CATALYTIC ENANTIOSELECTIVE SYNTHESIS OF SECONDARY ORGANOBORONATES AND PROGRESS TOWARDS THE TOTAL SYNTHESIS OF SARCODICTYINS

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Abstract: This dissertation will present three main projects focusing on the catalytic enantioselective synthesis of secondary organoboronic esters and progress towards the total synthesis of sarcodictyins. In the first project, a palladium-catalyzed enantioselective conjunctive cross-coupling reaction with propargylic electrophiles will be described. The tetra-substituted allenes are isolated with good yield and enantioselectivity and the beneficial effects of alcohol additives are investigated. The second project describes the enantioselective synthesis of α-boryl zinc reagents by a nickel-catalyzed carbozincation reaction. The *in situ* generated α-boryl zinc intermediate can be trapped by copper-mediated allylations, palladium-catalyzed Negishi cross-couplings, and cerium-mediated halogenation reactions to construct various chiral organoboranes. The synthetic utility of this methodology is showcased by the synthesis of natural products, including bruguierol A, (-)-aphanorphine, and (-)-enterolactone. The mechanism is studied with the assistance of EPR and deuterium-labeling experiments and a catalytic cycle through a Ni(I) intermediate is proposed. The third project depicts a synthetic route to essential precursors in the progress of the total synthesis of sarcodictyins. Various attempts to construct the ten-membered ring core of sarcodictyin have been made, including Sonogashira reaction, Dieckmann condensation, and lithium—halogen exchange process.

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To my friends and family

LIST OF ABBREVIATIONS

Ac: acetyl

acac: acetylacetonyl

ACN: acetylnitrile

Ad: adamantyl

aq.: aqueous

Ar: aryl

atm: atmosphere

$B_2(cat)_2$: bis(catecholato)diboron

$B_2(pin)_2$: bis(pinacolato)diboron

BBN: 9-borabicyclo[3.3.1]nonane

BHT: 2,6-di-tert-butyl-4-methylphenol

BINAP: 2,2'-bis(diohenylphosohino)-1,1'-binaphthyl

Bn: benzyl

Boc: *tert*-butyloxycarbonyl

BOX: bisoxazoline

Bz: benzoyl

cat.: catalyst or catalytic amount

cat: catechol

Cb: *N*, *N*-diisopropylcarbamoyl

Cbz: benzyloxycarbonyl

cod: 1,5-cyclooctadiene

conv.: conversion

Cp: cyclopentadienyl

18-Cr-6: 18-crown-6

CSA: camphorsulfonic acid

Cy: cyclohexyl

d: day(s)

dan: 1,8-diaminoaphthalene

DART: direct analysis in real time

dba: dibenzylideneacetone

DCC: *N, N'*-dicyclohexylcarbodiimide

DCE: dichloroethane

DCM: dichloromethane

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEAD: diethyl azodicarboxylate

DET: diethyl tartrate

DFT: density functional theory

DG: directing group

DIAD: diisopropyl azodicarboxylate

DIBAL: diisobutylaluminium hydride

DIPT: diisopropyl tartrate

DMA: dimethylacetamide

DMAP: 4-dimethylaminopyridine

DMDO: dimethyldioxirane

DME: dimethoxyethane

DMF: *N, N*-dimethylformamide

DMP: Dess-Martin periodinane

DMT: dimethyl tartrate

dmpd: 2,4-dimethylpenane-2,4-diol

DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DMSO: dimethyl sulfoxide

DPED: 1,2-diphenylethylene-1,2-diamine

dppbz: 1,2-bis(diphenylphosphino)benzene

dppf: 1,1'-bis(diphenylphosphino)ferrocene

dppp: 1,1'-bis(diphenylphosphino)propane

d.r.: diastereomeric ratio

dtbpy: 4,4'-di-tert-butyl-2,2'-dipyridyl

EAS: enantioselective allylic substitution

EDC: 1-ethyl-3-carbodiimide

EDTA: ethylenediaminetetraacetic acid

e.e.: enantiomeric excess

ent: enantiomeric

EPR: electron paramagnetic resonance

eq: equation(s)

equiv: equivalent

e.r.: enantiomeric ratio

Et: ethyl

Et_2O: diethyl ether

EtOAc: ethyl acetate

glyme: dimethoxyethane

h: hour(s)

H-bond: hydrogen bond

HG2: Hoveyda-Grubbs II Catalyst

HMDS: bis(trimethylsilyl)amide

HMPA: hexamethylphosphoramide

HOBt: hydroxybenzotriazole

HRMS: high resolution mass spectrometry

Hz: hertz

*i*Bu: isobutyl

IPA: isopropanol

Ipc: isopinocamphenyl

IPO: iminopyridine-oxazoline

*i*Pr: isopropyl

IR: infrared spectroscopy

LAH: lithium aluminum hydride

LDA: lithium diisopropylamine

LiTMP: lithium 2,2,6,6-tetramethylpiperidide

Lys: Lysine

M: molar

mac: methylated acenaphthoquinone

*m*CPBA: *meta*-chloroperoxybenzoic acid

Me: methyl

MeCN: acetylnitrile

mes: mesityl

min: minute(s)

MOM: methoxymethyl

MOP: 2-(dipenylphosphino)-2'-methoxy-1,1'-binaphthyl

M.S.: molecular sieves

Ms: mesylate

MTBE: methyl *tert*-butyl ether

MVK: methyl vinyl ketone

N/A: not available

NBS: *N*-bromosuccinimide

*n*Bu: *n*-butyl

NCS: *N*-chlorosuccinimide

neo: neopentylglycol

NHC: *N*-heterocyclic carbene

*n*Hex: *n*-hexyl

NIS: *N*-iodosuccinimide

NMO: *N*-methylmorpholine N-oxide

NMR: nuclear magnetic resonance

PCC: pyridinium chlorochromate

PDI: pyridine(diimine)

PG: protecting group(s)

Ph: phenyl

Piv: pivaloyl

PMB: *para*-methoxybenzyl

PMHS: polymethylhydrosiloxane

PMP: *para*-methoxyphenyl

ppm: parts per million

PPTS: pyridinium *p*-toluenesulfonate

PyBOX: pyridine bis(oxazoline)

quant: quantatitive

rac: racemic

r.r.: regioisomeric ratio

rt: room temperature

*s*Bu: *sec*-butyl

L-selectride: lithium tri-*sec*-butylborohydride

SFC: supercritical fluid chromatography

TADDOL: 2,2-dimethyl-α, α, α′, α′-tetraaryl-1,3-dioxolane-4,5-dimethanol

*t*Am*: tert*-amyl

TBAB: tetrabutylamonium bromide

TBAF: tetrabutylamonium fluoride

TBDPS: *tert*-butyldiphenylsilyl

TBHP: *tert*-butyl hydroperoxide

TBS: *tert*-butyldimethylsilyl

*t*Bu*: tert*-butyl

TCCA: trichloroisocyanuric acid

TEA: triethylamine

temp: temperature

TES: triethylsilyl

Tf: trifluoromethanesulfonyl

TFA: trifluoroacetic acid

TFAA: trifluoroacetic anhydride

THF: tetrahydrofuran

THP: tetrahydropyran

TIB: 2,4,6-triisopropylbenzoyl

TIPS: triisopropylsilyl

TLC: thin layer chromatography

TMDSO: 1,1,3,3-tetramethyldisiloxane

TMEDA: *N, N, N′, N′*-tetramethylethylenediamine

TMS: trimethylsilyl

TPAP: tetrapropylammonium perruthenate

TRIP: 3,3'-bis(2,4,6-triisopropylphenyl-2,2'-binaphtholate

Ts: *p*-toluenesulfonyl

UV: ultraviolet

XantPhos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

xylyl: dimethylphenyl

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Chapter One

Catalytic Enantioselective Synthesis of β-Allenyl Boronic Esters by Conjunctive Cross-Coupling with Propargylic Carbonates[1]

1.1 Introduction

Chiral secondary organoboronates (**1.1**, Scheme 1.1) are versatile building blocks in stereoselective synthesis. These compounds can undergo a range of stereospecific transformations that replace the boronic ester with a variety of functional groups (Scheme 1.1).[2] The transformations include oxidation[3] (**1.2**), amination[4] (**1.3**), olefination[5] (**1.4**), transition-metal-free cross-coupling[6] (**1.6**), halogenation[7] (**1.7**), homologation[8] (**1.8**), and alkynylation[9] (**1.9**). Furthermore, secondary organoboronates **1.1** can be converted to the BF_3K salt **1.5**,[10] which undergoes palladium-catalyzed Suzuki-Miyaura cross-coupling to furnish enantiomerically

(1) Aparece, M. D.; Hu, W.; Morken, J. P. *ACS Catal.* **2019**, *9*, 11381-11385.
(2) Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481-5494.
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(8) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687–1689.
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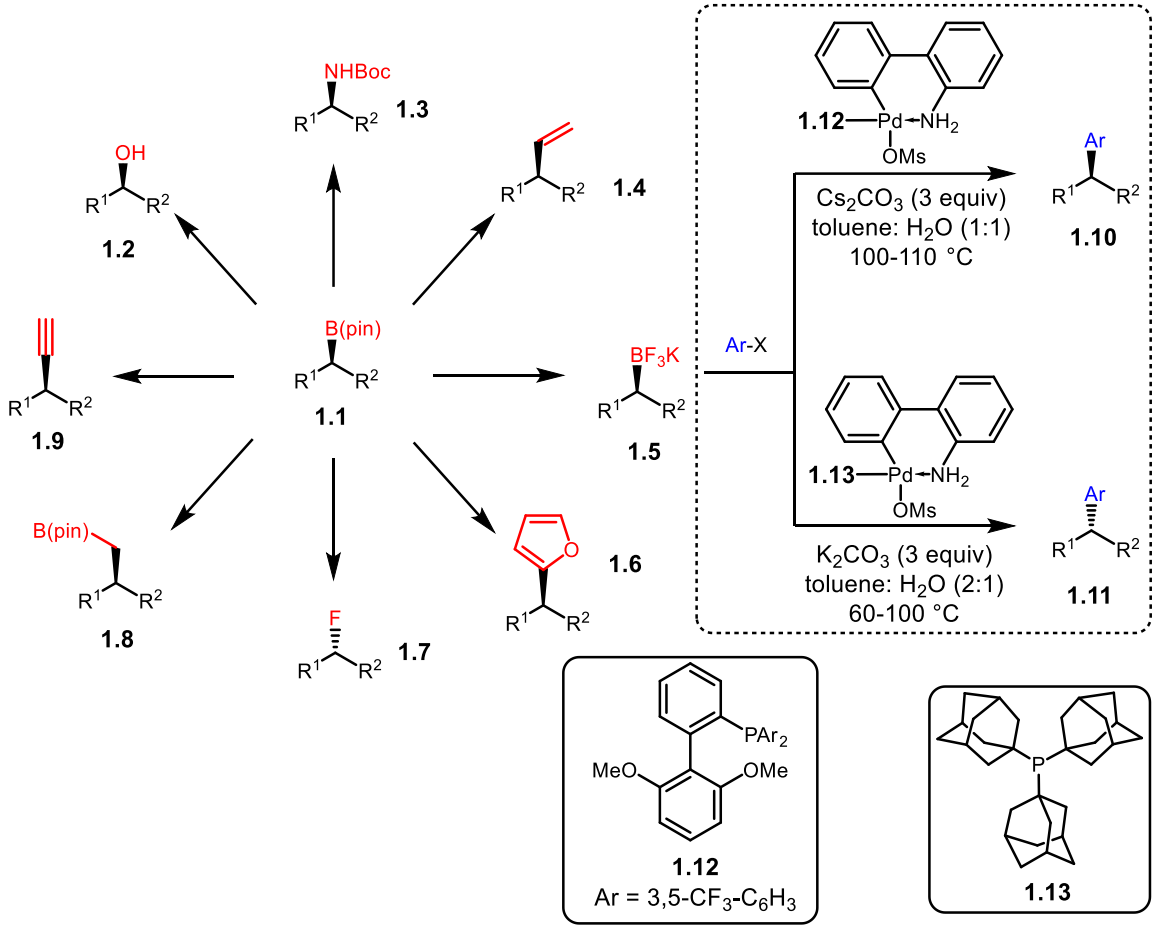
enriched aryl derivatives in either stereoretentive (**1.10**) or stereoinvertive (**1.11**) fashion.[11] The turnover in stereochemical outcome is realized by switching the ligand on palladium as demonstrated by the Biscoe and Sigman groups.[11] In addition to useful chemical reactivity, it is also advantageous that organoboronates are non-toxic, readily accessible, and environmentally benign. Unlike other organometallic reagents (*i.e.*, organozinc reagents and Grignard reagents), organoboranes are configurationally stable and can be stored and handled under an ambient atmosphere.[12]

Scheme 1.1. Reactions of Organoboronates



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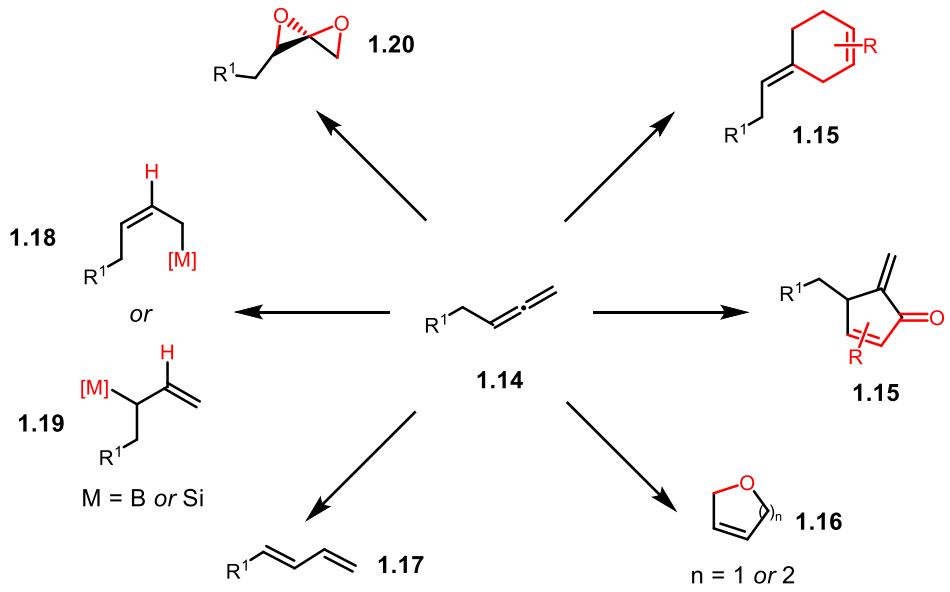
(12) Hall, D. G. Ed., Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials (Wiley-VCH, Weinheim, Germany, **2011**).

In this chapter, I will discuss the synthesis of allenyl boronates. Allenes are distinctive species in organic synthesis. Their unique reactivity that originates from the two independent sites of unsaturation (Scheme 1.2).[13] Allenes not only undergo alkenyl-like functionalization (*i.e.*, hydrometallation[14] (**1.18**, **1.19**), epoxidation[15] (**1.20**), and cycloaddition[16] (**1.15**, **1.16**)), but also exhibit distinct reactivity including cyclization [17] that produces heterocycles (**1.16**) and isomerization[18] to generate dienes (**1.17**).

Scheme 1.2. Reactions of Allenes



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(14) (a) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2013**, *19*, 7125-7132. (b) Miller, Z. D.; Li, W.; Belderrain, T. R.; Montgomery, *J. J. Am. Chem. Soc.* **2013**, *135*, 15282-15285. (c) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766-8773.
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(17) (a) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485-4488. For a review: Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994-2009.
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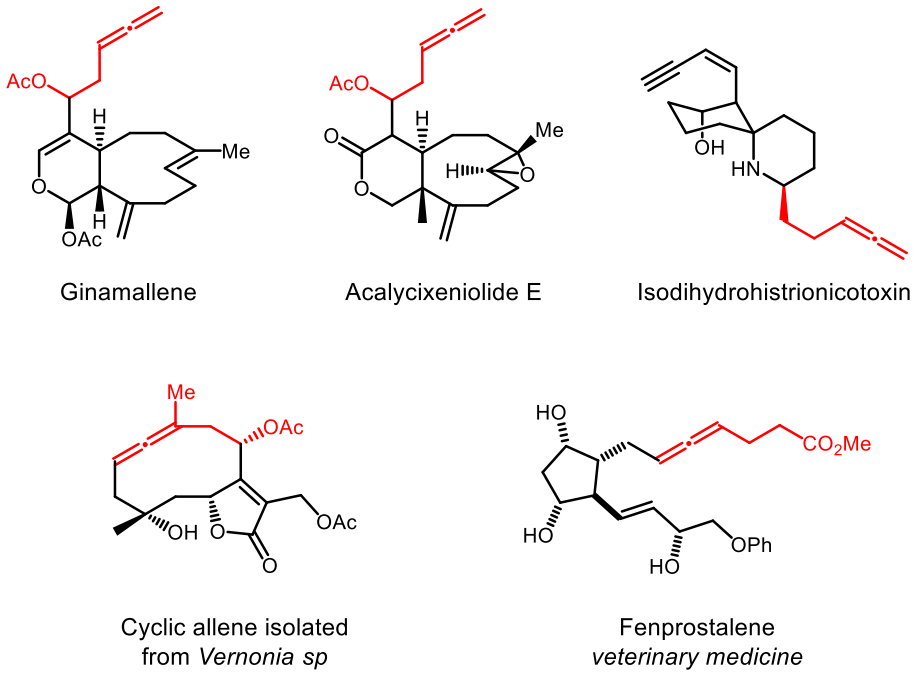
Allenes bearing a boryl group could benefit from the combined merits of both allenes and organoboronates. In addition, functionalized allenes are common motifs in both natural products and pharmaceutically active compounds (Scheme 1.3); the latter compounds could be derived from *β*-boryl allenes through the functionalization discussed above. This feature inspired us to expand the conjunctive cross-coupling reactions [19] developed by the Morken group to address the construction of *β*-boryl allenes, which not only enables the synthesis of highly functionalized organic building blocks, but also provides a useful strategy to prepare allene-containing natural products and lead compounds. This chapter will describe the development of catalytic enantioselective synthesis of *β*-allenyl boronic esters by conjunctive cross-coupling with propargylic carbonates.

Scheme 1.3. Functionalized Allenes in Natural Products and Pharmaceutically Active Compounds



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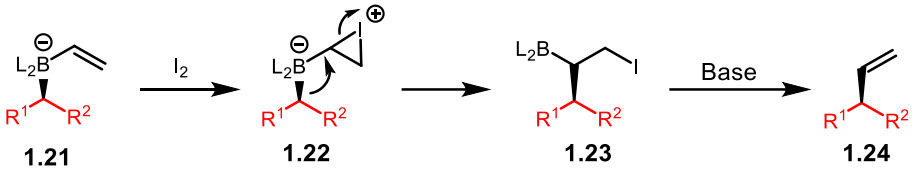
1.2 Background

1.2.1 Catalytic Conjunctive Cross-Coupling

The catalytic conjunctive cross-coupling reaction bears similarity to the Zweifel olefination reaction (Scheme 1.4).[4] The four-coordinate boron "ate" complex (**1.21**) can be generated from the addition of strong nucleophiles (organolithium reagents and Grignard reagents) to the tricoordinate organoboron compounds by addition to the vacant *p* orbital. In the Zweifel reaction, the vinyl boron "ate" complex **1.21** reacts with iodine to generate the cyclic iodonium ion intermediate **1.22**, which then undergoes the 1,2-metalate shift to furnish the *β*-boryl iodide **1.23**. Next, **1.23** undergoes *β*-elimination in the presence of base to deliver the olefin product **1.24**. Notably, the configuration of the migrating carbon group is retained throughout the reaction.

Scheme 1.4 Zweifel Olefination

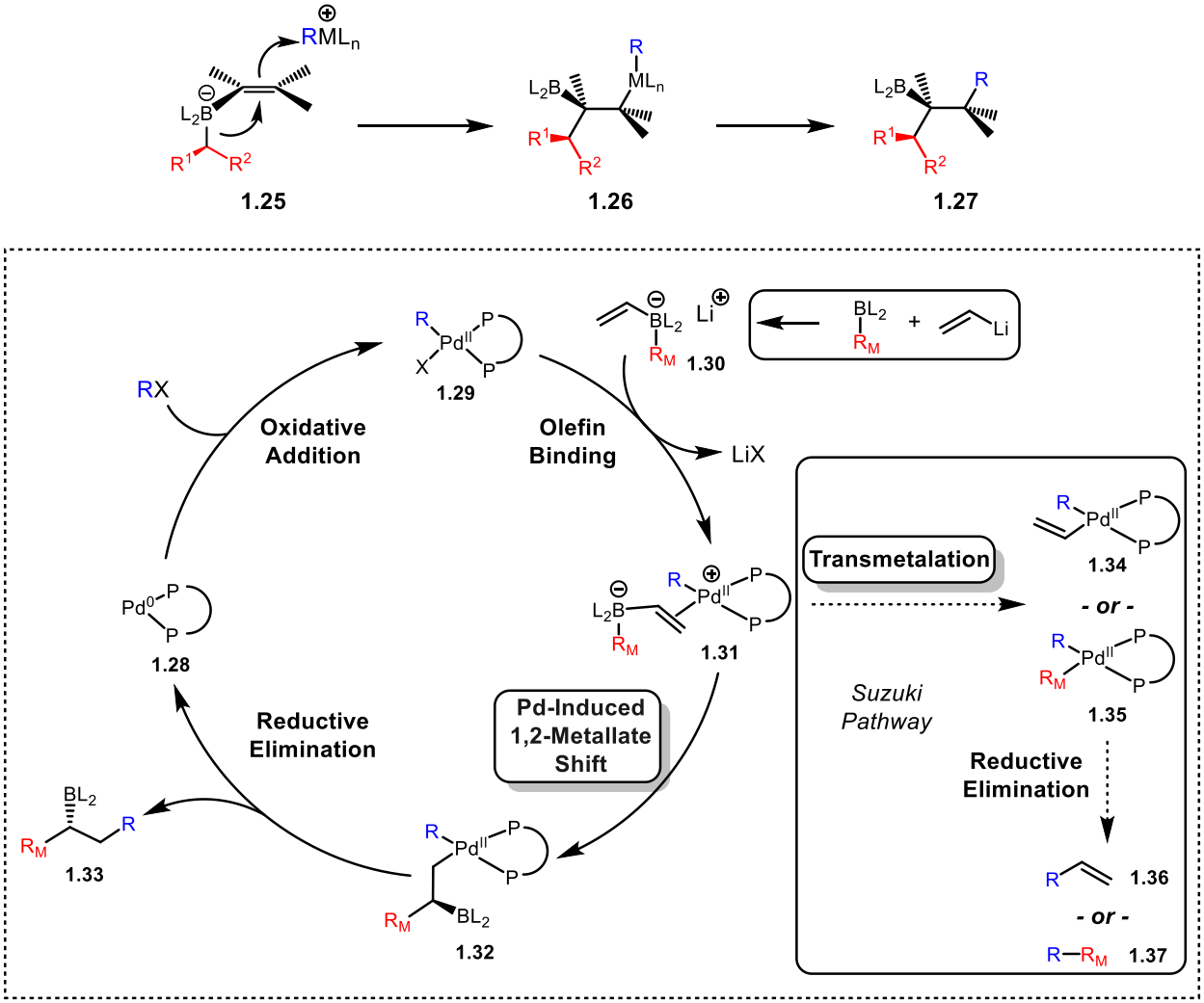


With the rapid development of transition-metal catalysis in the last two decades[20], our group hypothesized that we could replace iodine in the Zweifel reaction with chiral transition-metal catalysts to activate the alkene and induce the 1,2-metalate shift (Scheme 1.5, **1.25**). The *β*-boryl metallic intermediate **1.26** might be generated in an enantioselective manner. Subsequent

(20) (a) Johansson Seechurn, C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085. (b) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299-309.

reductive elimination would afford various secondary or tertiary organoboranes with versatile functionality and high enantioenrichment.[18]

Scheme 1.5. Catalytic Conjunctive Cross-Coupling



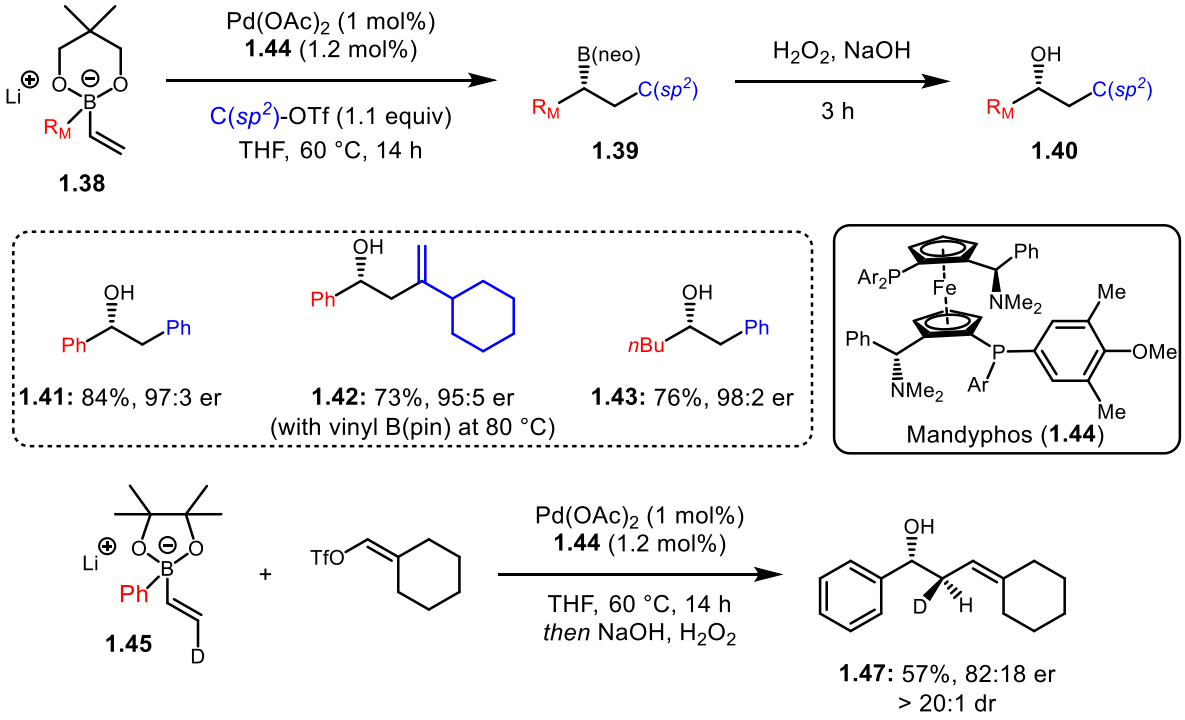
A catalytic cycle was proposed based on palladium catalysis (Scheme 1.5). We hypothesized that the Pd(0) complex **1.28** can first undergo oxidative addition with electrophiles to deliver Pd(II) intermediate **1.29**, which can bind with the boron "ate" complex **1.30** to furnish the palladium species **1.31**. Then, the *β*-boryl palladium intermediates **1.32** can be generated by

1,2-metalate shift, where discrimination of the prochiral faces of the alkene is achieved. Lastly, reductive elimination could occur to deliver the optically active organoboronate **1.33** and close the catalytic cycle. Of note, the intermediate **1.31** can also undergo direct transmetalation to afford the Suzuki-Miyaura cross-coupling type products (**1.36**, **1.37**), which are common side-products that were observed during the development of this methodology.[21]

In 2016, the first example of catalytic conjunctive cross-coupling reaction was developed by the Morken group.[19] This process employed neopentyl glycol-derived boron "ate" complex **1.38**, aryl/alkenyl electrophiles, and a palladium complex with the chiral bidentate phosphine ligand Mandyphos[22] (**1.44**) (Scheme 1.6). The secondary boronates **1.39** were oxidized under basic conditions, and the secondary alcohols **1.40** were isolated with good yield and enantioselectivity. Both aryl (**1.41**, **1.42**) and alkyl (**1.43**) groups were found to undergo migration. More importantly, conducting the reaction with deuterium-labeled substrate **1.45** delivered the product **1.47** with higher than 20:1 diastereoselectivity. This observation suggested a stereospecific process operates, which supported the proposed 1,2-metalate-shift-based mechanism.

(21) Myhill, J. A.; Wilhelmsen, C. A.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 15181-15185.
(22) Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 25-28.

Scheme 1.6. Catalytic Conjunctive Cross-Coupling with Neopentyl Glycol-Derived Borates

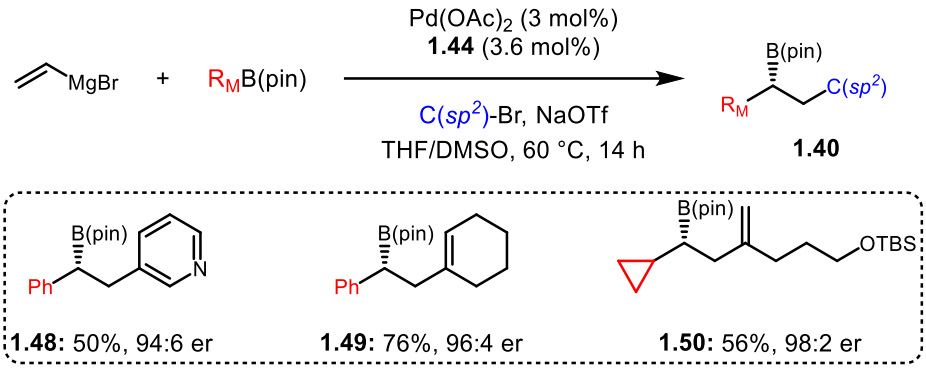


Later, the scope of conjunctive cross coupling was improved so that it may employ more readily available Grignard reagents and aryl halide electrophiles (Scheme 1.7). Challenges to accomplishing this are: 1) Grignard reagents are not as reactive as organolithiums to effectively form the boron "ate" complex; 2) halide ions inhibit the reaction, presumably due to competitive halide coordination with palladium.[23] NaOTf was employed as an additive to solve both challenges. It was hypothesized that NaOTf could both facilitate the formation of the boron "ate" complex by activating Grignard reagents, it could serve as a halide scavenger through salt metathesis.[23] The use of DMSO/THF as mixed solvent was also crucial for the high reactivity. The function of DMSO was studied by ^{11}B NMR experiments and was found to stabilize the boron "ate" complex towards decomposition. Under the improved condition, secondary boronates (**1.49**–

(23) Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153-3160.

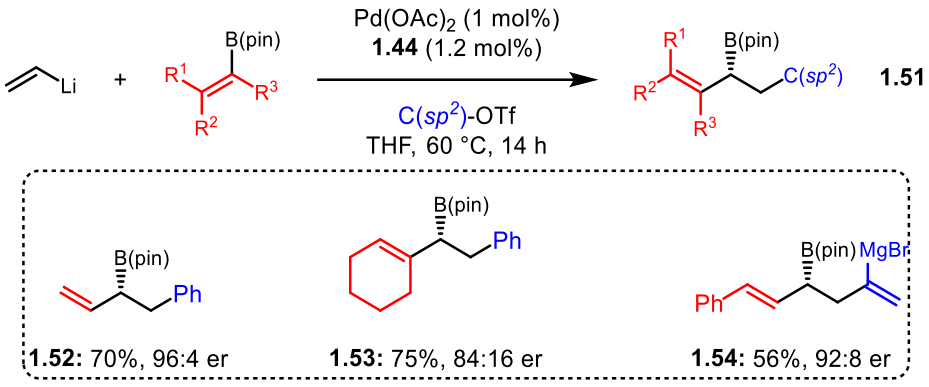
1.50) could be synthesized in a more practical procedure without compromising the yield and enantioselectivity.

Scheme 1.7. Conjunctive Cross-Coupling with Grignard Reagents and Halide Electrophiles



In 2017, the scope was further extended by the Morken group to employ alkenyl migrating groups. Enantioenriched allyl boronates **1.51**, which are latent substrates for stereospecific allyboration reactions,[24b] were synthesized with good yield and enantioselectivity (Scheme 1.8).[24] Notably, selective activation of the less hindered alkene for the di-alkenyl "ate" complex was observed.

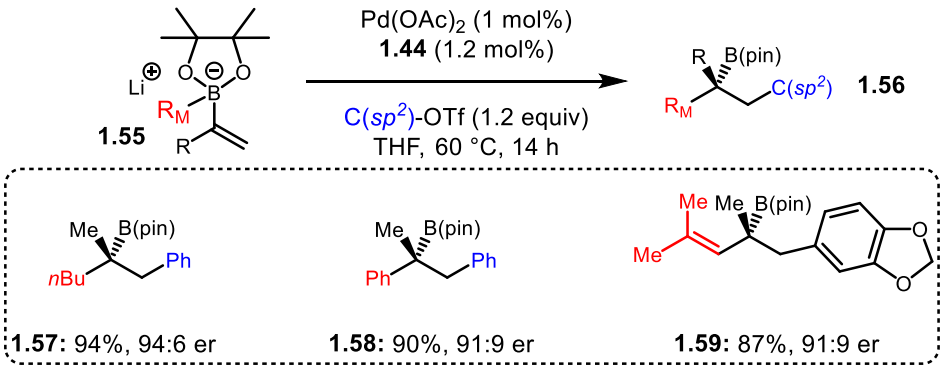
Scheme 1.8. Synthesis of Allylic Boronates by Catalytic Conjunctive Cross-Coupling



(24) (a) Edelstein, E. K.; Namirembe, S.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 5027-5030. (b) Chen, J. L. Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 5316-5319.

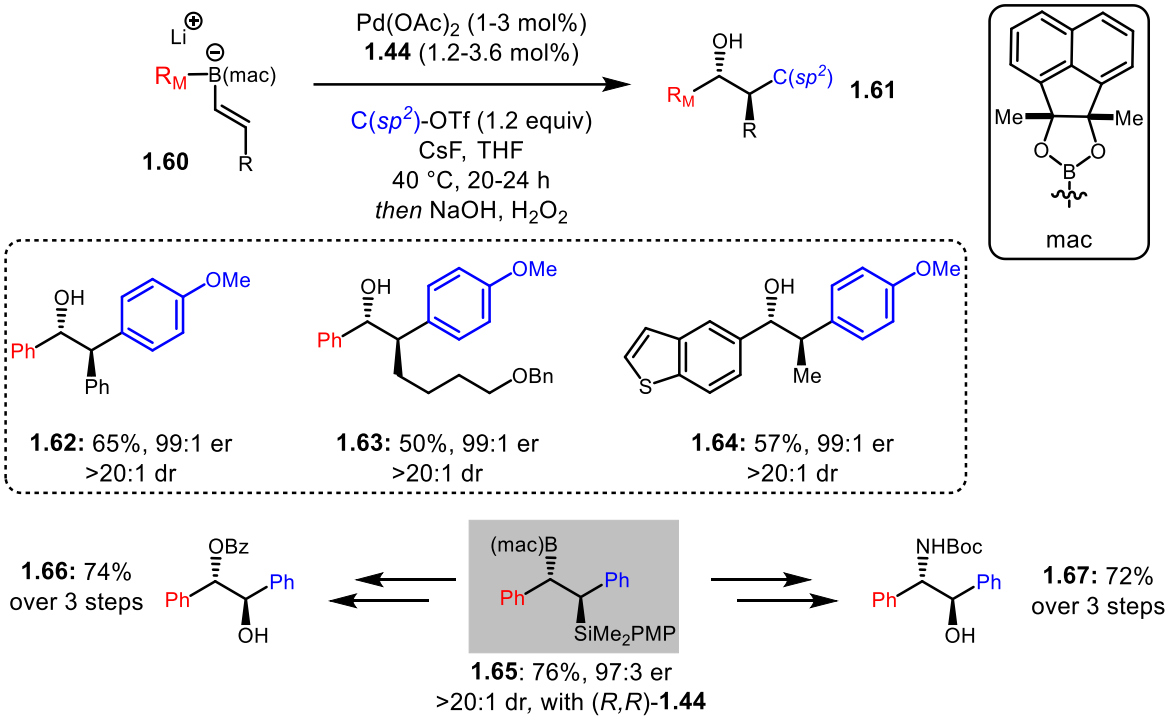
In 2018, boron "ate" complex **1.55** bearing an α-branched alkene moiety was successfully employed in the conjunctive cross-coupling reaction and furnished the tertiary alkyl boronates **1.56** (Scheme 1.9).[25] In the same year, β-branched boronates **1.61** were synthesized by the Morken group through conjunctive cross-coupling of β-branched boron "ate" complex **1.60** (Scheme 1.10).[21] The increased steric bulk of the alkene was found to alter the reactivity such that the Suzuki pathway became competitive (Scheme 1.5). To address this problem, "mac" (methylated acenaphthoquinone) ligand was devised; use of this ligand could suppress the direct transmetalation and facilitate the conjunctive cross-coupling reaction. A variety of β-branched boronates (**1.62**–**1.64**) were synthesized with good yield and excellent stereoselectivity. Furthermore, β-silyl boronates (**1.65**) were synthesized following the same strategy, which can be a general approach to deliver *trans*-diols (**1.66**) and *trans*-amino alcohols (**1.67**).[26]

Scheme 1.9. Synthesis of Tertiary Boronates by Catalytic Conjunctive Cross-Coupling



(25) Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 12799-12803.
(26) Meng, Y.; Kong, Z.; Morken, J. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 8456-8459.

Scheme 1.10. Synthesis of β-Branched Boronates by Catalytic Conjunctive Cross-Coupling

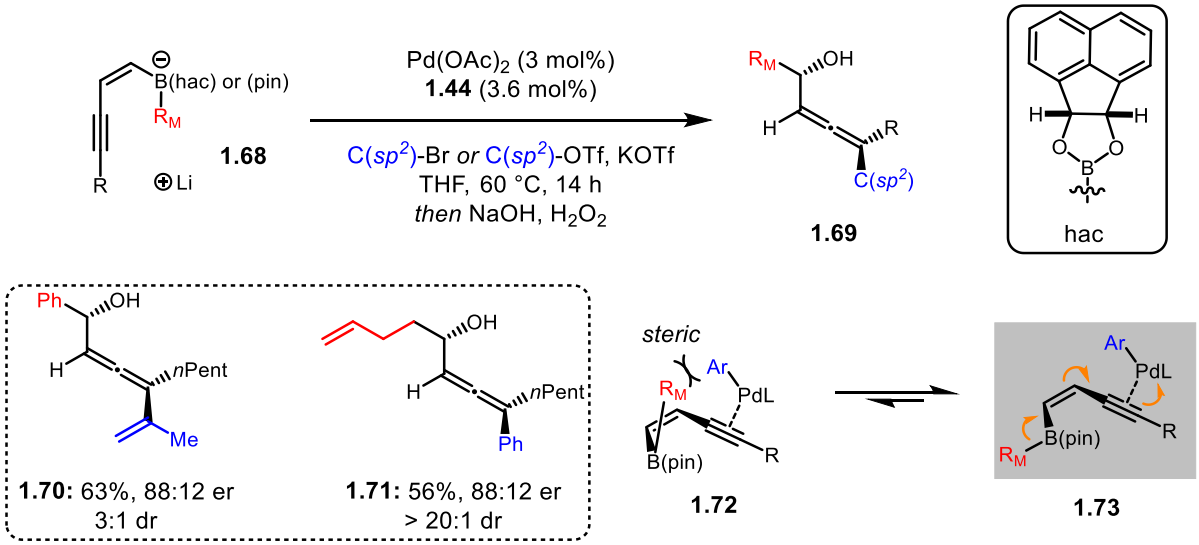


In 2020, the scope of conjunctive cross-coupling was further extended by the Morken group with enyne-derived boron "ate" complex **1.68** (Scheme 1.11).[27] α-Allenyl alcohols **1.69** were isolated with good yield, good enantioselectivity and moderate to high diastereoselectivity. The "hac" (hydrogenated acenaphthoquinone) ligand on boron was found to provide highest diastereoselectivity, presumably because of enhanced catalyst-substrate steric interactions. Interestingly, the *Z*-enyne afforded products with higher diastereoselectivity compared to the *E*-enyne. This observation was rationalized by the steric interactions between substrate and palladium. In the case of *Z*-enyne, the anti-conformer **1.73** appears to be more reactive than the syn-conformer **1.72** due to the steric repulsion between the migrating group and catalyst. In contrast, these two

(27) Law, C.; Kativhu, E.; Wang, J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 10311-10315.

conformers are not distinguishable in the *E*-enyne since the migrating group and catalyst are no longer proximal to each other, resulting in poor diastereoselectivity.

Scheme 1.11. Conjunctive Cross-coupling of Enyne Boron "Ate" Complex



Incorporation of allylic electrophiles in the conjunctive cross-coupling reaction had been investigated by the Morken group.[28a] Challenge was that the reaction could follow the inner-sphere type mechanism, where a pre-coordination of the "ate" complex nucleophile to palladium occurs, followed by 1,2-metallate shift and β-hydride elimination to generate the undesired alkenyl boronates.[28b,c]

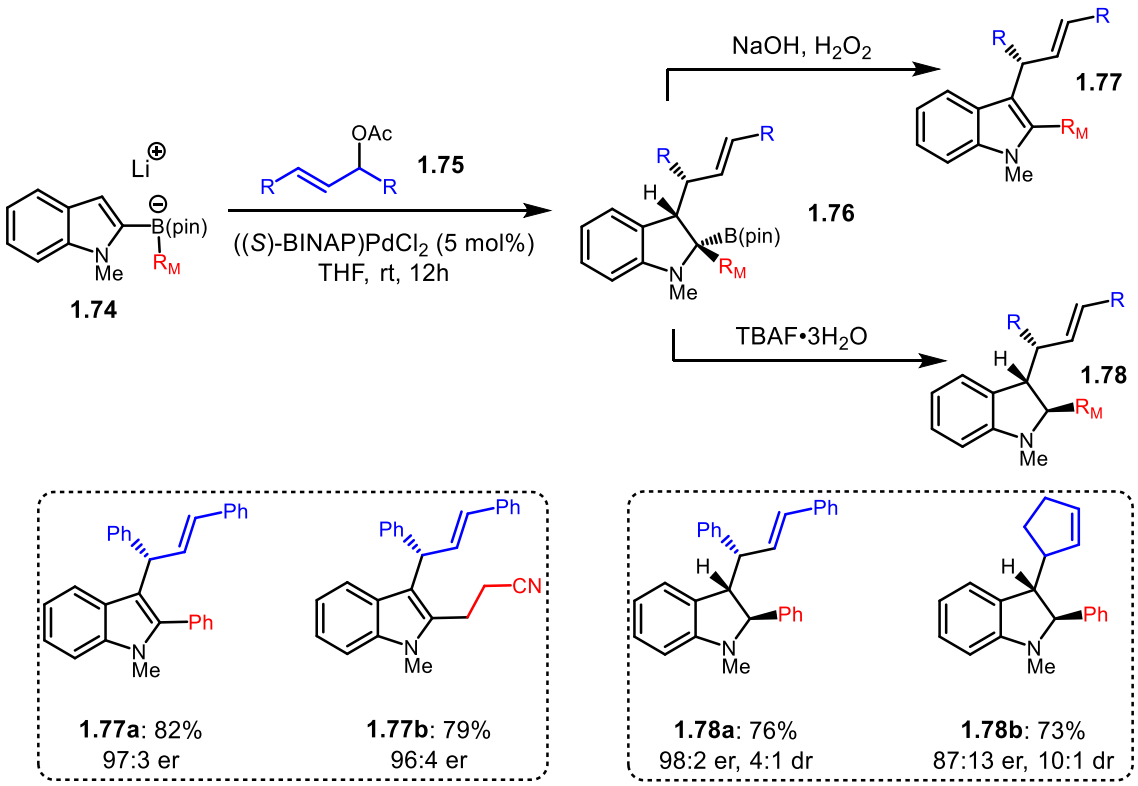
A conjunctive cross-coupling reaction with allylic electrophiles was accomplished by the Ready Group in 2017 with indole-derived borates **1.74** (Scheme 1.12).[29] In these experiments,

(28) (a) Aparece, M. D.; Gao, C.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 592-595. (b) Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard III, W. A. *J. Am. Chem. Soc.* **2012**, *134*, 19050-19060. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422.

(29) (a) Panda, S.; Ready, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 6038-6041. For 1,2-metallate shift with indole-derived borates, see: (b) Ishikura, M.; Terashima, M. J. *Chem. Soc., Chem. Commun.* **1991**, 1219-1221. (c) Ishikura,

BINAP was utilized as the chiral ligand instead and product **1.76** was subjected to two types of work-ups: 1) oxidation of the boron moiety which resulted in rearomatization of the indoline to afford indole-derivative **1.77**; 2) protodeborylation with TBAF•3H_2O to deliver indoline derivative **1.78**. Good yield, good enantioselectivity, and moderate diastereoselectivity were observed in both cases. However, the substrate scope of this reaction was limited to inherently activated indole substrates.

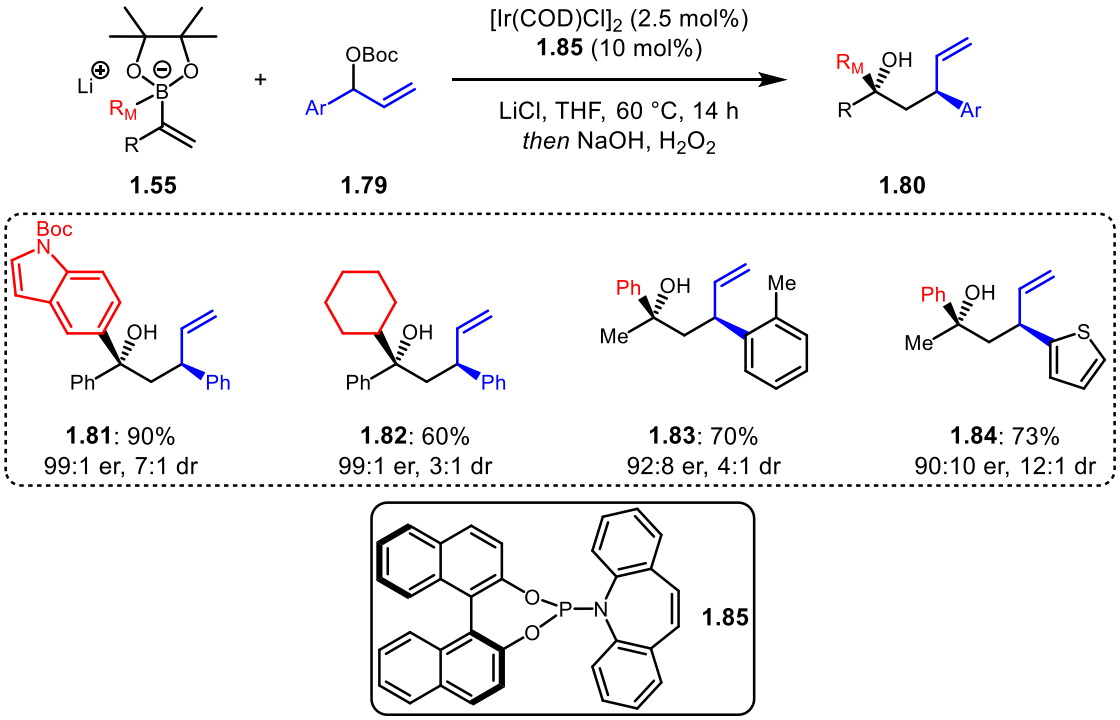
Scheme 1.12. Conjunctive Cross-Coupling with Indole-Derived Boron "Ate" Complex



M.; Kato, H. *Tetrahedron* **2002**, *58*, 9827-9838. (d) Das, S.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 4053-4057.

Catalytic conjunctive cross-coupling of allylic electrophiles with simple alkenyl boronic esters was later developed by the same group in 2021, taking advantage of iridium catalysis (Scheme 1.13).[30] Outer-sphere type mechanism, where nucleophile directly approaches from the face opposite to that occupied by iridium, avoided the undesired *β*-hydride elimination, and provided the desired allylation products **1.80**. Various functional groups could be tolerated. A racemization process[31] was proposed to rationalize the observed high enantioselectivity.

Scheme 1.13. Iridium-Catalyzed Conjunctive Cross-Coupling with Allylic Electrophiles

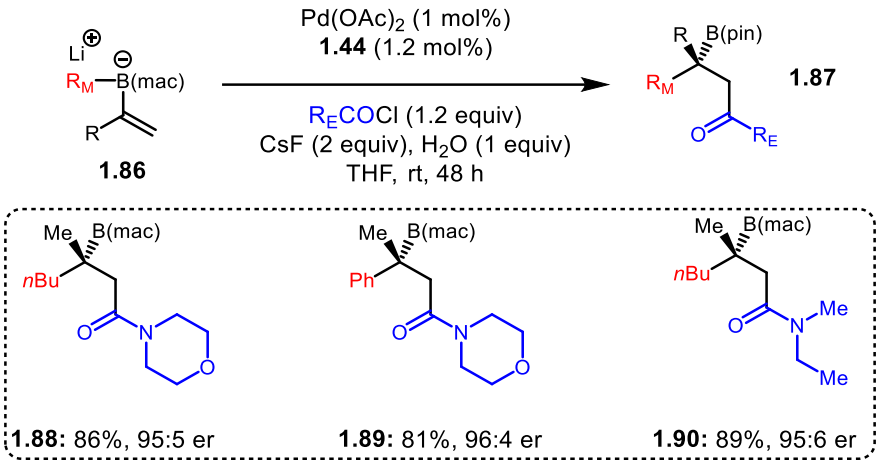


Recently, carbamoyl chlorides were employed in the catalytic conjunctive cross-coupling by the Morken Group (Scheme 1.14).[32] The use of CsF and water as additives were essential for

(30) Davis, C. R.; Luvaga, I. K.; Ready, J. M. *J. Am. Chem. Soc.* **2021**, *143*, 4921-4927.
(31) Huerta, F. F.; Minidis, A. B.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321-331.
(32) Wilhelmsen, C. A.; Zhang, X.; Myhill, J. A.; Morken, J. P. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116784.

high yield and enantioselectivity. Cesium fluoride was proposed to undergo salt metathesis with the boron "ate" complex **1.86** to generate a more reactive cesium complex *in situ*. Meanwhile, water could help dissolve CsF and enhance the reactivity. Additionally, it was proposed that water could activate the borates by facilitating the isomerization of two boron "ate" diastereomers. When other carboxylic acid derivatives (*i.e.*, acid chlorides) were investigated, significant background reaction, including the decomposition of the boron "ate", was observed.

Scheme 1.14. Catalytic Conjunctive Cross-Coupling with Carbamoyl Chlorides



Nickel catalyzed conjunctive-cross coupling reactions had also been developed by the Morken Group, which incorporated 9-BBN-derived borates[33], alkyl halides[34], and acid chlorides.[35] Because nickel catalysis is not the focus of this chapter, these methods will not be discussed in detail.

(33) Chierchia, M.; Law, C.; Morken, J. P. *Angew. Chem. Int. Ed.* **2017**, *56*, 11870-11874.
(34) (a) Lovinger, G. J.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 17293-17296. (b) Koo, S. M.; Vendola, A. J.; Momm, S. N.; Morken, J. P. *Org. Lett.* **2020**, *22*, 666-669.
(35) Law, C.; Meng, Y.; Koo, S. M.; Morken, J. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 6654-6658.

1.2.2 Selected Syntheses of Allenes

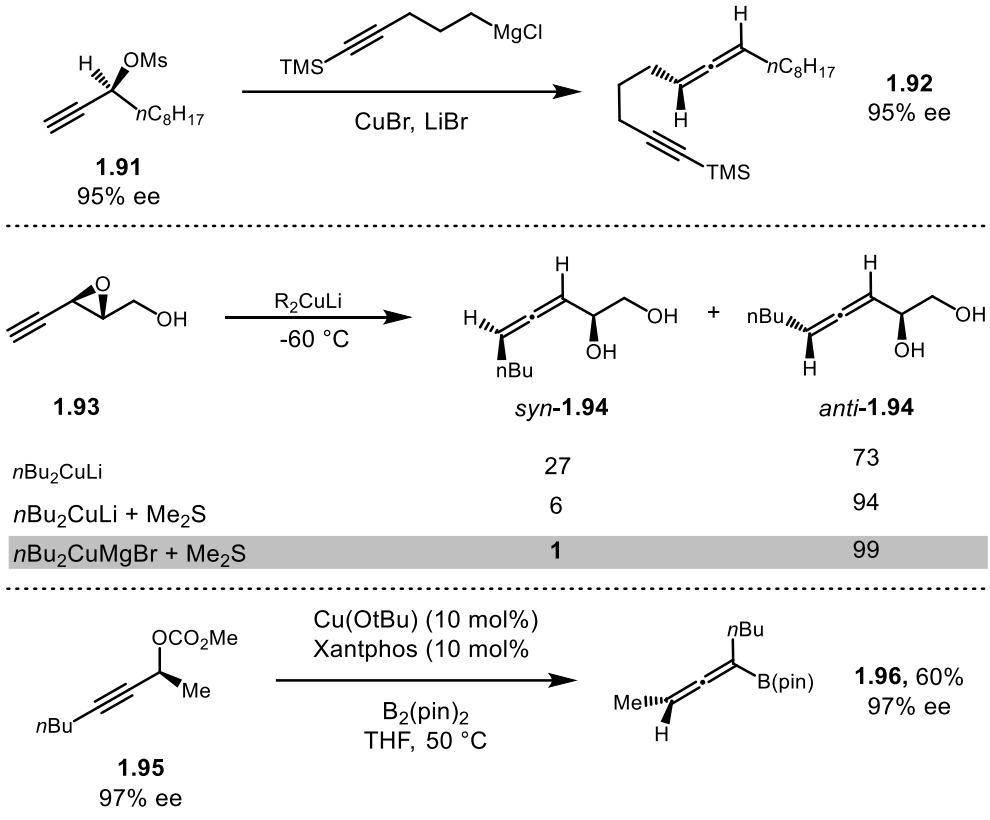
Due to their versatile reactivity, the synthesis of allenes has become a hot research topic in the last two decades.[12, 36] Both classical approaches and novel transition-metal catalyzed methodologies have been developed to extend the availability of functionalized allenes.

Copper-mediated *anti*-S_N2' substitution of propargylic electrophiles is one of the most popular approaches to synthesize allenes.[35] Organocuprates derived from organolithium, Grignard reagents, and bis(boronates) can all participate in this process.[35]

The reaction was found to be enantiospecific when enantiomerically enriched propargyl mesylate **1.91** was employed (Scheme 1.15, top equation).[37] Although organocuprates can cause isomerization and racemization of allenes (**1.94**) through a single electron transfer (SET) process,[38] addition of dimethyl sulfide was found to inhibit this process (Scheme 1.15, middle equation).[39] In addition, copper-boryl mediated allene synthesis was developed by the Sawamura group in 2008, enabling the synthesis of enantioenriched allenyl boronates **1.96** (Scheme 1.15, bottom equation).[40]

(36) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384-5418.
(37) Brummond, K. M.; Kerekes, A. D.; Wan, H. *J. Org. Chem.* **2002**, *67*, 5156-5163.
(38) Westmijze, H.; Nap, I.; Meijer, *J*.; Kleijn, H.; Vermeer, P. *Recueil des Travaux Chimiques des Pays-Bas* **1983**, *102*, 154-157.
(39) Oehlschlager, A. C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587-5590.
(40) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774-15775.

Scheme 1.15. Copper-Mediated S_N2' Substitution of Propargylic Electrophiles

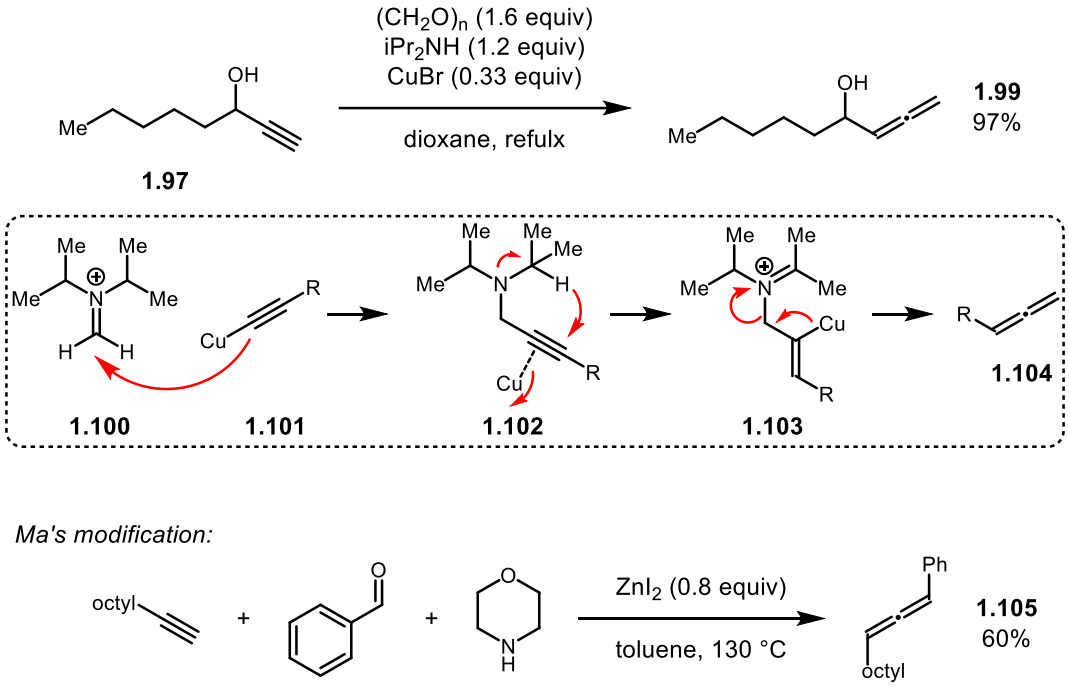


One classic synthetic route to allenes is the Crabbé reaction (Scheme 1.16).[41] For an example, alkyne **1.92** was homologated to the allene **1.99** by reacting with formaldehyde, CuBr, and base. The reaction mechanism was studied with deuterium-labeling experiments[42] and DFT calculations.[43] It was found that a Mannich-type reaction between alkynyl copper **1.101** and the *in situ* formed imine **1.100** could occur first to deliver intermediate **1.102**. Then, a formal *retro*-imino-ene reaction could furnish alkenyl copper intermediate **1.103**, which could be eliminated to

(41) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859-860.
(42) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P.; Crabbé, P. *J. Chem. Soc., Perkin Trans.* **1984**, 747-751.
(43) Zhang, X. *Asian J. Org. Chem.* **2014**, *3*, 309-313.

deliver allene product **1.104**. Later, a modification was made by the Ma group, where the use of morpholine and ZnI_2 led to a broader scope of aldehyde substrates with improved reactivity.[44]

Scheme 1.16. Crabbé Reaction and Modification by Ma

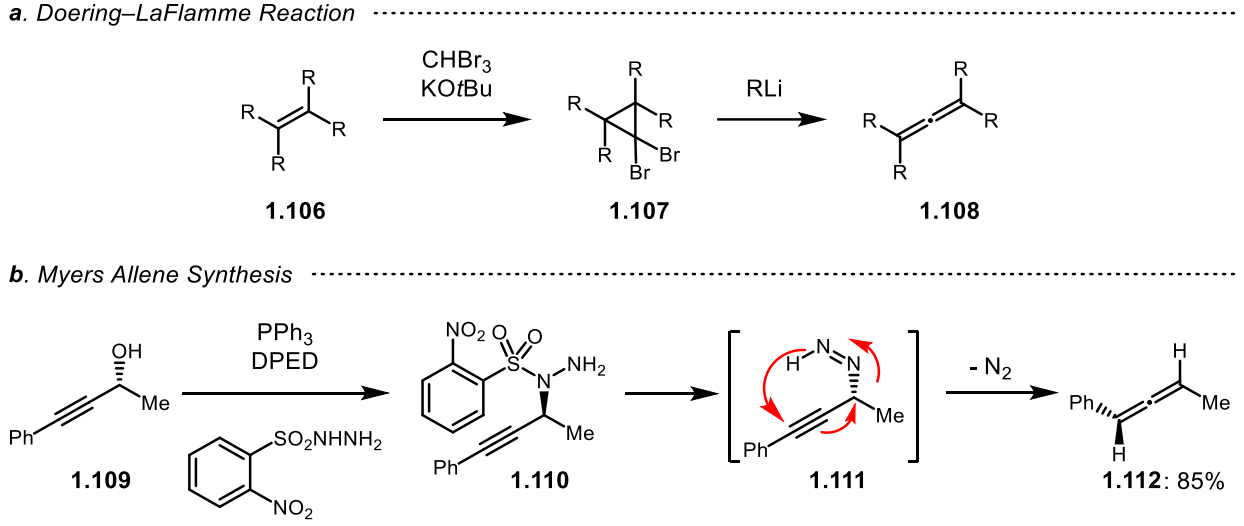


Allenes have also been synthesized from the Doering-LaFlamme reaction[45] (Scheme 1.17a) and Myers allene synthesis[46] (Scheme 1.17b). In the Doering-LaFlamme reaction, the dibromo cyclopropane intermediate **1.107** undergoes lithium-halogen exchange and α-elimination to generate a cyclopropyl carbene intermediate. Next, a formal electrocyclic reaction occurs to

(44) Kuang, J.; Ma, S. J. *Am. Chem. Soc.* **2010**, *132*, 1786-1787.
(45) Doering, W. v. E.; LaFlamme, P. *Tetrahedron* **1958**, *2*, 75-79.
(46) (a) Myers, A. G.; Finney, N. S. *J. Am. Chem. Soc.* **1990**, *112*, 9641-9643. (b) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493.

provide allene product **1.108**. In the case of Myers' allene synthesis, the propargyl hydrazine **1.110** undergoes elimination and *retro*-ene reaction to furnish allene product **1.112**. Notably, this synthetic route is enantiospecific due to the stereospecificity of both the Mitsunobu reaction and *retro*-ene process. An enantioselective modification has been accomplished by the Schaus group, where the propargyl hydrazine intermediates were synthesized by a catalytic Petasis reaction in an enantioselective manner.[47]

Scheme 1.17. Doering–LaFlamme Reaction and Myers Allene Synthesis

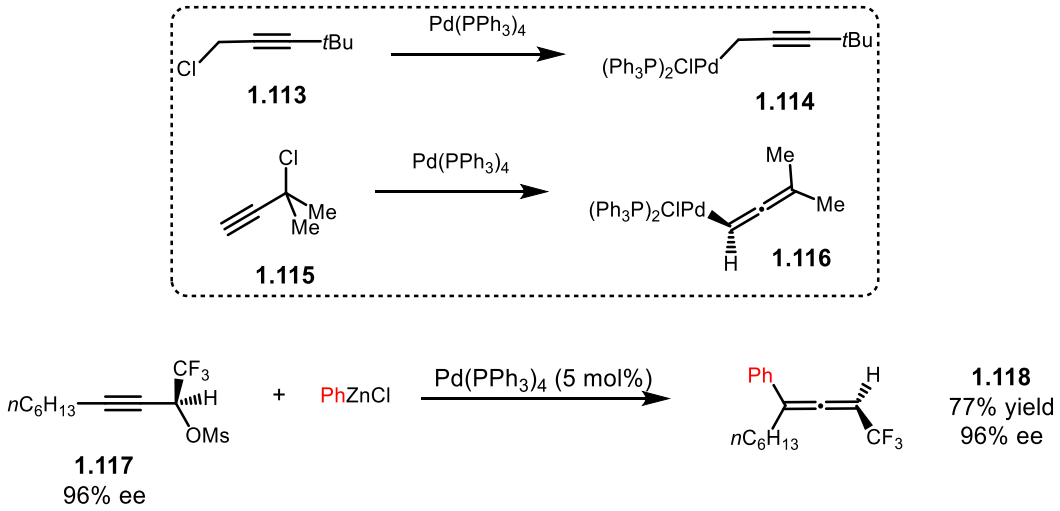


With the rapid development of transition-metal catalysis in the last two decades,[19] synthesizing allenes by transition-metal catalyzed cross-coupling reactions, especially in an enantioselective fashion, has become increasingly popular.[48] A common approach is palladium-catalyzed cross-coupling involving propargylic electrophiles, which has been extensively studied

(47) Jiang, Y.; Diagne, A. B.; Thomson, R. J.; Schaus, S. E. *J. Am. Chem. Soc.* **2017**, *139*, 1998-2005.
(48) Roy, R.; Saha, S. *RSC Advances* **2018**, *8*, 31129-31193.

since its discovery in early 1980s.[49] The oxidative addition of propargylic electrophiles with palladium catalyst was studied by the Vermeer group in the 1980s (Scheme 1.18).[49d,e] The outcome of this oxidative addition was highly dependent on the substituents of the propargyl halides. When γ-substituted propargyl chloride **1.113** reacts with Pd(0), propargyl palladium **1.114** was observed. In contrast, the allenyl palladium **1.116** was observed with α-disubstituted propargyl chloride **1.115**. Moreover, this oxidative addition could be stereospecific through a central–axial chirality transfer, as demonstrated by the Konno group (**1.118**).[50]

Scheme 1.18. Oxidative Addition of Palladium with Propargylic Electrophiles



Palladium-catalyzed enantioconvergent cross-coupling of propargyl electrophiles was developed by the Ma group in 2013 (Scheme 1.19).[51] The racemic propargyl carbonates **1.119** were converted to enantioenriched allenyl esters **1.120** with good yield and high enantiomeric

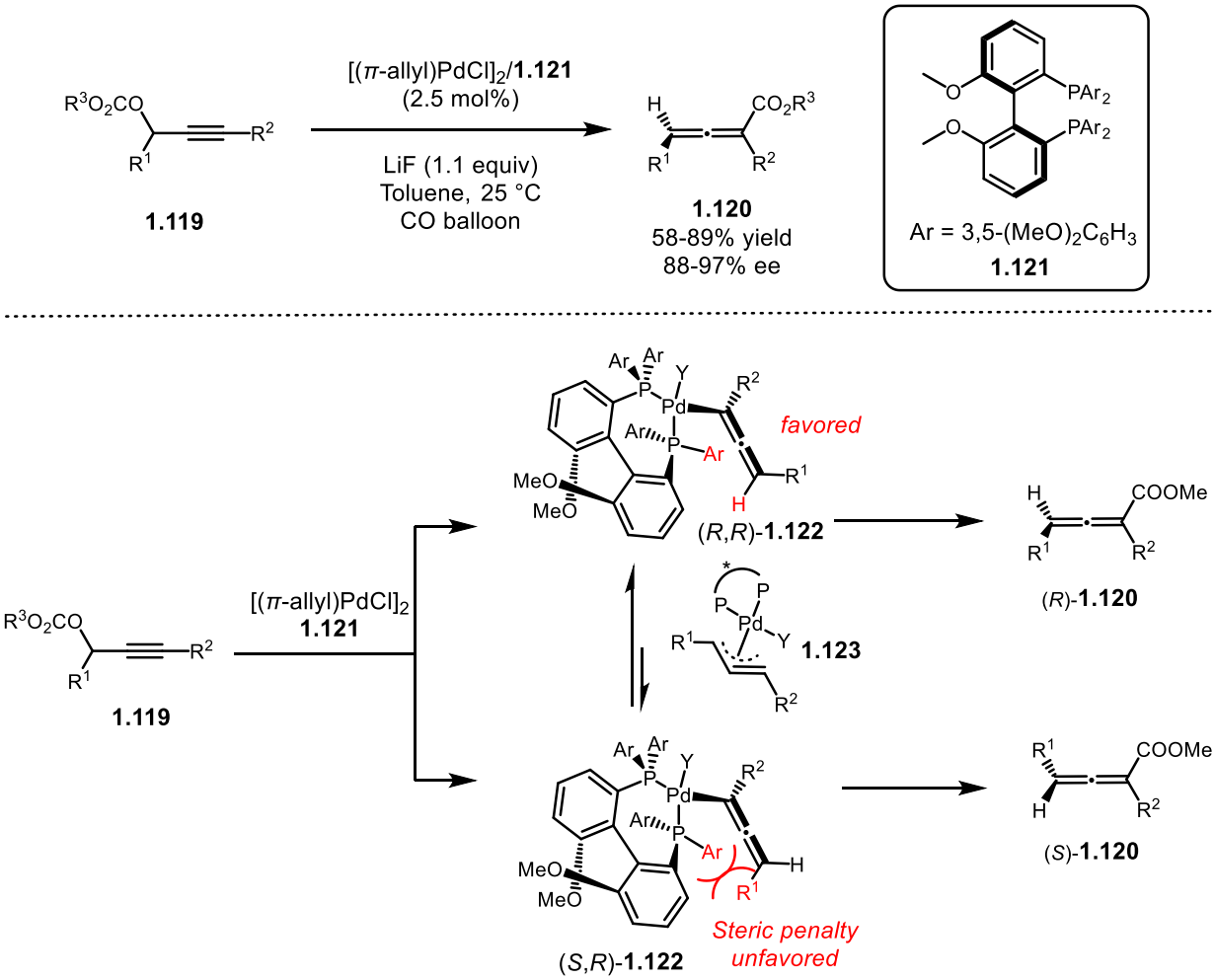
(49) (a) Tsuji, J.; Mandai, T. in Metal-catalyzed Cross-Coupling Reactions, Wiley-VCH, New York, **1998**, p. 455. (b) Mandai. T. in Handbook Organopalladium Chem. Org. Synth., Wiley-Interscience, New York, **2002**, p. 1827 (c) Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* **1980**, *21*, 5019-5020. (d) Elsevier, C. J.; Kleijn, H.; Ruitenberg, K.; Vermeer, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1529-1530. (e) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716-720.

(50) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, *29*, 1360-1361.

(51) Wang, Y.; Zhang, W.; Ma, S. *J. Am. Chem. Soc.* **2013**, *135*, 11517-11520.

enrichment. A racemization process of the allenyl palladium intermediate was proposed. An isomerization process could occur between the oxidative addition adducts (*R,R*)-**1.122** and (*S,R*)-**1.122** through a σ–π–σ rearrangement via the intermediacy of **1.123**.[52] The same strategy has also been utilized by the Hamada group for the synthesis of enantioenriched allenes from racemic materials.[53]

Scheme 1.19. Palladium-Catalyzed Enantioconvergent Synthesis of Allenes

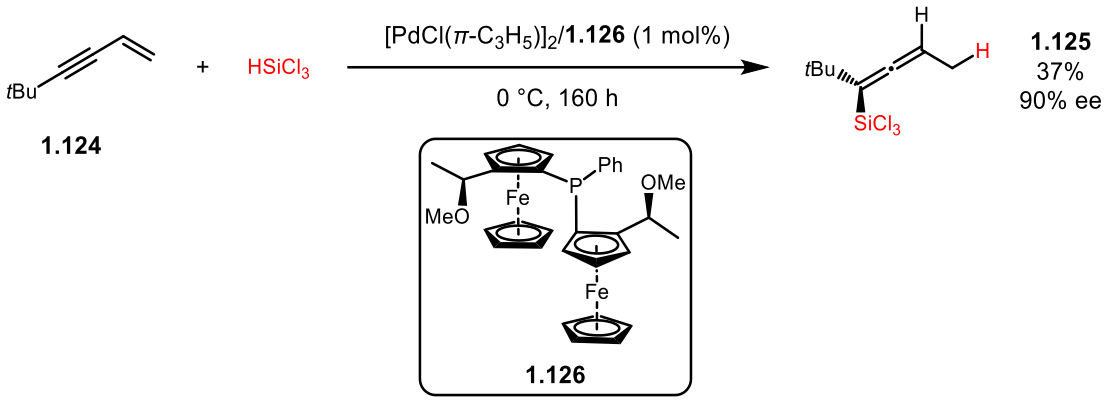


(52) Ogoshi, S.; Nishida, T.; Shinagawa, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 7164-7165.
(53) Nemoto, T.; Kanematsu, M.; Tamura, S.; Hamada, Y. *Adv. Synth. Catal.* **2009**, *351*, 1773-1778.

Transition metal-catalyzed 1,4-addition to enynes provides an alternative synthetic route to allenes. This strategy has been utilized by the Morken group in the catalytic conjunctive cross-coupling to synthesize α-allenyl boronates as previously described.[27]

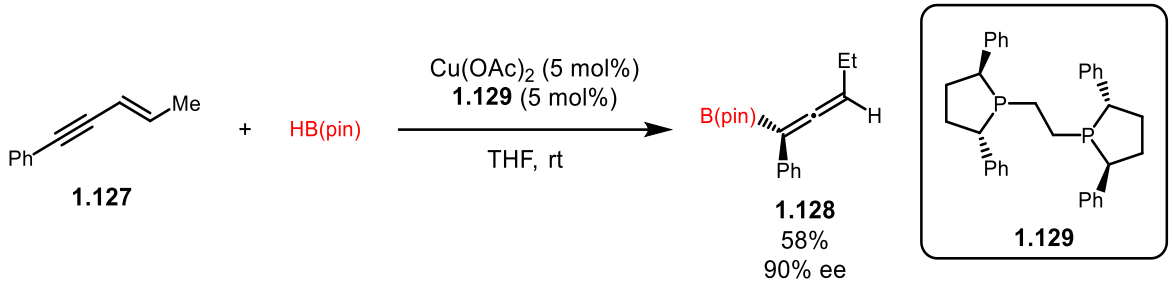
Palladium-catalyzed enantioselective 1,4-hydrosilylation of enyne was developed by the Hayashi Group in 2001 (Scheme 1.20).[54] The allenyl silane product **1.125** was synthesized with moderate yield and good enantioselectivity. Recently, a modification with lanthanum catalysis was developed by the Cui group with improved reactivity and broader substrate scope.[55] Furthermore, copper-catalyzed hydroboration of *E*-enyne **1.127** was accomplished by the Hoveyda and the Ge groups (Scheme 1.21).[56] Good yield and enantioselectivity were observed in the formation of allenyl boronates **1.128**.

Scheme 1.20. Palladium-Catalyzed 1,4-Hydrosilylation of Enynes



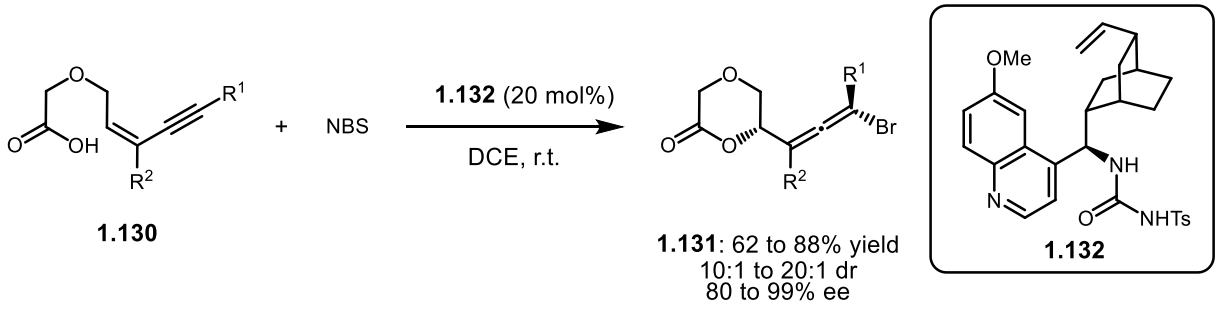
(54) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915-12916.
(55) Chen, W.; Jiang, C.; Zhang, J.; Xu, J.; Xu, L.; Xu, X.; Li, J.; Cui, C. *J. Am. Chem. Soc.* **2021**, *143*, 12913-12918.
(56) (a) Huang, Y.; Del Pozo, J.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2018**, *140*, 2643-2655. (b) Sang, H. L.; Yu, S.; Ge, S. *Organic Chemistry Frontiers* **2018**, *5*, 1284-1287.

Scheme 1.21. Copper-Catalyzed 1,4-Hydroboration of Enynes by Hoveyda



Small molecule organocatalysis has also been utilized in the construction of chiral allenes. Bromolactonization of enyne **1.130** was developed by the Tang group in 2010 with cinchonidine-derived amide **1.132** as the catalyst (Scheme 1.22).[57] The author proposes that catalyst **1.132** may serve as a bifunctional catalyst to activate both substrates by deprotonating the carboxylic acid and activating NBS through hydrogen bond.

Scheme 1.22. Small Molecule-Catalyzed Bromolactonization of Enynes

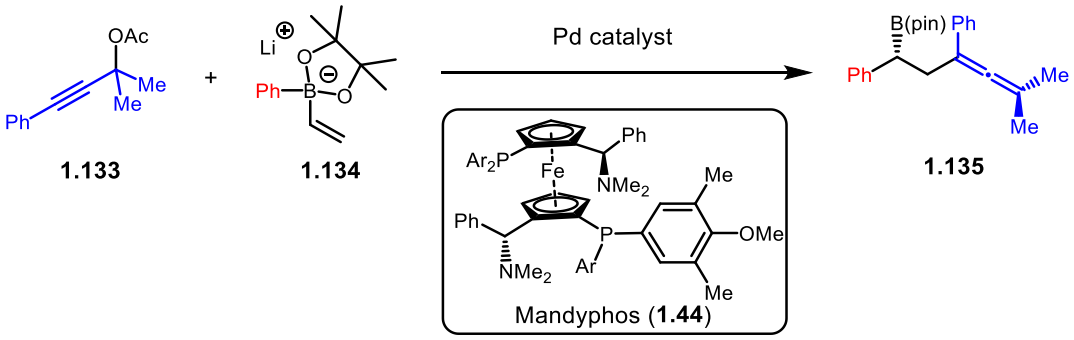


(57) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664-3665.

1.3 Optimization of Reaction Conditions[1]

Inspired by the versatility of allenes, we planned to replace the aryl/alkenyl electrophiles in the conjunctive cross-coupling reaction[19] with propargylic electrophiles to furnish *β*-allenyl boronate **1.135** (Scheme 1.23). Product *β*-allenyl boronates should have use in organic synthesis.

Scheme 1.23 Catalytic Conjunctive Coupling with Propargylic Acetate

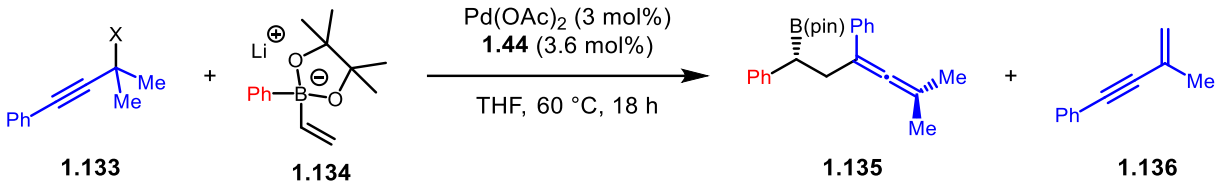


Following a typical procedure for the conjunctive cross-coupling reaction, vinyl borate **1.134**, generated from vinyllithium and phenyl boronic ester, was mixed with propargyl acetate (1.2 equiv), palladium acetate, and Mandyphos (**1.44**). The mixture was heated at 60 ºC under inert atmosphere, which delivered *β*-allenyl boronates **1.135** with 40% yield and 90:10 *er* (Table 1.1, entry 1). A significant amount of enyne side-product **1.136** was also observed. We hypothesized enyne **1.136** was generated from the *β*-hydride elimination of the propargylic palladium intermediate **1.138b** (Scheme 1.24).[58] Because propargyl electrophiles were consumed by this unproductive pathway, leading to a poor yield of the desired product **1.135**. We increased the stoichiometry of the electrophile to boost the yield (entry 2). However, this modification resulted

(58) Mandai, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 7615-7618.

in lower yield of the **1.135**. This observation suggested that excess propargyl acetate could lower the reactivity, either by accelerating the β-hydride elimination or by slowing down the conjunctive cross-coupling process.

Table 1.1. Effect of Reaction Conditions



1.133 **1.134** **1.135** **1.136**

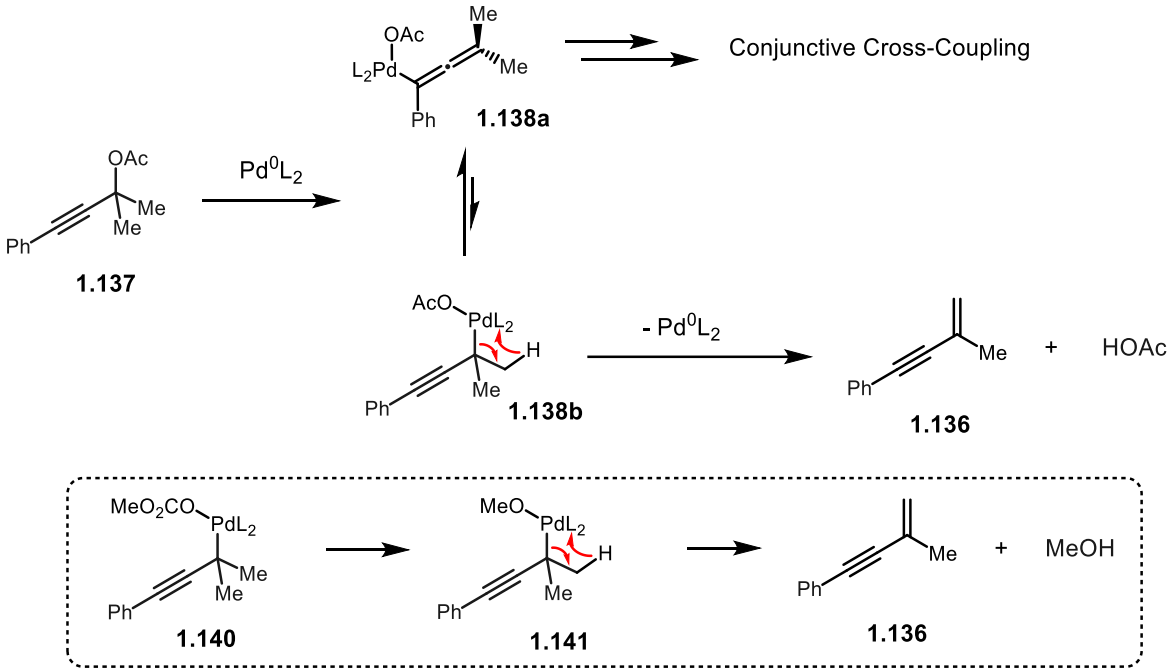
entry	X (equiv)	additive	**1.135** (%)[a]	**1.136** (%)[a,b]	er of **1.135**[c]
1	OAc (1.2)	None	40	55	90:10
2	OAc (2)	None	24	70	90:10
3[d]	OCO_2Me (1.2)	None	45	25	92:8
4[d]	OCO_2Me (2)	None	60	66	93:7
5[d]	OCO_2Me (3)	None	83	67	93:7
6[d]	OCO_2Me (4)	None	85	75	92:8
7[d]	OCO_2Me (1.2)	MeOH (2)	69	67	95:5
8[d]	**OCO_2Me (1.2)**	**MeOH (4)**	**83**[e]	**38**	**96:4**
9[d]	OCO_2Me (1.2)	MeOH (6)	86	23	97:3
10[d]	OCO_2Me (1.2)	EtOH (4)	77	60	95:5
11[d]	OCO_2Me (1.2)	2-BuOH (4)	44	78	91:9
12[d]	OCO_2Me (1.2)	TFE (4)	69	46	98:2
13[d]	OCO_2Me (1.2)	PhOH (4)	20	48	96:4

[a]Yields are by ^{1}H NMR versus an internal standard. [b]Yields are calculated based on **1.133**. [c]The enantiomer ratio of derived alcohol was determined by SFC analysis on a chiral stationary phase and in comparison to an authentic enantiomer mixture. [d]$Pd_2(dba)_3$ (1.5 mol%) was used instead of $Pd(OAc)_2$. [e]Yield for this experiment is after isolation and purification by column chromatography

To analyze this problem and find possible solutions, we considered reaction mechanism (Scheme 1.19): oxidative addition of the propargyl acetate with Pd(0) should generate allenyl

palladium **1.138a** and propargylic palladium **1.138b**, and they can be in equilibrium with each other through η^3-allenyl/propargyl intermediate.[59] Propargyl palladium **1.138b** could generate the enyne **1.136** through β-hydride elimination,[58] followed by reductive elimination to afford acetic acid. We hypothesized that the acetic acid ($pK_a = 4.8$) by-product is acidic enough to protonate the boron "ate" complex **1.134**, diminishing the yield of desired product.

Scheme 1.24. Generation of Enyne Side Products



To address this protonation problem, propargyl carbonate was considered as the electrophile with $Pd_2(dba)_3$ the palladium source (Table 1, entry 3). Oxidative addition adducts **1.140** should undergo decarboxylation. If β-hydride elimination occurs to deliver enyne **1.135**,

(59) (a) Baize, M. W.; Blosser, P. W.; Plantevin, V.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics* **1996**, *15*, 164-173. (b) Tsutsumi, K.; Ogoshi, S.; Kakiuchi, K.; Nishiguchi, S.; Kurosawa, H. *Inorg. Chim. Acta* **1999**, *296*, 37-44.

reductive elimination would only generate methanol (Scheme 1.24, bottom). Because methanol (pKa = 15.3) is less acidic than acetic acid, we hypothesized that it could be compatible with the borate **1.134**. Indeed, increasing the loading of propargyl carbonate led to a significant increase in the yield of both **1.135** and **1.136** (Table 1, entry 3-6). Curiously, a slight increase in the enantioselectivity was also observed (entry 4-5 compared to entry 3), suggesting that methanol as a side product might have a beneficial effect. However, the possibility that the minor variation in *er* originates from the different counterions (OAc *vs* OMe) for palladium, cannot be ruled out.

Methanol was the employed as an additive to examine its effect on the reaction (entry 7-9). To our delight, significant increases of both the yield and enantiomeric purity of product **1.135** were observed (comparing entry 7 to entry 3). *β*-Allenyl boronates **1.135** could be isolated with 83% yield and 96:4 *er* by the addition of four equivalents methanol (entry 8). When we further increased the equivalents of methanol, the effect became less pronounced (entry 9). Other alcohol additives were also investigated (entry 10-13). Ethanol (entry 10) and trifluoroethanol (TFE, entry 12) exhibit similar beneficial effects. A neglectable effect was observed with sterically hindered alcohol 2-BuOH (entry 11). Like acetic acid, acidic additives such as phenol (pK_a = 10, entry 13) were detrimental to the reaction. Overall, the condition described in entry 8 was selected as the optimized condition for the conjunctive cross-coupling with propargylic electrophiles.

1.4 Substrate Scope and Synthetic Utility[1]

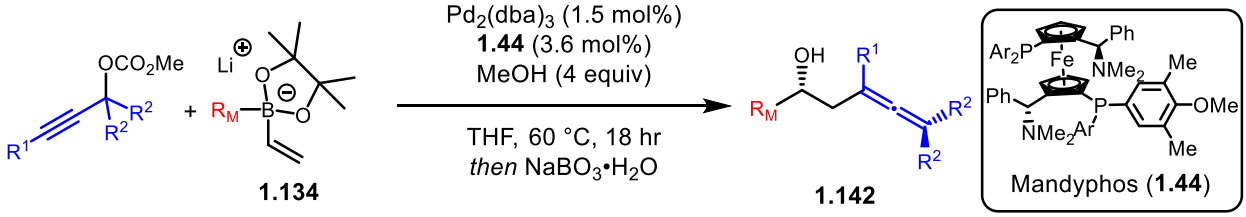
The substrate scope of catalytic enantioselective conjunctive cross-coupling reaction of propargylic carbonates was investigated (Scheme 1.25) with the optimized conditions (Table 1, entry 8). Products **1.142** were isolated as alcohols after oxidative work-up. Different substitution patterns can be well tolerated in the propargyl electrophiles (**1.143**-**1.159**), including electron-rich

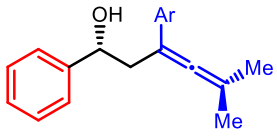
(1.143, **1.149**, **1.150**) and electron-deficient (**1.145**, **1.148**) arenes, heterocycles (**1.148-1.150**), alkenes (**1.154-1.155**), alkynes (**1.156**), and ethers (**1.157-1.158**). In addition to aryl migrating groups (**1.143**, **1.160-1.164**), alkenyl (**1.159**) and alkyl (**1.165-1.168**) migrating groups can be employed in the reaction. Trifluoroethanol (TFE) was found to be a better additive for the reaction with alkyl migrating groups, presumably because the electron-withdrawing trifluoromethyl group could further polarize the alkene and facilitate the 1,2-metallate shift. Of note, when γ-unsubstituted propargylic electrophiles (**1.169**) and γ-alkyl propargylic electrophiles (**1.170**) were subjected to the conjunctive-coupling, diminished yields were observed.

The versatility of allenes in organic synthesis inspired us to explore transformation of β-hydroxy allene products **1.142**. While conducting the conjunctive-coupling with 2-thiophenyl-substituted propargyl electrophile **1.171**, the interesting pyran derivative **1.172** was isolated as the product, presumably formed during the oxidative work-up (Scheme 1.26). The same cyclization process was observed with two other products (*i.e.*, **1.143** and **1.150**) but at a slower rate (usually >1 week for complete conversion; decomposition of starting material was also observed). Accelerated cyclization was observed if the unpurified material is kept in deuterated chloroform, likely due to trace acid present.[60] We considered the mechanism of this cyclization as follows: thiophene group could aid the protonation of the allene and deliver polyene intermediate **1.174**. Then, conversion to the dihydropyran through a nucleophilic cyclization might occur. Notably, the cyclization can be accomplished in a controllable way by treating with cationic gold catalysis (Scheme 1.26, **1.175-1.176**).[17]

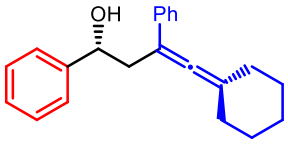
(60) Unger, I.; Semeluk, G. *Can. J. Chem.* **1966**, *44*, 1427-1436.

Scheme 1.25. Substrate Scope

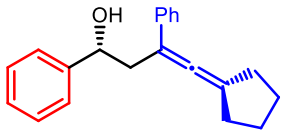




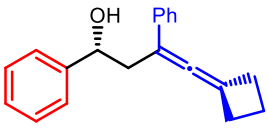
1.143, Ar = Ph: 82% yield, 96:4 er
1.144, Ar = *m*-xylyl: 79% yield, 96:4 er
1.145, Ar = *p*-CF_3Ph: 95% yield, 92:8 er
1.146, Ar = *p*-FPh: 57% yield, 94:6 er
1.147, Ar = 2-naphthyl: 81% yield, 96:4 er
1.148, Ar = 2-pyridyl: 69% yield, 98:2 er
1.149, Ar = 3-furyl: 74% yield, 97:3 er
1.150, Ar = 2-furyl: 47% yield, 96:4 er



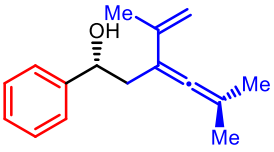
1.151, 84% yield
94:6 er



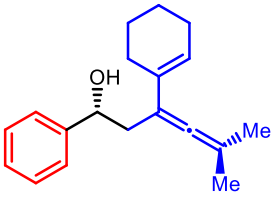
1.152, 69% yield
98:2 er



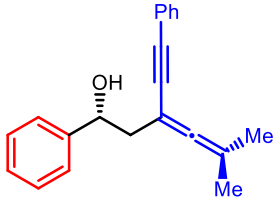
1.153, 68% yield
97:3 er



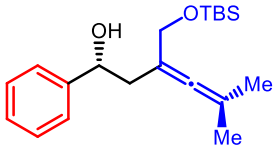
1.154, 37% yield
97:3 er



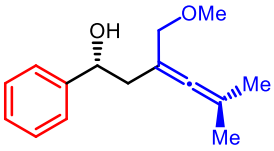
1.155, 91% yield
98:2 er



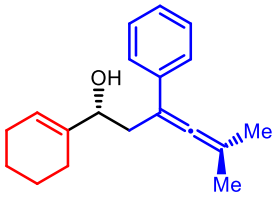
1.156, 68% yield
93:7 er



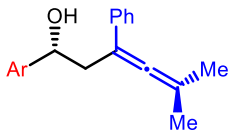
1.157, 91% yield
95:5 er



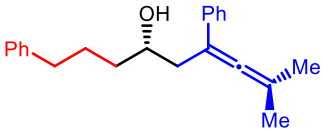
1.158, 80% yield
98:2 er



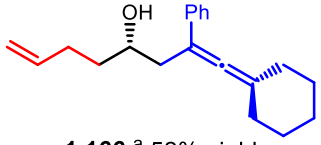
1.159, 61% yield
85:15 er



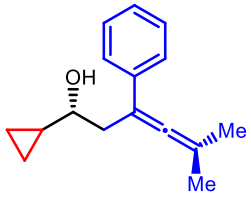
1.160, Ar = *p*-OMePh: 88% yield, 95:5 er
1.161, Ar = *p*-CF_3Ph: 64% yield, 98:2 er
1.162, Ar = *p*-BrPh: 89% yield, 97:3 er
1.163, Ar = *o*-ClPh: 84% yield, 98:2 er
1.164, Ar = *p*-Ph_2NPh 84% yield, 92:8 er



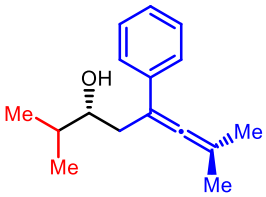
1.165,[a] 71% yield
92:8 er



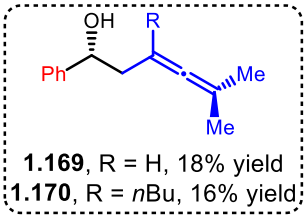
1.166,[a] 52% yield
93:7 er



1.167,[a] 60% yield
94:6 er



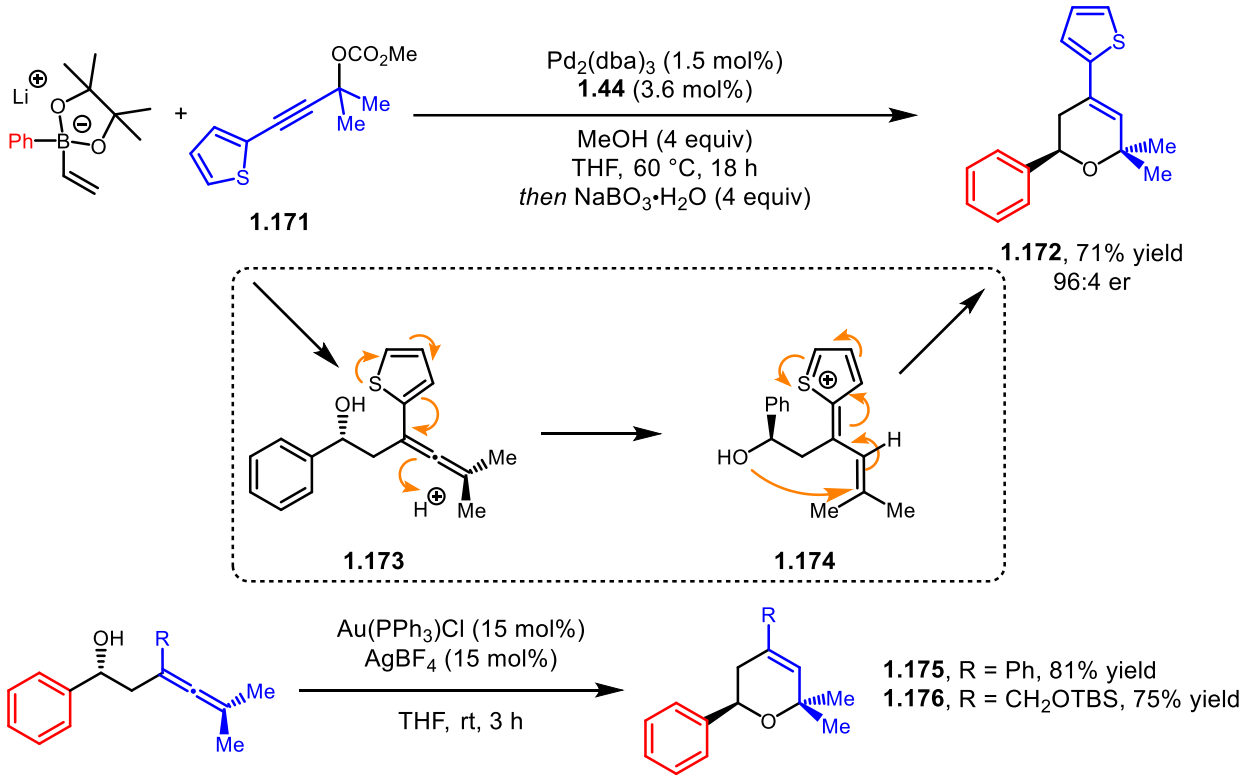
1.168,[a] 40% yield
89:11 er



1.169, R = H, 18% yield
1.170, R = *n*Bu, 16% yield

[a]TFE (4 equiv) was used

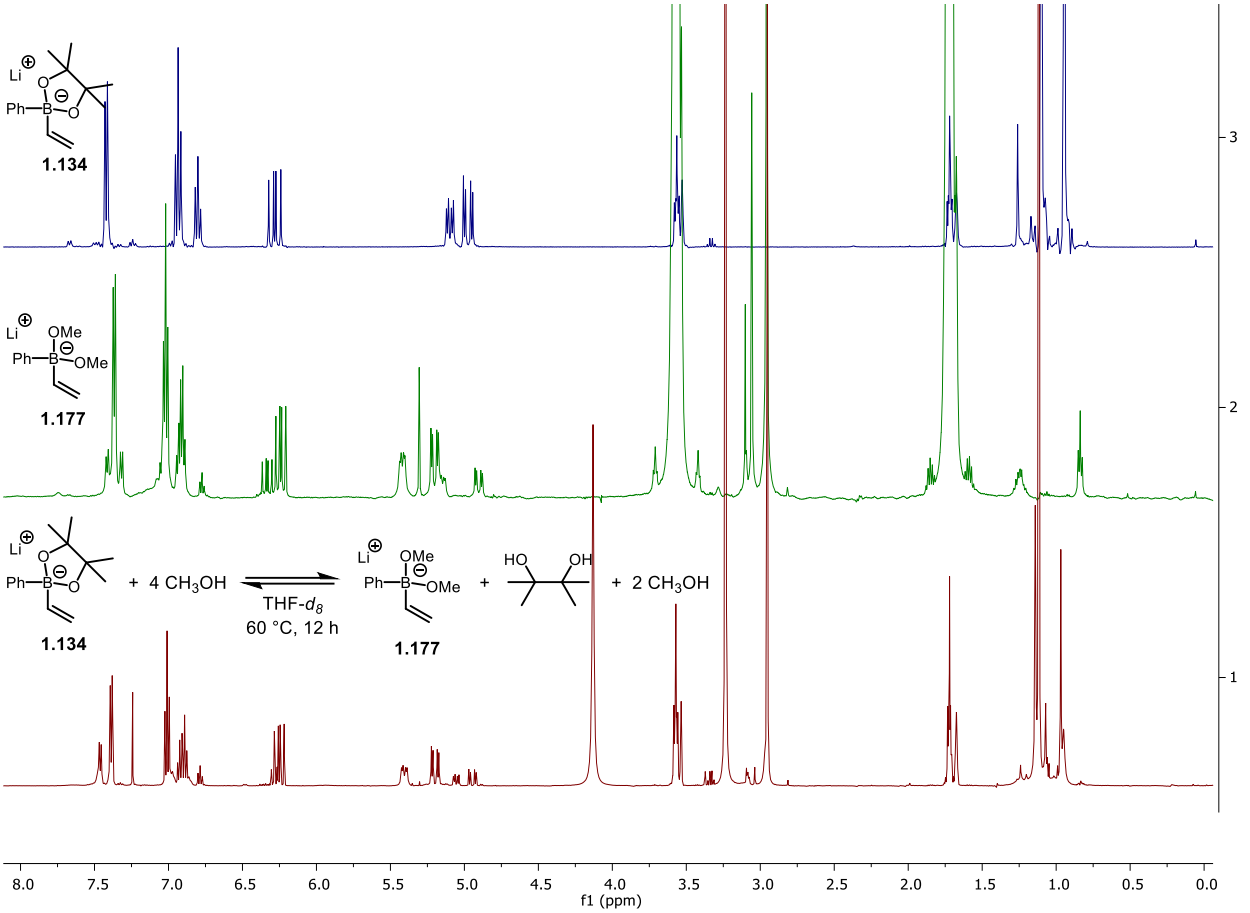
Scheme 1.26. Cyclization of β-Hydroxy Allenes to Dihydropyran Derivatives



1.5 Mechanistic Analysis

^{1}H NMR experiments were conducted to provide insight about the function of methanol. The phenyl vinyl pinacolato boron "ate" complex **1.134** and phenyl vinyl bismethanolato boron "ate" complex **1.177** were synthesized from vinyl lithium and corresponding boronic esters in deuterated THF (Figure 1.1). A new species was observed in the ^{1}H NMR upon mixing the boron "ate" complex **1.134** with four equivalents of methanol in deuterated THF (Figure 1.1, bottom equation). ^{1}H NMR resonances of this new species were consistent with the dimethoxy boron "ate" complex **1.177**. Of note, the minor set of alkene peaks in the spectrum of **1.177** corresponds to the bis(vinyl) boron "ate", generated from reaction between **1.177** and vinyllithium.

Figure 1.1. ^{1}H NMR Spectra of Phenyl Vinyl Pinacolato Boron "Ate" **1.134**, Phenyl Vinyl Bismethanolato Boron "Ate" **1.177**, and the Methanol Exchange Experiment on **1.134**.

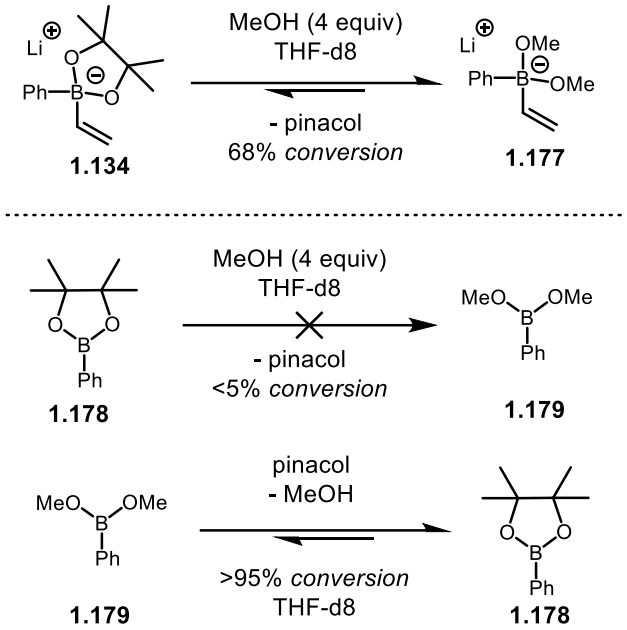


The ratio of **1.134**:**1.177** is 32:68 based on the integration. No such exchange was observed between the three-coordinate organoboronate **1.178** and methanol (Scheme 1.27). In contrast, treating the dimethoxy boronates **1.179** with pinacol resulted in more than 95% conversion to the pinacol boronates **1.178**. The unexpected equilibrium for four-coordinated borates **1.134** could be the result of release of ring strain from five-membered ring, or the equilibrium could favor the less hindered complex. On the other hand, the observed equilibrium for the three-coordinated boronic esters, favoring pinacol boronic ester, was consistent with experimental results from Brown,[61]

(61) Roy, C. D.; Brown, H. C. *J. Organomet. Chem.* **2007**, *692*, 784-790.

putatively due to increased entropy. Based on these observations, we hypothesized that the way methanol activates the boron "ate" complex is by replacing the pinacol ligand on the boron and providing a more reactive complex. Of note, such activation has already been demonstrated on three-coordinate boronates.[62,24b]

Scheme 1.27. Exchange Equilibria in Four-Coordinate Versus Three-Coordinate Organoboron Compounds

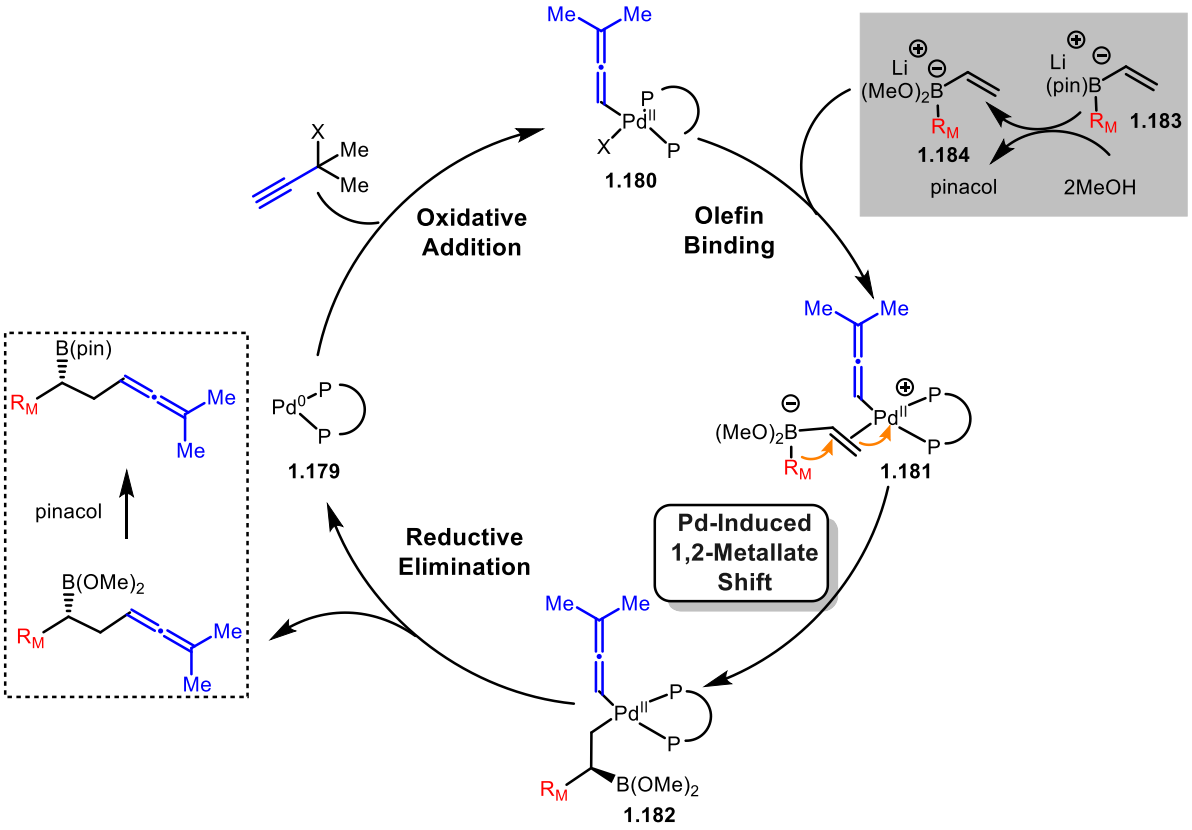


Collectively, we proposed the catalytic cycle in Scheme 1.28. First, Pd(0) complex **1.179** can undergo oxidative addition with propargyl electrophile to deliver allenyl palladium **1.180**. Meanwhile, the pinacol boron "ate" complex **1.183** could exchange the pinacol ligand with methanol to generate dimethoxy boron "ate" complex **1.184**. As the reactive intermediate, **1.184** can bind with the palladium intermediate **1.180** to furnish palladium intermediate **1.181**. Then,

(62) (a) Lee, D.; Williamson, C. L.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 8260−8267.; (b) Taylor, M. S. *Acc. Chem. Res.* **2015**, *48*, 295−305.; (c) Wu, H.; Garcia, J. M.; Haeffner, F.; Radomkit, S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 10585−10602. (d) Yan, L.; Meng, Y.; Haeffner, F.; Leon, R. M.; Crockett, M. P.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 3663−3673.

1,2-metalate shift and reductive elimination would occur to afford the product and close the catalytic cycle.

Scheme 1.28. *Proposed Catalytic Cycle*

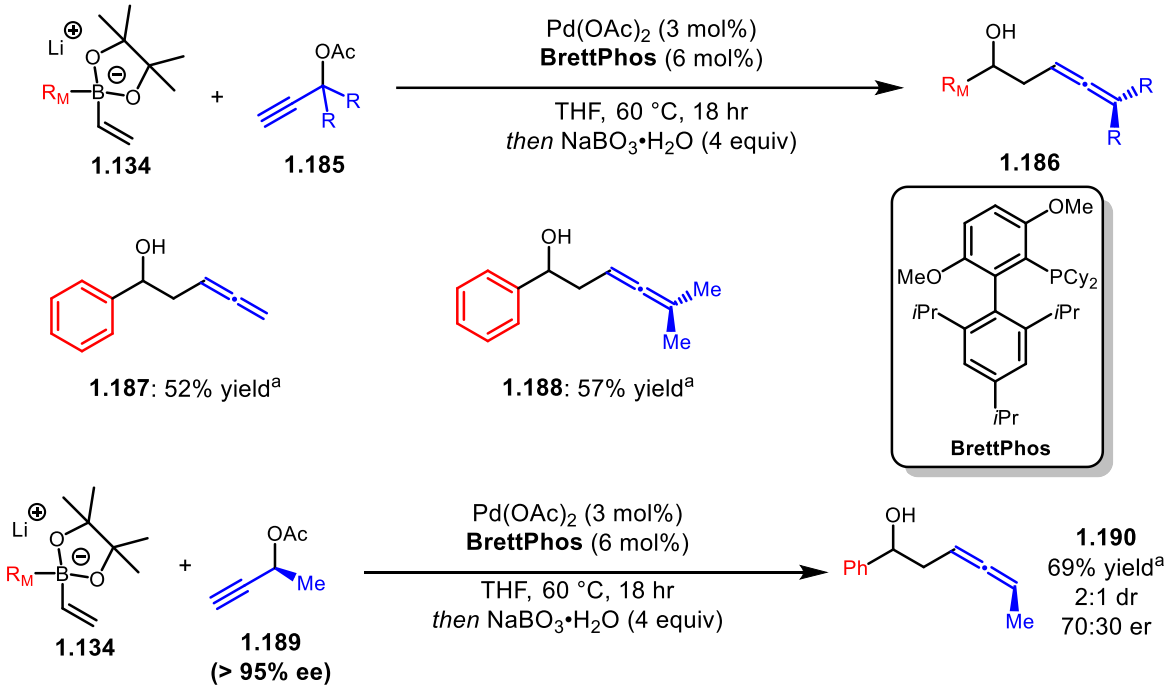


1.6 Efforts on the Extension of Scope: Novel Reactivity with BrettPhos

One unignorable drawback of the methodology described above is the limited substrate scope: poor yields were observed with propargylic electrophiles bearing fewer substituents (*i.e.*, primary, and secondary propargylic carbonates). The synthesis of terminal allenes and disubstituted allenes is critical because they are synthetically useful and generally more versatile than tetrasubstituted allenes.[14] A catalytic system with the monodentate BrettPhos was discovered that operates with γ-unsubstituted and terminal propargylic electrophiles (Scheme 1.29). Using this

ligand framework, terminal allene **1.187** and dimethyl substituted allene **1.188** could be synthesized with good yields. When enantioenriched propargyl acetate **1.189** was employed, erosion of the enantioenrichment was observed with product **1.190**. This racemization could arise from the σ–π–σ process[51] or from the metal-propargyl anion intermediate as proposed by Hoveyda for copper catalyst,[56a] a racemization process through SET is also possible.[38]

Scheme 1.29. Unsubstituted Propargylic Electrophiles



[a] Yield determined by ^{1}H NMR with internal standard

Inspired by this reactivity, we proposed that a chiral monodentate ligand could be a solution that would operate with a broader scope of propargylic electrophiles. Efforts had been made to discover a chiral monodentate phosphine ligand that can be utilized in the conjunctive cross-coupling to synthesize optically active terminal allenes or monosubstituted allenes. Various chiral

monodentate phosphine ligands (i.e., MOPs[63], phosphoramidites[64]) have been investigated. However, to date, only a trace amount of product (< 5%) was observed.

1.7 Conclusion

In conclusion, we developed a palladium-catalyzed enantioselective conjunctive cross-coupling reaction with propargylic electrophiles. The tetrasubstituted allenes were isolated with good yield and enantioselectivity. Beneficial effects of alcohol additives were discovered and found to likely operate through a ligand exchange process. The synthetic utility was showcased by the synthesis of dihydropyran derivatives. Moreover, an achiral catalytic system with BrettPhos has been developed to accommodate γ-unsubstituted and non-substituted propargylic electrophiles, although in a racemic manner.

(63) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354-362.
(64) Teichert, J. F.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 2486-2528.

1.8 Experimental Section[1]

1.8.1. General Information

^{1}H NMR spectra were recorded on a Varian Gemini-400 (400 MHz), Varian Gemini-500 (500 MHz), or Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Gemini-400 (100 MHz), Varian Gemini-500 (125 MHz), or Varian Gemini-600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer. Chemical shifts are reported in ppm using trifluoroacetic acid as the external standard (CF_3COOH: -76.55 ppm). Infrared (IR) spectra were recorded on a Bruker Alpha-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter and the values reported are averages of seven measurements. Direct analysis in real time-high resolution mass spectrometry (DART-HRMS) was performed at the Mass Spectrometry Facility, Boston College, Chestnut Hill, MA. Flash column chromatography was performed using silica gel (SiO_2, 230 x 450 Mesh, purchased from Silicycle). Thin layer chromatography (TLC) was performed on 25 μm silica gel aluminum backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm) and ceric ammonium molybdate (CAM) in ethanol or alkaline aqueous potassium permanganate ($KMnO_4$).

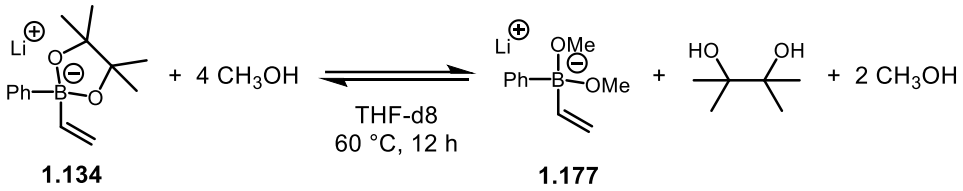
Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector with isopropanol as the modifier.

Anhydrous tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified using a Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after purging with argon. Anhydrous deuterated THF (THF-d_8) was purchased from Oakwood Chemicals and used without further purification. Tris(dibenzylideneacetone) dipalladium(0) ($Pd_2(dba)_3$), palladium(II) acetate ($Pd(OAc)_2$), bis(triphenylphosphine) palladium(II) dichloride ($PdCl_2(PPh_3)_2$), and (S_P,S_P)-MandyPhos were purchased from Strem Chemicals, Inc. and used without further purification. All pinacol and neopentyl glycol boronic esters not synthesized in-house according to literature procedures[19a] were purchased from Combi Blocks, Oakwood Chemicals, or Frontier Scientific and used without further purification. Vinyllithium solution in THF was prepared from tetravinyltin and *n*-butyllithium according to the literature procedure.[24] All other reagents were purchased from Aldrich, Alfa Aesar, or Acros and used without further purification.

1.8.2. Experimental Procedures

1.8.2.1. Exchange Equilibria NMR Studies in Four-Coordinate Versus Three-Coordinate Organoboron Compounds

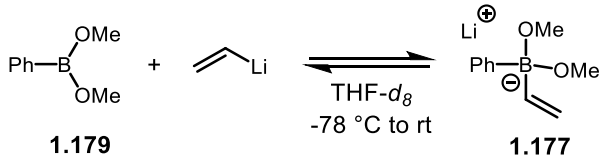
a. Pinacolato Boron 'Ate'–Methanol Exchange



1.134 **1.177**

In a glovebox filled with argon, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (30.6 mg, 0.15 mmol, 1 equiv) and anhydrous Et_2O (0.3 mL), sealed with a septum cap, and removed from the glovebox. Outside the glovebox under positive nitrogen pressure, the vial was cooled to 0 ºC in an ice-water bath, and vinyllithium solution in THF (0.15 mmol, 1 equiv) was added dropwise with stirring to form the 'ate' complex. The reaction vial was allowed to warm to room temperature and stir for 30 minutes. The solvent was carefully removed from the 'ate' complex under reduced pressure, and the 'ate' residue was kept under vacuum for 30 minutes before being brought back into the glovebox. In the glovebox, the 'ate' residue was re-dissolved in anhydrous deuterated THF (0.6 mL) and methanol (19.2 mg, 0.60 mmol, 4 equiv) was added. The vial was sealed with a polypropylene cap and electrical tape, brought out of the glovebox, and the reaction was allowed to stir at 60 ºC for 12 hours. After the vial was cooled to room temperature, the contents of the vial were transferred to an NMR tube and analyzed using ^{1}H NMR spectroscopy.

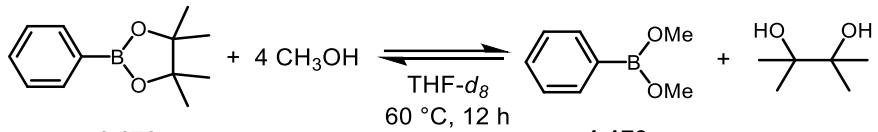
b. Independent Confirmation of Methanolato Boron 'Ate'



1.179 **1.177**

Dimethyl phenylboronate was prepared following a literature procedure:[65] An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with phenyl boronic acid (18.3 mg, 0.15 mmol, 1.2 equiv) and sealed with a septum cap. The atmosphere was exchanged with nitogen, trimethyl orthoformate (39.8 mg, 0.38 mmol, 3 equiv) and trifluoroacetic acid (2.2 mg, 0.019 mmol, 0.16 equiv) were added, and the reaction was allowed to stir for 15 minutes at room temperature. The volatiles were carefully removed under reduced pressure on the manifold vacuum, and the dimethyl phenylboronate residue was kept under vacuum for 30 minutes. This residue was then redissolved in anhydrous deuterated THF (0.6 mL), chilled to -78 °C in a dry ice-acetone bath, and vinyllithium solution in THF (0.13 mmol, 1 equiv) was added dropwise over ten minutes with stirring to form the 'ate' complex. The solution was allowed to come to room temperature, and the contents of the vial were transferred to an NMR tube and analyzed using ^{1}H NMR spectroscopy.

c. Phenyl Boronic Acid, Pinacol Ester–Methanol Exchange

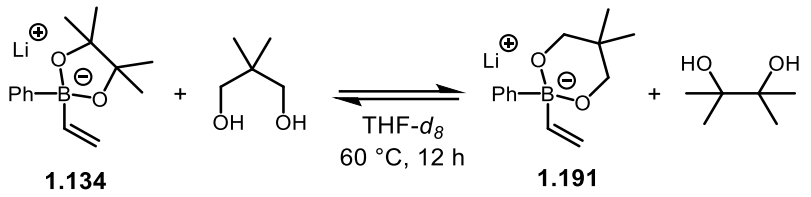


1.178 **1.179**

An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (30.6 mg, 0.15 mmol, 1 equiv) and sealed with a septum cap. The atmosphere was exchanged with nitrogen, anhydrous deuterated THF (0.6 mL) and methanol (19.2 mg, 0.60 mmol, 4 equiv) were added, and the reaction was allowed to stir at 60 ºC for 12 hours. After the vial was cooled to room temperature, the contents of the vial were transferred to an NMR tube and analyzed using ^{1}H NMR spectroscopy.

(65) Elkin, P. K.; Levin, V. V.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Arkhipov, D. E.; Korlyukov, A. A.; Tartakovsky, V. A. *Tetrahedron Lett.* **2011**, *52*, 5259.

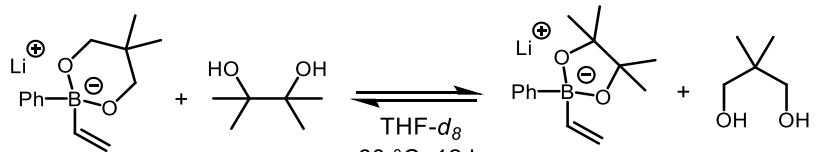
d. Pinacolato Boron 'Ate'–Neopentyl Glycol Exchange



1.134 **1.191**

In a glovebox filled with argon, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (30.6 mg, 0.15 mmol, 1 equiv) and anhydrous Et_2O (0.3 mL), sealed with a septum cap, and removed from the glovebox. Outside the glovebox under positive nitrogen pressure, the vial was cooled to 0 ºC in an ice-water bath, and vinyllithium solution in THF (0.15 mmol, 1 equiv) was added dropwise with stirring to form the 'ate' complex. The reaction vial was allowed to warm to room temperature and stir for 30 minutes. The solvent was carefully removed from the 'ate' complex under reduced pressure, and the 'ate' residue was kept under vacuum for 30 minutes before being brought back into the glovebox. In the glovebox, the 'ate' residue was re-dissolved in anhydrous deuterated THF (0.6 mL) and neopentyl glycol (15.6 mg, 0.15 mmol, 1 equiv) was added. The vial was sealed with a polypropylene cap and electrical tape, brought out of the glovebox, and the reaction was allowed to stir at 60 ºC for 12 hours. After the vial was cooled to room temperature, the contents of the vial were transferred to an NMR tube and analyzed using ^{1}H and ^{11}B NMR spectroscopy.

e. Neopentyl Glycolate Boron 'Ate'–Pinacol Exchange



1.191 **1.134**

In a glovebox filled with argon, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (28.5 mg, 0.15 mmol, 1 equiv) and anhydrous Et_2O (0.3 mL), sealed with a septum cap, and removed from the glovebox. Outside the glovebox under positive nitrogen pressure, the vial was cooled to 0 ºC in an ice-water bath, and vinyllithium solution in THF (0.15 mmol, 1 equiv) was added dropwise with stirring to form the 'ate' complex. The reaction vial was allowed to warm to room temperature and stir for 30 minutes. The solvent was carefully removed from the 'ate' complex under reduced pressure, and the 'ate' residue was kept under vacuum for 30 minutes before being brought back into the glovebox. In the glovebox, the 'ate' residue was re-dissolved in anhydrous deuterated THF (0.6 mL) and pinacol (17.7 mg, 0.15 mmol, 1 equiv) was added. The vial was sealed with a polypropylene cap and electrical tape, brought out of the glovebox, and the reaction was allowed to stir at 60 ºC for 12 hours. After the vial was cooled to room temperature, the contents of the vial were transferred to an NMR tube and analyzed using ^{1}H and ^{11}B NMR spectroscopy.

f. ^{1}H NMR Spectra for Exchange Equilibria Studies

Figure 1.1. ^{1}H NMR spectra of phenyl vinyl pinacolato boron 'ate' **1.134**, phenyl vinyl bismethanolato boron 'ate' **1.177**, and the methanol exchange experiment on **1.134**.

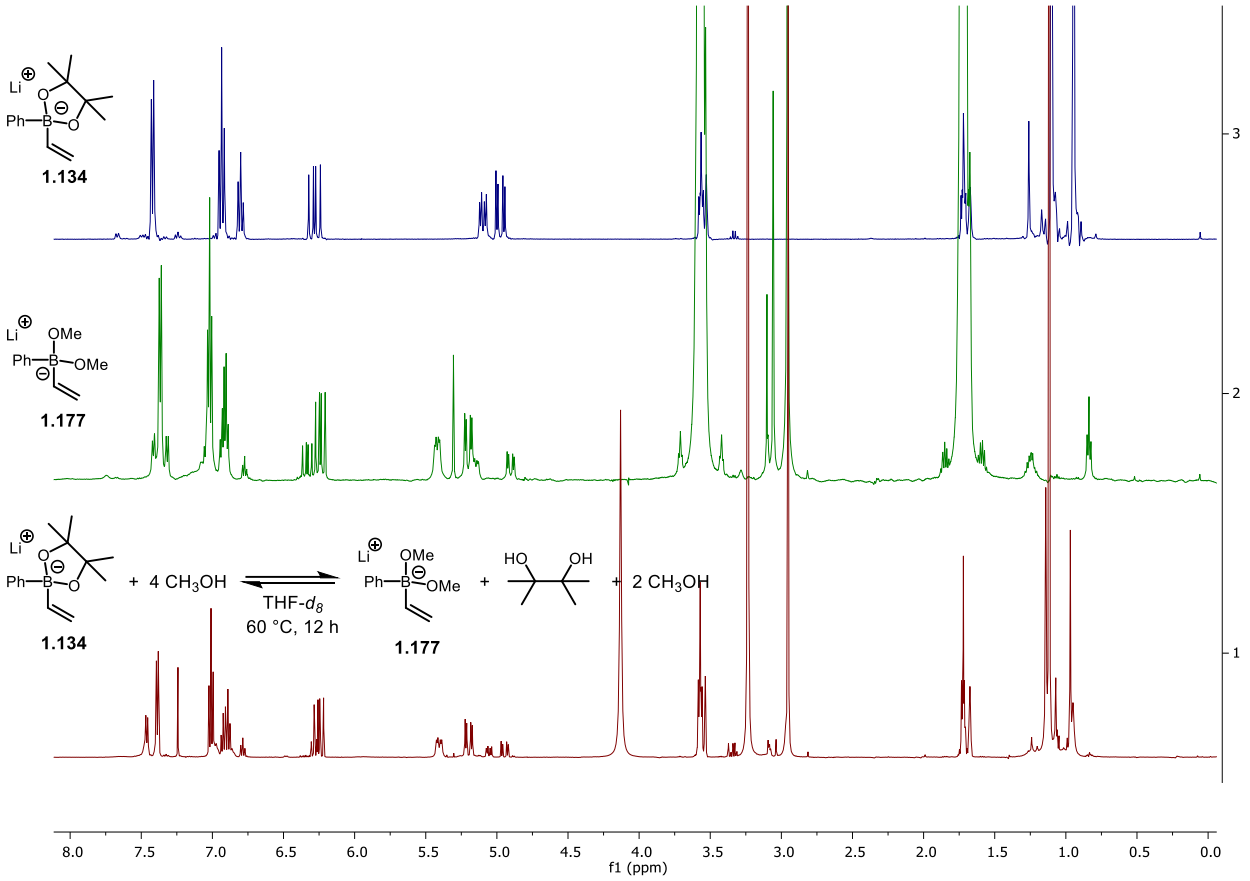
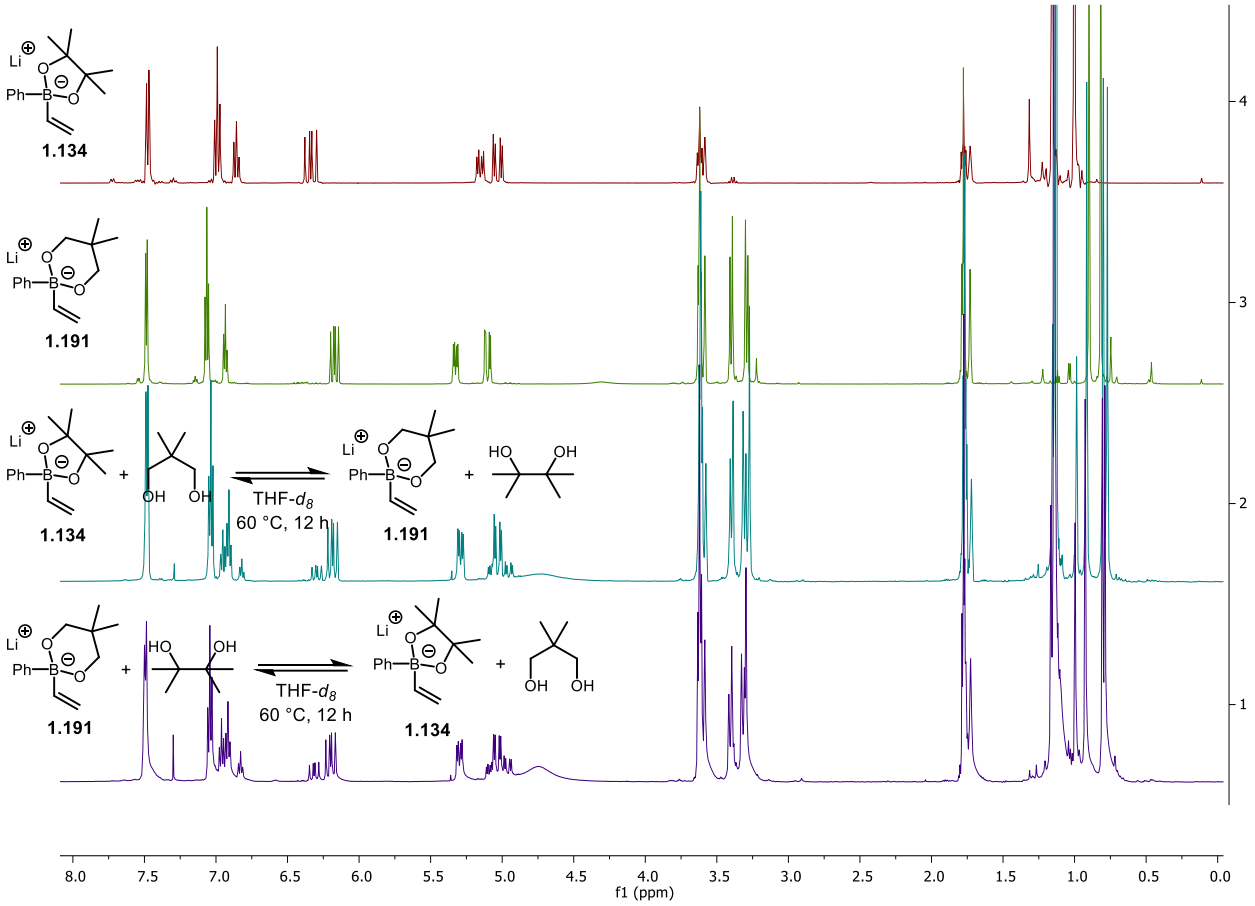
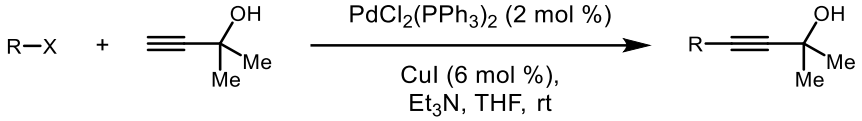


Figure 1.2. ^{1}H NMR spectra of phenyl vinyl pinacolato boron 'ate' **1.134**, phenyl vinyl neopentylglycolato boron 'ate' **1.191**, the neopentyl glycol exchange experiment on **1.134**, and the pinacol exchange experiment on **1.191**.



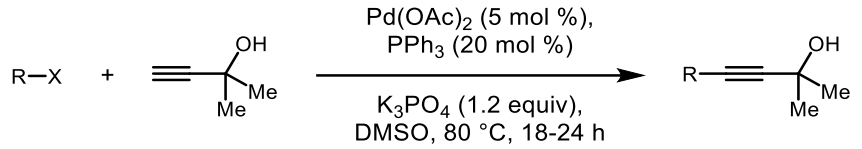
1.8.2.2. Sonogashira Cross-Coupling Procedures for the Preparation of Substituted Propargylic Alcohols

Method A: Procedure with Copper Co-Catalyst



Following a literature procedure:[66] An oven-dried vial equipped with a magnetic stir bar was charged with copper(I) iodide (6 mol %), bis(triphenylphosphine)palladium(II) dichloride (2 mol %), triethylamine (4.3 equiv), and arylhalide (1.05 equiv) in anhydrous THF (1 *M*) under nitrogen atmosphere. 2-methylbut-3-yn-2-ol (1 equiv) was added dropwise and the mixture was allowed to stir at room temperature. Upon completion as checked by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography to afford pure substituted propargylic alcohol product.

Method B: Copper-Free Procedure



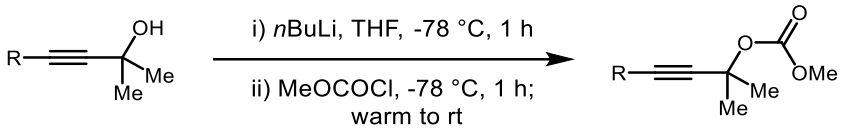
Following a literature procedure:[67] In a glovebox filled with argon, an oven-dried vial equipped with a magnetic stir bar was charged with aryl halide (1 equiv), 2-methyl-3-butyn-2-ol (1.5 equiv), palladium(II) acetate (5 mol %), triphenylphosphine (20 mol %), and anhydrous K_3PO_4 (1.2 equiv) in anhydrous DMSO (0.5 *M*). The vial was sealed, removed from the glovebox, and was allowed

(66) Peng, J.; Gao, Y.; Hu, W.; Gao, Y.; Hu, M.; Wu, W.; Ren, Y.; Jiang, H. *Org. Lett.* **2016**, *18*, 5924.
(67) Paegle, E.; Belyakov, S.; Petrova, M.; Liepinsh, E.; Arsenyan, P. *Eur. J. Org. Chem.* **2015**, *20*, 4389.

to stir at 80 °C for 12-24 h. After the vial was cooled to room temperature, the reaction mixture was quenched with EtOAc (15 × volume) and water (2 x volume) and was allowed to stir for an additional 30 min. The mixture was transferred to a separatory funnel and the aqueous phase was separated. The organic phase was washed with brine (4 x), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography to afford pure substituted propargylic alcohol product.

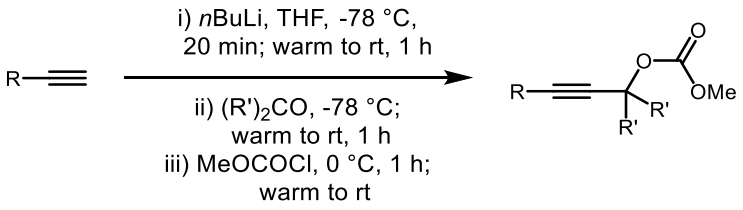
1.8.2.3. Procedures for the Preparation of Substituted Methyl Propargylic Carbonates

Method A: Propargylic Alcohols and Methyl Chloroformate



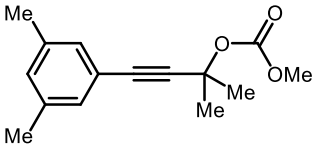
An oven-dried vial equipped with a magnetic stir bar was charged with propargylic alcohol (1 equiv) in anhydrous THF (0.25 *M*) under nitrogen atmosphere. The solution was chilled to -78 °C in a dry ice-acetone bath, and a hexane solution of *n*-butyllithium (1.1 equiv) was added dropwise. After 1 hour, methyl chloroformate (1.5 equiv) was added dropwise at -78 °C, and the solution was allowed to stir for 1 hour before being warmed to room temperature. Upon completion as checked by TLC, the reaction mixture was quenched by addition of water. The reaction mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted twice with hexane. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography to afford pure substituted methyl propargylic carbonate product.

Method B: Telescoped Acetylide Formation–Nucleophilic Addition to Ketone–Reaction with Methyl Chloroformate

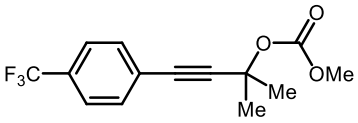


An oven-dried vial equipped with a magnetic stir bar was charged with alkyne (1 equiv) in anhydrous THF (0.25 *M*) under nitrogen atmosphere. The solution was chilled to -78 °C in a dry ice-acetone bath and a hexane solution of *n*-butyllithium (1.1 equiv) was added dropwise. After 20

minutes, the solution was warmed to room temperature and was allowed to stir for 1 hour. The solution was then chilled to -78 ℃, ketone (1 or 1.25 equiv) was added dropwise, and the solution was warmed to room temperature and was allowed to stir for one hour. The solution was then cooled to 0 ℃, methyl chloroformate (1.5 equiv) was added dropwise, and the solution was warmed to room temperature. Upon completion as checked by TLC, the reaction mixture was quenched by addition of water. The reaction mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted twice with hexane. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography to afford pure substituted methyl propargylic carbonate product.

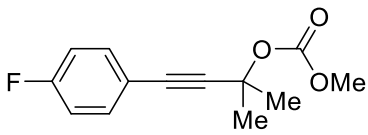


4-(3,5-dimethylphenyl)-2-methylbut-3-yn-2-yl methyl carbonate (1.192). Prepared according to the general procedure above (**Method A**) with 4-(3,5-dimethylphenyl)-2-methylbut-3-yn-2-ol (1.05 g, 5.58 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, yellow oil (821.0 mg, 60% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.08 (s, 2H), 6.94 (s, 1H), 3.78 (s, 3H), 2.27 (s, 6H), 1.78 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 137.9, 130.5, 129.7, 122.1, 88.8, 84.9, 74.9, 54.4, 29.1, 21.1.

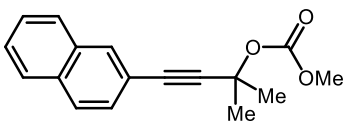


methyl {2-methyl-4-[4-(trifluoromethyl)phenyl]but-3-yn-2-yl} carbonate (1.193). Prepared according to the general procedure above (**Method A**) with 2-methyl-4-[4-(trifluoromethyl)phenyl]but-3-yn-2-ol (456.4 mg, 2.00 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in

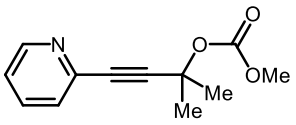
hexanes, stained in KMnO4) to afford clear, yellow oil (446.5 mg, 78% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 – 7.49 (m, 4H), 3.79 (s, 3H), 1.80 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 132.2, 130.4 (q, *J* = 32.7 Hz), 126.4, 125.3 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.1 Hz), 92.0, 83.3, 74.6, 54.6, 28.9.



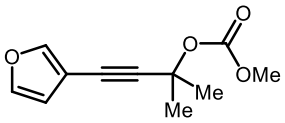
4-(4-fluorophenyl)-2-methylbut-3-yn-2-yl methyl carbonate (1.194). Prepared according to the general procedure above (**Method A**) with 4-(4-fluorophenyl)-2-methylbut-3-yn-2-ol (980.1 mg, 5.50 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, orange oil (1.25 g, 96% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) 7.45 – 7.39 (m, 2H), 7.03 – 6.96 (m, 2H), 3.78 (s, 3H), 1.78 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.7 (d, *J* = 249.8 Hz), 153.6, 133.9 (d, *J* = 8.4 Hz), 118.6 (d, *J* = 3.4 Hz), 115.5 (d, *J* = 22.1 Hz), 89.2 (d, *J* = 1.5 Hz), 83.5, 74.7, 54.4, 28.9. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -110.73.



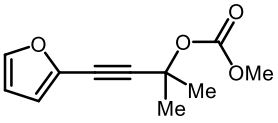
methyl [2-methyl-4-(naphthalen-2-yl)but-3-yn-2-yl] carbonate (1.195). Prepared according to the general procedure above (**Method A**) with 2-methyl-4-(naphthalen-2-yl)but-3-yn-2-ol (1.10 g, 5.23 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford yellow solid (1.00 g, 71% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.5 Hz, 1H), 7.84 – 7.74 (m, 3H), 7.52 – 7.45 (m, 3H), 3.80 (s, 3H), 1.84 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.7, 133.03, 132.98, 132.0, 128.6, 128.0, 127.89, 127.85, 126.8, 126.6, 119.8, 89.8, 85.0, 75.0, 54.5, 29.1.



methyl (2-methyl-4-(pyridin-2-yl)but-3-yn-2-yl) carbonate (1.196). Prepared according to the general procedure above (**Method A**) with 2-methyl-4-(pyridin-2-yl)but-3-yn-2-ol (261.0 mg, 1.62 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford a brown oil (227.2 mg, 64% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.9 Hz, 1H), 7.60 (app t, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.19 (dd, *J* = 7.6, 4.9 Hz, 1H), 3.74 (s, 3H), 1.78 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 150.0, 142.7, 136.2, 127.5, 123.1, 89.3, 83.8, 74.3, 54.5, 28.8.

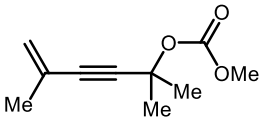


4-(furan-3-yl)-2-methylbut-3-yn-2-yl methyl carbonate (1.197). Prepared according to the general procedure above (**Method A**) with 4-(furan-3-yl)-2-methylbut-3-yn-2-ol (583.7 mg, 3.89 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, yellow oil (642.8 mg, 79% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 1H), 7.35 (t, *J* = 1.6 Hz, 1H), 6.44 (d, *J* = 1.9 Hz, 1H), 3.77 (s, 2H), 1.77 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.51, 146.08, 142.74, 112.61, 106.77, 91.24, 75.83, 74.68, 54.26, 28.85.

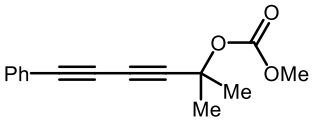


4-(furan-2-yl)-2-methylbut-3-yn-2-yl methyl carbonate (1.198). Prepared according to the general procedure above (**Method A**) with 4-(furan-3-yl)-2-methylbut-3-yn-2-ol (300.4 mg, 2.00 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear,

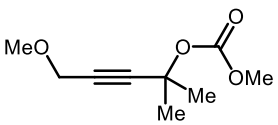
yellow oil (205.0 mg, 49% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.61 (d, *J* = 3.4 Hz, 1H), 6.37 (dd, *J* = 3.4, 1.9 Hz, 1H), 3.77 (s, 3H), 1.78 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 143.9, 136.5, 116.1, 111.0, 93.7, 75.1, 74.6, 54.6, 28.8.



2,5-dimethylhex-5-en-3-yn-2-yl methyl carbonate (1.199). Prepared according to the general procedure above (**Method B**) with 2-methylbut-1-en-3-yne (363.6 mg, 5.50 mmol, 1.1 equiv) and acetone (290.4 mg, 5.00 mmol, 1 equiv). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (801.1 mg, 88% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.30 (dd, *J* = 2.0, 1.0 Hz, 1H), 5.23 (app p, *J* = 1.7 Hz, 1H), 3.76 (s, 3H), 1.88 (dd, *J* = 1.6, 1.0 Hz, 3H), 1.72 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.5, 126.2, 122.5, 88.5, 85.7, 74.7, 54.3, 28.9, 23.3.

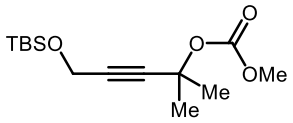


methyl (2-methyl-6-phenylhexa-3,5-diyn-2-yl) carbonate (1.200). Prepared according to the general procedure above (**Method A**) with 2-methyl-6-phenylhexa-3,5-diyn-2-ol (650.0 mg, 3.53 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (650.2 mg, 76% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 6.8 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.31 (app t, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 1.75 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.6, 132.6, 129.4, 128.5, 121.5, 82.1, 79.6, 74.3, 73.2, 69.6, 54.6, 28.7.

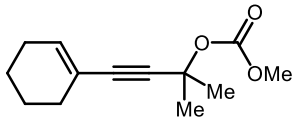


5-methoxy-2-methylpent-3-yn-2-yl methyl carbonate (1.201). Prepared according to the general procedure above (**Method B**) with 3-

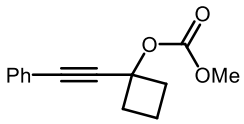
methoxyprop-1-yne (280.4 mg, 4.00 mmol, 1 equiv) and acetone (232.3 mg, 4.00 mmol, 1 equiv). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (501.5 mg, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.13 (s, 2H), 3.76 (s, 3H), 3.37 (s, 3H), 1.71 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 87.0, 80.6, 74.2, 59.9, 57.6, 54.4, 28.9.



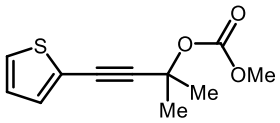
5-[(*tert*-butyldimethylsilyl)oxy]-2-methylpent-3-yn-2-yl methyl carbonate (1.202). Prepared according to the general procedure above (**Method B**) with *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (681.3 mg, 4.00 mmol, 1 equiv) and acetone (232.3 mg, 4.00 mmol, 1 equiv). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (578.2 mg, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.35 (s, 2H), 3.75 (s, 3H), 1.69 (s, 6H), 0.91 (s, 9H), 0.12 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 85.2, 83.5, 74.4, 54.4, 51.9, 28.9, 25.9, 18.4, -5.00.



4-(cyclohex-1-en-1-yl)-2-methylbut-3-yn-2-yl methyl carbonate (1.203). Prepared according to the general procedure above (**Method B**) with 1-ethynylcyclohex-1-ene (583.9 mg, 5.50 mmol) and acetone (290.4 mg, 5.00 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (800.0 mg, 72% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.11 (tt, J = 3.8, 1.7 Hz, 1H), 3.75 (s, 3H), 2.13 – 2.04 (m, 4H), 1.70 (s, 6H), 1.65 – 1.52 (m, 4H). **^{13}C NMR** δ 153.6, 135.8, 120.1, 86.9, 86.4, 75.1, 54.3, 29.20, 29.15, 25.7, 22.4, 21.6.

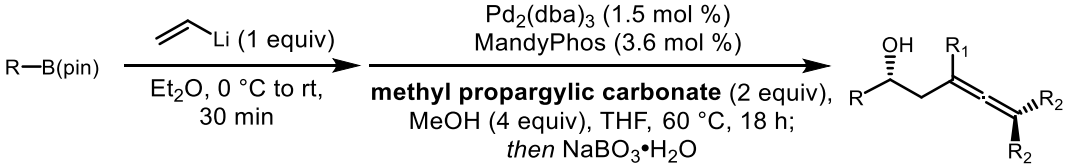


methyl [1-(phenylethynyl)cyclobutyl] carbonate (1.204). Prepared according to the general procedure above (**Method B**) with phenylacetylene (674.1 mg, 6.60 mmol) and cyclobutanone (498.9 mg, 6.00 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (1.32 g, 96% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.42 (m, 2H), 7.35 – 7.25 (m, 3H), 3.80 (s, 3H), 2.75 – 2.62 (m, 2H), 2.55 (qd, J = 9.7, 2.8 Hz, 2H), 2.10 – 1.89 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.7, 132.1, 128.6, 128.3, 122.6, 88.7, 84.9, 74.4, 54.7, 36.7, 14.3.



methyl [2-methyl-4-(thiophen-2-yl)but-3-yn-2-yl] carbonate (1.205). Prepared according to the general procedure above (**Method A**) with 2-methyl-4-(thiophen-2-yl)but-3-yn-2-ol (831.2 mg, 5.00 mmol). The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, yellow oil (850.0 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 – 7.24 (m, 1H), 7.22 (dd, J = 3.7, 1.2 Hz, 1H), 6.96 (dd, J = 5.2, 3.6 Hz, 1H), 3.78 (s, 3H), 1.79 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 132.8, 127.6, 127.0, 122.4, 93.3, 78.0, 74.9, 54.5, 28.9.

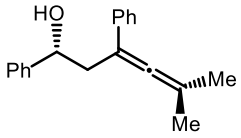
1.8.2.4. General Procedure for the Synthesis of β-Hydroxy Allenes by Conjunctive Cross-Coupling



In a glovebox filled with argon, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (4.1 mg, 0.0045 mmol, 0.015 equiv), (S_P,S_P)-MandyPhos (11.4 mg, 0.0108 mmol, 0.036 equiv), and anhydrous THF (1 mL). The Pd/ligand solution was allowed to stir for at least one hour at room temperature inside the glovebox. Meanwhile, a second oven-dried 2-dram vial equipped with a magnetic stir bar was charged with 2-aryl(or alkenyl or alkyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.30 mmol, 1 equiv) and anhydrous Et_2O (1 mL). This second vial was sealed with a septum cap and removed from the glovebox. Outside the glovebox under positive nitrogen pressure, the reaction vial was cooled to 0 ºC in an ice-water bath, and vinyllithium solution in THF (0.30 mmol, 1 equiv) was added dropwise with stirring to form the 'ate' complex. The reaction vial was allowed to warm to room temperature and stir for 30 minutes. The solvent was carefully removed from the 'ate' complex under reduced pressure, and the 'ate' residue was kept under vacuum for 30 minutes before being brought back into the glovebox. In the glovebox, the 'ate' residue was re-dissolved in anhydrous THF (1 mL), and the Pd/ligand solution was transferred into the reaction vial, followed by methyl propargylic carbonate (0.60 mmol, 2 equiv), ***either*** methanol (38.5 mg, 1.2 mmol, 4 equiv) ***or*** 2,2,2-trifluoroethanol (80.0 mg, 1.2 mmol, 4 equiv), and anhydrous THF (1 mL, used to rinse the Pd/ligand vial). The reaction vial was sealed with a polypropylene cap and electrical tape, brought out of the glovebox, and allowed to stir at 60 ºC for 18 hours. After the vial was cooled to room temperature, the reaction solution was filtered through a silica gel plug with Et_2O washing and concentrated under reduced pressure. If desired, the residue was purified by silica gel column chromatography prior to oxidation. For oxidation to the corresponding β-hydroxy allene, the β-allenyl boronic ester was dissolved in a THF/H_2O mixture (1:1 ratio, 3 mL), and sodium perborate tetrahydrate (4 equiv) was added. The

suspension was allowed to stir under air for 12-24 hours before being diluted with water (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography to afford pure product.

1.8.2.5. Characterization of β-Hydroxy Allene Products

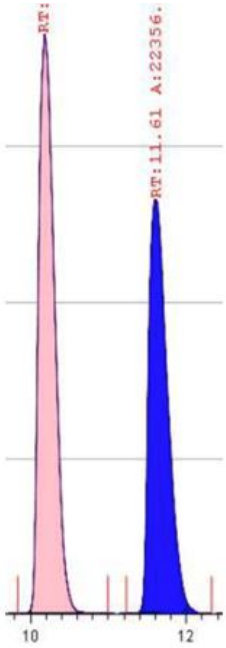


(*R*)-5-methyl-1,3-diphenylhexa-3,4-dien-1-ol (1.143). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), (147.8 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (66.7 mg, 84% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 6H), 7.32 (app t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 4.91 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.96 – 2.78 (m, 2H), 2.29 (d, *J* = 2.7 Hz, 1H), 1.77 (s, 3H), 1.73 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.4, 144.0, 137.6, 129.7, 128.53, 128.52, 127.6, 126.7, 126.2, 115.4, 100.4, 99.5, 72.8, 40.6, 20.6, 20.3. **IR** (neat) ν_{max} 2904 (m), 1596 (m), 1492 (s), 1442 (s), 1058 (s), 1029 (s), 911 (m), 757 (s), 699 (s) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{19}$ $[M+H–H_2O]^+$ calculated: 247.1481, found: 247.1476. **$[\alpha]_D^{20}$:** +33.9 (*c* = 3.20, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Chiral SFC (Chiracel O*J*-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-5-methyl-1,3-diphenylhexa-3,4-dien-1-ol (**1.143**).

Enantiomer mixture



Peak No	% Area	Area	RT (min)
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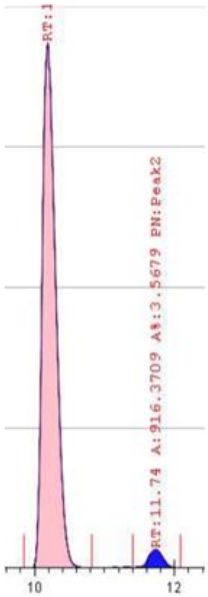
2	46.1008	22356.652	11.61
Total:	100	48495.159	

Standard conditions



Peak No	% Area	Area	RT (min)
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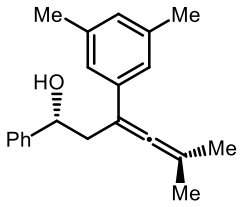
2	3.5679	916.3709	11.74
Total:	100	25683.8652	

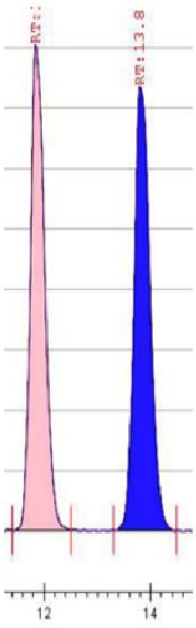


(*R*)-3-(3,5-dimethylphenyl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (1.144). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), 4-(3,5-dimethylphenyl)-2-methylbut-3-yn-2-yl methyl carbonate (147.8 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (70.0 mg, 80% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.9 Hz, 2H), 7.36 (app t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 6.97 (s, 2H), 6.86 (s, 1H), 4.94 – 4.84 (m, 1H), 2.91 – 2.77 (m, 2H), 2.31 (s, 3H), 2.29 (d, *J* = 2.2 Hz, 1H), 1.77 (s, 3H), 1.73 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.3, 144.1, 138.0, 137.6, 128.52, 128.51, 127.6, 126.2, 124.1, 100.5, 99.2, 72.8, 40.9, 21.6, 20.7, 20.4. **IR** (neat) ν_{max} 2911 (m), 1597 (s), 1452 (s), 1376 (m), 1184 (m), 1057 (s), 1037 (s), 846 (s) cm^{-1}. **HRMS** (DART+) for $C_{21}H_{23}$ $[M+H-H_2O]^+$ calculated: 275.1794, found: 275.1792. **$[\alpha]_D^{20}$:** +32.3 (*c* = 1.13, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Chiral SFC (Chiracel OD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-3-(3,5-dimethylphenyl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (**1.144**).

Enantiomer mixture



Peak No	% Area	Area	RT (min)
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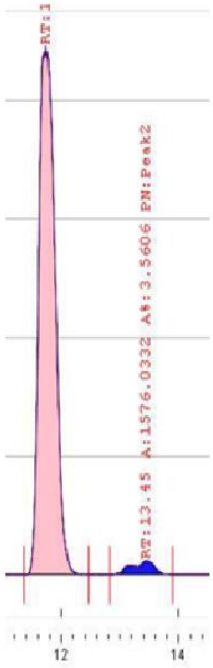
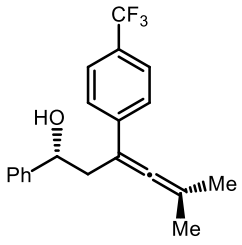
2	51.0547	15369.5597	13.8
Total:	100	30104.0832	

Standard conditions



Peak No	% Area	Area	RT (min)
1	96.4394	42687.0169	11.73
2	3.5606	1576.0332	13.45
Total:	100	44263.0501	

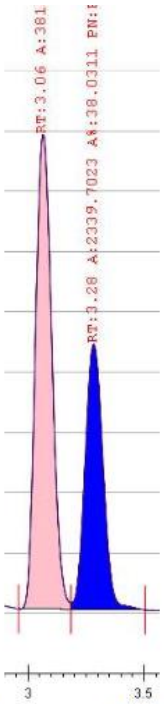


(*R*)-5-methyl-1-phenyl-3-[4-(trifluoromethyl)phenyl]hexa-3,4-dien-1-ol (1.145). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl {2-methyl-4-[4-(trifluoromethyl)phenyl]but-3-yn-2-yl} carbonate (171.8 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (95.6 mg, 96% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.42 – 7.34 (m, 4H), 7.29 (t, *J* = 6.9 Hz, 1H), 4.89 (dd, *J* = 7.6, 5.6 Hz, 1H), 2.99 – 2.81 (m, 2H), 2.23 (d, *J* = 7.5 Hz, 1H), 1.76 (s, 3H), 1.71 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.4, 143.8, 141.7, 129.8, 128.6, 128.5 (q, *J* = 32.4 Hz), 127.8, 126.3, 126.2, 125.4 (q, *J* = 3.6 Hz), 124.4 (q, *J* = 271.8 Hz), 115.4, 100.2, 99.7, 73.0, 40.2, 20.3, 20.1. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -62.39. **IR** (neat) ν_{max} 1614 (m), 1325 (s), 1163 (s), 1121 (s), 1067 (s), 1014 (m), 842 (m) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{18}F_3$ $[M+H–H_2O]^+$ calculated: 315.1355, found: 315.1343. **$[\alpha]_D^{20}$:** +25 (*c* = 0.85, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Chiral SFC (Chiracel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-5-methyl-1-phenyl-3-[4-(trifluoromethyl)phenyl]hexa-3,4-dien-1-ol (**1.145**).

Enantiomer mixture



Peak No	% Area	Area	RT (min)
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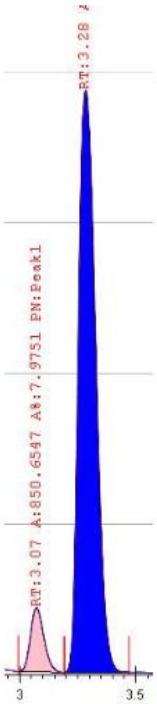
2	38.0311	2339.7023	3.28
Total:	100	6152.0739	

Standard conditions



Peak No	% Area	Area	RT (min)
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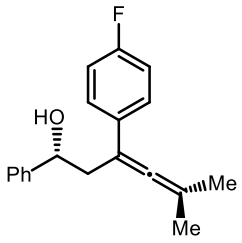
2	92.0249	9815.7572	3.28
Total:	100	10666.4119	

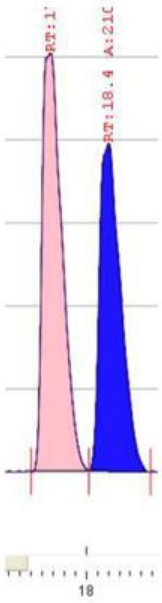


(*R*)-3-(4-fluorophenyl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (1.146). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), 4-(4-fluorophenyl)-2-methylbut-3-yn-2-yl methyl carbonate (94.5 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (34.0 mg, 60% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 7H), 7.00 (app t, *J* = 8.7 Hz, 2H), 4.88 (app t, *J* = 6.6 Hz, 1H), 2.84 (d, *J* = 6.6 Hz, 2H), 2.28 (d, *J* = 3.7 Hz, 1H), 1.76 (s, 3H), 1.71 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.2, 161.8 (d, *J* = 245.6 Hz), 143.9, 133.6 (d, *J* = 3.0 Hz), 128.5, 127.7, 127.6, 126.2, 115.3 (d, *J* = 21.5 Hz), 99.7, 99.6, 72.9, 40.7, 20.6, 20.3. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -116.37 (tt, *J* = 8.3, 5.4 Hz). **IR** (neat) ν_{max} 2908 (m), 1751 (m), 1702 (m), 1601 (m), 1507 (s), 1446 (m), 1363 (m), 1229 (s), 1158 (s), 1033 (s), 912 (m) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{18}F$ $[M+H-H_2O]^+$ calculated: 265.1387, found: 265.1385. **$[\alpha]_D^{20}$:** +33.4 (*c* = 1.40, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

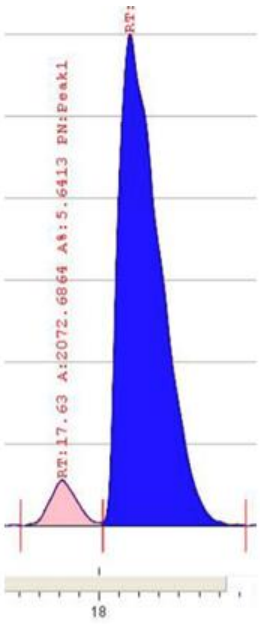
Chiral SFC (Chiracel OJ-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-3-(4-fluorophenyl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (**1.146**).

Enantiomer mixture

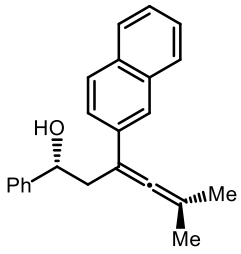


Peak No	% Area	Area	RT (min)
1	54.3168	25074.6615	17.37
2	45.6832	21089.0697	18.4
Total:	100	46163.7312	

Standard conditions



Peak No	% Area	Area	RT (min)
1	5.6413	2072.6864	17.63
2	94.3587	34668.852	18.31
Total:	100	36741.5384	



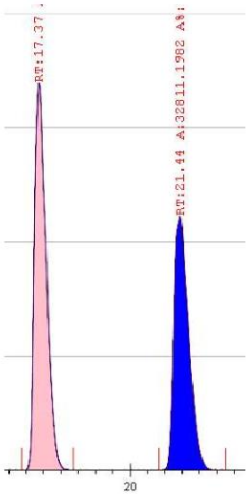
(*R*)-5-methyl-3-(naphthalen-2-yl)-1-phenylhexa-3,4-dien-1-ol (1.147).

Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl [2-methyl-4-(naphthalen-2-yl)but-3-yn-2-yl] carbonate (161.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, yellow oil (79.0 mg, 84% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 – 7.72 (m, 4H), 7.54 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.49 – 7.41 (m, 4H), 7.38 (app t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 4.99 (ddd, *J* = 6.6, 6.6, 2.5 Hz, 1H), 3.01 (app d, *J* = 6.5 Hz, 2H), 2.30 (d, *J* = 2.7 Hz, 1H), 1.81 (s, 3H), 1.76 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.1, 144.1, 135.0, 133.7, 132.5, 128.6, 128.1, 127.9, 127.69, 127.66, 126.26, 126.25, 125.8, 125.6, 123.6, 100.7, 99.9, 72.9, 40.6, 20.7, 20.4. **IR** (neat) ν_{max} 2906 (m), 1597 (m), 1504 (m), 1063 (s), 1020 (s), 889 (m), 855 (s), 818 (s), 699 (s) cm^{-1}. **HRMS** (DART+) for $C_{23}H_{23}O$ $[M+H]^+$ calculated: 315.1743, found: 315.1732. **$[\alpha]_D^{20}$:** +33.8 (*c* = 3.64, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

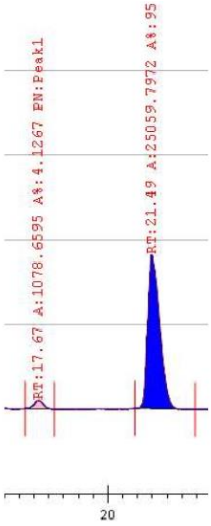
Chiral SFC (Chiracel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-5-methyl-3-(naphthalen-2-yl)-1-phenylhexa-3,4-dien-1-ol (**1.147**).

Enantiomer mixture

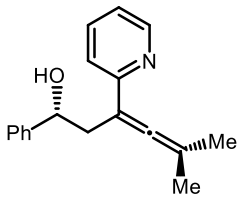


Peak No	% Area	Area	RT (min)
1	54.8158	39805.2637	17.37
2	45.1842	32811.1982	21.44
Total:	100	72616.4619	

Standard conditions



Peak No	% Area	Area	RT (min)
1	4.1267	1078.6595	17.67
2	95.8733	25059.7972	21.49
Total:	100	26138.4567	

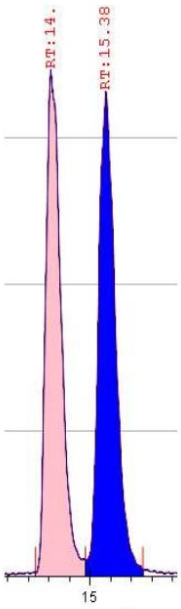


(*R*)-5-methyl-1-phenyl-3-(pyridin-2-yl)hexa-3,4-dien-1-ol (1.148). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl [2-methyl-4-(pyridin-2-yl)but-3-yn-2-yl] carbonate (131.5 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford red solid (57.1 mg, 72% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 4.9, 1.6, 0.9 Hz, 1H), 7.60 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.36 – 7.28 (m, 3H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.10 (ddd, *J* = 7.4, 5.0, 1.2 Hz, 1H), 5.05 (dd, *J* = 7.2, 2.9 Hz, 1H), 3.00 (dd, *J* = 14.2, 3.0 Hz, 1H), 2.89 (dd, *J* = 14.2, 7.2 Hz, 1H), 1.76 (s, 3H), 1.74 (s, 1H), 1.46 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.1, 157.7, 147.7, 145.6, 136.7, 128.1, 126.7, 126.0, 122.7, 121.0, 102.2, 98.6, 74.4, 41.5, 20.1, 19.7. **IR** (neat) ν_{max} 2907 (m), 2857 (m), 1591 (s), 1562 (s), 1429 (s), 1151 (m), 1061 (s), 785 (s), 744 (s) cm^{-1}. **HRMS** (DART+) for $C_{18}H_{20}NO$ $[M+H]^+$ calculated: 266.1539, found: 266.1538. **$[\alpha]_D^{20}$:** +2.09 (*c* = 2.37, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

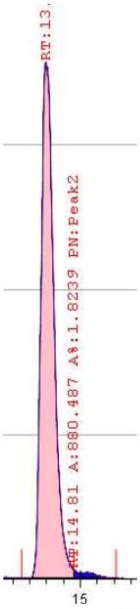
Chiral SFC (Chiracel ODR-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-5-methyl-1-phenyl-3-(pyridin-2-yl)hexa-3,4-dien-1-ol (**1.148**).

Enantiomer mixture

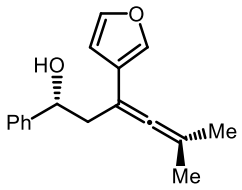


Peak No	% Area	Area	RT (min)
1	48.8869	45111.6645	14.04
2	51.1131	47166.0181	15.38
Total:	100	92277.6826	

Standard conditions



Peak No	% Area	Area	RT (min)
1	98.1761	47394.2007	13.99
2	1.8239	880.487	14.81
Total:	100	48274.6877	

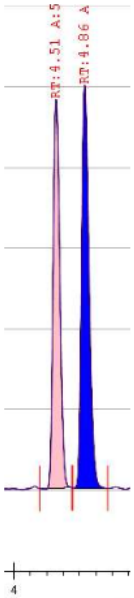


(*R*)-3-(furan-3-yl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (1.149). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), 4-(furan-3-yl)-2-methylbut-3-yn-2-yl methyl carbonate (124.9 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (58.6 mg, 77% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 6H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.34 (dd, *J* = 1.8, 1.0 Hz, 1H), 4.95 – 4.88 (m, 1H), 2.73 – 2.60 (m, 2H), 2.32 (s, 1H), 1.74 (s, 3H), 1.71 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.2, 143.9, 143.3, 138.1, 128.5, 127.7, 126.7, 126.2, 126.1, 124.3, 109.5, 99.2, 93.2, 72.8, 41.4, 20.7, 20.5. **IR** (neat) ν_{max} 2905 (m), 1492 (m), 1446 (m), 1360 (m), 1156 (m), 1047 (s), 1026 (s), 1013 (s), 871 (s) cm^{-1}. **HRMS** (DART+) for $C_{17}H_{15}O$ $[M+H-H_2O]^+$ calculated: 235.1117, found: 235.1120. **$[\alpha]_D^{20}$:** +30.6 (*c* = 2.93, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

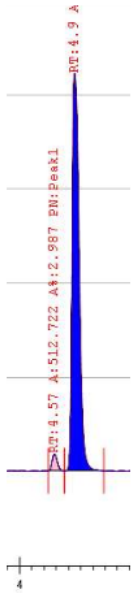
Chiral SFC (Chiracel OJ-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-3-(furan-3-yl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (**1.149**).

Enantiomer mixture

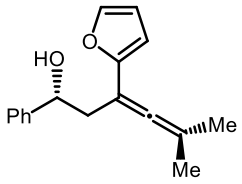


Peak No	% Area	Area	RT (min)
1	46.7033	5484.8617	4.51
2	53.2967	6259.2016	4.86
Total:	100	11744.0633	

Standard conditions



Peak No	% Area	Area	RT (min)
1	2.987	512.722	4.57
2	97.013	16652.3426	4.9
Total:	100	17165.0646	

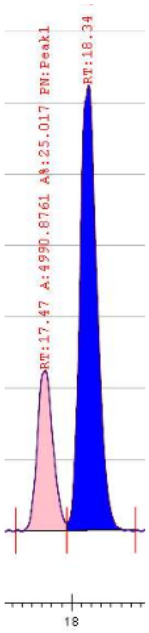


(*R*)-3-(furan-2-yl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (1.150). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), 4-(furan-2-yl)-2-methylbut-3-yn-2-yl methyl carbonate (124.9 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (37.1 mg, 49% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 7.38 – 7.34 (m, 3H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.39 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.20 (dd, *J* = 3.3, 0.8 Hz, 1H), 4.91 (dd, *J* = 8.1, 5.1 Hz, 1H), 2.80 – 2.66 (m, 2H), 2.27 (s, 1H), 1.77 (s, 3H), 1.72 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.0, 151.5, 143.8, 141.9, 128.5, 127.7, 126.7, 126.20, 126.15, 111.4, 106.0, 100.6, 93.1, 73.0, 40.3, 20.9, 20.6. **IR** (neat) ν_{max} 2973 (m), 2929 (m), 1665 (m), 1603 (m), 1492 (m), 1451 (m), 1362 (m), 1155 (m), 1056 (s), 1024 (s), 756 (s), 700 (s) cm^{-1}. **HRMS** (DART+) for $C_{17}H_{15}O$ $[M+H-H_2O]^+$ calculated: 235.1117, found: 235.1118. **$[\alpha]_D^{20}$:** +19.3 (*c* = 1.67, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

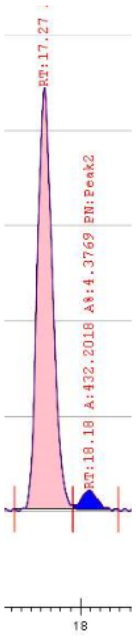
Chiral SFC (Chiracel OD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-3-(furan-2-yl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (**1.150**).

Enantiomer mixture

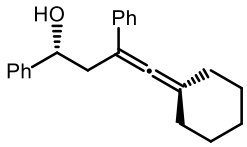


Peak No	% Area	Area	RT (min)
1	25.017	4990.8761	17.47
2	74.983	14959.0611	18.34
Total:	100	19949.9372	

Standard conditions



Peak No	% Area	Area	RT (min)
1	95.6231	9442.4882	17.27
2	4.3769	432.2018	18.18
Total:	100	9874.69	

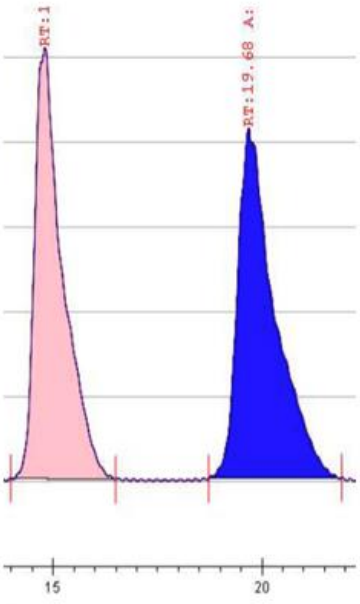


(*R*)-4-cyclohexylidene-1,3-diphenylbut-3-en-1-ol (1.151). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl (1-(phenylethynyl)cyclohexyl) carbonate (155.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford white solid (78.3 mg, 86% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (app t, *J* = 7.2 Hz, 4H), 7.39 – 7.25 (m, 5H), 7.20 (t, *J* = 7.3 Hz, 1H), 4.93 (app t, *J* = 6.6 Hz, 1H), 2.95 – 2.79 (m, 2H), 2.36 (d, *J* = 2.6 Hz, 1H), 2.28 – 2.14 (m, 3H), 2.14 – 2.06 (m, 1H), 1.74 – 1.48 (m, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.6, 144.0, 137.7, 128.6, 128.5, 127.6, 126.6, 126.2, 126.1, 107.0, 100.3, 72.8, 40.9, 31.7, 31.5, 27.8, 26.2. **IR** (neat) ν_{max} 2925 (s), 2851 (m), 1492 (m), 1446 (m), 1022 (m), 909 (w), 760 (s), 694 (s), 584 (w) cm^{-1}. **HRMS** (DART+) for $C_{22}H_{23}$ $[M+H-H_2O]^+$ calculated: 287.1794, found: 287.1791. **$[\alpha]_D^{20}$:** +30 (*c* = 3.9, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

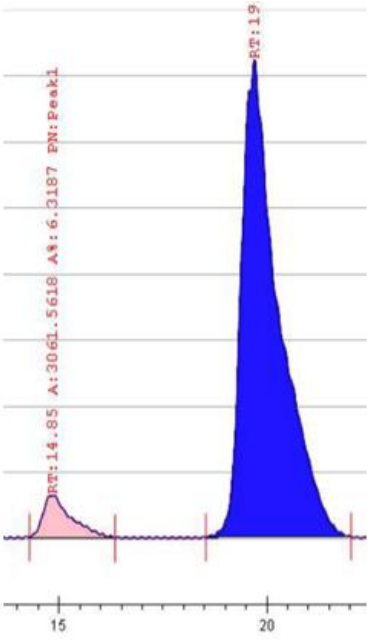
Chiral SFC (Chiracel AD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-4-cyclohexylidene-1,3-diphenylbut-3-en-1-ol (**1.151**).

Enantiomer mixture

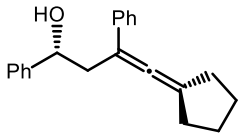


Peak No	% Area	Area	RT (min)
1	48.1874	23743.1266	14.8
2	51.8126	25529.3467	19.68
Total:	100	49272.4733	

Standard conditions



Peak No	% Area	Area	RT (min)
1	6.3187	3061.5618	14.85
2	93.6813	45391.1492	19.71
Total:	100	48452.711	

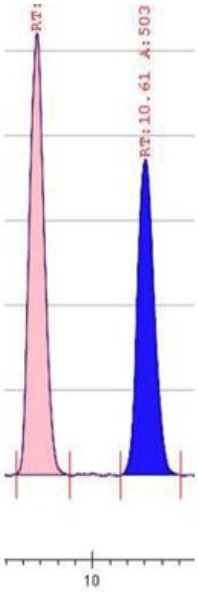


(*R*)-4-cyclopentylidene-1,3-diphenylbut-3-en-1-ol (1.152). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl (1-(phenylethynyl)cyclopentyl) carbonate (146.6 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford white solid (60.3 mg, 69% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.1 Hz, 2H), 7.40 – 7.34 (m, 4H), 7.32 (app t, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 4.92 (ddd, *J* = 7.9, 4.5, 2.7 Hz, 1H), 2.92 (dd, *J* = 15.2, 4.6 Hz, 1H), 2.85 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.53 – 2.41 (m, 2H), 2.40 – 2.28 (m, 3H), 1.81 – 1.69 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.9, 144.0, 137.7, 128.6, 128.52, 128.49, 127.6, 126.7, 126.2, 108.3, 102.9, 72.8, 40.7, 31.4, 31.1, 27.31, 27.27. **IR** (neat) ν_{max} 2953 (m), 2867 (w), 1946 (w), 1597 (w), 1492 (m), 1451 (m), 1022 (m), 756 (s), 693 (s) cm^{-1}. **HRMS** (DART+) for $C_{21}H_{21}$ $[M+H-H_2O]^+$ calculated: 273.1638, found: 273.1637. **$[\alpha]_D^{20}$:** +37.5 (*c* = 1.51, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

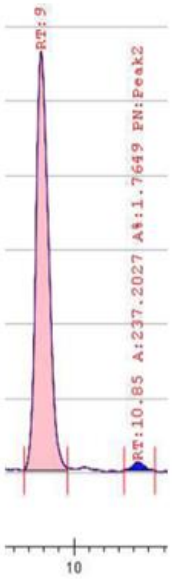
Chiral SFC (Chiracel OJ-H, 8% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-4-cyclopentylidene-1,3-diphenylbut-3-en-1-ol (**1.152**).

Enantiomer mixture

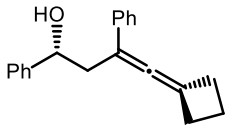


Peak No	% Area	Area	RT (min)
1	54.9069	6125.3499	9.36
2	45.0931	5030.5387	10.61
Total:	100	11155.8886	

Standard conditions



Peak No	% Area	Area	RT (min)
1	98.2351	13202.5213	9.56
2	1.7649	237.2027	10.85
Total:	100	13439.724	

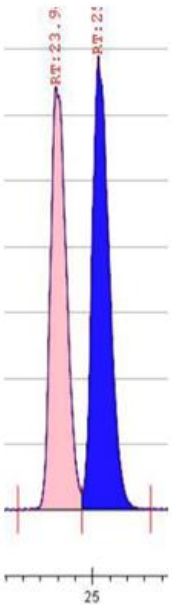


(*R*)-4-cyclobutylidene-1,3-diphenylbut-3-en-1-ol (1.153). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl [1-(phenylethynyl) cyclobutyl] carbonate (138.2 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford white solid (60.0 mg, 72% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 4H), 7.37 (app t, *J* = 7.5 Hz, 2H), 7.33 (app t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 4.95 (ddd, *J* = 7.8, 3.4, 3.4 Hz, 1H), 3.06 – 2.95 (m, 2H), 2.95 – 2.82 (m, 4H), 2.38 (d, *J* = 2.6 Hz, 1H), 2.09 – 1.96 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 195.7, 144.0, 137.4, 128.6, 128.5, 127.6, 127.0, 126.3, 126.1, 105.2, 104.9, 72.7, 40.9, 30.2, 30.0, 17.6. **IR** (neat) ν_{max} 2921 (m), 1947 (w), 1596 (w), 1494 (m), 1452 (m), 1022 (m), 910 (m), 762 (s), 693 (s) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{19}$ $[M+H–H_2O]^+$ calculated: 259.1481, found: 259.1475. **$[\alpha]_D^{20}$:** –37.5 (*c* = 1.85, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

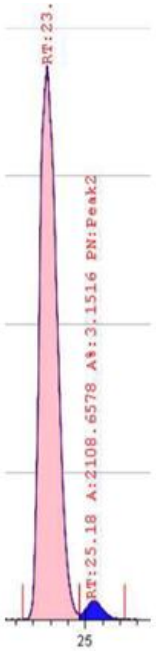
Chiral SFC (Chiracel OD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-4-cyclobutylidene-1,3-diphenylbut-3-en-1-ol (**1.153**).

Enantiomer mixture

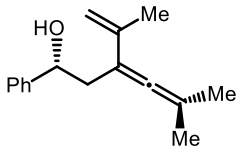


Peak No	% Area	Area	RT (min)
1	46.8363	41374.9214	23.94
2	53.1637	46964.5851	25.16
Total:	100	88339.5065	

Standard conditions



Peak No	% Area	Area	RT (min)
1	96.8484	64799.836	23.9
2	3.1516	2108.6578	25.18
Total:	100	66908.4938	

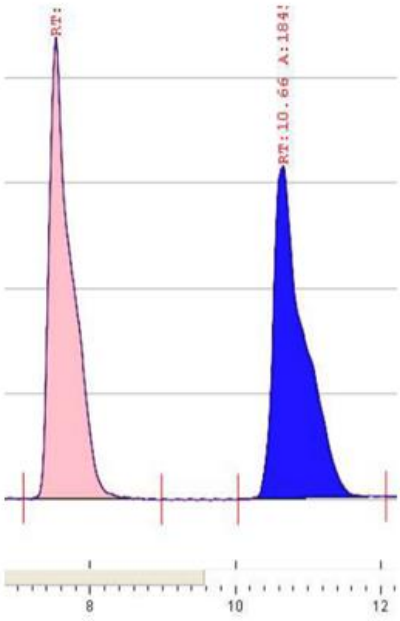


(*R*)-5-methyl-1-phenyl-3-(prop-1-en-2-yl)hexa-3,4-dien-1-ol (1.154). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), 2,5-dimethylhex-5-en-3-yn-2-yl methyl carbonate (109.3 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (29.1 mg, 42% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 4H), 7.30 – 7.24 (m, 1H), 4.96 (s, 1H), 4.91 (s, 1H), 4.86 (dd, *J* = 8.2, 5.0 Hz, 1H), 2.69 – 2.55 (m, 2H), 2.23 (s, 1H), 1.80 (s, 3H), 1.70 (s, 3H), 1.66 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.3, 144.2, 141.3, 128.5, 127.5, 126.1, 110.4, 102.3, 98.5, 72.9, 40.0, 22.1, 20.7, 20.4. **IR** (neat) ν_{max} 2975 (m), 2917 (s), 2857 (m), 2359 (w), 1953 (w), 1617 (m), 1450 (s), 1374 (m), 1185 (m), 1059 (m), 1035 (m), 879 (m), 699 (s) cm^{-1}. **HRMS** (DART+) for $C_{16}H_{21}O$ $[M+H]^+$ calculated: 229.1587, found: 229.1579. **$[\alpha]_D^{20}$:** +39 (*c* = 0.47, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

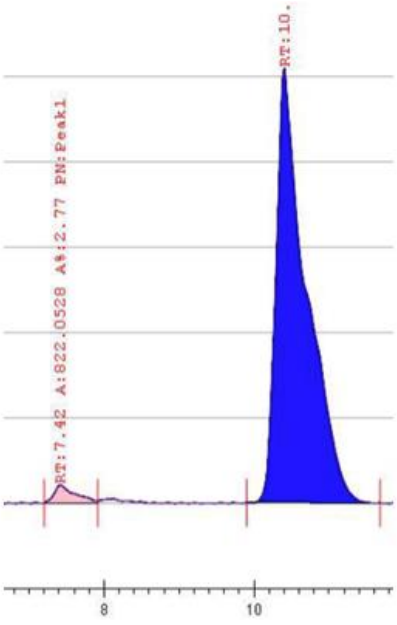
Chiral SFC (Chiracel AD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-5-methyl-1-phenyl-3-(prop-1-en-2-yl)hexa-3,4-dien-1-ol (**1.154**).

Enantiomer mixture

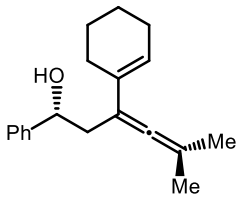


Peak No	% Area	Area	RT (min)
1	50.2758	18660.3216	7.53
2	49.7242	18455.6011	10.66
Total:	100	37115.9227	

Standard conditions



Peak No	% Area	Area	RT (min)
1	2.77	822.0528	7.42
2	97.23	28855.0809	10.41
Total:	100	29677.1337	

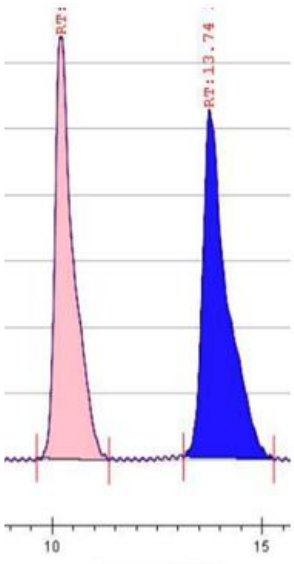


(*R*)-3-(cyclohex-1-en-1-yl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (1.155). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), 4-(cyclohex-1-en-1-yl)-2-methylbut-3-yn-2-yl methyl carbonate (133.4 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford white solid (73.7 mg, 92% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.1 Hz, 2H), 7.34 (app t, *J* = 7.5 Hz, 2H), 7.28 – 7.24 (m, 1H), 5.74 (app t, *J* = 4.1 Hz, 1H), 4.84 (ddd, *J* = 8.6, 2.9, 2.5 Hz, 1H), 2.62 (dd, *J* = 15.1, 4.1 Hz, 1H), 2.54 (dd, *J* = 15.1, 8.9 Hz, 1H), 2.30 (d, *J* = 2.6 Hz, 1H), 2.15 – 2.10 (m, 2H), 2.06 – 2.01 (m, 2H), 1.70 (s, 3H), 1.67 (s, 3H), 1.66 – 1.62 (m, 2H), 1.61 – 1.55 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.7, 144.3, 133.7, 128.4, 127.4, 126.1, 122.5, 102.5, 98.8, 72.8, 39.9, 27.4, 26.1, 23.1, 22.6, 21.0, 20.7. **IR** (neat) ν_{max} 2856 (m), 2833 (m), 1446 (m), 1360 (w), 1184 (w), 1060 (m), 1017 (m), 915 (w), 754 (m), 699 (s), 599 (w) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{23}$ $[M+H-H_2O]^+$ calculated: 251.1794, found: 251.1793. **$[\alpha]_D^{20}$:** +49.8 (*c* = 3.69, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

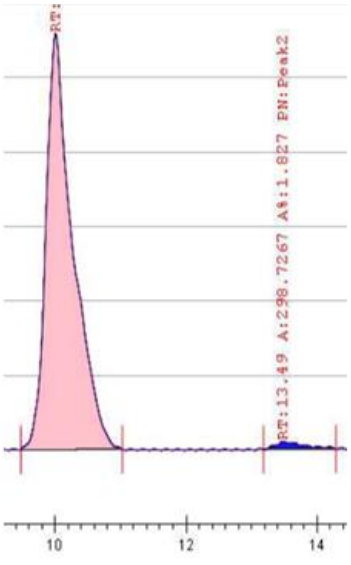
Chiral SFC (Chiracel AD-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-3-(cyclohex-1-en-1-yl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (**1.155**).

Enantiomer mixture

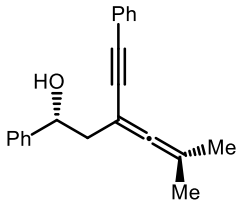


Peak No	% Area	Area	RT (min)
1	47.9539	9903.8983	10.21
2	52.0461	10749.0413	13.74
Total:	100	20652.9396	

Standard conditions



Peak No	% Area	Area	RT (min)
1	98.173	16051.7429	10.01
2	1.827	298.7267	13.49
Total:	100	16350.4696	

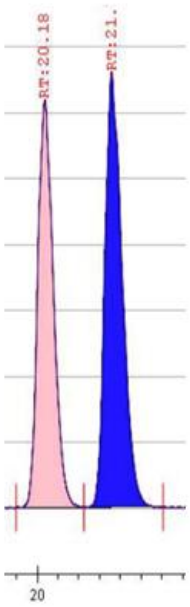


(*R*)-5-methyl-1-phenyl-3-(phenylethynyl)hexa-3,4-dien-1-ol (1.156). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl (2-methyl-6-phenylhexa-3,5-diyn-2-yl) carbonate (145.4 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford yellow solid (61.8 mg, 71% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 4H), 7.39 – 7.34 (m, 2H), 7.33 – 7.27 (m, 4H), 5.00 (app t, *J* = 6.7 Hz, 1H), 2.68 – 2.55 (m, 2H), 2.28 (s, 1H), 1.72 (s, 3H), 1.62 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.2, 143.6, 131.6, 128.5, 128.4, 128.2, 127.7, 126.2, 123.6, 97.9, 90.1, 85.8, 84.4, 73.0, 44.7, 20.5, 20.2. **IR** (neat) ν_{max} 2906 (m), 2206 (w), 1597 (m), 1491 (s), 1442 (s), 1273 (m), 1183 (m), 1057 (s), 1026 (s), 912 (m), 690 (s) cm^{-1}. **HRMS** (DART+) for $C_{21}H_{19}$ $[M+H-H_2O]^+$ calculated: 271.1481, found: 271.1485. **$[\alpha]_D^{20}$:** –14.5 (*c* = 2.09, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

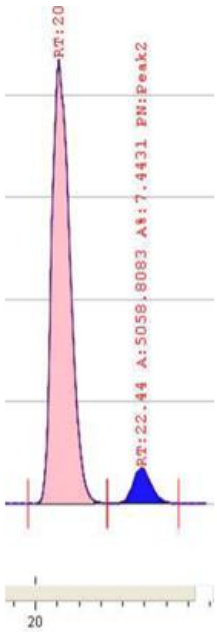
Chiral SFC (Chiracel OD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-5-methyl-1-phenyl-3-(phenylethynyl)hexa-3,4-dien-1-ol (**1.156**).

Enantiomer mixture

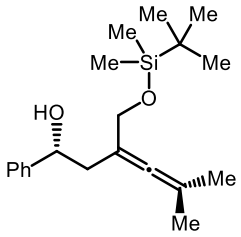


Peak No	% Area	Area	RT (min)
1	45.7521	32300.9941	20.18
2	54.2479	38298.9663	21.79
Total:	100	70599.9604	

Standard conditions



Peak No	% Area	Area	RT (min)
1	92.5569	62907.6657	20.53
2	7.4431	5058.8083	22.44
Total:	100	67966.474	

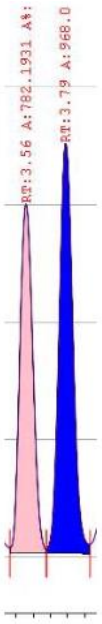


(*R*)-3-{[(*tert*-butyldimethylsilyl)oxy]methyl}-5-methyl-1-phenylhexa-3,4-dien-1-ol (1.157). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), 5-[(*tert*-butyldimethylsilyl)oxy]-2-methylpent-3-yn-2-yl methyl carbonate (171.9 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (91.8 mg, 92% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.1 Hz, 2H), 7.33 (app t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 4.82 (d, J = 8.6 Hz, 1H), 4.13 (s, 2H), 3.64 (s, 1H), 2.54 (dd, J = 14.6, 3.7 Hz, 1H), 2.39 (dd, J = 14.6, 8.7 Hz, 1H), 1.68 (s, 3H), 1.62 (s, 3H), 0.94 (s, 9H), 0.12 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 200.7, 144.5, 128.3, 127.2, 126.0, 98.5, 96.5, 73.4, 65.9, 41.5, 26.0, 20.7, 20.6, 18.5, -5.2. **IR** (neat) ν_{max} 2950 (m), 2926 (m), 2903 (m), 1360 (m), 1253 (s), 1056 (s), 836 (s), 776 (s), 699 (s) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{31}OSi$ $[M+H-H_2O]^+$ calculated: 315.2139, found: 315.2135. **$[\alpha]_D^{20}$:** +5.0 (c = 0.85, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

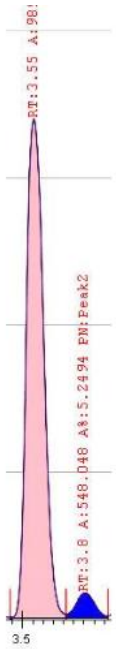
Chiral SFC (Chiracel OD-H, 8% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-3-{[(*tert*-butyldimethylsilyl)oxy]methyl}-5-methyl-1-phenylhexa-3,4-dien-1-ol (**1.157**).

Enantiomer mixture

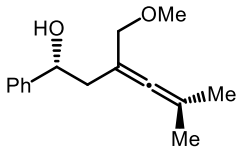


Peak No	% Area	Area	RT (min)
1	44.6897	782.1931	3.56
2	55.3103	968.084	3.79
Total:	100	1750.2771	

Standard conditions



Peak No	% Area	Area	RT (min)
1	94.7506	9892.0854	3.55
2	5.2494	548.048	3.8
Total:	100	10440.1334	

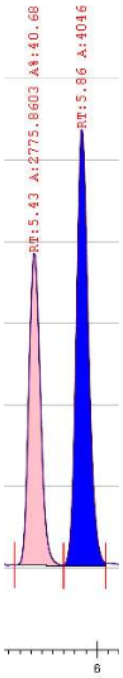


(*R*)-3-(methoxymethyl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (1.158). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), 5-methoxy-2-methylpent-3-yn-2-yl methyl carbonate (111.7 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (57.4 mg, 82% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.32 (app t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 4.80 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.87 (s, 2H), 3.39 (s, 1H), 3.31 (s, 3H), 2.51 (dd, *J* = 14.7, 4.2 Hz, 1H), 2.42 (dd, *J* = 14.7, 8.2 Hz, 1H), 1.67 (s, 3H), 1.60 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.1, 144.2, 128.3, 127.2, 126.0, 96.1, 95.3, 75.0, 73.3, 57.6, 41.4, 20.63, 20.61. **IR** (neat) ν_{max} 2976 (m), 2905 (m), 2852 (m), 2816 (m), 1492 (w), 1449 (m), 1189 (m), 1145 (w), 1082 (s), 1068 (s), 756 (m), 699 (s) cm^{-1}. **HRMS** (DART+) for $C_{14}H_{17}O$ $[M+H-H_2O]^+$ calculated: 201.1274, found: 201.1268. **$[\alpha]_D^{20}$:** +0.334 (*c* = 2.65, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

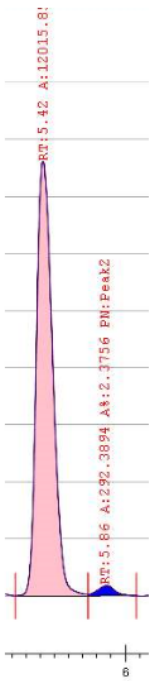
Chiral SFC (Chiracel OD-H, 6% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-3-(methoxymethyl)-5-methyl-1-phenylhexa-3,4-dien-1-ol (**1.158**).

Enantiomer mixture

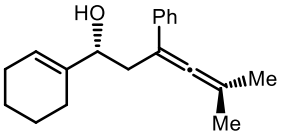


Peak No	% Area	Area	RT (min)
1	40.6883	2775.8603	5.43
2	59.3117	4046.3898	5.86
Total:	100	6822.2501	

Standard conditions



Peak No	% Area	Area	RT (min)
1	97.6244	12015.8529	5.42
2	2.3756	292.3894	5.86
Total:	100	12308.2423	

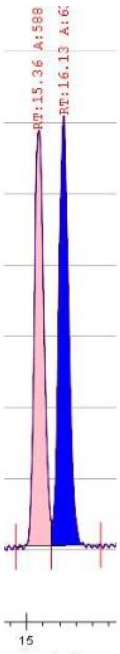


(*R*)-1-(cyclohex-1-en-1-yl)-5-methyl-3-phenylhexa-3,4-dien-1-ol (1.159). Prepared according to the general procedure above with 2-(cyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (62.4 mg, 0.30 mmol, 1 equiv), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (50.8 mg, 63% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 2H), 7.31 (app t, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 5.70 (s, 1H), 4.18 (app t, *J* = 6.4 Hz, 1H), 2.71 (dd, *J* = 14.9, 5.1 Hz, 1H), 2.61 (dd, *J* = 14.9, 7.9 Hz, 1H), 2.20 – 2.09 (m, 1H), 2.07 – 1.91 (m, 3H), 1.91 – 1.82 (m, 1H), 1.82 (s, 6H), 1.72 – 1.49 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.3, 139.2, 137.9, 128.5, 126.6, 126.2, 123.6, 100.5, 99.0, 74.8, 36.6, 25.2, 24.0, 22.8, 22.7, 20.8, 20.5. **IR** (neat) ν_{max} 2927 (s), 2857 (m), 2360 (w), 1597 (m), 1492 (m), 1446 (s), 1183 (m), 1086 (s), 1058 (s), 1013 (s), 919 (m), 759 (s), 693 (s) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{23}$ $[M+H–H_2O]^+$ calculated: 251.1794, found: 251.1794. **$[\alpha]_D^{20}$:** +10.9 (*c* = 2.32, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

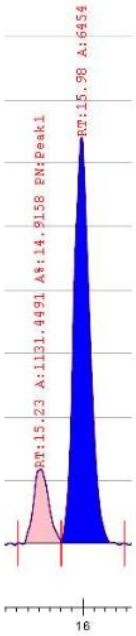
Chiral SFC (Chiracel OD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-1-(cyclohex-1-en-1-yl)-5-methyl-3-phenylhexa-3,4-dien-1-ol (**1.159**).

Enantiomer mixture

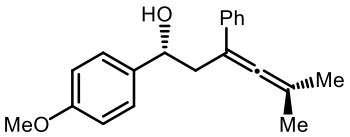


Peak No	% Area	Area	RT (min)
1	48.2825	5883.7822	15.36
2	51.7175	6302.372	16.13
Total:	100	12186.1542	

Standard conditions



Peak No	% Area	Area	RT (min)
1	14.9158	1131.4491	15.23
2	85.0842	6454.1309	15.98
Total:	100	7585.58	

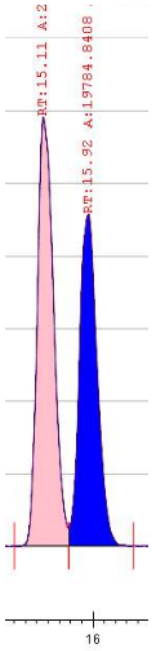


(*R*)-1-(4-methoxyphenyl)-5-methyl-3-phenylhexa-3,4-dien-1-ol (1.160). Prepared according to the general procedure above with 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70.2 mg, 0.30 mmol), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (78.4 mg, 89% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 2H), 7.36 – 7.30 (m, 5H), 6.91 (d, J = 8.6 Hz, 2H), 4.87 (app t, J = 6.5 Hz, 1H), 3.82 (s, 3H), 2.88 (m, 2H), 2.38 (br s, 1H), 1.77 (s, 3H), 1.74 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.5, 159.1, 137.6, 136.2, 131.7, 128.5, 128.3, 127.4, 126.6, 126.1, 113.8, 100.4, 99.3, 72.4, 55.4, 40.4, 20.5, 20.2. **IR** (neat) ν_{max} 1611 (m), 1510 (s), 1442 (m), 1246 (s), 1175 (m), 1035 (m), 829 (m) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{21}O$ $[M+H-H_2O]^+$ calculated: 277.1587, found: 277.1584. **$[\alpha]_D^{20}$:** +24 (c = 0.58, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

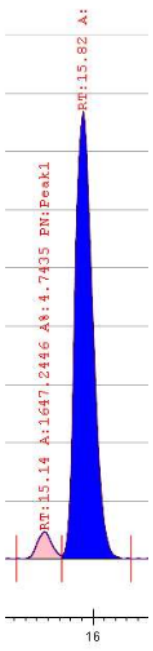
Chiral SFC (Chiracel OD-H, 6% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-1-(4-methoxyphenyl)-5-methyl-3-phenylhexa-3,4-dien-1-ol (**1.160**).

Enantiomer mixture

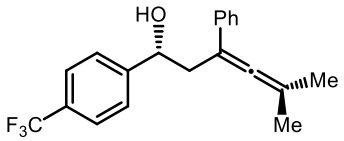


Peak No	% Area	Area	RT (min)
1	54.4678	23667.5303	15.11
2	45.5322	19784.8408	15.92
Total:	100	43452.3711	

Standard conditions



Peak No	% Area	Area	RT (min)
1	4.7435	1647.2446	15.14
2	95.2565	33078.7472	15.82
Total:	100	34725.9918	

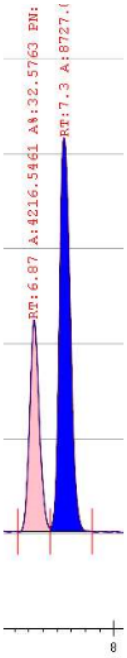


(*R*)-5-methyl-3-phenyl-1-[4-(trifluoromethyl)phenyl]hexa-3,4-dien-1-ol (1.161). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane (81.6 mg, 0.3 mmol), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (67.6 mg, 68% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.34 (app t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.1 Hz, 1H), 4.97 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.94 – 2.76 (m, 2H), 2.42 (d, *J* = 8.5 Hz, 1H), 1.79 (s, 3H), 1.72 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.4, 147.9, 137.3, 129.8 (q, *J* = 32.3 Hz), 128.6, 126.9, 126.5, 126.2, 125.4 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 273.3 Hz), 100.1, 99.8, 72.3, 40.8, 20.6, 20.2. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -62.51. **IR** (neat) ν_{max} 1689 (m), 1618 (m), 1448 (m), 1412 (m), 1321 (s), 1162 (s), 1120 (s), 1064 (s), 1015 (m), 730 (s), 692 (m) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{18}F_3$ $[M+H-H_2O]^+$ calculated: 315.1355, found: 315.1356. **$[\alpha]_D^{20}$:** +18.8 (*c* = 2.93, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

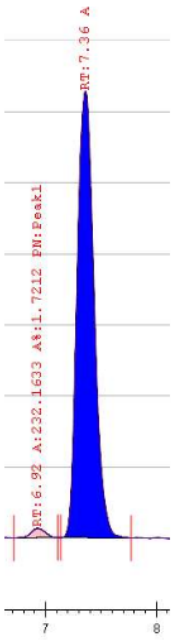
Chiral SFC (Chiracel OD-H, 6% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (R)-5-methyl-3-phenyl-1-(4-(trifluoromethyl)phenyl)hexa-3,4-dien-1-ol (**1.161**).

Enantiomer mixture

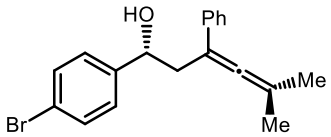


Peak No	% Area	Area	RT (min)
1	32.5763	4216.5461	6.87
2	67.4237	8727.035	7.3
Total:	100	12943.5811	

Standard conditions



Peak No	% Area	Area	RT (min)
1	1.7212	232.1633	6.92
2	98.2788	13256.122	7.36
Total:	100	13488.2853	

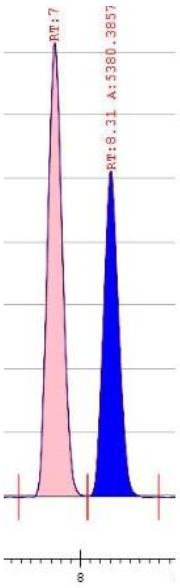


(*R*)-1-(4-bromophenyl)-5-methyl-3-phenylhexa-3,4-dien-1-ol (1.162). Prepared according to the general procedure above with 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84.9 mg, 0.30 mmol, 1 equiv), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (93.6 mg, 91% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.33 (app t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 4.87 (app t, *J* = 6.2 Hz, 1H), 2.83 (app d, *J* = 7.1 Hz, 2H), 2.39 (s, 1H), 1.79 (s, 3H), 1.74 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.4, 143.0, 137.4, 131.5, 128.6, 127.9, 126.8, 126.1, 121.3, 100.1, 99.6, 72.2, 40.6, 20.6, 20.3. **IR** (neat) ν_{max} 1589 (m), 1489 (s), 1444 (m), 1268 (m), 1182 (m), 1069 (s), 1009 (s), 760 (s), 694 (s) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{18}Br$ $[M+H–H_2O]^+$ calculated: 325.0586, found: 325.0577. **$[\alpha]_D^{20}$:** +17.9 (*c* = 4.47, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

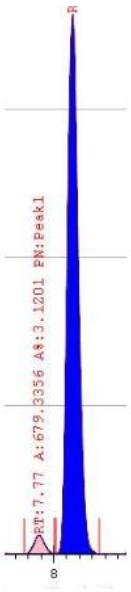
Chiral SFC (Chiracel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-1-(4-bromophenyl)-5-methyl-3-phenylhexa-3,4-dien-1-ol (**1.162**).

Enantiomer mixture

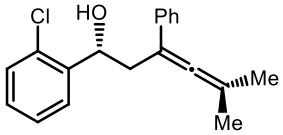


Peak No	% Area	Area	RT (min)
1	57.9445	7413.1497	7.74
2	42.0555	5380.3857	8.31
Total:	100	12793.5354	

Standard conditions



Peak No	% Area	Area	RT (min)
1	3.1201	679.3356	7.77
2	96.8799	21093.8102	8.29
Total:	100	21773.1458	

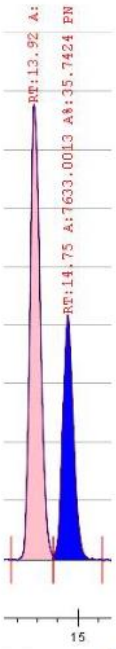


(*R*)-1-(2-chlorophenyl)-5-methyl-3-phenylhexa-3,4-dien-1-ol (1.163). Prepared according to the general procedure above with 2-(2-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (71.6 mg, 0.30 mmol, 1 equiv), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (78.0 mg, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.43 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.38 – 7.27 (m, 4H), 7.25 – 7.17 (m, 2H), 5.32 (ddd, *J* = 8.8, 3.3, 3.3 Hz, 1H), 3.04 (dd, *J* = 15.2, 3.9 Hz, 1H), 2.65 (dd, *J* = 15.2, 8.9 Hz, 1H), 2.40 (d, *J* = 2.9 Hz, 1H), 1.82 (s, 3H), 1.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.5, 141.4, 137.3, 132.2, 129.5, 129.1, 128.6, 127.4, 127.2, 126.8, 126.3, 100.4, 99.8, 69.2, 39.0, 20.6, 20.4. **IR** (neat) ν_{max} 1596 (m), 1492 (m), 1473 (m), 1442 (s), 1182 (m), 1127 (m), 1032 (s), 694 (s) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{18}Cl$ $[M+H-H_2O]^+$ calculated: 281.1092, found: 281.1088. **$[\alpha]_D^{20}$:** +49.9 (*c* = 3.90, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

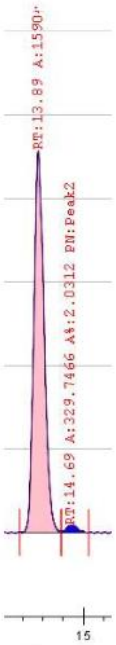
Chiral SFC (Chiracel OD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-1-(2-chlorophenyl)-5-methyl-3-phenylhexa-3,4-dien-1-ol (**1.163**).

Enantiomer mixture

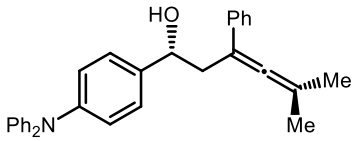


Peak No	% Area	Area	RT (min)
1	64.2576	13722.6187	13.92
2	35.7424	7633.0013	14.75
Total:	100	21355.62	

Standard conditions



Peak No	% Area	Area	RT (min)
1	97.9688	15904.2645	13.89
2	2.0312	329.7466	14.69
Total:	100	16234.0111	

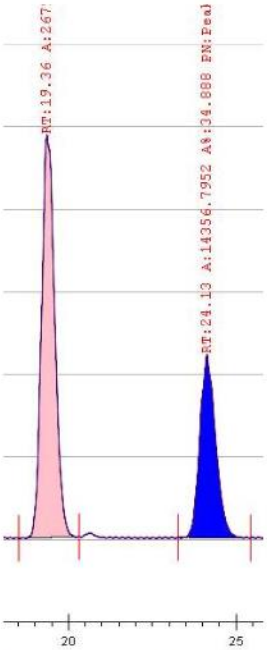


(*R*)-1-[4-(*N*,*N*-diphenylamino)phenyl] -5-methyl-3-phenylhexa-3,4-dien-1-ol (1.164). Prepared according to the general procedure above with *N*,*N*-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (111.4 mg, 0.30 mmol, 1 equiv), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford a dark yellow oil (111.2 mg, 86% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.8 Hz, 1H), 7.40 – 7.29 (m, 4H), 7.28 – 7.15 (m, 10H), 7.09 – 7.05 (m, 2H), 7.03 – 6.96 (m, 2H), 4.85 (app t, *J* = 6.6 Hz, 1H), 2.95 – 2.83 (m, 2H), 2.23 (s, 1H), 1.78 (s, 3H), 1.76 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 190.6, 153.5, 148.0, 147.3, 146.3, 143.5, 138.2, 137.6, 131.5, 130.7, 129.9, 129.3, 129.2, 129.1, 128.5, 127.2, 126.7, 126.5, 126.2, 125.3, 124.3, 124.2, 123.0, 122.8, 119.5, 100.4, 99.4, 72.6, 40.4, 20.6, 20.4. **IR** (neat) ν_{max} 1689 (m), 1581 (s), 1505 (m), 1487 (s), 1448 (m), 1313 (m), 1271 (s), 826 (m), 753 (s), 693 (s), 622 (m) cm^{-1}. **HRMS** (DART+) for $C_{31}H_{28}N$ $[M+H-H_2O]^+$ calculated: 414.2216, found: 414.2208. **$[\alpha]_D^{20}$:** +14.5 (*c* = 5.56, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

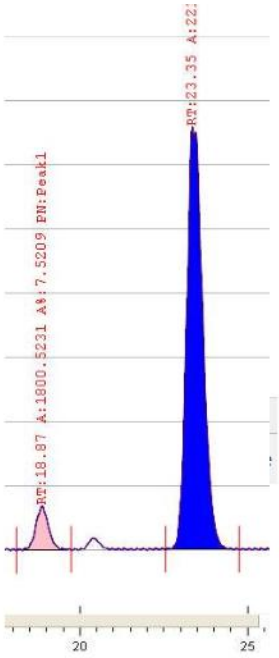
Chiral SFC (Chiracel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-1-[4-(*N*,*N*-diphenylamino)phenyl]-5-methyl-3-phenylhexa-3,4-dien-1-ol (**1.164**).

Enantiomer mixture

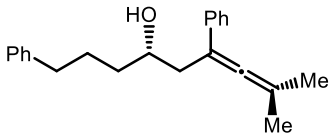


Peak No	% Area	Area	RT (min)
1	65.112	26794.267	19.36
2	34.888	14356.7952	24.13
Total:	100	41151.0622	

Standard conditions



Peak No	% Area	Area	RT (min)
1	7.5209	1800.5231	18.87
2	92.4791	22139.7678	23.35
Total:	100	23940.2909	

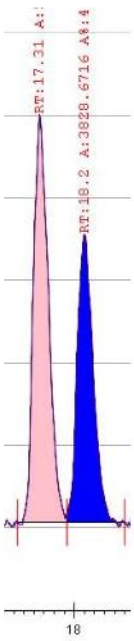


(*S*)-8-methyl-1,6-diphenylnona-6,7-dien-4-ol (1.165). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (73.9 mg, 0.3 mmol, 1 equiv), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and 2,2,2-trifluoroethanol (120.1 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (59.2 mg, 64% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.35 – 7.28 (m, 4H), 7.24 – 7.18 (m, 4H), 3.86 (dddd, *J* = 8.3, 8.3, 4.3, 4.3 Hz, 1H), 2.68 (app t, *J* = 7.7 Hz, 2H), 2.64 (dd, *J* = 15.0, 3.9 Hz, 1H), 2.50 (dd, *J* = 15.0, 8.5 Hz, 1H), 1.97 (s, 1H), 1.93 – 1.87 (m, 1H), 1.85 (s, 6H), 1.80 – 1.70 (m, 1H), 1.69 – 1.58 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.0, 142.5, 137.7, 128.6, 128.5, 128.4, 126.7, 126.2, 125.8, 100.7, 99.1, 70.2, 38.8, 36.6, 36.1, 27.7, 20.7, 20.5. **IR** (neat) ν_{max} 2933 (m), 2865 (w), 1718 (s), 1598 (m), 1493 (s), 1449 (s), 1362 (m), 1273 (m), 1173 (s), 755 (s), 699 (s) cm^{-1}. **HRMS** (DART+) for $C_{22}H_{25}$ $[M+H-H_2O]^+$ calculated: 289.1951, found: 289.1944. **$[\alpha]_D^{20}$:** +5.82 (*c* = 1.11, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

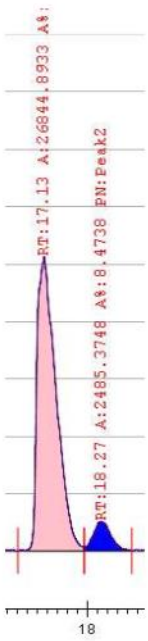
Chiral SFC (Chiracel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*S*)-8-methyl-1,6-diphenylnona-6,7-dien-4-ol (**1.165**).

