (m, 2H), 7.26 (dd, *J* = 7.1, 4.3 Hz, 3H), 6.43 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.20 (dd, *J* = 15.2, 10.3 Hz, 1H), 5.71 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.24 (d, *J* = 17.0 Hz, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 2.78–2.59 (m, 2H), 2.42–2.32 (m, 3H), 2.05 (t, *J* = 2.4 Hz, 1H), 2.03–1.94 (m, 1H), 1.83–1.73 (m, 1H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 142.3, 137.1, 137.0, 132.1, 128.5, 128.5, 125.9, 116.1, 82.4, 69.9, 41.1, 35.7, 33.5, 24.7; **HRMS (DART):** Calcd for $C_{16}H_{19}$ $[M+H]^+$: 211.1487; Found: 211.1497. Specific rotation: $[\alpha]_D^{20}$ +20.1 (*c* 0.54, $CHCl_3$) for a 86:14 er sample. Enantiomeric purity of **1.39** was determined by HPLC

analysis in comparison with authentic racemic material; Chiralcel OJ-H, 99.9% hexanes, 0.1% isopropanol, 0.3 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 40.015 | 55628982 | 49.753 |
| 2 | 50.953 | 56181682 | 50.247 |
| Total | | 111810664 | 100.000 |

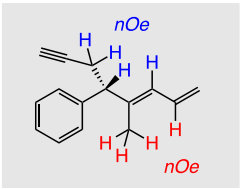



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 40.289 | 13458326 | 14.129 |
| 2 | 50.914 | 81793761 | 85.871 |
| Total | | 95252087 | 100.000 |

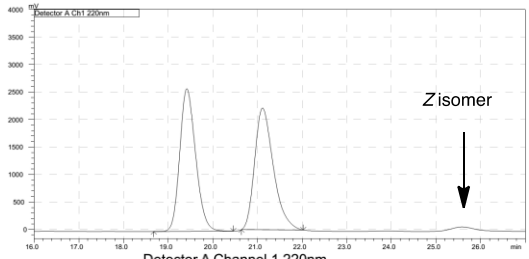
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 40.015 | 55628982 | 49.753 | 40.289 | 13458326 | 14.129 |
| 50.953 | 56181682 | 50.247 | 50.914 | 81793761 | 85.871 |

- **Characterization Data for Products with a Trisubstituted Alkene**



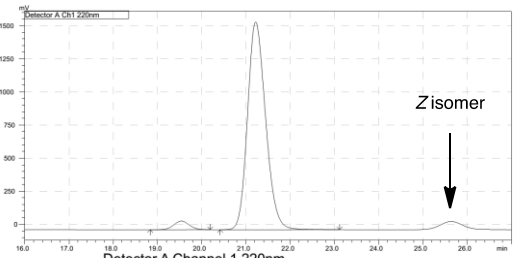

**(*R*,*E*)-(5-Methylocta-5,7-dien-1-yn-4-yl)benzene (1.40): IR(neat):** 3296 (m), 3084 (w), 3027 (w), 2917 (w), 2120 (w), 1812 (w), 1647 (w), 1600 (w), 1494 (m), 1451 (m), 1434 (w), 1381 (w), 1079 (w), 1029 (w), 988 (m), 903 (s), 751 (m), 700 (s), 636 (s), 547 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.25–7.20 (m, 3H), 6.60 (dt, *J* = 16.9, 10.4 Hz, 1H), 6.10 (d, *J* = 10.4 Hz, 1H), 5.23 (d, *J* = 16.9 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 3.55 (t, *J* = 7.6 Hz, 1H), 2.76–2.62 (m, 2H), 1.95 (s, 1H), 1.64 (s, 3H);**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 142.0, 139.5, 133.2, 128.5, 127.9, 126.9, 126.4, 116.6, 82.9, 69.9, 53.0, 23.1, 15.5; **HRMS (DART):** Calcd for $C_{15}H_{17}$ $[M+H]^+$: 197.1325; Found: 197.1335. Specific rotation: $[\alpha]_D^{20}$ +50.6 (*c* 0.27, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **1.40** was determined by HPLC analysis in comparison with authentic racemic material;

Chiralcel OD-H, 100% hexanes, 0.3 mL/min, 220 nm. The geometry of the double bond in compound **1.40** was assigned as *E* based on nOe experiments.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 19.417 | 64192155 | 49.805 |
| 2 | 21.114 | 64695841 | 50.195 |
| Total | | 128887996 | 100.000 |

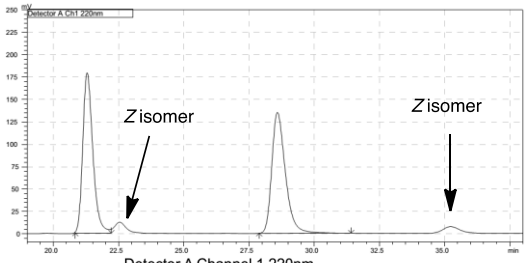



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 19.539 | 1589827 | 3.443 |
| 2 | 21.219 | 44581231 | 96.557 |
| Total | | 46171058 | 100.000 |

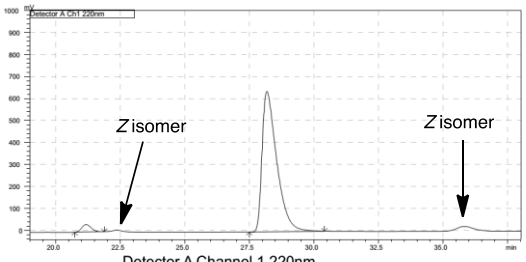
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 19.417 | 64192155 | 49.805 | 19.539 | 1589827 | 3.443 |
| 21.114 | 64695841 | 50.195 | 21.219 | 44581231 | 96.557 |

**(*R*,*E*)-1-Bromo-2-(5-methylocta-5,7-dien-1-yn-4-yl)benzene (1.41): IR(neat):** 3299 (s), 3083 (w), 3052 (w), 2916 (m), 2120 (w), 1808 (w), 1648 (m), 1598 (m), 1566 (m), 1467 (s), 1437 (s), 1382 (m), 1277 (w), 1023 (s), 988 (s), 905 (s), 752 (s), 725 (m), 635 (s), 554 (m), 446 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33–7.21 (m, 2H), 7.10 (ddd, *J* = 8.0, 7.1, 2.0 Hz, 1H), 6.62 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.09 (d, *J* = 10.4 Hz, 1H), 5.23 (d, *J* = 16.8 Hz, 1H), 5.11 (d, *J* = 10.4 Hz, 1H), 4.10 (t, *J* = 7.3 Hz, 1H), 2.73–2.61 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.70 (s, 3H); **$^{13}$C NMR (150 MHz, $CDCl_3$):** δ 141.1, 138.1, 133.2, 133.1, 128.8, 128.4, 127.6, 127.0, 125.8, 116.9, 82.3, 70.0, 50.8, 22.8, 16.7; **HRMS (DART):** Calcd for $C_{15}H_{16}Br$ $[M+H]^+$: 275.0435; Found: 275.0439. Specific rotation: $[\alpha]_D^{20}$ +94.5 (*c* 0.64, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **1.41** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.5 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 21.288 | 4826885 | 49.747 |
| 2 | 28.589 | 4875885 | 50.253 |
| Total | | 9702771 | 100.000 |

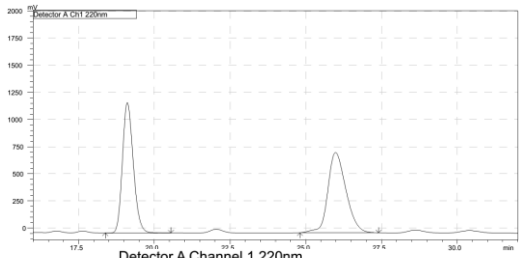


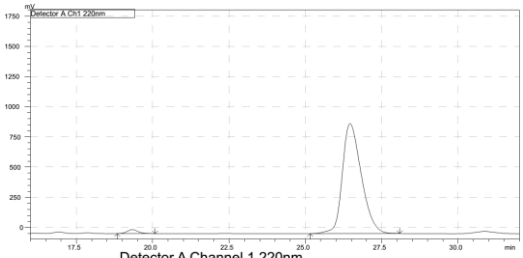

Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 21.178 | 855421 | 3.275 |
| 2 | 28.176 | 25266160 | 96.725 |
| Total | | 26121582 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 21.288 | 4826885 | 49.747 | 21.178 | 855421 | 3.275 |
| 28.589 | 4875885 | 50.253 | 28.176 | 25266160 | 96.725 |

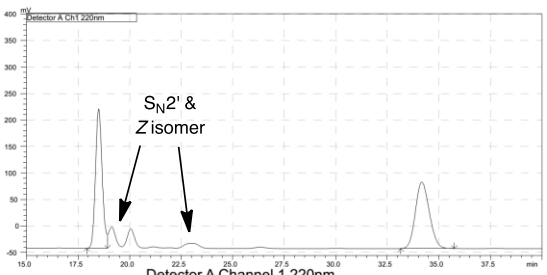
**(*R*,*E*)-1-Methyl-2-(5-methylocta-5,7-dien-1-yn-4-yl)benzene (1.42): IR(neat):** 3295 (m), 3047 (w), 2917 (m), 2855 (w), 2120 (w), 1646 (w), 1600 (w), 1490 (m), 1461 (m), 1435 (m), 1381 (m), 988 (m), 943 (s), 761 (m), 737 (m), 636 (s) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.21–7.10 (m, 4H), 6.60 (dt, *J* = 16.8, 10.5 Hz, 1H), 6.04 (d, *J* = 10.5 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 3.79 (t, *J* = 7.5 Hz, 1H), 2.72 (ddd, *J* = 16.7, 7.5, 2.6 Hz, 1H), 2.62 (ddd, *J* = 16.7, 7.5, 2.6 Hz, 1H), 2.36 (s, 3H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.64 (s, 3H); **$^{13}$C NMR (125MHz, $CDCl_3$):** δ 140.1, 139.0, 136.8, 133.2, 130.6, 126.7, 126.6, 126.1, 116.4, 83.0, 69.6, 48.5, 23.1, 19.9, 16.0; **HRMS (DART):** Calcd for $C_{16}H_{19}$ $[M+H]^+$: 211.1487; Found: 211.1477. Specific rotation: $[\alpha]_D^{20}$ +40.7 (*c* 0.58, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity of **1.42** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.3 mL/min, 220 nm.



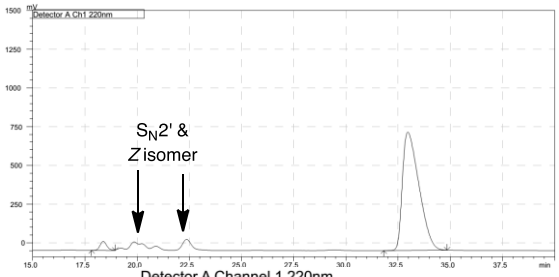

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 19.108 | 30061090 | 49.440 | 19.330 | 804624 | 1.999 |
| 25.984 | 30742076 | 50.560 | 26.458 | 39449763 | 98.001 |

**(*R*,*E*)-1-Methoxy-2-(5-methylocta-5,7-dien-1-yn-4-yl)benzene (1.43): IR(neat):** 3295 (w), 3080 (w), 3002 (w), 2936 (w), 2836 (w), 2115 (w), 1647 (w), 1598 (w), 1490 (m), 1462 (m), 1438 (m), 1229 (w), 1243 (s), 1105 (m), 1030 (m), 989 (w), 902 (m), 753 (m), 635 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.21 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H), 7.14 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.64 (dt, *J* = 17.2, 10.4 Hz, 1H), 6.10 (d, *J* = 10.4 Hz, 1H), 5.20 (dd, *J* = 17.2, 2.0 Hz, 1H), 5.07 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.06 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 2.68–2.61 (m, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.70 (s, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 157.5, 139.3, 133.4, 130.5, 127.9, 127.8, 126.3, 120.6, 116.0, 110.8, 83.4, 69.2, 55.6, 44.9, 22.4, 16.5; **HRMS (DART):** Calcd for $C_{16}H_{19}O$ $[M+H]^+$: 227.1436 Found: 227.1442. Specific rotation: $[\alpha]_D^{20}$ +77.6 (*c* 0.67, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **1.43** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 99.9% hexanes, 0.1% *i*-PrOH, 0.3 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 18.495 | 5952912 | 50.276 |
| 2 | 34.173 | 5887612 | 49.724 |
| Total | | 11840524 | 100.000 |

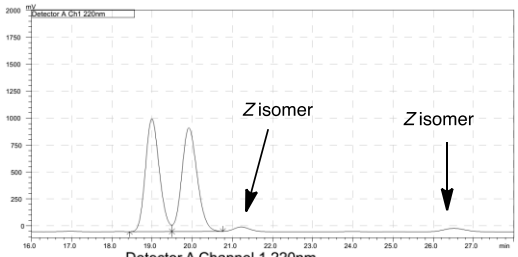



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 18.374 | 1339513 | 3.095 |
| 2 | 32.966 | 41944005 | 96.905 |
| Total | | 43283517 | 100.000 |

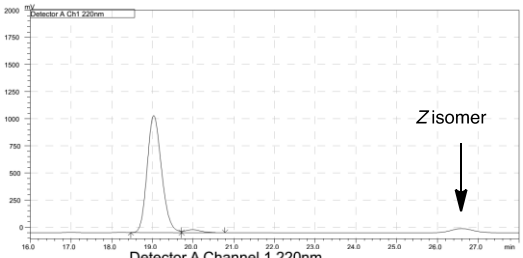
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 18.495 | 5952912 | 50.276 | 18.374 | 1339513 | 3.095 |
| 34.173 | 5887612 | 49.724 | 32.966 | 41944005 | 96.905 |

**(*R*,*E*)-1-Fluoro-3-(5-methylocta-5,7-dien-1-yn-4-yl)benzene (1.44): IR(neat):** 3303 (m), 3084 (w), 3046 (w), 2919 (w), 2121 (w), 1589 (s), 1487 (m), 1446 (m), 1382 (w), 1252 (m), 1135 (w), 988 (m), 905 (m), 985 (s), 731 (w), 698 (m), 640 (s), 521 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.30–7.24 (m, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.96–6.90 (m, 2H), 6.60 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.09 (d, *J* = 10.4 Hz, 1H), 5.25 (d, *J* = 16.8 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 3.54 (t, *J* = 7.6 Hz, 1H), 2.70–2.64 (m, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.64 (s, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 163.0 (d, $J_{CF}$ = 245.6 Hz), 144.6 (d, $J_{CF}$ = 6.8 Hz), 138.8, 133.0, 129.9 (d, $J_{CF}$ = 8.2 Hz), 126.8, 123.7 (d, $J_{CF}$ = 2.8 Hz), 117.1, 114.9 (d, $J_{CF}$ = 21.5 Hz), 113.8 (d, $J_{CF}$ = 21.1 Hz), 82.4, 70.2, 52.7 (d, $J_{CF}$ = 1.5 Hz), 23.0, 15.5; **$^{19}$F NMR (376 MHz, $CDCl_3$):** δ -113.3–-113.4 (m) **HRMS (DART):** Calcd for $C_{15}H_{16}F$ $[M+H]^+$: 215.1236 Found: 215.1236. Specific rotation: $[\alpha]_D^{20}$ +41.7 (*c* 0.60, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **1.44** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.3 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 18.993 | 25352777 | 49.777 |
| 2 | 19.915 | 25580209 | 50.223 |
| Total | | 50932986 | 100.000 |

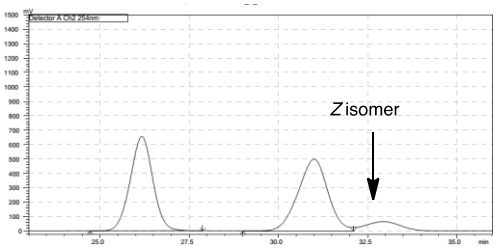



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 19.029 | 26622685 | 97.432 |
| 2 | 19.987 | 701586 | 2.568 |
| Total | | 27324271 | 100.000 |

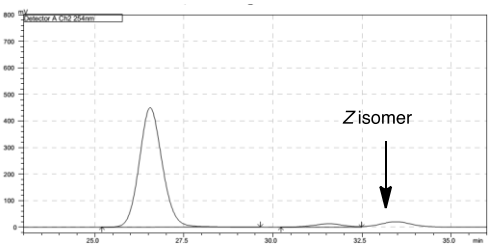
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 18.993 | 25352777 | 49.777 | 19.029 | 26622685 | 97.432 |
| 19.915 | 25580209 | 50.223 | 19.987 | 701596 | 2.568 |

**(*R,E*)-2-(5-Methylocta-5,7-dien-1-yn-4-yl)naphthalene (1.45): IR(neat):** 3296 (s), 3052 (m), 2915 (m), 2119 (w), 1646 (w), 1599 (m), 1507 (m), 1434 (m), 1381 (m), 1271 (w), 1019 (m), 902 (s), 856 (m), 817 (s), 747 (s), 640 (s), 477 (s) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.86–7.77 (m, 3H), 7.69 (s, 1H), 7.51–7.42 (m, 2H), 7.36 (dd, *J* = 8.5, 1.6 Hz, 1H), 6.64 (dt, *J* = 16.8, 10.5 Hz, 1H), 6.18 (d, *J* = 10.5 Hz, 1H), 5.27 (d, *J* = 16.8 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 3.73 (t, *J* = 7.6 Hz, 1H), 2.87–2.74 (m, 2H), 1.96 (td, *J* = 2.6, 1.0 Hz, 1H), 1.67 (s, 3H); **$^{13}$C NMR (150 MHz, $CDCl_3$):** δ 139.4, 139.4, 133.5, 133.2, 132.6, 128.1, 127.9, 127.7, 126.7, 126.5, 126.4, 126.1, 125.7, 116.8, 82.8, 70.1, 53.1, 23.0, 15.6; **HRMS (DART):** Calcd for $C_{19}H_{19}$ $[M+H]^+$: 247.1487 Found: 247.1484. Specific rotation: $[\alpha]_D^{20}$ +64.5 (*c* 0.88, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **1.45** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OJ-H, 98% hexanes, 2% isopropanol, 0.5 mL/min, 220 nm.




Detector A Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 26.169 | 28891567 | 49.683 |
| 2 | 30.999 | 29260211 | 50.317 |
| Total | | 58151778 | 100.000 |

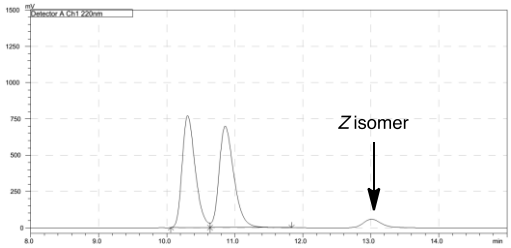



Detector A Channel 2 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 26.549 | 20188174 | 96.297 |
| 2 | 31.574 | 776354 | 3.703 |
| Total | | 20964528 | 100.000 |

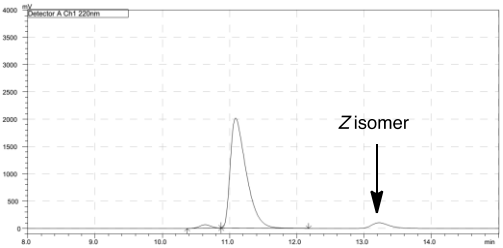
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 26.169 | 28891567 | 49.683 | 26.549 | 20188174 | 96.297 |
| 30.999 | 29260211 | 50.317 | 31.574 | 776354 | 3.703 |

**(*R*,*E*)-1-Chloro-4-(5-methylocta-5,7-dien-1-yn-4-yl)benzene (1.46): IR(neat):** 3311 (m), 3042 (w), 2924 (s), 2853 (m), 2163 (w), 1650 (w), 1491 (m), 1461 (w), 1378 (w), 1092 (m), 1015 (m), 903 (m), 822 (m), 638 (m) $cm^{-1}$; **$^{1}$H NMR (600 MHz, $CDCl_3$):** δ 7.29–7.26 (m, 2H), 7.17–7.14 (m, 2H), 6.58 (dt, *J* = 16.8, 10.2 Hz, 1H), 6.06 (d, *J* = 10.2 Hz, 1H), 5.24 (dd, *J* = 16.8, 1.9 Hz, 1H), 5.11 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.51 (t, *J* = 7.6 Hz, 1H), 2.71–2.59 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.62 (s, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 140.4, 139.0, 133.0, 132.6, 129.4, 128.6, 126.6, 117.1, 82.4, 70.2, 52.3, 23.1, 15.6; **HRMS (DART):** Calcd for $C_{15}H_{16}Cl$ $[M+H]^+$: 231.0941 Found: 231.0943. Specific rotation: $[\alpha]_D^{20}$ +78.6 (*c* 0.33, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **1.46** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-3, 100% hexanes, 0.5 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.306 | 10320911 | 49.452 |
| 2 | 10.858 | 10549846 | 50.548 |
| Total | | 20870757 | 100.000 |

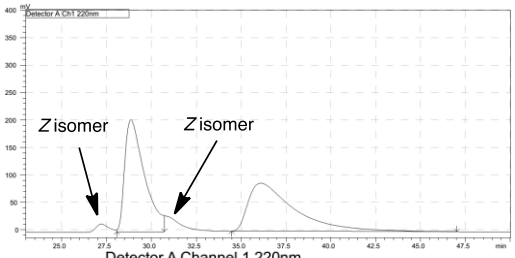



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.636 | 735130 | 2.176 |
| 2 | 11.090 | 33051700 | 97.824 |
| Total | | 33786830 | 100.000 |

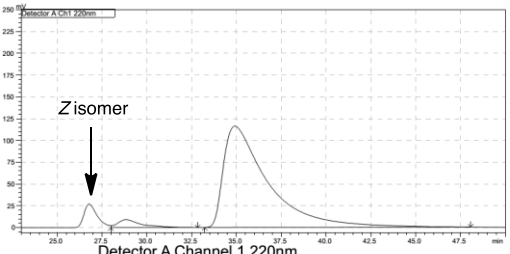
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 10.306 | 10320911 | 49.452 | 10.636 | 735130 | 2.176 |
| 10.858 | 10549846 | 50.548 | 11.090 | 33051700 | 97.824 |

**(*R,E*)-1-Bromo-4-(5-methylocta-5,7-dien-1-yn-4-yl)benzene (1.47): IR(neat):** 3300 (m), 3083 (w), 3043 (w), 2923 (m), 2854 (w), 2119 (w), 1648 (w),1597 (w), 1487 (s), 1434 (m), 1402 (m), 1381 (w), 1180 (w), 1073 (m), 1011 (s), 988 (m), 905 (m), 818 (m), 768 (w), 718 (w), 642 (s), 548 (m), 480 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.45–7.41 (m, 2H), 7.12–7.09 (m, 2H), 6.59 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.07 (d, *J* = 10.4 Hz, 1H), 5.24 (d, *J* = 16.8 Hz, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 3.50 (t, *J* = 7.6 Hz, 1H), 2.72–2.59 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.62 (s, 3H); **$^{13}$C NMR (150 MHz, $CDCl_3$):** δ 140.9, 138.9, 133.0, 131.6, 129.8, 126.7, 120.7, 117.1, 82.4, 70.3, 52.4, 23.0, 15.6; **HRMS (DART):** Calcd for $C_{15}H_{16}Br$ $[M+H]^+$: 275.0435 Found: 275.0437. Specific rotation: $[\alpha]_D^{20}$ +54.1 (*c* 1.00, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **1.47** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel AD-H, 100% hexanes, 0.3 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 28.851 | 15650940 | 49.674 |
| 2 | 36.096 | 15856574 | 50.326 |
| Total | | 31507514 | 100.000 |



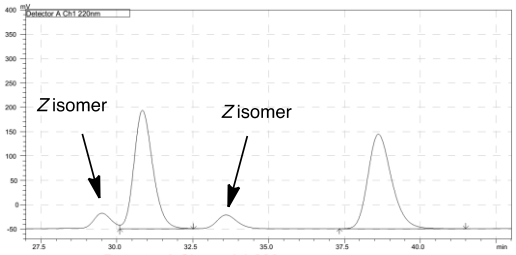

Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 28.833 | 904710 | 4.288 |
| 2 | 34.914 | 20192834 | 95.712 |
| Total | | 21097544 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 28.851 | 15650940 | 49.674 | 28.833 | 904710 | 4.288 |
| 36.09 | 15856574 | 50.326 | 34.914 | 20192834 | 95.712 |

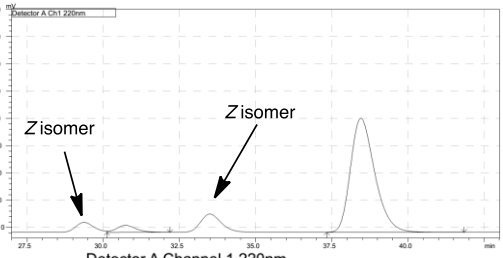
**(*R,E*)-1-(5-Methylocta-5,7-dien-1-yn-4-yl)-4-nitrobenzene (1.48): IR(neat):** 3299 (m), 3085 (w), 2918 (w), 2858 (w), 2172 (w), 1647 (m), 1519 (s), 1435 (w), 1347 (s), 1110 (w), 989 (w), 909 (m), 856 (m), 751 (w), 702 (m), 647 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):**

δ 8.20–8.15 (m, 2H), 7.44–7.38 (m, 2H), 6.58 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.09 (d, *J* = 10.4 Hz, 1H), 5.26 (d, *J* = 16.8 Hz, 1H), 5.16 (d, *J* = 10.4 Hz, 1H), 3.64 (d, *J* = 7.6 Hz, 1H), 2.79–2.64 (m, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.63 (s, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 149.5, 147.1, 137.9, 132.6, 129.0, 127.4, 123.7, 117.8, 81.7, 70.8, 52.8, 22.9, 15.7; **HRMS (DART):** Calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1181 Found: 242.1187. Specific rotation: $[\alpha]_D^{20}$ –32.2 (*c* 0.31, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **1.48** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel AD-H, 99.5% hexanes, 0.5% isopropanol, 0.3 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 30.840 | 10623920 | 50.229 |
| 2 | 38.619 | 10526904 | 49.771 |
| Total | | 21150825 | 100.000 |



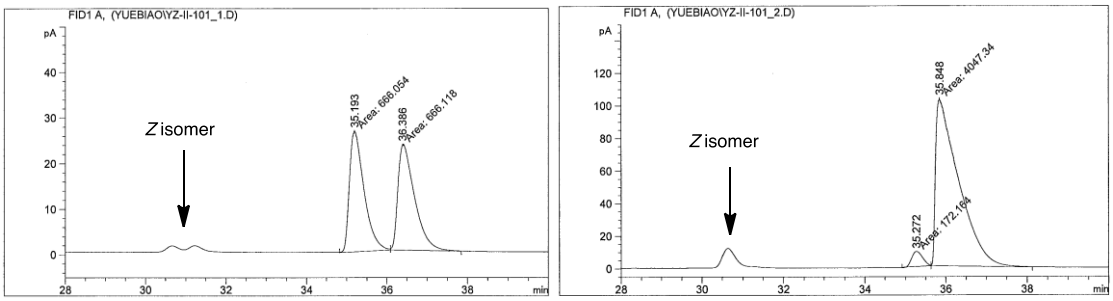

Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 30.730 | 2962277 | 4.870 |
| 2 | 38.454 | 57860632 | 95.130 |
| Total | | 60822910 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 30.840 | 10623920 | 50.229 | 30.730 | 2962277 | 4.870 |
| 38.619 | 10526904 | 49.771 | 38.454 | 75860632 | 95.130 |

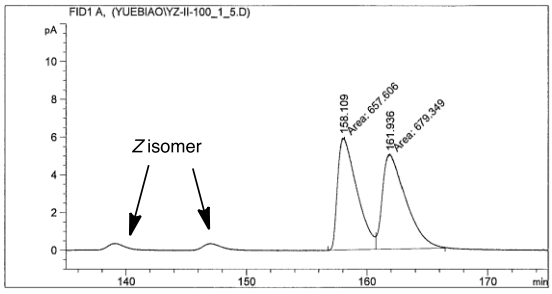
**(*R*,*E*)-3-(5-Methylocta-5,7-dien-1-yn-4-yl)furan (1.49): IR(neat):** 3300 (m), 3085 (w), 2919 (m), 2857 (w), 2122 (w), 1649 (w), 1502 (m), 1433 (w), 1382 (w), 1185 (m), 1069 (w), 1025 (m), 990 (m), 904 (m), 873 (s), 789 (m), 759 (m), 643 (s), 599 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.36 (t, *J* = 1.7 Hz, 1H), 7.31–7.30 (m, 1H), 6.59 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.27 (dd, *J* = 1.7, 0.8 Hz, 1H), 6.04 (d, *J* = 10.4 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 3.46 (t, *J* = 7.5 Hz, 1H), 2.66–2.54 (m, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.69 (s, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 143.0, 139.4, 138.9, 133.1, 127.2, 126.2, 116.7, 110.4, 82.6, 70.0, 44.8, 22.8, 14.2; **HRMS (DART):** Calcd for $C_{13}H_{15}O$

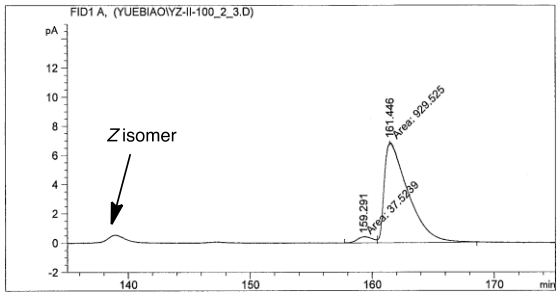
[M+H]$^+$: 187.1123 Found: 187.1126. Specific rotation: $[\alpha]_D^{20}$ –46.6 (*c* 0.48, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **1.49** was determined by GC analysis in comparison with authentic racemic material; CDB/DM column 100 °C, 15 psi.




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 35.193 | 666.05365 | 49.99760 | 35.272 | 172.16367 | 4.08019 |
| 36.386 | 666.11768 | 50.00240 | 35.848 | 4047.34009 | 95.91981 |

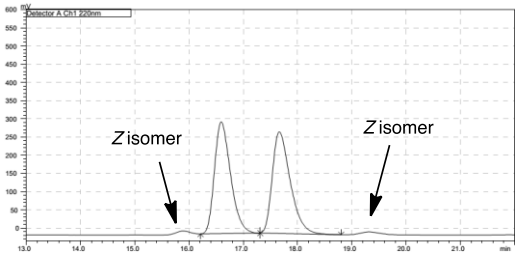
**(*R,E*)-3-(5-Methylocta-5,7-dien-1-yn-4-yl)thiophene (1.50): IR(neat):** 3298 (m), 3083 (w), 2020 (w), 2854 (w), 2119 (w), 1647 (w), 1597 (w), 1418 (w), 1381 (w), 989 (m), 904 (m), 860 (w), 838 (w), 778 (s), 650 (w), 578 (s) cm$^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.26–7.24 (m, 1H), 7.06–7.05 (m, 1H), 6.94 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.60 (dt, *J* = 16.8, 10.5 Hz, 1H), 6.07 (d, *J* = 10.5 Hz, 1H), 5.21 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.09 (dd, *J* = 10.5, 1.6 Hz, 1H), 3.65 (t, *J* = 7.5 Hz, 1H), 2.76–2.62 (m, 2H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.66 (s, 3H); **$^{13}$C NMR (150 MHz, $CDCl_3$):** δ 142.9, 139.2, 133.1, 127.8, 127.1, 125.5, 120.9, 116.7, 82.7, 70.0, 49.0, 23.0, 14.5; **HRMS (DART):** Calcd for $C_{13}H_{15}S$ [M+H]$^+$: 203.0894 Found: 203.0899. Specific rotation: $[\alpha]_D^{20}$ –51.0 (*c* 0.42, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **1.50** was determined by GC analysis in comparison with authentic racemic material; CDB/DM column 100 °C, 10 psi.



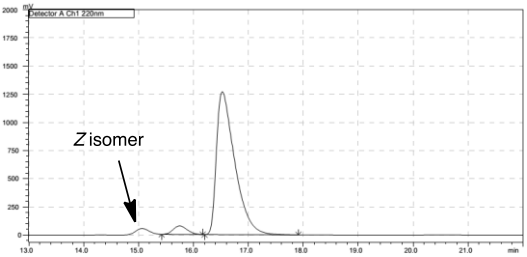

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 158.109 | 657.60571 | 49.18682 | 159.291 | 37.52395 | 3.88025 |
| 161.936 | 679.34930 | 50.81318 | 161.446 | 929.52484 | 96.11975 |

**(*R*,*E*)-(4-Methyl-3-(prop-2-yn-1-yl)hepta-4,6-dien-1-yl)benzene (1.51): IR(neat):** 3303 (m), 3083 (w), 3026 (m), 2926 (s), 2860 (m), 2117 (w), 1646 (w), 1602 (w), 1496 (m), 1454 (m), 1382 (w), 1031 (w), 987 (m), 901 (s), 748 (m), 699 (s), 638 (s) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.31–7.26 (m, 2H), 7.23–7.13 (m, 3H), 6.64 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.96 (d, *J* = 10.4 Hz, 1H), 5.18 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.08 (dd, *J* = 10.4, 2.0 Hz, 1H), 2.65–2.45 (m, 2H), 2.36–2.26 (m, 1H), 2.32–2.29 (m, 2H), 1.97 (t, *J* = 2.5 Hz, 1H), 1.95–1.85 (m, 1H), 1.80–1.69 (m, 1H), 1.74 (d, *J* = 1.2 Hz, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 142.3, 139.3, 133.1, 128.5, 128.4, 127.9, 125.9, 116.0, 83.0, 69.6, 47.6, 34.1, 33.8, 23.6, 13.1; **HRMS (DART):** Calcd for $C_{17}H_{21}$ $[M+H]^+$: 225.1643 Found: 225.1653. Specific rotation: $[\alpha]_D^{20}$ –2.2 (*c* 0.90, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **1.51** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-H, 100% hexanes, 0.5 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 16.590 | 6348366 | 49.734 |
| 2 | 17.662 | 6416304 | 50.266 |
| Total | | 12764669 | 100.000 |




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 15.746 | 1359230 | 4.406 |
| 2 | 16.524 | 29491919 | 95.594 |
| Total | | 30851149 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 16.590 | 6348366 | 49.734 | 15.746 | 1359230 | 4.406 |
| 17.662 | 6416304 | 50.266 | 16.524 | 29491919 | 95.594 |

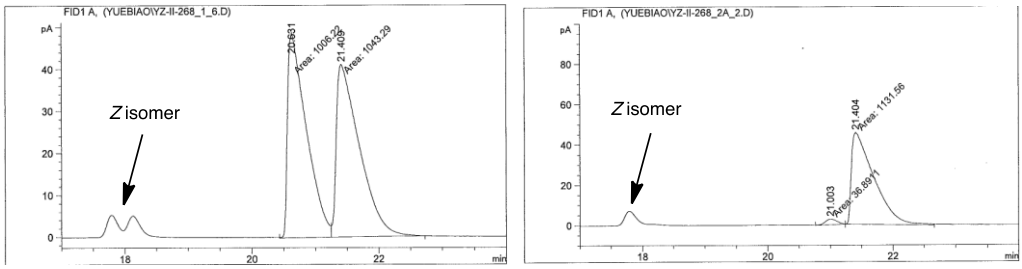
- **Procedure for Catalytic $S_N2$"- and Enantioselective Propargyl Substitution to Cyclic Dienyl Phosphates**

An oven-dried 1-dram vial equipped with a stir bar was charged with imidazolinium salt **imid-1.4** (4.0 mg, 5.5 μmol), NaOMe (8.1 mg, 150 μmol), and CuCl (0.5 mg, 5.0 μmol) in a $N_2$-filled glove box. The vial was sealed with a cap (phenolic open top cap with a red PFTE/white silicon septum) and electrical tape, and removed from the glove box. $CH_2Cl_2$ (0.5 mL) was added and the mixture was allowed to stir for 1 h under $N_2$ at 22 °C (the mixture turned light blue-green). The allenyl–B(pin) compound **1.30** (35.9 μL, 0.20 mmol) was subsequently added through a syringe, and the mixture was allowed to stir at 22 °C for 30 min. At this point, allylic phosphate (26.0 mg, 0.10 mmol) was added (at 22 °C), and the mixture was allowed to stir for 16 h. The mixture was passed through a short plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$ (3.0 mL). The organic layer was concentrated in vacuo, resulting in yellow oil residue, which was purified by silica gel chromatography (hexanes, $R_f$ = 0.30) to afford **1.52** as colorless oil (10.4 mg, 0.071 mmol, 71% yield).

- **Characterization Data for Cyclic Products with a Trisubstituted Olefin**

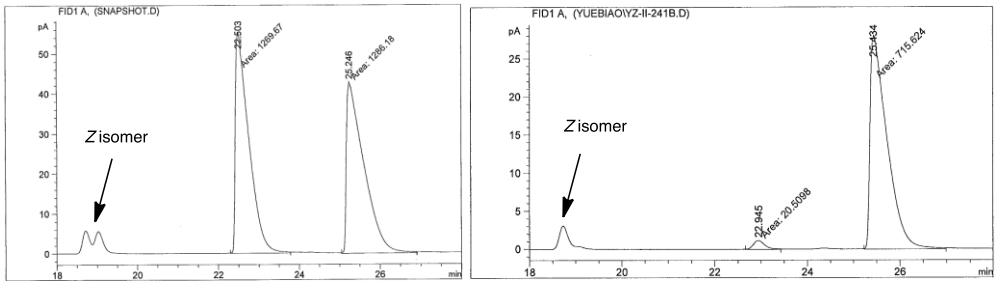
**(*R*,*E*)-1-Allylidene-2-(prop-2-yn-1-yl)cyclopentane (1.52): IR(neat):** 3312 (m), 3011 (w), 2924 (s), 2854 (s), 2114 (w), 1974 (w), 1655 (w), 1461 (m), 1378 (w), 989 (w), 631 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 6.44 (dt, *J* = 17.0, 10.5 Hz, 1H), 5.96 (dq, *J* = 10.5, 2.4 Hz, 1H), 5.10 (d, *J* = 17.0 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 2.67–2.57 (m, 1H), 2.52–2.36 (m, 3H), 2.21 (ddd, *J* = 16.8, 8.4, 2.7 Hz, 1H), 2.04–1.96 (m, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.83–1.75 (m, 1H), 1.68–1.56 (m, 1H), 1.54–1.46 (m, 1H); **$^{13}$C NMR (100**

**MHz, $CDCl_3$):** δ 149.4, 134.7, 121.7, 114.9, 83.5, 68.9, 43.6, 32.4, 30.1, 24.0, 23.3; **HRMS (DART):** Calcd for $C_{11}H_{15}$ $[M+H]^+$: 147.1147 Found: 147.1173; Specific rotation: $[\alpha]_D^{20}$ +97.6 (*c* 0.32, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **1.52** was determined by GC analysis in comparison with authentic racemic material; CDB/DM column 100 °C, 10 psi.



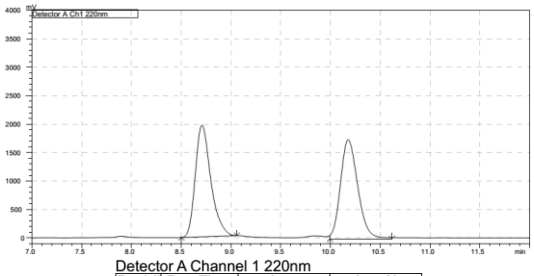

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 20.631 | 1006.22052 | 49.09570 | 21.003 | 36.89113 | 3.15727 |
| 21.409 | 1043.28796 | 50.90430 | 21.404 | 1131.55896 | 96.84273 |

**(*R*,*E*)-1-Allylidene-2-(prop-2-yn-1-yl)cyclohexane (1.53): IR(neat):** 3308 (m), 3083 (w), 2927 (s), 2855 (m), 2151 (w), 1646 (w), 1447 (m), 1261 (w), 1006 (m), 899 (m), 802 (w), 631 (m) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 6.65 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.83 (d, *J* = 10.4 Hz, 1H), 5.17 (d, *J* = 16.8 Hz, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 2.53–2.48 (m, 1H), 2.42 (td, *J* = 9.6, 9.0, 2.6 Hz, 1H), 2.35–2.30 (m, 2H), 2.12–2.05 (m, 1H), 1.99 (t, *J* = 2.5 Hz, 1H), 1.95–1.87 (m, 1H), 1.75–1.67 (m, 1H), 1.65–1.58 (m, 1H), 1.52–1.40 (m, 3H); **$^{13}$C NMR (150 MHz, $CDCl_3$):** δ 144.8, 132.6, 121.9, 115.9, 83.5, 69.6, 43.6, 33.3, 28.3, 28.0, 24.5, 22.1; **HRMS (DART):** Calcd for $C_{12}H_{17}$ $[M+H]^+$: 161.133 Found: 161.1328. Specific rotation: $[\alpha]_D^{20}$ +6.5 (*c* 0.63, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **1.53** was determined by GC analysis in comparison with authentic racemic material; CDB/DM column 100 °C, 15 psi.



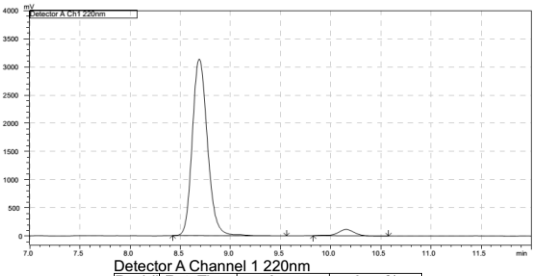

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 22.503 | 1269.67322 | 49.67699 | 22.945 | 20.50983 | 2.78615 |
| 25.246 | 1286.18433 | 50.32301 | 25.434 | 715.62421 | 97.21385 |

**(*R,E*)-1-Allylidene-2-(prop-2-yn-1-yl)cycloheptane (1.54): IR(neat):** 3306 (m), 3084 (w), 2921 (s), 2852 (m), 2117 (w), 1640 (w), 1449 (m), 1350 (w), 988 (m), 898 (s), 629 (s) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 6.60 (dt, *J* = 16.8, 10.8 Hz, 1H), 5.89 (dt, *J* = 10.8, 0.9 Hz, 1H), 5.14 (ddd, *J* = 16.8, 2.2, 0.9 Hz, 1H), 5.03 (ddd, *J* = 10.8, 2.2, 0.9 Hz, 1H), 2.57–2.50 (m, 1H), 2.47–2.38 (m, 1H), 2.27–2.19 (m, 2H), 2.12–2.03 (m, 1H), 1.96 (t, *J* = 2.7 Hz, 2H), 1.88–1.67 (m, 3H), 1.33–1.14 (m, 4H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 146.8, 133.0, 127.7, 115.6, 83.5, 69.4, 46.8, 33.1, 30.9, 29.7, 27.2, 26.1, 26.1; **HRMS (DART):** Calcd for $C_{13}H_{19}$ $[M+H]^+$: 175.1487 Found: 175.1478. Specific rotation: $[\alpha]_D^{20}$ +124.0 (*c* 0.35, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **1.54** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.5 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.708 | 21243332 | 50.284 |
| 2 | 10.177 | 21003722 | 49.716 |
| Total | | 42247054 | 100.000 |




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.689 | 32925022 | 96.297 |
| 2 | 10.153 | 1266267 | 3.703 |
| Total | | 34191289 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 8.708 | 21243332 | 50.284 | 8.689 | 32925022 | 96.297 |
| 10.177 | 21003722 | 49.716 | 10.153 | 1266267 | 3.703 |

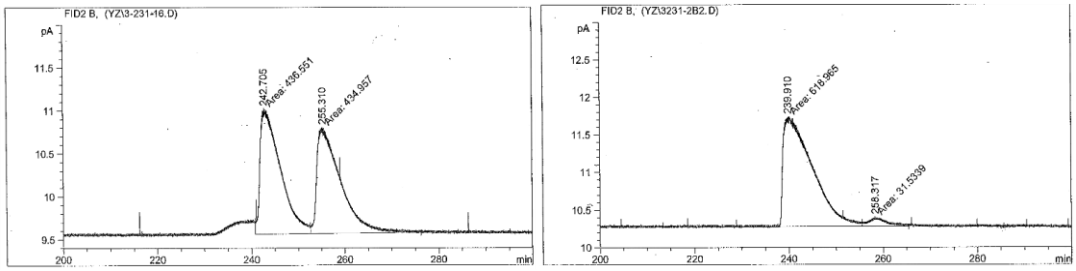
- **Procedure for Catalytic $S_N2$"- and Enantioselective Silyl Allenyl Substitutions**

An oven-dried 1-dram vial equipped with a stir bar was charged with **imid-1.4 (**4.0 mg, 5.5 μmol) or **imid-1.3** (4.7 mg, 5.5 μmol), NaOMe (8.1 mg, 150 μmol), and CuCl (0.5 mg, 5.0 μmol) in a $N_2$-filled glove box. The vial was capped (phenolic open top cap with a red PFTE/white silicon septum) and sealed with electrical tape, and then removed from the glove box. $CH_2Cl_2$ (0.5 mL) was added and the mixture was allowed to stir for 1 h under $N_2$ at 22 °C (the mixture turned light blue-green). Propargyl–B(pin) compound **1.55** (47.6 mg, 0.20 mmol) was added to the mixture through a syringe, and the resulting mixture was allowed to stir at 22 °C for 30 min. At this point, allylic phosphate (29.6 mg, 0.10 mmol) was added (at 22 °C), and the mixture was allowed to stir for 16 h. The solution was then passed through a short plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$ (3.0 mL). The organic layer was concentrated in vacuo, resulting in yellow oil residue, which was purified by silica gel chromatography (hexanes, $R_f$ = 0.30) to afford **1.56** as colorless oil (18.8 mg, 0.071 mmol, 74% yield).

- **Characterization Data for Silyl Allenyl Substitution Products**

**(*R,E*)-Trimethyl(4-phenylocta-1,2,5,7-tetraen-3-yl)silane (1.56): IR(neat):** 3084 (w), 3062 (w), 3027 (w), 2956 (w), 2896 (w), 1924 (m), 1648 (w), 1601 (w), 1493 (m), 1452 (w), 1406 (w), 1248 (m), 1002 (m), 900 (w), 838 (s), 815 (m), 754 (m), 699 (m) $cm^{-1}$; **$^1$H NMR (600 MHz, Benzene-$d_6$):** δ 7.27–7.23 (m, 2H), 7.19–7.13 (m, 2H), 7.08–7.04 (m, 1H), 6.33 (dt, *J* = 17.0, 9.8 Hz, 1H), 6.10 (dd, *J* = 15.0, 7.1 Hz, 1H), 6.06 (dd, *J* = 15.0, 9.8 Hz, 1H), 5.03 (dd, *J* = 17.0, 1.8 Hz, 1H), 4.91 (dd, *J* = 9.8, 1.8 Hz, 1H), 4.43 (dd, *J* = 11.0,

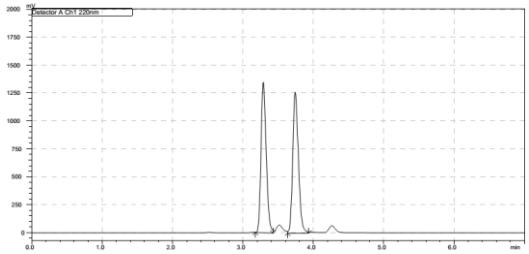
2.5 Hz, 1H), 4.38 (dd, *J* = 11.0, 2.5 Hz, 1H), 4.00 (dt, *J* = 7.1, 2.5 Hz, 1H), 0.05 (s, 9H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 209.8, 143.3, 137.6, 137.0, 130.6, 128.4, 128.4, 126.6, 116.0, 98.5, 71.0, 48.7, –1.2; **HRMS (DART):** Calcd for $C_{17}H_{23}Si$ $[M+H]^+$: 255.1564 Found: 255.1575. Specific rotation: $[\alpha]_D^{20}$ –91.8 (*c* 0.77, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **1.56** was determined by GC analysis in comparison with authentic racemic material; CDGTA column 100 °C, 9 psi.




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 242.705 | 436.55090 | 50.09142 | 239.910 | 618.96460 | 95.15235 |
| 255.310 | 434.95749 | 49.90858 | 258.317 | 31.53386 | 4.84765 |

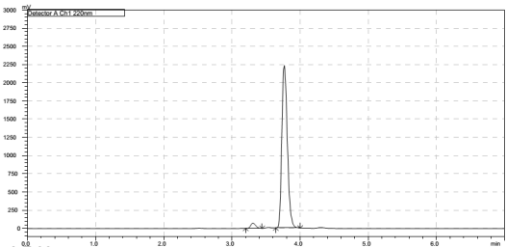
**(*R*,*E*)-(4-(2-Methoxyphenyl)octa-1,2,5,7-tetraen-3-yl)trimethylsilane (1.57): IR(neat)** 3084 (w), 2999 (w), 1956 (w), 2836 (w), 1924 (m), 1648 (w), 1598 (w), 1489 (m), 1464 (m), 1439 (w), 1288 (w), 1245 (s), 1051 (w), 1031 (m), 948 (w), 899 (s), 752 (s) $cm^{-1}$; **$^1$H NMR (500 MHz, Benzene-$d_6$):** δ 7.43 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 6.37 (dt, *J* = 16.8, 10.1 Hz, 1H), 6.24 (dd, *J* = 15.0, 10.1 Hz, 1H), 6.15 (dd, *J* = 15.0, 7.5 Hz, 1H), 5.02 (d, *J* = 16.8 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 4.85–4.79 (m, 1H), 4.45 (dd, *J* = 10.8, 2.7 Hz, 1H), 4.39 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.32 (s, 3H), 0.12 (s, 9H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 209.9, 156.5, 137.3, 137.3, 131.5, 130.5, 129.4, 127.5, 120.4, 115.5, 110.6, 98.4, 70.8, 55.6, 39.9, –1.3; **HRMS (DART):** Calcd for $C_{18}H_{25}Si$ $[M+H]^+$: 285.1669 Found: 285.1654. Specific rotation: $[\alpha]_D^{20}$ –68.1 (*c* 1.09, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **1.57** was

determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-3, 100% hexanes, 0.8 mL/min, 220 nm.



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 3.289 | 6971649 | 49.545 |
| 2 | 3.743 | 7099740 | 50.455 |
| Total | | 14071389 | 100.000 |

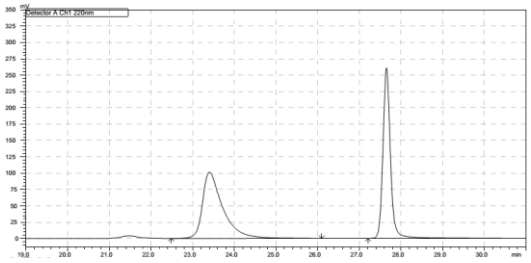


Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 3.307 | 365787 | 2.825 |
| 2 | 3.767 | 12582436 | 97.175 |
| Total | | 12948223 | 100.000 |

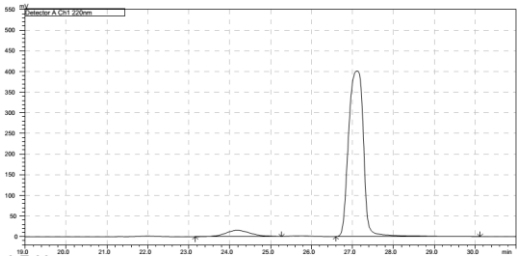
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 3.289 | 6971649 | 49.545 | 3.307 | 365787 | 2.825 |
| 3.743 | 7099740 | 50.455 | 3.767 | 12582436 | 97.175 |

**(*R*,*E*)-Trimethyl(4-(4-nitrophenyl)octa-1,2,5,7-tetraen-3-yl)silane (1.58): IR(neat):** 3086 (w), 2957 (w), 2896 (w), 1924 (m), 1596 (w), 1519 (s), 1345 (s), 1249 (m), 1110 (w), 1104 (m), 840 (s), 754 (w), 699 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 8.15 (d, *J* = 7.0 Hz, 2H), 7.38 (d, *J* = 7.0 Hz, 2H), 6.33 (dt, *J* = 17.0, 10.1 Hz, 1H), 6.02 (dd, *J* = 15.2, 10.1 Hz, 1H), 5.92 (dd, *J* = 15.2, 7.8 Hz, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 4.52 (dt, *J* = 11.4, 1.9 Hz, 1H), 4.46 (dt, *J* = 11.4, 1.9 Hz, 1H), 4.05 (d, *J* = 7.8 Hz, 1H), 0.03 (s, 9H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 210.1, 151.1, 146.8, 136.4, 135.4, 132.0, 129.2, 123.7, 117.3, 97.9, 71.7, 48.5, –1.1; **HRMS (DART):** Calcd for $C_{17}H_{22}NO_2Si$ $[M+H]^+$: 300.1414 Found: 300.1401. Specific rotation: $[\alpha]_D^{20}$ –102.0 (*c* 0.53, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **1.58** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-3, 100% hexanes, 1.0 mL/min, 220 nm.



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 23.402 | 3417933 | 50.803 |
| 2 | 27.653 | 3309883 | 49.197 |
| Total | | 6727816 | 100.000 |

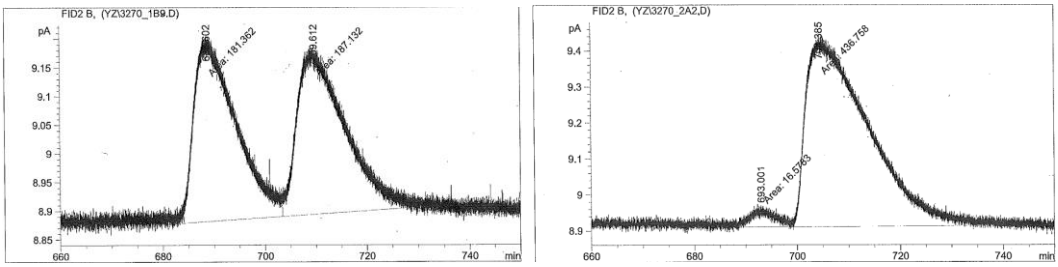


Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 24.181 | 684557 | 6.346 |
| 2 | 27.113 | 10103302 | 93.654 |
| Total | | 10787860 | 100.000 |

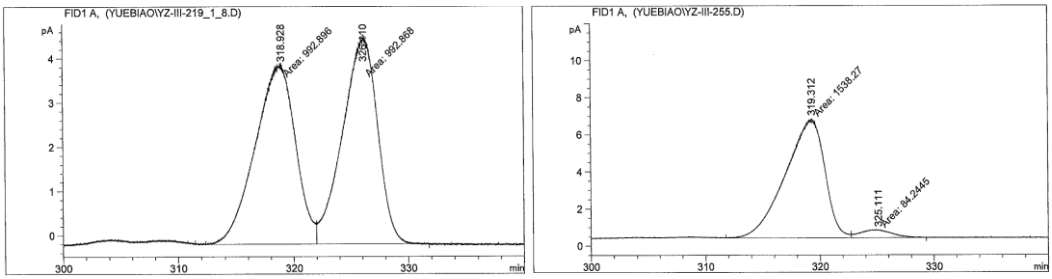
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 23.402 | 3417933 | 50.803 | 24.181 | 684557 | 6.346 |
| 27.653 | 3309883 | 49.197 | 27.113 | 10103302 | 93.654 |

**(*S*,*E*)-Trimethyl(4-phenethylocta-1,2,5,7-tetraen-3-yl)silane (1.59): IR(neat):** 3086 (w), 3027 (w), 2955 (w), 2857 (w), 1925 (m), 1648 (w), 1603 (w), 1496 (w), 1454 (w), 1248 (m), 1003 (m), 951 (w), 899 (w), 838 (s), 752 (m), 698 (m), 627 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.28 (t, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 3H), 6.34 (dt, *J* = 17.0, 10.4 Hz, 1H), 6.04 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.60 (dd, *J* = 15.2, 8.9 Hz, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.49–4.41 (m, 2H), 2.66–2.54 (m, 3H), 1.97–1.87 (m, 1H), 1.82–1.71 (m, 1H), 0.09 (s, 9H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 208.7, 142.6, 138.3, 137.1, 130.8, 128.6, 128.4, 125.8, 115.6, 97.8, 70.7, 42.4, 37.2, 34.0, –1.1; **HRMS (DART):** Calcd for $C_{19}H_{27}Si$ $[M+H]^+$: 283.1877 Found: 283.1879. Specific rotation: $[\alpha]_D^{20}$ +189.7 (*c* 1.02, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **1.59** was determined by GC analysis in comparison with authentic racemic material; CDGTA column 90 °C, 20 psi.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 688.602 | 181.36168 | 49.21702 | 693.001 | 16.57826 | 3.65695 |
| 709.612 | 187.13213 | 50.78298 | 704.385 | 436.75781 | 96.34305 |

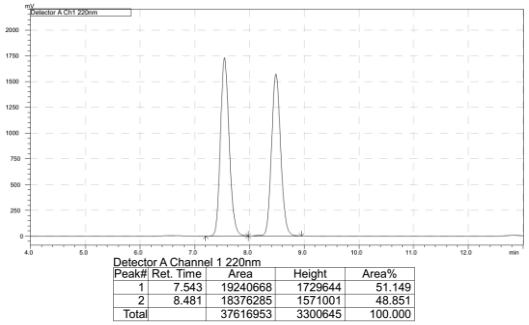
**(*R*,*E*)-Trimethyl(5-methyl-4-phenylocta-1,2,5,7-tetraen-3-yl)silane (1.60): IR(neat):** 3083 (w), 3025 (w), 2956 (w), 2900 (w), 2016 (w), 1926 (m), 1646 (w), 1600 (w), 1494 (w), 1451 (w), 1379 (w), 1248 (m), 987 (w), 905 (w), 839 (s), 812 (m), 754 (m), 699 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.39–7.22 (m, 2H), 7.23–7.14 (m, 3H), 6.60 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.90 (d, *J* = 10.4 Hz, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 4.42–4.35 (m, 1H), 4.33–4.27 (m, 1H), 3.94 (s, 1H), 1.74 (s, 3H), 0.05 (s, 9H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 210.1, 141.9, 140.4, 133.4, 129.1, 128.0, 127.7, 126.5, 116.0, 97.3, 70.6, 54.8, 17.1, –1.2; **HRMS (DART):** Calcd for $C_{18}H_{25}Si$ $[M+H]^+$: 269.1720 Found: 269.1716. Specific rotation: $[\alpha]_D^{20}$ +70.4 (*c* 0.50, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **1.60** was determined by GC analysis in comparison with authentic racemic material; CDB/DM column 90 °C, 12 psi.




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 318.928 | 992.89612 | 50.00071 | 319.312 | 1538.27393 | 94.80779 |
| 326.110 | 992.86804 | 49.99929 | 325.111 | 84.24449 | 5.19221 |

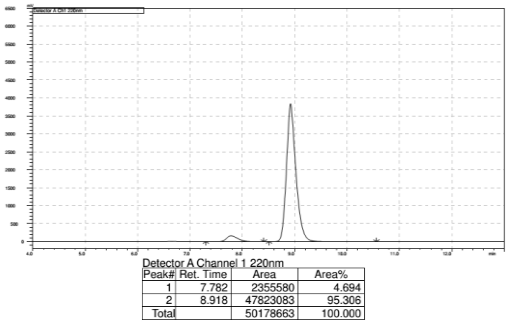
**(*R*,*E*)-(4-(2-Methoxyphenyl)-5-methylocta-1,2,5,7-tetraen-3-yl)trimethylsilane (1.61): IR(neat):** 3082 (w), 2956 (w), 2835 (w), 1926 (s), 1647 (w), 1598 (w), 1489 (s), 1464 (w), 1439 (w), 1242 (s), 1103 (w), 1033 (w), 988 (w), 905 (w), 840 (s), 753 (s) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.21–7.13 (m, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H),

6.62 (dt, *J* = 16.8, 10.7 Hz, 1H), 5.87 (d, *J* = 10.7 Hz, 1H), 5.09 (d, *J* = 16.8 Hz, 1H), 5.01 (d, *J* = 10.7 Hz, 1H), 4.42 (s, 1H), 4.33 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.24 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.80 (s, 3H), 1.75 (s, 3H), 0.04 (s, 9H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 210.1, 157.1, 140.2, 133.6, 130.6, 129.8, 127.4, 127.4, 120.0, 115.4, 110.5, 97.4, 70.3, 55.7, 46.2, 17.7, −1.3; **HRMS (DART):** Calcd for $C_{19}H_{27}OSi$ $[M+H]^+$: 299.1826 Found: 299.1810. Specific rotation: $[\alpha]_D^{20}$ +44.3 (*c* 0.47, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **1.61** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-3, 100% hexanes, 0.3 mL/min, 220 nm.



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Height | Area% |
|---|---|---|---|---|
| 1 | 7.543 | 19240668 | 1729644 | 51.149 |
| 2 | 8.481 | 18376285 | 1571001 | 48.851 |
| Total | | 37616953 | 3300645 | 100.000 |



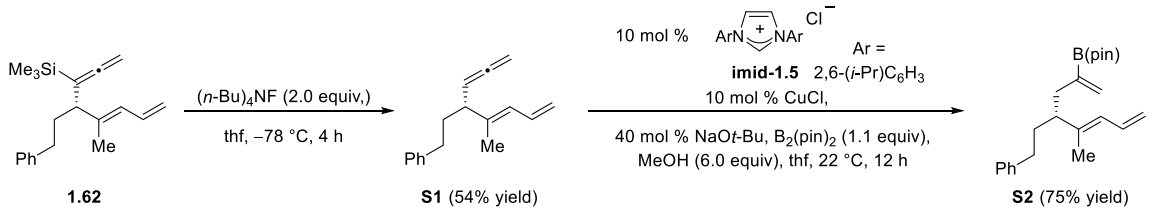
Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 7.782 | 2355580 | 4.694 |
| 2 | 8.918 | 47823083 | 95.306 |
| Total | | 50178663 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 7.543 | 19240668 | 51.149 | 7.782 | 2355580 | 4.694 |
| 8.481 | 18376285 | 48.851 | 8.918 | 47823083 | 95.306 |

**(*S*,*E*)-Trimethyl(5-methyl-4-phenethylocta-1,2,5,7-tetraen-3-yl)silane (1.62):** **IR(neat):** 3027 (w), 2954 (w), 2859 (w), 1923 (m), 1644 (w), 1604 (w), 1496 (w), 1454 (w), 1247 (m), 986 (w), 901 (w), 838 (s), 811 (m), 751 (m), 698 (m), 625 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ7.36–7.23 (m, 2H), 7.22–7.15 (m, 3H), 6.58 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.93 (d, *J* = 10.4 Hz, 1H), 5.14 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.04 (dd, *J* = 10.4, 2.1 Hz, 1H), 4.47 (qd, *J* = 10.7, 2.3 Hz, 2H), 2.67 (tt, *J* = 7.2, 2.4 Hz, 1H), 2.62–2.46 (m, 2H), 1.99–1.77 (m, 2H), 1.67 (s, 3H), 0.07 (s, 9H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 209.1, 142.8, 140.7, 133.4, 128.6, 128.4, 127.5, 125.8, 115.6, 96.7, 70.4, 48.4, 34.9, 34.3, 13.1,

–1.1; **HRMS (DART):** Calcd for $C_{20}H_{29}Si$ $[M+H]^+$: 297.2033 Found: 297.2036. Specific rotation: $[\alpha]_D^{20}$ +194.0 (*c* 1.24, $CHCl_3$) for a 96:4 er sample. Enantiopurity of **1.62** was determined after silyl removal and proto-boryl addition to the allene.




**Proto-Desilylation of a Silyl Allene (S1):** In an oven-dried 1-dram vial equipped with a stir bar was charged with silyl allene **1.62** (12.1 mg, 0.041 mmol) and thf (200 μL). The mixture was cooled to –78 °C and charged with tetra(*n*-butyl)ammonium fluoride (1.0 M in thf, 0.082 mL, 0.082 mmol) in a dropwise manner. The solution was the allowed to stir for 4 h at – 78 °C, after which $H_2O$ and $Et_2O$ were added, the organic layer was separated, and the aqueous layer was washed with $Et_2O$ (3 x 2 mL). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The resulting oil was purified by silica gel chromatography (hexanes) to afford **S1** as colorless oil (5.0 mg, 22.3 μmol, 54% yield).

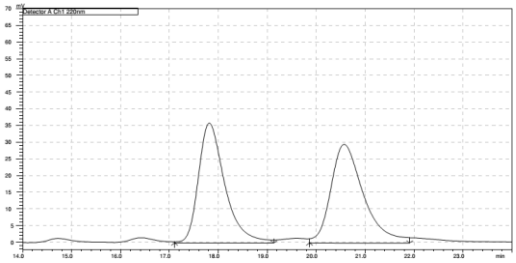
**(*R*,*E*)-(4-Methyl-3-(propa-1,2-dien-1-yl)hepta-4,6-dien-1-yl)benzene (S1): IR(neat):** 3026 (w), 2925 (s), 2855 (m), 1953 (m), 1646 (w), 1603 (w), 1496 (w), 1454 (w), 1379 (w), 987 (w), 900 (m), 843 (m), 747 (w), 699 (m) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.31–7.25 (m, 2H), 7.21–7.15 (m, 3H), 6.60 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.94 (d, *J* = 10.5 Hz, 1H), 5.15 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.10 (q, *J* = 6.8 Hz, 1H), 5.05 (dd, *J* = 10.5, 2.1 Hz, 1H), 4.76 (dd, *J* = 6.8, 2.8 Hz, 2H), 2.78–2.71 (m, 1H), 2.66–2.51 (m, 2H), 1.82 (q, *J* = 7.8 Hz, 2H), 1.73 (s, 3H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 208.5, 142.5, 140.5, 133.3, 128.6, 128.4, 126.7, 125.9, 115.9, 92.9, 76.1, 47.7, 34.2, 33.9, 13.7; **HRMS (DART):**

Calcd for $C_{17}H_{21}$ $[M+H]^+$: 225.1638 Found: 225.1639. Specific rotation: $[\alpha]_D^{20}$ +68.0 (*c* 0.25, $CHCl_3$).

**Catalytic Proto-Boryl Addition to an Allene (S2):** In a $N_2$-filled glove-box, an oven-dried 1-dram vial equipped with a stir bar was charged with CuCl (0.2 mg, 1.9 μmol), 1,3-Bis-(2,6-diisopropylphenyl)imidazolium chloride (0.8 mg, 1.9 μmol), NaO$^t$Bu (0.7 mg, 7.6 μmol) and thf (200 μL). The mixture was allowed to stir for 1 h under $N_2$ at 22 °C. $B_2(pin)_2$ (5.3 mg, 21.0 μmol) was then added to the mixture and the resulting mixture was allowed to stir at 22 °C for 30 min. Allene **S1** (4.3 mg, 19.0 μmol) and methanol (3.7 mg, 0.11 mmol) were added to the mixture at 22 °C, after which it was allowed to stir at 22 °C for 12 h, passed through a short plug of silica gel (4 cm x 1 cm), and eluted with $Et_2O$ (3.0 mL). The organic layer was concentrated in vacuo, resulting in yellow oil residue, which was purified by silica gel chromatography (hexanes:ethyl acetate 10:1, $R_f$ = 0.50) to afford **S2** as colorless oil (5.0 mg, 0.014 mmol, 75% yield).

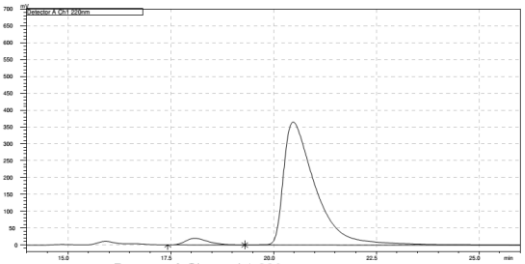
**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(5-methyl-4-phenethylocta-1,5,7-trien-2-yl)-1,3,2-dioxaborolane (S2): IR(neat):** 3026 (w), 2977 (m), 2926 (m), 2857 (w), 1645 (w), 1612 (w), 1414 (m), 1369 (s), 1308 (s), 1202 (w), 1142 (s), 987 (w), 896 (m), 863 (m), 747 (w), 699 (m) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.31–7.20 (m, 2H), 7.18–7.06 (m, 3H), 6.58 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.83 (d, *J* = 10.5 Hz, 1H), 5.75 (d, *J* = 3.5 Hz, 1H), 5.53 (d, *J* = 3.5 Hz, 1H), 5.07 (dd, *J* = 16.8, 2.2 Hz, 1H), 4.98 (dd, *J* = 10.5, 2.2 Hz, 1H), 2.53 (ddd, *J* = 13.8, 10.3, 5.3 Hz, 1H), 2.45 (ddd, *J* = 13.8, 10.3, 6.6 Hz, 1H), 2.37–2.30 (m, 1H), 2.30–2.16 (m, 2H), 1.77–1.58 (m, 5H), 1.23 (d, *J* = 2.7 Hz, 12H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 143.0, 141.1, 133.5, 130.5, 128.6, 128.3, 127.6, 125.7, 114.8, 83.4, 48.8, 40.3, 34.9, 34.1, 24.9, 24.9, 12.7; **HRMS (DART)**: Calcd for $C_{23}H_{34}BO_2$ $[M+H]^+$: 353.2646

Found: 353.2642. Specific rotation: $[\alpha]_D^{20}$ –10.4 (*c* 0.25, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **S2** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-3, 100% hexanes, 0.3 mL/min, 220 nm.



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 17.813 | 1346068 | 49.457 |
| 2 | 20.570 | 1375607 | 50.543 |
| Total | | 2721676 | 100.000 |

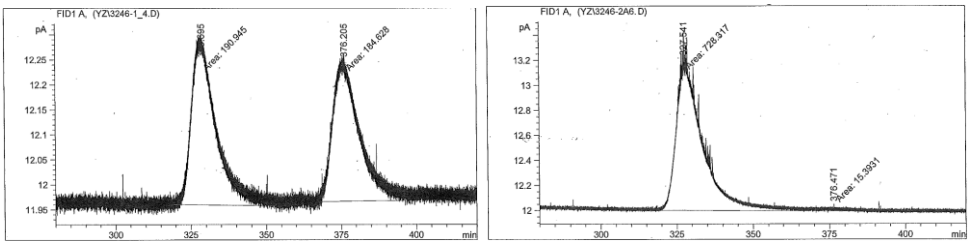


Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 18.087 | 759658 | 3.737 |
| 2 | 20.477 | 19567861 | 96.263 |
| Total | | 20327518 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 17.813 | 1346068 | 49.457 | 18.087 | 759658 | 3.737 |
| 20.570 | 1375607 | 50.543 | 20.477 | 19567861 | 96.263 |

**(*S*,*E*)-(1-(2-Allylidenecyclohexyl)propa-1,2-dien-1-yl)trimethylsilane (1.63): IR(neat):** 3084 (w), 2929 (m), 2854 (w), 2159 (w), 1927 (m), 1646 (w), 1446 (w), 1248 (m), 986 (w), 899 (m), 838 (s), 756 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 6.63 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.86 (d, *J* = 10.5 Hz, 1H), 5.13 (dd, *J* = 16.8, 2.2 Hz, 1H), 4.99 (dd, *J* = 10.5, 2.2 Hz, 1H), 4.42–4.36 (m, 2H), 2.74–2.68 (m, 1H), 2.58–2.50 (m, 1H), 2.14–2.07 (m, 1H), 1.85–1.65 (m, 3H), 1.65–1.56 (m, 1H), 1.55–1.45 (m, 2H), 0.09 (s, 9H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 209.3, 145.7, 132.8, 123.4, 115.3, 96.8, 69.8, 45.3, 34.3, 28.7, 28.4, 24.9, –1.0; **HRMS (DART):** Calcd for $C_{15}H_{25}Si$ $[M+H]^+$: 233.1720 Found: 233.1713; Specific rotation: $[\alpha]_D^{20}$ +294.0 (*c* 0.64, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity of **1.63** was determined by GC analysis in comparison with authentic racemic material; CD-αTA column 80 °C, 12 psi.




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 328.695 | 190.94482 | 50.84102 | 327.541 | 728.31744 | 97.93022 |
| 376.205 | 184.62752 | 49.15898 | 376.471 | 15.39314 | 2.06978 |

- **Procedures for Functionalization of Products and the Corresponding Characterization Data**

**Coupling of an Alkyne with Iodoacrylate (1.83):** In a $N_2$-filled glove box, an oven-dried 1-dram vial equipped with a stir bar was charged with $Pd(PPh_3)_2Cl_2$ (1.4 mg, 2.0 μmol), CuI (0.4 mg, 2.0 μmol), ethyl *cis*-3-iodoacrylate **1.82** (9.0 mg, 40.0 μmol) and $Et_3N$ (200 μL). Alkyne **1.32** was then added, and the vial was sealed with a cap and electrical tape and removed from the glove box. The mixture was allowed to stir at 50 °C for 12 h, after which the mixture was allowed to cooled to 22 °C, and $H_2O$ (0.5 mL) and $Et_2O$ (0.5 mL) were added. The organic layer was separated and the aqueous layer was washed with $Et_2O$ (3 x 1 mL). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The resulting yellow oil was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford **1.83** as pale yellow oil (12.1 mg, 0.043 mmol, 98% yield).

**Ethyl (*R*,2*Z*,8*E*)-7-phenylundeca-2,8,10-trien-4-ynoate (1.83): IR(neat):** 3087 (w), 3031 (w), 2980 (w), 2904 (w), 2205 (w), 1723 (s), 1608 (m), 1453 (w), 1413 (w), 1285 (w), 1182 (s), 1006 (m), 903 (w), 817 (w), 760 (w), 700 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.36–7.27 (m, 2H), 7.27–7.20 (m, 3H), 6.35 (dt, *J* = 17.0, 10.1 Hz, 1H), 6.21–5.93 (m, 4H), 5.14 (d, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.67 (q,

*J* = 6.8 Hz, 1H), 2.87 (dt, *J* = 6.8, 2.3 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 164.9, 142.8, 137.0, 136.1, 131.8, 128.7, 127.9, 127.8, 126.9, 123.7, 116.6, 101.6, 79.4, 60.4, 47.4, 27.3, 14.4; **HRMS (DART)**: Calcd for $C_{19}H_{21}O_2$ $[M+H]^+$: 281.1542 Found: 281.1553. Specific rotation: $[\alpha]_D^{20}$ –20.7 (*c* 0.61, $CHCl_3$).

**Hydroboration of Alkyne 1.40:** In a $N_2$-filled glove box, an oven-dried 1-dram vial equipped with a stir bar was charged with $Cp_2ZrHCl$ (2.6 mg, 10 μmol), $Et_3N$ (1.0 mg, 10 μmol), **1.40** (19.6 mg, 100 μmol) and thf (0.5 mL), after which HB(pin) (14.0 mg, 110 μmol) was added. The vial was sealed with a cap and electrical tape, and removed from the glove box. The mixture was allowed to stir for 16 at 60 °C, after which it was allowed to cool to 22 °C. The volatiles were removed in vacuo and the resulting yellow oil was purified by silica gel chromatography (50:1→20:1 hexanes:ethyl acetate) to **1.84** as a colorless oil (23.2 mg, 0.72 mmol, 72% yield).

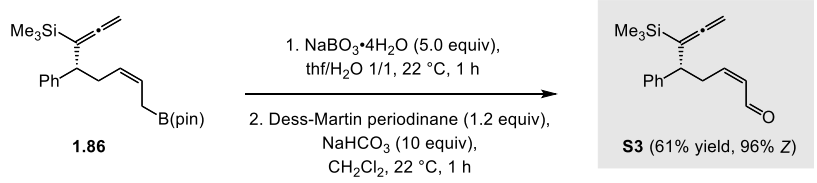
**4,4,5,5-Tetramethyl-2-((*R*,1*E*,5*E*)-5-methyl-4-phenylocta-1,5,7-trien-1-yl)-1,3,2-dioxaborolane (1.84): IR(neat):** 3024 (w), 2977 (m), 2929 (w), 1637 (m), 1494 (w), 1450 (w), 1361 (s), 1323 (s), 1272 (w), 1243 (w), 1144 (s), 971 (m), 900 (m), 849 (m), 700 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.31–7.23 (m, 2H), 7.23–7.16 (m, 3H), 6.65–6.47 (m, 2H), 6.07 (d, *J* = 10.9 Hz, 1H), 5.45 (dt, *J* = 17.9, 1.5 Hz, 1H), 5.18 (dd, *J* = 16.8, 2.2 Hz, 1H), 5.05 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.42 (t, *J* = 7.6 Hz, 1H), 2.82–2.49 (m, 2H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.24 (s, 12H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 152.3, 143.0, 140.7, 133.4, 128.4, 128.0, 126.4, 126.1, 116.0, 83.2, 53.4, 39.3, 24.9, 24.9, 15.2; **HRMS (DART):** Calcd for $C_{21}H_{30}BO_2$ $[M+H]^+$: 325.2339 Found: 325.2342. Specific rotation: $[\alpha]_D^{20}$ +15.7 (*c* 0.09, $CHCl_3$).

**Hydroboration/Oxidation of Alkyne 1.53:** In a $N_2$-filled glove box, an oven-dried 1-dram vial equipped containing a stir bar was charged with $Cp_2ZrHCl$ (43.8 mg, 0.17 mmol), $Et_3N$ (17.2 mg, 0.17 mmol), **1.53** (276.8 mg, 1.73 mmol) and thf (5 mL). To this mixture was added HB(pin) (264.9 mg, 2.07 mmol). The vial was sealed with a cap and electrical tape, and removed from the glove box. The mixture was allowed to stir for 16 h at 60 °C, after which the mixture was allowed to cool to 22 °C, passed through a short plug of silica gel and celite, and washed with thf. Removal of the volatiles in vacuo left behind yellow oil, which was treated with $NaBO_3$•$4H_2O$ (1.33 g, 8.65 mmol), thf (3.0 mL), $H_2O$ (3.0 mL); the mixture was allowed to stir for 1 h in 22 °C, wfter which $H_2O$ (3.0 mL) and $Et_2O$ (3.0 mL) were added, and the organic layer was separated. The aqueous layer was washed with $Et_2O$ (3 x 1 mL), and the combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The resulting oil was purified by silica gel chromatography (50:1→20:1→10:1 hexanes:ethyl acetate) to afford **1.85** as a colorless oil (247.3 mg, 1.38 mmol, 80% yield).

**(*R*,*E*)-3-(2-Allylidenecyclohexyl)propanal (1.85): IR(neat):** 3083 (w), 2926 (s), 2854 (m), 2716 (w), 1722 (s), 1644 (m), 1596 (w), 1447 (m), 1419 (w), 1389 (w), 1360 (w), 987 (s), 897 (s), 806 (w), 664 (m) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 9.77 (d, *J* = 1.6 Hz, 1H), 6.62 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.78 (d, *J* = 10.5 Hz, 1H), 5.14 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.01 (dd, *J* = 10.5, 2.1 Hz, 1H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.33–2.26 (m, 1H), 2.25–2.17 (m, 1H), 2.13–2.06 (m, 1H), 2.02–1.95 (m, 1H), 1.77–1.59 (m, 4H), 1.56–1.41 (m, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 202.7, 145.1, 132.5, 123.1, 115.6, 44.3, 42.4, 33.7, 28.1, 26.9, 24.3, 23.3; **HRMS (DART):** Calcd for $C_{12}H_{19}O$ $[M+H]^+$: 179.1436 Found: 179.1445. Specific rotation: $[\alpha]_D^{20}$ +65.7 (*c* 0.66, $CHCl_3$).

**Catalytic Proto-Boryl addition to a Diene (1.86):** In a $N_2$-filled glove box, an oven-dried 1-dram vial equipped with a stir bar was charged with CuCl (0.25 mg, 2.5 μmol), biphep (1.3 mg, 2.5 μmol), NaO$^t$Bu (1.0 mg, 10.0 μmol) and thf (0.3 mL). The mixture was allowed to stir for 5 min at 22 °C under $N_2$, after which $B_2(pin)_2$ (15.2 mg, 0.06 mmol) was added. The resulting mixture was allowed to stir for 5 min before it was charged with diene **1.56** (12.7 mg, 0.05 mmol) and *i*-PrOH (6.0 mg, 0.10 mmol). The mixture was allowed to stir for 1 h, after which it was passed through a short plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$ (3.0 mL). The volatiles were removed in vacuo and the resulting in yellow oil residue was purified by silica gel chromatography (hexanes:ethyl acetate, $R_f$ = 0.40) to afford **1.86** as colorless oil (15.8 mg, 0.042 mmol, 83% yield).

**(*R*,*E*)-Trimethyl(4-phenyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-1,2,6-trien-3-yl)silane (1.86): IR(neat)** 3024 (w), 2978 (m), 1926 (m), 1601 (w), 1379 (m), 1324 (s), 1248 (m), 1144 (s), 969 (m), 839 (s), 755 (m), 699 (m) cm$^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.27–7.20 (m, 4H), 7.18–7.13 (m, 1H), 5.50–5.40 (m, 1H), 5.33–5.23 (m, 1H), 4.53 (d, *J* = 2.4 Hz, 2H), 3.16 (tt, *J* = 7.3, 2.4 Hz, 1H), 2.65–2.51 (m, 1H), 2.43–2.32 (m, 1H), 1.69–1.50 (m, 2H), 1.24 (s, 12H), –0.08 (s, 9H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 208.9, 144.9, 128.4, 128.1, 126.3, 126.2, 125.1, 98.9, 83.3, 70.9, 45.6, 35.0, 24.9, 24.9, –1.3; **HRMS (DART):** Calcd for $C_{23}H_{36}BO_2Si$ $[M+H]^+$: 383.2572 Found: 383.2567. Specific rotation: $[\alpha]_D^{20}$ –114.7 (*c* 0.90, $CHCl_3$).



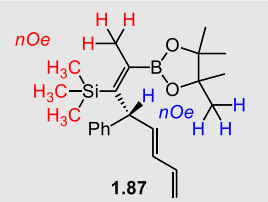
**Oxidation of allyl boronate 1.86 (S3):** In a 1 dram vial was added **1.83** (16.2 mg, 42 μmol), thf (0.2 mL) and $H_2O$ (0.2 mL). Sodium perborate tetrahydrate (32.6 mg, 210 μmol) was added to the mixture in 22 °C. The mixture was allowed to stir for 1 h, after which it was passed through a short plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$. The volatiles were removed in vacuo, resulting in colorless oil, which was passed through a silica gel with hexanes:ethyl acetate 10:1 to afford 11 mg of the corresponding alcohol as colorless oil. Subsequently, the allylic alcohol (6.2 mg, 23 μmol) was dissolved in $CH_2Cl_2$ (0.2 mL), $NaHCO_3$ (19.3 mg, 230 μmol) and Dess–Martin periodinane (11.6 mg, 27 μmol) was added at 22 °C. The resulting mixture was allowed to stir for 1 h, after which it was passed through a short plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$. The volatiles were removed in vacuo, leaving behind colorless oil residue, which was purified by silica gel chromatography (hexanes:ethyl acetate 20:1, $R_f$ = 0.30) to afford **S3** as colorless oil (4.0 mg, 0.015 mmol, 61% overall yield). The *E/Z* ratio of **1.86** was determined by analysis of the $^1$H NMR spectrum of **S3** as the alkene-related signals for **1.86** overlap when obtained in a number of different solvents.

**(*R*,*Z*)-5-Phenyl-6-(trimethylsilyl)octa-2,6,7-trienal (S3): IR(neat):** 3027 (w), 2956 (w), 1925(m), 1680 (s), 1492 (m), 1453 (w), 1248 (m), 1113 (w), 930 (w), 838 (s), 756 (m), 700 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.92 (d, *J* = 8.1 Hz, 1H), 7.31–7.26 (m, 2H), 7.24–7.18 (m, 3H), 6.53 (dt, *J* = 11.2, 8.0 Hz, 1H), 5.89 (ddt, *J* = 11.2, 8.1, 1.6 Hz, 1H), 4.64 (dd, J = 11.0, 2.5 Hz, 1H), 4.59 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.29 (tt, *J* = 7.4, 2.5 Hz, 1H), 3.22–3.12 (m, 1H), 2.95–2.85 (m, 1H), –0.08 (s, 9H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 208.9, 191.2, 151.4, 143.1, 130.8, 128.6, 128.2, 127.1, 98.4, 71.9, 45.1, 35.8, –1.3;

**HRMS (DART)**: Calcd for $C_{17}H_{23}OSi$ $[M+H]^+$: 271.1513 Found: 271.1515. Specific rotation: $[\alpha]_D^{20}$ –258.6 (*c* 0.20, $CHCl_3$).

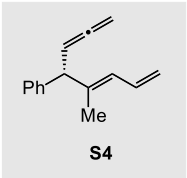
**Catalytic Boron–Hydride Addition to a Silyl–Substituted Allene (1.87):** In an oven-dried 1-dram vial equipped with a stir bar was charged with $Pd(OAc)_2$ (0.3 mg, 1.5 μmol) and toluene (150 μL). To this mixture was added **1.56** (7.6 mg, 0.030 mmol), $B_2(pin)_2$ (9.9 mg, 0.039 mmol) and HOAc (1.7 μL, 0.030 mmol) sequentially. The mixture was allowed to warm to 50 °C and stir at this temperature for 18 h, after which it was allowed to cool to 22 °C. The volatiles were then removed in vacuo, and the resulting dark oil was purified by silica gel chromatography (hexanes:ethyl acetate 20:1, $R_f$ = 0.30) to afford **1.87** as colorless oil (9.9 mg, 0.026 mmol, 86% yield).

**Trimethyl((*R*,2*Z*,5*E*)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-2,5,7-trien-3-yl)silane (1.87): IR(neat):** 2977 (m), 1371 (m), 1333 (s), 1299 (s), 1271 (m), 1248 (m), 1129 (s), 848 (s), 748 (m), 699 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.30–7.24 (m, 4H), 7.19–7.14 (m, 1H), 6.46 (dt, *J* = 17.0, 10.1 Hz, 1H), 6.22 (dd, *J* = 15.1, 10.1 Hz, 1H), 6.13 (dd, *J* = 15.1, 7.8 Hz, 1H), 5.15 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.05 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.89 (d, *J* = 7.8 Hz, 1H), 2.01 (s, 3H), 1.25 (s, 12H), -0.06 (s, 9H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 154.1, 144.1, 137.5, 135.8, 133.4, 128.0, 127.8, 125.9, 115.8, 83.5, 55.5, 25.0, 24.9, 21.3, 1.8; **HRMS (DART):** Calcd for $C_{23}H_{36}BO_2Si$ $[M+H]^+$: 383.2572 Found: 383.2561. Specific rotation: $[\alpha]_D^{20}$ –35.9 (*c* 0.50, $CHCl_3$). The stereochemical identity of the tetrasubstituted alkene was determined through nOe experiments.




1.87

**Removal of the Silyl moiety from a Silyl-Substituted Allene (S4):** In an oven-dried 1-dram vial equipped with a stir bar was charged with silyl allene **1.60** (13.4 mg, 0.05 mmol) and thf (200 μL). The mixture was allowed to cool to –78 °C and (*n*-Bu)$_4$NF (1.0 M in thf, 0.1 mL, 0.1 mmol) was added dropwise. The mixture was allowed to stir for 4 h at –78 °C, after which it was charged with $H_2O$ and $Et_2O$. The layers were then separated and the aqueous layer was washed with $Et_2O$ (3 x 2 mL). The combined organic layers were dried over $Na_2SO_4$ and the volatiles were removed in vacuo. The resulting yellow oil was purified by silica gel chromatography (hexanes) to afford **S4** as colorless solid (5.5 mg, 28.0 μmol, 56% yield).



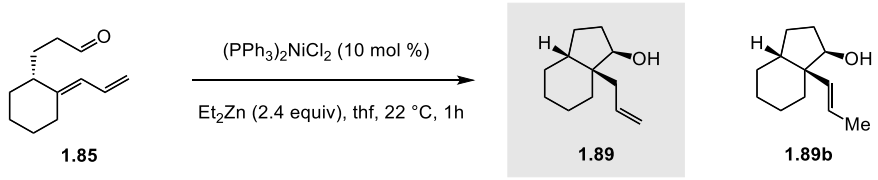

**S4**

**(*R*,*E*)-(5-Methylocta-1,2,5,7-tetraen-4-yl)benzene (S4): IR(neat):** 3083 (w), 3026 (w), 2922 (w), 2855 (w), 1956 (m), 1646 (w), 1600 (m), 1492 (w), 1451 (w), 1380 (w), 988 (m), 904 (m), 846 (m), 753 (w), 700 (s), 637 (w) cm$^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.33–7.28 (m, 2H), 7.25–7.19 (m, 3H), 6.61 (dt, *J* = 16.8, 10.5 Hz, 1H), 6.09 (d, *J* = 10.5 Hz, 1H), 5.48–5.38 (m, 1H), 5.20 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.09 (dd, *J* = 10.5, 2.1 Hz, 1H), 4.71 (dd, *J* = 6.6, 2.4 Hz, 2H), 4.07 (d, *J* = 7.8 Hz, 1H), 1.68 (s, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 208.7, 142.0, 140.3, 133.3, 128.4, 128.4, 127.1, 126.7, 116.5, 92.2, 76.0, 54.1,

15.9; **HRMS (DART):** Calcd for $C_{15}H_{17}$ $[M+H]^+$: 197.1325 Found: 197.1323. Specific rotation: $[\alpha]_D^{20}$ +67.5 (*c* 0.23, $CHCl_3$).

**Catalytic Proto-Boryl Addition to an Allene (1.88):** In a $N_2$-filled glove-box, an oven-dried 1-dram vial equipped with a stir bar was charged with CuCl (0.2 mg, 2.0 μmol), 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride (0.8 mg, 2.0 μmol), NaO*t*-Bu (0.8 mg, 8.0 μmol) and thf (300 μL). The mixture was allowed to stir for 1 h, after which it was charged with $B_2(pin)_2$ (5.6 mg, 22.0 μmol). The solution was allowed to stir for another 30 min, after which allene **S4** (4.0 mg, 20.0 μmol) and methanol (3.8 mg, 0.12 mmol) were added, and the mixture was allowed to stir for 12 h. The solution was then passed through a short plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$ (3.0 mL). The volatiles were removed in vacuo, resulting in yellow oil residue, which was purified by silica gel chromatography (hexanes:ethyl acetate 10:1, $R_f$ = 0.50) to afford **1.88** as colorless oil (4.7 mg, 0.014 mmol, 72% yield).

**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(5-methyl-4-phenylocta-1,5,7-trien-2-yl)-1,3,2-dioxaborolane (1.88): IR(neat):** 3026 (w), 2977 (m), 2928 (w), 1645 (w), 1600 (w), 1447 (w), 1415 (m), 1370 (s), 1309 (s), 1213 (w), 1139 (s), 988 (w), 943 (w), 899 (w), 865 (w), 700 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.30–7.21 (m, 2H), 7.22–7.13 (m, 3H), 6.55 (dt, *J* = 16.8, 10.5 Hz, 1H), 6.05 (d, *J* = 10.8 Hz, 1H), 5.77 (d, *J* = 3.4 Hz, 1H), 5.53 (d, *J* = 3.4 Hz, 1H), 5.14 (dd, *J* = 16.8, 2.2 Hz, 1H), 5.01 (dd, *J* = 10.1, 2.2 Hz, 1H), 3.59 (t, *J* = 7.8 Hz, 1H), 2.71 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.63 (dd, *J* = 13.5, 7.6 Hz, 1H), 1.58 (s, 3H), 1.23 (s, 12H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 143.5, 141.4, 133.6, 131.1, 128.3, 128.2, 126.3, 126.2, 115.5, 83.5, 54.1, 38.2, 25.0, 15.0; **HRMS (DART):** Calcd for $C_{21}H_{30}BO_2$ $[M+H]^+$: 325.2333 Found: 325.2334. Specific rotation: $[\alpha]_D^{20}$ –10.1 (*c* 0.15, $CHCl_3$).




1.85 1.89 1.89b

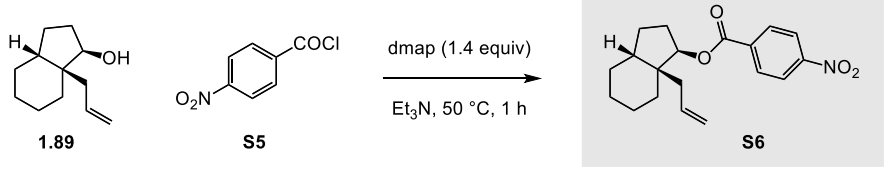
**Phosphine-Ni-Catalyzed Cyclization (1.89):** In a $N_2$-filled glove-box, an oven-dried 1-dram vial equipped with a stir bar was charged with bis(triphenylphosphine)nickel(II) dichloride $Ni(PPh_3)Cl_2$ (3.3 mg, 5 μmol), **1.85** (8.9 mg, 50 μmol) and thf (0.25 mL). This mixture was then charged with $Et_2Zn$ (1.5 M in toluene, 80.0 μL, 120 μmol) in a dropwise manner. The reaction vessel was sealed with a cap and electrical tape, and removed from the glove box, and the mixture was allowed to stir for 1 h. At this point, $H_2O$ (1.0 mL) and $Et_2O$ (1.0 mL) were added to, the layers were separated, and the aqueous layer was washed with $Et_2O$ (3 x 2 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. The resulting yellow oil was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford **1.89** as colorless oil (5.6 mg, 0.031 mmol, 62% yield, single diastereomer, 93:7 mixture of **1.89** and **1.89b**).

**(1*R*,3a*R*,7a*S*)-7a-Allyloctahydro-1H-inden-1-ol (1.89): IR(neat):** 3409 (br), 3071 (w), 2925 (s), 2858 (m), 1638 (w), 1461 (w), 1448 (w), 1056 (m), 1029 (w), 993 (w), 955 (w), 908 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 5.92 (ddt, *J* = 17.4, 10.1, 7.3 Hz, 1H), 5.15–5.04 (m, 2H), 3.85 (dd, *J* = 6.5, 2.1 Hz, 1H), 2.39 (ddt, *J* = 14.4, 7.3, 1.4 Hz, 1H), 2.15 (dd, *J* = 14.3, 7.4 Hz, 2H), 1.97–1.89 (m, 1H), 1.86–1.75 (m, 1H), 1.66–1.58 (m, 1H), 1.57–1.35 (m, 9H), 1.05–0.94 (m, 1H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 136.5, 116.7, 79.7, 47.3, 41.0, 36.1, 31.5, 27.2, 25.9, 24.9, 21.3; **HRMS (DART):** Calcd for $C_{12}H_{19}$ $[M+H-H_2O]^+$: 163.1487 Found: 163.1485. Specific rotation: $[\alpha]_D^{20}$ –21.8 (*c* 0.25, $CHCl_3$).

**Catalytic Cross-Metathesis of 1.85 (1.91):** In a $N_2$-filled glove box, an oven-dried 1-dram vial equipped with a stir bar was charged with **1.85** (8.9 mg, 50 μmol), **1.90** (44.1 mg, 250 μmol) and $CH_2Cl_2$ (0.15 mL). A solution of complex **R-1.1** (2.1 mg, 3.5 μmol) dissolved in $CH_2Cl_2$ (0.1 mL) solution was then added. The vessel was sealed with a cap and electrical tape, and removed from the glove box, and the mixture was allowed to stir for 2 h, after which acetonitrile (0.5 mL) was then added, the mixture was passed through a plug of silica gel and celite, and the volatiles were removed in vacuo. The resulting yellow oil was purified by silica gel chromatography (100:0→100:1→50:1 $CH_2Cl_2$:diethyl ether) to afford **1.91** as colorless oil (9.5 mg, 0.035 mmol, 75% yield, 89:11 *E*/*Z*).

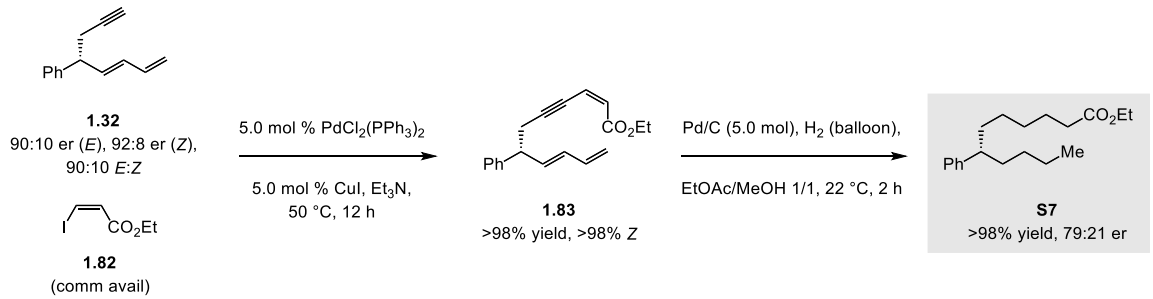
**3-((*R*,*E*)-2-((*E*)-4-(Methoxymethoxy)but-2-en-1-ylidene)cyclohexyl)propanal (1.91): IR(neat):** 2926 (s), 2854 (m), 2718 (w), 1723 (s), 1654 (w), 1448 (m), 1387 (w), 1359 (w), 1212 (w), 1149 (m), 1104 (m), 1039 (s), 967 (m), 921 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.77 (t, *J* = 1.6 Hz, 1H), 6.54 (ddt, *J* = 15.2, 10.9, 1.4 Hz, 1H), 5.77 (d, *J* = 10.9 Hz, 1H), 5.70 (dt, *J* = 15.2, 6.4 Hz, 1H), 4.65 (s, 2H), 4.10 (dd, *J* = 6.4, 1.3 Hz, 2H), 3.38 (s, 3H), 2.40 (td, *J* = 7.5, 1.6 Hz, 2H), 2.34–2.27 (m, 1H), 2.24–2.15 (m, 1H), 2.13–2.05 (m, 1H), 2.04–1.91 (m, 1H), 1.76–1.58 (m, 4H), 1.56–1.38 (m, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 202.7, 145.5, 128.9, 127.4, 121.7, 95.7, 68.0, 55.4, 44.4, 42.4, 33.7, 28.1, 26.9, 24.3, 23.2; **HRMS (DART):** Calcd for $C_{15}H_{28}NO_3$ $[M+NH_4]^+$: 270.2069 Found: 270.2080. Specific rotation: $[\alpha]_D^{20}$ +36.0 (*c* 0.30, $CHCl_3$).

- **Determination of Absolute Stereochemistry**



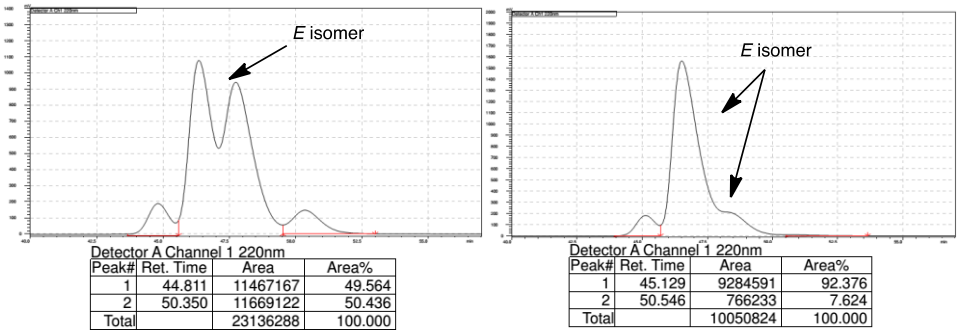
**Preparation of *p*-Nitrobenzoate Derivative of 1.89 (S6):** An oven-dried 1-dram vial equipped with a stir bar was charged with 4-dimethylaminopyridine (4.0 mg, 33 μmol), **1.89** (4.1 mg, 23 μmol) and $Et_3N$ (0.5 mL), followed by *p*-nitrobenzoyl chloride (42.7 mg, 230 μmol), and the resulting mixture was allowed to stir for 1 h at 50 °C. After the solution was allowed to cool to 22 °C, $Et_2O$ (0.5 mL) and $H_2O$ (0.5 mL) were added. The layers were separated and the aqueous layer was washed with $Et_2O$ (3 × 1 mL). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo, affording yellow oil, which was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford **S6** as colorless solid (2.9 mg, 9.6 μmol, 42% yield).

**(1*R*,3a*R*,7a*S*)-7a-Allyloctahydro-1H-inden-1-yl 4-nitrobenzoate (S6): IR(neat):** 2927 (m), 2857 (w), 1721 (s), 1607 (w), 1462 (w), 1346 (m), 1276 (s), 1117 (m), 1015 (w), 918 (w), 873(w), 848 (w), 719 (m) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 8.31–8.27 (m, 2H), 8.21–8.17 (m, 2H), 5.76–5.66 (m, 1H), 5.14 (d, *J* = 5.9 Hz, 1H), 5.00–4.93 (m, 2H), 2.48 (dd, *J* = 14.2, 8.4 Hz, 1H), 2.38 (t, *J* = 16.4 Hz, 1H), 2.25 (dd, *J* = 14.3, 6.1 Hz, 1H), 2.14–2.07 (m, 1H), 1.92–1.84 (m, 1H), 1.77–1.69 (m, 2H), 1.65–1.58 (m, 1H), 1.53–1.42 (m, 6H), 1.15–1.08 (m, 1H); **$^{13}$C NMR (150 MHz, $CDCl_3$):** δ 164.3, 150.6, 136.4, 135.1, 130.7, 123.7, 117.4, 83.4, 46.9, 41.8, 36.3, 29.6, 26.9, 26.0, 24.9, 21.1, 21.0; **HRMS (DART):** Calcd for $C_{19}H_{27}N_2O_4$ $[M+NH_4]^+$: 347.1971 Found: 347.1982. Specific rotation: $[\alpha]_D^{20}$ –22.7 (*c* 0.15, $CHCl_3$). Melting point: 68–69 °C.




Enantiomeric purity of ester **S7**, obtained from **1.32** (90:10 *E*:*Z*, 90:10 er), decreased to 79:21, suggesting that the major enantiomer of the *Z* isomer is opposite of that of the *E* isomer. Accordingly, the major enantiomer for the *Z* isomer was assigned to be *S*.

Enantiomeric purity of ***Z*-1.32** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-H, 100% hexanes, 0.2 mL/min, 220 nm.



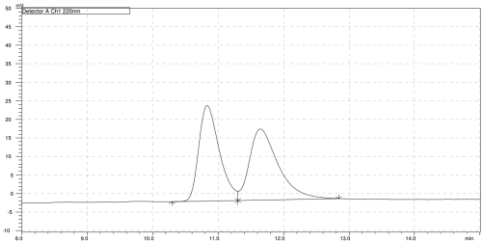

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 44.811 | 11467167 | 49.564 | 45.129 | 9284591 | 92.376 |
| 50.350 | 11669122 | 50.436 | 50.546 | 766233 | 7.624 |

**Hydrogenation of 1.83:**[33] In a 1-dram vial charged with palladium on carbon (10 wt% Pd, 1.5 mg, 1.4 μmol), **1.83** (7.9 mg, 0.028 mmol), MeOH (0.1 mL) and EtOAc (0.1 mL). The vial was purged with $N_2$ and attached to a $H_2$-filled ballon, and the mixture was allowed to stir for 2 h. The mixture was then passed through a plug of silica gel and celite and concentrated in vacuo. The resulting yellow oil was purified by silica gel chromatography

(33) Compound **1.32** that was made from the $S_N2''$ reaction of **1.31** using the same condition in Table 1. Entry 10.

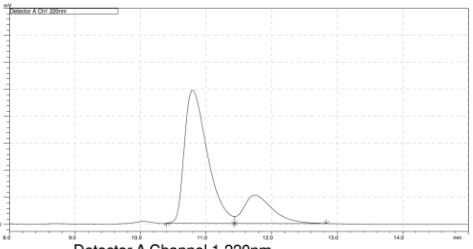
(10:1 hexanes:ethyl acetate) to afford **S7** as pale yellow oil (8.0 mg, 0.028 mmol, >98% yield).

**Ethyl (*S*)-7-phenylundecanoate (S7): IR(neat):** 2927 (s), 2856 (m), 1736 (s), 1494 (w), 1453 (w), 1374 (w), 1178 (m), 1031 (w), 761 (w), 700 (m) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.32–7.23 (m, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 6.5 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.45 (tt, *J* = 9.6, 5.4 Hz, 1H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.66–1.58 (m, 2H), 1.58–1.47 (m, 4H), 1.33–1.20 (m, 7H), 1.20–1.04 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 174.0, 146.4, 128.3, 127.8, 125.9, 60.3, 46.1, 36.9, 36.8, 34.5, 30.0, 29.4, 27.4, 25.0, 22.9, 14.4, 14.2; **HRMS (DART):** Calcd for $C_{19}H_{31}O_2$ $[M+H]^+$: 291.2319 Found: 291.2311. Specific rotation: $[\alpha]_D^{20}$ +2.9 (*c* 0.51, $CHCl_3$) for a 79:21 er sample. Enantiomeric purity of **S7** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel AD-H, 99.9% hexanes, 0.1% isopropanol, 0.8 mL/min, 220 nm.



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.831 | 562755 | 49.030 |
| 2 | 11.644 | 585028 | 50.970 |
| Total | | 1147783 | 100.000 |

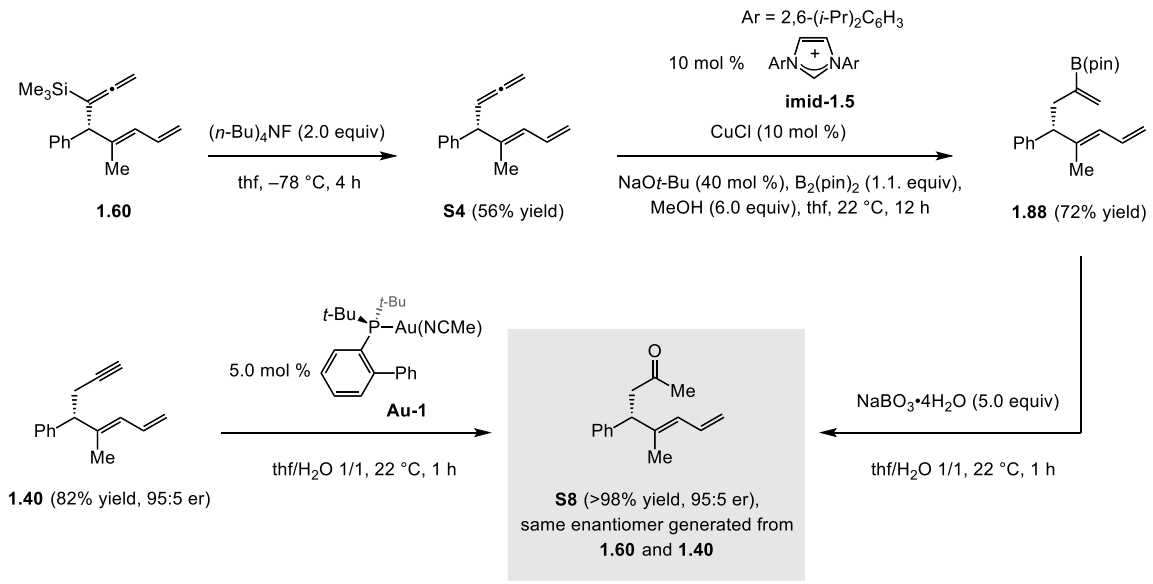


Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.793 | 3005116 | 79.008 |
| 2 | 11.744 | 798420 | 20.992 |
| Total | | 3803536 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 10.831 | 562755 | 49.030 | 10.793 | 3005116 | 79.008 |
| 11.644 | 585028 | 50.970 | 11.744 | 798420 | 20.992 |

- **Determination of the Stereochemistry Identity of Allenyl $S_N2''$-Substitution Products**

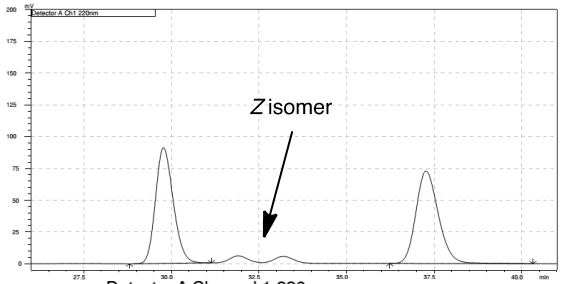



**Oxidation of Alkenyl–B(pin) 1.88 (S8):** A 1-dram vial was charged with alkenyl–B(pin) **1.88** (4.7 mg, 14 μmol), thf (0.1 mL), and $H_2O$ (0.1 mL). To this was added sodium perborate tetrahydrate (15.4 mg, 100 μmol), and the resulting mixture was allowed to stir for 1 h. The solution was then passed through a short plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$ (3.0 mL). The volatiles were removed in vacuo, leaving behind yellow oil, which was purified by silica gel chromatography (hexanes:ethyl acetate 10:1, $R_f = 0.30$) to afford **S8** as colorless oil (3.0 mg, 0.014 mmol, >98% yield).

**(*R*,*E*)-5-Methyl-4-phenylocta-5,7-dien-2-one (S8): IR(neat):** 3026 (w), 2923 (m), 2853 (w), 2023 (w), 1718 (s), 1645 (w), 1494 (w), 1417 (w), 1356 (m), 1160 (m), 988 (w), 904 (m), 701 (s) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.32–7.24 (m, 2H), 7.22–7.17 (m, 3H), 6.56 (dt, $J$ = 16.8, 10.4 Hz, 1H), 6.01 (d, $J$ = 10.7 Hz, 1H), 5.20 (dd, $J$ = 16.9, 2.0 Hz, 1H), 5.07 (dd, $J$ = 10.3, 2.1 Hz, 1H), 3.88 (t, $J$ = 7.5 Hz, 1H), 3.00–2.85 (m, 2H), 2.08 (s, 3H), 1.64 (s, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 207.3, 142.4, 140.2, 133.2, 128.6, 127.9, 126.8, 125.6, 116.6, 49.1, 47.5, 30.7, 16.0; **HRMS (DART):** Calcd for $C_{15}H_{19}O$ $[M+H]^+$: 215.1430 Found: 215.1425. Specific rotation: $[\alpha]_D^{20}$ +33.7 (*c* 0.16, $CHCl_3$).

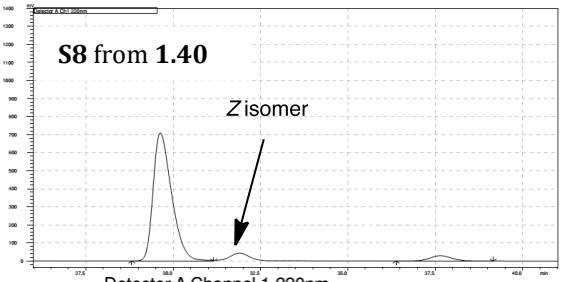
**Catalytic Hydration of Alkyne 1.40 (S8):** Complex **Au-1** (1.9 mg) was placed in a 1-dram vial and a solution of **1.40** (9.8 mg, 0.05 mmol) in MeOH (0.5 mL), $H_2O$ (0.05 mL) was added. The mixture was allowed to stir for 24 h, after which it was passed through a short plug of silica gel (4 cm x 1 cm) and $Na_2SO_4$, and was then eluted with $Et_2O$ (3.0 mL). Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes:ethyl acetate 10:1, $R_f$ = 0.30) to afford **S8** as colorless oil (8.2 mg, 0.041 mmol, 82% yield).

The major enantiomer of **S8**, generated from **1.40**, and **1.60** proved to be identical based on HPLC analysis. Therefore, the major enantiomer of **1.60** was determined to be *R*.



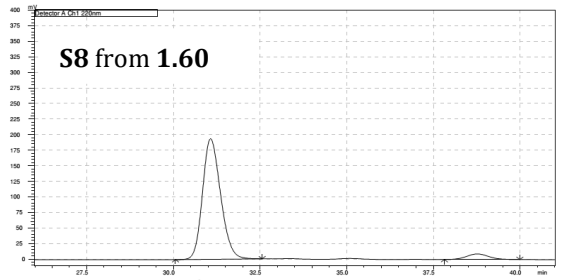

Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 29.771 | 3210409 | 49.778 |
| 2 | 37.269 | 3239070 | 50.222 |
| Total | | 6449479 | 100.000 |




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 29.628 | 26154625 | 95.271 |
| 2 | 37.646 | 1298159 | 4.729 |
| Total | | 27452784 | 100.000 |



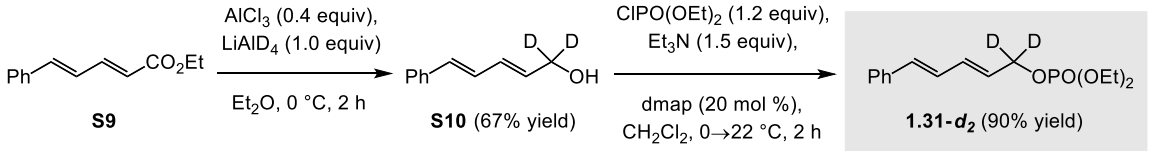

Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 31.069 | 7035052 | 94.709 |
| 2 | 38.767 | 393047 | 5.291 |
| Total | | 7428099 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 29.771 | 3210409 | 49.778 | 29.628 | 26154625 | 95.271 |
| 37.269 | 3239070 | 50.222 | 37.646 | 1298159 | 4.729 |

| Retention Time | Area | Area% |
|---|---|---|
| 31.069 | 7035052 | 94.709 |
| 38.767 | 393047 | 5.291 |

- **Kinetic Isotope Experiments**[34]



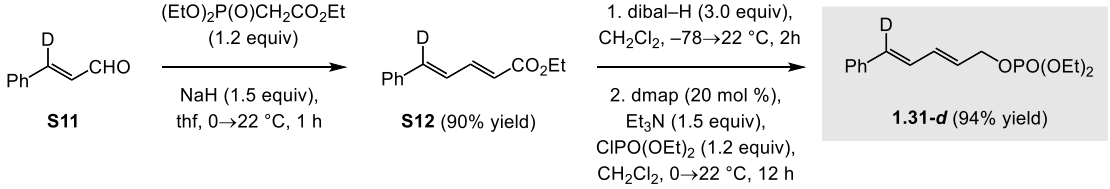

**Reduction of S9:**[35] An oven-dried 100 mL round bottom flask equipped containing a stir bar was charged with lithium aluminum deuteride (42.0 mg, 1.0 mmol) and $Et_2O$ (3.0 mL). The solution was then cooled to 0 °C and aluminum chloride (53.3mg, 0.4 mmol) was added in six portions, and the resulting mixture was allowed to stir for 20 min (at 0 °C). At this point, the mixture was charged (slow addition) with a solution of **S9**[36] (207.3 mg, 1.0 mmol) in $Et_2O$ (3.0 mL), and the resulting mixture was allowed to stir for 2 h at 0 ºC. The solution was poured into an Erlenmeyer flask that contained ice and a solution of aqueous saturated potassium sodium tartrate, and this concoction was allowed to stir for 1 h at 22 ºC. The layers were separated and the aqueous layer was washed with $Et_2O$ (3 × 30 mL). The combined organic layers were dried with $Na_2SO_4$ and the volatiles were removed in vacuo, affording yellow oil, which was purified by silica gel chromatography (5:1 hexanes:ethyl acetate) to afford **S10** as colorless oil (109.3 mg, 0.67 mmol, 67% yield).

**S10** was converted to **1.31-*d*$_2$** according to an established procedure.[31]

**Diethyl-((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl-1,1-*d*$_2$) phosphate (1.31-*d*$_2$): IR(neat)** 3026 (w), 2983 (m), 2909 (w), 1644 (w), 1492 (w), 1448 (w), 1393 (w), 1369 (w), 1271 (s), 1165 (m), 1019 (s), 913 (m), 820 (m), 759 (m), 692 (m), 509 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.28–7.15 (m, 1H), 6.77

(34) Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012,** *51*, 3066.
(35) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948–8964.
(36) Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676–10681.

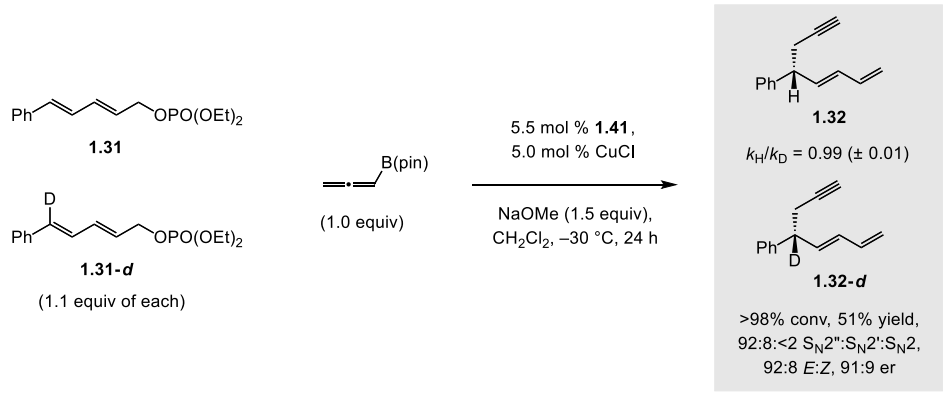
(dd, $J$ = 15.6, 10.5 Hz, 1H), 6.60 (d, $J$ = 15.6 Hz, 1H), 6.48 (dd, $J$ = 15.2, 10.5 Hz, 1H), 5.89 (d, $J$ = 15.2 Hz, 1H), 4.13 (p, $J$ = 7.3 Hz, 4H), 1.35 (t, $J$ = 7.3 Hz, 6H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 136.9, 134.6, 134.3, 128.8, 128.0, 127.6, 127.2 (d, $J_{CP}$ = 6.6 Hz), 126.6, 67.4–67.0 (m), 63.9 (d, $J_{CP}$ = 6.0 Hz), 16.3 (d, $J_{CP}$ = 6.8 Hz); **HRMS (ESI$^+$):** Calcd for $C_{15}H_{19}D_2NaO_4P$ $[M+Na]^+$: 321.1195; Found: 321.1203.




**1.31-*d*** was synthesized from **S11**[37] according to an established procedure.[31]

**Diethyl-((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl-5-*d*) phosphate (1.31-*d*): IR(neat):** 2983 (w), 2908 (w), 1644 (w), 1494 (w), 1447 (m), 1392 (m), 1216 (s), 1166 (m), 1026 (s), 1000 (s), 969 (s), 851 (m), 800 (m), 775 (s), 692 (m), 501 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.42–7.36 (m, 2H), 7.34–7.28 (m, 2H), 7.26–7.20 (m, 1H), 6.76 (d, $J$ = 10.6 Hz, 1H), 6.47 (ddq, $J$ = 15.2, 10.6, 1.2 Hz, 1H), 5.89 (dt, $J$ = 15.2, 6.4 Hz, 1H), 4.68–4.55 (m, 2H), 4.18–4.06 (m, 4H), 1.34 (tt, $J$ = 7.0, 1.0 Hz, 6H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 136.8, 134.3, 134.2–133.6 (m), 128.7, 128.0, 127.5, 127.3 (d, $J_{CP}$ = 6.7 Hz), 126.6, 67.7 (d, $J_{CP}$ = 5.4 Hz), 63.9 (d, $J_{CP}$ = 5.8 Hz), 16.2 (d, $J_{CP}$ = 6.8 Hz); **HRMS (ESI$^+$):** Calcd for $C_{15}H_{20}DNaO_4P$ $[M+Na]^+$: 320.1132; Found: 320.1139.

(37) Poudel, T. N.; Lee, Y. R. *Org. Lett.* **2015**, *17*, 2050–2053.




**Competition experiment between 1.32 and 1.32-*d* and determination of the secondary kinetic isotope effect (SKIE) for C–C bond formation at Cε:** In a $N_2$-filled glove box an oven-dried 1-dram vial (labeled "Vial 1") equipped with a stir bar was charged with imidazolinium **imid-1.4** (4.0 mg, 5.5 μmol), NaOMe (8.1 mg, 150 μmol), and CuCl (0.5 mg, 5.0 μmol). The vial was sealed with a cap (phenolic open top cap with a red PFTE/white silicon septum) and electrical tape, and removed from the glove box. To this mixture was addded $CH_2Cl_2$ (0.4 mL), which was then allowed to stir under a $N_2$ atmosphere for 1 h, during which time the solution turned pale blue-green. The allenyl–B(pin) compound (18.0 mg, 0.10 mmol) was added through a syringe and the mixture was allowed to stir for 30 min.

In an $N_2$-filled glove box a second oven-dried 1-dram vial (labeled "Vial 2") was equipped with **1.31** (32.6 mg, 0.11 mmol), **1.31-*d*** (32.7 mg, 0.11 mmol) and $CH_2Cl_2$ (0.1 mL). The solution in Vial 2 was then transferred to Vial 1, which was beforehand allowed to cool to –78 ºC, and the mixture was allowed to cool to –30 ºC and stir att this temperatire for 24 h. The solution was then passed through a short plug of silica gel (4 cm x 1 cm) and eluted with $Et_2O$. The filtrate was concentrated *in vacuo* and the resulting yellow oil was purified by silica gel chromatography (hexanes, $R_f$ = 0.30) to afford a mixture of **1.32** and **1.32-*d*** as colorless oil (9.3 mg, 0.051 mmol, 51% yield). The ratio of **1.32**:**1.32-*d*** was determined

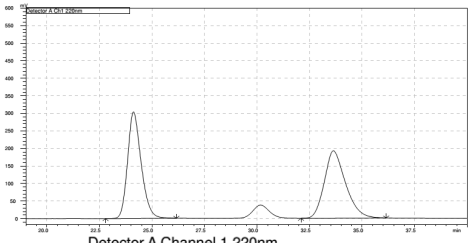
by analysis of the $^{1}$H NMR spectrum of the purified product (integration of resonances corresponding to the olefin, the alkyne, and the benzylic units).

The relative rates corresponding to the reactions with **1.31** and **1.31-*d***, respectively, were determined using the following formula:

$$k_H/k_D = n_{4a}/n_{4a\text{-}d}$$

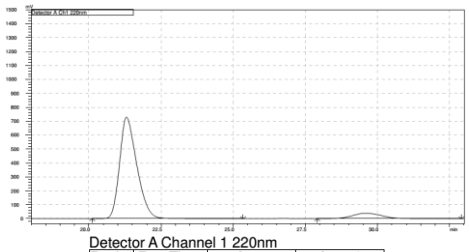
According, we measured SKIE ($k_H/k_D$ = 0.99 +/– 0.01) as the average of three independent experiments (0.99, 0.98, 0.99).

**(*R*,*E*)-(Octa-5,7-dien-1-yn-4-yl-4-d)benzene (1.32-*d*): IR(neat):** 3300 (m), 3026 (w), 2924 (m), 2852 (w), 2159 (w), 1603 (w), 1494 (m), 1448 (w), 1430 (w), 1261 (w), 1079 (w), 1005 (s), 952 (w), 904 (m), 759 (w), 699 (s), 638 (s) cm$^{-1}$; **$^{1}$H NMR (600 MHz, $CDCl_3$):** δ 7.35–7.29 (m, 2H), 7.25–7.21 (m, 3H), 6.34 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.11 (dd, *J* = 15.3, 10.2 Hz, 1H), 5.93 (d, *J* = 15.3 Hz, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 2.65–2.57 (m, 2H), 1.97 (t, *J* = 2.6 Hz, 1H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 142.7, 136.9, 136.0, 131.7, 128.7, 127.7, 126.9, 116.7, 82.5, 70.1, 47.2–46.8 (m), 25.5; **HRMS (DART):** Calcd for $C_{14}H_{14}D$ $[M+H]^+$: 184.1231; Found: 184.1234. Enantiomeric purity of the mixture of **1.32** and **1.32-*d*** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OJ-H, 100% hexanes, 0.8 mL/min, 220 nm.



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 24.114 | 13646594 | 50.269 |
| 2 | 33.630 | 13500520 | 49.731 |
| Total | | 27147114 | 100.000 |

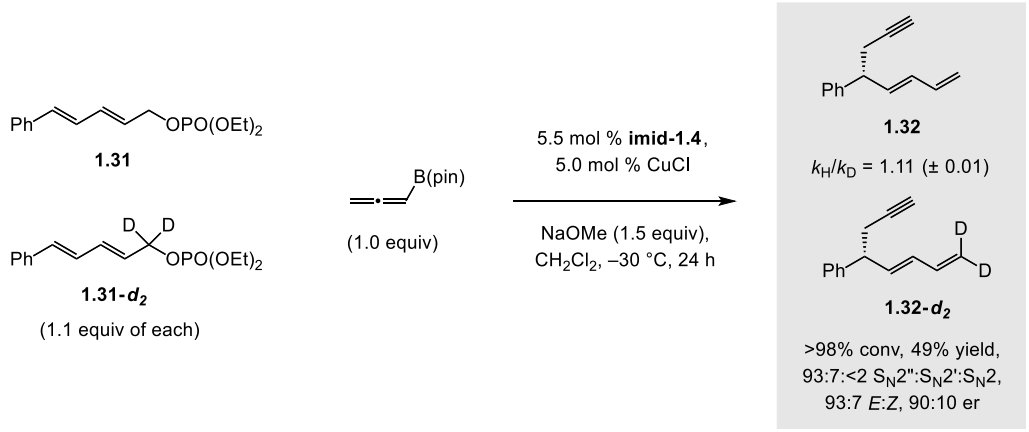


Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 21.301 | 30307471 | 91.596 |
| 2 | 29.587 | 2780618 | 8.404 |
| Total | | 33088090 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 24.114 | 13646594 | 50.269 | 21.301 | 30307471 | 91.596 |
| 33.630 | 13500520 | 49.731 | 29.587 | 2780618 | 8.404 |




**Competition experiment between 1.31 and 1.31-*d*$_2$ and determination of the secondary kinetic isotope effect (SKIE) for C–O bond cleavage at Cα:** The same procedure as was described above was followed, except that **1.31-*d*$_2$** was used as the reagent instead of **1.31-*d***. The transformation thus afforded a mixture of **1.32** and **1.32-*d*$_2$** as colorless oil (9.0 mg, 0.049 mmol, 49% yield). The **1.32**:**1.32-*d*$_2$** ratio was determined by analysis of the $^1$H NMR spectrum of the purified product (integration of resonances corresponding to olefin, alkyne and benzylic units).

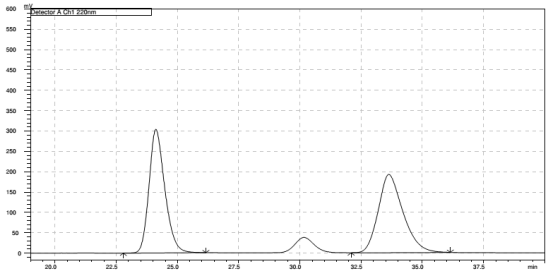
The relative rates corresponding to the reactions with **1.31** and **1.31-*d*$_2$**, respectively, were determined using the following formula:

$$k_H/k_D = n_{4a}/n_{4a\text{-}d2}$$

We thus measured SKIE ($k_H/k_D$ = 1.11 +/– 0.01) as the average of three independent experiments (1.11, 1.11, 1.11).

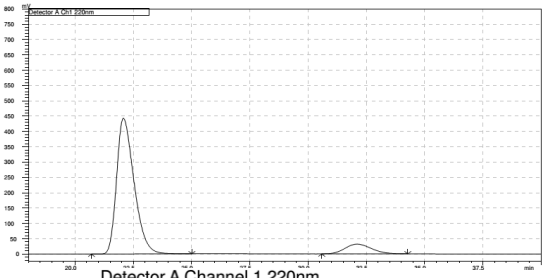
**(*R*,*E*)-(Octa-5,7-dien-1-yn-4-yl-8,8-*d*$_2$)benzene (1.32-*d*$_2$): IR(neat):** 3298 (w), 3027 (w), 2924 (w), 2119 (w), 1601 (w), 1494 (w), 1453 (w), 1261 (w), 1028 (w), 977 (m), 758 (w), 722 (m), 699 (s), 638 (m) cm$^{-1}$; **$^1$H NMR (600 MHz, CDCl$_3$):** δ 7.36–7.29 (m, 2H), 7.27–

7.21 (m, 3H), 6.33 (d, $J$ = 10.3 Hz, 1H), 6.12 (dd, $J$ = 15.3, 10.3 Hz, 1H), 5.93 (dd, $J$ = 15.3, 7.2 Hz, 1H), 3.59 (q, $J$ = 7.2 Hz, 1H), 2.62 (dt, $J$ = 7.2, 2.6 Hz, 2H), 1.98 (t, $J$ = 2.6 Hz, 1H); **$^{13}$C NMR (150 MHz, CDCl$_3$):** δ 142.7, 136.7, 136.0, 131.7, 128.7, 127.8, 126.9, 116.2 (p, $J$ = 24.2 Hz), 82.5, 70.2, 47.4, 25.6. **HRMS (DART):** Calcd for $C_{14}H_{13}D_2$ $[M+H]^+$: 185.1294; Found: 185.1295. Enantiomeric purity of the mixture between **1.32** and **1.32-*d*$_2$** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OJ-H, 100% hexanes, 0.8 mL/min, 220 nm.



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 24.114 | 13646594 | 50.269 |
| 2 | 33.630 | 13500520 | 49.731 |
| Total | | 27147114 | 100.000 |

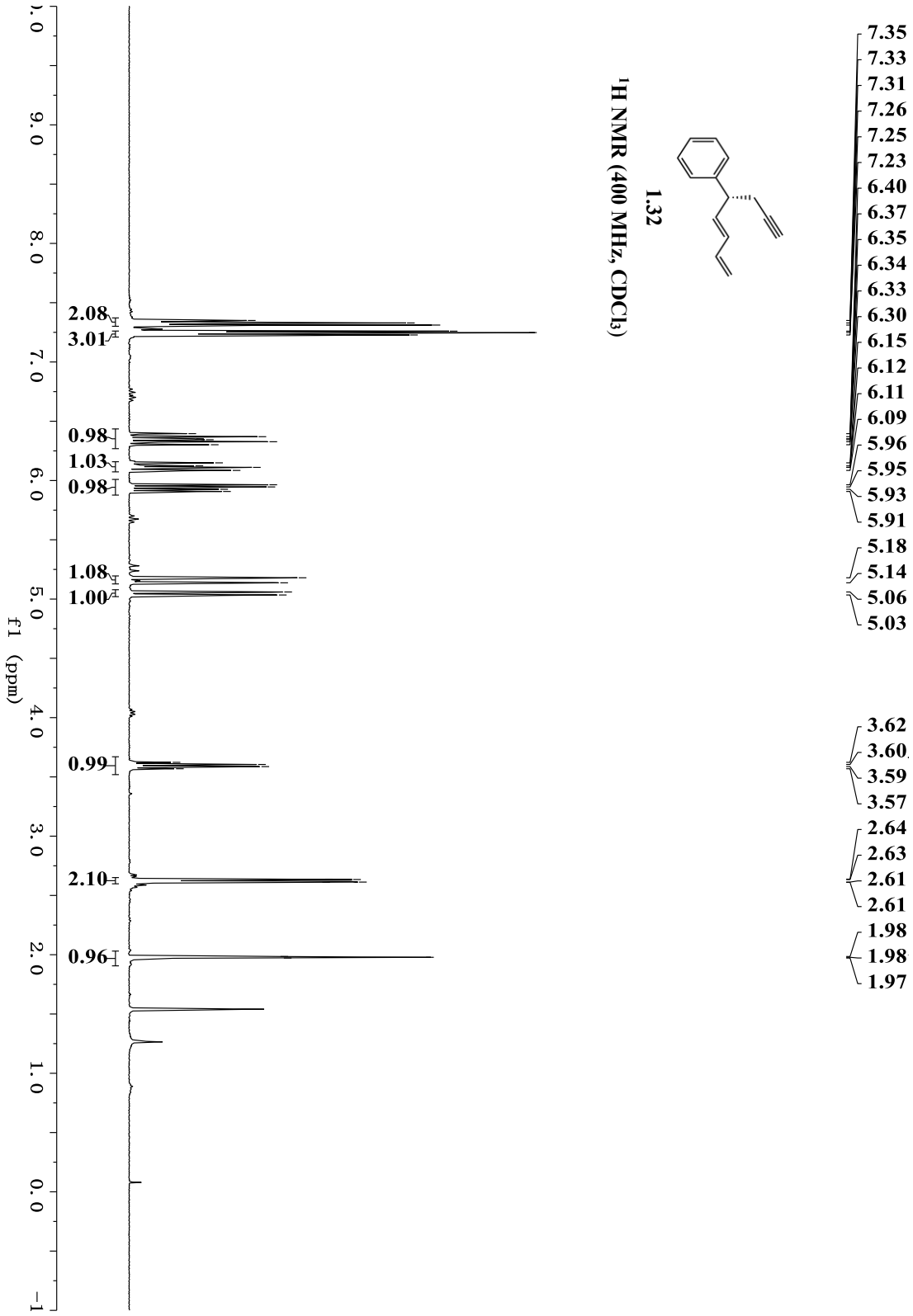


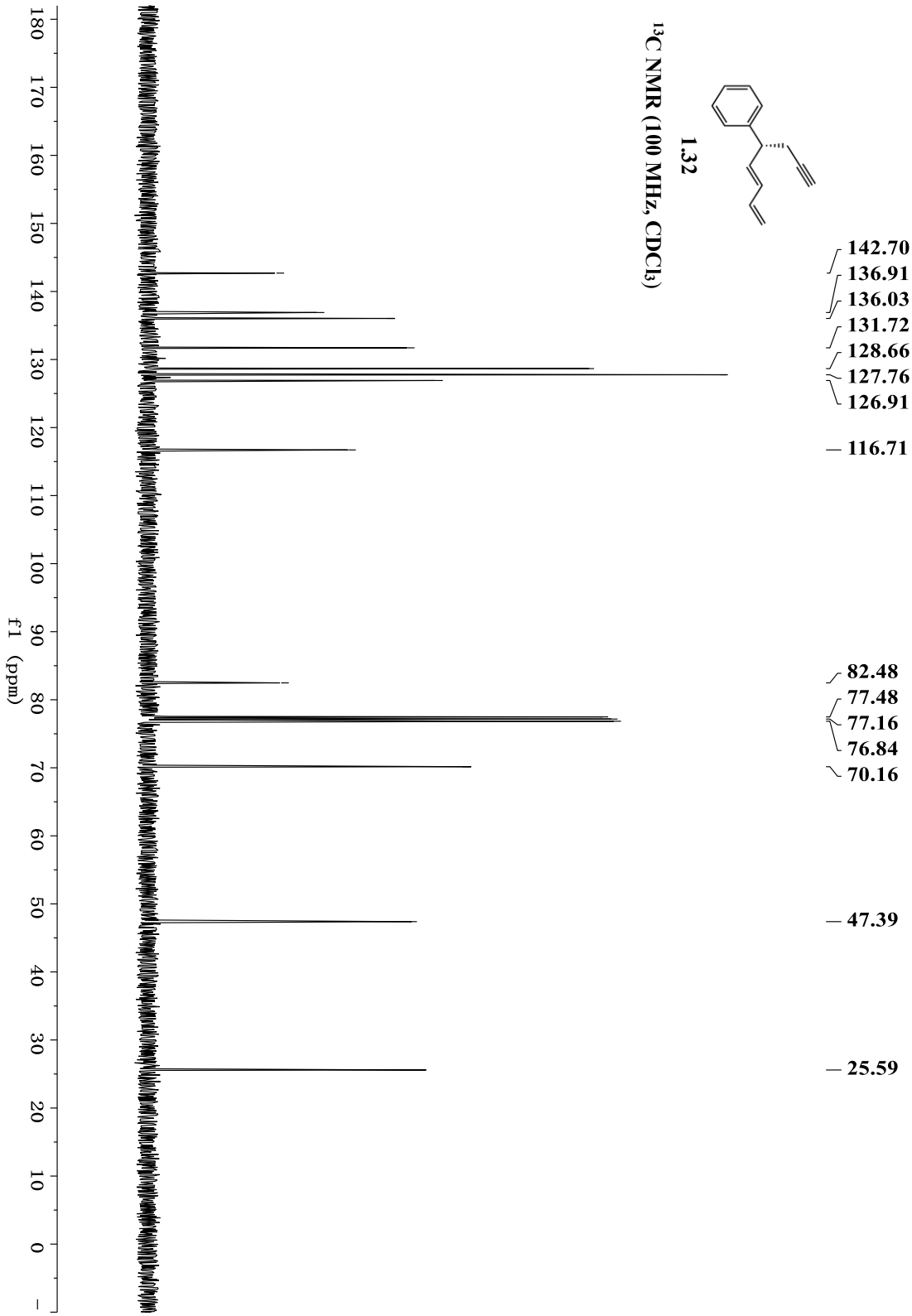
Detector A Channel 1 220nm

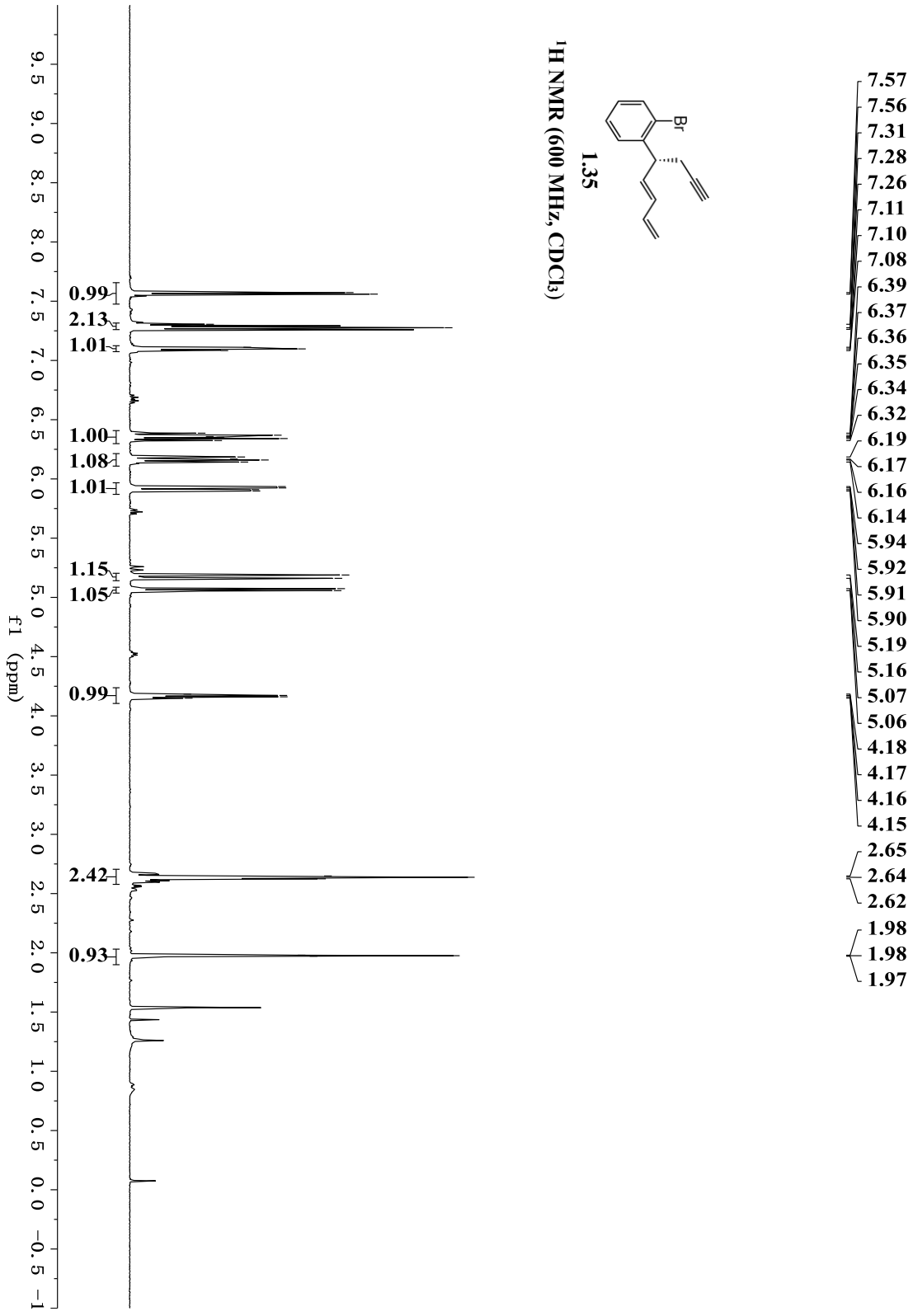
| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 22.072 | 23165713 | 90.131 |
| 2 | 32.104 | 2536612 | 9.869 |
| Total | | 25702325 | 100.000 |

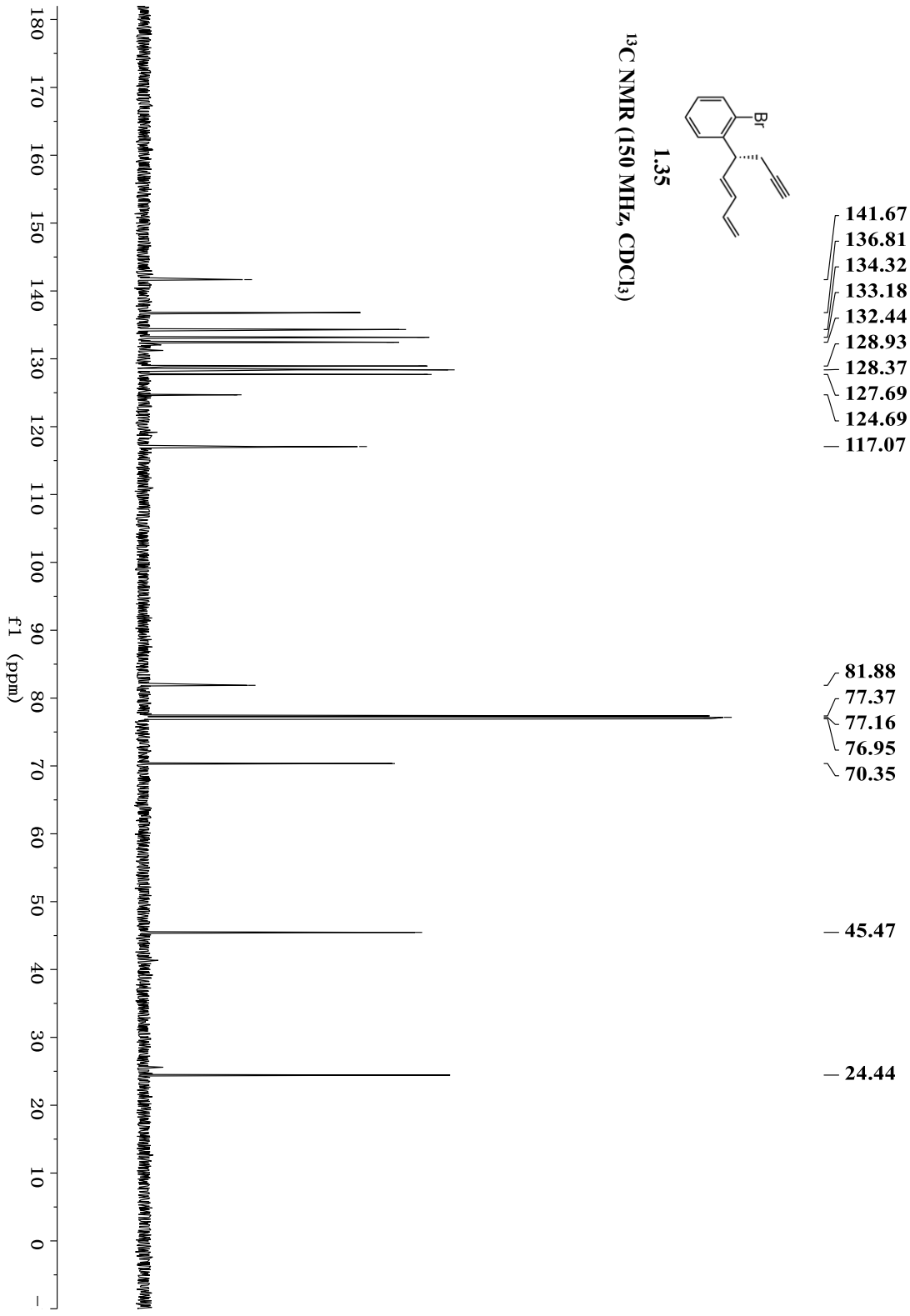
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 24.114 | 13646594 | 50.269 | 22.072 | 23165713 | 90.131 |
| 33.630 | 13500520 | 49.731 | 32.104 | 2536612 | 9.869 |

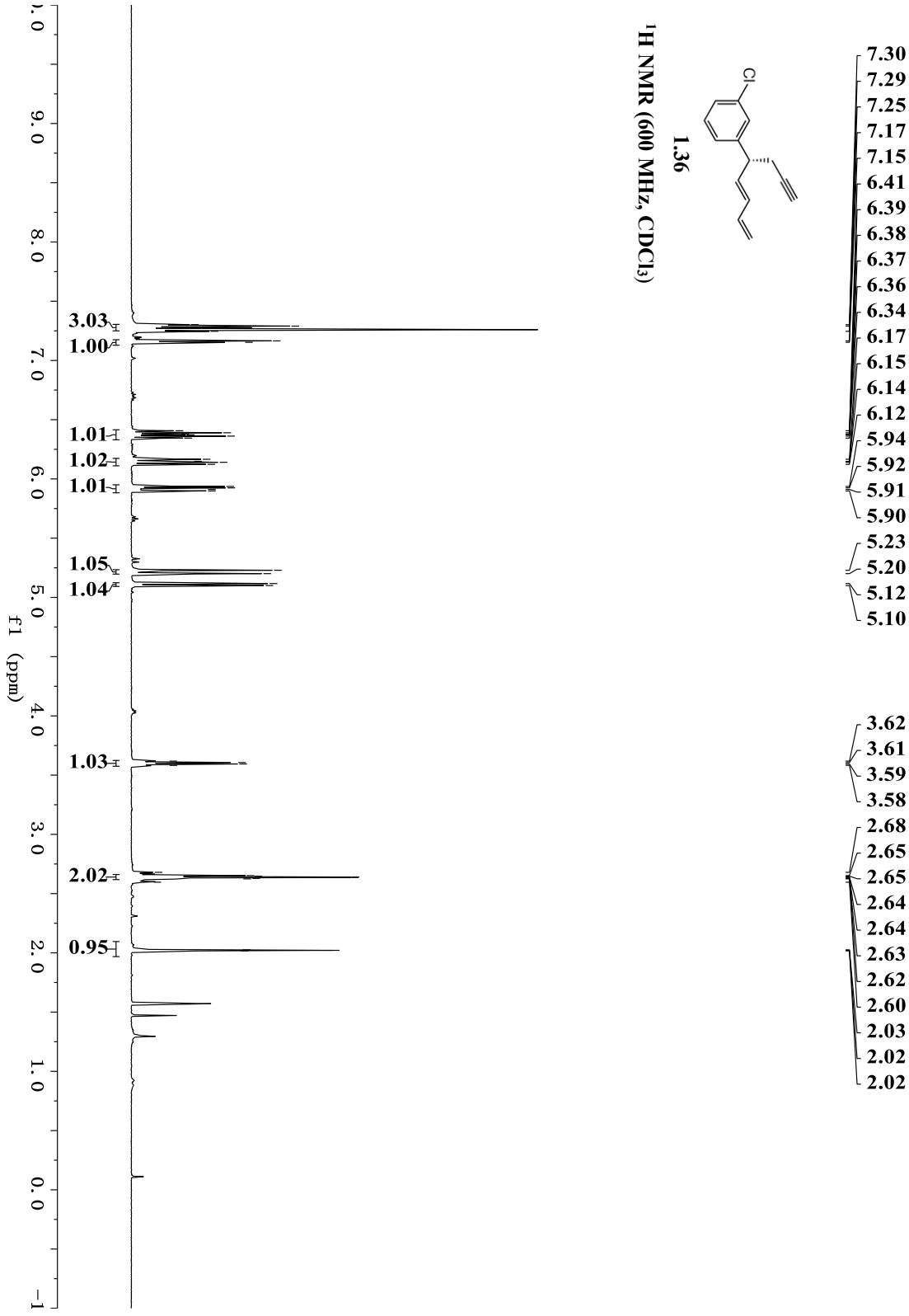
- **NMR spectra**

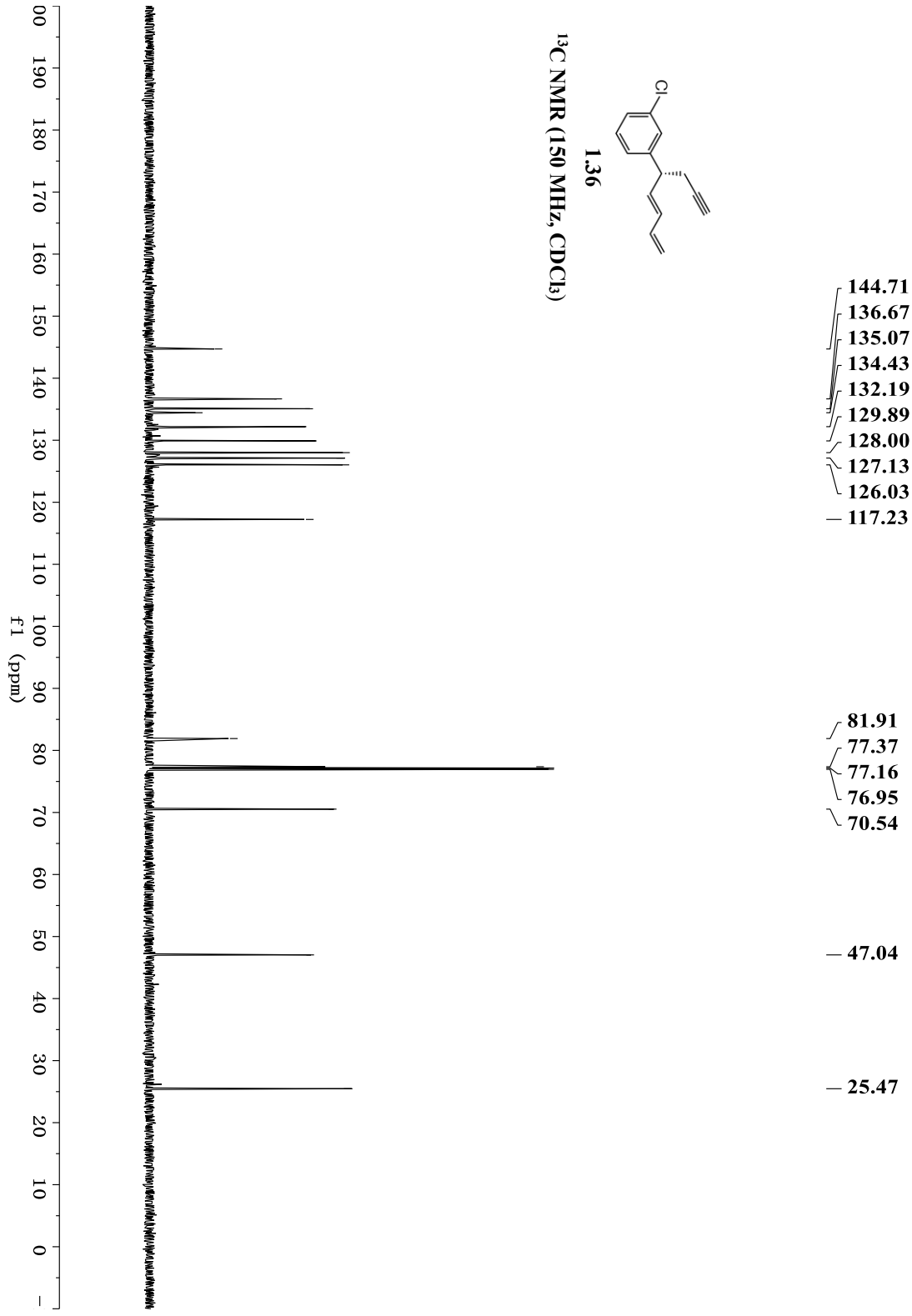

1.32
$^1$H NMR (400 MHz, CDCl$_3$)
7.35
7.33
7.31
7.26
7.25
7.23
6.40
6.37
6.35
6.34
6.33
6.30
6.15
6.12
6.11
6.09
5.96
5.95
5.93
5.91
5.18
5.14
5.06
5.03
3.62
3.60
3.59
3.57
2.64
2.63
2.61
2.61
1.98
1.98
1.97
2.08
3.01
0.98
1.03
0.98
1.08
1.00
0.99
2.10
0.96
f1 (ppm)

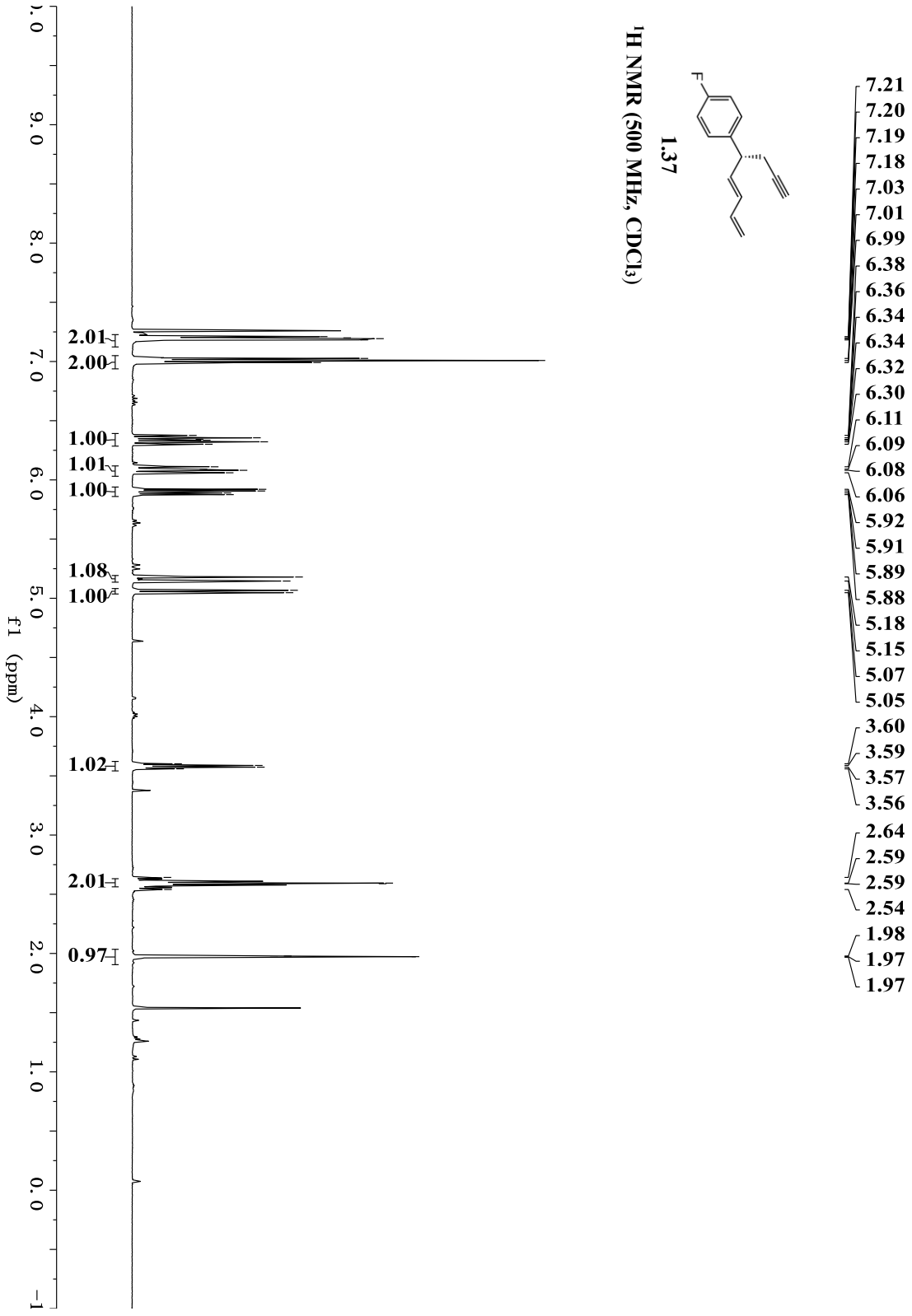

1.32
$^{13}$C NMR (100 MHz, CDCl$_3$)
142.70
136.91
136.03
131.72
128.66
127.76
126.91
116.71
82.48
77.48
77.16
76.84
70.16
47.39
25.59
f1 (ppm)

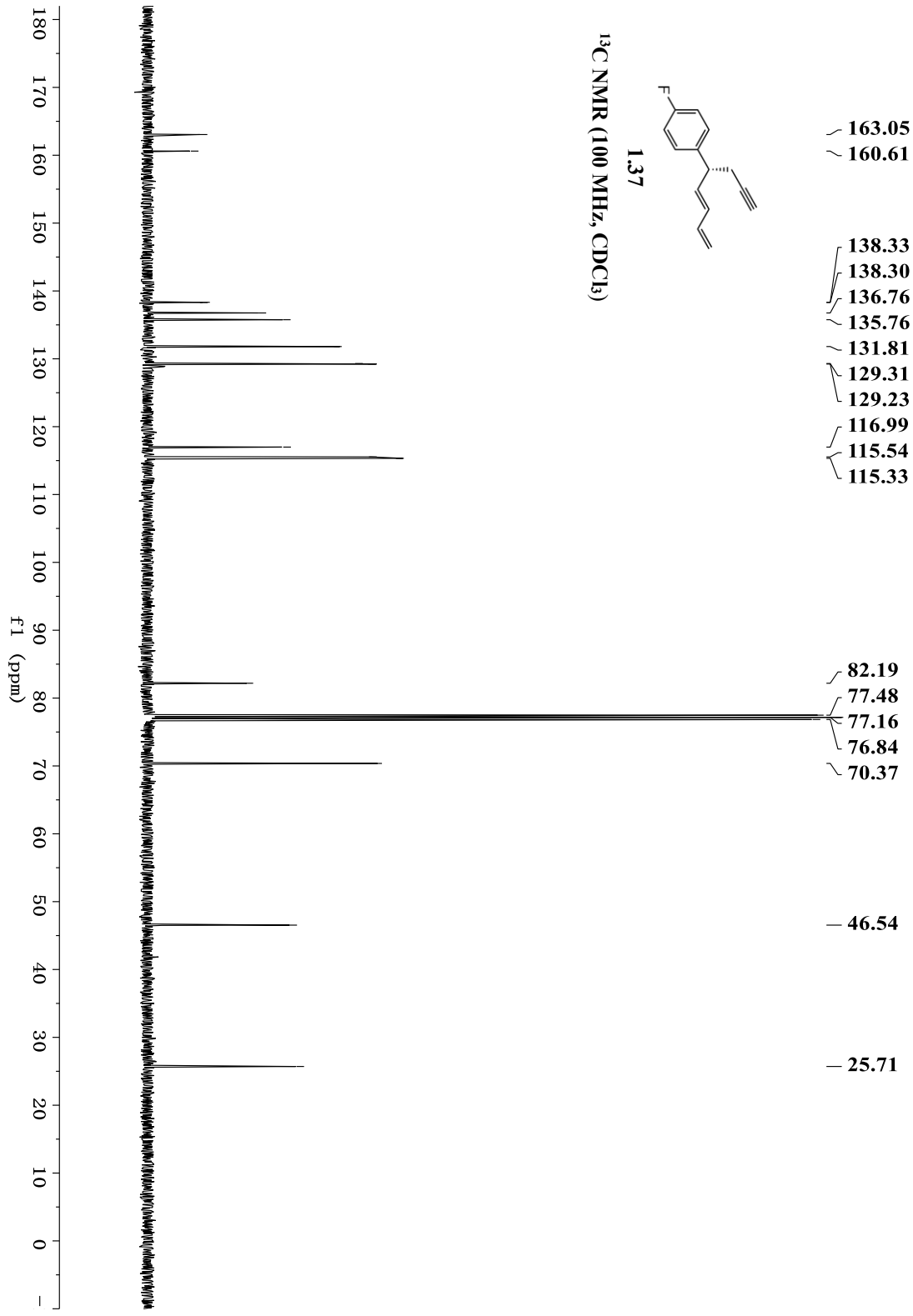

1.35
$^1$H NMR (600 MHz, CDCl$_3$)
Br
7.57
7.56
7.31
7.28
7.26
7.11
7.10
7.08
6.39
6.37
6.36
6.35
6.34
6.32
6.19
6.17
6.16
6.14
5.94
5.92
5.91
5.90
5.19
5.16
5.07
5.06
4.18
4.17
4.16
4.15
2.65
2.64
2.62
1.98
1.98
1.97
0.99
2.13
1.01
1.00
1.08
1.01
1.15
1.05
0.99
2.42
0.93
f1 (ppm)

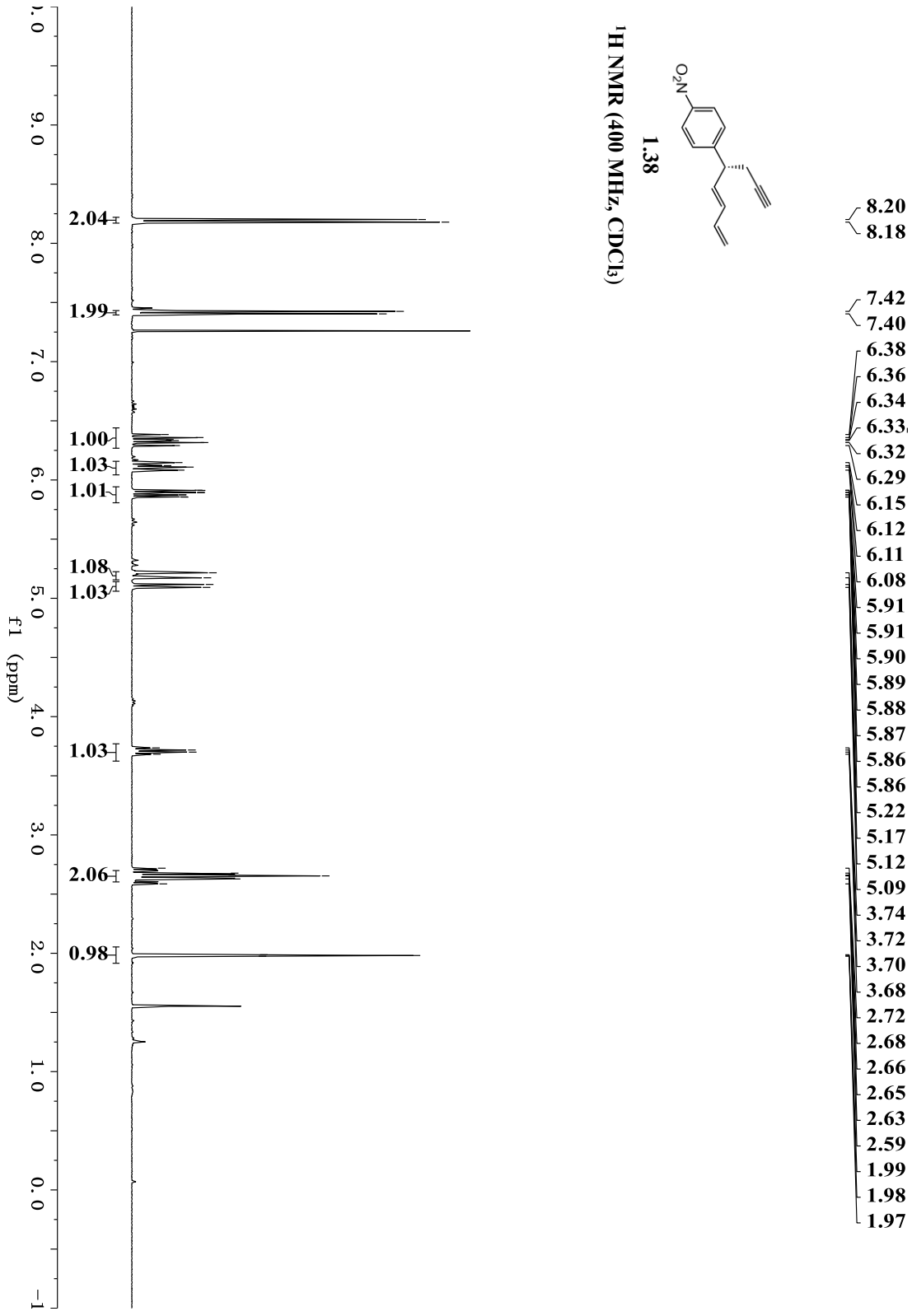

1.35
$^{13}$C NMR (150 MHz, CDCl$_3$)
Br
141.67
136.81
134.32
133.18
132.44
128.93
128.37
127.69
124.69
117.07
81.88
77.37
77.16
76.95
70.35
45.47
24.44
f1 (ppm)

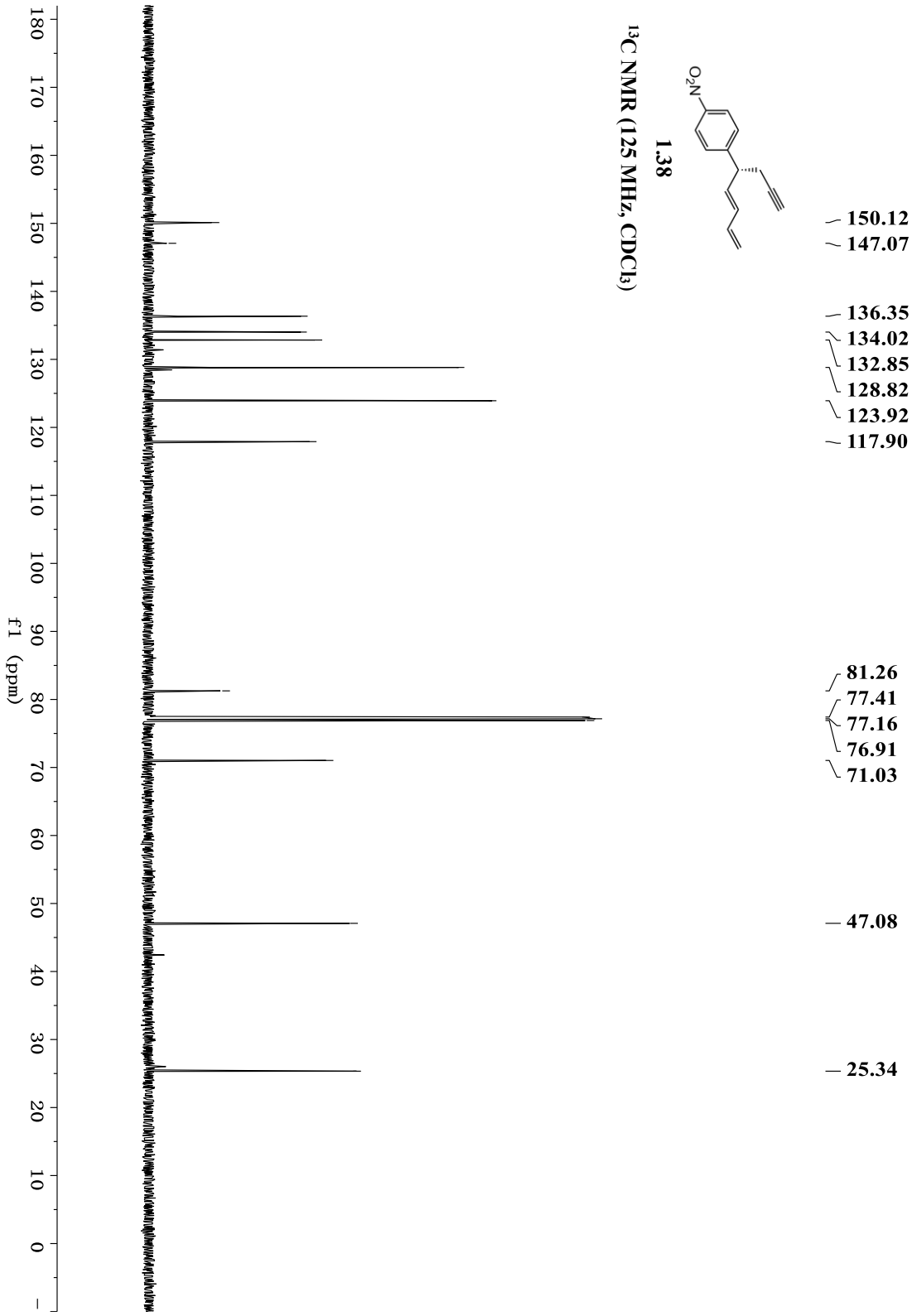

1.36
$^1$H NMR (600 MHz, CDCl$_3$)
Cl
7.30
7.29
7.25
7.17
7.15
6.41
6.39
6.38
6.37
6.36
6.34
6.17
6.15
6.14
6.12
5.94
5.92
5.91
5.90
5.23
5.20
5.12
5.10
3.62
3.61
3.59
3.58
2.68
2.65
2.65
2.64
2.64
2.63
2.62
2.60
2.03
2.02
2.02
3.03
1.00
1.01
1.02
1.01
1.05
1.04
1.03
2.02
0.95
f1 (ppm)

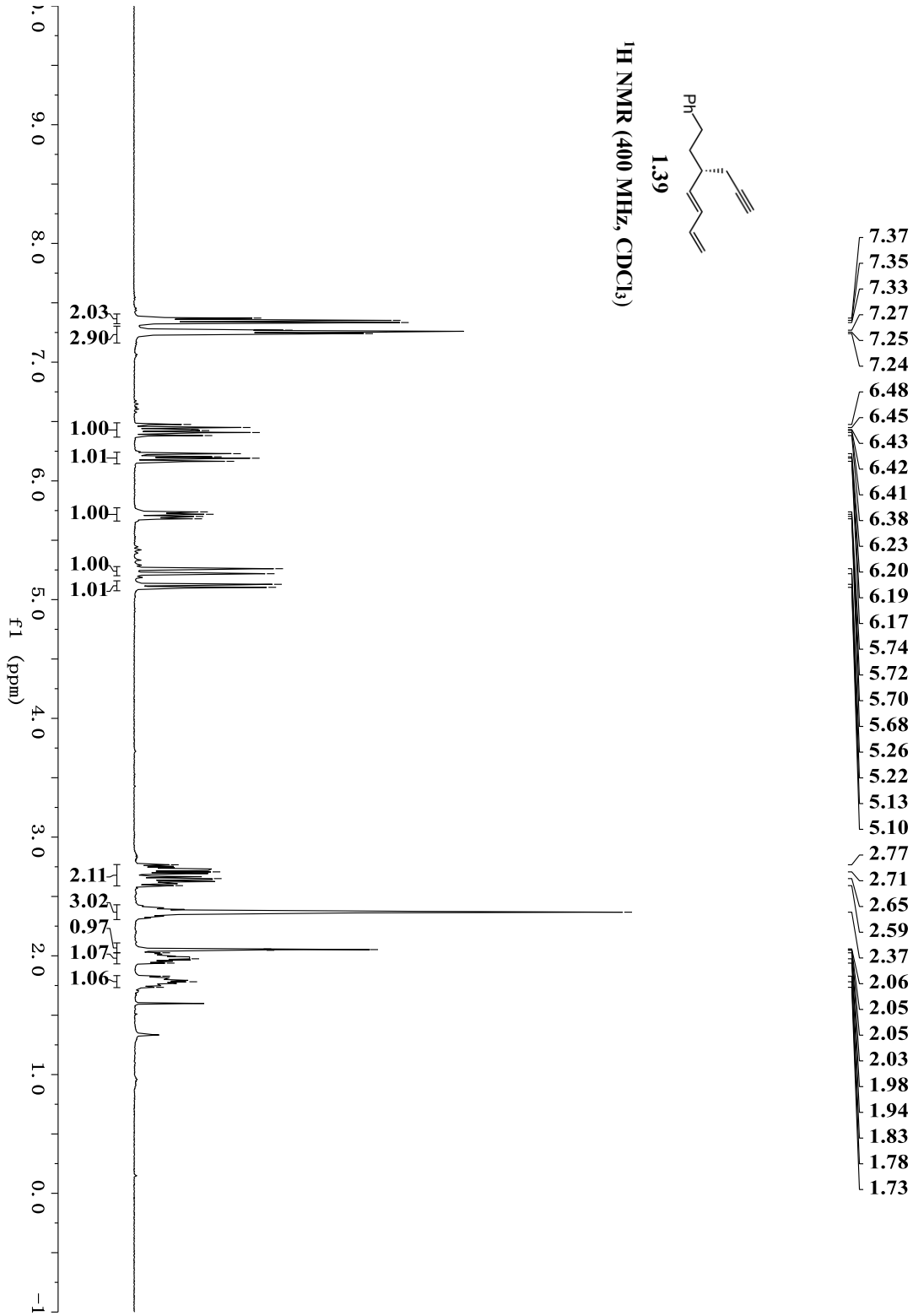

Cl
1.36
$^{13}$C NMR (150 MHz, CDCl$_3$)
144.71
136.67
135.07
134.43
132.19
129.89
128.00
127.13
126.03
117.23
81.91
77.37
77.16
76.95
70.54
47.04
25.47
f1 (ppm)

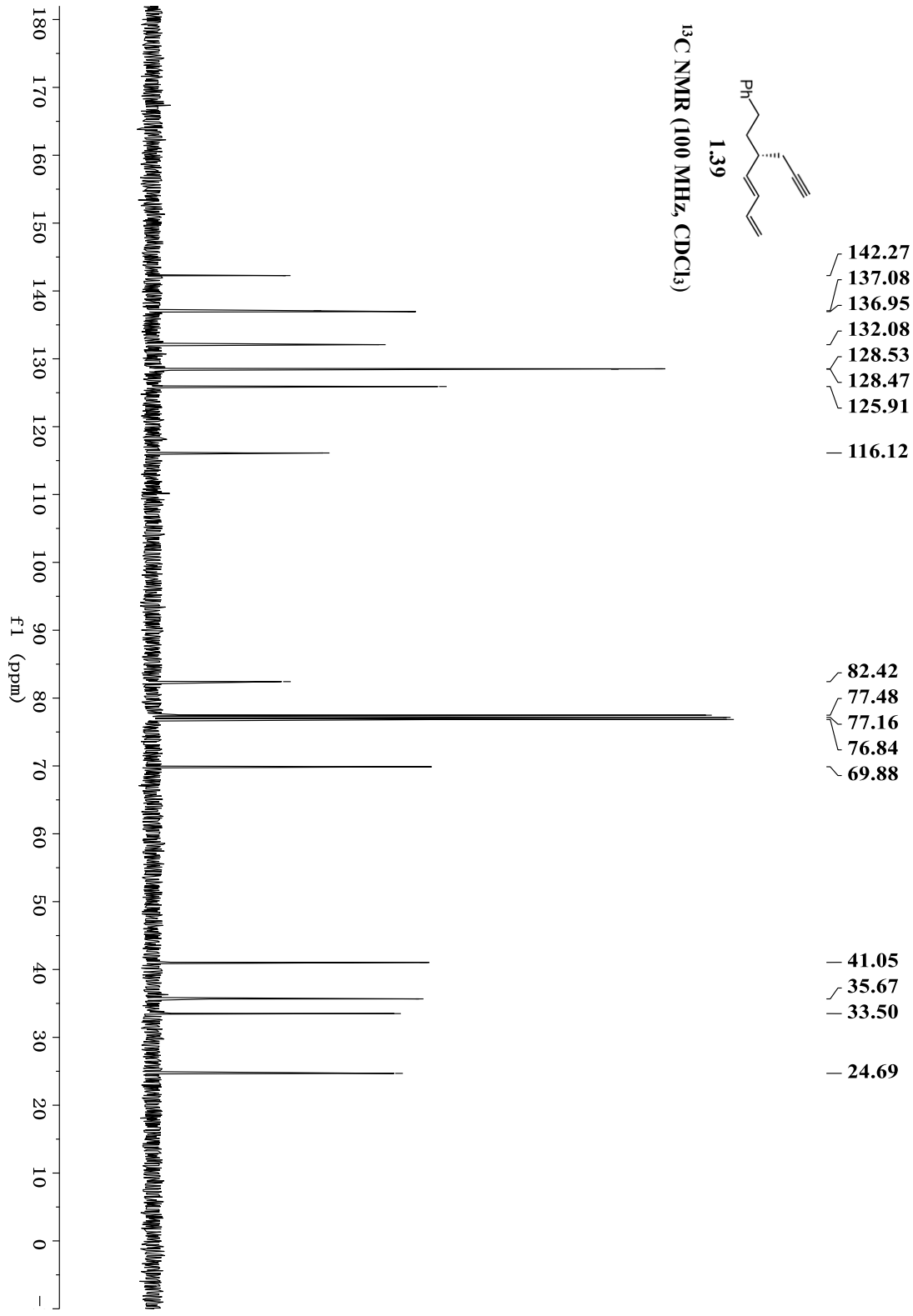

1.37
¹H NMR (500 MHz, CDCl₃)
F
7.21
7.20
7.19
7.18
7.03
7.01
6.99
6.38
6.36
6.34
6.34
6.32
6.30
6.11
6.09
6.08
6.06
5.92
5.91
5.89
5.88
5.18
5.15
5.07
5.05
3.60
3.59
3.57
3.56
2.64
2.59
2.59
2.54
1.98
1.97
1.97
2.01
2.00
1.00
1.01
1.00
1.08
1.00
1.02
2.01
0.97
f1 (ppm)

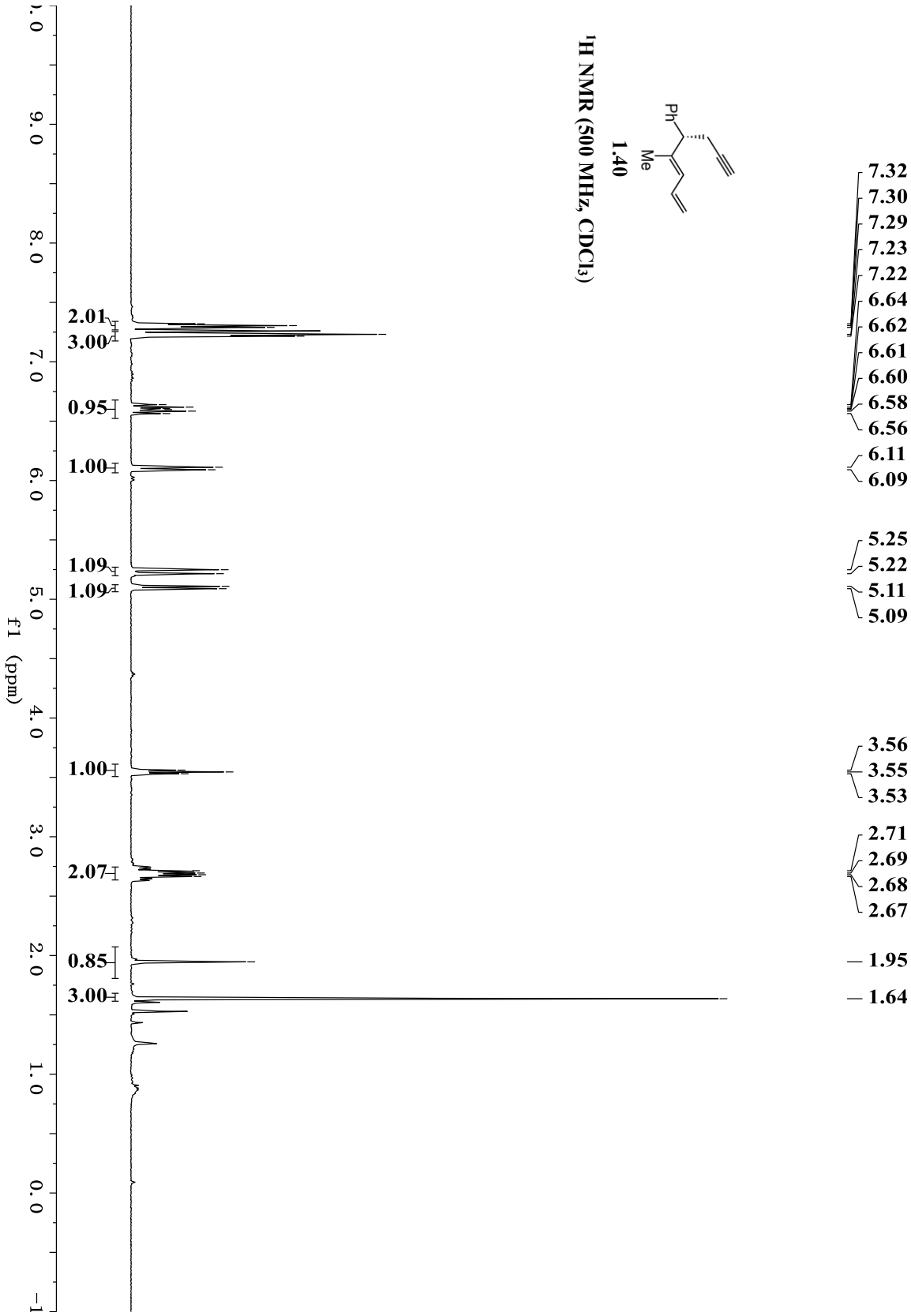

1.37
$^{13}$C NMR (100 MHz, CDCl$_3$)
F
163.05
160.61
138.33
138.30
136.76
135.76
131.81
129.31
129.23
116.99
115.54
115.33
82.19
77.48
77.16
76.84
70.37
46.54
25.71
f1 (ppm)

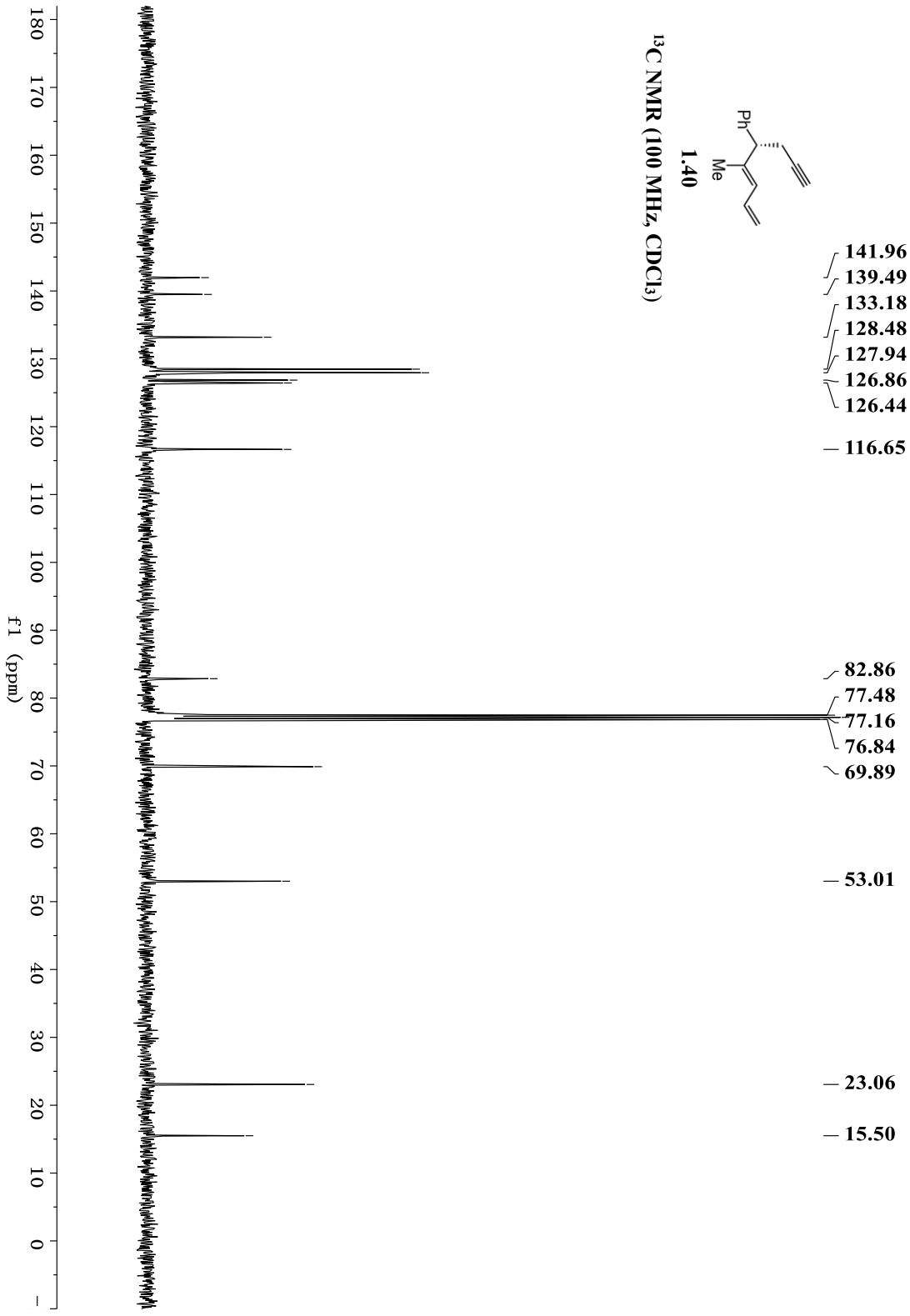

1.38
$^1$H NMR (400 MHz, CDCl$_3$)
O$_2$N
8.20
8.18
7.42
7.40
6.38
6.36
6.34
6.33
6.32
6.29
6.15
6.12
6.11
6.08
5.91
5.91
5.90
5.89
5.88
5.87
5.86
5.86
5.22
5.17
5.12
5.09
3.74
3.72
3.70
3.68
2.72
2.68
2.66
2.65
2.63
2.59
1.99
1.98
1.97
2.04
1.99
1.00
1.03
1.01
1.08
1.03
1.03
2.06
0.98
f1 (ppm)

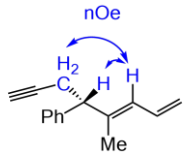

$^{13}$C NMR (125 MHz, CDCl$_3$)
1.38
O$_2$N
150.12
147.07
136.35
134.02
132.85
128.82
123.92
117.90
81.26
77.41
77.16
76.91
71.03
47.08
25.34
f1 (ppm)


1.39
$^1$H NMR (400 MHz, CDCl$_3$)
Ph
7.37
7.35
7.33
7.27
7.25
7.24
6.48
6.45
6.43
6.42
6.41
6.38
6.23
6.20
6.19
6.17
5.74
5.72
5.70
5.68
5.26
5.22
5.13
5.10
2.77
2.71
2.65
2.59
2.37
2.06
2.05
2.05
2.03
1.98
1.94
1.83
1.78
1.73
2.03
2.90
1.00
1.01
1.00
1.00
1.01
2.11
3.02
0.97
1.07
1.06
f1 (ppm)


1.39
$^{13}$C NMR (100 MHz, CDCl$_3$)
Ph
142.27
137.08
136.95
132.08
128.53
128.47
125.91
116.12
82.42
77.48
77.16
76.84
69.88
41.05
35.67
33.50
24.69
f1 (ppm)

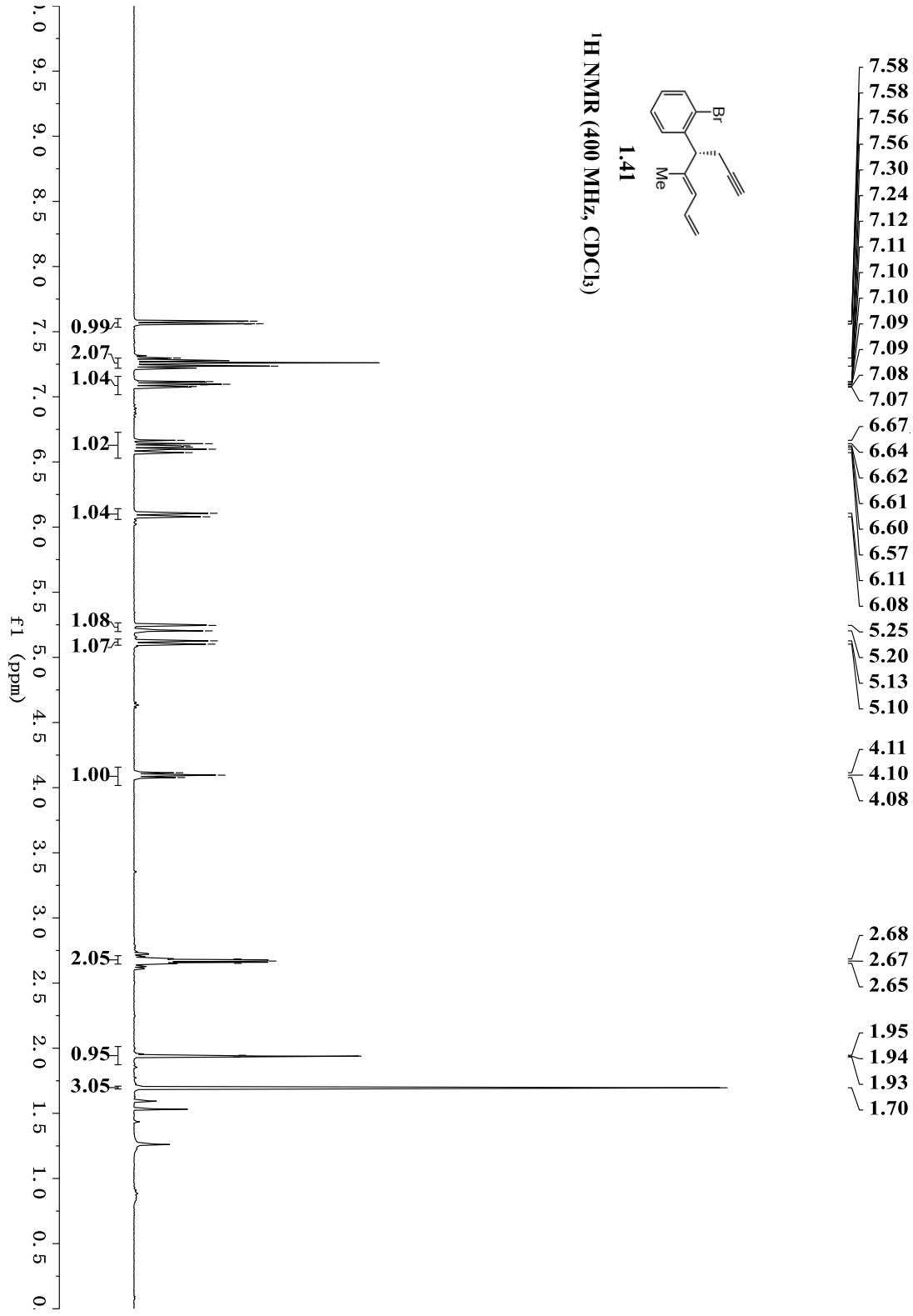

1H NMR (500 MHz, CDCl3)
Ph
Me
1.40
7.32
7.30
7.29
7.23
7.22
6.64
6.62
6.61
6.60
6.58
6.56
6.11
6.09
5.25
5.22
5.11
5.09
3.56
3.55
3.53
2.71
2.69
2.68
2.67
1.95
1.64
2.01
3.00
0.95
1.00
1.09
1.09
1.00
2.07
0.85
3.00
f1 (ppm)

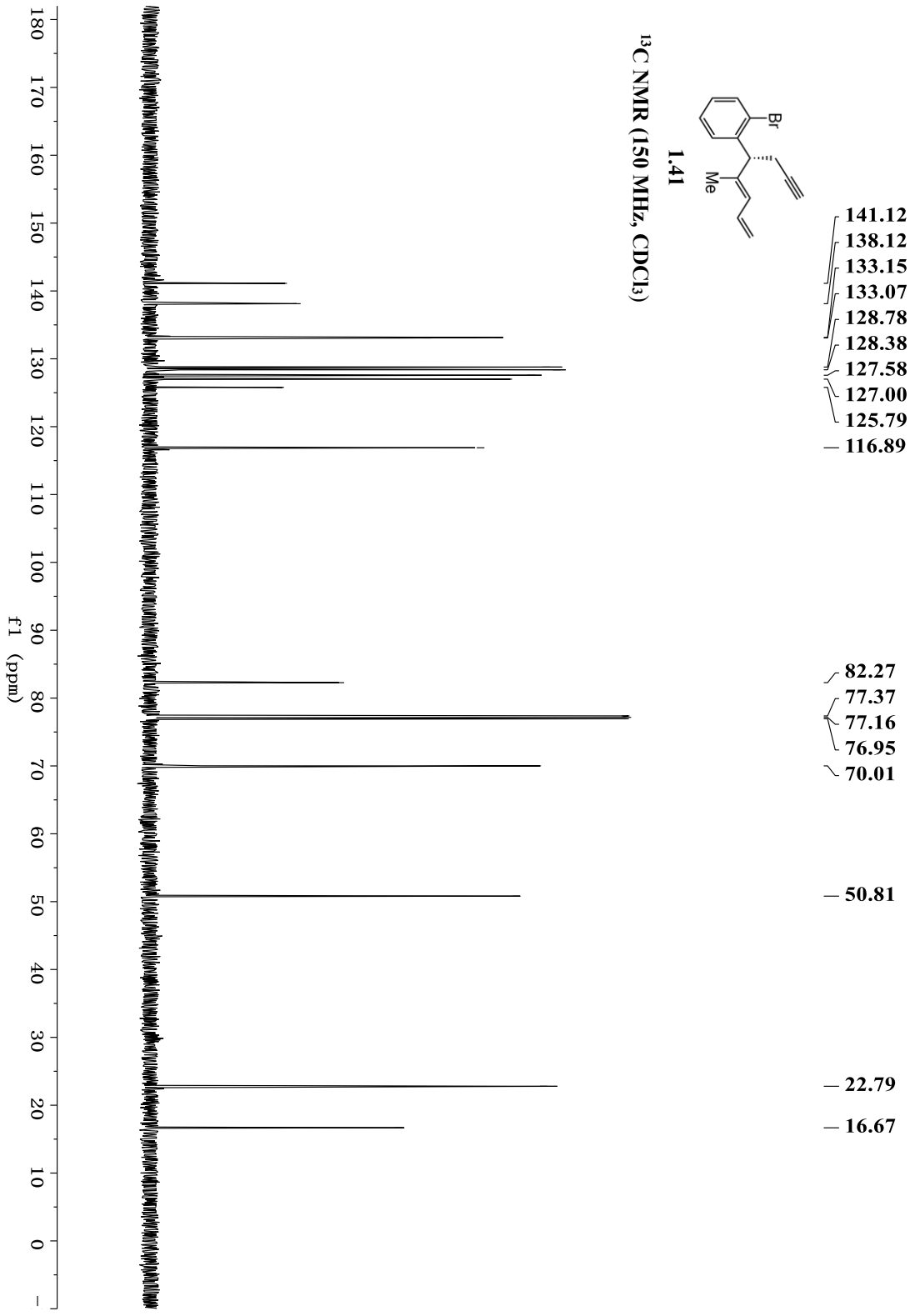

$^{13}$C NMR (100 MHz, CDCl$_3$)
1.40
Ph
Me
141.96
139.49
133.18
128.48
127.94
126.86
126.44
116.65
82.86
77.48
77.16
76.84
69.89
53.01
23.06
15.50
f1 (ppm)