Enantiomer mixture

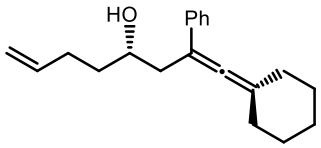


Peak No	% Area	Area	RT (min)
1	57.0975	5095.4566	17.31
2	42.9025	3828.6716	18.2
Total:	100	8924.1282	

Standard conditions



Peak No	% Area	Area	RT (min)
1	91.5262	26844.8933	17.13
2	8.4738	2485.3748	18.27
Total:	100	29330.2681	

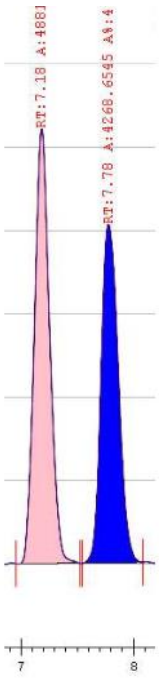


(*S*)-1-cyclohexylidene-2-phenylocta-1,7-dien-4-ol (1.166). Prepared according to the general procedure above with 2-but-3-enyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (54.6 mg, 0.3 mmol), methyl (1-(phenylethynyl)cyclohexyl) carbonate (155.0 mg, 0.60 mmol, 2 equiv), and 2,2,2-trifluoroethanol (120.1 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (32.6 mg, 38% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.31 (app t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 5.87 (dddd, *J* = 16.9, 10.1, 6.6, 6.6, 1H), 5.06 (dddd, *J* = 17.1, 1.7, 1.7, 1.7 Hz, 1H), 4.98 (dddd, *J* = 10.2, 2.2, 1.3, 1.3 Hz, 1H), 3.93 – 3.82 (m, 1H), 2.64 (dd, *J* = 15.1, 4.0 Hz, 1H), 2.51 (dd, *J* = 15.1, 8.3 Hz, 1H), 2.34 – 2.12 (m, 6H), 1.99 (s, 1H), 1.73 – 1.64 (m, 6H), 1.60 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.3, 138.8, 137.9, 128.5, 126.6, 126.1, 114.8, 106.7, 100.4, 69.9, 38.8, 36.1, 31.8, 31.6, 30.3, 27.87, 27.86, 26.2. **IR** (neat) ν_{max} 2924 (s), 2850 (m), 1639 (w), 1596 (w), 1504 (w), 1445 (m), 1054 (w), 907 (m), 758 (s), 693 (s) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{25}$ $[M+H-H_2O]^+$ calculated: 265.1951, found: 265.1956. **$[\alpha]_D^{20}$:** +7.2 (*c* = 0.83, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

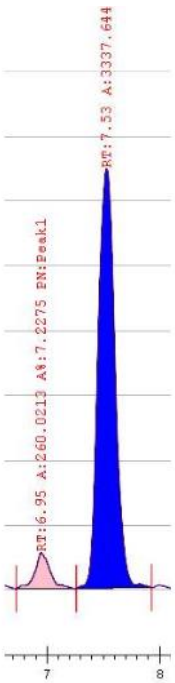
Chiral SFC (Chiracel OJ-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*S*)-1-cyclohexylidene-2-phenylocta-1,7-dien-4-ol (**1.166**).

Enantiomer mixture

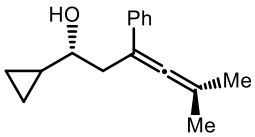


Peak No	% Area	Area	RT (min)
1	53.351	4881.9225	7.18
2	46.649	4268.6545	7.78
Total:	100	9150.577	

Standard conditions



Peak No	% Area	Area	RT (min)
1	7.2275	260.0213	6.95
2	92.7725	3337.644	7.53
Total:	100	3597.6653	

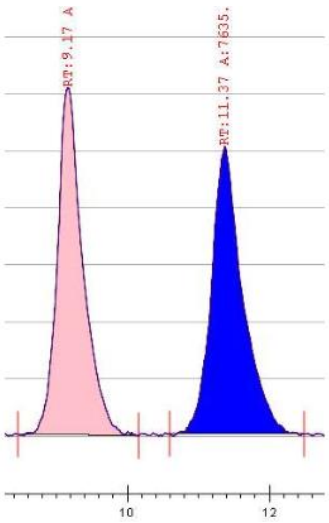


(*R*)-1-cyclopropyl-5-methyl-3-phenylhexa-3,4-dien-1-ol (1.167). Prepared according to the general procedure above with 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (60.0 mg, 0.30 mmol, 1 equiv), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (44.1 mg, 64% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.31 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.19 (app t, *J* = 7.3 Hz, 1H), 3.15 (dddd, *J* = 8.4, 3.7, 2.0, 2.0 Hz, 1H), 2.80 (dd, *J* = 15.0, 3.7 Hz, 1H), 2.65 (dd, *J* = 15.0, 8.6 Hz, 1H), 1.98 (d, *J* = 2.4 Hz, 1H), 1.839 (s, 3H), 1.835 (s, 3H), 1.01 (dddd, *J* = 9.8, 8.1, 8.1, 4.9 Hz, 1H), 0.58 – 0.48 (m, 2H), 0.41 – 0.34 (m, 1H), 0.29 – 0.22 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.2, 137.8, 128.5, 126.6, 126.2, 100.6, 99.0, 74.8, 38.7, 20.7, 20.5, 17.4, 2.9, 2.5. **IR** (neat) ν_{max} 1716 (m), 1215 (m), 1176 (m), 1025 (m), 961 (m), 748 (s), 697 (s), 665 (m) cm^{-1}. **HRMS** (DART+) for $C_{16}H_{19}$ $[M+H-H_2O]^+$ calculated: 211.1481, found: 211.1485. **$[\alpha]_D^{20}$:** +10.5 (*c* = 2.21, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

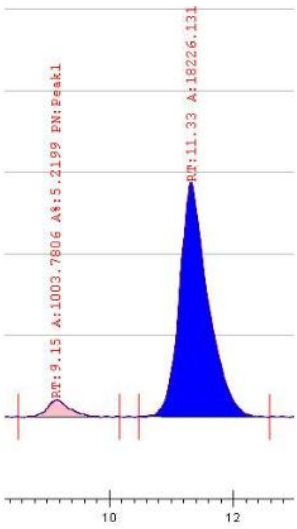
Chiral SFC (Chiracel AD-H, 6% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-1-cyclopropyl-5-methyl-3-phenylhexa-3,4-dien-1-ol (**1.167**).

Enantiomer mixture

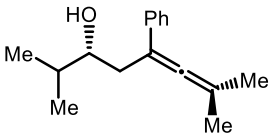


Peak No	% Area	Area	RT (min)
1	50.034	7646.0945	9.17
2	49.966	7635.7026	11.37
Total:	100	15281.7971	

Standard conditions



Peak No	% Area	Area	RT (min)
1	5.2199	1003.7806	9.15
2	94.7801	18226.1312	11.33
Total:	100	19229.9118	

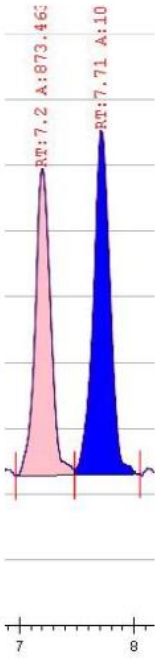


(*R*)-2,7-dimethyl-5-phenylocta-5,6-dien-3-ol (1.168). Prepared according to the general procedure above with 2-isopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (51.0 mg, 0.3 mmol), methyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate (131.0 mg, 0.60 mmol, 2 equiv), and 2,2,2-trifluoroethanol (120.1 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (30.8 mg, 45% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.3 Hz, 2H), 7.32 (app t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 3.60 (ddd, *J* = 9.0, 5.0, 3.0 Hz, 1H), 2.70 (dd, *J* = 15.0, 3.1 Hz, 1H), 2.42 (dd, *J* = 15.0, 9.3 Hz, 1H), 1.90 (s, 1H), 1.85 (s, 3H), 1.84 (s, 3H), 1.81 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.1, 137.8, 128.5, 126.7, 126.2, 101.0, 99.1, 74.7, 35.8, 33.3, 20.8, 20.5, 19.1, 17.6. **IR** (neat) ν_{max} 2956 (s), 2929 (s), 2905 (s), 2870 (s), 1492 (m), 1445 (m), 1362 (m), 1182 (m), 1051 (m), 998 (m), 760 (s), 693 (s) cm^{-1}. **HRMS** (DART+) for $C_{16}H_{21}$ $[M+H-H_2O]^+$ calculated: 213.1638, found: 213.1641. **$[\alpha]_D^{20}$:** +18.1 (*c* = 1.44, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

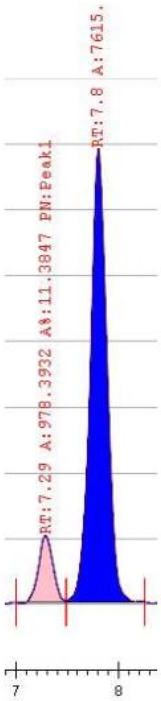
Chiral SFC (Chiracel AD-H, 6% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-2,7-dimethyl-5-phenylocta-5,6-dien-3-ol (**1.168**).

Enantiomer mixture

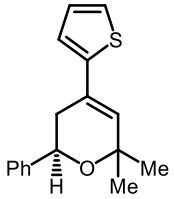


Peak No	% Area	Area	RT (min)
1	45.2149	873.4634	7.2
2	54.7851	1058.341	7.71
Total:	100	1931.8044	

Standard conditions



Peak No	% Area	Area	RT (min)
1	11.3847	978.3932	7.29
2	88.6153	7615.5013	7.8
Total:	100	8593.8945	

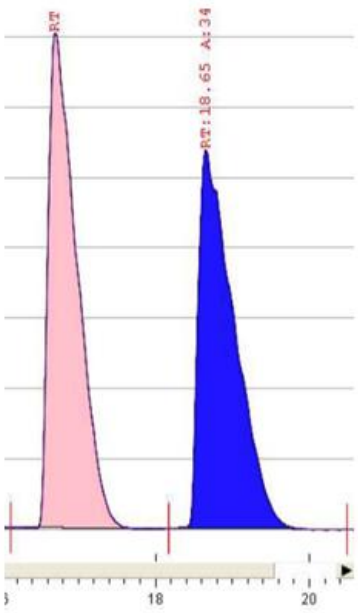


(*R*)-6,6-dimethyl-2-phenyl-4-(thiophen-2-yl)-3,6-dihydro-2*H*-pyran (1.172). Prepared according to the general procedure above with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61.2 mg, 0.30 mmol, 1 equiv), methyl (2-methyl-4-(thiophen-2-yl)but-3-yn-2-yl) carbonate (134.6 mg, 0.60 mmol, 2 equiv), and methanol (38.5 mg, 1.2 mmol, 4 equiv). The crude product was purified by silica gel column chromatography (0% → 30% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, yellow oil (57.6 mg, 71% yield), which spontaneously cyclized to the 3,6-dihydro-2*H*-pyran. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (d, J = 7.4 Hz, 2H), 7.39 (app t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.17 (dd, J = 4.5, 1.7 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.11 (d, J = 2.1 Hz, 1H), 4.84 (dd, J = 10.2, 3.6 Hz, 1H), 2.67 – 2.52 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.0, 142.8, 129.9, 128.6, 127.7, 127.6, 127.5, 126.4, 123.7, 122.3, 74.0, 71.1, 35.3, 29.9, 26.1. **IR** (neat) 2972 (s), 1495 (m), 1453 (m), 1379 (m), 1360 (m), 1239 (s), 1151 (s), 1068 (s), 1025 (m), 976 (m), 751 (s), 558 (m) cm^{-1}. **HRMS** (DART+) for $C_{17}H_{19}OS$ $[M+H]^+$ calculated: 271.1151, found: 271.1141. **$[\alpha]_D^{20}$:** +37.7 (c = 2.81, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

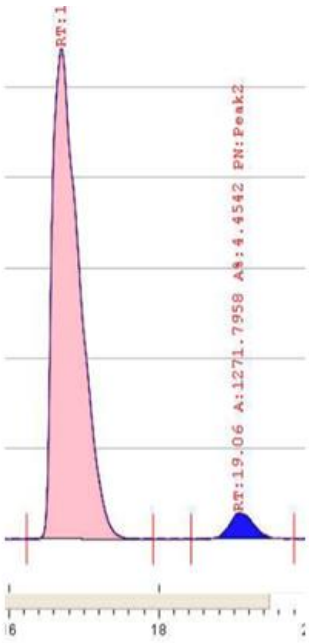
Chiral SFC (Chiracel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) analysis of (*R*)-6,6-dimethyl-2-phenyl-4-(thiophen-2-yl)-3,6-dihydro-2H-pyran (**1.172**).

Enantiomer mixture



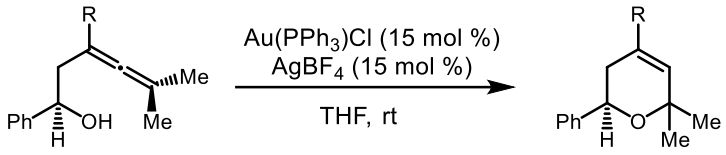
Peak No	% Area	Area	RT (min)
1	50.8503	36056.7765	16.7
2	49.1497	34850.9108	18.65
Total:	100	70907.6873	

Standard conditions

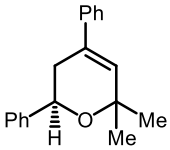


Peak No	% Area	Area	RT (min)
1	95.5458	27281.2136	16.7
2	4.4542	1271.7958	19.06
Total:	100	28553.0094	

1.8.2.6. General Procedure for the Gold-Catalyzed Cyclization of β-Hydroxy Allenes to 3,6-Dihydro-2H-pyran Derivatives



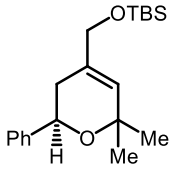
Following a modified literature procedure:[68] A vial equipped with a magnetic stir bar was charged with triphenylphosphinegold(I) chloride (0.15 equiv), silver tetrafluoroborate (0.15 equiv), and THF (0.015 *M*) and was allowed to stir for five minutes. A solution of β-hydroxy allene (1 equiv) in THF (0.1 *M*) was added, and the resulting solution was was allowed to stir at room temperature. Upon completion as checked by TLC, the reaction solution was filtered through a silica gel plug with Et_2O washing, concentrated under reduced pressure, and purified by silica gel column chromatography to afford pure product.



(*R*)-6,6-dimethyl-2,4-diphenyl-3,6-dihydro-2*H*-pyran (1.175). Prepared according to the general procedure above with (*R*)-5-methyl-1,3-diphenylhexa-3,4-dien-1-ol (**1.143**, 63.8 mg, 0.24 mmol, 1 equiv) in THF (2.4 mL), and triphenylphosphinegold(I) chloride (17.9 mg, 0.036 mmol, 0.15 equiv) and silver tetrafluoroborate (7.0 mg, 0.036 mmol, 0.15 equiv) in THF (2.4 mL). The crude product was purified by silica gel column chromatography (15% EtOAc in hexanes, stained in $KMnO_4$) to afford white solid (51.7 mg, 81% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.1 Hz, 2H), 7.43 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.40 (app t, *J* = 7.6 Hz, 2H), 7.35 (app t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H), 6.13 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.85 (dd, *J* = 9.4, 4.3 Hz, 1H), 2.69 – 2.55 (m, 2H),

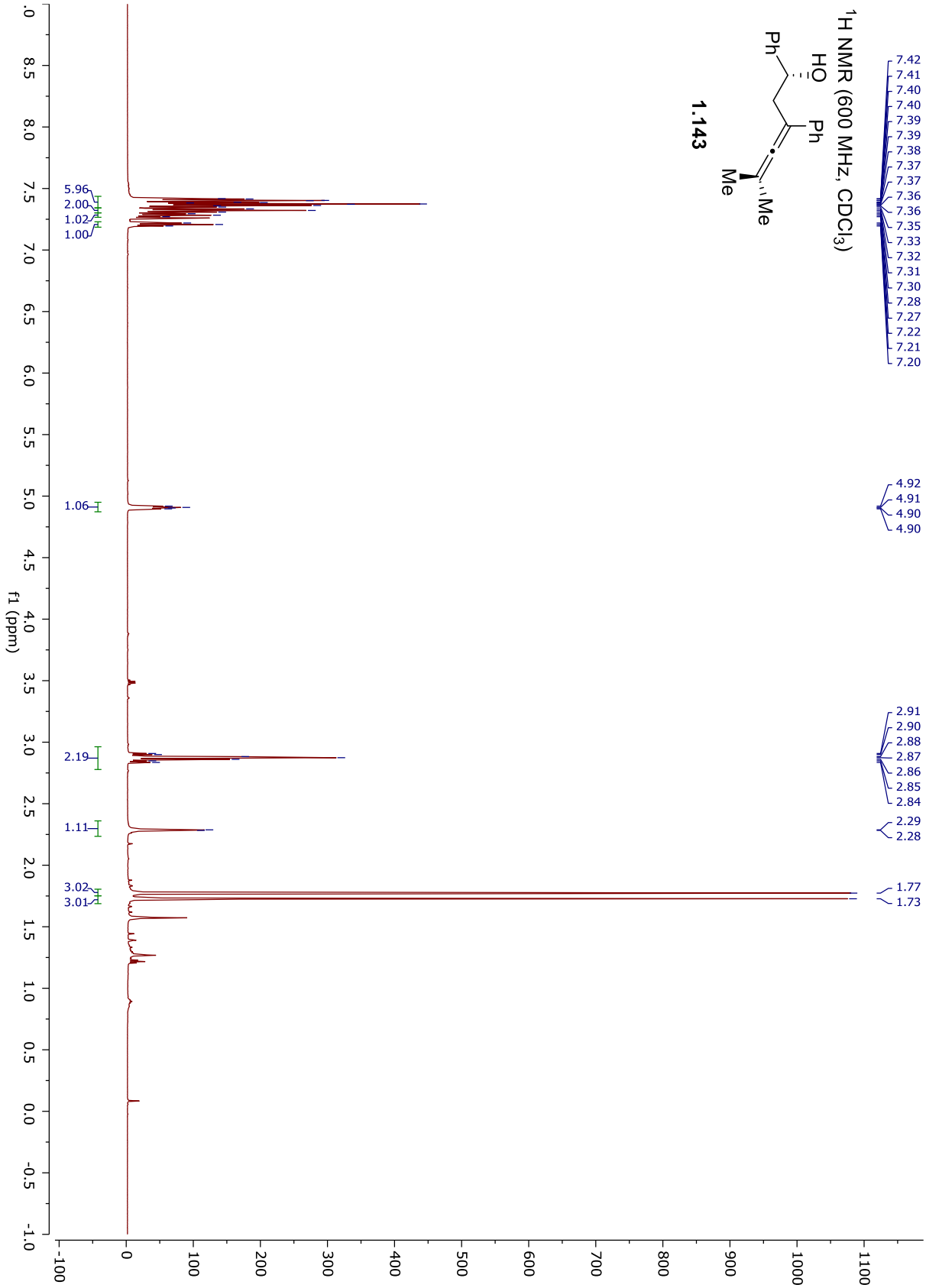
(68) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.

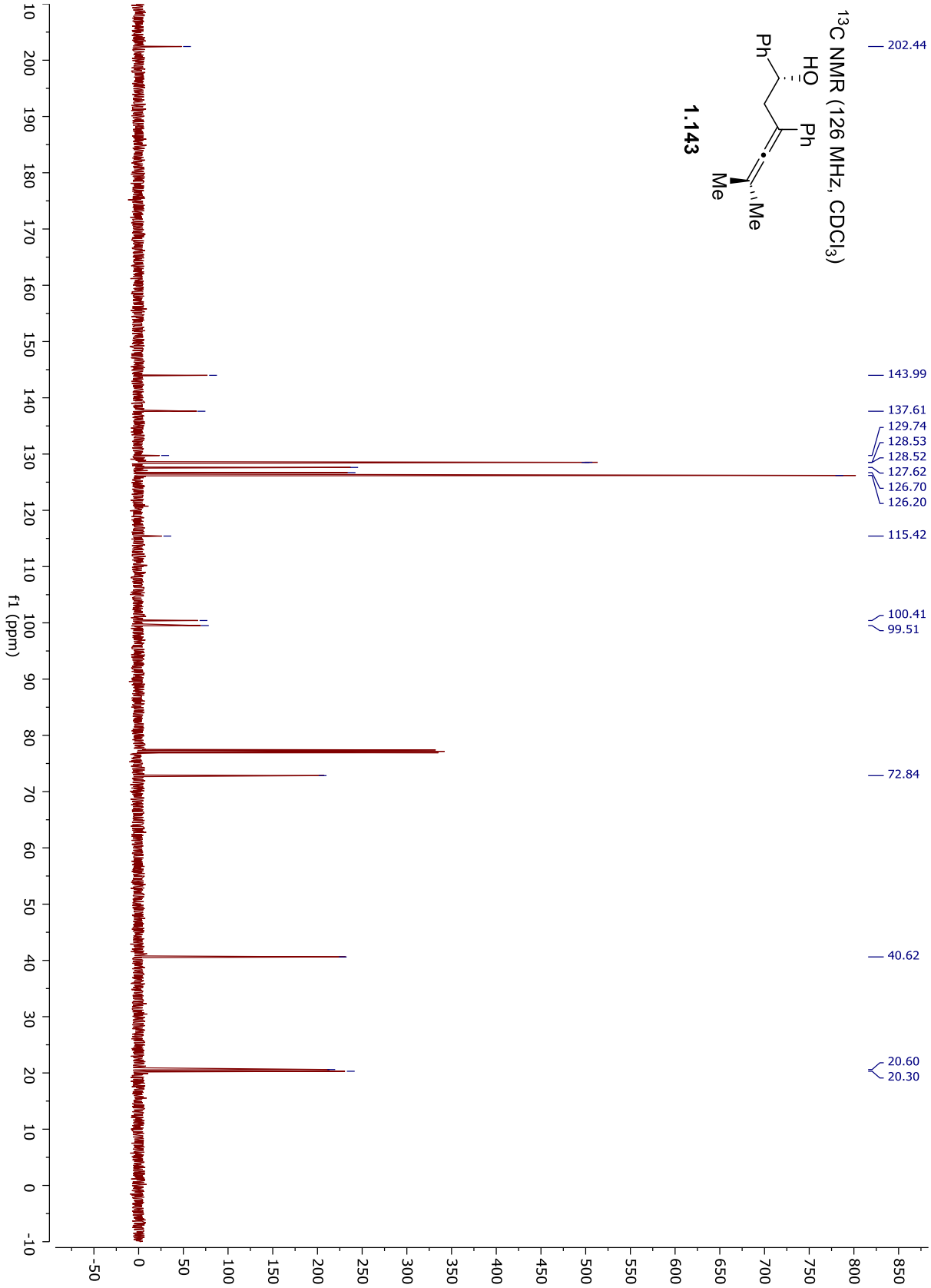
1.47 (s, 3H), 1.46 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.1, 140.4, 132.8, 131.2, 128.59, 128.56, 127.6, 127.4, 126.4, 125.1, 74.1, 71.4, 35.1, 30.0, 26.2. **IR** (neat) ν_{max} 2969 (m), 1494 (m), 1445 (m), 1376 (m), 1358 (m), 1160 (m), 1091 (m), 1067 (m), 1027 (m), 695 (s) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{19}$ $[M+H-H_2O]^+$ calculated: 247.1481, found: 247.1478. **$[\alpha]_D^{20}$:** +76.5 (*c* = 2.59, $CHCl_3$, *l* = 50 mm).

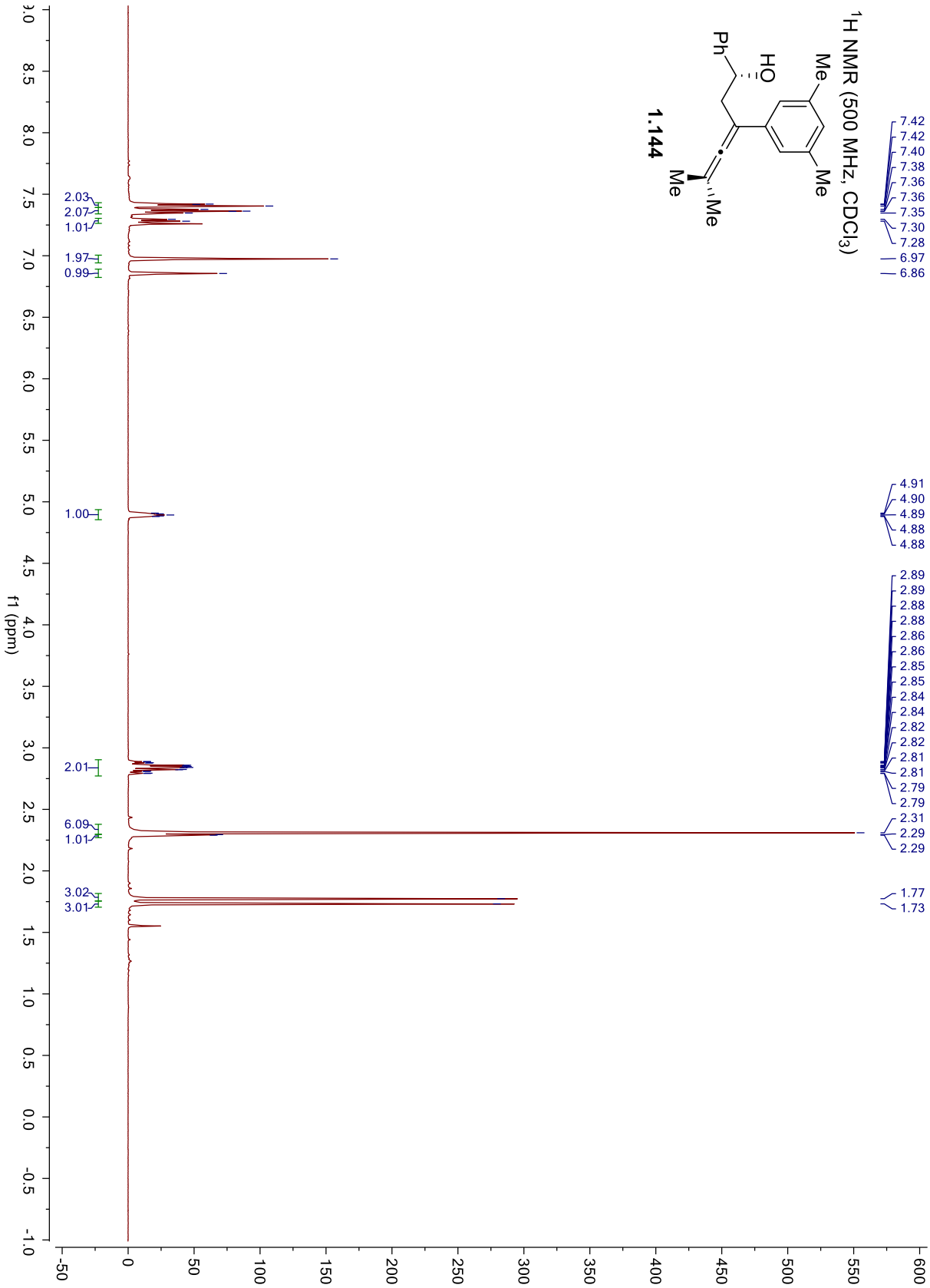


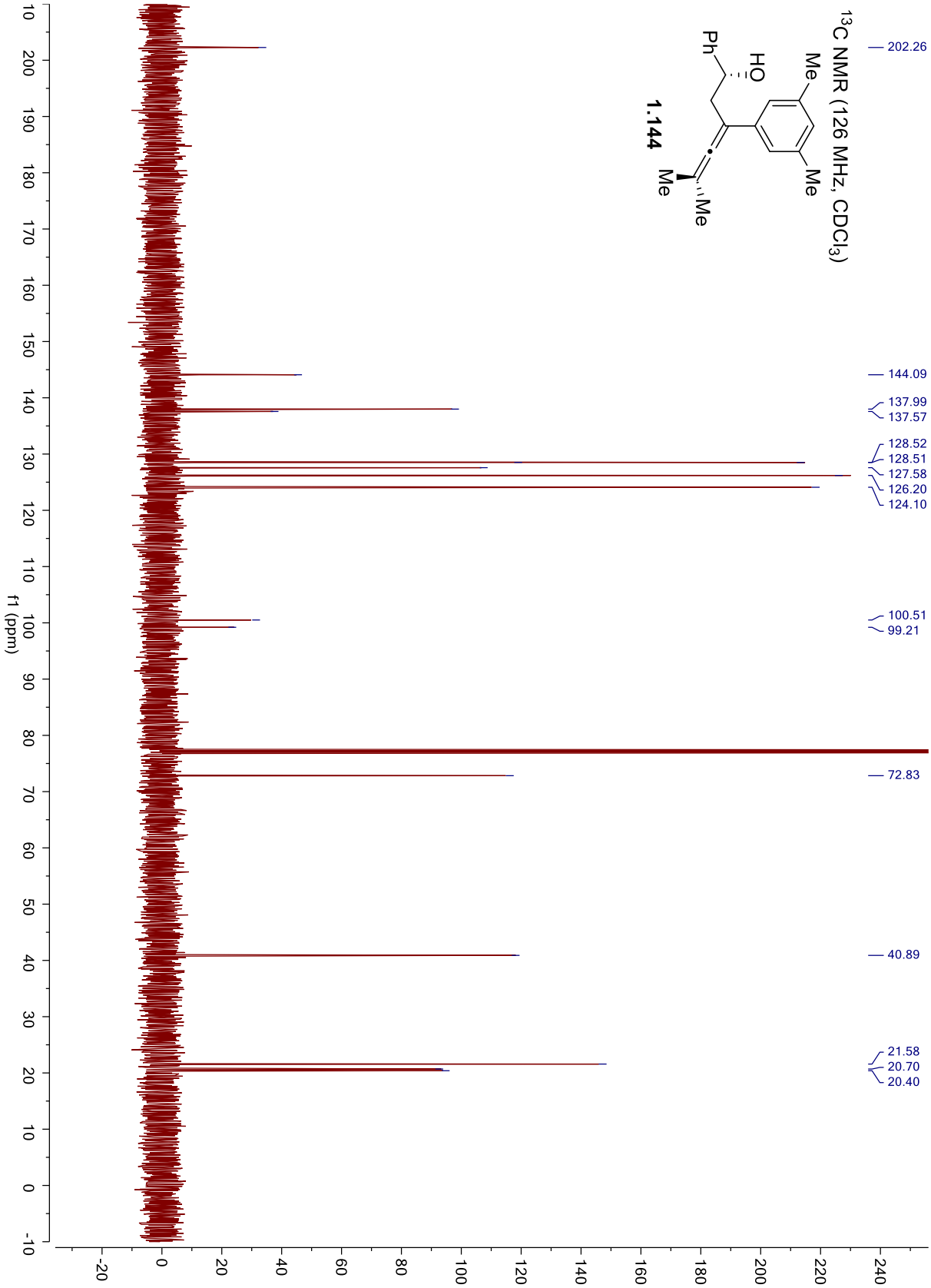
(*R*)-*tert*-butyl[(6,6-dimethyl-2-phenyl-3,6-dihydro-2*H*-pyran-4-yl)methoxy] dimethylsilane (1.176s). Prepared according to the general procedure above with (*R*)-3-{[(*tert*-butyldimethylsilyl)oxy]methyl}-5-methyl-1-phenylhexa-3,4-dien-1-ol (**1.157**, 133.0 mg, 0.40 mmol, 1 equiv) in THF (4 mL), and triphenylphosphinegold(I) chloride (29.7 mg, 0.060 mmol, 0.15 equiv) and silver tetrafluoroborate (11.7 mg, 0.060 mmol, 0.15 equiv) in THF (4 mL). The crude product was purified by silica gel column chromatography (15% EtOAc in hexanes, stained in $KMnO_4$) to afford clear, colorless oil (100.0 mg, 75% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.0 Hz, 2H), 7.35 (app t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 5.64 (m, 1H), 4.70 (dd, *J* = 9.2, 4.7 Hz, 1H), 4.08 (s, 2H), 2.21 – 2.06 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.2, 133.7, 128.6, 128.5, 127.5, 126.3, 73.6, 71.0, 66.3, 33.1, 29.8, 26.12, 26.10, 18.6, -5.0, -5.1. **IR** (neat) ν_{max} 2854 (m), 1470 (m), 1461 (m), 1251 (s), 1199 (m), 1177 (m), 1128 (s), 1065 (s), 1005 (m), 835 (s), 775 (s), cm^{-1}. **HRMS** (DART+) for $C_{20}H_{31}OSi$ $[M+H-H_2O]^+$ calculated: 315.2139, found: 315.2138. **$[\alpha]_D^{20}$:** +67.3 (*c* = 2.02, $CHCl_3$, *l* = 50 mm).

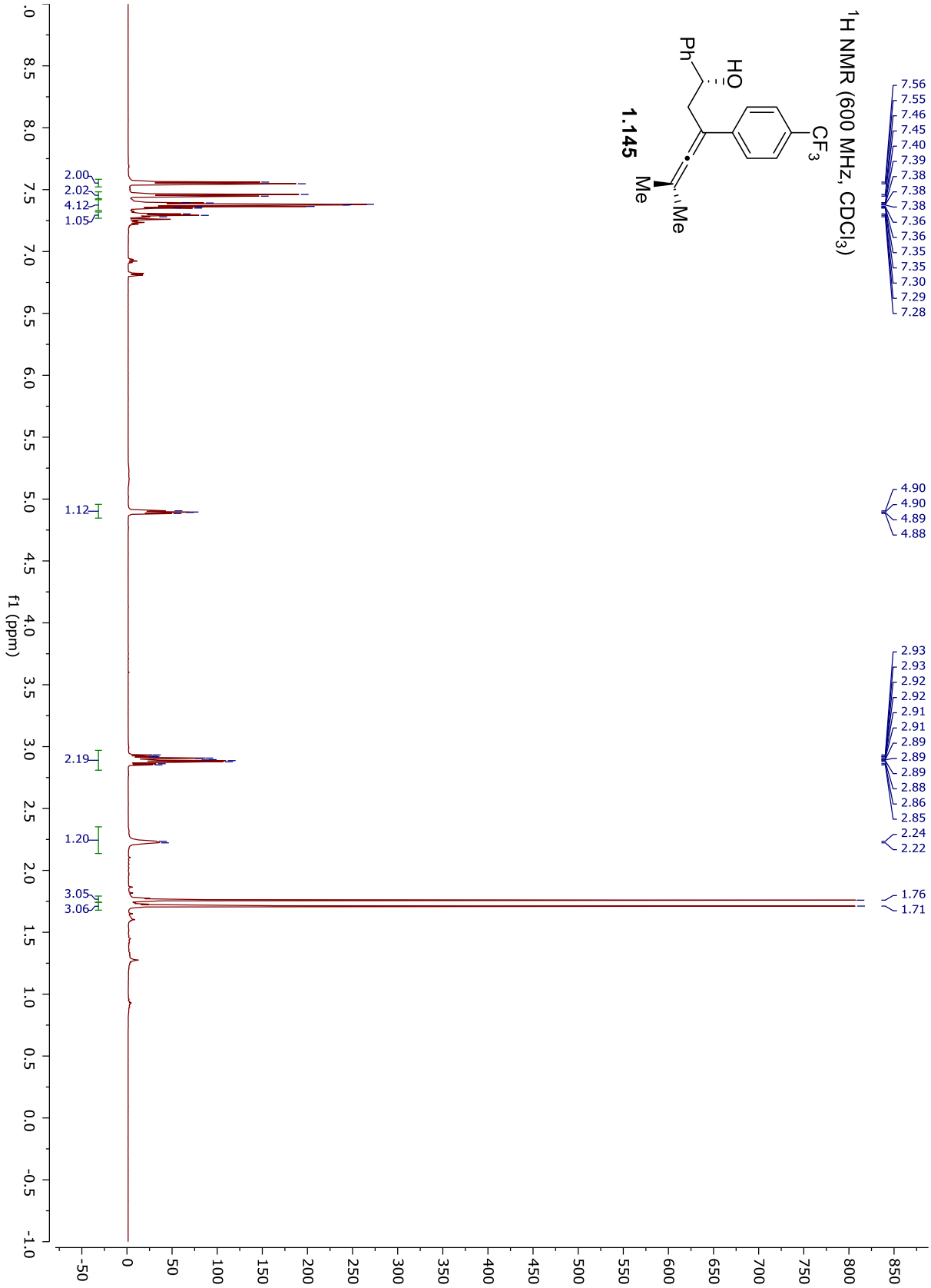
1.8.3. ^{1}H NMR and ^{13}C NMR Spectra

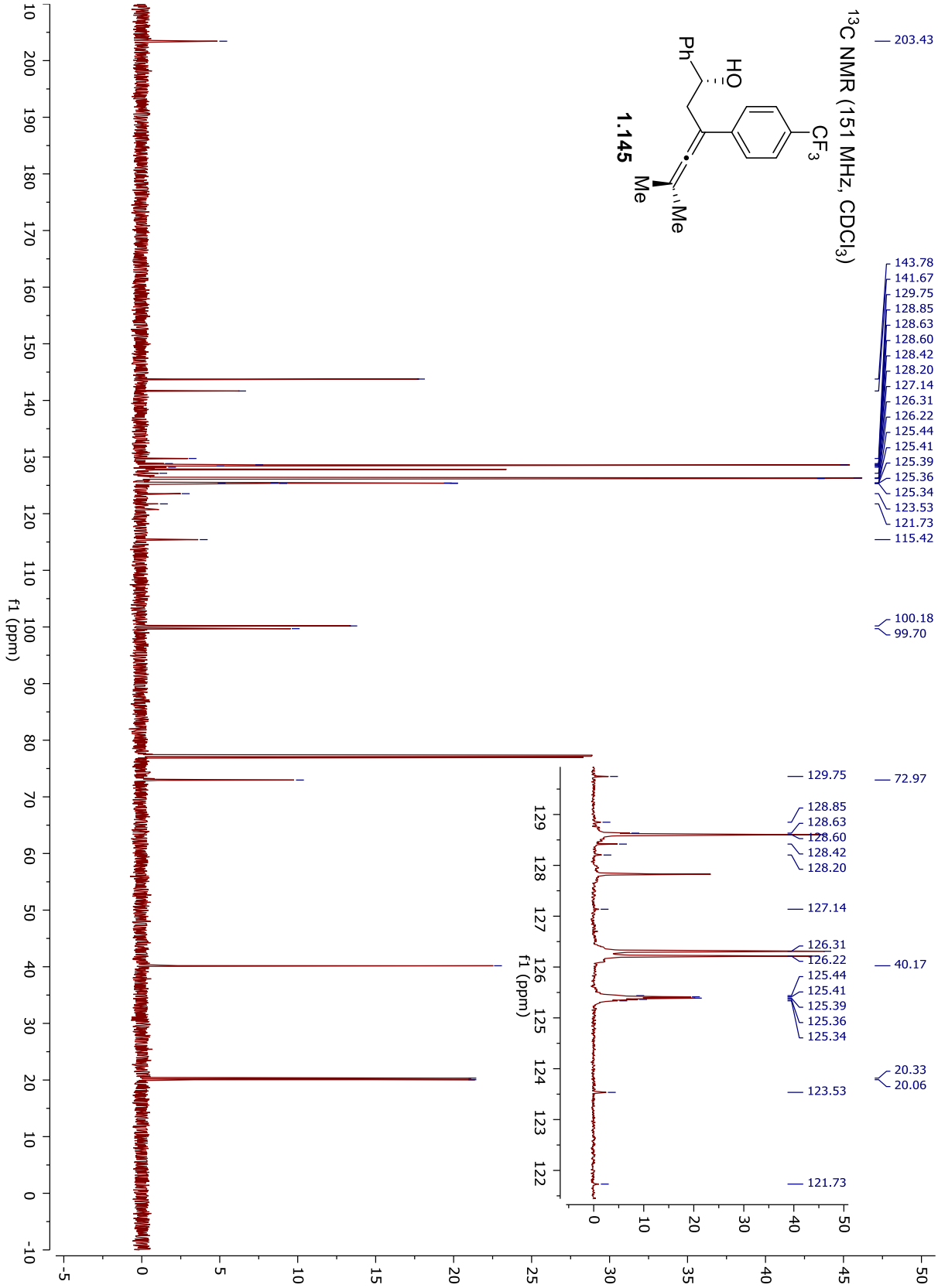

^{1}H NMR (600 MHz, CDCl$_3$)
1.143
HO
Ph
Ph
Me
Me
7.42
7.41
7.40
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.33
7.32
7.31
7.30
7.28
7.27
7.22
7.21
7.20
4.92
4.91
4.90
4.90
2.91
2.90
2.88
2.87
2.86
2.85
2.84
2.29
2.28
1.77
1.73
5.96
2.00
1.02
1.00
1.06
2.19
1.11
3.02
3.01
f1 (ppm)

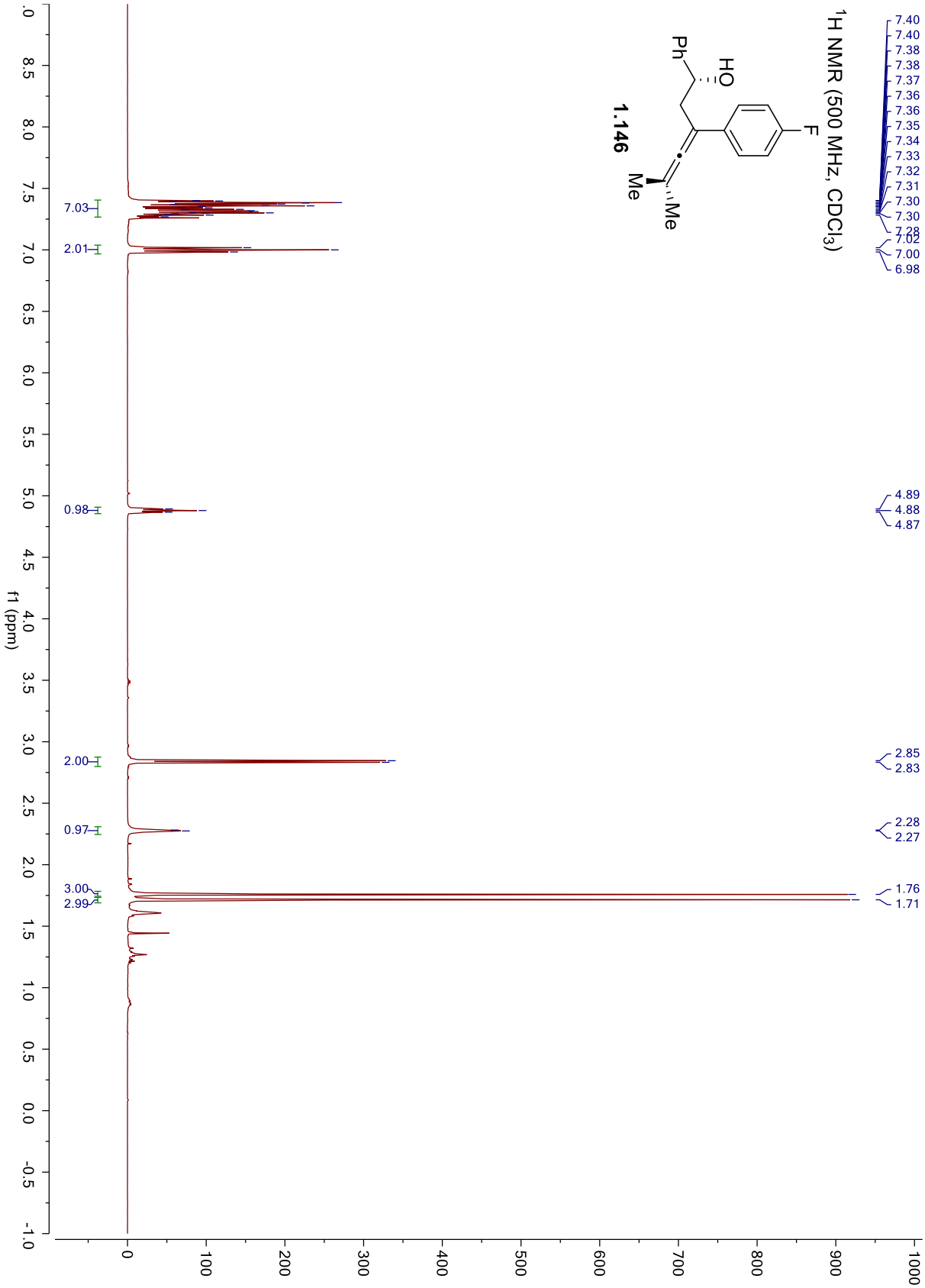

^{13}C NMR (126 MHz, CDCl$_3$)
1.143
HO
Ph
Ph
Me
Me
202.44
143.99
137.61
129.74
128.53
128.52
127.62
126.70
126.20
115.42
100.41
99.51
72.84
40.62
20.60
20.30
f1 (ppm)

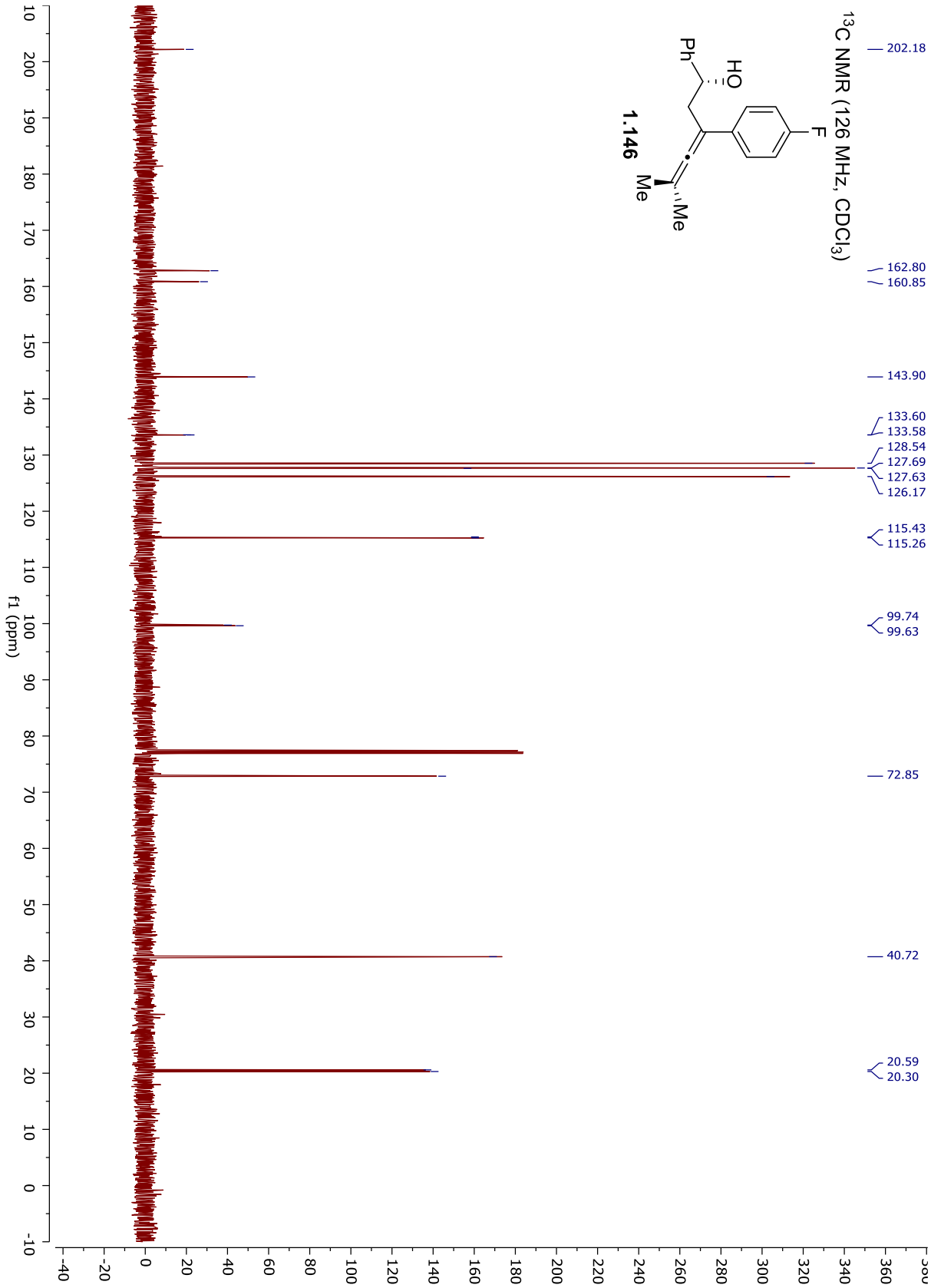

1H NMR (500 MHz, CDCl3)
1.144
Ph
HO
Me
Me
Me
Me
7.42
7.42
7.40
7.38
7.36
7.36
7.35
7.30
7.28
6.97
6.86
4.91
4.90
4.89
4.88
4.88
2.89
2.89
2.88
2.88
2.86
2.86
2.85
2.85
2.84
2.84
2.82
2.82
2.81
2.81
2.79
2.79
2.31
2.29
2.29
1.77
1.73
2.03
2.07
1.01
1.97
0.99
1.00
2.01
6.09
1.01
3.02
3.01
f1 (ppm)

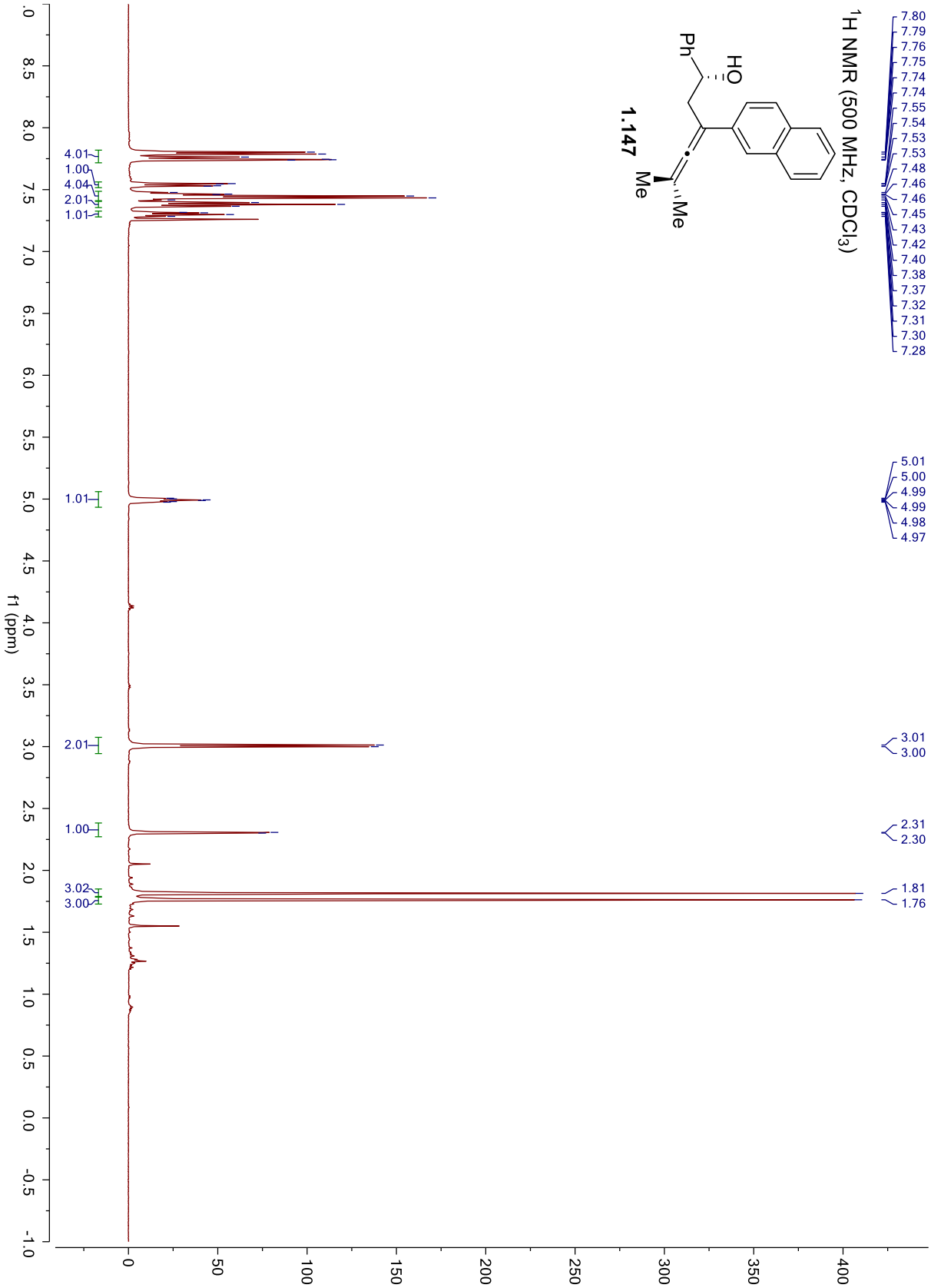

^{13}C NMR (126 MHz, CDCl$_3$)
1.144
Ph
HO
Me
Me
Me
Me
202.26
144.09
137.99
137.57
128.52
128.51
127.58
126.20
124.10
100.51
99.21
72.83
40.89
21.58
20.70
20.40
f1 (ppm)

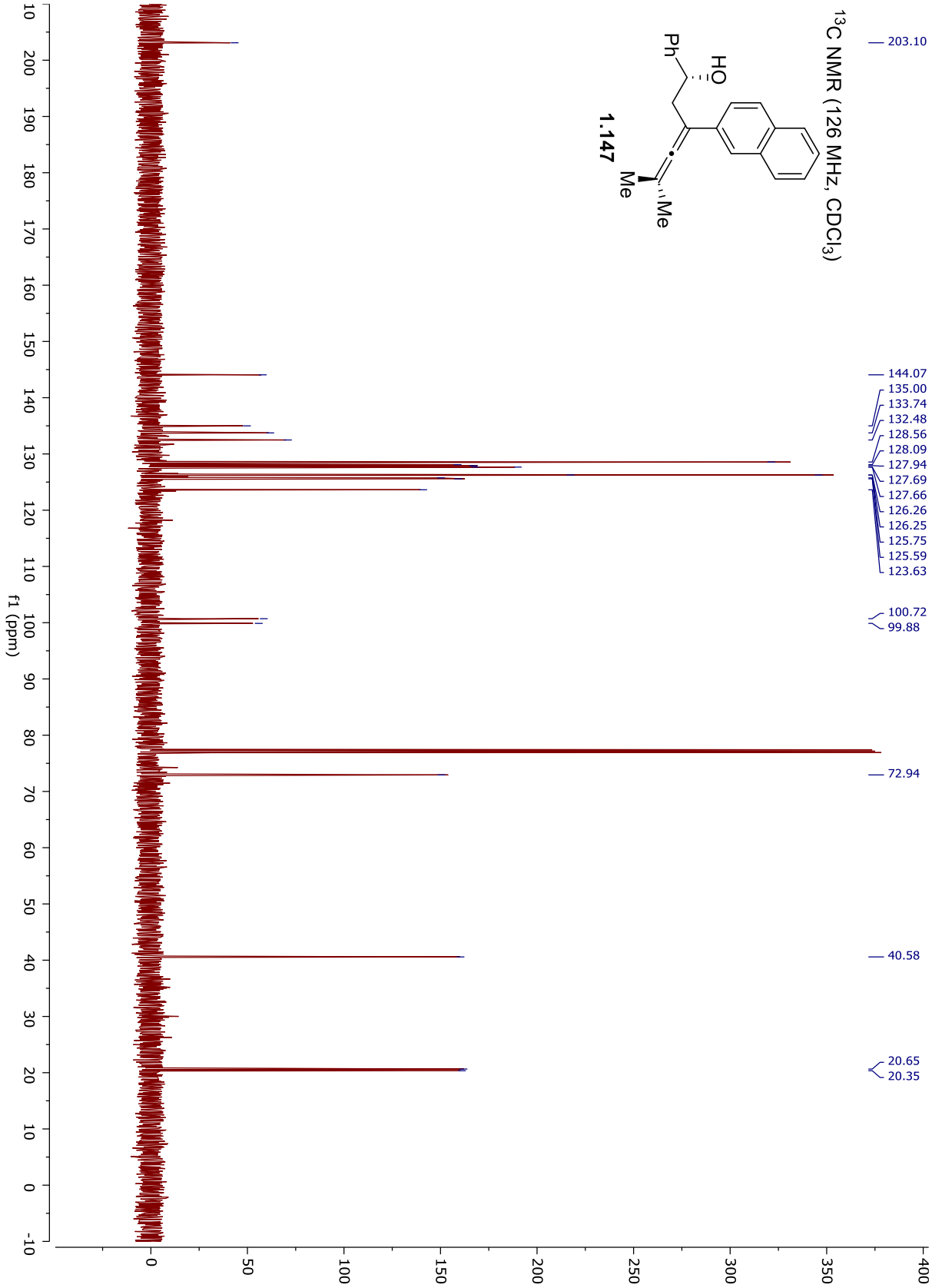

^{1}H NMR (600 MHz, CDCl$_3$)
1.145
Ph
HO
CF$_3$
Me
Me
7.56
7.55
7.46
7.45
7.40
7.39
7.38
7.38
7.38
7.36
7.36
7.35
7.35
7.30
7.29
7.28
4.90
4.90
4.89
4.88
2.93
2.93
2.92
2.92
2.91
2.91
2.89
2.89
2.89
2.88
2.86
2.85
2.24
2.22
1.76
1.71
2.00
2.02
4.12
1.05
1.12
2.19
1.20
3.05
3.06
f1 (ppm)


^{13}C NMR (151 MHz, CDCl$_3$)
1.145
Ph
HO
CF$_3$
Me
Me
203.43
143.78
141.67
129.75
128.85
128.63
128.60
128.42
128.20
127.14
126.31
126.22
125.44
125.41
125.39
125.36
125.34
123.53
121.73
115.42
100.18
99.70
72.97
40.17
20.33
20.06
f1 (ppm)


^{1}H NMR (500 MHz, CDCl$_3$)
1.146
Ph
HO
F
Me
Me
7.40
7.40
7.38
7.38
7.37
7.36
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.30
7.28
7.02
7.00
6.98
4.89
4.88
4.87
2.85
2.83
2.28
2.27
1.76
1.71
7.03
2.01
0.98
2.00
0.97
3.00
2.99
f1 (ppm)


^{13}C NMR (126 MHz, CDCl$_3$)
1.146
Ph
HO
F
Me
Me
202.18
162.80
160.85
143.90
133.60
133.58
128.54
127.69
127.63
126.17
115.43
115.26
99.74
99.63
72.85
40.72
20.59
20.30
f1 (ppm)


^{1}H NMR (500 MHz, CDCl$_3$)
1.147
Ph
HO
Me
Me
f1 (ppm)
7.80
7.79
7.76
7.75
7.74
7.74
7.55
7.54
7.53
7.53
7.48
7.46
7.46
7.45
7.43
7.42
7.40
7.38
7.37
7.32
7.31
7.30
7.28
5.01
5.00
4.99
4.99
4.98
4.97
3.01
3.00
2.31
2.30
1.81
1.76
4.01
1.00
4.04
2.01
1.01
1.01
2.01
1.00
3.02
3.00


^{13}C NMR (126 MHz, CDCl$_3$)
1.147
Ph
HO
Me
Me
203.10
144.07
135.00
133.74
132.48
128.56
128.09
127.94
127.69
127.66
126.26
126.25
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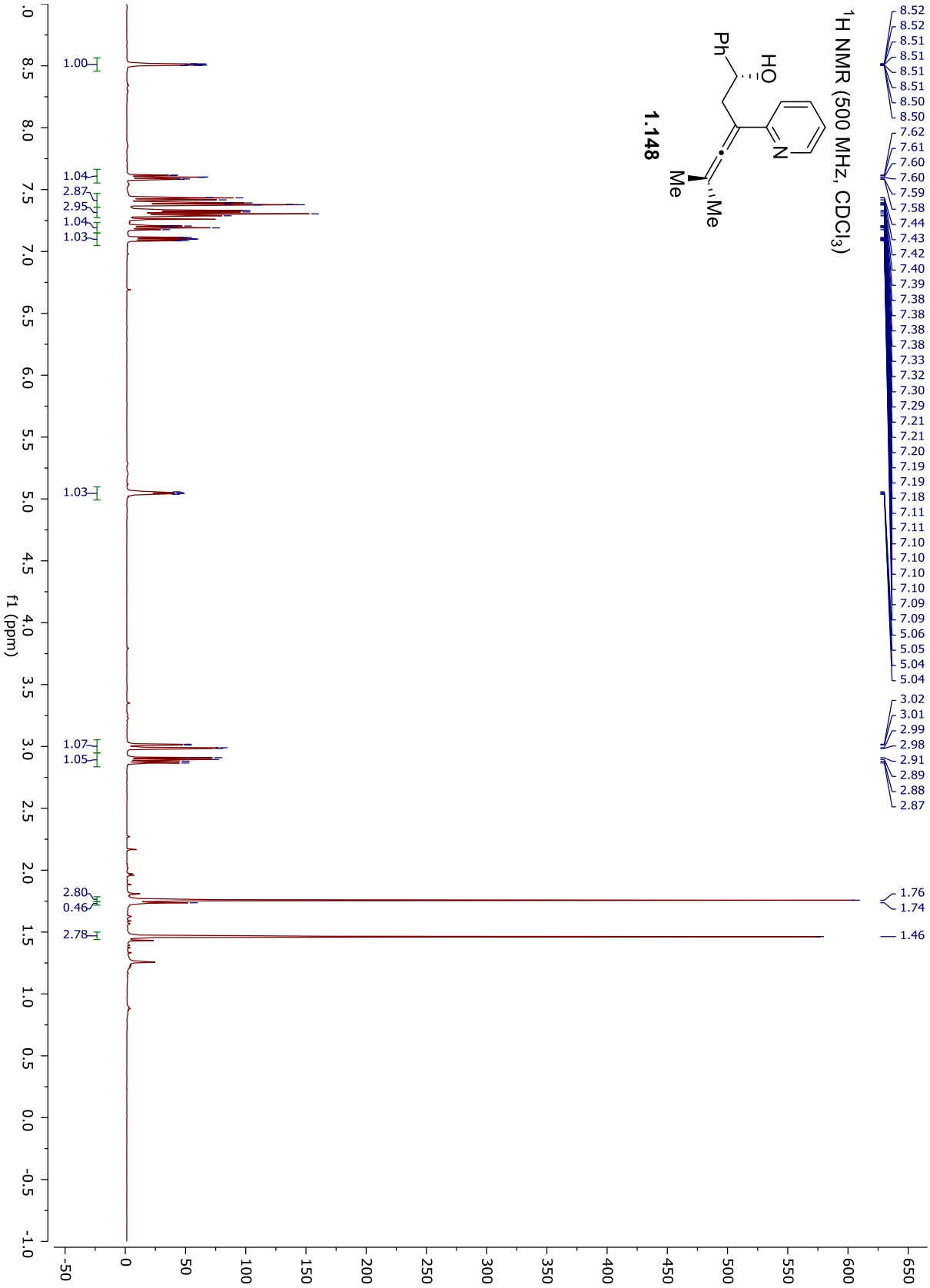
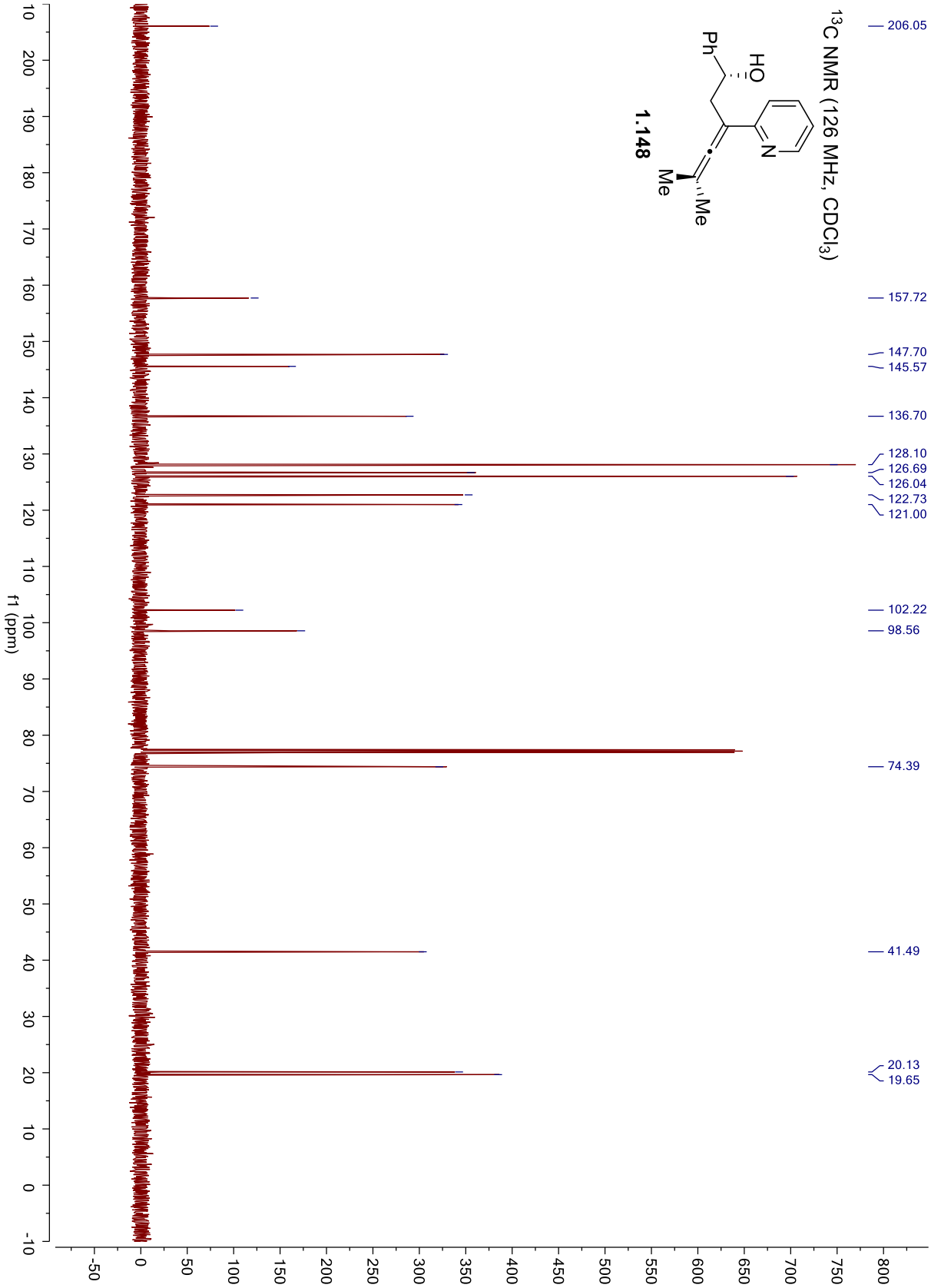
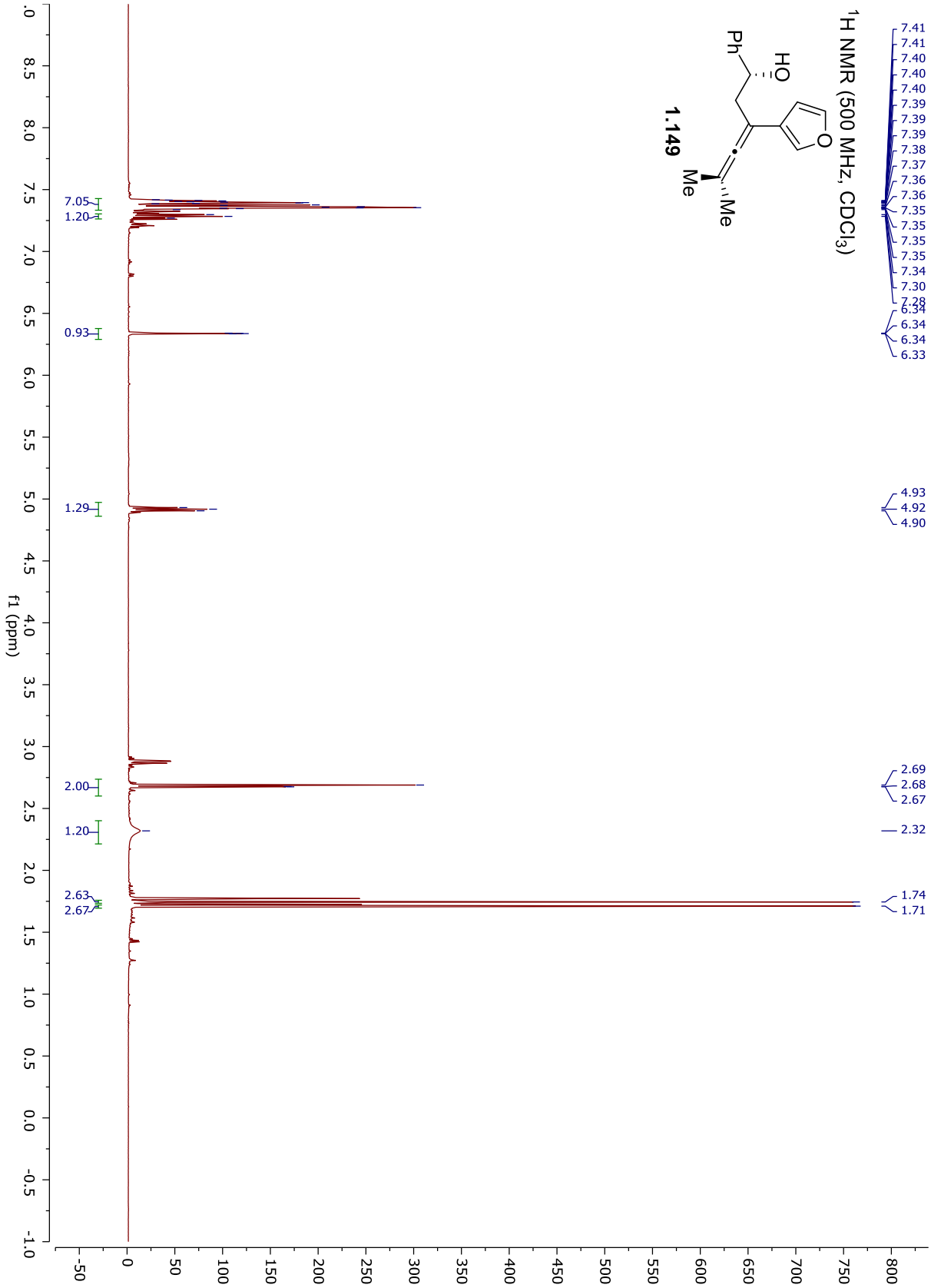
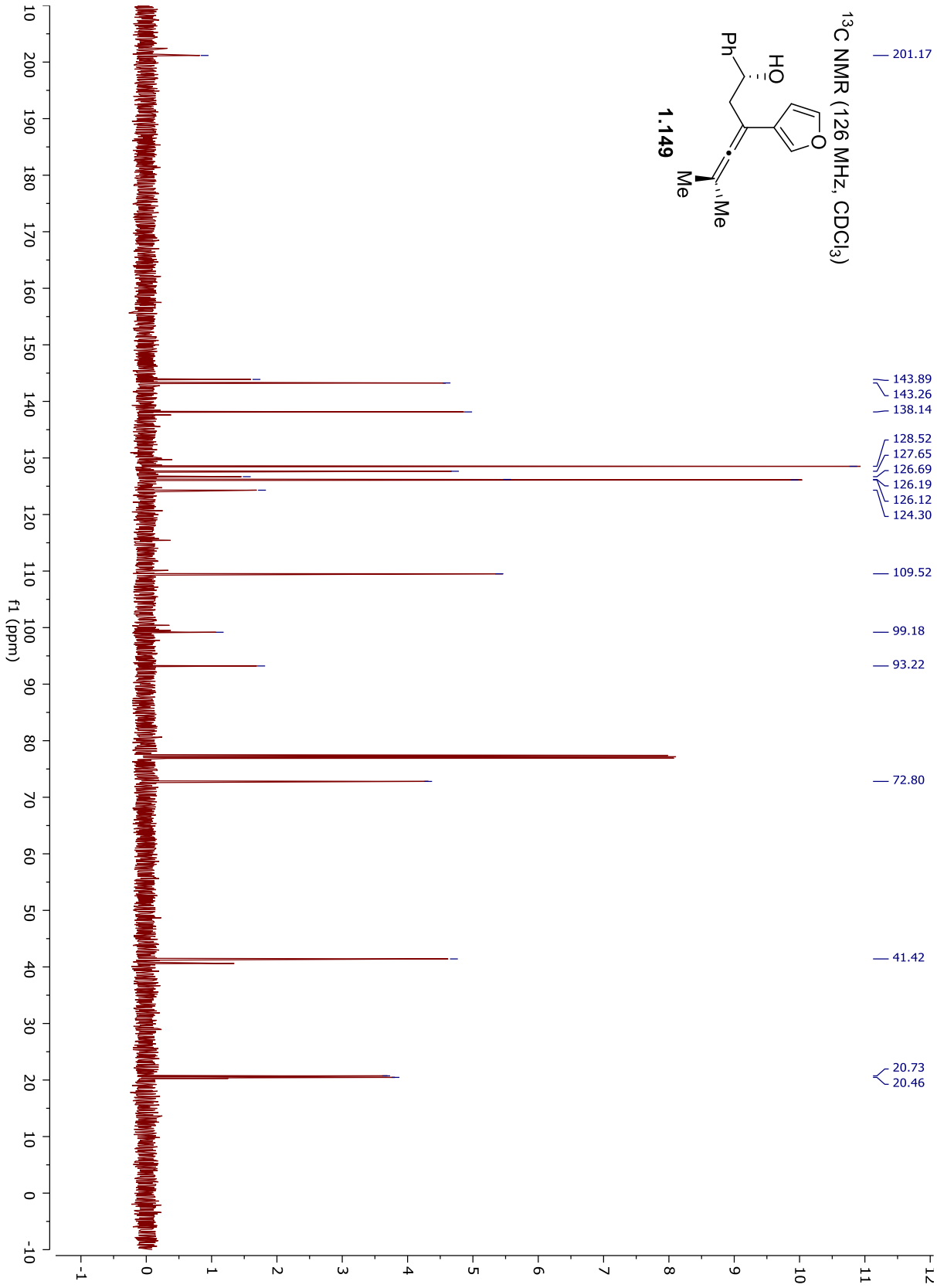
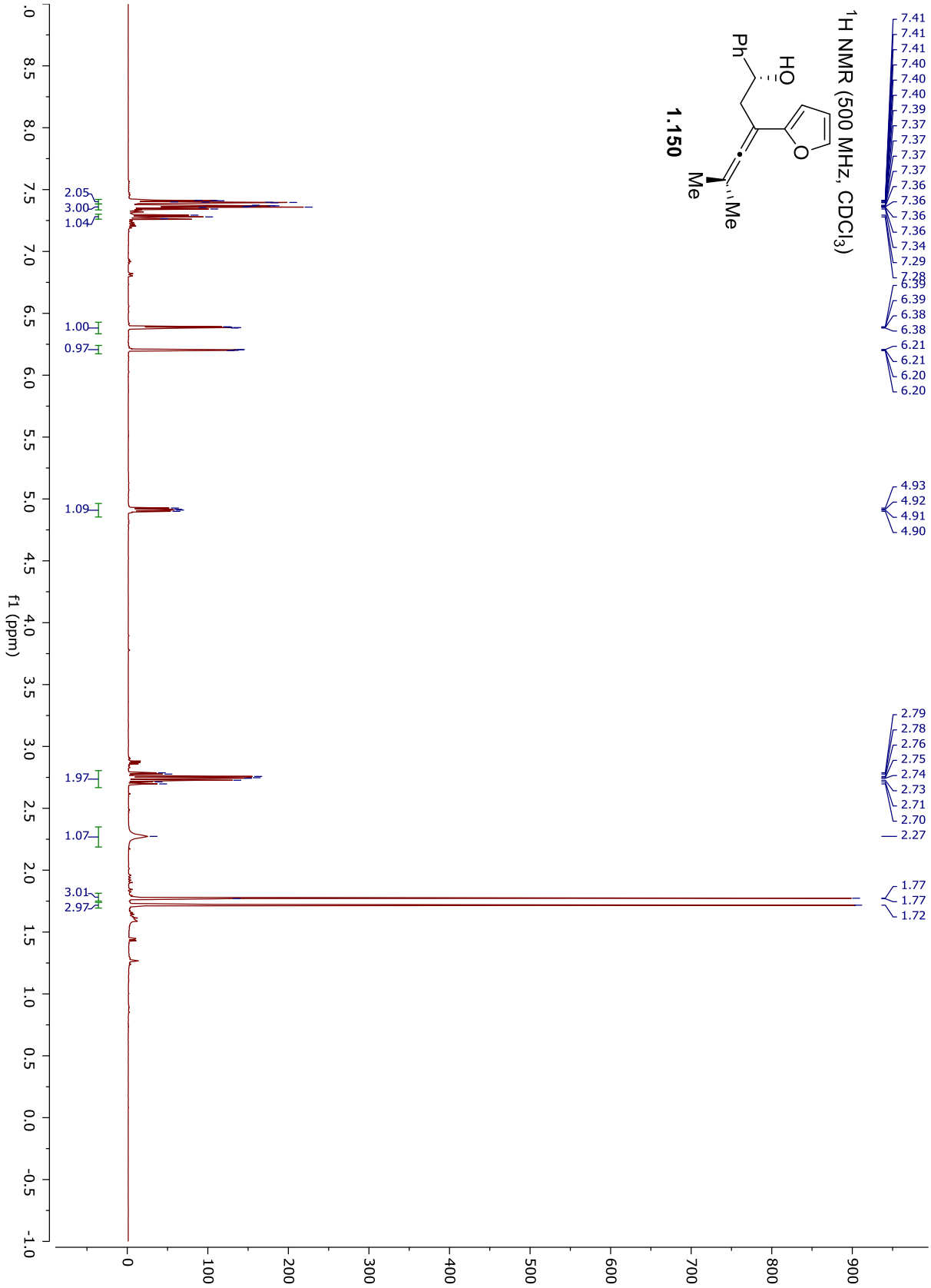
125.59
123.63
100.72
99.88
72.94
40.58
20.65
20.35
f1 (ppm)

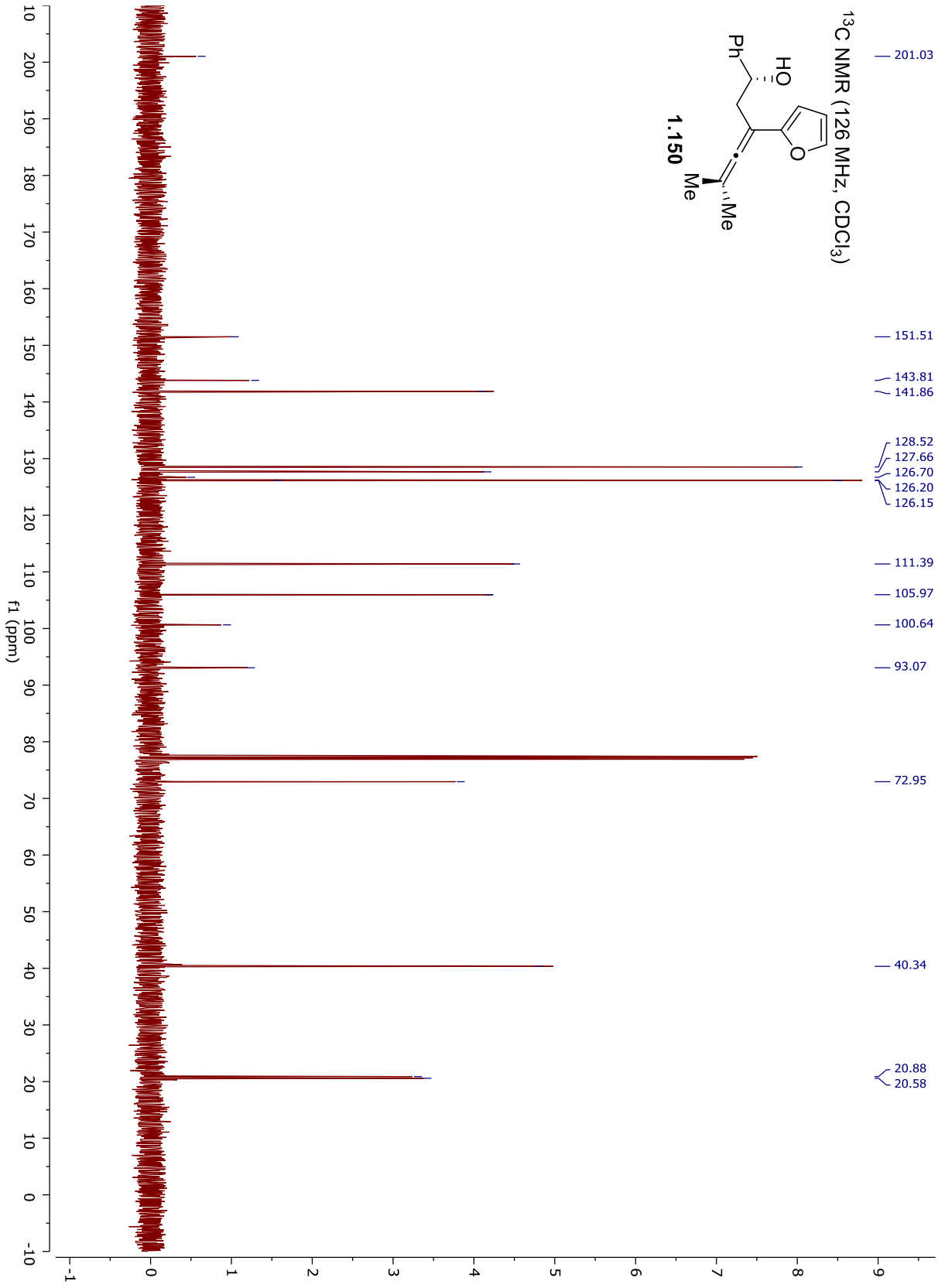

^{1}H NMR (500 MHz, CDCl$_3$)
1.148
HO
Ph
N
Me
Me
f1 (ppm)
1.00
1.04
2.87
2.95
1.04
1.03
1.03
1.07
1.05
2.80
0.46
2.78
8.52
8.52
8.51
8.51
8.51
8.51
8.51
8.50
8.50
7.62
7.61
7.60
7.60
7.59
7.58
7.44
7.43
7.42
7.40
7.39
7.38
7.38
7.38
7.38
7.33
7.32
7.30
7.29
7.21
7.21
7.20
7.19
7.19
7.18
7.11
7.11
7.10
7.10
7.10
7.10
7.09
7.09
5.06
5.05
5.04
5.04
3.02
3.01
2.99
2.98
2.91
2.89
2.88
2.87
1.76
1.74
1.46

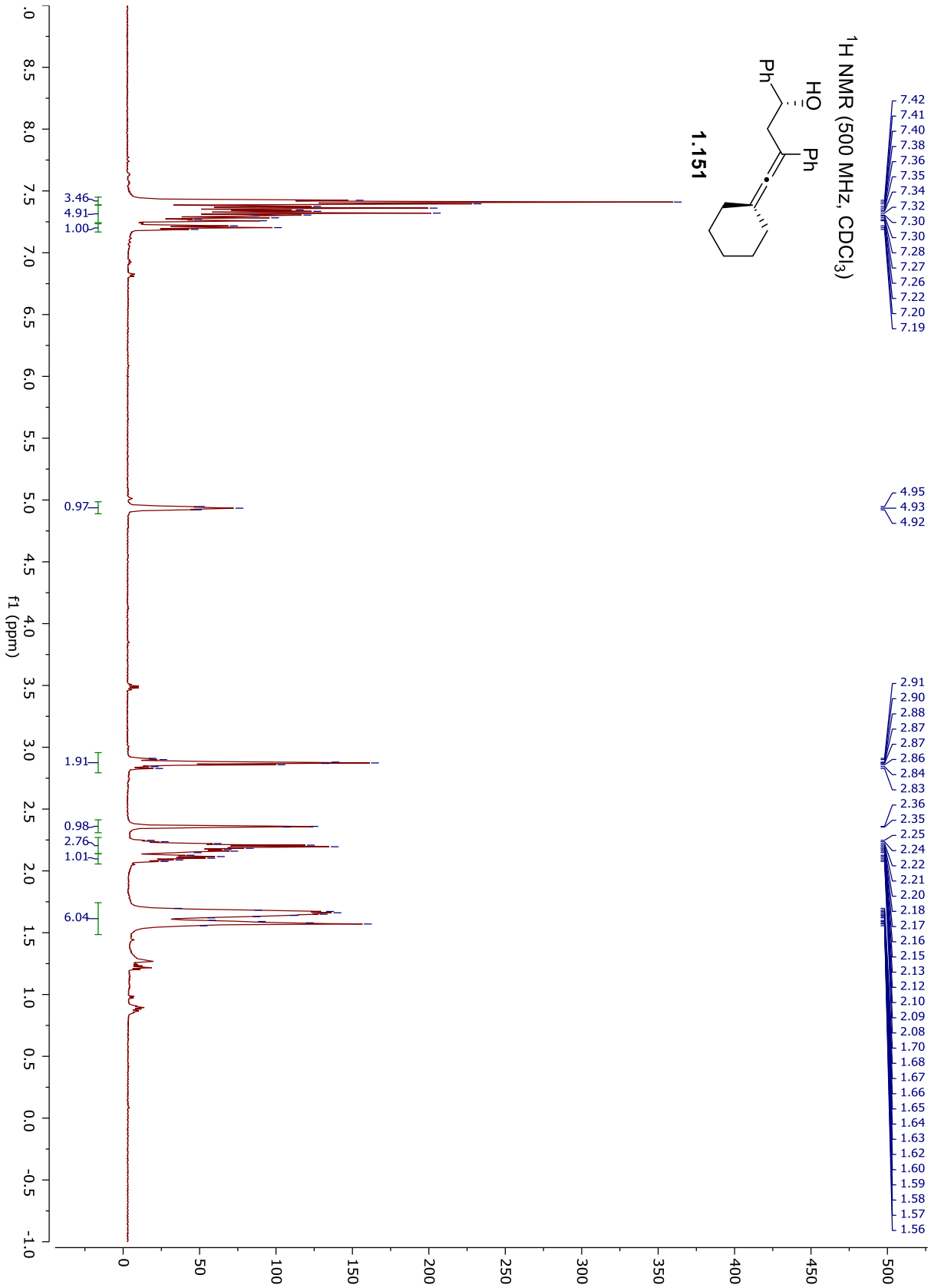

^{13}C NMR (126 MHz, CDCl$_3$)
1.148
Ph
HO
N
Me
Me
206.05
157.72
147.70
145.57
136.70
128.10
126.69
126.04
122.73
121.00
102.22
98.56
74.39
41.49
20.13
19.65
f1 (ppm)

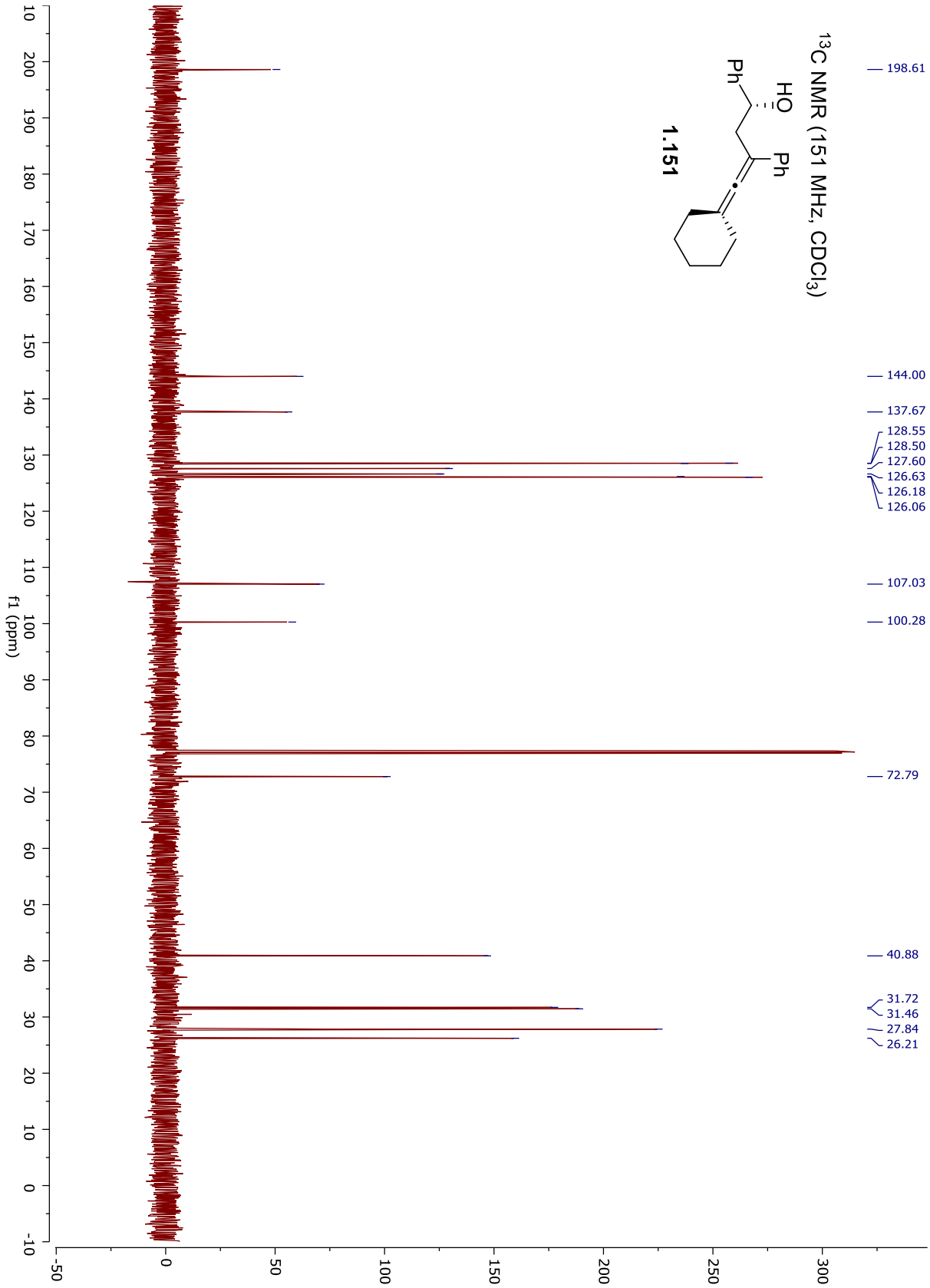

1H NMR (500 MHz, CDCl3)
HO
Ph
O
Me
Me
1.149
7.41
7.41
7.40
7.40
7.40
7.39
7.39
7.39
7.38
7.37
7.36
7.36
7.35
7.35
7.35
7.35
7.34
7.30
7.28
6.34
6.34
6.34
6.33
4.93
4.92
4.90
2.69
2.68
2.67
2.32
1.74
1.71
7.05
1.20
0.93
1.29
2.00
1.20
2.63
2.67
f1 (ppm)

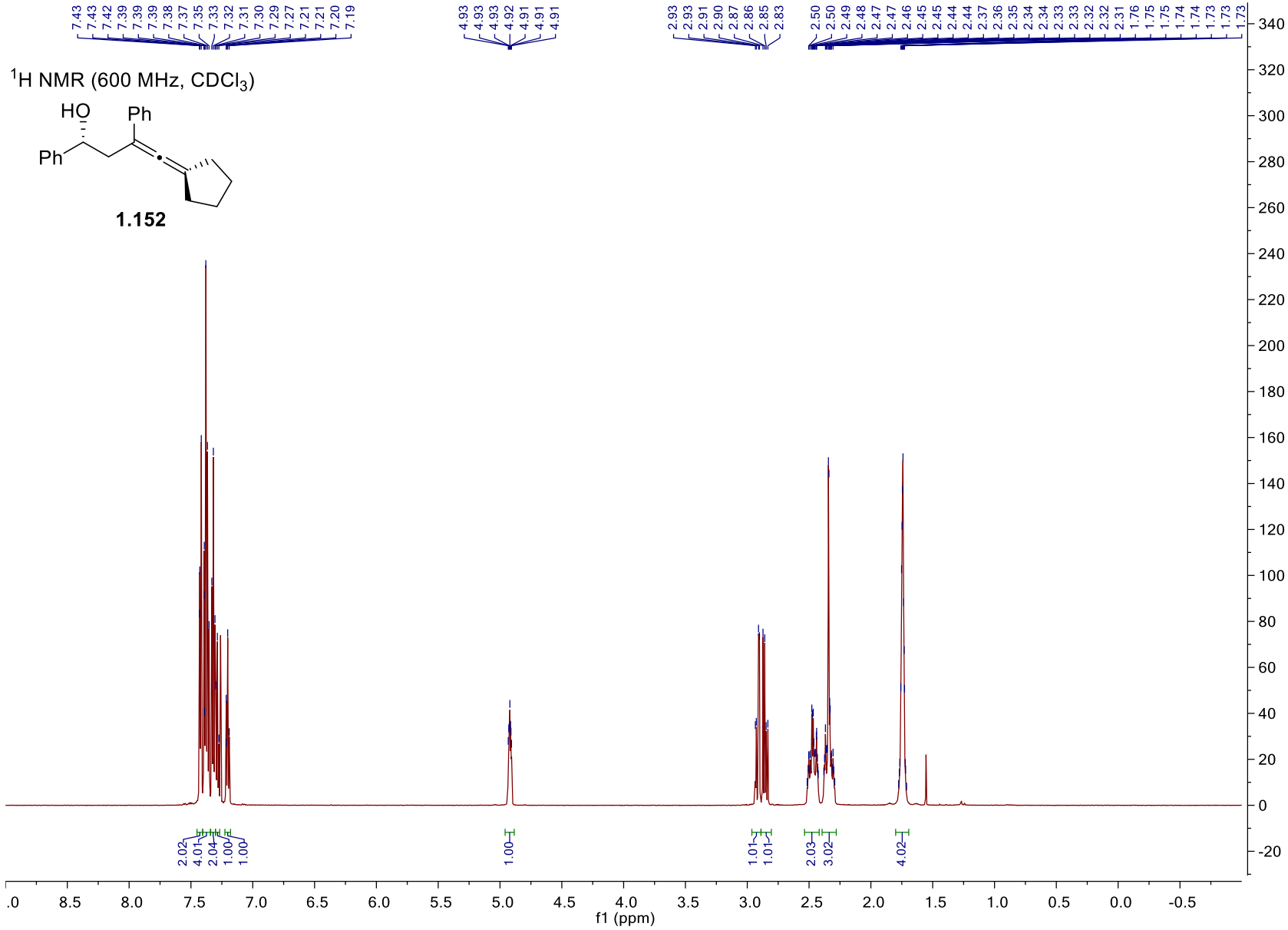

^{13}C NMR (126 MHz, CDCl$_3$)
1.149
Ph
HO
O
Me
Me
201.17
143.89
143.26
138.14
128.52
127.65
126.69
126.19
126.12
124.30
109.52
99.18
93.22
72.80
41.42
20.73
20.46
f1 (ppm)

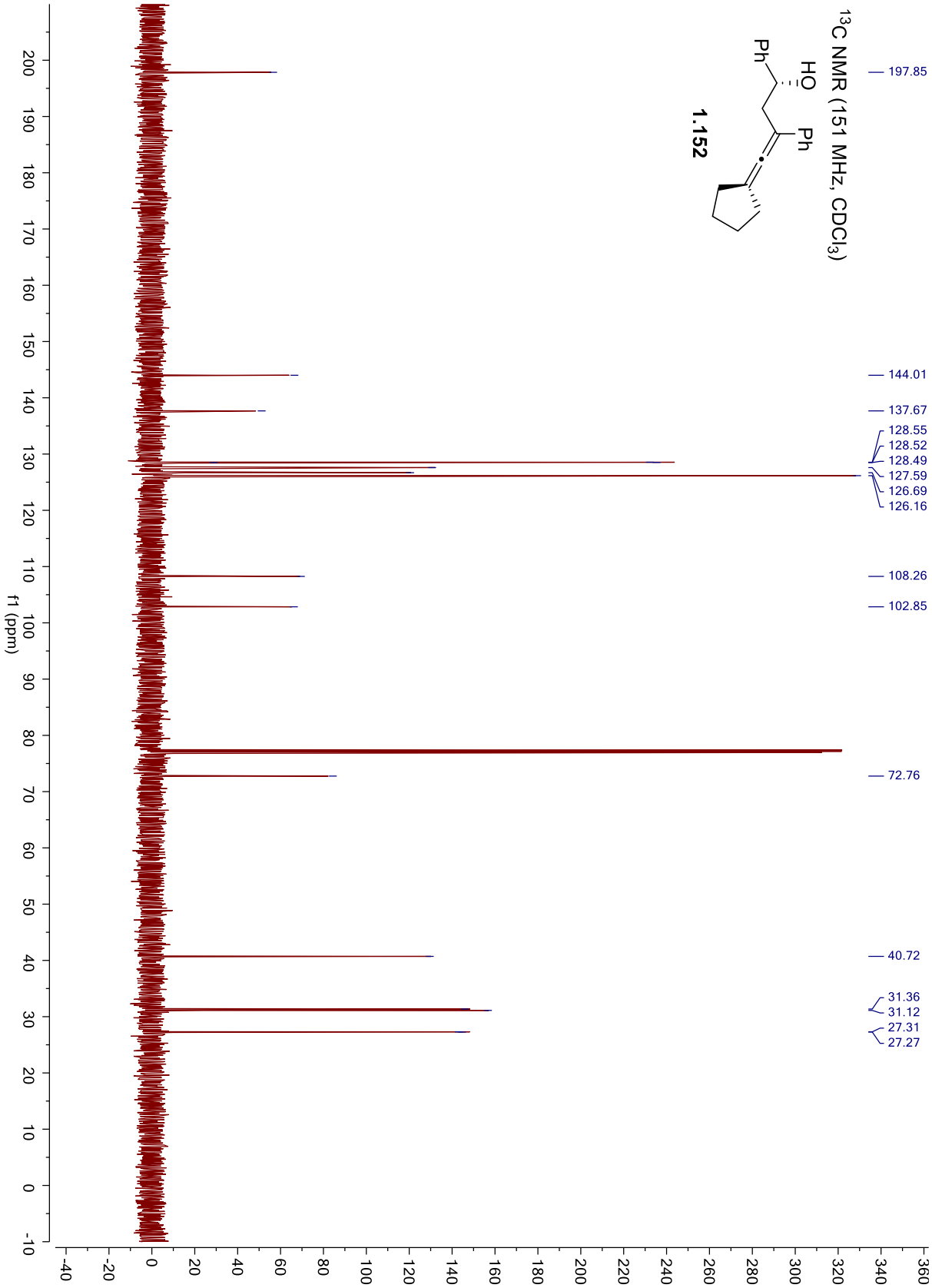

^{1}H NMR (500 MHz, CDCl$_3$)
1.150
Ph
HO
O
Me
Me
7.41
7.41
7.41
7.40
7.40
7.40
7.39
7.37
7.37
7.37
7.37
7.36
7.36
7.36
7.36
7.34
7.29
7.28
6.39
6.39
6.38
6.38
6.21
6.21
6.20
6.20
4.93
4.92
4.91
4.90
2.79
2.78
2.76
2.75
2.74
2.73
2.71
2.70
2.27
1.77
1.77
1.72
2.05
3.00
1.04
1.00
0.97
1.09
1.97
1.07
3.01
2.97
f1 (ppm)

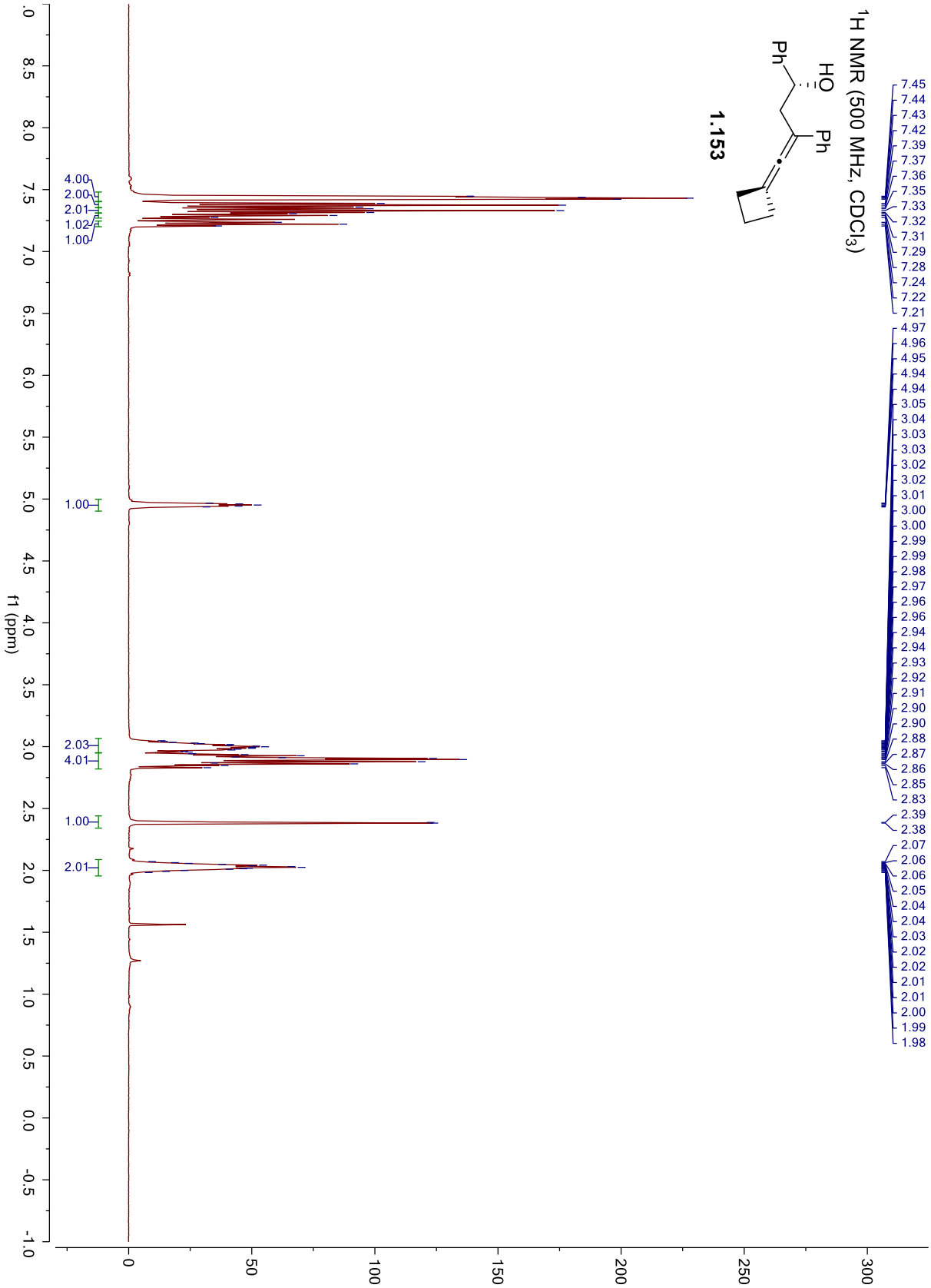

^{13}C NMR (126 MHz, CDCl$_3$)
Ph
HO
O
Me
Me
1.150
201.03
151.51
143.81
141.86
128.52
127.66
126.70
126.20
126.15
111.39
105.97
100.64
93.07
72.95
40.34
20.88
20.58
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
1.151
HO
Ph
Ph
7.42
7.41
7.40
7.38
7.36
7.35
7.34
7.32
7.30
7.30
7.28
7.27
7.26
7.22
7.20
7.19
4.95
4.93
4.92
2.91
2.90
2.88
2.87
2.87
2.86
2.84
2.83
2.36
2.35
2.25
2.24
2.22
2.21
2.20
2.18
2.17
2.16
2.15
2.13
2.12
2.10
2.09
2.08
1.70
1.68
1.67
1.66
1.65
1.64
1.63
1.62
1.60
1.59
1.58
1.57
1.56
3.46
4.91
1.00
0.97
1.91
0.98
2.76
1.01
6.04
f1 (ppm)


^{13}C NMR (151 MHz, CDCl$_3$)
1.151
Ph
HO
Ph
198.61
144.00
137.67
128.55
128.50
127.60
126.63
126.18
126.06
107.03
100.28
72.79
40.88
31.72
31.46
27.84
26.21
f1 (ppm)


7.43 7.43 7.42 7.39 7.39 7.39 7.38 7.37 7.35 7.33 7.32 7.31 7.30 7.29 7.27 7.21 7.21 7.20 7.19
4.93 4.93 4.93 4.92 4.91 4.91 4.91
2.93 2.93 2.91 2.90 2.87 2.86 2.85 2.83
2.50 2.50 2.49 2.48 2.47 2.47 2.46 2.45 2.45 2.44 2.44 2.37 2.36 2.35 2.34 2.34 2.33 2.33 2.32 2.32 2.31 1.76 1.75 1.75 1.74 1.74 1.73 1.73 1.73
1H NMR (600 MHz, CDCl3)
HO
Ph
Ph
1.152
2.02 4.01 2.04 1.00 1.00
1.00
1.01 1.01
2.03 3.02
4.02
f1 (ppm)


^{13}C NMR (151 MHz, CDCl$_3$)
1.152
Ph
HO
Ph
197.85
144.01
137.67
128.55
128.52
128.49
127.59
126.69
126.16
108.26
102.85
72.76
40.72
31.36
31.12
27.31
27.27
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
HO
Ph
Ph
1.153
f1 (ppm)
4.00
2.00
2.01
1.02
1.00
1.00
2.03
4.01
1.00
2.01
7.45
7.44
7.43
7.42
7.39
7.37
7.36
7.35
7.33
7.32
7.31
7.29
7.28
7.24
7.22
7.21
4.97
4.96
4.95
4.94
4.94
3.05
3.04
3.03
3.03
3.02
3.02
3.01
3.00
3.00
2.99
2.99
2.98
2.97
2.96
2.96
2.94
2.94
2.93
2.92
2.91
2.90
2.90
2.88
2.87
2.86
2.85
2.83
2.39
2.38
2.07
2.06
2.06
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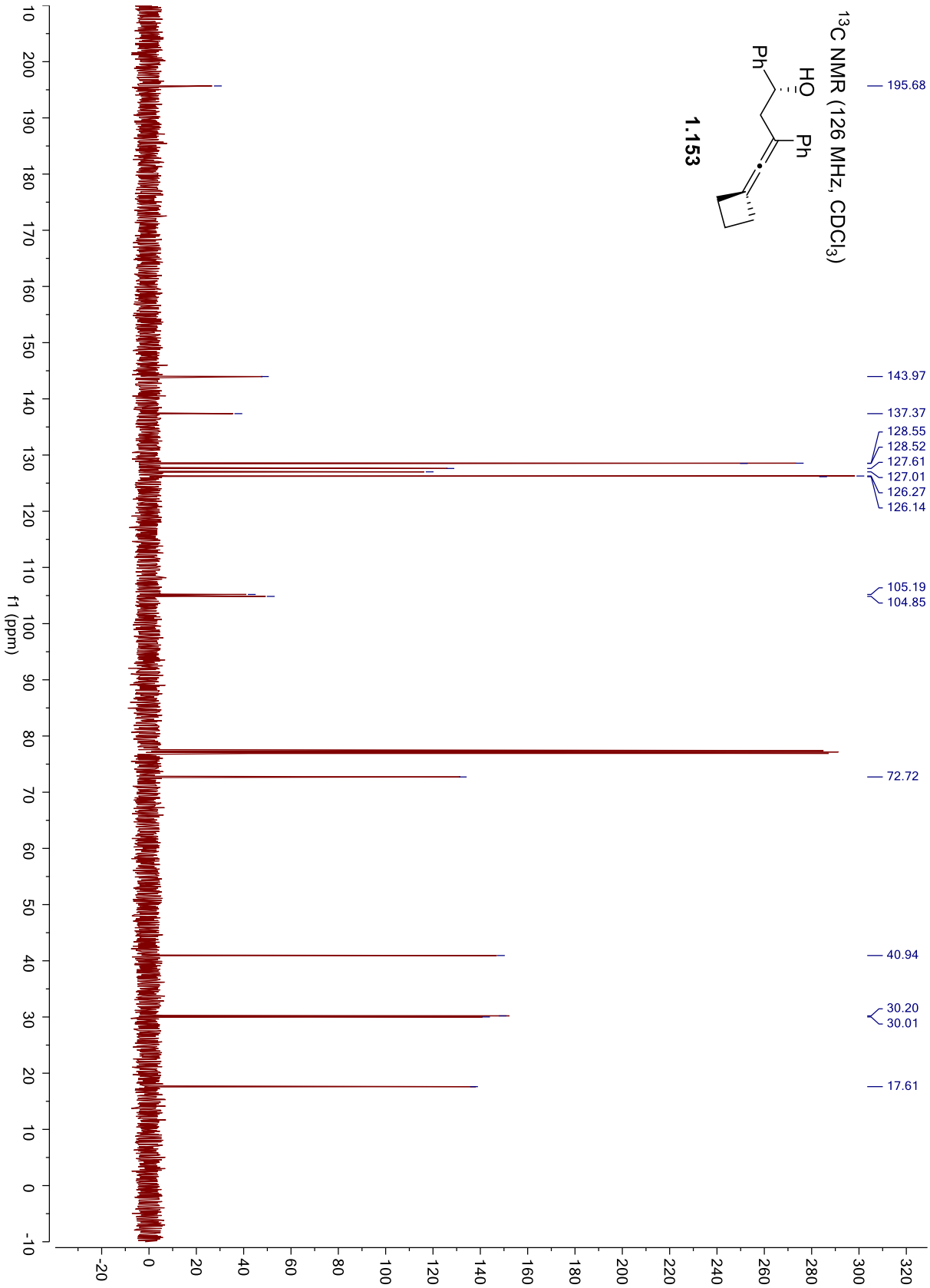
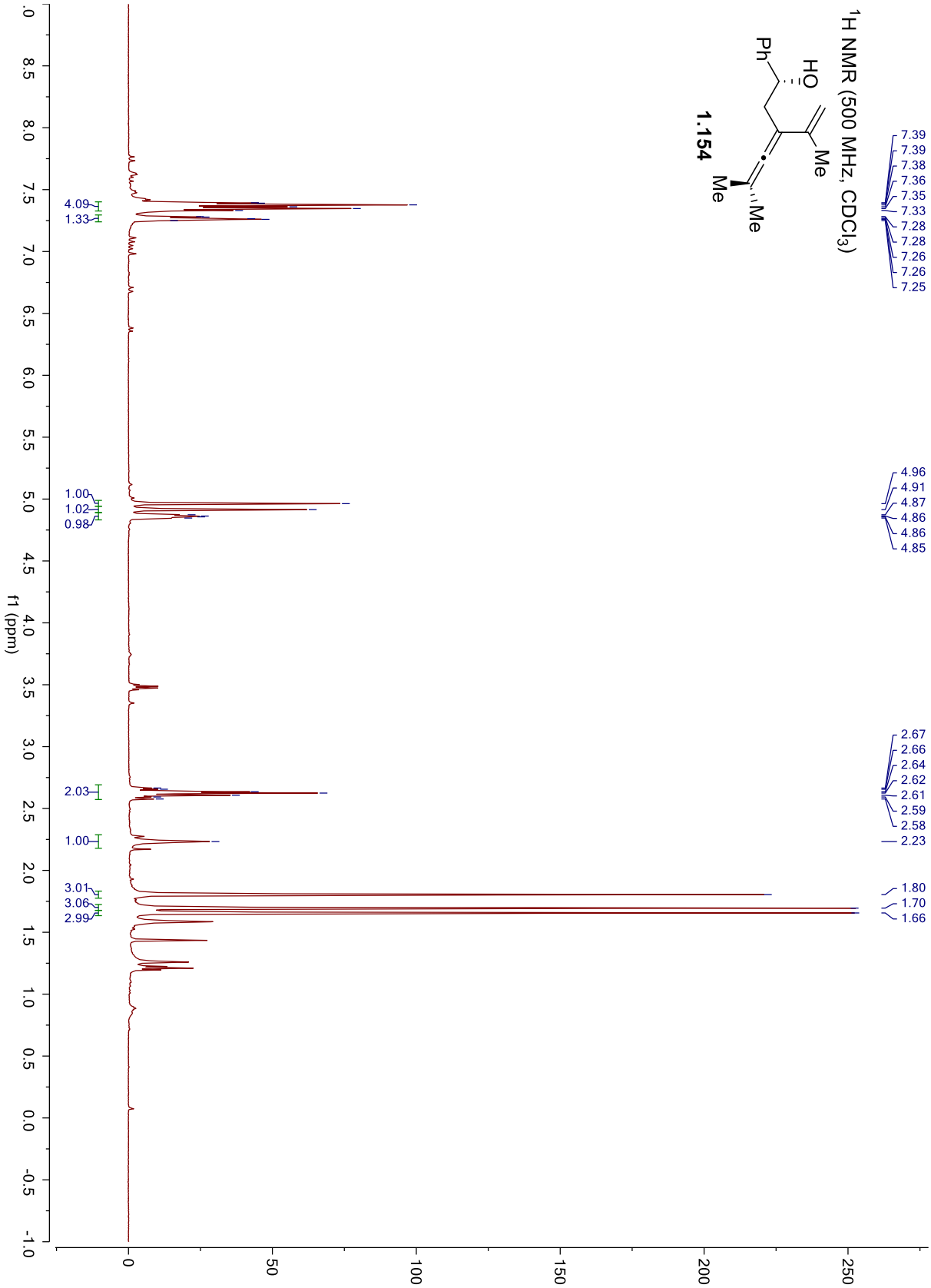
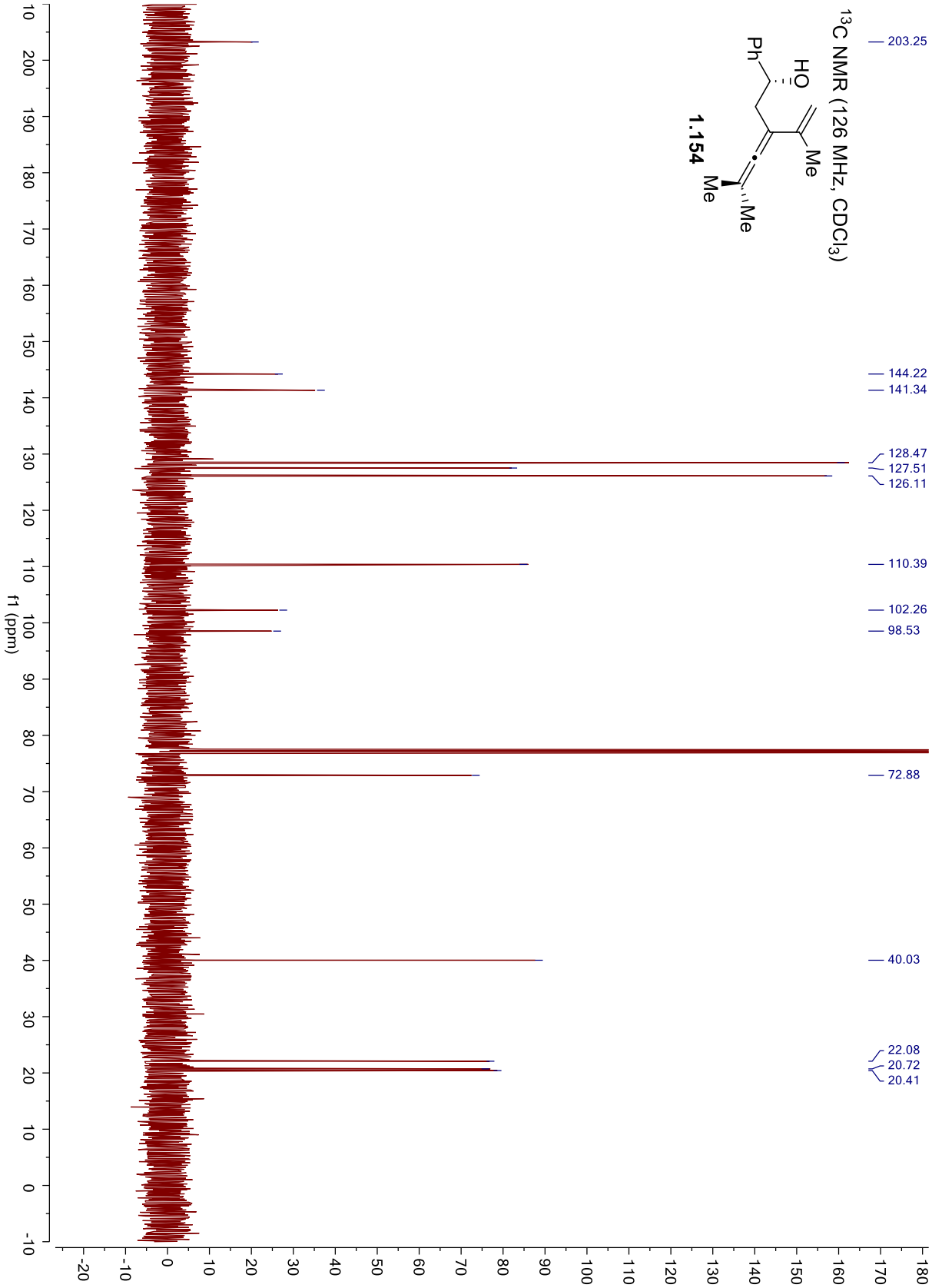
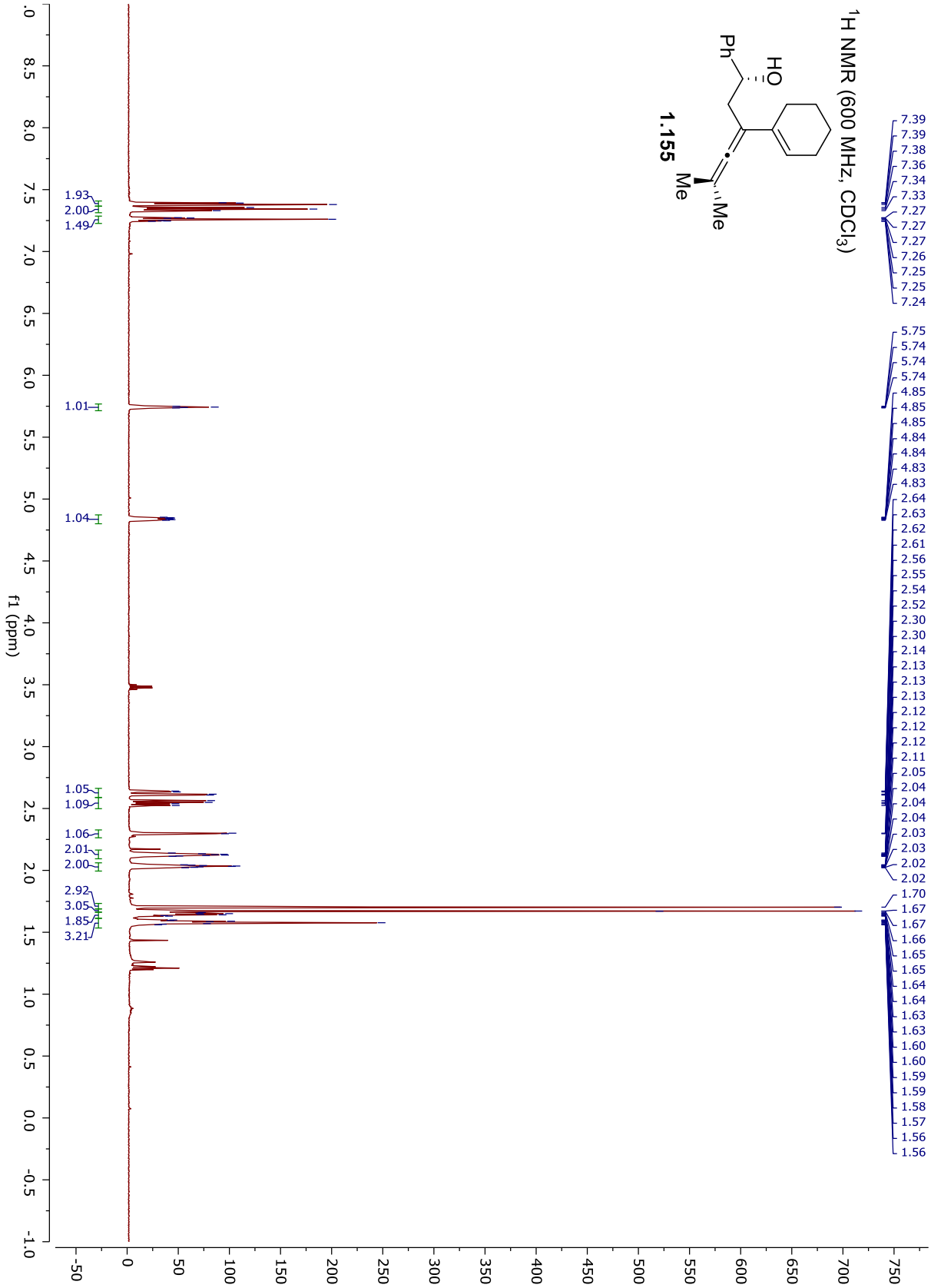
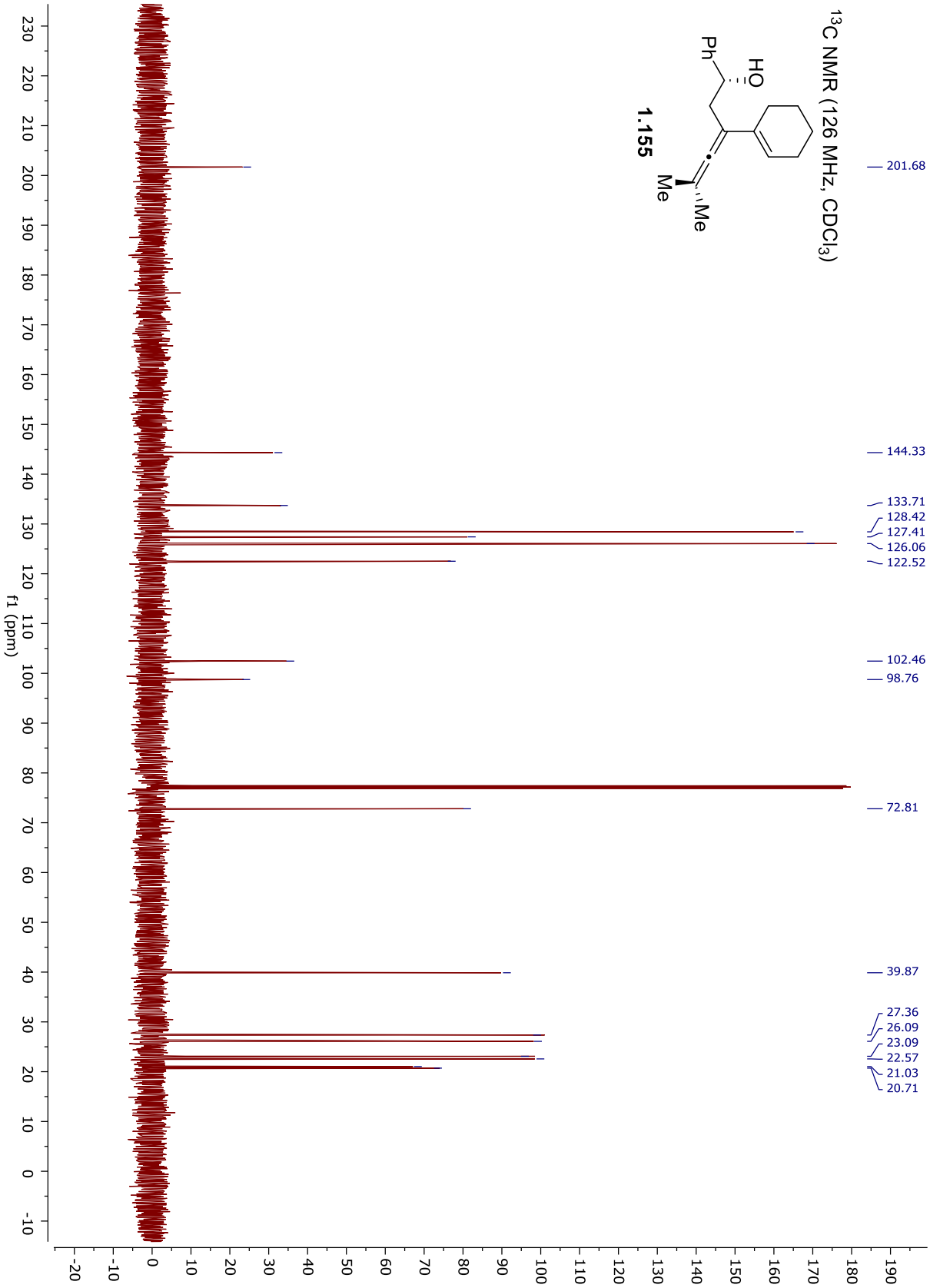
2.04
2.03
2.02
2.02
2.01
2.01
2.00
1.99
1.98

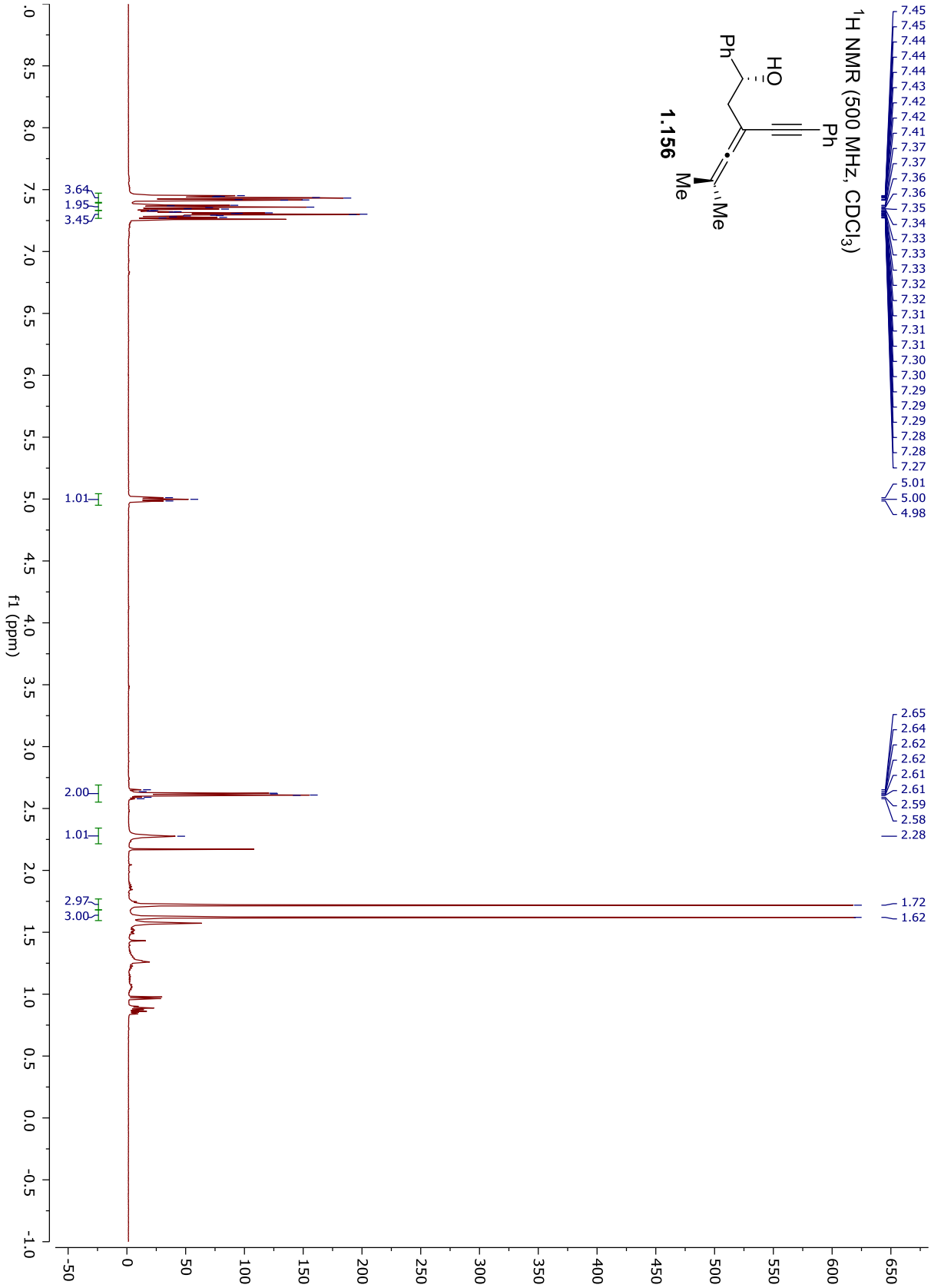

^{13}C NMR (126 MHz, CDCl$_3$)
1.153
Ph
HO
Ph
195.68
143.97
137.37
128.55
128.52
127.61
127.01
126.27
126.14
105.19
104.85
72.72
40.94
30.20
30.01
17.61
f1 (ppm)

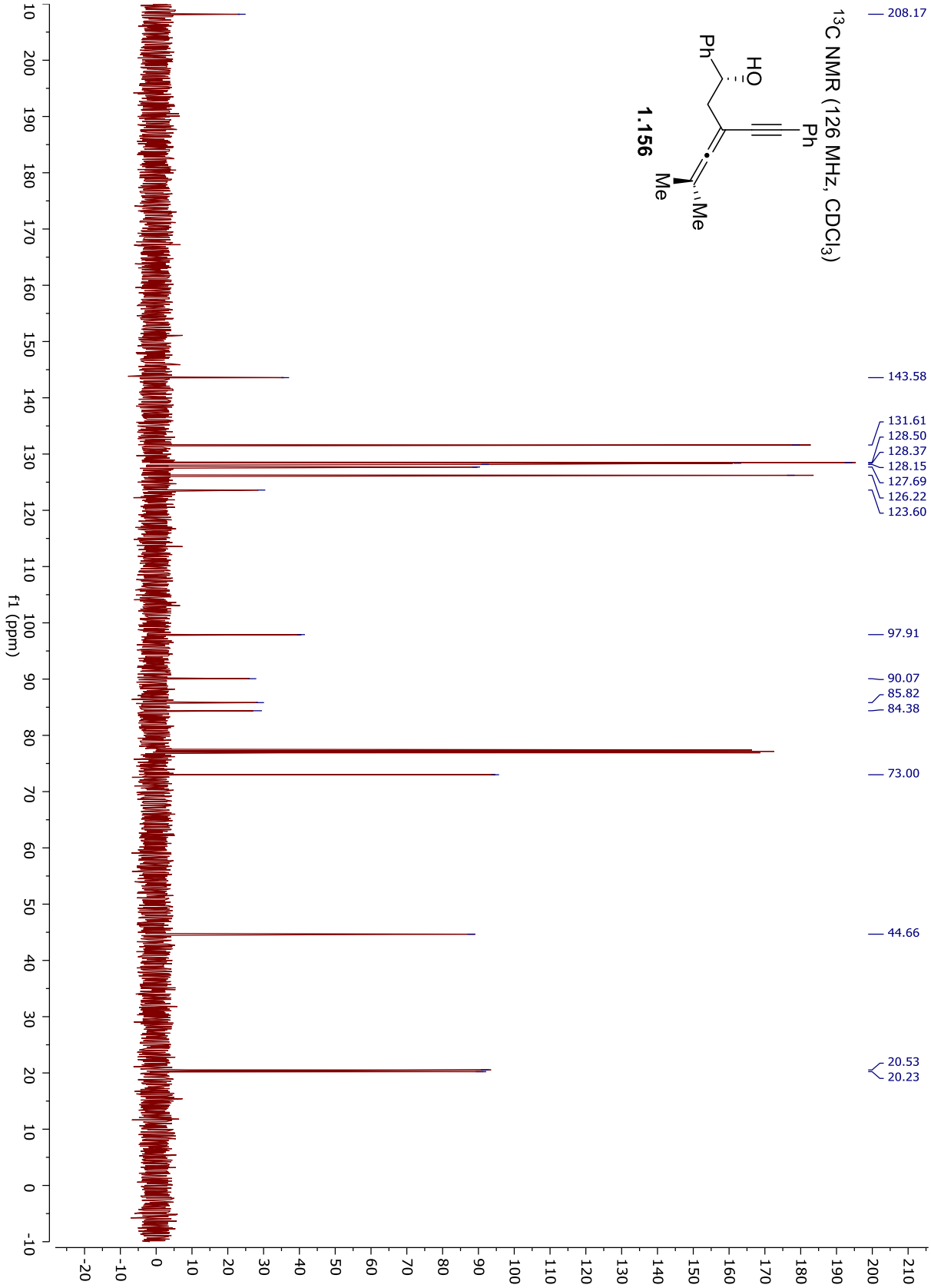

^{1}H NMR (500 MHz, CDCl$_3$)
1.154
Ph
HO
Me
Me
Me
7.39
7.39
7.38
7.36
7.35
7.33
7.28
7.28
7.26
7.26
7.25
4.96
4.91
4.87
4.86
4.86
4.85
2.67
2.66
2.64
2.62
2.61
2.59
2.58
2.23
1.80
1.70
1.66
4.09
1.33
1.00
1.02
0.98
2.03
1.00
3.01
3.06
2.99
f1 (ppm)

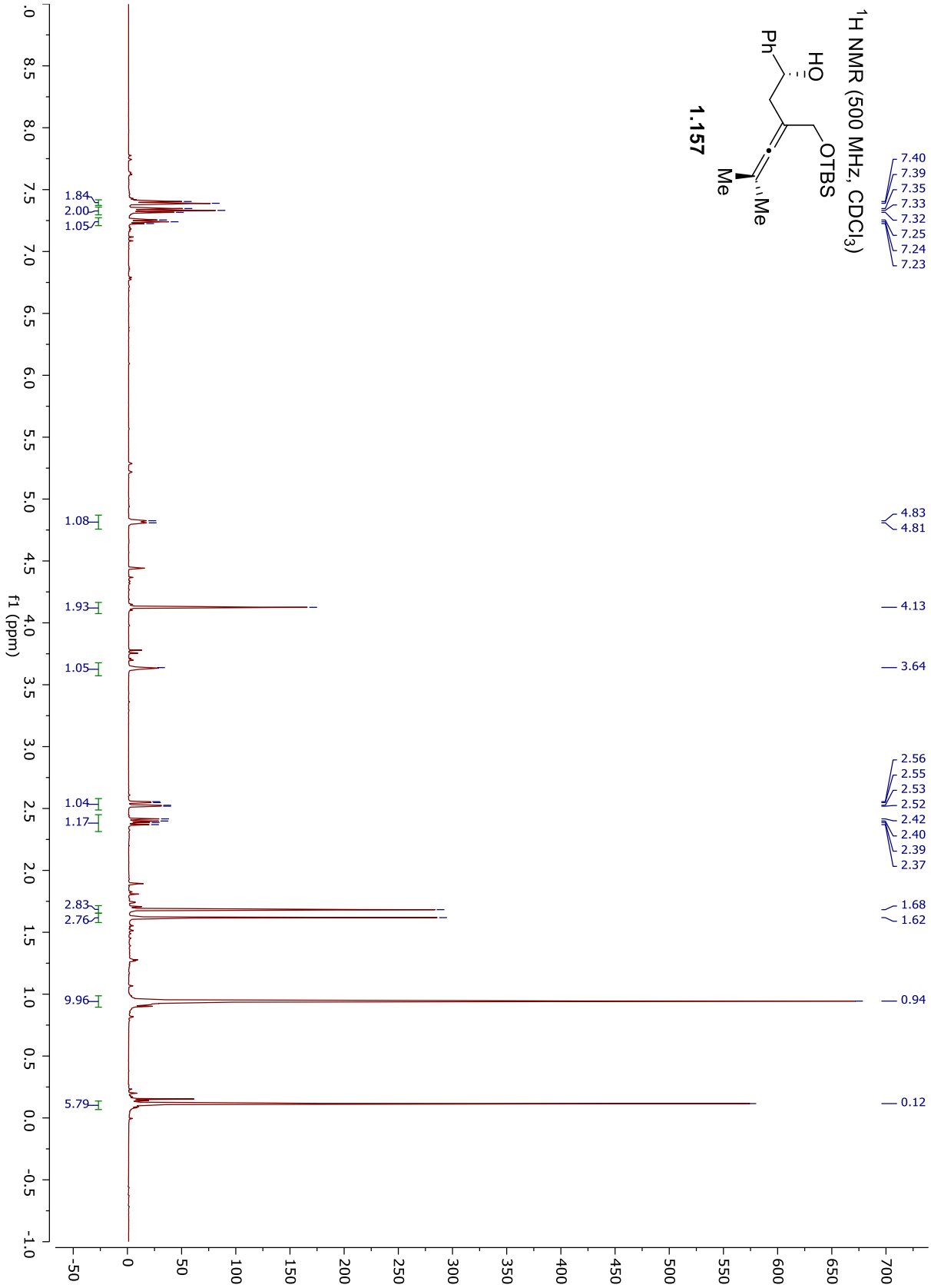

^{13}C NMR (126 MHz, CDCl$_3$)
1.154
Ph
HO
Me
Me
Me
203.25
144.22
141.34
128.47
127.51
126.11
110.39
102.26
98.53
72.88
40.03
22.08
20.72
20.41
f1 (ppm)

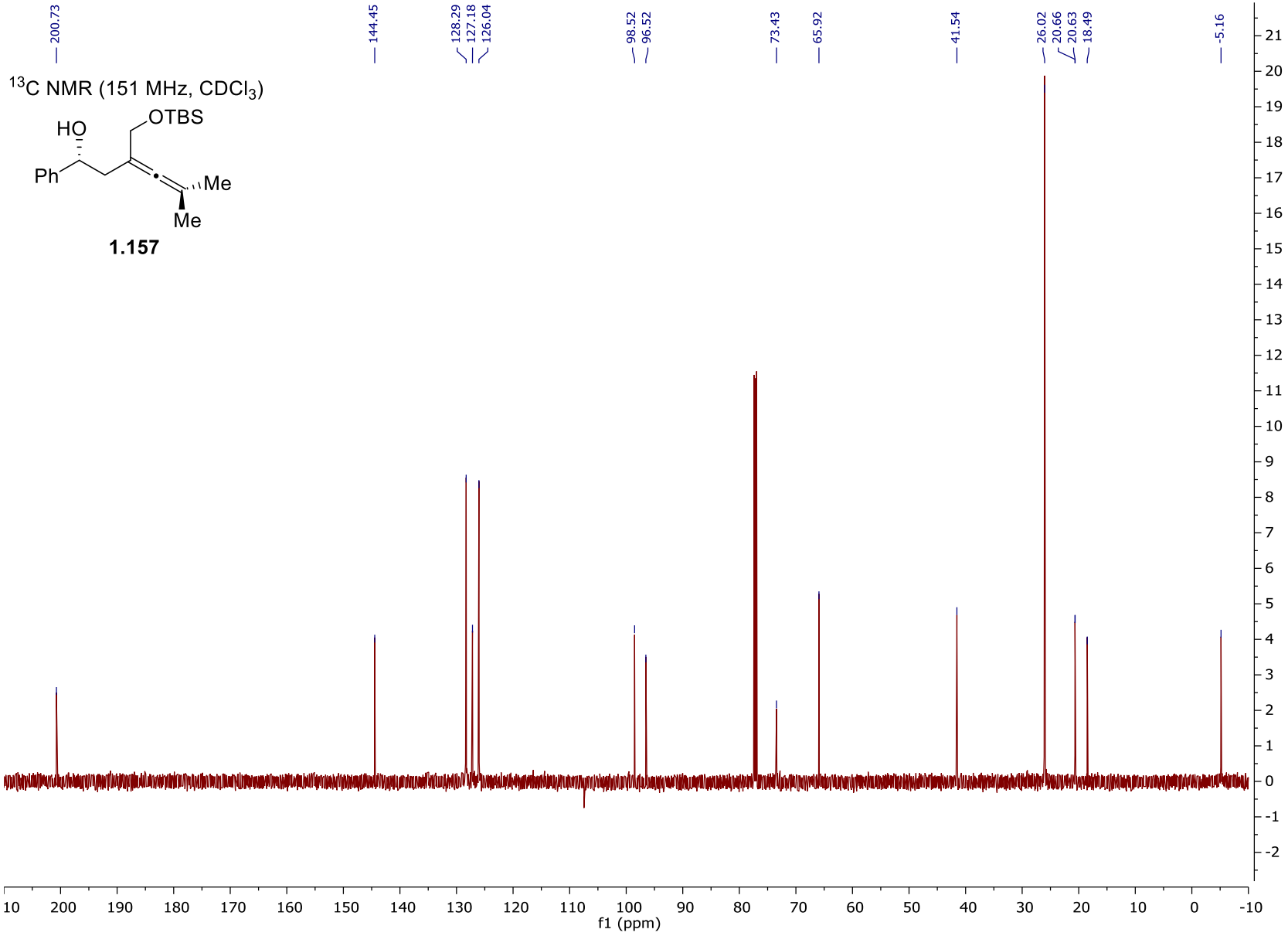

^{1}H NMR (600 MHz, CDCl$_3$)
HO
Ph
Me
Me
1.155
f1 (ppm)

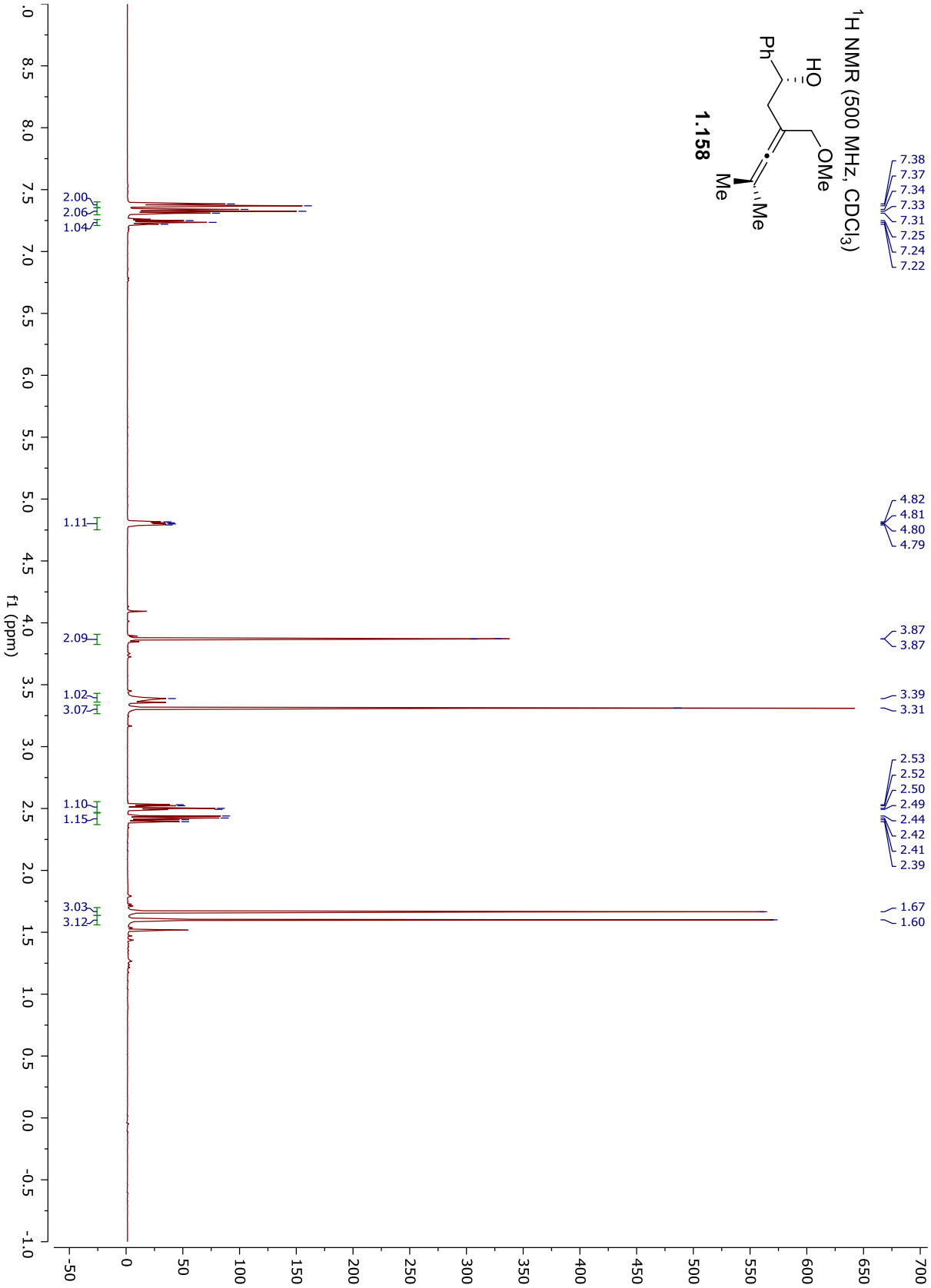

^{13}C NMR (126 MHz, CDCl$_3$)
1.155
Ph
HO
Me
Me
201.68
144.33
133.71
128.42
127.41
126.06
122.52
102.46
98.76
72.81
39.87
27.36
26.09
23.09
22.57
21.03
20.71
f1 (ppm)

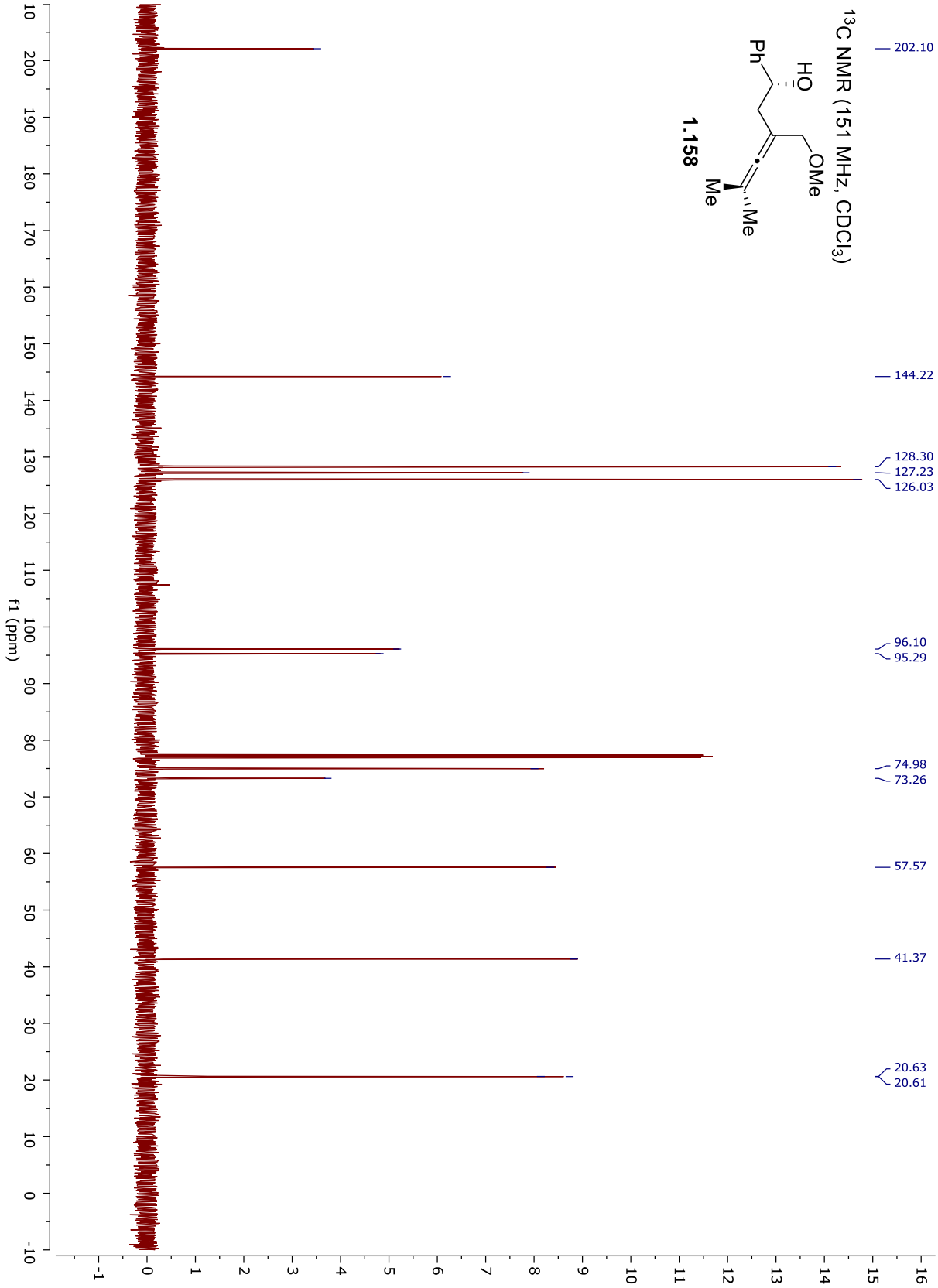

^{1}H NMR (500 MHz, CDCl$_3$)
1.156
Ph
HO
Ph
Me
Me
7.45
7.45
7.44
7.44
7.44
7.43
7.42
7.42
7.41
7.37
7.37
7.36
7.36
7.35
7.34
7.33
7.33
7.33
7.32
7.32
7.31
7.31
7.31
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.27
5.01
5.00
4.98
2.65
2.64
2.62
2.62
2.61
2.61
2.59
2.58
2.28
1.72
1.62
3.64
1.95
3.45
1.01
2.00
1.01
2.97
3.00
f1 (ppm)

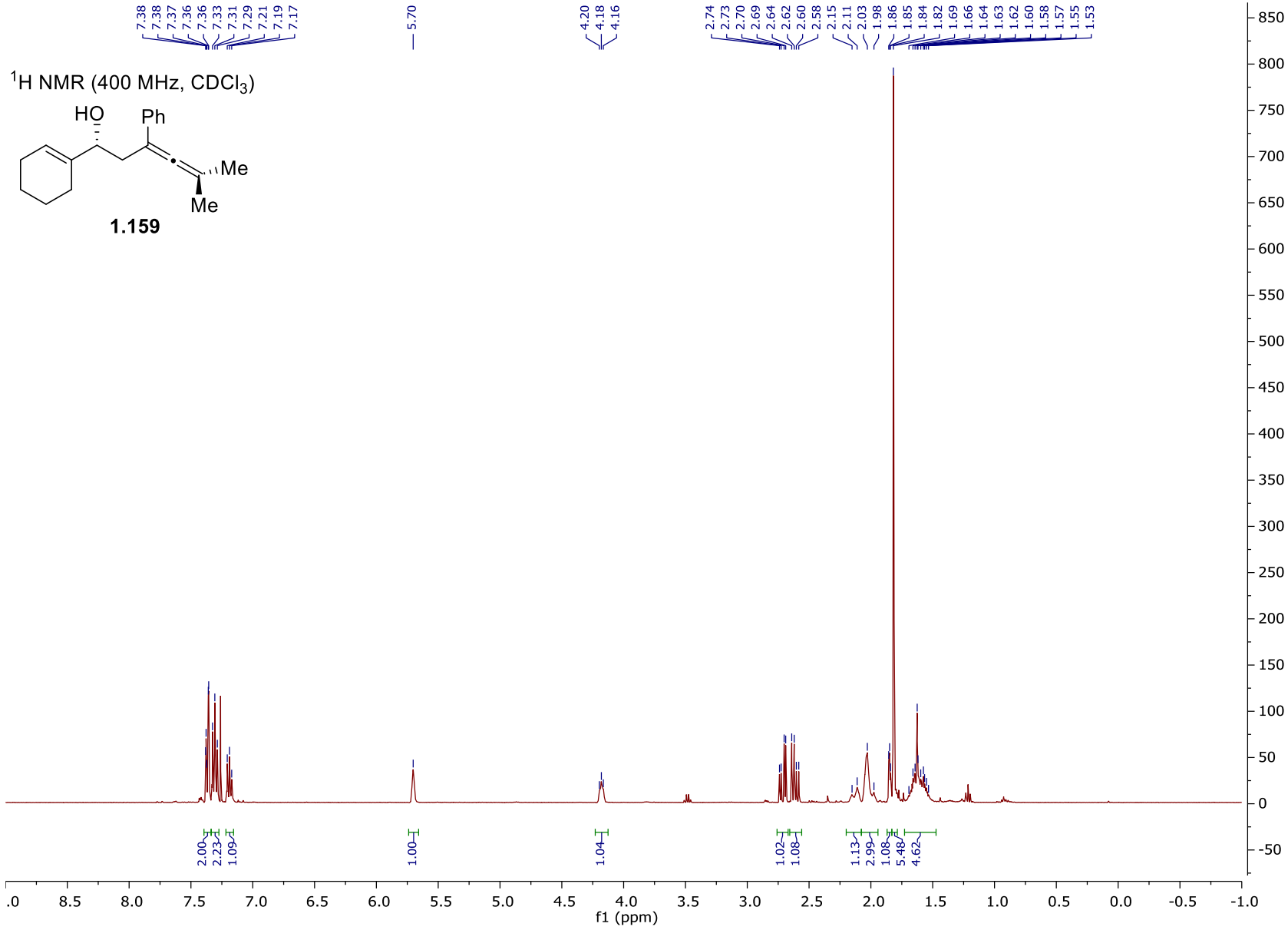

^{13}C NMR (126 MHz, CDCl$_3$)
1.156
Ph
HO
Ph
Me
Me
208.17
143.58
131.61
128.50
128.37
128.15
127.69
126.22
123.60
97.91
90.07
85.82
84.38
73.00
44.66
20.53
20.23
f1 (ppm)

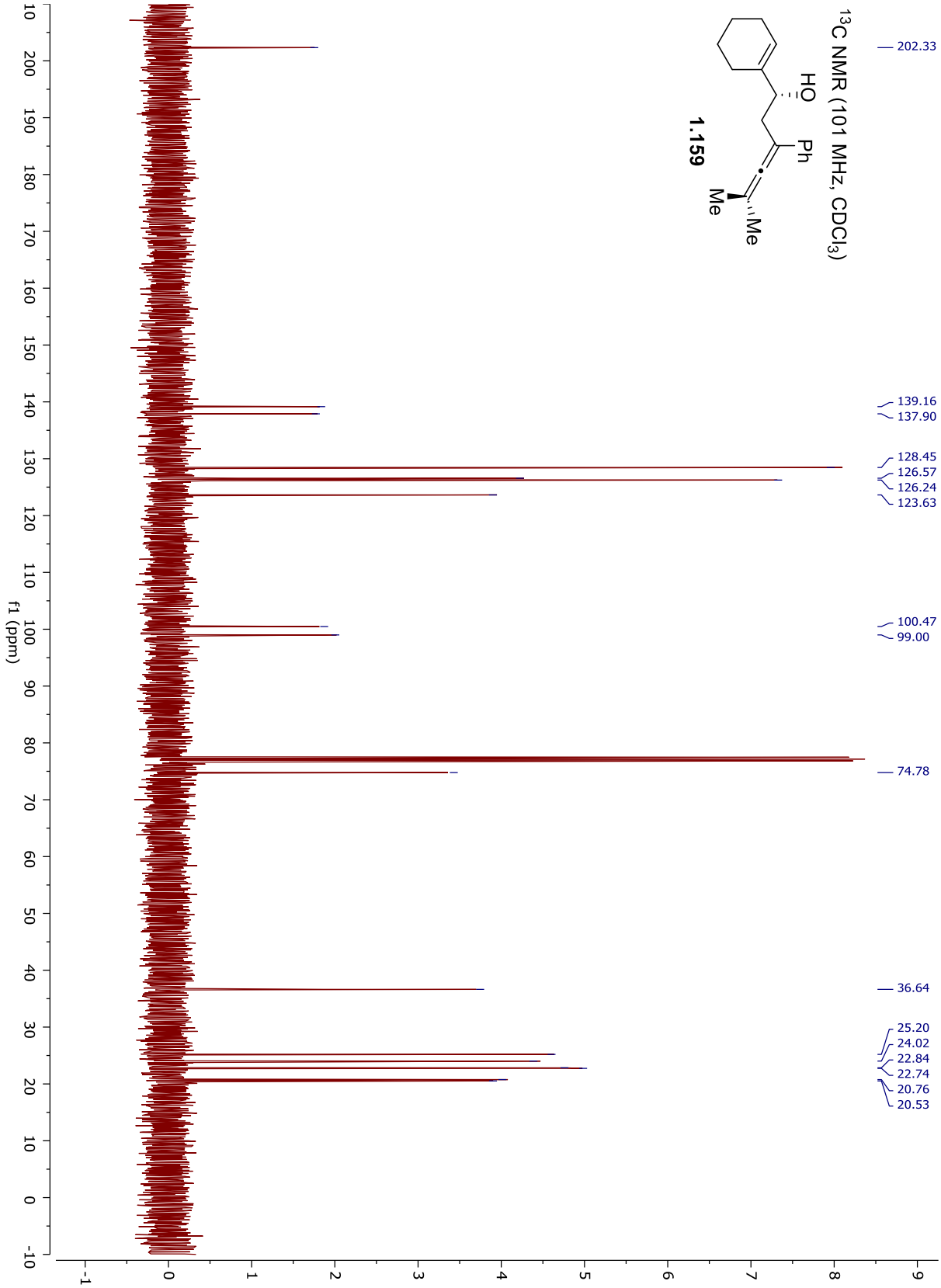

1H NMR (500 MHz, CDCl3)
HO
Ph
OTBS
Me
Me
1.157
7.40
7.39
7.35
7.33
7.32
7.25
7.24
7.23
4.83
4.81
4.13
3.64
2.56
2.55
2.53
2.52
2.42
2.40
2.39
2.37
1.68
1.62
0.94
0.12
1.84
2.00
1.05
1.08
1.93
1.05
1.04
1.17
2.83
2.76
9.96
5.79
f1 (ppm)

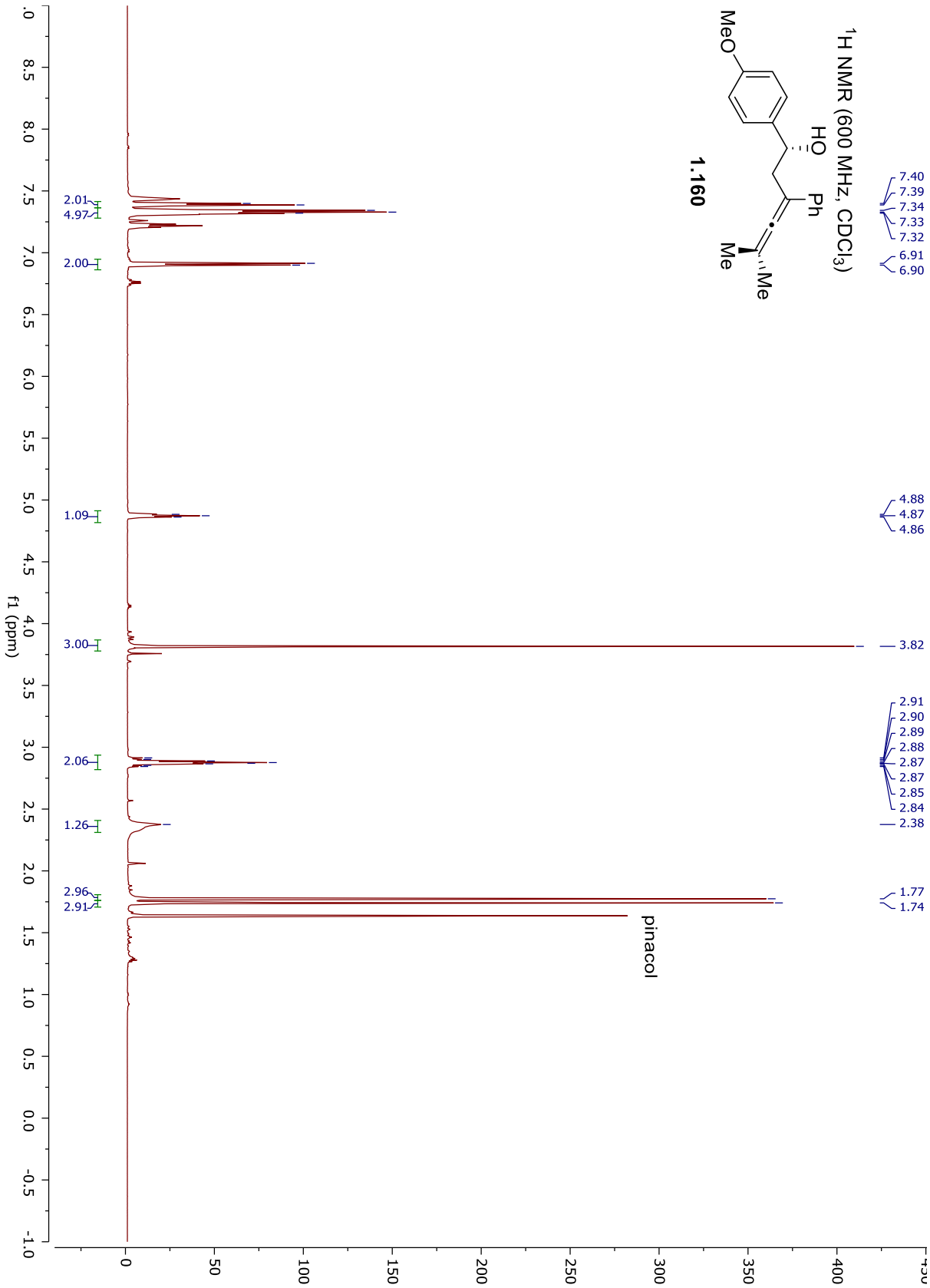

200.73
144.45
128.29
127.18
126.04
98.52
96.52
73.43
65.92
41.54
26.02
20.66
20.63
18.49
-5.16
^{13}C NMR (151 MHz, $CDCl_3$)
HO
OTBS
Ph
Me
Me
1.157
f1 (ppm)

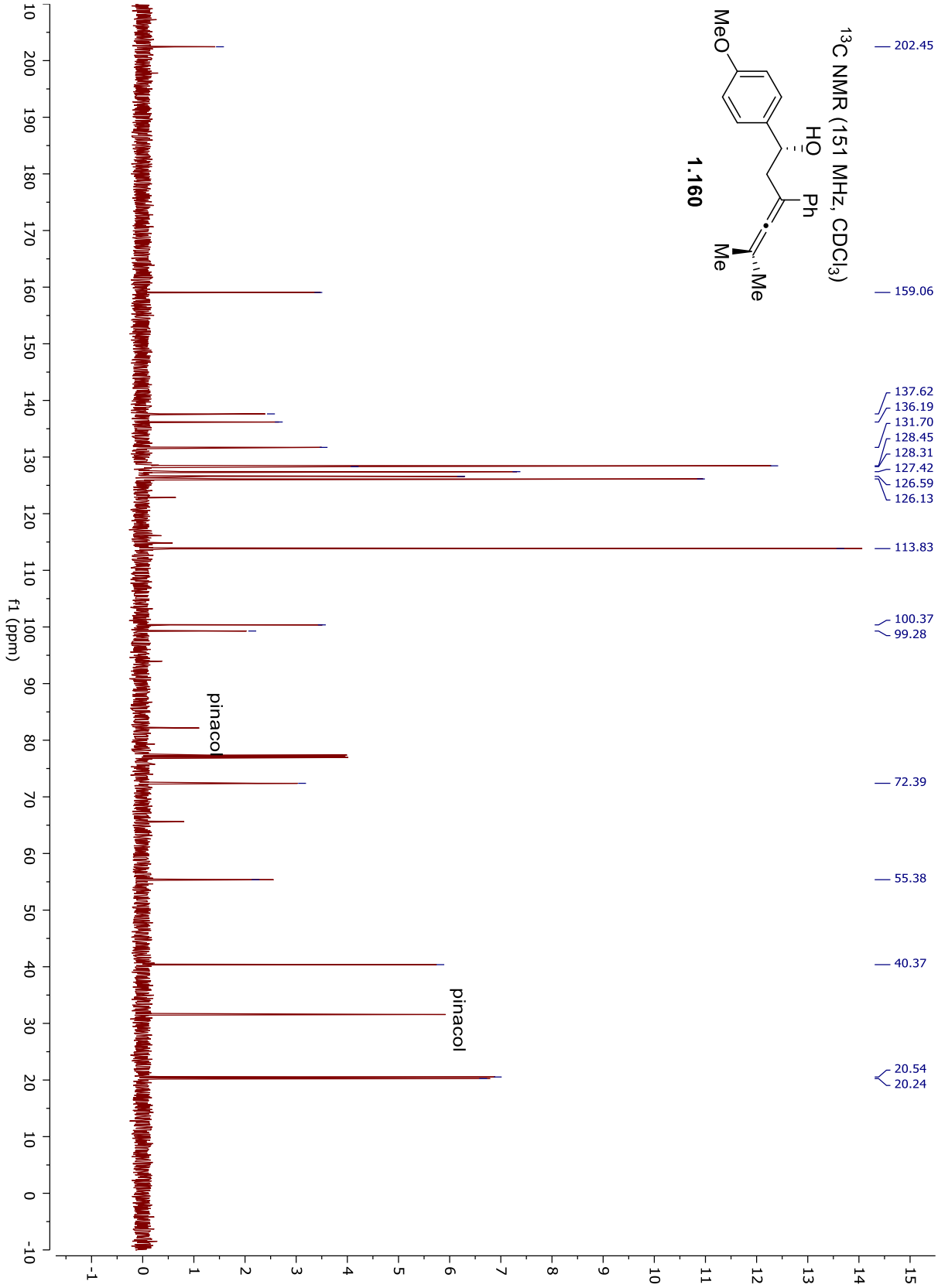

^{1}H NMR (500 MHz, CDCl$_3$)
HO
Ph
OMe
Me
Me
1.158
f1 (ppm)
7.38
7.37
7.34
7.33
7.31
7.25
7.24
7.22
4.82
4.81
4.80
4.79
3.87
3.87
3.39
3.31
2.53
2.52
2.50
2.49
2.44
2.42
2.41
2.39
1.67
1.60
2.00
2.06
1.04
1.11
2.09
1.02
3.07
1.10
1.15
3.03
3.12

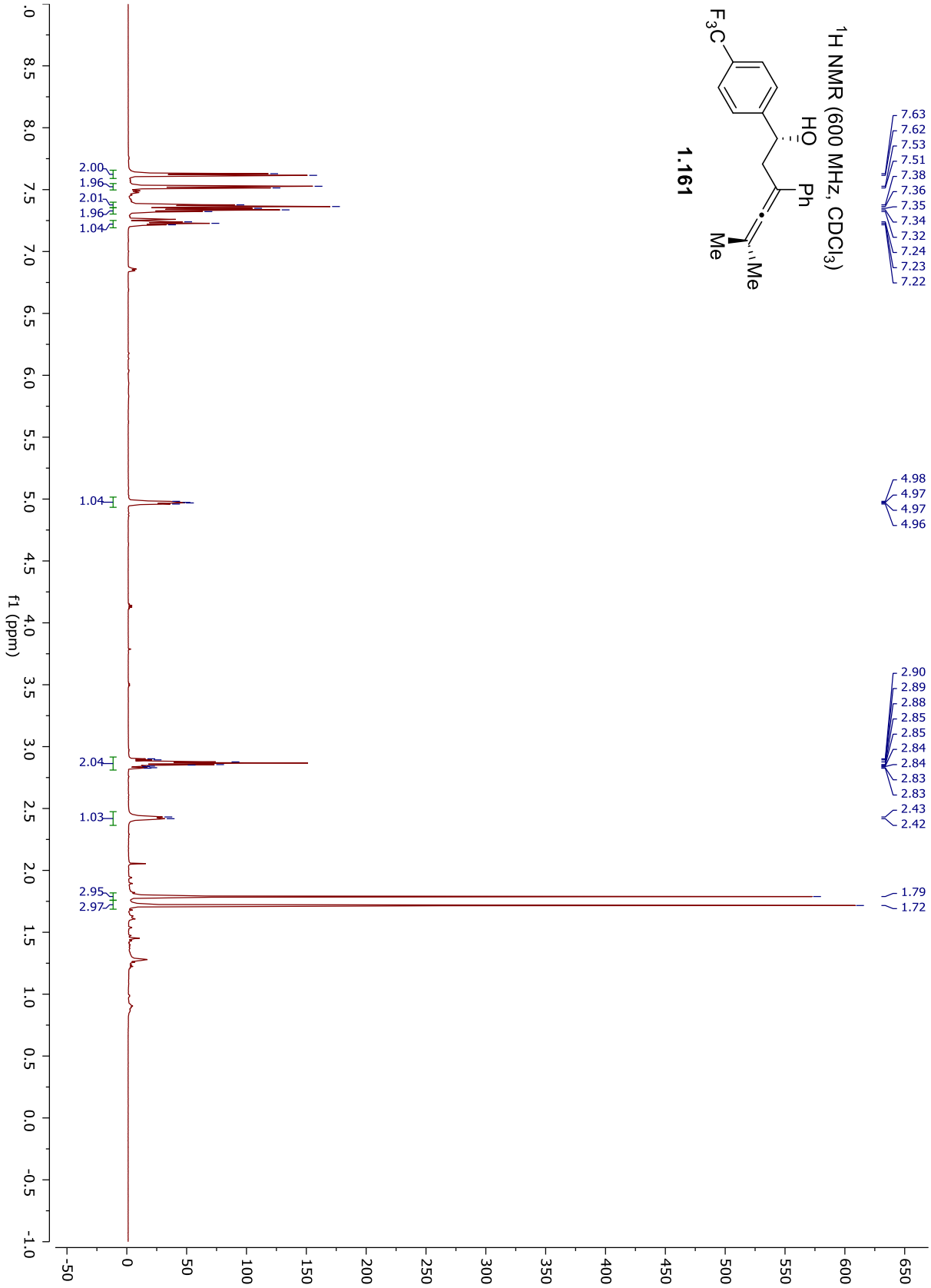

^{13}C NMR (151 MHz, CDCl$_3$)
1.158
Ph
HO
OMe
Me
Me
202.10
144.22
128.30
127.23
126.03
96.10
95.29
74.98
73.26
57.57
41.37
20.63
20.61
f1 (ppm)


7.38
7.38
7.37
7.36
7.36
7.33
7.31
7.29
7.21
7.19
7.17
5.70
4.20
4.18
4.16
2.74
2.73
2.70
2.69
2.64
2.62
2.60
2.58
2.15
2.11
2.03
1.98
1.86
1.85
1.84
1.82
1.69
1.66
1.64
1.63
1.62
1.60
1.58
1.57
1.55
1.53
^{1}H NMR (400 MHz, $CDCl_3$)
HO
Ph
Me
Me
1.159
2.00
2.23
1.09
1.00
1.04
1.02
1.08
1.13
2.99
1.08
5.48
4.62
f1 (ppm)


^{13}C NMR (101 MHz, CDCl$_3$)
1.159
HO
Ph
Me
Me
202.33
139.16
137.90
128.45
126.57
126.24
123.63
100.47
99.00
74.78
36.64
25.20
24.02
22.84
22.74
20.76
20.53
f1 (ppm)


^{1}H NMR (600 MHz, $CDCl_3$)
MeO
HO
Ph
Me
Me
1.160
7.40
7.39
7.34
7.33
7.32
6.91
6.90
4.88
4.87
4.86
3.82
2.91
2.90
2.89
2.88
2.87
2.87
2.85
2.84
2.38
1.77
1.74
pinacol
2.01
4.97
2.00
1.09
3.00
2.06
1.26
2.96
2.91
f1 (ppm)


^{13}C NMR (151 MHz, CDCl$_3$)
MeO
HO
Ph
Me
Me
1.160
202.45
159.06
137.62
136.19
131.70
128.45
128.31
127.42
126.59
126.13
113.83
100.37
99.28
72.39
55.38
40.37
20.54
20.24
pinacol
pinacol
f1 (ppm)


^{1}H NMR (600 MHz, CDCl$_3$)
1.161
F$_3$C
HO
Ph
Me
Me
7.63
7.62
7.53
7.51
7.38
7.36
7.35
7.34
7.32
7.24
7.23
7.22
4.98
4.97
4.97
4.96
2.90
2.89
2.88
2.85
2.85
2.84
2.84
2.83
2.83
2.43
2.42
1.79
1.72
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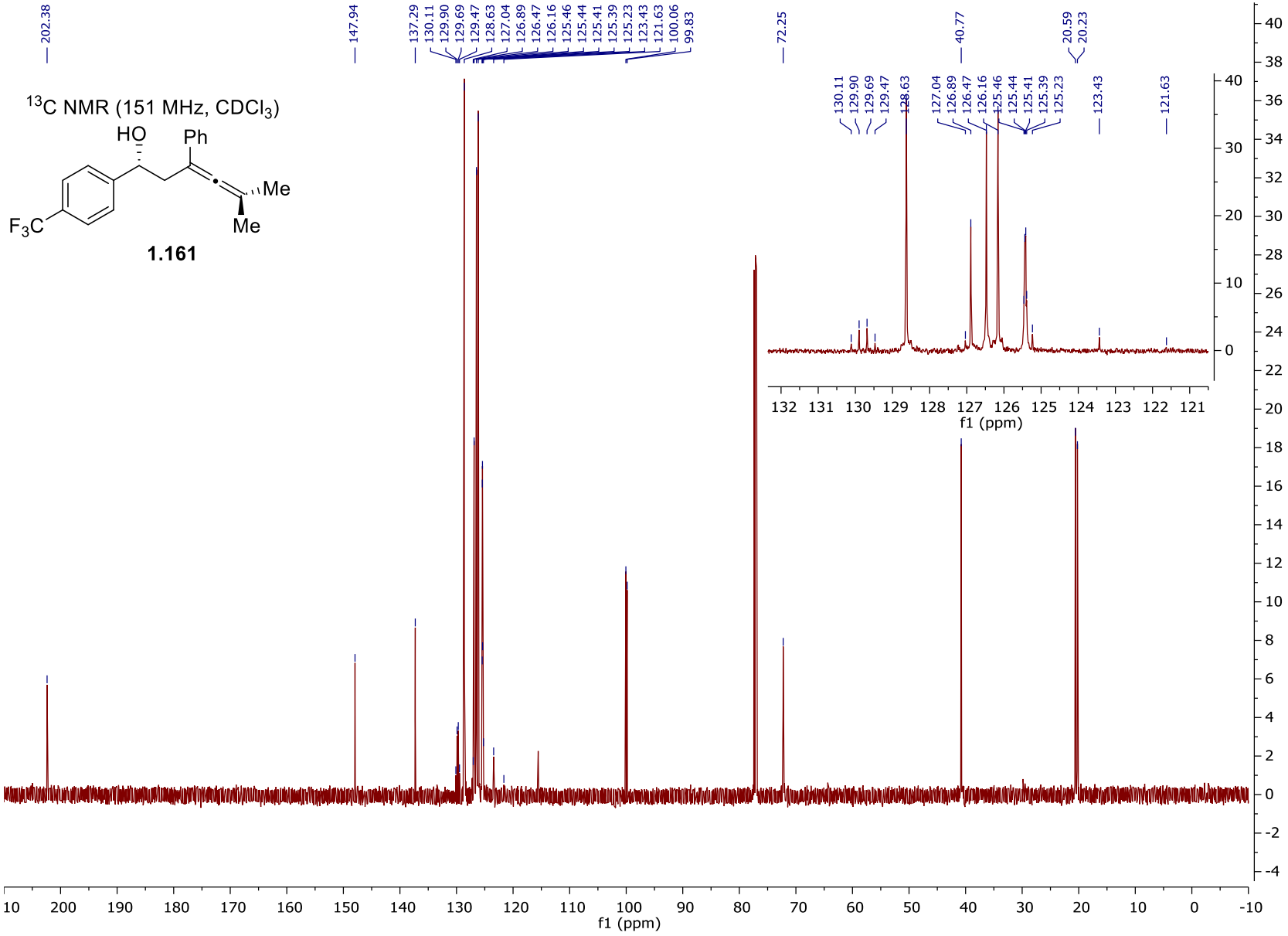
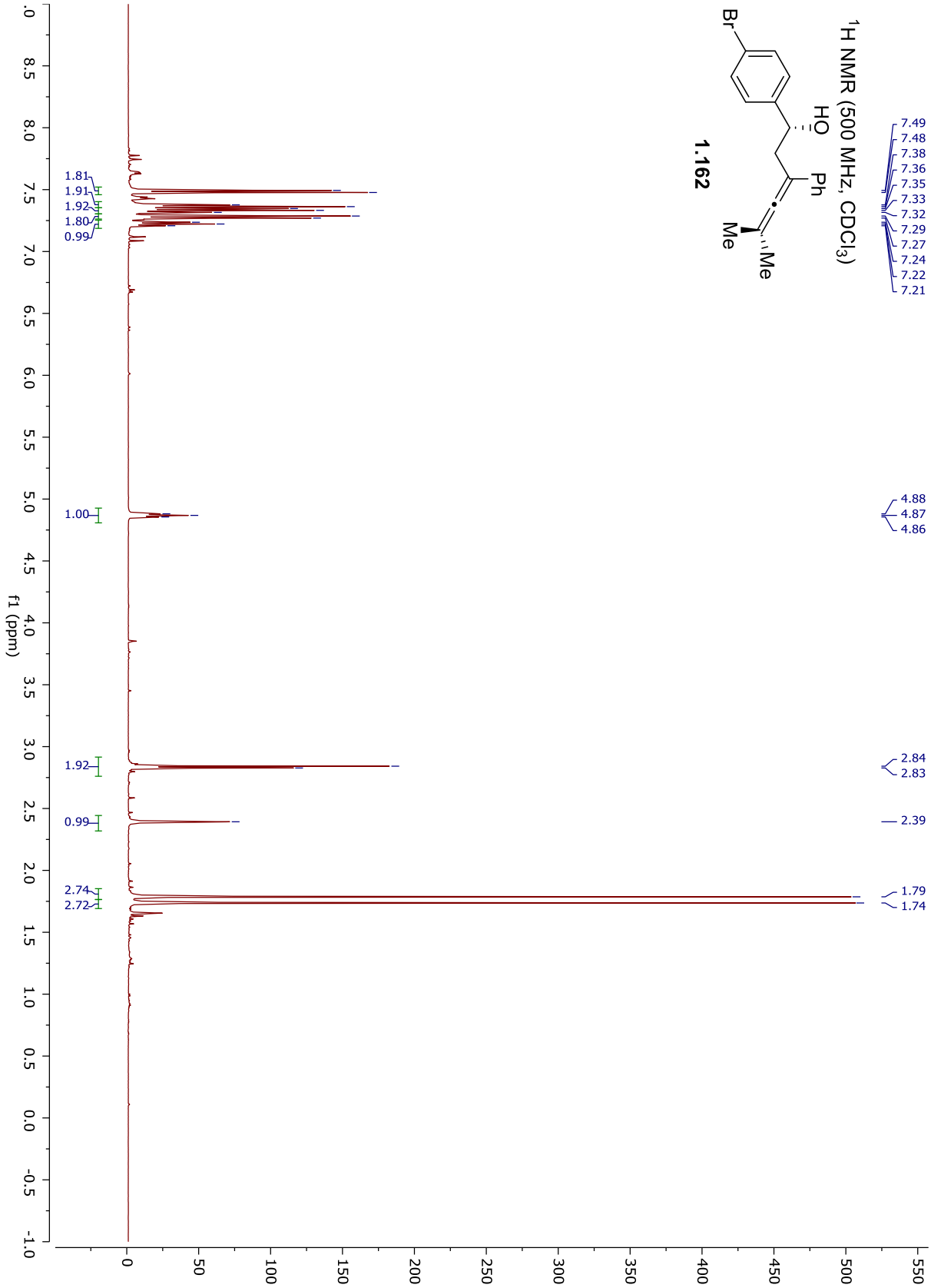
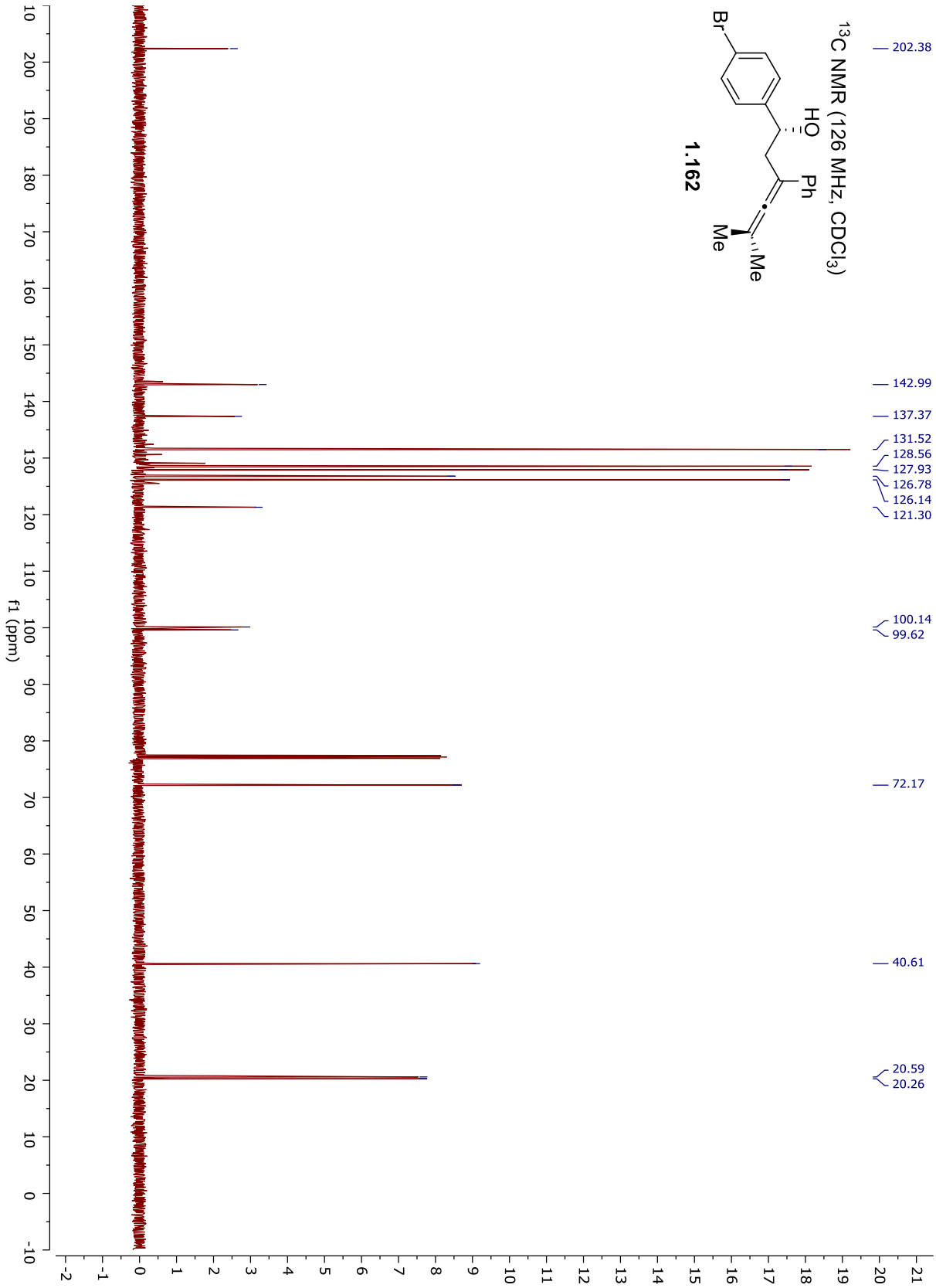
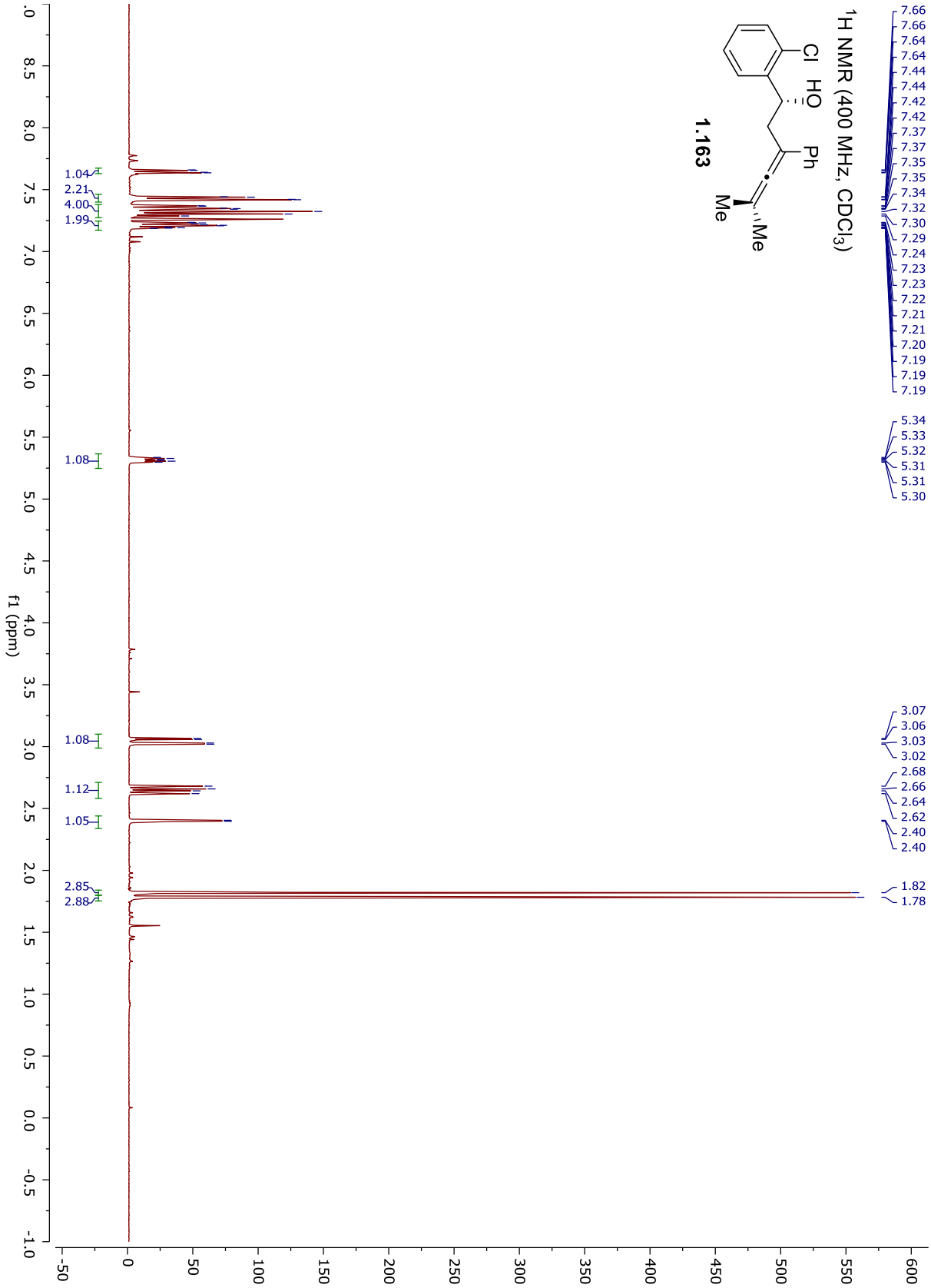
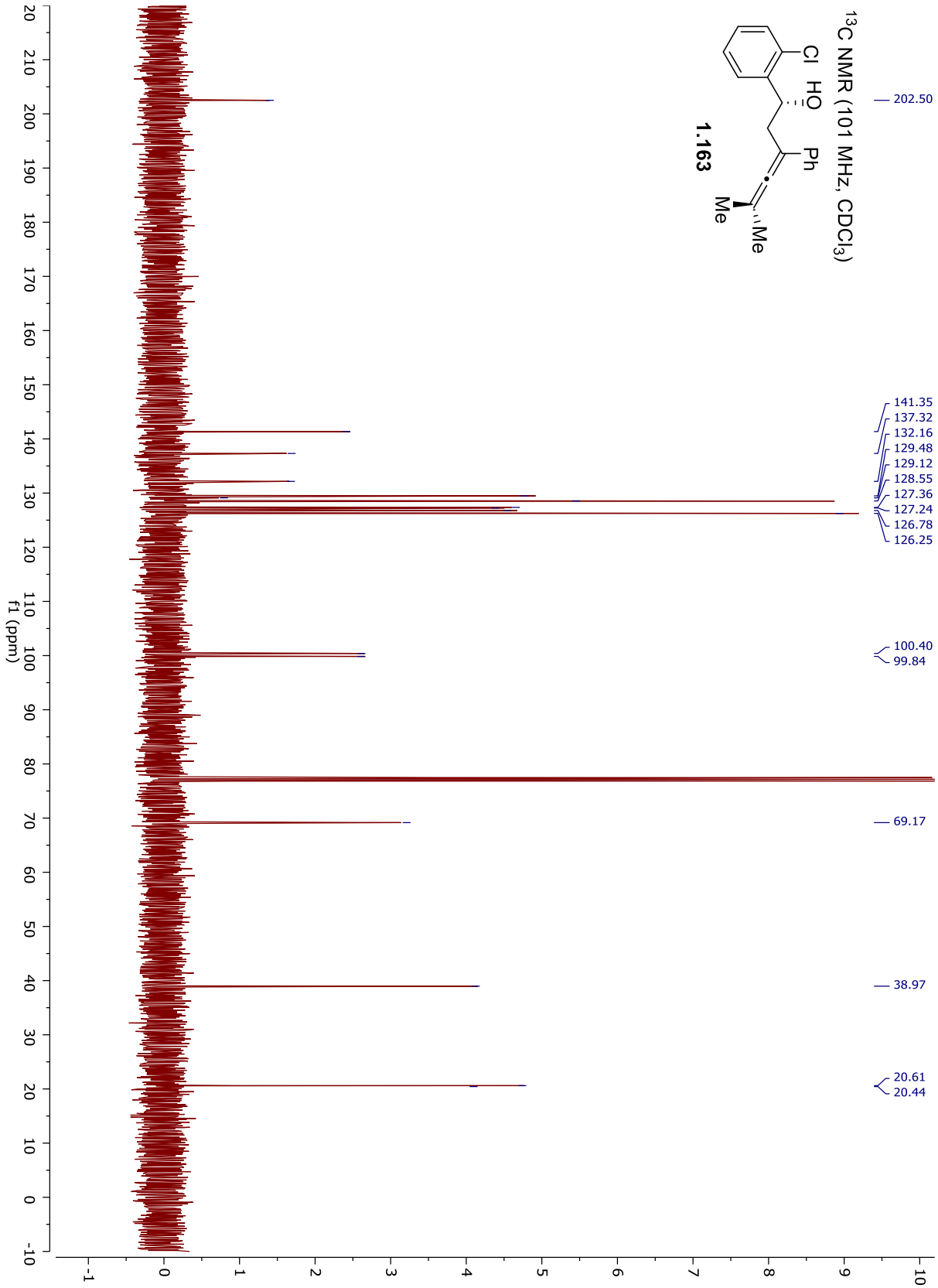
2.04
1.03
2.95
2.97
f1 (ppm)


202.38
147.94
137.29
130.11
129.90
129.69
129.47
128.63
127.04
126.89
126.47
126.16
125.46
125.44
125.41
125.39
125.23
123.43
121.63
100.06
99.83
72.25
40.77
20.59
20.23
^{13}C NMR (151 MHz, CDCl$_3$)
HO
Ph
Me
Me
F$_3$C
1.161
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
1.162
Br
HO
Ph
Me
Me
7.49
7.48
7.38
7.36
7.35
7.33
7.32
7.29
7.27
7.24
7.22
7.21
4.88
4.87
4.86
2.84
2.83
2.39
1.79
1.74
1.81
1.91
1.92
1.80
0.99
1.00
1.92
0.99
2.74
2.72
f1 (ppm)


^{13}C NMR (126 MHz, CDCl$_3$)
1.162
Br
HO
Ph
Me
Me
202.38
142.99
137.37
131.52
128.56
127.93
126.78
126.14
121.30
100.14
99.62
72.17
40.61
20.59
20.26
f1 (ppm)


^{1}H NMR (400 MHz, $CDCl_3$)
1.163
Cl
HO
Ph
Me
Me
7.66
7.66
7.64
7.64
7.44
7.44
7.42
7.42
7.37
7.37
7.35
7.35
7.34
7.32
7.30
7.29
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.19
7.19
7.19
5.34
5.33
5.32
5.31
5.31
5.30
3.07
3.06
3.03
3.02
2.68
2.66
2.64
2.62
2.40
2.40
1.82
1.78
1.04
2.21
4.00
1.99
1.08
1.08
1.12
1.05
2.85
2.88
f1 (ppm)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Me
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129.12
128.55
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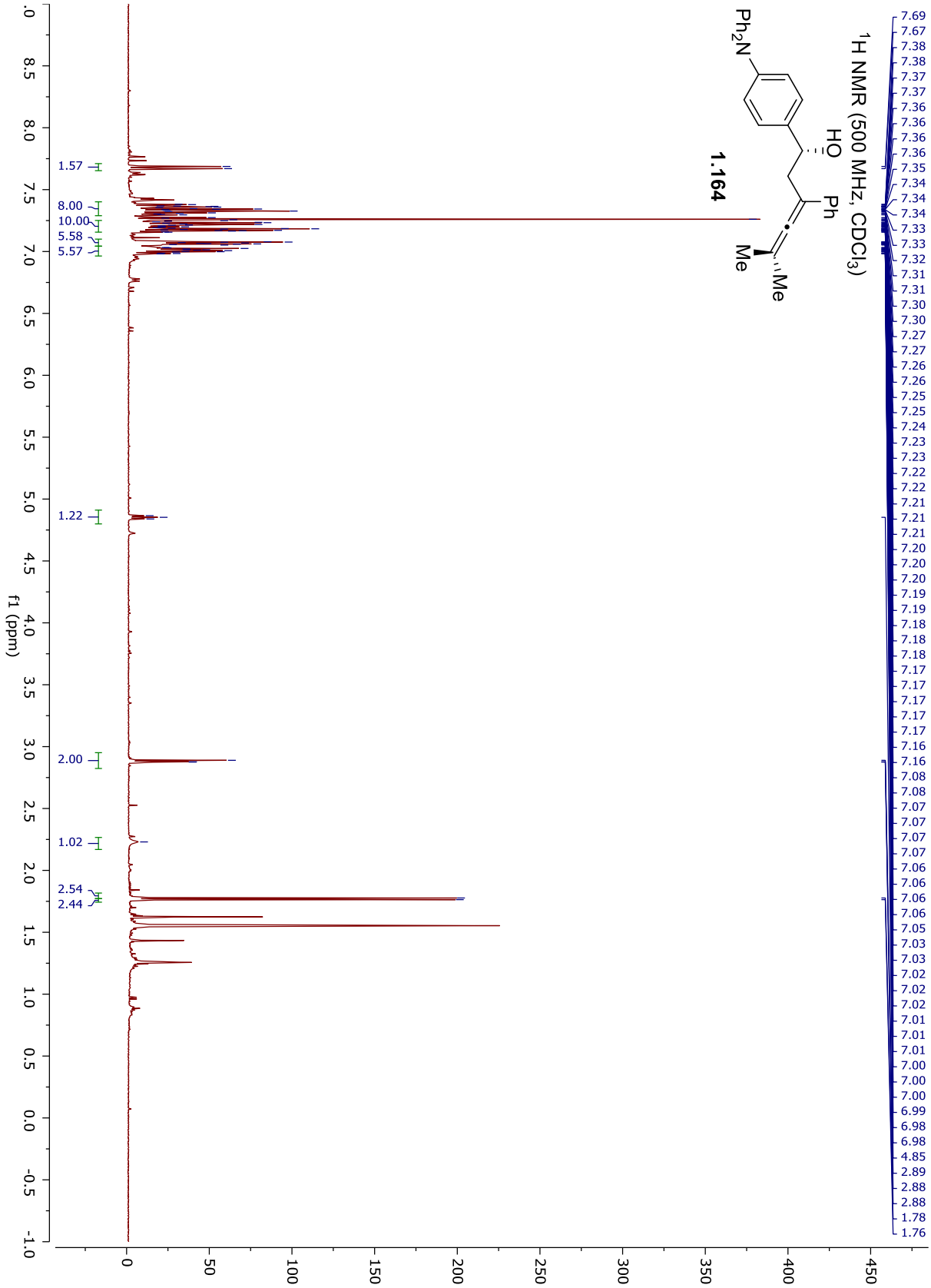
126.78
126.25
100.40
99.84
69.17
38.97
20.61
20.44
f1 (ppm)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HO
Ph
Me
Me
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f1 (ppm)
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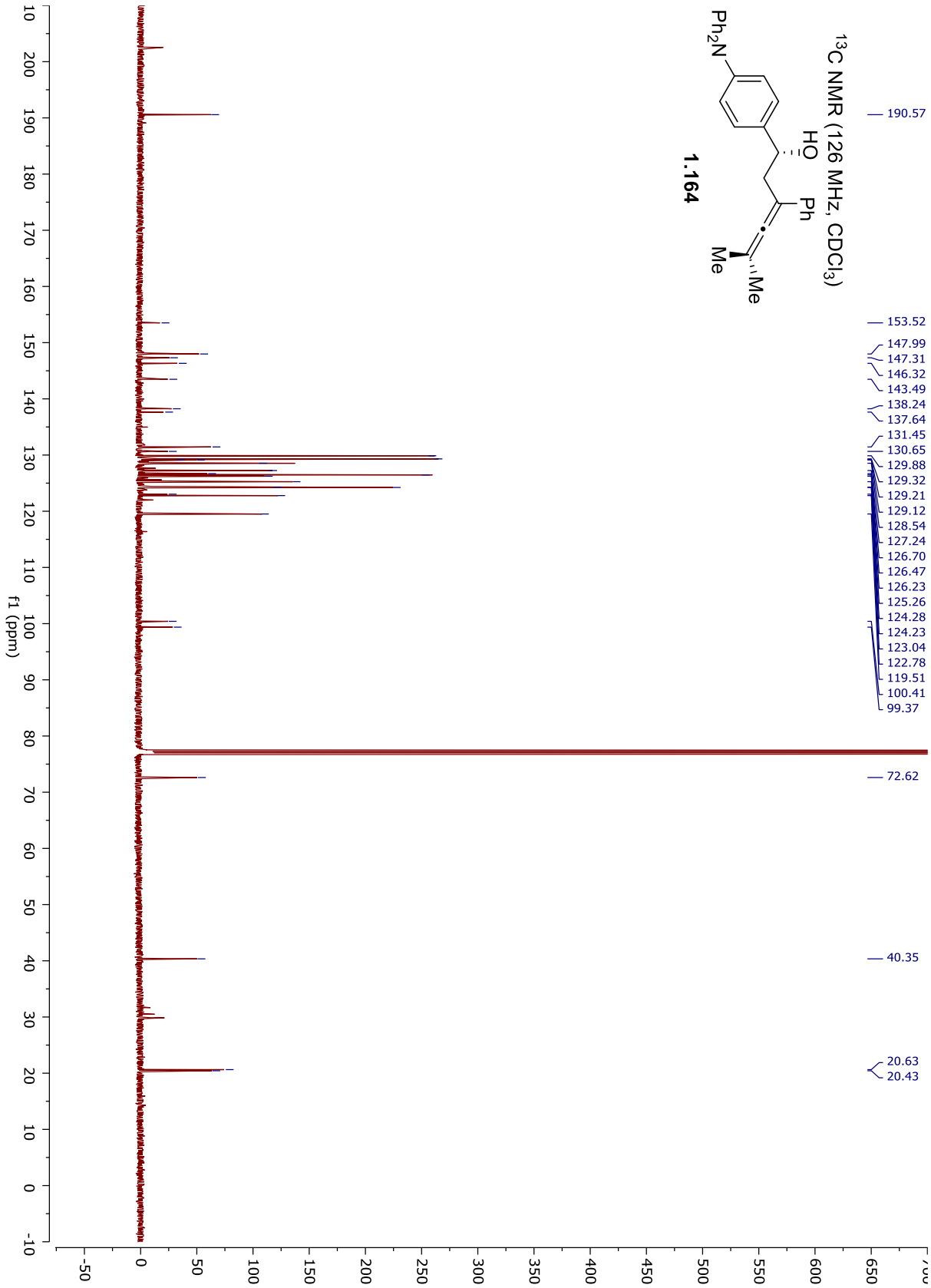
5.57
1.22
2.00
1.02
2.54
2.44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Ph
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Me
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146.32
143.49
138.24
137.64
131.45
130.65
129.88
129.32
129.21
129.12
128.54
127.24
126.70
126.47
126.23
125.26
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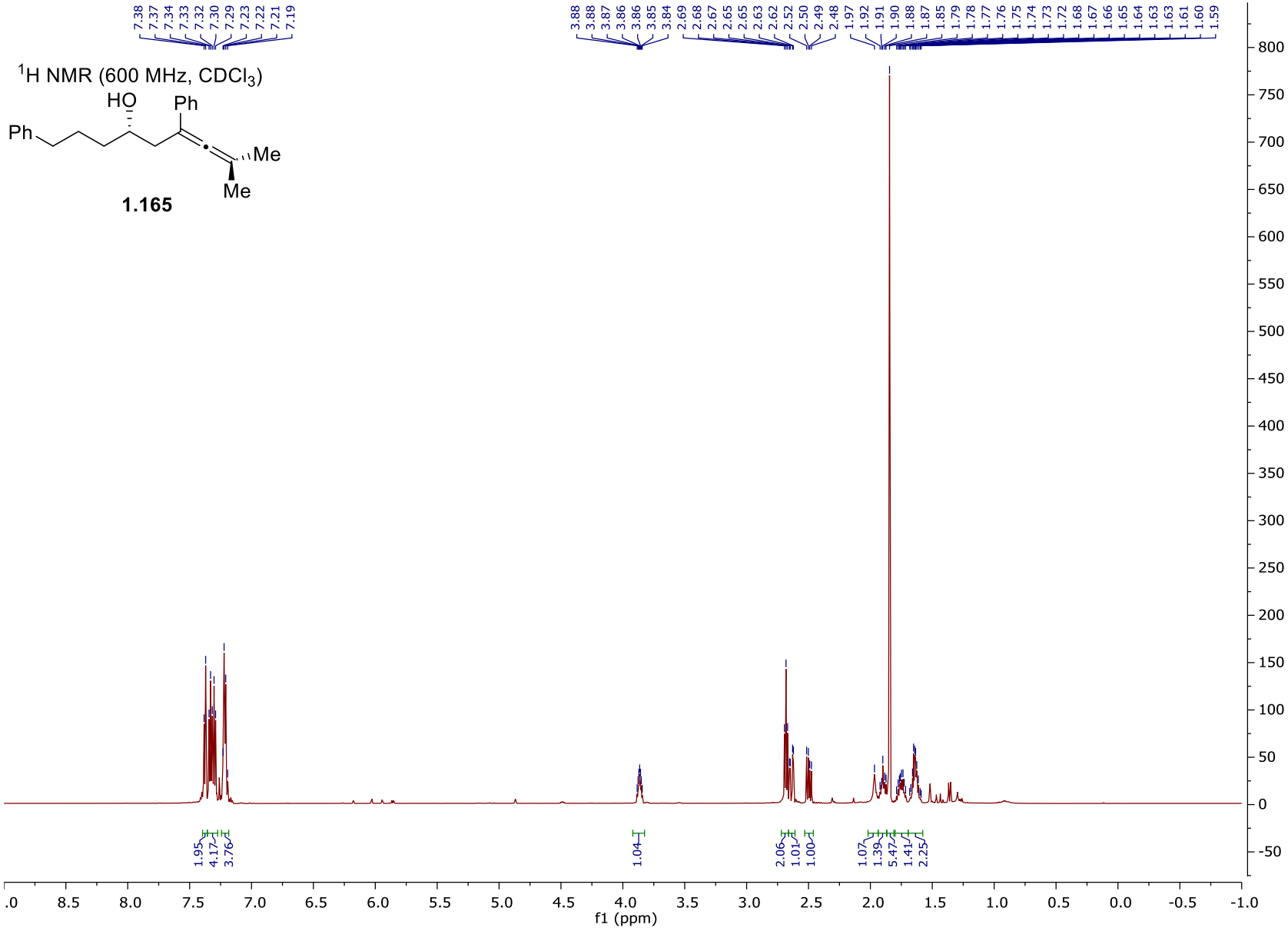
f1 (ppm)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3.87
3.86
3.86
3.85
3.84
2.69
2.68
2.67
2.65
2.65
2.63
2.62
2.52
2.50
2.49
2.48
1.97
1.92
1.91
1.90
1.88
1.87
1.85
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1.75
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1.66
1.65
1.64
1.63
1.63
1.61
1.60
1.59
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HO
Ph
Ph
Me
Me
1.165
1.95
4.17
3.76
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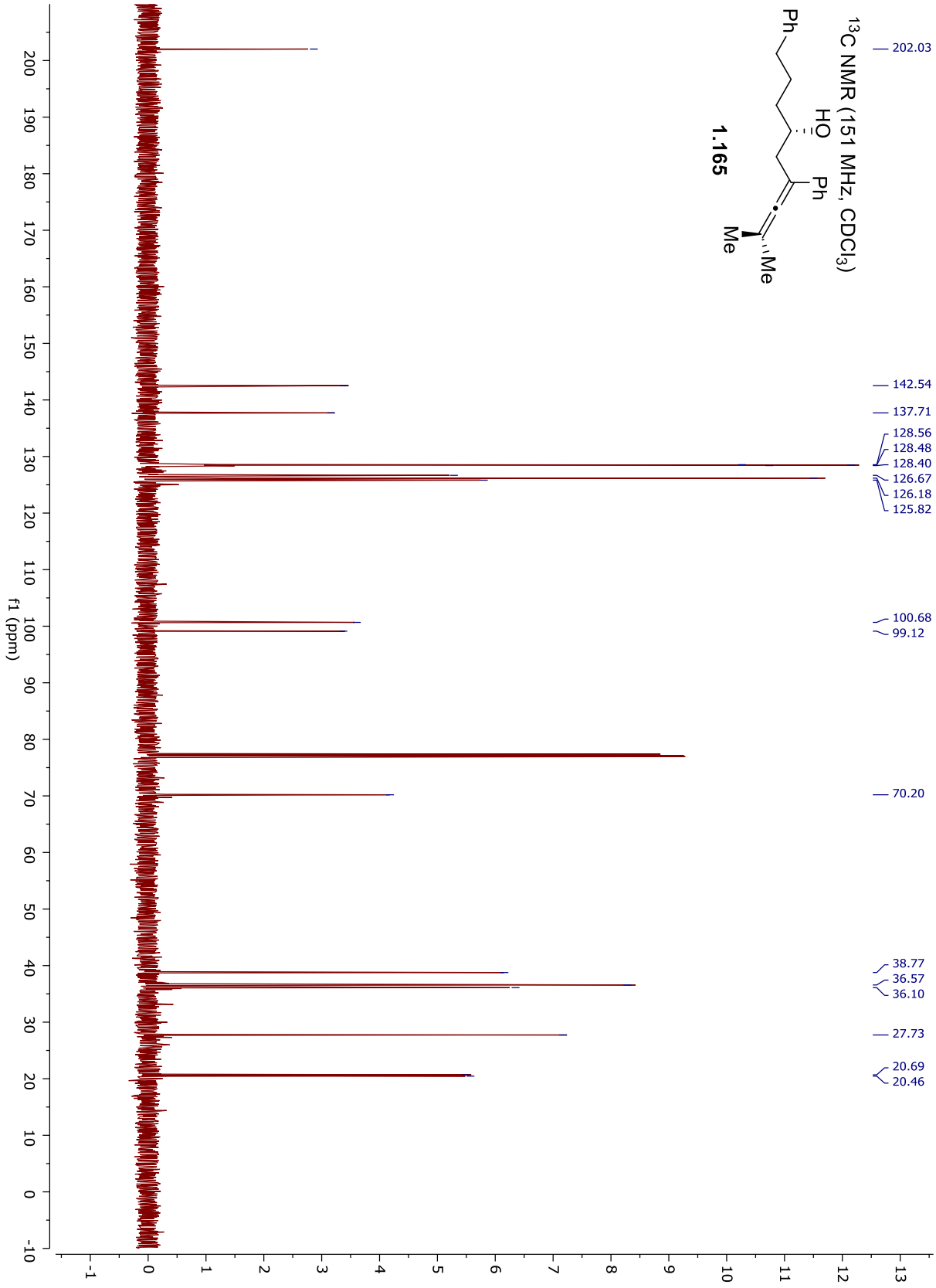
2.06
1.01
1.00
1.07
1.39
5.47
1.41
2.25
f1 (ppm)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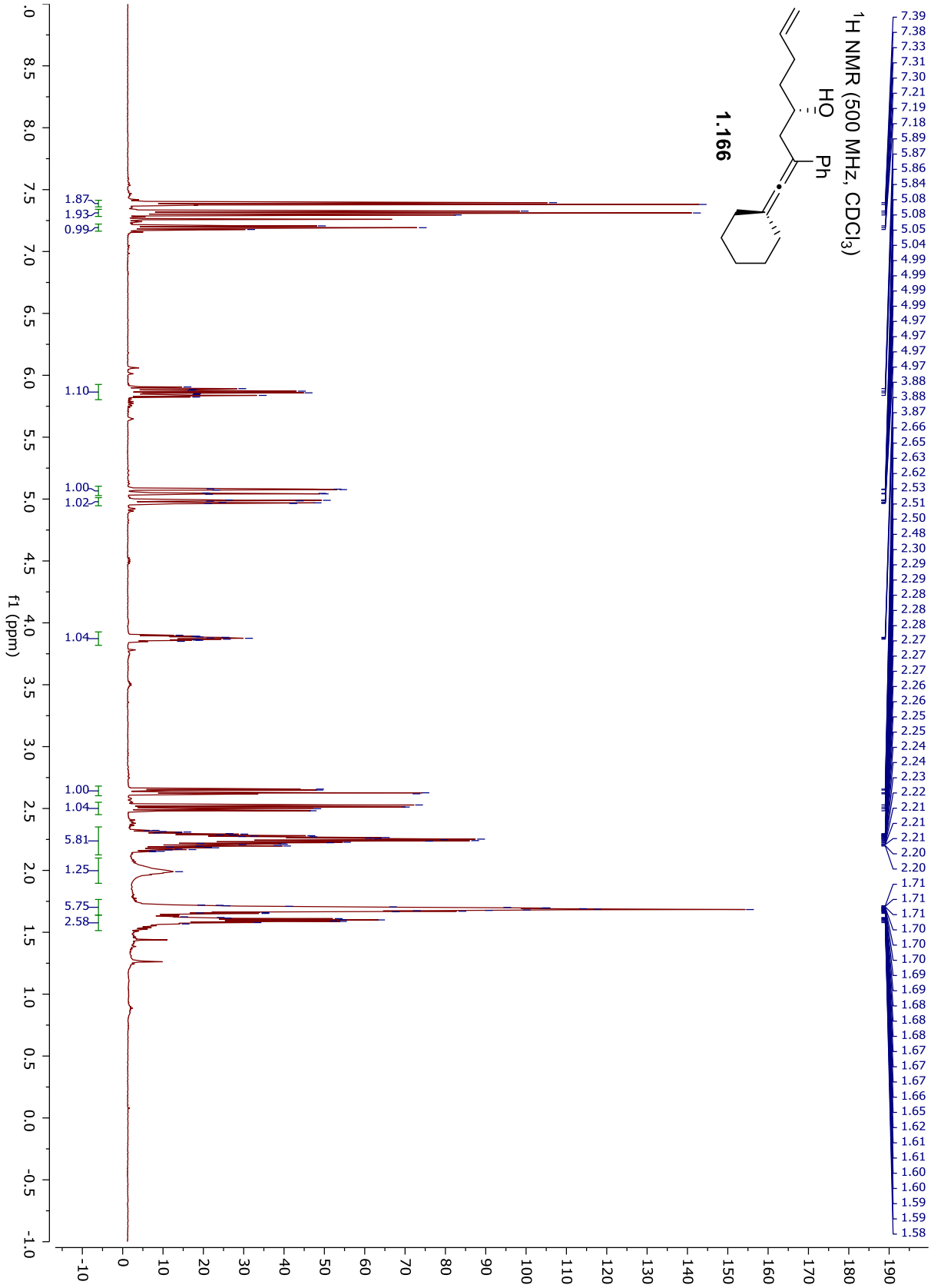
20.46
f1 (ppm)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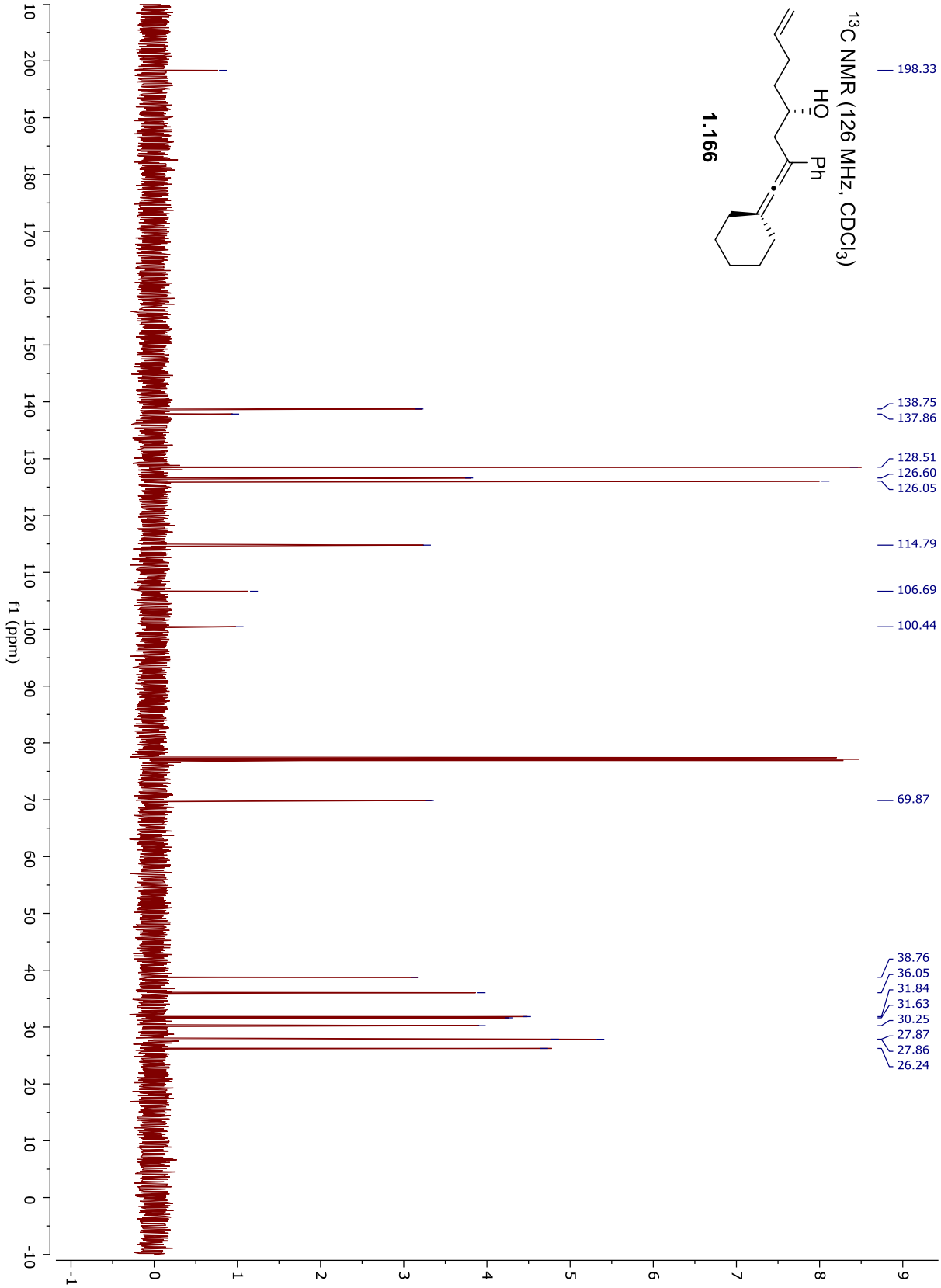
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106.69
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36.05
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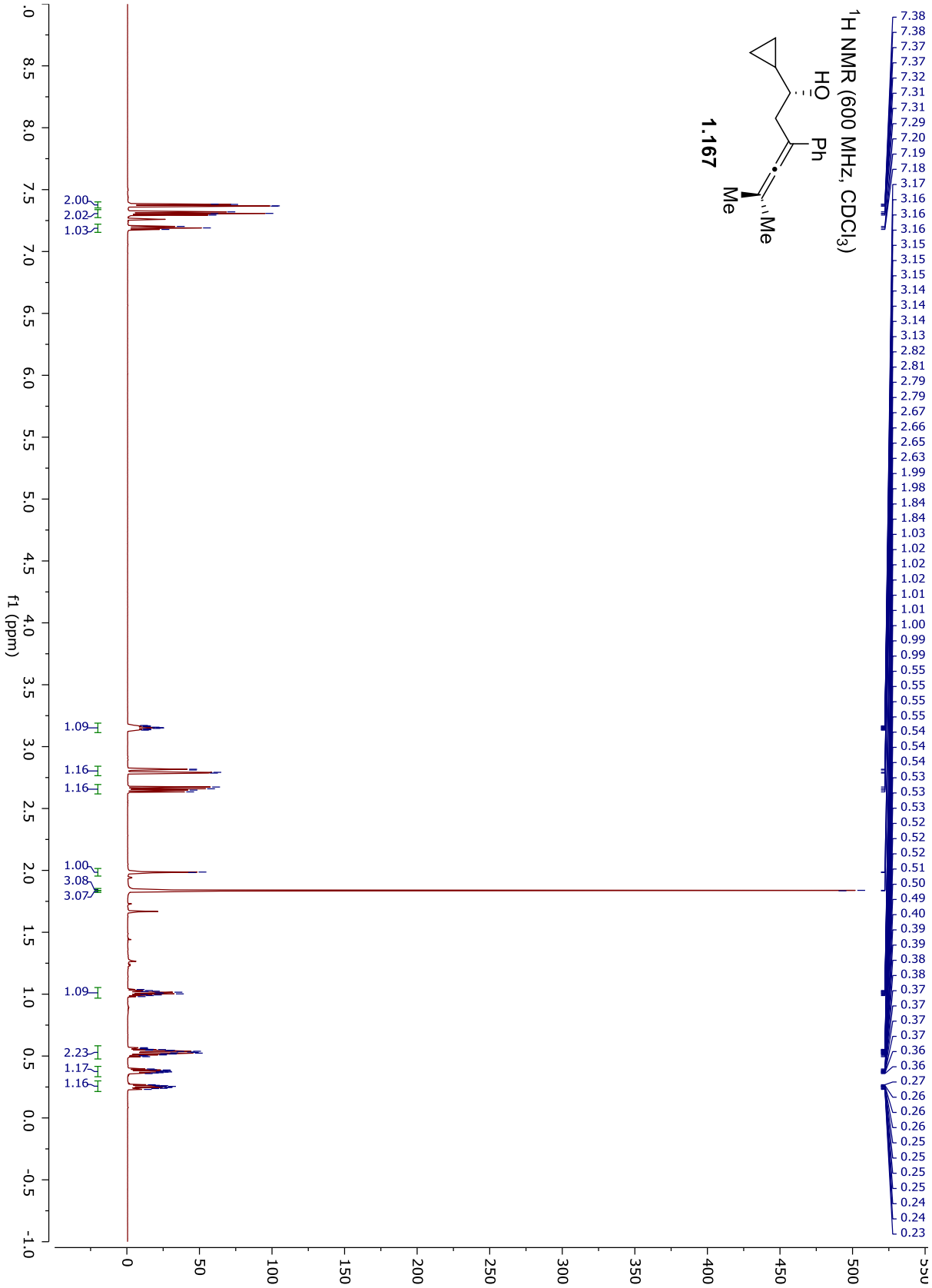
31.63
30.25
27.87
27.86
26.24
f1 (ppm)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Ph
Me
Me
f1 (ppm)
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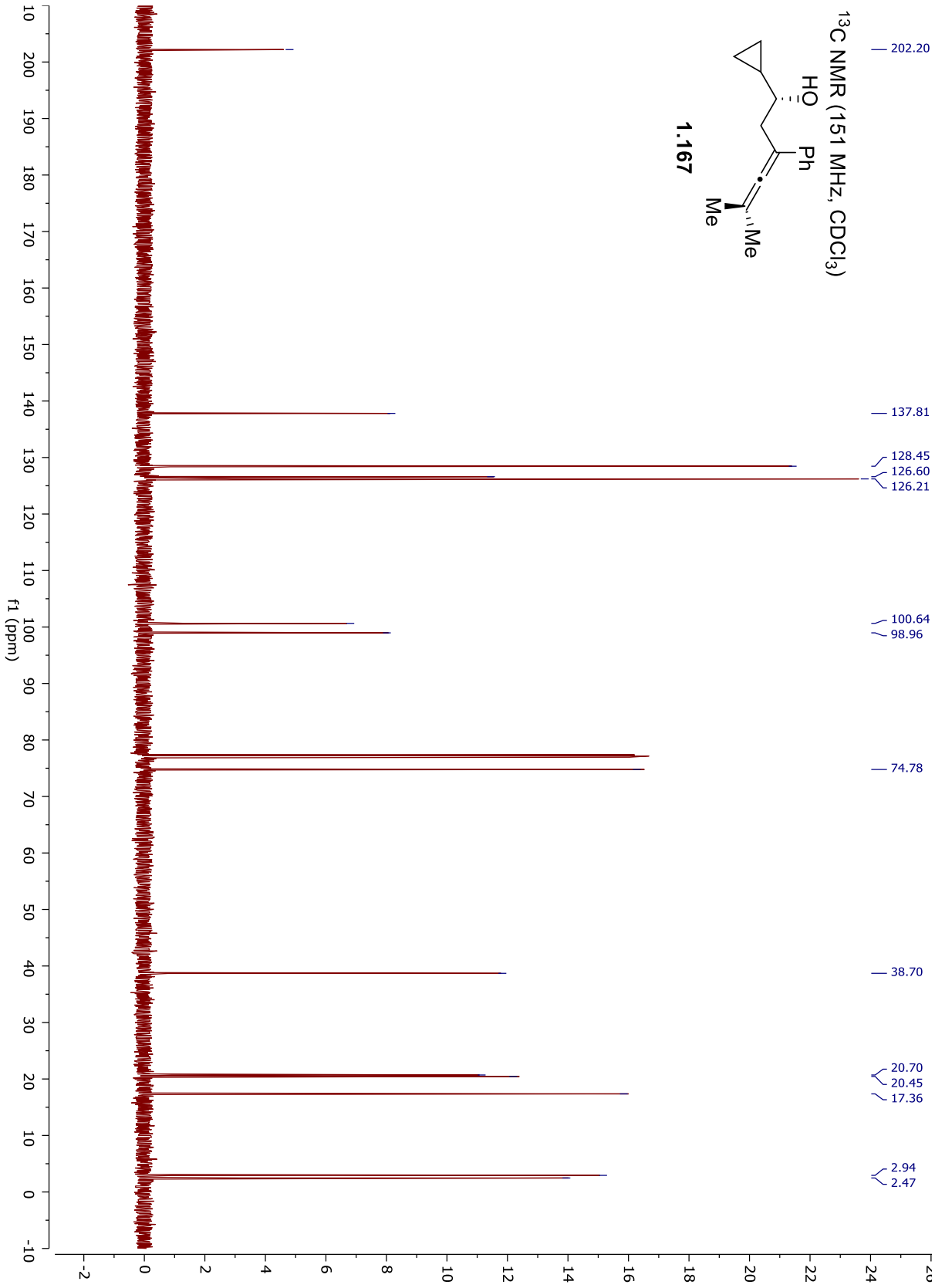
3.07
1.09
2.23
1.17
1.16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HO
Ph
Me
Me
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128.45
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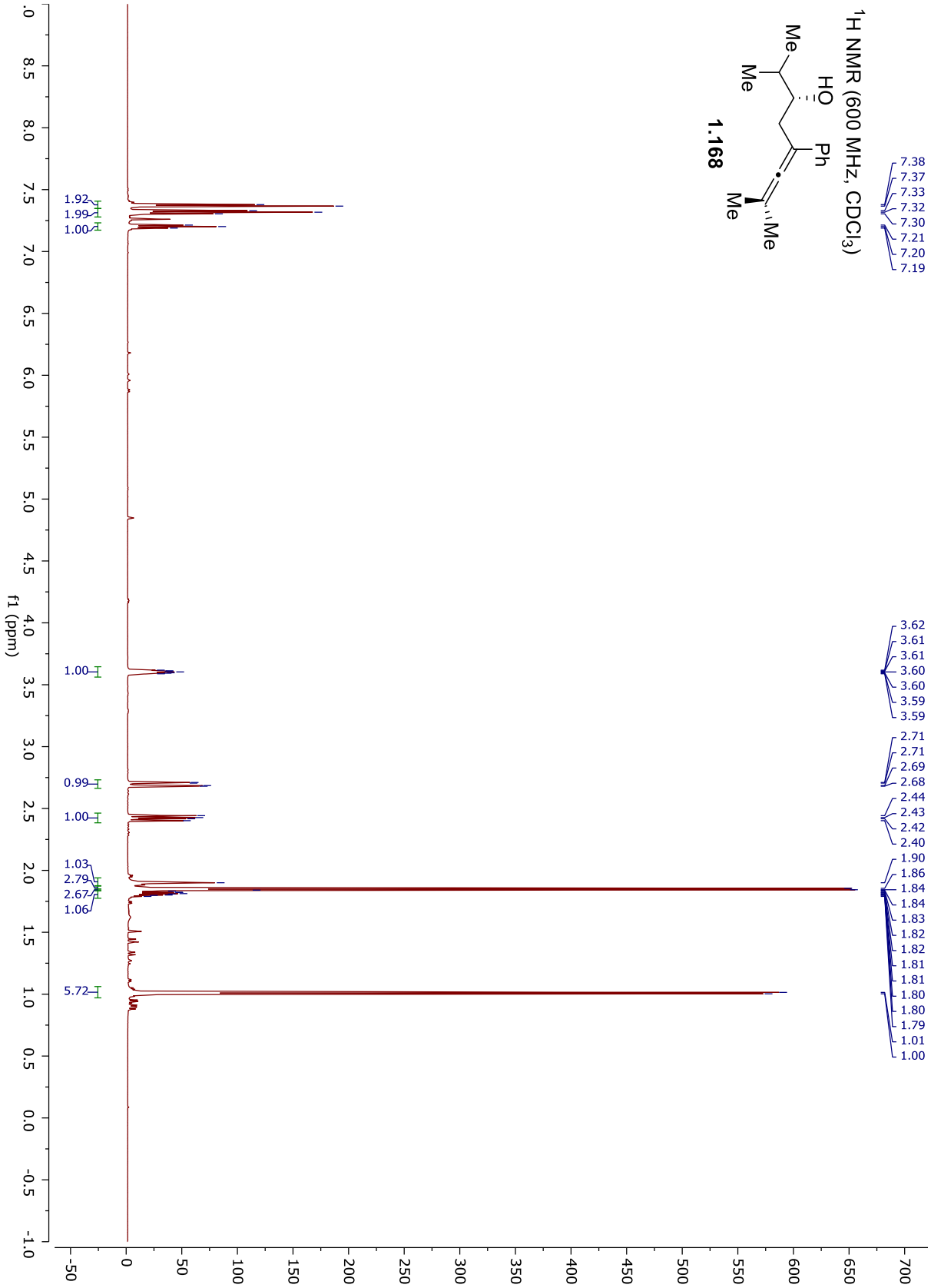
20.45
17.36
2.94
2.47
f1 (ppm)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Me
HO
Ph
Me
Me
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7.30
7.21
7.20
7.19
3.62
3.61
3.61
3.60
3.60
3.59
3.59
2.71
2.71
2.69
2.68
2.44
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1.82
1.81
1.81
1.80
1.80
1.79
1.01
1.00
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1.00
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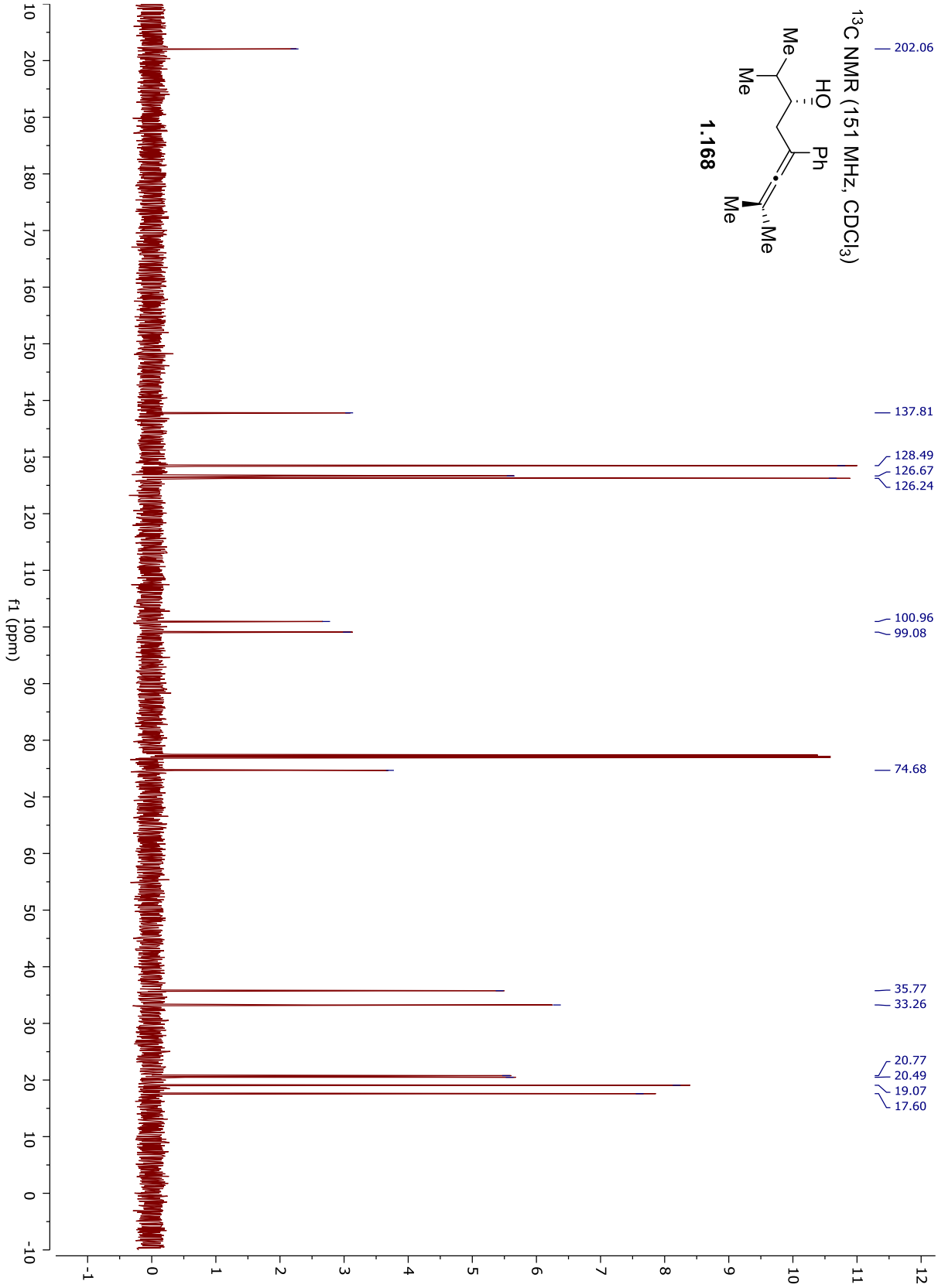
f1 (ppm)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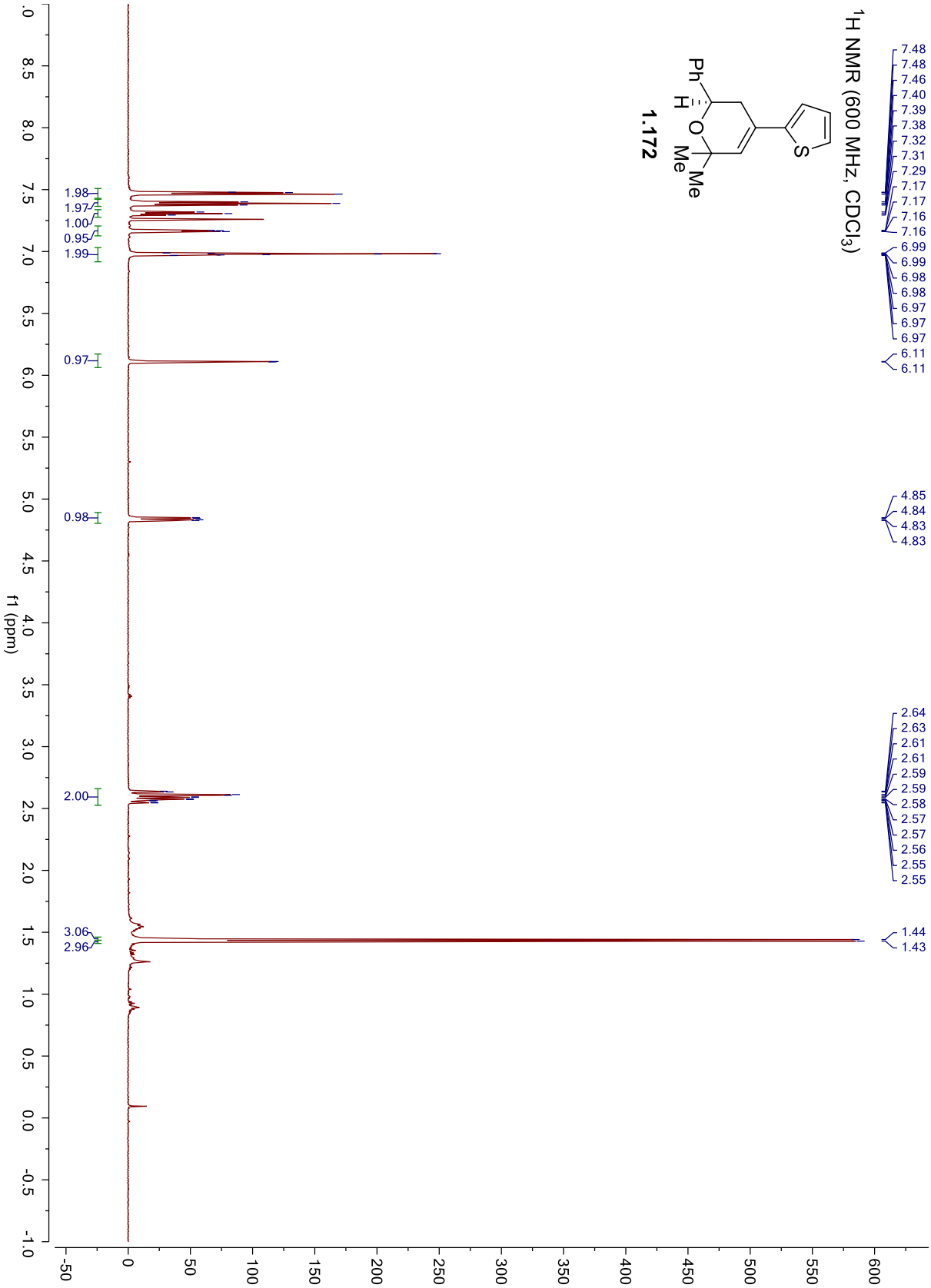
Me
HO
Ph
Me
Me
202.06
137.81
128.49
126.67
126.24
100.96
99.08
74.68
35.77
33.26
20.77
20.49
19.07
17.60
f1 (ppm)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Me
Me
S
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7.48
7.46
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7.39
7.38
7.32
7.31
7.29
7.17
7.17
7.16
7.16
6.99
6.99
6.98
6.98
6.97
6.97
6.97
6.11
6.11
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2.57
2.56
2.55
2.55
1.44
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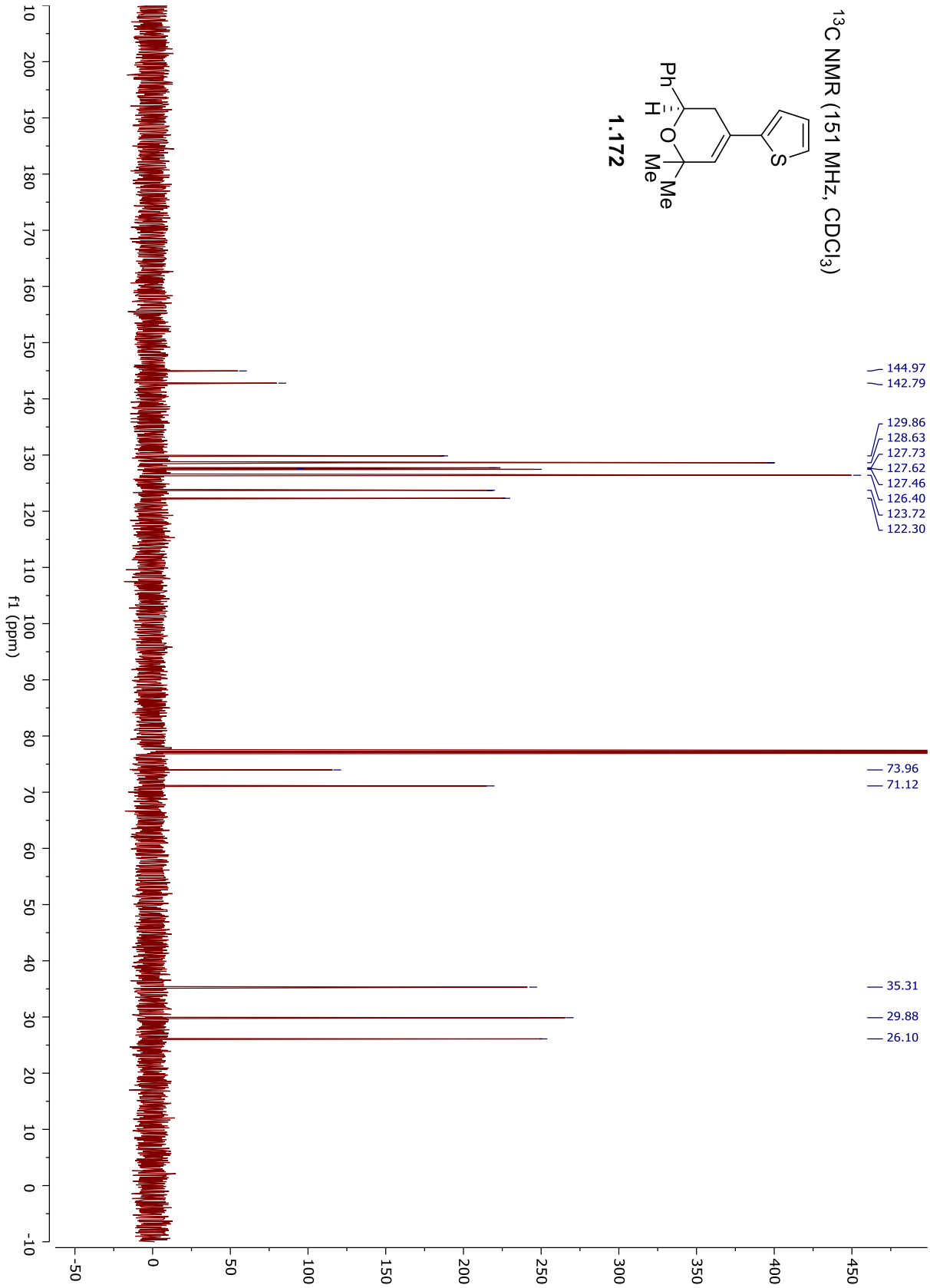
0.95
1.99
0.97
0.98
2.00
3.06
2.96
f1 (ppm)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Ph
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Me
Me
S
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127.62
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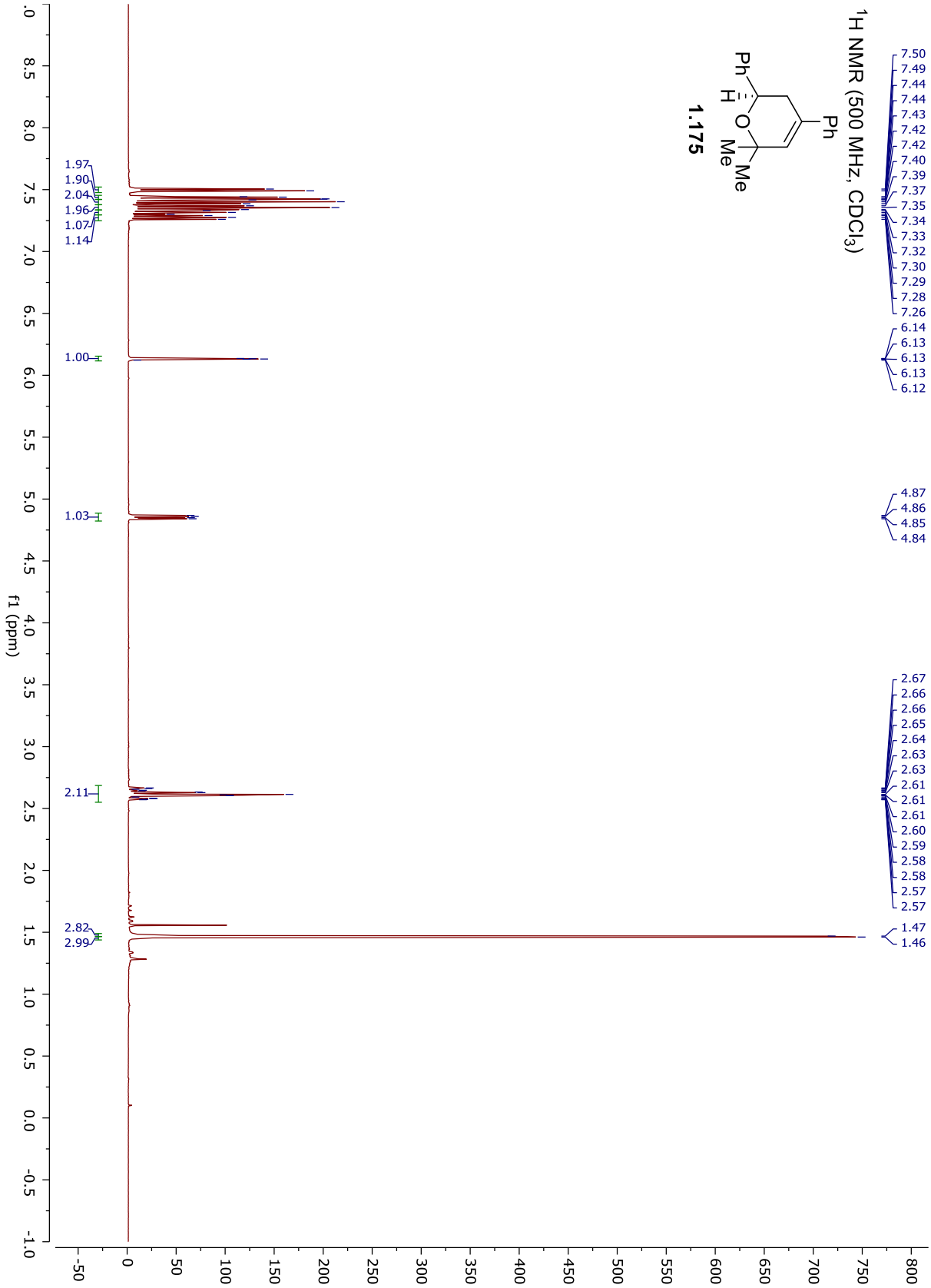
126.40
123.72
122.30
73.96
71.12
35.31
29.88
26.10
f1 (ppm)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2.64
2.63
2.63
2.61
2.61
2.61
2.60
2.59
2.58
2.58
2.57
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1.47
1.46
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1.14
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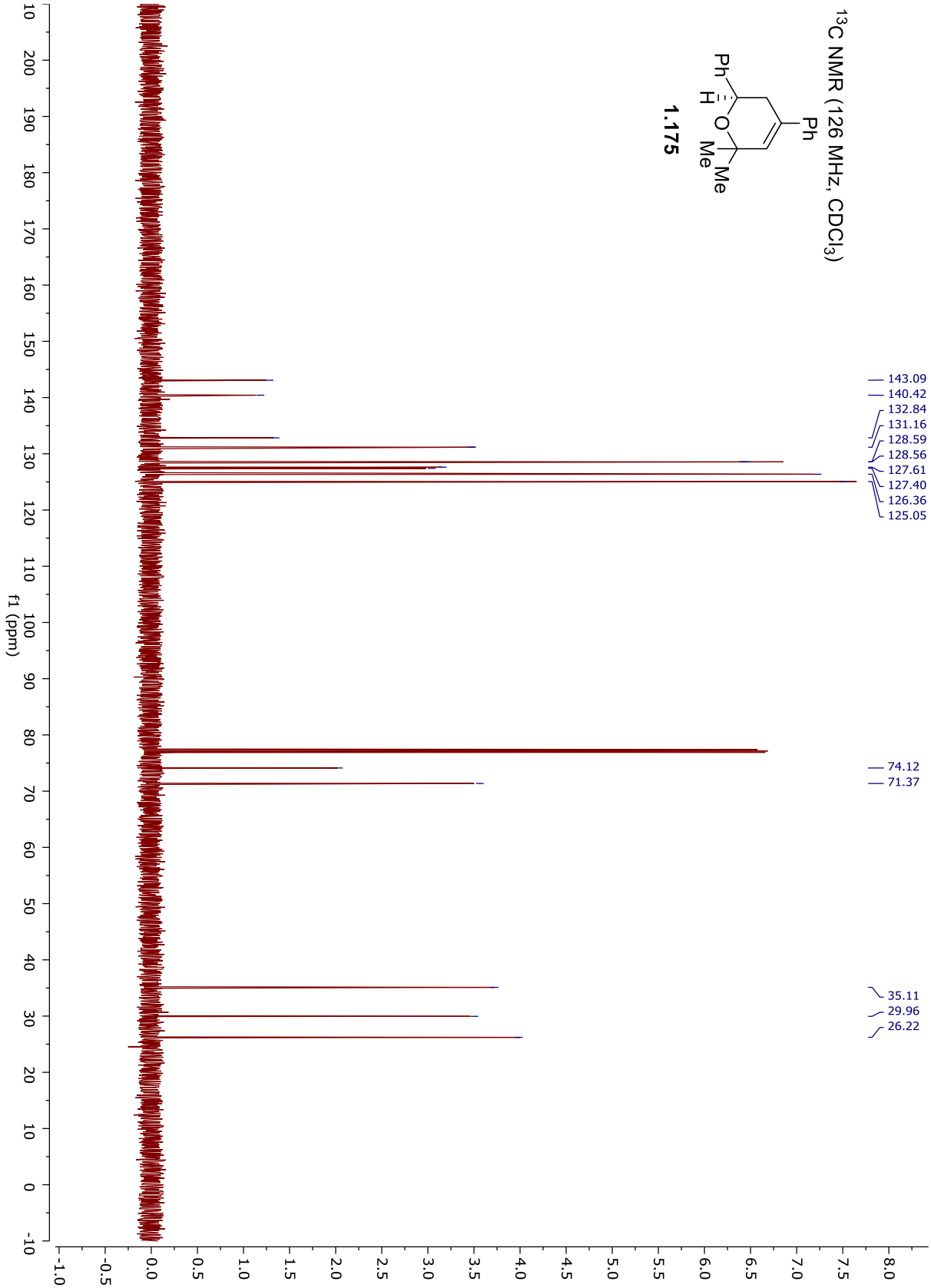
f1 (ppm)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O
Me
Me
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128.59
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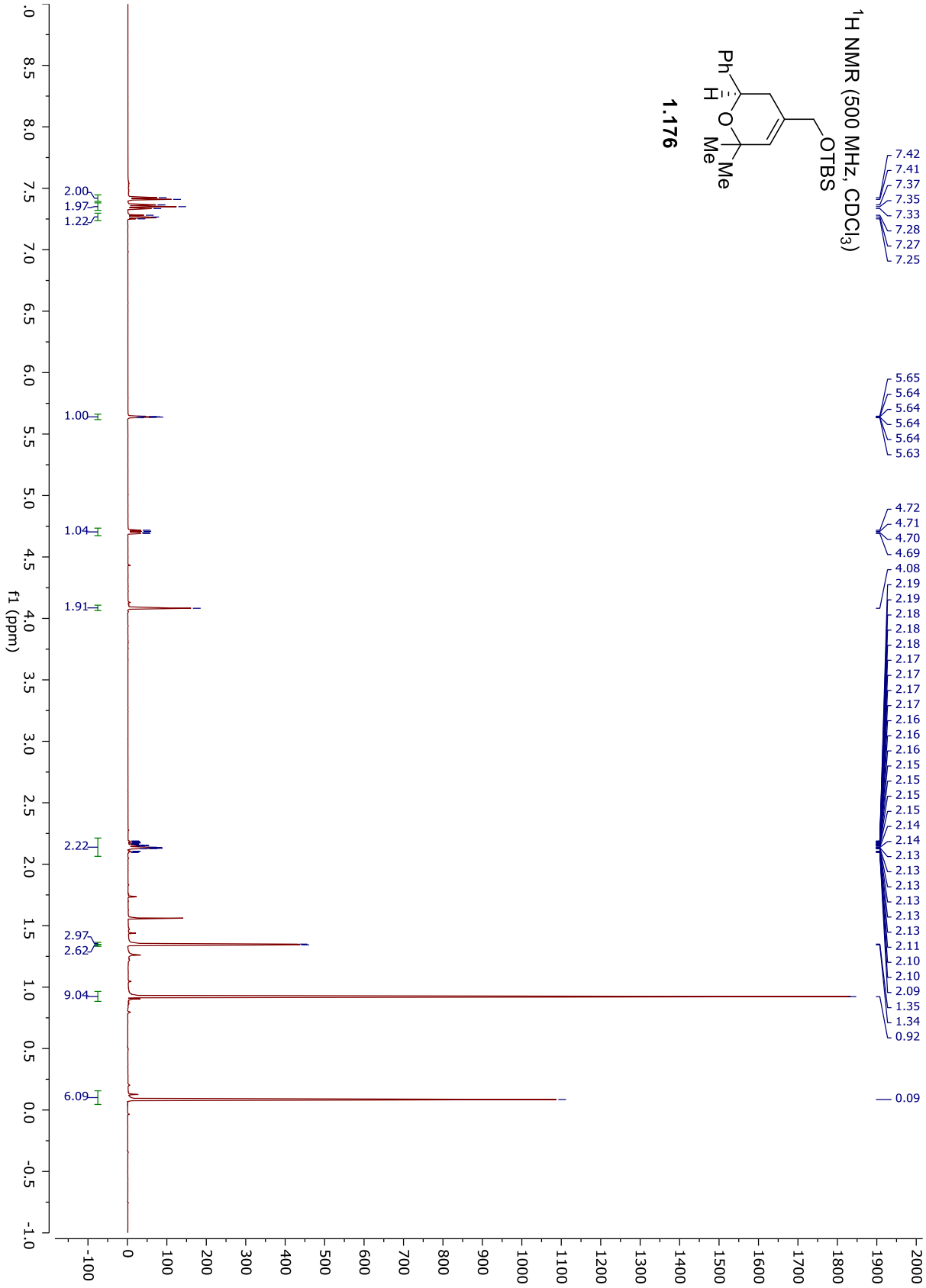
127.40
126.36
125.05
74.12
71.37
35.11
29.96
26.22
f1 (ppm)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2.13
2.13
2.13
2.13
2.13
2.13
2.11
2.10
2.10
2.09
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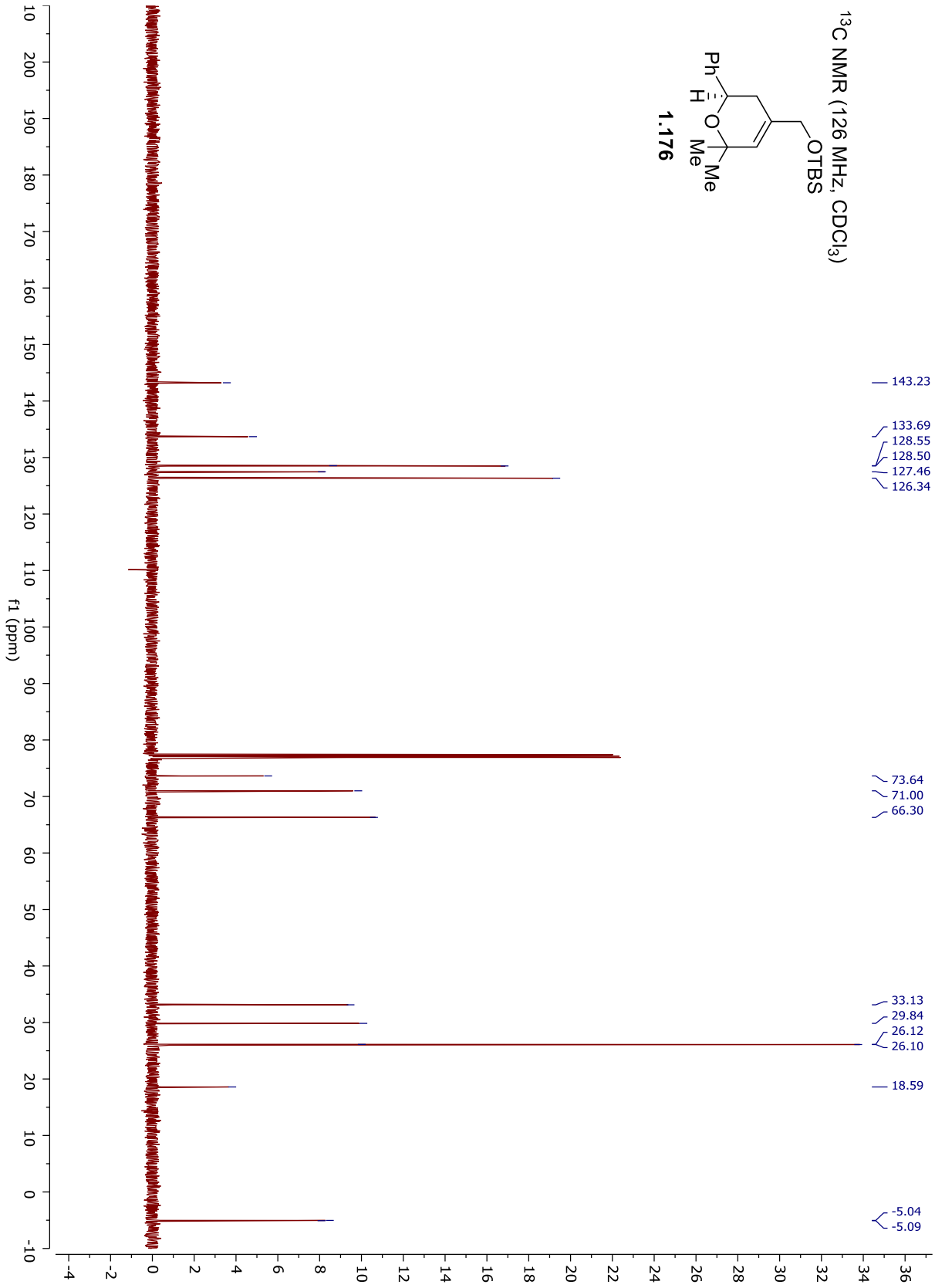
f1 (ppm)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Ph
H
O
Me
Me
OTBS
1.176
143.23
133.69
128.55
128.50
127.46
126.34
73.64
71.00
66.30
33.13
29.84
26.12
26.10
18.59
-5.04
-5.09
f1 (ppm)

Chapter Two

Enantiomerically Enriched α-Borylzinc Reagents by Nickel-Catalyzed Carbozincation of Vinylboronic Esters[1]

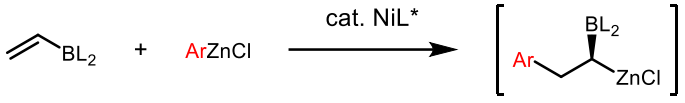
2.1 Introduction

Alkylzinc reagents are useful nucleophiles in organic synthesis because of their broad functional group compatibility and high capacity to engage in carbon-carbon and carbon-heteroatom bond forming reactions.[2] Even though organozinc reagents possess higher configurational stability[3] than organolithium and organomagnesium compounds, only achiral alkylzinc reagents have been widely employed in asymmetric synthesis;[4] chiral secondary alkylzinc reagents have been utilized in few examples, and with limited scope.[5] Challenges remain in: 1) stereocontrol when using racemic organozinc compounds in cross-coupling reactions (*i.e.*, stereoconvergent reactions), and 2) limited accessibility of enantioenriched

(1) Zhang, C.; Hu, W.; Lovinger, G. J.; Jin, J.; Chen, J.; Morken, J. P. *J. Am. Chem. Soc.* **2021**, *143*, 14189-14195.
(2) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117-2188.
(3) (a) Witanowski, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 737-741. (b) Klein, S.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1994**, *59*, 2925-2926. (c) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. Preparation and Applications of Functionalized Organozinc Compounds. In Organic Reactions; Overman, L. E., Ed.; Wiley: 2001; Vol. 58, p 417.
(4) (a) Huo, H. H.; Gorsline, B. J.; Fu, G. C. *Science* **2020**, *367*, 559-564. (b) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946-10949. (c) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016**, 6, 1540-1552.
(5) (a) Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 2748-2761. (b) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538-3539. (c) Beng, T. K.; Gawley, R. E. *Org. Lett.* **2011**, *13*, 394. (d) Skotnitzki, J.; Kremsmair, A.; Keefer, D.; Gong, Y.; de VivieRiedle, R.; Knochel, P. *Angew. Chem., Int. Ed.* **2020**, *59*, 320-324. (e) Murakami, K.; Yorimitsu, H. *J. Org. Chem.* **2013**, *9*, 278-291.

organozinc reagents in general. In this chapter, a strategy is described that overcomes the latter challenge by generating enantioenriched chiral organozinc reagents from the functionalization of alkenes. Enantioselective carbozincation of alkenyl boronic esters **2.1** with arylzinc reagents **2.2** gives a general approach to α-boryl alkylzinc compounds **2.3** with synthetically useful yields and good enantioselectivities (Scheme 2.1).

Scheme 2.1. Carbozincation of Alkenyl Boronates



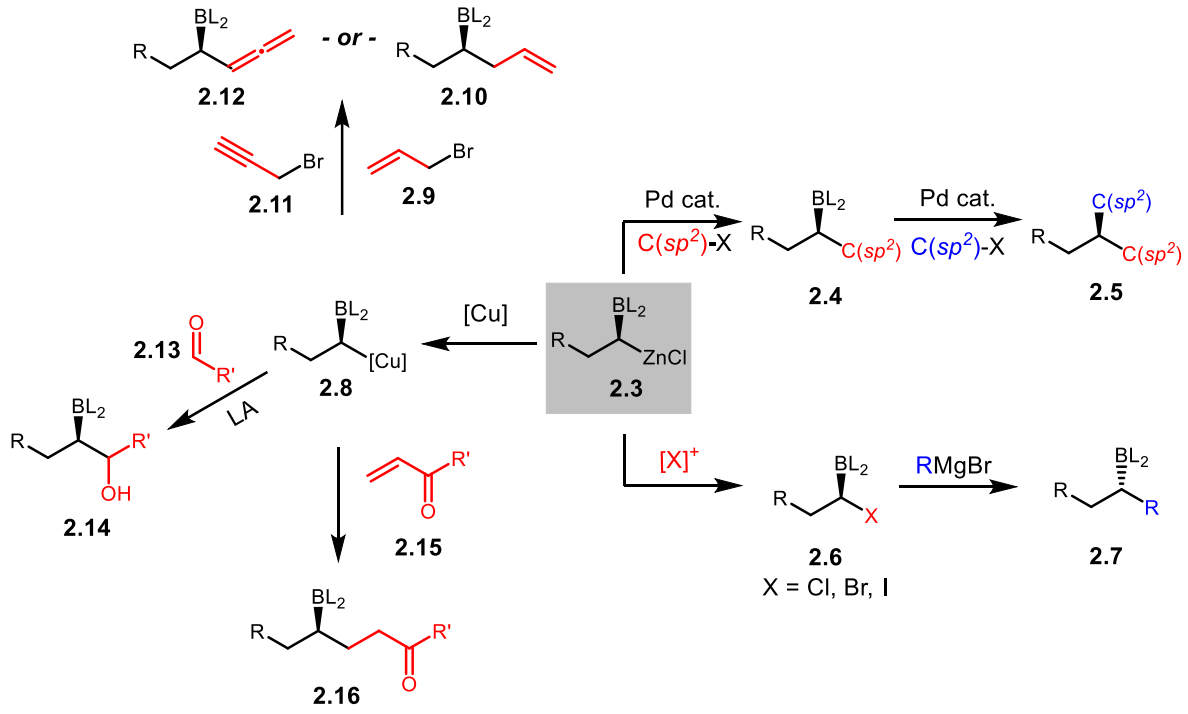
2.1 **2.2** **2.3**

The α-borylalkylzinc species **2.3** generated in the above-mentioned reaction is a versatile building block in organic synthesis.[6] It has been reported to couple with a broad range of electrophiles to give diverse and useful secondary alkyl boronic esters, which can be further used in a second carbon—carbon or carbon—heteroatom bond construction reaction (Scheme 2.2).[2] For example, α-borylalkylzinc compounds **2.3** can participate in the Negishi cross-coupling to generate secondary organoboronates **2.4**,[6c] which could be further converted to compounds **2.5** through Suzuki-Miyaura cross-coupling reaction.[7] α-Borylalkylzinc species **2.3** can also react with electrophilic halogenation reagents, such as NIS, to generate α-boryl halides **2.6**,[1] which could undergo stereospecific Matterson homologation[8] to deliver secondary organoboronates **2.7**.

(6) (a) Knochel, P. *J. Am. Chem. Soc.* **1990**, *112*, 7431-7433. (b) Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956-1958. (c) Watanabe, T.; Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1993**, *444*, C1-C3. (d) Nakamura, M.; Hara, K.; Hatakeyama, T.; Nakamura, E. *Org. Lett.* **2001**, *3*, 3137-3140.
(7) Glasspoole, B. W.; Oderinde, M. S.; Moore, B. D.; Antoft-Finch, A.; Crudden, C. M. *Synthesis* **2013**, *45*, 1759-1763.
(8) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588-7590.

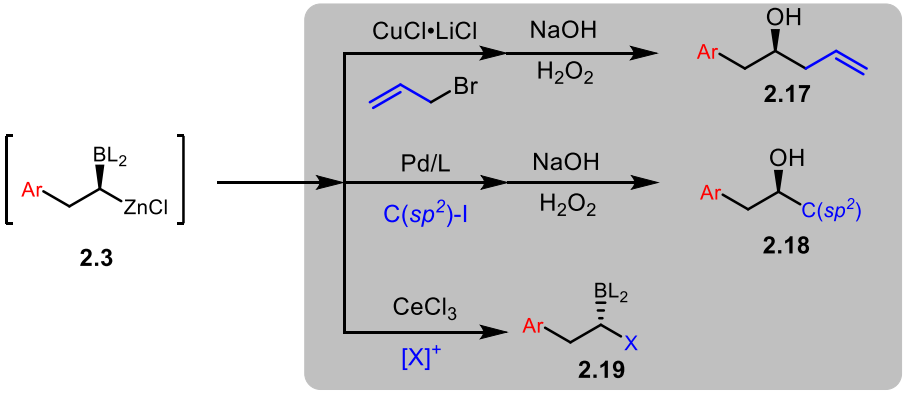
On the other hand, after transmetalation from zinc to copper, the resulting α-boryl copper intermediates **2.8** can react with allyl bromides (**2.9**),[6a] propargyl bromides (**2.11**),[6a] aldehydes (**2.13**),[6a] and Michael acceptors[6a] (**2.15**) to furnish homoallylic boronates (**2.10**), allenic boronates (**2.12**), secondary boronates (**2.14**), and γ-boryl carbonyls (**2.16**), respectively.

Scheme 2.2. Reactions of α-Boryl Zinc Species



This chapter will showcase that α-boryl zinc species generated from carbozincation can be *in situ* subjected to copper-mediated allylations, palladium-catalyzed Negishi cross-couplings, and cerium-mediated halogenation reactions (Scheme 2.3).

Scheme 2.3. Reactions of α-Boryl Zinc Species Generated from Carbozincation



2.2 Background

In this section, the background of enantioselective synthesis of α-boryl zinc reagents will be reviewed, which includes advances in the use of α-boryl organometallic reagents in asymmetric synthesis and the development of transition metal-catalyzed carbozincation of alkenes.

2.2.1 Synthesis of α-Boryl Organometallic Reagents[9]

α-Boryl organometallic reagents are potent and distinctive building blocks in asymmetric synthesis. Because the valance-deficient feature of tri-coordinated boron can stabilize the negative charge at an adjacent carbon atom,[10] α-boryl organometallic reagents often exhibit unusual reactivity compared to non-stabilized organometallic reagents. For example, geminal bis(boronates) are known to undergo deborylative alkylation of electrophiles in the absence of

(9) Zhang, C.; Hu, W.; Morken, J. P. *ACS Catal.* **2021**, *11*, 10660-10680.
(10) (a) Kawashima, T.; Yamashita, N.; Okazaki, R. *J. Am. Chem. Soc.* **1995**, *117*, 6142−6143.; (b) Pelter, A.; Buss, D.; Colclough, E.; Singaram, B. *Tetrahedron* **1993**, *49*, 7077−7103. (c) Olmstead, M. M.; Power, P. P.; Weese, K. J.; Doedens, R. J *J. Am. Chem. Soc.* **1987**, *109*, 2541−2542. (d) Pelter, A.; Singaram, B.; Williams, L.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 623−626. (e) Rathke, M. W.; Kow, R. *J. Am. Chem. Soc.* **1972**, *94*, 6854−6856.

transition metal catalysts.[11] Of similar significance, the reaction products that arise from reaction of the geminal bimetallic moiety often possess considerable synthetic utility. For example, α-boryl zinc[6] and zirconocene [12] reagents can participate in coupling reactions with many electrophiles delivering chiral organoboron compounds as the product. Importantly, the resulting alkyl boronic esters are chemically and configurationally stable synthetic building blocks that can be used in many stereospecific reactions.[13]

Even though α-metalated organoboronates have shown their importance in the synthesis of complex molecules since the 1990s,[14] until the last decade little progress has been made in the field related to asymmetric synthesis. In this section, I will give a brief overview about the preparation and application of chiral metalated organoboronates based on B, Zr, and Zn. These compounds are all configurationally and chemically stable reagents that play important roles in the synthesis of enantioenriched organic compounds.

2.2.2 Synthesis of Geminal Bis(boronates)[9]

Geminal bis(boronates) have attracted wide attention due to two unique features.[15] First, the air- and moisture-stability of this reagent class allows for dry-box free manipulations, leading to increased practicality. Second, prochiral geminal bisboryl species can be readily prepared

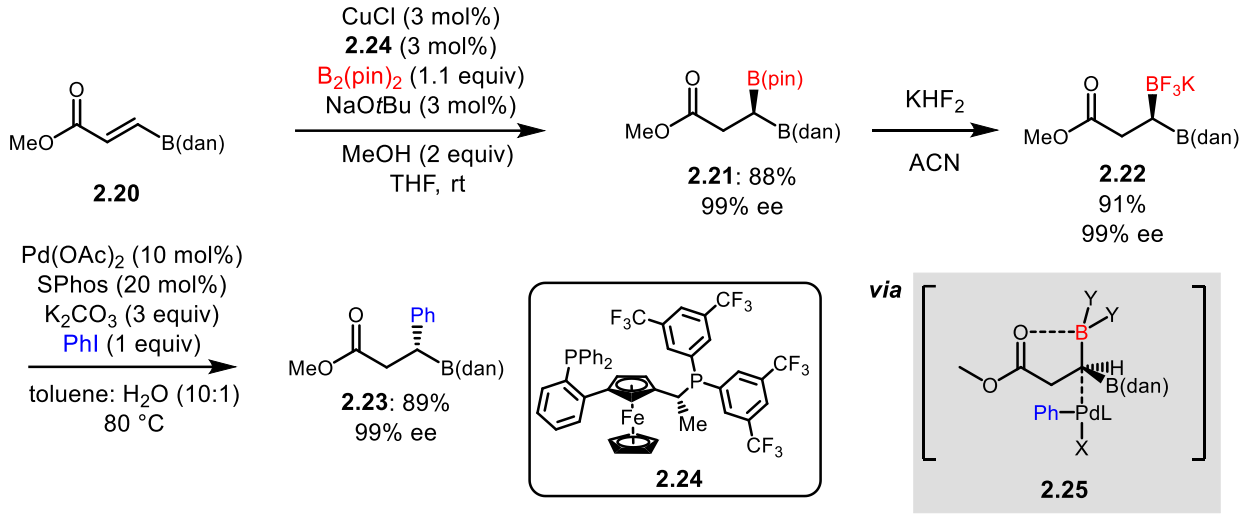
(11) Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581−10584.
(12) (a) Zheng, B.; Deloux, L.; Skrzypczak-Jankun, E.; Cheesman, B. V.; Pereira, S.; Srebnik, M.; Sabat, M. *J. Mol. Struct.* **1996,** *374*, 291–297. (b) Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1995,** *36*, 1805–1808. (c) Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995,** *60*, 486–487. (d) Pereira, S.; Srebnik, M. *J. Org. Chem.* **1995,** *60*, 4316–4317. (e) Skrzypczak-Jankun, E.; Cheesman, B. V.; Zheng, B.; Lemert, R. M.; Asthana, S.; Srebnik, M. *J. Chem. Soc. Chem. Commun.* **1994**, 127–128. (f) Zheng, B.; Srebnik, M. *Tetrahedron Lett.* **1993,** *34*, 4133–4136. (g) Zheng, B.; Deloux, L.; Pereira, S.; Skrzypczak-Jankun, E.; Cheesman, B. V.; Sabat, M.; Srebnik, M. *Appl. Organomet. Chem.* **1996,** *10*, 267–278.
(13) (a) Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481–5494. (b) Hall, D. G., *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials, Second Edition*. Wiley-VCH: 2011.
(14) Marek, I.; Normant, J. F. *Chem. Rev.* **1996,** *96*, 3241–3267.
(15) (a) Wu, C. Q.; Wang, J. B. *Tetrahedron Lett.* **2018,** *59*, 2128–2140. (b) Nallagonda, R.; Padala, K.; Masarwa, A. *Org. Biomol. Chem.* **2018,** *16*, 1050–1064. (c) Miralles, N.; Maza, R. J.; Fernández, E. *Adv. Synth. Catal.* **2018**, *360*, 1306–1327.

from commercially available precursors including methylene bis(boronates), geminal dibromides, alkynes,[16] alkenes,[17] ketones,[18] diazo compounds,[19] and esters.[20] However, only a few synthetic methods have been described to provide enantioenriched *gem*-bisboryl compounds.

The first synthesis of enantiomerically enriched geminal bis(boronates) was reported by Hall and co-workers in 2011 (Scheme 2.4).[21] With the combination of $B_2(pin)_2$ and a chiral copper catalyst, they accomplished an enantioselective boron conjugate addition to 3-boryl acrylate derivative **2.20**, affording geminal bisboryl carboxyl ester **2.21** in 99% enantiomeric excess. The subsequent chemo- and stereoselective Suzuki–Miyaura cross-coupling with sp^2 carbon electrophiles gave access to secondary boronates **2.23** with excellent levels of enantiomeric purity. X-ray analysis of product **2.21** suggested possible coordination between the carbonyl oxygen and the pinacolato ligand. During the cross-coupling, chelating interactions are expected to be stronger with trifluoroborate-derived substrates due to the formation of the derived boronic acid intermediate *in situ*; such coordination facilitates the challenging transmetalation between palladium and alkyl boronates that occurs in the Suzuki–Miyaura reaction.[21, 22] Of note, the B(dan) (dan = 1,8-diaminonaphthalene) unit was proposed to stabilize the α-boryl Pd(II) intermediate, which suppresses potential unproductive β-hydride elimination pathway.

(16) (a) Zuo, Z. Q.; Huang, Z. *Org. Chem. Front.* **2016,** *3*, 434–438. (b) Lee, S.; Li, D.; Yun, J. *Chem. Asian J.* **2014,** *9*, 2440–2443. (c) Endo, K.; Hirokami, M.; Shibata, T. *Synlett* **2009**, 1331–1335. (d) Docherty, J. H.; Nicholson, K.; Dominey, A. P.; Thomas, S. P. *ACS Catal.* **2020,** *10*, 4686–4691.
(17) (a) Hu, M.; Ge, S. Z. *Nat. Commun.* **2020**, *11*, 765. (b) Li, L.; Gong, T. J.; Lu, X.; Xiao, B.; Fu, Y. *Nat. Commun.* **2017**, *8*, 345.
(18) Wang, L.; Zhang, T.; Sun, W.; He, Z. Y.; Xia, C. G.; Lan, Y.; Liu, C. *J. Am. Chem. Soc.* **2017,** *139*, 5257–5264.
(19) (a) Li, H.; Shangguan, X. H.; Zhang, Z. K.; Huang, S.; Zhang, Y.; Wang, J. B. *Org. Lett.* **2014,** *16*, 448–451. (b) Wommack, A. J.; Kingsbury, J. S. *Tetrahedron Lett.* **2014,** *55*, 3163–3166.
(20) He, Z. Y.; Zhu, Q.; Hu, X.; Wang, L.; Xia, C. G.; Liu, C. *Org. Chem. Front.* **2019,** *6*, 900–907.
(21) Lee, J. C.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011,** *3*, 894–899.
(22) Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817–5819.

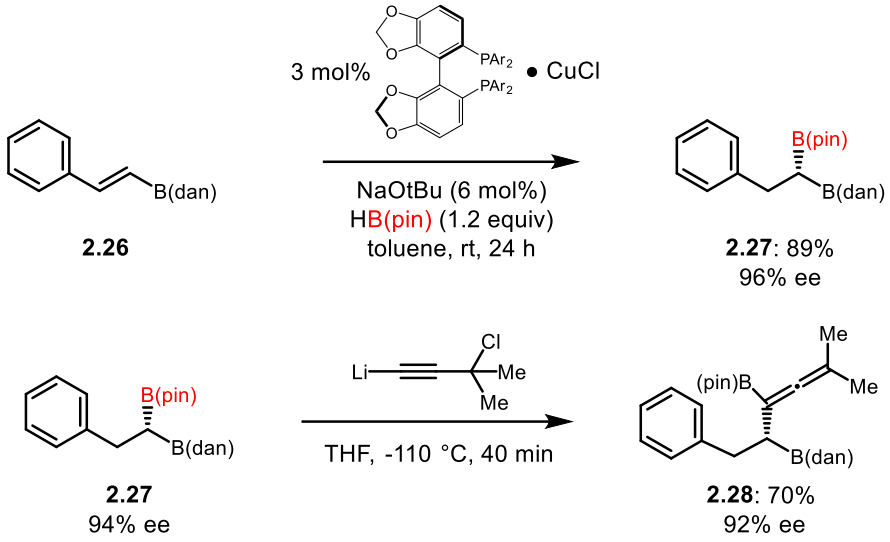
Scheme 2.4. Copper-Catalyzed Enantioselective Conjugate Borylation to Alkenyl Boronic Esters



Asymmetric hydroboration of alkenes is also a well-established method for the synthesis of chiral alkylboronates.[23] Taking advantage of this approach, the Yun group developed the copper-catalyzed hydroboration of alkenyl B(dan) **2.26** resulting in 1,1-diboryl species **2.27** with excellent regio- and enantioselectivity (Scheme 2.5).[24] The reaction was shown to proceed through Cu–H addition to the C–C double bond, with the resulting chiral α-boryl copper intermediate then undergoing σ-bond metathesis with pinacolborane to provide the *gem*-bisboryl product **2.27**. The regioselectivity of the Cu–H addition step was proposed to be controlled by the electron-deficient nature of the boron group. Despite its decreased Lewis acidity, the B(dan) group reacted with improved regioselectivity relative to B(pin).[24] This outcome is proposed to occur because the planarity of the B(dan) group allows it to accommodate an adjacent bulky Cu–L moiety more easily. In addition to reporting the catalytic reaction, the Yun group also described a chemoselective homologation of the chiral bis(boronates) to afford **2.28** wherein the B(pin) unit was selectively converted with the retention of enantiomeric purity.

(23) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957–5026.
(24) Feng, X.; Jeon, H.; Yun, J. *Angew. Chem. Int. Ed.* **2013,** *52*, 3989–3992.

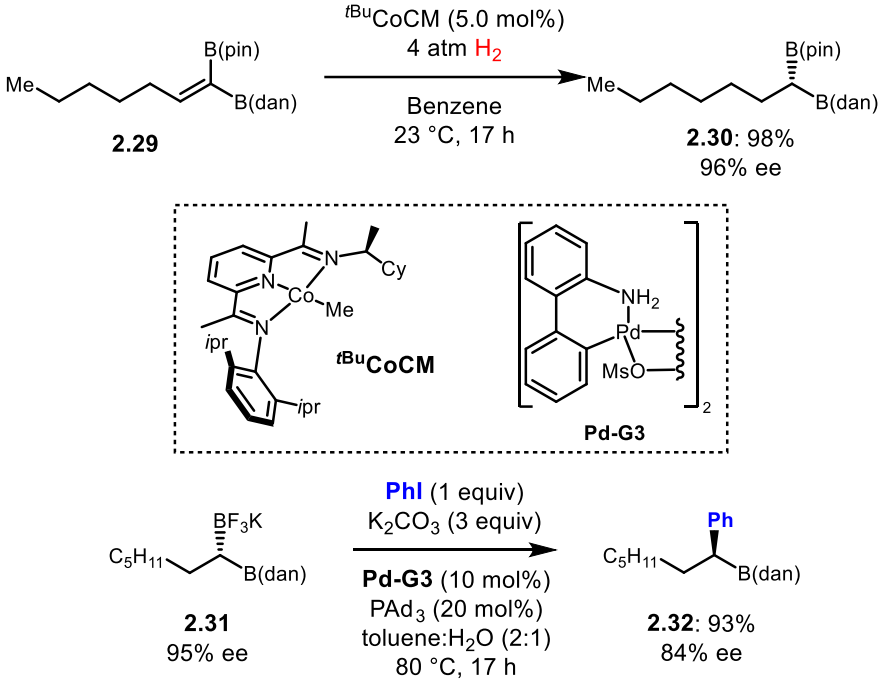
Scheme 2.5. Copper-Catalyzed Enantioselective Hydroboration to Alkenyl Boronic Esters



As an alternative to the Yun hydroboration, Chirik and co-workers reported the asymmetric hydrogenation of 1,1-diboryl alkenes **2.29** to produce enantioenriched geminal bisboryl compounds such as **2.30** (Scheme 2.6).[25] This team identified the C_1-symmetric pyridine(diimine) (PDI) ligand on cobalt as an efficient and stereoselective catalyst for this transformation. Mechanistic studies revealed that use of sterically unencumbered boronate groups, such as B(dan) or B(cat), is essential to obtain the observed reactivity and enantioselectivity. Similar to Yun's observation, deuterium-labeling experiments suggested that less encumbered boron ligands allow for higher α-selectivity during the migratory insertion into a Co—H to form a boron-stabilized alkylcobalt intermediate. The chiral *gem*-bis(boronates) were converted to trifluoroborate salts **2.31**, which were further applied in a stereoinvertive Suzuki–Miyaura cross-coupling reaction to furnish **2.32**.

(25) Viereck, P.; Krautwald, S.; Pabst, T. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2020,** *142*, 3923–3930.

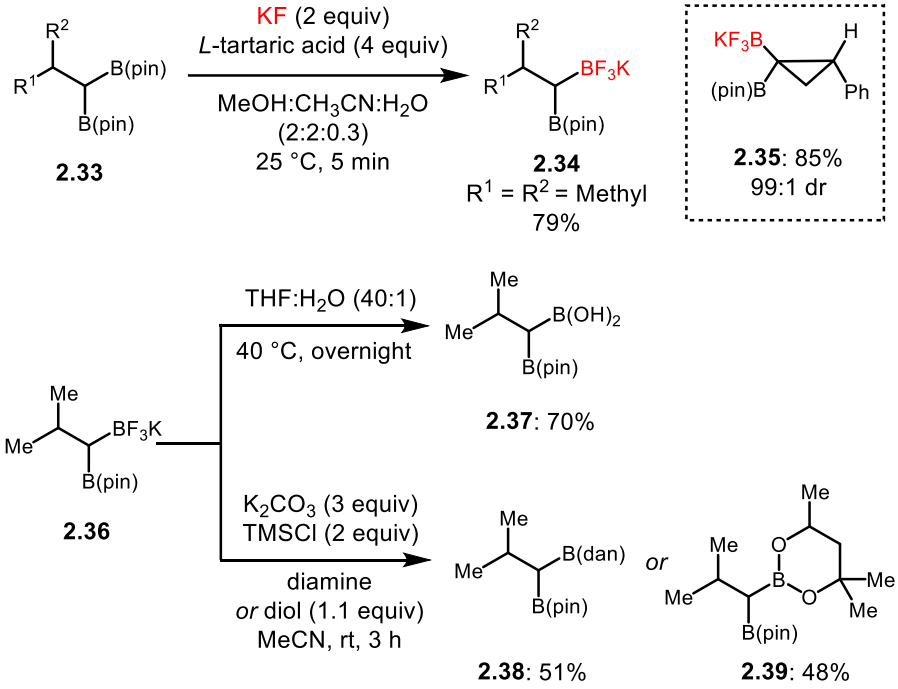
Scheme 2.6. Enantioselective Hydrogenation to Alkenyl *gem*-bis(boronates)



More recently, the Masarwa group established a diastereoselective desymmetrization strategy to produce chiral geminal bis(boronates) **2.34**.[26] In this strategy, diastereotopic B(pin) groups were differentiated during a "trifluorination" process (Scheme 2.7). However, high diastereoselectivity was only achieved with cyclopropane derivatives (i.e., **2.35**). The resulting *gem*-diboron salts **2.36** can be readily converted to different unsymmetrical *gem*-bis(boronates) **2.37-2.39**.

(26) Kumar, N.; Reddy, R. R.; Masarwa, A. *Chem. Eur. J.* **2019,** *25*, 8008–8012.

Scheme 2.7. Desymmetrization of Alkyl *gem*-Diboronates through "Trifluorination" Process

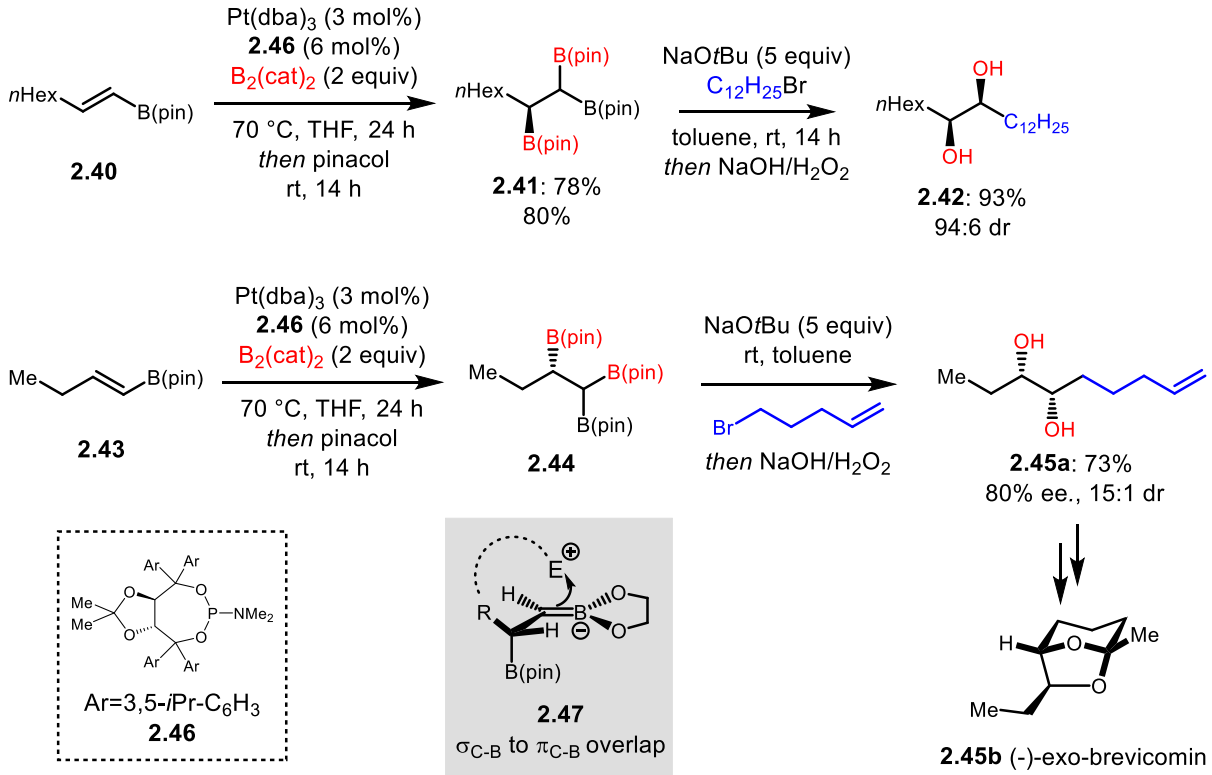


Instead of generating chirality by using nonidentical boryl groups, another approach towards chiral *gem*-bis(boronates) is to construct a stereogenic center close to the prochiral *gem*-bisboryl motif. Taking advantage of this neighboring stereogenic center, diastereoselective functionalization of one of the boryl groups can be realized. Following this strategy, in 2014, platinum-catalyzed enantioselective diboration of alkenyl boronic esters **2.40** (Scheme 2.8) was developed by the Morken group for the preparation of enantioenriched 1,1,2-tris(boronates) **2.41**.[27] The tris(boronate) can be employed in subsequent substrate-controlled diastereoselective deborylative alkylation reactions, which afforded syn-diols **2.42** upon oxidation. In the deborylative alkylation step, hyperconjugation between the non-reacting carbon–boron σ-bond and an adjacent carbon–boron π bond was proposed to increase the nucleophilicity of the reactive intermediate and influence the stereochemical outcome of the reaction (**2.47**). This

(27) Coombs, J. R.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014,** *136*, 16140–16143.

reaction was applied as a key step in the stereoselective formal synthesis of **2.45b** starting from the diboration of **2.43**.

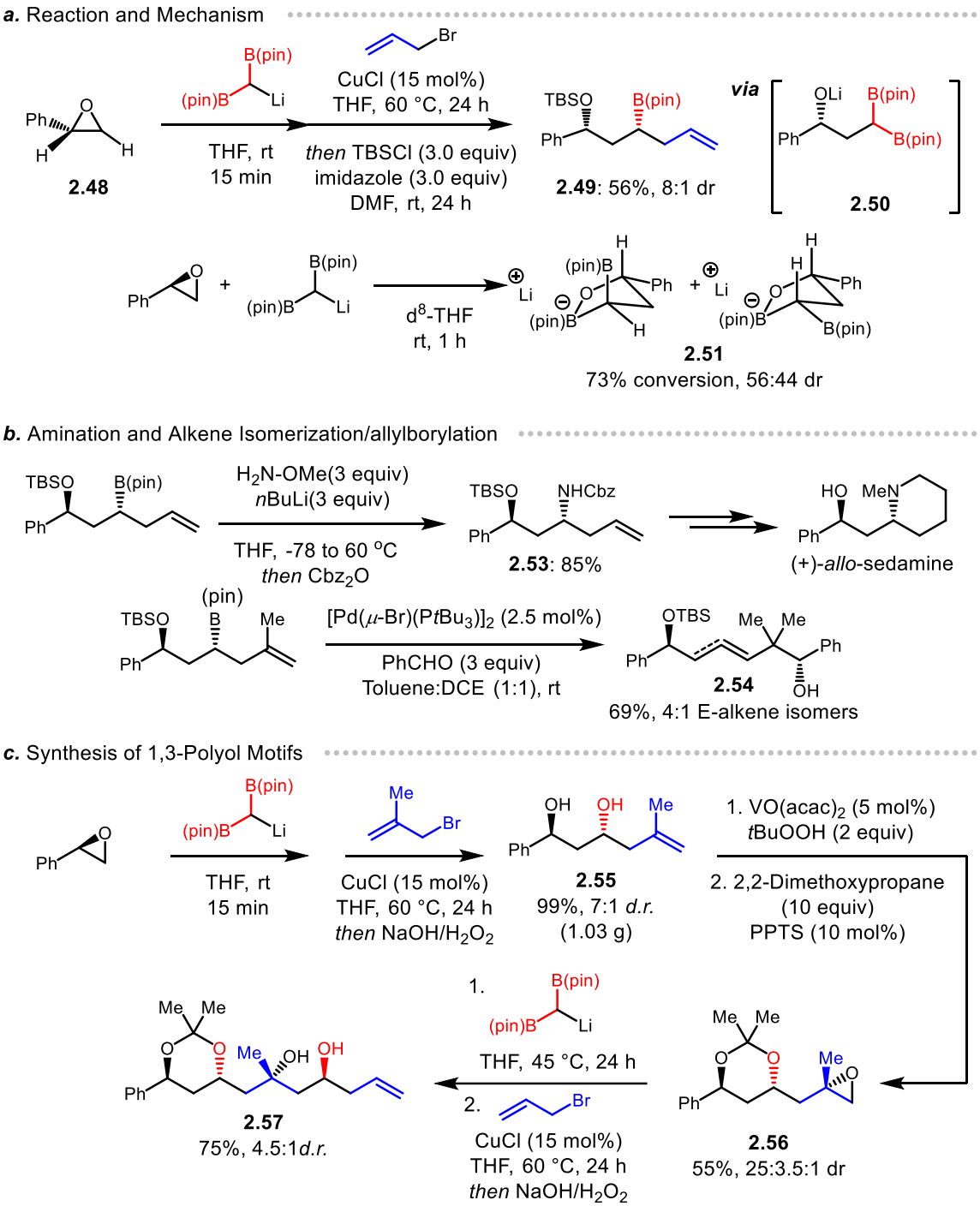
Scheme 2.8. Platinum-Catalyzed Diboration of Alkenyl Boronic Esters



Enantioenriched boronic esters **2.49** were synthesized by Meek and co-workers in a one-pot three-component coupling reaction between lithiated methylenebis(Bpin), chiral epoxides **2.48**, and allyl electrophiles (Scheme 2.9a).[28] The chiral *gem*-diboronic esters **2.50** generated by the ring opening of epoxides, were not isolated but coupled with allyl electrophiles *in situ* in the presence of a copper catalyst. Different substitution patterns in the epoxide were well tolerated though *trans*-epoxides resulted it low conversion and selectivity. To reveal the source of high diastereoselectivity, mechanistic studies were conducted. Monitoring the reaction by ^{1}H NMR revealed non-selective reaction to form both diastereomers of cyclic boron "ate" intermediate **2.51**, which were then consumed at a similar rate by Cu-catalyzed reaction with the electrophile. This observation suggests that high diastereoselectivity obtained from the reaction arises either from diastereoconvergent transmetalation of the cyclic intermediates to the copper catalyst, or a dynamic kinetic resolution of the α-boryl copper intermediate. Various applications of products were shown including amination of the boronic ester for the formal synthesis of (+)-allo-sedamine, and alkene isomerization/allylboration to furnish compound **2.54** (Scheme 2.9b). The synthesis of 1,3-polyol motif **2.57** was accomplished by two consecutive sequences of epoxide opening/allylation (Scheme 2.9c).

(28) Murray, S. A.; Liang, M. Z.; Meek, S. J. *J. Am. Chem. Soc.* **2017,** *139*, 14061–14064.

Scheme 2.9. Diastereoselective One-Pot Three-component Coupling of Lithiated Methylene BisB(pin), Epoxide and Allyl Bromide

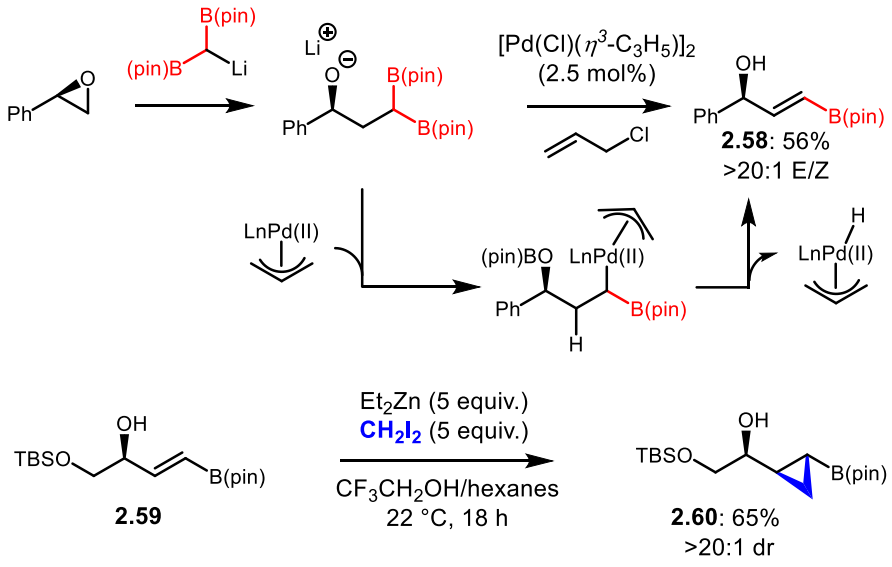


By applying the same epoxide opening/transmetalation strategy to palladium catalysis, the reactivity was altered such that a dehydroboration reaction occurred and furnished alkenyl

boronic esters **2.58** with high E-selectivity (Scheme 2.10).[29] A Pd-catalyzed *β*-hydride elimination was proposed to account for the formation of the double bond. To demonstrate the synthetic utility of products, a hydroxyl-directed Simmons-Smith reaction was employed to prepare cyclopropane **2.60** with high diastereoselectivity.

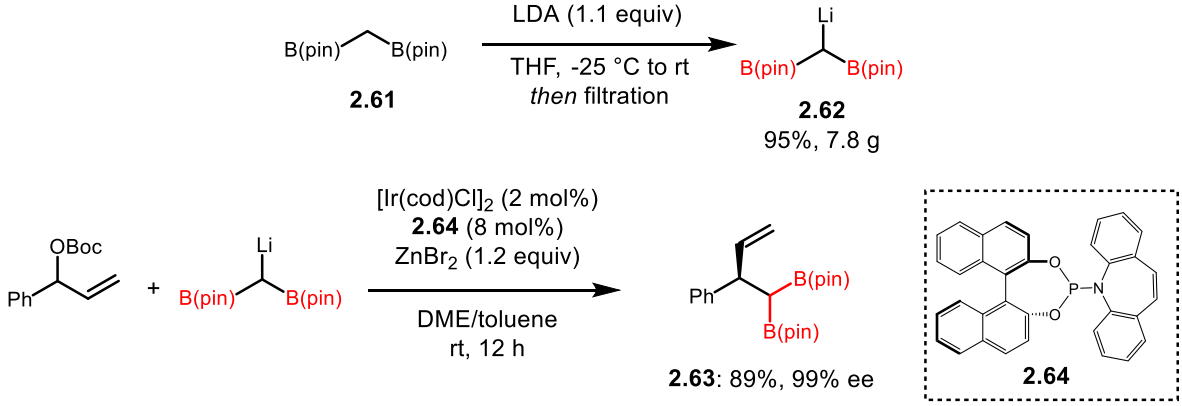
In 2018, an Ir-catalyzed asymmetric allylic substitution reaction of metalated methylenebis(boronates) **2.62** (Scheme 2.11) was developed by the Cho group.[30] This process provides enantioenriched *gem*-diborylalkanes **2.63** with good yields and excellent enantioselectivity. Of note, lithiated (diborylmethyl)lithium reagent **2.62** was prepared and isolated on an 8-gram scale. Furthermore, a series of transformations of the product were executed including functionalization of the alkene and the *gem*-diboron motif.

Scheme 2.10. Synthesis of Alkenyl Boronic Esters through Palladium-Catalyzed Dehydroboration



(29) Murray, S. A.; Luc, E. C. M.; Meek, S. J. *Org. Lett.* **2018,** *20*, 469–472.
(30) Lee, Y.; Park, J.; Cho, S. H. *Angew. Chem. Int. Ed.* **2018,** *57*, 12930–12934.

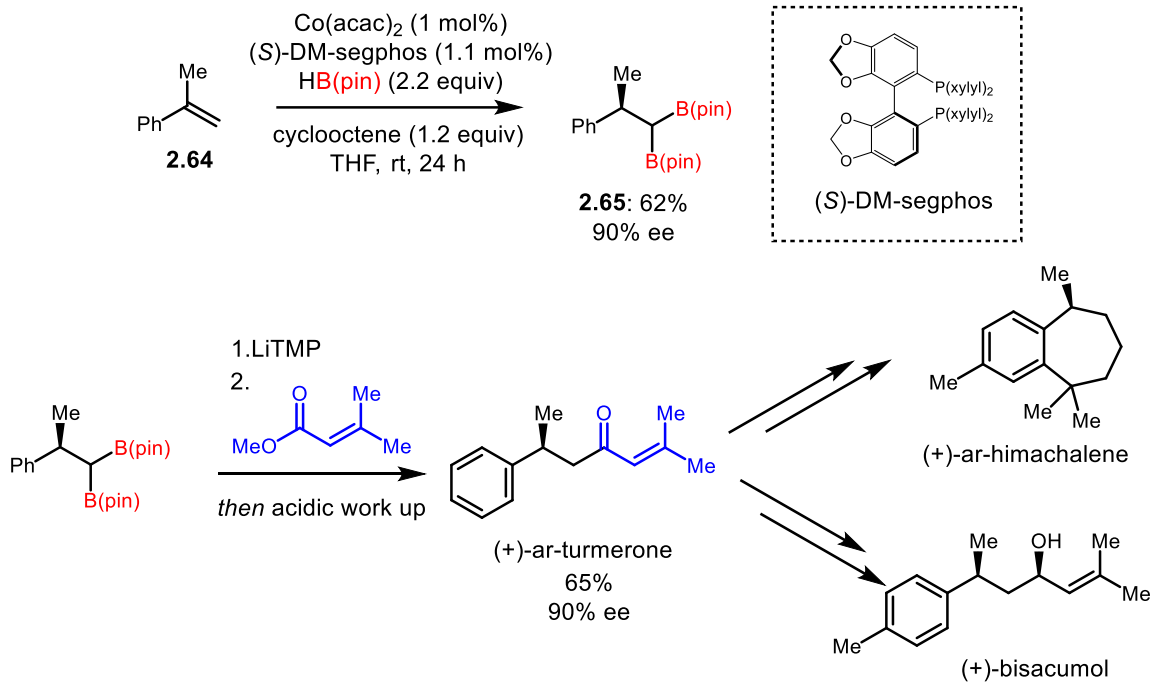
Scheme 2.11. Iridium-Catalyzed Asymmetric Allylic Substitution with Lithiated Methylene BisB(pin)



After Cho's report, Ge and co-workers reported a chiral cobalt complex-catalyzed enantioselective diborylation of 1,1-disubstituted alkenes **2.64** to construct *gem*-bis(boronates) bearing a *β*-stereogenic center (Scheme 2.12).[31] By using cyclooctene as a hydrogen acceptor, alkenes with a wide range of functional groups were successfully transformed into bisboryl species **2.65**. However, monoborylated alkanes were observed as a major byproduct in some cases. Of note, the reaction can be conducted on gram-scale while still occurring in good yield and selectivity. The synthetic utility of the diborylation was further demonstrated by the synthesis of (+)-ar-turmerone, which is a key intermediate towards the total synthesis of (+)-ar-himachalene[32] and (+)-bisacumol[33].

(31) Teo, W. J.; Ge, S. *Angew. Chem. Int. Ed.* **2018,** *57*, 12935–12939.
(32) Mori, K. *Tetrahedron: Asymmetry* **2005,** *16*, 685–692.
(33) Li, A. P.; Yue, G. R.; Li, Y.; Pan, X. F.; Yang, T. K. *Tetrahedron: Asymmetry* **2003,** *14*, 75–78.

Scheme 2.12. Cobalt-Catalyzed Enantioselective Diborylation of 1,1-Disubstituted Alkenes



2.2.3 Synthesis of α-Boryl Zirconocenes[9]

Racemic α-boryl zirconocenes can be readily accessed by hydrozirconation of alkenyl boronates with Schwartz's reagent. This reaction occurs under mild conditions and has broad functional group compatibility. Srebnik and co-workers investigated the fundamental properties of the geminal bimetallic reagent including X-ray analysis, NMR studies, and reactivity such as halogenation, amination and copper-catalyzed nucleophilic substitution and addition reactions.[12a,12d-g,34]

Enantioenriched α-boryl zirconocenes **2.67** were also synthesized by the Srebnik group using a strategy involving diastereoselective hydrozirconation of chiral alkenyl boronic esters **2.66** with Schwartz's reagent. Good yield and selectivity were achieved after quenching the

(34) Zheng, B.; Srebnik, M. *Tetrahedron Lett.* **1994**, *35*, 6247–6250.

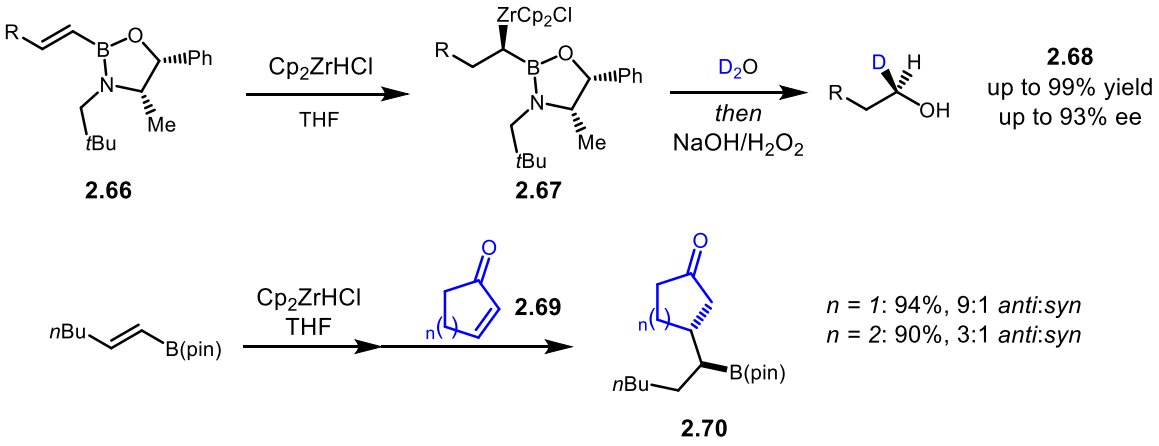
resulting α-boryl zirconocenes with D_2O. Oxidation of the boronic ester furnished the enantiomerically enriched α-deuterated alcohols **2.67**.[35] Similar to the α-boryl zinc analog reported by Knochel, copper-catalyzed conjugate addition of α-boryl zirconocenes to cyclic unsaturated enones **2.69** was also investigated and found to favor the anti-product **2.70** (Scheme 2.13a).[12g]

A chemoselective cross-coupling reaction between α-boryl zirconocenes and aryl halides was described by the Qi group (Scheme 2.13b).[36] The α-boryl zirconocenes **2.72** were generated by a boron-directed "chain walking" with alkylzirconocenes **(2.74**), which were synthesized from hydrozirconation of internal alkene **2.71** with Schwartz's reagent. A nickel–bipyridine complex, in conjunction with blue LEDs, was demonstrated to be an efficient catalyst system for the cross-coupling reaction between α-boryl zirconocenes **2.72** and aryl halides. The reaction exhibits good yield, chemoselectivity and functional group compatibility. Moreover, an enantioselective version (56% *ee*) was achieved by utilizing a chiral bis(oxazoline) ligand **2.75** on nickel.

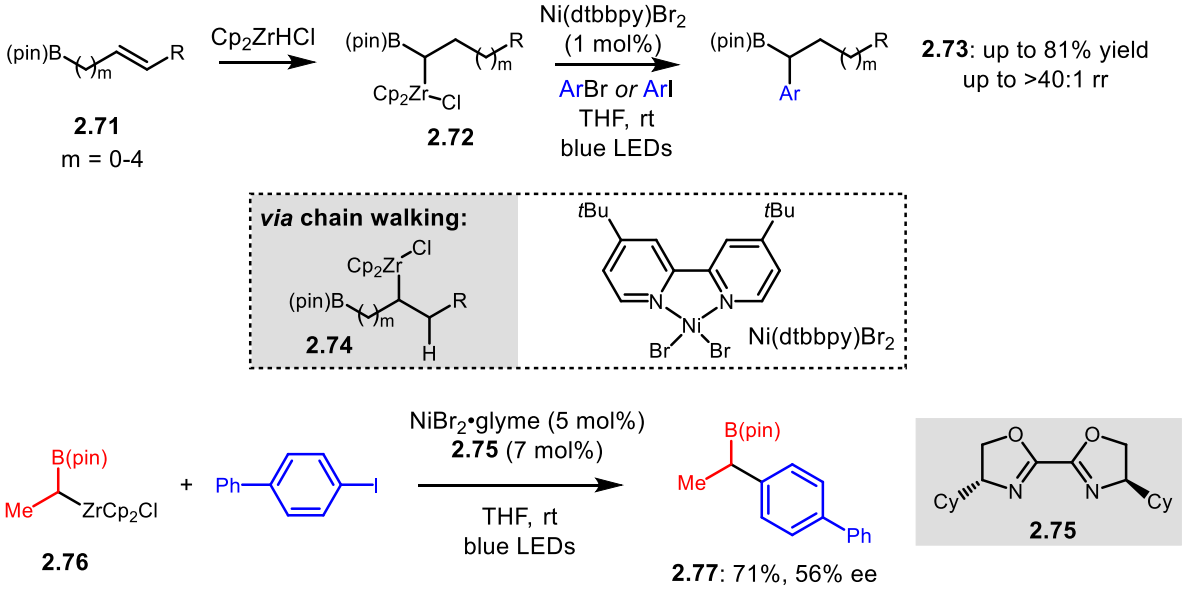
(35) Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995,** *60*, 486-487.
(36) Yang, C.; Gao, Y. D.; Bai, S. L.; Jiang, C.; Qi, X. B. *Am. Chem. Soc.* **2020,** *142*, 11506–11513.

Scheme 2.13. Preparation of Enantioenriched α-Boryl Zirconocenes

a. Synthesis of α-Boryl Zirconocenes by Diasereoselective Hydrozirconation



b. Chain-Walking Hydrozirconation Followed by Cross-Coupling of α-Boryl Zirconocenes



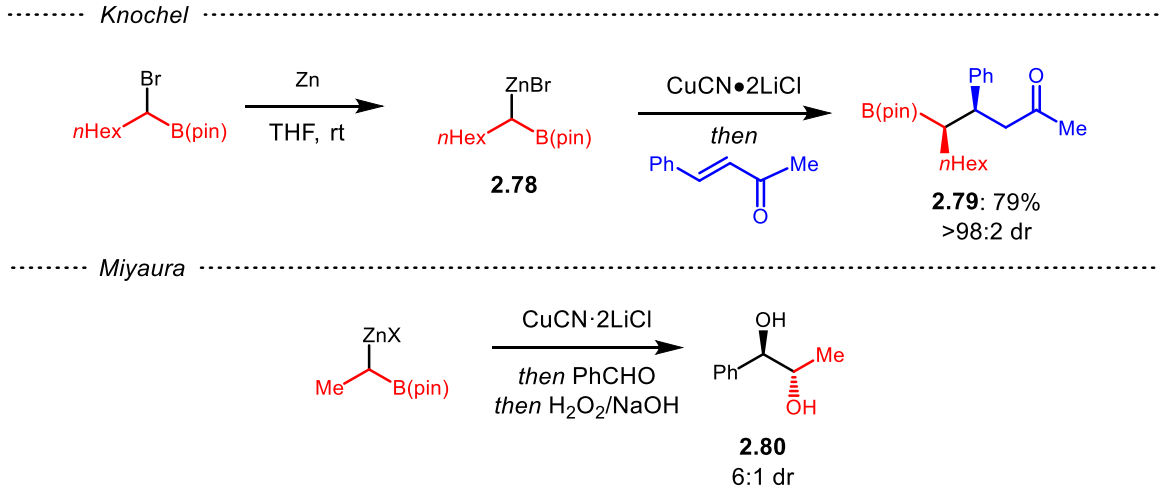
2.2.4 Synthesis of α-Boryl Zinc Reagents[9]

Historically, achiral and racemic α-boryl zinc species have been synthesized by either zinc insertion into α-boryl halides[6a] or carbozincation of alkenyl boronates.[6d] To the best of our

knowledge, the only known example for the preparation of enantioenriched α-boryl zinc compounds is accomplished by our group.[1]

In 1990, Knochel and co-workers described the first synthesis of α-boryl zinc compound **2.78** by a zinc insertion reaction[6a] and demonstrated that the addition of CuCN•2LiCl furnishes nucleophilic α-boryl cuprate intermediates, which can add to a variety of electrophiles. It is noteworthy that the reaction of some β-branched Michael acceptors, including alkenyl malonates and benzylideneacetone, exhibited excellent diastereoselectivity. Miyaura and co-workers later discovered that the addition of α-borylzinc reagents to aldehydes occurs with useful levels of diastereoselectivity and furnishes *anti*-diols **2.80** after oxidation of the boronic ester (Scheme 2.14).[37]

Scheme 2.14. Synthesis of α-Boryl Zinc Reagents by Zinc Insertion



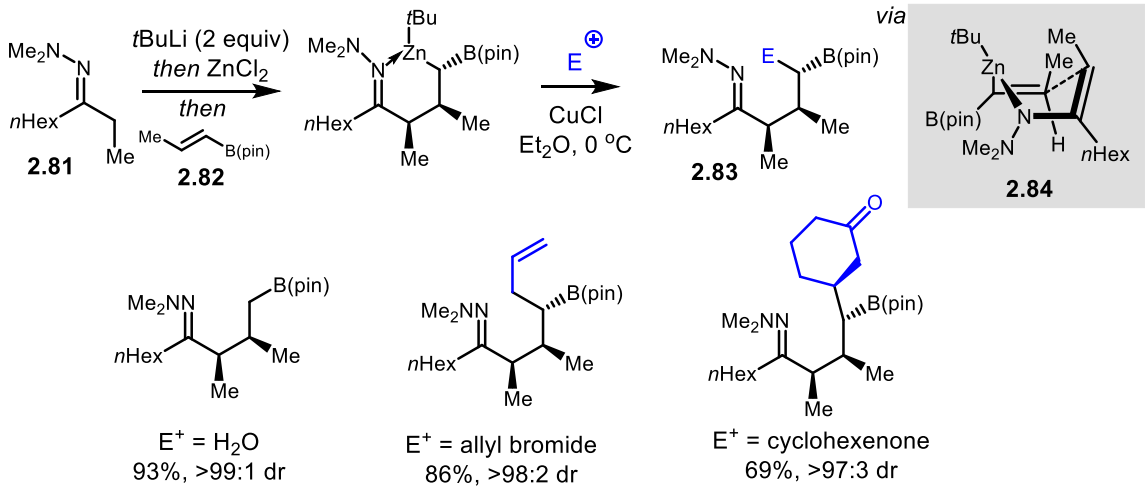
(37) Sakai, M.; Saito, S.; Kanai, G.; Suzuki, A.; Miyaura, N. *Tetrahedron* **1996,** *52*, 915–924.

Carbozincation of alkenyl boronic esters **2.82** with zincated hydrazone **2.81** was developed by the Nakamura group.[6d,38] This process affords isomerically-enriched β,γ-branched alkyl boronates **2.83** upon reaction with electrophiles (Scheme 2.15a). Both syn- and anti-diastereomers can be obtained by employing *E* or *Z* alkenyl boronates as starting material (Scheme 2.15b). The synthetic usefulness was demonstrated by the synthesis of **2.87**. To address **2.87**, hydrazone **2.86** obtained by carbozincation was hydrolyzed to the corresponding ketone with slightly erosion of stereochemistry. The ketone was further transformed to 1,4-diol **2.87** after hydrogenation of the alkene, reduction of carbonyl group, and oxidation of the boronic ester. A follow-up report from the same group further showcased the utility in asymmetric synthesis by starting with enantiomerically enriched hydrazone **2.90**.[39] Of note, DFT calculations suggest that the carbozincation reaction occurs by a highly ordered six-membered boat-like transition state **2.84**, as the coordination of zinc and imine or hydrazone effectively lowered the activation energy and the steric repulsion between "dummy" tert-butyl ligand on zinc and bulky pinacol ligand on boron.

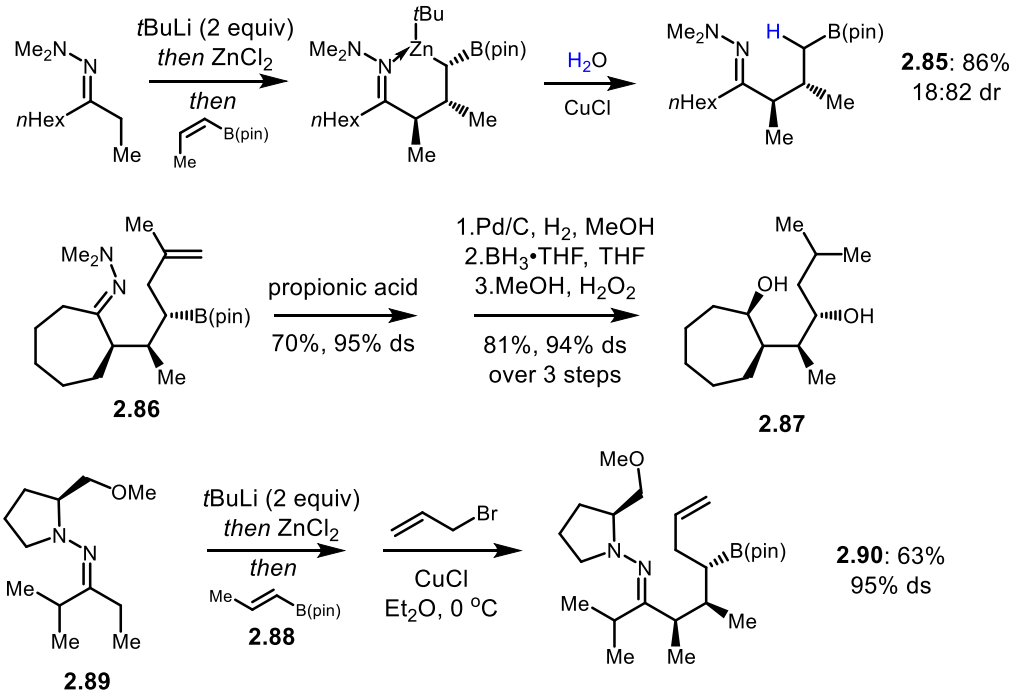
(38) Nakamura, M.; Hatakeyama, T.; Hara, K.; Fukudome, H.; Nakamura, E. *J. Am. Chem. Soc.* **2004,** *126*, 14344–14345.
(39) Hatakeyama, T.; Nakamura, M.; Nakamura, B. *J. Am. Chem. Soc.* **2008,** *130*, 15688–15701.

Scheme 2.15. Carbozincation of Alkenyl Boronic Esters with Metalated Hydrazones

a. Reaction and Proposed Mechanism



b. Reaction of Z-Alkenylboronates and Synthetic Applications



2.2.5 Catalytic Carbozincation of Alkenes

Traditionally, most organozinc reagents are prepared from zinc insertion with the corresponding alkyl halides.[40] A typical example is the Reformatsky reaction (Scheme 2.16a):[41] the organozinc reagent **2.92** can be generated from the α-bromo ester **2.91** through zinc insertion, and then react with aldehydes to afford alcohol product **2.93**. However, the radical nature of the zinc insertion process limits its application in the preparation of enantioenriched organozinc reagents.[42] Alternatively, transmetalation methods have been developed for the preparation of optically active organozinc reagents (Scheme 2.16b). Knochel and co-workers utilized lithium-halogen exchange with secondary alkyl iodides (**2.94**) to afford enantioenriched alkyllithium species, which could be converted to alkylzinc reagent **2.95** by transmetalation.[43] More importantly, the resulting alkylzinc species could be subjected to Negishi cross-coupling reactions to produce aryl products **2.96** in up to 100% enantiospecificity. Furthermore, the stereospecific transmetalation from boron to zinc was discovered by the same group in 2000 and provided cyclic zinc reagents **2.98**,[44] which could participate in various copper-mediated functionalization.

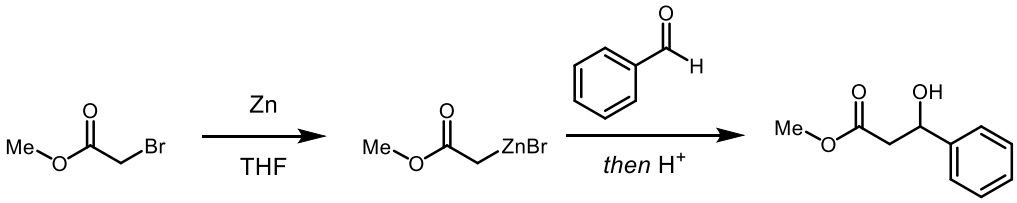
Despite the excellent stereospecificity demonstrated in these processes, tedious preparation of the corresponding enriched precursors is inevitable, especially for substrates bearing complicated functional groups. Accordingly, transition metal-catalyzed carbometallation as an alternative approach to chiral organozinc reagents has attracted the attention of synthetic

(40) Huo, S. *Org. Lett.* **2003**, *5*, 423-425.
(41) Reformatsky, S. *J. Russ. Phys. Chem. Soc.* **1890**, *22*, 44.
(42) Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H. P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415-2432.
(43) Skotnitzki, J.; Kremsmair, A.; Keefer, D.; Gong, Y.; Vivie-Riedle, R.; Knochel, P. *Angew. Chem. Int. Ed.* **2020**, *59*, 320–324.
(44) Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Eur. J. Chem.* **2000**, *6*, 2748-2761.

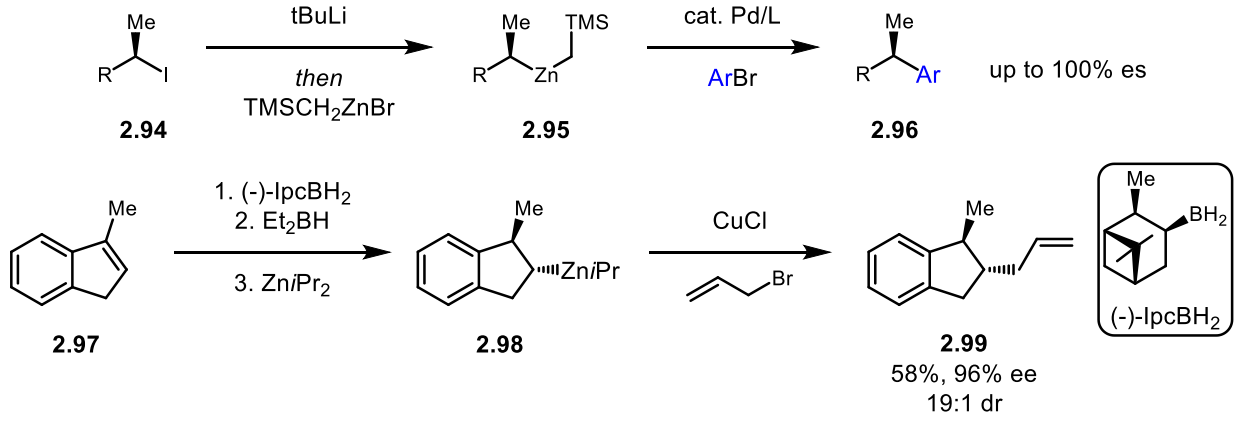
chemists. Starting with readily accessible alkenes **2.101**, concerted migratory insertion followed by stereospecific transmetalation can deliver the organozinc reagents **2.104** with good stereoselectivity (Scheme 2.16c).

Scheme 2.16. Preparation of Organozinc Reagent

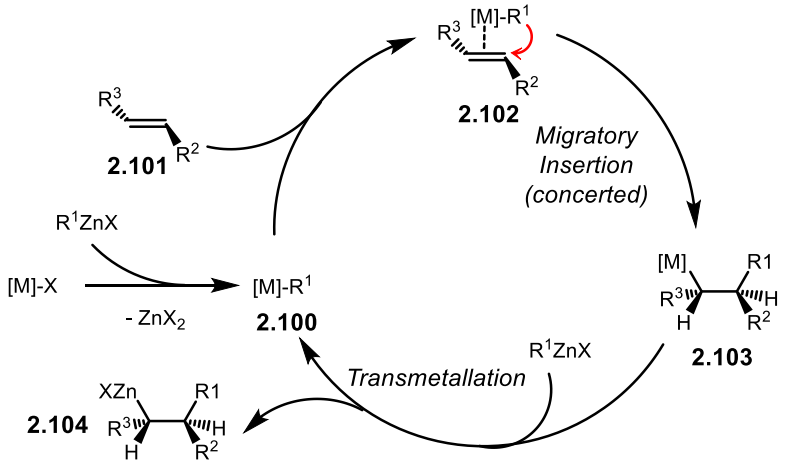
a. Zinc Insertion



b. Transmetallation



c. Transition Metal Catalyzed Alkene Carbozincation

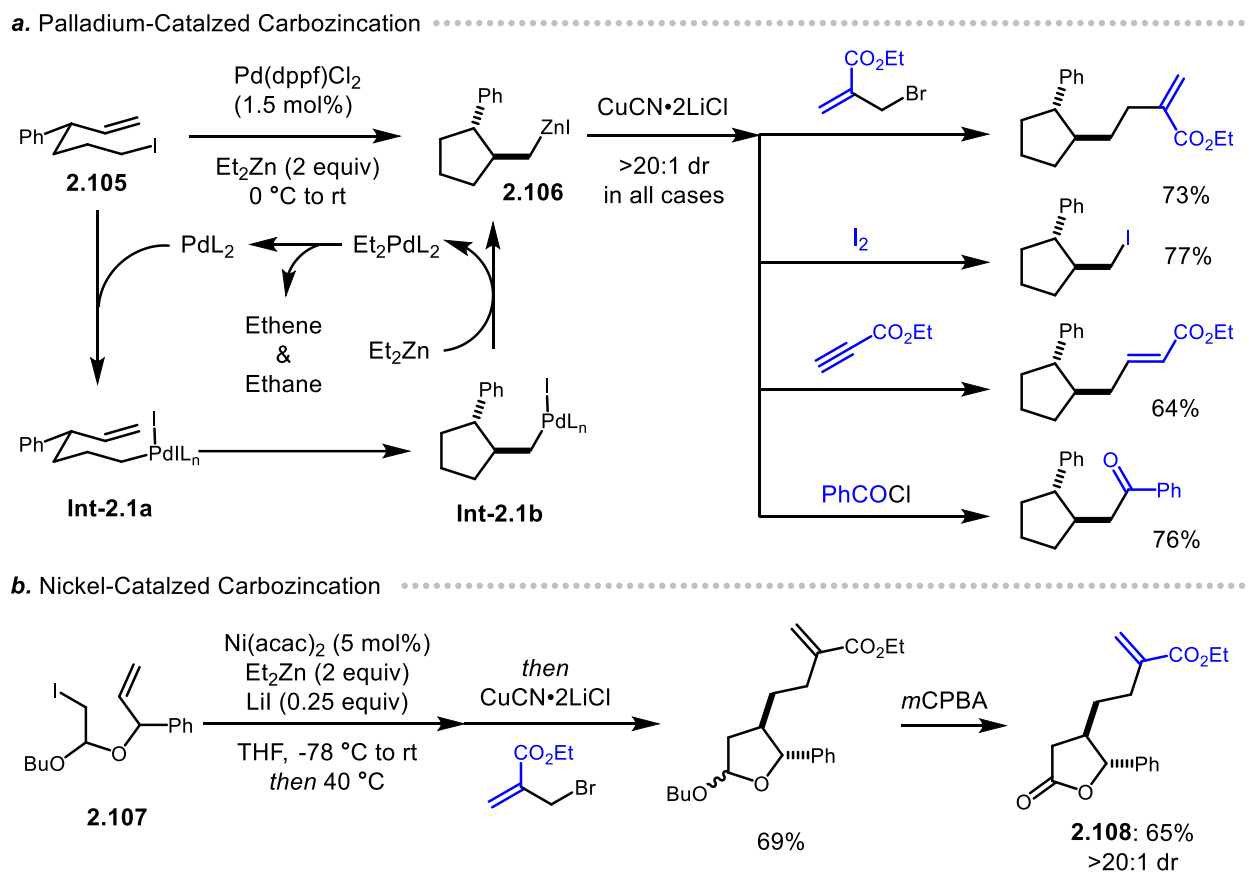


Early examples of transition metal-catalyzed carbozincation reactions were achieved intramolecularly. The first transition metal-catalyzed reaction was developed by the Knochel group in 1993 (Scheme 2.17a).[45] They treated the alkyl iodide compound **2.105** with a palladium catalyst and diethyl zinc to furnish the organozinc intermediate **2.106** with excellent diastereoselectivity. According to the proposed mechanism, after oxidative addition with alkyl halides, the alkyl palladium species **Int-2.1a** undergoes a C–Pd bond homolysis. The resulting alkyl radical will undergo addition reaction to the C–C double bond followed by recombination with palladium to generate intermediate **Int-2.1b** prior to the formation of **2.106**.[46] The organozinc product **2.106** can participate in various transformations including allylation, iodination, and conjugate addition reactions. Later in 1994, the same group developed a nickel-catalyzed carbozincation of allyl ether substrates **2.107**, which are less reactive in the palladium system (Scheme 2.17b).[47] The organozinc intermediate can be converted to lactone **2.108** through allylation and oxidation. Good yield and excellent diastereoselectivity were observed with the product.

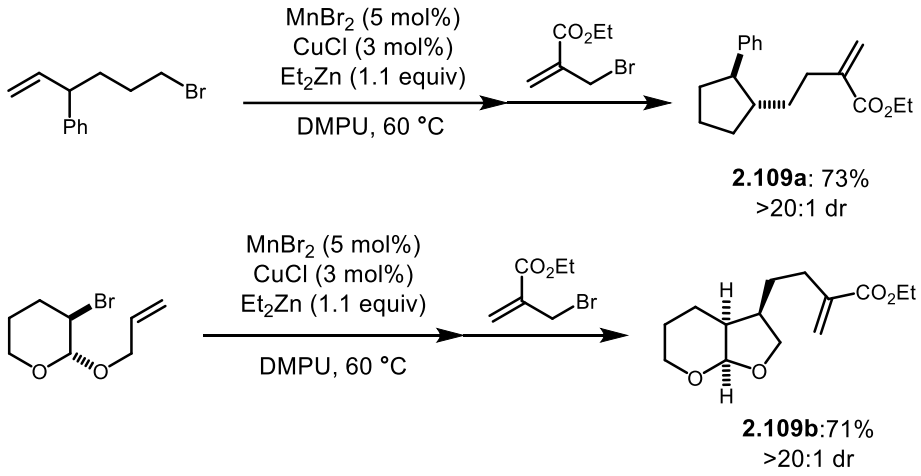
Knochel and co-workers also developed a manganese dibromide and copper chloride co-catalyzed carbozincation reaction (Scheme 2.18).[48] The allylation products **2.109a** and **2.109b** were isolated with good yield and diastereoselectivity.

(45) Stadtmuller, H.; Lentz, R.; Tucker, C. E.; Studemann, T.; Dorner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027–7028.
(46) Stadtmuller, H.; Tucker, C. E.; Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 7911–7914.
(47) Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743-5753.
(48) Riguet, E.; Klement, I.; Reddy, C. K.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 5865–5868.

Scheme 2.17. Intramolecular Carbozincations

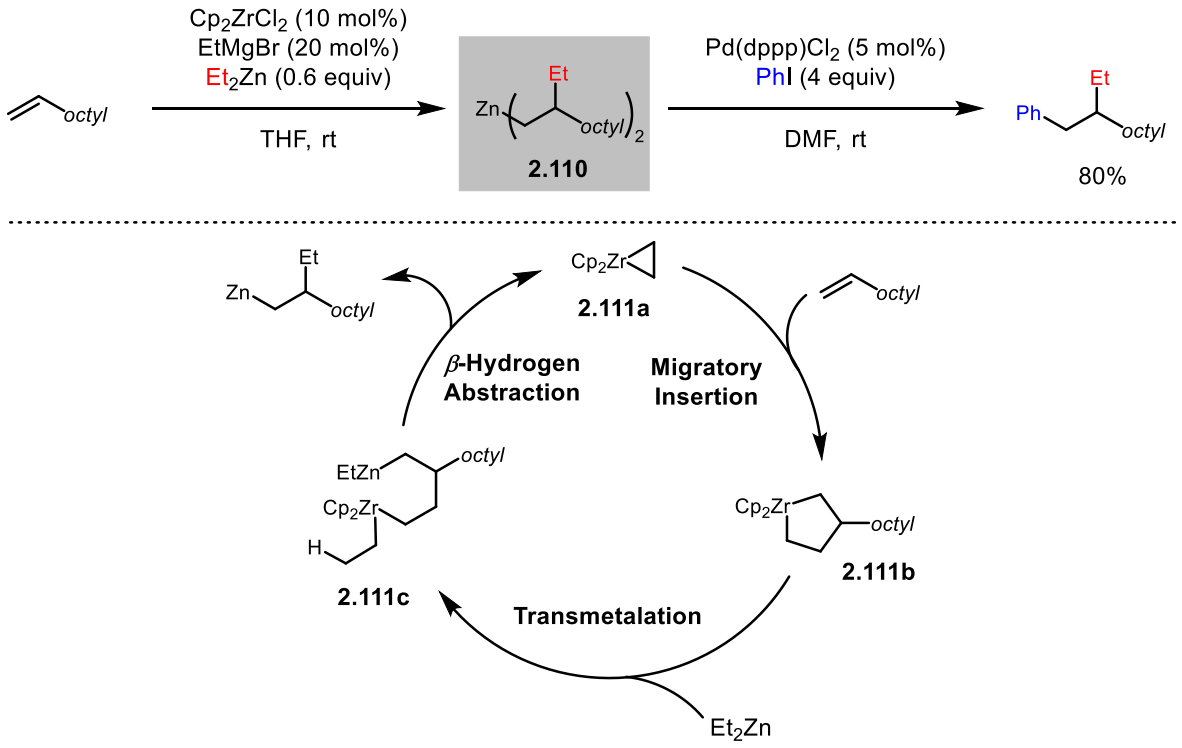


Scheme 2.18. $MnBr_2$-CuCl-Catalyzed Carbozincation



In 2000, the Negishi group developed a zirconium(IV)-catalyzed intermolecular carbozincation between terminal alkene and diethylzinc to deliver secondary organozinc compounds **2.110**, which can *in situ* couple with aryl halides to deliver products **2.111a** (Scheme 2.19).[49] In the proposed reaction mechanism, cyclopropyl zirconocene **2.111b** can react with an alkene to furnish metallacyclopentane **2.111c**, which can be converted to the organozinc product through transmetalation and selective β-hydrogen abstraction from less hindered ethyl group.

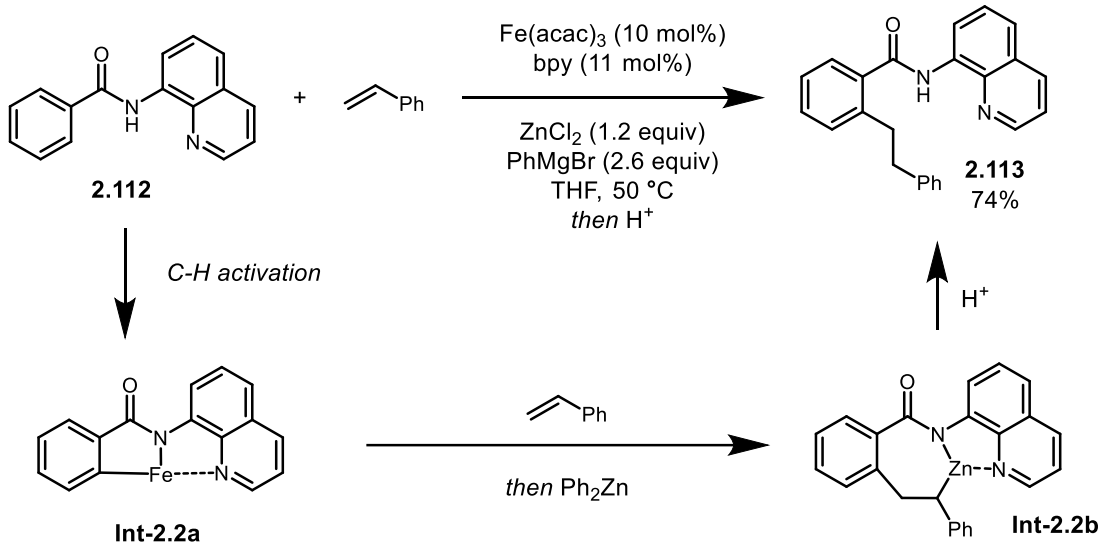
Scheme 2.19. Zirconium-Catalyzed Ethylzincation



(49) (a) Gagneur, S.; Montchamp, J.; Negishi, E. *Organometallics* **2000**, *19*, 2417–2419. For a magnesium-based version of this reaction by Hoveyda, see: (b) Morken, J. P.; Didiuk, M. T.; Hoverda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997–6998. (c) Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097–7104.

Recently, the Nakamura group demonstrated the iron-catalyzed carbozincation reaction depicted in Scheme 2.20.[50] First, directed by an 8-aminoquinoline moiety, an iron complex could undergo a C–H activation of **2.112** to deliver intermediate **Int-2.2a**. Then, compound **Int-2.2a** undergoes migratory insertion and transmetalation to afford organozinc compound **Int-2.2b**, which is quenched by acid to furnish the alkylation product **2.113**. The large excess of Grignard reagent is necessary to reduce the Fe(III) precursor to putative Fe(II) active species. The organozinc intermediate **Int-2.2b** failed to participate in palladium-catalyzed Negishi cross-coupling; the author proposes that the 8-aminoquinoline moiety can serve as a latent ligand on zinc, decreasing its nucleophilicity.

Scheme 2.20. Iron-catalyzed Directed Alkylation



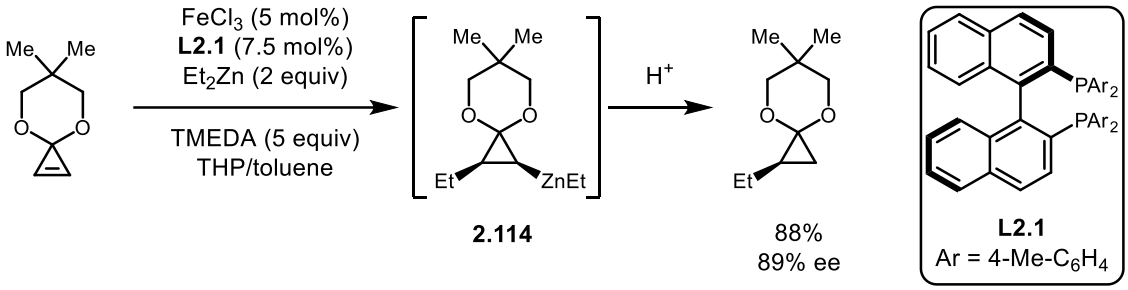
Transition metal-catalyzed enantioselective carbozincation is underdeveloped. Limited literature reports can be found, and the substrate scope is limited to either the strained cyclopropenes or other highly activated olefins. In 2000, Nakamura and co-workers developed

(50) Ilies, L.; Zhou, Y.; Yang, H.; Matsubrara, T.; Shang, R.; Nakamura, E. *ACS Catal.* **2018**, *8*, 11478–11482.

the first example of transition metal-catalyzed enantioselective carbozincation reaction. This process employed iron trichloride in the presence of BINAP-derived chiral ligand **L2.1** (Scheme 2.21).[51a] The protonation product **2.114** was isolated with good yield and enantioselectivity. The addition of TMEDA is beneficial for obtaining high stereoselectivity.

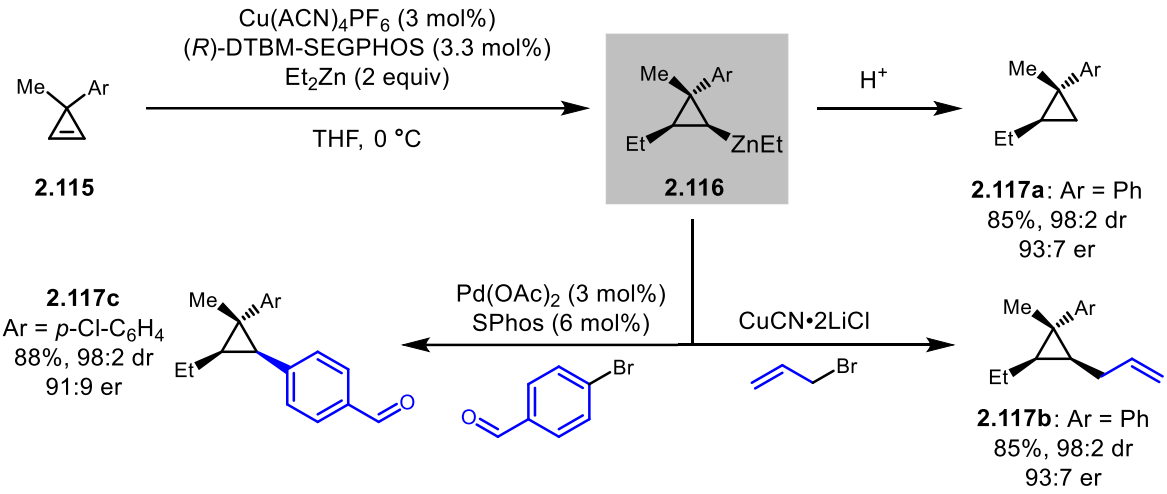
Later in 2015, the Marek group demonstrated the copper-catalyzed enantioselective carbozincation of cyclopropenes **2.115** (Scheme 2.22).[51b] In addition to protonating the organozinc intermediate **2.116**, palladium-catalyzed Negishi cross-couplings, as well as copper-mediated allylation, were conducted to afford various cyclopropenes (**2.117a**-**2.117c**) with both high diastereo- and enantioselectivity. Of note, sensitive functional groups, such as aldehydes, are well tolerated in this process (**2.117c**).

Scheme 2.21. Iron-Catalyzed Enantioselective Carbozincation of Cyclopropenes



(51) (a) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978–979.; (b) Muller, D. S.; Marek, I. *J. Am. Chem. Soc.*, **2015**, *137*, 15414–15417.

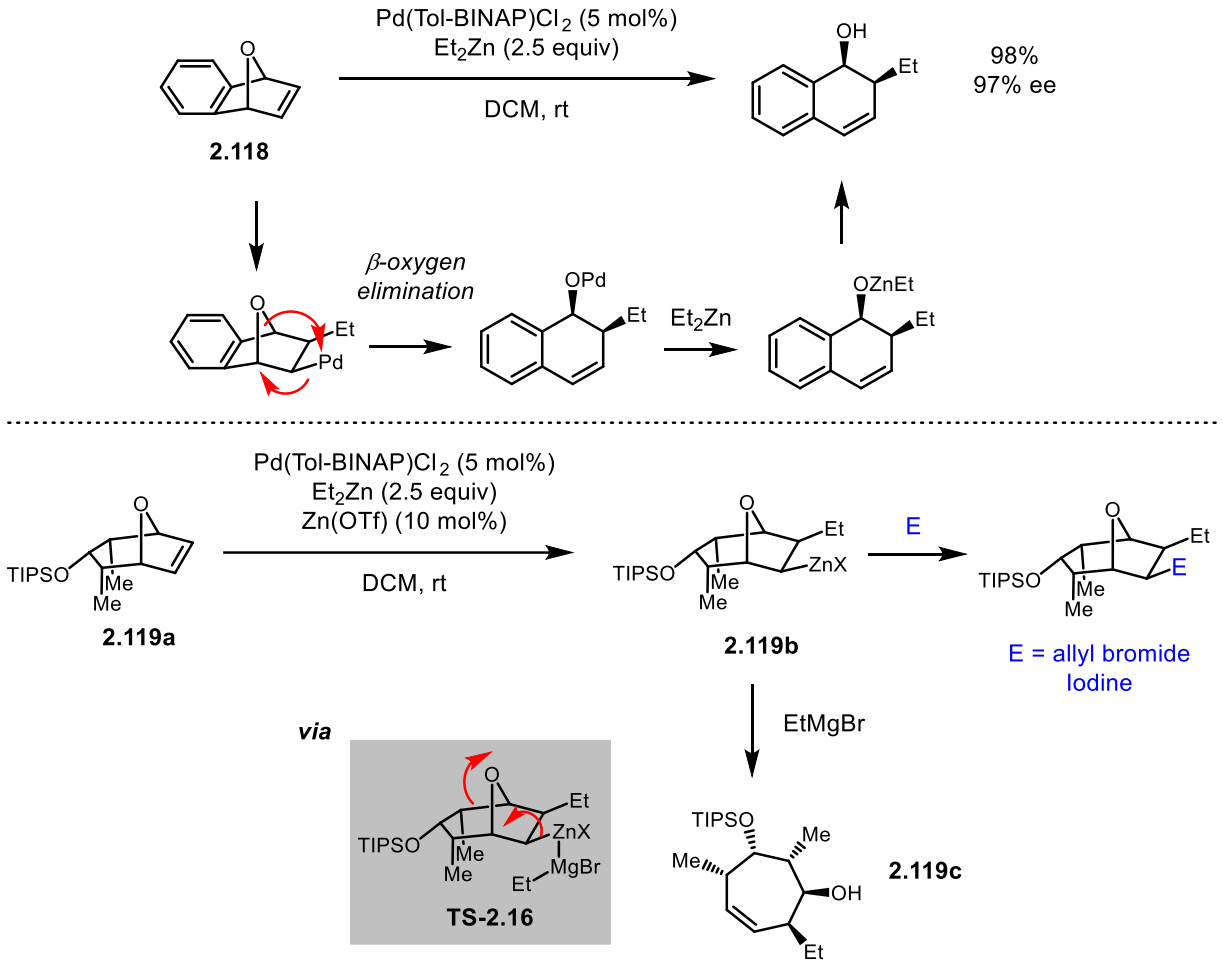
Scheme 2.22. Copper-Catalyzed Enantioselective Carbozincation of Cyclopropenes



In 2004, the Lautens group developed a palladium-catalyzed enantioselective carbozincation of [3.2.1]oxabicyclic alkenes (Scheme 2.23).[52] First, they employed substrate **2.118**, where they observed that the alkyl palladium intermediate undergoes *β*-oxygen elimination to deliver the ring-opened product. An alternative reactivity was discovered with TIPS-protected substrate **2.119a**, which could deliver the alkylzinc species through direct transmetalation. It is noteworthy that instead of reacting with electrophiles, the organozinc reagents **2.119b** can undergo elimination upon the addition of ethyl magnesium bromide thereby furnishing the ring open product **2.119c**. Ethyl magnesium bromide is proposed to form the zin "ate" complex to facilitate the *β*-oxygen elimination of **2.119b** (via **TS-2.16**).

(52) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.*, **2004**, *126*, 1437–1447.

Scheme 2.23. Palladium-Catalyzed Enantioselective Alkylative Ring Open



2.2.6 Synthesis of Enantioenriched Secondary Homoallylic Boronates[9]

While investigating synthetic utilities of the nickel-catalyzed enantioselective carbonation reaction, we tested the reactivity of the *in situ* generated α-boryl zin species with various electrophiles. The most reactive electrophile is the allylic halide, which could afford homoallylic boronates, and then homoallylic alcohols after oxidation. Both homoallylic boronates and alcohols are motives of interest for synthetic chemists.[9,53] Therefore, in the following two

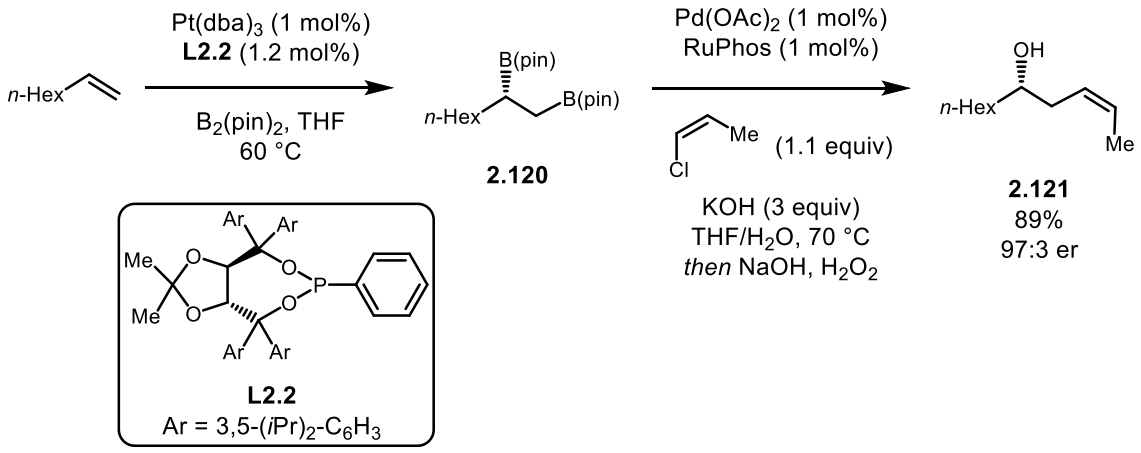
(53) Yus, M.; Gonzalez-´ Gomez, J. C.; Foubelo, F.´ *Chem. Rev.* **2011**, *111*, 7774-7851.

sections, I will review examples for the synthesis of enantioenriched secondary homoallylic boronates /alcohols and compare these methods to the nickel-catalyzed carbozincation reactions.

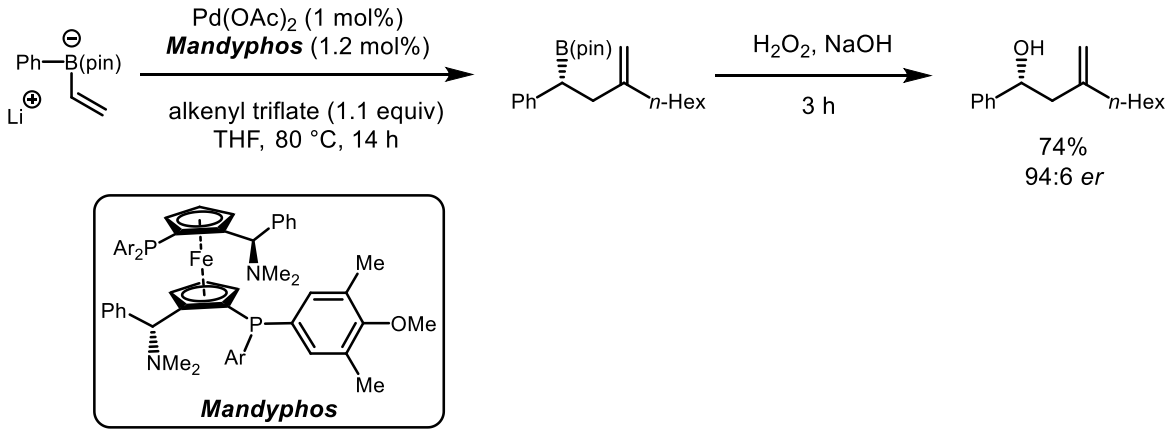
In 2014, the Morken group developed a tandem diboration/cross-coupling reaction cascade of alkenes to deliver homoallylic boronates (Scheme 2.24a).[54] Pt-catalyzed diboration

Scheme 2.24. Synthesis of Homoallylic Boronates Developed by the Morken Group

a. Diboration/Cross-Coupling Cascade



b. Conjunctive Cross-Coupling



(54) Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2014**, *505*, 386-390.

of simple alkene afforded vicinal bis(boronates) **2.120**, which then underwent Pd-catalyzed chemoselective Suzuki cross-coupling to deliver homoallylic boronate or homoallylic alcohol **2.121** after oxidation of the boron moiety. Notably, both alkene diboration and Suzuki cross-coupling could be accomplished in a one-pot manner. Another approach to homoallylic boronates was later developed by the same group through catalytic conjunctive cross-coupling with alkenyl electrophiles (Scheme 2.24b).[55] See Chapter one for more detailed discussion regarding the conjunctive cross-coupling reaction.

Hoveyda and co-workers described a Cu-NHC catalyzed enantioselective allylic substitution (EAS) of methylenebisB(pin) to allylic phosphates (Scheme 2.25).[56] The EAS reaction exhibited high SN2' selectivity to afford branched homoallylic boronates, which were converted enantiomerically enriched alcohols. The sulfonate motif installed on the ligand scaffold was crucial for obtaining the observed regioselectivity. It was proposed that the sulfonate participates in an alkali metal bridge (**Int-2.3**) with the Lewis basic phosphate unit, which results in a well-defined transition structure. A wide range of aryl and alkyl substituents can be tolerated.

In 2016, Niu and co-workers provided an alternative method for allylation by employing well-established iridium-catalyzed asymmetric allylic substitution reaction. In this instance, reaction between methylenebisB(pin) and allyl carbonates was examined (Scheme 2.26).[57] The addition of a silver salt is essential for the desired reactivity and selectivity. Although detailed mechanisms for the enhancement effect caused by silver salts remain unclear, control

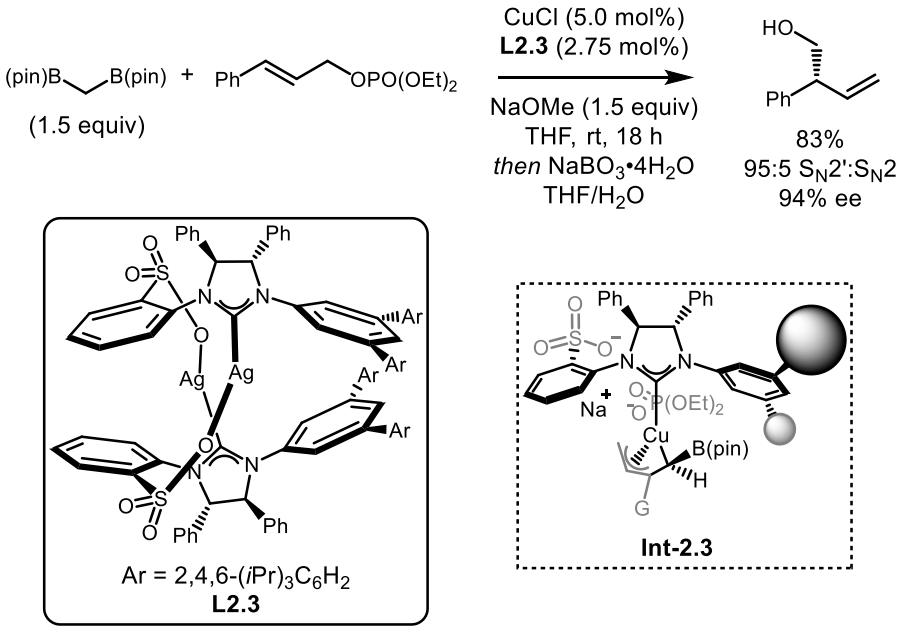
(55) (a) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science* **2016**, *351*, 70-74. For reviews on conjunctive cross-couping: (b) Namirembe, S.; Morken, J. P. *Chem. Soc. Rev.* **2019**, *48*, 3464-3474. (c) Wang, H.; Jing, C.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2020**, *59*, 16859-16872.

(56) Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3455–3458.

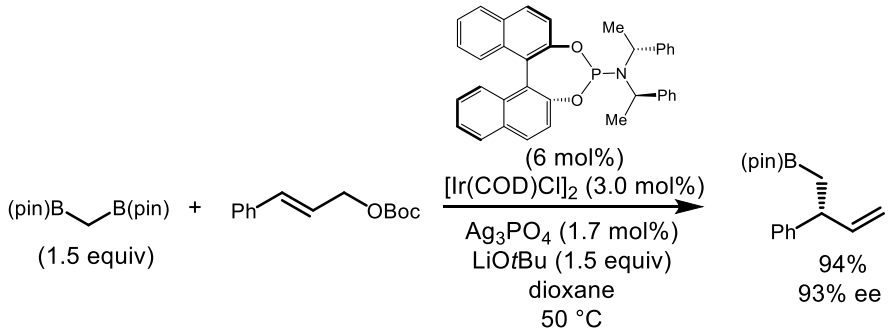
(57) Zhan, M.; Li, R. Z.; Mou, Z. D.; Cao, C. G.; Liu, J.; Chen, Y. W.; Niu, D. W. *ACS Catal*. **2016**, *6*, 3381–3386.

experiments showed that the Ag ion has a bigger contribution to the reaction efficiency and selectivity compared with the other counterions.

Scheme 2.25. Copper-Catalyzed Enantioselective Allylic Substitution of Methylene Bis(boronates) to Allylic Phosphates



Scheme 2.26. Iridium-Catalyzed Asymmetric Allylic Substitution with Methylene Diboronates

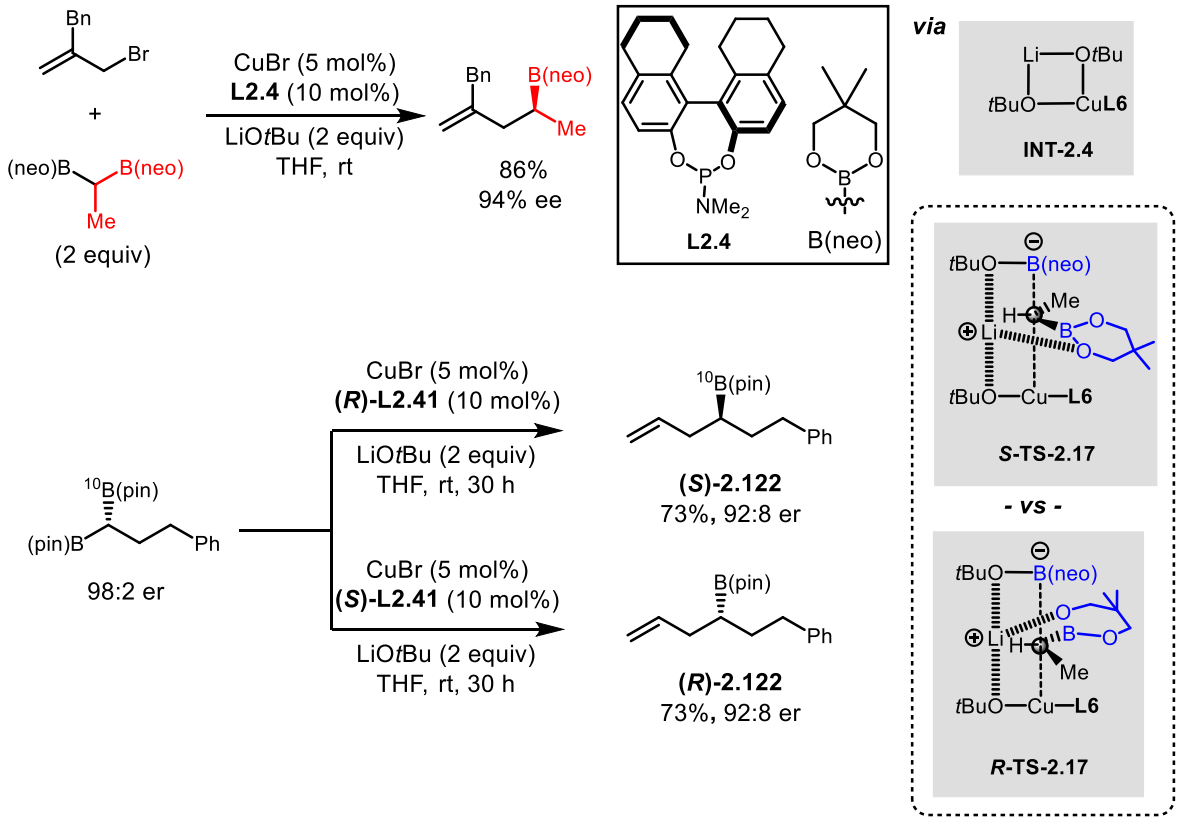


Recently, the Cho group developed a copper-catalyzed enantiotropic-group-selective allylation of *gem*-diborylalkanes.[58] This method afforded functionalized homoallylic boronates in

(58) Kim, M.; Park, B.; Shin, M.; Kim, S.; Kim, J.; Baik, M.-H.; Cho, S. H. J. Am. Chem. Soc. **2021**, *143*, 1069−1077.

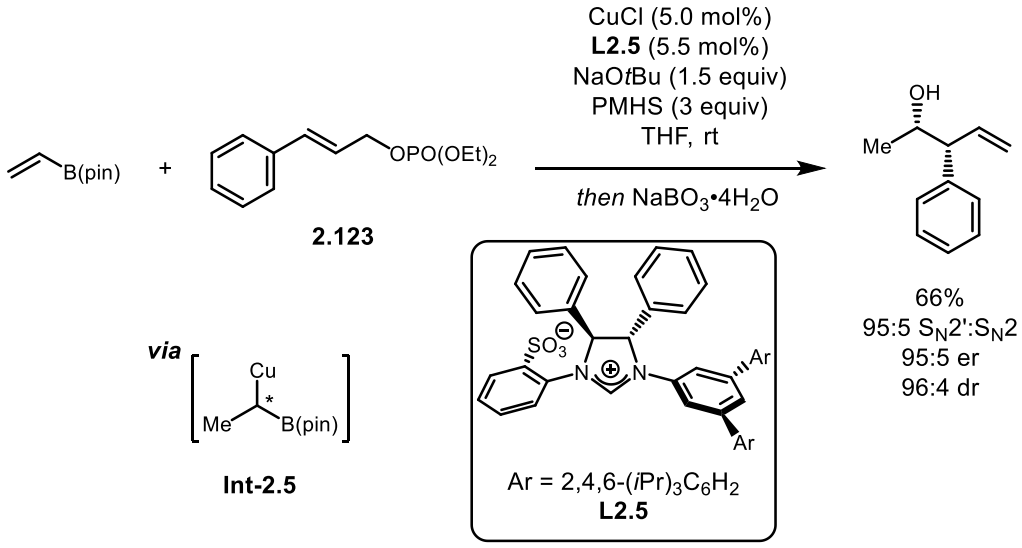
good yield and high stereoselectivity (Scheme 2.27). Density functional theory (DFT) based calculations suggested that a cyclic Lewis acid-base pair intermediate **Int-2.4** was first formed between LiOtBu and *t*BuO–Cu, which served as a bridge during the process of C–B bond cleavage and Cu–B bond formation. Distortion-interaction analysis of the two transition states suggested that shorter distance between substrate and copper in the ***S*-TS-2.17** over ***R*-TS-2.17** is the key factor for the observed enantioselectivity. A stereoinvertive transmetalation between *gem*-diborylalkanes and copper catalysis was proposed based on the outcome of reactions with isotopically chiral boronate substrates.

Scheme 2.27. Copper-Catalyzed Enantioselective Allylation of *gem*-Bis(boronates)



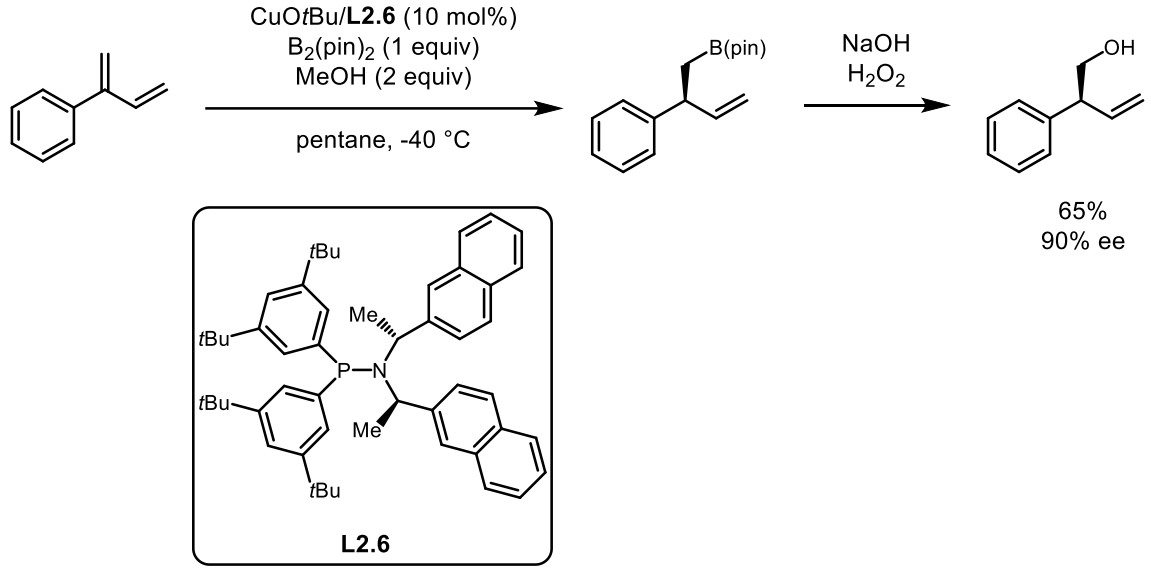
Homoallylic boronates can also be obtained from alkene precursors through Cu–H or Cu-B addition. For instance, the Hoveyda group described a catalytic enantioselective Cu–H addition to vinyl boronic esters (Scheme 2.28).[59] The generated α-boryl copper species **Int-2.5** can undergo *ins situ* allylation with allylic phosphate to deliver homoallylic boronates with high chemo-, and diastereoselectivity. The chiral sulfonate containing NHC ligand **L2.5** was developed as the optimized ligand. In 2018, synthesis of homoallylic boronates through the enantioselective borylcupration of 1,3-diene was developed by Mazet and co-workers (Scheme 2.29).[60] Good yield and enantioselectivity were obtained by employing phosphanamine **L2.6** as the chiral ligand.

Scheme 2.28. Copper-Catalyzed Enantioselective Allylation of *Vinyl Boronic Esters through α-boryl Copper Intermediate*



(59) Lee, J.; Torker, S.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2017**, *56*, 821-826.
(60) Liu, Y.; Fiorito, D.; Mazet, C. *Chem. Sci.* **2018**, *9*, 5284−5288.

Scheme 2.29. Enantioselective Borylcupration of 1,3-Diene

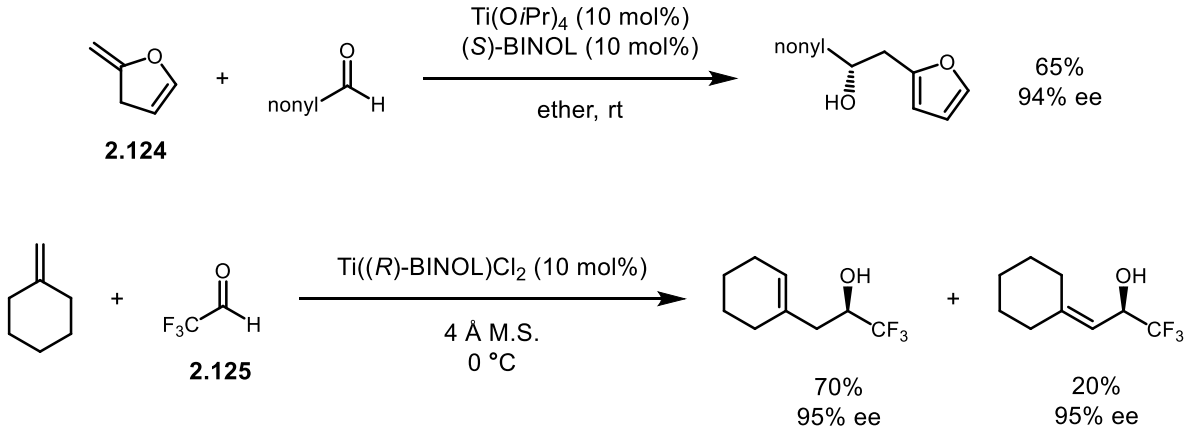


2.2.7 Synthesis of Enantioenriched Secondary Homoallylic Alcohols

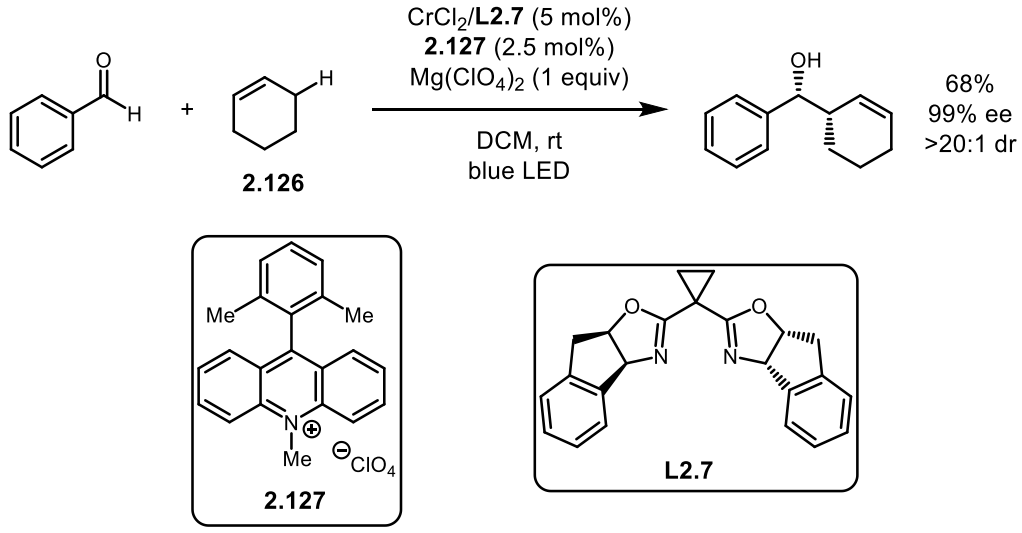
One classical approach to homoallylic alcohol is the carbonyl-ene reaction.[61] Early catalytic enantioselective examples were limited to either activated alkene (**2.124**)[62] or highly electrophilic aldehyde (**2.125**) (Scheme 2.30).[63] The catalytic asymmetric allylation of aldehydes with inactivated alkenes **2.126** and benzaldehyde was developed by Mitsunuma and co-workers in 2019 (Scheme 2.31).[64] They utilized the photoredox catalyst to activate the alkene and promoted the allylation with chromium catalyst and chiral ligand **L2.7**. Allylic alcohol products were delivered with good enantioselectivity and *Syn*-selectivity. The magnesium salt additive was proposed to stabilize the cationic radical intermediate generated from the photoredox process.

(61) Clarke, M. L.; France, M. B. *Tetrahedron* **2008**, *64*, 9003-9031.
(62) Miles, H. W.; Dethoff, A. E.; Tuson, H. H.; Ulas, G. Kishner's *J. Org. Chem*. **2005**, *70*, 2862-2865.
(63) Mikami, K.; Yajima, T.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimaru, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85-98.
(64) Mitsunuma, H.; Tanabe, S.; Fuse, H.; Ohkubo, K.; Kanai, M. *Chem. Sci.* **2019**, *10*, 3459-3465.

Scheme 2.30. Enantioselective Carbonyl-Ene Reaction with Activated Substrates



Scheme 2.31. Chromium/Photo-Catalyzed Allylation of Aldehydes with Unactuated Alkenes

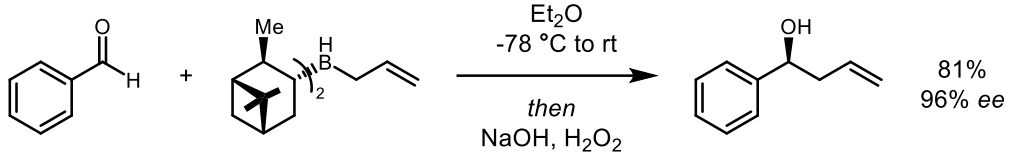


Another approach to homoallylic alcohols is the allylation of aldehydes. Prior to the discovery of chiral catalysis, introduction of the allylic moiety to carbonyl compounds, especially with decent stereocontrol, required the use of chiral organometallic reagents in stoichiometric amounts. For example, the well-known Brown[65] and Roush[66] allylation provided access to homoallylic alcohols with moderate to high optical purity (Scheme 2.32).

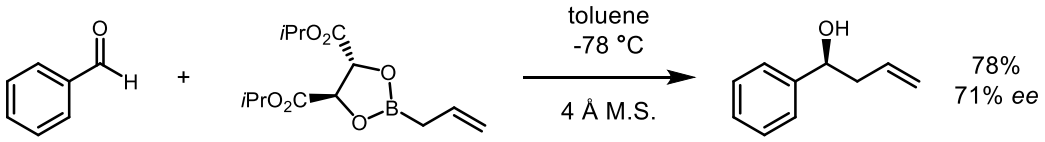
(65) H. C. Brown, M. C. Desai, P. K. Jadhav, *J. Org. Chem.* **1982**, *47*, 5065-5069.

Scheme 2.32. Brown Allylation and Roush Allylation

Brown:



Roush:

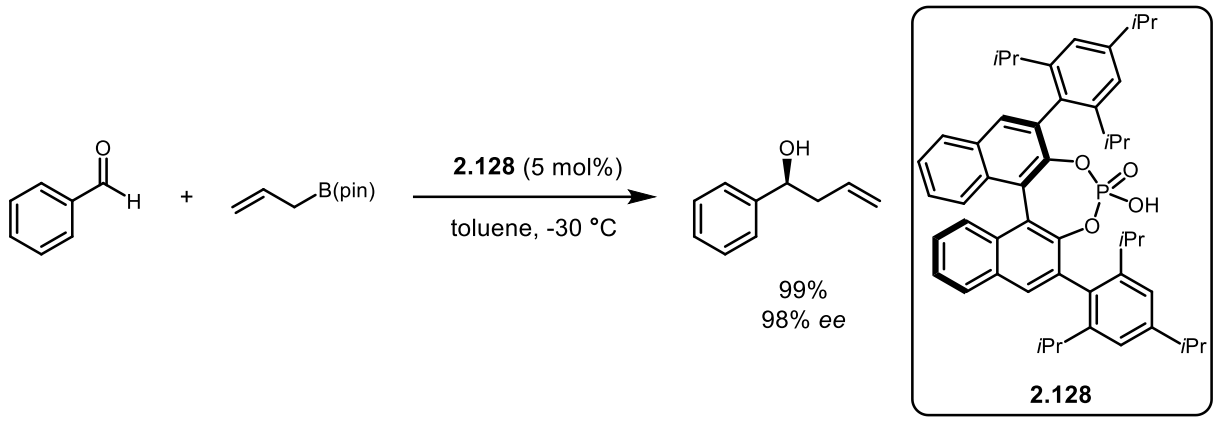


During the past decades, the fast development of numerous chiral catalysts enabled catalytic enantioselective allylation.[53] In the following part, I will discuss selected examples of catalytic enantioselective allylation reactions with different allylic derivatives.

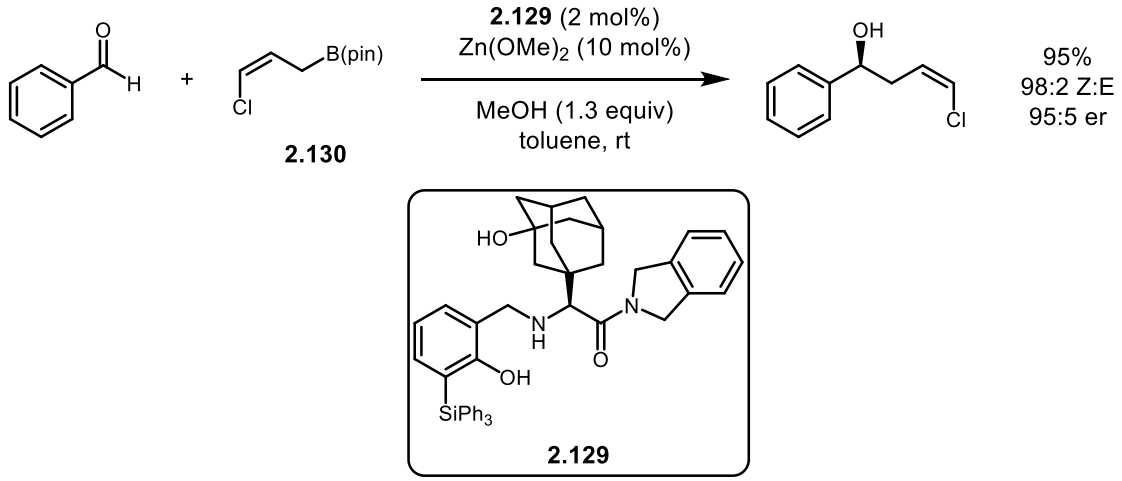
In 2010, Jain and Antilla utilized the chiral phosphoric acid catalyst **2.128** to promote the allylboration of aldehydes and delivered the homoallylic alcohol with excellent yield and enantioselectivity (Scheme 2.33).[67] Recently, the Hoveyda Group developed a *Z*-selective allylboration of aldehydes with a proton-activated, chiral aminophenol-boryl catalyst **2.129** (Scheme 2.34).[68] The *Z*-homoallylic alcohol was furnished in high enantiomeric purity. It is noteworthy that the starting material Z-allylic boronate **2.130** could be obtained through a catalytic cross-metathesis reaction developed by the same group.[69]

(66) W. R. Roush, A. E. Walts, L. K. Hoong, *J. Am. Chem. Soc.* **1985**, 107, 8186-8190.
(67) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884-11886.
(68) Morrison, R. J.; van der Mei, F. W.; Romiti, F.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2020**, *142*, 436−447.
(69) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459−465.

Scheme 2.33. Chiral Phosphoric Acid-Catalyzed Allylboration of Aldehydes



Scheme 2.34. Z-Selective Allylboration of Aldehydes



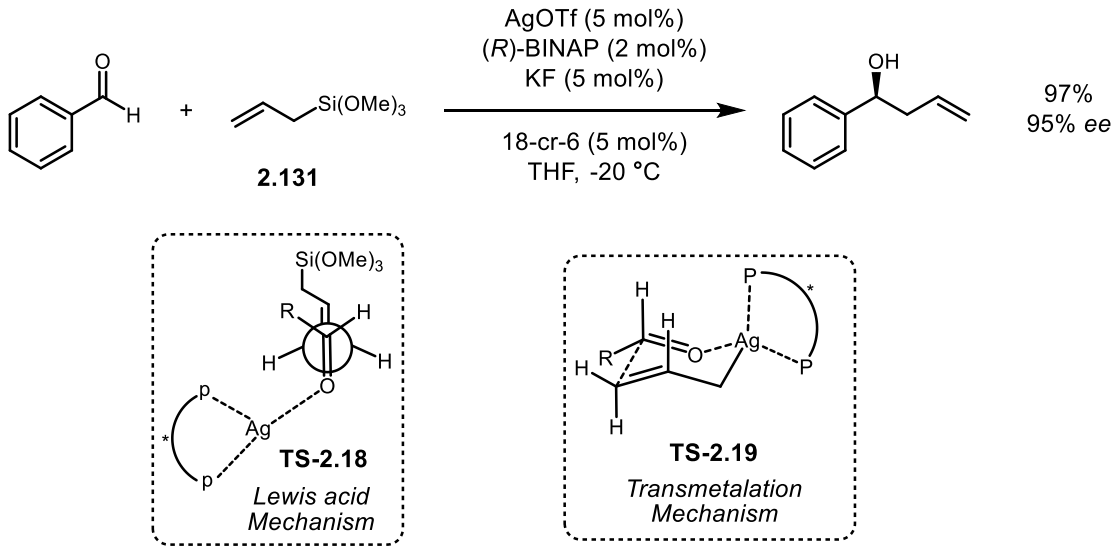
Silver-catalyzed enantioselective allylation with allylic siloxane **2.131** was accomplished by Yamamoto and co-workers (Scheme 2.35).[70] Homoallylic alcohol products were delivered with good yield and enantioselectivity. An acyclic antiperiplanar transition state (Lewis acid mechanism, **TS-2.18**) and a chair-like transition state (transmetalation mechanism, **TS-2.19**) were proposed for plausible reaction mechanisms. Allylation with allylic trichlorosilane **2.132**

(70) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593-5601.

was developed by the Denmark group with chiral bisphosphoramide **Cat-1** (Scheme 2.36).[71] A cationic silane intermediate **2.133a** was proposed, which can be generated through the ionization of a chloride ion. Next, the aldehyde could bind to the cationic silicon, followed by allyl transfer to deliver the product (**2.133b**).

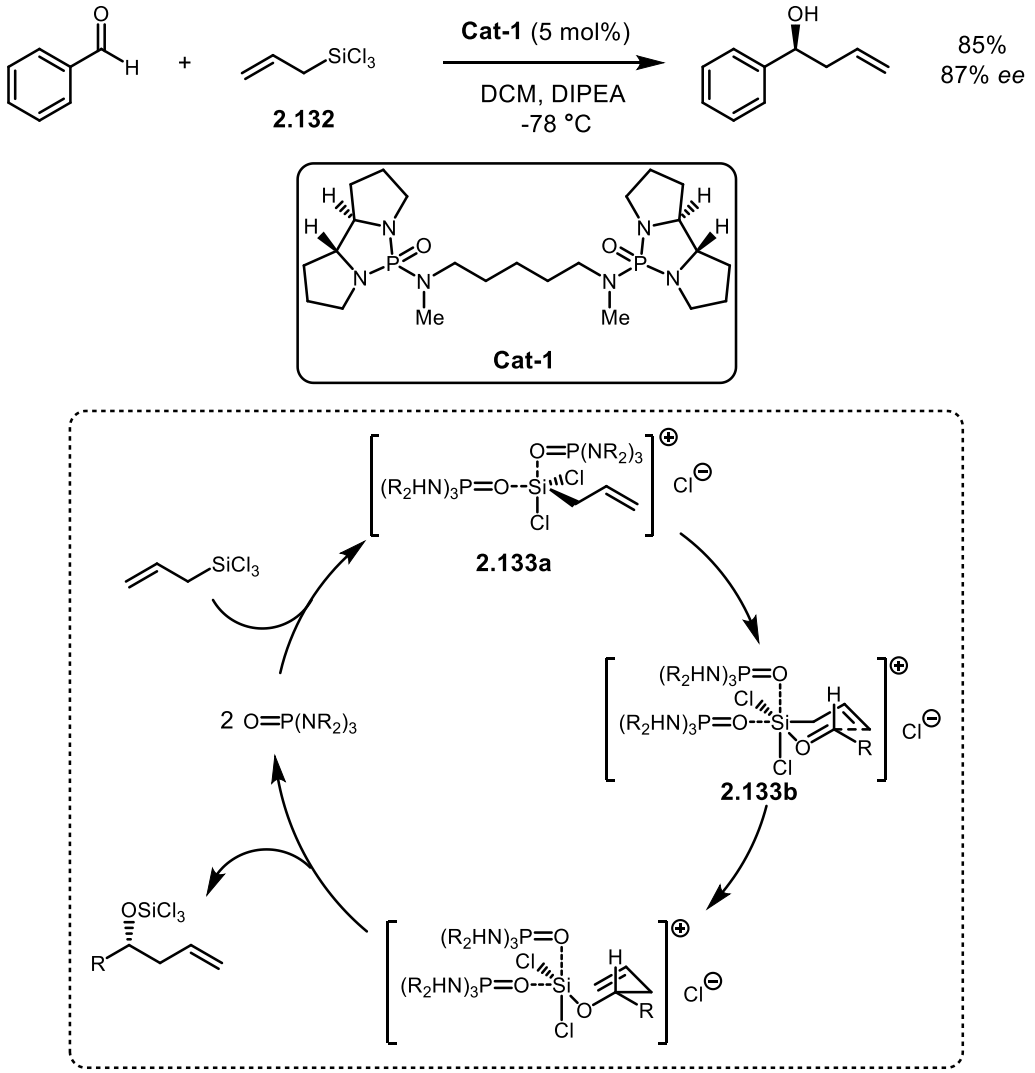
Enantioselective allylation of aldehydes with allyltin reagents **2.134** was accomplished by Maruoka and co-workers to deliver homoallylic alcohol with good yield and selectivity (Scheme 2.37). The titanium catalyst **2.135** can be readily prepared from triisopropoxytitanium chloride in two steps.

Scheme 2.35. Silver-Catalyzed Allylation of Aldehydes with Allylic Silanes

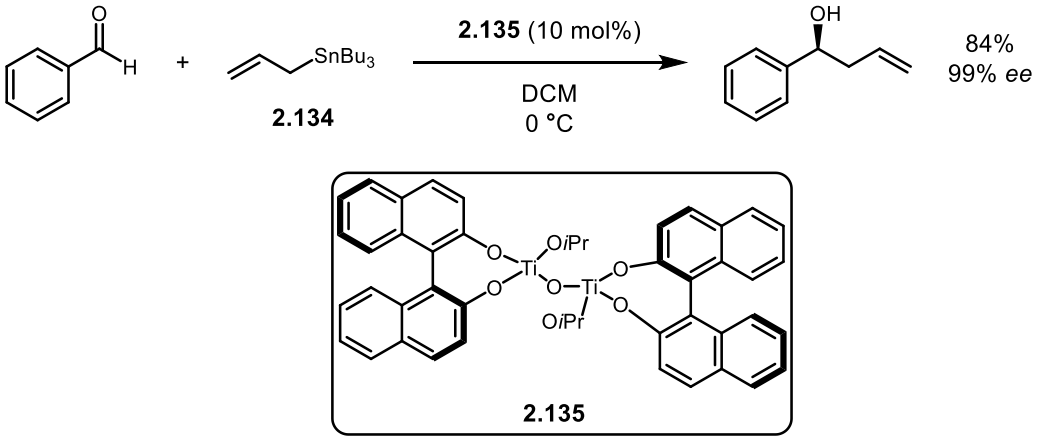


(71) (a) Denmark, S. E.; Fu, J.; Coe, D. M.; Su, X.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **2006**, *71*, 1513-1522. (b) Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523-1536.

Scheme 2.36. Bisphosphoramide-Catalyzed Allylation of Aldehydes with Allylic Silanes

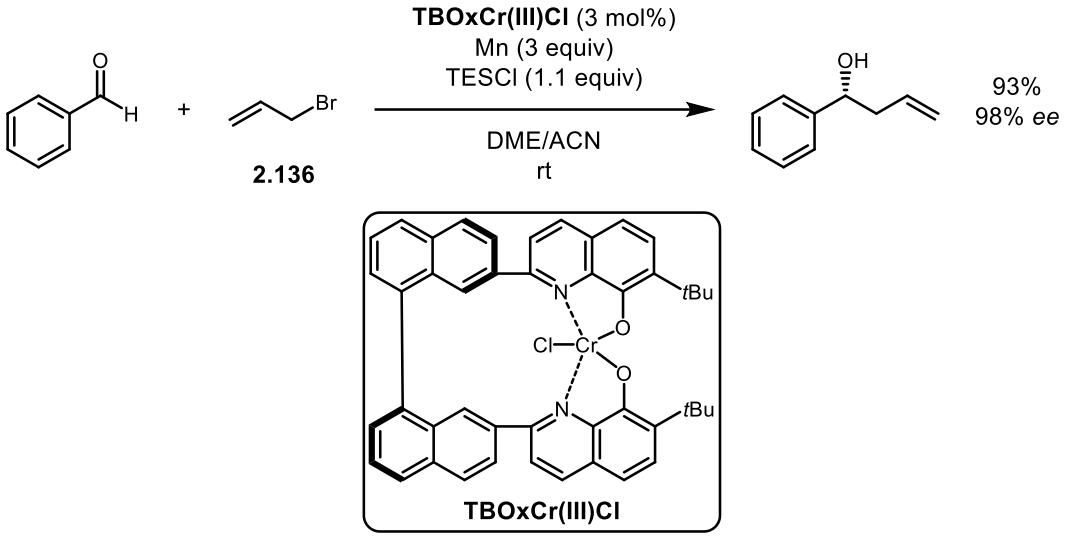


Scheme 2.37. Titanium-Catalyzed Allylation of Aldehydes with Allylic Stannane



Enantioselective Nozaki-Hiyama reaction with allyl bromide **2.136** and catalyst TBOxCr(III)Cl was developed the Yamamoto group (Scheme 2.38).[72] Excellent yield and enantioselectivity were achieved during this process.

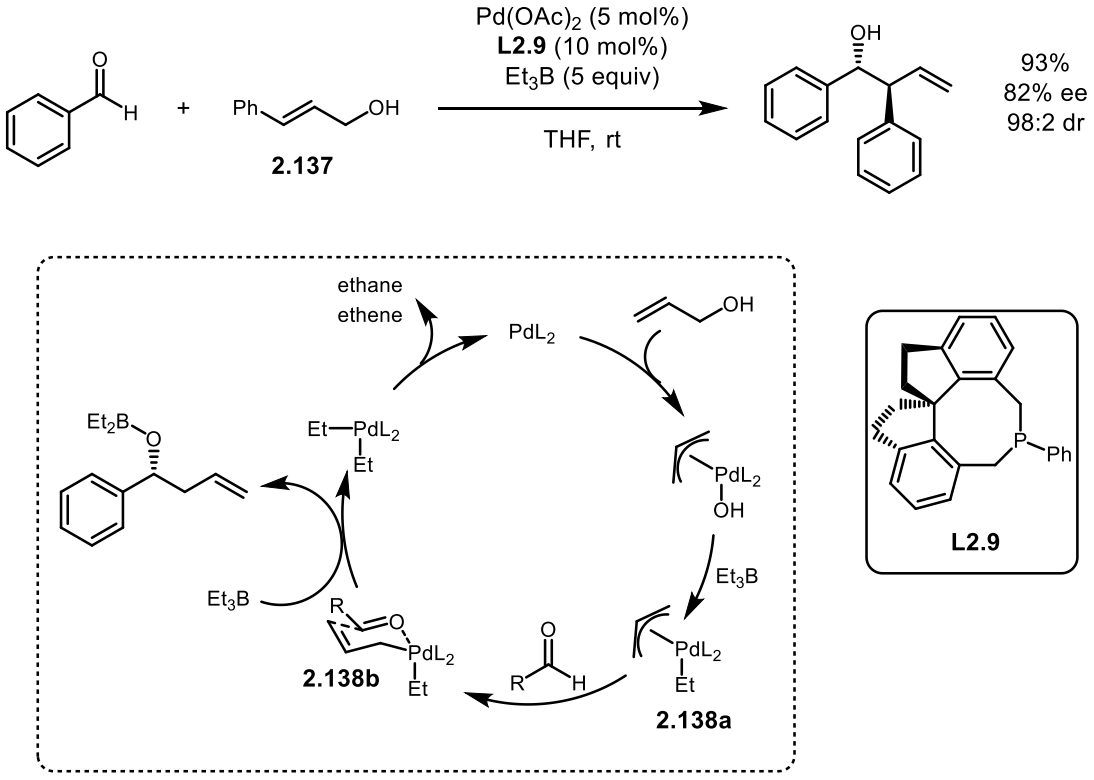
Scheme 2.38. Enantioselective Nozaki-Hiyama Reaction



Allylic alcohols have been employed as allylation reagents for aldehydes as well. Zhou and co-workers developed the enantioselective allylation of benzaldehyde with allylic alcohol **2.137** (Scheme 2.39).[73] Palladium (II) acetate and monodentate phosphine ligand **L2.9** were found to be the optimized catalyst. The function of triethyl borane is to transmetalation with palladium to form electron-rich nucleophilic palladium species **2.137a**, which can participate in the allyl transfer process through a chair-like transition state (**2.137b**).

(72) Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198-13199.
(73) (a) Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*, 233-2335. (b) Qiao, X.-C.; Zhu, S.-F.; Chen, W.-Q.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2010**, *21*, 1216-1220.

Scheme 2.39. Palladium-Catalyzed Enantioselective Allylation with Allylic Alcohols



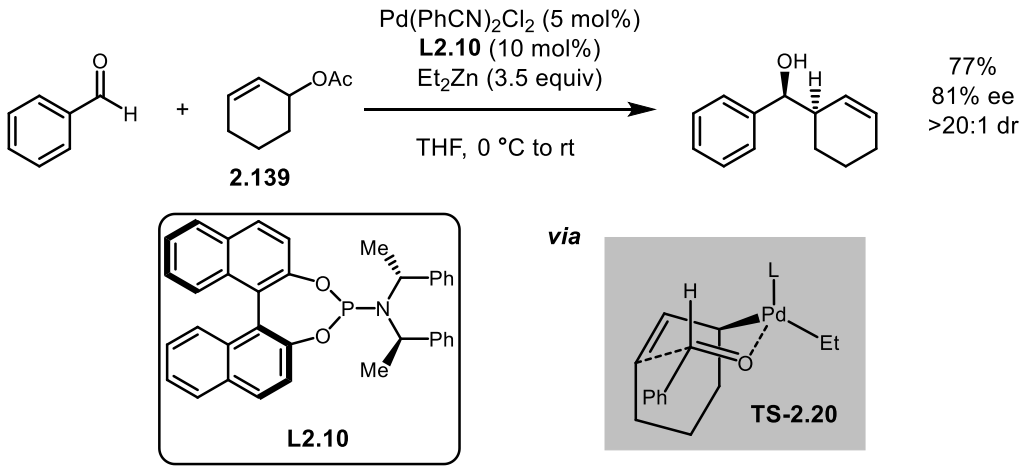
Allyl acetates were utilized as a more readily available and bench-stable surrogate of allylmetal reagents in the enantioselective carbonyl allylations. Palladium-catalyzed Enantioselective dialkylzinc-mediated allylation of aldehydes with allylic acetates **2.139** was achieved by Feringa and co-workers (Scheme 2.40a).[74] Monodentate phosphine ligand **L2.10** was found to be the optimized ligand. The role of diallyl zinc was proposed to alkylate the palladium intermediate to facilitate the formation of η^1-allylpalladium species, which could react with aldehyde through a chair-like transition state (**TS-2.20**) to deliver homoallylic alcohol product with *syn*-selectivity. Iridium-catalyzed allylation of aldehydes and alcohols was accomplished by the Krische group (Scheme 2.40b).[75] Good yield and high enantioselectivity

(74) Howell, G. P.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2006**, *4*, 1278-1283.
(75) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340-6341.

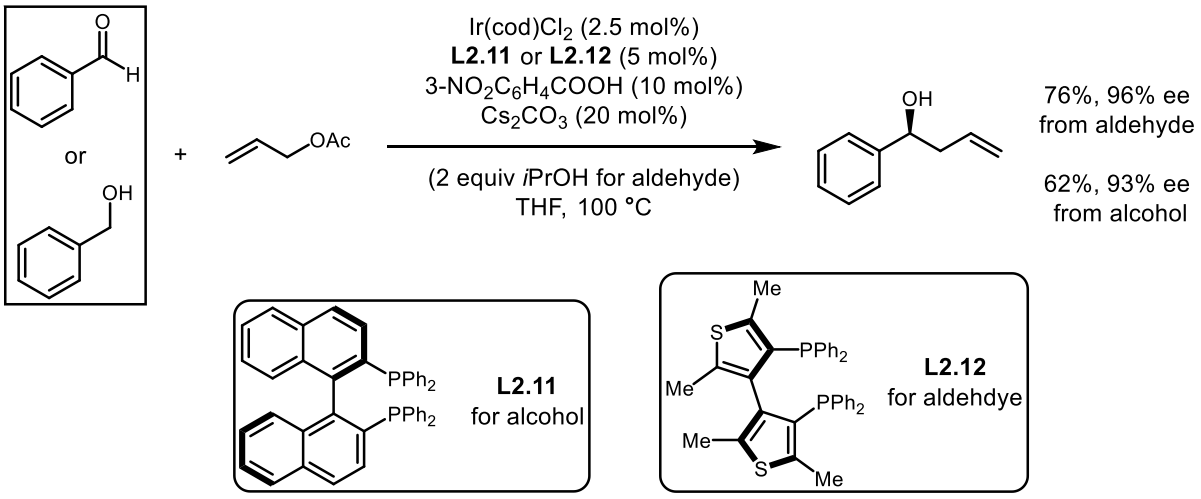
were obtained from both aldehyde and alcohol substrates. Notably, the addition of isopropyl alcohol is essential for aldehyde substrates, which helps to regenerate the active iridium species.

Scheme 2.40. Enantioselective Allylations with Allylic Acetates

a. Palladium-Catalyzed Allylation



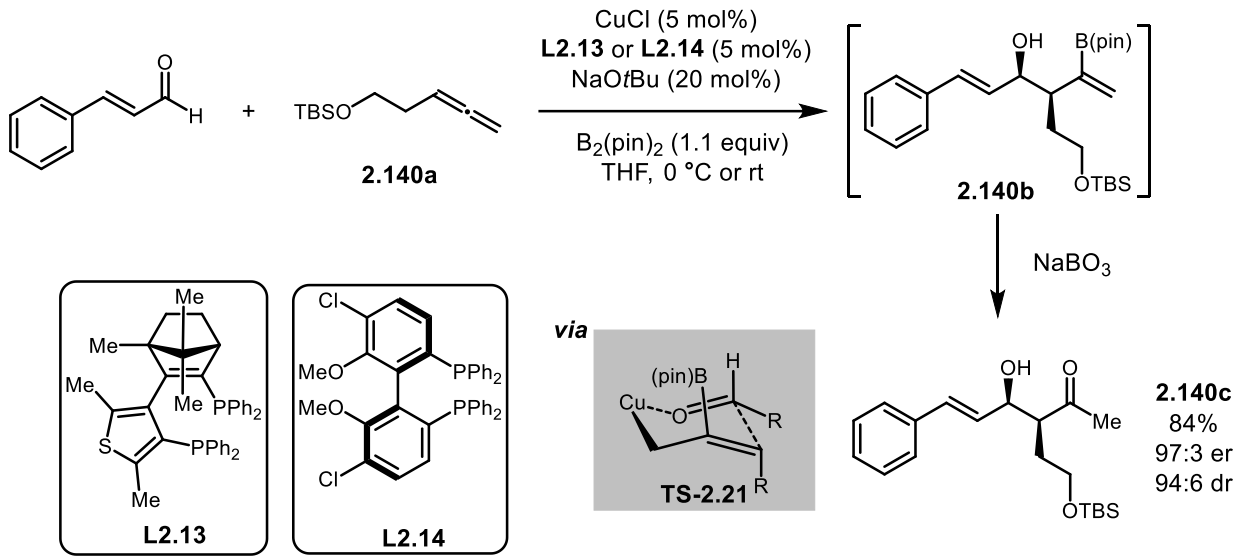
b. Iridium-Catalyzed Allylation



Allylation with *in situ* generated allylic metallic intermediates was also developed. For example, the Hoveyda group developed a copper-catalyzed enantioselective borylcupration of allene **2.140a**, the *in situ* generated allyl copper intermediate can react with aldehydes to afford

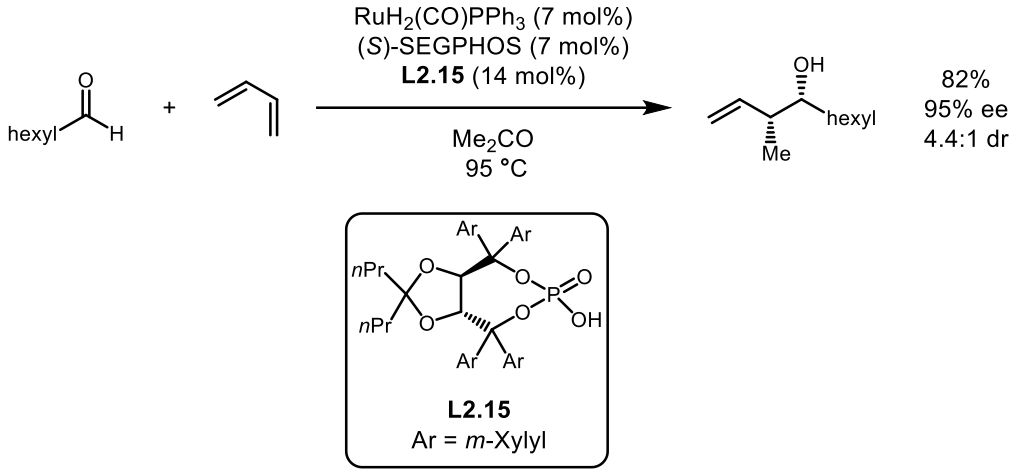
homoallylic alcohol product **2.140b** (Scheme 2.41).[76] Product **2.140b** was not isolated, but *in situ* oxidized to ester **2.140c**. Excellent yield, enantioselective, and diastereoselectivity were observed. A six-membered ring transition state (**TS-2.21**) was proposed to account for the generation of *syn*-product. In 2012, the Krische group accomplished the enantioselective hydrohydroxyalkylation of butadiene with ruthenium catalyst to deliver the crotylation product with good yield, good enantioselectivity, and moderate diastereoselectivity (Scheme 2.42).[77]

Scheme 2.41. Copper-Catalyzed Enantioselective Borylcupration of Allenes



(76) Meng, F.; Jang, H.; Jung, B; Hoveyda, A. H.; *Angew. Chem. Int. Ed.* **2013**, *52*, 5046-5051.
(77) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, 134, 20628-20631.

Scheme 2.42. Ruthenium-Catalyzed Enantioselective Hydrohydroxyalkylation of Butadiene



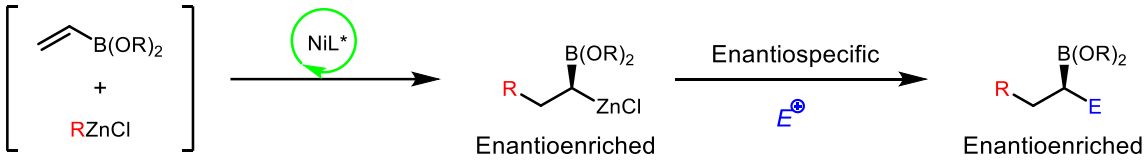
In summary, various catalytic methods have been developed to deliver homoallylic boronates and alcohols. Homoallylic boronates could be obtained from allylation of *gem*-bis(boronates) or allylation of *in situ* generated α-boryl copper species (See Section 2.2.6). On the other hand, homoallylic alcohols were commonly synthesized from the allylation of aldehydes (See Section 2.2.7).

The main advantage of the nickel-catalyzed carbozincation is that it exhibits good functional group tolerance, such as alcohol and ketone groups (See Section 2.5 for more information). Alcohols cannot be tolerated in the allylation of *gem*-bis(boronates) since a strong base is generally required to activate the *gem*-diboryl group; besides, ketones are generally not tolerated in the allylation of aldehydes because undesired allylation with ketone could occur. Therefore, it is valuable to develop the nickel-catalyzed carbozincation of vinylboronic esters to furnish homoallylic boronates, especially with sensitive functional groups. Moreover, we also developed the downstream Negishi coupling and halogenation of *in situ* generated α-boryl zinc intermediates, which further showcased the synthetic utility of the carbozincation reaction.

2.3 Discovery of the Ni-Catalyzed Carbozincation

To the best of our knowledge, enantioselective carbozincation of terminal alkenes had not been reported in the literature. Taking advantage of a chiral nickel catalyst, we realized the carbozincation of alkenyl boronates to prepare enantioenriched α-boryl zinc reagents (Scheme 2.43).

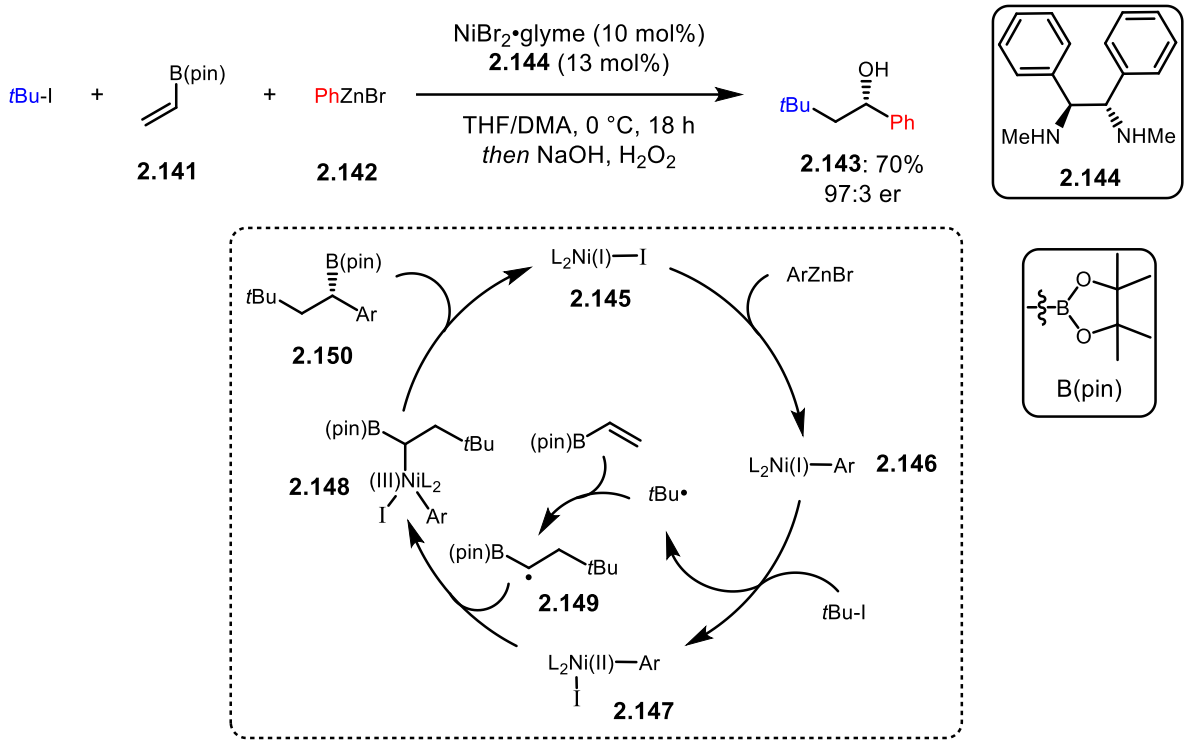
Scheme 2.43. Enantioselective Carbozincation of Vinylboronates



Development of this process was inspired by previously developed nickel-catalyzed radical addition/cross-coupling reaction (Scheme 2.44),[78] where a three-component coupling among tertiary alkyl iodides, vinyl boronic ester **2.141**, and arylzinc reagents **2.142** was proceeded to furnish secondary boronate products in an enantioselective fashion. Mechanistically, nickel halide **2.145** could first transmetalate with arylzinc reagents to generate aryl nickel intermediate **2.146**, which then undergoes a single-electron-transfer with the alkyl iodide to afford Ni(II) compound **2.147** and a tertiary carbon radical. The radical species could then undergo radical addition with the vinyl boronic ester to afford secondary radical intermediate **2.149**, which recombines with **2.147** to furnish Ni(III) intermediate **2.148**. Subsequent reductive elimination delivers product **2.148** and regenerates **2.145** to close the catalytic cycle.

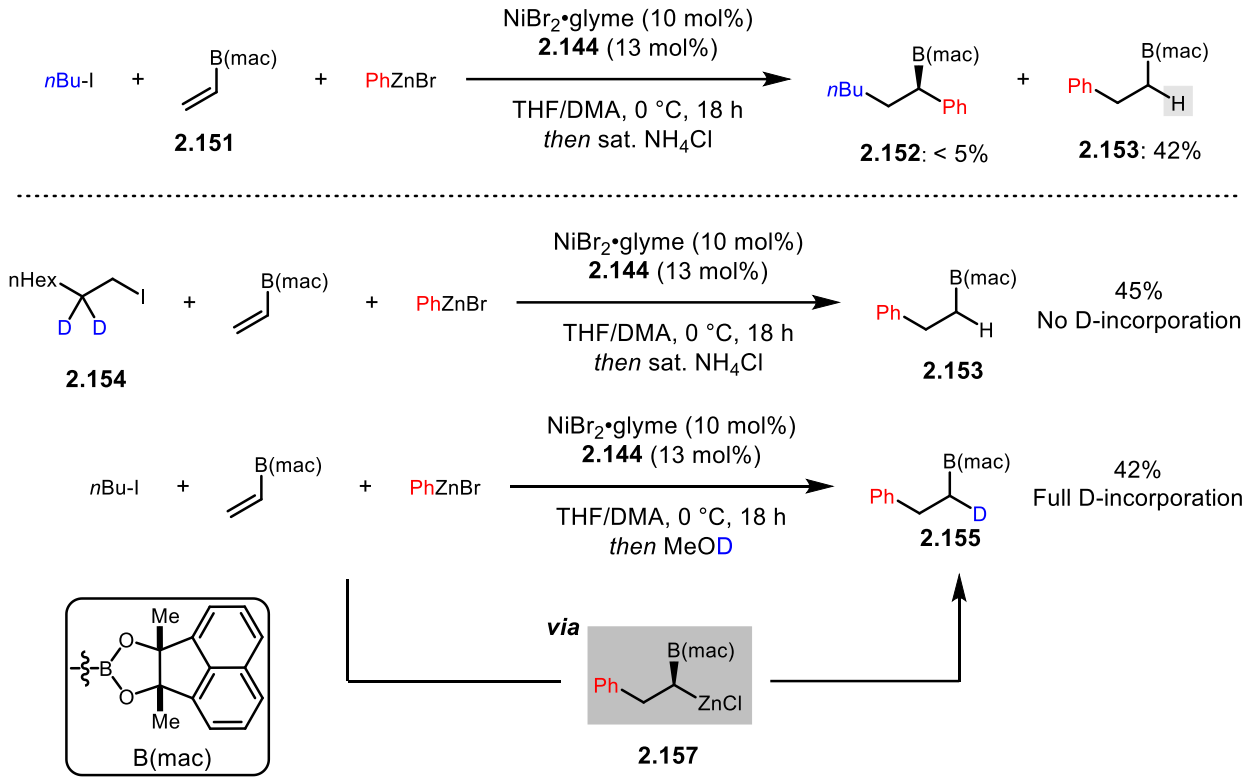
(78) Chierchia, M. P.; Xu, P.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 14245–14249.

Scheme 2.44. Nickel-Catalyzed Radical Addition/Cross-Coupling Reaction



During our attempts to employ primary alkyl iodides in the reaction, we altered the ligand on boron to the mac (methylated acenaphthoquinone) ligand. This alternation led to an outcome where desired product **2.152** was not observed. Instead, the major product was phenyl ethyl boronic ester **2.153**, which could be the product of a carbozincation process (Scheme 2.45, top equation). To investigate how this product was generated, we synthesized the deuterium-labeled alkyl iodide **2.154** and subjected it to the reaction. No deuterium incorporation in the product **2.153** was observed, which suggests the α-boryl hydrogen is not derived from the β-hydride elimination of the alkyl halides. On the other hand, deuterated compound **2.55** was isolated when we quenched the reaction with deuterated methanol (Scheme 2.45, bottom equations). This observation indicates that a stoichiometric amount of α-boryl organometallic reagent is produced, and it is most likely to be the α-boryl zinc species **2.157** based on the reaction conditions.

Scheme 2.45. Nickel-Catalyzed Carbozincation of Vinylboronates: Initial Studies



2.4 Reaction Optimizations

To investigate the stereoselectivity of the carbozincation reaction, we trapped the α-boryl zinc intermediate with allyl bromide in the presence of copper chloride (Table 2.1, top equation). After boron oxidation, homoallylic alcohol product **2.158** was isolated and found to be almost racemic (52:48, entry 1). Then, different combinations of solvents were examined, the combination of THF/DMSO resulted in the highest yield (entry 4). Next, lower reaction temperatures were employed, and we observed a significant increase in the enantioselectivity albeit with a decrease in yield (entry 4-6, 22-23). The alkyl halide was found to be required for the reaction, presumably acting as an oxidant. Thus, different oxidants were investigated (entry 7-10), and methyl iodide was found to be the optimal one, which delivered the product with 63%

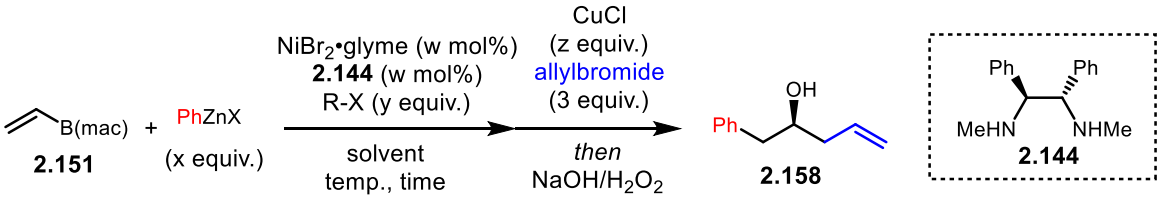
yield; changing the counterion of arylzinc reagents from chloride to bromide, iodide, or triflate resulted in diminished yield (entry 11-13).

One major problem we encountered during the optimization was that the reaction outcome was difficult to reproduce. We observed that the THF/DMSO solvent mixture could freeze at -40 ℃ due to the relatively high freezing point of DMSO. The frozen solvent could influence the stirring and result in diminished reactivity. One solution is to replace the DMSO with another polar aprotic solvent. However, we found that DMSO is indispensable for the observed high stereoselectivity. DMSO is more than a solvent in this reaction; presumably, it can be a ligand for the nickel.[79] Alternatively, we reduced the proportion of DMSO and add a second polar aprotic solvent with a lower freezing point to keep the reaction homogeneous. After screening, DMF was found to be the optimal choice, which afforded the product with comparable yield and good reproducibility (Table 2.1, entry 14; Table 2.2 entry 12-14).

In addition to the variables examined above, the stoichiometry of methyl iodide was investigated (entry 14-17), and we found that 0.5 equivalents of methyl iodide were enough to obtain the optimal yield. As for the reaction time, a comparable yield was obtained after 12 hours (entry 18), albeit further shortening of the reaction time led to a lower yield. Of note, the allylation can be accomplished with a catalytic amount of copper (entry 19). Lowering the reaction temperature to -50 ℃ resulted in diminished yield of the desired product with higher enantioselectivity (entry 24).

(79) Diao, T.; White, P.; Guzei, I.; Stahl, S. S. *Inorg. Chem.* **2012**, *51*, 11898-11909.

Table 2.1. Optimizations of the Ni-Catalyzed Carbozincation

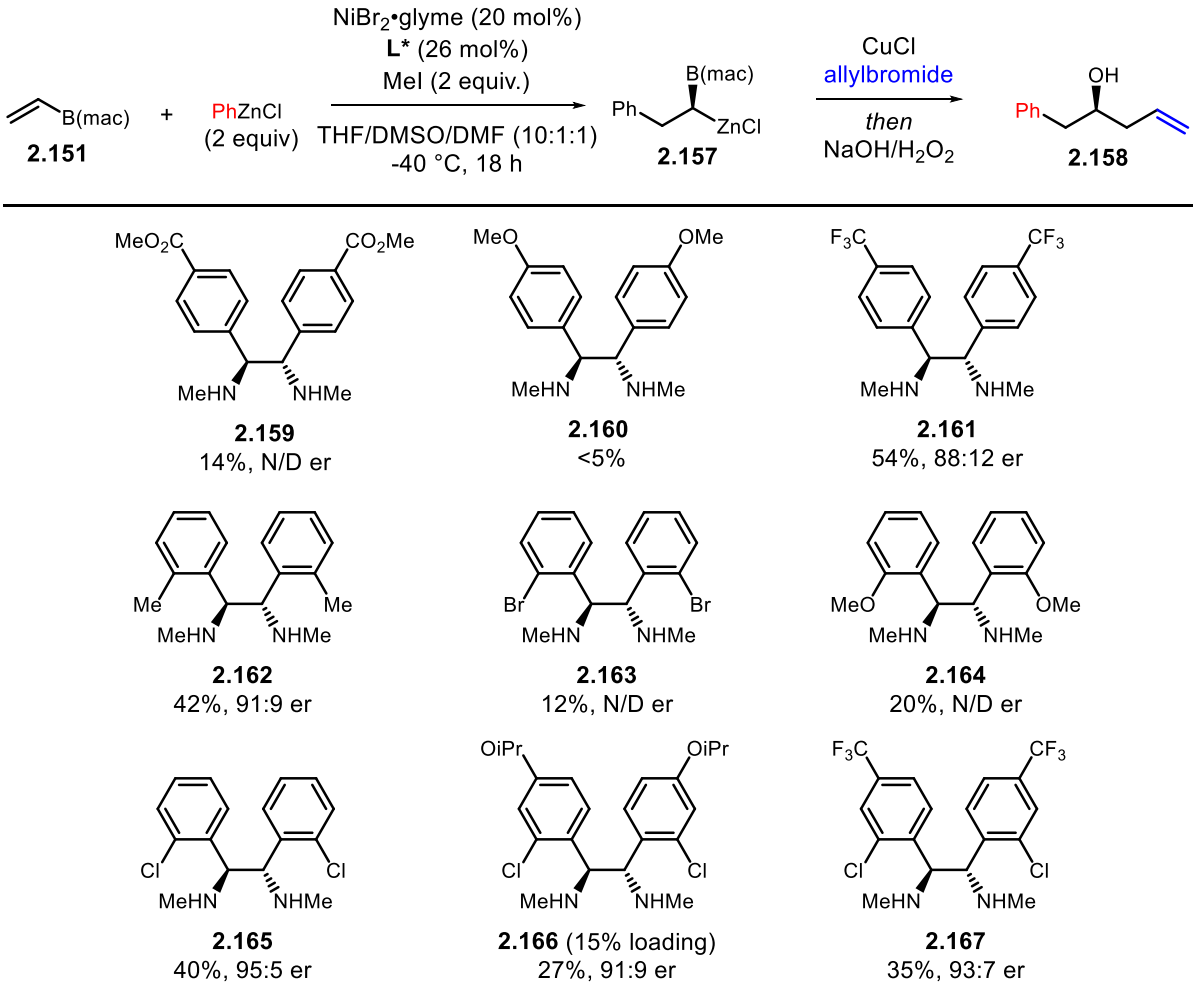


Entry	R-X	Zn species	solvent	temp. (°C)	time (h)	w	x	y	z	yield	er
1	*n*BuI	PhZnCl•LiCl	THF/DMF (5:1)	0	18	10	2	2	0.5	42%	52:48
2	*n*BuI	PhZnCl•LiCl	THF/DMA (5:1)	0	18	10	2	2	0.5	42%	N/A
3	*n*BuI	PhZnCl•LiCl	THF	0	18	10	2	2	0.5	23%	N/A
4	*n*BuI	PhZnCl•LiCl	THF/DMSO (5:1)	0	18	10	2	2	0.5	56%	53:47
5	*n*BuI	PhZnCl•LiCl	THF/DMSO (5:1)	-20	18	10	2	2	0.5	42%	75:25
6	*n*BuI	PhZnCl•LiCl	THF/DMSO (5:1)	-40	18	20	2	2	0.5	45%	86:14
7	MeI	PhZnCl•LiCl	THF/DMSO (5:1)	-40	18	20	2	2	0.5	63%	86:14
8	*n*BuBr	PhZnCl•LiCl	THF/DMSO (5:1)	-40	18	20	2	2	0.5	<5%	N/A
9	Me_2SO_4	PhZnCl•LiCl	THF/DMSO (5:1)	-40	18	20	2	2	0.5	<5%	N/A
10	MeOTf	PhZnCl•LiCl	THF/DMSO (5:1)	-40	18	20	2	2	0.5	<5%	N/A
11	MeI	PhZnBr•LiBr	THF/DMSO (5:1)	-40	18	20	2	2	0.5	<5%	N/A
12	MeI	PhZnI•LiI	THF/DMSO (5:1)	-40	18	20	2	2	0.5	<5%	N/A
13	MeI	PhZnOTf•LiOTf	THF/DMSO (5:1)	-40	18	20	2	2	0.5	<5%	N/A
14	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	20	2	2	0.5	59%	89:11
15	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	20	2	1	0.5	59%	89:11
16	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	20	2	0.5	0.5	56%	89:11
17	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	20	2	0.25	0.5	34%	90:10
18	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	12	20	2	2	0.5	59%	89:11
19	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	20	2	2	0.1	59%	89:11
20	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	20	2	2	1	58%	89:11
21	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	20	3	2	0.5	58%	89:11
22	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	15	2	2	0.5	50%	89:11
23	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-40	18	10	2	2	0.5	41%	90:10
24	MeI	PhZnCl•LiCl	THF/DMSO/DMF (10:1:1)	-50	18	20	2	2	0.5	19%	93:7

Different chiral diamine ligands on nickel were also investigated. The results are summarized in Scheme 2.46. Addition of substituents to the phenyl ring of the diamine ligand usually resulted in poor reactivity, such as that observed with *para*-CO_2Me (**2.159**), *para*- and *ortho*-OMe (**2.160**, **2.164**), and *ortho*-Br (**2.163**). We found that *ortho* substituents such as *ortho* Me (**2.162**) and *ortho*-Cl (**2.165**) provided products with higher enantioselectivity but lower yield. We hypothesized that the *ortho* substituents in the phenyl ring are helpful to rigidify the chiral catalysts; however, the enhanced bulkiness could hamper the binding between nickel and substrates, leading to decreased reactivity. Another hypothesis for the lower reactivity of **2.165** is its poor solubility, as we observed solids precipitate while mixing **2.165** with nickel in THF at room temperature. Ligand **2.166** was accordingly prepared. Even though it exhibits better solubility while mixing with nickel at room temperature, the yield and selectivity are not improved.

Lastly, various ligands on boron were studied. We found that the mac ligand (**2.151**) is especially effective for this reaction as lower yield or diminished selectivity were observed in all other cases (Table 2.2, entry 1-9). We hypothesized that the steric bulkiness of the mac ligand might be the crucial feature for its effectiveness in this reaction: it helps avoid undesired side reactions, such as methylation reactions via oxidative addition. Increasing the reaction concentration resulted in lower enantioselectivity (entry 10), while decreasing the concentration led to lower yield (entry 11). Different nickel catalyst precursors were investigated as well (entry 15-17), and no significant variations in yield and selectivity were observed. Collectively, entry 1 in Table 2.2 was chosen as the optimal condition. Of note, under this condition, the rest of the mass balance (40%) is unreacted starting material (**2.151**).