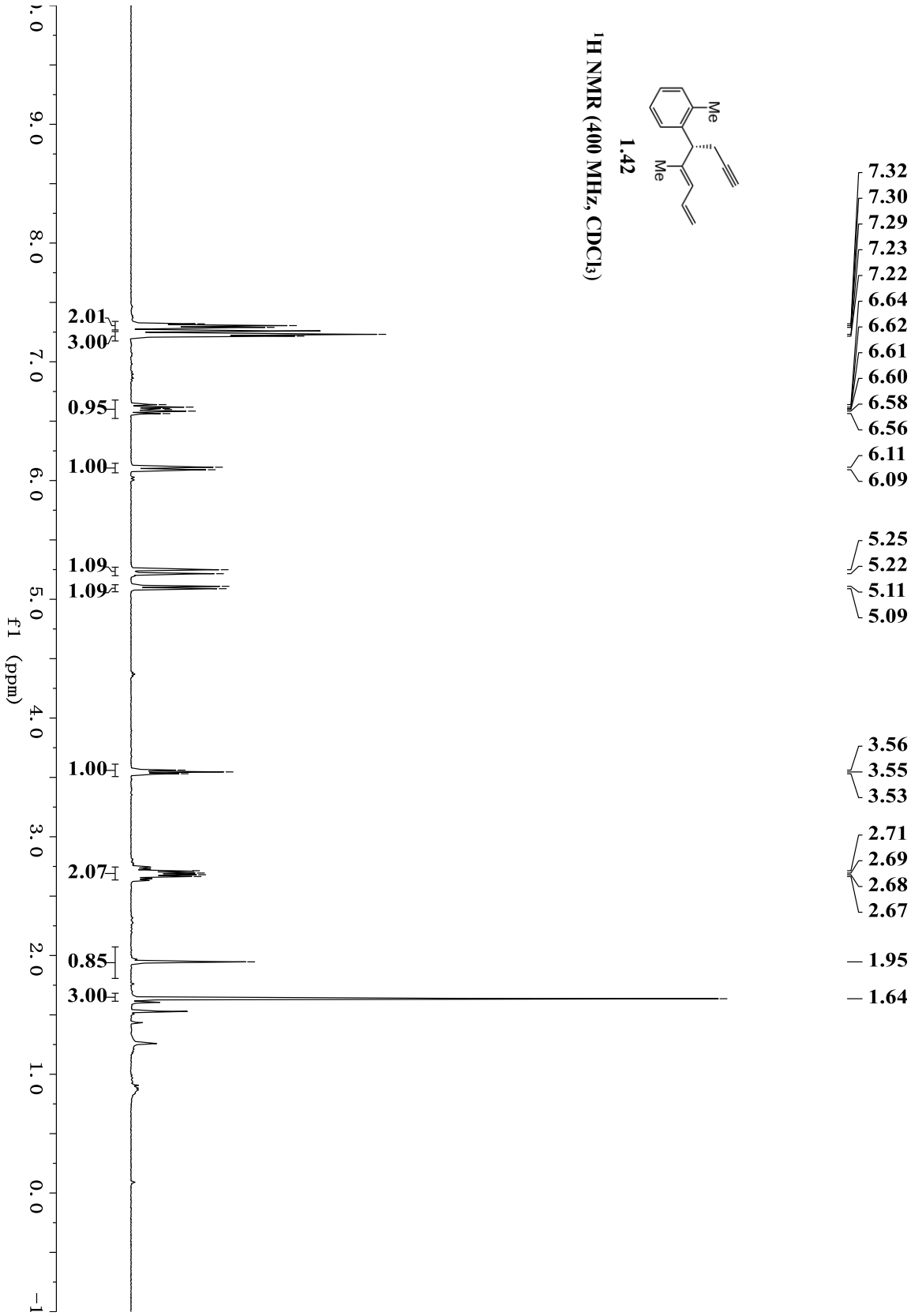


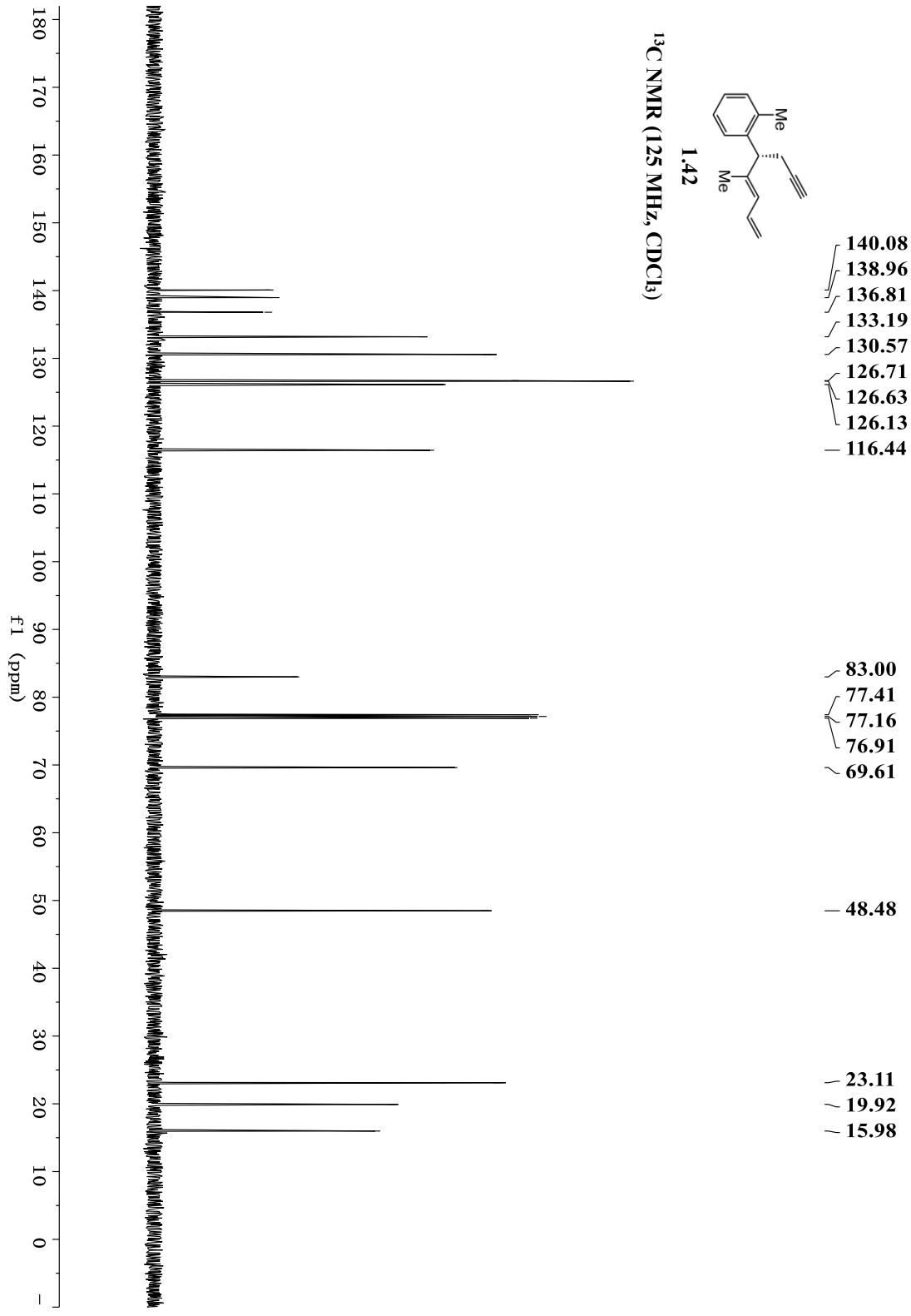

**1D nOe for 1.40**

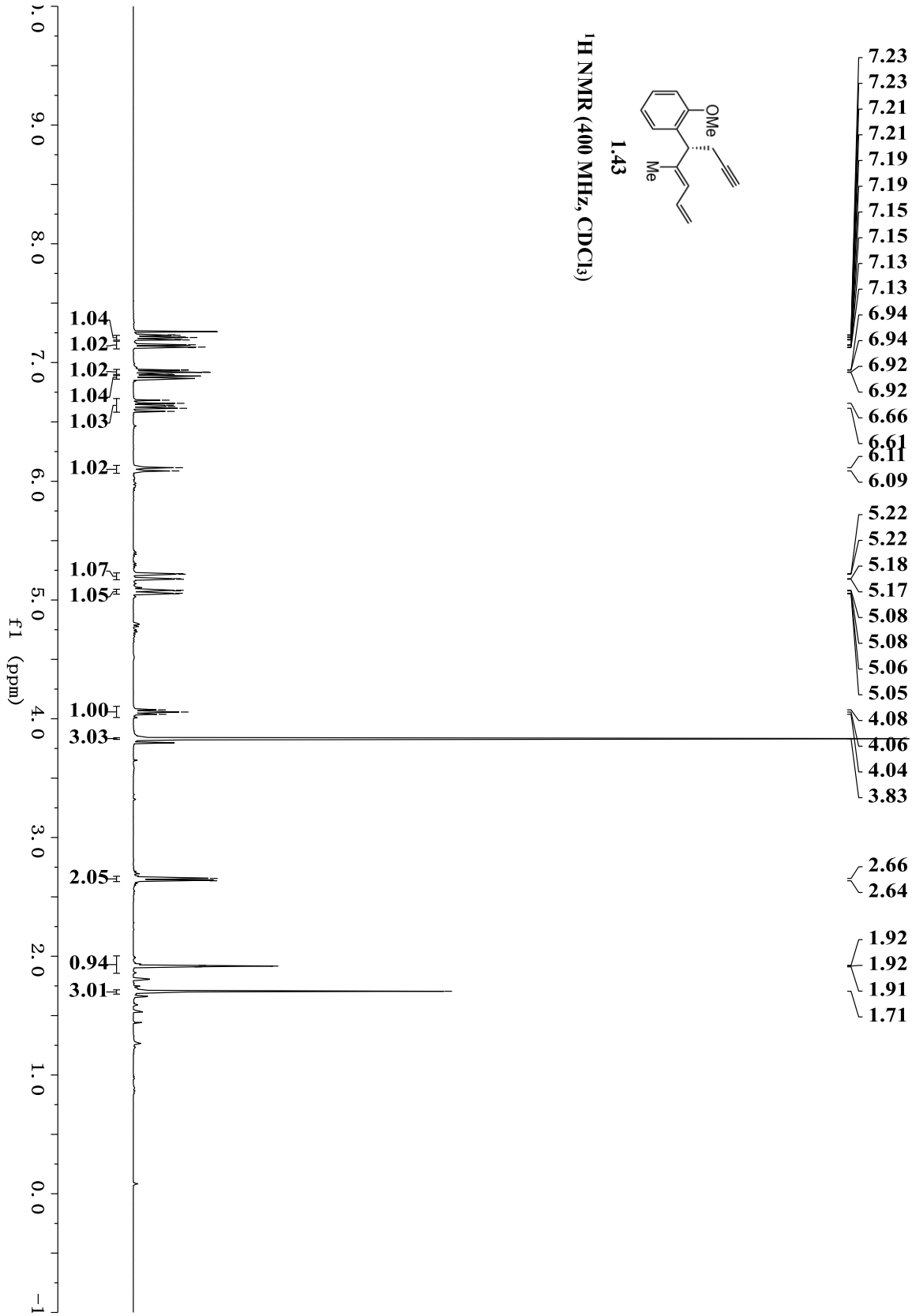
1D nOe for 1.40
Ph
CH3
H
nOe
6.633
6.606
6.591
6.580
6.564
6.537
3.548
3.528
3.511
1.621
f1 (ppm)

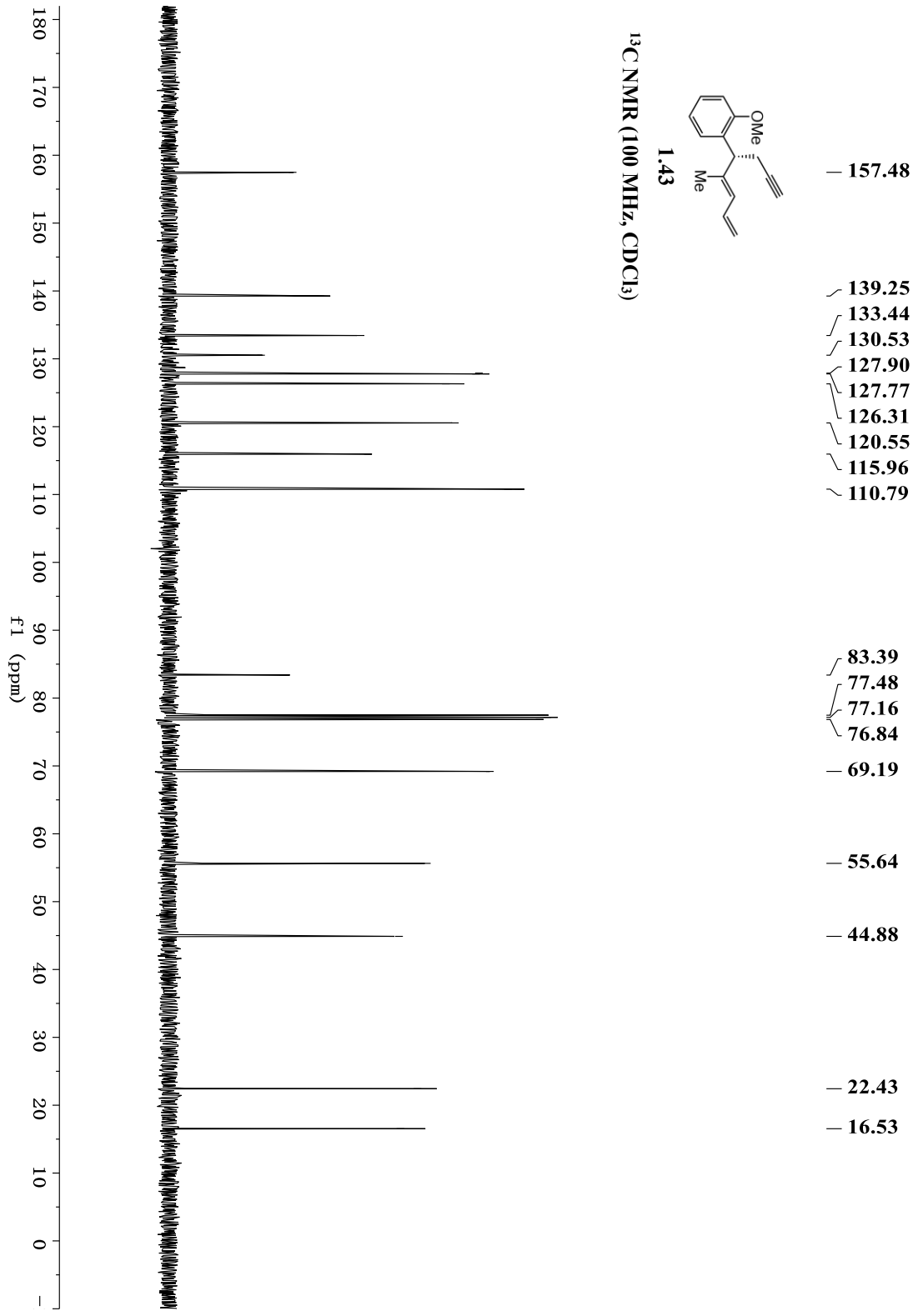

1H NMR (400 MHz, CDCl3)
1.41
Br
Me
7.58
7.58
7.56
7.56
7.30
7.24
7.12
7.11
7.10
7.10
7.09
7.09
7.08
7.07
6.67
6.64
6.62
6.61
6.60
6.57
6.11
6.08
5.25
5.20
5.13
5.10
4.11
4.10
4.08
2.68
2.67
2.65
1.95
1.94
1.93
1.70
0.99
2.07
1.04
1.02
1.04
1.08
1.07
1.00
2.05
0.95
3.05
f1 (ppm)

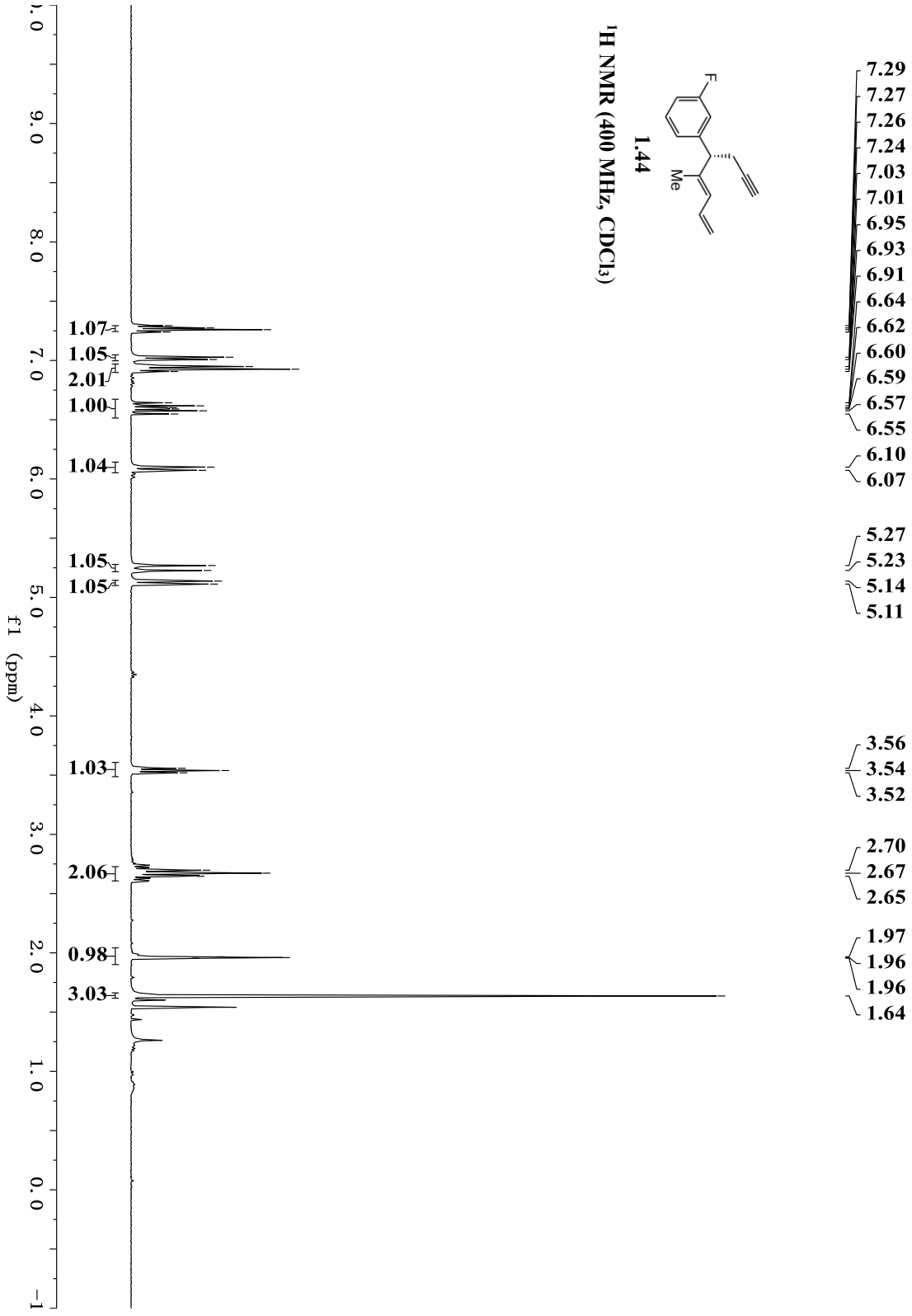

$^{13}$C NMR (150 MHz, CDCl$_3$)
1.41
Br
Me
141.12
138.12
133.15
133.07
128.78
128.38
127.58
127.00
125.79
116.89
82.27
77.37
77.16
76.95
70.01
50.81
22.79
16.67
f1 (ppm)

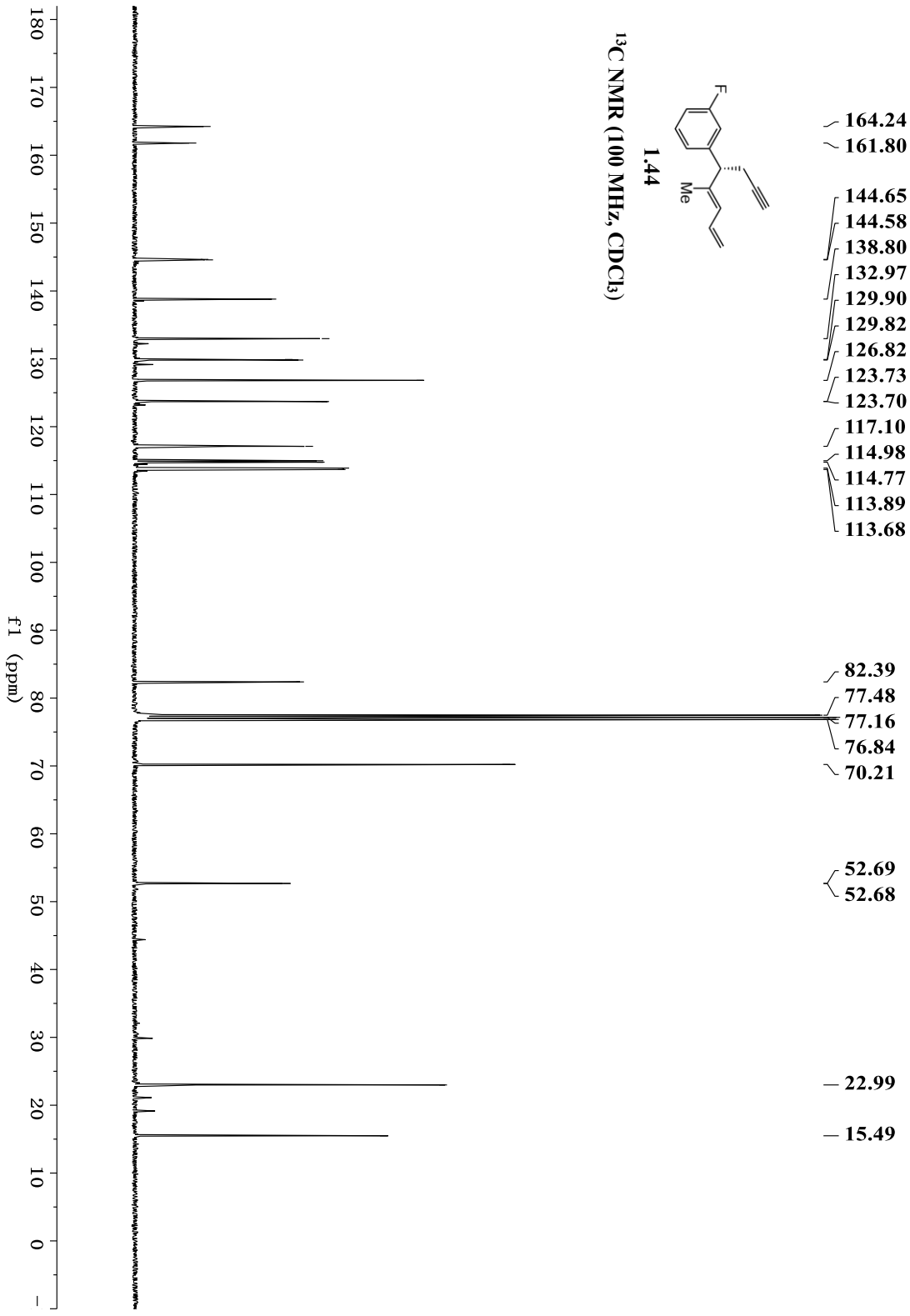

1H NMR (400 MHz, CDCl3)
1.42
Me
Me
7.32
7.30
7.29
7.23
7.22
6.64
6.62
6.61
6.60
6.58
6.56
6.11
6.09
5.25
5.22
5.11
5.09
3.56
3.55
3.53
2.71
2.69
2.68
2.67
1.95
1.64
2.01
3.00
0.95
1.00
1.09
1.09
1.00
2.07
0.85
3.00
f1 (ppm)

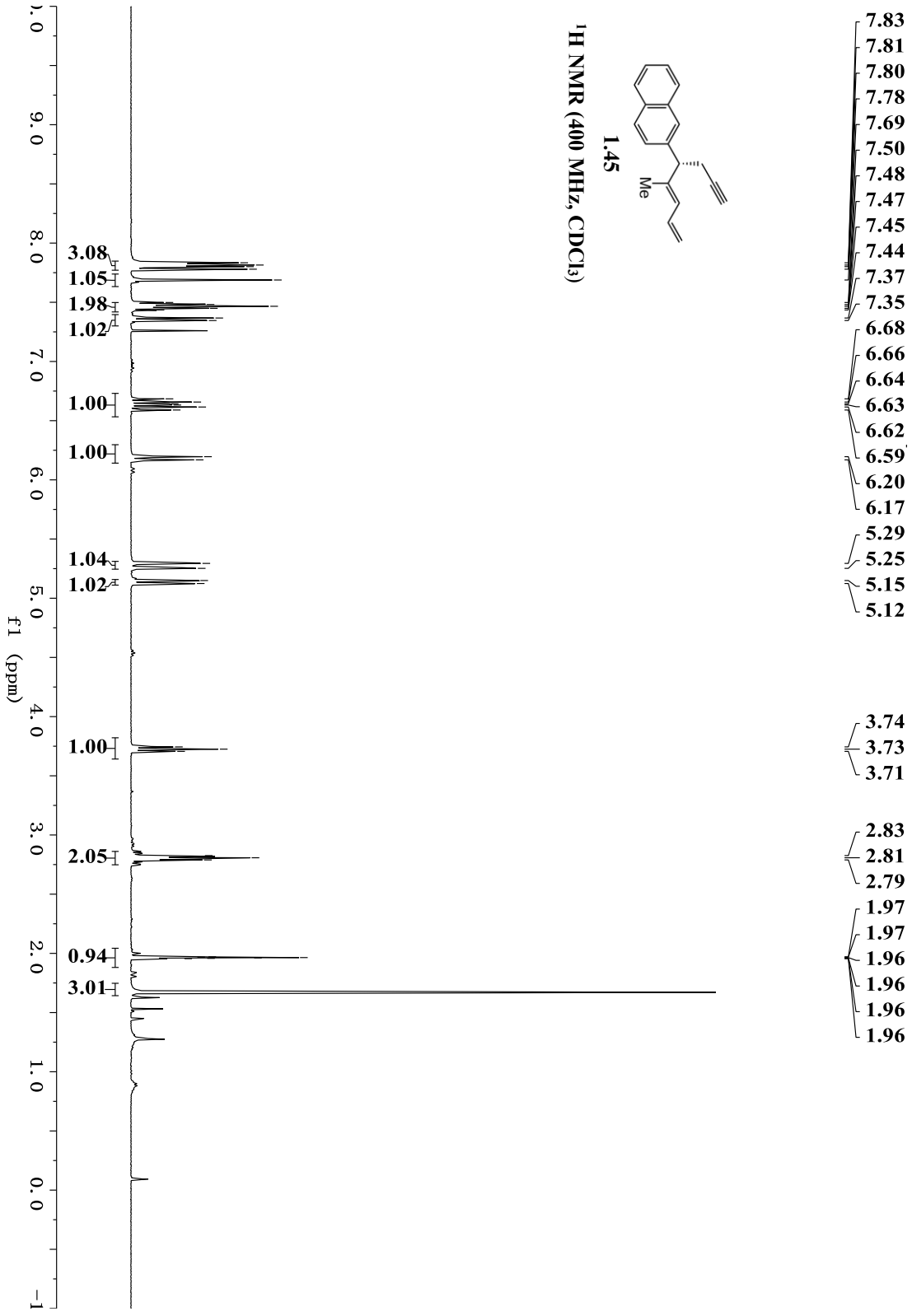

$^{13}$C NMR (125 MHz, CDCl$_3$)
1.42
Me
Me
140.08
138.96
136.81
133.19
130.57
126.71
126.63
126.13
116.44
83.00
77.41
77.16
76.91
69.61
48.48
23.11
19.92
15.98
f1 (ppm)

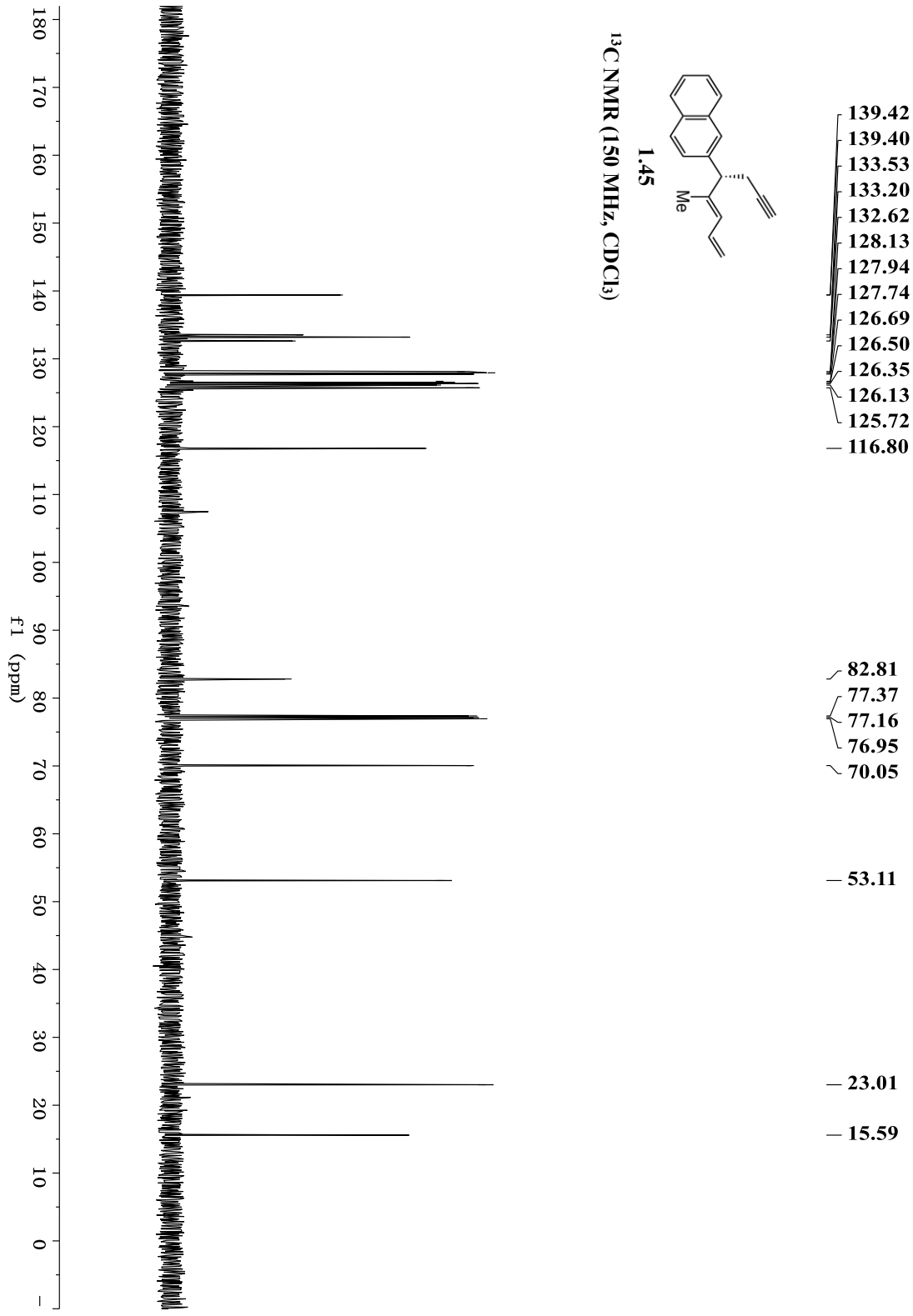

1.43
$^1$H NMR (400 MHz, CDCl$_3$)
OMe
Me
7.23
7.23
7.21
7.21
7.19
7.19
7.15
7.15
7.13
7.13
6.94
6.94
6.92
6.92
6.66
6.61
6.11
6.09
5.22
5.22
5.18
5.17
5.08
5.08
5.06
5.05
4.08
4.06
4.04
3.83
2.66
2.64
1.92
1.92
1.91
1.71
1.04
1.02
1.02
1.04
1.03
1.02
1.07
1.05
1.00
3.03
2.05
0.94
3.01
f1 (ppm)

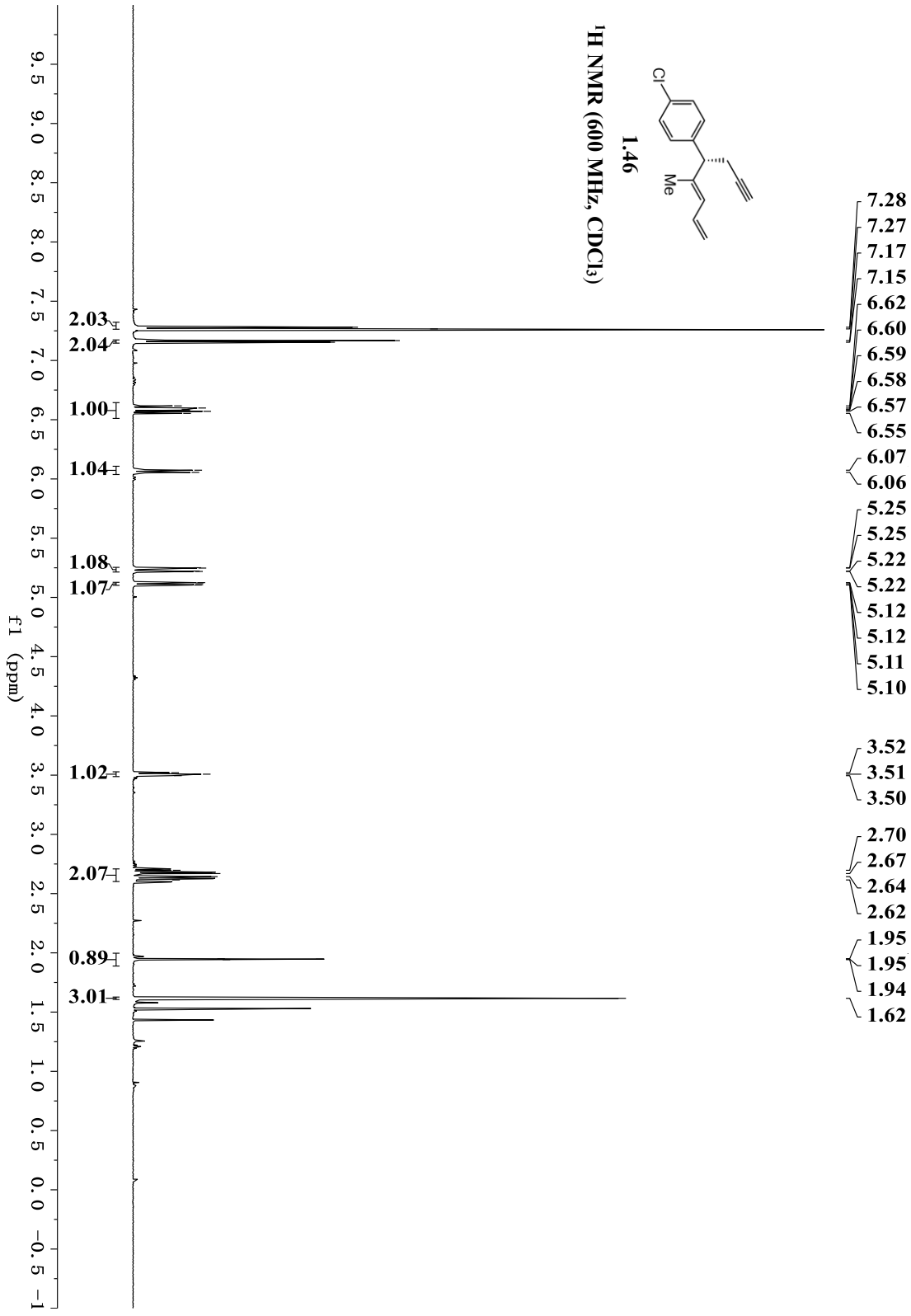

1.43
$^{13}$C NMR (100 MHz, CDCl$_3$)
OMe
Me
157.48
139.25
133.44
130.53
127.90
127.77
126.31
120.55
115.96
110.79
83.39
77.48
77.16
76.84
69.19
55.64
44.88
22.43
16.53
f1 (ppm)

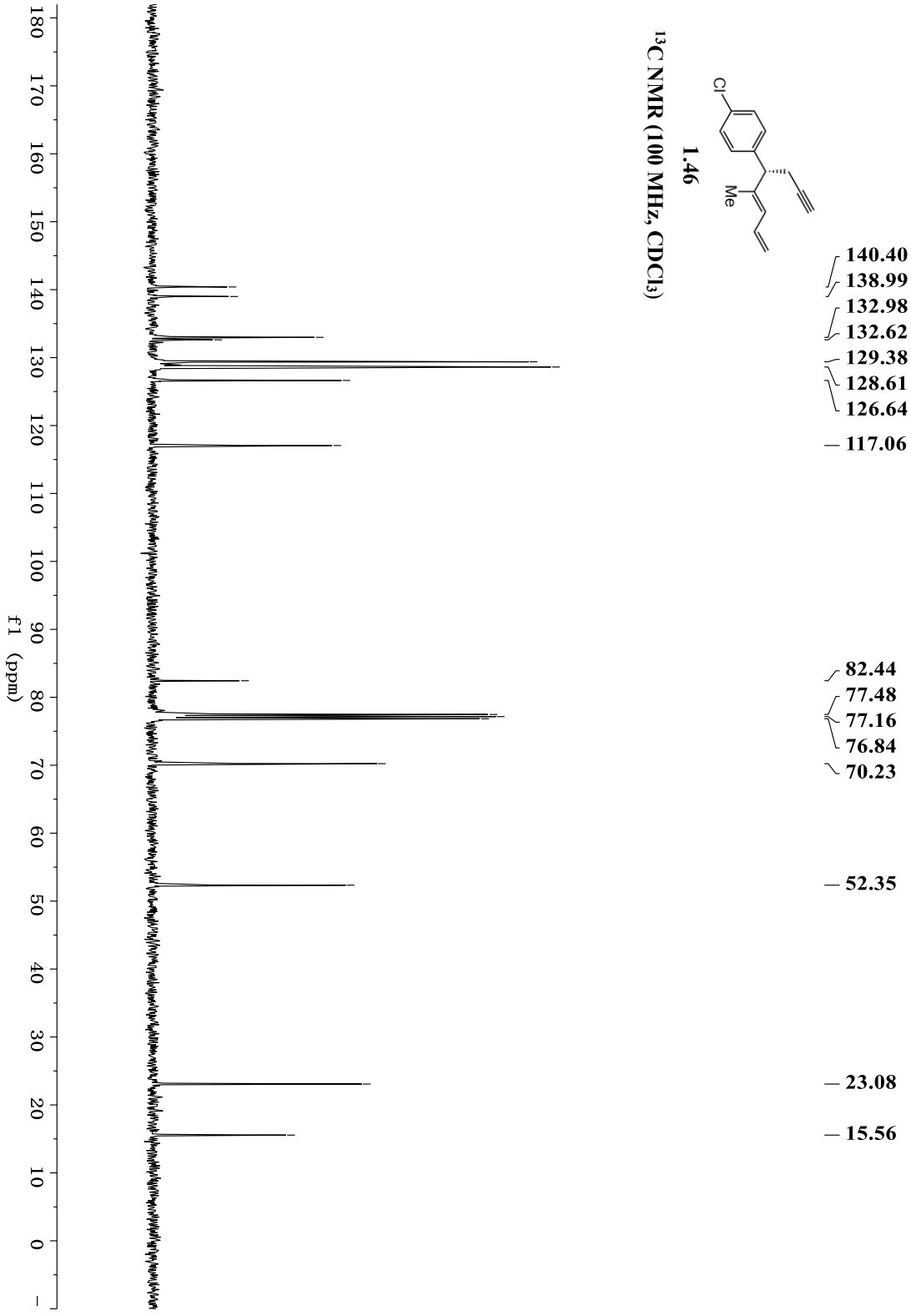

1H NMR (400 MHz, CDCl3)
1.44
F
Me
7.29
7.27
7.26
7.24
7.03
7.01
6.95
6.93
6.91
6.64
6.62
6.60
6.59
6.57
6.55
6.10
6.07
5.27
5.23
5.14
5.11
3.56
3.54
3.52
2.70
2.67
2.65
1.97
1.96
1.96
1.64
1.07
1.05
2.01
1.00
1.04
1.05
1.05
1.03
2.06
0.98
3.03
f1 (ppm)

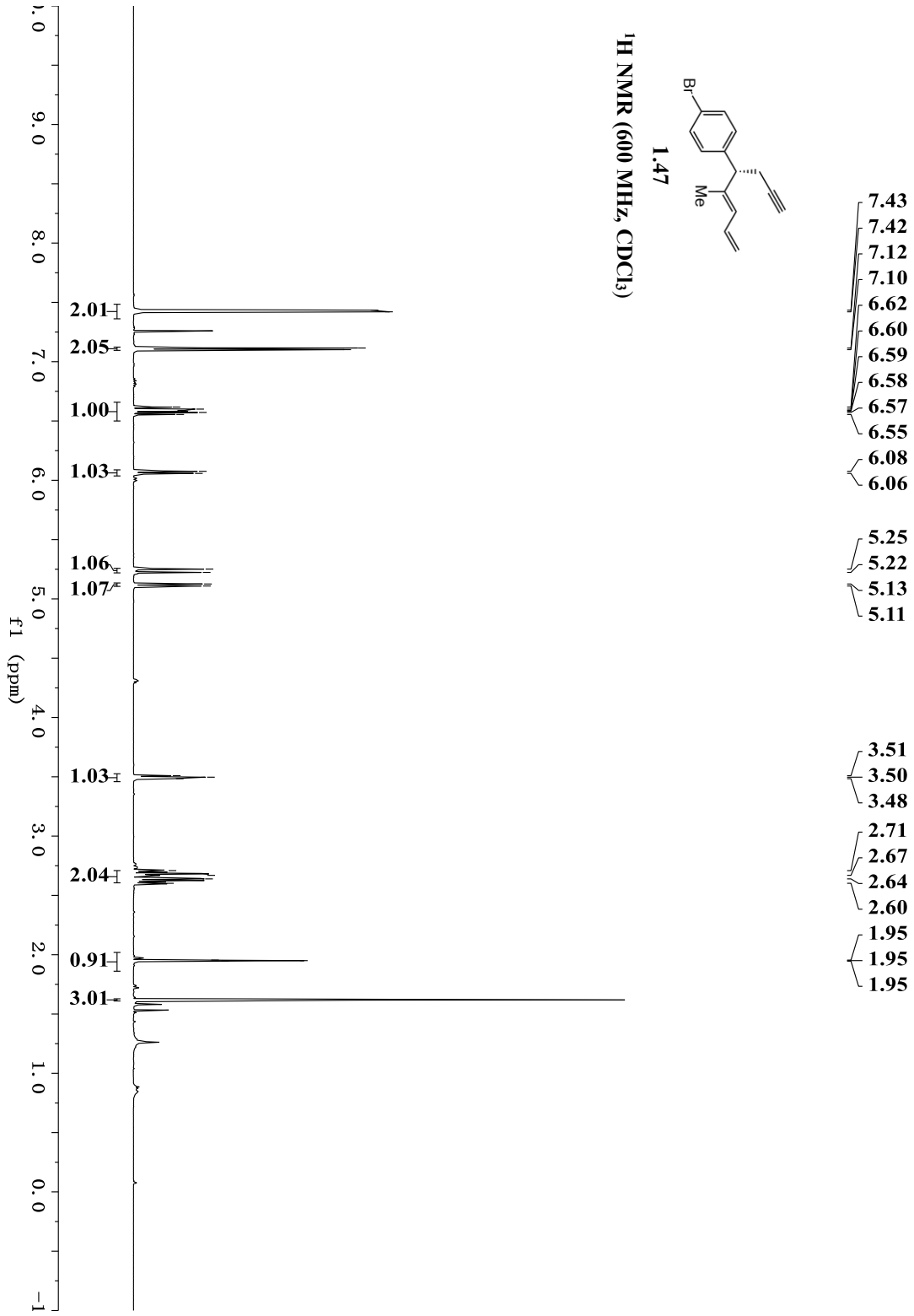

13C NMR (100 MHz, CDCl3)
1.44
F
Me
164.24
161.80
144.65
144.58
138.80
132.97
129.90
129.82
126.82
123.73
123.70
117.10
114.98
114.77
113.89
113.68
82.39
77.48
77.16
76.84
70.21
52.69
52.68
22.99
15.49
f1 (ppm)

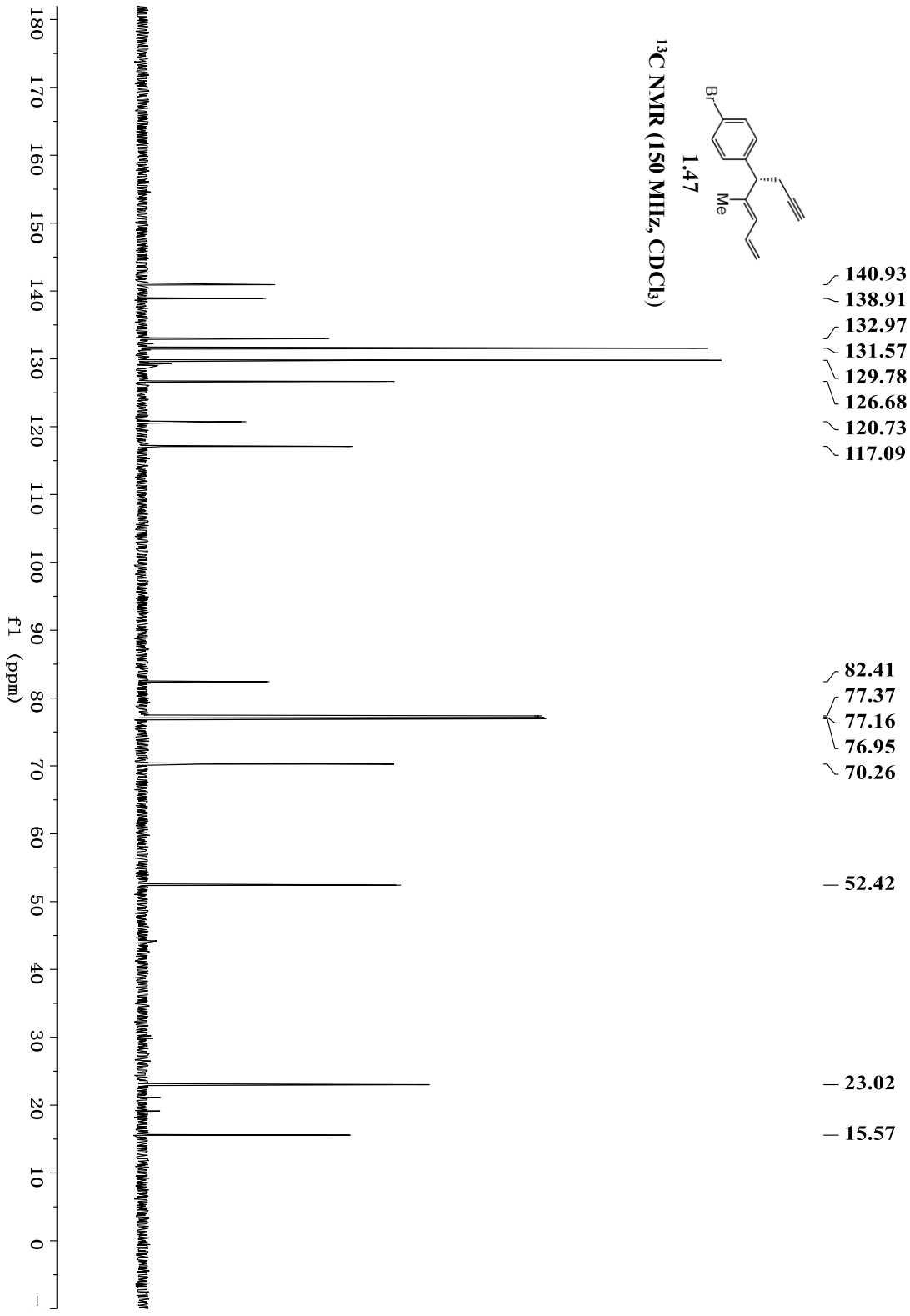

1.45
Me
7.83
7.81
7.80
7.78
7.69
7.50
7.48
7.47
7.45
7.44
7.37
7.35
6.68
6.66
6.64
6.63
6.62
6.59
6.20
6.17
5.29
5.25
5.15
5.12
3.74
3.73
3.71
2.83
2.81
2.79
1.97
1.97
1.96
1.96
1.96
1.96
1.96
3.08
1.05
1.98
1.02
1.00
1.00
1.04
1.02
1.00
2.05
0.94
3.01
f1 (ppm)

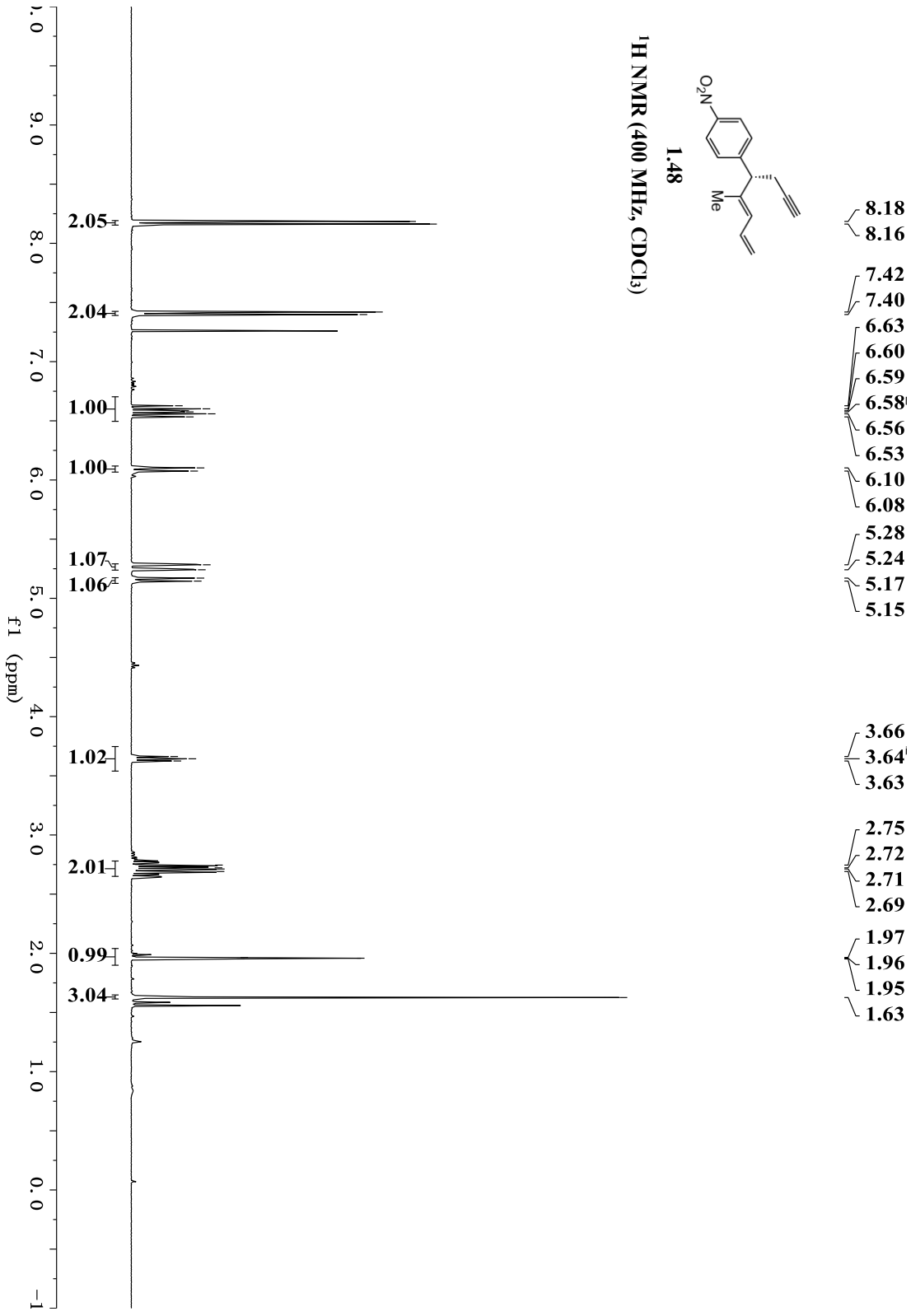

$^{13}$C NMR (150 MHz, CDCl$_3$)
1.45
Me
139.42
139.40
133.53
133.20
132.62
128.13
127.94
127.74
126.69
126.50
126.35
126.13
125.72
116.80
82.81
77.37
77.16
76.95
70.05
53.11
23.01
15.59
f1 (ppm)

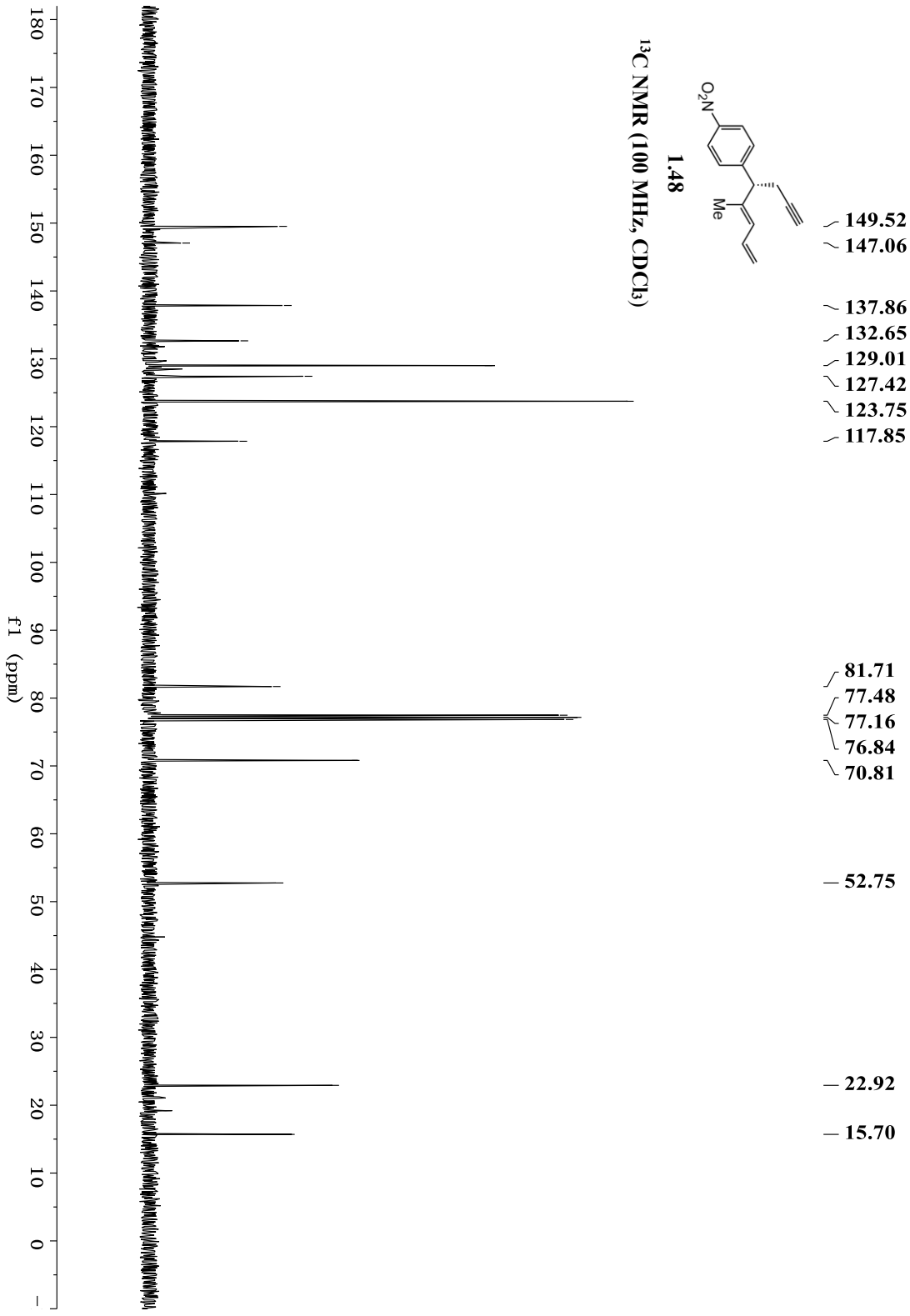

1H NMR (600 MHz, CDCl3)
1.46
Cl
Me
7.28
7.27
7.17
7.15
6.62
6.60
6.59
6.58
6.57
6.55
6.07
6.06
5.25
5.25
5.22
5.22
5.12
5.12
5.11
5.10
3.52
3.51
3.50
2.70
2.67
2.64
2.62
1.95
1.95
1.94
1.62
2.03
2.04
1.00
1.04
1.08
1.07
1.02
2.07
0.89
3.01
f1 (ppm)

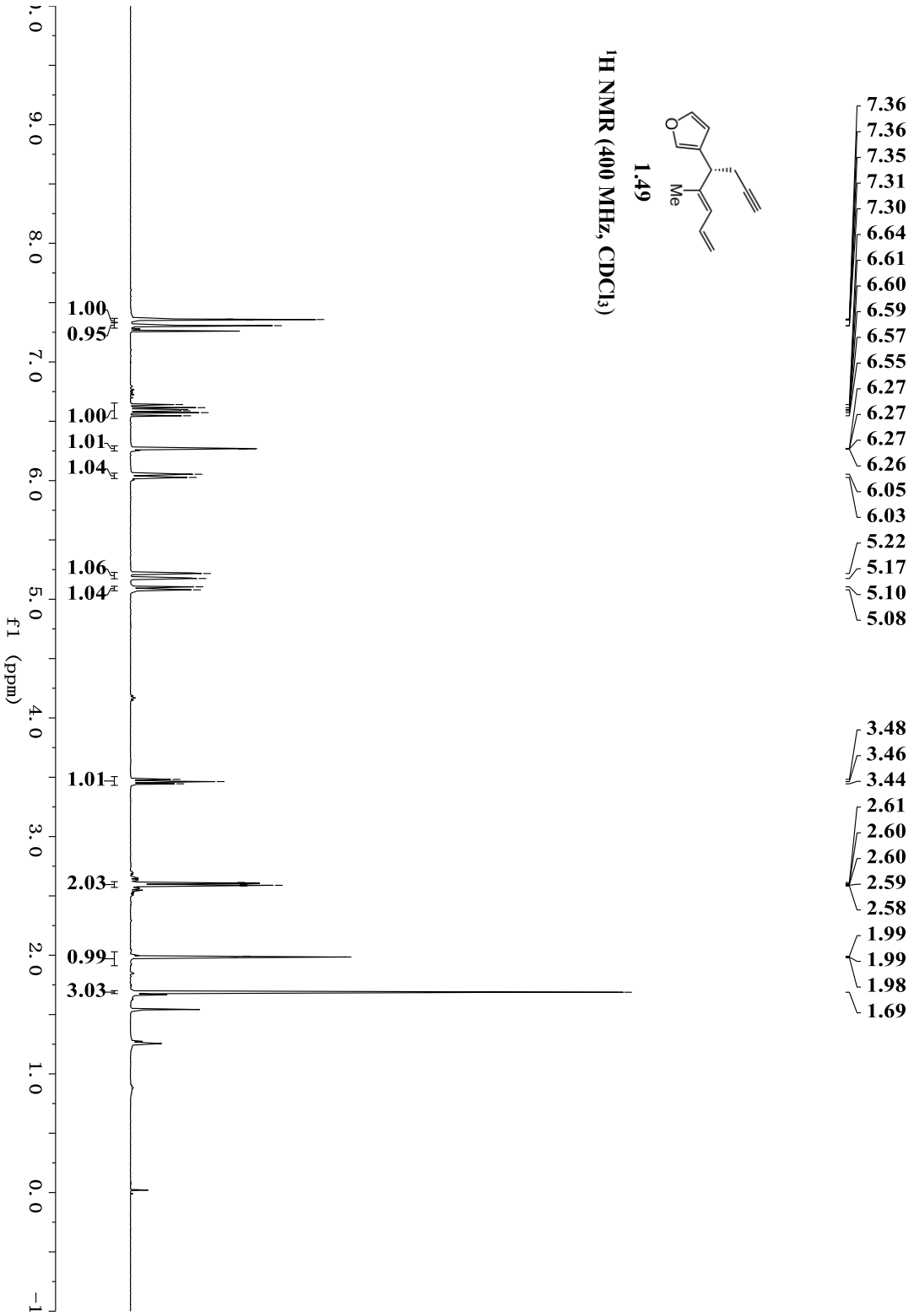

$^{13}$C NMR (100 MHz, CDCl$_3$)
1.46
Cl
Me
140.40
138.99
132.98
132.62
129.38
128.61
126.64
117.06
82.44
77.48
77.16
76.84
70.23
52.35
23.08
15.56
f1 (ppm)

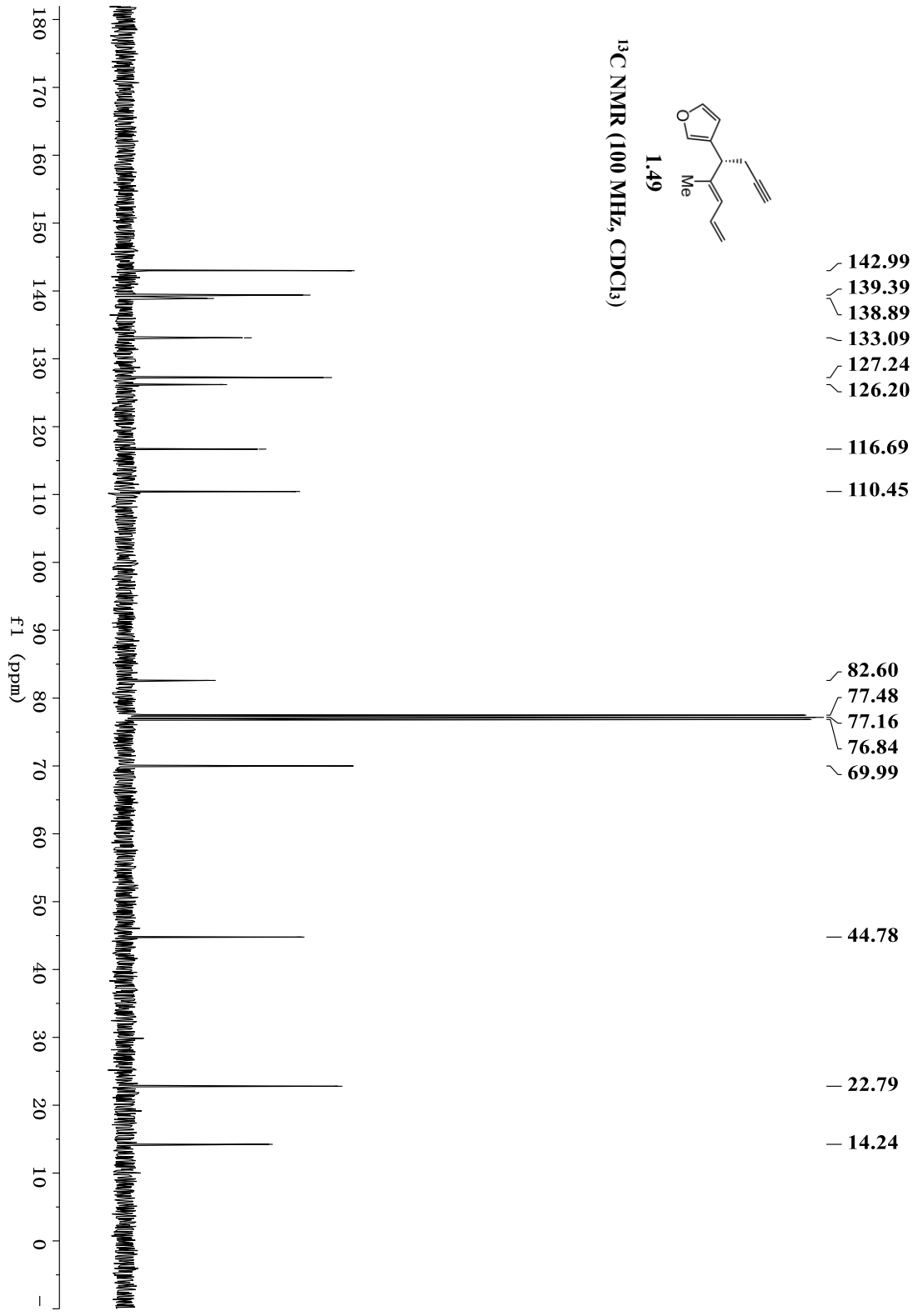

1.47
Br
Me
7.43
7.42
7.12
7.10
6.62
6.60
6.59
6.58
6.57
6.55
6.08
6.06
5.25
5.22
5.13
5.11
3.51
3.50
3.48
2.71
2.67
2.64
2.60
1.95
1.95
1.95
2.01
2.05
1.00
1.03
1.06
1.07
1.03
2.04
0.91
3.01
f1 (ppm)

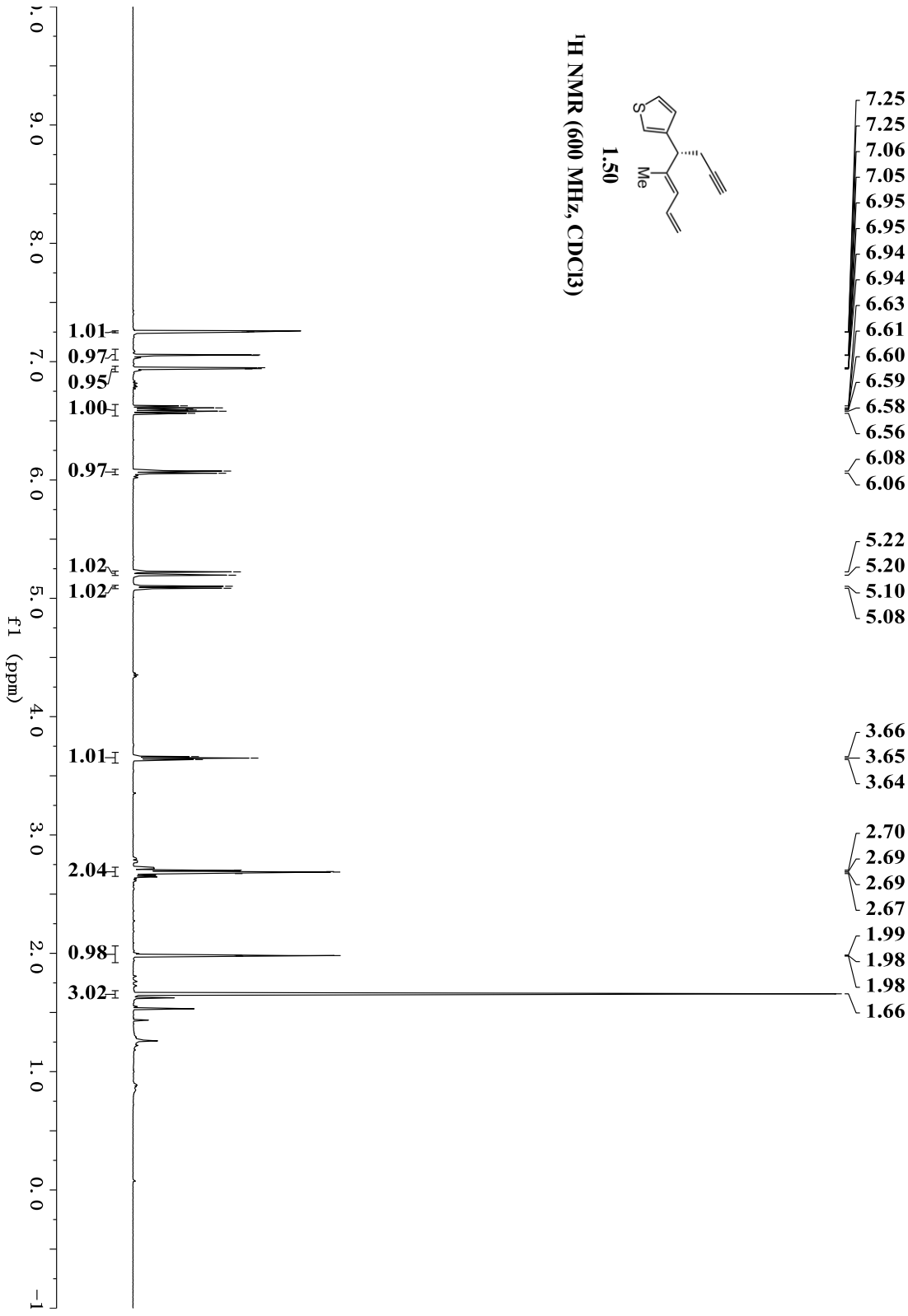

Br
Me
1.47
13C NMR (150 MHz, CDCl3)
140.93
138.91
132.97
131.57
129.78
126.68
120.73
117.09
82.41
77.37
77.16
76.95
70.26
52.42
23.02
15.57
f1 (ppm)

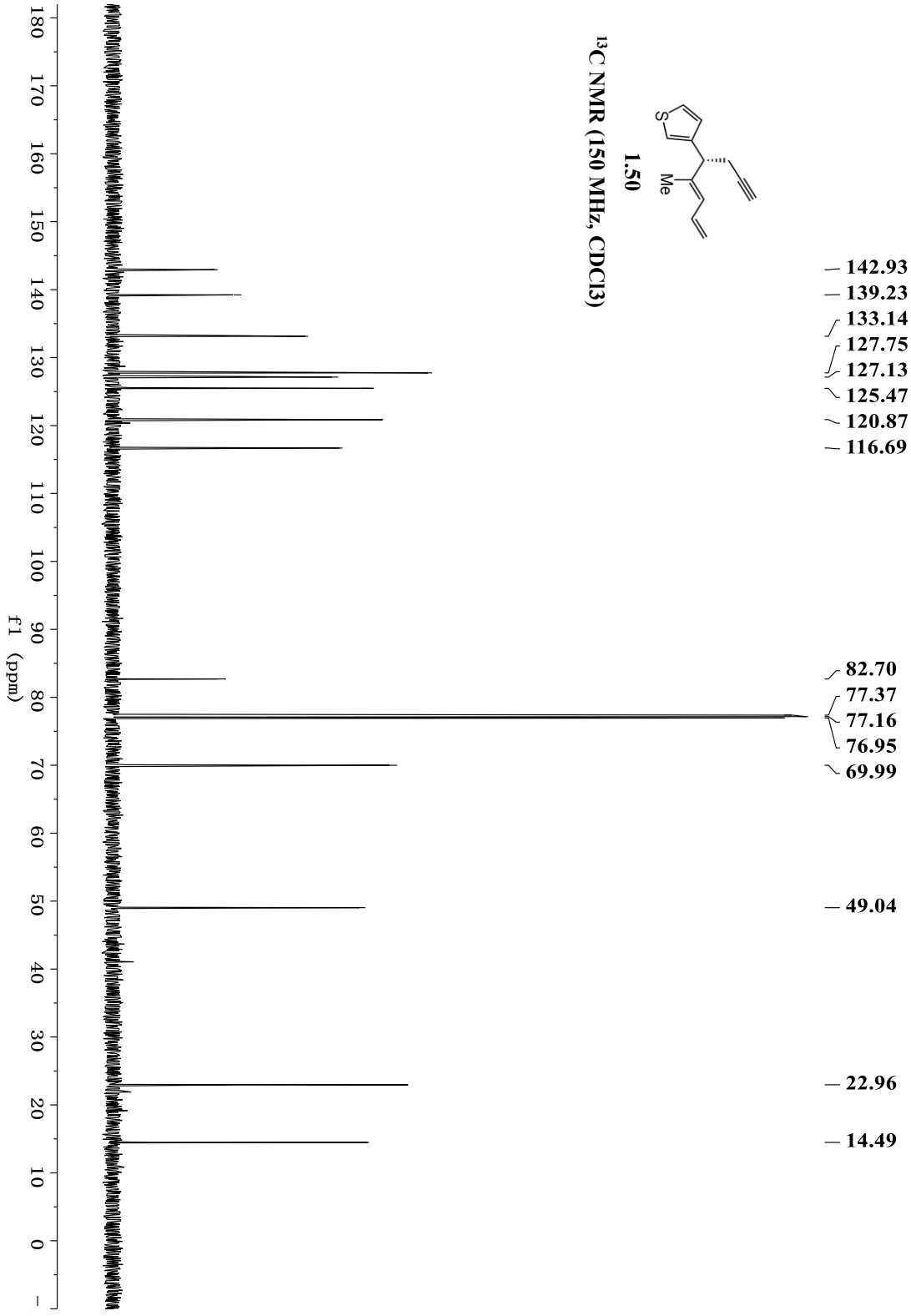

1.48
$^1$H NMR (400 MHz, CDCl$_3$)
O$_2$N
Me
8.18
8.16
7.42
7.40
6.63
6.60
6.59
6.58
6.56
6.53
6.10
6.08
5.28
5.24
5.17
5.15
3.66
3.64
3.63
2.75
2.72
2.71
2.69
1.97
1.96
1.95
1.63
2.05
2.04
1.00
1.00
1.07
1.06
1.02
2.01
0.99
3.04
f1 (ppm)

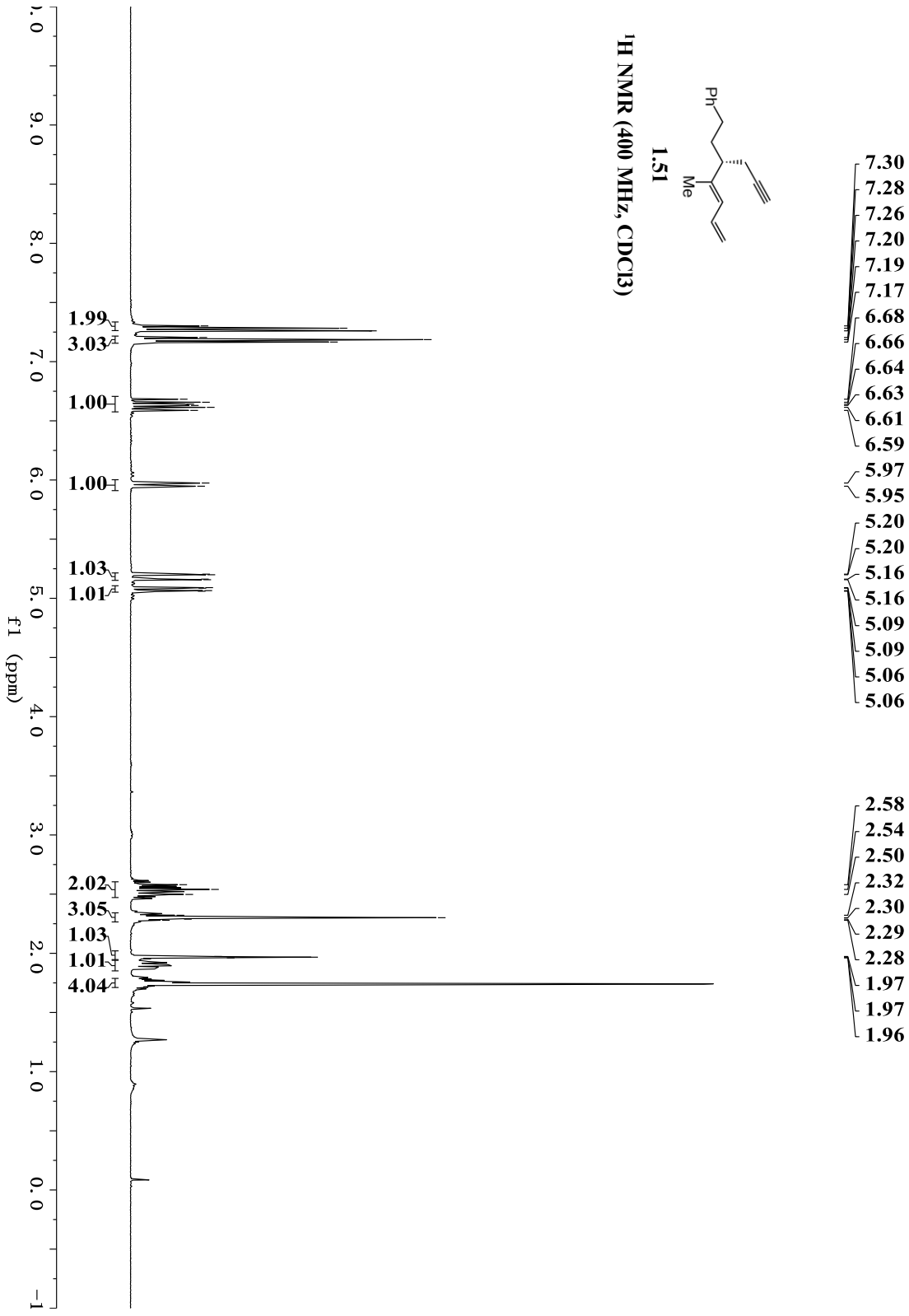

$^{13}$C NMR (100 MHz, CDCl$_3$)
1.48
O$_2$N
Me
149.52
147.06
137.86
132.65
129.01
127.42
123.75
117.85
81.71
77.48
77.16
76.84
70.81
52.75
22.92
15.70
f1 (ppm)

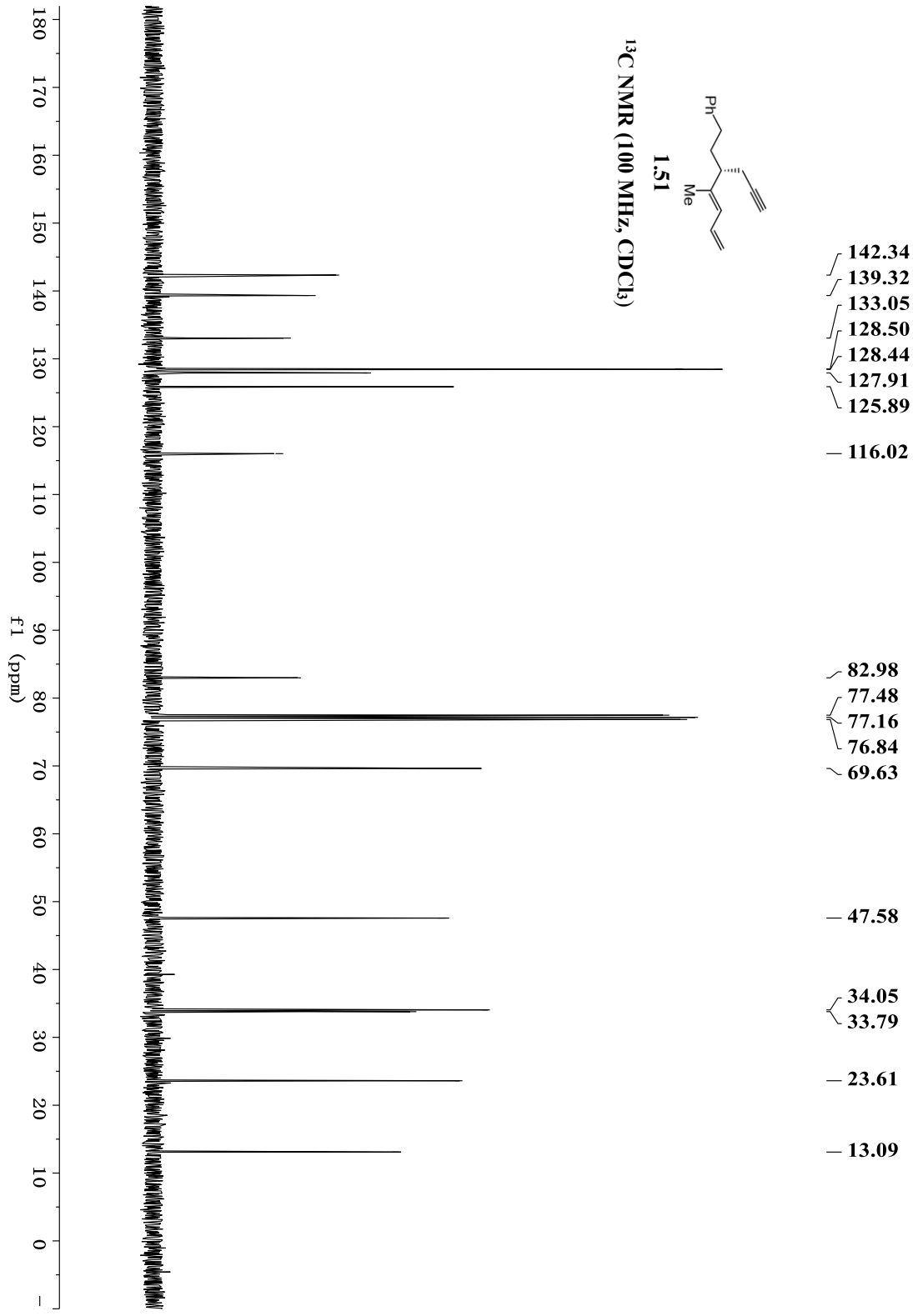

1.49
Me
1H NMR (400 MHz, CDCl3)
7.36
7.36
7.35
7.31
7.30
6.64
6.61
6.60
6.59
6.57
6.55
6.27
6.27
6.27
6.26
6.05
6.03
5.22
5.17
5.10
5.08
3.48
3.46
3.44
2.61
2.60
2.60
2.59
2.58
1.99
1.99
1.98
1.69
1.00
0.95
1.00
1.01
1.04
1.06
1.04
1.01
2.03
0.99
3.03
f1 (ppm)

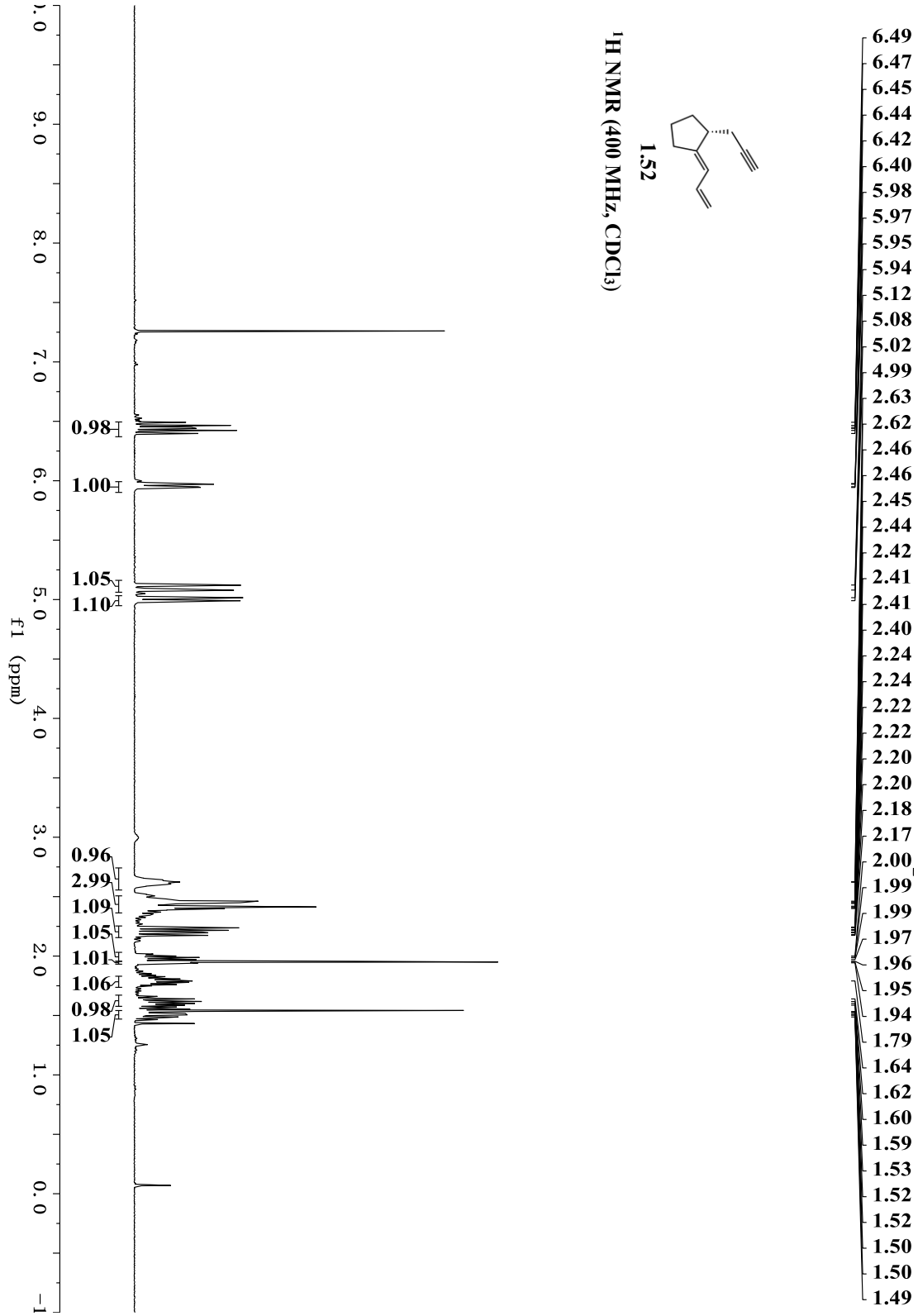

$^{13}$C NMR (100 MHz, CDCl$_3$)
1.49
Me
O
142.99
139.39
138.89
133.09
127.24
126.20
116.69
110.45
82.60
77.48
77.16
76.84
69.99
44.78
22.79
14.24
f1 (ppm)


1H NMR (600 MHz, CDCl3)
1.50
Me
S
7.25
7.25
7.06
7.05
6.95
6.95
6.94
6.94
6.63
6.61
6.60
6.59
6.58
6.56
6.08
6.06
5.22
5.20
5.10
5.08
3.66
3.65
3.64
2.70
2.69
2.69
2.67
1.99
1.98
1.98
1.66
1.01
0.97
0.95
1.00
0.97
1.02
1.02
1.01
2.04
0.98
3.02
f1 (ppm)

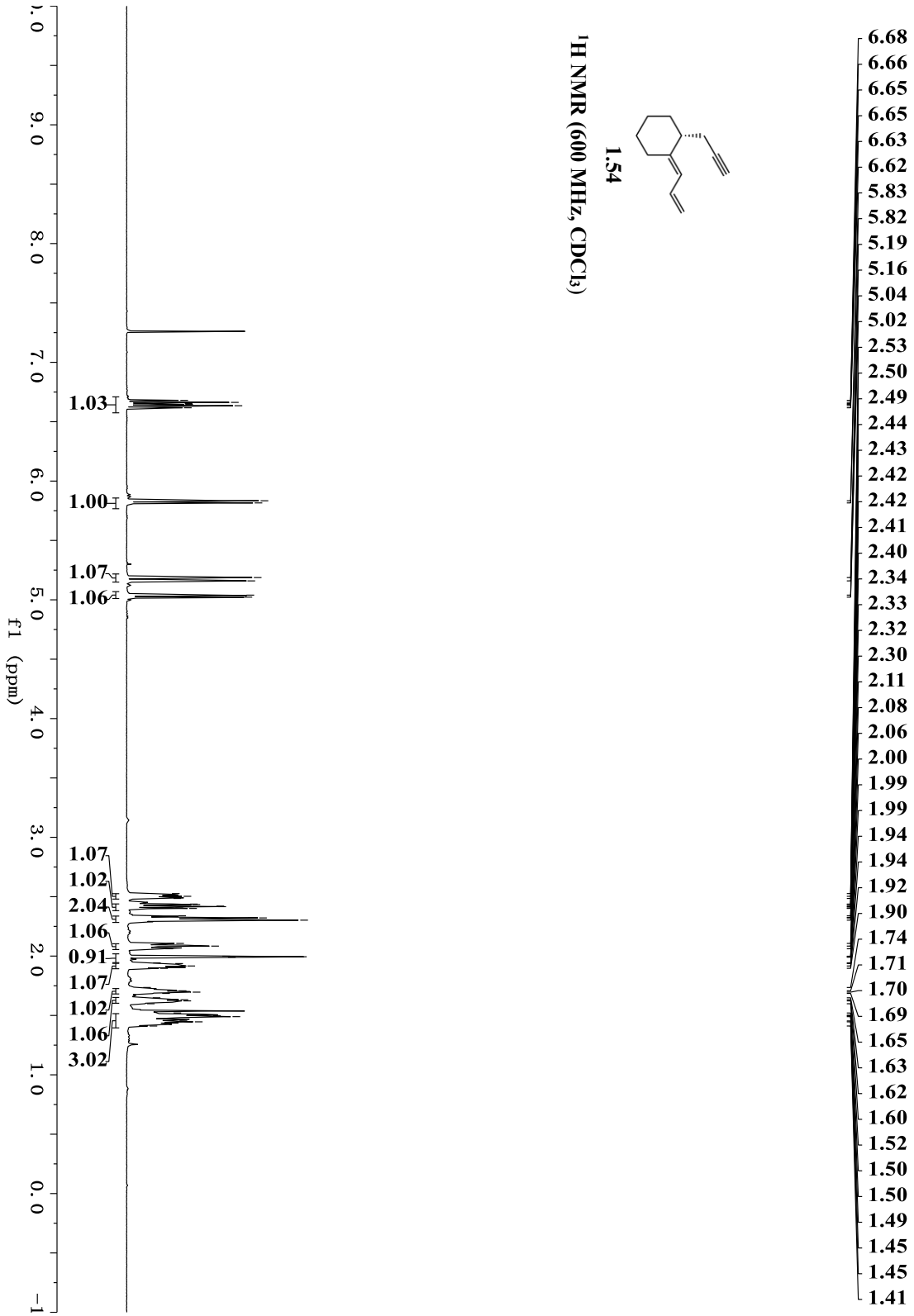

13C NMR (150 MHz, CDCl3)
1.50
S
Me
142.93
139.23
133.14
127.75
127.13
125.47
120.87
116.69
82.70
77.37
77.16
76.95
69.99
49.04
22.96
14.49
f1 (ppm)

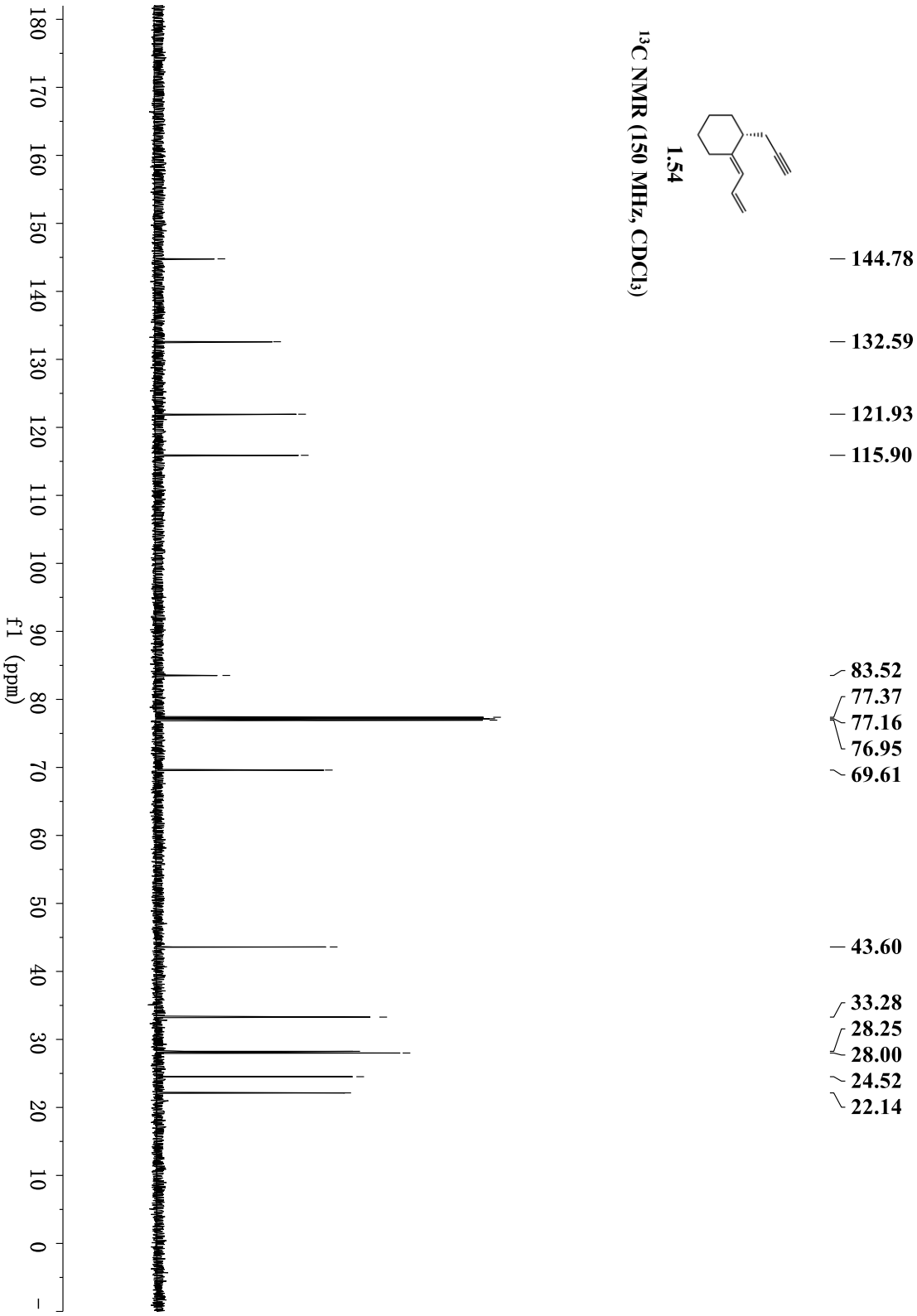

1H NMR (400 MHz, CDCl3)
1.51
Ph
Me
7.30
7.28
7.26
7.20
7.19
7.17
6.68
6.66
6.64
6.63
6.61
6.59
5.97
5.95
5.20
5.20
5.16
5.16
5.09
5.09
5.06
5.06
2.58
2.54
2.50
2.32
2.30
2.29
2.28
1.97
1.97
1.96
1.99
3.03
1.00
1.00
1.03
1.01
2.02
3.05
1.03
1.01
4.04
f1 (ppm)

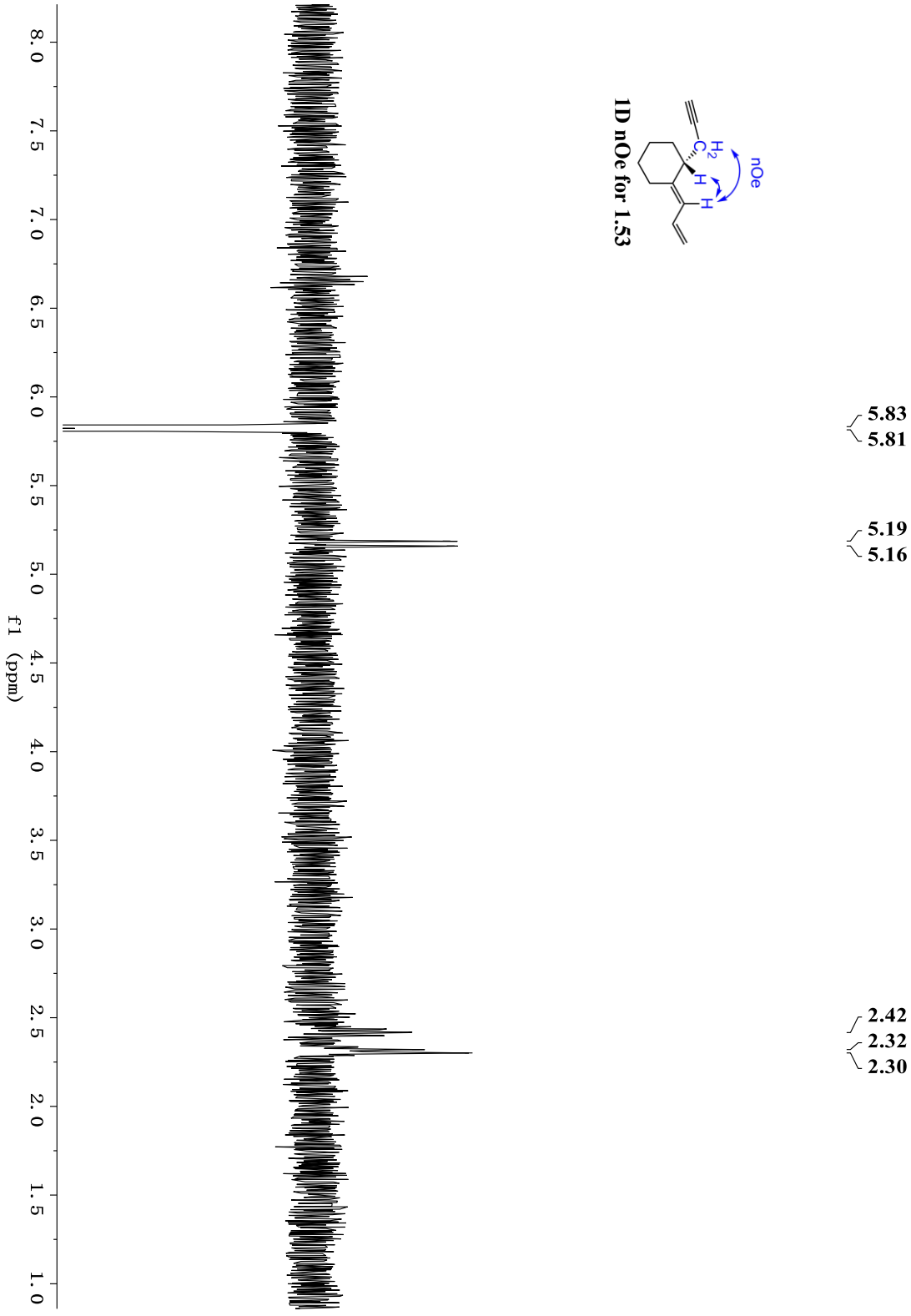

Ph
Me
1.51
$^{13}$C NMR (100 MHz, $CDCl_3$)
142.34
139.32
133.05
128.50
128.44
127.91
125.89
116.02
82.98
77.48
77.16
76.84
69.63
47.58
34.05
33.79
23.61
13.09
f1 (ppm)

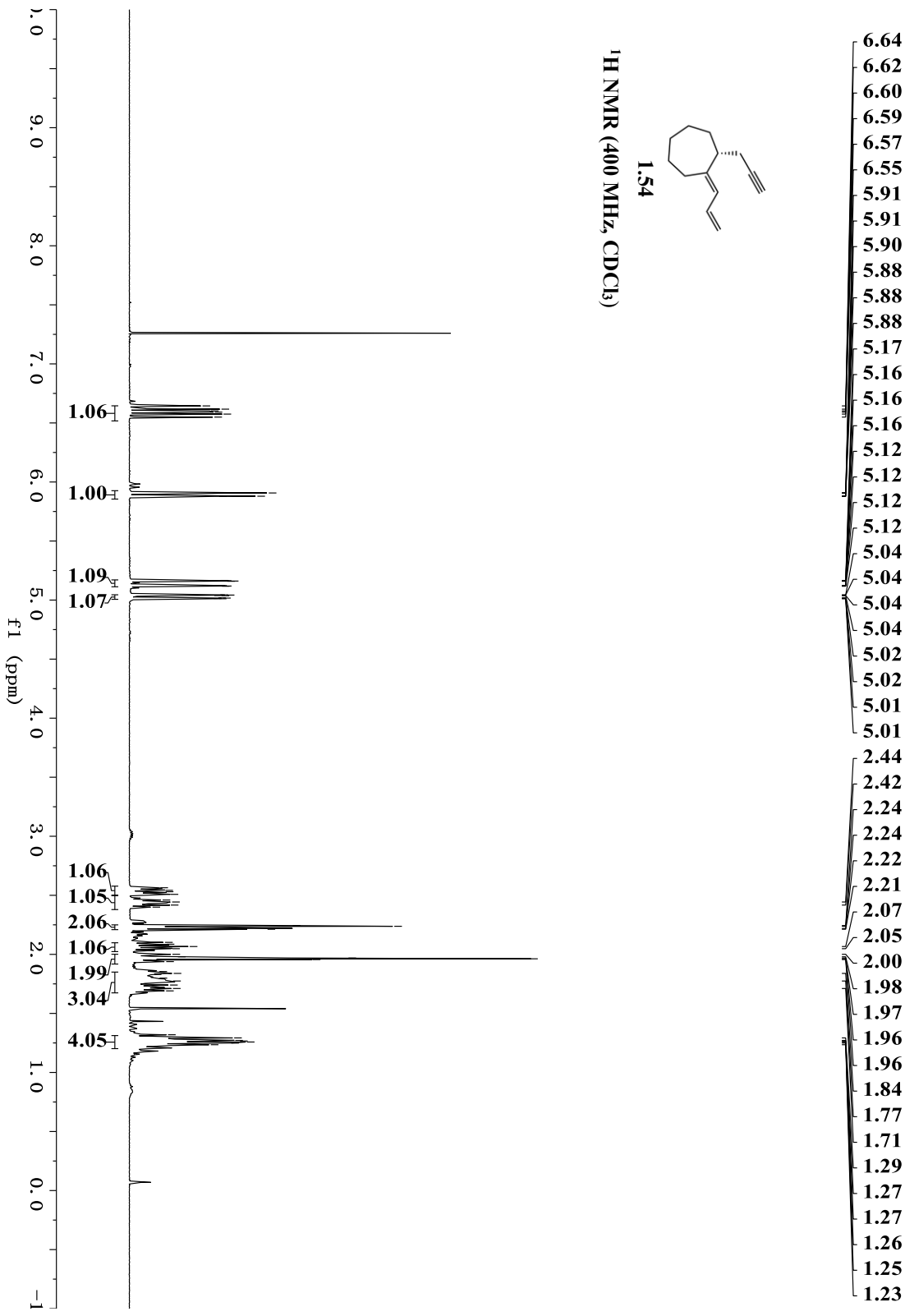

1.52
¹H NMR (400 MHz, CDCl₃)
6.49
6.47
6.45
6.44
6.42
6.40
5.98
5.97
5.95
5.94
5.12
5.08
5.02
4.99
2.63
2.62
2.46
2.46
2.45
2.44
2.42
2.41
2.41
2.40
2.24
2.24
2.22
2.22
2.20
2.20
2.18
2.17
2.00
1.99
1.99
1.97
1.96
1.95
1.94
1.79
1.64
1.62
1.60
1.59
1.53
1.52
1.52
1.50
1.50
1.49
0.98
1.00
1.05
1.10
0.96
2.99
1.09
1.05
1.01
1.06
0.98
1.05
f1 (ppm)

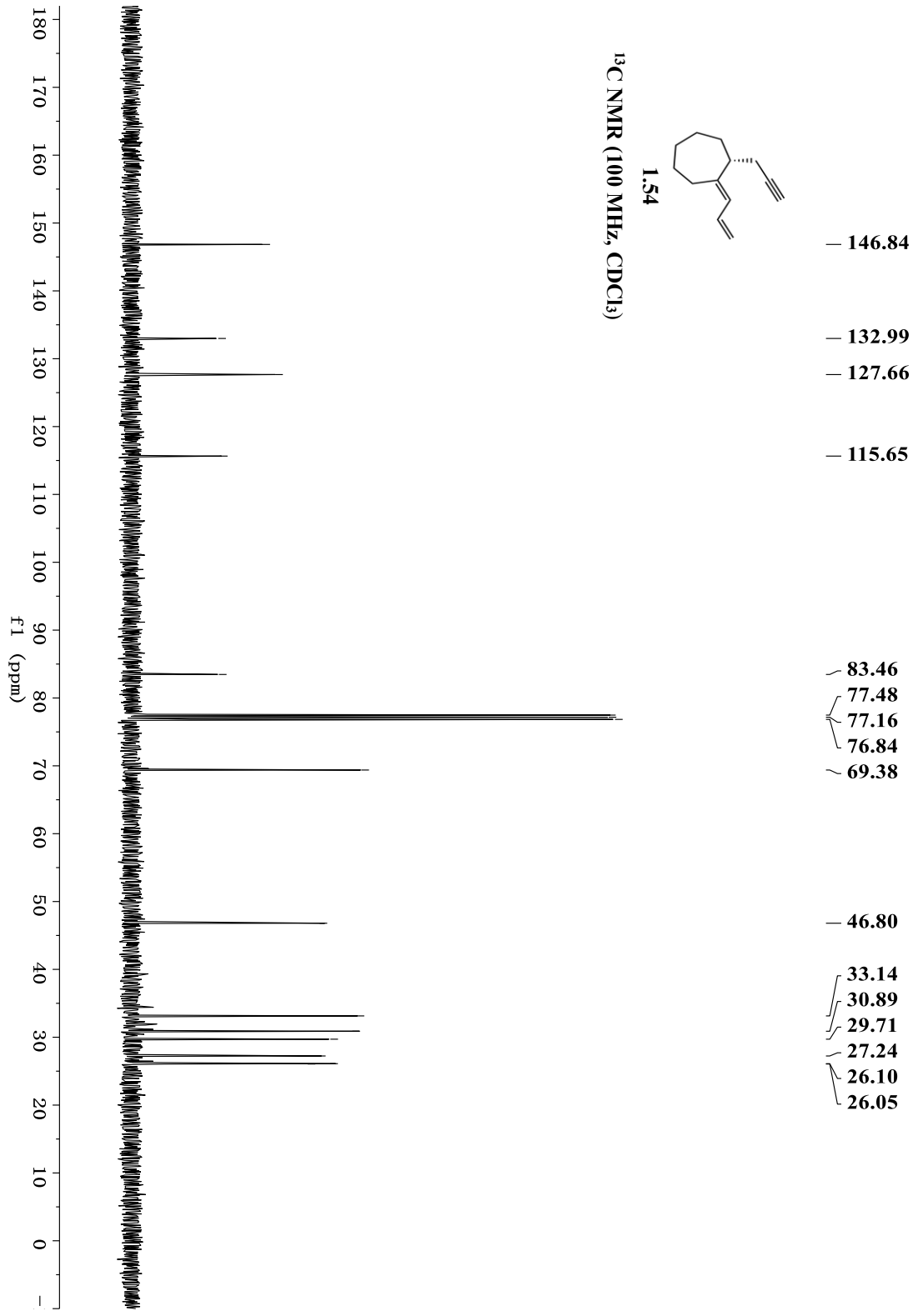
1.52
$^{13}$C NMR (100 MHz, CDCl$_3$)
149.44
134.68
121.74
114.92
83.54
77.48
77.16
76.90
76.84
68.88
43.60
32.42
30.05
24.03
23.32
f1 (ppm)

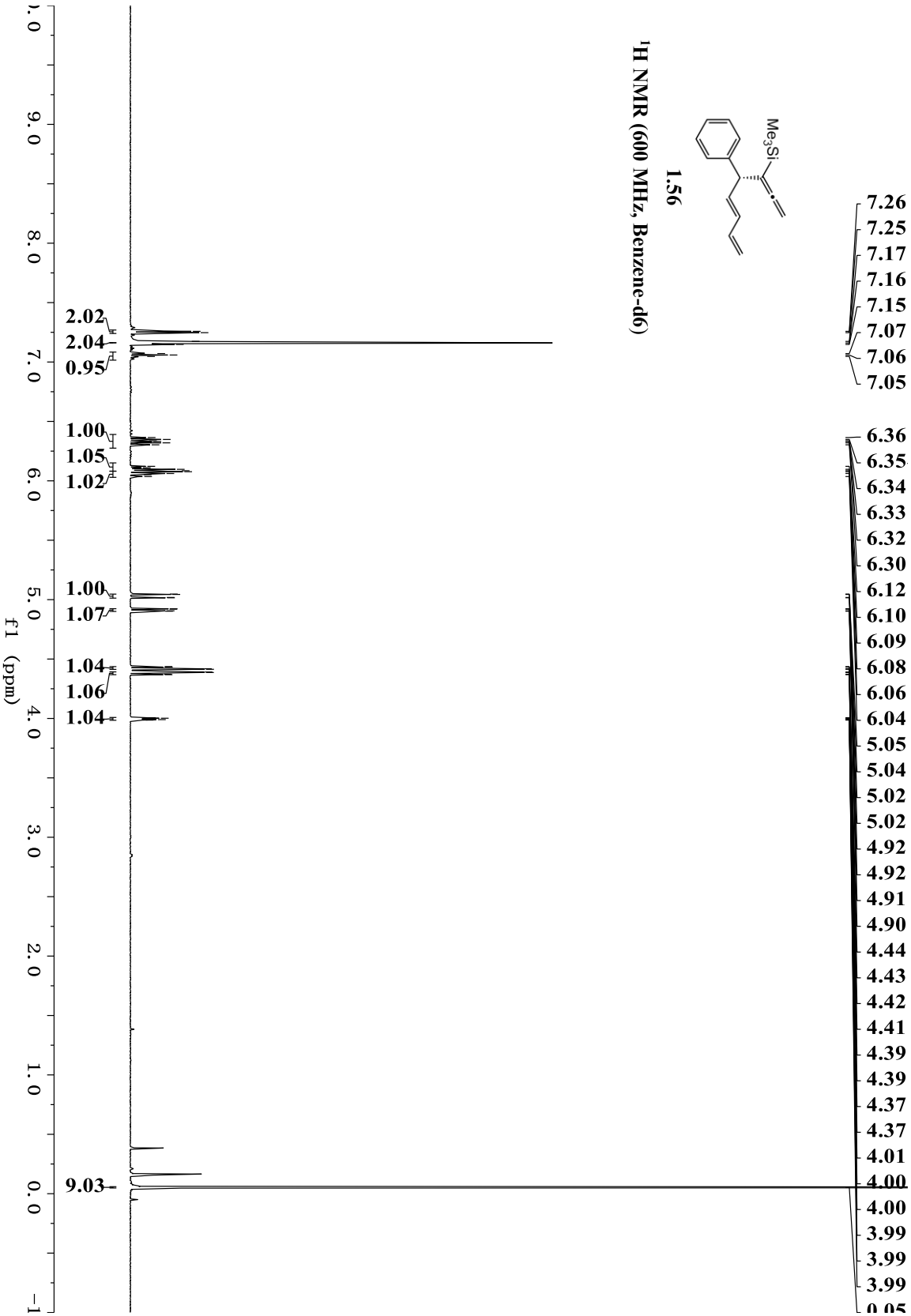

1.54
$^1$H NMR (600 MHz, CDCl$_3$)
f1 (ppm)
1.03
1.00
1.07
1.06
1.07
1.02
2.04
1.06
0.91
1.07
1.02
1.06
3.02
6.68
6.66
6.65
6.65
6.63
6.62
5.83
5.82
5.19
5.16
5.04
5.02
2.53
2.50
2.49
2.44
2.43
2.42
2.42
2.41
2.40
2.34
2.33
2.32
2.30
2.11
2.08
2.06
2.00
1.99
1.99
1.94
1.94
1.92
1.90
1.74
1.71
1.70
1.69
1.65
1.63
1.62
1.60
1.52
1.50
1.50
1.49
1.45
1.45
1.41

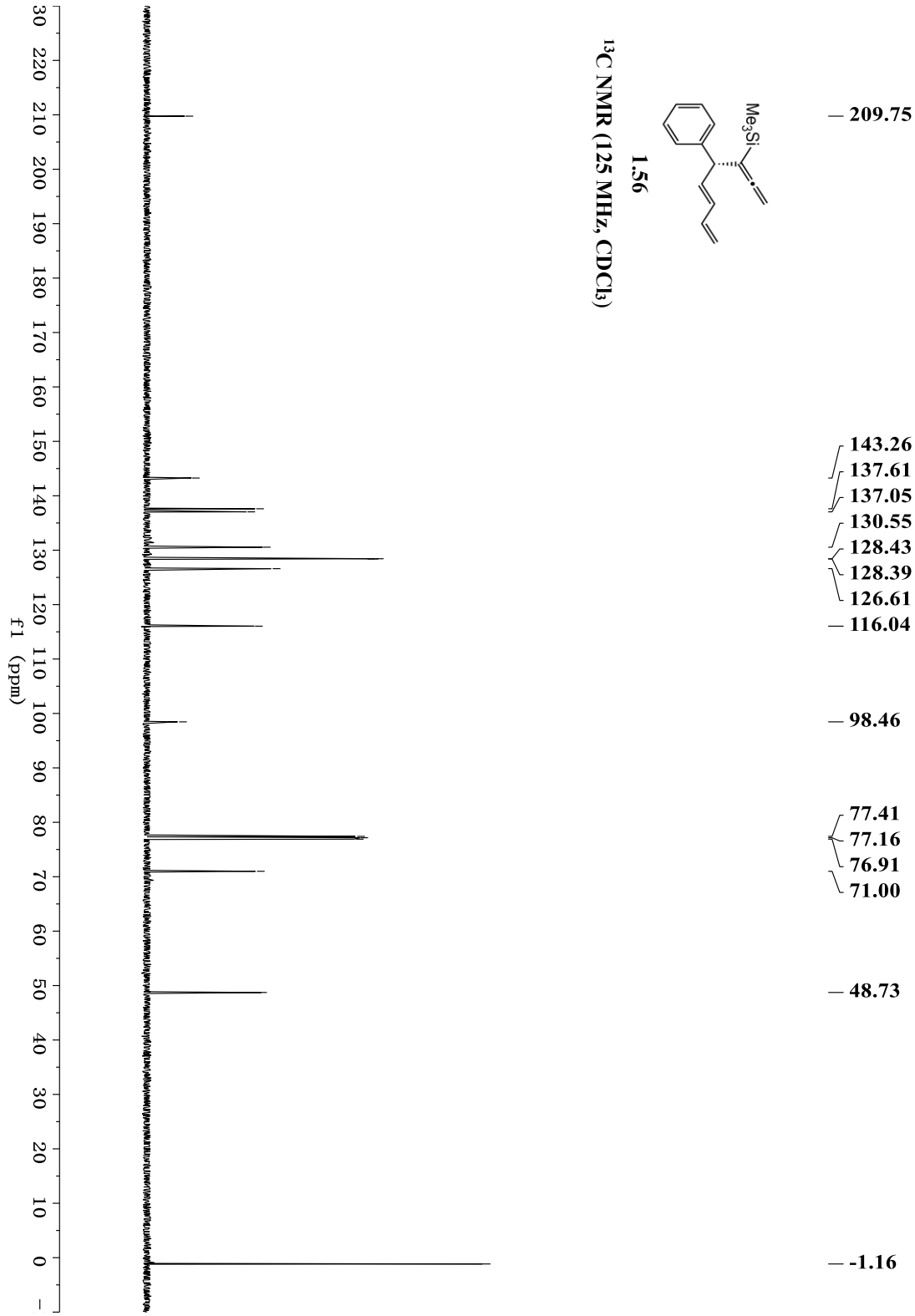

1.54
$^{13}$C NMR (150 MHz, CDCl$_3$)
144.78
132.59
121.93
115.90
83.52
77.37
77.16
76.95
69.61
43.60
33.28
28.25
28.00
24.52
22.14
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


1D nOe for 1.53
nOe
H2
H
H
5.83
5.81
5.19
5.16
2.42
2.32
2.30
f1 (ppm)
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


1.54
¹H NMR (400 MHz, CDCl₃)
6.64
6.62
6.60
6.59
6.57
6.55
5.91
5.91
5.90
5.88
5.88
5.88
5.17
5.16
5.16
5.16
5.12
5.12
5.12
5.12
5.04
5.04
5.04
5.04
5.02
5.02
5.01
5.01
2.44
2.42
2.24
2.24
2.22
2.21
2.07
2.05
2.00
1.98
1.97
1.96
1.96
1.84
1.77
1.71
1.29
1.27
1.27
1.26
1.25
1.23
1.06
1.00
1.09
1.07
1.06
1.05
2.06
1.06
1.99
3.04
4.05
f1 (ppm)

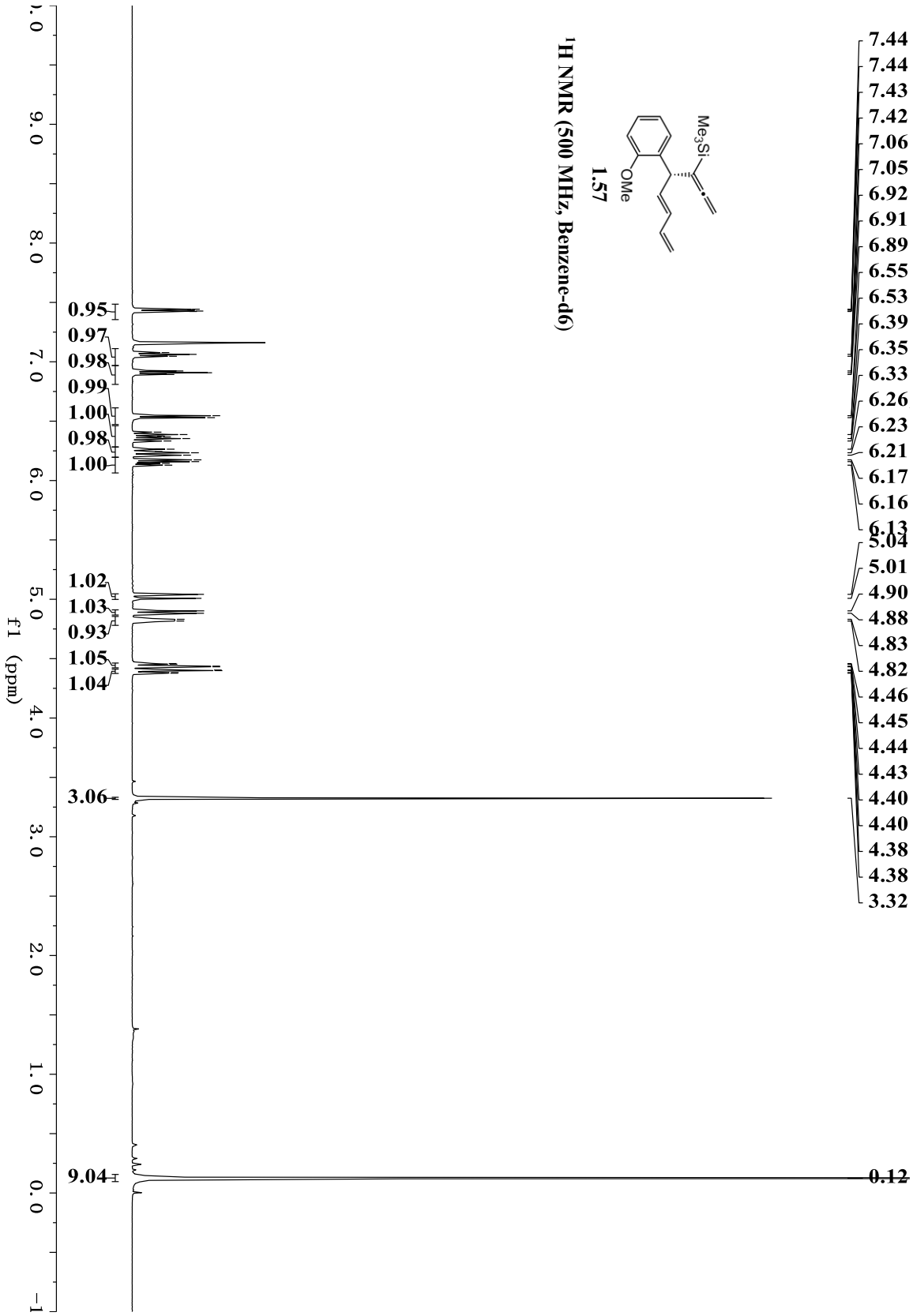

1.54
$^{13}$C NMR (100 MHz, CDCl$_3$)
146.84
132.99
127.66
115.65
83.46
77.48
77.16
76.84
69.38
46.80
33.14
30.89
29.71
27.24
26.10
26.05
f1 (ppm)

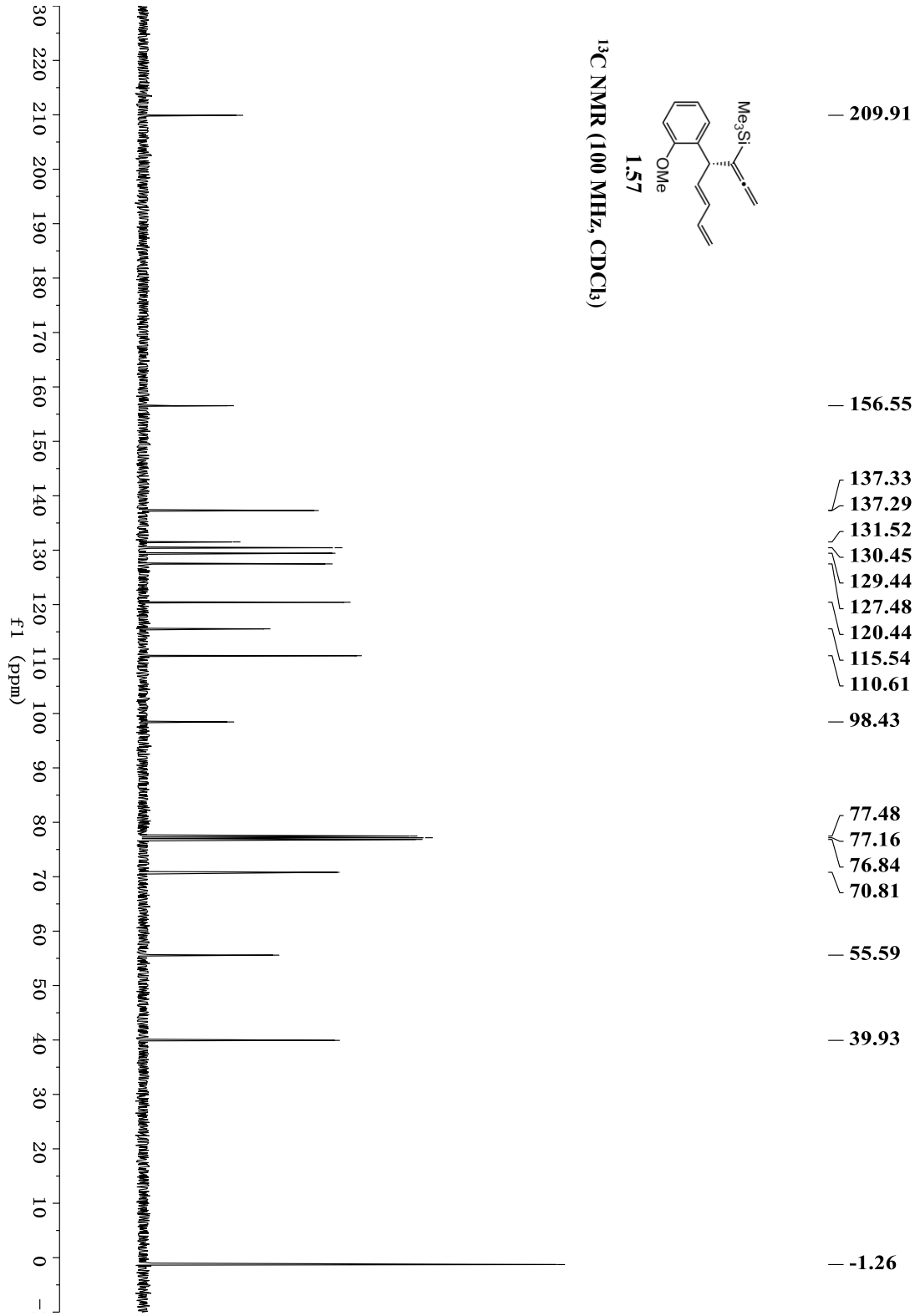

1.56
$^1$H NMR (600 MHz, Benzene-d6)
Me3Si
7.26
7.25
7.17
7.16
7.15
7.07
7.06
7.05
6.36
6.35
6.34
6.33
6.32
6.30
6.12
6.10
6.09
6.08
6.06
6.04
5.05
5.04
5.02
5.02
4.92
4.92
4.91
4.90
4.44
4.43
4.42
4.41
4.39
4.39
4.37
4.37
4.01
4.00
4.00
3.99
3.99
3.99
2.02
2.04
0.95
1.00
1.05
1.02
1.00
1.07
1.04
1.06
1.04
9.03
f1 (ppm)

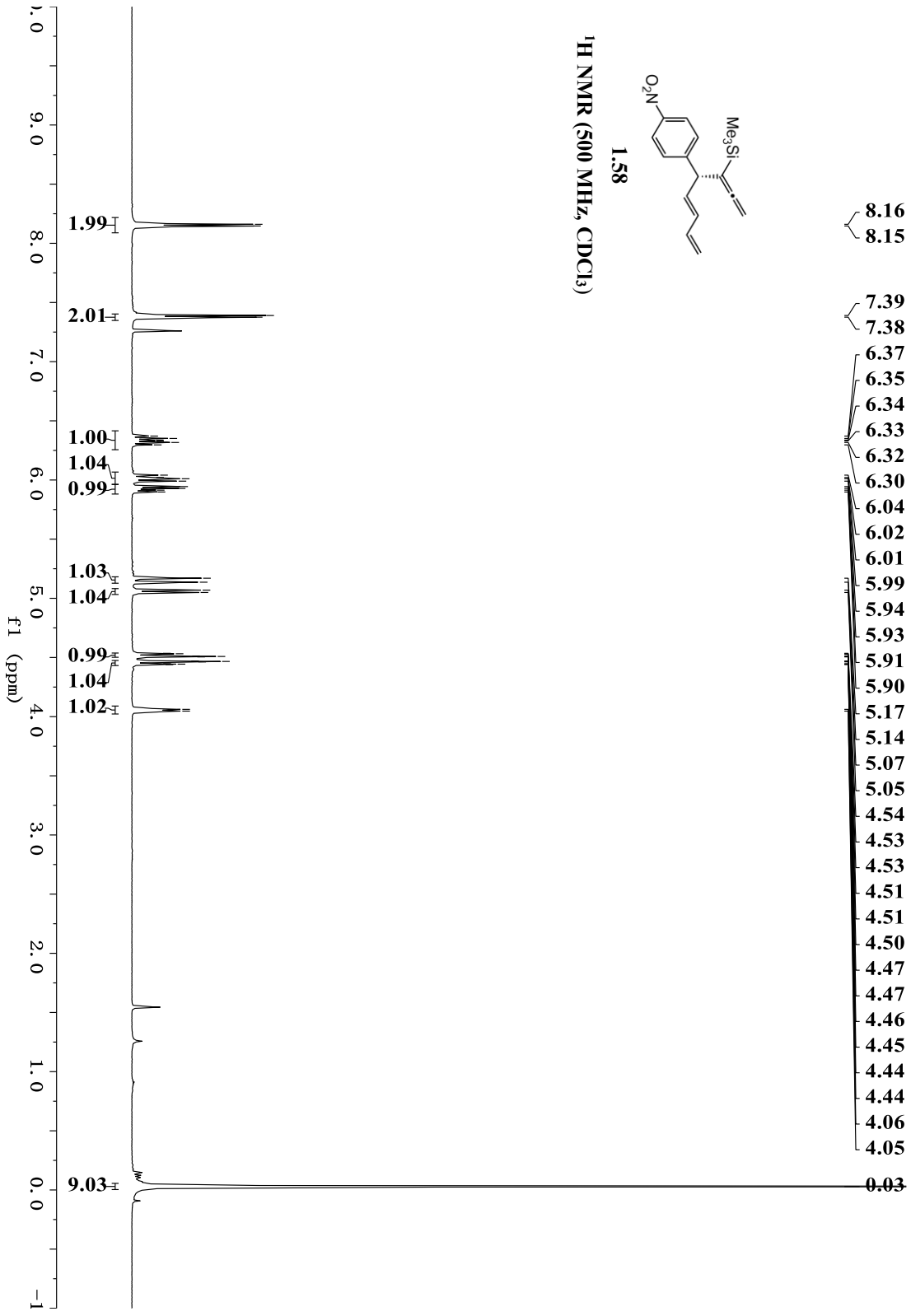


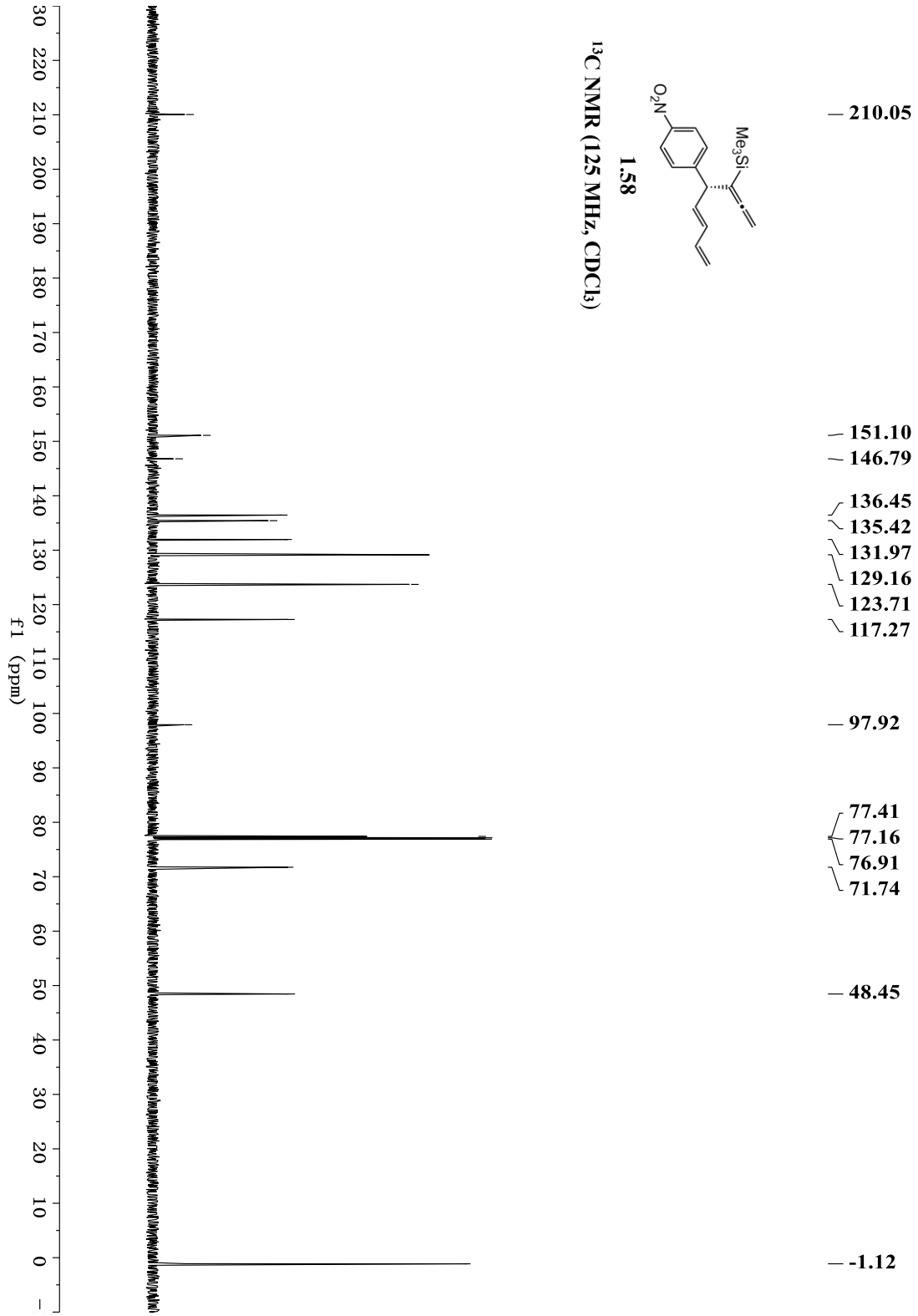

**1.56**

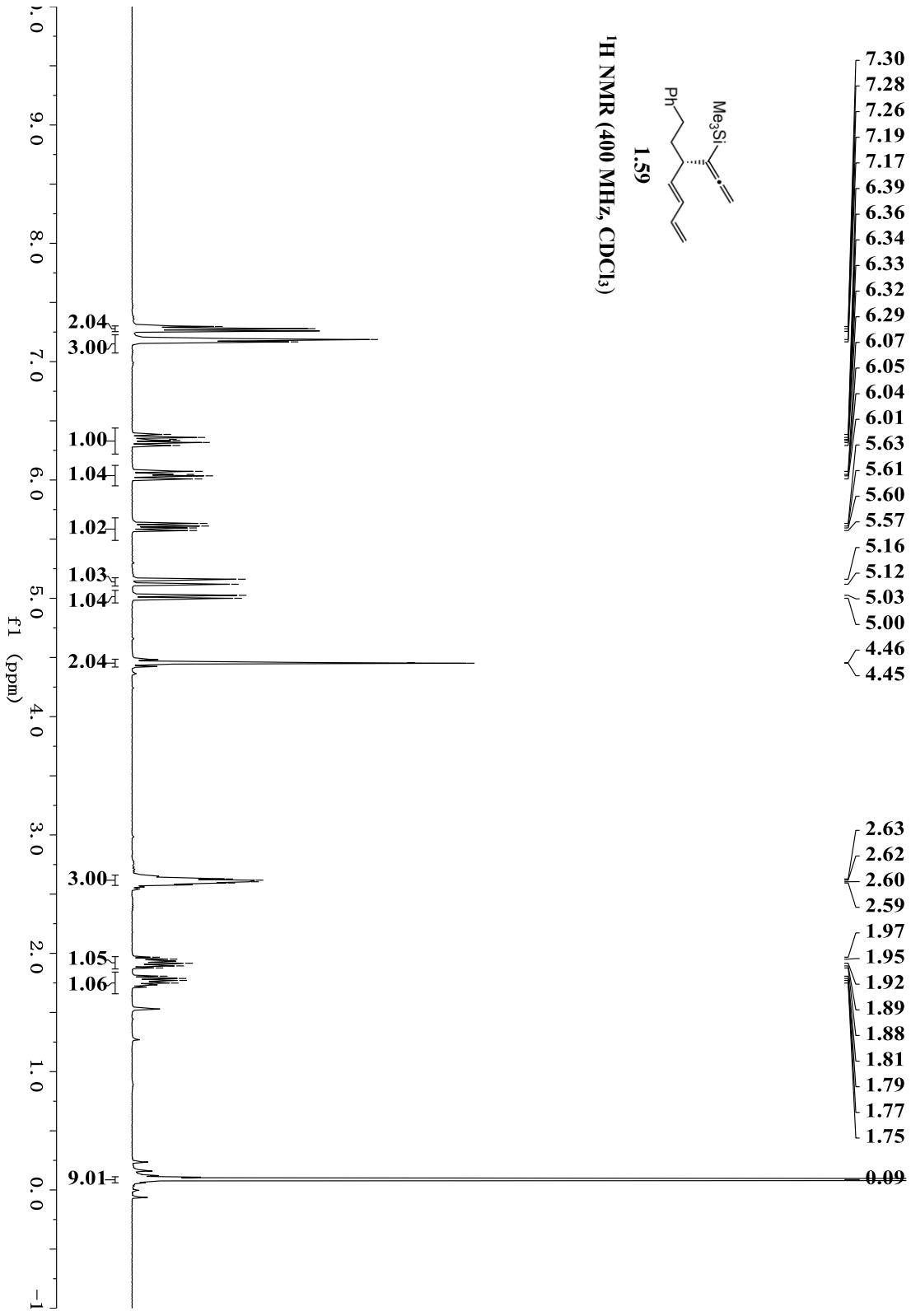
**$^{13}$C NMR (125 MHz, $CDCl_3$)**

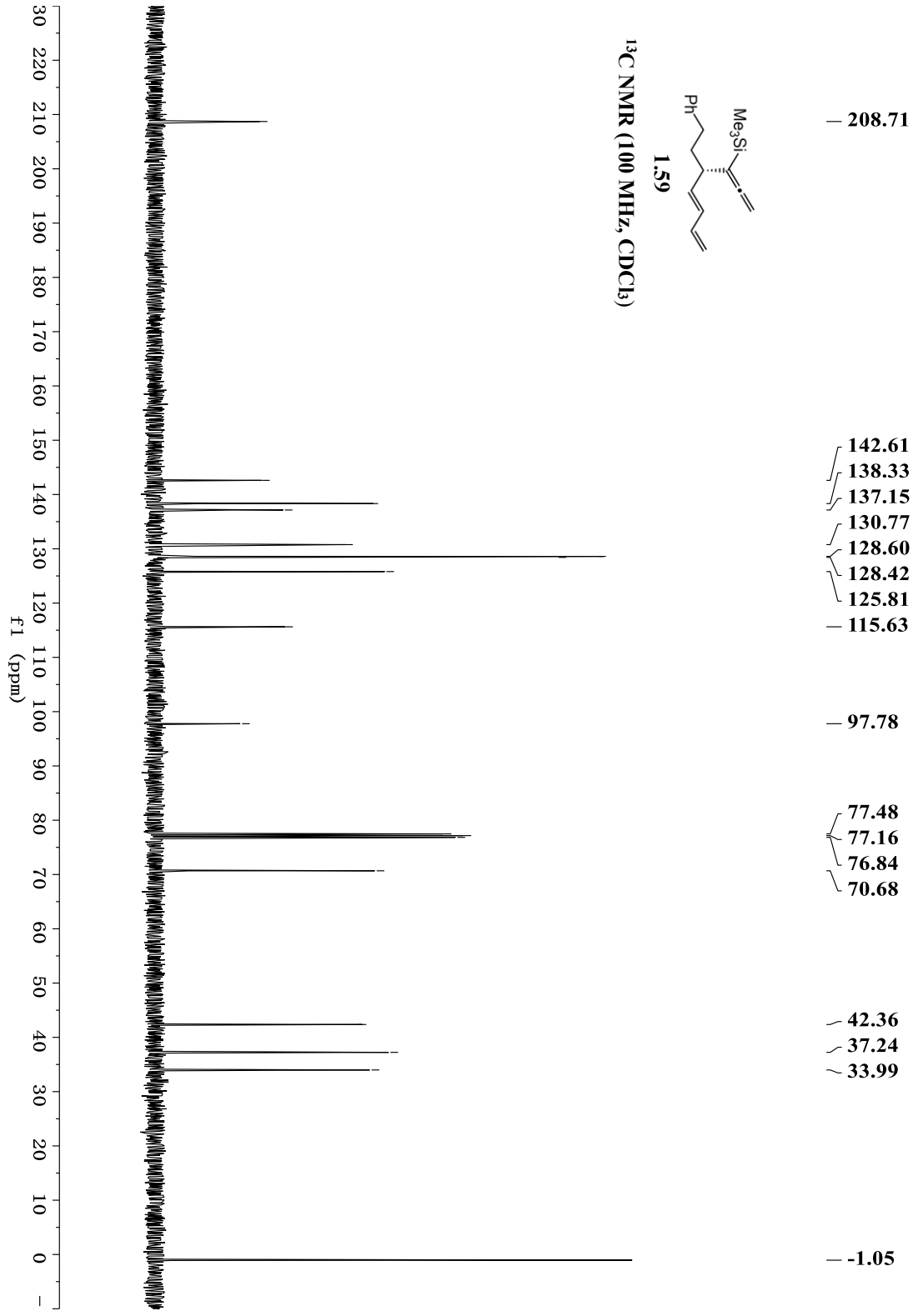

1H NMR (500 MHz, Benzene-d6)
1.57
Me3Si
OMe
7.44
7.44
7.43
7.42
7.06
7.05
6.92
6.91
6.89
6.55
6.53
6.39
6.35
6.33
6.26
6.23
6.21
6.17
6.16
6.13
5.04
5.01
4.90
4.88
4.83
4.82
4.46
4.45
4.44
4.43
4.40
4.40
4.38
4.38
3.32
0.12
0.95
0.97
0.98
0.99
1.00
0.98
1.00
1.02
1.03
0.93
1.05
1.04
3.06
9.04
f1 (ppm)

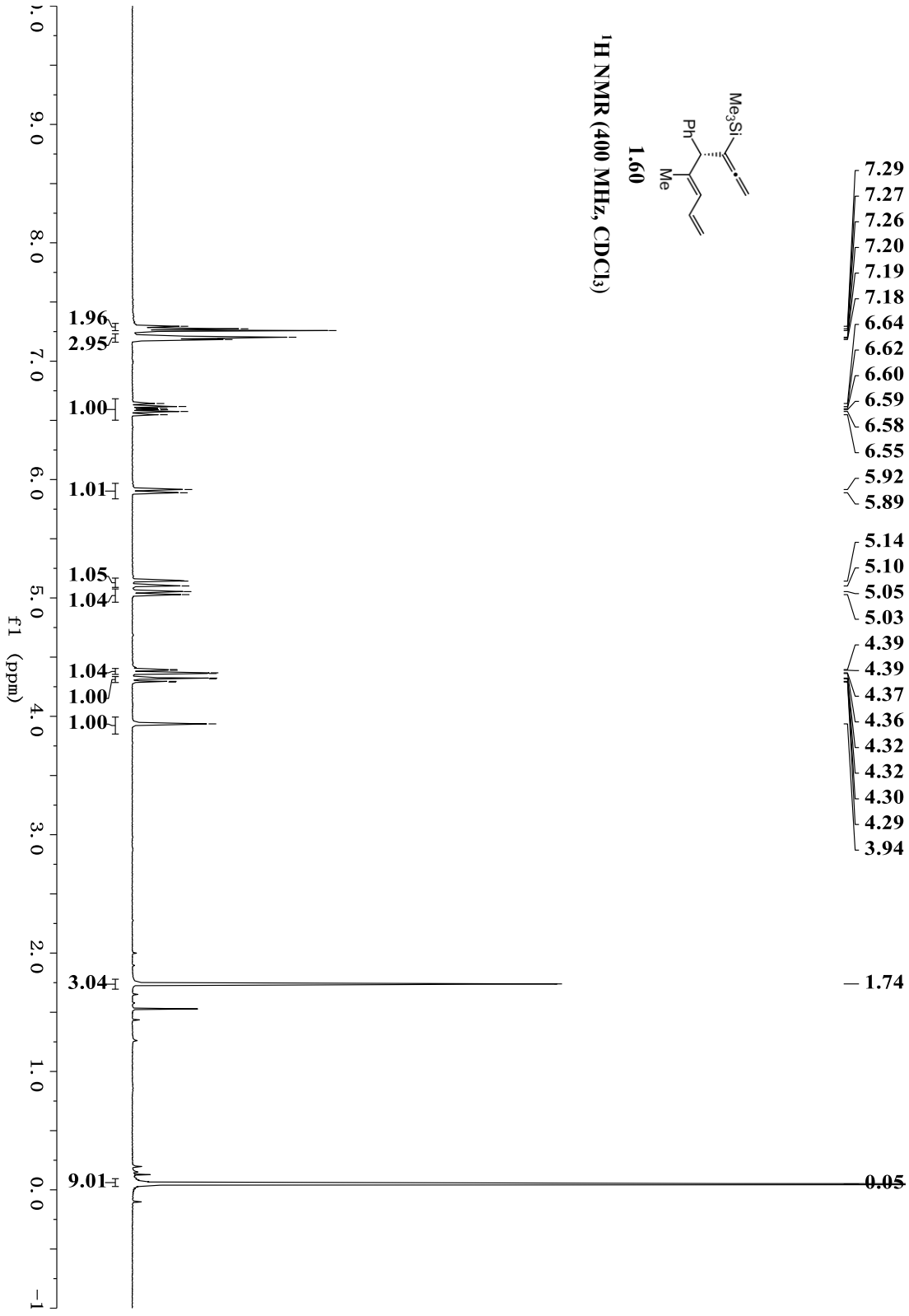

$^{13}$C NMR (100 MHz, CDCl$_3$)
1.57
OMe
Me$_3$Si
f1 (ppm)
209.91
156.55
137.33
137.29
131.52
130.45
129.44
127.48
120.44
115.54
110.61
98.43
77.48
77.16
76.84
70.81
55.59
39.93
-1.26

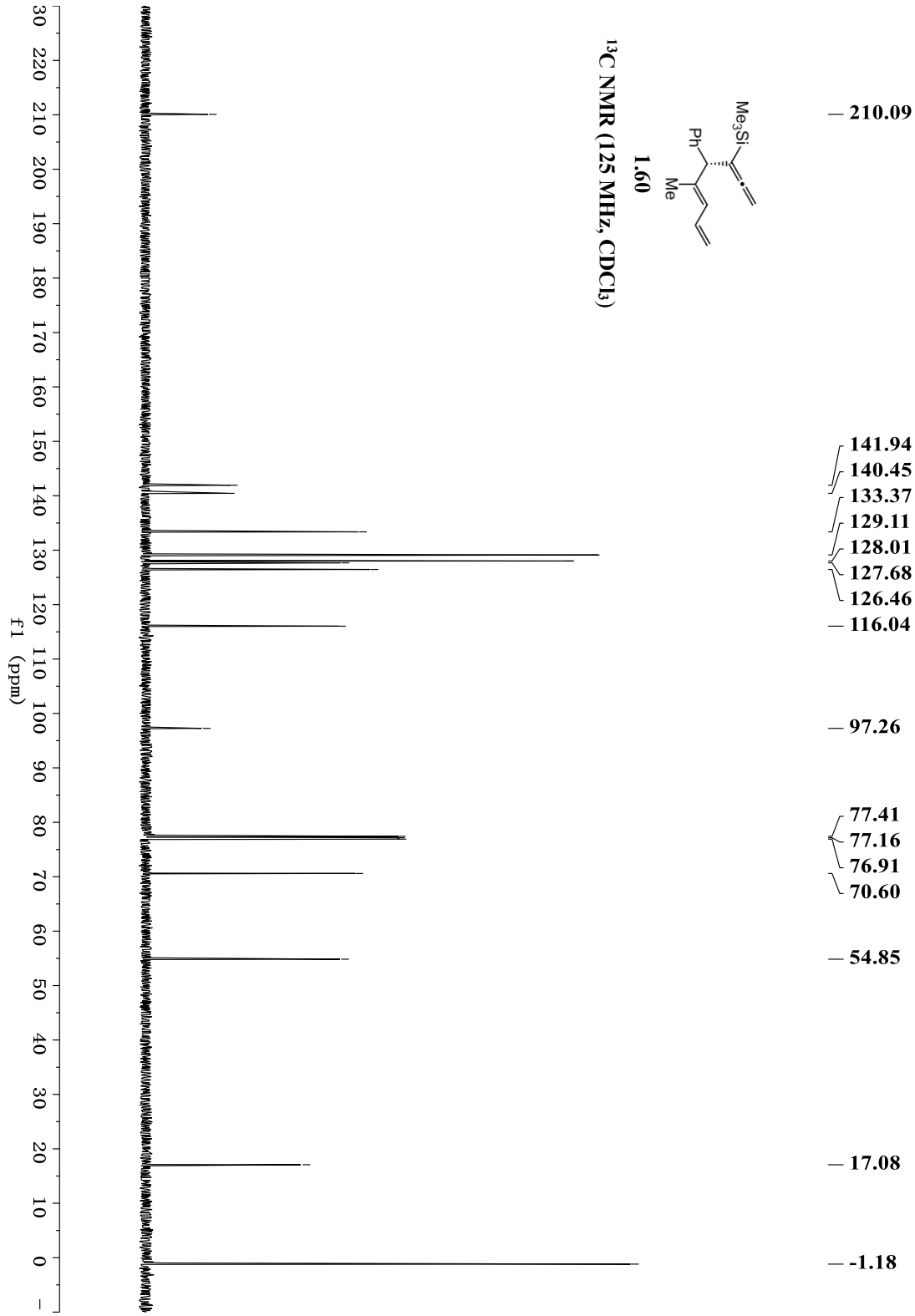

1.58
$^1$H NMR (500 MHz, CDCl$_3$)
O$_2$N
Me$_3$Si
f1 (ppm)
1.99
2.01
1.00
1.04
0.99
1.03
1.04
0.99
1.04
1.02
9.03
8.16
8.15
7.39
7.38
6.37
6.35
6.34
6.33
6.32
6.30
6.04
6.02
6.01
5.99
5.94
5.93
5.91
5.90
5.17
5.14
5.07
5.05
4.54
4.53
4.53
4.51
4.51
4.50
4.47
4.47
4.46
4.45
4.44
4.44
4.06
4.05
0.03

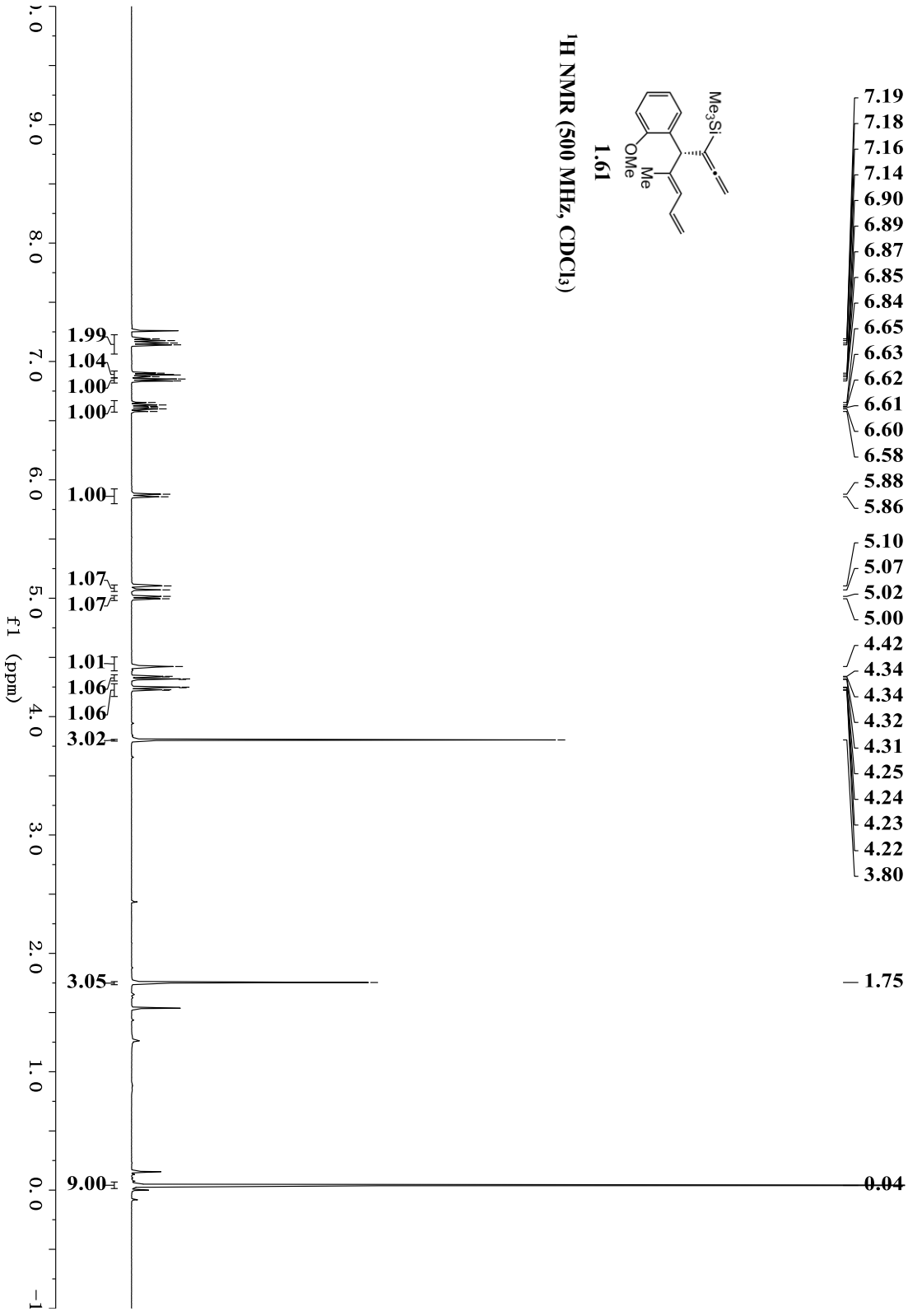

$^{13}$C NMR (125 MHz, CDCl$_3$)
1.58
O2N
Me3Si
210.05
151.10
146.79
136.45
135.42
131.97
129.16
123.71
117.27
97.92
77.41
77.16
76.91
71.74
48.45
-1.12
f1 (ppm)

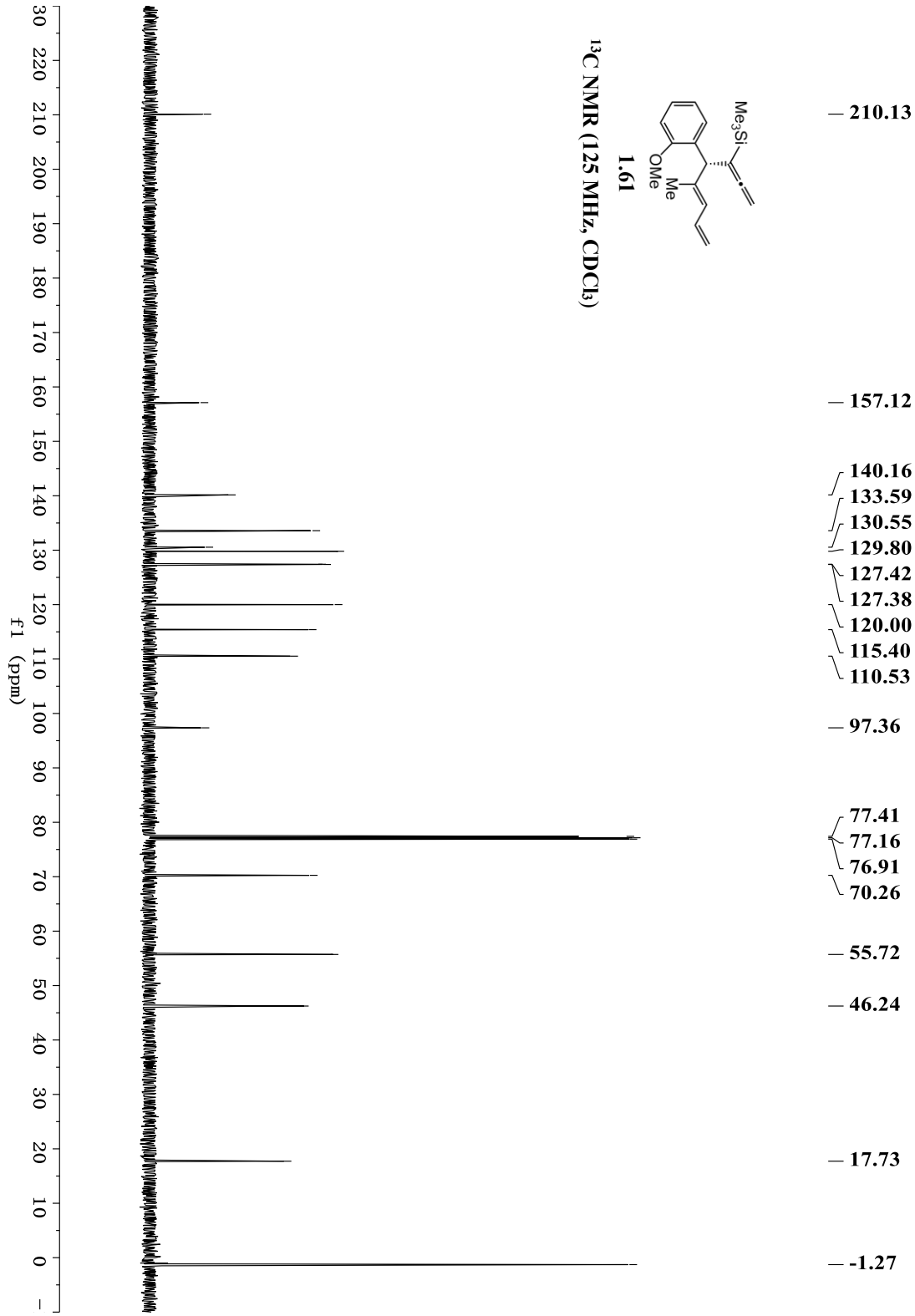

1H NMR (400 MHz, CDCl3)
1.59
Ph
Me3Si
f1 (ppm)
7.30
7.28
7.26
7.19
7.17
6.39
6.36
6.34
6.33
6.32
6.29
6.07
6.05
6.04
6.01
5.63
5.61
5.60
5.57
5.16
5.12
5.03
5.00
4.46
4.45
2.63
2.62
2.60
2.59
1.97
1.95
1.92
1.89
1.88
1.81
1.79
1.77
1.75
0.09
2.04
3.00
1.00
1.04
1.02
1.03
1.04
2.04
3.00
1.05
1.06
9.01

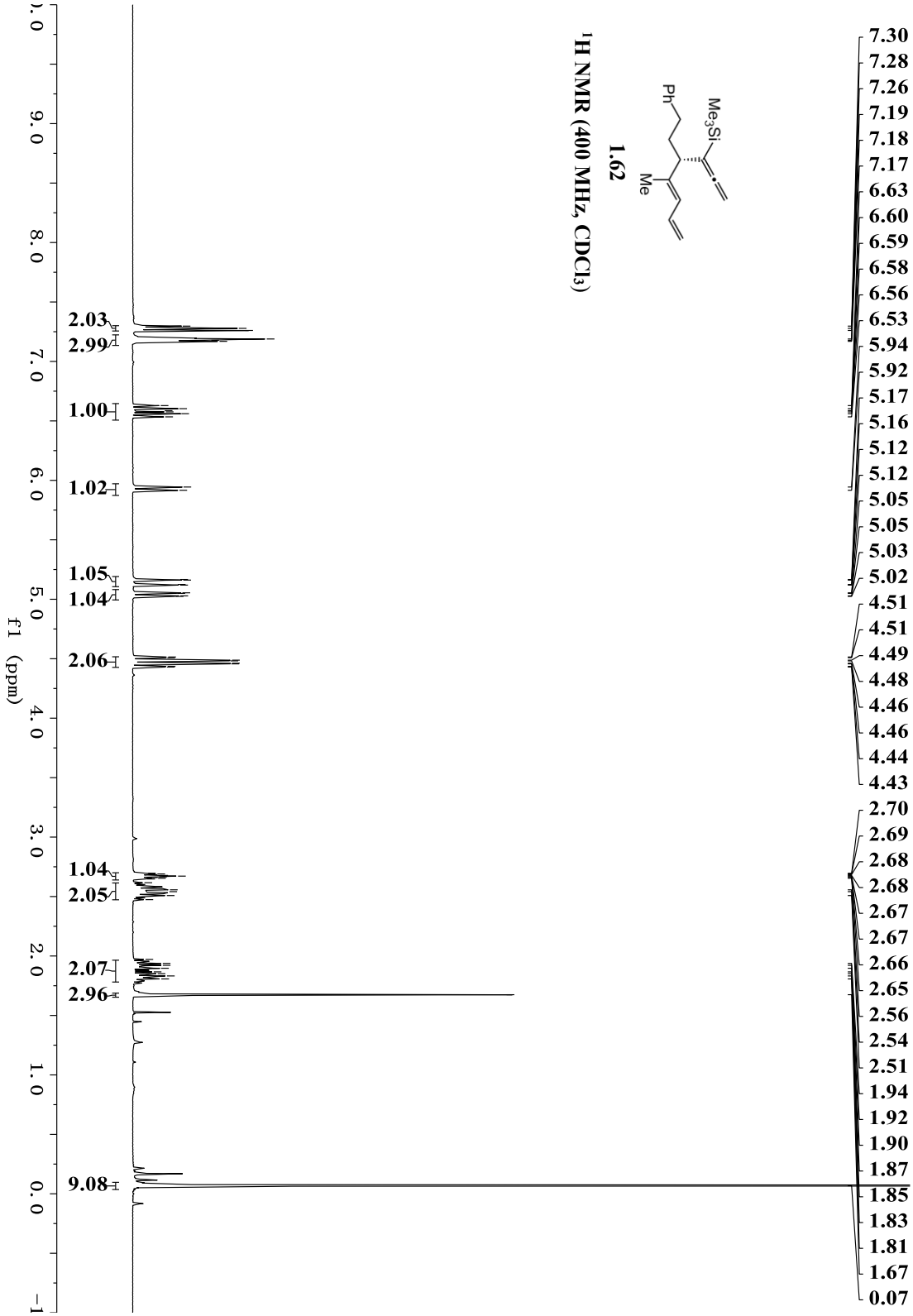

Ph
Me3Si
1.59
13C NMR (100 MHz, CDCl3)
208.71
142.61
138.33
137.15
130.77
128.60
128.42
125.81
115.63
97.78
77.48
77.16
76.84
70.68
42.36
37.24
33.99
-1.05
f1 (ppm)

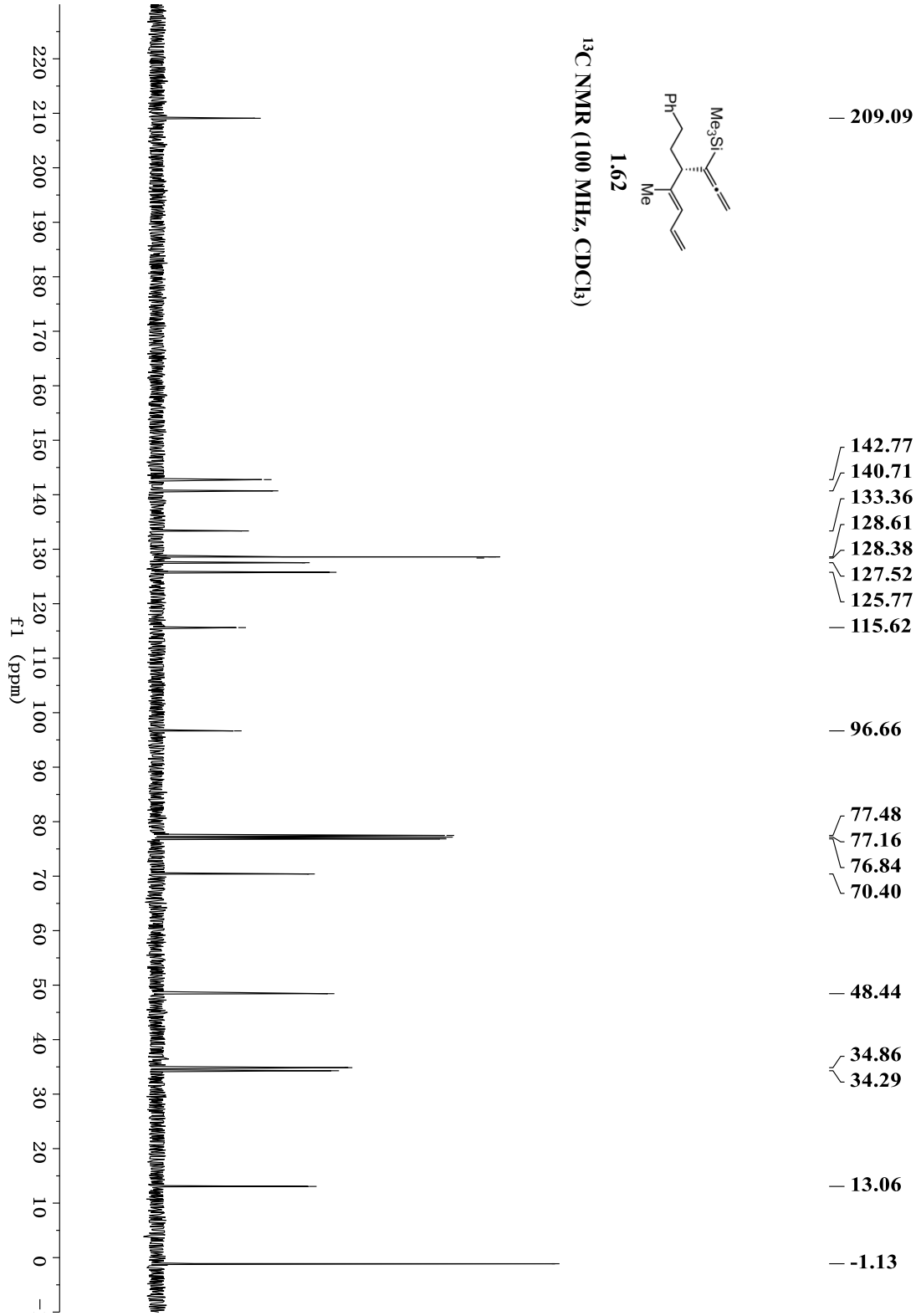

Me3Si
Ph
Me
1.60
1H NMR (400 MHz, CDCl3)
7.29
7.27
7.26
7.20
7.19
7.18
6.64
6.62
6.60
6.59
6.58
6.55
5.92
5.89
5.14
5.10
5.05
5.03
4.39
4.39
4.37
4.36
4.32
4.32
4.30
4.29
3.94
1.74
0.05
1.96
2.95
1.00
1.01
1.05
1.04
1.04
1.00
1.00
3.04
9.01
f1 (ppm)


Me3Si
Ph
Me
1.60
13C NMR (125 MHz, CDCl3)
210.09
141.94
140.45
133.37
129.11
128.01
127.68
126.46
116.04
97.26
77.41
77.16
76.91
70.60
54.85
17.08
-1.18
f1 (ppm)

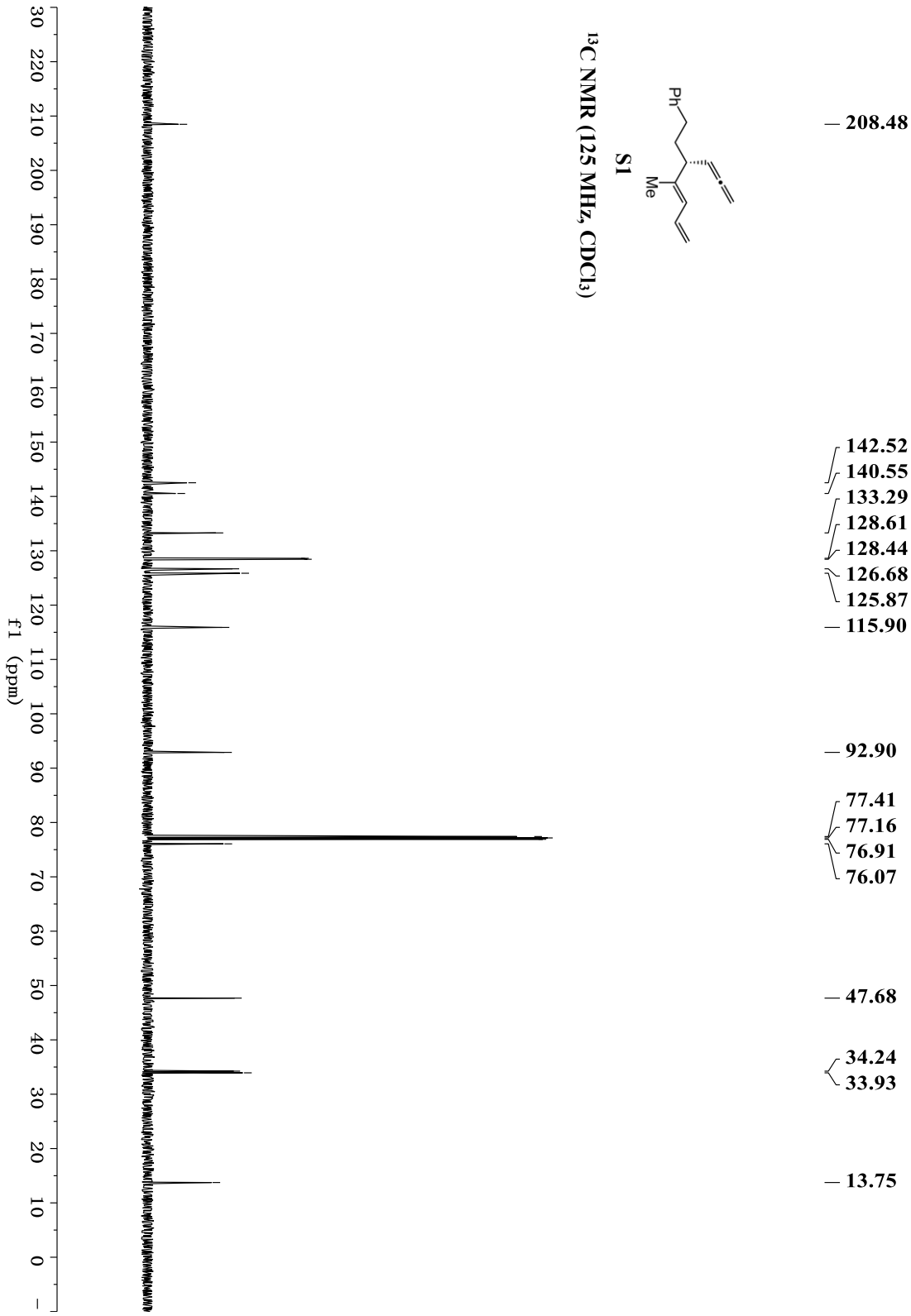

1H NMR (500 MHz, CDCl3)
1.61
Me3Si
OMe
Me
7.19
7.18
7.16
7.14
6.90
6.89
6.87
6.85
6.84
6.65
6.63
6.62
6.61
6.60
6.58
5.88
5.86
5.10
5.07
5.02
5.00
4.42
4.34
4.34
4.32
4.31
4.25
4.24
4.23
4.22
3.80
1.75
0.04
1.99
1.04
1.00
1.00
1.00
1.07
1.07
1.01
1.06
1.06
3.02
3.05
9.00
f1 (ppm)

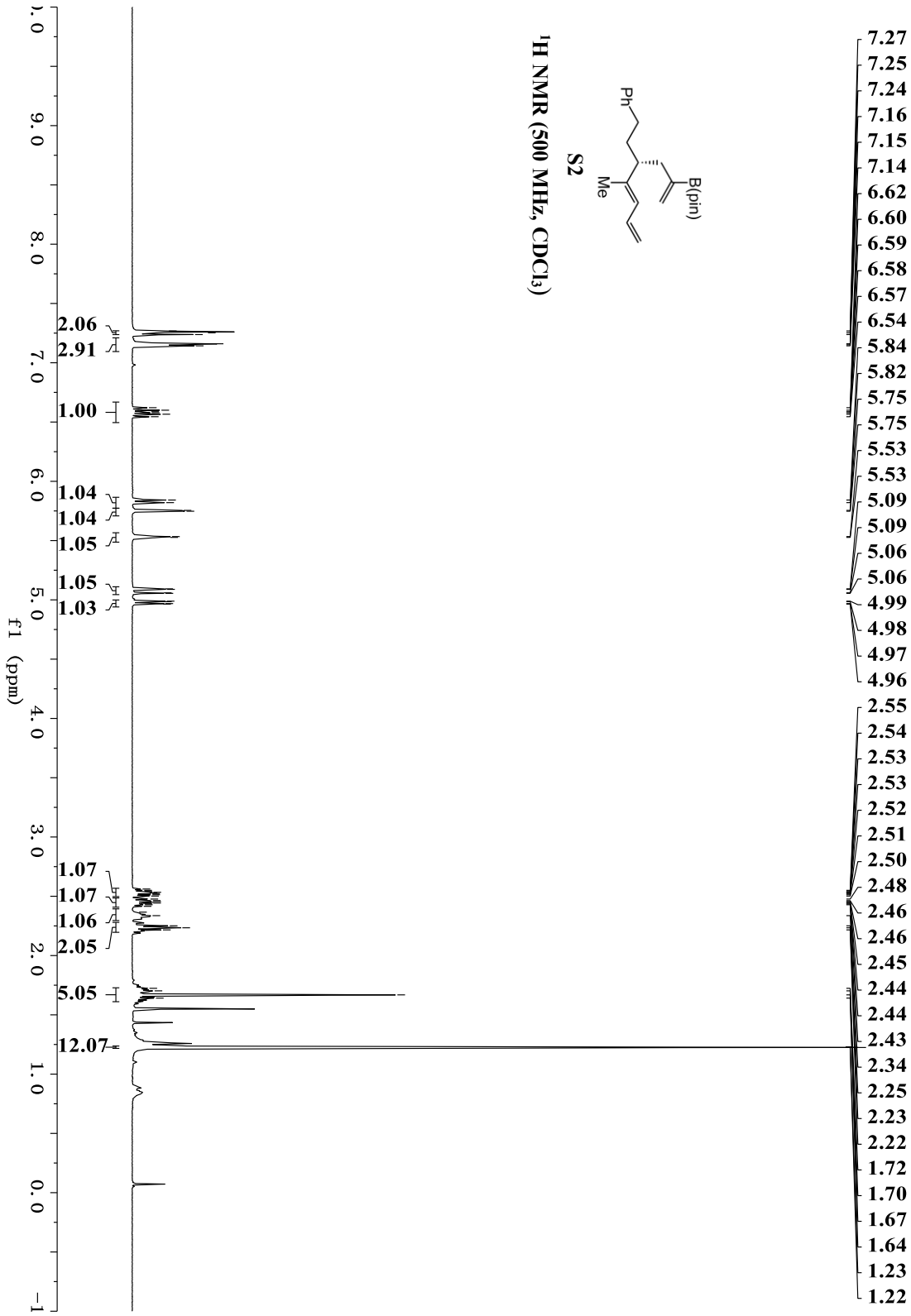

1.61
$^{13}$C NMR (125 MHz, CDCl$_3$)
Me$_3$Si
OMe
Me
210.13
157.12
140.16
133.59
130.55
129.80
127.42
127.38
120.00
115.40
110.53
97.36
77.41
77.16
76.91
70.26
55.72
46.24
17.73
-1.27
f1 (ppm)


1.62
$^1$H NMR (400 MHz, CDCl$_3$)
Ph
Me$_3$Si
Me
f1 (ppm)
2.03
2.99
1.00
1.02
1.05
1.04
2.06
1.04
2.05
2.07
2.96
9.08
7.30
7.28
7.26
7.19
7.18
7.17
6.63
6.60
6.59
6.58
6.56
6.53
5.94
5.92
5.17
5.16
5.12
5.12
5.05
5.05
5.03
5.02
4.51
4.51
4.49
4.48
4.46
4.46
4.44
4.43
2.70
2.69
2.68
2.68
2.67
2.67
2.66
2.65
2.56
2.54
2.51
1.94
1.92
1.90
1.87
1.85
1.83
1.81
1.67
0.07

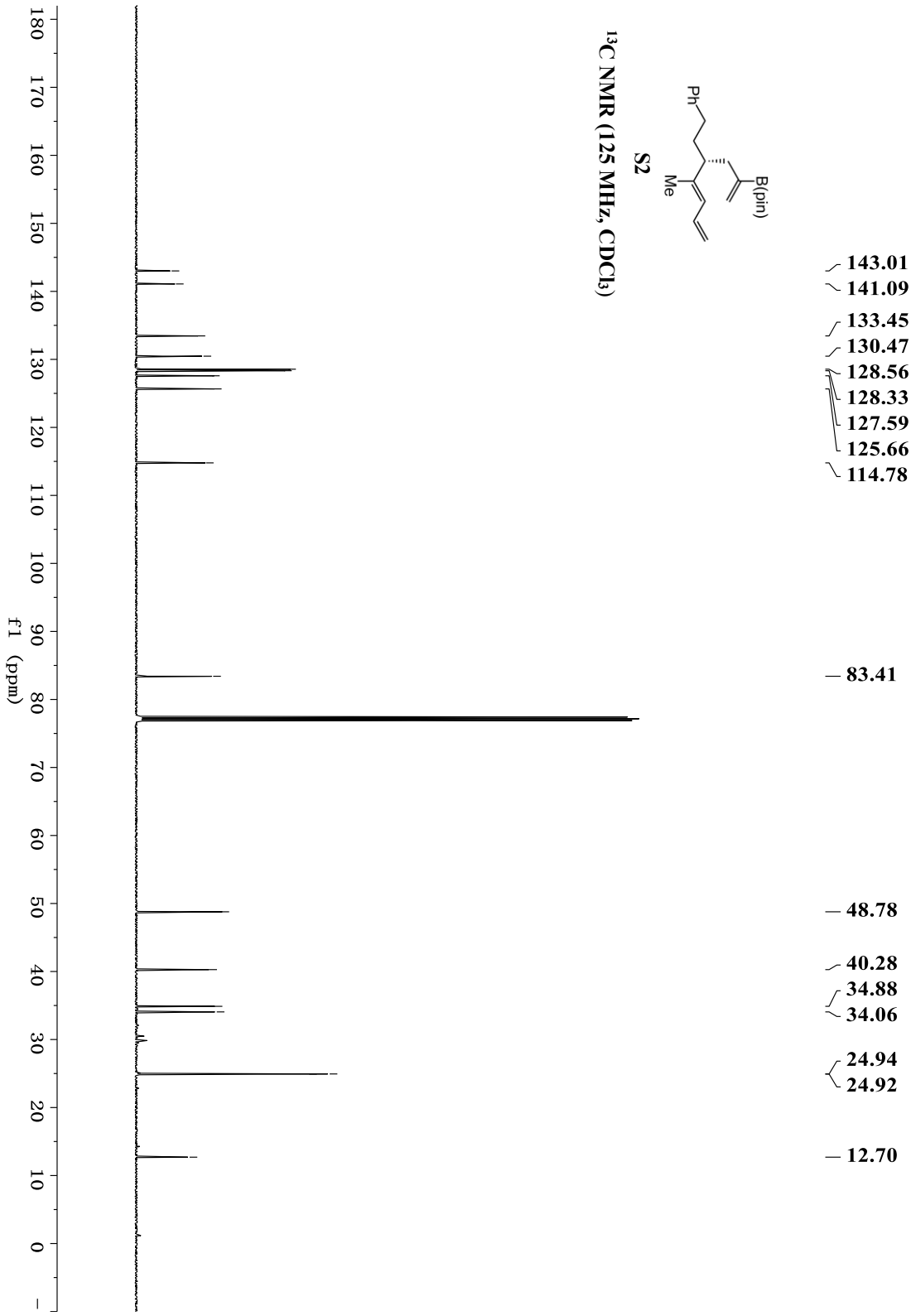

Me3Si
Ph
Me
1.62
13C NMR (100 MHz, CDCl3)
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 –
209.09
142.77
140.71
133.36
128.61
128.38
127.52
125.77
115.62
96.66
77.48
77.16
76.84
70.40
48.44
34.86
34.29
13.06
-1.13

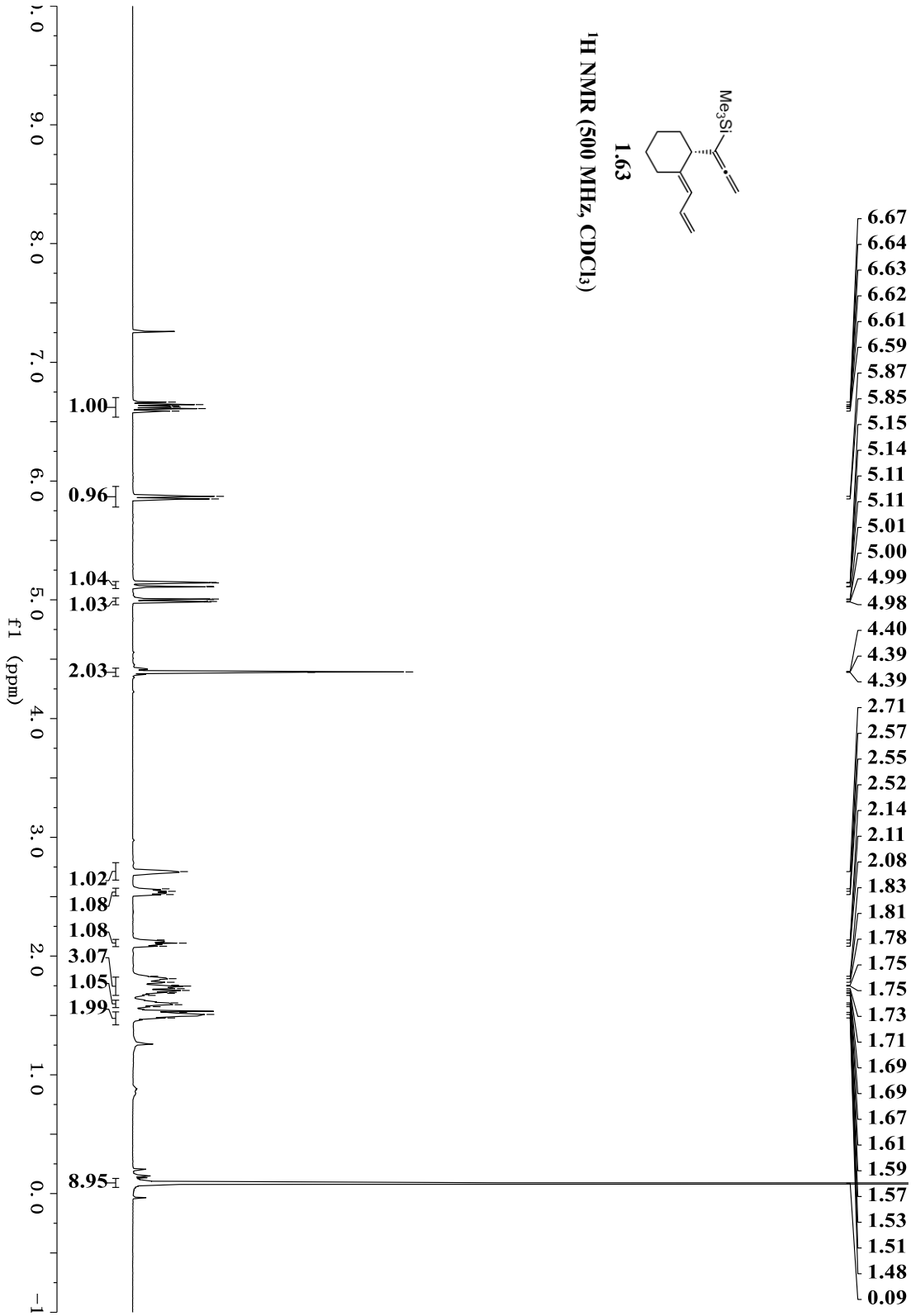
1H NMR (500 MHz, CDCl3)
S1
Ph
Me
7.29
7.28
7.26
7.19
7.18
7.17
6.64
6.62
6.60
6.59
6.58
6.56
5.95
5.93
5.17
5.17
5.14
5.13
5.12
5.11
5.09
5.08
5.06
5.06
5.04
5.04
4.77
4.77
4.76
4.75
2.76
2.75
2.74
2.72
2.64
2.61
2.59
2.57
2.53
1.84
1.83
1.81
1.80
1.73
2.05
3.03
1.00
1.04
1.08
0.97
1.05
2.07
1.05
2.06
2.06
3.05
f1 (ppm)

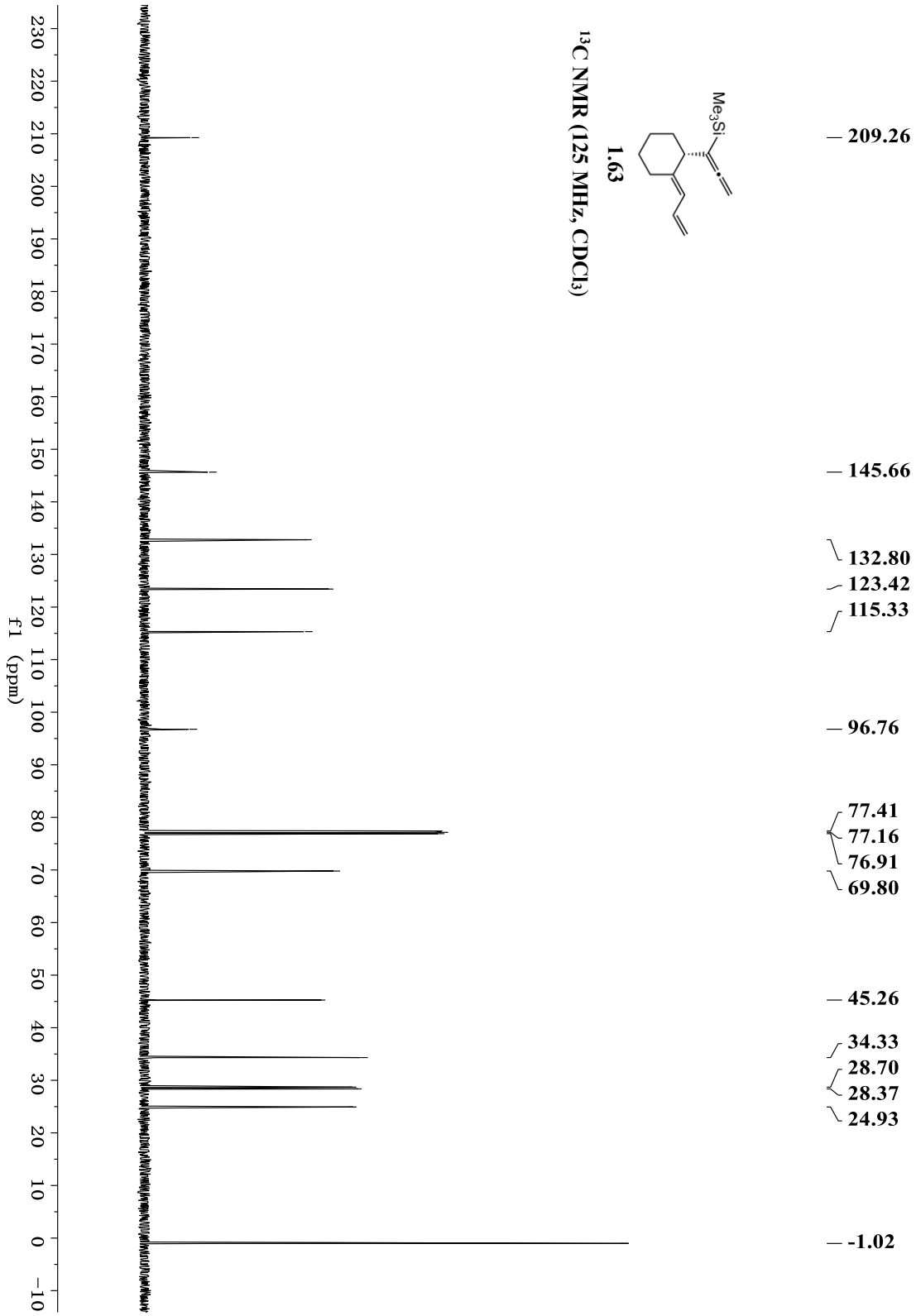

$^{13}$C NMR (125 MHz, CDCl$_3$)
S1
Ph
Me
208.48
142.52
140.55
133.29
128.61
128.44
126.68
125.87
115.90
92.90
77.41
77.16
76.91
76.07
47.68
34.24
33.93
13.75
f1 (ppm)

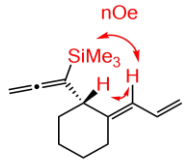



$^1$H NMR (500 MHz, $CDCl_3$)

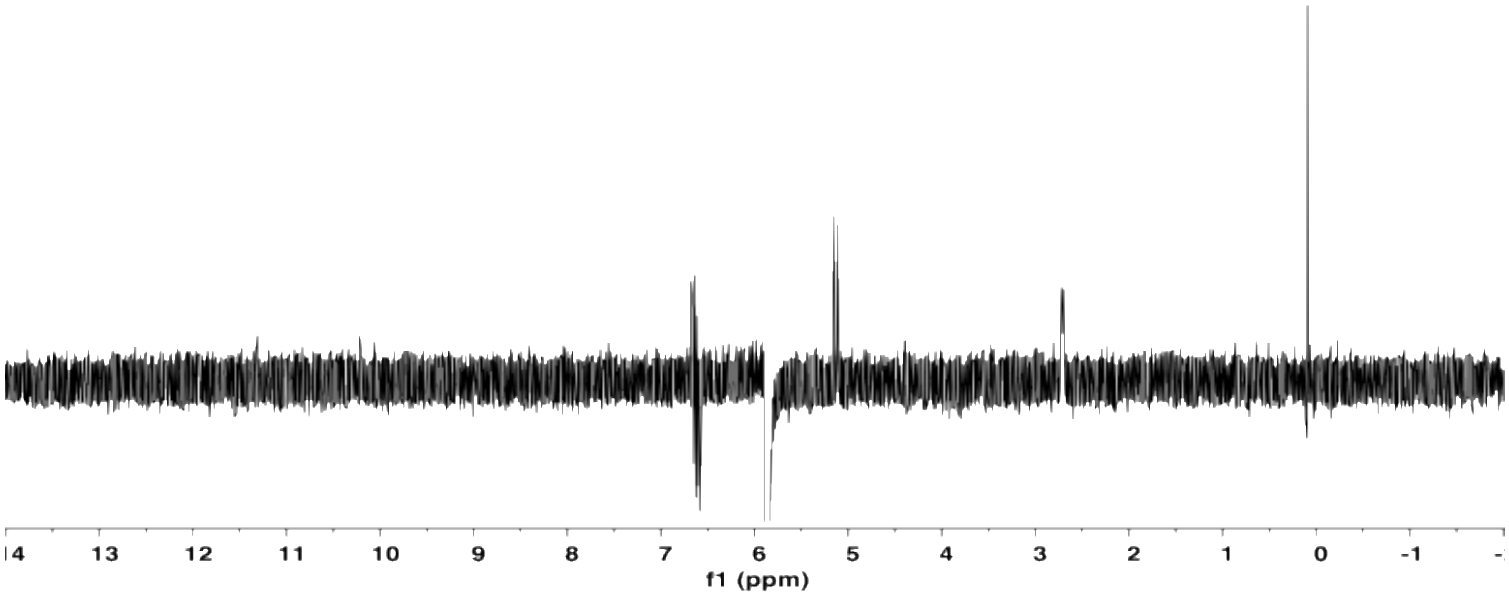

$^{13}$C NMR (125 MHz, CDCl$_3$)
S2
Ph
Me
B(pin)
143.01
141.09
133.45
130.47
128.56
128.33
127.59
125.66
114.78
83.41
48.78
40.28
34.88
34.06
24.94
24.92
12.70
f1 (ppm)

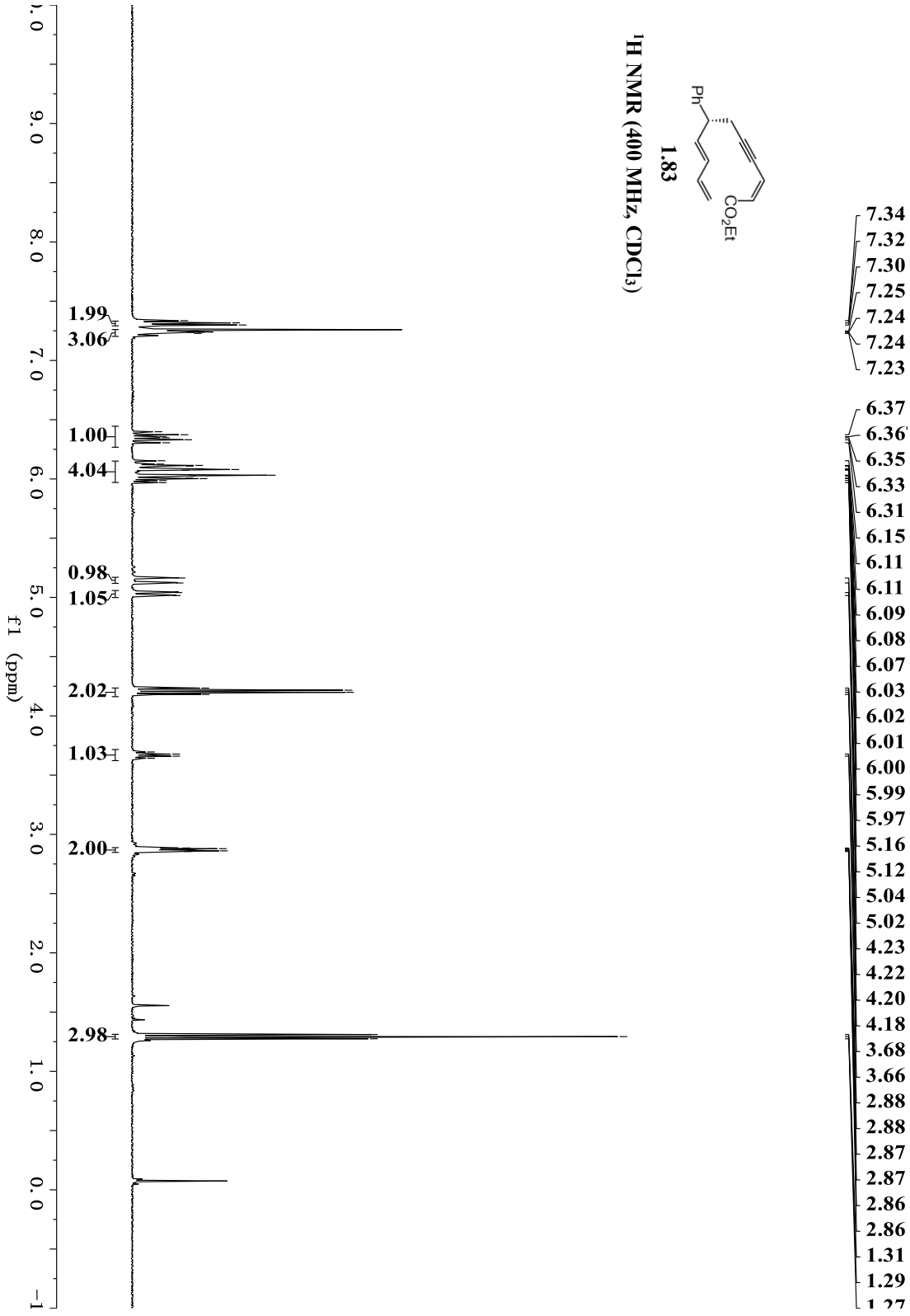

Me3Si
1.63
1H NMR (500 MHz, CDCl3)
f1 (ppm)
1.00
0.96
1.04
1.03
2.03
1.02
1.08
1.08
3.07
1.05
1.99
8.95
6.67
6.64
6.63
6.62
6.61
6.59
5.87
5.85
5.15
5.14
5.11
5.11
5.01
5.00
4.99
4.98
4.40
4.39
4.39
2.71
2.57
2.55
2.52
2.14
2.11
2.08
1.83
1.81
1.78
1.75
1.75
1.73
1.71
1.69
1.69
1.67
1.61
1.59
1.57
1.53
1.51
1.48
0.09