Scheme 2.46. Ligand Optimizations

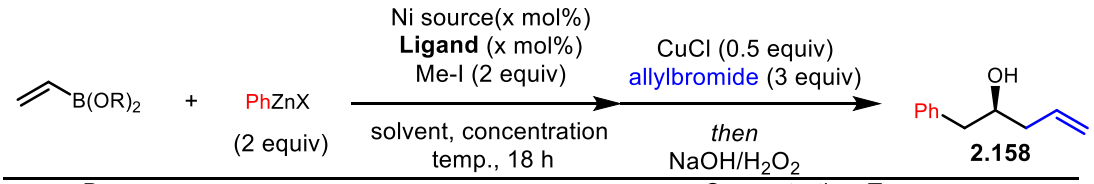


2.5 Substrate Scope and Mechanistic Analysis

2.5.1 Nucleophile Scope

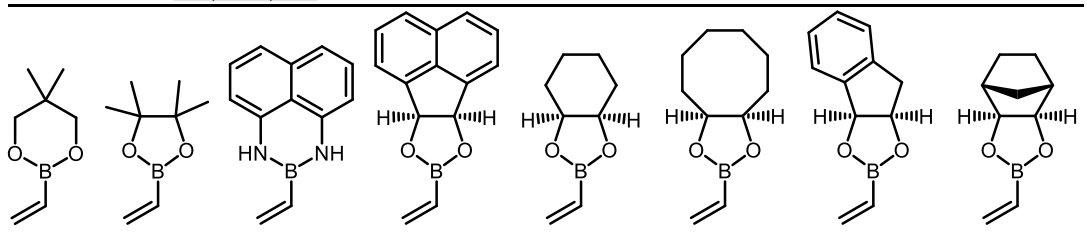
Using the optimized conditions, we investigated the substrate scope for the tandem carbozincation/trapping reaction. First, different organozinc reagents were examined with the copper-mediated allylation used to trap the α-boryl zinc intermediate. As shown in Scheme 2.47, different substituent patterns could be well tolerated. For arylzinc reagents bearing *ortho* alkyl (2.176), halogen (2.177 to 2.179), and methoxy (2.180) groups, slightly diminished yields were

Table 2.2. Optimizations of the Ni-Catalyzed Carbozincation (*continued*)



2.158

Entry	Boron species	Ni source	Ligand	x	Solvent	Concentration (M)	Temp. (°C)	Yield	er
1	**2.151**	$NiBr_2$•glyme	**2.144**	20	THF/DMF/DMSO (10:1:1)	0.083 M	-40	59%	89:11
2	**2.168**	$NiBr_2$•glyme	**2.144**	20	THF/DMF/DMSO (10:1:1)	0.083 M	-40	40%	N/A
3	**2.169**	$NiBr_2$•glyme	**2.144**	20	THF/DMF/DMSO (10:1:1)	0.083 M	-40	9%	55:45
4	**2.170**	$NiBr_2$•glyme	**2.144**	10	THF/DMF/DMSO (10:1:1)	0.083 M	-40	<5%	N/A
5	**2.171**	$NiBr_2$•glyme	**2.144**	10	THF/DMSO (5:1)	0.083 M	-20	24%	79:21
6	**2.172**	$NiBr_2$•glyme	**2.144**	10	THF/DMSO (5:1)	0.083 M	-20	13%	68:32
7	**2.173**	$NiBr_2$•glyme	**2.144**	10	THF/DMSO (5:1)	0.083 M	-20	26%	71:29
8	**2.174**	$NiBr_2$•glyme	**2.144**	10	THF/DMSO (5:1)	0.083 M	-30	22%	88:12
9	**2.175**	$NiBr_2$•glyme	**2.144**	10	THF/DMSO (5:1)	0.083 M	-30	41%	83:17
10	**2.141**	$NiBr_2$•glyme	**2.144**	20	THF/DMF/DMSO (10:1:1)	0.167 M	-40	47%	71:29
11	**2.141**	$NiBr_2$•glyme	**2.144**	20	THF/DMF/DMSO (10:1:1)	0.042 M	-40	27%	91:9
12	**2.141**	$NiBr_2$•glyme	**2.165**	10	THF/MeCN/DMSO (10:1:1)	0.083 M	-40	13%	93:7
13	**2.141**	$NiBr_2$•glyme	**2.165**	10	THF/Acetone/DMSO (10:1:1)	0.083 M	-40	23%	87:13
14	**2.141**	$NiBr_2$•glyme	**2.165**	10	THF/EtOAc/DMSO (10:1:1)	0.083 M	-40	12%	88:12
15	**2.141**	$NiCl_2$•glyme	**2.144**	20	THF/DMF/DMSO (10:1:1)	0.083 M	-40	55%	89:11
16	**2.141**	$Ni(COD)_2$	**2.144**	20	THF/DMF/DMSO (10:1:1)	0.083 M	-40	59%	89:11
17	**2.141**	(TMEDA) Ni(o-Tol)Cl	**2.144**	20	THF/DMF/DMSO (10:1:1)	0.083 M	-40	59%	89:11

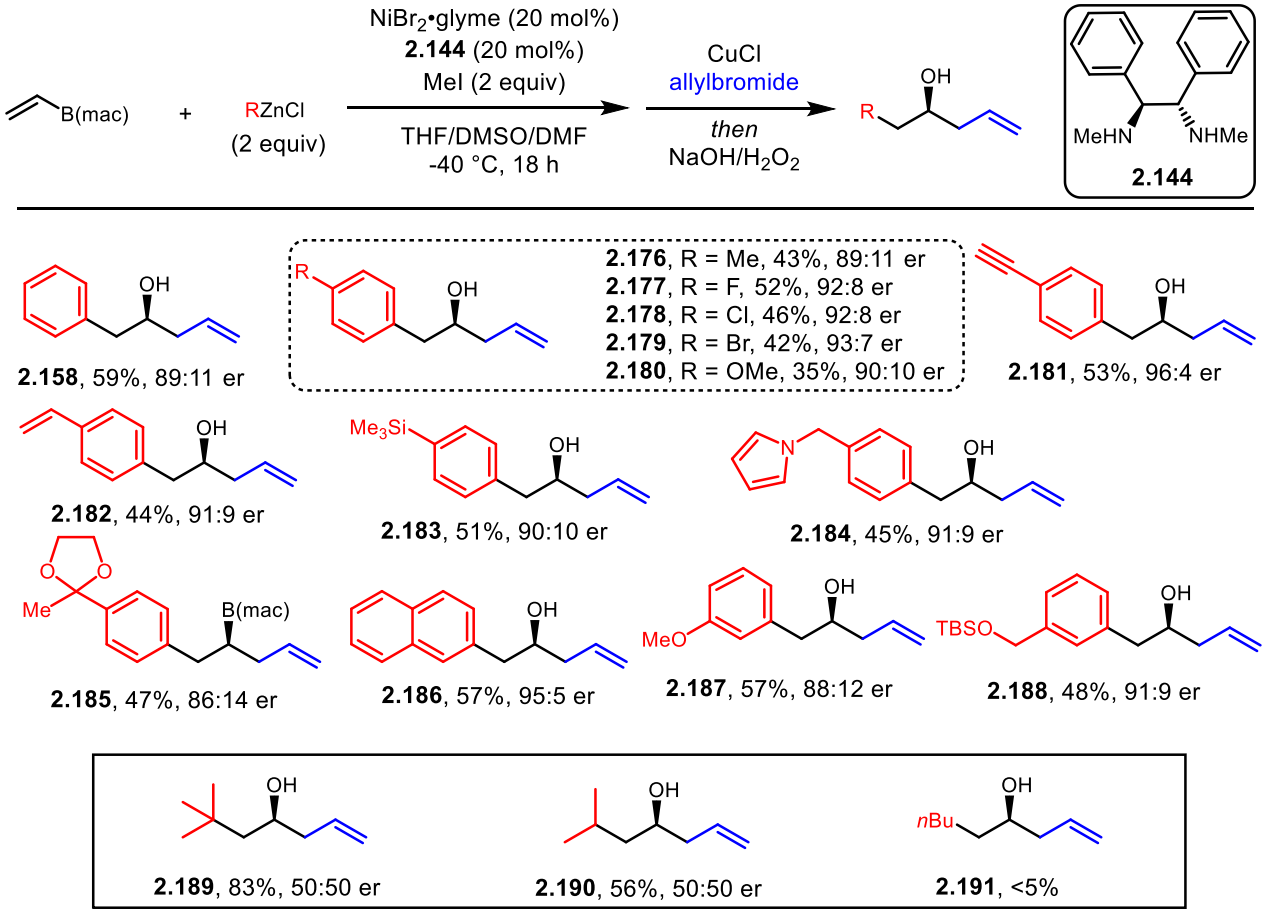


2.168 **2.169** **2.170** **2.171** **2.172** **2.173** **2.174** **2.175**

observed. Yields for alkynyl (**2.181**), vinyl (**2.182**), silyl (**2.183**), and acetal (**2.185**) substituted arylzinc reagents were comparable. Heterocycles (**2.184**) can be tolerated as well. 2-Napthylzinc chloride afforded the corresponding product **2.186** with good yield and excellent enantioselectivity. Moreover, *meta* methoxy (**2.187**) and alkyl substituents (**2.188**) are tolerated.

When secondary and tertiary alkylzinc reagents were applied in this reaction, products **2.189** and **2.190** were formed in a racemic manner, suggesting a radical process might be operating.[78] Employing primary alkylzinc reagents, which would generate a less stable radical,[80] resulted in no conversion of the starting material.

Scheme 2.47. Nucleophile Scope



(80) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255-263.

2.5.2 Allylation Scope

The scope of the copper-mediated allylation reaction was studied (Scheme 2.48). Various sensitive functional groups can be tolerated in this reaction, including halides (**2.193**), heterocycles (**2.195**), esters (**2.196**), ketones (**2.198**), alkynes (**2.199**), boronic esters (**2.201**), and free alcohols (**2.202**). For branched allyl electrophiles, moderate (**2.197**, **2.201**) to high (**2.198**, **2.199**, **2.202**) *E/Z* selectivity is observed. The propargyl electrophiles can also be accommodated in the reaction to deliver allenyl product **2.203** in an S_N2' manner. Of note, a complex mixture was observed with unsubstituted propargyl electrophiles, presumably because of the further transmetalation between the allenyl product and copper complex.[81]

2.5.3 Negishi Cross-Coupling

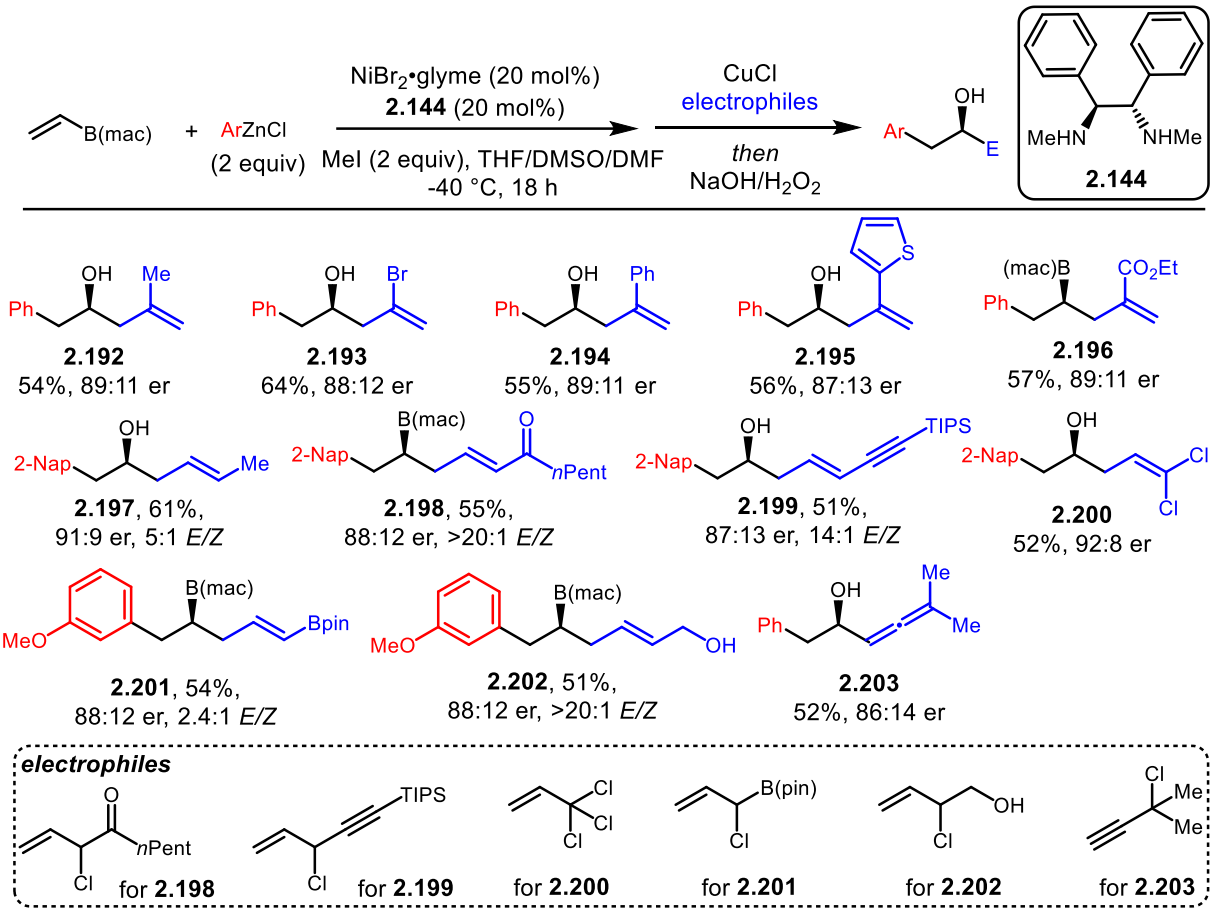
The investigation of α-boryl zinc reagents in the palladium-catalyzed Negishi cross-coupling reaction was predominantly done by Dr. Chenlong Zhang and Jingjia Chen, I will summarize the result in the following section (Scheme 2.49).

After Ni-catalyzed carbozincation reaction, palladium (II) acetate, triphenyl phosphine, and aryl halides were added to reaction mixture. Under these conditions, low yield and moderate enantioselectivity of **2.204** were observed (entry 1). We hypothesized that the lower yield is due to the competitive oxidative addition between palladium and methyl iodide, which could poison the catalyst and lead to side reactions. While the oxidative addition of palladium with aryl halides preferentially undergoes a concerted mechanism, the oxidative addition with methyl iodide typically occurs by an S_N2 type mechanism.[82a] Taking advantage of this distinction, we planned to improve the reaction condition by switching to electron-deficient ligands for palladium, which could lower the nucleophilicity of the metal and slow down the S_N2-type

(81) Chen, M. *Chem. Commun.* **2021**, *57*, 9212-9215.

oxidative addition process. To our delight, higher yield and enantioselectivity were obtained with P(*p*-FPh)$_3$ (entry 2) and P(*p*-CF$_3$Ph)$_3$ (entry 3). Alkenyl iodides were examined as electrophiles, and these successfully afforded the allylic alcohol **2.205** with good yield and stereoselectivity.

Scheme 2.48. Copper-Mediated Allylation Scope

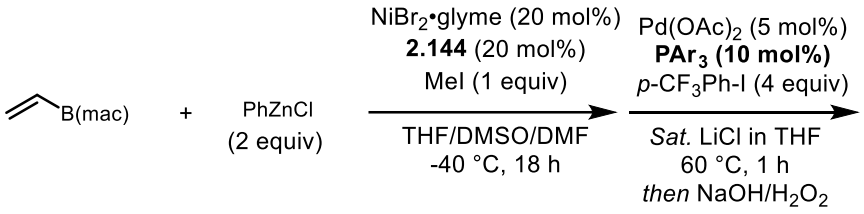


The addition of LiCl is crucial for the high enantiospecificity of the cross-coupling reaction (entry 2 and entry 4). Based on previous literature,[82b-c] use of LiCl could help facilitate the transmetalation between α-boryl zinc intermediate and palladium by forming a zinc "ate"

(82) (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, *6th Edition*, **2014**, Wiley: New Jersey, pp 168–170. ISBN 978-1-118-13807-6.; (b) McCann, L. C.; Hunter, H. N.; Clyburne, J. A. C.; Organ, M. G. *Angew. Chem.* **2012**, *124*, 7130–7133. (c) Hunter, H. N.; Hadei, N.; Blagojevic, V.; Patschinski, P.; Achonduh, G. T.; Arola, S.; Bohme, D. K.; Organ, M. G. *Chem. Eur. J.* **2011**, *17*, 7845–7851.

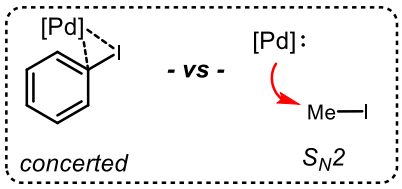
complex and minimizing the racemization of α-boryl zinc reagents (see Section 2.5.6. for more details of racemization).

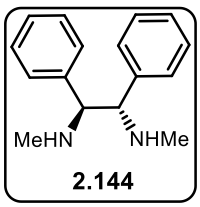
Scheme 2.49. Palladium-Catalyzed Negishi Cross-Coupling



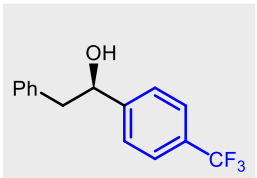
Entry	PAr_3	yield (%)	er
1	PPh_3	25%	80:20
2	P(*p*-FPh)$_3$	44%	87:13
3	P(*p*-CF_3Ph)$_3$	44%	87:13
4[a]	P(*p*-FPh)$_3$	42%	81:19

a) Reaction run without LiCl.

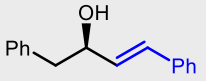




2.144



2.204



2.205
55%, 86:14 er

2.5.4 Halogenation of the α-Boryl Zinc Reagents

Halogenation of the alkyl α-boryl zinc intermediate was also studied. Preliminary experiments with I_2 and NIS at -20 °C afford the α-boryl iodide **2.206** with poor enantioselectivity (Scheme 2.50, entry 1-2). We hypothesized that the α-boryl iodide **2.206** could racemize in the presence of lithium iodide by formation of an iodoboron "ate" complex **2.211** (Scheme 2.50, bottom equation), followed by a 1,2-metallate shift to deliver the other enantiomer **2.212**. Thus, we investigated electrophilic brominating and chlorinating reagents. The corresponding products α-boryl bromide **2.207** and α-boryl chloride **2.208** should be more

configurationally stable because racemization of those products through 1,2-metallate shift should be slower due to stronger C–Br and C–Cl bonds.[55] Indeed, a significant increase in enantioselectivity was observed when either NBS or bromine were employed at -78 ℃ (entry 3-4).

In contrast, chlorinating reagents NCS and **2.209** afforded the α-boryl halides with diminished yield and stereoselectivity (entry 5-6). To our delight, chlorinating reagent TCCA[83] **2.210** was found to furnish the product **2.208** with high enantioselectivity. However, the yield was low (entry 7). Further optimization of chlorination conditions with various Lewis acids revealed cerium trichloride as an effective additive; the product was synthesized with improved yield (entry 8). We hypothesized that the Lewis acid could activate the chlorinating reagents, thus improving the reactivity.

Notably, the absolute configuration of the furnished α-boryl halide is opposite to the absolute configuration of the secondary boronates synthesized from the copper-mediated allylations and palladium-catalyzed cross-couplings. A detailed discussion of the stereochemical course of those transformations will be included in Section 2.5.6.

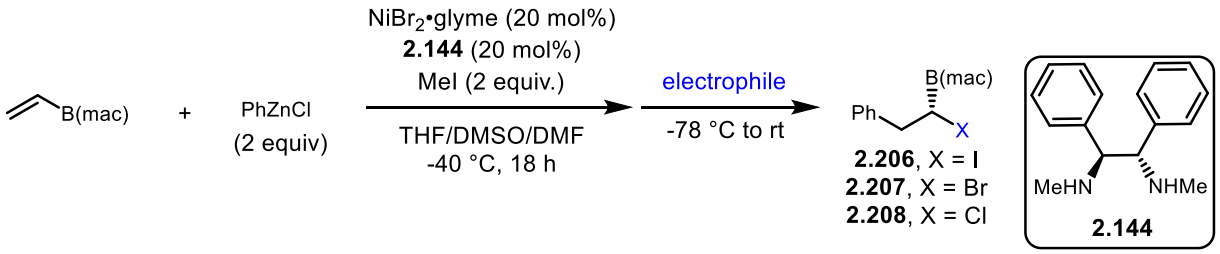
2.5.5 Synthetic Applications

To demonstrate the synthetic utility of this reaction, we first conducted a formal synthesis of bruguierol A (Scheme 2.51a). Starting from the allylation product **2.201**, boron oxidation followed by alcohol oxidation afforded lactone **2.213**, an intermediate in the total synthesis of

(83) Gaspa, S.; Carraro, M.; Pisano, L.; Porcheddu, A.; De Luca, L. *Eur. J. Org. Chem.* **2019**, *2019*, 3544-3552.

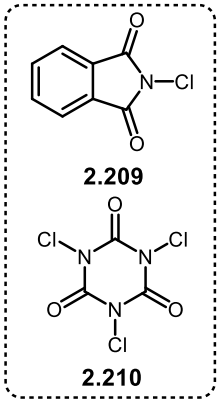
bruguierol A by the Hoveyda group.[84] Of note, this transformation represents a general approach to enantiomerically enriched branched γ-butyrolactones.

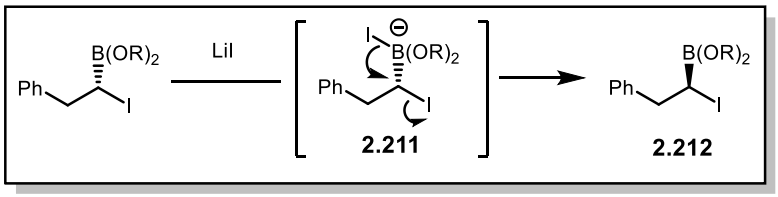
Scheme 2.50. Halogenation of α-Boryl Zinc Reagents



Entry	electrophile	X	yield	er
1[a]	I_2	I	77%	55:45
2[a]	NIS	I	64%	59:41
3	NBS	Br	58%	81:19
4	Br_2	Br	57%	83:17
5	NCS	Cl	26%	75:25
6	**2.209**	Cl	<5%	N/A
7	**2.210**	Cl	18%	88:12
8[b]	**2.210**	Cl	40%	88:12

a) reactions run at -20 °C
b) with $CeCl_3$ (0.5 equiv)





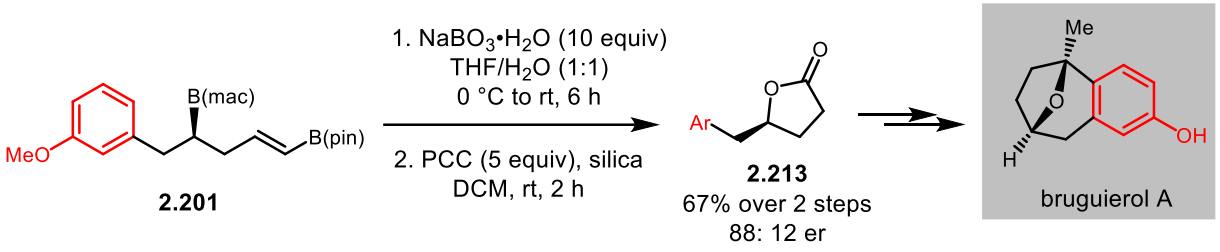
In addition, as the *in situ* generated α-boryl zinc reagents fail to participate in conjugate addition reactions, we demonstrated that one can synthesize a "conjugate addition" analog from the allylation product **2.200**. After protecting the alcohol as a silyl ether, the dichloroalkene

(84) Meng, F. K.; Jang, H. J.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 3204–3214.

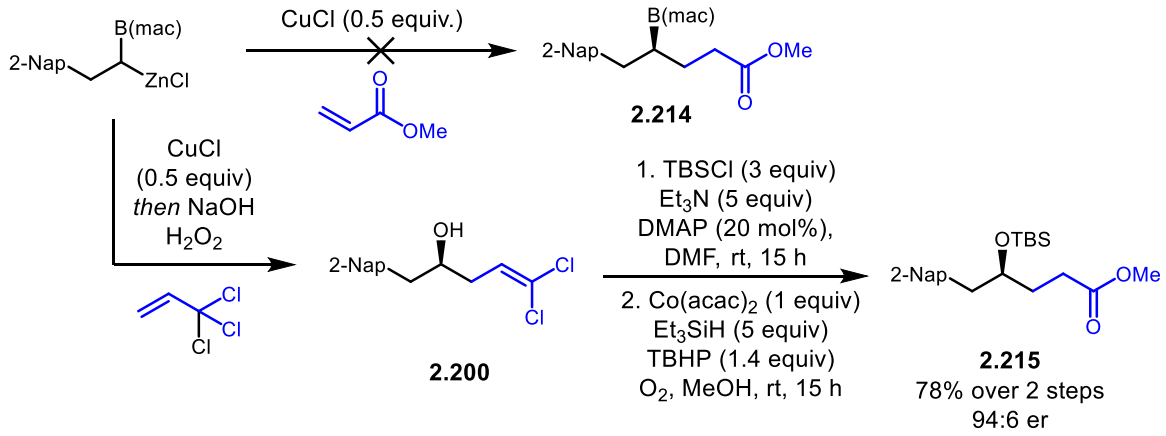
moiety can be converted to the methyl ester through cobalt-mediated hydration[85] (Scheme 2.51b). No erosion of the enantiomeric enrichment is observed during the sequence.

Scheme 2.51. Synthetic Applications

a. Formal Synthesis of Bruguierol A



b. Synthesis of γ-Hydroxy Ester



We also accomplished the total synthesis of (-)-aphanorphine from the allylation product **2.216** (Scheme 2.52a). First, **2.216** was subjected to an intramolecular boron amination reaction[86a] to construct the pyrrolidine ring, where the choice of the protecting group on nitrogen

(85) Ma, X.; Herzon, S. B. *J. Org. Chem.* **2016**, *81*, 8673–8695.
(86) (a) Xu, P.; Zhang, M.; Ingoglia, B.; Allais, C.; Dechert-Schmitt, A. M. R.; Singer, R. A.; Morken, J. P. *Org. Lett.* **2021**, *23*, 3379–3383. (b) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695.

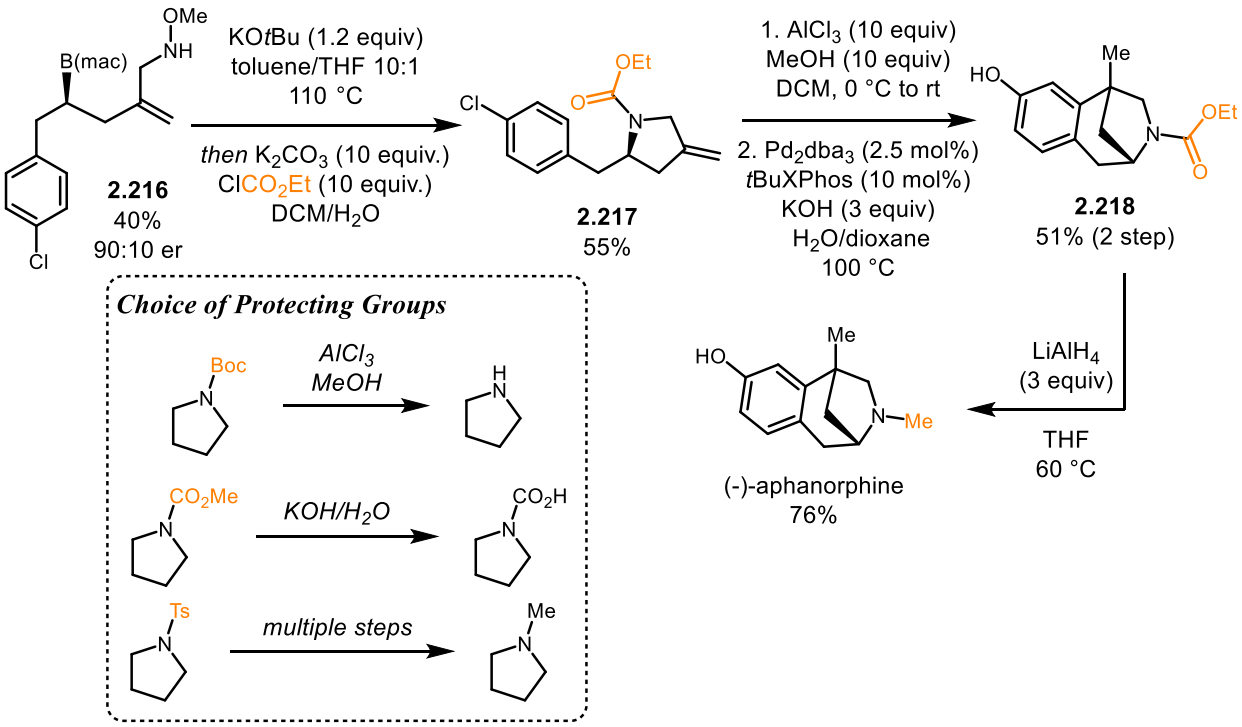
was found to be critical for the synthesis. Acid-sensitive groups (i.e., Boc) cannot be tolerated under the Friedel-Crafts conditions needed for ring closure, while base-sensitive groups (i.e., methyl carbonate) could be hydrolyzed during a palladium-catalyzed hydroxylation reaction.[61b] Sulfonyl-based protecting groups (i.e., tosyl) are stable in both conditions, but their removal requires multiple steps. Ultimately, we decided to use the ethyl carbamate as the protecting group, since it exhibits well balanced stability under acidic and basic conditions. Following protection, **2.217** was subjected to Friedel-Craft alkylation and palladium-catalyzed hydroxylation to deliver the intermediate **2.218** where the protecting group remained intact. More importantly, the ethyl carbamate can be converted to desired methylamine in one step by treatment with LAH. Overall, the synthesis was accomplished in 4 steps. A significant advantage of this route is that product of the final reduction does not require purification by column; natural product (-)-aphanorphine can be quickly isolated by trituration with ether after aqueous workup.

Application of the carbozincation to synthesis of (-)-enterolactone is shown in Scheme 2.52b.[87] The allylation product **2.219** was converted to alcohol **2.220** through Matteson homologation and boron oxidation. Then, dihydroxylation followed by diol cleavage furnished an acetal intermediate, which was then oxidized to lactone **2.221** with PCC. Diastereoselective alkylation and demethylation with boron tribromide delivered the natural product (-)-enterolactone with good yield.

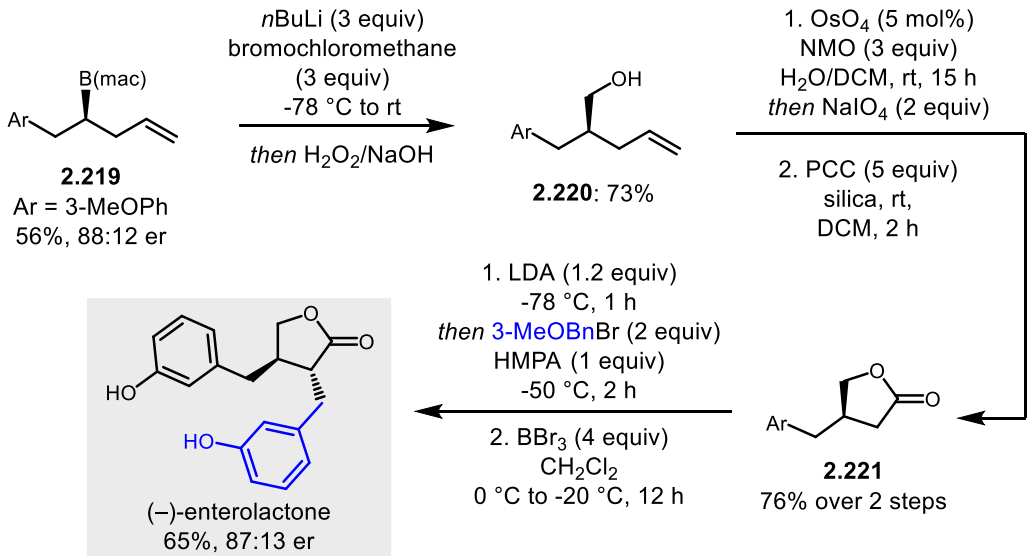
(87) Allais, F.; Pla, T. J.; Ducrot, P.-H. *Synthesis* **2011**, *2011*, 1456-1464.

Scheme 2.52. Synthetic Applications (*continued*)

a. Total Synthesis of (-)-aphanorphine



b. Synthesis of (-)-enterolactone

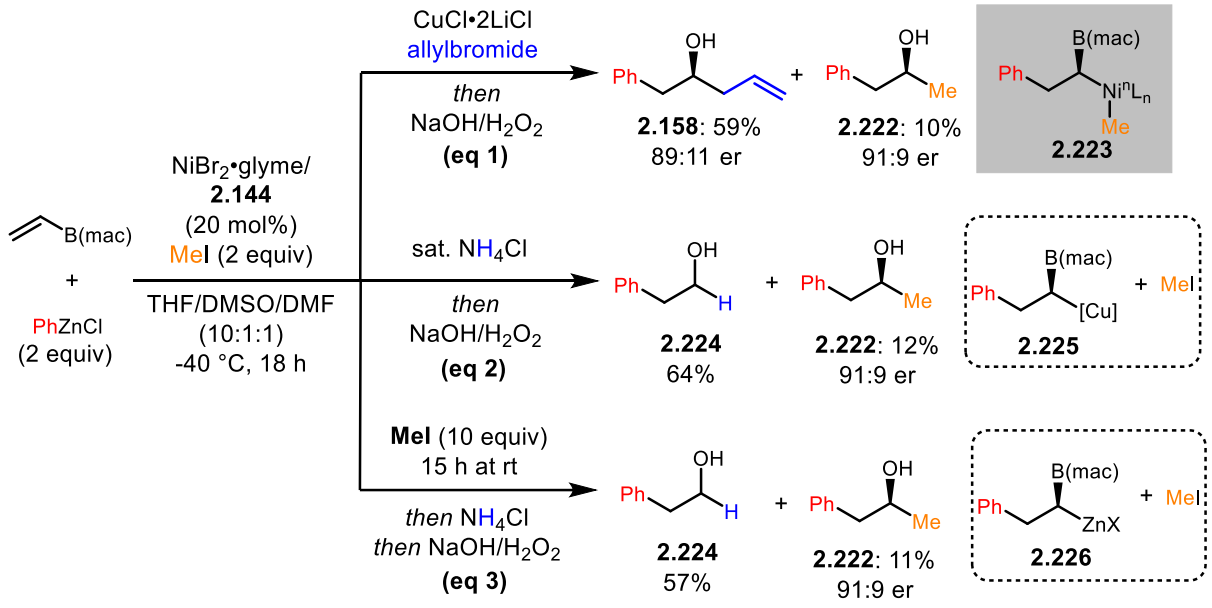


2.5.6 Mechanistic Analysis

The mechanistic study was predominantly accomplished by Dr. Chenlong Zhang and Dr. Jing Jin (EPR experiments), I will summarize the result in the following section to provide a complete story of the carbozincation reaction.

Under the optimal carbozincation conditions, 10% methylation side product **2.222** was observed with 91:1 er (Scheme 2.53, eq 1). Three plausible mechanisms were proposed for the generation of this side product. First, **2.222** could be generated from reductive elimination from the α-boryl nickel intermediate **2.223**; second, it could be generated from the methylation of α-boryl copper intermediate **2.225** upon the addition of CuCl; third, it could be generated from the reaction between the α-boryl zinc reagent **2.226** and methyl iodide. To probe these possibilities, we first quenched the carbozincation directly with saturated ammonium chloride (Scheme 2.53, eq 2). A comparable yield of methylation product **2.222** was isolated as in eq 1 and it had the identical enantiomeric ratio, which rules out a mechanism involving α-boryl copper **2.225** because **2.222** can be obtained without CuCl. Next, we quenched the reaction with excess methyl iodide: the yield of **2.222** was not increased (Scheme 2.53, eq 3). This observation indicates that no reaction occurred between α-boryl zinc **2.226** and methyl iodide under the reaction conditions. Collectively, we proposed that **2.222** is generated from the reductive elimination of α-boryl nickel **2.223**.

Scheme 2.53. Probing the Origin of Methylation Product **2.222**



Next, the stereochemical aspects of the carbozincation were studied with deuterium labeling experiments (Scheme 2.54). The *trans* deuterium-labeled vinyl boronic ester **2.227** was synthesized and subjected to the carbozincation reaction (Scheme 2.54a). The α-boryl zinc intermediate was then trapped with allyl chloride, and the resulting homoallylic alcohol was reduced to alkyl alcohol **2.228** with Pd/C under hydrogen. The deuterium-labeled α-boryl zinc intermediate was also subjected to the palladium-catalyzed Negishi cross-coupling reaction to furnish benzylic alcohol **2.230**. For comparison, *anti*-**2.228** was synthesized from the palladium-catalyzed conjunctive cross-coupling reaction.[88] By comparing the ^{1}H NNR shift of **2.228** to *anti*-**2.228** and the ^{1}H NNR shift of **2.229** and **2.230** to reported authentic spectra, we confirmed that all products (**2.228**, **2.229**, **2.230**) were formed with high *anti* selectivity. Hence, we propose that the α-boryl nickel intermediate is generated from β-migratory insertion process (**2.231**)

(88) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science*, **2016**, *351*, 70–74.

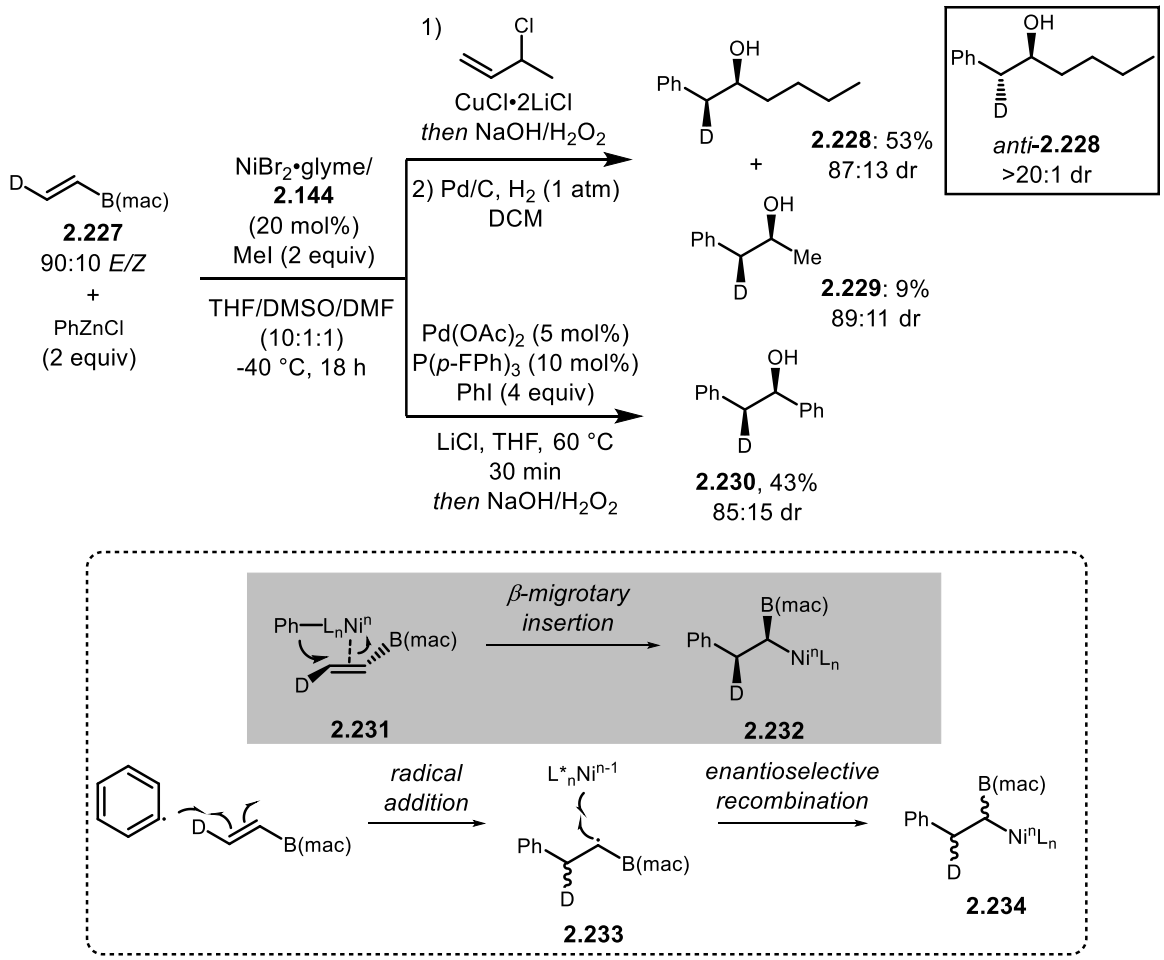
rather than from the radical addition and recombination with nickel (**2.233**); if the latter process operated, the product should be generated as a 50:50 mixture of diastereomers.

Based on the experimental data, the stereochemical aspects for the transformation of α-boryl zinc reagents was proposed (Scheme 2.54b). According to the literature[89], the reductive elimination between dialkyl nickel species is stereoretentive (**2.235** to **2.236**). Thus, the absolute configuration of α-boryl methyl products **2.236** should reflect the absolute configuration of the α-boryl nickel intermediates **2.235**. As the cross-coupling products **2.239** and allylation products **2.241** have the identical absolute configuration as the α-boryl methyl products **2.236**, we propose palladium-catalyzed cross-coupling reactions (**2.235** to **2.239**) and copper-mediated allylation (**2.235** to **2.241**) are overall retentive processes starting from the α-boryl nickel intermediates **2.235**. On the other hand, because the halogenation products **2.224** exhibit the opposite absolute configuration compared to **2.236**, halogenation reactions (**2.235** to **2.242**) are overall invertive. Nevertheless, as we failed to determine the absolute configuration of α-boryl zinc **2.237**, the stereochemical information for the transmetalation between nickel and zinc (**2.235** to **2.237**) and the reactions between α-boryl zinc **2.237** and electrophiles (**2.237** to **2.239**, **2.241**, **2.242**) still have some uncertainty.

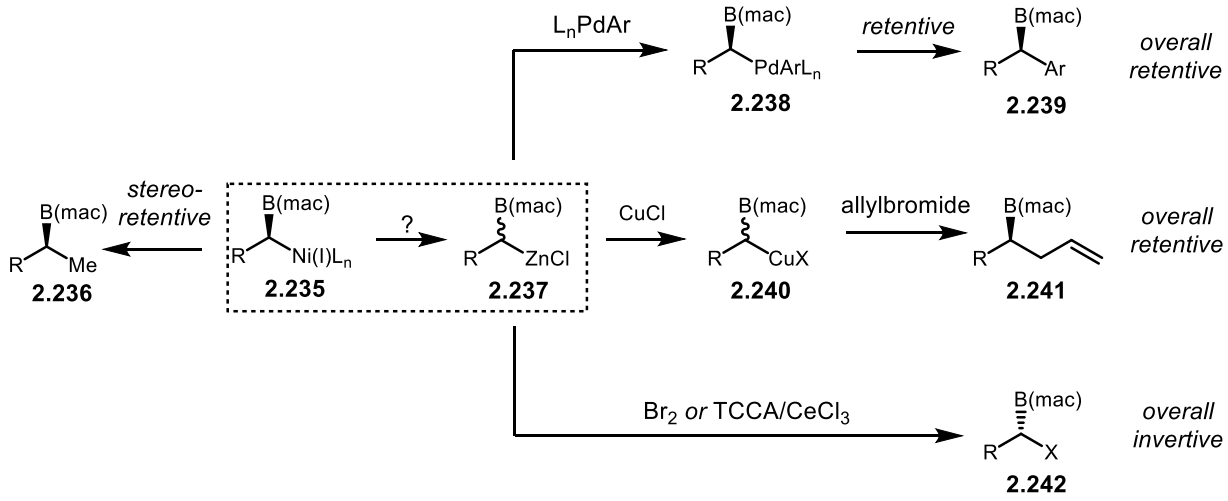
(89) (a) Stille, J. K., *The Chemistry of the Metal-Carbon Bond*, Vol.2, Wiley: New York, **1985**, chap. 9. (b) Zhou, Q.; Cobb, K. M.; Tan, T.; Watson, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 12057–12060.

Scheme 2.54. Deuterium Labeling Experiments

a. Deuterium Label Experiments



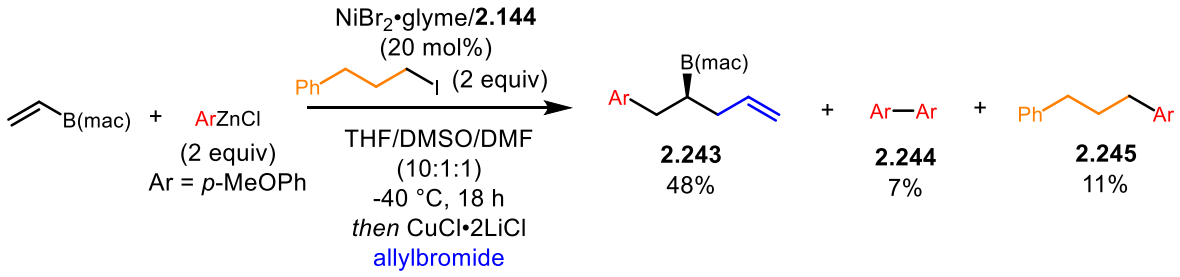
b. Stereochemical Courses



When 3-phenyliodopropane was used in the reaction, byproducts **2.244** and **2.245** were isolated (Scheme 2.55). The former is likely generated from a cross-nucleophile-coupling, and the latter is generated from the cross-coupling between the arylzinc and the alkyl iodide. More importantly, the overall yield of these two species (about 18%) is close to the catalyst loading (20%), which implies the function of alkyl iodide is to activate Ni precursors, presumably by bimetallic oxidative addition[90] and reductive elimination to furnish productive Ni(I) species.

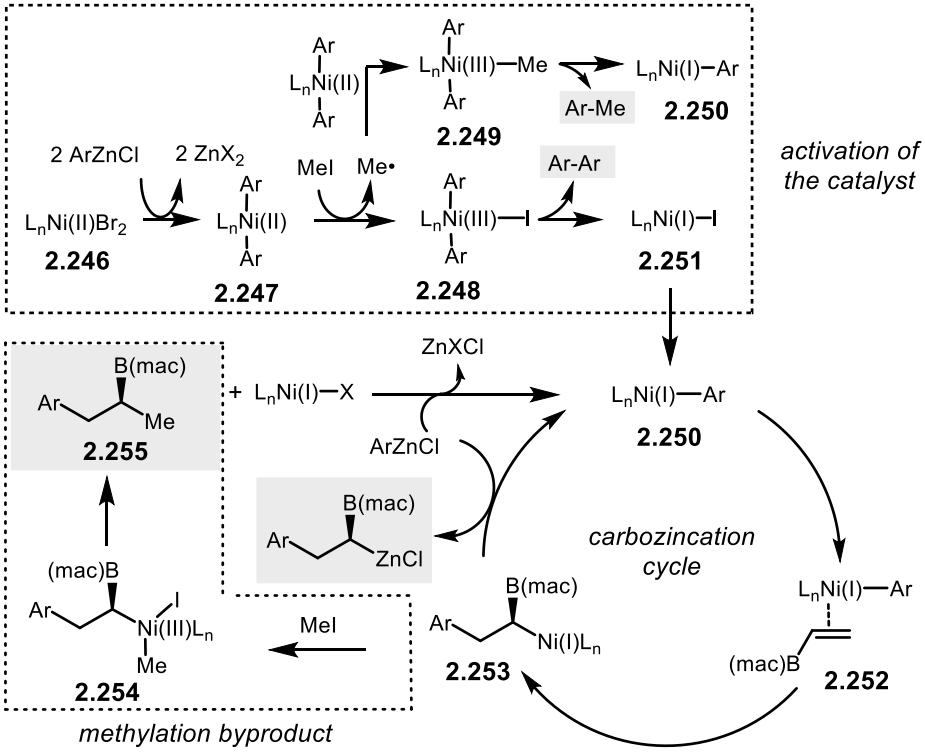
Electron paramagnetic resonance (EPR) experiments[1] suggested that carbozincation reaction is catalyzed by Ni(I) species. Based on that, the catalytic cycle is proposed in Scheme 2.56. The nickel(II) precursor **2.246** will first transmetalate twice with arylzinc reagents to afford diaryl Ni(II) **2.247**, which could then undergo bimetallic oxidative addition[90] with alkyl iodides to furnish Ni(III) intermediates **2.248** and **2.249**. Both compounds can be converted to productive Ni(I) species **2.250** through either reductive elimination/transmetalation or reductive elimination process. Next, a productive carbozincation cycle (**2.250** to **2.252** to **2.253**) delivers the product and regenerates **2.250** to turn over the catalyst. Meanwhile, the α-boryl nickel intermediate **2.253** could undergo oxidative addition with iodomethane to generate Ni(III) species **2.254**, which can reductively eliminate to deliver the methylation side product **2.255**.

Scheme 2.55. The Function of Alkyl Iodides



(90) (a) Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. L. *J. Am. Chem. Soc.* **2013**, *135*, 12004–12012. (b) Breitenfeld, J.; Wodrich, M. D.; Hu, X. L. *Organometallics* **2014**, *33*, 5708–5715.

Scheme 2.56. Proposed Catalytic Cycle



2.6 Conclusion

In summary, we have accomplished the first enantioselective synthesis of α-boryl zinc reagents by nickel-catalyzed carbozincation reaction. The *in situ* generated α-boryl zinc intermediate can be trapped by copper-mediated allylations, palladium-catalyzed Negishi cross-couplings, and cerium-mediated halogenation reactions to construct various chiral organoboranes. A robust functional group tolerance is demonstrated in these processes. In addition, the synthetic utility of this methodology is highlighted by the synthesis of natural products, including bruguierol A, (-)-aphanorphine, and (-)-enterolactone. More importantly, the mechanism is

studied with the assistance of EPR and deuterium-labeling experiments. A catalytic cycle, highlighting a Ni(I) intermediate, is proposed.

2.7 Experimental Section[1]

2.7.1. General Information

^{1}H NMR spectra were recorded on either a Varian *Gem*ini-500 (500 MHz), Varian *Gem*ini-600 (600 MHz), or Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a Varian *Gem*ini-500 (125 MHz), Varian *Gem*ini-600 (150 MHz) or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.2 ppm). ^{11}B NMR spectra were recorded on a Varian *Gem*ini-500 (128 MHz) or Varian *Gem*ini-600 (160 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian *Gem*ini-500 (470 MHz) spectrometer.

Infrared spectra were measured with a Nicolet Avatar 320 spectrometer with a Smart Miracle accessory. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. High-resolution mass spectrometry (DART) was performed at the Mass Spectrometry Facility, Boston College, Chestnut Hill, MA. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh)

purchased from Silicycle. Thin layer chromatography (TLC) was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), ceric ammonium molybdate (CAM) in ethanol or phosphomolybdic acid, cerium(IV) sulfate in ethanol with sulfuric acid (Seebach), and potassium permanganate in 10% sodium hydroxide.

Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector with isopropanol as the modifier or a Jasco SFC-4000 Analytical SFC with isopropanol as the modifier. Analytical chiral high performance liquid chromatography (HPLC) measurements were carried out on a Shimadzu HPLC system with Chiralcel IB column.

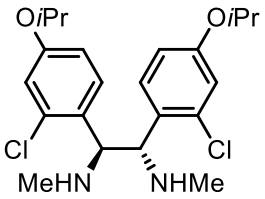
X-band electron paramagnetic resonance (EPR) spectra were recorded on a Bruker EMX-Plus spectrometer (Bruker BioSpin). Simulations of the EPR spectra were performed using the EPR simulation program Aniso-SpinFit in Xenon.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon (Ar). Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM) and toluene were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after purging with nitrogen gas. Dimethyl sulfide (DMSO) was purchased from ACROS and used without further purification. *n*BuLi and PhLi solution were purchased from Aldrich and titrated with BHT (using 1,10-phenanthroline as indicator) before use. Other reagents were purchased from Aldrich, Alfa Aesar, Acros, Oakwood, Strem, Combi-Blocks, or TCI America and used without further purification.

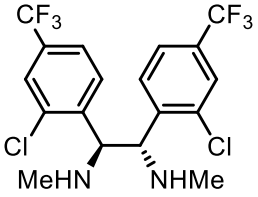
2.7.2. Experimental Procedures

2.7.2.1 Ligand Synthesis

Ligand **2.144**[91], **2.160-2.161**[92], **2.159**[93], **2.162**[91], **2.163-2.164**[92] and **2.165–2.167**[91] are synthesized according to literatures. All spectra data are in accordance with literatures.



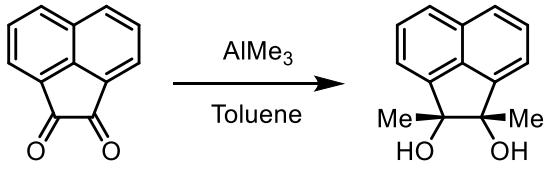
(*1S,2S*)-1,2-bis(2-chloro-4-isopropoxyphenyl)-N^1, N^2-dimethylethane-1,2-diamine (**2.166**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.6 Hz, 2H), 6.74 – 6.65 (m, 4H), 4.50 – 4.36 (m, 2H), 4.27 (s, 2H), 2.27 (d, *J* = 1.5 Hz, 6H), 1.27 (d, *J* = 6.1, 12H).



(*1S,2S*)-1,2-bis(2-chloro-4-(trifluoromethyl)phenyl)-N^1, N^2-dimethylethane -1,2-diamine (**2.167**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.47 – 7.43 (m, 4H), 4.35 (s, 2H), 2.24 (s, 6H).

2.7.2.2 Preparation of Substrates

A. Procedure for the preparation of 1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol (2.262)

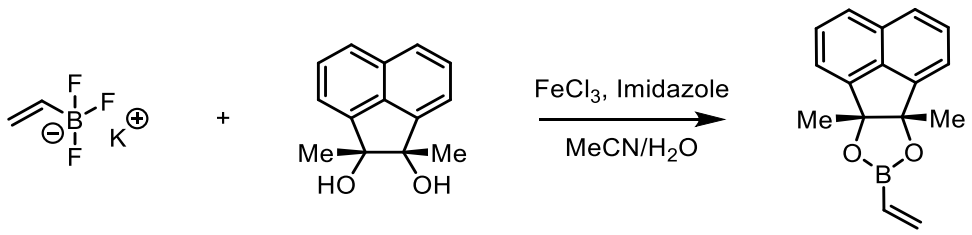


The title compound was synthesized following a previous report[94] from our group with modifications. A flame-dried 3-neck 2000 mL round bottom flask was equipped with stir bar, a

(91) Kuznetsov, V. F.; Jefferson, G. R.; Yap, G. P. A.; Alper, H. *Organometallics* **2002,** *21*, 4241–4248.
(92) Masuda, Y.; Fu, G. C. *Org. Synth.* **2019,** *96*, 245–257.
(93) Zhou, M. K.; Li, K. D.; Chen, D. P.; Xu, R. H.; Xu, G. Q.; Tang, W. J. *J. Am. Chem. Soc.* **2020,** *142*, 10337–10342.

reflux condenser fitted to the middle neck. Acenaphthoquinone (15.0 g, 82.3 mmol) and toluene (1 L) was added to the flask. The other two necks were sealed with rubber septa and the entire system was then purged with dry N_2 for 30 minutes. Trimethyl aluminum (19.7 mL, 206 mmol, 2.5 equiv.) was added dropwise via syringe. Upon completion of addition, the reaction was allowed to stir for 3 hours at room temperature, cooled to 0 °C and quenched by slow addition of 30 ml water. The reaction was diluted with 300 ml THF and allowed to stir overnight at room temperature. The mixture was passed through a pad of silica gel to remove the insoluble salts and the residual was washed with EtOAc. The solvent was then removed under reduced pressure and the crude product was recrystallized in hot EtOAc. The resulting precipitate was collected by filtration and rinsed with pentane to yield pure *syn*-1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol as off-white crystals (10.5 g, 49.0 mmol, 60% yield). All spectral data are in accordance with the literature[94].

B. Procedure for the Preparation of vinylB(mac) (2.151)

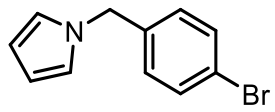


To a 250 mL round bottom flask equipped with a magnetic stir bar was added *syn*-1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol (**2.262**) (4.0 g, 18.7 mmol), potassium vinyltrifluoroborate (2.75 g, 20.5 mmol, 1.1 equiv.), imidazole (3.81 g, 56.01 mmol, 3 equiv.), iron(III) trichloride (151.4 mg, 0.93 mmol, 0.05 equiv.) and 100 mL MeCN/ H_2O (1:1 v/v). The reaction was allowed to stir at room temperature overnight. After that, the solution was diluted

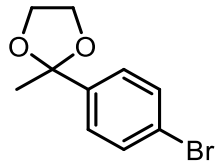
(94) Myhill, J. A.; Wihelmsen, C. A.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2018,** *140*, 15181–15185.

with water (50 mL) and Et_2O (100 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-5% EtOAc/Hexanes, stain in $KMnO_4$) to afford the product as white solid (4.1 g, 16.4 mmol, 88% yield). All spectral data are in accordance with the literature[94].

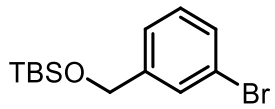
C. Procedures for the Preparation of Aryl Bromides



1-(4-bromobenzyl)-1H-pyrrole (2.263). Prepared according to literature procedure[95] starting from 4-bromobenzyl chloride. All spectral data are in accordance with the literature.[96]

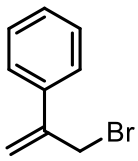


2-(4-bromophenyl)-2-methyl-1,3-dioxolane (2.264). Prepared according to literature procedure.[97] All spectral data are in accordance with the literature.[97]



((3-bromobenzyl)oxy)(tert-butyl)dimethylsilane (2.265). Prepared according to literature procedure.[98] All spectral data are in accordance with the literature.[98]

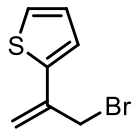
D. Procedures for the Preparation of Electrophiles



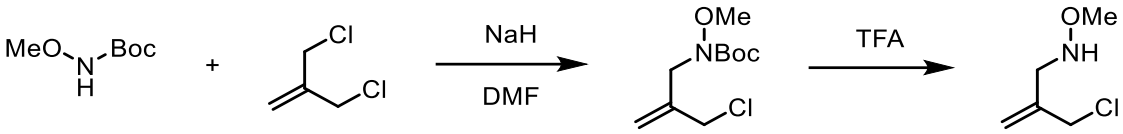
(3-bromoprop-1-en-2-yl)benzene (2.266). The titled compound was prepared according to literature procedure.[99] All spectral data are in accordance with the

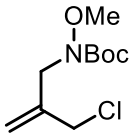
(95) Liu, S. S.; Tzschucke, C. C. *Eur. J. Org. Chem.* **2016,** *2016*, 3509–3513.
(96) Borghs, J. C.; Lebedev, Y.; Rueping, M.; El-Sepelgy, O. *Org. Lett.* **2019,** *21*, 70–74.
(97) Sakai, A.; Ohta, E.; Yoshimoto, Y.; Tanaka, M.; Matsui, Y.; Mizuno, K.; Ikeda, H. *Chem. Eur. J.* **2015,** *21*, 18128–18137.
(98) Yang, M. H.; Hunt, J. R.; Sharifi, N.; Altman, R. A. *Angew. Chem. Int. Edit.* **2016,** *55*, 9080–9083.

literature.[99]

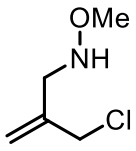


2-(3-bromoprop-1-en-2-yl)thiophene (2.267). The titled compound was prepared according to literature procedure[100] and purified by column chromatography (silica gel, 0-3% EtOAc/Hexanes, stain in $KMnO_4$) to furnish the titled compound as yellow oil(13% yield). All spectral data are in accordance with the literature.[101]





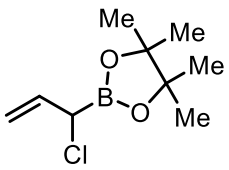
***tert*-butyl (2-(chloromethyl)allyl)(methoxy)carbamate (2.268).** To a suspension of sodium hydride (60% dispersion in mineral oil) (1.32 g, 33.0 mmol, 1.1 equiv.) in DMF (45 mL) was added dropwise a solution of *tert*-butyl methoxycarbamate (4.42 g, 30.0 mmol, 1 equiv.) in DMF (15 mL) under N_2 atmosphere. The reaction mixture was allowed to stir at room temperature for 20 minutes followed by the dropwise addition of 3-chloro-2-chloromethyl-propene (3.94 g, 31.5 mmol, 1.05 equiv.) and the reaction was allowed to stir at room temperature until the completion was confirmed by TLC. The reaction solution was partitioned between ethyl acetate and water and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers are dried over Na_2SO_4, filtered, and concentrated under reduced pressure to furnish the titled compound as colorless oil (4.75 g, 20.1 mmol, 67% yield) which is used in the next step without further purification.



***N*-(2-(chloromethyl)allyl)-*O*-methylhydroxylamine (2.269).** To a stirred solution of *tert*-butyl (2-(chloromethyl)allyl)(methoxy)carbamate (**2.268**) (4.75 g, 20.1

(99) Tripathi, C. B.; Mukherjee, S. *Angew. Chem. Int. Edit.* **2013,** *52*, 8450–8453.
(100) Duan, Z. C.; Hu, X. P.; Zhang, C.; Wang, D. Y.; Yu, S. B.; Zheng, Z. *J. Org. Chem.* **2009,** *74*, 9191–9194.
(101) Muller, T.; Vaccher, C.; Vaccher, M. P.; Flouquet, N. *Synth. Commun.* **1998,** *28*, 2343–2354.

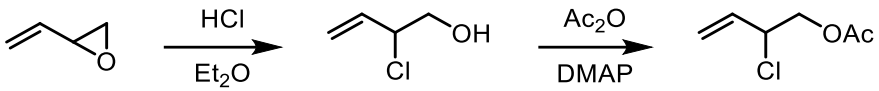
mmol, 1 equiv.) in 120 mL DCM was added trifluoroacetic acid (15.5 mL, 201 mmol, 10 equiv.) at room temperature. The reaction was allowed to stir for 3 hours and quenched by pouring into 100 mL saturated sodium bicarbonate solution. The organic layer was separate and washed with saturated sodium bicarbonate solution (30 mL × 5), dried over Na_2SO_4, and concentrated carefully under reduced pressure to furnish the titled compound as yellow oil(2.2 g, 16.2 mmol, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (s, 1H), 5.21 (s, 1H), 4.18 (s, 2H), 3.64 (s, 2H), 3.53 – 3.51 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0, 117.8, 62.1, 54.0, 46.6. IR (neat) ν_{max} 2936 (s), 2896 (s), 2809 (m), 1650 (w), 1439 (s), 1260 (m), 1053 (m), 1010 (s), 925 (s), 858 (w), 752 (s). HRMS (DART) for $C_5H_{11}NOCl$ $[M+H]^+$: calculated: 136.0524, found: 136.0528.

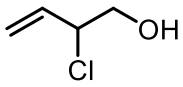


2-(1-chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.270). The titled compound was prepared according to literature procedure [102] with modifications. An oven-dried 250 mL round bottom flask was equipped with a magnetic stir bar and sealed with rubber septa. Then, the flask was evacuated and refilled with N_2 for 3 times. After that, 100 mL THF and dichloromethane (0.7 mL, 11 mmol, 1.1 equiv.) was added to the flask and the solution was cooled to -96 °C with Et_2O/liquid N_2 bath under N_2. *n*-Butyl lithium (2.58 M in Et_2O, 4.3 mL, 11.0 mmol, 1.1 equiv.) was added dropwise to the flask. Upon completion of the addition, vinyl boronic acid pinacol ester (1.7 mL, 10 mmol, 1 equiv.) was added in one portion. The solution was slowly warmed to room temperature and allowed to stir overnight. Then, the solvent was removed under reduced pressure and the crude product was redissolved in Et_2O and passed through a pad of silica gel with Et_2O. The solvent was removed

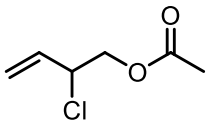
(102) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980,** *102*, 7588–7590.

under reduced pressure to afford the product as yellow oil (1.84 g, 91% yield). All spectral data are in accordance with the literature.[103]



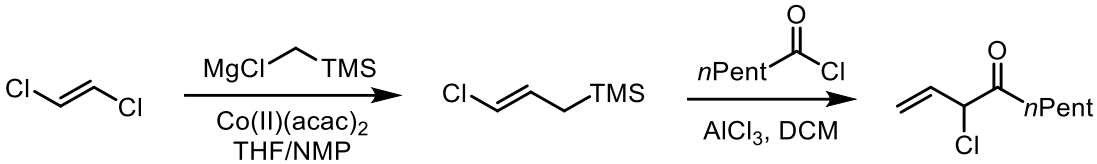


2-chlorobut-3-en-1-ol (2.271). The titled compound was synthesized according to literature[104] and was used in the reactions without further purification.

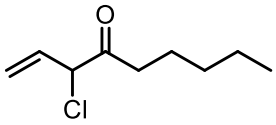


2-chlorobut-3-en-1-yl acetate (2.272). To an oven-dried 2-dram vial equipped with a magnetic stir bar was added 2-chlorobut-3-en-1-ol (**2.271**) (180.0 mg, 1.69 mmol, 1 equiv.), 4-Dimethylaminopyridine (247.7 mg, 2.03 mmol, 1.2 equiv.) and DCM (2 mL). The solution was cooled to 0 °C followed by the addition of acetic anhydride (344.9 mg, 3.38 mmol, 2 equiv.). The reaction was warmed to room temperature and allowed to stir overnight. After that, the solution was passed through a plug of silica with Et_2O, and the solvent was removed carefully under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-5% Et_2O/Hexanes, stain in $KMnO_4$) to afford the titled compound as colorless oil (95 mg, 0.64 mmol, 38% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.40 (dt, *J* = 16.9, 1.0 Hz, 1H), 5.28 (dt, *J* = 10.3, 0.9 Hz, 1H), 4.55 – 4.51 (m, 1H), 4.31 – 4.21 (m, 2H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 134.6, 119.5, 66.9, 58.9, 20.9. IR (neat) ν_{max} 3090 (w), 2947 (w), 1743 (s), 1645 (w), 1381 (w), 1365 (w), 1216 (s), 1039 (s), 987 (m), 934 (m), 707 (m). HRMS (DART) for $C_6H_{10}O_2Cl$ $[M+H]^+$: calculated: 149.0364, found: 149.0370.

(103) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529–1535.
(104) Kadesch, R. G. *J. Am. Chem. Soc.* **1946,** *68*, 41–45.



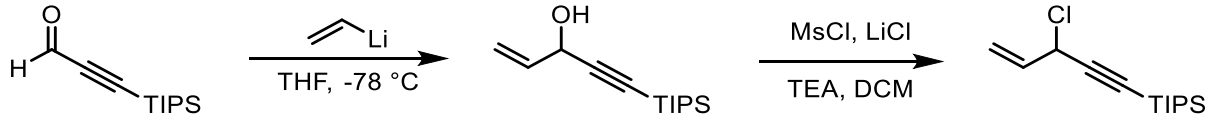
[(E)-3-chloroallyl]-trimethyl-silane (2.273) was synthesized according to literature procedure with modifications.[105] To an oven-dried 100 mL round bottom flask equipped with magnetic stir bar was added Co(II)(acac)$_2$ (36.9 mg, 0.14 mmol, 0.01 equiv.) and the flask was sealed with a rubber septum. Then, the flask was evacuated and refilled with N_2 for three times. Upon completion, 20 mL THF, 5 mL NMP and (*E*)-1,2-dichloroethylene (2.2 mL, 28.7 mmol, 2 equiv.) was added to the flask and the reaction was cooled to 0 °C with ice/water bath under N_2. 10.0 mL trimethylsilylmethyl magnesium chloride solution (1.43 M in THF, 14.3 mmol, 1 equiv.) was added dropwise and the reaction was allowed to stir at 0 °C for 1 hour. The reaction was quenched with 100 mL water and extracted twice with 100 mL pentane. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was carefully removed under reduced pressure to afford the crude product as yellow oil (1.48 g, 69% yield) and was used in the next step without further purification.

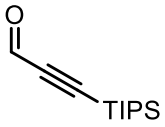


3-chloronon-1-en-4-one (2.274) was prepared according to literature procedure with modifications.[106] To an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar was added $AlCl_3$ (866.7 mg, 6.50 mmol, 1.3 equiv.) and sealed with rubber septa. The vial was evacuated and refilled with N_2 (three times). Then, dry DCM (10.0 mL) was added followed by the dropwise addition of hexanoyl chloride (0.69 mL, 5.0 mmol, 1 equiv.) at -20 °C. The solution was allowed to stir at -20 °C for 1 hour followed by the dropwise addition of [(E)-3-chloroallyl]-trimethyl-silane (**2.273**) (966.6 mg, 6.50 mmol, 1.3

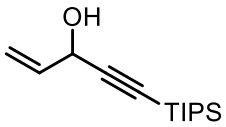
(105) Kamachi, T.; Kuno, A.; Matsuno, C.; Okamoto, S. *Tetrahedron Lett.* **2004,** *45*, 4677–4679.
(106) Ochiai, M.; Fujita, E. *Tetrahedron Lett.* **1980,** *21*, 4369–4372.

equiv.) in 5.0 mL DCM and allowed to stir for another 2 hours. Then, the reaction was warmed to room temperature and poured into water (100 mL). The mixture was extracted with Et_2O (100 mL), and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-5% EtOAc/Hexanes, stain in $KMnO_4$) to furnish the titled compound as yellow oil(834.2 mg, 4.8 mmol, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 – 5.92 (m, 1H), 5.49 (dt, *J* = 16.9, 1.0 Hz, 1H), 5.38 (dt, *J* = 10.2, 0.9 Hz, 1H), 4.73 (dt, *J* = 8.0, 1.0 Hz, 1H), 2.69 – 2.53 (m, 2H), 1.65 – 1.57 (m, 2H), 1.34 – 1.24 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 132.5, 120.8, 64.7, 38.5, 31.4, 23.5, 22.6, 14.1. IR (neat) ν_{max} 2957 (s), 2931 (s), 2861 (m), 1720 (s), 1619 (w), 1466 (m), 1406 (m), 984 (m), 934 (s), 778 (m), 726 (m). HRMS (DART) for $C_9H_{16}ClO$ $[M+H]^+$: calculated: 175.0884, found: 175.0878.





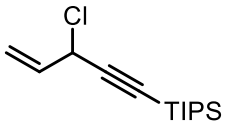
3-(triisopropylsilyl)propiolaldehyde (2.275). The titled compound was prepared according to literature.[107] All spectral data are in accordance with the literature.[82]



5-(triisopropylsilyl)pent-1-en-4-yn-3-ol (2.276). An oven-dried 250 mL round bottom flask equipped with a magnetic stir bar was sealed with a rubber septum. The flask was evacuated and refilled with dry N_2 (three times). 3-(Triisopropylsilyl)propiolaldehyde (**2.275**) (2.1 g, 10 mmol, 1 equiv.) and 100 mL dry Et_2O was added to the flask under N_2. The solution was cooled to -78 °C followed by the dropwise

(107) Cocq, K.; Saffon-Merceron, N.; Coppel, Y.; Poidevin, C.; Maraval, V.; Chauvin, R. *Angew. Chem. Int. Edit.* **2016,** *55*, 15133–15136.

addition of 6.54 mL THF solution of vinyl lithium (1.53 M, 10.0 mmol, 1 equiv.). After that, the reaction was allowed to stir at -78 °C for 2 hours, quenched with saturated ammonium chloride solution and warmed to room temperature. The reaction was diluted with Et_2O, and the organic layer was separated. The aqueous layer was extracted twice with Et_2O. The combine organic phase was passed through a pad of silica with Et_2O and concentrated under reduced pressure to furnish the desired product as yellow oil(1.84 g, 7.72 mmol, 77% yield). The product obtained was used in the next step without further purification.



(3-chloropent-4-en-1-yn-1-yl)triisopropylsilane (2.277). The titled compound was synthesized according to literature procedure with modifications.[108] To a 250 mL round bottom flask equipped with a magnetic stir bar was added 5-triisopropylsilylpent-1-en-4-yn-3-ol (**2.276**) (1.84 g, 7.72 mmol, 1 equiv.) in 40 mL DCM, triethylamine (1.56 g, 15.4 mmol, 2 equiv.), lithium chloride (654.2 mg, 15.4 mmol, 2 equiv.) and the solution was cooled to 0 °C. Then, mesyl chloride (1.06 g, 9.26 mmol, 1.2 equiv.) was added dropwise and the reaction was warmed to room temperature and allowed to stir overnight. After that, the reaction was passed through a pad of silica with Et_2O and concentrated under reduced pressure to afford a 1:1 mixture of regio isomers. The crude product was purified by column chromatography with hexanes to furnish the desired product as colorless oil (316 mg, 1.23 mmol, 16% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 – 5.95 (m, 1H), 5.64 – 5.55 (m, 1H), 5.27 (dd, *J* = 9.9, 0.9 Hz, 1H), 5.10 (dd, *J* = 6.1, 1.4 Hz, 1H), 1.09 (s, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 118.1, 102.4, 90.6, 48.8, 18.7, 11.3. IR (neat) ν_{max} 2944 (s), 2892 (m), 2866 (s), 1463 (m), 1051 (w), 998 (m), 908 (m), 883 (s), 752 (m), 677 (s). HRMS (DART) for $C_{14}H_{26}SiCl$ $[M+H]^+$: calculated: 257.1487, found: 257.1495.

(108) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992,** *33*, 4345–4348.

2.7.2.3 Experimental Procedures for Preparation of Solutions of Organometallic Reagents

General Procedure A: Preparation of 0.4 M Phenylzinc(II) Chloride Solution from Commercial Organolithium Solution.

In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added zinc(II) dichloride (136.3 mg, 1.00 mmol, 1 equiv.) and 1.96 mL THF. The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the solution was cooled to 0 °C under dry N_2. 0.54 mL phenyl lithium solution (1.86 M in dibutyl ether, 1.0 mmol) was added dropwise while stirring vigorously. Upon completion, the solution was warmed to room temperature and allowed to stir for 15 minutes and used in the reaction without further purification.

General Procedure B: Preparation of 0.4 M Arylzinc(II) Chloride Solution from Aryl Bromide.

In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added aryl bromide (1.05 mmol, 1.05 equiv.) and 0.86 mL THF. The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the solution was cooled to -78 °C with a dry ice/ acetone bath under dry N_2. 0.39 mL *n*-butyl lithium solution (2.58 M in hexanes, 1.00 mmol, 1 equiv.) was added by a speed of 1 drop per 2 seconds or slower. Upon completion, the solution was allowed to stir at -78 °C for 30 minutes before 1.25 mL zinc(II) dichloride solution (0.8 M in THF, 1.00 mmol, 1 equiv.) was added in one portion. The solution was warmed to room temperature, allowed to stir for 15 minutes, and used in the reaction without further purification.

2.7.2.4 Experimental Procedures for the Carbozincation/ Trapping with Electrophiles

General Procedure E: Carbozincation/ Copper-Mediated Allylation or Allenylation

In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S*, *2S*)-N, N'-dimethyl-1,2-diphenyl-1,2-ethylenediamine (**2.144**) (9.6 mg, 0.040 mmol, 0.2 equiv.) *or* (12.4 mg, 0.052 mmol, 0.26 equiv.), 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.) and 1 mL THF. The mixture was allowed to stir for 5 minutes to obtain a homogenous solution. Then, 0.2 mL DMF was added and allowed to stir for 5 minutes followed by the addition of 0.2 mL DMSO and iodomethane (56.8 mg, 0.40 mmol, 2 equiv.). The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the reaction was cooled to -40 °C under N_2 and 1.0 mL arylzinc(II) chloride *solution* (0.4 M in THF, 0.40 mmol, 2 equiv.) was added. The vial was taped and allowed to stir for 18 hours at -40 °C before the allyl electrophile (0.6 mmol, 3 equiv.) and a 0.5 mL THF solution of copper(I) chloride (9.9 mg, 0.1 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.2 mmol, 1 equiv.) was added. The reaction was allowed to stir for additional 3 hours at -40 °C, quenched with 1 mL saturated aqueous ammonium chloride solution and warmed to room temperature. The organic layer was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug with Et_2O and the solvent was removed under reduced pressure to furnish the crude product.

Unless otherwise noted, the product was isolated and characterized as the corresponding alcohol after oxidation by the following procedure: The crude product was dissolved in 2 mL THF followed by the addition of 1 mL 3 M aqueous sodium hydroxide solution and 1 mL hydrogen peroxide (30% w/w in water) while stirring. The reaction was allowed to stir at room temperature for 30 minutes. After that, the reaction was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug and concentrated under reduced pressure. The crude product was purified by column chromatography to furnish the desired product.

General Procedure E: Tandem Enantioselective Carbozincation/ Palladium-Catalyzed Cross-Coupling

In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S*, *2S*)-N,N'-dimethyl-1,2-diphenyl-1,2-ethylenediamine (**2.144**) (9.6 mg, 0.040 mmol, 0.2 equiv.), 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.) and 1 mL THF. The mixture was allowed to stir for 5 minutes to obtain a homogenous solution. Then, 0.2 mL DMF was added and allowed to stir for 5 minutes followed by the addition of 0.2 mL DMSO and iodomethane (28.4 mg, 0.2 mmol, 1 equiv.). The reaction was sealed with a septum cap and removed from the glove box. Outside the glove box, the reaction was cooled to -40 °C under N_2 and 1 mL arylzinc(II) chloride solution (0.4 M in THF, 0.4 mmol, 2 equiv.) was added. The vial was taped and allowed to stir for 18 h at -40 °C. After that, palladium acetate (2.3 mg, 0.01 mmol, 0.05 equiv.), tris(4-fluorophenyl)phosphine (6.3 mg, 0.02 mmol, 0.1 equiv.) and the *aryl or alkenyl iodide* (0.80 mmol, 4 equiv.) was dissolved in 1 mL Sat. THF solution of LiCl and added to the

reaction. The reaction was then immediately removed from the cold bath and heated at 60 °C for 30 minutes. Upon completion, the reaction was cooled to room temperature and quenched with 1 mL saturated aqueous ammonium chloride solution. The organic layer was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug with Et_2O and the solvent was removed under reduced pressure to afford the crude product.

Unless otherwise noted, the product was isolated as the corresponding alcohol after oxidation by the following procedure: The crude product was dissolved in 2 mL THF followed by the addition of 1 mL 3 M aqueous sodium hydroxide solution and 1 mL hydrogen peroxide (30% w/w in water). The reaction was allowed to stir at room temperature for 30 minutes. After that, the organic layer was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug and concentrated under reduced pressure. The crude product was purified by column chromatography to furnish the desired product.

General Procedure F: Tandem Enantioselective Carbozincation/ Bromination

In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S*, *2S*)-N, N'-dimethyl-1,2-diphenyl-1,2-ethylenediamine (**2.144**) (9.6 mg, 0.040 mmol, 0.2 equiv.), 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.) and 1 mL THF. The mixture was allowed to stir for 5 minutes to obtain a homogenous solution. Then, 0.2 mL DMF was added and allowed to stir for 5 minutes followed by the addition of 0.2 mL DMSO and iodomethane

(56.8 mg, 0.40 mmol, 2 equiv.). The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the reaction was cooled to -40 °C under N_2 and 1.0 mL arylzinc(II) chloride solution (0.4 M in THF, 0.40 mmol, 2 equiv.) was added. The vial was taped and allowed to stir for 18 hours at -40 °C. After that, the reaction was cooled to -78 °C under N_2. Bromine (0.05 mL, 1.0 mmol, 5 equiv.) was added dropwise to the reaction while stirring vigorously. The reaction was allowed to stir for 1 hour at -78 °C, quenched with 1 mL saturated aqueous sodium thiosulfate solution and warmed to room temperature. The organic layer was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug with Et_2O and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-3-10% ethyl acetate in hexanes, stain in CAM) to furnish the desired product.

General Procedure G: Tandem Enantioselective Carbozincation/ Chlorination

In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S*, *2S*)-N, N'-dimethyl-1,2-diphenyl-1,2-ethylenediamine (**2.144**) (12.4 mg, 0.052 mmol, 0.26 equiv.), 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.) and 1 mL THF. The mixture was allowed to stir for 5 minutes to obtain a homogenous solution. Then, 0.2 mL DMF was added and allowed to stir for 5 minutes followed by the addition of 0.2 mL DMSO and iodomethane (56.8 mg, 0.40 mmol, 2 equiv.). The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the reaction was cooled to -40 °C under N_2 and 1.0 mL arylzinc(II) chloride solution (0.4 M in THF, 0.40 mmol, 2 equiv.) was added. The vial was taped and allowed to stir for 18 hours at -40 °C. After that, the solution was added to a allowed

to stir slurry (precooled to -78 °C) of cerium(III) chloride (24.6 mg, 0.10 mmol, 0.5 equiv.), trichloroisocyanuric acid (232.4 mg, 1.0 mmol, 5 equiv.) and 1 mL ethyl acetate. The reaction was allowed to stir for 1 hour at -78 °C, quenched with 1 mL saturated aqueous sodium thiosulfate solution and warmed to room temperature. The organic layer was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug with Et_2O and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-5-10% ethyl acetate in hexanes, stain in CAM) to furnish the desired product.

General Procedure H: Tandem Carbozincation/Palladium-Catalyzed Stereoconvergent Cross-Couping

In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), N, N'-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.), 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.) and 1 mL THF. The mixture was allowed to stir for 5 minutes to obtain a homogenous solution. Then, 0.4 mL DMSO and 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) was added. The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the reaction was cooled to -0 °C under N_2 and 1.0 mL organozinc(II) chloride solution (0.4 M in THF, 0.40 mmol, 2 equiv.) was added. The vial was taped and allowed to stir for 18 hours at 4 ℃ (cold room). After that, in a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added palladium acetate (2.2 mg, 0.01 mmol, 0.05 equiv.), a chiral ligand (0.012 mmol, 0.06 equiv.) and 0.5 mL THF. The solution was

allowed to stir at room temperature for 20 min. A 0.5 mL THF solution containing copper(I) chloride (9.9 mg, 0.1 mmol, 0.5 equiv.), lithium chloride (8.5 mg, 0.2 mmol, 1 equiv.) and the aryl electrophile (0.6 mmol, 3 equiv.) was added to the solution. The combined solution was then removed from glove box and transferred to the carbozincation reaction via syringe. The reaction was allowed to stir at 0 ℃ for another 24 hours. Upon completion, the reaction was quenched with 1 mL saturated aqueous ammonium chloride solution and warmed to room temperature. The organic layer was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug with Et_2O and the solvent was removed under reduced pressure to afford the crude product.

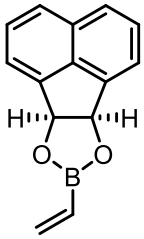
Unless otherwise noted, the product was isolated as the corresponding alcohol after oxidation by the following procedure: The crude product was dissolved in 2 mL THF followed by the addition of 1 mL 3 M aqueous sodium hydroxide solution and 1 mL hydrogen peroxide (30% w/w in water). The reaction was allowed to stir at room temperature for 30 minutes. After that, the organic layer was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug and concentrated under reduced pressure. The crude product was purified by column chromatography to furnish the desired product.

General Procedure I: Tandem Enantioselective Silylzincation/ Copper-Mediated Allylation

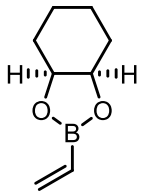
In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S*, *2S*)-N,N'-dimethyl-1,2-diphenyl-1,2-ethylenediamine (**2.144**) (9.6 mg, 0.040 mmol, 0.2 equiv.), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (vinylB(pin))

(50.0 mg, 0.20 mmol, 1 equiv.) and 0.8 mL THF. The mixture was allowed to stir for 5 minutes to obtain a homogenous solution. Then, zinc(II) chloride (27.3 mg, 0.2 mmol, 1 equiv.), 0.4 mL DMF was added and allowed to stir for 5 minutes followed by the addition of 0.2 mL MeCN and iodomethane (56.8 mg, 0.40 mmol, 2 equiv.). The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the reaction was cooled to -40 °C under N_2 and 1.0 mL silylzinc(II) chloride solution (obtained by **General Method A** using the corresponding silyllithium solution, 0.4 M in THF, 0.40 mmol, 2 equiv.) was added. The vial was taped and allowed to stir for 18 hours at -40 °C before allyl bromide (0.6 mmol, 3 equiv.) and a 0.5 mL THF solution containing copper(I) chloride (9.9 mg, 0.1 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.2 mmol, 1 equiv.) was added. The reaction was allowed to stir for additional 3 hours at -40 °C, quenched with 1 mL saturated aqueous ammonium chloride solution and warmed to room temperature. The organic layer was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug with Et_2O and the solvent was removed under reduced pressure. The crude product was purified by preparative thin layer chromatography (PTLC) to furnish the desired product.

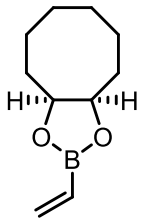
Compounds **2.168**[109] and **2.170**[110] were synthesized according to literatures. The diols for **2.171–2.175** were synthesized according to literature[111]. **2.171–2.175** were synthesized according to the method introduced in Section 2.7.2.2.B.



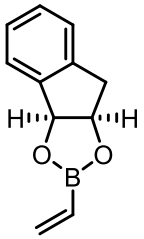
(6bR,9aS)-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.171**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 6.9 Hz, 2H), 7.59 (dd, J = 8.1, 6.9 Hz, 2H), 6.24 – 6.11 (m, 3H), 6.01 (dd, J = 13.7, 4.1 Hz, 1H), 5.85 (dd, J = 19.5, 13.7 Hz, 1H).



(3aR,7aS)-2-vinylhexahydrobenzo[d][1,3,2]dioxaborole (**2.172**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (dd, J = 19.5, 4.0 Hz, 1H), 6.08 – 6.00 (m, 1H), 5.90 (dd, J = 19.5, 13.6 Hz, 1H), 4.39 (s, 2H), 1.88 – 1.77 (m, 2H), 1.77 – 1.65 (m, 2H), 1.58 – 1.4 (m, 2H), 1.42 –1.29 (m, 2H).



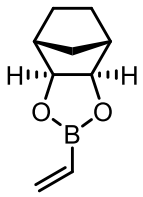
(3aR,9aS)-2-vinyloctahydrocycloocta[d][1,3,2]dioxaborole (**2.173**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (dd, J = 19.6, 4.0 Hz, 1H), 6.03 (dd, J = 13.8, 4.0 Hz, 1H), 5.93 – 5.80 (m, 1H), 4.46 – 4.33 (m, 2H), 1.99 – 1.79 (m, 4H), 1.72 – 1.60 (m, 2H), 1.55 – 1.35 (m, 4H), 1.36 – 1.21 (m, 2H).



(3aS,8aR)-2-vinyl-3a,8a-dihydro-8H-indeno[1,2-d][1,3,2]dioxaborole (**2.174**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 7.3, Hz, 1H), 7.36 – 7.23 (m, 3H), 6.16 (dd,

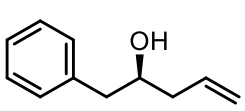
(109) Kaminsky, L.; Wilson, R. J.; Clark, D. A. *Org. Lett.* **2015,** *17*, 3126–3129.
(110) Cain, D. L.; McLaughlin, C.; Molloy, J. J.; Carpenter-Warren, C.; Anderson, N. A.; Watson, A. J. B. *Synlett* **2019,** *30*, 787–791.
(111) Dalmizrak, D.; Goksu, H.; Gultekin, M. S. *RSC Adv.* **2015,** *5*, 20751–20755.

J = 19.6, 4.0 Hz, 1H), 6.01 (dd, J = 13.7, 4.0 Hz, 1H), 5.85 (dd, J = 19.6, 13.7 Hz, 1H), 5.78 (d, J = 6.6 Hz, 1H), 5.24 (td, J = 6.8, 1.6 Hz, 1H), 3.37 (ddt, J = 17.6, 6.8, 1.1 Hz, 1H), 3.25 – 3.14 (m, 1H).



(3aR,4S,7R,7aS)-2-vinylhexahydro-4,7-methanobenzo[d][1,3,2]dioxaborole (**2.175**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (dd, J = 19.6, 4.0 Hz, 1H), 6.04 (dd, J = 13.8, 3.9 Hz, 1H), 5.86 (dd, J = 19.7, 13.7 Hz, 1H), 4.26 (s, 2H), 2.30 (s, 2H), 1.62 – 1.55 (m, 2H), 1.52 – 1.48(m, 2H), 1.22 – 1.17 (m, 1H), 1.10 – 1.01 (m, 2H).

2.7.2.5. Full Characterization and Proof of Stereochemistry



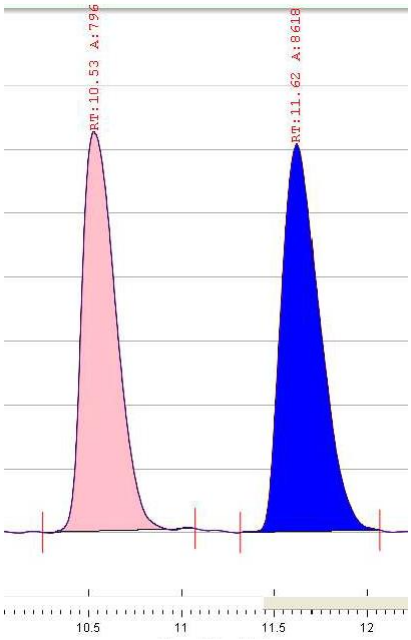
(*S*)-1-phenylpent-4-en-2-ol (2.158). The reaction was performed according to **General Procedure E** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**, 0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (19.1 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 – 5.80 (m, 1H), 5.21 – 5.12 (m, 2H), 3.94 – 3.86 (m, 1H), 2.83 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.74 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.41 – 2.30 (m, 1H), 2.29 – 2.19 (m, 1H), 1.70 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 118.1, 102.4, 90.6, 48.8, 18.7, 11.3. IR (neat) ν_{max} 3374 (br), 3063 (w), 3027 (w), 2922 (w), 1640 (w), 1495 (w), 1454 (w), 1078 (m), 1031 (m), 914 (m), 744 (s), 699 (s). HRMS (DART) for $C_{11}H_{18}NO$ $[M+NH_4]^+$: calculated: 180.1383, found: 180.1384. $[\alpha]^{20}_D$: +10.1 (c = 0.5, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by comparing the optical rotation with the literature.[112]

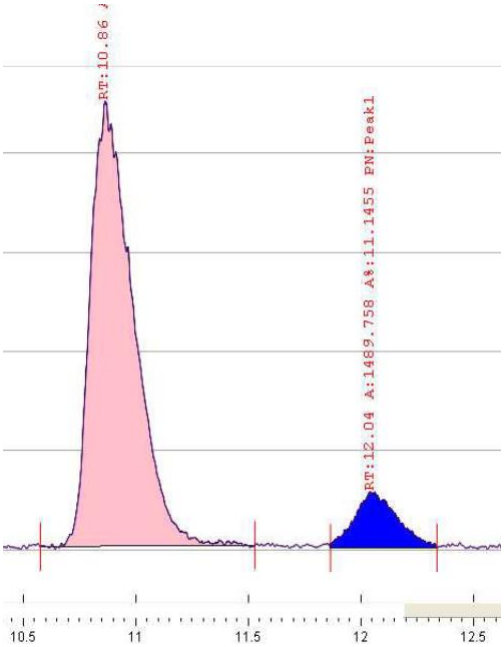
Chiral SFC (Chiracel OJ-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-phenylpent-4-en-2-ol

Racemic Material



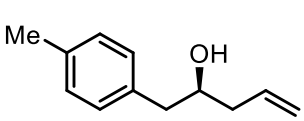
Peak No	% Area	Area	RT (min)
1	48.0419	7968.6542	10.53
2	51.9581	8618.2353	11.62
Total:	100	16586.8895	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	88.8545	11876.6376	10.86
2	11.1455	1489.758	12.04
Total:	100	13366.3956	

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



(*S*)-1-(*p*-tolyl)pent-4-en-2-ol (2.176). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 4-methylphenylzinc(II) chloride solution (prepared according to **General Procedure B** using 4-bromotoluene, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (15.2 mg, 43% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.08 (m, 4H), 5.92 – 5.81 (m, 1H), 5.20 – 5.12 (m, 2H), 3.91 – 3.83 (m, 1H), 2.79 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.69 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.39 – 2.30 (m, 4H), 2.28 – 2.18 (m, 1H), 1.70 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 135.4, 135.0, 129.48, 129.47, 129.4, 118.2, 71.9, 43.0, 41.4, 21.2. IR (neat) ν_{max} 3389 (br), 3075 (w), 3004 (w), 2922 (s), 1641 (w), 1612 (w), 1515 (s), 1434 (m), 1038 (s), 914 (s), 801 (s). HRMS (DART) for $C_{13}H_{15}$ $[M+H-H_2O]^+$: calculated: 159.1168, found: 159.1167. $[\alpha]^{20}_D$: +4.75 (c = 0.73, $CHCl_3$, *l* = 50 mm).

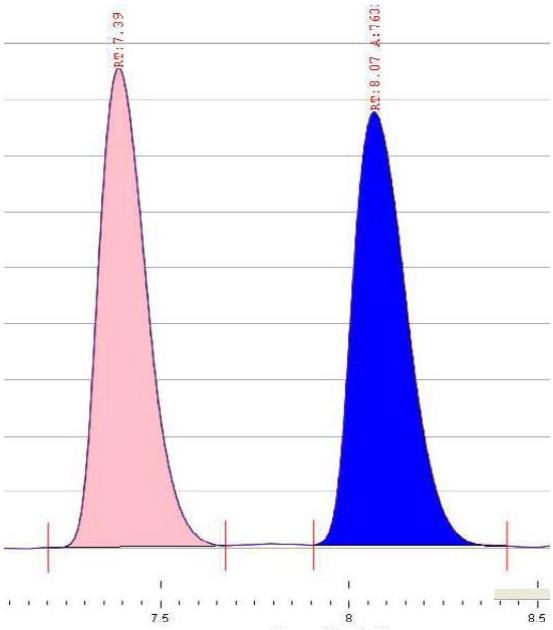
Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent

(instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

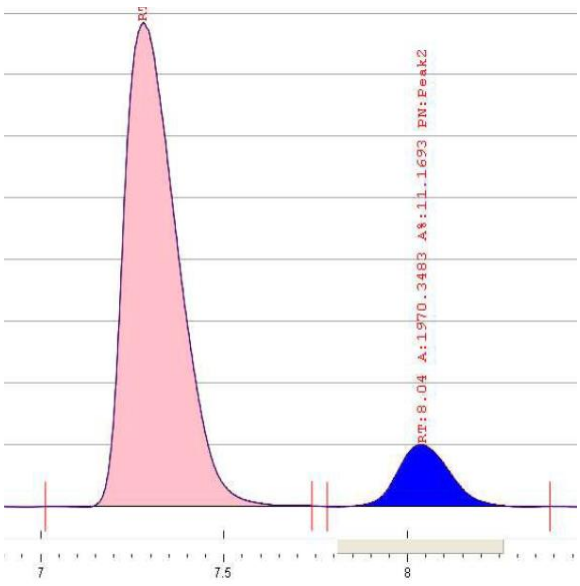
Chiral SFC (Chiracel OJ-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(p-tolyl)pent-4-en-2-ol

Racemic Material

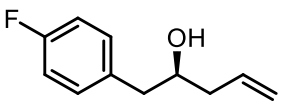


Peak No	% Area	Area	RT (min)
1	49.5213	7488.7239	7.39
2	50.4787	7633.4988	8.07
Total:	100	15122.2227	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	88.8307	15670.4408	7.28
2	11.1693	1970.3483	8.04
Total:	100	17640.7891	



(*S*)-1-(4-fluorophenyl)pent-4-en-2-ol (2.177). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 4-fluorophenylzinc(II) chloride solution (prepared according to **General Procedure B** using 1-bromo-4-fluorobenzene, 0.4 M in THF, 1 mL, 0.4

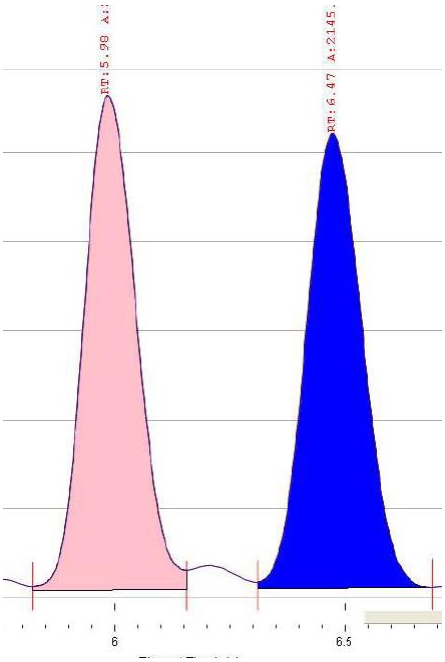
mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (18.4 mg, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.14 (m, 2H), 7.04 – 6.96 (m, 2H), 5.91 – 5.79 (m, 1H), 5.20 – 5.12 (m, 2H), 3.89 – 3.83 (m, 1H), 2.79 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.70 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.38 – 2.25 (m, 1H), 2.25 – 2.16 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7, 161.1, 134.7, 134.3, 134.2, 131.0, 131.0, 118.6, 115.5, 115.4, 71.8, 42.5, 41.4. IR (neat) ν_{max} 3387 (br), 3075 (w), 2977 (w), 2924 (w), 1641 (w), 1601 (m), 1509 (s), 1222 (s), 917 (w), 817 (w), 762 (w). HRMS (DART) for $C_{11}H_{12}F$ $[M+H-H_2O]^+$: calculated: 163.0918, found: 163.0919. $[\alpha]^{20}_D$: +9.55 (c = 0.37, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

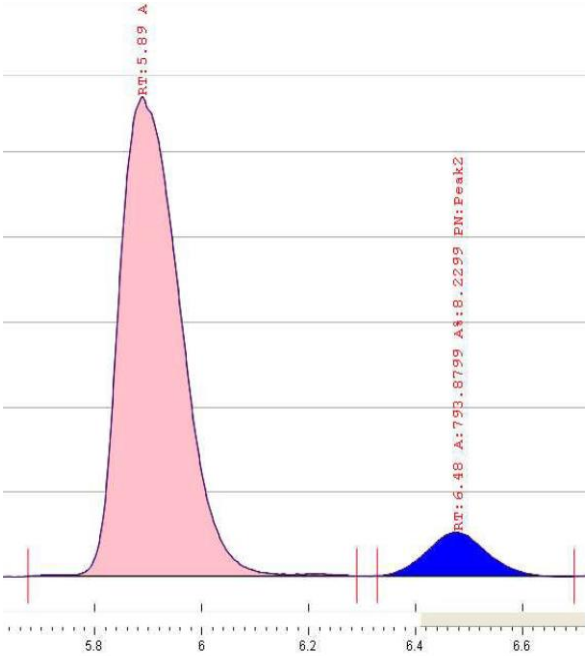
Chiral SFC (Chiracel OJ-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-fluorophenyl)pent-4-en-2-ol

Racemic Material

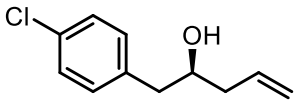


Peak No	% Area	Area	RT (min)
1	50.2645	2168.2525	5.98
2	49.7355	2145.4321	6.47
Total:	100	4313.6846	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	91.7701	8852.3939	5.89
2	8.2299	793.8799	6.48
Total:	100	9646.2738	



(*S*)-1-(4-chlorophenyl)pent-4-en-2-ol (2.178). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 4-chlorophenylzinc(II) chloride solution (prepared according to **General Procedure B** using 1-bromo-4-chlorobenzene, 0.4 M in THF, 1 mL, 0.4

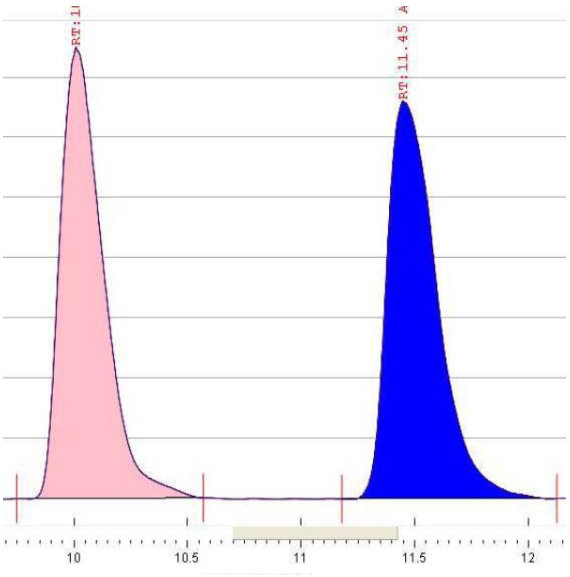
mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (18.1 mg, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.91 – 5.78 (m, 1H), 5.20 – 5.12 (m, 2H), 3.90 – 3.81 (m, 1H), 2.78 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.70 (dd, *J* = 13.7, 7.9, 1H), 2.35 – 2.27 (m, 1H), 2.25 – 2.15 (m, 1H), 1.66 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1, 134.6, 132.5, 131.0, 128.8, 118.7, 71.6, 42.7, 41.4. IR (neat) ν_{max} 3378 (br), 3076 (w), 2977 (w), 2924 (w), 1641 (w), 1492 (s), 1437 (w), 1408 (w), 1090 (m), 1016 (m), 917 (m). HRMS (DART) for $C_{11}H_{12}Cl$ $[M+H-H_2O]^+$: calculated: 179.0622, found: 179.0631. $[\alpha]^{20}_D$: +10.5 (c = 0.86, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

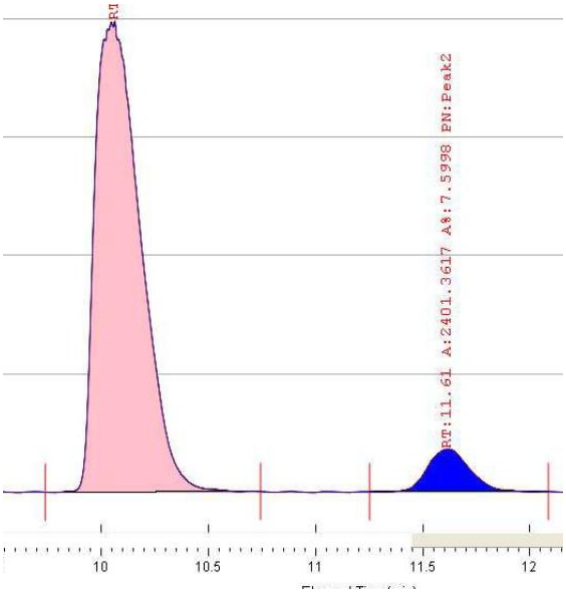
Chiral SFC (Chiracel OJ-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-chlorophenyl)pent-4-en-2-ol

Racemic Material

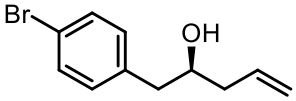


Peak No	% Area	Area	RT (min)
1	49.3009	19535.4978	10.01
2	50.6991	20089.5684	11.45
Total:	100	39625.0662	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	92.4002	29196.1726	10.06
2	7.5998	2401.3617	11.61
Total:	100	31597.5343	



(*S*)-1-(4-bromophenyl)pent-4-en-2-ol (2.179). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 4-bromophenylzinc(II) chloride solution (prepared according to **General Procedure B** using 1,4-dibromobenzene, 0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified

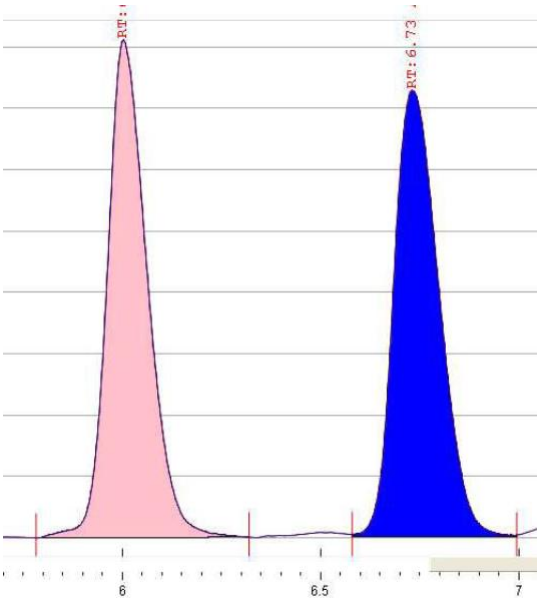
by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (20.3 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 5.92 – 5.77 (m, 1H), 5.21 – 5.11 (m, 2H), 3.91 – 3.81 (m, 1H), 2.77 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.68 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.25 – 2.14 (m, 1H), 1.68 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 134.6, 131.7, 131.4, 120.5, 118.7, 71.6, 42.8, 41.4. IR (neat) ν_{max} 3366 (br), 3075 (w), 2976 (w), 2924 (m), 1488 (s), 1404 (m), 1072 (s), 1012 (s), 917 (m), 829 (m), 794 (m). HRMS (DART) for $C_{11}H_{12}Br$ $[M+H-H_2O]^+$: calculated: 223.0133, found: 223.0117. $[\alpha]^{20}_D$: +6.41 (c = 1.05, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

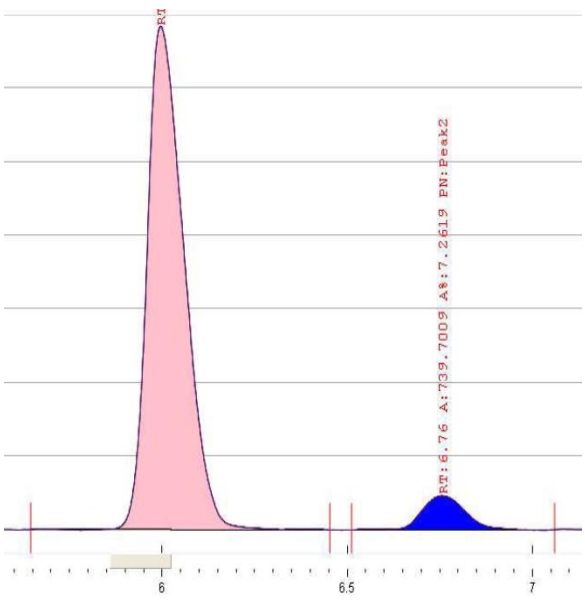
Chiral SFC (Chiracel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-bromophenyl)pent-4-en-2-ol

Racemic Material

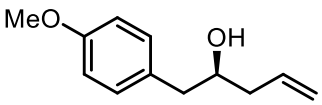


Peak No	% Area	Area	RT (min)
1	49.8359	5688.7688	6
2	50.1641	5726.2309	6.73
Total:	100	11414.9997	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	92.7381	9446.3114	6
2	7.2619	739.7009	6.76
Total:	100	10186.0123	



(*S*)-1-(4-methoxyphenyl)pent-4-en-2-ol (2.180). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 4-methoxyphenylzinc(II) chloride solution (prepared according to **General Procedure B** using 1-bromo-4-methoxybenzene, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude

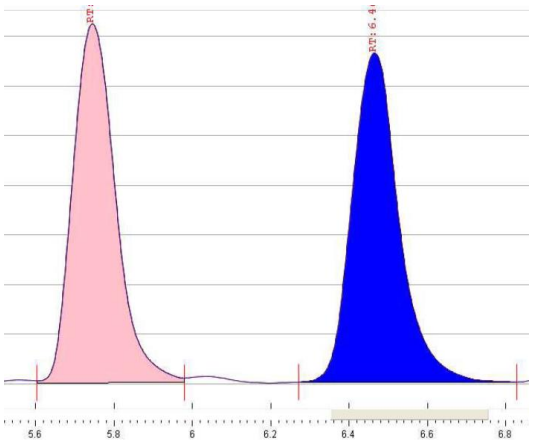
mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (13.5 mg, 35% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.11 (m, 2H), 6.89 – 6.83 (m, 2H), 5.92 – 5.81 (m, 1H), 5.20 – 5.10 (m, 2H), 3.88 – 3.81 (m, 1H), 3.80 (s, 3H), 2.77 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.67 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.24 – 2.17 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 135.0, 130.6, 118.2, 114.2, 72.0, 55.5, 42.5, 41.3. IR (neat) ν_{max} 3408 (br), 2931 (w), 2835 (w), 1611 (w), 1511 (s), 1464 (w), 1230 (w), 1245 (s), 1178 (m), 1035 (m), 807 (m). HRMS (DART) for $C_{12}H_{15}O$ $[M+H-H_2O]^+$: calculated: 175.1117, found: 175.1125. $[\alpha]^{20}_D$: +5.30 (c = 0.39, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

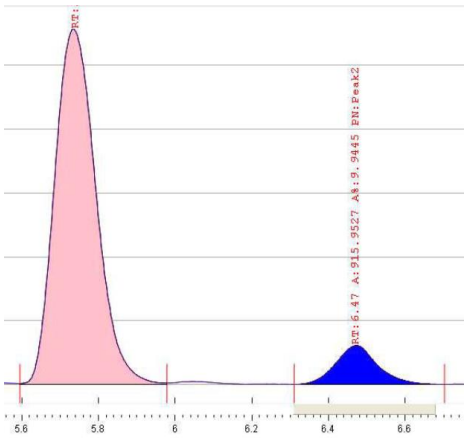
Chiral SFC (Chiracel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-methoxyphenyl)pent-4-en-2-ol

Racemic Material

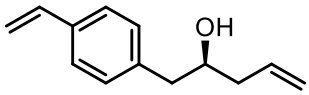


Peak No	% Area	Area	RT (min)
1	49.9524	5468.9111	5.74
2	50.0476	5479.3302	6.46
Total:	100	10948.2413	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	90.0555	8294.6761	5.74
2	9.9445	915.9527	6.47
Total:	100	9210.6288	



(*S*)-1-(4-vinylphenyl)pent-4-en-2-ol (2.182). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 4-vinylphenylzinc(II) chloride solution (prepared according to **General Procedure B** using 4-bromostyrene, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (17.3 mg, 46% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 –

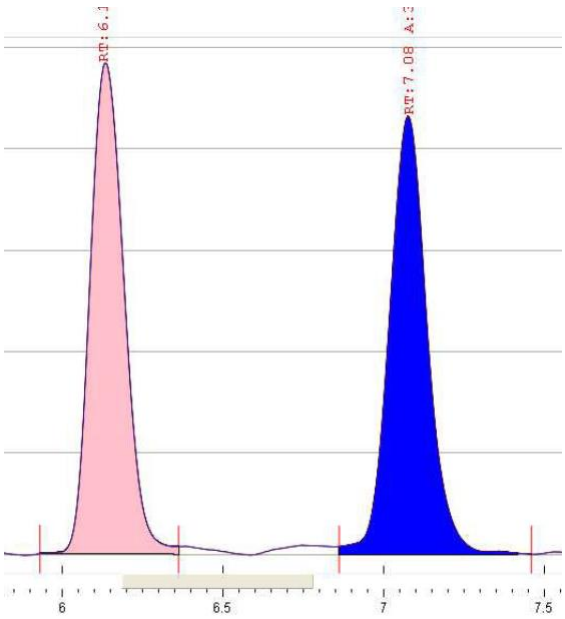
7.34 (m, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 6.71 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.92 – 5.82 (m, 1H), 5.71 (d, *J* = 1.1 Hz, 1H), 5.22 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.20 – 5.13 (m, 2H), 3.92 – 3.84 (m, 1H), 2.81 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.72 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.38 – 2.29 (m, 1H), 2.27 – 2.19 (m, 1H), 1.72 (br s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.2, 136.7, 136.1, 134.8, 129.8, 126.6, 118.4, 113.6, 71.8, 43.2, 41.4. IR (neat) ν_{max} 3389 (br), 3082 (w), 3005 (w), 2924 (m), 1640 (w), 1629 (w), 1511 (m), 1407 (m), 990 (s), 908 (s), 839 (m). HRMS (DART) for $C_{13}H_{17}O$ $[M+H]^+$: calculated: 189.1274, found: 189.1277. $[\alpha]^{20}_D$: +6.89 (c = 0.89, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

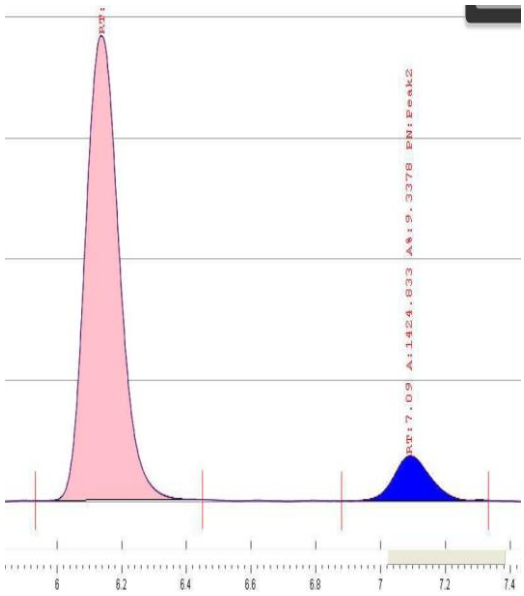
Chiral SFC (Chiracel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-vinylphenyl)pent-4-en-2-ol

Racemic Material

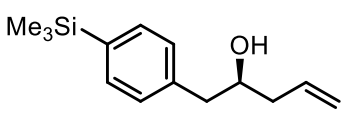


Peak No	% Area	Area	RT (min)
1	50.0086	3545.2097	6.13
2	49.9914	3543.9911	7.08
Total:	100	7089.2008	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	90.6622	13833.9749	6.14
2	9.3378	1424.833	7.09
Total:	100	15258.8079	



(*S*)-1-(4-(trimethylsilyl)phenyl)pent-4-en-2-ol (2.183). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), (4-(trimethylsilyl)phenyl)zinc(II) chloride solution (prepared according to **General Procedure B** using (4-bromophenyl)trimethylsilane, 0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium

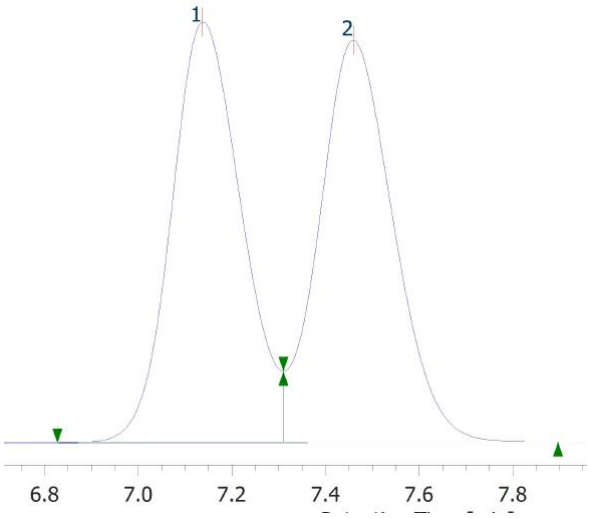
chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (23.9 mg, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H), 7.25 – 7.20 (m, 2H), 5.93 – 5.83 (m, 1H), 5.22 – 5.11 (m, 2H), 3.93 – 3.88 (m, 1H), 2.82 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.73 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.41 – 2.31 (m, 1H), 2.27 – 2.20 (m, 1H), 0.27 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 138.5, 134.9, 133.8, 129.1, 118.3, 71.8, 43.5, 41.4, -0.9. IR (neat) ν_{max} 3389 (br), 3067 (w), 3011 (w), 2954 (m), 1248 (m), 1109 (m), 1037 (w), 1038 (w), 852 (s), 837 (s), 756 (m). HRMS (DART) for $C_{14}H_{21}Si$ $[M+H-H_2O]^+$: calculated: 217.1407, found: 217.1407. $[\alpha]^{20}_D$: +5.81 (c = 1.09, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

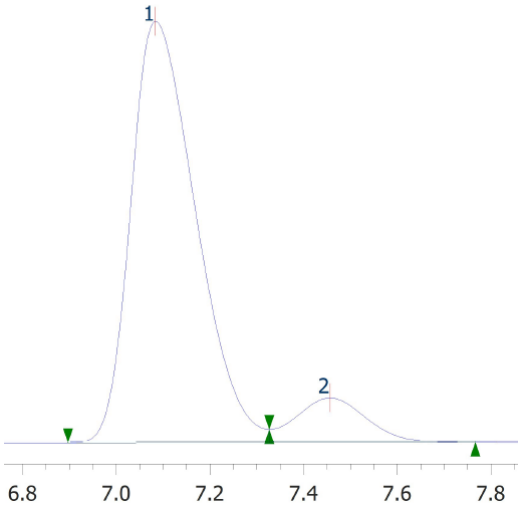
Chiral SFC (Chiracel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 200-400 nm) – analysis of (S)-1-(4-(trimethylsilyl)phenyl)pent-4-en-2-ol

Racemic Material

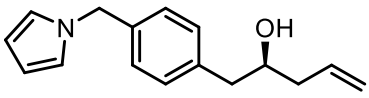


#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	9	7.137	7546016	724046	49.638
2	Unknown	9	7.460	7656202	692702	50.362

Standard Conditions



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	9	7.083	10734365	1114612	89.764
2	Unknown	9	7.457	1224108	117827	10.236



(*S*)-1-(4-((1H-pyrrol-1-yl)methyl)phenyl)pent-4-en-2-ol (2.184). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), (4-((1H-pyrrol-1-yl)methyl)phenyl)zinc(II) chloride solution (prepared according to **General Procedure B** using 1-(4-bromobenzyl)-1H-pyrrole **(S-1)**, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was

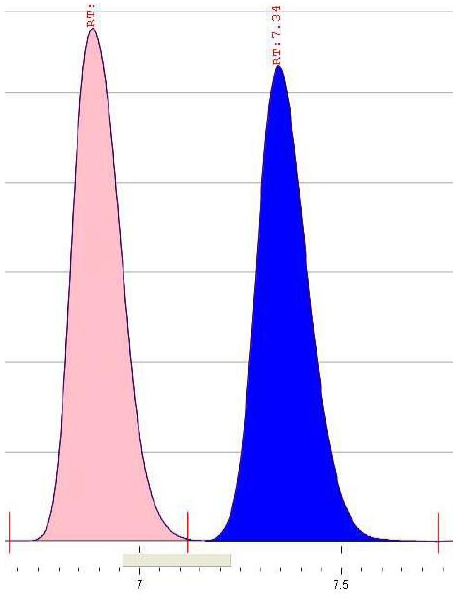
purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as yellow oil(21.7 mg, 57% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.70 (t, *J* = 2.1 Hz, 2H), 6.19 (t, *J* = 2.1 Hz, 2H), 5.90 – 5.82 (m, 1H), 5.20 – 5.13 (m, 2H), 5.05 (s, 2H), 3.90 – 3.82 (m, 1H), 2.80 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.71 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.26 – 2.17 (m, 1H), 1.67 (br s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.1, 136.6, 134.7, 129.9, 127.4, 121.3, 118.5, 108.7, 71.7, 53.2, 43.0, 41.4. IR (neat) ν_{max} 3403 (br), 3074 (w), 2922 (w), 1640 (w), 1497 (m), 1437 (w), 1279 (m), 1087 (m), 1067 (w), 916 (m), 723 (s). HRMS (DART) for $C_{16}H_{20}NO$ $[M+H]^+$: calculated: 242.1539, found: 242.1543. $[\alpha]^{20}_D$: +5.32 (c = 0.99, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

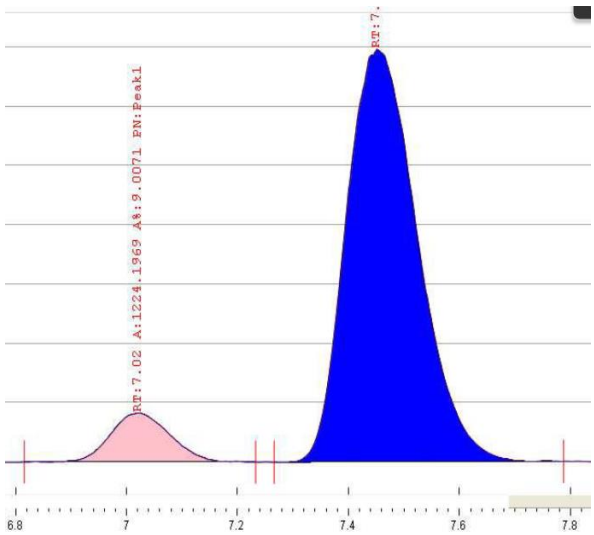
Chiral SFC (Chiracel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-((1H-pyrrol-1-yl)methyl)phenyl)pent-4-en-2-ol

Racemic Material

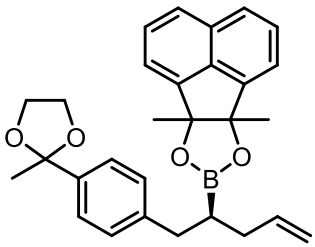


Peak No	% Area	Area	RT (min)
1	50.3118	9735.0354	6.88
2	49.6882	9614.3632	7.34
Total:	100	19349.3986	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	9.0071	1224.1969	7.02
2	90.9929	12367.2659	7.45
Total:	100	13591.4628	



6b,9a-dimethyl-8-((*S*)-1-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)pent-4-en-2-yl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (2.185). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), (4-(2-methyl-1,3-dioxolan-2-yl)phenyl)zinc(II) chloride solution (prepared according to **General Procedure B** using 2-(4-bromophenyl)-2-

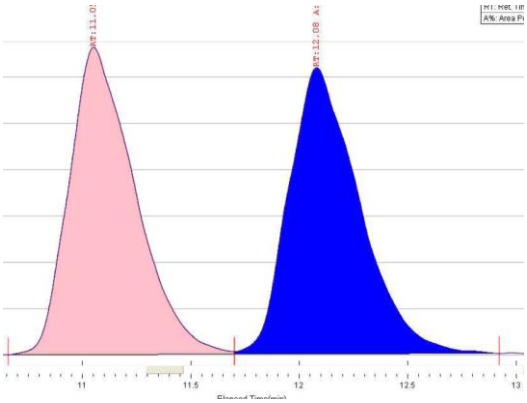
methyl-1,3-dioxolane **(S-2)**, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The product was not oxidized but isolate as boronic ester by column chromatography (silica gel, 0-50% toluene in hexanes, stain in CAM) to furnish the titled compound as colorless oil (42.7 mg, 47% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 2H), 7.64 – 7.51 (m, 3H), 7.47 (dd, *J* = 7.0, 0.7 Hz, 1H), 7.05 – 6.99 (m, 2H), 6.88 – 6.81 (m, 2H), 5.73 – 5.64 (m, 1H), 4.89 – 4.81 (m, 1H), 4.79 – 4.73 (m, 1H), 4.04 – 3.92 (m, 2H), 3.72 – 3.61 (m, 2H), 2.60 (d, *J* = 7.9 Hz, 2H), 2.16 – 2.07 (m, 2H), 1.71 (s, 3H), 1.68 (s, 3H), 1.56 (s, 3H), 1.41 – 1.31 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.90, 144.87, 141.5, 140.4, 138.1, 134.8, 131.5, 128.59, 128.55, 125.4, 125.3, 125.0, 119.6, 119.5, 115.3, 109.0, 92.0, 91.9, 64.47, 64.45, 36.8, 35.4, 27.7, 22.09, 22.07. ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.80. IR (neat) ν_{max} 3044 (w), 2982 (w), 2930 (w), 2887 (w), 1639 (w), 1373 (s), 1314 (m), 1243 (m), 1198 (m), 1116 (s), 1077 (s), 825 (s). HRMS (DART) for $C_{29}H_{32}BO_4$ $[M+H]^+$: calculated: 455.2388, found: 455.2403. $[\alpha]^{20}_D$: +9.65 (c = 0.85, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

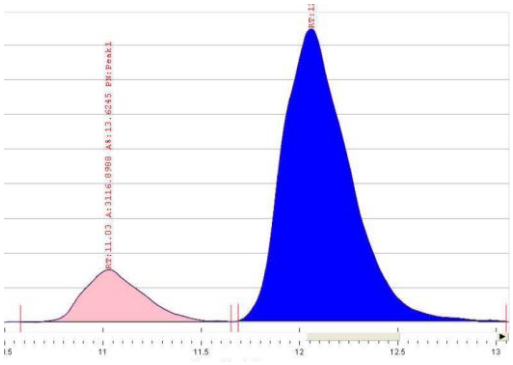
Chiral SFC (Chiracel AD-H, 4% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 6b,9a-dimethyl-8-((S)-1-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)pent-4-en-2-yl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole

Racemic Material

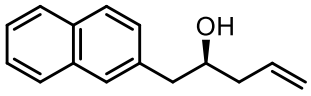


Peak No	% Area	Area	RT (min)
1	50.048	13998.0516	11.05
2	49.952	13971.1784	12.08
Total:	100	27969.23	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	13.6245	3116.8988	11.03
2	86.3755	19760.1939	12.06
Total:	100	22877.0927	



(*S*)-1-(naphthalen-2-yl)pent-4-en-2-ol (2.186). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), naphthalen-2-ylzinc(II) chloride solution (prepared according to **General Procedure B** using 2-bromonaphthalene, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish

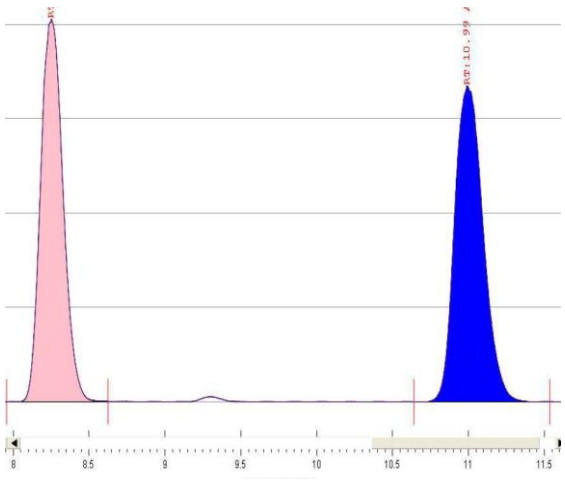
the titled compound as colorless oil (24.2 mg, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 3H), 7.69 (s, 1H), 7.52 – 7.41 (m, 2H), 7.41 – 7.34 (m, 1H), 5.97 – 5.83 (m, 1H), 5.22 – 5.15 (m, 2H), 4.04 – 3.95 (m, 1H), 3.00 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.90 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.43 – 2.36 (m, 1H), 2.31 – 2.24 (m, 1H), 1.76 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1, 134.8, 133.7, 132.5, 128.4, 128.1, 128.0, 127.8, 127.7, 126.3, 125.7, 118.4, 71.8, 43.6, 41.5. IR (neat) ν_{max} 3389 (br), 3053 (w), 2920 (w), 1639 (w), 1600 (w), 1508 (w), 1270 (w), 1216 (w), 1039 (m), 915 (m), 812 (s), 749 (s). HRMS (DART) for $C_{15}H_{15}$ $[M+H-H_2O]^+$: calculated: 195.1168, found: 195.1164. $[\alpha]^{20}_D$: +2.38 (c = 1.01, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

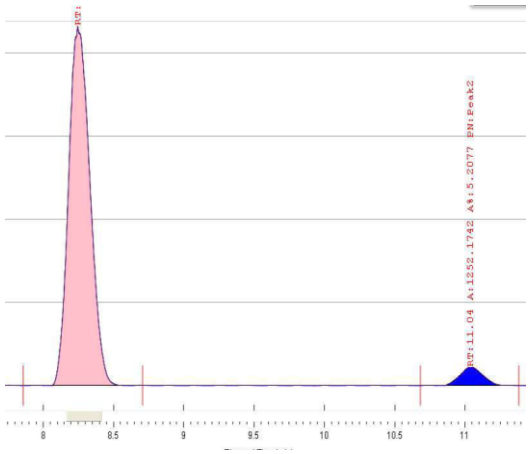
Chiral SFC (Chiracel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(naphthalen-2-yl)pent-4-en-2-ol

Racemic Material

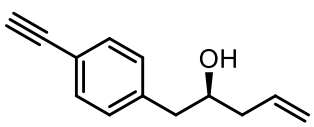


Peak No	% Area	Area	RT (min)
1	48.7841	20826.4521	8.25
2	51.2159	21864.6551	10.99
Total:	100	42691.1072	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	94.7923	22792.3469	8.25
2	5.2077	1252.1742	11.04
Total:	100	24044.5211	



(*S*)-1-(4-ethynylphenyl)pent-4-en-2-ol (2.181). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), (4-((trimethylsilyl)ethynyl)phenyl)zinc(II) chloride (prepared according to **General Procedure B** using ((4-bromophenyl)ethynyl)trimethylsilane, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). After oxidation of the product, the crude mixture was dissolved in 1mL THF and treated with 1 mL tetrabutylammonium fluoride solution (1 M in THF). The solution was allowed to stir

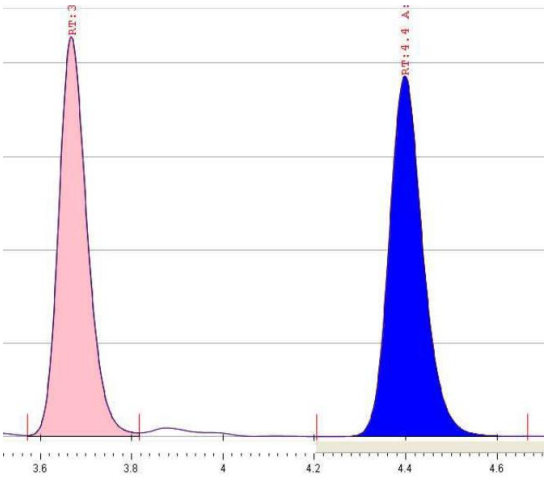
at room temperature for 2 h before being quenched by 1 mL saturated ammonium chloride. The aqueous layer was extracted twice with Et_2O, and the combined organic layer was passed through a plug of silica with Et_2O. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (19.7 mg, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 2H), 7.22 – 7.16 (m, 2H), 5.91 – 5.79 (m, 1H), 5.20 – 5.12 (m, 2H), 3.91 – 3.82 (m, 1H), 3.05 (s, 1H), 2.81 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.73 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.25 – 2.15 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 134.6, 132.4, 129.6, 120.4, 118.6, 83.7, 77.2, 71.6, 43.3, 41.4. IR (neat) ν_{max} 3381 (br), 3294 (s), 3077 (w), 2976 (w), 2923 (m), 1641 (w), 1508 (m), 1435 (w), 1275 (w), 1040 (s), 918 (s). HRMS (DART) for $C_{13}H_{15}O$ $[M+H]^+$: calculated: 187.1117, found: 187.1117. $[\alpha]^{20}_D$: +12.1 (c = 0.74, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

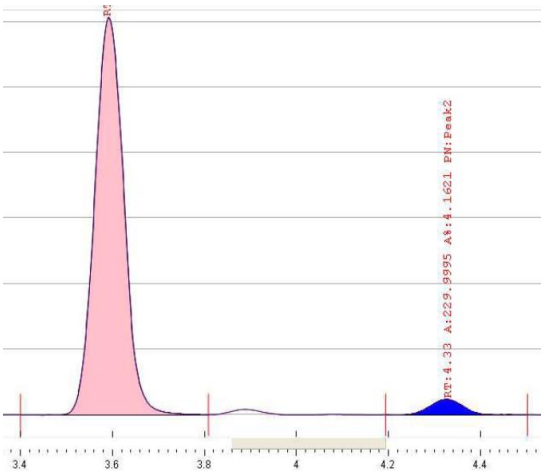
Chiral SFC (Chiracel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-ethynylphenyl)pent-4-en-2-ol

Racemic Material

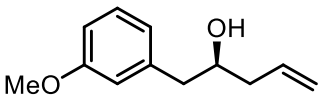


Peak No	% Area	Area	RT (min)
1	48.433	9264.1119	3.67
2	51.567	9863.5761	4.4
Total:	100	19127.688	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	95.8379	5296.0412	3.59
2	4.1621	229.9995	4.33
Total:	100	5526.0407	



(*S*)-1-(3-methoxyphenyl)pent-4-en-2-ol (2.187). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 3-methoxyphenylzinc(II) chloride solution (prepared according to **General Procedure B** using 1-bromo-3-methoxybenzene, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (21.5 mg, 56% yield). ^{1}H NMR

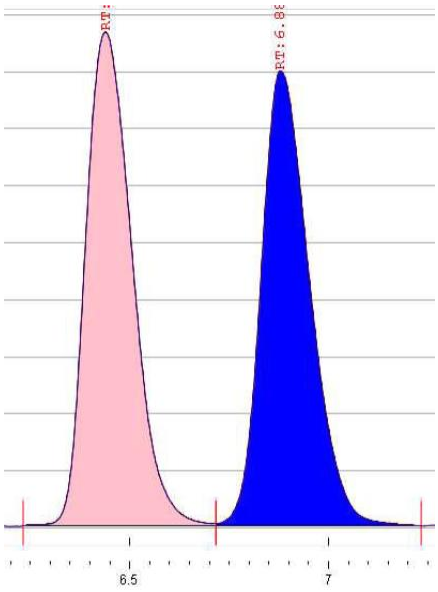
(500 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 1H), 6.84 – 6.75 (m, 3H), 5.93 – 5.81 (m, 1H), 5.20 – 5.12 (m, 2H), 3.94 – 3.85 (m, 1H), 3.80 (s, 3H), 2.80 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.70 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.39 – 2.30 (m, 1H), 2.28 – 2.20 (m, 1H), 1.75 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 140.2, 134.9, 129.7, 121.9, 118.30, 118.28, 115.3, 112.0, 71.8, 55.3, 43.5, 41.4. IR (neat) ν_{max} 3413 (br), 3074 (w), 2920 (w), 2835 (w), 1601 (m), 1489 (m), 1258 (s), 1152 (s), 1042 (s), 996 (m), 915 (m). HRMS (DART) for $C_{12}H_{15}O$ $[M+H-H_2O]^+$: calculated: 175.1117, found: 175.1110. $[\alpha]^{20}_D$: +6.14 (c = 0.99, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

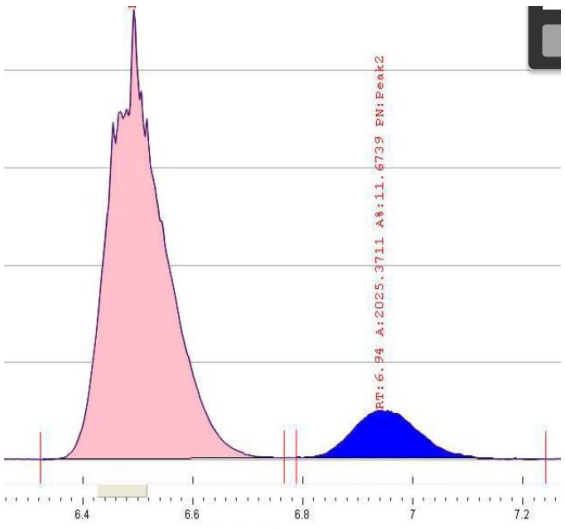
Chiral SFC (Chiracel OJ-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(3-methoxyphenyl)pent-4-en-2-ol

Racemic Material

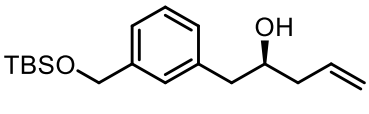


Peak No	% Area	Area	RT (min)
1	50.9521	6999.85	6.44
2	49.0479	6738.2401	6.88
Total:	100	13738.0901	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	88.3261	15324.1991	6.49
2	11.6739	2025.3711	6.94
Total:	100	17349.5702	



(*S*)-1-(3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl) pent-4-en-2-ol (2.188). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), (3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl) zinc(II) chloride solution (prepared according to **General Procedure B** using ((3-bromobenzyl)oxy)(tert-butyl)dimethylsilane **(S-3)**, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg,

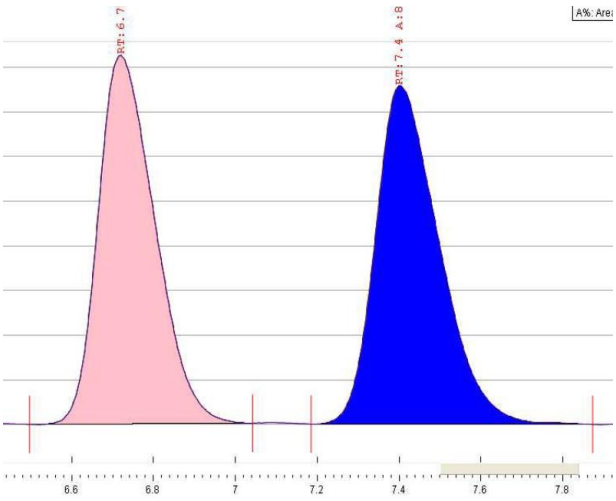
0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (29.4 mg, 48% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 1H), 7.22 – 7.18 (m, 2H), 7.11 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.92 – 5.82 (m, 1H), 5.18 – 5.13 (m, 2H), 4.74 (s, 2H), 3.93 – 3.86 (m, 1H), 2.82 (dd, *J* = 13.6, 5.0 Hz, 1H), 2.73 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.26 – 2.19 (m, 1H), 1.71 (br s, 1H), 0.95 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.9, 138.4, 134.9, 128.6, 128.2, 127.3, 124.5, 118.3, 71.9, 65.1, 43.5, 41.3, 26.1, 18.6, -5.0. IR (neat) ν_{max} 3432 (br), 2954 (m), 2928 (m), 2896 (w), 2856 (m), 1472 (w), 1254 (m), 1104 (m), 1079 (m), 837 (s), 777 (m). HRMS (DART) for $C_{18}H_{34}NO_2Si$ $[M+NH_4]^+$: calculated: 324.2353, found: 324.2353. $[\alpha]^{20}_D$: +4.39 (c = 0.88, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

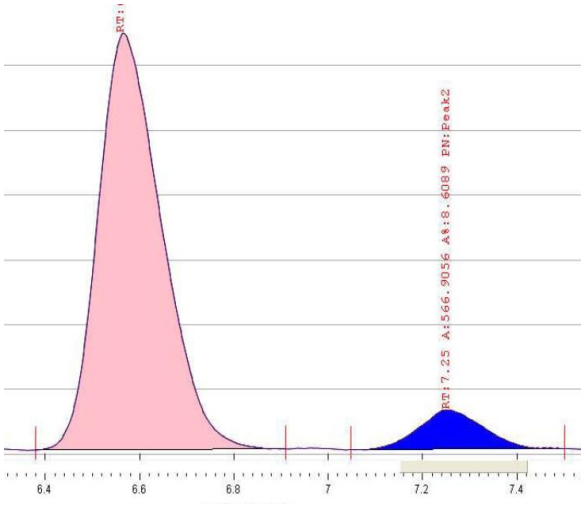
Chiral SFC (Chiracel OD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)pent-4-en-2-ol

Racemic Material

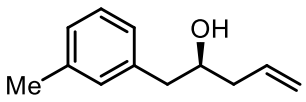


Peak No	% Area	Area	RT (min)
1	49.1997	7917.4576	6.72
2	50.8003	8175.0477	7.4
Total:	100	16092.5053	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	91.3911	6018.1694	6.56
2	8.6089	566.9056	7.25
Total:	100	6585.075	



(*S*)-1-(*m*-tolyl)pent-4-en-2-ol (2.278). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole **(2.151)** (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.4 mg, 0.052 mmol, 0.26 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 3-methylphenylzinc(II) chloride solution (prepared according to **General Procedure B** using 3-bromotoluene, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified

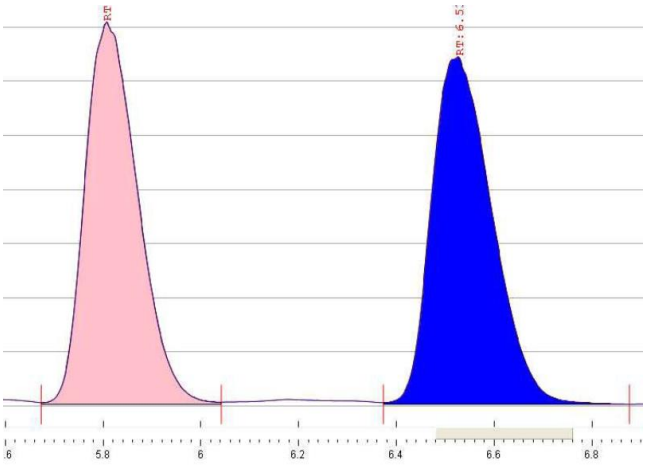
by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (19.7 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 1H), 7.11 – 6.97 (m, 3H), 5.92 – 5.83 (m, 1H), 5.21 – 5.12 (m, 2H), 3.93 – 3.84 (m, 1H), 2.80 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.69 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.39 – 2.29 (m, 4H), 2.28 – 2.19 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 138.3, 134.9, 130.4, 128.6, 127.4, 126.6, 118.2, 71.9, 43.4, 41.4, 21.6. IR (neat) ν_{max} 3403 (br), 3074 (w), 3013 (w), 2919 (s), 1640 (m), 1609 (m), 1434 (m), 1353 (w), 1040 (s), 997 (m), 914 (s). HRMS (DART) for $C_{12}H_{15}$ $[M+H-H_2O]^+$: calculated: 159.1168, found: 159.1173. $[\alpha]^{20}_D$: +9.50 (c = 1.01, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

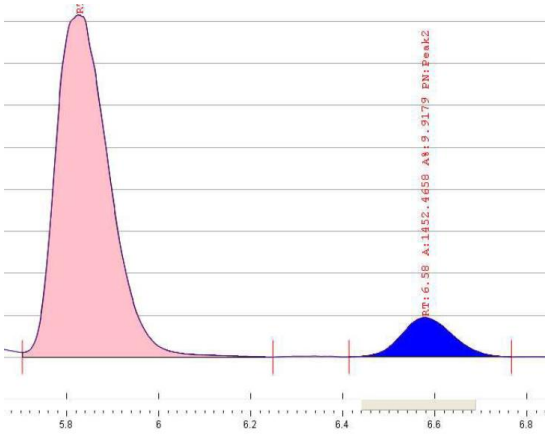
Chiral SFC (Chiracel OJ-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(m-tolyl)pent-4-en-2-ol

Racemic Material

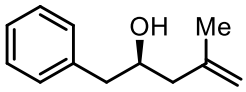


Peak No	% Area	Area	RT (min)
1	49.0412	10596.9535	5.81
2	50.9588	11011.3111	6.53
Total:	100	21608.2646	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	90.0821	13192.4821	5.83
2	9.9179	1452.4658	6.58
Total:	100	14644.9479	



(*S*)-4-methyl-1-phenylpent-4-en-2-ol (2.192). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), 3-bromo-2-methylprop-1-ene (81.0 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (18.7 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m,

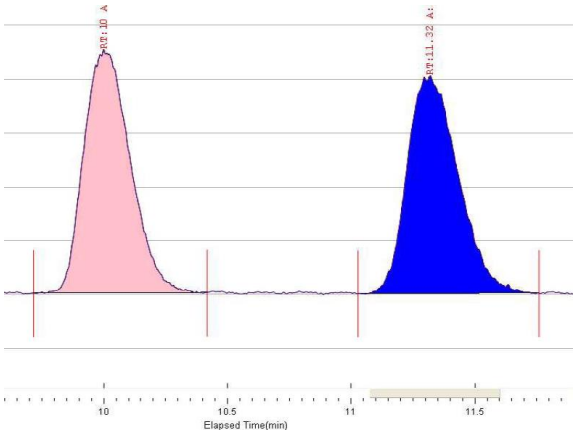
2H), 7.29 – 7.03 (m, 3H), 4.89 (s, 1H), 4.85 – 4.80 (m, 1H), 4.04 – 3.92 (m, 1H), 2.83 – 2.71 (m, 2H), 2.26 (dd, J = 13.9, 4.2 Hz, 1H), 2.18 (dd, J = 13.8, 8.8 Hz, 1H), 1.76 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 138.7, 129.6, 128.7, 126.6, 113.7, 70.0, 45.7, 43.8, 22.6. IR (neat) ν_{max} 3415 (br), 3073 (w), 3027 (w), 2932 (m), 1647 (w), 1496 (m), 1453 (m), 1080 (s), 891 (s), 747 (s), 700 (s). HRMS (DART) for $C_{12}H_{15}$ $[M+H-H_2O]^+$: calculated: 159.1168, found: 159.1173. $[\alpha]^{20}_D$: +14.6 (c = 0.82, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

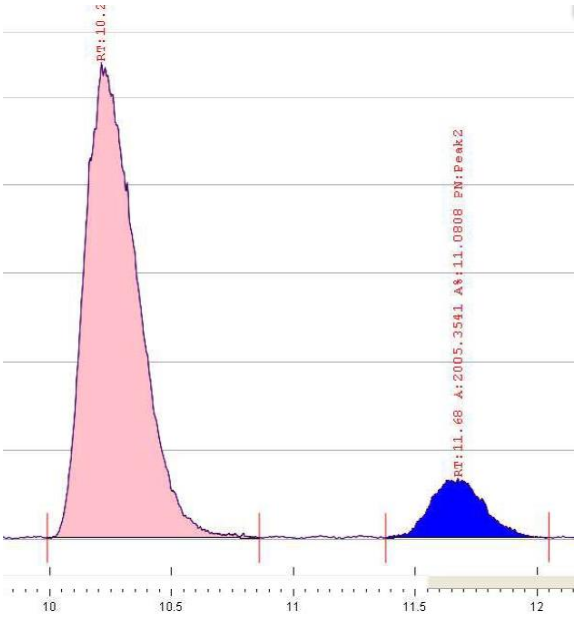
Chiral SFC (Chiracel OD-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-4-methyl-1-phenylpent-4-en-2-ol

Racemic Material

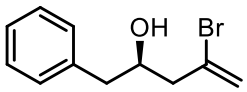


Peak No	% Area	Area	RT (min)
1	50.3646	5871.0591	10
2	49.6354	5786.0505	11.32
Total:	100	11657.1096	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	88.9192	16092.136	10.21
2	11.0808	2005.3541	11.68
Total:	100	18097.4901	



(*R*)-4-bromo-1-phenylpent-4-en-2-ol (2.193). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), 2,3-dibromoprop-1-ene (119.9 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride

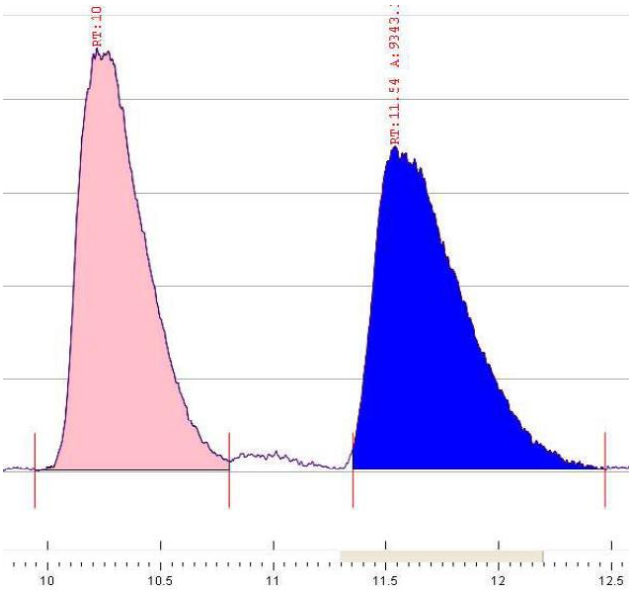
(8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (30.5 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.27 – 7.20 (m, 3H), 5.70 (d, *J* = 1.7 Hz, 1H), 5.54 (d, *J* = 1.6 Hz, 1H), 4.24 – 4.13 (m, 1H), 2.85 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.73 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.59 (d, *J* = 6.3 Hz, 2H), 1.77 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 130.7, 129.6, 128.8, 126.9, 119.9, 70.2, 48.8, 43.0. IR (neat) ν_{max} 3398 (br), 3062 (w), 3027 (w), 2917 (w), 1630 (m), 1496 (w), 1454 (w), 1118 (m), 1079 (m), 890 (s), 700 (s). HRMS (DART) for $C_{11}H_{12}Br$ $[M+H-H_2O]^+$: calculated: 223.0117, found: 223.0111. $[\alpha]^{20}_D$: +7.11 (c = 1.35, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

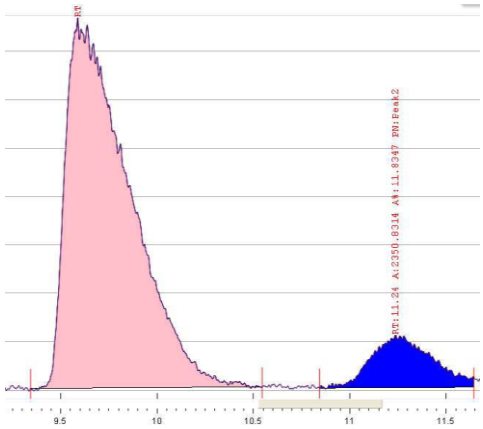
Chiral SFC (Chiracel AS-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-4-bromo-1-phenylpent-4-en-2-ol

Racemic Material

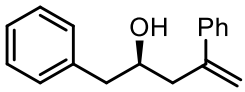


Peak No	% Area	Area	RT (min)
1	50.0143	9348.5228	10.22
2	49.9857	9343.19	11.54
Total:	100	18691.7128	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	88.1653	17513.1076	9.59
2	11.8347	2350.8314	11.24
Total:	100	19863.939	



(*R*)-1,4-diphenylpent-4-en-2-ol (2.194). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), (3-bromoprop-1-en-2-yl)benzene (118.2 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column

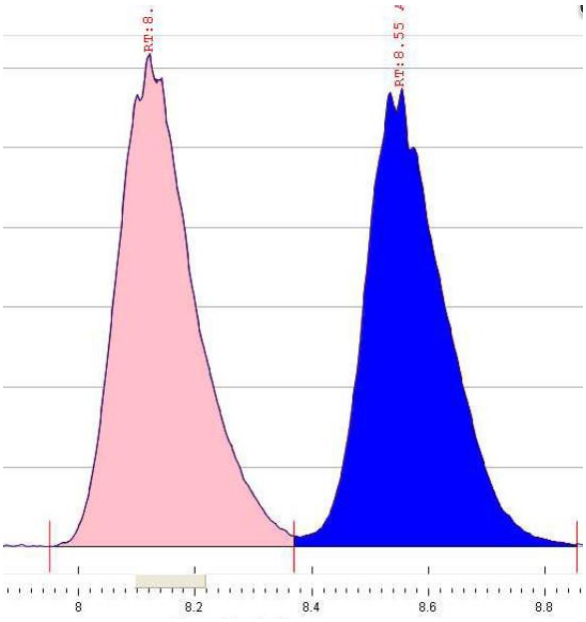
chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (27.2 mg, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 7H), 7.25 – 7.21 (m, 1H), 7.20 – 7.16 (m, 2H), 5.42 (d, *J* = 1.5 Hz, 1H), 5.20 (q, *J* = 1.3 Hz, 1H), 3.90 (m, 1H), 2.87 – 2.80 (m, 2H), 2.76 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.67 – 2.60 (m, 1H), 1.72 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 140.7, 138.6, 129.6, 128.7, 128.6, 127.9, 126.7, 126.4, 115.5, 70.7, 43.6, 43.3. IR (neat) ν_{max} 3416 (br), 3082 (w), 3026 (w), 2922 (w), 1626 (w), 1494 (m), 1453 (w), 1078 (m), 1038 (m), 897 (m), 778 (s), 687 (s). HRMS (DART) for $C_{17}H_{17}$ $[M+H-H_2O]^+$: calculated: 221.1325, found: 221.1333. $[\alpha]^{20}_D$: +7.04 (c = 1.23, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

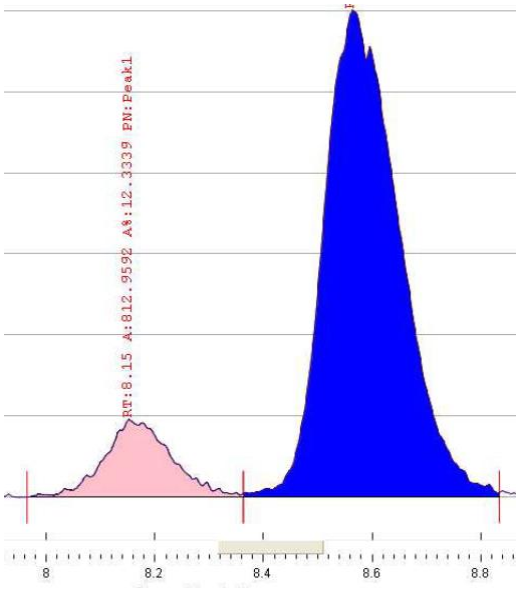
Chiral SFC (Chiracel OJ-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1,4-diphenylpent-4-en-2-ol

Racemic Material

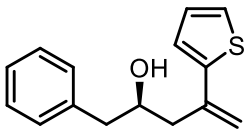


Peak No	% Area	Area	RT (min)
1	51.1767	11364.8116	8.12
2	48.8233	10842.2102	8.55
Total:	100	22207.0218	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	12.3339	812.9592	8.15
2	87.6661	5778.2851	8.56
Total:	100	6591.2443	



(*R*)-1-phenyl-4-(thiophen-2-yl)pent-4-en-2-ol (2.195). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), 2-(3-bromoprop-1-en-2-yl)thiophene (121.9 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture

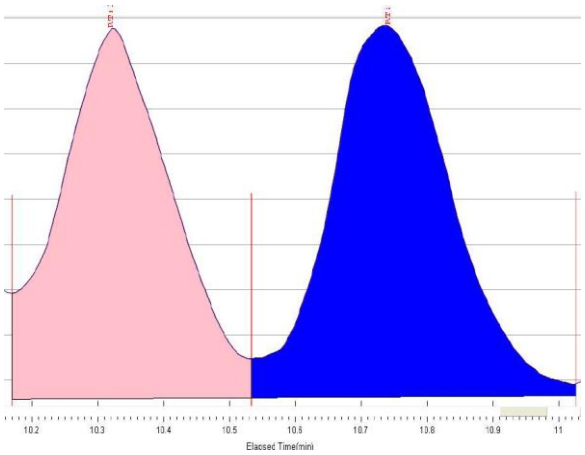
was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (27.4 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.21 (m, 4H), 7.19 – 7.16 (m, 1H), 7.00 – 6.89 (m, 2H), 5.52 (s, 1H), 5.08 (s, 1H), 4.11 – 4.01 (m, 1H), 2.91 – 2.79 (m, 2H), 2.79 – 2.71 (m, 1H), 2.56 (dd, *J* = 14.1, 8.7 Hz, 1H), 1.80 (br s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.6, 138.6, 138.5, 129.6, 128.7, 127.6, 126.7, 124.9, 124.0, 113.8, 71.0, 43.7, 43.5. IR (neat) ν_{max} 3411 (br), 3105 (w), 3026 (w), 2923 (w), 1739 (w), 1654 (w), 1496 (w), 1415 (w), 1230 (m), 1080 (m), 700 (s). HRMS (DART) for $C_{15}H_{17}OS$ $[M+H]^+$: calculated: 245.0995, found: 245.0994. $[\alpha]^{20}_D$: -0.600 (c = 1.00, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

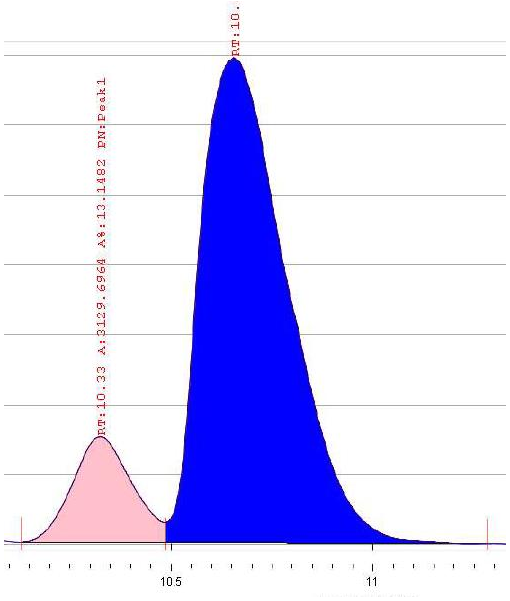
Chiral SFC (Chiracel OJ-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1-phenyl-4-(thiophen-2-yl)pent-4-en-2-ol

Racemic Material

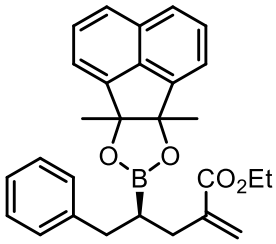


Peak No	% Area	Area	RT (min)
1	47.6244	1936.6058	10.32
2	52.3756	2129.8079	10.74
Total:	100	4066.4137	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	13.1482	3129.6964	10.33
2	86.8518	20673.483	10.66
Total:	100	23803.1794	



Ethyl (*4R*)-4-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-2-methylene-5-phenylpentanoate (2.196). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), ethyl 2-(bromomethyl)acrylate (115.8 mg, 0.60

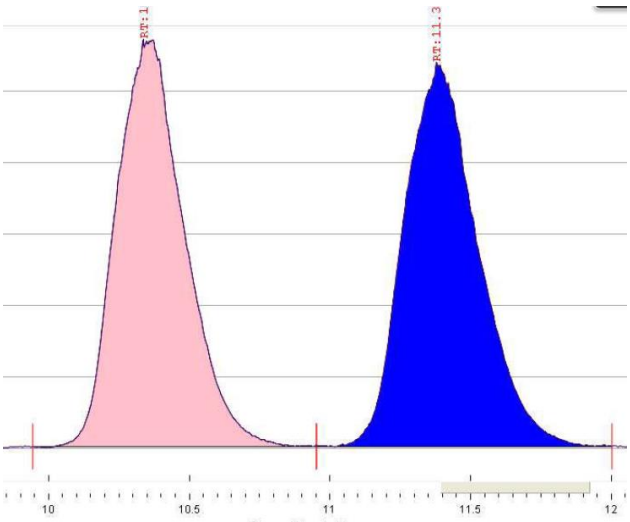
mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The product was not oxidized but isolated as boronic ester by column chromatography (silica gel, 0-20% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (50.1 mg, 57% yield). ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.79 (app dd, *J* = 8.1, 6.1 Hz, 2H), 7.62 – 7.53 (m, 2H), 7.51 (d, *J* = 6.9 Hz, 1H), 7.43 (d, *J* = 6.9 Hz, 1H), 6.96 – 6.81 (m, 5H), 5.80 (s, 1H), 5.24 (s, 1H), 4.12 – 4.03 (m, 2H), 2.67 – 2.52 (m, 2H), 2.44 – 2.29 (m, 2H), 1.68 (s, 3H), 1.64 (s, 3H), 1.61 – 1.54 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 145.0, 144.9, 141.4, 140.4, 134.9, 131.5, 128.7, 128.6, 128.0, 125.6, 125.3, 125.2, 125.0, 119.54, 119.48, 91.94, 91.90, 60.6, 37.7, 33.8, 22.1, 22.0, 14.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 34.32. IR (neat) ν_{max} 3026 (w), 2979 (w), 2931 (w), 1713 (s), 1626 (w), 1585 (w), 1496 (w), 1380 (m), 1319 (m), 1185 (m), 1117 (s), 1078 (m). HRMS (DART) for $C_{28}H_{30}BO_4$ $[M+H]^+$: calculated: 441.2232, found: 441.2243. $[\alpha]^{20}_D$: +4.94 (c = 1.08, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

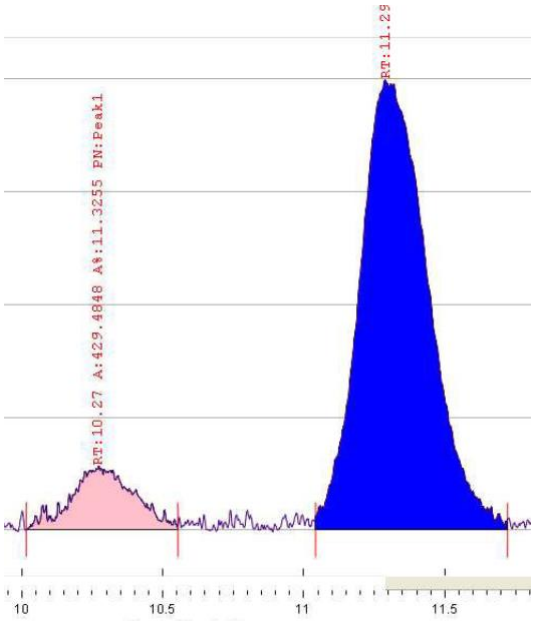
Chiral SFC (Chiracel AD-H, 4% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of Ethyl (4R)-4-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-2-methylene-5-phenylpentanoate

Racemic Material

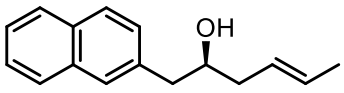


Peak No	% Area	Area	RT (min)
1	49.6584	19236.4128	10.34
2	50.3416	19501.074	11.38
Total:	100	38737.4868	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	11.3255	429.4848	10.27
2	88.6745	3362.7129	11.29
Total:	100	3792.1977	

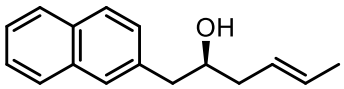


(*S,E*)-1-(naphthalen-2-yl)hex-4-en-2-ol (2.197). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), naphthalen-2-ylzinc(II) chloride solution (prepared according to **General Procedure B**) (0.4M in THF, 1 mL, 0.4 mmol, 2 equiv.), 3-chloro-1-butene (54.3 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10

mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (27.6 mg, 61% yield). The diastereomeric ratio of the alkene was determined to be 5:1 by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 3H), 7.71 – 7.66 (m, 1H), 7.49 – 7.43 (m, 2H), 7.40 – 7.35 (m, 1H), 5.65 – 5.56 (m, 1H), 5.55 – 5.46 (m, 1H), 4.01 – 3.89 (m, 1H), 2.98 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.89 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.38 – 2.27 (m, 1H), 2.24 – 2.16 (m, 1H), 1.80 – 1.76 (br s, 1H), 1.74 – 1.70 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.3, 133.7, 132.4, 129.2, 128.3, 128.02, 128.00, 127.8, 127.7, 127.1, 126.2, 125.6, 72.1, 43.5, 40.2, 18.3. IR (neat) ν_{max} 3404 (br), 3052 (w), 3019 (w), 2916 (s), 2854 (w), 1600 (w), 1508 (m), 1438 (m), 1037 (m), 969 (s), 814 (s), 749 (s). HRMS (DART) for $C_{16}H_{17}$ $[M+H-H_2O]^+$: calculated: 209.1325, found: 209.1335. $[\alpha]^{20}_D$: -2.65 (c = 1.03, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.



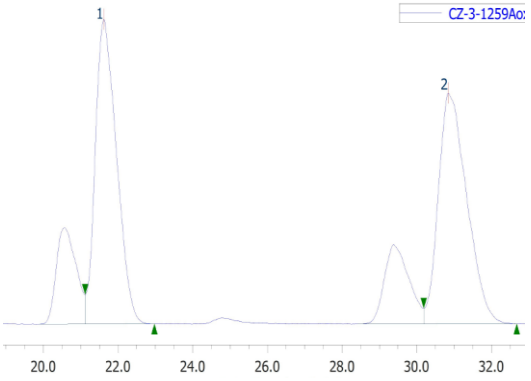
(*S,E*)-1-(naphthalen-2-yl)hex-4-en-2-ol (2.197). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), naphthalen-2-ylzinc(II) chloride solution (prepared according to **General Procedure B**) (0.4M in THF, 1 mL, 0.4 mmol, 2 equiv.), 3-chloro-1-butene (54.3 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (27.6 mg, 61% yield). The diastereomeric ratio of the alkene was determined to be 5:1 by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 3H), 7.71 – 7.66 (m, 1H), 7.49 – 7.43 (m, 2H), 7.40 – 7.35 (m, 1H), 5.65 – 5.56 (m, 1H), 5.55 – 5.46 (m, 1H), 4.01 – 3.89 (m, 1H), 2.98 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.89 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.38 – 2.27 (m, 1H), 2.24 – 2.16 (m, 1H), 1.80 – 1.76 (br s, 1H), 1.74 – 1.70 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.3, 133.7, 132.4, 129.2, 128.3, 128.02, 128.00, 127.8, 127.7, 127.1, 126.2, 125.6, 72.1, 43.5, 40.2, 18.3. IR (neat) ν_{max} 3404 (br), 3052 (w), 3019 (w), 2916 (s), 2854 (w), 1600 (w), 1508 (m), 1438 (m), 1037 (m), 969 (s), 814 (s), 749 (s). HRMS (DART) for $C_{16}H_{17}$ $[M+H-H_2O]^+$: calculated: 209.1325, found: 209.1335. $[\alpha]^{20}_D$: -2.65 (c = 1.03, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel OJ-H, 5% IPA, 3 mL/min, 100 bar, 40 °C, 200-400 nm) – analysis of (S,E)-1-(naphthalen-2-yl)hex-4-en-2-ol

Racemic Material



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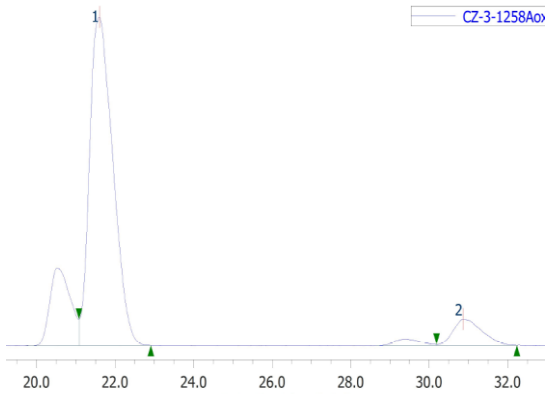
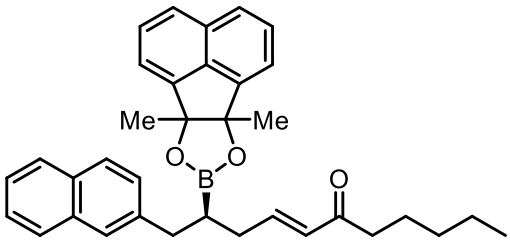
Standard Conditions



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	9	21.597	16363091	396947	91.109
2	Unknown	9	30.857	1596755	31638	8.891



(*2S,E*)-2-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-(naphthalen-2-yl) undec-4-en-6-one (2.198). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), naphthalen-2-ylzinc(II) chloride solution (prepared according to **General Procedure B**) (0.4M in THF, 1 mL, 0.4 mmol, 2 equiv.), 3-chlorononon-1-en-4-one (104.8 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture

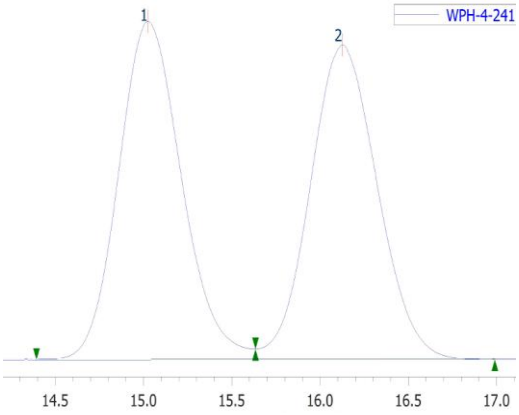
was not oxidized but isolated as the boronic ester by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as white solid (56.8 mg, 55% yield). The diastereomeric ratio of the alkene was determined to be >20:1 by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.73 (m, 2H), 7.72 – 7.69 (m, 1H), 7.61 – 7.45 (m, 6H), 7.43 (s, 1H), 7.41 – 7.34 (m, 2H), 7.08 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.61 (dt, *J* = 15.9, 7.2 Hz, 1H), 5.86 (dt, *J* = 15.9, 1.4 Hz, 1H), 2.86 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.79 (dd, *J* = 13.6, 7.5 Hz, 1H), 2.32 – 2.21 (m, 2H), 2.21 – 2.12 (m, 2H), 1.69 (s, 3H), 1.64 (s, 3H), 1.62 – 1.59 (m, 1H), 1.52 – 1.41 (m, 2H), 1.34 – 1.25 (m, 2H), 1.25 – 1.15 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 146.5, 144.63, 144.58, 138.8, 134.7, 133.5, 132.1, 131.5, 131.2, 128.64, 128.59, 127.8, 127.7, 127.6, 127.5, 127.0, 125.9, 125.5, 125.4, 125.2, 119.57, 119.55, 92.22, 92.17, 39.6, 37.2, 33.8, 31.7, 24.1, 22.7, 22.2, 22.0, 14.2. IR (neat) ν_{max} 3048 (w), 2955 (m), 2929 (s), 2859 (w), 1694 (m), 1672 (m), 1628 (m), 1379 (s), 1314 (m), 1116 (s), 1077 (s), 825 (s), 780 (s). HRMS (DART) for $C_{35}H_{38}BO_3$ $[M+H]^+$: calculated: 517.2909, found: 517.2917. $[\alpha]^{20}_D$: -9.93 (c = 1.00, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel OD-H, 15% IPA, 3 mL/min, 100 bar, 40 °C, 200-400 nm) – analysis of (2S,E)-2-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-(naphthalen-2-yl)undec-4-en-6-one

Racemic Material



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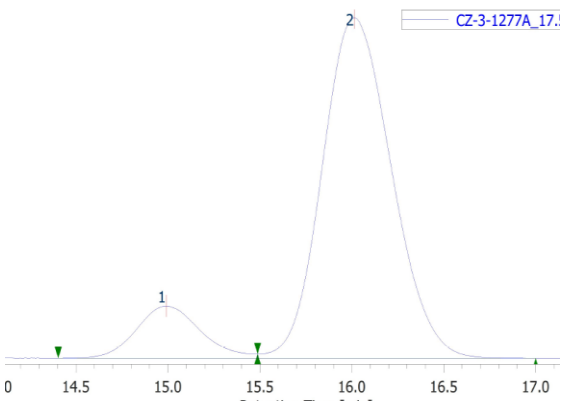
Standard Conditions



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
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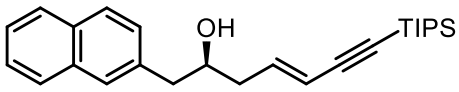
2	Unknown	9	16.013	23042108	877992	87.601



(*S,E*)-1-(naphthalen-2-yl)-7-(triisopropylsilyl) hept-4-en-6-yn-2-ol (2.199). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), naphthalen-2-ylzinc(II) chloride solution (prepared according to **General Procedure B**) (0.4M in THF, 1 mL, 0.4 mmol, 2 equiv.), (3-chloropent-4-en-1-yn-1-yl)triisopropylsilane (154.1 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified

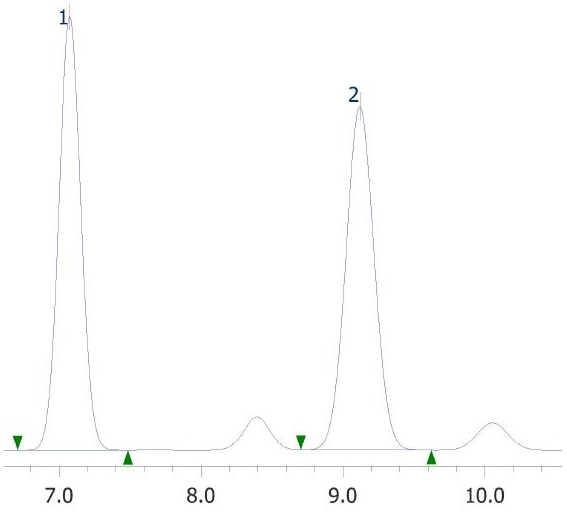
by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (40.1 mg, 51% yield). The diastereomeric ratio of the alkene was determined to be 14:1 by ^{1}H NMR analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 3H), 7.69 – 7.66 (m, 1H), 7.51 – 7.42 (m, 2H), 7.36 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.12 (dt, *J* = 10.9, 7.5 Hz, 1H), 5.71 (d, *J* = 10.9, 1H), 4.11 – 4.04 (m, 1H), 3.03 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.90 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.72 – 2.68 (m, 1H), 2.64 – 2.59 (m, 1H), 1.13 – 1.03 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 135.9, 133.7, 132.5, 128.4, 128.1, 127.9, 127.8, 127.7, 126.3, 125.7, 112.4, 103.7, 96.1, 72.2, 44.1, 38.0, 18.8, 11.4. IR (neat) ν_{max} 3412 (br), 3053 (w), 2941 (s), 2889 (m), 2864 (s), 2146 (m), 1462 (m), 1383 (w), 1035 (m), 1016 (m), 883 (s), 814 (m). HRMS (DART) for $C_{26}H_{37}OSi$ $[M+H]^+$: calculated: 393.2608, found: 393.2616. $[\alpha]^{20}_D$: -56.3 (c = 0.75, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel OD-H, 15% IPA, 3 mL/min, 100 bar, 40 °C, 200-400 nm) – analysis of (S,E)-1-(naphthalen-2-yl)-7-(triisopropylsilyl)hept-4-en-6-yn-2-ol

Racemic Material



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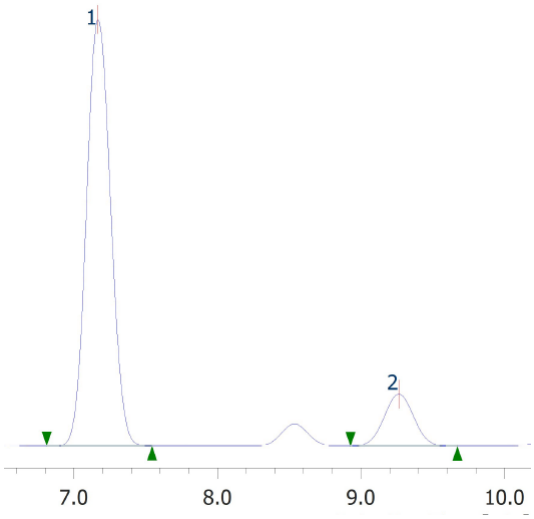
Standard Conditions



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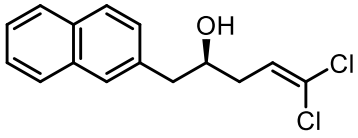


(*S*)-5,5-dichloro-1-(naphthalen-2-yl)pent-4-en-2-ol (2.200). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), naphthalen-2-ylzinc(II) chloride solution (prepared according to **General Procedure B**) (0.4M in THF, 1 mL, 0.4 mmol, 2 equiv.), 3,3,3-trichloroprop-1-ene (87.2 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography

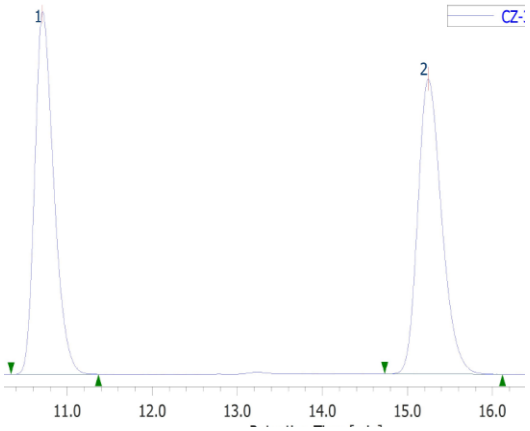
(silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as white solid (29.3 mg, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.77 (m, 3H), 7.53 – 7.43 (m, 2H), 7.37 – 7.31 (m, 1H), 6.06 (t, *J* = 7.3 Hz, 1H), 4.08 – 3.97 (m, 1H), 3.00 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.86 (dd, *J* = 13.7, 8.5 Hz, 1H), 2.55 – 2.38 (m, 2H), 1.70 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.3, 133.7, 132.5, 128.6, 128.2, 127.9, 127.70, 127.69, 126.4, 126.3, 125.9, 122.0, 71.4, 43.9, 37.1. IR (neat) ν_{max} 3377 (br), 3052 (w), 2917 (w), 1621 (w), 1600 (w), 1508 (w), 1052 (m), 914 (m), 886 (m), 811 (s), 749 (s). HRMS (DART) for $C_{15}H_{13}Cl_2$ $[M+H-H_2O]^+$: calculated: 263.0389, found: 263.0396. $[\alpha]^{20}_D$: -11.7 (c = 1.01, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel OJ-H, 15% IPA, 3 mL/min, 100 bar, 40 °C, 200-400 nm) – analysis of (S)-5,5-dichloro-1-(naphthalen-2-yl)pent-4-en-2-ol

Racemic Material



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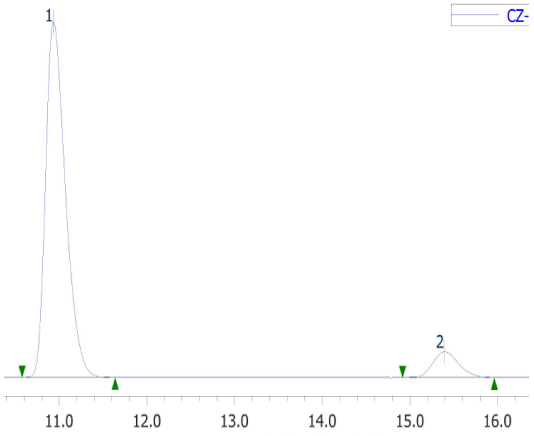
Standard Conditions



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
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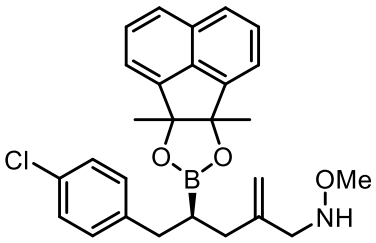
2	Unknown	9	15.393	1637575	78525	8.915



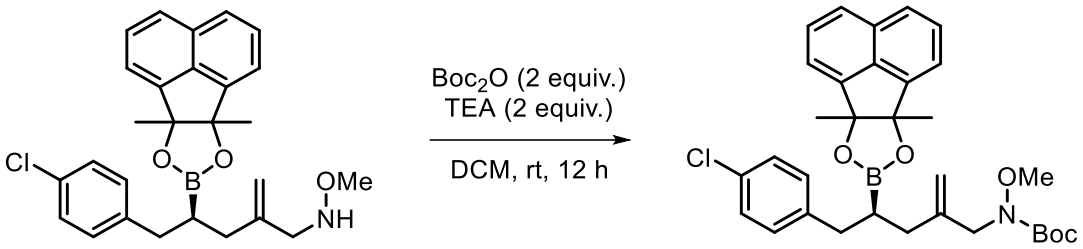
_N_-((_4R_)-5-(4-chlorophenyl)-4-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-2-methylenepentyl)-O-methylhydroxylamine (2.216). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 4-chlorophenylzinc(II) chloride solution (prepared according to **General Procedure B**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), *N*-(2-(chloromethyl)allyl)-*O*-methylhydroxylamine (81.4 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20

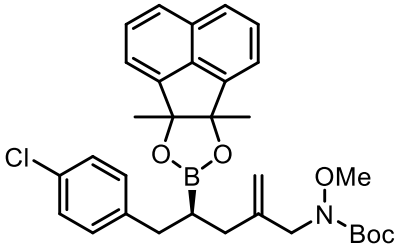
mmol, 1 equiv.). The product was not oxidized but isolated as boronic ester by column chromatography (silica gel, 0-50% ethyl acetate in hexanes, buffered with 1% Et_3N, stain in CAM) to furnish the titled compound as yellow oil(37.9 mg, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.65 – 7.53 (m, 3H), 7.46 (d, *J* = 6.9 Hz, 1H), 6.89 – 6.85 (m, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.72 (s, 1H), 4.67 (s, 1H), 3.42 (d, *J* = 13.6 Hz, 1H), 3.25 (d, *J* = 13.7 Hz, 1H), 3.20 (s, 3H), 2.65 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.49 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.12 (d, *J* = 8.3 Hz, 2H), 1.69 (s, 6H), 1.38 – 1.28 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 143.8, 140.7, 134.7, 131.5, 131.1, 130.1, 128.8, 128.7, 128.0, 125.20, 125.15, 119.6, 119.4, 113.5, 91.1, 61.3, 55.8, 36.9, 36.5, 22.5, 22.2. ^{11}B NMR (160 MHz, $CDCl_3$) δ 26.43. IR (neat) ν_{max} 3043 (w), 2978 (w), 2930 (m), 2857 (w), 1649 (w), 1491 (m), 1380 (s), 1316 (m), 1116 (s), 1080 (s), 826 (m), 783 (s). HRMS (DART) for $C_{27}H_{30}BClNO_3$ $[M+H]^+$: calculated: 462.2002, found: 462.2003. $[\alpha]^{20}_D$: -1.44 (c = 1.02, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

Enantiomeric ratio was determined after protecting with Boc by the following procedure:

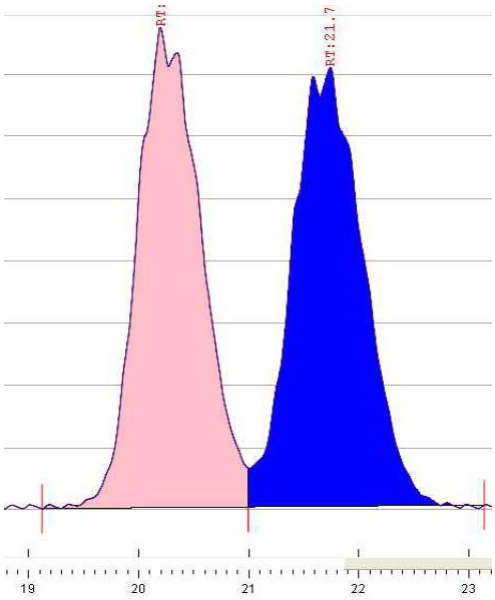




tert-Butyl ((*4R*)-5-(4-chlorophenyl)-4-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho [1,2-d][1,3,2] dioxaborol-8-yl)-2-methylenepentyl) (methoxy) carbamate (2.279). To a stirred solution of *N*-((*4R*)-5-(4-chlorophenyl)-4-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-2-methylenepentyl)-O-methylhydroxyl-amine (**2.216**) (20 mg, 0.043 mmol, 1 equiv.) in DCM (2 mL) was added triethylamine (0.02 mL, 0.14 mmol, 3.3 equiv.) and boc anhydride (18.9 mg, 0.086 mmol, 2 equiv.). The reaction was allowed to stir at room temperature overnight. Then, the reaction was passed through a silica gel plug with Et_2O and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the desired product as yellow oil(22.7 mg, 93% yield).

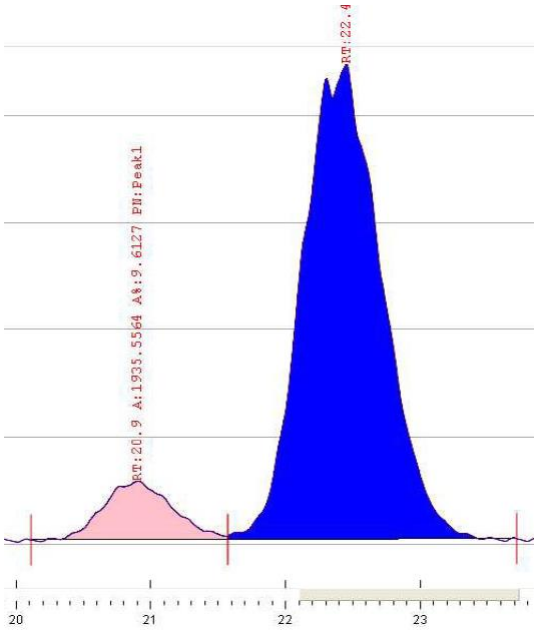
Chiral SFC (Chiracel AD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of tert-butyl ((4R)-5-(4-chlorophenyl)-4-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-2-methylenepentyl)(methoxy)carbamate

Racemic Material

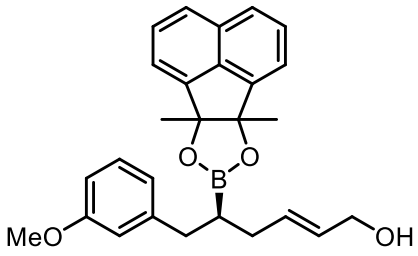


Peak No	% Area	Area	RT (min)
1	49.5864	15707.2097	20.2
2	50.4136	15969.2206	21.74
Total:	100	31676.4303	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	9.6127	1935.5564	20.9
2	90.3873	18199.7683	22.45
Total:	100	20135.3247	



(5*S*,*E*)-5-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho [1,2-d][1,3,2]dioxaborol-8-yl)-6-(3-methoxyphenyl) hex-2-en-1-ol (2.202). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 3-methoxyphenylzinc(II) chloride solution

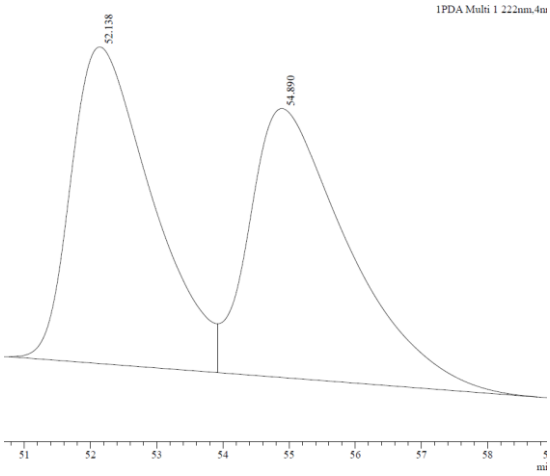
(prepared according to **General Procedure B**) (0.4M in THF, 1 mL, 0.4 mmol, 2 equiv.), 2-chlorobut-3-en-1-ol (63.9 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude product was not oxidized but isolated as the boronic ester by column chromatography (silica gel, 0-30% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (43.7 mg, 51% yield). The diastereomeric ratio of the alkene was determined to be >20:1 by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 2H), 7.63 – 7.57 (m, 2H), 7.52 (d, *J* = 6.9 Hz, 2H), 6.94 (t, *J* = 7.8 Hz, 1H), 6.66 – 6.55 (m, 3H), 5.47 – 5.36 (m, 1H), 5.30 – 5.21 (m, 1H), 3.69 (s, 3H), 3.64 – 3.53 (m, 2H), 2.67 (dd, *J* = 13.4, 8.5 Hz, 1H), 2.59 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.12 – 2.00 (m, 2H), 1.72 (s, 3H), 1.67 (s, 3H), 1.47 – 1.37 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 145.0, 144.9, 143.5, 134.7, 131.8, 131.4, 130.1, 129.1, 128.64, 128.61, 125.4, 125.3, 121.3, 119.6, 119.5, 114.4, 111.2, 92.0, 91.9, 63.5, 55.2, 37.1, 33.6, 22.2, 22.0. ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.21. IR (neat) ν_{max} 3435 (br), 2973 (w), 2930 (s), 2856 (w), 1601 (m), 1584 (m), 1381 (s), 1262 (s), 1117 (s), 1078 (s), 970 (m), 780 (s). HRMS (DART) for $C_{27}H_{28}BO_3$ $[M+H-H_2O]^+$: calculated: 411.2126, found: 411.2132. $[\alpha]^{20}_D$: +0.792 (c = 1.02, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

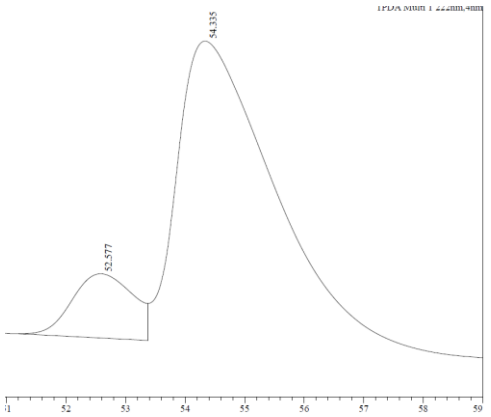
Chiral HPLC (Chiralcel IB, 1% IPA-hexanes, 0.8 mL/min, 222 nm) – analysis of (5S,E)-5-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-6-(3-methoxyphenyl)hex-2-en-1-ol

Racemic Material

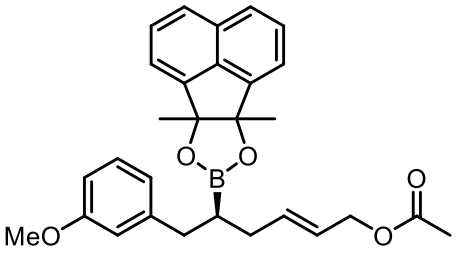


Peak#	Ret. Time	Area	Area%
1	52.138	9034386	49.162
2	54.890	9342287	50.838
Total		18376672	100.000

Standard Conditions



Peak#	Ret. Time	Area	Area%
1	52.577	3655226	11.685
2	54.335	27625833	88.315
Total		31281060	100.000



(*5S,E*)-5-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-6-(3-methoxyphenyl)hex-2-en-1-yl acetate (2.280). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 3-methoxyphenylzinc(II) chloride solution (prepared according to **General Procedure B**) (0.4M in THF, 1 mL, 0.4 mmol, 2 equiv.), 2-chlorobut-3-en-1-yl acetate **(S-10)** (89.2 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg,

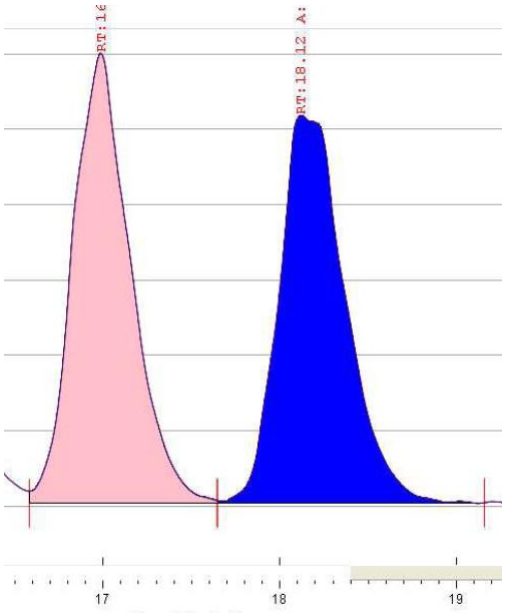
0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude product was not oxidized but isolated as the boronic ester by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (48.0 mg, 51% yield). The diastereomeric ratio of the alkene was determined to be 7.7:1 by ^{1}H NMR analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 – 7.77 (m, 2H), 7.61 – 7.56 (m, 2H), 7.53 – 7.48 (m, 2H), 6.89 – 6.83 (m, 1H), 6.60 – 6.53 (m, 2H), 6.50 (dt, *J* = 7.7, 1.2 Hz, 1H), 5.61 – 5.52 (m, 1H), 5.35 – 5.26 (m, 1H), 4.18 – 4.08 (m, 2H), 3.66 (d, *J* = 2.8 Hz, 3H), 2.63 (dd, *J* = 13.4, 8.4 Hz, 1H), 2.56 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.13 – 2.05 (m, 2H), 2.00 (s, 3H), 1.71 (s, 3H), 1.68 (s, 3H), 1.42 – 1.37 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 159.5, 144.9, 144.8, 143.3, 135.2, 134.7, 131.5, 129.0, 128.6, 125.4, 125.3, 124.8, 121.2, 119.6, 114.4, 111.3, 92.02, 91.97, 65.1, 55.1, 37.0, 33.6, 22.2, 22.0, 21.1. ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.27. IR (neat) ν_{max} 3044 (w), 2972 (w), 2929 (w), 2852 (w), 1737 (s), 1584 (w), 1455 (w), 1380 (m), 1315 (m), 1261 (s), 1239 (s), 1117 (m), 780(m). HRMS (DART) for $C_{29}H_{35}BNO_5$ $[M+NH_4]^+$: calculated: 488.2603, found: 488.2617. $[\alpha]^{20}_D$: -0.759 (c = 0.79, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

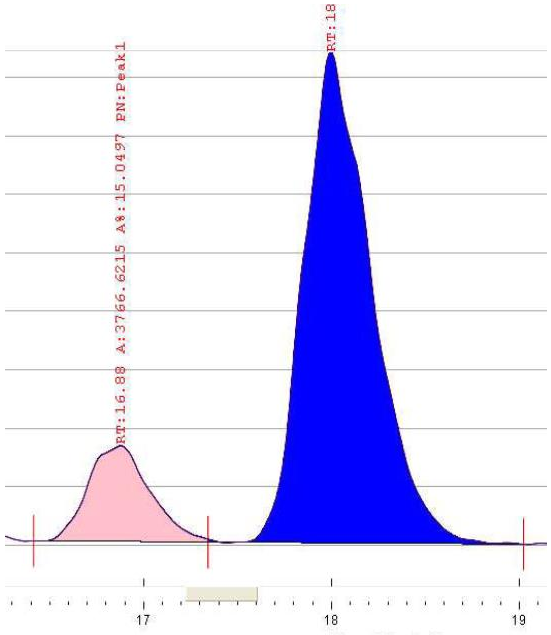
Chiral SFC (Chiracel OD-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (5S,E)-5-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-6-(3-methoxyphenyl)hex-2-en-1-yl acetate

Racemic Material

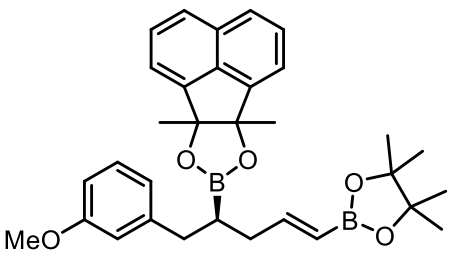


Peak No	% Area	Area	RT (min)
1	50.1217	13599.0671	16.99
2	49.8783	13533.006	18.12
Total:	100	27132.0731	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	15.0497	3766.6215	16.88
2	84.9503	21261.2976	18
Total:	100	25027.9191	



8-((*S,E*)-1-(3-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-en-2-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho [1,2-d][1,3,2]dioxaborole (2.201). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-

ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 3-methoxyphenylzinc(II) chloride solution (prepared according to **General Procedure B**) (0.4M in THF, 1 mL, 0.4 mmol, 2 equiv.), 2-(1-chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (121.5 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude product was not oxidized but isolated as the boronic ester by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to afford the titled compound as colorless oil (56.6 mg, 54% yield). The diastereomeric ratio of the alkene was determined to be 2.4:1 by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 2H), 7.64 – 7.50 (m, 3H), 7.50 – 7.44 (m, 1H), 6.76 (td, *J* = 7.7, 1.6 Hz, 1H), 6.61 – 6.47 (m, 3H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.39 (dd, *J* = 17.9, 1.6 Hz, 1H), 3.60 (s, 3H), 2.59 (dd, *J* = 7.7, 2.9 Hz, 2H), 2.29 – 2.13 (m, 2H), 1.69 (s, 6H), 1.50 – 1.38 (m, 1H), 1.24 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 153.9, 144.9, 144.8, 143.4, 134.8, 131.5, 128.9, 128.59, 128.56, 125.31, 125.28, 121.3, 119.6, 119.6, 114.2, 111.3, 92.0, 83.1, 55.1, 37.1, 36.8, 25.0, 24.9, 22.2, 22.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.27, 29.49. IR (neat) ν_{max} 2977 (m), 2930 (w), 1636 (w), 1601 (w), 1379 (m), 1360 (s), 1319 (m), 1262 (m), 1145 (s), 1117 (m), 1078 (w), 780(m). HRMS (DART) for $C_{32}H_{39}B_2O_5$ $[M+H]^+$: calculated: 525.2978, found: 525.2990. $[\alpha]^{20}_D$: -1.17 (c = 1.08, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

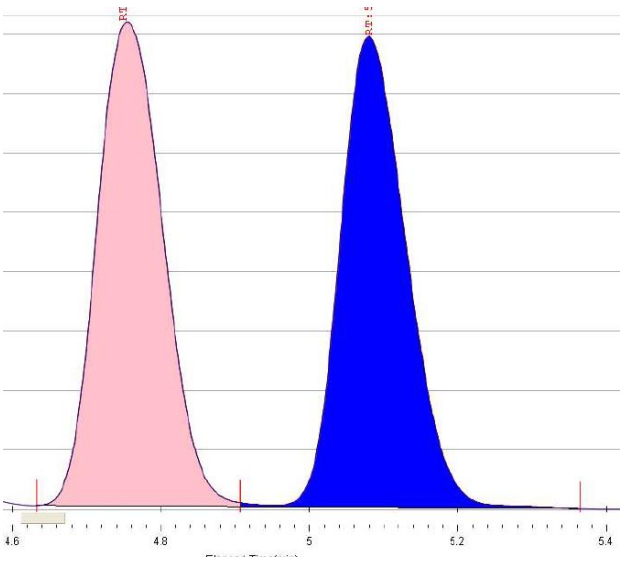
Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent

(instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

The enantioselectivity was determined after oxidizing the product to the γ-lactone (See Section 2.7.2.7 for details).

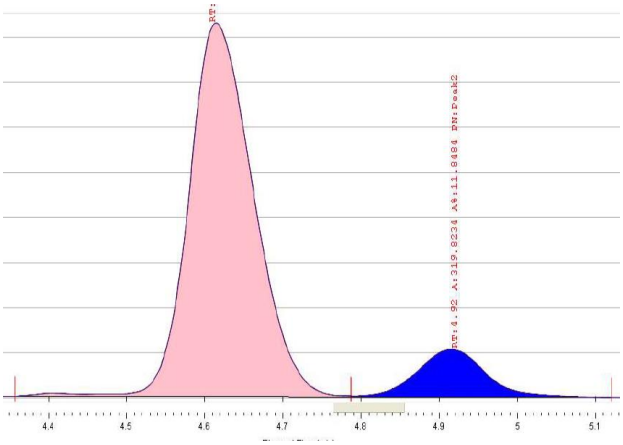
Chiral SFC (Chiracel OD-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-5-(3-methoxybenzyl)dihydrofuran-2(3H)-one

Racemic Material

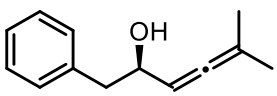


Peak No	% Area	Area	RT (min)
1	50.5334	5004.8892	4.75
2	49.4666	4899.2332	5.08
Total:	100	9904.1224	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	88.1516	2379.4748	4.61
2	11.8484	319.8234	4.92
Total:	100	2699.2982	



(*R*)-5-methyl-1-phenylhexa-3,4-dien-2-ol (2.203). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), 3-chloro-3-methylbut-1-yne (61.5 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by

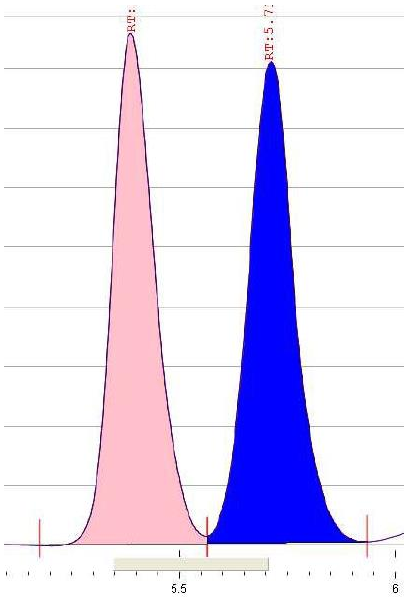
column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (19.6 mg, 52% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 5.14 – 5.10 (m, 1H), 4.35 (app q, *J* = 6.2 Hz, 1H), 2.91 – 2.82 (m, 2H), 1.65 (d, *J* = 2.9 Hz, 3H), 1.63 (d, *J* = 2.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.0, 138.1, 129.8, 128.5, 126.5, 99.3, 93.2, 71.0, 44.2, 20.7, 20.6. IR (neat) ν_{max} 3361 (br), 3028 (w), 2980 (w), 2934 (m), 2909 (m), 1968 (w), 1496 (w), 1453 (m), 1410 (w), 1206 (w), 1030 (s), 699 (s). HRMS (DART) for $C_{13}H_{17}O$ $[M+H]^+$: calculated: 189.1274, found: 189.1275. $[\alpha]^{20}_D$: -21.1 (c = 0.83, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure D** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

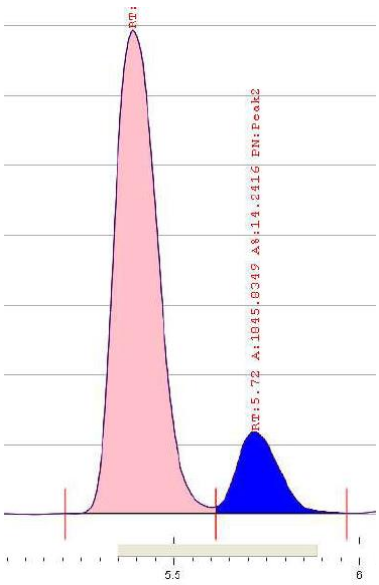
Chiral SFC (Chiracel OD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-5-methyl-1-phenylhexa-3,4-dien-2-ol

Racemic Material

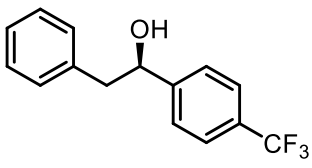


Peak No	% Area	Area	RT (min)
1	49.6003	5922.2764	5.39
2	50.3997	6017.7162	5.71
Total:	100	11939.9926	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	85.7584	11115.0348	5.39
2	14.2416	1845.8349	5.72
Total:	100	12960.8697	



(*R*)-2-phenyl-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (2.204). The reaction was performed according to **General Procedure E** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho [1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (28.4 mg, 0.20 mmol, 1 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), palladium acetate (2.3 mg, 0.01 mmol, 0.05 equiv.),

tris(4-fluorophenyl)phosphine (6.3 mg, 0.02 mmol, 0.1 equiv.) and 1-iodo-4-(trifluoromethyl)benzene (217.6 mg, 0.80 mmol, 4 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as white solid (23.4 mg, 44% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.23 (m, 3H), 7.23 – 7.16 (m, 2H), 4.97 (dd, *J* = 8.7, 4.6 Hz, 1H), 3.05 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.96 (dd, *J* = 13.7, 8.7 Hz, 1H), 2.05 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 137.5, 129.7, 128.9, 127.1, 126.4, 125.5 (q, *J* = 3.8 Hz), 123.3, 74.8, 46.3. IR (neat) ν_{max} 3391 (br), 3063 (w), 3030 (w), 2923 (w), 1496 (w), 1420 (w), 1325 (s), 1164 (m), 1123 (m), 1067 (m), 1017 (w), 841 (w). HRMS (DART) for $C_{15}H_{17}NOF_3$ $[M+NH_4]^+$: calculated: 284.1257, found: 284.1268. $[\alpha]^{20}_D$: +8.03 (c = 0.44, $CHCl_3$, *l* = 50 mm).

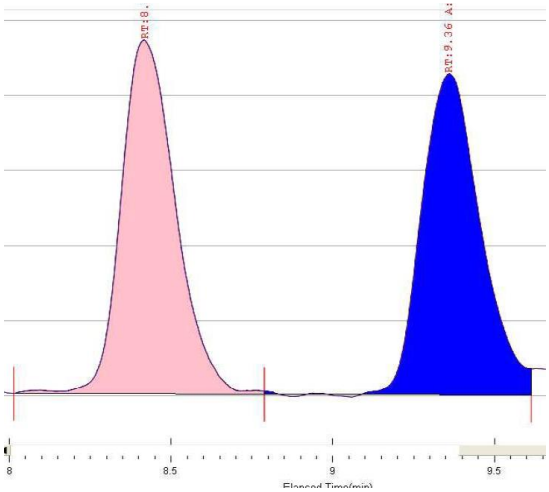
Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure E** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by comparing optical rotation with the literature.[113]

(113) Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017,** *139*, 3153–3160.

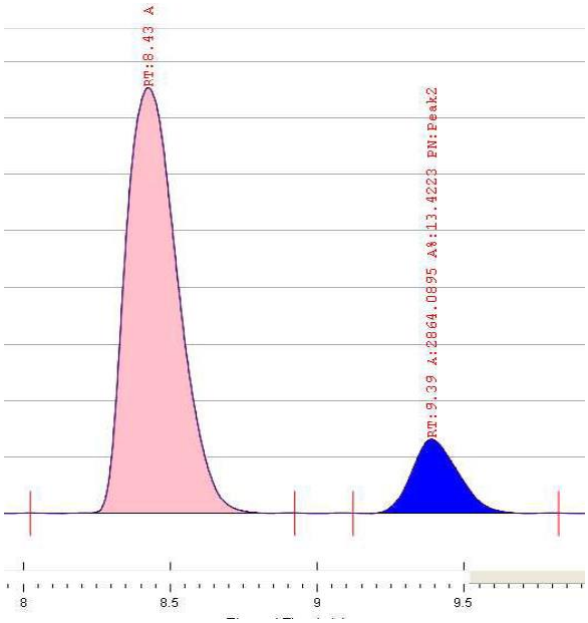
Chiral SFC (Chiracel OD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-phenyl-1-(4-(trifluoromethyl)phenyl)ethan-1-ol

Racemic Material

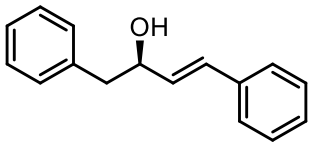


Peak No	% Area	Area	RT (min)
1	50.5233	2760.4463	8.42
2	49.4767	2703.2671	9.36
Total:	100	5463.7134	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	86.5777	18474.2523	8.43
2	13.4223	2864.0895	9.39
Total:	100	21338.3418	



(*R,E*)-1,4-diphenylbut-3-en-2-ol (2.205). The reaction was performed according to **General Procedure E** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2] dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (28.4 mg, 0.20 mmol, 1 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), palladium acetate (2.3 mg, 0.01 mmol, 0.05 equiv.), tris(4-fluorophenyl)phosphine (6.3 mg, 0.02 mmol, 0.1 equiv.) and (*E*)-(2-iodovinyl)benzene (184.0 mg, 0.80 mmol, 4 equiv.). The crude

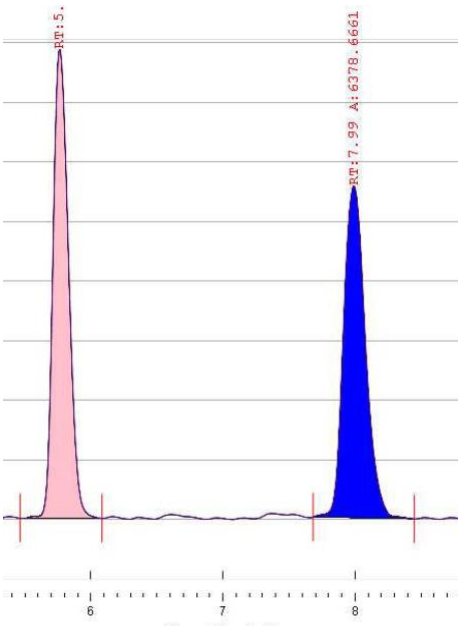
mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as yellow oil(24.7 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.36 – 7.31 (m, 4H), 7.30 – 7.23 (m, 4H), 6.61 (dd, *J* = 15.9, 1.3 Hz, 1H), 6.30 (dd, *J* = 15.9, 6.3 Hz, 1H), 4.57 – 4.51 (m, 1H), 2.99 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.90 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.80 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 136.9, 131.7, 130.6, 129.8, 128.74, 128.73, 127.8, 126.8, 126.7, 73.6, 44.4. IR (neat) ν_{max} 3382 (br), 3082 (w), 3026 (w), 2918 (m), 2856 (m), 1494 (m), 1453 (w), 1096 (w), 1030 (w), 967 (m), 743 (s), 694 (s). HRMS (DART) for $C_{16}H_{15}$ $[M+H-H_2O]^+$: calculated: 207.1168, found: 207.1173. $[\alpha]^{20}_D$: -9.40 (c = 1.23, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure E** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant, 0.4 mL DMSO as the cosolvent (instead of 0.2 mL DMF and 0.2 mL DMSO). The reaction was performed at 0 °C. Absolute stereochemistry was assigned by analogy.

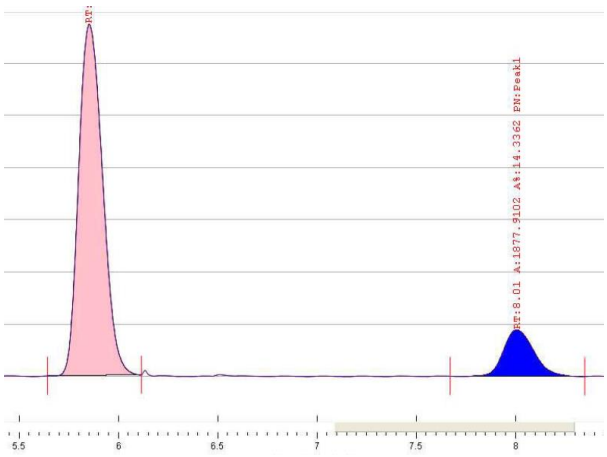
Chiral SFC (Chiracel OD-H, 15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R,E)-1,4-diphenylbut-3-en-2-ol

Racemic Material

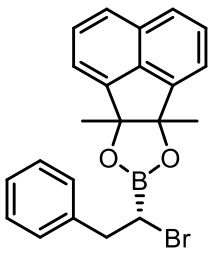


Peak No	% Area	Area	RT (min)
1	50.0514	6391.7995	5.76
2	49.9486	6378.6661	7.99
Total:	100	12770.4656	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	85.6638	11221.1592	5.85
2	14.3362	1877.9102	8.01
Total:	100	13099.0694	



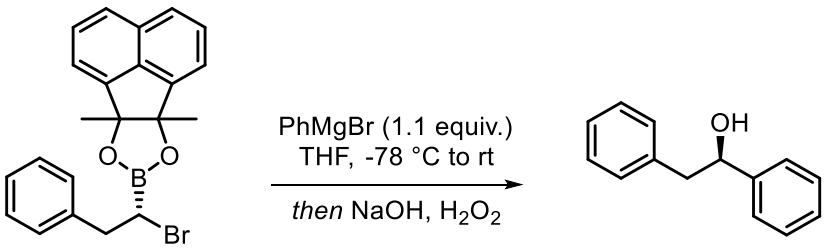
8-((*S*)-1-bromo-2-phenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho-[1,2-d][1,3,2]dioxaborole (2.207). The reaction was performed according to **General Procedure F** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.) and bromine

(0.05 mL, 1.0 mmol, 5 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-3-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as white solid (46.4 mg, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 2H), 7.67 – 7.60 (m, 1H), 7.61 – 7.53 (m, 2H), 7.52 – 7.47 (m, 1H), 7.05 – 6.98 (m, 1H), 6.98 – 6.90(m, 4H), 3.39 (app t, *J* = 8.4 Hz, 1H), 3.16 (dd, *J* = 13.6, 8.9 Hz, 1H), 3.08 (dd, *J* = 13.6, 8.0 Hz, 1H), 1.78 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 144.1, 138.9, 134.9, 131.5, 128.9, 128.67, 128.66, 128.3, 126.7, 125.60, 125.58, 119.8, 119.7, 93.0, 92.9, 40.6, 22.0, 21.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.59. IR (neat) ν_{max} 3029 (w), 2973 (w), 2928 (w), 2851 (w), 1497 (w), 1378 (s), 1337 (m), 1248 (w), 1116 (m), 1076 (m), 826 (m), 778 (m). HRMS (DART) for $C_{22}H_{24}BNO_2Br$ $[M+NH_4]^+$: calculated: 424.1078, found: 424.1087. $[\alpha]^{20}_D$: +1.21 (c = 0.99, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure F** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant. The carbozincation reaction was performed at 0 °C while bromination was carried out at -78 °C.

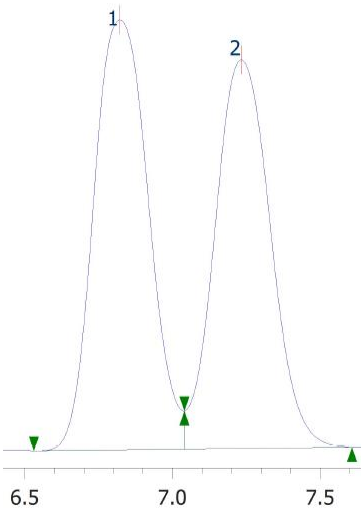
Absolute stereochemistry was assigned by a stereoinvertive Matteson reaction following the procedure below:



In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic sitr bar was added 8-((*S*)-1-bromo-2-phenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (56.5 mg, 0.14 mmol, 1 equiv.) in 1 mL THF. The vial was sealed with a septum cap and removed from the glove box. The reaction was cooled to -78 °C under N_2 atmosphere followed by the dropwise addition of phenylmagnesium(II) bromide (1 M in THF, 0.15 mL, 0.15 mmol, 1.1 equiv.). The solution was slowly warmed to room temperature and allowed to stir overnight. After that, the reaction was diluted with Et_2O and passed through a silica gel plug. The solvent was removed under vacuum. The crude produce was dissolved in 2 mL THF followed by the addition of 1 mL 3M NaOH solution and 1 mL H_2O_2 solution (30% w/w in water). The reaction was allowed to stir for 30 minutes and diluted with Et_2O. The aqueous layer was extracted with Et_2O twice and the combined organic layer was passed through a silica gel plug. The solvent was removed, and the crude product was purified by automated silica gel column chromatography (Biotage, 0-3-10% ethyl acetate in hexanes, stain in CAM) to furnish (*R*)-1,2-diphenylethan-1-ol as white solid (21.0 mg, 76% yield). $[\alpha]^{20}_D$: +6.74 (c = 0.87, $CHCl_3$, *l* = 50 mm). The absolute configuration of the product was assigned by comparing the optical rotation with literature.[63]

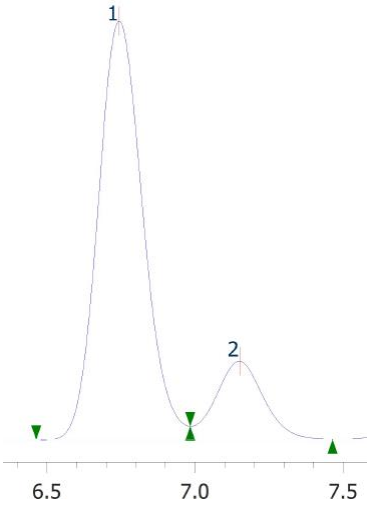
Chiral SFC (Chiracel OD-H, 10% IPA, 3 mL/min, 100 bar, 40 °C, 200-400 nm) – analysis of 8-((R)-1-bromo-2-phenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole

Racemic Material

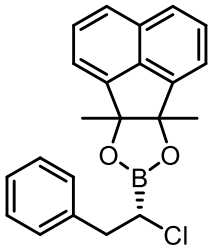


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	9	6.820	19612347	1526806	52.044
2	Unknown	9	7.233	18071863	1380635	47.956

Standard Conditions



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	9	6.743	9909304	941066	83.431
2	Unknown	9	7.150	1967912	175950	16.569



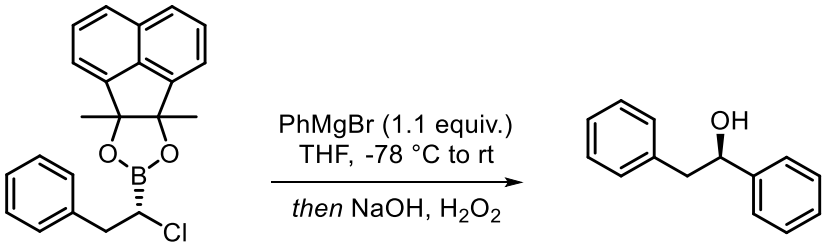
8-((*S*)-1-chloro-2-phenylethyl)-6b,9a-dimethyl-6b,9a-dihydro acenaphtho-[1,2-d][1,3,2]dioxaborole (2.208). The reaction was performed according to **General Procedure G** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), cerium(III) chloride (24.6 mg, 0.10 mmol, 0.5 equiv.) and trichloroisocyanuric acid (232.4 mg, 1.0 mmol, 5

equiv.). The crude mixture was purified by automated silica gel column chromatography (Biotage, 0-5-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as white solid (29.0 mg, 40% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.62 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.52 – 7.48 (m, 1H), 7.05 – 6.98 (m, 1H), 6.98 – 6.92 (m, 4H), 3.53 (app t, *J* = 7.9 Hz, 1H), 3.05 (dd, *J* = 13.7, 7.7 Hz, 1H), 3.01 (dd, *J* = 13.7, 8.0 Hz, 1H), 1.77 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.10, 144.06, 138.1, 134.9, 131.5, 129.1, 128.69, 128.67, 128.2, 126.7, 125.63, 125.60, 119.84, 119.81, 93.1, 93.0, 81.0, 40.6, 22.03, 21.97. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.52. IR (neat) ν_{max} 3029 (w), 2975 (w), 2930 (w), 2855 (w), 1497 (w), 1378 (s), 1348 (m), 1339 (m), 1116 (s), 1076 (s), 826 (m), 779 (s). HRMS (DART) for $C_{22}H_{21}BClO_2$ $[M+H]^+$: calculated: 363.1318, found: 363.1313. $[\alpha]^{20}_D$: +5.50 (c = 0.86, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry

Racemic compound was prepared according to **General Procedure G** employing nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), *N,N'*-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.) as the catalyst, 1-iodobutane (73.6 mg, 0.40 mmol, 2 equiv.) as the oxidant. The carbozincation reaction was performed at 0 °C while chlorination was carried out at -78 °C.

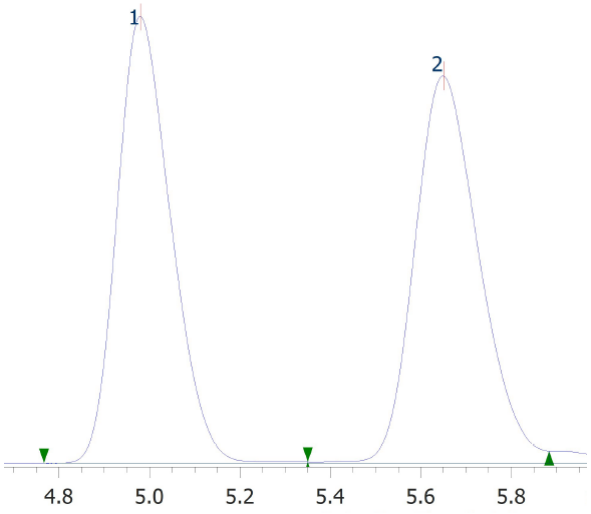
Absolute stereochemistry was assigned by a stereoinvertive Matteson reaction following the procedure below:



In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic sitr bar was added 8-((*S*)-1-chloro-2-phenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (17.6 mg, 0.49 mmol, 1 equiv.) in 1 mL THF. The vial was sealed with a septum cap and removed from the glove box. The reaction was cooled to -78 °C under N_2 atmosphere followed by the dropwise addition of phenylmagnesium(II) bromide (1 M in THF, 0.05 mL, 0.053 mmol, 1.1 equiv.). The solution was slowly warmed to room temperature and allowed to stir overnight. After that, the reaction was diluted with Et_2O and passed through a silica gel plug. The solvent was removed under vacuum. The crude produce was dissolved in 2 mL THF followed by the addition of 1 mL 3M NaOH solution and 1 mL H_2O_2 solution (30% w/w in water). The reaction was allowed to stir for 30 minutes and diluted with Et_2O. The aqueous layer was extracted with Et_2O twice and the combined organic layer was passed through a silica gel plug. The solvent was removed, and the crude product was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish (*R*)-1,2-diphenylethan-1-ol as white solid (6.2 mg, 64% yield). $[\alpha]^{20}_D$: +8.09 (c = 0.31, $CHCl_3$, *l* = 50 mm). The absolute configuration of the product was assigned by comparing the optical rotation with literature.[63]

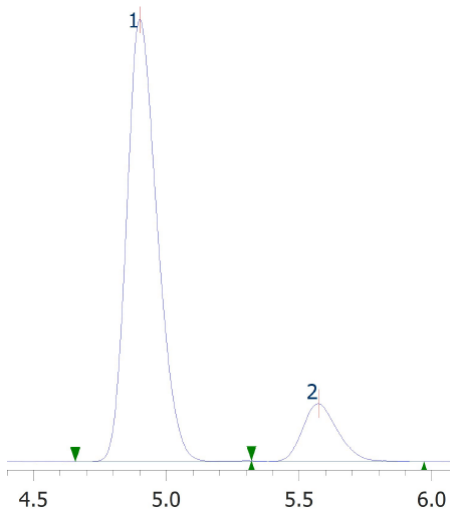
Chiral SFC (Chiracel OJ-H, 10% IPA, 3 mL/min, 100 bar, 40 °C, 200-400 nm) – analysis of 8-((S)-1-chloro-2-phenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole

Racemic Material

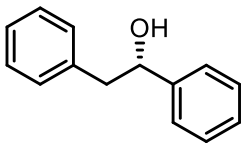


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	9	4.980	2124905	256371	49.228
2	Unknown	9	5.650	2191525	222026	50.772

Standard Conditions



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	9	4.900	2830232	352639	86.825
2	Unknown	9	5.573	429449	46102	13.175



(*S*)-1,2-diphenylethan-1-ol (2.286). The reaction was performed according to **General Procedure H** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), N, N'-dimethyl-1,2-ethylenediamine (2.3 mg, 0.026 mmol, 0.13 equiv.), iodobutane (73.6 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), palladium acetate (2.2 mg, 0.01 mmol, 0.05 equiv.), Mandyphos M004-1 (**1.44**) (12.6 mg, 0.012 mmol, 0.06 equiv.), copper(I) chloride (9.9 mg, 0.1 mmol, 0.5 equiv.), lithium chloride (8.5 mg, 0.2 mmol, 1 equiv.) and phenyl triflate

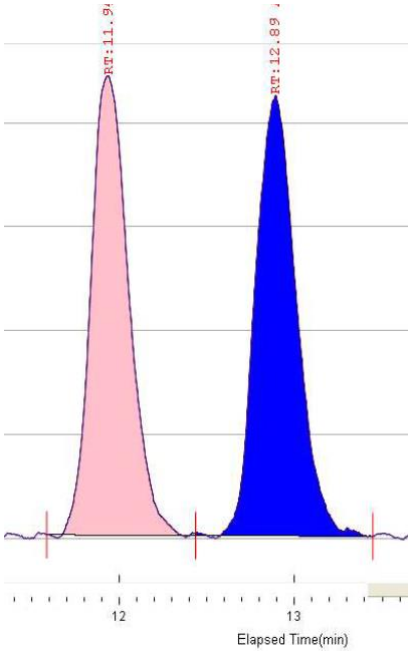
(135.7 mg, 0.6 mmol, 3 equiv.). The crude mixture was purified by column chromatography (Silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as white solid (19.0 mg, 48% yield). All spectra data are in accordance with literature.[63]

Analysis of Stereochemistry

Racemic compound was prepared according to literature.[63] Absolute configuration was assigned by comparing SFC trace with literature.[63]

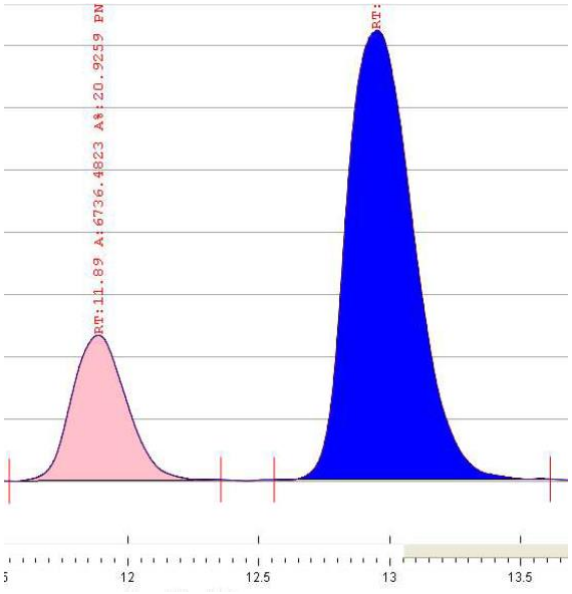
Chiral SFC (Chiracel OD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-290 nm) – analysis of (S)-1,2-diphenylethan-1-ol.

Racemic Material

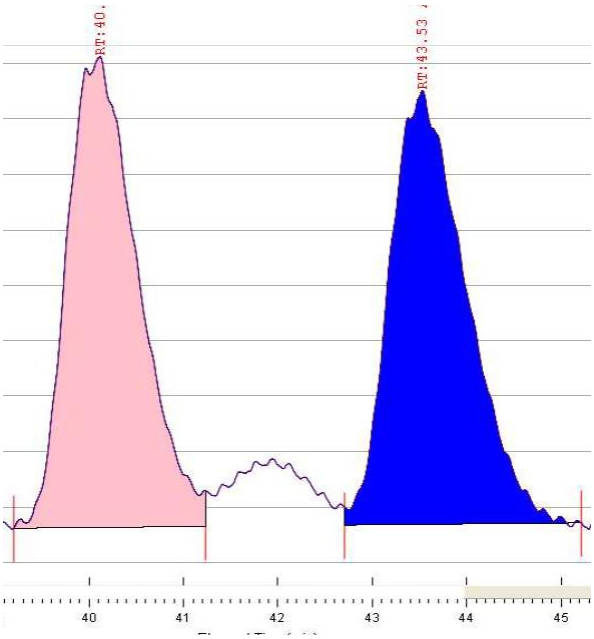


Peak No	% Area	Area	RT (min)
1	49.2528	3320.8574	11.94
2	50.7472	3421.6148	12.89
Total:	100	6742.4722	

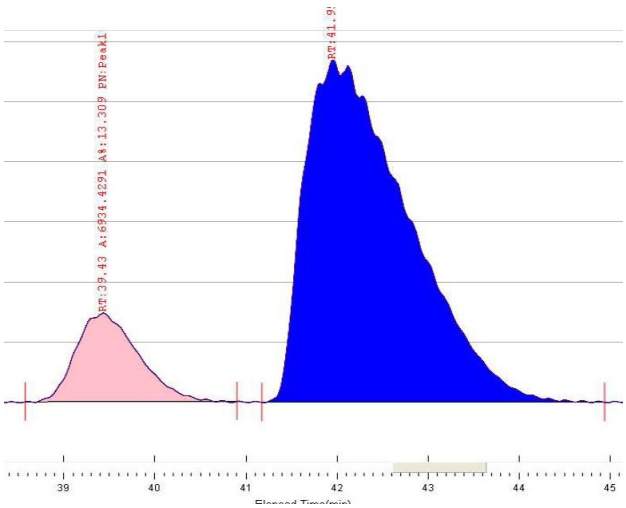
Standard Conditions



Peak No	% Area	Area	RT (min)
1	20.9259	6736.4823	11.89
2	79.0741	25455.5526	12.95
Total:	100	32192.0349	



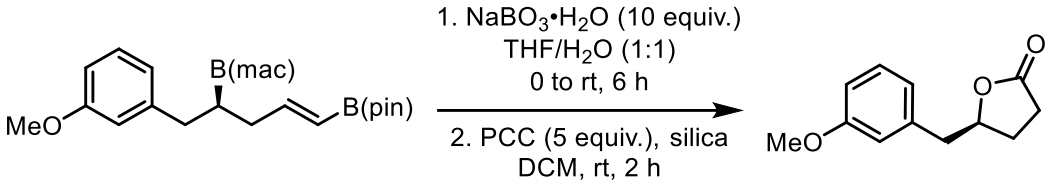
Peak No	% Area	Area	RT (min)
1	50.3094	8981.9292	40.12
2	49.6906	8871.4441	43.53
Total:	100	17853.3733	

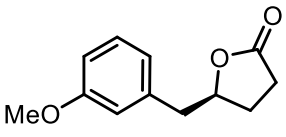


Peak No	% Area	Area	RT (min)
1	13.309	6934.4291	39.43
2	86.691	45168.9136	41.95
Total:	100	52103.3427	

2.7.2.6. Procedures for the Further Transformations of the Products

A. Synthesis of γ-Butyrolactone

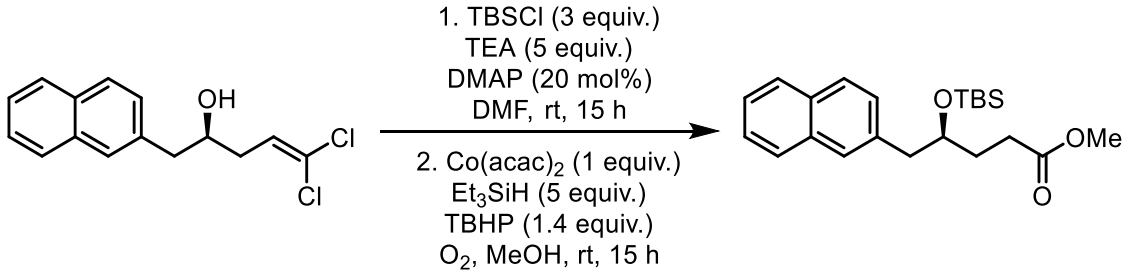


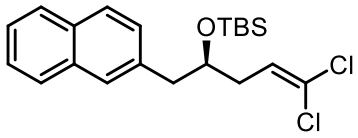


(*S*)-5-(3-methoxybenzyl)dihydrofuran-2(3H)-one (2.213). To a 25 mL round bottom flask equipped with a magnetic stir bar was added 8-((*S,E*)-1-(3-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-en-2-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.201**) (38.7 mg, 0.074 mmol, 1 equiv.), 1 mL THF and 1 mL water. The solution was cooled to 0 °C followed by the addition of sodium perborate monohydrate (73.7 mg, 0.74 mmol, 10 equiv.). The

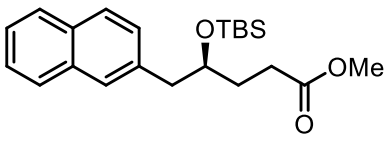
reaction was warmed to room temperature and allowed to stir for 6 h. Then, the reaction was diluted with 1 mL water and extracted three times with Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was then dissolved in 2 mL DCM followed by the addition of 200 mg silica. After that, pyridinium chlorochromate (79.6 mg, 0.37 mmol, 5 equiv.) was added as solid while stirring vigorously. The reaction was allowed to stir at room temperature for 1 hour and quenched by passing through a pad of silica with Et_2O. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, 0-35% ethyl acetate in hexanes, stain in $KMnO_4$) to furnish the titled compound as colorless oil (15.2 mg, 0.049 mmol, 67% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.9 Hz, 1H), 6.84 – 6.75 (m, 3H), 4.77 – 4.70 (m, *J* = 7.3, 6.2 Hz, 1H), 3.80 (s, 3H), 3.05 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.90 (dd, *J* = 14.0, 6.3 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.41 – 2.34 (m, 1H), 2.29 – 2.22 (m, 1H), 2.00 – 1.91 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 160.0, 137.6, 129.8, 121.9, 115.4, 112.5, 80.9, 55.4, 41.5, 28.8, 27.3. IR (neat) ν_{max} 2937 (w), 1998 (w), 1771 (s), 1602 (w), 1585 (w), 1260 (m), 1178 (m), 1039 (m), 918 (w), 782 (w). HRMS (DART) for $C_{12}H_{15}O_3$ $[M+H]^+$: calculated: 207.1016, found: 207.1020.

B. Synthesis of γ-Silyloxy Ester





(*S*)-tert-Butyl((5,5-dichloro-1-(naphthalen-2-yl)pent-4-en-2-yl)oxy)dimethylsilane (2.281). To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (*S*)-5,5-dichloro-1-(naphthalen-2-yl)pent-4-en-2-ol (**2.200**)(21.3 mg, 0.076 mmol, 1 equiv.), 4-dimethylaminopyridine (DMAP) (1.9 mg, 0.015 mmol, 0.2 equiv.), 0.5 mL DMF and triethyl amine (0.05 mL, 0.38 mmol, 5 equiv.). The reaction was cooled to 0 °C followed by the addition of *tert*-butyldimethylsilyl chloride (34.3 mg, 0.23 mmol, 3 equiv.). The reaction was wormed to room temperature and allowed to stir overnight. Upon completion, the reaction was diluted with water and the aqueous layer was extracted twice with Et_2O. The combined organic layer was passed through a silica gel plug and concentrated under vacuum. The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in $KMnO_4$) to furnish the titled compound as colorless oil (27.3 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 3H), 7.66 – 7.60 (m, 1H), 7.52 – 7.39 (m, 2H), 7.32 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.00 (dd, *J* = 7.8, 6.9 Hz, 1H), 4.10 – 4.02 (m, 1H), 2.96 – 2.84 (m, 2H), 2.43 – 2.23 (m, 2H), 0.87 (s, 9H), -0.01 (s, 3H), -0.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 133.7, 132.4, 128.4, 128.3, 128.0, 127.8, 127.7, 126.8, 126.1, 125.5, 121.4, 72.4, 44.2, 37.3, 26.0, 18.2, -4.7, -4.8.

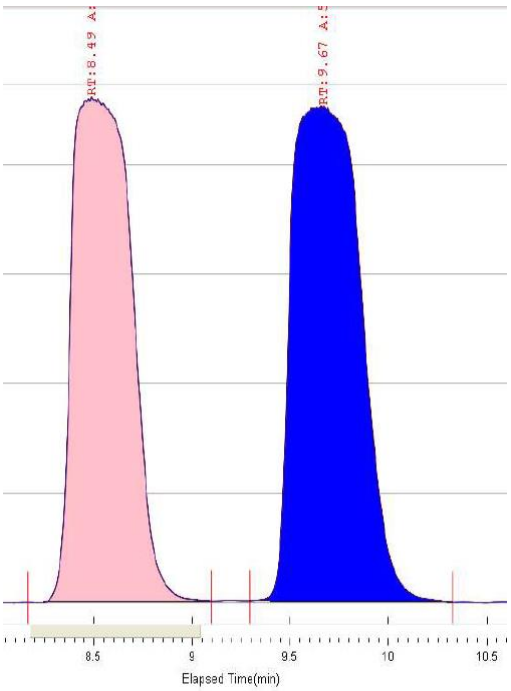


Methyl (*S*)-4-((tert-butyldimethylsilyl)oxy)-5-(naphthalen-2-yl)pentanoate (2.215). To a 25 mL round bottom flask equipped with a magnetic stir bar was added (*S*)-tert-butyl((5,5-dichloro-1-(naphthalen-2-yl)pent-4-en-2-yl)oxy)dimethylsilane (16 mg, 0.040 mmol, 1 equiv.), cobalt(II) acetylacetonate (10.4 mg, 0.040 mmol, 1 equiv.). The flask was sealed with rubber

septa and purged with O_2 for 20 minutes. Then, 1 mL dry MeOH, triethylsilane (23.5 mg, 0.20 mmol, 5 equiv.) and *tert*-butyl hydroperoxide (5.5 M in decane, 0.01 mL, 1.4 equiv.) was added to the reaction via syringe. The solution was allowed to stir at room temperature overnight. Upon completion, the reaction was diluted with Et_2O, passed through a silica gel plug with Et_2O, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in $KMnO_4$) to furnish the desired product as colorless oil (12.3 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 3H), 7.63 – 7.59 (m, 1H), 7.49 – 7.39 (m, 2H), 7.34 – 7.28 (m, 1H), 4.06 – 3.97 (m, 1H), 3.65 (s, 3H), 2.95 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.86 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.51 – 2.33 (m, 2H), 1.87 – 1.78 (m, 1H), 1.78 – 1.68 (m, 1H), 0.87 (s, 9H), 0.00 (s, 3H), -0.16 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 136.4, 133.7, 132.3, 128.32, 128.29, 127.9, 127.8, 127.6, 126.1, 125.4, 72.6, 51.7, 44.2, 31.8, 30.0, 26.0, 18.2, -4.55, -4.60. IR (neat) ν_{max} 3050 (w), 2952 (m), 2928 (m), 2856 (m), 1739 (s), 1436 (w), 1361 (w), 1256 (m), 1085 (m), 836 (s). HRMS (DART) for $C_{22}H_{33}O_3Si$ $[M+H]^+$: calculated: 373.2194, found: 373.2187.

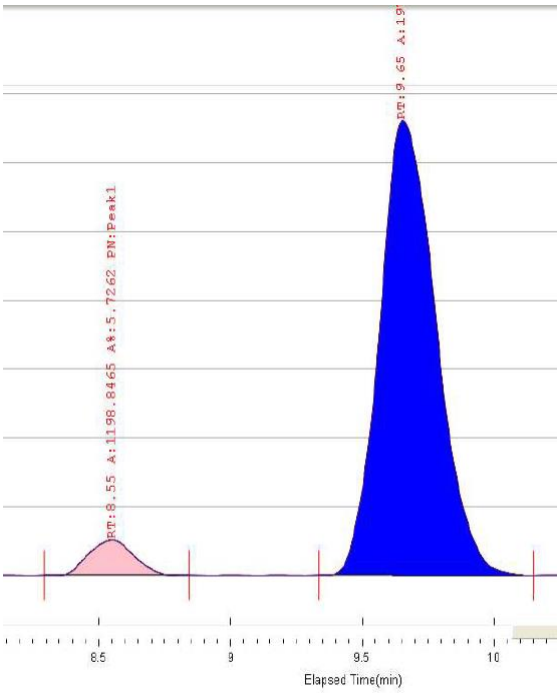
Chiral SFC (Chiracel OJ-H, 3% IPA, 3 mL/min, 100 bar, 40 °C, 200-400 nm) – analysis of Methyl (S)-4-((tert-butyldimethylsilyl)oxy)-5-(naphthalen-2-yl)pentanoate

Racemic Material



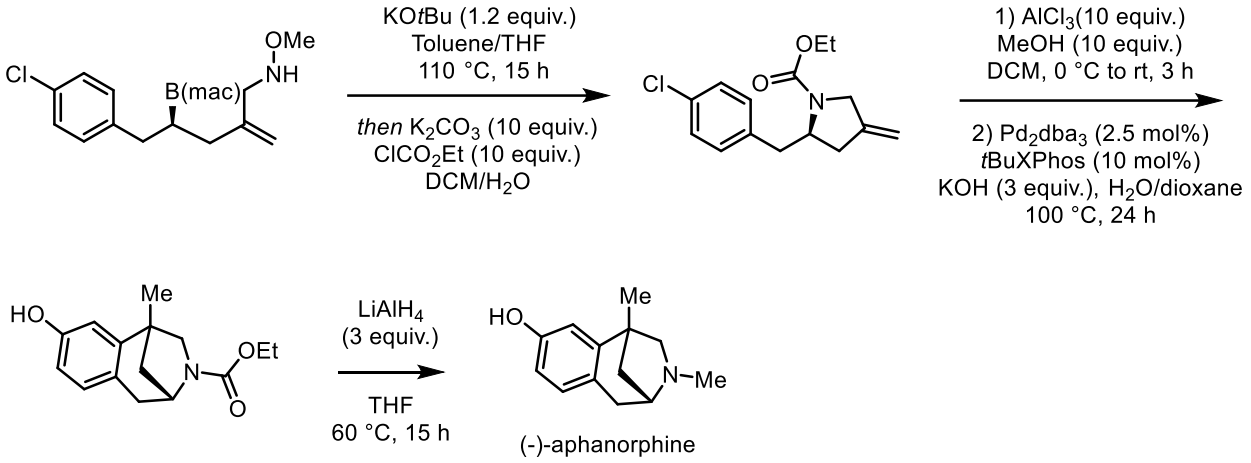
Peak Info			
Peak No	**% Area**	**Area**	**RT (min)**
1	46.5491	48208.738	8.49
2	53.4509	55356.534	9.67
Total:	100	103565.272	

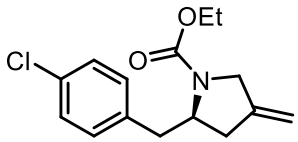
Standard Conditions



Peak Info			
Peak No	**% Area**	**Area**	**RT (min)**
1	5.7262	1198.8465	8.55
2	94.2738	19737.4354	9.65
Total:	100	20936.2819	

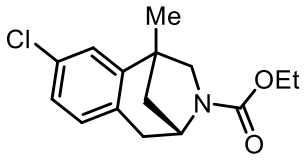
2.7.2.7. Synthesis of (-)-Aphanorphine



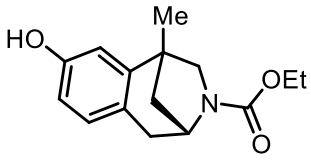


Ethyl (*R*)-2-(4-chlorobenzyl)-4-methylenepyrrolidine-1-carboxylate (2.217). In a glove box under Ar, to an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar was added *N*-((4*R*)-5-(4-chlorophenyl)-4-(6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-2-methylenepentyl)-O-methylhydroxylamine (**2.216**) (160.0 mg, 0.35 mmol, 1 equiv.), potassium *tert*-butoxide (50.5 mg, 0.45 mmol, 1.3 equiv.), 4 mL dry toluene and 0.4 mL dry THF. The vial was sealed with a screw cap (DWK Life Science Kimble^{TM} closures for 20 mL glass and plastic scintillation vials) and removed from the glove box. The solution was heated at 110 °C for 15 hours. After cooled to room temperature, the solvent was removed under reduced pressure. The mixture was dissolved in 4 mL DCM followed by the addition of potassium carbonate (478.9 mg, 3.5 mmol, 10 equiv.) in 4 mL water. The solution was cooled to 0 °C followed by the dropwise addition of ethyl chloroformate (0.33 mL, 3.5 mmol, 10 equiv.). The reaction was warmed to room temperature and allowed to stir for 4 hours. After that, the organic layer was passed through a silica gel plug. The aqueous layer was extracted three times with Et_2O and passed through the silica gel plug. The solvent was removed under reduced pressure and the

crude product was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stained in $KMnO_4$) to furnish the titled compound as yellow oil(53.5 mg, 55% yield). ^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 7.31 – 7.16 (m, 2H), 7.08 (m, 2H), 5.13 – 4.85 (m, 2H), 4.37 – 3.98 (m, 4H), 3.92 – 3.77 (m, 1H), 3.04 (br s, 0.5H), 2.86 (br s, 0.5H), 2.63 – 2.42 (m, 2H), 2.25 (d, J = 15.2 Hz, 1H), 1.34 – 1.09 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 154.8, 137.1, 132.3, 130.9, 128.6, 108.3&108.0, 61.2, 58.7&58.5, 50.40, 39.9&38.9, 37.0&35.9, 30.5&29.8, 14.9. IR (neat) ν_{max} 2978 (w), 2929 (w), 2863 (w), 1699 (s), 1491 (w), 1416 (m), 1381 (m), 1111 (m), 1016 (w), 889 (w). HRMS (DART) for $C_{15}H_{19}ClNO_2$ $[M+H]^+$: calculated: 280.1099, found: 280.1100.

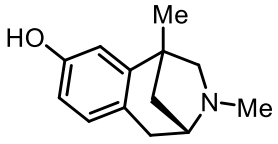


Ethyl (4*R*)-8-chloro-1-methyl-1,2,4,5-tetrahydro-3H-1,4-methanobenzo[d]azepine-3-carboxylate (2.282). In a glove box under Ar, to a flame-dried 100 mL round bottom flask equipped with a magnetic stir bar was added aluminum trichloride (446.8 mg, 3.4 mmol, 15 equiv.). The flask was sealed with a rubber septum and removed from the glove box. Outside the glove box, 10 mL dry DCM was added to the flask under N_2 atmosphere. The slurry was cooled to 0 °C followed by the addition of ethyl (*R*)-2-(4-chlorobenzyl)-4-methylenepyrrolidine-1-carboxylate (62.5 mg, 0.22 mmol, 1 equiv.) in 10 mL DCM and methanol (0.14 mL, 3.4 mmol, 15 equiv.) via syringe. The reaction was warmed to room temperature and allowed to stir for 3 hours. After that, the reaction was quenched by adding 10 mL water. The organic layer was separated and passed through a pad of silica. The aqueous layer was extracted 3 times with DCM and passed through the pad of silica. The combined organic layer was concentrated under reduced pressure and the product obtained was used in the next step without further purification.



Ethyl (4*R*)-8-hydroxy-1-methyl-1,2,4,5-tetrahydro-3H-1,4-methanobenzo[d]azepine-3-carboxylate (2.218). In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added tris(dibenzylideneacetone)dipalladium(0) (5.1 mg, 0.0054 mmol, 0.025 equiv.), potassium hydroxide (37.4 mg, 0.66 mmol, 3 equiv.) and ethyl (4*R*)-8-chloro-1-methyl-1,2,4,5-tetrahydro-3H-1,4-methanobenzo[d]azepine-3-carboxylate (**2.282**) obtained from last step. The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, 0.4 mL 1,4-dioxane and 0.4 mL deionized water was added to the reaction via syringe. The reaction was heated at 100 °C for 24 hours. After that, the reaction was cooled to room temperature and quenched by adding 1 mL 1M HCl solution. The aqueous layer was extracted 3 times with Et_2O, and the combined organic layer was passed through a silica gel plug with Et_2O. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, 0-30% ethyl acetate in hexanes, stain in $KMnO_4$) to furnish the titled compound as yellow solid (29.3 mg, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.03 (br s, 0.5H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.82 (br s, 0.5H), 6.78 (dd, *J* = 21.8, 2.6 Hz, 1H), 6.71 – 6.64 (m, 1H), 4.50 – 4.42 (m, 0.5H), 4.40 – 4.33 (m, 0.5H), 4.16 (q, *J* = 7.1 Hz, 1H), 4.13 – 4.07 (m, 0.5H), 4.07 – 3.98 (m, 0.5H), 3.37 (d, *J* = 9.9 Hz, 1H), 3.24 (t, *J* = 10.1 Hz, 1H), 3.17 – 3.09 (m, 0.5H), 3.06 – 2.98 (m, 0.5H), 2.89 (dt, *J* = 16.7, 3.7 Hz, 1H), 2.03 – 1.83 (m, 2H), 1.47 (s, 1.5H), 1.42 (s, 1.5H), 1.28 (t, *J* = 7.1 Hz, 1.5H), 1.19 (t, *J* = 7.1 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 155.3&155.1, 154.9&154.7, 146.0&145.8, 130.7&130.5, 125.0&124.5, 114.2&114.0, 110.9&110.7, 61.8&61.5, 61.4&61.2, 55.1&55.0, 42.3&41.77, 41.75&40.9, 36.5&35.9, 21.0&20.9, 15.0&14.8. IR (neat) ν_{max} 3301 (br), 2963 (w), 2930 (w),

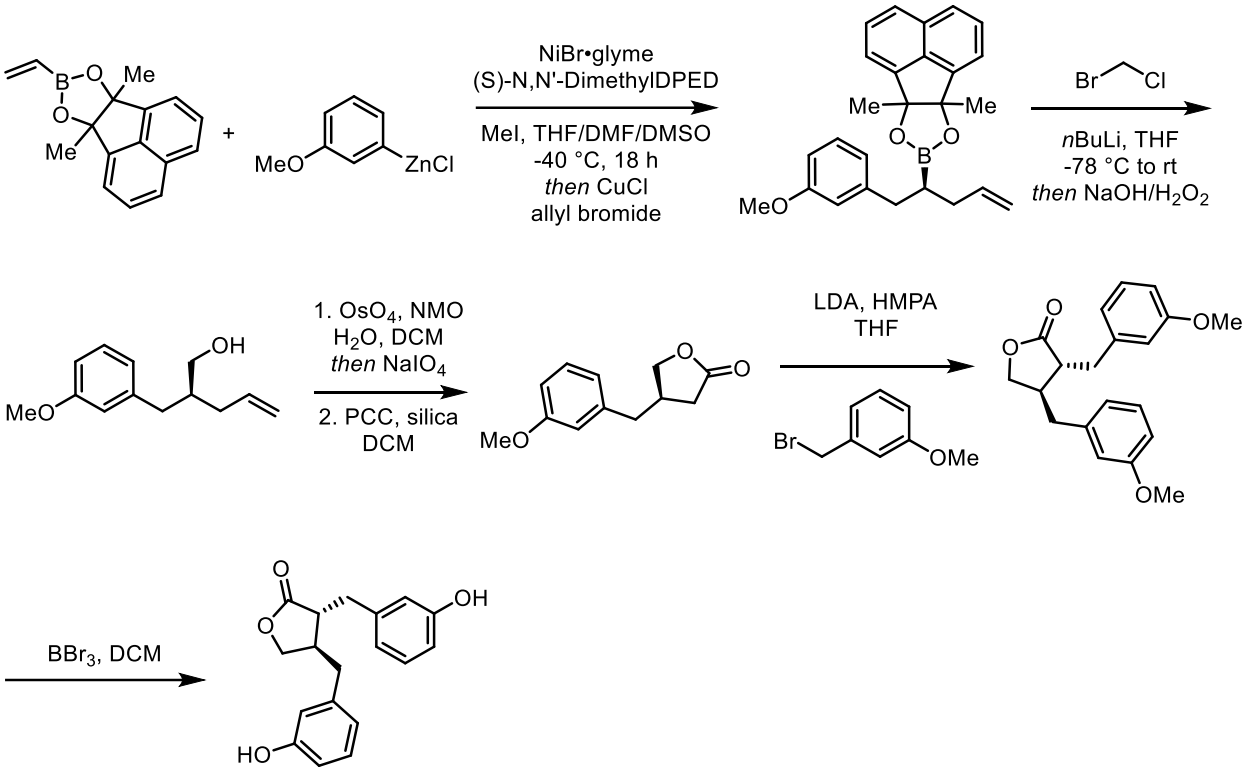
2873 (w), 1666 (s), 1611 (m), 1431 (s), 1383 (m), 1326 (m), 1171 (m), 1102 (m). HRMS (DART) for $C_{15}H_{20}NO_3$ $[M+H]^+$: calculated: 262.1438, found: 262.1445.

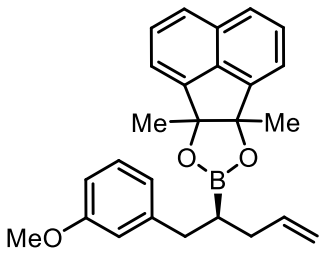


(-)-aphanorphine (2.283). In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added lithium aluminum hydride (12.0 mg, 0.29 mmol, 4 equiv.) and 0.5 mL THF. The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the reaction was cooled to 0 °C followed by the addition of ethyl (4*R*)-8-hydroxy-1-methyl-1,2,4,5-tetrahydro-3H-1,4-methanobenzo[d]azepine-3-carboxylate (21.0 mg, 0.080 mmol, 1 equiv.) in 1 mL THF. The reaction was then heated at 60 °C for 18 hours. After the mixture was cooled to room temperature, the reaction was quenched by carefully adding 1 mL water. The aqueous layer was extracted 3 times with ethyl acetate. The combined organic layers were passed through a plug of celite, dried over sodium sulfate and concentrated under vacuum. The crude product was washed with Et_2O (2 mL × 2) to furnish the titled compound as white solid (12.5 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.1 Hz, 1H), 6.71 – 6.60 (m, 1H), 6.53 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.55 – 3.45 (m, 1H), 3.06 (d, *J* = 16.8 Hz, 1H), 2.95 – 2.83 (m, 2H), 2.82 – 2.72 (m, 1H), 2.52 (s, 3H), 2.05 (dd, *J* = 11.4, 5.8 Hz, 1H), 1.89 (d, *J* = 11.2 Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 147.2, 130.49, 130.47, 114.1, 110.5, 71.1, 62.5, 43.2, 42.1, 41.4, 34.9, 21.4. IR (neat) ν_{max} 3167 (br), 2957 (s), 2932 (s), 2873 (m), 2788 (w), 1610 (s), 1580 (m), 1495 (s), 1449 (s), 1239 (s), 1136 (w), 732 (m). HRMS (DART) for $C_{13}H_{18}NO$ $[M+H]^+$: calculated: 204.1383, found: 204.1379. $[\alpha]^{20}_D$: -16.7 (c = 0.43, MeOH, *l* = 50 mm) {lit[114]. $[\alpha]^{21}_D$: -23.6 (c = 0.20, MeOH, >99% ee)}.

(114) Tamura, O.; Yanagimachi, T.; Kobayashi, T.; Ishibashi, H. *Org. Lett.* **2001,** *3*, 2427–2429.

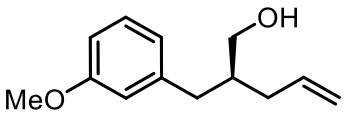
2.7.2.8. Synthesis of (-)-Enterolactone





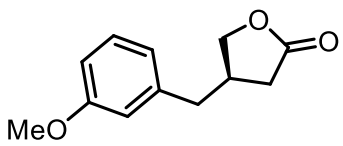
8-((*S*)-1-(3-methoxyphenyl)pent-4-en-2-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (2.219). The reaction was performed according to **General Procedure D** with 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.151**) (50.0 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S*, *2S*)-*N*,*N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (12.4 mg, 0.052 mmol, 0.26 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), 3-methoxyphenylzinc(II) chloride solution (prepared according to **General Procedure B**, 0.4 M in THF, 1 mL, 0.40 mmol, 2 equiv.), allyl bromide (72.6 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was not oxidized but isolated as boronic ester by column

chromatography (silica gel, 0-70% DCM in hexanes, stain in CAM) to furnish the titled compound as colorless oil (44.6 mg, 56% yield). ^{1}H NMR (600 MHz, cdcl$_3$) δ 7.81 – 7.78 (m, 2H), 7.62 – 7.56 (m, 2H), 7.53 (dd, *J* = 7.1, 0.8 Hz, 1H), 7.50 (dd, *J* = 6.9, 0.8 Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.61 – 6.53 (m, 2H), 6.50 – 6.48 (m, 1H), 5.72 – 5.63 (m, 1H), 4.85 – 4.79 (m, 1H), 4.76 – 4.72 (m, 1H), 3.65 (s, 3H), 2.63 (dd, *J* = 13.4, 8.5 Hz, 1H), 2.59 (dd, *J* = 13.4, 7.4 Hz, 1H) , 2.13 – 2.07 (m, 2H), 1.73 (s, 3H), 1.70 (s, 3H), 1.44 – 1.37 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.4, 144.9, 144.9, 143.5, 138.1, 134.8, 131.5, 128.9, 128.56, 128.55, 125.30, 125.27, 121.2, 119.54, 119.53, 115.3, 114.3, 111.2, 92.0, 91.9, 55.1, 36.9, 35.2, 22.2, 22.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.32. IR (neat) ν_{max} 3045 (w), 2974 (w), 2930 (w), 2834 (w), 1601 (m), 1584 (m), 1379 (s), 1312 (m), 1242 (s), 1117 (s), 1178 (s). HRMS (DART) for $C_{26}H_{28}BO_3$ $[M+H]^+$: calculated: 399.2126, found: 399.2127. $[\alpha]^{20}_D$: +4.95 (c = 0.35, $CHCl_3$, *l* = 50 mm).



(*S*)-2-(3-methoxybenzyl)pent-4-en-1-ol (2.220). In a glovebox under Ar atmosphere, to an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar was added 8-((*S*)-1-(3-methoxyphenyl)pent-4-en-2-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (400.0 mg, 1.0 mmol, 1 equiv.) and THF (10 mL). The vial was sealed with rubber septa and removed from glovebox. Then, bromochloromethane (0.20 mL, 3.0 mmol, 3 equiv.) was added to the solution under N_2 and the reaction was cooled to -78 °C followed by the dropwise addition of *n*-butyl lithium (2.61M in Hexanes, 1.15 mL, 3.0 mmol, 3 equiv.). Upon completion, the reaction was slowly wormed to room temperature and allowed to stir overnight. After that, the reaction was cooled to 0 °C and 2 mL sodium hydroxide solution (3M in water) and 2 mL hydrogen peroxide (30% w/w in water) was added under air. The reaction was allowed to stir at room temperature for 1 h. Then, the reaction was diluted with Et_2O (10 mL). The organic layer was separated, and the aqueous layer

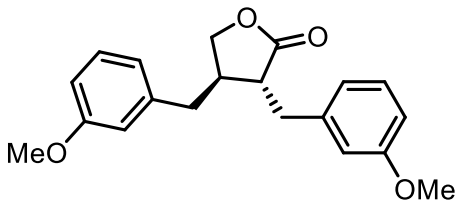
was extracted with Et_2O (10 mL × 2). The combined organic layer was passed through a pad of silica with Et_2O, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-20% ethyl acetate in hexanes, stain in $KMnO_4$) to furnish the titled compound as colorless oil (151 mg, 0.73 mmol, 73% yield). All spectral data are in accordance with the literature.[115] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (td, J = 7.5, 1.0 Hz, 1H), 6.80 – 6.72 (m, 3H), 5.89 – 5.79 (m, 1H), 5.12 – 5.00 (m, 2H), 3.80 (s, 3H), 3.59 – 3.52 (m, 2H), 2.66 – 2.57 (m, 2H), 2.18 – 2.10 (m, 2H), 1.97 – 1.88 (m, 1H), 1.37 (br s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.8, 142.3, 137.0, 129.5, 121.8, 116.8, 115.2, 111.4, 65.0, 55.3, 42.5, 37.5, 35.7.



(*R*)-4-(3-methoxybenzyl)dihydrofuran-2(3H)-one (2.221). To a stirred solution of (*S*)-2-(3-methoxybenzyl)pent-4-en-1-ol (135.0 mg, 0.65 mmol, 1 equiv.), N-methylmorpholine N-oxide (230.0 mg, 1.96 mmol, 3 equiv.) and water (0.35 mL, 19.6 mmol, 30 equiv.) in 5 mL DCM was added osmium (VIII) tetroxide (0.067M in *t*BuOH, 0.5 mL, 0.033 mmol, 0.05 equiv.). The reaction was allowed to stir at room temperature overnight. After the complete consumption of the starting material was confirmed by TLC, sodium periodate (280.0 mg, 1.31 mmol, 2 equiv.) was added and the reaction was allowed to stir for another 30 minutes. Then, the reaction was quenched by adding 2 mL Sat. sodium thiosulfate solution, diluted with brine, and extracted with DCM (10 mL X 2). The combined organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was then dissolved in 10 mL DCM followed by the addition of silica (500 mg) and pyridinium chlorochromate (215.6 mg, 1 mmol, 5 equiv.). The reaction was allowed to stir for 2 hours and quenched by passing through a pad of silica with Et_2O. The solvent was removed under reduced pressure and the crude product was purified by column

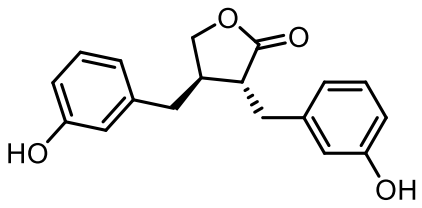
(115) Allais, F.; Pla, T. J. L.; Ducrot, P. *Synthesis* **2011,** *9*, 1456–1464.

chromatography (silica gel, 0-30% ethyl acetate in hexanes, stain in $KMnO_4$) to furnish the titled compound as colorless oil (102.0 mg, 76% yield). All spectral data are in accordance with the literature.[71] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 1H), 6.81 – 6.77 (m, 1H), 6.76 – 6.71 (m, 1H), 6.69 (app t, *J* = 2.1 Hz, 1H), 4.34 (dd, *J* = 9.1, 7.0 Hz, 1H), 4.04 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.80 (s, 3H), 2.92 – 2.81 (m, 1H), 2.83 – 2.69 (m, 2H), 2.65 – 2.57 (m, 1H), 2.34 – 2.25 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.0, 160.1, 140.0, 130.0, 121.1, 114.8, 112.0, 72.8, 55.4, 39.1, 37.2, 34.4.



(3*R*,4*R*)-3,4-bis(3-methoxybenzyl)dihydrofuran-2(3H)-one (2.284). In a glovebox under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added diisopropylamine (50.1 mg, 0.49 mmol, 1.2 equiv.) and 1 mL THF. The vial was sealed with a septum cap and removed from the glove box. Outside the glovebox, *n*-butyllithium (2.55 M in hexanes, 0.19 mL, 0.49 mmol, 1.2 equiv.) was added to the solution dropwise at 0 °C under N2 atmosphere. The reaction was allowed to stir at 0 °C for 10 min and cooled to -78 °C. (*R*)-4-(3-methoxybenzyl)dihydrofuran-2(3H)-one (85 mg, 0.41 mmol, 1 equiv.) in 1 mL THF was added dropwise and the reaction was allowed to stir at -78 °C for 1 hour. After that, 3-methoxybenzyl bromide (165.7 mg, 0.82 mmol, 2 equiv.) in 1 mL THF was added dropwise followed by HMPA (0.07 mL, 0.41 mmol, 1 equiv.). The reaction was warmed to -50 °C and allowed to stir for another 2 hours. Then, the reaction was gradually warmed to -20 °C and quenched by adding 1 mL Sat. ammonium chloride solution. The mixture was warmed to room temperature and diluted with Et_2O. The organic layer was passed through a pad of silica and the aqueous layer was extracted twice with Et_2O and passed through the pad of silica. The solvent was removed under reduced pressure and the crude product was purified by

column chromatography (silica gel, 0-30% ethyl acetate in hexanes, stain in $KMnO_4$) to furnish the titled compound as colorless oil (115.5 mg, 86% yield). The diastereomeric ratio of the product was determined to be >20:1 by ^1H NMR analysis. All spectral data are in accordance with the literature.[71] ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 2H), 6.83 – 6.71 (m, 4H), 6.63 – 6.57 (m, 1H), 6.53 (dd, *J* = 2.6, 1.6 Hz, 1H), 4.11 (dd, *J* = 9.1, 7.2 Hz, 1H), 3.86 (dd, *J* = 9.1, 7.8 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.06 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.92 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.66 – 2.57 (m, 2H), 2.56 – 2.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 160.0, 139.7, 139.5, 129.92, 129.86, 121.8, 121.1, 115.0, 114.7, 112.6, 112.1, 71.4, 55.4, 55.3, 46.6, 41.5, 38.8, 35.4.

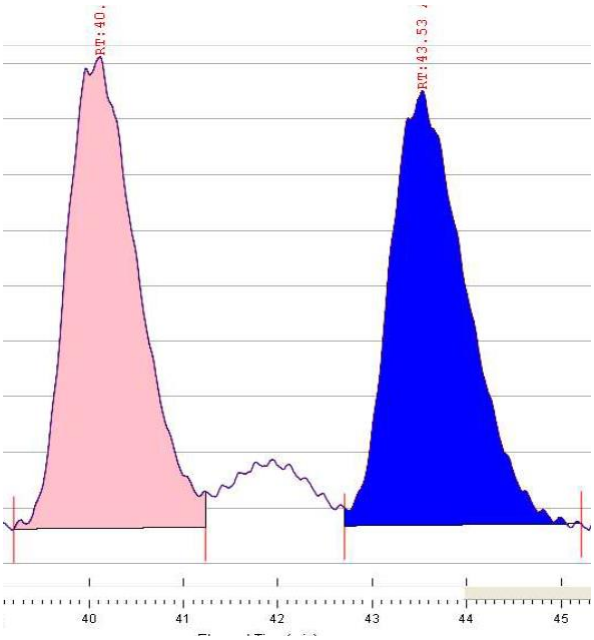


(-)-enterolactone (2.285). In a glovebox under Ar atmosphere, to an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar was added (3*R*,4*R*)-3,4-bis(3-methoxybenzyl)dihydrofuran-2(3H)-one (120.0 mg, 0.37 mmol, 1 equiv.) and 8 mL dry DCM. The vial was sealed with a rubber septum and removed from the glove box. The solution was cooled to 0 °C followed by the dropwise addition of boron tribromide (1M in DCM, 1.47 mL, 1.47 mmol, 4 equiv.). The reaction was allowed to stir at 0 °C for 1 hour and at -20 °C overnight. Then, the reaction was quenched by adding 10 mL water. The organic layer was separated, and the aqueous layer was extracted with DCM (10 mL × 2). The combined organic layer was passed through a pad of silica and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (silica gel, 0-30% ethyl acetate in DCM, stain in CAM) to furnish the titled compound as white solid (83.0 mg, 75% yield). ^1H NMR (600 MHz, $CDCl_3$) δ 7.15 (dt, *J* = 18.5, 7.8 Hz, 2H), 6.75 – 6.68 (m, 3H), 6.66 – 6.57 (m, 2H), 6.49 – 6.45 (m, 1H), 5.16 (s, 1H), 5.09 (s, 1H), 4.13 (dd, *J* =

9.2, 7.0 Hz, 1H), 3.89 – 3.84 (m, 1H), 2.99 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.90 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.62 – 2.56 (m, 2H), 2.54 – 2.46 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 178.9, 156.0, 140.0, 139.6, 130.18, 130.16, 122.0, 121.4, 116.4, 115.8, 114.2, 114.0, 71.5, 46.5, 41.2, 38.5, 34.9. IR (neat) ν_{max} 3360 (br), 2929 (w), 1743 (s), 1588 (s), 1488 (w), 1456 (m), 1354 (w), 1233 (m), 1158 (s), 1015 (m), 785 (m). HRMS (DART) for $C_{18}H_{19}O_4$ $[M+H]^+$: calculated: 299.1278, found: 299.1283. $[\alpha]^{20}_D$: -32.6 (c = 0.71, $CHCl_3$, *l* = 50 mm) {lit[71]. $[\alpha]^{25}_D$: -38.4 (c = 0.2, $CHCl_3$)}.

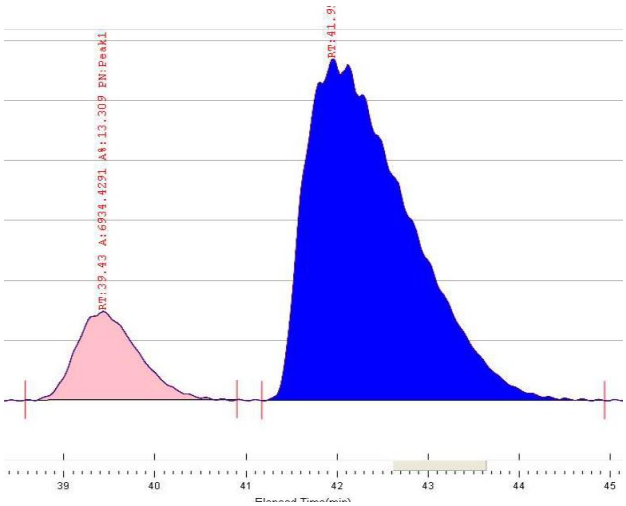
Chiral SFC (Chiracel OJ-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (-)-enterolactone

Racemic Material



Peak No	% Area	Area	RT (min)
1	50.3094	8981.9292	40.12
2	49.6906	8871.4441	43.53
Total:	100	17853.3733	

Standard Conditions

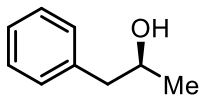


Peak No	% Area	Area	RT (min)
1	13.309	6934.4291	39.43
2	86.691	45168.9136	41.95
Total:	100	52103.3427	

2.7.2.9. Procedures for the reactions in Section 2.5.6.

A. Procedures for the reactions in Scheme 2.34

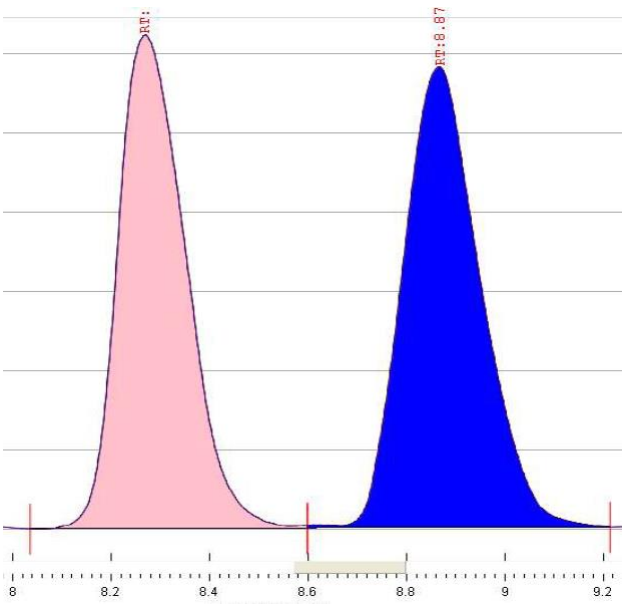
For first equation, the reaction was performed according to **General Procedure D**. 1-phenylpropan-2-ol (**2.222**) was isolated by column chromatography (silica gel, 0-10% EtOAc/Hexanes, stain in CAM) as colorless oil (2.7 mg, 10% yield).



1-phenylpropan-2-ol (**2.222**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.20 (m, 3H), 4.07 – 3.99 (m, 1H), 2.80 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.70 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.25 (dd, *J* = 6.2, 1.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 129.6, 128.8, 126.7, 69.1, 46.0, 23.0.

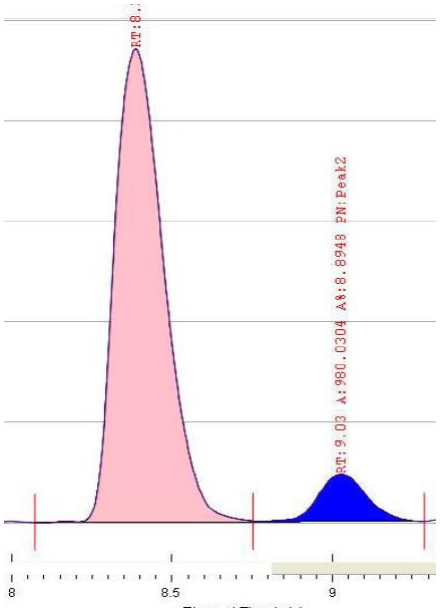
Chiral SFC (Chiracel OJ-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-phenylpropan-2-ol

Racemic Material



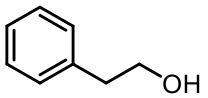
Peak No	% Area	Area	RT (min)
1	48.4241	5952.9161	8.27
2	51.5759	6340.3838	8.87
Total:	100	12293.2999	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	91.1052	10037.929	8.39
2	8.8948	980.0304	9.03
Total:	100	11017.9594	

For second equation, the reaction was performed according to **General Procedure D**, except that instead of trapping with allyl bromide, the reaction was quenched by adding 1 mL saturated ammonium chloride solution. Then, the reaction was wormed to room temperature and allowed to stir for another 30 minutes before passing through a silica gel plug. 1-phenylpropan-2-ol (**2.222**) (colorless oil, 3.3 mg, 12% yield) and 2-phenylethan-1-ol (**2.224**) (colorless oil, 15.6 mg, 64% yield) were isolated by column chromatography (silica gel, 0-25% EtOAc/Hexanes, stain in CAM).

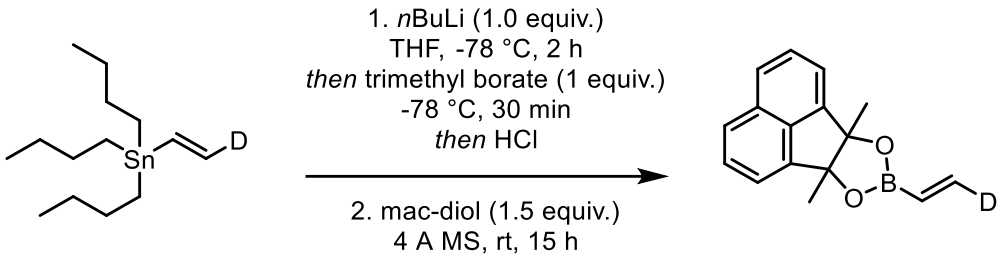


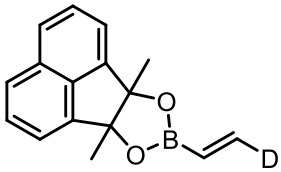
2-phenylethan-1-ol (**2.224**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 1H), 7.28 – 7.20 (m, 2H), 3.87 (t, *J* = 6.6 Hz, 1H), 2.88 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 129.2, 128.8, 126.7, 63.9, 39.4.

For eq 3, the reaction was performed according to **General Procedure D**, except that instead of trapping with allyl bromide, methyl iodide (283.9 mg, 2.0 mmol, 10 equiv.) was added and the reaction was allowed to stir for another 15 hours at room temperature. After that, the reaction was quenched by adding 1 mL saturated ammonium chloride solution and allowed to stir for another 30 minutes. 1-phenylpropan-2-ol (**2.222**) (colorless oil, 3.0 mg, 11% yield) and 2-phenylethan-1-ol (**2.224**) (colorless oil, 13.9 mg, 57% yield) were isolated by column chromatography (silica gel, 0-20% EtOAc/Hexanes, stain in CAM).

2.7.2.10. Deuterium Labeling Experiments

A. Synthesis of D-labeled vinyl B(mac)

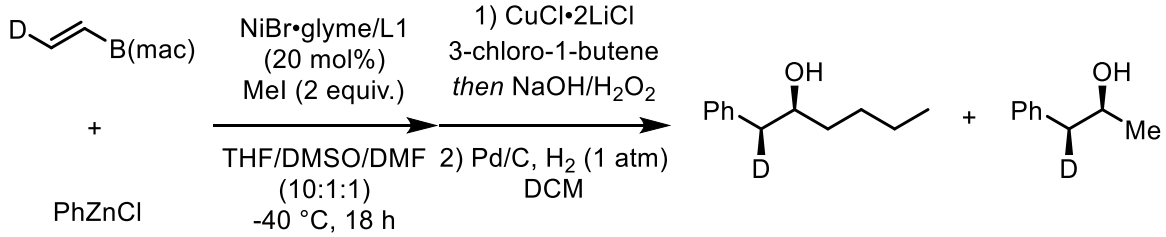


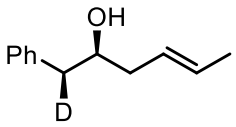


(*E*)-6b,9a-dimethyl-8-(vinyl-2-*d*)-6b,9a-dihydroacenaphtho [1,2-d][1,3,2]dioxaborole (2.227). In a glove box under Ar atmosphere, to an oven-dried 250mL round bottom flask equipped with a magnetic stir bar was added (*E*)-tributyl(vinyl-2-*d*)stannane (prepared according to literature)[63] (1.6 g, 2.0 mmol, 1 equiv.), 20 mL THF and the flask was sealed with a rubber septum and removed from the glove box. Outside the glove box, the solution was cooled to -78 °C followed by the dropwise addition of *n*-butyl lithium solution (2.61 M in hexanes, 0.77 mL, 2.0 mmol, 1 equiv.) under N_2. Upon completion, the reaction was allowed to stir for 2 hours at -78 °C before trimethyl borate (0.23 mL, 2.0 mmol, 1 equiv.) was added to the reaction in one portion. The reaction was allowed to stir for another 30 minutes at -78 °C. Then, the reaction was quenched with 20 mL 1 M aqueous HCl solution, warmed to room temperature and allowed to stir for 15 minutes. The aqueous layer was extracted with Et_2O (20 mL × 3). The combined organic layer was dried over sodium sulfate and added to a 250 mL round bottom flask containing a magnetic stir bar, 1,2-dimethylacenaphthylene-1,2-diol (646.6 mg, 3.0 mmol, 1.5 equiv.) and 4 A molecular sieves (1 g) under N_2. The reaction was allowed to stir at room temperature overnight. After that, the mixture was passed through a pad of silica with Et_2O and concentrated under reduced pressure. The tin reagents were removed by column chromatography (silica gel, 0-5% ethyl acetate in hexanes, stain in $KMnO_4$). The mixture obtained was further purified by column chromatography (silica gel, 0-50% toluene in hexanes, stain in $KMnO_4$) to furnish the desired product as white

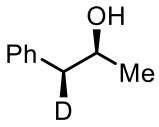
solid (311.3 mg, 62% yield). The diastereomeric ratio of the compound was determined to be 90:10 E/Z by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.0 Hz, 2H), 7.66 – 7.59 (m, 4H), 6.14 (d, *J* = 19.8 Hz, 1H), 5.84 (d, *J* = 19.8 Hz, 1H), 1.84 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 138.4 – 136.1 (m), 134.9, 131.5, 128.6, 125.4, 119.6, 92.1, 22.2. ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.62. IR (neat) ν_{max} 3029 (w), 2991 (w), 2975 (w), 2931 (w), 2247 (w), 1595 (m), 1380 (m), 1344 (s), 1327 (s), 1224 (m), 1117 (m), 1076 (m), 1006 (m). HRMS (DART) for $C_{16}H_{15}DBO_2$ $[M+H]^+$: calculated: 252.1306, found: 252.1311.

B. Procedures for the reactions in Scheme 2.53



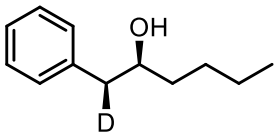


(*1S,2S*)-1-phenylpropan-1-*d*-2-ol (2.287). The reaction was performed according to **General Procedure D** with (*E*)-6b,9a-dimethyl-8-(vinyl-2-*d*)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (50.2 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (56.8 mg, 0.40 mmol, 2 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), 3-chloro-1-butene (54.3 mg, 0.60 mmol, 3 equiv.), copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (20.9 mg, 59% yield, 87:13 dr, 4:1 E/Z). ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 7.35 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 5.61 – 5.54 (m, 1H), 5.53 – 5.43 (m, 1H), 3.83 (dt, *J* = 7.8, 5.0 Hz, 1H), 2.85 – 2.75 (m, 1H), 2.35 – 2.22 (m, 1H), 2.19 – 2.10 (m, 1H), 1.71 (app dq, *J* = 6.3, 1.3 Hz, 3H).



(*1S,2S*)-1-phenylpropan-1-*d*-2-ol (2.229). The titled compound was isolated from the reaction described above by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (2.5 mg,

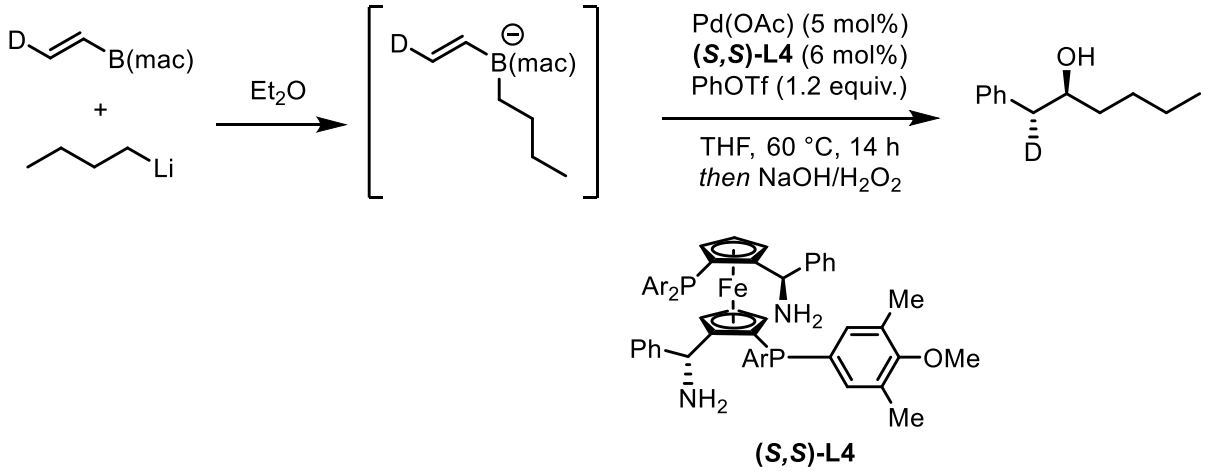
9% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.26 – 7.20 (m, 3H), 4.07 – 3.97 (m, 1H), 2.81 – 2.74 (m, 1H, PhC**H**D), 1.25 (d, *J* = 6.2 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 129.6, 128.8, 126.7, 77.5, 77.2, 77.0, 69.0, 45.8 – 45.5 (m, Ph**C**HD), 23.0. The stereochemistry was determined by comparing ^{1}H NMR spectrum with the literature.[116]

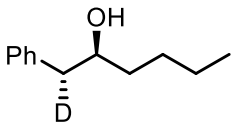


(*1S,2S*)-1-phenylhexan-1-*d*-2-ol (2.228). To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (*1S,2S*)-1-phenylpropan-1-d-2-ol (18.90 mg, 0.11 mmol, 1 equiv.), Pd/C (20 mg) and DCM (2 mL). H_2 gas was bubbled through the solution for 10 min and the solution was allowed to stir under H_2 atmosphere (balloon) for 3 hours at room temperature. After that, the solution was passed through a plug of silica gel with Et_2O and concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (17.3 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.26 – 7.20 (m, 3H), 3.87 – 3.77 (m, 1H), 2.87 – 2.80 (m, 1H, PhC**H**D), 1.61 – 1.28 (m, 6H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 129.6, 128.7, 126.6, 72.8, 44.2 – 43.7 (m, Ph**C**HD), 36.7, 28.1, 22.9, 14.3. IR (neat) ν_{max} 3402 (br), 3028 (w), 2956 (m), 2929 (s), 2859 (w), 1495 (w), 1451 (w), 1243 (w), 1076 (w), 699 (s). HRMS (DART) for $C_{12}H_{16}D$ $[M+H-H_2O]^+$: calculated: 162.1388, found: 162.1389.

The stereochemistry was determined to be *syn* by comparing ^{1}H NMR spectrum with authenitc (*1R,2S*)-1-phenylhexan-1-*d*-2-ol synthesized by the following procedure:

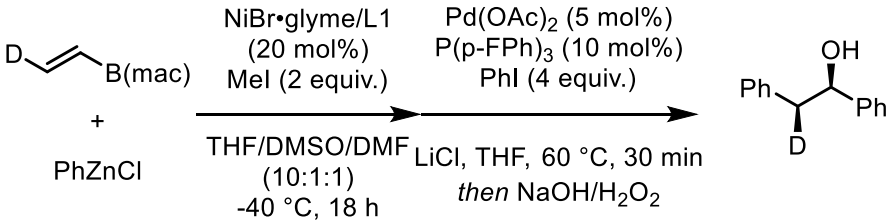
(116) Lee, Y. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009,** *131*, 3160–3161.

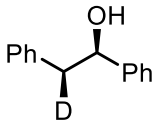




(*1R,2S*)-1-phenylhexan-1-*d*-2-ol (*anti*-2.228). The titled compound was synthesized according to literature[63]. To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added (*E*)-6b,9a-dimethyl-8-(vinyl-2-*d*)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (25.1 mg, 0.10 mmol, 1 equiv.) and diethyl ether (0.2 mL), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0 ℃ followed by the dropwise addition of *n*-butyllithium (2.55 M in hexanes, 0.04 mL, 0.1 mmol, 1 equiv.). The reaction vial was warmed to room temperature and allowed to stir for 30 minutes. Then, the solvent was carefully removed under reduced pressure, and the reaction vial was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stirbar in the glovebox was added palladium(II) acetate (1.1 mg, 0.005 mmol, 0.05 equiv.), **(*S,S*)-L4** (6.3 mg, 0.006 mmol, 0.06 equiv.), and THF (0.2 mL). The $Pd(OAc)_2$/**(*S,S*)-L4** solution was allowed to stir for 20 minutes at room temperature. Then the $Pd(OAc)_2$/**(*S,S*)-L4** solution was transferred into the reaction vial, followed by THF (0.3 mL), and phenyl triflate (27.1 mg, 0.12 mmol, 1.2 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 60 ℃ for 14 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel

plug with diethyl ether, and concentrated under reduced pressure. The crude mixture was dissolved in THF (2 mL) followed by the addition of 1 mL 3 M NaOH and 1 mL hydrogen peroxide solution (30% w/w in water). The reaction mixture was warmed to room temperature and allowed to stir for 30 minutes. The reaction mixture was diluted with Et_2O, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were passed through a silica gel plug and concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (11.0 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 3.86 – 3.77 (m, 1H), 2.68 – 2.59 (m, 1H, PhC**H**D), 1.56 – 1.30 (m, 6H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 129.6, 128.7, 126.6, 72.9, 44.1 – 43.7 (m, Ph**C**HD), 36.7, 28.1, 22.9, 14.3. IR (neat) ν_{max} 3402 (br), 3028 (w), 2956 (m), 2929 (s), 2859 (w), 1495 (w), 1451 (w), 1243 (w), 1076 (w), 699 (s). HRMS (DART) for $C_{12}H_{16}D$ [M+H-H_2O]$^+$: calculated: 162.1388, found: 162.1389.





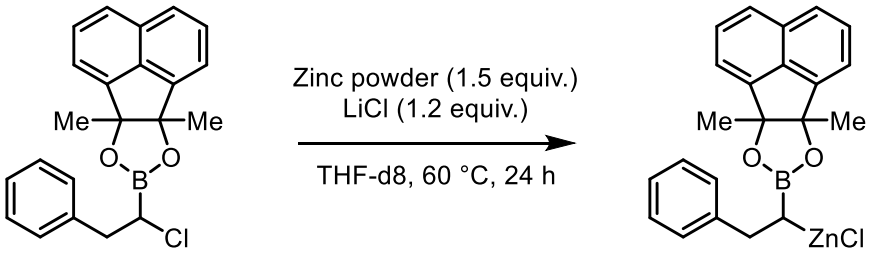
(*1R,2S*)-1,2-diphenylethan-2-*d*-1-ol (2.230). The reaction was performed according to **General Procedure E** with (*E*)-6b,9a-dimethyl-8-(vinyl-2-*d*)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (50.2 mg, 0.20 mmol, 1 equiv.), nickel(II) bromide ethylene glycol dimethyl ether complex (12.3 mg, 0.040 mmol, 0.2 equiv.), (*1S, 2S*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine (9.6 mg, 0.040 mmol, 0.2 equiv.), iodomethane (28.4 mg, 0.20 mmol, 1 equiv.), phenylzinc(II) chloride solution (prepared according to **General Procedure A**) (0.4 M in THF, 1 mL, 0.4 mmol, 2 equiv.), palladium acetate (2.3 mg, 0.01 mmol,

0.05 equiv.), tris(4-fluorophenyl)phosphine (6.3 mg, 0.02 mmol, 0.1 equiv.) and iodobenzene (163.3 mg, 0.80 mmol, 4 equiv.). The crude mixture was purified by column chromatography (silica gel, 0-10% ethyl acetate in hexanes, stain in CAM) to furnish the titled compound as colorless oil (17.1 mg, 43% yield, 85:15 dr). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.33 – 7.27 (m, 3H), 7.25 – 7.18 (m, 3H), 4.90 (d, *J* = 4.8 Hz, 1H), 3.08 – 3.02 (m, 1H, PhC**H**D), 1.97 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 138.2, 129.7, 128.7, 128.6, 127.8, 126.8, 126.1, 75.5, 46.1 – 45.7 (m, Ph**C**HD). The stereochemistry was determined by comparing ^{1}H NMR spectrum with the literature.[117]

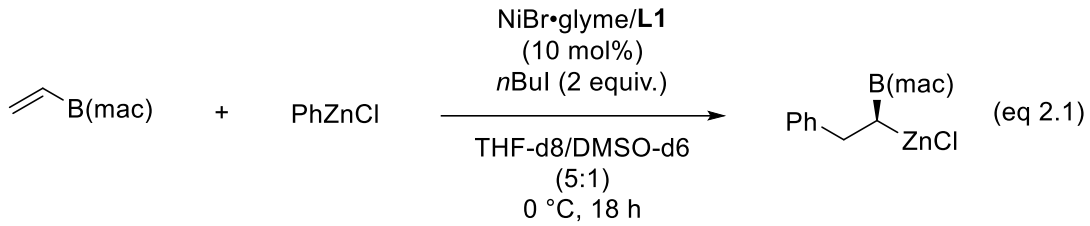
(117) Sagae, T.; Ogawa, S.; Furukawa, N. *Tetrahedron Lett.* **1993,** *34*, 4043–4046.

C. Procedures for monitoring the epimerization of 2.261 by ^{1}H NMR

^{1}H NMR spectrum of α-borylzinc reagent synthesized by zinc insertion was obtained by the following procedure:



In a glovebox under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added 8-(1-chloro-2-phenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (465 mg, 1.28 mmol, 1 equiv.), lithium chloride (65.2 mg, 1.54 mmol, 1.2 equiv.), zinc powder (125.8 mg, 1.92 mmol, 1.5 equiv.) and 2 mL THF-d8. The vial was sealed with a polypropylene cap and removed from the glovebox. The solution was heated at 60 °C for 24 hours. After that, the solution was taken into the glovebox and 0.5 mL solution was transferred to an oven-dried NMR tube. The NMR tube was sealed with a polyethylene cap and electrical tape and removed from the glovebox. ^{1}H NMR spectrum was then collected at room temperature. After that, 0.2 mL DMF-d7 and 0.2 mL DMSO-d6 were added to the 2-dram vial and allowed to stir for 3 hours at room temperature (Figure 2.1a). ^{1}H NMR spectrum was collected at room temperature (Figure 2.1b).

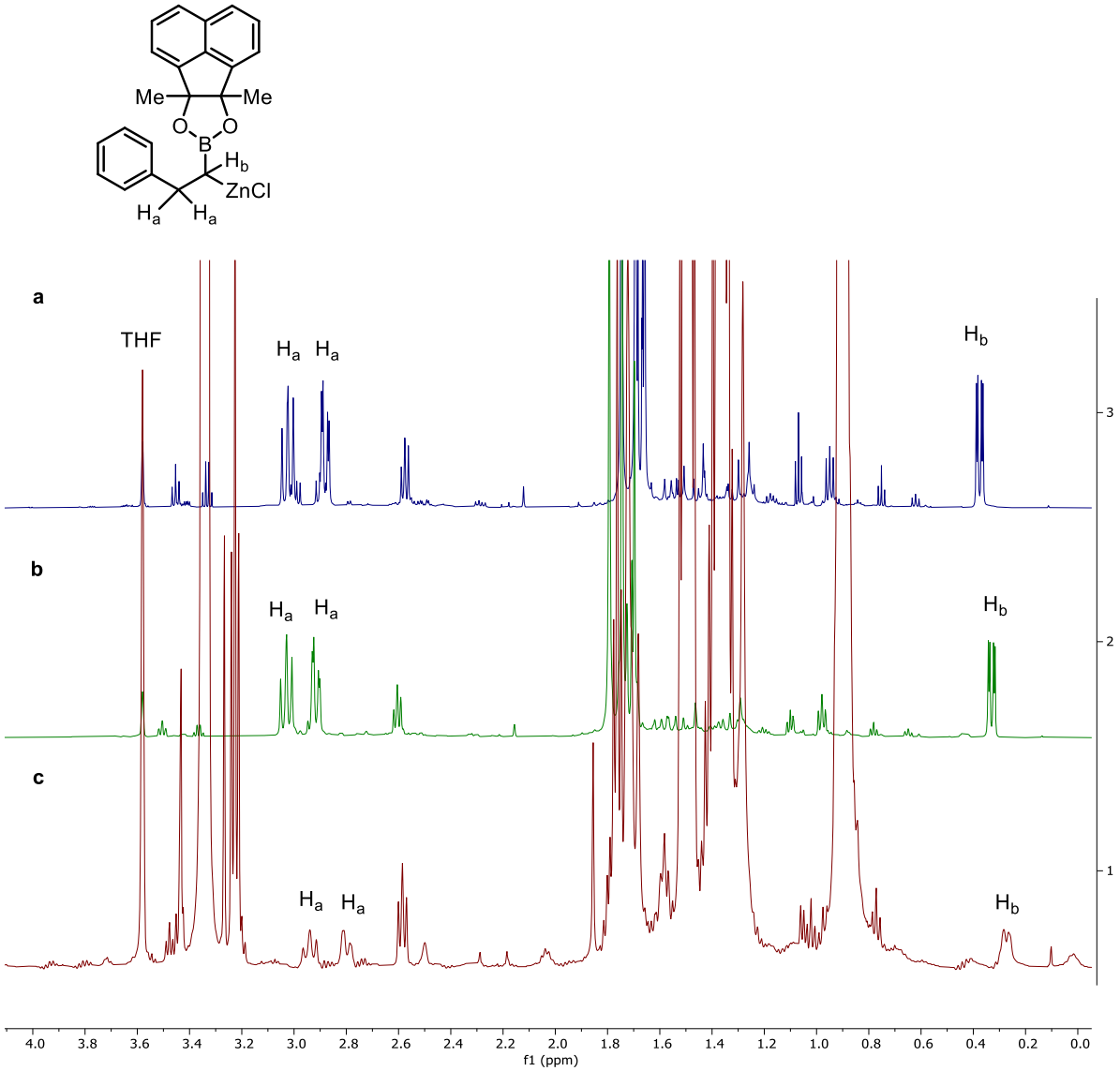


(eq 2.1)

The ^{1}H NMR spectrum of a carbozincation reaction run at 0 °C in THF-d8/ DMSO-d6 (5:1) was collected by the following procedure:

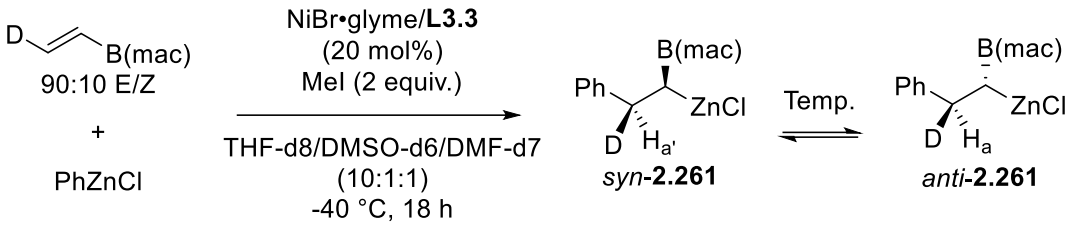
In a glove box under Ar atmosphere, to an oven-dried 2-dram vial equipped with a magnetic stir bar was added nickel(II) bromide ethylene glycol dimethyl ether complex (6.2 mg, 0.020 mmol, 0.1 equiv.), (*1S*, *2S*)-N,N'-dimethyl-1,2-diphenyl-1,2-ethylenediamine (6.3 mg, 0.026 mmol, 0.13 equiv.), 6b,9a-dimethyl-8-vinyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (50.0 mg, 0.20 mmol, 1 equiv.) and 1 mL THF. The mixture was allowed to stir for 5 minutes to obtain a homogenous solution. Then, 0.4 mL DMSO was added and allowed to stir for 30 minutes followed by the addition of iodobutane (73.8 mg, 0.40 mmol, 2 equiv.). The vial was sealed with a septum cap and removed from the glove box. Outside the glove box, the reaction was cooled to 0 °C under N_2 and 1.0 mL phenylzinc(II) chloride solution (0.4 M in THF, 0.40 mmol, 2 equiv., prepared according to **General Procedure A**) was added. The vial was taped and allowed to stir for 18 hours at 0 °C. After that, the reaction was warmed to room temperature and taken into a glovebox under Ar. 0.5 mL solution of the reaction was transferred to an oven-dried NMR tube. The NMR tube was sealed with a polyethylene cap and electrical tape and removed from the glovebox. ^{1}H NMR spectrum was then collected at room temperature (Figure 2.1c).

Figure 2.1. ^{1}H NMR spectra of α-borylzinc reagents



* The spectra are referenced by the THF peak at δ 3.58 ppm. (a) ^{1}H NMR spectrum of α-borylzinc reagents generated from zinc insertion in THF-d8. (b) ^{1}H NMR spectrum of α-borylzinc reagents generated from zinc insertion in THF-d8/DMSO-d6/DMF-d7. (c) ^{1}H NMR spectrum of the reaction described in eq 2.1.

Those results indicate the chemical shifts of the protons of α-borylzinc reagents can be slightly influenced by other components of the solution.

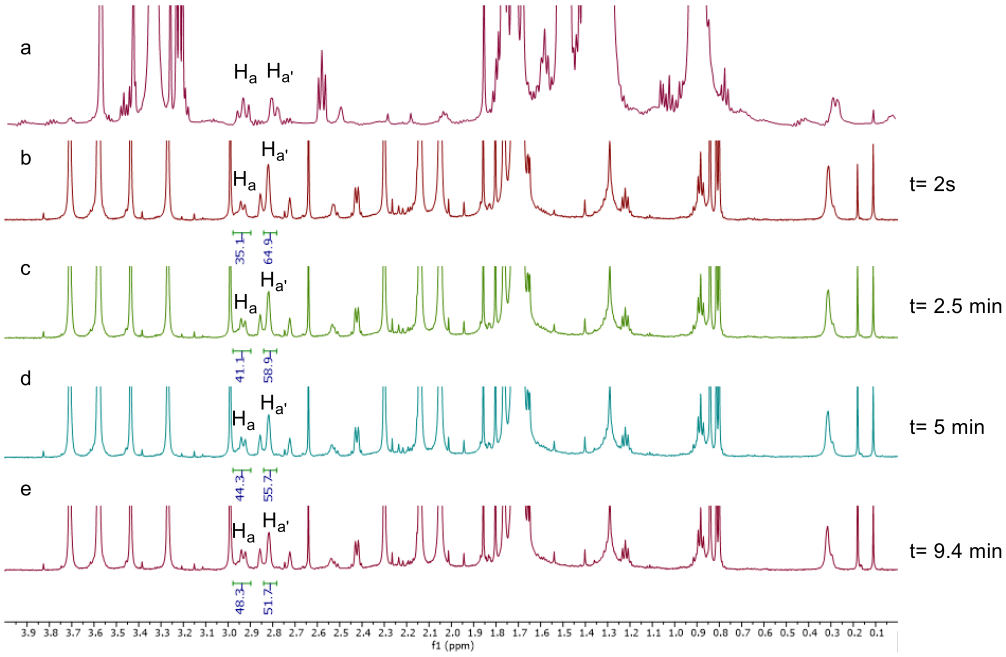


The monitor of the epimerization of **2.261** at different temperatures was accomplished by the following procedures:

The carbozincation reaction was performed according to **General Procedure D** employing THF-d8, DMSO-d6 and DMF-d7 as the solvent. After stirring for 18 hours, 0.5 mL of the reaction solution was transferred via syringe to an oven-dried NMR tube, which is sealed with a rubber septum, taped, purged with dry N_2, and precooled to -40 °C with a cold bath (acetone with individual pieces of dry ice). ^{1}H NMR spectra were then collected every X minute during Y hours in which X and Y were dependent on the temperatures.

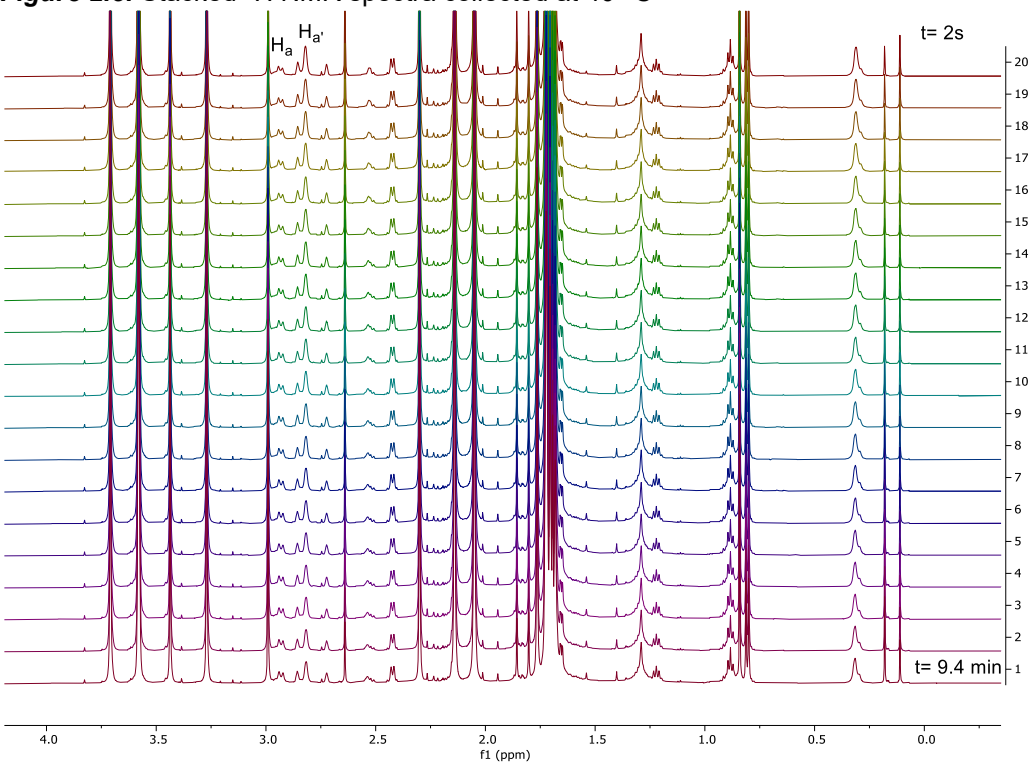
For T= 40 °C, ^{1}H NMR was collected every 30 seconds for 10 minutes (See Figure 2.2 for representative spectra and integration of the diastereotopic protons and Figure 2.3 for stacked ^{1}H NMR spectra collected at 40 °C).

Figure 2.2. Representative spectra and integration of the diastereotopic protons



*The spectra are referenced by the THF peak at δ 3.58 ppm.

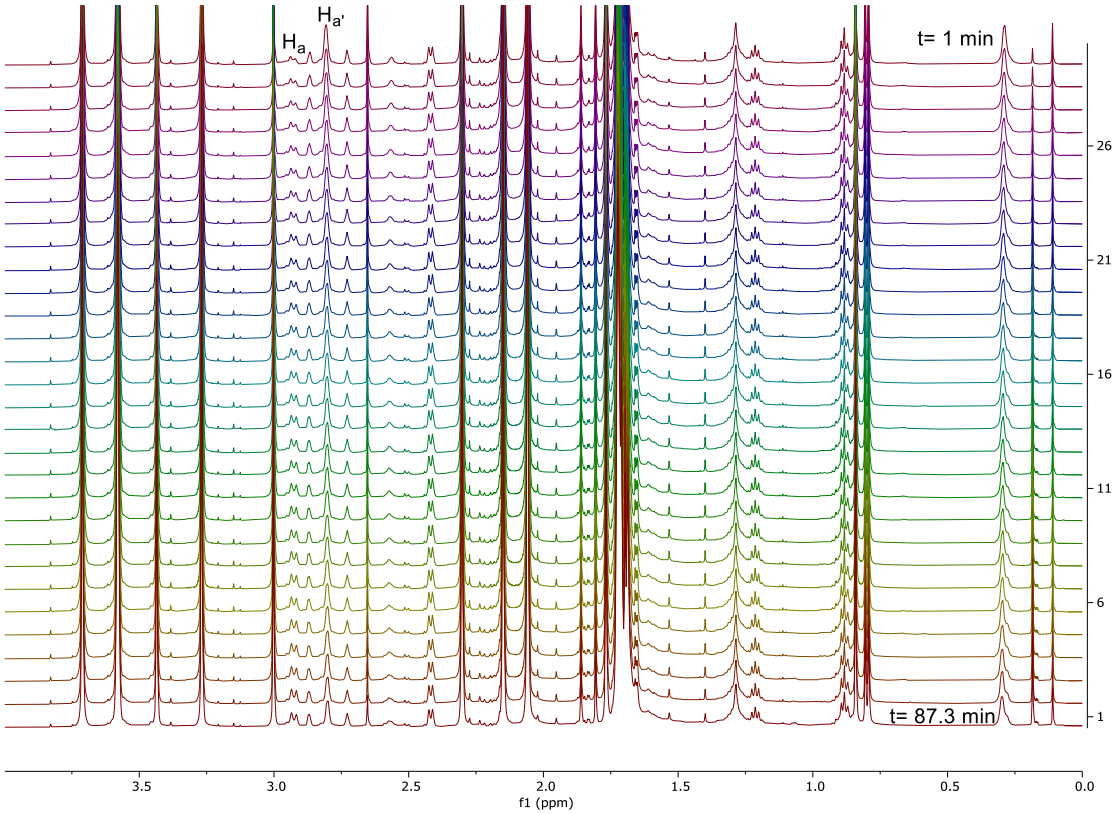
Figure 2.3. Stacked ^{1}H NMR spectra collected at 40 °C



*The spectra are referenced by the THF peak at δ 3.58 ppm.

For T= 25 °C, ^{1}H NMR was collected every 3 minutes for 1.5 hours (Figure 2.4).

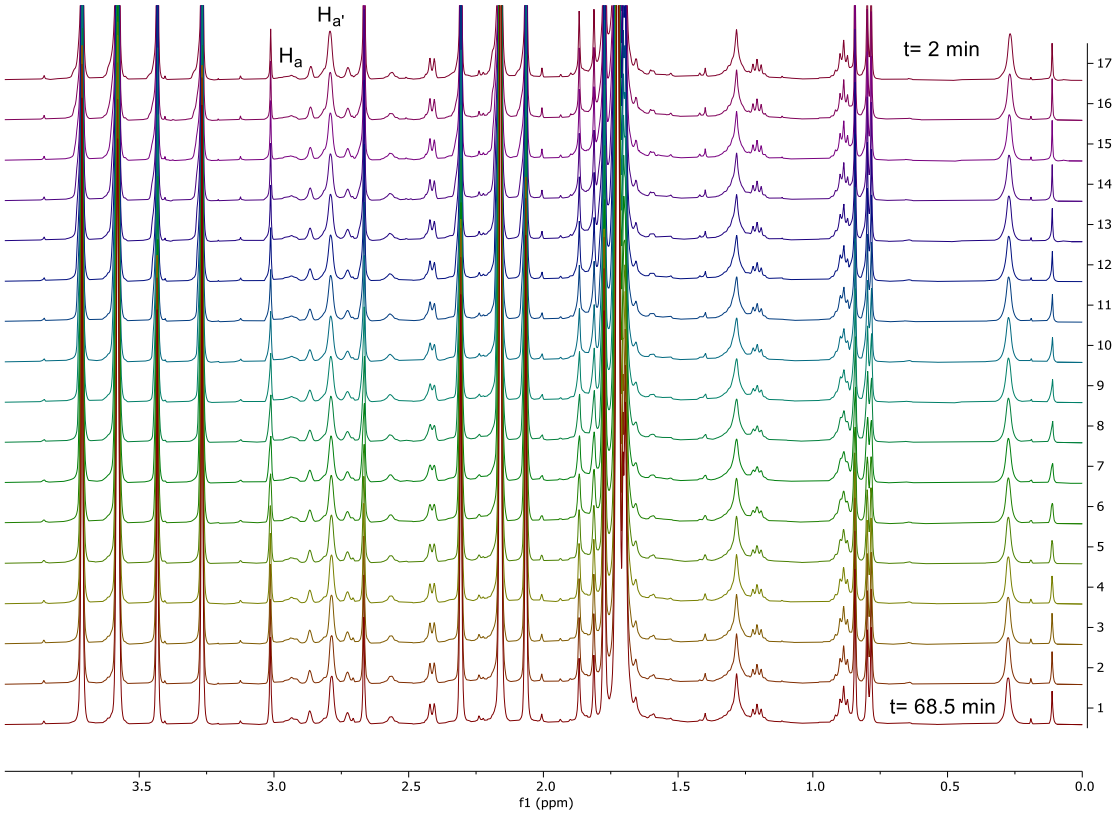
Figure 2.4. Stacked ^{1}H NMR spectra collected at 25 °C



*The spectra are referenced by the THF peak at δ 3.58 ppm.

For T= 5 °C, ^{1}H NMR was collected every 4 minutes for 70 minutes (Figure 2.5).

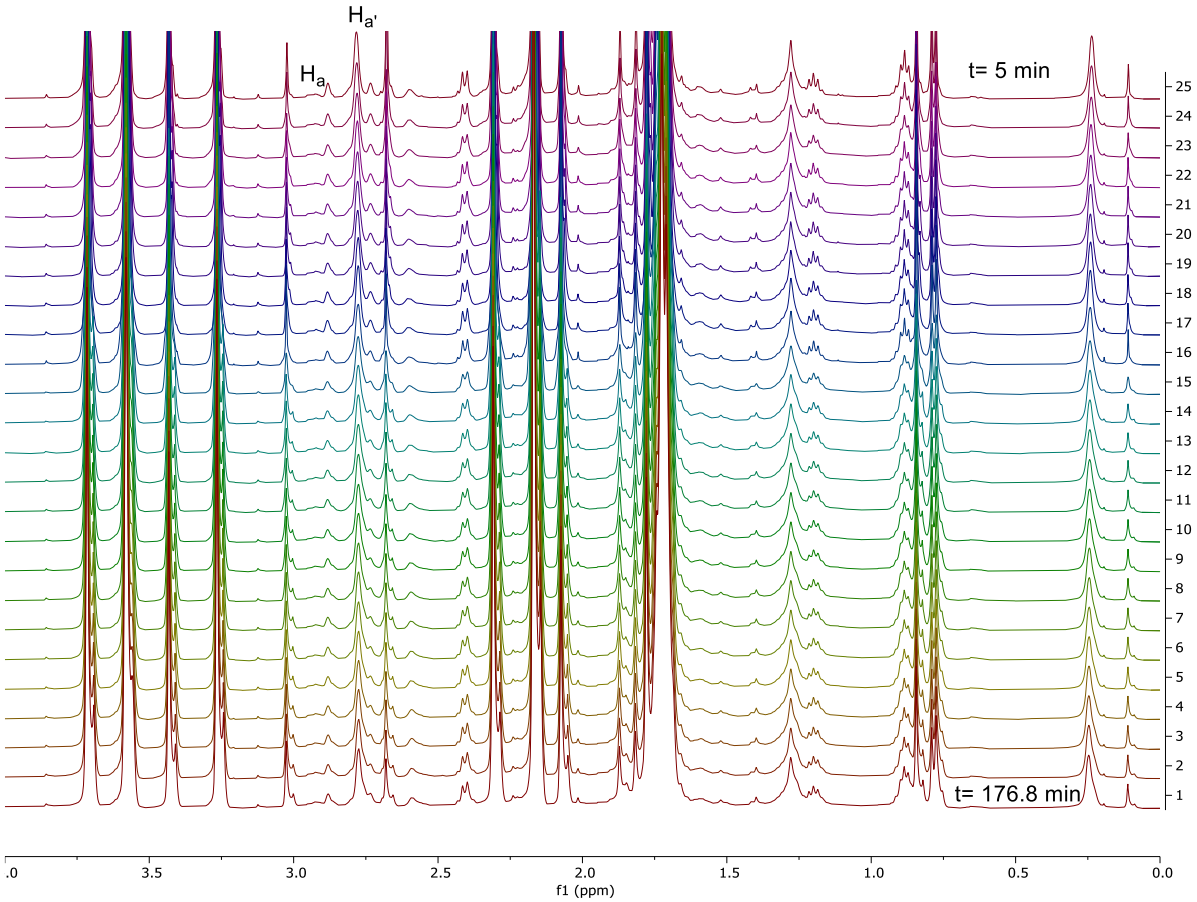
Figure 2.5. Stacked ^{1}H NMR spectra collected at 5 °C



*The spectra are referenced by the THF peak at δ 3.58 ppm.

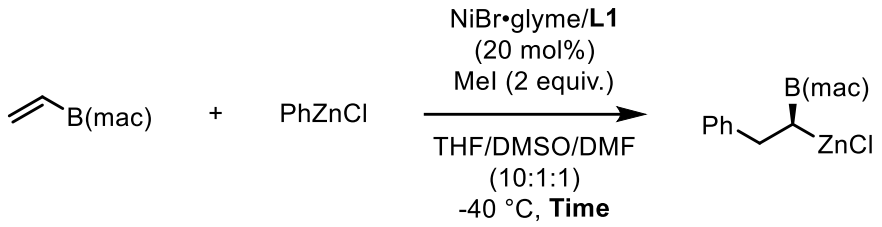
For T= -10 °C, ^{1}H NMR was collected every 7 minutes for 3 hours (Figure 2.6).

Figure 2.6. Stacked ^{1}H NMR spectra collected at -10 °C



*The spectra are referenced by the THF peak at δ 3.58 ppm.

2.8.2.11. Electron Paramagnetic Resonance (EPR) Experiments.



The carbozincation reaction was performed according to **General Procedure D** and allowed to stir at -40 °C for certain amount of time before 0.35 mL *or* 0.4 mL solution of the reaction was transferred via syringe to an oven dried EPR tube which was sealed with a rubber septum, taped, purged with dry N_2, and precooled to -78 °C with a dry ice/ acetone bath. (***Note:*** *The syringe used was wrapped by aluminum foil and put into a freezer at -40 °C overnight before used in the experiment. This is to prevent the warmup of the solution during the transfer to the EPR tube, which would cause the decomposition of active catalyst. The aluminum foil is to prevent moisture.*) Then, the sample in the EPR tube was frozen by liquid nitrogen and the EPR tube was vacuumed. To the rest of the solution was added allylbromide (72.6 mg, 0.60 mmol, 3 equiv.) and a 0.5 mL THF solution of copper(I) chloride (9.9 mg, 0.10 mmol, 0.5 equiv.) and lithium chloride (8.5 mg, 0.20 mmol, 1 equiv.). The reaction was allowed to stir for additional 3 hours at -40 °C, quenched with 1 mL saturated aqueous ammonium chloride solution and warmed to room temperature. The organic layer was diluted with Et_2O and separated. The aqueous layer was extracted twice with Et_2O. The combined organic solution was passed through a silica gel plug with Et_2O and the solvent was removed under reduced pressure. ^1H NMR was taken with 1,3,5-trimethoxybenzene as an internal standard to determine the yield of the reaction.

X-band EPR spectrum of the sample was collected at 10 K with $\nu = 9.4$ GHz at 0.002 mW power and a modulation amplitude of 4 G (Figure 2.7).

Figure 2.7. X-band EPR Spectrum of the Reaction and Simulated Spectrum

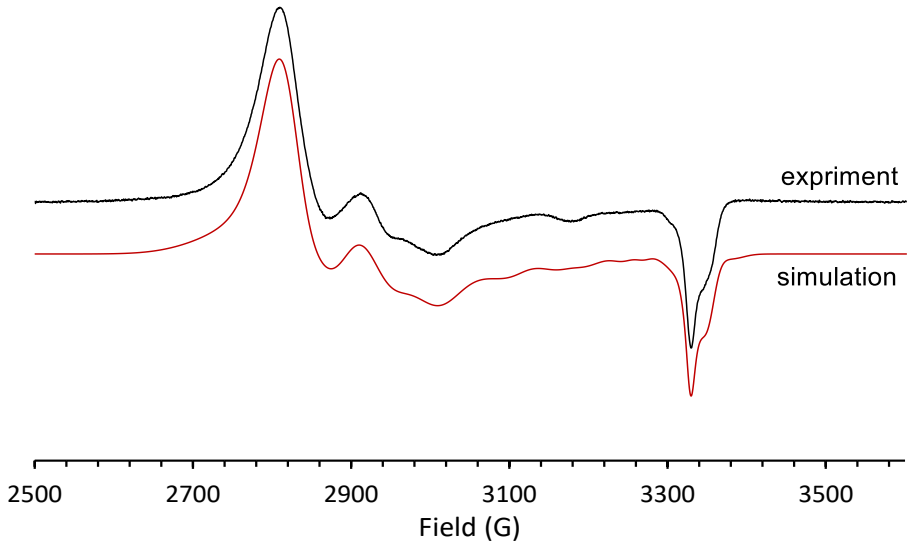
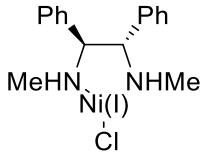
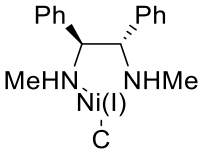


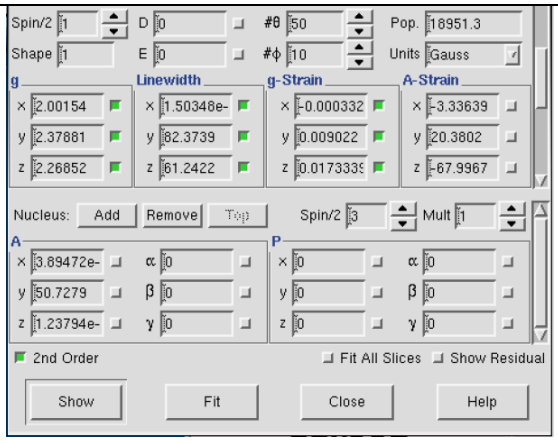
Table 2.3. Parameters Used for the Simulated Spectrum in Figure 2.7.



2.243



2.244



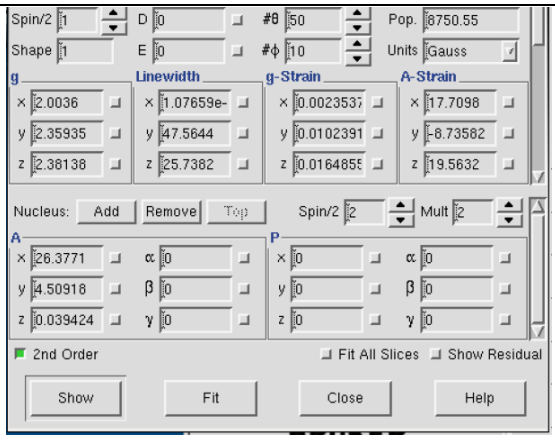
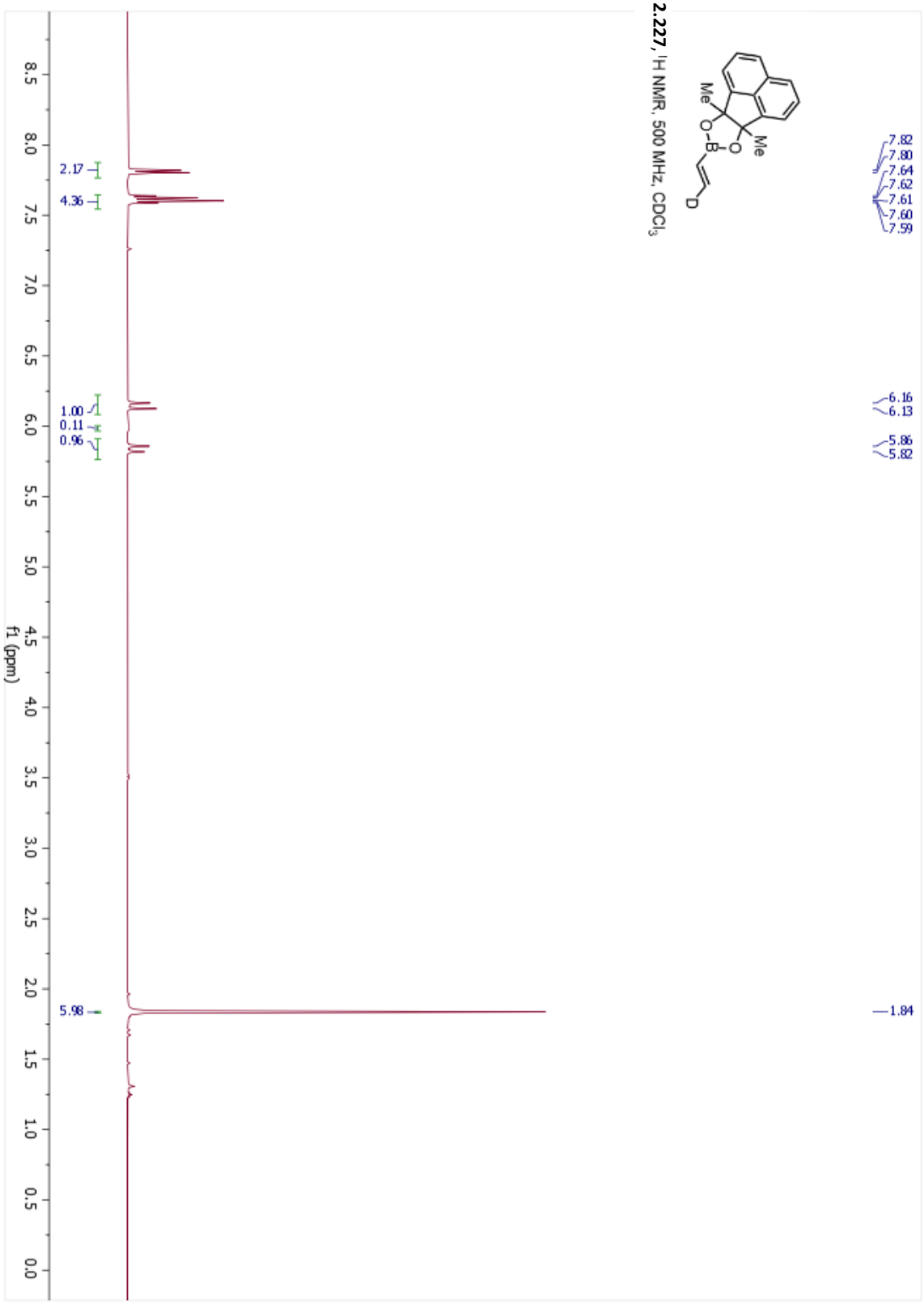


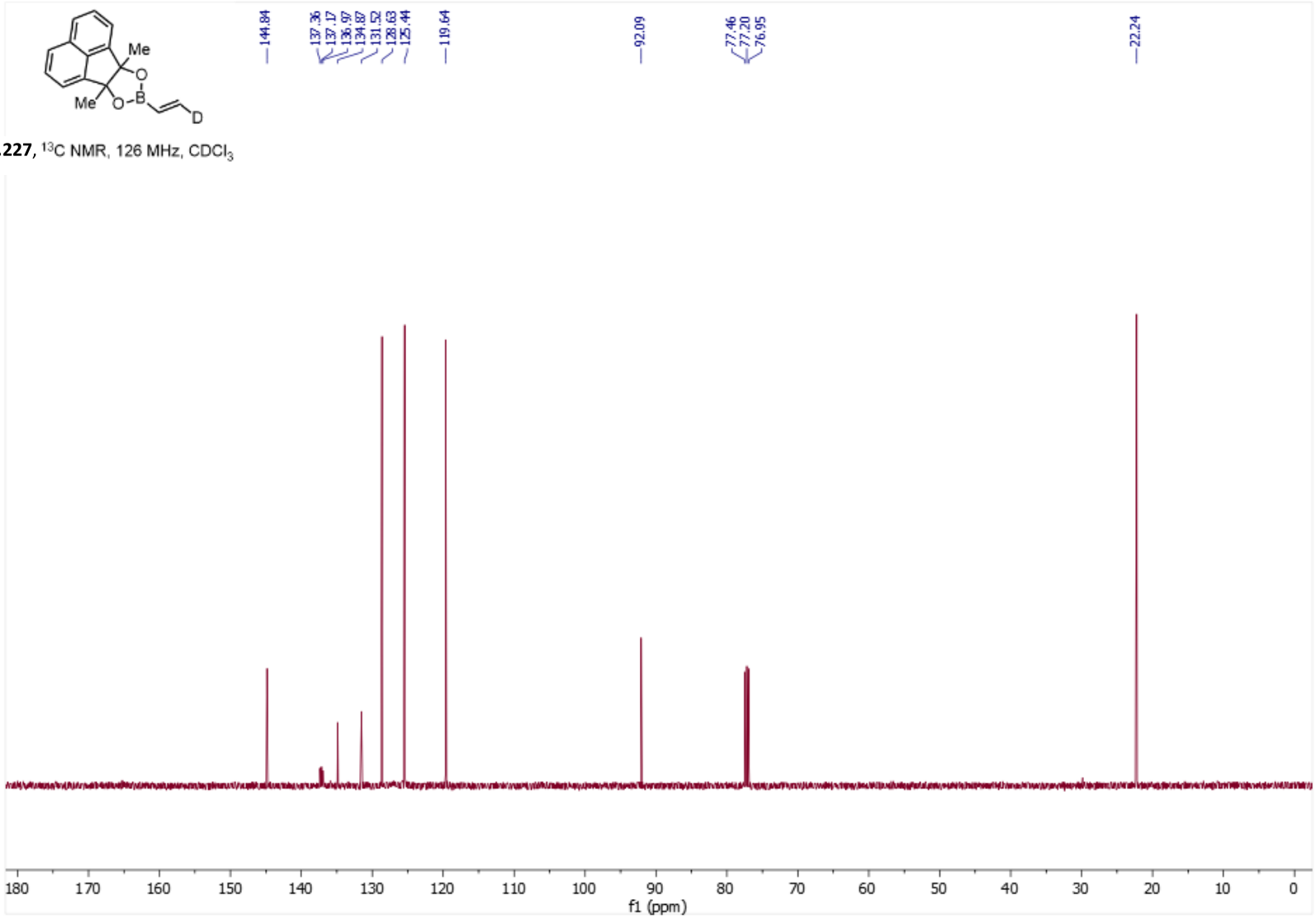
Figure 2.8. Data for the Quantification of Ni(I) Species and the Yield of the Reactions.

entry	Reaction Time (min)	Volumn of solution taken(mL)	Total Electronic Spins ($\times 10^{17}$)	Amount of Ni(I) species ($\times 10^{17}$)	Percentage of the Ni(I) species over total amount of [Ni] (%)	yield (%)
1	10	0.4	3.92	1.96	48.8	1
2	60	0.4	6.12	3.06	76.2	5
3	120	0.4	6.60	3.30	82.2	13
4	180	0.4	7.54	3.77	93.9	20
5	240	0.35	5.80	2.90	82.5	29
6	300	0.35	5.52	2.76	78.5	35
7	360	0.35	4.26	2.13	60.6	42
8	600	0.35	2.86	1.43	40.7	51
9	720	0.4	2.88	1.44	35.9	50
10	840	0.4	2.18	1.09	27.2	54
11	960	0.4	1.14	0.57	14.2	59
12	1080	0.4	1.10	0.55	13.7	59

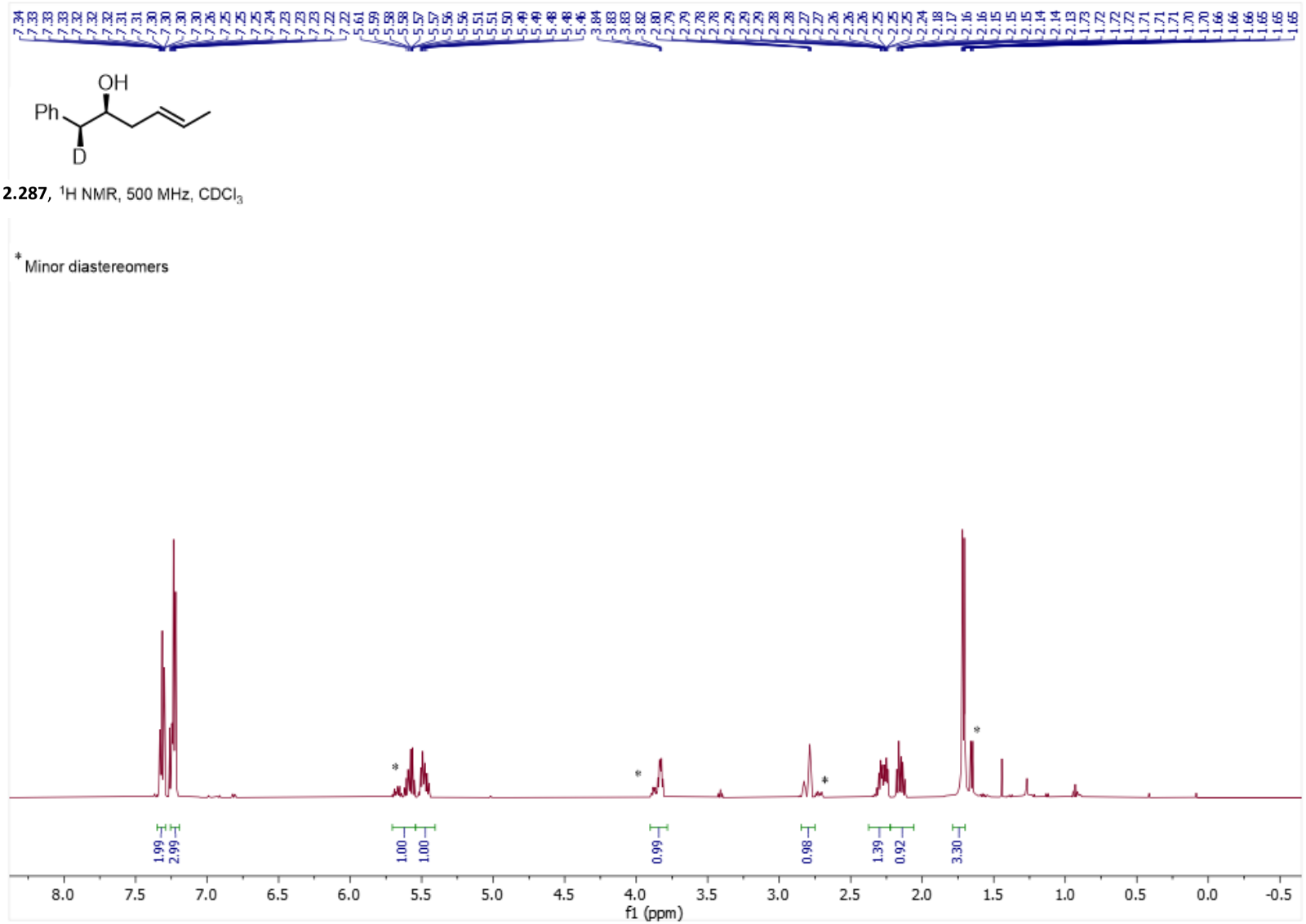
2.7.3. Spectral Data.

2.7.3.1. ^{1}H NMR Spectra of Deuterium Labeling Experiments

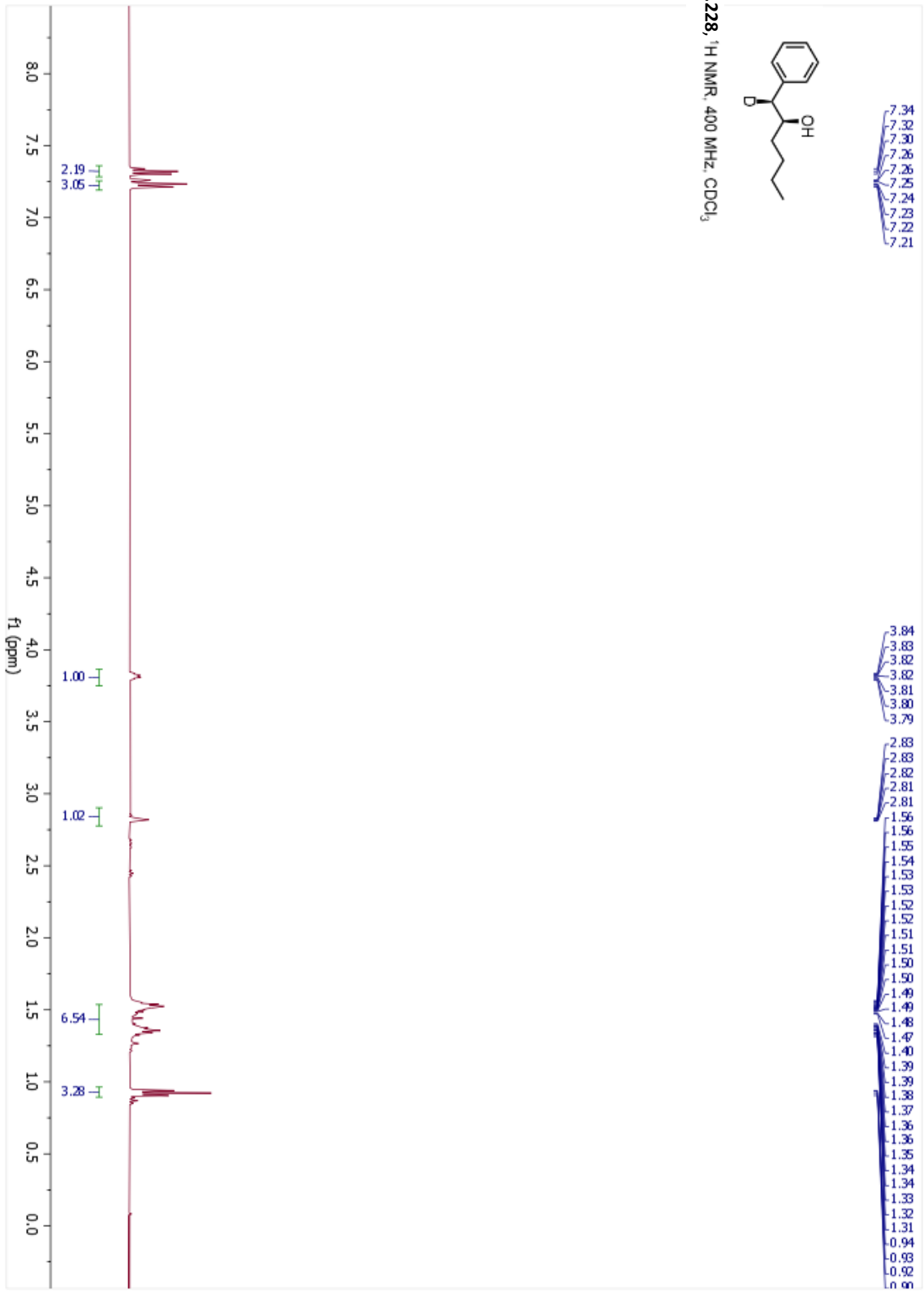

2.227, ^{1}H NMR, 500 MHz, $CDCl_3$
Me
Me
O
O
B
D
7.82
7.80
7.64
7.62
7.61
7.60
7.59
6.16
6.13
5.86
5.82
1.84
2.17
4.36
1.00
0.11
0.96
5.98
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

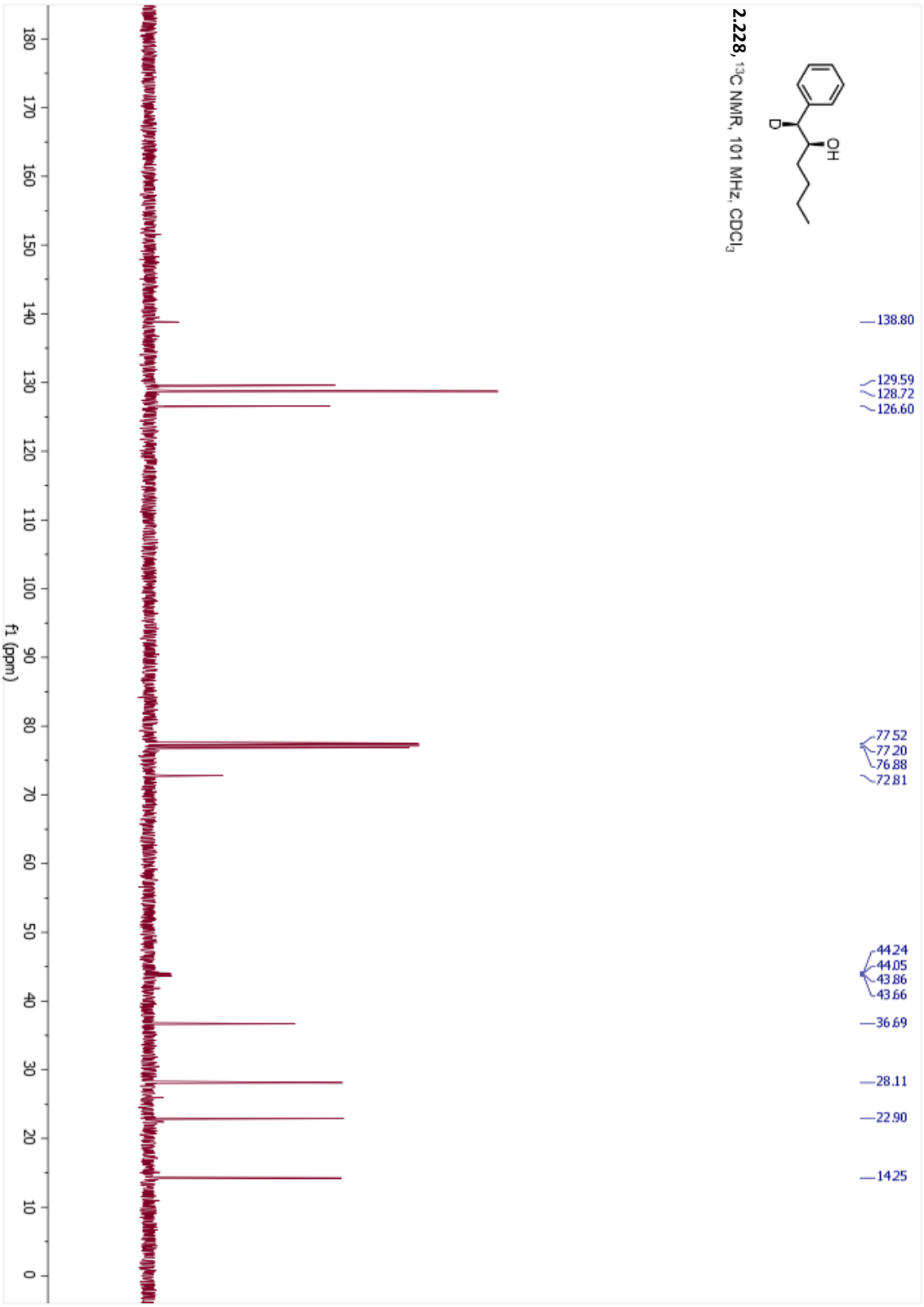


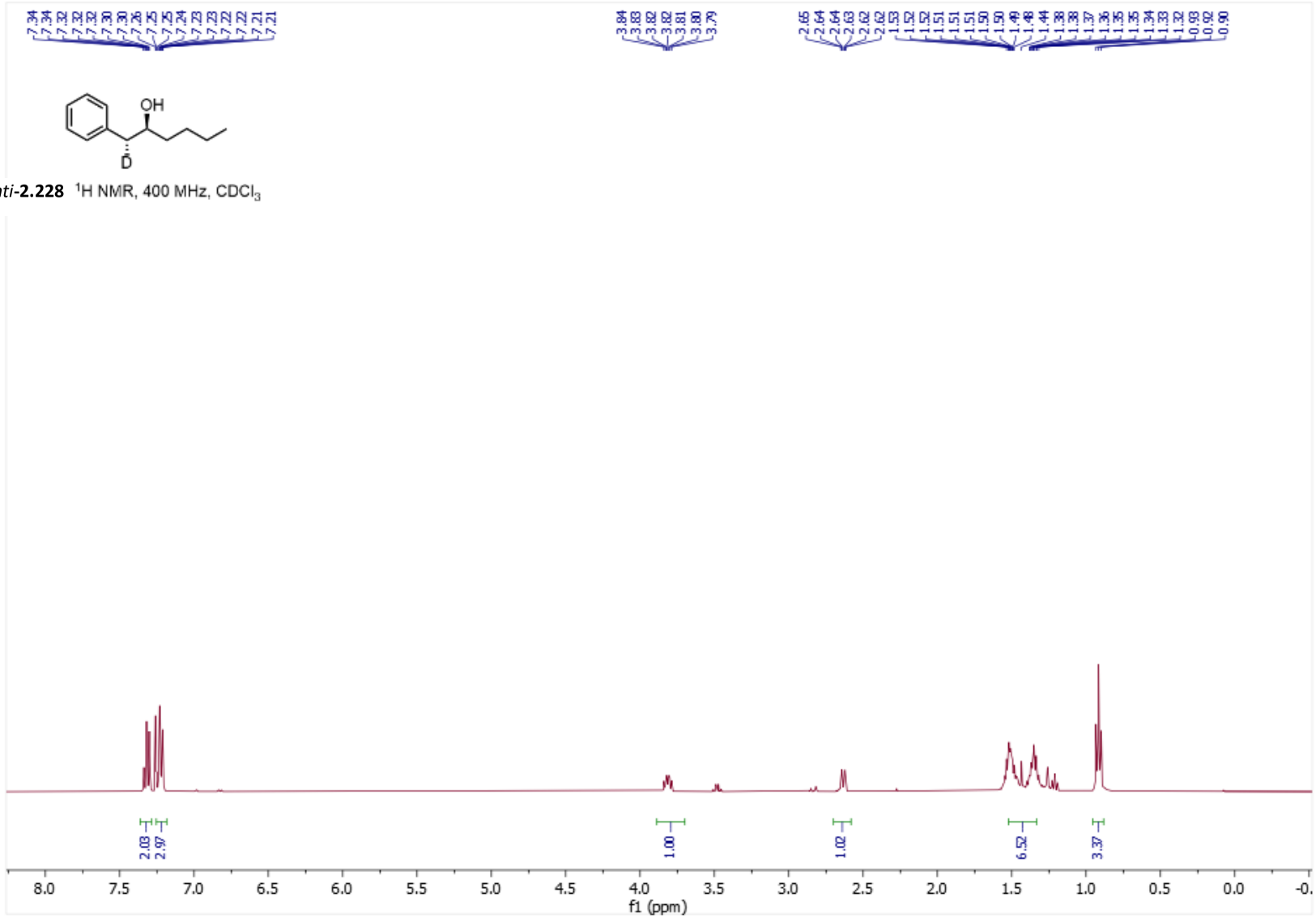
2.227, ^{13}C NMR, 126 MHz, $CDCl_3$



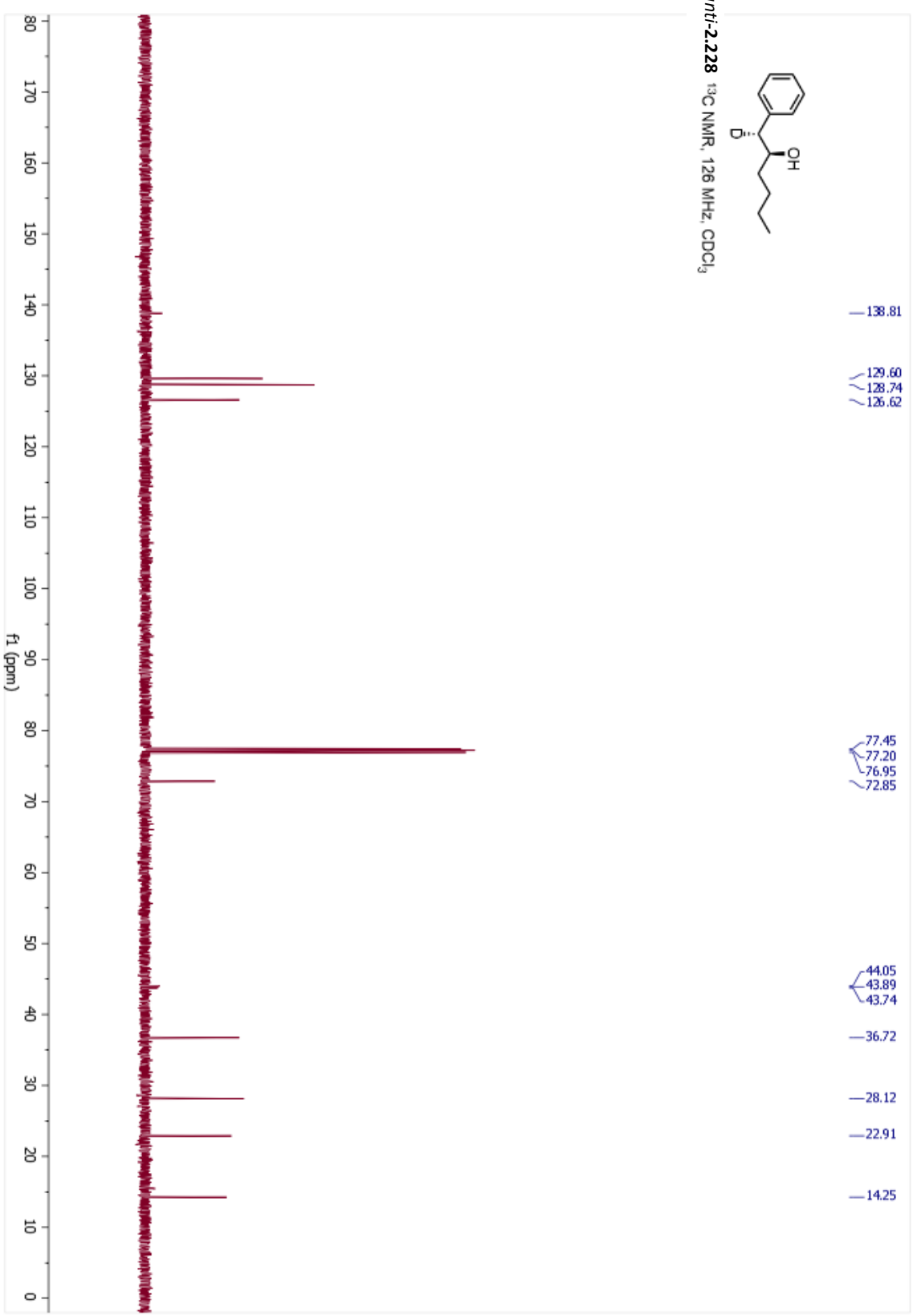
2.287, ^{1}H NMR, 500 MHz, $CDCl_3$

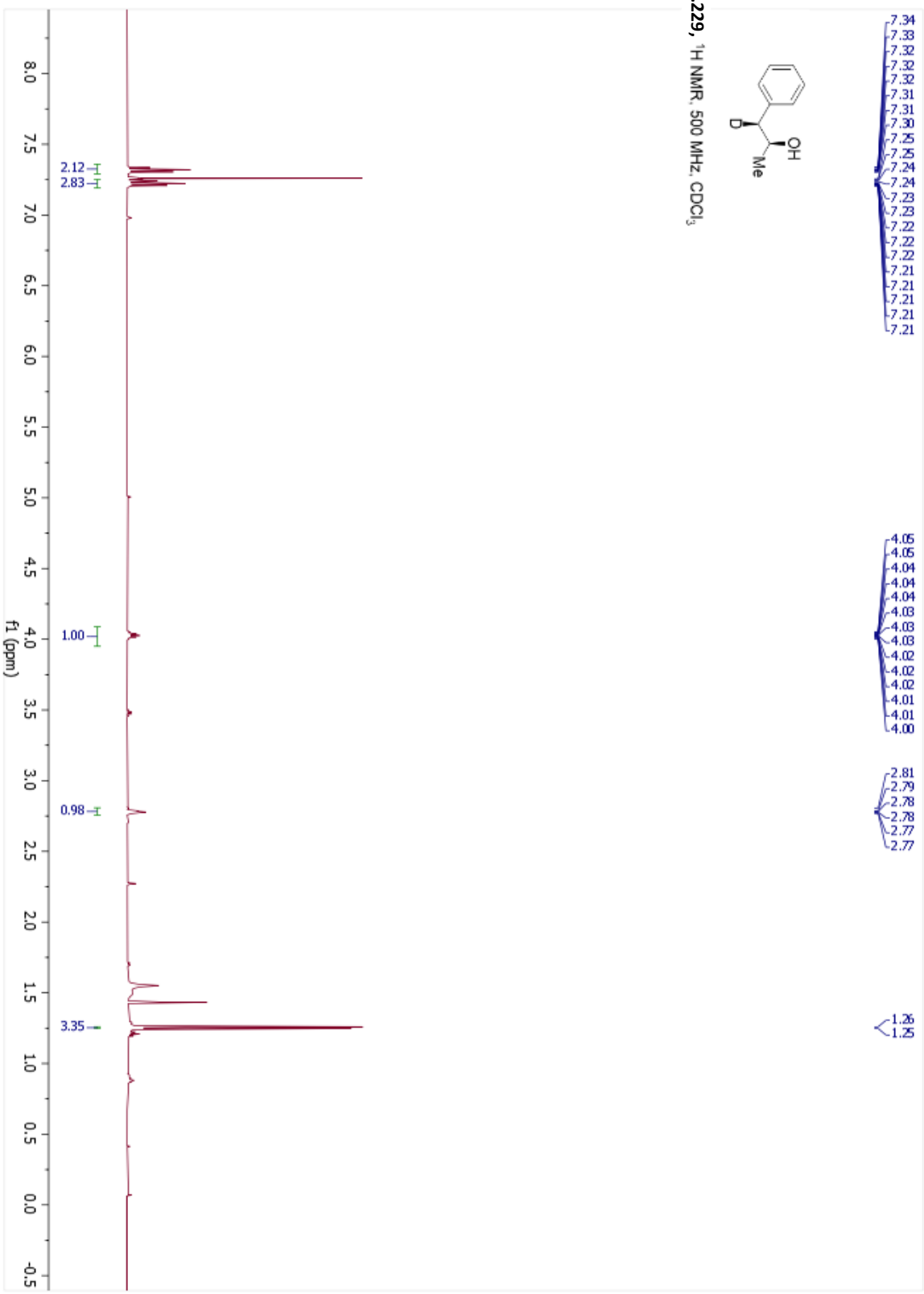

2.228, ^{1}H NMR, 400 MHz, $CDCl_3$
OH
7.34
7.32
7.30
7.26
7.26
7.25
7.24
7.23
7.22
7.21
3.84
3.83
3.82
3.82
3.81
3.80
3.79
2.83
2.83
2.82
2.81
2.81
1.56
1.56
1.55
1.54
1.53
1.53
1.52
1.52
1.51
1.51
1.50
1.50
1.49
1.49
1.48
1.47
1.40
1.39
1.39
1.38
1.37
1.36
1.36
1.35
1.34
1.34
1.33
1.32
1.31
0.94
0.93
0.92
2.19
3.05
1.00
1.02
6.54
3.28
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
0.5
0.0

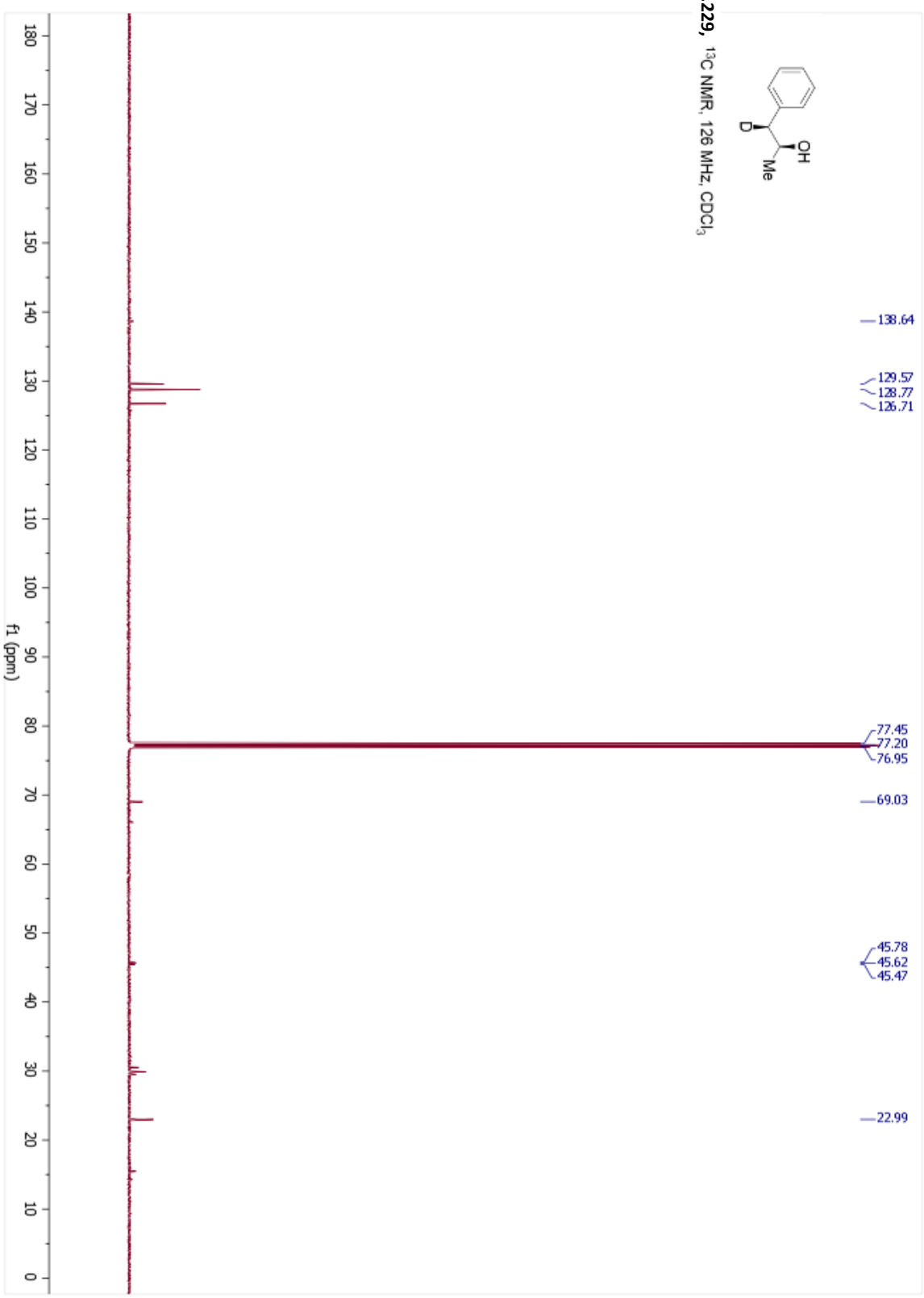

2.228, ^{13}C NMR, 101 MHz, $CDCl_3$
D
OH
138.80
129.59
128.72
126.60
77.52
77.20
76.88
72.81
44.24
44.05
43.86
43.66
36.69
28.11
22.90
14.25
f1 (ppm)

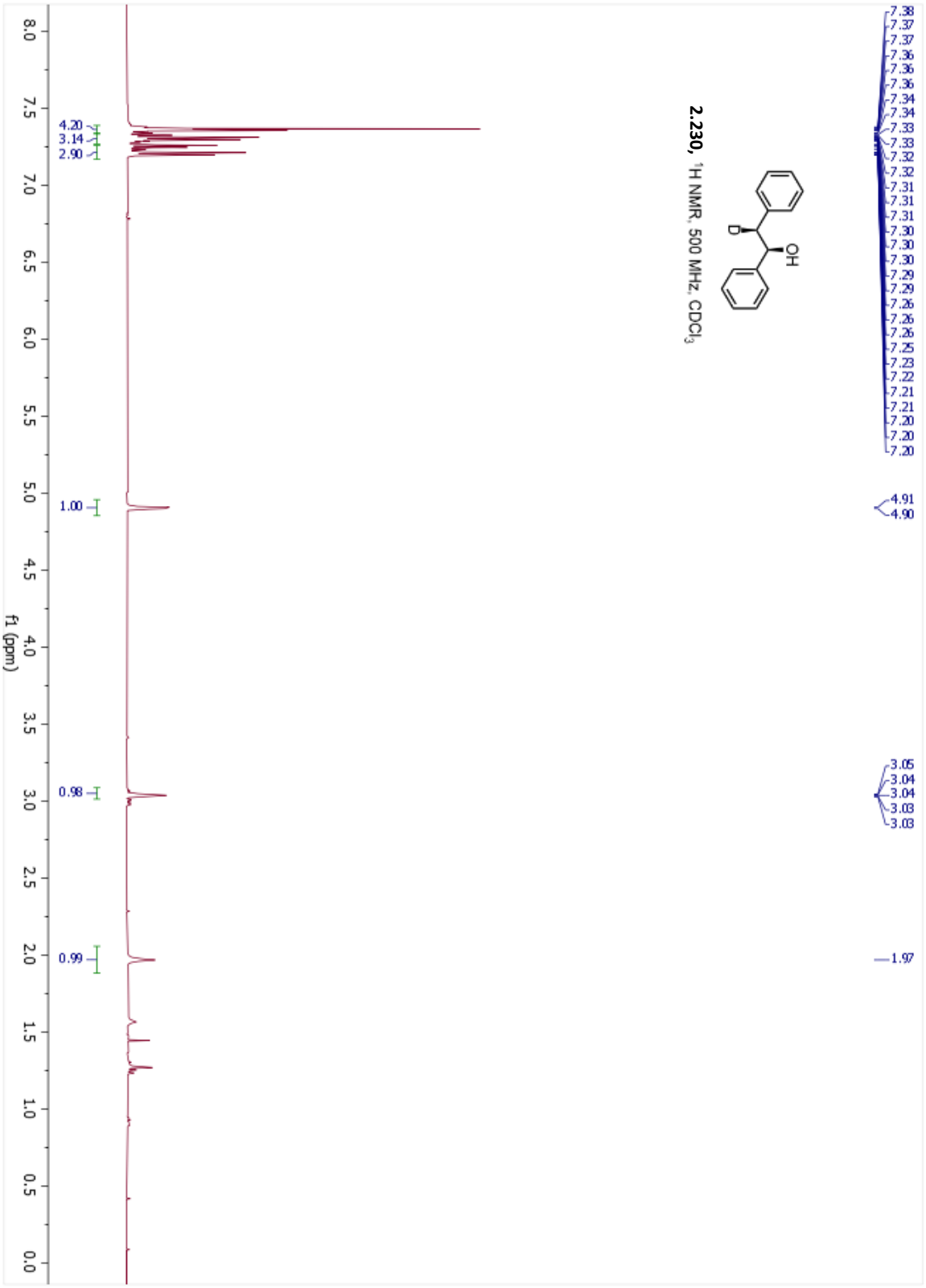


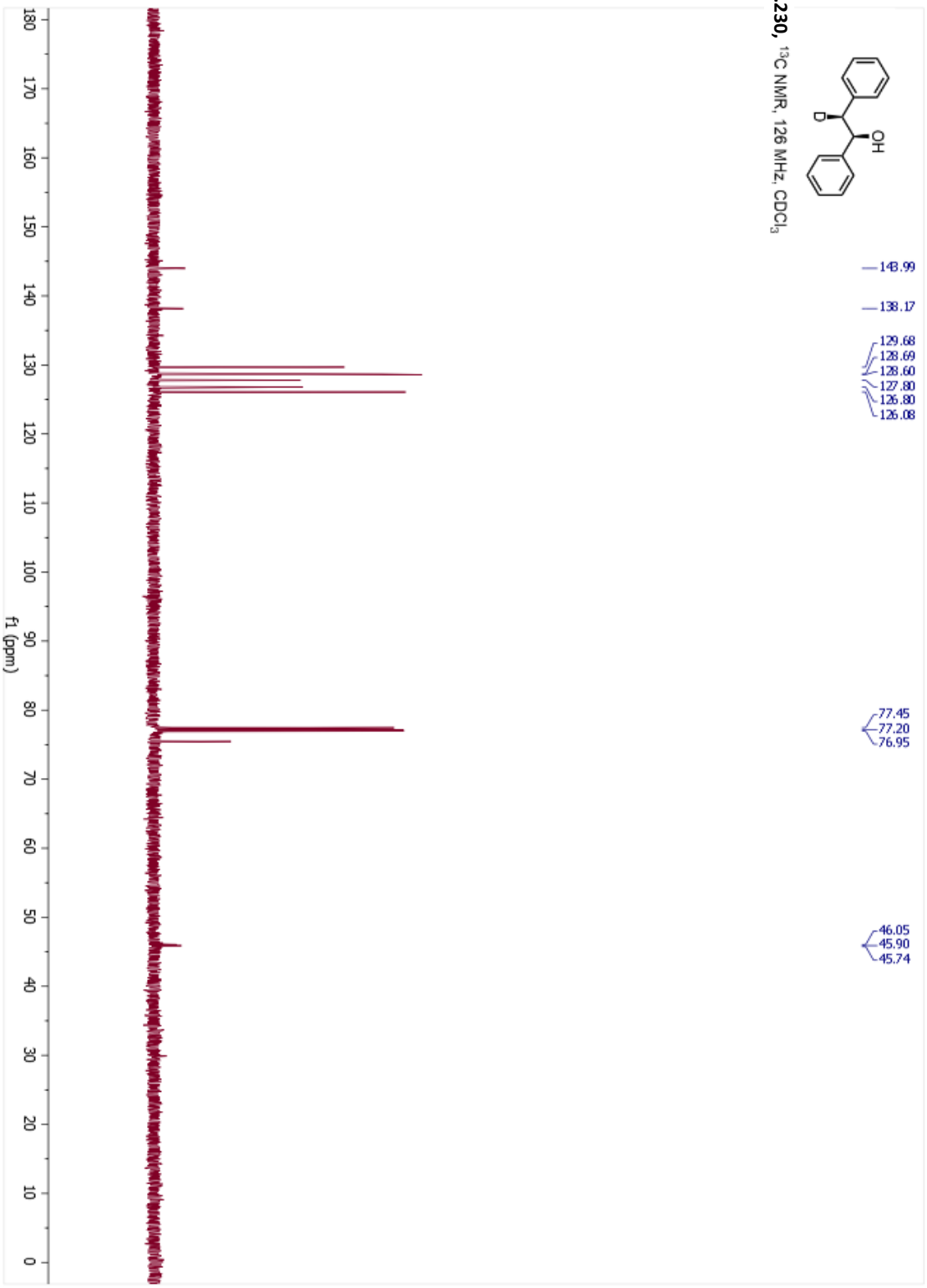
anti-**2.228** ^{1}H NMR, 400 MHz, $CDCl_3$


anti-2.228 13C NMR, 126 MHz, CDCl3
OH
D
138.81
129.60
128.74
126.62
77.45
77.20
76.95
72.85
44.05
43.89
43.74
36.72
28.12
22.91
14.25
f1 (ppm)

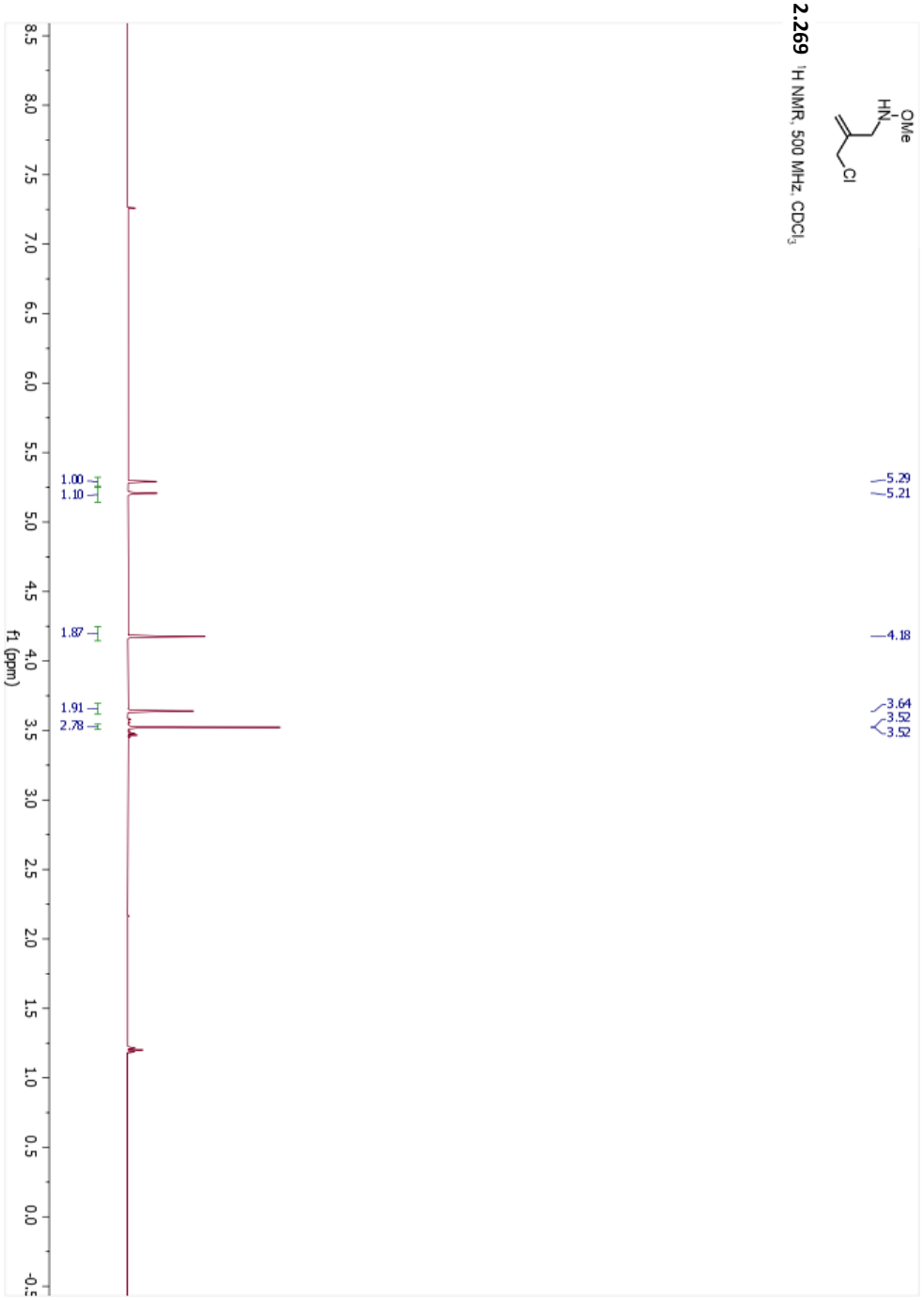

2.229, ^{1}H NMR, 500 MHz, $CDCl_3$
OH
Me
D
7.34
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.25
7.25
7.24
7.24
7.23
7.23
7.22
7.22
7.22
7.21
7.21
7.21
7.21
7.21
4.05
4.05
4.04
4.04
4.04
4.03
4.03
4.03
4.03
4.02
4.02
4.02
4.01
4.01
4.00
2.81
2.79
2.78
2.78
2.77
2.77
1.26
1.25
2.12
2.83
1.00
0.98
3.35
f1 (ppm)

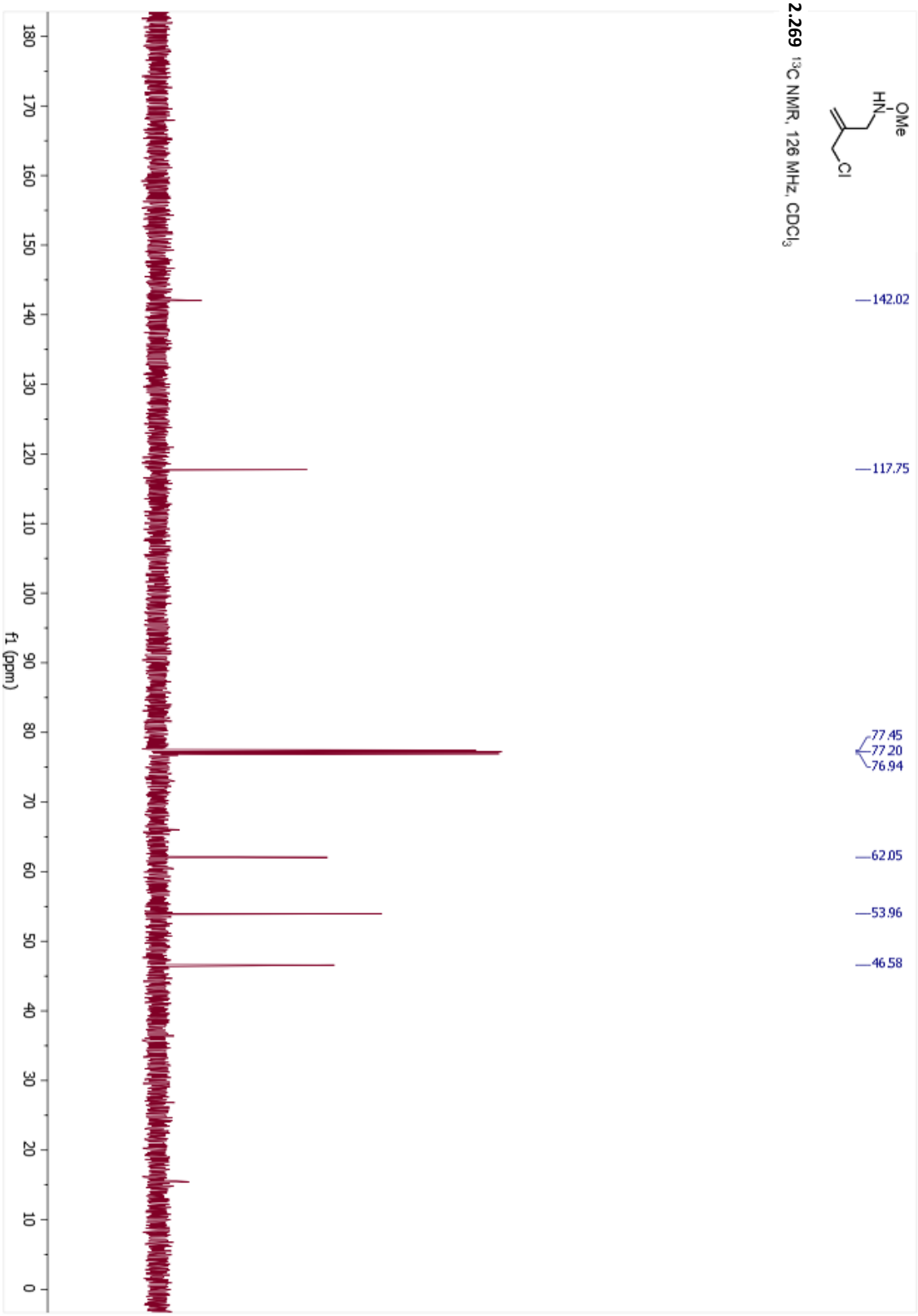

2.229, ^{13}C NMR, 126 MHz, $CDCl_3$
D
OH
Me
138.64
129.57
128.77
126.71
77.45
77.20
76.95
69.03
45.78
45.62
45.47
22.99
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

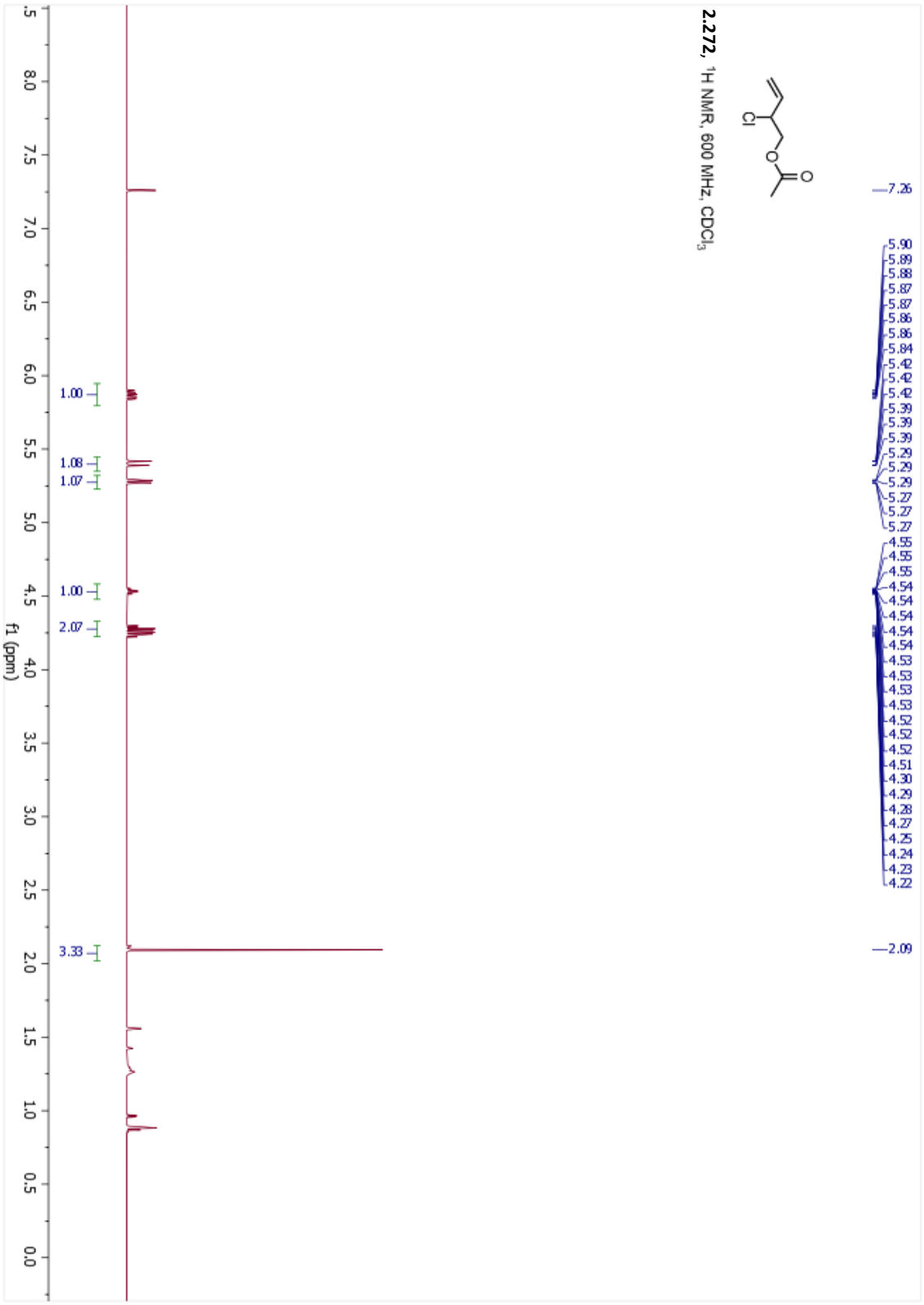

2.230, ^{1}H NMR, 500 MHz, CDCl$_3$
OH
7.38
7.37
7.37
7.36
7.36
7.36
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.31
7.30
7.30
7.30
7.29
7.29
7.26
7.26
7.26
7.25
7.23
7.22
7.21
7.21
7.20
7.20
7.20
4.91
4.90
3.05
3.04
3.04
3.03
3.03
1.97
4.20
3.14
2.90
1.00
0.98
0.99
f1 (ppm)

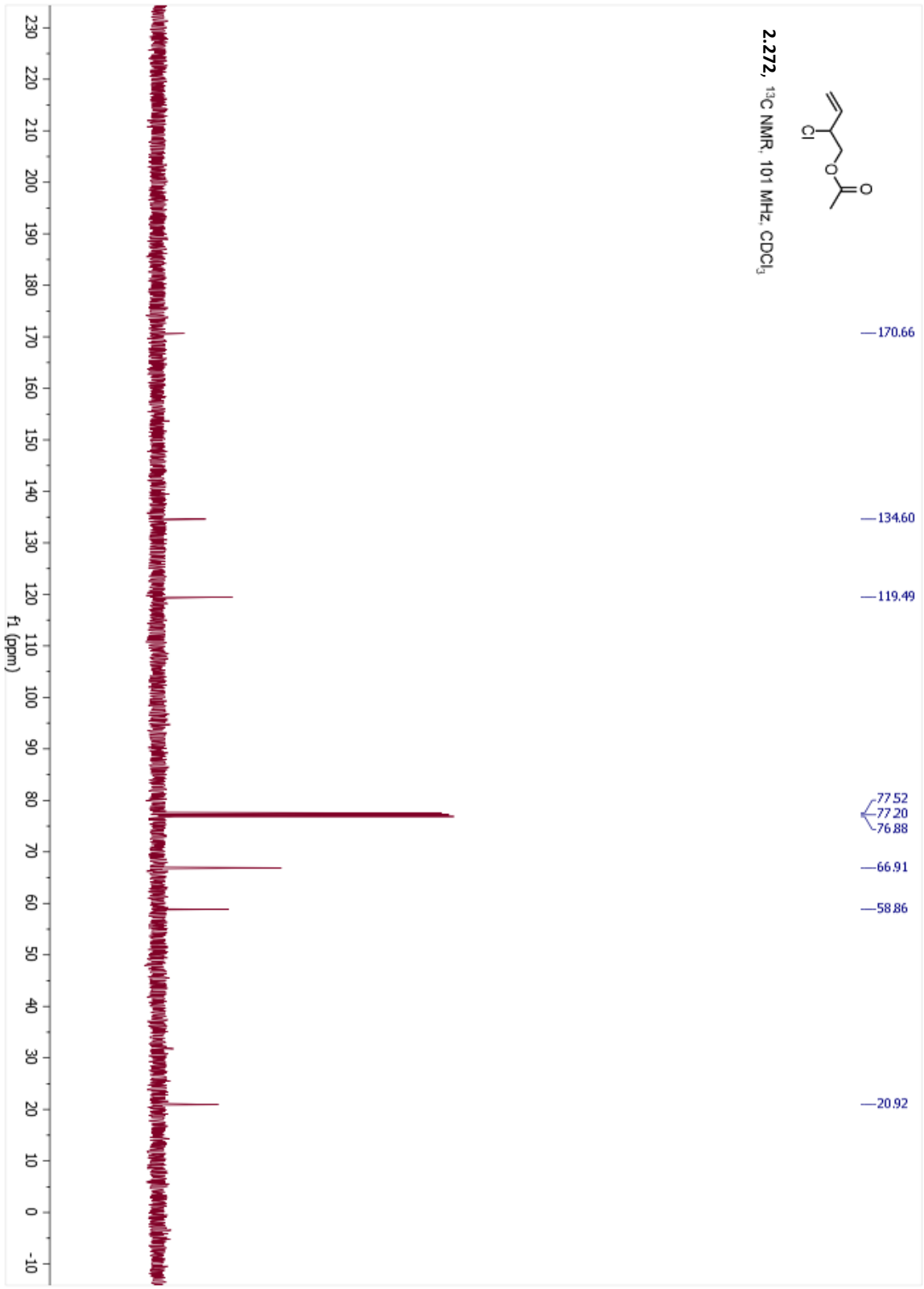

2.230, ^{13}C NMR, 126 MHz, $CDCl_3$
D
OH
143.99
138.17
129.68
128.69
128.60
127.80
126.80
126.08
77.45
77.20
76.95
46.05
45.90
45.74
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

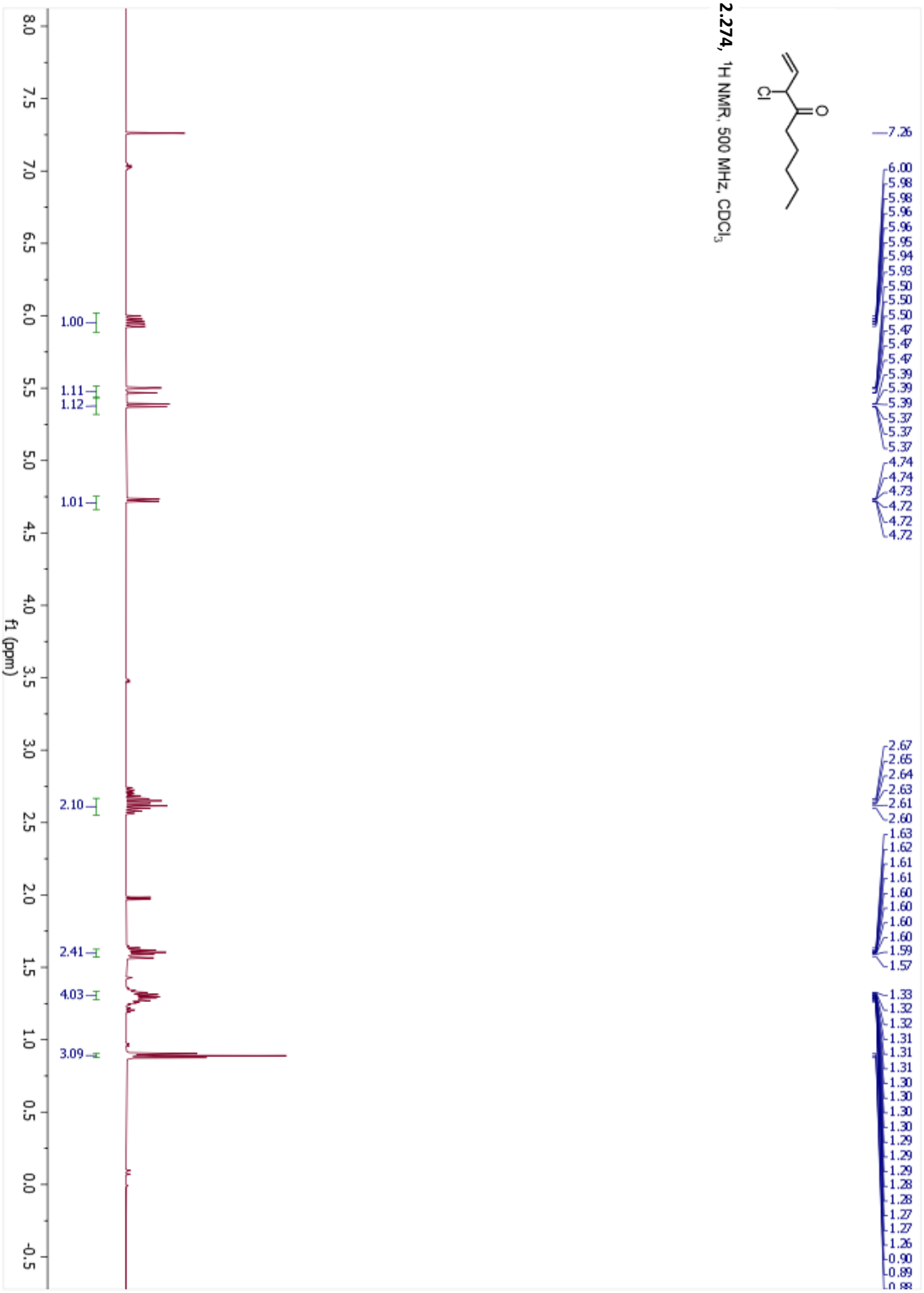
2.7.3.2. ^{1}H NMR and ^{13}C NMR Spectra

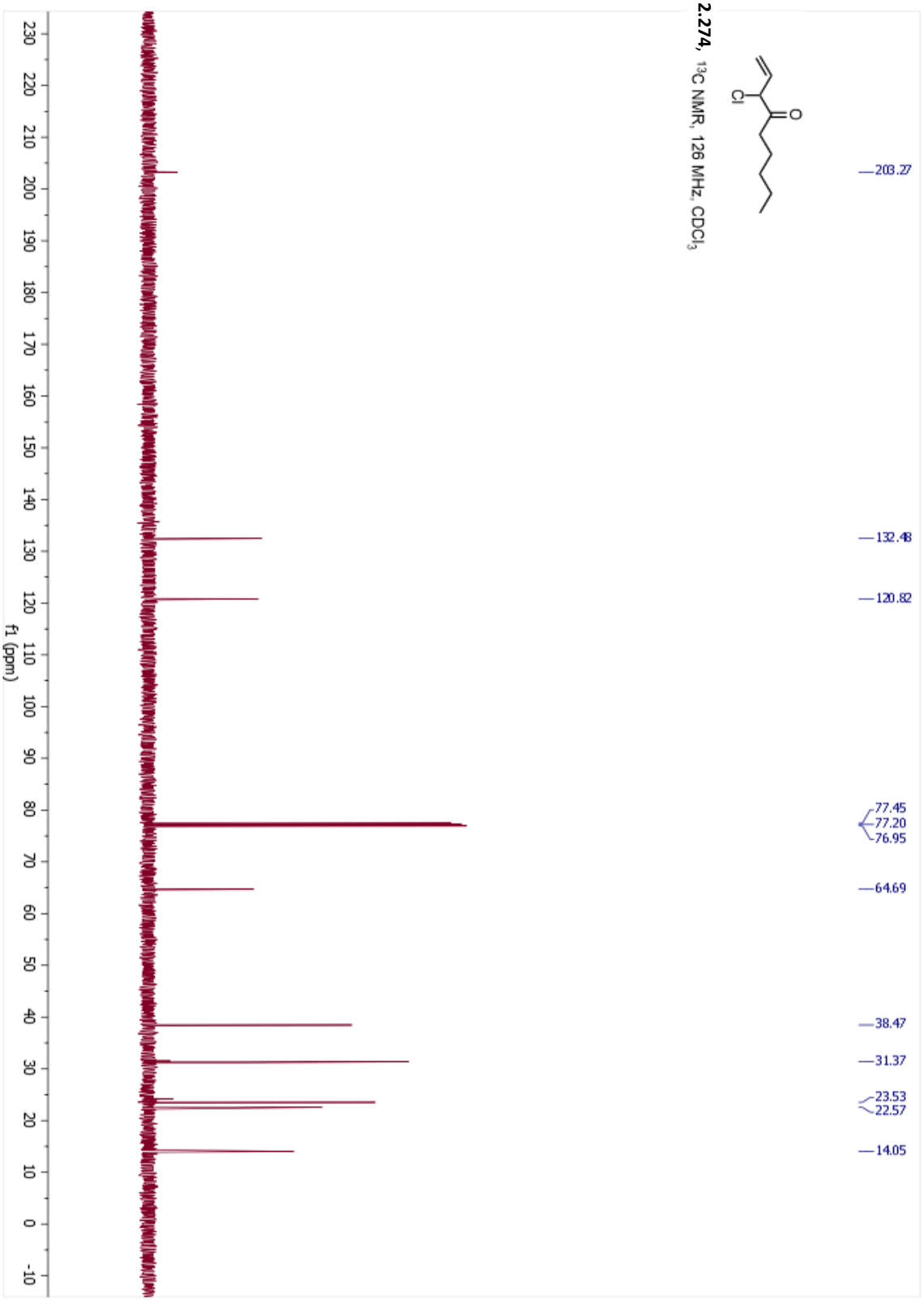


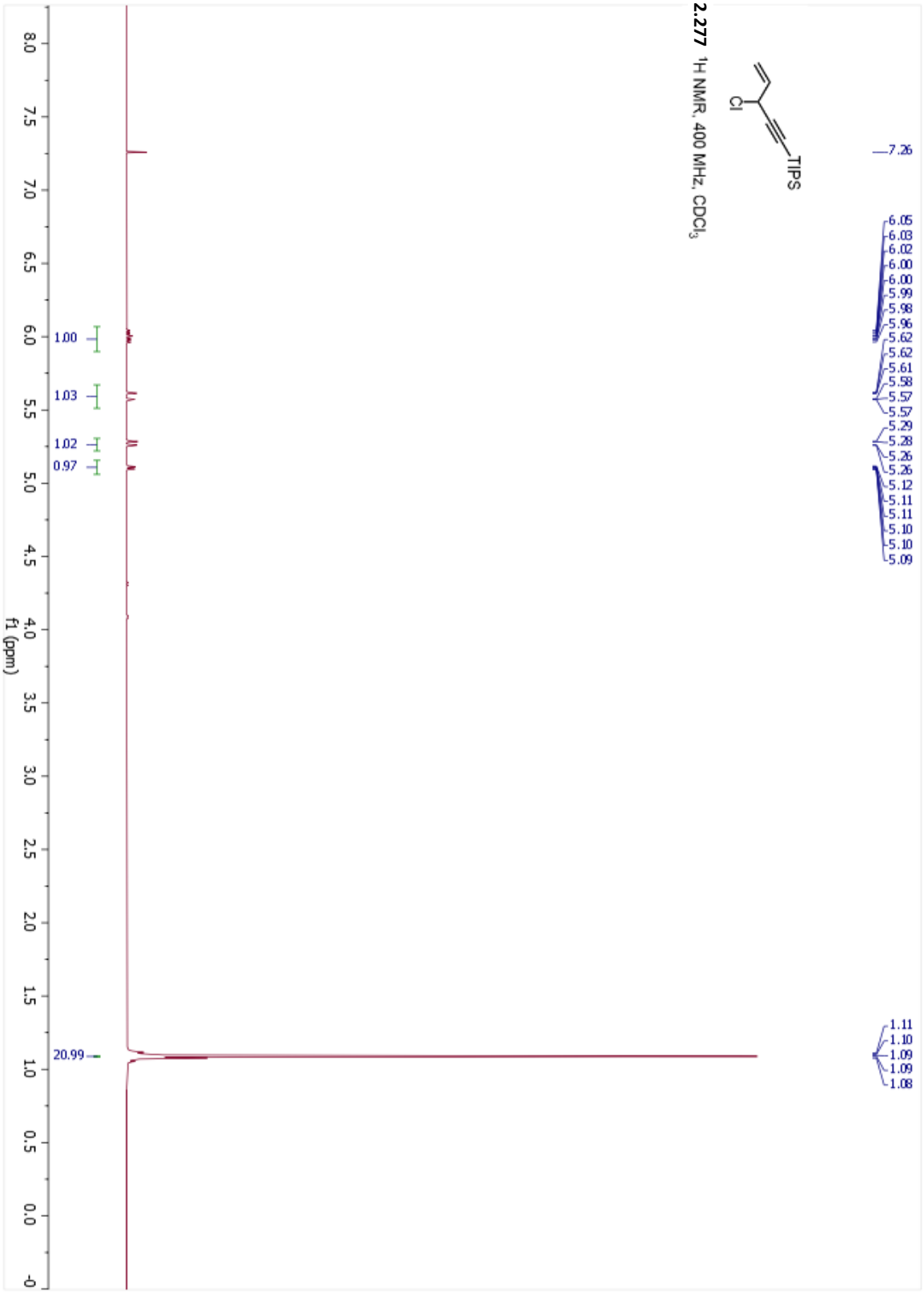

2.269 13C NMR, 126 MHz, CDCl3
OMe
HN
Cl
142.02
117.75
77.45
77.20
76.94
62.05
53.96
46.58
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

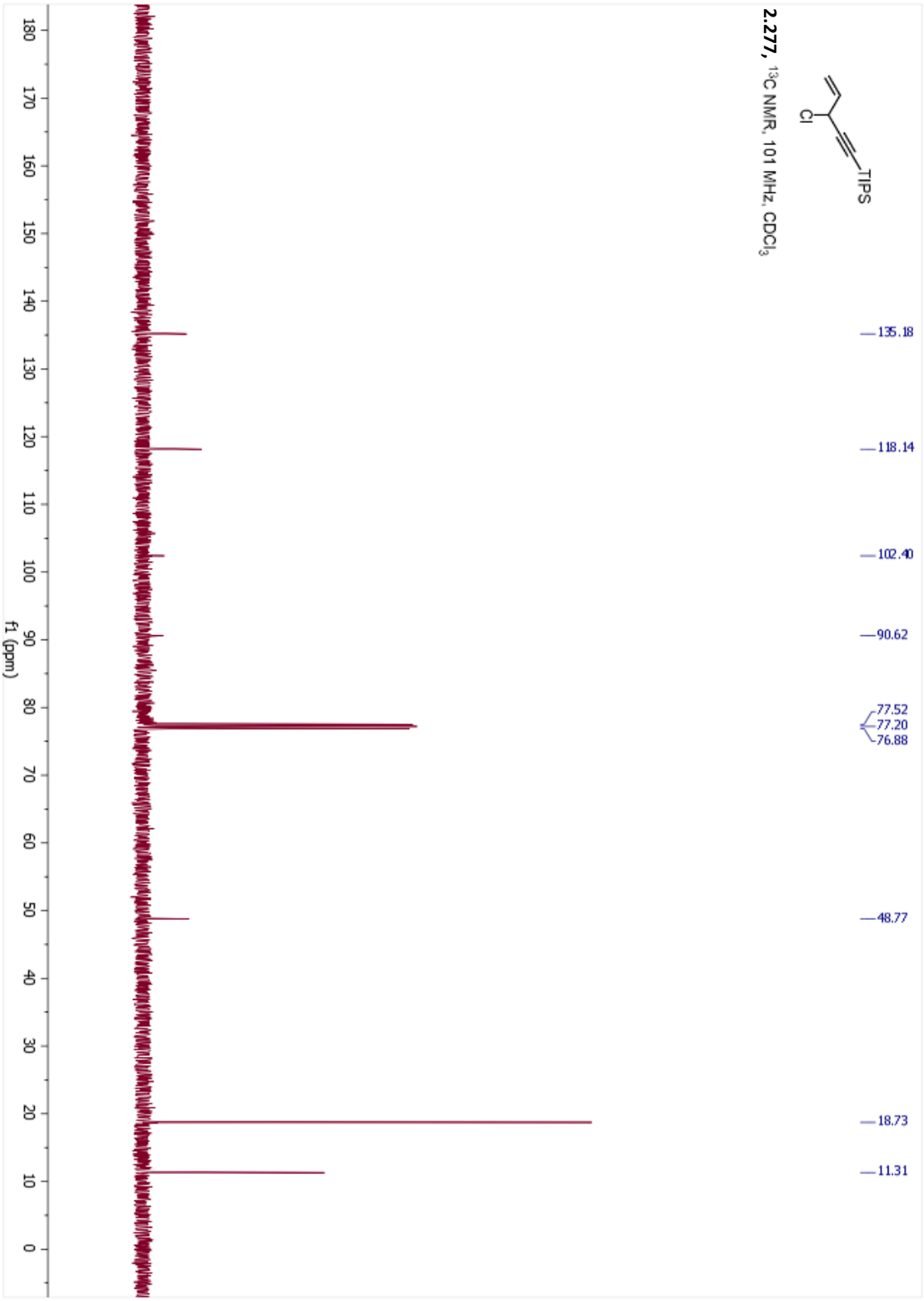

2.272, ^{1}H NMR, 600 MHz, $CDCl_3$
Cl
O
O
7.26
5.90
5.89
5.88
5.87
5.87
5.86
5.86
5.84
5.42
5.42
5.42
5.39
5.39
5.39
5.29
5.29
5.29
5.27
5.27
5.27
4.55
4.55
4.55
4.54
4.54
4.54
4.54
4.54
4.53
4.53
4.53
4.53
4.52
4.52
4.52
4.51
4.30
4.29
4.28
4.27
4.25
4.24
4.23
4.22
2.09
1.00
1.08
1.07
1.00
2.07
3.33
f1 (ppm)

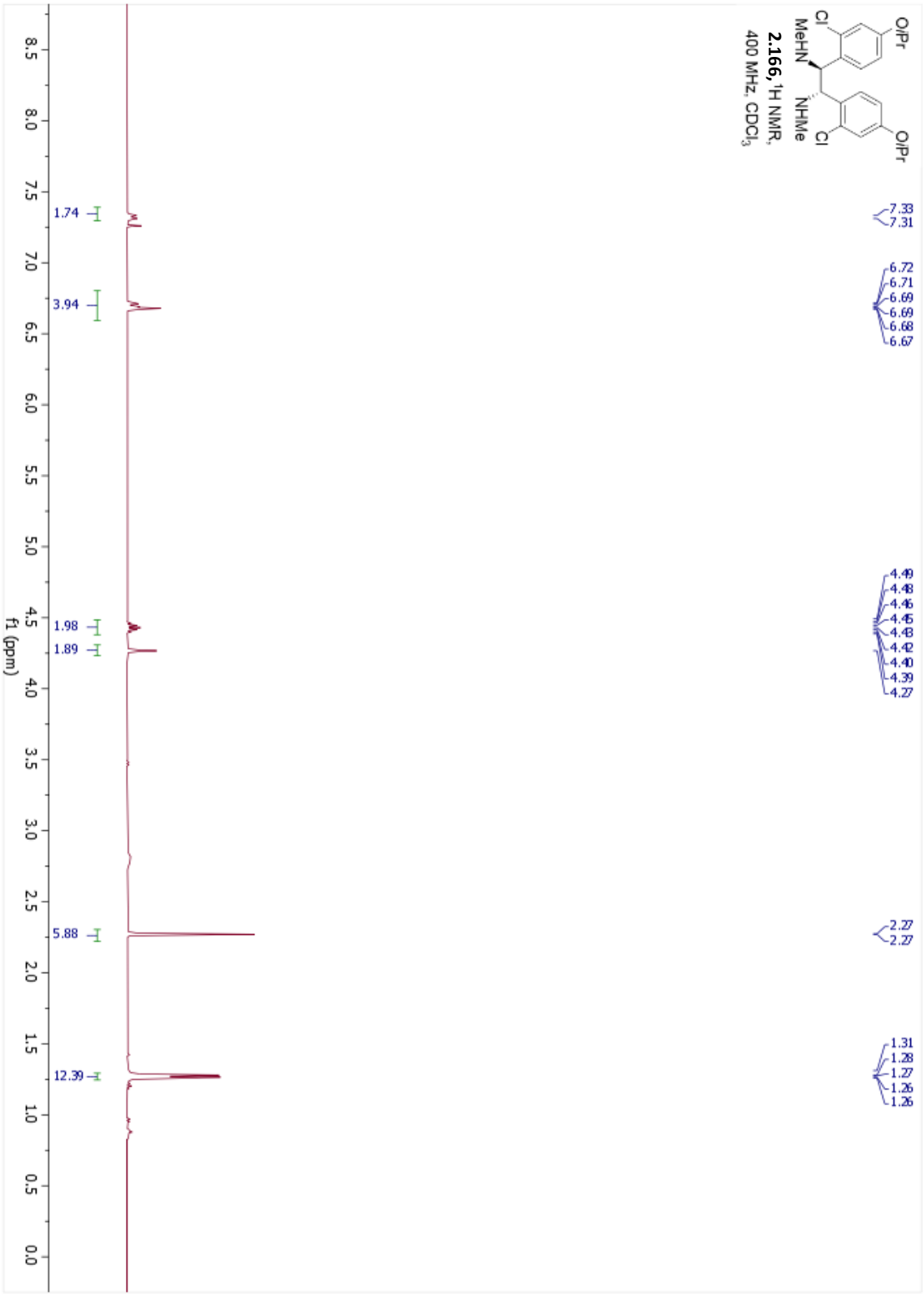

2.272, ^{13}C NMR, 101 MHz, $CDCl_3$
Cl
O
O
170.66
134.60
119.49
77.52
77.20
76.88
66.91
58.86
20.92
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

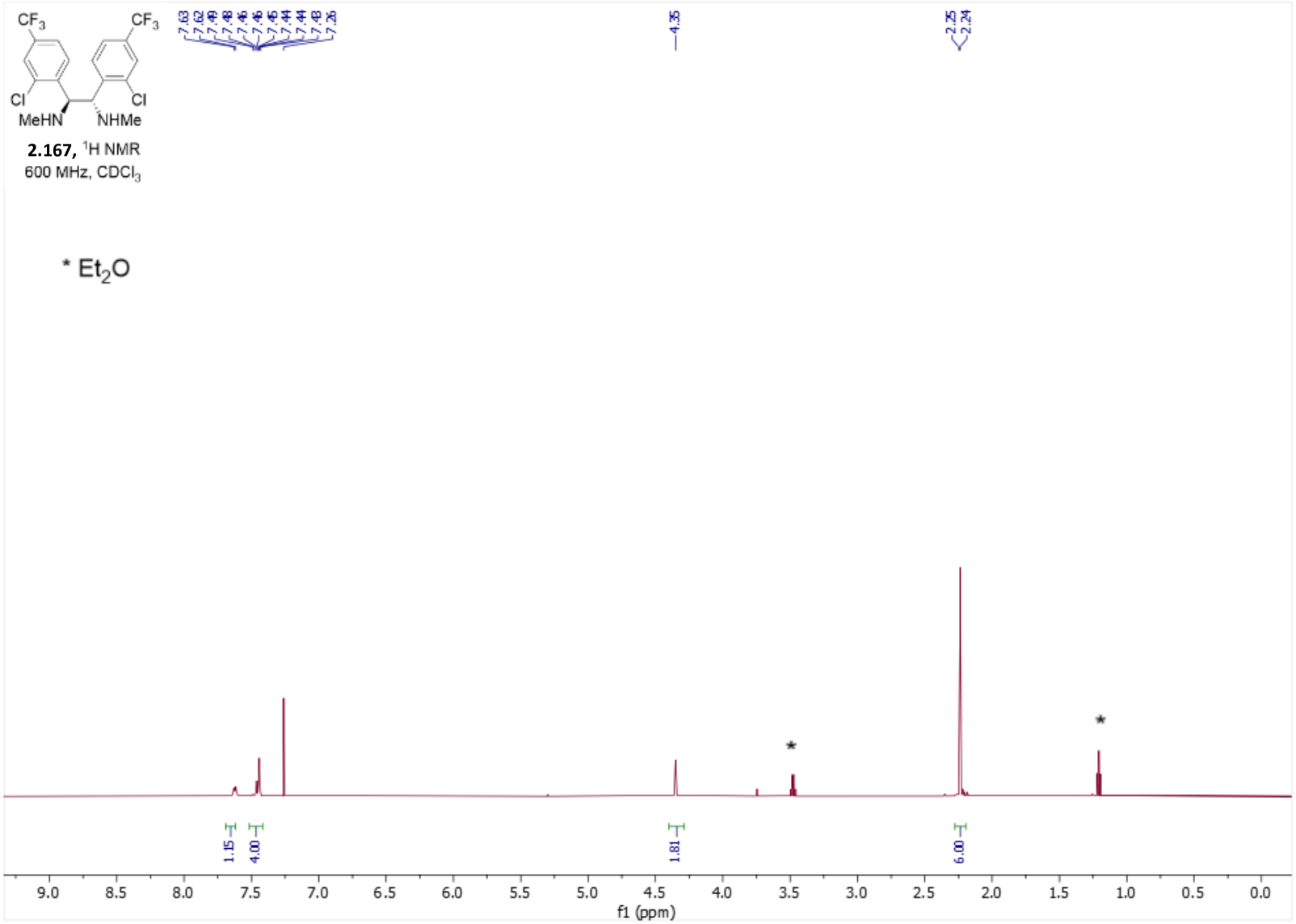

2.274, 1H NMR, 500 MHz, CDCl3
Cl
O
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1.00
1.11
1.12
1.01
2.10
2.41
4.03
3.09
7.26
6.00
5.98
5.98
5.96
5.96
5.95
5.94
5.93
5.50
5.50
5.50
5.47
5.47
5.47
5.39
5.39
5.39
5.37
5.37
5.37
4.74
4.74
4.73
4.72
4.72
4.72
2.67
2.65
2.64
2.63
2.61
2.60
1.63
1.62
1.61
1.61
1.60
1.60
1.60
1.60
1.59
1.57
1.33
1.32
1.32
1.31
1.31
1.31
1.30
1.30
1.30
1.30
1.29
1.29
1.29
1.28
1.28
1.27
1.27
1.26
0.90
0.89

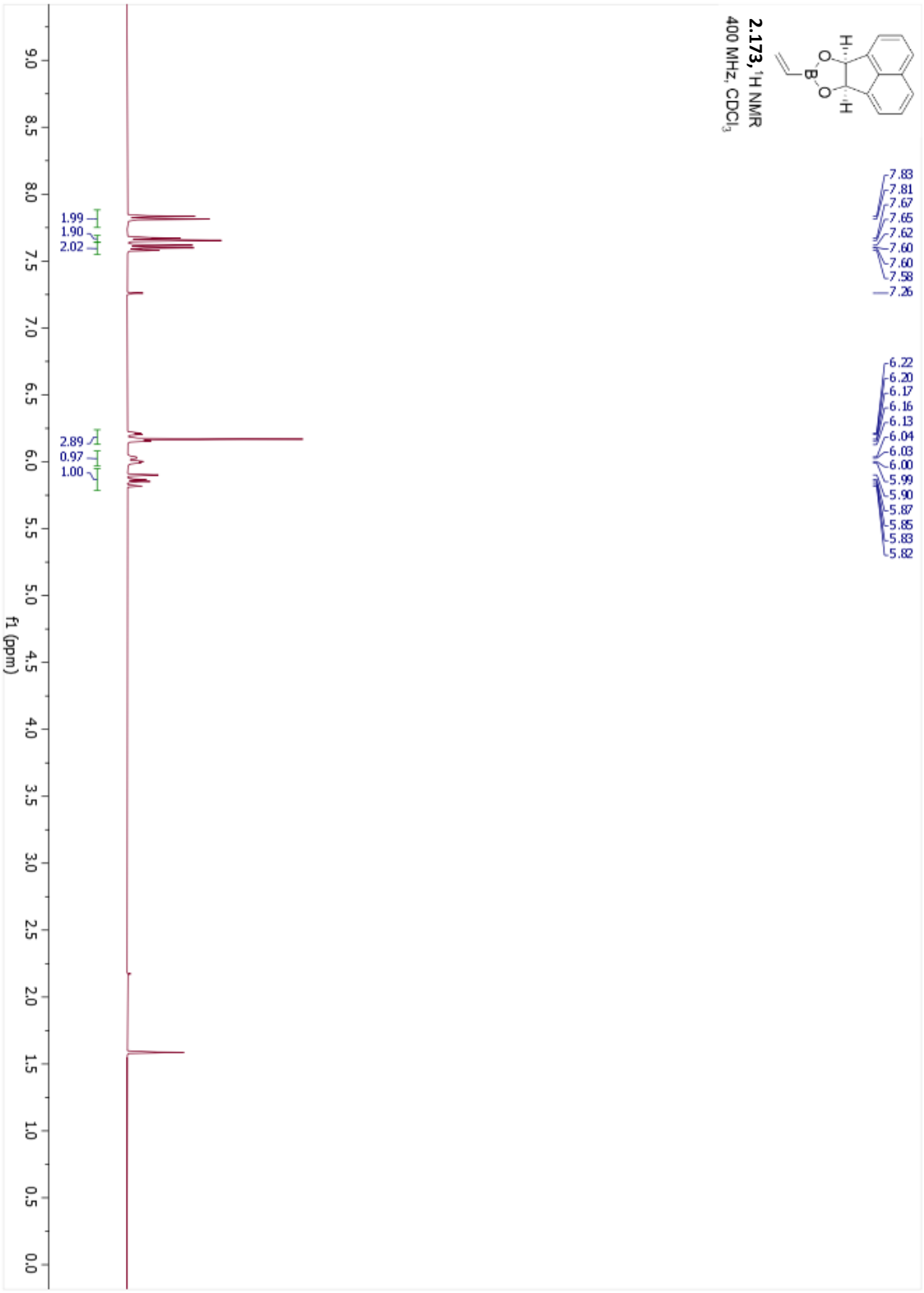

2.274, ^{13}C NMR, 126 MHz, $CDCl_3$
Cl
O
203.27
132.48
120.82
77.45
77.20
76.95
64.69
38.47
31.37
23.53
22.57
14.05
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

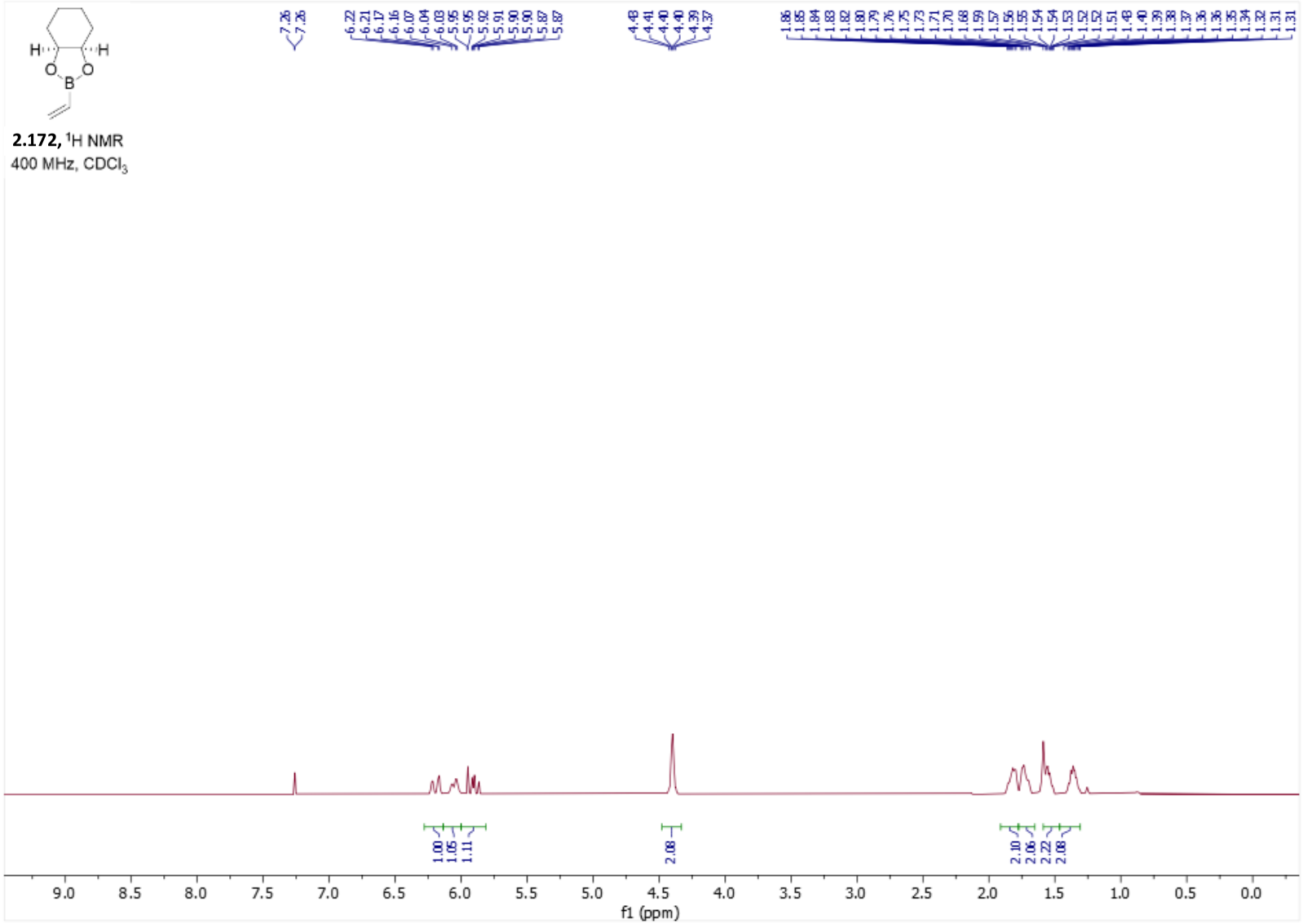

2.277 ¹H NMR, 400 MHz, CDCl3
Cl
TIPS
7.26
6.05
6.03
6.02
6.00
6.00
5.99
5.98
5.96
5.62
5.62
5.61
5.58
5.57
5.57
5.29
5.28
5.26
5.26
5.12
5.11
5.11
5.10
5.10
5.09
1.11
1.10
1.09
1.09
1.08
1.00
1.03
1.02
0.97
20.99
f1 (ppm)


2.277, ^{13}C NMR, 101 MHz, $CDCl_3$
Cl
TIPS
135.18
118.14
102.40
90.62
77.52
77.20
76.88
48.77
18.73
11.31
f1 (ppm)

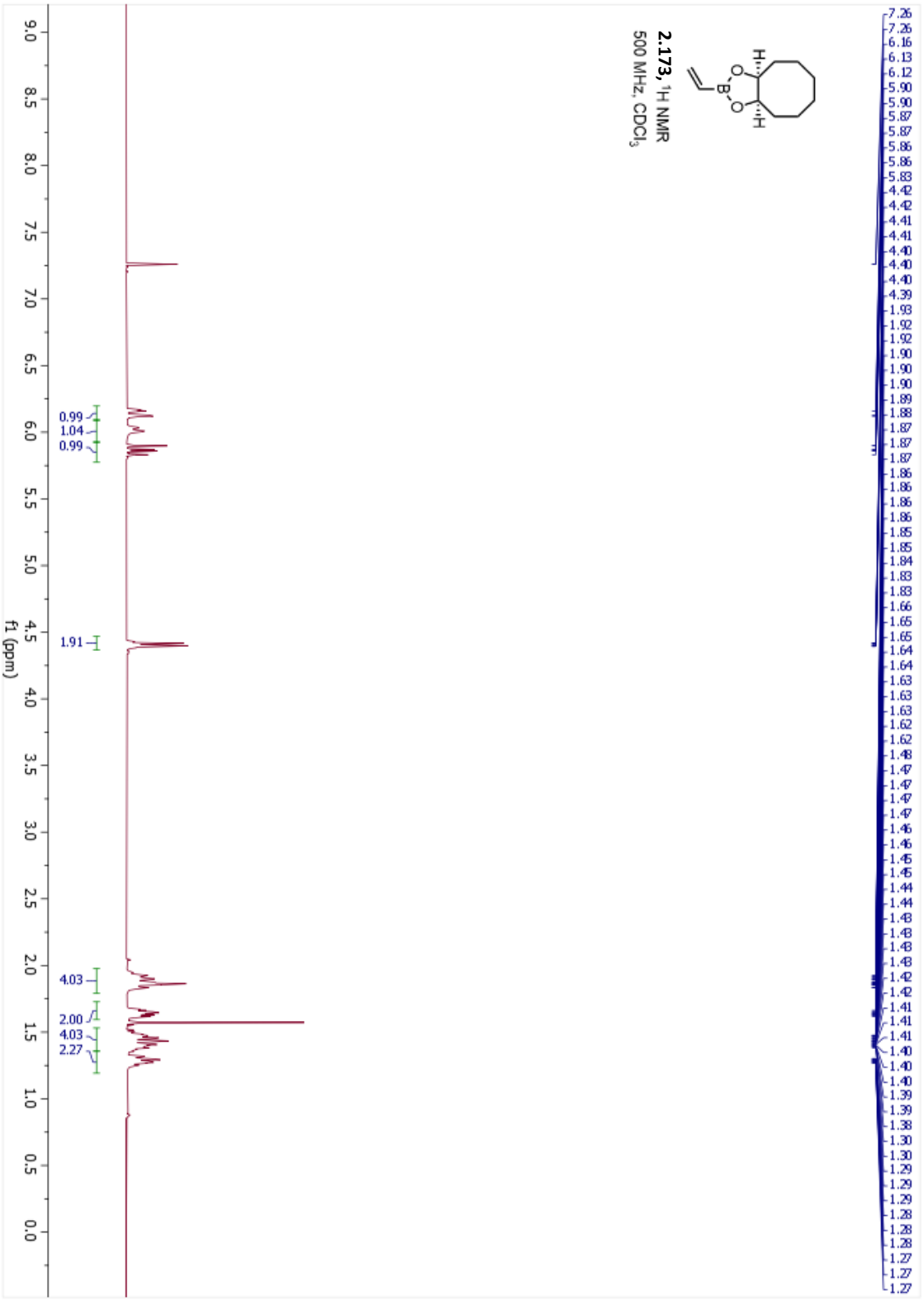

2.166, ^{1}H NMR,
400 MHz, $CDCl_3$
OiPr
Cl
MeHN
NHMe
Cl
OiPr
7.33
7.31
6.72
6.71
6.69
6.69
6.68
6.67
4.49
4.48
4.46
4.45
4.43
4.42
4.40
4.39
4.27
2.27
2.27
1.31
1.28
1.27
1.26
1.26
1.74
3.94
1.98
1.89
5.88
12.39
f1 (ppm)

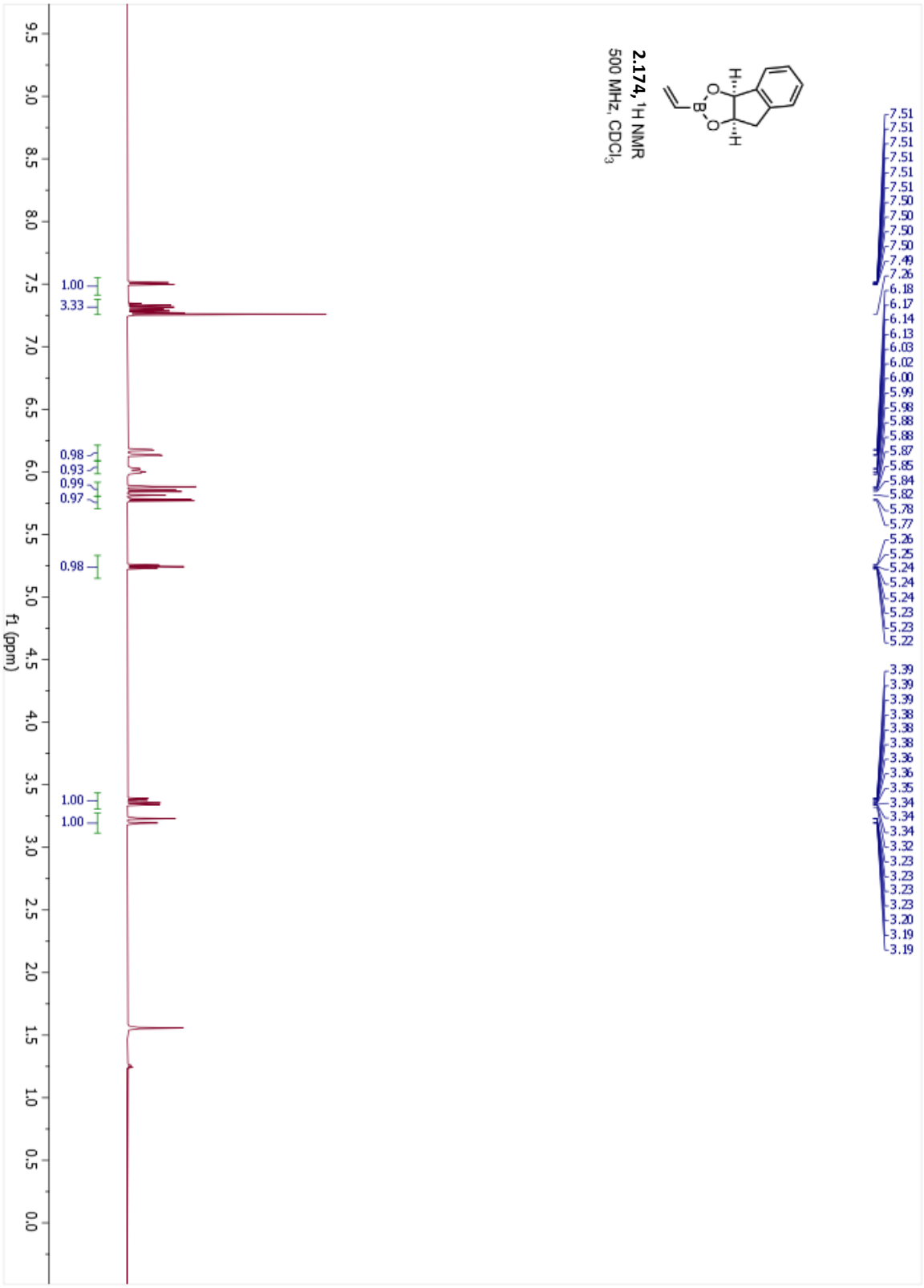

CF3
CF3
Cl
Cl
MeHN
NHMe
7.63
7.62
7.49
7.48
7.46
7.46
7.45
7.44
7.44
7.43
7.26
4.35
2.25
2.24
2.167, 1H NMR
600 MHz, CDCl3
* Et2O
*
*
1.15
4.00
1.81
6.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

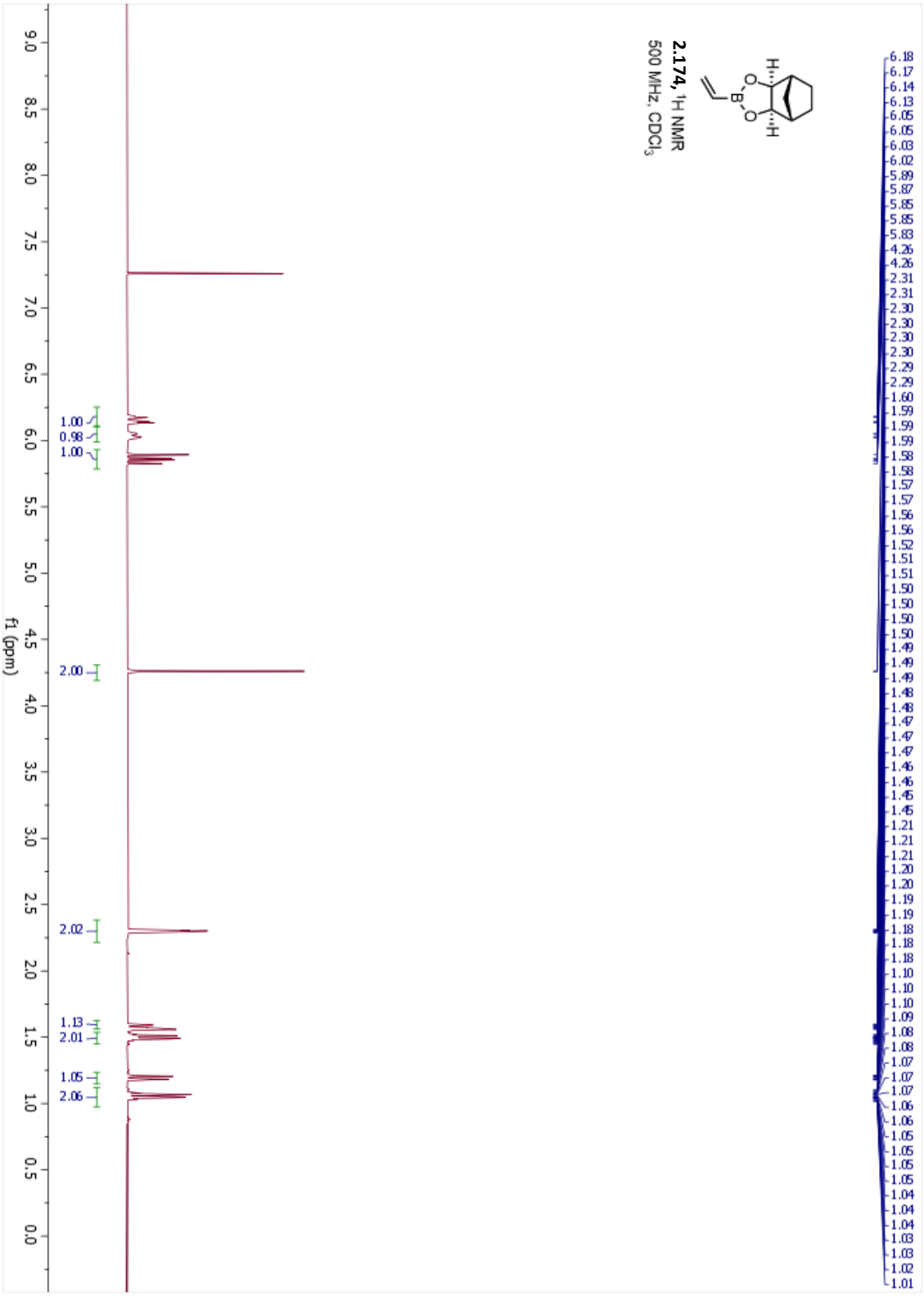

2.173, ^{1}H NMR
400 MHz, CDCl$_3$
7.83
7.81
7.67
7.65
7.62
7.60
7.60
7.58
7.26
6.22
6.20
6.17
6.16
6.13
6.04
6.03
6.00
5.99
5.90
5.87
5.85
5.83
5.82
1.99
1.90
2.02
2.89
0.97
1.00
f1 (ppm)