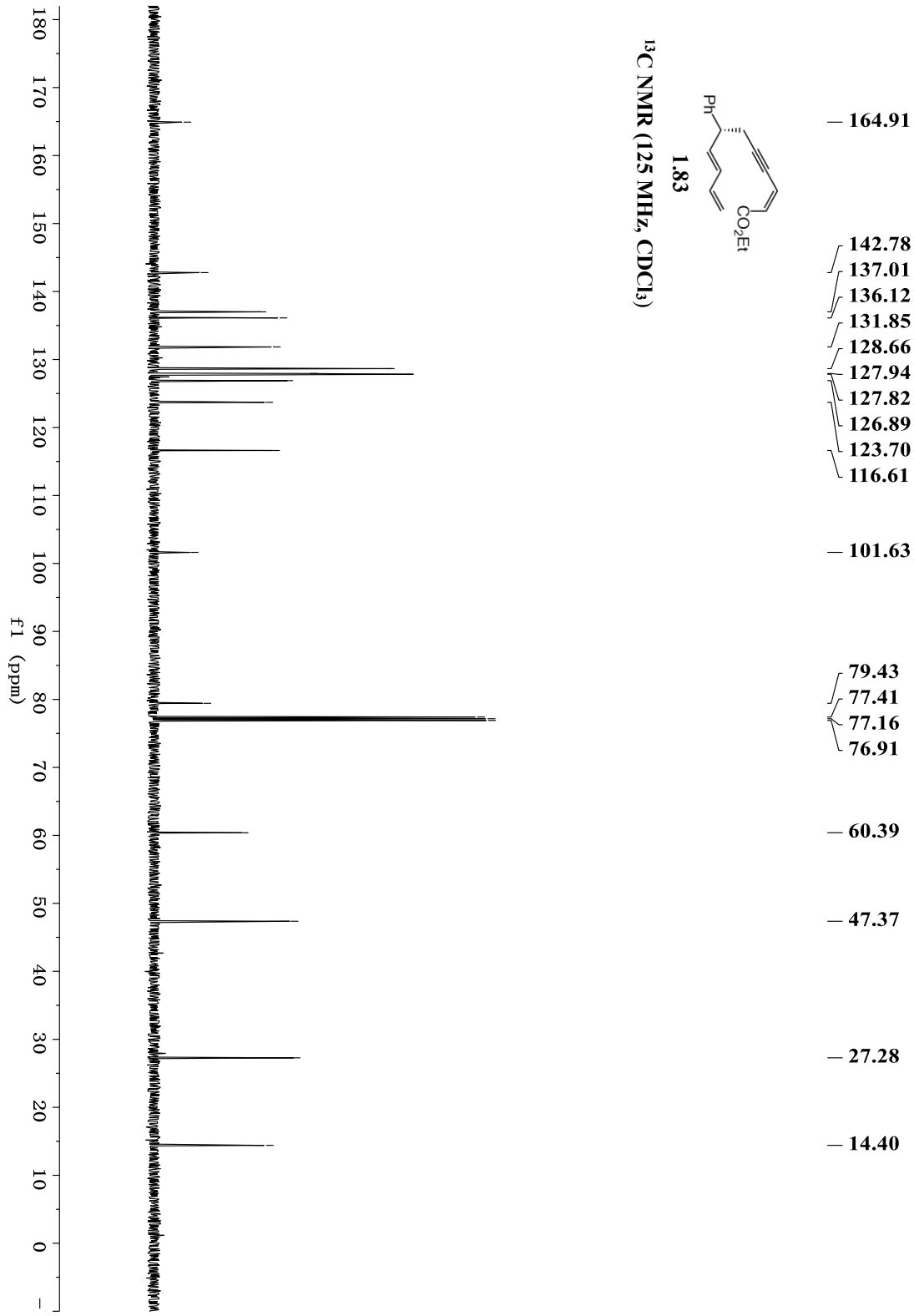

Me3Si
1.63
13C NMR (125 MHz, CDCl3)
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
209.26
145.66
132.80
123.42
115.33
96.76
77.41
77.16
76.91
69.80
45.26
34.33
28.70
28.37
24.93
-1.02

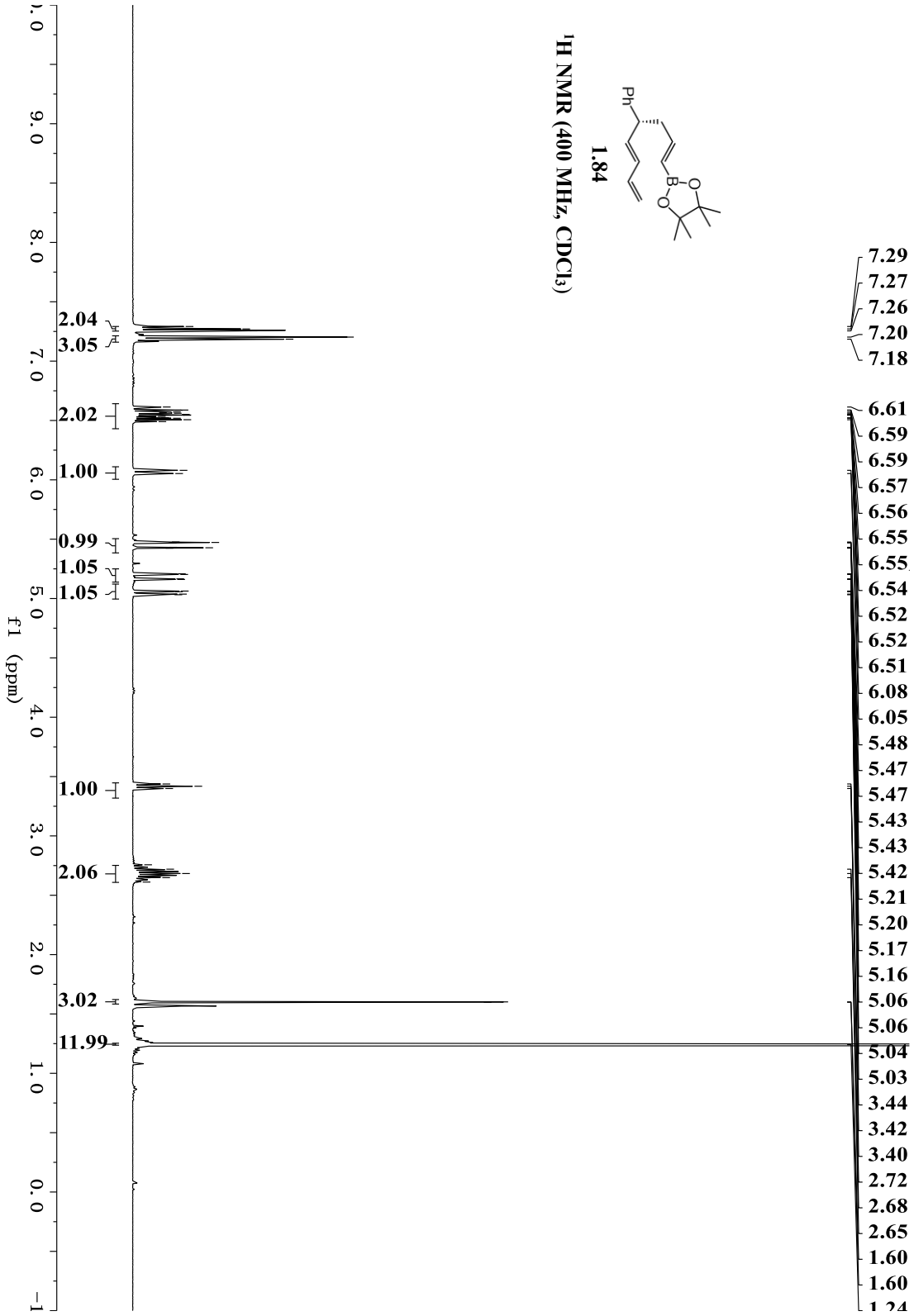


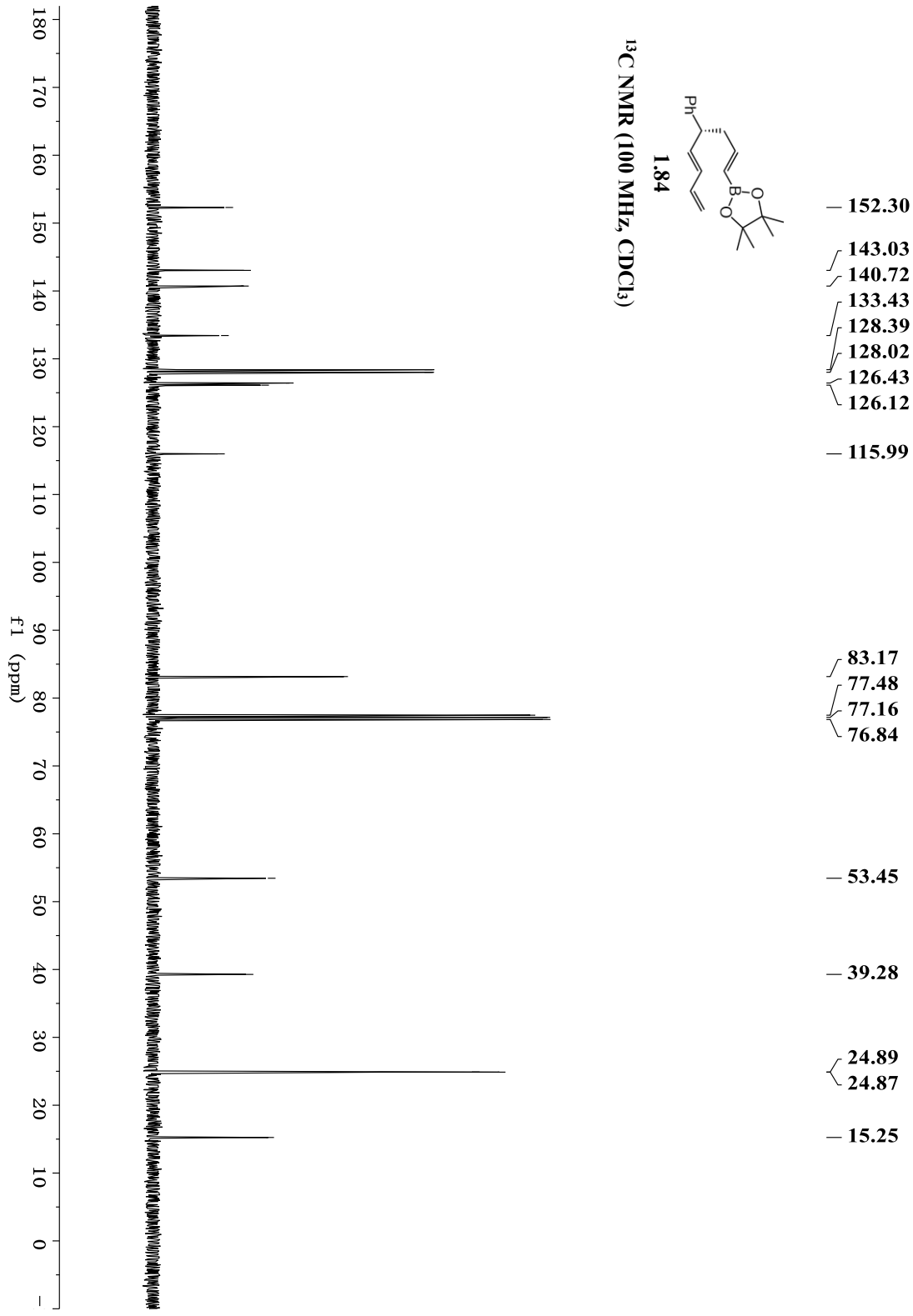

**1D nOe for 1.63**




1.83
Ph
CO2Et
1H NMR (400 MHz, CDCl3)
7.34
7.32
7.30
7.25
7.24
7.24
7.23
6.37
6.36
6.35
6.33
6.31
6.15
6.11
6.11
6.09
6.08
6.07
6.03
6.02
6.01
6.00
5.99
5.97
5.16
5.12
5.04
5.02
4.23
4.22
4.20
4.18
3.68
3.66
2.88
2.88
2.87
2.87
2.86
2.86
1.31
1.29
1.27
1.99
3.06
1.00
4.04
0.98
1.05
2.02
1.03
2.00
2.98
f1 (ppm)

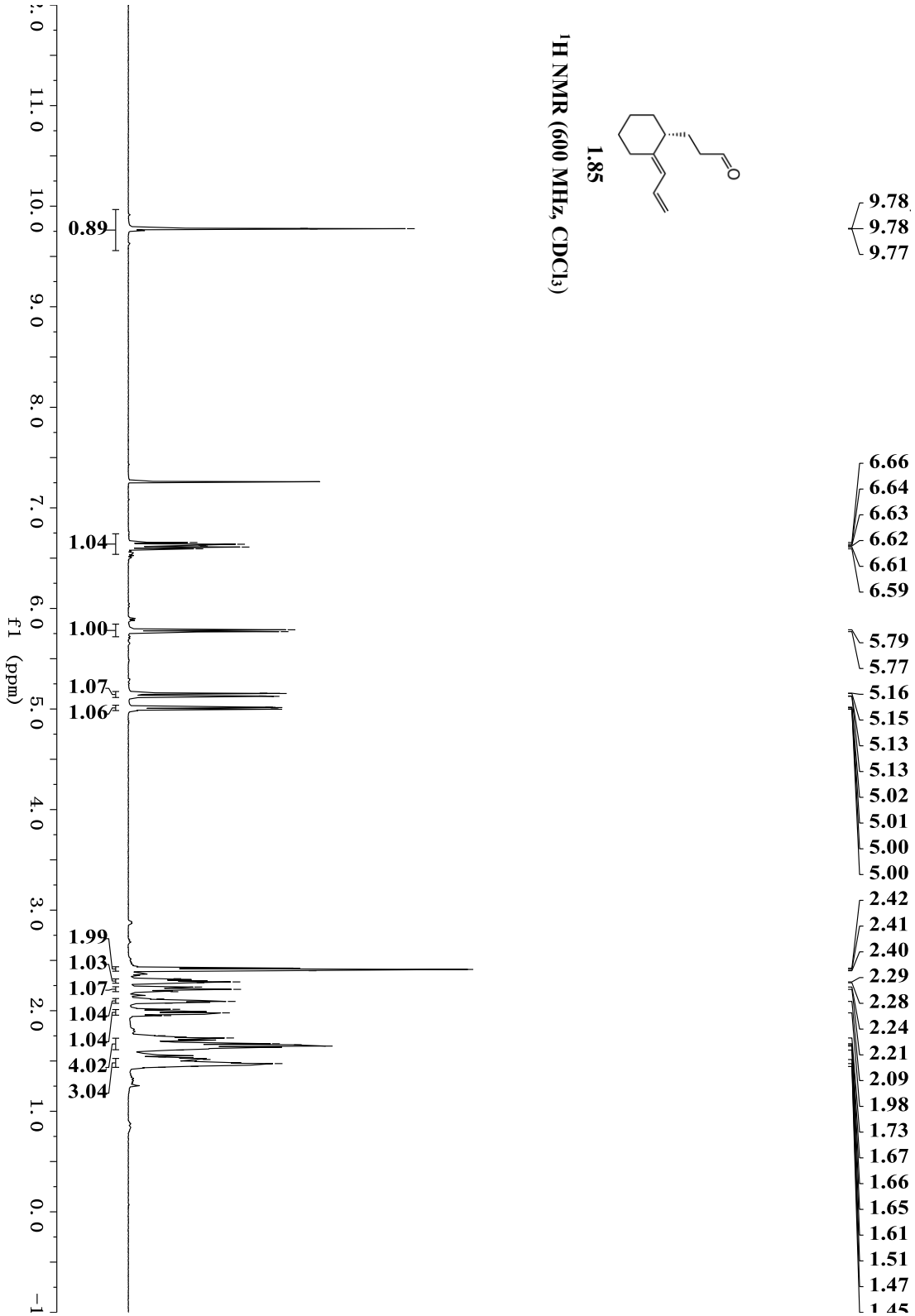

f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Ph
CO2Et
1.83
13C NMR (125 MHz, CDCl3)
164.91
142.78
137.01
136.12
131.85
128.66
127.94
127.82
126.89
123.70
116.61
101.63
79.43
77.41
77.16
76.91
60.39
47.37
27.28
14.40

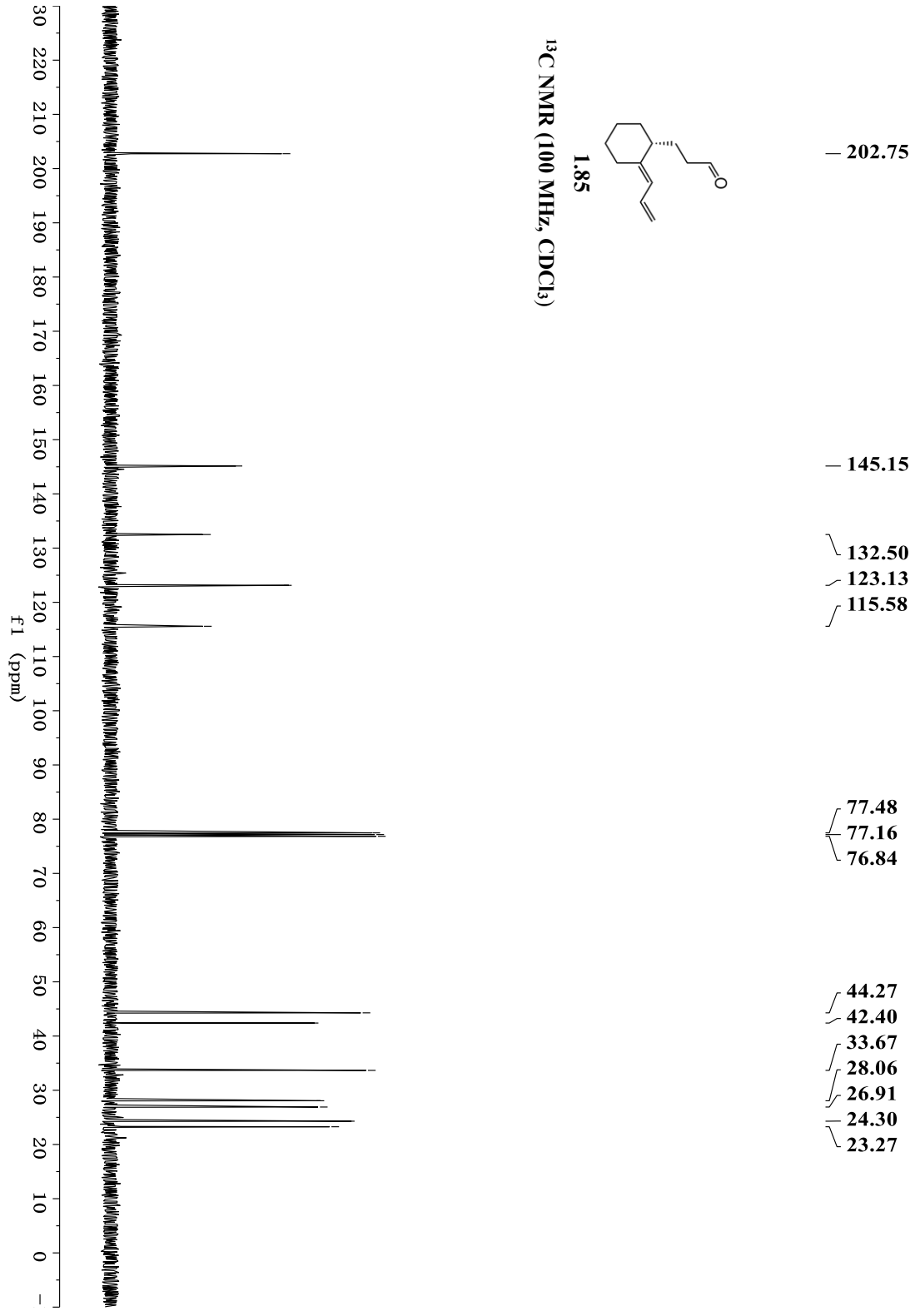

1H NMR (400 MHz, CDCl3)
1.84
Ph
O
B
O
f1 (ppm)
2.04
3.05
2.02
1.00
0.99
1.05
1.05
1.00
2.06
3.02
11.99
7.29
7.27
7.26
7.20
7.18
6.61
6.59
6.59
6.57
6.56
6.55
6.55
6.54
6.52
6.52
6.51
6.08
6.05
5.48
5.47
5.47
5.43
5.43
5.42
5.21
5.20
5.17
5.16
5.06
5.06
5.04
5.03
3.44
3.42
3.40
2.72
2.68
2.65
1.60
1.60
1.24

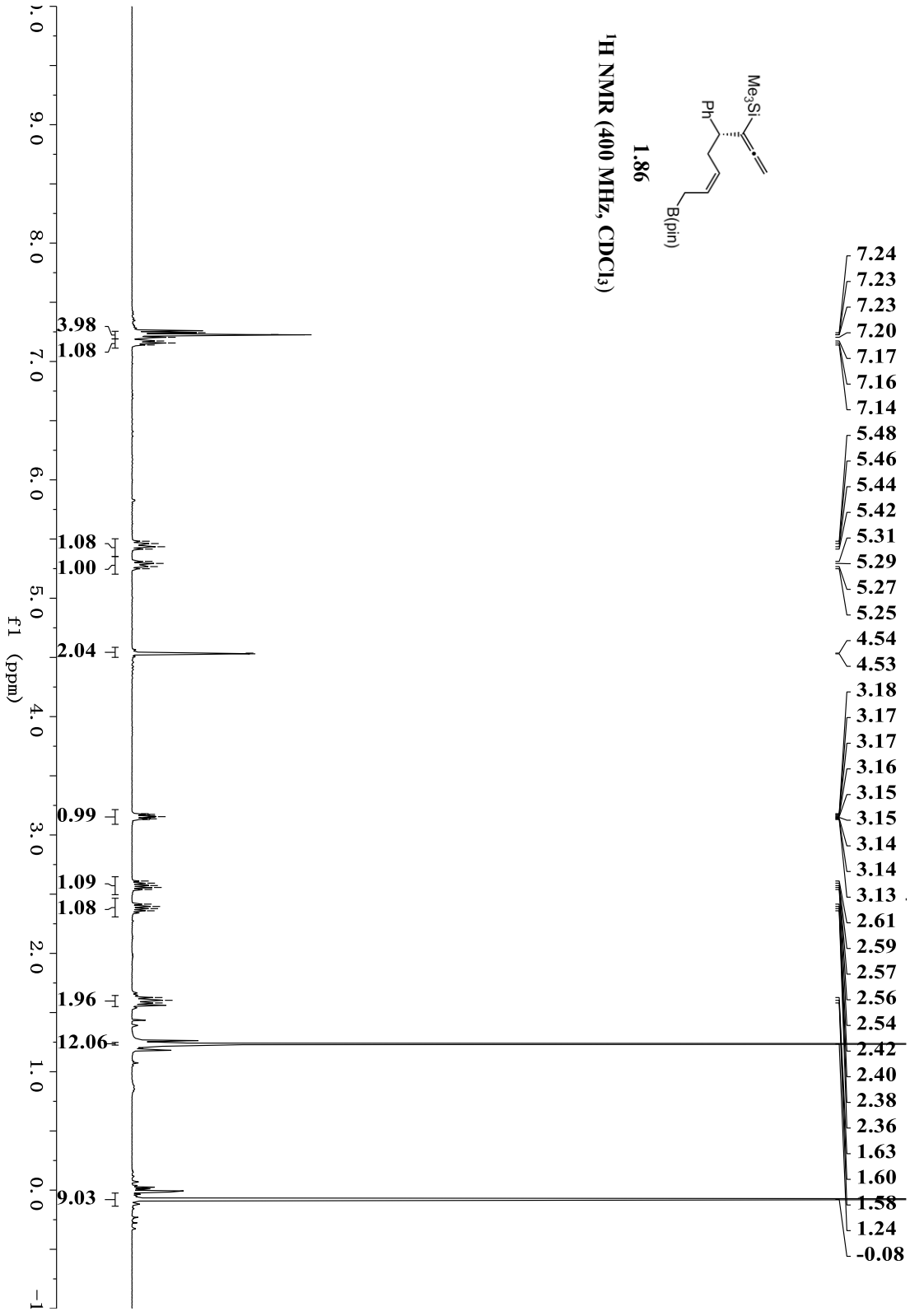



**1.84**

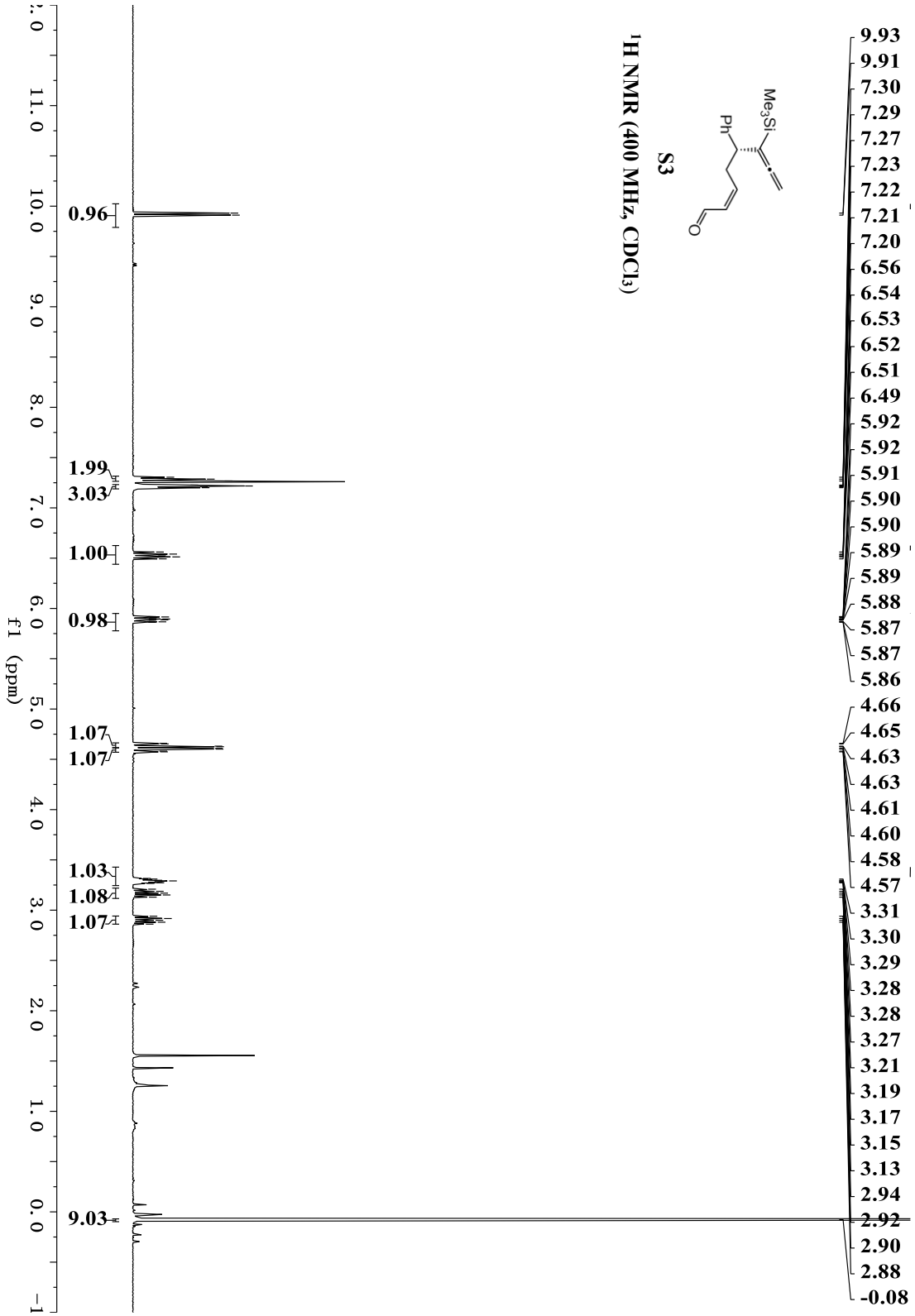
**$^{13}$C NMR (100 MHz, $CDCl_3$)**

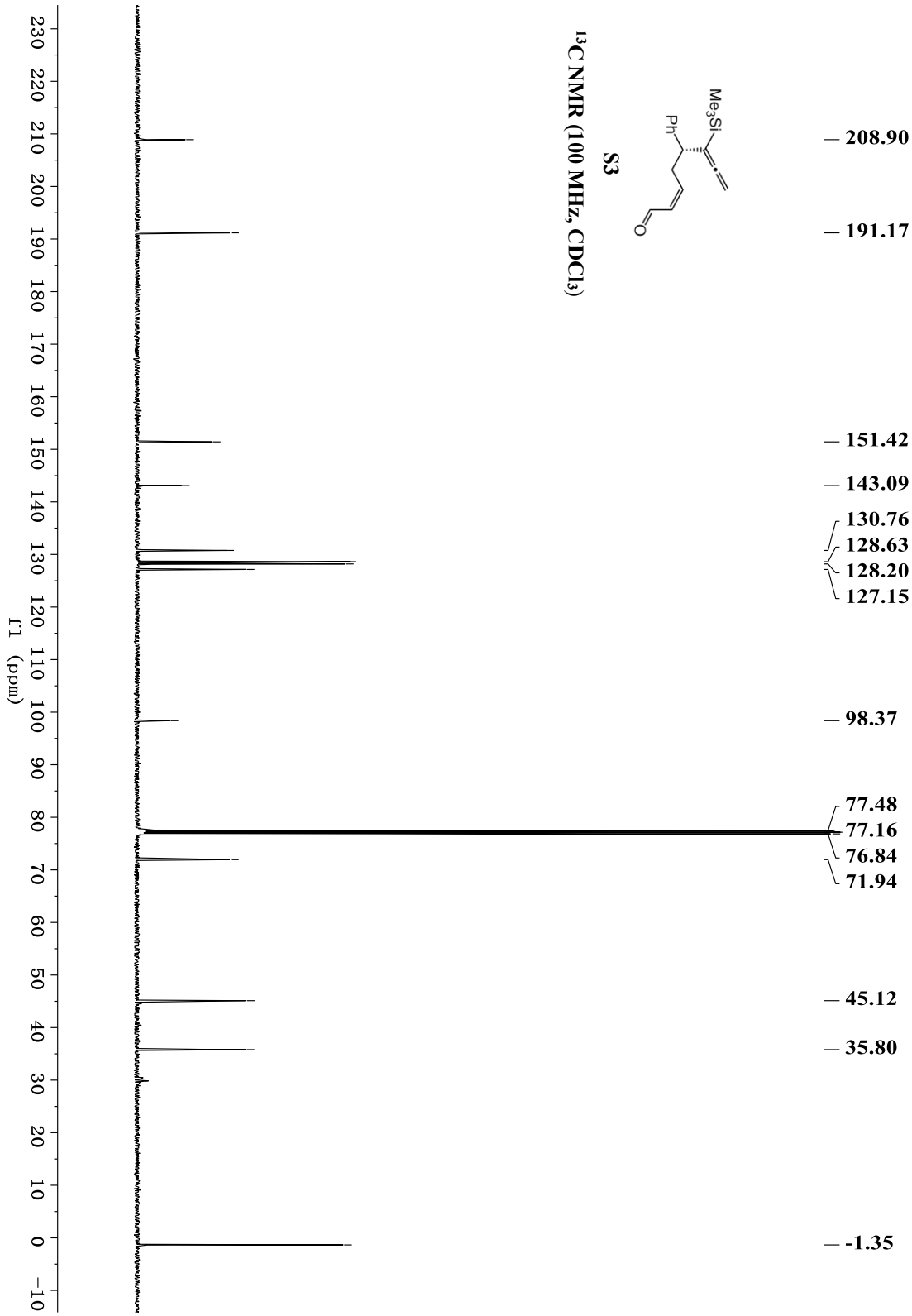

1.85
¹H NMR (600 MHz, CDCl₃)
O
f1 (ppm)
0.89
1.04
1.00
1.07
1.06
1.99
1.03
1.07
1.04
1.04
4.02
3.04
9.78
9.78
9.77
6.66
6.64
6.63
6.62
6.61
6.59
5.79
5.77
5.16
5.15
5.13
5.13
5.02
5.01
5.00
5.00
2.42
2.41
2.40
2.29
2.28
2.24
2.21
2.09
1.98
1.73
1.67
1.66
1.65
1.61
1.51
1.47

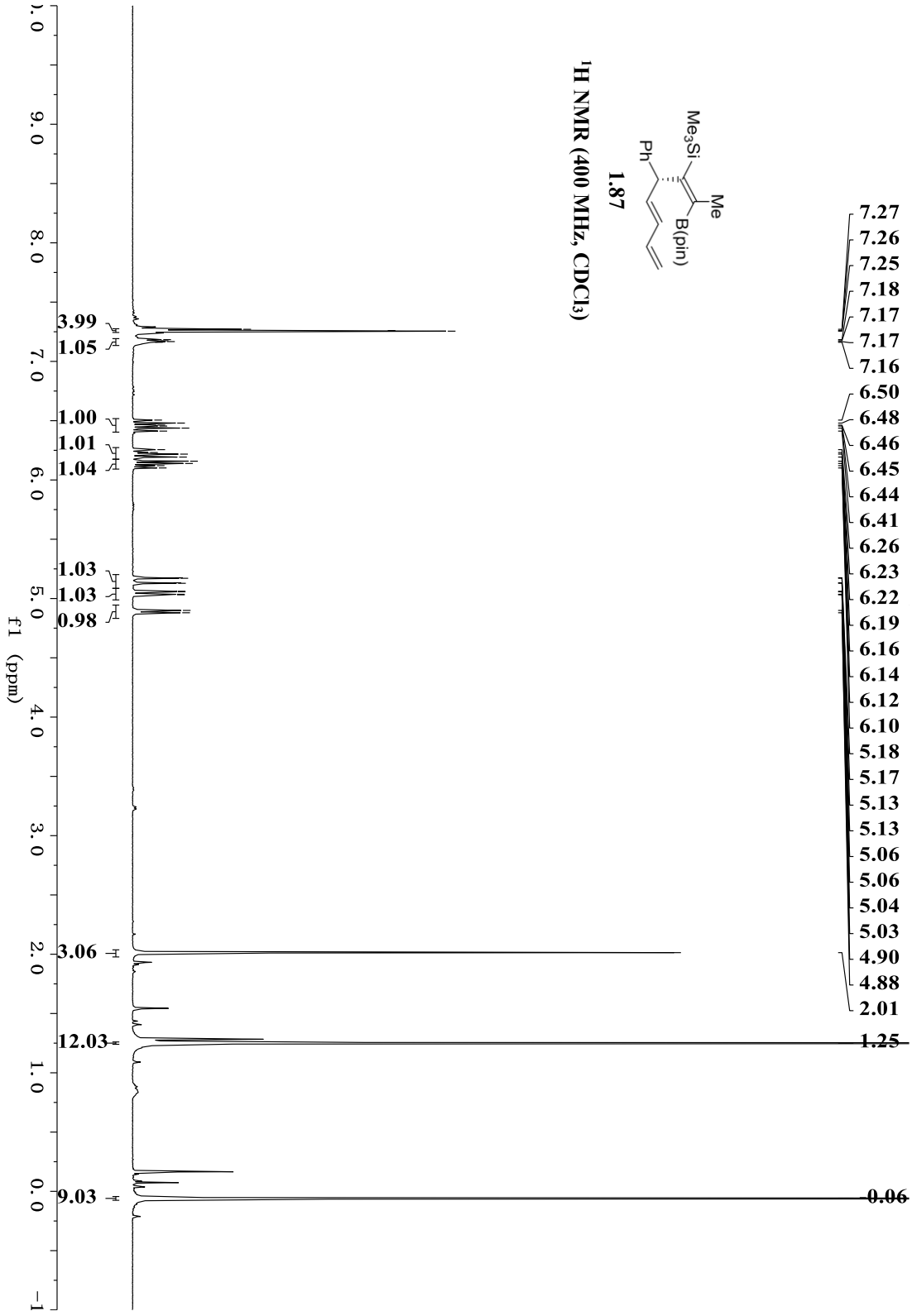

1.85
$^{13}$C NMR (100 MHz, CDCl$_3$)
202.75
145.15
132.50
123.13
115.58
77.48
77.16
76.84
44.27
42.40
33.67
28.06
26.91
24.30
23.27
f1 (ppm)

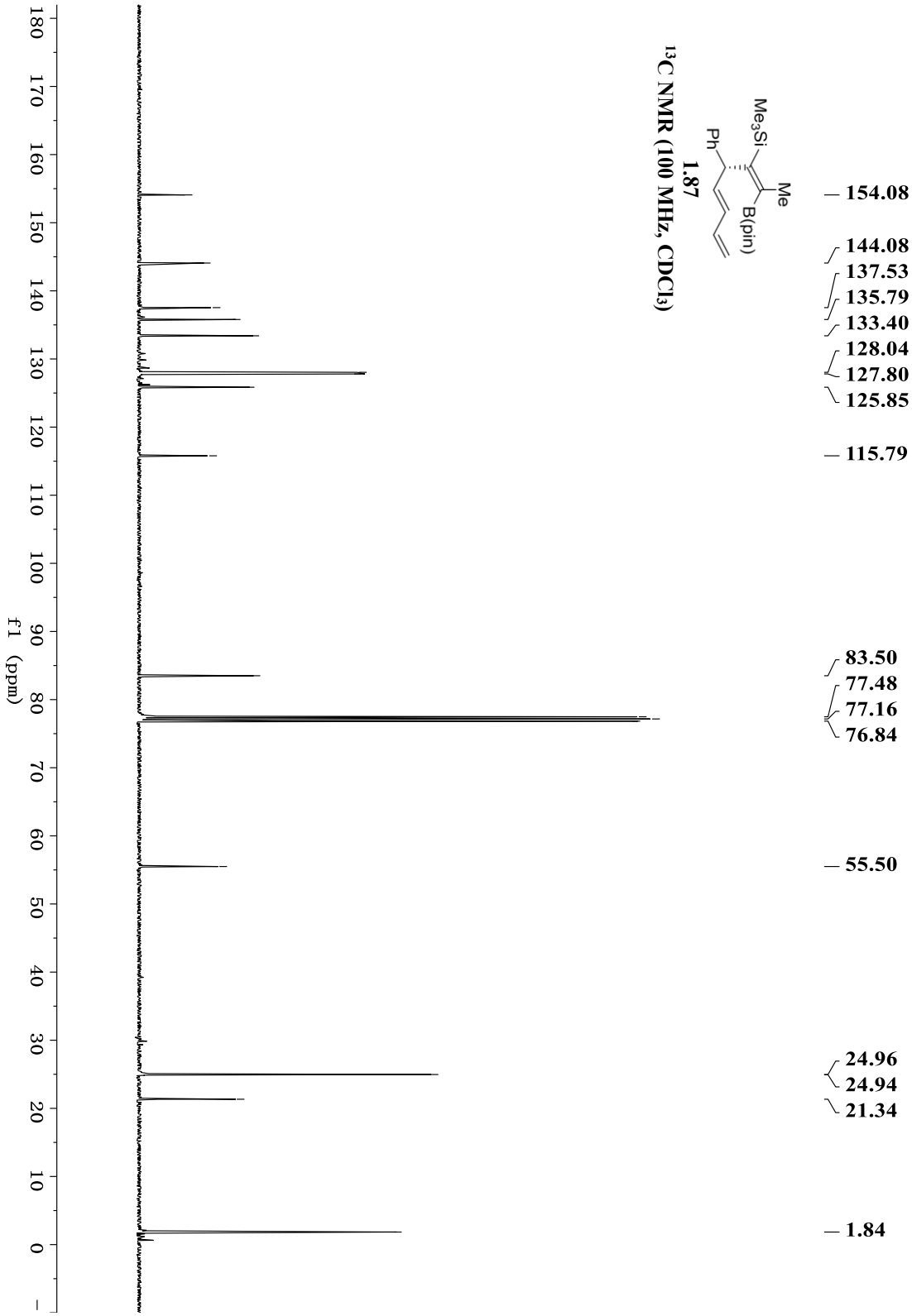

1.86
$^1$H NMR (400 MHz, CDCl$_3$)
Me$_3$Si
Ph
B(pin)
7.24
7.23
7.23
7.20
7.17
7.16
7.14
5.48
5.46
5.44
5.42
5.31
5.29
5.27
5.25
4.54
4.53
3.18
3.17
3.17
3.16
3.15
3.15
3.14
3.14
3.13
2.61
2.59
2.57
2.56
2.54
2.42
2.40
2.38
2.36
1.63
1.60
1.58
1.24
-0.08
3.98
1.08
1.08
1.00
2.04
0.99
1.09
1.08
1.96
12.06
9.03
f1 (ppm)

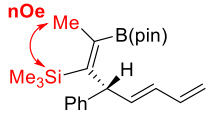
1.86
$^{13}$C NMR (100 MHz, CDCl$_3$)
Me$_3$Si
Ph
B(pin)
208.90
144.93
128.35
128.12
126.30
126.22
125.13
98.90
83.31
77.48
77.16
76.84
70.94
45.60
34.96
24.93
24.92
-1.27
f1 (ppm)


S3
$^1$H NMR (400 MHz, CDCl$_3$)
Me$_3$Si
Ph
O
9.93
9.91
7.30
7.29
7.27
7.23
7.22
7.21
7.20
6.56
6.54
6.53
6.52
6.51
6.49
5.92
5.92
5.91
5.90
5.90
5.89
5.89
5.88
5.87
5.87
5.86
4.66
4.65
4.63
4.63
4.61
4.60
4.58
4.57
3.31
3.30
3.29
3.28
3.28
3.27
3.21
3.19
3.17
3.15
3.13
2.94
2.92
2.90
2.88
-0.08
0.96
1.99
3.03
1.00
0.98
1.07
1.07
1.03
1.08
1.07
9.03
f1 (ppm)


S3
$^{13}$C NMR (100 MHz, CDCl$_3$)
Me$_3$Si
Ph
O
208.90
191.17
151.42
143.09
130.76
128.63
128.20
127.15
98.37
77.48
77.16
76.84
71.94
45.12
35.80
-1.35
f1 (ppm)

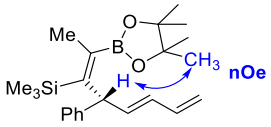

1.87
$^1$H NMR (400 MHz, CDCl$_3$)
Me$_3$Si
Me
Ph
B(pin)
f1 (ppm)
3.99
1.05
1.00
1.01
1.04
1.03
1.03
0.98
3.06
12.03
9.03
7.27
7.26
7.25
7.18
7.17
7.17
7.16
6.50
6.48
6.46
6.45
6.44
6.41
6.26
6.23
6.22
6.19
6.16
6.14
6.12
6.10
5.18
5.17
5.13
5.13
5.06
5.06
5.04
5.03
4.90
4.88
2.01
1.25
0.06


Me3Si
Me
Ph
B(pin)
1.87
13C NMR (100 MHz, CDCl3)
154.08
144.08
137.53
135.79
133.40
128.04
127.80
125.85
115.79
83.50
77.48
77.16
76.84
55.50
24.96
24.94
21.34
1.84
f1 (ppm)


nOe
Me
B(pin)
Me3Si
H
Ph

**1D nOe of 1.87**

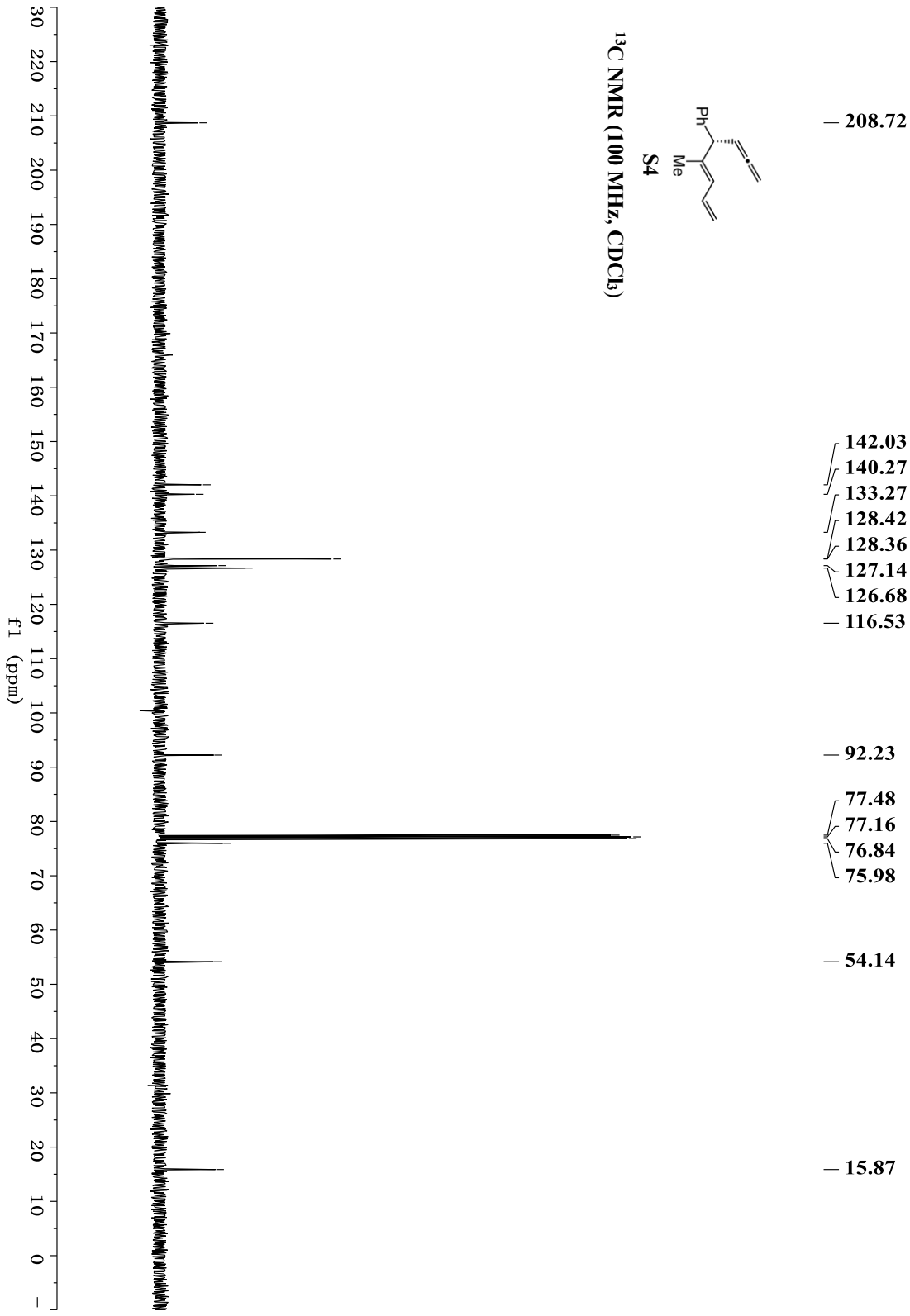

2.007
1.245
-0.067
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)


Me
O
B
O
CH3
nOe
Me3Si
H
Ph

**1D nOe of 1.87**

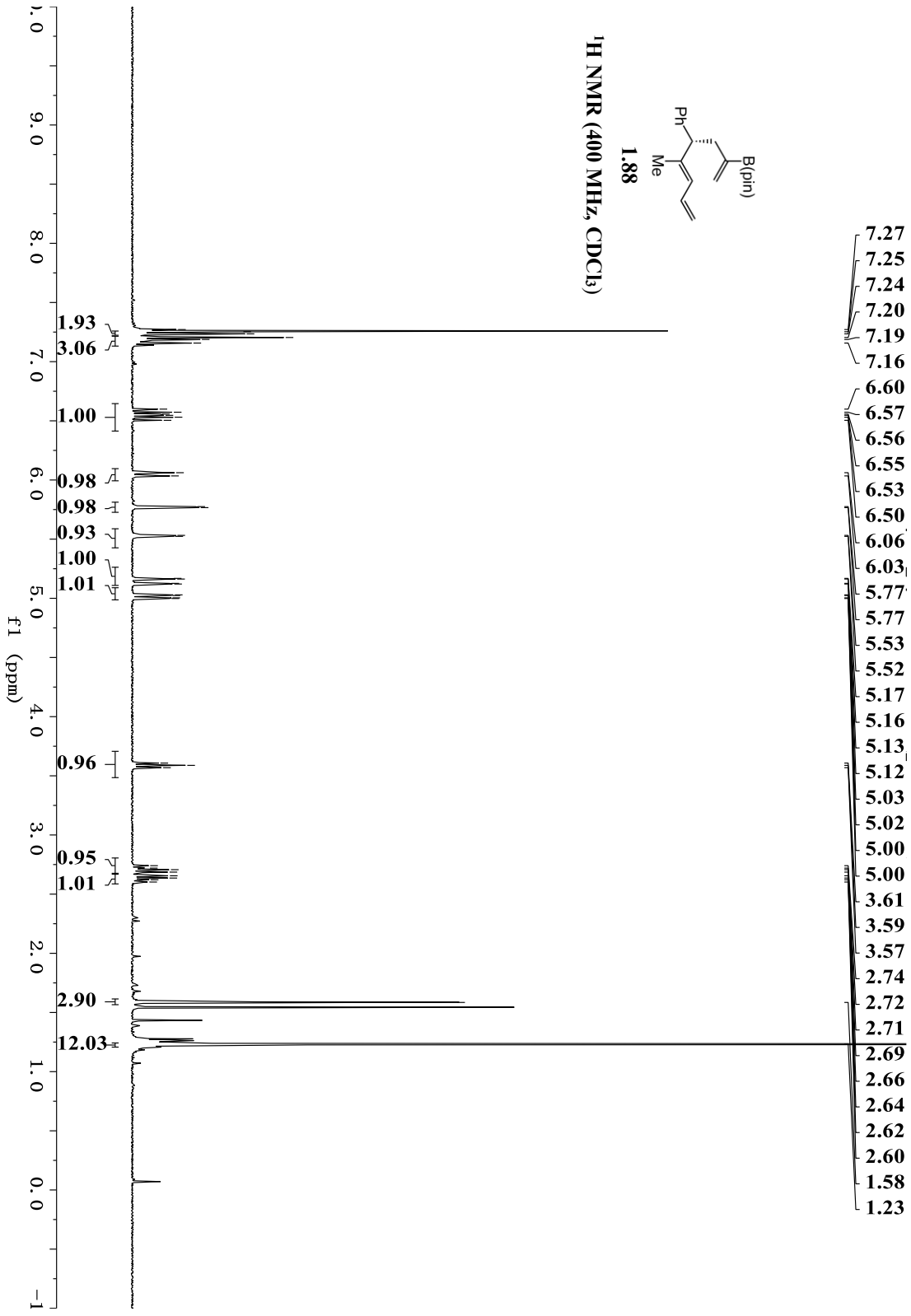

7.253
4.894
4.878
2.007
1.245
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

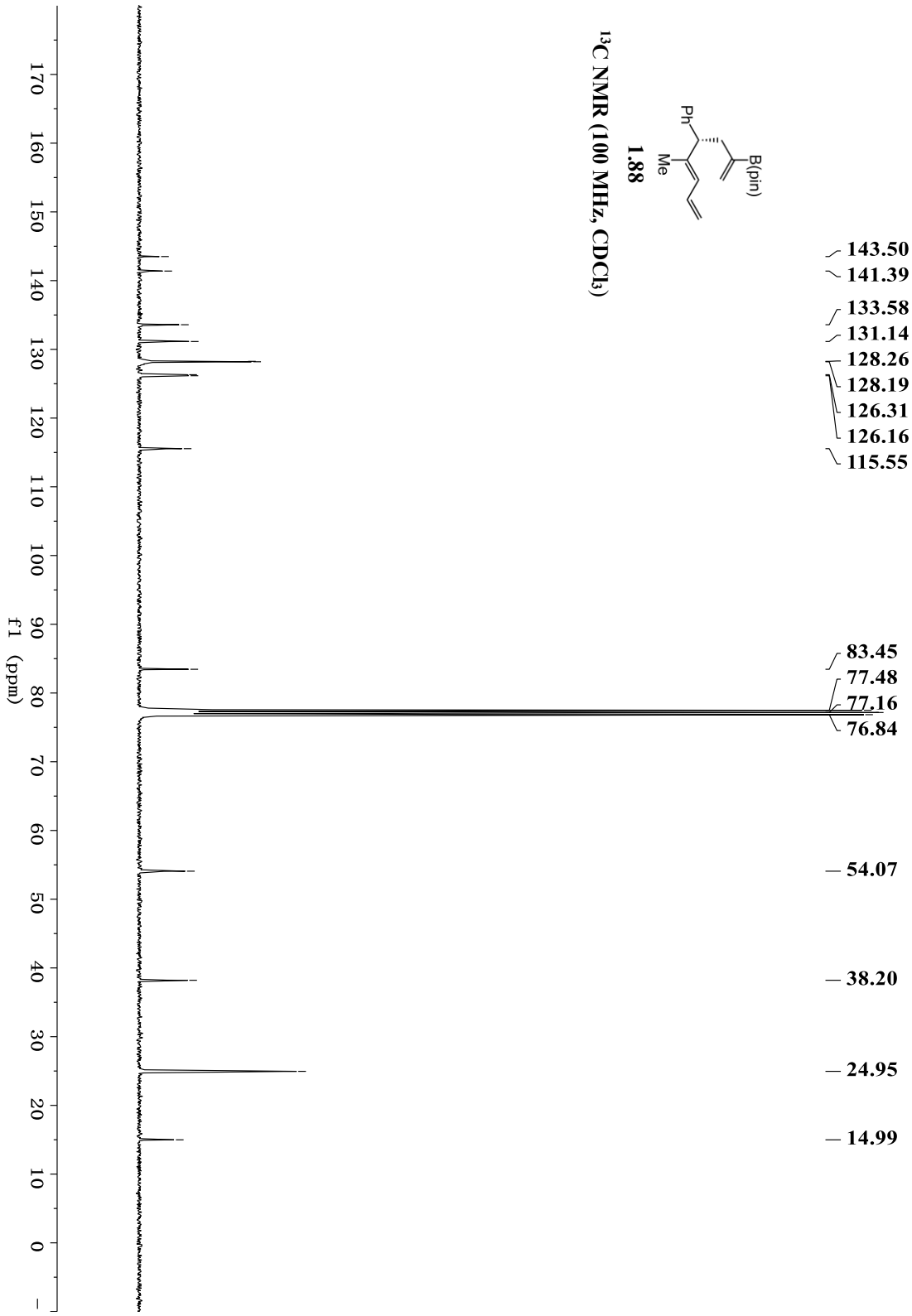
$^1$H NMR (400 MHz, CDCl$_3$)
S4
Ph
Me
7.32
7.30
7.29
7.24
7.22
6.66
6.63
6.61
6.60
6.59
6.56
6.10
6.08
5.46
5.44
5.42
5.41
5.23
5.22
5.19
5.18
5.10
5.10
5.08
5.07
4.72
4.71
4.70
4.70
4.08
4.06
1.68
2.00
2.93
1.00
1.01
0.98
1.06
1.07
2.08
1.02
3.02
f1 (ppm)

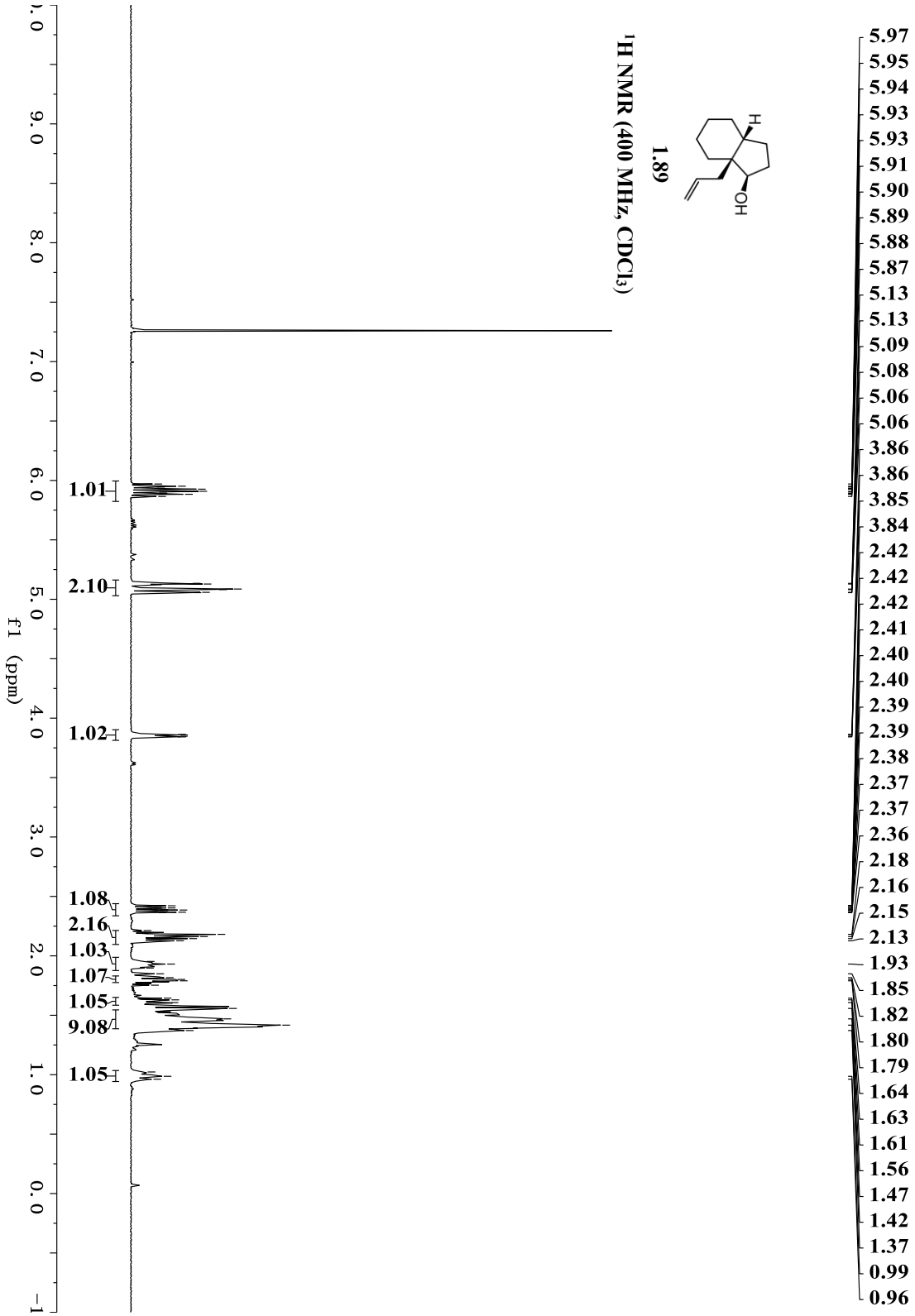


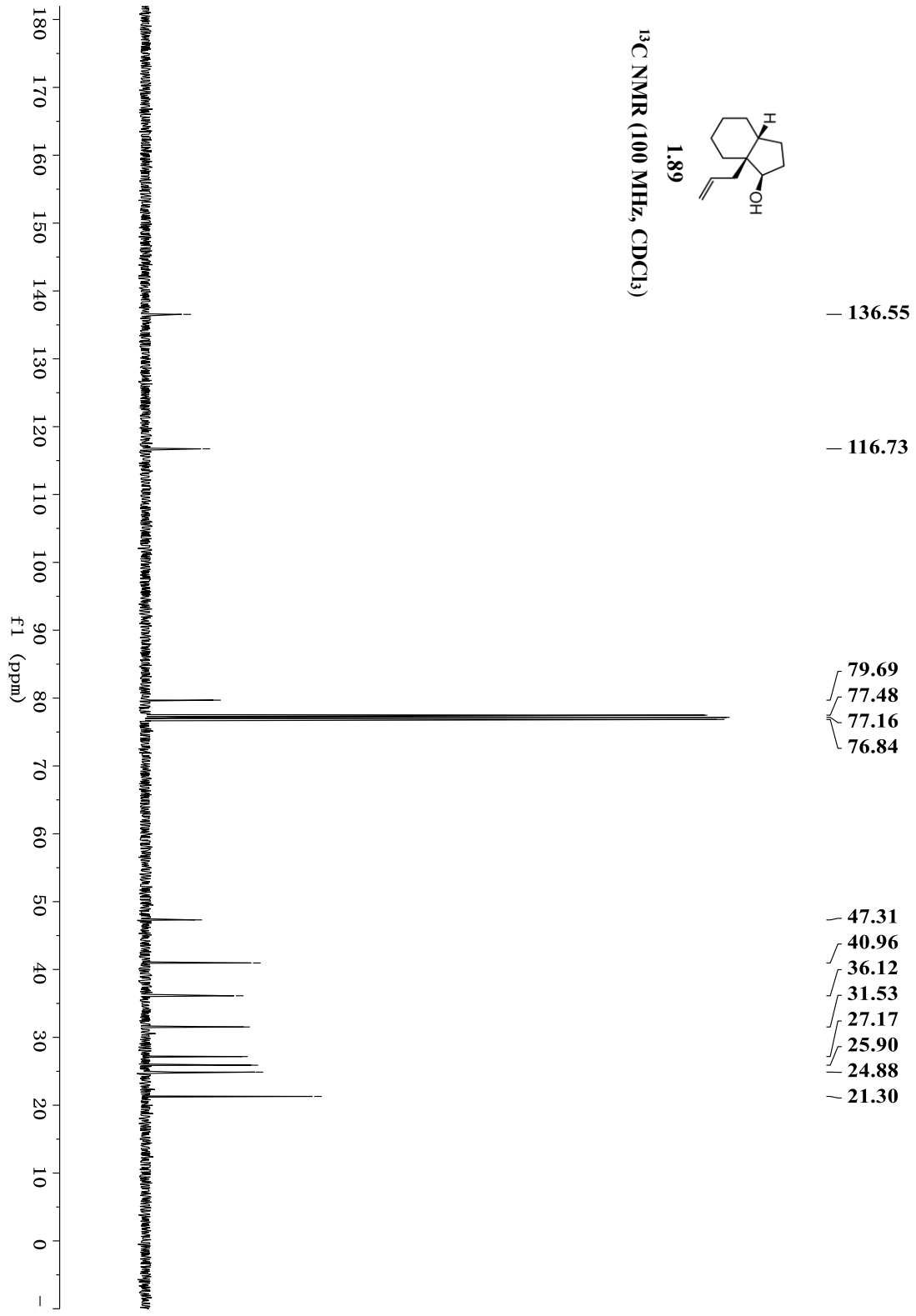

**$^{13}$C NMR (100 MHz, CDCl$_3$)**

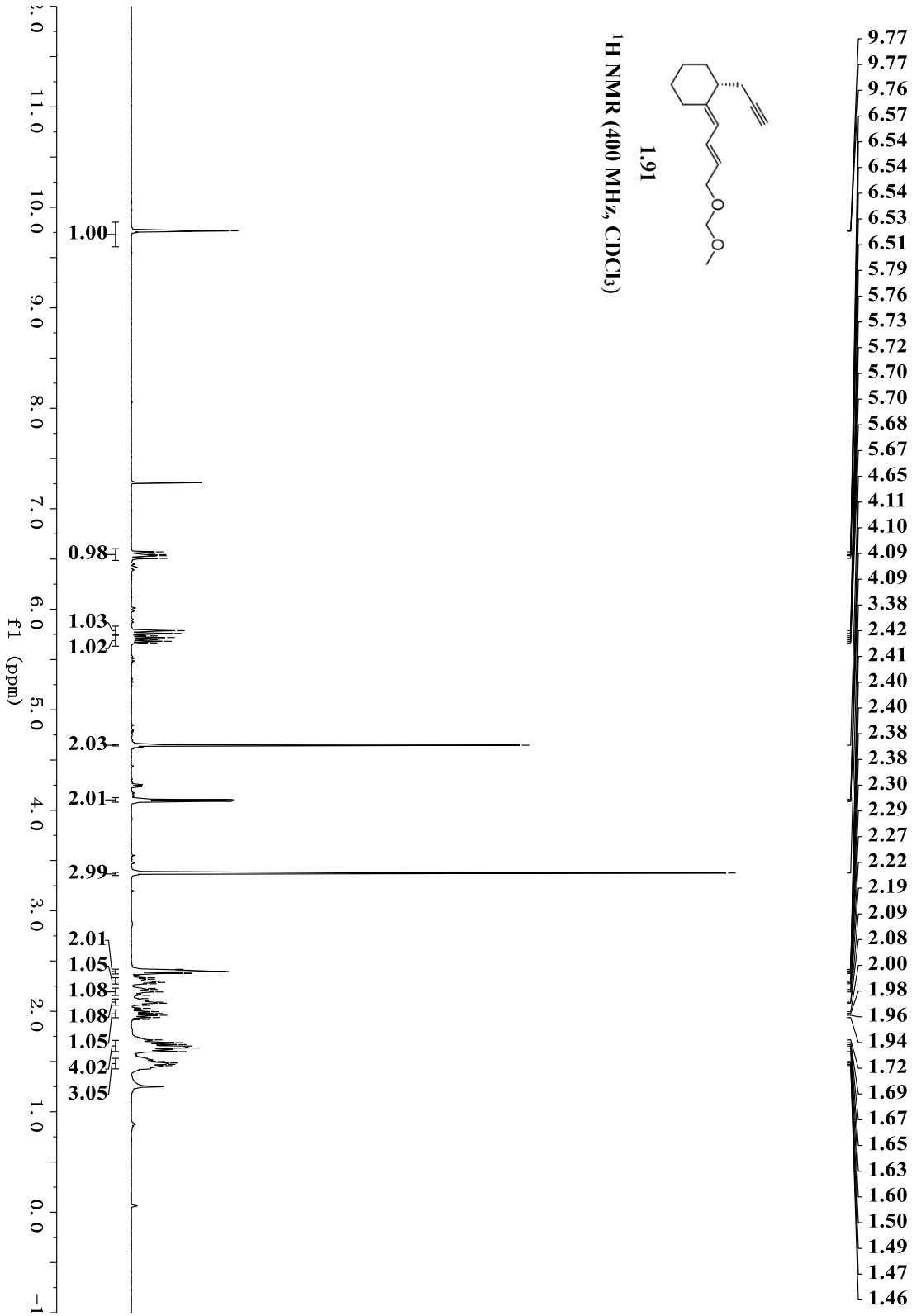
**S4**

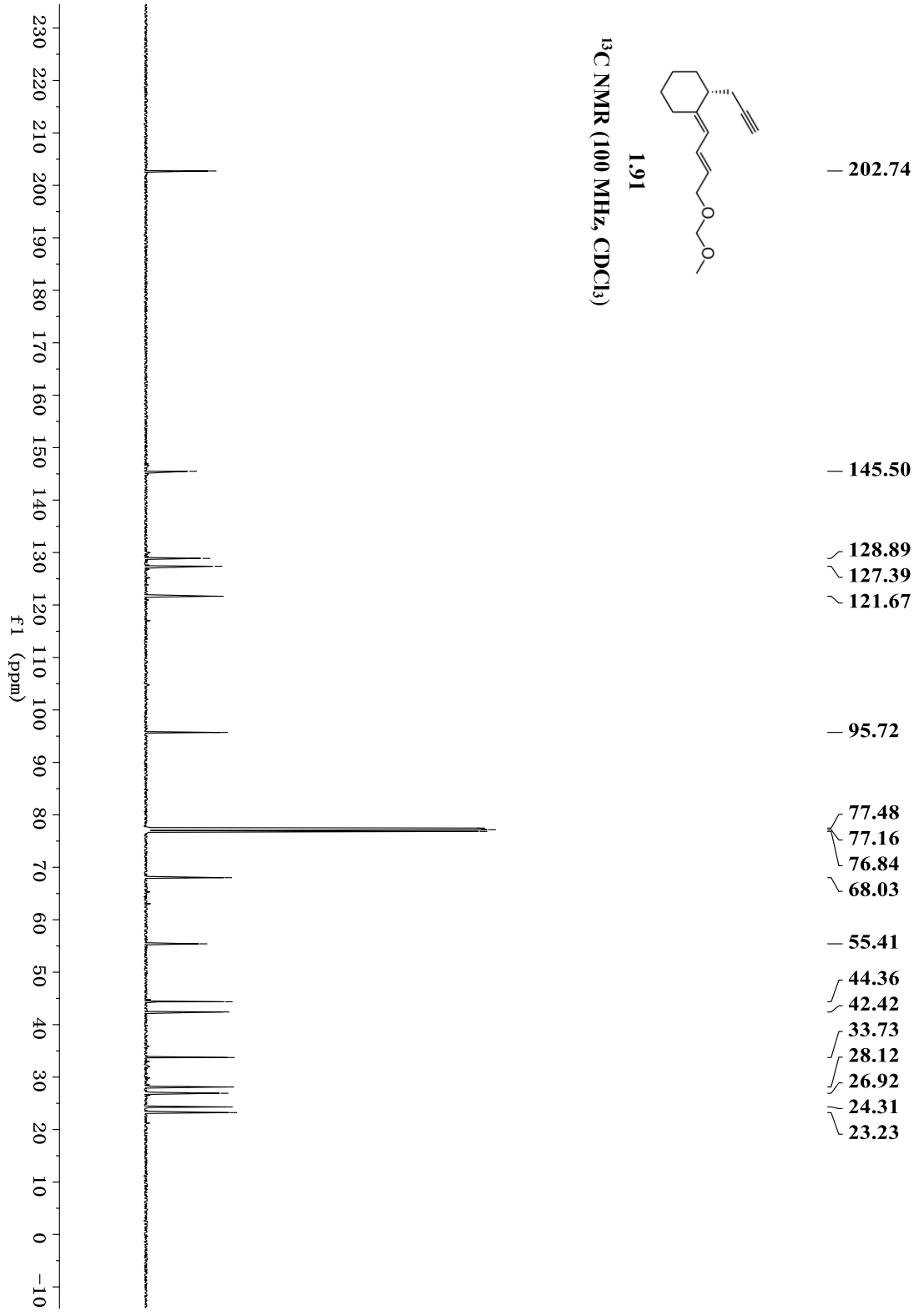

1H NMR (400 MHz, CDCl3)
1.88
Ph
Me
B(pin)
f1 (ppm)
1.93
3.06
1.00
0.98
0.98
0.93
1.00
1.01
0.96
0.95
1.01
2.90
12.03
7.27
7.25
7.24
7.20
7.19
7.16
6.60
6.57
6.56
6.55
6.53
6.50
6.06
6.03
5.77
5.77
5.53
5.52
5.17
5.16
5.13
5.12
5.03
5.02
5.00
5.00
3.61
3.59
3.57
2.74
2.72
2.71
2.69
2.66
2.64
2.62
2.60
1.58
1.23

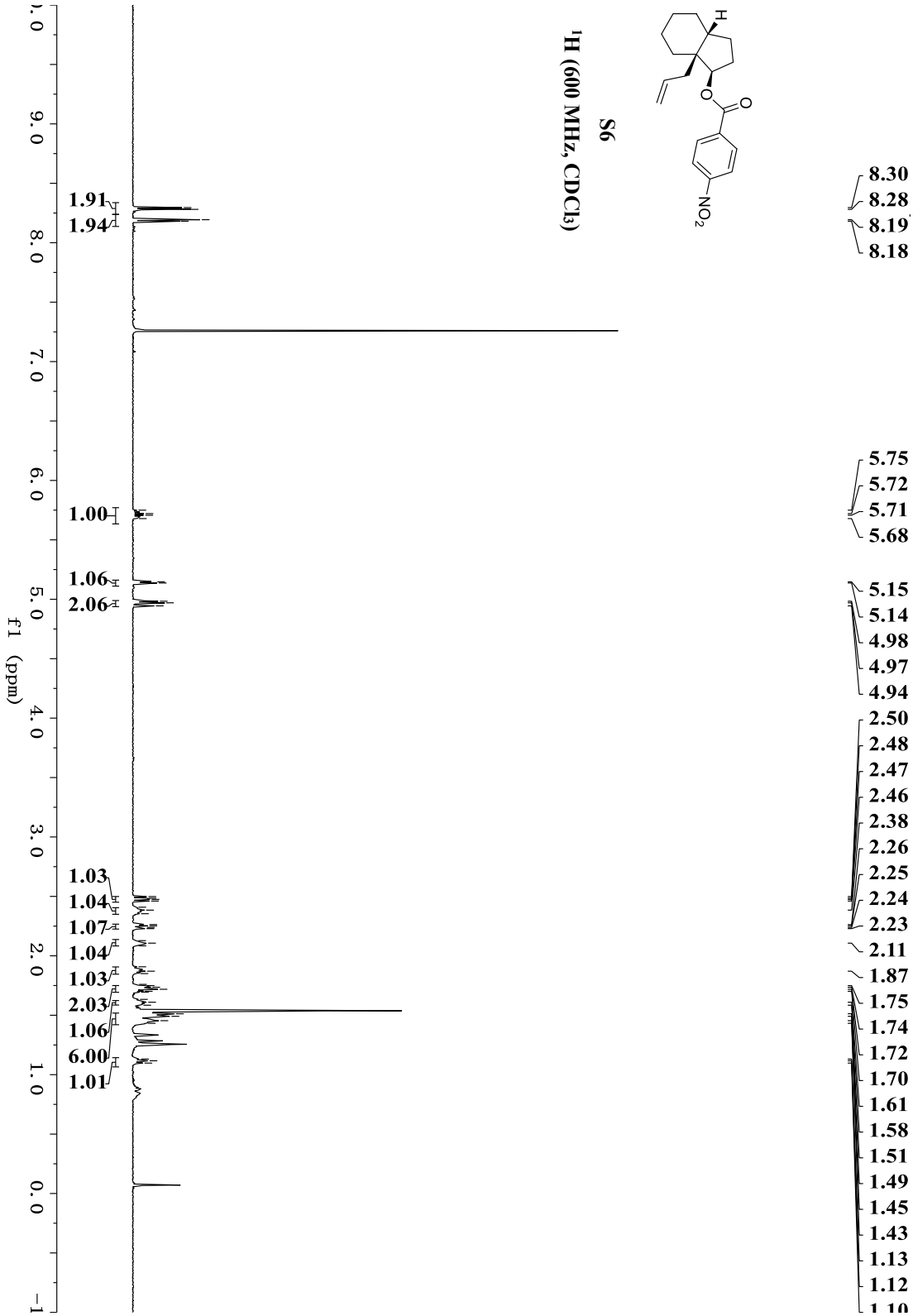

$^{13}$C NMR (100 MHz, CDCl$_3$)
1.88
Ph
Me
B(pin)
143.50
141.39
133.58
131.14
128.26
128.19
126.31
126.16
115.55
83.45
77.48
77.16
76.84
54.07
38.20
24.95
14.99
f1 (ppm)

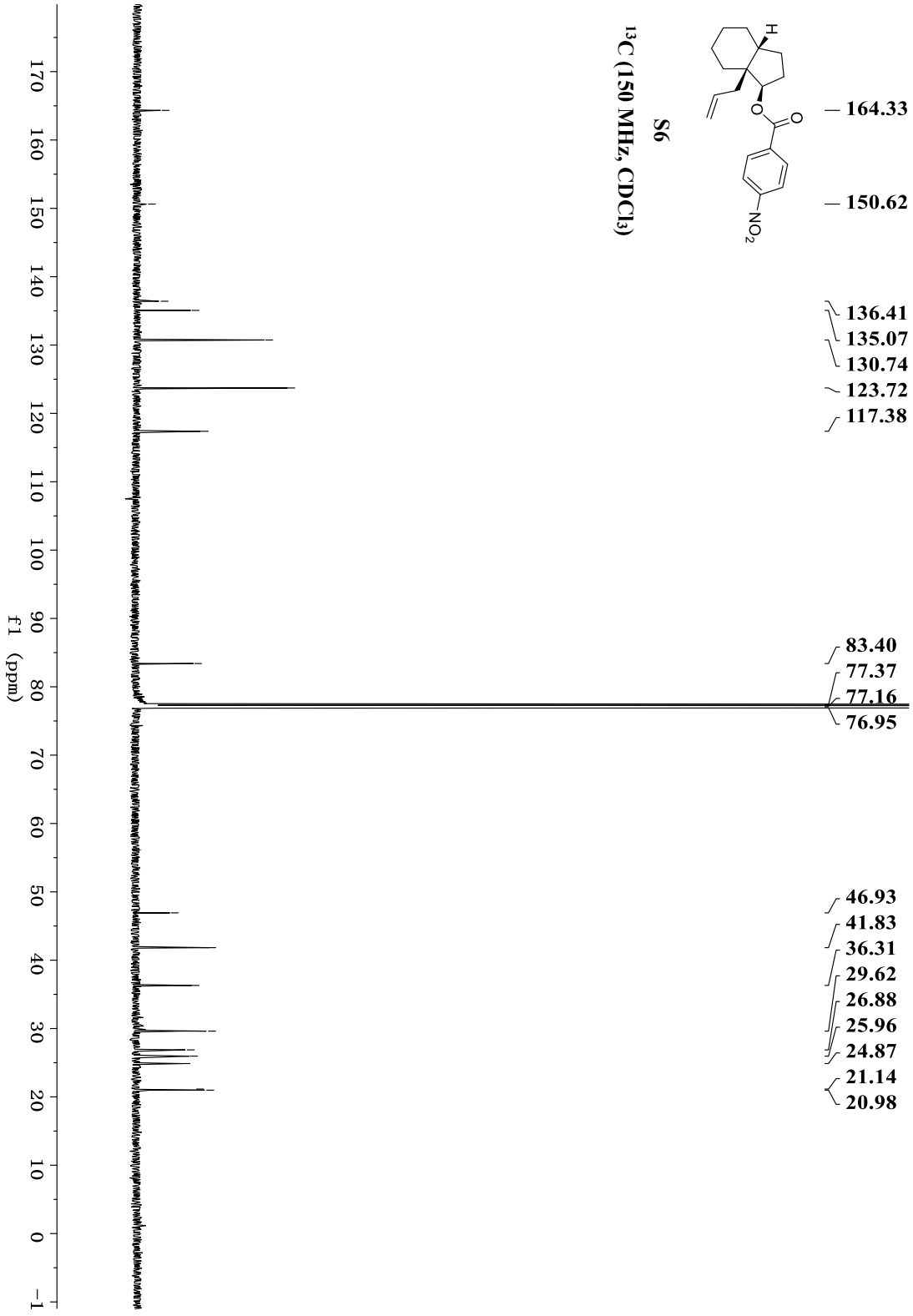

1H NMR (400 MHz, CDCl3)
1.89
OH
H
5.97
5.95
5.94
5.93
5.93
5.91
5.90
5.89
5.88
5.87
5.13
5.13
5.09
5.08
5.06
5.06
3.86
3.86
3.85
3.84
2.42
2.42
2.42
2.41
2.40
2.40
2.39
2.39
2.38
2.37
2.37
2.36
2.18
2.16
2.15
2.13
1.93
1.85
1.82
1.80
1.79
1.64
1.63
1.61
1.56
1.47
1.42
1.37
0.99
0.96
1.01
2.10
1.02
1.08
2.16
1.03
1.07
1.05
9.08
1.05
f1 (ppm)

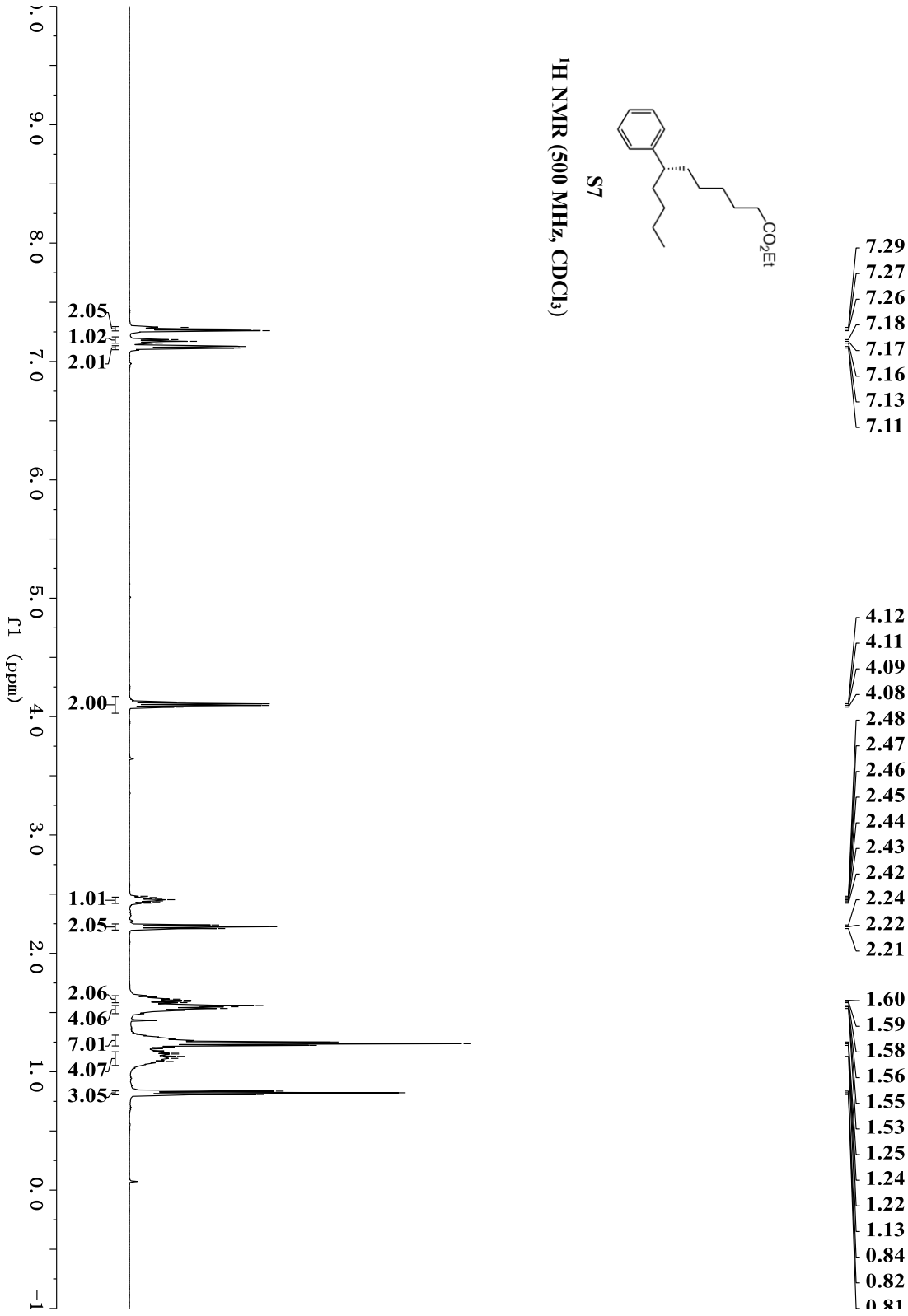

$^{13}$C NMR (100 MHz, CDCl$_3$)
1.89
OH
136.55
116.73
79.69
77.48
77.16
76.84
47.31
40.96
36.12
31.53
27.17
25.90
24.88
21.30
f1 (ppm)


1H NMR (400 MHz, CDCl3)
1.91
f1 (ppm)
1.00
0.98
1.03
1.02
2.03
2.01
2.99
2.01
1.05
1.08
1.08
1.05
4.02
3.05
9.77
9.77
9.76
6.57
6.54
6.54
6.54
6.53
6.51
5.79
5.76
5.73
5.72
5.70
5.70
5.68
5.67
4.65
4.11
4.10
4.09
4.09
3.38
2.42
2.41
2.40
2.40
2.38
2.38
2.30
2.29
2.27
2.22
2.19
2.09
2.08
2.00
1.98
1.96
1.94
1.72
1.69
1.67
1.65
1.63
1.60
1.50
1.49
1.47
1.46


1.91
$^{13}$C NMR (100 MHz, $CDCl_3$)
202.74
145.50
128.89
127.39
121.67
95.72
77.48
77.16
76.84
68.03
55.41
44.36
42.42
33.73
28.12
26.92
24.31
23.23
f1 (ppm)


S6
$^1$H (600 MHz, CDCl$_3$)
f1 (ppm)
1.91
1.94
1.00
1.06
2.06
1.03
1.04
1.07
1.04
1.03
2.03
1.06
6.00
1.01
8.30
8.28
8.19
8.18
5.75
5.72
5.71
5.68
5.15
5.14
4.98
4.97
4.94
2.50
2.48
2.47
2.46
2.38
2.26
2.25
2.24
2.23
2.11
1.87
1.75
1.74
1.72
1.70
1.61
1.58
1.51
1.49
1.45
1.43
1.13
1.12
1.10


S6
$^{13}$C (150 MHz, CDCl$_3$)
H
O
O
NO$_2$
164.33
150.62
136.41
135.07
130.74
123.72
117.38
83.40
77.37
77.16
76.95
46.93
41.83
36.31
29.62
26.88
25.96
24.87
21.14
20.98
f1 (ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−1


S7
$^1$H NMR (500 MHz, CDCl$_3$)
CO$_2$Et
7.29
7.27
7.26
7.18
7.17
7.16
7.13
7.11
4.12
4.11
4.09
4.08
2.48
2.47
2.46
2.45
2.44
2.43
2.42
2.24
2.22
2.21
1.60
1.59
1.58
1.56
1.55
1.53
1.25
1.24
1.22
1.13
0.84
0.82
0.81
2.05
1.02
2.01
2.00
1.01
2.05
2.06
4.06
7.01
4.07
3.05
f1 (ppm)

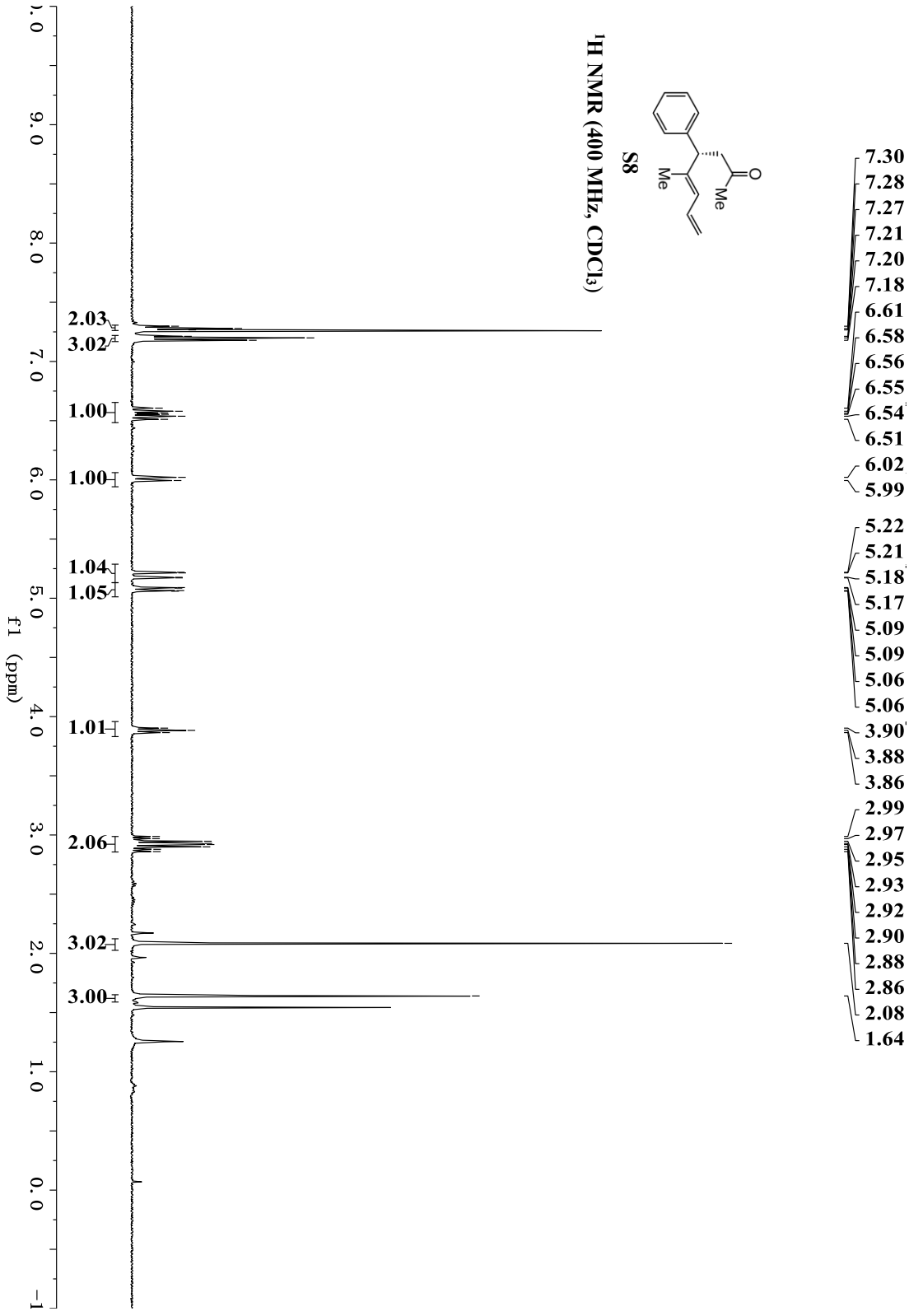
**S7**

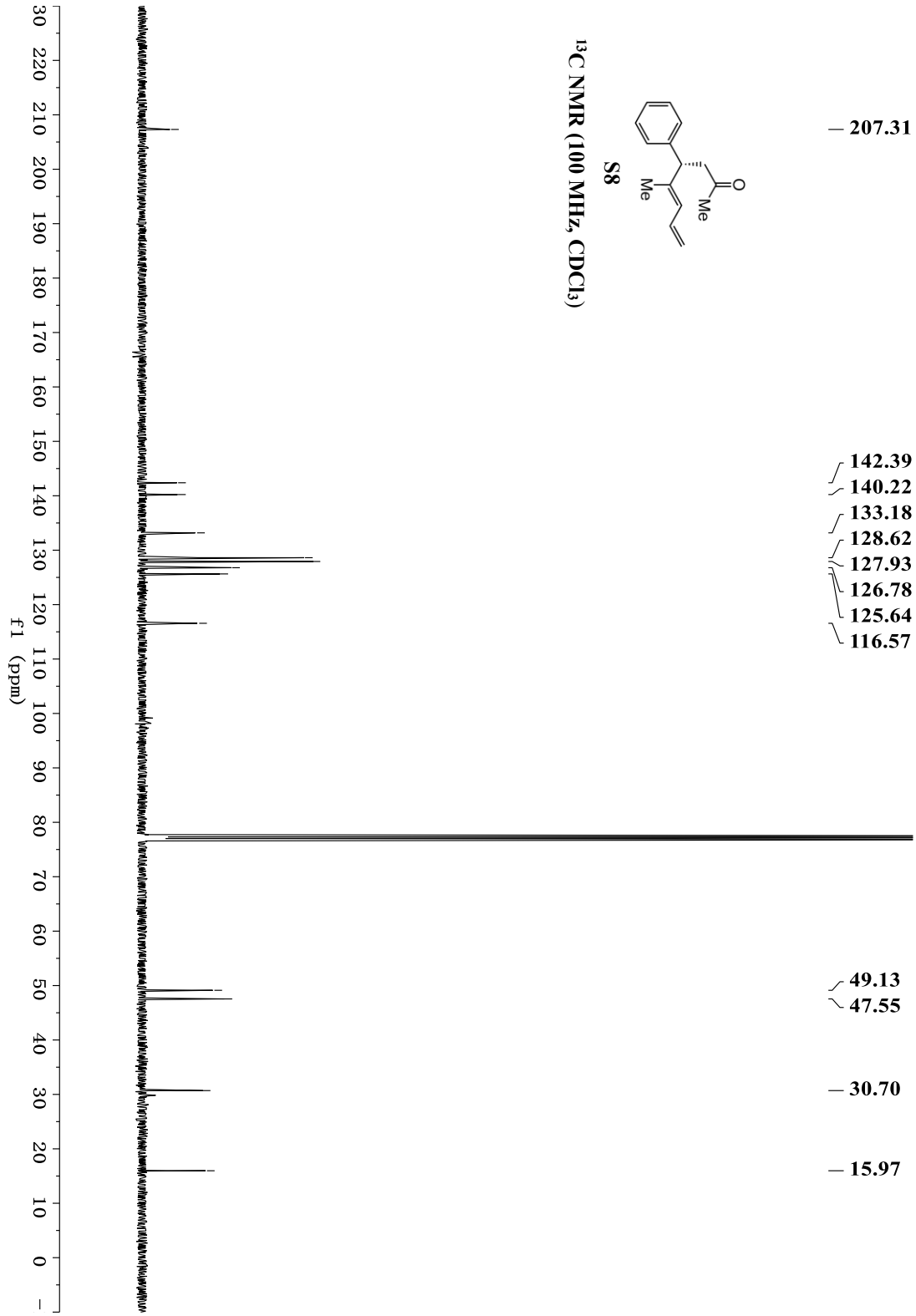
**$^{13}$C NMR (125 MHz, $CDCl_3$)**

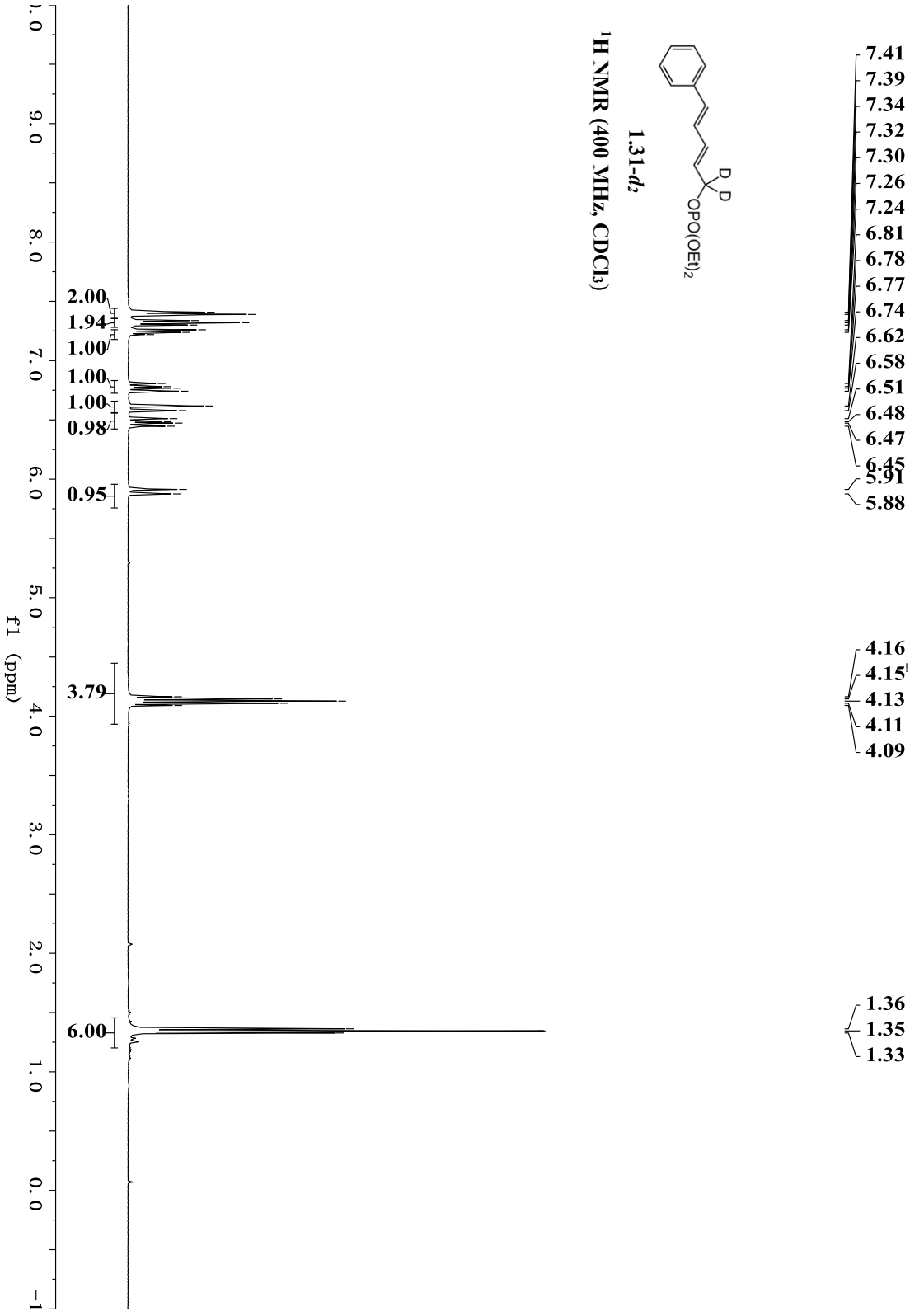


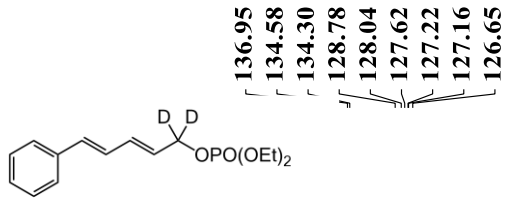

173.99
146.35
128.31
127.78
125.89
77.41
77.16
76.91
60.27
46.14
36.88
36.83
34.49
29.98
29.37
27.39
25.02
22.93
14.39
14.16

f1 (ppm)


¹H NMR (400 MHz, CDCl₃)
S8
Me
Me
O
7.30
7.28
7.27
7.21
7.20
7.18
6.61
6.58
6.56
6.55
6.54
6.51
6.02
5.99
5.22
5.21
5.18
5.17
5.09
5.09
5.06
5.06
3.90
3.88
3.86
2.99
2.97
2.95
2.93
2.92
2.90
2.88
2.86
2.08
1.64
2.03
3.02
1.00
1.00
1.04
1.05
1.01
2.06
3.02
3.00
f1 (ppm)

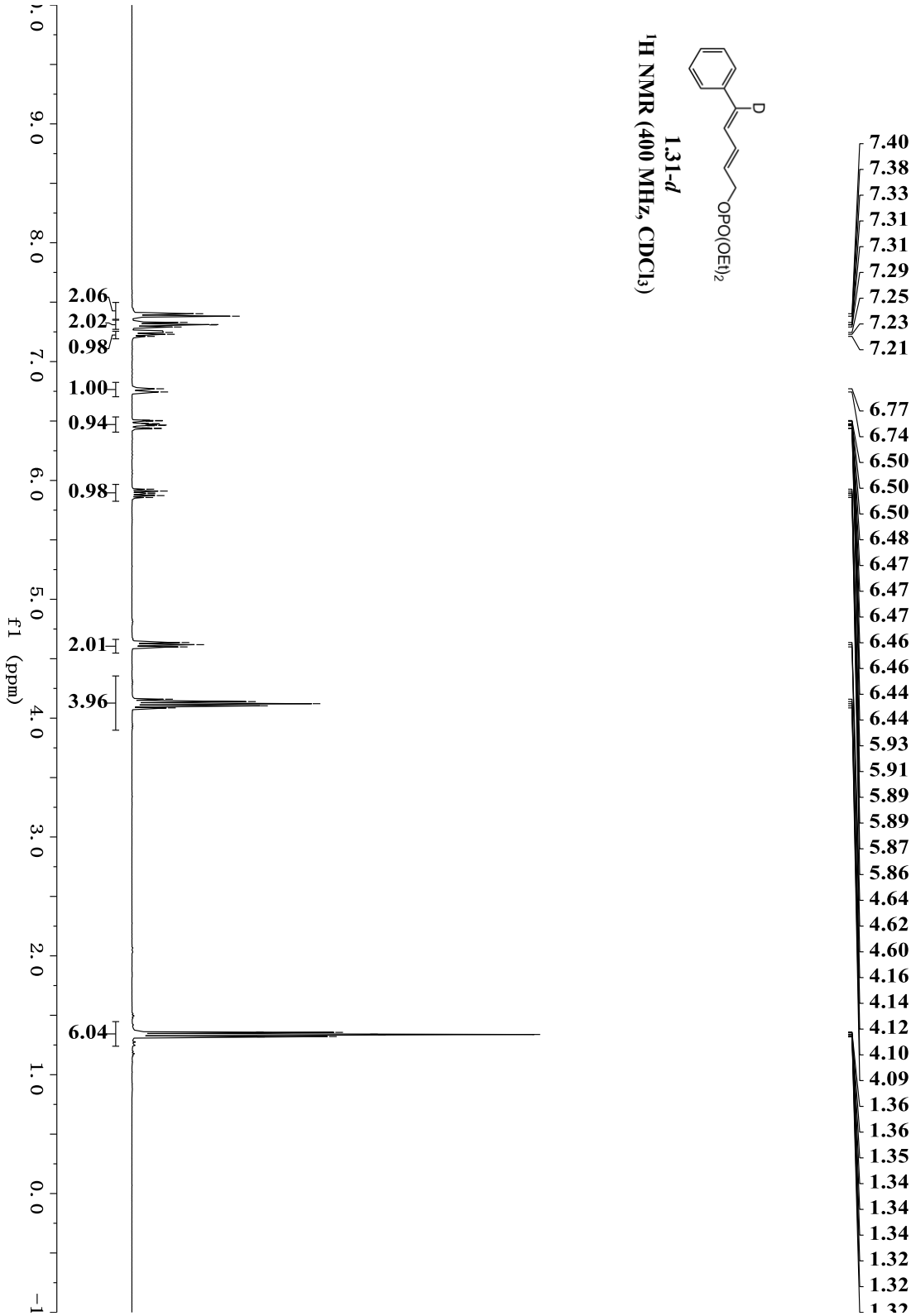

S8
$^{13}$C NMR (100 MHz, CDCl$_3$)
Me
Me
O
207.31
142.39
140.22
133.18
128.62
127.93
126.78
125.64
116.57
49.13
47.55
30.70
15.97
f1 (ppm)

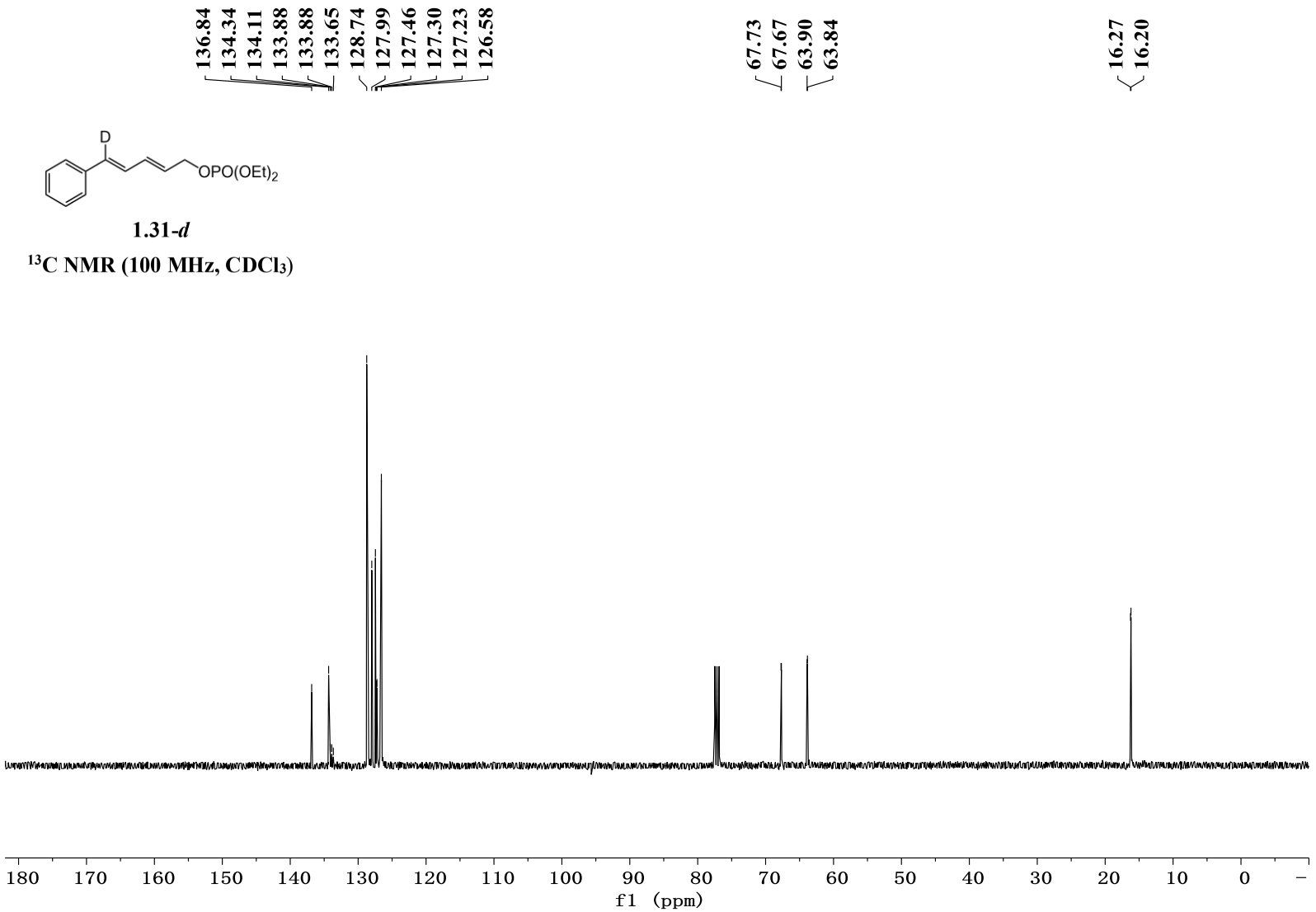

1.31-d2
1H NMR (400 MHz, CDCl3)
D
D
OPO(OEt)2
7.41
7.39
7.34
7.32
7.30
7.26
7.24
6.81
6.78
6.77
6.74
6.62
6.58
6.51
6.48
6.47
6.45
5.91
5.88
4.16
4.15
4.13
4.11
4.09
1.36
1.35
1.33
2.00
1.94
1.00
1.00
1.00
0.98
0.95
3.79
6.00
f1 (ppm)




**1.31-*d*2**

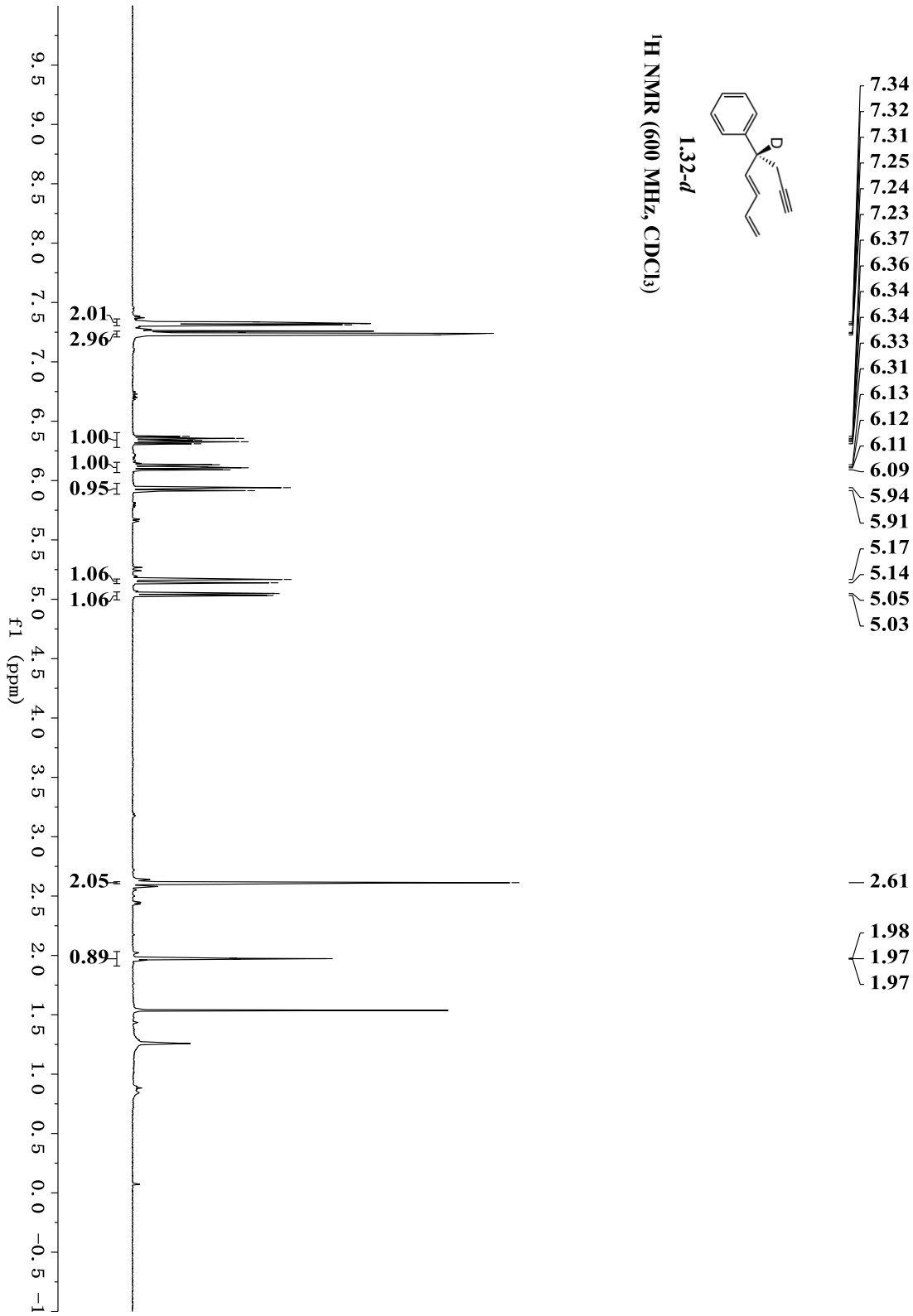
**$^{13}$C NMR (100 MHz, $CDCl_3$)**

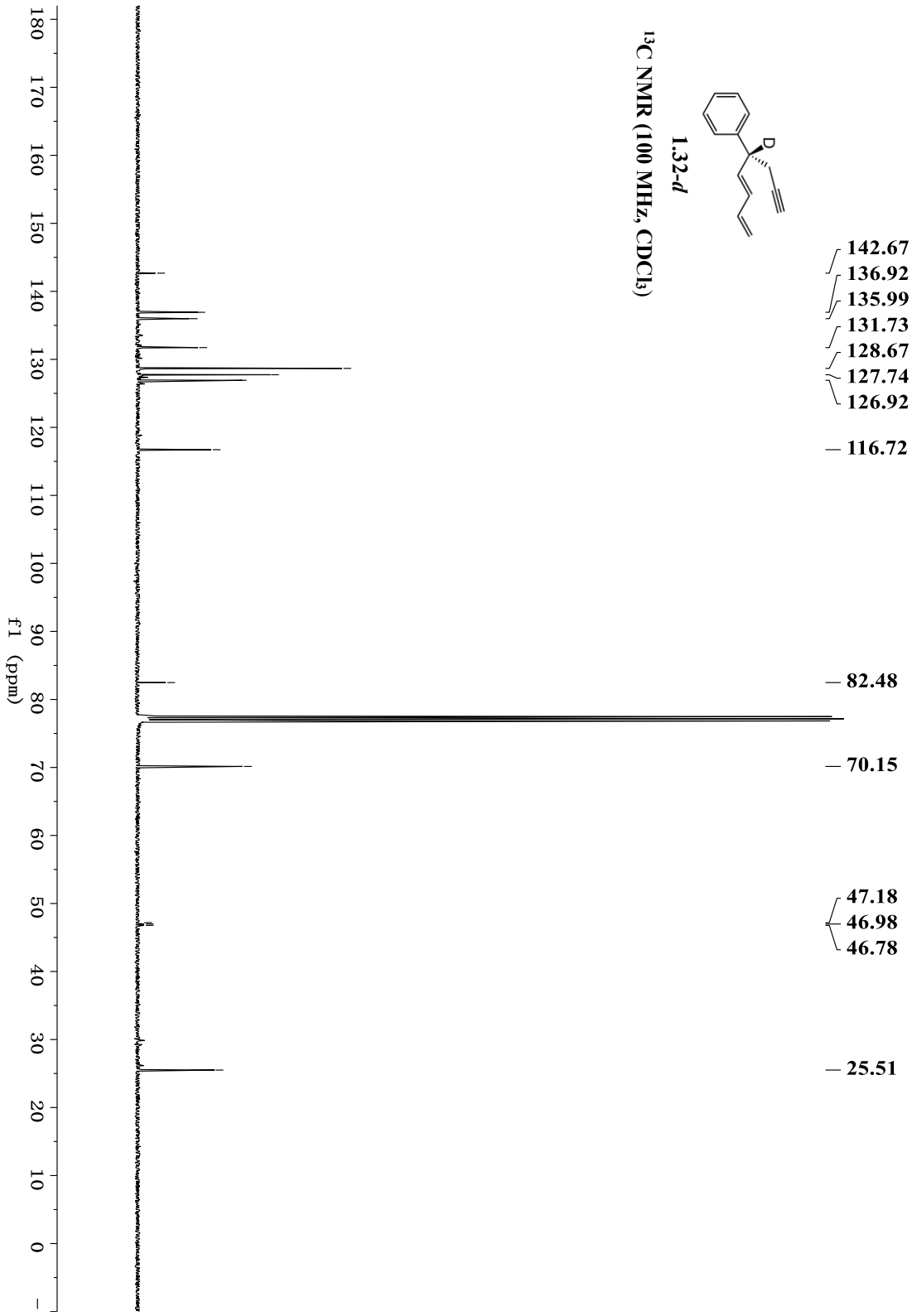

1.31-d
¹H NMR (400 MHz, CDCl₃)
D
OPO(OEt)₂
7.40
7.38
7.33
7.31
7.31
7.29
7.25
7.23
7.21
6.77
6.74
6.50
6.50
6.50
6.48
6.47
6.47
6.47
6.46
6.46
6.44
6.44
5.93
5.91
5.89
5.89
5.87
5.86
4.64
4.62
4.60
4.16
4.14
4.12
4.10
4.09
1.36
1.36
1.35
1.34
1.34
1.34
1.32
1.32
1.32
2.06
2.02
0.98
1.00
0.94
0.98
2.01
3.96
6.04
f1 (ppm)



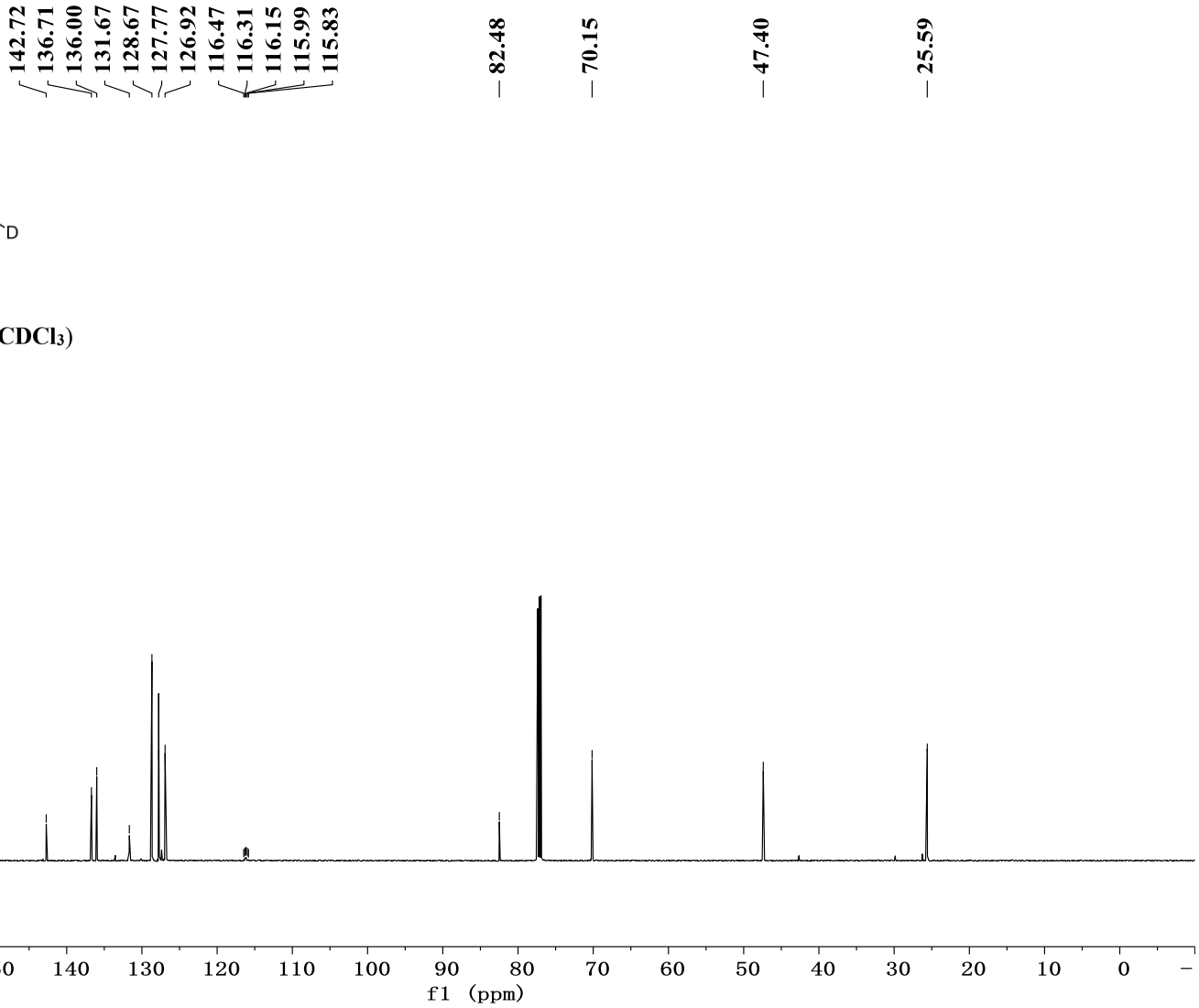

**1.31-*d***

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


1.32-d
1H NMR (600 MHz, CDCl3)
D
7.34
7.32
7.31
7.25
7.24
7.23
6.37
6.36
6.34
6.34
6.33
6.31
6.13
6.12
6.11
6.09
5.94
5.91
5.17
5.14
5.05
5.03
2.61
1.98
1.97
1.97
2.01
2.96
1.00
1.00
0.95
1.06
1.06
2.05
0.89
f1 (ppm)

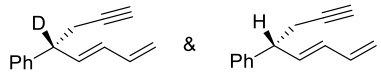

$^{13}$C NMR (100 MHz, CDCl$_3$)
1.32-*d*
D
142.67
136.92
135.99
131.73
128.67
127.74
126.92
116.72
82.48
70.15
47.18
46.98
46.78
25.51
f1 (ppm)

1.32-$d_2$
$^1$H NMR (600 MHz, CDCl$_3$)
7.34
7.32
7.31
7.25
7.24
7.23
6.34
6.32
6.14
6.12
6.11
6.09
5.95
5.94
5.93
5.91
3.61
3.60
3.59
3.57
2.63
2.63
2.62
2.62
2.62
2.61
1.98
1.98
1.97
2.06
3.05
1.00
1.03
1.06
1.05
2.01
0.98
f1 (ppm)



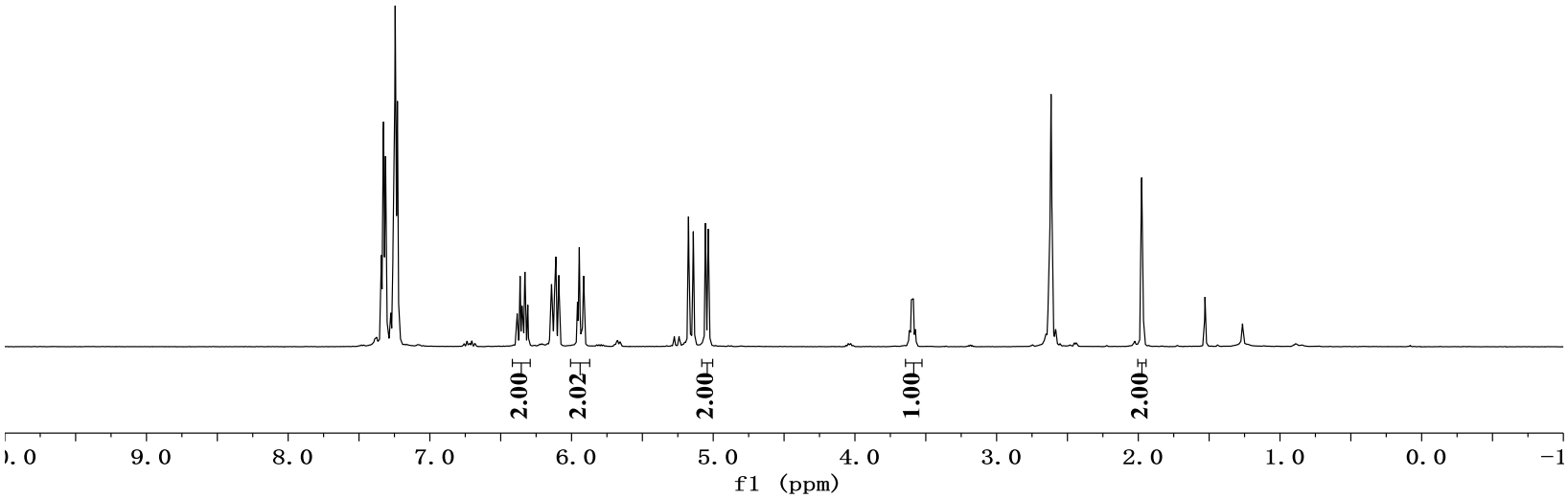

**1.32-*d*$_2$**

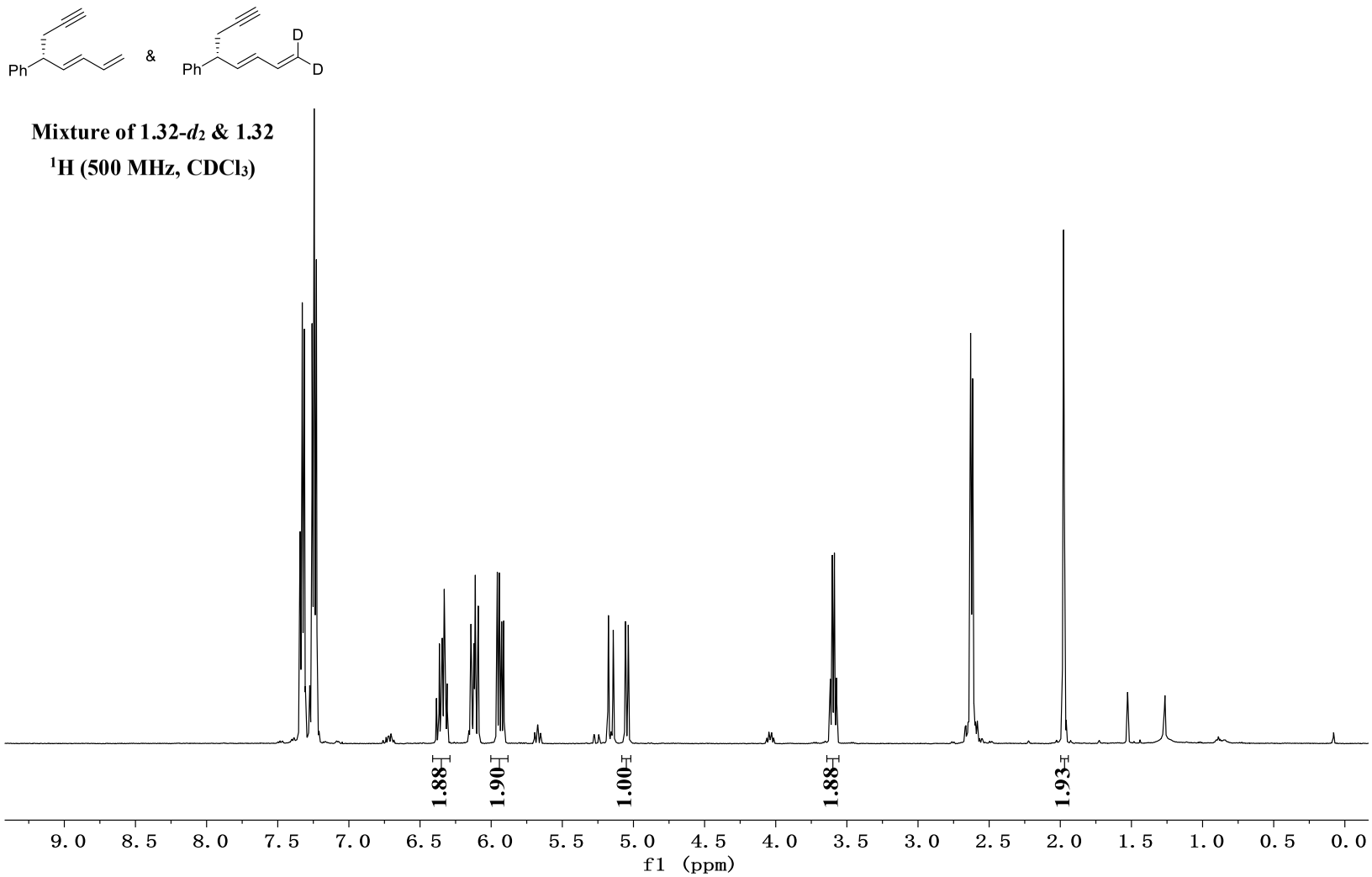
**$^{13}$C NMR (150 MHz, $CDCl_3$)**




**Mixture of 1.32-*d* & 1.32**

**$^1$H (500 MHz, $CDCl_3$)**




Ph
&
Ph
D
D
Mixture of 1.32-$d_2$ & 1.32
$^1$H (500 MHz, $CDCl_3$)
1.88
1.90
1.00
1.88
1.93
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
f1 (ppm)

# CHAPTER 2

# NHC–Copper–Hydride-Catalyzed Enantioselective Processes with Allenyl Boronates and its Application in Natural Product Synthesis

## 2.1 Introduction

Catalytic enantioselective synthesis of versatile organic compounds is critical to the development of chemical synthesis and medicine. Especially important are transformations that combine simple building blocks to form complex molecules selectively. This type of transformation is generally referred to as multicomponent process, a subject extentively investigated in the Hoveyda group.[1] A rapidly emerging class of multicomponent reactions is one by which an alkene or allene is first converted to an organocopper intermediate, which then react in situ with an electrophile.[2] Early studies were focused on processes catalyzed by a Cu–B(pin) complex, regio- and enantioselective addition of which to an alkene

(1) Hoveyda, A. H.; Koh, M. J.; Lee, K.; Lee, J. in *Organic Reactions*; Denmark, S. E. Eds.; Wiley–VCH, **2020**, pp. 959–1055.

(2) (a) Shimizu, Y.; Kanai, M. *Tetrahedron Lett.* **2014**, *55*, 3727–3737. (b) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Tetrahedron* **2015**, *71*, 2183–2197.

or allene was followed by protonolysis,[3] or addition to a C-[4] or N-based[5] electrophile. A parallel set of protocols, involving similar types of substrates, are Cu–H-catalyzed transformations[6,7]. The major distinction between the two processes is that the products generated by the Cu–B(pin)-catalyzed transformations contain a versatile C–B bond, which can be further functionalized to access a variety of desirable derivatives. A case in point is a Cu–B(pin)-catalyzed process involving the combination of monosubstituted allene and allylic phosphate (Scheme 2.1). Organocopper **2.1** is generated first followed by its reaction with an allylic phosphate to afford **2.2**, a compound that contains a valuable

(3) (a) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160–3161. (b) Lee, Y.; Jung, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235. (c) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079–7082. (d) Jang, H.; Jung, B.; Hoveyda, A. H. *Org. Lett.* **2014**, *16*, 4658–4661.

(4) (a) Meng, F.; Jang, H.; Jung, B.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 5046–5051. (b) Meng, F., Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 11304–11307. (c) Lee, J.; Radomkit, S.; Torker, S.; del Pozo, J.; Hoveyda, A. H. *Nat. Chem.* **2018**, *10*, 99–108. (d) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367–374. (e) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. *Nature* **2016**, *537*, 387–393. (f) Yeung, K.; Ruscoe, R. E.; Rae, J.; Pulis, A. P.; Procter, D. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 11912–11916.

(5) (a) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934–4937. (b) Kato, K.; Hirano, K.; Miura, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 14400–14404.

(6) For representative hydro-amino addition, see: (a) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed*. **2013**, *52*, 10830–10834. (b) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746–15749.

(7) For representative Cu–H-catalyzed reactions involving carbon-based nucleophiles, see: (a) Wang, Y. M.; Bruno, N. C.; Placeres, À. L.; Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 10524–10527. (b) Yang, Y.; Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 9787–9790. (c) Wang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5024–5027. (d) Bandar, J. S.; Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, 138, 5821–5824. (e) Yang, Y.; Perry, I. B.; Liu, P.; Buchwald, S. L. *Science* **2016,** *353*, 144–150. (f) Yu, S.; Sang, H. L.; Ge, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 15896–15900. (g) Gui, Y. Y.; Hu, N.; Chen, X. W.; Liao, L. L.; Ju, T.; Ye, J. H.; Zhang, Z.; Li, J.; Yu, D. G. *J. Am. Chem. Soc.* **2017**, *139*, 17011–17014.

stereochemically defined trisubstituted alkenyl–B(pin). The utility of this approach was demonstrated by gram-scale total syntheses of bioactive natural products rottnestol and herboxidiene.[3d]

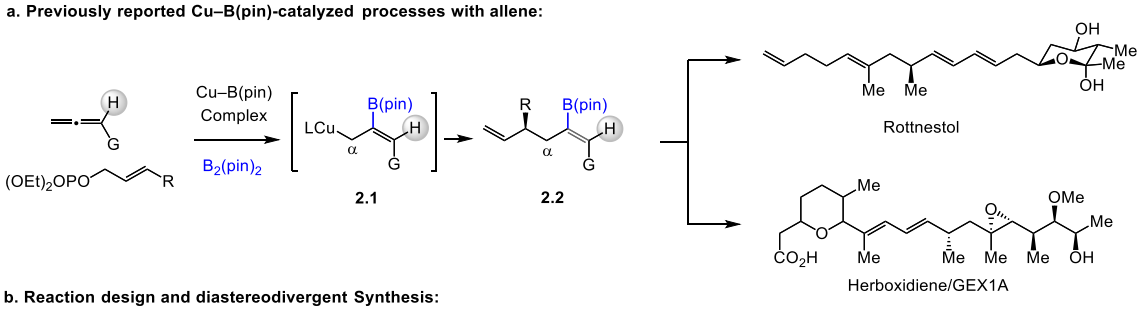
A related, but considerably less developed strategy for the synthesis of multifunctional organoboron compounds would be facilitated by a Cu–H catalyst with a readily available organoboron compound. The process would involve the initial conversion of an allenyl–B(pin) compound to organocopper intermediate **2.3-*E***, which may isomerize to the more stable *Z* isomer, and then react with an allylic phosphate to afford dienyl and boron-containing product **2.4**. In contrast to the compound generated by the previously developed Cu–B(pin)-catalyzed transformation, in which the C–B bond is prone to branched functionalizations, the boronate in **2.4** can be easily used to implement linear chain extension.

For instance, catalytic cross-metathesis could transform the vinyl moiety to an allylic phosphate, which can be subjected to another enantioselective allylic substitution to furnish either 1,6-diene **2.6** or its diastereomer **2.6'**, depending on the catalyst enantiomer used. However, it would be required that the organocopper intermediate reacts with the allylic phosphate with interference by the Lewis acidic boron center. The alkenyl–B(pin) moiety may be converted to another allylic phosphate **2.7**/**2.7'** through a homologation/oxidation/phosphorylation sequence. A third catalyst-controlled allylic substitution would

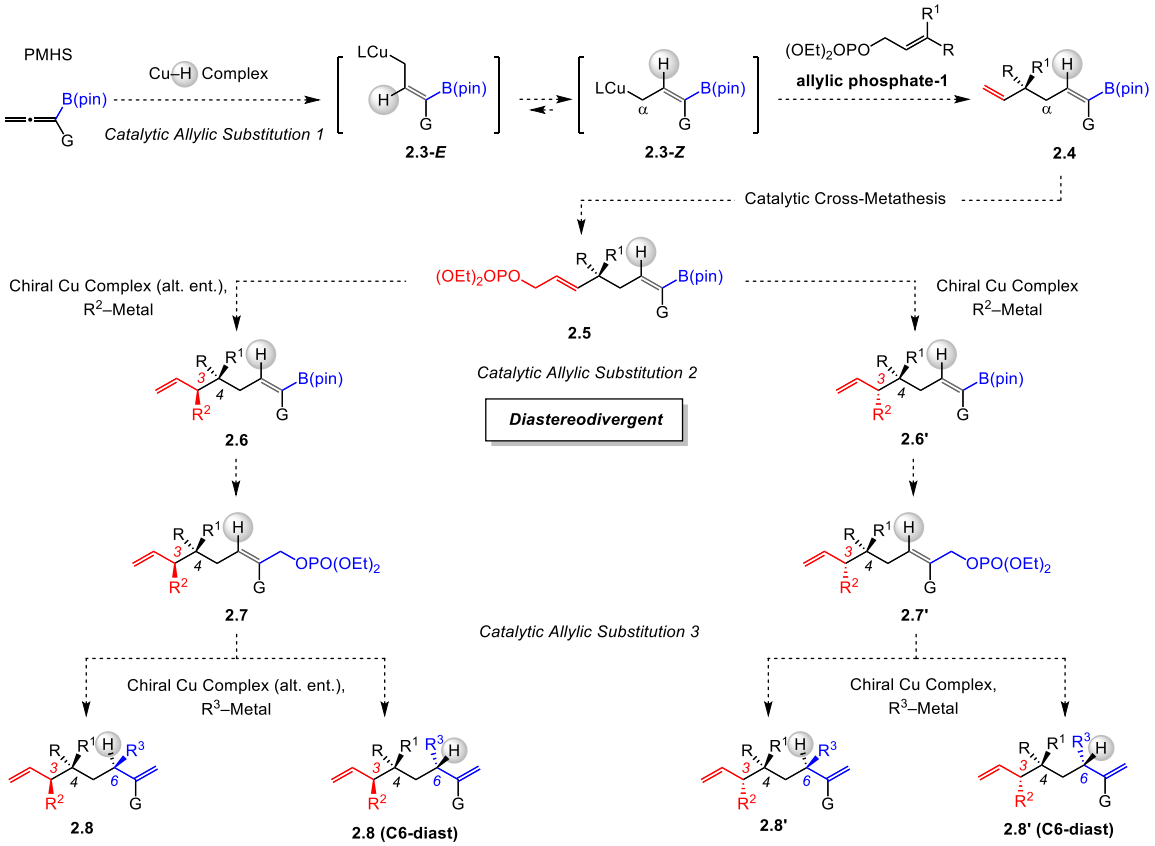
then furnish 1,7-diene **2.8** or its diastereomers. By performing the same sequence with the opposite catalyst enantiomer, the remaining four diastereomers may be obtained.

***Scheme 2.1.*** Related Previous Advances and Aim of this Study

**a. Previously reported Cu–B(pin)-catalyzed processes with allene:**



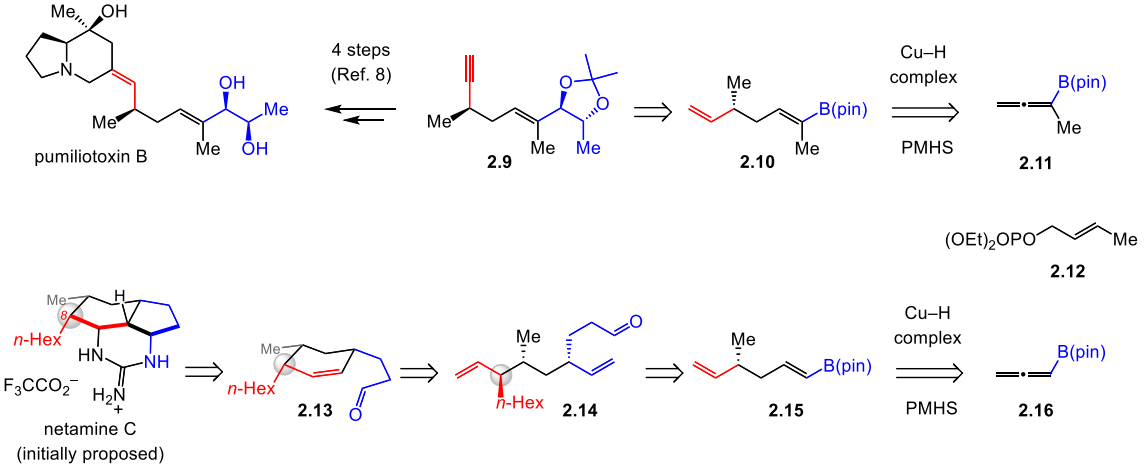

**b. Reaction design and diastereodivergent Synthesis:**




The proposed strategy would be applicable to enantioselective synthesis of a number of different natural products and their diastereomers. We surmised that the combination of allenyl–B(pin) **2.11** and

allylic phosphate **2.12** in the Cu–H-catalyzed process could deliver alkenyl–B(pin) **2.10**, which might then be subjected to diastereoselective cross-coupling. The subsequent conversion of the alkene to an alkyne would afford 1,5-enyne **2.9**, a compound used previously in the total synthesis[8] of anti-malarial, cardiotonic natural product pumiliotoxin B.[9] Reaction of the same allylic phosphate (**2.12**), but this time with a monosubstituted allenyl–B(pin) **2.16**, would furnish alkenyl–B(pin) **2.15**. Subsequent modifications following the sequence outlined in Scheme 2.1b would deliver 1,7-dienyl aldehyde **2.14**, which may be transformed to cyclohexene-containing aldehyde **2.13** by catalytic ring-closing metathesis en route to the first enantioselective total synthesis of naturally occurring anti-tumor agent,

***Scheme 2.2.*** Synthetic Utility of the Multicomponent Process




(8) Lin, N. H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062−9072.

(9) Daly, J. W.; McNeal, E. T.; Gusovsky, F. *Biochim. Biophys. Acta, Mol. Cell Res.* **1987**, *930*, 470−474.

netamine C (Scheme 2.2).[10] It is worth noting that the stereochemistry at C8 of this compound was under debate when we decided to undertake the studies described below.[11] We reasoned that because our approach would allow us to prepare either netamine C stereoisomer, we would be able to confirm the correct stereochemical identity of the natural product.

## 2.2 Background

Multicomponent reactions involving a Cu–B(pin) have been developed by a large number of research groups.[3,4,5] However, transformations merging Cu–H addition to unsaturated compounds and allylic substitutions are uncommon. Even more scarce are those involving a boron-containing reagent, generating versatile organoboron products.

### 2.2.1 Cu–H-Catalyzed enantioselective allylic substitution involving non-boryl, hydrocarbon-based organocopper intermediates

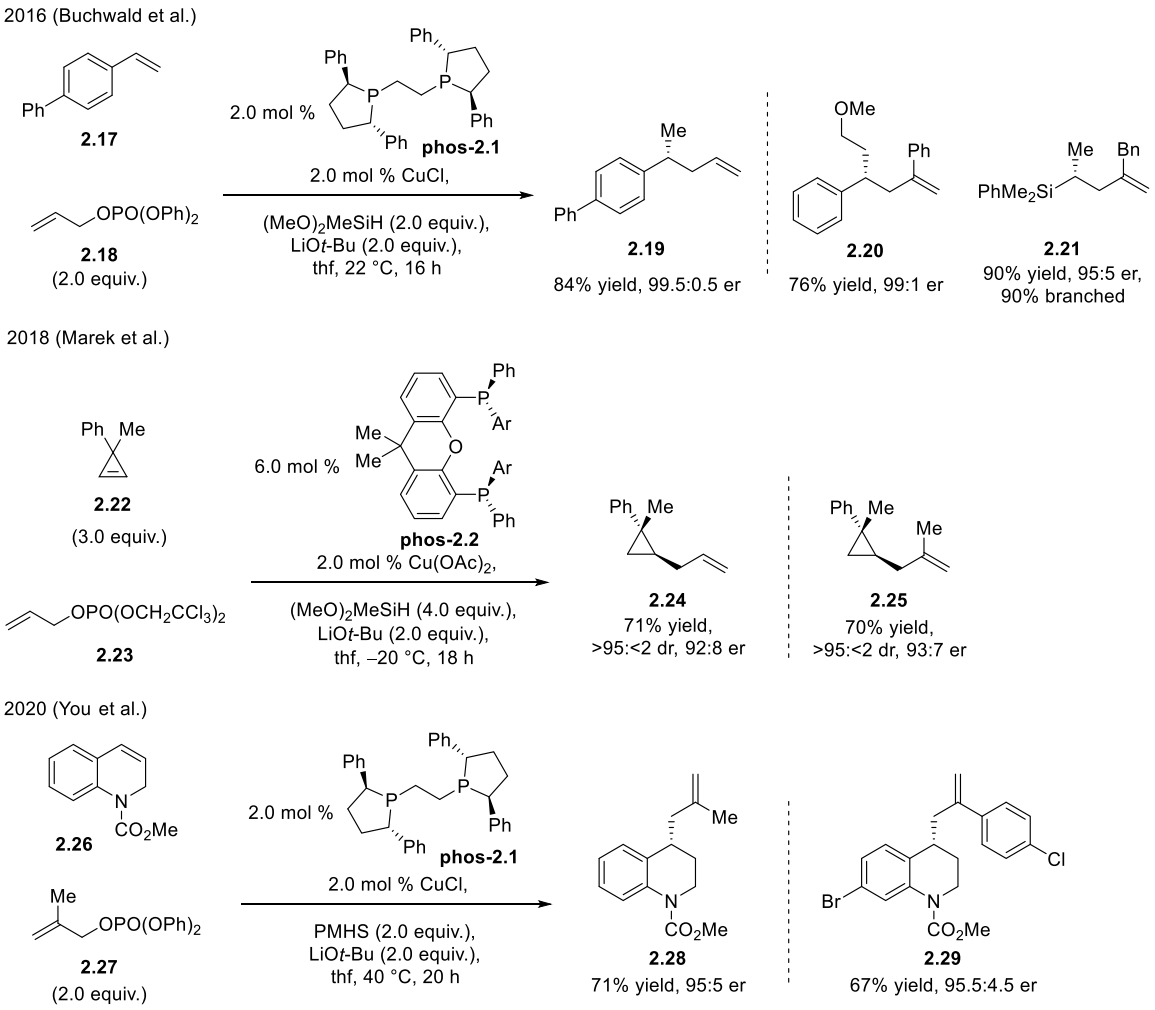
In 2016, the Buchwald group reported the first example of an enantioselective Cu–H addition to unsaturated compounds followed by allylic substitution (Scheme 2.3).[7c] Reactions promoted by chiral ligand **phos-2.1** were efficient as well as highly regio- and enantioselective. A 1,2-disubstituted aryl

(10) Sorek, H.; Rudi, A.; Gueta, S.; Reyes, F.; Martin, M. J.; Aknin, M.; Gaydou, E.; Vacelet, J.; Kashman, Y. *Tetrahedron* **2006**, *62*, 8838−8843.

(11) Yu, M.; Pochapsky, S. S.; Snider, B. B. *J. Org. Chem.* **2008**, *73*, 9065−9074.

olefin was found to be suitable substrates, furnishing 1,1-disubstituted alkene **2.20** in 76% yield and 99:1 er. Although the majority of the substrates tested were styrenyl, one example of an alkenyl silane starting material was reported to afford **2.21** in 90% yield, 90% branched selectivity and 95:5 er. Later in 2018, Marek and coworkers showed that the same process can be carried out with cyclopropenes.[12]

***Scheme 2.3.*** Cu–H-Catalyzed Multicomponent Process Involving Addition to Olefins and Allylic Substitution




(12) Sommer, H.; Marek, I. *Chem. Sci.,* **2018**, *9*, 6503–6508.

Disubstituted cyclopropene **2.22** was converted to trisubstituted cyclopropane **2.24** in 71% yield, >98:2 dr, and 92:8 er through a transformation catalyzed by phosphine–Cu complex derived from **phos-2.2**. You *et al.* have extended this approach to transformations involving 1,2-dihydroquionolines, efficient and selective process that were carried out under similar conditions as developed by the Buchwald group (Scheme 2.3).[13]

Alkynes have also been used in Cu–H multicomponent processes. In 2017, Xiong and coworkers outline a process that entails Cu–H addition to an alkyne affording Cu–allyl species that undergoes enantioselective allylic substitution to furnish 1,4-diene **2.33** (Scheme 2.4).[14] Notably, this latter set of transformations were promoted by an NHC–Cu catalyst generated in situ from sulfonate-containing **imid-2.1**. Although the reactions were efficient and enantioselective, aryl-substituted alkynes and aryl-substituted allylic phosphates were required for high regio- and enantioselectivity (transformation of an alkyl-substituted substrate afforded 1,4-diene **2.35** in 76.5:23.5 er); these factors severely limit the applicability of the method. Furthermore, reactions involving disubstituted allylic phosphates did not lead to any desired product. Although an explanation is not given, in all likelihood competitive Cu–H reduction of the less substituted allylic phosphate is far more facile than addition to an alkyne.

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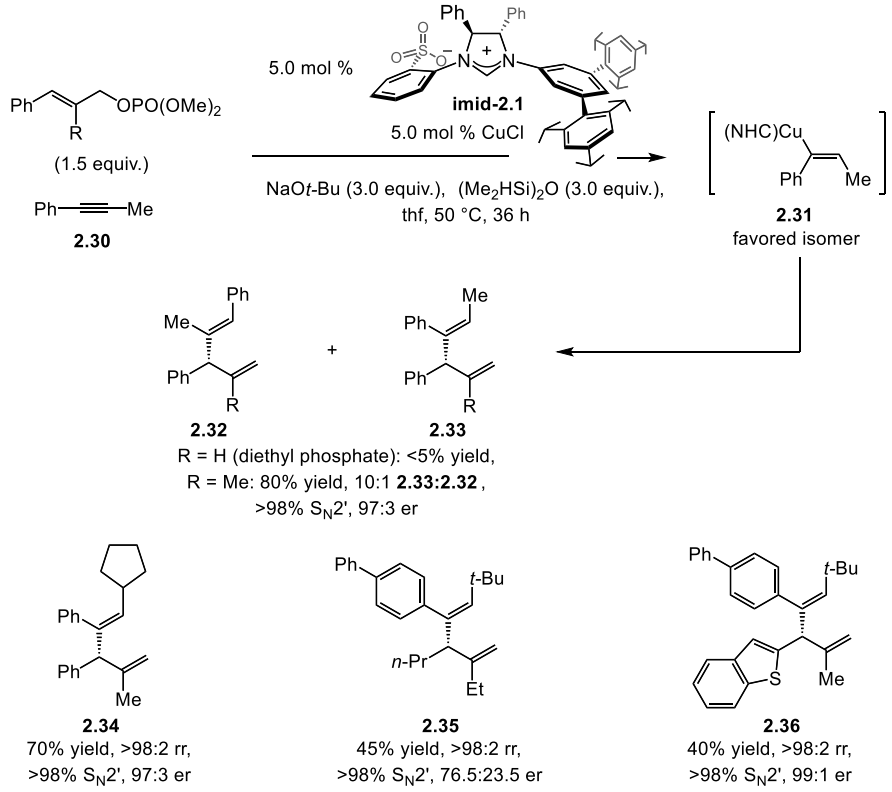
(13) Xu-Xu, Q. -F.; Zhang, X.; You, S. -L. *Org. Lett.* **2020**, *22*, 1530−1534.

(14) Xu, G.; Zhao, H.; Fu, B.; Cang, A.; Zhang, G.; Zhang, Q.; Xiong, T.; Zhang, Q. *Angew. Chem. Int. Ed.* **2017**, *56*, 13130 –13134.

***Scheme 2.4.*** Cu–H Catalyzed Multicomponent Process Involving Addition to Alkynes and Allylic Substitution

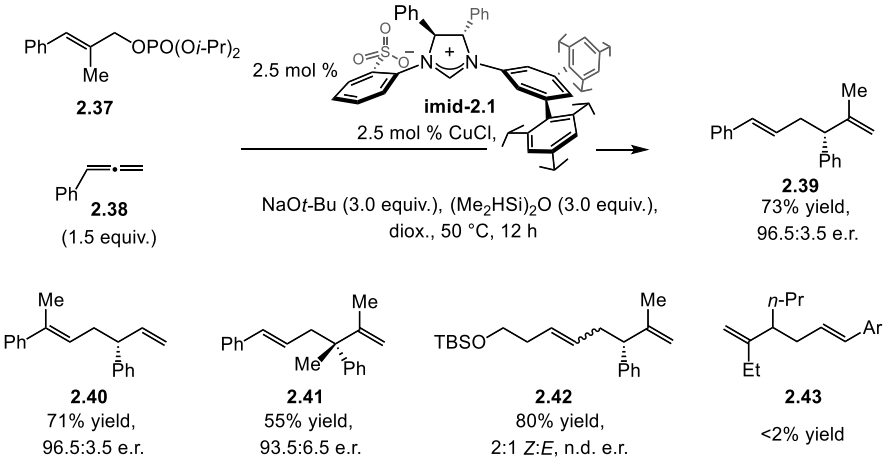



In 2019, during the final stages of investigations described below, Xiong and coworkers reported another Cu–H-catalyzed multicomponent strategy involving initial addition to an allene (Scheme 2.5).[15] As before, sulfonate imidazolinium salt **imid-2.1** was found to be the optimal NHC precursor. Di- and trisubstituted alkene-containing allylic phosphates were thus converted to the desired products in high efficiency and enantioselectivity. Mono- as well as 1,1-disubstituted allenes proved to be suitable substrates, affording stereochemically defined disubstituted or trisubstituted olefin respectively (e.g., **2.39** and **2.40**). Products containing a quaternary stereogenic center could also be synthesized (e.g., **2.41**).

(15) Xu, G.; Fu, B.; Zhao, H.; Li, Y.; Zhang, G.; Wang, Y.; Xiong, T.; Zhang, Q. *Chem. Sci.,* **2019**, *10*, 1802–1806.

Nevertheless, transformations with alkyl-substituted allenes generated nearly equal mixtures of *E* and *Z* isomers (e.g., 1,5-diene **2.42** in 2:1 *Z:E* selectivity), and when an alkyl-substituted allylic phosphate was used, none of the desired product could be detected (e.g., <2% **2.43**). As noted above, these are serious limitations that render these protocols of minimal use for synthesis of bioactive entities.

***Scheme 2.5.*** Cu–H Catalyzed Multicomponent Process Involving Addtition to Allenes and Allylic Substitution

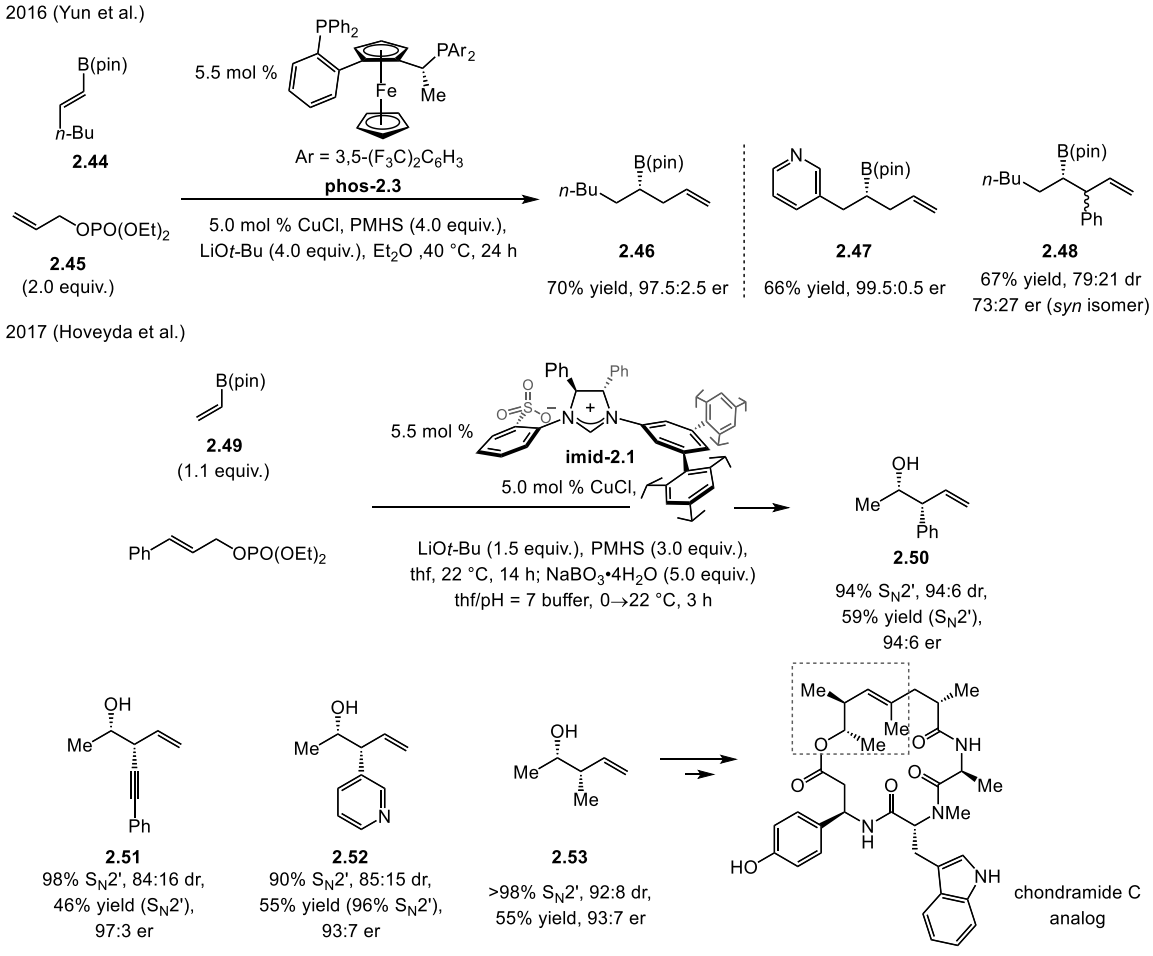



## 2.2.2 Cu–H-Catalyzed enantioselective allylic substitutions involving a boron-containing organocopper intermediates

As was briefly discussed (see Section 2.1), an alternative way to prepare boron-containing compounds is by a process that entails initial Cu–H addition to an unsaturated substrated that already contains a boryl moiety. For such a strategy to be effective, not only must high levels of $S_N2'$ selectivity and enantioselectivity be attainable, the Cu–alkoxide complex must react preferentially with a silyl hydride reagent to produce the desired Cu–H species faster than it would react with the starting

organoboron compound. What is more, the Cu–H complex must add chemoselectively to the unsaturated organoboron compound more readily than the allylic phosphate substrate to generate an unsaturated hydrocarbon byproduct. It is perhaps owing to these multiple challenges that this type of transformation has been much less developed. In fact, at the time we began our studies, there were only a pair of related examples reported.

***Scheme 2.6.*** Cu–H-Catalyzed Multicomponent Process Involving Addition to Boron-Containing Alkenes




In the first case, the Yun group developed a strategy entailing the addition of a Cu–H species to an alkenyl–B(pin) compound, followed by allylic substitution to deliver secondary boronic ester **2.46**

enantioselectivity (Scheme 2.6).[16] Aryl- and alkyl-substituted alkenyl–B(pin) were found to react efficiently and selectively with monosubstituted allylic phosphates (e.g., **2.47**). Nevertheless, when a disubstituted allylic phosphate was used, the transformation was less enantioselective and the secondary boronic ester **2.48** was formed in 79:21 dr.

In 2017, the Hoveyda group disclosed a related set of transformations catalyzed by a sulfonate NHC–Cu complex (Scheme 2.6),[17] and involving a combination of commercially available vinyl–B(pin) (**2.49**) and a disubstituted allylic phosphate. Reactions were efficient and highly diastereo- and enantioselective, and were shown to proceed readily in the presence of a range of polar/Lewis basic functional units, including a pyridinyl, an alkenyl, or an alkynyl unit (e.g., **2.51, 2.52**). Methyl-substituted allylic phosphate was used to prepare a key fragment utilized formerly for enantioselective synthesis of a biologically active analog of natural product chondramide C.

## 2.3 NHC–Copper–Hydride-Catalyzed Multicomponent Enantioselective Reactions Involving Allenyl Boronates

### 2.3.1 Key problems to be addressed

(16) Han, J. T.; Jang, W. J.; Kim, N.; Yun, J. *J. Am. Chem. Soc.* **2016**, *138*, 15146−15149.

(17) Lee, J.; Torker, S.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2017**, *56*, 821−826.

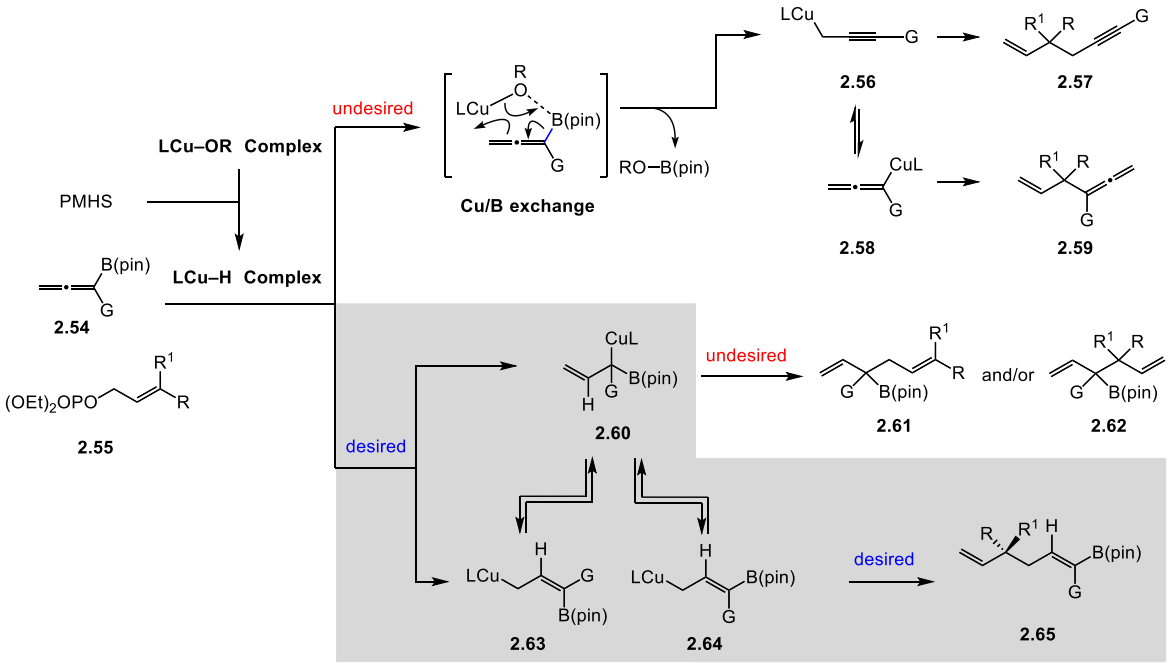
Multicomponent processes entailing a Cu–H catalyst, an allenyl–B(pin) and an allylic phosphate would deliver products that bear an alkenyl–B(pin), which is more easily modifiable than an alkyl–B(pin), such as the products generated in one of the aforementioned methods (see Scheme 2.6).

The proposed plan posed several distinct challenges (Scheme 2.7a). The first involved chemoselective addition of a Cu–H complex to an allene as opposed to it participating in a B/Cu exchange. Allenyl–B(pin) compounds have indeed been widely utilized as precursors for in situ formation of allenyl–Cu or propargyl–Cu intermediates.[18] The Cu/B exchange involving an allenyl–B(pin) compound is facile probably owing to the involvement of a six-membered ring transition state (Scheme 2.7). This would not be the case with an alkenyl–B(pin) species. If Cu/B exchange were to occur, propargyl–Cu **2.56** would be generated, and the ensuing allylic substitution would afford enyne byproduct **2.57**. Alternatively, propargyl–Cu intermediate **2.56** could isomerize to allenyl–Cu species **2.58** (particularly favored when G = H), affording undesired allene **2.59**. In the desired pathway, Cu–H would preferentially add to the allenyl–B(pin) compound prior to transmetalation to generate allyl–Cu species **2.60**, **2.63**, or **2.64**. These three intermediates can interconvert, and if allyl–Cu **2.60** is favored,

(18) (a) Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638−6639. (b) Wei, X.-F.; Shimizu, Y.; Kanai, M. *ACS Cent. Sci*. **2016**, *2*, 21–26. (c) Smith, M. W.; Zhou, Z.; Gao, A. X.; Shimbayashi, T.; Snyder, S. A. *Org. Lett*. **2017**, *19*, 1004−1007.

alkyl–B(pin) byproducts **2.61** or **2.62** would be formed. Only when allyl–Cu **2.64** is obtained preferentially can allylic substitution furnish the desired alkenyl–B(pin) **2.65**.

***Scheme 2.7.*** Various Selectivity Challenges

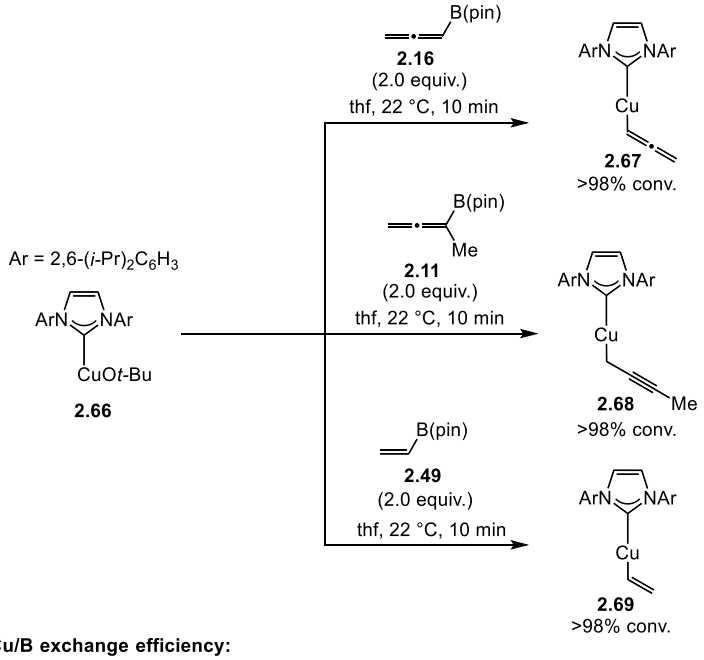



To probe feasibility and to study the efficiency of the Cu/B exchange step with different organoboron reagents, we carried out experiments with stoichiometric amounts of a Cu-based complex (Scheme 2.8). We probed the facility of transmetalation of NHC–Cu-complex **2.66** with an alkenyl–B(pin) and an allenyl–B(pin) compound. In either case, Cu/B exchange proceeded to >98% conversion within just 10 minutes. An important mechanistic point is that, depending on the substituents on the allenyl–B(pin) compounds, the identity of the most stable organocopper intermediate changes (Scheme 2.8a). In the case of a monosubstituted allenyl–B(pin) **(2.16),** it is allenyl–Cu **2.67** that is generated exclusively, whereas when there is a methyl substituent at the carbon that is attached to the

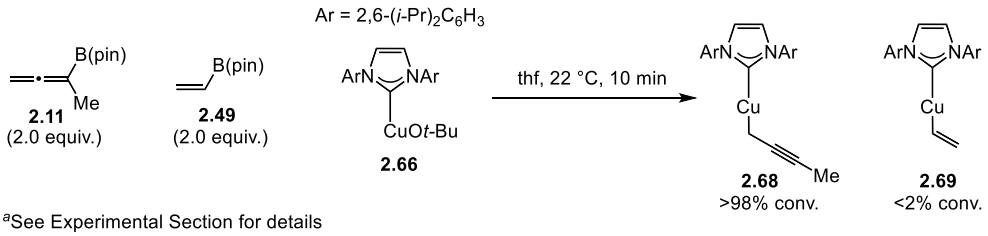
boryl unit (**2.17**), the favored product is propargyl–Cu **2.68**. When an equal mixture of allenyl–B(pin) **2.11** and alkenyl–B(pin) **2.49** were subjected to the same conditions, only allenyl–B(pin) reacted (Scheme 2.8b).

***Scheme 2.8.*** The Efficiency of Cu/B Exchange[a]

**a. Transmetalation of allenyl–B(pin) and alkenyl–B(pin):**




**b. Relative Cu/B exchange efficiency:**



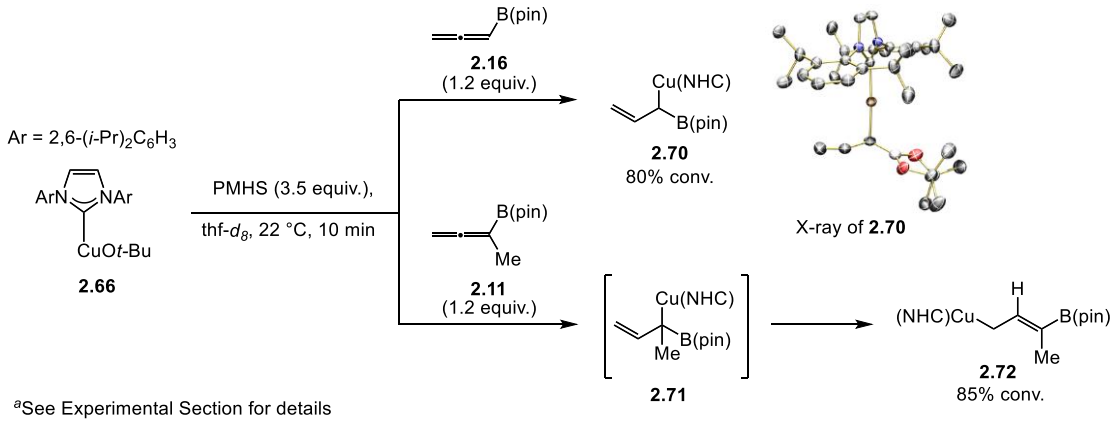

[a]See Experimental Section for details

To investigate the relative rate of the Cu–H addition compared to Cu/B exchange, we treated a sample of monosubstituted allenyl–B(pin) **2.16** with PMHS (polymethylhydrosiloxane) and NHC–Cu complex **2.66** (Scheme 2.9). After ten minutes lapsed, the sole detectable product (by $^1$H NMR analysis) was the branched Cu–allyl species **2.70,** which is formed through Cu–H addition to allenyl–B(pin) **2.16**.

This finding indicated that Cu–H addition is more facile than Cu/B exchange. In line with the aforementioned hypothesis, when 1,1-disubstituted allenyl–B(pin) **2.11** was used, linear Cu–allyl isomer **2.72** was formed preferentially (85% conv). It is worth noting that, as supported by X-ray as well as NMR studies, the most stable isomer of the organocopper intermediate generated from the reaction with monosubstituted allenyl–B(pin) (**2.16**) is that wherein the Cu(NHC) moiety is bound to the more sterically hindered carbon connected to the B(pin) moiety. The fact that the branched Cu–allyl species **2.70** is favored could be because the accumulation of electron density at the carbon center is stabilized by the Lewis acidic boron atom. As a consequence, the transformation involving 1,1-disubstituted allenyl–B(pin) **2.11** would likely involve branched Cu–allyl species **2.71**, where steric pressure between the methyl group and the B(pin) moiety would cause its collapse to linear Cu–allyl isomer **2.72.** The generation of **2.70** and **2.71** was supported by a study carried out by Meek *et al.* where the intermediacy of similar sterically congested Cu–allyl isomer was proposed.[19] Whether the greater stability of the branched Cu–allyl species **2.70** would result in an inefficient process remained to be seen.

(19) Green, J. C.; Zanghi, J. M.; Meek, S. J. *J. Am. Chem. Soc.* **2020**, *142*, 1704−1709.

***Scheme 2.9.*** Regioselectivity of the Cu–H addition to allenyl boronates[a]




[a]See Experimental Section for details

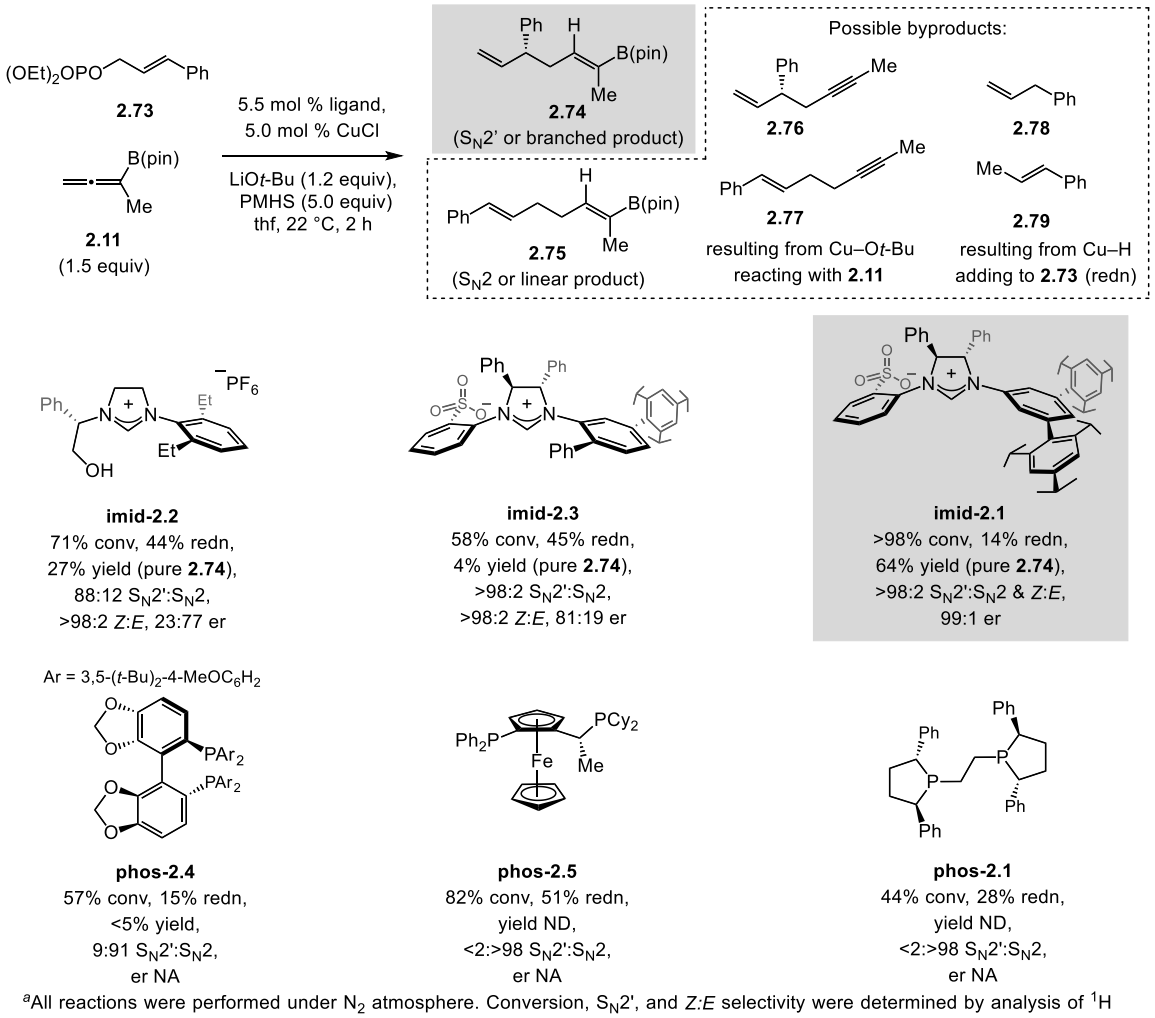
### 2.3.2 Establishing feasibility and identification of an effective catalyst

We selected 1,1-disubstituted allenyl–B(pin) **2.11,** disubstituted allylic phosphate **2.73,** and PMHS as the reactants for our initial model studies. The choice of **2.11** (vs monosubstituted allenyl–B(pin) **2.16**) was because its reaction would be less complicated as it would mainly entail the intermediacy of linear Cu–allyl intermediate **2.72**. According to the earlier studies (Scheme 2.8 and 2.9), we surmised that a large excess of PMHS and the sizable LiO*t*-Bu would favor the generation of Cu–H over Cu/B exchange. However, we also appreciated the fact that excess PMHS could accelerate the competitive Cu–H addition to the allylic phosphate. Our hope was that an optimal catalyst would provide the desired chemoselectivity.

With **imid-2.2**, the optimal ligand in the Cu–B(pin)-catalyzed allylic substitutions with monosubstituted (non-boryl) allenes (Scheme 2.1a), 44% reduction byproduct (mixture of monosubstituted alkene **2.78** and styrene **2.79**) was detected and enantioselectivity was low (23:77 er;

Scheme 2.10). We then examined several sulfonate imidazolinium salts as catalyst precursors; there is ample evidence that the corresponding NHC–Cu complexes can contain a metal salt bridge between the

***Scheme 2.10.*** Ligand Screening for Reactions with 1,1-Disubstituted Allenyl Boronate[a]




[a]All reactions were performed under $N_2$ atmosphere. Conversion, $S_N2'$, and *Z*:*E* selectivity were determined by analysis of $^1H$ NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See Experimental Section for details. Abbreviations: redn, reduction; NA, not applicable.

sulfonate and the phosphate group, an interaction the engenders high $S_N2'$ selectivity.[20] The transformation with **imid-2.3** was more regio- and enantioselective than with **imid-2.2** but the desired

(20) (a) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948−8964; (b) Hoveyda, A. H.; Zhou, Y.; Shi, Y.; Brown, M. K.; Wu, H.; Torker, S. *Angew. Chem., Int. Ed.* **2020** doi: 10.1002/anie.202003755

product was isolated in <5% yield, as Cu–H reduction proved to be the dominant pathway. Somewhat to our surprise, the reaction involving **imid-2.1** afforded just 14% reduction byproduct, while alkenyl–B(pin) **2.74** was isolated in 64% yield, >98:2 $S_N2$':$S_N2$ selectivity, and 99:1 er. These findings demonstrated that the substitution pattern at the N-aryl ring of the NHC ligand plays a crucial role regarding the relative rate of Cu–H addition to allylic phosphate versus an and allenyl–B(pin) compound. Another factor that emerged as essential to facility of Cu/B exchange compared to Cu–H addition to the allene was the amount of LiO*t*-Bu used. More specifically, with 2.5 equivalents of the metal alkoxide, monosubstituted alkene **2.76** was generated preferentially (**2.74**:**2.76** = 14:86). Cu-based catalysts derived from a variety of phosphine ligands, previously used in other enantioselective Cu–H-catalyzed multicomponent reactions, were found to be ineffective.[6,7] Reactions with **phos-2.4**, **phos-2.5** and **phos-2.1** suffered from low chemo- and regioselectivity, affording significant amounts of Cu–H reduction byproduct (15% to 51%), along with low $S_N2$'selectivity (Scheme 2.10).

### 2.3.3 Scope of the method

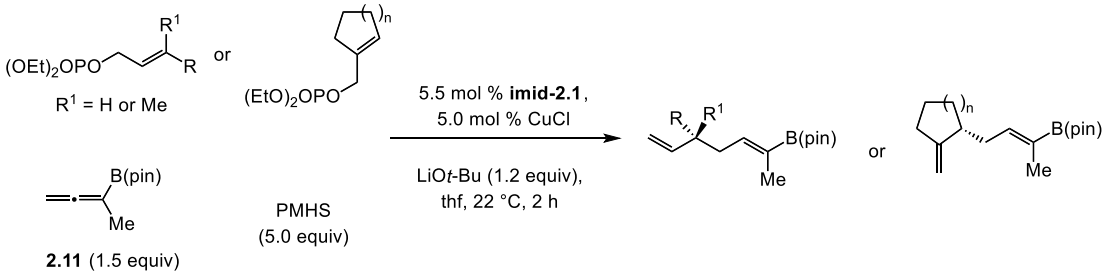
A variety of 1,2-disubstituted allylic phosphates that bear an alkenyl–aryl moiety were evaluated (Scheme 2.11). Reactions involving electron-withdrawing (**2.80, 2.81, 2.82**), electron-donating (**2.84**), sterically congested (**2.83**), and heterocyclic aryl-substituted substrates afforded the desired products in 53–71% yield, 96:4 to >98:2 $S_N2$':$S_N2$ selectivity, >98:2 *Z:E* selectivity, and 98:2–99:1 er.

Alkyl-substituted (**2.87**) and cyclic allylic phosphates (**2.88, 2.89**) reacted with disubstituted allenyl boronate **2.11**, affording products in 52–63% yield, 94–98% $S_N2$' selectivity, >98:2 *Z:E* ratio, and 91:9–95:5 er (Scheme 2.11a).

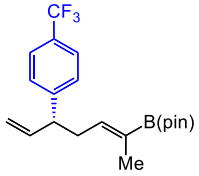
Transformations involving trisubstituted allylic phosphates, affording products containing a quaternary stereogenic center, were equally efficient and selective. Transformations involving alkyl-substituted (**2.90, 2.95, 2.96**) allylic phosphates readily proceeded to completion, furnishing the corresponding desired products in 60–74% yield, 95% to >98% $S_N2$':$S_N2$ selectivity selectivity, >98% *Z* selectivity, and 94:6–96:4 er.

An assortment of aryl-substituted allylic phosphates were investigated. Thus, products containing aryl- and heteroaryl- substituted quaternary centers and a stereochemically defined trisubstituted alkenyl–B(pin) were isolated in high regio- and enantioselectivity (Scheme 2.11b). These findings are particularly noteworthy because the Cu–B(pin)-catalyzed allylic substitution reactions involving alkyl-substituted allenes afforded $S_N2$ products only.[4d] However, when a 1,2-disubstituted allylic phosphate was involved, processes were exceptionally $S_N2$' selective. Such drastic difference in regioselectivity may be the consequence of steric pressure induced by the sizable B(pin) moiety and the additional substituent of the trisubstituted olefin (vs a disubstituted olefin). A Cu–H-catalyzed process involving an allenyl–B(pin) is more $S_N2$'-selective probably because the relatively large boronate is

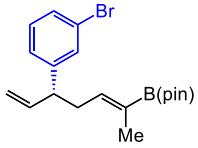
***Scheme 2.11.*** Scope of Catalytic Processes with 1,1-Disubstituted Allenyl Boronate[a]



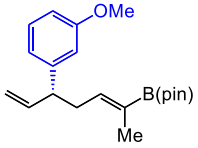

**a. Products bearing a tertiary carbon stereogenic center:**



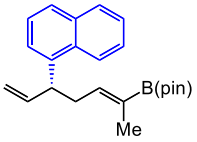

**2.80**
63% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 99:1 er



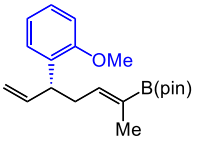

**2.81**
64% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 99:1 er



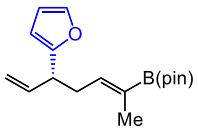

**2.82**
71% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 99:1 er



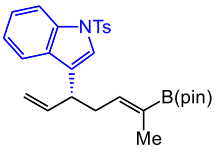

**2.83**
57% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 98:2 er



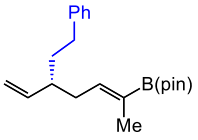

**2.84**
65% yield,
96:4 $S_N2':S_N2$,
>98:2 *Z*:*E*, 99:1 er



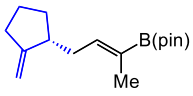

**2.85**
59% yield,
96:4 $S_N2':S_N2$,
>98:2 *Z*:*E*, 99:1 er



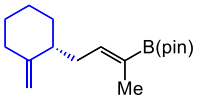

**2.86**
53% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 99:1 er




**2.87**
52% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 91:9 er

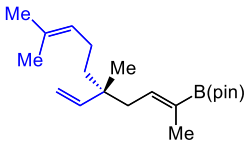



**2.88**
63% yield,
94:6 $S_N2':S_N2$,
>98:2 *Z*:*E*, 92:8 er

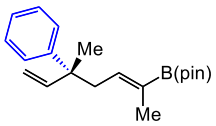



**2.89**
55% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 95:5 er

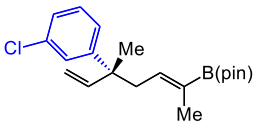
**b. Products bearing a quaternary carbon stereogenic center:**



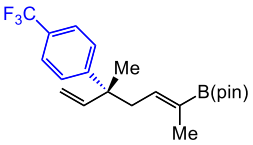

**2.90**
74% yield,
95:5 $S_N2':S_N2$,
>98:2 *Z*:*E*, 95:5 er



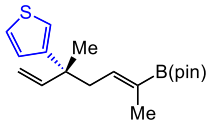

**2.91**
69% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 94:6 er



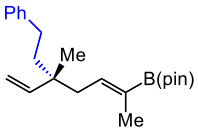

**2.92**
71% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 96:4 er



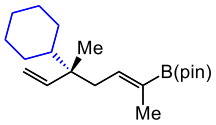

**2.93**
76% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 94:6 er



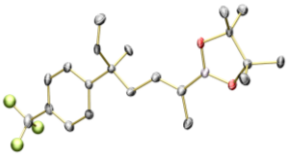

**2.94**
59% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 93:7 er




**2.95**[b]
60% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 96:4 er




**2.96**[b]
65% yield,
>98:2 $S_N2':S_N2$,
>98:2 *Z*:*E*, 94:6 er



X-ray of **2.93**

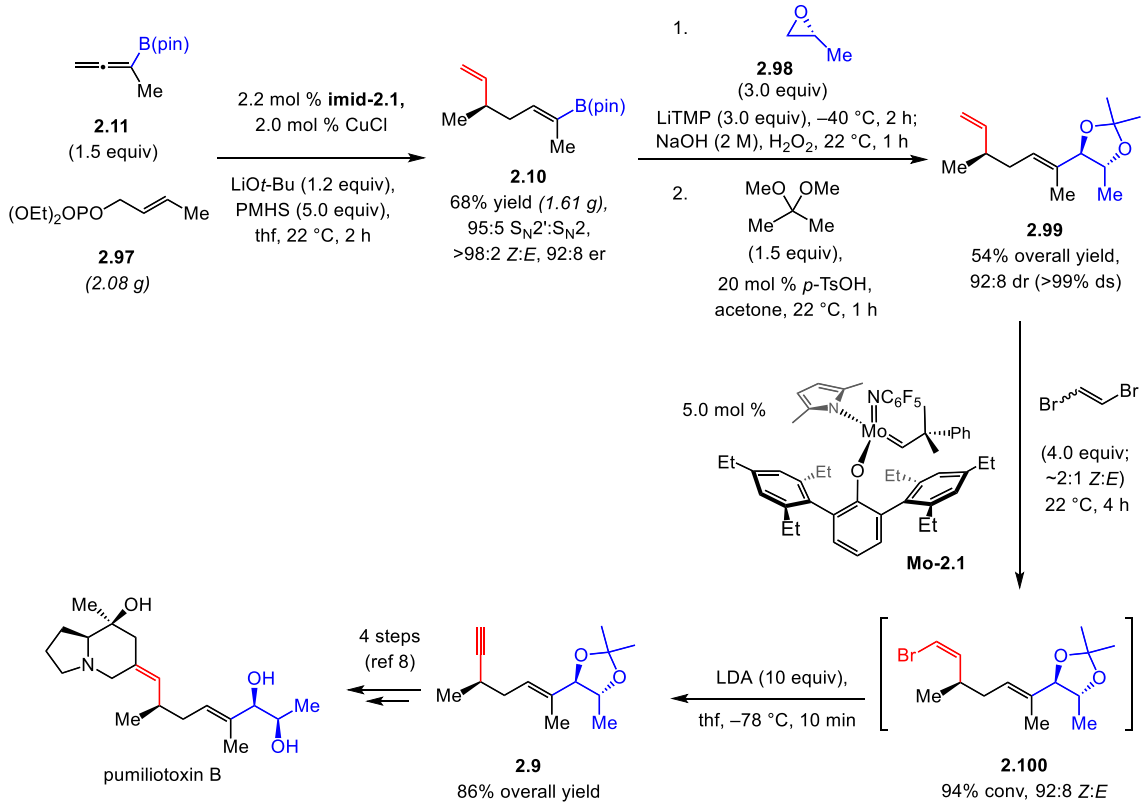
[a]All reactions were performed under $N_2$ atmosphere. Conversion (>98% in all cases), $S_N2'$, and *Z*:*E* selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). Reaction mixtures typically contain 10–20% of side products from allylic phosphate reduction. [b]With 2.0 equiv **2.11** . See the Experimental Section for details.

more distal from the site of the C–C bond formation.

### 2.3.4 Formal enantioselective synthesis of pumiliotoxin B

The products obtained through the use of this catalytic multicomponent method can be modified at their either terminus (vinyl and alkenyl–B(pin)). Accordingly, many desirable compounds can be synthesized, the linear fragment of pumiliotoxin B being a case in point.[8] To access this enyne-containing fragment (**2.09**), which can be transformed to pumiliotoxin B in just four steps, we first prepared more than a gram of alkenyl–B(pin) **2.10** in 68% yield, 95:5 $S_N2'$:$S_N2$, >98:2 *Z*:*E* and 92:8 er through a

***Scheme 2.12.*** Application to Diastereo- and Enantioselective Synthesis of the Linear Fragment of Pumiliotoxin B[a]




[a]All reactions were performed under $N_2$ atmosphere. $S_N2'$, and *Z*:*E* selectivity were determined by analysis of $^1H$ NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Experimental Section for details.

reaction catalyzed by the NHC–Cu complex derived from **imid-2.1** (2.2 mol %) . We subsequently utilized the strategy introduced by Aggarwal[21] to convert the trisubstituted alkenyl–B(pin) to masked diol **2.99** in 54% yield and 92:8 dr (Scheme 2.12).

The next step was to convert the monosubstituted alkene in **2.99** to an alkyne to access enyne **2.9**. When a dibromo addition/H–Br elimination sequence was attempted,[22] a complex mixture Br-containing compounds was obtained. Furthermore, oxidative cleavage of the monosubstituted-alkene to an aldehyde and then subjecting it to the Ohira-Bestmann[23] conditions led to the desired alkyne in a 1:1 mixture of diastereomers, presumably due to the base-promoted epimerization of the α-stereogenic center of the aldehyde.[24] We then realized that an alkenyl halide can eliminate easily under basic conditions to afford the corresponding alkyne,[25] and a cross-metathesis strategy for synthesis of alkenyl halides from terminal alkenes has recently be disclosed by Hoveyda and coworkers.[26] In the presence of 5.0 mol % Mo-based complex **Mo-2.1**, the reaction between 1,5-diene **2.99** and commercially available 1,2-dibormoethene proceeded to 94% conversion, affording alkenyl bromide **2.100** in 92:8 *Z:E*

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(21) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165−168.

(22) Kutsumura, N.; Inagaki, M.; Kiriseko, A.; Saito, T. *Synthesis* **2015**, *47*, 1844−1850.

(23) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *6*, 521−522.

(24) Monti, C.; Sharon, O.; Gennari, C. *Chem. Commun*. **2007**, *41*, 4271−4273.

(25) Okutani, M.; Mori, Y. *J. Org. Chem*. **2009**, *74*, 442−444.

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

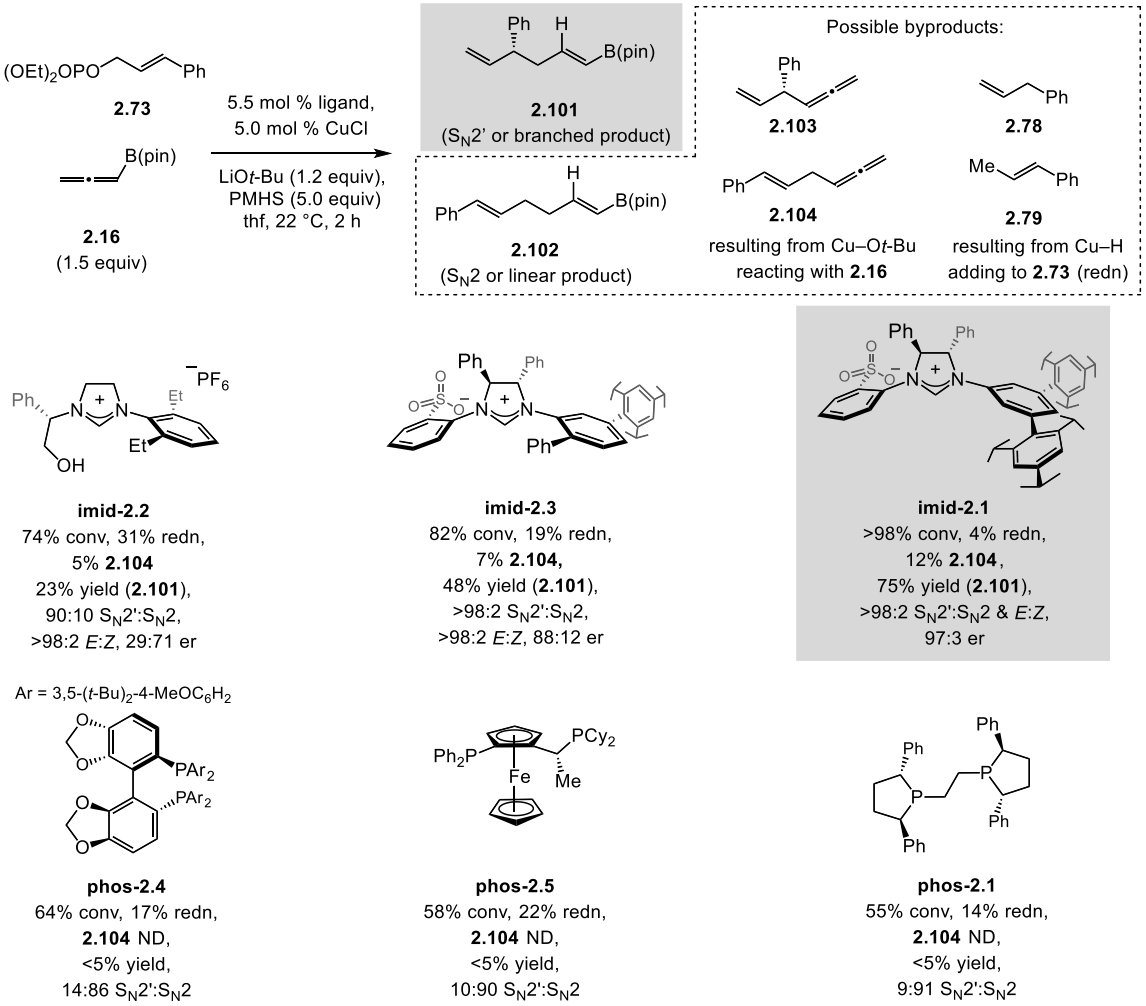
selectivity. Subsequent elimination caused by the addition of LDA furnished enyne **2.9** in 86% overall yield. It is worth noting that Ru-based complexes cannot catalyze the transformation to afford alkenyl halides,[26] and that *Z* selectivity in the first step is important as HBr elimination occurs faster with these isomers (anti elimination).[25]

We were thus able to prepare enyne **2.9** in seven steps and 32% overall yield, which is more efficient compared to the eleven-step sequence reported by Overman *et al.* in their landmark disclosure.[8] Although the previously reported yield is higher (39%), the amount of waste that is generated in eleven steps is also larger. Moreover, we were able to reduce the time needed to complete the sequence from 108 to just 10 hours.

### 2.3.5 Reactions with monosubstituted allenyl boronate

Monosubstituted allenyl–B(pin) **2.16** reacted with Cu–H complex to afford the branched organocopper compound **2.70** preferentially (Scheme 2.9), but the subsequent reaction with an allylic phosphate afforded ~30% of the reduction byproduct and no more than minimal amounts of the desired product (result with **imid-2.2**, Scheme 2.13). Ensuing ligand screening revealed that Cu–H addition to the allylic phosphate is problematic with reactions promoted by Cu-based catalysts derived from phosphine ligands (**phos-2.1, phos-2.4** and **phos-2.5,** Scheme 2.13). Importantly, under the optimal conditions developed from reactions with 1,1-disubstituted allenyl–B(pin), monosubstituted allene **2.16**

***Scheme 2.13.*** Ligand Screening for Reactions with Monosubstituted Allenyl Boronate[a]



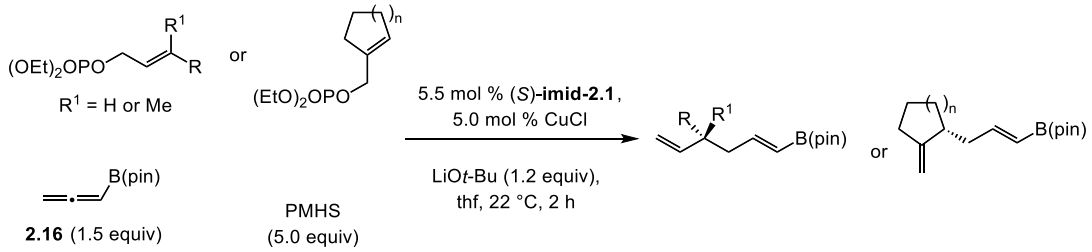

[a]All reactions were performed under $N_2$ atmosphere. Conversion, $S_N2'$, and *E:Z* selectivity were determined by analysis of $^1H$ NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See Experimental Section for details. Abbreviations: redn, reduction; ND, not determined.

was transformed to the desired 1,5-diene product (**2.101**) in 75% yield and 97:3 er; there was only 4% of the reduction byproducts formed (**2.78**, **2.79**) generated, along with 12% **2.104**, which is derived from $S_N2$ mode of addition. The formation of **2.104** is likely because the involvement of a less hindered allenyl–B(pin) accelerates the Cu/B exchange process. Increasing the amount of metal alkoxide led to

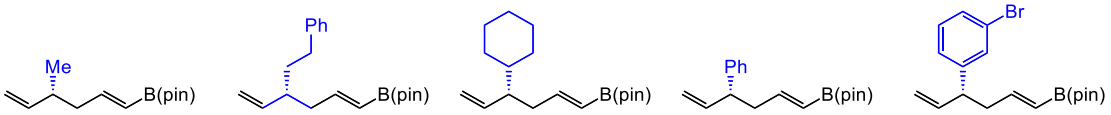
more facile Cu/B exchange, generating larger amounts of the allene-containing byproduct (**2.103**; >98% with 3.0 equiv. LiO*t*-Bu).

Catalytic multicomponent processes involving monosubstituted allenyl–B(pin) **2.16** has considerable scope. Alkyl-substituted 1,5-dienes, whether containing a linear (**2.15, 2.105**) or a branched hydrocarbon chain (**2.106**) were synthesized in 74–83% yield, >98:2 *E:Z* selectivity, >98% $S_N2'$ selectivity, and 93:7–98:2 er (Scheme 2.14a). Reactions of aryl-substituted allylic phosphates, regardless of their electronic attributes, proceeded to >98% conversion to afford the corresponding alkenyl–B(pin) products (**2.101, 2.108–2.109**) in 68–75% yield and with exceptional $S_N2'$:$S_N2$ ratios, *E:Z* selectivities, and enantioselectivities. Transformations involving cyclic allylic phosphates furnished the corresponding alkenyl–B(pin) products (**2.110-2.112**) efficiently and enantioselectively. It is worth noting that, through the use of different catalyst enantiomers, either diastereomeric form of alkenyl–B(pin) **2.111** could be generated in high dr, indicating strong catalyst control.