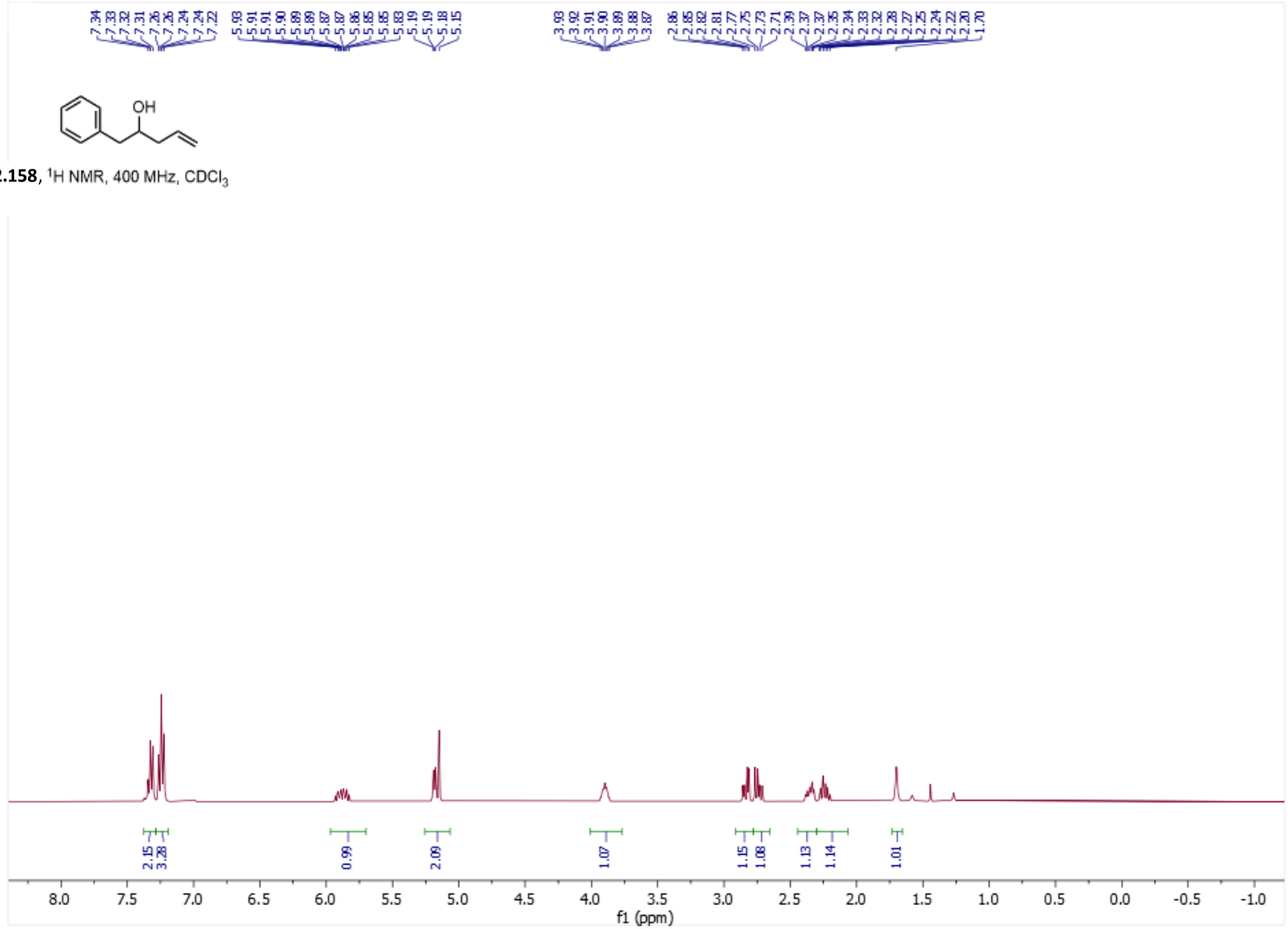


2.172, ^{1}H NMR
400 MHz, $CDCl_3$


2.173, 1H NMR
500 MHz, CDCl3
f1 (ppm)
0.99
1.04
0.99
1.91
4.03
2.00
4.03
2.27

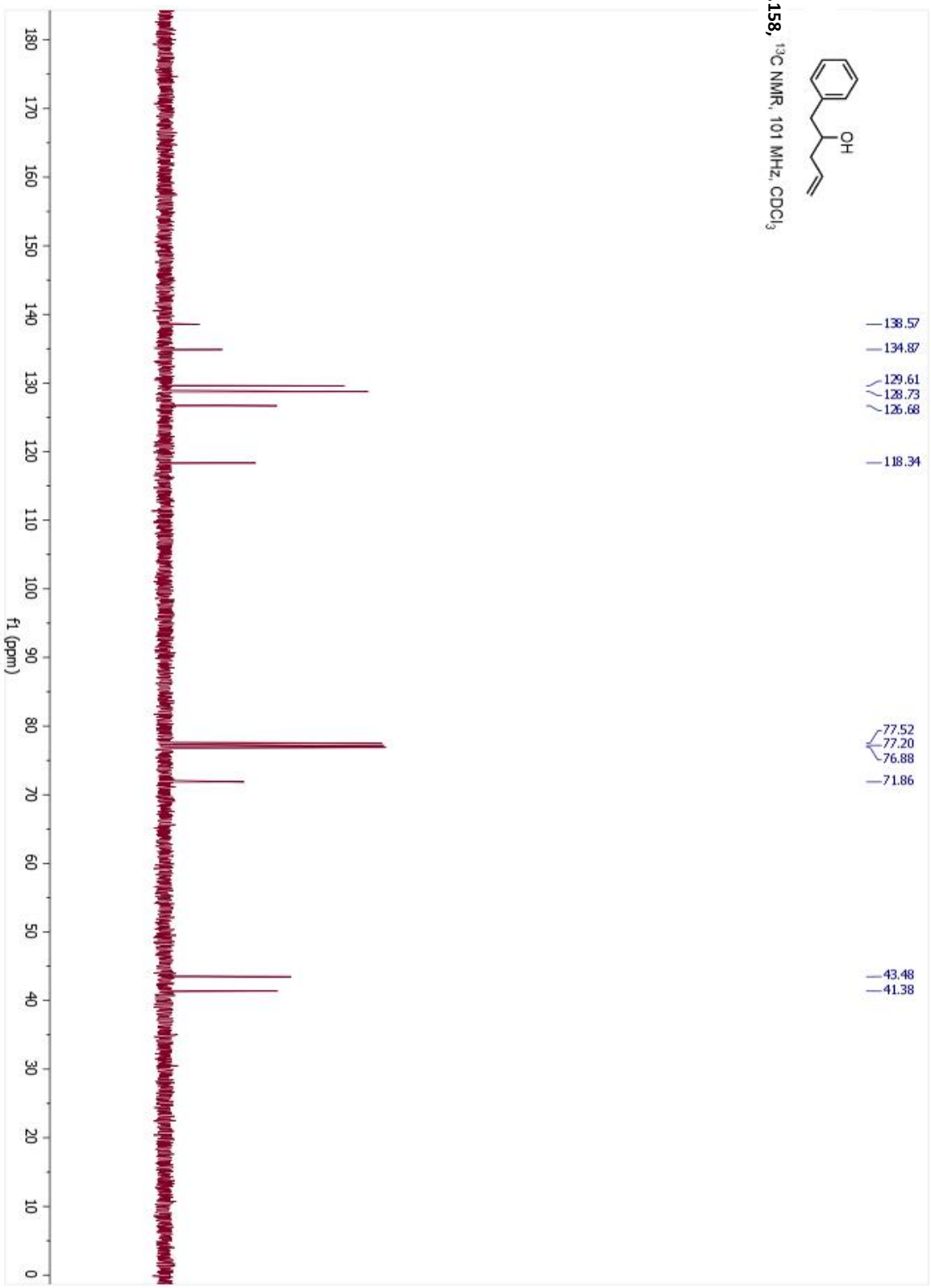

2.174, 1H NMR
500 MHz, CDCl3
f1 (ppm)
1.00
3.33
0.98
0.93
0.99
0.97
0.98
1.00
1.00

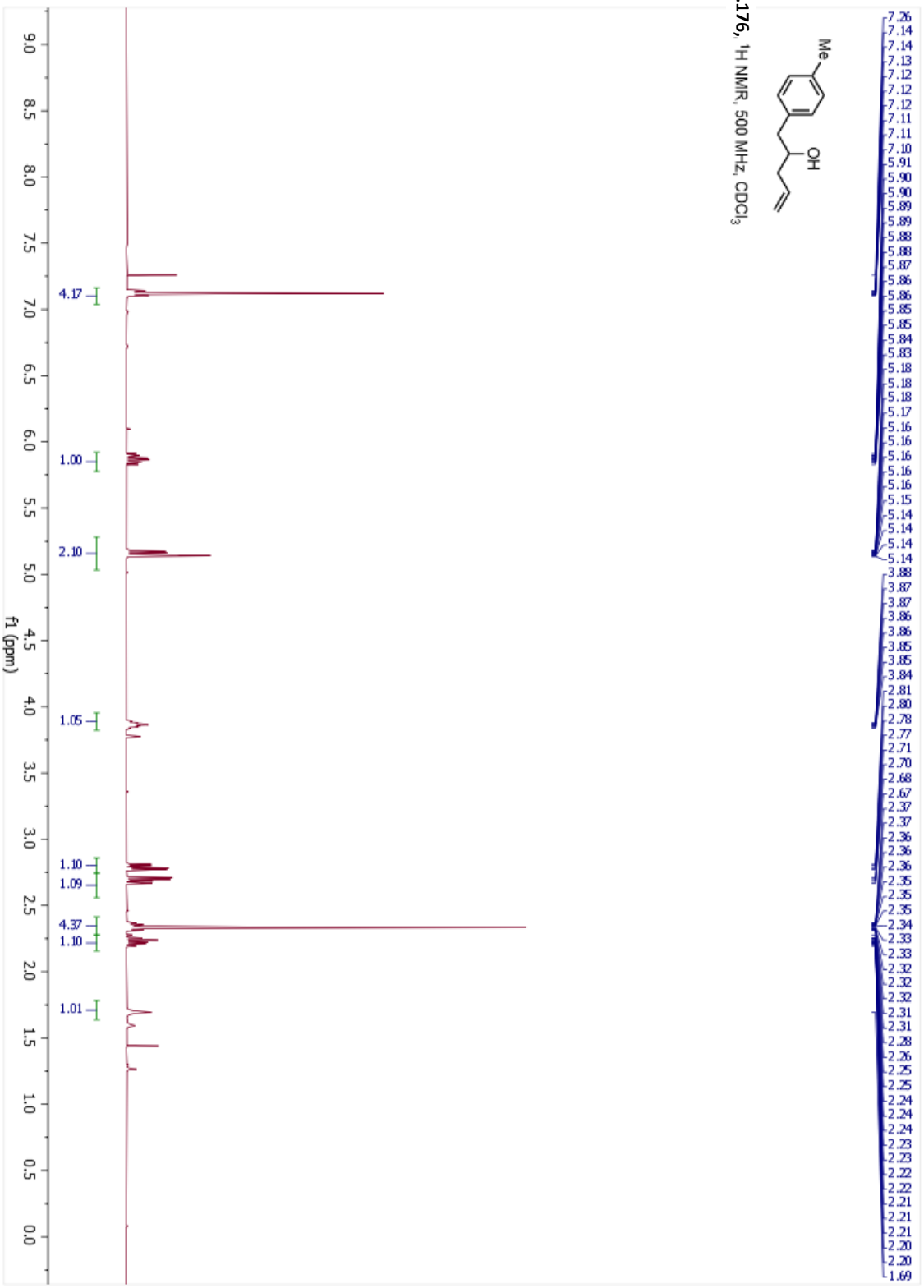

2.174, 1H NMR
500 MHz, CDCl3
f1 (ppm)
1.00
0.98
1.00
2.00
2.02
1.13
2.01
1.05
2.06

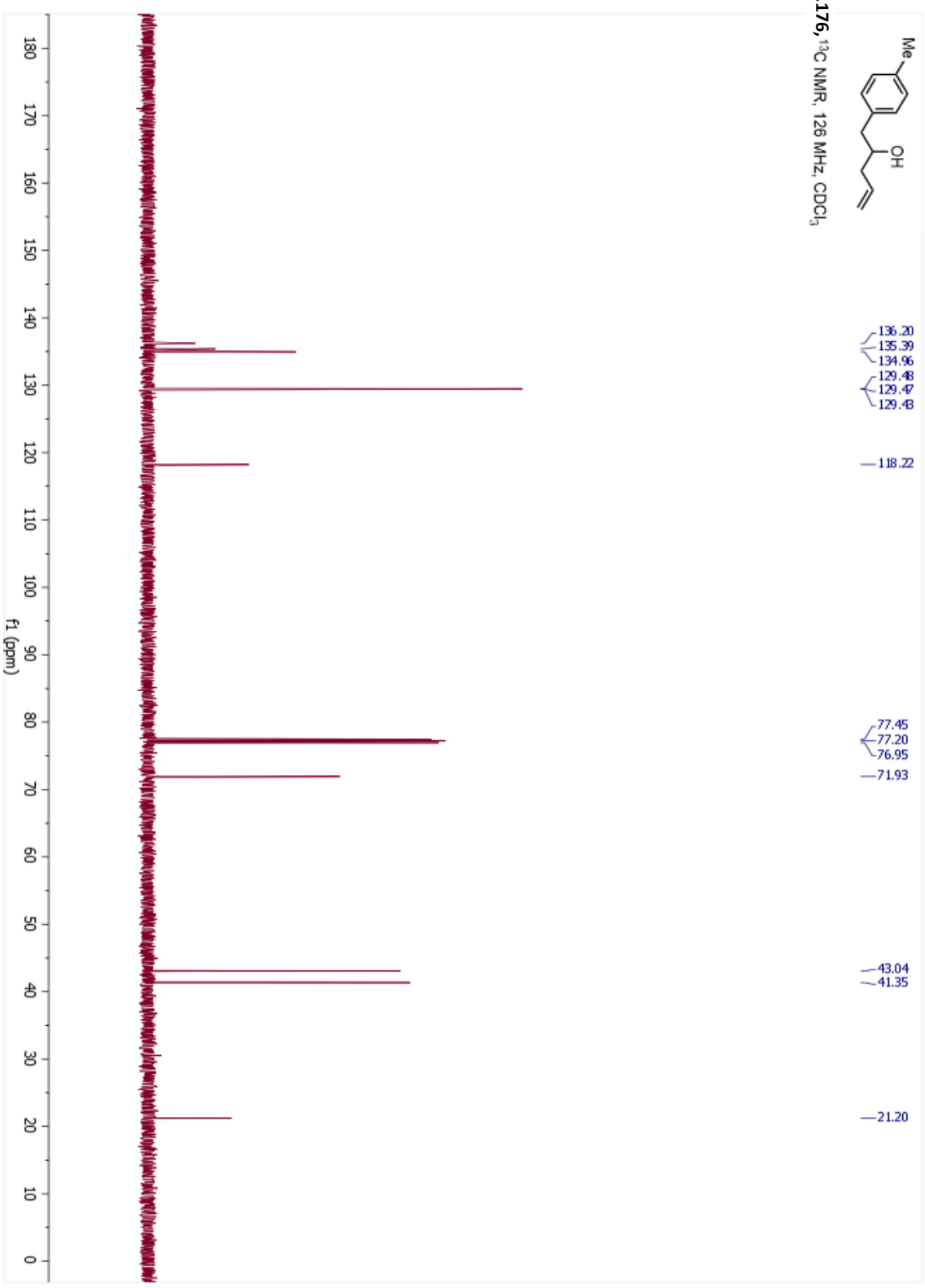


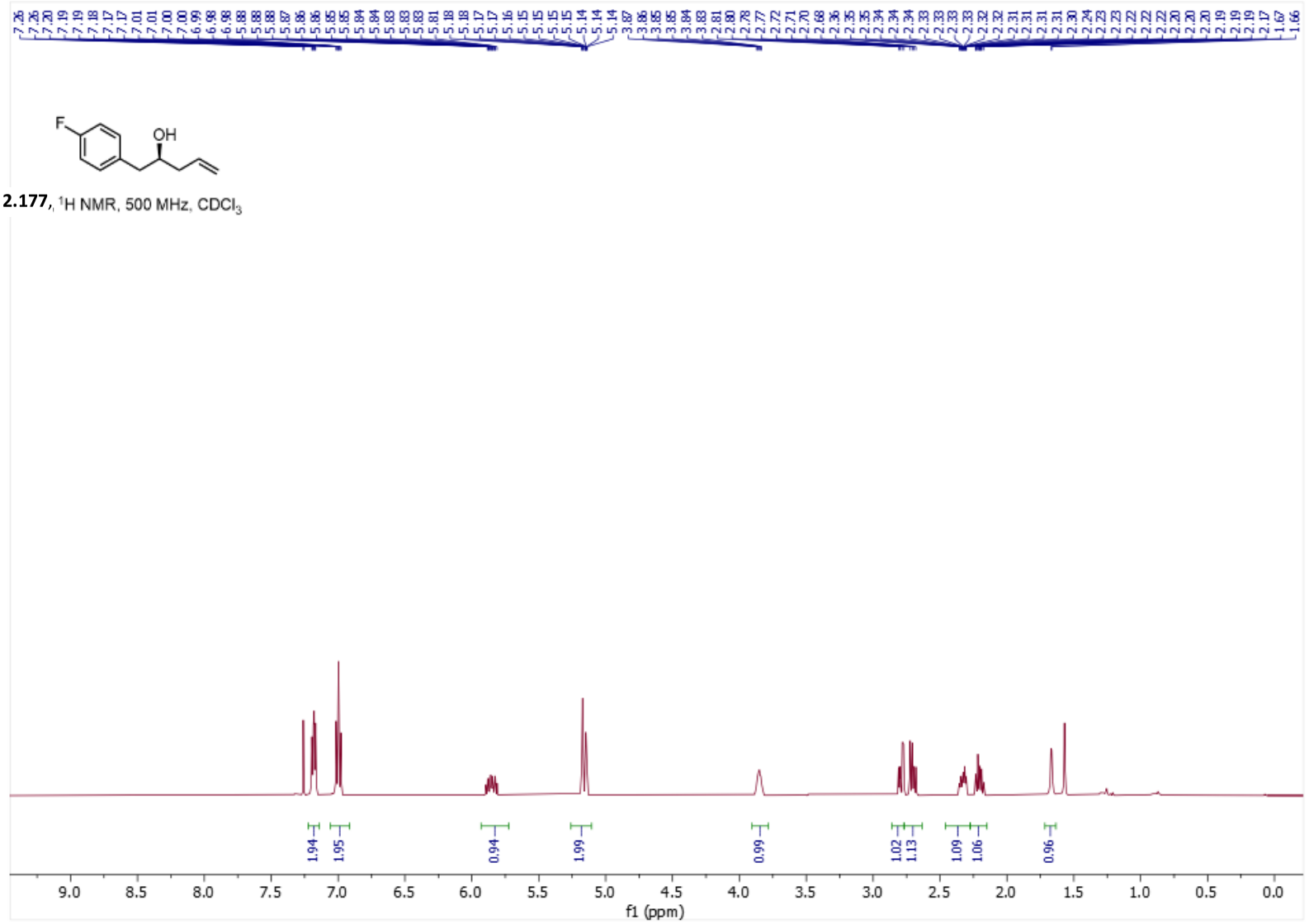
2.158, ^{1}H NMR, 400 MHz, $CDCl_3$

2.158, ^{13}C NMR, 101 MHz, $CDCl_3$

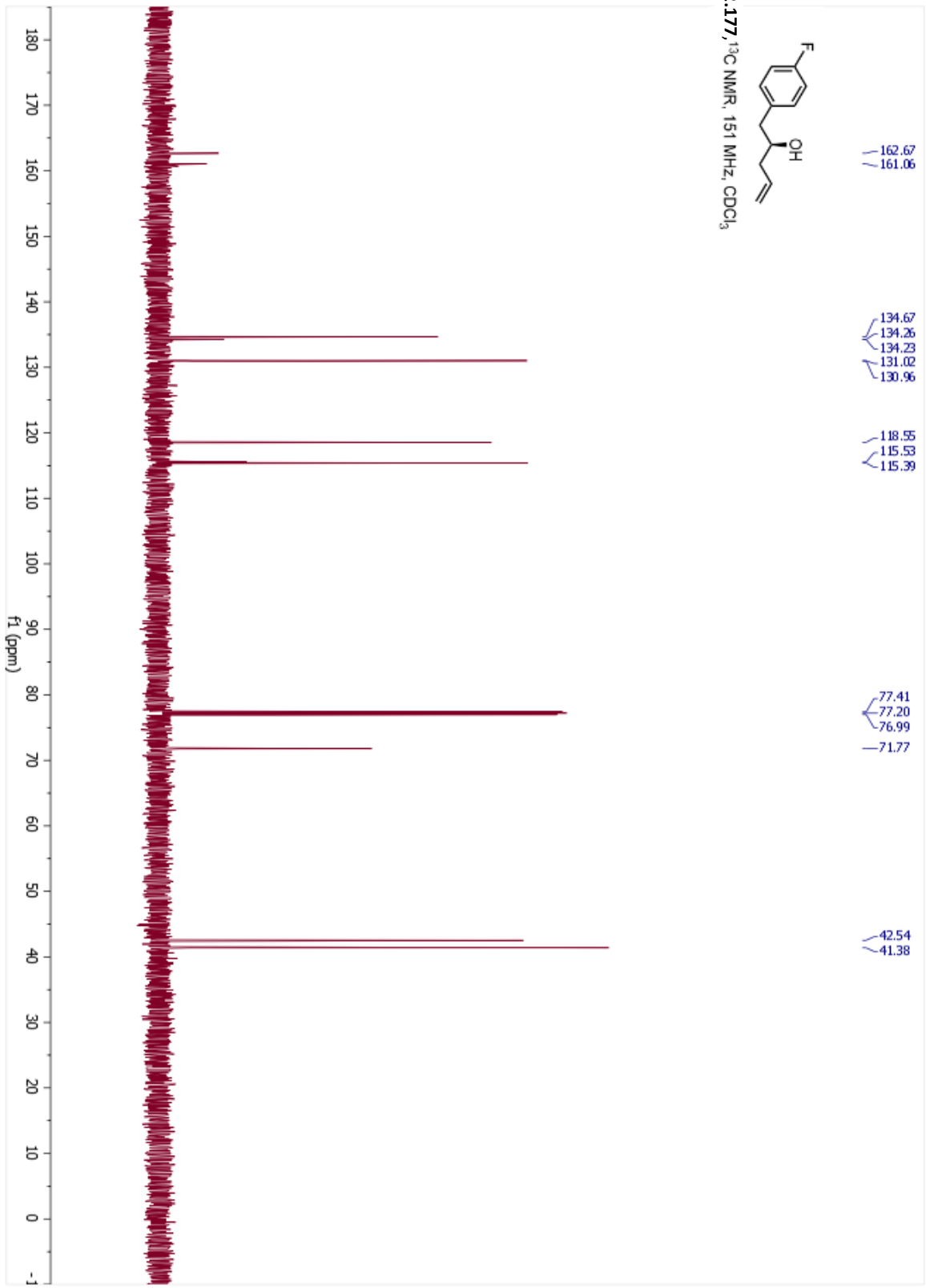


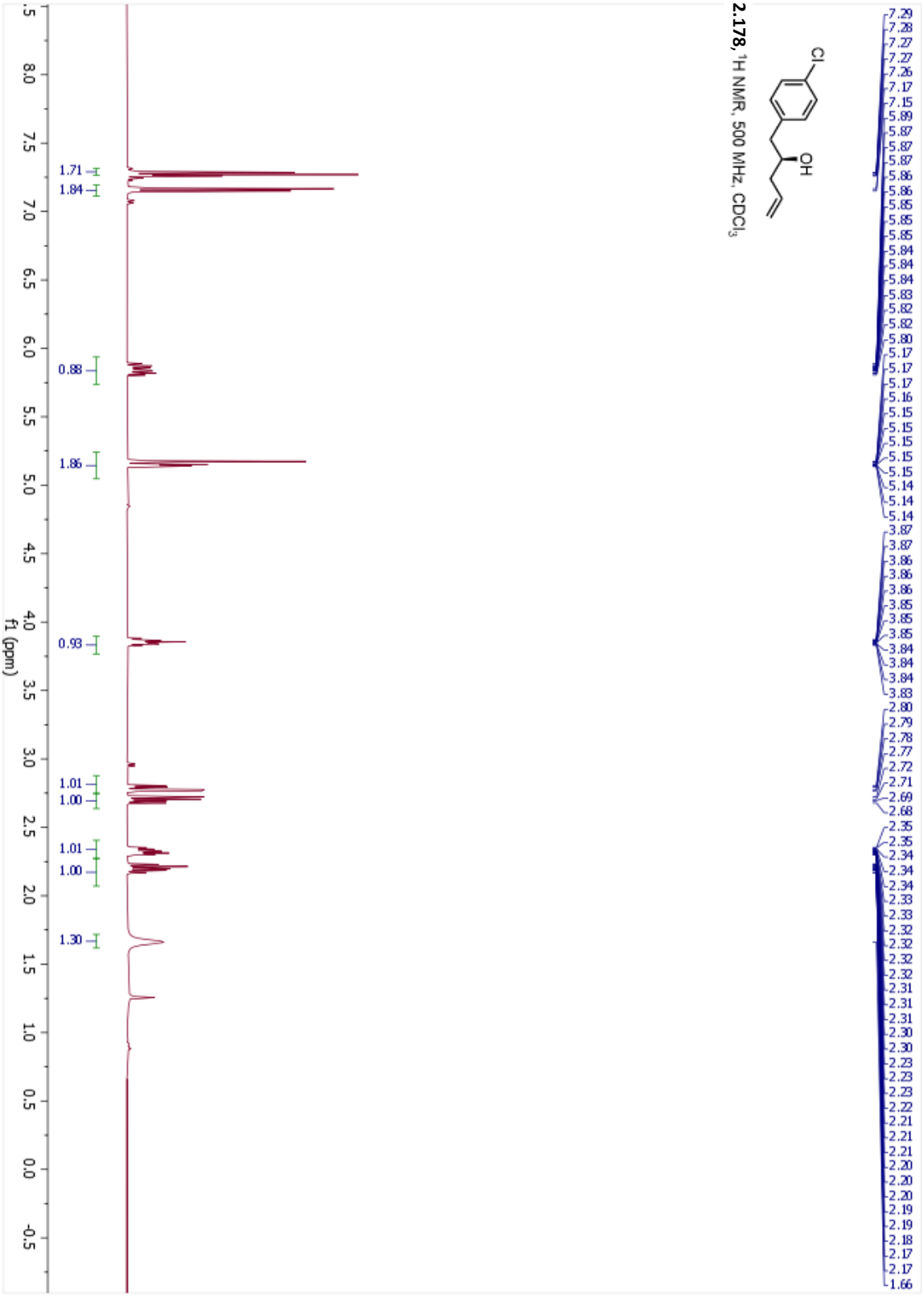

2.176, 1H NMR, 500 MHz, CDCl3
Me
OH
f1 (ppm)
4.17
1.00
2.10
1.05
1.10
1.09
4.37
1.10
1.01

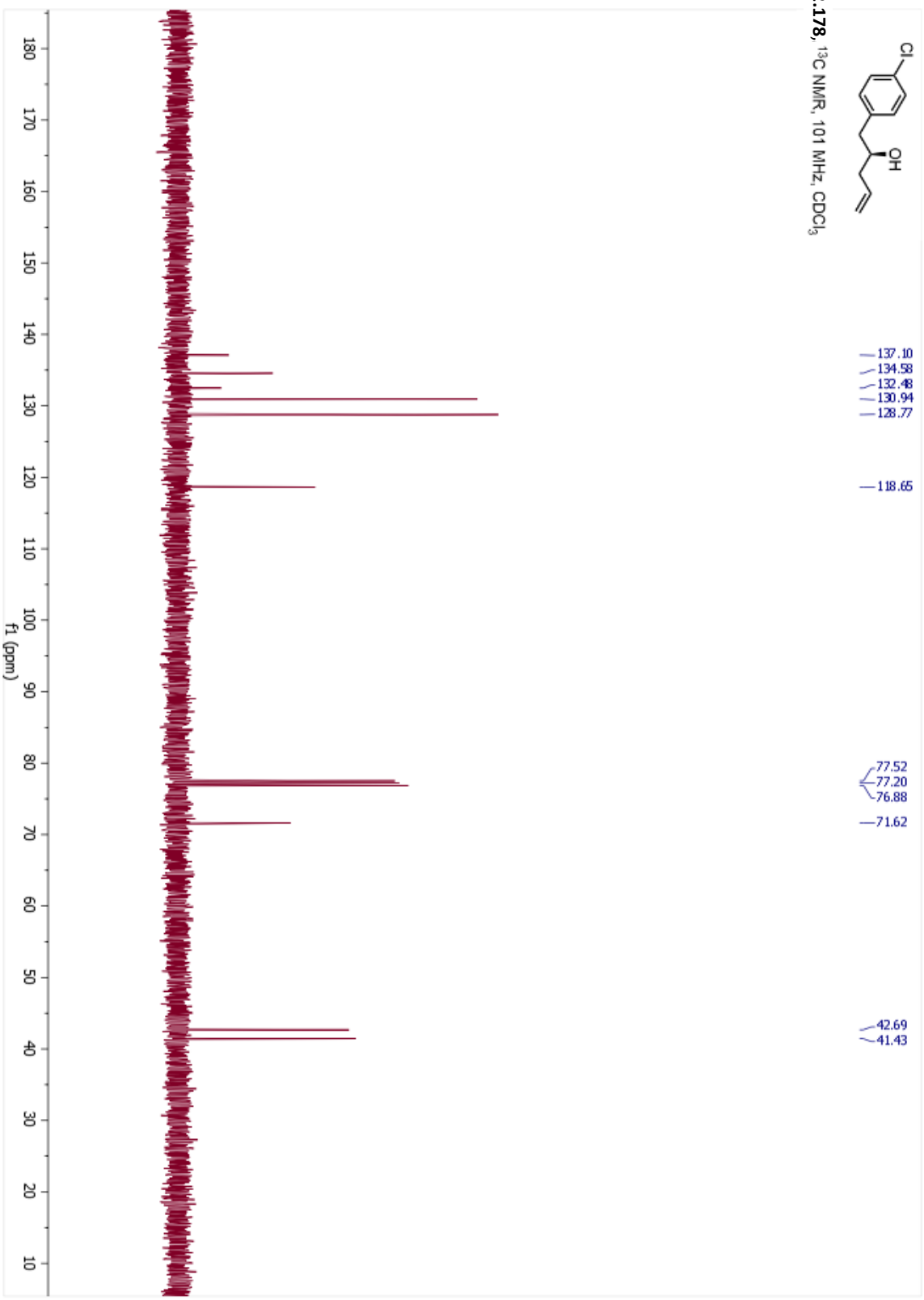

2.176, 13C NMR, 126 MHz, CDCl3
Me
OH
136.20
135.39
134.96
129.48
129.47
129.43
118.22
77.45
77.20
76.95
71.93
43.04
41.35
21.20
f1 (ppm)

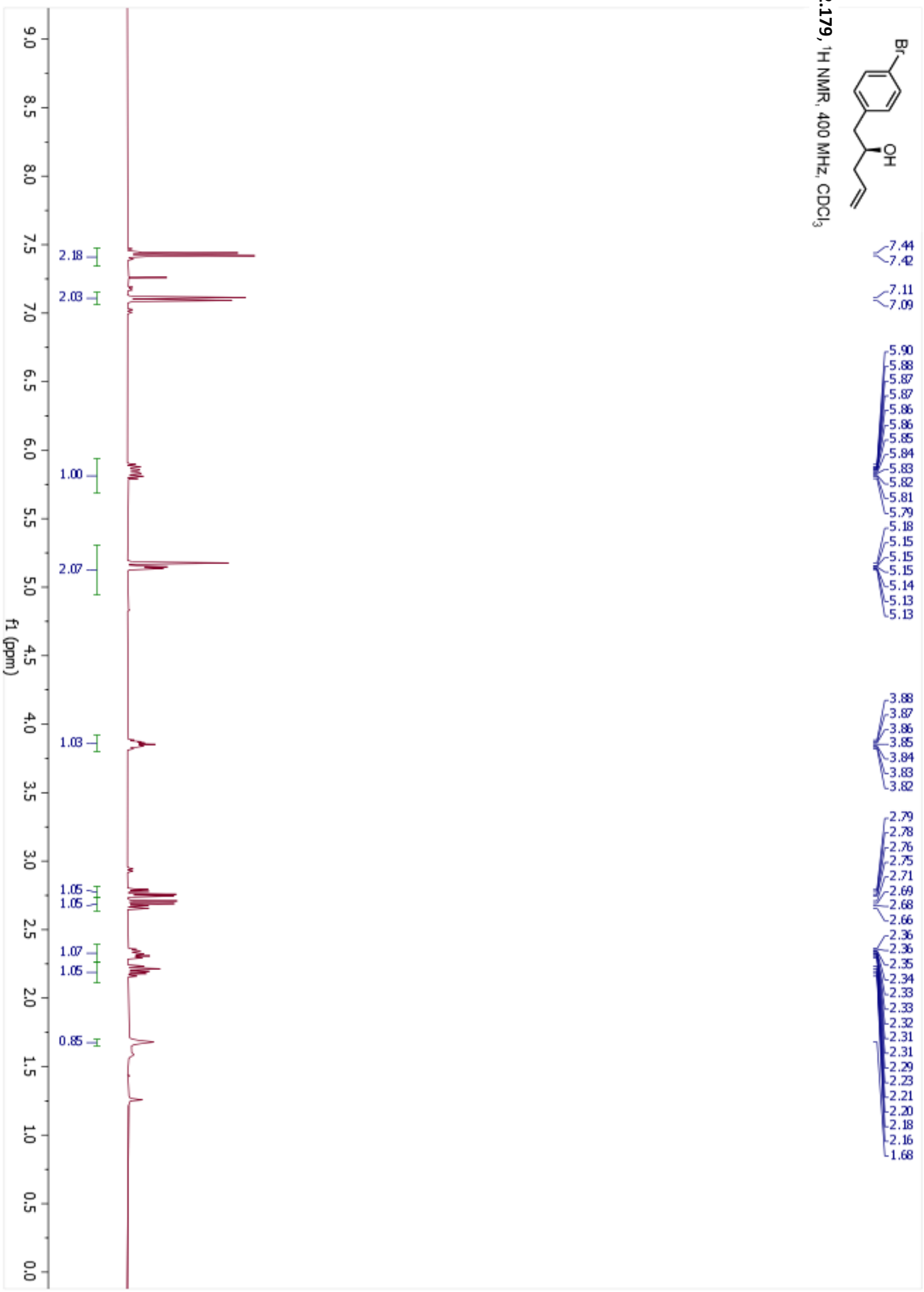


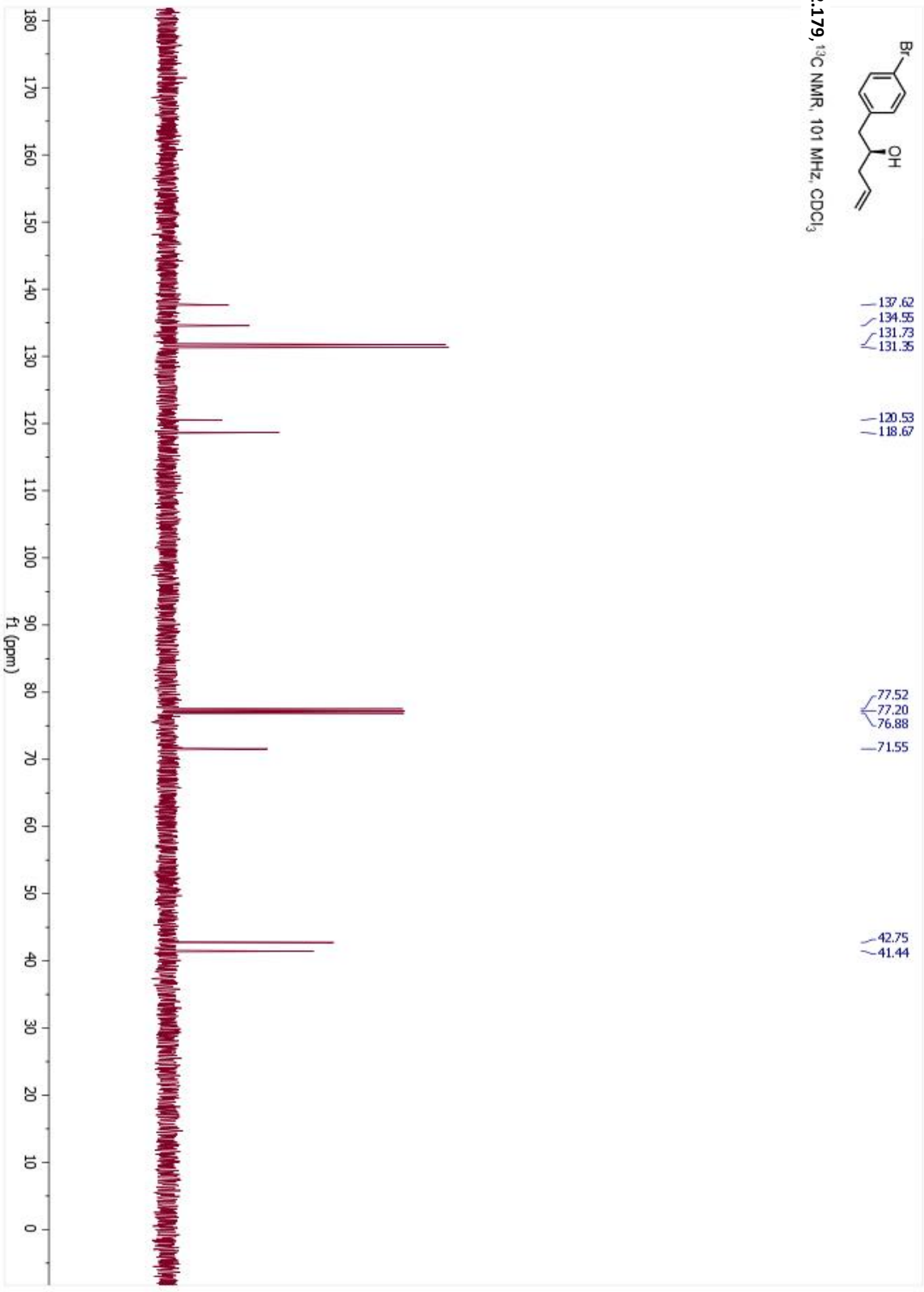
2.177, ^{1}H NMR, 500 MHz, $CDCl_3$

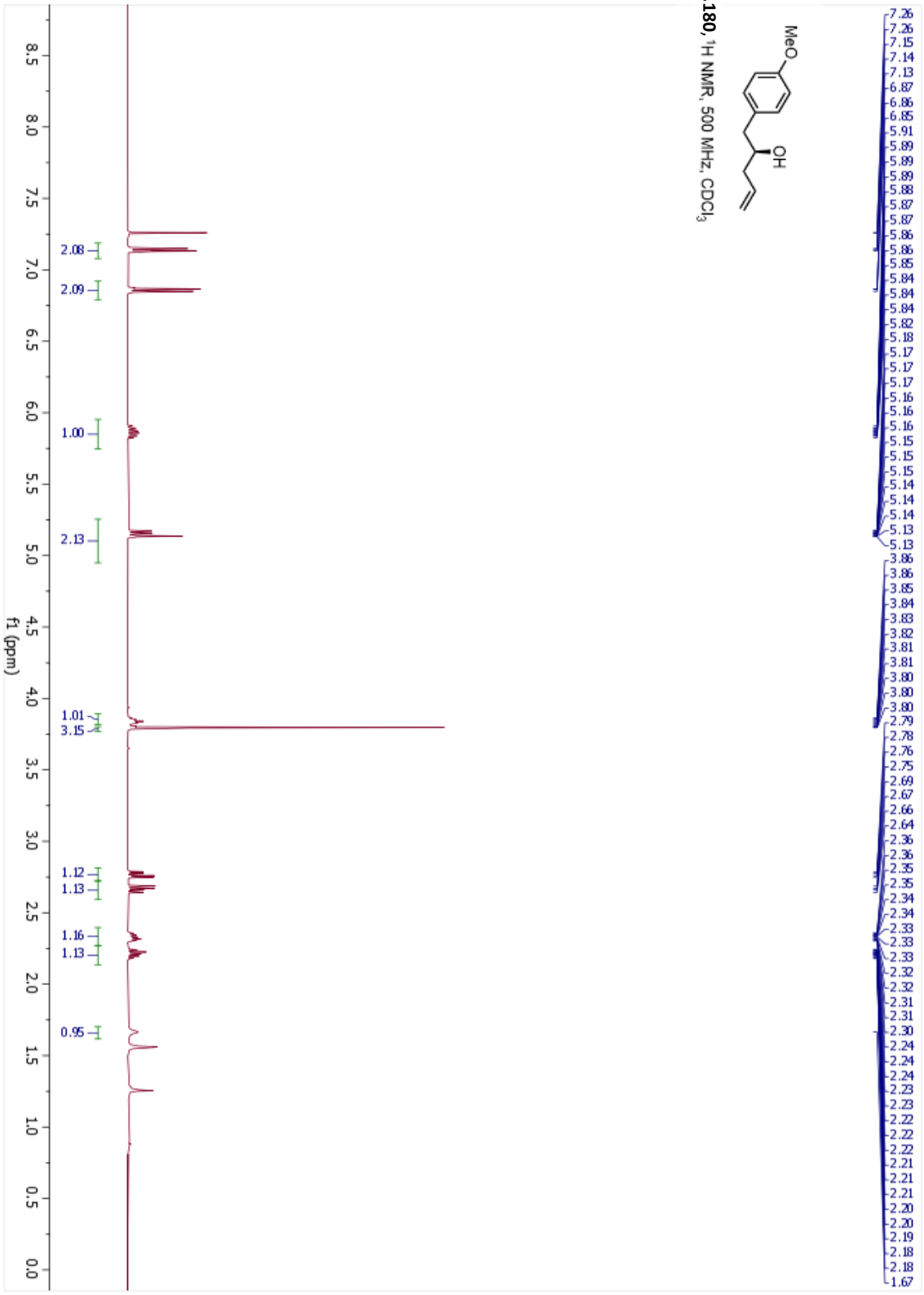

2.177, ^{13}C NMR, 151 MHz, CDCl$_3$
F
OH
162.67
161.06
134.67
134.26
134.23
131.02
130.96
118.55
115.53
115.39
77.41
77.20
76.99
71.77
42.54
41.38
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

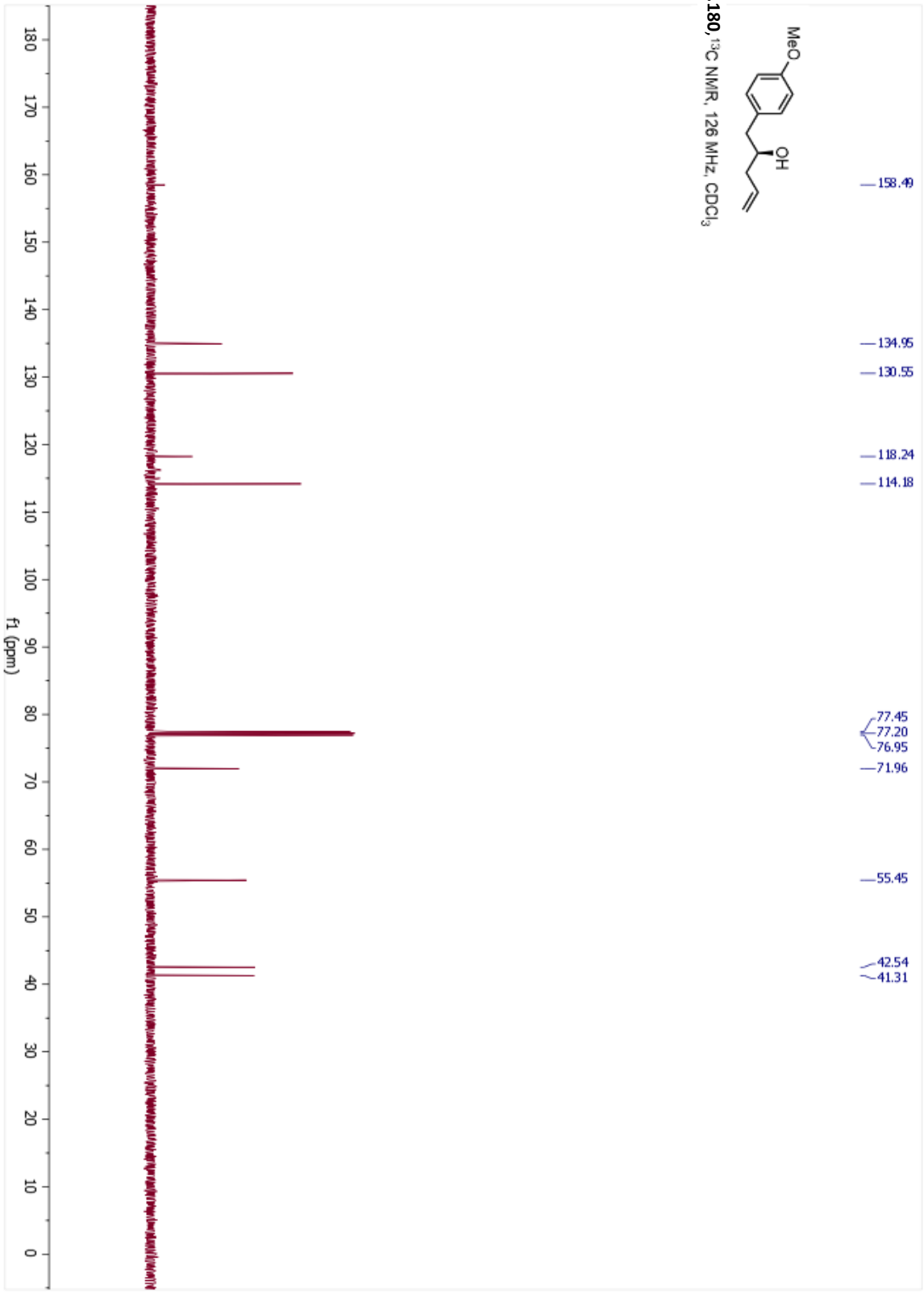

2.178, ^{1}H NMR, 500 MHz, $CDCl_3$
Cl
OH
f1 (ppm)
1.71
1.84
0.88
1.86
0.93
1.01
1.00
1.01
1.00
1.30

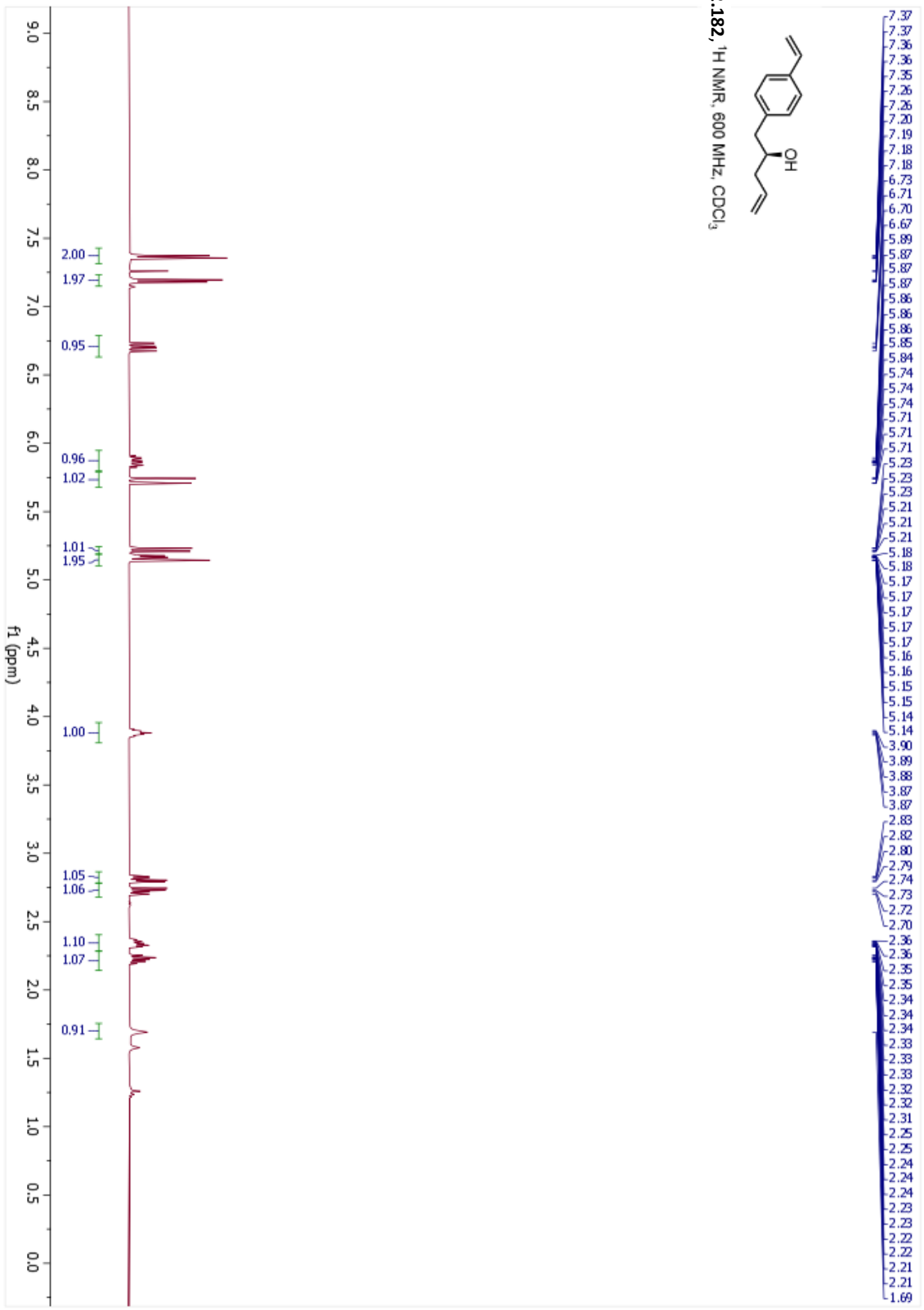

2.178, ^{13}C NMR, 101 MHz, $CDCl_3$
Cl
OH
137.10
134.58
132.48
130.94
128.77
118.65
77.52
77.20
76.88
71.62
42.69
41.43
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

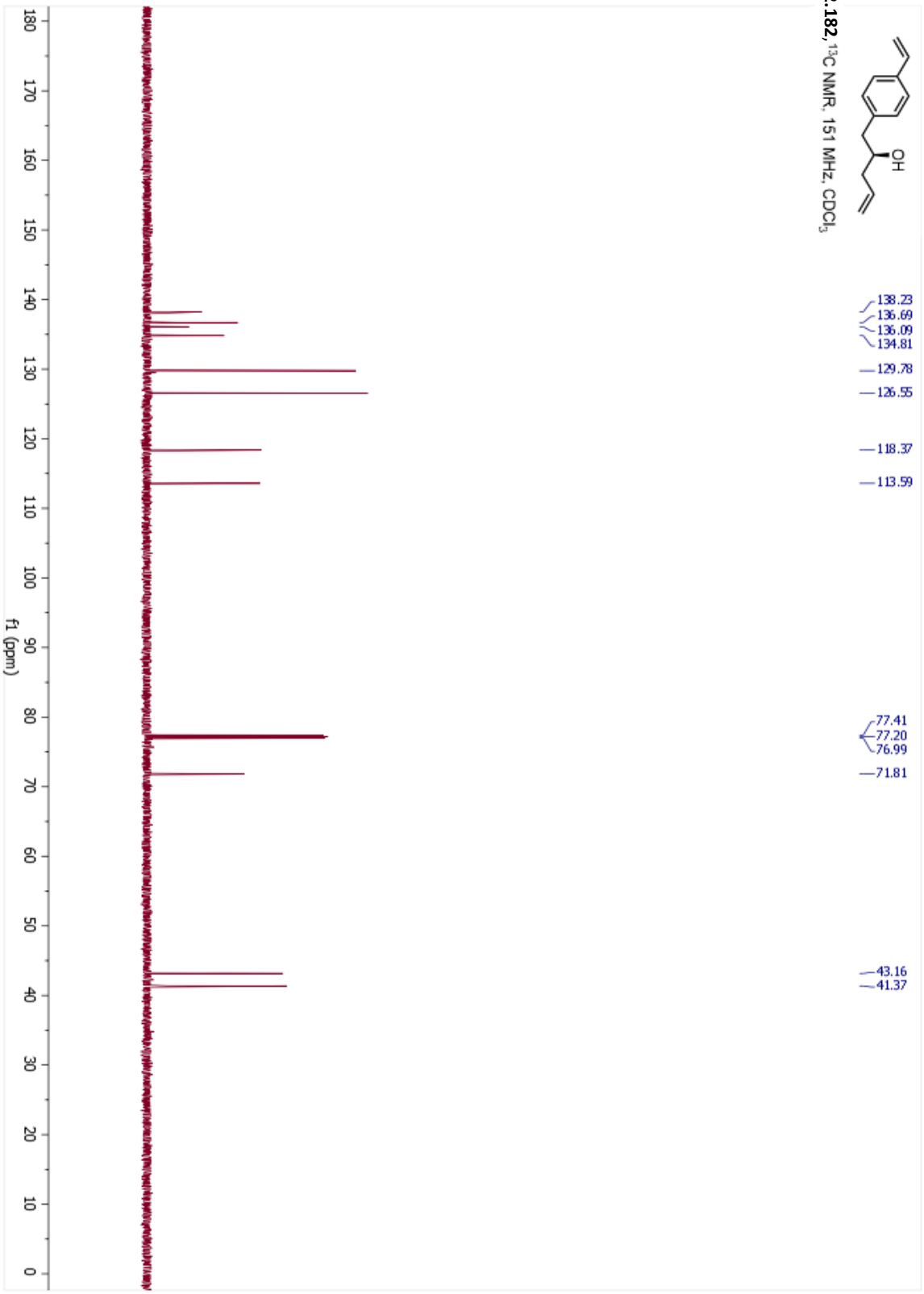

2.179, ^{1}H NMR, 400 MHz, $CDCl_3$
Br
OH
7.44
7.42
7.11
7.09
5.90
5.88
5.87
5.87
5.86
5.86
5.85
5.84
5.83
5.82
5.81
5.79
5.18
5.15
5.15
5.15
5.14
5.13
5.13
3.88
3.87
3.86
3.85
3.84
3.83
3.82
2.79
2.78
2.76
2.75
2.71
2.69
2.68
2.66
2.36
2.36
2.35
2.34
2.33
2.33
2.32
2.31
2.31
2.29
2.23
2.21
2.20
2.18
2.16
1.68
2.18
2.03
1.00
2.07
1.03
1.05
1.05
1.07
1.05
0.85
f1 (ppm)

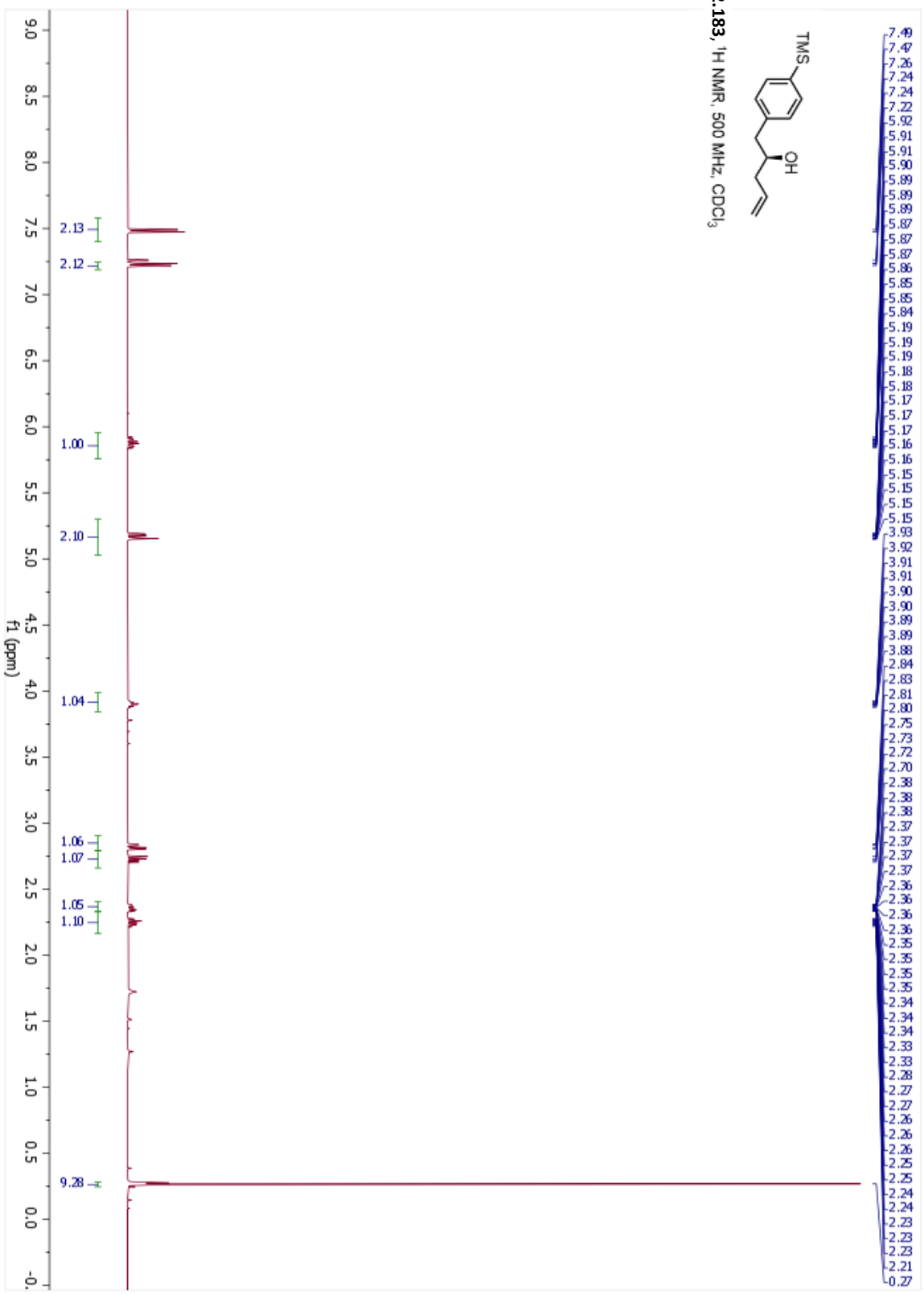

2.179, ^{13}C NMR, 101 MHz, CDCl$_3$
Br
OH
137.62
134.55
131.73
131.35
120.53
118.67
77.52
77.20
76.88
71.55
42.75
41.44
f1 (ppm)


2.180, ^{1}H NMR, 500 MHz, $CDCl_3$
MeO
OH
f1 (ppm)
2.08
2.09
1.00
2.13
1.01
3.15
1.12
1.13
1.16
1.13
0.95


2.180, 13C NMR, 126 MHz, CDCl3
MeO
OH
158.49
134.95
130.55
118.24
114.18
77.45
77.20
76.95
71.96
55.45
42.54
41.31
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

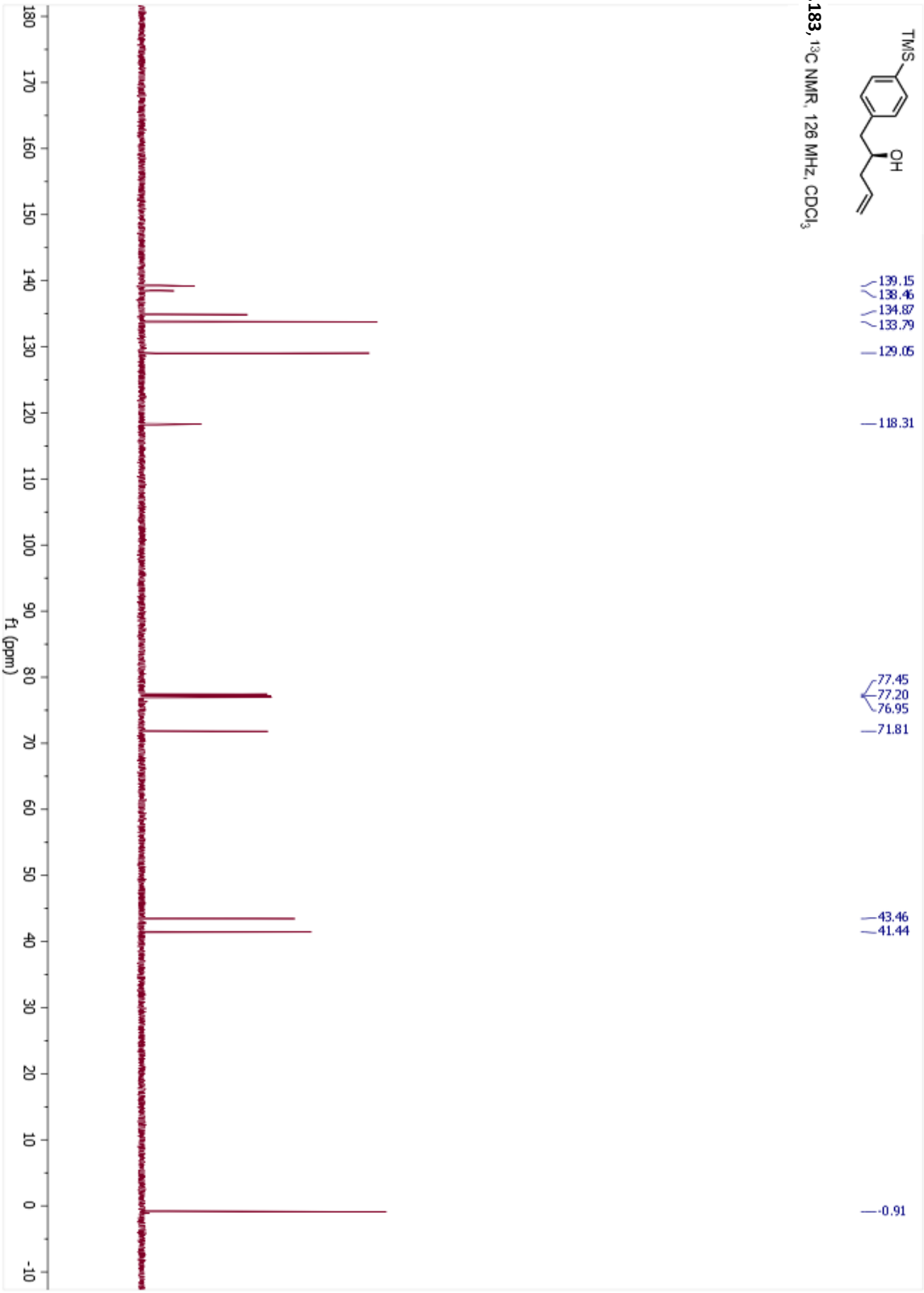

2.182, ^{1}H NMR, 600 MHz, $CDCl_3$
OH
f1 (ppm)
2.00
1.97
0.95
0.96
1.02
1.01
1.95
1.00
1.05
1.06
1.10
1.07
0.91

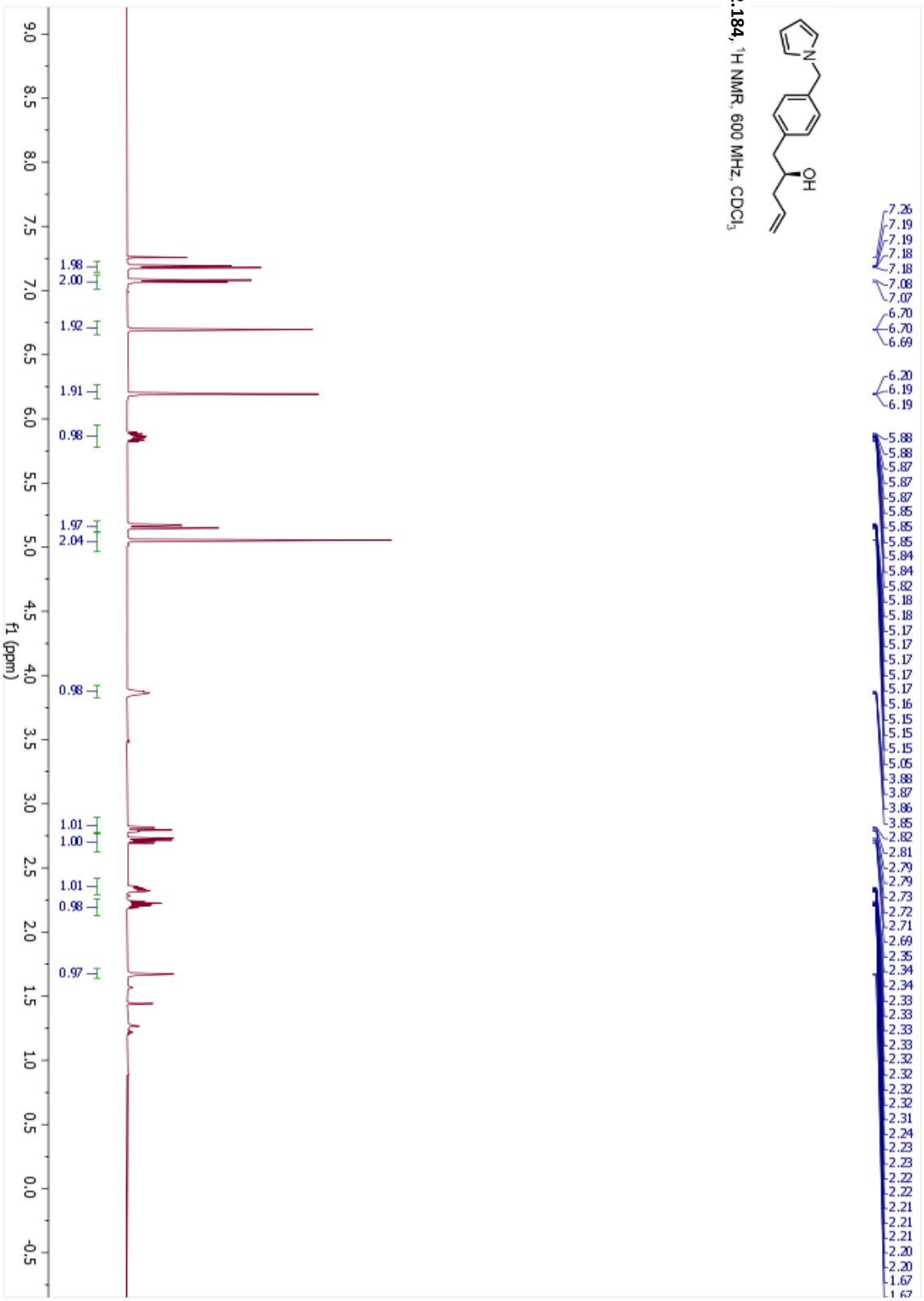

2.182, 13C NMR, 151 MHz, CDCl3
OH
138.23
136.69
136.09
134.81
129.78
126.55
118.37
113.59
77.41
77.20
76.99
71.81
43.16
41.37
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

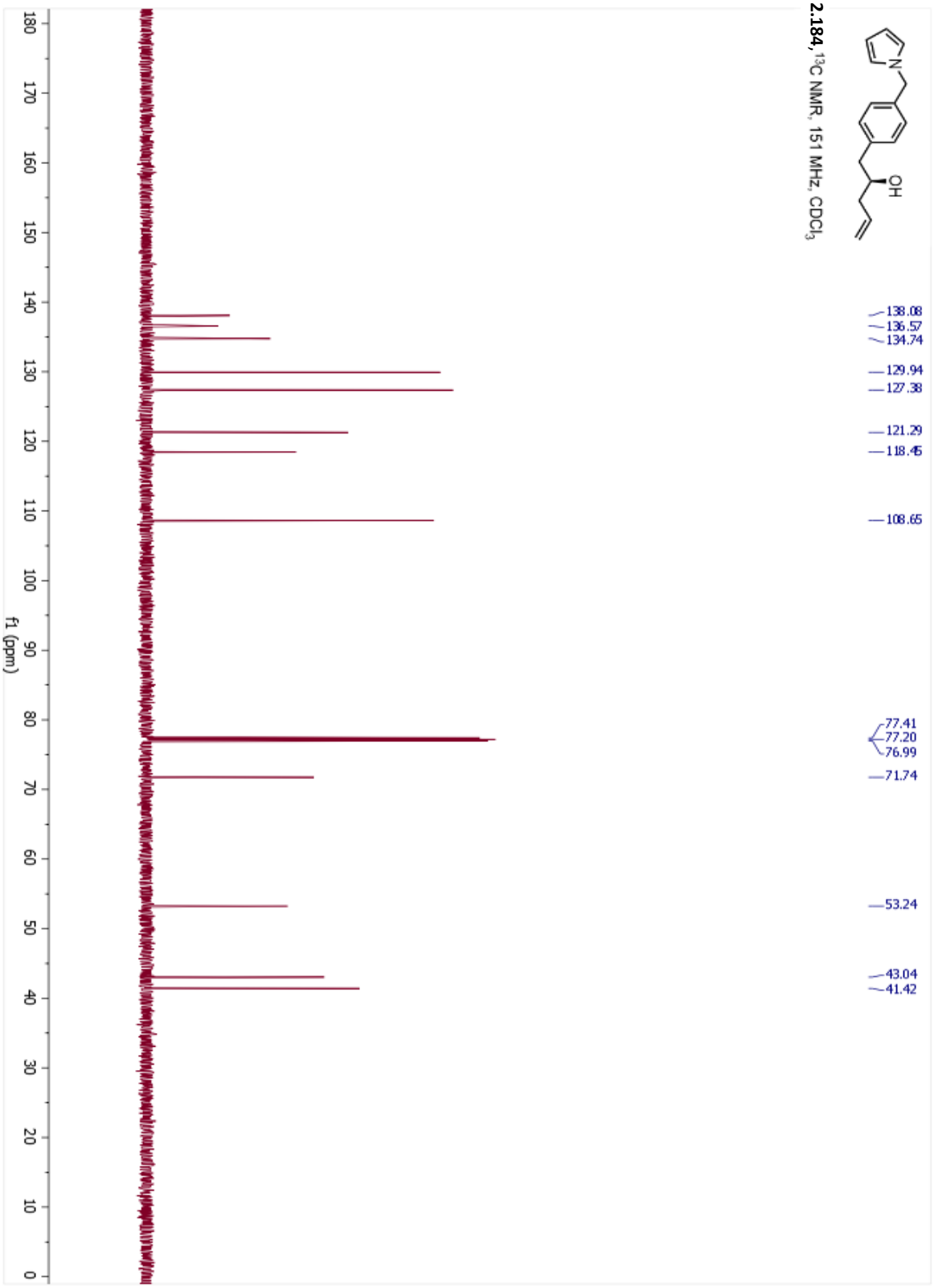


2.183, ^{1}H NMR, 500 MHz, $CDCl_3$

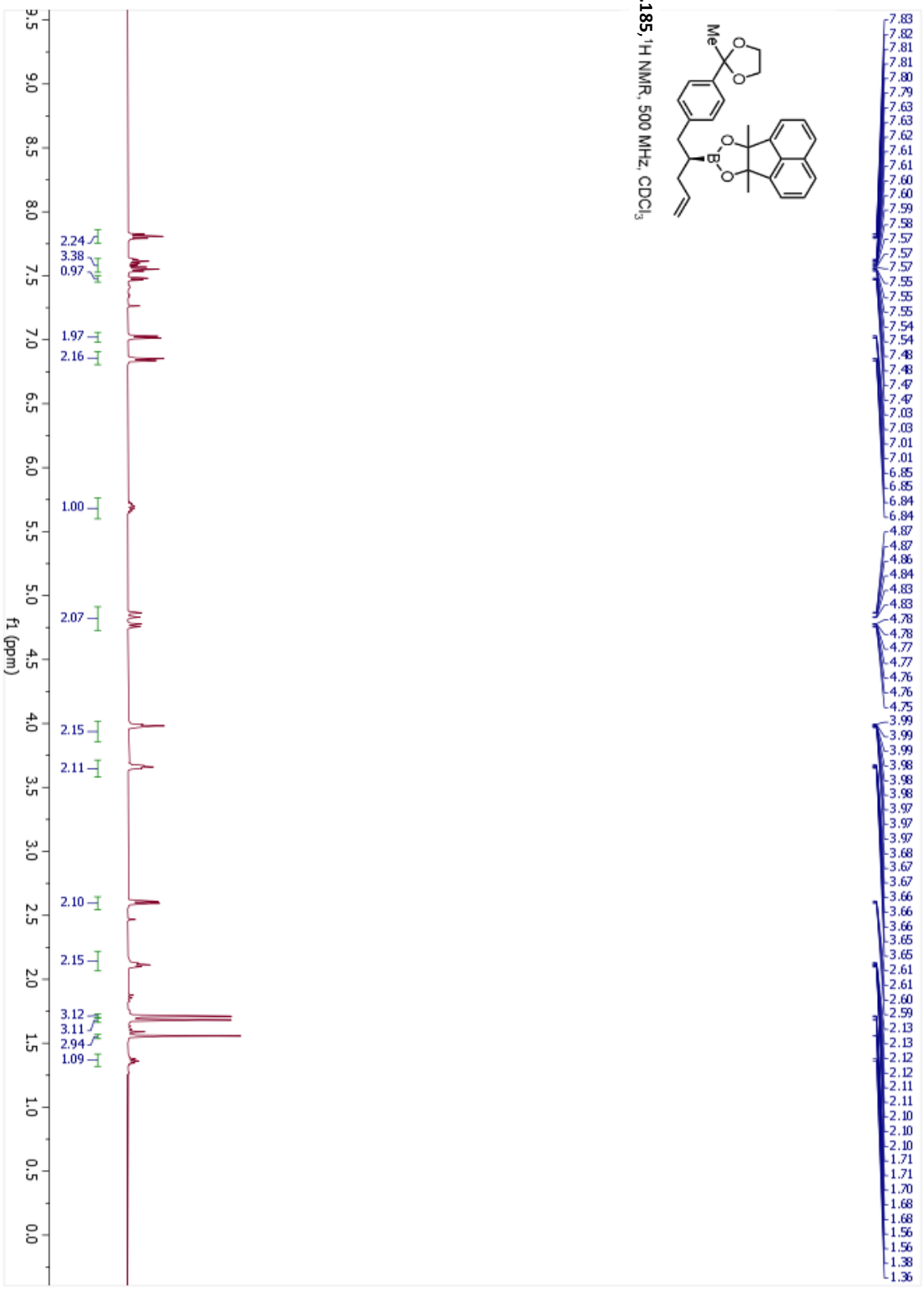
2.183, ^{13}C NMR, 126 MHz, $CDCl_3$



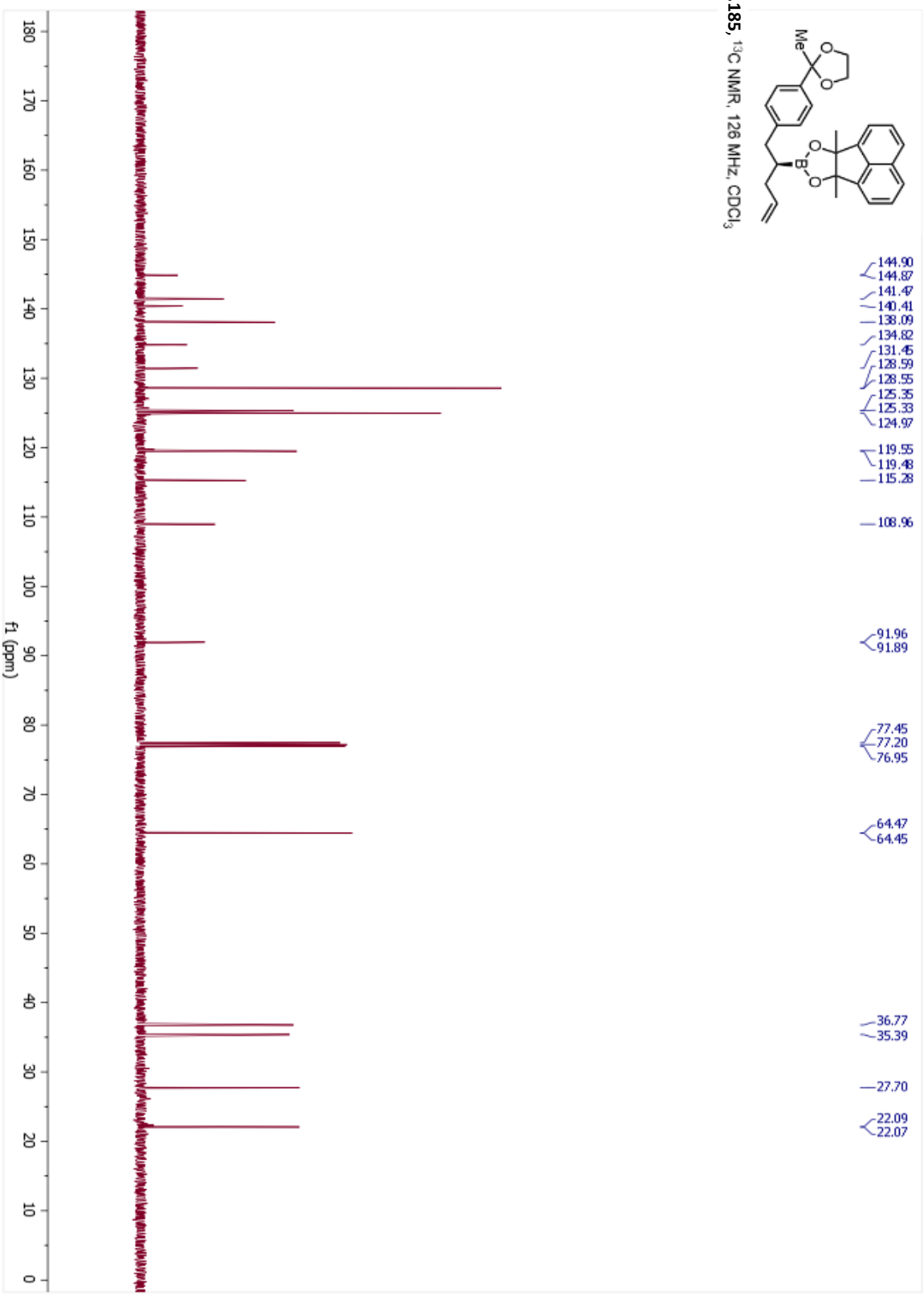

2.184, ^{1}H NMR, 600 MHz, $CDCl_3$
OH
f1 (ppm)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
1.98 2.00 1.92 1.91 0.98 1.97 2.04 0.98 1.01 1.00 1.01 0.98 0.97
7.26 7.19 7.19 7.18 7.18 7.08 7.07 6.70 6.70 6.69 6.20 6.19 6.19
5.88 5.88 5.87 5.87 5.87 5.85 5.85 5.85 5.84 5.84 5.82 5.18 5.18 5.17 5.17 5.17 5.17 5.17 5.16 5.15 5.15 5.15 5.05
3.88 3.87 3.86 3.85
2.82 2.81 2.79 2.79 2.73 2.72 2.71 2.69 2.35 2.34 2.34 2.33 2.33 2.33 2.33 2.32 2.32 2.32 2.32 2.31 2.24 2.23 2.23 2.22 2.22 2.21 2.21 2.21 2.20 2.20 1.67

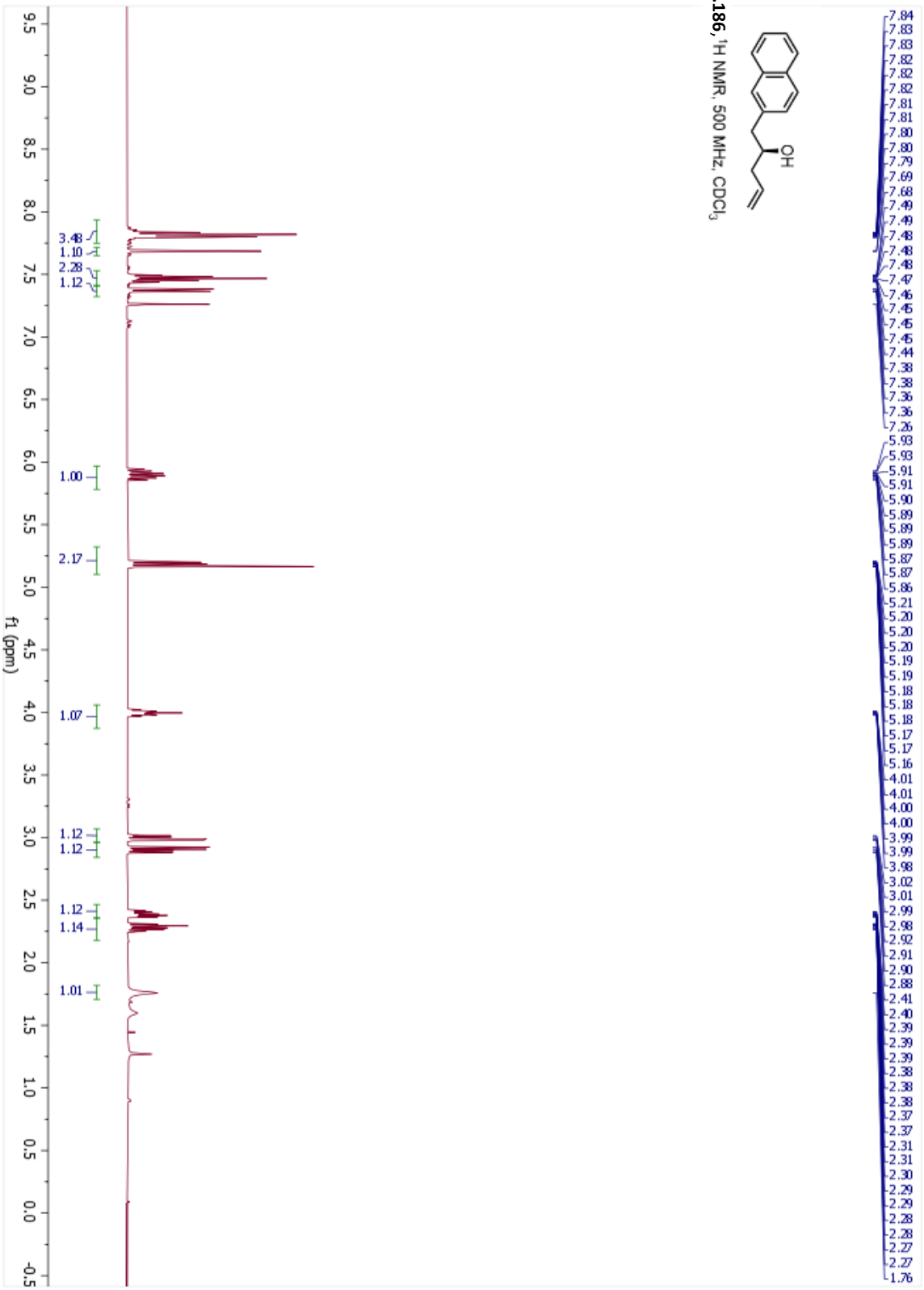

2.184, 13C NMR, 151 MHz, CDCl3
OH
138.08
136.57
134.74
129.94
127.38
121.29
118.45
108.65
77.41
77.20
76.99
71.74
53.24
43.04
41.42
f1 (ppm)

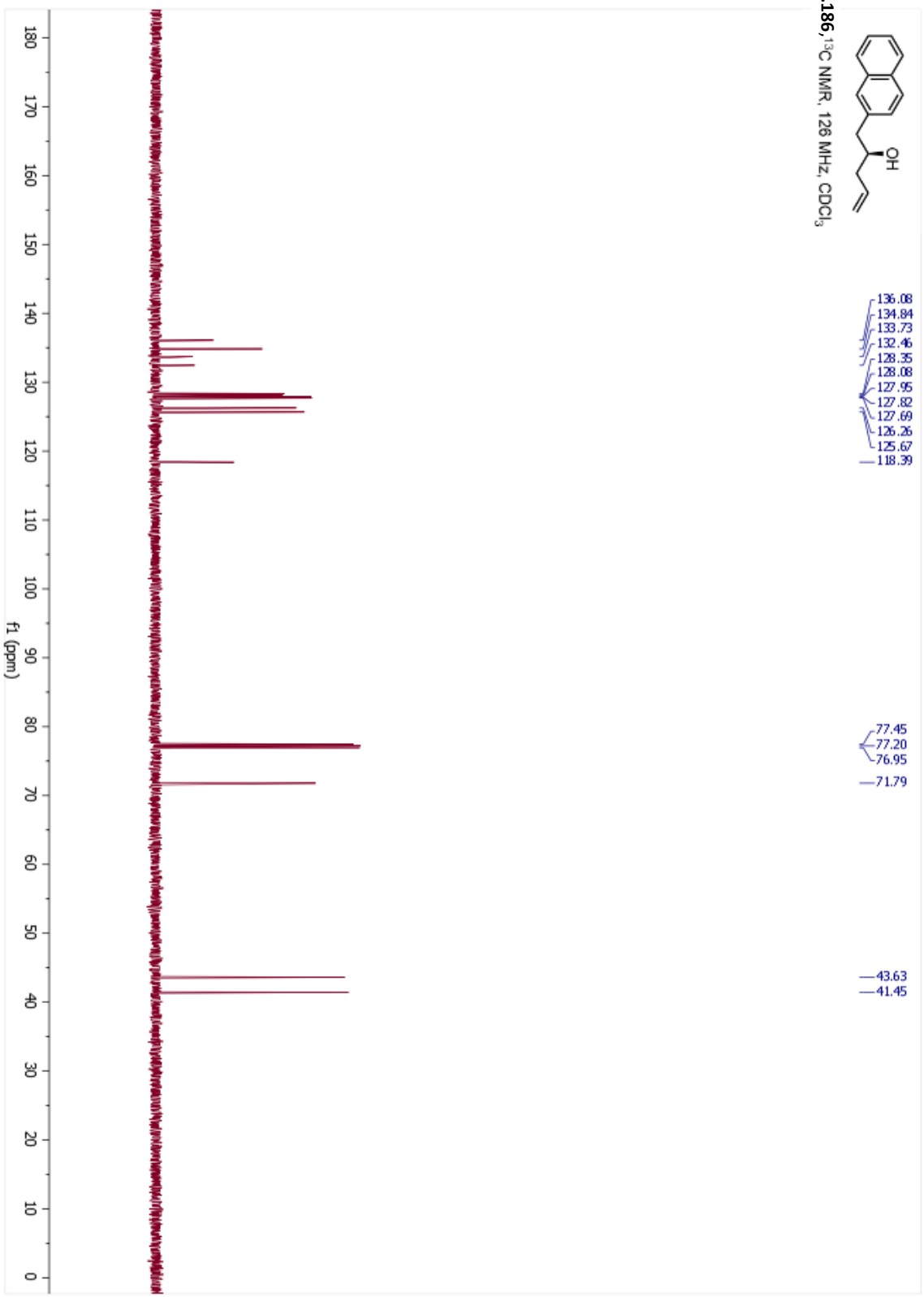
2.185, ^{1}H NMR, 500 MHz, $CDCl_3$

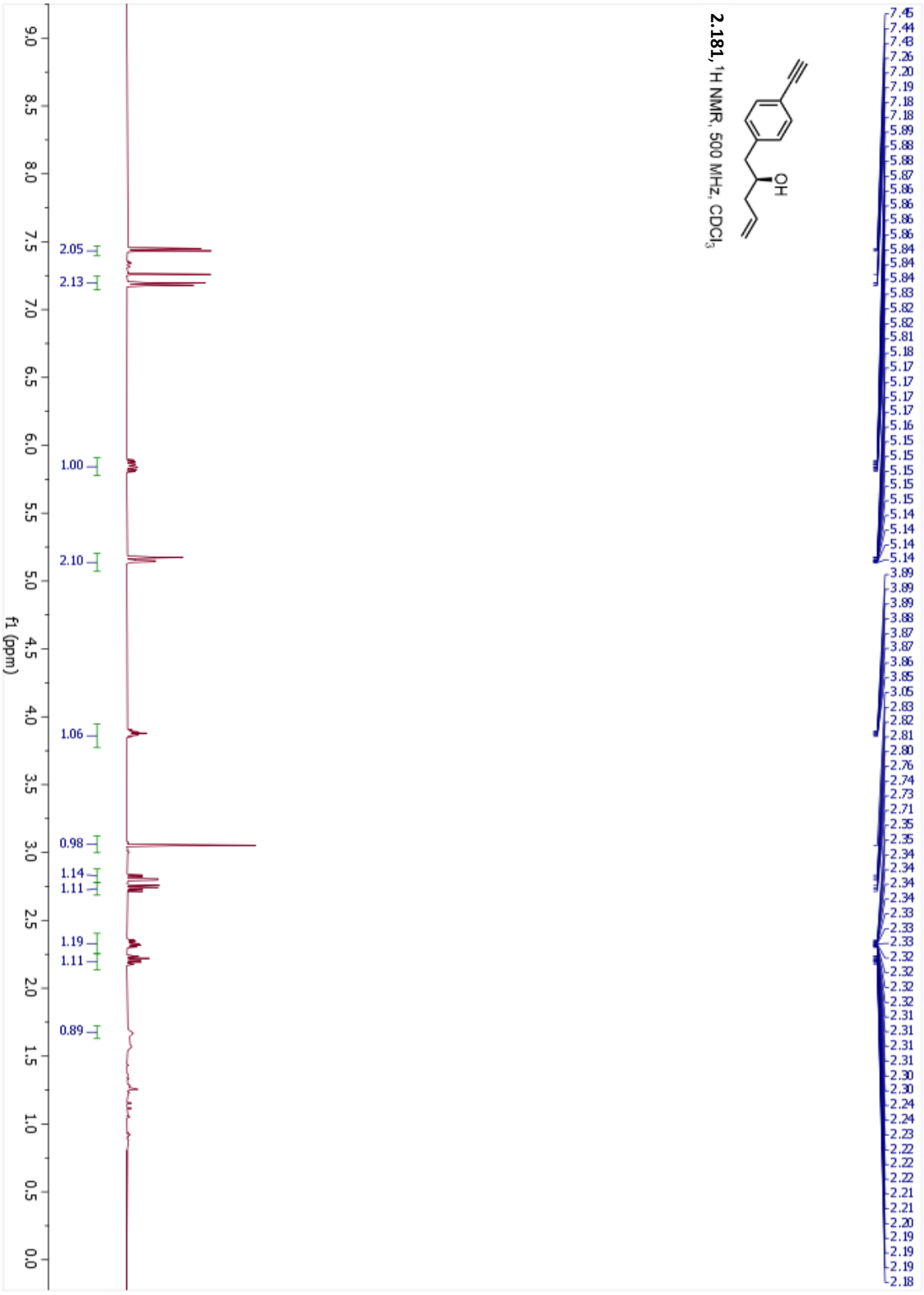


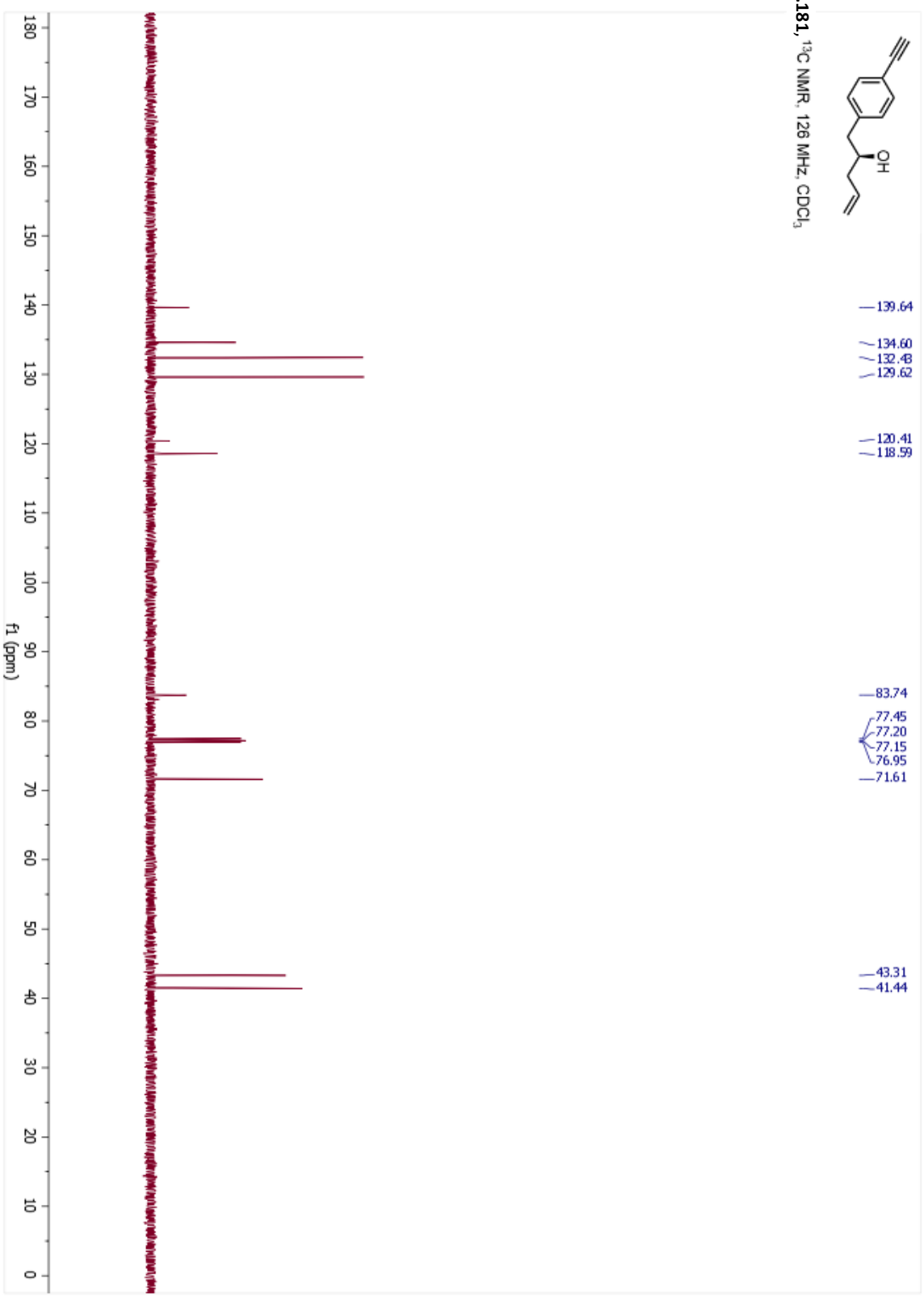
2.185, ^{13}C NMR, 126 MHz, $CDCl_3$

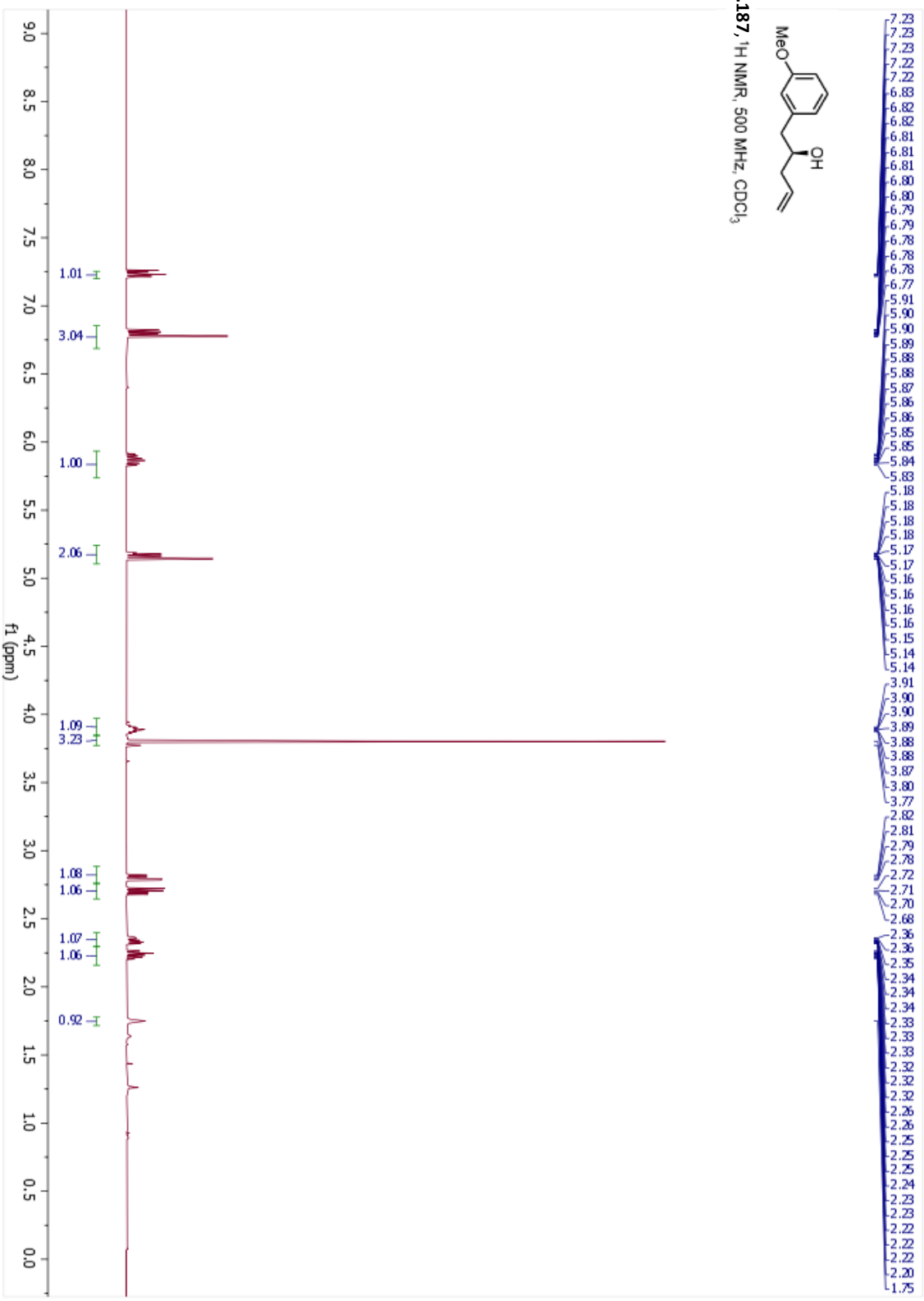


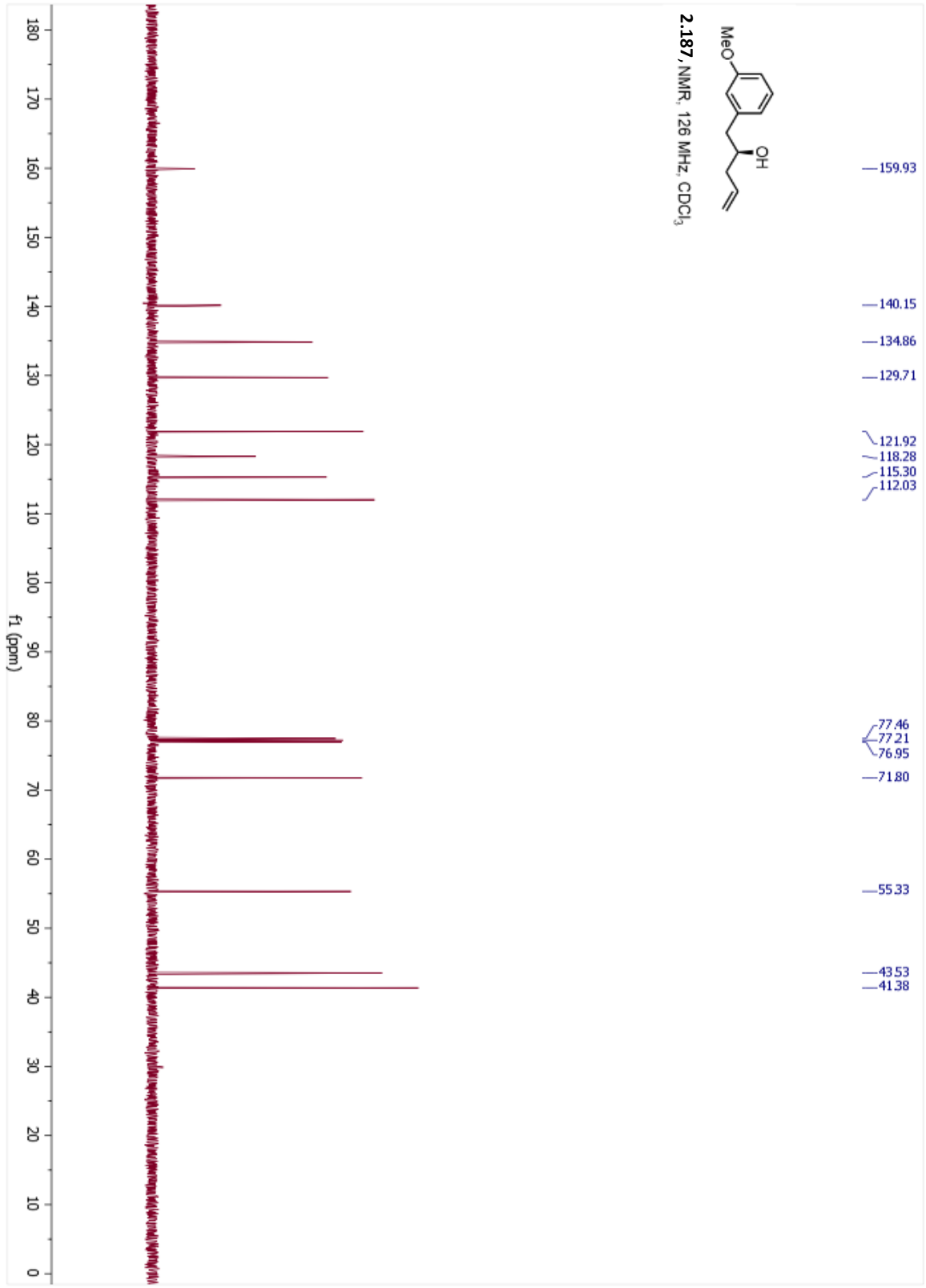

2.186, ^{1}H NMR, 500 MHz, $CDCl_3$
OH
f1 (ppm)
3.48
1.10
2.28
1.12
1.00
2.17
1.07
1.12
1.12
1.12
1.14
1.01

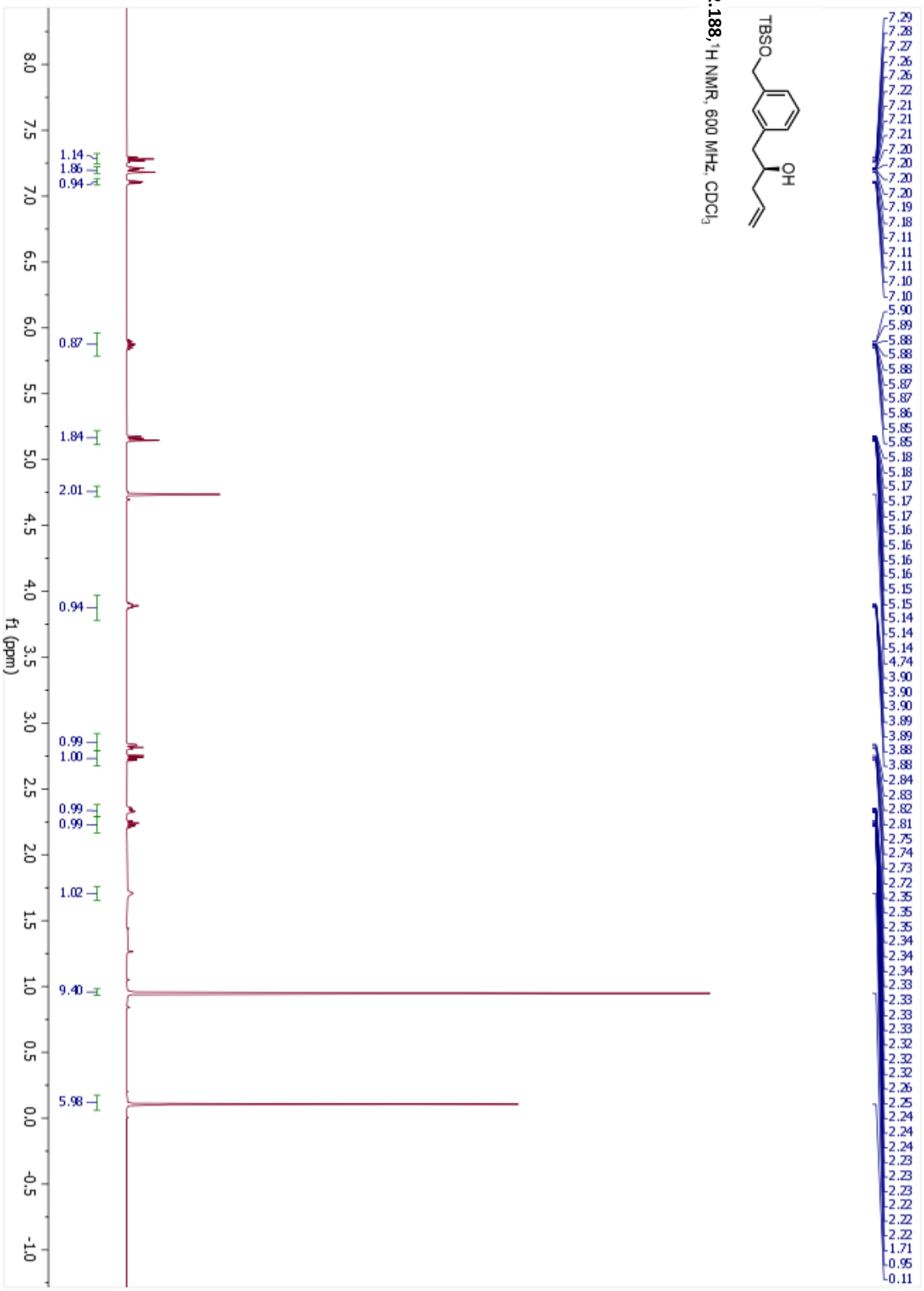

2.186, ^{13}C NMR, 126 MHz, CDCl$_3$
OH
136.08
134.84
133.73
132.46
128.35
128.08
127.95
127.82
127.69
126.26
125.67
118.39
77.45
77.20
76.95
71.79
43.63
41.45
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


2.181, ^{1}H NMR, 500 MHz, $CDCl_3$
OH
f1 (ppm)
2.05
2.13
1.00
2.10
1.06
0.98
1.14
1.11
1.19
1.11
0.89

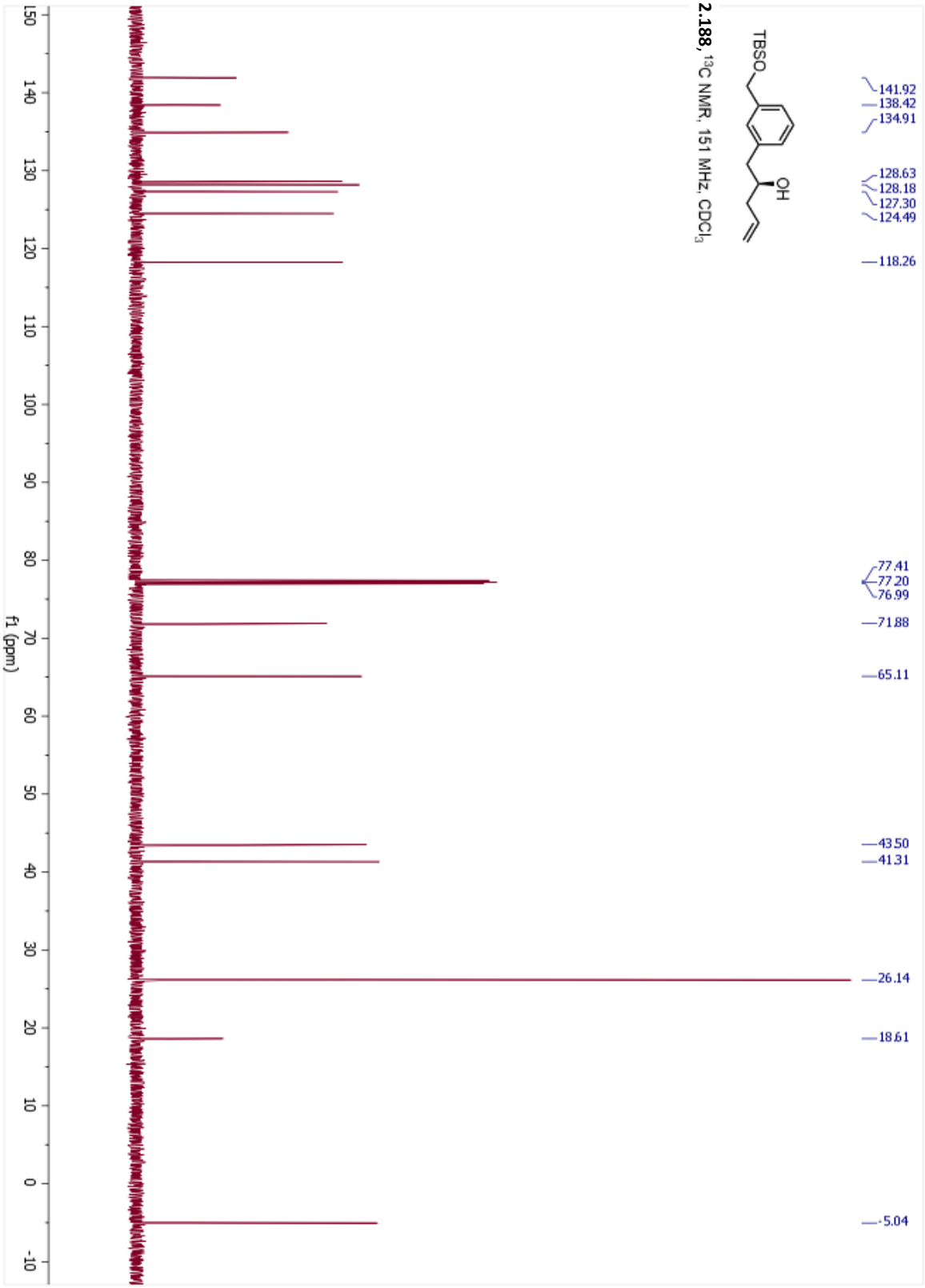

2.181, ^{13}C NMR, 126 MHz, $CDCl_3$
OH
139.64
134.60
132.48
129.62
120.41
118.59
83.74
77.45
77.20
77.15
76.95
71.61
43.31
41.44
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

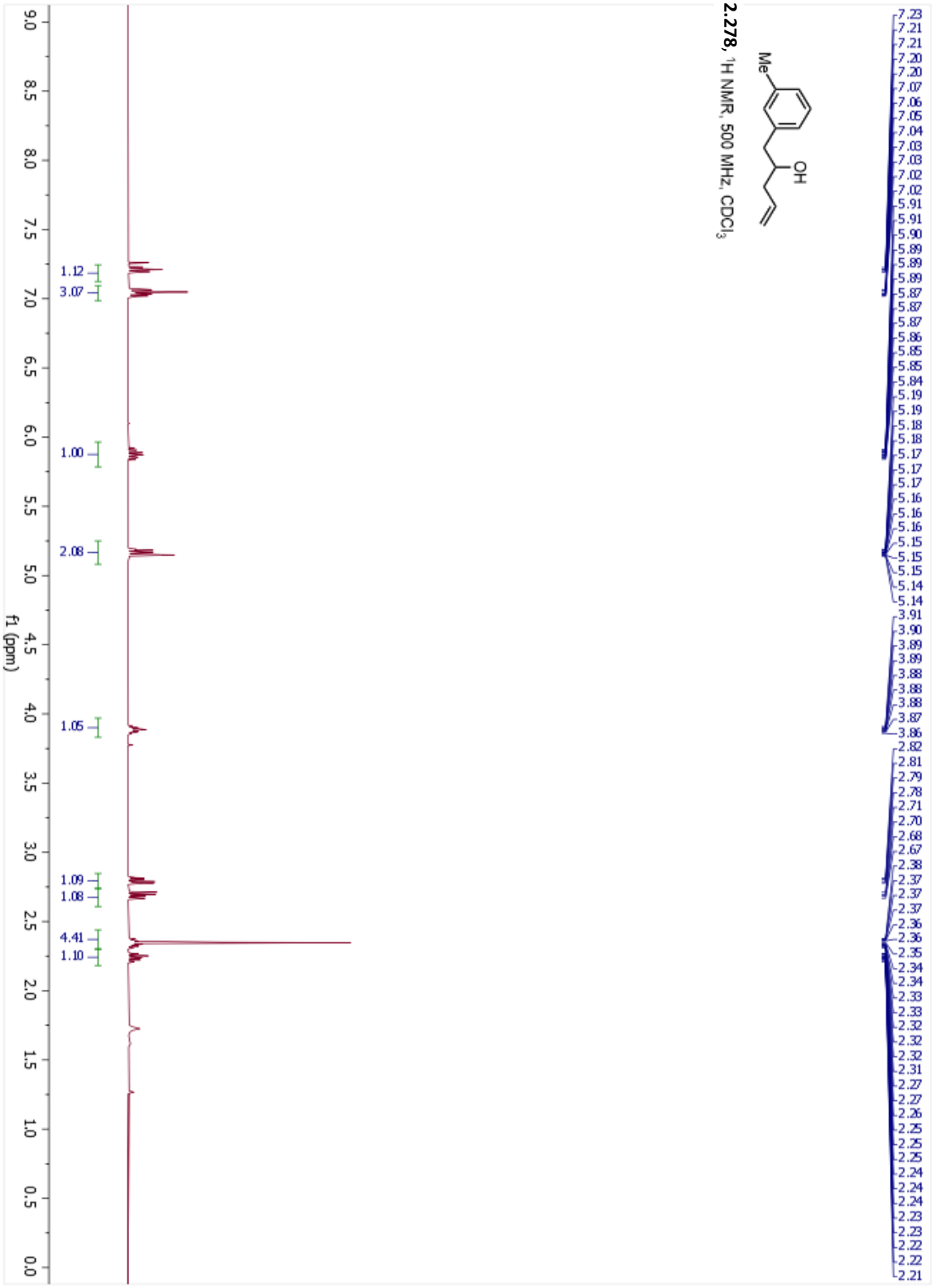

2.187, 1H NMR, 500 MHz, CDCl3
MeO
OH
f1 (ppm)
1.01
3.04
1.00
2.06
1.09
3.23
1.08
1.06
1.07
1.06
0.92

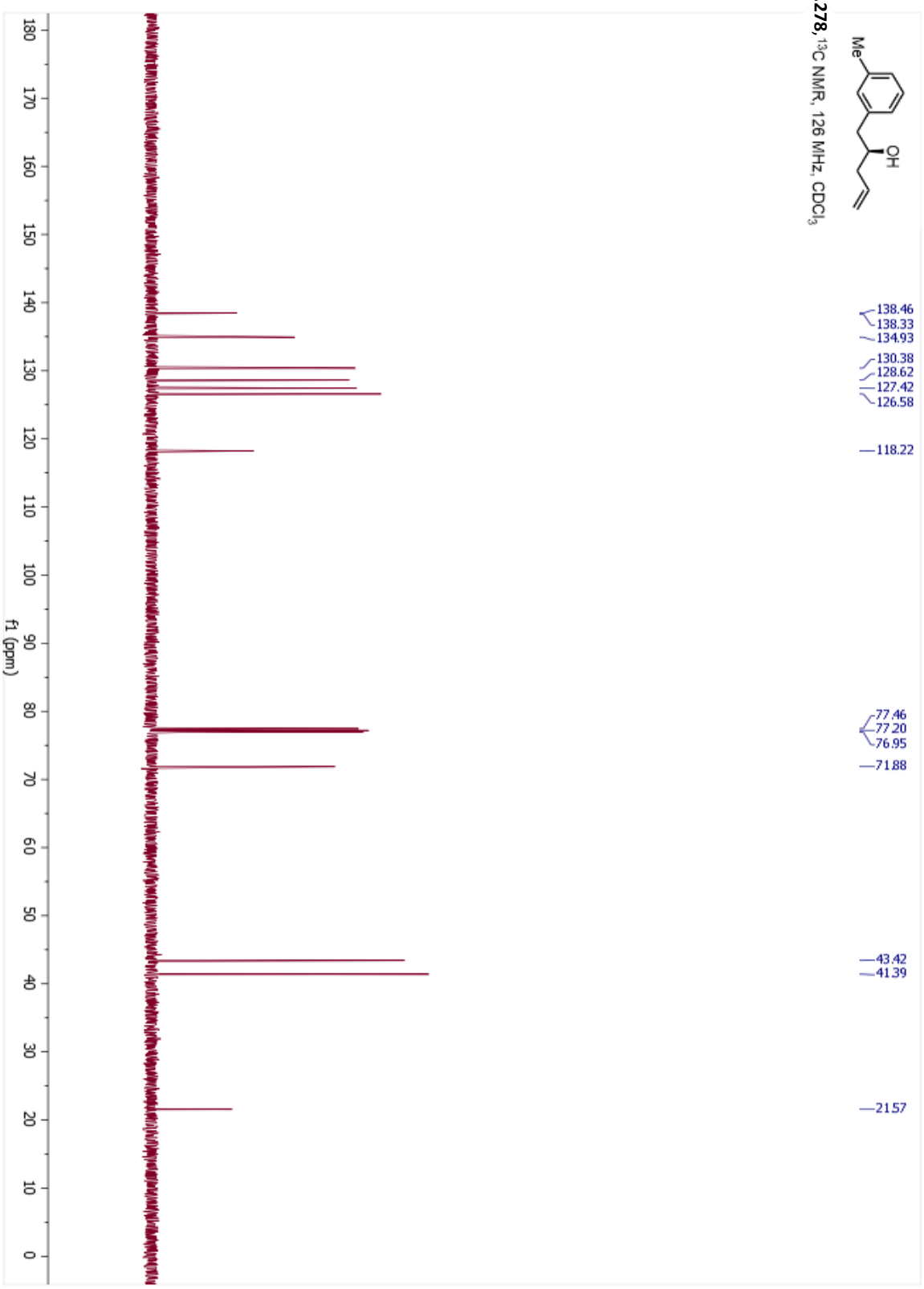

2.187, NMR, 126 MHz, CDCl3
MeO
OH
159.93
140.15
134.86
129.71
121.92
118.28
115.30
112.03
77.46
77.21
76.95
71.80
55.33
43.53
41.38
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

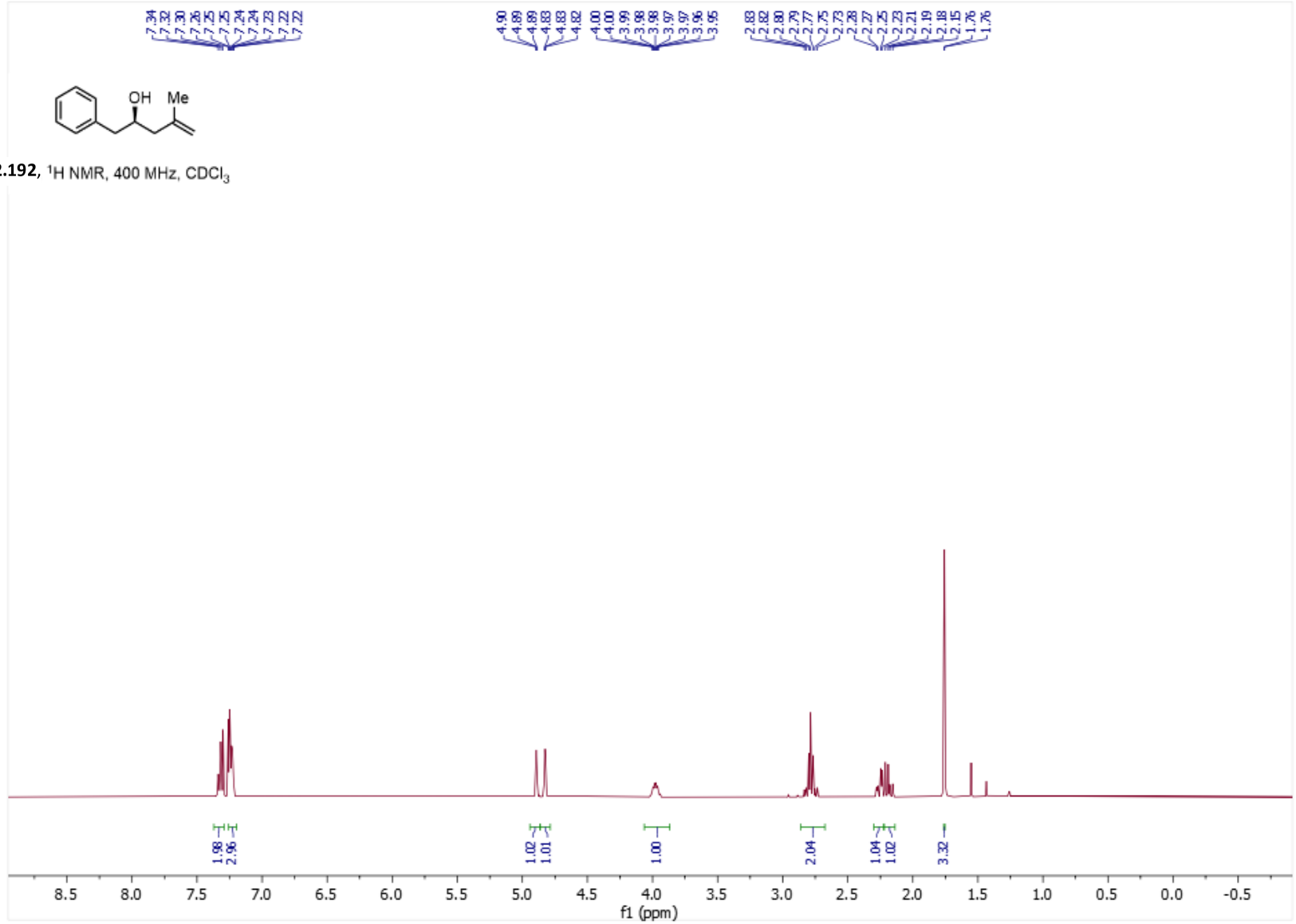


2.188, ^{1}H NMR, 600 MHz, $CDCl_3$

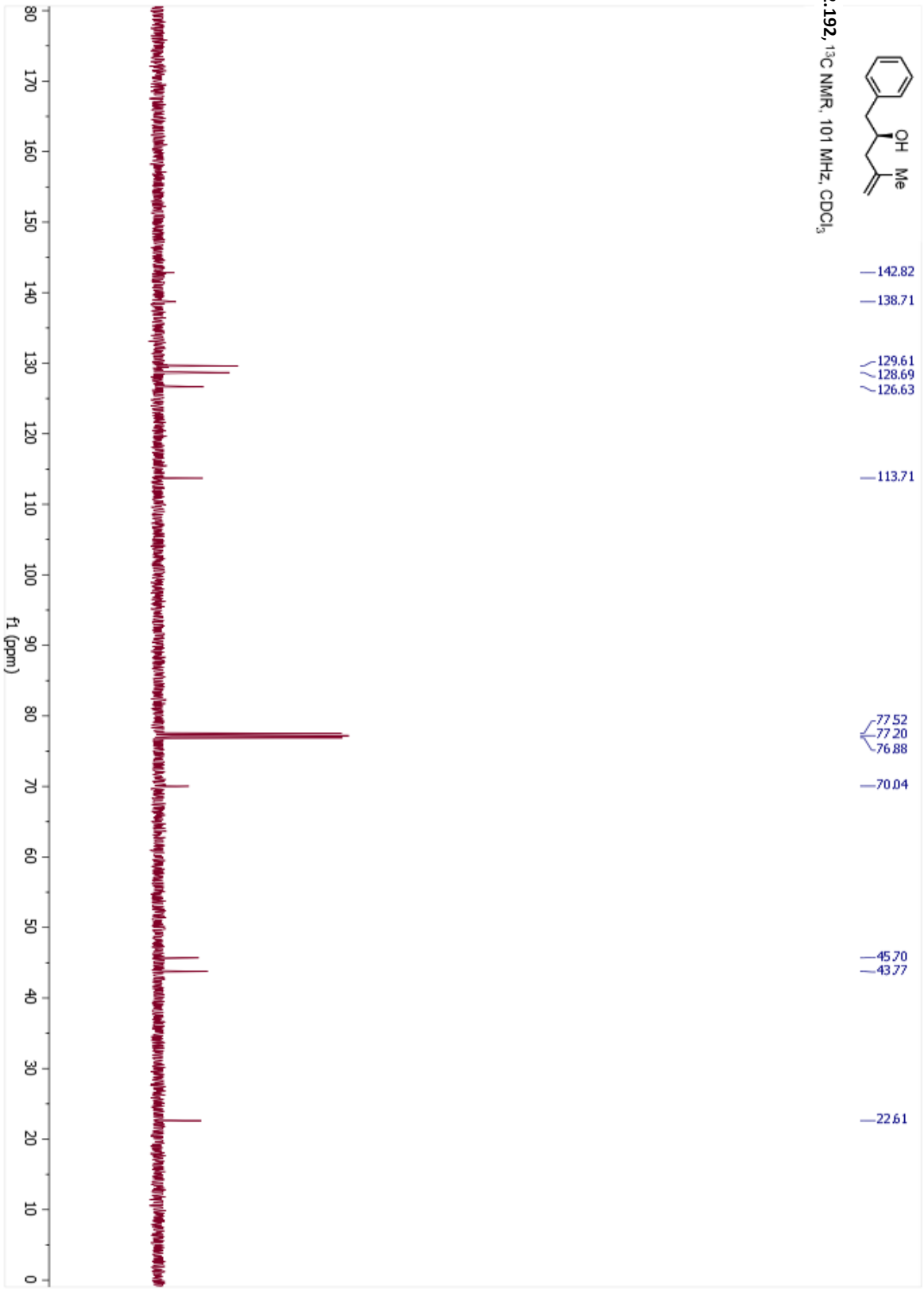

2.188, 13C NMR, 151 MHz, CDCl3
TBSO
OH
141.92
138.42
134.91
128.63
128.18
127.30
124.49
118.26
77.41
77.20
76.99
71.88
65.11
43.50
41.31
26.14
18.61
-5.04
f1 (ppm)

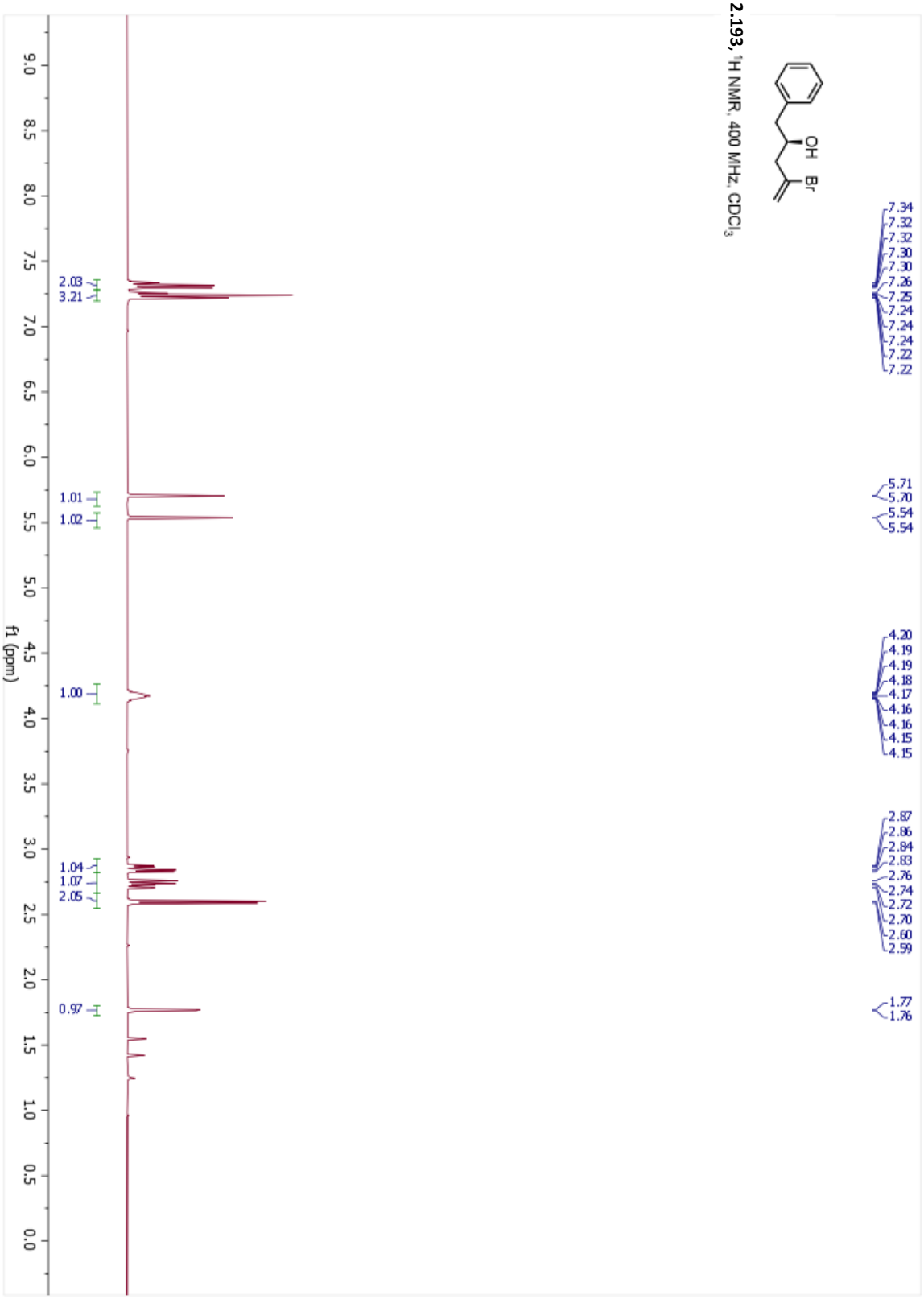

2.278, ^{1}H NMR, 500 MHz, $CDCl_3$
Me
OH
f1 (ppm)
1.12
3.07
1.00
2.08
1.05
1.09
1.08
4.41
1.10

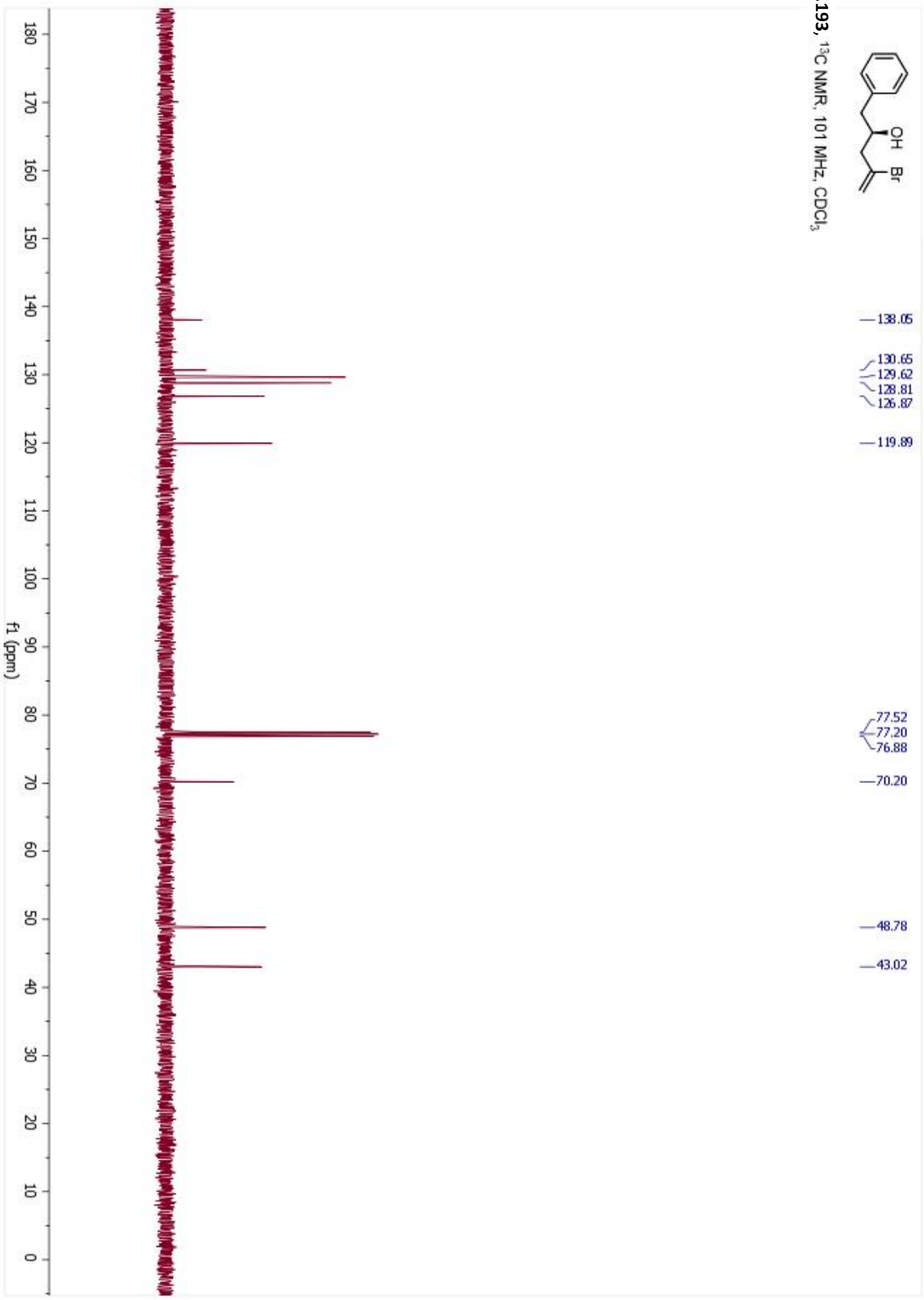

2.278, 13C NMR, 126 MHz, CDCl3
Me
OH
138.46
138.33
134.93
130.38
128.62
127.42
126.58
118.22
77.46
77.20
76.95
71.88
43.42
41.39
21.57
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

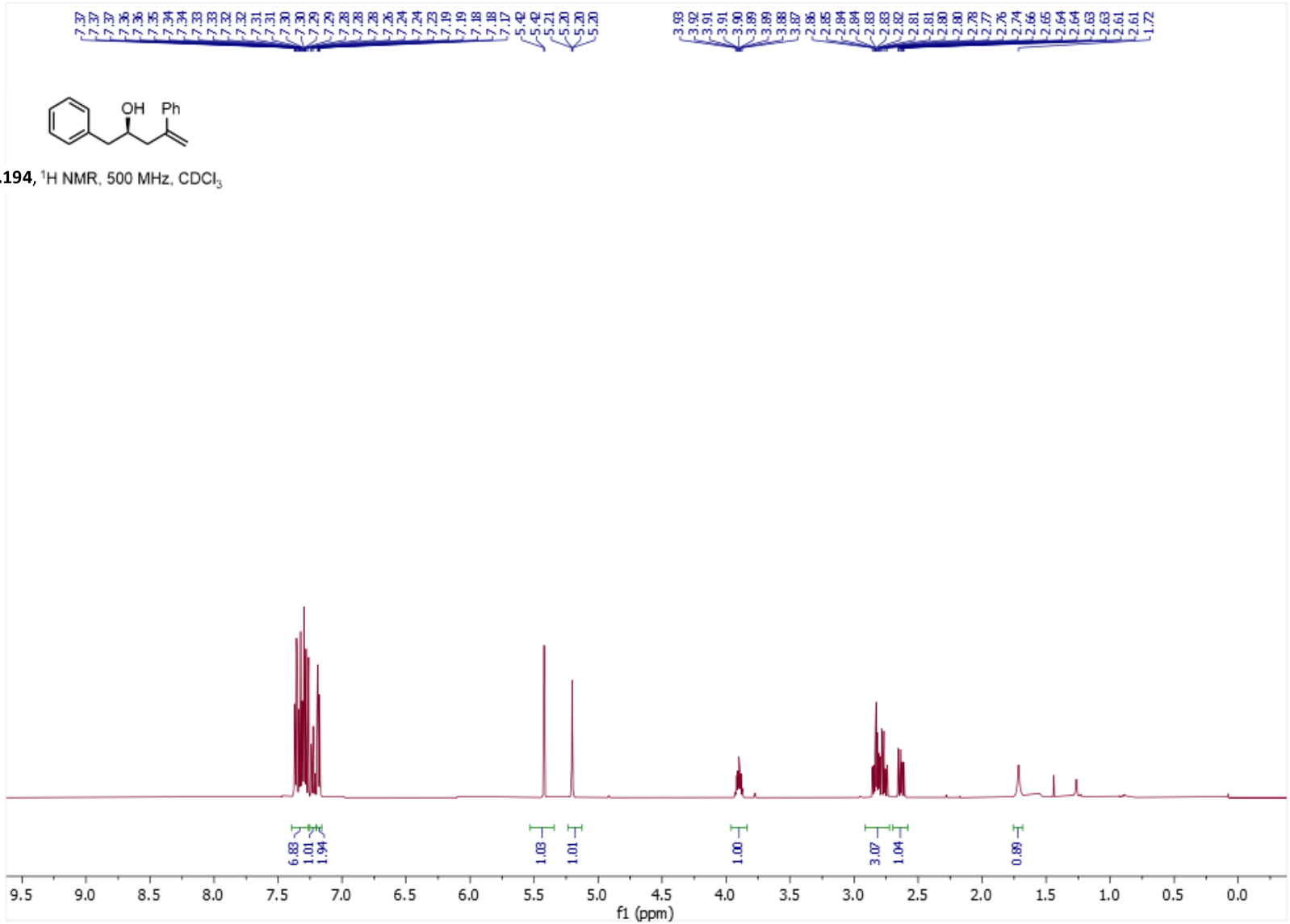


2.192, ^{1}H NMR, 400 MHz, $CDCl_3$

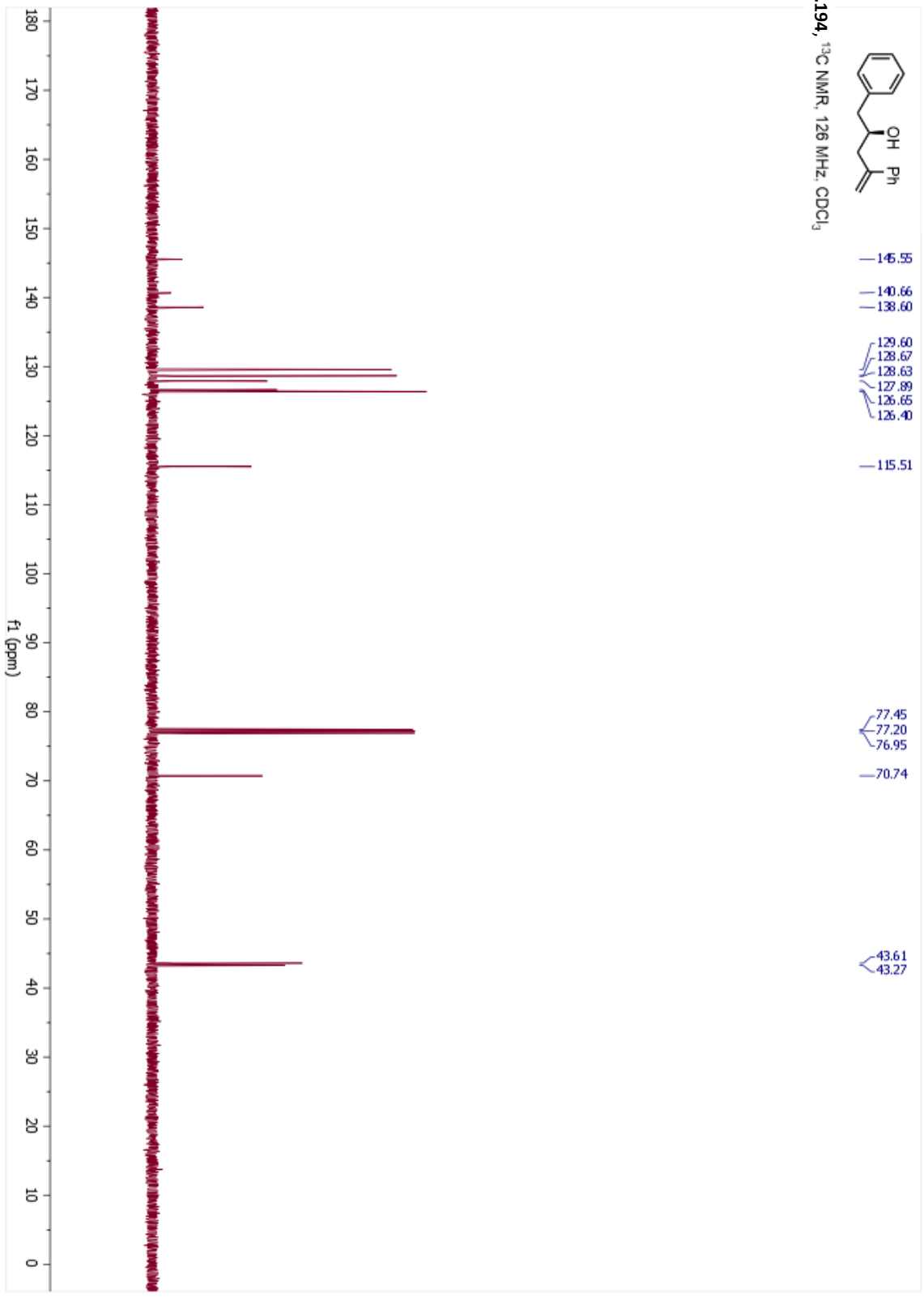

2.192, 13C NMR, 101 MHz, CDCl3
OH
Me
142.82
138.71
129.61
128.69
126.63
113.71
77.52
77.20
76.88
70.04
45.70
43.77
22.61
f1 (ppm)

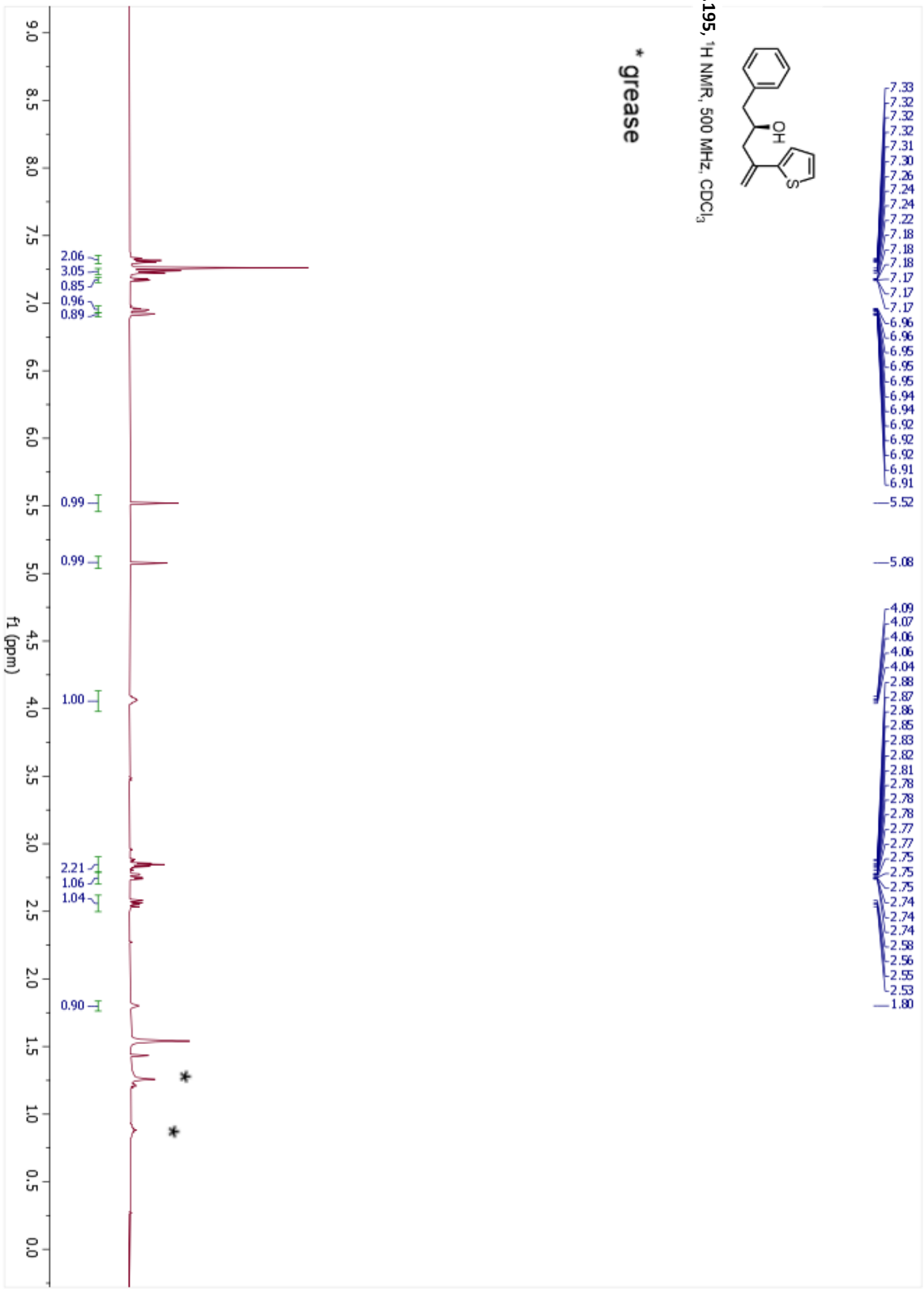

2.193, ^{1}H NMR, 400 MHz, $CDCl_3$
OH
Br
7.34
7.32
7.32
7.30
7.30
7.26
7.25
7.24
7.24
7.24
7.22
7.22
5.71
5.70
5.54
5.54
4.20
4.19
4.19
4.18
4.17
4.16
4.16
4.15
4.15
2.87
2.86
2.84
2.83
2.76
2.74
2.72
2.70
2.60
2.59
1.77
1.76
2.03
3.21
1.01
1.02
1.00
1.04
1.07
2.05
0.97
f1 (ppm)

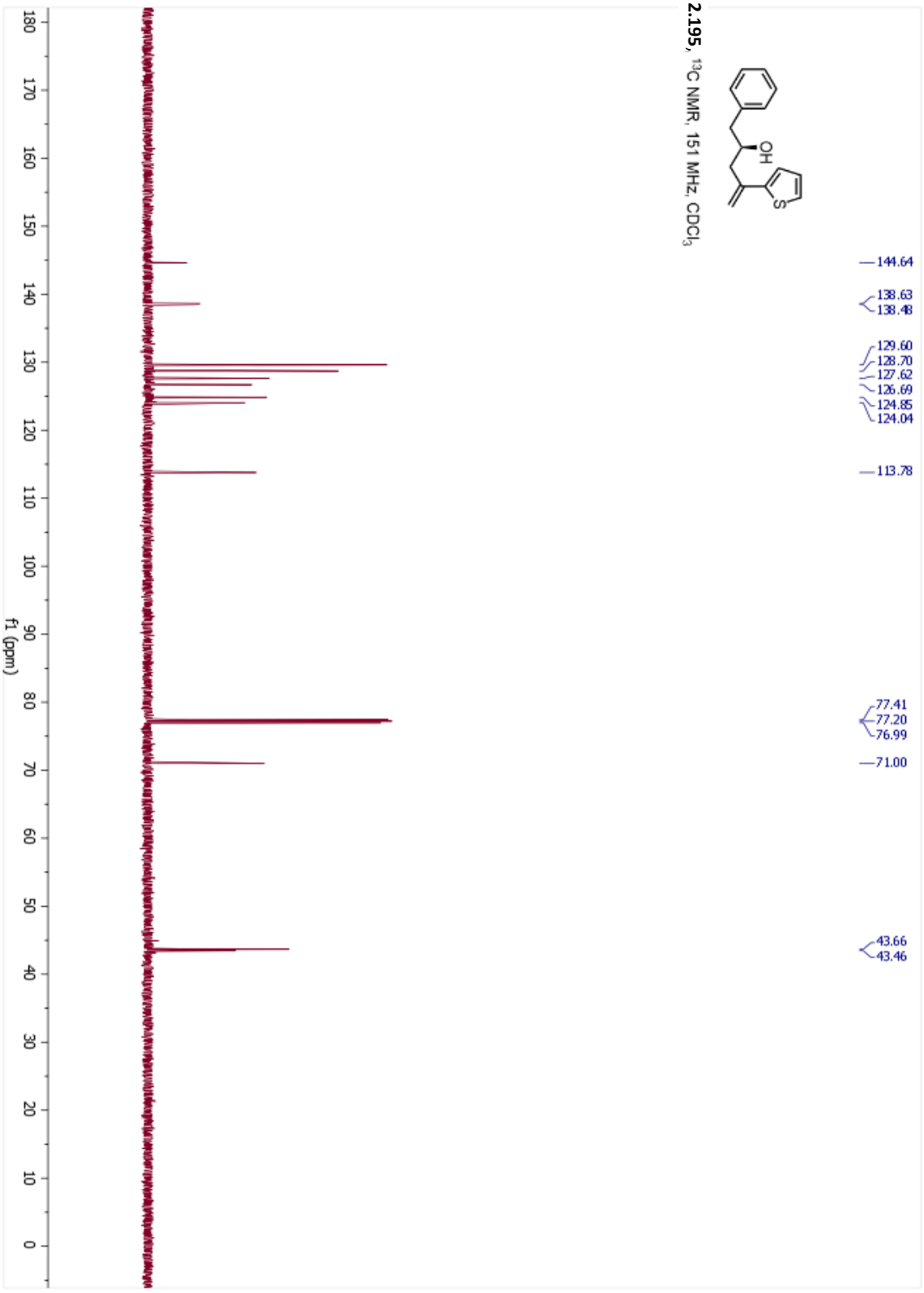

2.193, ^{13}C NMR, 101 MHz, $CDCl_3$
OH
Br
138.05
130.65
129.62
128.81
126.87
119.89
77.52
77.20
76.88
70.20
48.78
43.02
f1 (ppm)

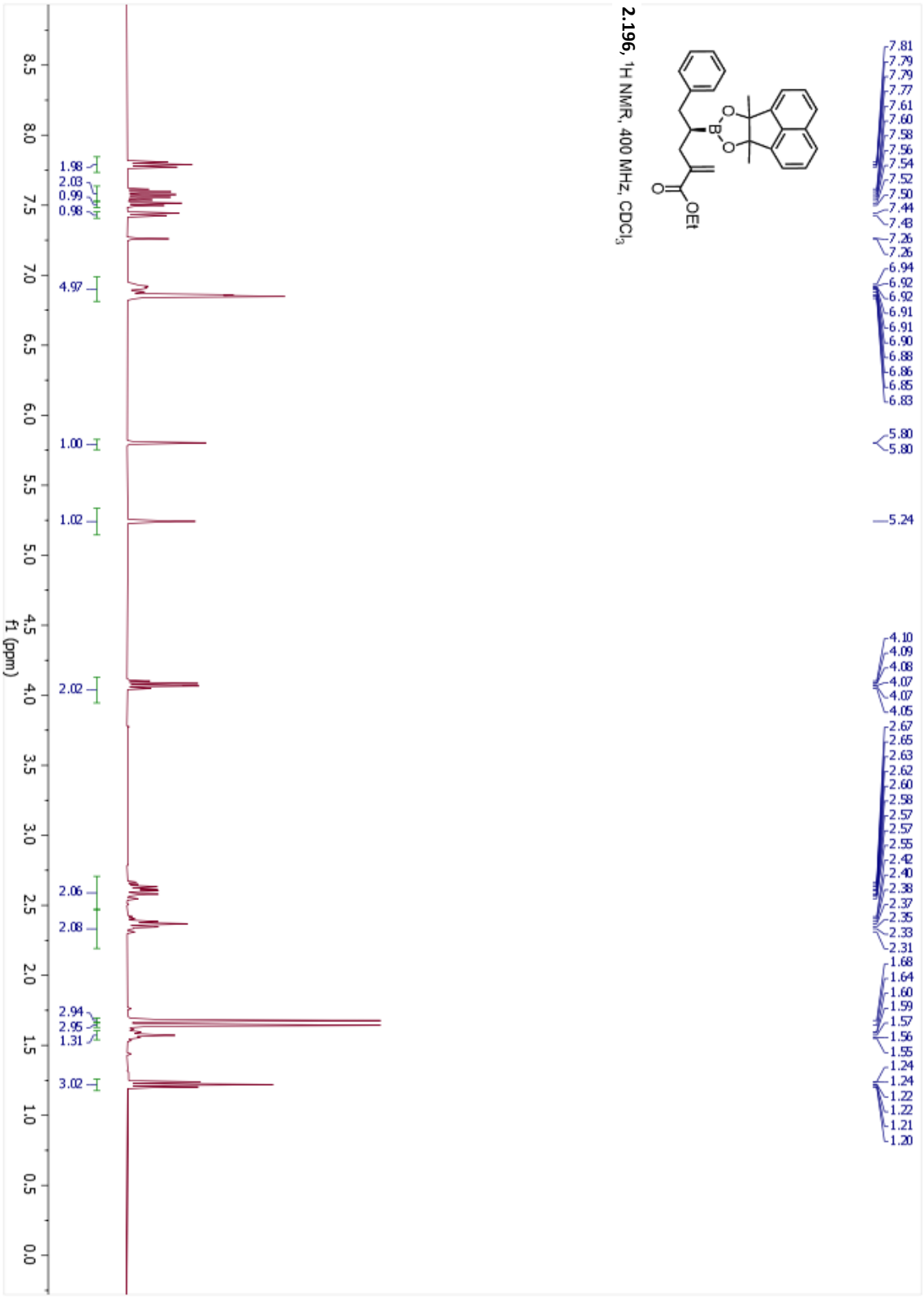


2.194, ^{1}H NMR, 500 MHz, $CDCl_3$

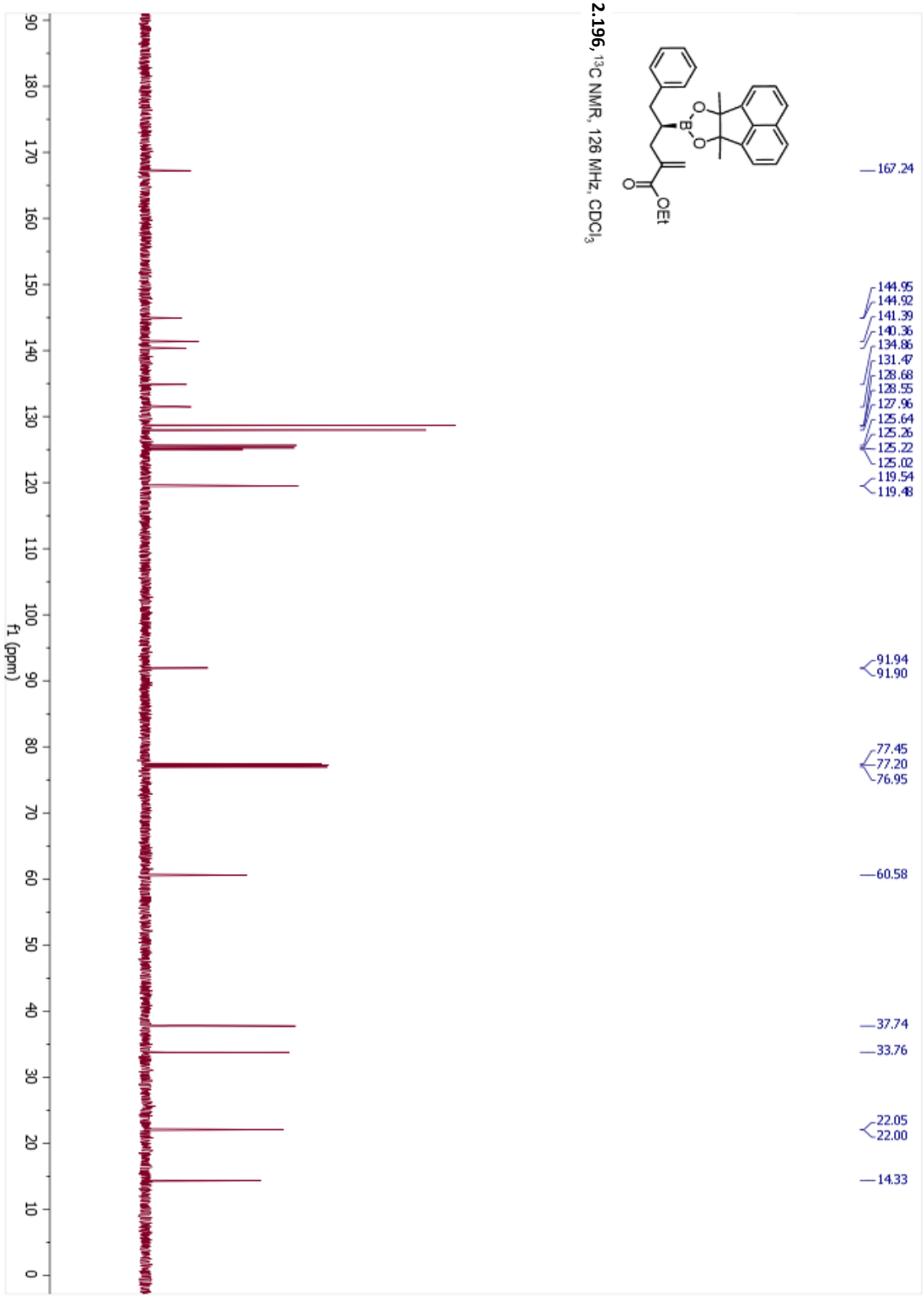

2.194, ^{13}C NMR, 126 MHz, $CDCl_3$
OH
Ph
145.55
140.66
138.60
129.60
128.67
128.63
127.89
126.65
126.40
115.51
77.45
77.20
76.95
70.74
43.61
43.27
f1 (ppm)

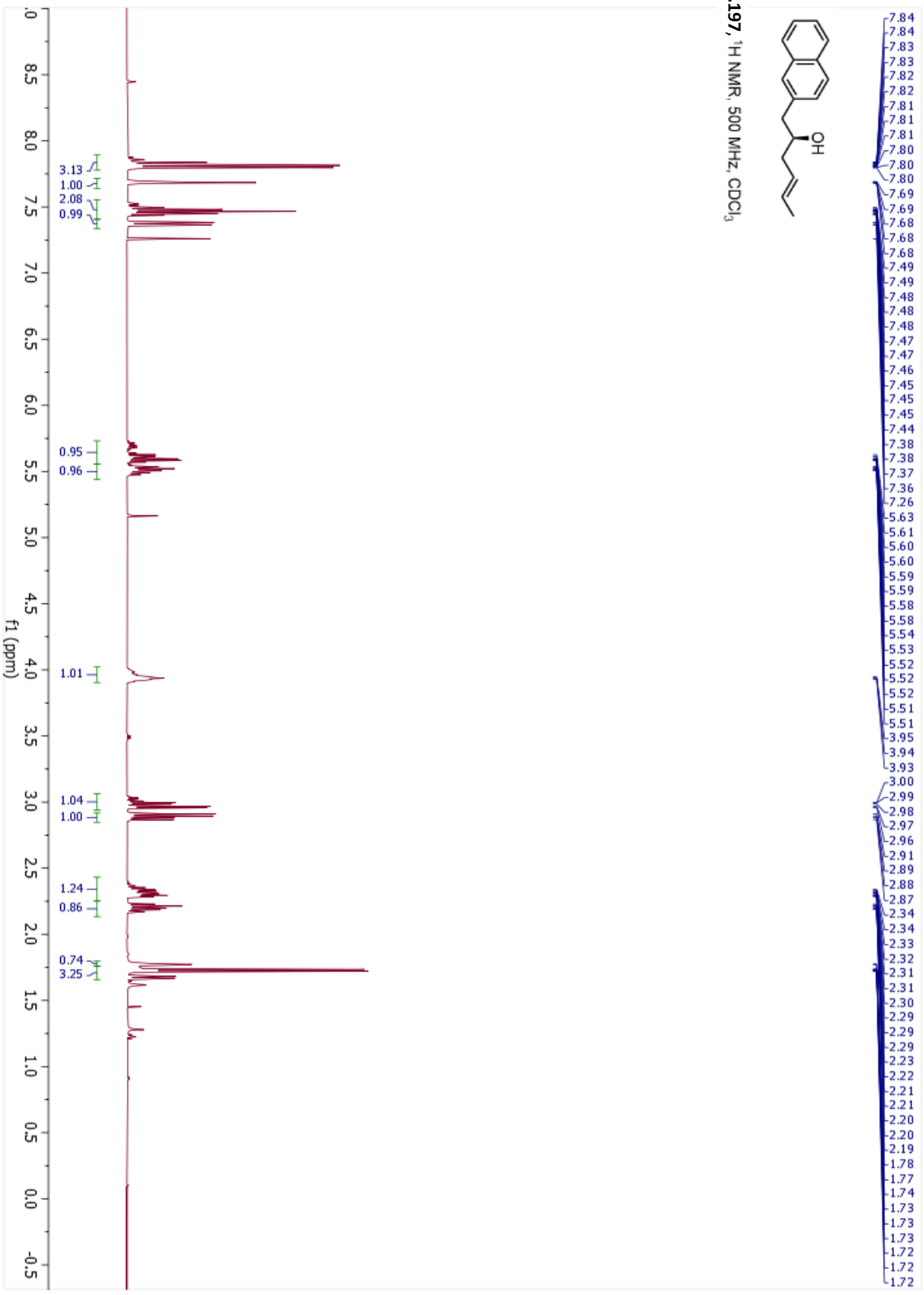

2.195, ^{1}H NMR, 500 MHz, $CDCl_3$
OH
S
* grease
7.33
7.32
7.32
7.32
7.31
7.30
7.26
7.24
7.24
7.22
7.18
7.18
7.18
7.17
7.17
7.17
6.96
6.96
6.95
6.95
6.95
6.94
6.94
6.92
6.92
6.92
6.91
6.91
5.52
5.08
4.09
4.07
4.06
4.06
4.04
2.88
2.87
2.86
2.85
2.83
2.82
2.81
2.78
2.78
2.78
2.77
2.77
2.75
2.75
2.75
2.74
2.74
2.74
2.58
2.56
2.55
2.53
1.80
2.06
3.05
0.85
0.96
0.89
0.99
0.99
1.00
2.21
1.06
1.04
0.90
f1 (ppm)

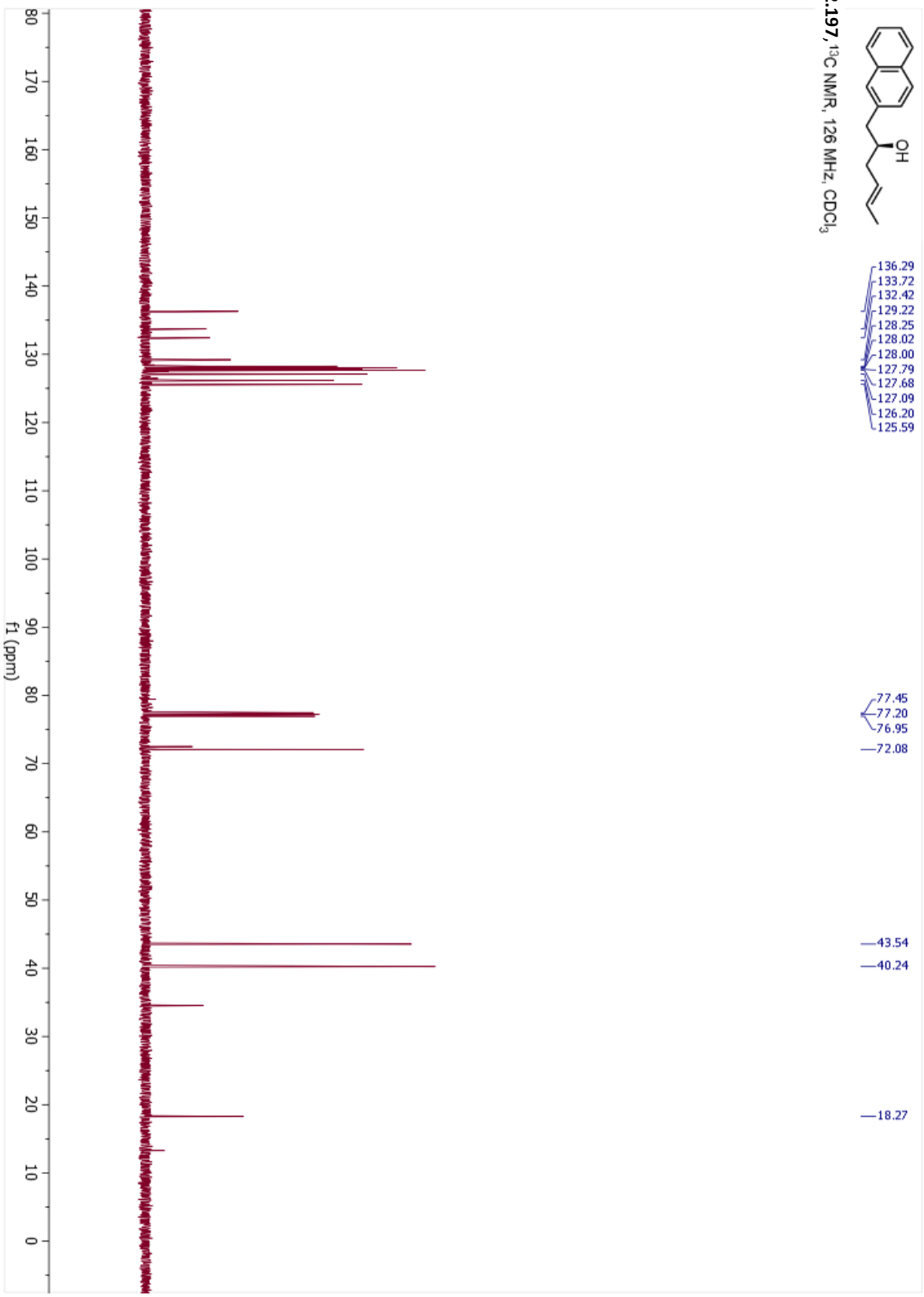

2.195, 13C NMR, 151 MHz, CDCl3
OH
S
144.64
138.63
138.48
129.60
128.70
127.62
126.69
124.85
124.04
113.78
77.41
77.20
76.99
71.00
43.66
43.46
f1 (ppm)

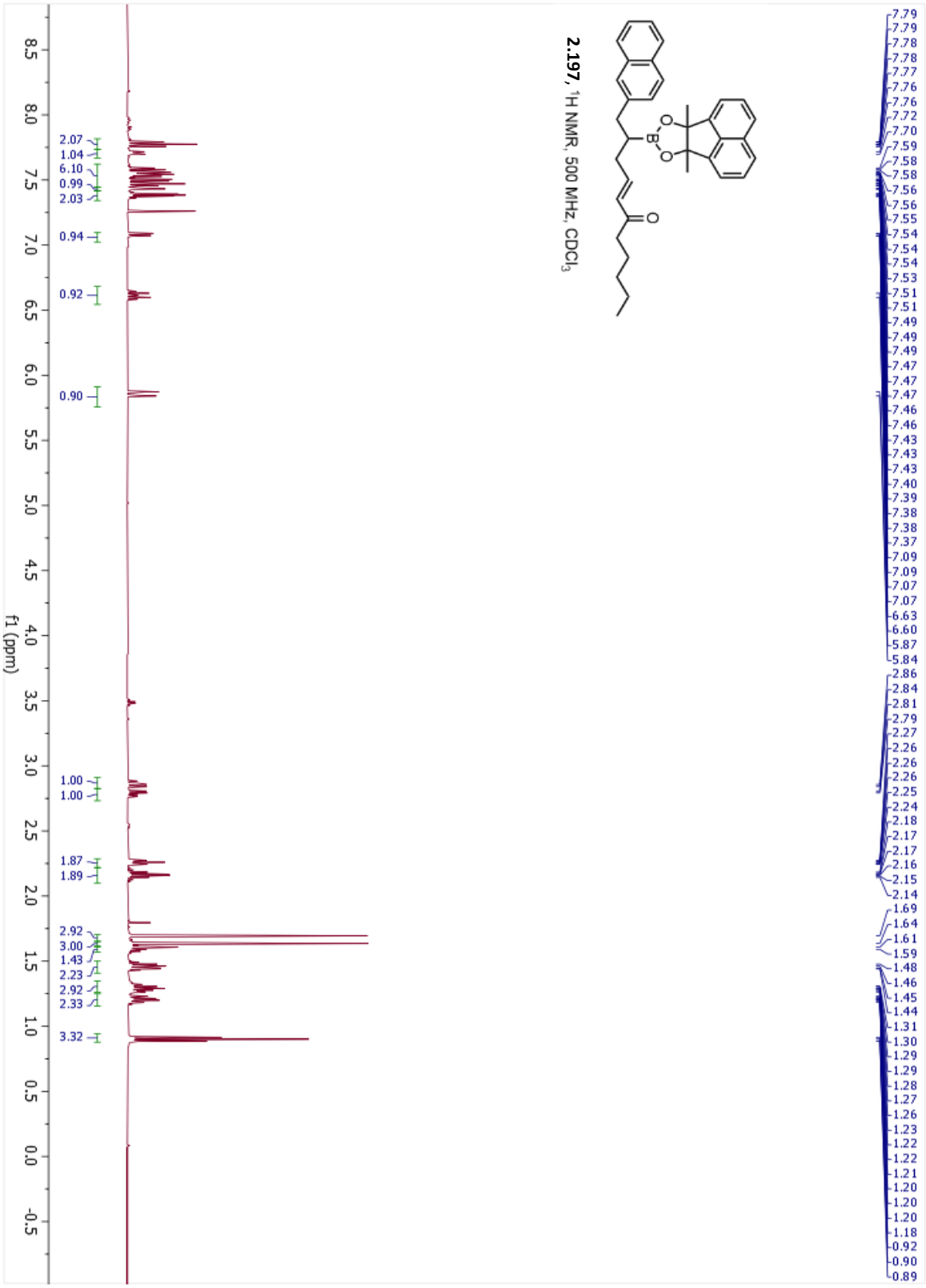

2.196, 1H NMR, 400 MHz, CDCl3
OEt
f1 (ppm)
1.98
2.03
0.99
0.98
4.97
1.00
1.02
2.02
2.06
2.08
2.94
2.95
1.31
3.02
7.81
7.79
7.79
7.77
7.61
7.60
7.58
7.56
7.54
7.52
7.50
7.44
7.43
7.26
7.26
6.94
6.92
6.92
6.91
6.91
6.90
6.88
6.86
6.85
6.83
5.80
5.80
5.24
4.10
4.09
4.08
4.07
4.07
4.05
2.67
2.65
2.63
2.62
2.60
2.58
2.57
2.57
2.55
2.42
2.40
2.38
2.37
2.35
2.33
2.31
1.68
1.64
1.60
1.59
1.57
1.56
1.55
1.24
1.24
1.22
1.22
1.21
1.20

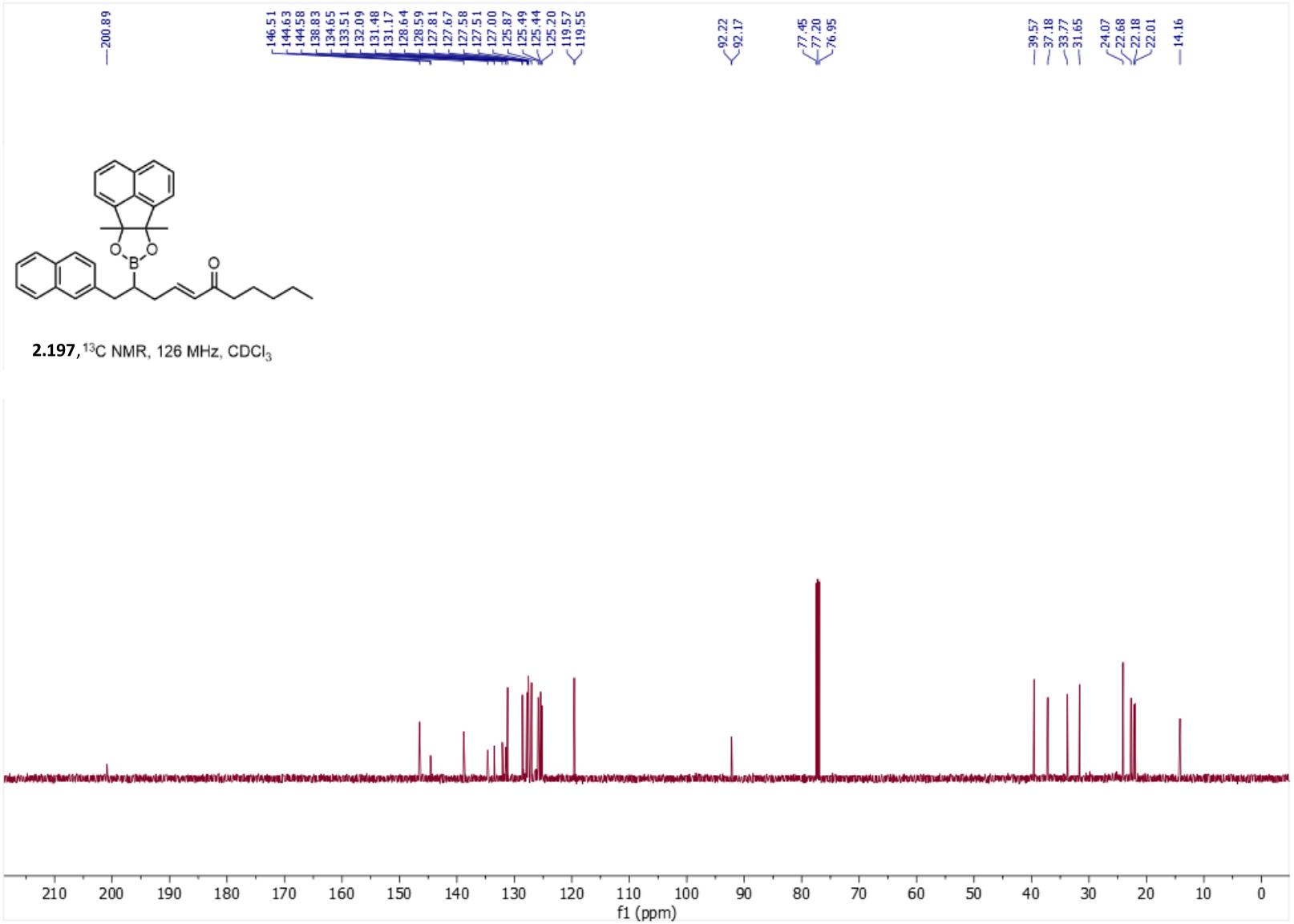
f


2.196, ^{13}C NMR, 126 MHz, $CDCl_3$
OEt
f1 (ppm)
167.24
144.95
144.92
141.39
140.36
134.86
131.47
128.68
128.55
127.96
125.64
125.26
125.22
125.02
119.54
119.48
91.94
91.90
77.45
77.20
76.95
60.58
37.74
33.76
22.05
22.00
14.33

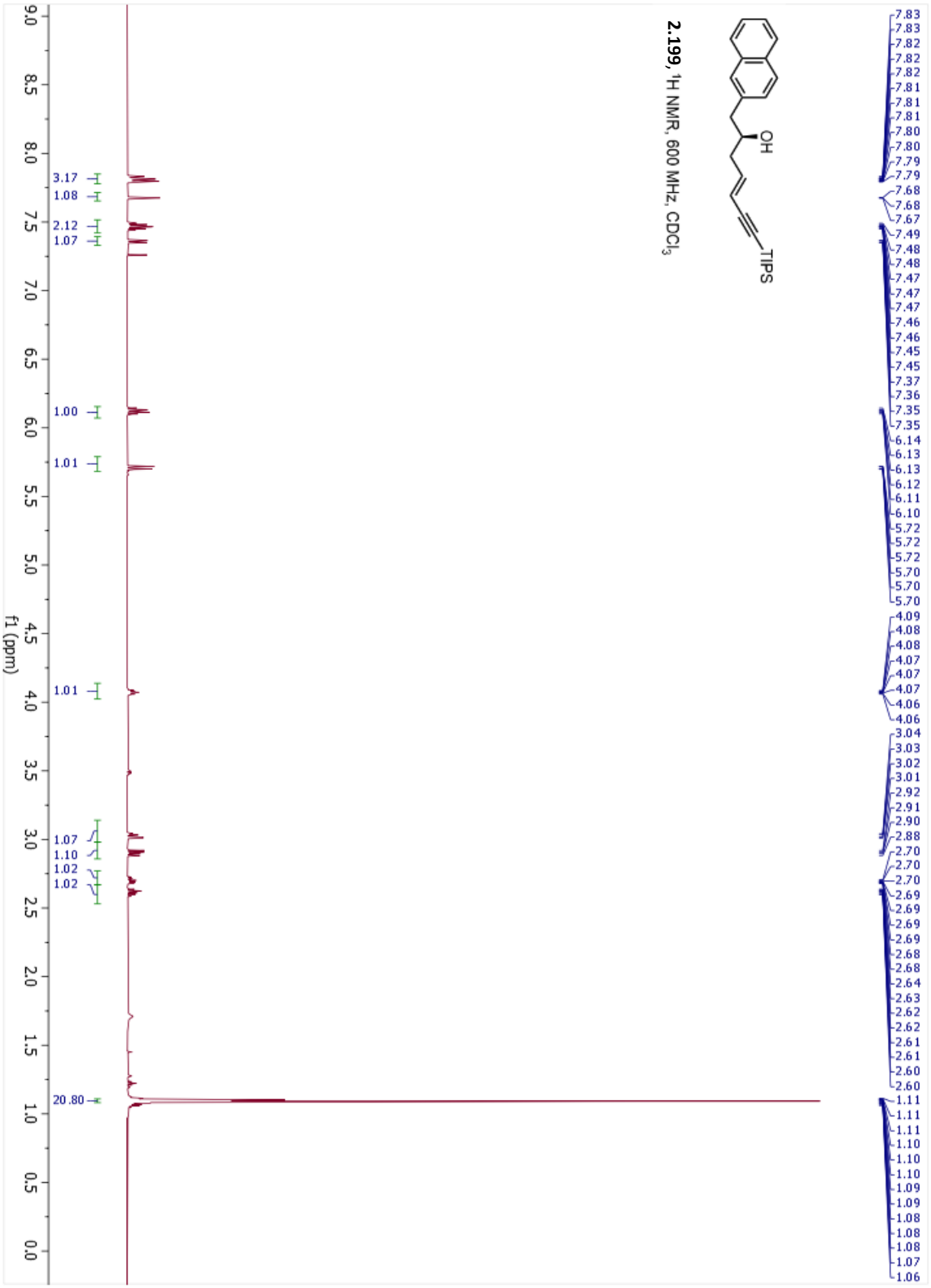

2.197, ^{1}H NMR, 500 MHz, $CDCl_3$
OH
f1 (ppm)
3.13
1.00
2.08
0.99
0.95
0.96
1.01
1.04
1.00
1.24
0.86
0.74
3.25

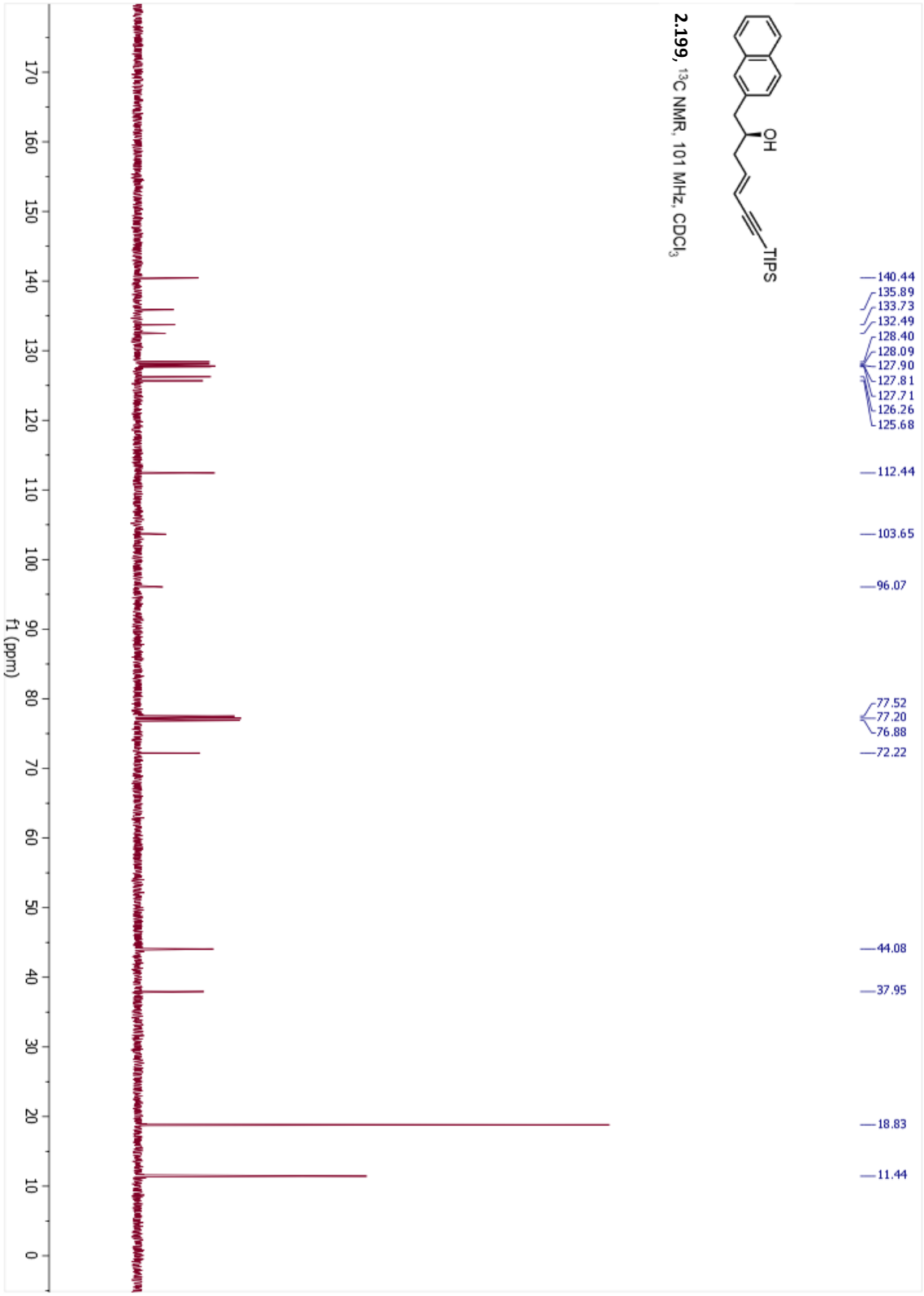

2.197, 13C NMR, 126 MHz, CDCl3
OH
136.29
133.72
132.42
129.22
128.25
128.02
128.00
127.79
127.68
127.09
126.20
125.59
77.45
77.20
76.95
72.08
43.54
40.24
18.27
f1 (ppm)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

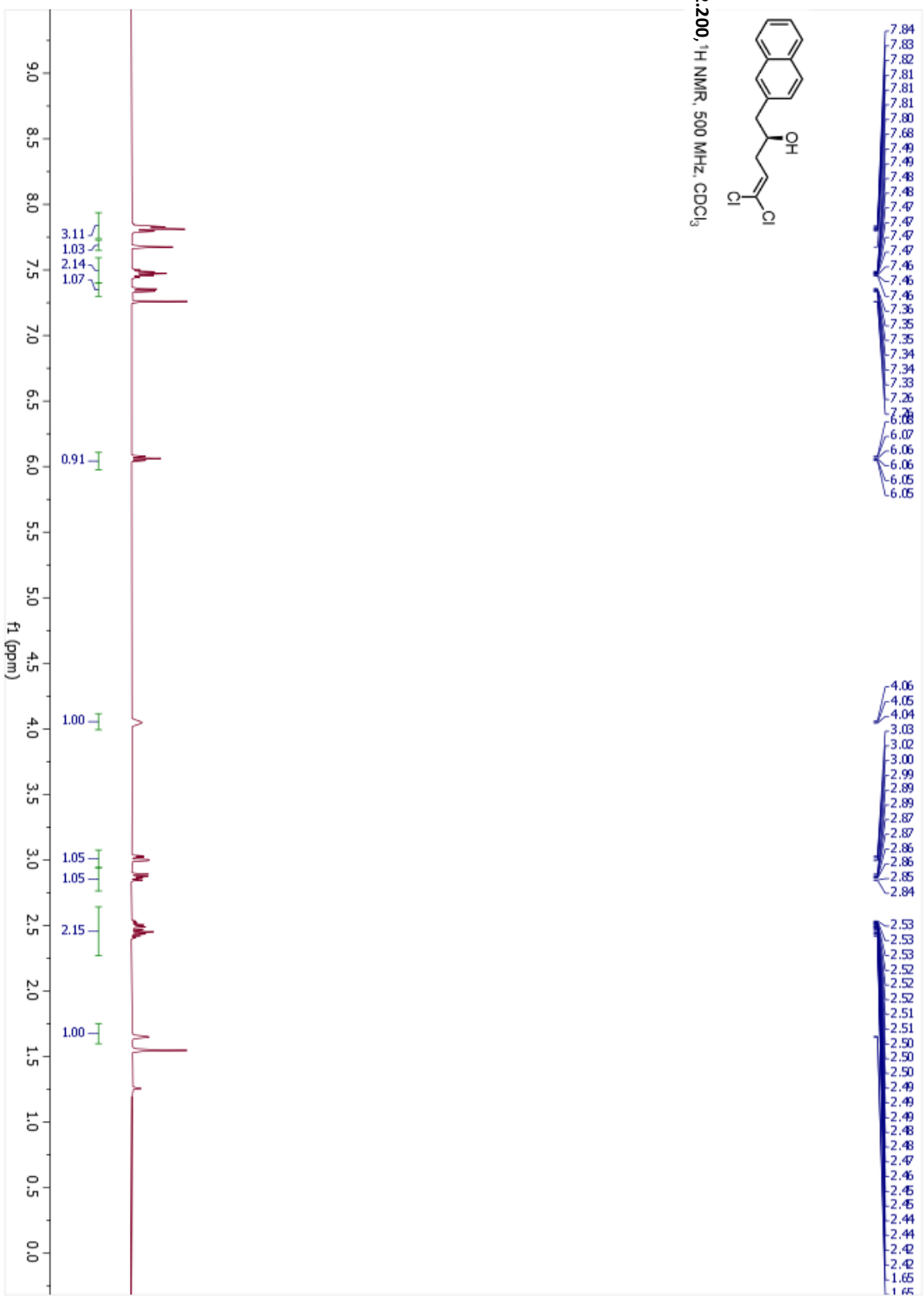

2.197, ^{1}H NMR, 500 MHz, $CDCl_3$
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
2.07
1.04
6.10
0.99
2.03
0.94
0.92
0.90
1.00
1.00
1.87
1.89
2.92
3.00
1.43
2.23
2.92
2.33
3.32
7.79
7.79
7.78
7.78
7.77
7.76
7.76
7.72
7.70
7.59
7.58
7.58
7.56
7.56
7.55
7.54
7.54
7.54
7.53
7.51
7.51
7.49
7.49
7.49
7.47
7.47
7.47
7.46
7.46
7.43
7.43
7.43
7.40
7.39
7.38
7.38
7.37
7.09
7.09
7.07
7.07
6.63
6.60
5.87
5.84
2.86
2.84
2.81
2.79
2.27
2.26
2.26
2.26
2.25
2.24
2.18
2.17
2.17
2.16
2.15
2.14
1.69
1.64
1.61
1.59
1.48
1.46
1.45
1.44
1.31
1.30
1.29
1.29
1.28
1.27
1.26
1.23
1.22
1.22
1.21
1.20
1.20
1.20
1.18
0.92
0.90
0.89

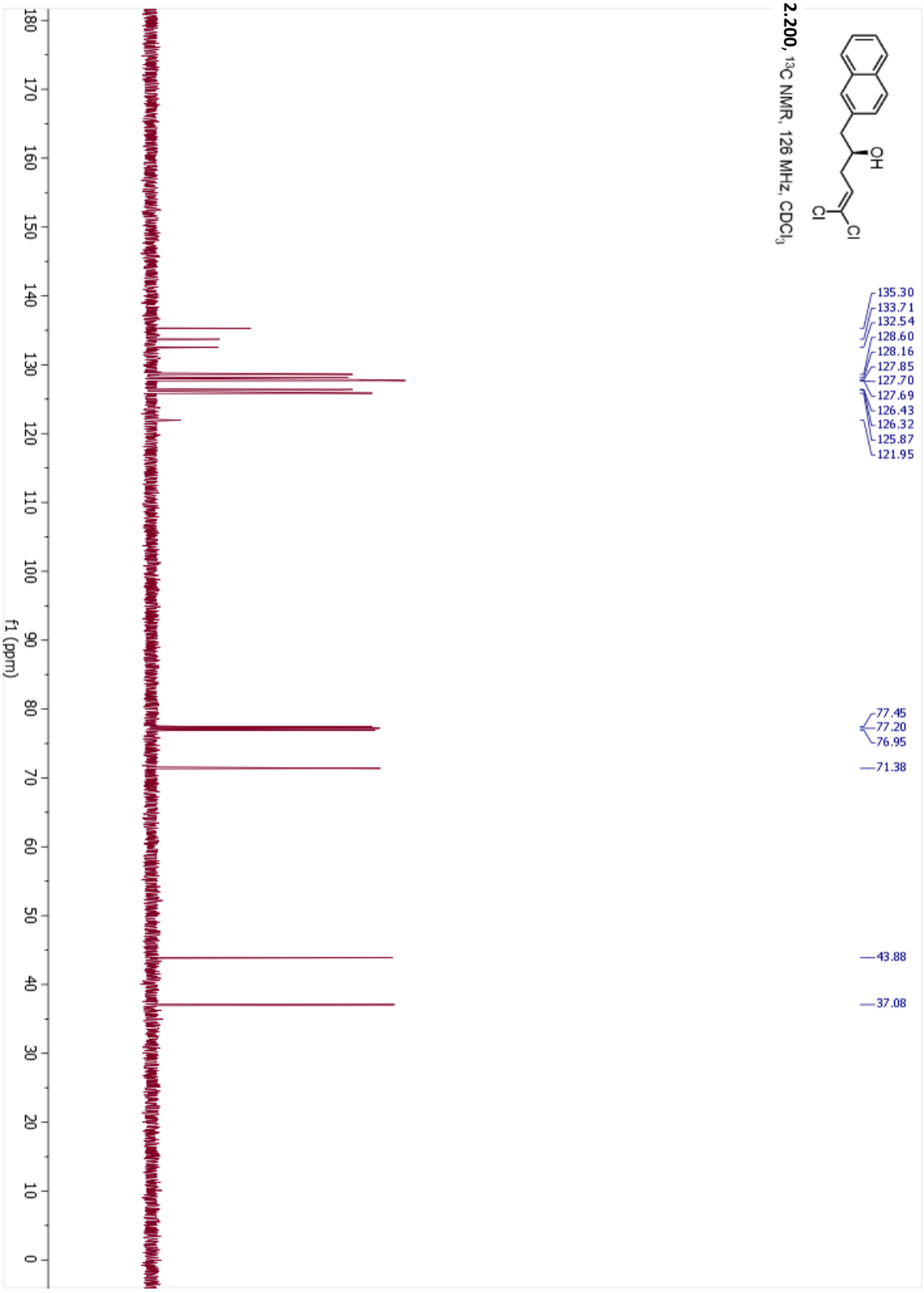


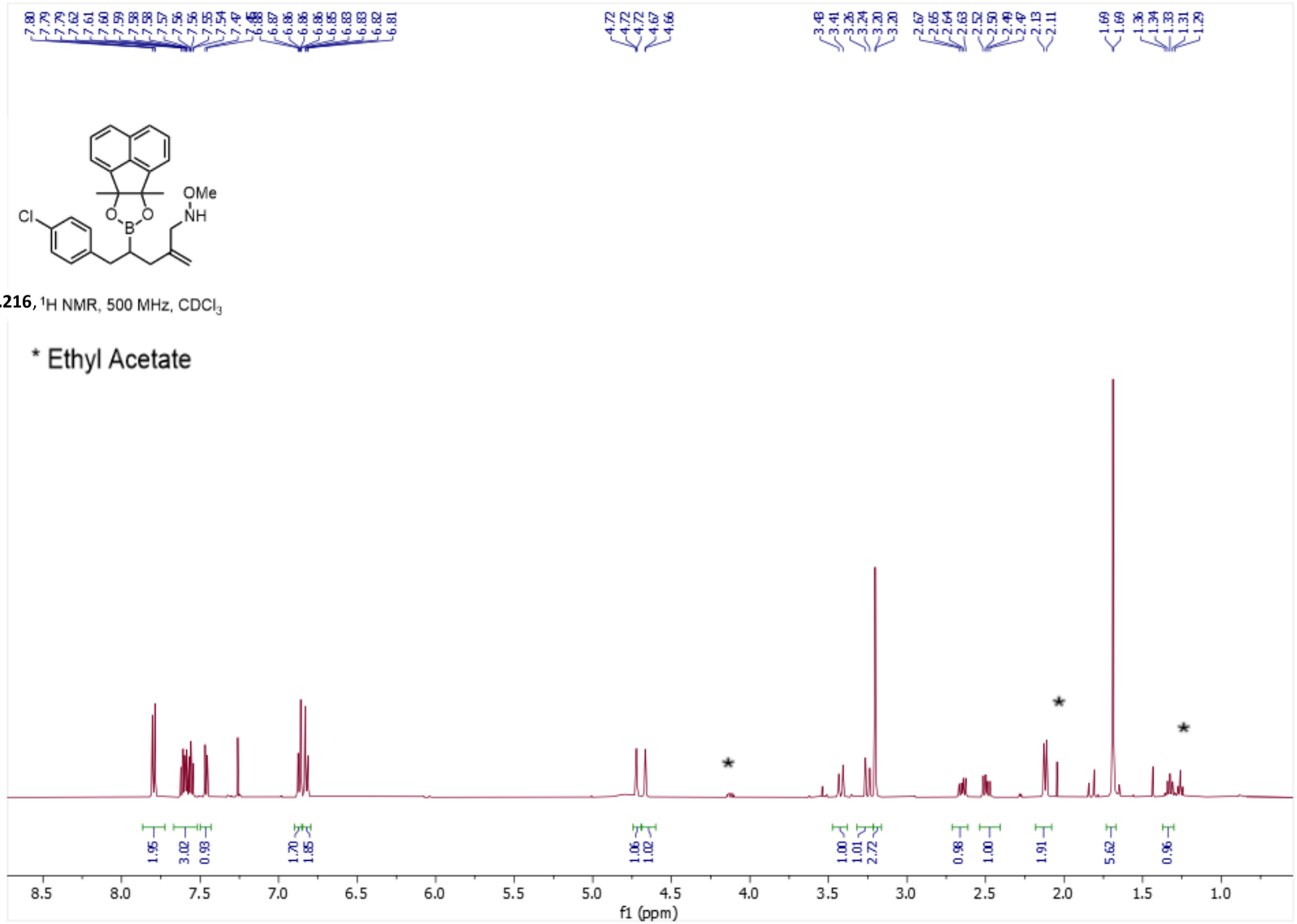
2.197, ^{13}C NMR, 126 MHz, $CDCl_3$


2.199, 1H NMR, 600 MHz, CDCl3
OH
TIPS
f1 (ppm)
3.17
1.08
2.12
1.07
1.00
1.01
1.01
1.07
1.10
1.02
1.02
20.80

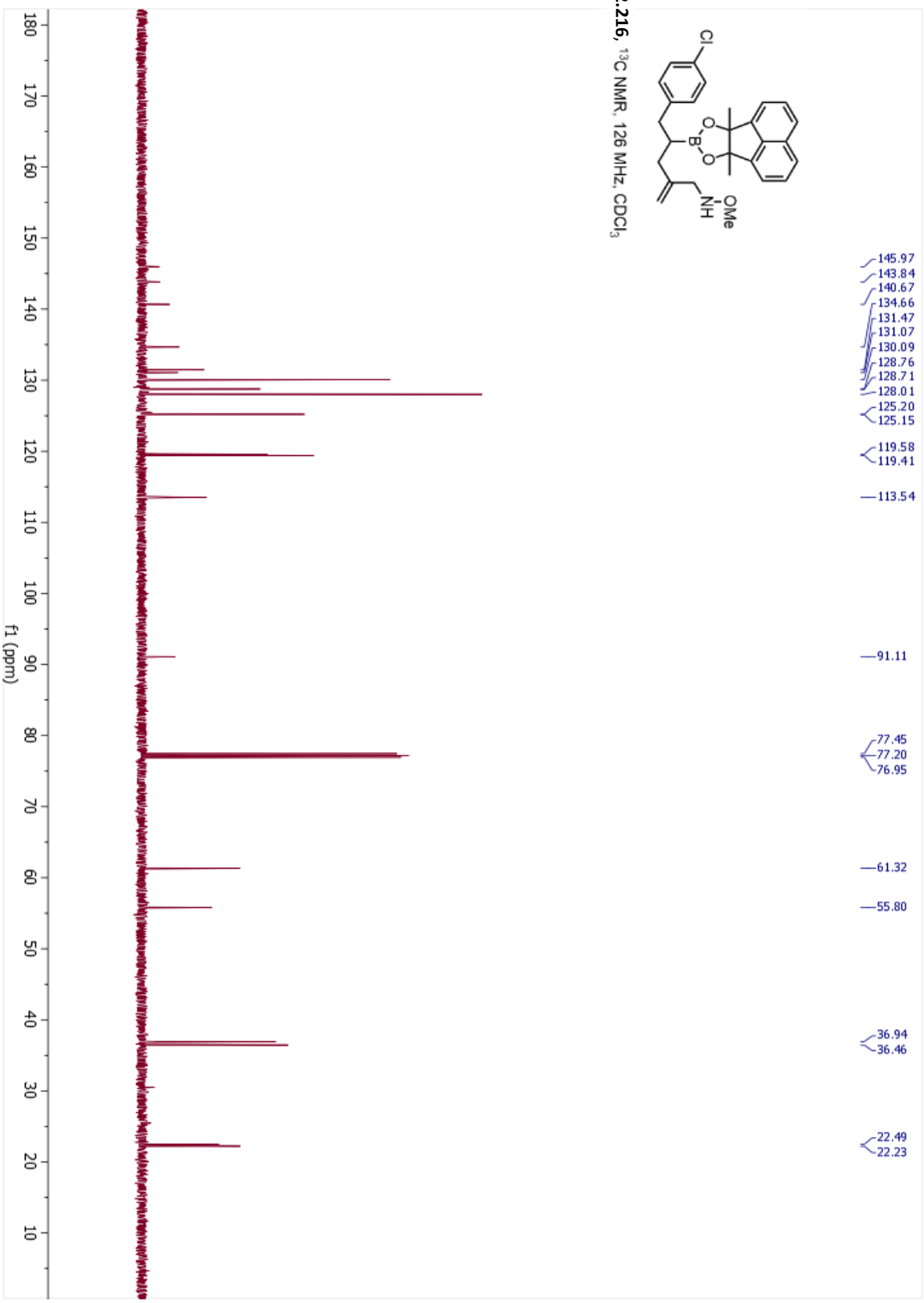

2.199, ^{13}C NMR, 101 MHz, CDCl$_3$
OH
TIPS
140.44
135.89
133.73
132.49
128.40
128.09
127.90
127.81
127.71
126.26
125.68
112.44
103.65
96.07
77.52
77.20
76.88
72.22
44.08
37.95
18.83
11.44
f1 (ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

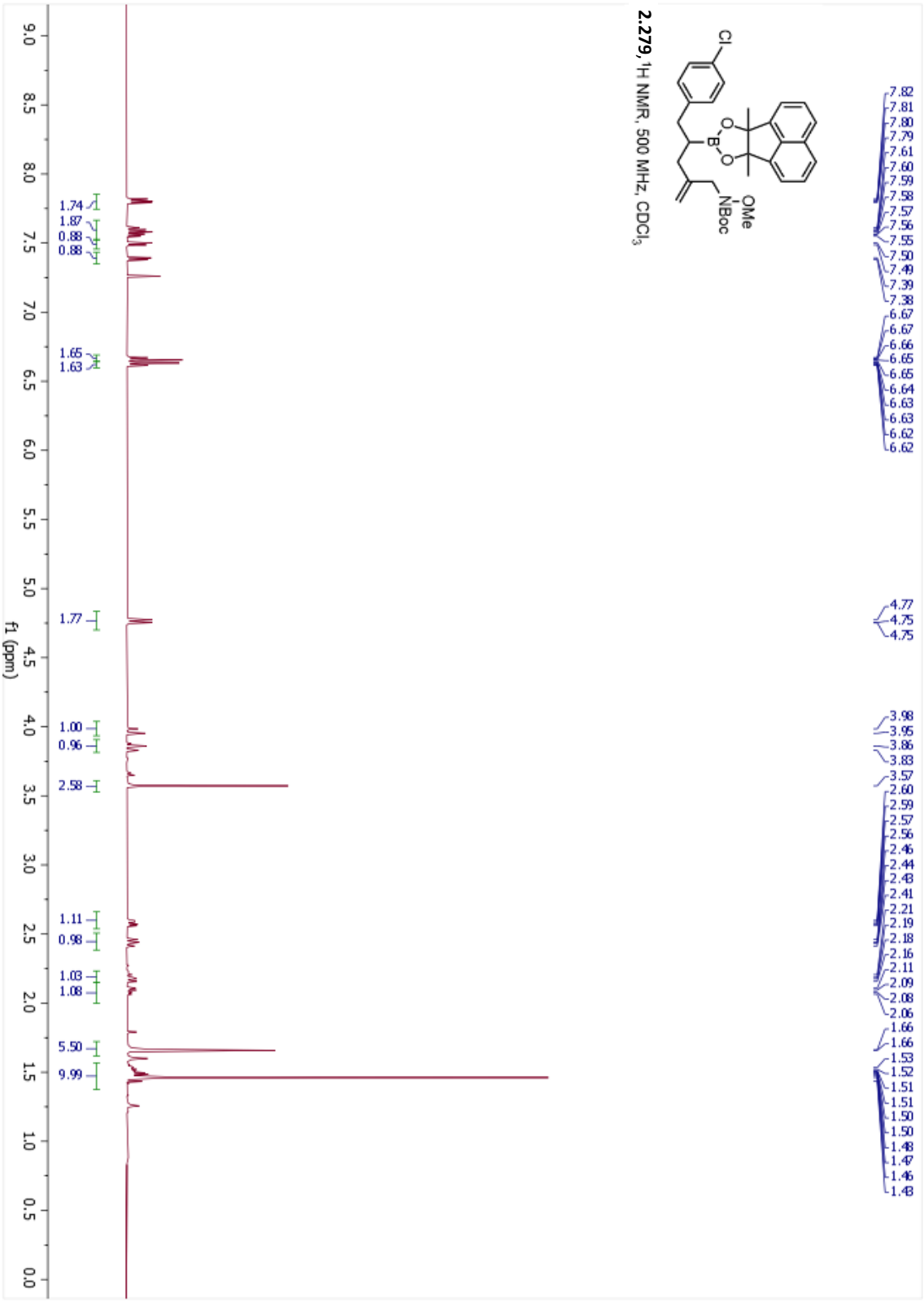

2.200, ^{1}H NMR, 500 MHz, $CDCl_3$
OH
Cl
Cl
f1 (ppm)
3.11
1.03
2.14
1.07
0.91
1.00
1.05
1.05
2.15
1.00

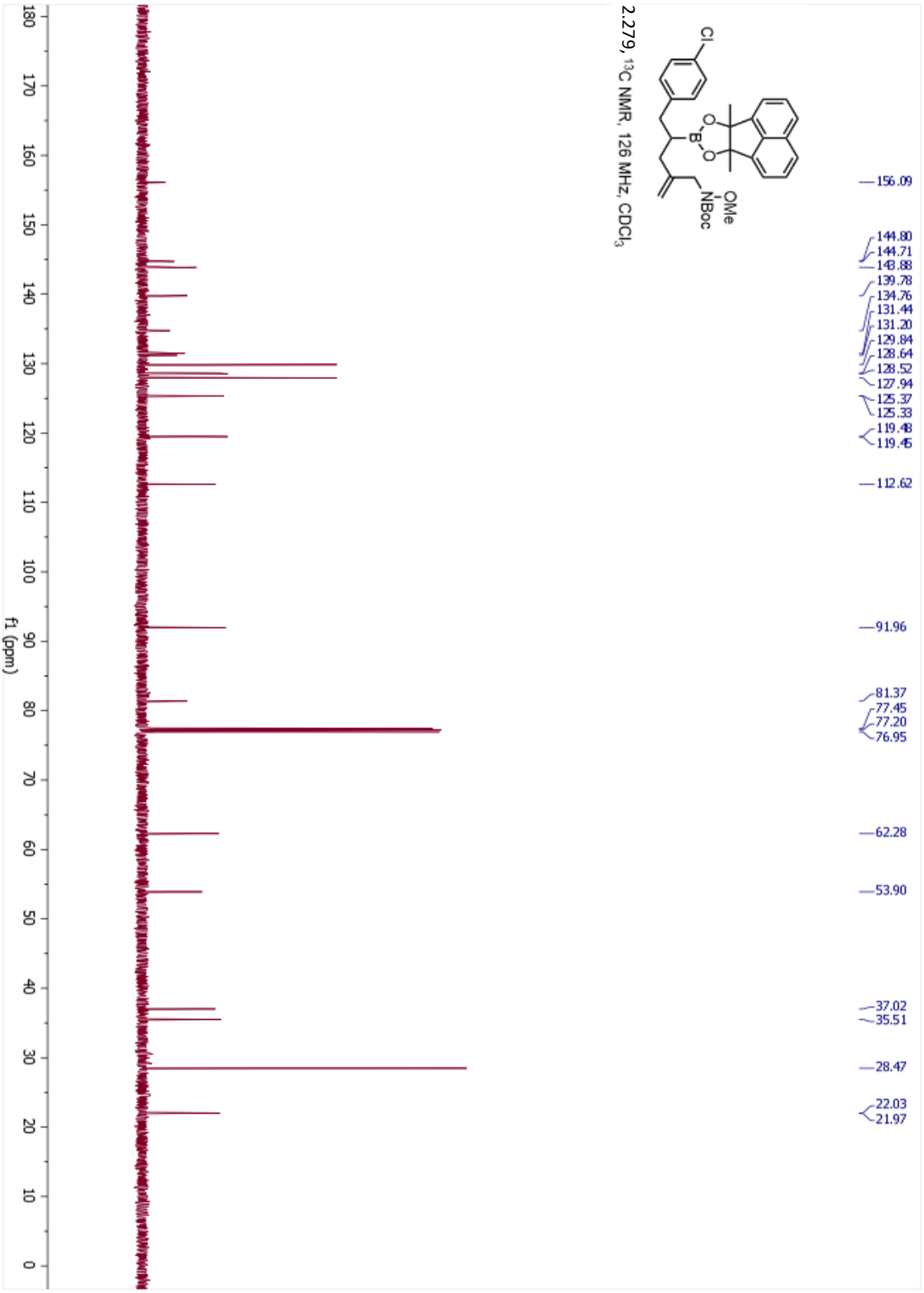

2.200, ^{13}C NMR, 126 MHz, CDCl$_3$
OH
Cl
Cl
135.30
133.71
132.54
128.60
128.16
127.85
127.70
127.69
126.43
126.32
125.87
121.95
77.45
77.20
76.95
71.38
43.88
37.08
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