***Scheme 2.14.*** Scope of Catalytic Processes with Monosubstituted Allenyl Boronate[a]




**a. Products bearing a tertiary carbon stereogenic center:**



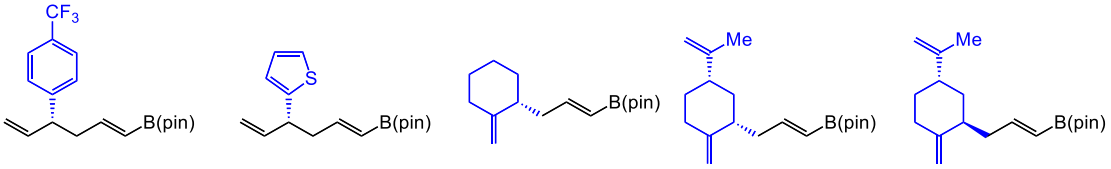

**2.15**
74% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 93:7 er

**2.105**
82% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 95:5 er

**2.106**
83% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 98:2 er

**2.101**
75% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 97:3 er

**2.107**
68% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 99:1 er




**2.108**
72% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 99:1 er

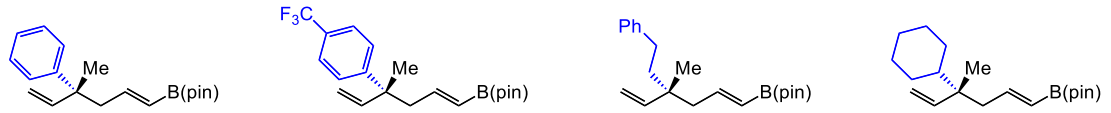
**2.109**
72% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 97:3 er

**2.110**
56% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 97:3 er

**2.111**
63% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, 96:4 dr

**2.112**[b]
63% yield,
>98:2 $S_N2':S_N2$,
>98:2 *E*:*Z*, >98:2 dr

**b. Products bearing a quaternary carbon stereogenic center:**




**2.113**
64% yield (pure $S_N2'$),
80:20 $S_N2':S_N2$,
95:5 *E*:*Z*, 92:8 er

**2.114**
82% yield (pure $S_N2'$),
88:12 $S_N2':S_N2$,
>98:2 *E*:*Z*, 92:8 er

**2.115**[c]
73% yield (pure $S_N2'$),
90:10 $S_N2':S_N2$,
94:6 *E*:*Z*, 94:6 er

**2.116**
67% yield (pure $S_N2'$),
87:13 $S_N2':S_N2$,
94:6 *E*:*Z*, 95:5 er

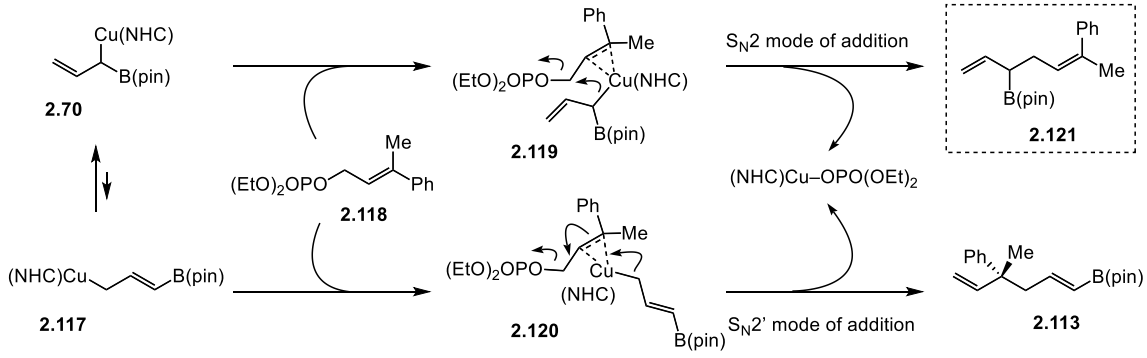
[a]All reactions were performed under $N_2$ atmosphere. Conversion (>98% in all cases), $S_N2'$, and *Z*:*E* selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). Reaction mixtures typically contain 5% of side products from allylic phosphate reduction. [b](*R*)-**imid-2.1** was used. [c]For 6 h at 4 °C. See the Experimental Section for details.

As was the case with reactions of disubstituted allenyl–B(pin) **2.11**, reactions of monosubstituted allenyl–B(pin) **2.16** with trisubstituted allylic phosphates afforded 1,5-dienes, which contain a quaternary carbon stereogenic center, in high yield and enantioselectivity (Scheme 2.14b). However, the

reaction with an *ortho*-bromophenyl substituted allylic phosphate was inefficient (*ortho*-bromo derivative of alkyl–B(pin) **2.121** in 10% yield, >98:2 $S_N2$:$S_N2$', 65:35 er).

We found it noteworthy that reactions between a monosubstituted allenyl–B(pin) and a trisubstituted allylic phosphate were less $S_N2$'-selective (80:20–90:10 $S_N2$':$S_N2$) than when a disubstituted electrophile was involved. In contrast to the $S_N2$-addition products generated with disubstituted allylic phosphates (see Scheme 2.10 and 2.13), in transformations that involve a trisubstituted variant the byproducts are chiral alkyl–B(pin) compounds (e.g., **2.121**, Scheme 2.15). These findings imply that, while branched Cu–allyl species **2.70** might be a more stable intermediate compared to linear Cu–allyl complex **2.117**, the high $S_N2$' selectivity in reactions involving the latter (Scheme 2.14a) probably arises from its greater reactivity (i.e., Curtin-Hammett kinetics are operative). For processes that involve a trisubstituted allylic phosphate, transformation via transition state **2.120** (leading to $S_N2$' addition isomer) suffers from more severe steric strain, allowing the $S_N2$ pathway (via transition state **2.119**) to become more competitive.

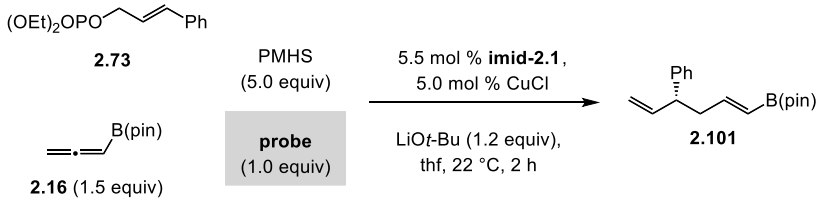
***Scheme 2.15.*** A Rationale for the Lower $S_N2$' Selectivity for **2.113**–**2.116**

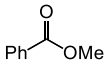
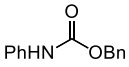
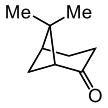
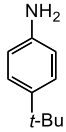
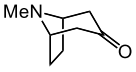


### 2.3.6 Functional group compatibility

To investigate functional group compatibility of the multicomponent process further, we carried out representative reactions in the presence of compounds containing various polar moieties (Scheme 2.16). A carbamate, a carboxylic ester, and an unprotected aniline were fully recovered and had no detectable impact on the catalytic process (entry a, b, c). However, in the presence of acetophenone, although alkenyl–B(pin) **2.101** was generated with similar selectivity and in slightly lower yield, ketone reduction was observed, resulting in complete consumption of the ketone to afford 56% of the

***Scheme 2.16.*** Probing Polar Functional Group Compatibility[a]




| | probe | results | | probe | results |
|---|---|---|---|---|---|
| a) |  | 76% yield, >98:2 $S_N2'$:$S_N2$, >98:2 *E*:*Z*, 97:3 er; *>98% probe recovered* | d) |  | 54% yield, >98:2 $S_N2'$:$S_N2$, >98:2 *E*:*Z*, 97:3 er; *<2% probe recovered: 56% 2° alcohol* |
| b) |  | 73% yield, >98:2 $S_N2'$:$S_N2$, >98:2 *E*:*Z*, 98:2 er; *>98% probe recovered* | e) |  | 65% yield, >98:2 $S_N2'$:$S_N2$, >98:2 *E*:*Z*, 98:2 er; *87% probe recovered (10% 2° alcohol)* |
| c) |  | 68% yield, >98:2 $S_N2'$:$S_N2$, >98:2 *E*:*Z*, 97:3 er; *92% probe recovered* | f) |  | 56% yield, >98:2 $S_N2'$:$S_N2$, >98:2 *E*:*Z*, 97:3 er; *24% probe recovered (72% 2° alcohol)* |

[a]All reactions were performed under $N_2$ atmosphere. $S_N2'$, *Z*:*E* selectivity, and the products derived from the probe were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities ere determined by HPLC analysis (±1%). See the Experimental Section for details.

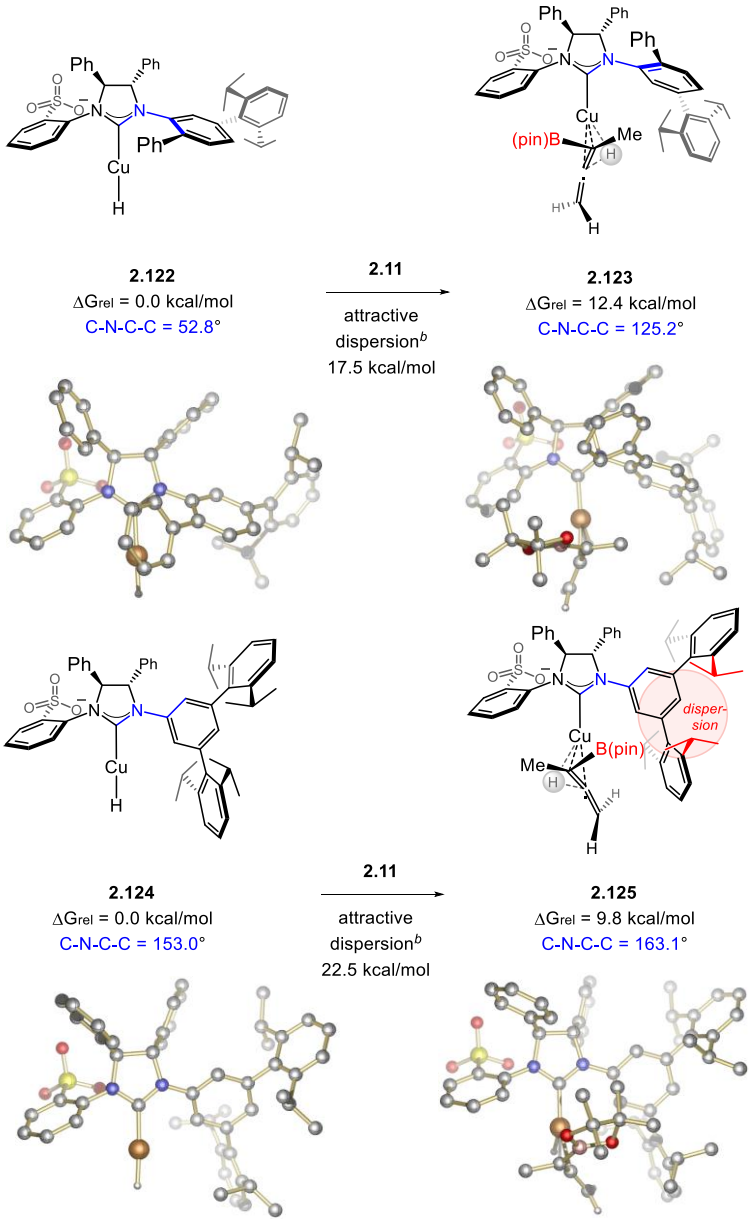
corresponding alcohol in 75:25 er (entry d). The latter complication was less of an issue with more sterically hindered ketones (entries e–f).

### 2.3.7 The origin of the unique selectivity generated by NHC–Cu catalyst derived from sulfonate imid-2.1

To probe why the catalyst derived from **imid-2.1** is significantly more effective (64% yield, 14% redn, 99:1 er) compared to **imid-2.3** (<5% yield, 45% redn), we carried out a number of control experiments, which indicated that the Cu–H complexes derived from **imid-2.3** and **imid-2.1** react with allylic phosphates at similar rates. This finding indicated that it is the ability of Cu–H to add to the allenyl–B(pin) that determines catalyst efficiency. Subsequent DFT studies (Scheme 2.17) showed that the energy barrier for the addition of the Cu–H complex derived from **imid-2.3** to allenyl–B(pin) is higher than that which corresponds to the reaction of the complex derived from **imid-2.1** (12.4 kcal/mol vs 9.8 kcal/mol). The aforementioned energy difference might be due to several factors: (1) The absence of an *ortho*-substituent in transition state **2.125** allows the N-aryl ring to rotate such that it can be coplanar with the imidazolinium ring; this is supported by the difference in dihedral angle (C–N–C–C dihedral angle is 163.1° vs 125.2° for **2.125** and **2.123** respectively). In this way, steric repulsion between the allene and the N-aryl ring can be minimized. (2) In transition state **2.125**, corresponding to Cu–H addition involving the complex derived from **imid-2.1,** the B(pin) moiety is oriented toward the N-aryl

ring, which may be owing to an attractive dispersion force between the isopropyl group and the pinacol ester.[27] The magnitude of Grimme's D2 dispersion on the reaction barriers indicates that the

***Scheme 2.17.*** Regarding Higher Efficiency with **imid-2.1** (vs **imid-2.3**)[a]




[a]DFT calculations were carried out at the MN15/Def2-TZVPP//M06-L/Def2-SVP level.
[b]Corresponds to Grimme $D_2$ dispersion obtained at the ωB97XD/Def2-TZVPP//M06-L/Def2-SVP level.

(27) Wagner, J. P.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 12274−12296.

corresponding attractive forces are about 5.0 kcal/mol larger for conversion of NHC–Cu–H complex **2.124** to **2.125** (22.5 kcal/mol vs 17.5 kcal/mol for conversion of NHC–Cu–H complex **2.122** to transition state **2.123**). Nevertheless, although there has been recent support for such interactions,[27] the validity of the calculations regarding dispersion interactions in solution remains subject to debate.[28]

## 2.4 Total Synthesis of Netamine C

To highlight and challenge the utility of the catalytic method, we carried out the first enantioselective total synthesis of netamine C. These types of guanidine-containing natural products are usually synthesized through structural alteration of an amine or by condensation of a guanidinyl compound with an α-halocarbonyl or an enone.[29] We reasoned that through the multicomponent process, we should be able to access easily the cyclohexene-containing aldehyde **2.13**, in which a guanidine group may be installed by a cycloaddition reaction. To the best of our knowledge, this approach has not been previously explored.

To begin, we prepared 1.73 grams of alkenyl–B(pin) **2.15** through the Cu–H-catalyzed process with 2.0 mol% catalyst loading. This route is more efficient, enantioselective and shorter compared to

(28) Yang, L.; Adam, C.; Nichol, G. S.; Cockroft, S. L. *Nat. Chem.* **2013**, *5*, 1006−1010.

(29) Ma, Y.; De, S.; Chen, C. *Tetrahedron* **2015**, *71*, 1145−1173.

the 3-step route accessing **2.15** through an enantioselective allylic substitution, previously published by our group (**2.15** is afforded in 41% overall yield and 91:9 er).[20] Cross-metathesis of **2.15** and bis-phosphate **2.126** catalyzed by a Ru-based catalyst afforded allylic phosphate *E*-**2.128** in 69% yield and 95:5 *E:Z* selectivity. The chemoselectivity of the reaction is exceptional, which allowed us to use the alkeny–B(pin) moiety as a masked allylic phosphate for another allylic substitution (Scheme 2.18).

Next, we prepared the adjacent stereogenic carbon center through catalyst-controlled $S_N2'$-selective and enantioselective allylic substitution. However, because of the presence of Lewis acidic boryl moiety, organometallic compounds such as an alkyllithium, an alkylmagnesium halide, a dialkylzinc or a trialkylaluminum species, all commonly used, would not be applicable in the case. We were aware of two possible reported approaches, one entailing in situ generated alkylborane and a *Z*-allylic chloride[30] and the other involving an alkylzinc halide and an aryl-substituted secondary carbonate.[31] In the former disclosure, the only example of a reaction involving an α-branched substrate was minimally efficient and non-selective. Furthermore, not only would the latter approach would require priori synthesis of a secondary allylic alcohol, necessitating multiple manipulations, there are

(30) Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 18573−18576.

(31) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2015**, *54*, 7644−7647.

also no examples of addition to an alkyl-substituted substrate. Accordingly, we needed to find an alternative solution.

Preliminary studies indicated that an alkylzinc halide would be a suitable reagent – one that that, although mild, is sufficiently reactive. After optimization studies, we found that the **imid-2.1**-derived Cu complex is an effective catalyst, in the presence of which reaction of *E*-allylic phosphate *E*-**2.128** afforded 1,6-diene (*R, R*)-**2.129** in 70% yield and 76:24 dr. Later on, we discovered that efficiency as well as stereoselectivity can be improved by using *Z*-allylic phosphate *Z*-**2.128**, prepared through *Z*-selective cross-metathesis catalyzed by a Ru-based catechothiolate complex.[32] Under the same condition as was used for the allylic substitution with the *E* isomer, 1,6-diene **2.129** was isolated in 81% yield and 89:11 dr (Scheme 2.18).

The alkenyl–B(pin) moiety was then converted to an allylic alcohol by Matteson homologation, and this was followed by oxidation of the B(pin) group. The derived allylic alcohol was transformed to the corresponding allylic phosphate (*R,R*)-**2.131** in 77% overall yield and >98:2 *E:Z* selectivity. Another enantioselective multicomponent allylic substitution involving allenyl–B(pin) **2.16** was then performed, followed by oxidation of the B(pin) moiety to afford aldehyde (*R,R,S*)-**2.14** in 65% yield and 96:4 dr. Ring-closing metathesis in the presence of **Ru-2.1** furnished cyclohexene (*R,R,S*)-**2.13** in 93% yield

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

(Scheme 2.18). The three stereogenic centers were thus generated selectively through catalyst-controlled allylic substitution processes, promoted by the NHC–Cu complex derived from **imid-2.1.**

We surmised that the polycyclic ring might be accessed by [4+2] cycloaddition reaction[33] involving **2.133a**. To obtain **2.133a**, we first prepared the corresponding N-guanidinyl acetal (*R,R,S*)- **2.132** according to a previously reported procedure (73% yield, Scheme 2.18).[34] Our hope was that subsequent subjection to trifluoroacetic acid at 110 °C (microwave) followed by catalytic hydrogenation would furnish the desired polycyclic core. However, it was **2.134**, an undesired diastereomer, that was obtained predominately in 58% yield and 88:12 dr. Transition state analysis indicated that the reaction proceeding via **2.133a** (*endo* form) may engender considerable steric repulsion between the carboxybenzyl protecting group and the methyl unit in the six-membered ring, favoring the *exo* mode addition (**2.133b**). Deprotection before cycloaddition did not afford any of the desired product either.

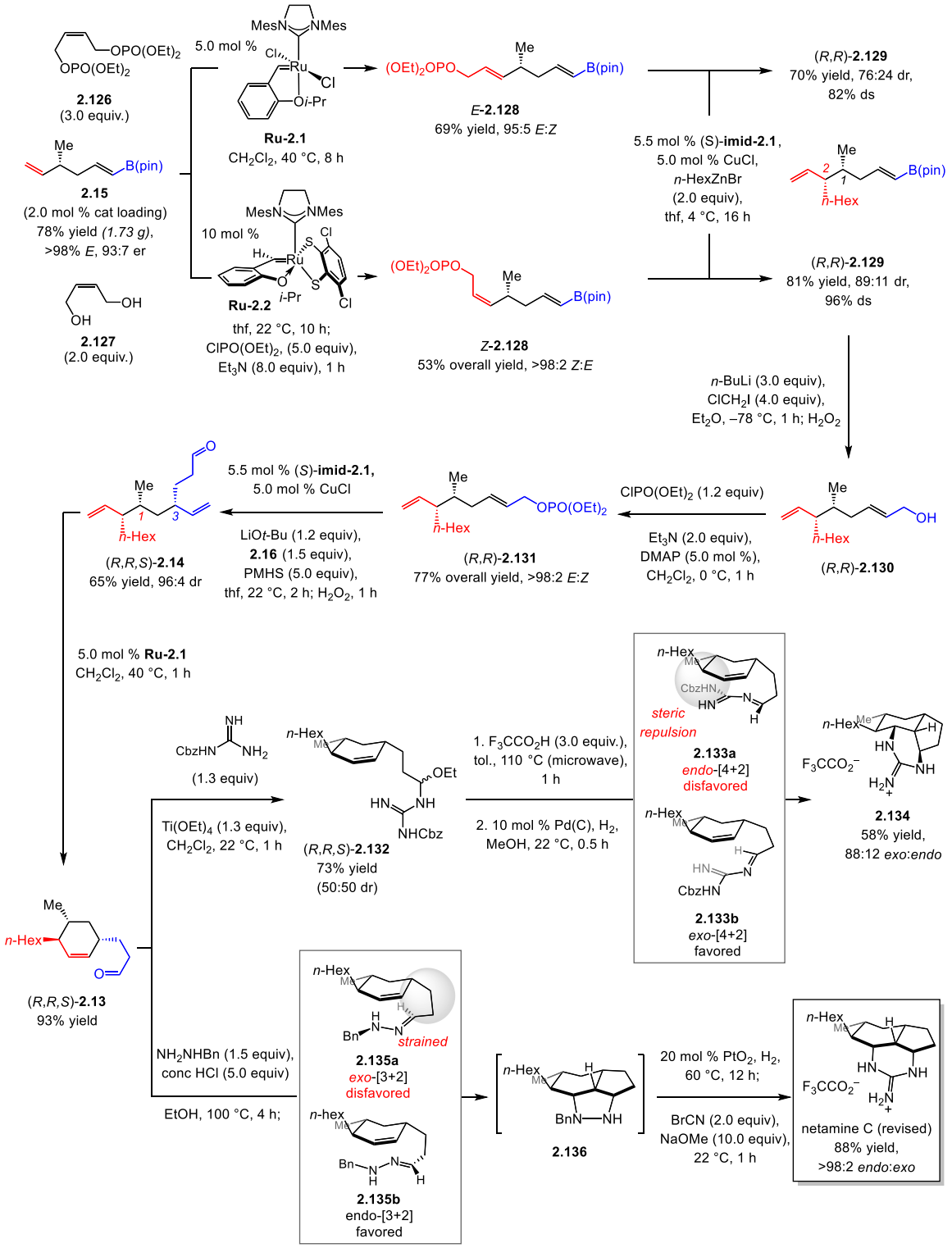
We therefore turned our attention to another strategy, namely, one involving [3+2] cycloaddition.[35] We envisioned that the proper orientation of the *exo* transition state **2.135a** would cause severe strain, and the protecting group in *endo* transition state **2.135b** would be more distal from the

(33) Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525−1534.

(34) Li, M.; Luo, B.; Liu, Q.; Hu, Y.; Ganesan, A.; Huang, P.; Wen, S. *Org. Lett.* **2014**, *16*, 10−13.

(35) (a) Frank, E.; Mucsi, Z.; Zupkó, I.; Réthy, B.; Falkay, G.; Schneider, G.; Wölfling, J. *J. Am. Chem. Soc.* **2009**, *131*, 3894−3904. (b) Nájera, C.; Sansano, J. M.;Yus, M. *Org. Biomol. Chem*. **2015**, *13*, 8596−8636.

***Scheme 2.18.*** Total Synthesis of the Revised Netamine C Isomer[a]



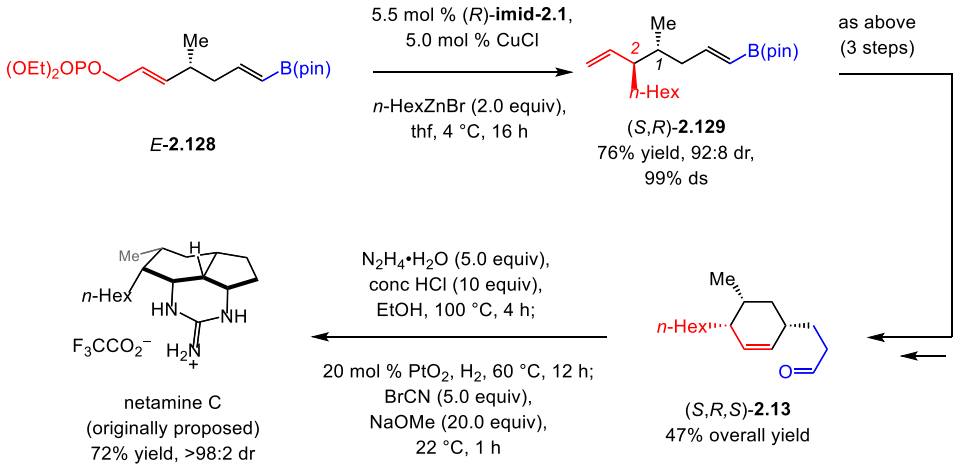

[a]All reactions were performed under $N_2$ atmosphere. $CS_N2'$, and *Z*:*E* selectivity were determined by analysis of $^1H$ NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Experimental Section for details.

methyl unit, relieving steric pressure, thus favoring *endo* addition. In the event, condensation of the aldehyde with benzylhydrazine afforded the corresponding hydrazone, which was heated to 100 °C for four hours to afford polycyclic hydrazine product **2.136** as a single diastereomer. Ensuing hydrogenolysis and treatment with NaOMe and BrCN resulted in the formation of netamine C (revised structure) in 88% yield and >98:2 dr. Comparison of the $^{1}H$ and $^{13}C$ NMR spectra indicated that this compound is identical to the natural product, supporting Snider's proposal.[11]

To confirm the structural assignment while highlighting the diastereodivergency of the multicomponent process, we also synthesized the originally proposed isomer. The same sequence was used to prepare *E*-allylic phosphate *E*-**2.128,** which was treated with *n*-hexylzinc bromide under the aforementioned conditions (Scheme 2.18) except that *R* ligand enantiomer was used. The alternative diastereomer, namely, (*S,R*)-**2.129** was thus generated in 76% yield and 92:8 dr. Comparison of the data for (*S*)-**imid-2.1** indicated that *E*-**2.128** and (*R*)-**imid-2.1** is the matched combination. 1,6-Diene (*S,R*)-**2.129** was then converted to aldehyde (*S,R,S*)-**2.13** as before (47% overall yield). Treatment of (*S,R,S*)-**2.13** with unprotected hydrazine hydrate, a solution of concentrated HCl, followed by hydrogenolysis and treatment with BrCN allowed us to obtain the originally proposed netamine C in 72% yield as a single diastereomer. Benzyl hydrazine did not lead to the desired product, probably due to the steric

repulsion between the *n*-hexyl unit and the benzyl protecting group. Further analysis of the spectra data confirmed the fact that this is not the correct stereoisomer of the natural product.

***Scheme 2.19.*** Diastereo- and Enantioselective Total synthesis of the Originally Proposded Netamine C Isomer




[a]All reactions were performed under $N_2$ atmosphere. Diastereoselectivity were determined by analysis of $^1H$ NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). See the Experimental Section for details.

## 2.5 Conclusions

This chapter described the development a broadly applicable, efficient, regio- and enantioselective method for synthesis of readily modifiable organoboron compounds. The catalyst not only exhibits a unique ability to promote multicomponent processes efficiently and with high stereochemical control, it may be used for stereodivergent allylic substitution with an alkylzinc halide, which, to the best of our knowledge, is the first example its kind. Mechanistic investigations indicated

that the substituent on the N-aryl moiety play a critical role in controlling the relative rate of Cu–H addition to allenyl–B(pin) as opposed to allylic phosphate – key for an efficient multicomponent process.

Being able to access a versatile compound allowed us to conduct functionalizations at terminus of the 1,5-diene product, providing an effective method for preparation of a wide range of compounds. Apropos the linear fragment of pumiliotoxin B, the alkenyl–B(pin) group was first used in a diastereoselective homologation-type reaction, and the terminal alkene was subsequently transformed to an alkyne by *Z*-selective cross-metathesis/elimination, a sequence that has not been widely used for alkyne synthesis, and one that further highlights the versatility of unsaturated organoboron compounds. Netamine C was synthesized by first transforming the terminal alkene to an allylic phosphate and then the alkenyl–B(pin) to the same moiety. Two additional catalytic allylic substitution reactions, catalyzed by **imid-2.1**, established two additional stereogenic centers. Owing to the diastereoconvergency of the approach, both stereoisomers of netamine C could be synthesized, allowing us to confirm unambiguously the stereochemical isentity of the natural product.

## 2.6 Experimentals

- **General**

Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, $\lambda_{max}$

in $cm^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). $^{1}H$ NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), Varian Unity INOVA 500 (500 MHz) or Varian Unity INOVA 600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm, thf-$d_8$: δ 3.58 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), and integration. $^{13}C$ NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer, Varian Unity INOVA 500 (125 MHz) or a Varian Unity INOVA 600 (150 MHz) 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). High-resolution mass spectrometry was performed on a JEOL AccuTOF DART (positive mode) or ESI (positive mode) at the Mass Spectrometry Facility at Boston College. Enantiomeric ratios were determined by GC analysis (Alltech Associated alpha dex (30 m x 0.25 mm) or HPLC analysis (Chiral Technologies Chiralpak AZ–H (4.6 x 250 mm), Chiralcel OD–H (4.6 x 250 mm), Chiralpak AD–H (4.6 x 250 mm), Chiralcel OJ–H (4.6 x 250 mm), Chiralcel OK (4.6 x 250 mm), Chiralcel OZ–H (4.6 x 250 mm), and Chiralcel OZ–3 (4.6 x 150 mm) in comparison with authentic racemic materials. Specific rotations were measured on an ATAGO® AP-300 Automatic Polarimeter or a Rudolph Research Analytical Autopol IV Polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry $N_2$ in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system: toluene, benzene and hexanes were purified through a copper oxide and alumina column; $CH_2Cl_2$ and $Et_2O$ were purged with Ar and purified by passage through two alumina columns. Tetrahydrofuran (THF, Fisher Scientific, Inc., THF-$d_8$, Oakwood) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. Ethanol (Fisher Scientific, Inc.) was purified by distillation from Mg (Fisher Scientific) prior to use. All work-up and purification procedures were carried out in air and with reagent grade solvents (purchased from Fisher Scientific, Inc.). The glove box used was $N_2$-filled.

- **Reagents**

**Allenylboronic acid pinacol ester (2.16):** purchased from TCI and used as received.

**Benzylhydrazine:** prepared according to previously reported procedures.[36]

**(*R*)-(-)-5,5'-Bis[di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole (phos-2.4):** purchased from Strem and used as received.

(36) Malachowski, W. P., Tie, C., Wang, K. & Broadrup, R. L. *J. Org. Chem*. **2002**, *67*, 8962–8969.

**(–)-1,2-Bis((2*R*, 5*R*)-2,5-diphenylphospholano)ethane (phos-2.1):** purchased from Strem and used as received.

**2-(Buta-2,3-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.11):** prepared according to previously reported procedures.[37]

***n*-Butyllithium (*n*-BuLi, 2.5 M in hexane):** as purchased from Aldrich and used as received.

***N*-Cbz-guanidine:** purchased from Combi-Blocks and used as received.

**Chloroiodomethane:** purchased from Oakwood and used as received.

**Copper (I) chloride (CuCl):** purchased from Strem and used as received.

**1,2-Dibromoethene:** purchased from TCI and used as received.

**Cyanogen bromide (BrCN):** purchased from Aldrich and used as received.

**Dichloro(2-isopropoxyphenylmethylene) (tricyclohexylphosphine)ruthenium(II) (Ru-2.1):** purchased from AK Scientific and used as received.

**Diethyl chlorophosphate:** purchased from Alfa Aesar and used as received.

**(*R*)-1-[(*S*$_P$)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (phos-2.5):** purchased from Strem and used as received.

**Diisobutylaluminum hydride (dibal–H):** purchased (neat) from Aldrich and used as received.

(37) Zhao, T. S. N., Yang, Y., Lessing, T. & Szabó, K. J. *J. Am. Chem. Soc*. **2014**, *136*, 7563–7566.

**4-Dimethylaminopyridine (DMAP):** purchased from Oakwood and used as received.

***n*-Hexylzinc bromide (0.5 M in THF):** purchased from Alfa Aesar and used as received.

**Hydrazine monohydrate:** purchased from Aldrich and used as received.

**Hydrochloric acid (HCl):** purchased from Fisher and used as received.

**Hydrogen peroxide (30 wt% in $H_2O$):** purchased from Oakwood and used as received.

**Imid-2.2:** prepared according to previously reported procedures.[38]

**Imid-2.3:** prepared according to previously reported procedures.[39]

**Lithium *t*-butoxide (LiO*t*-Bu):** purchased from Strem and used as received.

**Lithium diisopropylamide (LDA, 1.0 M in THF/hexane):** purchased from Aldrich and used as received.

**Lithium 2,2,6,6-tetramethylpiperidide (LTMP):** purchased from Aldrich and used as received.

**Complex Mo-2.1:** prepared according to previously reported procedures.[40]

**Platinum(IV) oxide ($PtO_2$):** purchased from Acros and used as received.

**Poly(methylhydrosiloxane) (PMHS):** purchased from Alfa Aesar and used as received.

**(*R*)-(+)-Propylene oxide:** purchased from TCI and used as received.

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(38) Meng, F., McGrath, K. P. & Hoveyda, A. H. *Nature* **2014***, 513*, 367–374.

(39) Shi, Y., Jung, B., Torker, S. & Hoveyda, A. H. *J. Am. Chem. Soc.* **2015***, 137*, 8948–8964.

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

**Sodium bicarbonate ($NaHCO_3$):** purchased from Fisher Scientific and used as received.

**Sodium hydroxide (NaOH):** purchased from Fisher Scientific and used as received.

**Sodium methoxide (NaOMe):** purchased from Strem and used as received.

**Titanium(IV) ethoxide:** purchased from Strem and used as received.

**Triethyl phosphonoacetate:** purchased from Oakwood and used as received.

**Triethylamine:** purchased from Fisher Scientific and distilled over $CaH_2$ prior to use.

***p*-Toluenesulfonic acid monohydrate:** purchased from Oakwood and used as received.

- **Procedure for Cu–H-Catalyzed Multicomponent Allylic Substitutions**

In a $N_2$-filled glove box, an oven-dried 2-dram vial with magnetic stir bar was charged with CuCl (0.5 mg, 0.005 mmol), (*S*)-**imid-2.1** (4.7 mg, 0.0055 mmol), LiO*t*-Bu (9.6 mg, 0.12 mmol), and freshly distilled tetrahydrofuran (THF, 0.5 mL). The mixture was premixed for 30 min before PMHS (30.0 mg, 0.50 mmol), allenyl boronic acid pinacol ester **2.11** (27.0 mg, 0.15 mmol) and additional THF (0.5 mL) were added, causing the solution to turn dark-red immediately. After 10 min, allylic phosphate (27.3 mg, 0.10 mmol) was added (at 22 °C). The vial was sealed with electrical tape before removal from the glove box, and the mixture was allowed to stir for 2 h at 22 °C, after which it was passed through a short plug of oven-dried silica gel and eluted with $Et_2O$. The organic layer was concentrated under reduced pressure,

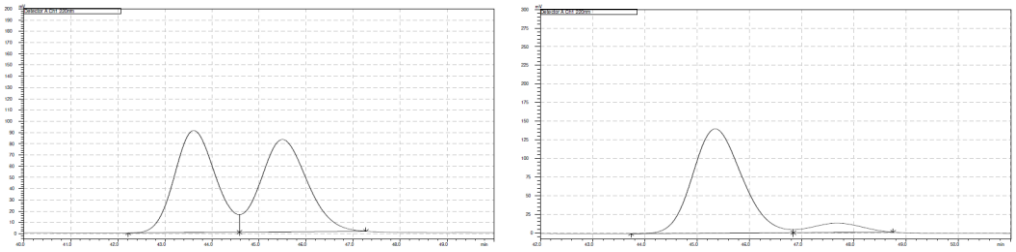
affording yellow oil, which was purified by silica gel chromatography (3:1→1:1→1:3 hexanes:$CH_2Cl_2$) to afford **2.74** as colorless oil (20.6 mg, 0.0643 mmol, 64% yield).

Please note: For the reactions in preparation of **2.113**-**2.116**, if the reaction is quenched with a saturated aqueous solution of $NH_4Cl$ the $S_N2$ byproduct can be made to decompose readily, and thus the yield reported correspond to pure $S_N2$' addition isomers.

- **Products with a Tertiary Carbon Stereogenic Center**

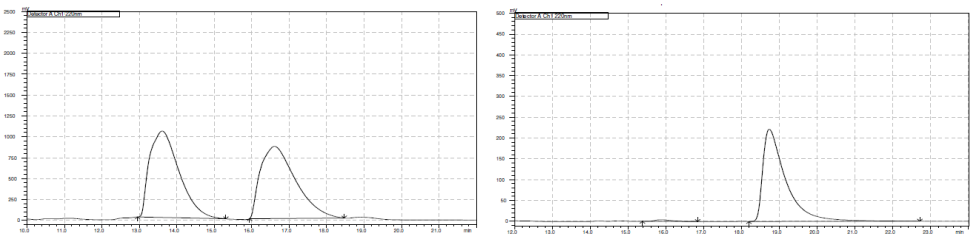
**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(5-methylhepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.10): IR (neat):** 2973 (w), 2154 (w), 1368 (w), 1269 (w), 1040 (s), 902 (m), 765 (m) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 6.32 (t, *J* = 6.3 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.02–4.85 (m, 2H), 2.31–2.23 (m, 1H), 2.20–2.08 (m, 1H), 1.67 (s, 3H), 1.26 (s, 12H), 1.01 (d, *J* = 6.7 Hz, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 144.6, 144.4, 112.5, 83.2, 37.3, 35.8, 24.9 (d, *J* = 2.2 Hz), 19.7, 14.2; **HRMS (DART):** Calcd for $C_{14}H_{26}BO_2$ $[M+H]^+$: 237.2020. Found: 237.2020; **Specific rotation:** $[\alpha]_D^{20}$ +3.7 (*c* 0.29, $CHCl_3$) for a 92:8 er sample. Enantiomeric purity of **2.10** was determined by HPLC analysis of the corresponding methyl ester produced through carbonylation of alkenyl B(pin)[41] in comparison with authentic racemic material; Chiralpak AZ-H, 100% hexanes, 0.3 mL/min, 220 nm.

(41) Yamamoto, Y. *Adv. Synth. Catal.* **2010**, *352*, 478–492.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 43.612 | 5495339 | 49.288 | 45.346 | 9151573 | 91.669 |
| 45.500 | 5654120 | 50.712 | 47.682 | 831674 | 8.331 |

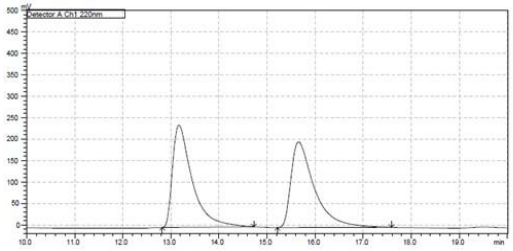
**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(5-phenylhepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.74). IR (neat)**: 3028 (w), 2977 (s), 2930 (w), 2154 (w), 1632 (m), 1601 (w), 1493 (w), 1370 (s), 1341 (s), 1303 (w), 1135 (s), 1110 (s), 1060 (s), 906 (s), 860 (m), 767 (m), 668 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ = 7.29 (t, *J* = 7.6 Hz, 2H), 7.23–7.16 (m, 3H), 6.30 (dt, *J* = 6.8, 3.4 Hz, 1H), 5.99 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H), 5.07–5.01 (m, 2H), 3.41 (q, *J* = 7.3 Hz, 1H), 2.61–2.49 (m, 2H), 1.65 (s, 3H), 1.24 (s, 12H); **$^{13}$C NMR ($CDCl_3$, 151 MHz)**: δ = 144.2, 143.9, 141.7, 128.5, 127.8, 126.4, 114.6, 83.2, 49.2, 34.7, 24.9 (d, *J* = 2.6 Hz), 14.3; **HRMS (ESI$^+$)**: Calcd for $C_{19}H_{31}BO_2N$ $[M+NH_4]^+$: 316.2483. Found: 316.2475; **Specific rotation**: $[\alpha]_D^{20}$ +2.1 (*c* 1.2, $CHCl_3$) for an enantiomerically enriched sample of 99:1 er Enantiomeric purity of **2.76** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.5 mL/min, 220 nm.

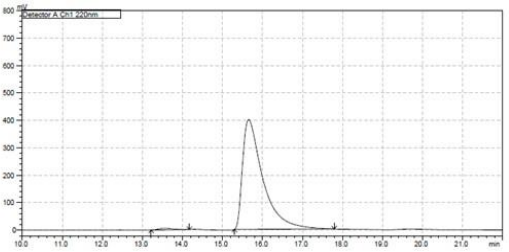


| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 13.610 | 56788053 | 50.163 | 15.871 | 116709 | 1.241 |

| | | | | | |
|---|---|---|---|---|---|
| 16.610 | 56419903 | 49.837 | 18.790 | 9286946 | 98.759 |

**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(5-(4-(trifluoromethyl)phenyl)hepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.80): IR (neat):** 2926 (w), 1716 (m), 1325 (s), 1164 (m), 1123 (m), 1068 (s), 1017 (w), 841 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.54 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 6.24 (t, *J* = 6.2 Hz, 1H), 5.97 (ddd, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.12–5.00 (m, 2H), 3.47 (q, *J* = 7.2 Hz, 1H), 2.61–2.49 (m, 2H), 1.64 (s, 3H), 1.24 (s, 12H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 148.2, 143.0, 140.7, 128.7 (q, *J* = 32.2 Hz), 128.2, 125.5 (q, *J* = 3.8 Hz), 115.5, 83.3, 49.0, 34.5, 24.9 (d, *J* = 2.6 Hz), 14.3; **$^{19}$F NMR (376 MHz, $CDCl_3$):** δ –62.11; **HRMS (DART):** Calcd for $C_{20}H_{30}BF_3O_2N$ $[M+NH_4]^+$: 384.2322. Found: 384.2306; **Specific rotation:** $[\alpha]_D^{20}$ +3.3 (*c* 1.2, $CHCl_3$) for a 99:1 er sample. Enantiomeric purity of **2.80** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.5 mL/min, 220 nm.

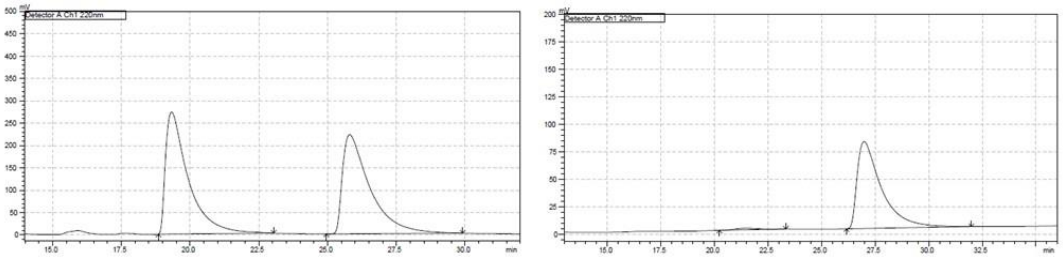




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 13.169 | 6795907 | 50.307 | 13.551 | 136085 | 0.957 |
| 15.658 | 6712839 | 49.693 | 15.653 | 14080904 | 99.043 |

**(*R*,*Z*)-2-(5-(3-Bromophenyl)hepta-2,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.81): IR (neat):** 2974 (w), 1712 (w), 1472 (m), 1438 (m), 1370 (m), 1329 (m), 1143 (s), 1072 (m), 981 (m), 850(m), 762 (w), 672 (m) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.36–7.30 (m, 2H), 7.18–7.10 (m, 2H),

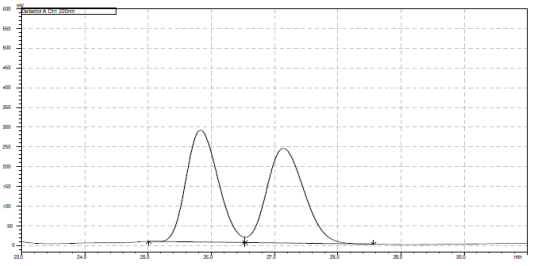
6.28–6.21 (m, 1H), 5.94 (ddd, $J$ = 17.3, 10.3, 7.1 Hz, 1H), 5.11–5.01 (m, 2H), 3.37 (q, $J$ = 7.3 Hz, 1H), 2.60–2.43 (m, 2H), 1.63 (s, 3H), 1.24 (s, 12H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 146.5, 143.2, 140.8, 131.0, 130.1, 129.5, 126.5, 122.6, 115.3, 83.3, 48.8, 34.5, 24.9 (d, $J$ = 2.6 Hz), 14.3; **HRMS (DART):** Calcd for $C_{19}H_{30}BBrO_2N$ $[M+NH_4]^+$: 394.1553; Found: 394.1551; **Specific rotation:** $[\alpha]_D^{20}$ +3.5 (*c* 1.2, $CHCl_3$) for a 99:1 er sample. Enantiomeric purity of **2.81** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.5 mL/min, 220 nm.

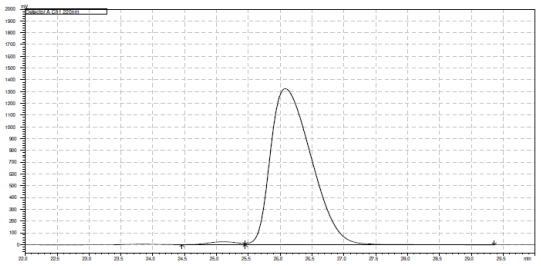


| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 19.327 | 15693182 | 50.477 | 21.499 | 94077 | 1.478 |
| 25.803 | 15396630 | 49.523 | 26.984 | 6272069 | 98.522 |

**(*R*,*Z*)-2-(5-(3-Methoxyphenyl)hepta-2,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.82):** **IR (neat):** 2974 (w), 1714 (w), 1630 (w), 1368 (m), 1260 (m), 1041 (s), 905 (s), 859 (m), (m), 765 (s), 1699 (w), 668 (s) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.21 (t, $J$ = 7.6 Hz, 1H), 6.81 (d, $J$ = 7.5 Hz, 1H), 6.78–6.70 (m, 2H), 6.30 (td, $J$ = 6.9, 6.0, 3.5 Hz, 1H), 5.97 (dddd, $J$ = 17.3, 10.3, 7.3, 1.5 Hz, 1H), 5.08–4.97 (m, 2H), 3.80 (s, 3H), 3.37 (q, $J$ = 7.4 Hz, 1H), 2.61–2.45 (m, 2H), 1.65 (s, 3H), 1.24 (s, 12H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 159.8, 145.9, 143.9, 141.4, 129.5, 120.2, 114.7, 113.7, 111.6, 83.2, 55.3, 49.2, 34.7, 24.9 (d, $J$ = 2.6 Hz), 14.3; **HRMS (DART):** Calcd for $C_{20}H_{30}BO_3$ $[M+H]^+$: 329.2288.

Found: 329.2297; **Specific rotation:** $[\alpha]_D^{20}$ +2.9 (*c* 0.77, $CHCl_3$) for a 99:1 er sample. Enantiomeric purity of **2.82** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 99.9% hexanes, 0.3 mL/min, 220 nm.



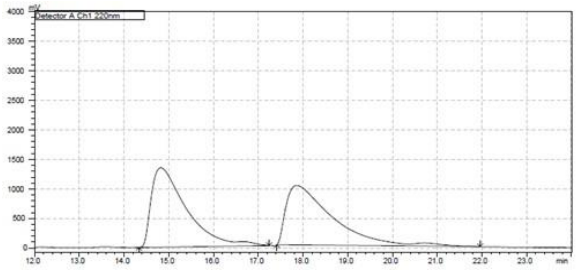


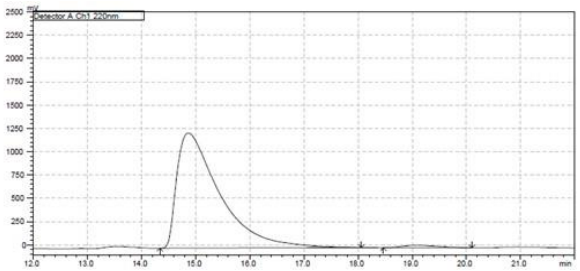
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 25.830 | 9919852 | 50.312 | 25.105 | 764854 | 1.286 |
| 27.140 | 9796740 | 49.688 | 26.080 | 58707230 | 98.714 |

**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(5-(naphthalen-1-yl)hepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.83):**

**IR (neat):** 2973 (w), 2929 (w), 1714 (w), 1598 (w), 1410 (w), 1810 (w), 1340 (m), 1213 (m), 1041 (s), 905 (m), 859 (s), 765 (m), 699 (m), 668 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.10 (d, J = 8.2 Hz, 1H), 7.88–7.83 (m, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.54–7.36 (m, 4H), 6.40 (t, *J* = 6.8 Hz, 1H), 6.12 (ddd, J = 17.1, 10.3, 6.7 Hz, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 5.06 (d, *J* = 17.4 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 1H), 2.79–2.65 (m, 2H), 1.68 (s, 3H), 1.24 (s, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 144.2, 141.1, 140.1, 134.1, 131.7, 129.0, 127.0, 125.9, 125.7, 125.5, 124.3, 123.7, 115.3, 83.3, 43.7, 34.4, 24.9 (d, J = 2.6 Hz), 14.4; **HRMS (DART):** Calcd for $C_{23}H_{30}BO_2$ $[M+H]^+$: 349.2333. Found: 349.2334; **Specific rotation:** $[\alpha]_D^{20}$ –7.5 (*c* 0.08, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity of **2.83** was determined

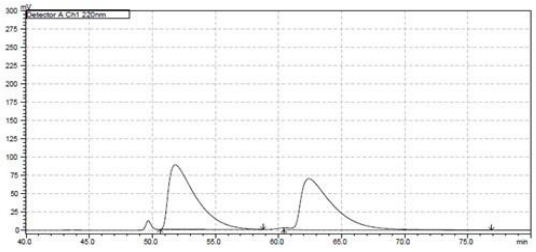
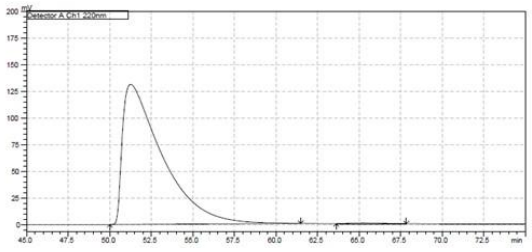
by HPLC analysis in comparison with authentic racemic material; Chiralpak AD-H, 100% hexanes, 0.3 mL/min, 220 nm.





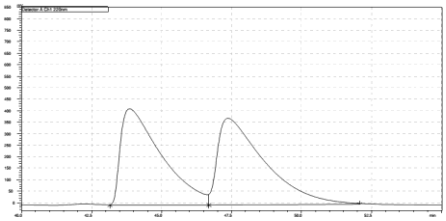
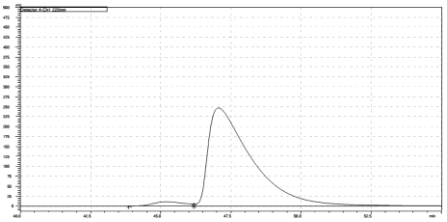
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 14.821 | 73355520 | 50.189 | 14.864 | 67929251 | 98.220 |
| 17.862 | 72804224 | 49.811 | 19.085 | 1230913 | 1.780 |

**(*R*,*Z*)-2-(5-(2-Methoxyphenyl)hepta-2,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.84):** **IR (neat):** 2973 (m), 2930 (w), 2163 (w), 1714 (w), 1490 (m), 1368 (m), 1030 (s), 905 (m), 859 (w), 752 (s), 668 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.22–7.10 (m, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.34 (t, *J* = 6.7 Hz, 1H), 6.03 (ddd, *J* = 17.2, 10.4, 7.0 Hz, 1H), 5.08–4.96 (m, 2H), 3.89 (q, *J* = 7.3 Hz, 1H), 3.81 (s, 3H), 2.61–2.46 (m, 2H), 1.65 (s, 3H), 1.24 (s, 12H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 157.0, 144.8, 141.0, 132.8, 128.1, 127.2, 120.7, 114.5, 110.8, 83.2, 55.5, 41.7, 33.8, 24.9 (d, *J* = 2.6 Hz), 14.2; **HRMS (DART):** Calcd for $C_{20}H_{30}BO_3$ $[M+H]^+$: 329.2282. Found: 329.2279; **Specific rotation:** $[\alpha]_D^{20}$ +2.8 (*c* 0.82, $CHCl_3$) for a 99:1 er sample. Enantiomeric purity of **2.84** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-H, 100% hexanes, 0.5 mL/min, 220 nm.

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 51.810 | 13395214 | 52.038 | 51.252 | 21900263 | 99.510 |
| 62.409 | 12345992 | 47.962 | 65.139 | 107797 | 0.490 |

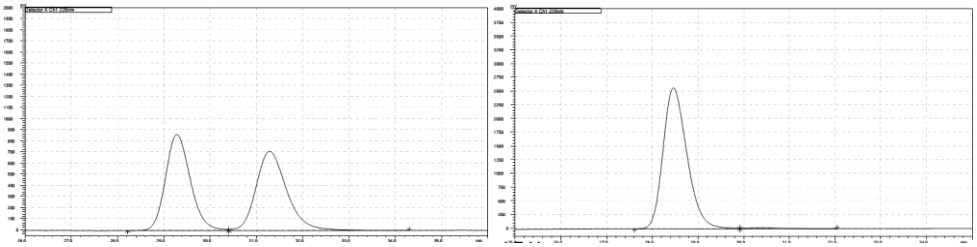
**(*R*,*Z*)-2-(5-(Furan-2-yl)hepta-2,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.85): IR (neat):** 2975 (m), 2924 (w), 2858 (w), 1631 (w), 1409 (w), 1369 (s), 1344 (m), 1303 (m), 1145 (m), 860 (w), 730 (w), 668 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.33 (s, 1H), 6.34–6.23 (m, 2H), 6.03 (d, *J* = 2.9 Hz, 1H), 5.89 (ddd, *J* = 17.4, 10.2, 7.7 Hz, 1H), 5.14–5.01 (m, 2H), 3.50 (q, *J* = 7.4 Hz, 1H), 2.63 (dt, *J* = 14.2, 6.6 Hz, 1H), 2.49 (dt, *J* = 15.1, 7.5 Hz, 1H), 1.68 (s, 3H), 1.25 (s, 12H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 157.0, 143.1, 141.4, 138.8, 115.8, 110.2, 105.1, 83.3, 42.9, 32.6, 24.9 (d, *J* = 2.4 Hz), 14.3; **HRMS (DART):** Calcd for $C_{17}H_{26}BO_3$ $[M+H]^+$: 289.1975. Found: 289.1975; **Specific rotation:** $[\alpha]_D^{20}$ –11.8 (*c* 0.090, $CHCl_3$) for a 99:1 er sample. Enantiomeric purity of **2.85** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.3 mL/min, 220 nm.

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 43.852 | 42723043 | 49.210 | 45.194 | 800521 | 2.920 |

| | | | | | |
|---|---|---|---|---|---|
| 47.368 | 44095022 | 50.790 | 47.058 | 26614809 | 97.080 |

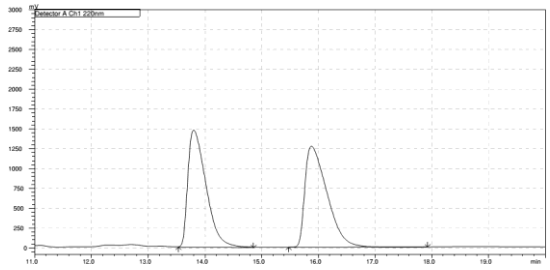
**(*R*,*Z*)-3-(6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,5-dien-3-yl)-1-tosyl-1H-indole (2.86): IR (neat):** 2974 (w), 2925 (w), 1630 (w), 1596 (w), 1446 (m), 1368 (s), 1303 (m), 1274 (m), 1172 (s), 1130 (s), 1094 (m), 986 (w), 745 (m), 664 (m), 581 (m), 537 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.03–7.87 (m, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.35 (s, 1H), 7.32–7.25 (m, 1H), 7.24–7.15 (m, 3H), 6.34 (t, *J* = 6.5 Hz, 1H), 5.95 (ddd, *J* = 17.2, 10.3, 7.1 Hz, 1H), 5.11–4.99 (m, 2H), 3.62 (q, *J* = 7.2 Hz, 1H), 2.69–2.53 (m, 2H), 2.33 (s, 3H), 1.66 (s, 3H), 1.25 (s, 12H); .**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 144.8, 143.4, 139.9, 135.6, 135.4, 130.6, 129.9, 126.9, 125.1, 124.7, 123.0, 122.9, 120.3, 115.5, 113.9, 83.3, 40.1, 33.5, 25.0, 24.9, 21.7, 14.4; **HRMS (DART):** Calcd for $C_{28}H_{35}BNO_4S$ $[M+H]^+$: 492.2374. Found: 492.2383; **Specific rotation:** $[\alpha]_D^{20}$ –12.0 (c 0.26, $CHCl_3$) for a 99:1 er sample. Enantiomeric purity of **2.86** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ-H, 98% hexanes, 0.3 mL/min, 220 nm.

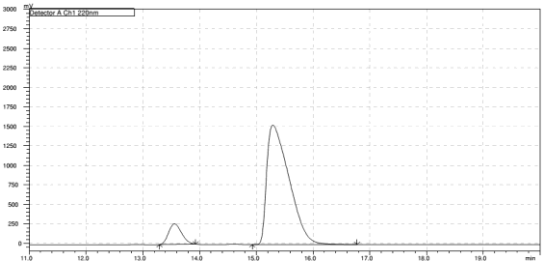


| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 29.279 | 32323881 | 49.484 | 28.461 | 93581085 | 98.892 |
| 31.283 | 32998485 | 50.516 | 30.392 | 1048410 | 1.108 |

**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(5-phenethylhepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.87): IR (neat):** 3026 (w), 2975 (m), 2922 (m), 1630 (m), 1409 (m), 1369 (s), 1344 (m), 1302 (m), 1077 (m), 860

(w), 698 (w), 666 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.27 (dd, *J* = 9.0, 5.8 Hz, 2H), 7.18 (d, *J* = 6.7 Hz, 3H), 6.31 (t, *J* = 5.6 Hz, 1H), 5.69 (dt, *J* = 17.0, 8.6 Hz, 1H), 5.08–5.00 (m, 2H), 2.72–2.62 (m, 1H), 2.58–2.49 (m, 1H), 2.30–2.13 (m, 3H), 1.81–1.72 (m, 1H), 1.68 (s, 3H), 1.64–1.57 (m, 1H), 1.26 (s, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 144.2, 142.8, 142.5, 128.6, 128.4, 125.8, 114.9, 83.2, 43.2, 36.2, 34.3, 33.6, 24.9, 14.3; **HRMS (DART):** Calcd for $C_{21}H_{32}BO_2$ $[M+H]^+$: 327.2490. Found: 327.2489; **Specific rotation:** $[\alpha]_D^{20}$ +10.1 (*c* 0.19, $CHCl_3$) for a 90:10 er sample. Enantiomeric purity of **2.87** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 99.5% hexanes, 0.5 mL/min, 220 nm.

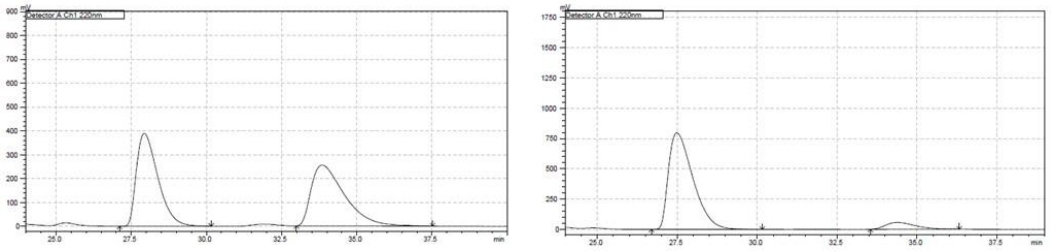




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 13.802 | 32930384 | 49.034 | 13.556 | 4186099 | 9.122 |
| 15.878 | 34228544 | 50.966 | 15.290 | 14702312 | 90.878 |

**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(4-(2-methylenecyclopentyl)but-2-en-2-yl)-1,3,2-dioxaborolane (2.88): IR (neat):** 2953 (m), 2922 (s), 2853 (w), 1369 (s), 1301 (w), 1138 (m), 1269 (m), 1060 (w), 907 (w), 766 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 6.37 (t, *J* = 6.9 Hz, 1H), 4.89 (s, 1H), 4.83 (s, 1H), 2.45–2.32 (m, 3H), 2.16–2.06 (m, 1H), 1.93–1.84 (m, 1H), 1.69 (s, 3H), 1.34–1.28 (m, 4H), 1.26 (s, 12H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 156.7, 145.2, 104.5, 83.2, 43.7, 33.6, 33.3, 32.9, 25.0, 24.2, 14.2;

**HRMS (DART):** Calcd for $C_{16}H_{28}BO_2$ $[M+H]^+$: 263.2177. Found: 263.2186; **Specific rotation:** $[\alpha]_D^{20}$ +8.3 (*c* 0.73, $CHCl_3$) for a 92:8 er sample. Enantiomeric purity of **2.88** was determined by HPLC analysis of the corresponding methyl ester produced through carbonylation of alkenyl B(pin)[41] in comparison with authentic racemic material; Chiralcel OK, 100% hexanes, 0.8 mL/min, 220 nm.

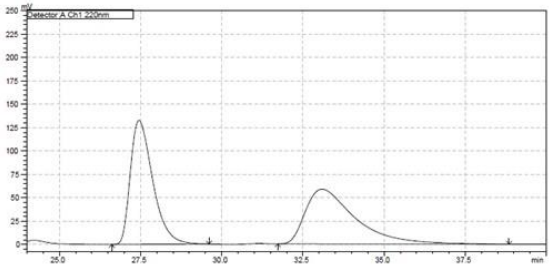


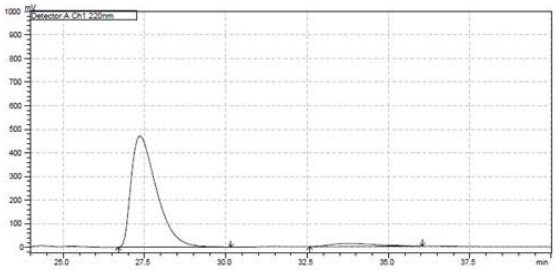
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 27.933 | 19349561 | 49.522 | 27.488 | 42245430 | 92.253 |
| 33.846 | 19699635 | 50.448 | 34.385 | 3547539 | 7.747 |

**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(4-(2-methylenecyclohexyl)but-2-en-2-yl)-1,3,2-dioxaborolane (2.89):**

**IR (neat):** 2974 (w), 2924 (s), 2852 (m), 1631 (w), 1369 (s), 1340 (w), 1301 (m), 1146 (w), 1133 (m), 1111 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 6.32 (t, *J* = 6.7 Hz, 1H), 4.66 (s, 1H), 4.57 (s, 1H), 2.38–2.32 (m, 1H), 2.28 (dd, *J* = 12.6, 4.4 Hz, 1H), 2.20 (dt, *J* = 15.5, 7.9 Hz, 1H), 2.12 (dt, *J* = 9.5, 4.8 Hz, 1H), 2.04–1.98 (m, 1H), 1.80 (dd, *J* = 12.3, 5.0 Hz, 1H), 1.69 (s, 3H), 1.68–1.63 (m, 1H), 1.47–1.38 (m, 2H), 1.32–1.26 (m, 1H), 1.26 (s, 12H), 1.19–1.12 (m, 1H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 153.1, 145.5, 105.4, 83.2, 42.8, 35.8, 33.9, 31.9, 28.9, 25.3, 25.0, 24.9 (d, *J* = 4.1 Hz), 14.3; **HRMS (DART):** Calcd for $C_{17}H_{30}BO_2$ $[M+H]^+$: 277.2334. Found: 277.2335; **Specific rotation:** $[\alpha]_D^{20}$ +2.1 (*c* 0.62, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **2.89** was determined by HPLC analysis of the

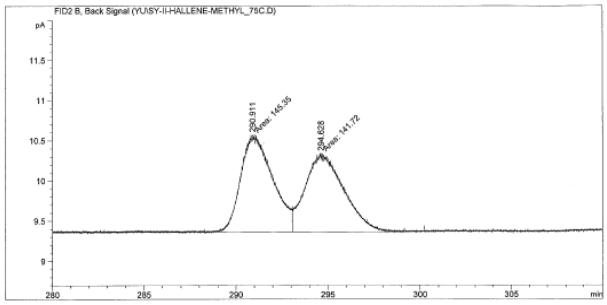
corresponding methyl ester produced through carbonylation of alkenyl B(pin)[41] in comparison with authentic racemic material; Chiralcel OK, 100% hexanes, 0.5 mL/min, 220 nm.

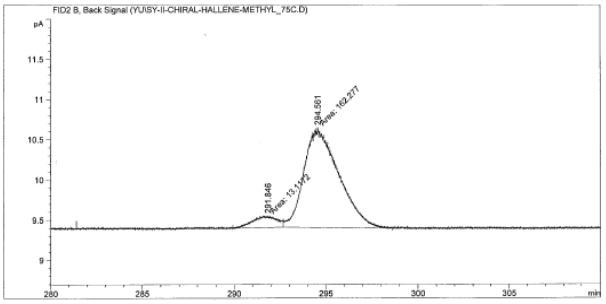




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 27.452 | 6360018 | 50.308 | 27.358 | 25489024 | 95.369 |
| 33.094 | 6282121 | 49.692 | 33.785 | 1237738 | 4.631 |

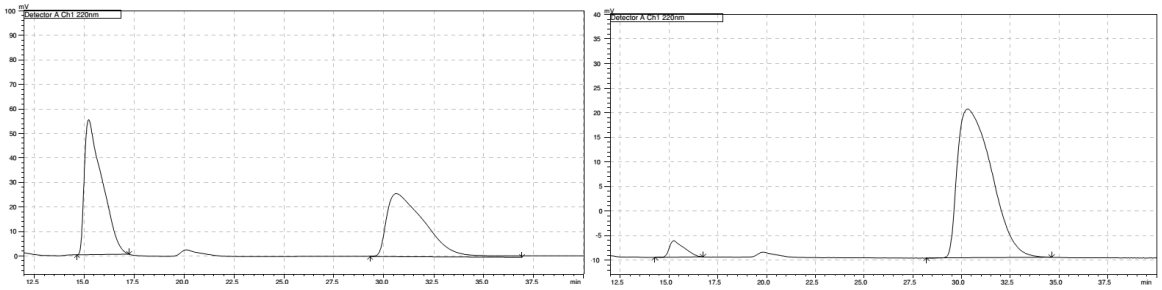
**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(4-methylhexa-1,5-dien-1-yl)-1,3,2-dioxaborolane (2.15): IR (neat):** 2975 (m), 2925 (w), 1637 (m), 1455 (w), 1396 (w), 1359 (s), 1318 (m), 1265 (w), 1237 (w), 1213 (w), 1143 (s), 995 (w), 969 (w), 909 (w), 849 (m) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 6.58 (dt, *J* = 17.9, 6.7 Hz, 1H), 5.76 (ddd, *J* = 17.3, 10.4, 6.8 Hz, 1H), 5.44 (d, *J* = 17.9 Hz, 1H), 5.03–4.87 (m, 2H), 2.36–2.19 (m, 2H), 2.11 (dt, *J* = 14.1, 7.1 Hz, 1H), 1.56 (s, 3H), 1.26 (s, 12H), 1.00 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 152.7, 144.1, 112.8, 83.2, 43.2, 36.9, 24.9, 19.7; **HRMS (DART):** Calcd for $C_{13}H_{24}BO_2$ $[M+H]^+$: 223.1869. Found: 223.1865; **Specific rotation:** $[\alpha]_D^{20}$ –4.1 (*c* 0.54, $CHCl_3$) for a 93:7 er sample. Enantiomeric purity of **2.15** was determined by GC analysis in comparison with authentic racemic material; alpha dex, 15 psi, 75 °C.



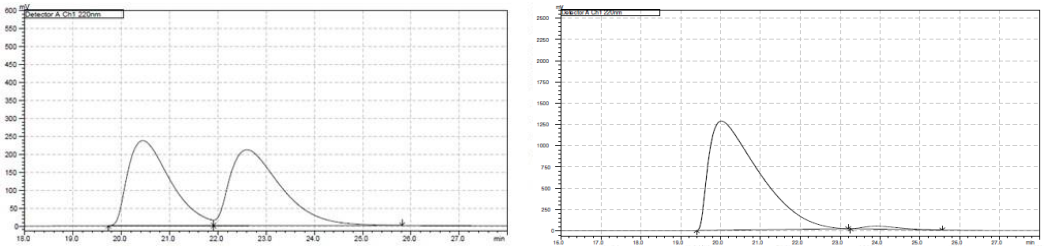

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 290.911 | 145.34981 | 50.63217 | 291.846 | 13.11721 | 7.47871 |
| 294.628 | 141.72029 | 49.36783 | 294.561 | 162.27673 | 92.52129 |

**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(4-phenethylhexa-1,5-dien-1-yl)-1,3,2-dioxaborolane (2.105): IR (neat):** 3023 (w), 2975 (w), 2924 (w), 1636 (m), 1359 (s), 1318 (m), 1143 (s), 995 (w), 970 (w), 911 (w), 849 (w), 637 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.31–7.22 (m, 2H), 7.20–7.13 (m, 3H), 6.56 (dt, *J* = 17.9, 6.6 Hz, 1H), 5.66 (ddd, *J* = 17.2, 10.3, 8.0 Hz, 1H), 5.43 (d, *J* = 18.1 Hz, 1H), 5.12–4.92 (m, 2H), 2.65 (ddd, *J* = 13.9, 10.4, 5.3 Hz, 1H), 2.52 (ddd, *J* = 13.8, 10.3, 6.4 Hz, 1H), 2.27–2.13 (m, 3H), 1.79–1.69 (m, 1H), 1.62–1.51 (m, 2H), 1.26 (s, 12H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 152.3, 142.7, 142.2, 128.6, 128.4, 125.8, 120.7 (br), 115.1, 83.2, 42.8, 41.8, 36.1, 33.5, 24.9; **HRMS (DART):** Calcd for $C_{20}H_{30}BO_2$ $[M+H]^+$: 313.2333. Found: 313.2335; **Specific rotation:** $[\alpha]_D^{20}$ +11.2 (*c* 0.38, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **2.105** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 99.9% hexanes, 0.8 mL/min, 220 nm.



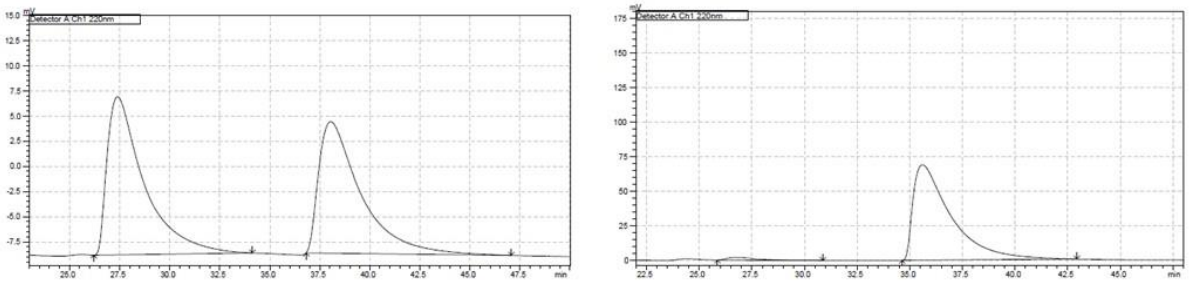
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 15.225 | 3405720 | 50.081 | 15.235 | 177097 | 4.591 |
| 30.624 | 3394754 | 49.919 | 30.331 | 3679973 | 95.409 |

**(*R*,*E*)-2-(4-Cyclohexylhexa-1,5-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.106): IR (neat):** 2974 (w), 2920 (s), 2850 (m), 1636 (s), 1446 (m), 1360 (s), 1318 (m), 1268 (w), 1143 (s), 1106 (m), 1057 (m), 996 (w), 970 (m), 909 (m), 849 (m), 770 (w), 674 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 6.55 (dt, *J* = 17.9, 6.8 Hz, 1H), 5.60 (dt, *J* = 18.9, 9.9 Hz, 1H), 5.41 (d, *J* = 17.9 Hz, 1H), 5.04–4.85 (m, 2H), 2.38–2.23 (m, 1H), 2.18 (dt, *J* = 14.3, 7.2 Hz, 1H), 2.04–1.89 (m, 1H), 1.76–1.59 (m, 5H), 1.26 (s, 12H), 1.24–1.04 (m, 4H), 1.00 (qd, *J* = 12.6, 2.4 Hz, 1H), 0.94–0.85 (m, 1H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 153.4, 140.7, 115.4, 83.1, 49.1, 41.1, 38.6, 31.2, 29.4, 26.8, 26.75, 26.70, 24.9 (d, *J* = 1.6 Hz); **HRMS (DART):** Calcd for $C_{18}H_{32}BO_2$ $[M+H]^+$: 291.2495. Found: 291.2498; **Specific rotation:** $[\alpha]_D^{20}$ +9.1 (*c* 1.38, $CHCl_3$) for a 98:2 er sample. Enantiomeric purity of **2.106** was determined by HPLC analysis of the corresponding methyl ester produced through carbonylation of alkenyl B(pin)[41] in comparison with authentic racemic material; Chiralpak AS-H, 100% hexanes, 0.5 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 20.446 | 14453470 | 48.183 | 20.017 | 11295585 | 98.149 |
| 22.600 | 15543486 | 51.817 | 23.909 | 2119280 | 1.851 |

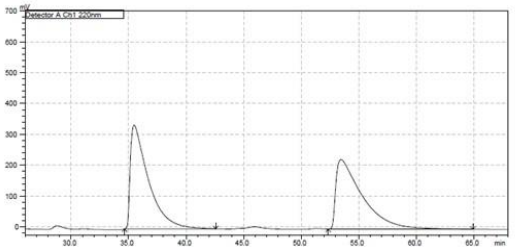
**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(4-phenylhexa-1,5-dien-1yl)-1,3,2-dioxaborolane (2.101): IR (neat):** 2975 (m), 2925 (w), 1724 (w), 1636 (w), 1447 (m), 1360 (m), 1322 (m), 1269 (m), 1141 (s), 908 (m), 849 (m), 759 (m), 699 (s), 672 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.29 (t, *J* = 7.7 Hz, 2H), 7.21–7.17 (m, 3H), 6.55 (dt, *J* = 17.9, 6.6 Hz, 1H), 5.96 (ddd, *J* = 17.2, 10.3, 7.3 Hz, 1H), 5.46 (d, *J* = 17.9 Hz, 1H), 5.08–4.98 (m, 2H), 3.42 (q, *J* = 7.3 Hz, 1H), 2.60 (t, *J* = 7.1 Hz, 2H), 1.25 (s, 12H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 152.0, 143.9, 141.5, 128.6, 127.8, 126.4, 114.8, 83.2, 48.9, 41.9, 24.9; **HRMS (DART):** Calcd for $C_{18}H_{29}BO_2N$ $[M+NH_4]^+$: 302.2291. Found: 302.2283. Specific rotation: $[\alpha]_D^{20}$ +3.3 (*c* 1.1, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **2.101** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.5 mL/min, 220 nm.

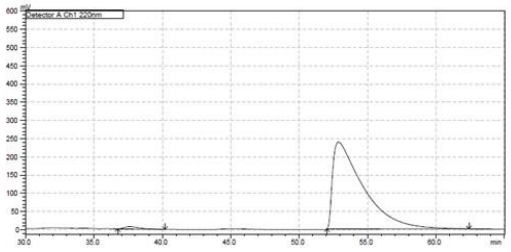


| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 27.401 | 2016218 | 51.271 | 26.740 | 187144 | 2.852 |
| 38.044 | 1916264 | 48.729 | 35.606 | 8670259 | 97.148 |

**(*R*,*E*)-2-(4-(3-Bromophenyl)hexa-1,5-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.107):**

**IR (neat):** 2974 (w), 2924 (w), 1725 (w), 1637 (w), 1566 (w), 1472 (m), 1361 (m), 1323 (m), 1268 (m), 1215 (m), 1141 (s), 1071 (m), 907 (m), 849 (m), 781 (s), 695 (m), 671 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.34–7.30 (m, 2H), 7.19–7.07 (m, 2H), 6.51 (dt, *J* = 17.9, 6.6 Hz, 1H), 5.91 (ddd, *J* = 17.5, 10.1, 7.3 Hz, 1H), 5.44 (d, *J* = 17.9 Hz, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 3.39 (q, *J* = 7.3 Hz, 1H), 2.64–2.50 (m, 2H), 1.25 (s, 12H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 151.2, 146.1, 140.7, 130.9, 130.2, 129.6, 126.5, 122.7, 115.4, 83.2, 48.6, 41.6, 24.9; **HRMS (DART):** Calcd for $C_{18}H_{28}BBrO_2N$ $[M+NH_4]^+$: 380.1396. Found: 380.1385; **Specific rotation:** $[\alpha]_D^{20}$ +4.6 (*c* 1.2, $CHCl_3$) for a 99:1 er sample. Enantiomeric purity of **2.107** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.5 mL/min, 220 nm.

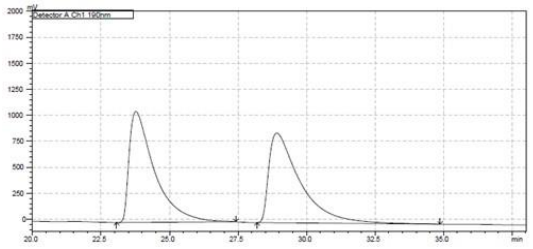


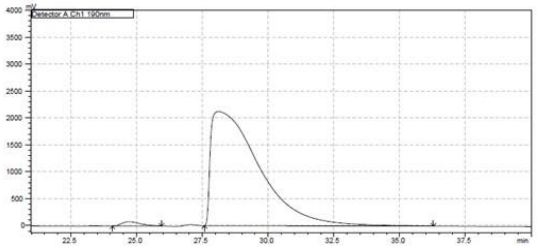


| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 35.482 | 36803489 | 50.588 | 37.608 | 500035 | 1.328 |
| 53.472 | 35948195 | 49.412 | 52.877 | 37146073 | 98.672 |

**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(4-(4-(trifluoromethyl)phenyl)hexa-1,5-dien-1-yl)-1,3,2-dioxaborolane (2.108): IR (neat):** 2976 (w), 2924 (w), 1725 (w), 1438 (w), 1371 (w), 1322 (s), 1269 (s), 1162 (m), 1119 (s), 1066 (s), 1016 (m), 908 (w), 843 (m), 769 (w), 672 (w), 605 (w) $cm^{-1}$; **$^1$H NMR**

**(600 MHz, $CDCl_3$):** δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.50 (dt, *J* = 17.9, 6.6 Hz, 1H), 5.94 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.45 (dt, *J* = 17.7, 1.6 Hz, 1H), 5.15–4.98 (m, 2H), 3.49 (q, *J* = 7.3 Hz, 1H), 2.65–2.54 (m, 2H), 1.24 (s, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 151.0, 147.8, 140.6, 128.7 (q, *J* = 32.4 Hz), 128.2, 125.5 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 270.4 Hz), 115.6, 83.3, 48.7, 41.6, 24.9; **$^{19}$F NMR (376 MHz, $CDCl_3$):** δ –62.33; **HRMS (DART):** Calcd for $C_{19}H_{28}BF_3O_2N$ $[M+NH_4]^+$: 370.2165. Found: 370.2175**; Specific rotation:** $[\alpha]_D^{20}$ +3.2 (*c* 0.81, $CHCl_3$) for a 99:1 er sample. Enantiomeric purity of **2.108** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 100% hexanes, 0.5 mL/min, 220 nm.

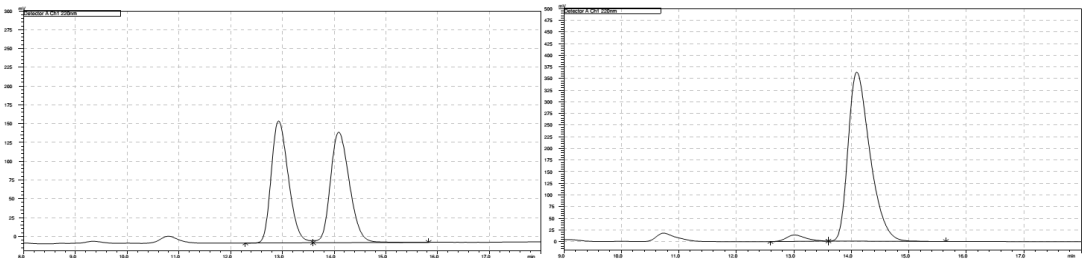




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 23.772 | 68659412 | 49.998 | 24.708 | 4082671 | 1.468 |
| 28.914 | 68665282 | 50.002 | 28.113 | 274087000 | 98.532 |

**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(4-(thiophen-2-yl)hexa-1,5-dien-1-yl)-1,3,2-dioxaborolane (2.109): IR (neat):** 2975 (w), 2925 (w), 1637 (m), 1437 (w), 1360 (s), 1322 (m), 1232 (w), 1144 (s), 970 (w), 849 (w), 695 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.15 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.83 (d, *J* = 3.5 Hz, 1H), 6.57 (dt, *J* = 17.9, 6.6 Hz, 1H), 5.92 (ddd, *J* = 17.4, 9.9, 7.7 Hz, 1H), 5.49 (dt, *J* = 17.9, 1.5 Hz, 1H), 5.17–5.02 (m, 2H), 3.71 (q, *J* = 7.4 Hz, 1H), 2.74–2.54 (m, 2H), 1.25 (s,

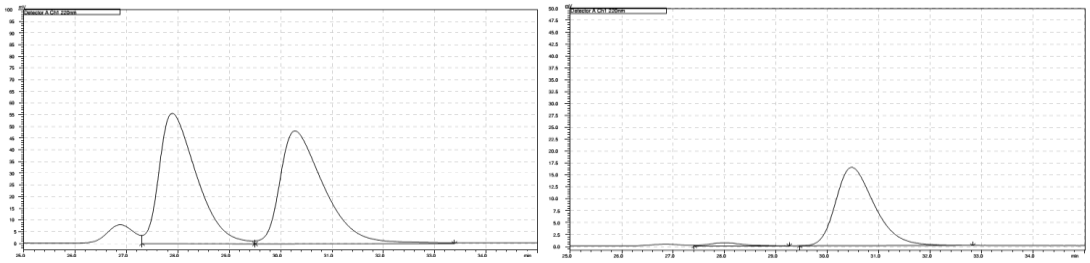
12H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 151.1, 147.6, 140.8, 126.8, 123.8, 123.6, 115.4, 83.2, 44.3, 42.8, 24.9; **HRMS (DART):** Calcd for $C_{28}H_{35}BNO_4S$ $[M+H]^+$: 291.1585. Found: 291.1597; **Specific rotation:** $[\alpha]_D^{20}$ –11.5 (*c* 0.73, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **2.109** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OD-H, 99.9% hexanes, 0.5 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 12.925 | 3738109 | 49.870 | 13.012 | 317387 | 3.206 |
| 14.087 | 3757643 | 50.130 | 14.094 | 9582728 | 96.794 |

**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(3-(2-methylenecyclohexyl)prop-1-en-1-yl)-1,3,2-dioxaborolane (2.110): IR (neat):** 2975 (w), 2925 (m), 1852 (w), 1636 (m), 1445 (w), 1358 (s), 1319 (m), 1268 (w), 1145 (s), 971 (w), 849 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 6.61 (dt, *J* = 17.9, 6.4 Hz, 1H), 5.45 (d, *J* = 18.0 Hz, 1H), 4.66 (s, 1H), 4.57 (s, 1H), 2.52–2.42 (m, 1H), 2.30–2.21 (m, 1H), 2.21–2.08 (m, 2H), 2.05–1.95 (m, 1H), 1.85–1.75 (m, 1H), 1.73–1.60 (m, 2H), 1.47–1.36 (m, 2H), 1.26 (s, 12H), 1.20–1.08 (m, 1H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 153.5, 152.7, 105.6, 83.2, 42.4, 39.2, 35.7, 33.8, 28.9, 25.1, 24.9, 24.9; **HRMS (DART):** Calcd for $C_{16}H_{28}BO_2$ $[M+H]^+$: 263.2177. Found: 263.2175; **Specific rotation:** $[\alpha]_D^{20}$ +6.9 (*c* 0.43, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **2.110** was determined

by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-H, 100% hexanes, 0.5 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 27.888 | 2825960 | 49.542 | 28.000 | 27880 | 3.135 |
| 30.278 | 2878176 | 50.458 | 30.471 | 861449 | 96.865 |

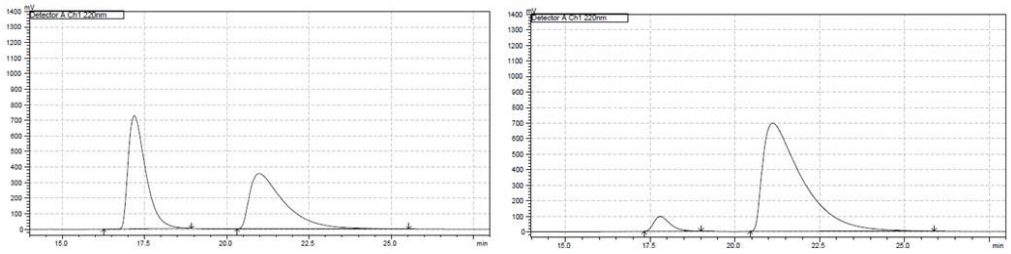
**4,4,5,5-Tetramethyl-2-((*E*)-3-((1*S*,5*S*)-2-methylene-5-(prop-1-en-2-yl)cyclohexyl)prop-1-en-1-yl)-1,3,2-dioxaborolane (2.111): IR (neat):** 3080 (w), 2975 (m), 2926 (m), 2852 (w), 1637 (m), 1440 (w), 1357 (s), 1319 (m), 1144 (s), 996 (w), 970 (w), 888 (m), 848 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 6.63 (dt, *J* = 17.9, 6.3 Hz, 1H), 5.47 (d, *J* = 17.8 Hz, 1H), 4.74–4.56 (m, 4H), 2.62–2.50 (m, 1H), 2.38 (dt, *J* = 13.0, 3.4 Hz, 1H), 2.16–2.01 (m, 4H), 1.96–1.79 (m, 2H), 1.69 (d, *J* = 1.2 Hz, 3H), 1.30–1.24 (m, 13H), 0.95 (q, *J* = 12.1 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 153.3, 152.1, 150.1, 108.8, 105.2, 83.2, 45.7, 41.5, 39.34, 39.30, 36.9, 33.9, 25.0, 24.9, 20.9; **HRMS (DART):** Calcd for $C_{19}H_{32}BO_2$ $[M+H]^+$: 303.2490. Found: 303.2491; **Specific rotation:** $[\alpha]_D^{20}$ +4.0 (*c* 0.15, $CHCl_3$) for a 96:4 dr sample.

**4,4,5,5-Tetramethyl-2-((*E*)-3-((1*R*,5*S*)-2-methylene-5-(prop-1-en-2-yl)cyclohexyl)prop-1-en-1-yl)-1,3,2-dioxaborolane (2.112): IR (neat):** 3066 (w), 2975 (m), 2927 (m), 2852 (w), 1637 (m), 1444 (w), 1360 (s), 1319 (m), 1144 (s), 1000 (w), 971 (w), 889 (m), 848 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):**

δ 6.54 (dt, *J* = 17.9, 6.8 Hz, 1H), 5.42 (d, *J* = 17.8 Hz, 1H), 4.73–4.46 (m, 4H), 2.53–2.44 (m, 1H), 2.40–2.29 (m, 2H), 2.27–2.08 (m, 3H), 1.88–1.71 (m, 2H), 1.69 (s, 3H), 1.53–1.39 (m, 1H), 1.31–1.23 (m, 13H); **$^{13}$C NMR (101MHz, $CDCl_3$):** δ 153.1, 150.9, 150.0, 108.8, 108.2, 83.2, 42.6, 39.3, 39.1, 36.5, 33.2, 31.2, 24.9 (d, *J* = 2.7 Hz), 21.1; **HRMS (DART):** Calcd for $C_{19}H_{32}BO_2$ $[M+H]^+$: 303.2490. Found: 303.2502; **Specific rotation:** $[\alpha]_D^{20}$ –30.8 (*c* 0.40, $CHCl_3$) for a >98:2 dr sample.

- **Products with a Quaternary Carbon Stereogenic Center**

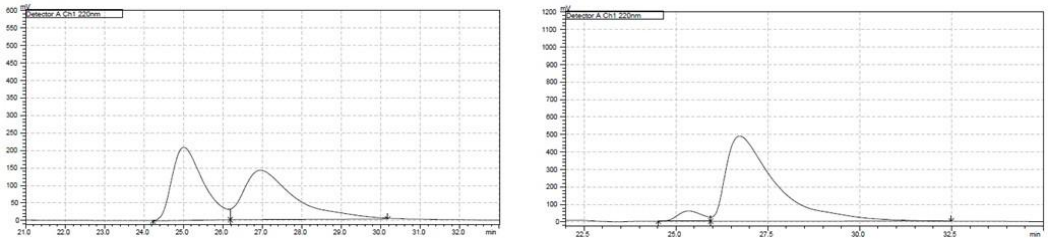
**(*R,Z*)-2-(5,9-Dimethyl-5-vinyldeca-2,8-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.90):** **IR (neat):** 2968 (w), 1714 (w), 1445 (w), 1365 (w), 1268 (m), 1034 (s), 902 (s), 872 (w), 762 (s) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 6.33 (t, *J* = 7.3 Hz, 1H), 5.76 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.09 (t, *J* = 7.5 Hz, 1H), 5.02–4.89 (m, 2H), 2.17 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.11 (dd, J = 14.7, 6.9 Hz, 1H), 1.87 (q, *J* = 7.9 Hz, 2H), 1.67 (s, 6H), 1.58 (s, 3H), 1.36–1.31 (m, 2H), 1.25 (s, 12H), 1.00 (s, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 147.0, 142.6, 131.2, 125.2, 111.9, 83.2, 40.6, 40.2, 39.7, 25.8, 24.9 (d, *J* = 3.4 Hz), 23.1, 23.0, 17.7, 14.3; **HRMS (DART):** Calcd for $C_{20}H_{36}BO_2$ $[M+H]^+$: 319.2803. Found: 319.2803; **Specific rotation:** $[\alpha]_D^{20}$ +4.7 (*c* 0.38, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **2.90** was determined by HPLC analysis of the corresponding methyl ester produced through carbonylation of alkenyl B(pin)[41] in comparison with authentic racemic material; Chiralpak AD-H, 100% hexanes, 0.5 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 17.184 | 27020752 | 50.942 | 17.800 | 3168060 | 5.351 |
| 20.983 | 26021487 | 49.058 | 21.118 | 56034616 | 94.649 |

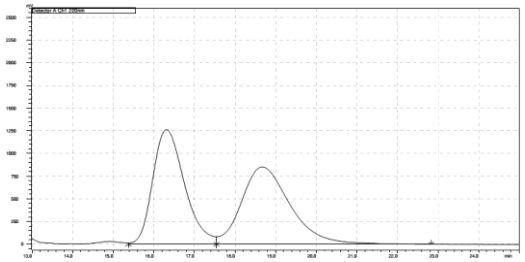
**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(5-methyl-5-phenylhepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.91):**

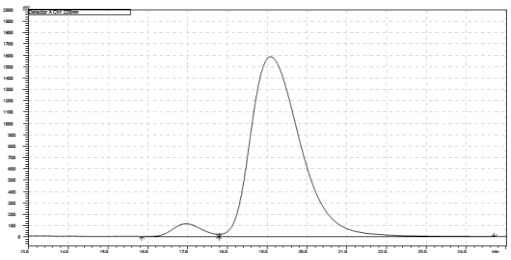
**IR (neat):** 2973 (w), 2925 (w), 1716 (w), 1444 (w), 1410 (w), 1369 (m), 1303 (w), 1269 (m), 1077 (s), 906 (s), 764 (m), 700 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.36–7.27 (m, 4H), 7.18 (tt, *J* = 6.7, 1.4 Hz, 1H), 6.24 (td, *J* = 7.0, 1.7 Hz, 1H), 6.06 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.12 (dd, *J* = 10.7, 1.2 Hz, 1H), 5.05 (dd, *J* = 17.5, 1.2 Hz, 1H), 2.67–2.55 (m, 2H), 1.66 (s, 3H), 1.39 (s, 3H), 1.23 (s, 12H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 147.5, 146.6, 142.3, 128.2, 126.8, 126.0, 112.4, 83.2, 44.6, 39.9, 25.3, 24.9, 14.4; **HRMS (DART):** Calcd for $C_{20}H_{30}BO_2$ $[M+H]^+$: 313.2339. Found: 313.2349; **Specific rotation:** $[\alpha]_D^{20}$ +5.6 (*c* 0.53, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **2.91** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AD-H, 100% hexanes, 0.2 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 25.007 | 11560948 | 47.765 | 25.343 | 2662403 | 5.527 |
| 26.950 | 12642626 | 52.235 | 26.733 | 45509942 | 94.473 |

**(*R,Z*)-2-(5-(3-Chlorophenyl)-5-methylhepta-2,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.92): IR (neat):** 2974 (m), 2929 (w), 1629 (w), 1593 (w), 1466 (w), 1410 (m), 1369 (m), 1344 (m), 1303 (m), 1145 (m), 918 (w), 860 (w), 784 (w), 666 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.31–7.29 (m, 1H), 7.24–7.20 (m, 2H), 7.19–7.14 (m, 1H), 6.18 (td, *J* = 7.0, 1.8 Hz, 1H), 6.02 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.15 (dd, *J* = 10.7, 1.1 Hz, 1H), 5.07 (dd, *J* = 17.5, 1.1 Hz, 1H), 2.64–2.50 (m, 2H), 1.64 (s, 3H), 1.37 (s, 3H), 1.23 (s, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 149.6, 145.8, 141.6, 134.1, 129.4, 127.3, 126.2, 125.1, 113.0, 83.3, 44.7, 39.8, 25.3, 24.9 (d, *J* = 3.3 Hz), 14.4; **HRMS (DART):** Calcd for $C_{20}H_{29}BO_2Cl$ $[M+H]^+$: 347.1944. Found: 347.1934; **Specific rotation:** $[\alpha]_D^{20}$ +17.8 (c 0.30, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **2.92** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OJ-H, 100% hexanes, 0.3 mL/min, 220 nm.

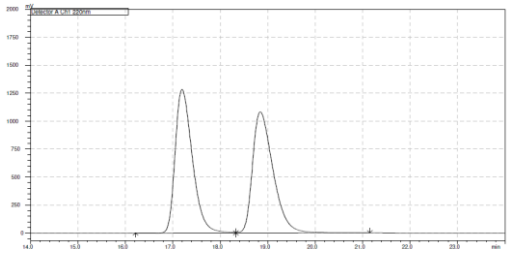


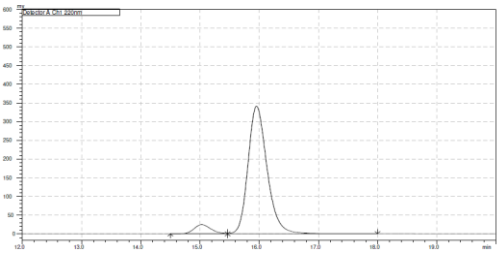


| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 16.313 | 68552140 | 49.246 | 16.957 | 5809718 | 4.097 |
| 18.671 | 70651389 | 50.754 | 19.079 | 136011666 | 95.903 |

**(*R,Z*)-4,4,5,5-Tetramethyl-2-(5-methyl-5-(4-(trifluoromethyl)phenyl)hepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.93): M. P.:** 53-55 °C; **IR (neat):** 2976 (w), 2931 (w), 1629 (w), 1410 (w), 1369 (w), 1326 (s), 1165 (m), 1123 (m), 1078 (m), 1015 (w), 837 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.55

(d, $J$ = 8.4 Hz, 2H), 7.44 (d, $J$ = 8.3 Hz, 2H), 6.17 (td, $J$ = 7.0, 1.8 Hz, 1H), 6.04 (dd, $J$ = 17.5, 10.7 Hz, 1H), 5.16 (dd, $J$ = 10.8, 1.1 Hz, 1H), 5.07 (dd, $J$ = 17.4, 1.1 Hz, 1H), 2.67–2.54 (m, 2H), 1.66–1.63 (m, 3H), 1.41 (s, 3H), 1.22 (s, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 151.5, 145.8, 141.3, 128.3 (q, $J$ = 32.4 Hz), 127.3, 125.1 (q, $J$ = 3.8 Hz), 124.5 (q, $J$ = 270.4 Hz) 113.2, 83.3, 44.8, 39.8, 25.3, 24.9 (d, $J$ = 1.9 Hz), 14.4; **$^{19}$F NMR (376 MHz, $CDCl_3$):** δ –62.37; **HRMS (DART):** Calcd for $C_{21}H_{29}BO_2F_3$ $[M+H]^+$: 381.2207. Found: 381.2199; **Specific rotation:** $[\alpha]_D^{20}$ +11.1 (*c* 0.21, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **2.93** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-3, 100% hexanes, 1.0 mL/min, 220 nm.

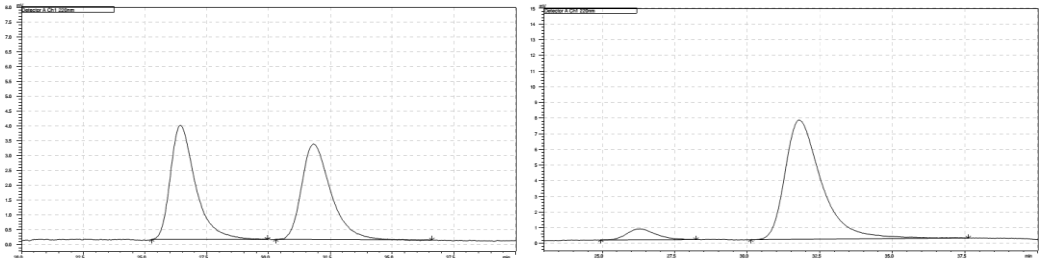




| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 17.191 | 32340850 | 50.056 | 15.031 | 488779 | 6.024 |
| 18.842 | 32268593 | 49.944 | 15.956 | 7625033 | 93.976 |

**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(5-methyl-5-(thiophen-3-yl)hepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.94): IR (neat):** 2974 (m), 2929 (w), 1629 (w), 1409 (w), 1368 (s), 1342 (m), 1302 (m), 1144 (m), 912 (w), 859 (w), 780 (w), 666 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.26–7.23 (m, 1H), 7.03–7.00 (m, 1H), 7.00–6.97 (m, 1H), 6.26 (tt, $J$ = 7.1, 1.7 Hz, 1H), 6.05 (dd, $J$ = 17.4, 10.6 Hz, 1H), 5.06 (d, $J$ = 10.6 Hz, 1H), 4.99 (d, $J$ = 17.4 Hz, 1H), 2.62–2.50 (m, 2H), 1.66 (s, 3H), 1.39 (s, 3H), 1.24 (s, 12H); **$^{13}$C**

**NMR (126 MHz, $CDCl_3$):** δ 149.1, 146.2, 142.0, 127.2, 125.1, 119.6, 112.2, 83.2, 43.0, 40.3, 25.2, 24.9, 14.4; **HRMS (DART):** Calcd for $C_{18}H_{28}BO_2S$ $[M+H]^+$: 319.1898. Found: 319.1901; **Specific rotation:** $[\alpha]_D^{20}$ +2.8 (*c* 0.57, $CHCl_3$) for a 93:7 er sample. Enantiomeric purity of **2.94** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-H, 100% hexanes, 1.0 mL/min, 220 nm.

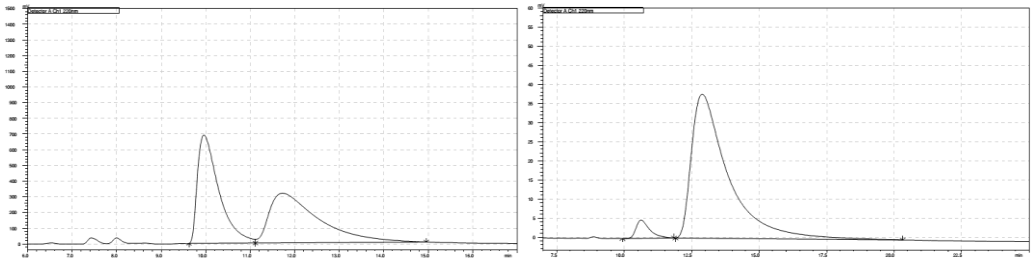


| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 26.433 | 270877 | 50.703 | 26.299 | 48364 | 6.773 |
| 31.816 | 263363 | 49.297 | 31.772 | 665662 | 93.227 |

**(*R*,*Z*)-4,4,5,5-Tetramethyl-2-(5-methyl-5-phenethylhepta-2,6-dien-2-yl)-1,3,2-dioxaborolane (2.95):**

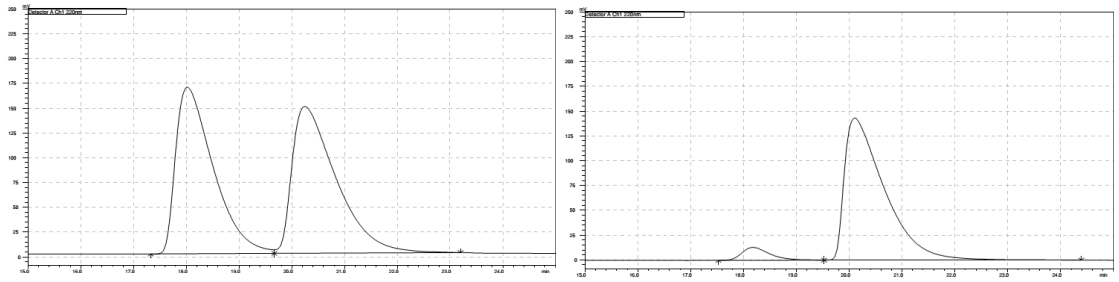
**IR (neat):** 3023 (w), 2974 (m), 2929 (w), 1629 (w), 1454 (w), 1369 (s), 1347 (m), 1302 (m), 1144 (m), 1100 (w), 911 (w), 859 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.29–7.23 (m, 2H), 7.19–7.12 (m, 3H), 6.36 (td, *J* = 7.3, 1.8 Hz, 1H), 5.83 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.07 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.00 (dd, *J* = 17.5, 1.4 Hz, 1H), 2.55–2.46 (m, 2H), 2.29–2.12 (m, 2H), 1.69 (s, 3H), 1.67–1.59 (m, 2H), 1.26 (s, 12H), 1.07 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$):**δ 146.7, 143.4, 142.3, 128.5, 128.4, 125.7, 112.3, 83.2, 42.8, 40.4, 39.7, 30.9, 25.0, 24.9, 23.1, 14.4; **HRMS (DART):** Calcd for $C_{22}H_{34}BO_2$ $[M+H]^+$: 341.2646. Found: 341.2643; **Specific rotation:** $[\alpha]_D^{20}$ –1.7 (*c* 0.73, $CHCl_3$) for a 96:4 er sample. Enantiomeric

purity of **2.95** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AD-H, 100% hexanes, 0.5 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 9.959 | 23148172 | 48.665 | 10.625 | 168144 | 4.488 |
| 11.724 | 24417862 | 51.335 | 12.890 | 3578699 | 95.512 |

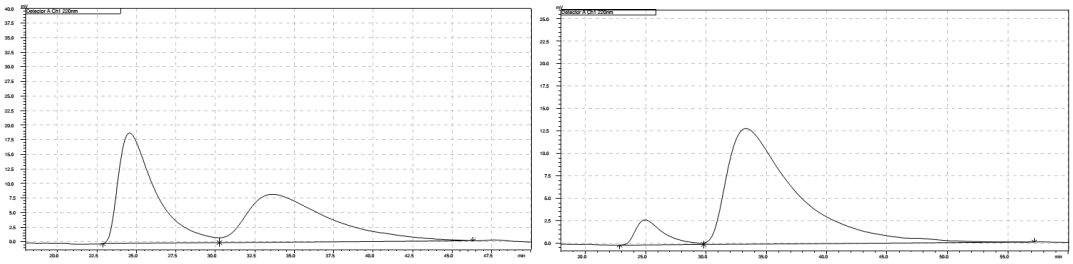
**(*R*,*Z*)-2-(5-Cyclohexyl-5-methylhepta-2,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.96): IR (neat):** 2974 (m), 2923 (s), 2850 (m), 1627 (w), 1410 (w), 1369 (s), 1301 (m), 1145 (m), 666 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 6.31 (t, *J* = 6.3 Hz, 1H), 5.75 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.01 (dd, *J* = 10.9, 1.6 Hz, 1H), 4.88 (dd, *J* = 17.6, 1.6 Hz, 1H), 2.25 (dd, *J* = 14.9, 7.8 Hz, 1H), 2.10 (dd, *J* = 14.9, 6.6 Hz, 1H), 1.80–1.69 (m, 4H), 1.69–1.59 (m, 4H), 1.25 (s, 12H), 1.21–1.02 (m, 4H), 1.02–0.85 (m, 5H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 146.2, 143.2, 112.3, 83.1, 46.1, 42.8, 37.6, 27.9, 27.4, 27.3, 26.9, 25.0, 24.9, 19.6, 14.4; **HRMS (DART):** Calcd for $C_{22}H_{34}BO_2$ $[M+H]^+$: 319.2803. Found: 319.2798; **Specific rotation:** $[\alpha]_D^{20}$ +5.9 (*c* 0.14, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **2.96** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-3, 100% hexanes, 0.5 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 18.017 | 8331115 | 49.180 | 18.177 | 475870 | 5.954 |
| 20.247 | 8609089 | 50.820 | 20.107 | 7516910 | 94.046 |

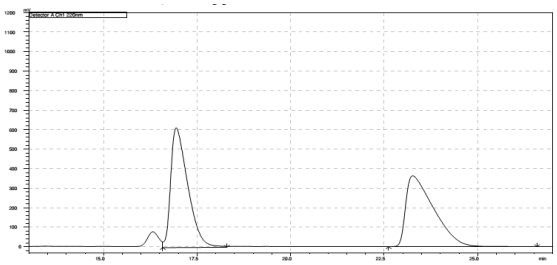
**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(4-methyl-4-phenylhexa-1,5-dien-1-yl)-1,3,2-dioxaborolane (2.113):**

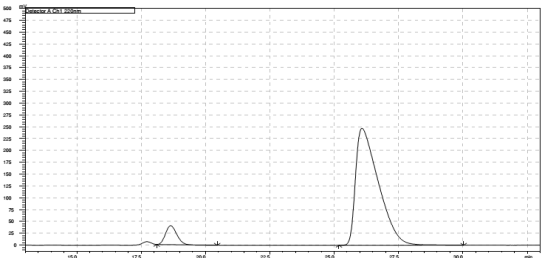
**IR (neat):** 2975 (m), 2927 (w), 1635 (m), 1444 (m), 1359 (s), 1324 (s), 998 (w), 849 (w), 763 (w), 699 (m) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.37–7.27 (m, 4H), 7.22–7.15 (m, 1H), 6.44 (dt, *J* = 17.9, 7.0 Hz, 1H), 6.03 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.46 (d, *J* = 17.8 Hz, 1H), 5.12 (dd, *J* = 10.7, 1.2 Hz, 1H), 5.04 (dd, *J* = 17.4, 1.2 Hz, 1H), 2.65 (d, *J* = 7.0 Hz, 2H), 1.37 (s, 3H), 1.24 (d, *J* = 0.7 Hz, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 150.6, 147.1, 146.4, 128.3, 126.7, 126.1, 112.4, 83.1, 47.9, 44.3, 25.3, 24.9; **HRMS (DART):** Calcd for $C_{19}H_{28}BO_2$ $[M+H]^+$: 299.2177. Found: 299.2180; **Specific rotation:** $[\alpha]_D^{20}$ +8.4 (*c* 0.50, $CHCl_3$) for a 92:8 er sample. Enantiomeric purity of **2.113** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AD-H, 100% hexanes, 0.4 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 24.563 | 3102576 | 50.784 | 24.936 | 451117 | 8.159 |
| 33.557 | 3006776 | 49.216 | 33.332 | 5077621 | 91.841 |

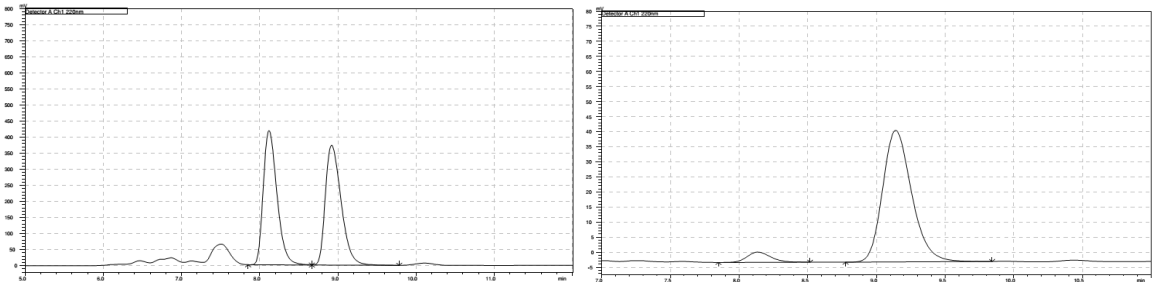
**(*R*,*E*)-4,4,5,5-tetramethyl-2-(4-methyl-4-(4-(trifluoromethyl)phenyl)hexa-1,5-dien-1-yl)-1,3,2-dioxaborolane (2.114): IR (neat):** 2976 (w), 2928 (w), 1636 (m), 1396 (m), 1360 (m), 1325 (s), 1165 (m), 1124 (m), 1179 (w), 1014 (w), 919 (w), 839 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 6.38 (dt, *J* = 17.8, 7.0 Hz, 1H), 6.01 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.46 (d, *J* = 17.8 Hz, 1H), 5.16 (d, *J* = 10.7 Hz, 1H), 5.06 (d, *J* = 17.5 Hz, 1H), 2.65 (d, *J* = 7.0 Hz, 2H), 1.39 (s, 3H), 1.23 (s, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 151.1, 149.6, 145.6, 128.4 (q, *J* = 32.5 Hz), 127.2, 125.2 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 270.5 Hz), 113.2, 83.2, 47.8, 44.5, 25.3, 24.9 (d, *J* = 1.5 Hz); **$^{19}$F NMR (376 MHz, $CDCl_3$):** δ −62.40; **HRMS (DART):** Calcd for $C_{20}H_{27}BO_2F_3$ $[M+H]^+$: 367.2051. Found: 367.2047; **Specific rotation:** $[\alpha]_D^{20}$ +18.1 (*c* 0.34, $CHCl_3$) for a 92:8 er sample. Enantiomeric purity of **2.114** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-H, 99.9% hexanes, 0.5 mL/min, 220 nm.





| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 16.940 | 19408791 | 50.778 | 18.645 | 1208999 | 7.360 |
| 23.262 | 18813867 | 49.222 | 26.079 | 15217248 | 92.640 |

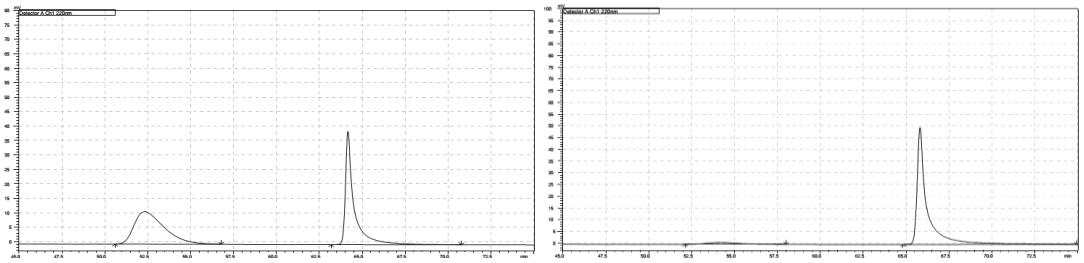
**(*R*,*E*)-4,4,5,5-Tetramethyl-2-(4-methyl-4-phenethylhexa-1,5-dien-1-yl)-1,3,2-dioxaborolane (2.115): IR (neat):** 3023 (w), 2974 (m), 2928 (w), 1636 (m), 1454 (w), 1360 (s), 1321 (m), 1144 (m), 999 (w), 970 (w), 912 (w), 849 (w), 698 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.29–7.23 (m, 2H), 7.19–7.13 (m, 3H), 6.59 (dt, *J* = 17.8, 7.2 Hz, 1H), 5.81 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.47 (d, *J* = 17.8 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.99 (d, *J* = 17.5 Hz, 1H), 2.55–2.48 (m, 2H), 2.29–2.20 (m, 2H), 1.65–1.57 (m, 2H), 1.26 (s, 12H), 1.06 (s, 3H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 150.7, 146.5, 143.3, 128.5, 128.4, 125.7, 112.5, 83.2, 47.8, 42.8, 40.0, 30.8, 24.9, 23.2; **HRMS (DART):** Calcd for $C_{21}H_{32}BO_2$ $[M+H]^+$: 327.2490. Found: 327.2492; **Specific rotation:** $[\alpha]_D^{20}$ –56.7 (*c* 0.04, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **2.115** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-H, 99.5% hexanes, 0.5 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 8.118 | 5118308 | 49.522 | 8.136 | 40162 | 5.891 |
| 8.920 | 5217034 | 50.478 | 9.140 | 641580 | 94.109 |

***(R,E)*-2-(4-Cyclohexyl-4-methylhexa-1,5-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.116): IR (neat):** 2976 (m), 2924 (s), 2851 (m), 1635 (m), 1448 (w), 1359 (s), 1321 (m), 1213 (w), 1145 (s), 1000 (w), 971 (w), 910 (w), 849 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 6.55 (dt, *J* = 17.8,

7.1 Hz, 1H), 5.74 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.41 (d, *J* = 17.7 Hz, 1H), 5.02 (dd, *J* = 10.9, 1.5 Hz, 1H), 4.88 (dd, *J* = 17.6, 1.5 Hz, 1H), 2.21 (d, *J* = 7.1 Hz, 2H), 1.80–1.57 (m, 5H), 1.26 (s, 12H), 1.22–0.99 (m, 4H), 0.99–0.85 (m, 5H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 151.6, 145.9, 112.5, 83.1, 45.9, 45.8, 42.5, 27.8, 27.3, 27.2, 26.9, 24.9, 19.8; **HRMS (DART):** Calcd for $C_{19}H_{34}BO_2$ $[M+H]^+$: 305.2646. Found: 305.2642; **Specific rotation:** $[\alpha]_D^{20}$ +7.2 (*c* 0.19, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **2.116** was determined by HPLC analysis in comparison with authentic racemic material; Chiralcel OZ-H, 100% hexanes, 0.8 mL/min, 220 nm.



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 52.322 | 1369972 | 50.269 | 54.158 | 93006 | 4.470 |
| 64.166 | 1355307 | 49.731 | 65.810 | 1987537 | 95.530 |

- **Procedure for Polar Functional Group Compatibility Experiments**

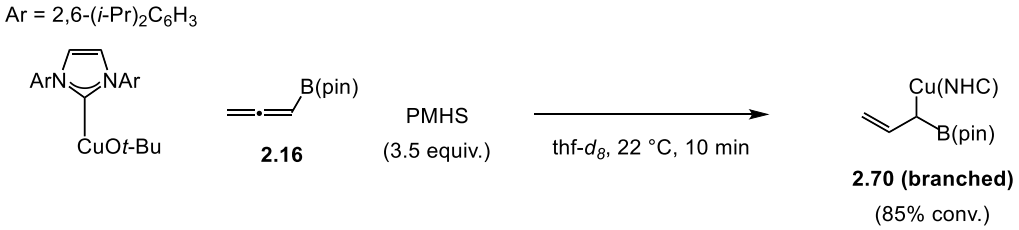
In a $N_2$-filled glove box, an oven-dried 2-dram vial with magnetic stir bar was charged with CuCl (0.5 mg, 0.005 mmol), (*S*)-**imid-2.1** (4.7 mg, 0.0055 mmol), LiO*t*-Bu (9.6 mg, 0.12 mmol), and freshly distilled tetrahydrofuran (THF, 0.5 mL). The mixture was premixed for 30 min before PMHS (30.0 mg, 0.50 mmol), allenyl boronic acid pinacol ester **2.16** (24.9 mg, 0.15 mmol) and additional THF (0.5 mL) were added, causing the solution to turn dark-red immediately. After 10 min, a solution of allylic

phosphate **2.73** (27.3 mg, 0.10 mmol) and probe (0.10 mmol) in THF (0.5 mL) was added to the reaction (at 22 °C). The vial was sealed with electrical tape before removal from the glove box, and the mixture was allowed to stir for 2 h at 22 °C, after which it was quenched with an aqueous solution of sat. $NH_4Cl$ (0.1 mL). The mixture was stirred for 15 min before it was passed through a short plug of oven-dried silica gel and eluted with EtOAc. The organic layer was concentrated under reduced pressure, affording yellow oil, which was purified by silica gel chromatography (1:1 hexanes:$CH_2Cl_2$→1:1 hexanes: EtOAc) to afford **2.101** and recovered probe as colorless oil.

- **Mechanistic Experiments**

To gain insight regarding the ground state structure of the intermediate generated by Cu–H addition to allenes **2.11** and **2.16**, we carried out the experiments described below.

***NHC–Cu–allyl complex derived from allene 2.16***



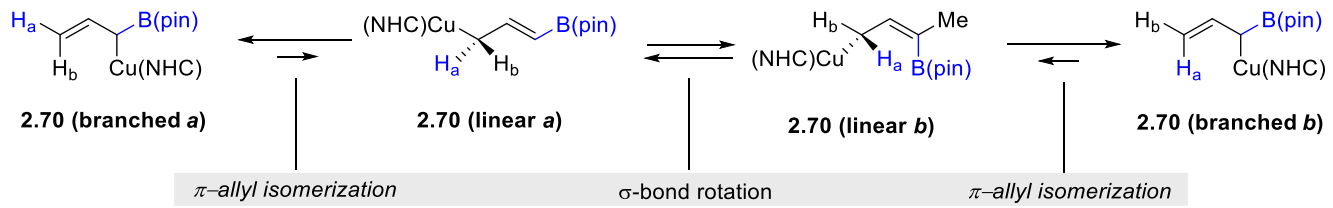

In a glove box, an oven-dried 2-dram vial equipped with a stir bar was charged with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]CuO*t*-Bu[42] (10.6 mg, 0.02 mmol) and thf-$d_8$. This mixture was charged with PMHS (4.3 mg, 0.07 mmol) and the mixture was allowed to stir for 1 min, after which **2.16**

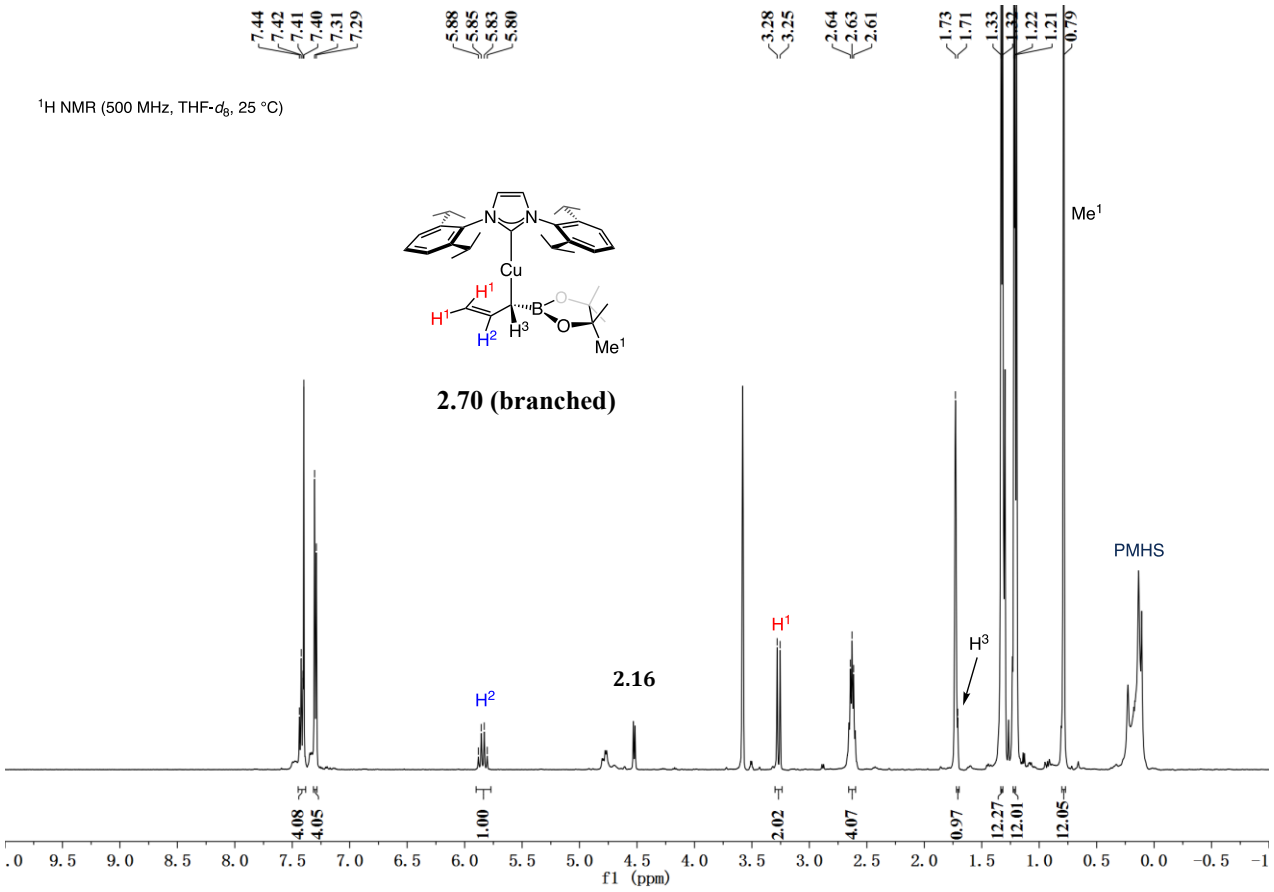
(42) Mankad, N. P., Laitar, D. S. & Sadighi, J. P. *Organometallics* **2004***, 23***,** 3369–3371.

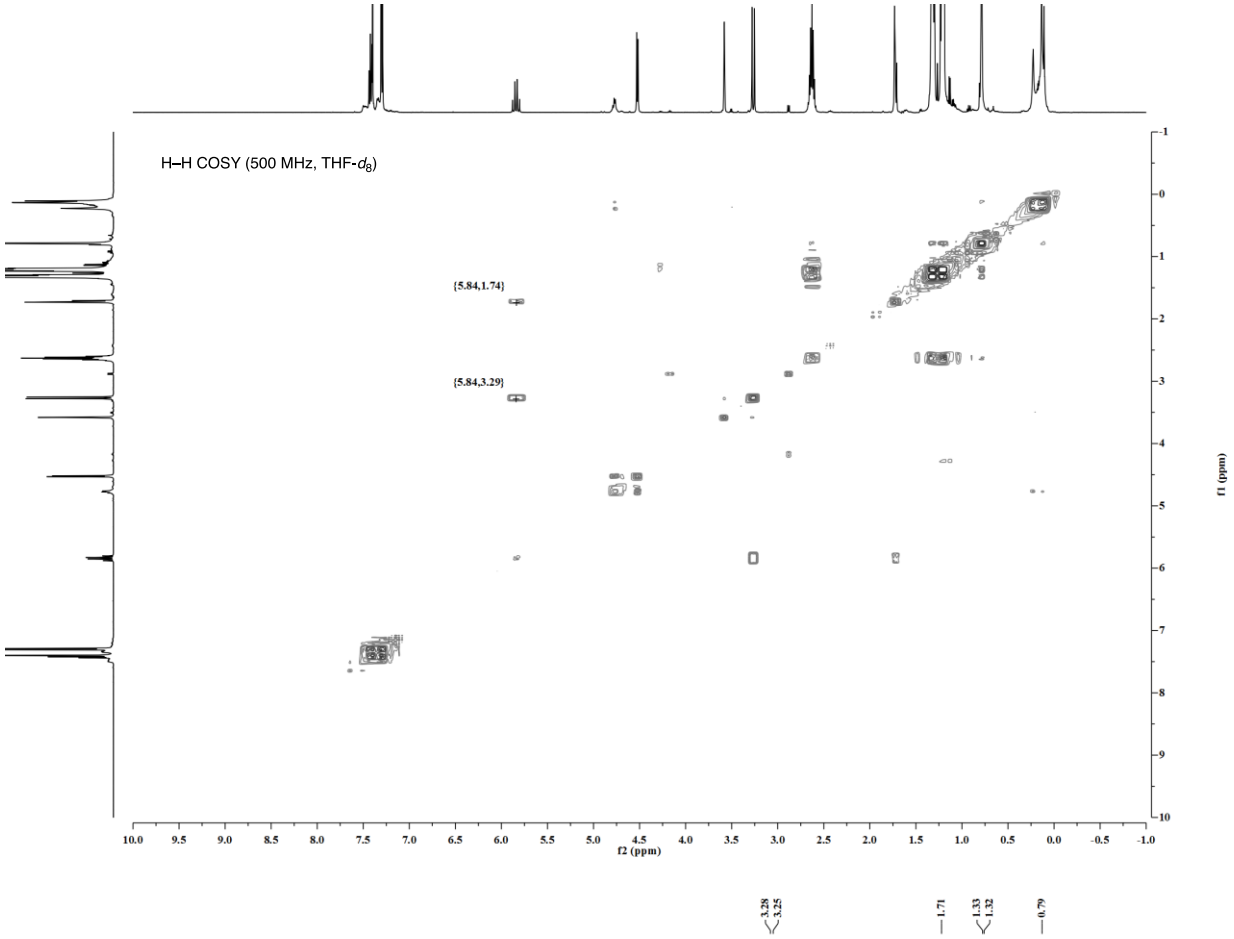
(4.0 mg, 0.024 mmol) was added and the mixture was allowed to stir for 10 min. Suitable crystals for X-ray diffraction were obtained by vapor diffusion of hexanes into a saturated solution of the Cu–allyl complex in a hexanes:$Et_2O$ mixture (1:2) in a freezer of a glovebox at –40 °C. Analysis of $^1$H NMR of the unpurified mixture indicated that there was 85% conversion, and the identity of the product was ascertained by $^1$H NMR, HH-COSY and nOe experiments, indicating it to be **2.70 (branched)** or **Cu–2.70 (linear)**, depending on the temperature (see below). **$^1$H NMR (500 MHz, THF-*d*$_8$ at 25 °C)** δ 7.42 (t, *J* = 7.7 Hz, 2H), 7.40 (s, 2H), 7.30 (d, *J* = 7.7 Hz, 4H), 5.84 (q, *J* = 12.8 Hz, 1H), 3.27 (d, *J* = 13.1 Hz, 2H), 2.69–2.50 (m, 4H), 1.73–1.69 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 12H), 1.22 (d, *J* = 4.7 Hz, 12H), 0.79 (s, 12H). **$^1$H NMR (500 MHz, THF-*d*$_8$ at –30 °C)** δ 7.55 (d, *J* = 2.4 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 4H), 5.81 (q, *J* = 12.9 Hz, 1H), 3.27 (d, *J* = 13.2 Hz, 2H), 2.62–2.45 (m, 4H), 1.66 (d, *J* = 12.2 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 12H), 1.21 (d, *J* = 7.0 Hz, 12H), 0.75 (s, 12H).

The presence of two identical terminal alkene protons in the $^1$H NMR spectrum indicate that there is rapid equilibrium between **2.70 (branched a)** and **2.70 (branched b)**. This olefin isomerization process probably proceeds, as shown below, via **2.70 (linear a-b**) through a sequence of π-allyl isomerization and σ-bond rotation. The step that separate **2.70 (branced a)** and **2.70 (branced b)** are likely fast, and since only **2.70 (branched)** can be detected, it is at least 3 kcal/mol lower in energy than **2.70 (linear**).

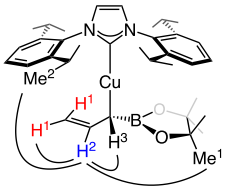
To confirm this hypothesis and gain additional insight, we carried out the variable temperature spectroscopic experiments, described below.



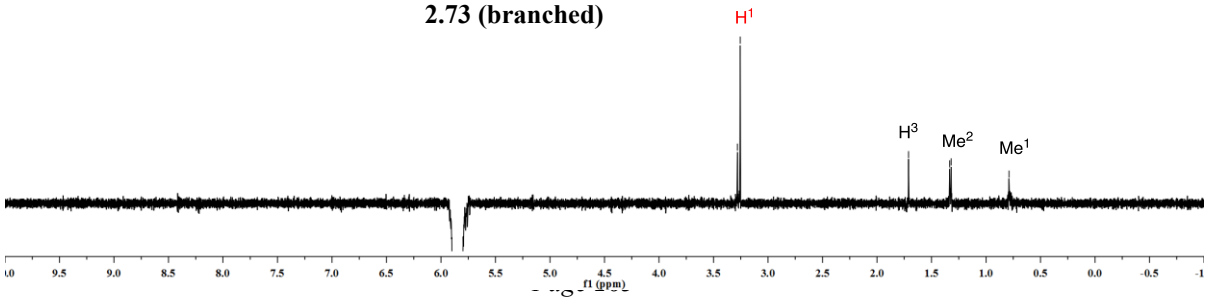






1D NOSEY (500 MHz, THF-$d_8$)




**2.73 (branched)**

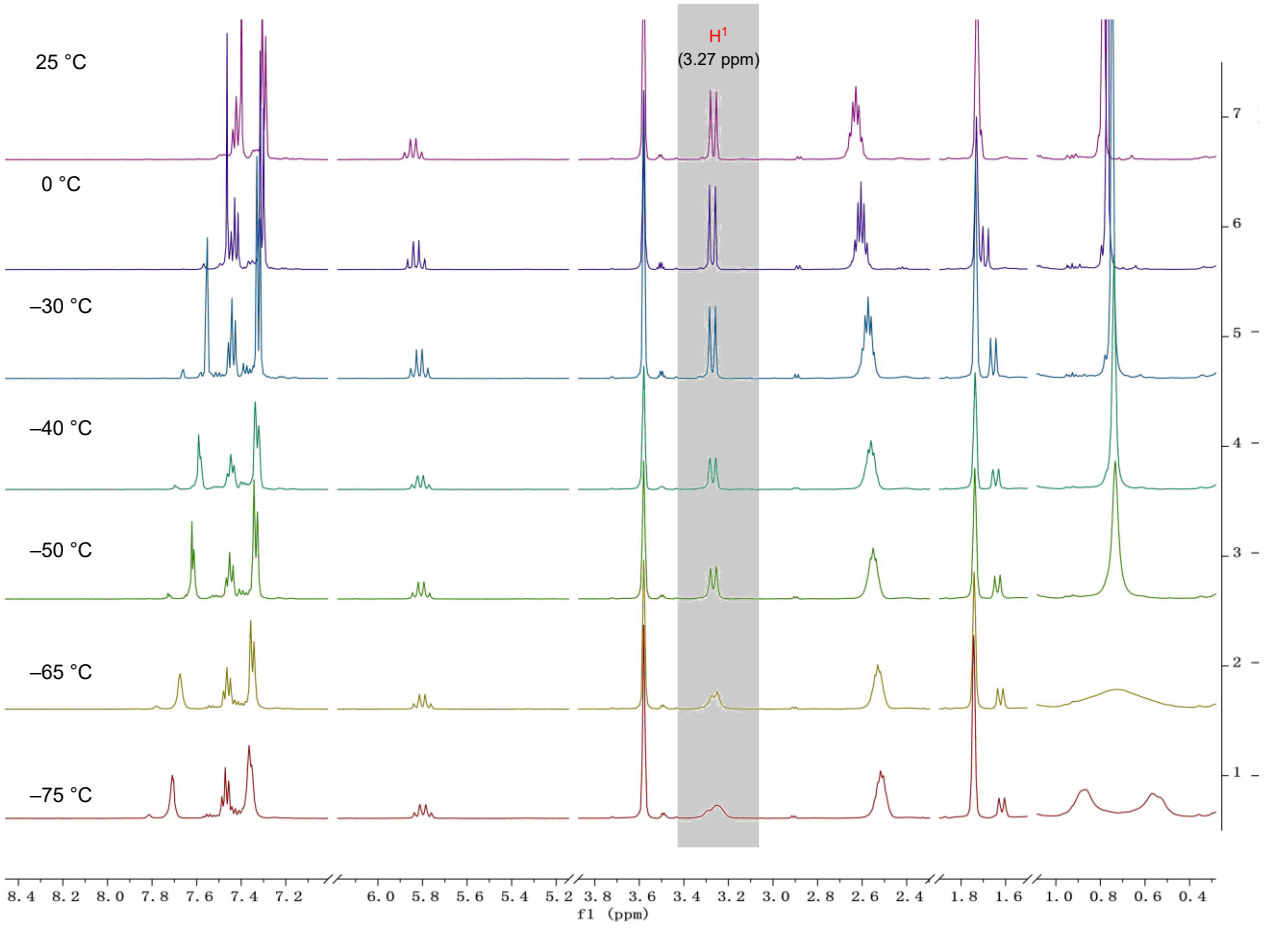


***Variable temperature NMR experiments***

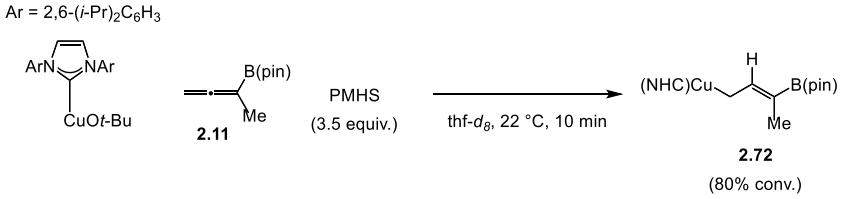
A sample of **2.70 (branched)** in THF-$d_8$ was placed in a J-Young NMR tube, which was then placed in the pre-cooled probe (–75 °C) of a 500 MHz NMR spectrometer. The sample was allowed to warm in 10–30 °C intervals, for each of which a spectrum was recorded. Prior to each acquisition the probe temperature was allowed to equilibrate for ~15 min.

The spectra acquired at −75 °C did not reveal the presence of any other isomer, indicating that, as predicted, the abovementioned equilibrium involving **2.70 (branched)** and **2.70 (linear)** is rapid. However, the dissymmetric signal at δ 3.27 ppm implies that equilibriation is slower at −75 °C, and the terminal protons appear to be in different chemical environments.

*Conclusion*: **2.70 (branched)** is likely the energetically favored ground state isomer, which is in rapid equilibrium with **2.70 (linear)** isomers.

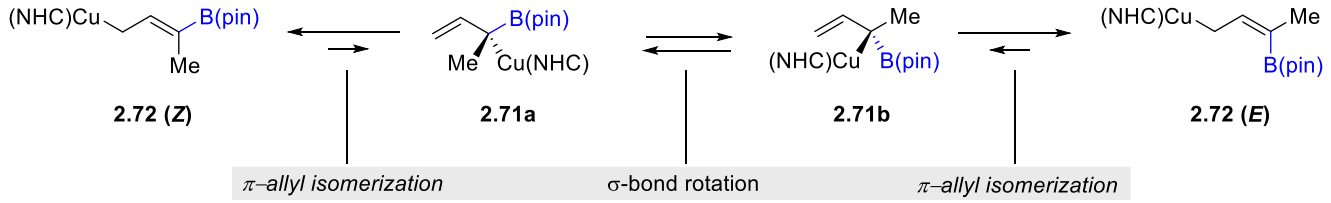


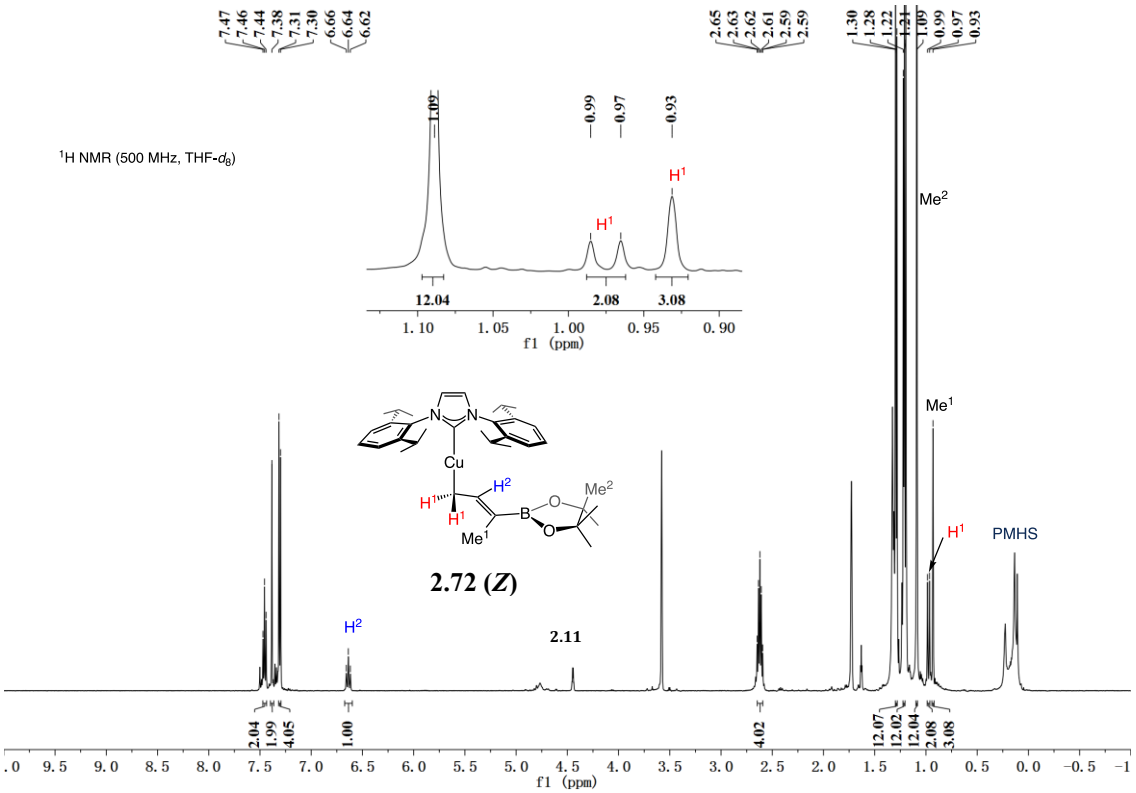

***NHC–Cu–allyl complex derived from allene 2.11***

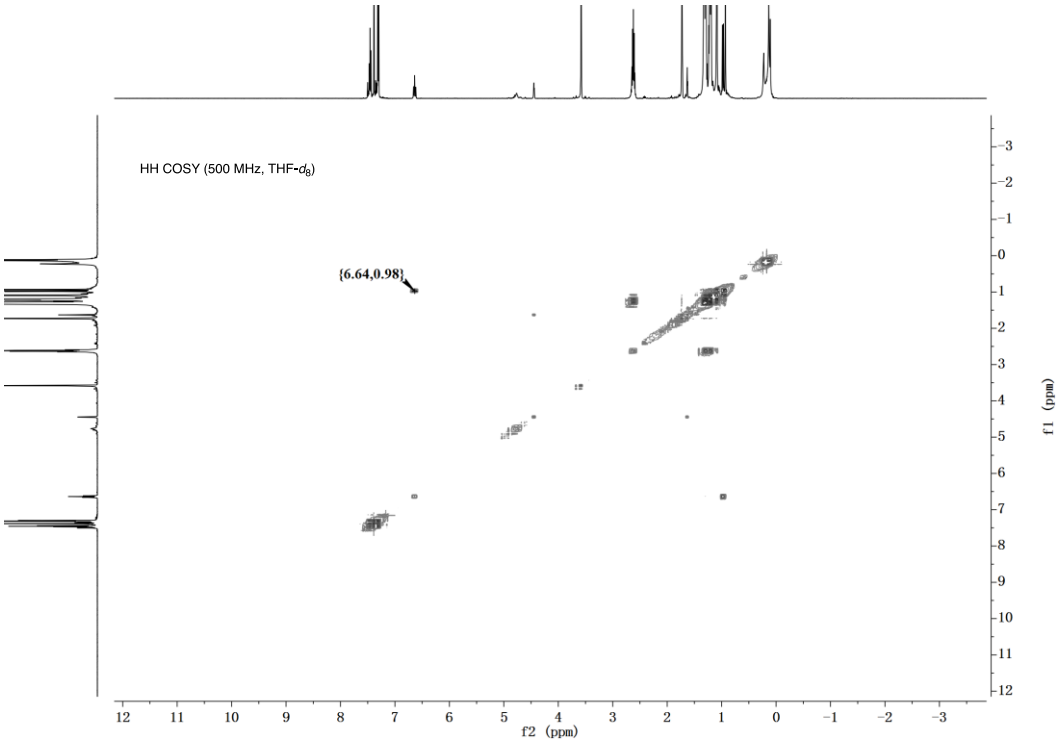



In a glove box, an oven-dried 2-dram vial equipped with a stir bar was charged with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]CuO*t*-Bu (5.3 mg, 0.01 mmol) and thf-$d_8$. PMHS (2.1 mg, 0.035 mmol) was added at 22 °C and the mixture was allowed to stir for 1 min, after which it was charged with 1,1-disubstituted allene **2.11** (2.2 mg, 0.012 mmol) and the mixture was allowed to stir for 10 min.

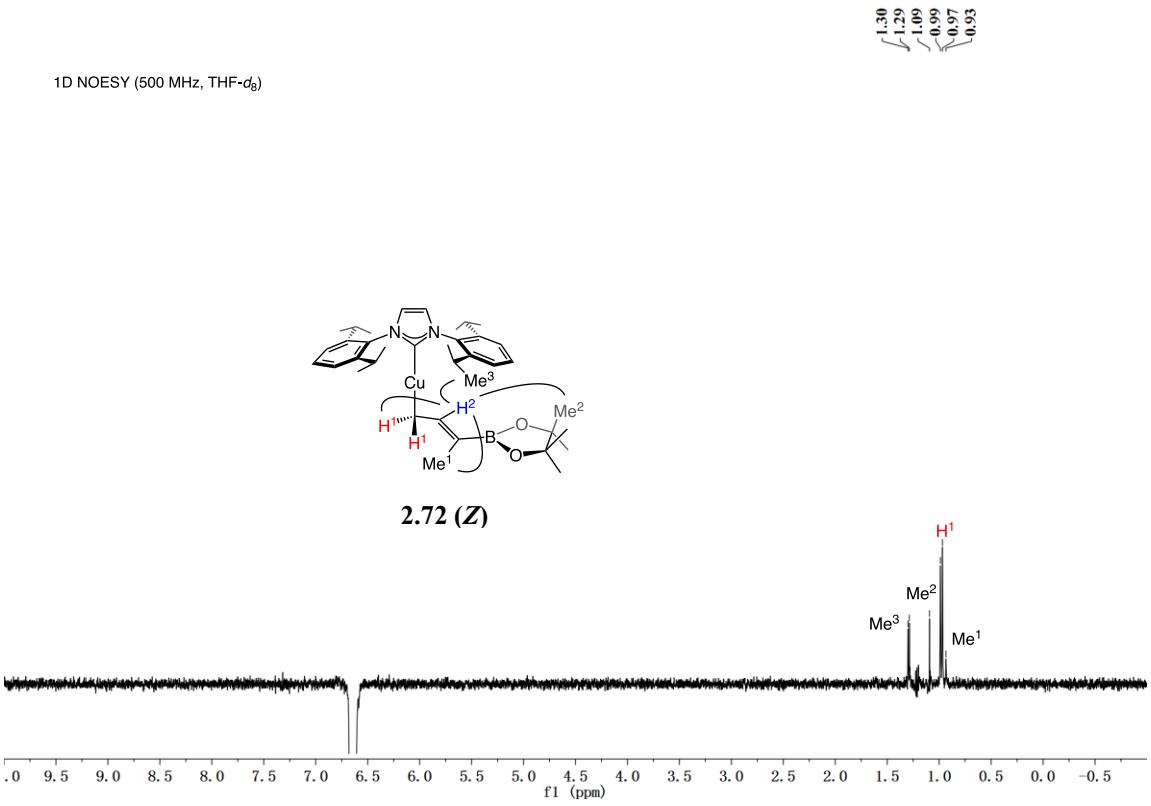
Analysis of $^{1}$H NMR spectrum of the unpurified mixture indicated that 80% conversion to **2.72**. The identity of the copper complex was established through $^{1}$H NMR, HH-COSY and nOe experiments involving the unpurified mixture. In the 1D nOe experiment, irradiation of $H^2$ led to enhancement of signals at $Me^2$ (at the B(pin)) as well as $Me^1$ (at the NAr unit of the NHC ligand) suggesting the existence of rapid equilibrium between **2.72 (*Z*)** and **2.72 (*E*)** via **2.71a-b**, as illustrated above. **$^{1}$H NMR (500 MHz, THF-*d*$_8$)** δ 7.46 (t, *J* = 7.7 Hz, 2H), 7.38 (s, 2H), 7.31 (d, *J* = 7.6 Hz, 4H), 6.64 (t, *J* = 10.0 Hz, 1H), 2.67–2.57 (m, 4H), 1.29 (d, *J* = 6.8 Hz, 12H), 1.22 (d, *J* = 5.7 Hz, 12H), 1.09 (s, 12H), 0.98 (d, *J* = 10.0 Hz, 2H), 0.93 (s, 3H).




$^1$H NMR (500 MHz, THF-$d_8$)
Me$^2$
Me$^1$
H$^1$
PMHS
H$^2$
2.11
2.72 (Z)
f1 (ppm)

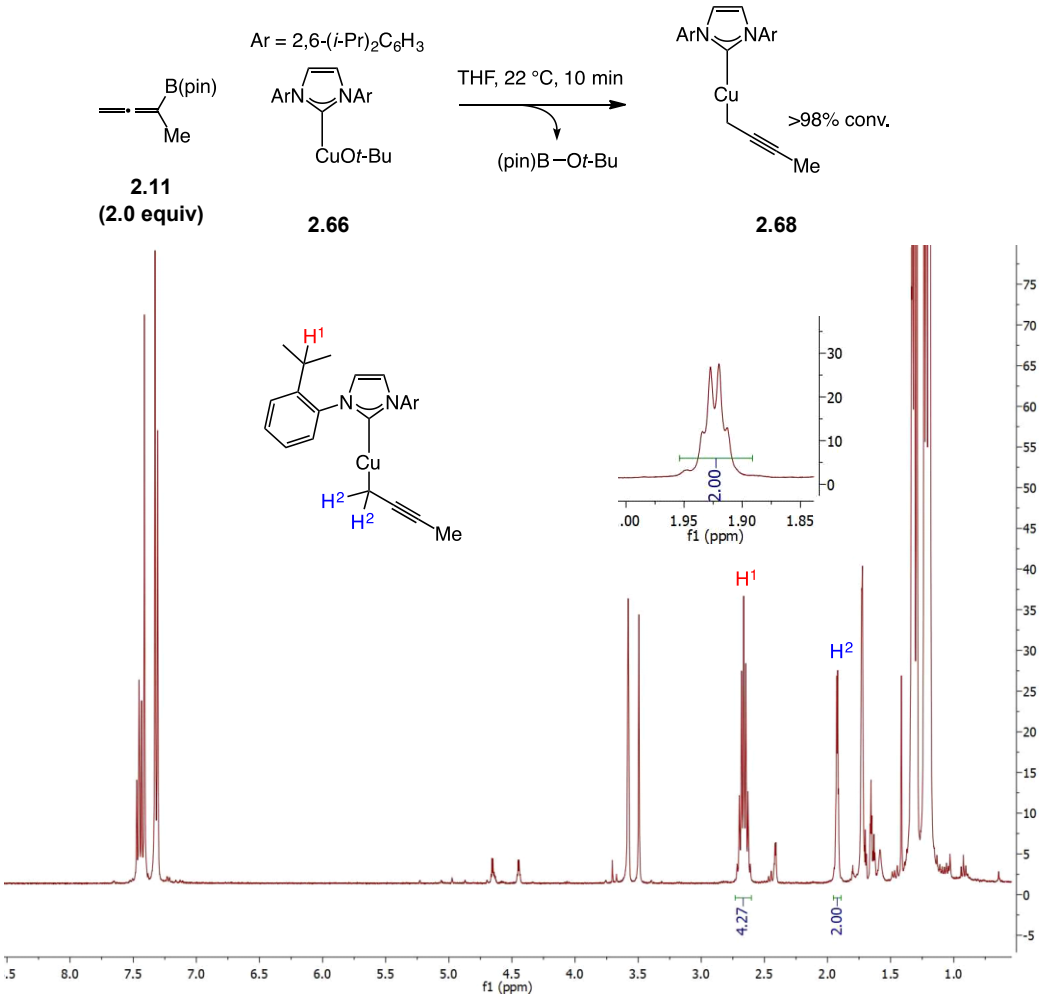

HH COSY (500 MHz, THF-$d_8$)
{6.64,0.98}
f1 (ppm)
f2 (ppm)

1D NOESY (500 MHz, THF-$d_8$)

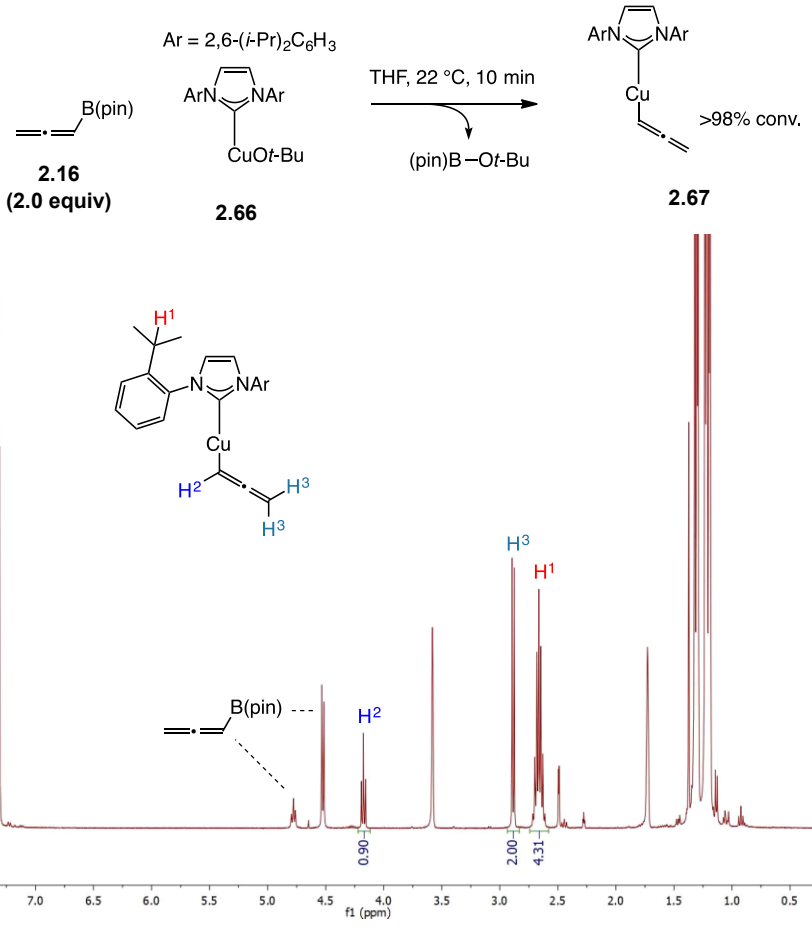



***B/Cu exchange between organoboron compounds and NHC–Cu–Ot-Bu complexes***

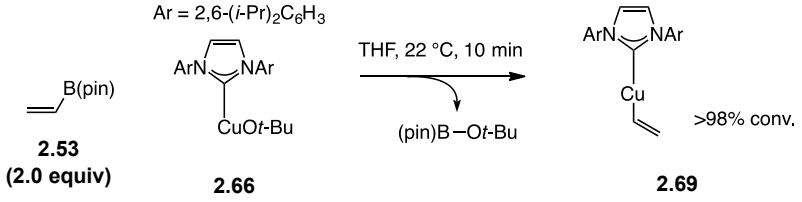
In an $N_2$-filled glove box, an oven-dried 2-dram vial was charged with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]CuO*t*-Bu (10.0 mg, 0.019 mmol). The mixture was charged with THF-$d_8$ (0.5 mL) and allowed to stir for five min, resulting in a clear colorless solution. Allenyl–B(pin) **2.11**, (6.9 mg, 0.038 mmol) was then added through syringe and the resulting colorless solution was transferred to a J-young NMR tube. Reaction progress was monitored by $^1$H NMR spectroscopy. Key signals are highlighted below.

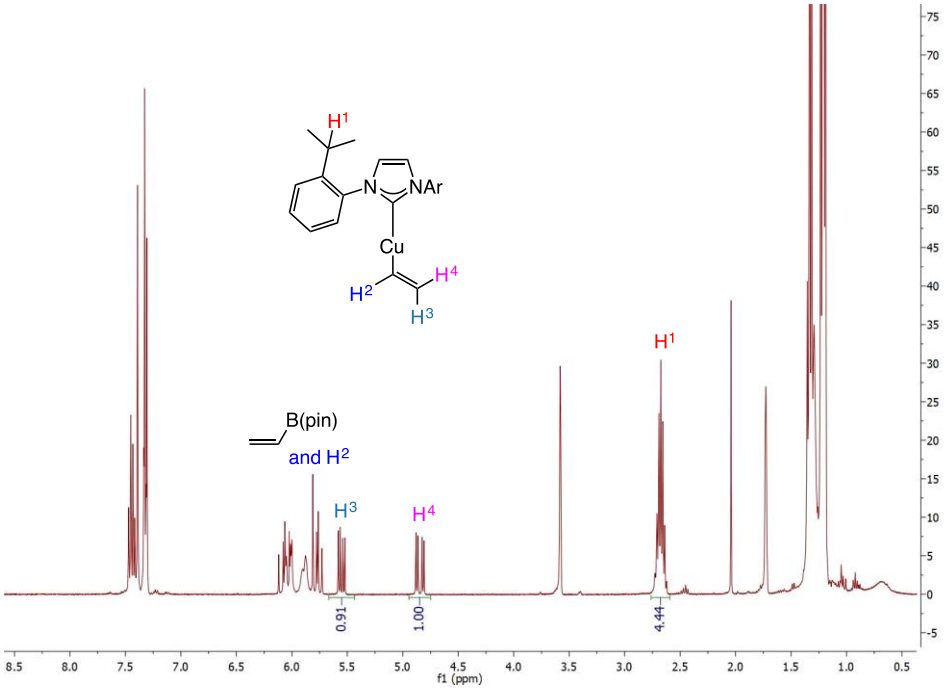

Ar = 2,6-(i-Pr)2C6H3
B(pin)
Me
ArN
NAr
CuOt-Bu
THF, 22 °C, 10 min
(pin)B–Ot-Bu
Cu
>98% conv.
Me
2.11
(2.0 equiv)
2.66
2.68
H1
H2
H2
Me
4.27
2.00
f1 (ppm)

In an $N_2$-filled glove box, an oven-dried 2-dram vial was charged with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]CuO*t*-Bu (10 mg, 0.019 mmol). The mixture was charged with thf-$d_8$ (0.5 mL) and then allowed to stir for five min, resulting in a clear colorless solution. At this point, allenyl–B(pin) **2.16**, (6.8 μL, 0.038 mmol) was added by syringe and the resulting colorless solution was transferred to a J-young NMR tube. Reaction progress was monitored by $^1$H NMR spectroscopy. Key signals are highlighted below.



In an $N_2$-filled glove box, an oven-dried 2-dram vial was charged with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]CuO*t*-Bu (10 mg, 0.019 mmol). The mixture was charged with THF-$d_8$ (0.5 mL) and allowed to stir for five min, resulting in a clear colorless solution. Vinyl–B(pin) **2.53**, (6.5 μL, 0.038 mmol) was added through syringe and the resulting colorless solution was transferred to a J-young NMR tube. Reaction progress was monitored by $^1$H NMR spectroscopy. Key signals are highlighted below.

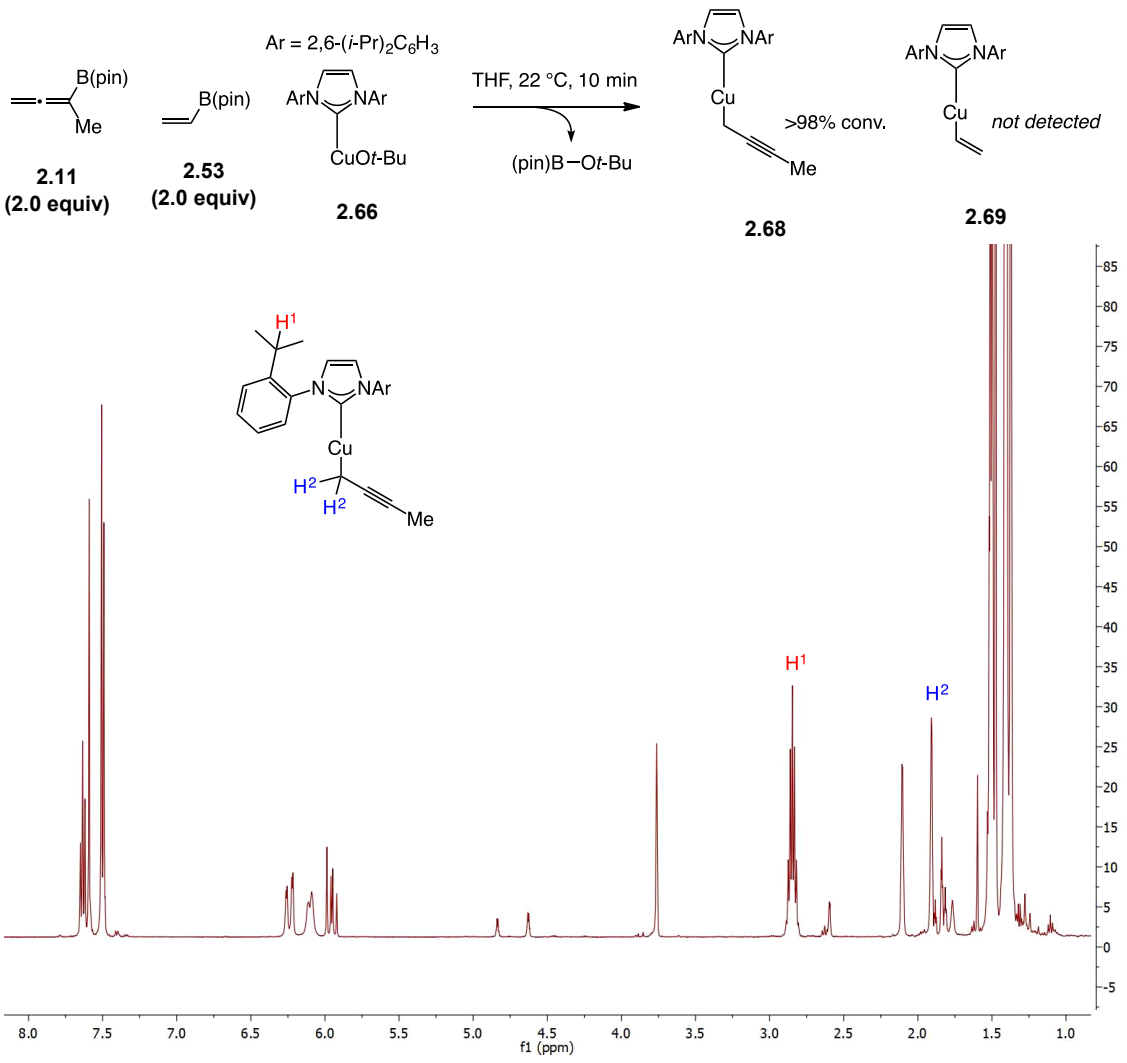



Control experiments show that allenyl–B(pin) compounds **2.16** and **2.11** as well as vinyl–B(pin) undergo B/Cu exchange with an NHC–Cu–alkoxide complex in less than 10 minutes.

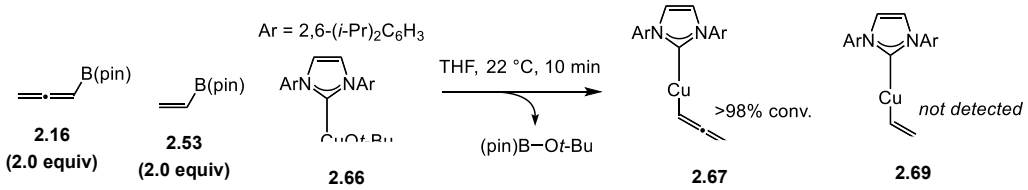
***Competition experiments between vinyl–B(pin) and allenyl–B(pin) compounds 2.11 and 2.16***

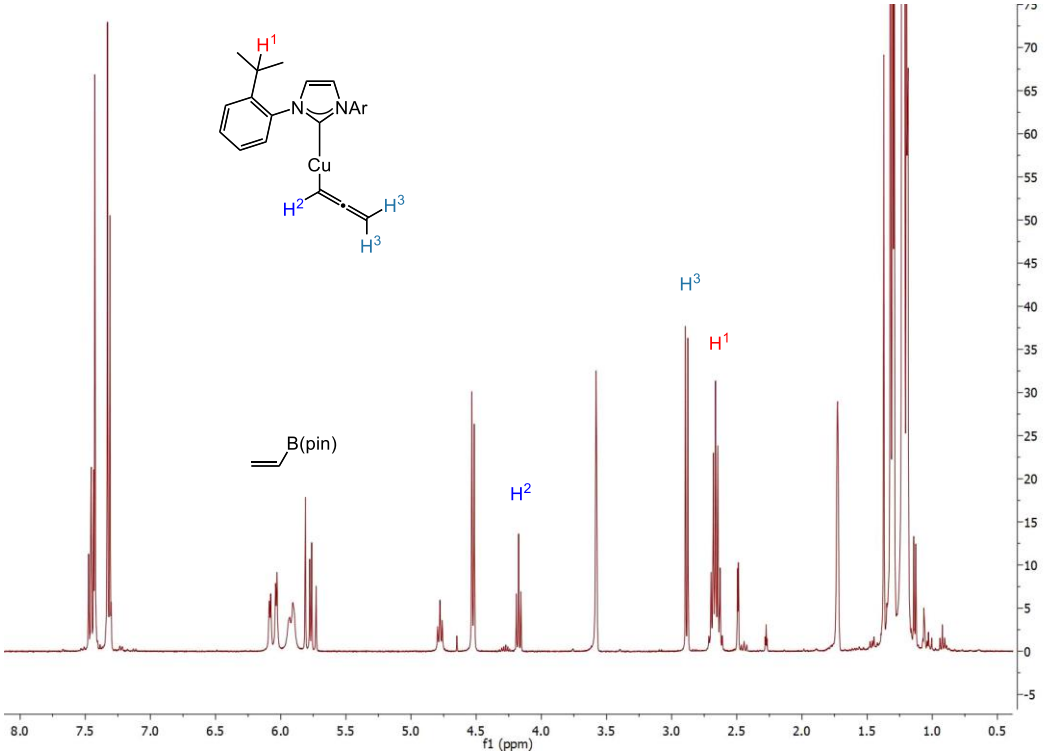
In an $N_2$-filled glove box, an oven-dried 2-dram vial was charged with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]CuO*t*-Bu (10.0 mg, 0.019 mmol). The mixture was charged with THF-$d_8$ (0.25 mL) and allowed to stir for five min, resulting in a clear colorless solution. A separate vial was charged with allenyl–B(pin) **2.11** (6.8 μL, 0.038 mmol) and vinyl–B(pin) (6.5 μL, 0.038 mmol), and the mixture was dissolved in THF-$d_8$ (0.25 mL) resulting colorless solution. Both solutions were mixed and transferred to a J-young NMR tube. Reaction progress was monitored by $^1$H NMR spectroscopy.




In an $N_2$-filled glove box, an oven-dried 2-dram vial was charged with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]CuO*t*-Bu (10.0 mg, 0.019 mmol). The mixture was charged with THF-$d_8$ (0.25 mL) and allowed to stir for five min, resulting in a clear colorless solution. A separate vial was charged with allenyl–B(pin) **2.16** (6.8 μL, 0.038 mmol) and vinyl–B(pin) (6.5 μL, 0.038 mmol), and the mixture was dissolved in THF-$d_8$ (0.25 mL), resulting colorless solution. Both solutions were

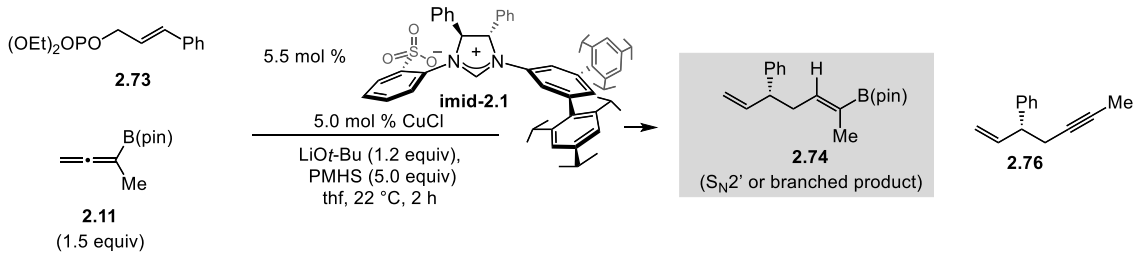
mixed and transferred to a J-young NMR tube. Reaction progress was monitored by $^{1}$H NMR spectroscopy.



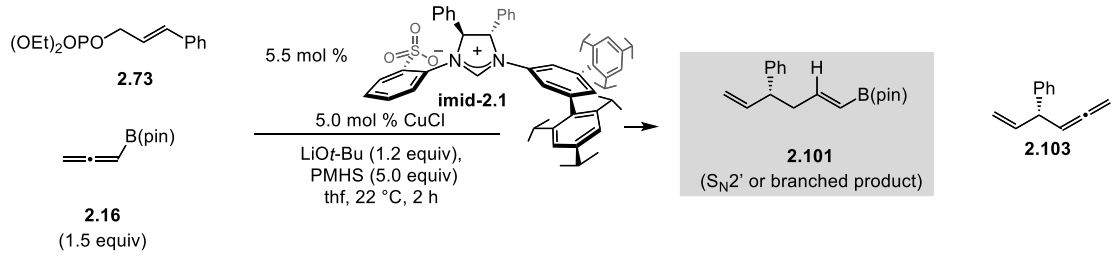

***Reactions with varying quantities of metal-alkoxide and PMHS***

***Table S2.1.*** The Impact of Different Amounts of Metal-Alkoxide and PMHS on a Reaction with **2.11**[a]




| Entry | Equiv (LiOt-Bu; PMHS) | Conv. (%)[b]; Yield (%)[c] | 2.76:2.78 |
|---|---|---|---|
| 1 | 2.5; 3.0 | >98; 8 | 14:86 |
| 2 | 1.5; 3.0 | >98; 53 | 74:26 |
| 3 | 1.2; 3.0 | >98; 64 | 89:11 |
| 4 | 1.2; 5.0 | >98; 69 | 96:4 |

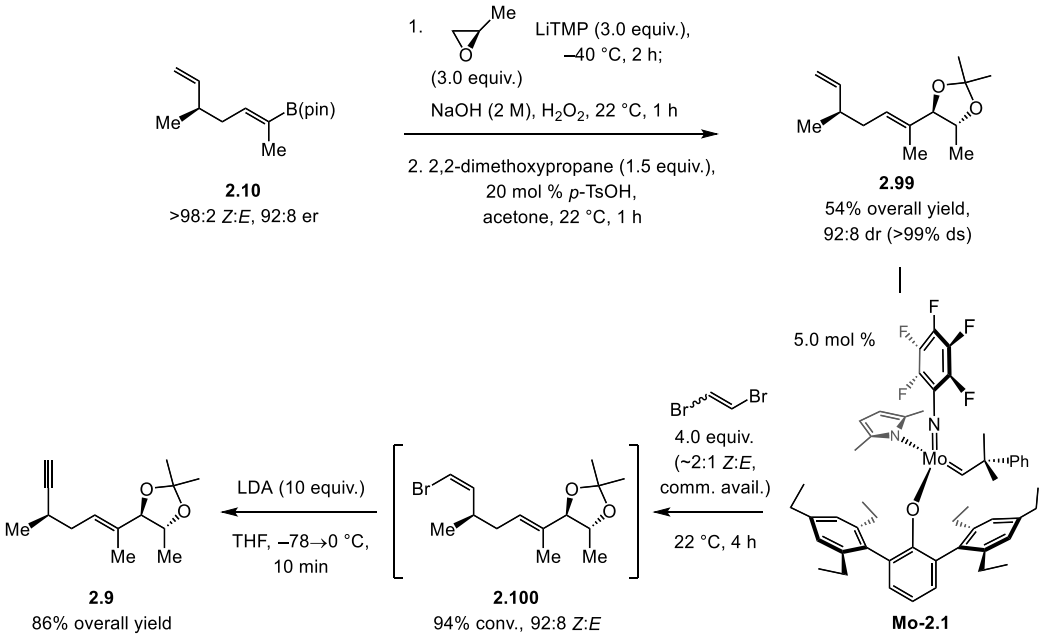
***Table S2.2.*** The Impact of Different Amounts of Metal-Alkoxide and PMHS on a Reaction with **2.16** [a]




| Entry | Equiv (LiOt-Bu; PMHS) | Conv. (%)[b]; Yield (%)[c] | 2.76:2.78 |
|---|---|---|---|
| 1 | 2.5; 3.0 | >98; ND | <2:>98 |
| 2 | 1.5; 3.0 | >98; 54 | 61:39 |
| 3 | 1.2; 3.0 | >98; 71 | 82:18 |
| 4 | 1.2; 5.0 | >98; 75 | 88:12 |

[a]Reactions were performed under $N_2$ atm. [b]Conv. and product ratios determined by analysis of the 400 MHz $^1$H NMR spectra of unpurified product mixtures. [c]Yield of purified product. ND, not determined.

- **Formal Synthesis of Pumiliotoxin B**




**(4*R*,5*R*)-2,2,4-Trimethyl-5-((*R*,*E*)-5-methylhepta-2,6-dien-2-yl)-1,3-dioxolane (2.99):** In a glove box, an oven-dried vial containing a stir bar was charged with LiTMP (132 mg, 0.900 mmol) and THF (5.0 mL). The vial was sealed with a septum and electrical tape, and removed from the glove box. The mixture was allowed to stir for 30 min at 22 °C, after which it was allowed to cool to –40 °C. To this solution was added sequentially (*R*)-(+)-propylene oxide (52.3 mg, 0.900 mmol) and **2.10** (70.8 mg, 0.300 mmol) (at –40 °C). The solution was allowed to stir for 2 h at –40 °C before it was allowed to warm to 0 °C at which time the reaction was quenched by the addition of a saturated solution of aqueous NaOH (3.0 mL, 2 M) and $H_2O_2$ (100 μL, 30% wt. in $H_2O$). The mixture was then allowed to warm to 22 °C and stir for 1 h, after which an aqueous solution of saturated $Na_2S_2O_3$ (2.0 mL) was added. The mixture was allowed to stir for 10 min at 22 °C. The layers were separated and the aqueous layer was washed with $Et_2O$ (3 x

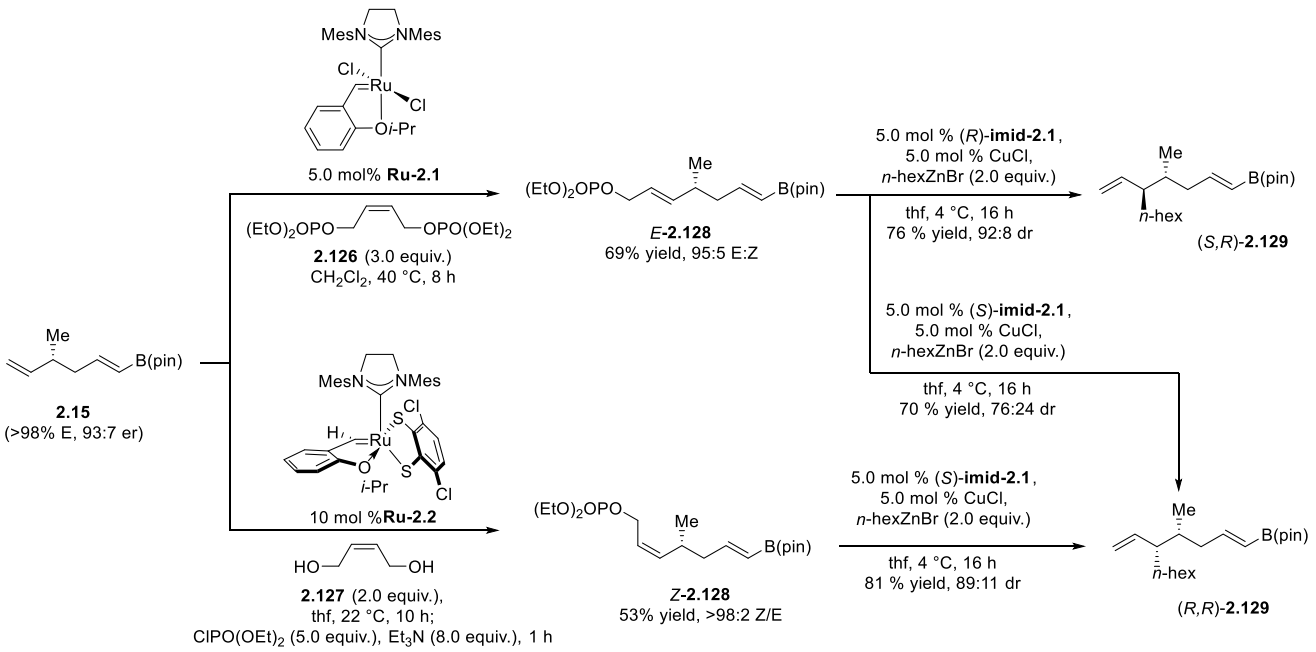
20 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. The resulting orange oil was purified by a short column of silica gel. To a solution of the diol at 22 °C in acetone (5.0 mL) were sequentially added 2,2-dimethoxypropane (46.9 mg, 0.450 mmol) and *p*-toluenesulfonic acid monohydrate (11.4 mg, 0.0600 mmol). The mixture was allowed to stir for 1 h at 22 °C and then it was charged with an aqueous solution of saturated $NaHCO_3$ (50 μL). The mixture was allowed to pass through a short plug of silica gel and eluted with EtOAc. The volatiles were removed in vacuo and the resulting yellow oil was purified by silica gel chromatography (30:1→10:1 hexanes:EtOAc) to afford **2.99** as pale yellow oil (36.2 mg, 0.161 mmol, 54% overall yield). **IR (neat):** 3076 (s), 2982 (m), 2931 (m), 2877 (m), 1640 (w), 1455 (m), 1377 (s), 1370 (s), 1238 (s), 1175 (m), 1098 (s), 1065 (w), 1036 (s), 993 (w), 911 (m), 863 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$)**: δ 5.75 (ddd, J = 17.3, 10.4, 7.1 Hz, 1H), 5.51 (t, J = 7.4 Hz, 1H), 5.00–4.90 (m, 2H), 3.90–3.82 (m, 2H), 2.21 (p, J = 6.4 Hz, 1H), 2.14–2.02 (m, 2H), 1.64 (s, 3H), 1.42 (s, 6H), 1.21 (d, J = 5.0 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$)**: 144.1, 131.8, 128.5, 112.8, 108.1, 88.9, 74.5, 37.8, 34.8, 27.7, 27.1, 19.5, 17.1, 11.7; **HRMS (DART):** Calcd for $C_{14}H_{25}O_2$ $[M+H]^+$: 225.1849. Found: 225.1853; Specific rotation: $[\alpha]_D^{20}$ –1.9 (*c* 1.7, $CHCl_3$).

**(4*R*,5*R*)-2,2,4-Trimethyl-5-((*R*,*E*)-5-methylhept-2-en-6-yn-2-yl)-1,3-dioxolane (2.9):** In a $N_2$-filled glove box, an oven-dried 2-dram vial equipped with a stir bar was charged with **2.99** (22.4 mg, 0.100

mmol), 1,2-dibromoethylene (74.3 mg, 0.4 mmol), and **Mo-2.1** (50 μL, 0.1 M in benzene, 5.0 μmol) were added. The vial was capped, sealed, and removed from the glove box. The mixture was allowed to stir for 4 h at 22 °C, after which it was charged with THF (1.0 mL) and allowed to cool to −78 °C. To this solution at −78 °C was added LDA in a dropwise manner (1.0 mL, 1.0 M in THF, 1.0 mmol). The resulting solution was allowed to warm to 0 °C and stir for 10 min before the addition of an aqueous solution of saturated $NH_4Cl$ (50 μL). The mixture was passed through a short plug of silica gel and eluted with $Et_2O$. The volatiles were concentrated *in vacuo* and and the resulting yellow oil was purified by silica gel chromatography (30:1→10:1 hexanes: $Et_2O$) to afford **2.9** as colorless oil (19.1 mg, 0.0860 mmol, 86% yield). **IR (neat):** 3342 (w), 2996 (m), 2914 (w), 2123 (m), 1477 (s), 1412(w), 1362 (m), 1223 (m), 1134 (w), 1004 (m), 772 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 5.60 (t, *J* = 7.3 Hz, 1H), 3.91 (d, *J* = 8.6 Hz, 1H), 3.88–3.83 (m, 1H), 2.51 (q, *J* = 6.7 Hz, 1H), 2.31–2.19 (m, 2H), 2.04 (d, *J* = 2.1 Hz, 1H), 1.67 (s, 3H), 1.43 (s, 6H), 1.23 (d, *J* = 5.7 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 133.2, 126.9, 108.2, 88.7, 88.6, 74.7, 68.6, 34.7, 27.7, 27.1, 25.9, 20.5, 17.2, 11.9; **HRMS (DART):** Calcd for $C_{14}H_{23}O_2$ $[M+H]^+$: 223.1693. Found: 223.1688; **Specific rotation:** $[\alpha]_D^{20}$ – 11.4 (*c* 1.0, $CHCl_3$).

- **Synthesis of and Stereochemical Assignment for Netamine C**

***Synthesis of alkenyl boronates (S,R)-2.129 and (R,R)-2.129***




**Diethyl ((*R*,2*E*,6*E*)-4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,6-dien-1-yl) phosphate (*E*-2.128):** In a glove box, an oven-dried vial equipped containing a stir bar was charged with **2.15** (555 mg, 2.50 mmol) and **2.126** (2.70 g, 7.50 mmol). To this mixture was added **Ru-2.1** (78.3 mg, 2.07 mmol) in $CH_2Cl_2$ (0.5 mL). The vial was sealed with a cap and electrical tape, and removed from the glove box. The solution was allowed to stir for 8 h at 40 °C and then allowed to cool to 22 °C. The volatiles were removed under reduced pressure and the resulting red oil residue was purified by silica gel chromatography (10:1→2:1→1:1 hexanes:EtOAc) to afford ***E*-2.128** as red oil (667 mg, 1.72 mmol, 69% yield). **IR (neat):** 2976 (s), 2926 (s), 1637 (s), 1456 (s), 1391 (w), 1360 (s), 1321 (m), 1264 (m), 1165 (w), 1144 (m), 1102 (w), 1030 (s), 970 (s), 848 (w), 802 (w), 525 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 6.54 (dt, *J* = 17.8, 6.8 Hz, 1H), 5.74 (dd, *J* = 15.5, 6.9 Hz, 1H), 5.57 (dtd, *J* = 15.5, 6.3, 1.3

Hz, 1H), 5.43 (d, $J$ = 17.9 Hz, 1H), 4.51–4.45 (m, 2H), 4.11 (p, $J$ = 7.1 Hz, 4H), 2.32 (p, $J$ = 6.8 Hz, 1H), 2.23 (dtd, $J$ = 13.0, 6.5, 1.5 Hz, 1H), 2.15–2.09 (m, 1H), 1.33 (td, $J$ = 7.1, 1.1 Hz, 6H), 1.26 (s, 12H), 1.01 (d, $J$ = 6.7 Hz, 3H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 152.1, 141.1, 123.1 (d, $J$ = 6.7 Hz), 83.2, 68.3 (d, $J$ = 5.6 Hz), 63.8 (d, $J$ = 5.8 Hz), 43.1, 35.5, 24.9, 19.6, 16.3 (d, $J$ = 6.8 Hz); **HRMS (DART):** Calcd for $C_{18}H_{35}BO_6P$ $[M+H]^+$: 389.2259. Found: 389.2250; **Specific rotation:** $[\alpha]_D^{20}$ –13.7 (*c* 0.30, $CHCl_3$).

**Diethyl ((*R*,2*Z*,6*E*)-4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,6-dien-1-yl) phosphate (*Z*-2.128):** In a glove box, an oven-dried vial equipped with a stir bar was charged with **2.15** (444 mg, 2.00 mmol) and **2.127** (352 mg, 4.00 mmol). To this mixture was added **Ru-2.2** (76.5 mg, 0.10 mmol) in thf (0.1 mL). The solution was allowed to stir for 5 h at 22 °C and an additional aliquot of **Ru-2.2** (76.5 mg, 0.10 mmol) in thf (0.1 mL) was added. The vial was sealed with a cap and electrical tape, and removed from the glove box. The solution was allowed to stir for 5 h at 22 °C and then cooled to 0 °C. To this mixture was sequentially added at 0 °C $Et_3N$ (2.20 mL, 16.0 mmol), $ClPO(OEt)_2$ (1.45 mL, 10.0 mmol), and 4-dimethylaminopyridine (12.2 mg, 0.1 mmol). The solution was allowed to warm to 22 °C and stir for 1 h before the addition of an aqueous solution of saturated $NaHCO_3$ (50 μL). The mixture was passed through a short plug of silica gel and eluted with EtOAc. The volatiles were removed *in vacuo* and the resulting red oil was purified by silica gel chromatography (10:1→2:1→1:1 hexanes:EtOAc) to afford ***Z*-2.128** as orange oil (413 mg, 1.06 mmol, 53% yield). **IR (neat):** 2958 (m),

2936 (m), 2925 (m), 2871 (w), 1732 (s), 1637 (w), 1394 (w), 1360 (m), 1317 (m), 1268 (m), 1165 (w), 1144 (w), 1036 (s), 992 (m), 981 (m) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$)**: δ 6.50 (dt, *J* = 17.8, 6.9 Hz, 1H), 5.53 (dt, *J* = 11.2, 6.8 Hz, 1H), 5.48– 5.37 (m, 2H), 4.66–4.47 (m, 2H), 4.10 (p, *J* = 7.4 Hz, 4H), 2.59 (dq, *J* = 9.7, 6.8 Hz, 1H), 2.13 (t, *J* = 6.9 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 6H), 1.25 (s, 12H), 0.98 (d, *J* = 6.7 Hz, 3H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 151.7, 140.3, 123.2 (d, J = 6.8 Hz), 83.2, 63.8 (d, *J* = 5.9 Hz), 63.3 (d, *J* = 5.7 Hz), 43.6, 31.9, 24.9, 20.8, 16.3 (d, *J* = 6.7 Hz); **HRMS (DART):** Calcd for $C_{18}H_{35}BO_6P$ $[M+H]^+$: 389.2259. Found: 389.2252; Specific rotation: $[\alpha]_D^{20}$ +24.1 (*c* 0.61, $CHCl_3$).

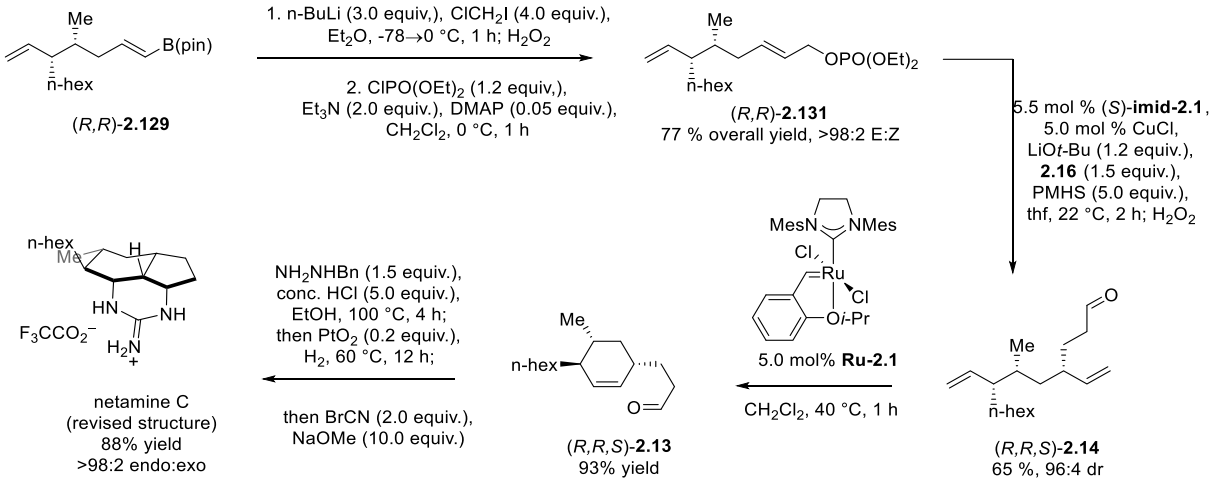
**4,4,5,5-Tetramethyl-2-((4*R*,5*S*,*E*)-4-methyl-5-vinylundec-1-en-1-yl)-1,3,2-dioxaborolane [(*S,R*)-2.129]:** In a glove box, an oven-dried vial equipped with a stir bar was charged with CuCl (5.0 mg, 0.050 mmol), (*R*)-**imid-2.1** (43.0 mg, 0.05 mmol), *n*-hexylzinc bromide (4.0 mL, 0.5 M in THF, 2.0 mmol). The solution was allowed to stir for 1 h at 22 °C and then to cool to –40 °C. To this mixture at –40 °C was added *E*-**2.128** (388 mg, 1.0 mmol). The vial was sealed with electrical tape before removal from the glove box, and the mixture was allowed to stir for 16 h at 4 °C, after which it was diluted with $CH_2Cl_2$ (20.0 mL) followed by a saturated solution of aqueous $NH_4Cl$ (0.5 mL). The mixture was then passed through a short plug of oven-dried silica gel and eluted with $Et_2O$. The organic layer was concentrated in vacuo and the resulting yellow oil was purified by silica gel chromatography (1:3 hexanes:$CH_2Cl_2$) to afford (*S,R*)-**2.129** as pale yellow oil (242 mg, 0.0757 mmol, 76% yield, 92:8 dr). **IR(neat)** 2956 (m),

2923 (s), 2854 (m), 2358 (m), 1636 (s), 1456 (w), 1388 (w), 1361 (s), 1318 (m), 1145 (s), 996 (m), 970 (m), 910 (m), 848 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 6.58 (dt, J = 18.0, 6.9 Hz, 1H), 5.54 (ddd, J = 17.1, 10.3, 9.2 Hz, 1H), 5.41 (d, J = 17.9 Hz, 1H), 5.00 (dd, J = 10.3, 2.3 Hz, 1H), 4.93 (dd, J = 17.1, 2.2 Hz, 1H), 2.19 (dt, J = 12.7, 5.5 Hz, 1H), 1.97–1.89 (m, 2H), 1.60 (td, J = 12.7, 6.5 Hz, 1H), 1.35–1.12 (m, 22H), 0.88–0.85 (m, 3H), 0.80 (d, J = 6.9 Hz, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$)**: δ 153.9, 140.1, 115.8, 83.1, 48.3, 41.9, 36.3, 32.5, 32.0, 29.6, 27.5, 24.9 (d, J = 1.8 Hz), 22.8, 15.5, 14.2; **HRMS (DART):** Calcd for $C_{20}H_{38}BO_2$ $[M+H]^+$: 321.2959. Found: 321.2959; Specific rotation: $[\alpha]_D^{20}$ –31.4 (*c* 0.32, $CHCl_3$).

**4,4,5,5-Tetramethyl-2-((4*R*,5*R*,*E*)-4-methyl-5-vinylundec-1-en-1-yl)-1,3,2-dioxaborolane [(*R*,*R*)-2.129]:** was prepared following the above procedure but with (*S*)-**imid-2.1** and *Z*-**2.128**. **IR(neat):** 2973 (m), 2956 (m), 2924 (s), 2854 (s), 1636 (s), 1457 (w), 1397 (w), 1362 (s), 1319 (m), 1268 (w), 1145 (s), 996 (w), 970 (w), 910 (w), 848 (w) $cm^{-1}$; $^1$H NMR **(400 MHz, $CDCl_3$):** δ 6.57 (ddd, *J* = 17.8, 7.5, 6.2 Hz, 1H), 5.54 (ddd, *J* = 17.1, 10.2, 9.2 Hz, 1H), 5.40 (dt, *J* = 17.9, 1.4 Hz, 1H), 5.00 (dd, *J* = 10.3, 2.2 Hz, 1H), 4.92 (dd, *J* = 16.9, 1.8 Hz, 1H), 2.31 (dddd, *J* = 14.0, 5.8, 4.0, 1.5 Hz, 1H), 1.88–1.77 (m, 2H), 1.62–1.50 (m, 1H), 1.41–1.16 (m, 22H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); $^{13}$C **NMR (101 MHz, $CDCl_3$):** δ 154.2, 141.5, 115.4, 83.1, 49.5, 40.3, 36.5, 32.0, 31.2, 29.6, 27.6, 24.9 (d, *J* = 1.7

Hz), 22.8, 17.3, 14.2; **HRMS (DART):** Calcd for $C_{20}H_{38}BO_2$ $[M+H]^+$: 321.2959. Found: 321.2953; **Specific rotation:** $[\alpha]_D^{20}$ –6.9 (*c* 1.0, $CHCl_3$).

***Netamine C (the revised structure)***




**Diethyl ((5*R*,6*R*,*E*)-5-methyl-6-vinyldodec-2-en-1-yl) phosphate (*R,R*)-2.131:** To a vial equipped with a stir bar was added (*R,R*)-**2.129** (271 mg, 0.846 mmol), chloroiodomethane (246 μL, 3.38 mmol) and $Et_2O$ (5.0 mL). To this solution at −78 °C in a dropwise manner was added *n*-BuLi (1.0 mL, 2.5 M in hexanes, 2.50 mmol). The mixture was allowed to warm to 0 °C over the course of 1 h after which the reaction was quenched by the addition of an aqueous solution of 1M NaOH (2.0 mL) and $H_2O_2$ (300 μL, 30% wt. in $H_2O$). The mixture was allowed to warm to 22 °C and stir for 1 h, after which an aqueous solution of saturated $Na_2S_2O_3$ (2.0 mL) was added. The mixture was allowed to stir at 22 °C for 30 min. The layers were separated, and the aqueous layer was washed with $Et_2O$ (3 x 10 mL). The combined

organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. The resulting yellow oil was purified by a short column. To a solution of the the allyl alcohol in $CH_2Cl_2$ (5.0 mL) were sequentially added at 0 °C $Et_3N$ (235 μL, 1.69 mmol), $ClPO(OEt)_2$ (147 μL, 1.02 mmol) and 4-dimethylaminopyridine (5.17 mg, 0.0423 mmol). The mixture was allowed to stir for 1 h at 0 °C after which the reaction was quenched by the addition of an aqueous solution of saturated $NaHCO_3$ (50 μL). The mixture was passed through a short plug of silica gel and eluted with EtOAc. The volatiles were removed under reduced pressure and the yellow oil was purified by silica gel chromatography (10:1→1:1 hexanes:EtOAc) to afford (*R,R*)-**2.131** as colorless oil (235 mg, 0.652 mmol, 77% overall yield). **IR (neat):** 2955 (w), 2923 (m), 2853 (w), 1457 (w), 1377 (w), 1263 (m), 1165 (w), 1031 (s), 1005 (s), 971 (s), 910 (w), 817 (w), 807 (w), 526 (w) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 5.75 (dt, *J* = 14.4, 7.0 Hz, 1H), 5.63–5.49 (m, 2H), 5.01 (dd, *J* = 10.3, 2.1 Hz, 1H), 4.93 (dd, *J* = 17.1, 2.0 Hz, 1H), 4.50–4.46 (m, 2H), 4.10 (q, *J* = 7.4 Hz, 4H), 2.24–2.16 (m, 1H), 1.87–1.72 (m, 2H), 1.53–1.46 (m, 1H), 1.35–1.17 (m, 16H), 0.91–0.82 (m, 6H); $^{13}$C NMR **(126 MHz, $CDCl_3$):** δ 141.5, 135.7, 125.7 (d, *J* = 6.6 Hz), 115.5, 68.3 (d, *J* = 5.6 Hz), 63.8 (d, *J* = 5.8 Hz), 49.4, 37.0, 36.5, 32.0, 31.2, 29.6, 27.6, 22.8, 17.0, 16.30 (d, *J* = 6.7 Hz), 14.2; **HRMS (DART):** Calcd for $C_{19}H_{38}O_4P$ $[M+H]^+$: 361.2502. Found: 361.2498; **Specific rotation:** $[\alpha]_D^{20}$ +4.2 (*c* 0.48, $CHCl_3$).

**(4*S*,6*R*,7R)-6-Methyl-4,7-divinyltridecanal (*R,R,S*)-2.14:** In a glove box, an oven-dried vial equipped with a magnetic stir bar was charged with CuCl (2.5 mg, 0.025 mmol), (*S*)-**imid-2.1** (23.6 mg, 0.0275 mmol), LiO*t*-Bu (48.0 mg, 0.12 mmol), and freshly distilled THF (2.5 mL). The solution was premixed for 30 min before PMHS (150 mg, 2.50 mmol), allenyl boronic acid pinacol ester **2.16** (135 mg, 0.75 mmol) and additional THF (2.5 mL) were added. The solution immediately turned dark-red. After 10 min, at 22 °C allylic phosphate (*R,R*)-**2.131** (180 mg, 0.50 mmol) was added. The vial was sealed with electrical tape before removal from the glove box, and the resulting mixture was allowed to stir for 2 h at 22 °C, after which the reaction was quenched by the addition of an aqueous solution of 1M NaOH (1.0 mL) and $H_2O_2$ (200 μL, 30% wt. in $H_2O$) at 0 °C. The mixture was allowed to warm to 22 °C and stir for 1 h, after which an aqueous solution of saturated $Na_2S_2O_3$ (1.0 mL) was added. The mixture was allowed to stir at 22 °C for 30 min and then the layers were separated, and the aqueous layer was washed with $Et_2O$ (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. The resulting yellow oil was purified by silica gel chromatography (20:1→1:1 hexanes:$Et_2O$) to afford (*R,R,S*)-**6** as colorless oil (86.1 mg, 0.326 mmol, 65% yield). **IR (neat):** 2954 (m), 2922 (s), 2853 (m), 1726 (s), 1638 (w), 1457 (w), 1418 (w), 1377 (w), 1047 (w), 910 (s) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 9.76 (s, 1H), 5.53 (dt, *J* = 17.2, 9.8 Hz, 1H), 5.37 (dt, *J* = 17.2, 9.7 Hz, 1H), 5.06–4.88 (m, 4H), 2.49–2.35 (m, 2H), 2.02 (dtd, *J* = 13.5, 9.2, 3.6 Hz, 1H), 1.78 (tt, *J* = 8.7, 3.8 Hz, 1H), 1.69 (td, *J* = 13.4, 7.9

Hz, 1H), 1.54–1.42 (m, 2H), 1.39–1.16 (m, 11H), 1.07–1.00 (m, 1H), 0.88 (t, $J$ = 6.8 Hz, 3H), 0.81 (d, $J$ = 6.7 Hz, 3H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 202.8, 142.0 141.5, 116.1, 115.3, 50.3, 42.1, 41.8, 38.7, 34.0, 32.0, 31.5, 29.6, 28.3, 27.7, 22.8, 17.1, 14.2; **HRMS (DART):** Calcd for $C_{18}H_{33}O$ $[M+H]^+$: 265.2526. Found: 265.2520; **Specific rotation:** $[\alpha]_D^{20}$ +13.7 (*c* 1.0, $CHCl_3$).