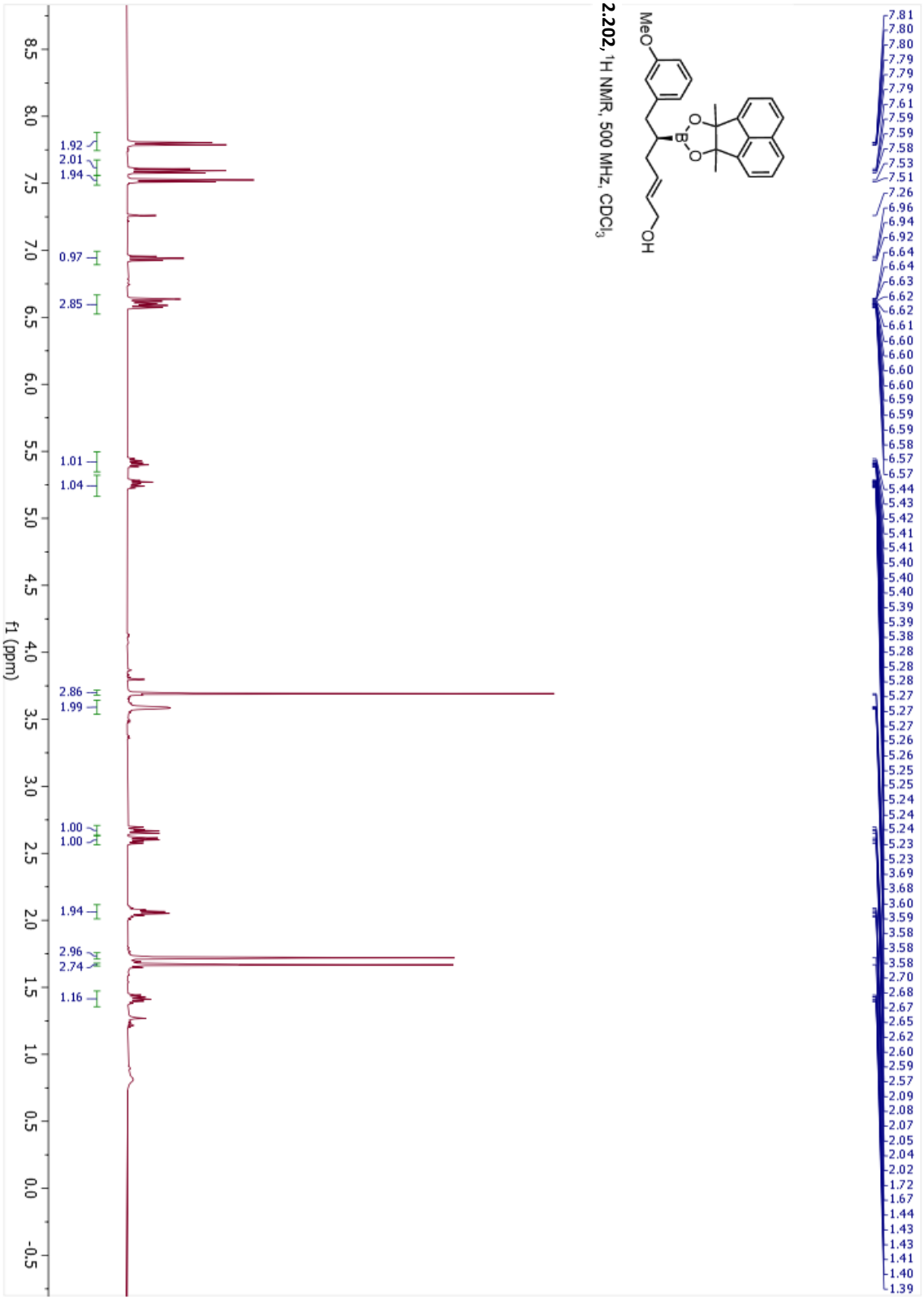


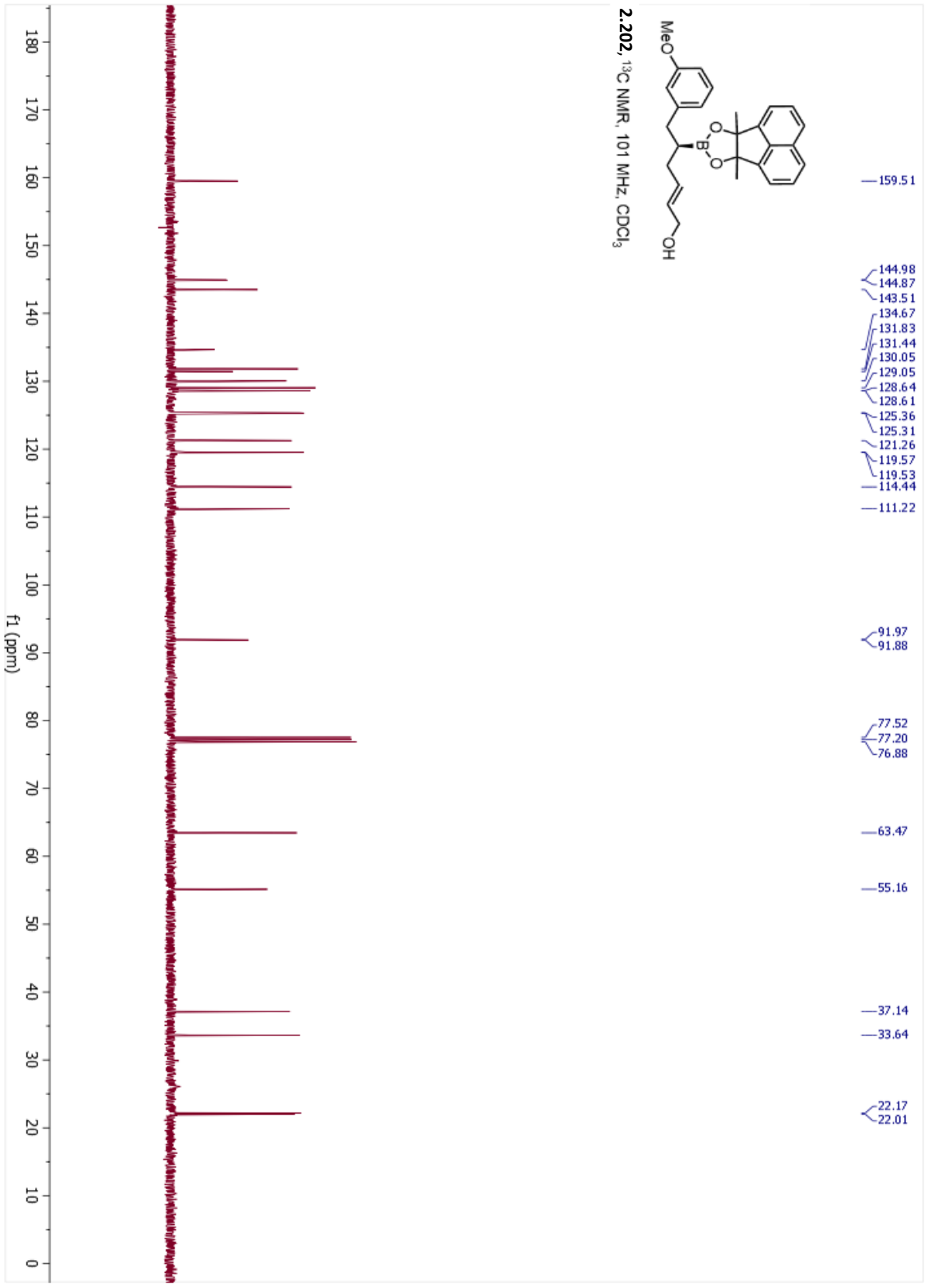
2.216, ^{1}H NMR, 500 MHz, $CDCl_3$

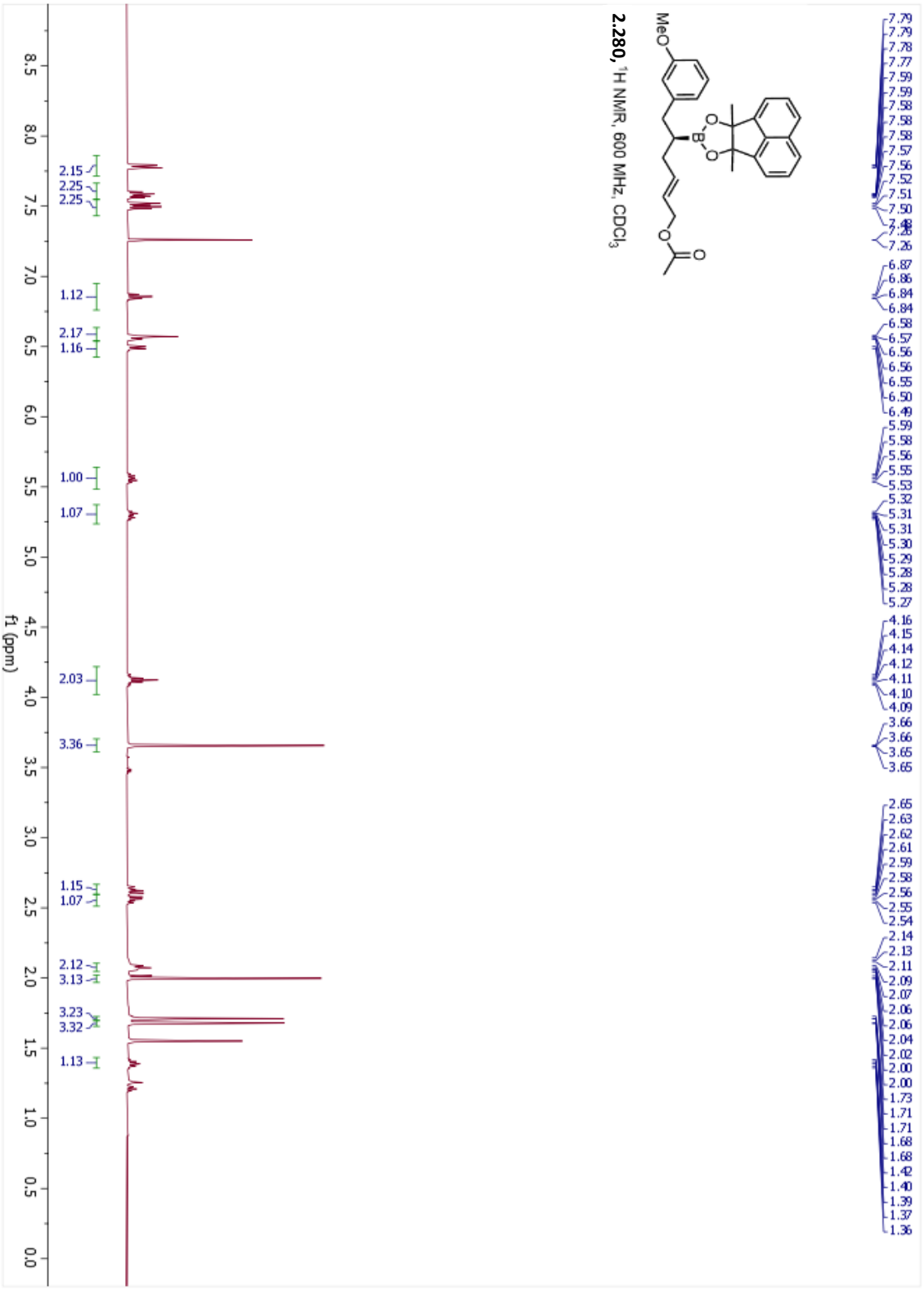

2.216, ^{13}C NMR, 126 MHz, $CDCl_3$
Cl
O
B
O
NH
OMe
145.97
143.84
140.67
134.66
131.47
131.07
130.09
128.76
128.71
128.01
125.20
125.15
119.58
119.41
113.54
91.11
77.45
77.20
76.95
61.32
55.80
36.94
36.46
22.49
22.23
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

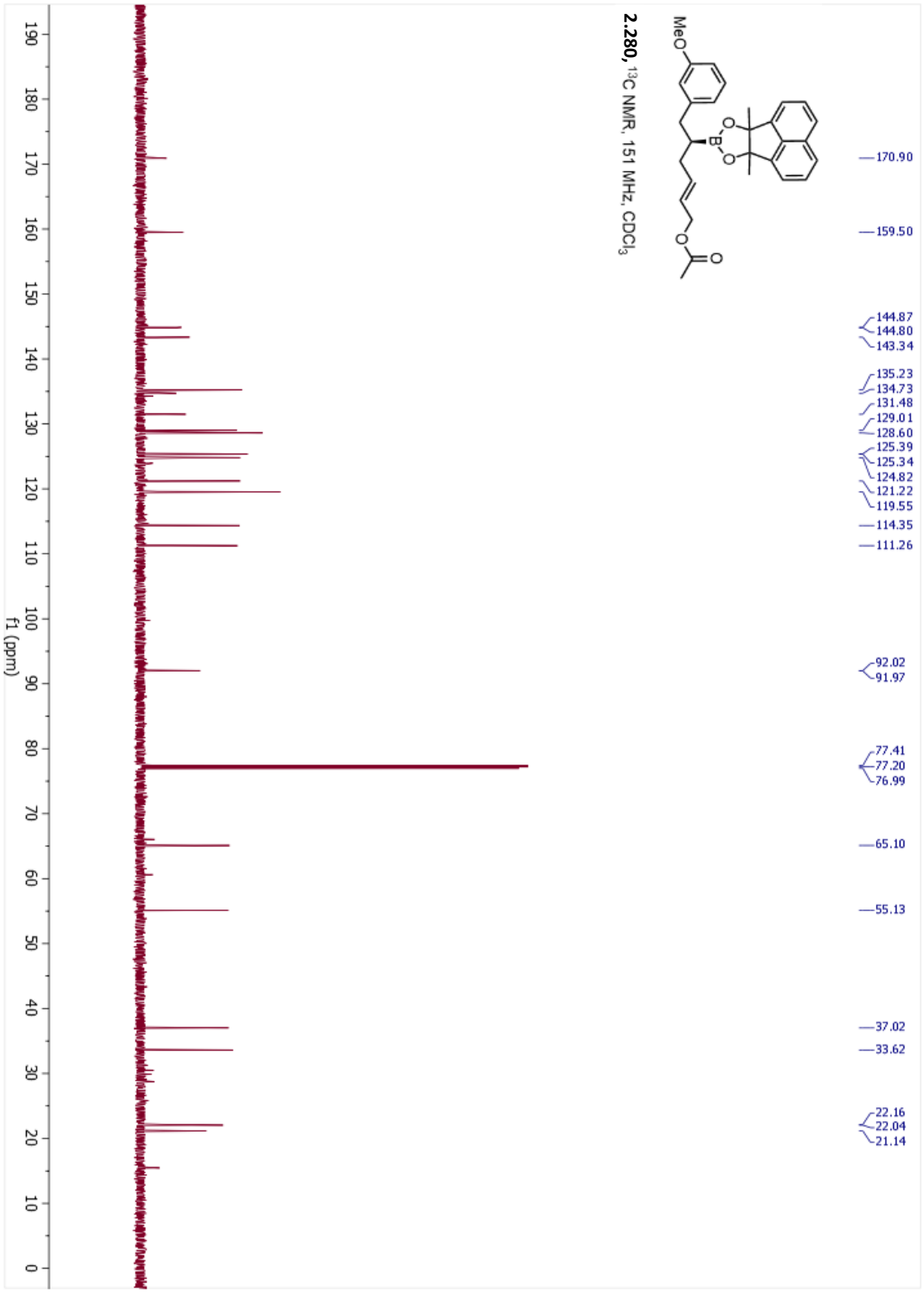

2.279, 1H NMR, 500 MHz, CDCl3
Cl
O
B
O
OMe
NBoc
7.82
7.81
7.80
7.79
7.61
7.60
7.59
7.58
7.57
7.56
7.55
7.50
7.49
7.39
7.38
6.67
6.67
6.66
6.65
6.65
6.64
6.63
6.63
6.62
6.62
4.77
4.75
4.75
3.98
3.95
3.86
3.83
3.57
2.60
2.59
2.57
2.56
2.46
2.44
2.43
2.41
2.21
2.19
2.18
2.16
2.11
2.09
2.08
2.06
1.66
1.66
1.53
1.52
1.51
1.51
1.50
1.50
1.48
1.47
1.46
1.43
1.74
1.87
0.88
0.88
1.65
1.63
1.77
1.00
0.96
2.58
1.11
0.98
1.03
1.08
5.50
9.99
f1 (ppm)
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

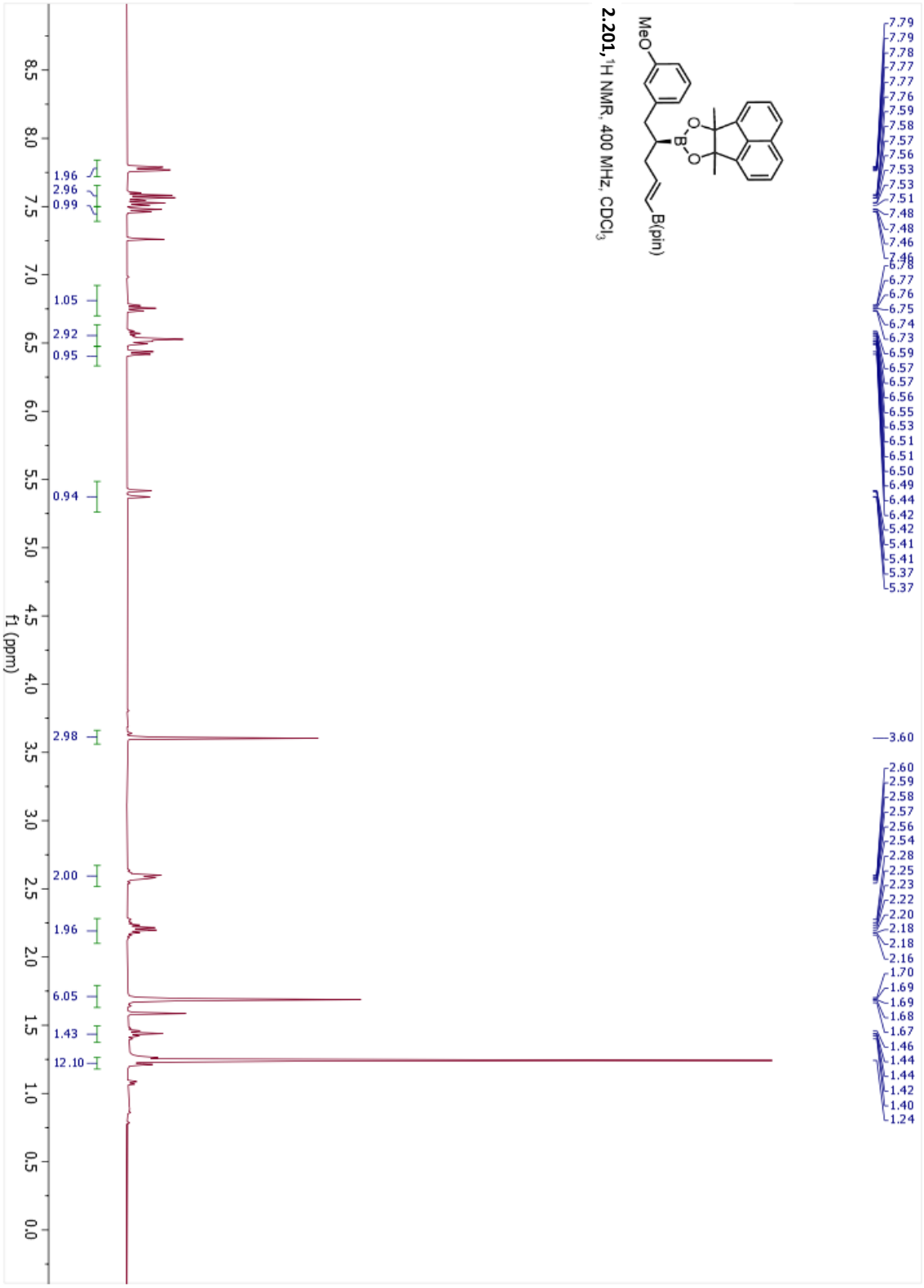

2.279, ^{13}C NMR, 126 MHz, $CDCl_3$
Cl
O
B
O
OMe
NBoc
156.09
144.80
144.71
143.88
139.78
134.76
131.44
131.20
129.84
128.64
128.52
127.94
125.37
125.33
119.48
119.45
112.62
91.96
81.37
77.45
77.20
76.95
62.28
53.90
37.02
35.51
28.47
22.03
21.97
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


2.202, 1H NMR, 500 MHz, CDCl3
MeO
OH
B
O
O
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1.92
2.01
1.94
0.97
2.85
1.01
1.04
2.86
1.99
1.00
1.00
1.94
2.96
2.74
1.16
7.81
7.80
7.80
7.79
7.79
7.79
7.61
7.59
7.59
7.58
7.53
7.51
7.26
6.96
6.94
6.92
6.64
6.64
6.63
6.62
6.62
6.61
6.60
6.60
6.60
6.60
6.59
6.59
6.59
6.58
6.57
6.57
5.44
5.43
5.42
5.41
5.41
5.40
5.40
5.40
5.39
5.39
5.38
5.28
5.28
5.28
5.27
5.27
5.27
5.26
5.26
5.25
5.25
5.24
5.24
5.24
5.23
5.23
3.69
3.68
3.60
3.59
3.58
3.58
3.58
2.70
2.68
2.67
2.65
2.62
2.60
2.59
2.57
2.09
2.08
2.07
2.05
2.04
2.02
1.72
1.67
1.44
1.43
1.43
1.41
1.40
1.39

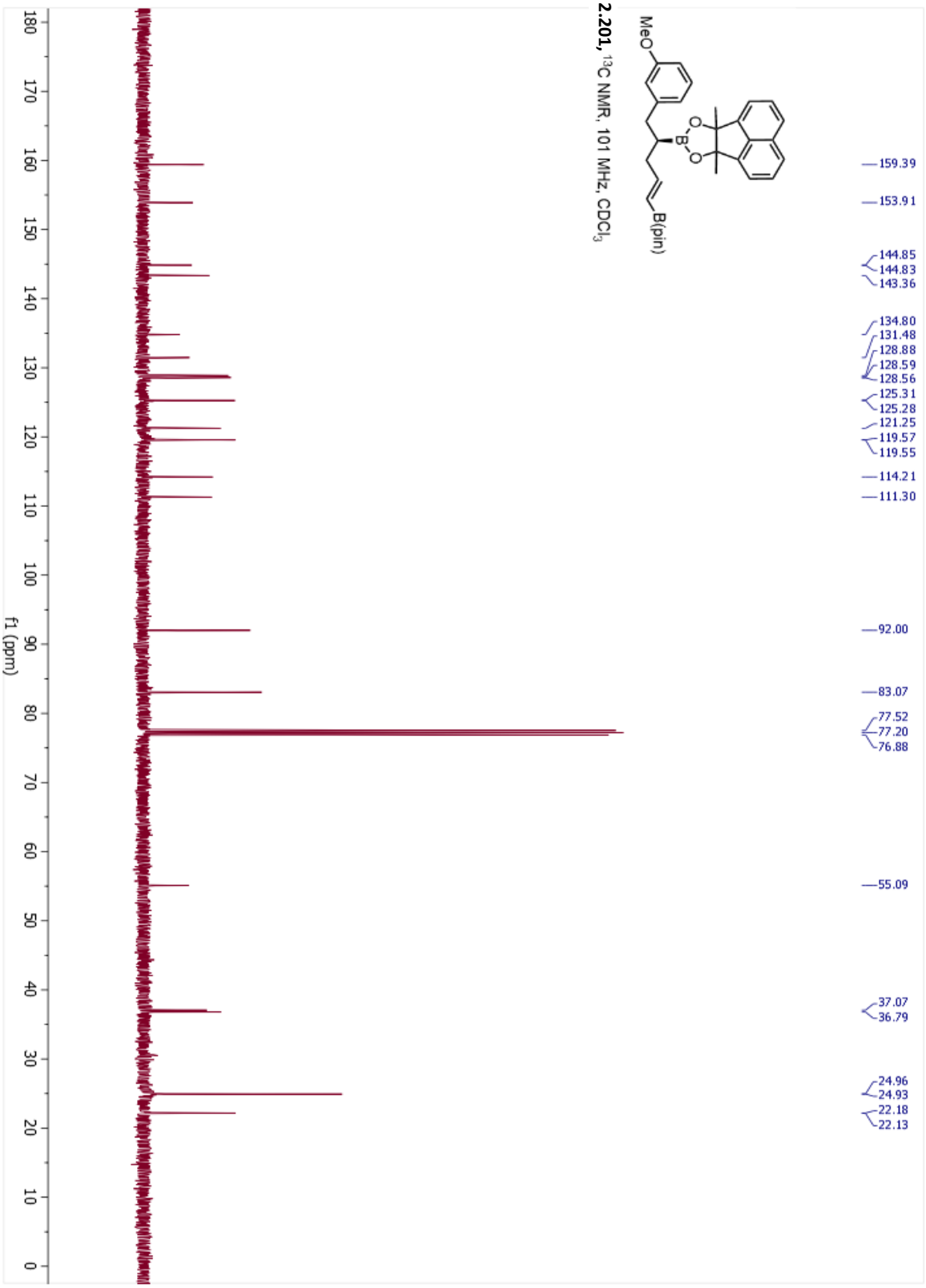

2.202, ^{13}C NMR, 101 MHz, $CDCl_3$
MeO
OH
B
O
O
159.51
144.98
144.87
143.51
134.67
131.83
131.44
130.05
129.05
128.64
128.61
125.36
125.31
121.26
119.57
119.53
114.44
111.22
91.97
91.88
77.52
77.20
76.88
63.47
55.16
37.14
33.64
22.17
22.01
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

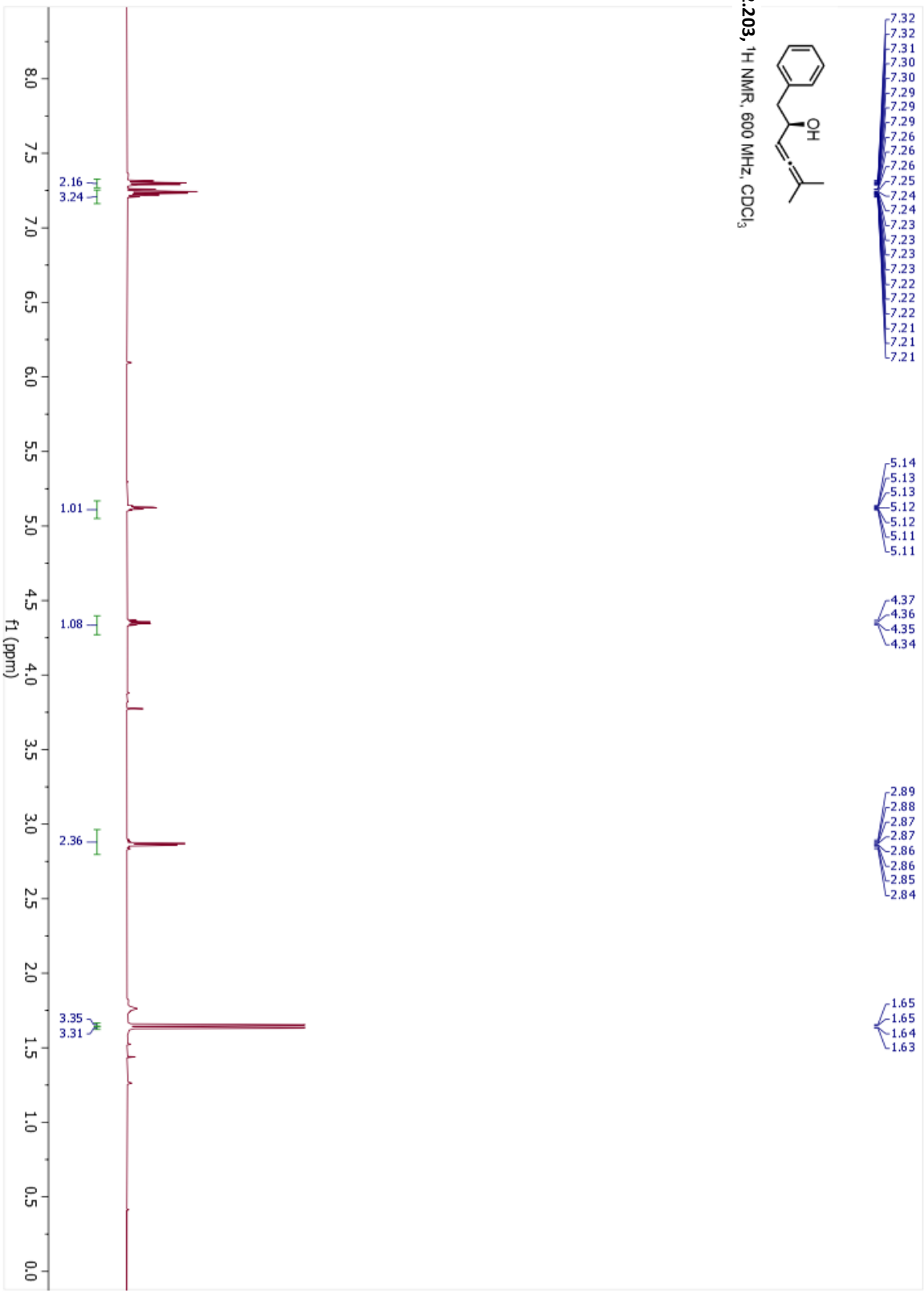

2.280, ^{1}H NMR, 600 MHz, $CDCl_3$
MeO
O
B
O
O
O
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.15
2.25
2.25
1.12
2.17
1.16
1.00
1.07
2.03
3.36
1.15
1.07
2.12
3.13
3.23
3.32
1.13
7.79
7.79
7.78
7.77
7.59
7.59
7.58
7.58
7.58
7.57
7.56
7.52
7.51
7.50
7.26
6.87
6.86
6.84
6.84
6.58
6.57
6.56
6.56
6.55
6.50
6.49
5.59
5.58
5.56
5.55
5.53
5.32
5.31
5.31
5.30
5.29
5.28
5.28
5.27
4.16
4.15
4.14
4.12
4.11
4.10
4.09
3.66
3.66
3.65
3.65
2.65
2.63
2.62
2.61
2.59
2.58
2.56
2.55
2.54
2.14
2.13
2.11
2.09
2.07
2.06
2.06
2.04
2.02
2.00
2.00
1.73
1.71
1.71
1.68
1.68
1.42
1.40
1.39
1.37
1.36

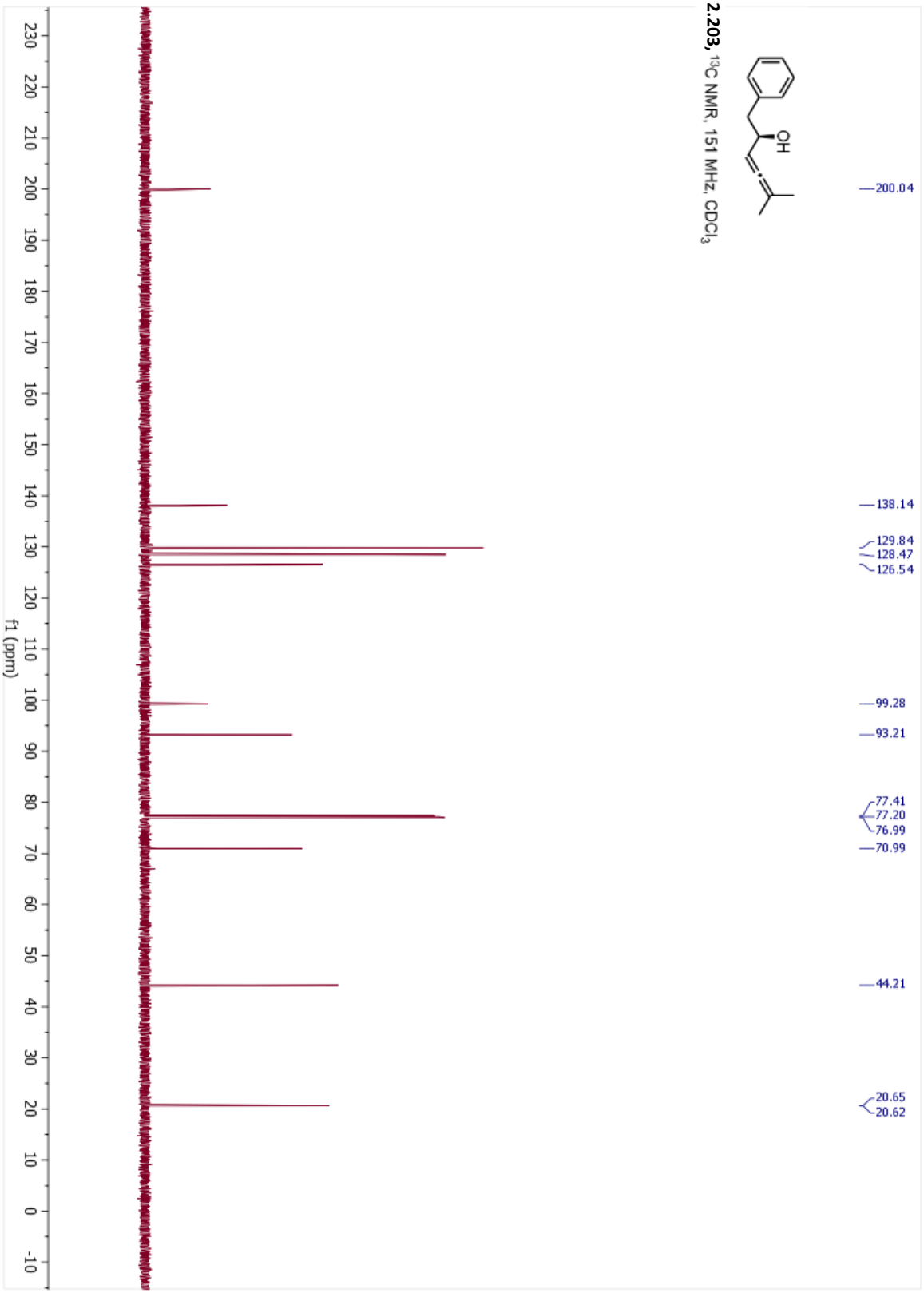

2.280, 13C NMR, 151 MHz, CDCl3
MeO
O
B
O
O
170.90
159.50
144.87
144.80
143.34
135.23
134.73
131.48
129.01
128.60
125.39
125.34
124.82
121.22
119.55
114.35
111.26
92.02
91.97
77.41
77.20
76.99
65.10
55.13
37.02
33.62
22.16
22.04
21.14
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

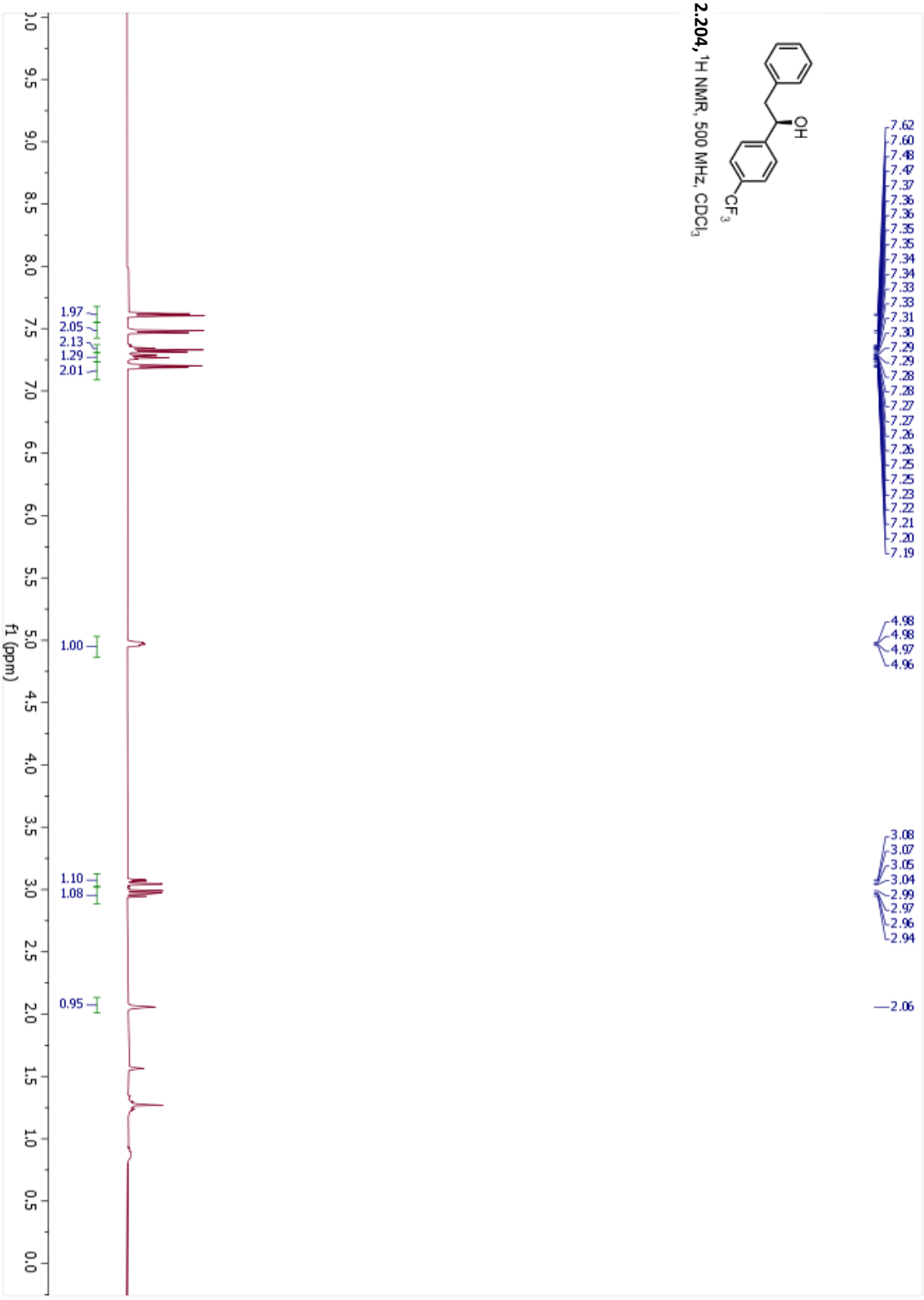


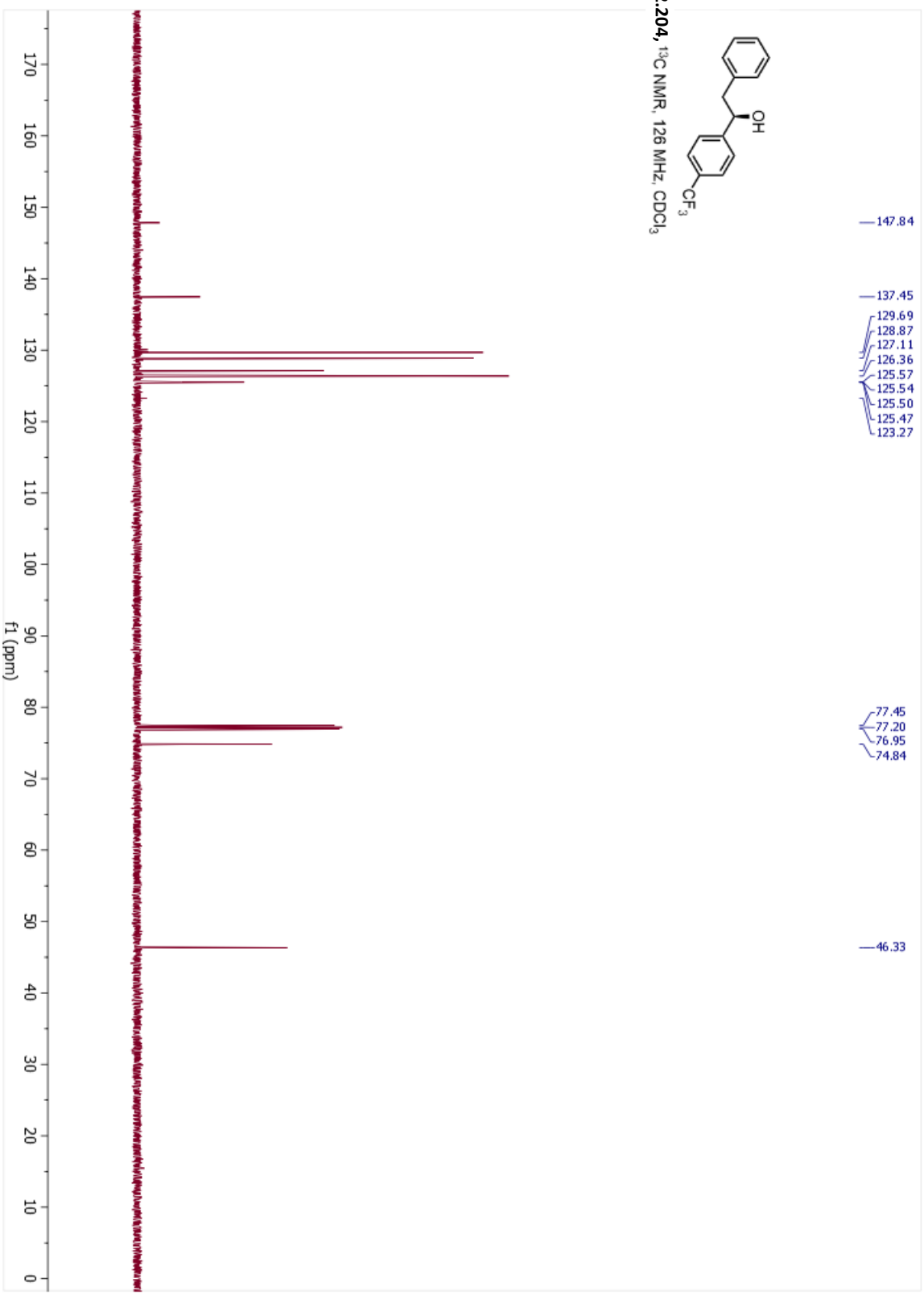
2.201, ^{1}H NMR, 400 MHz, $CDCl_3$

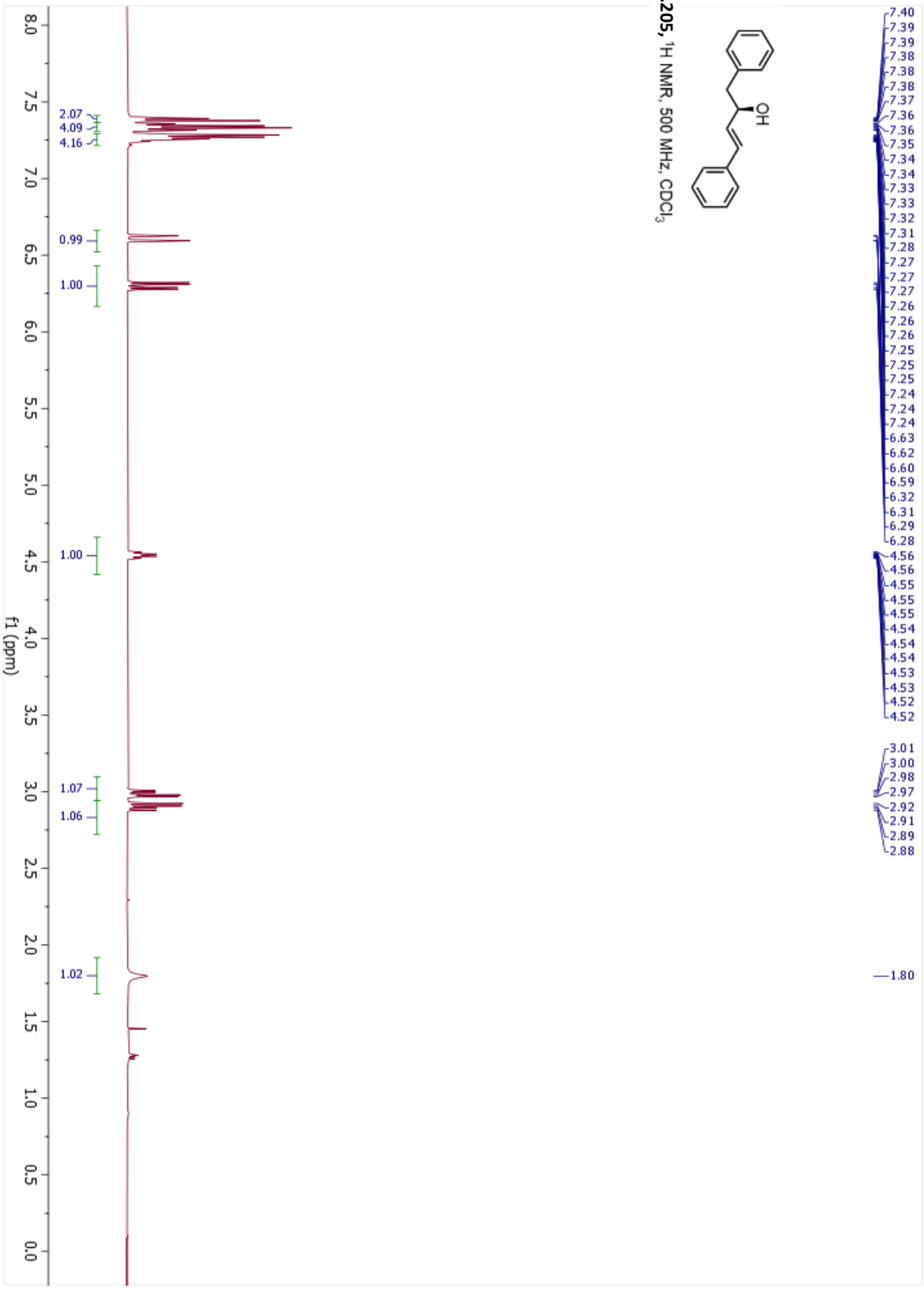

2.201, ^{13}C NMR, 101 MHz, $CDCl_3$
MeO
B(pin)
159.39
153.91
144.85
144.83
143.36
134.80
131.48
128.88
128.59
128.56
125.31
125.28
121.25
119.57
119.55
114.21
111.30
92.00
83.07
77.52
77.20
76.88
55.09
37.07
36.79
24.96
24.93
22.18
22.13
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

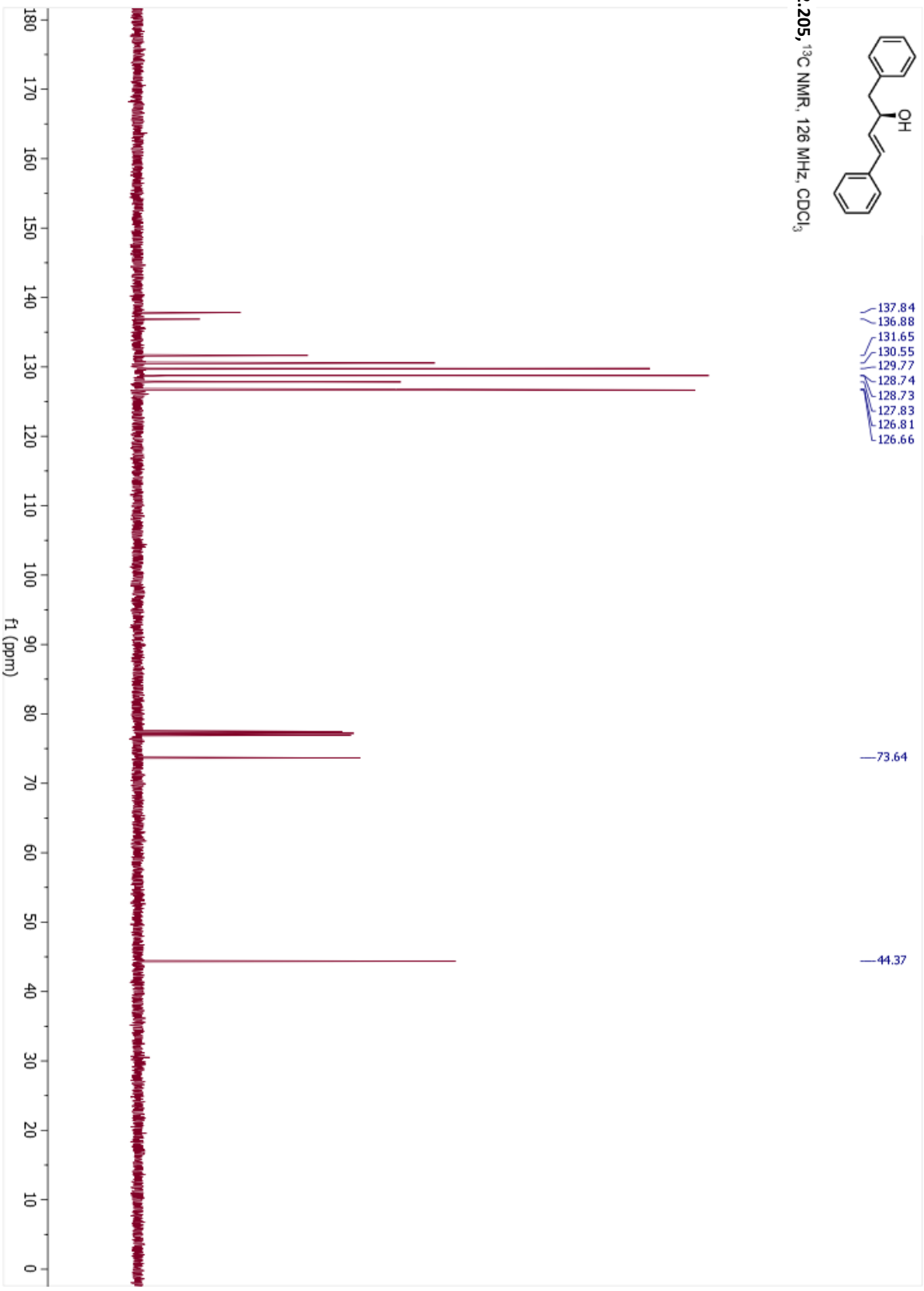

2.203, ^{1}H NMR, 600 MHz, $CDCl_3$
OH
7.32
7.32
7.31
7.30
7.30
7.29
7.29
7.29
7.26
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.23
7.23
7.22
7.22
7.22
7.21
7.21
7.21
5.14
5.13
5.13
5.12
5.12
5.11
5.11
4.37
4.36
4.35
4.34
2.89
2.88
2.87
2.87
2.86
2.86
2.85
2.84
1.65
1.65
1.64
1.63
2.16
3.24
1.01
1.08
2.36
3.35
3.31
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
0.5
0.0

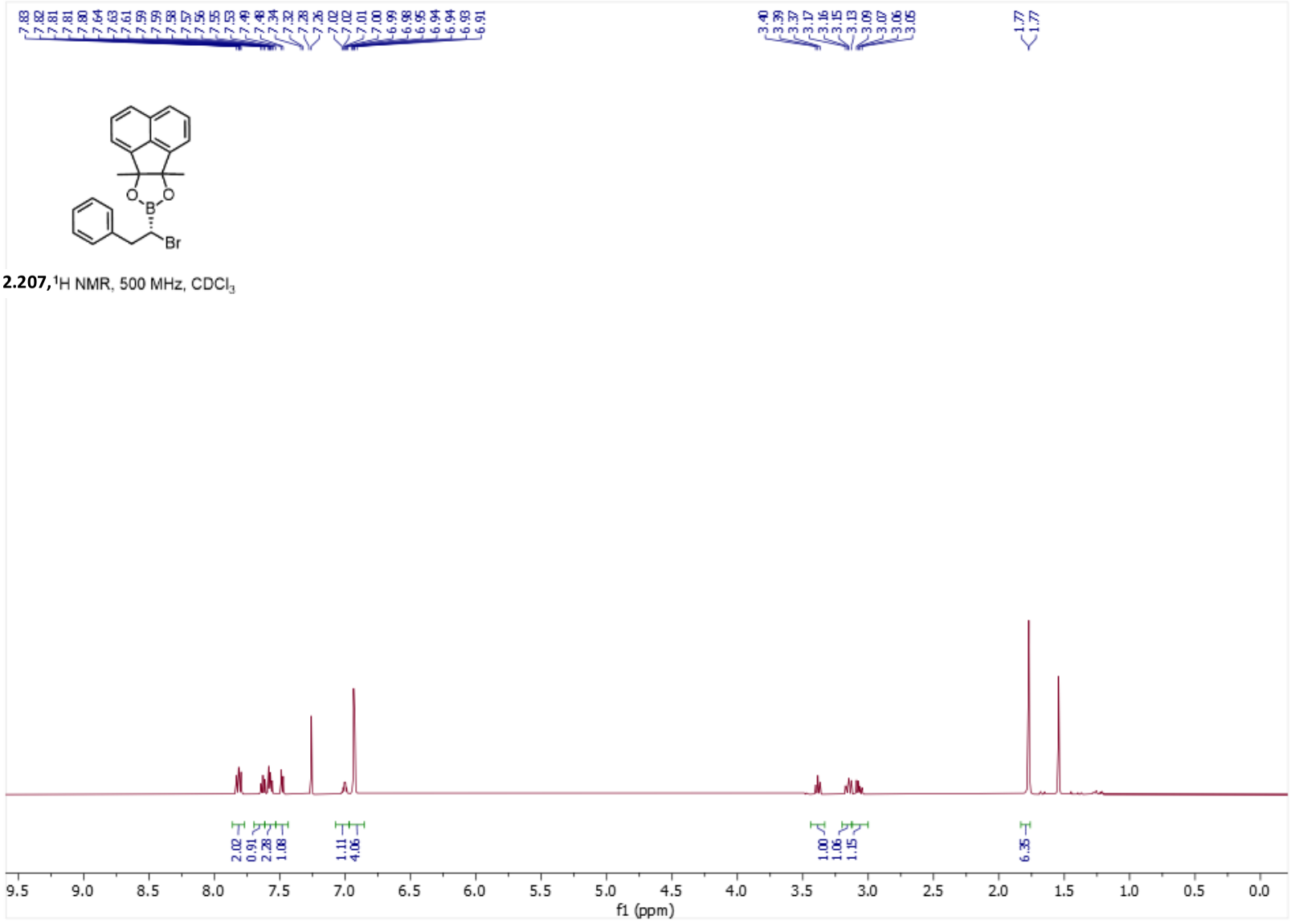

2.203, ^{13}C NMR, 151 MHz, $CDCl_3$
OH
200.04
138.14
129.84
128.47
126.54
99.28
93.21
77.41
77.20
76.99
70.99
44.21
20.65
20.62
f1 (ppm)


2.204, ^{1}H NMR, 500 MHz, $CDCl_3$
OH
CF_3
7.62
7.60
7.48
7.47
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.31
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.23
7.22
7.21
7.20
7.19
4.98
4.98
4.97
4.96
3.08
3.07
3.05
3.04
2.99
2.97
2.96
2.94
2.06
1.97
2.05
2.13
1.29
2.01
1.00
1.10
1.08
0.95
f1 (ppm)

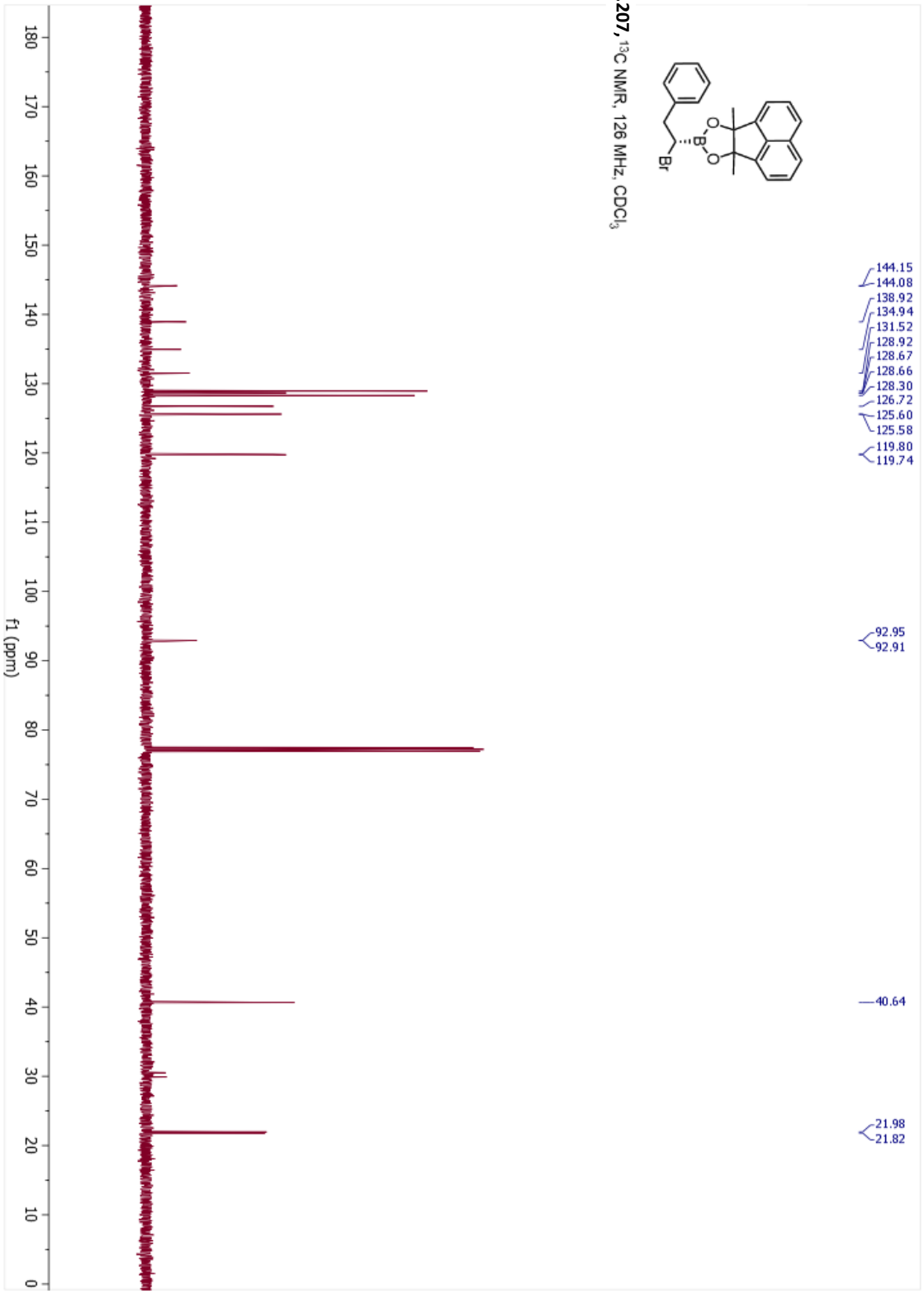

2.204, 13C NMR, 126 MHz, CDCl3
OH
CF3
147.84
137.45
129.69
128.87
127.11
126.36
125.57
125.54
125.50
125.47
123.27
77.45
77.20
76.95
74.84
46.33
f1 (ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

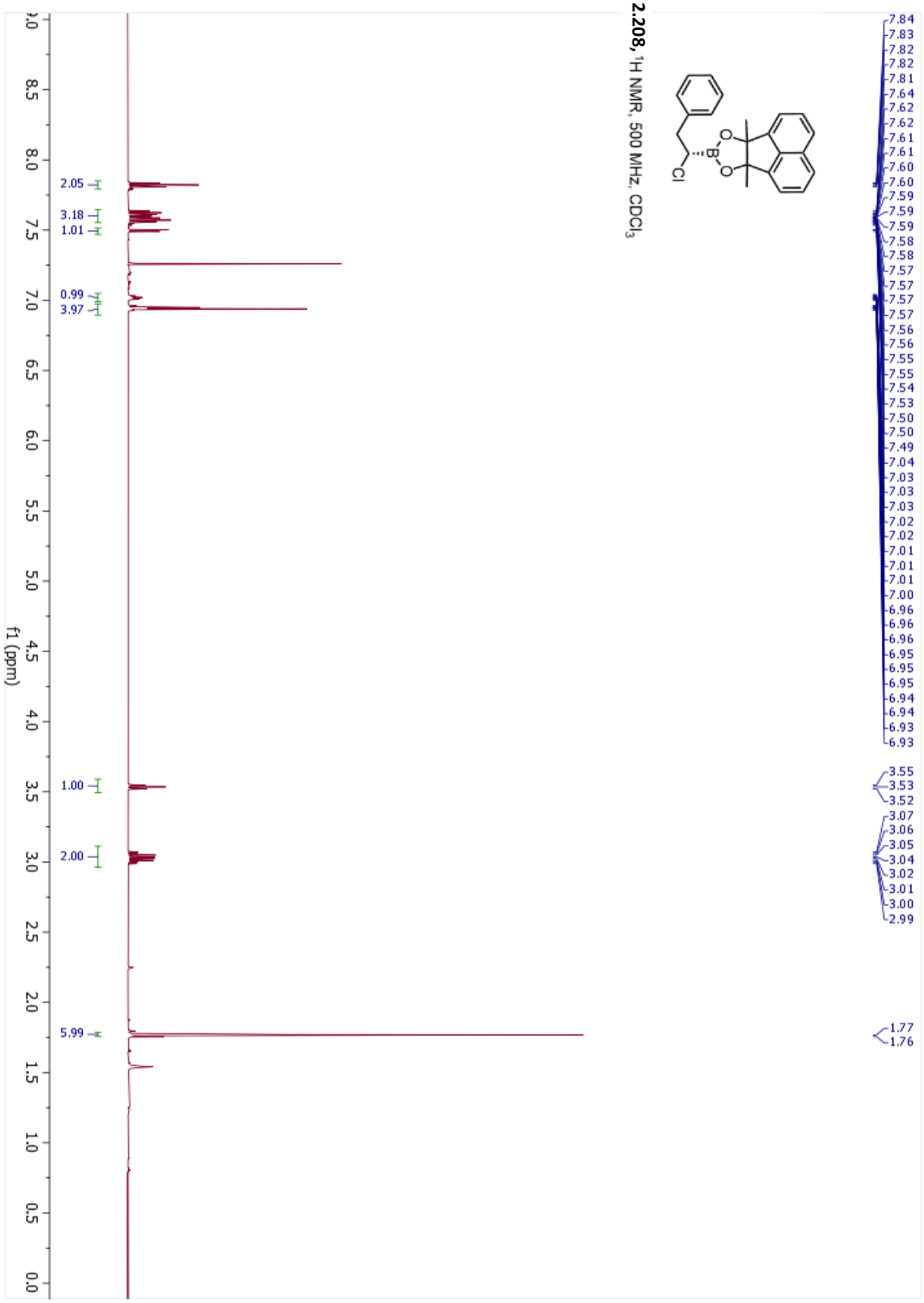

2.205, 1H NMR, 500 MHz, CDCl3
OH
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.07
4.09
4.16
0.99
1.00
1.00
1.07
1.06
1.02
7.40
7.39
7.39
7.38
7.38
7.38
7.37
7.36
7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.28
7.27
7.27
7.27
7.26
7.26
7.26
7.25
7.25
7.25
7.24
7.24
7.24
6.63
6.62
6.60
6.59
6.32
6.31
6.29
6.28
4.56
4.56
4.55
4.55
4.55
4.54
4.54
4.54
4.53
4.53
4.52
4.52
3.01
3.00
2.98
2.97
2.92
2.91
2.89
2.88
1.80

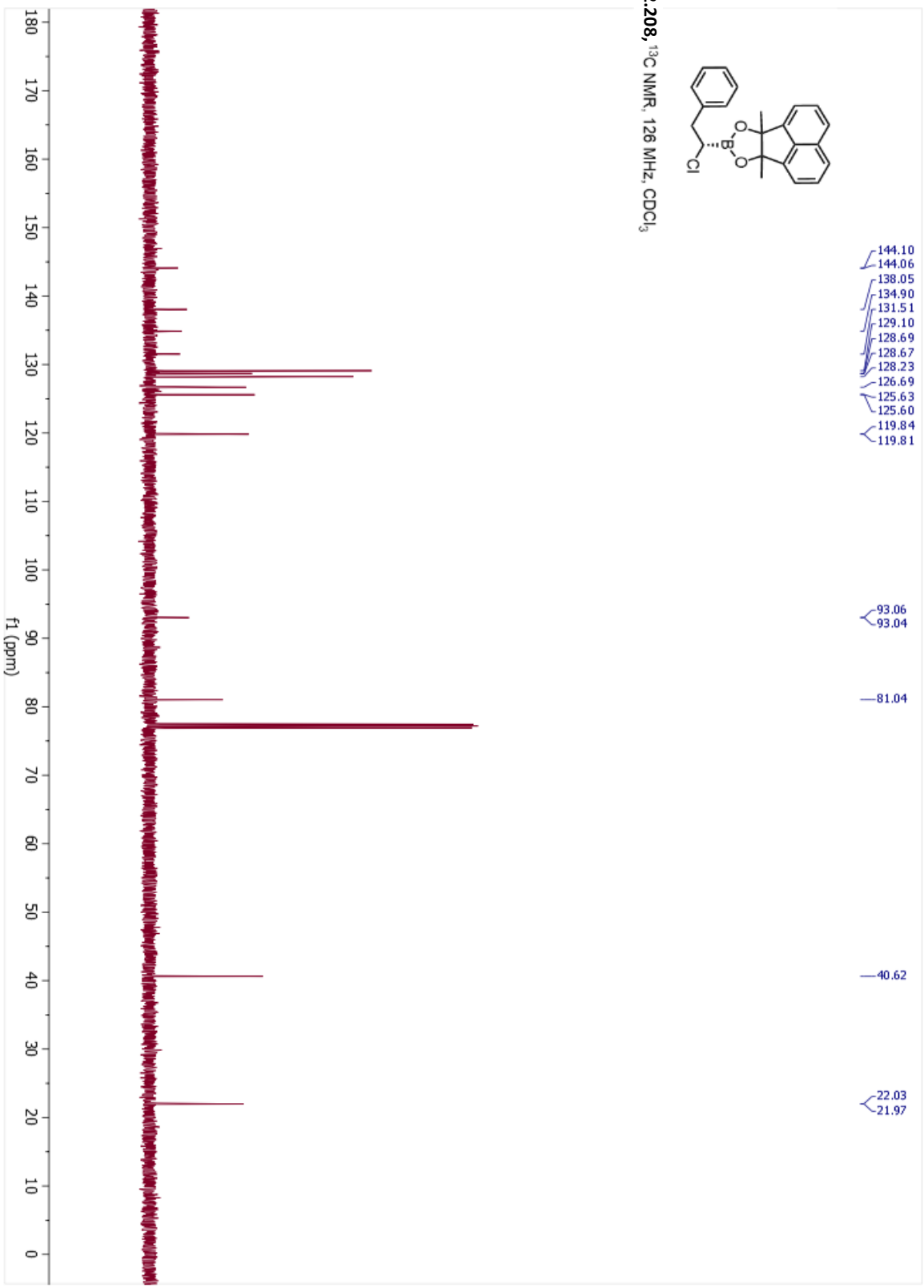

2.205, 13C NMR, 126 MHz, CDCl3
OH
137.84
136.88
131.65
130.55
129.77
128.74
128.73
127.83
126.81
126.66
73.64
44.37
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

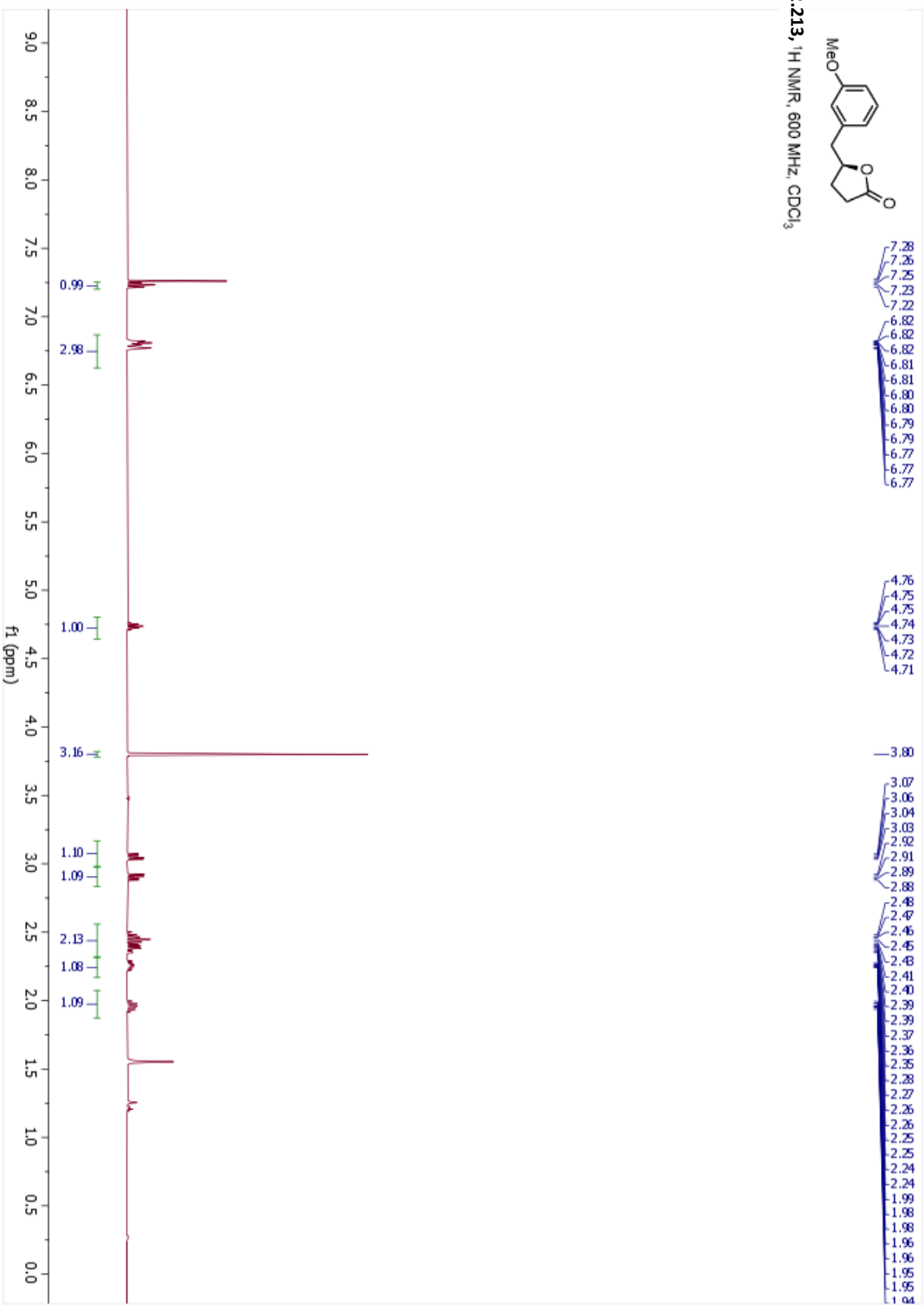


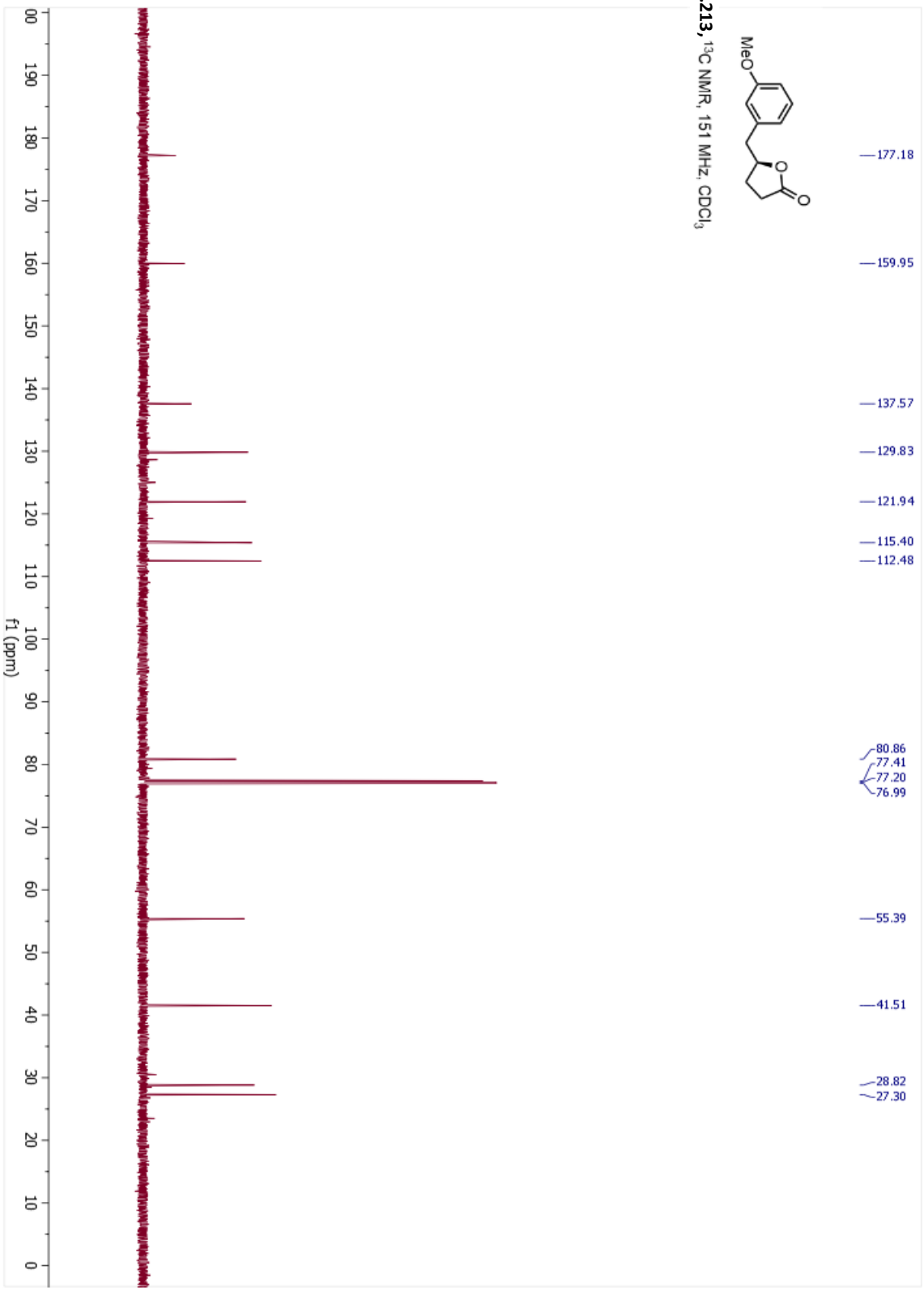
2.207, ^{1}H NMR, 500 MHz, $CDCl_3$

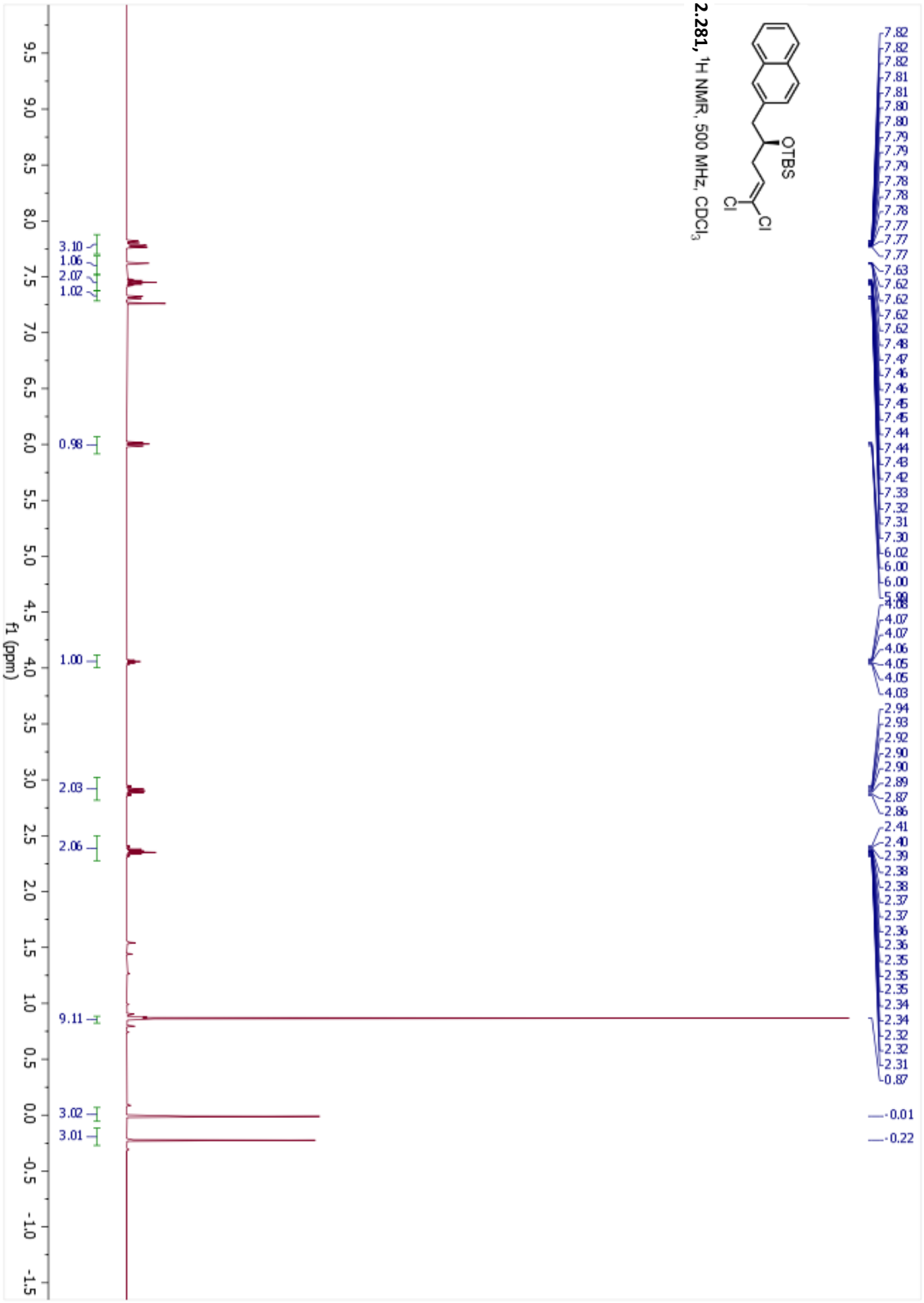

2.207, 13C NMR, 126 MHz, CDCl3
Br
144.15
144.08
138.92
134.94
131.52
128.92
128.67
128.66
128.30
126.72
125.60
125.58
119.80
119.74
92.95
92.91
40.64
21.98
21.82
f1 (ppm)

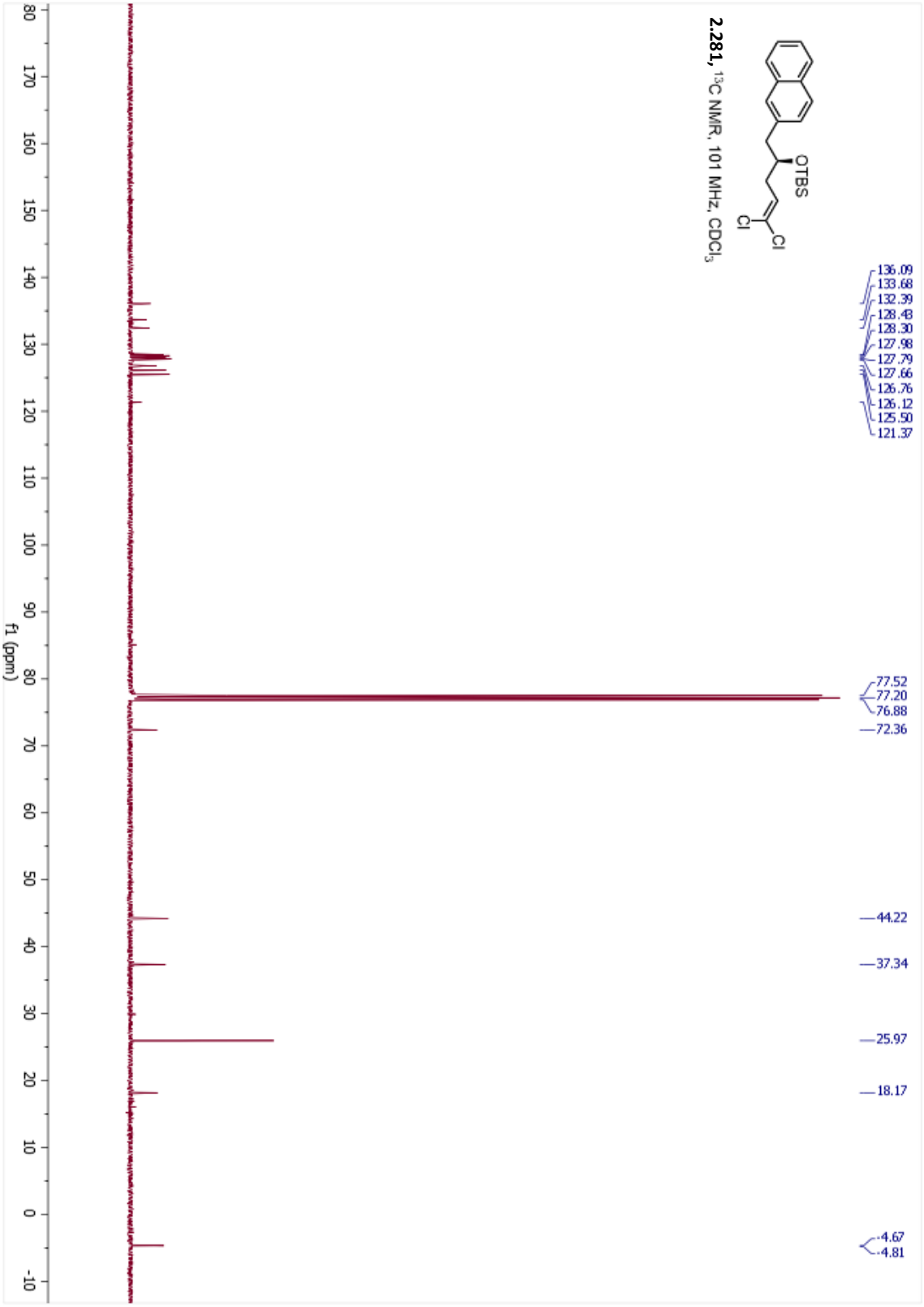

2.208, ^{1}H NMR, 500 MHz, $CDCl_3$
Cl
B
O
O
f1 (ppm)
2.05
3.18
1.01
0.99
3.97
1.00
2.00
5.99
7.84
7.83
7.82
7.82
7.81
7.64
7.62
7.62
7.61
7.61
7.60
7.60
7.59
7.59
7.59
7.58
7.58
7.57
7.57
7.57
7.57
7.56
7.56
7.55
7.55
7.54
7.53
7.50
7.50
7.49
7.04
7.03
7.03
7.03
7.02
7.02
7.01
7.01
7.01
7.00
6.96
6.96
6.96
6.95
6.95
6.95
6.94
6.94
6.93
6.93
3.55
3.53
3.52
3.07
3.06
3.05
3.04
3.02
3.01
3.00
2.99
1.77
1.76

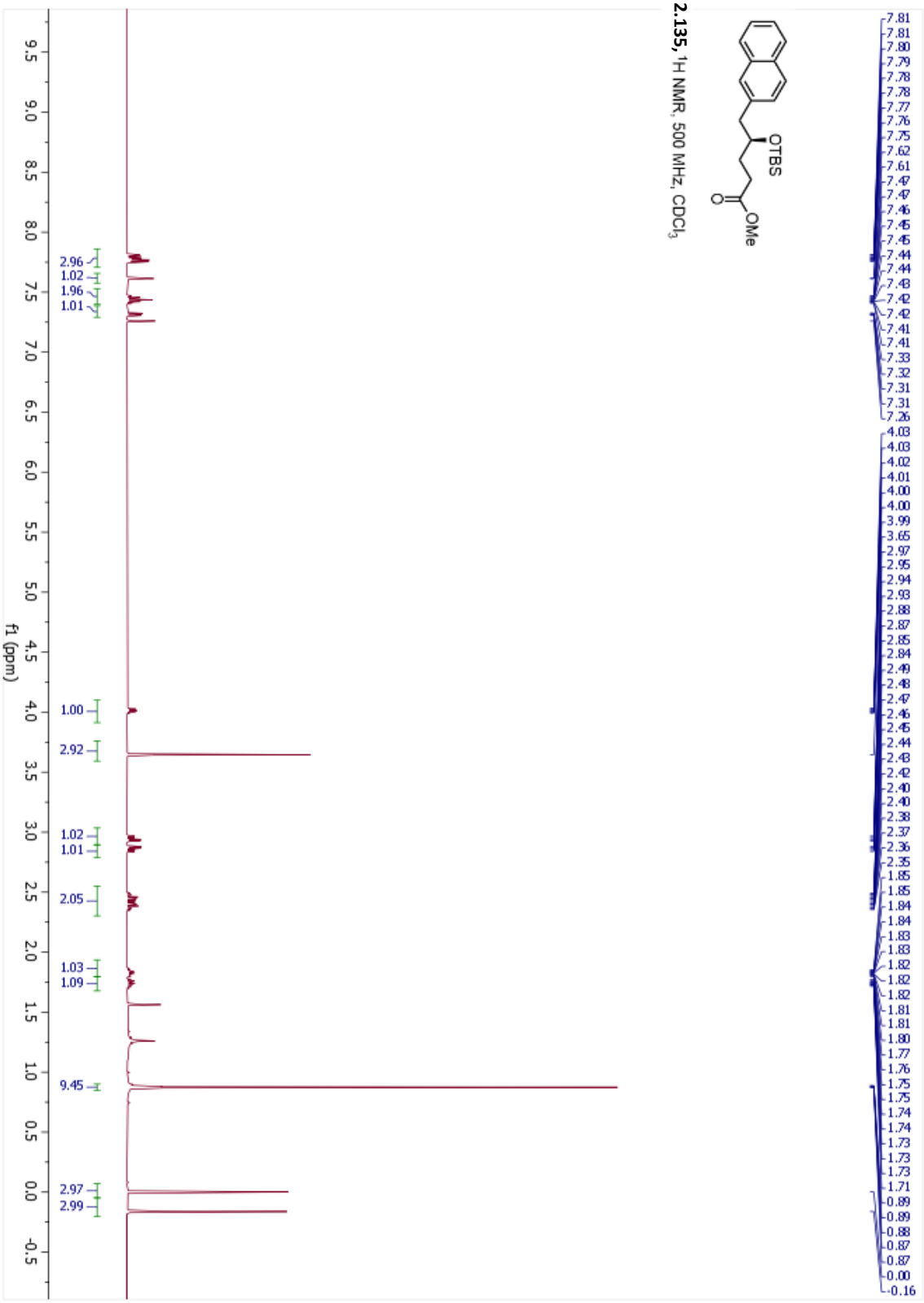

2.208, ^{13}C NMR, 126 MHz, $CDCl_3$
144.10
144.06
138.05
134.90
131.51
129.10
128.69
128.67
128.23
126.69
125.63
125.60
119.84
119.81
93.06
93.04
81.04
40.62
22.03
21.97
f1 (ppm)

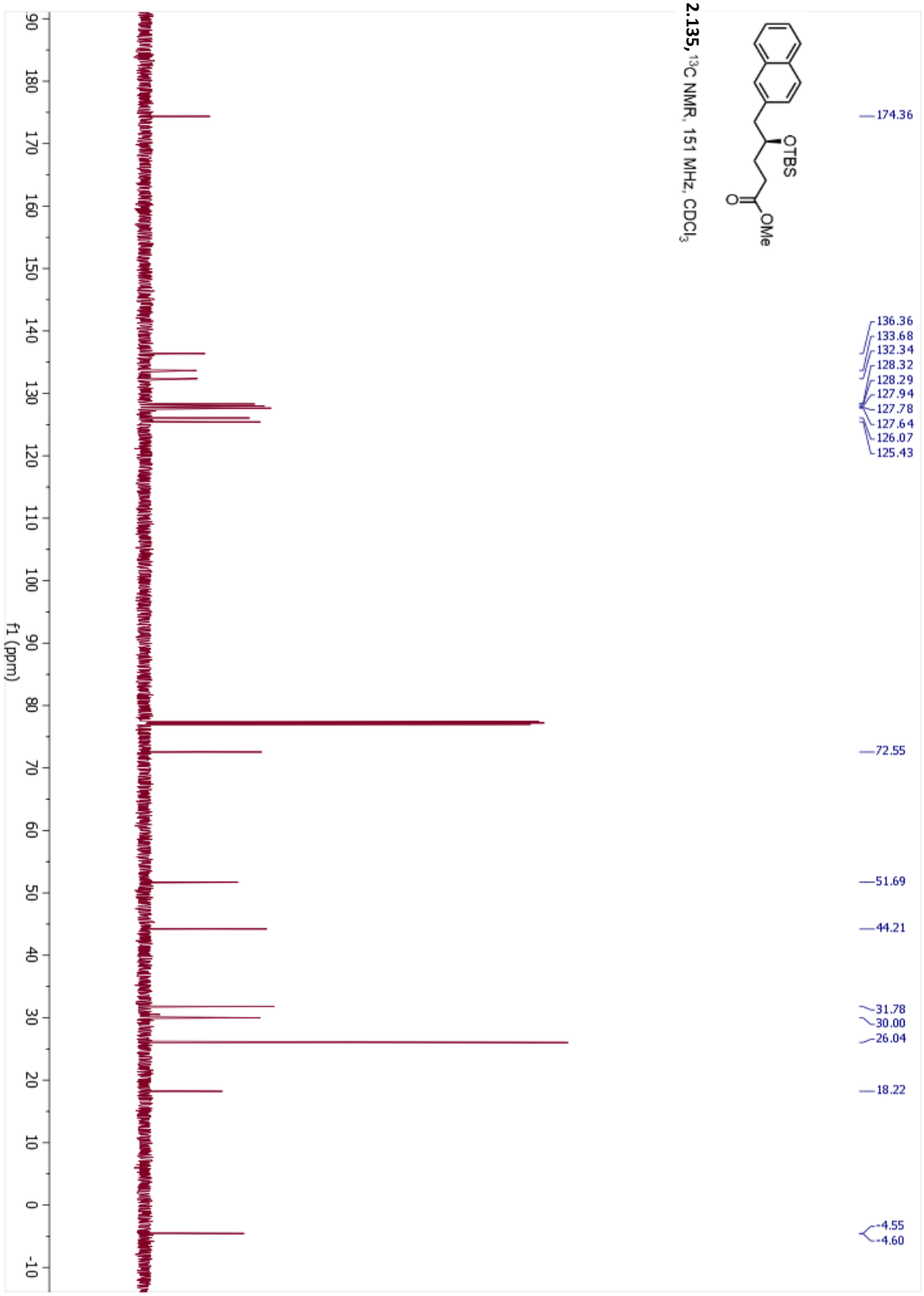

2.213, ^{1}H NMR, 600 MHz, $CDCl_3$
MeO
O
O
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.99
2.98
1.00
3.16
1.10
1.09
2.13
1.08
1.09
7.28
7.26
7.25
7.23
7.22
6.82
6.82
6.82
6.81
6.81
6.80
6.80
6.79
6.79
6.77
6.77
6.77
4.76
4.75
4.75
4.74
4.73
4.72
4.71
3.80
3.07
3.06
3.04
3.03
2.92
2.91
2.89
2.88
2.48
2.47
2.46
2.45
2.43
2.41
2.40
2.39
2.39
2.37
2.36
2.35
2.28
2.27
2.26
2.26
2.25
2.25
2.24
2.24
1.99
1.98
1.98
1.96
1.96
1.95
1.95

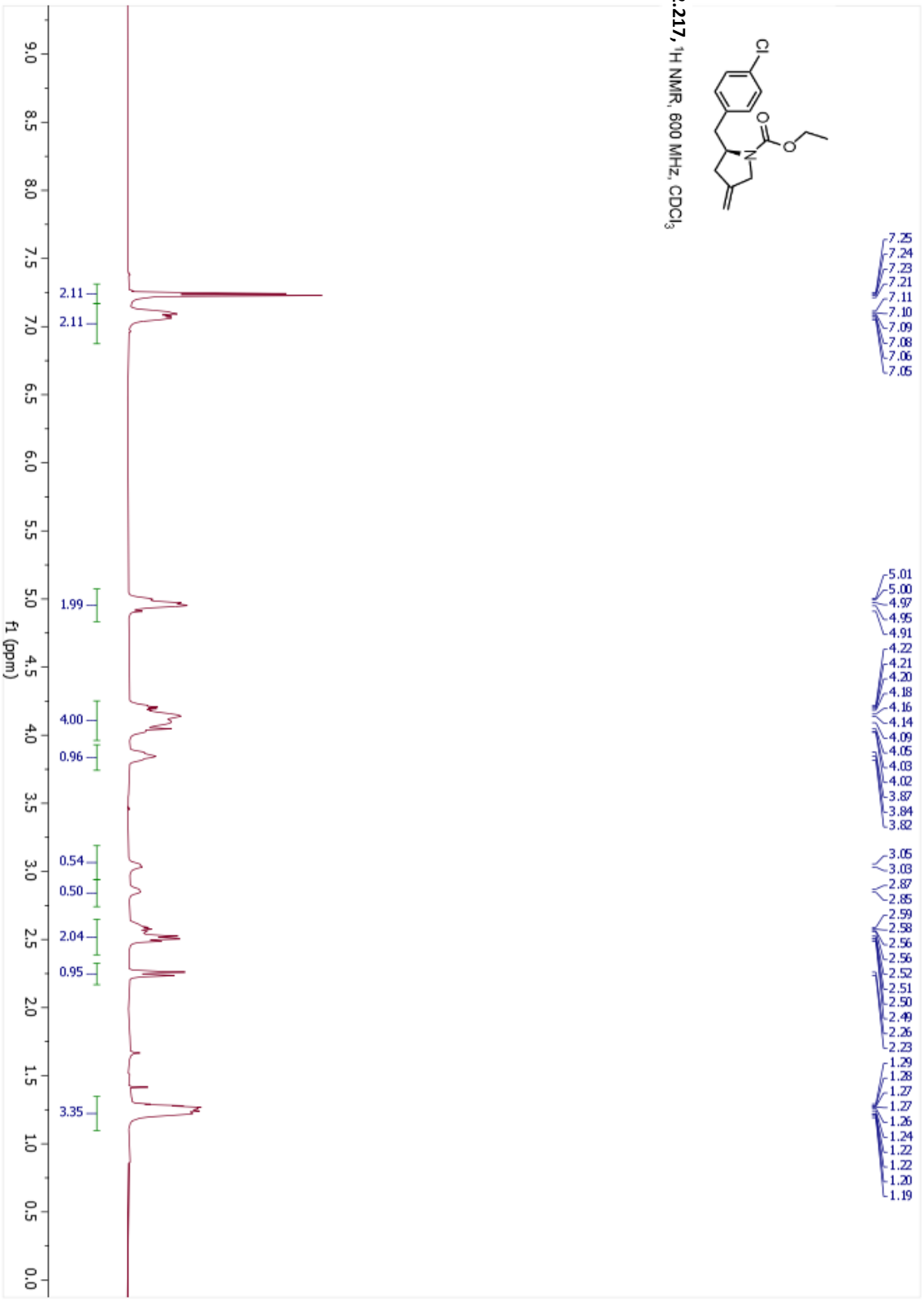

2.213, ^{13}C NMR, 151 MHz, $CDCl_3$
MeO
O
O
177.18
159.95
137.57
129.83
121.94
115.40
112.48
80.86
77.41
77.20
76.99
55.39
41.51
28.82
27.30
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

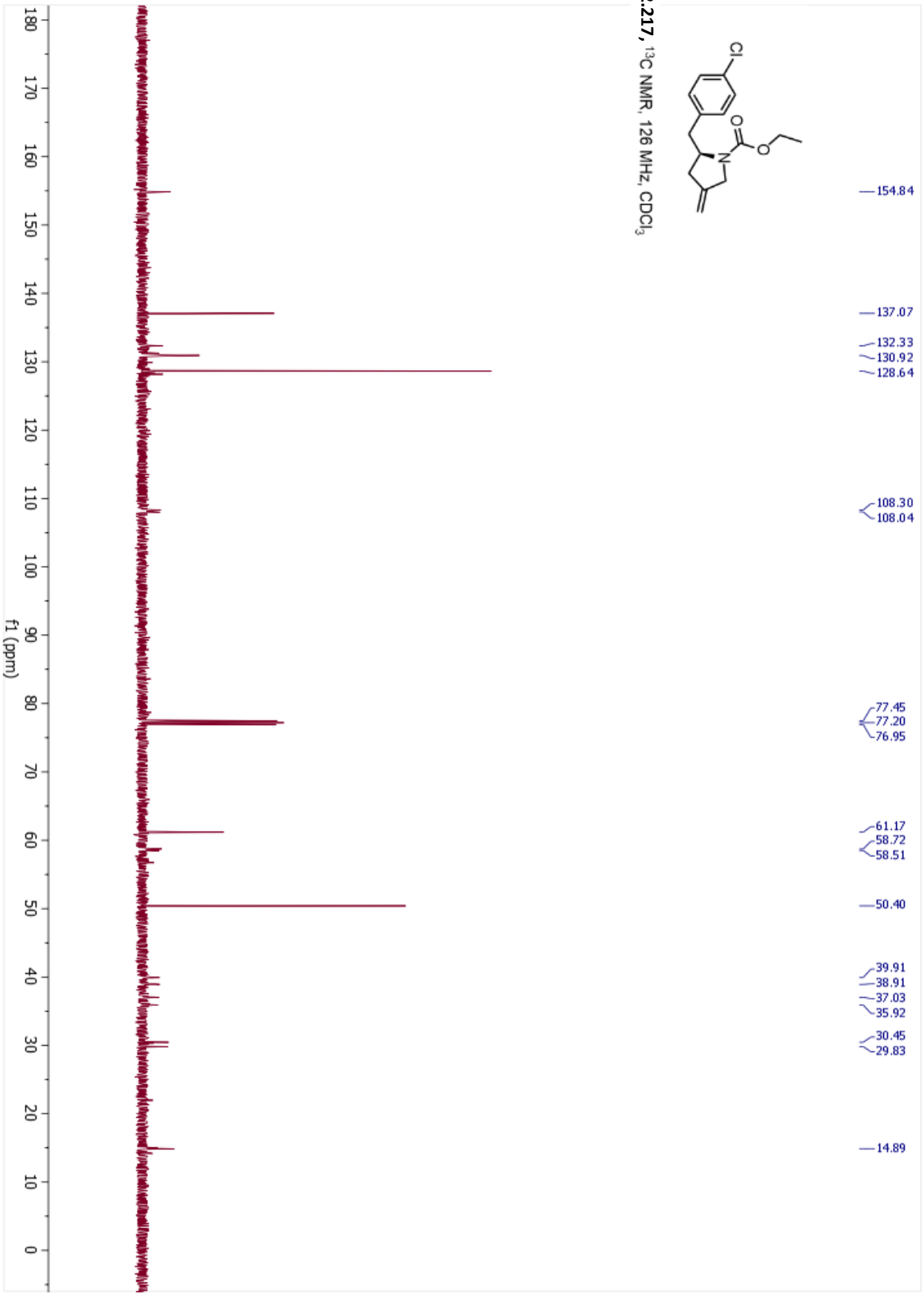

2.281, ^{1}H NMR, 500 MHz, $CDCl_3$
OTBS
Cl
Cl
f1 (ppm)
3.10
1.06
2.07
1.02
0.98
1.00
2.03
2.06
9.11
3.02
3.01
7.82
7.81
7.80
7.79
7.78
7.77
7.63
7.62
7.48
7.47
7.46
7.45
7.44
7.43
7.42
7.33
7.32
7.31
7.30
6.02
6.00
4.08
4.07
4.06
4.05
4.03
2.94
2.93
2.92
2.90
2.89
2.87
2.86
2.41
2.40
2.39
2.38
2.37
2.36
2.35
2.34
2.32
2.31
0.87
0.01
0.22

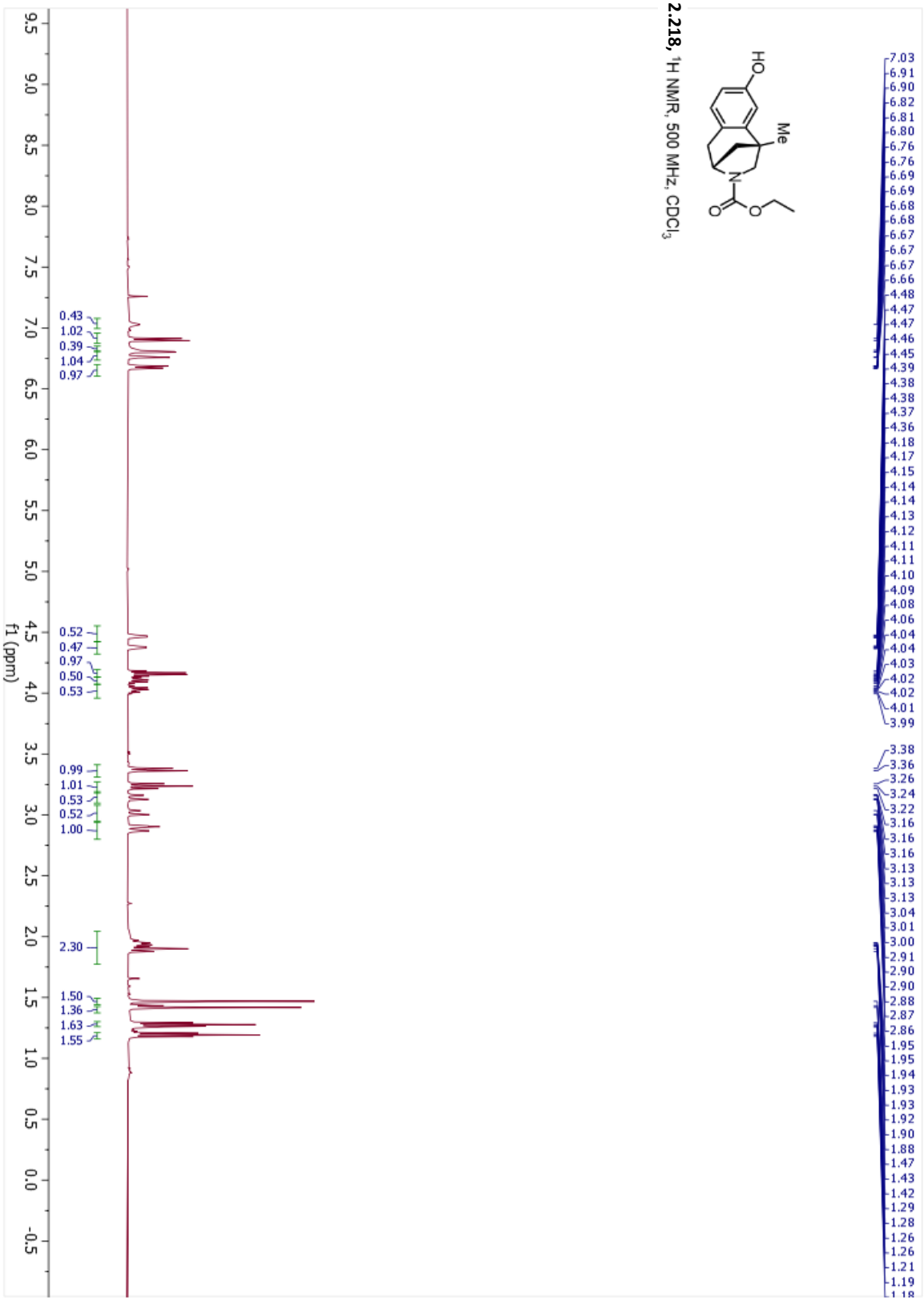

2.281, ^{13}C NMR, 101 MHz, $CDCl_3$
OTBS
Cl
Cl
136.09
133.68
132.39
128.43
128.30
127.98
127.79
127.66
126.76
126.12
125.50
121.37
77.52
77.20
76.88
72.36
44.22
37.34
25.97
18.17
-4.67
-4.81
f1 (ppm)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

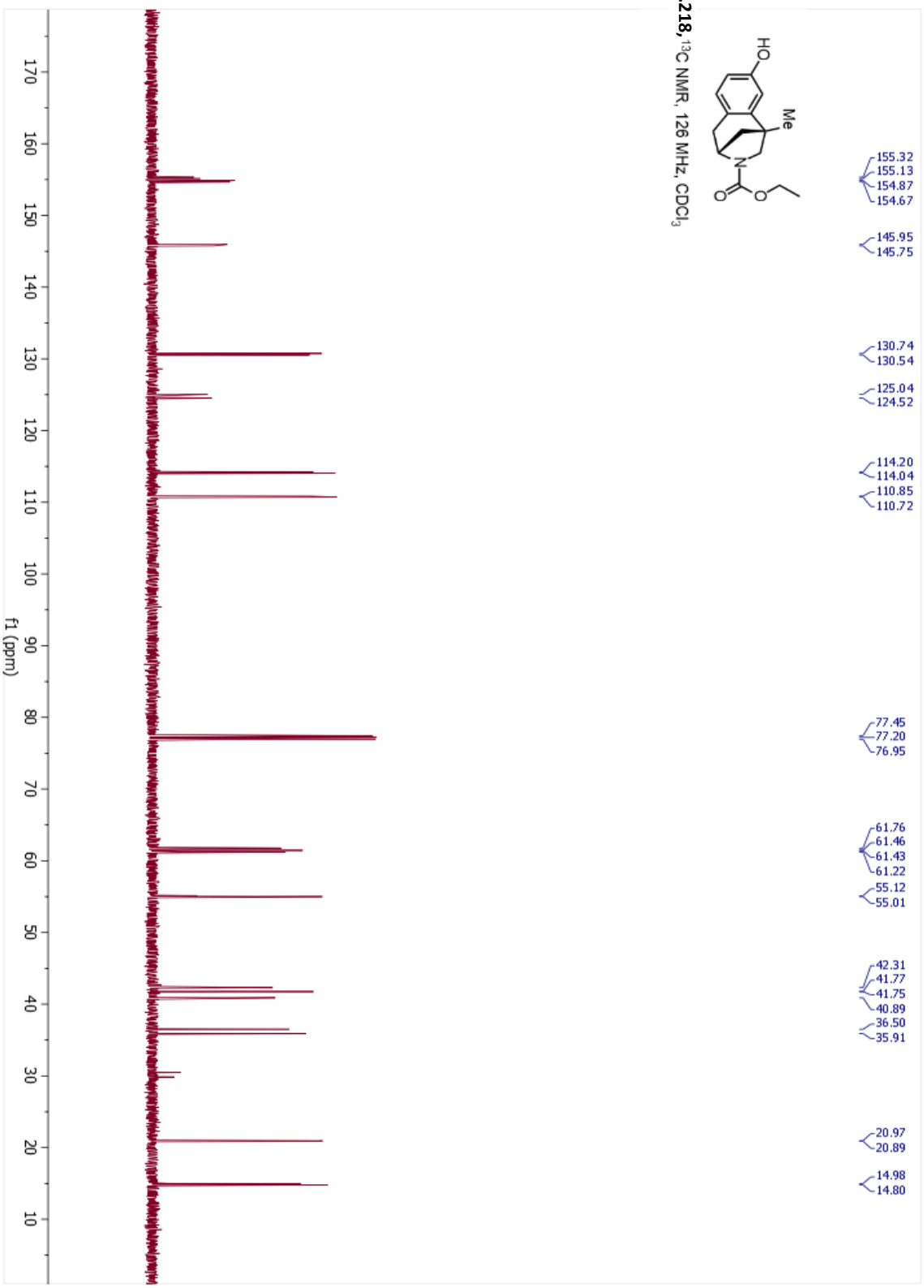

2.135, 1H NMR, 500 MHz, CDCl3
OTBS
OMe
f1 (ppm)
2.96
1.02
1.96
1.01
1.00
2.92
1.02
1.01
2.05
1.03
1.09
9.45
2.97
2.99

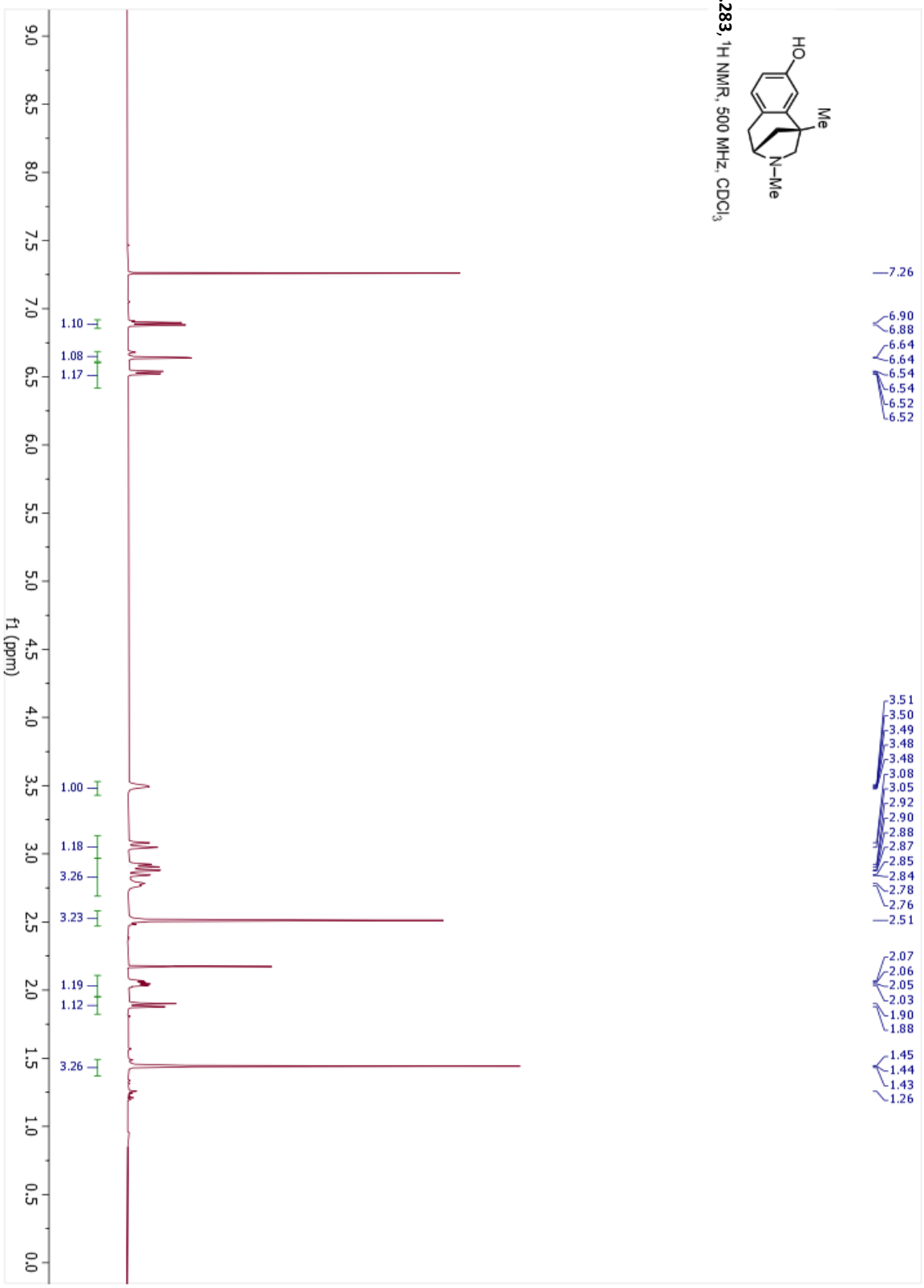

2.135, ^{13}C NMR, 151 MHz, $CDCl_3$
OTBS
OMe
174.36
136.36
133.68
132.34
128.32
128.29
127.94
127.78
127.64
126.07
125.43
72.55
51.69
44.21
31.78
30.00
26.04
18.22
-4.55
-4.60
f1 (ppm)

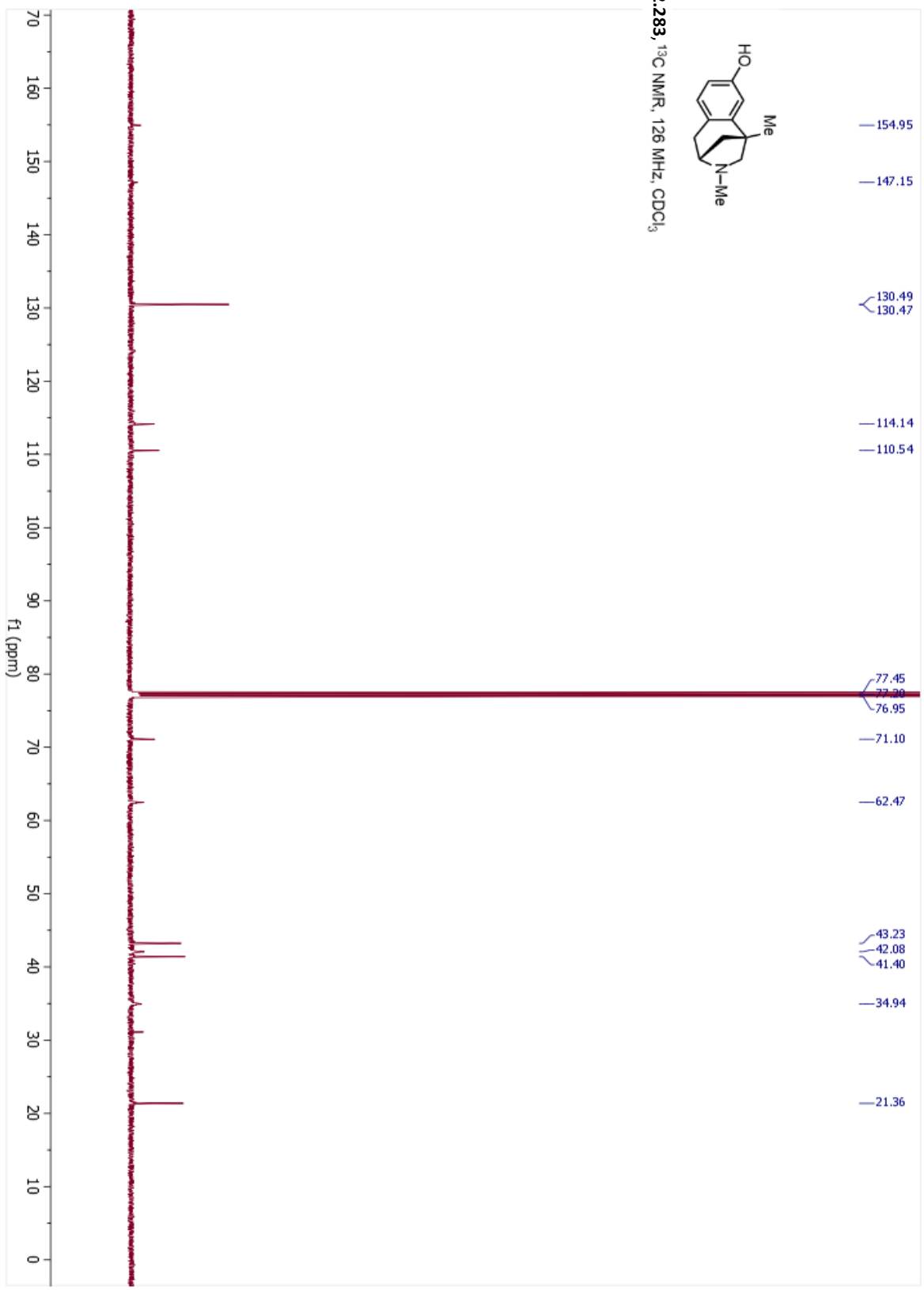

2.217, ^{1}H NMR, 600 MHz, $CDCl_3$
Cl
O
O
N
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.11
2.11
1.99
4.00
0.96
0.54
0.50
2.04
0.95
3.35
7.25
7.24
7.23
7.21
7.11
7.10
7.09
7.08
7.06
7.05
5.01
5.00
4.97
4.95
4.91
4.22
4.21
4.20
4.18
4.16
4.14
4.09
4.05
4.03
4.02
3.87
3.84
3.82
3.05
3.03
2.87
2.85
2.59
2.58
2.56
2.56
2.52
2.51
2.50
2.49
2.26
2.23
1.29
1.28
1.27
1.27
1.26
1.24
1.22
1.22
1.20
1.19

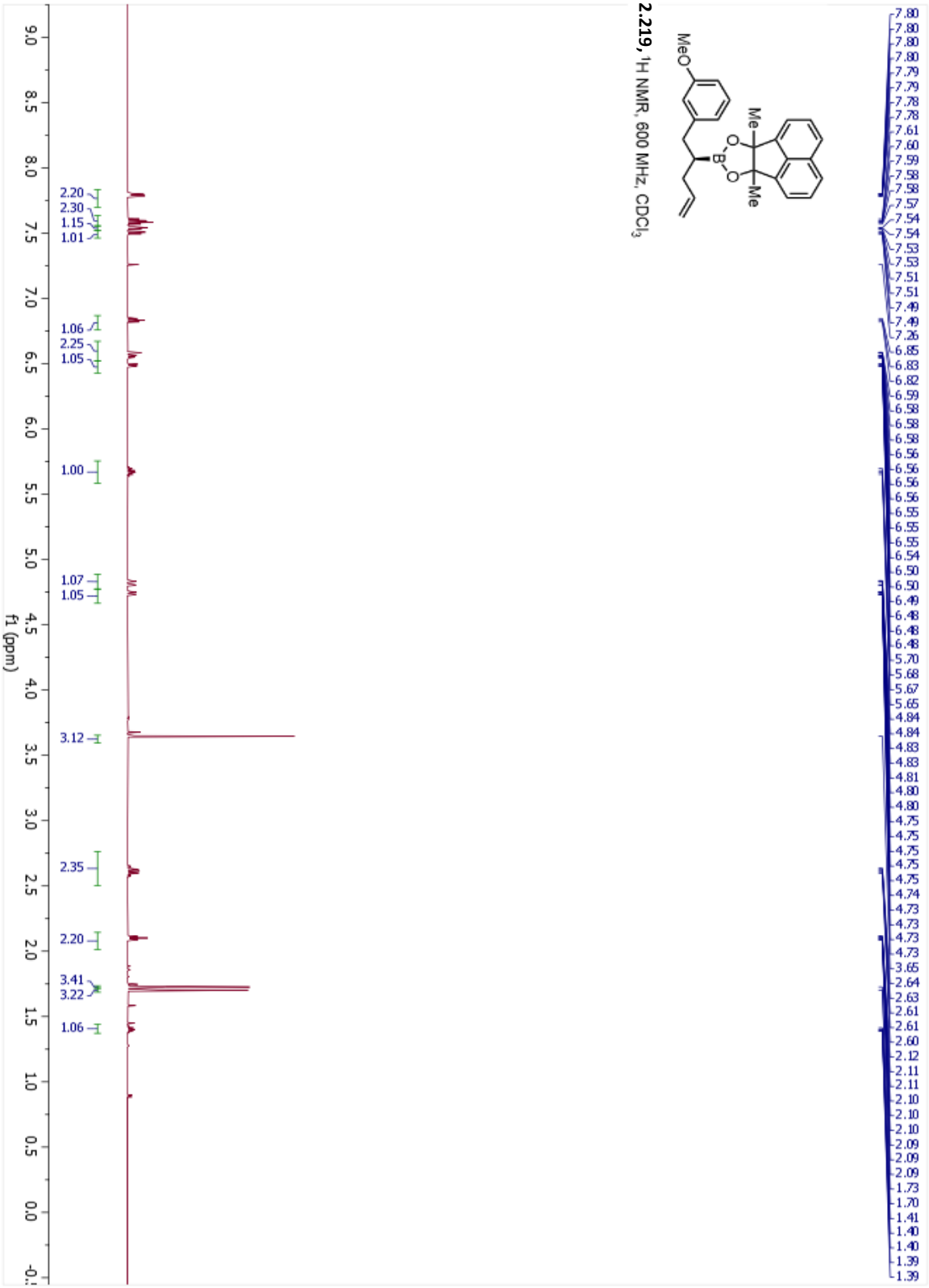

2.217, ^{13}C NMR, 126 MHz, $CDCl_3$
Cl
O
O
N
154.84
137.07
132.33
130.92
128.64
108.30
108.04
77.45
77.20
76.95
61.17
58.72
58.51
50.40
39.91
38.91
37.03
35.92
30.45
29.83
14.89
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


2.218, ^{1}H NMR, 500 MHz, $CDCl_3$
HO
Me
N
O
O
f1 (ppm)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
0.43
1.02
0.39
1.04
0.97
0.52
0.47
0.97
0.50
0.53
0.99
1.01
0.53
0.52
1.00
2.30
1.50
1.36
1.63
1.55
7.03 6.91 6.90 6.82 6.81 6.80 6.76 6.76 6.69 6.69 6.68 6.68 6.67 6.67 6.67 6.66
4.48 4.47 4.47 4.46 4.45 4.39 4.38 4.38 4.37 4.36 4.18 4.17 4.15 4.14 4.14 4.13 4.12 4.11 4.11 4.10 4.09 4.08 4.06 4.04 4.04 4.03 4.02 4.02 4.01 3.99
3.38 3.36 3.26 3.24 3.22 3.16 3.16 3.16 3.13 3.13 3.13 3.04 3.01 3.00 2.91 2.90 2.90 2.88 2.87 2.86 1.95 1.95 1.94 1.93 1.93 1.92 1.90 1.88 1.47 1.43 1.42 1.29 1.28 1.26 1.26 1.21 1.19 1.18

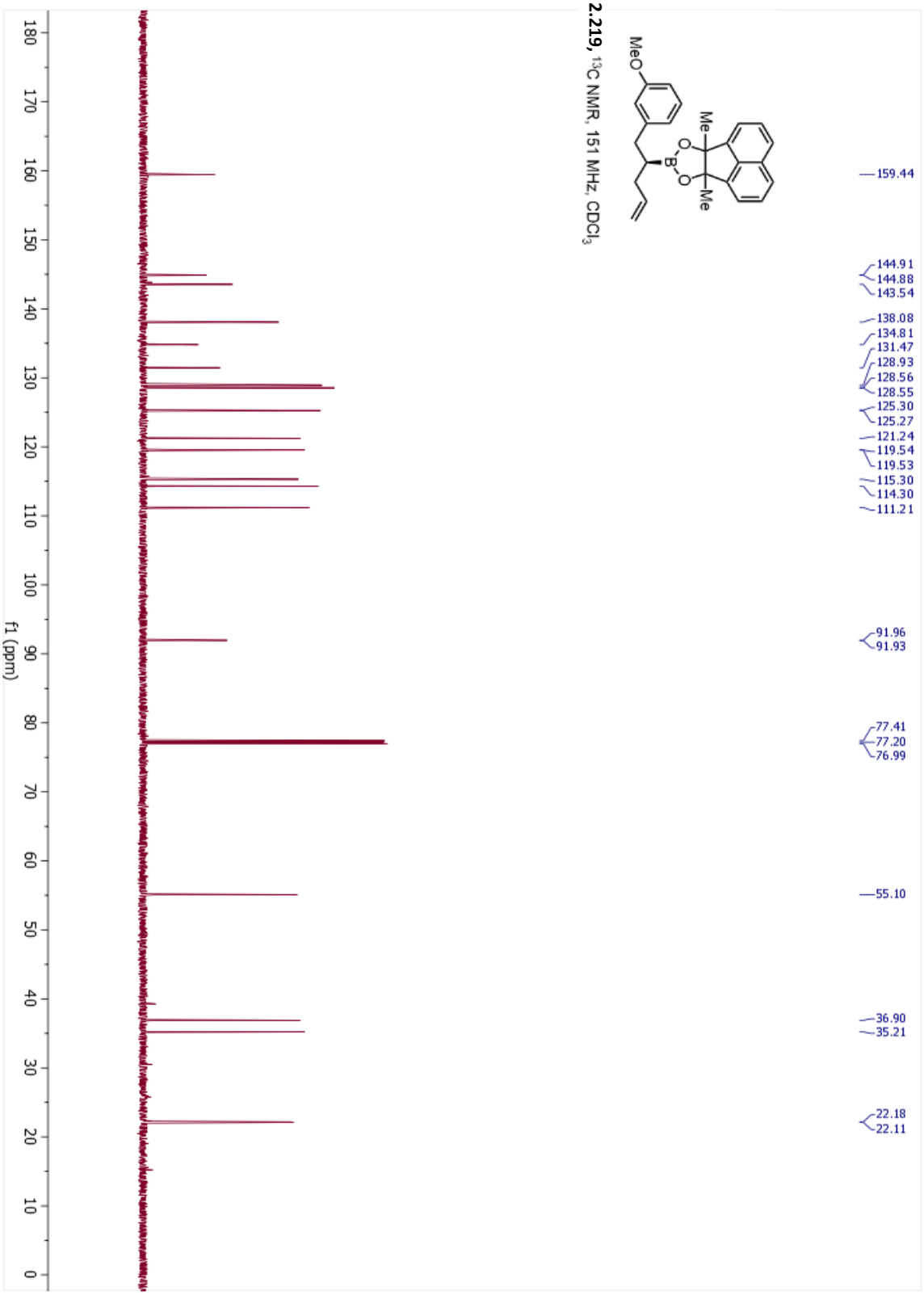

2.218, 13C NMR, 126 MHz, CDCl3
HO
Me
N
O
O
155.32
155.13
154.87
154.67
145.95
145.75
130.74
130.54
125.04
124.52
114.20
114.04
110.85
110.72
77.45
77.20
76.95
61.76
61.46
61.43
61.22
55.12
55.01
42.31
41.77
41.75
40.89
36.50
35.91
20.97
20.89
14.98
14.80
f1 (ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

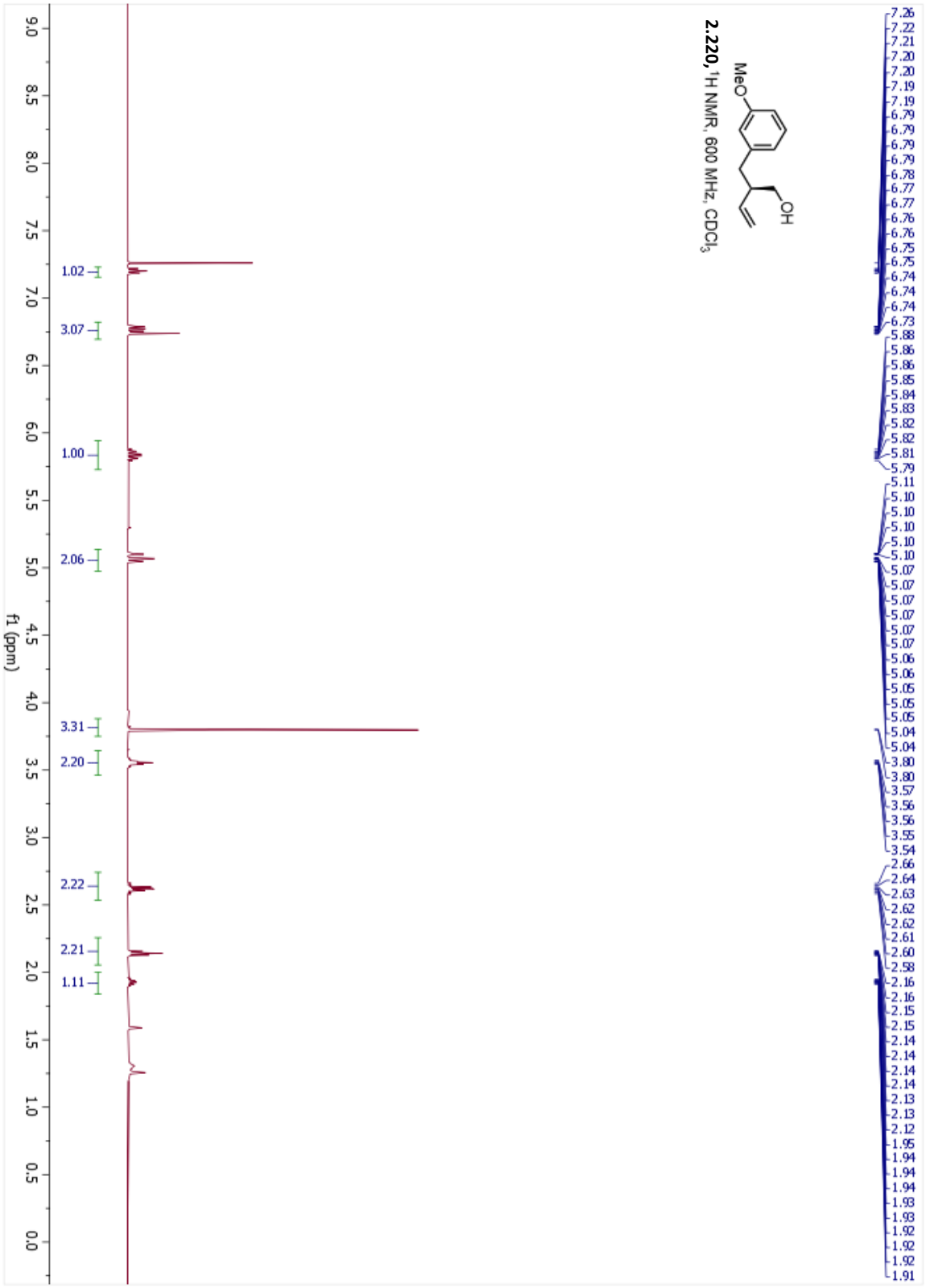

2.283, ^{1}H NMR, 500 MHz, CDCl$_3$
HO
Me
N–Me
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.10
1.08
1.17
1.00
1.18
3.26
3.23
1.19
1.12
3.26
7.26
6.90
6.88
6.64
6.64
6.54
6.54
6.52
6.52
3.51
3.50
3.49
3.48
3.48
3.08
3.05
2.92
2.90
2.88
2.87
2.85
2.84
2.78
2.76
2.51
2.07
2.06
2.05
2.03
1.90
1.88
1.45
1.44
1.43
1.26

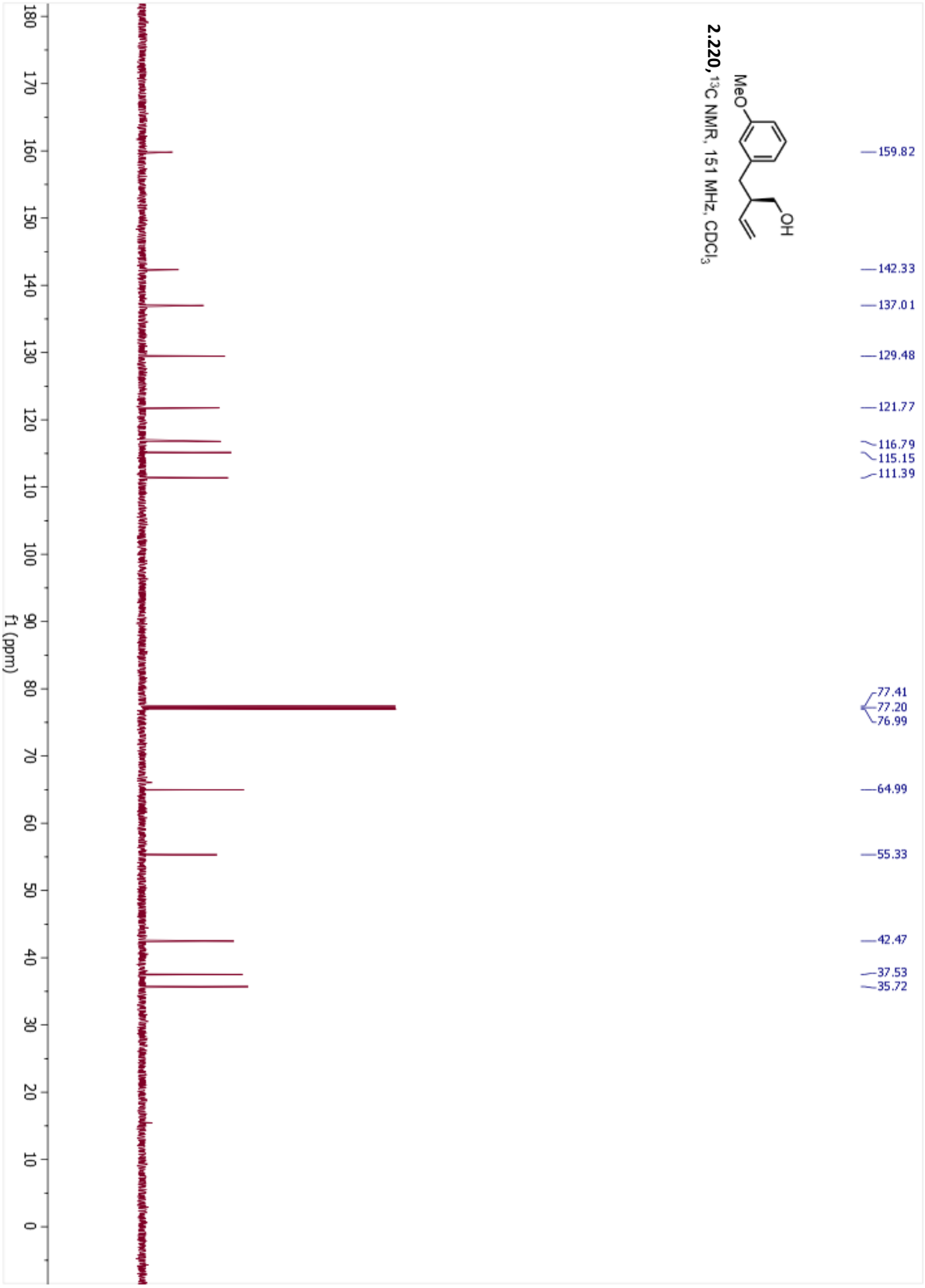

2.283, ^{13}C NMR, 126 MHz, $CDCl_3$
HO
Me
N–Me
154.95
147.15
130.49
130.47
114.14
110.54
77.45
77.20
76.95
71.10
62.47
43.23
42.08
41.40
34.94
21.36
f1 (ppm)
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

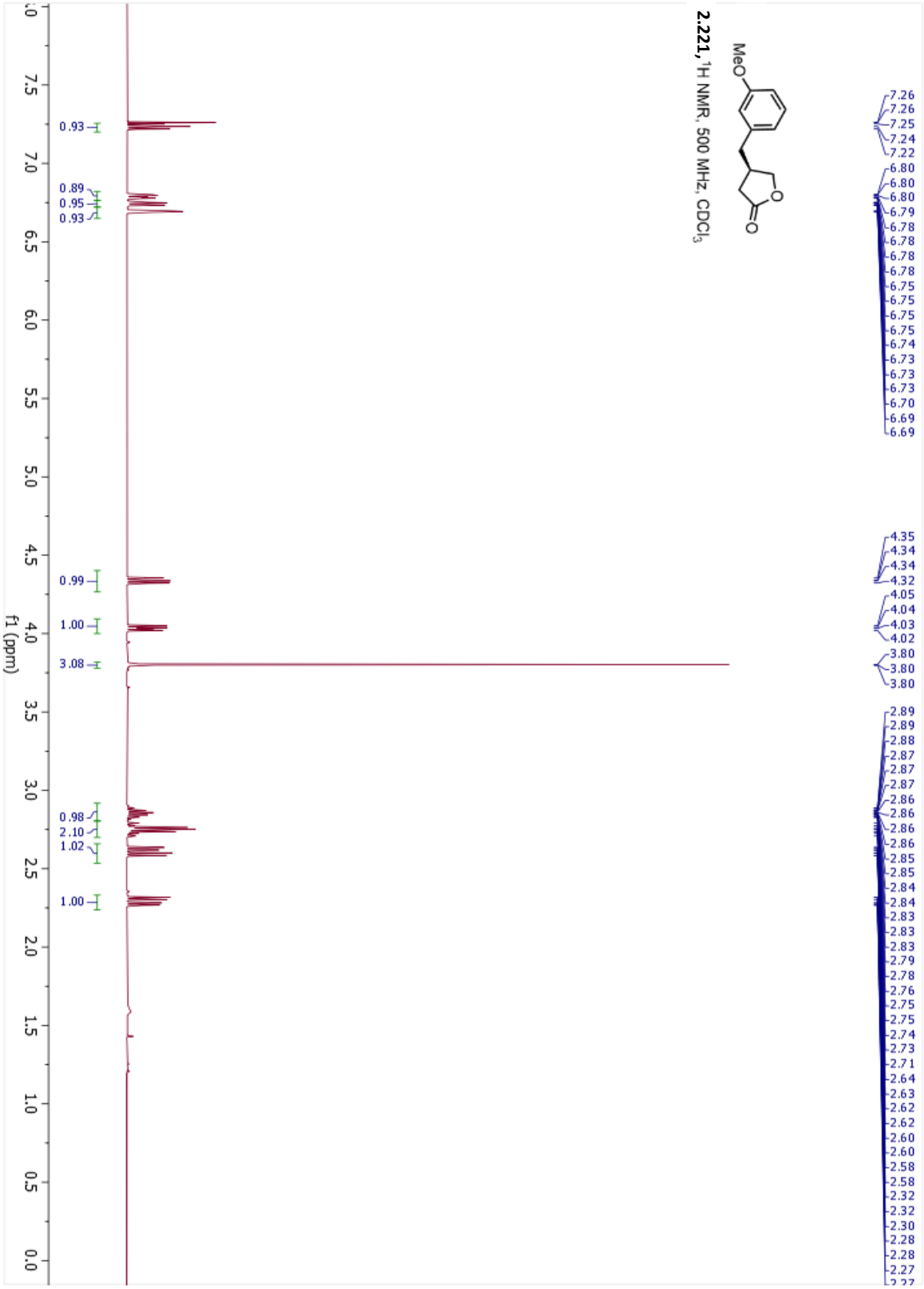

MeO
Me
Me
2.219, ^{1}H NMR, 600 MHz, $CDCl_3$
f1 (ppm)
2.20
2.30
1.15
1.01
1.06
2.25
1.05
1.00
1.07
1.05
3.12
2.35
2.20
3.41
3.22
1.06

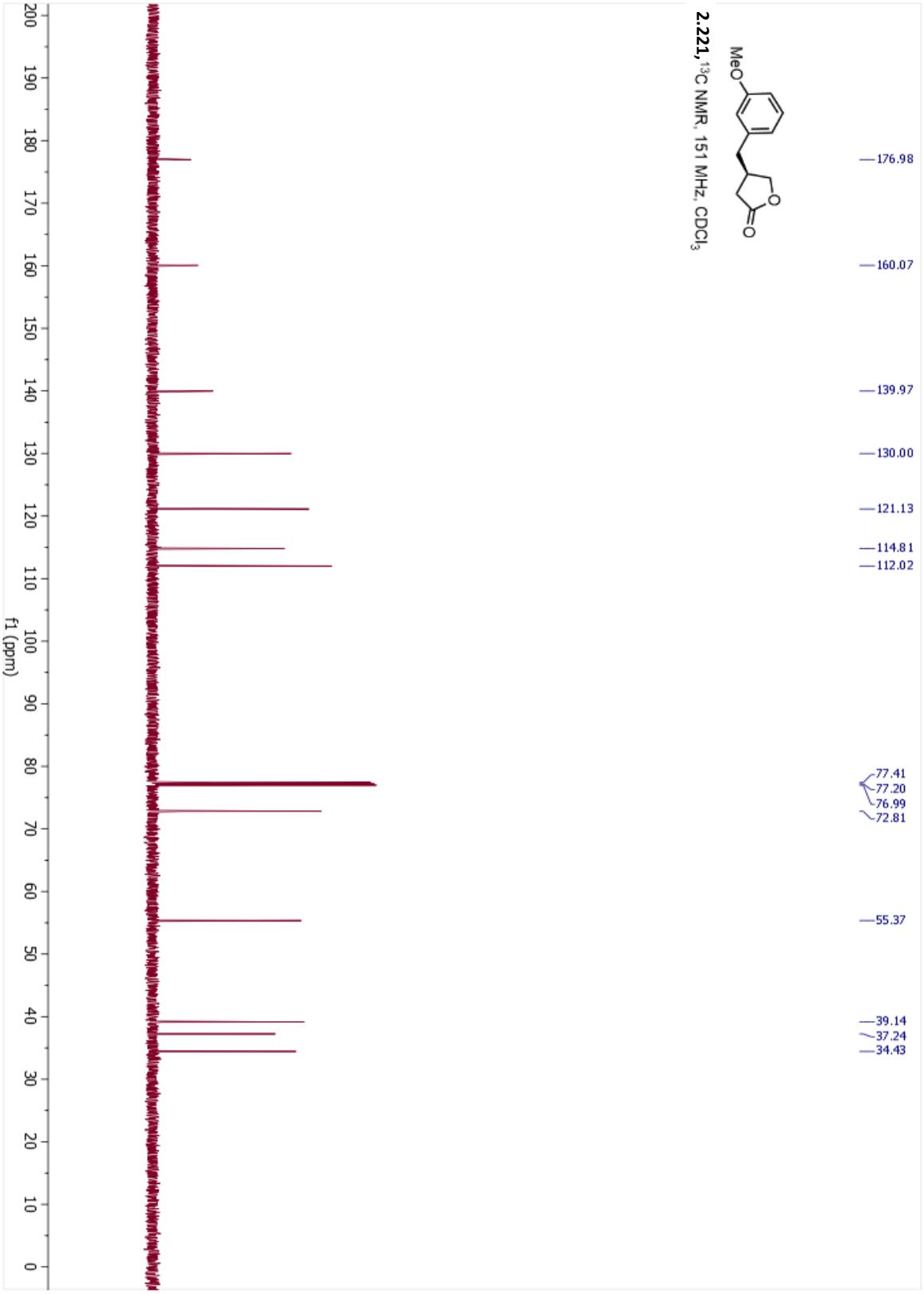
2.219, ^{13}C NMR, 151 MHz, $CDCl_3$

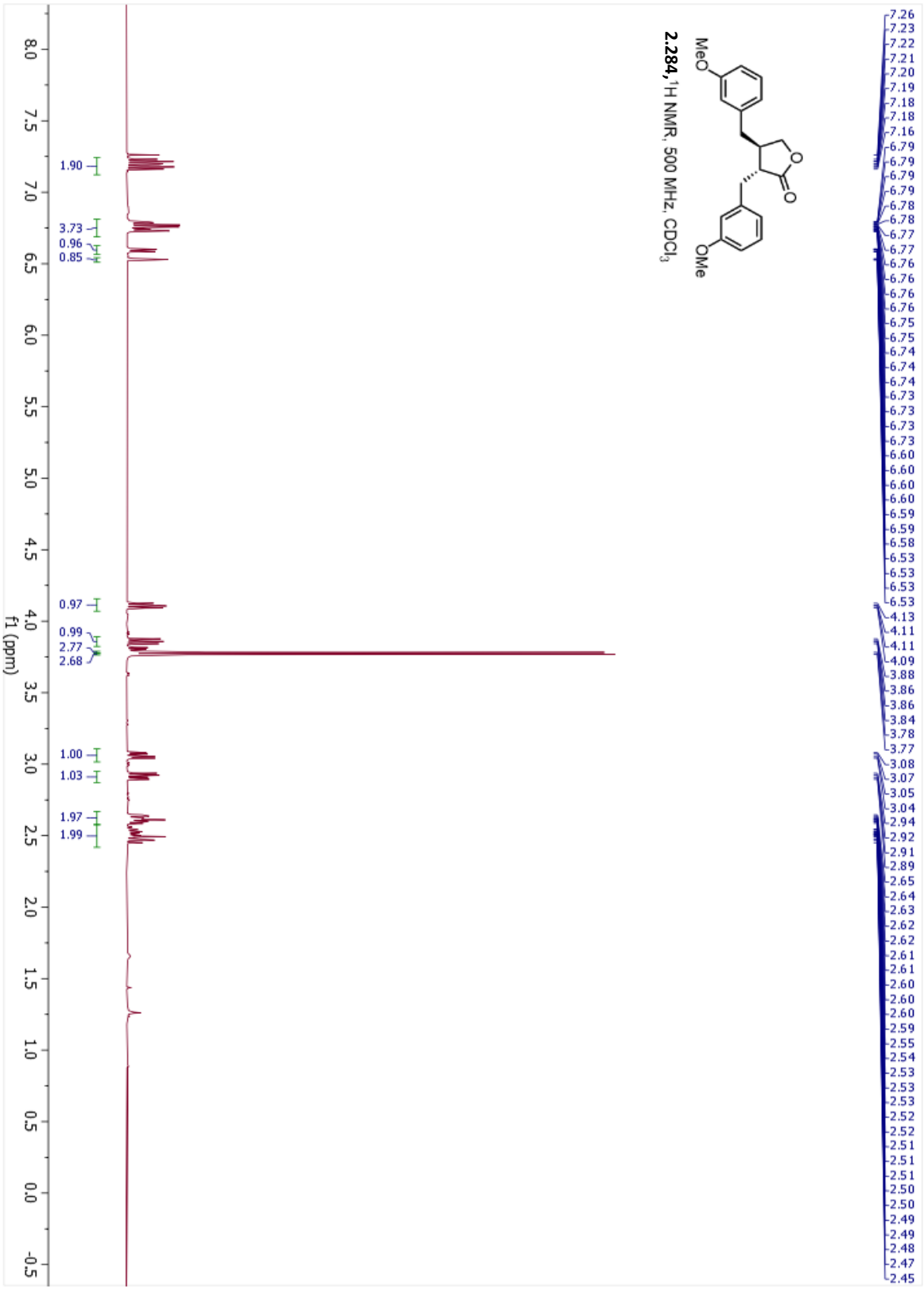


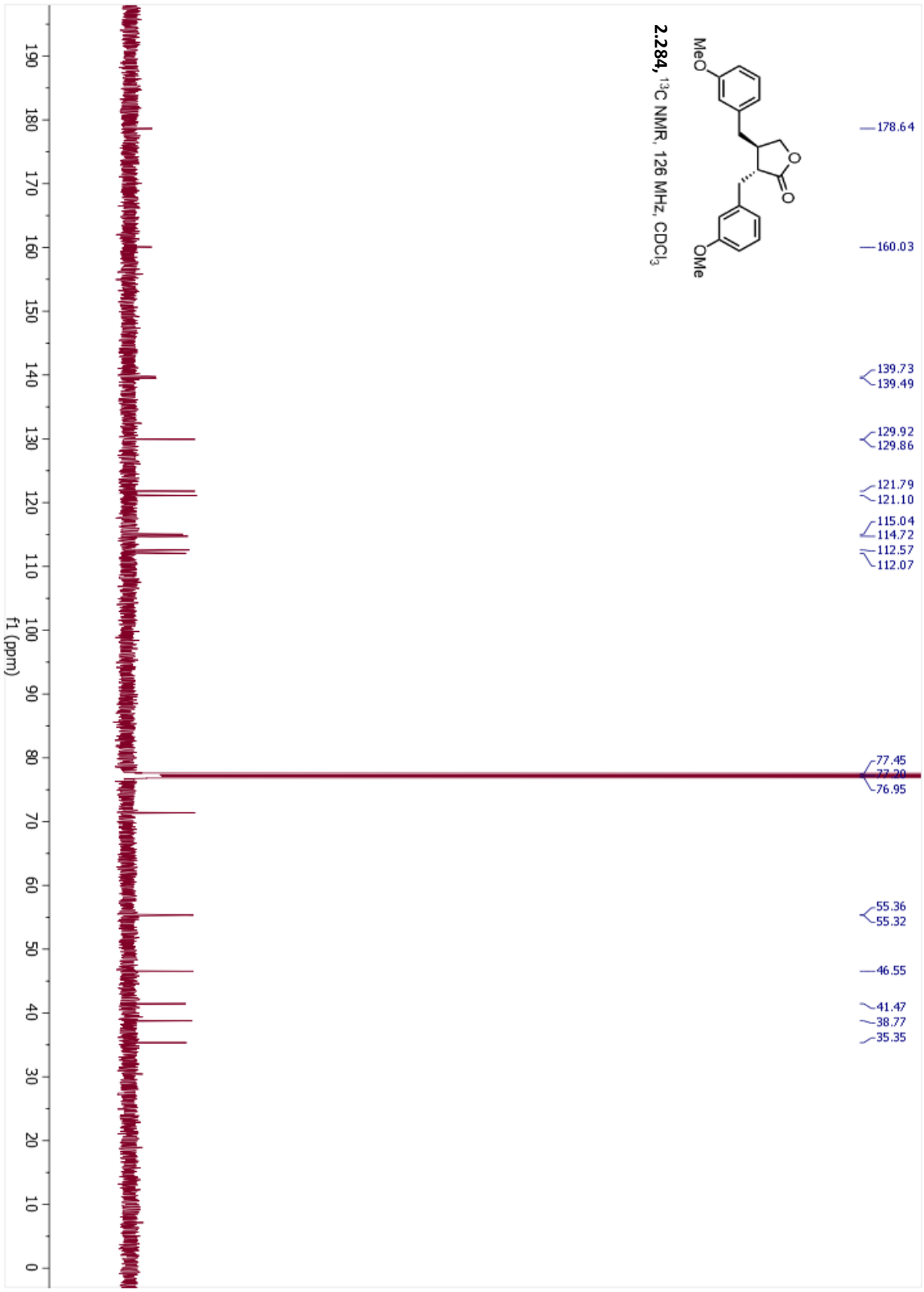

2.220, ^{1}H NMR, 600 MHz, $CDCl_3$
MeO
OH
f1 (ppm)
1.02
3.07
1.00
2.06
3.31
2.20
2.22
2.21
1.11

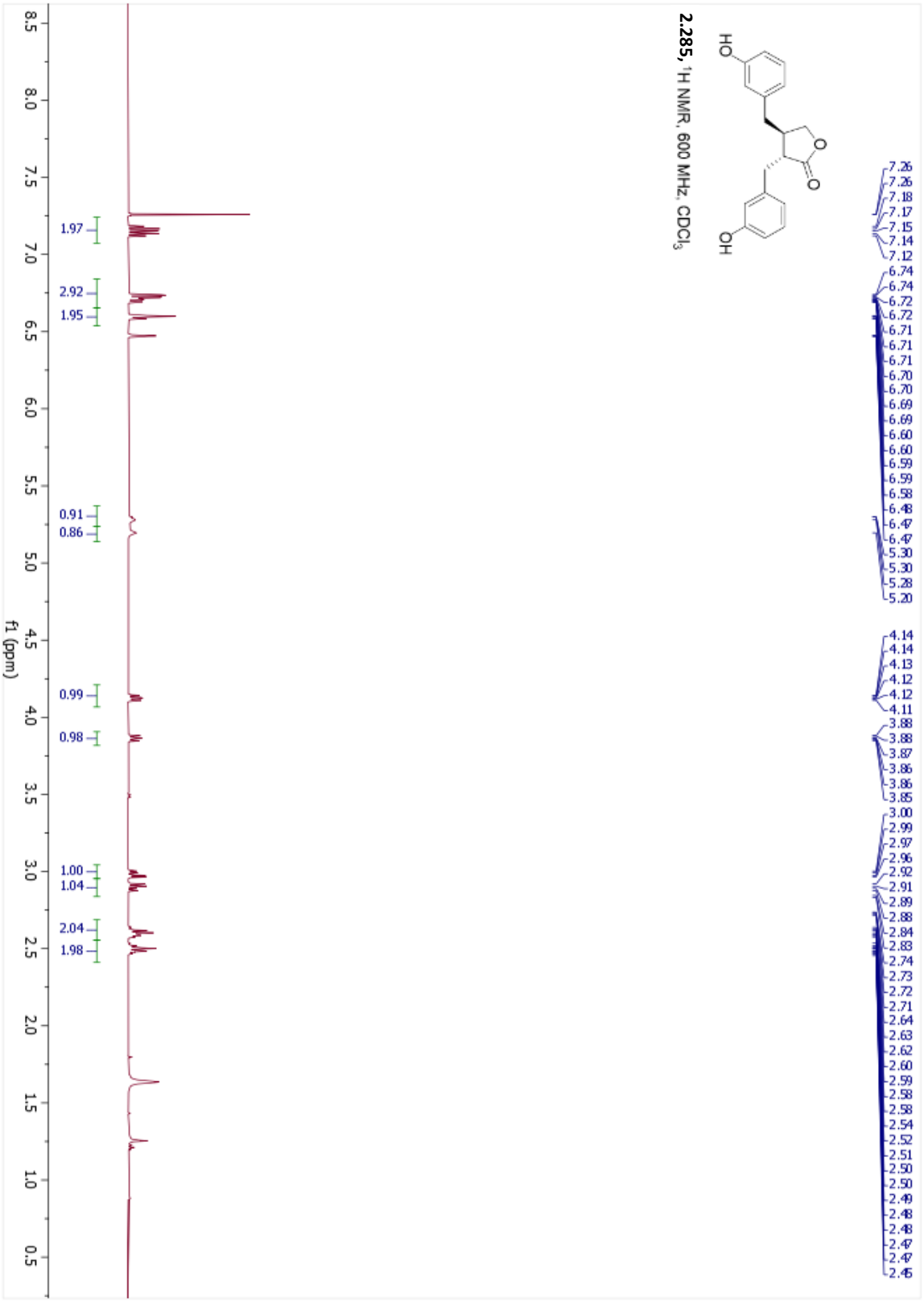

2.220, ^{13}C NMR, 151 MHz, $CDCl_3$
MeO
OH
159.82
142.33
137.01
129.48
121.77
116.79
115.15
111.39
77.41
77.20
76.99
64.99
55.33
42.47
37.53
35.72
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


2.221, ^{1}H NMR, 500 MHz, $CDCl_3$
MeO
O
O
f1 (ppm)
0.93
0.89
0.95
0.93
0.99
1.00
3.08
0.98
2.10
1.02
1.00
7.26
7.26
7.25
7.24
7.22
6.80
6.80
6.80
6.79
6.78
6.78
6.78
6.78
6.75
6.75
6.75
6.75
6.74
6.73
6.73
6.73
6.70
6.69
6.69
4.35
4.34
4.34
4.32
4.05
4.04
4.03
4.02
3.80
3.80
3.80
2.89
2.89
2.88
2.87
2.87
2.87
2.86
2.86
2.86
2.86
2.85
2.85
2.84
2.84
2.83
2.83
2.83
2.79
2.78
2.76
2.75
2.75
2.74
2.73
2.71
2.64
2.63
2.62
2.62
2.60
2.60
2.58
2.58
2.32
2.32
2.30
2.28
2.28
2.27


2.221, ^{13}C NMR, 151 MHz, $CDCl_3$
MeO
O
O
176.98
160.07
139.97
130.00
121.13
114.81
112.02
77.41
77.20
76.99
72.81
55.37
39.14
37.24
34.43
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


2.284, 1H NMR, 500 MHz, CDCl3
MeO
OMe
O
O
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
0.5
0.0
-0.5
1.90
3.73
0.96
0.85
0.97
0.99
2.77
2.68
1.00
1.03
1.97
1.99
7.26
7.23
7.22
7.21
7.20
7.19
7.18
7.18
7.16
6.79
6.79
6.79
6.79
6.78
6.78
6.77
6.77
6.76
6.76
6.76
6.76
6.75
6.75
6.74
6.74
6.74
6.73
6.73
6.73
6.73
6.60
6.60
6.60
6.60
6.59
6.59
6.58
6.53
6.53
6.53
6.53
4.13
4.11
4.11
4.09
3.88
3.86
3.86
3.84
3.78
3.77
3.08
3.07
3.05
3.04
2.94
2.92
2.91
2.89
2.65
2.64
2.63
2.62
2.62
2.61
2.61
2.60
2.60
2.60
2.59
2.55
2.54
2.53
2.53
2.53
2.52
2.52
2.51
2.51
2.51
2.50
2.50
2.49
2.49
2.48
2.47
2.45


2.284, ^{13}C NMR, 126 MHz, $CDCl_3$
MeO
OMe
O
O
178.64
160.03
139.73
139.49
129.92
129.86
121.79
121.10
115.04
114.72
112.57
112.07
77.45
77.20
76.95
55.36
55.32
46.55
41.47
38.77
35.35
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


2.285, ^{1}H NMR, 600 MHz, $CDCl_3$
HO
O
O
OH
f1 (ppm)
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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
1.97
2.92
1.95
0.91
0.86
0.99
0.98
1.00
1.04
2.04
1.98
7.26
7.26
7.18
7.17
7.15
7.14
7.12
6.74
6.74
6.72
6.72
6.71
6.71
6.71
6.70
6.70
6.69
6.69
6.60
6.60
6.59
6.59
6.58
6.48
6.47
6.47
5.30
5.30
5.28
5.20
4.14
4.14
4.13
4.12
4.12
4.11
3.88
3.88
3.87
3.86
3.86
3.85
3.00
2.99
2.97
2.96
2.92
2.91
2.89
2.88
2.84
2.83
2.74
2.73
2.72
2.71
2.64
2.63
2.62
2.60
2.59
2.58
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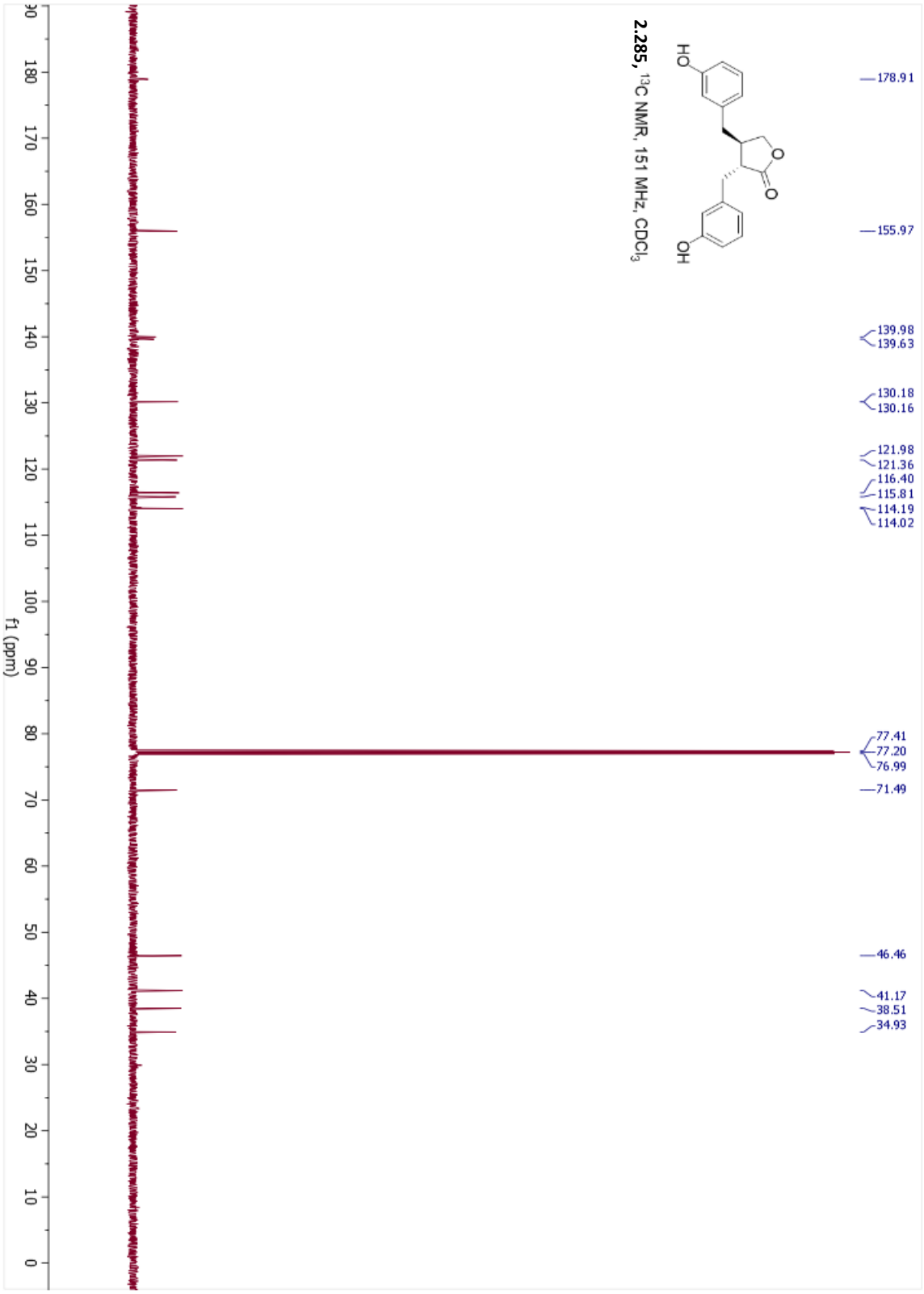
2.49
2.48
2.48
2.47
2.47
2.45


2.285, ^{13}C NMR, 151 MHz, CDCl$_3$
HO
O
O
OH
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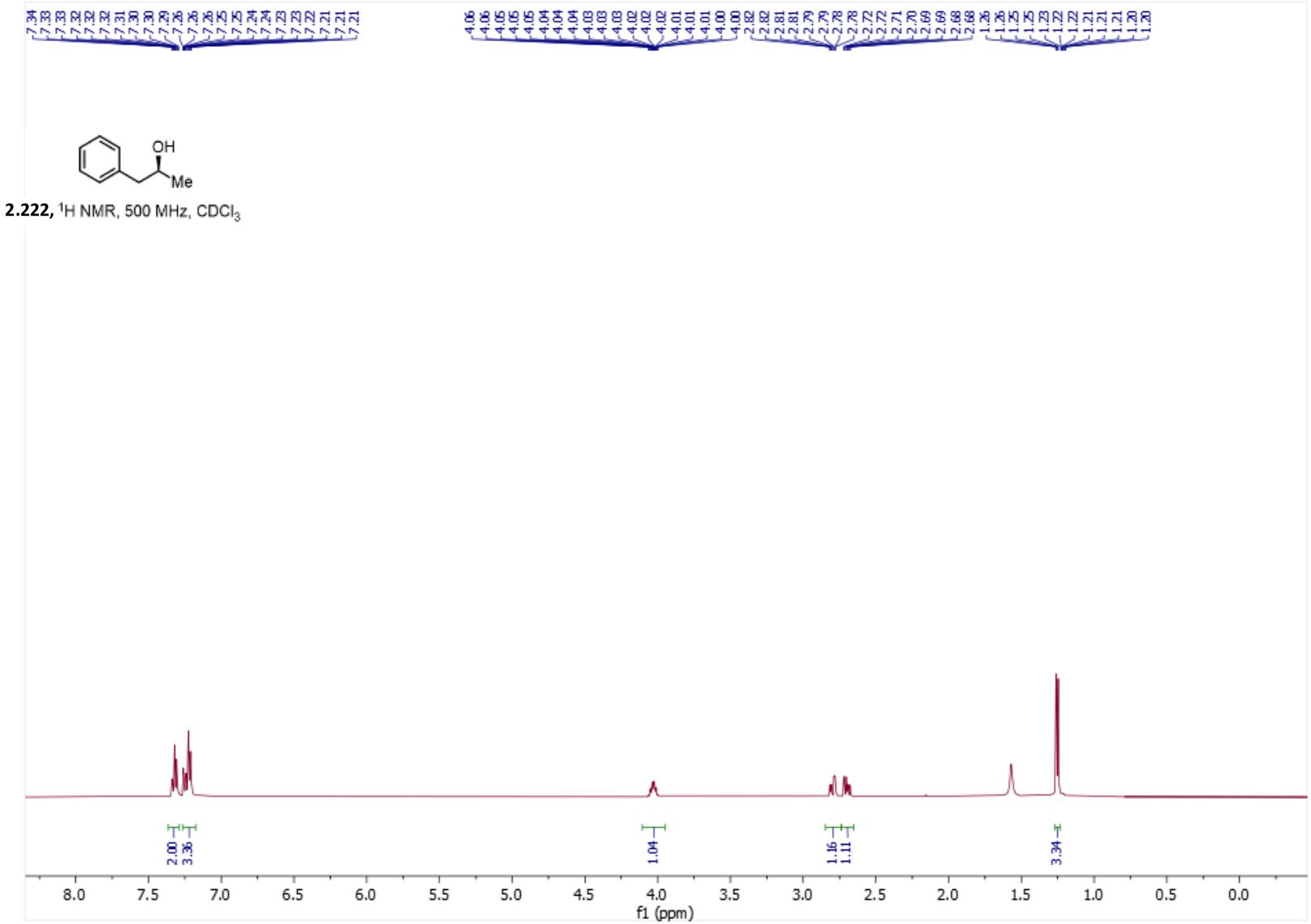
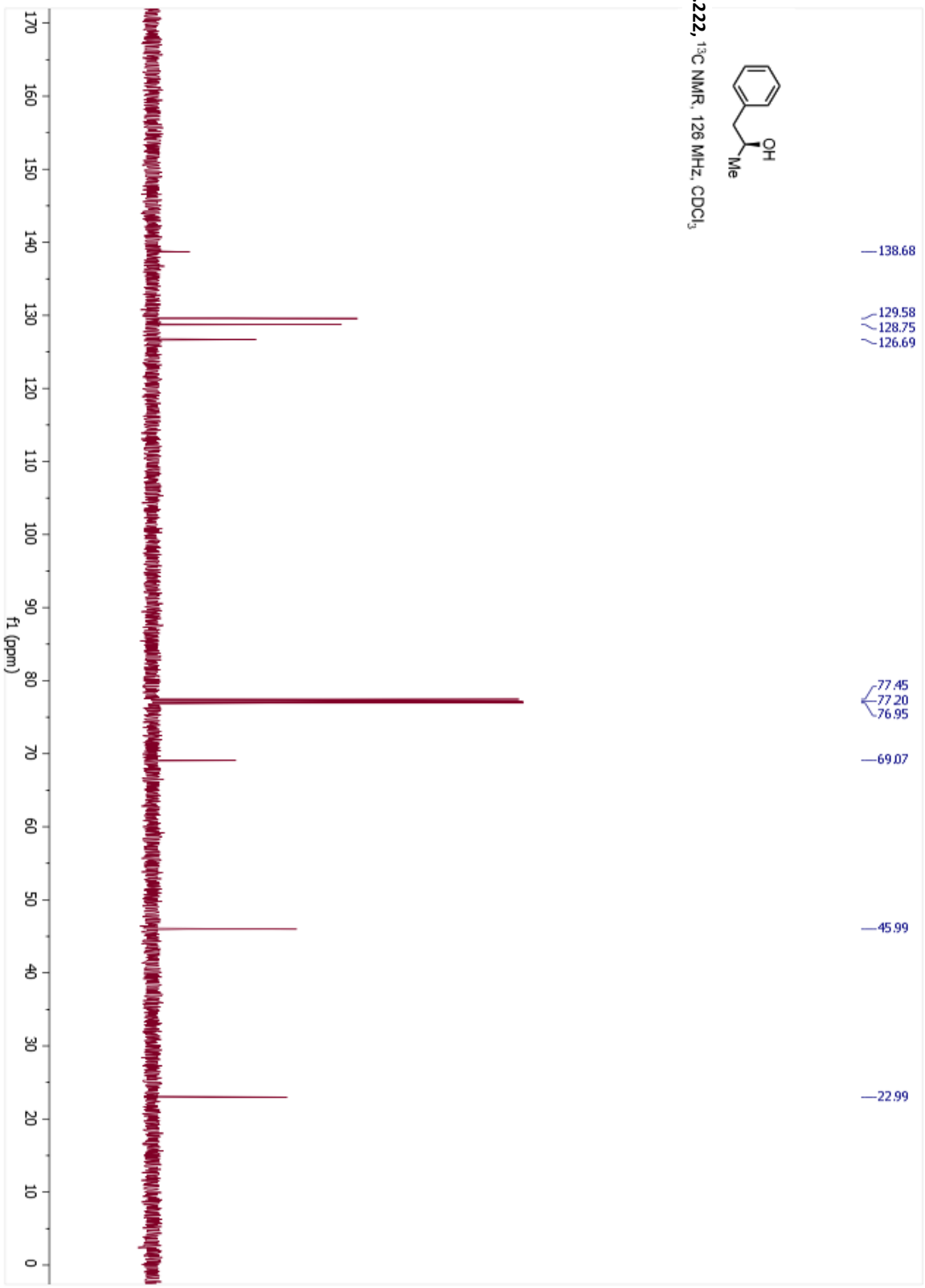
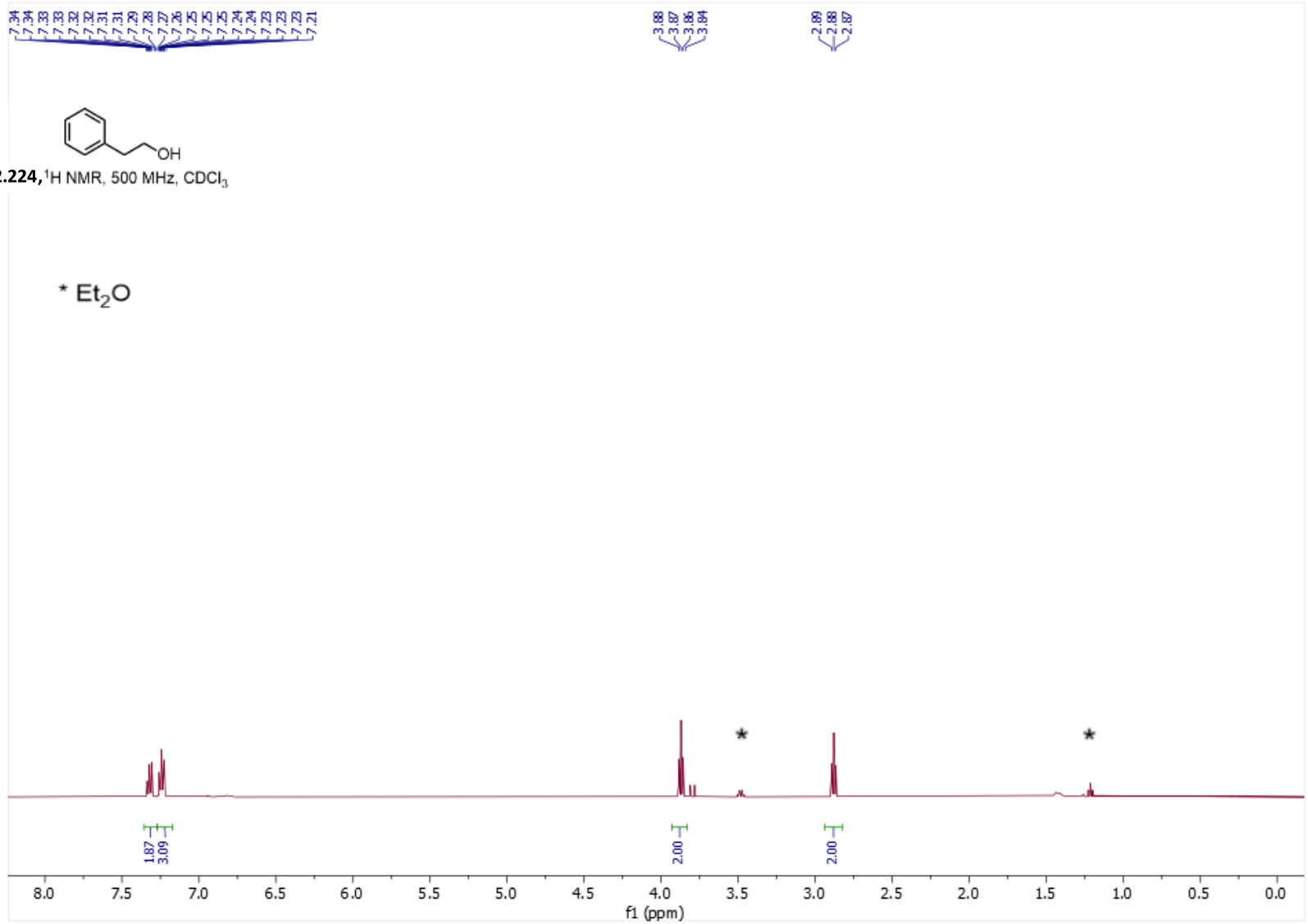
155.97
139.98
139.63
130.18
130.16
121.98
121.36
116.40
115.81
114.19
114.02
77.41
77.20
76.99
71.49
46.46
41.17
38.51
34.93
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

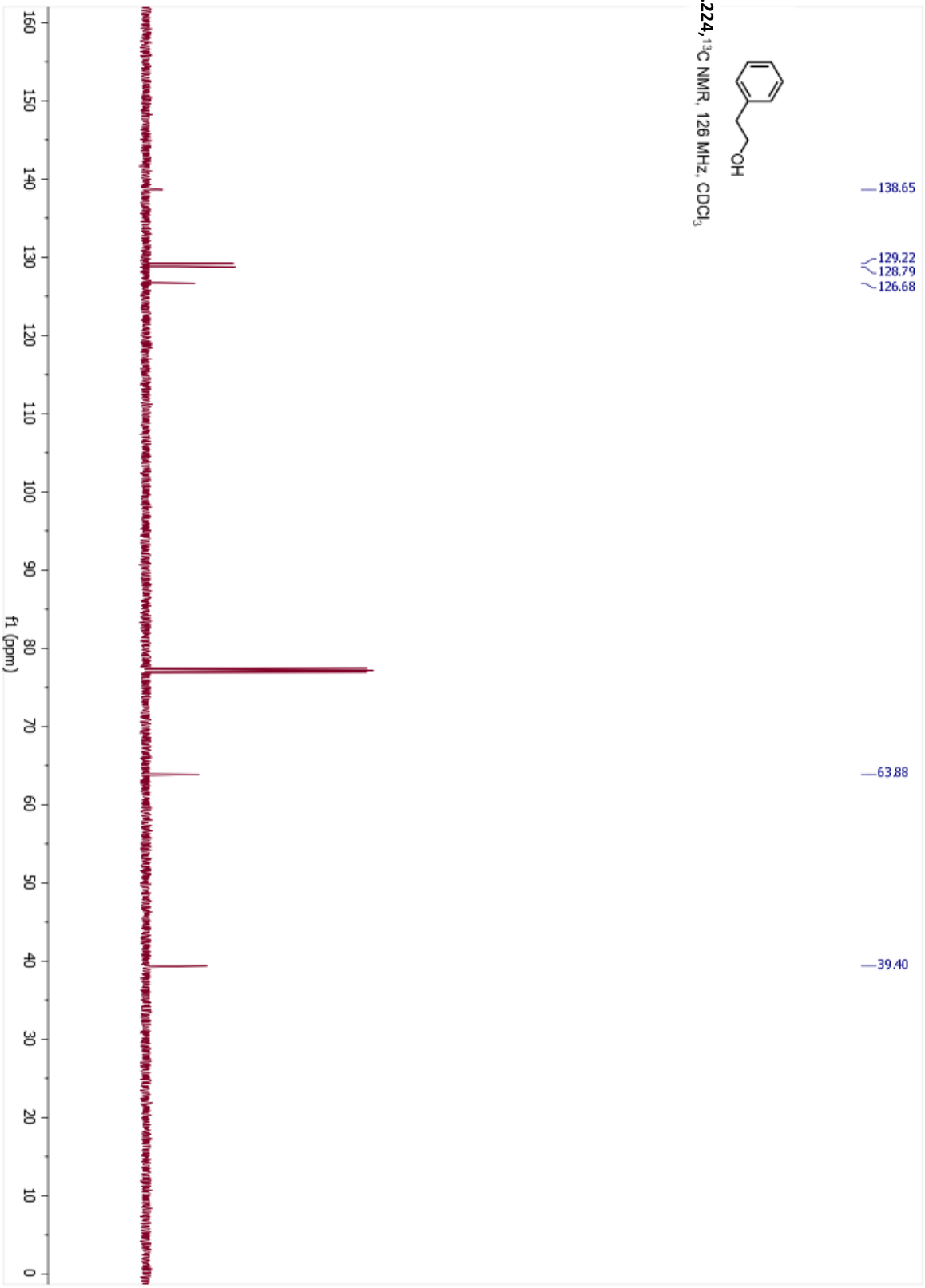


2.222, ^{1}H NMR, 500 MHz, $CDCl_3$


2.222, ^{13}C NMR, 126 MHz, $CDCl_3$
OH
Me
138.68
129.58
128.75
126.69
77.45
77.20
76.95
69.07
45.99
22.99
f1 (ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



2.224, ^{1}H NMR, 500 MHz, $CDCl_3$


2.224, ^{13}C NMR, 126 MHz, $CDCl_3$
OH
138.65
129.22
128.79
126.68
63.88
39.40
f1 (ppm)
160
150
140
130
120
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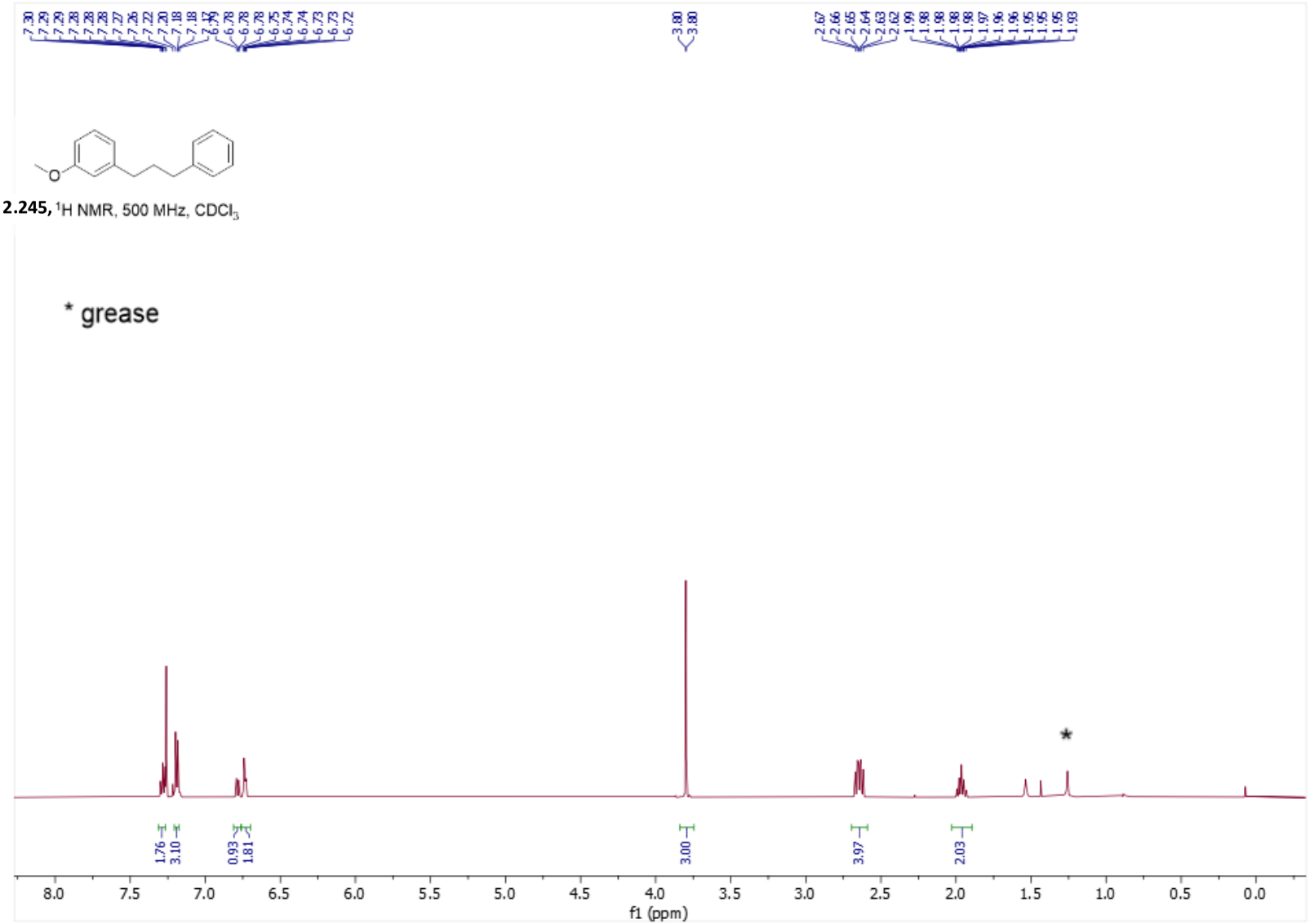
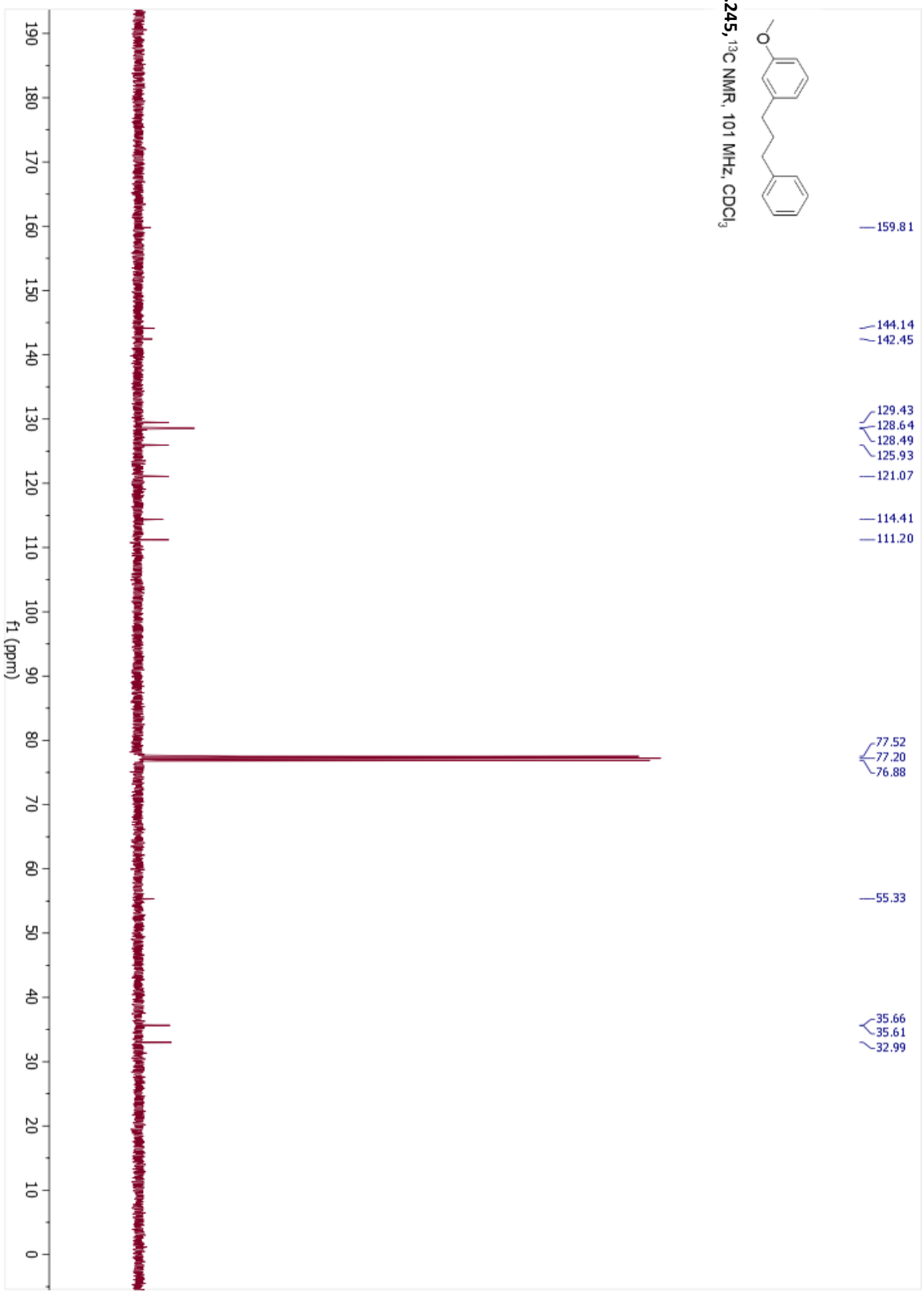
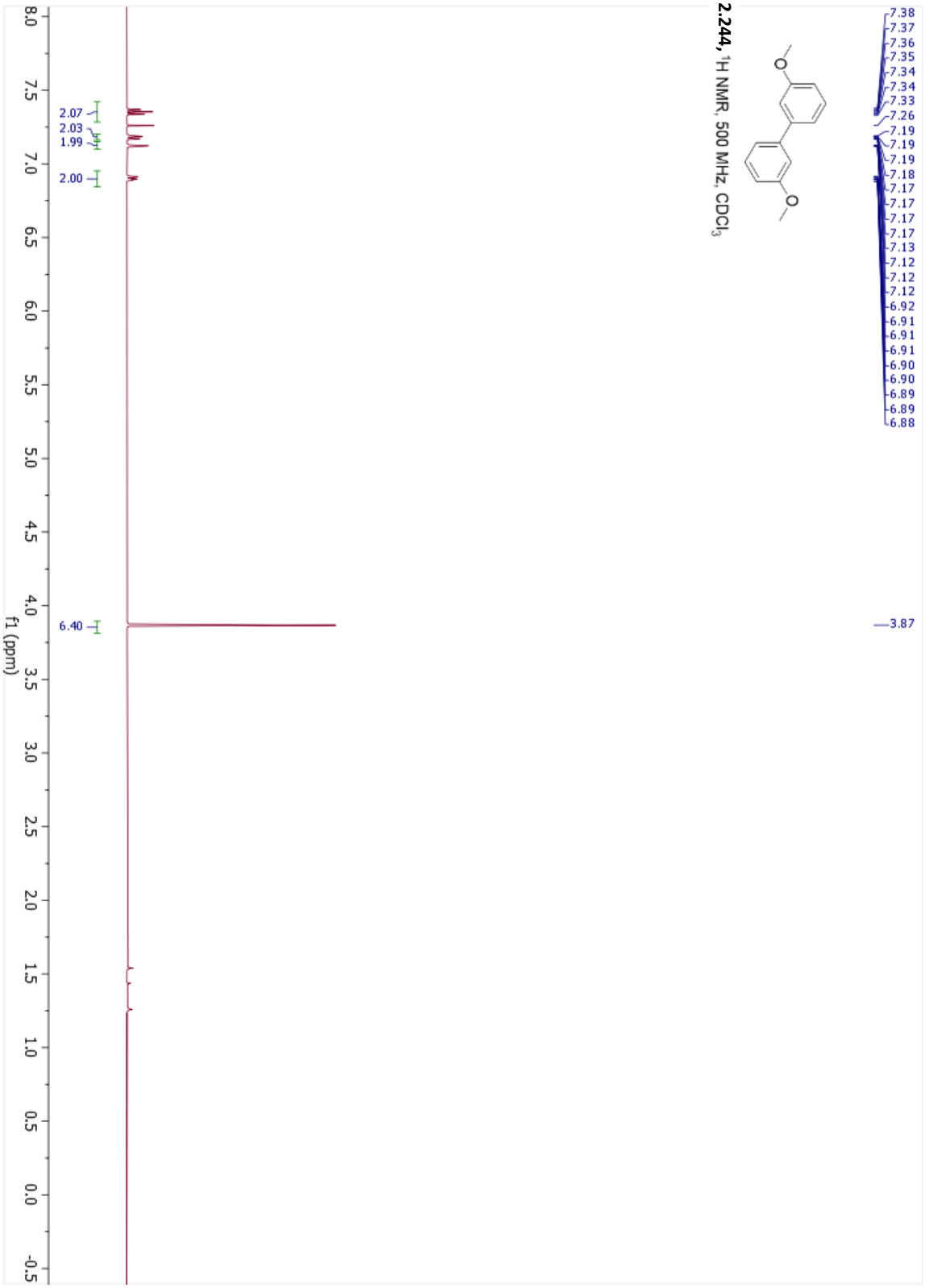
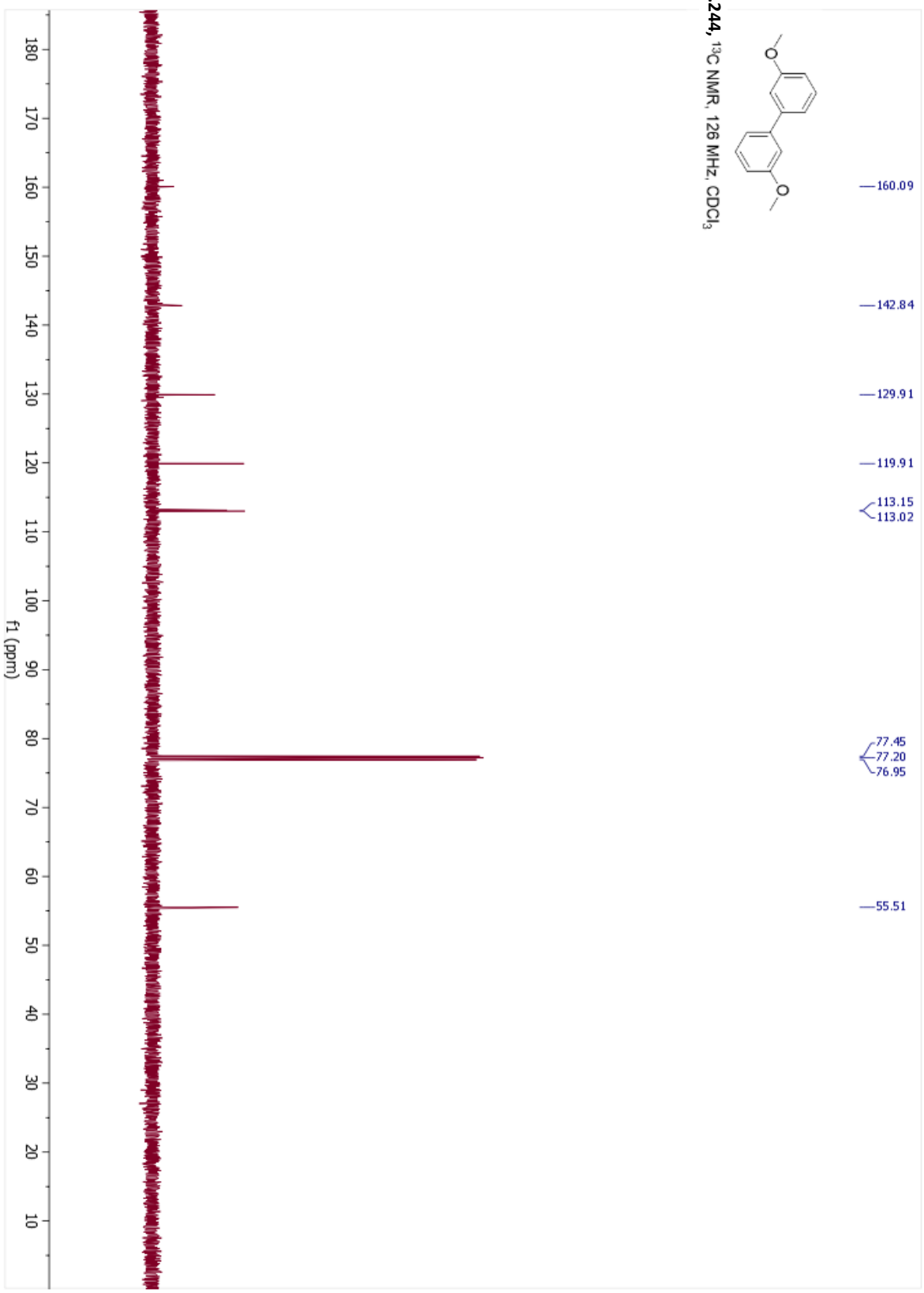
90
80
70
60
50
40
30
20
10
0



2.245, ^{1}H NMR, 500 MHz, $CDCl_3$


2.245, ^{13}C NMR, 101 MHz, CDCl$_3$
159.81
144.14
142.45
129.43
128.64
128.49
125.93
121.07
114.41
111.20
77.52
77.20
76.88
55.33
35.66
35.61
32.99
f1 (ppm)


2.244, ^{1}H NMR, 500 MHz, $CDCl_3$
7.38
7.37
7.36
7.35
7.34
7.34
7.33
7.26
7.19
7.19
7.19
7.18
7.17
7.17
7.17
7.17
7.13
7.12
7.12
7.12
6.92
6.91
6.91
6.91
6.90
6.90
6.89
6.89
6.88
3.87
2.07
2.03
1.99
2.00
6.40
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
0.5
0.0
-0.5


2.244, ^{13}C NMR, 126 MHz, $CDCl_3$
160.09
142.84
129.91
119.91
113.15
113.02
77.45
77.20
76.95
55.51
f1 (ppm)

Chapter Three

Progress Towards the Total Synthesis of the Sarcodictyins and Related Natural Products

3.1 Introduction

The success of paclitaxel (Taxol) as an anticancer agent has drawn a great deal of interest among medicinal chemists and synthetic chemists.[1] Despite the substantial antitumor activity that makes it effective in the treatment of ovarian cancer, breast cancer, and lung cancer, Taxol has toxic side effects and suffers from phenotypic resistance.[2] A more general antitumor reagent with similar cytotoxicity and biological mechanisms would be valuable. The marine-derived sarcodictyin family of natural products has been identified as a novel candidate to address some of Taxol's limitations.[2] Since the first isolation of sarcodictyin in 1987, the limited supply of those compounds from nature has inspired numerous efforts towards its total synthesis.[1] However, only two synthetic approaches have resulted in the total synthesis of these materials. The Danishefsky

(1) Cao, Y.-N.; Zheng, L.-L.; Wang, D.; Liang, X.-X.; Gao, F.; Zhou, X.-L. *Eur. J. Med. Chem.* **2018**, *143*, 806–828.

(2) Nicolaou, K. C.; Pfefferkorn, J.; Xu, J.; Winssinger, N.; Ohshima, T.; Kim, S.; Hosokawa, S.; Vourloumis, D.; Van Delft, F.; Li, T. *Chem. Pharm. Bull.* **1999**, *47*, 1199–1213.

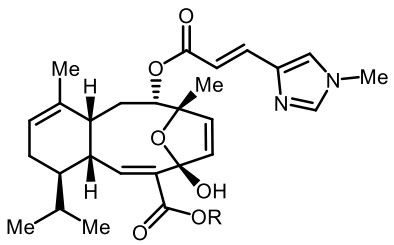
group[3] achieved the total synthesis of eleutherobin, and the Nicolaou group[2] synthesized a diverse library of sarcodicyins for biological studies.

From a synthetic point of view, the structure of sarcodictyins feature a rigid bicyclic [8,4,0]tetradecatriene framework with a bridging oxygen atom, three endocyclic alkenes, and various sensitive functional groups including hemiacetals, ketals, esters, and enones (Scheme 3.1). The diversity of functionality brings challenges to synthetic chemists as different functional groups must be installed in a proper sequence to prevent the decomposition of synthetic precursors. Even though the previous syntheses are important, they required multiple steps to arrive at the desired natural products, and entailed tedious manipulation of the protecting groups. A shorter and more scalable synthetic route to the sarcodictyins would be valuable and may provide sufficient materials for biological studies. We envisioned that this goal could be achieved by incorporating organoboron chemistry into the synthetic route. The versatility of the organoboron reactions in constructing the C—C bond and C—hetero bonds can accommodate various functionalities in the natural products.[4a] Importantly, organoboronates are configurationally and chemically stable,[4b] which may provide an opportunity to achieve functionalizations in a proper sequence and avoid any incompatibilities. This chapter discusses our progress to the total synthesis of sarcodictyin A and B and efforts to construct the [8,4,0]tetradecatriene skeleton via various methods.

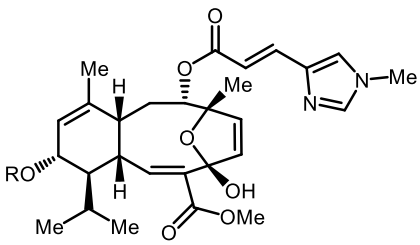
(3) (a) Chen, X.-T.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 185–187. (b) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 789–792. (c) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999,** *121,* 6563–6579.

(4) (a) Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481-5494. (b) Hall, D. G. Ed., Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials (Wiley-VCH, Weinheim, Germany, 2011).

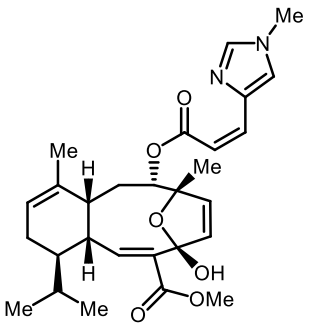
Scheme 3.1. Natural Products in the Sarcodictyins Family



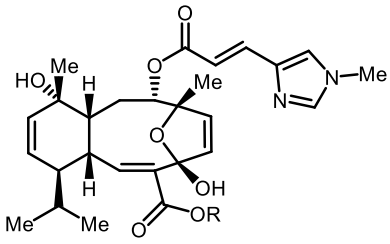
Sarcodictyin A (**3.1**): R = Me
Sarcodictyin B (**3.2**): R = Et



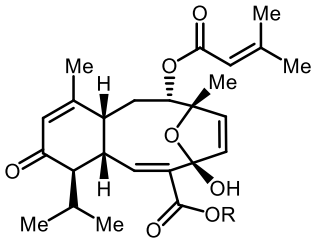
Sarcodictyin C (**3.3**): R = H
Sarcodictyin D (**3.4**): R = Ac



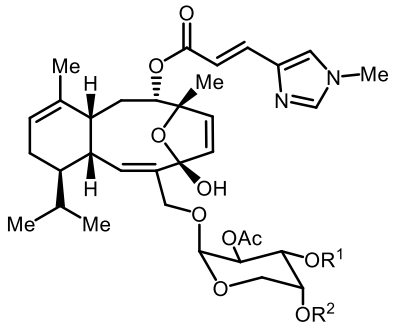
Sarcodictyin E
(**3.5**)



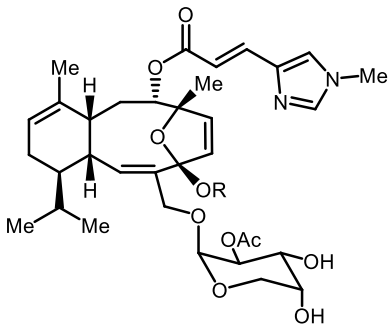
Sarcodictyin F
(**3.6**)



Valvidone A
(**3.7**)



Eleuthoside A (**3.8**): R^1 = Ac, R^2 = H
Eleuthoside B (**3.9**): R^1 = H, R^2 = Ac



Eleutherobin (**3.10**): R = Me
Desmethyl eleutherobin (**3.11**): R = H

3.2 Background

3.2.1 Isolation of Sarcodictyins

Sarcodictyins belong to 2,11-cyclized cembranoid diterpenoids. The first two isolated natural products in this family are sarcodictyins A (**3.1**) and B (**3.2**), which were isolated from the ethanol extract of mediterranean stoloniferan coral *Sarcodictyon roseum* by the Pietra group in 1987.[5a] Later, the same group isolated the sarcodictyins C, D, E, F (**3.3** to **3.6**) also from *Sarcodictyon roseum.*[5b] The structurally related natural product eleutherobin (**3.10**) was isolated from a rare alcyonacean *Eleutherobia* species in 1995 by Lindel *et al*.[6] Its acetylated derivatives eleuthoside A (**3.8**) and B (**3.9**) were isolated by the Kashamn group from soft coral *Eleuthrobia aurea*.[7] Notably, sarcodictyin A (**3.1**) was also found in the sample of this species.[7]

3.2.2 Microtubule Stabilizing Agent[1,8]

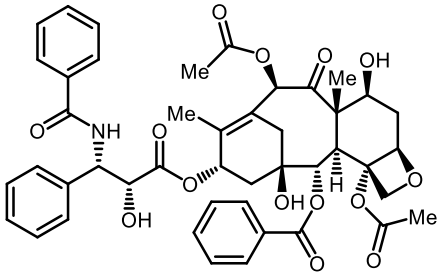
One significant focus of cancer chemotherapy is to promote the apoptosis of cancer cells. Antitumor drugs that can stop cancer cell division by interrupting microtubule dynamics have become increasingly popular because microtubules play an essential role in cell mitosis, which can be easily influenced by changing cell environment such as temperature, osmotic pressure, and the introduction of drug substances.[1] Anticancer agents that destabilize microtubules and prevent tubule polymerization are categorized as microtubule destabilizing agent. On the other hand, those that stabilize microtubules and nucleate tubule polymerization are categorized as microtubule

(5) (a) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019–2027. (b) D'Ambrosio, M.; Guerriero, A.; Pietra, R. *Helv. Chim. Acta* **1988**, *71*, 964–976.
(6) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744–8745.
(7) Ketzinel, S.; Rudi, A.; Schleyer, M.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **1996**, *59*, 873–875.
(8) Ballatore, C.; Smith, A. B.; Lee, V. M.-Y.; Trojanowski, J. Q.; Brunden, K. R. Chapter 11 - Microtubule Stabilization. In *Developing Therapeutics for Alzheimer's Disease*; Wolfe, M. S., Ed.; Academic Press: Boston, **2016**; 305–326.

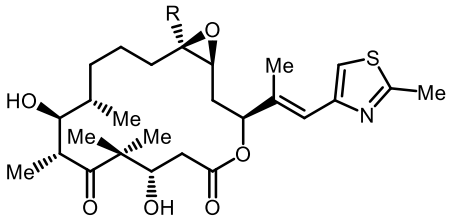
stabilizing agents.[9] Sarcodictyins are unique microtubule stabilizing agents derived from the marine organism and are pursued as drug candidates.[10]

The most famous microtubule stabilizing agent is paclitaxel (Taxol) (**3.12**).[11] It is the first natural product that was found to inhibit cell mitosis by interrupting tubulin dynamics. Its discovery created a novel field in the research of natural medicinal chemistry.[1] Moreover, the development of semi-synthesis and total synthesis of paclitaxel was a popular topic for synthetic chemists in the 1990s due to the low content of paclitaxel in producing plants.[1] Epothilone is another well-known microtubule stabilizing agent isolated from a bacterium in 1993. Epothilone A (**3.8**) and B (**3.9**) were discovered to have superior drug potencies compared to paclitaxel, particularly due to their higher solubility in water and higher availability in nature.[12]

Scheme 3.2. Microtubule Stabilizing Agents



Paclitacel (Taxol)
(**3.12**)



Epothilone A (**3.13**): R = H
Epothilone B (**3.14**): R = CH_3

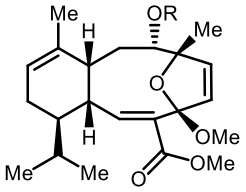
(9) (a) Horwitz, S. B. *Trends Pharmacol. Sci*. **1992**, *13*, 134. (b) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.
(10) Newman, D.; Cragg, G. *J. Nat. Prod.* **2004**, *67*, 1216-1238.
(11) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327.
(12) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem. Int. Ed.* **1996**, *35*, 1567–1569.

3.2.3 Biological Potency of Sarcodictyins

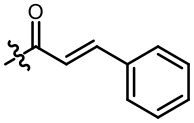
The biological properties of sarcodictyins were studied by the Nicolaou group. They synthesized an extensive library of sarcodictyins, including naturally occurring compounds and unnatural sarcodictyin derivatives.[2,13] The biological potency of these compounds was evaluated by measuring their ability to promote tubulin polymerization, and their cytotoxicity toward different cancer cell lines.[2] The results are summarized in Table 3.1. Sarcodiytin B (**3.2**) exhibits a similar level of cytotoxicity towards ovarian cancer cells (1A9) compared to paclitaxel B (**3.12**) and epothilone A&B (**3.8**). However, sarcodictyin's activity against taxol-resistant cell lines (1A9PTX10 and 1A9PTX22) were still poor. The activities of natural sarcodictyins against prostate (PC3), melanoma (LOX-IMV1), and breast (MCF-7) cancer cell lines were also investigated by NIH researchers (Table 3.2). In general, sarcodictyins exhibit a relatively poor cytotoxicity (IC50 200-500 nM, entry 2, and entry 3), but eleutherobin (**3.10**) and the methyl ketal derivatives of sarcodictyin A (**3.18**) are comparably potent compared to paclitaxel (**3.12**) and epothilones (**3.8** and **3.9**) (entry 6 and entry 7). The synthesis and structural modification of sarcodictyins could open an opportunity to discover novel antitumor agents.

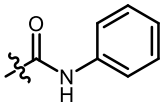
(13) (a) Nicolaou, K. C.; Kim, S.; Pfefferkorn, J.; Xu, J.-Y.; Ohshima, T.; Hosokawa, S.; Vourloumis, D.; Li, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 1418–1421. (b) Nicolaou, K. C.; Winssinger, N.; Vourloumis, D.; Ohshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J.-Y.; Li, T. *J. Am. Chem. Soc.* **1998**, *120*, 10814–10826.

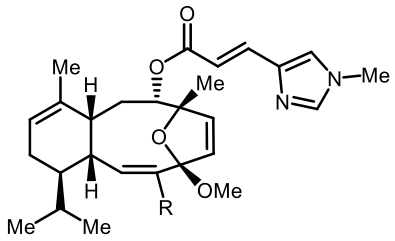
Scheme 3.3. Selected Sarcodictyin Analogs



3.15: R = Ac

3.16: R = 

3.17: R = 



3.18: R = CO_2Me
3.19: R = CH_2OH
3.20: R = CH_2OAc
3.21: R = CH_2NHAc
3.22: R = CH_2NHBz
3.23: R = CHO
3.24: R = CONHBn
3.25: R = CONHMe
3.26: R = *n*Pr
3.27: R = $CH_2CH{=}CH_2$

Table 3.1. Cytotoxcicity Data for Sarcodictyin Analogs[2]

entry	Compound	%Tubulin Polymerization	Inhibition of carcinoma cell growth IC_{50} (nM)		
			1A9	1A9PTX10	1A9PTX22
1	paclitacel (**3.12**)	65	2	50	40
2	epothilone A (**3.13**)	73	2	19	4
3	epothilone B (**3.14**)	97	0.04	0.035	0.04
4	sarcodictyin A (**3.1**)	67	240	140	360
5	sarcodictyin B (**3.2**)	71	2	160	80
6	**3.15**	0	nd	nd	nd
7	**3.16**	6	nd	nd	nd
8	**3.17**	4	nd	nd	nd
9	**3.18**	72	70	4	84
10	**3.19**	37	800	>2000	>2000
11	**3.20**	37	1050	>2000	1620
12	**3.21**	30	800	1600	1200
13	**3.22**	5	nd	nd	nd
14	**3.23**	4	600	400	600
15	**3.24**	75	500	1400	700
16	**3.25**	52	45	65	60
17	**3.26**	69	3	4	5
18	**3.27**	51	9	12	10

Table 3.2. Biological Activity for Microtubule Stabilizing Agents[2]

entry	Compound	Inhibition of carcinoma cell growth IC_{50} (nM)					
		PC3	LOX-IMV1	MFC-7	1A9	1A9PTX10	1A9PTX22
1	paclitacel (**3.12**)	4	6	2	4	60	60
2	epothilone A (**3.13**)	10	10	5	10	40	10
3	epothilone B (**3.14**)	0.9	0.9	0.4	1	3	1
4	sarcodictyin A (**3.1**)	200	400	300	300	200	300
5	sarcodictyin B (**3.2**)	200	500	400	300	300	300
6	eleutherobin (**3.10**)	20	30	10	40	60	30
7	**3.18**	50	80	300	20	20	10

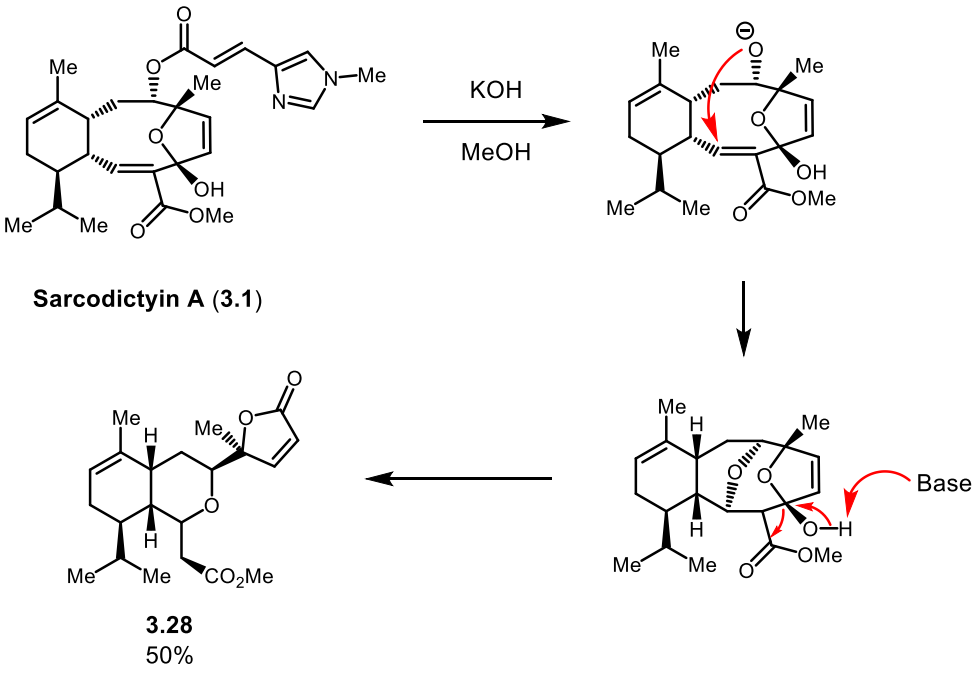
3.2.4 Structure-Activity Relationship Analysis of Sarcodictyins

The structure-activity relationship (SAR) analysis of the sarcodictyin family was also disclosed by the Nicolaou group.[2] Based on their studies (Table 3.1), the urocanic ester moiety on the side chain was found to be essential for the effect on tubulin polymerization. Sarcodictyin derivatives bearing acetate, cinnamate, and carbamate could barely promote the polymerization process (entry 6 to 8). Additionally, the C-4 alkyl ketal derivative exhibited remarkably higher cytotoxicity than the natural hemiketal (entry 9). Various substitution patterns in the C-15 were studied as well; replacing the ester group with alcohol, amine, aldehyde, or amide generally resulted in a loss of both tubulin polymerization activity and antiproliferative activity towards cancer cells (entry 10 to 16).

Modification of the alkene with alkyl and alkenyl substituents improved cytotoxicity (entry 17 to 18). Eleutherobin bearing a C-15 glycosyloxy substituent was a much more efficient antitumor agent than sarcodictyin A. In one revealing experiment, treatment of sarcodictyin A with base resulted in the saponification of urocanic ester, followed by intramolecular conjugate addition

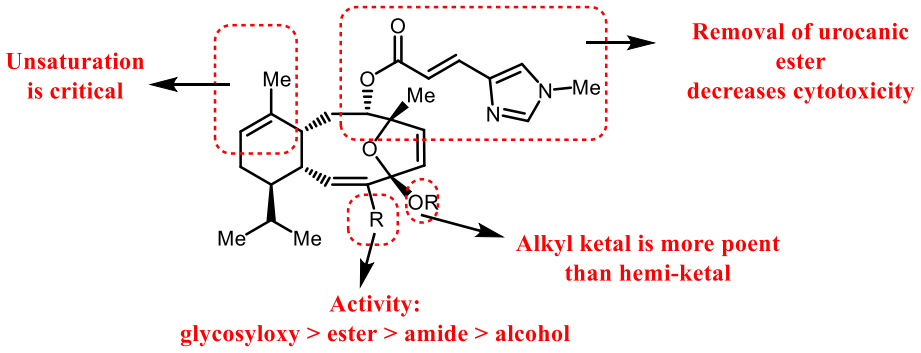
and *retro*-Claisen reaction to afford a bicyclic compound **(3.28)** (Scheme 3.4).[2] This experiment suggested that sarcodictyins can potentially react with endogenous nucleophiles and this might be responsible for cell apoptosis. The pharmacophore of sarcodictyins is summarized in Scheme 3.5 based on work from Nicolaou[2] and Ojima[14]. All four indicated moieties are important for the biological potency (Scheme 3.5).

Scheme 3.4. Base-promoted Degradation of Sarcodictyin A



(14) Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S.; He, L.; Horwitz, S. B.; Kuduk, S. D.; Danishefsky, S. J. *Proc. Natl. Acad. Sci.* **1999**, *96*, 4256–4261.