**3-((1*S*,4*S*,5*R*)-4-Hexyl-5-methylcyclohex-2-en-1-yl)propanal (*R,R,S*)-2.13:** In a glove box, an oven-dried 2-dram vial equipped with a stir bar was charged with (*R,R,S*)-**2.14** (81.3 mg, 0.307 mmol). To this was added **Ru-2.1** (9.6 mg, 0.0154 mmol) in $CH_2Cl_2$ (1.0 mL). The vial was sealed with a cap and electrical tape, and removed from the glove box. The mixture was allowed to stir for 1 h at 40 °C and then cool to 22 °C. The volatiles were removed under reduced pressure and the resulting red oil was purified by silica gel chromatography (20:1→1:1 hexanes:$Et_2O$) to afford (*R,R,S*)-**2.13** as colorless oil (67.7 mg, 0.286 mmol, 93% yield). **IR (neat):** 2952 (m), 2922 (s), 2853 (m), 1725 (m), 1456 (w), 1376 (w), 724 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 9.78 (s, 1H), 5.60 (d, $J$ = 10.0 Hz, 1H), 5.48 (d, $J$ = 10.4 Hz, 1H), 2.47 (t, $J$ = 7.6 Hz, 2H), 2.15 (br s, 1H), 1.72–1.49 (m, 5H), 1.38–1.18 (m, 11H), 0.96 (d, $J$ = 6.6 Hz, 3H), 0.88 (t, $J$ = 6.7 Hz, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 202.9, 132.3, 130.4, 43.2, 41.3, 38.8, 35.7, 33.6, 33.0, 32.0, 29.9, 28.5, 26.1, 22.8, 20.5, 14.3; **HRMS (DART):** Calcd for $C_{16}H_{29}O$ $[M+H]^+$: 237.2213. Found: 237.2207; **Specific Specific rotation:** $[\alpha]_D^{20}$ –47.6 (*c* 0.58, $CHCl_3$).

**Netamine C (revised structure):** In a glove box, an oven-dried 2-dram vial equipped with a stir bar was charged with (*R,R,S*)-**2.13** (37.8 mg, 0.160 mmol), benzyl hydrazine (29.3 mg, 0.240 mmol), and ethanol (2.0 mL) and stirred at 22 °C for 10 min. To this solution was added hydrochloric acid (67 μL, 36.5% wt, 0.800 mmol). The vial was sealed with a cap and electrical tape, and removed from the glove box. The resulting mixture was allowed to stir for 4 h at 100 °C and then cool to 22 °C. To this solution was added $PtO_2$ (7.4 mg, 0.032 mmol), after which the vial was purged with $H_2$ and then a $H_2$-filled ballon was attached.[43] The mixture was allowed to stir for 16 h at 60 °C. The mixture was then allowed to cool to 22 °C and MeONa (86.4 mg, 1.6 mmol) and BrCN (33.9 mg, 0.32 mmol) were added sequentially.[44] The solution was allowed to stir for 1 h and then filtered through cotton and eluted with MeOH (10 mL). The volatiles were removed under reduced pressure and the resulting yellow oil was purified by C18 silica gel chromatography (3:1:0.01→1:5:0.01 $H_2O$:MeOH:trifluoroacetic acid) to afford netamine C (trifluoroacetate salt**)** as colorless oil (54.8 mg, 0.140 mmol, 88% yield). Note: due to highly polarized nature of guanidine-containing compound netamine C (revised structure), <5% unseperable impurities was contained in the product fraction.

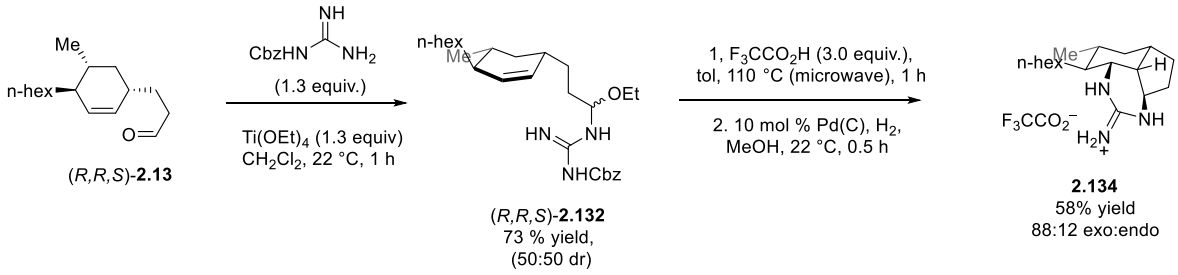
**Netamine C (revised structure): IR (neat):** 3268 (br), 2952 (m), 2926 (s), 2855(m), 1674 (s), 1636 (s), 1457 (w), 1425 (w), 1200 (s), 1179 (s), 1135 (m), 635 (w), 801 (w), 760 (w) $cm^{-1}$; **$^1$H NMR (500 MHz,**

(43) Arakawa, Y., Goto, T., Kawase, K. & Yushifuji, S. *Chem. Pharm. Bull. Jpn.***1995***, 43*, 535–536.

(44) Ishikawa, F., Kosasayama, A., Nakamura, S., Konno, T. *Chem. Pharm. Bull. Jpn.* **1978***, 26*, 3658–3665.

**$CDCl_3$):** δ 7.49 (br s, 1H), 7.28 (br s, 1H), 6.86 (br s, 1H), 3.86 (dd, *J* = 6.5, 4.0 Hz, 1H), 3.51 (dd, *J* = 5.1, 1.5 Hz, 1H), 2.32 (dt, *J* = 11.5, 5.7 Hz, 1H), 2.13–2.02 (m, 1H), 1.94 (dt, *J* = 13.9, 7.3 Hz, 1H), 1.83 (dd, *J* = 13.3, 6.0 Hz, 1H), 1.69–1.58 (m, 2H), 1.38–1.17 (m, 13H), 1.08–1.03 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 154.8, 53.8, 49.9, 45.1, 35.8, 35.1, 34.8, 34.7, 34.5, 33.4, 31.7, 30.4, 29.4, 27.5, 23.1, 22.6, 14.0; **HRMS (DART):** Calcd for $C_{17}H_{32}N_3$ $[M+H]^+$: 278.2591. Found: 278.2600; **Specific rotation:** $[\alpha]_D^{20}$ +6.9 (*c* 0.50, MeOH).

***Polycyclic compound 2.134***



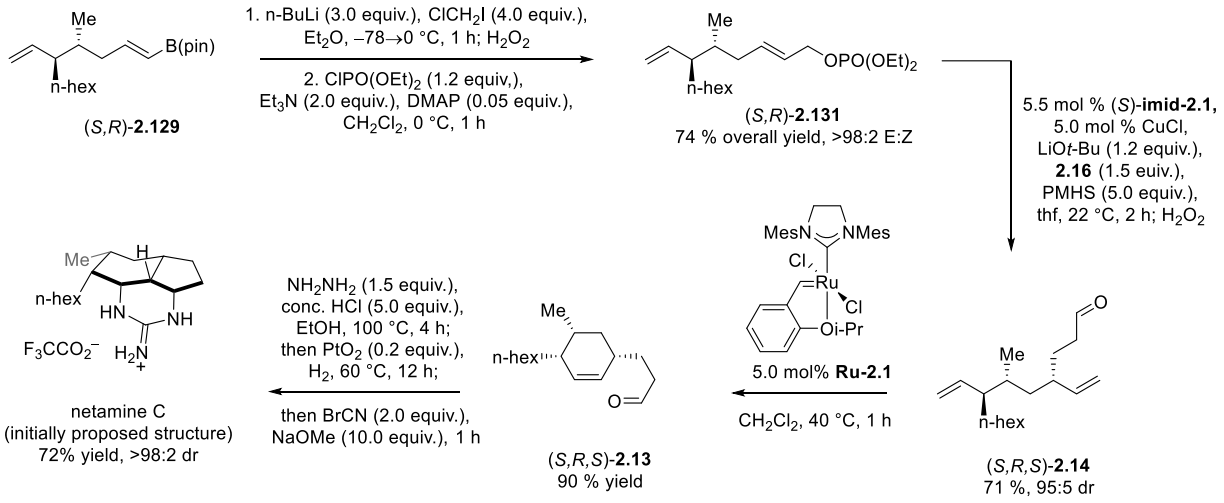

***N*-Guanidinyl acetal (*R,R,S*)-2.132:** To an oven-dried 2-dram vial equipped with a stir bar were sequentially added (*R,R,S*)-**2.13** (18.4 mg, 0.0778 mmol), *N*-Cbz guanidine (19.5 mg, 0.101 mmol) and $CH_2Cl_2$ (1.0 mL). To this solution at 0 °C and in a dropwise manner was added $Ti(OEt)_4$ (23 μL, 0.101 mmol). The mixture was allowed to warm to 22 °C and stir for 1 h, after which it was loaded onto a short column of silica gel; subsequent silica gel chromatography (5:1→1:2 hexanes:EtOAc) afforded (*R,R,S*)-**2.132** as pale white foam (26.3 mg, 0.0574 mmol, 73% yield). **IR (neat):** 2952 (m), 2923 (s), 2853 (m), 1649 (s), 1621 (s), 1584 (s), 1454 (m), 1377 (m), 1283 (s), 1103 (s), 802 (w), 730 (w), 697 (w) $cm^{-1}$; **$^1$H**

**NMR (600 MHz, $CDCl_3$):** δ 7.70 (br s, 1H), 7.41–7.24 (m, 5H), 6.73 (s, 2H), 5.58 (d, *J* = 10.3 Hz, 1H), 5.47 (d, *J* = 9.7 Hz, 1H), 5.10 (s, 2H), 4.66 (s, 1H), 3.58 (dt, *J* = 14.2, 7.1 Hz, 1H), 3.46–3.38 (m, 1H), 2.10 (s, 1H), 1.89–1.79 (m, 1H), 1.78–1.70 (m, 1H), 1.70–1.62 (m, 2H), 1.56–1.50 (m, 1H), 1.45–1.20 (m, 13H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 6.6 Hz, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 164.2, 162.4, 137.7, 132.1, 130.8, 130.8, 128.5, 128.1, 127.8, 84.0, 66.6, 61.0, 43.4, 39.2, 36.1, 36.0, 33.9, 33.3, 32.1, 31.8, 31.8, 29.9, 26.3, 22.8, 20.5, 15.2, 14.1; **HRMS (ESI):** Calcd for $C_{27}H_{44}N_3O_3$ $[M+H]^+$: 458.3377. Found: 458.3378; **Specific rotation:** $[\alpha]_D^{20}$ –35.2 (*c* 0.50, $CHCl_3$).

**Polycyclic compound 2.134:** In a glove box, an oven-dried microwave pressure vessel was charged with (*R,R,S*)-**2.132** (13.3 mg, 0.029 mmol), toluene (1.0 mL) and trifluoroacetic acid (9.9 mg, 0.087 mmol). The vessel was sealed with a cap and removed from the glove box, and the solution was allowed for 10 min to stir at 22 °C. The mixture was placed in a microwave synthesizer (200 W) for 1 h at 100 °C, after which the volatiles were removed in vacuo. The resulting pale-yellow oil was dissolved in MeOH (1.0 mL) and Pd/C (1.3 mg, 10% wt) was added to the resulting solution was added. The solution was purged with $H_2$ and the vial was affixed with a $H_2$-filled ballon. The mixture was allowed to stir for 30 min at 22 °C. The volatiles were removed in vacuo and the resulting yellow oil was purified by C18 silica gel chromatography (3:1:0.01→1:5:0.01 $H_2O$:MeOH:trifluoroacetic acid) to afford **2.134** (trifluoroacetate salt) as colorless oil (6.6 mg, 0.0169 mmol, 58% yield, 88:12 *exo*/*endo*). **IR (neat):** 2952 (m), 2925 (s),

2870 (m), 1683 (s), 1610 (m), 1459 (w), 1377 (w), 1201 (s), 1280 (m), 1135 (w), 836 (w), 801 (w), 721 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 8.17 (s, 1H), 8.09 (s, 1H), 7.03 (s, 1H), 3.52–3.44 (m, 2H), 2.23 (dt, *J* = 14.4, 7.0 Hz, 1H), 2.19–2.12 (m, 2H), 1.88 (dt, *J* = 12.1, 6.5 Hz, 1H), 1.66–1.60 (m, 1H), 1.54–1.49 (m, 1H), 1.48–1.41 (m, 2H), 1.34–1.22 (m, 10H), 1.20–1.12 (m, 2H), 0.91–0.86 (m, 6H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 155.8, 52.7, 48.7, 46.4, 43.9, 40.4, 33.7, 32.6, 32.0, 30.0, 29.7, 29.1, 26.8, 23.8, 22.8, 19.2, 14.2; **HRMS (DART):** Calcd for $C_{17}H_{32}N_3$ $[M+H]^+$: 278.2591. Found: 278.2585; **Specific rotation:** $[\alpha]_D^{20}$ +23.9 (*c* 0.16, $CHCl_3$).

***Netamine C (the initially proposed structure)***




**((5*R*,6*S*,*E*)-5-Methyl-6-vinyldodec-2-en-1-yl) [(*S*,*R*)-2.131]:** The same procedure as described above for synthesis of (*R*,*R*)-**2.131** was followed to obtain (*S*,*R*)-**2.131** as colorless oil (286 mg, 0.794 mmol, 74% overall yield). **IR (neat):** 2956 (m), 2924 (s), 2853 (m), 1276 (m), 1034 (s), 1007 (s), 973 (s) $cm^{-1}$;

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 5.75 (dt, *J* = 14.8, 7.2 Hz, 1H), 5.63–5.49 (m, 2H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.93 (d, *J* = 17.1 Hz, 1H), 4.48 (t, *J* = 7.4 Hz, 2H), 4.10 (p, *J* = 7.2 Hz, 4H), 2.09 (dt, *J* = 13.6, 6.5 Hz, 1H), 1.96–1.83 (m, 2H), 1.54 (hept, *J* = 7.6, 7.1 Hz, 1H), 1.36–1.20 (m, 16H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 140.0, 135.6, 125.8 (d, *J* = 6.6 Hz), 115.9, 68.3 (d, *J* = 5.5 Hz), 63.8 (d, *J* = 5.9 Hz), 48.3, 38.0, 36.7, 32.6, 32.0, 29.6, 27.7, 22.8, 16.3 (d, *J* = 6.7 Hz), 15.3, 14.2; **HRMS (DART):** Calcd for $C_{19}H_{38}O_4P$ $[M+H]^+$: 361.2502. Found: 361.2508; **Specific rotation:** $[\alpha]_D^{20}$ –2.3 (*c* 0.32, $CHCl_3$).

**(4*S*,6*R*,7*S*)-6-Methyl-4,7-divinyltridecanal [(*S,R,S*)-2.14]:** In a glove box, an oven-dried vial with magnetic stir bar was charged with CuCl (2.5 mg, 0.025 mmol), (*S*)-**imid-2.1** (23.6 mg, 0.0275 mmol), LiO*t*-Bu (48.0 mg, 0.12 mmol), freshly distilled THF (2.5 mL). The solution was pre-mixed for 30 min before PMHS (150 mg, 2.50 mmol), allenyl boronic acid pinacol ester **2.16** (135 mg, 0.75 mmol) and more THF (2.5 mL) were added. The solution immediately turned dark-red. After 10 min at 22 °C, allylic phosphate (*S,R*)-**2.131** (180 mg, 0.50 mmol) was added. The vial was sealed with electrical tape before removal from the glove box, and stirring was allowed to continue for 2 h at 22 °C after which the reaction was quenched by the addition at 0 °C of an aqueous solution of 1 M NaOH (1.0 mL) and $H_2O_2$ (200 μL, 30% wt. in $H_2O$). The mixture was allowed to warm to 22 °C and stir for 1 h, after which it was charged with an aqueous solution of saturated $Na_2S_2O_3$ (1.0 mL). The resulting mixture was allowed to stir for

30 min at 22 °C. The layers were separated, and the aqueous layer was washed with $Et_2O$ (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. The resulting yellow oil was purified by silica gel chromatography (20:1→1:1 hexanes:$Et_2O$) to afford (*S,R,S*)-**2.14** as colorless oil (93.3 mg, 0.353 mmol, 71% yield). **IR (neat):** 2968 (m), 2924 (s), 2953 (m), 1719 (m), 1458 (w), 1410 (w), 1365 (w), 1044 (w), 910 (s) $cm^{-1}$; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.76 (t, *J* = 1.6 Hz, 1H), 5.55 (ddd, *J* = 17.1, 10.3, 9.2 Hz, 1H), 5.40 (ddd, *J* = 17.0, 10.2, 9.2 Hz, 1H), 5.05–4.87 (m, 4H), 2.42 (tdd, *J* = 8.6, 6.4, 1.7 Hz, 2H), 2.04 (ddq, *J* = 14.1, 9.5, 4.4 Hz, 1H), 1.82 (tt, *J* = 9.0, 4.6 Hz, 1H), 1.75–1.62 (m, 1H), 1.54–1.43 (m, 2H), 1.35–1.07 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 202.8, 142.1, 140.6, 115.8, 115.4, 49.7, 42.1, 41.6, 40.8, 33.9, 32.4, 32.0, 29.6, 27.9, 27.7, 22.8, 14.9, 14.2; **HRMS (DART):** Calcd for $C_{18}H_{33}O$ $[M+H]^+$: 265.2526. Found: 265.2525; **Specific rotation:** $[\alpha]_D^{20}$ +5.7 (*c* 0.60, $CHCl_3$).

**3-((1*S*,4*R*,5*R*)-4-Hexyl-5-methylcyclohex-2-en-1-yl)propanal [(*S,R,S*)-2.13]:** In a glove box, an oven-dried 2-dram vial equipped with a stir bar was charged with (*S,R,S*)-**2.14** (89.2 mg, 0.337 mmol). To this compound was added **Ru-2.1** (10.6 mg, 0.0169 mmol) in $CH_2Cl_2$ (1.0 mL). The vial was sealed with a cap and electrical tape, and removed from the glove box. The mixture was allowed to stir for 1 h at 40 °C and then cooled to 22 °C. The volatiles were removed under reduced pressure and the residue was purified by silica gel chromatography (20:1→1:1 hexanes:$Et_2O$) to afford (*S,R,S*)-**2.13** as colorless oil

(71.9 mg, 0.304 mmol, 90% yield). **IR (neat):** 2952 (m), 2922 (s), 2854 (m), 1726 (s), 1452 (w), 1376 (w), 1119 (w), 1049 (w), 771 (w), 736 (w) $cm^{-1}$; **$^1$H NMR (500 MHz, $CDCl_3$):** δ 9.78 (s, 1H), 5.83 (ddd, *J* = 10.1, 5.1, 2.5 Hz, 1H), 5.47 (d, *J* = 9.1 Hz, 1H), 2.46 (t, *J* = 7.6 Hz, 2H), 2.20–2.11 (m, 1H), 1.98–1.89 (m, 1H), 1.83 (dqd, *J* = 14.4, 7.0, 2.5 Hz, 1H), 1.68 (tt, *J* = 13.0, 6.0 Hz, 2H), 1.57 (dq, *J* = 15.9, 7.6 Hz, 1H), 1.49–1.16 (m, 10H), 1.07–0.99 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$):** δ 202.9, 133.1, 130.0, 41.4, 38.9, 36.4, 32.9, 32.1, 32.1, 30.1, 30.0, 28.4, 27.7, 22.8, 19.3, 14.3; **HRMS (DART):** Calcd for $C_{16}H_{29}O$ $[M+H]^+$: 237.2213. Found: 237.2213; **Specific rotation:** $[\alpha]_D^{20}$ +96.7 (*c* 1.3, $CHCl_3$).

**Netamine C (initially proposed structure):** In a glove box, an oven-dried 2-dram vial equipped with a stir bar was charged with (*S,R,S*)-**2.13** (10.9 mg, 0.0461 mmol), hydrazine monohydrate (11.5 mg, 0.230 mmol), and EtOH (1.0 mL) and stirred at 22 °C for 10 min. To the solution was added HCl (39 μL, 36.5% wt, 0.46 mmol). The vial was sealed with a cap and electrical tape, and removed from the glove box. The solution was allowed to stir for 4 h at 100 °C and then cool to 22 °C. To this solution was added $PtO_2$ (2.1 mg, 9.2 μmol),[43] after which the solution was purged with $H_2$ and the vial was affixed with a $H_2$-filled ballon; the mixture was allowed to stir for 16 h at 60 °C, and then was allowed to cool to 22 °C and sequentially charged with MeONa (49.7 mg, 0.92 mmol) and BrCN (24.4 mg, 0.23 mmol).[44] The mixture was allowed to stir for 1 h and then filtered through cotton and eluted with MeOH. The volatiles

were removed in vacuo and the resulting yellow oil was purified by C18 silica gel chromatography (3:1:0.01→1:5:0.01 $H_2O$:MeOH:trifluoroacetic acid) to afford netamine C (initially proposed structure, trifluoroacetate salt) as colorless oil (12.9 mg, 0.0331 mmol, 72% yield). Note: due to highly polarized nature of guanidine-containing compound netamine C (initially proposed structure), <5% unseperable impurities was contained in the product fraction.

**Netamine C (initially proposed structure): IR (neat):** 3198 (br), 2953 (m), 2924 (s), 2854 (m), 1671 (s), 1456 (w), 1427 (w), 1377 (w), 1339 (w), 1201 (s), 1181 (m), 1135 (m), 834 (w), 800 (w), 721 (w) $cm^{-1}$; **$^1$H NMR (600 MHz, $CDCl_3$):** δ 8.49 (s, 1H), 7.59 (s, 1H), 7.16 (s, 1H), 3.77 (t, *J* = 4.4 Hz, 1H), 3.68 (d, *J* = 6.4 Hz, 1H), 2.29 (dt, *J* = 11.3, 5.7 Hz, 1H), 2.20–2.13 (m, 1H), 2.03 (dt, *J* = 13.1, 8.0 Hz, 1H), 1.93–1.84 (m, 2H), 1.70–1.59 (m, 2H), 1.46–1.38 (m, 1H), 1.36–1.16 (m, 12H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H); **$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 154.7, 119.1 ($CF_3CO_2^-$), 53.0, 50.0, 40.3, 39.4, 38.6, 33.7, 32.8, 31.9, 31.9, 30.0, 29.9, 29.8, 29.6, 29.5, 29.0, 28.2, 28.2, 22.8, 22.7, 18.3, 14.2; **HRMS (DART):** Calcd for $C_{17}H_{32}N_3$ $[M+H]^+$: 278.2591. Found: 278.2579; **Specific rotation:** $[\alpha]_D^{20}$ −19.9 (*c* 0.16, MeOH).

- **Comparison of Analytical Data for Natural and Synthetic Netamine C**

***Table S2.3.*** $^{1}$H NMR data ($CDCl_3$)

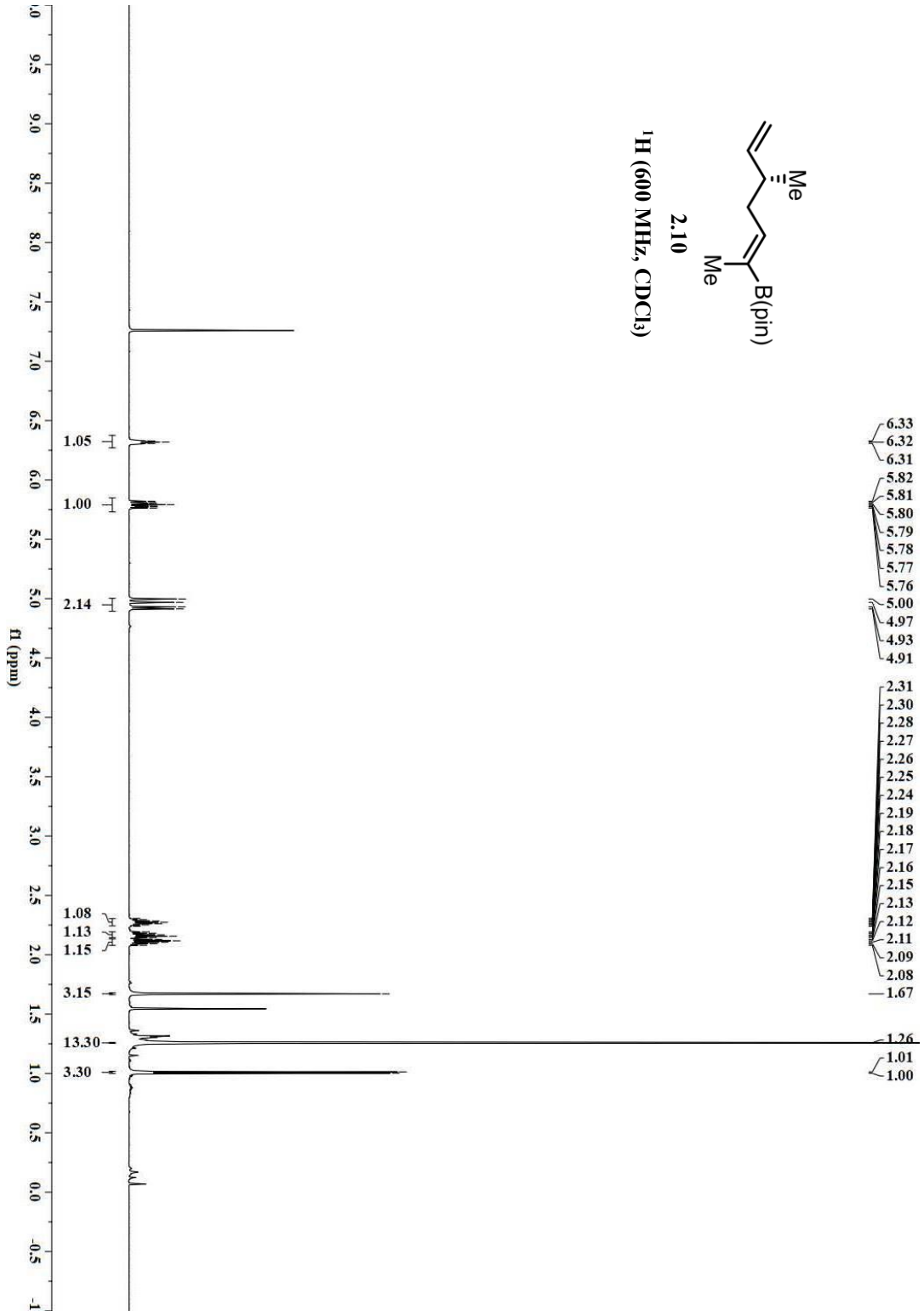
| **Natural** $\delta_H$ [ppm, mult, *J* (Hz)*] 500 MHz | **Synthetic** (revised structure) $\delta_H$ [ppm, mult, *J* (Hz)] 500 MHz | **Difference** (Natural–Synthetic) $\Delta\delta_H$ (ppm) |
|---|---|---|
| 7.67 1 H, br s | 7.49 1 H, br s | 0.18 |
| 7.53 1 H, br s | 7.28 1 H, br s | 0.25 |
| 6.93 2 H, br s | 6.86 2 H, br s | 0.07 |
| 3.86 1 H, m, (6.2, 3.9) | 3.86 1 H, dd, 6.5, 4.0 | 0 |
| 3.51 1 H, br d, (5.0, 1.5) | 3.51 1 H, dd, 5.1, 1.5 | 0 |
| 2.32 1 H, m, (11.1, 5.9) | 2.32 1 H, dt, 11.5, 5.7 | 0 |
| 2.08 1 H, m | 2.13–2.02 1 H, m | – |
| 1.94 1 H, m | 1.94 1 H, dt, 13.9, 7.3 | 0 |
| 1.84 1 H, dd, (13.0, 5.0) | 1.83 1 H, dd, 13.3, 6.0 | 0.01 |
| 1.63 2 H, m | 1.69–1.58 2 H, m | – |
| 1.36 1 H, m | | |
| 1.31 2 H, m | | |
| 1.30 1 H, m | 1.38–1.17 13 H, m | – |
| 1.28 6 H, m | | |
| 1.27 2 H, m | | |
| 1.21 1 H, m | | |
| 1.06 1 H, m | 1.08–1.03 1 H, m | – |
| 1.02 3 H, d | 1.01 3 H, d, 6.8 | 0.01 |
| 0.89 3 H, t (7.0) | 0.88 3 H, t, 6.9 | 0.01 |

* Coupling constants given in parentheses are for netamine A because coupling constants for netamine C were not provided.

***Table S2.4.*** $^{13}C$ NMR data ($CDCl_3$)

| **Natural** $\delta_C$ (ppm) 126 MHz | **Synthetic** (revised structure) $\delta_C$ (ppm) 126 MHz | **Difference** (Natural–Synthetic) $\Delta\delta_C$ (ppm) |
|---|---|---|
| 154.9 | 154.8 | 0.1 |
| 53.7 | 53.8 | −0.1 |
| 49.8 | 49.9 | −0.1 |
| 45.0 | 45.1 | −0.1 |
| 35.8 | 35.8 | 0 |
| 35.1 | 35.1 | 0 |
| 34.8 | 34.8 | 0 |
| 34.7 | 34.7 | 0 |
| 34.5 | 34.5 | 0 |
| 33.4 | 33.4 | 0 |
| 31.7 | 31.7 | 0 |
| 30.4 | 30.4 | 0 |
| 29.4 | 29.4 | 0 |
| 27.5 | 27.5 | 0 |
| 23.1 | 23.1 | 0 |
| 22.6 | 22.6 | 0 |
| 14.0 | 14.0 | 0 |

- **NMR Spectra**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Me
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1.15
3.15
13.30
3.30
6.33
6.32
6.31
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5.81
5.80
5.79
5.78
5.77
5.76
5.00
4.97
4.93
4.91
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2.24
2.19
2.18
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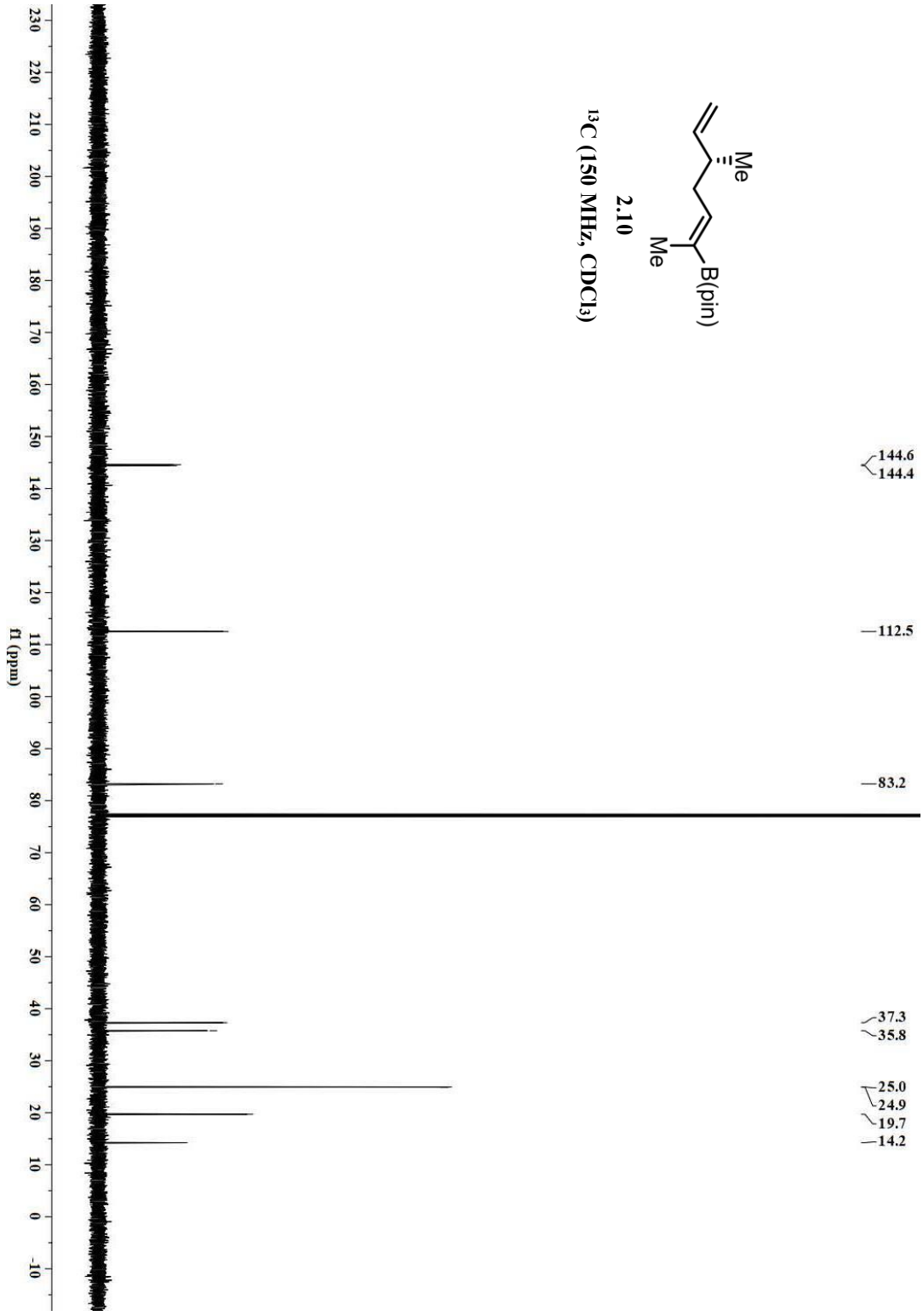
1.26
1.01
1.00


Me
B(pin)
Me
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13C (150 MHz, CDCl3)
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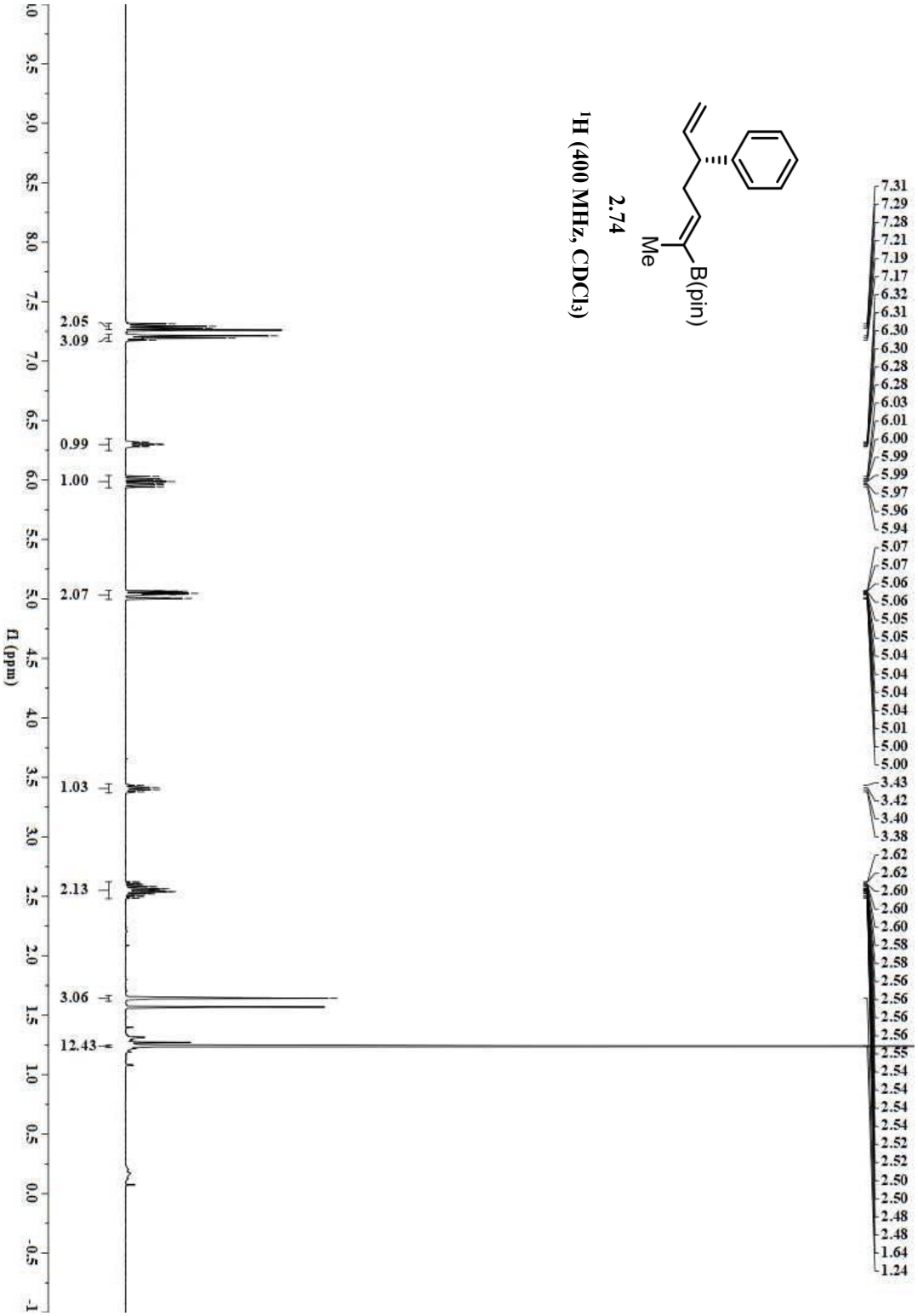
25.0
24.9
19.7
14.2
f1 (ppm)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B(pin)
Me
f1 (ppm)
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3.09
0.99
1.00
2.07
1.03
2.13
3.06
12.43
7.31
7.29
7.28
7.21
7.19
7.17
6.32
6.31
6.30
6.30
6.28
6.28
6.03
6.01
6.00
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5.99
5.97
5.96
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5.07
5.07
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5.00
5.00
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3.38
2.62
2.62
2.60
2.60
2.60
2.58
2.58
2.56
2.56
2.56
2.56
2.55
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2.50
2.50
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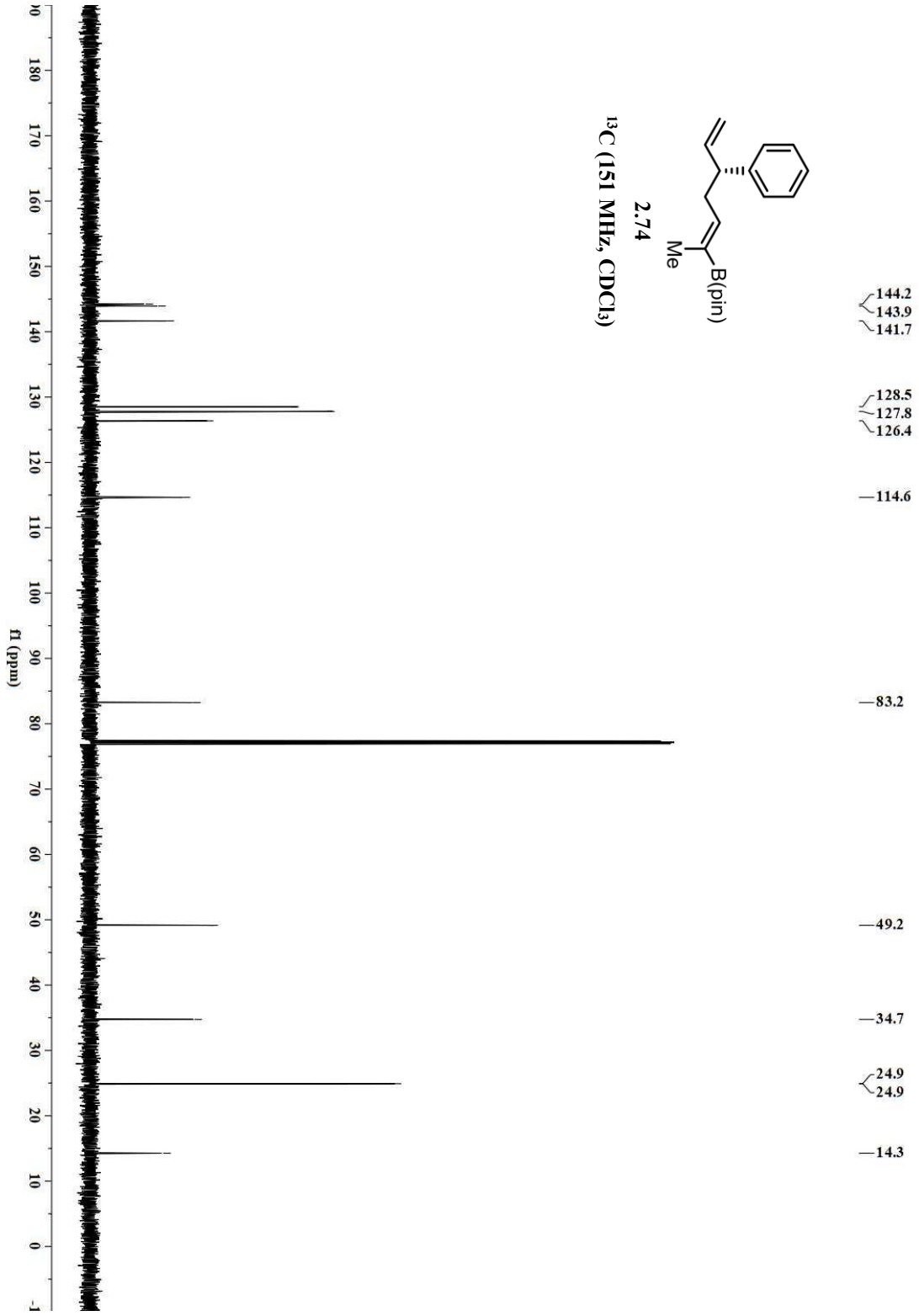
2.48
1.64
1.24


2.74
$^{13}$C (151 MHz, CDCl$_3$)
B(pin)
Me
144.2
143.9
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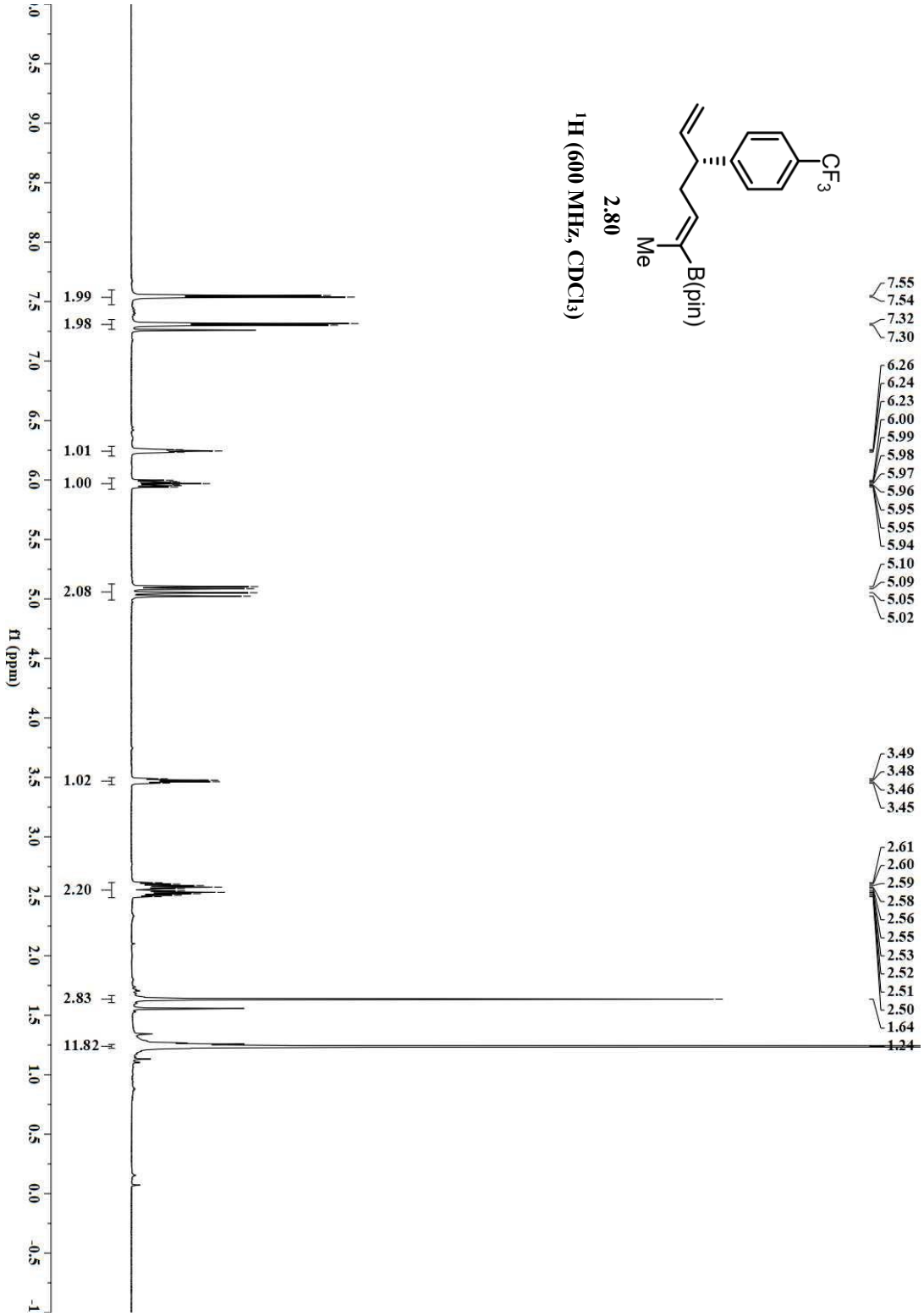
49.2
34.7
24.9
24.9
14.3
f1 (ppm)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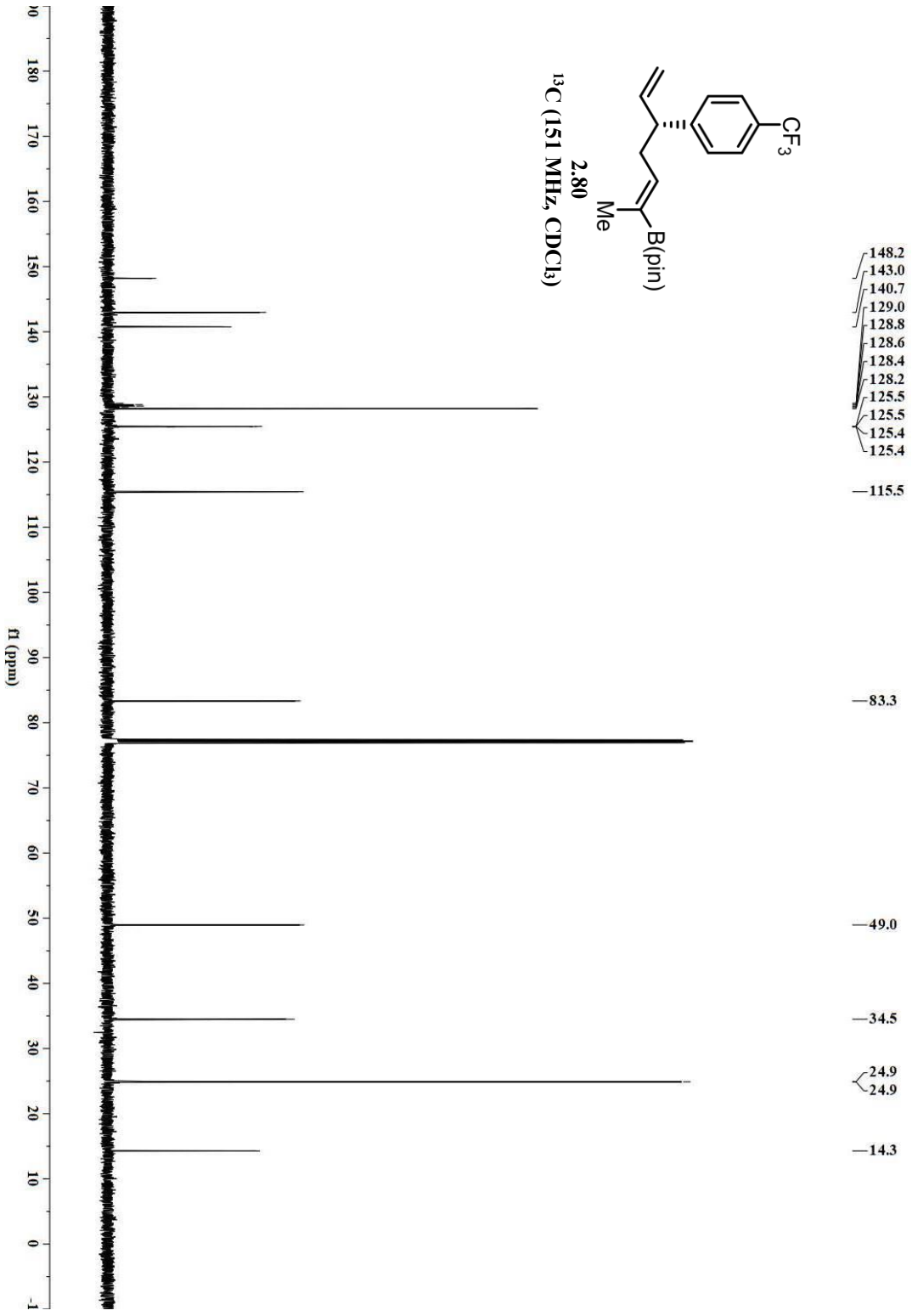
CF$_3$
B(pin)
Me
7.55
7.54
7.32
7.30
6.26
6.24
6.23
6.00
5.99
5.98
5.97
5.96
5.95
5.95
5.94
5.10
5.09
5.05
5.02
3.49
3.48
3.46
3.45
2.61
2.60
2.59
2.58
2.56
2.55
2.53
2.52
2.51
2.50
1.64
1.24
1.99
1.98
1.01
1.00
2.08
1.02
2.20
2.83
11.82
f1 (ppm)


2.80
$^{13}$C (151 MHz, CDCl$_3$)
CF$_3$
B(pin)
Me
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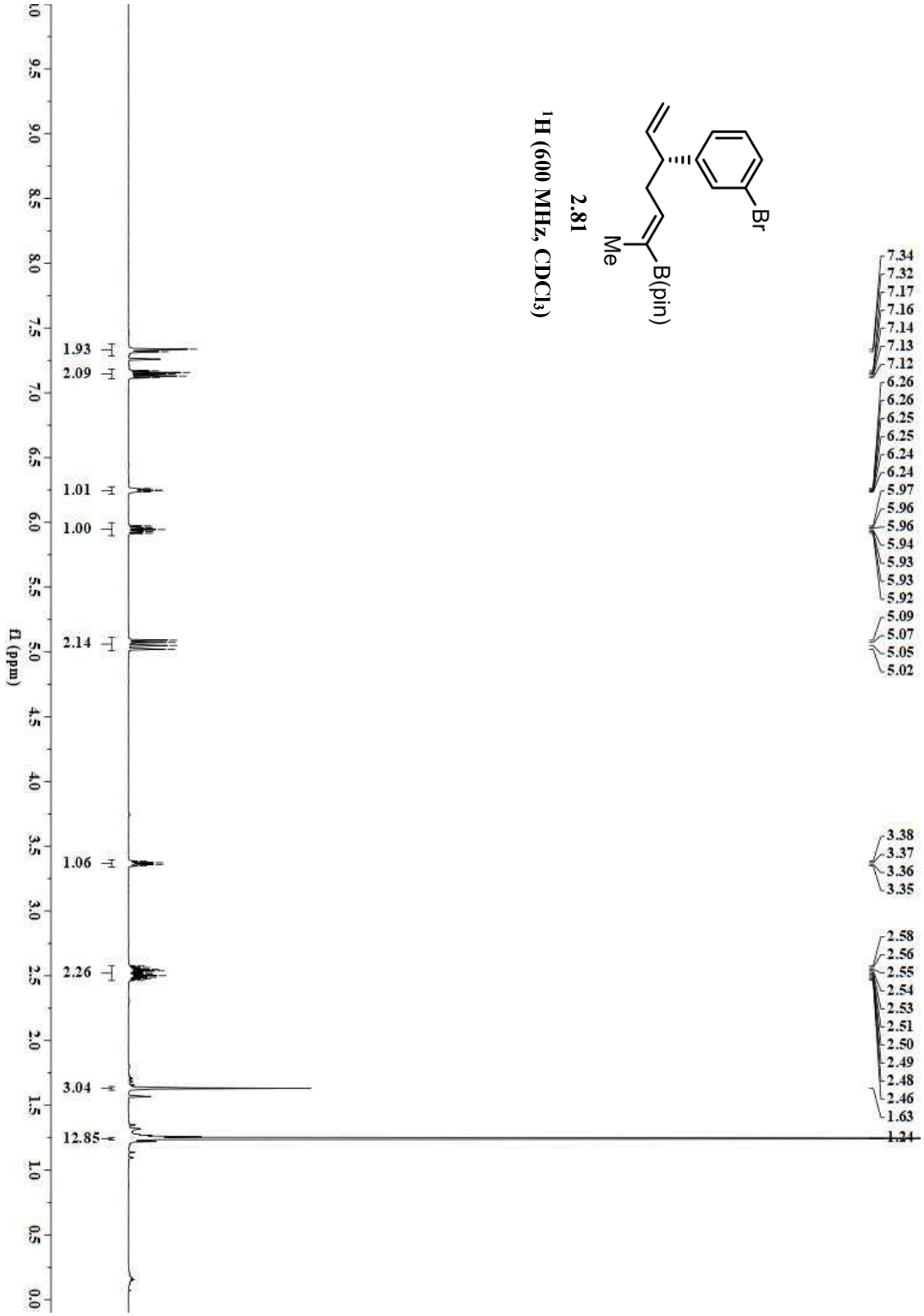
143.0
140.7
129.0
128.8
128.6
128.4
128.2
125.5
125.5
125.4
125.4
115.5
83.3
49.0
34.5
24.9
24.9
14.3
f1 (ppm)


Br
B(pin)
Me
2.81
¹H (600 MHz, CDCl₃)
f1 (ppm)
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2.09
1.01
1.00
2.14
1.06
2.26
3.04
12.85
7.34
7.32
7.17
7.16
7.14
7.13
7.12
6.26
6.26
6.25
6.25
6.24
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5.96
5.96
5.94
5.93
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5.09
5.07
5.05
5.02
3.38
3.37
3.36
3.35
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2.50
2.49
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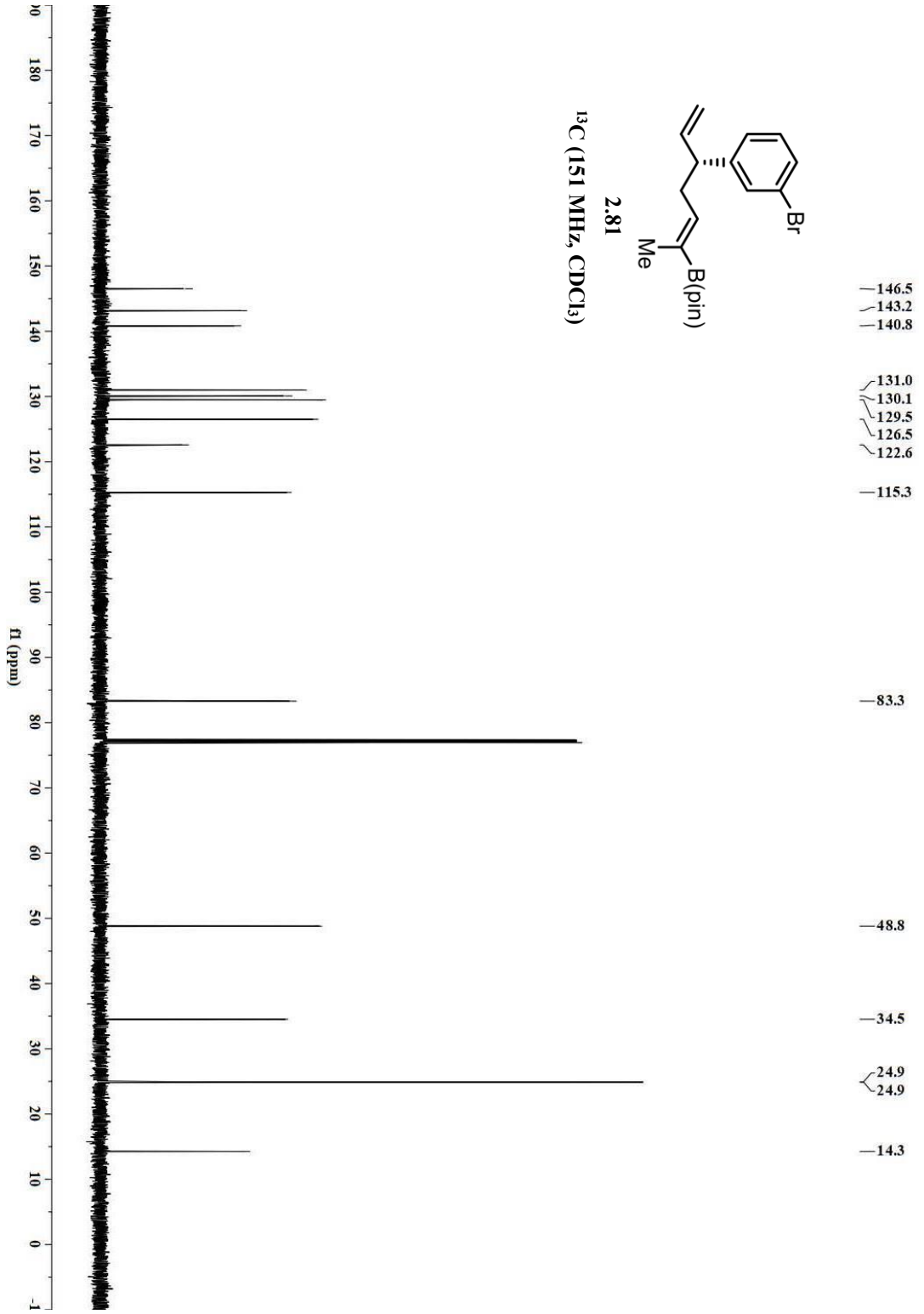
2.46
1.63
1.24


2.81
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Br
B(pin)
Me
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143.2
140.8
131.0
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129.5
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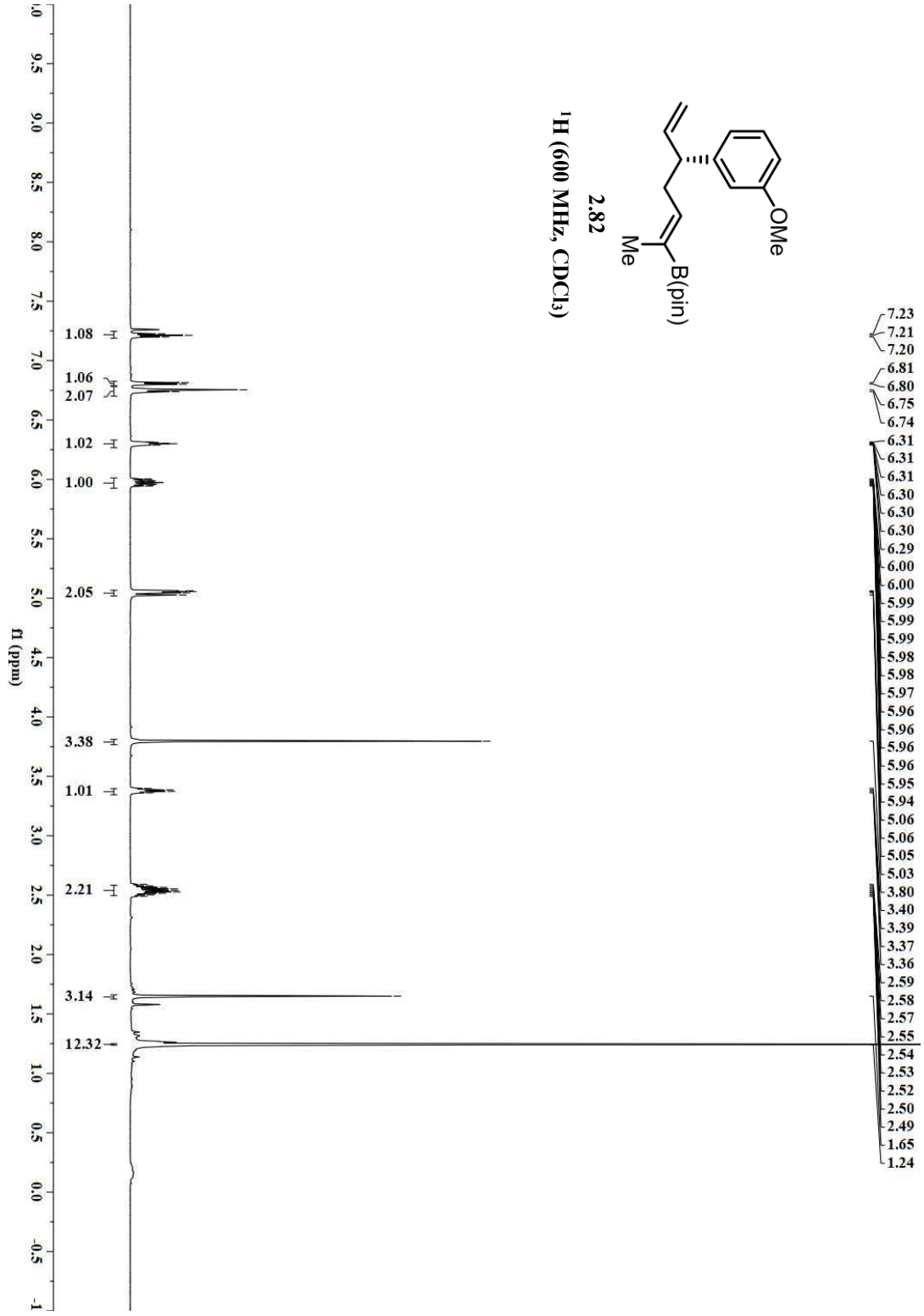
122.6
115.3
83.3
48.8
34.5
24.9
24.9
14.3
f1 (ppm)


2.82
$^1$H (600 MHz, CDCl$_3$)
OMe
B(pin)
Me
f1 (ppm)
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1.06
2.07
1.02
1.00
2.05
3.38
1.01
2.21
3.14
12.32
7.23
7.21
7.20
6.81
6.80
6.75
6.74
6.31
6.31
6.31
6.30
6.30
6.30
6.29
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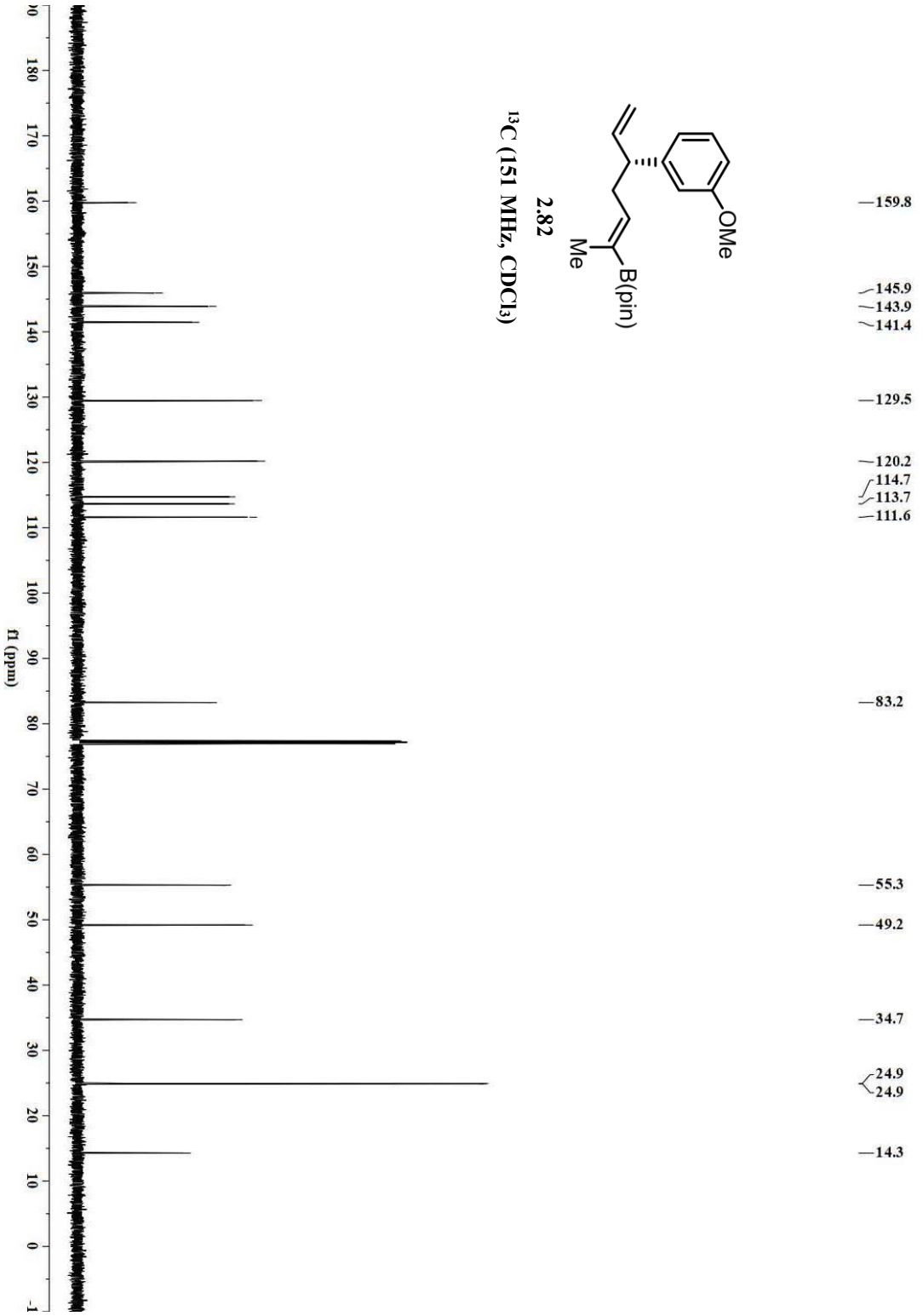
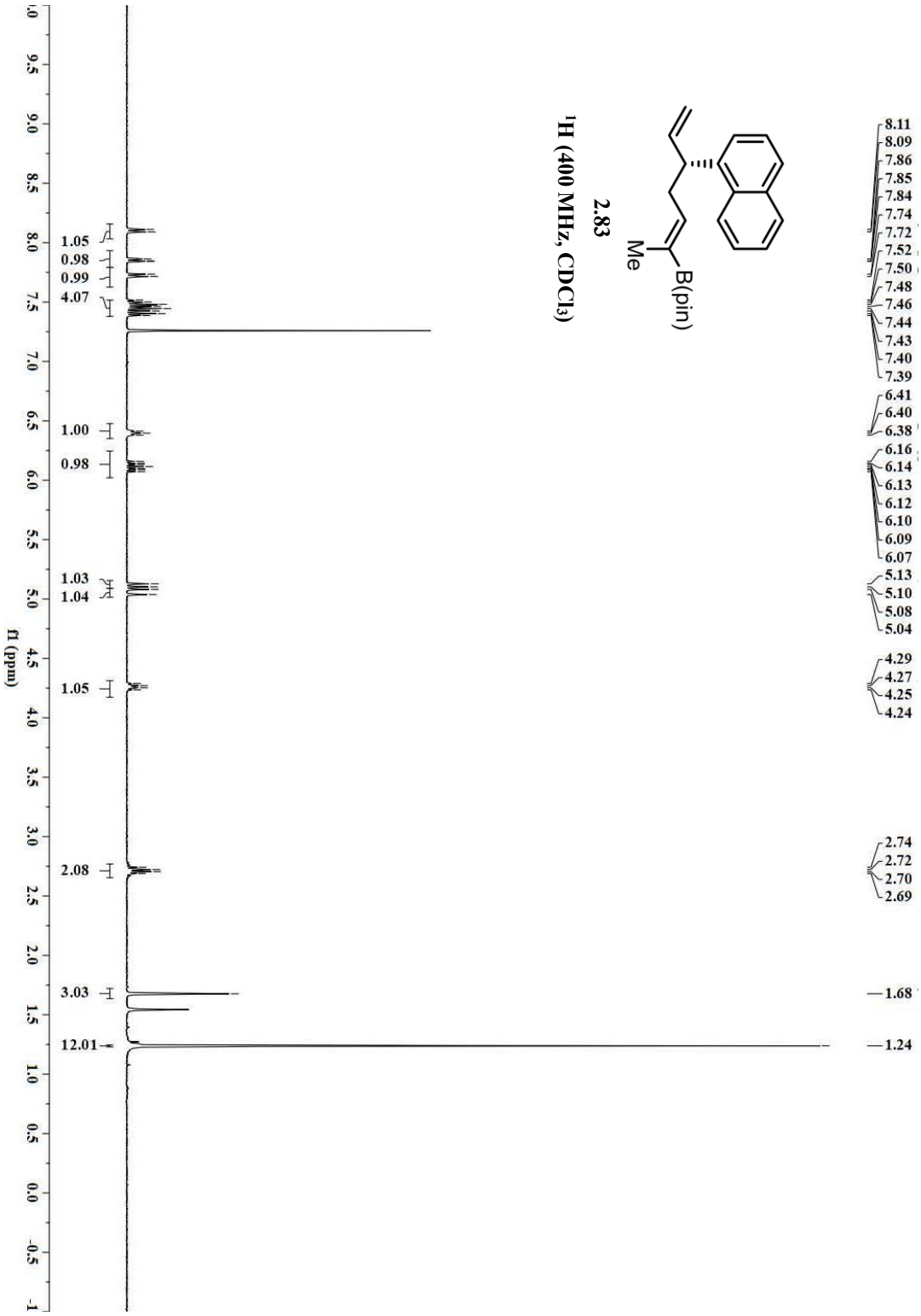
1.24




**2.82**

**$^{13}$C (151 MHz, CDCl$_3$)**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0.98
1.03
1.04
1.05
2.08
3.03
12.01
8.11
8.09
7.86
7.85
7.84
7.74
7.72
7.52
7.50
7.48
7.46
7.44
7.43
7.40
7.39
6.41
6.40
6.38
6.16
6.14
6.13
6.12
6.10
6.09
6.07
5.13
5.10
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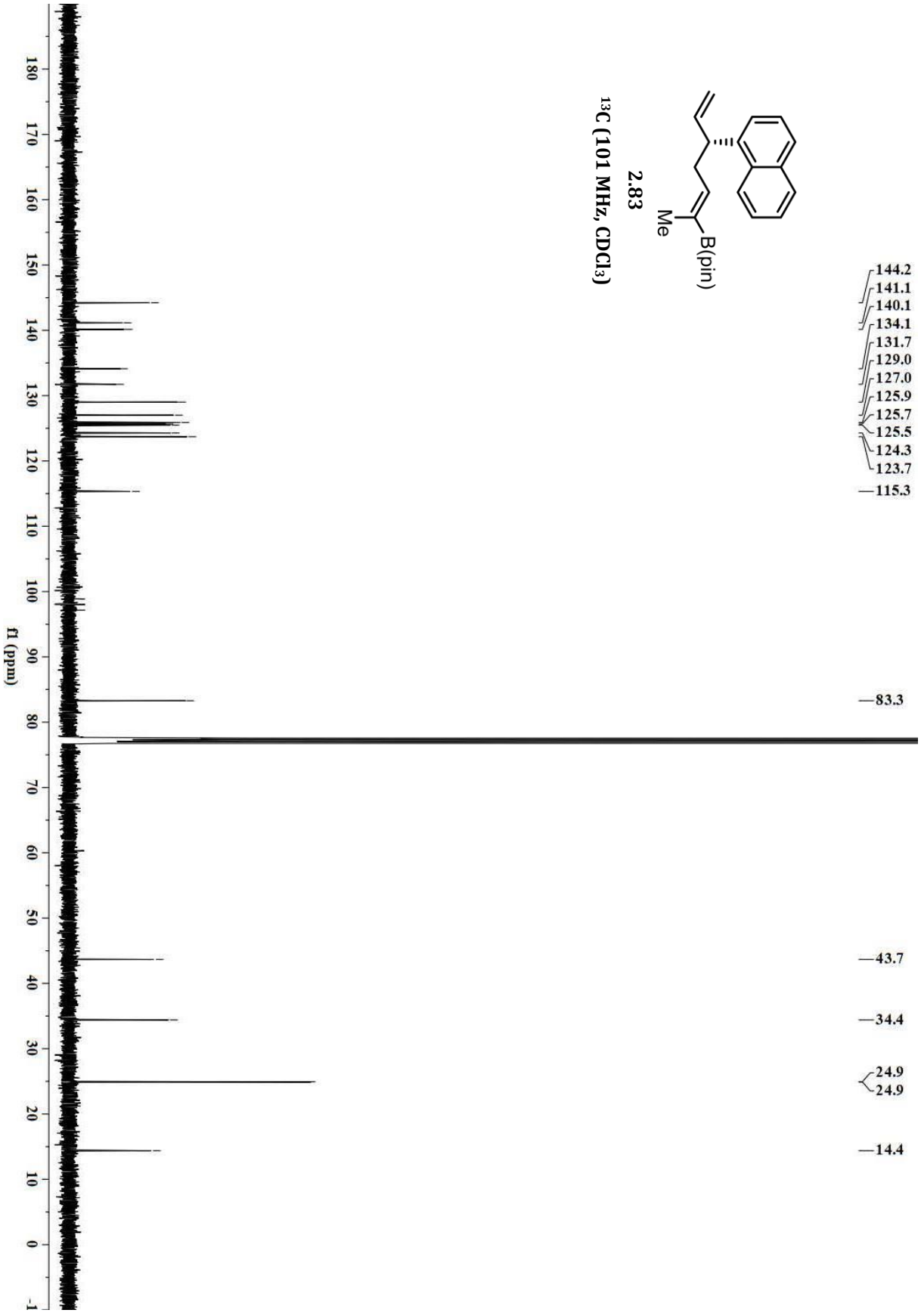
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$^{13}$C (101 MHz, CDCl$_3$)
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134.1
131.7
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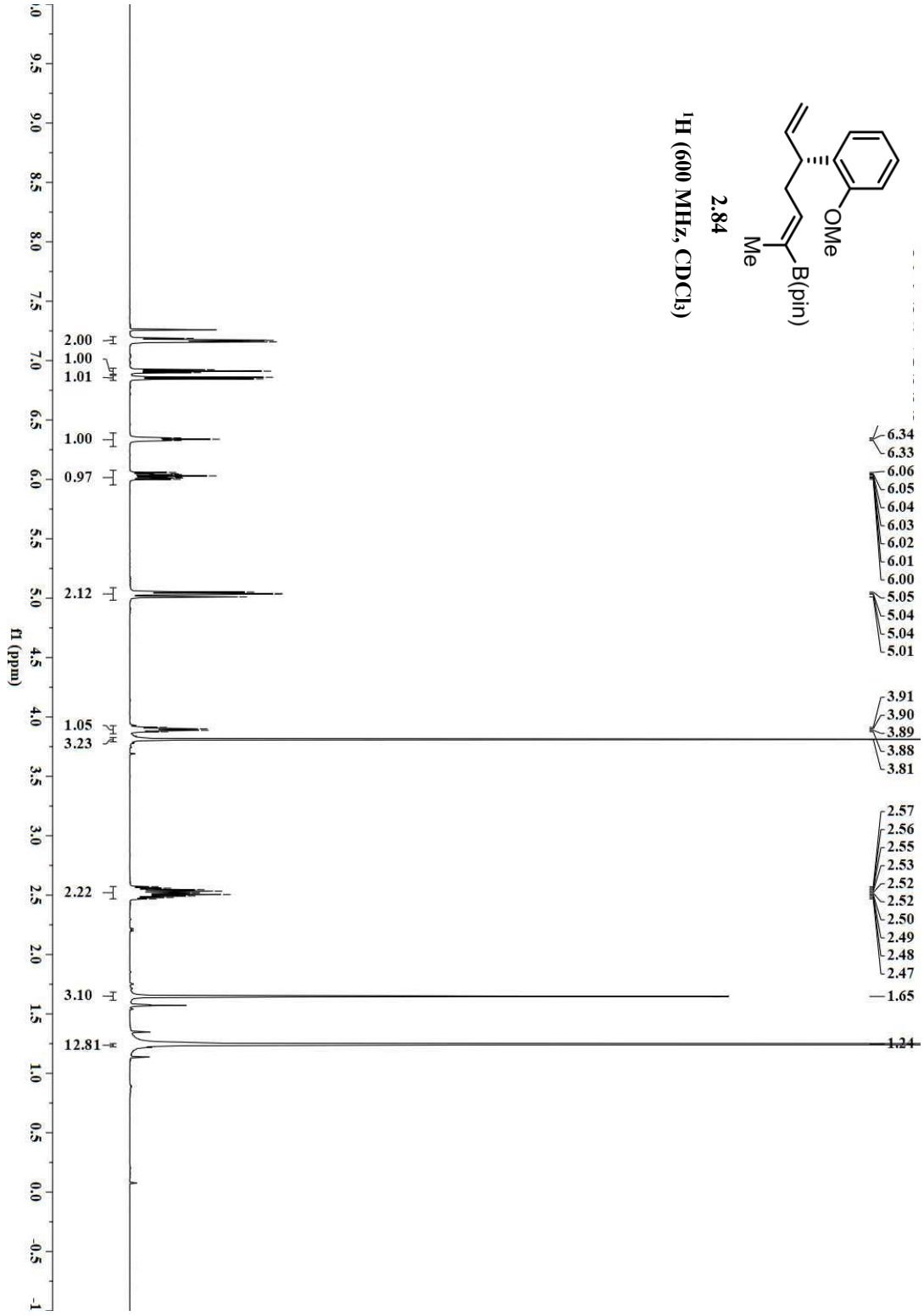
127.0
125.9
125.7
125.5
124.3
123.7
115.3
83.3
43.7
34.4
24.9
24.9
14.4
f1 (ppm)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$^1$H (600 MHz, CDCl$_3$)
OMe
B(pin)
Me
f1 (ppm)
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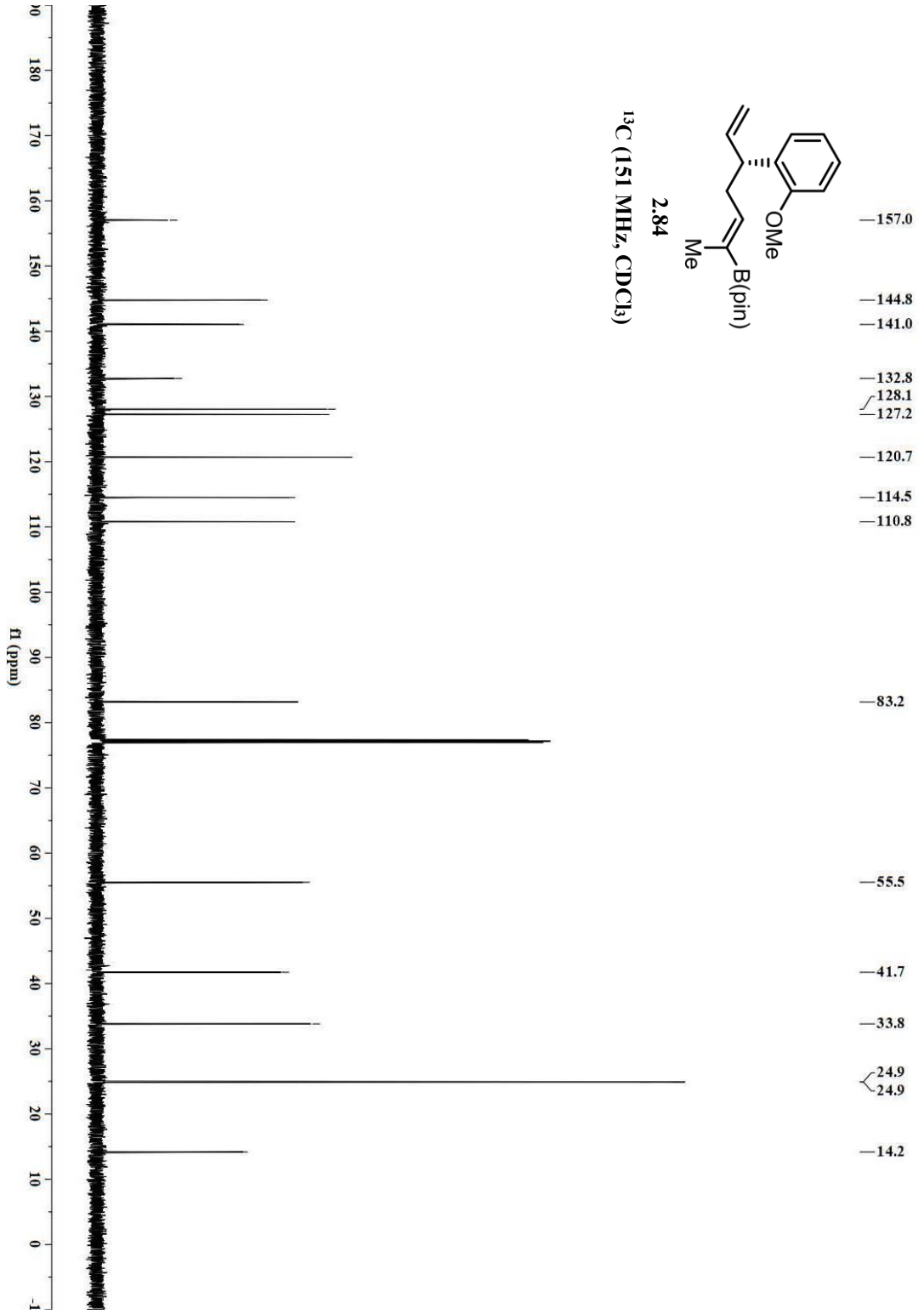
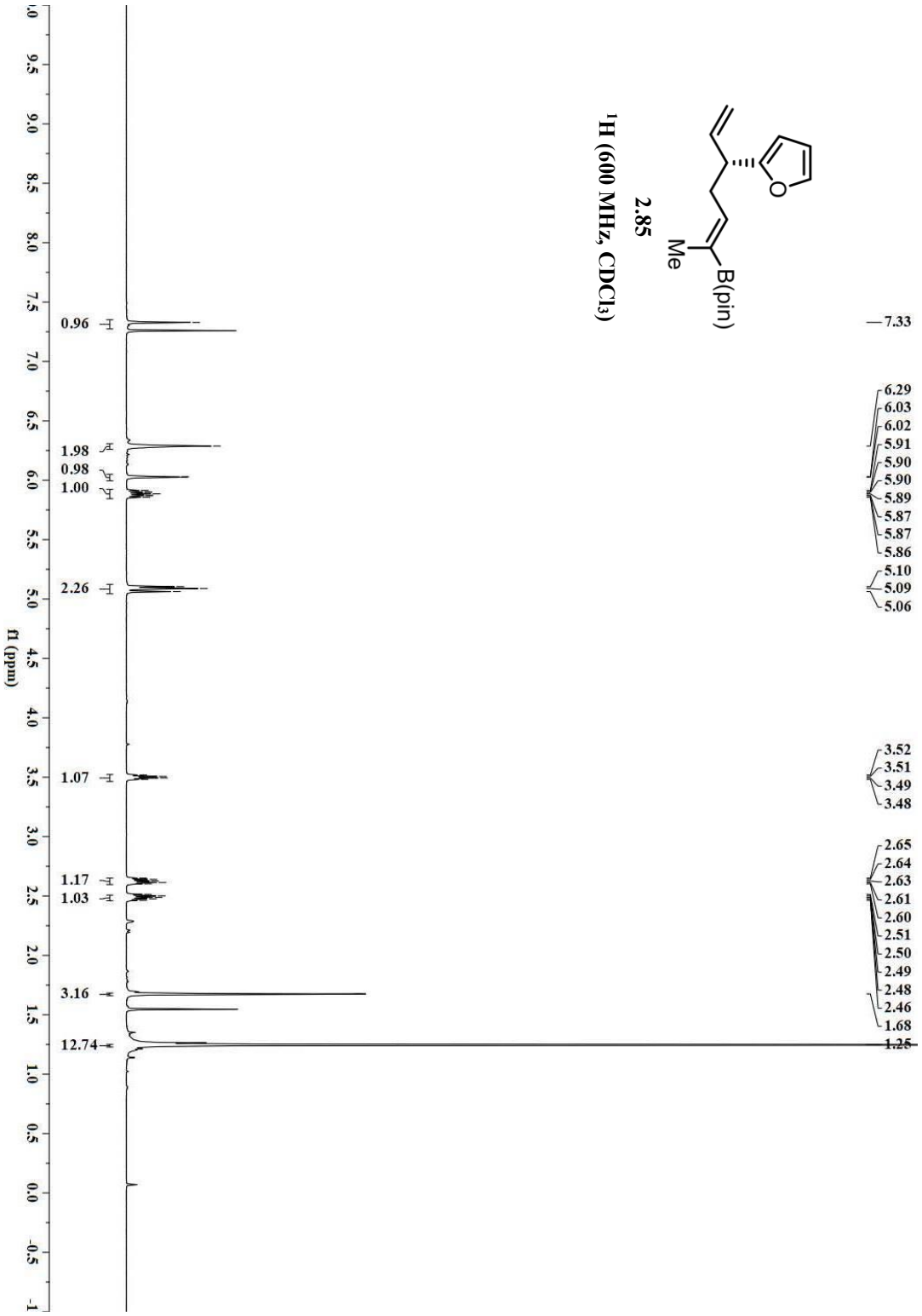
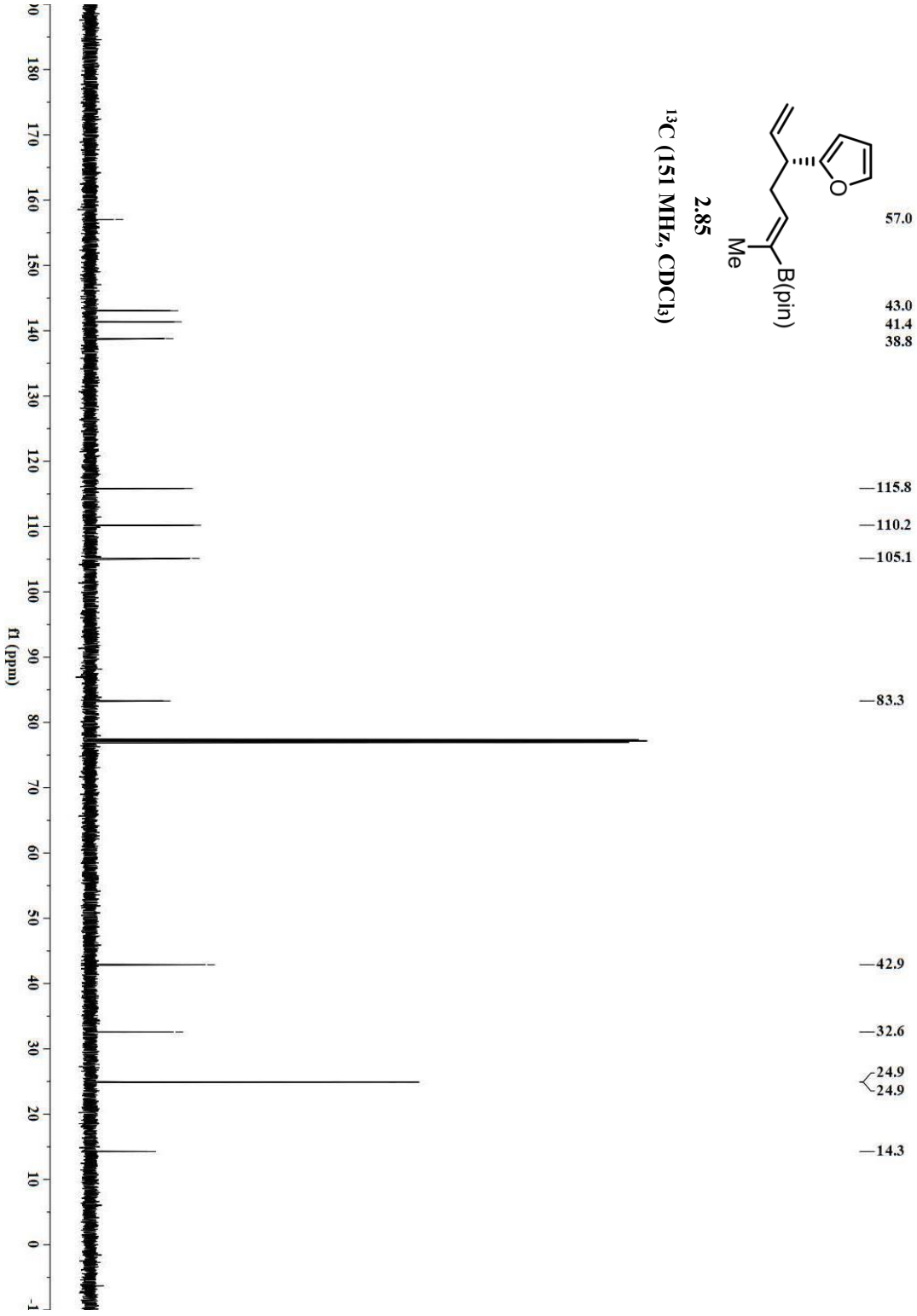
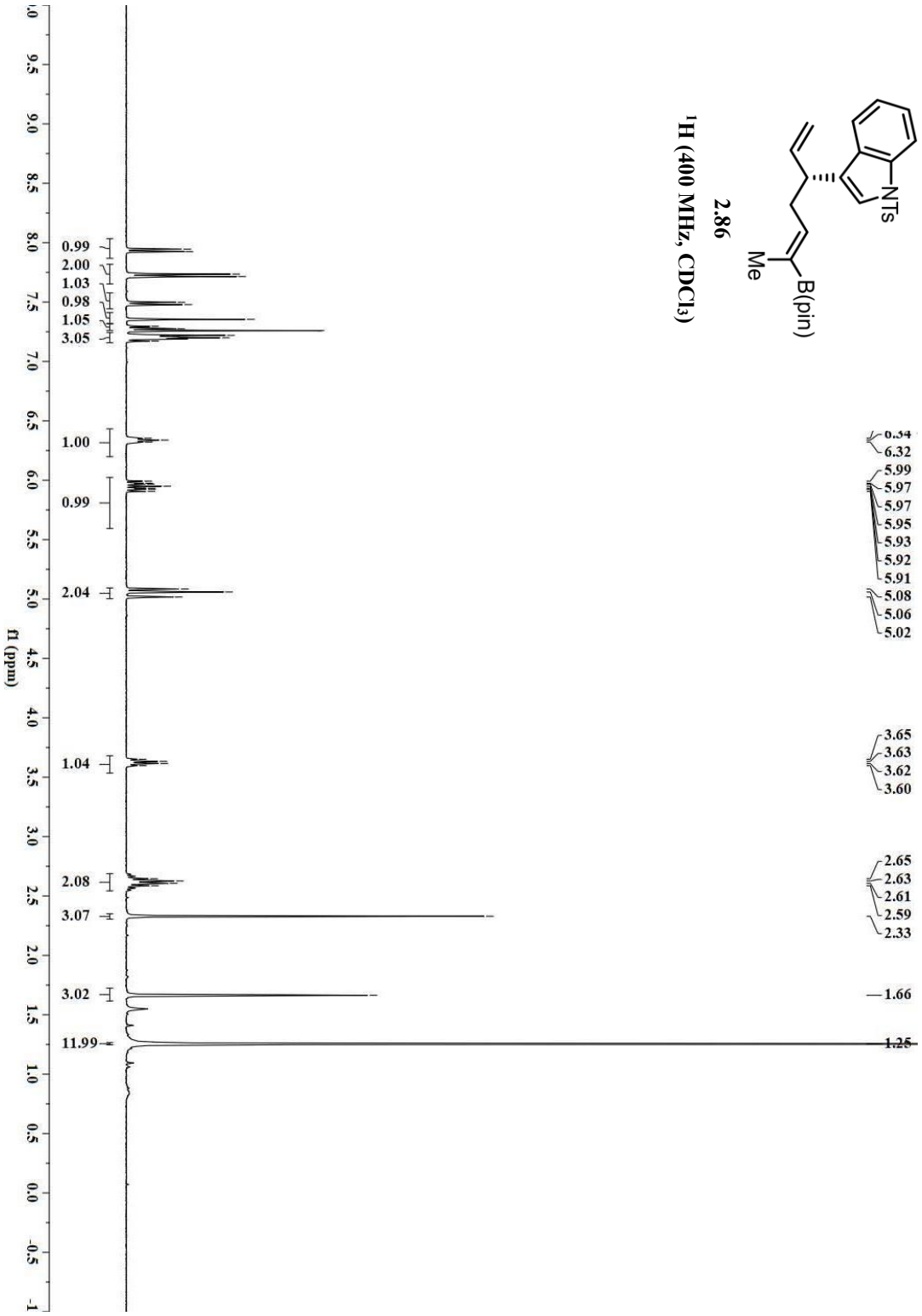
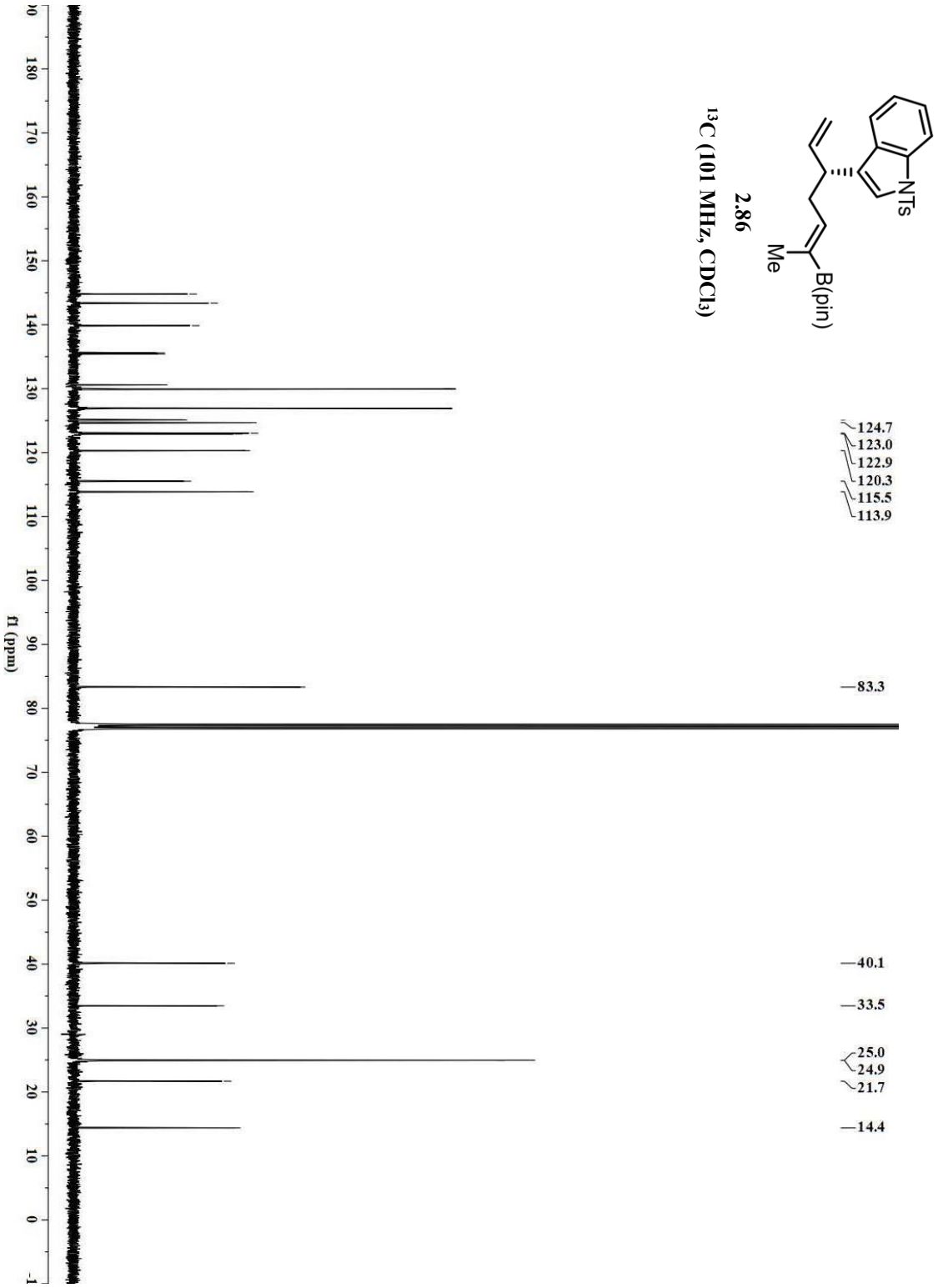
1.00
1.01
1.00
0.97
2.12
1.05
3.23
2.22
3.10
12.81
6.34
6.33
6.06
6.05
6.04
6.03
6.02
6.01
6.00
5.05
5.04
5.04
5.01
3.91
3.90
3.89
3.88
3.81
2.57
2.56
2.55
2.53
2.52
2.52
2.50
2.49
2.48
2.47
1.65
1.24

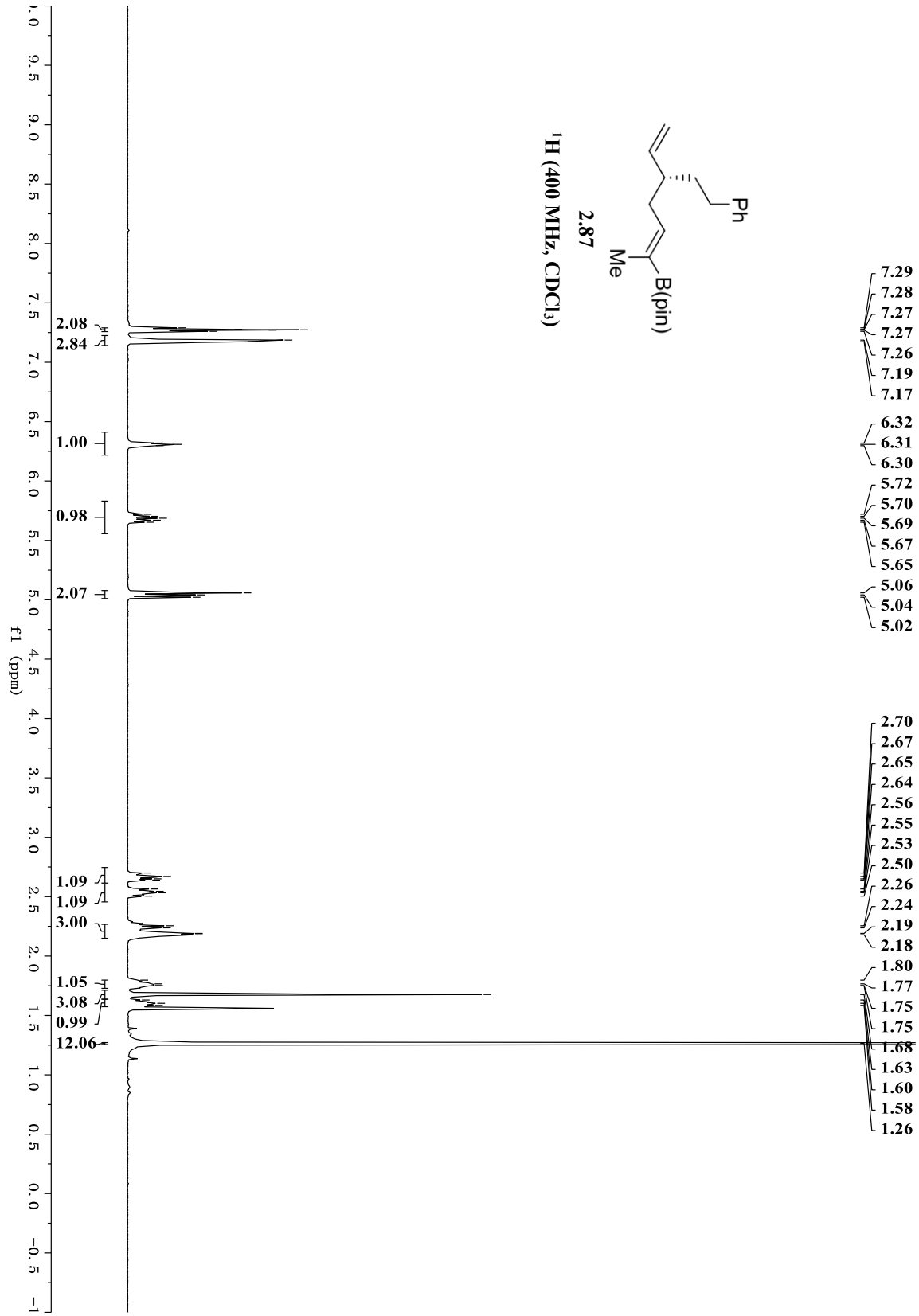

2.84
$^{13}$C (151 MHz, CDCl$_3$)
OMe
Me
B(pin)
157.0
144.8
141.0
132.8
128.1
127.2
120.7
114.5
110.8
83.2
55.5
41.7
33.8
24.9
24.9
14.2
f1 (ppm)

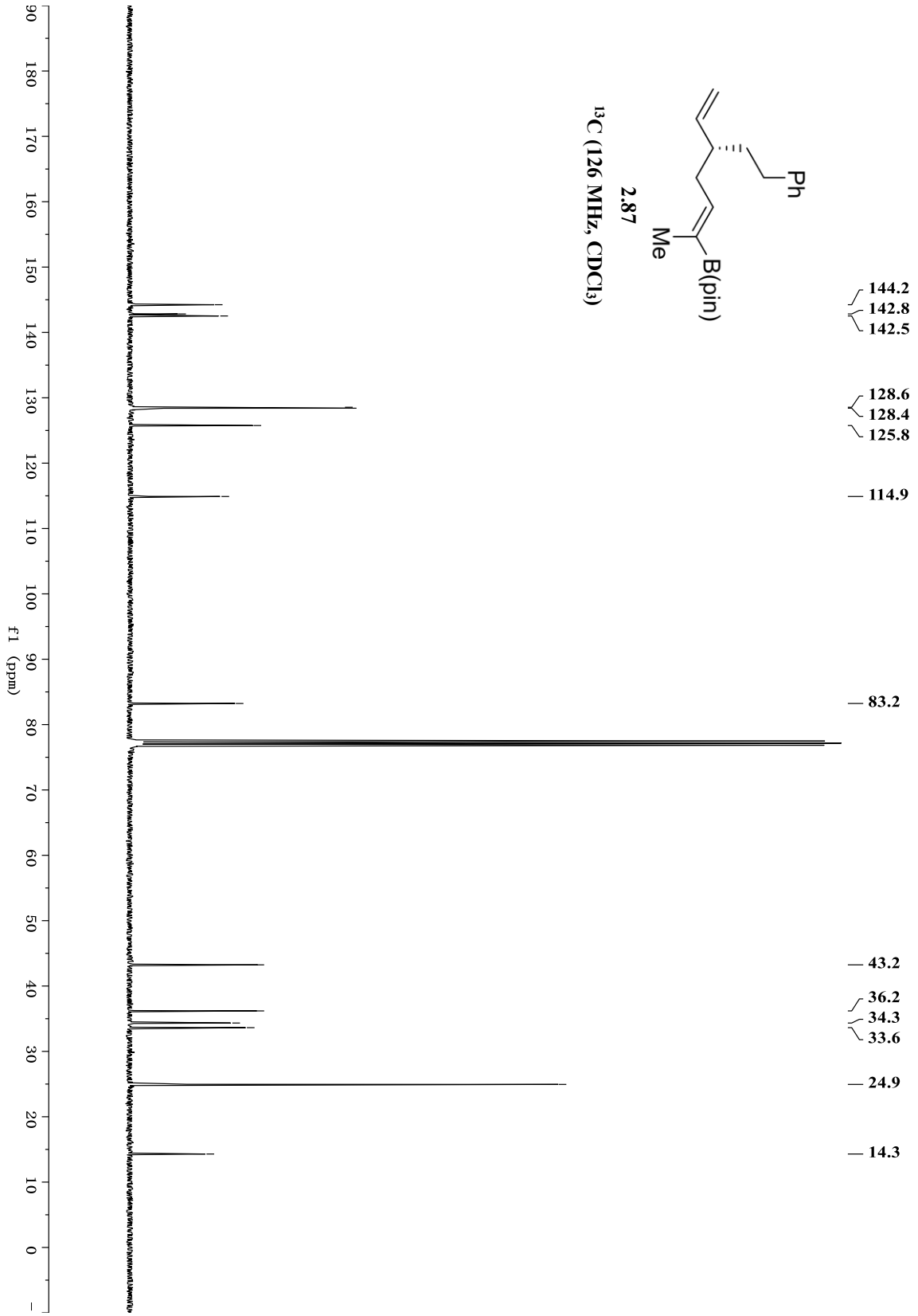

2.85
$^1$H (600 MHz, CDCl$_3$)
B(pin)
Me
O
f1 (ppm)
0.96
1.98
0.98
1.00
2.26
1.07
1.17
1.03
3.16
12.74
7.33
6.29
6.03
6.02
5.91
5.90
5.90
5.89
5.87
5.87
5.86
5.10
5.09
5.06
3.52
3.51
3.49
3.48
2.65
2.64
2.63
2.61
2.60
2.51
2.50
2.49
2.48
2.46
1.68
1.25

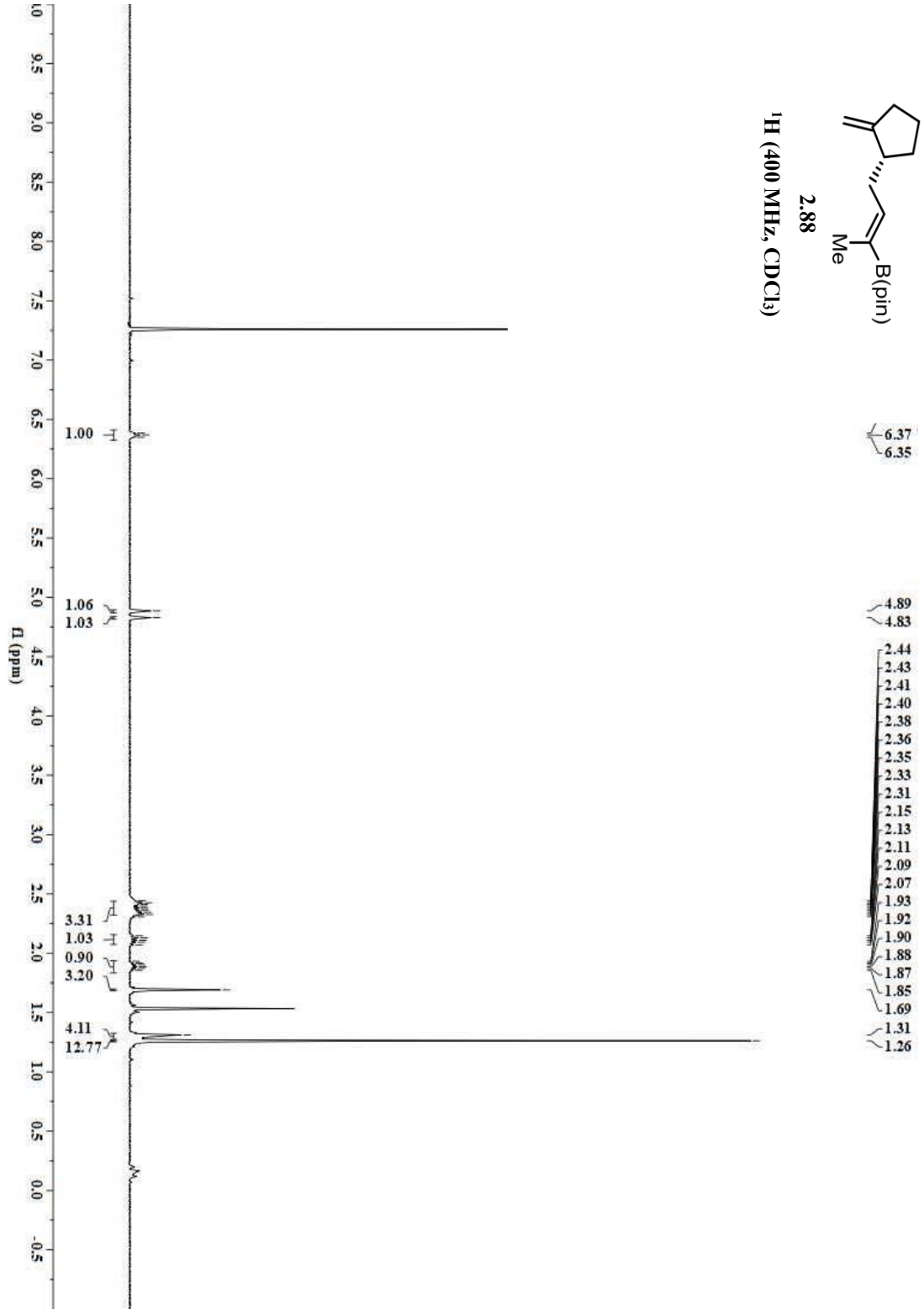

2.85
$^{13}$C (151 MHz, CDCl$_3$)
B(pin)
Me
57.0
43.0
41.4
38.8
115.8
110.2
105.1
83.3
42.9
32.6
24.9
24.9
14.3
f1 (ppm)

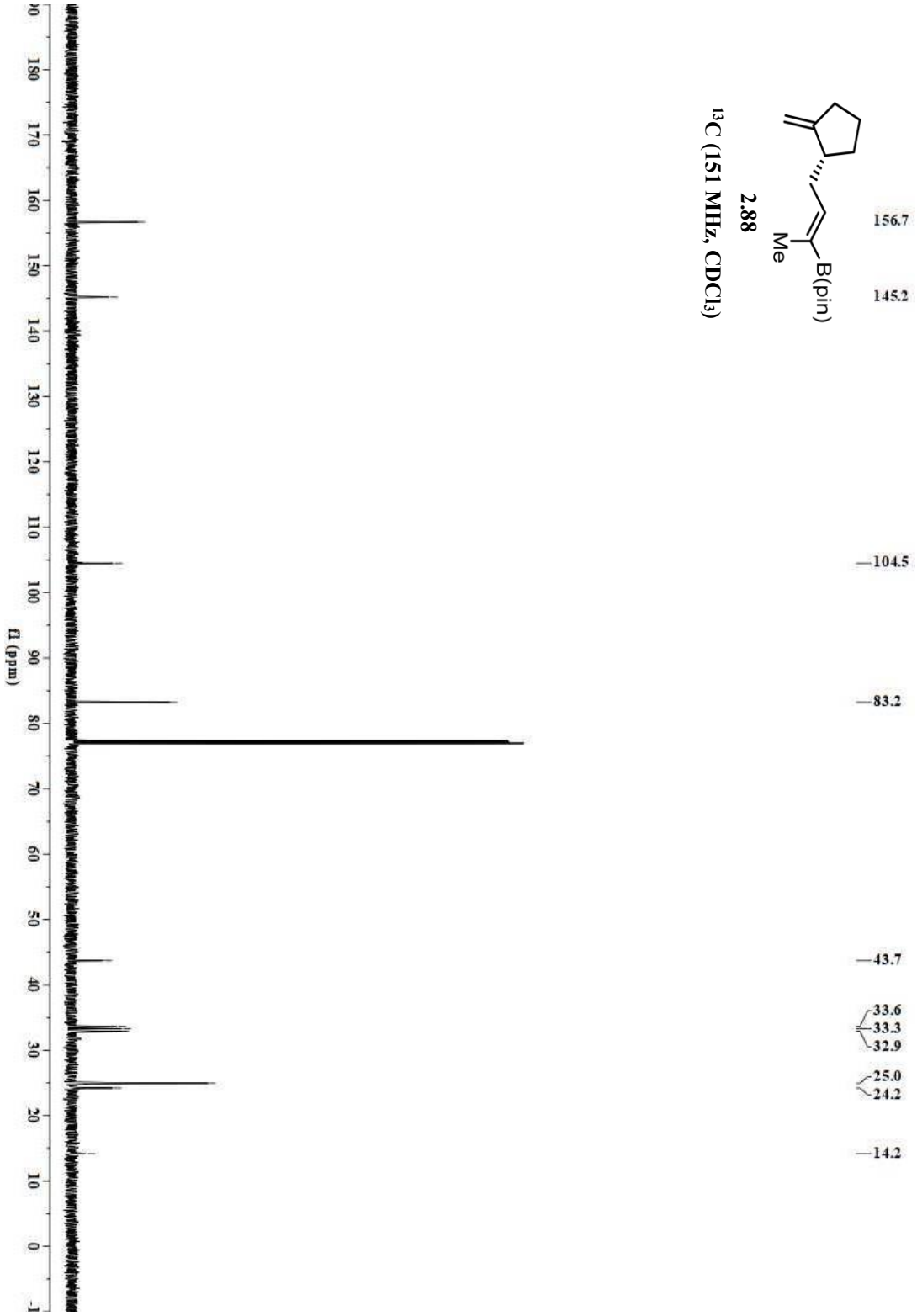

NTs
B(pin)
Me
2.86
¹H (400 MHz, CDCl₃)
f1 (ppm)
0.99
2.00
1.03
0.98
1.05
3.05
1.00
0.99
2.04
1.04
2.08
3.07
3.02
11.99
6.34
6.32
5.99
5.97
5.97
5.95
5.93
5.92
5.91
5.08
5.06
5.02
3.65
3.63
3.62
3.60
2.65
2.63
2.61
2.59
2.33
1.66
1.25


2.86
$^{13}$C (101 MHz, CDCl$_3$)
NTs
B(pin)
Me
124.7
123.0
122.9
120.3
115.5
113.9
83.3
40.1
33.5
25.0
24.9
21.7
14.4
f1 (ppm)


2.87
$^1$H (400 MHz, CDCl$_3$)
Ph
B(pin)
Me
7.29
7.28
7.27
7.27
7.26
7.19
7.17
6.32
6.31
6.30
5.72
5.70
5.69
5.67
5.65
5.06
5.04
5.02
2.70
2.67
2.65
2.64
2.56
2.55
2.53
2.50
2.26
2.24
2.19
2.18
1.80
1.77
1.75
1.75
1.68
1.63
1.60
1.58
1.26
2.08
2.84
1.00
0.98
2.07
1.09
1.09
3.00
1.05
3.08
0.99
12.06
f1 (ppm)

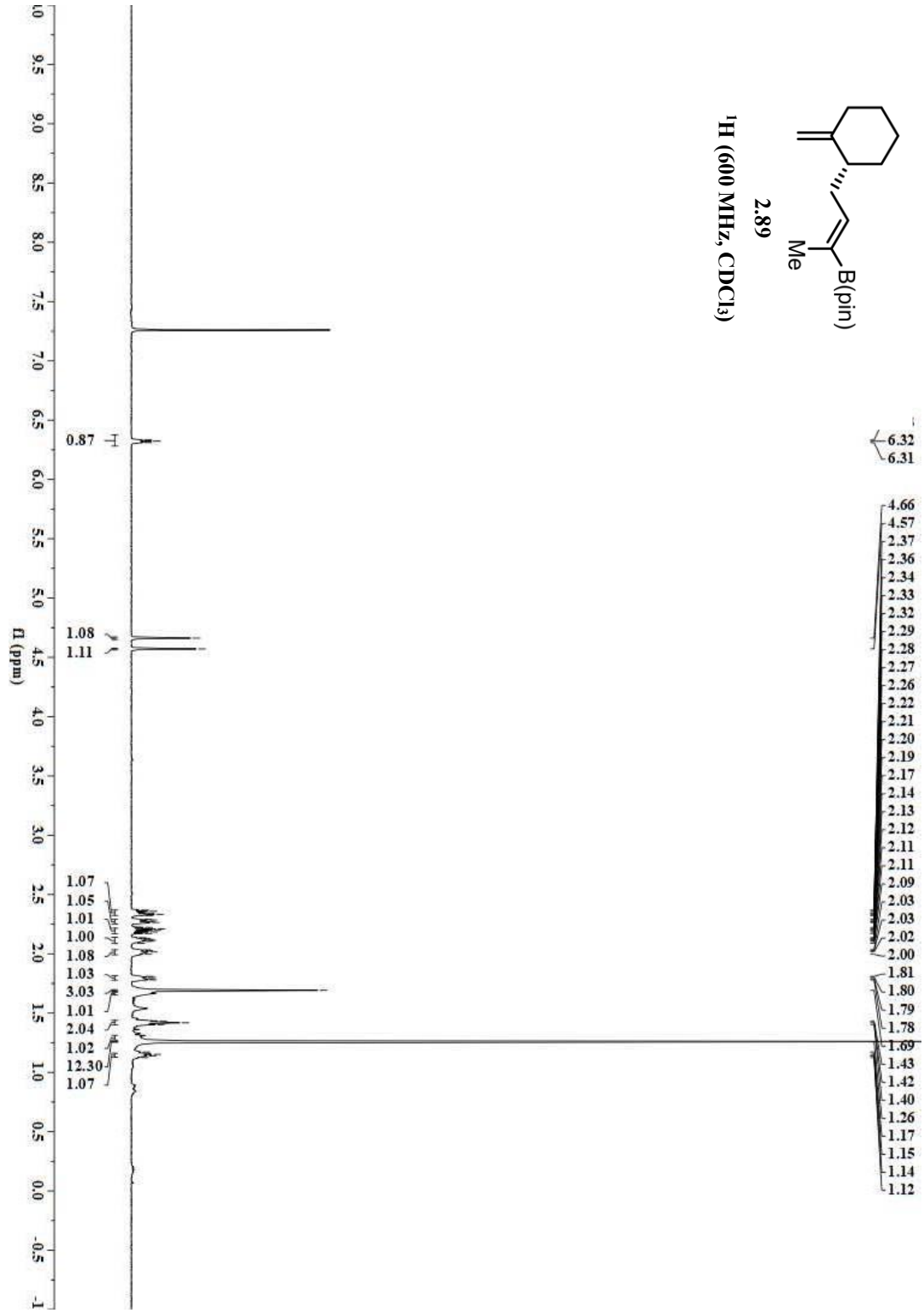

Ph
B(pin)
Me
2.87
13C (126 MHz, CDCl3)
144.2
142.8
142.5
128.6
128.4
125.8
114.9
83.2
43.2
36.2
34.3
33.6
24.9
14.3
f1 (ppm)

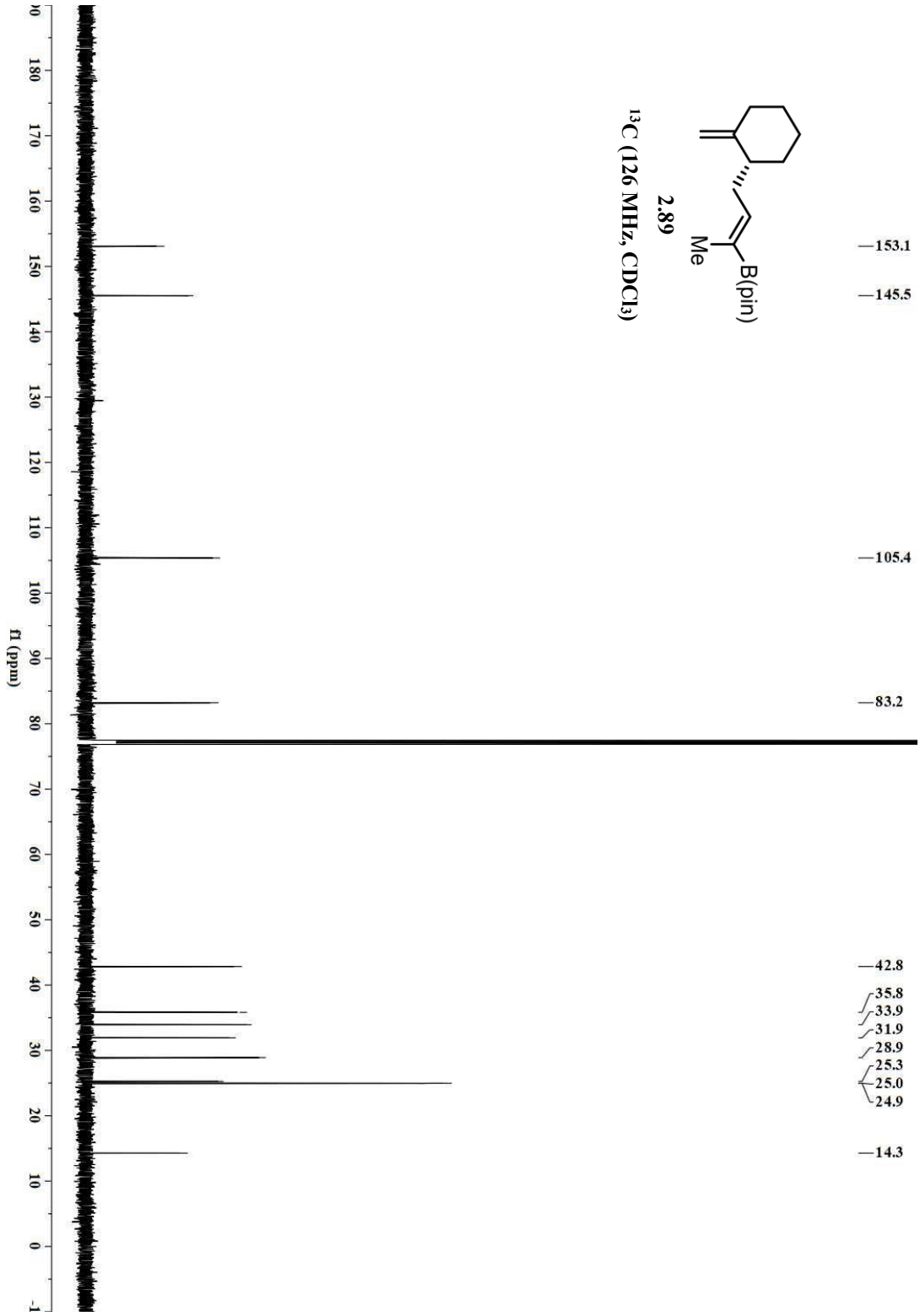

B(pin)
Me
2.88
¹H (400 MHz, CDCl3)
f1 (ppm)
1.00
1.06
1.03
3.31
1.03
0.90
3.20
4.11
12.77
6.37
6.35
4.89
4.83
2.44
2.43
2.41
2.40
2.38
2.36
2.35
2.33
2.31
2.15
2.13
2.11
2.09
2.07
1.93
1.92
1.90
1.88
1.87
1.85
1.69
1.31
1.26

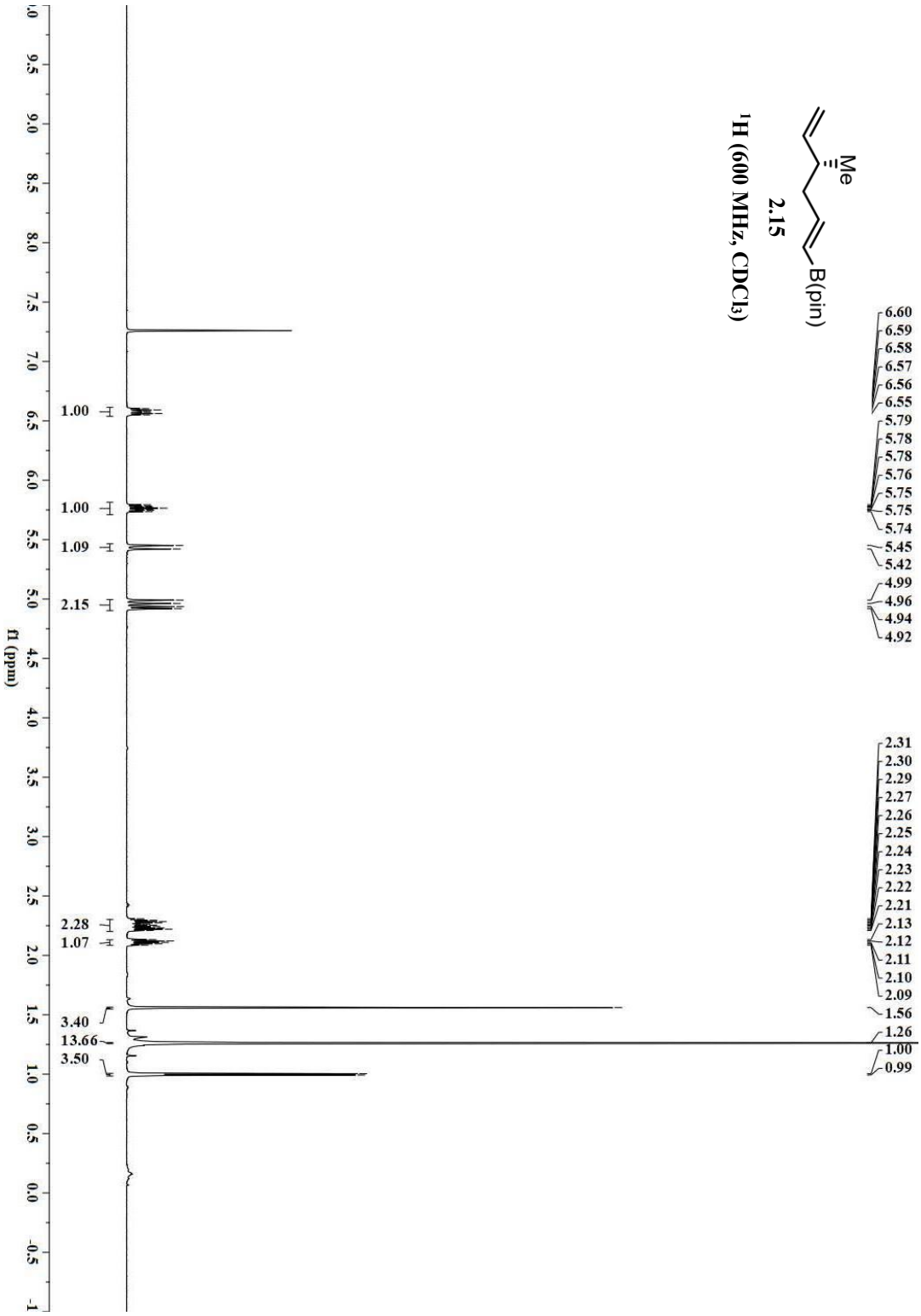


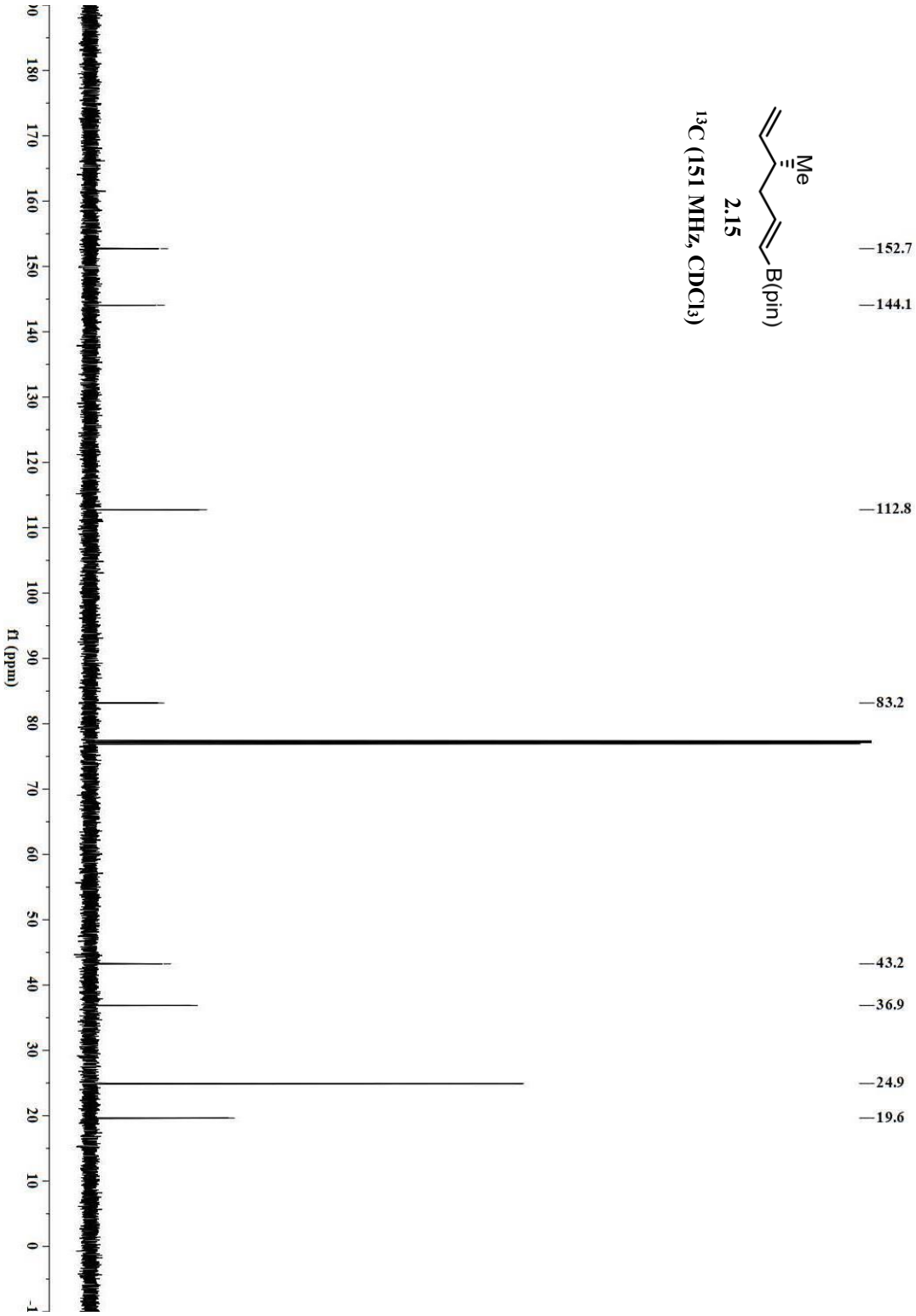

**2.88**

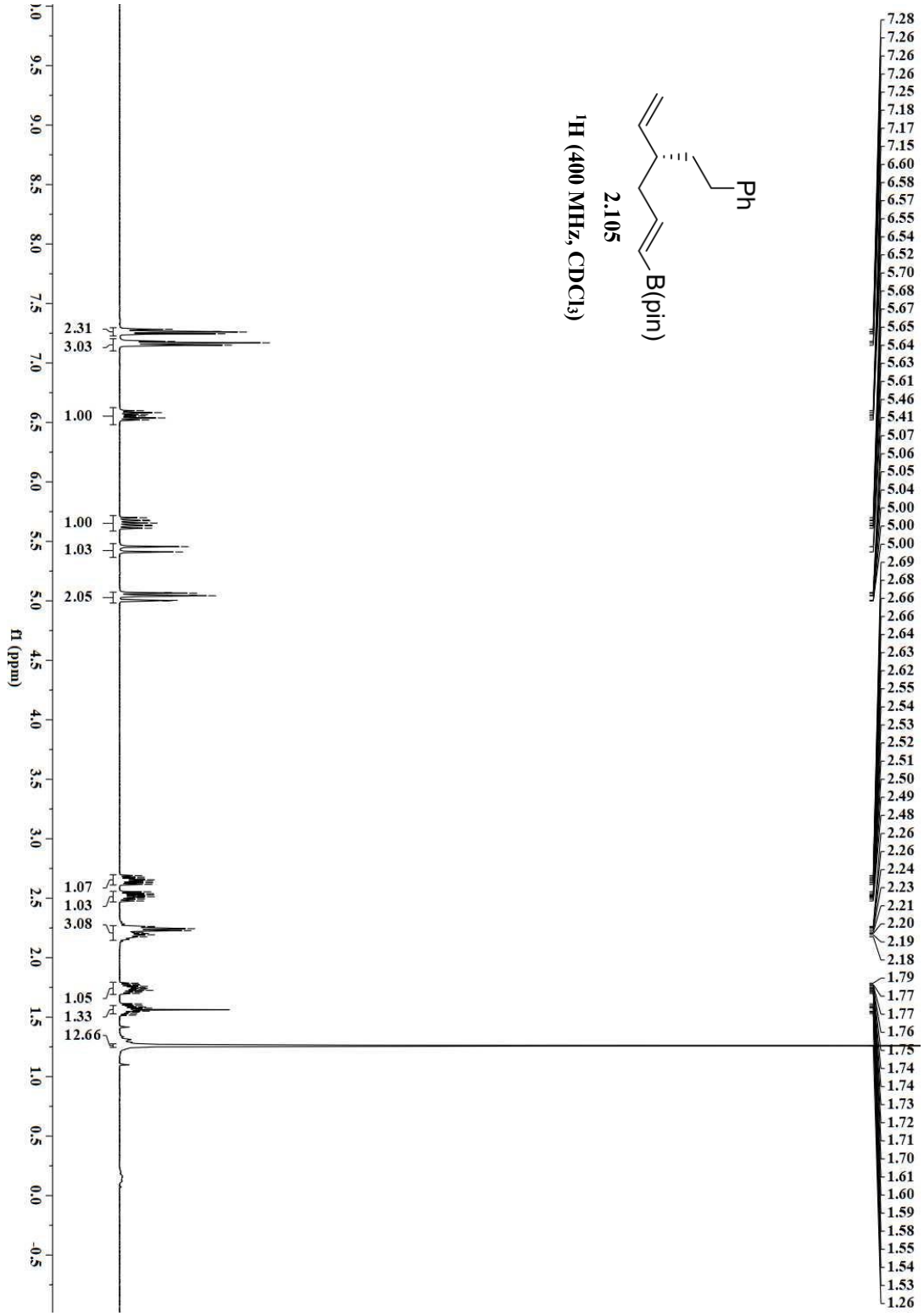
**$^{13}$C (151 MHz, $CDCl_3$)**

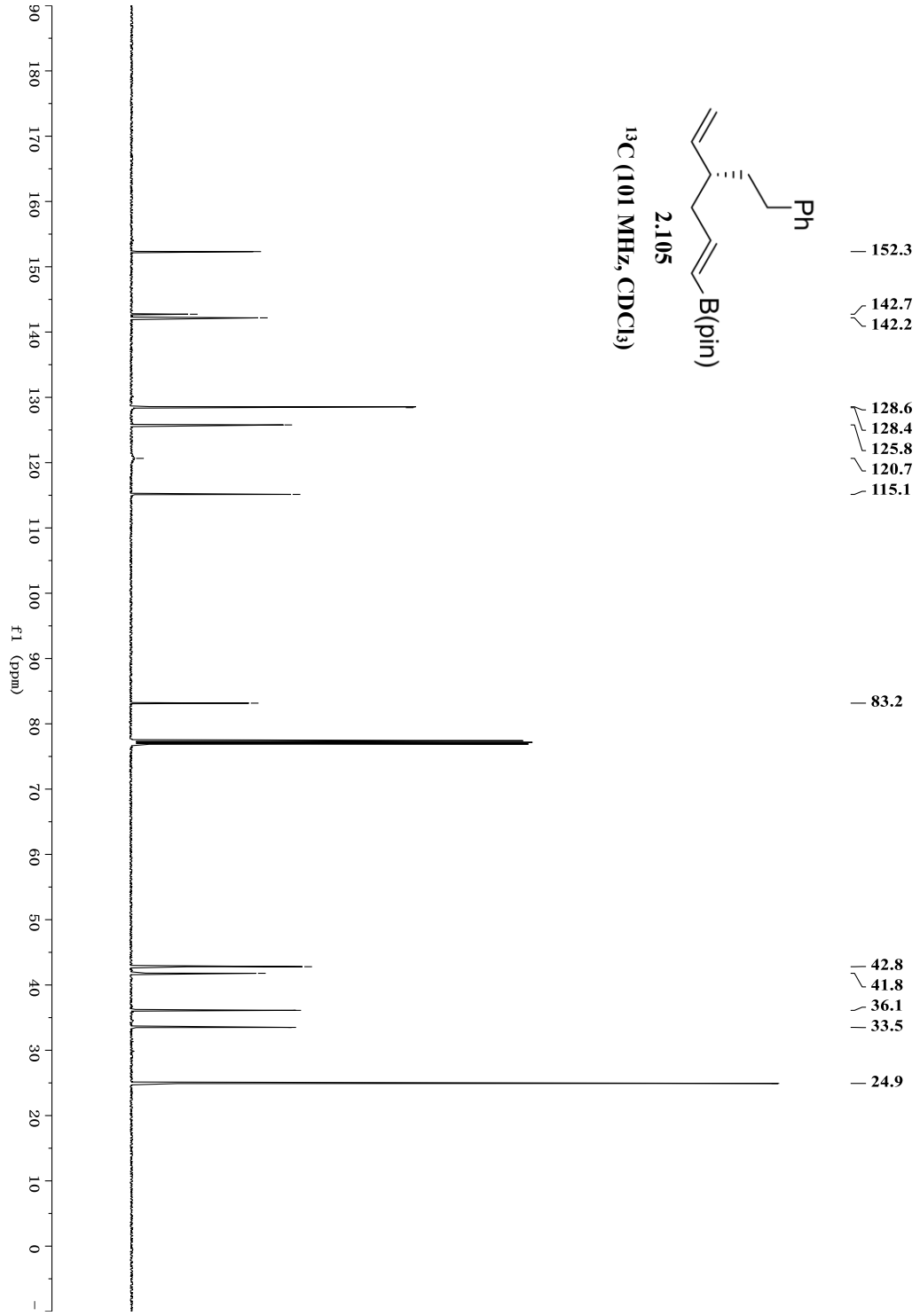

B(pin)
Me
2.89
¹H (600 MHz, CDCl₃)
f1 (ppm)
6.32
6.31
4.66
4.57
2.37
2.36
2.34
2.33
2.32
2.29
2.28
2.27
2.26
2.22
2.21
2.20
2.19
2.17
2.14
2.13
2.12
2.11
2.11
2.09
2.03
2.03
2.02
2.00
1.81
1.80
1.79
1.78
1.69
1.43
1.42
1.40
1.26
1.17
1.15
1.14
1.12
0.87
1.08
1.11
1.07
1.05
1.01
1.00
1.08
1.03
3.03
1.01
2.04
1.02
12.30
1.07

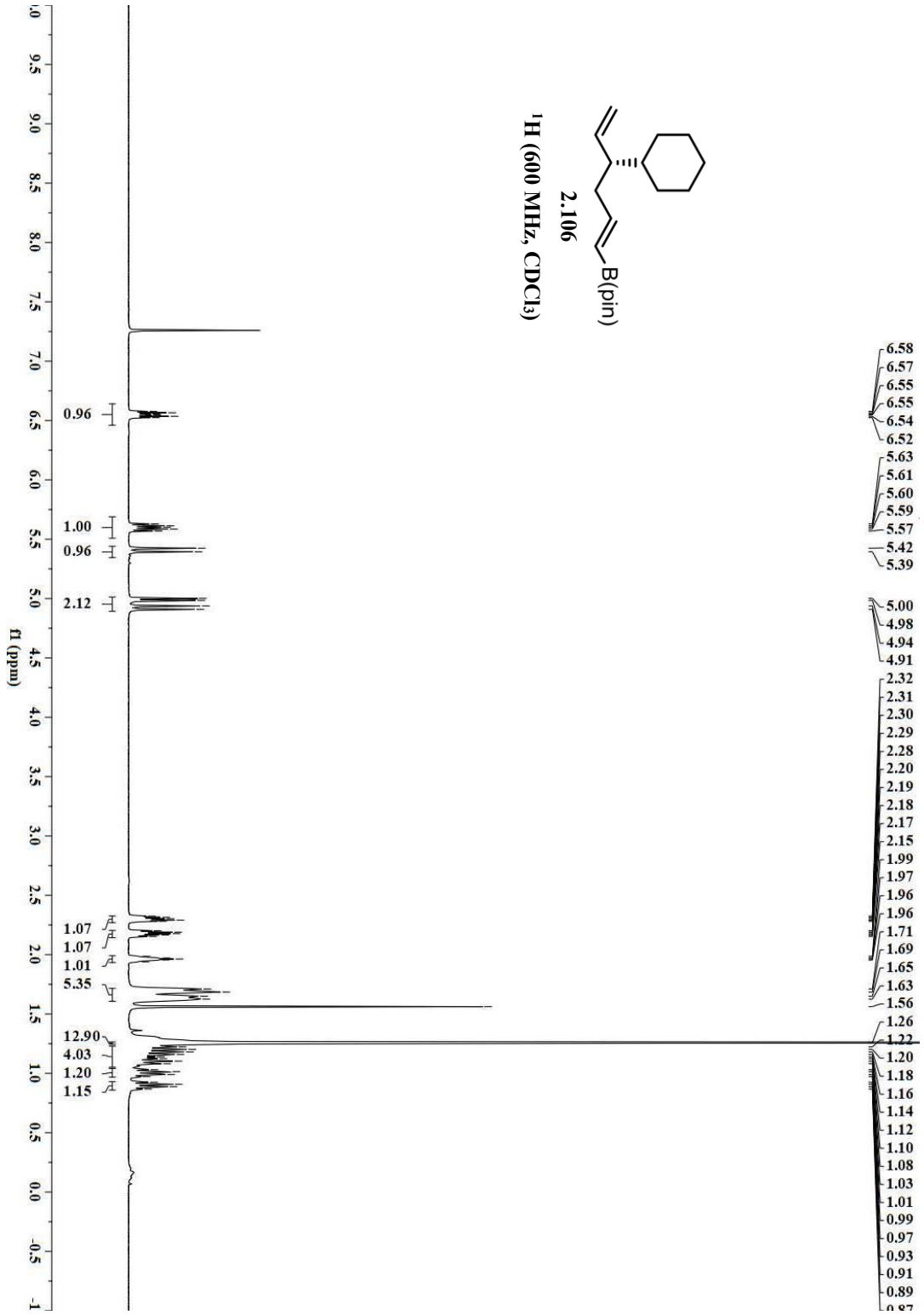

2.89
$^{13}$C (126 MHz, CDCl$_3$)
B(pin)
Me
153.1
145.5
105.4
83.2
42.8
35.8
33.9
31.9
28.9
25.3
25.0
24.9
14.3
f1 (ppm)

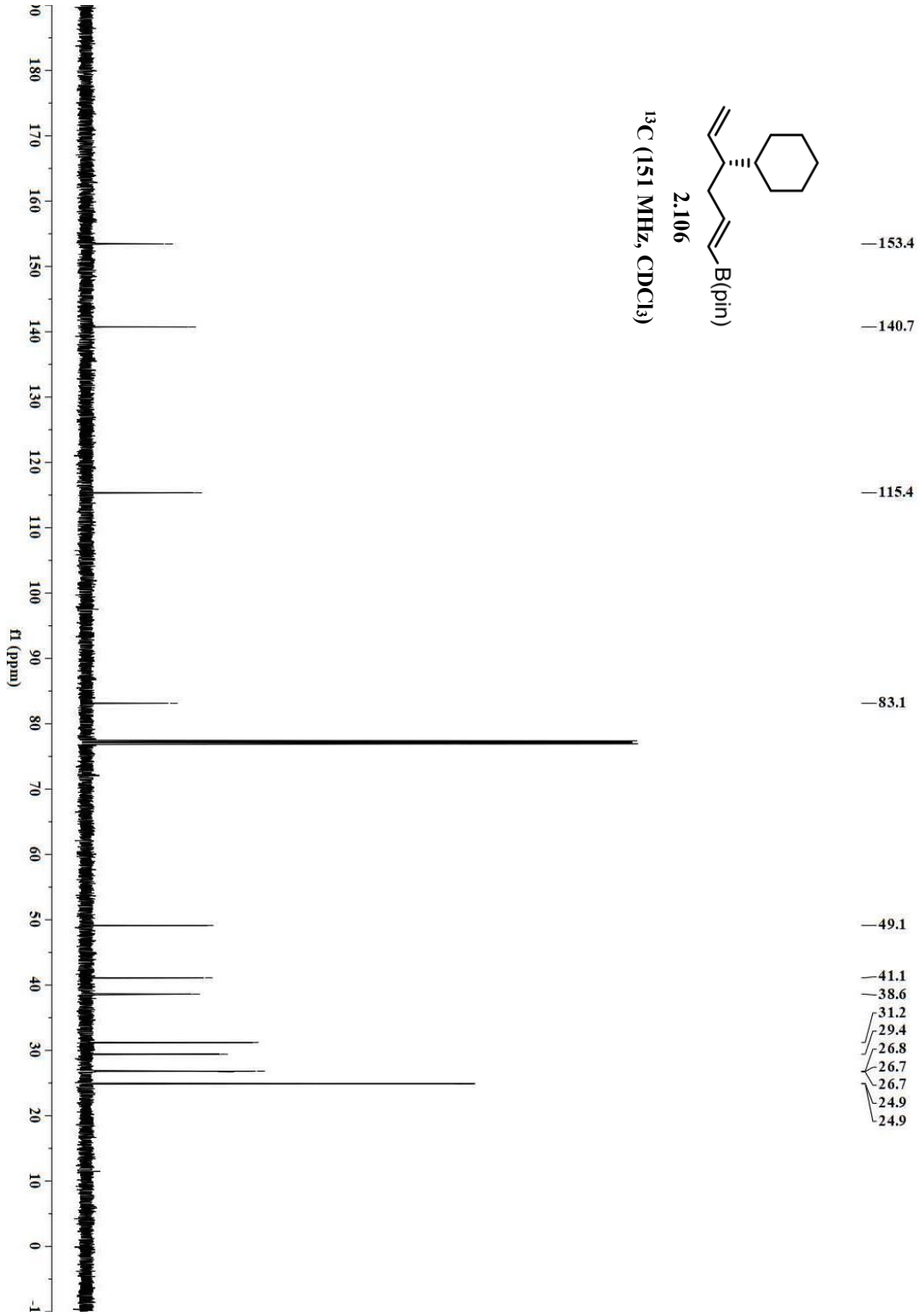

Me
B(pin)
2.15
¹H (600 MHz, CDCl₃)
f1 (ppm)
1.00
1.00
1.09
2.15
2.28
1.07
3.40
13.66
3.50
6.60
6.59
6.58
6.57
6.56
6.55
5.79
5.78
5.78
5.76
5.75
5.75
5.74
5.45
5.42
4.99
4.96
4.94
4.92
2.31
2.30
2.29
2.27
2.26
2.25
2.24
2.23
2.22
2.21
2.13
2.12
2.11
2.10
2.09
1.56
1.26
1.00
0.99

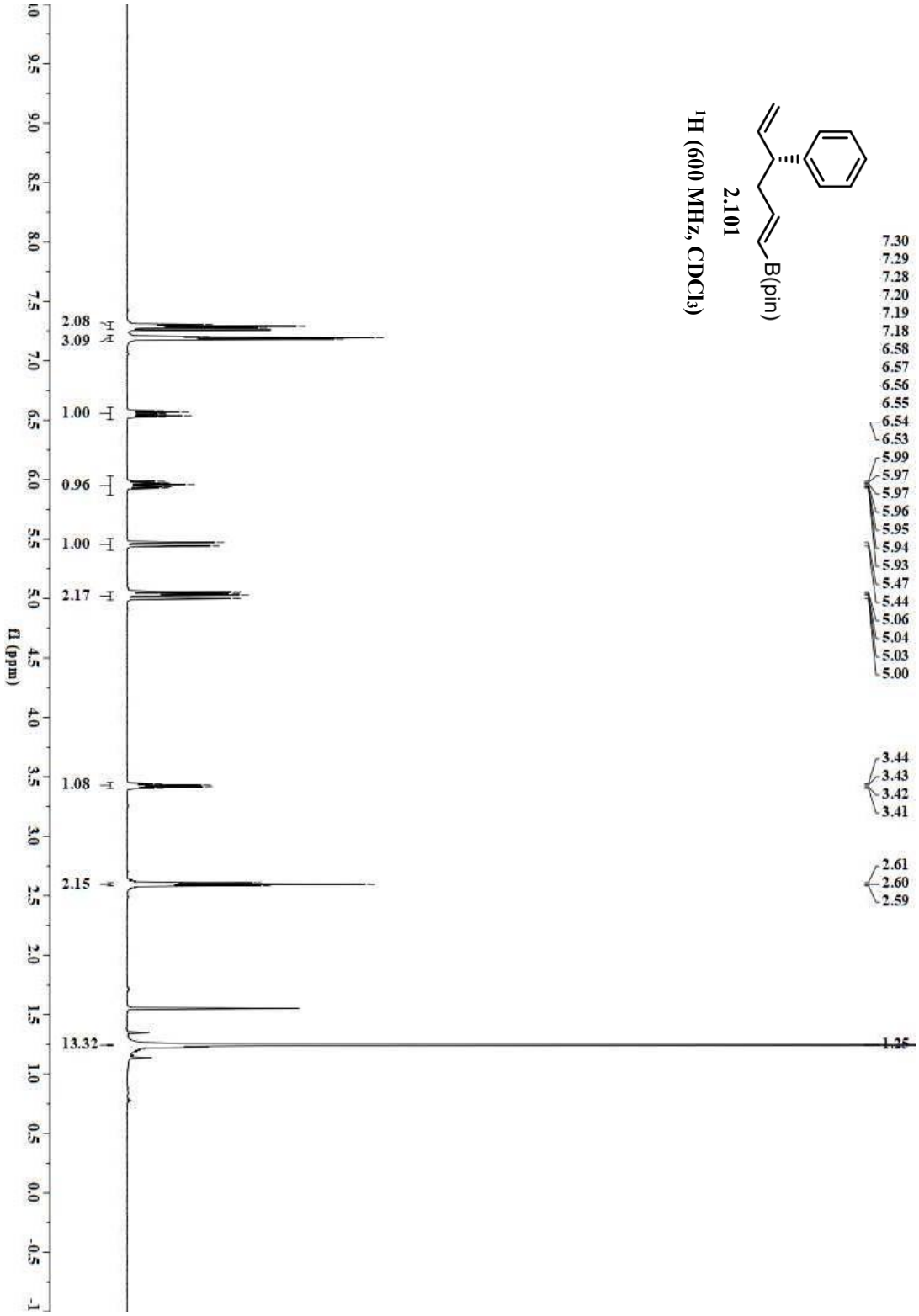

Me
B(pin)
2.15
$^{13}$C (151 MHz, CDCl$_3$)
—152.7
—144.1
—112.8
—83.2
—43.2
—36.9
—24.9
—19.6
f1 (ppm)

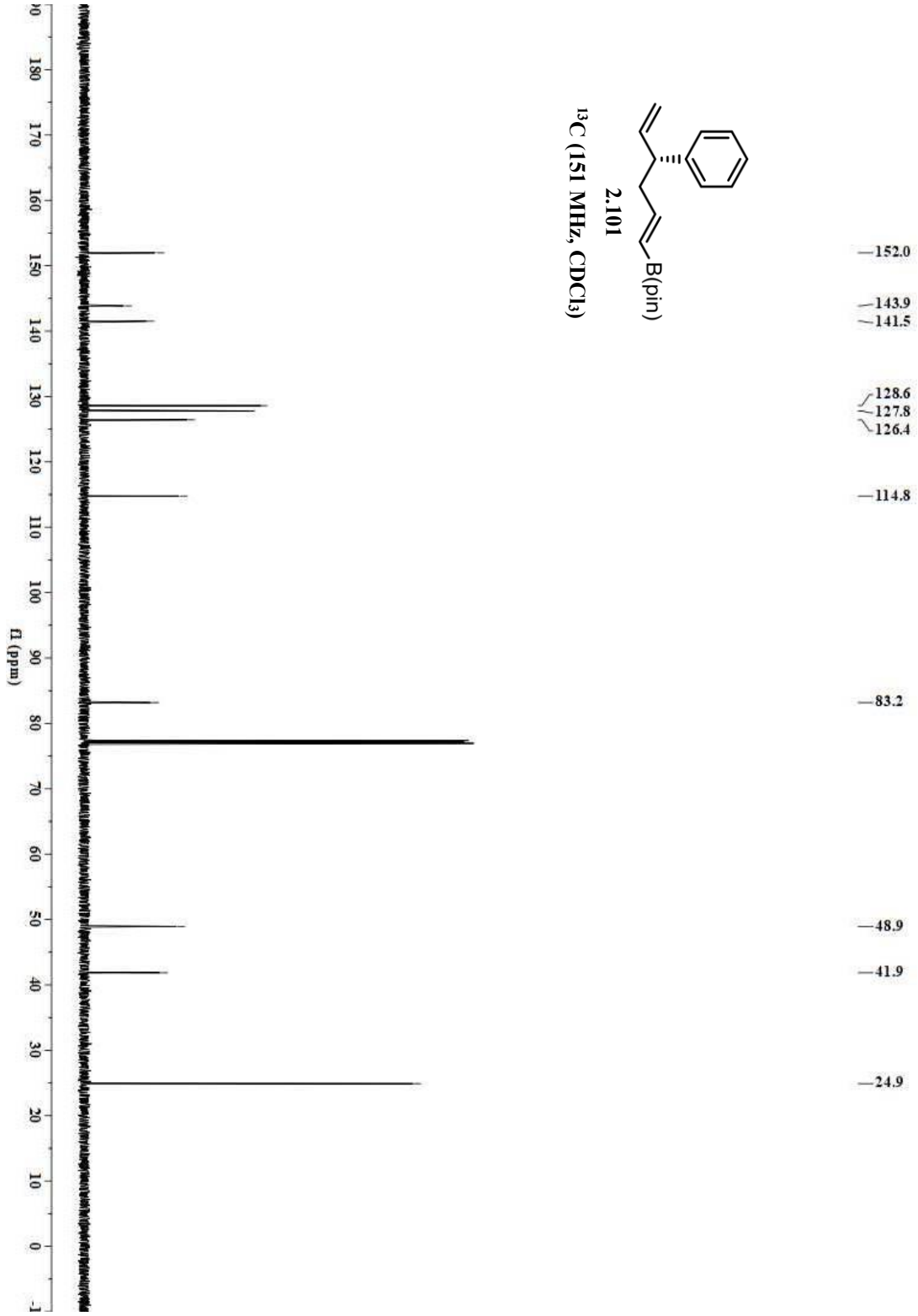

Ph
B(pin)
2.105
¹H (400 MHz, CDCl₃)
f1 (ppm)
2.31
3.03
1.00
1.00
1.03
2.05
1.07
1.03
3.08
1.05
1.33
12.66

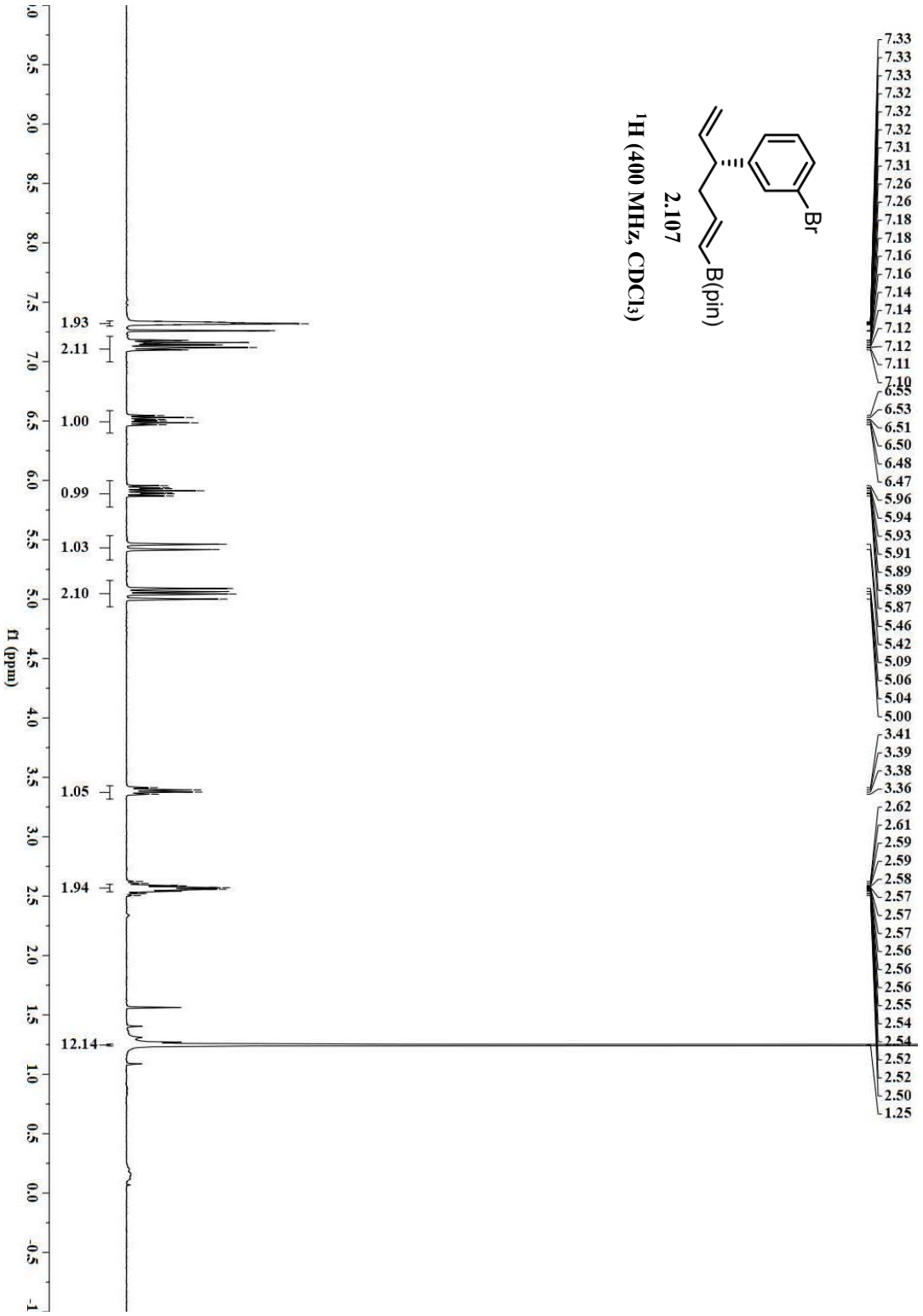

Ph
B(pin)
2.105
13C (101 MHz, CDCl3)
152.3
142.7
142.2
128.6
128.4
125.8
120.7
115.1
83.2
42.8
41.8
36.1
33.5
24.9
f1 (ppm)

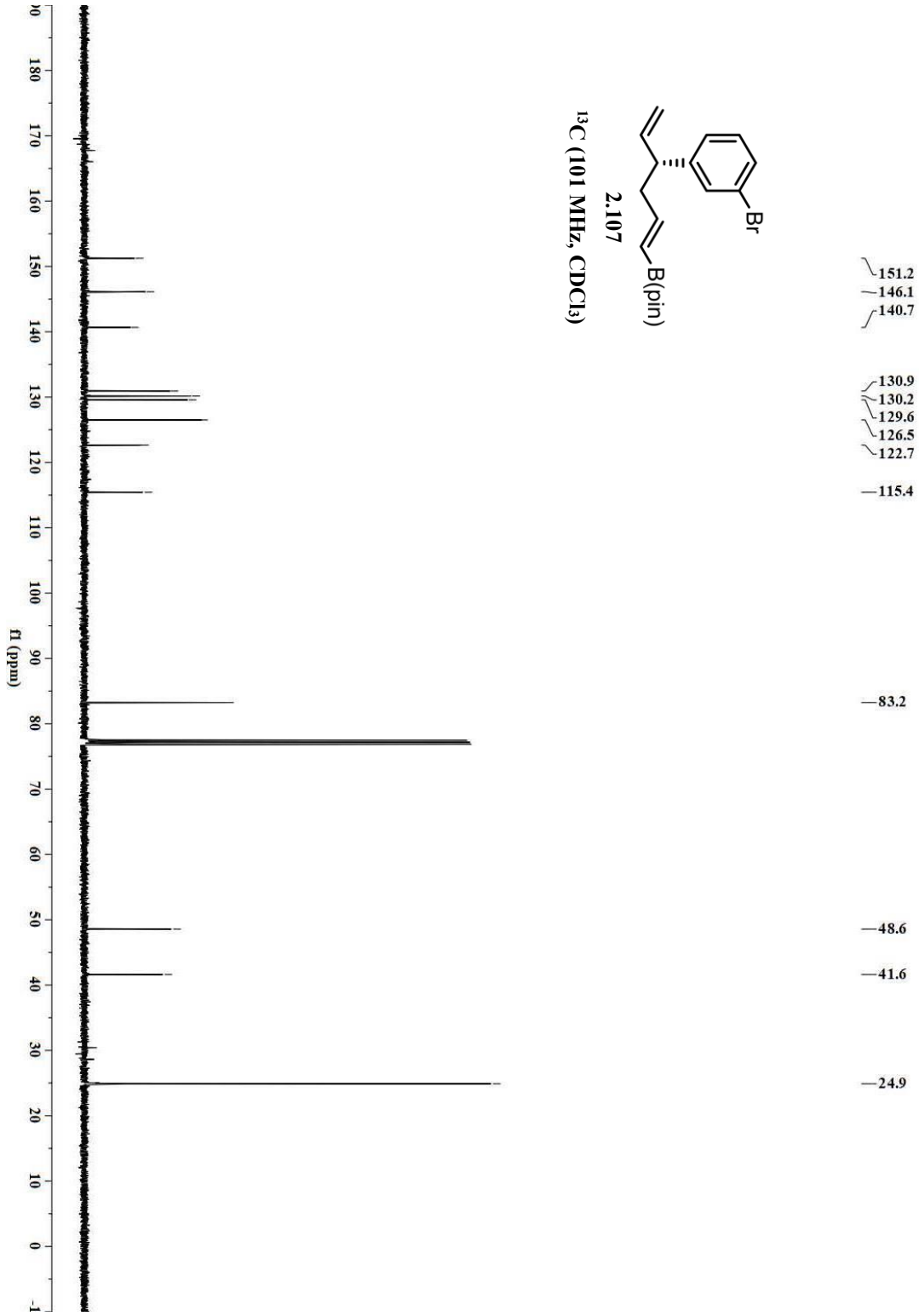

B(pin)
2.106
¹H (600 MHz, CDCl3)
f1 (ppm)
0.96
1.00
0.96
2.12
1.07
1.07
1.01
5.35
12.90
4.03
1.20
1.15
6.58
6.57
6.55
6.55
6.54
6.52
5.63
5.61
5.60
5.59
5.57
5.42
5.39
5.00
4.98
4.94
4.91
2.32
2.31
2.30
2.29
2.28
2.20
2.19
2.18
2.17
2.15
1.99
1.97
1.96
1.96
1.71
1.69
1.65
1.63
1.56
1.26
1.22
1.20
1.18
1.16
1.14
1.12
1.10
1.08
1.03
1.01
0.99
0.97
0.93
0.91
0.89

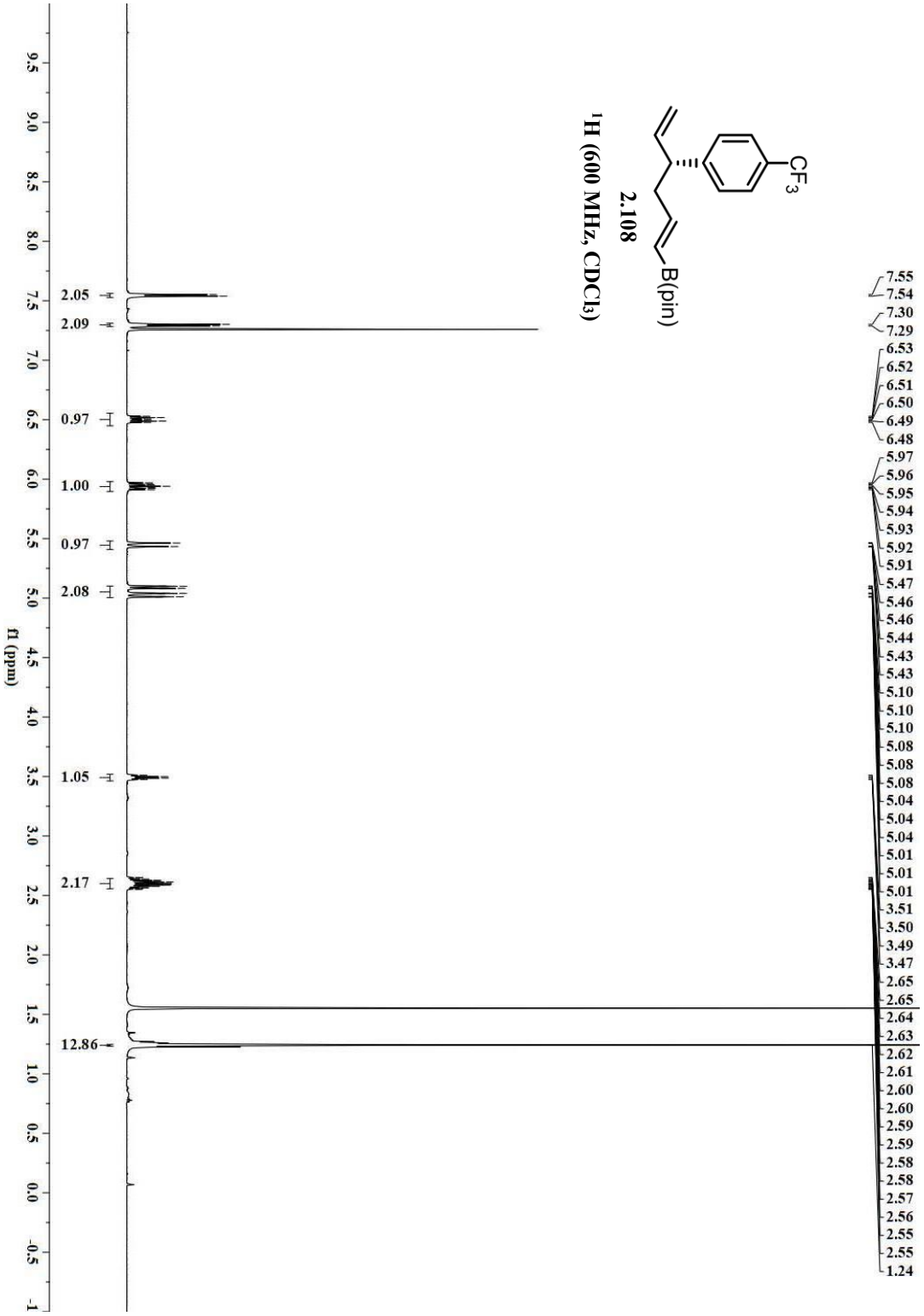

2.106
$^{13}$C (151 MHz, CDCl$_3$)
B(pin)
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
153.4
140.7
115.4
83.1
49.1
41.1
38.6
31.2
29.4
26.8
26.7
26.7
24.9
24.9

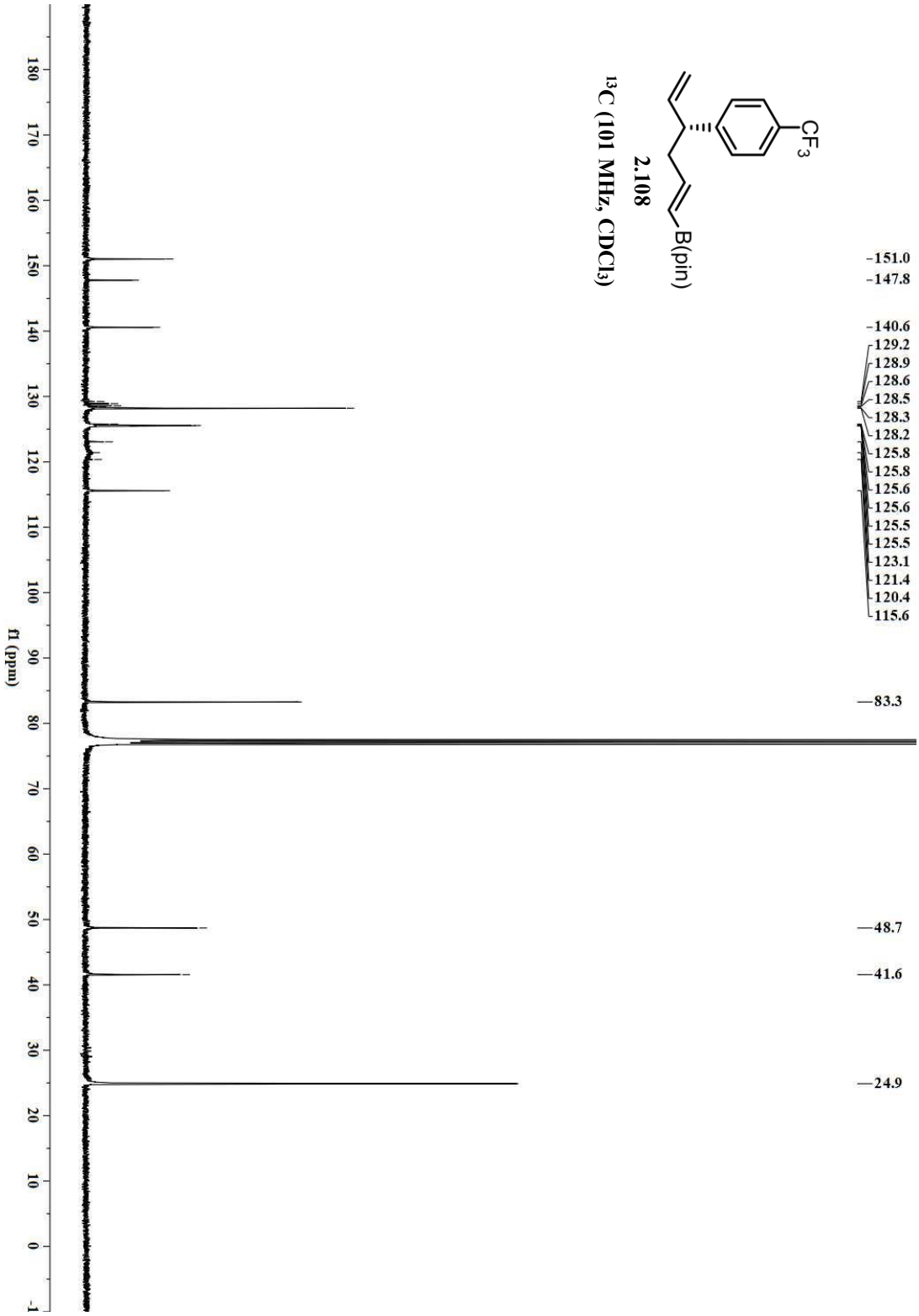

2.101
$^1$H (600 MHz, CDCl$_3$)
B(pin)
7.30
7.29
7.28
7.20
7.19
7.18
6.58
6.57
6.56
6.55
6.54
6.53
5.99
5.97
5.97
5.96
5.95
5.94
5.93
5.47
5.44
5.06
5.04
5.03
5.00
3.44
3.43
3.42
3.41
2.61
2.60
2.59
1.25
2.08
3.09
1.00
0.96
1.00
2.17
1.08
2.15
13.32
f1 (ppm)

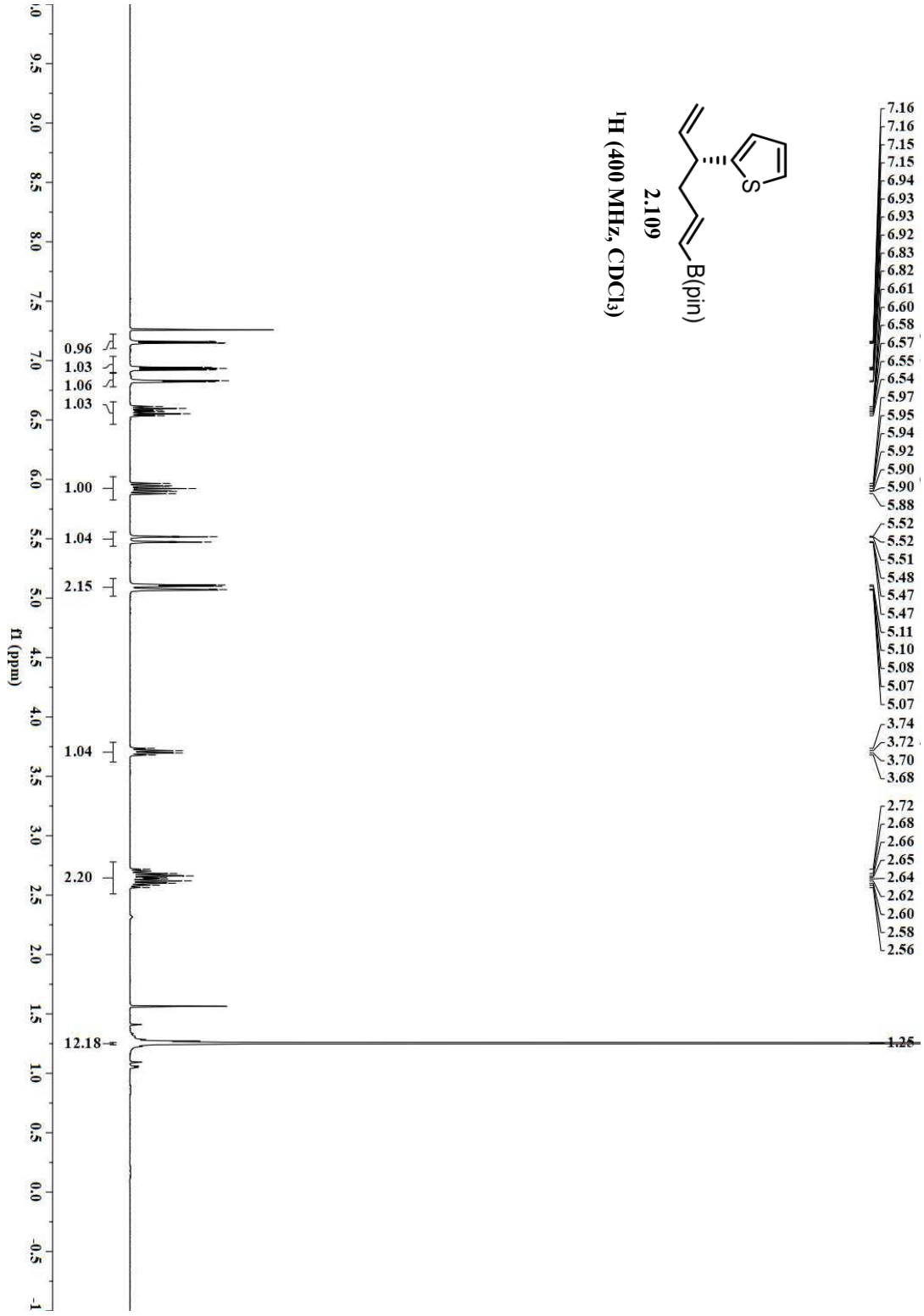

B(pin)
2.101
$^{13}$C (151 MHz, CDCl$_3$)
f1 (ppm)
152.0
143.9
141.5
128.6
127.8
126.4
114.8
83.2
48.9
41.9
24.9

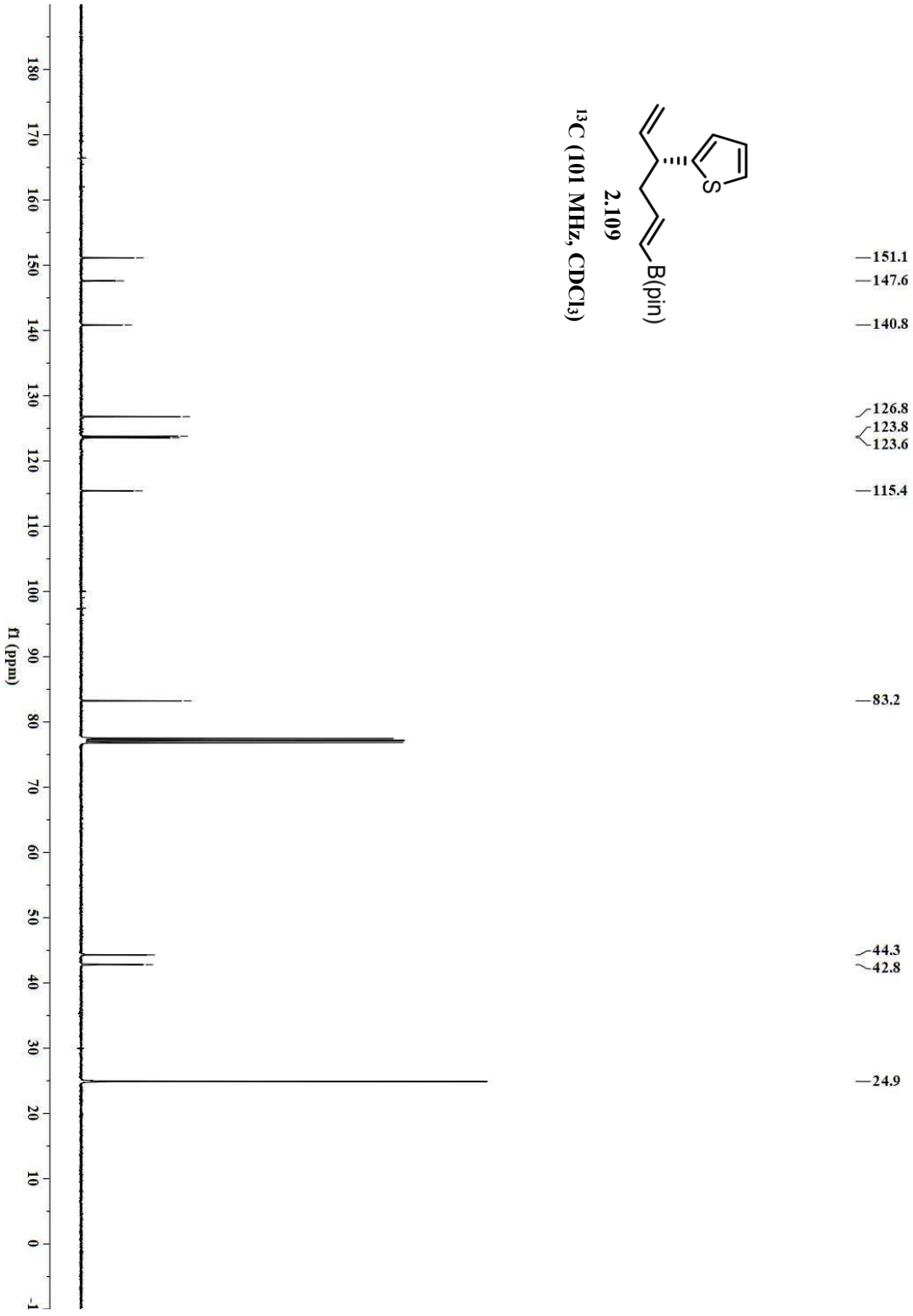

2.107
$^1$H (400 MHz, CDCl$_3$)
B(pin)
Br
f1 (ppm)
1.93
2.11
1.00
0.99
1.03
2.10
1.05
1.94
12.14

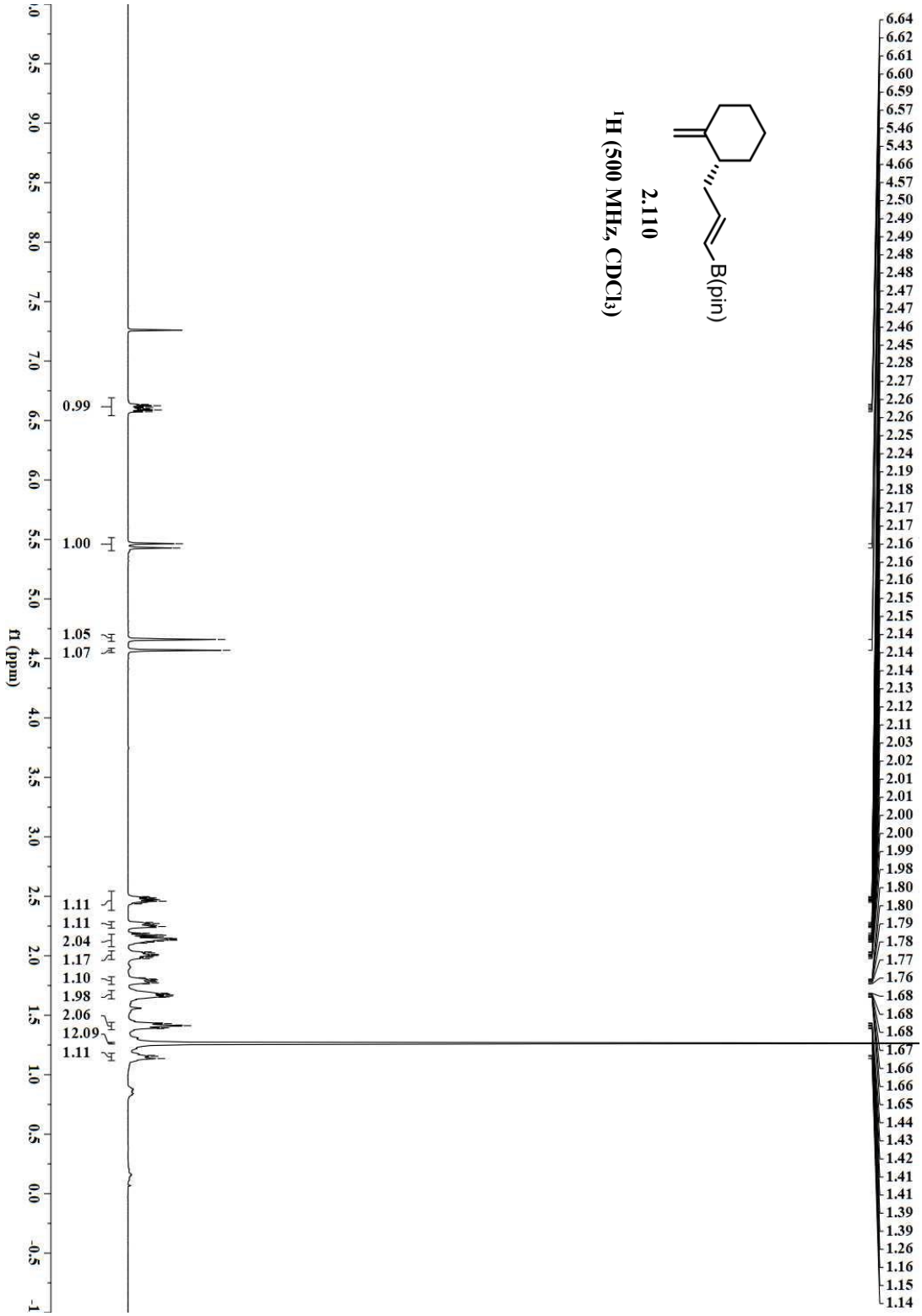

Br
B(pin)
2.107
13C (101 MHz, CDCl3)
151.2
146.1
140.7
130.9
130.2
129.6
126.5
122.7
115.4
83.2
48.6
41.6
24.9
f1 (ppm)

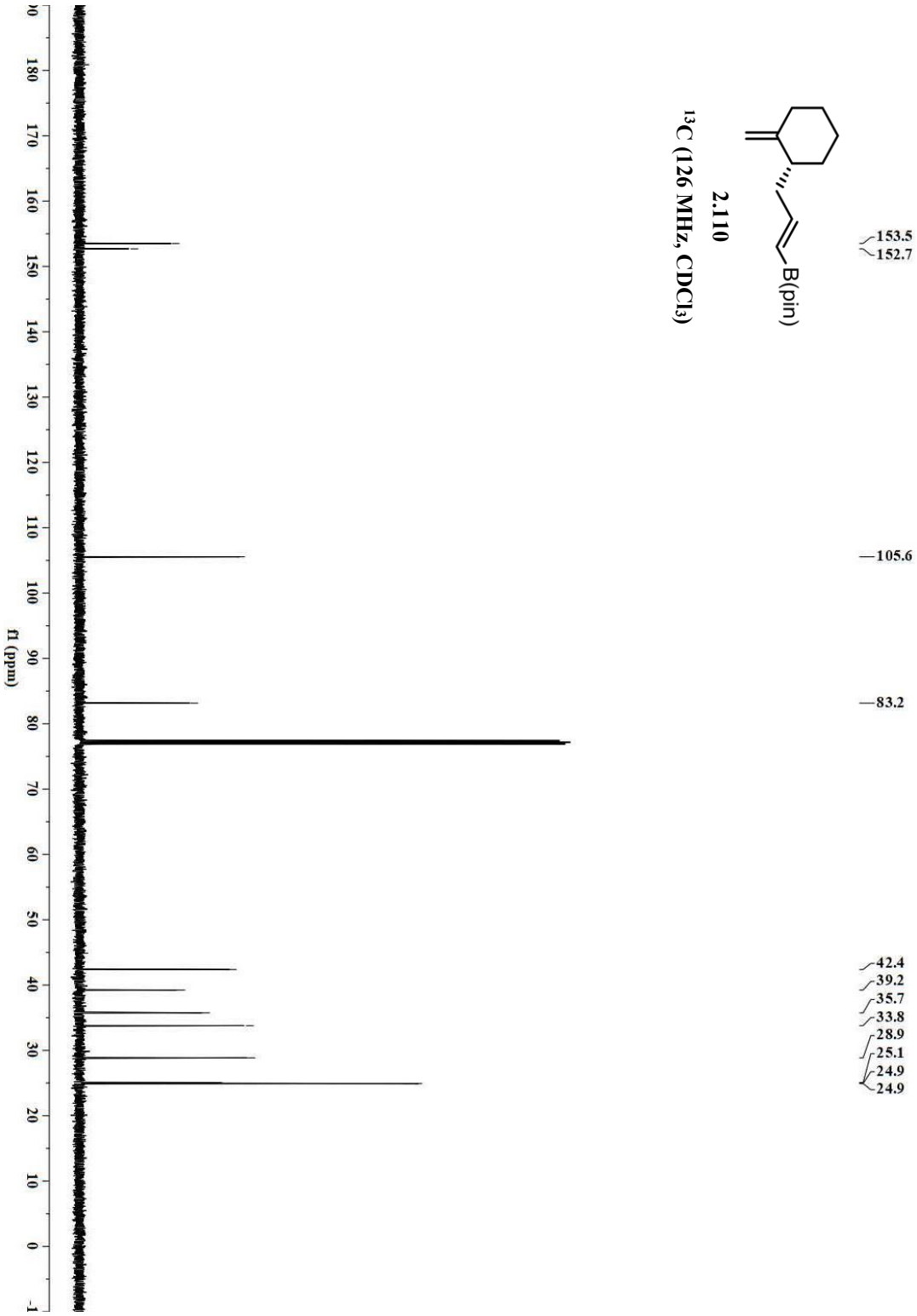

2.108
$^1$H (600 MHz, CDCl$_3$)
B(pin)
CF$_3$
f1 (ppm)
2.05
2.09
0.97
1.00
0.97
2.08
1.05
2.17
12.86
7.55
7.54
7.30
7.29
6.53
6.52
6.51
6.50
6.49
6.48
5.97
5.96
5.95
5.94
5.93
5.92
5.91
5.47
5.46
5.46
5.44
5.43
5.43
5.10
5.10
5.10
5.08
5.08
5.08
5.04
5.04
5.04
5.01
5.01
5.01
3.51
3.50
3.49
3.47
2.65
2.65
2.64
2.63
2.62
2.61
2.60
2.60
2.59
2.59
2.58
2.58
2.57
2.56
2.55
2.55
1.24


2.108
$^{13}$C (101 MHz, CDCl$_3$)
CF$_3$
B(pin)
151.0
147.8
140.6
129.2
128.9
128.6
128.5
128.3
128.2
125.8
125.8
125.6
125.6
125.5
125.5
123.1
121.4
120.4
115.6
83.3
48.7
41.6
24.9
f1 (ppm)


2.109
$^1$H (400 MHz, CDCl$_3$)
B(pin)
S
f1 (ppm)
0.96
1.03
1.06
1.03
1.00
1.04
2.15
1.04
2.20
12.18
7.16
7.16
7.15
7.15
6.94
6.93
6.93
6.92
6.83
6.82
6.61
6.60
6.58
6.57
6.55
6.54
5.97
5.95
5.94
5.92
5.90
5.90
5.88
5.52
5.52
5.51
5.48
5.47
5.47
5.11
5.10
5.08
5.07
5.07
3.74
3.72
3.70
3.68
2.72
2.68
2.66
2.65
2.64
2.62
2.60
2.58
2.56
1.25

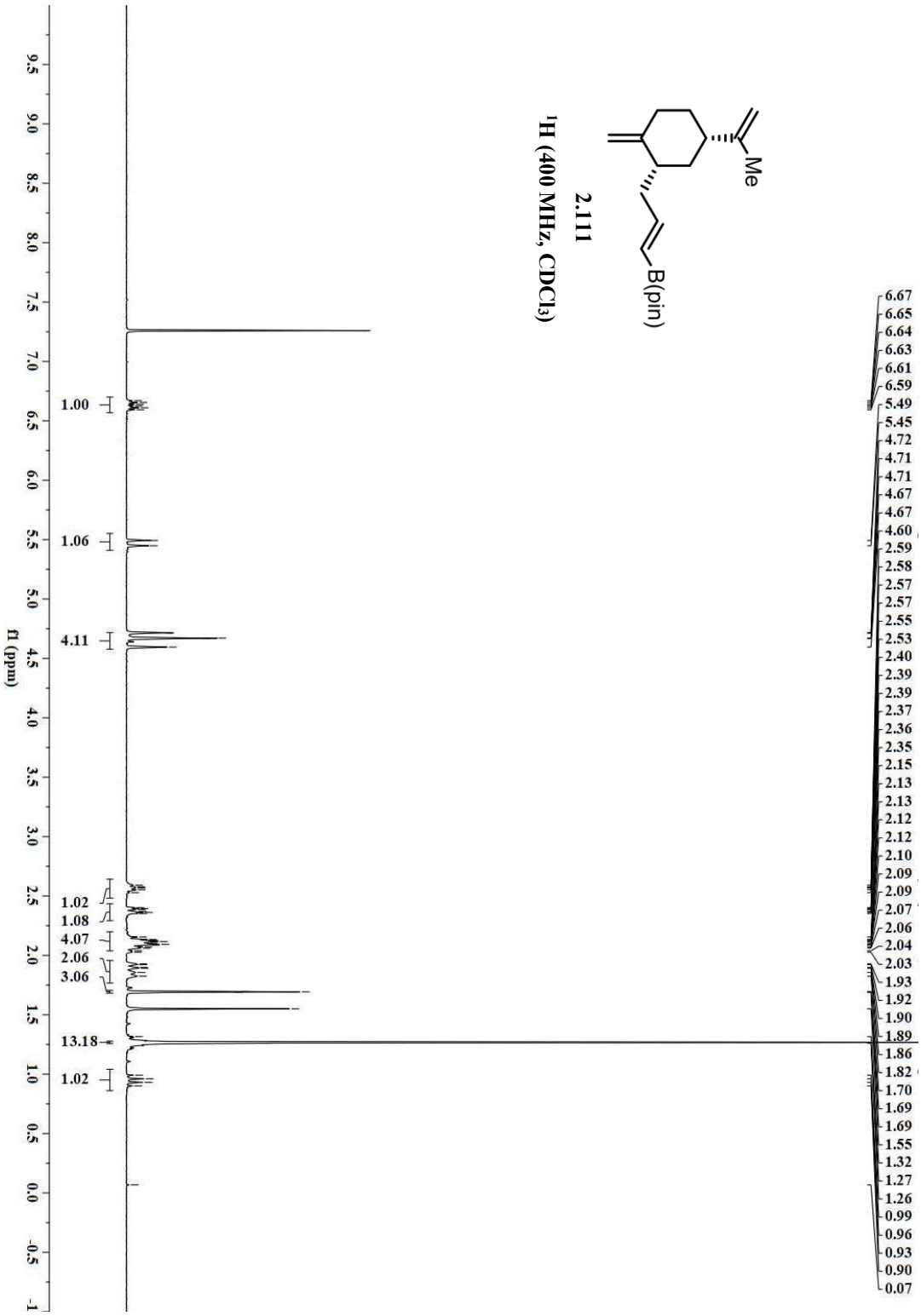

2.109
$^{13}$C (101 MHz, CDCl$_3$)
B(pin)
S
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
151.1
147.6
140.8
126.8
123.8
123.6
115.4
83.2
44.3
42.8
24.9

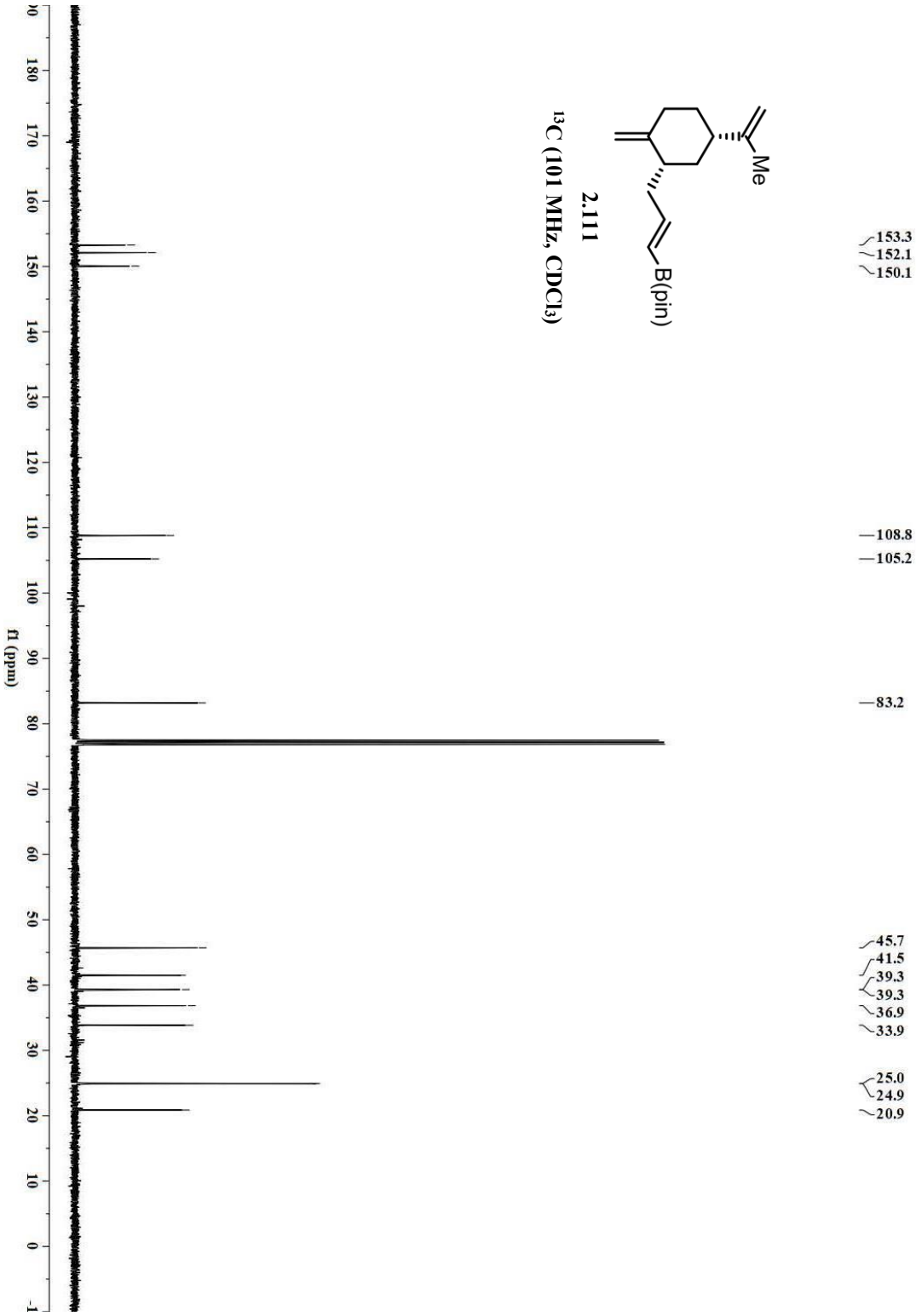

B(pin)
2.110
¹H (500 MHz, CDCl₃)
f1 (ppm)
0.99
1.00
1.05
1.07
1.11
1.11
2.04
1.17
1.10
1.98
2.06
12.09
1.11

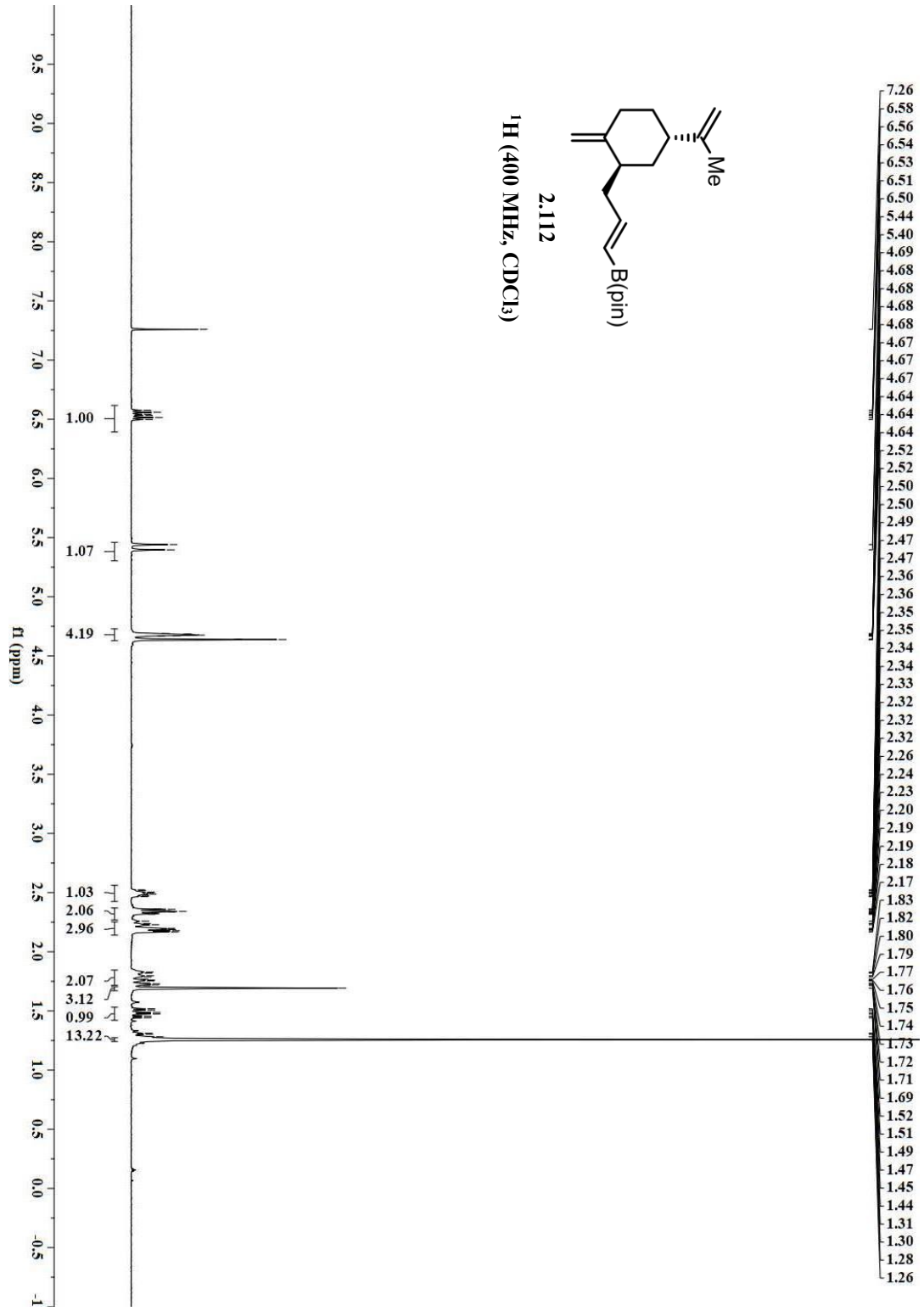


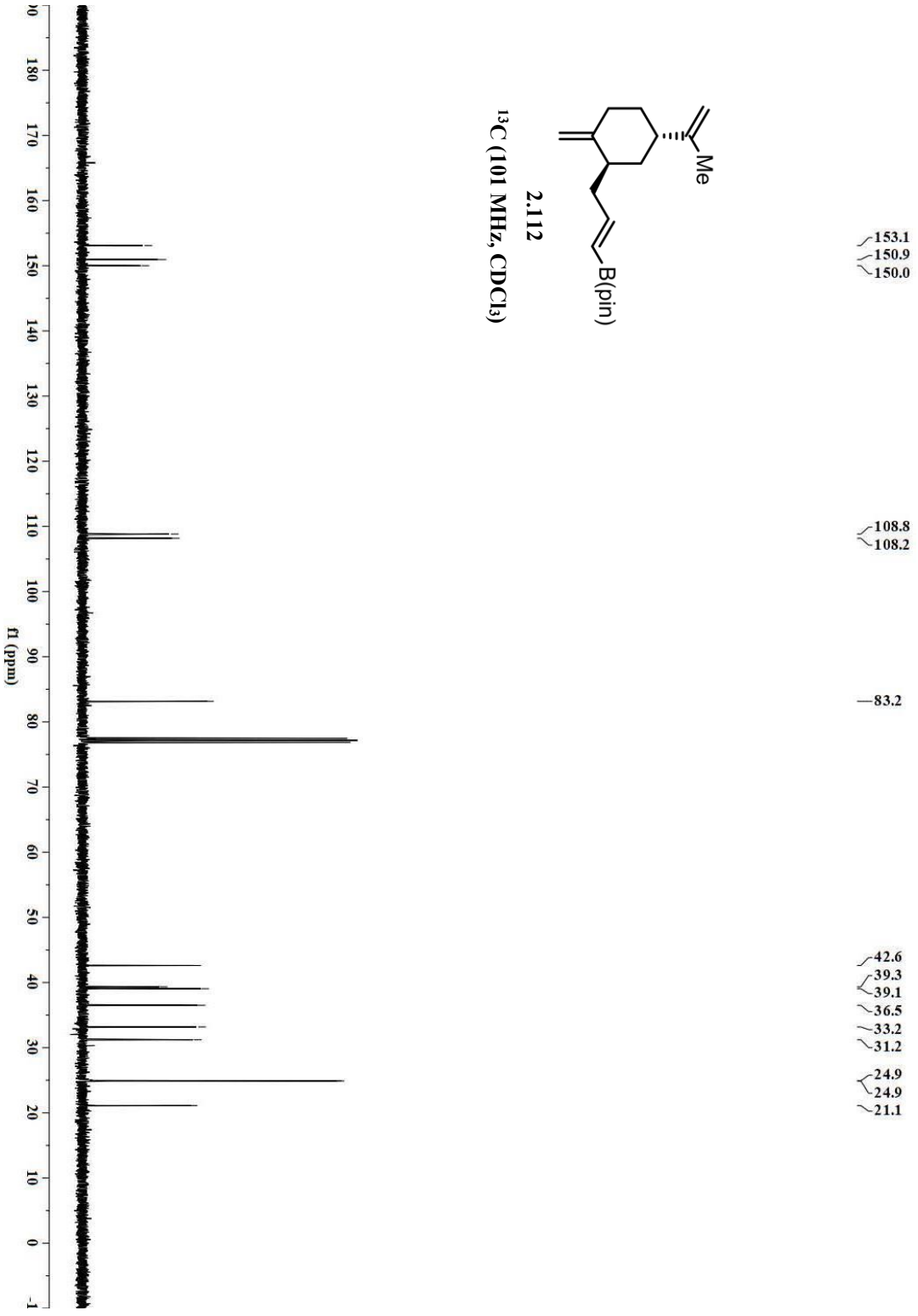

**2.110**

**$^{13}$C (126 MHz, $CDCl_3$)**


Me
B(pin)
2.111
¹H (400 MHz, CDCl₃)
f1 (ppm)
1.00
1.06
4.11
1.02
1.08
4.07
2.06
3.06
13.18
1.02

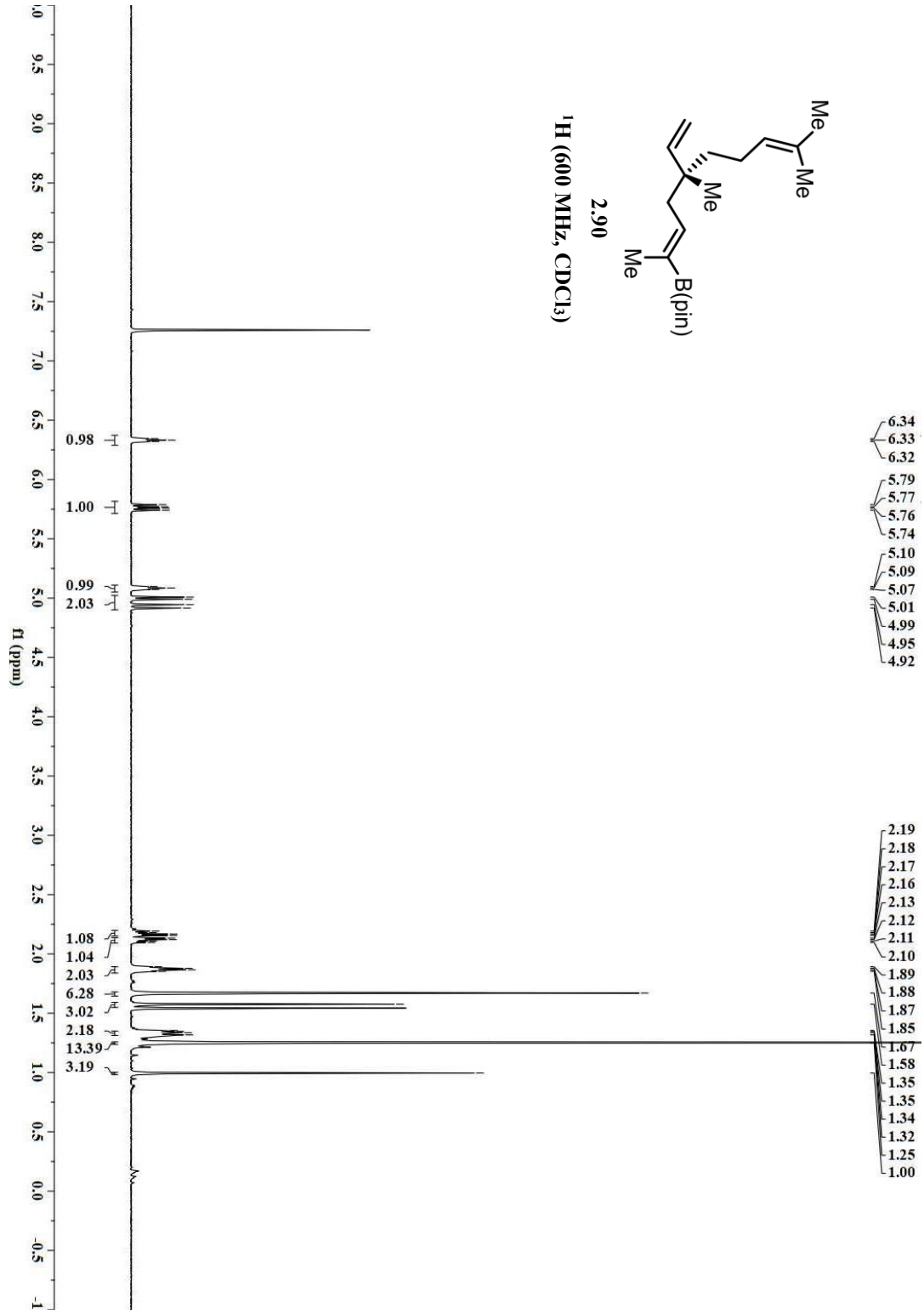

Me
B(pin)
2.111
$^{13}$C (101 MHz, CDCl$_3$)
153.3
152.1
150.1
108.8
105.2
83.2
45.7
41.5
39.3
39.3
36.9
33.9
25.0
24.9
20.9
f1 (ppm)

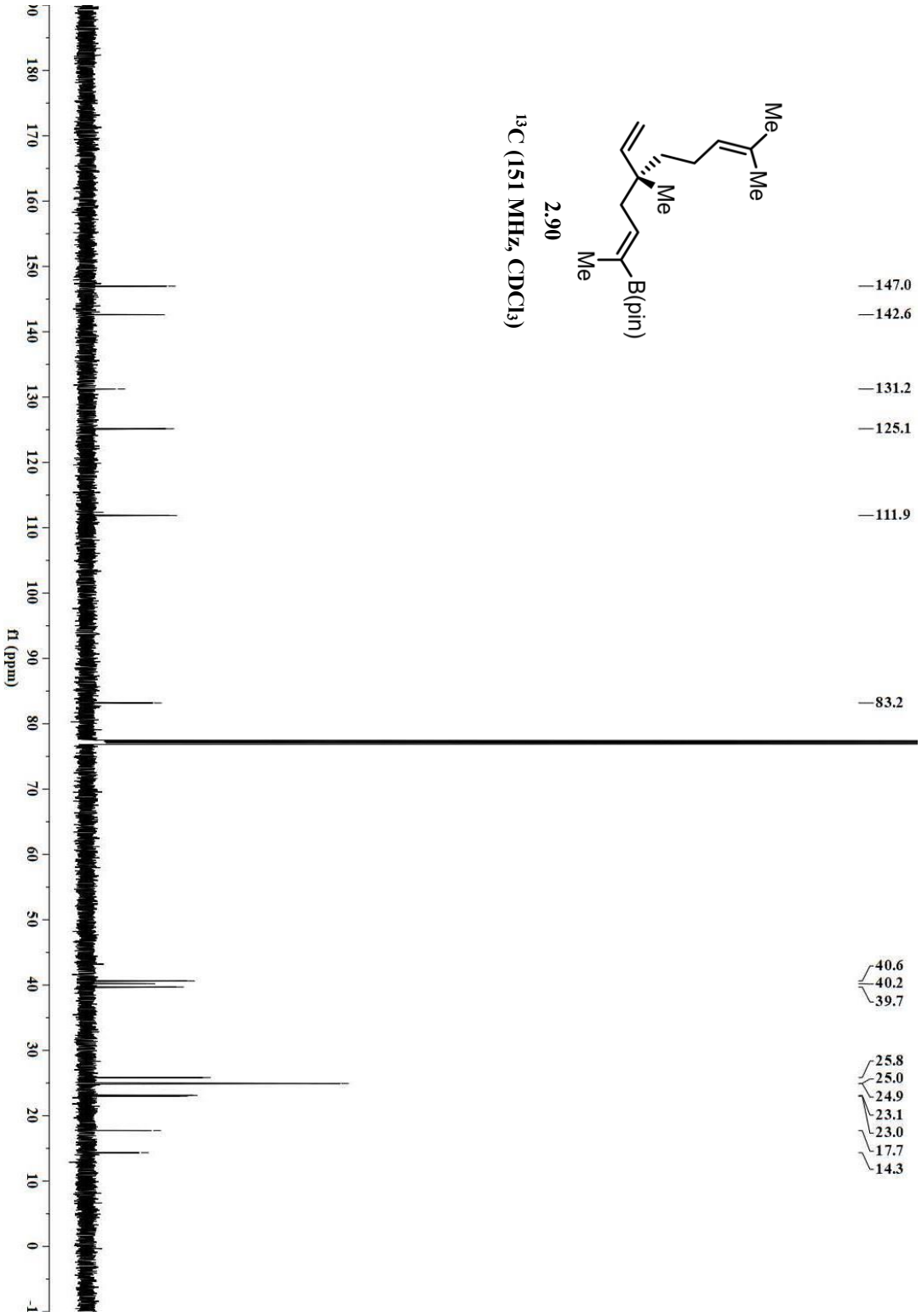

2.112
$^1$H (400 MHz, CDCl$_3$)
Me
B(pin)
f1 (ppm)
1.00
1.07
4.19
1.03
2.06
2.96
2.07
3.12
0.99
13.22
7.26
6.58
6.56
6.54
6.53
6.51
6.50
5.44
5.40
4.69
4.68
4.68
4.68
4.68
4.67
4.67
4.67
4.64
4.64
4.64
2.52
2.52
2.50
2.50
2.49
2.47
2.47
2.36
2.36
2.35
2.35
2.34
2.34
2.33
2.32
2.32
2.32
2.26
2.24
2.23
2.20
2.19
2.19
2.18
2.17
1.83
1.82
1.80
1.79
1.77
1.76
1.75
1.74
1.73
1.72
1.71
1.69
1.52
1.51
1.49
1.47
1.45
1.44
1.31
1.30
1.28
1.26

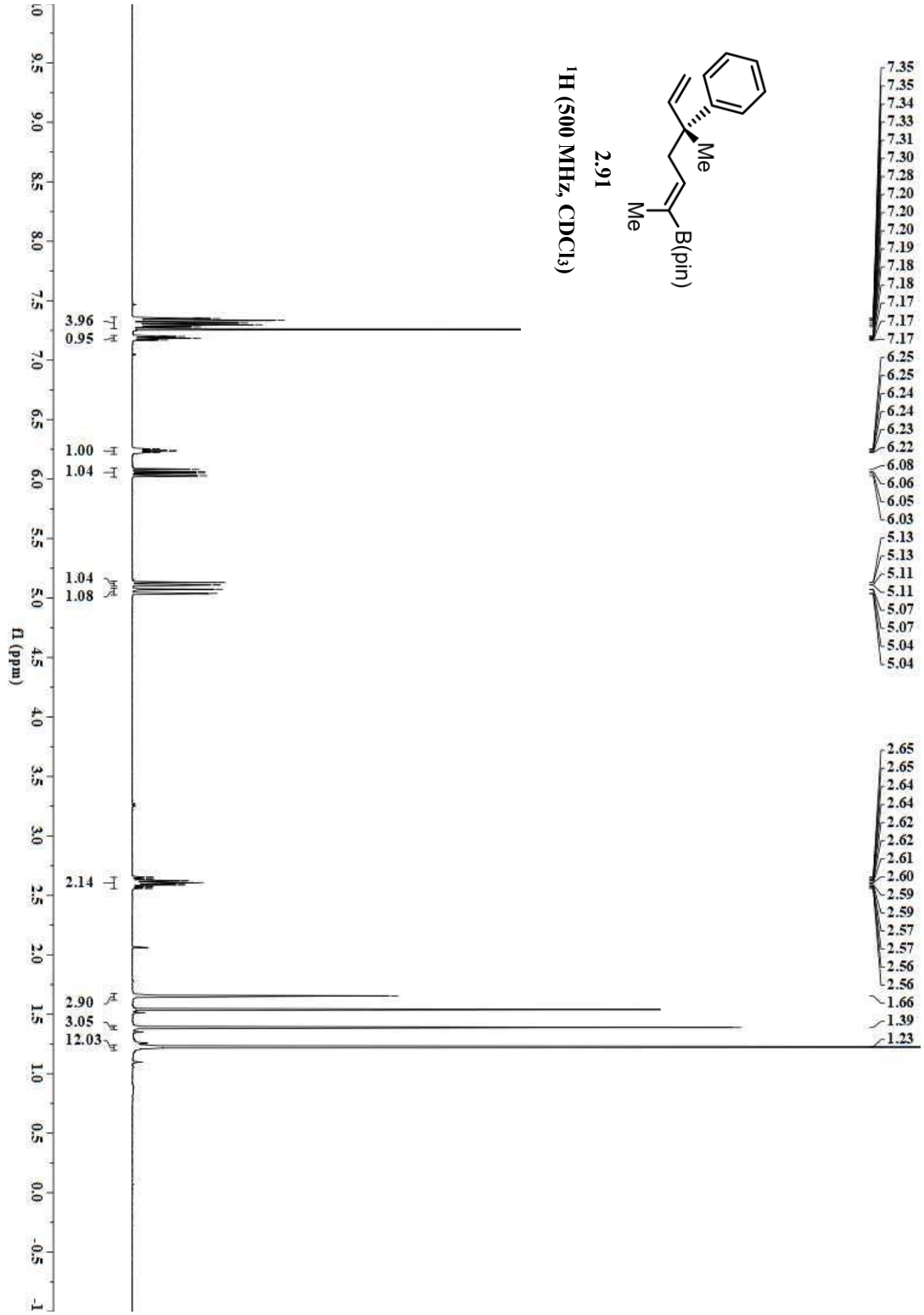


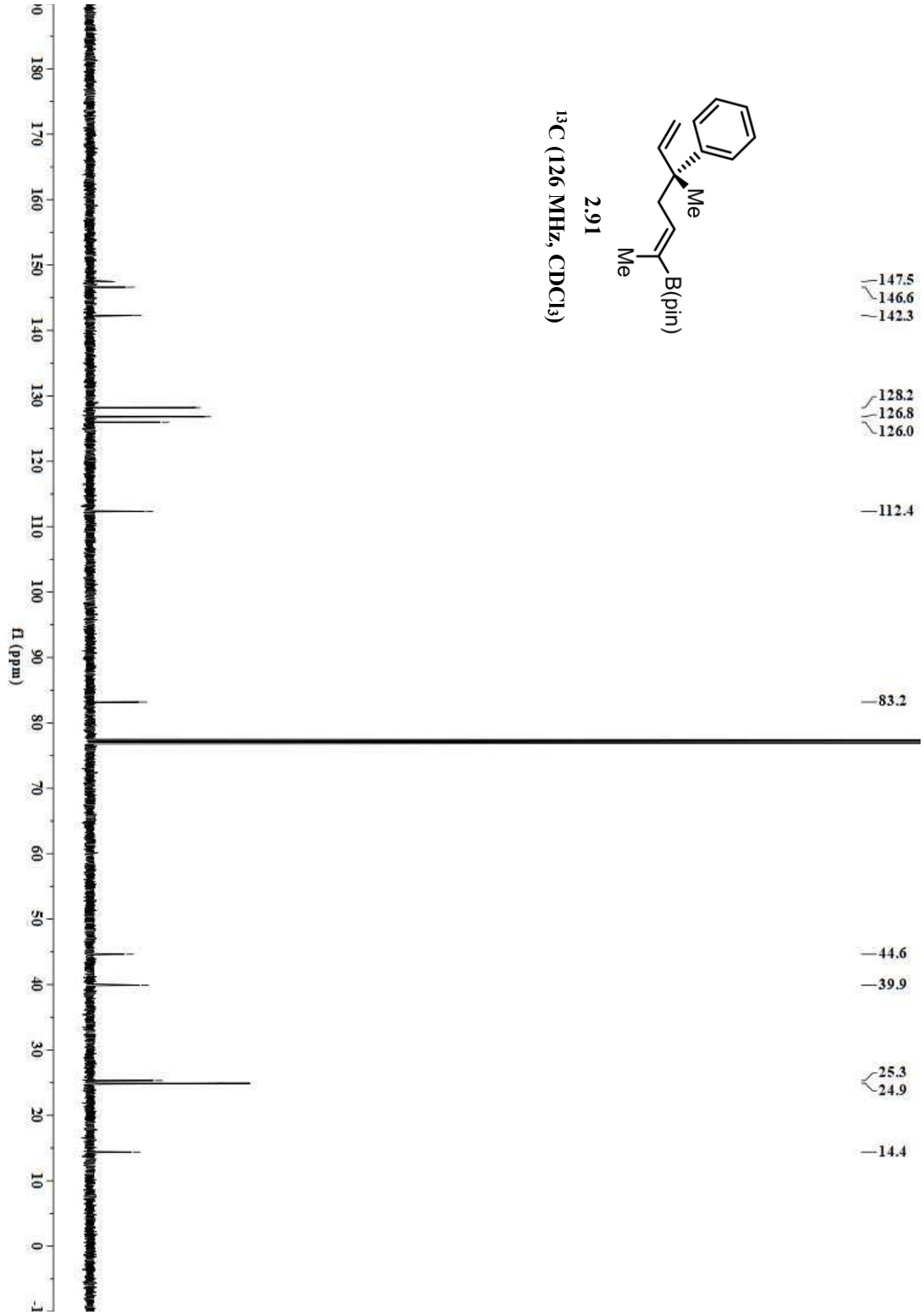

**2.112**

**$^{13}$C (101 MHz, $CDCl_3$)**


Me
Me
Me
Me
B(pin)
2.90
$^1$H (600 MHz, CDCl$_3$)
f1 (ppm)
0.98
1.00
0.99
2.03
1.08
1.04
2.03
6.28
3.02
2.18
13.39
3.19
6.34
6.33
6.32
5.79
5.77
5.76
5.74
5.10
5.09
5.07
5.01
4.99
4.95
4.92
2.19
2.18
2.17
2.16
2.13
2.12
2.11
2.10
1.89
1.88
1.87
1.85
1.67
1.58
1.35
1.35
1.34
1.32
1.25
1.00

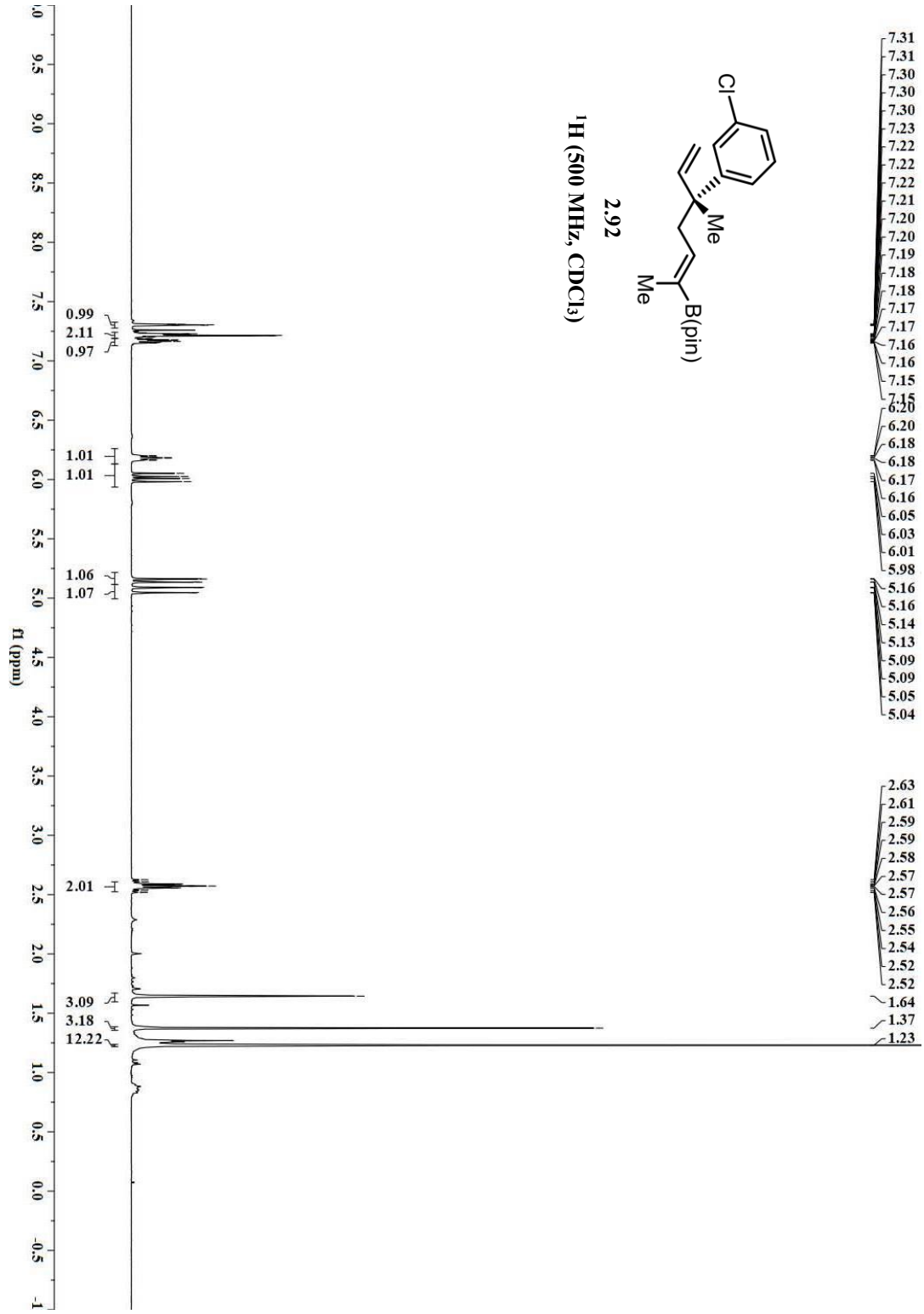

Me
Me
Me
Me
B(pin)
2.90
$^{13}$C (151 MHz, CDCl$_3$)
147.0
142.6
131.2
125.1
111.9
83.2
40.6
40.2
39.7
25.8
25.0
24.9
23.1
23.0
17.7
14.3
f1 (ppm)

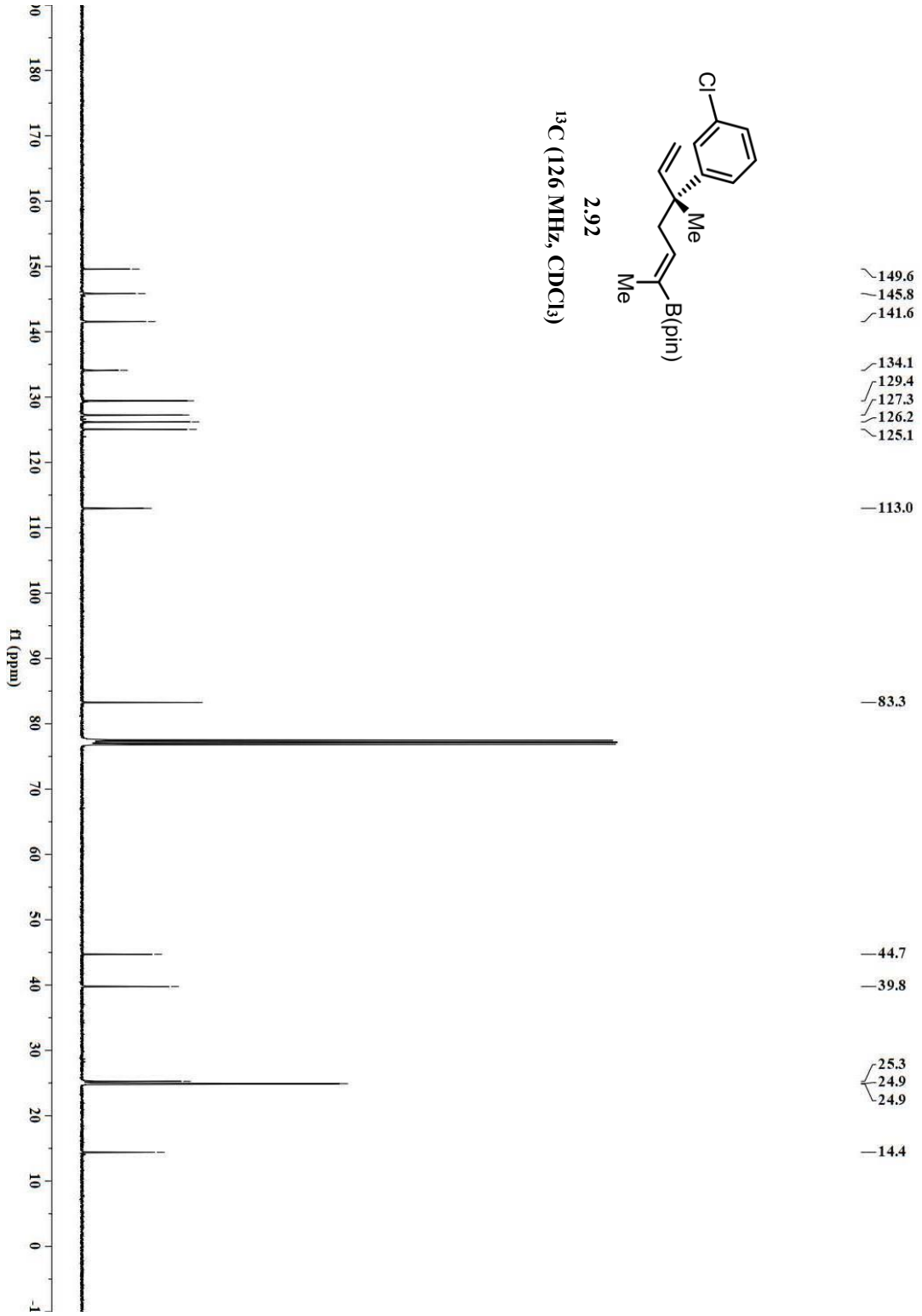

2.91
$^1$H (500 MHz, CDCl$_3$)
Me
Me
B(pin)
7.35
7.35
7.34
7.33
7.31
7.30
7.28
7.20
7.20
7.20
7.19
7.18
7.18
7.17
7.17
7.17
6.25
6.25
6.24
6.24
6.23
6.22
6.08
6.06
6.05
6.03
5.13
5.13
5.11
5.11
5.07
5.07
5.04
5.04
2.65
2.65
2.64
2.64
2.62
2.62
2.61
2.60
2.59
2.59
2.57
2.57
2.56
2.56
1.66
1.39
1.23
3.96
0.95
1.00
1.04
1.04
1.08
2.14
2.90
3.05
12.03
f1 (ppm)

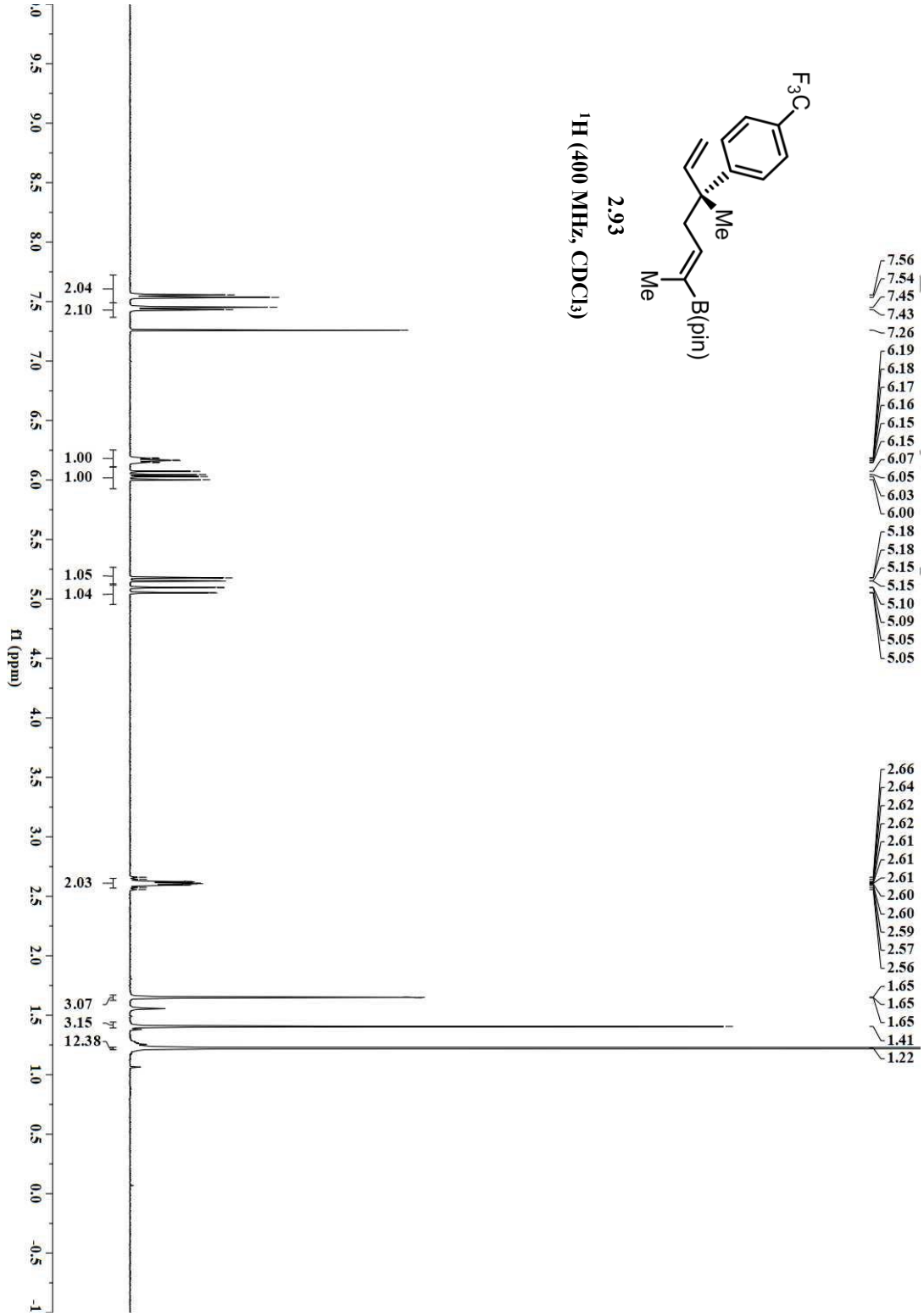


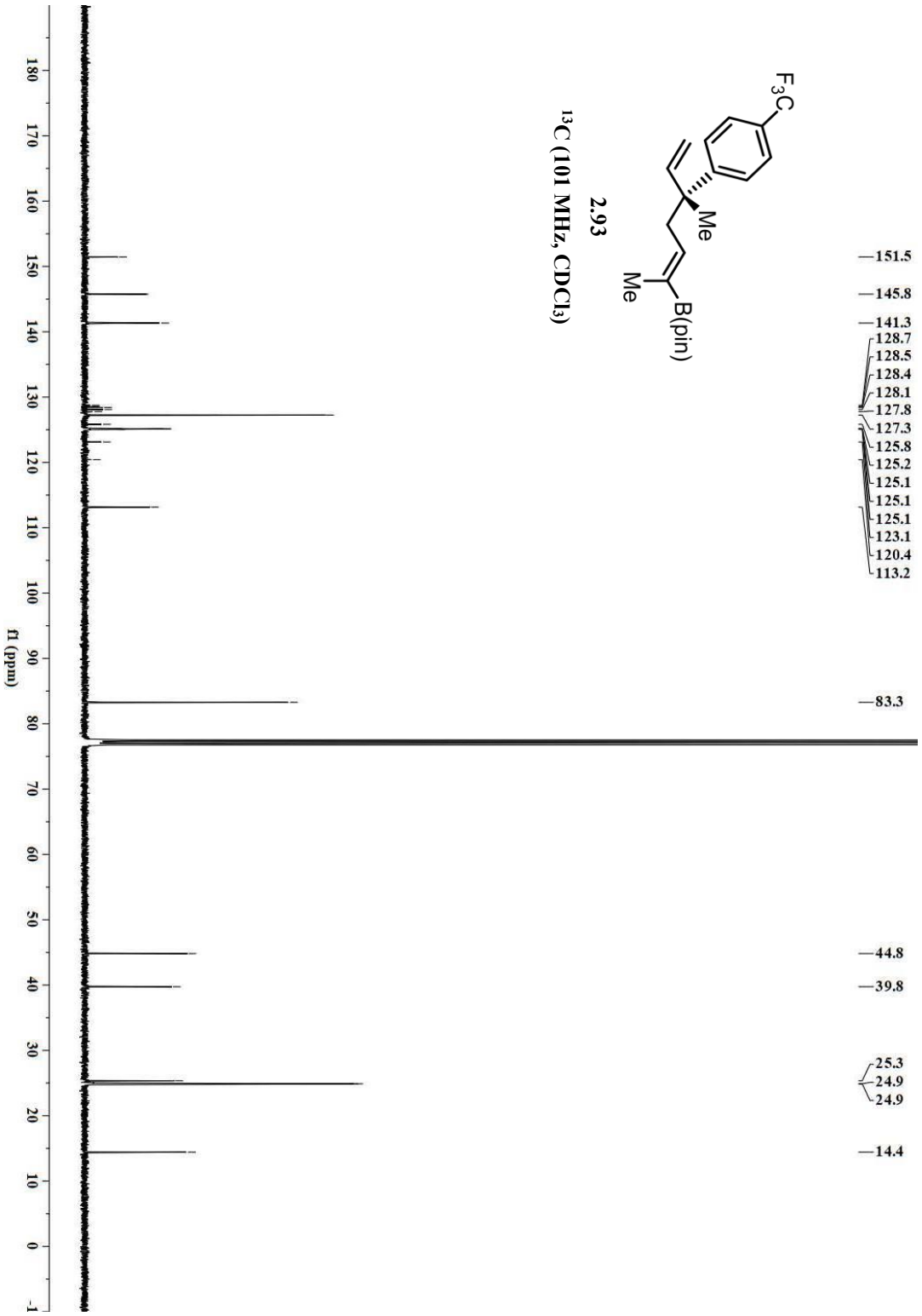

**2.91**

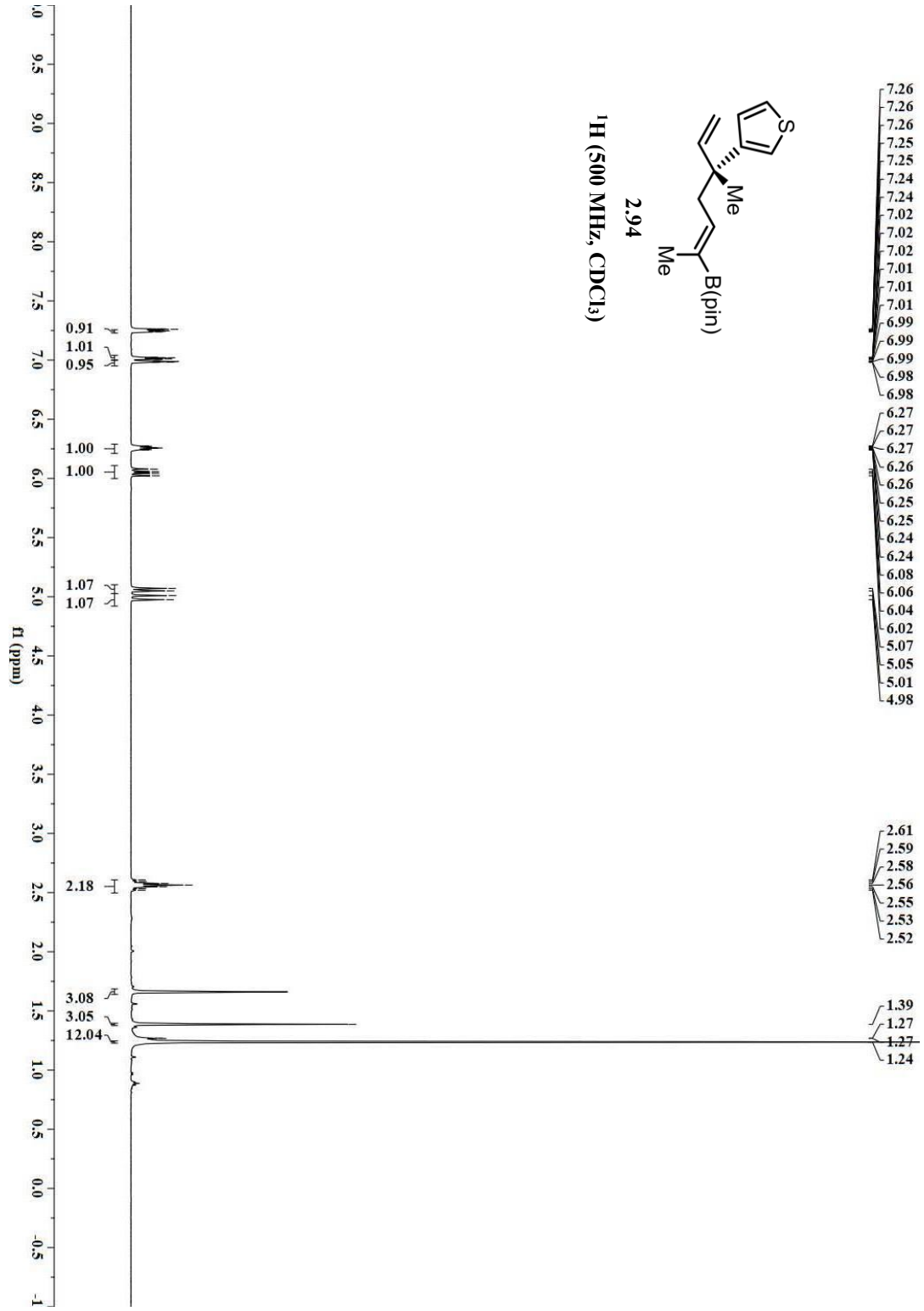
**$^{13}$C (126 MHz, $CDCl_3$)**

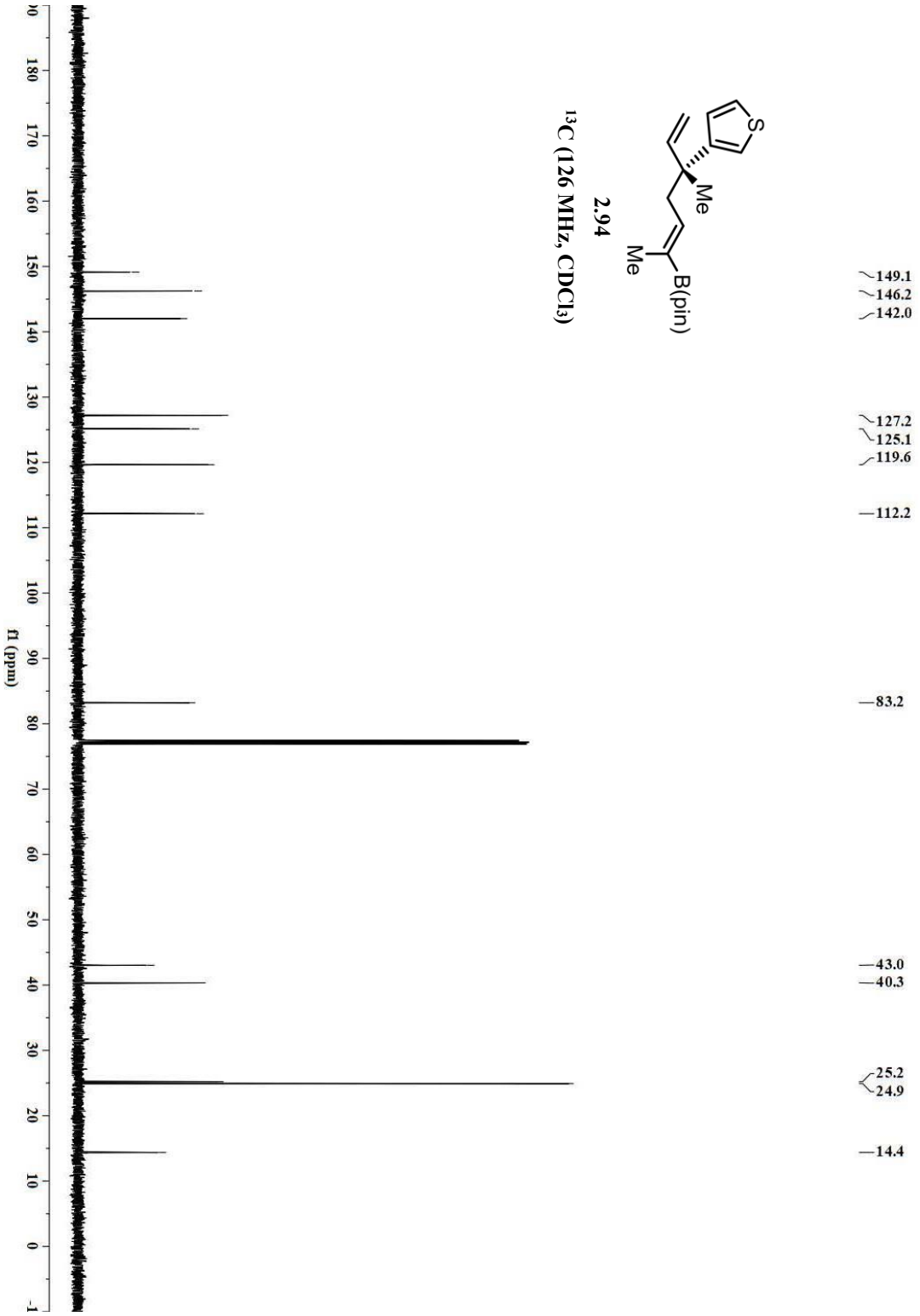

2.92
$^1$H (500 MHz, CDCl$_3$)
Cl
Me
Me
B(pin)
7.31
7.31
7.30
7.30
7.30
7.23
7.22
7.22
7.22
7.21
7.20
7.20
7.19
7.18
7.18
7.17
7.17
7.16
7.16
7.15
7.15
6.20
6.20
6.18
6.18
6.17
6.16
6.05
6.03
6.01
5.98
5.16
5.16
5.14
5.13
5.09
5.09
5.05
5.04
2.63
2.61
2.59
2.59
2.58
2.57
2.57
2.56
2.55
2.54
2.52
2.52
1.64
1.37
1.23
0.99
2.11
0.97
1.01
1.01
1.06
1.07
2.01
3.09
3.18
12.22
f1 (ppm)

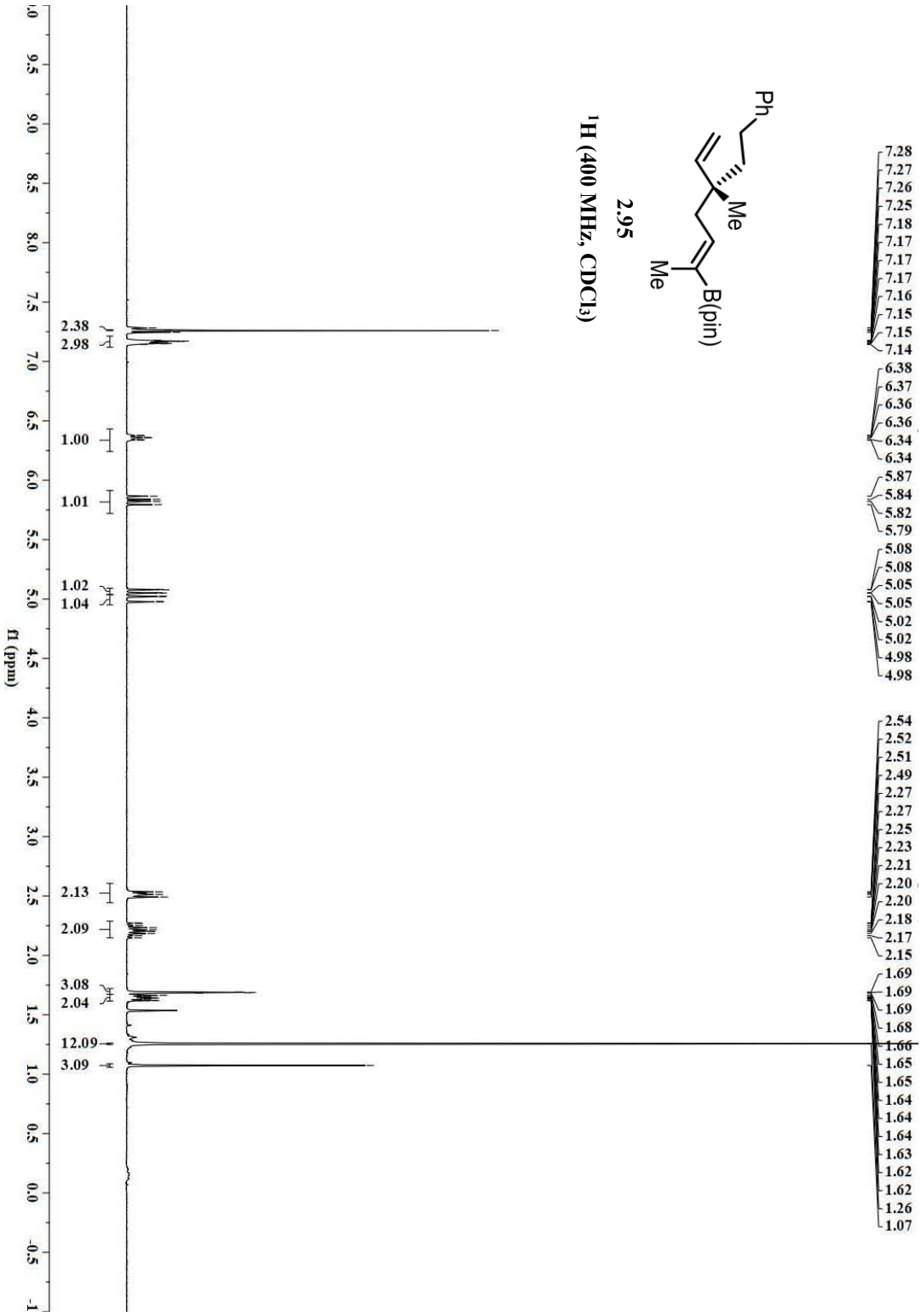

Cl
Me
Me
B(pin)
2.92
$^{13}$C (126 MHz, CDCl$_3$)
149.6
145.8
141.6
134.1
129.4
127.3
126.2
125.1
113.0
83.3
44.7
39.8
25.3
24.9
24.9
14.4
f1 (ppm)

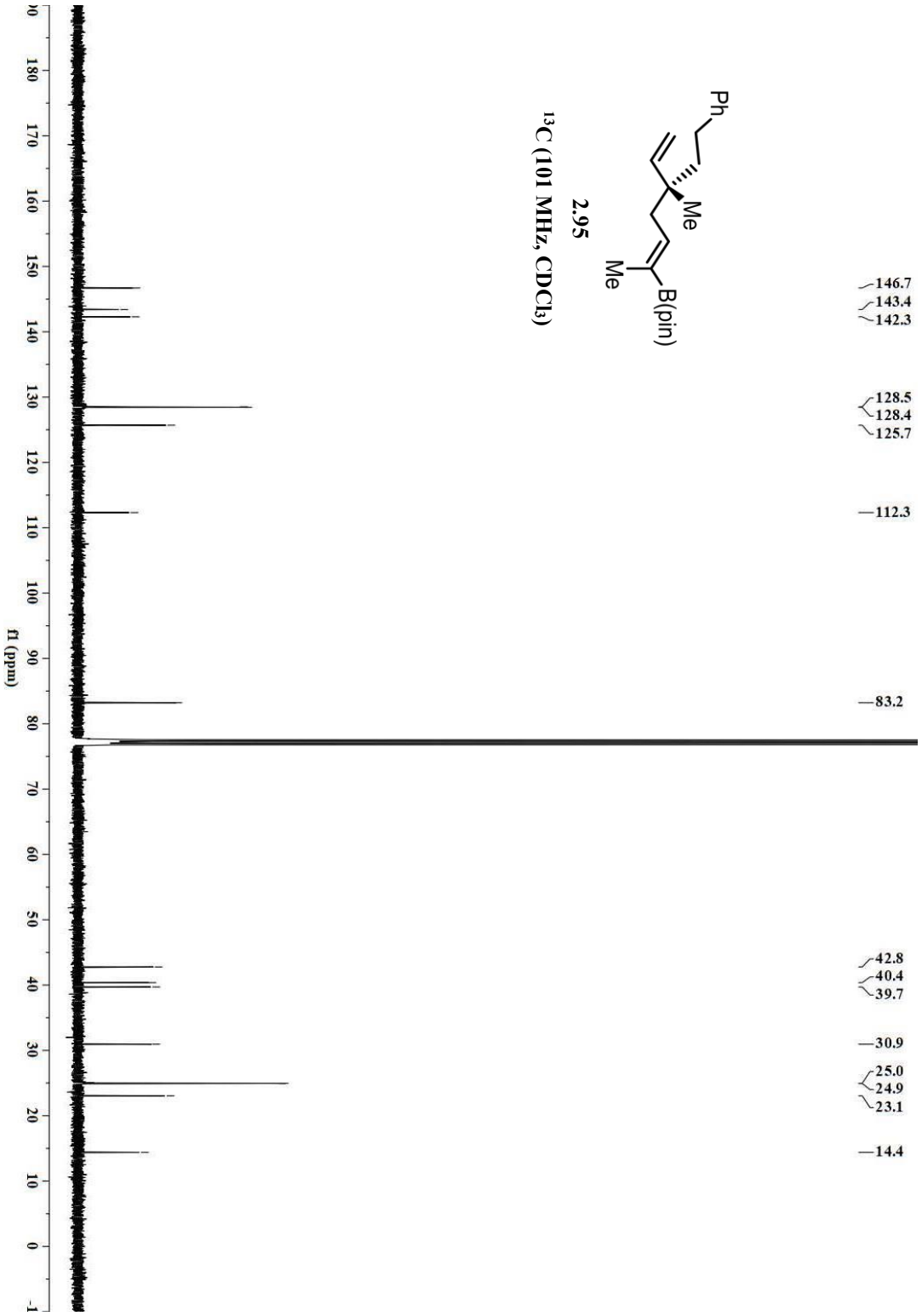

2.93
$^1$H (400 MHz, CDCl$_3$)
F$_3$C
Me
Me
B(pin)
f1 (ppm)
2.04
2.10
1.00
1.00
1.05
1.04
2.03
3.07
3.15
12.38
7.56
7.54
7.45
7.43
7.26
6.19
6.18
6.17
6.16
6.15
6.15
6.07
6.05
6.03
6.00
5.18
5.18
5.15
5.15
5.10
5.09
5.05
5.05
2.66
2.64
2.62
2.62
2.61
2.61
2.61
2.60
2.60
2.59
2.57
2.56
1.65
1.65
1.65
1.41
1.22

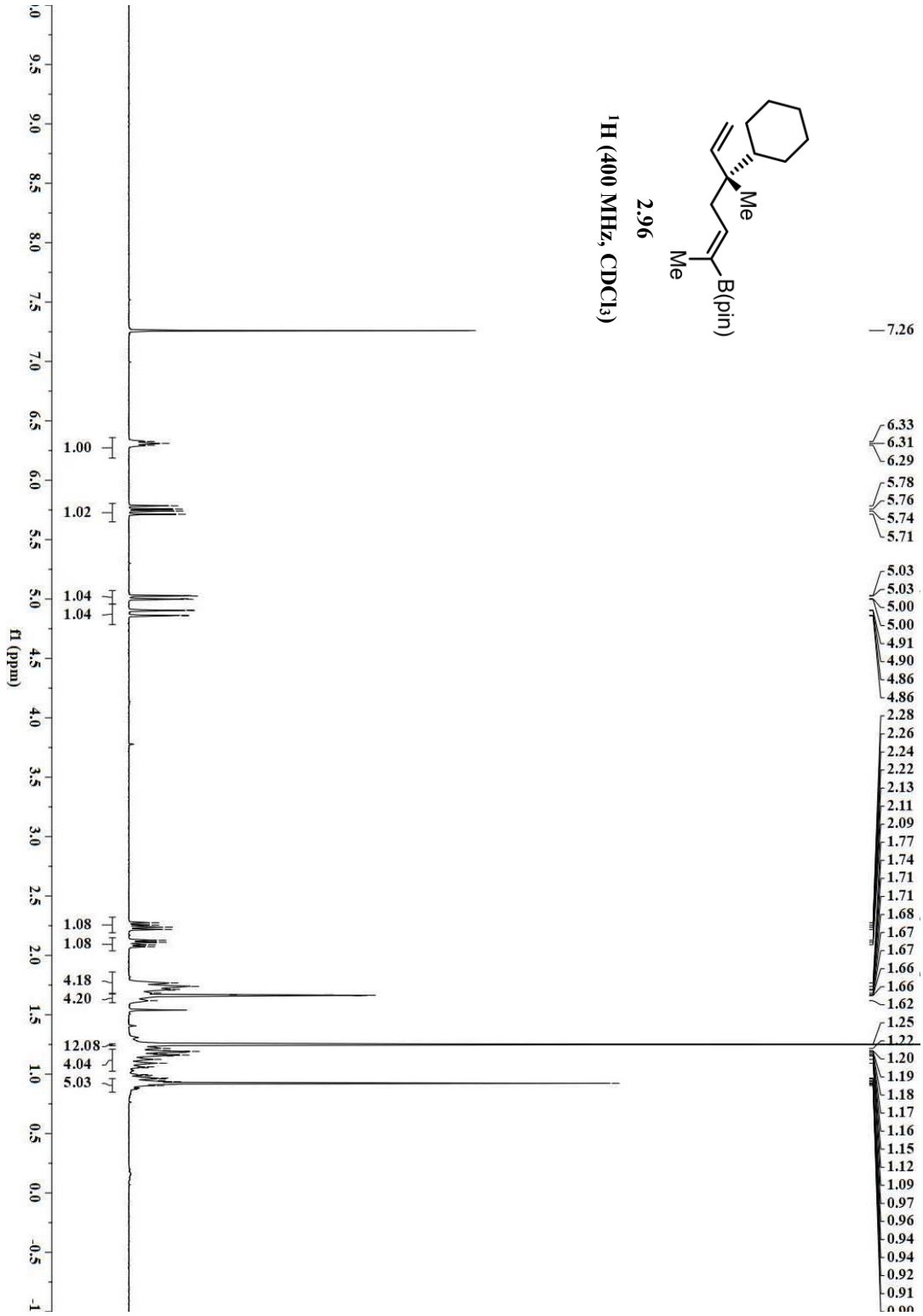

F3C
Me
Me
B(pin)
2.93
13C (101 MHz, CDCl3)
151.5
145.8
141.3
128.7
128.5
128.4
128.1
127.8
127.3
125.8
125.2
125.1
125.1
125.1
123.1
120.4
113.2
83.3
44.8
39.8
25.3
24.9
24.9
14.4
f1 (ppm)

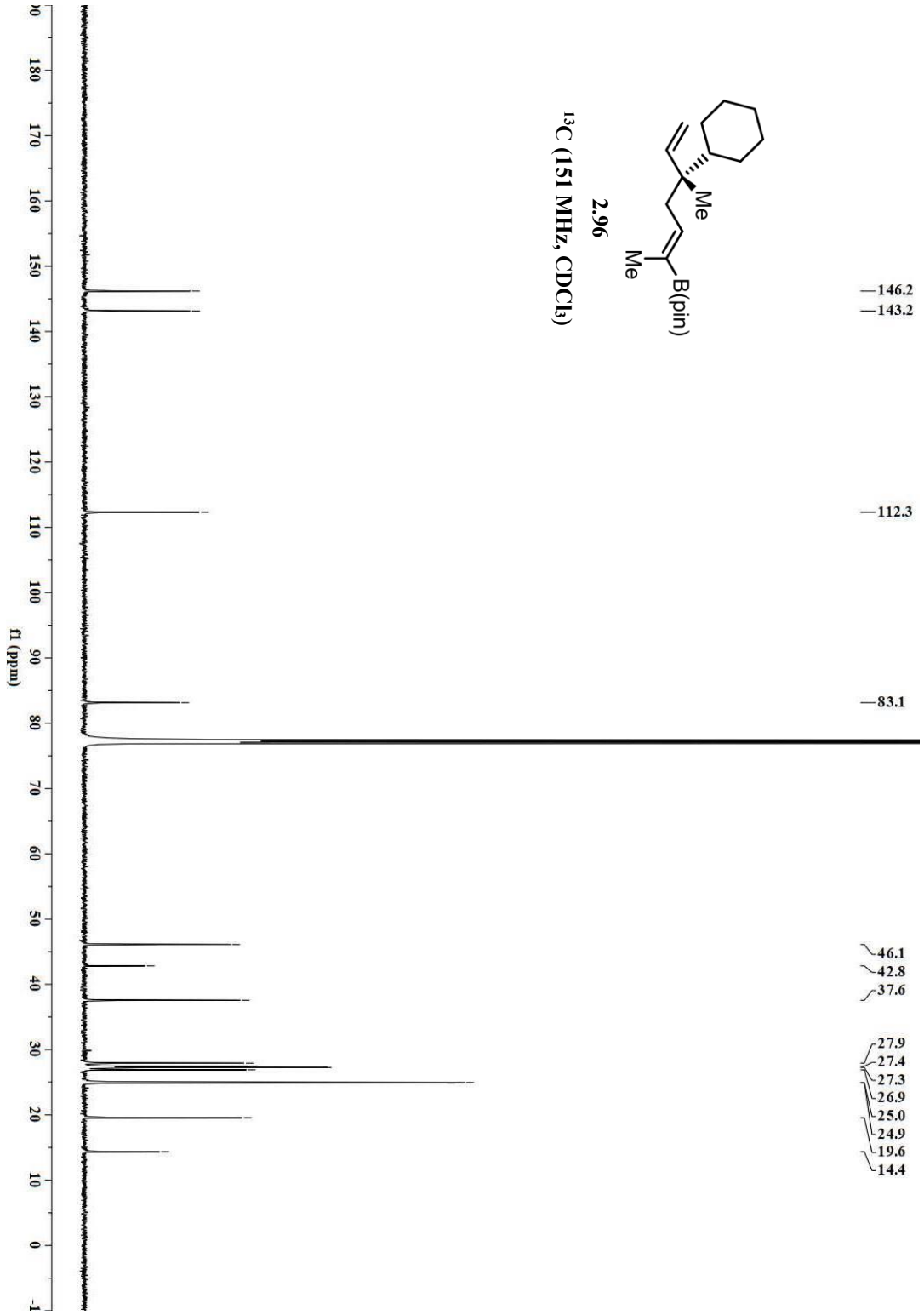

2.94
$^1$H (500 MHz, CDCl$_3$)
Me
Me
B(pin)
S
f1 (ppm)
0.91
1.01
0.95
1.00
1.00
1.07
1.07
2.18
3.08
3.05
12.04
7.26
7.26
7.26
7.25
7.25
7.24
7.24
7.02
7.02
7.02
7.01
7.01
7.01
6.99
6.99
6.99
6.98
6.98
6.27
6.27
6.27
6.26
6.26
6.25
6.25
6.24
6.24
6.08
6.06
6.04
6.02
5.07
5.05
5.01
4.98
2.61
2.59
2.58
2.56
2.55
2.53
2.52
1.39
1.27
1.27
1.24

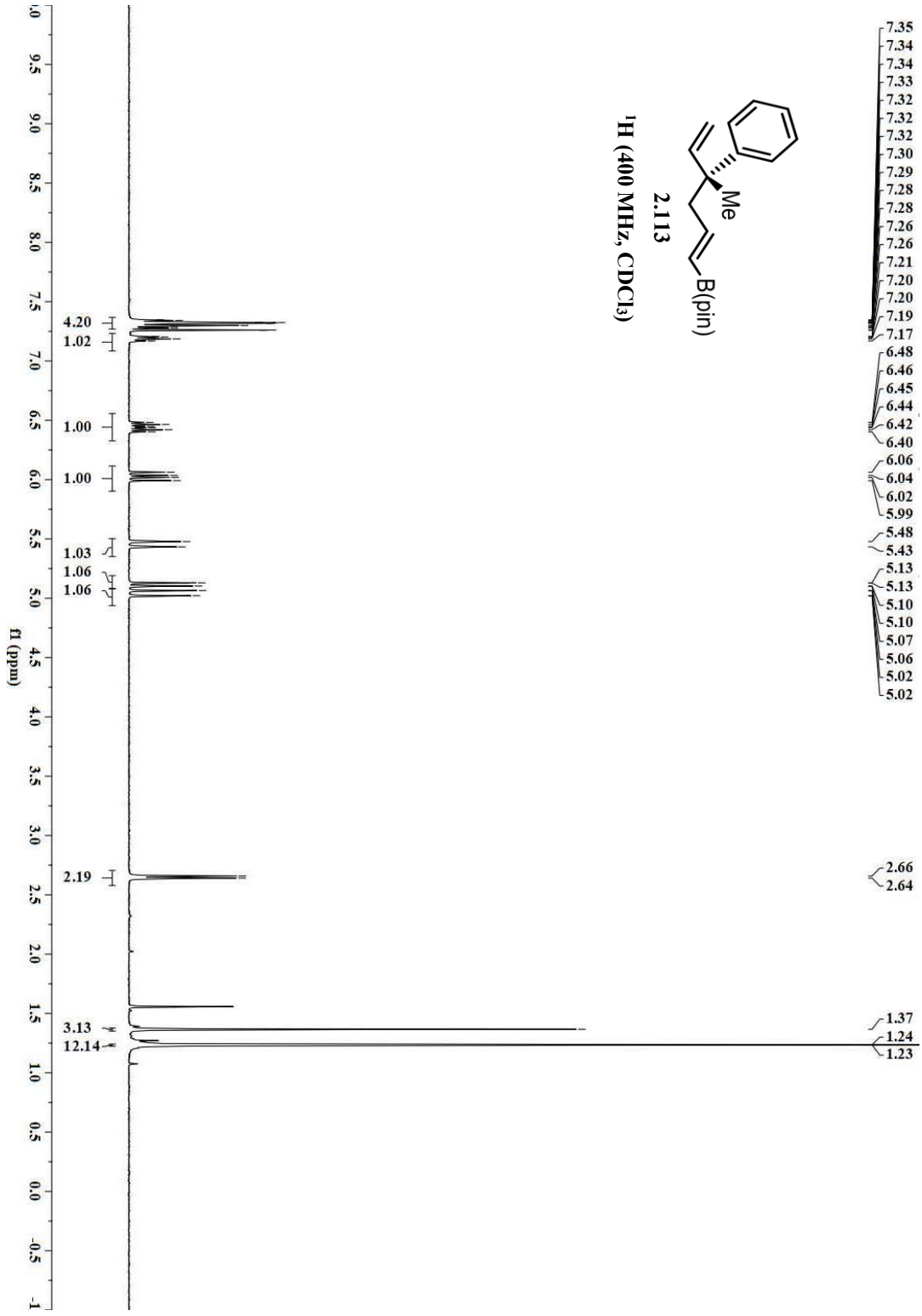

S
Me
Me
B(pin)
2.94
13C (126 MHz, CDCl3)
149.1
146.2
142.0
127.2
125.1
119.6
112.2
83.2
43.0
40.3
25.2
24.9
14.4
f1 (ppm)

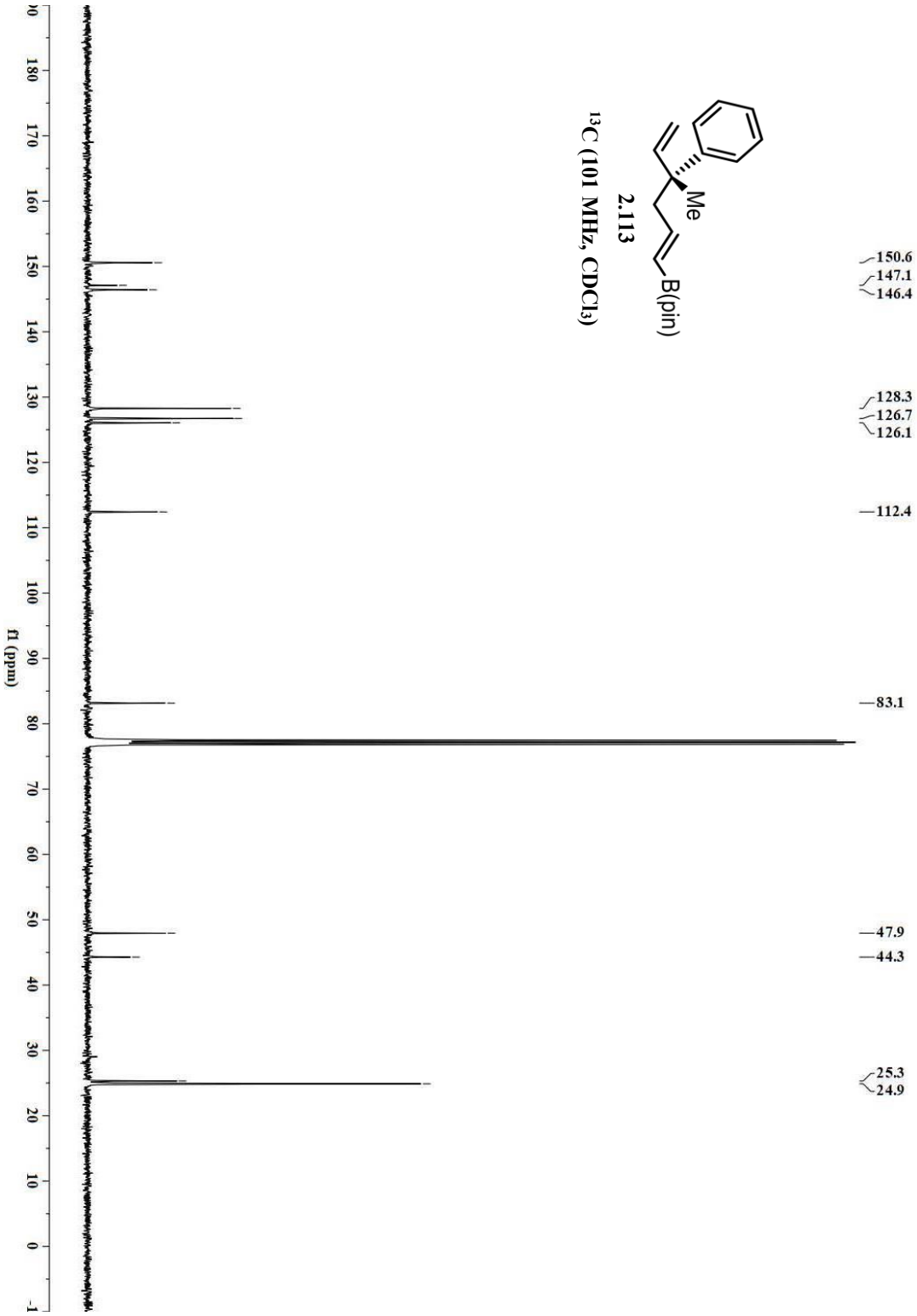

Ph
Me
Me
B(pin)
2.95
$^1$H (400 MHz, CDCl$_3$)
f1 (ppm)
2.38
2.98
1.00
1.01
1.02
1.04
2.13
2.09
3.08
2.04
12.09
3.09
7.28
7.27
7.26
7.25
7.18
7.17
7.17
7.17
7.16
7.15
7.15
7.14
6.38
6.37
6.36
6.36
6.34
6.34
5.87
5.84
5.82
5.79
5.08
5.08
5.05
5.05
5.02
5.02
4.98
4.98
2.54
2.52
2.51
2.49
2.27
2.27
2.25
2.23
2.21
2.20
2.20
2.18
2.17
2.15
1.69
1.69
1.69
1.68
1.66
1.65
1.65
1.64
1.64
1.64
1.63
1.62
1.62
1.26
1.07

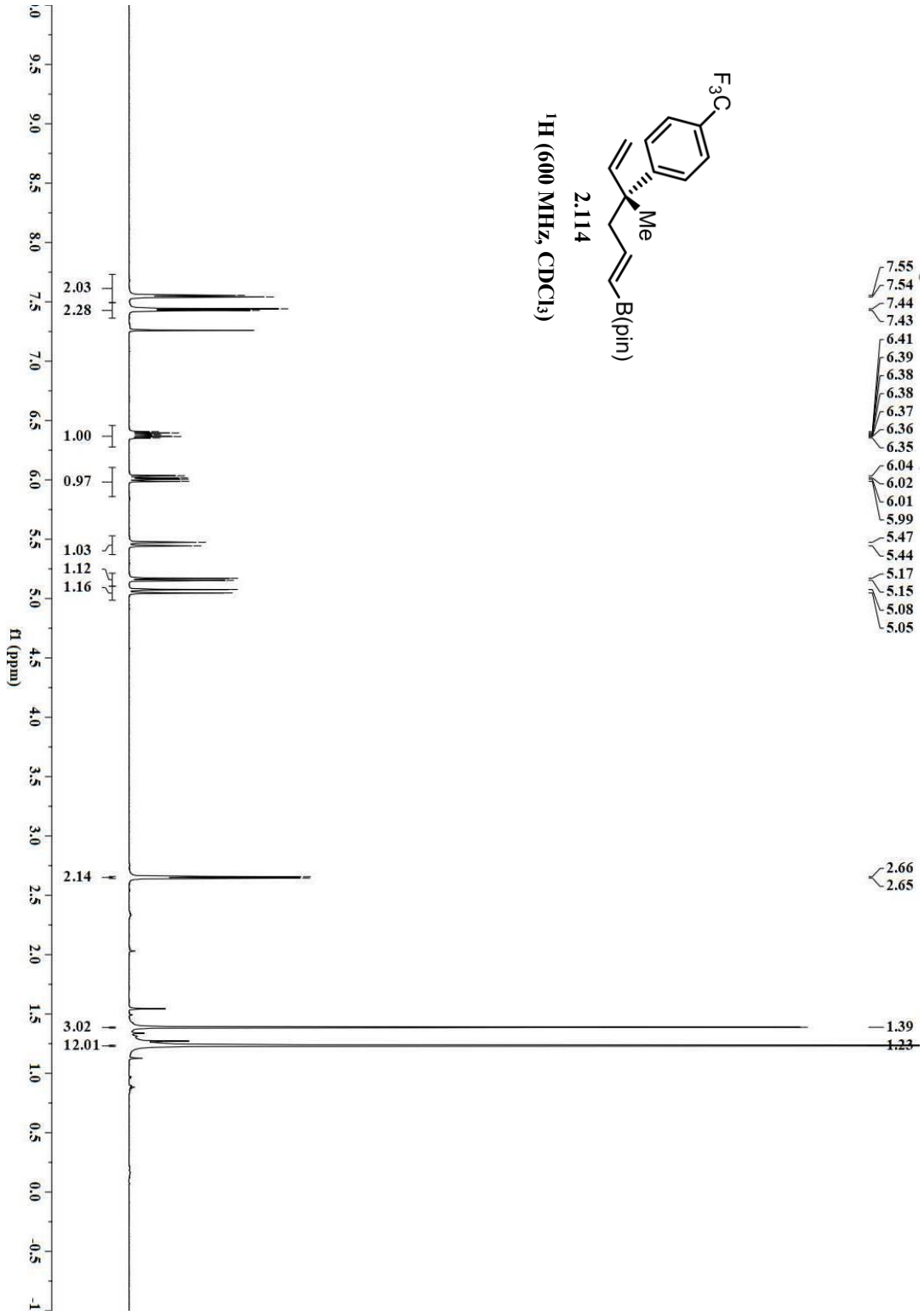

Ph
Me
Me
B(pin)
2.95
$^{13}$C (101 MHz, CDCl$_3$)
146.7
143.4
142.3
128.5
128.4
125.7
112.3
83.2
42.8
40.4
39.7
30.9
25.0
24.9
23.1
14.4
f1 (ppm)

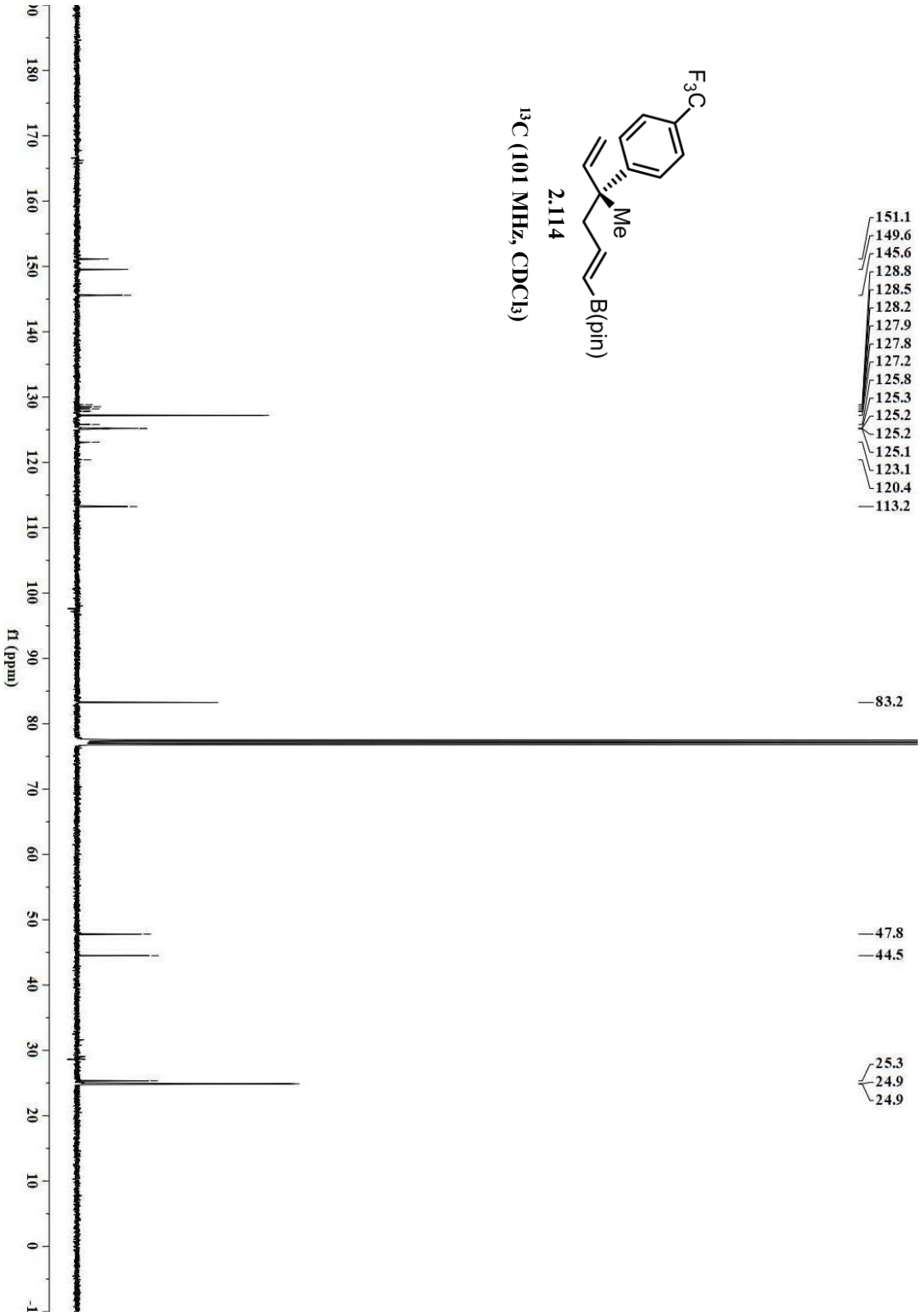

2.96
$^1$H (400 MHz, CDCl$_3$)
Me
Me
B(pin)
f1 (ppm)
7.26
6.33
6.31
6.29
5.78
5.76
5.74
5.71
5.03
5.03
5.00
5.00
4.91
4.90
4.86
4.86
2.28
2.26
2.24
2.22
2.13
2.11
2.09
1.77
1.74
1.71
1.71
1.68
1.67
1.67
1.66
1.66
1.62
1.25
1.22
1.20
1.19
1.18
1.17
1.16
1.15
1.12
1.09
0.97
0.96
0.94
0.94
0.92
0.91
1.00
1.02
1.04
1.04
1.08
1.08
4.18
4.20
12.08
4.04
5.03

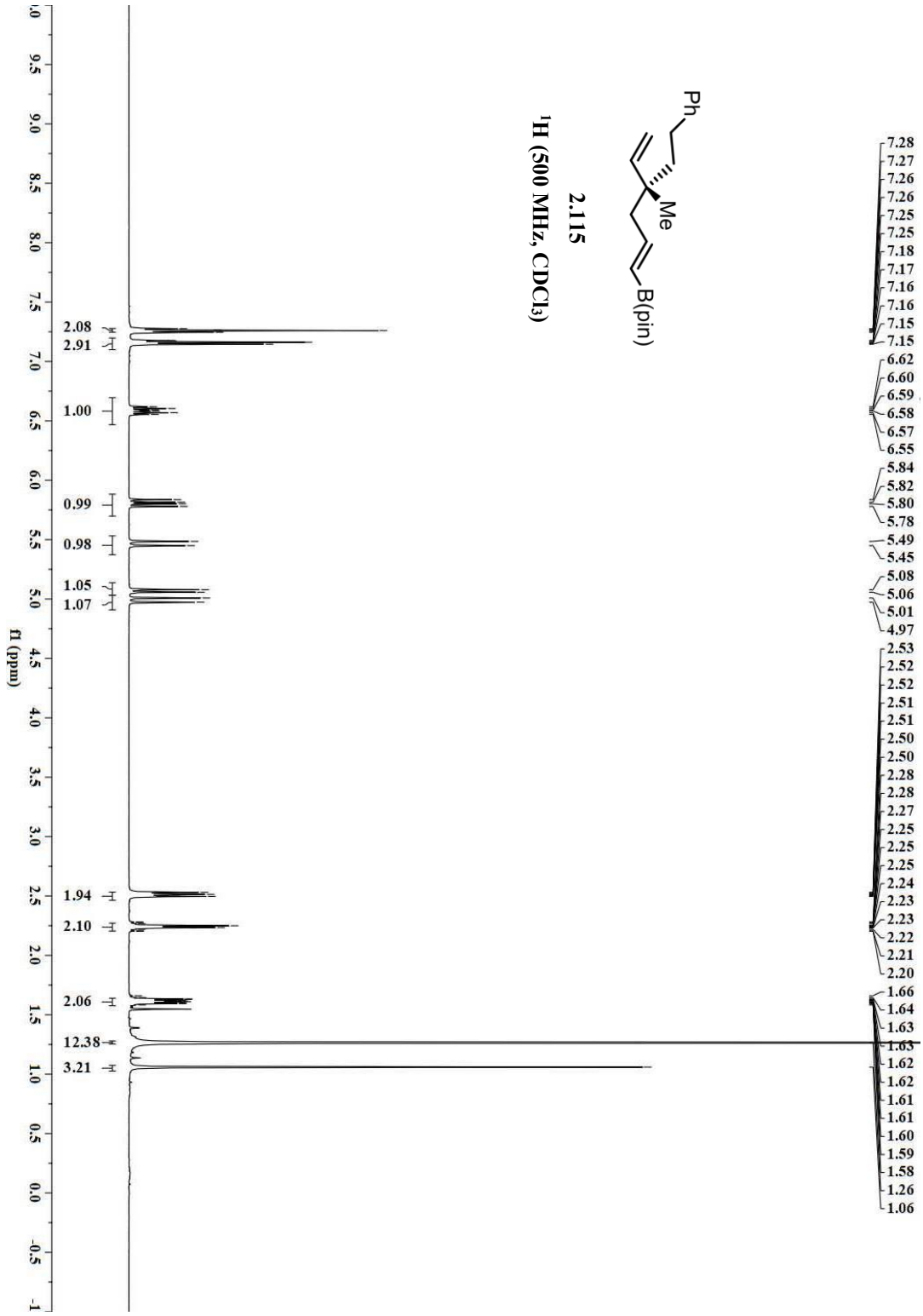

Me
Me
B(pin)
2.96
$^{13}$C (151 MHz, CDCl$_3$)
146.2
143.2
112.3
83.1
46.1
42.8
37.6
27.9
27.4
27.3
26.9
25.0
24.9
19.6
14.4
f1 (ppm)

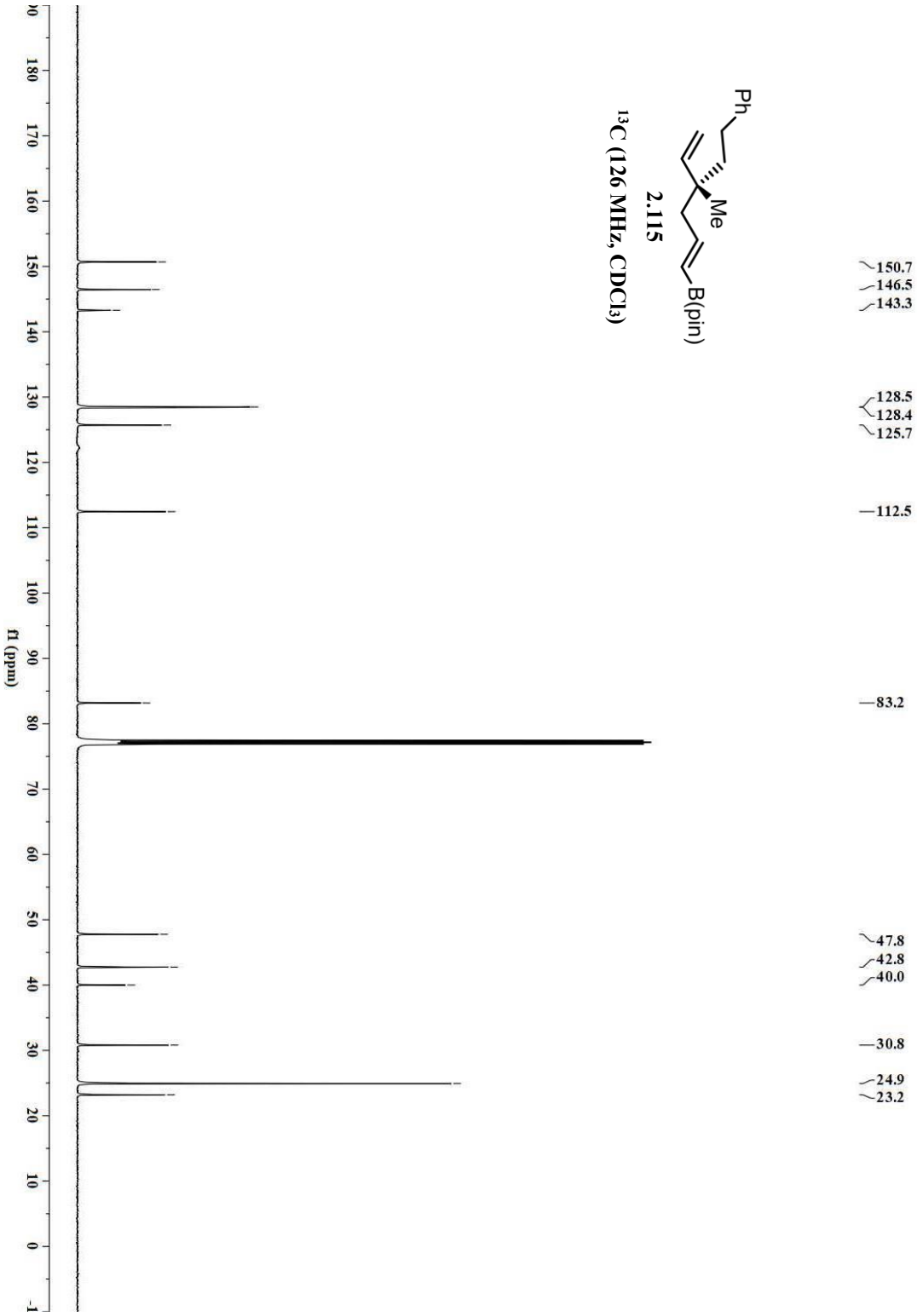

Me
B(pin)
2.113
$^1$H (400 MHz, CDCl$_3$)
f1 (ppm)
4.20
1.02
1.00
1.00
1.03
1.06
1.06
2.19
3.13
12.14
7.35
7.34
7.34
7.33
7.32
7.32
7.32
7.30
7.29
7.28
7.28
7.26
7.26
7.21
7.20
7.20
7.19
7.17
6.48
6.46
6.45
6.44
6.42
6.40
6.06
6.04
6.02
5.99
5.48
5.43
5.13
5.13
5.10
5.10
5.07
5.06
5.02
5.02
2.66
2.64
1.37
1.24
1.23

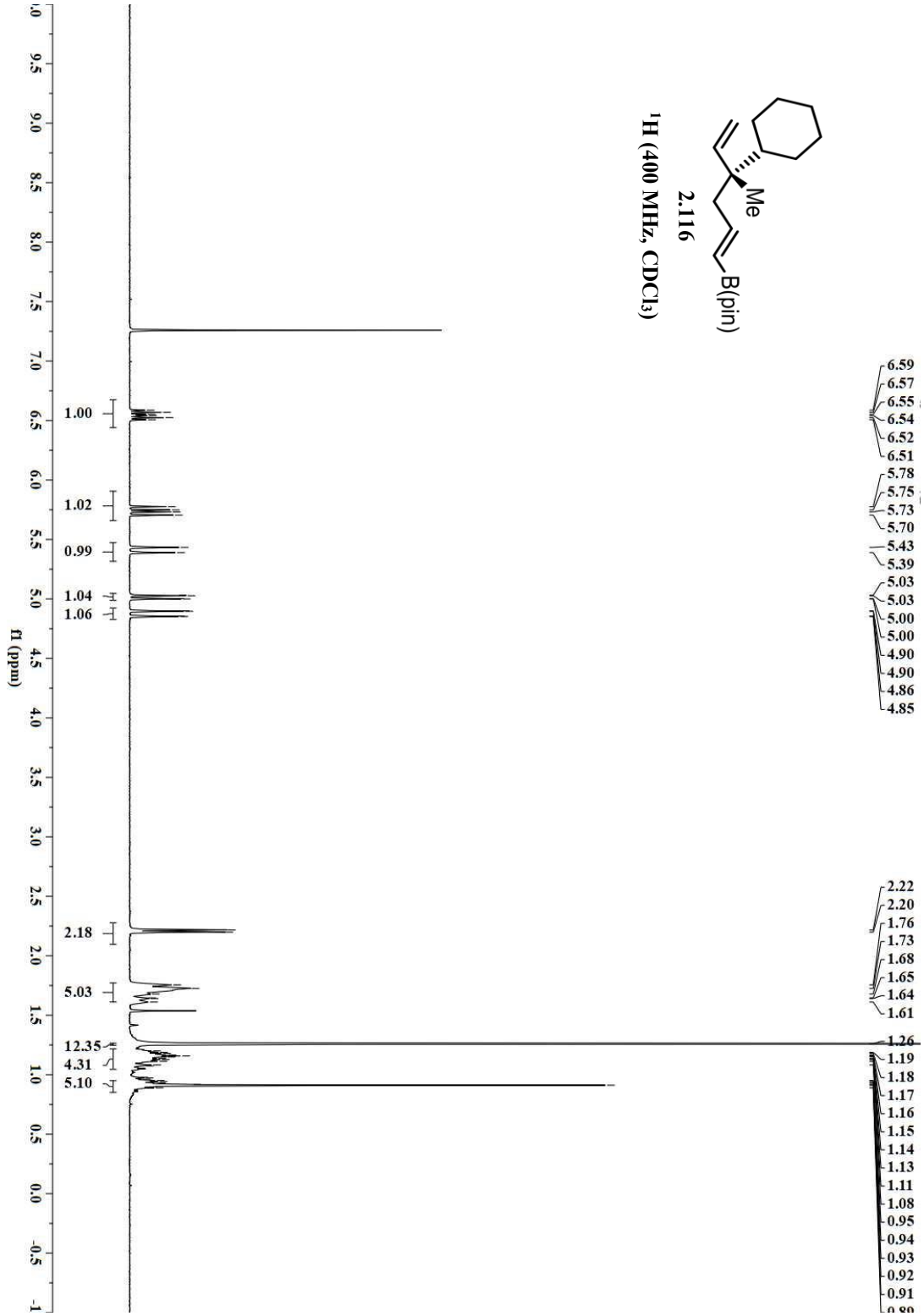

Me
B(pin)
2.113
$^{13}$C (101 MHz, CDCl$_3$)
150.6
147.1
146.4
128.3
126.7
126.1
112.4
83.1
47.9
44.3
25.3
24.9
f1 (ppm)

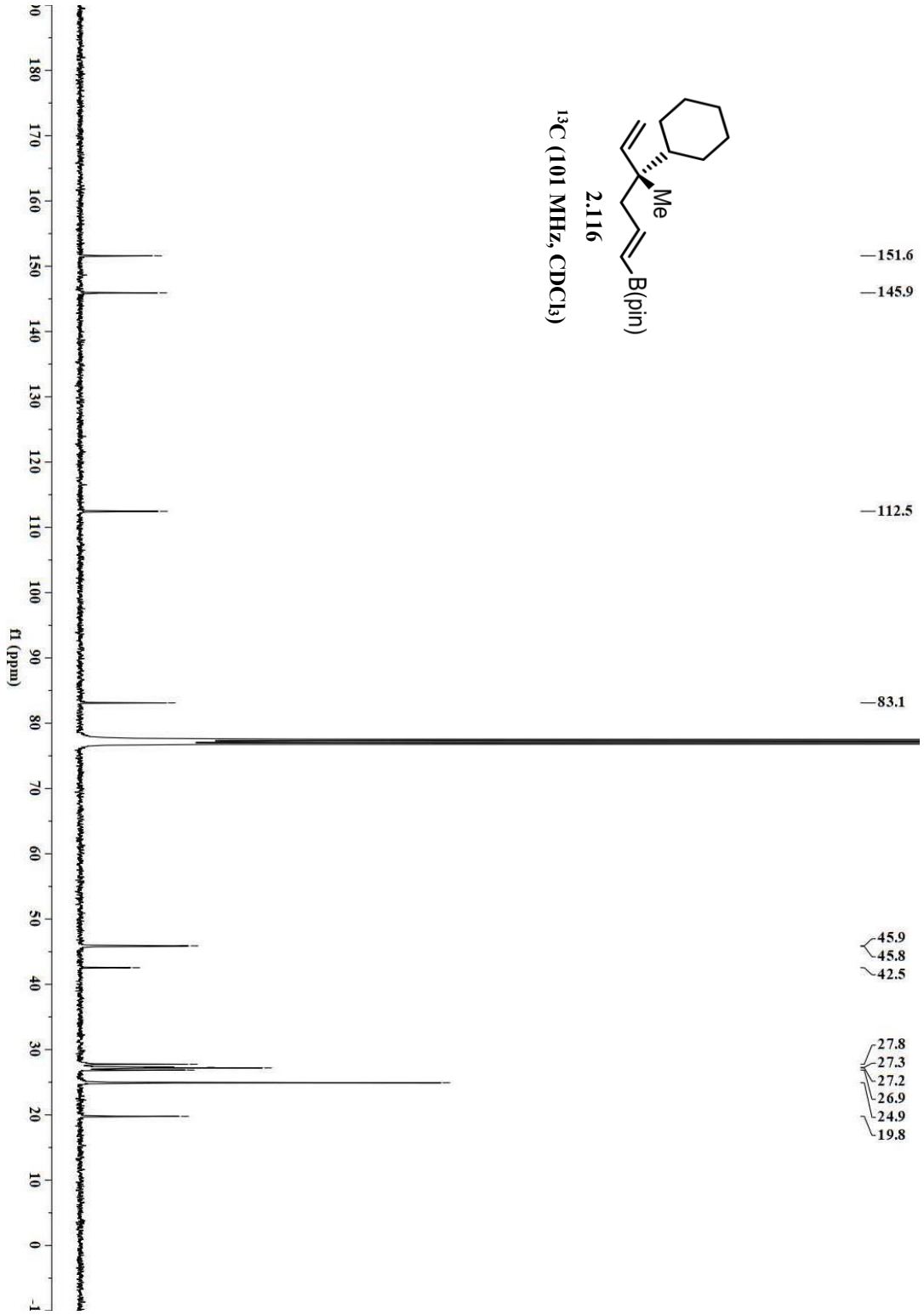

F3C
Me
B(pin)
2.114
1H (600 MHz, CDCl3)
f1 (ppm)
2.03
2.28
1.00
0.97
1.03
1.12
1.16
2.14
3.02
12.01
7.55
7.54
7.44
7.43
6.41
6.39
6.38
6.38
6.37
6.36
6.35
6.04
6.02
6.01
5.99
5.47
5.44
5.17
5.15
5.08
5.05
2.66
2.65
1.39
1.23

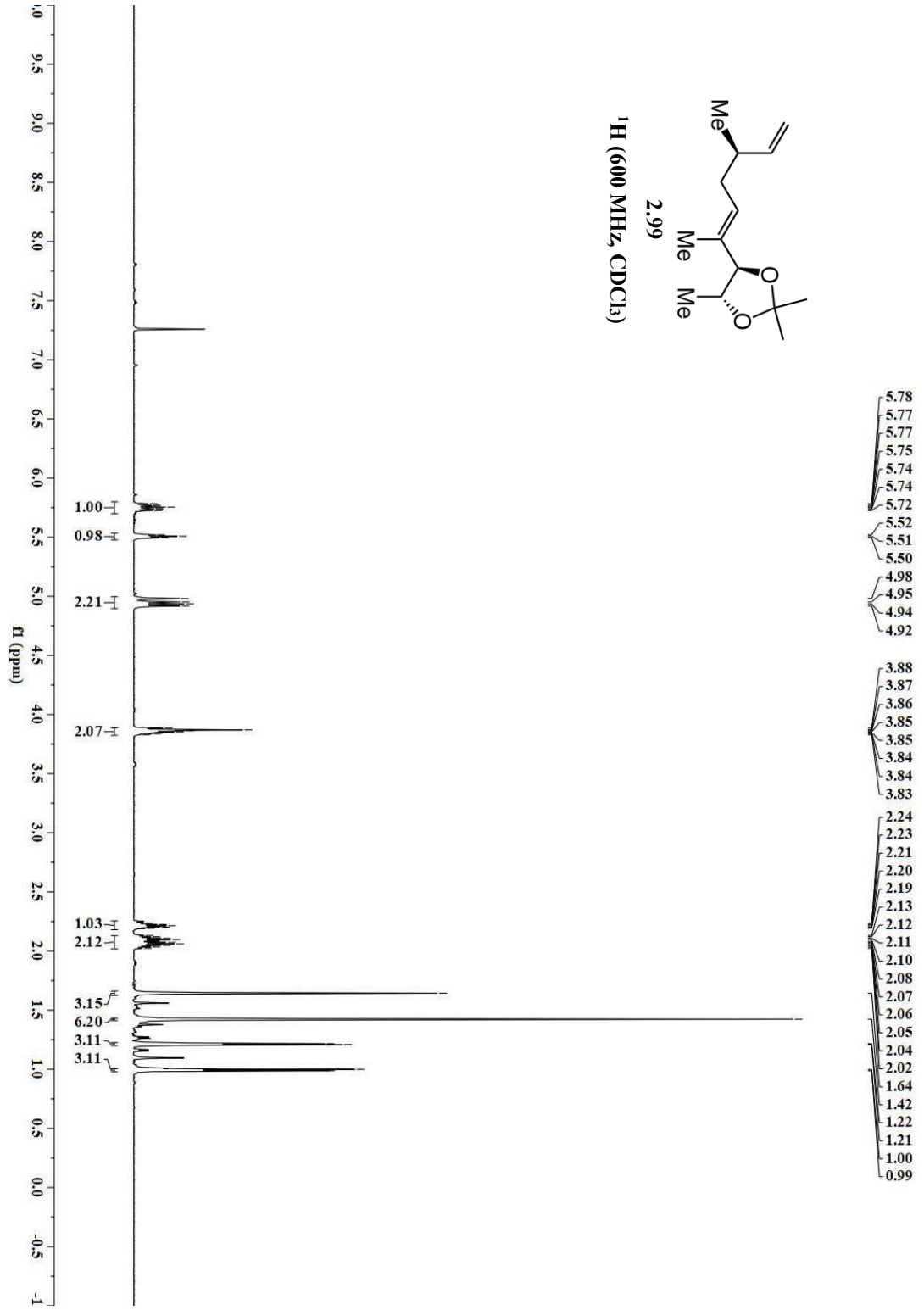

F3C
Me
B(pin)
2.114
13C (101 MHz, CDCl3)
151.1
149.6
145.6
128.8
128.5
128.2
127.9
127.8
127.2
125.8
125.3
125.2
125.2
125.1
123.1
120.4
113.2
83.2
47.8
44.5
25.3
24.9
24.9
f1 (ppm)

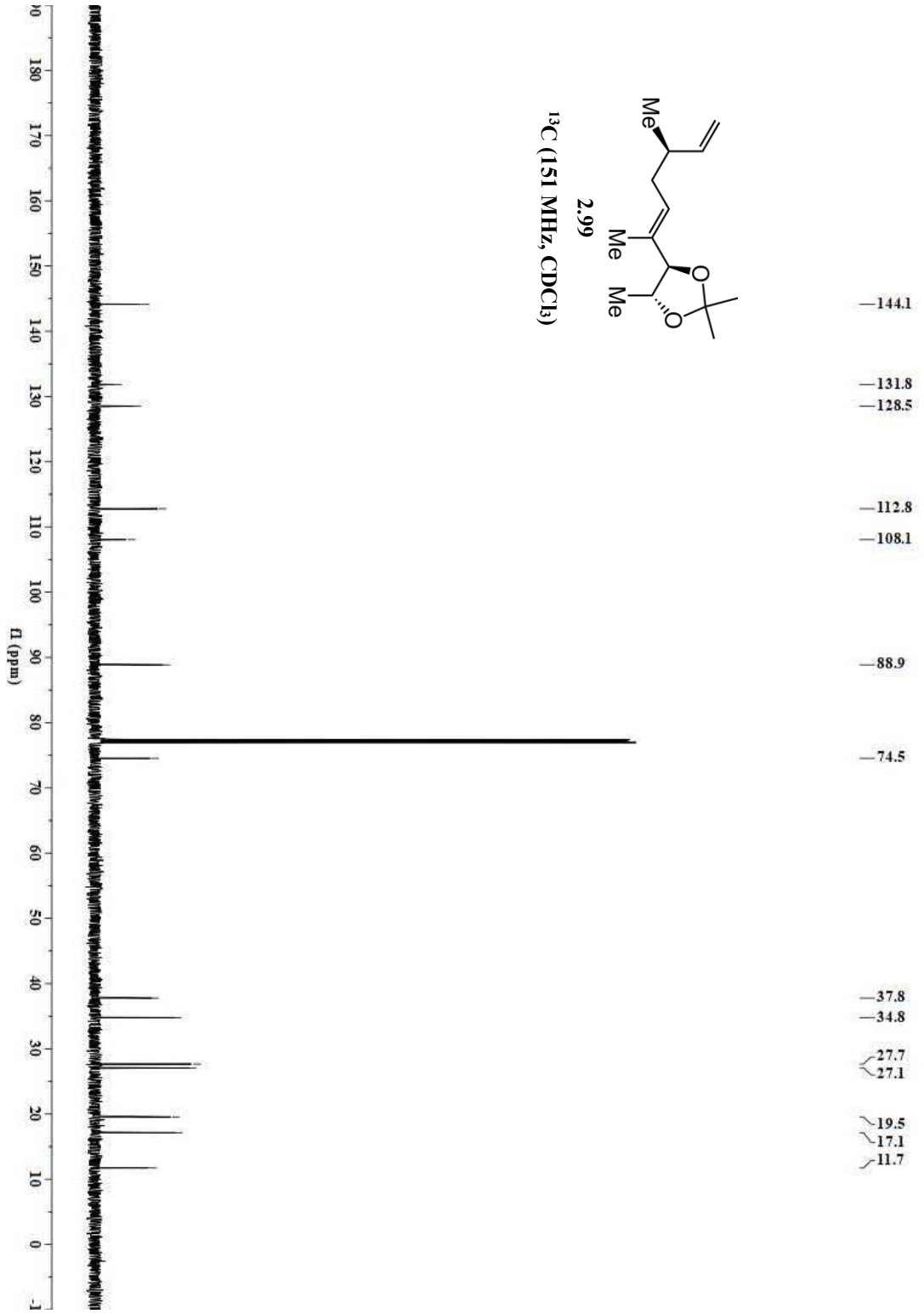

2.115
$^1$H (500 MHz, CDCl$_3$)
Ph
Me
B(pin)
f1 (ppm)
2.08
2.91
1.00
0.99
0.98
1.05
1.07
1.94
2.10
2.06
12.38
3.21
7.28
7.27
7.26
7.26
7.25
7.25
7.18
7.17
7.16
7.16
7.15
7.15
6.62
6.60
6.59
6.58
6.57
6.55
5.84
5.82
5.80
5.78
5.49
5.45
5.08
5.06
5.01
4.97
2.53
2.52
2.52
2.51
2.51
2.50
2.50
2.28
2.28
2.27
2.25
2.25
2.25
2.24
2.23
2.23
2.22
2.21
2.20
1.66
1.64
1.63
1.63
1.62
1.62
1.61
1.61
1.60
1.59
1.58
1.26
1.06

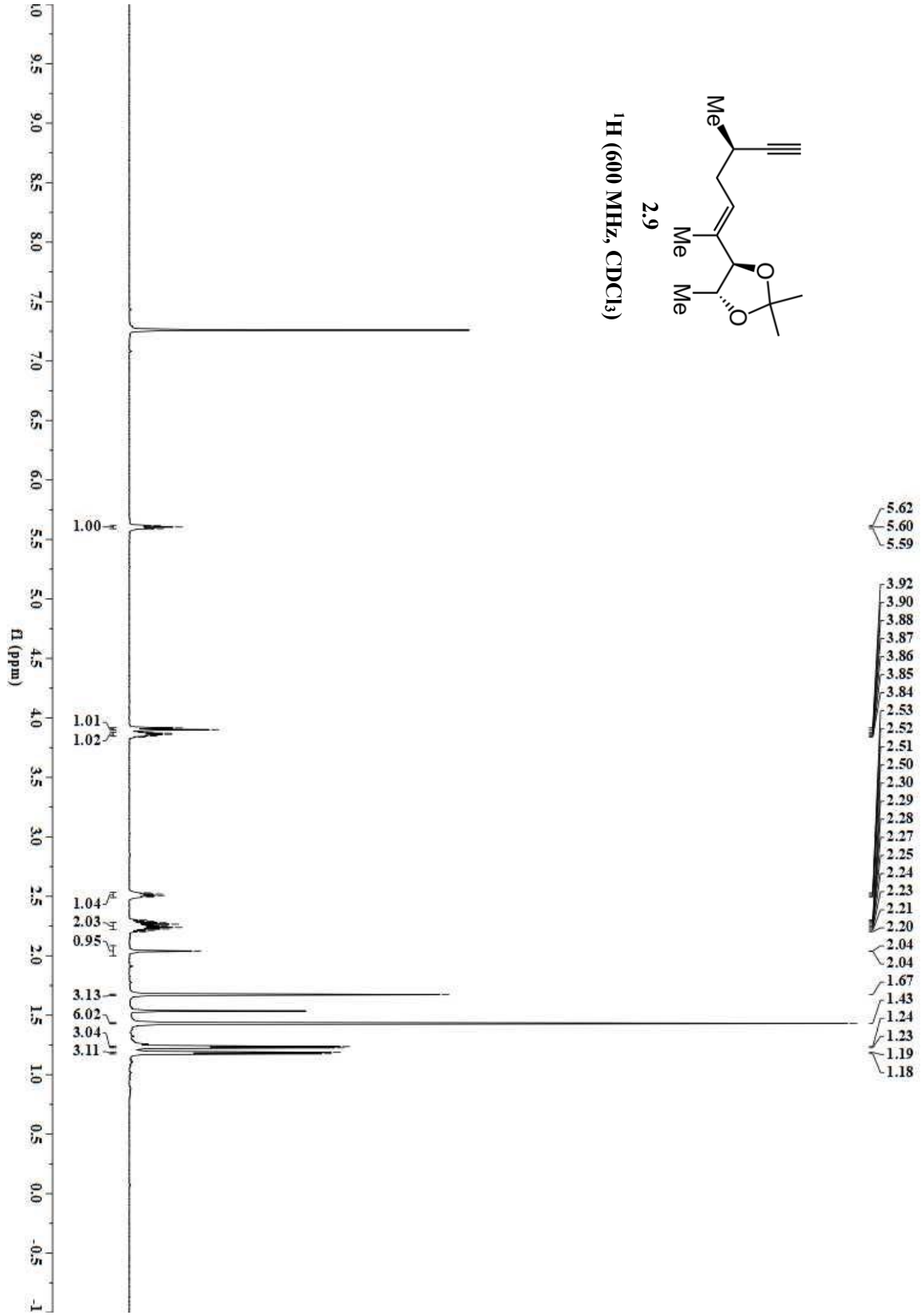

Ph
Me
B(pin)
2.115
$^{13}$C (126 MHz, CDCl$_3$)
150.7
146.5
143.3
128.5
128.4
125.7
112.5
83.2
47.8
42.8
40.0
30.8
24.9
23.2
f1 (ppm)

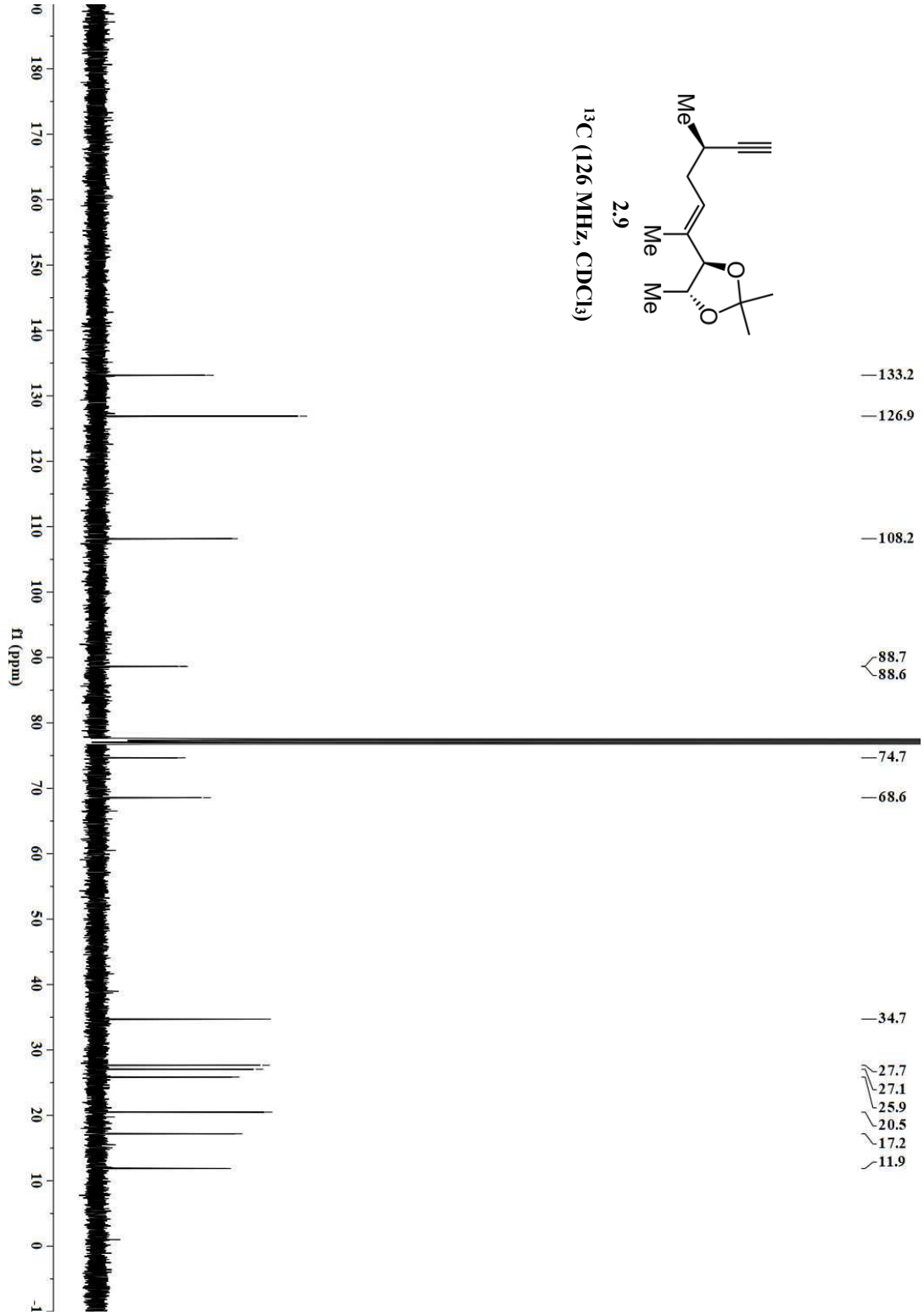

Me
B(pin)
2.116
$^1$H (400 MHz, CDCl$_3$)
f1 (ppm)
1.00
1.02
0.99
1.04
1.06
2.18
5.03
12.35
4.31
5.10
6.59
6.57
6.55
6.54
6.52
6.51
5.78
5.75
5.73
5.70
5.43
5.39
5.03
5.03
5.00
5.00
4.90
4.90
4.86
4.85
2.22
2.20
1.76
1.73
1.68
1.65
1.64
1.61
1.26
1.19
1.18
1.17
1.16
1.15
1.14
1.13
1.11
1.08
0.95
0.94
0.93
0.92
0.91

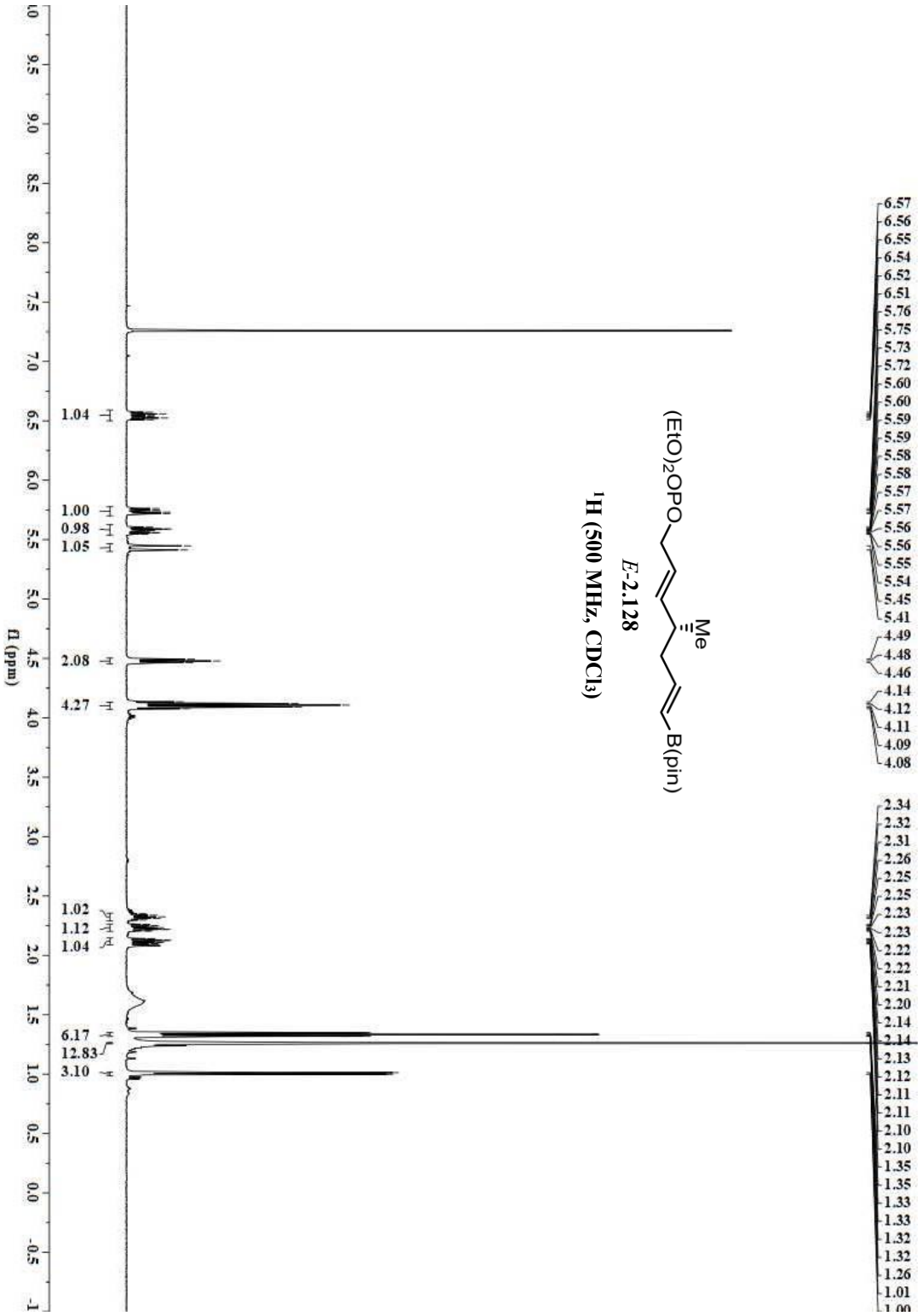

Me
B(pin)
2.116
$^{13}$C (101 MHz, CDCl$_3$)
f1 (ppm)
151.6
145.9
112.5
83.1
45.9
45.8
42.5
27.8
27.3
27.2
26.9
24.9
19.8

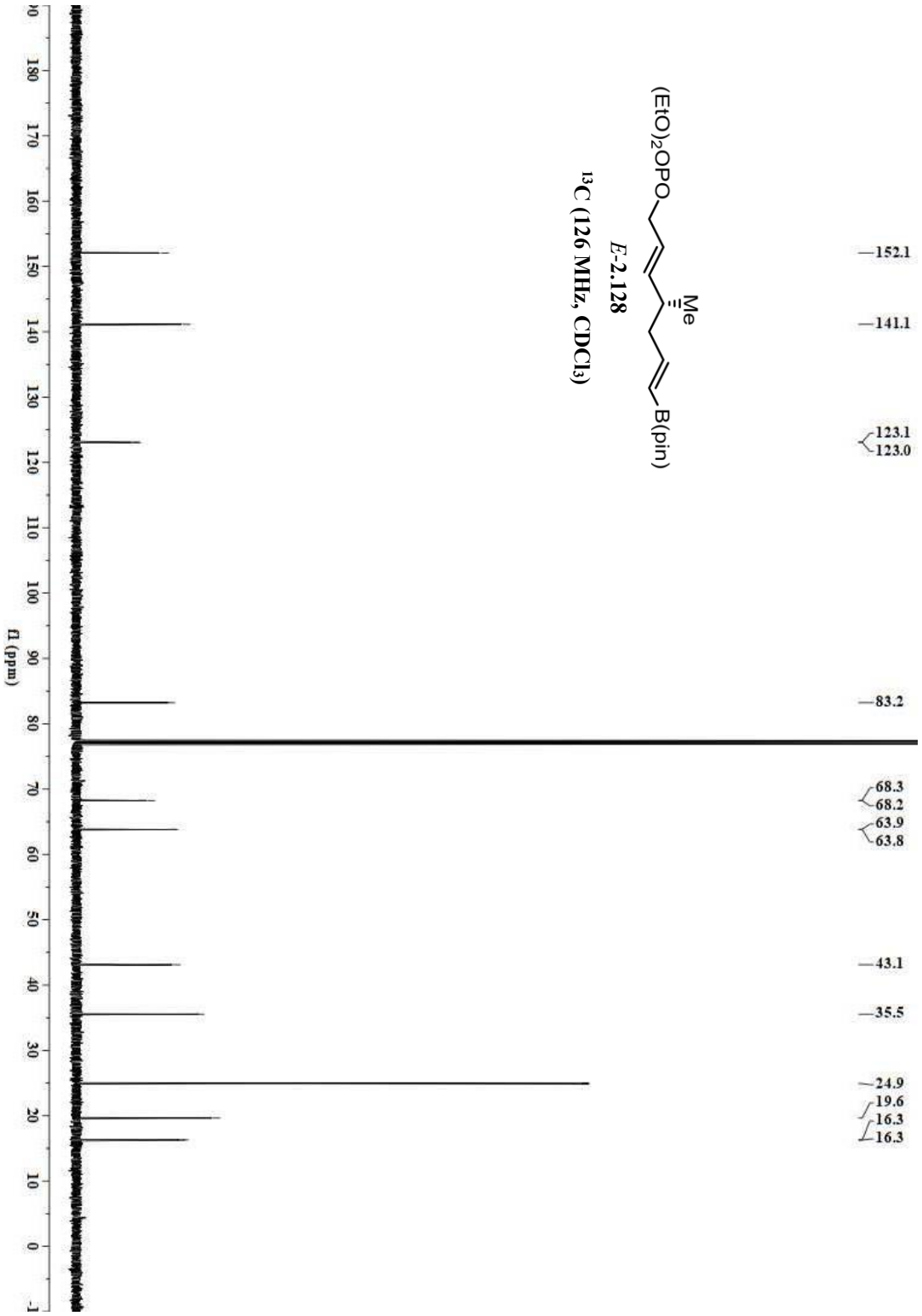

2.99
1H (600 MHz, CDCl3)
Me
Me
Me
O
O
f1 (ppm)
1.00
0.98
2.21
2.07
1.03
2.12
3.15
6.20
3.11
3.11
5.78
5.77
5.77
5.75
5.74
5.74
5.72
5.52
5.51
5.50
4.98
4.95
4.94
4.92
3.88
3.87
3.86
3.85
3.85
3.84
3.84
3.83
2.24
2.23
2.21
2.20
2.19
2.13
2.12
2.11
2.10
2.08
2.07
2.06
2.05
2.04
2.02
1.64
1.42
1.22
1.21
1.00
0.99

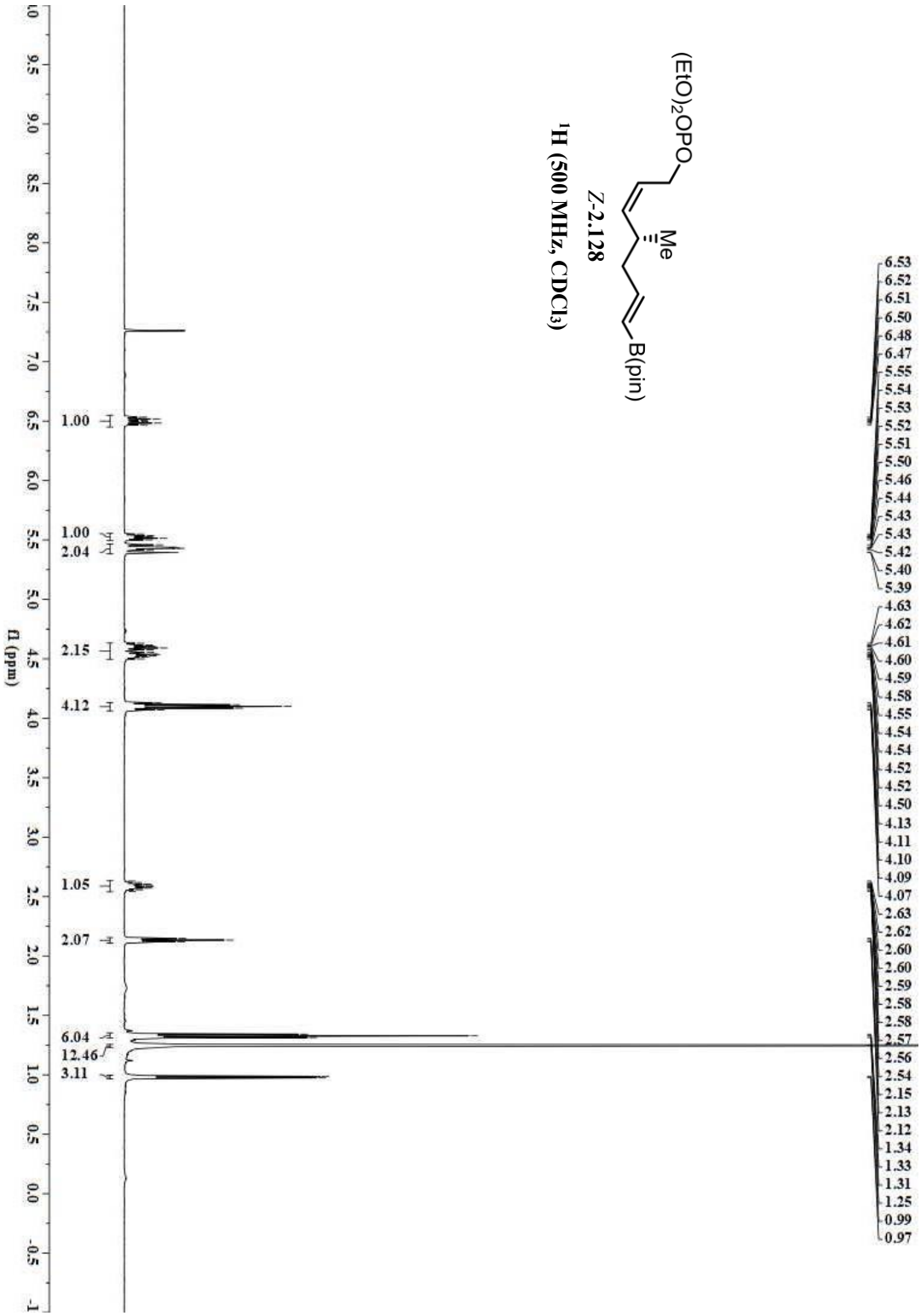

Me
Me
Me
O
O
2.99
$^{13}$C (151 MHz, CDCl$_3$)
f1 (ppm)
144.1
131.8
128.5
112.8
108.1
88.9
74.5
37.8
34.8
27.7
27.1
19.5
17.1
11.7

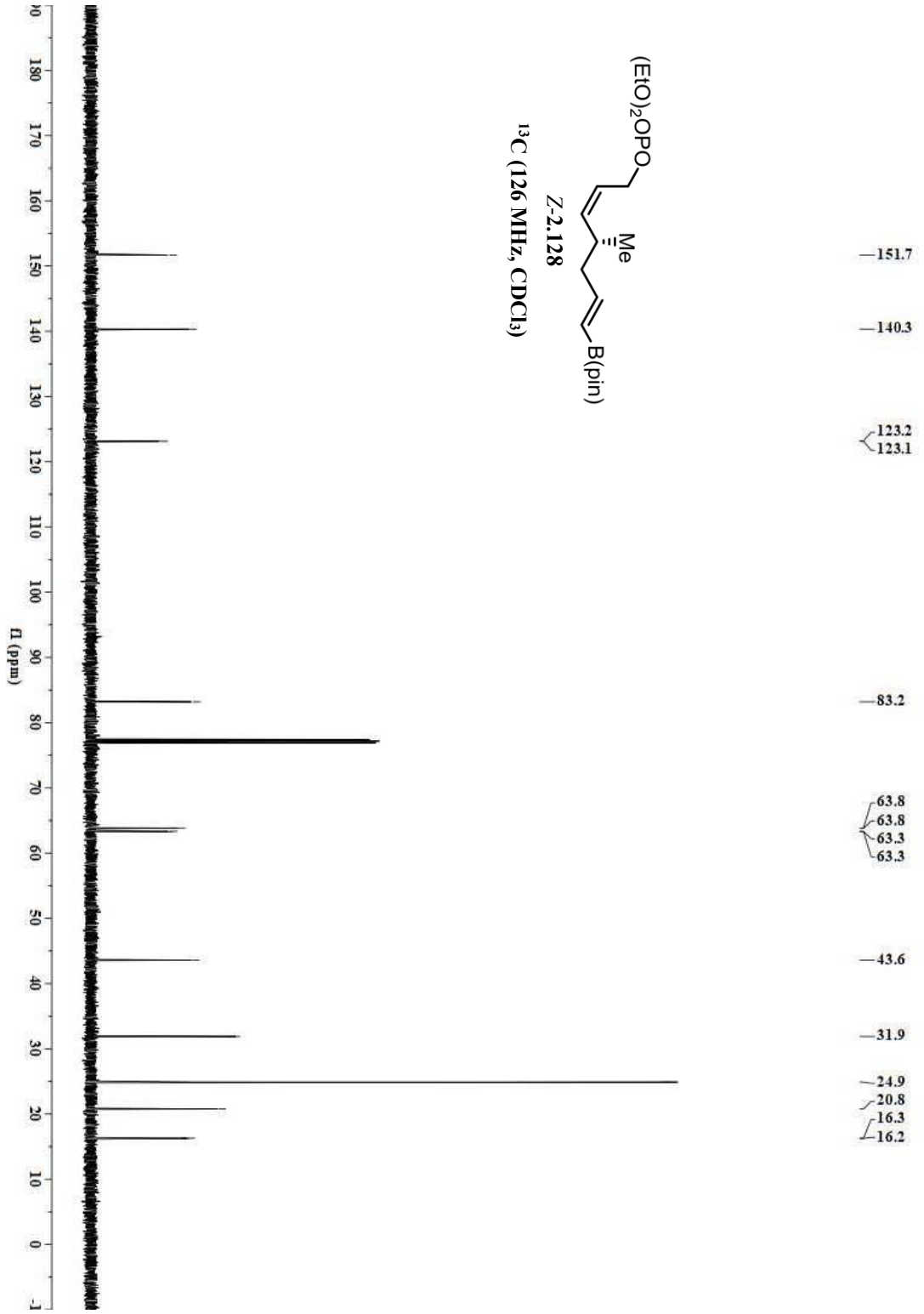

Me
Me
Me
O
O
2.9
$^1$H (600 MHz, CDCl$_3$)
f1 (ppm)
1.00
1.01
1.02
1.04
2.03
0.95
3.13
6.02
3.04
3.11
5.62
5.60
5.59
3.92
3.90
3.88
3.87
3.86
3.85
3.84
2.53
2.52
2.51
2.50
2.30
2.29
2.28
2.27
2.25
2.24
2.23
2.21
2.20
2.04
2.04
1.67
1.43
1.24
1.23
1.19
1.18

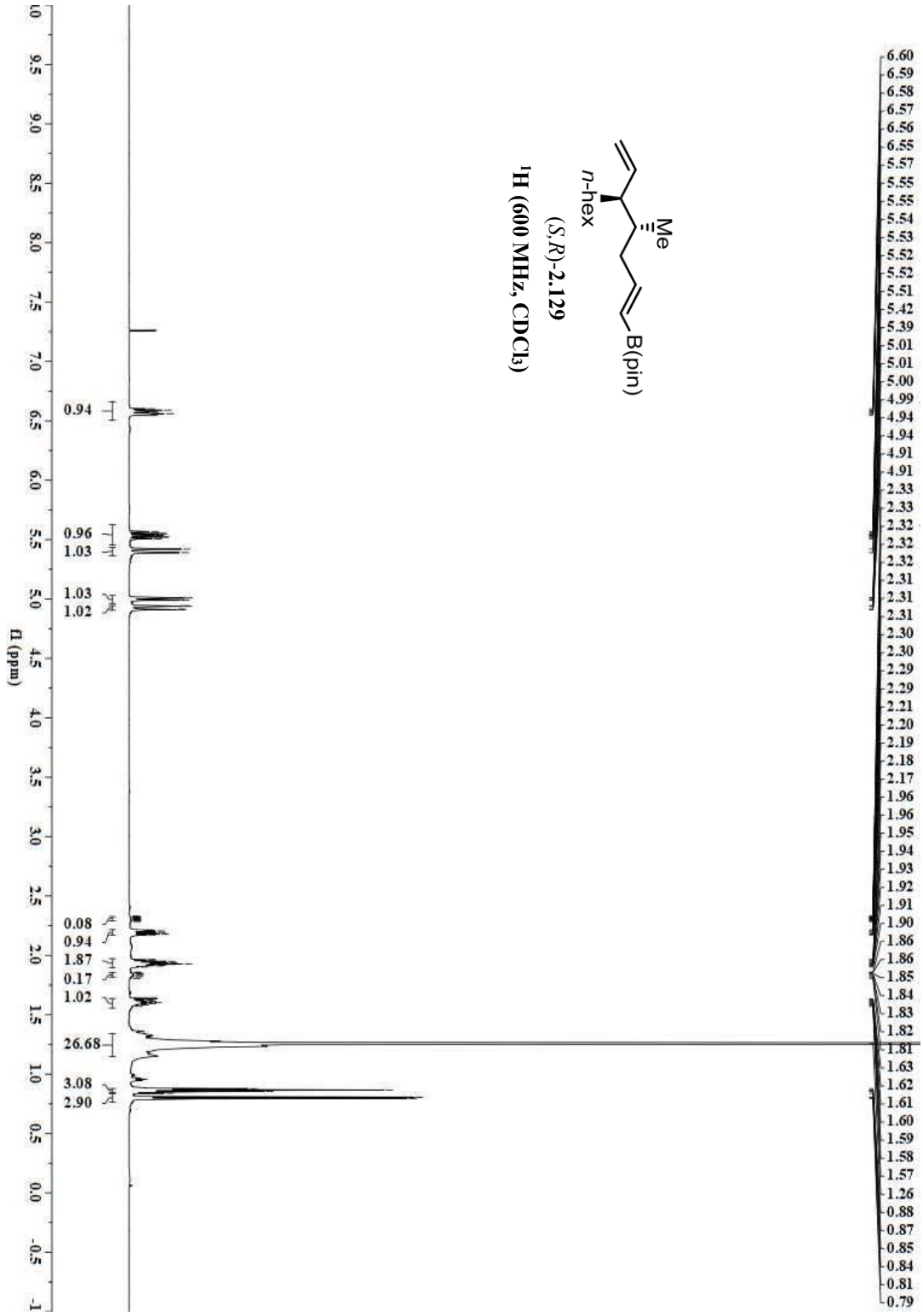

Me
Me
Me
O
O
2.9
$^{13}$C (126 MHz, CDCl$_3$)
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
133.2
126.9
108.2
88.7
88.6
74.7
68.6
34.7
27.7
27.1
25.9
20.5
17.2
11.9

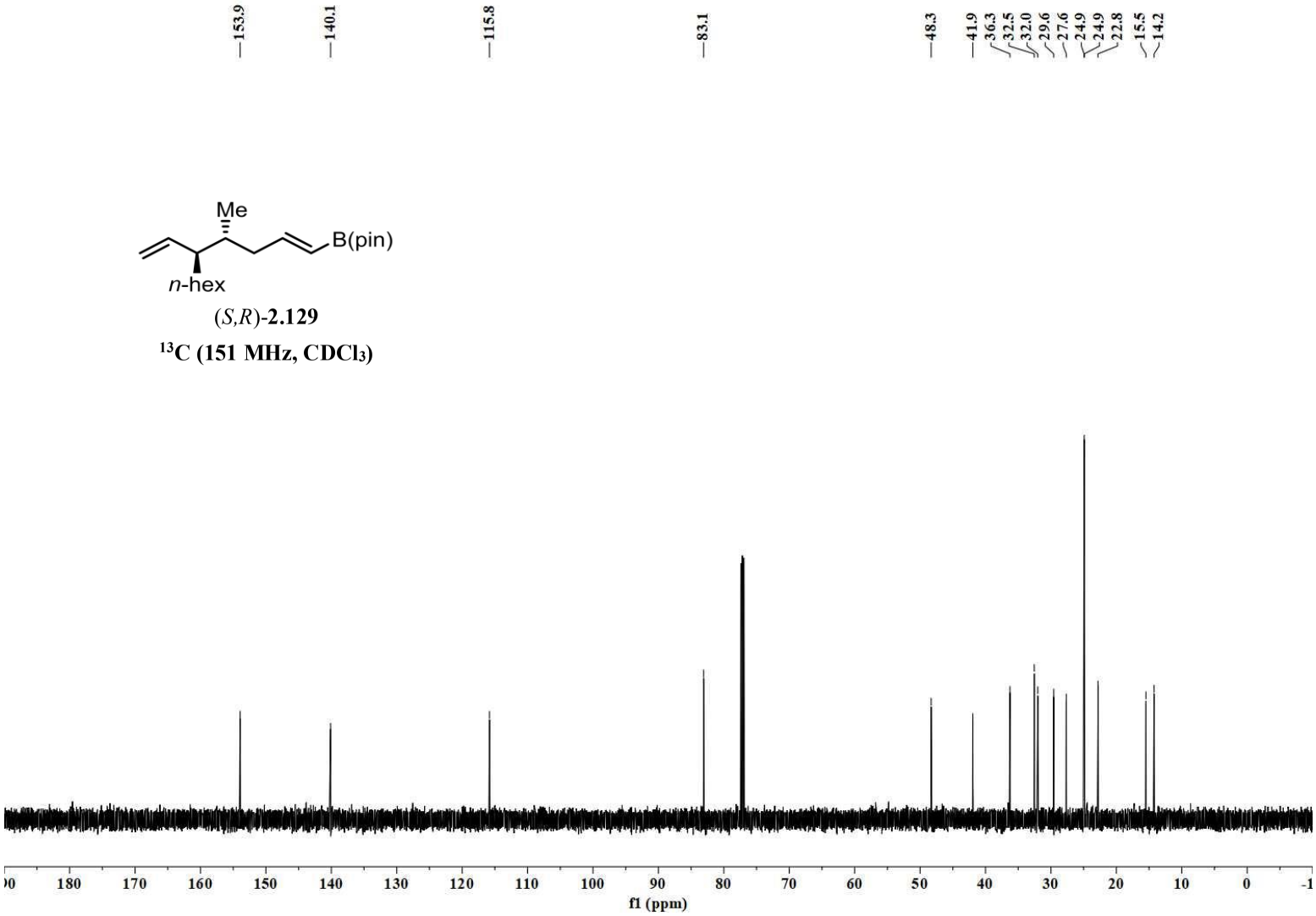

(EtO)2OPO
Me
B(pin)
E-2.128
1H (500 MHz, CDCl3)
f1 (ppm)
1.04
1.00
0.98
1.05
2.08
4.27
1.02
1.12
1.04
6.17
12.83
3.10


(EtO)2OPO
Me
B(pin)
E-2.128
13C (126 MHz, CDCl3)
f1 (ppm)
152.1
141.1
123.1
123.0
83.2
68.3
68.2
63.9
63.8
43.1
35.5
24.9
19.6
16.3
16.3


(EtO)2OPO
Me
B(pin)
Z-2.128
1H (500 MHz, CDCl3)
f1 (ppm)
1.00
1.00
2.04
2.15
4.12
1.05
2.07
6.04
12.46
3.11

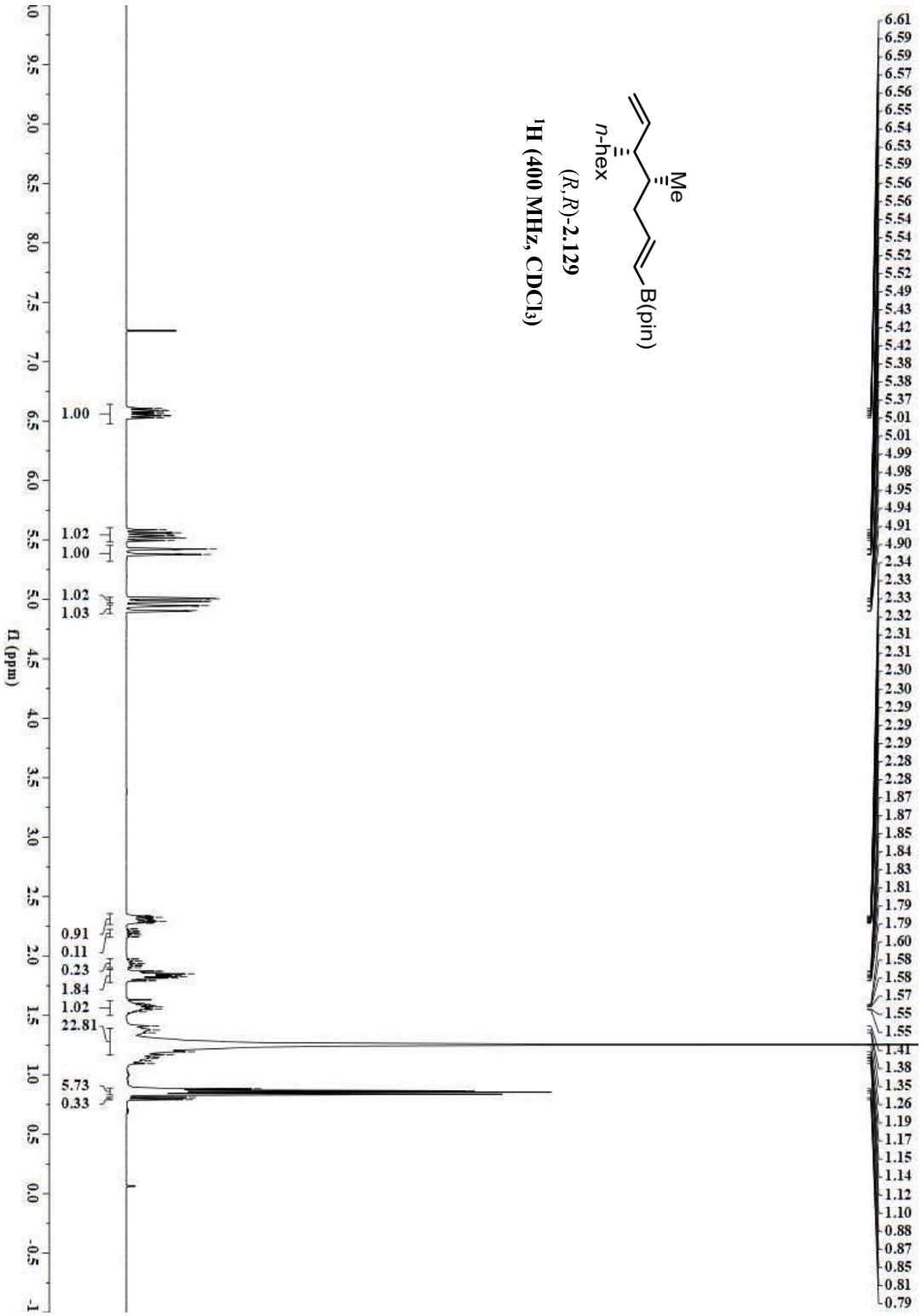

(EtO)2OPO
Me
B(pin)
Z-2.128
13C (126 MHz, CDCl3)
f1 (ppm)
151.7
140.3
123.2
123.1
83.2
63.8
63.8
63.3
63.3
43.6
31.9
24.9
20.8
16.3
16.2

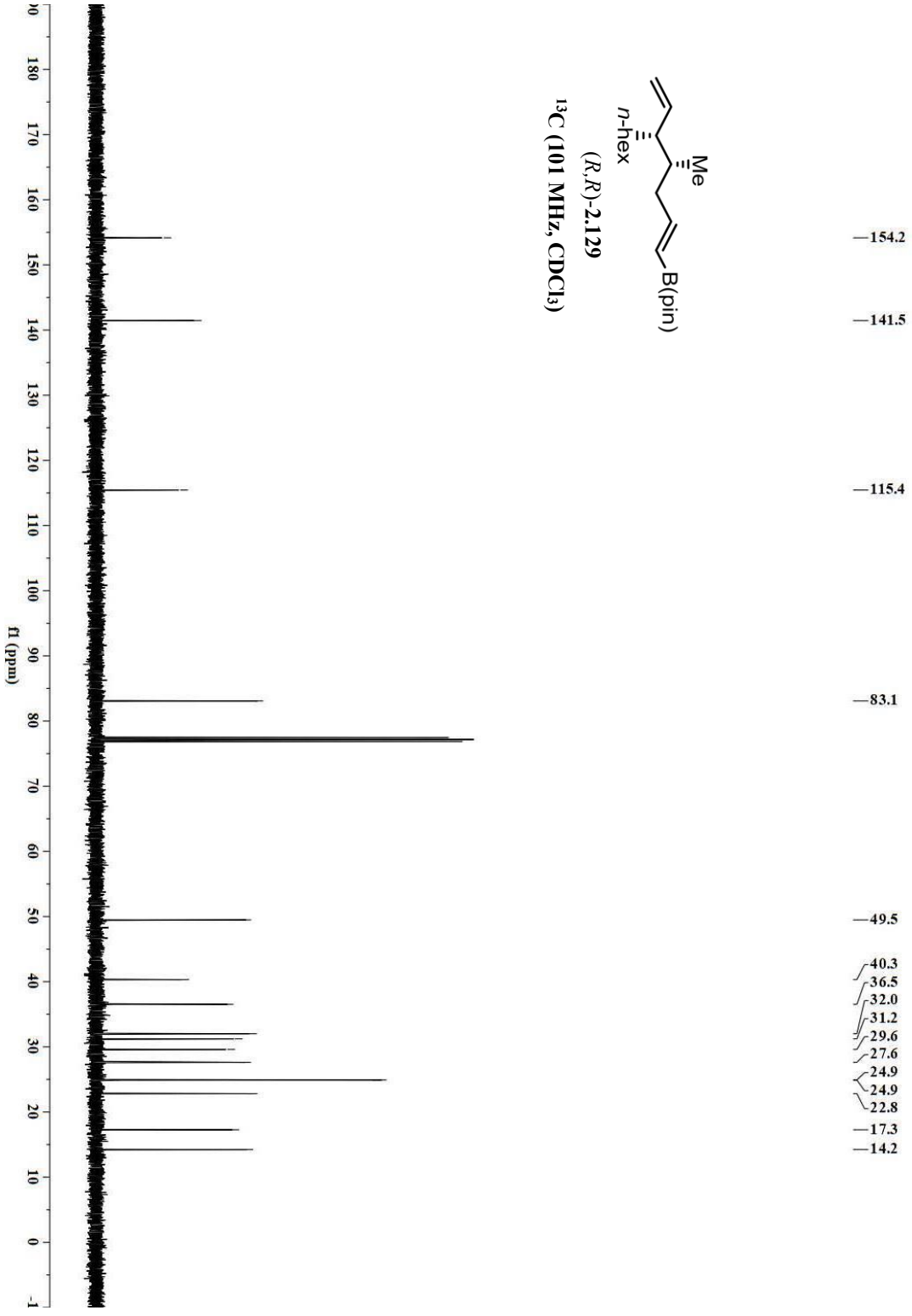

Me
n-hex
B(pin)
(S,R)-2.129
¹H (600 MHz, CDCl₃)
f1 (ppm)
0.94
0.96
1.03
1.03
1.02
0.08
0.94
1.87
0.17
1.02
26.68
3.08
2.90

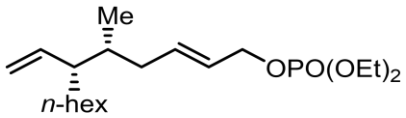



(*S,R*)-**2.129**

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

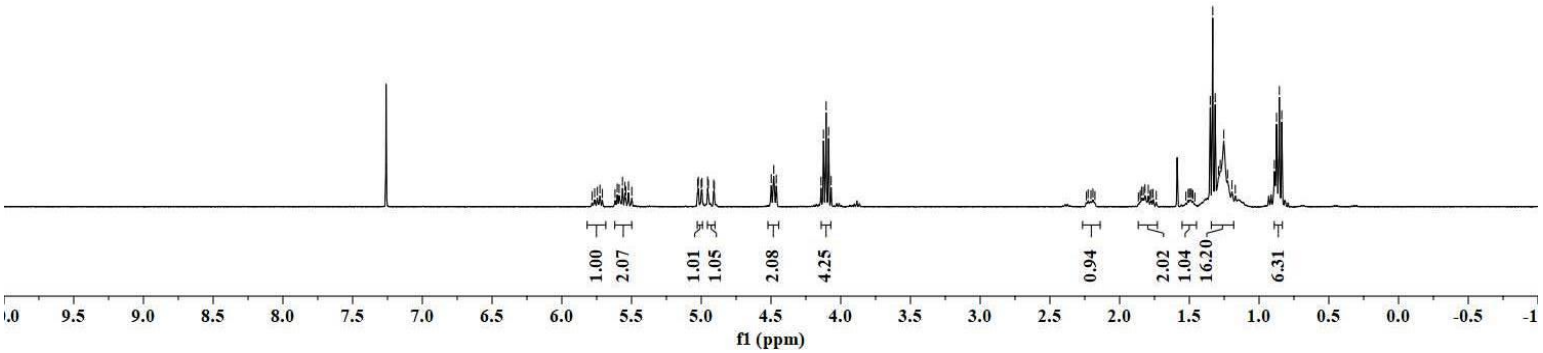

Me
n-hex
B(pin)
(R,R)-2.129
1H (400 MHz, CDCl3)
f1 (ppm)
1.00
1.02
1.00
1.02
1.03
0.91
0.11
0.23
1.84
1.02
22.81
5.73
0.33

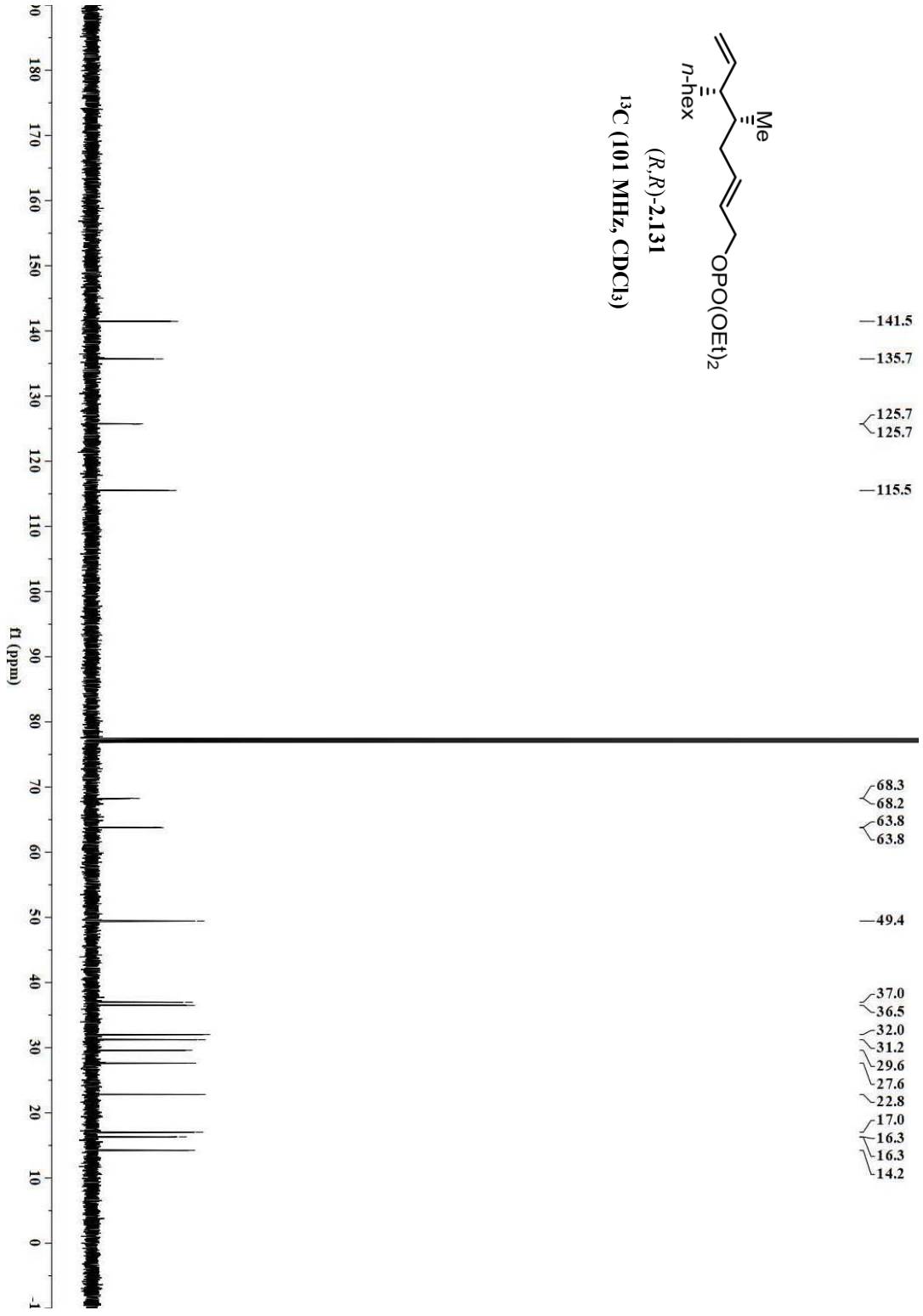

Me
n-hex
B(pin)
(R,R)-2.129
13C (101 MHz, CDCl3)
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
154.2
141.5
115.4
83.1
49.5
40.3
36.5
32.0
31.2
29.6
27.6
24.9
24.9
22.8
17.3
14.2

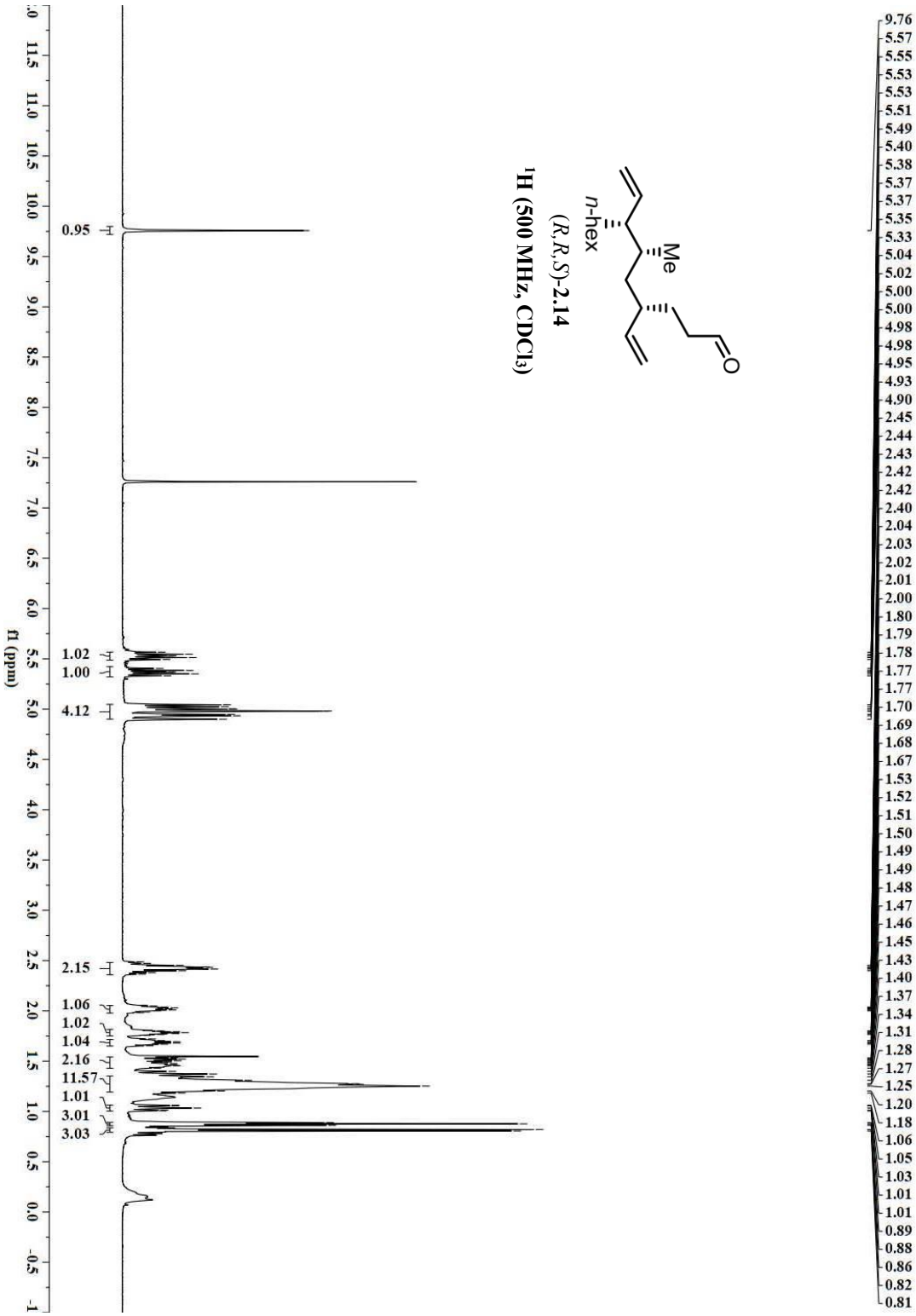



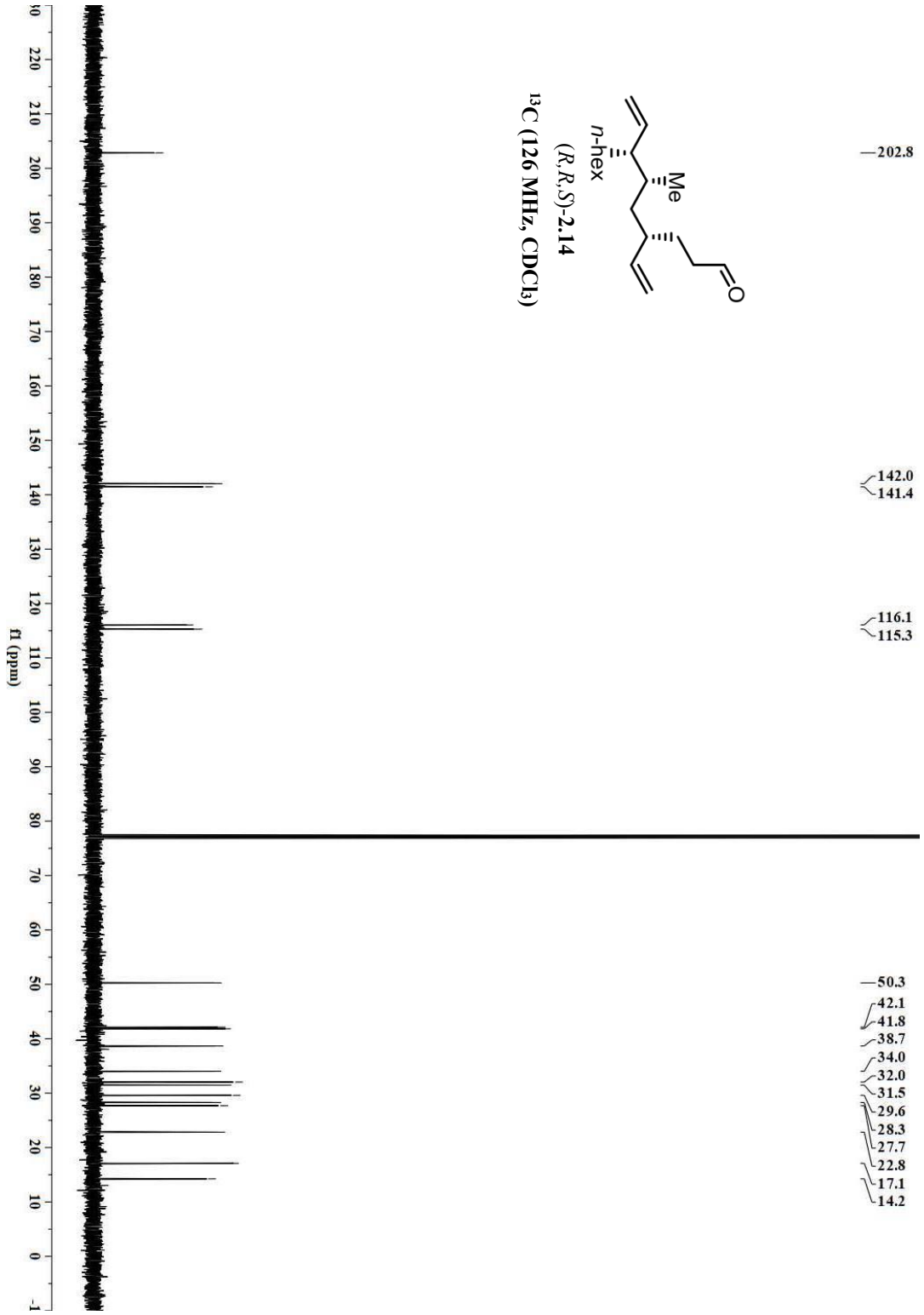

(*R,R*)-**2.131**

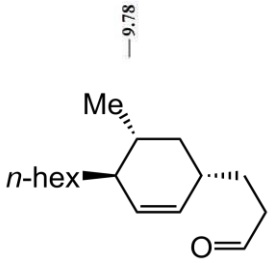
**$^1$H (400 MHz, CDCl$_3$)**




Me
n-hex
OPO(OEt)2
(R,R)-2.131
13C (101 MHz, CDCl3)
141.5
135.7
125.7
125.7
115.5
68.3
68.2
63.8
63.8
49.4
37.0
36.5
32.0
31.2
29.6
27.6
22.8
17.0
16.3
16.3
14.2
f1 (ppm)

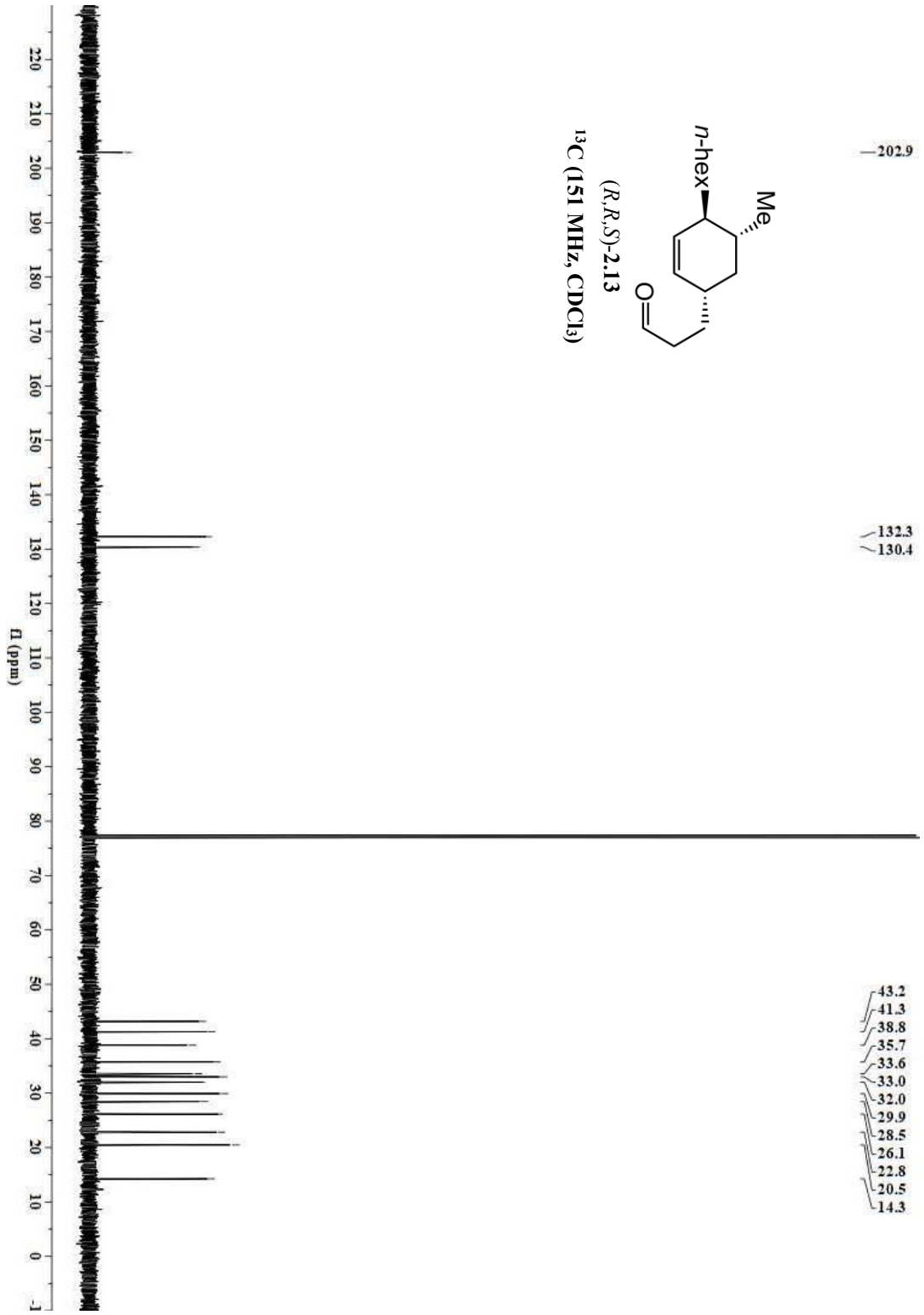

(R,R,S)-2.14
1H (500 MHz, CDCl3)
n-hex
Me
O
f1 (ppm)
0.95
1.02
1.00
4.12
2.15
1.06
1.02
1.04
2.16
11.57
1.01
3.01
3.03

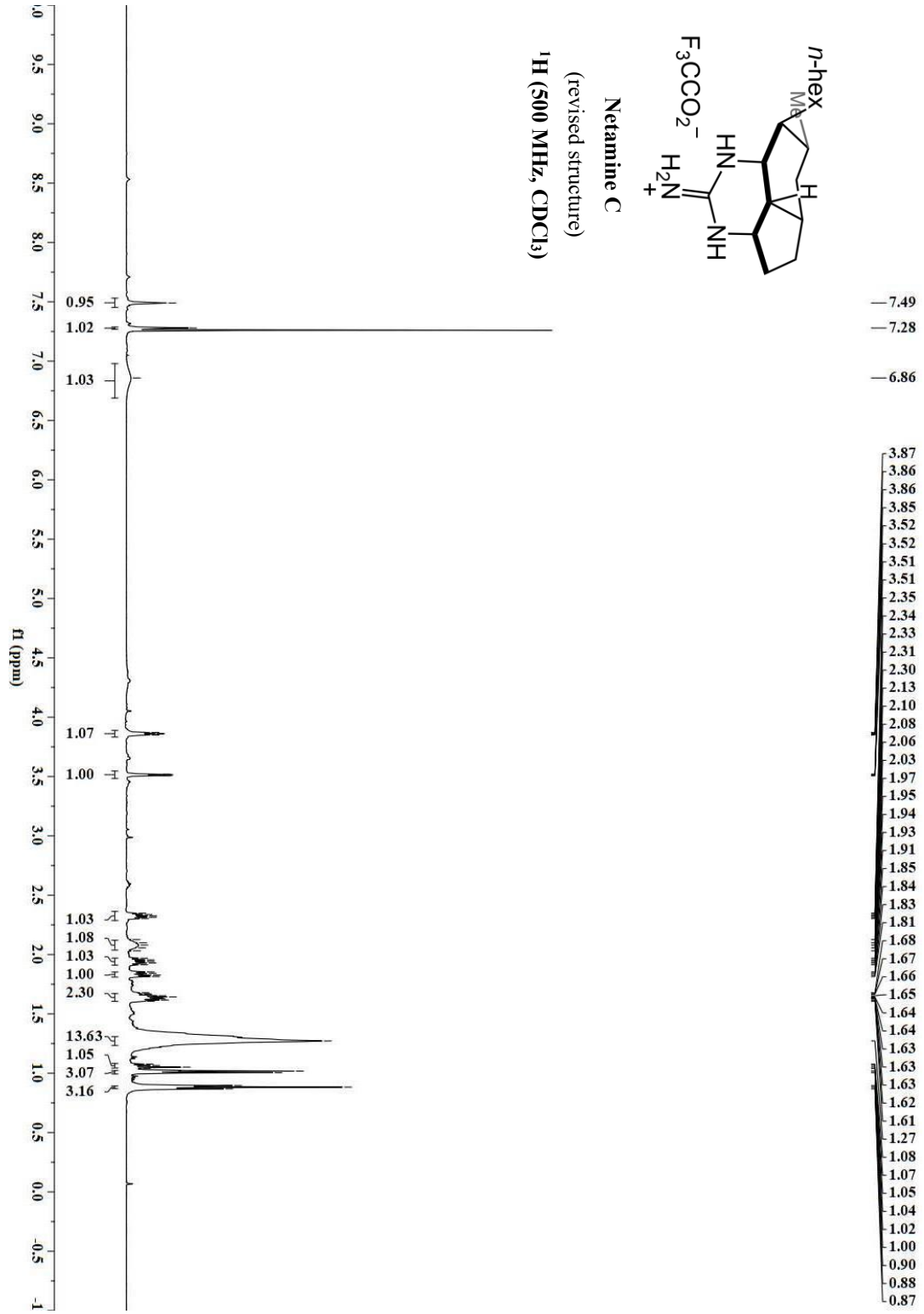

(R,R,S)-2.14
13C (126 MHz, CDCl3)
Me
n-hex
O
202.8
142.0
141.4
116.1
115.3
50.3
42.1
41.8
38.7
34.0
32.0
31.5
29.6
28.3
27.7
22.8
17.1
14.2
f1 (ppm)

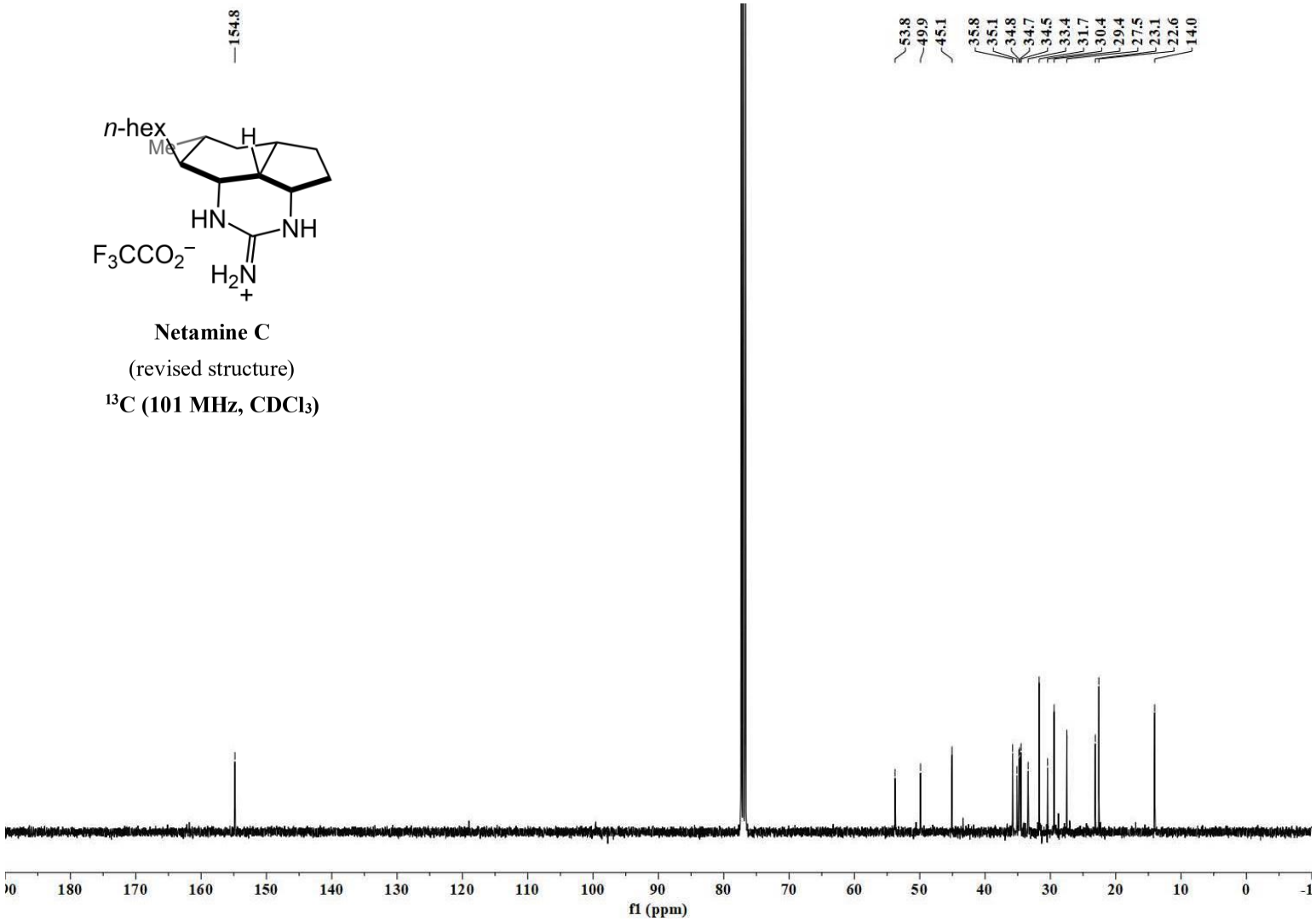



(*R,R,S*)-**2.13**

**$^1$H (600 MHz, $CDCl_3$)**


Me
n-hex
O
(R,R,S)-2.13
13C (151 MHz, CDCl3)
202.9
132.3
130.4
43.2
41.3
38.8
35.7
33.6
33.0
32.0
29.9
28.5
26.1
22.8
20.5
14.3
f1 (ppm)

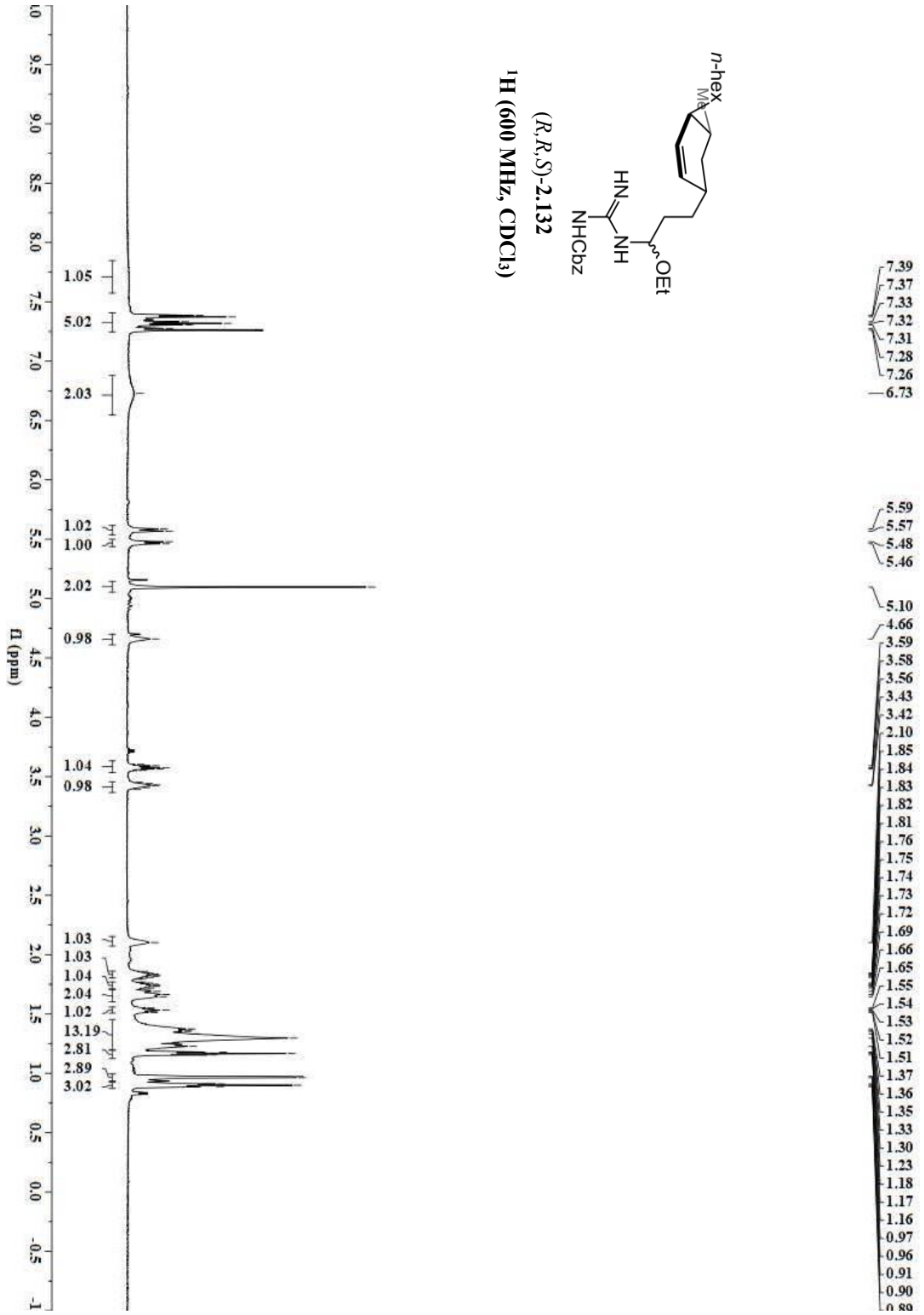

Netamine C
(revised structure)
¹H (500 MHz, CDCl₃)
n-hex
Me
HN
NH
H
H₂N
+
F₃CCO₂⁻
f1 (ppm)
0.95
1.02
1.03
1.07
1.00
1.03
1.08
1.03
1.00
2.30
13.63
1.05
3.07
3.16
7.49
7.28
6.86
3.87
3.86
3.86
3.85
3.52
3.52
3.51
3.51
2.35
2.34
2.33
2.31
2.30
2.13
2.10
2.08
2.06
2.03
1.97
1.95
1.94
1.93
1.91
1.85
1.84
1.83
1.81
1.68
1.67
1.66
1.65
1.64
1.64
1.63
1.63
1.63
1.62
1.61
1.27
1.08
1.07
1.05
1.04
1.02
1.00
0.90
0.88
0.87

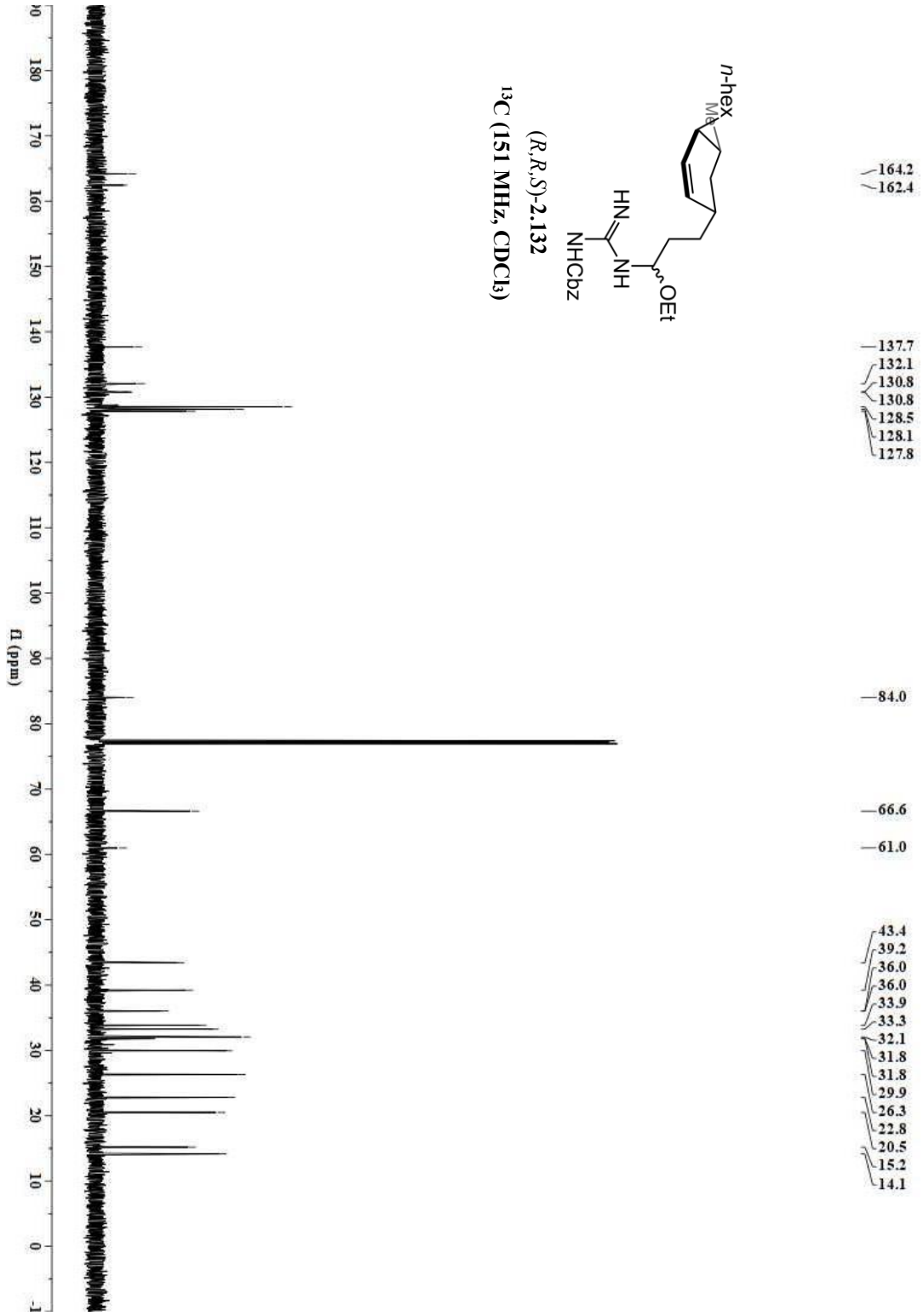


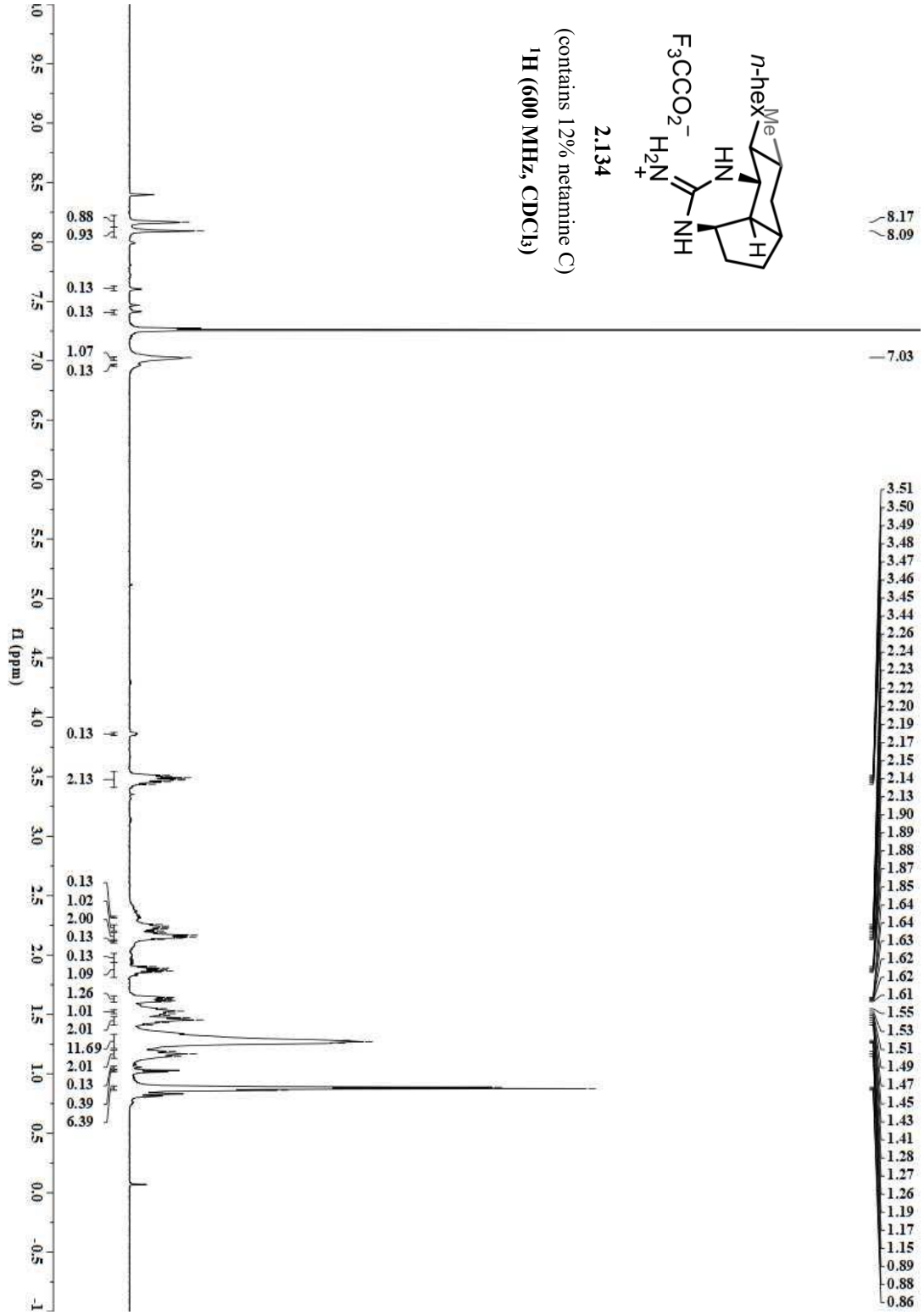

**Netamine C**

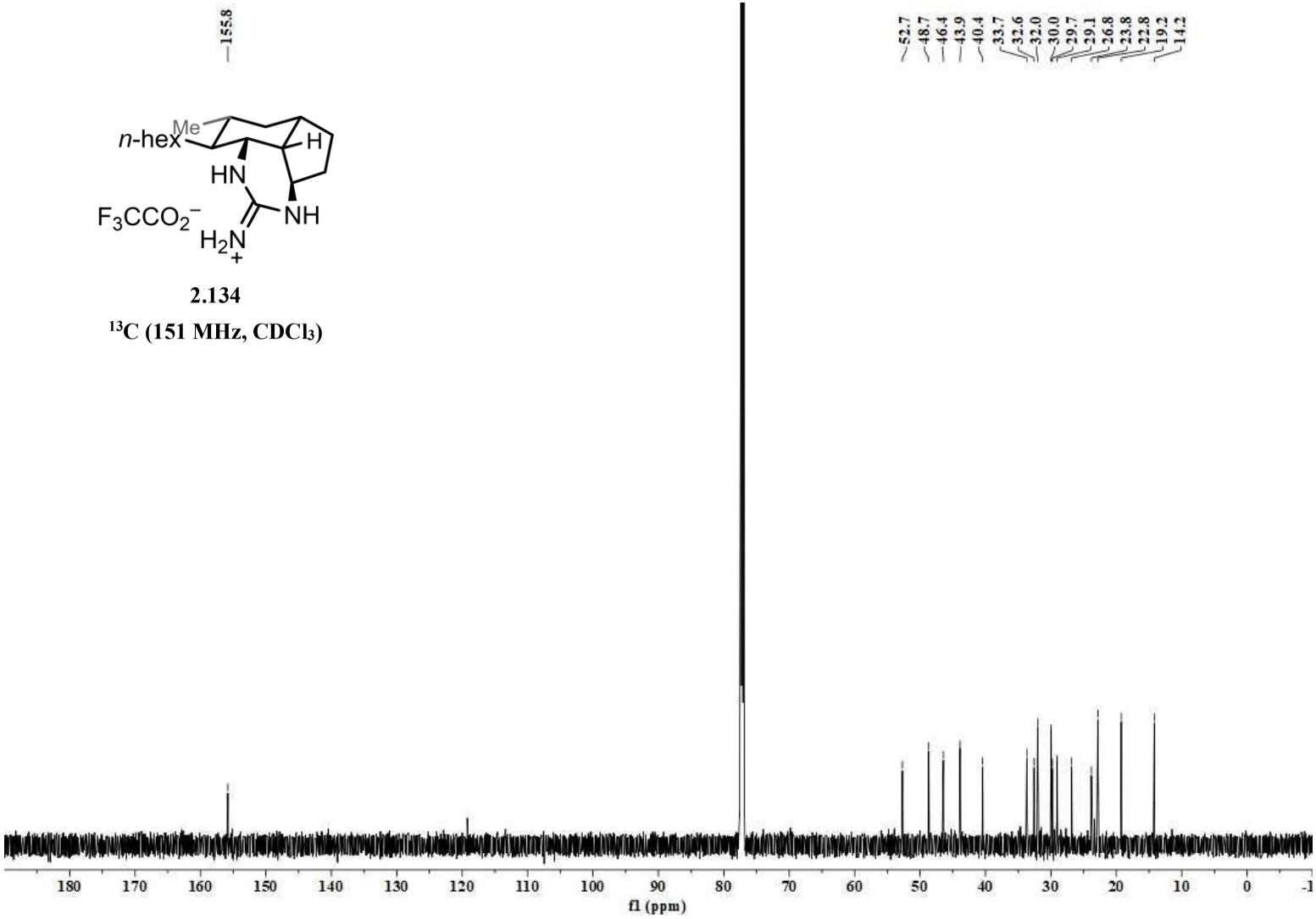
(revised structure)

**$^{13}$C (101 MHz, $CDCl_3$)**


n-hex
Me
HN
NH
NHCbz
OEt
(R,R,S)-2.132
¹H (600 MHz, CDCl₃)
f1 (ppm)
1.05
5.02
2.03
1.02
1.00
2.02
0.98
1.04
0.98
1.03
1.03
1.04
2.04
1.02
13.19
2.81
2.89
3.02
7.39
7.37
7.33
7.32
7.31
7.28
7.26
6.73
5.59
5.57
5.48
5.46
5.10
4.66
3.59
3.58
3.56
3.43
3.42
2.10
1.85
1.84
1.83
1.82
1.81
1.76
1.75
1.74
1.73
1.72
1.69
1.66
1.65
1.55
1.54
1.53
1.52
1.51
1.37
1.36
1.35
1.33
1.30
1.23
1.18
1.17
1.16
0.97
0.96
0.91
0.90
0.89

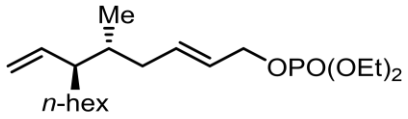

(R,R,S)-2.132
13C (151 MHz, CDCl3)
n-hex
Me
HN
NH
NHCbz
OEt
164.2
162.4
137.7
132.1
130.8
130.8
128.5
128.1
127.8
84.0
66.6
61.0
43.4
39.2
36.0
36.0
33.9
33.3
32.1
31.8
31.8
29.9
26.3
22.8
20.5
15.2
14.1
f1 (ppm)


n-hex
Me
HN
H
F3CCO2−
H2N+
NH
2.134
(contains 12% netamine C)
1H (600 MHz, CDCl3)
f1 (ppm)
8.17
8.09
7.03
3.51
3.50
3.49
3.48
3.47
3.46
3.45
3.44
2.26
2.24
2.23
2.22
2.20
2.19
2.17
2.15
2.14
2.13
1.90
1.89
1.88
1.87
1.85
1.64
1.64
1.63
1.62
1.62
1.61
1.55
1.53
1.51
1.49
1.47
1.45
1.43
1.41
1.28
1.27
1.26
1.19
1.17
1.15
0.89
0.88
0.86
0.88
0.93
0.13
0.13
1.07
0.13
0.13
2.13
0.13
1.02
2.00
0.13
0.13
1.09
1.26
1.01
2.01
11.69
2.01
0.13
0.39
6.39



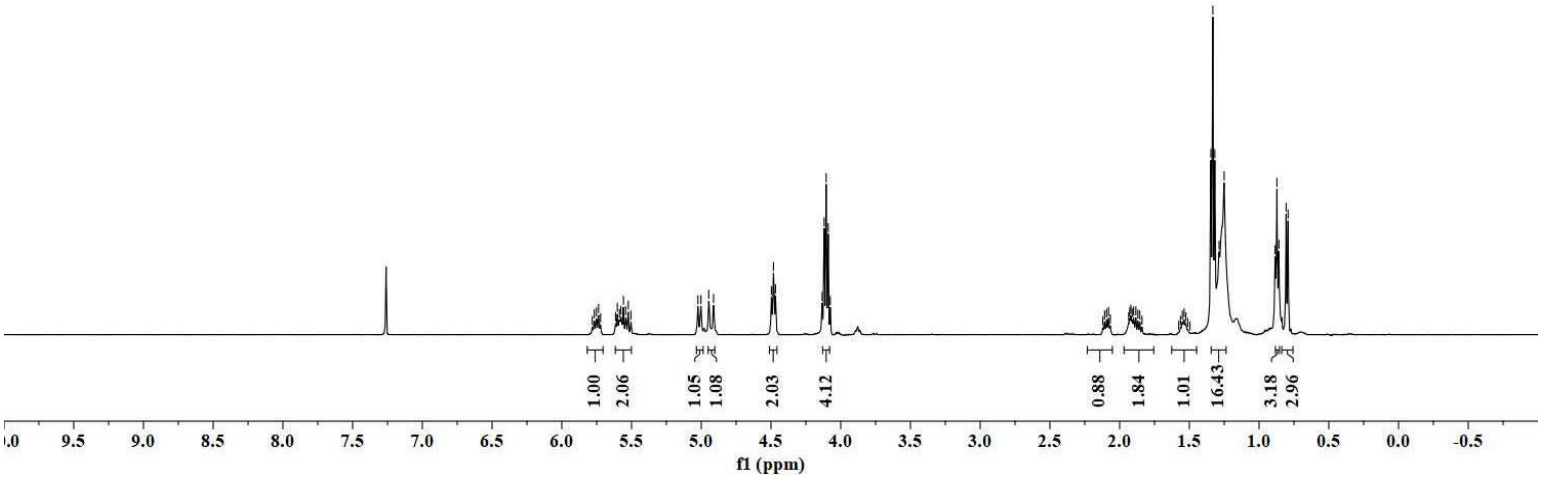

**2.134**

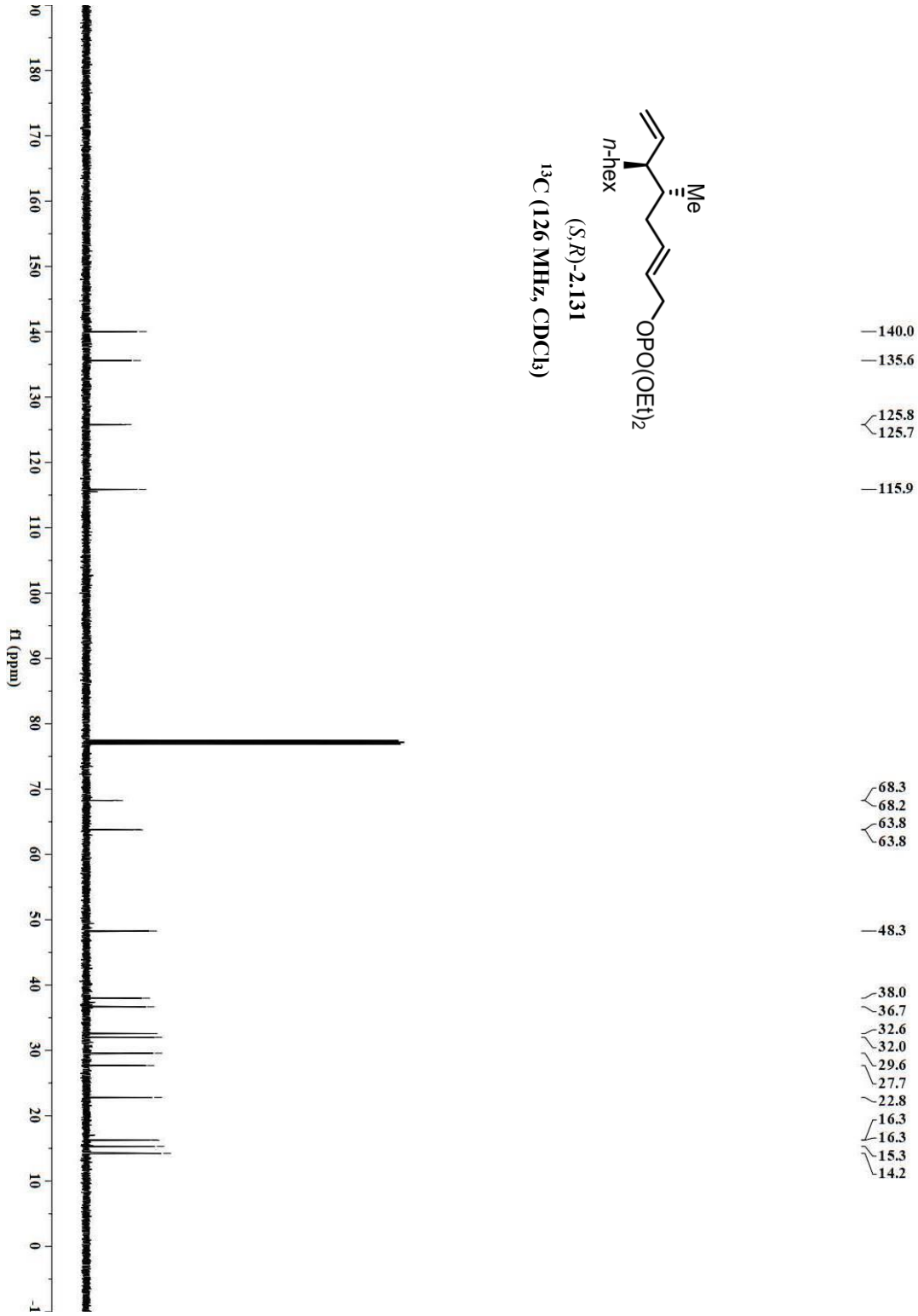
**$^{13}$C (151 MHz, $CDCl_3$)**

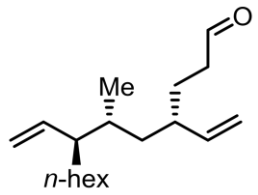




(*S,R*)-**2.131**

**$^1$H (500 MHz, $CDCl_3$)**

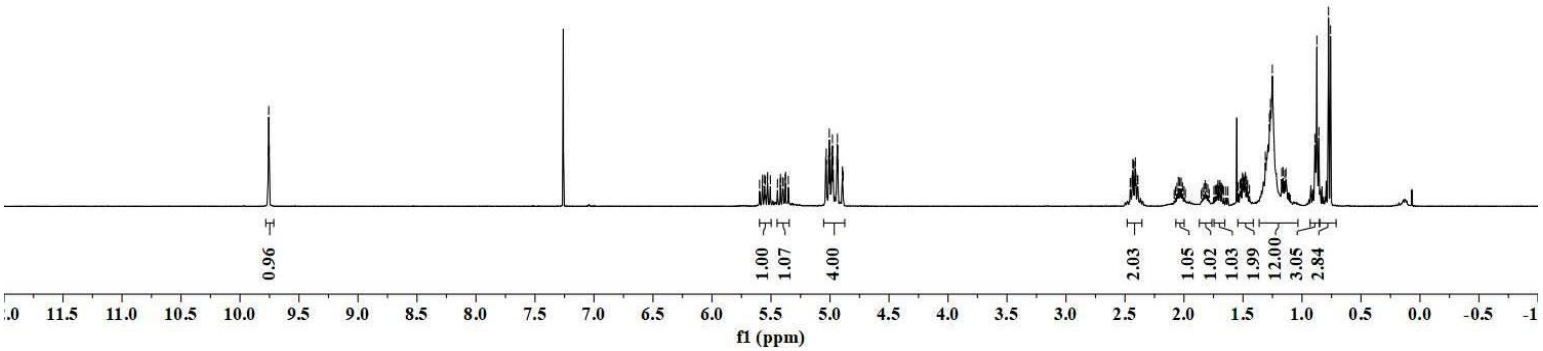


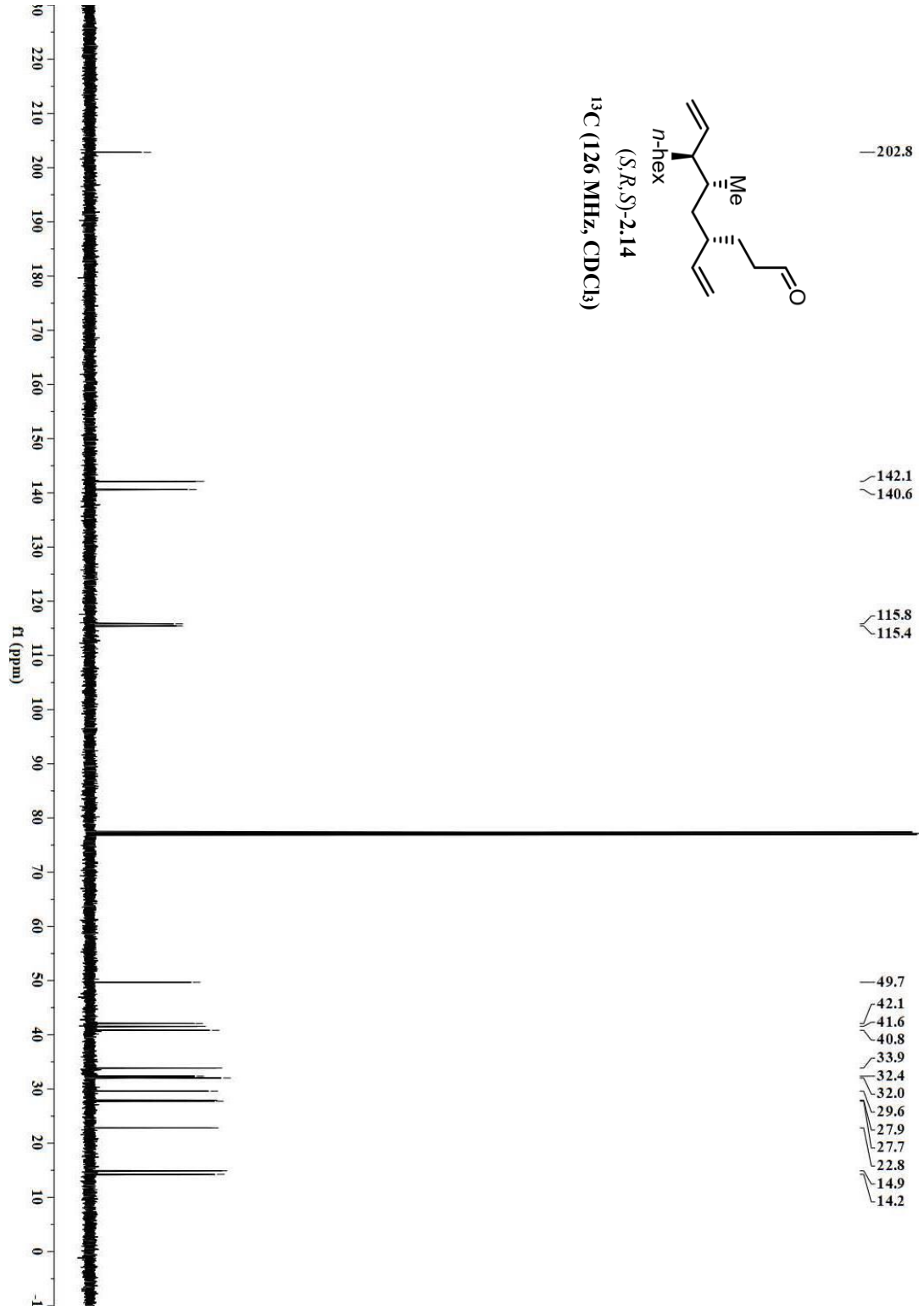

Me
n-hex
OPO(OEt)2
(S,R)-2.131
13C (126 MHz, CDCl3)
140.0
135.6
125.8
125.7
115.9
68.3
68.2
63.8
63.8
48.3
38.0
36.7
32.6
32.0
29.6
27.7
22.8
16.3
16.3
15.3
14.2
f1 (ppm)

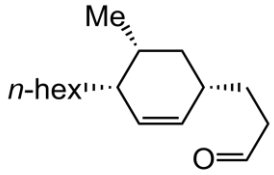




(*S,R,S*)-**2.14**

**$^1$H (400 MHz, CDCl$_3$)**

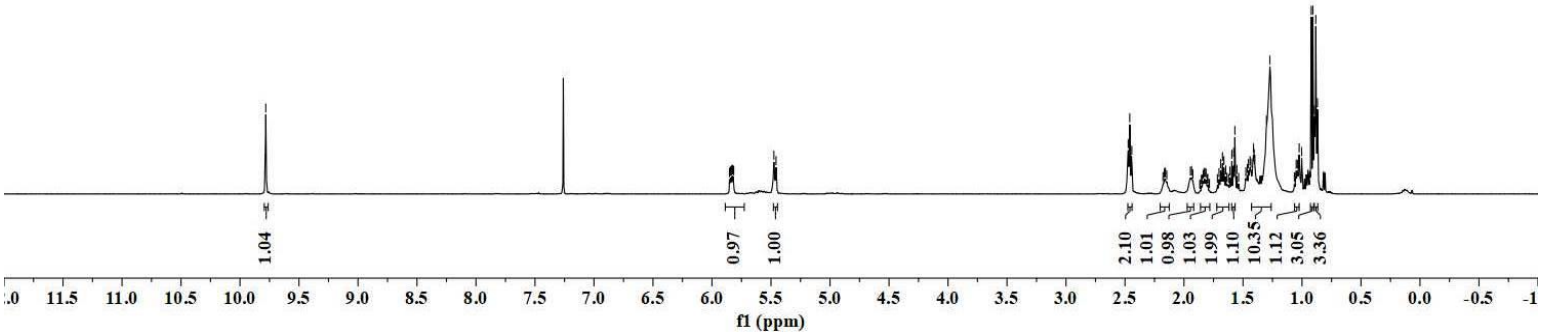


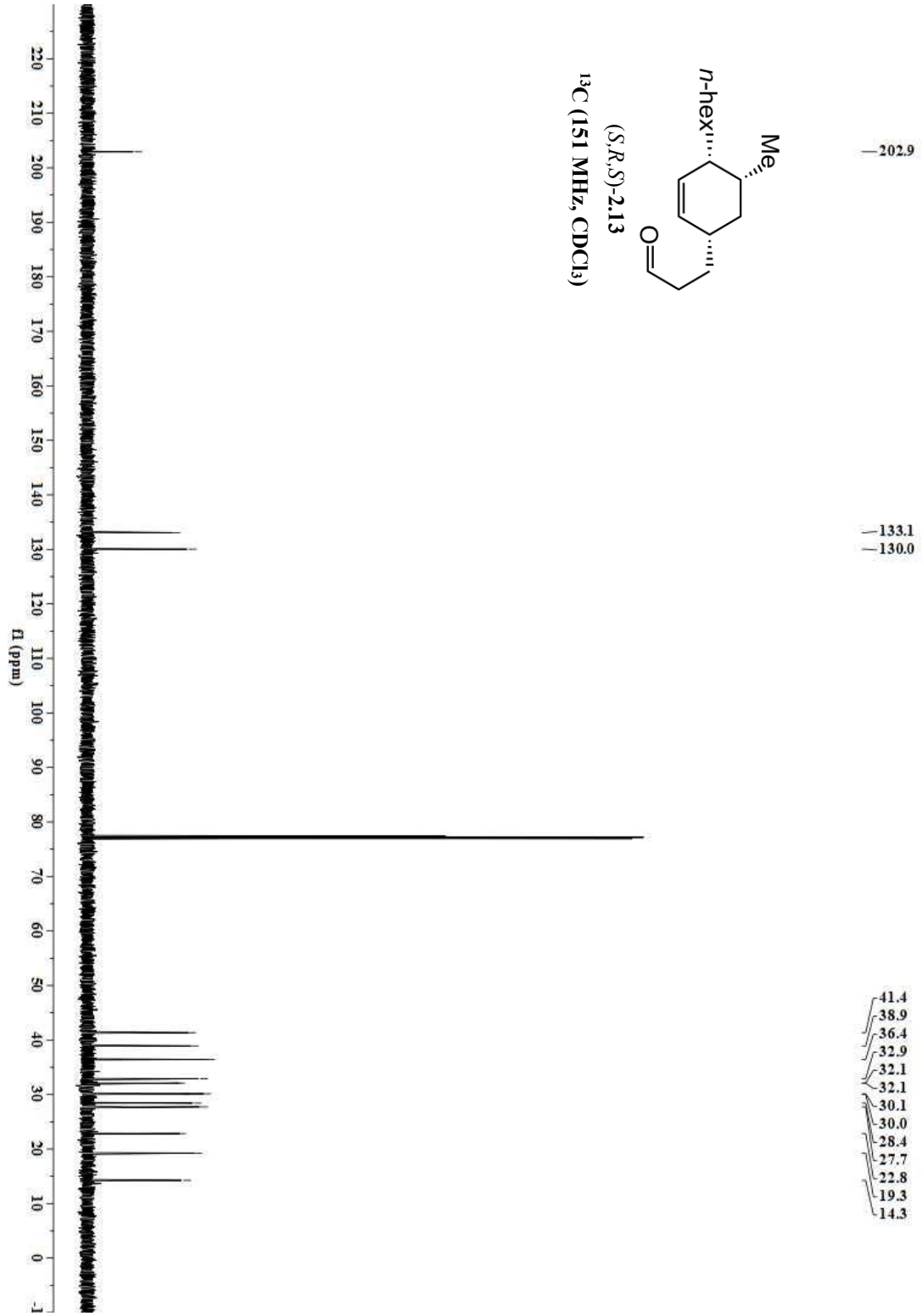

(S,R,S)-2.14
13C (126 MHz, CDCl3)
n-hex
Me
O
202.8
142.1
140.6
115.8
115.4
49.7
42.1
41.6
40.8
33.9
32.4
32.0
29.6
27.9
27.7
22.8
14.9
14.2
f1 (ppm)

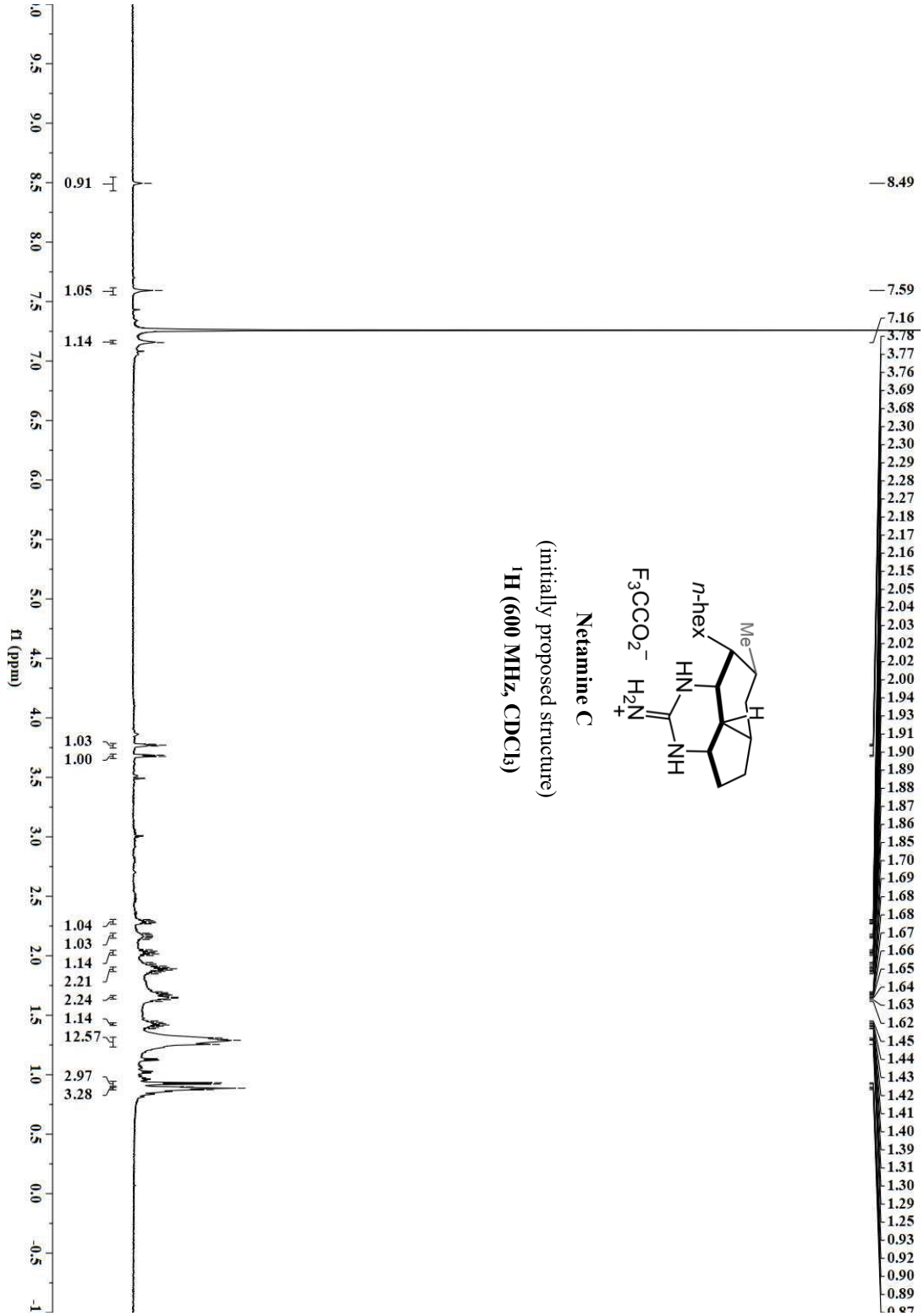




(*S,R,S*)-**2.13**

**$^1$H (400 MHz, CDCl$_3$)**



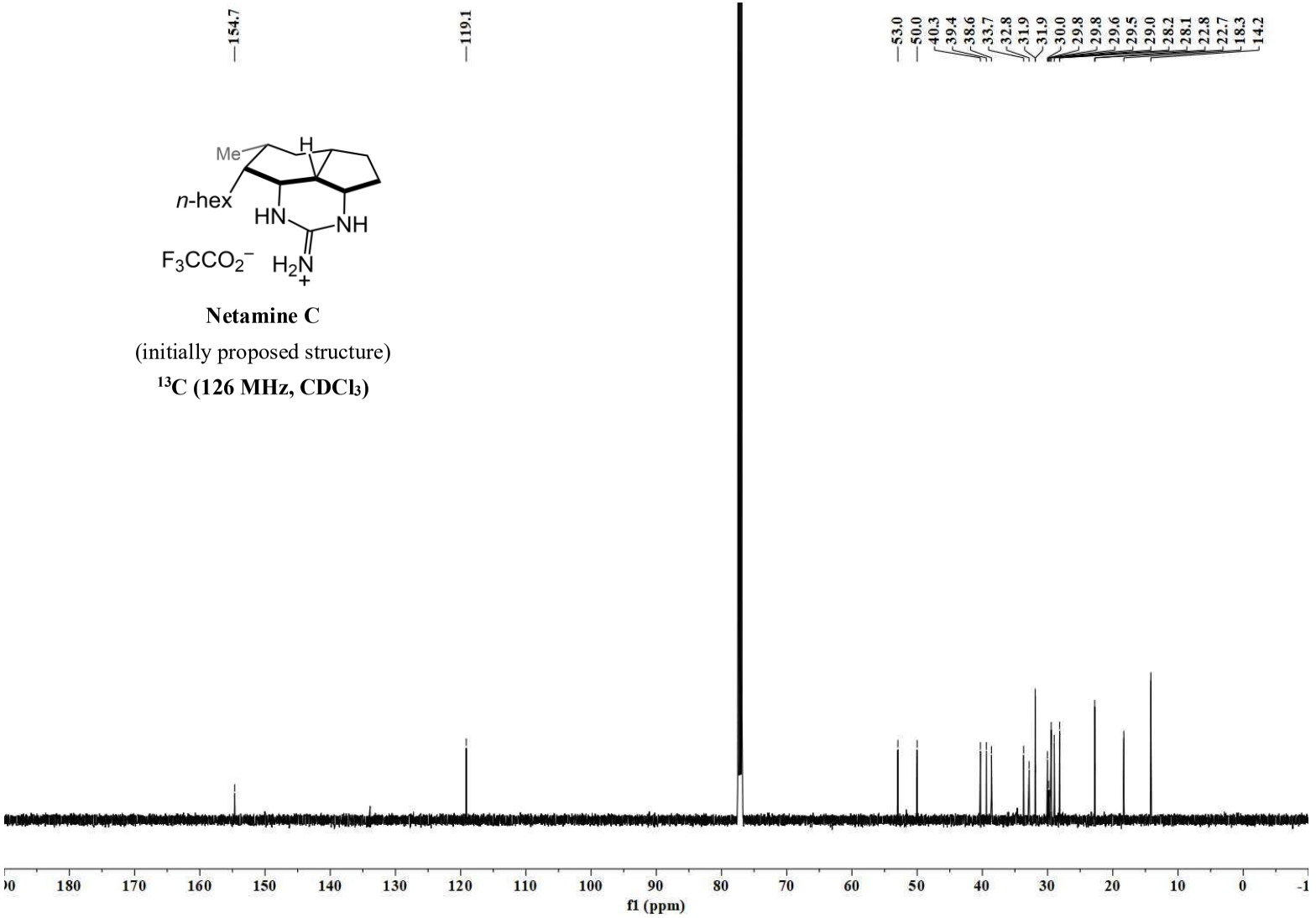

Me
n-hex
O
(S,R,S)-2.13
13C (151 MHz, CDCl3)
202.9
133.1
130.0
41.4
38.9
36.4
32.9
32.1
32.1
30.1
30.0
28.4
27.7
22.8
19.3
14.3
f1 (ppm)




**Netamine C**

(initially proposed structure)

**$^1$H (600 MHz, $CDCl_3$)**




**Netamine C**

(initially proposed structure)

**$^{13}$C (126 MHz, $CDCl_3$)**

# CHAPTER 3

# Catalytic Enantioselective Prenyl Conjugate Addition Reactions

## 3.1 Introduction

The prenyl moiety is found in a great number of biologically active and medicinally relevant compounds (Scheme 3.1),[1] and is the major component in the biosynthesis of terpenoid species.[2] What is more, functionalization of a prenyl moiety allows access a variety of potentially valuable derivatives. A direct method for synthesis of such entities would be through catalytic enantioselective conjugate prenyl addition. Catalytic enantioselective conjugate addition (ECA) reactions have been the subject of intense scrutiny during the past two decades. Nonetheless, the existing protocols have been confined to additions of simple alkyl units.[3] Additions of alkenyl[4] or aryl[5] moieties often require precious metal salts (e.g., Rh-based), and only more recently have Cu-

(1) Li, S. *Nat. Prod. Rep*. **2010**, *27*, 57−78.

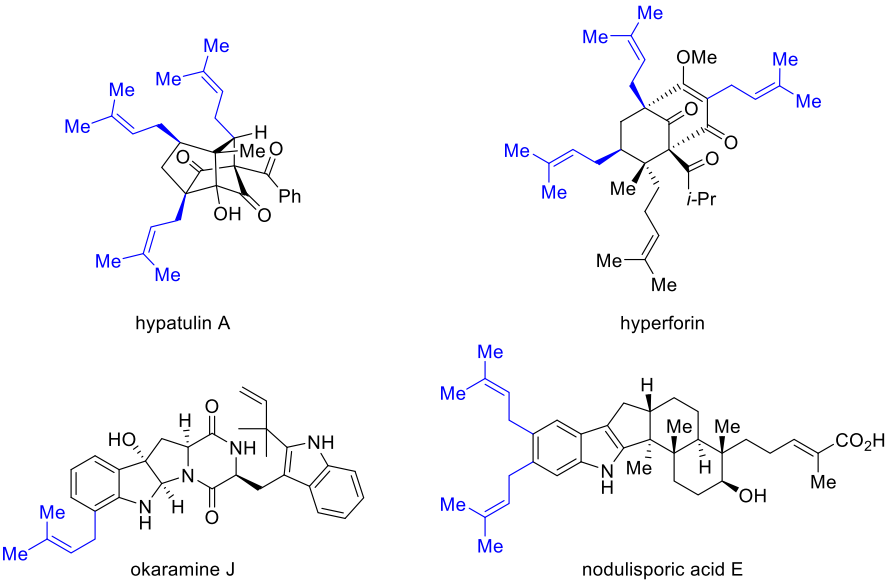
(2) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem*. **2000**, *209*, 97−173.

(3) For recent reviews on Cu-based complex catalyzed enantioselective conjugate additions, see: (a) *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A.; Krause, N.; Woodward, S.Eds; VCo: Weinheim, 2004, pp 33−68. (b) *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCo: Weinheim, Germany, 2010; pp 71−168. (c) Wang, S.-Y.; Loh, T.-P. *Chem. Commun*. **2009**, *46*, 8694−8703. (d) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev*. **2008**, *108*, 2824−2852. (e) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res*. **2007**, *40*, 179−188. (f) Alexakis, A.; Ba¨ kwall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796−2823. (g) Christoffers, J.; Koripelly, G.; Rösiak, A.; Rossle, M. *Synthesis* **2007**, 1279−1300. (h) von Zezschwitz, P. *Synthesis* **2008**, 1809−1831.

(4) Müller, D.; Alexakis, A. *Chem. Commun*., **2012**, *48*, 12037–12049.

(5) (a) Hayashi, T. *Synlett*, **2001**, 879-887. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev*. **2003**, *103*, 2829−2844.

***Scheme 3.1.*** Prenyl Group Containing Natural Products




based complexes[6] and non-transition metal catalysts[7] been used to promote ECA processes.

Catalytic ECA of allyl moieties are relatively uncommon.[8,9,10,11,12] One reason for this paucity is that allylmetal entities are exceptionally nucleophilic, resulting in facile non-catalytic pathways and significant amounts of 1,2-addition products. Catalytic ECA of a prenyl group is still more challenging because the regioselectivity (prenyl vs reverse prenyl addition) can be an

(6) (a) Albrow, V. E.; Blake, A. J.; Fryatt, R.; Wilson, C.; Woodward, S. *Eur. J. Org. Chem.* **2006**, 2549–2557. (b) Robert, T.; Velder, J.; Schmalz, H.-G. *Angew. Chem. Int. Ed*. **2008**, *47*, 7718 –7721. (c) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem. Int. Ed*. **2008**, *47*, 8211–8214. (d) Lee, K.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455–4462. (e) Müller, D.; Tissot, M.; Alexakis, A. *Org. Lett*. **2011**, *12*, 3040–3043. (f) Takatsu, K.; Shintani, R.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 5548 –5552. (g) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2011**, *133*, 736–739. (h) Cottet, P.; Müller, D.; Alexakis, A. *Org. Lett*. **2013**, *15*, 828–831. (i) Chong, Q.; Yue, Z.; Zhang, S.; Ji, C.; Cheng, F.; Zhang, H.; Hong, X.; Meng, F. *ACS Catal.* **2017**, *7*, 5693−5698.

(7) Nguyen, T. N.; May, J. A. *Tetrahedron Letters* **2017**, *58*, 1535–1544.

(8) Shizuka, M.; Snapper, M. L. *Angew. Chem. Int. Ed*. **2008**, *47*, 5049–5051.

(9) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc*. **2008**, *130*, 4978–4983.

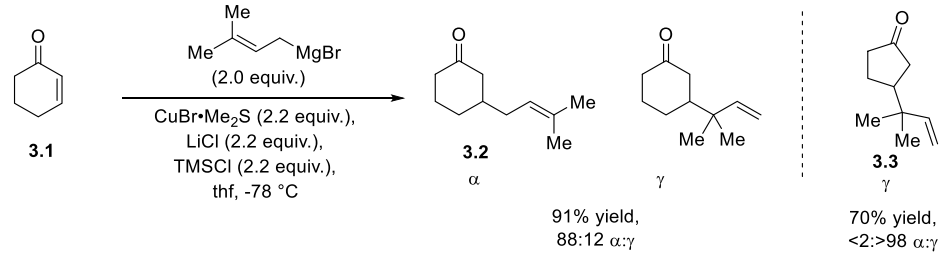
(10) Kuang, Y.; Liu, X.; Chang, L.; Wang, M.; Lin, L.; Feng, X. *Org. Lett*. **2011**, *13*, 3814–3817.

(11) Yanagida, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2011**, *50*, 7910–7914.

(12) Tang, Q.; Fu, K.; Ruan, P.; Dong, S.; Su, Z.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed*. **2019**, *58*, 11846–11851.

issue. For example, as reported by Lipshutz,[13] whereas prenyl conjugate addition of cyclohexenone afforded **3.2** predominantly, in the case of cyclopentenone, the alternative γ isomer **3.3** was formed preferentially (Scheme 3.2). A mechanistic study for this variation in selectivity was not provided, making it difficult to design experiments that address this regioselectivity problem.

***Scheme 3.2***. Regioselectivity of Prenyl Conjugate Addition

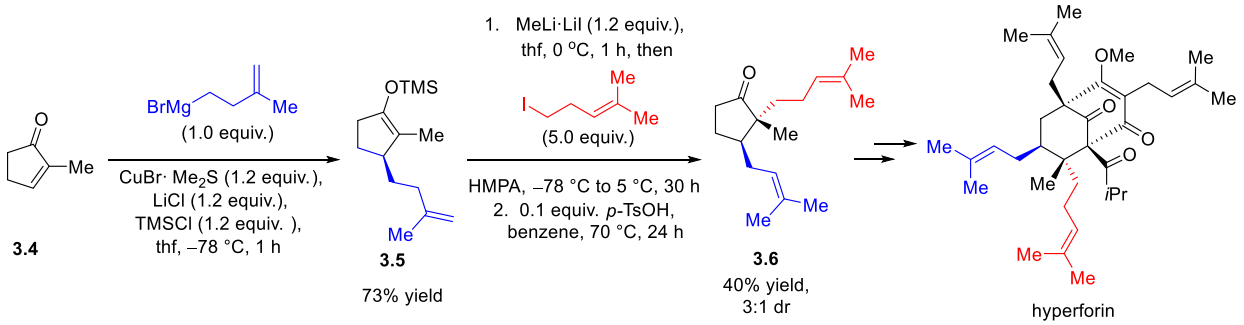



The limitation of this important set of transformations is underlined in a total synthesis study by Maimone et al.[14] whose synthesis of hyperforin (racemic; Scheme 3.3) began with conjugate addition of an alkyl moiety; the resulting silyl enol ether was then reacted with the appropriate alkyl iodide to generate the desired intermediate bearing an α-quaternary carbon stereogenic center. Still, accessing the desired β-prenyl ketone compound **3.6** required a subsequent olefin isomerization step. Thus, the conversion of enone **3.4** to **3.6** required three operations, including a step that required HMPA, and afforded the desired compound in 29% overall yield and 3:1 diastereomeric ratio (dr). It is worth nothing that the latter set of transformations are without a doubt the least efficient aspect of the otherwise concise 10-step total synthesis.

(13) Lipshutz, B. H.; Hackmann, C. *J. Org. Chem*. **1994**, *59*, 7437–7444.

(14) Ting, C. P.; Maimone, T. J. *J. Am. Chem. Soc*. **2015**, *137*, 10516–10519.

***Scheme 3.3.*** A Case in Point Regarding the Need for Efficient Prenyl ECA




## 3.2 Background

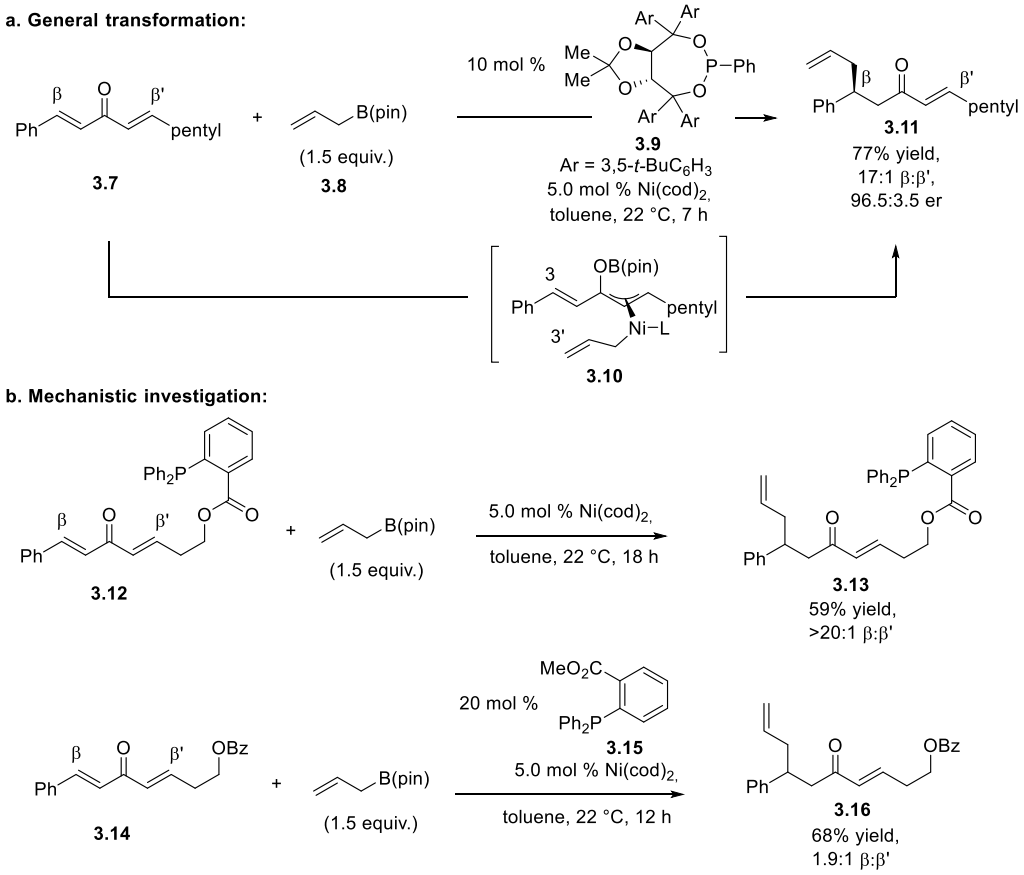
### 3.2.1 Catalytic enantioselective conjugate additions of allyl moieties

Catalytic methods for ECA of allyl groups are rare, and the small number of existing methods are limited in scope. The first strategy was reported by Morken and co-workers in 2008.[15] It was reported that reaction between dialkylidene ketone **3.7** and allyl–B(pin) in the presence of a phosphine–Ni complex proceeded to afford **3.11** as major product in 77% yield, 17:1 regioselectivity, and 96.5:3.5 er (Scheme 3.4a). Transformations involving a range of dissymmetric dialkylidene ketones were investigated. However, the presence of two conjugate alkenes is required for efficient transformation. It was demonstrated that the reaction involving the **3.12**, which contains a tethered phosphane moiety, led to exclusive reaction in the arylidene site (see **3.13**, Scheme 3.4b). In contrast, when a transformation was performed in the presence of (non-tethered) phosphane **3.15**, regioselectivity was considerably diminished (1.9:1 β:β'). Later on, Morken *et al*. showed that that a phosphine–Pd complex can be used to catalyze these transformations.[16]

(15) (a) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214–2215. (b) ref. 9

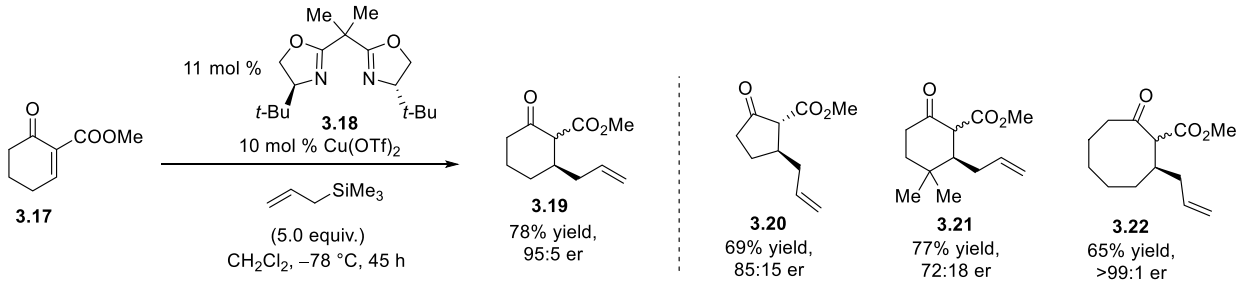
(16) Brozek, L. A; Sieber, J. D.; Morken, J. P. *Org. Lett*. **2011**, *13*, 995–997.

***Scheme 3.4.*** Ni-Based Complex Catalyzed Enantioselective Allyl Conjugate Addition



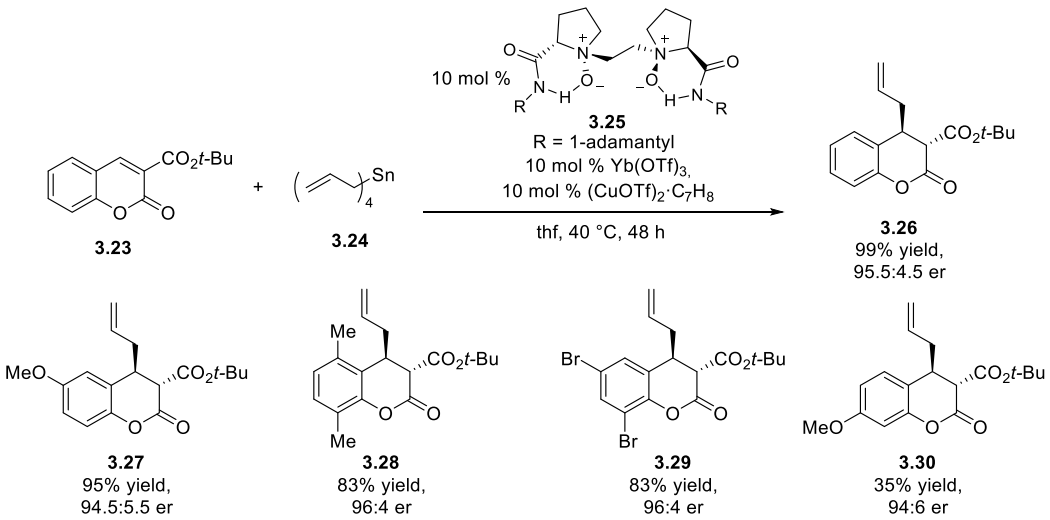

The first example of enantioselective allyl conjugate addition to cyclic enones was also published in 2008, this time by a different group at Boston College.[8] Snapper and Shizuka demonstrated that bis(oxazoline) ligand **3.18** can be used for ECA of allyltrimethylsilane to cyclic enone **3.17**, furnishing **3.19** in 78% yield and 95:5 er (Scheme 3.5), and the transformation involving cyclooctenone delivers desired product in 65% yield and >99:1 er. Nevertheless, reactions were found to be less enantioselective with cyclopentanone or when a more hindered cyclohexanone was used as the substrate (85:15 er and 72:18 er for **3.20** and **3.21**, respectively).

***Scheme 3.5.*** Enantioselective Allyl Conjugate Addition to Cyclic Enones




In 2011, Feng group reported a method for enantioselective allyl conjugate addition to coumarin and its derivatives.[10] Specifically, a *N,N'*-dioxide-Yb complex was used to promote reaction between tetraallyltin and coumarin **3.23**, affording the derived 1,4-addition product in 99% yield and 95.5:4.5 er (Scheme 3.6); copper(I) triflate was used as co-catalyst to improve the efficiency. Coumarin derivatives with substituents at the C5, C6, and C8 positions reacted efficiently and enantioselectively (**3.27, 3.28, 3.29**). However, tin toxicity and inferior atom-economy associated with the use of tetraallyltin notwithstanding, reaction efficiency was much reduced with a substituent at C7 (e.g., **3.30** in 35% yield).

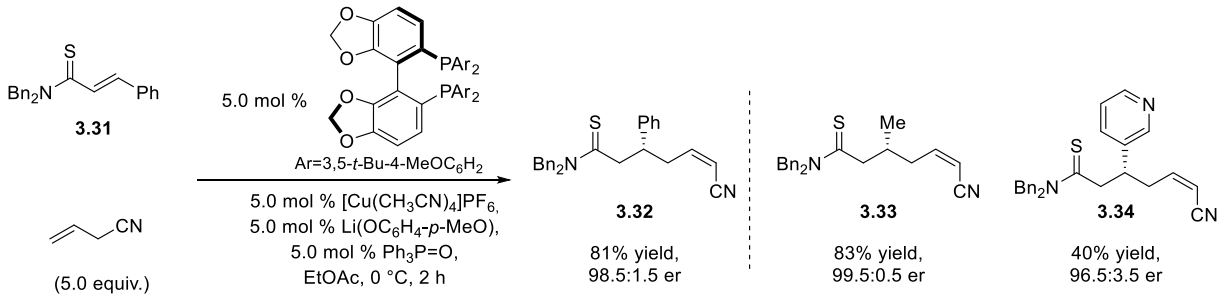
***Scheme 3.6.*** Enantioselective Allyl Conjugate Addition to Coumarin Derivatives




Shibasaki and Kumagai have developed a catalytic enantioselective conjugate addition strategy involving allyl cyanide and thioamide-based electrophiles.[11] Products containing a

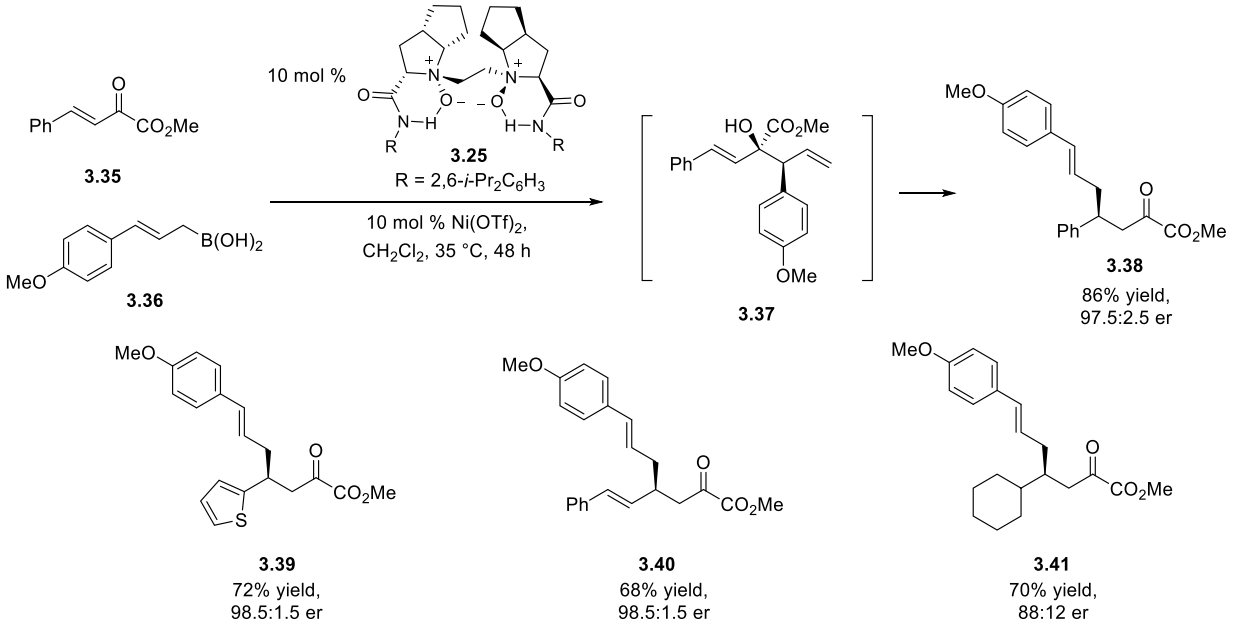
*Z*-alkenyl cyanide were thus generated in 40–81% yield and 96.5:3.5–99.5:0.5 er (Scheme 3.6). Transformations with alkyl- and heteroaryl-substituted thioamides were found to be efficient and enantioselective, but the presence of a pyridyl moiety led to lower yields (e.g. **3.33, 3.34**). Another shortcoming of the method is that the more versatile cinnamamides do not react to give desired product.

***Scheme 3.7.*** Enantioselective Allyl Cyanide Conjugate Addition to Thioamide




Most recently, Feng and co-workers demonstrated that allyl conjugate addition products may be obtained through a process entailing enantioselective 1,2-addition followed by stereoretentive oxy-Cope rearrangement (Scheme 3.8).[12] A reaction promoted by **3.25** and $Ni(OTf)_2$ delivered ketoester **3.38** in 86% yield and 97.5:2.5 er. Heteroaryl-, alkenyl-, as well as alkyl-substituted ketoesters were found to react efficiently, affording products with a slightly lower enantioselectivity in the case of aliphatic electrophiles (e.g., **3.41**). By carrying out the reaction at –20 °C, 1,2-addition product **3.37** could be isolated in 93% yield and 98.5:1.5 er. The aryl group on the allylboronic acid is crucial for efficiency of the oxy-Cope rearrangement, as such processes do not proceed otherwise.

***Scheme 3.8.*** Enantioselective Allyl Conjugate Addition through an oxy-Cope Rearrangement




### 3.2.2 Catalytic enantioselective conjugate additions involving an in situ generated copper–allyl species

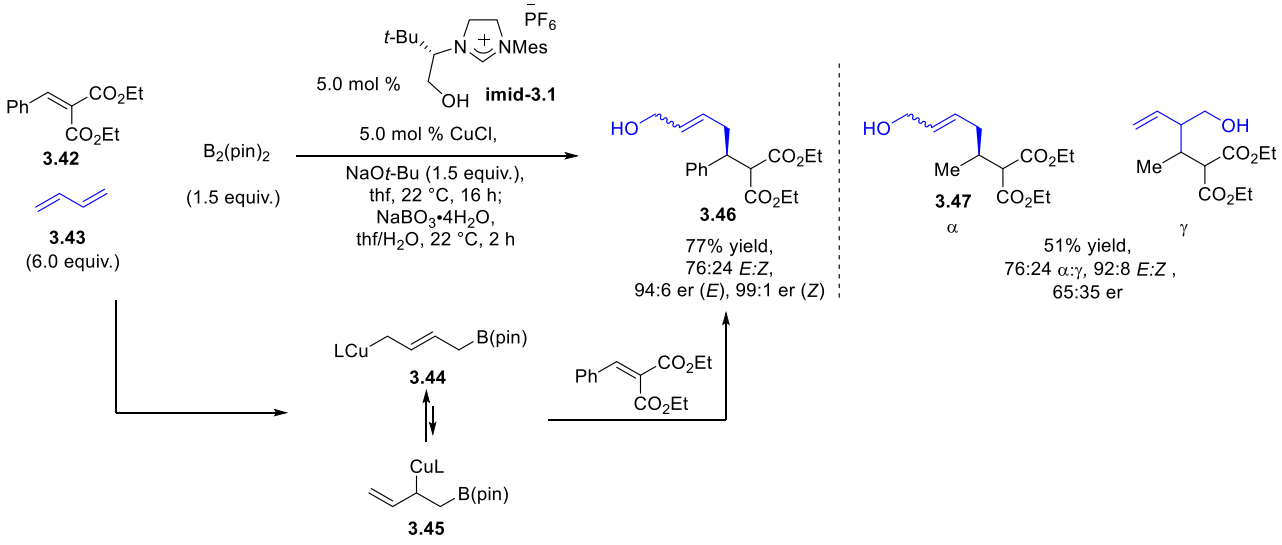
Multicomponent catalytic transformations represent an emerging strategy that can be used for enantioselective addition of various in situ generated Cu–allyl compounds to various electrophiles. An early example, including applications of multicomponent allylic substitutions to gram scale syntheses of bioactive molecules, was reported by Hoveyda *et al.* in 2014[17] and subsequently related conjugate addition processes were disclosed by the same group in 2016.[18] One set of reaction begins by the addition of a NHC–Cu–B(pin) complex to butadiene to generate allyl–Cu **3.45**, and subsequent isomerization to **3.44** occurs, likely drive by release of steric pressure. 1,4-Addition of **3.44** to enoate **3.42** followed by C–B bond oxidation thus afforded **3.46** in 77% yield, 76:24 *E:Z* selectivity and 94:6 er (for the *E* isomer; Scheme 3.9). While a variety of

(17) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367−374.

(18) (a) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. *Nature* **2016**, *537*, 387−393; (b) Li, X.; Meng, F.; Torker, S.; Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2016**, *55*, 9997–10002.

aryl-substituted enoates were found to be suitable substrates, the transformation involving an alkyl-substituted acceptor was less efficient and selective, affording **3.47** in 51% yield as a mixture of α, γ isomers in low er (65:35).

***Scheme 3.9.*** Multicomponent Strategy for Enantioselective Allyl Conjugate Addition



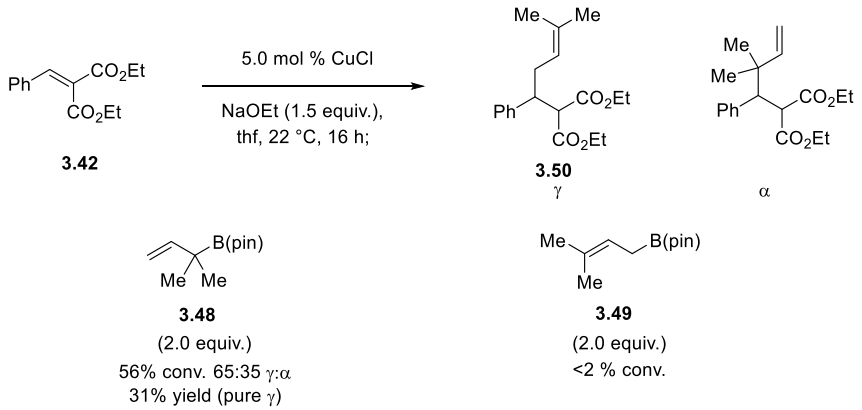

## 3.3 NHC–Cu-Catalyzed Enantioselective Prenyl Conjugate Additions

### 3.3.1 Identification of optimal reaction conditions

From the outset we realized that identification of a suitable nucleophilic reagent would be crucial, as it must be sufficiently unreactive so that there is minimal uncatalyzed reaction while nucleophilic enough so that it can participate in a catalytic process. We surmised that an organoboron compound could found that satisfies the latter criteria. Accordingly, we first probed the reactions of prenyl- and 3,3-dimethylallyl–B(pin) compounds in the presence of catalytic amount of CuCl, 1.5 equivalents of NaOEt in the absence of a chiral ligand. With 3,3-dimethylallyl–B(pin) **3.48**, the reaction proceeded to 56% conversion and afforded **3.50** as a 65:35 mixture of α:γ isomers. In contrast, the transformation with prenyl–B(pin) **3.49** did not yield any

of the desired product (<2%). These early findings indicated that, while **3.48** is likely more reactive, **3.49** would be less prone to uncatalyzed addition.

***Scheme 3.10.*** Preliminary Prenyl Addition with Different Organoboron Reagent[a]

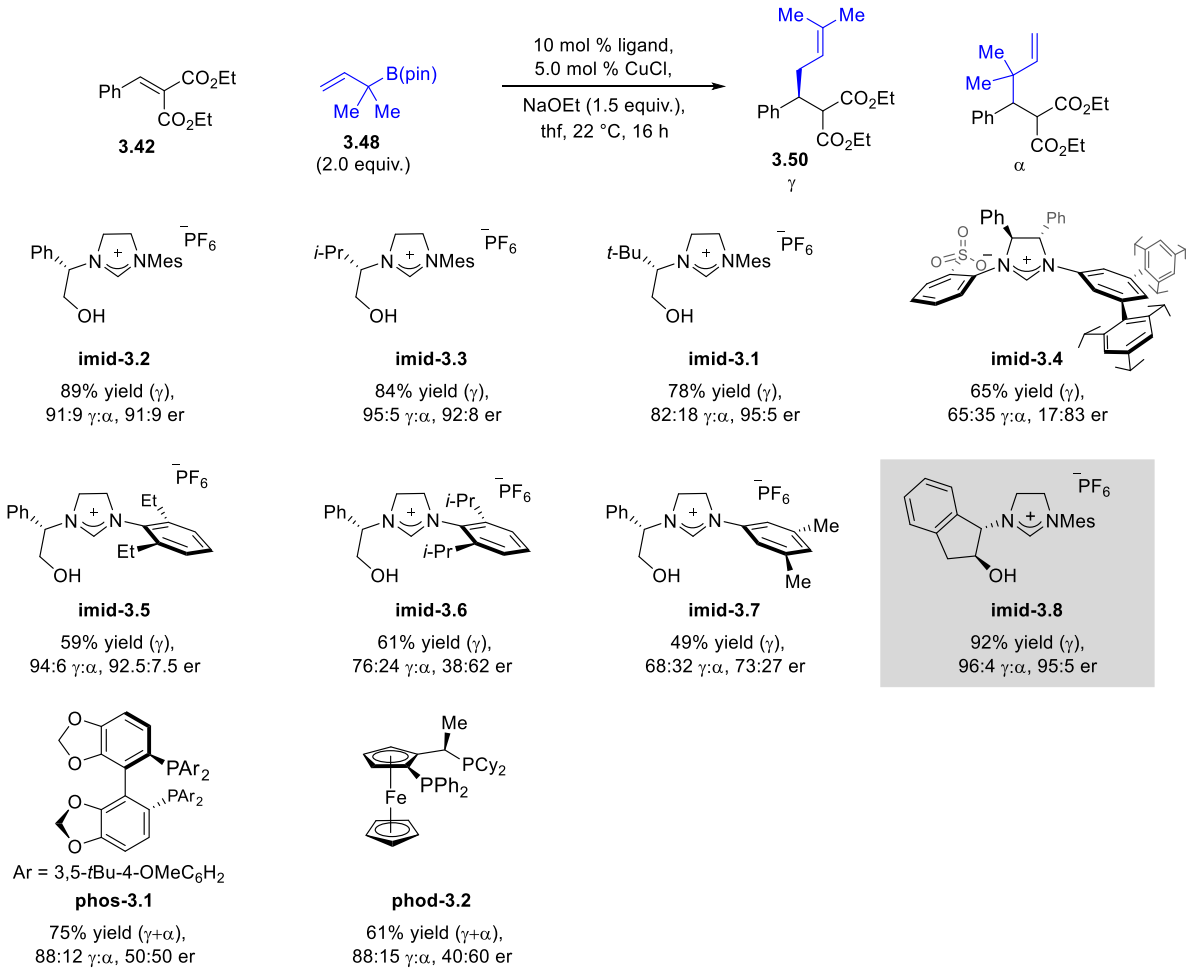



[a]All reactions were performed under $N_2$ atmosphere. Conversion,γ:α selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products (±5%).

Next, we set out to identify an effective chiral ligand, the derived Cu-based complex of which would facilitate conjugate addition with 3,3-dimethylallyl–B(pin) (Scheme 3.11). We selected to use 5.0 mol % CuCl and 10 mol % of a ligand to prevent any uncatalyzed reaction. The transformation with the Cu complex derived from imidazolinium salt **imid-3.2** was efficient, affording **3.50** in 89% yield, 91:9 γ:α selectivity, and 91:9 er. Some improvement in γ:α selectivity was observed when valine-derived ligand **imid-3.3** was used instead (84% yield, 95:5 γ:α, 92:8 er). When *tert*-leucine-derived ligand **imid-3.1** was used, regioselectivity suffered (82:18 γ:α) but enantioselectivity improved (95:5 er), and the NHC–Cu complex derived from sulfonate imidazolinium salt **imid-3.4** did not promote the reaction with similar efficiency or selectivity. Additional screening indicated that altering the size of and the substitution pattern within the N-aryl moiety (e.g., **imid-3.5, imid-3.6** and **imid-3.7**) of an NHC ligand can impact efficiency and/or selectivities. Eventually, we were able to determine that the Cu-based catalyst derived from an amino indanol-derived NHC, first introduced by Hayashi,[6f] is capable of promoting prenyl

conjugate addition to generate **3.50** in 92% yield, 96:4 γ:α selectivity, and 95:5 er. Reactions with phosphine-based ligands **phos-3.1** and **phos-3.2**, previously used in various Cu-based complex catalyzed enantioselective transformations,[19] afforded **3.50** in low er.

***Scheme 3.11.*** Ligand Screening for Prenyl Conjugate Addition[a]




[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Experimental Section for details.

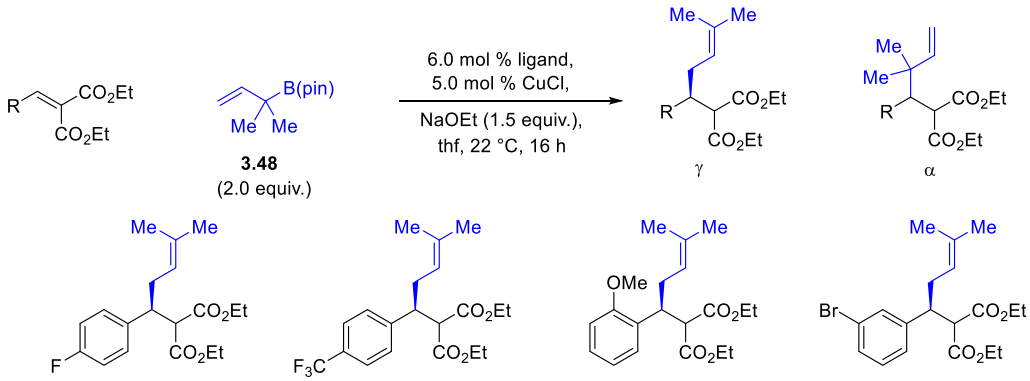
## 3.3.2 Reactions with acyclic substrates

### *3.3.2.1. Aryl- and heteroaryl-substituted enoates.*

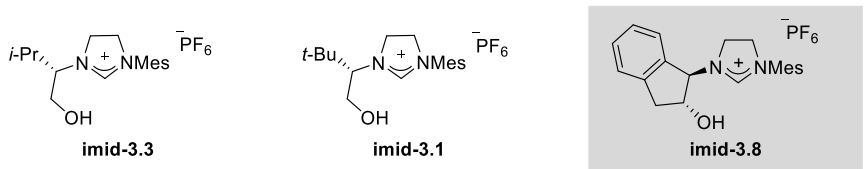
(19) (a) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746−15749. (b) López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784−12785.

Because the initial data obtained for reactions involving the use of ligand precursors **imid-3.1, imid-3.3** and **imid-3.8** were similar, we chose to investigate the ability of the derived NHC–Cu complexes to serve as catalysts further (Scheme 3.12). In the presence of **imid-3.8**, reactions were generally more enantioselective than when **imid-3.1** and **imid-3.3** were used. The exception was the transformation with an electron-rich enoate: although **3.53** was formed in higher er with **imid-3.1** as the ligand precursor (93:7 er vs 87:13 er and 88:12 er with **imid-3.8** and **imid-3.3**, respectively), the efficiency was higher when **imid-3.8** was used (93% yield vs 55% yield with **imid-3.1**). Furthermore, the reactions promoted by catalysts derived from **imid-3.1** afforded products in no more than 72:28–79:21 γ:α selectivity. In contrast, transformations promoted by catalysts derived from imidazolinium salt **imid-3.3** were less efficient and less enantioselective,

***Schem 3.12.*** Effectiveness of Different Ligands on DIfferent Enonates[a]




| | 3.51 | 3.52 | 3.53 | 3.54 |
|---|---|---|---|---|
| **imid-3.3** | 76% yield, 97:3 γ:α, 93.5:6.5 er | 69% yield, 96:4 γ:α, 93:7 er | 68% yield, >98:2 γ:α, 88:12 er | 80% yield, 96:4 γ:α,95:5 er |
| **imid-3.1** | 58% yield, 75:25 γ:α, 94:6 er | 40% yield, 72:28 γ:α,90:10 er | 55% yield, >98:2 γ:α, 93:7 er | 42% yield, 79:21 γ:α, 94:6 er |
| **imid-3.8** | 75% yield, 95:5 γ:α, 95:5 er | 86% yield, 94:6 γ:α, 96:4 er | 93% yield, 96:4 γ:α, 87:13 er | 90% yield, 93:7 γ:α, 95:5 er |

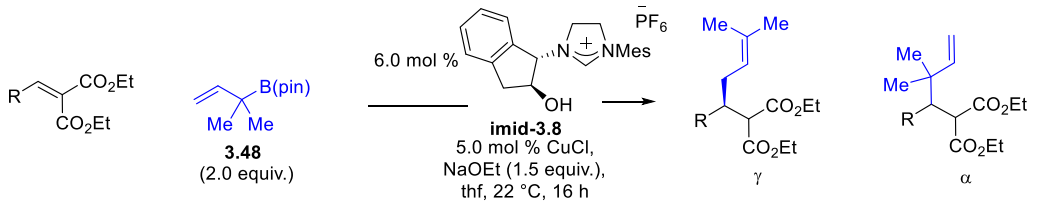


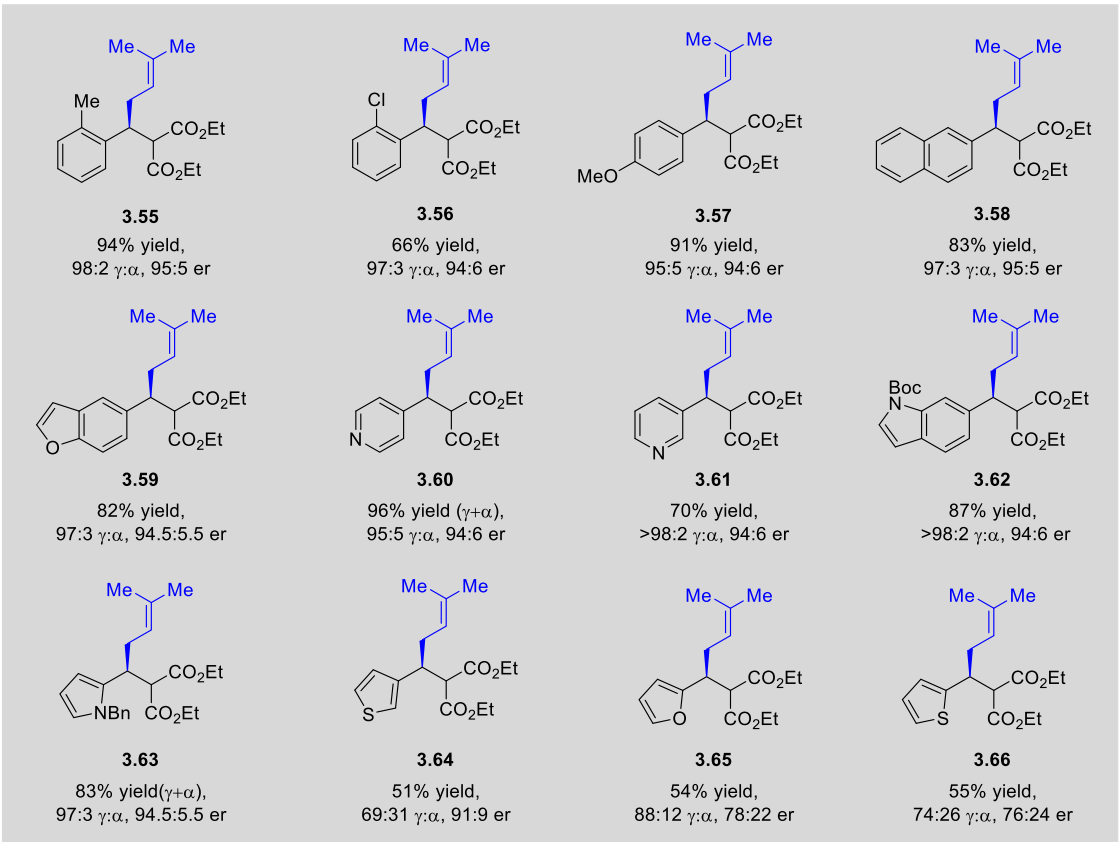

[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Experimental Section for details.

while considerably more γ-selective (96:4– >98:2 vs 93:7–96:4 with **imid-3.8**). Owing to the fact that, if necessary, the γ and α isomer can be easily separated through silica gel chromatography, we settled upon **imid-3.8** as the overall most suitable chiral ligand precursor.

We found that catalytic transformation of various aryl-substituted enoates, including pyridinyl-, benzofuranyl-, pyrrolyl-, and indolyl-substituted enoates afford the desired products (**3.55–3.63**) in 66%–96% yield, >95:5 γ:α selectivity and 94:6–95:5 er (Scheme 3.13). Reactions involving furyl and thienyl substrates were somewhat less efficient (51–55% for **3.64–3.66**) and

***Scheme 3.13.*** Enantioselective Prenyl Conjugate Additions with Aryl-Substituted Enoates



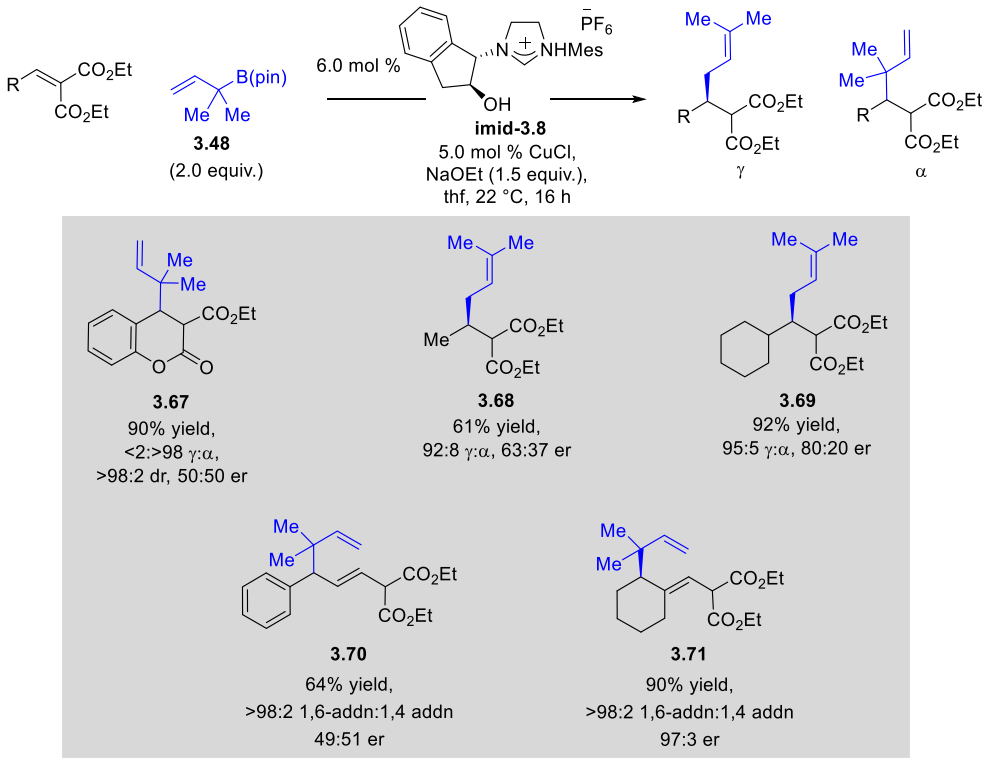




[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Experimental Section for details.

afforded products with lower regio- and enantioselectivity (69:31-88:12 γ:α and 76:24-91:9 er); this might be due to the unfavorable coordinating effect of the Lewis basic heteroatoms within these substrates. Reaction in the presence of Lewis acidic additive did not lead to an improvement in regioselectivity (e.g., **3.66** was generated in 74:26 γ:α and 76:24 er with 1.0 equivalent of $MgCl_2$ additive, <2:>98 γ:α ratio with 1.0 equivalent $ZnCl_2$).

Transformations involving a coumarin-derived enonate delivered the α-addition product exclusively in the racemic form (**3.67**, Scheme 3.14). This might be due to the higher reactivity of the substrate induced an outer sphere γ addition when both carbonyls are coordinating to Cu. Therefore, the chiral ligand is further away from the C–C bond formation site, leading to racemic product. Alkyl-substituted enoates reacted to afford desired γ-addition product preferentially (92:8 and 95:5 γ:α selectivity for **3.68** and **3.69**, respectively). However, the enantioselectivities were lower compared to the aforementioned aryl-substituted substrates (63:37 and 80:20 er for **3.68** and **3.69**, respectively), which is probably the result of the smaller size of alkyl moieties. Compounds **3.70** and **3.71**, arising from 1,6-addition, were generated exclusively when alkenyl-substituted α,β-unsaturated dienoates were used. Whereas an aryl-substituted dienoate reacted to afford racemic product (**3.70**), the er was high in the case of the corresponding cyclohexyl-substituted variant (**3.71**; 97:3 er). This might be owning to the more competitive uncatalyzed reaction with a more reactive aryl substrate.

***Scheme 3.14.*** Enantioselective Prenyl Conjugate Addition to Coumarin-, Alkenyl- and Alkyl-Substituted Enoates



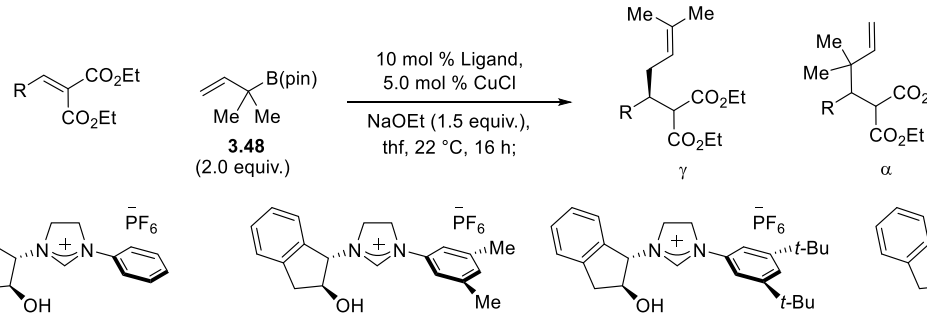

[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivity were determined by analysis of $^1H$ NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Experimental Section for details.

### *3.3.2.2. Alkyl-substituted enoates*

To improve the enantioselectivity of prenyl conjugate additions to alkyl-substituted enoates, we prepared and probed the effectiveness of Cu-based chiral catalysts derived from a variety of indanol-derived imidazolinium salts (Scheme 3.15). Reactions involving the cyclohexyl-substituted substrate performed with catalysts that contain an NHC ligand that does not bear an *ortho*-substituted N-aryl ring were less enantioselective (70:30 and 60:40 er for **imid-3.9** and **imid-3.10**, respectively; vs 80:20 er with NHC ligand precursor **imid-3.8**). Although higher er was observed in the case of methyl-substituted product **3.68** (79:21 and 82:18 er with **imid-3.9** and **imid-3.10** respectively, vs 63:37 er with **imid-3.8**), the results were hardly optimal.

The catalyst derived from the ligand precursor with *meta*-methyl substituents in its N-aryl moiety (**imid-3.10**) was more enantioselective (82:18 er), but further increasing the size of the *meta* substituent did not improve matters (69:31 er with **imid-3.11**). Use of NHC–Cu catalysts that contain ligands with larger *ortho* N-aryl substituents did not result in any improvement (e.g., 55:45–89:11 γ:α and 47:53-76:24 er with **imid-3.12** and **imid-3.13**). Notably, when anthracenyl imidazolinium salt **imid-3.14** was used, **3.69** was isolated in 65% yield, with 94:6 γ:α selectivity, and in 88:12 er.

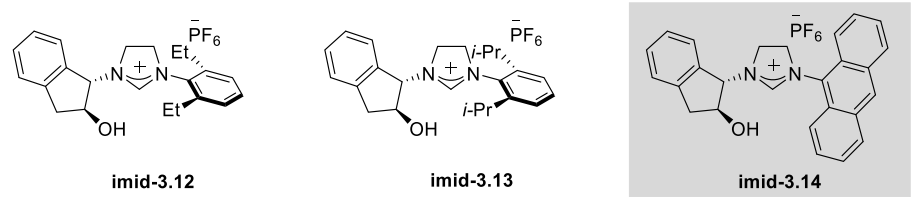
***Scheme 3.15.*** Ligand Screening for Prenyl Addition Involving Alkyl-Substituted Enoates







| | imid-3.9 | imid-3.10 | imid-3.11 | imid-3.8 |
|---|---|---|---|---|
| **3.69 R= Cy** | 93% yield, >98:2 γ:α, 70:30 er | 79% yield, >98:2 γ:α, 60:40 er | 53% yield, 98:2 γ:α, 61:39 er | 92% yield(γ+α), 95:5 γ:α, 80:20 er |
| **3.68 R= Me** | 55% yield, 98:2 γ:α, 79:21 er | 47% yield, 98:2 γ:α, 82:18 er | 42% yield(γ+α), 88:12 γ:α, 69:31 er | 61% yield(γ+α), 92:8 γ:α, 63:37 er |



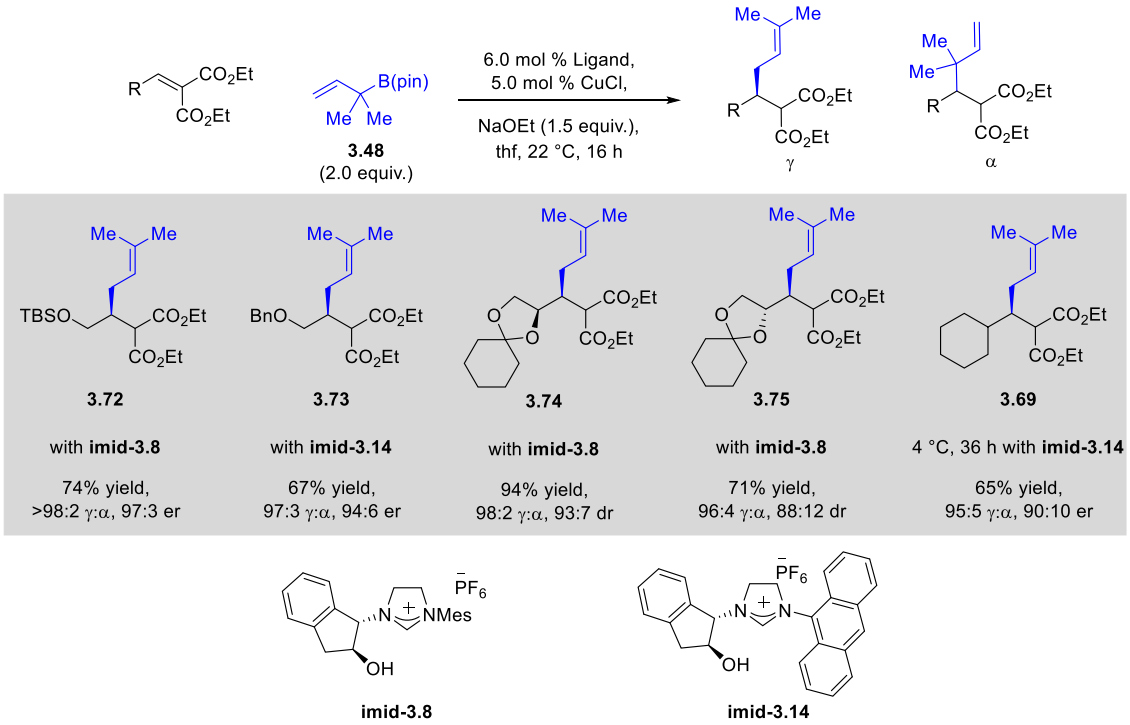

| | imid-3.12 | imid-3.13 | imid-3.14 |
|---|---|---|---|
| **3.69 R= Cy** | 70% yield(γ+α), 89:11 γ:α, 76:24 er | 73% yield(γ+α), 65:35 γ:α, 47:53 er | 65% yield(γ+α), 94:6 γ:α, 88:12 er |
| **3.68 R= Me** | 51% yield(γ+α), 87:13 γ:α, 70:30 er | 33% yield(γ+α), 55:45 γ:α, 51:49 er | 49% yield(γ+α), 94:6 γ:α, 77:23 er |

[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Experimental Section for details.

With reasonably effective chiral catalysts in hand, we proceeded to explore the scope of enantioselective prenyl conjugate additions to alkyl-substituted enoates (Scheme 3.16). By using imidazolinium salt **imid-3.8**, we were able to isolate silyl ether **3.72** in 74% yield, >98:2 γ:α ratio,

and 97:3 er. The same transformation with **imid-3.14** results in slightly lower yield (60%) and er (95:5). In the case of benzyl ether **3.73**, N-anthracenyl ligand **imid-3.14** emerged as the superior choice and we isolated **3.73** in 67% yield, 97:3 γ:α selectivity, and 94:6 er; transformation with the catalyst derived from **imid-3.8** gave **3.73** in lower γ:α selectivity (71% yield, 91:9 γ:α, 94:6 er). When enantiomerically pure enoates were used, either diastereomer could be obtained, indicating strong catalyst control; for instance, **3.74** and **3.75** were generated in 94% and 71% yield, 98:2 and 96:4 γ:α selectivity, and 93:7 and 88:12 dr, respectively. Finally, we find that cyclohexyl-substituted **3.69** can be synthesized in higher enantioselectivity when the reaction is performed at 4 °C (65% yield, 95:5 γ:α ratio, 90:10 er).

***Scheme 3.16.*** Enantioselective Prenyl Conjugate Addition to Alkyl-Subtituted Enoates




[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Experimental Section for details.

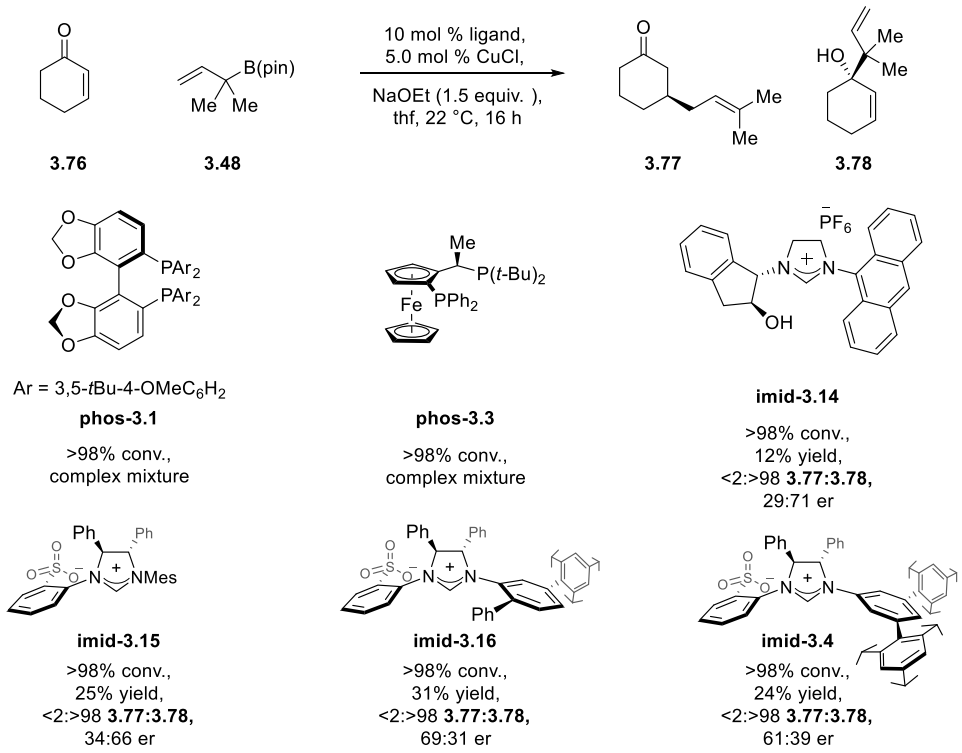
### 3.3.3 Reactions with cyclic substrates

#### *3.3.3.1. Cyclic enones*

This is an important substrate set because the corresponding products can be used to synthesize numerous natural products (Scheme 3.1 and 3.3).[1] Compared to acyclic α,β-unsaturated diesters, cyclic enones are more reactive, perhaps owing to a more conformationally rigid structure, allowing for a more favorable alkene π*/carbonyl π* orbital overlap. However, this also means that the uncatalyzed reaction might be more facile, resulting in lowering of er values.

We began with probing catalytic prenyl additions to cyclohexanone (Scheme 3.17). Reactions promoted by Cu-based catalysts derived from phosphine ligands **phos-3.1** and **phos-3.3** only led to substrate decomposition (Scheme 3.17). When indanol-derived imidazolinium salt **imid-3.14** was used, the transformation afforded 1,2-addition product **3.78** in 12% yield and 29:71

***Scheme 3.17.*** Ligand Screening for Prenyl Conjugate Addition to Cyclohexenone[a]

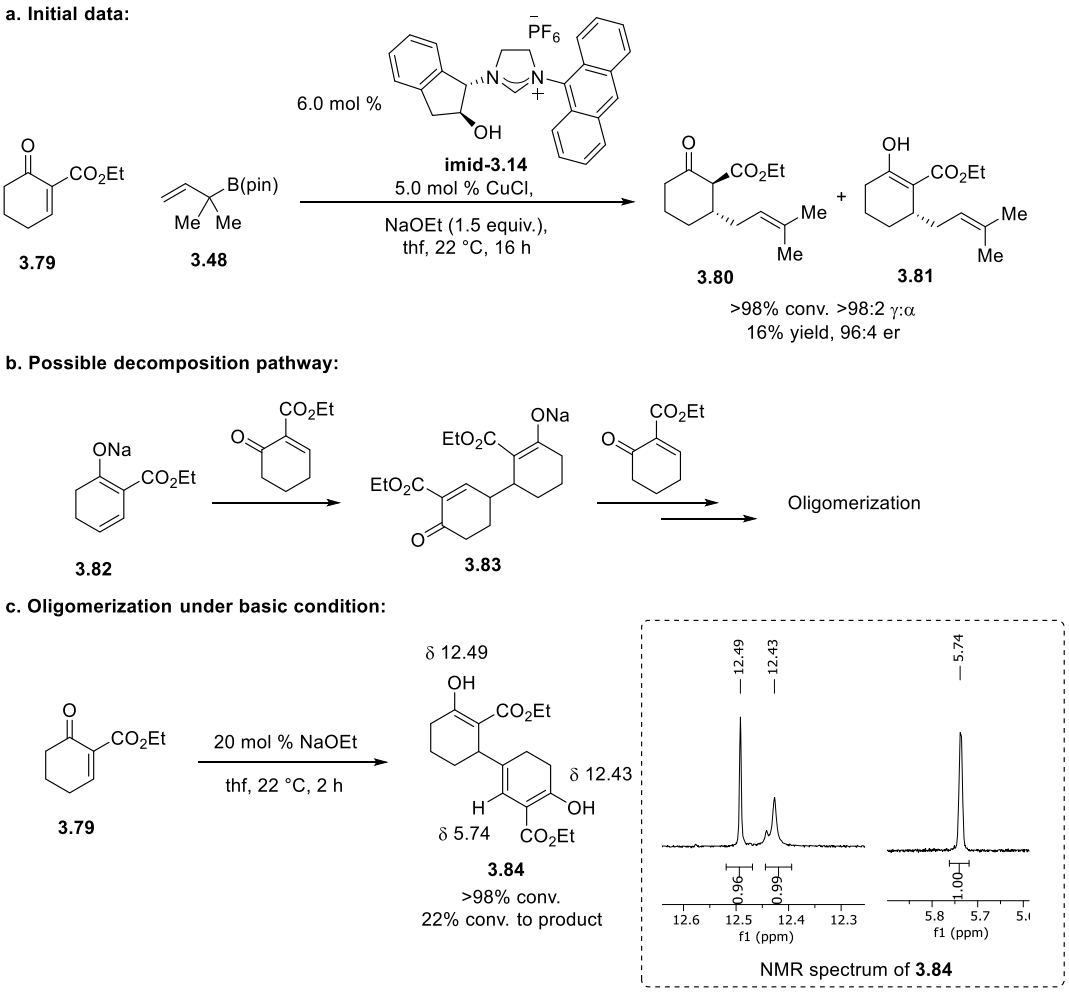



[a]All reactions were performed under $N_2$ atmosphere. **3.94:3.95** selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products (±5%). Enantioselectivities were determined by GC analysis (±1%). See the Experimental Section for details.

er. Sulfonate NHC–Cu complexes catalyzed the 1,2-addition in higher efficiency but with lower enantioselectivity. The 1,2-addition product **3.78** may be converted to **3.77** through oxy-Cope rearrangement; however, it would be difficult to improve enantioselectivity because the minimal distinction between the two enantiotopic alkene faces of enone **3.76**.

Catalytic prenyl addition to cyclic β-keto-esters proved to be more enantioselective. The transformation involving between enone **3.79** and allyl boronate **3.48** resulted in the formation of a mixture of **3.80** and its enol form **3.81** in 16% yield, >98:2 γ:α selectivity, and 96:4 er (Scheme 3.18a). None of the 1,2-addition byproduct could be detected, probably because of the increased LUMO coefficient at C4 (compared to cyclohexanone). We surmised that the low yield was because of facile side reaction involving conjugative substrate homocoupling (and oligomerization) with the enol form serving as the nucleophile (Scheme 3.18b). This hypothesis is supported by the observation that **3.79** underwent dimerization when treated with 20 mol% of NaOEt, affording **3.84.** The structure of **3.84** was supported by the NMR signals shown in Scheme 3.18c as the representative peaks in δ 12.49 and 12.43 ppm indicated that two enol moieties are present in this molecule.

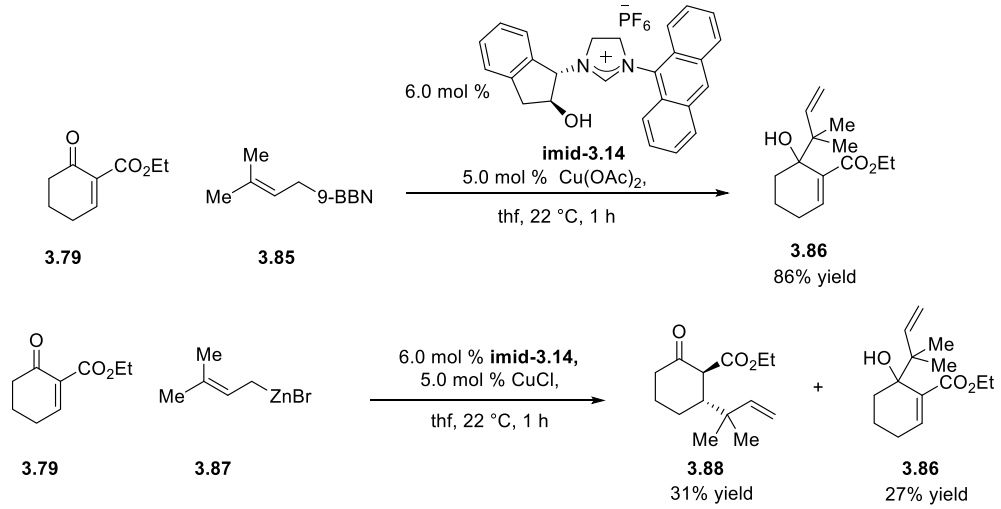
***Scheme 3.18.*** Prenyl Conjugate Addition of α-Ester Containing Cyclohexenone




[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Enantioselectivities were determined by GC analysis of the decarboxylated derivative (±1%). See the Experimental Section for details.

To avoid the use of metal alkoxide, and thus minimize substrate homocoupling, several alternative prenyl-based reagents were investigated (Scheme 3.19). The reaction involving cyclic keto-ester **3.79** and (dialkyl)prenylboron compound **3.85** afforded 1,2-addition byproduct **3.86** in 86% yield. Similarly, when prenyl–ZnBr was used, a mixture 1,2- and 1,4-addition products derived from preferential α mode of reaction were generated (i.e., **3.88** and **3.86** in 31% and 27% yield, respectively).

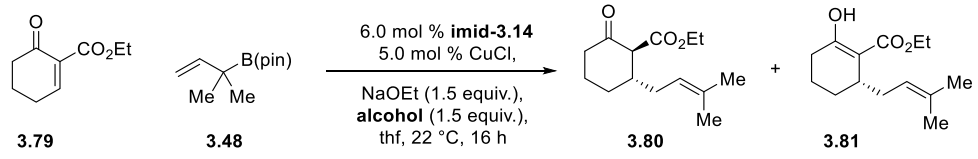
***Scheme 3.19.*** Prenyl Conjugate Addition without Metal Alkoxide




[a]All reactions were performed under $N_2$ atmosphere. See the Experimental Section for details.

As an alternative strategy to suppress substrate oligomerization, we chose to attenuate the basicity of the intermediate metal enolate (e.g., see **3.82**, in Scheme 3.18) by performing the reaction in the presence of an alcohol. Various of alcohols were examined as an additive. While the transformation involving methanol, *iso*-propanol and *tert*-butanol did not show significant improvement in the efficiency, the reaction with ethanol emerged as more efficient, affording the desired product with similarly high enantioselectivity (compared to when no alcohol was present; 96:4 er; Scheme 3.20).

***Scheme 3.20.*** Prenyl Conjugate Addition in the Presence of Different Alcohols



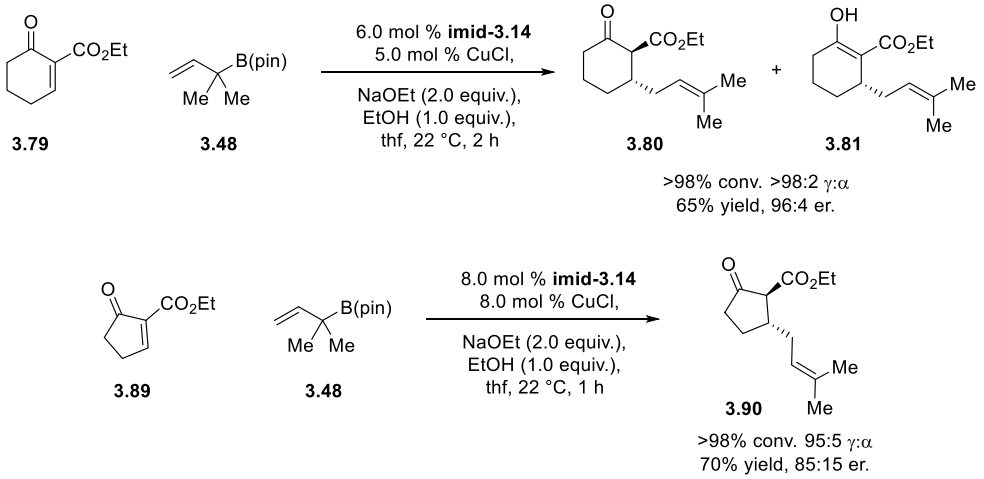

| No alcohol | MeOH | EtOH | *i*-PrOH | *t*-BuOH |
|---|---|---|---|---|
| >98% conv. >98:2 γ:α<br>16% yield, 96:4 er | >98% conv. 92:8 γ:α<br>9% yield, ND er | >98% conv. >98:2 γ:α<br>37% yield, 96:4 er | >98% conv. >98:2 γ:α<br>16% yield, ND er | >98% conv. 92:8 γ:α<br>14% yield, ND er |

[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivities were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Enantioselectivities were determined by GC analysis of the decarboxylated derivative (±1%). See the Experimental Section for details.

The above findings indicate that although a decrease in basicity does suppress substrate homocoupling/oligomerization, it diminishes the rate of the conjugate addition as well, and that a

better balance between these opposing factors was needed. Further adjustment of the amount of the metal alkoxide and of the alcohol additive led us to establish that with 2.0 equivalent of NaOEt and 1.0 equivalent of EtOH, **3.80**/**3.81** can be isolated in 65% yield, >98:2 γ:α selectivity, and 96:4 er. Moreover, the transformation involving the corresponding five-membered ring substrate (**3.89**) furnished the desired product (**3.90**) in 70% yield, 95:5 γ:α selectivity, and 85:15 er.

***Scheme 3.21.*** Enantioselective Prenyl Conjugate Addition of Cyclic Substrates



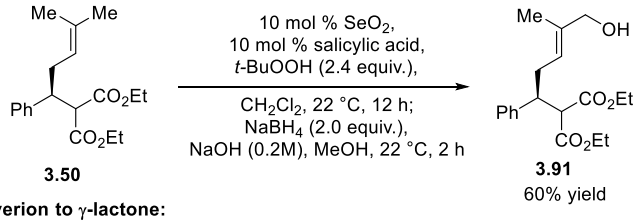

[a]All reactions were performed under $N_2$ atmosphere. γ:α Selectivity were determined by analysis of $^1$H NMR spectra of the unpurified mixtures (±2%). Enantioselectivities were determined by GC analysis of the decarboxylated derivative (±1%). See the Experimental Section for details.

## 3.4 Functionalization of products

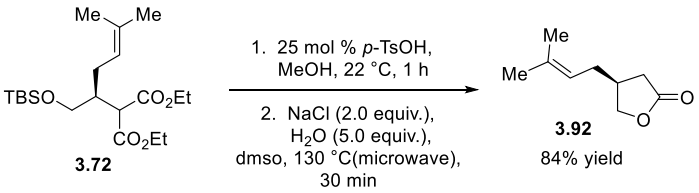
Products obtained through catalytic enantioselective prenyl conjugate addition are versatile and can be transformed to other valuable and otherwise difficult-to-access molecules (Scheme 3.22). This is an area that requires further investigation but representative examples, shown in Scheme 3.22, are illustrative. Subjection of compound **3.50** to allylic oxidation conditions resulted in the formation of stereochemically defined trisubstituted allylic alcohol **3.91** in 60% yield and >98:2 *E:Z* ratio. Deprotection of the silyl group of **3.72** and subsequent carboxyl group removal generated γ-lactone **3.92**.

***Scheme 3.22.*** Functionalizations of the Prenyl Addition Products[a]

**a. Allylic oxidation:**




**b. Converion to γ-lactone:**




[a]All reactions were performed under $N_2$ atmosphere. See the Experimental Section for details.

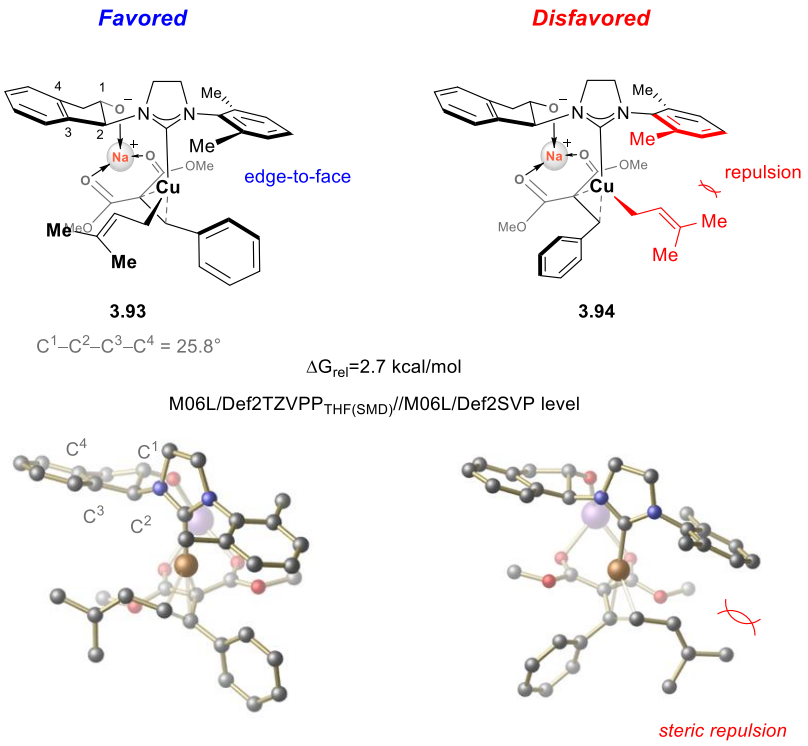
## 3.5 Mechanistic investigations

### 3.5.1 Regarding the origin of enantioselectivity

DFT studies indicate that during the C–C bond forming step, which is likely the stereochemistry-determining event, the hydroxy group is coordinated to a sodium cation to form a cationic salt bridge with the diester moiety of the enoate (Scheme 3.23).[18] In the more favorable represented by mode of addition **3.93**, the enoate substituent is positioned below the N-aryl moiety, allowing for C–H-π (edge-to-face) interaction,[18b] to stabilize the transition state. In contrast, in the less favored mode of reaction represented by **3.94**, there are no such stabilizing interactions. What is more, in the latter complex, the prenyl group is oriented toward the 2,6-dimethylphenyl group to avoid clashing with the substrate, instead engendering steric pressure with the dimethylphenyl unit. In the case of alkyl-substituted enoates, because there are no edge-to-face stabilizing interactions possible, the energy difference between competing transition states is lower, and an

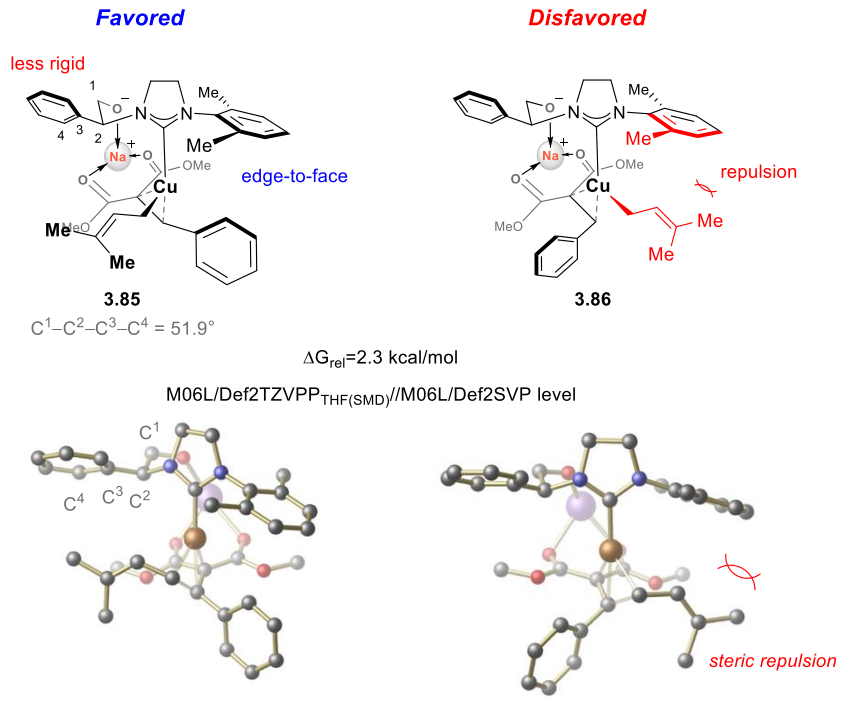
anthracenyl-containing NHC ligand is needed to exacerbate repulsive interaction with the prenyl moiety, resulting in improved enantioselectivity.

***Scheme 3.23.*** Stereochemical Model for Reaction with Aryl-Substituted Enoates




Another noteworthy question was why enantioselectivity is higher with indanol-derived **imid-3.8** (vs phenylalanine-derived **imid-3.2**). DFT studies (Scheme 3.24) suggest that in the more favorable transition state, the substrate's aryl group is again oriented towards the dimethylphenyl ring to engender edge-to-face association. As before, the unfavorable steric repulsion between the prenyl group and dimethylphenyl group accounts for mode of addition **3.86** being less favored. However, the two favored modes of addition represented by **3.83** and **3.85** are dissimilar in that the indanol ring is conformationally more rigid, as reflected in the $C^1$–$C^2$–$C^3$–$C^4$ dihedral angles (25.8° in **3.83** and 51.9° in **3.85**). In contrast, the aryl moiety in **3.85** can easily rotate around the $C^2$–$C^3$ bond, causing steric interaction with prenyl group.

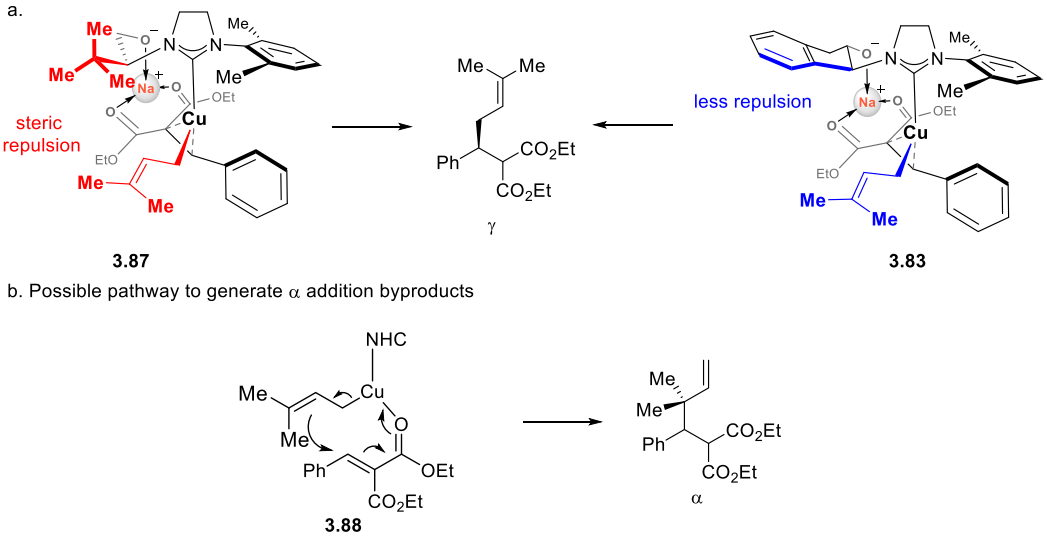
***Scheme 3.24.*** Stereochemical Model for Reaction with Aryl-Substituted Enoates




### 3.5.2 Regarding the regioselectivity variations

We have also carried out studies to shed light on the possible origin of higher γ:α selectivity observed for reactions involving the NHC–Cu catalyst derived from *tert*-leucine-based imidazolinium salt **imid-3.1** versus that generated from indanol-derived **imid-3.8** (see Scheme 3.12). The reaction promoted by **imid-3.1** may proceed via a transition state that contains a cationic salt bridge between the diester and hydroxyl moiety (**3.87**, Scheme 3.25). Because the phenyl group is positioned below the N-aryl moiety, the prenyl group is likely oriented towards the *t*-Bu unit to minimize steric repulsion with the phenyl group. This gives rise to steric pressure between the *tert*-butyl and the prenyl groups, thus increasing the energy of mode of addition **3.87**. Transformation via intermediate **3.88,** entailing a γ-prenyl transfer to furnish the α-addition product, would therefore be more favorable and the γ:α selectivity would be lower when **imid-3.1** is used as ligand precursor.

***Scheme 3.25.*** Proposed Stereochemistry Model for Explanation of Regioselectivity Variation




## 3.6 Conclusions

The investigations described in this chapter have resulted in the development of the first method for catalytic enantioselective prenyl conjugate addition. The NHC–Cu catalyst derived from indenyl imidazolinium salt **imid-3.8** was found to promote reactions efficiently and with high regio- and enantioselectivity. Through a slight modification of ligand structure, we were able to identify a catalyst that can be used to catalyze enantioselective prenyl additions to a wider range of enoates, including acyclic substrates that are alkyl-substituted and cyclic β-keto-esters. Mechanistic (DFT) studies suggest that transformations likely proceed through a transition state that contains a cationic salt bridge, stabilized by an edge-to-face association that causes additions to aryl-substituted enoates to be more enantioselective. Future studies, which will entail applications to the total synthesis of complex molecule natural products will undoubtedly illustrate the considerable importance and utility of the catalytic protocol.

## 3.7 Experimentals

- **General**

Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, $\lambda_{max}$ in $cm^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). $^{1}H$ NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, m = multiplet app = apparent), and coupling constants (Hz). $^{13}C$ NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College. Elemental microanalyses were performed at Robertson Microlit Laboratories (Madison, NJ). Enantiomeric ratios were determined by high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Chiral Technologies Chiralcel OJ-H (4.6 x 250 mm), Chiral Technologies Chiralcel OD-H (4.6 x 250 mm), Chiral Technologies Chiralcel OZ-H (4.6 x 250 mm)) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter. Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry $N_2$ in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Dichloromethane (Fisher Scientific, Inc.) was purified by being passed through two alumina columns under a positive pressure of dry argon by a modified Innovative Technologies purification system. Tetrahydrofuran (Aldrich Chemical Co.) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise

specified. Methanol (Aldrich Chemical Co.) was distilled over $CaH_2$. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Doe & Ingalls) under air.

- **Reagents**

**Copper (I) chloride**: was purchased from Strem and used as received.

**Diethyl benzylidenemalonate (3.42):** was purchased from Aldrich Chemical Co. and used as received.

**Enoate** (substrate for **3.51**–**3.66, 3.89-3.92**)**:** prepared according to previously reported procedures.[20]

**Imidazolinium salts (imid-3.1–imid-3.3, imid-3.5–imid-3.7):** were prepared according to previously reported procedures. [21]

**Imid-3.4:** were prepared according to previously reported procedures.[22]

**Imidazolinium salts (imid-3.8, imid-3.9–imid-3.14):** were prepared according to previously reported procedures.[23]

**Sodium methoxide (NaOEt)** was purchased from Strem and used as received.

**4,4,5,5-Tetramethyl-2-(2-methylbut-3-en-2-yl)-1,3,2-dioxaborolane (3.48)** was prepared according to previously reported procedures.[24]

## Procedure for NHC–Cu-catalyzed prenyl conjugate additions to enoates:

In an $N_2$-filled glove box, an oven-dried vial (4 mL) with a magnetic stir bar was charged

(20) Allen, C. F. H.; Spangler, F. W. *Org. Syn.* **1945***, 25*, 42.

(21) Clavier, H.; Coutable, L.; Toupet, L.; Guillemin, J.-C.; Mauduit, M. J. *J. Organomet. Chem.* **2005***, 690*, 5237–5254.

(22) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490−1493.

(23) Takatsu, K.; Shintani, R.; Hayashi, T. *Angew. Chem. Int. Ed*. **2011**, *50*, 5548–5552.

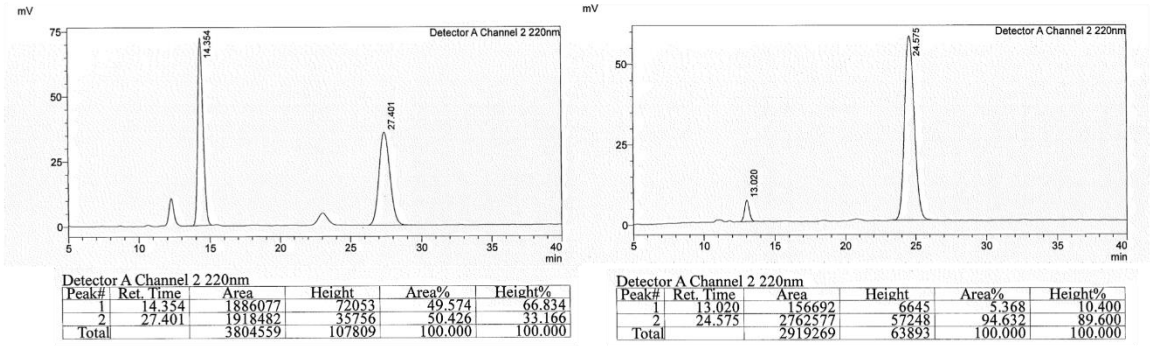
(24) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136,* 7092−7100.

with imidazolinium salt **imid-3.8** (2.8 mg, 0.006 mmol), CuCl (0.5 mg, 0.005 mmol,), NaOEt (10.2 mg, 0.150 mmol) and tetrahydrofuran (thf, 0.5 mL). The vessel was sealed with a cap (phenolic open top cap with red PTFE/white silicone septum) and the solution was allowed to stir at 22 °C for 1.0 hour. 1,1-Dimethylallyl–B(pin) **3.48** (29.4 mg, 0.150 mmol) was added to the solution, causing it to turn dark brown immediately. The mixture was allowed to stir at 22 °C for 10 min under an atmosphere of $N_2$. enoate **3.42** (24.8 mg, 0.100 mmol) were added through a syringe. The vial was re-sealed with a cap (phenolic open top cap with red PTFE/white silicone septum) and removed from the glove box. The resulting solution was allowed to stir at 22 °C for 16 hours before the reaction was quenched by passing the mixture through a short plug of silica gel and eluted with $Et_2O$. The filtrate was concentrated *in vacuo* to provide yellow oil, which was purified by silica gel chromatography (hexanes/ethyl acetate = 75:1 to 60:1) to afford the **3.50** as colorless oil (27.0 mg, 0.085 mmol, 85% yield).

- **Characterization Data for Diesters with a Tertiary Carbon Stereogenic Center**

**Diethyl (*S*)-2-(4-methyl-1-phenylpent-3-en-1-yl)malonate (3.50). IR (neat):** 3030 (w), 2980 (w), 2931 (w), 1752 (s), 1729 (s), 1496 (w), 1453 (m), 1368 (m), 1310 (m), 1248 (s), 1175 (s), 1146 (s), 1112 (m), 1096 (m), 1031 (s), 861 (w), 757 (m), 699 (s), 574 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.30–7.27 (m, 2H), 7.22–7.19 (m, 3H), 4.93 (t, *J* = 8.0 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.93–3.88 (m, 2H), 3.72 (d, *J* = 10.4 Hz, 1H), 3.44 (td, *J* = 10.0, 4.4 Hz, 1H), 2.50–2.43 (m, 1H), 2.36–2.29 (m, 1H), 1.60 (s, 3H), 1.49 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.7, 168.0, 141.1, 133.8, 128.5, 128.2, 126.8, 121.0, 61.6, 61.2, 58.1, 46.0, 32.9, 25.8, 17.8, 14.2, 13.8. **HRMS (ESI$^+$)**: Calcd for $C_{19}H_{27}O_4$ $[M+H]^+$: 319.1909; Found: 319.1912. Specific rotation: $[\alpha]_D^{20.0}$ –7.89 (*c* 1.85, $CHCl_3$) for a 95:5 er sample.

Enantiomeric purity of **3.50** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.




Detector A Channel 2 220nm

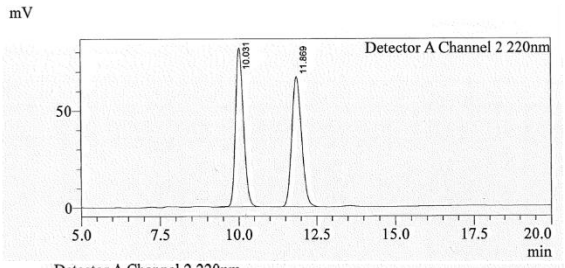
| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 14.354 | 1886077 | 72053 | 49.574 | 66.834 |
| 2 | 27.401 | 1918482 | 35756 | 50.426 | 33.166 |
| Total | | 3804559 | 107809 | 100.000 | 100.000 |

Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 13.020 | 156692 | 6645 | 5.368 | 10.400 |
| 2 | 24.575 | 2762577 | 57248 | 94.632 | 89.600 |
| Total | | 2919269 | 63893 | 100.000 | 100.000 |

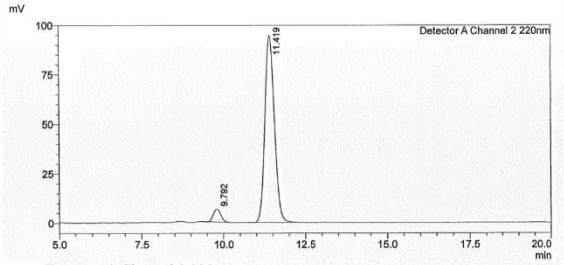
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 14.354 | 1886077 | 49.574 | 13.020 | 156692 | 5.368 |
| 27.401 | 1918482 | 50.426 | 24.575 | 2762577 | 94.632 |

**Diethyl (*S*)-2-(1-(4-fluorophenyl)-4-methylpent-3-en-1-yl)malonate** (**3.62**): **IR (neat)**: 2980 (w), 2931 (w), 1752 (s), 1730 (s), 1605 (w), 1509 (s), 1446 (w), 1368 (m), 1307 (m), 1223 (s), 1175 (s), 1147 (s), 1098 (s), 1031 (s), 860 (w), 831 (s), 570 (w), 546 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.16–7.13 (m, 2H), 6.94 (t, *J* = 8.8 Hz, 2H), 4.87 (t, *J* = 7.2 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.90 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.64 (d, *J* = 11.2 Hz, 1H), 3.40 (td, J = 10.4, 4.8 Hz, 1H), 2.45–2.38 (m, 1H), 2.29–2.21 (m, 1H), 1.57 (s, 3H), 1.45 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.5, 167.9, 161.8 (d, $J_{CF}$ = 243.6 Hz), 136.8 (d, $J_{CF}$ = 3.1 Hz), 134.1, 130.0 (d, $J_{CF}$ = 7.6 Hz), 120.7, 115.1 (d, $J_{CF}$ = 21.2 Hz), 61.7, 61.3, 58.1, 45.2, 33.0, 25.8, 17.8, 14.2, 13.9. **HRMS (DART $^+$)**: Calcd for $C_{19}H_{26}O_4F$ $[M+H]^+$: 337.1815; Found: 337.1816. Specific rotation: $[\alpha]_D^{20.0}$ –5.66 (*c* 1.16, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **3.62** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 10.031 | 1475038 | 81766 | 50.007 | 54.986 |
| 2 | 11.869 | 1474630 | 66938 | 49.993 | 45.014 |
| Total | | 2949668 | 148704 | 100.000 | 100.000 |

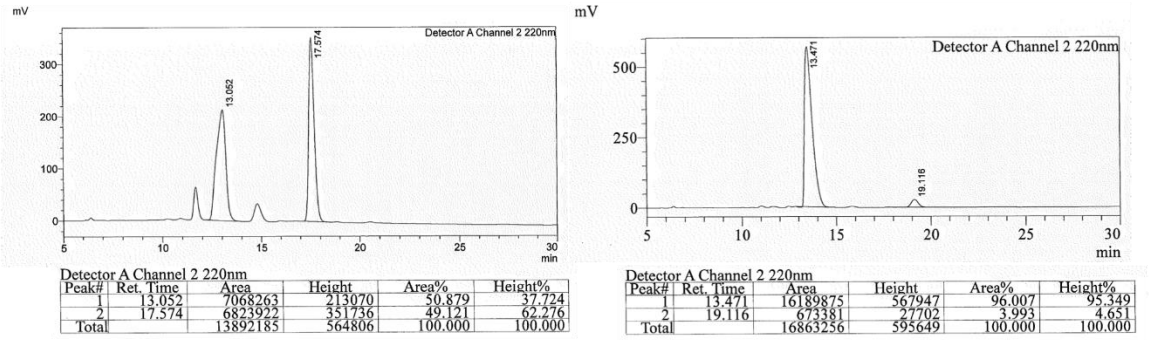



Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 9.792 | 103030 | 6580 | 5.076 | 6.524 |
| 2 | 11.419 | 1926828 | 94273 | 94.924 | 93.476 |
| Total | | 2029858 | 100853 | 100.000 | 100.000 |

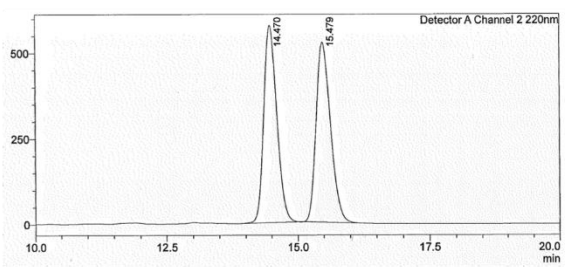
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 10.031 | 1475038 | 50.007 | 9.792 | 103030 | 5.076 |
| 11.869 | 1474630 | 49.993 | 11.419 | 1926828 | 94.924 |

**Diethyl (*S*)-2-(4-methyl-1-(4-(trifluoromethyl)phenyl)pent-3-en-1-yl)malonate** (**3.63**): **IR (neat)**: 2981 (w), 2931 (w), 1752 (s), 1731 (s), 1619 (w), 1447 (w), 1421 (w), 1370 (w), 1324 (s), 1250 (s), 1162 (s), 1113 (s), 1068 (s), 1033 (s), 1018 (s), 833 (s), 732 (w), 610 (m), 444 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.86 (t, *J* = 7.2 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.70 (d, *J* = 10.4 Hz, 1H), 3.52–3.45 (m, 1H), 2.48–2.42 (m, 1H), 2.34–2.26 (m, 1H), 1.58 (s, 3H), 1.44 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.3, 167.7, 145.48, 148.47, 134.6, 129.2 (q, $J_{CF}$ = 31.9 Hz), 128.9, 125.2 (q, $J_{CF}$ = 3.8 Hz), 120.3, 61.9, 61.5, 57.6, 45.7, 32.7, 25.8, 17.8, 14.2, 13.8. **HRMS (DART$^+$)**: Calcd for $C_{20}H_{26}F_3O_4$ $[M+H]^+$: 387.1783; Found: 387.1782. Specific rotation: $[\alpha]_D^{20.0}$ –11.2 (*c* 2.97, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **3.63** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OD–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm



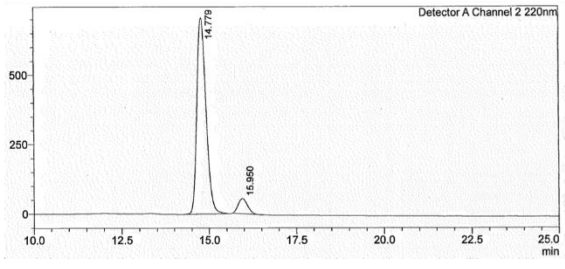

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 13.052 | 7068263 | 50.879 | 13.471 | 16189875 | 96.007 |
| 17.574 | 6823922 | 49.121 | 19.116 | 673381 | 3.993 |

**Diethyl (*S*)-2-(1-(2-methoxyphenyl)-4-methylpent-3-en-1-yl)malonate** (**3.64**): **IR (neat)**: 2979 (w), 2931 (w), 1752 (s), 1730 (s), 1600 (w), 1586 (w), 1493 (m), 1462 (m), 1440 (m), 1368 (m), 1307 (s), 1242 (s), 1175 (s), 1146 (s), 1117 (m), 1096 (m), 1027 (s), 861 (w), 751 (s), 523 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.15 (td, *J* = 7.6, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.84–6.80 (m, 2H), 4.92 (t, *J* = 7.2 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.00 (d, *J* = 10.8 Hz, 1H), 3.91–3.85 (m, 2H), 3.82 (s, 3H), 3.70 (td, *J* = 10.4, 4.8 Hz, 1H), 2.51–2.44 (m, 1H), 2.39–2.33 (m, 1H), 1.55 (s, 3H), 1.44 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 169.1, 168.5, 157.9, 133.2, 130.2, 129.0, 127.9, 121.8, 120.3, 110.8, 61.4, 61.0, 56.1, 55.4, 30.8, 25.8, 17.7, 14.3, 13.9. **HRMS (DART $^+$)**: Calcd for $C_{20}H_{29}O_5$ $[M+H]^+$: 349.2015; Found: 349.2007. Specific rotation: $[\alpha]_D^{20.0}$ –5.50 (*c* 1.09, $CHCl_3$) for a 93:7 er sample. Enantiomeric purity of **3.64** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OD–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 14.470 | 10087012 | 575159 | 50.184 | 52.295 |
| 2 | 15.479 | 10013159 | 524667 | 49.816 | 47.705 |
| Total | | 20100171 | 1099826 | 100.000 | 100.000 |

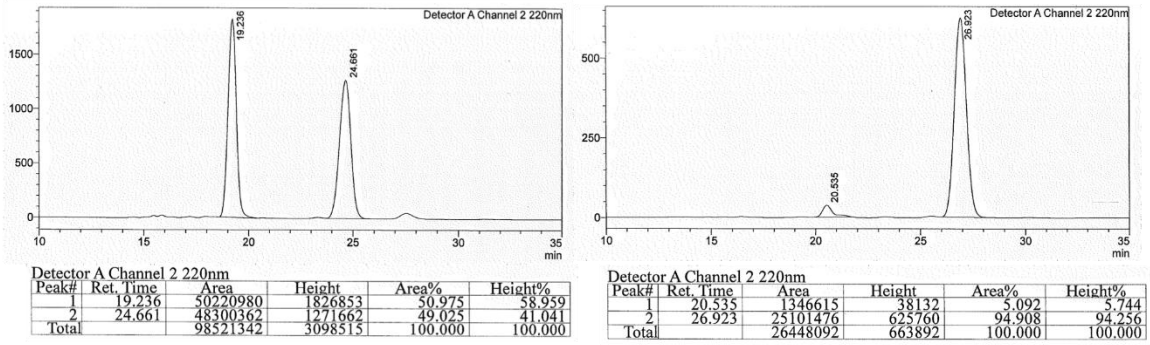



Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 14.779 | 12798830 | 705545 | 92.633 | 92.824 |
| 2 | 15.950 | 1017838 | 54542 | 7.367 | 7.176 |
| Total | | 13816667 | 760086 | 100.000 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 14.470 | 10087012 | 50.184 | 14.779 | 12798830 | 92.633 |
| 15.479 | 10013159 | 49.816 | 15.950 | 1017838 | 7.367 |

**Diethyl (*S*)-2-(1-(3-bromophenyl)-4-methylpent-3-en-1-yl)malonate** (**3.65**): **IR (neat)**: 2979 (w), 2931 (w), 1752 (s), 1730 (s), 1594 (w), 1567 (w), 1474 (w), 1446 (w), 1429 (w), 1368 (m), 1302 (m), 1247 (s), 1176 (s), 1147 (s), 1112 (m), 1096 (m), 1074 (m), 1030 (s), 997 (w), 784 (m), 662 (w), 440 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.33–7.31 (2H, m), 7.13–7.11 (2H, m), 6.84–6.80 (2H, m), 4.88 (1H, t, *J* = 7.2 Hz), 4.23 (2H, q, *J* = 7.2 Hz), 3.92 (2H, q, *J* = 7.2 Hz), 3.65 (1H, d, *J* = 10.8 Hz), 3.38 (1H, td, *J* = 10.0, 4.8 Hz), 2.45–2.39 (1H, m), 2.30–2.23 (1H, m), 1.59 (3H, s), 1.46 (3H, s), 1.29 (3H, t, *J* = 7.2 Hz), 0.97 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.4, 167.8, 143.6, 134.5, 131.6, 130.0, 129.8, 127.3, 122.3, 120.5, 61.8, 61.4, 57.7, 45.6, 32.7, 25.8, 17.8, 14.2, 13.9. **HRMS (DART$^+$)**: Calcd for $C_{19}H_{26}BrO_4$ $[M+H]^+$: 397.1014; Found: 397.1009. Specific rotation: $[\alpha]_D^{20.0}$ –12.0 (*c* 2.39, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **3.65** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 2 220nm

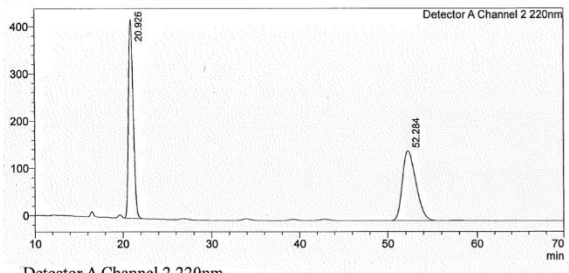
| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 19.236 | 50220980 | 1826853 | 50.975 | 58.959 |
| 2 | 24.661 | 48300362 | 1271662 | 49.025 | 41.041 |
| Total | | 98521342 | 3098515 | 100.000 | 100.000 |

Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 20.535 | 1346615 | 38132 | 5.092 | 5.744 |
| 2 | 26.923 | 25101476 | 625760 | 94.908 | 94.256 |
| Total | | 26448092 | 663892 | 100.000 | 100.000 |

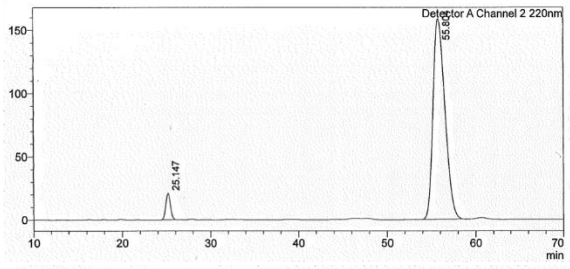
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 19.236 | 50220980 | 50.975 | 20.535 | 1346615 | 5.092 |
| 24.661 | 48300362 | 49.025 | 26.923 | 25101476 | 94.908 |

**Diethyl (*S*)-2-(4-methyl-1-(*o*-tolyl)pent-3-en-1-yl)malonate** (**3.55**): **IR (neat)**: 2978 (w), 2928 (w), 2856 (w), 1753 (s), 1731 (s), 1493 (w), 1464 (w), 1446 (w), 1368 (s), 1307 (s), 1250 (s), 1175 (s), 1146 (s), 1114 (m), 1096 (m), 1032 (s), 861 (w), 756 (m), 726 (m), 594 (w) , 455 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.13–7.12 (2H, m), 7.10–7.05 (2H, m), 4.90 (1H, t, *J* = 7.2 Hz), 4.24 (2H, q, *J* = 7.2 Hz), 3.85 (2H, q, *J* = 7.2 Hz), 3.81–3.72 (2H, m), 2.45–2.38 (1H, m), 2.35 (3H, s), 2.26–2.18 (1H, m), 1.57 (3H, s), 1.44 (3H, s), 1.30 (3H, t, *J* = 7.2 Hz), 0.90 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.8, 168.1, 139.8, 137.1, 133.9, 130.3, 126.5, 126.4, 125.9, 120.7, 61.6, 61.2, 57.9, 40.2, 33.3, 25.8, 20.1, 17.7, 14.3, 13.7. HRMS ($ESI^+$): Calcd for $C_{20}H_{29}O_4$ $[M+H]^+$: 333.2066; Found: 333.2057. Specific rotation: $[\alpha]_D^{20.0}$ –21.8 (*c* 2.17, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **3.55** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 20.926 | 15224891 | 420235 | 49.268 | 73.988 |
| 2 | 52.284 | 15677312 | 147742 | 50.732 | 26.012 |
| Total | | 30902203 | 567976 | 100.000 | 100.000 |

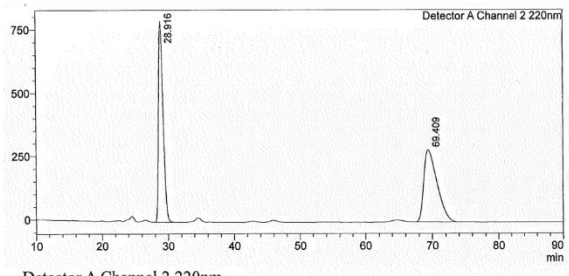



Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 25.147 | 762174 | 20925 | 4.894 | 11.646 |
| 2 | 55.804 | 14810692 | 158748 | 95.106 | 88.354 |
| Total | | 15572865 | 179673 | 100.000 | 100.000 |

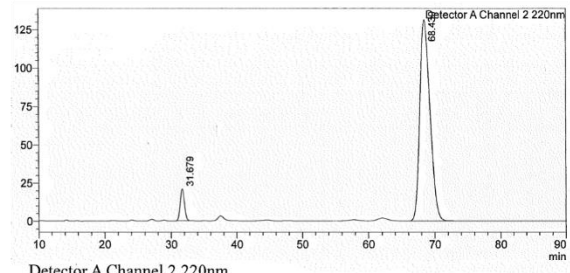
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 20.926 | 15224891 | 49.268 | 25.147 | 762174 | 4.894 |
| 52.284 | 15677312 | 50.732 | 55.804 | 14810692 | 95.106 |

**Diethyl (*S*)-2-(1-(2-chlorophenyl)-4-methylpent-3-en-1-yl)malonate** (**3.56**): **IR (neat)**: 2980 (w), 2932 (w), 1731 (s), 1476 (w), 1443 (w), 1369 (m), 1305 (m), 1247 (s), 1176 (s), 1148 (s), 1110 (m), 1096 (m), 1035 (s), 862 (w), 754 (s), 456 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.32 (1H, d, *J* = 7.2 Hz), 7.20–7.17 (2H, m), 7.17–7.09 (1H, m), 4.93 (1H, tt, *J* = 7.2, 1.2 Hz), 4.24 (2H, q, *J* = 7.6 Hz), 3.85 (2H, q, *J* = 7.2 Hz), 4.10 (1H, s, br), 3.98–3.88 (2H, m), 2.86–2.82 (1H, m), 2.48–2.38 (2H, m), 1.57 (3H, s), 1.42 (3H, s), 1.28 (3H, t, *J* = 7.2 Hz), 0.98 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.4, 167.8, 138.8, 134.8, 134.5, 129.8, 127.8, 126.7, 120.2, 61.7, 61.4, 56.6, 31.7, 29.8, 25.8, 17.7, 14.2, 13.8. **HRMS (ESI$^+$)**: Calcd for $C_{19}H_{26}ClO_4$ $[M+H]^+$: 353.1520; Found: 353.1515. Specific rotation: $[\alpha]_D^{20.0}$ –5.84 (*c* 1.09, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **3.56** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 28.916 | 38790432 | 791678 | 49.511 | 73.586 |
| 2 | 69.409 | 39556842 | 284171 | 50.489 | 26.414 |
| Total | | 78347274 | 1075849 | 100.000 | 100.000 |

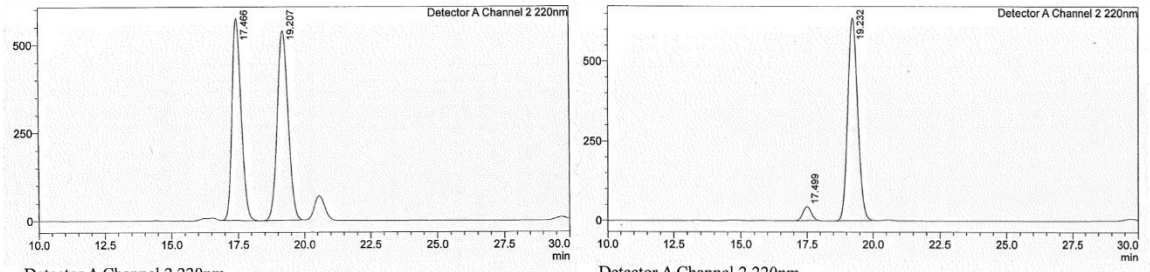



Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 31.679 | 947731 | 20851 | 6.258 | 13.706 |
| 2 | 68.430 | 14196315 | 131276 | 93.742 | 86.294 |
| Total | | 15144046 | 152127 | 100.000 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 28.916 | 38790432 | 49.511 | 31.679 | 947731 | 6.258 |
| 69.409 | 39556842 | 50.489 | 68.430 | 14196315 | 93.742 |

**Diethyl (*S*)-2-(1-(4-methoxyphenyl)-4-methylpent-3-en-1-yl)malonate** (**3.57**): **IR (neat)**: 2979 (w), 2933 (w), 1752 (s), 1729 (s), 1611 (w), 1512 (s), 1463 (w), 1444 (w), 1368 (m), 1303 (m), 1246 (s), 1177 (s), 1146 (s), 1113 (s), 1096 (m), 1033 (s), 861 (w), 828 (s), 573 (w) , 551 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.10 (2H, d, *J* = 8.4 Hz), 6.79 (2H, d, *J* = 8.8 Hz), 4.89 (1H, tt, *J* = 7.2, 1.2 Hz), 4.22 (2H, q, *J* = 7.2 Hz), 3.89 (2H, qd, *J* = 7.2, 1.6 Hz), 3.77 (3H, s), 3.63 (1H, d, *J* = 11.2 Hz), 3.36 (1H, td, *J* = 10.0, 4.8 Hz), 2.44–2.37 (1H, m), 2.29–2.22 (1H, m), 1.58 (3H, s), 1.47 (3H, s), 1.28 (3H, t, *J* = 7.2 Hz), 0.97 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.7, 168.1, 158.4, 133.7, 133.1, 129.5, 121.2, 113.6, 61.6, 61.2, 58.3, 55.3, 45.2, 33.0, 25.8, 17.8, 14.2, 13.9. **HRMS (ESI$^+$)**: Calcd for $C_{20}H_{29}O_5$ $[M+H]^+$: 349.2028; Found: 349.2015. Specific rotation: $[\alpha]_D^{20.0}$ –7.27 (*c* 1.54, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **3.57** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 17.466 | 13665820 | 573904 | 47.138 | 51.582 |
| 2 | 19.207 | 15325167 | 538700 | 52.862 | 48.418 |
| Total | | 28990987 | 1112604 | 100.000 | 100.000 |

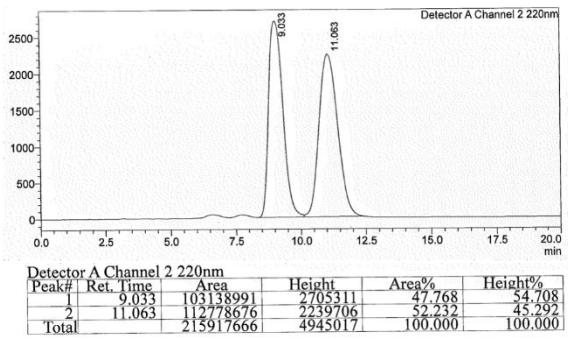
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 17.499 | 1007488 | 44451 | 5.654 | 6.518 |
| 2 | 19.232 | 16810671 | 637541 | 94.346 | 93.482 |
| Total | | 17818159 | 681992 | 100.000 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 17.466 | 13665820 | 47.138 | 17.499 | 1007488 | 5.654 |
| 19.207 | 15325167 | 52.862 | 19.232 | 16810671 | 94.346 |

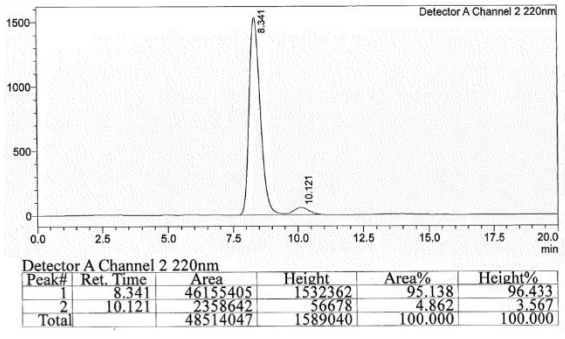
**Diethyl (*S*)-2-(4-methyl-1-(naphthalen-2-yl)pent-3-en-1-yl)malonate** (**3.58**): **IR (neat)**: 3055 (w), 2979 (w), 2931 (w), 1751 (s), 1728 (s), 1600 (w), 1508 (w), 1445 (w), 1368 (m), 1302 (m), 1246 (s), 1174 (s), 1145 (s), 1112 (m), 1095 (m), 1029 (s), 856 (s), 817 (s), 746 (s), 662 (w) , 477

(s) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.80–7.75 (3H, m), 7.64 (1H, s), 7.47–7.41(2H, m), 7.36 (1H, td, *J* = 8.4, 1.2 Hz), 4.93 (1H, t, *J* = 7.2 Hz), 4.26 (2H, q, *J* = 7.2 Hz), 3.87–3.78 (3H, m), 3.61 (1H, td, *J* = 11.2, 4.4 Hz), 2.56–2.50 (1H, m), 2.46–2.38 (1H, m), 1.55 (3H, s), 1.48 (3H, s), 1.31 (3H, t, *J* = 7.2 Hz), 0.85 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.6, 168.0, 138.7, 133.9, 133.4, 132.6, 127.9, 127.7, 127.4, 126.6, 126.0, 125.6, 121.0, 61.7, 61.2, 58.1, 46.0, 32.8, 25.8, 17.9, 14.3, 13.8. **HRMS (DART$^+$)**: Calcd for $C_{23}H_{29}O_4$ $[M+H]^+$: 369.2066; Found: 369.2061. Specific rotation: $[\alpha]_D^{20.0}$ –18.6 (*c* 2.05, $CHCl_3$) for a 95:5 er sample. Enantiomeric purity of **3.58** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 9.033 | 103138991 | 2705311 | 47.768 | 54.708 |
| 2 | 11.063 | 112778676 | 2239706 | 52.232 | 45.292 |
| Total | | 215917666 | 4945017 | 100.000 | 100.000 |



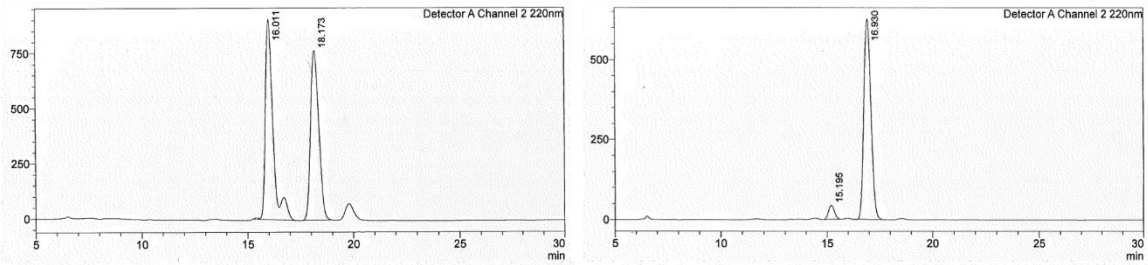

Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 8.341 | 46155405 | 1532362 | 95.138 | 96.433 |
| 2 | 10.121 | 2358642 | 56678 | 4.862 | 3.567 |
| Total | | 48514047 | 1589040 | 100.000 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 9.033 | 101138991 | 47.768 | 8.341 | 46155405 | 95.138 |
| 11.063 | 112778676 | 52.232 | 10.121 | 2358642 | 4.862 |

**Diethyl (*S*)-2-(1-(benzofuran-5-yl)-4-methylpent-3-en-1-yl)malonate (3.59)**: **IR (neat)**: 2979 (w), 2930 (w), 1751 (s), 1728 (s), 1468 (m), 1445 (m), 1368 (m), 1301 (m), 1248 (s), 1175 (s), 1148 (s), 1128 (s), 1111 (s), 1096 (m), 1030 (s), 880 (m), 861 (m), 811 (m), 769 (m), 738 (s), 650 (w), 442 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 600 MHz)**: δ 7.57 (1H, d, *J* = 2.0 Hz), 7.42 (1H, d, *J* = 1.6 Hz), 7.39 (1H, d, *J* = 8.8 Hz), 7.13 (1H, dd, *J* = 8.4, 1.6 Hz), 4.90 (1H, t, *J* = 7.2 Hz), 4.24 (2H, q, *J* = 7.2 Hz), 3.88–3.80 (2H, m), 3.72 (1H, d, *J* = 10.4 Hz), 3.51 (1H, td, *J* = 10.0, 4.8 Hz), 2.51–2.45 (1H, m), 2.38–2.30 (1H, m), 1.56 (3H, s), 1.47 (3H, s), 1.29 (3H, t, *J* = 7.2 Hz), 0.88 (3H, t,

$J$ = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.7, 168.1, 154.1, 145.2, 135.6, 133.7, 127.4, 124.8, 121.1, 121.0, 111.0, 106.7, 61.6, 61.2, 58.6, 45.9, 33.3, 25.8, 17.8, 14.2, 13.8. **HRMS (ESI$^+$)**: Calcd for $C_{21}H_{27}O_5$ $[M+H]^+$: 359.1858; Found: 359.1843. Specific rotation: $[\alpha]_D^{20.0}$ –12.7 (*c* 1.91, $CHCl_3$) for a 94.5:5.5 er sample. Enantiomeric purity of **3.59** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 254 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 16.011 | 22904843 | 907080 | 52.412 | 54.136 |
| 2 | 18.173 | 20797074 | 768478 | 47.588 | 45.864 |
| Total | | 43701917 | 1675559 | 100.000 | 100.000 |

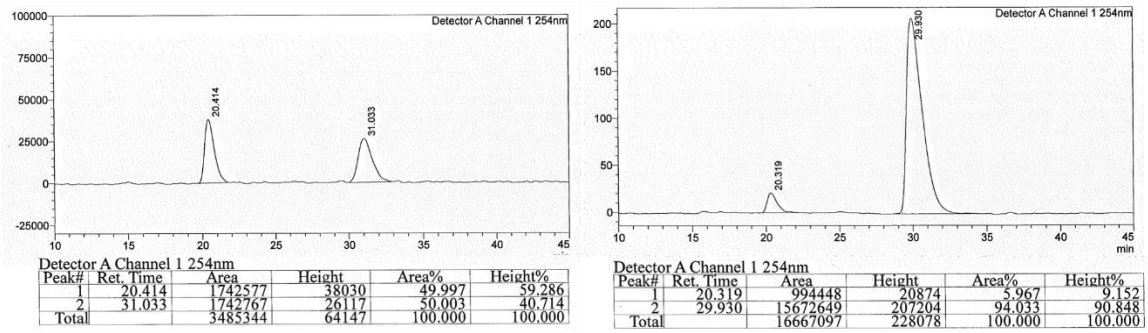
Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 15.195 | 847985 | 43669 | 5.471 | 6.520 |
| 2 | 16.930 | 14652586 | 626114 | 94.529 | 93.480 |
| Total | | 15500571 | 669782 | 100.000 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 16.011 | 22904843 | 52.412 | 15.195 | 847985 | 5.471 |
| 18.173 | 20797074 | 47.588 | 16.930 | 14652586 | 94.529 |

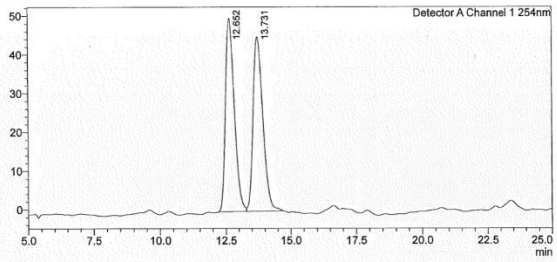
**Diethyl (*S*)-2-(4-methyl-1-(pyridin-4-yl)pent-3-en-1-yl)malonate** (**3.60**): **IR (neat)**: 2980 (w), 2936 (w), 1728 (s), 1599 (m), 1559 (w), 1446 (m), 1416 (m), 1369 (m), 1300 (m), 1235 (s), 1174 (s), 1148 (s), 1128 (s), 1095 (m), 1071 (s), 1028 (s), 858 (m), 821 (m), 769 (m), 586 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 600 MHz)**: δ 8.48 (2H, d, $J$ = 4.0 Hz), 7.11 (2H, d, $J$ = 6.4 Hz), 4.85 (1H, t, $J$ = 7.2 Hz), 4.23 (2H, q, $J$ = 7.2 Hz), 3.91 (2H, qd, $J$ = 7.2, 2.4 Hz), 3.69 (1H, d, $J$ = 11.2 Hz), 3.40 (1H, td, $J$ = 10.0, 4.8 Hz), 2.45–2.39 (1H, m), 2.32–2.24 (1H, m), 1.57 (3H, s), 1.42 (3H, s), 1.28 (3H, t, $J$ = 7.2 Hz), 0.96 (3H, t, $J$ = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.1, 167.5, 150.6, 149.7, 134.9, 123.9, 119.9, 61.9, 61.6, 56.9, 45.2, 32.3, 25.8, 17.8, 14.2, 13.8. **HRMS (DART$^+$)**: Calcd for $C_{18}H_{26}NO_4$ $[M+H]^+$: 320.1862; Found: 320.1869. Specific rotation: $[\alpha]_D^{20.0}$ –8.57 (*c* 1.19, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **3.60** was determined by HPLC analysis in

comparison with authentic racemic material; Chiralpak OZ–H column, 95% hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.



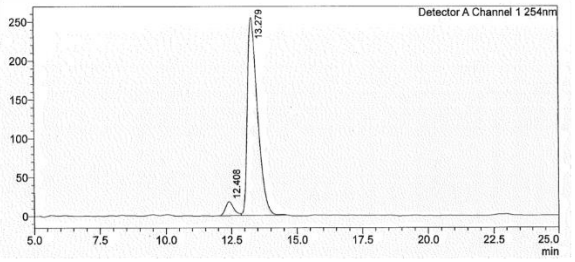

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 20.414 | 1742577 | 49.997 | 20.319 | 994448 | 5.967 |
| 31.033 | 1742767 | 50.003 | 29.930 | 15672649 | 94.033 |

**Diethyl (*S*)-2-(4-methyl-1-(pyridin-3-yl)pent-3-en-1-yl)malonate (3.61): IR (neat)**: 2980 (w), 2933 (w), 1729 (s), 1572 (w), 1446 (m), 1426 (m), 1369 (m), 1302 (m), 1257 (s), 1240 (s), 1219 (s), 1173 (s), 1147 (s), 1111 (m), 1096 (m), 1024 (s), 861 (m), 809 (m), 715 (s), 627 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 8.43 (2H, m), 7.22 (1H, dt, *J* = 7.6, 2.0 Hz), 7.19 (1H, dd, *J* = 7.6, 4.8 Hz), 4.87 (1H, t, *J* = 7.2 Hz), 4.23 (2H, q, *J* = 7.2 Hz), 3.90 (2H, qd, *J* = 7.2, 1.6 Hz), 3.70 (1H, d, *J* = 10.4 Hz), 3.44 (1H, td, *J* = 10.0, 4.4 Hz), 2.48–2.41 (1H, m), 2.33–2.26 (1H, m), 1.57 (3H, s), 1.42 (3H, s), 1.28 (3H, t, *J* = 7.2 Hz), 0.96 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.3, 167.7, 150.3, 148.3, 136.6, 135.8, 134.8, 123.2, 120.1, 61.9, 61.5, 57.3, 43.4, 32.6, 25.8, 17.8, 14.2, 13.9. **HRMS (DART$^+$)**: Calcd for $C_{18}H_{26}NO_4$ $[M+H]^+$: 320.1862; Found: 320.1850. Specific rotation: $[\alpha]_D^{20.0}$ –5.42 (*c* 1.61, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **3.61** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 95% hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.




Detector A Channel 1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 12.652 | 1195002 | 49964 | 50.277 | 52.563 |
| 2 | 13.731 | 1181826 | 45091 | 49.723 | 47.437 |
| Total | | 2376829 | 95055 | 100.000 | 100.000 |

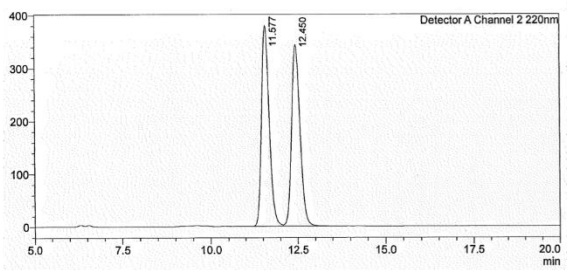



Detector A Channel 1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 12.408 | 419260 | 18158 | 5.706 | 6.660 |
| 2 | 13.279 | 6928379 | 254494 | 94.294 | 93.340 |
| Total | | 7347639 | 272652 | 100.000 | 100.000 |

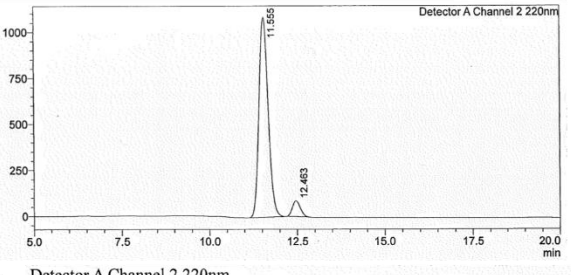
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 12.652 | 1195002 | 50.277 | 12.408 | 419260 | 5.706 |
| 13.731 | 1181826 | 49.723 | 13.279 | 6928379 | 94.294 |

**Diethyl (*S*)-2-(1-(1-(*tert*-butoxycarbonyl)-1*H*-indol-6-yl)-4-methylpent-3-en-1-yl)malonate (3.62)**: **IR (neat)**: 2979 (w), 2932 (w), 1729 (s), 1529 (w), 1480 (w), 1439 (m), 1369 (m), 1335 (s), 1252 (s), 1211 (m), 1219 (s), 1170 (s), 1144 (s), 1128 (s), 1096 (m), 1078 (m), 1024 (s), 908 (m), 855 (m), 818 (m), 767 (m), 729 (s), 652 (m), 466 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 8.02 (1H, s), 7.53 (1H, d, *J* = 3.6 Hz), 7.42 (1H, d, *J* = 8.0 Hz), 7.07 (1H, d, *J* = 8.0 Hz), 6.49 (1H, d, *J* = 3.6 Hz), 4.93 (1H, t, *J* = 7.2 Hz), 4.26-4.19 (2H, m) 3.86 (2H, q, *J* = 7.2 Hz), 3.75 (1H, d, *J* = 10.4 Hz), 3.55 (1H, td, *J* = 10.0, 4.4 Hz), 2.52–2.46 (1H, m), 2.41–2.34 (1H, m), 1.67 (9H, s), 1.56 (3H, s), 1.48 (3H, s), 1.29 (3H, t, *J* = 7.2 Hz), 0.93 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.8, 168.1, 149.8, 137.5, 135.4, 133.6, 129.5, 125.9, 123.6, 121.3, 120.5, 115.0, 107.2, 83.6, 61.6, 61.2, 58.5, 46.3, 33.2, 28.3, 25.8, 17.9, 14.2, 13.8. **HRMS (ESI$^+$):** Calcd for $C_{26}H_{39}O_6N_2$ $[M+NH_4]^+$: 475.2808; Found: 475.2811. Specific rotation: $[\alpha]_D^{20.0}$ –8.15 (*c* 2.65, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **3.62** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OD–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 11.577 | 5913937 | 379688 | 50.282 | 52.516 |
| 2 | 12.450 | 5847648 | 343303 | 49.718 | 47.484 |
| Total | | 11761585 | 722991 | 100.000 | 100.000 |

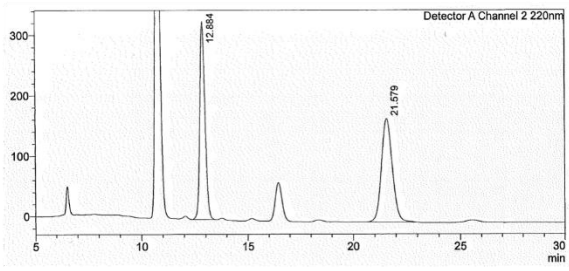



Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 11.555 | 19969066 | 1086794 | 93.747 | 92.703 |
| 2 | 12.463 | 1331850 | 85542 | 6.253 | 7.297 |
| Total | | 21300916 | 1172336 | 100.000 | 100.000 |

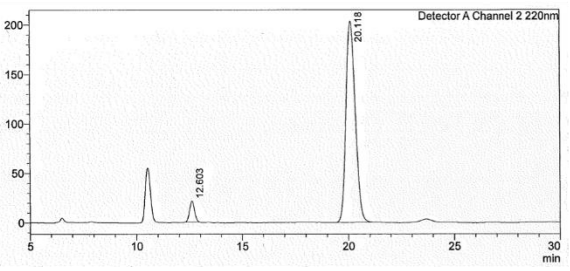
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 11.577 | 5913937 | 50.282 | 11.555 | 19969066 | 93.747 |
| 12.450 | 5847648 | 49.718 | 12.463 | 1331850 | 6.253 |

**Diethyl (*S*)-2-(1-(1-benzyl-1*H*-pyrrol-2-yl)-4-methylpent-3-en-1-yl)malonate (3.63)**: **IR (neat)**: 2979 (w), 2929 (w), 1750 (s), 1729 (s), 1496 (w), 1477 (w), 1452 (m), 1368 (m), 1300 (m), 1242 (s), 1176 (s), 1146 (s), 1096 (m), 1078 (m), 1028 (s), 861 (w), 778 (m), 705 (s), 622 (w), 613 (w), 443 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 500 MHz)**: δ 7.34–7.23 (3H, m), 7.08 (1H, d, *J* = 7.6 Hz), 6.52–6.50 (1H, m), 6.08 (1H, t, *J* = 3.2 Hz), 5.98–5.97 (1H, m), 5.20 (1H, d, *J* = 8.0 Hz), 5.02 (1H, d, *J* = 8.0 Hz), 4.79 (1H, t, *J* = 7.2 Hz), 4.19 (2H, q, *J* = 7.2 Hz) 3.97 (2H, q, *J* = 7.2 Hz), 3.60–3.51 (2H, m), 2.19 (2H, d, *J* = 6.4 Hz), 1.52 (3H, s), 1.41 (3H, s), 1.27 (3H, t, *J* = 7.2 Hz), 1.06 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.6, 168.3, 138.7, 133.9, 132.8, 128.68, 128.65, 127.4, 127.1, 120.9, 107.5, 106.5, 83.6, 61.6, 61.4, 58.1, 50.4, 36.3, 32.8, 25.9, 17.7, 14.2, 14.0. **HRMS (DART$^+$)**: Calcd for $C_{24}H_{32}O_4N$ $[M+H]^+$: 398.2331; Found: 398.2346. Specific rotation: $[\alpha]_D^{20.0}$ 1.69 (*c* 2.13, $CHCl_3$) for a 94.5:5.5 er sample. Enantiomeric purity of **3.63** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 12.884 | 5499273 | 327739 | 47.450 | 65.620 |
| 2 | 21.579 | 6090333 | 171708 | 52.550 | 34.380 |
| Total | | 11589606 | 499448 | 100.000 | 100.000 |




Detector A Channel 2 220nm

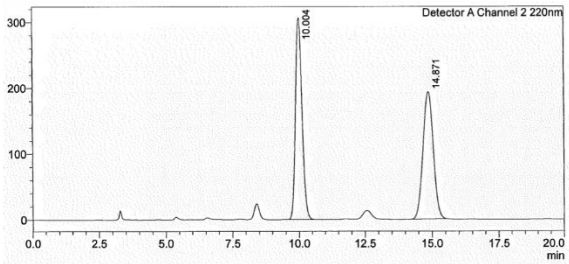
| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 12.603 | 355854 | 21459 | 5.456 | 9.542 |
| 2 | 20.118 | 6166678 | 203440 | 94.544 | 90.458 |
| Total | | 6522532 | 224900 | 100.000 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 12.884 | 5499273 | 47.450 | 12.603 | 355854 | 5.456 |
| 21.579 | 6090333 | 52.550 | 20.118 | 6166678 | 94.544 |

**Diethyl (*S*)-2-(4-methyl-1-(thiophen-3-yl)pent-3-en-1-yl)malonate** (**3.64**): **IR (neat)**: 2979 (w), 2929 (w), 1751 (s), 1728 (s), 1446 (m), 1413 (w), 1368 (m), 1301 (m), 1255 (s), 1236 (s), 1174 (s), 1145 (s), 1112 (m), 1096 (m), 1030 (s), 904 (w), 858 (m), 836 (m), 782 (m), 657 (m), 428 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 500 MHz)**: δ 7.20 (1H, dd, *J* = 4.8, 3.2 Hz), 6.99 (1H, d, *J* = 3.2 Hz), 6.96 (1H, d, *J* = 4.8 Hz), 4.95 (1H, t, *J* = 7.2 Hz), 4.21 (2H, q, *J* = 7.2 Hz) 3.95 (2H, q, *J* = 7.2 Hz), 3.64 (1H, d, *J* = 10.0 Hz), 3.60–3.55 (1H, m), 2.45–2.39 (1H, m), 2.32–2.25 (1H, m), 1.61 (3H, s), 1.48 (3H, s), 1.28 (3H, t, *J* = 7.2 Hz), 1.02 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.6, 168.2, 141.8, 134.1, 61.6, 61.3, 57.8, 41.2, 32.7, 25.9, 17.7, 14.2, 13.9. **HRMS (DART$^+$)**: Calcd for $C_{17}H_{25}SO_4$ $[M+H]^+$: 325.1474; Found: 325.1486. Specific rotation: $[\alpha]_D^{20.0}$ 1.21 (*c* 0.99, $CHCl_3$) for a 91:9 er sample.

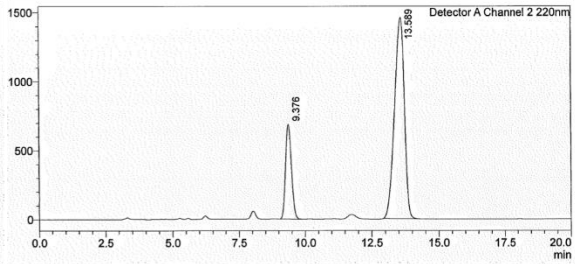
**Diethyl (*S*)-2-(1-(furan-2-yl)-4-methylpent-3-en-1-yl)malonate** (**3.65**): **IR (neat)**: 2981 (w), 2931 (w), 1752 (s), 1731 (s), 1505 (w), 1446 (w), 1368 (m), 1303 (m), 1258 (s), 1239 (s), 1146 (s), 1112 (m), 1096 (m), 1031 (s), 1011 (s), 861 (m), 805 (m), 731 (s), 599 (m), 438 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.30 (1H, t, *J* = 0.8 Hz), 6.25 (1H, t, *J* = 2.0 Hz), 6.05 (1H, d, *J* = 3.2 Hz), 4.98 (1H, t, *J* = 7.2 Hz), 4.21 (2H, q, *J* = 7.2 Hz), 4.01 (2H, qd, *J* = 7.2, 2.0 Hz), 3.70 (1H, d, *J* = 9.6 Hz), 3.57–3.51 (1H, m), 2.39 (1H, t, *J* = 7.2 Hz), 1.63 (3H, s), 1.51 (3H, s), 1.27 (3H, t, *J*

= 7.2 Hz), 1.11 (3H, t, *J* = 7.2 Hz); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.3, 168.1, 154.5, 142.5, 134.3, 120.7, 110.2, 107.1, 61.6, 61.4, 56.0, 39.4, 30.5, 25.9, 17.7, 14.2, 14.0. **HRMS (DART$^+$)**: Calcd for $C_{17}H_{25}O_5$ $[M+H]^+$: 309.1702; Found: 309.1712. Specific rotation: $[\alpha]_D^{20.0}$ –0.72 (*c* 1.11, $CHCl_3$) for a 78:22 er sample. Enantiomeric purity of **3.65** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.




Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 10.004 | 5236899 | 306125 | 50.101 | 61.283 |
| 2 | 14.871 | 5215705 | 193399 | 49.899 | 38.717 |
| Total | | 10452604 | 499524 | 100.000 | 100.000 |



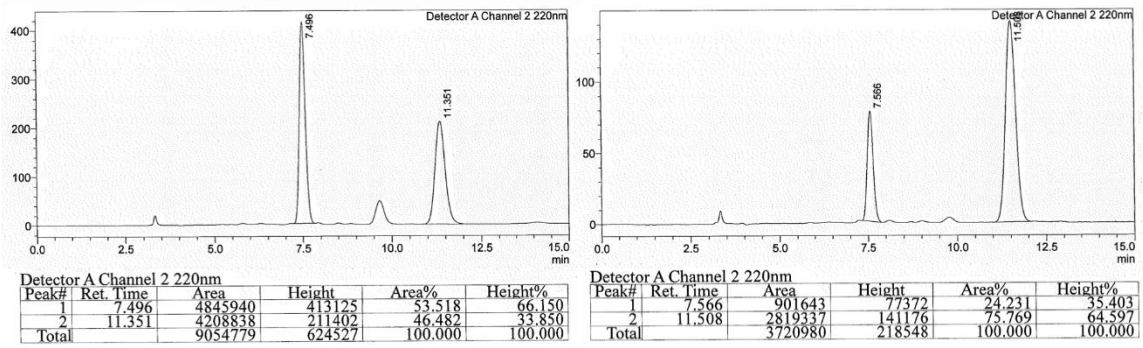

Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 9.376 | 10572351 | 687770 | 22.190 | 32.037 |
| 2 | 13.589 | 37072252 | 1459057 | 77.810 | 67.963 |
| Total | | 47644602 | 2146827 | 100.000 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 10.004 | 5236899 | 50.101 | 9.376 | 10572351 | 22.190 |
| 14.871 | 5215705 | 49.899 | 13.589 | 37072252 | 77.810 |

**Diethyl (*S*)-2-(4-methyl-1-(thiophen-2-yl)pent-3-en-1-yl)malonate** (**3.66**): **IR (neat)**: 2980 (w), 2930 (w), 1751 (s), 1730 (s), 1444 (w), 1368 (m), 1303 (m), 1259 (s), 1238 (s), 1149 (s), 1113 (m), 1096 (m), 1030 (s), 852 (m), 827 (m), 695 (s), 613 (w), 533 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.14 (d, *J* = 5.2 Hz, 1H), 6.88 (d, *J* = 5.2, 3.6 Hz, 1H), 6.84 (d, *J* = 3.6 Hz, 1H), 5.01 (t, *J* = 7.2 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H) 3.98 (q, *J* = 7.2 Hz, 2H), 3.78–3.72 (m, 1H), 3.65 (d, *J* = 10.4 Hz, 1H), 2.52–2.46 (m, 1H), 2.38–2.30 (m, 1H), 1.63 (s, 3H), 1.52 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 168.3, 167.9, 144.5, 134.5, 126.4, 125.6, 124.0, 120.8, 61.7, 61.4, 58.7, 41.2, 33.8, 25.9, 17.9, 14.2, 13.9. **HRMS (DART$^+$)**: Calcd for $C_{17}H_{25}SO_4$ $[M+H]^+$: 325.1474; Found: 325.1473. Specific rotation: $[\alpha]_D^{20.0}$ 4.86 (*c* 1.07, $CHCl_3$) for a 76:24 er sample. Enantiomeric purity of **3.66** was determined by HPLC analysis in

comparison with authentic racemic material; Chiralpak OZ–H column, 99% hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.




Detector A Channel 2 220nm

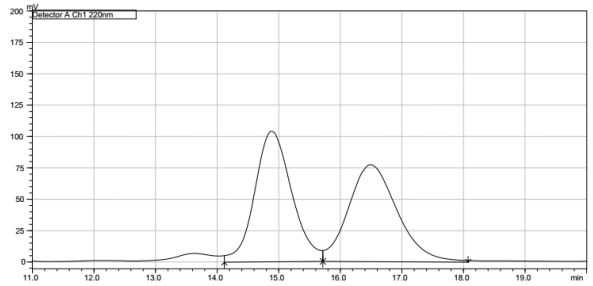
| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 7.496 | 4845940 | 413125 | 53.518 | 66.150 |
| 2 | 11.351 | 4208838 | 211402 | 46.482 | 33.850 |
| Total | | 9054779 | 624527 | 100.000 | 100.000 |

Detector A Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% | Height% |
|---|---|---|---|---|---|
| 1 | 7.566 | 901643 | 77372 | 24.231 | 35.403 |
| 2 | 11.508 | 2819337 | 141176 | 75.769 | 64.597 |
| Total | | 3720980 | 218548 | 100.000 | 100.000 |

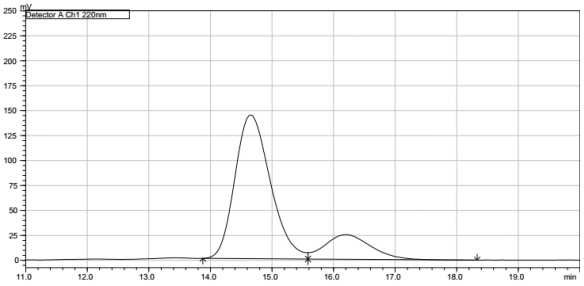
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 7.496 | 4845940 | 53.518 | 7.566 | 901643 | 24.231 |
| 11.351 | 4208838 | 46.482 | 11.508 | 2819337 | 75.769 |

**Diethyl (S)-2-(5-methylhex-4-en-2-yl)malonate (3.68): IR (neat):** 2977 (w), 2931 (w), 1730 (s), 1447 (w), 1368 (w), 1305 (m), 1240 (m), 1153 (m), 1032 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ $^1$H NMR (400 MHz, $CDCl_3$) δ 5.1 (t, *J* = 7.5 Hz, 1H), 4.2 (q, *J* = 7.2 Hz, 4H), 3.2 (d, *J* = 8.0 Hz, 1H), 2.3 – 2.2 (m, 1H), 2.1 (dt, *J* = 13.2, 6.2 Hz, 1H), 1.9 (dt, *J* = 15.0, 8.0 Hz, 1H), 1.7 (s, 3H), 1.6 (s, 3H), 1.3 (t, *J* = 7.1 Hz, 6H), 1.0 (d, *J* = 6.8 Hz, 3H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.2, 169.0, 133.9, 121.8, 61.3, 61.2, 57.2, 34.2, 33.0, 26.0, 18.0, 17.1, 14.3, 14.3; **HRMS (DART$^+$)**: Calcd for $C_{14}H_{25}O_4$ $[M+H]^+$: 257.1747; Found: 257.1750. Specific rotation: $[\alpha]_D^{20.0}$ 1.11 (*c* 0.6, $CHCl_3$) for a 82:18 er sample. Enantiomeric purity of **3.68** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OJ-H column, 99% hexanes, 1% *i*PrOH, 0.8 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 14.882 | 4347589 | 50.566 |
| 2 | 16.494 | 4250193 | 49.434 |
| Total | | 8597782 | 100.000 |

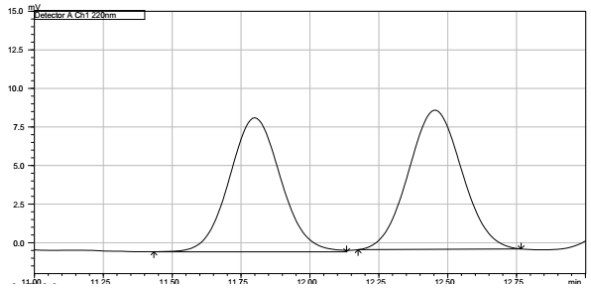



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 14.657 | 5765998 | 81.892 |
| 2 | 16.197 | 1274942 | 18.108 |
| Total | | 7040940 | 100.000 |

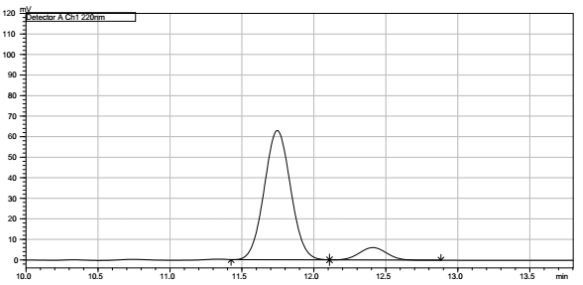
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 14.882 | 4347589 | 50.566 | 14.657 | 5765998 | 81.892 |
| 16.494 | 4250193 | 49.434 | 16.197 | 1274942 | 18.108 |

**Diethyl (*R*)-2-(1-cyclohexyl-4-methylpent-3-en-1-yl)malonate (3.69): IR (neat):** 2977 (w), 2922 (m), 2850 (w), 1728 (s), 1447 (w), 1367 (w), 1300 (w), 1218 (w), 1148 (m), 1096 (w), 1032 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 5.0 (t, *J* = 6.9 Hz, 1H), 4.3–4.0 (m, 4H), 3.4 (d, *J* = 7.2 Hz, 1H), 2.2–2.1 (m, 2H), 2.1–2.0 (m, 1H), 1.7 (d, *J* = 12.0 Hz, 2H), 1.7 (s, 3H), 1.7–1.6 (m, 3H), 1.6 (s, 3H), 1.4 (td, *J* = 11.6, 3.4 Hz, 1H), 1.3 (td, *J* = 7.1, 3.9 Hz, 6H), 1.2–1.0 (m, 5H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 169.7, 169.5, 132.5, 123.9, 61.3, 61.2, 54.5, 44.6, 40.4, 31.3, 29.4, 27.7, 27.1, 26.9, 26.7, 26.0, 17.9, 14.2, 14.2; **HRMS (DART$^+$)**: Calcd for $C_{19}H_{33}O_4$ $[M+H]^+$: 325.2373; Found: 325.2372. Specific rotation: $[\alpha]_D^{20.0}$ 5.35 (*c* 0.59, $CHCl_3$) for a 91:9 er sample. Enantiomeric purity of **3.69** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ-H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 11.799 | 113124 | 48.075 |
| 2 | 12.454 | 122184 | 51.925 |
| Total | | 235308 | 100.000 |

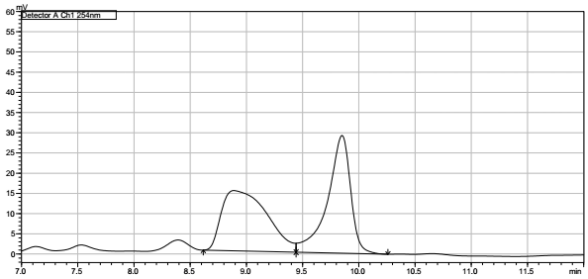



Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 11.746 | 803277 | 90.985 |
| 2 | 12.410 | 79592 | 9.015 |
| Total | | 882869 | 100.000 |

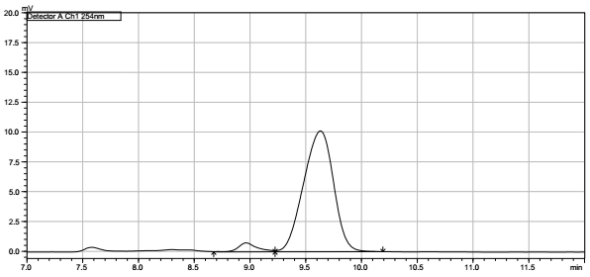
| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 11.799 | 113124 | 48.075 | 11.746 | 803277 | 90.985 |
| 12.454 | 122184 | 51.925 | 12.410 | 79592 | 9.015 |

**Diethyl (*S*,*E*)-2-((2-(2-methylbut-3-en-2-yl)cyclohexylidene)methyl)malonate (3.71): IR (neat):** 2931 (m), 2862 (w), 1732 (s), 1446 (w), 1365 (w), 1299 (m), 1177 (m), 1146 (m), 1033 (m), 908 (w), 859 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 5.96–5.83 (m, 1H), 5.51 (d, *J* = 9.5 Hz, 1H), 4.95–4.86 (m, 2H), 4.30 (d, *J* = 9.3 Hz, 1H), 4.24–4.12 (m, 4H), 2.26 (dt, *J* = 13.8, 4.5 Hz, 1H), 2.15–2.00 (m, 2H), 1.7 –1.52 (m, 4H), 1.43–1.32 (m, 2H), 1.25 (td, *J* = 7.1, 4.0 Hz, 6H), 1.03 (d, *J* = 2.2 Hz, 6H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 169.0, 168.8, 148.4, 145.8, 117.1, 110.7, 61.5, 61.5, 53.5, 51.1, 40.2, 27.8, 27.6, 27.4, 26.9, 26.4, 23.4, 14.2, 14.2; **HRMS (DART$^+$)**: Calcd for $C_{19}H_{31}O_4$ $[M+H]^+$: 323.2217; Found: 323.2230. Specific rotation: $[\alpha]_D^{20.0}$ –57.97 (*c* 1.51, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **3.71** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OD-H column, 99% hexanes, 1% *i*PrOH, 0.5 mL/min, 220 nm.




Detector A Channel 1 254nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 8.888 | 421469 | 50.437 |
| 2 | 9.850 | 414158 | 49.563 |
| Total | | 835627 | 100.000 |



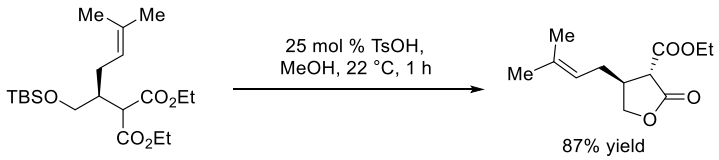

Detector A Channel 1 254nm

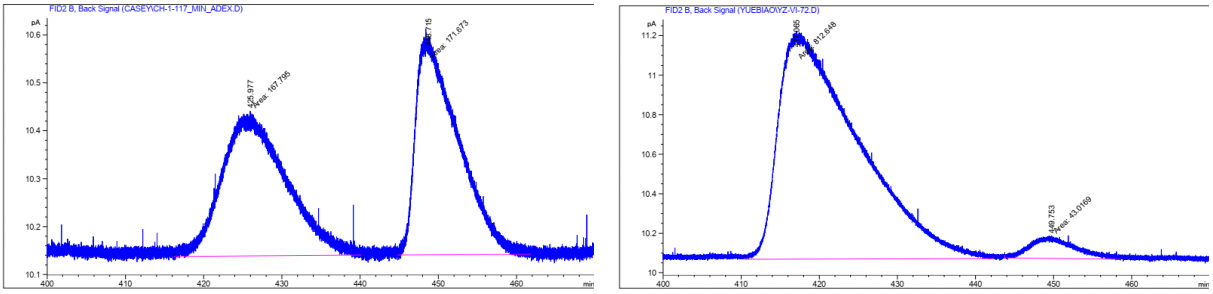
| Peak# | Ret. Time | Area | Height | Area% |
|---|---|---|---|---|
| 1 | 8.964 | 8856 | 756 | 4.469 |
| 2 | 9.632 | 189313 | 10133 | 95.531 |
| Total | | 198169 | 10889 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 8.888 | 421469 | 50.437 | 8.964 | 8856 | 4.469 |
| 9.850 | 414158 | 49.563 | 9.632 | 189313 | 95.531 |

**Diethyl (*S*)-2-(1-((tert-butyldimethylsilyl)oxy)-5-methylhex-4-en-2-yl)malonate (3.72): IR (neat):** 2954 (w), 2927 (w), 2855 (w), 1730 (s), 1463 (w), 1367 (w), 1299 (w), 1248 (m), 1150 (m), 1096 (s), 1029 (m), 834 (s), 774 (s), 668 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 5.08 (t, *J*

= 7.3 Hz, 1H), 4.23–4.12 (m, 4H), 3.59 (d, *J* = 4.8 Hz, 2H), 3.57 (d, *J* = 7.9 Hz, 1H), 2.32–2.23 (m, 1H), 2.22–2.11 (m, 1H), 2.06–1.97 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H), 1.25 (td, *J* = 7.1, 3.4 Hz, 6H), 0.87 (s, 9H), 0.00 (d, *J* = 1.9 Hz, 6H); **$^{13}$C NMR (CDCl$_3$, 100 MHz)**: δ 169.3, 169.2, 133.8, 122.0, 62.3, 61.3, 61.2, 52.9, 41.7, 27.2, 26.0, 25.9, 18.4, 17.9, 14.2, 14.2, -5.5, -5.5; **HRMS (DART$^+$)**: Calcd for $C_{20}H_{39}O_5Si$ $[M+H]^+$: 387.2561; Found: 387.2563. Specific rotation: $[\alpha]_D^{20.0}$ –11.41 (*c* 0.66, $CHCl_3$) for a 97:3 er sample. Enantiomeric purity of **3.72** was determined by GC analysis of the derivative shown below in comparison with authentic racemic material; α dex column, 120 °C, 15 psi.

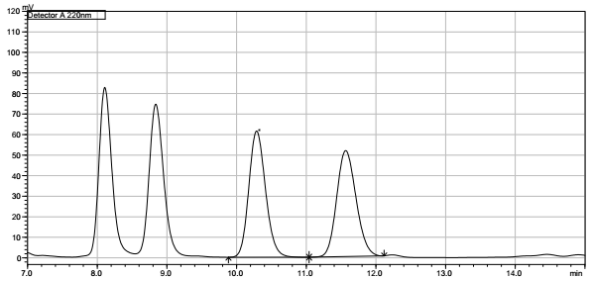


| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 425.977 | 167.795 | 49.429 | 417.065 | 812.649 | 94.973 |
| 448.715 | 171.673 | 50.571 | 449.753 | 43.017 | 5.027 |

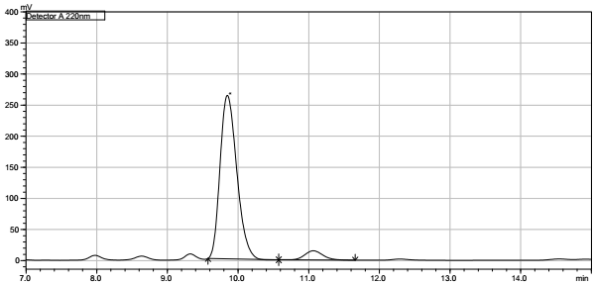
**Diethyl (*S*)-2-(1-(benzyloxy)-5-methylhex-4-en-2-yl)malonate (3.73): IR (neat):** 3029 (w), 2977 (w), 2917 (w), 2855 (w), 1729 (s), 1453 (w), 1367 (w), 1303 (w), 1233 (m), 1153 (m), 1110 (m), 1029 (m), 737 (w), 698 (w) cm$^{-1}$; **$^1$H NMR (CDCl$_3$, 400 MHz)**: δ 7.37–7.24 (m, 5H), 5.07 (t, *J* = 7.7 Hz, 1H), 4.44 (s, 2H), 4.20–4.07 (m, 4H), 3.59 (d, *J* = 7.5 Hz, 1H), 3.50 (d, *J* = 5.4 Hz, 2H), 2.52–2.40 (m, 1H), 2.25–2.05 (m, 2H), 1.69 (s, 3H), 1.58 (s, 3H), 1.23 (dt, *J* = 9.7, 7.1 Hz, 6H); **$^{13}$C NMR (CDCl$_3$, 100 MHz)**: δ 169.2, 169.1, 138.6, 134.1, 128.4, 127.7, 127.6, 121.7, 73.2,

70.2, 61.3, 61.3, 53.3, 39.8, 27.9, 26.0, 17.9, 14.2, 14.2; **HRMS (DART$^+$)**: Calcd for $C_{21}H_{31}O_5$ $[M+H]^+$: 363.2166; Found: 363.2173. Specific rotation: $[\alpha]_D^{20.0}$ –5.8 (*c* 1.05, $CHCl_3$) for a 94:6 er sample. Enantiomeric purity of **3.73** was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak OZ-H column, 99% hexanes, 1% *i*PrOH, 0.8 mL/min, 220 nm.




Detector A 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 10.287 | 1024558 | 50.687 |
| 2 | 11.566 | 996793 | 49.313 |
| Total | | 2021351 | 100.000 |




Detector A 220nm

| Peak# | Ret. Time | Area | Conc. |
|---|---|---|---|
| 1 | 9.848 | 4317345 | 94.256 |
| 2 | 11.064 | 263109 | 5.744 |
| Total | | 4580454 | |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 10.287 | 1024558 | 50.687 | 9.848 | 4317345 | 94.256 |
| 11.566 | 996793 | 49.313 | 11.064 | 263109 | 5.744 |

**Diethyl 2-((S)-4-methyl-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)pent-3-en-1-yl)malonate (3.74):**

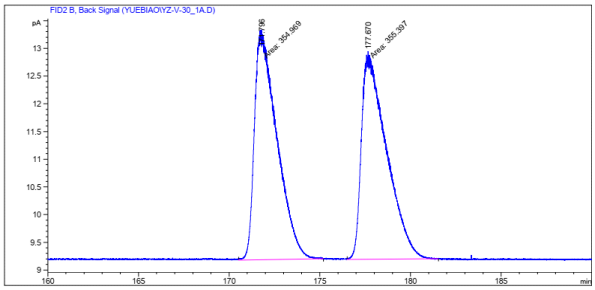
**IR (neat)** 2930 (m), 2856 (w), 1729 (s), 1446 (w), 1366 (w), 1252 (m), 1160 (s), 1098 (s), 1030 (s), 934 (m), 847 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 5.10 (t, *J* = 7.3 Hz, 1H), 4.26 (dd, *J* = 12.8, 6.3 Hz, 1H), 4.23–4.06 (m, 4H), 3.96 (dd, *J* = 8.1, 6.4 Hz, 1H), 3.67 (t, *J* = 7.9 Hz, 1H), 3.49 (d, *J* = 6.0 Hz, 1H), 2.54–2.45 (m, 1H), 2.23 (q, *J* = 6.4 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.62–1.57 (m, 4H), 1.56–1.50 (m, 4H), 1.43–1.32 (m, 2H), 1.27 (td, *J* = 7.1, 2.0 Hz, 6H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 169.2, 168.9, 134.0, 122.1, 109.4, 75.8, 66.7, 61.5, 52.5, 41.1, 36.1, 34.9, 26.8, 26.0, 25.3, 24.1, 23.9, 17.9, 14.2; **HRMS (DART$^+$)**: Calcd for $C_{21}H_{35}O_6$ $[M+H]^+$: 383.2428; Found: 383.2433. Specific rotation: $[\alpha]_D^{20.0}$ –2.67 (*c* 0.53, $CHCl_3$) for a 93:7 dr sample.

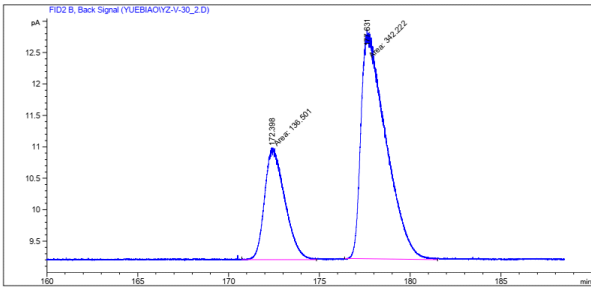
**Diethyl 2-((*S*)-4-methyl-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)pent-3-en-1-yl)malonate (3.75):**

**IR (neat)** 2977 (w), 2932 (m), 2859 (w), 1729 (s), 1447 (w), 1366 (w), 1277 (m), 1230 (m), 1162

(s), 1099 (s), 1033 (m), 931 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 5.01 (t, *J* = 7.5 Hz, 1H), 4.22–4.09 (m, 4H), 3.97 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.71 (d, *J* = 5.4 Hz, 1H), 3.55 (t, *J* = 7.9 Hz, 1H), 2.40–2.30 (m, 1H), 2.14 (t, *J* = 7.0 Hz, 2H), 1.66 (s, 3H), 1.59–1.54 (m, 7H), 1.52 (s, br, 4H), 1.35 (s, br, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 169.3, 168.9, 134.2, 121.6, 109.1, 76.6, 68.5, 61.3, 61.1, 52.7, 43.2, 36.3, 35.1, 27.5, 25.9, 25.3, 24.1, 23.9, 17.9, 14.2, 14.2; **HRMS (DART$^+$)**: Calcd for $C_{21}H_{35}O_6$ $[M+H]^+$: 383.2428; Found: 383.2433. Specific rotation: $[\alpha]_D^{20.0}$ 0.94 (*c* 1.77, $CHCl_3$) for a 88:12 dr sample.

**1-(2-Methylbut-3-en-2-yl)cyclohex-2-en-1-ol (3.78): IR (neat)** 2955 (m), 2920 (s), 2850 (m), 1462 (w), 1377 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 6.05 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.91 (ddd, *J* = 10.3, 5.4, 2.2 Hz, 1H), 5.77 (ddd, *J* = 10.2, 2.7, 1.5 Hz, 1H), 5.08 (dd, *J* = 9.2, 1.6 Hz, 1H), 5.04 (d, *J* = 15.7 Hz, 1H), 2.08–1.96 (m, 1H), 1.94–1.82 (m, 1H), 1.77–1.57 (m, 5H), 1.05 (s, 6H); **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 145.3, 132.0, 129.6, 113.2, 72.7, 43.6, 31.1, 25.3, 22.1, 21.6, 19.0; **HRMS (DART$^+$)**: Calcd for $C_{11}H_{17}$ $[M+H-H_2O]^+$: 149.1325; Found: 149.1322. Specific rotation: $[\alpha]_D^{20.0}$ 36.85 (*c* 0.17, $CHCl_3$) for a 71:29 er sample. Enantiomeric purity of **3.78** was determined by GC analysis in comparison with authentic racemic material; α dex column, 70 °C, 15 psi.

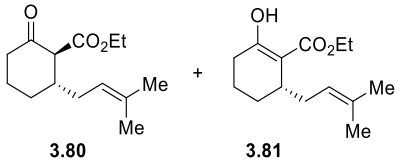



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 171.796 | 354.969 | 49.970 | 172.398 | 136.501 | 28.514 |
| 177.670 | 355.397 | 50.030 | 177.631 | 342.222 | 71.486 |

**Procedure for NHC–Cu-catalyzed prenyl conjugate additions to cyclic enoates:**

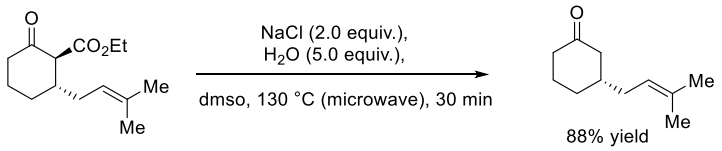
In an $N_2$-filled glove box, an oven-dried vial (4 mL) with a magnetic stir bar was charged with imidazolinium salt **imid-3.14** (3.1 mg, 0.006 mmol), CuCl (0.5 mg, 0.005 mmol,), NaOEt (13.6 mg, 0.2 mmol) and tetrahydrofuran (thf, 0.4 mL). The vessel was sealed with a cap (phenolic open top cap with red PTFE/white silicone septum) and the solution was allowed to stir at 22 °C for 1.0 hour. 1,1-Dimethylallyl–B(pin) **3.48** (29.4 mg, 0.150 mmol) was added to the solution, causing it to turn dark brown immediately. The mixture was allowed to stir at 22 °C for 5 min under an atmosphere of $N_2$. Ethanol (4.6 mg, 0.100 mmol) was added at 22 °C and the mixture was allowed to stir for 1 min before enoate **3.79** (16.8 mg, 0.100 mmol) in thf (0.1 mL) were added over 5 min through a syringe. The vial was re-sealed with a cap (phenolic open top cap with red PTFE/white silicone septum) and removed from the glove box. The resulting solution was allowed to stir at 22 °C for 1.0 h before the reaction was quenched by addition of saturated aqueous solution of $NH_4Cl$ and passing the mixture through a short plug of silica gel and eluted with $Et_2O$. The filtrate was concentrated in vacuo to provide yellow oil, which was purified by silica gel chromatography (3:1 to 1:1 hexanes/dichloromethane then 20:1 hexanes/ethyl acetate) to afford the **3.80/3.81** as colorless oil (15.4 mg, 0.065 mmol, 65% yield).

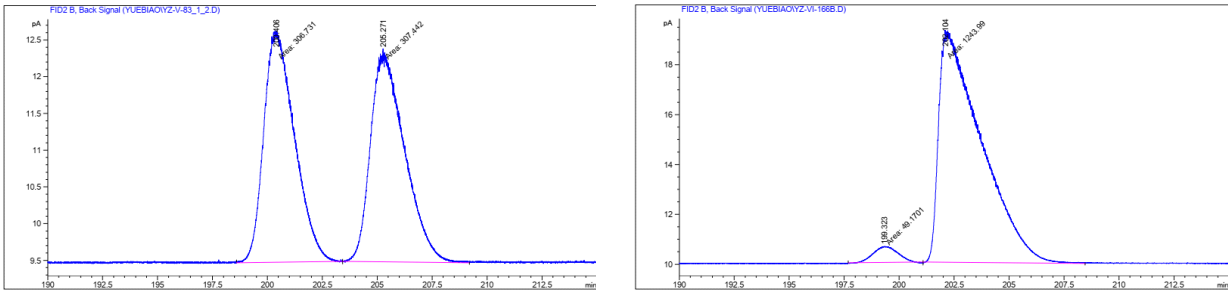



**3.80** **3.81**

**Ethyl (1*S*,2*S*)-2-(3-methylbut-2-en-1-yl)-6-oxocyclohexane-1-carboxylate (4:1 ketone 3.80 and enol 3.81 mixture): IR (neat)** 2922 (m), 2852 (w), 1740 (s), 1711 (s), 1642 (w), 1447 (w), 1370 (w), 1286 (w), 1254 (m), 1217 (m), 1141 (m), 1041 (w), 837 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 12.44 (s, $1H_{enol}$), 5.18–5.06 (m, $1H_{enol+ketone}$), 4.30–4.12 (m, $2H_{enol+ketone}$), 3.13 (d, $J$ = 11.0 Hz, $1H_{ketone}$), 2.61–2.49 (m, $1H_{enol}$), 2.51–2.41 (m, $1H_{ketone}$), 2.34–2.19 (m, $2H_{enol+ketone}$),

2.13–1.92 (m, $4H_{enol+ketone}$), 1.77–1.64 (m, $4H_{enol+ketone}$), 1.61 (s, $3H_{enol}$), 1.58 (s, $3H_{ketone}$), 1.51–1.37 (m, $1H_{enol+ketone}$), 1.28 (t, $J$ = 7.2 Hz, $3H_{enol+ketone}$); **$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ $206.6_{ketone}$, $173.0_{enol}$, $172.9_{enol}$, $170.0_{ketone}$, $134.5_{ketone}$, $132.5_{enol}$, $123.6_{enol}$, $120.7_{ketone}$, $102.5_{enol}$, $63.2_{ketone}$, $61.0_{ketone}$, $60.3_{enol}$, $41.8_{ketone}$, $41.3_{ketone}$, $33.2_{ketone}$, $32.7_{enol}$, $32.4_{enol}$, $29.8_{enol}$, $29.3_{enol}$, $29.1_{ketone}$, $26.0_{ketone}$, $25.9_{enol}$, $25.2_{enol}$, $24.9_{ketone}$, $17.9_{ketone}$, $17.2_{enol}$, $14.4_{enol}$, $14.3_{ketone}$; **HRMS (DART$^+$)**: Calcd for $C_{14}H_{23}O_3$ $[M+H]^+$: 239.1642; Found: 239.1653. Specific rotation: $[\alpha]_D^{20.0}$ −1.55 (*c* 0.65, $CHCl_3$) for a 96:4 er sample. Enantiomeric purity of **3.80** was determined by GC analysis of the derivative shown below in comparison with authentic racemic material; α dex column, 90 °C, 12 psi.

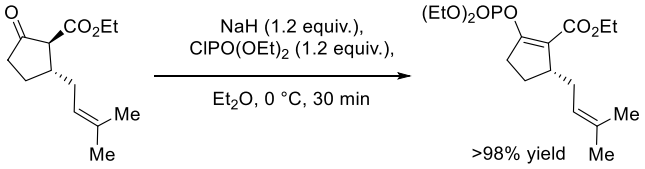


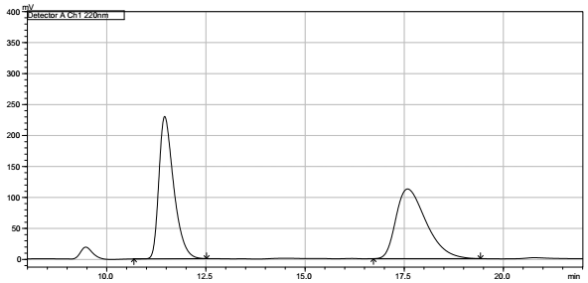



| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 200.406 | 306.731 | 49.942 | 199.323 | 49.170 | 3.802 |
| 205.271 | 307.442 | 50.058 | 202.104 | 1243.986 | 96.198 |

**Ethyl (1*S*,2*S*)-2-(3-methylbut-2-en-1-yl)-5-oxocyclopentane-1-carboxylate (3.90): IR (neat)** 2963 (m), 2925 (m), 2853 (w), 1754 (s), 1724 (s), 1454 (w), 1405 (w), 1333 (w), 1301 (w), 1191 (w), 1123 (m), 1029 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 5.12 (tt, $J$ = 7.5, 1.5 Hz, 1H), 4.18 (qd, $J$ = 7.1, 2.5 Hz, 2H), 2.83 (d, $J$ = 11.3 Hz, 1H), 2.69–2.56 (m, 1H), 2.47–2.27 (m, 2H), 2.27–2.10 (m, 3H), 1.69 (s, 3H), 1.60 (s, 3H), 1.58–1.44 (m, 1H), 1.27 (t, $J$ = 7.1 Hz, 3H); **$^{13}$C NMR**

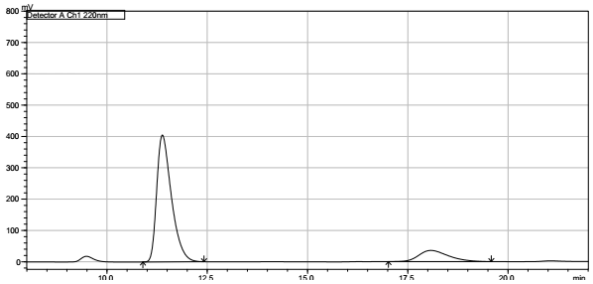
**(CDCl$_3$, 100 MHz):** δ 212.2, 169.6, 134.3, 120.8, 61.4, 61.3, 42.0, 38.6, 32.6, 27.0, 25.9, 17.9, 14.4; **HRMS (DART$^+$)**: Calcd for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1485; Found: 225.1487. Specific rotation: $[\alpha]_D^{20.0}$ 26.83 (*c* 0.78, $CHCl_3$) for a 85:15 er sample. Enantiomeric purity of **3.90** was determined by HPLC analysis of the derivative shown below in comparison with authentic racemic material; Chiralpak OJ-H column, 99% hexanes, 1% *i*PrOH, 0.8 mL/min, 220 nm.




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 11.460 | 5959575 | 50.048 |
| 2 | 17.586 | 5948168 | 49.952 |
| Total | | 11907744 | 100.000 |




Detector A Channel 1 220nm

| Peak# | Ret. Time | Area | Area% |
|---|---|---|---|
| 1 | 11.380 | 10326146 | 84.997 |
| 2 | 18.077 | 1822655 | 15.003 |
| Total | | 12148801 | 100.000 |

| Retention Time | Area | Area% | Retention Time | Area | Area% |
|---|---|---|---|---|---|
| 11.460 | 5959575 | 50.048 | 11.380 | 10326146 | 84.997 |
| 17.586 | 5948168 | 49.952 | 18.077 | 1822655 | 15.003 |

**Procedure for allylic oxidation to synthesize 3.91:**

In an oven-dried vial with a magnetic stir bar was charged with SeO2 (1.1 mg, 0.010 mmol), salicylic acid (1.4 mg, 0.010 mmol), **3.50** (31.8 mg, 0.100 mmol) and dichloromethane (1.0 mL). *t*-BuOOH (17% in $H_2O$, 127 μL, 0.240 mmol) was added to the mixture dropwise at 22 °C under $N_2$ atmosphere. The resulting mixture was allowed to stir at 22 °C for 16 h before aqueous solution of NaOH (0.2M, 0.5 mL), MeOH (0.5 mL) and $NaBH_4$ (7.6 mg, 0.200 mmol) were added subsequently at 22 °C. Then the mixture was allowed to stir at 22 °C for 2 h before the reaction was quenched by addition of saturated aqueous solution of $NH_4Cl$. The organic layer was separated

and the aqueous layer was washed with dichloromethane (5.0 mL x 3). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The resulting colorless oil was purified by silica gel column chromatography (3:1 hexanes:ethyl acetate) to afford **3.91** as colorless oil (20.1 mg, 0.060 mmol, 60% yield).

**Diethyl (*S*,*E*)-2-(5-hydroxy-4-methyl-1-phenylpent-3-en-1-yl)malonate (3.91): IR (neat)** 3487 (w, br), 2979 (w), 2934 (w), 2862 (w), 1729 (s), 1453 (w), 1368 (w), 1311 (m), 1250 (m), 1150 (m), 1029 (m), 861 (w), 760 (w), 701 (m) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.28–7.22 (m, 2H), 7.21–7.15 (m, 3H), 5.19 (t, *J* = 7.3 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.94–3.82 (m, 4H), 3.69 (d, *J* = 10.7 Hz, 1H), 3.44 (td, *J* = 10.3, 4.4 Hz, 1H), 2.49 (ddd, *J* = 12.5, 7.4, 4.6 Hz, 1H), 2.43–2.30 (m, 1H), 1.52 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 168.6, 167.9, 140.7, 137.1, 128.5, 128.4, 127.1, 122.7, 68.8, 61.7, 61.3, 58.1, 45.6, 32.4, 14.2, 13.8, 13.8; **HRMS (DART$^+$)**: Calcd for $C_{19}H_{25}O_4$ $[M+H-H_2O]^+$: 317.1747; Found: 317.1750. Specific rotation: $[\alpha]_D^{20.0}$ −7.38 (*c* 0.70, $CHCl_3$) for a 95:5 er sample.

**Procedure for converting 3.72 to γ-lactone 3.92:**

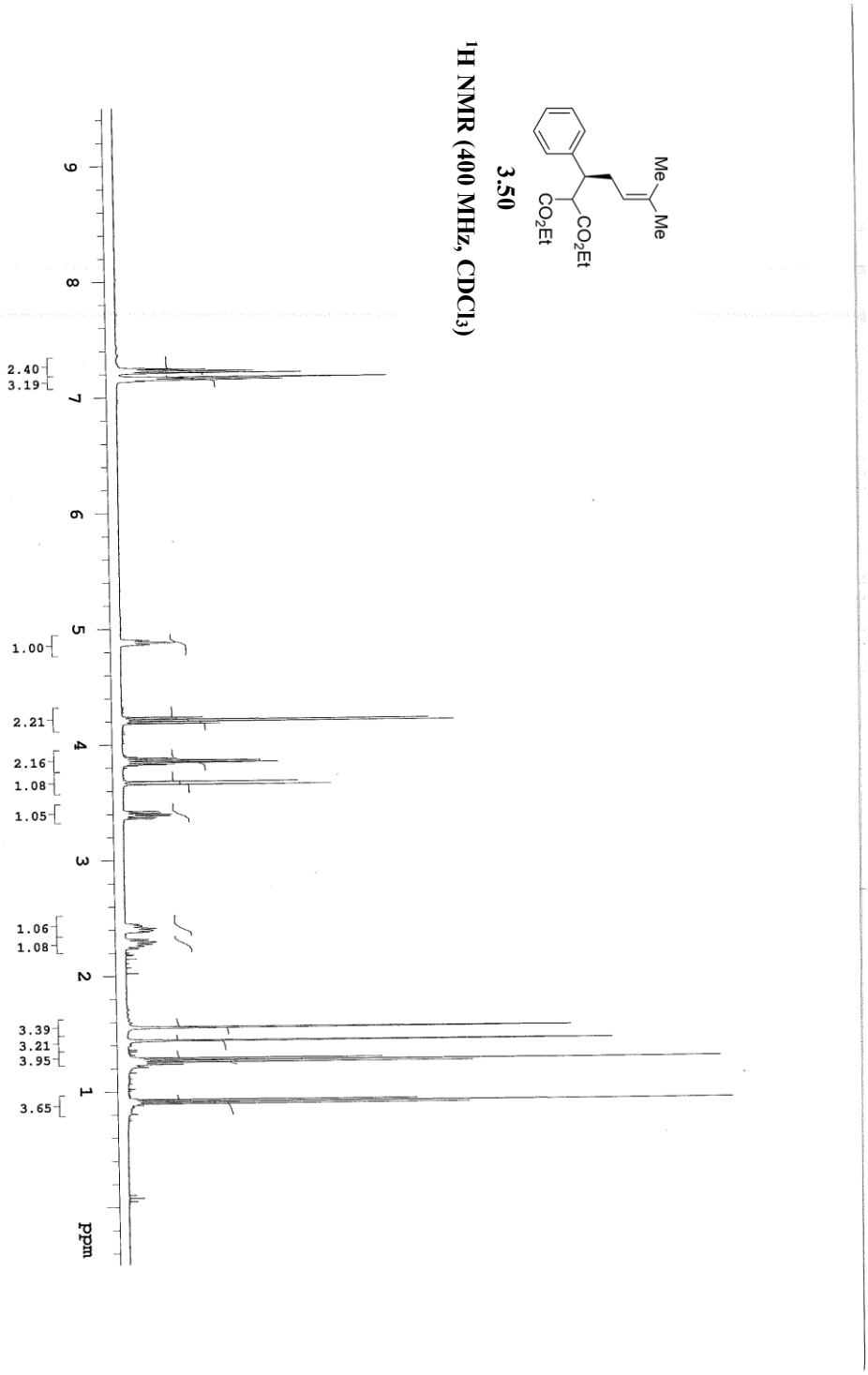
In an oven-dried vial with a magnetic stir bar was charged with *p*-TsOH (4.3 mg, 0.025 mmol), **3.72** (38.6 mg, 0.100 mmol) and MeOH (1.0 mL). The vial was sealed and the mixture was allowed to stir at 22 °C for 2 h before $Et_2O$ and saturated aqueous solution of $NaHCO_3$ were added. The organic layer was separated and the aqueous layer was washed with $Et_2O$ (3.0 mL x 3). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The resulting colorless oil was passed through a short plug of silica gel to afford ester containing γ-lactone as colorless oil.

In an oven-dried microwave pressure vessel was charged with the ester containing γ-lactone (0.100 mmol), NaCl (11.7 mg, 0.200 mmol), $H_2O$ (9.0 μL, 0.500 mmol) and dmso (0.5 mL). The vial was

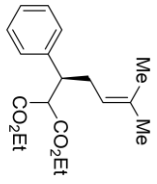
sealed with a cap and placed in a microwave synthesizer (50 W) for 30 min at 130 °C, after which $H_2O$ and $Et_2O$ were added. The organic layer was separated and the aqueous layer was washed with $Et_2O$ (5.0 mL x 3). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The resulting colorless oil was purified by silica gel column chromatography (20:1 hexanes:ethyl acetate) to afford **3.92** as colorless oil (13.0 mg, 0.084 mmol, 84% yield).

**(*S*)-4-(3-Methylbut-2-en-1-yl)dihydrofuran-2(*3H*)-one (3.92): IR (neat)** 2967 (w), 2911 (w), 1769 (s), 1418 (w), 1375 (w), 1164 (s), 1016 (m), 994 (m), 835 (w), 685 (w) $cm^{-1}$; **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 5.05 (t, *J* = 7.4 Hz, 1H), 4.37 (dd, *J* = 9.1, 7.1 Hz, 1H), 3.97 (dd, *J* = 9.1, 5.8 Hz, 1H), 2.66–2.51 (m, 2H), 2.28–2.13 (m, 2H), 1.72 (s, 3H), 1.62 (s, 3H); **$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 177.4, 135.1, 120.1, 73.0, 35.9, 34.1, 31.4, 25.9, 18.0; **HRMS (DART$^+$)**: Calcd for $C_9H_{15}O_2$ $[M+H]^+$: 155.1067; Found: 155.1069. Specific rotation: $[\alpha]_D^{20.0}$ –21.69 (*c* 0.85, $CHCl_3$) for a 97:3 er sample.

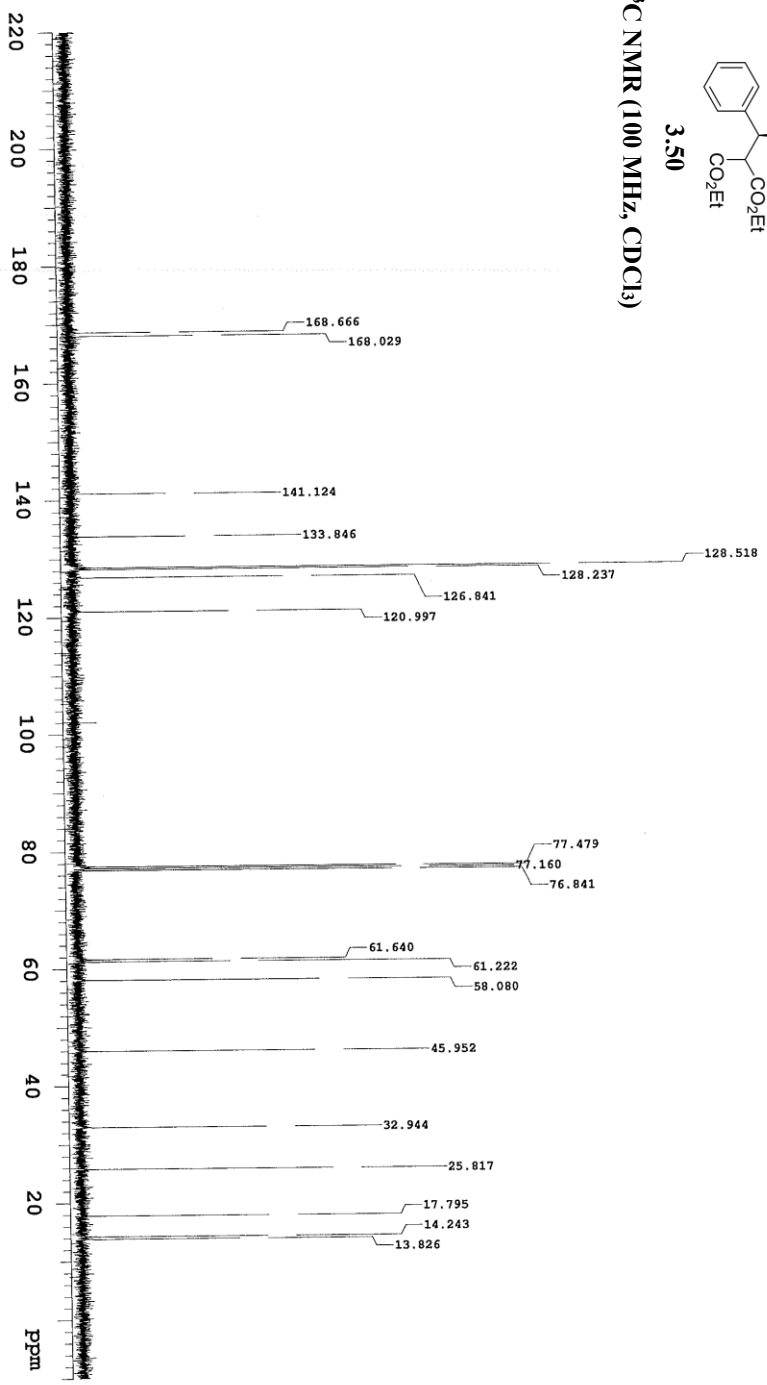
- **NMR Spectra**


3.50
$^1$H NMR (400 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
2.40
3.19
1.00
2.21
2.16
1.08
1.05
1.06
1.08
3.39
3.21
3.95
3.65
ppm

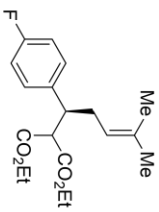
**3.50**




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



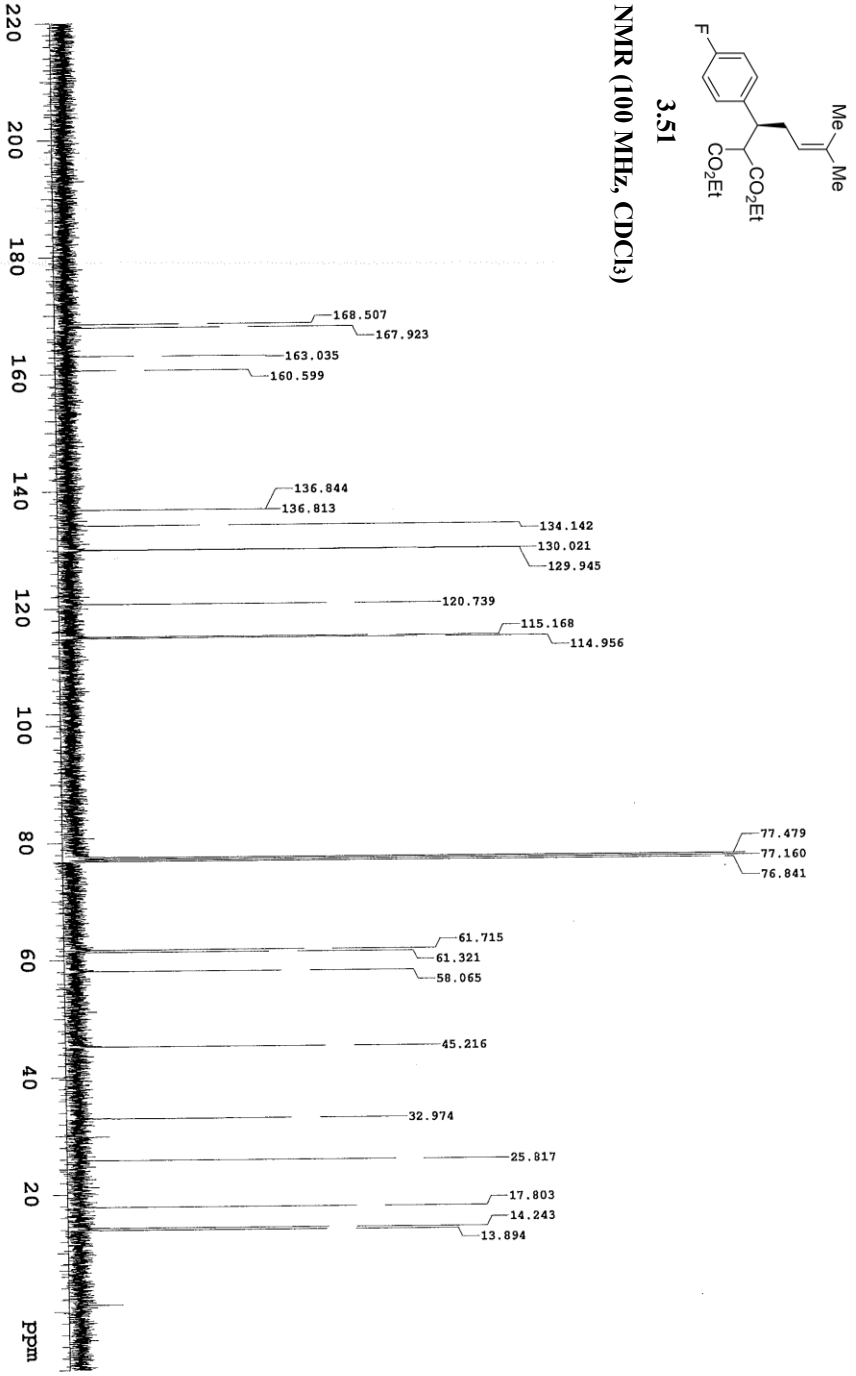
**3.51**

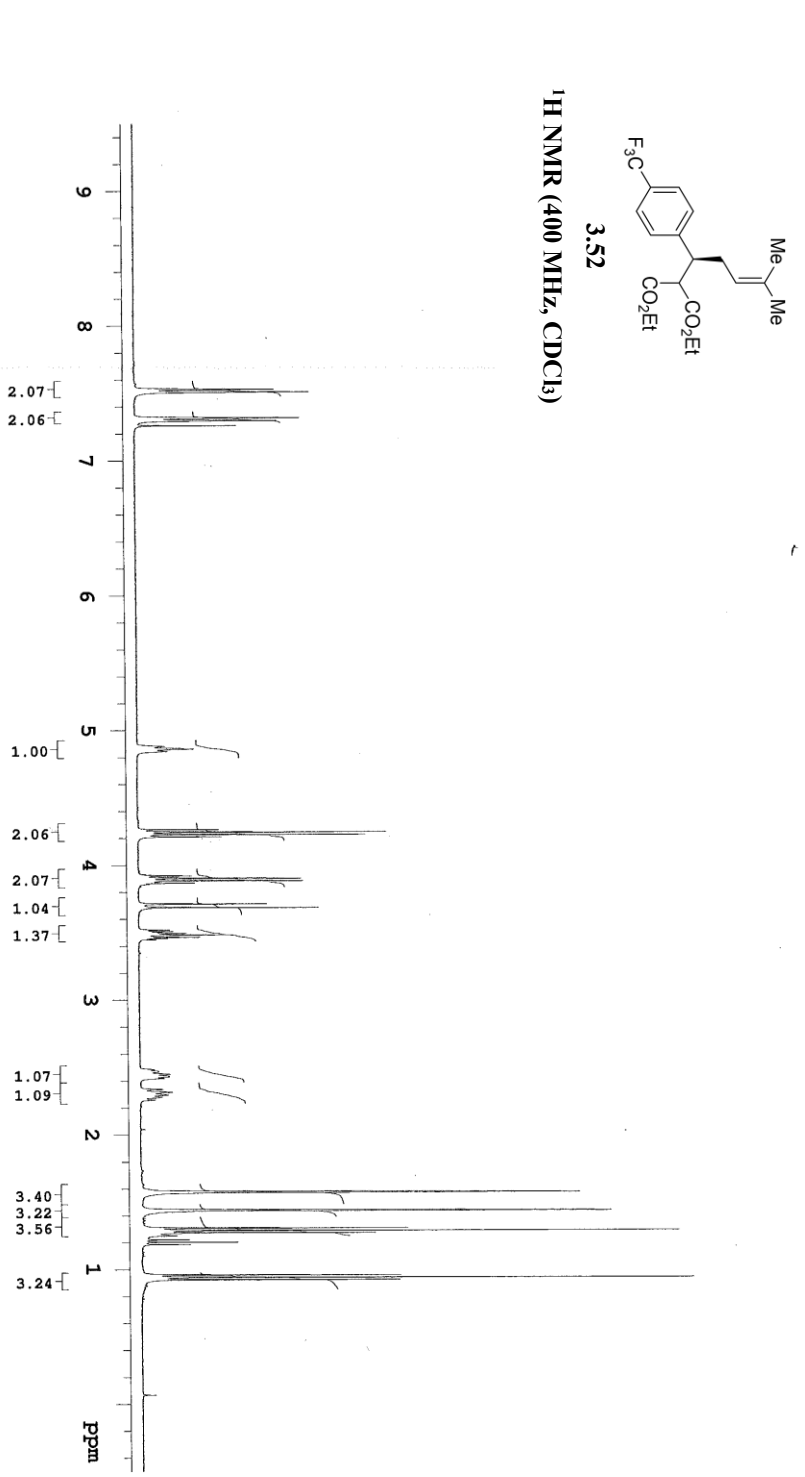



**$^1$H NMR (400 MHz, $CDCl_3$)**

**3.51**

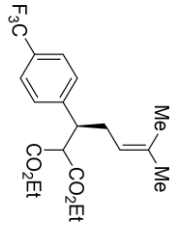
**$^{13}$C NMR (100 MHz, CDCl$_3$)**

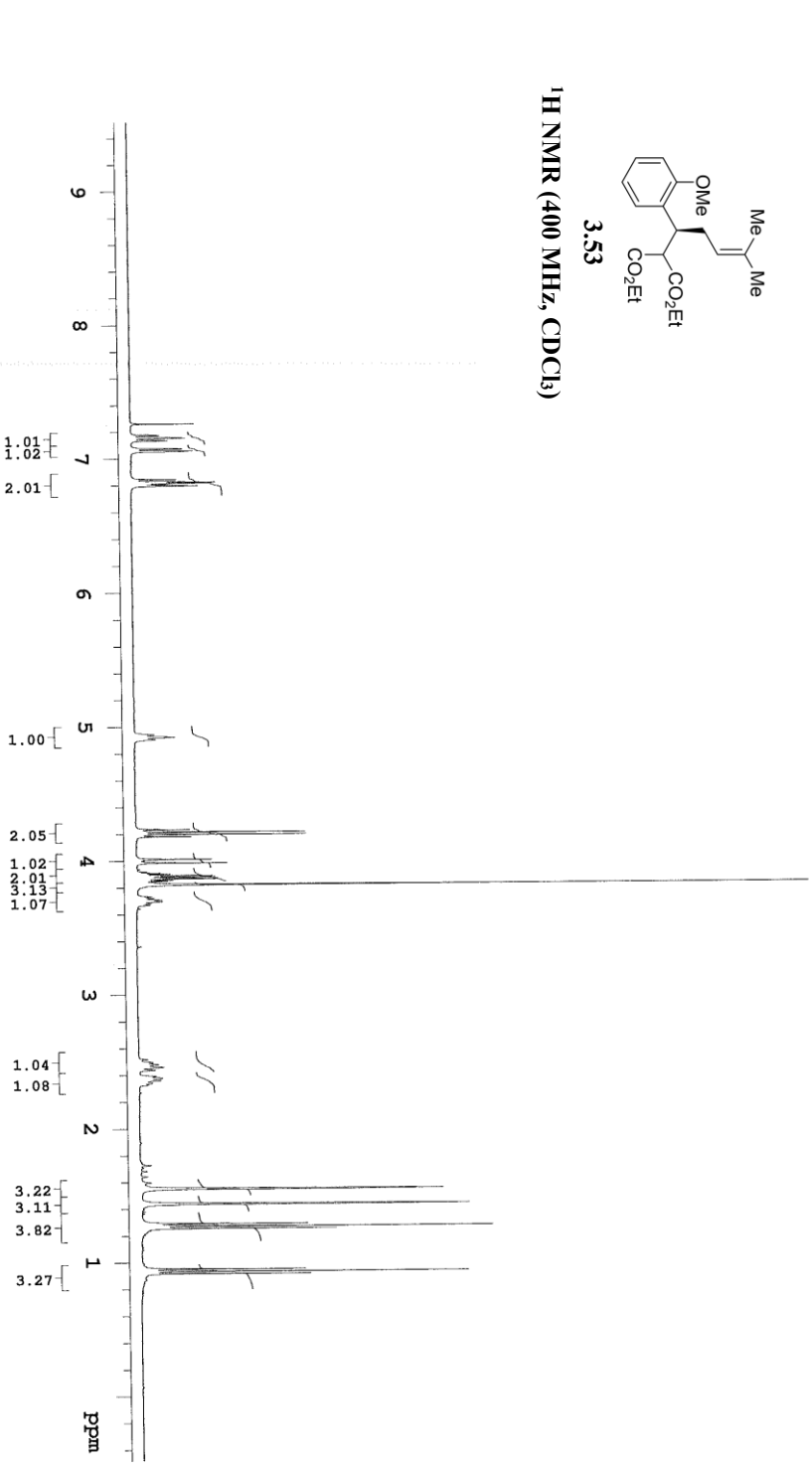


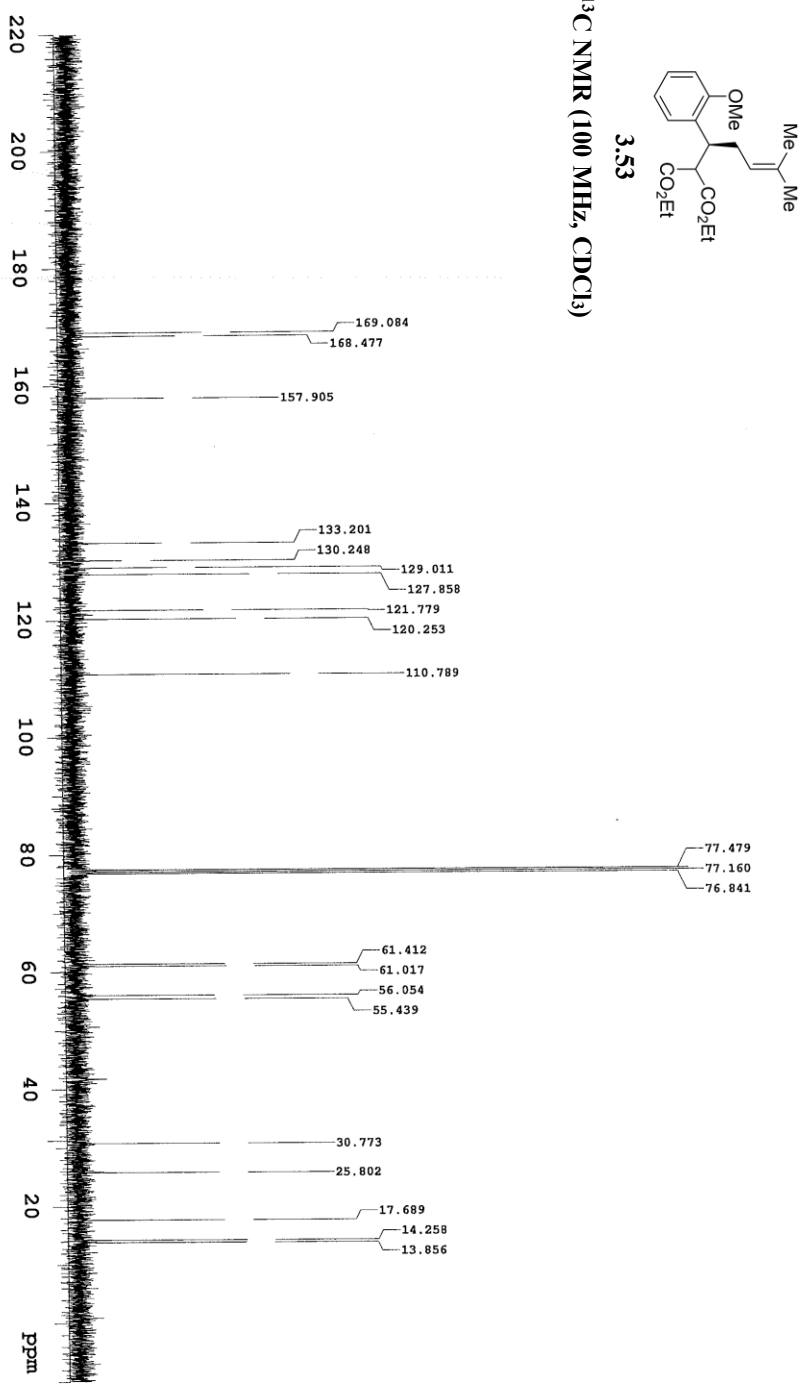

Me
Me
CO2Et
CO2Et
F3C
3.52
1H NMR (400 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
ppm
2.07
2.06
1.00
2.06
2.07
1.04
1.37
1.07
1.09
3.40
3.22
3.56
3.24

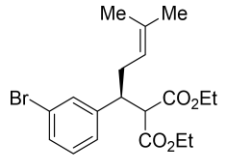
**$^{13}$C NMR (100 MHz, $CDCl_3$)**

**3.52**




Me
Me
OMe
CO2Et
CO2Et
3.53
1H NMR (400 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
ppm
1.01
1.02
2.01
1.00
2.05
1.02
2.01
3.13
1.07
1.04
1.08
3.22
3.11
3.82
3.27


3.53
$^{13}$C NMR (100 MHz, CDCl$_3$)
OMe
Me
Me
CO$_2$Et
CO$_2$Et
169.084
168.477
157.905
133.201
130.248
129.011
127.858
121.779
120.253
110.789
77.479
77.160
76.841
61.412
61.017
56.054
55.439
30.773
25.802
17.689
14.258
13.856
220
200
180
160
140
120
100
80
60
40
20
ppm

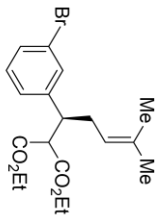



**3.54**

**$^1$H NMR (500 MHz, $CDCl_3$)**

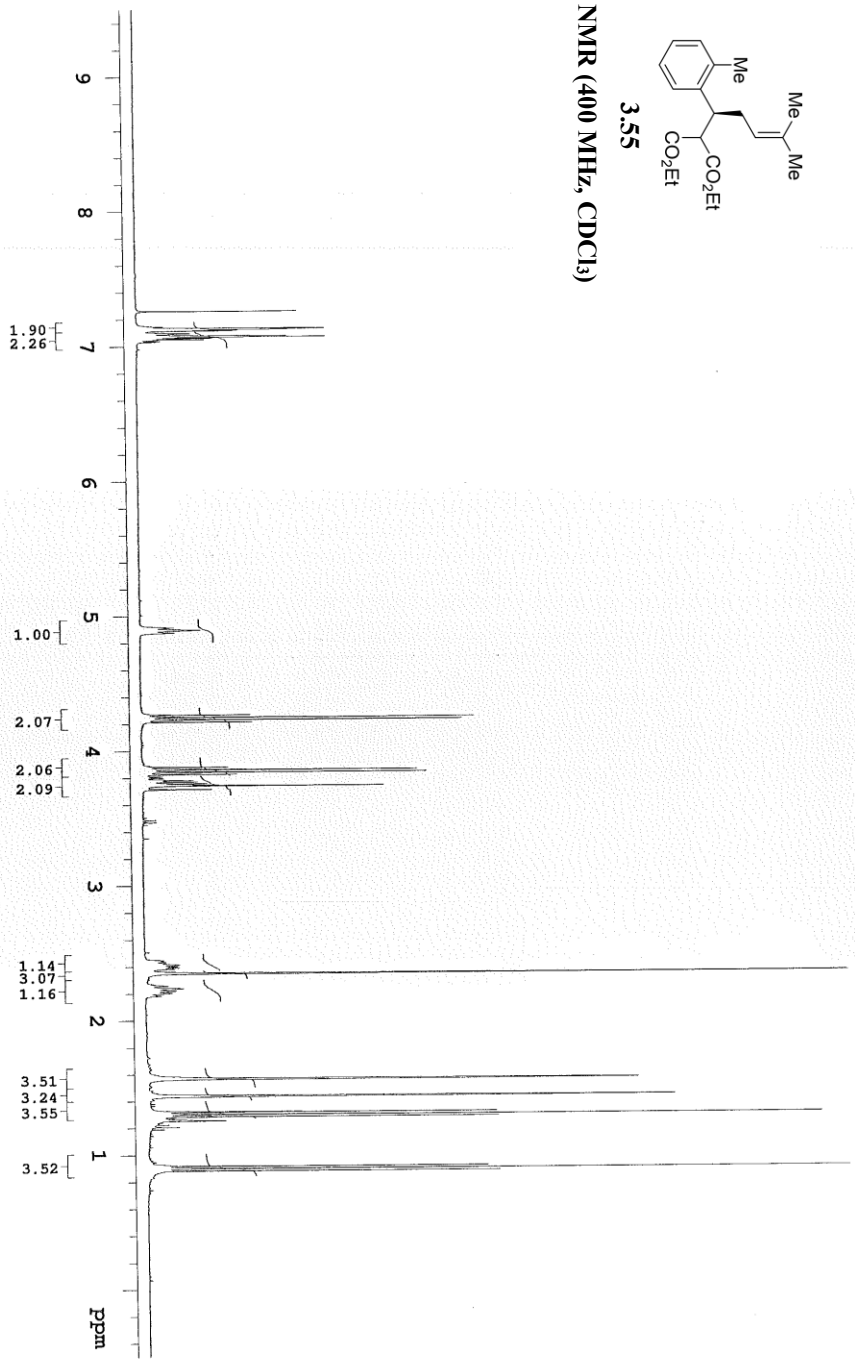
**$^{13}$C NMR (100 MHz, $CDCl_3$)**

**3.54**

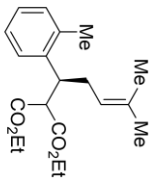


**3.55**

**$^1$H NMR (400 MHz, CDCl$_3$)**



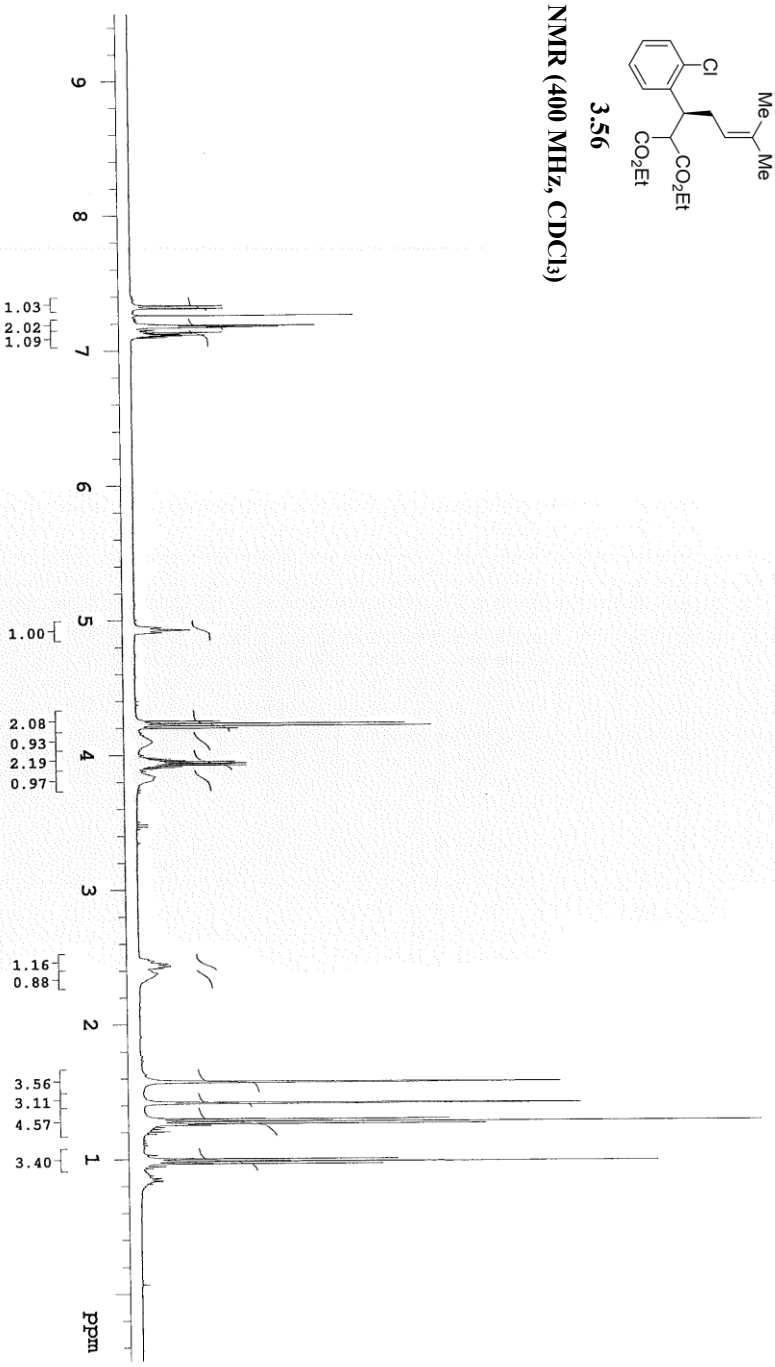
**3.55**

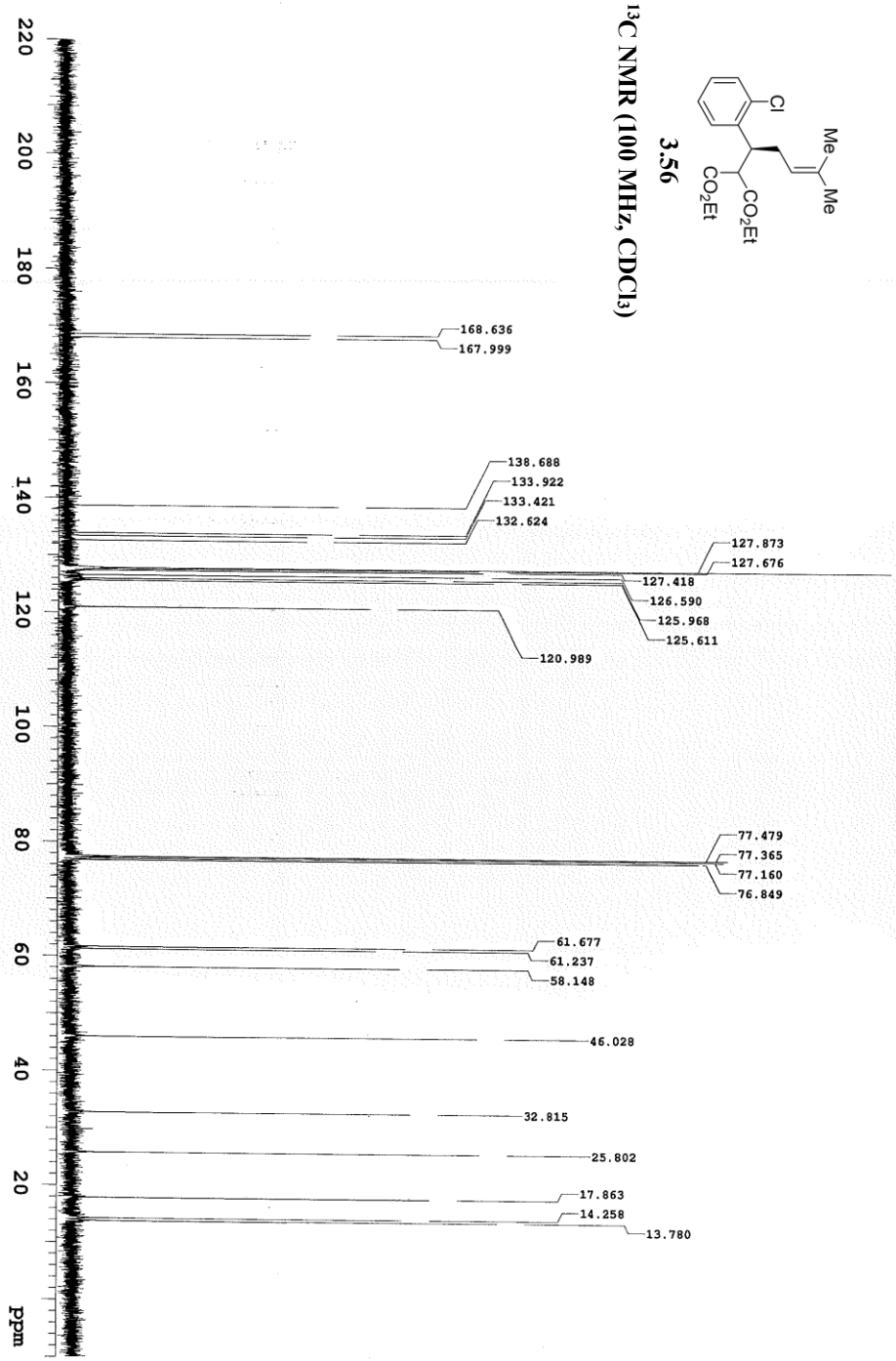


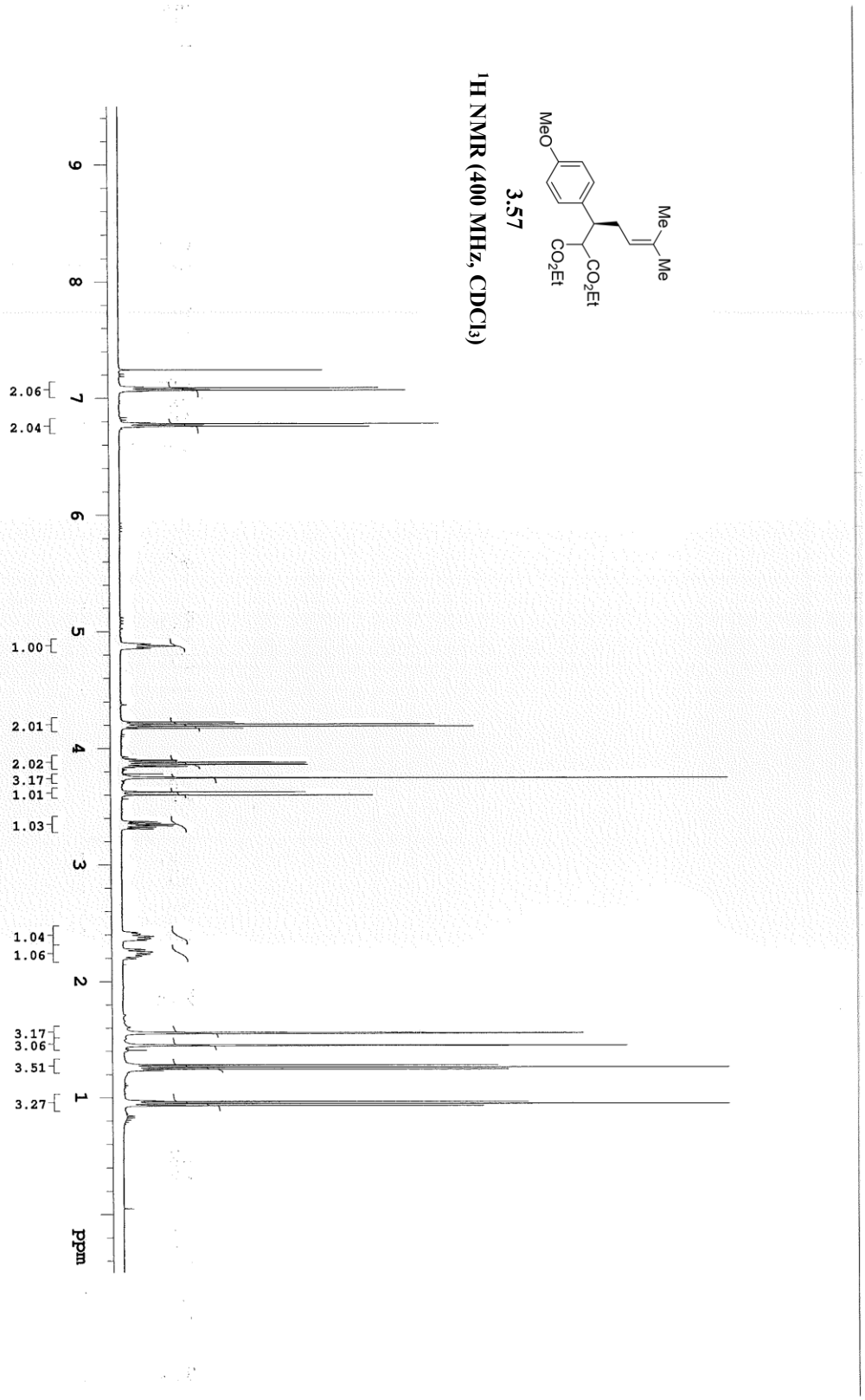

**$^{13}$C NMR (100 MHz, $CDCl_3$)**

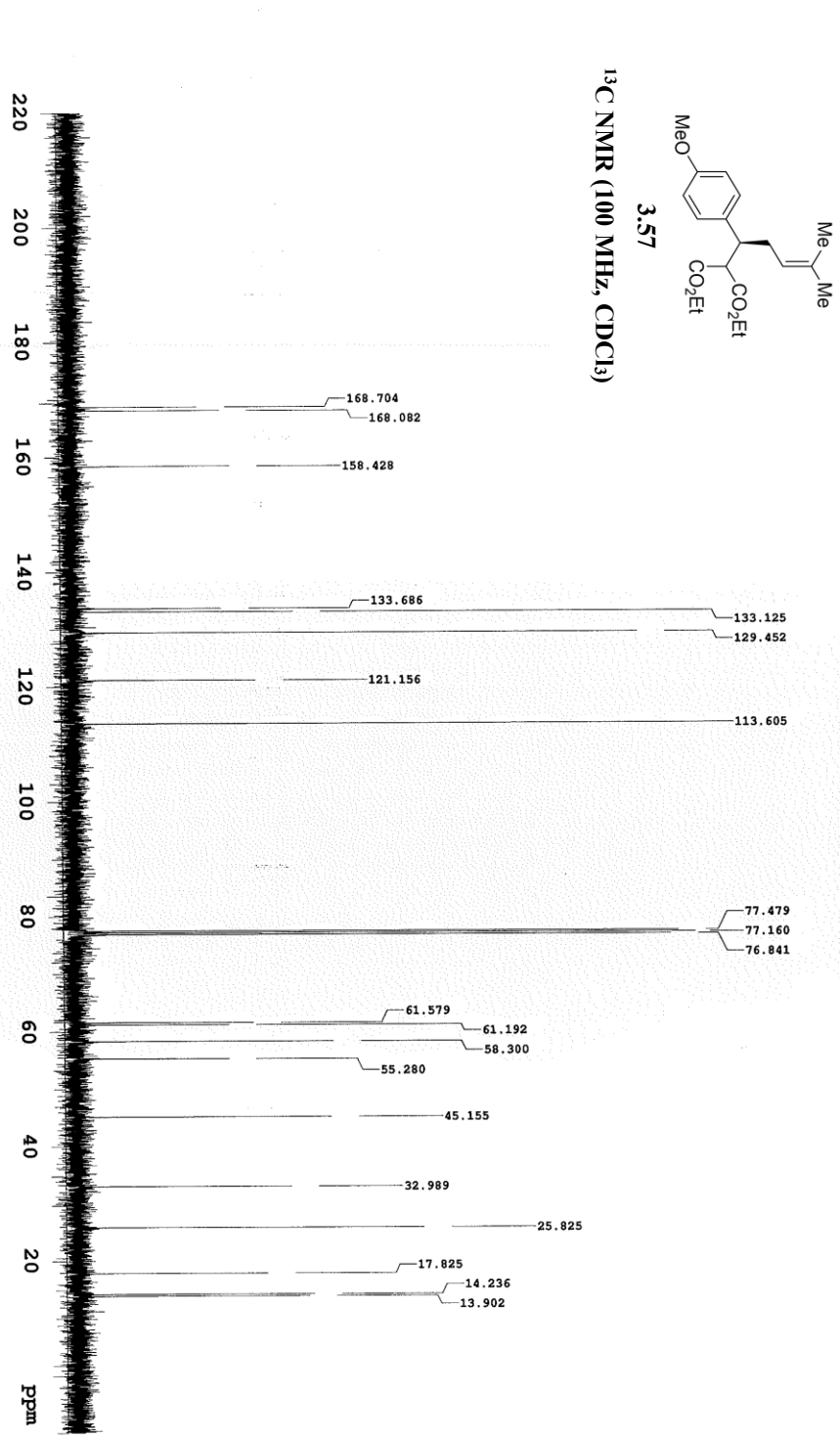
**3.56**

**$^1$H NMR (400 MHz, CDCl$_3$)**

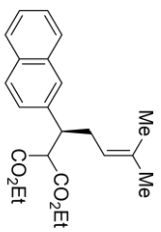



3.56
$^{13}$C NMR (100 MHz, CDCl$_3$)
Cl
Me
Me
CO$_2$Et
CO$_2$Et
168.636
167.999
138.688
133.922
133.421
132.624
127.873
127.676
127.418
126.590
125.968
125.611
120.989
77.479
77.365
77.160
76.849
61.677
61.237
58.148
46.028
32.815
25.802
17.863
14.258
13.780
220
200
180
160
140
120
100
80
60
40
20
ppm


MeO
Me
Me
CO2Et
CO2Et
3.57
1H NMR (400 MHz, CDCl3)
2.06
2.04
1.00
2.01
2.02
3.17
1.01
1.03
1.04
1.06
3.17
3.06
3.51
3.27
ppm

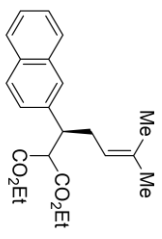

MeO
Me
Me
CO2Et
CO2Et
3.57
13C NMR (100 MHz, CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
168.704
168.082
158.428
133.686
133.125
129.452
121.156
113.605
77.479
77.160
76.841
61.579
61.192
58.300
55.280
45.155
32.989
25.825
17.825
14.236
13.902

**3.58**



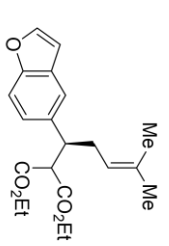

**$^1$H NMR (400 MHz, $CDCl_3$)**

**3.58**

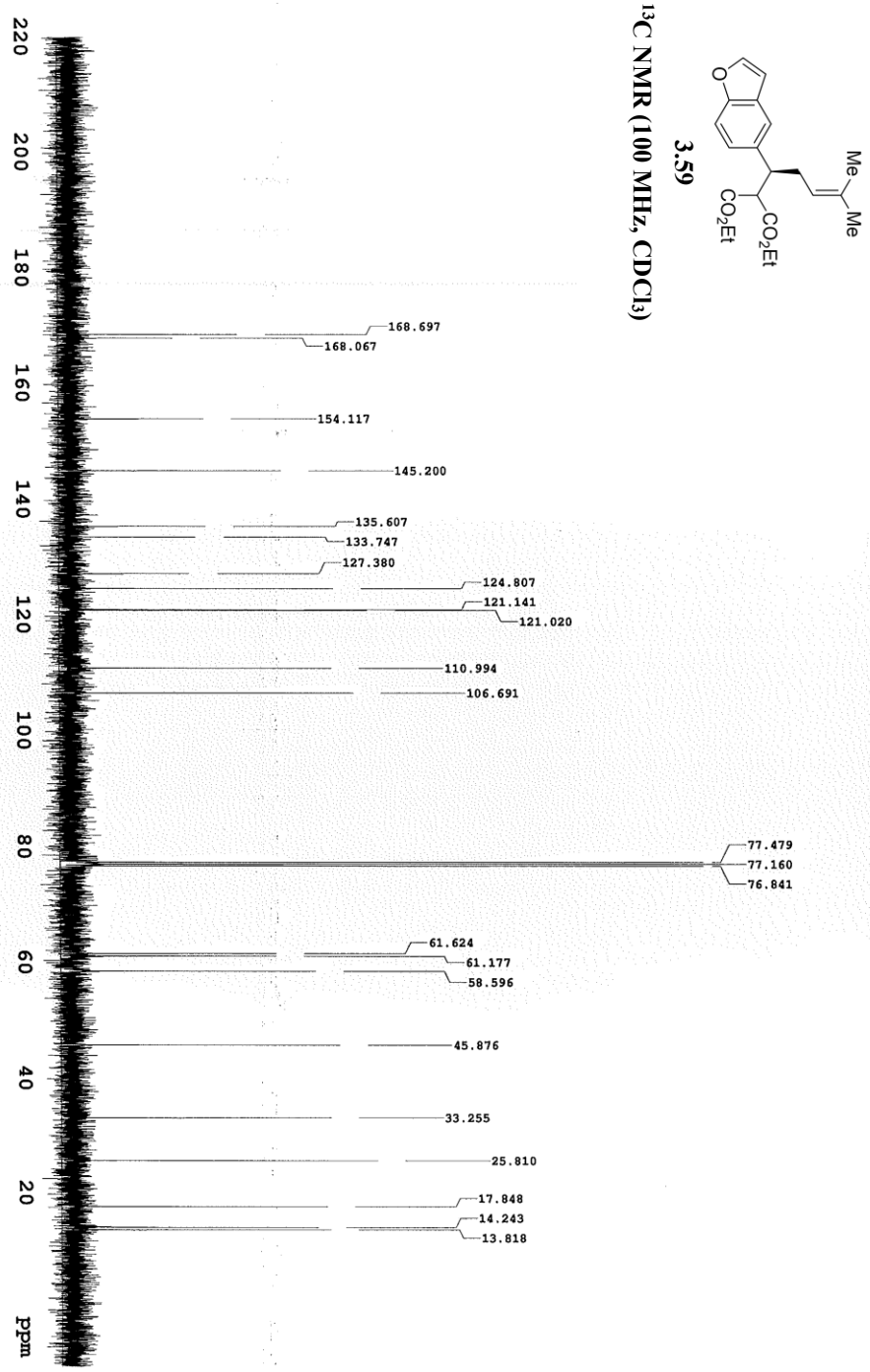


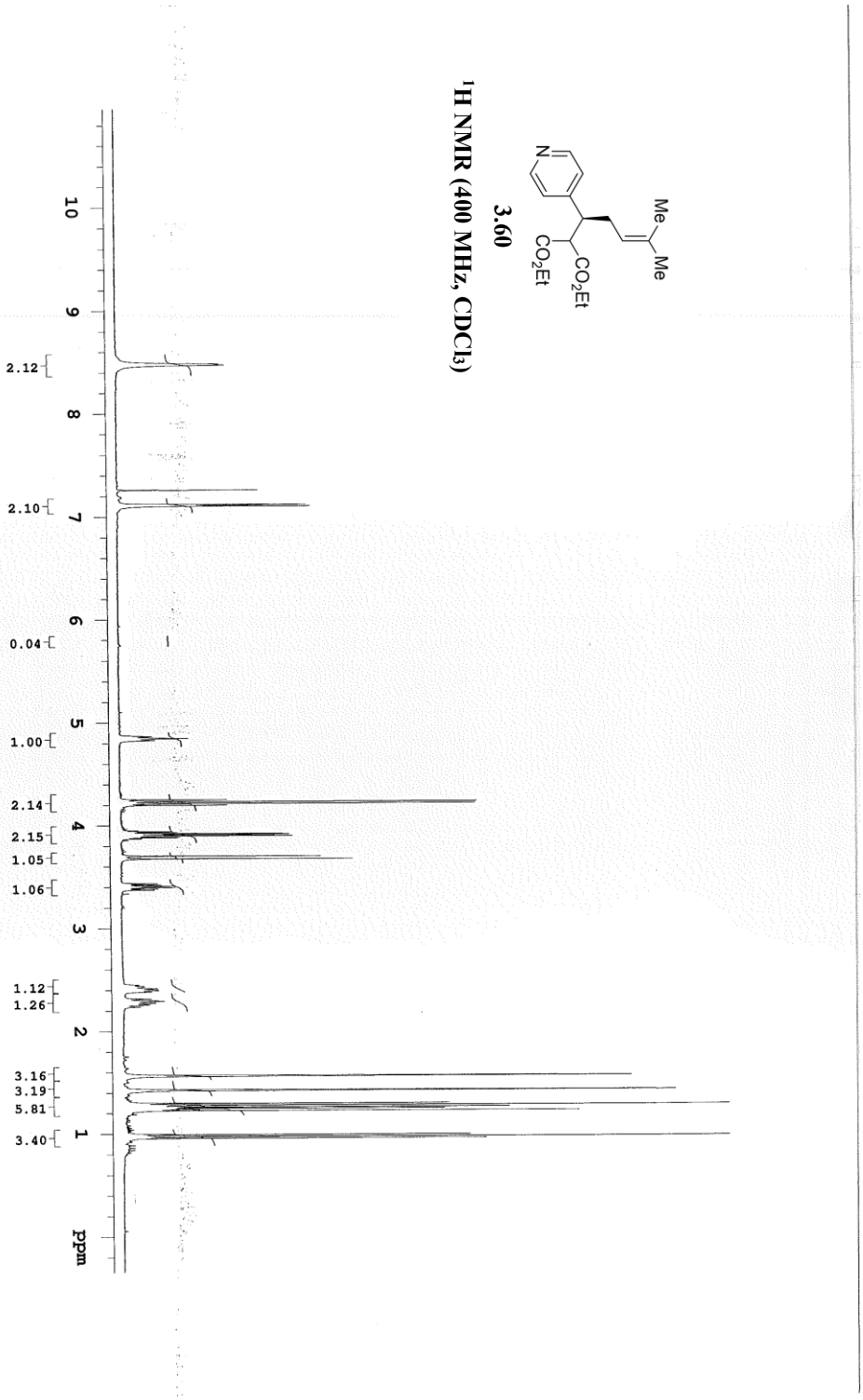

**$^{13}$C NMR (100 MHz, CDCl$_3$)**

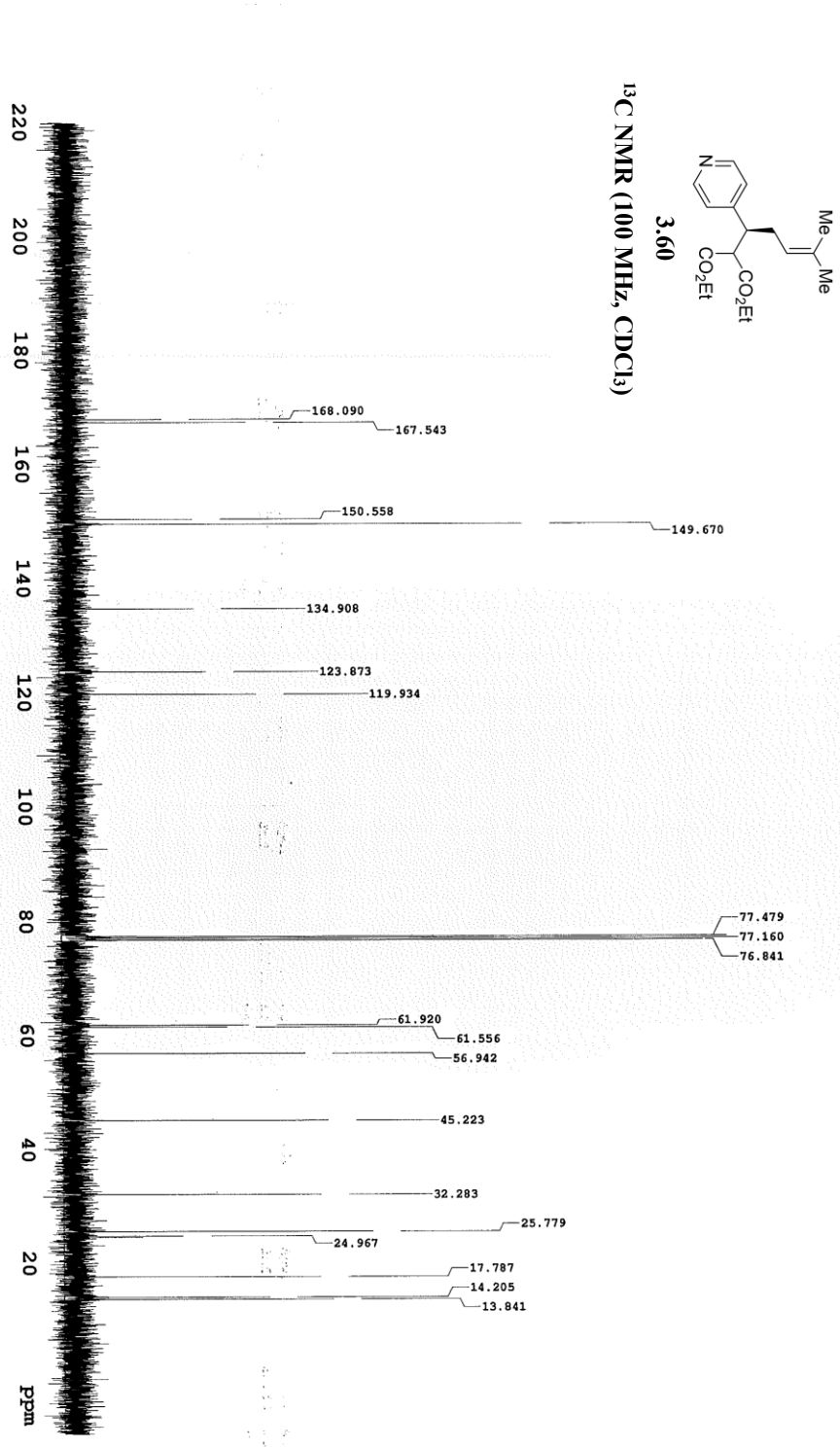
**3.59**

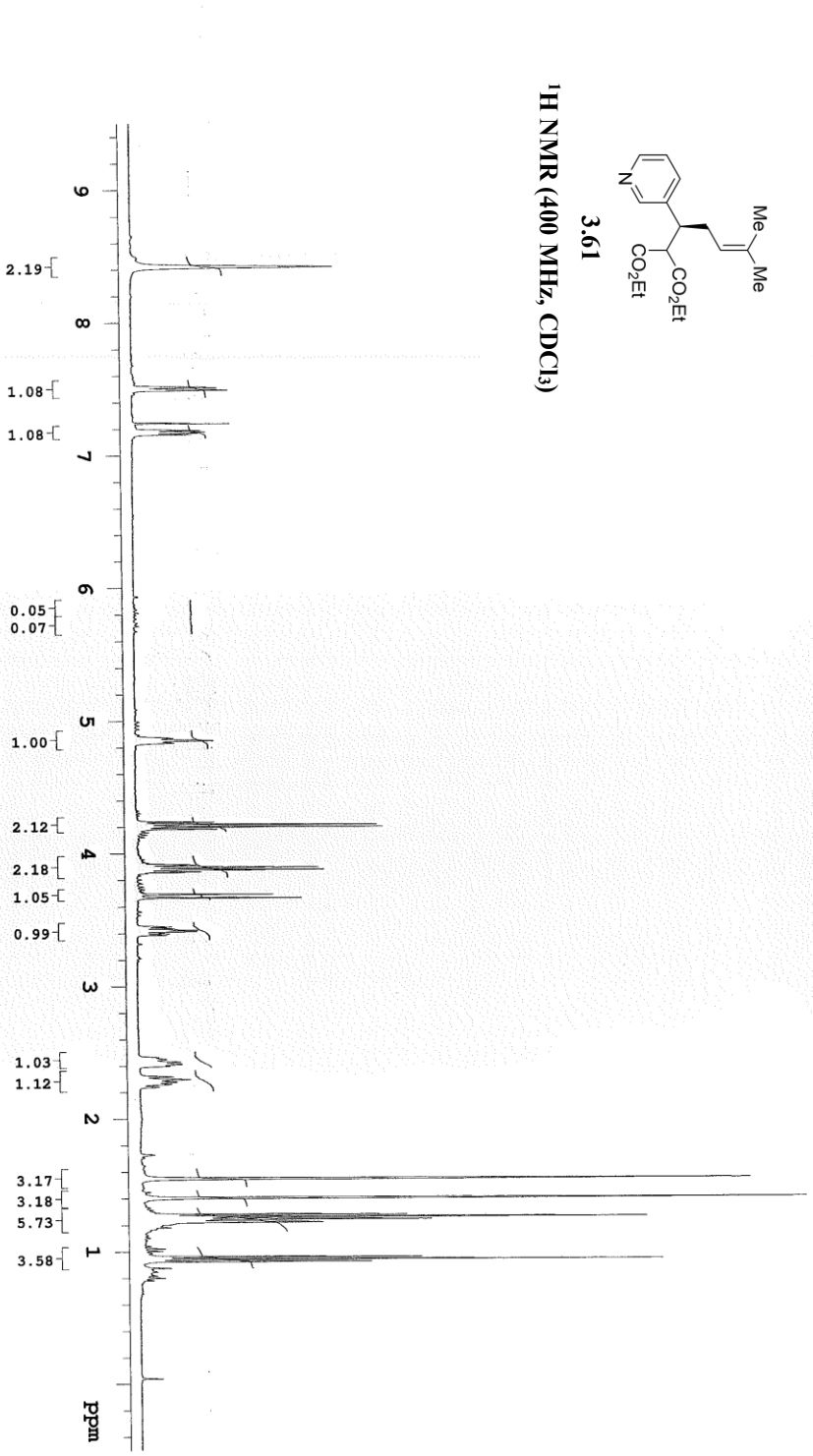



**$^1$H NMR (400 MHz, $CDCl_3$)**

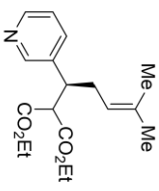

3.59
$^{13}$C NMR (100 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
O
220
200
180
160
140
120
100
80
60
40
20
ppm
168.697
168.067
154.117
145.200
135.607
133.747
127.380
124.807
121.141
121.020
110.994
106.691
77.479
77.160
76.841
61.624
61.177
58.596
45.876
33.255
25.810
17.848
14.243
13.818


Me
Me
CO2Et
CO2Et
N
3.60
1H NMR (400 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
2.12
2.10
0.04
1.00
2.14
2.15
1.05
1.06
1.12
1.26
3.16
3.19
5.81
3.40


3.60
$^{13}$C NMR (100 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
N
220
200
180
160
140
120
100
80
60
40
20
ppm
168.090
167.543
150.558
149.670
134.908
123.873
119.934
77.479
77.160
76.841
61.920
61.556
56.942
45.223
32.283
25.779
24.967
17.787
14.205
13.841

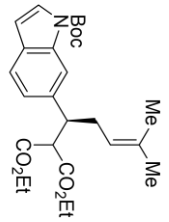

Me
Me
CO2Et
CO2Et
N
3.61
1H NMR (400 MHz, CDCl3)
2.19
1.08
1.08
0.05
0.07
1.00
2.12
2.18
1.05
0.99
1.03
1.12
3.17
3.18
5.73
3.58
ppm

**3.61**



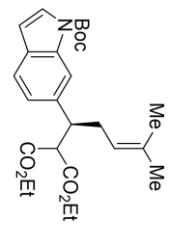

**$^{13}$C NMR (100 MHz, $CDCl_3$)**

**3.62**

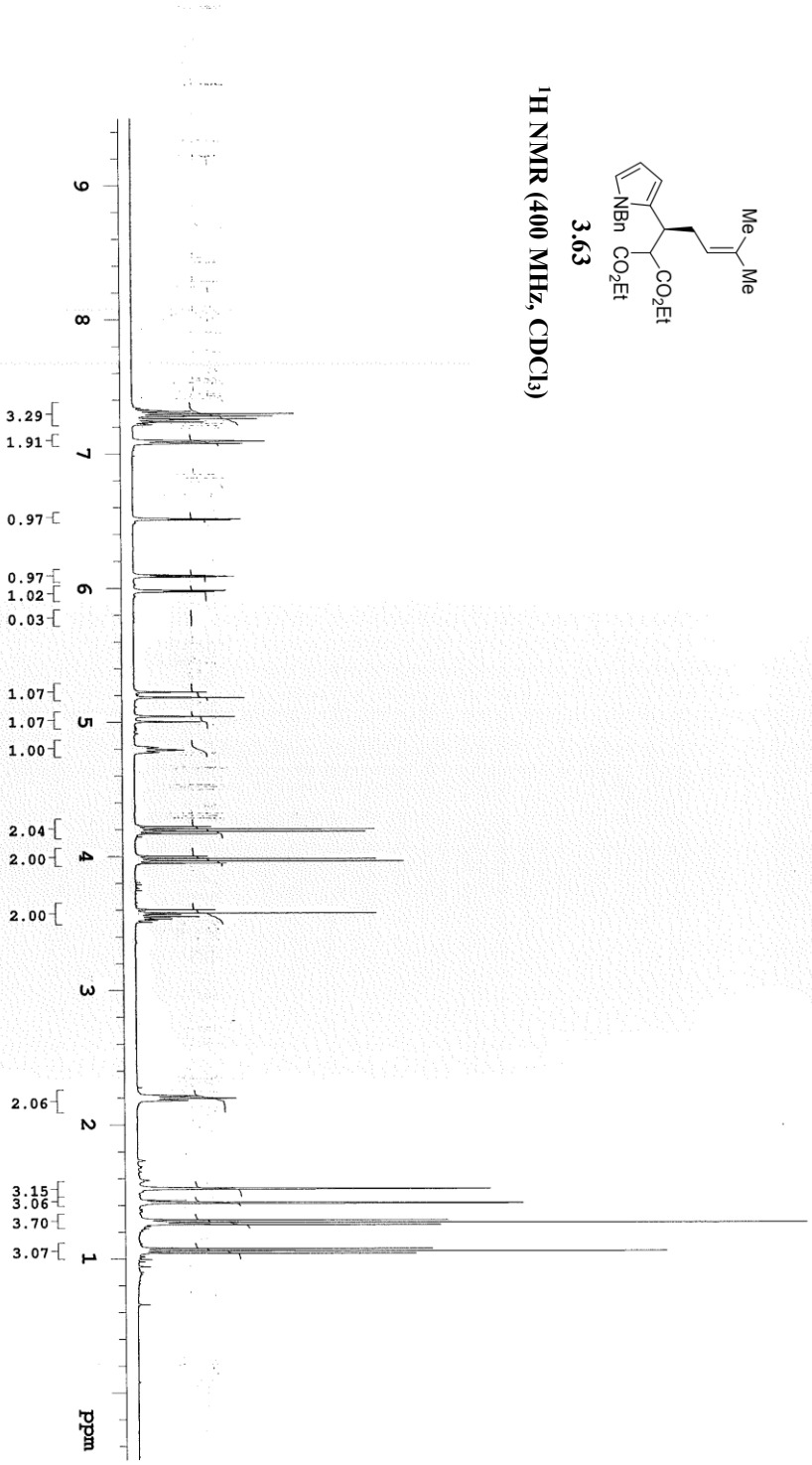



**$^1$H NMR (400 MHz, CDCl$_3$)**

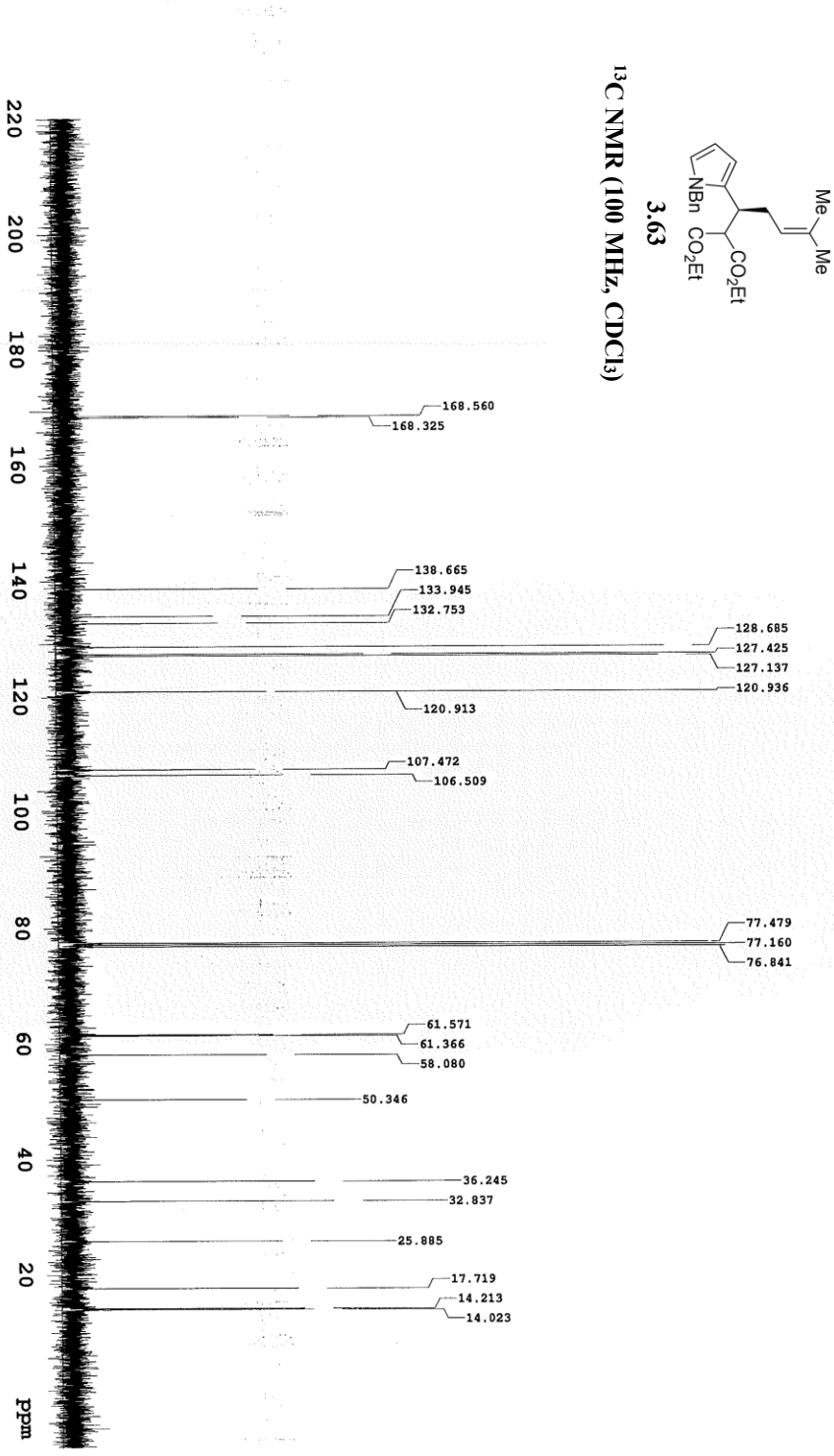
**3.62**



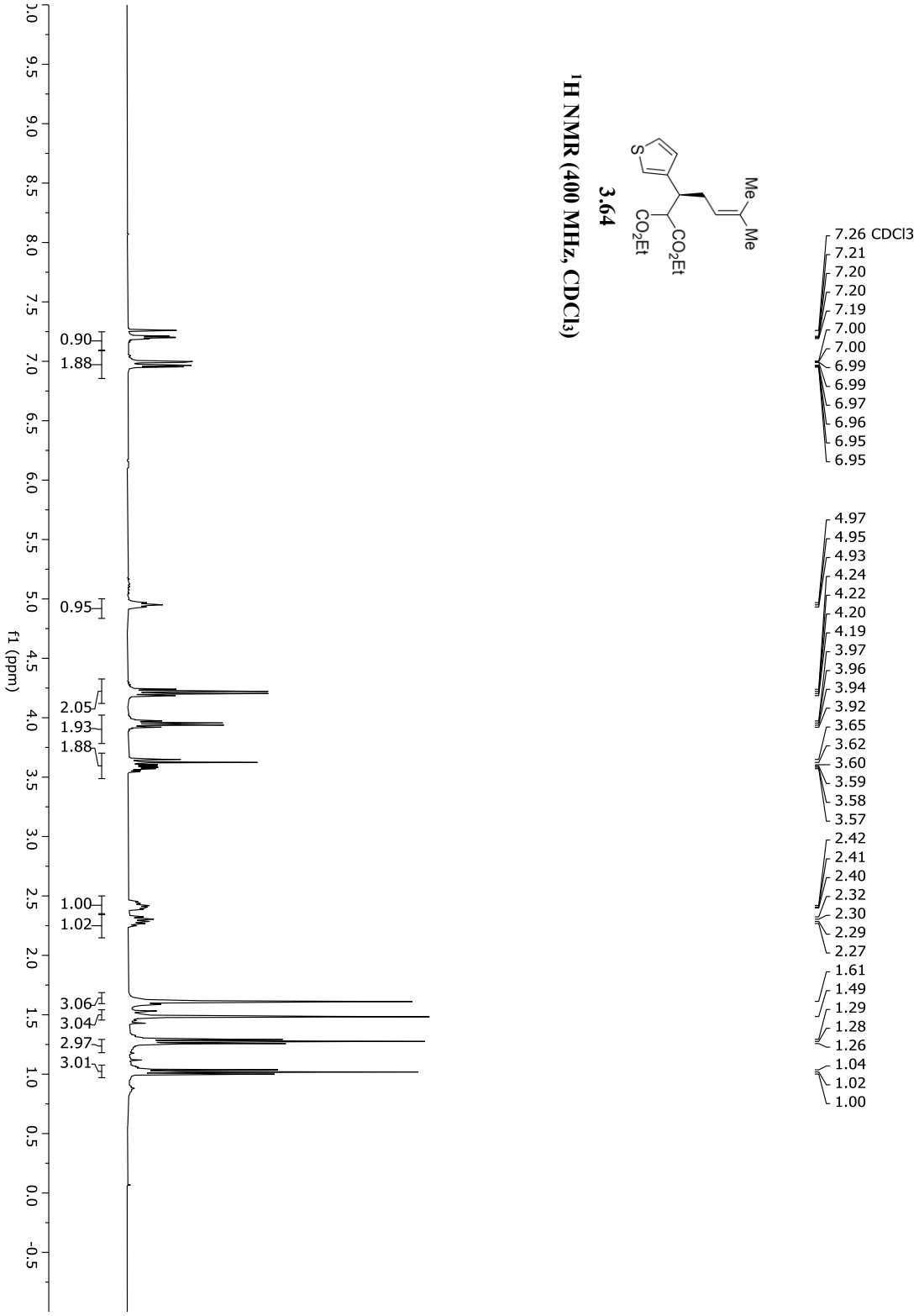

**$^{13}$C NMR (100 MHz, $CDCl_3$)**

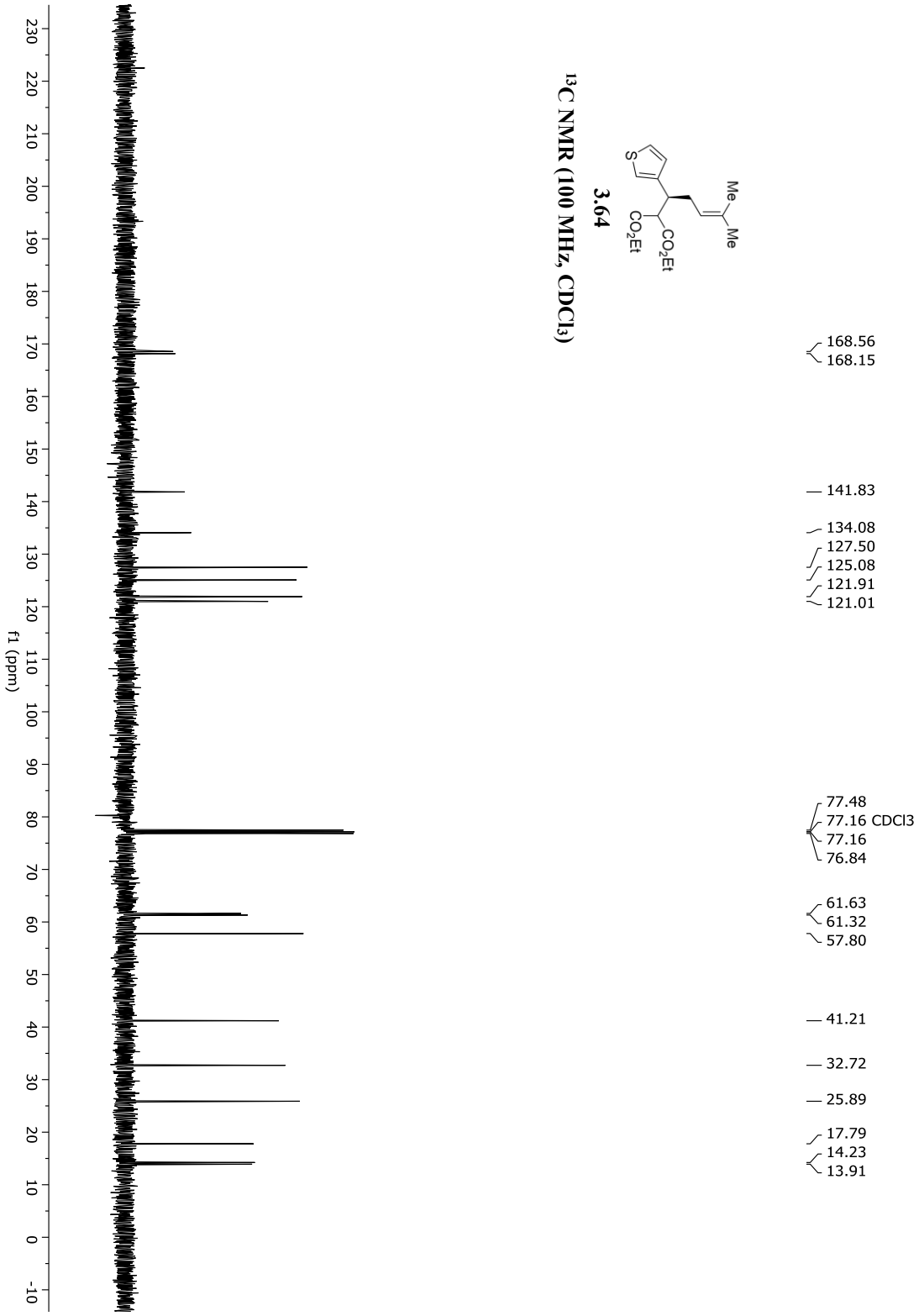

Me
Me
CO2Et
NBn CO2Et
3.63
1H NMR (400 MHz, CDCl3)
3.29
1.91
0.97
0.97
1.02
0.03
1.07
1.07
1.00
2.04
2.00
2.00
2.06
3.15
3.06
3.70
3.07
9
8
7
6
5
4
3
2
1
ppm

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

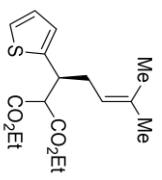



**3.63**


3.64
$^1$H NMR (400 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
S
7.26 CDCl3
7.21
7.20
7.20
7.19
7.00
7.00
6.99
6.99
6.99
6.97
6.96
6.95
6.95
4.97
4.95
4.93
4.24
4.22
4.20
4.19
3.97
3.96
3.94
3.92
3.65
3.62
3.60
3.59
3.58
3.57
2.42
2.41
2.40
2.32
2.30
2.29
2.27
1.61
1.49
1.29
1.28
1.26
1.04
1.02
1.00
0.90
1.88
0.95
2.05
1.93
1.88
1.00
1.02
3.06
3.04
2.97
3.01
f1 (ppm)

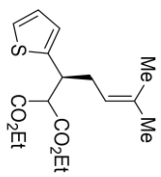

3.64
$^{13}$C NMR (100 MHz, CDCl$_3$)
S
CO$_2$Et
CO$_2$Et
Me
Me
168.56
168.15
141.83
134.08
127.50
125.08
121.91
121.01
77.48
77.16 CDCl3
77.16
76.84
61.63
61.32
57.80
41.21
32.72
25.89
17.79
14.23
13.91
f1 (ppm)

**$^1$H NMR (400 MHz, CDCl$_3$)**




**3.66**

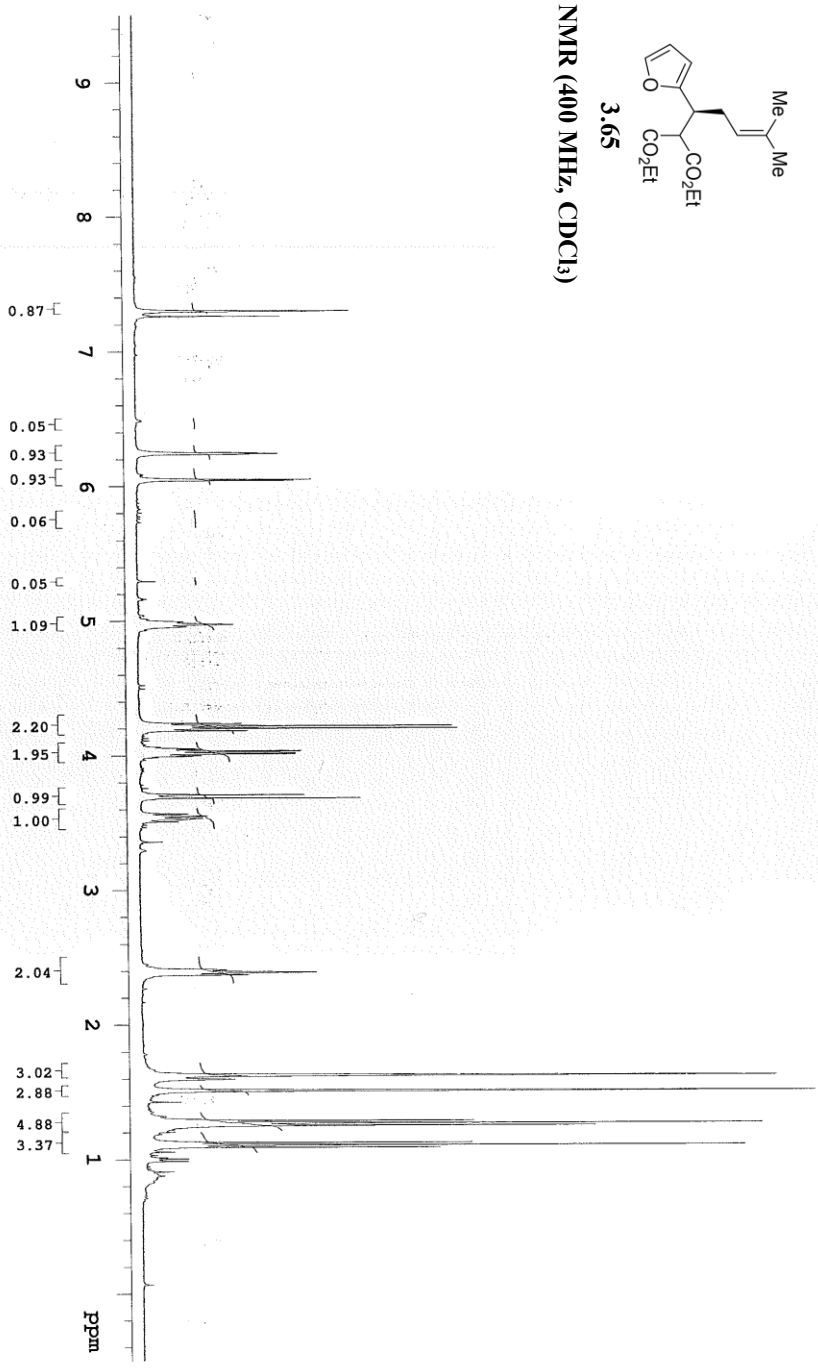
**3.66**



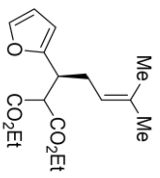

**$^{13}$C NMR (100 MHz, $CDCl_3$)**

**3.65**

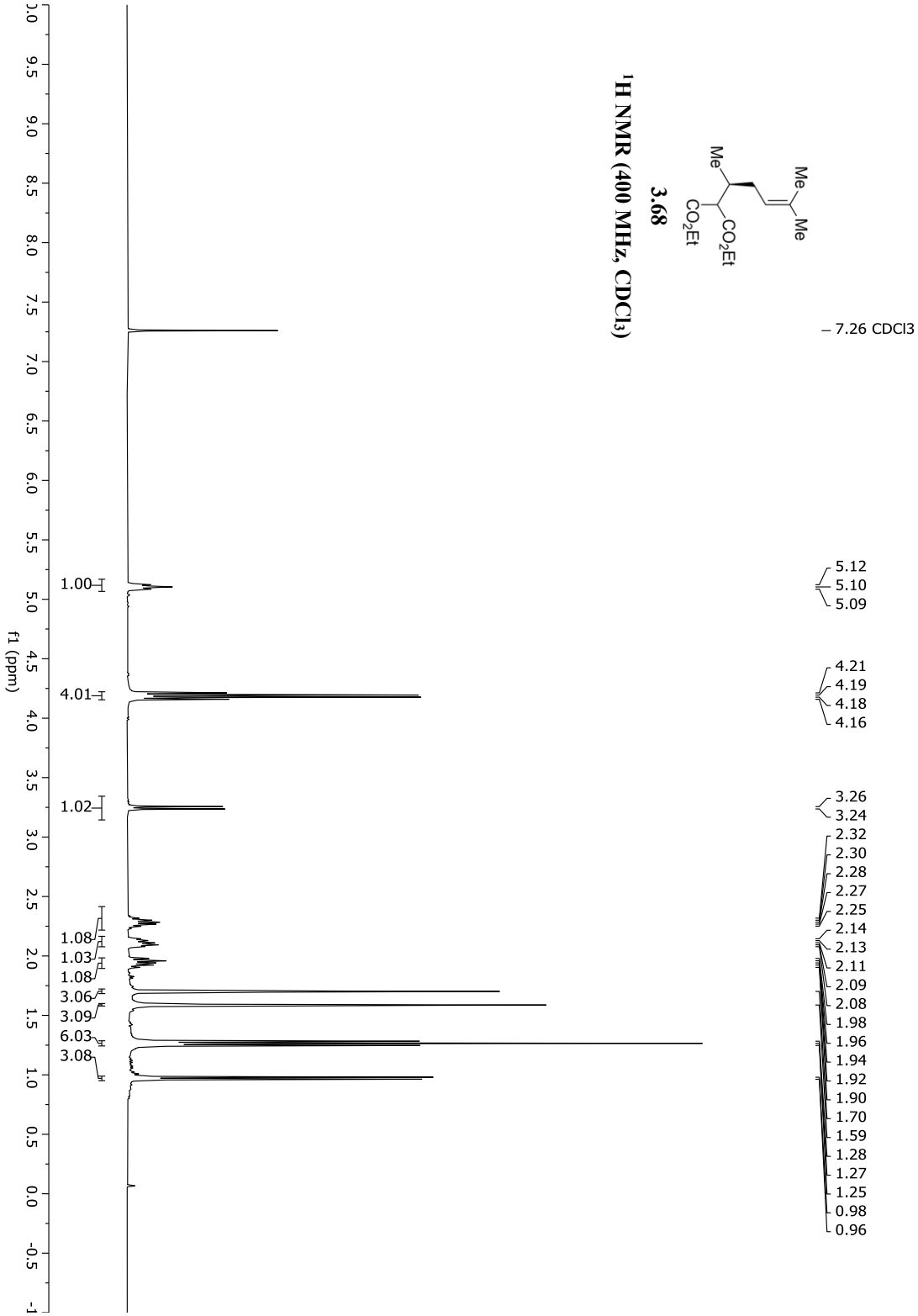
**$^1$H NMR (400 MHz, CDCl$_3$)**

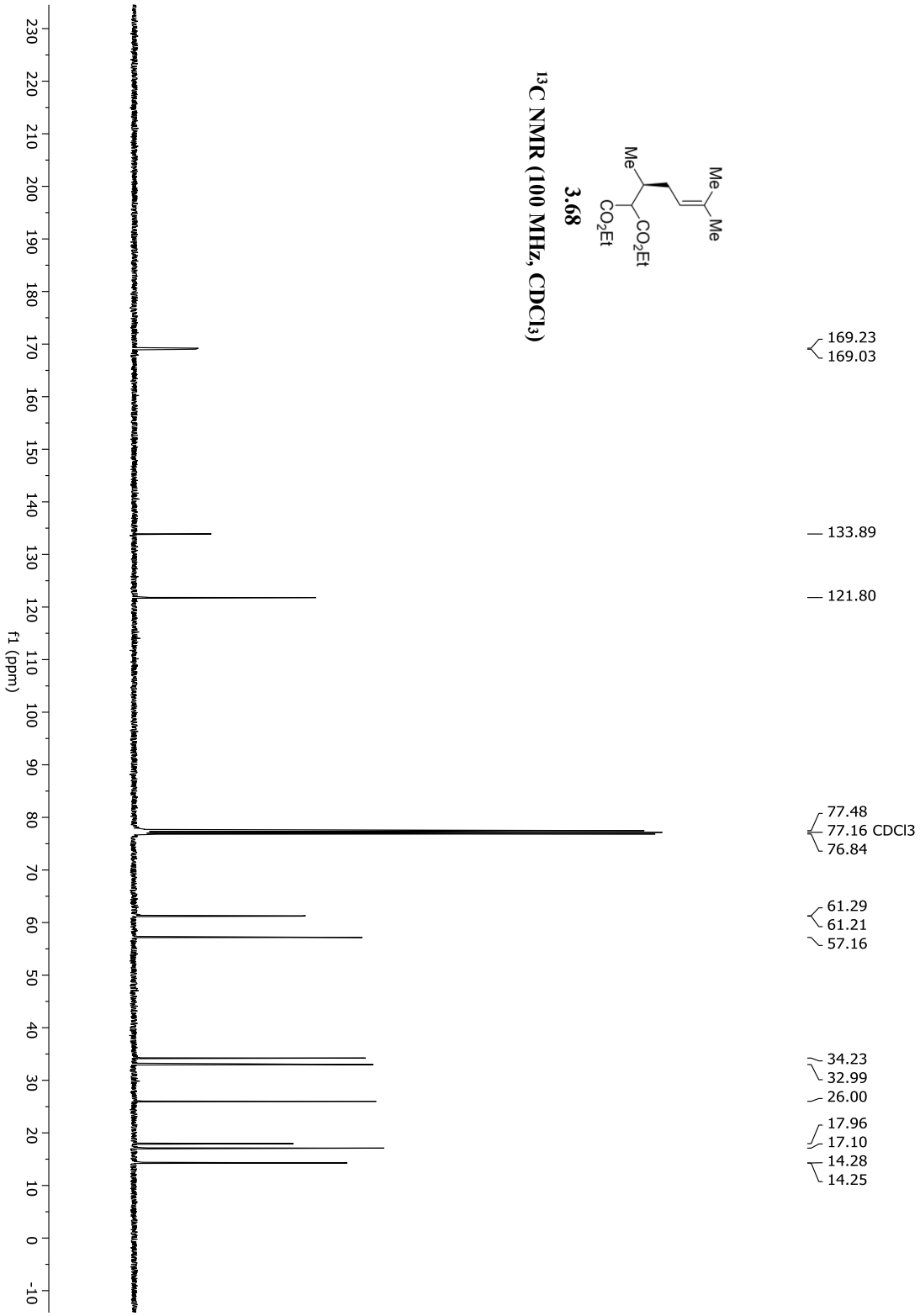


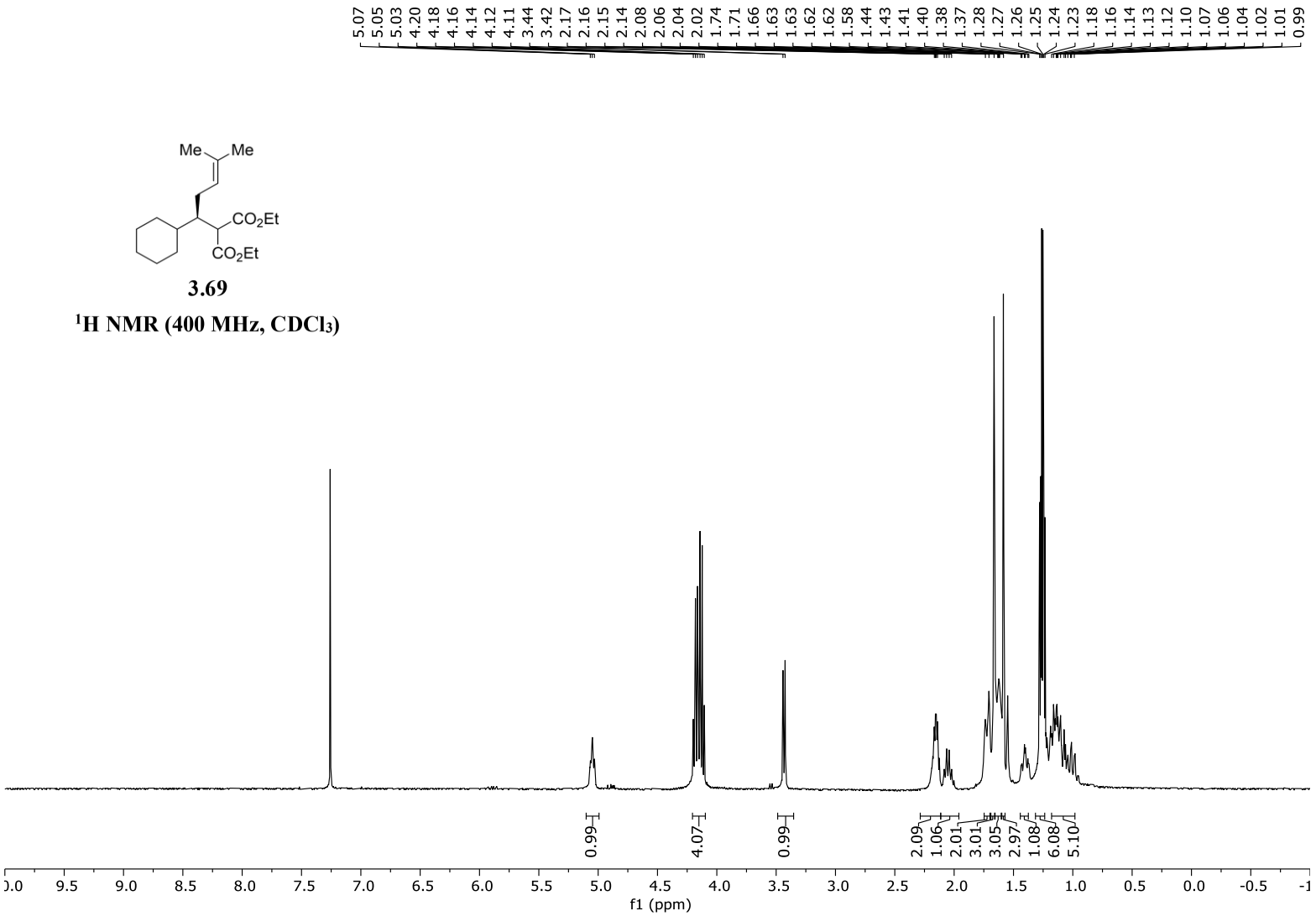
**3.65**




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

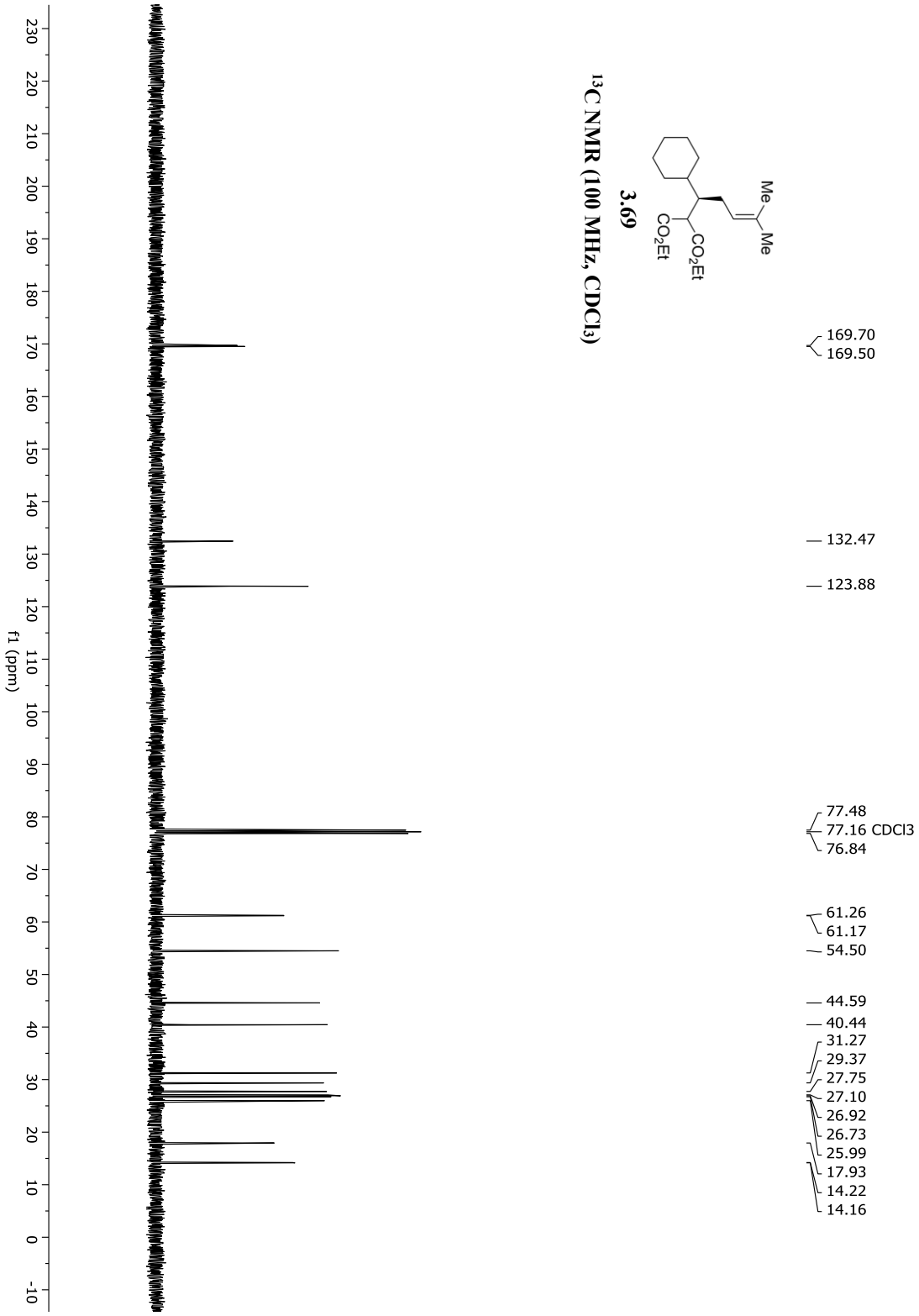

3.68
$^1$H NMR (400 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
Me
– 7.26 CDCl3
5.12
5.10
5.09
4.21
4.19
4.18
4.16
3.26
3.24
2.32
2.30
2.28
2.27
2.25
2.14
2.13
2.11
2.09
2.08
1.98
1.96
1.94
1.92
1.90
1.70
1.59
1.28
1.27
1.25
0.98
0.96
1.00
4.01
1.02
1.08
1.03
1.08
3.06
3.09
6.03
3.08
f1 (ppm)

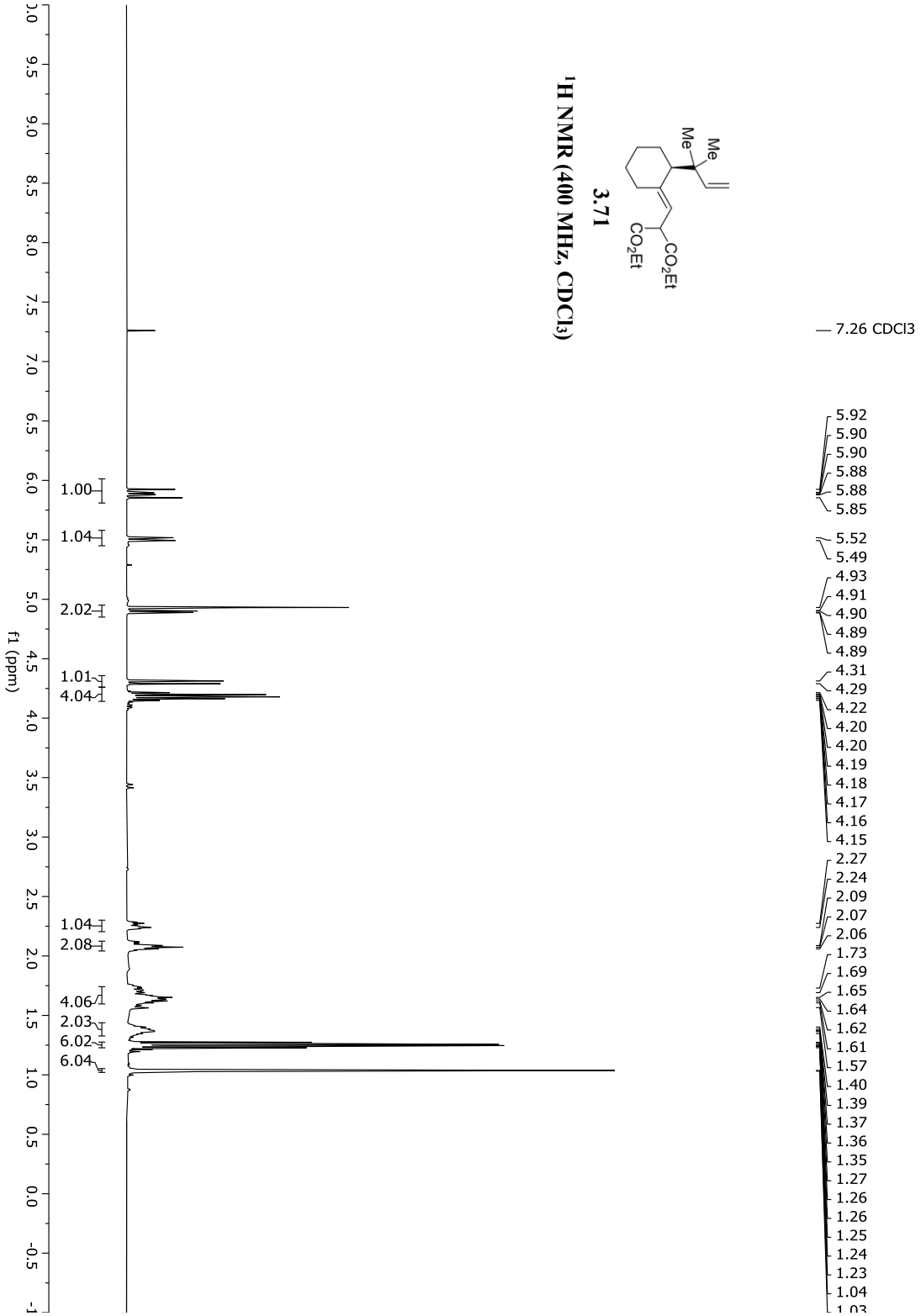

Me
Me
CO2Et
Me
CO2Et
3.68
13C NMR (100 MHz, CDCl3)
169.23
169.03
133.89
121.80
77.48
77.16 CDCl3
76.84
61.29
61.21
57.16
34.23
32.99
26.00
17.96
17.10
14.28
14.25
f1 (ppm)

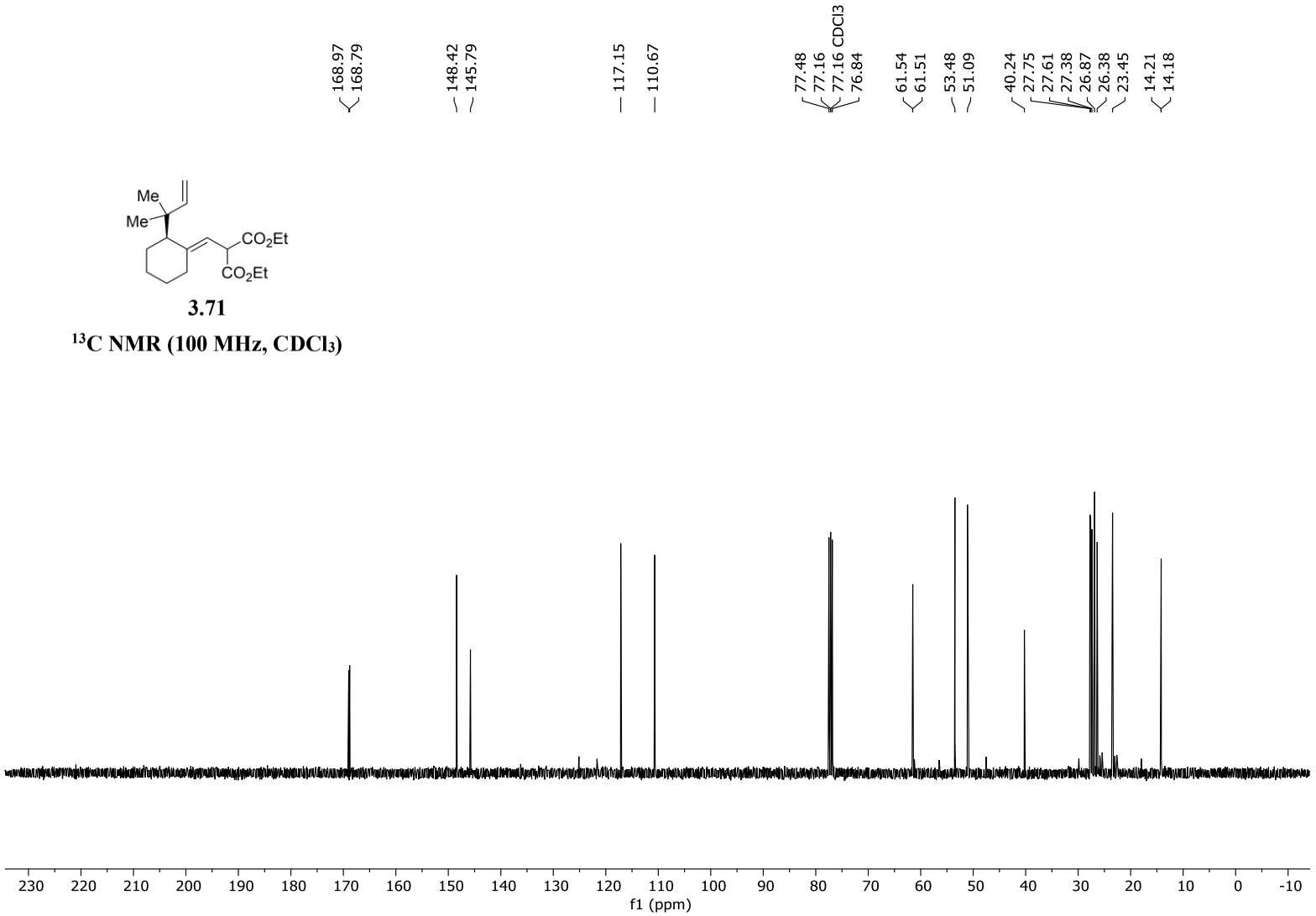



**3.69**

**$^1$H NMR (400 MHz, $CDCl_3$)**

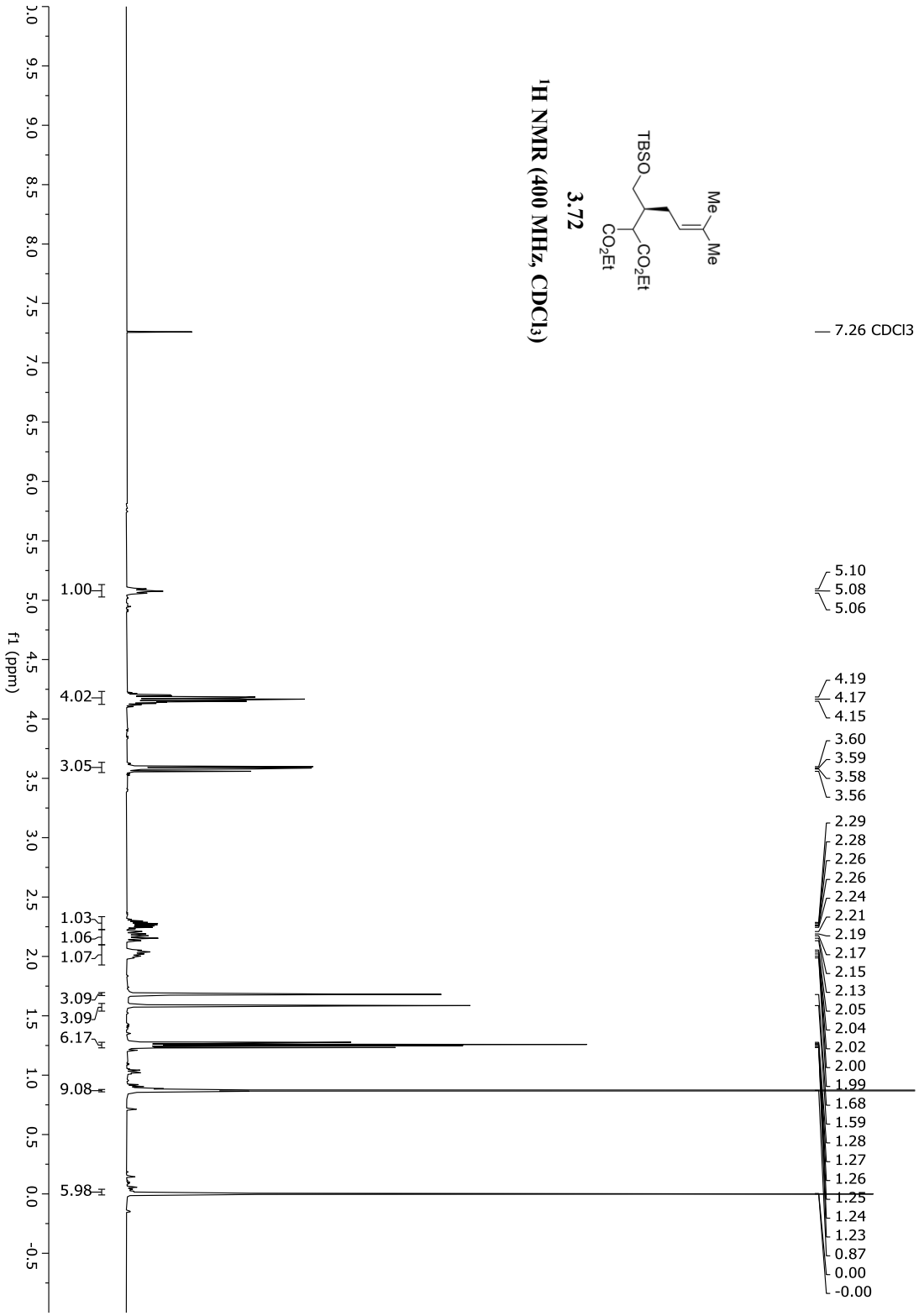

3.69
$^{13}$C NMR (100 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
169.70
169.50
132.47
123.88
77.48
77.16 CDCl3
76.84
61.26
61.17
54.50
44.59
40.44
31.27
29.37
27.75
27.10
26.92
26.73
25.99
17.93
14.22
14.16
f1 (ppm)

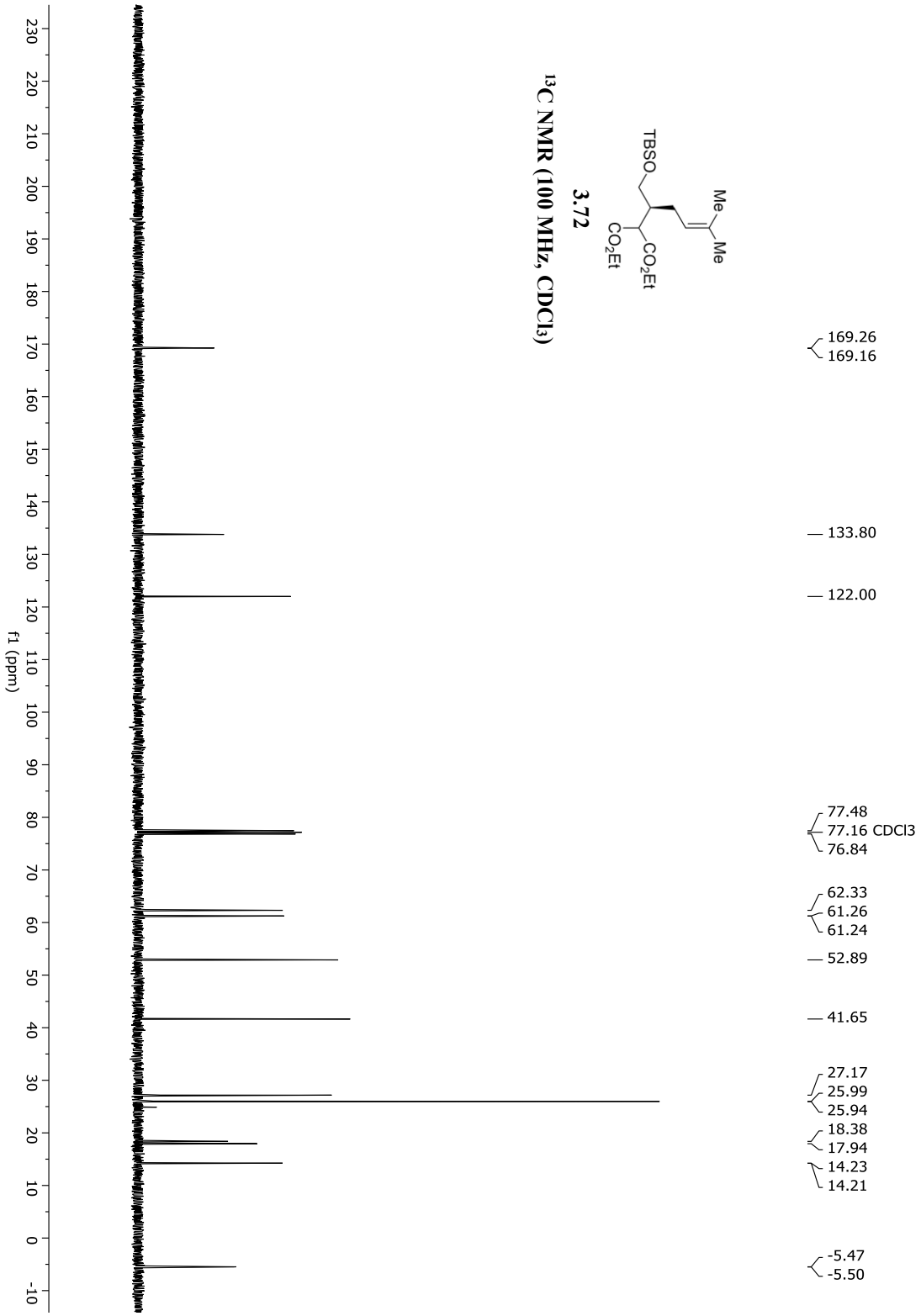

3.71
$^1$H NMR (400 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
7.26 CDCl3
5.92
5.90
5.90
5.88
5.88
5.85
5.52
5.49
4.93
4.91
4.90
4.89
4.89
4.31
4.29
4.22
4.20
4.20
4.19
4.18
4.17
4.16
4.15
2.27
2.24
2.09
2.07
2.06
1.73
1.69
1.65
1.64
1.62
1.61
1.57
1.40
1.39
1.37
1.36
1.35
1.27
1.26
1.26
1.25
1.24
1.23
1.04
1.03
1.00
1.04
2.02
1.01
4.04
1.04
2.08
4.06
2.03
6.02
6.04
f1 (ppm)

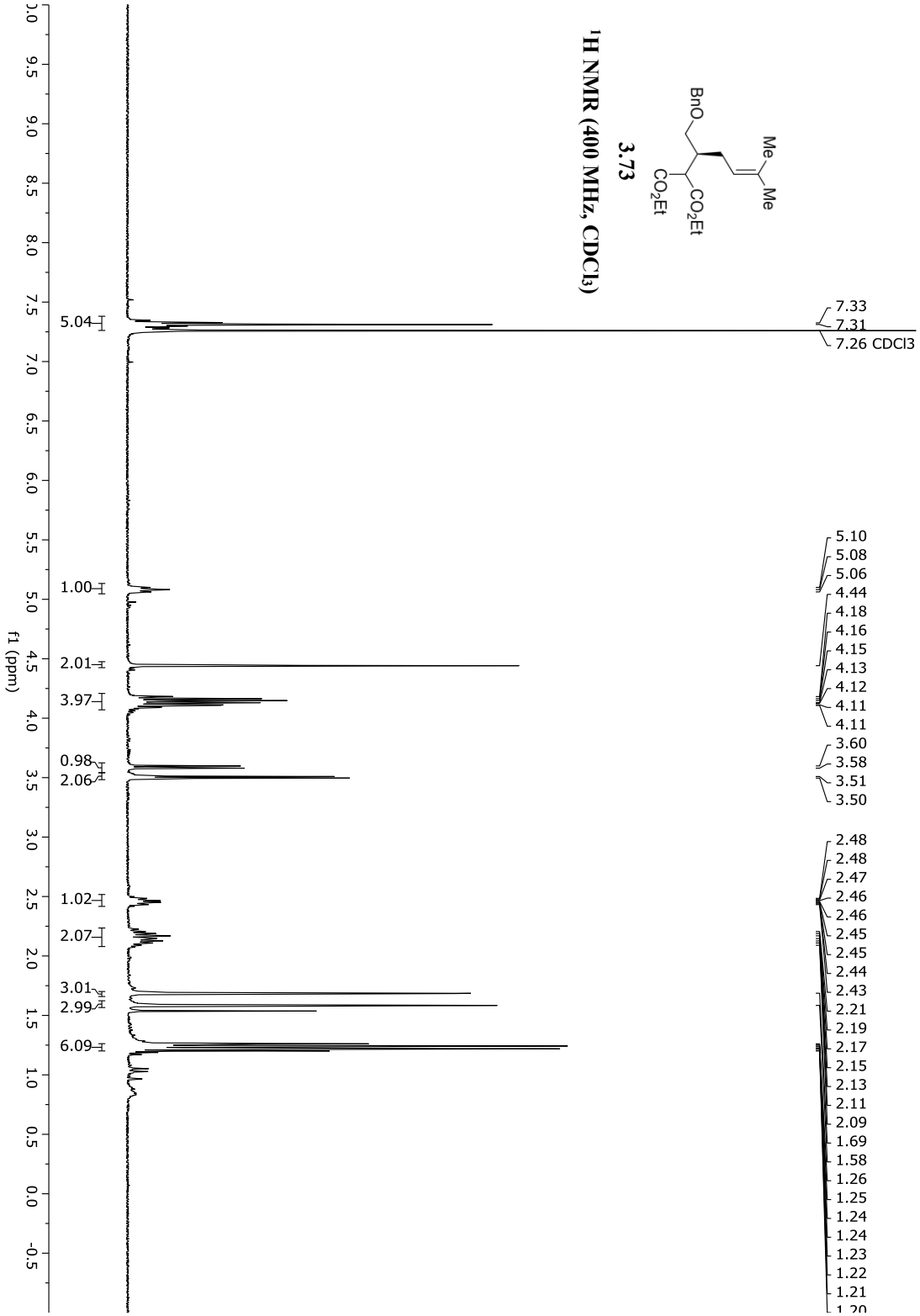


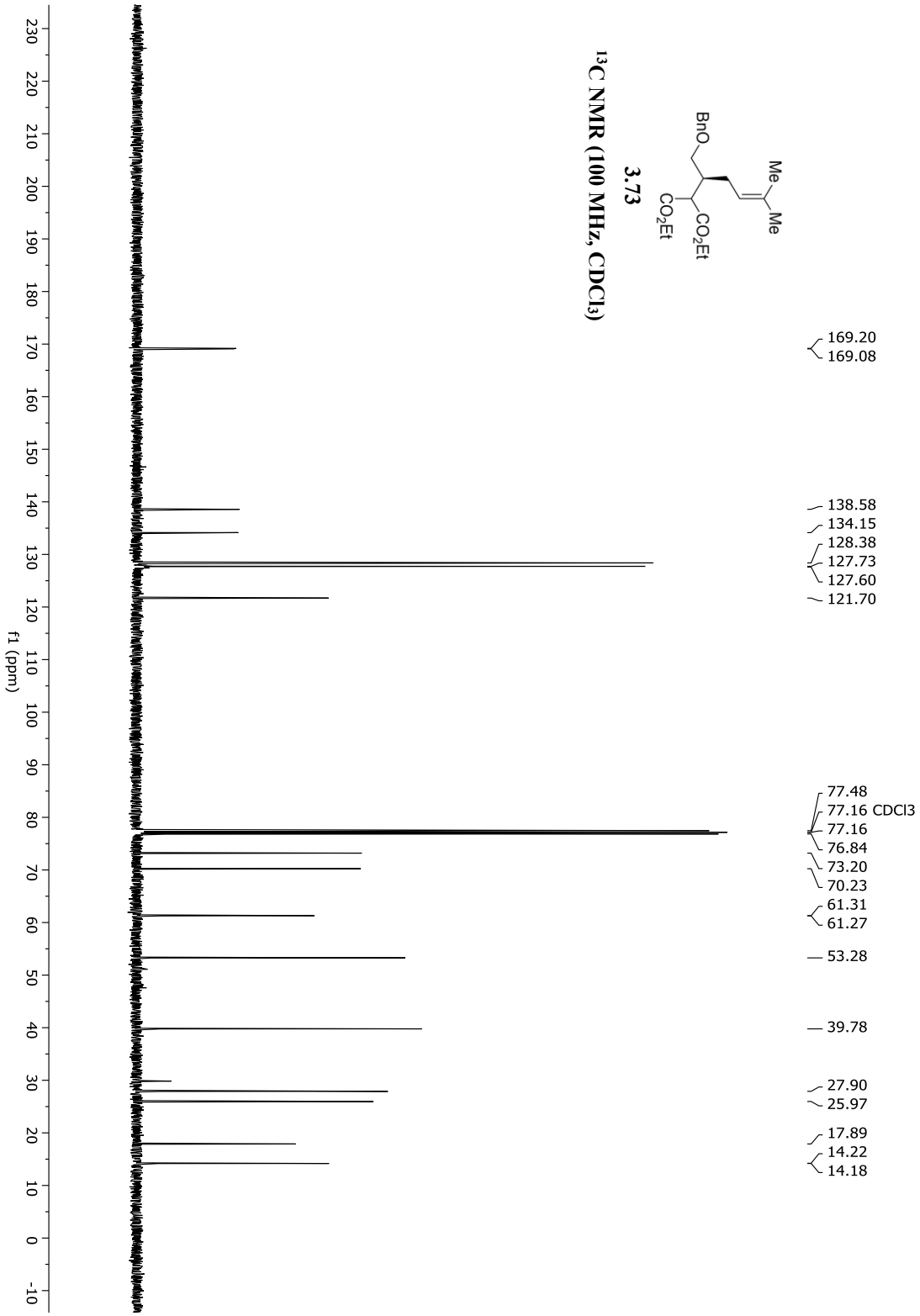

**3.71**

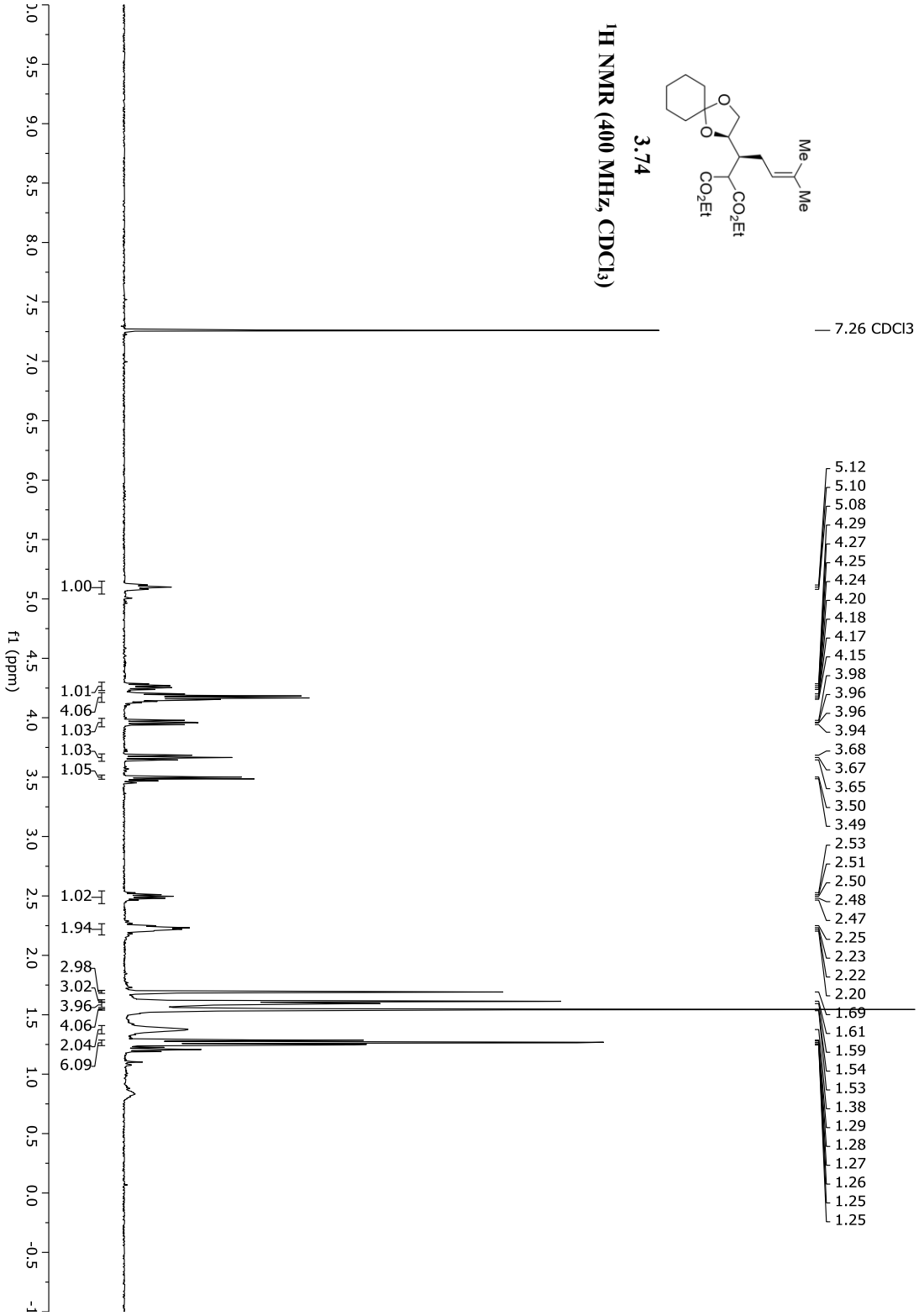
**$^{13}$C NMR (100 MHz, $CDCl_3$)**

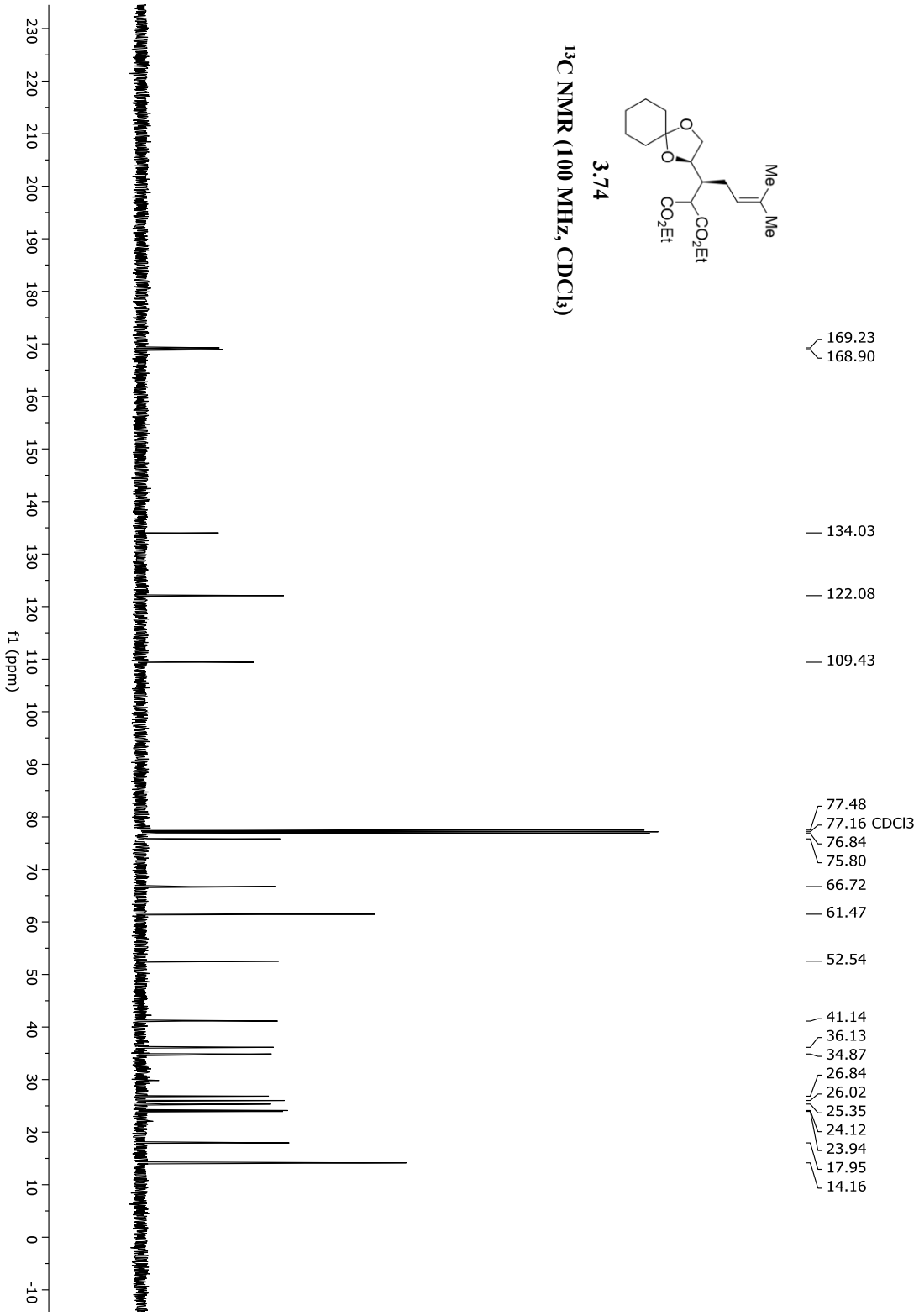

3.72
$^1$H NMR (400 MHz, CDCl$_3$)
TBSO
CO$_2$Et
CO$_2$Et
Me
Me
f1 (ppm)
7.26 CDCl3
1.00
4.02
3.05
1.03
1.06
1.07
3.09
3.09
6.17
9.08
5.98
5.10
5.08
5.06
4.19
4.17
4.15
3.60
3.59
3.58
3.56
2.29
2.28
2.26
2.26
2.24
2.21
2.19
2.17
2.15
2.13
2.05
2.04
2.02
2.00
1.99
1.68
1.59
1.28
1.27
1.26
1.25
1.24
1.23
0.87
0.00
-0.00

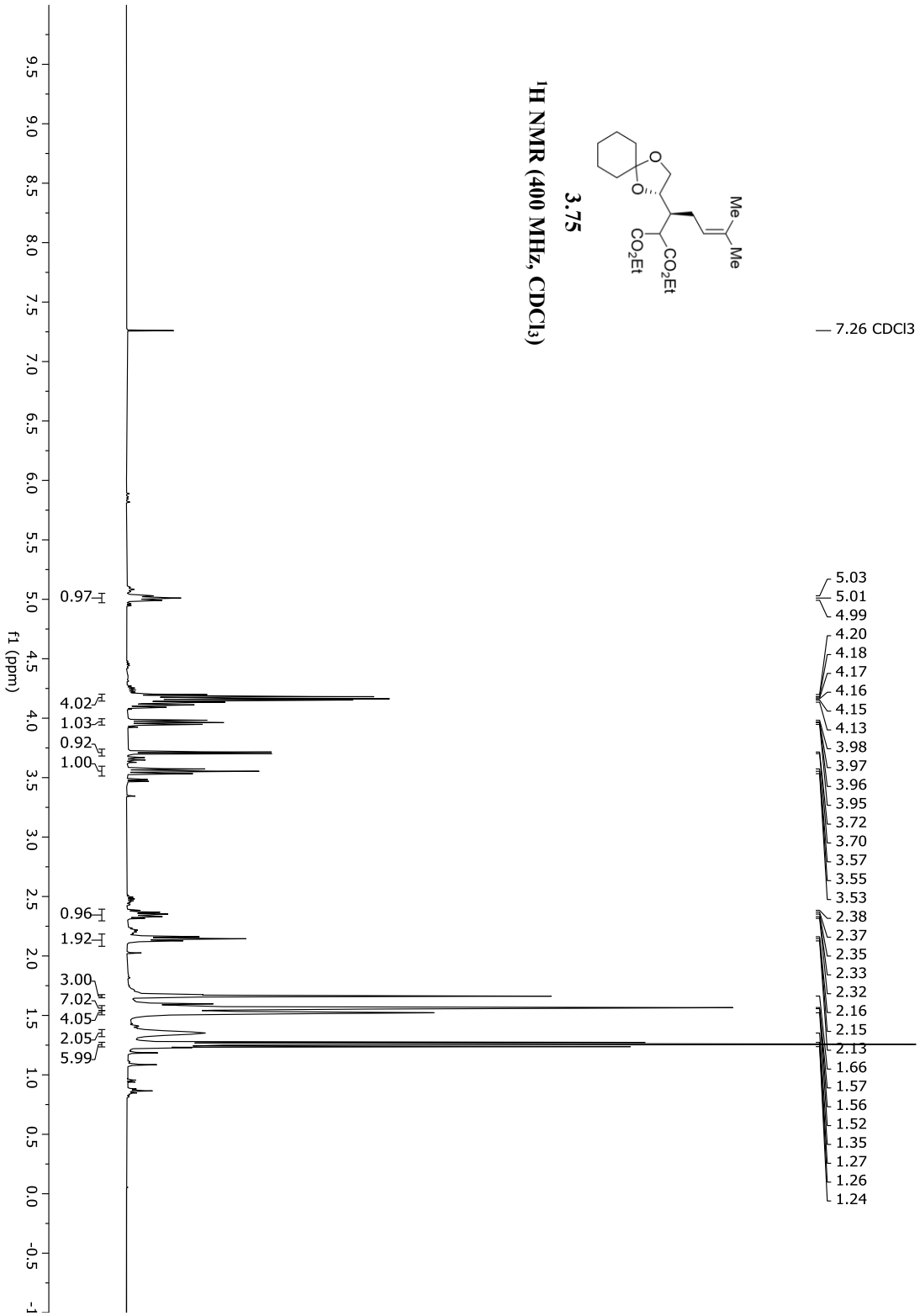

3.72
$^{13}$C NMR (100 MHz, CDCl$_3$)
TBSO
CO$_2$Et
CO$_2$Et
Me
Me
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
169.26
169.16
133.80
122.00
77.48
77.16 CDCl3
76.84
62.33
61.26
61.24
52.89
41.65
27.17
25.99
25.94
18.38
17.94
14.23
14.21
-5.47
-5.50

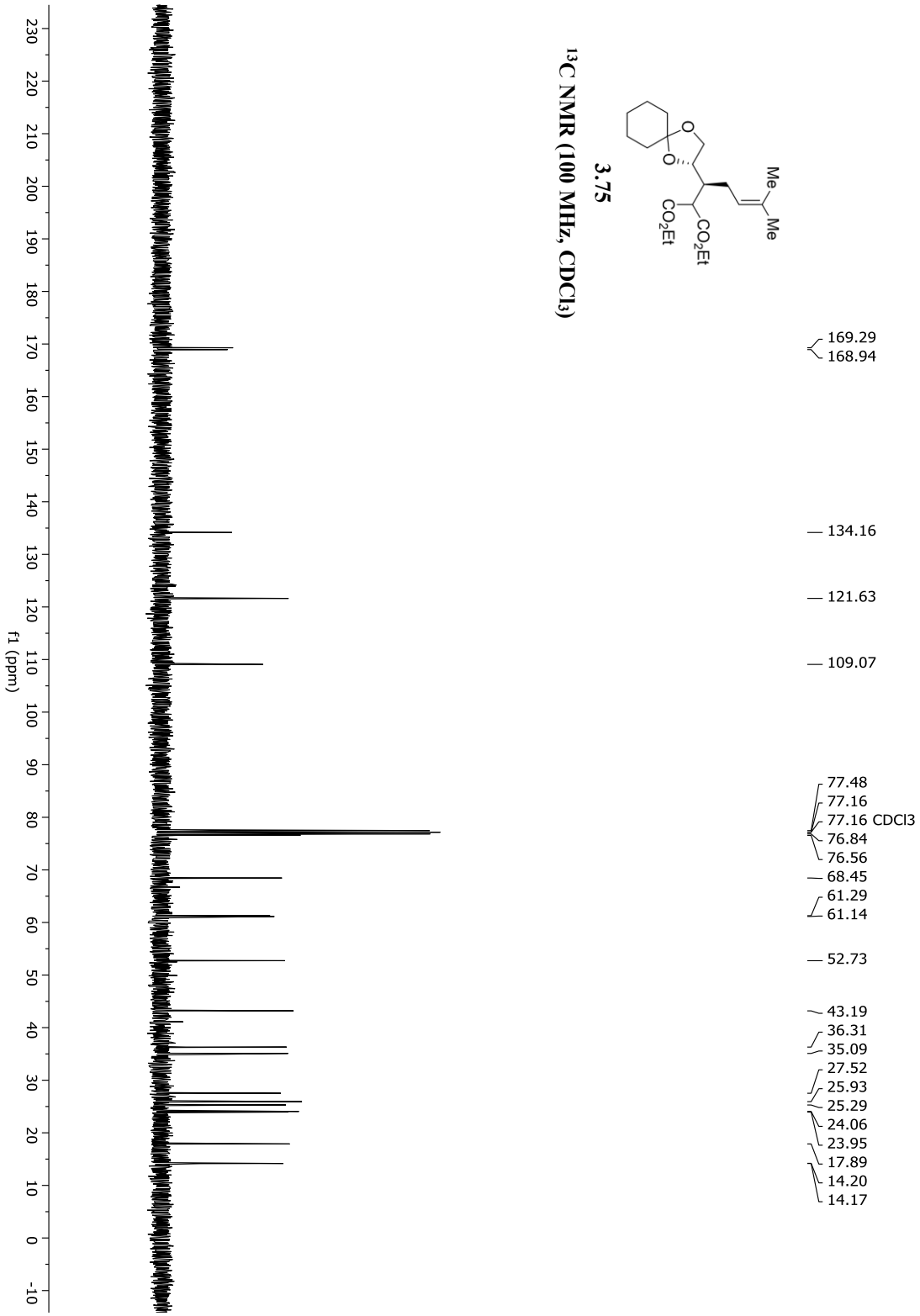

3.73
$^1$H NMR (400 MHz, CDCl$_3$)
BnO
Me
Me
CO$_2$Et
CO$_2$Et
f1 (ppm)
5.04
1.00
2.01
3.97
0.98
2.06
1.02
2.07
3.01
2.99
6.09
7.33
7.31
7.26 CDCl3
5.10
5.08
5.06
4.44
4.18
4.16
4.15
4.13
4.12
4.11
4.11
3.60
3.58
3.51
3.50
2.48
2.48
2.47
2.46
2.46
2.45
2.45
2.44
2.43
2.21
2.19
2.17
2.15
2.13
2.11
2.09
1.69
1.58
1.26
1.25
1.24
1.24
1.23
1.22
1.21

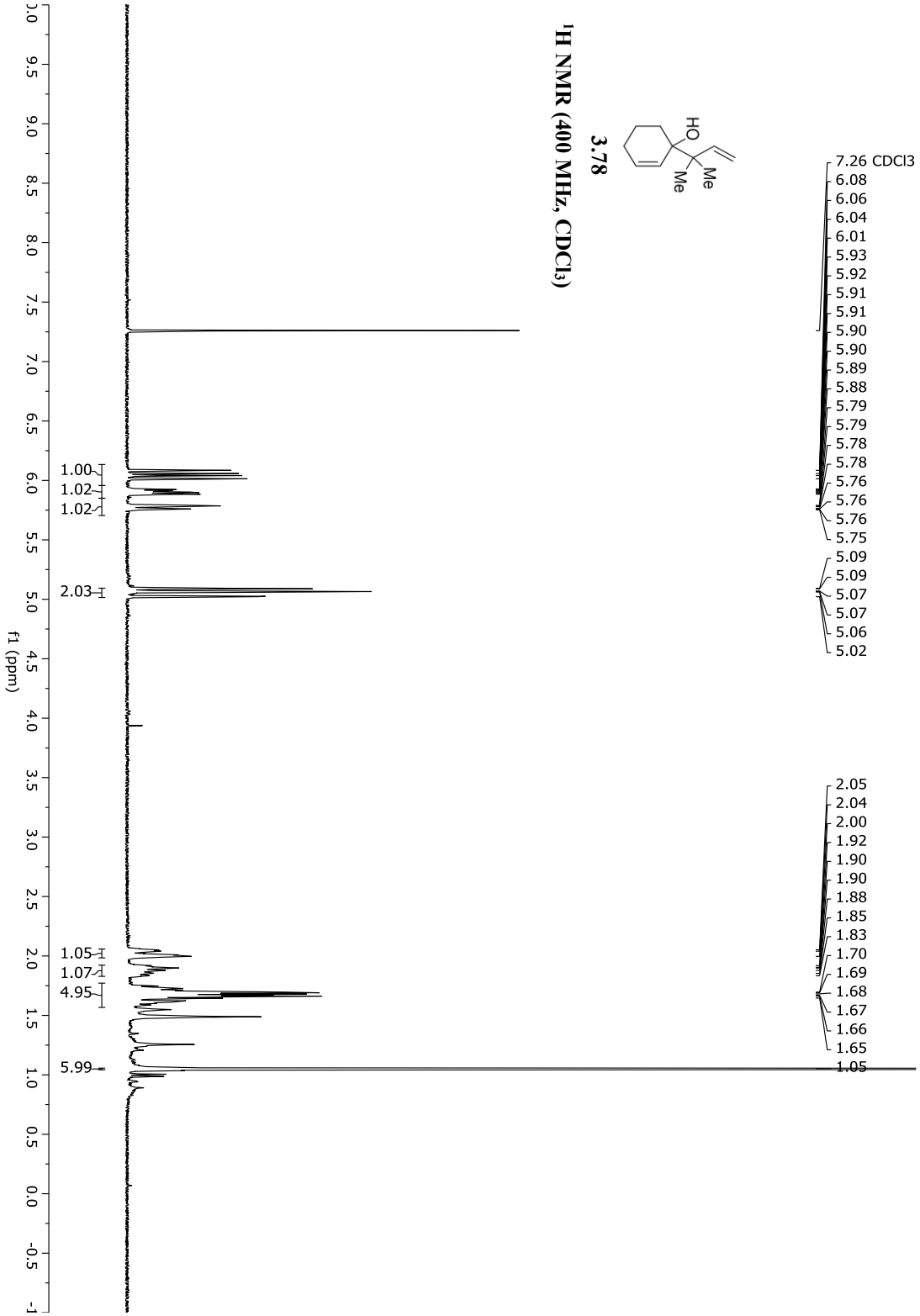

13C NMR (100 MHz, CDCl3)
3.73
BnO
CO2Et
CO2Et
Me
Me
169.20
169.08
138.58
134.15
128.38
127.73
127.60
121.70
77.48
77.16 CDCl3
77.16
76.84
73.20
70.23
61.31
61.27
53.28
39.78
27.90
25.97
17.89
14.22
14.18
f1 (ppm)


3.74
$^1$H NMR (400 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
7.26 CDCl3
f1 (ppm)

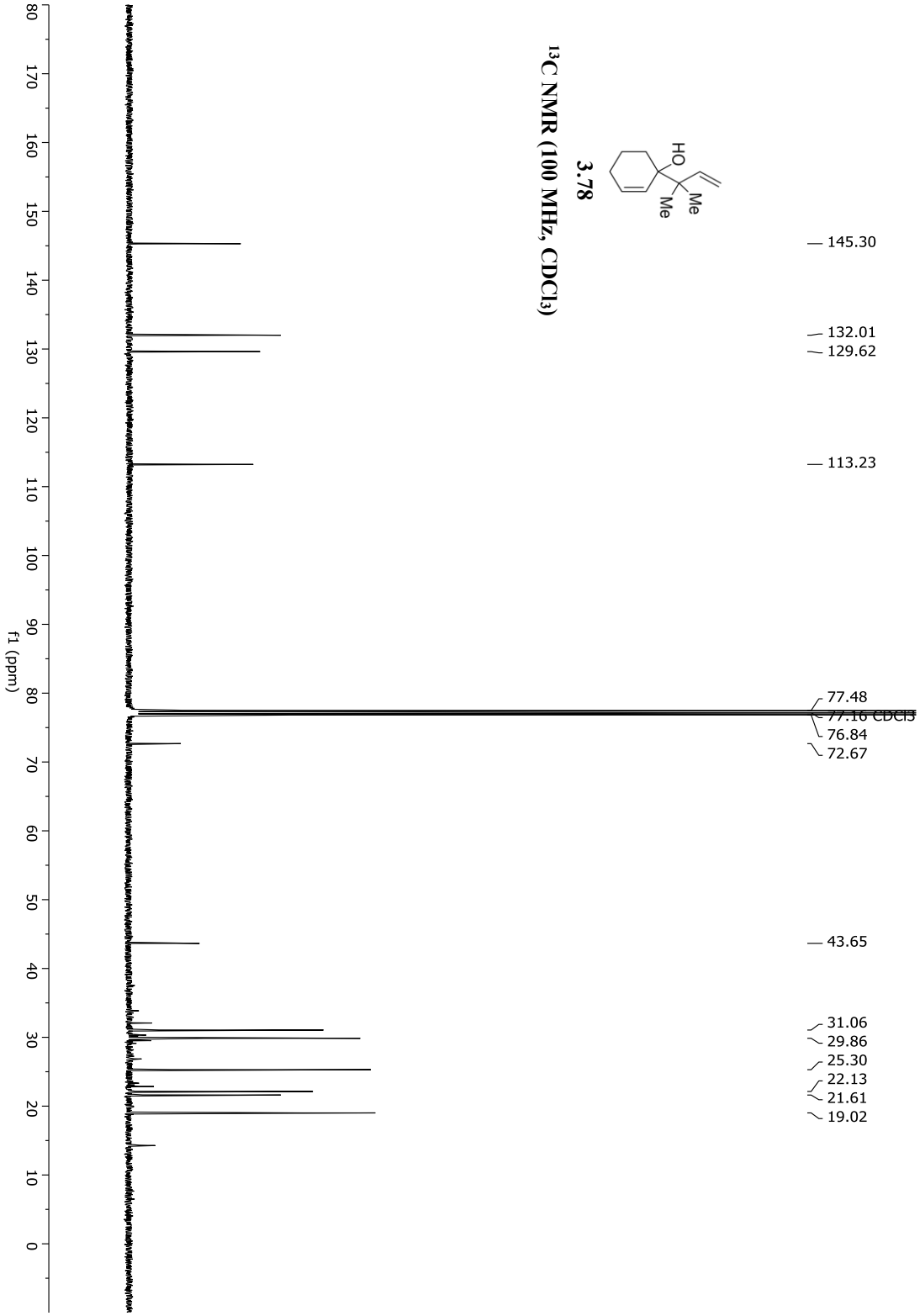

3.74
$^{13}$C NMR (100 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
O
O
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
169.23
168.90
134.03
122.08
109.43
77.48
77.16 CDCl3
76.84
75.80
66.72
61.47
52.54
41.14
36.13
34.87
26.84
26.02
25.35
24.12
23.94
17.95
14.16

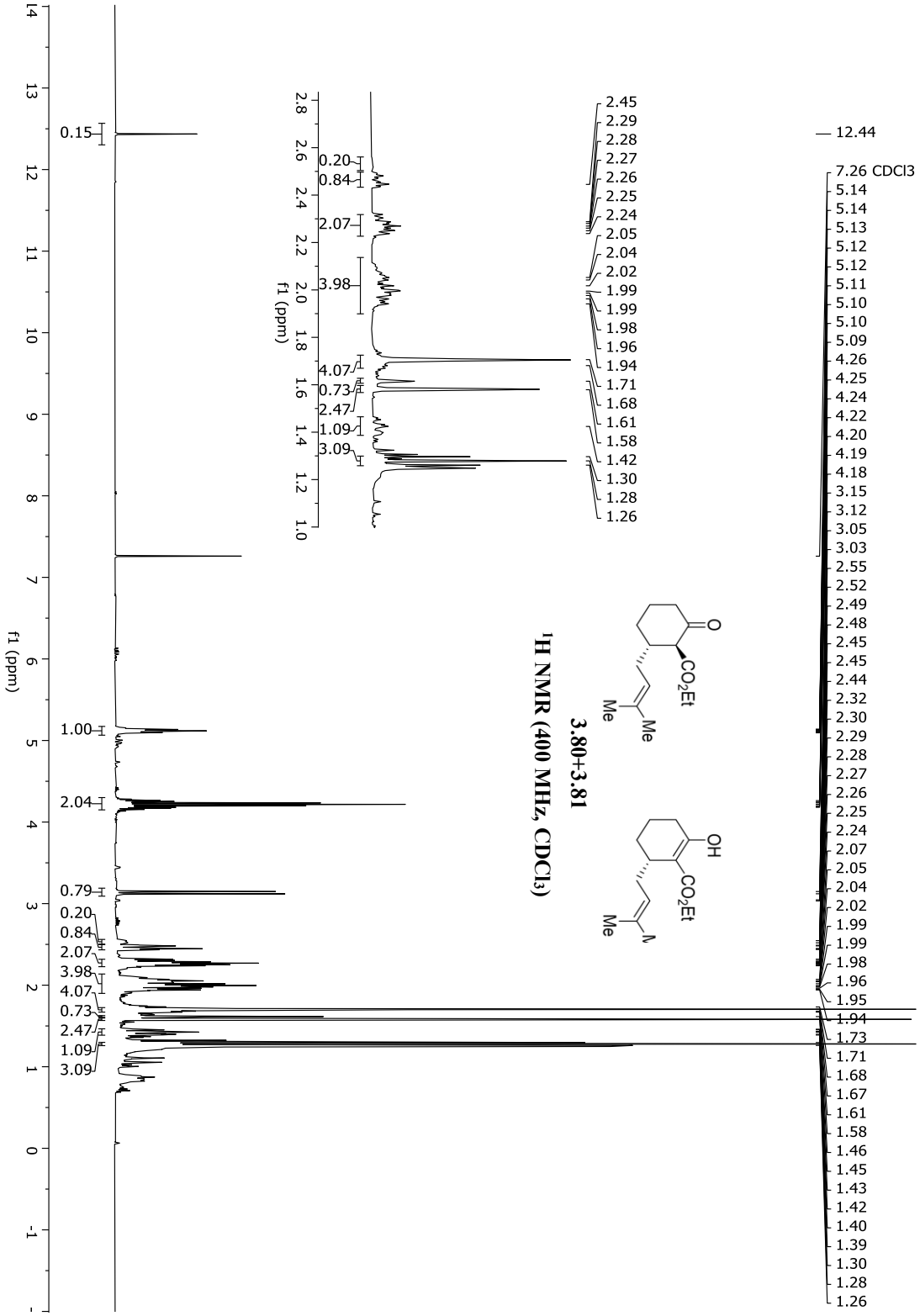

3.75
$^1$H NMR (400 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
7.26 CDCl3
f1 (ppm)
0.97
4.02
1.03
0.92
1.00
0.96
1.92
3.00
7.02
4.05
2.05
5.99
5.03
5.01
4.99
4.20
4.18
4.17
4.16
4.15
4.13
3.98
3.97
3.96
3.95
3.72
3.70
3.57
3.55
3.53
2.38
2.37
2.35
2.33
2.32
2.16
2.15
2.13
1.66
1.57
1.56
1.52
1.35
1.27
1.26
1.24

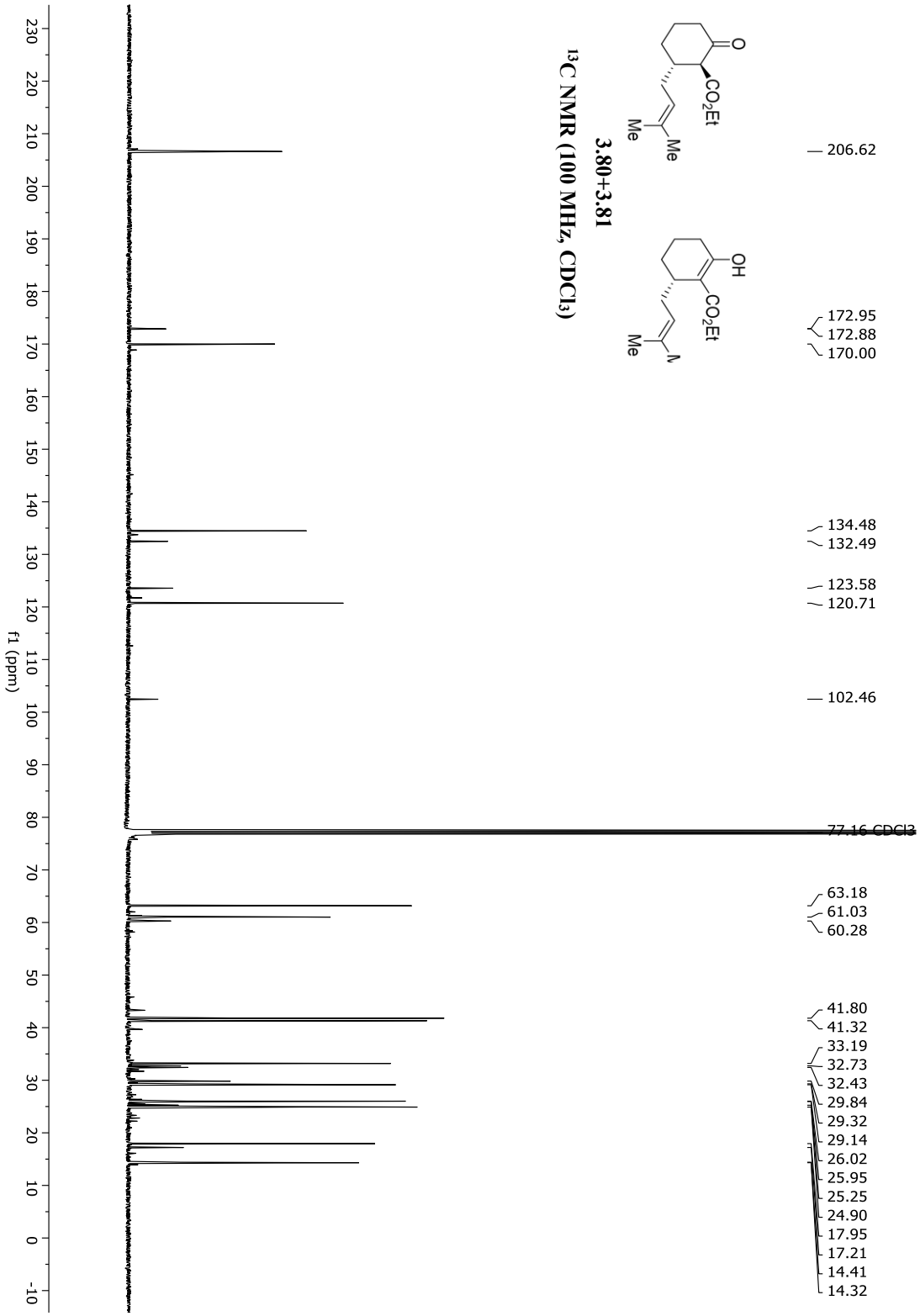

3.75
$^{13}$C NMR (100 MHz, CDCl$_3$)
Me
Me
CO$_2$Et
CO$_2$Et
169.29
168.94
134.16
121.63
109.07
77.48
77.16
77.16 CDCl3
76.84
76.56
68.45
61.29
61.14
52.73
43.19
36.31
35.09
27.52
25.93
25.29
24.06
23.95
17.89
14.20
14.17
f1 (ppm)

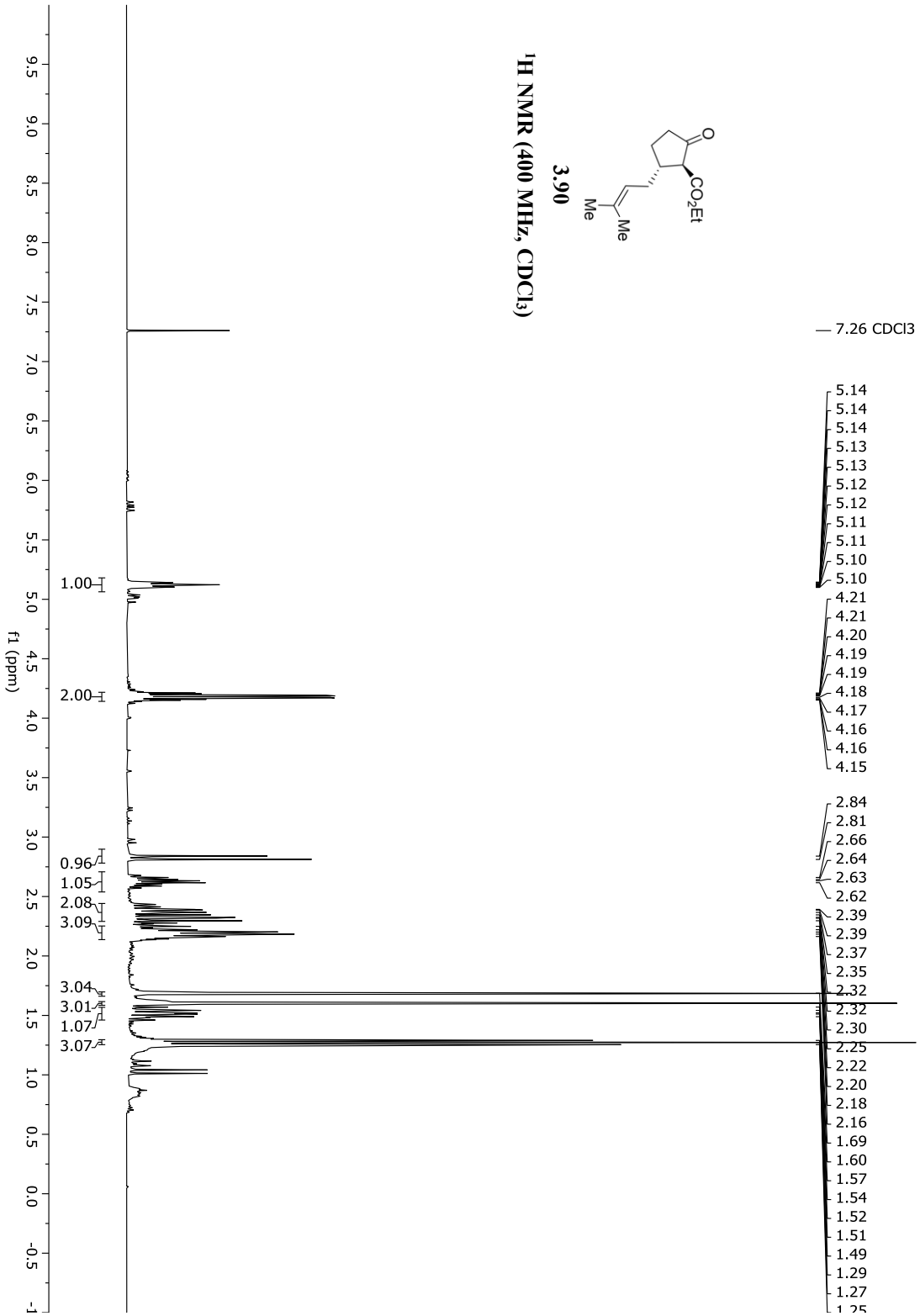



**$^1$H NMR (400 MHz, $CDCl_3$)**


3.78
$^{13}$C NMR (100 MHz, CDCl$_3$)
HO
Me
Me
145.30
132.01
129.62
113.23
77.48
77.16 CDCl3
76.84
72.67
43.65
31.06
29.86
25.30
22.13
21.61
19.02
f1 (ppm)


3.80+3.81
$^1$H NMR (400 MHz, CDCl$_3$)
CO$_2$Et
Me
OH
f1 (ppm)
7.26 CDCl3
12.44


3.80+3.81
13C NMR (100 MHz, CDCl3)
O
CO2Et
Me
Me
OH
CO2Et
Me
206.62
172.95
172.88
170.00
134.48
132.49
123.58
120.71
102.46
77.16 CDCl3
63.18
61.03
60.28
41.80
41.32
33.19
32.73
32.43
29.84
29.32
29.14
26.02
25.95
25.25
24.90
17.95
17.21
14.41
14.32
f1 (ppm)


3.90
$^1$H NMR (400 MHz, CDCl$_3$)
CO$_2$Et
Me
Me
O
f1 (ppm)
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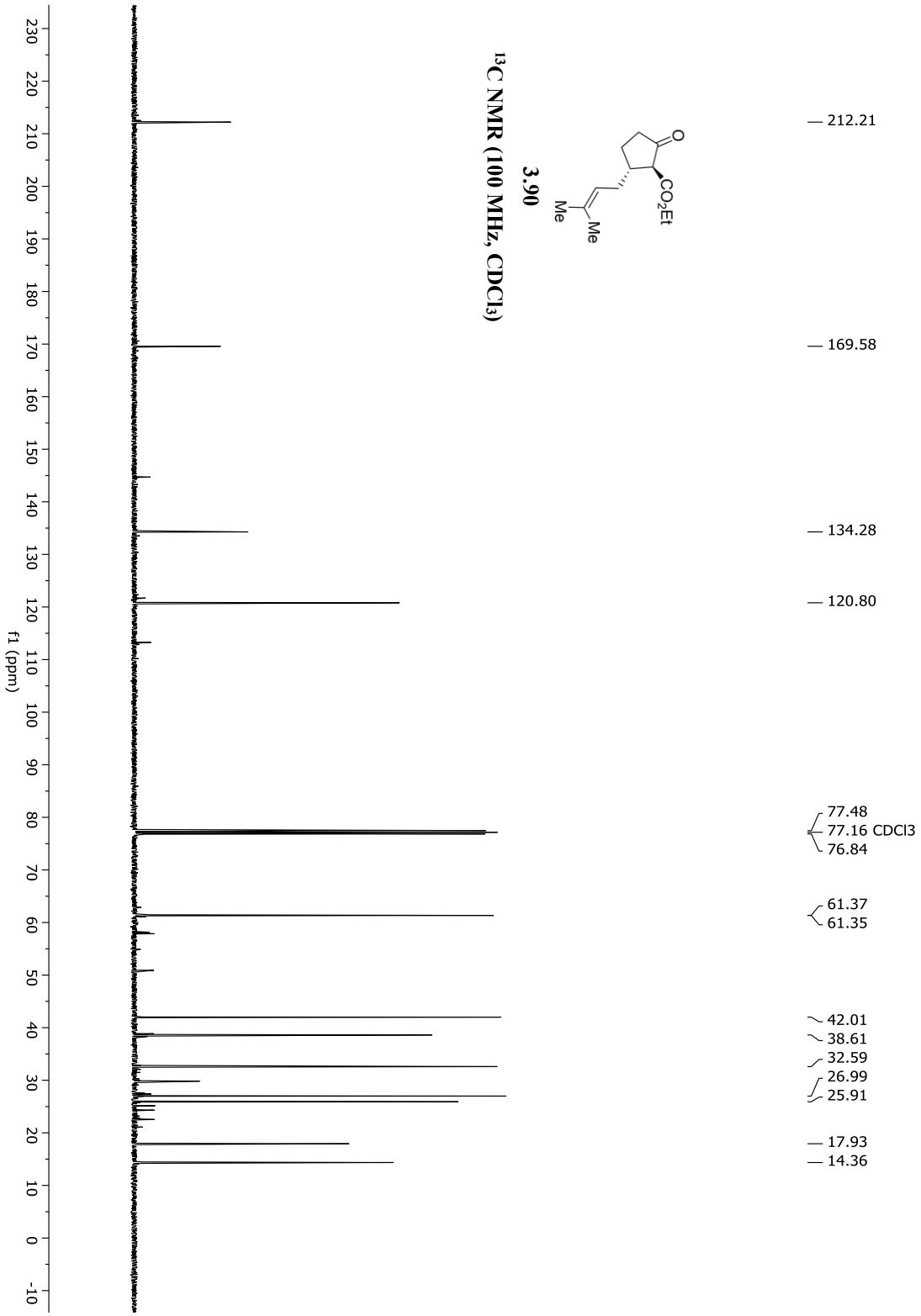
1.00
2.00
0.96
1.05
2.08
3.09
3.04
3.01
1.07
3.07
7.26 CDCl3
5.14 5.14 5.14 5.13 5.13 5.12 5.12 5.11 5.11 5.10 5.10
4.21 4.21 4.20 4.19 4.19 4.18 4.17 4.16 4.16 4.15
2.84 2.81 2.66 2.64 2.63 2.62 2.39 2.39 2.37 2.35 2.32 2.32 2.30 2.25 2.22 2.20 2.18 2.16 1.69 1.60 1.57 1.54 1.52 1.51 1.49 1.29 1.27 1.25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3.90
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Me
Me
O
212.21
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120.80
77.48
77.16 CDCl3
76.84
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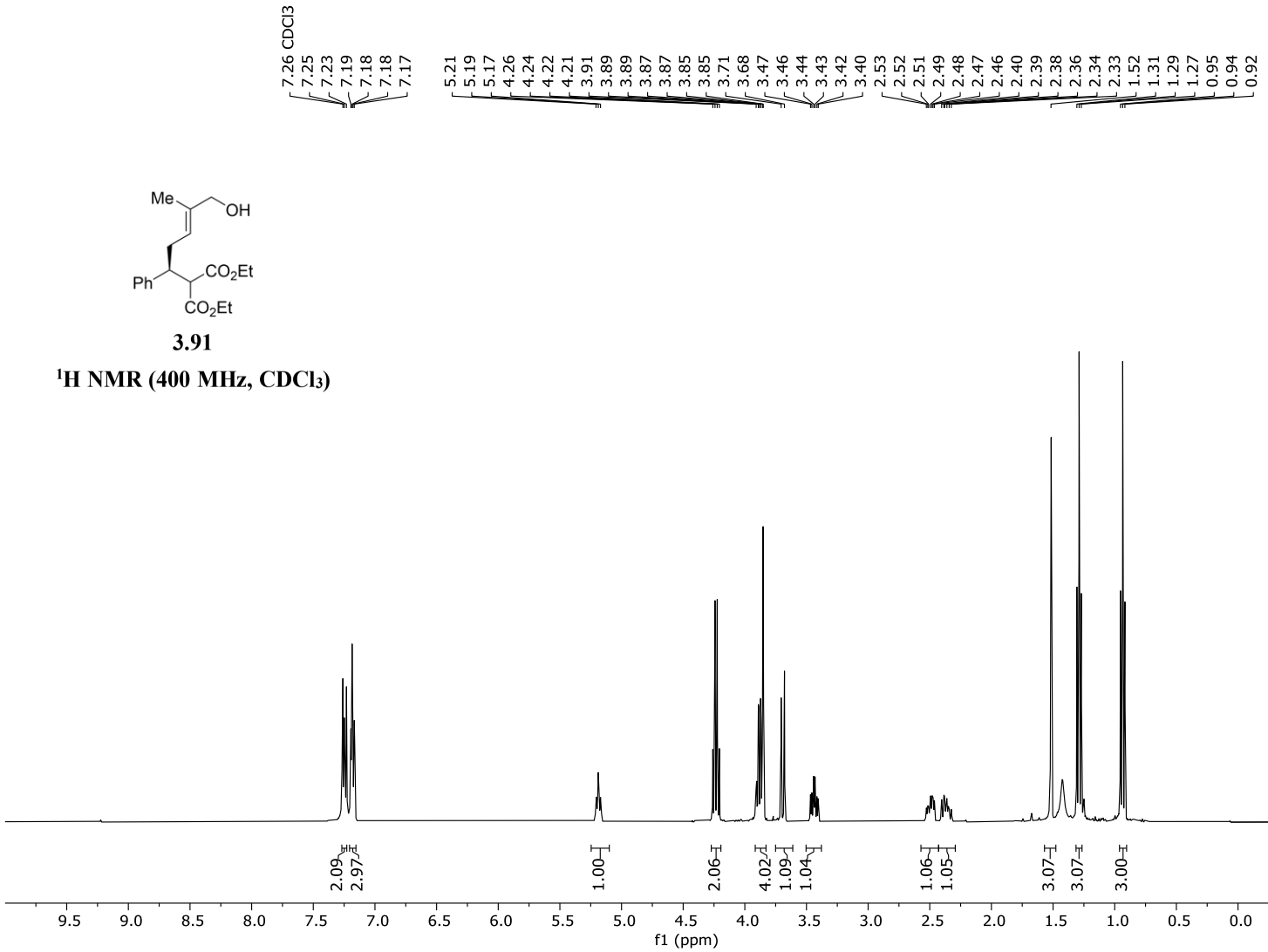
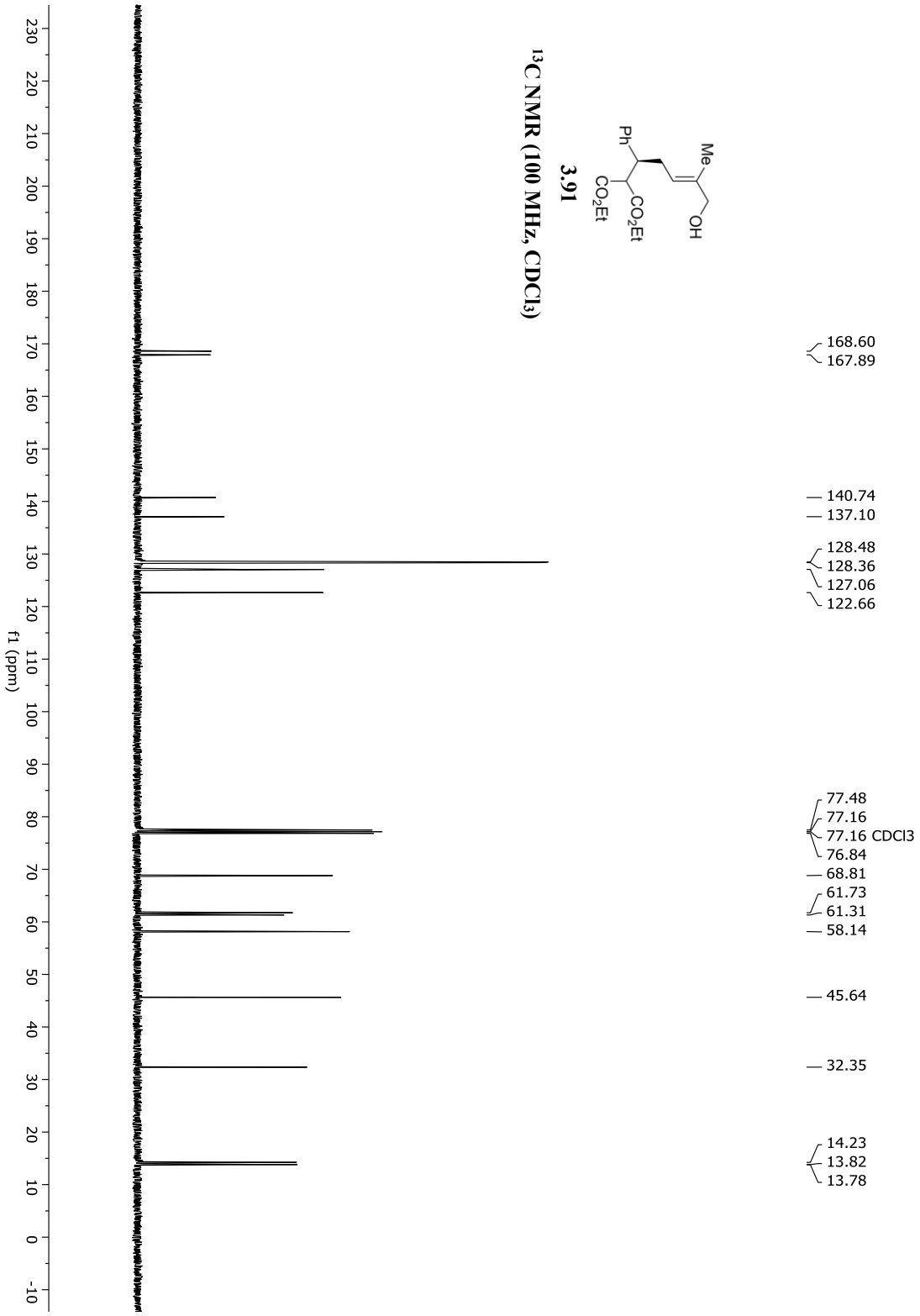
61.35
42.01
38.61
32.59
26.99
25.91
17.93
14.36
f1 (ppm)




**3.91**

**$^1$H NMR (400 MHz, $CDCl_3$)**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CO$_2$Et
Me
OH
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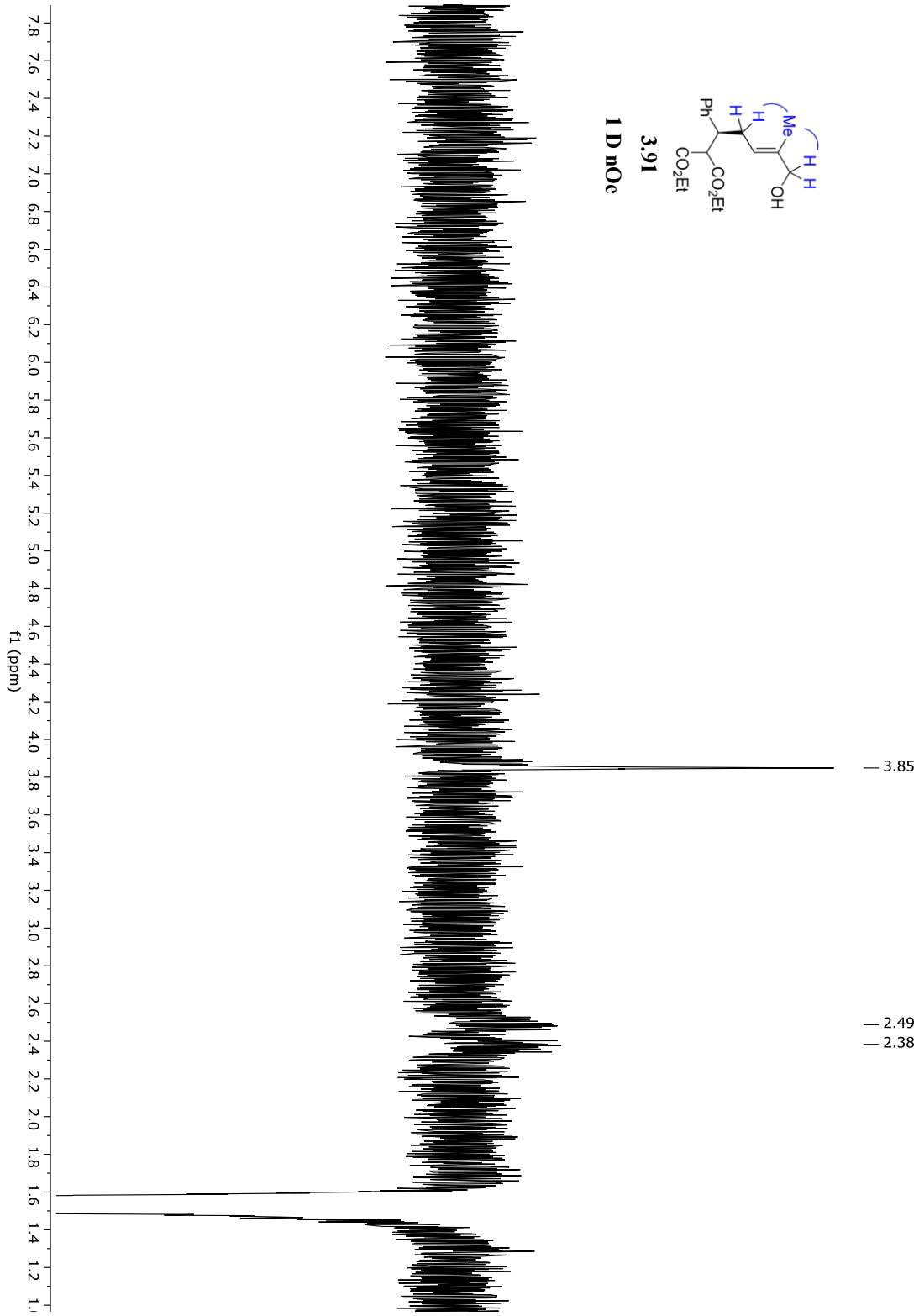
167.89
140.74
137.10
128.48
128.36
127.06
122.66
77.48
77.16
77.16 CDCl3
76.84
68.81
61.73
61.31
58.14
45.64
32.35
14.23
13.82
13.78
f1 (ppm)


3.91
1 D nOe
Ph
CO2Et
CO2Et
H
H
Me
H H
OH
f1 (ppm)
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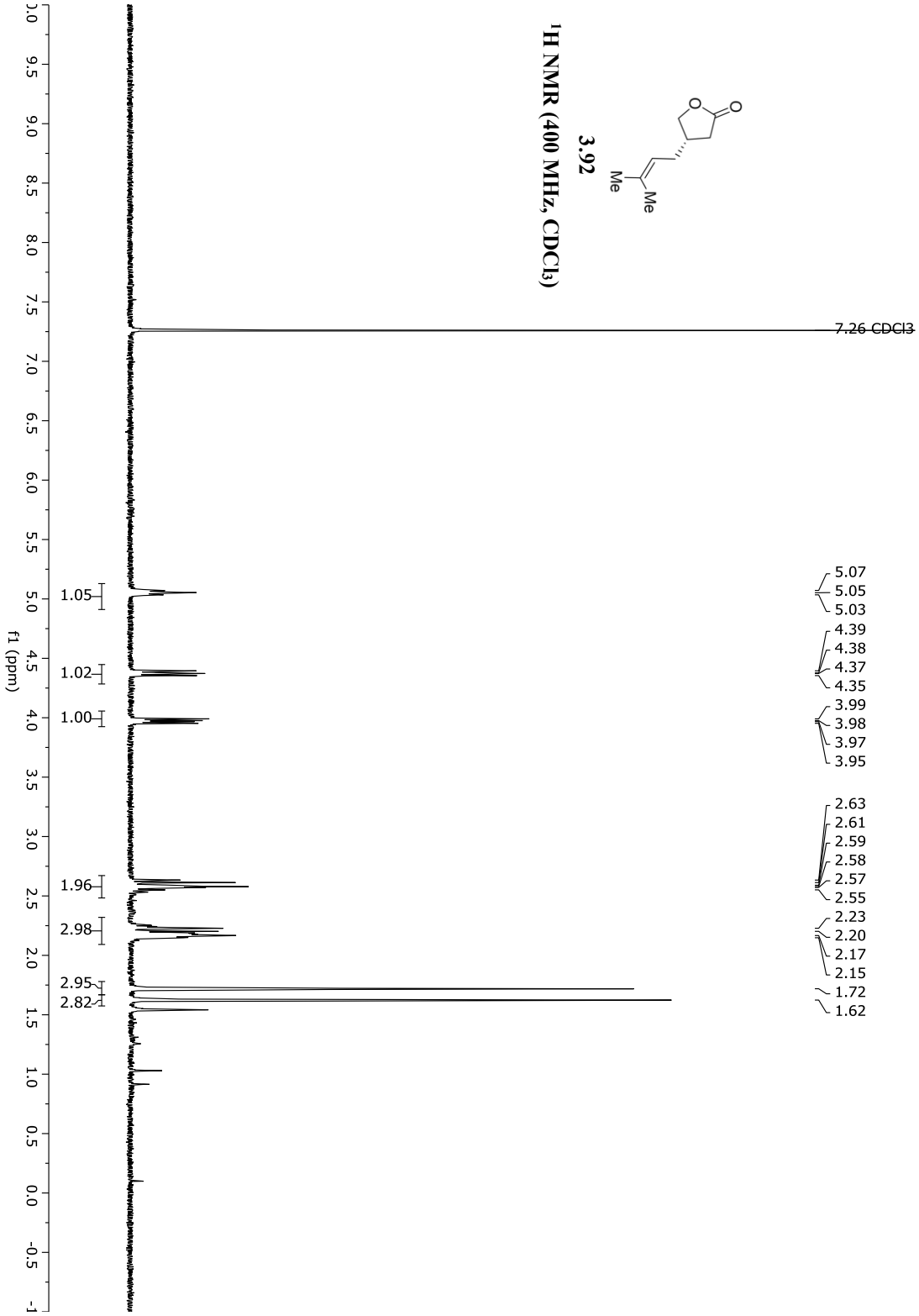
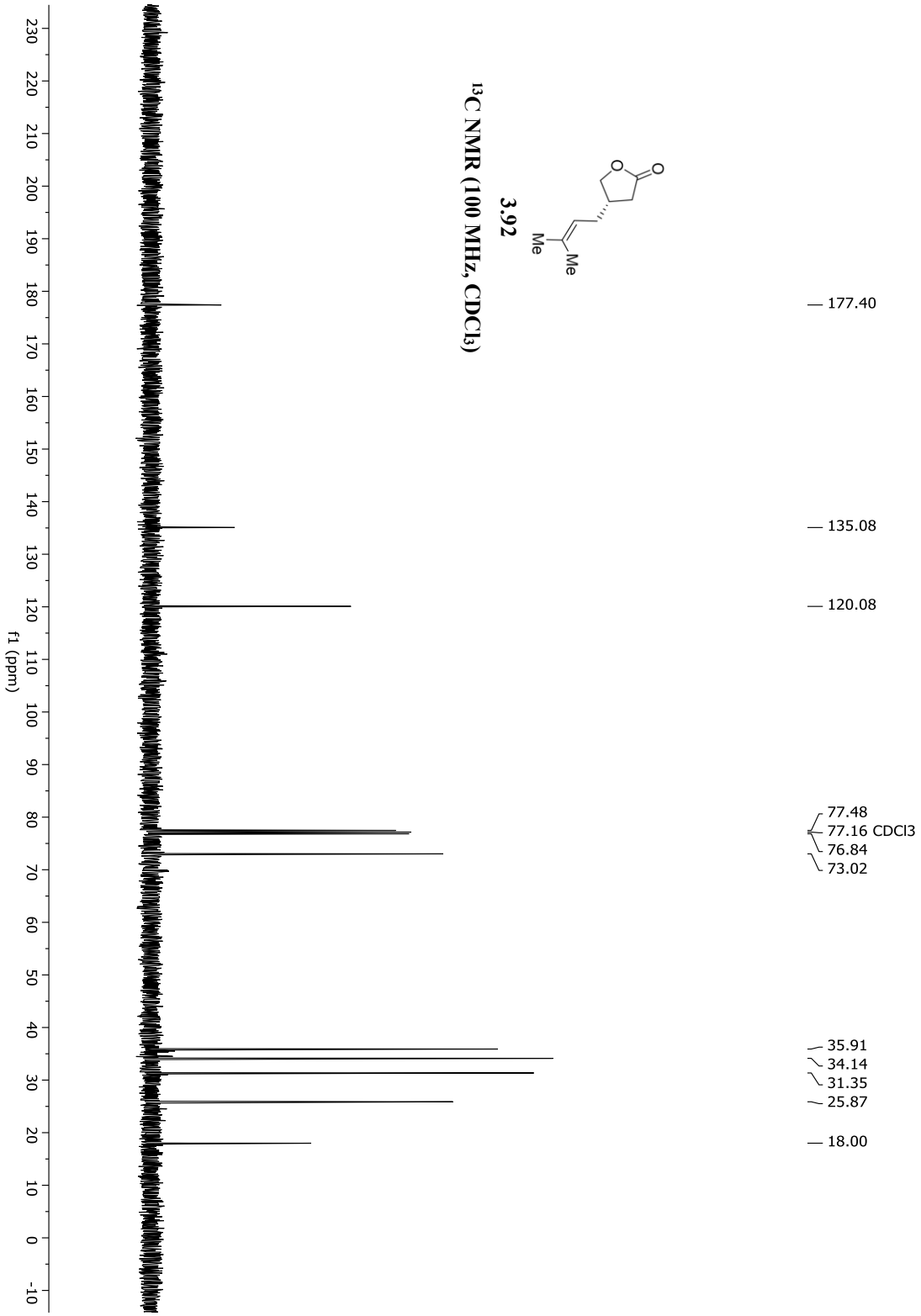
3.85
2.49
2.38




**$^1$H NMR (400 MHz, $CDCl_3$)**


3.92
$^{13}$C NMR (100 MHz, CDCl$_3$)
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Me
177.40
135.08
120.08
77.48
77.16 CDCl3
76.84
73.02
35.91
34.14
31.35
25.87
18.00
f1 (ppm)

- **DFT studies and coordinates after optimization with M06L/DF-Def2SVP$_{THF(SMD)}$**

88

3.93/ sum of electronic and free enery: -3721.200817 a.u. / lowest freq: -264.5166 cm-1

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| C | -0.88265 | -3.90003 | -0.15593 |
| H | -0.99060 | -4.27403 | -1.18972 |
| C | -0.49668 | -1.59813 | -0.00131 |
| C | 1.46413 | -2.94629 | -0.48294 |
| C | 2.41668 | -3.11513 | 0.54020 |
| C | 1.83063 | -2.88665 | -1.84119 |
| C | 3.76371 | -3.22623 | 0.17654 |
| C | 3.19111 | -2.99710 | -2.15960 |
| C | 4.14703 | -3.17005 | -1.16220 |
| H | 5.20331 | -3.25533 | -1.43006 |
| Cu | 0.40892 | 0.11024 | -0.11375 |
| N | -1.80950 | -1.78835 | 0.16775 |
| N | 0.09481 | -2.80581 | -0.11489 |
| C | 1.54025 | 1.86703 | -0.30793 |
| C | 3.02962 | 1.82174 | -0.47077 |
| C | 3.75381 | 3.01809 | -0.40327 |
| C | 3.73062 | 0.63616 | -0.73289 |
| C | 5.13997 | 3.02979 | -0.57461 |
| C | 5.11062 | 0.64313 | -0.90887 |
| C | 5.82386 | 1.84258 | -0.82883 |
| H | 5.68524 | 3.97544 | -0.51494 |
| H | 5.63618 | -0.29481 | -1.10904 |
| H | 6.90771 | 1.84943 | -0.96925 |
| C | 0.92228 | 1.75615 | 1.06703 |
| H | 3.17690 | -0.30815 | -0.77464 |
| Na | -1.04042 | 0.79027 | 3.76608 |
| H | 4.51744 | -3.35635 | 0.95836 |
| H | 3.49675 | -2.94373 | -3.20835 |
| H | -0.56983 | -4.74603 | 0.47169 |
| C | 0.80462 | -2.71974 | -2.91689 |
| H | 0.35678 | -3.68572 | -3.20093 |
| H | -0.02672 | -2.06890 | -2.60807 |
| H | 1.24602 | -2.29628 | -3.82847 |
| C | 1.98524 | -3.16374 | 1.97001 |
| H | 1.43257 | -2.25689 | 2.26108 |
| H | 1.30215 | -4.00547 | 2.16174 |
| H | 2.84262 | -3.27234 | 2.64589 |
| H | -3.04923 | -3.48275 | -0.20169 |
| H | 3.22212 | 3.95462 | -0.20725 |
| H | 1.15379 | 2.78990 | -0.74533 |
| C | 1.53820 | 1.08470 | 2.19682 |
| C | -0.31597 | 2.48518 | 1.31249 |
| O | 2.66499 | 0.41080 | 1.85528 |
| O | 1.15654 | 1.07844 | 3.36781 |
| O | -0.96280 | 2.54141 | 2.35456 |
| O | -0.75133 | 3.15576 | 0.21425 |
| C | -2.02052 | 3.77214 | 0.31625 |
| H | -2.09517 | 4.41344 | 1.20458 |
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| H | -2.82539 | 3.02161 | 0.35804 |
| C | 3.43664 | -0.12351 | 2.91280 |
| H | 2.84864 | -0.78359 | 3.56414 |
| H | 4.25024 | -0.69079 | 2.44551 |
| H | 3.86764 | 0.67657 | 3.53322 |
| C | -2.72571 | -0.73393 | 0.52804 |
| H | -2.13452 | 0.20465 | 0.45200 |
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| C | -4.98140 | -0.04650 | 0.49527 |
| C | -4.22002 | -1.02710 | -1.60329 |
| C | -6.24984 | 0.15246 | -0.04853 |
| C | -4.45092 | 0.22242 | 1.86669 |
| C | -5.49352 | -0.81932 | -2.14355 |
| H | -3.43038 | -1.49494 | -2.20212 |
| C | -6.49825 | -0.23051 | -1.37131 |
| H | -7.04879 | 0.59629 | 0.55326 |
| H | -5.70629 | -1.12126 | -3.17263 |
| H | -7.49097 | -0.07626 | -1.80295 |
| C | -3.26637 | -0.78994 | 2.00678 |
| O | -2.37708 | -0.59904 | 2.96013 |
| C | 0.97350 | 0.92864 | -2.02820 |
| H | 1.67565 | 1.60134 | -2.52969 |
| H | 1.35406 | -0.09747 | -2.16147 |
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| H | -1.06192 | 0.19891 | -2.35094 |
| C | -1.00715 | 2.21354 | -2.92564 |
| C | -0.28486 | 3.50912 | -3.09298 |
| C | -2.45323 | 2.23549 | -3.29517 |
| H | -3.01412 | 2.96759 | -2.68821 |
| H | -2.93688 | 1.25775 | -3.16557 |
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88
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C 2.41929 -3.23742 -1.78539
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Cu 0.43813 0.06782 -0.23705
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O 1.61627 0.20298 3.27570
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H -0.04111 4.05803 -1.96773
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87
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H -0.76917 -4.37191 -1.54331
C -0.49446 -1.66945 -0.28370
C 1.60460 -2.91354 -0.50893
C 2.33143 -2.71507 0.68354
C 2.24215 -3.21804 -1.72572
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H 2.30670 -2.39018 2.81506
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| | | | |
|---|---|---|---|
| H | -3.24009 | -1.97287 | -2.17777 |
| C | -6.46270 | -0.90820 | -1.89161 |
| H | -7.28382 | 0.07337 | -0.15076 |
| H | -5.35336 | -1.89446 | -3.46142 |
| H | -7.39633 | -0.87039 | -2.45836 |
| H | 3.17111 | 3.11156 | -2.09954 |
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| H | 4.84662 | 2.90533 | -2.65257 |