Scheme 3.5. Pharmacophore of Sarcodictyins



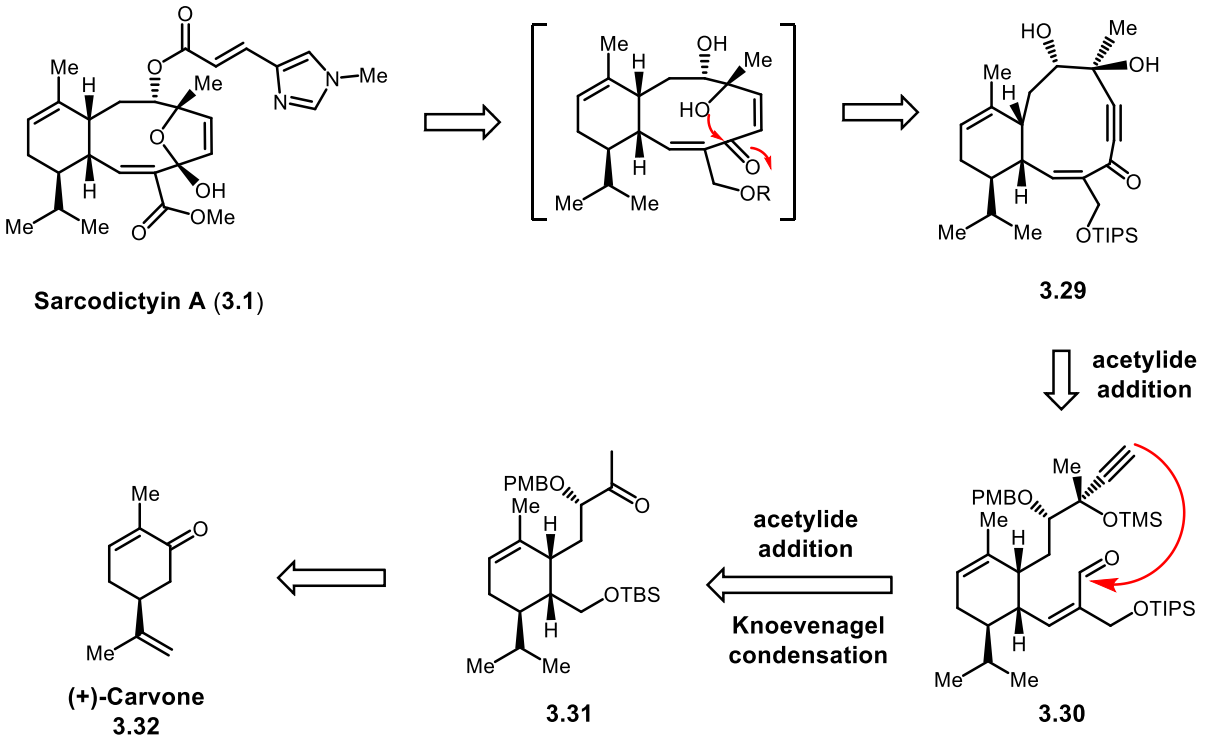
3.3 Prior Syntheses of Sarcodictyins and Analogues

3.3.1 Total Synthesis of Sarcodictyins A by the Nicolaou group

The first and the only total synthesis of sarcodictyin A (**3.1**) and B (**3.2**) was developed by the Nicolaou group to support *in vitro* and *in vivo* assays and SAR studies.[15] According to the proposed retrosynthetic analysis in Scheme 3.6, the oxygen-bridged tricyclic structure could be formed in the late stage by reduction of the alkyne in compound **3.29** followed by hemiketal formation. They proposed that an intramolecular acetylide addition could afford the 10-membered ring core structure (**3.28**). The aldehyde moiety in intermediate **3.30** could be constructed by Knoevenagel condensation, and the propargyl alcohol could be derived from the ketone through the addition of acetylide. Compound **3.31** could be synthesized from naturally abundant chiral building block (+)-carvone (**3.32**).

(15) (a) Nicolaou, K. C., Xu, J.-Y., Kim, S., Ohshima, T., Hosokawa, S., Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353–11354. (b) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661–8673.

Scheme 3.6. Retrosynthetic Analysis of Sarcodictyin A

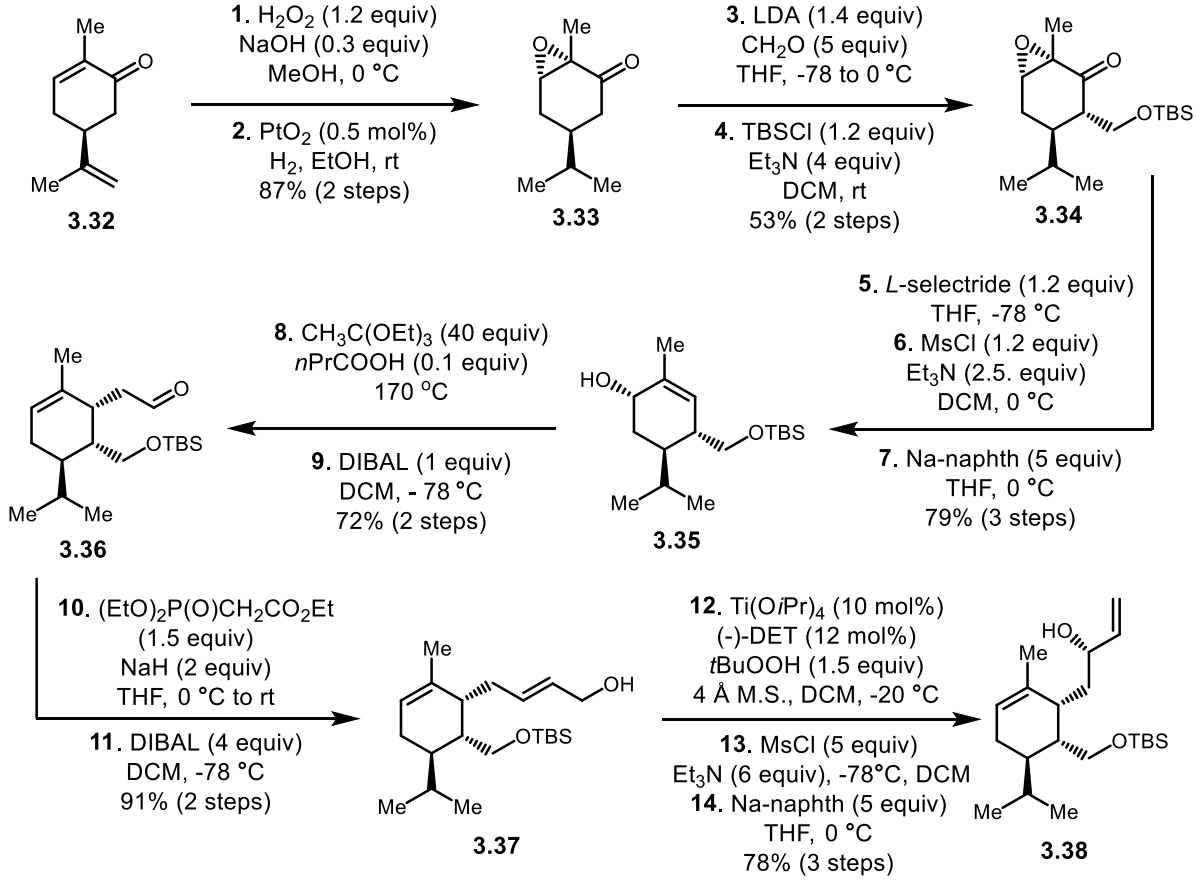


The forward synthesis started with (+)-carvone (**3.32**) (Scheme 3.7). Diastereoselective epoxidation of the enone followed by hydrogenation of the isopropene afforded the epoxide **3.33**; α-alkylation of the ketone and protection delivered the TBS-ether **3.34**. The ketone was then converted to the corresponding mesylate by reduction and mesylation, and the mesylate then underwent a reductive epoxide opening with sodium naphthalenide and followed by elimination to afford the allylic alcohol **3.35**. The synthesis of intermediate **3.35** is based on a modification of Trost's approach.[16] Next, Johnson-Claisen rearrangement[17] of the allylic alcohol using triethyl orthoformate furnished the ethyl ester, which was reduced to aldehyde **3.36** with DIBAL. Next,

(16) Trost, B. M.; Tasker, A. S.; Ruther, G.; Brands, A. *J. Am. Chem. Soc*. **1991**, *113*, 670.
(17) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

the *E*-allylic alcohol **3.37** was synthesized through a Horner–Wadsworth–Emmons olefination[18] followed by another DIBAL reduction. Sharpless asymmetric epoxidation[19] of the allylic alcohol **3.37** generated the *β*-epoxy alcohol, which was then converted to allylic alcohol **3.38** through mesylation and reductive epoxide opening.

Scheme 3.7. Synthesis of Allylic Alcohol Intermediate **3.38**

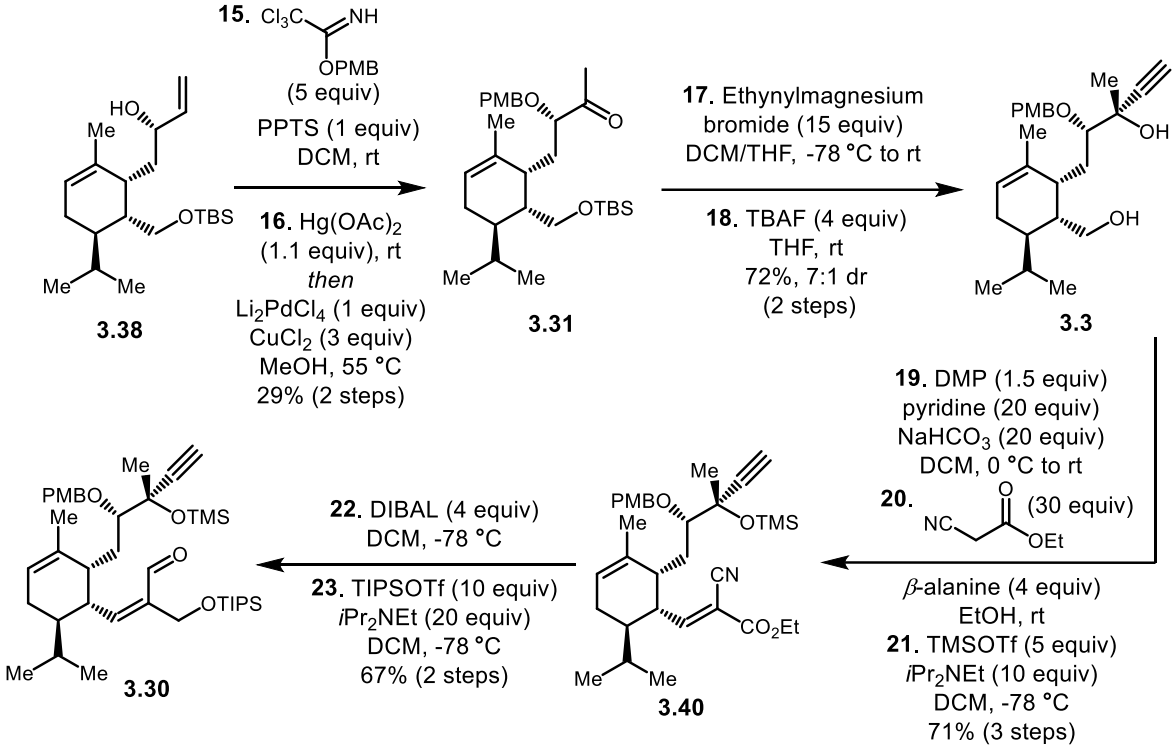


(18) Wadsworth, W. *Org. React.* **1977**, *25*, 73.

(19) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. H.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

After the alcohol was protected as a PMB ether, oxymercuration of the alkene followed by transmetalation to palladium and *β*-hydride elimination delivered ketone **3.31** (Scheme 3.8).[20] The propargyl alcohol intermediate was generated by acetylide addition (step 17). Subsequently, the primary alcohol was oxidized to an aldehyde with DMP[21] after deprotecting of the TBS group with TBAF. Knoevenagel condensation of the aldehyde afforded the trisubstituted alkene with exclusive *E*-stereoisomer; compound **3.40** was synthesized after protecting the propargylic alcohol with TMSOTf. Reduction of **3.40** with DIBAL-H and protection of allylic alcohol with TIPSOTf furnished enone **3.30**.

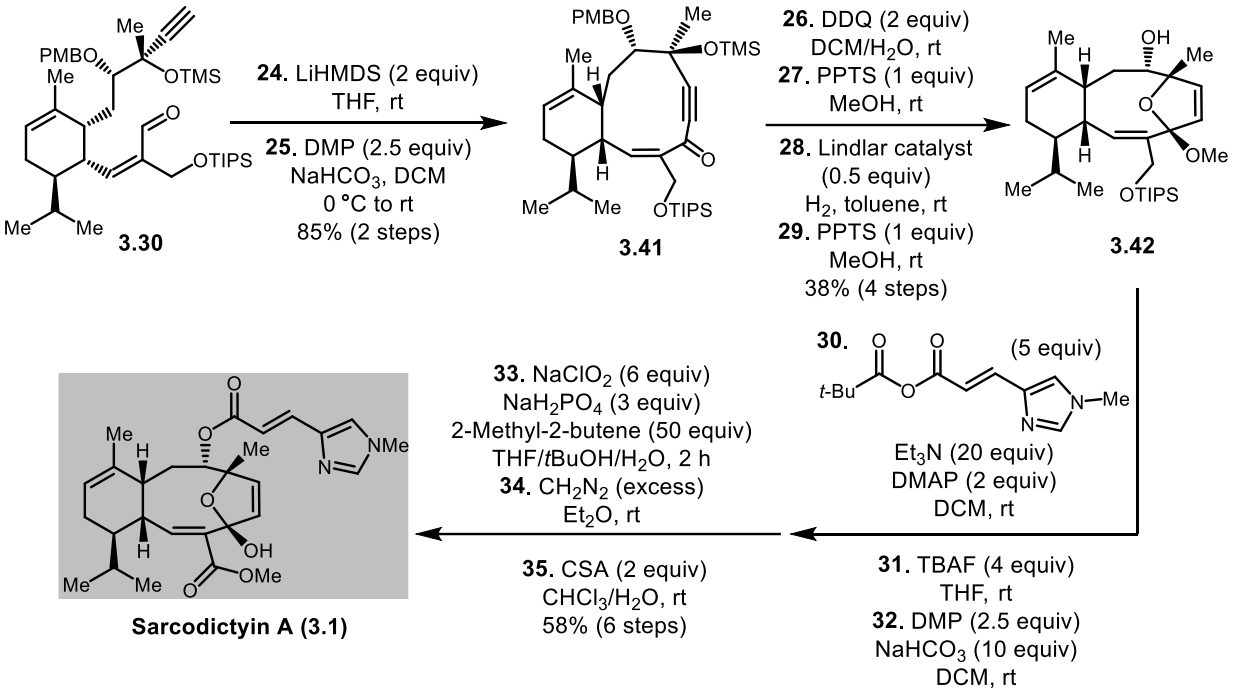
Scheme 3.8. Synthesis of Cyclization Precursor **3.30**



(20) Rodeheaver, G. T.; Hunt, D. F. *Chem. Comm.* **1971**, 818.
(21) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

An intramolecular acetylide addition with LiHMDS was conducted to construct the 10-membered ring and alkynyl ketone **3.41** was then synthesized through DMP oxidation (Scheme 3.9). Compound **3.41** was treated with DDQ and then acid to remove the PMB and the TMS protecting groups. The alkyne was reduced with Lindlar's catalyst under hydrogen atmosphere and was then converted to hemiketal **3.42** with PPTS in methanol. After transesterification to install the urocanic ester moiety[22], the primary TIPS-ether was deprotected and sequentially oxidized to the corresponding carboxylic acid (Step 30 to 33). Lastly, sarcodictyin A (**3.1**) was synthesized through esterification with diazomethane and acetal hydrolysis. The total synthesis of sarcodictyin A was accomplished within 35 steps.

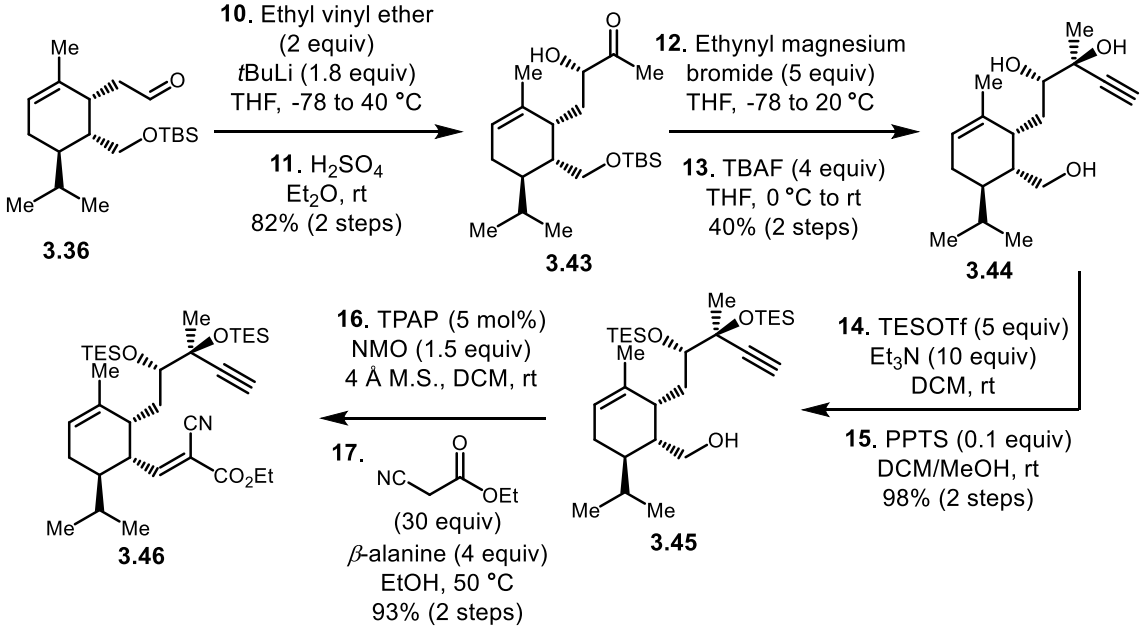
Scheme 3.9. Completion of the Synthesis



(22) Viguerie, N. L.; Sergueeva, N.; Damiot, M.; Mawlawi, H.; Riviere, M.; Lattes, A. *Heterocycles* **1994**, *37*, 1561.

Nicolaou further shortened and improved the synthetic route to achieve a more efficient and flexible synthesis of sarcodictyin A&B and their unnatural derivatives (Scheme 3.10).[2, 23] In this route, the aldehyde compound **3.36** reacted with lithiated ethyl vinyl ether followed by hydrolysis with sulfuric acid to deliver ketone **3.43**. Acetylide addition and deprotection of the silyl ether with TBAF afforded triol **3.44**, which was converted to compound **3.45** through a global TES protection and selective deprotection of the primary silyl ether. The primary alcohol was oxidized with TPAP/NMO, and the aldehyde then underwent the Knoevenagel condensation to deliver the *E*-alkene **3.46**.

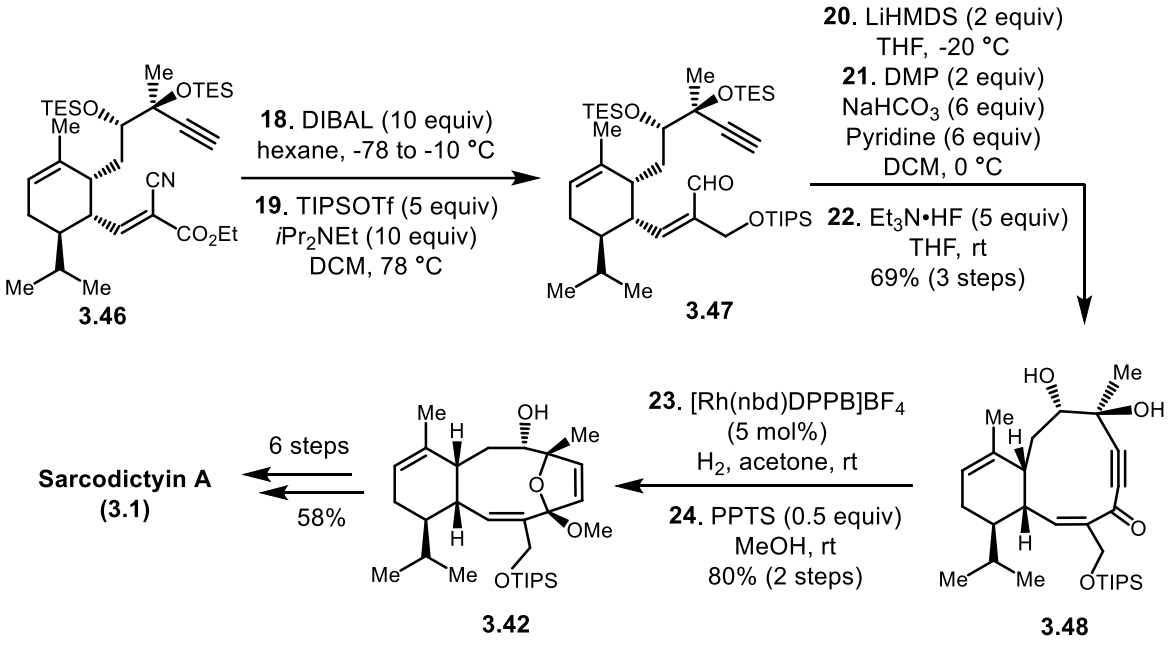
Scheme 3.10. Second Generation of Total Synthesis by the Nicolaou Group (Forward)



(23) Nicolaou, K. C.; van Delft, F. L.; Ohshima, T.; Vourloumis, D.; Xu, J. Y.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2520–2524.

Alkenyl aldehyde **3.47** was then synthesized by DIBAL reduction of **3.46** followed by silyl protection of the alcohol (Scheme 3.11). Next, cyclization was accomplished by an intramolecular acetylide addition, and the afforded propargyl alcohol then oxidized to furnish the alkynyl ketone intermediate. Compound **3.48** was accessed by selective deprotection. In this scenario, the alkyne reduction was conducted with a ruthenium catalyst, which exhibited superior chemoselectivity than Lindlar's catalyst (step 23), as fewer over-reduced side products were observed. Ketal **3.42** was formed upon reaction with PPTS in methanol. The ketal was then subjected to an established route to deliver the desired natural product with an overall longest linear sequence of 30 steps. This synthetic strategy was also employed by the Nicolaou group as a template to synthesize sarcodictyin B (**3.2**),[14a] eleutherobin (**3.10**),[24] and their unnatural derivatives (**3.15 to 3.27**).[2]

Scheme 3.11. Second Generation of Total Synthesis by the Nicolaou Group (End)



(24) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**. *120*, 8674–8680.

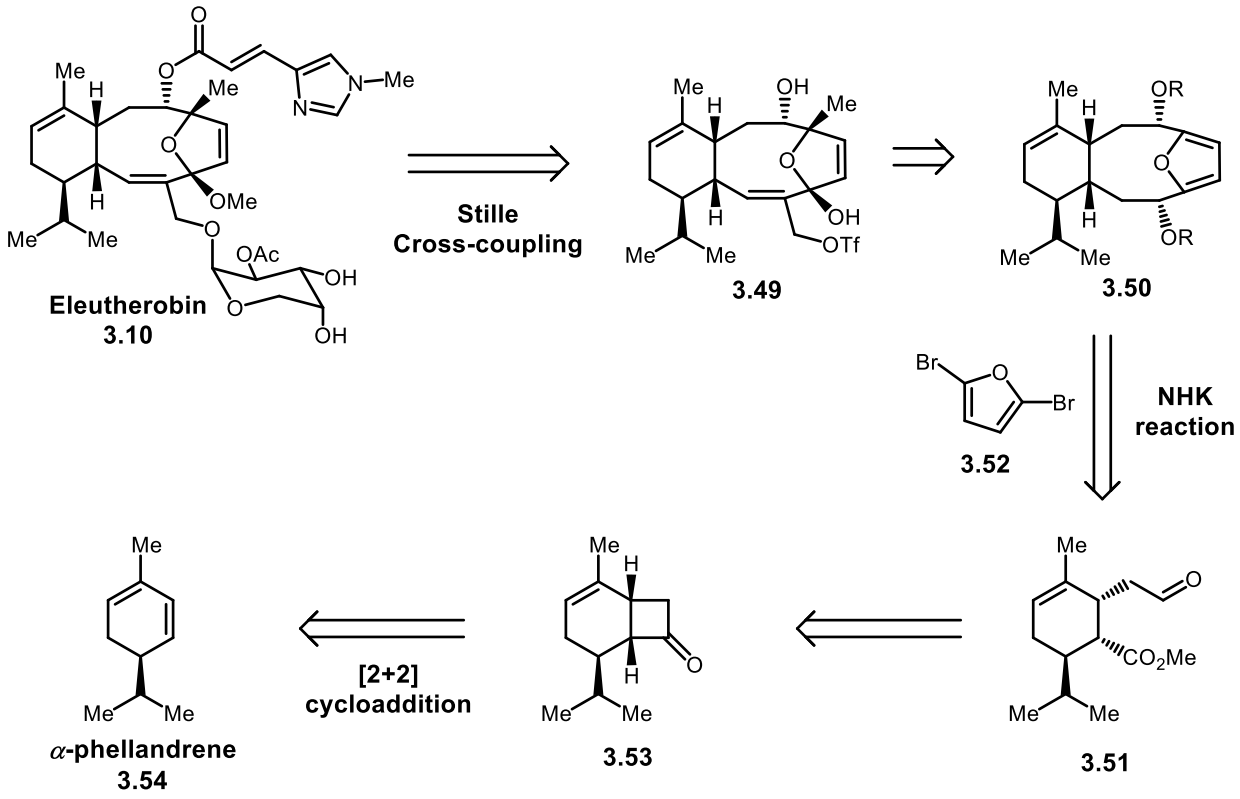
3.3.2 Total Synthesis of Eleutherobin by the Danishefsky group

An alternative synthetic route to construct the cyclic core of sarcodictyins was developed by the Danishefsky group and it was used to accomplish the total synthesis of eleutherobin (**3.10**).[3] The retrosynthetic analysis is summarized in Scheme 3.12. First, the glycosyloxy moiety was installed through the Stille cross-coupling reaction from alkyl triflate **3.49**, which could be derived from the tricyclic furyl compound **3.50**. The 10-membered ring core could be constructed through a Nozaki-Hiyama-Kishi reaction[25] between **3.51** and **3.52**. The aldehyde **3.51** could be synthesized by ring fragmentation of bicyclic compound **3.53**, which could be derived from [2+2] cycloaddition between α-phellandrene **3.54** and ketene.

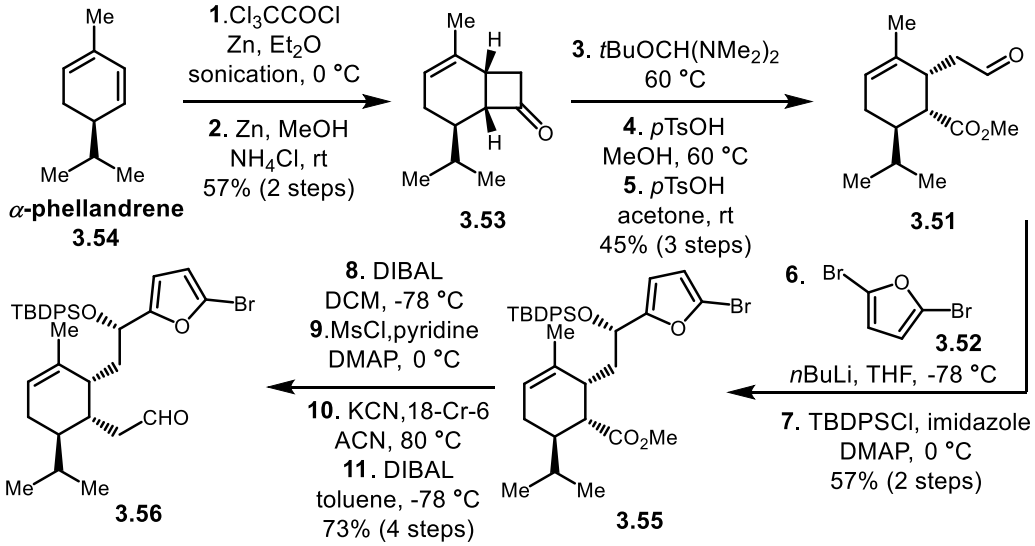
The synthesis started with the [2+2] cycloaddition between α-phellandrene **3.54** and the *in situ* generated dichloroketene; only one diastereomer was obtained after purification by silica gel chromatography (Scheme 3.13). Cyclobutanone **3.53** was synthesized through reductive bis-dechlorination of the dichloride intermediate. Treating **3.53** with Bredereck reagent[26] afforded the imine intermediate, which underwent methanolysis and de-acetalization to provide aldehyde **3.51**.[27] The aryl lithium generated via lithium halogen exchange of dibromofuran could react with **3.51** to afford the furan intermediate **3.55**. Next, **3.55** was converted to homologated aldehyde **3.56** through a DIBAL reduction/mesylation/cyanation/DIBAL reduction sequence.

(25) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. For review: Gil, A.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2017**, *117*, 8420–8446.
(26) Bredereck, H.; Effenberger, F.; Simchen, G. *Chem. Ber.* **1963**, *96*, 1350.
(27) Trost, B. M.; Preckel, M.; Leichter, L. M. *J. Am. Chem. Soc.* **1975**, *97*, 2224.

Scheme 3.12. Retrosynthetic Analysis of Eleutherobin



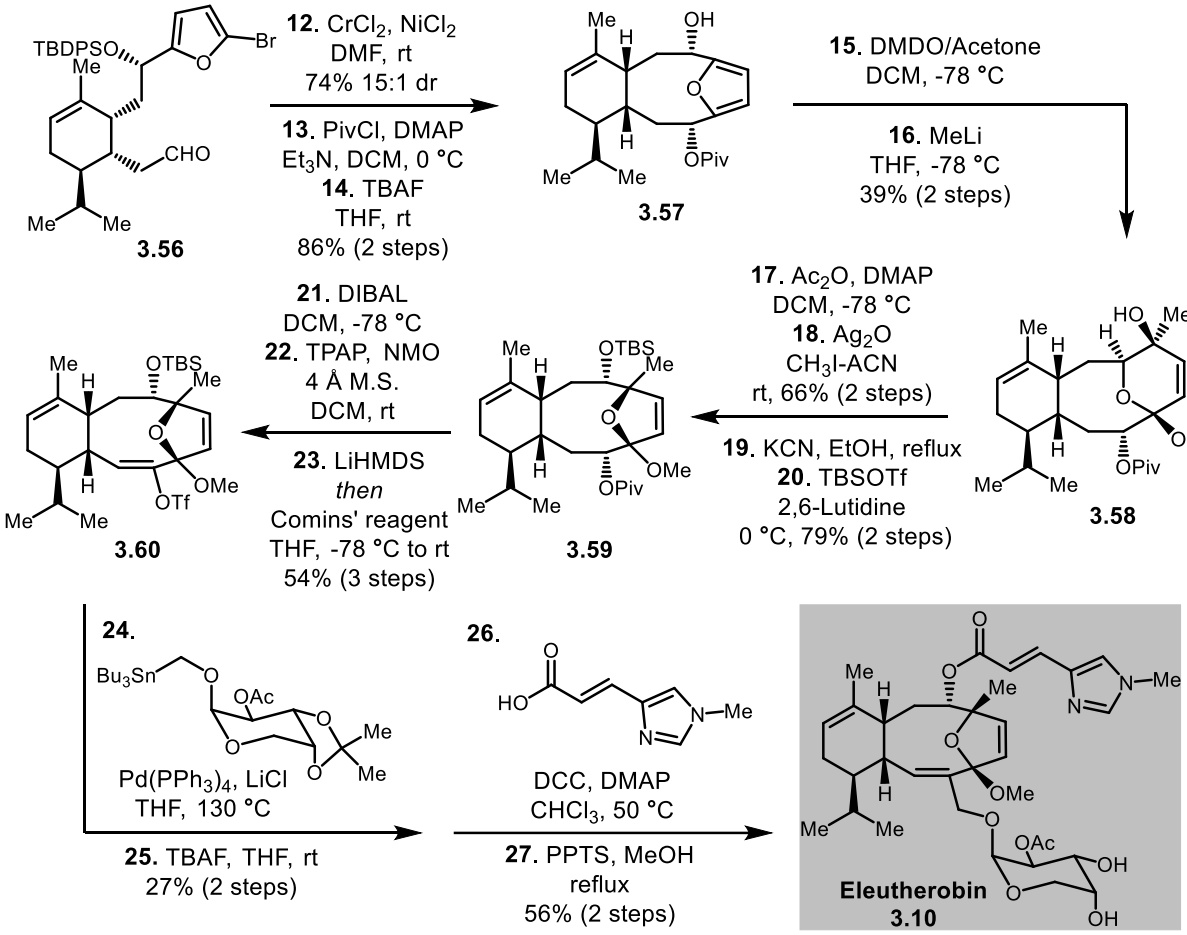
Scheme 3.13. Total Synthesis of Eleutherobin by Danishefsky (Forward Synthesis)



At this stage, Nozaki-Kishi reaction[25] was employed to construct the 10-membered ring core (Scheme 3.14, Step 12). The resulting secondary alcohol was protected with PivCl and silyl protection (TBDPS) was removed with TBAF to give compound **3.57**. Hydroxy group-directed epoxidation[28,29] of **3.57** followed by rearrangement afforded the pyranone intermediate, which could react with methyllithium to deliver tertiary alcohol **3.58**. Rearrangement of the dihydropyran to the dihydrofuran was facilitated by the formation of a secondary acetate (Step 17), which was then converted into the methyl ketal (Step 18). The acetate was removed with KCN in ethanol, and the resulting alcohol was protected with TBSCl to afford compound **3.59**. Subsequently, the pivalate could be deprotected by DIBAL, and the corresponding alcohol was converted to the alkenyl triflate **3.60** through Ley-Griffith oxidation and triflation. After screening different conditions, the Stille cross-coupling conditions developed by Buchwald[30] was utilized to install the glycosyloxy moiety (Step 24). Lastly, the total synthesis was completed by silyl deprotection with TBAF, and esterification with the assistance of DCC followed by acetonide removal. The desired natural product eleutherobin (**3.10**) was synthesized within the overall 27 steps.

(28) Chow, K.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 4211.
(29) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Murray, R. W.; Singh, M. *Org. Synth*. **1997**, *74*, 91.
(30) Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics* **1989**, *8*, 1593.

Scheme 3.14. Total Synthesis of Eleutherobin by Danishefsky (Completion of Synthesis)



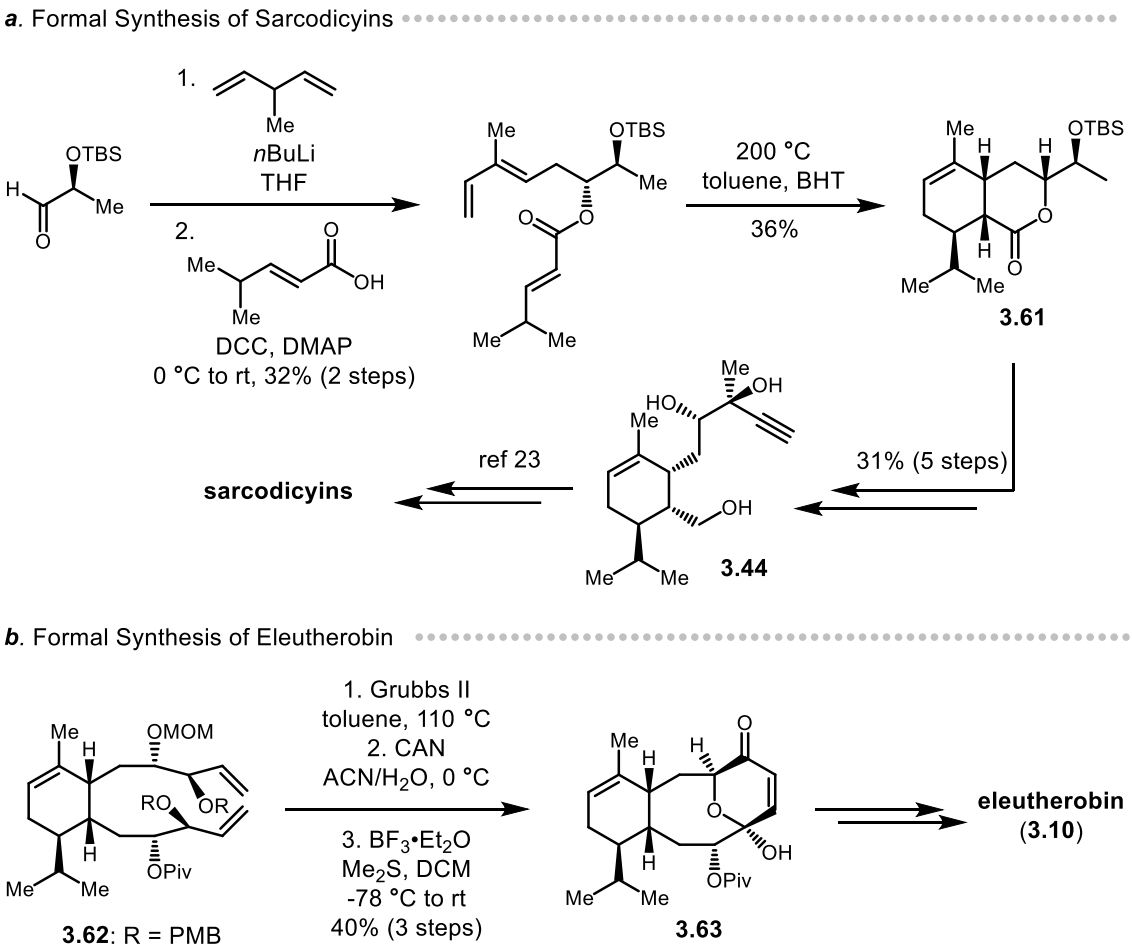
3.3.3 Formal Synthesis of Sarcodicyins

The formal synthesis of sarcodictyins through intermediate **3.44** was developed by the Metz group (Scheme 3.15a).[31] The key step in this synthesis was an intramolecular Diels–Alder reaction to construct the bicyclic intermediate **3.61**, which could be converted to **3.44** in 5 steps. On the other hand, the formal synthesis of eleutherobin was accomplished by the Gennari group

(31) Ritter, N.; Metz, P. *Synlett* **2003**, *15*, 2422–2424.

in 2005 (Scheme 3.15b).[32] They constructed the 10-membered ring through a ring close metathesis from compound **3.62**. After oxidation of the allylic alcohol and deprotection of the MOM ether, they synthesized compound **3.63**, an intermediate in Danishefsky's total synthesis of eleutherobin.

Scheme 3.15. Formal Synthesis of Sarcodictyins

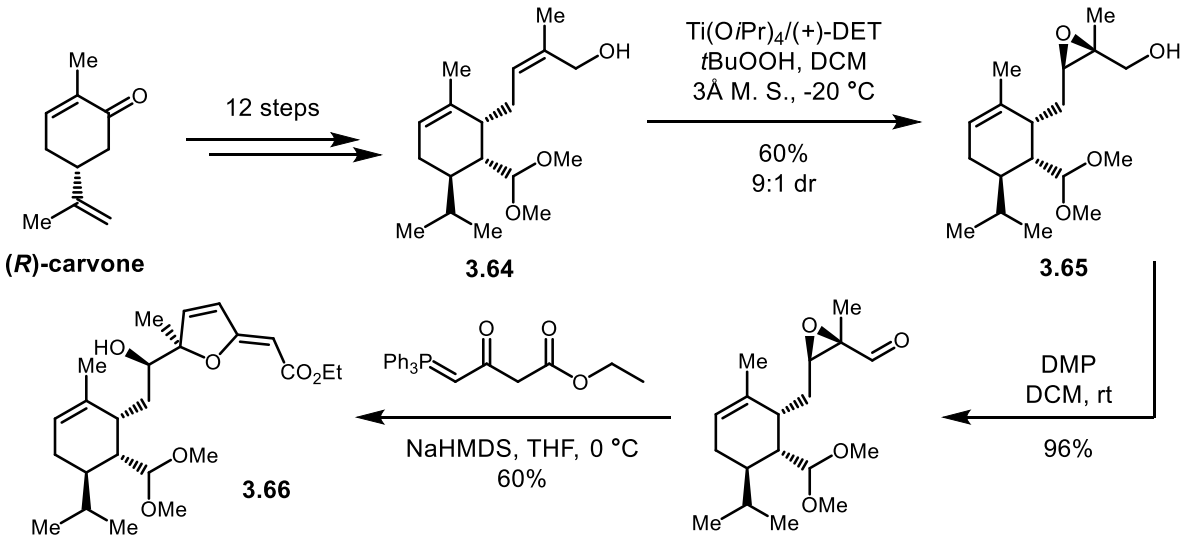


(32) (a) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 588–591. (b) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem. Eur. J.* **2006**, *12*, 51–62. (c) Gennari, C.; Castoldi, D.; Sharon, O. *Pure Appl. Chem*. **2007**, *79*, 173–180.

3.3.4 Synthesis of the Advanced Intermediate

The total synthesis of sarcodictyins was also studied by the Gennari group.[33] They synthesized fully-functionalized cyclization precursor **3.66** (Scheme 3.16). In this synthesis, the naturally abundant (R)-carvone was first converted to the allylic alcohol **3.64**, which was then subjected to the Sharpless asymmetric epoxidation to furnish epoxide **3.65** with good diastereoselectivity. After oxidation of the primary alcohol, Wittig olefination of the resulting aldehyde furnished the dihydrofuran intermediate **3.66** through an olefination/enolate cyclization (epoxide opening) sequence. The reaction was highly *Z*-selective, presumably because the *E*-alkenyl ester cannot participate in the cyclization reaction. However, cyclization of **3.66** through aldol-type reactions was unsuccessful. The author proposed that the steric bulkiness exerted by the isopropyl group resulted in the poor reactivity.

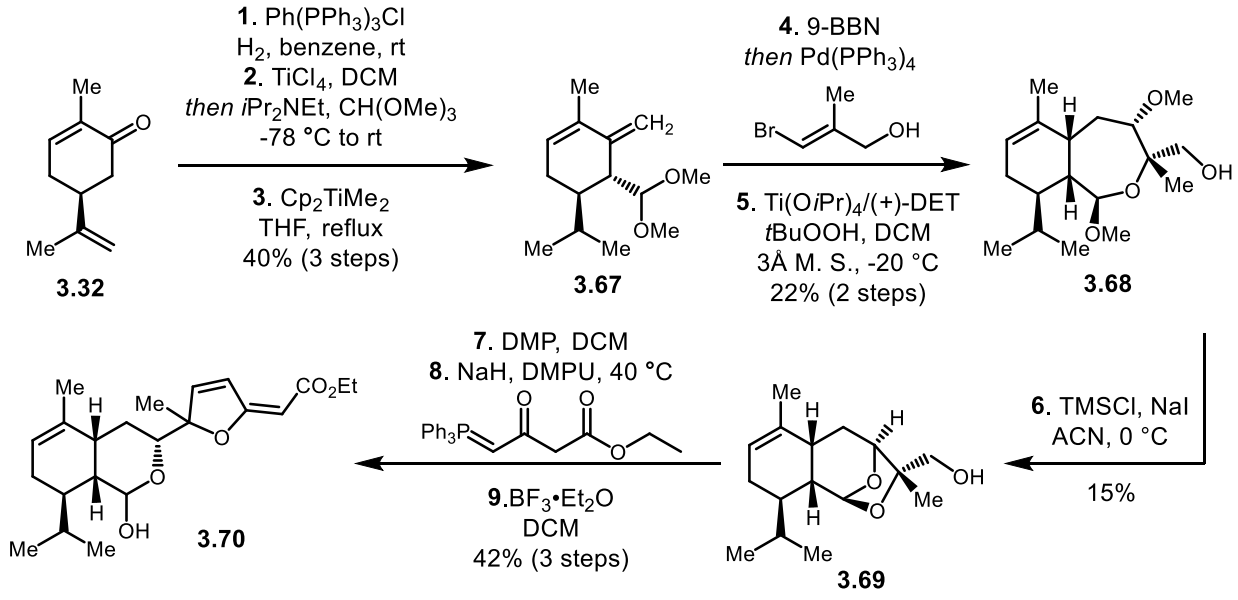
Scheme 3.16. Synthesis of Advance Intermediate **3.66** by Gennari



(33) Ceccarelli, S. M.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, 57, 8531–8542.

Good efforts have also been made by the Magnus group in the total synthesis of sarcodictyins.[34] They started their synthesis with (*S*)-carvone **3.32** (Scheme 3.17), which was converted to diene **3.67** through sequential hydrogenation, alkylation, and olefination. Next, hydroboration of **3.67** with 9-BBN followed by palladium-catalyzed Suzuki cross-coupling delivered an allylic alcohol, which was subjected to the Sharpless asymmetric epoxidation to deliver compound **3.68**. The generated epoxide is not chemically stable and could undergo an intramolecular ring opening *in situ* to furnish compound **3.68**. Similar reactivity has been observed by the Gennari group as well.[33] Treating **3.67** with TMSI delivered demethylated acetal **3.69**, however, the reactivity was poor. After oxidation of the alcohol and olefination of the corresponding aldehyde, the resulted enone then underwent rearrangement in the presence of Lewis acid to afford the advanced intermediate **3.70**. Unfortunately, the Magnus group terminated this project when the Nicolaou group reported a successful route to this natural product.

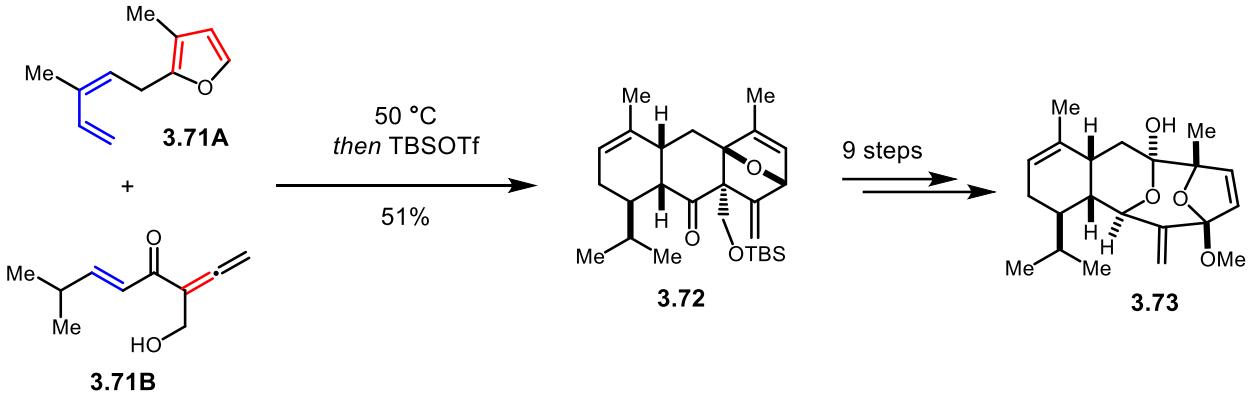
Scheme 3.17. Synthesis of Advance Intermediate **3.70** by Magnus



(34) Carter, R.; Hodgetts, L.; McKenna, J.; Magnus, P.; Wren, S. *Tetrahedron* **2000**, *56*, 4367–4382.

In an alternative approach, advanced intermediate **3.73** was synthesized by the Winkler group (Scheme 3.18).[35] The key transformation in their strategy is a tandem Diels-Alder reaction between diene **3.71A** and dienophile **3.71B** to construct the tetracyclic compound **3.72** in a diastereoselective fashion. Next, **3.72** could be converted to advanced intermediate **3.73** in nine steps. Compound **3.73** already exhibited a close structural resemblance to sarcodictyins. However, to this date, the completion of this synthesis has not been reported.

Scheme 3.18. Synthesis of Advance Intermediate **3.73** by Winkler



Syntheses of the sarcodictyin analogs have also been accomplished by multiple groups through similar strategies demonstrated above such as: acetylide addition by the Valeev group[36],

(35) Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5*, 1805–1808.

(36) (a) Sharipov, B. T.; Pershin, A. A.; Pilipenko, A. N.; Salikhov, Sh. M.; Valeev, F. A., *Russ. J. Org. Chem.* **2013**, *49*, 1437. (b) Sharipov, B. T.; Pershin, A. A.; Salikhov, Sh. M.; Valeev, F. A.; *Russ. J. Org. Chem.* **2014**, *50*, 1258. (c) Pershin, A. A.; Sharipov, B. T.; Salikhov, Sh. M.; Valeev, F. A., *Russ. J. Org. Chem.* **2015**, *51*, 1536. (d) Sharipov, B. T.; Pershin, A. A.; Salikhov, Sh. M.; Valeev, F. A., *Russ. J. Org. Chem.* **2016**, *52*, 721–726. (e) Sharipov, B. T.; Pershin, A. A.; Valeev, F. A. *Mendeleev Communications* **2017**, *27*, 119–121.

Nozaki-Hiyama-Kishi reaction by the Bermejo group[37], and olefin metathesis by the Holmes group[38] and Gennari group[39].

3.4 Progress towards Total Synthesis of Sarcodictyins (1st Attempt)[40]

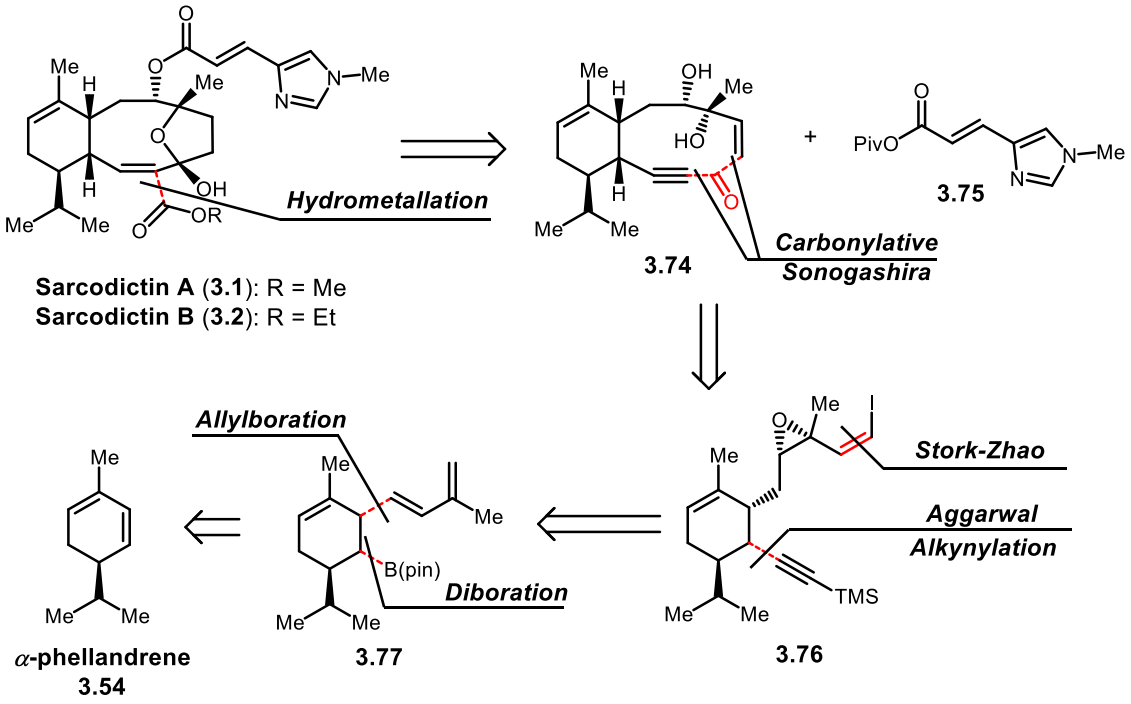
3.4.1 Retrosynthetic Analysis

Inspired by the total synthesis from the Danishefsky group,[3] α-phellandrene (**3.54**) was chosen as our starting point as it accommodates the absolute configuration of sarcodictyin A and B. More importantly, the diene moiety, adjacent to the sterically hindered isopropyl group, could potentially undergo a diastereoselective difunctionalization to install useful functionality with the desired steric outcome.[41] With that idea in mind, we proposed the retrosynthetic analysis shown in Scheme 3.19. First, we planned to construct the ester moiety in a late stage by hydrometallation of an alkyne followed by trapping of the alkenyl metallic intermediate with a chloroformate. The alkynyl ketone intermediate **3.74** could be synthesized by the palladium-catalyzed intramolecular carbonylative Sonogashira reaction from the alkenyl iodide **3.76**, which could be derived from diene species **3.77**. The alkyne could be furnished from a boronic ester by Aggarwal's modified

(37) Sandoval, C.; López-Pérez, J. L.; Bermejo, F. *Tetrahe*dr*on* **2007**, 63, 11738–11747.
(38) (a) Chiang, G. C. H.; Bond, A. D.; Ayscough, A.; Pain, G.; Ducki, S.; Holmes, A. B. *Chem. Commun.,* **2005**, 1860–1862. (b) Mak, S. Y. F.; Chiang, G. C. H.; Davidson, J. E. P.; Davies, J. E.; Ayscough, A.; Pain, G.; Burton, J. W.; Holmes, A. B. *Tetrahe*dr*on: Asymmetry* **2009**, *20*, 921–944.
(39) (a) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Monti, D.; Gennari, C. *Tetrahe*dr*on Lett.* **2001**, *42*, 9187–9190. (b) Beumer, R.; Bayón, P.; Bugada, P.; Ducki, S.; Mongelli, N.; F. Riccardi Sirtori, J. Telser, C. Gennari. *Tetrahe*dr*on Lett*. **2003**, *44*, 681-684. (c) R. Beumer, P. Bayón, P. Bugada, S. Ducki, N. Mongelli, Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahe*dr*on* **2003**, *59*, 8803-8820. (d) Castoldi, D.; Caggiano, L.; Bayón, P.; Costa, A. M.; Cappella, P.; Sharon, O.; Gennari, C. *Tetrahe*dr*on* **2005**, *61*, 2123–2139.
(40) Myhill, J. A. Development of Catalytic Conjunctive Cross-Coupling Reactions and Progress Towards the Total Synthesis of the Sarcodictyins. Ph.D. Thesis. Boston College. **2020**
(41) (a) Poe, S. L.; Morken, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 4189. (b) Hong, K.; Morken, J. P. *J. Org. Chem.* **2011**, *76*, 9102–9108.

Zweifel reaction[42] and the alkenyl iodide could be constructed under Stork-Zhao condition.[43] Compound **3.77** was proposed to be synthesized by a stereoselective one-pot diboration/allylboration/elimination sequence from α-phellandrene **3.54.**

Scheme 3.19. Retrosynthetic Analysis of Sarcodictyin A and B



3.4.2 Forward Synthesis

We began our synthesis with the platinum-catalyzed 1,4-diboration of α-phellandrene **3.54**. Following the condition developed by our group,[41] bis(boronate) **3.78** was obtained with good yield (Scheme 3.20a). In the proposed mechanism, the platinum (II) species **3.81** would bind to the disubstituted alkene from the less hindered side. It would then undergo the 1,2-migratory insertion, the η^1- η^3- η^1 isomerization, and the reductive elimination to deliver product **3.78** as a single diastereomer. Notably, this reaction could be conducted on up to 50 g scale with extremely

(42) Wang, Y.; Noble, A.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2016**, *55*, 4270–4274.
(43) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174.

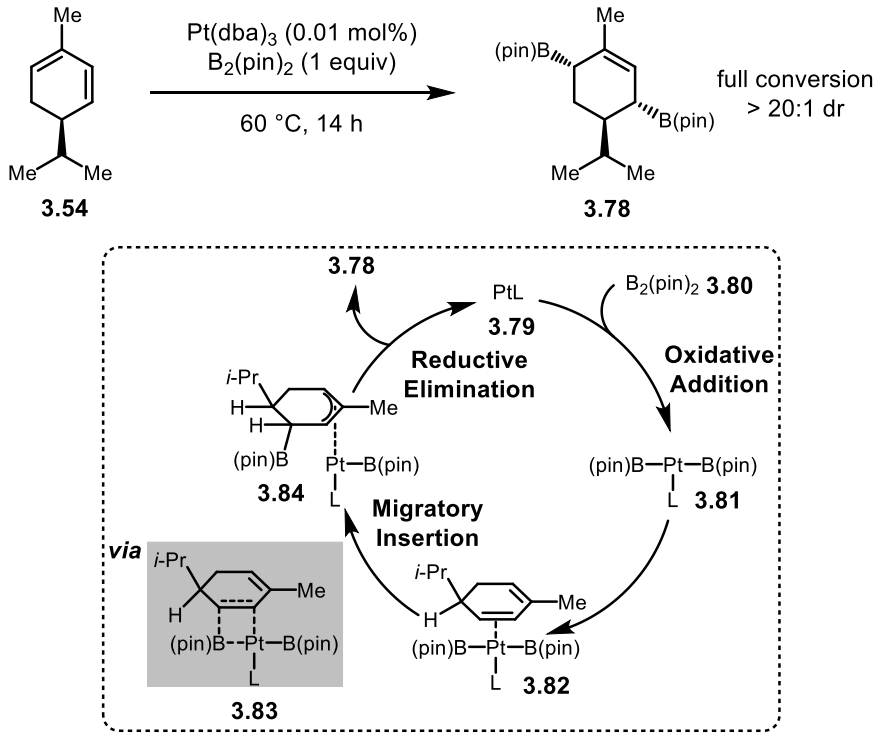
low catalyst loading and under ambient atmosphere. Even though the solvent is not required for this reaction, the stir bar can stick to the $B_2(pin)_2$ solids resulting in poor stirring, especially on a larger scale (> 5g). In this case, adding a small potion of toluene (10-30 mL) helps render the reaction homogeneous.

The bis(boronate) compound **3.78** was not purified but used *in situ* in a subsequent allylboration reaction with prenal (Scheme 3.20b).[44] We observed that both allylic boron moieties participated in the allylboration reaction. The allylic alcohol intermediate would eliminate at elevated temperature through a sigmatropic rearrangement mechanism to deliver the diene product as a mixture of two regiomers **3.84** and **3.85**. Even though two regiomers (**3.84** and **3.85**) were separable, they are just barely so and require multiple column chromatography with toluene as the developing solvent to obtain pure **3.84**. Accordingly, a superior condition with higher selectivity would simplify the purification process. After screening different catalysts, trifluoroacetic acid (TFA) was proven to be effective for allylboration and elimination and delivered the product with good yield and selectivity (entry 2, Table 3.3). Other commonly used acid-catalysts such as BF_3•Et_2O and TsOH•H_2O led to decomposition (entry 3 and entry 5). We recently discovered that the BINOL-derived phosphoric acid **3.87**[45] afforded the product with a higher regioisomeric ratio albeit a lower yield (entry 6). Attempts to boost the yield by increasing the reaction temperature or catalyst loading were unsuccessful. The addition of $NiCl_2$ after the completion of the reaction could decompose the pinacol byproduct and simplifies the work-up procedure for large-scale reactions.

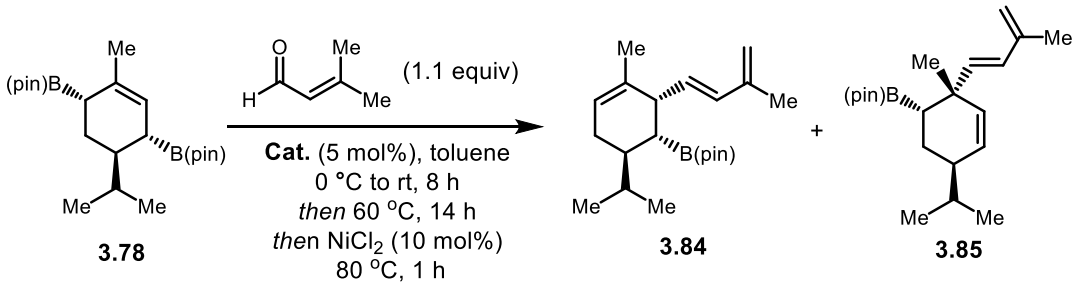
(44) Lachance, H.; Hall, D. G. In *Organic Reactions*, Denmark, S. E., Ed.; John Wiley & Sons, Inc. **2008**, *73*, 1–573.
(45) Barrio, P.; Rodríguez, E.; Fustero, S. *The Chemical Record* **2016**, *16*, 2046–2060.

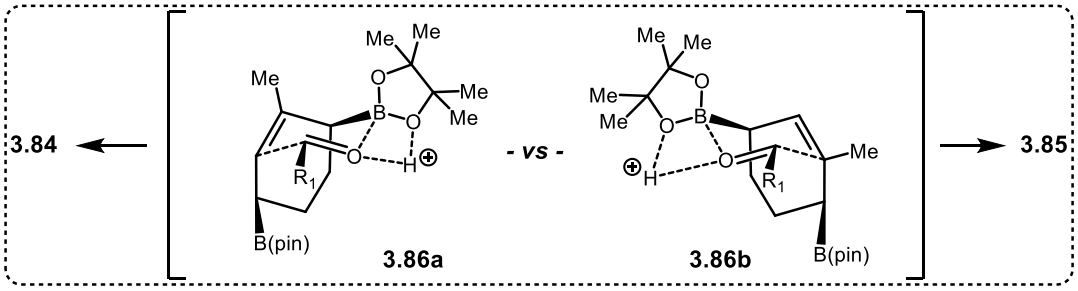
Scheme 3.20. Diboration/Allylboration/Elimination Sequence

a. Pt-Catalyzed Diboration



b. Acid-Catalyzed Allylation/Elimination





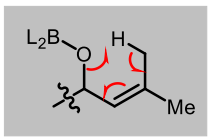
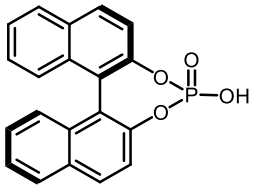


Table 3.3. Effects of Acid Catalysts for Allyboration/Elimination Sequence

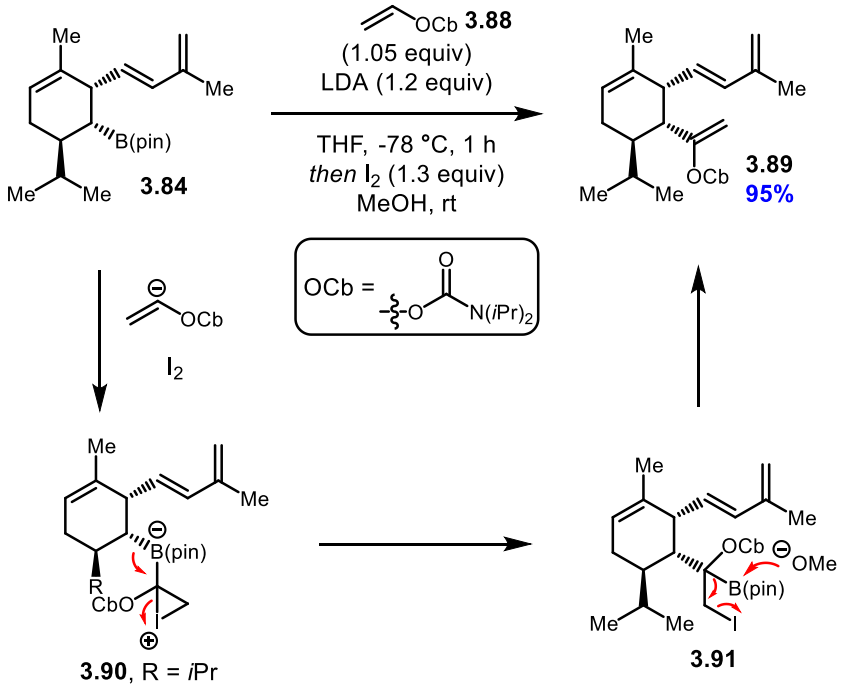
entry	**Cat.**	Yiled	**3.84**:**3.85**
1	None	no conversion	N.A.
2	BF_3 •Et_2O	N.A.	N.A.
3 (*Optimized*)	TFA	70%	7:1
4	TsOH•H_2O	N.A.	N.A.
5	$(PhO)_2POOH$ **3.86**	40%	3:1
6	**3.87**	10%	10:1



3.87

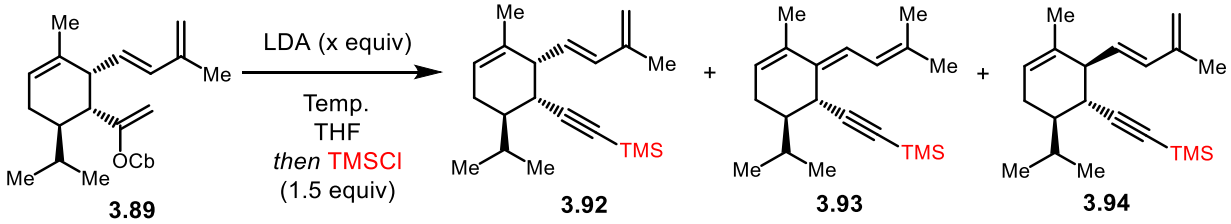
Next, secondary boronate **3.84** was subjected to the Aggarwal-modified Zweifel olefination with vinyl carbamate **3.88** (Scheme 3.21).[42] After formation of the tetracoordinated boron "ate" complex, the addition of iodine induces the 1,2-metalate shift to form intermediate **3.91**, which undergoes an *E2* elimination to deliver the alkenyl carbamate product **3.89** with excellent yield and stereospecificity.

Scheme 3.21. Zweifel Olefination



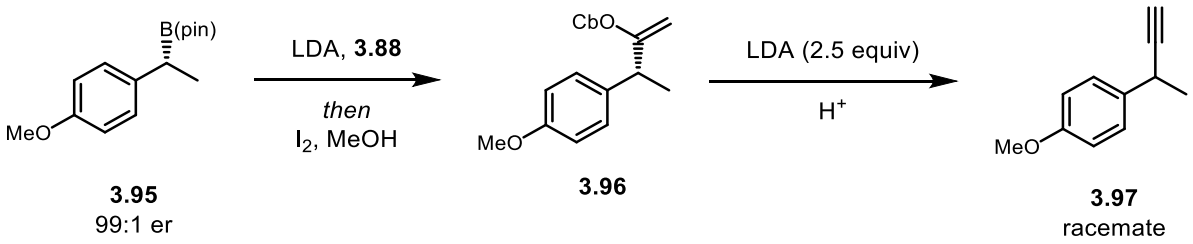
Compound **3.89** was subjected to an elimination reaction with LDA to furnish the desired alkyne **3.92** (Table 3.4). Compound **3.92** was obtained with 60% NMR yield (entry 3, Table 3.4), following the condition reported by the Aggarwal group.[42] However, we also observed the generation of triene **3.93** and epimerized side product **3.94**, generated from the undesired post-reaction deprotonation of the doubly allylic C—H bond. Interestingly, Aggarwal also observed similar side reactions while optimizing the alkynylation with benzylic boronate **3.95** (Scheme 3.22).[42] Complete racemization was observed for product **3.97** after treating the carbamate intermediate **3.96** with LDA. More importantly, from our standpoint, side products **3.93** and **3.94** were not separatable from **3.92**, which was detrimental for later reactions. To prevent the undesired deprotonation, we reduced the equivalents of LDA (entry 1 and entry 2). To our delight, two equivalents of LDA were efficient to afford the product **3.92** with increased yield and chemoselectivity. Simplify the reaction set-up by adding the LDA at 0 °C resulted in a diminished yield (entry 4).

Table 3.4. Optimizations of Elimination Reaction



entry	x	Temp (°C)	Conversion (%)	% NMR yield		
				3.92	**3.93**	**3.94**
1	1.7	-78 to rt	82%	75%	None	Trace
2 (*Optimized*)	2	-78 to rt	95%	82%	Trace	10%
3	2.5	-78 to rt	100%	60%	15%	20%
4	2	0 to rt	95%	60%	25%	8%

Scheme 3.22. Deprotonation Observed by Aggarwal



3.95
99:1 er

3.96

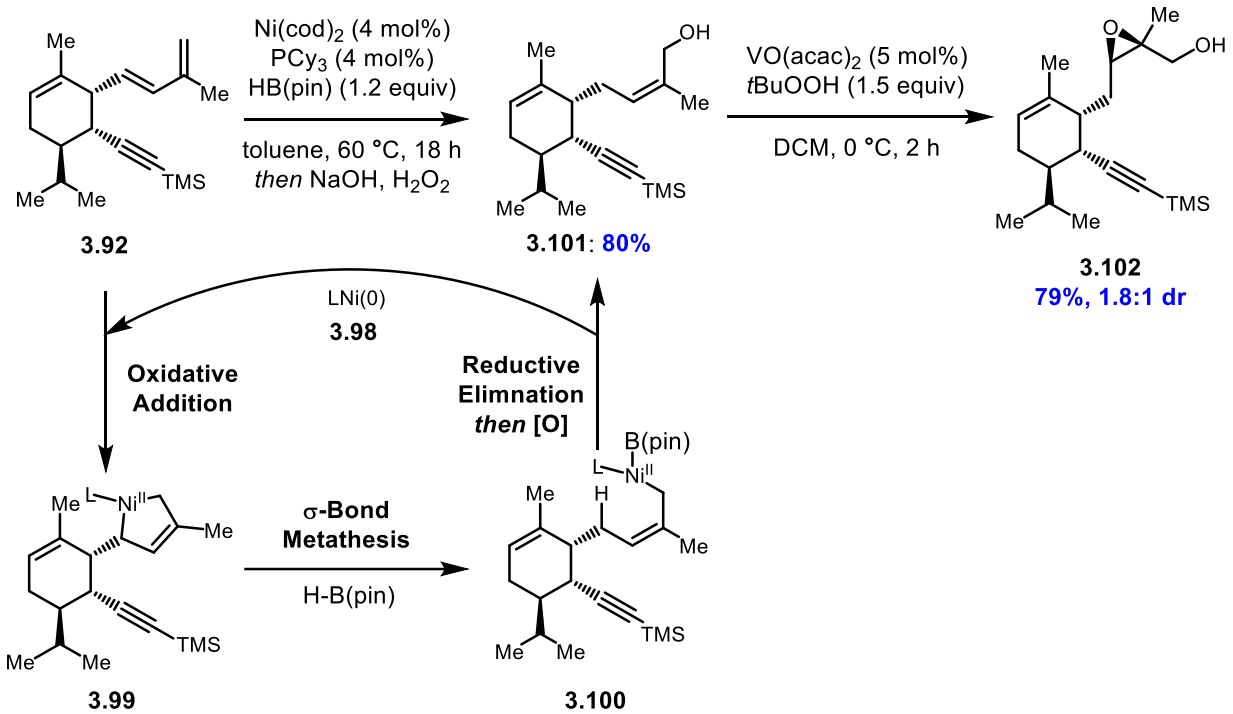
3.97
racemate

Subsequently, alkyne **3.92** was converted to allylic alcohol **3.101** through a nickel-catalyzed 1,4-hydroboration and boron-oxidation process following conditions developed by the Morken group (Scheme 3.23).[46] In this reaction, the Ni(0) species **3.98** will first undergo oxidative addition with the diene to generate the metallacyclopentane intermediate **3.99**, which then undergoes a σ-bond metathesis with HBpin to generate allylic nickel intermediate **3.100**. Reductive elimination of **3.99** regenerates Ni(0) species **3.98** and furnishes the allylic boronate, which could then be oxidized to the allylic alcohol product **3.101** with sodium hydroxide and hydrogen peroxide. One drawback of this reaction is that the nickel source, $Ni(cod)_2$, is air-sensitive and must be handled inside the glove box. We thus investigated the reaction with air-stable and less expensive nickel precursor $Ni(PCy_3)_2Cl_2$. Even through reaction with $Ni(PCy_3)_2Cl_2$ could deliver the product, the prerequisite catalyst requires activation with *n*-BuLi led to poor reproducibility as the *n*-BuLi can also react with minor impurities in substrate **3.93**. As a result, we decided to retain the condition with $Ni(cod)_2$. One notable feature of this sequence is that the alkynyl trimethyl silane remained intact in the boron-oxidation condition.

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

Vanadium-catalyzed epoxidation[47] of **3.101** was conducted to deliver compound **3.102**; however, the diastereoselectivity was unsatisfying (Scheme 3.23). This is not surprising since the existing stereoegenic centers are far from the allylic alcohol moiety, resulting in poor substrate control. At this point, however, epoxide **3.102** was carried forward to the following reactions as a mixture of two diastereomers.The absolute configuration of the major diastereomer **3.102** was first assigned by comparison of ^{1}H NMR chemical shifts with related structures of known configuration,[33,34] which was further supported by outcome using of Sharpless epoxidation reaction as discussed in the following section.

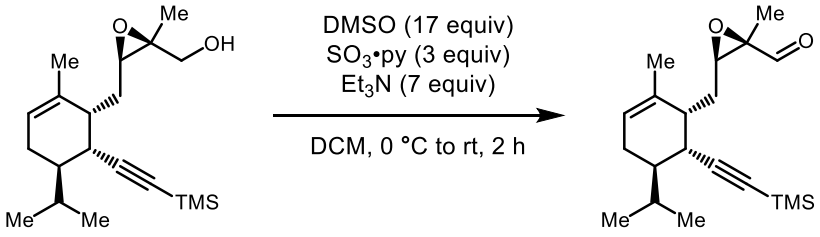
Scheme 3.23. 1,4-Hydroboration/Oxidation and Epoxidation



(47) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137. (b) Marshall, J. A.; Van Devender, E. A. *J. Org. Chem*. **2001**, *66*, 8037–8041.

Oxidation of alcohol **3.102** with the Parikh-Doering reaction[48] afforded aldehyde **3.103** in good yield (Scheme 3.24). Other oxidation methods, for example: the Ley oxidation[49], were also efficient for this transformation. Aldehyde **3.103** was then converted to the *cis*-alkenyl iodide **3.104** under the Stork-Zhao olefination condition[43] (Scheme 3.25). It is noteworthy that under these conditions, we could always observe about 15% of the terminal alkyne side product **3.105**, which presumably was generated from the elimination of **3.104** with base. We hypothesized the adjacent epoxide moiety polarizes the alkene C—H bond and thus facilitates this side reaction. Careful control of the reaction time was therefore critical: running the reaction for 40 minutes led to a lower yield of the desired product with more alkyne generated. In contrast, shortening the reaction time to 25 minutes resulted in incomplete conversion of the starting material. The addition of HMPA significantly boosted the diastereoselectivity and increased the reproducibility of the reaction.

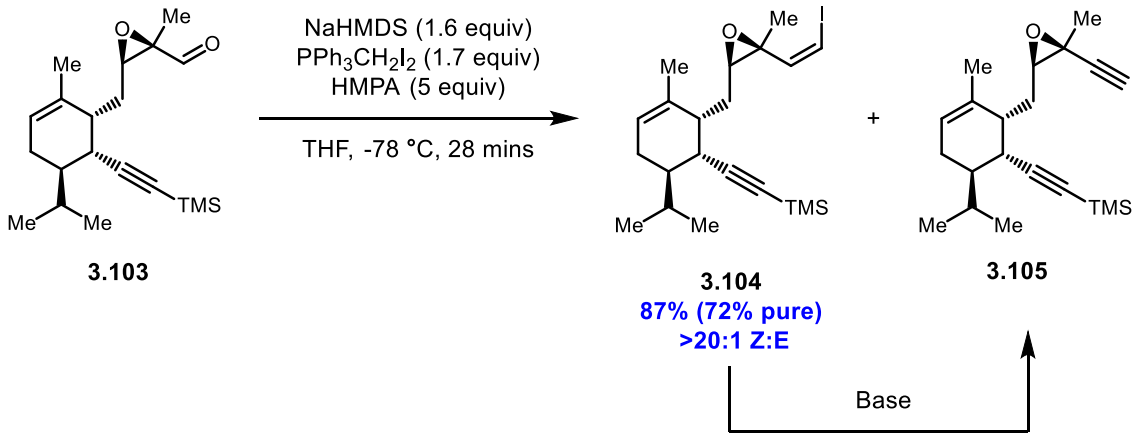
Scheme 3.24. Parikh-Doering Oxidation



3.102 **3.103** **93%**

(48) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
(49) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **2002**, *1994*, 639–666.

Scheme 3.25. Stork-Zhao-Wittig Olefination



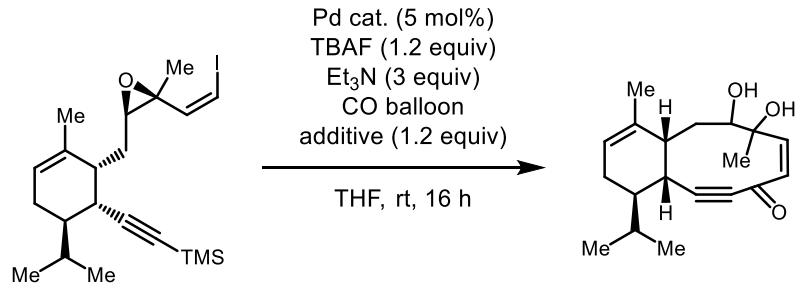
As the alkyne **3.105** was not separatable from the alkenyl iodide **3.104**, we subjected the mixture to a palladium-catalyzed carbonylative Sonogashira reaction. Following a literature procedure,[50] the desired product was delivered in 18% yield (Table 3.5, entry 1). Interestingly, the product was isolated as diol **3.112**, where the epoxide had been hydrolzed. More importantly, we observed that unreacted starting material was recovered as epoxide. These observations suggested that the epoxide would be more labile after the 10-membered ring was formed, possibly due to ring strain. Next, we added benzoic acid in the hope that it would act as a nucleophile and facilitate epoxide opening. While we observed increased yield of desired product **3.112** (entry 2), no benzoate was observed. Presumably, the benzoate could be formed at first and was hydrolyzed during the work-up. The function of benzoic acid could be very complicated: in addition to opening the epoxide, it could also stabilize the catalyst by serving as a ligand or it might change the polarity of reaction environment. To further optimize the reaction, we investigated different phosphine ligands (entry 3 to 5), palladium sources (entry 6), and carboxylic acid additives (entry 7, 8). The

(50) Arcadi, A.; Cacchi, S.; Marinelli, F.; Pace, P.; Sanzi, G. *Synlett* **1995**, *1995*, 823–824.

combination of $Pd(OAc)_2$/Xantphos with formic acid was ultimately found to afford the product with a synthetically useful yield (entry 8).

The mechanism for the carbonylative coupling is proposed in Scheme 3.26. After oxidative addition with palladium, intermediate **3.106** could undergo CO insertion and transmetalation with the silyl alknyne to afford the intermediate **3.108**. Next, reductive elimination followed by epoxide opening delivers the product. It is also possible that the epoxide is opened before reductive elimination to release the ring strain.

Table 3.5. Optimizations of Carbonylative Sonogashira Reaction



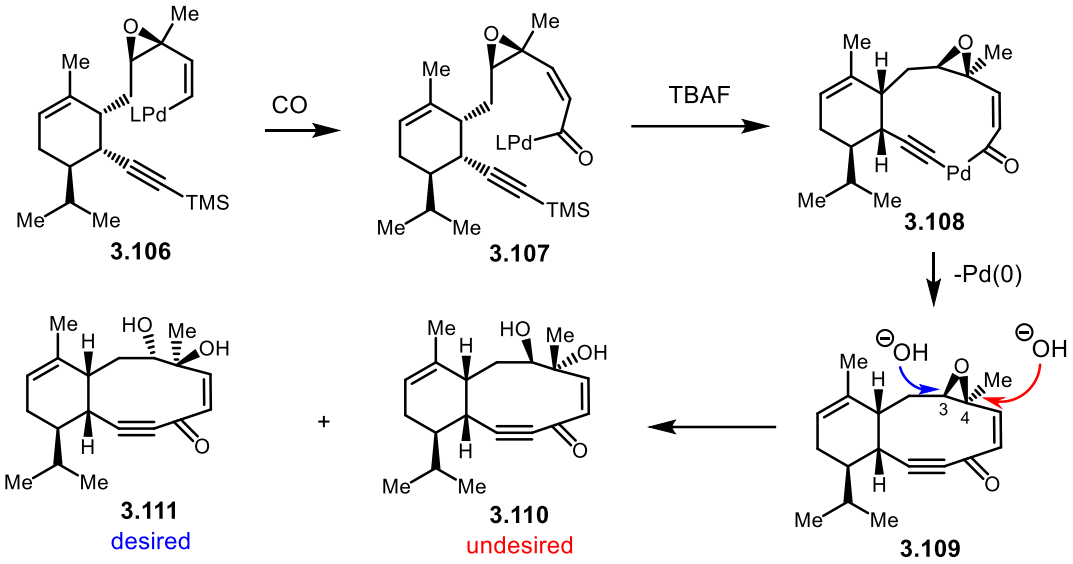
3.104
(contain 20%~30% **3.105**)

3.112

entry	Pd cat.	Additive	Yield*
1	$PdCl_2$/Xantphos	NA	18%
2	$PdCl_2$/Xantphos	Benzoic Acid	30%
3	$PdCl_2/PPh_3$	Benzoic Acid	<5%
4	$PdCl_2$/dppp	Benzoic Acid	<5%
5	$PdCl_2$/*rac*-Binap	Benzoic Acid	20%
6	$Pd(OAc)_2$/Xantphos	Benzoic Acid	41%
7	$Pd(OAc)_2$/Xantphos	Acetic Acid	37%
8 (*Optimized*)	$Pd(OAc)_2$/Xantphos	Formic Acid	50%

*Yield is adjusted based on the purity of starting material

Scheme 3.26. Proposed Mechanism

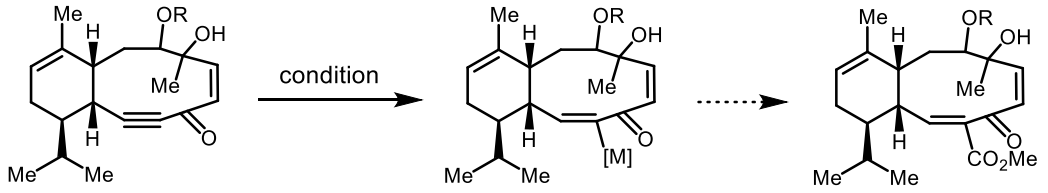


When diastereomerically pure starting material **3.104** was utilized, the diol **3.112** was also isolated as a pure diastereomer, which indicated that the epoxide opening process is stereospecific. Based on the reaction conditions, it seems that the epoxide opening occurs at either C-3 or C-4 position selectively, through an S_N2 type mechanism. Even though the C-3 position is less sterically hindered, the contra steric epoxide opening at tertiary C-4 is also reasonable as this site is an allylic position. We attempted to determine the configuration of the diol by X-ray, but we have not been able to obtain single crystal of **3.112**. On the other hand, 1D and 2D NMR spectra of **3.112** were not very informative. At this stage, we cannot rule out the possibility of either mechanism. And, so far, the major diastereomer has not been identified.

With presumed alkyne in hand, hydrometallation conditions were examined to generate intermediate **3.114**, which could potentially react with methyl chloroformates to establish the desired ester functionality (Scheme 3.25). The starting material was found to be unreactive under

radical-induced hydrostannation [51], hydrozirconation [52], and hydroalumination [53] reactions. Hydrocupration with Stryker reagent[54] only afforded side product **3.116**, where the copper hydride was added to the alkene (Scheme 3.27). To our delight, the palladium-catalyzed hydrostannation[55] could be utilized to deliver the desired product **3.117** with a moderate yield (Scheme 3.28). The resulting alkenyl stannane **3.117** was chromatographically stable and could be isolated from the remaining starting materials.

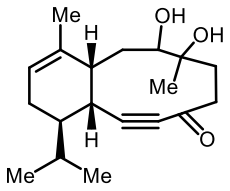
Scheme 3.27. Unsuccessful Hydrometallation of alkynes



3.112: R = H
3.113: R = TMS

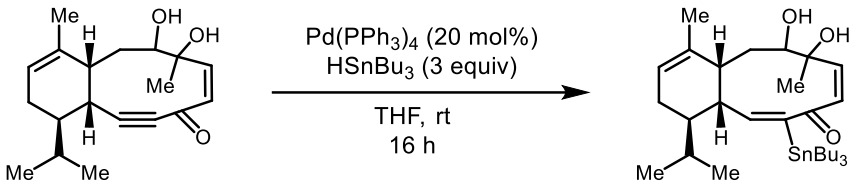
3.114

3.115

R = TMS		R = H	
condition	**Result**	**condition**	**Result**
Schwartz's reagent (2.1 equiv) THF, rt	no conversion	AIBN (0.1 equiv) *or* Et_3B (0.5 equiv) $HSnBu_3$ (2 equiv) toluene, 80 °C	no conversion
DIBAL (2.2 equiv) HMPA (3 equiv) THF, rt	no conversion	stryker reagent (0.5 equiv) toluene, rt	 **3.116** observed by NMR

(51) (a) Nativi, C.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 820–826. (b)Nozaki, K.; Oshima, K.; Uchimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547−2549. For a review of hydrostannation of alkyne: Alami, M.; Hamze, A.; Provot, O. *ACS Catal.* **2019**, *9*, 3437–3466.
(52) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679–680.
(53) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1037–1040.
(54) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293.
(55) Rossi, R.; Carpita, A.; Cossi. P. *Tetrahe*dr*on Lett.* **1992**, *33*, 4495-4498.

Scheme 3.28. Pd-Catalyzed Hydrostannation of Alkyne **3.112**

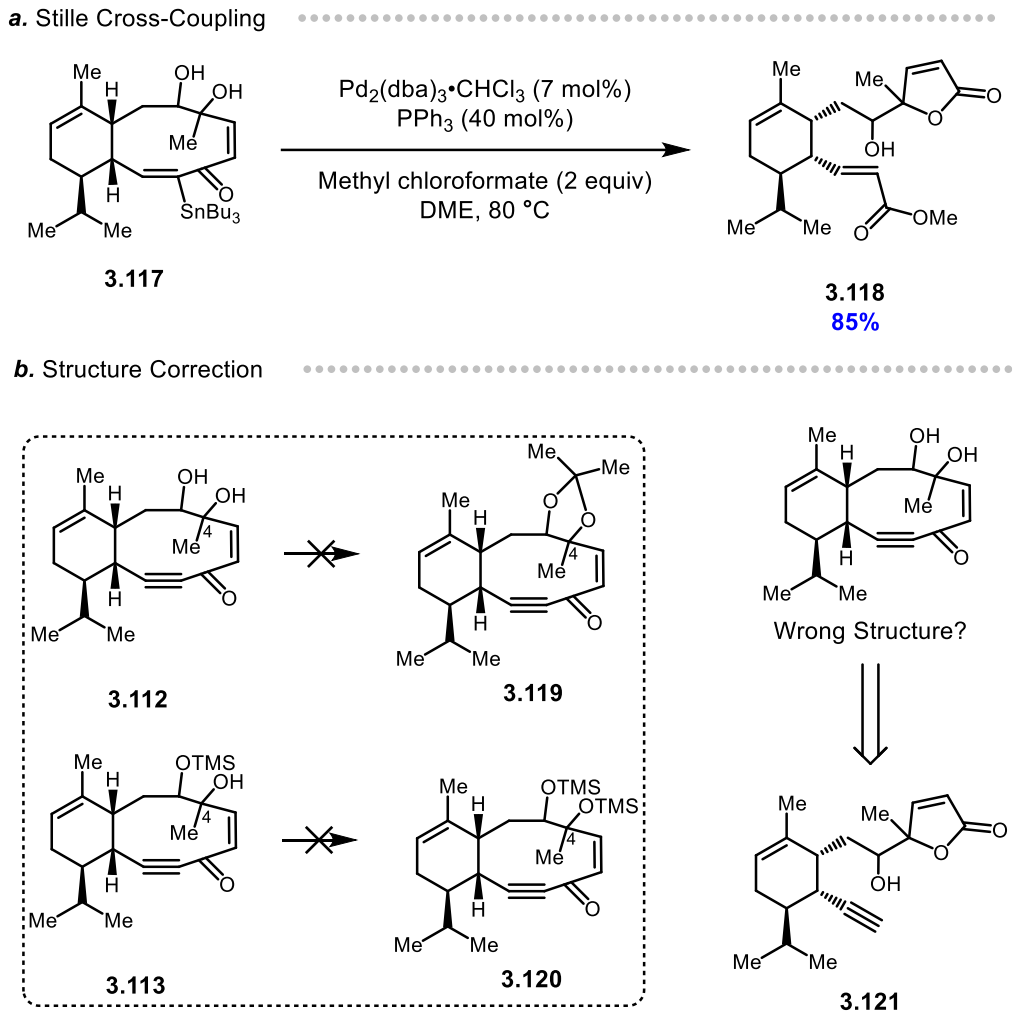


3.112 **3.117**
50%

With presumed alkenyl stannane **3.117** in hand, Stille cross-coupling[56] with methyl chloroformate was conducted (Scheme 3.29a). From this reaction, the product was identified as the lactone species **3.118**. This puzzling result brought the identity of **3.117** into question. Along with the formation of **3.118**, attempted protections of the tertiary C-4 alcohol by either forming the acetonide or converting it to the silyl ether failed (**3.119**, **3.120**). Collectively, these observations suggest C-4 alcohol might not exist (Scheme 3.29b). Collectively, it is possible that lactone species **3.121 is** the actual product from the Sonogashira reaction. As we were unable to obtain a single crystal, we cannot rule out the possibility that the 10-membered ring compound was formed, but decomposed to the lactone during the hydrostannation or Stille cross-coupling reactions. Accordingly, we decided to synthesize compound **3.121** by another route and compare its spectra with compound **3.112** to identify the structure of compounds generated by this sequence.

(56) Fujiwara, S.; Cadou, R.; Yamaoka, Y.; Takasu, K.; Yamada, K. *Eur. J. Org. Chem.* **2015**, *2015*, 1264–1272.

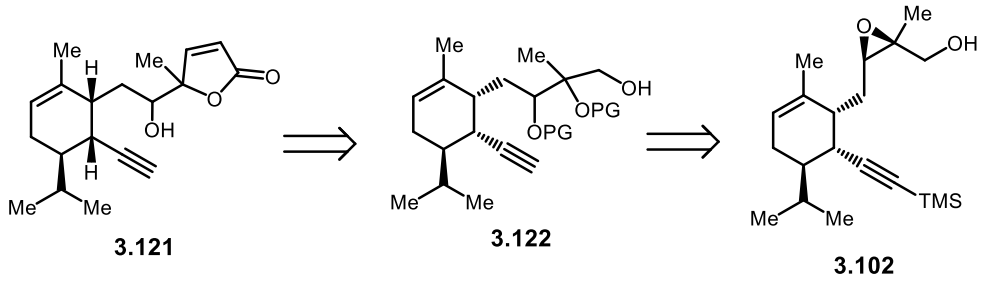
Scheme 3.29. Stille Cross-Coupling and Structure Correction



3.4.3 Synthesis of the Lactone Intermediate

A brief retrosynthetic analysis was proposed (Scheme 3.30). Taking advantage of the previously established synthetic route, lactone **3.121** could be derived from triol intermediate **3.122**, which could be synthesized from the epoxide opening reaction of readily available epoxide **3.102**.

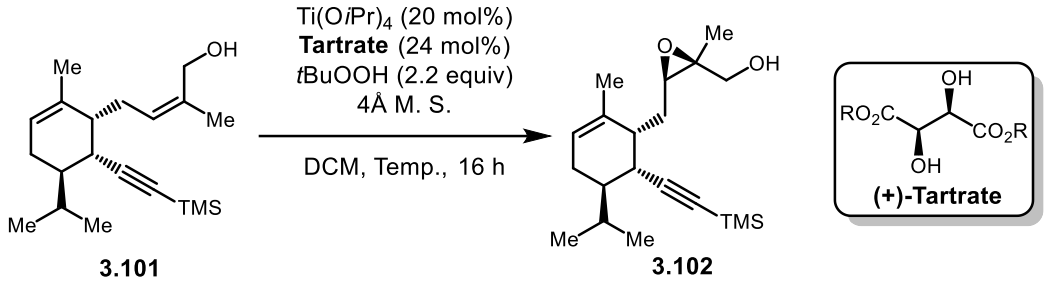
Scheme 3.30. Proposed Synthetic Route of Lactone **3.121**



We optimized the epoxidation of **3.101** with Sharpless asymmetric epoxidation (SAE) conditions [57] to synthesize **3.102** with higher diastereoselectivity (Table 3.6), The overall selectivity was low with standard epoxidation conditions (entry 1-4), which was also observed by Magnus with similar substrates[34]. Specifically, the less bulky (+)-dimethyl tartrate was found to be the optimal ligand and afforded the product with 4.3:1 dr, favoring the α-epoxide (entry 4). While the opposite enantiomer (-)-DMT is used, the β-epoxide is produced as the major product with diminished dr (entry 5). The background reaction without tartrate afforded the product with 1.5:1 dr, which is consistent with previous results using vanadium-catalysis. (entry 6). Even though lowering the reaction temperature led to higher diastereoselectivity, significant diminution of reactivity was observed (entry 7-8).

(57) Finn, M. G.; Sharpless, K. B. *Asymm. Synth.* **1985**, *5*, 247.

Table 3.6. Optimizations of Alkene Epoxidation with Sharpless' Conditions



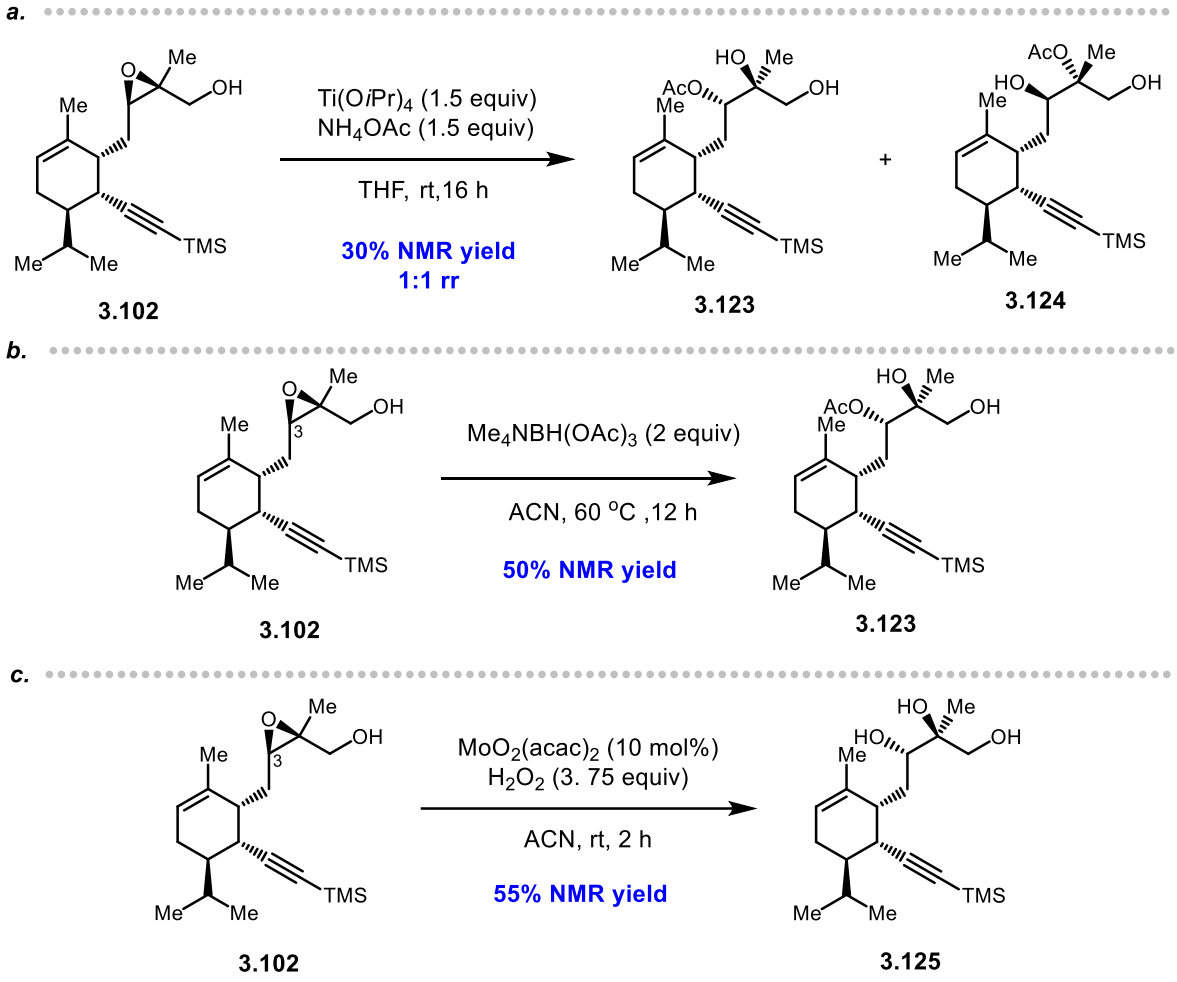
entry	Tartrate	Temp. (°C)	Conversion	dr
1	(+)-Diisopropyl Tartrate	-20	full	3:1
2	(+)-Diethyl Tartrate	-20	full	4:1
3	(+)-Dibenzyl Tartrate	-20	full	4:1
4 (*Optimized*)	(+)-Dimethyl Tartrate	-20	Full (76% i.y.)	4.3:1
5	(-)-Dimethyl Tartrate	-20	full	1:1.6
6	None	-20	full	1.5:1
7	(+)-Dimethyl Tartrate	-35	50%	5:1
8	(+)-Dimethyl Tartrate	-78	10%	N.A.

Next, we planned to utilize the free alcohol as a directing group to conduct the epoxide opening reaction in a regioselective and diastereospecific fashion. First, we investigated conditions developed by the Sharpless group.[58] With Ti(O*i*Pr)$_4$ as the Lewis acid and ammonium acetate as the nucleophile (Scheme 3.31a), low yield was observed, and the product was isolated as a mixture of two regioisomers **3.123** and **3.124**. We then examined the ring opening with $NH_4BH(OAc)_3$,[59] which could first react with the hydroxyl group and deliver the acetate intramolecularly to open the epoxide at the C-3 position (Scheme 3.31b). Product **3.123** was obtained with 50% NMR yield and in a diastereospecific manner. However, we failed to improve the yield by changing the solvent or adjusting the temperature. On the other hand, the molybdenum-catalyzed ring-opening

(58) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557–1560.
(59) Honda, T.; Mizutani, H. *Heterocycles* **1998**, *9*, 1753–1757.

hydration developed by the Wang group[60] could deliver triol **3.125** in a stereospecific fashion, a moderate yield was observed as well (Scheme 3.31c). While this route appeared promising, selective functionalization of the three alcohols in **3.125** could be challenging.

Scheme 3.31. Investigations for Epoxide Opening Reactions



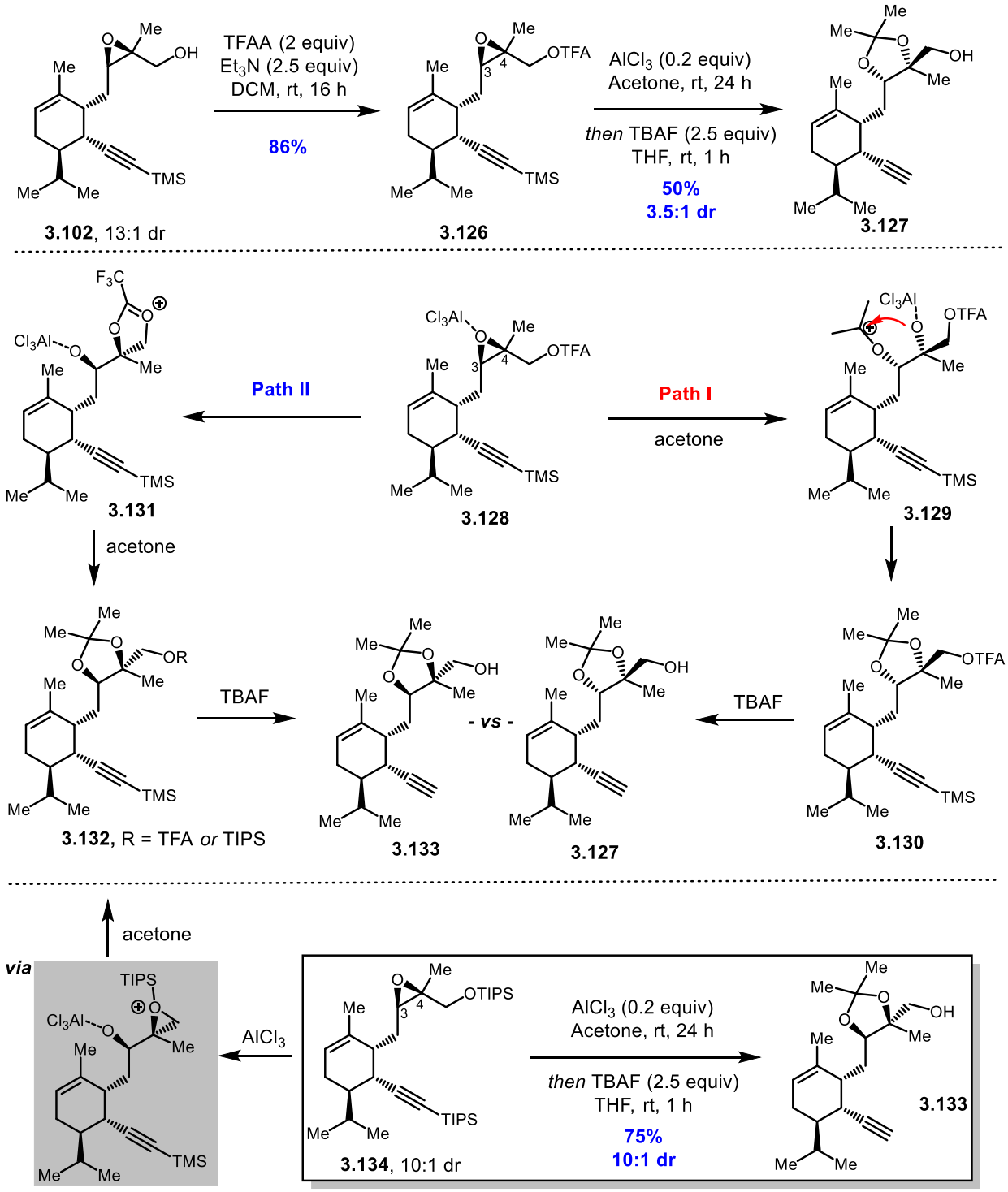
Alternatively, epoxide **3.102** was converted to acetonide **3.127** following the protocol developed by Díez[61] (Scheme 3.32). Even through moderate yield and stereoselectivity were

(60) Fan, P.; Su, S.; Wang, C. *ACS Catal.* **2018**, *8*, 6820–6826.
(61) Díez, D.; Beneitez, M. T.; Marcos, I. S.; Garrido, N.; Basabe, P.; Urones, J. G. *Tetrahedron: Asymmetry* **2002**, *13*, 639–646.

observed, the C-3 and C-4 hydroxy groups in the product **3.127** were already protected by the formation of acetonide. Unlike diol **3.123** and triol **3.125**, there is only one free alcohol in **3.137**, which could simplify the following reactions. Slight erosion of the diastereomeric ratio from **3.102** to **3.127** could be attributed to the two different reaction pathways, as shown in Scheme 3.24. In the pathway I with acetone as the nucleophile, the epoxide could open from the C-3 position in an S_N2 manner to afford intermediate **3.129**, which could then undergo cyclization to deliver acetonide **3.130**. [62] Alternatively, an intramolecular ring opening could occur to furnish intermediate **3.131**, which could then react with acetone to afford acetonide **3.132**. In this pathway, undesired diastereomer **3.133** would be obtained after deprotection. Even though pathway I could be favored due to the electron-withdrawing nature of the trifluoroacetate group (TFA), pathway II could not be completely inhibited, leading to the generation of undesired diastereomer. Notably, the addition of TBAF removes the silyl group in the alkyne and converts the trifluoroacetate to free alcohol. The selectivity for epoxide opening could be altered by changing the protecting group in the alcohol, as shown in Scheme 3.29 bottom equation. Epoxide **3.134** was converted to undesired acetonide **3.133** with excellent diastereoselectivity when the electron donating TIPS group was used. In this scenario, pathway II was the dominant pathway as the nucleophilicity of the ether oxygen was strengthened.

(62) Colvin, E. W.; Robertson, A. D.; Wakharkar, S. *J. Chem. Soc., Chem. Commun*. **1983**, 312–314

Scheme 3.32. Proposed Mechanism for Acetalization



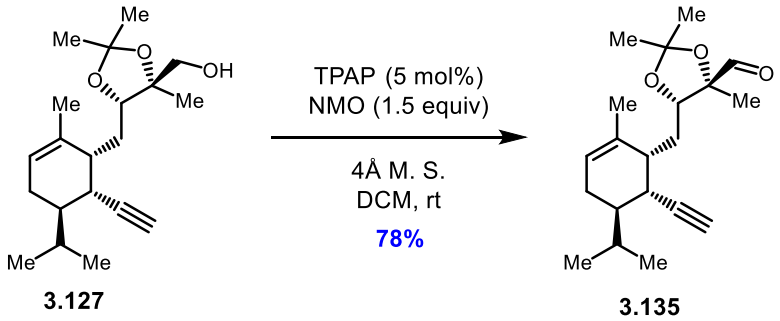
Alcohol **3.127** was oxidized to corresponding aldehyde **3.135** through Ley-Griffith oxidation (Scheme 3.33a).[48] Of note, the Parikh–Doering oxidation was not compatible with substrate **3.127**; low conversion of the starting material was observed. Then, aldehyde **3.135** was subjected to the Still-Gennari Olefination[63] to furnish *cis*-alkenyl ester **3.137** (Scheme 3.33b). Moderate yield and *Z/E* selectivity were observed. Lastly, lactone **3.138** was furnished by deprotection and lactonization under acidic conditions (Scheme 3.33c).

The ^{1}H NMR and ^{13}C NMR spectra of **3.138** were compared with the product of the Sonogashira coupling (**3.112**) to identify the correct structure (Scheme 3.33c). Identical spectra[64] were observed for both ^{1}H NMR and ^{13}C NMR, indicating that the correct structure of the product from the Sonogashira coupling is lactone **3.112**. Notably, the major diastereomer **3.138** isolated from this route corresponds to the minor diastereomer isolated from the Sonogashira coupling, which indicates that the epoxide was opened at the tertiary C-4 position during the Sonogashira reaction.

(63) Still, W.C.; Gennari, C., *Tetrahe*dr*on Lett.* **1983**, *24*, 4405.
(64) Chemical shifts and coupling constants are identical for each diastereomer, the ratio of two diastereomers is different, see experimental section of **3.138** for more detail.

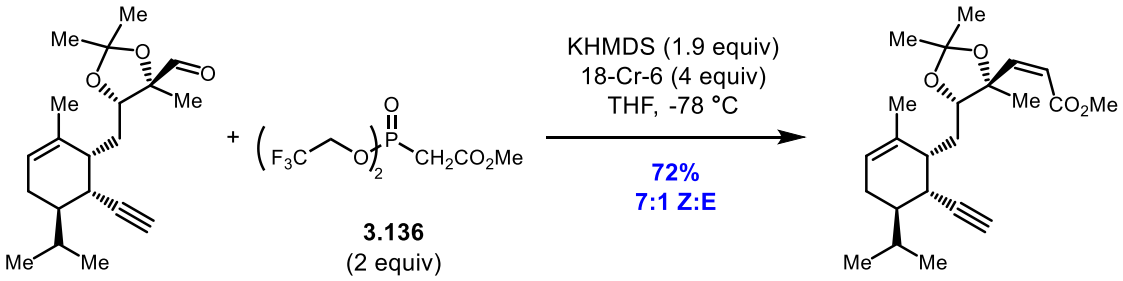
Scheme 3.33. Completion of the Lactone Synthesis and Structure Correction

a. Ley Oxidation



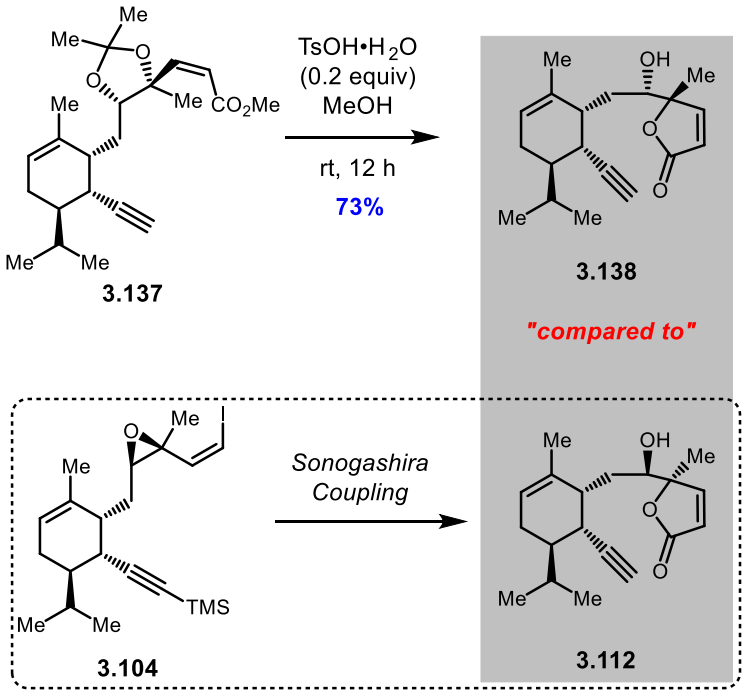
3.127 **3.135**

b. Still-Gennari Olefination



3.135 **3.136** (2 equiv) **3.137**

c. Lactonization and Structure Correction of **3.112**



3.137 **3.138** ***"compared to"*** **3.104** **3.112**

*Identical NMR spectra observed compared to the minor diastereomer of **3.112***

3.5 Progress towards Total Synthesis of Sarcodictyins (2nd Attempt)

3.5.1 Learning from the Failure: Mechanistic Proposals of Sonogashira Coupling

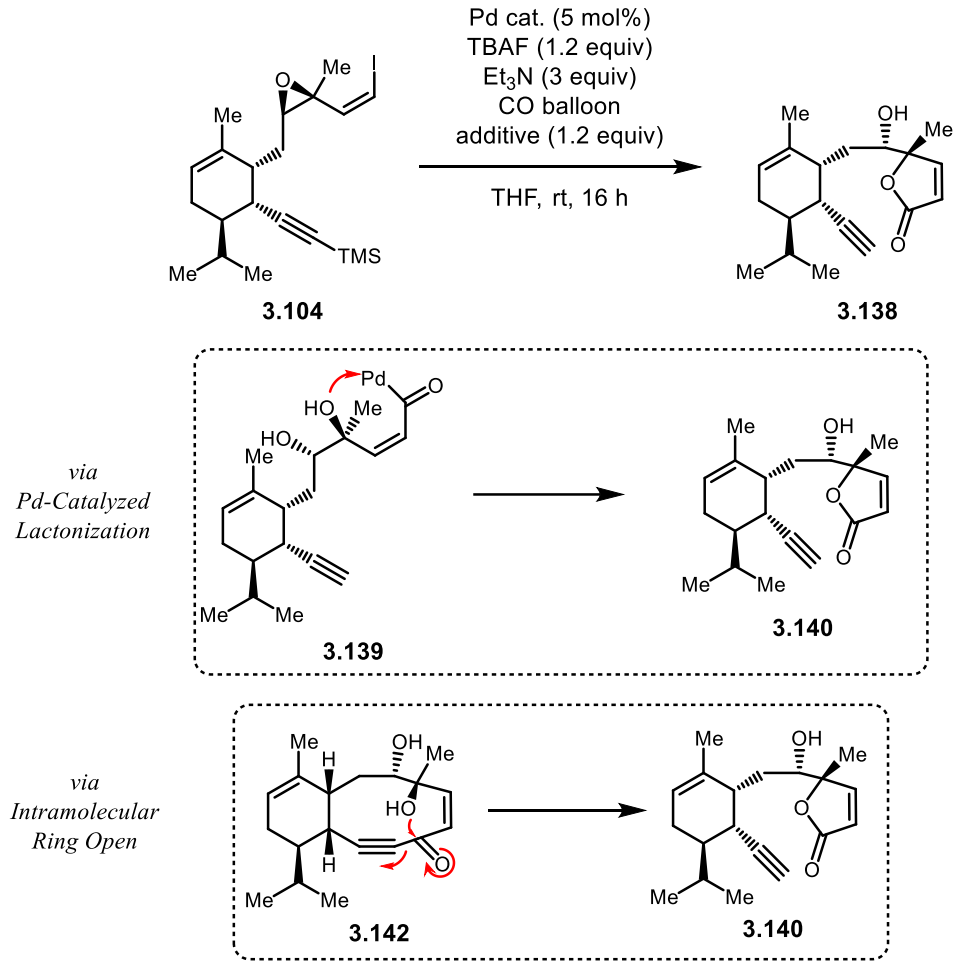
Even though synthetic route through the carbonylative Sonogashira reaction did not provide the correct product, we were still curious about the reaction mechanism. It was not apparent that the product **3.138** could be generated from the alkenyl iodide species **3.104**. More importantly, better understanding of the reaction mechanism could benefit future investigation of alternative cyclization approaches. Two plausible reaction mechanisms were proposed (Scheme 3.34). Instead of transmetalation with the silyl-protected alkyne, the palladium complex could undergo ligand exchange with *in situ* generated tertiary alcohol (**3.139**), and afford the lactone product **3.140** through reductive elimination. This scenario might operate if the transmetalation between the alkyne and palladium is challenging. Alternatively, 10-membered ring intermediate **3.142** could be generated by the Sonogashira reaction. However, intermediate **3.142** might be structurally unstable and decompose to the lactone species **3.140** under the reaction conditions or during the work-up. Collectively, the failure of the carbonylative Sonogashira reaction revealed the potential obstacles in synthesizing the alkynyl ketone moiety within a 10-membered ring skeleton. Therefore, we decided to revise our synthetic route to exclude the synthesis of alkynyl ketone intermediate.

As a revised route, we first planned to conduct a Dieckmann condensation[65] from intermediate **3.143** to construct the 10-membered ring (Scheme 3.35). Alkyl ester **3.144** could be converted to the desired natural product through desaturation. Additionally, cyclization through an alkenyl anion intermediate **3.145** was proposed. Compound **3.145** could be synthesized from the

(65) Khademi, Z.; Heravi, M. M. *Tetrahe*dr*on* **2022**, *103*, 132573.

corresponding alkynyl ester by hydrometallation. After the synthesis of **3.146**, natural product sarcodicyins could be furnished by the installment of urocanic ester.

Scheme 3.34. Mechanistic Proposals for Sonogashira Reaction

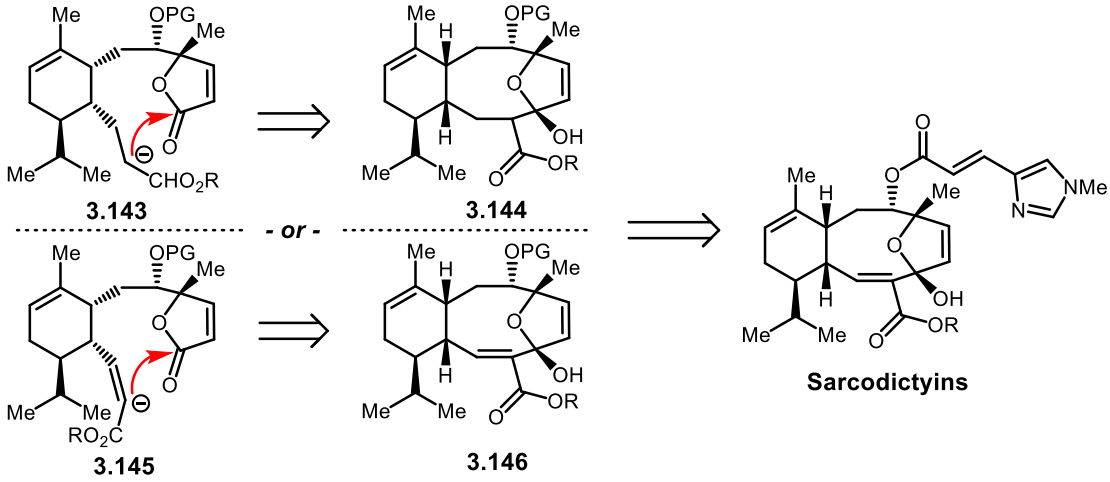


3.5.2 Retrosynthetic Analysis

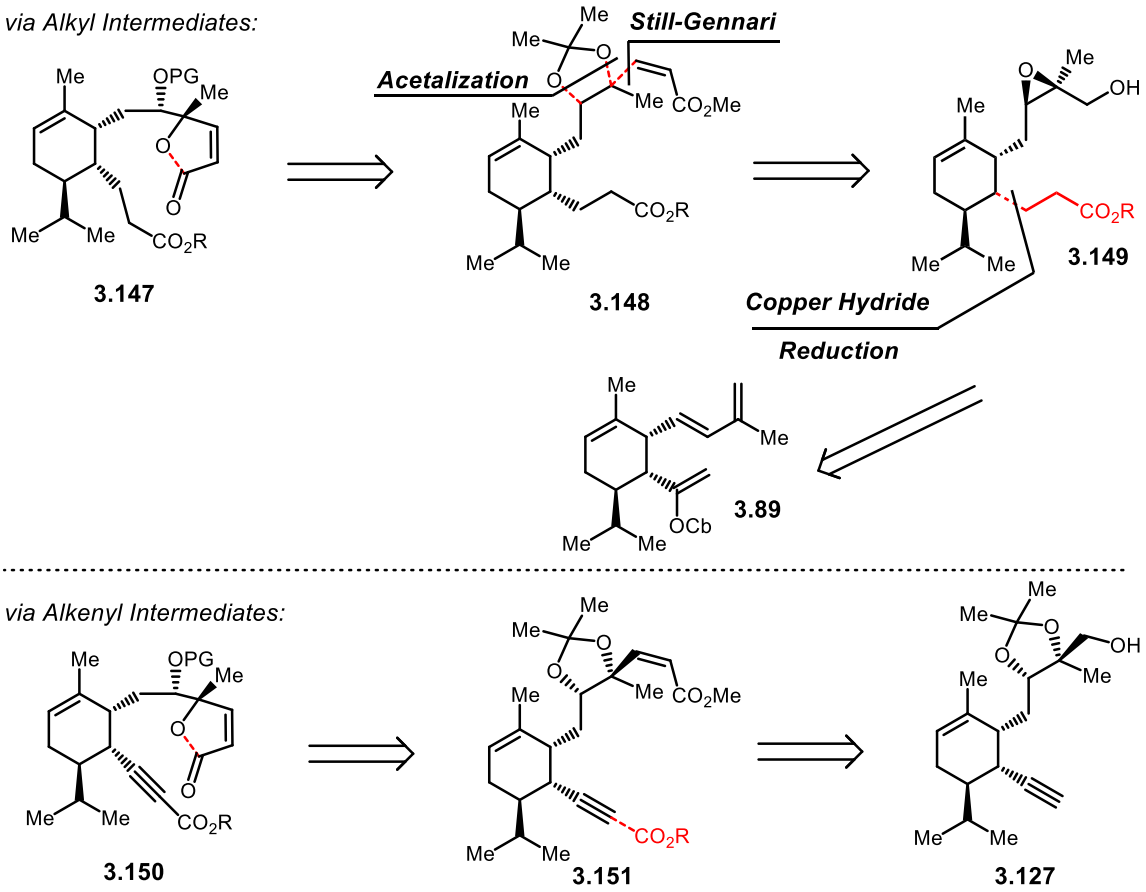
The retrosynthetic analysis for cyclization precursors **3.147** and **3.150** is proposed in Scheme 3.37. The alkyl ester **3.147** could be derived from the epoxide **3.149** through previously established lactonization, Still-Gennari olefination, and acetalization reactions. The alkyl ester moiety in **3.149** could be synthesized by copper hydride-promoted reduction of the corresponding alkynyl ester, which could be obtained from the elimination of **3.89**. On the other hand, precursor

3.150 for hydrometallation could be synthesized from the available intermediate **3.127** through the functionalization of the terminal alkyne.

Scheme 3.35. Synthetic Proposals to Construct the 10-Membered Ring



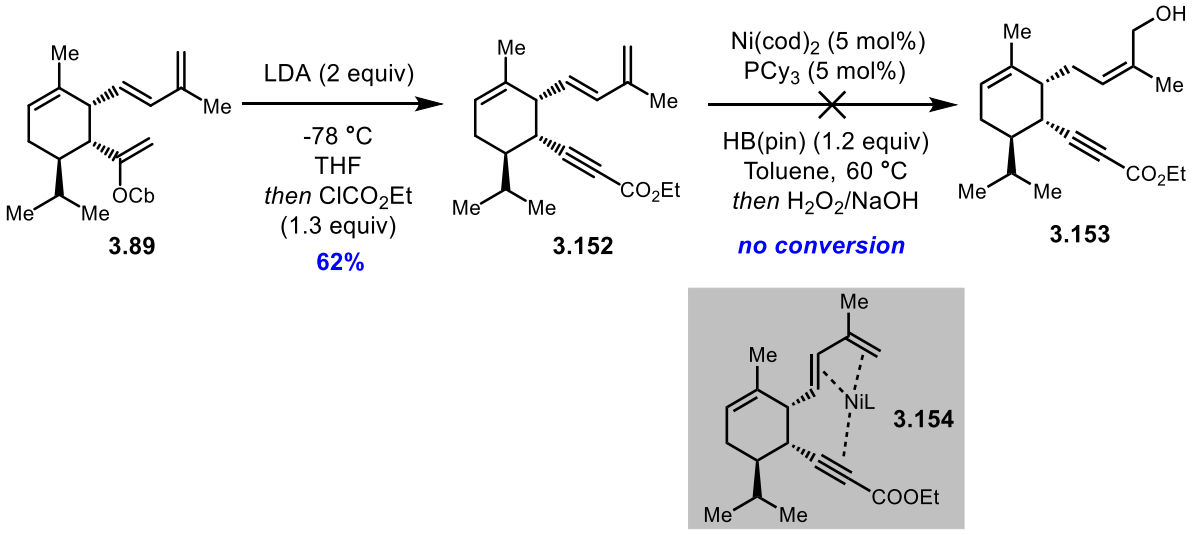
Scheme 3.37. Retrosynthetic Analysis of Cyclization Precursors



3.5.2. Progress towards Cyclization by a Dieckmann Condensation

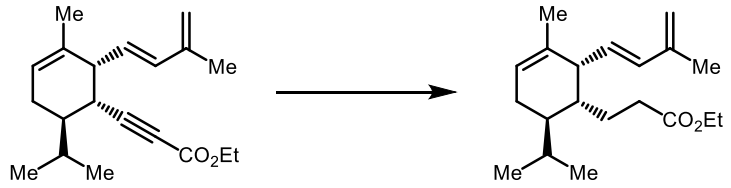
To initiate studies of the Dieckmann-based route to sarcodicyin, the alkenyl carbamate compound **3.89** was subjected to the elimination reaction with LDA, and the resulting alkynyl anion was trapped with ethyl chloroformate to deliver the alkynyl ester **3.152** (Scheme 3.38). The previously discussed alkene isomerization problem was more severe with this substrate as the alkynyl ester is more electron-withdrawing than the trimethylsilyl alkyne, which could increase the acidity of the adjacent double allylic proton. As a result, the yield of **3.152** was relatively low compared to the analogue reactions with chlorotrimethylsilane as electrophile. Next, when **3.152** was used in the nickel catalyzed 1.4-hydroboration reaction, no conversion of the starting material was observed. We hypothesized that the alkynyl ester moiety could serve as a ligand for nickel, which would poison the catalyst and prevent the reaction with diene. This problem might be solved if we reduced the alkyne to the alkane.

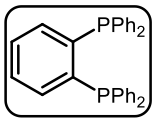
Scheme 3.38. A New Challenge in 1,4-Hydroboration Reaction



To study the reduction of alkynyl ester, various metal hydride reagents were examined. The results are summarized in Scheme 3.39. The reactivity of metal hydrides generated *in situ* from $NaBH_4$ was complicated: copper hydride[66] did not react with the **3.152**, while nickel hydride[67] and cobalt hydride[68] appeared to be too reactive as the diene moieties were also reduced under reaction conditions. To our delight, the copper hydride reagent[69] generated from polymethylhydrosiloxane (PMHS) exhibited exceptional reactivity and chemoselectivity to furnish the desired product **3.155**, despite the limitation that the unreacted PMHS coeluted with the desired product. To address this, a large excess of sodium hydroxide was added to help depolymerize the PMHS and facilitate its removal.

Scheme 3.39. Reduction of Alkynyl Ester

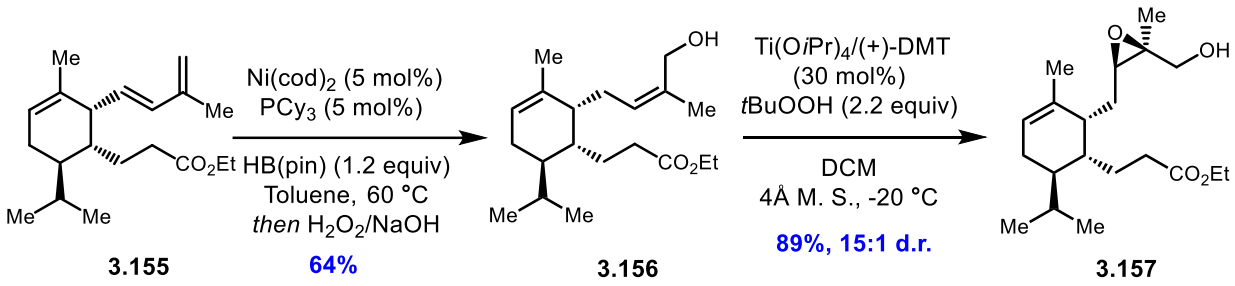


Condition	Result	Condition	Result
$CuCl_2$ (1 equiv) $NaBH_4$ (4 equiv) MeOH, 0 °C	**no conversion**	$CoCl_2$•$6H_2O$ (0.2 equiv) $NaBH_4$ (4 equiv) EtOH, rt	**diene reduced**
$NiCl_2$•$6H_2O$ (0.3 equiv) $NaBH_4$ (4 equiv) H_2 balloon MeOH, 0 °C to rt	**diene reduced**	$Cu(OAc)_2$/Ligand (8 mol%) PMHS (6 equiv) *t*BuOH (4 equiv) toluene, rt, 16 h *then* 3N NaOH, rt, 24 h	 **92%**

(66) Saitman, A.; Sullivan, S. D. E.; Theodorakis, E. A. *Tetrahedron Letters* **2013**, *54*, 1612–1615.
(67) Xu, H.; Li, S.-N.; Yang, Y.-Q.; Zhou, Y.; Yang, Q.-Z.; Bian, Q.-H.; Zhong, J.-C.; Wang, M. *Tetrahedron: Asymmetry* **2014**, *25* (20), 1372–1375.
(68) Jagdale, A. R.; Paraskar, A. S.; Sudalai, A. *Synthesis* **2009**, *2009*, 660–664.
(69) Baker, B. A.; Bošković, Ž. V.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 289–292.

Compound **3.155** was subjected to the nickel catalyzed 1,4-hydroboration, and the desired product **3.156** was obtained in a good yield (Scheme 3.40). Next, the Sharpless asymmetric epoxidation of allylic alcohol **3.156** afforded the epoxide **3.157**. Notably, the diastereoselectivity of this reaction was much higher than the reaction of **3.101** (Table 3.6).[70]

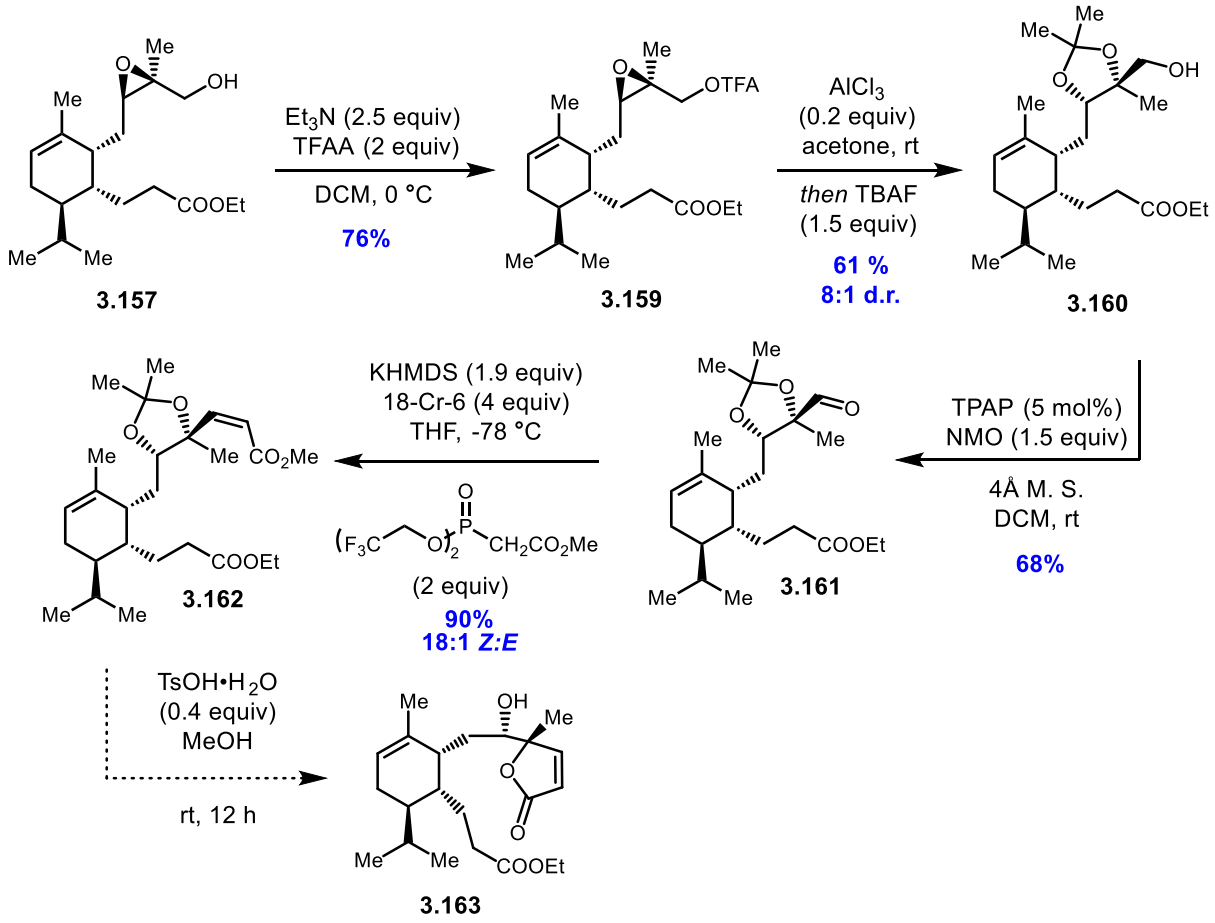
Scheme 3.40. Hydroboration and SAE reaction



With epoxide **3.157** in hand, synthesis of cyclization precursor **3.164** was accomplished with an established route (Scheme 3.41). The epoxide was first converted into the acetonide **3.160**, followed by oxidation and Still-Gennari olefination to deliver compound **3.162**. However, despite numerous attempts, **3.162** could not be converted to lactone **3.163**.

(70) (a) Williams, I. D.; Pedersen, S. F.; Sharpless, K. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 6430–6431.; (b) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106–113.

Scheme 3.41. Complete Synthesis of Cyclization Precursor **3.162**

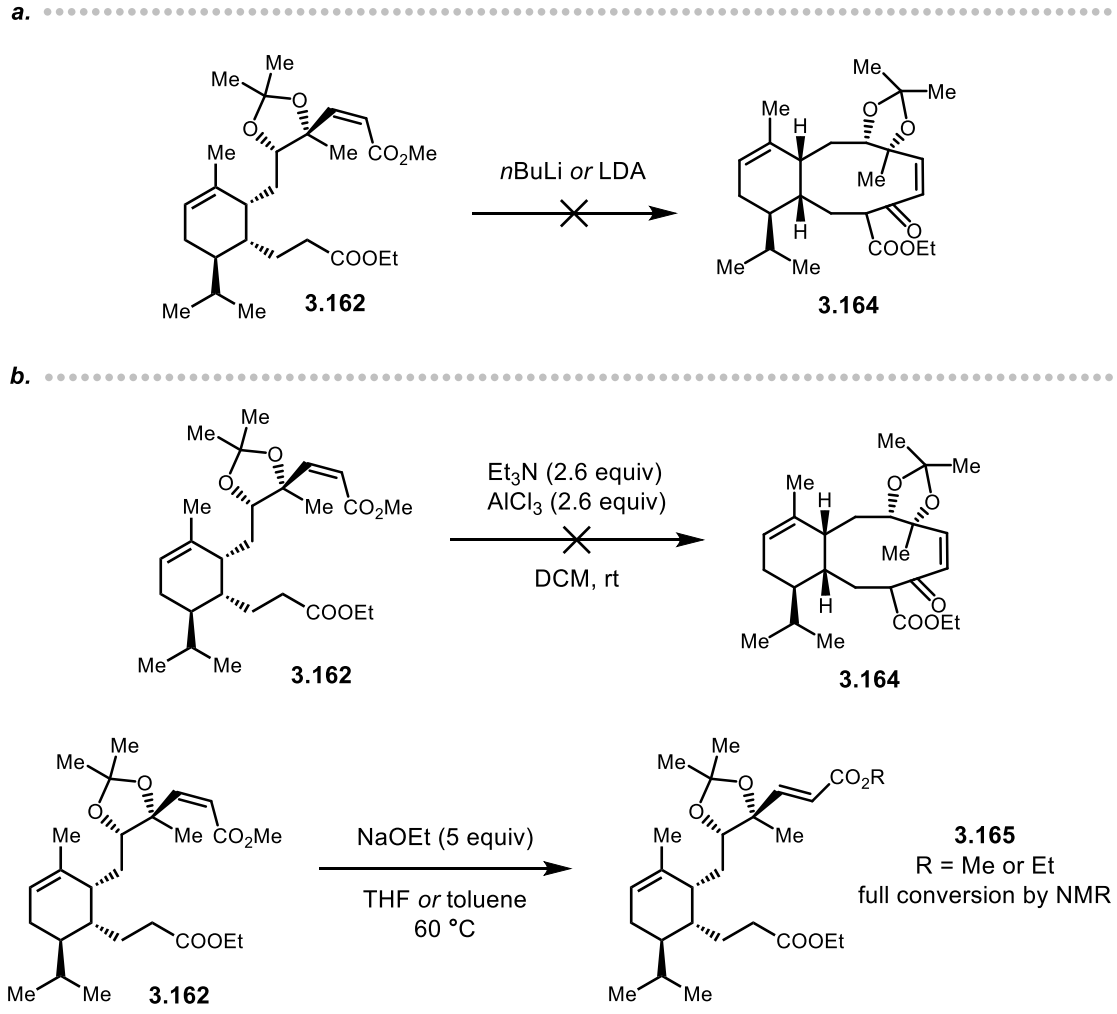


Dieckmann condensation of alkenyl ester **3.162** was then tested (Scheme 3.42a). The desired product was not observed while using LDA or *n*BuLi as the base, even though full conversion of the starting material was observed. The disappearance of the alkenyl ester peak was observed in the crude ^{1}H NMR, suggesting that the ester moiety might decompose under reaction conditions. We hypothesized that the LDA and butyl lithium were too reactive that they could also serve as nucleophiles, therefore milder conditions with the weaker base Et_3N in the presence of Lewis acid was examined (Scheme 3.42b).[71] In this epxeriments, decomposition of the starting

(71) Peçanha, E. P.; Barreiro, E. J.; Fraga, C. A. *Química Nova* **1997**, *20*, 435–437.

material was still observed, presumably due to the decomposition of acetonide moiety under acidic conditions. When alkoxide base was utilized at elevated temperature, alkene isomerization (*Z* to *E*) was observed for alkenyl ester **3.162**. In this reaction, the ethoxide could serve as a nucleophile and undergo conjugate addition/elimination with alkenyl ester to isomerize the alkene.[72]

Scheme 3.42. Dieckmann Condensation

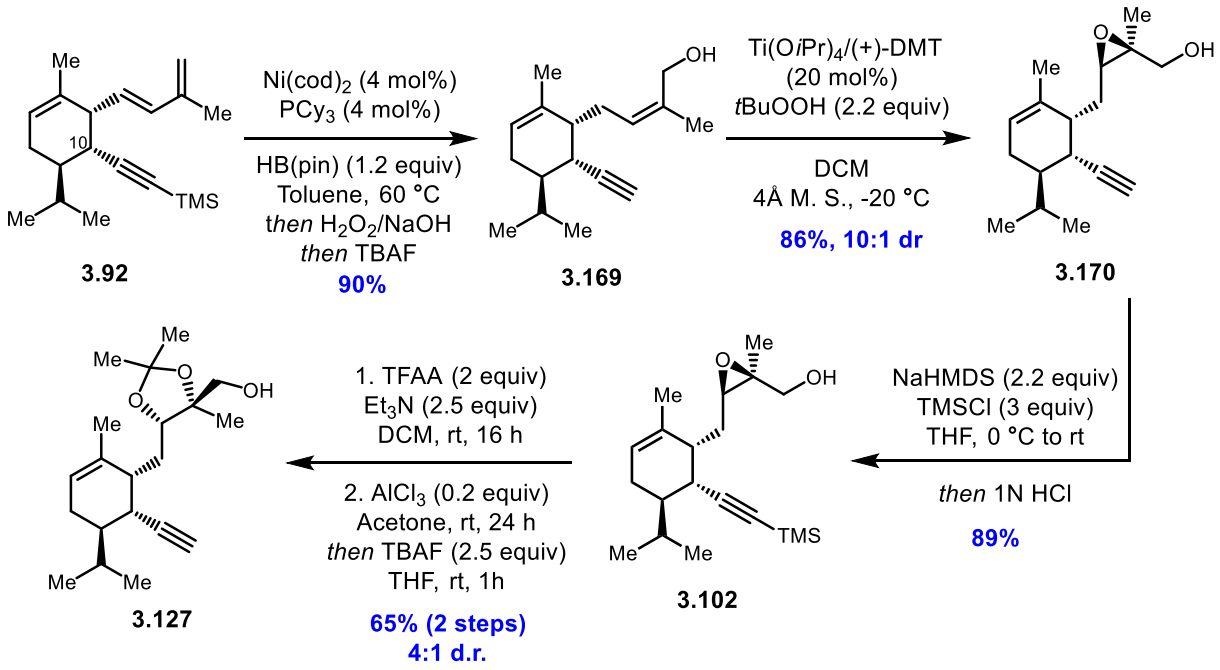


(72) Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709.

3.5.4 Progress towards Cyclization through Alkenyl Intermediate

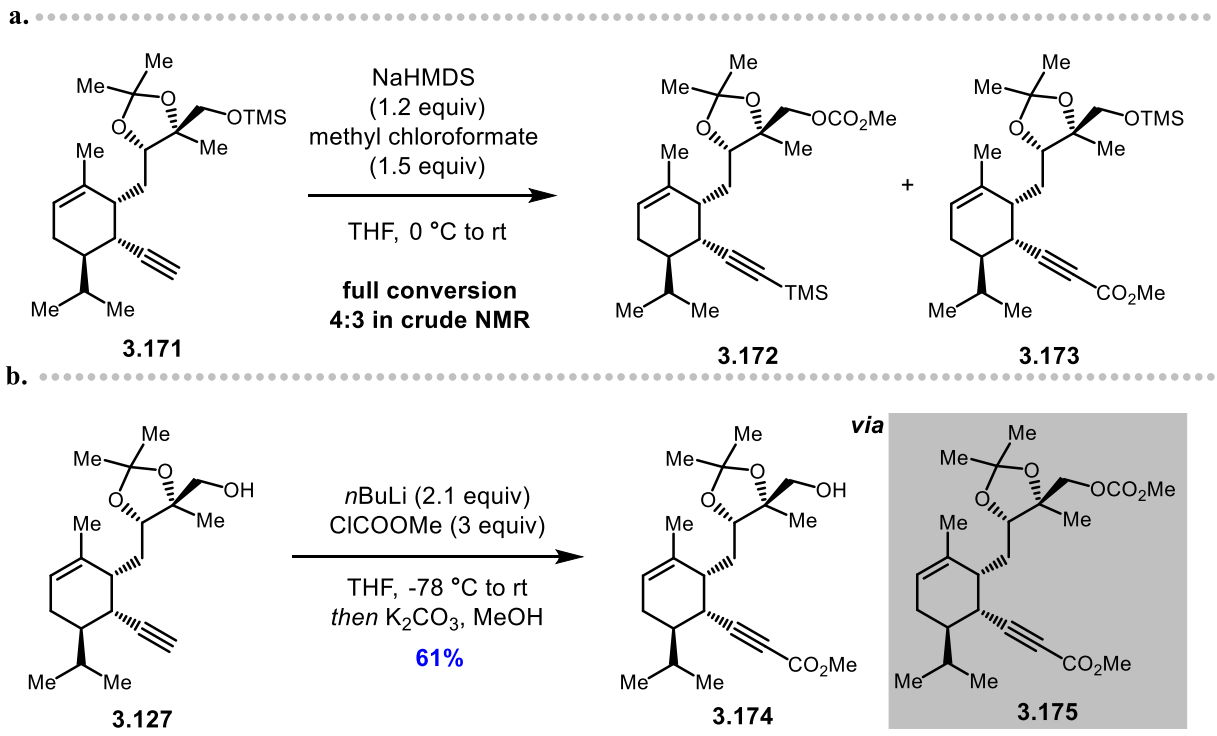
As an alternative to the Dieckmann approach, use of alkenyl anions was studied. The synthesis of cyclization precursor **3.150** was initiated with compound **3.92** (Scheme 3.43). A less bulky substituent in the C-10 branch was beneficial for boosting the diastereoselectivity of the epoxidation as mentioned above, therefore, we modified the synthetic route by removing the TMS protecting group in the alkyne before the epoxidation reaction. Epoxidation of the terminal alkyne **3,169** afforded the epoxide **3.170** with an improved diastereomeric ratio (10:1 *vs.* 4:1). Then, the alkyne was reprotected with the trimethylsilyl group as the terminal alkyne was not compatible with the follwoing acetonization reaction. The *β*-epoxy alcohol **3.102** was converted to acetonide **3.127** as previously described.

Scheme 3.43. Forward Synthesis



Next, the terminal alkyne **3.127** was converted to the alkynyl ester **3.173**. We first tried to deprotonate alkyne **3.171** with NaHMDS and trap the alkynyl anion with methyl chloroformate (Scheme 3.44a). To our surprise, a mixture of desired product **3.173** and side product **3.172** was observed. Compound **3.172** could be generated from the *retro*-Brook rearrangement. Ultimately, after installing the methyl ester moiety in both alcohol and alkyne, methyl carbonate moiety was found to undergo selectivity hydrolysis to furnish the desired product **3.174** by the treatment of potassium carbonate in methanol (Scheme 3.44b).[73]

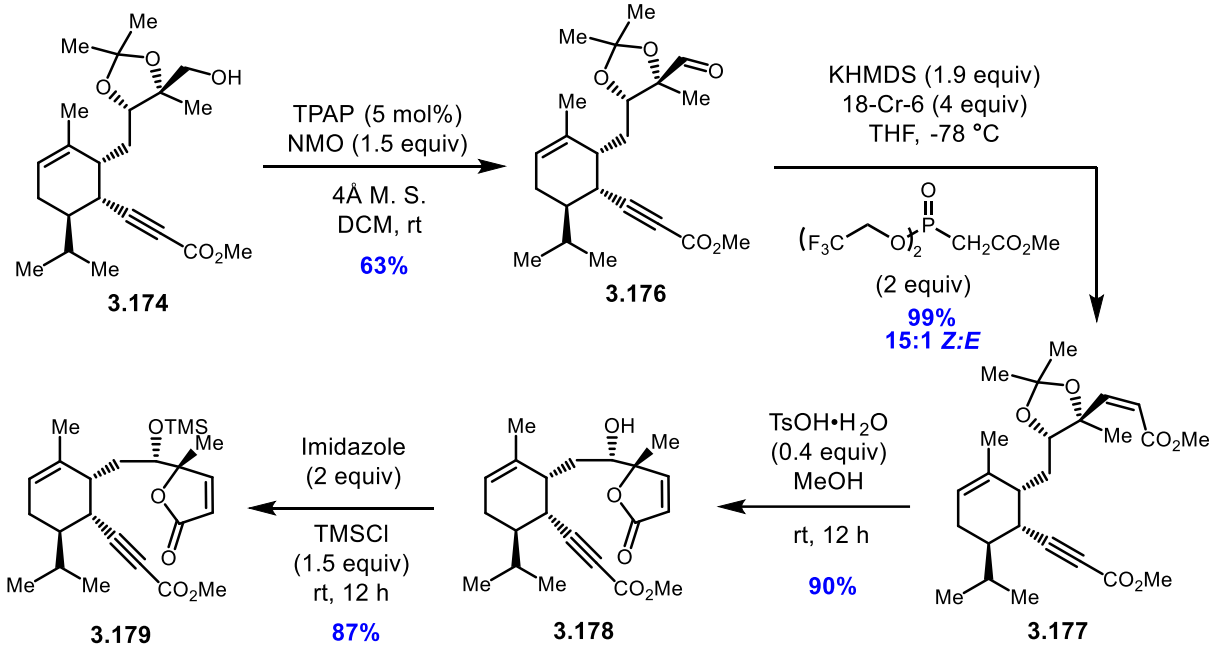
Scheme 3.44. Synthesis of Alkynyl Ester **3.174**



(73) Boglio, C.; Stahlke, S.; Thorimbert, S.; Malacria, M. *Org. Lett.* **2005**, *7*, 4851–4854.

Subsequently, compound **3.174** was converted to precursors **3.177** and **3.179** through the established route (Scheme 3.45): oxidation of the alcohol **3.174** and olefination of the resulting aldehyde **3.176** delivered the *cis*-alkenyl ester **3.177** in good yield and diastereoselectivity, which could be further converted to the lactone species **3.179** by deprotecting the diol and protecting the alcohol with silyl ether.

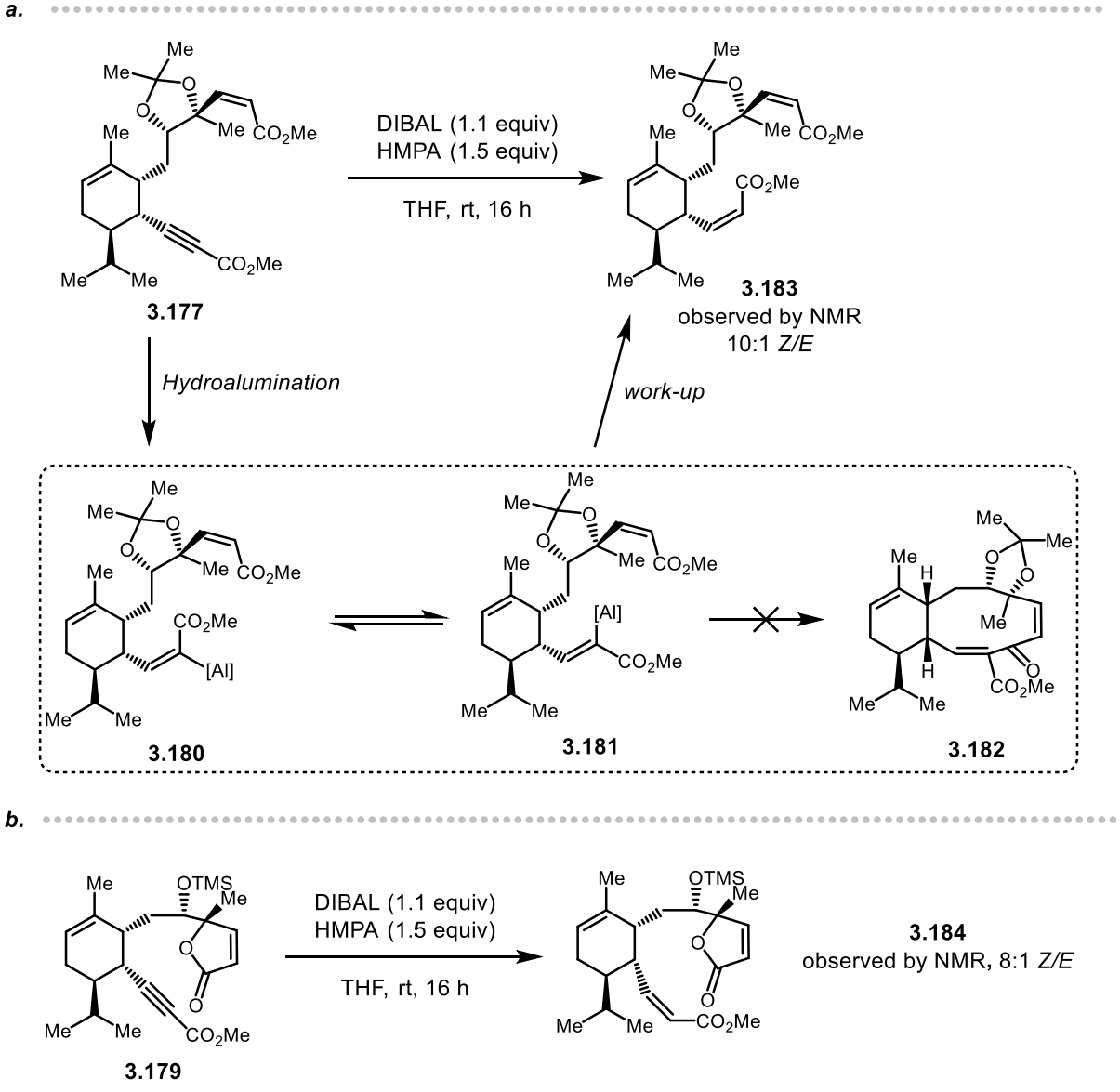
Scheme 3.45. Synthesis of Cyclization Precursor **3.179**



Hydroalumination[46] of the alkynyl ester was conducted first with conditions developed by the Saegusa group (Scheme 3.46a). The addition of HMPA as a ligand for aluminum prevents it from reducing the ester and thus facilitates the hydroalumination process. To accomplish ring closure considered, after the hydroalumination, *trans*-alkenyl aluminum **3.180** might undergo isomerization to *cis*-alkenyl aluminum **3.181**, which might react with the methyl ester intramolecularly to construct the 10-membered ring. However, we only observed the generation

of compound **3.183** after work-up. Therefore, we tried to facilitate nucleophilic addition by adding Lewis acid (*i.e.*, BF_3**.**Et_2O) and elevating the reaction temperature. However, no desired product was observed. Hydroalumination of lactone **3.179** afforded the reduction product **3.184** as well (Scheme 3.46b).

Scheme 3.46. Cyclization through Hydroalumination



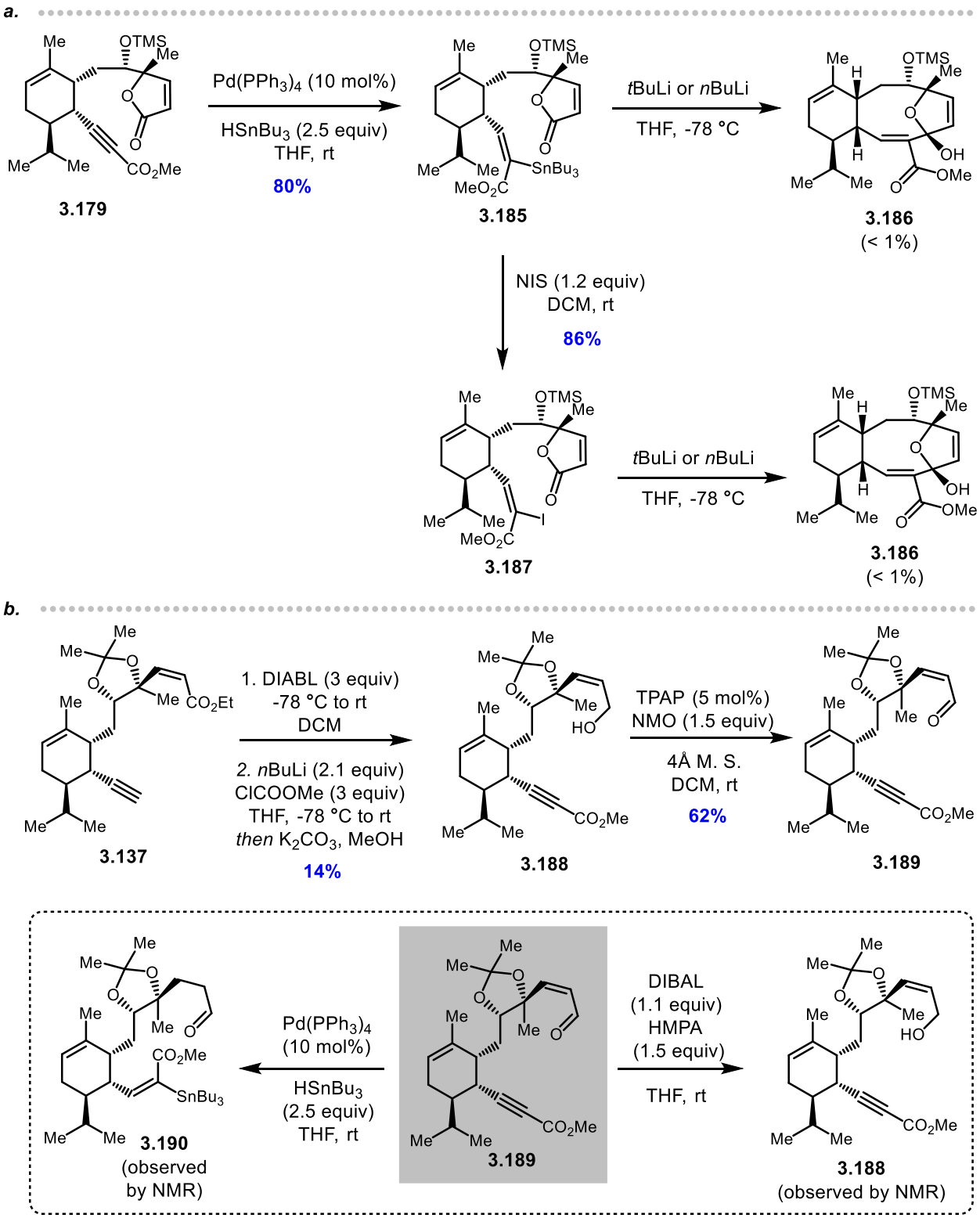
Because aldehydes are generally more electrophilic than esters and lactones, we proposed that cyclization through aldehyde precursors could be more feasible. Synthesis of aldehyde compound **3.189** was conducted from intermediate **3.137** through reduction, alkynyl ester formation, and oxidation (Scheme 3.47b). However, hydroalumination of **3.189** reduced the aldehyde to the alcohol **3.188**. Moreover, the major product of hydrostannation was identified as **3.190**, where the enone was reduced. This observation suggested that replacing the ester with the aldehyde could potentially facilitate the cyclization reaction as the aldehyde was more reactive. Nonetheless, the aldehyde moiety also brought extra difficulties to the preparation of precursors.

3.6 Summary and Future Directions

Staring with α-phellandrene, a synthetic route to critical precursors FOR the progress of the synthesis of sarcodictyins was developed. Modifying the current strategy and developing the synthetic route to the desired natural product is currently ongoing in the laboratory.

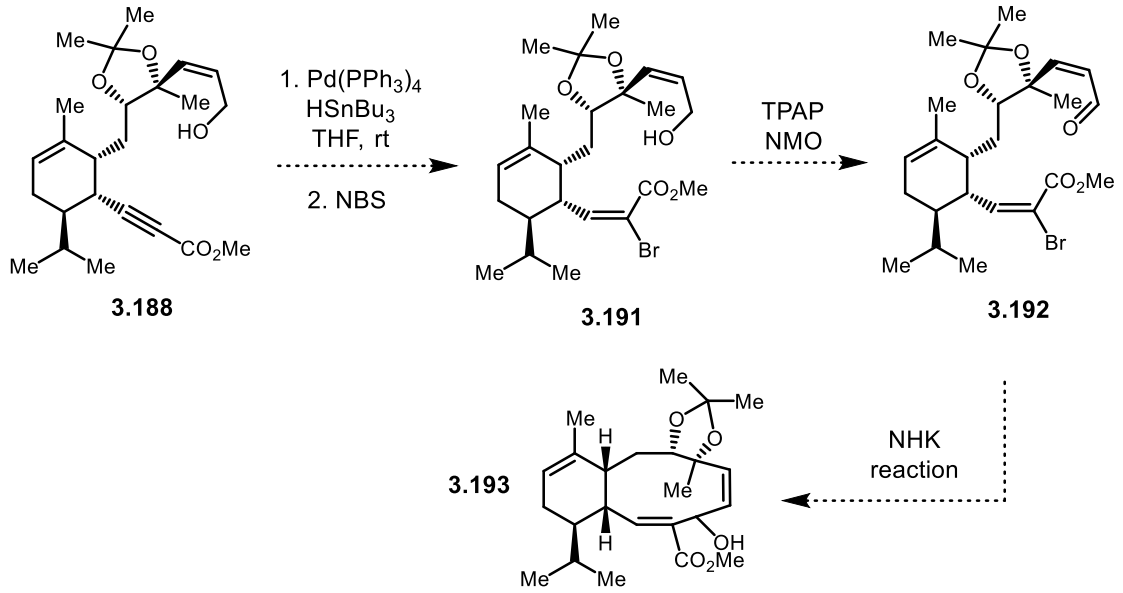
The most challenging part for this synthesis is the construction of the 10-membered ring. We have tried various strategies including palladium-catalyzed intramolecular Sonogashira cross-coupling, Dieckmann condensation, aldol condensation, and hydrometallations to construct the 10-memberd ring core of the natural product and we will keep working on the optimization of current approaches.

Scheme 3.47. Cyclization through Alkenyl Stannane



Some alternative strategies are proposed as future plans. First, we can modify our route to aldehyde **3.192** by conducting the hydrostannation and bromination first (Scheme 3.48). The resulting alkenyl bromide **3.191** could undergo oxidation to deliver **3.192** (Scheme 3.48). The aldehyde **3.192** is a promising precursor for cyclization through intramolecular Nozaki-Hiyama-Kishi reaction, which is a well-known reaction for building molecules with moderate and large ring sizes.[25] However, *E* to *Z* isomerization of the *in situ* generated alkenyl chromium is requisite for this process, which is not precedented in the literature to the best of our knowledge.

Scheme 3.48. Construction of 10-Membered Ring through Nozaki–Hiyama–Kishi Reaction



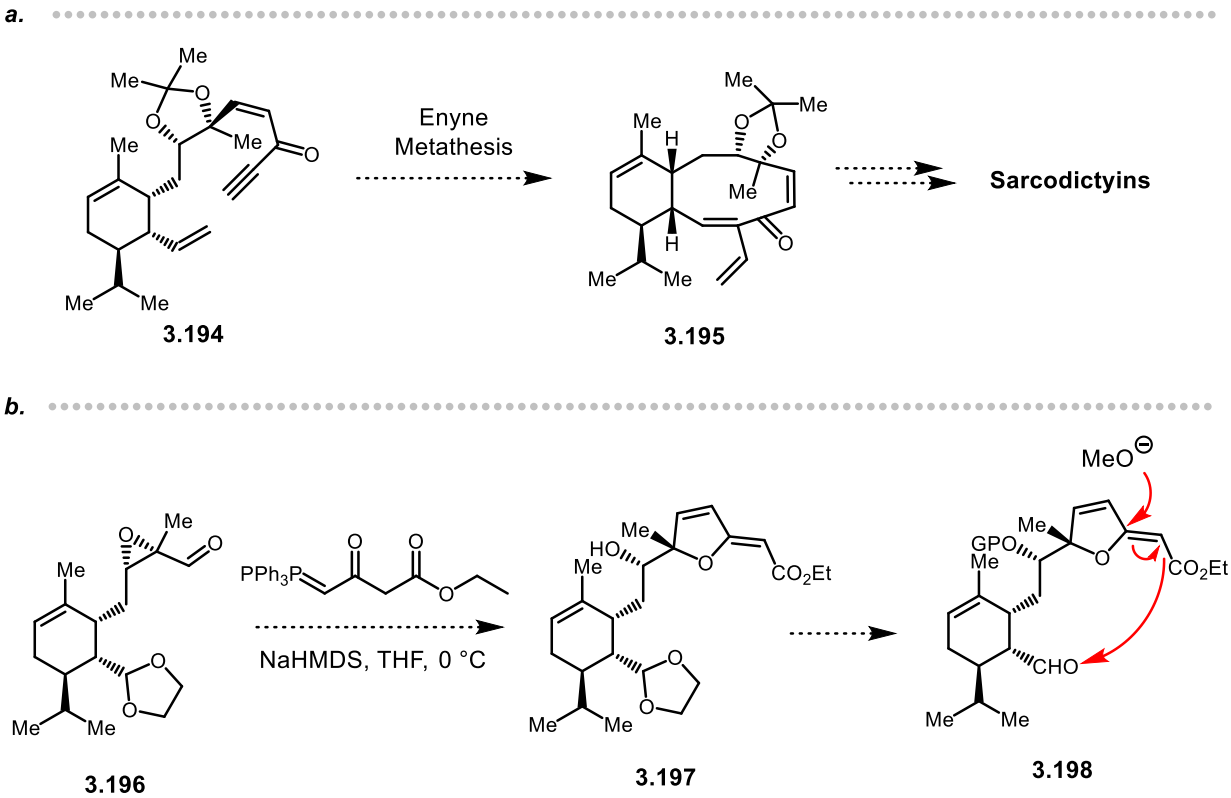
Enyne metathesis[74] of compound **3.194** could be an alternative method for the construction of the 10-member ring. Product **3.195** could be converted to sarcodictyins through oxidative cleavage of the terminal alkene (Scheme 3.49a). However, both enyne metathesis and alkene cleavage reactions could be challenging. The ring strain of the 10-membered ring could make the

(74) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104* (3), 1317–1382.

metathesis reaction thermodynamically disfavored, and the existence of multiple alkenes in the substrate will hamper the selectivity of oxidative cleavage.

Furthermore, inspired by the report from the Gennari group[33], we could convert epoxide **3.196** to dihydrofuran **3.197** under Wittig conditions, which could be further converted to precursor **3.198** (Scheme 3.49b). Cyclization through Michael addition/Aldol condensation could be feasible.

Scheme 3.49. Other Strategies to Construct the 10-Memberd Ring



3.7 Experimental Section

3.7.1 General Information

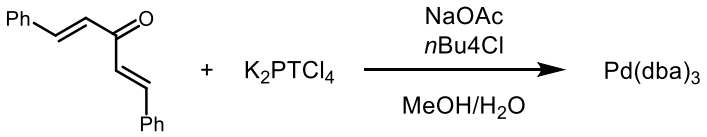
^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), Varian Gemini-600 (600 MHz), or Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl3: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a Varian Gemini-500 (125 MHz), Varian Gemini-600 (150 MHz) or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl3: 77.2 ppm).

Infrared spectra were measured with a Nicolet Avatar 320 spectrometer with a Smart Miracle accessory. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. High-resolution mass spectrometry (DART) was performed at the Mass Spectrometry Facility, Boston College, Chestnut Hill, MA. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography (TLC) was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm) and potassium permanganate in 10% sodium hydroxide.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon (Ar). Tetrahydrofuran (THF), diethyl ether (Et2O), dichloromethane (DCM) and toluene were purified using Pure Solv MD-4 solvent purification system, from Innovative

Technology, Inc., by passing the solvent through two activated alumina columns after purging with nitrogen gas. α–phellandrene (≥75%, stabilized) was purchased from Aldrich and used as received. Tetra-*n*-butylammonium fluoride (TBAF, 1 M solution in THF) was purchased from Oakwood Chemical and used as received. Diisobutylaluminum hydride (DIBAL, 1 M solution in cyclohexane) was purchased from Sigma-Aldrich and used as received. n-Butyllithium (2.5 M in hexane) was purchased from Sigma-Aldrich and used as received. tert-Butyl hydroperoxide solution (packed in FEP bottles, ~5.5 M in decane (over molecular sieve 4Å)) was purchased from Sigma-Aldrich and used as received. Triethylamine (500 mL in Sure/Seal™) was purchased from Sigma-Aldrich and used as received. Aluminium chloride (anhydrous ≥99.985% (metals basis)) was purchased from Alfa Aesar and used as received. Sodium bis(trimethylsilyl)amide (2 m in THF, AcroSeal®) was purchased Acros Organics and used as received. All other reagents were purchased from Aldrich, Alfa Aesar, Acros, Combi Blocks, or Oakwood Chemicals and used without further purification.

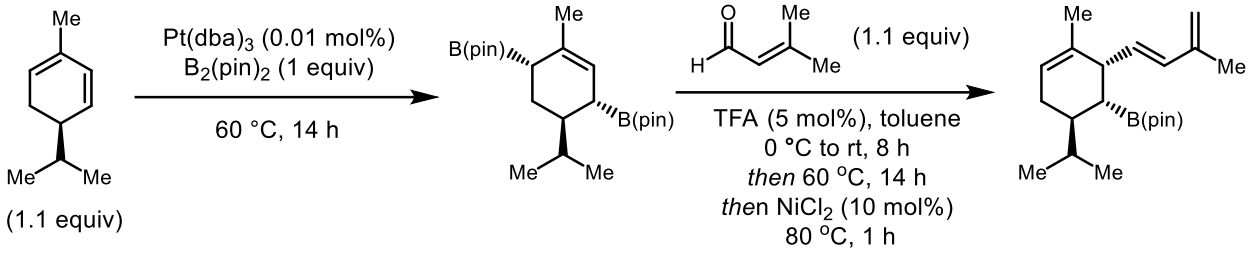
3.7.2 Experimental Procedures



$Pt(dba)_3$ (tris-(dibenzylideneacetone)platinum) was prepared according to a literature procedure with slight modification.[75] Sodium acetate (2.11 g, 25.72 mmol, 18 equiv), tetrabutylammoniumchloride (1.19 g, 4.29 mmol, 3 equiv) and trans, transdibenzylideneacetone (2.34 g, 10.00 mmol, 7 equiv) were added to a 250 mL, two-neck round bottom flask equipped with a magnetic stir bar and reflux condenser. The solids were dissolved in MeOH (65 mL) and

(75) Szymaniak, A. A.; Zhang, C.; Coombs, J. R.; Morken, J. P. *ACS Catal*. **2018**, *8*, 2897.

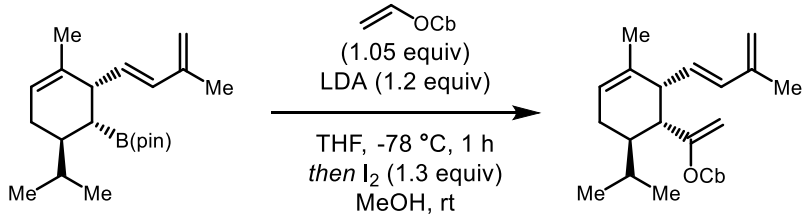
heated to 70 °C until full dissolution. In a separate vial, tetrachloro(dipotassio)platinum (593 mg, 1.43 mmol, 1 equiv) was dissolved in H_2O (4 mL), and heated gently until full dissolution, then charged into the reaction flask. The reaction was heated to 70° C for 3 hours, then transferred to a 1 L round bottom flask using acetone to rinse the flask. The solution is concentrated under vacuum by rotary evaporator, and the residual water and methanol are removed by repeated azeotropic evaporation with acetone. The solids are transferred to a fritted funnel with Et_2O to facilitate the transfer, then washed sequentially with cold H_2O (2x25 mL), acetone (3x25 mL), and Et_2O (1x25 mL). The solid is dried under vacuum to yield $Pt(dba)_3$ as brown solid (552 mg, 0.61 mmol, 43%). Spectral data are in accordance with the literature.



Note: the reaction is conducted open to air. α-Phellandrene was determined to be ~84% by mass (1H NMR with tetrachloroethane as the internal standard), and the density of the mixture is 0.861 g/mL at ~4 °C.

2-((1R,2S,6S)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.84). The title compound was prepared according to a modified literature procedure.[41] Bis(pinacolato)diboron (25.39 g, 100 mmol, 1 equiv) was added to round bottom flask with a magnetic stir bar, followed by 5-isopropyl-2-methylcyclohexa-1,3-diene (23.55 mL, 125.00 mmol, 84% pure, 1.25 equiv) and tris-(dibenzylideneacetone)platinum

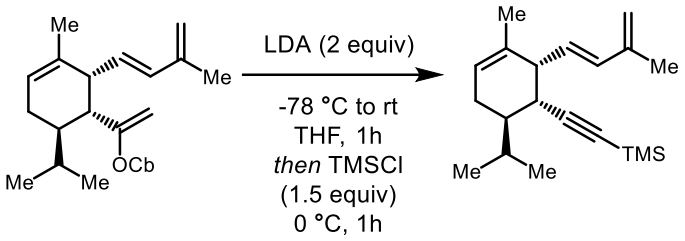
(9 mg, 0.01 mmol, 0.0001 equiv). The reaction was heated to 60 °C for 15 hours. The reaction mixture was diluted with toluene (60 mL), then 3-methylbut-2-enal (10.5 mL, 110.00 mmol, 1.1 equiv) was added. The reaction was cooled to 0 °C and trifluoroacetic acid (0.39 mL, 5.00 mmol, 0.05 equiv) was added. The reaction was allowed to slowly warm to room temperature over 8 hours, then allowed to stir at 60 °C for 15 hours. Nickel(II) chloride hexahydrate, (2.38 g, 10.00 mmol, 0.1 equiv) was added to the crude mixture and it was allowed to stir at 80 °C for 1 hour then transferred to a separatory funnel (rinse with hexane). The organic layer was washed with H_2O (100 mL) then brine (100 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated (azeotrope with EtOAc to remove the residual toluene). The crude product was purified by silica gel column chromatography with 0-5% EtOAc/hexane eluent (R_f = 0.3 in 5% EtOAc/hexane) to yield the title compound (23g, 69.6 mmol, 70%) as colorless oil (7:1 rr). Or the crude product was purified by silica gel column chromatography with 0-40% toluene/hexane eluent (R_f = 0.4 in 50% toluene/hexane, undesired regiomeric isomer **3.85** R_f = 0.5 in 50% toluene/hexane) to yield the title compound (19 g, 57.5 mmol, 57% yield) as colorless oil (>20:1 *r.r.*). Spectral data are in accordance with the literature.[40]



Note: 2-chloroethyl diisopropylcarbamate was prepared according to a literature procedure.[40]

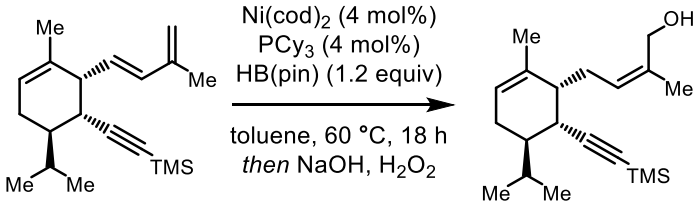
Preparation of LDA: diisopropylamine (9 mL, 63.77 mmol) was dissolved in THF (40 mL) and cooled to -78 °C, then nBuLi (2.5 M, 25.51 mL) was added. The reaction was allowed to stir at 0 °C for 30 minutes, then used directly (~0.86 M).

1-((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)vinyl diisopropylcarbamate (3.89). The title compound was prepared according to a modified literature procedure.[42] 2-((1R,2S,6S)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11 g, 33.3 mmol, 1.0 equiv) was added to a 500 mL round bottom flask, followed by vinyl-diisopropylcarbamate (6.2mL, 35.0 mmol, 1.05 equiv) and anhydrous THF (33.3 mL). To this, freshly prepared LDA (0.86M, 44.5 mL, 1.15 equiv) was added at –78 °C, and the resulting solution was allowed to stir for 1 hour at –78 °C. Next, a solution of iodine (11.0 g, 38.3 mmol, 1.3 equiv) in methanol (67.4 mL, 50 equiv) was added in one portion, and the reaction was allowed to stir for 5 min at –78 °C, then at room temperature for 1 hour. The reaction was then quenched with saturated aqueous sodium thiosulfate (200 mL) and transferred to a separatory funnel. The lower layer (of three) was removed, and the organic layer was sequentially washed with H_2O (2x100 mL) then brine (1x100mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. The crude product was purified by column chromatography with 0-6% EtOAc/hexane eluent (R_f = 0.2 in 5% EtOAc/hexane) to yield the title compound (11.84 g, 31.6 mmol, 95% yield) as colorless oil. Spectral data are in accordance with the literature.[40]

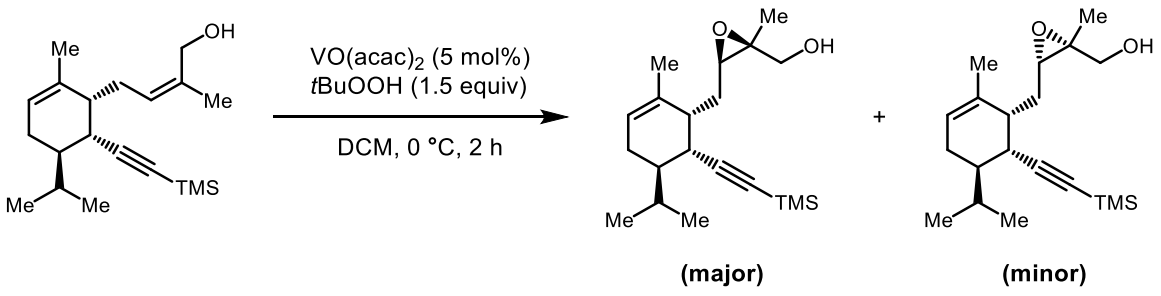


Note: Preparation of LDA: diisopropylamine (9.7 mL, 68.7 mmol) was dissolved in THF (36 mL) and cooled to -78 °C, then nBuLi (2.5 M, 24.1 mL) was added. The reaction was allowed to stir at 0 °C for 30 minutes, then used directly (~0.86 M).

(((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1 yl)ethynyl)trimethylsilane (3.92). The title compound was prepared according to a modified literature procedure.[42] 1-((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)vinyl diisopropylcarbamate (11.3 g, 30.25 mmol) was added to a 250 mL round bottom flask, and dissolved in THF (30 mL). At -78 °C, LDA (0.86 M, 70.3 mL, 2.0 equiv) was added, then the reaction was allowed to stir at RT for 1 hour. Next, the reaction was cooled to 0 °C and chloro(trimethyl)silane (5.76 mL, 45.4 mmol, 1.5 equiv) was added, and the reaction was allowed to stir at 0 °C for 1 hour. The reaction was diluted with Et_2O (100 mL) and transferred to a separatory funnel, then extracted with H_2O (2x100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. The crude product was filtered through a plug of silica gel with hexane as the eluent (R_f = 0.3 in Hexane) to yield the title compound (7.4 g, 24.6 mmol, 81% yield) as colorless oil. Spectral data are in accordance with the literature.[40]

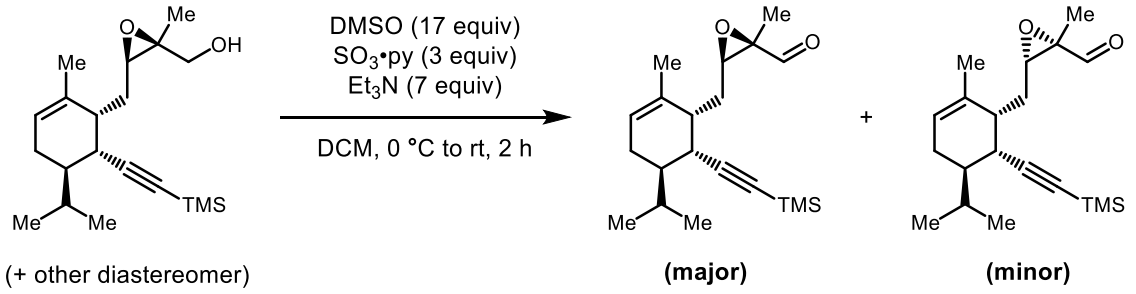


(Z)-4-((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)-2-methylbut-2-en-1-ol (3.101). The title compound was prepared according to a modified literature procedure.[46] To an oven-dried 250 mL RBF was added $Ni(cod)_2$ (458 mg, 1.66 mmol, 0.04 equiv), PCy_3 (467 mg, 1.66 mmol, 0.04 equiv), (((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1- yl)ethynyl)trimethylsilane (12.5 g, 41.6 mmol, 1 equiv.), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7.24 mL, 49.9 mmol, 1.2 equiv.), and toluene (42 mL). The reaction was allowed to stir at 60 °C overnight. The reaction solution was transferred to a separatory funnel and the organic layer was washed with H_2O (2x50 mL) then brine (50 mL). The organic layer was dried over sodium sulfate, then filtered, and concentrated. The crude product was was dissolved in THF (62 mL) and cooled to 0 °C. To this was added NaOH (3 M in H_2O, 41.5 mL, 124.8 mmol, 3 equiv) and H_2O_2 (29% aqueous solution, 19.5 mL, 183.4 mmol, 4.4 equiv), and the reaction was allowed to stir at RT for 1 hour. The reaction was cooled to 0 °C and quenched with saturated aqueous sodium thiosulfate (50 mL) (caution: exothermic, gas evolution), then transferred to a separatory funnel. The aqueous layer was removed, and the organic layer was washed with H_2O (2x50 mL) then brine (1x75mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. The crude product was purified by silica gel column chromatography with 5-10% EtOAc/hexane (R_f = 0.3 in 10% EtOAc/hexane) as the eluent, to yield the title compound (10.6 g, 33.3 mmol, 80% yield) as colorless oil. Spectral data are in accordance with the literature.[40]



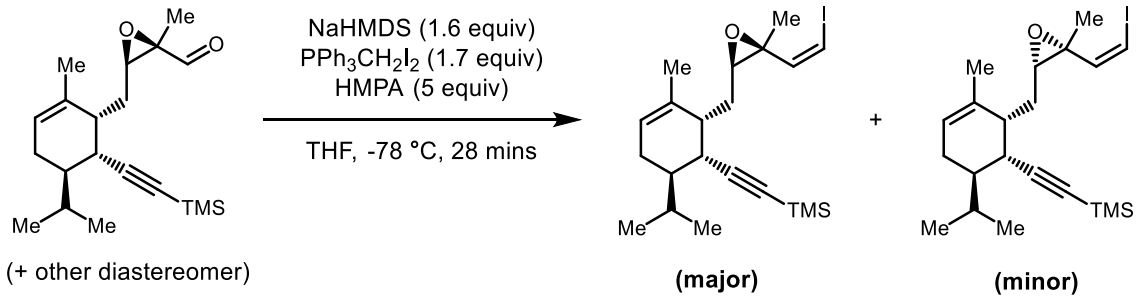
Note: reaction is conducted open to air and the solvent is not anhydrous.

((2S,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.102 (major)) and **((2R,3S)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.102 (minor))**. The title compounds were prepared according to a modified literature procedure.[47b] (Z)-4-((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)-2-methylbut-2-en-1-ol (6.1 g, 19.2 mmol, 1 equiv) was added to a 200 mL round bottom flask and dissolved in DCM (38 mL). The reaction was cooled to 0 °C and vanadyl acetylacetonate (254 mg, 0.96 mmol, 0.05 equiv) was added, followed by tert-butyl hydroperoxide (5.5 M in nonane, 5.2 mL, 28.7 mmol, 1.5 equiv). The reaction was allowed to stir at 0 °C for 2 hours, then dimethyl sulfide (1.4 mL, 19.2 mmol, 1 equiv.) was added to quench the reaction, and allowed to stir for another 30 minutes. The reaction mixture was filtered through a plug of silica gel with Et_2O as the eluent. The crude product was purified by silica gel column chromatography with 5-10% EtOAc/hexane (R_f = 0.2 in 10% EtOAc/hexane) as the eluent to yield the title compounds (5.04 g, 15.1 mmol, 79% combined yield, 1.7:1 dr) as colorless oil. Spectral data are in accordance with the literature.[40]



(2R,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxirane2-carbaldehyde (3.103 (major)) and **(2S,3S)-3-(((1R,5R,6R)-5-**

isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxirane2-carbaldehyde (3.103 (minor)). A solution of sulfur trioxide pyridine complex (7.19 g, 45.2 mmol, 3 equiv) in anhydrous DMSO (18.2 mL, 256 mmol, 17 equiv) was allowed to stir at RT for 15 minutes, then added to a 100 mL round bottom flask containing a solution of ((2S,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2- yl)methanol (+ other diastereomer) (5.04 g, 15.1 mmol, 1 equiv) and triethylamine (14.7 mL, 105 mmol, 7 equiv) in anhydrous DCM (15 mL) at 0 °C. The reaction was allowed to stir at RT 2 hours, then filtered through a plug of silica gel with Et_2O as the eluent and concentrated. The crude material was filtered through a plug of silica with 10% EtOAc/hexane as the eluent, then concentrated. The resulting oil was purified by silica gel column chromatography with 2% EtOAc/hexane to 4% as EtOAc/hexane the eluent (R_f = 0.5 in 5% EtOAc/hexane) to yield the title compounds (4.65 g, 14.0 mmol, 93% yield) as colorless oil. Spectral data are in accordance with the literature.[40]

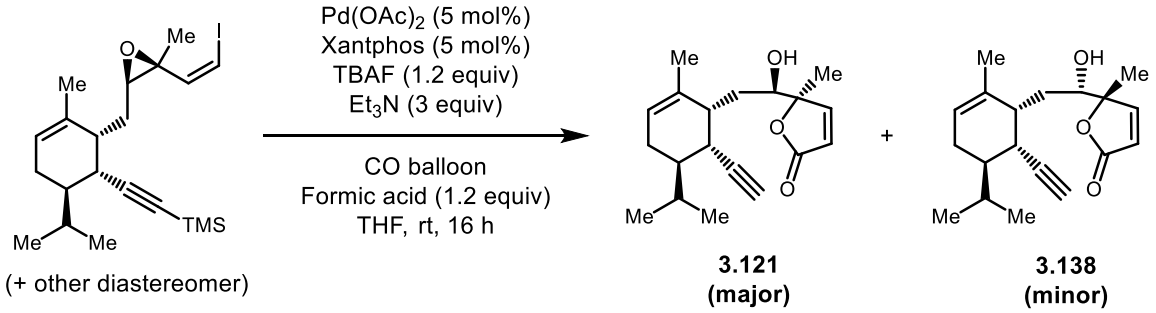


Note: (Iodomethyl)-triphenylphosphonium iodide was prepared according to a literature procedure.[76]

(((1R,2R,6R)-2-(((2R,3S)-3-((Z)-2-iodovinyl)-3-methyloxiran-2-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)ethynyl)trimethylsilane (3.104 (major)) and **(((1R,2R,6R)-2-**

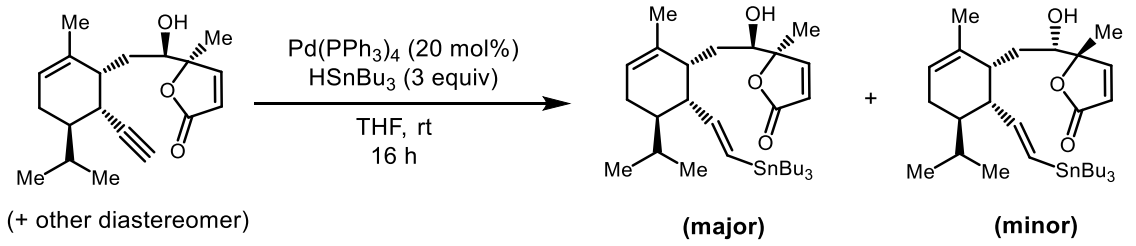
(76) Dias, L. C.; Ferreira, M. A. B. *J. Org. Chem*. **2012**, *77*, 4046−4062.

(((2S,3R)-3-((Z)-2-iodovinyl)-3-methyloxiran-2-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)ethynyl)trimethylsilane (3.104 (minor)). The title compound was prepared according to a modified literature procedure.[43] In a 250 mL oven-dried round bottom flask, to solution of (Iodomethyl)-triphenylphosphonium iodide (4.26 g, 8.03 mmol, 1.6 equiv) in THF (24 mL) was 0 °C and added a solution of NaHMDS (1 M, 8.03 mL) in THF under N_2. This was allowed to stir for 10 minutes at RT, then cooled to -78 °C and HMPA (4.50 g, 25.11 mmol, 4.37 mL) was added immediately follow by a solution of (2S,3S)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxirane2-carbaldehyde (1.67 g, 5.02 mmol) in THF (15 mL). The reaction was allowed to stir at -78 °C for 28 minutes then quenched with methanol (643.59 mg, 20.09 mmol, 813.64 μL). Reaction was filtered through a fritted funnel and concentrated, then filtered through a plug of silica with 10% EtOAc/hexane and concentrated. The resulting oil was purified by silica gel column chromatography with 0-2% EtOAc/hexane (R_f = 0.4 in 5% EtOAc/hexane) to yield the title compounds (2.0 g, 4.38 mmol, 87% yield, >18:1 *Z:E,* containing 28% **3.105** by molarity) as a pale yellow oil. Spectral data are in accordance with the literature.[40]



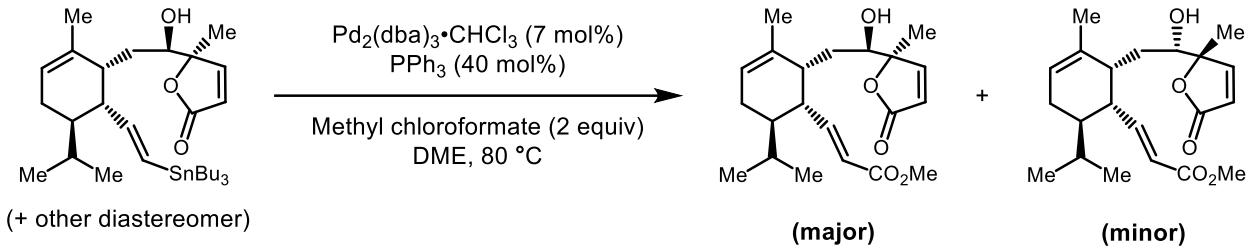
(R)-5-((R)-2-((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)-1-hydroxyethyl)-5-methylfuran-2(5H)-one (3.121) and **(S)-5-((S)-2-((1R,5R,6R)-6-ethynyl-5-**

isopropyl-2-methylcyclohex-2-en-1-yl)-1-hydroxyethyl)-5-methylfuran-2(5H)-one (3.138). The title compound was prepared according to a modified literature procedure.[50] In glovebox, to a 2-dram vial were added (((1R,2R,6R)-2-(((2R,3S)-3-((Z)-2-iodovinyl)-3-methyloxiran-2-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1 yl)ethynyl)trimethylsilane (91 mg, 0.20 mmol, 1 equiv, 74% pure). $Pd(OAc)_2$ (2.25 mg, 0.01 mmol, 0.05 equiv), Xantphos (6.36 mg, 0.011 mmol, 0.06 equiv), triethylamine (0.084 mL, 0.6 mmol, 3 equiv) and THF (1 mL). The vial was sealed with a septum cap, brought out of the glove box, and placed under a positive pressure of N_2. Next, TBAF (1 M in THF, 0.26mL, 0.26 mmol, 1.3 equiv) and formic acid (0.009mL, 2.4 mmol, 1.2 equiv) were added. The N_2 pressure was removed, and the reaction was allowed to stir under an atmospheric pressure of carbon monoxide (balloon). The reaction was allowed to stir at RT for 15 hours then filtered through a plug of silica gel with Et_2O as the eluent, then concentrated. The crude product was purified by silica gel column chromatography with 10-20% EtOAc/hexane (R_f = 0.6 in 30% EtOAc/hexane) as the eluent to yield the title compounds (22.4 mg, 0.074 mmol, 37% yield, adjusted yield is 50% based on the purity of starting material, 1.7:1 dr) as yellow solid. Spectral data are in accordance with the literature.[40]



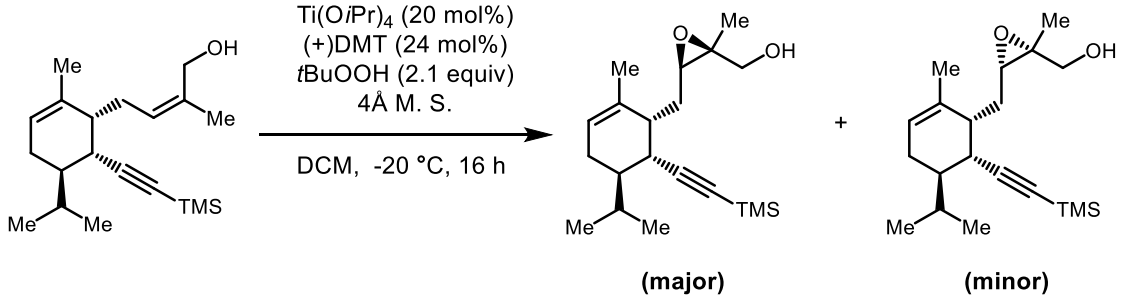
(R)-5-((R)-1-Hydroxy-2-((1R,5R,6R)-5-isopropyl-2-methyl-6-((E)-2-(tributylstannyl)vinyl)cyclohex-2-en-1-yl)ethyl)-5-methylfuran-2(5H)-one (3.117 (major)) and **(S)-5-((S)-1-hydroxy-2-((1R,5R,6R)-5-isopropyl-2-methyl-6-((E)-2-**

(tributylstannyl)vinyl)cyclohex-2-en-1-yl)ethyl)-5-methylfuran-2(5H)-one (3.117 (minor)). The title compound was prepared according to a modified literature procedure.[55] To an oven-dried, argon-filled flask was added $Pd(PPh_3)_4$ (69 mg, 0.06 mmol, 0.2 equiv). Freshly distilled THF (3 mL) was added, and the solution was allowed to stir for 10 min until the solids had dissolved. (R)-5-((R)-2-((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)-1-hydroxyethyl)-5-methylfuran-2(5H)-one (90 mg, 0.3 mmol, 1 equiv) was added, followed by slow addition of neat Tributyltin hydride (260 mg, 0.24 mL, 0.9 mmol, 3 equiv) over 10 min. The reaction was allowed to stir under argon at RT for 16 hours. Once complete, the solvent was evaporated under vacuum and the crude mixture was purified by silica gel column chromatography with 0-12% EtOAc/hexane (R_f = 0.2 in 17% EtOAc/hexane) as the eluent to yield the title compounds (88mg, 0.15 mmol, 50%, 8:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric mixture and the presence of trace unidentified byproducts in the product mixture.) **3.117 (Major)** and **3.117 (Minor)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 5.6 Hz, 1H), 6.02 (d, *J* = 5.6 Hz, 1H), 5.99-5.87 (m, 2H), 5.35 (s, 1H), 3.75-3.71 (m, 1H), 2.42-2.39 (m, 1H), 2.30 (m, 1H), 2.16 (d, *J* = 5.5 Hz, 1H), 2.01-1.96 (m, 1H), 1.86-1.82 (m, 1H), 1.70-1.65 (m, 4H), 1.56-1.37 (m, 14H), 1.33-1.25 (m, 8H), 0.91-0.83 (m, 21H), 0.75 (d, *J* = 6.6 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 158.9, 158.8, 158.5, 152.6, 152.0, 135.5, 129.9, 129.5, 121.9, 121.9, 121.5, 121.3, 91.7, 91.4, 77.4, 77.2, 76.9, 73.4, 72.8, 51.3, 48.4, 41.3, 40.3, 38.8, 37.1, 36.4, 32.2, 31.5, 30.8, 30.4, 29.4, 29.29, 29.25, 29.2, 28.8, 28.1, 28.1, 28.0, 27.6, 27.4, 27.3, 27.2, 24.30, 24.0, 22.1, 22.0 21.9, 21.1, 20.9, 20.8, 20.1, 19.9, 19.2, 18.5, 18.1, 15.4, 13.83, 13.76, 11.0, 10.9, 9.9, 9.70, 9.66, 9.62, 8.33, 8.27.; IR (neat) ν_{max} 2955 (s), 2926 (s), 1750 (s), 1458 (w), 818 (w).; HRMS (DART) for $C_{31}H_{55}O_3Sn$ $[M+H]^+$ calculated: 593.317, found: 593.318.



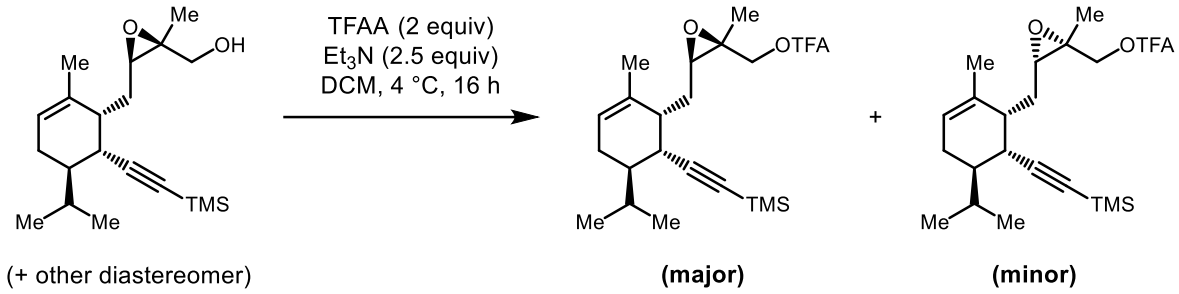
Methyl (E)-3-((1R,2R,6R)-2-((R)-2-hydroxy-2-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)acrylate (3.118 (major)) and **methyl (E)-3-((1R,2R,6R)-2-((S)-2-hydroxy-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)acrylate (3.118 (minor))**. The title compound was prepared according to a modified literature procedure.[56] (R)-5-((R)-1-Hydroxy-2-((1R,5R,6R)-5-isopropyl-2-methyl-6-((E)-2-(tributylstannyl)vinyl)cyclohex-2-en-1-yl)ethyl)-5-methylfuran-2(5H)-one (59.4 mg, 0.10 mmol, 1 equiv), $[Pd_2(dba)_3]$•$CHCl_3$ (7.3 mg, 7 mol%), Ph_3P (10.5 mg, 40 mol%), and $ClCO_2Me$ (18.9 mg, 0.2 mmol, 2 equiv) were dissolvedin DME (1 mL) in an oven-dried 2-dram vial under argon. The solution was allowed to stir at 80 °C for 12 h. After the addition of H_2O (5 mL), the mixture was cooled to RT and extracted with EtOAc (2 mL) twice. The combined organic layers were washed with brine (5 mL), dried with sodium sulfate, and concentrated in vacuo. The crude material was purified by silica gel column chromatography with 10-25% EtOAc/hexane (R_f = 0.1 in 17% EtOAc/hexane) as the eluent to yield the title compounds (30.7 mg, 0.085 mmol, 85% yield, 8:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.118 (major)**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 5.7 Hz, 1H), 6.91 (dd, *J* = 15.6, 10.6 Hz, 1H), 6.05 (d, *J* = 5.6 Hz, 1H), 5.85 (d, *J* = 15.7 Hz, 1H), 5.39 (s, 1H), 3.70 (s, 3H), 3.57 – 3.52 (m, 1H), 2.59 (ddd, *J* = 11.0, 8.0, 4.9 Hz, 1H), 2.45 (d, *J* = 5.7 Hz, 1H), 2.38 – 2.34 (m, 1H), 2.01 – 1.95 (m, 1H), 1.90 – 1.84 (m, 1H), 1.66 (s, 3H), 1.64 – 1.45 (m, 6H), 1.42 (s,

3H), 0.90 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.7 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 166.8, 158.8, 152.2, 134.9, 121.94, 121.91, 121.6, 91.8, 77.4, 77.2, 76.9, 73.7, 51.6, 42.8, 40.6, 37.7, 31.7, 28.4, 24.1, 21.7, 20.9, 18.6, 17.7.; IR (neat) ν_{max} 1757 (s), 1721 (s), 1269 (m), 1250 (m), 820 (m).; HRMS (DART) for $C_{21}H_{31}O_5$ $[M+H]^+$ calculated: 363.217, found: 363.216. $[\alpha]^{20}_D$: -43.4 (c = 1.00, $CHCl_3$, l = 50 mm).



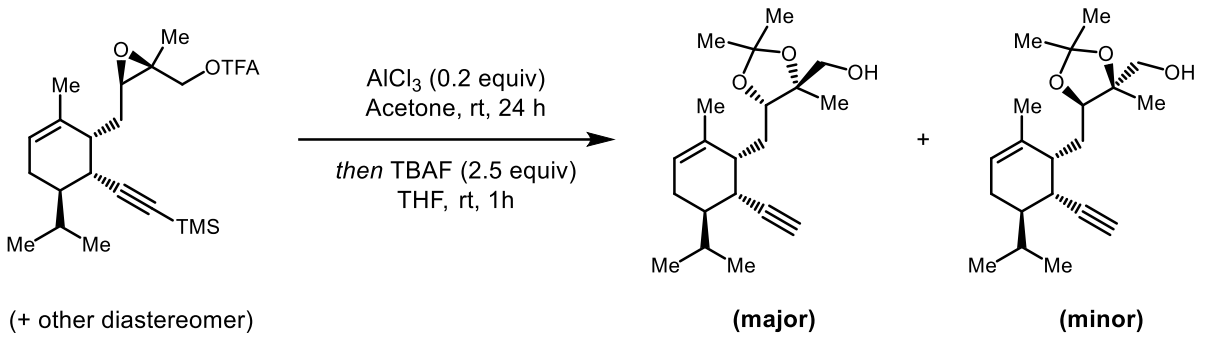
((2S,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.102 (major)) and **((2R,3S)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.102 (minor))**. The title compounds were prepared according to a modified literature procedure.[57] To a stirred suspension of powdered (+) dimethyl tartrate (562 mg, 3.16 mmol, 0.24 equiv) and 4Å molecular seives (1.3 g) in dry DCM (26 ml) was added Ti(OiPr)$_4$ (0.78 mL, 2.63 mmol, 0.2 equiv) at -25 °C (dry ice bath) and allowed to stir vigorously for 25 min, tBuOOH (5.5 M in decane, anhydrous, 5.02 mL, 2.1 equiv) was added and the mixture allowed to stir for 25 min. (Z)-4-((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)-2-methylbut-2-en-1-ol (4.19 g, 13.15 mmol, 1 equiv) in DCM (26 mL) was added and mixture was allowed to stir for 25 mins. The flask was then put into a freezer (-20 °C) and kept for 16 hours before diluting with Et_2O (50 ml), and filtering through a pad of Celite, washing

thoroughly with Et_2O. The filtrate is washed with brine (100 mL) and the organic layer was dried over sodium sulfate, then filtered and concentrated in vacuo. The crude material (4.3:1 dr determined by ^1H NMR) was purified by silica gel column chromatography with 0-10% EtOAc/hexane (R_f = 0.2 in 10% EtOAc/hexane) as the eluent to yield the title compounds in two fractions (2.42 g, 7.25 mmol, 55% yield, 12:1 dr; 0.95g, 2.75 mmol, 21%, 2:1 dr; overall 3.35 g, 10 mmol, 76% yield) as colorless oil. (Note: Two diastereomers are not separatable in TLC, but they can be partly separated by column, the desired diastereomer will be eluted first. the high dr fraction was obtained by taking ^1H NMR of different fractions and selectively collect the fractions with high dr) Spectral data are in accordance with the literature.[40]



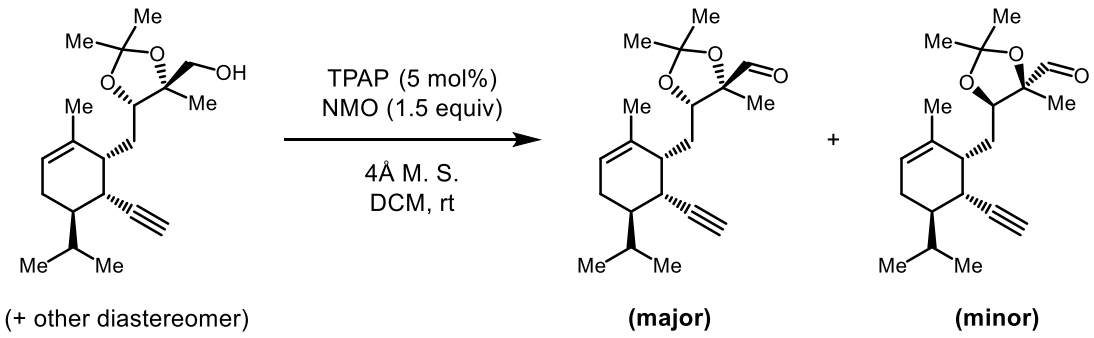
((2S,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methyl 2,2,2-trifluoroacetate (3.126 (major)) and **((2R,3S)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methyl 2,2,2-trifluoroacetate (3.126 (minor))**. To a 100 mL round bottom flask equipped with a stir bar, was added ((2R,3S)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (4.12 g, 12.31 mmol, 1 equiv) followed by dichloromethane (18 mL) under N_2. The reaction was cooled to 0 °C in an ice bath and charged with Et_3N (4.29 mL, 30.8 mmol, 2.5 equiv) followed by dropwise

addition of trifluoroacetic anhydride (3.3 mL, 23.4 mmol. 1,9 equiv). The reaction was allowed to stir in the cold room (4 °C) for 16 hours. The reaction was then diluted with deionized water (50 mL) and extracted twice with diethyl ether (50 mL), the organic layers were combined and washed with 1M HCl (2 x 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuo. The crude material was purified by silica gel column chromatography with 0-5% EtOAc/hexane as the eluent to yield the title compounds (6.03 g, 14 mmol, 85% yield, 13:1 dr) as colorless oil. (Note: Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.126(major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (s, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 3.10 (dd, *J* = 8.3, 4.6 Hz, 1H), 2.63 (dd, *J* = 11.1, 4.8 Hz, 1H), 2.34 (q, *J* = 5.7 Hz, 1H), 2.24 (dt, *J* = 14.6, 5.1 Hz, 1H), 2.18 (qd, *J* = 7.0, 4.3 Hz, 1H), 2.00 – 1.92 (m, 1H), 1.82 – 1.73 (m, 1H), 1.71 (d, *J* = 1.9 Hz, 3H), 1.66 (ddd, *J* = 14.6, 8.3, 6.4 Hz, 1H), 1.57 (tdd, *J* = 10.5, 6.2, 4.2 Hz, 1H), 1.40 (s, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.14 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 122.9, 108.1, 88.9, 77.4, 77.2, 76.9, 69.3, 63.7, 58.7, 40.6, 37.6, 36.2, 29.2, 28.5, 24.3, 24.3, 22.8, 20.9, 19.8, 15.6, 0.2.; IR (neat) ν_{max} 2960 (w), 1788 (m), 1249 (m), 1147 (s), 840 (s), 701 (m).; HRMS (DART) for $C_{24}H_{34}O_3F_3Si$ $[M+H]^+$ calculated: 431.222, found: 431.222. $[\alpha]^{20}_D$: 62.4 (c = 1.00, $CHCl_3$, l = 50 mm).



((4S,5S)-5-(((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methanol (3.127 (major)) and **((4R,5R)-5-(((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methanol (3.127 (minor))**. The title compounds were prepared according to a modified literature procedure.[61] To a solution of aluminum trichloride (281 mg, 2.10 mmol, 0.2 equiv) in acetone (23 mL) was slowly added ((2S,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methyl 2,2,2-trifluoroacetate (4.53 g, 10.52 mmol, 1 equiv) at RT under N_2. The mixture was neutralized with a solution of NaHCO3 (5%) and extracted with EtOAc (2 x 50 mL). The combined organic layers washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. TBAF (1 M, 26.30 mL, 26.3 mmol, 2.5 equiv) was added to the residue and the mixture was allowed to stir at rt for 2 hours before diluting with Et_2O (100 mL). Then, the mixture was washed with water (2 x 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude material was purified by silica gel column chromatography with 10-20% EtOAc/hexane (R_f = 0.1 in 17% EtOAc/hexane) as the eluent to yield the title compounds (1.7 g, 5.3 mmol, 50% yield, 3.5:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, ^{1}H NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.127(major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.32 (dd, *J* = 9.9, 2.4 Hz,

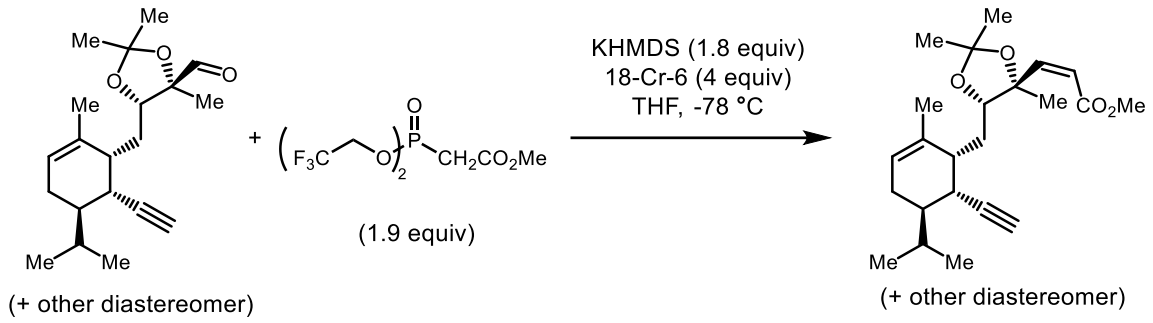
2H), 3.56 – 3.44 (m, 3H), 2.71 (ddd, *J* = 8.8, 4.9, 2.5 Hz, 1H), 2.40 – 2.31 (m, 1H), 2.12 (d, *J* = 2.4 Hz, 1H), 2.10 – 1.97 (m, 3H), 1.86 – 1.78 (m, 1H), 1.71 (s, 3H), 1.70 – 1.63 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.07 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 121.0, 107.2, 85.8, 82.8, 77.5, 71.4, 65.8, 39.0, 38.1, 33.7, 31.2, 28.9, 27.9, 26.8, 24.2, 22.0, 20.8, 18.9, 17.5.; **3.127(minor)**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1, 122.2, 107.2, 86.0, 83.1, 76.3, 71.6, 66.0, 65.5, 37.5, 35.3, 31.3, 28.3, 26.8, 24.1, 23.7, 20.9, 19.0, 15.9, 15.4.; IR (neat) ν_{max} 2958 (s), 2932 (s), 1456 (m), 1376 (s), 1091 (s), 628 (m).; HRMS (DART) for $C_{20}H_{33}O_3$ $[M+H]^+$ calculated: 321.242, found: 321.242. $[\alpha]^{20}_D$: 44.7 (c = 0.675, $CHCl_3$, l = 50 mm).



(4R,5S)-5-(((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolane-4-carbaldehyde (3.135 (major)) and (4S,5R)-5-(((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolane-4-carbaldehyde (3.135 (minor)). The title compounds were prepared according to a modified literature procedure.[77] In an oven-dried 100 mL round bottom flask under argaon, ((4S,5S)-5-(((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methanol (1.48g, 4.62 mmol, 1 equiv) was dissolved in DCM (14 mL) containing

(77) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Journal of the Chemical Society, Chemical Communications* **1987**, No. 21, 1625–1627.

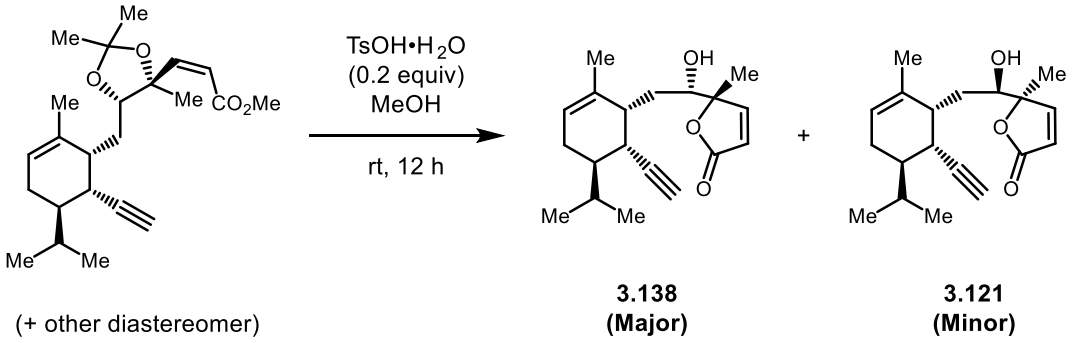
both the molecular sieves (0.9 g) and N-Methylmorpholine N-oxide (812 mg, 6.93 mmol, 1.5 equiv). After stirring the mixture for 10 min, Tetrapropylammonium perruthenate (81 mg, 0.23 mmol, 0.05 equiv) was added and the reaction was allowed to stir for 6 hours. When complete, the mixture was diluted with Et_2O and filtrated through a pad of silica gel, washing thoroughly with Et_2O. The filtrate was then concentrated in vacuo and purified by silica gel column chromatography with 0-7% EtOAc/hexane as the eluent to yield the title compounds (1.14 g, 3.6 mmol, 78% yield, 3.8:1 dr) as colorless oil. (Note: Note: NMR data is tentatively assigned due to the diastereomeric isomers, ^{1}H NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.135 (major)：**^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 5.35 (s, 1H), 4.41 (dd, *J* = 10.4, 2.4 Hz, 1H), 2.65 (ddd, *J* = 9.3, 4.9, 2.5 Hz, 1H), 2.37 – 2.31 (m, 1H), 2.09 – 2.05 (m, 1H), 2.04 (d, *J* = 2.5 Hz, 1H), 1.80 (dddd, *J* = 18.0, 8.0, 3.7, 1.9 Hz, 1H), 1.74 – 1.72 (m, 1H), 1.69 (s, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.19 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 4H), 0.82 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5, 135.4, 121.3, 109.5, 86.0, 85.5, 77.4, 77.2, 76.9, 76.6, 71.8, 38.7, 37.9, 33.6, 30.6, 28.5, 27.9, 26.5, 24.2, 21.9, 20.8, 17.1, 16.0.; **3.135 (minor)：**^{13}C NMR (126 MHz, $CDCl_3$) δ 202.3, 135.7, 122.5, 109.5, 86.4, 85.9, 75.8, 71.8, 66.0, 37.3, 35.1, 31.2, 28.5, 28.3, 24.1, 23.6, 20.8, 16.3, 15.8, 15.4.; IR (neat) ν_{max} 2959 (s), 2930 (s), 1737 (s), 1378 (s), 1220 (m), 1096 (s).; HRMS (DART) for $C_{20}H_{31}O_3$ $[M+H]^+$ calculated: 319.227, found: 319.228. $[\alpha]^{20}_D$: 50 (c = 0.80, $CHCl_3$, l = 50 mm).



Note: condition is not optimized, and the reaction cannot reach full conversion in this condition. The remaing starting material is not separatable from the product. The product is isolated as a mixture and used directly into the next step without further purification.

Methyl (Z)-3-((4S,5S)-5-(((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)acrylate (3.137 (major)) and **Methyl (Z)-3-((4R,5R)-5-(((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)acrylate (3.137 (minor))**. The title compounds were prepared according to a modified literature procedure.[63] A solution of methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (2.11 g, 6.6 mmol, 1.9 equiv) and 18-Crown-6 (3.69 g, 13.9 mmol, 4 equiv) in THF (17 mL) was allowed to stir at - 78°C under N_2, then a solution of KHMDS (0.5 M, 12.55 mL, 1.8 equiv) in THF was added. This was allowed to stir for 10 minutes at -78 °C. Then a solution of (4R,5S)-5-(((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolane-4-carbaldehyde (1.11 g, 3.49 mmol, 1 equiv) in THF (17 mL) was introduced at -78°C. The reaction was allowed to stir at -78 °C for 1 hour and it was quenched with sat. NH_4Cl (100 mL). The aqueous layer was extracted twice with Et_2O (50 mL) and the combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude material was purified by silica gel column chromatography with 0-5% EtOAc/hexane (Rf = 0.3 in 5% EtOAc/hexane) as the eluent to yield

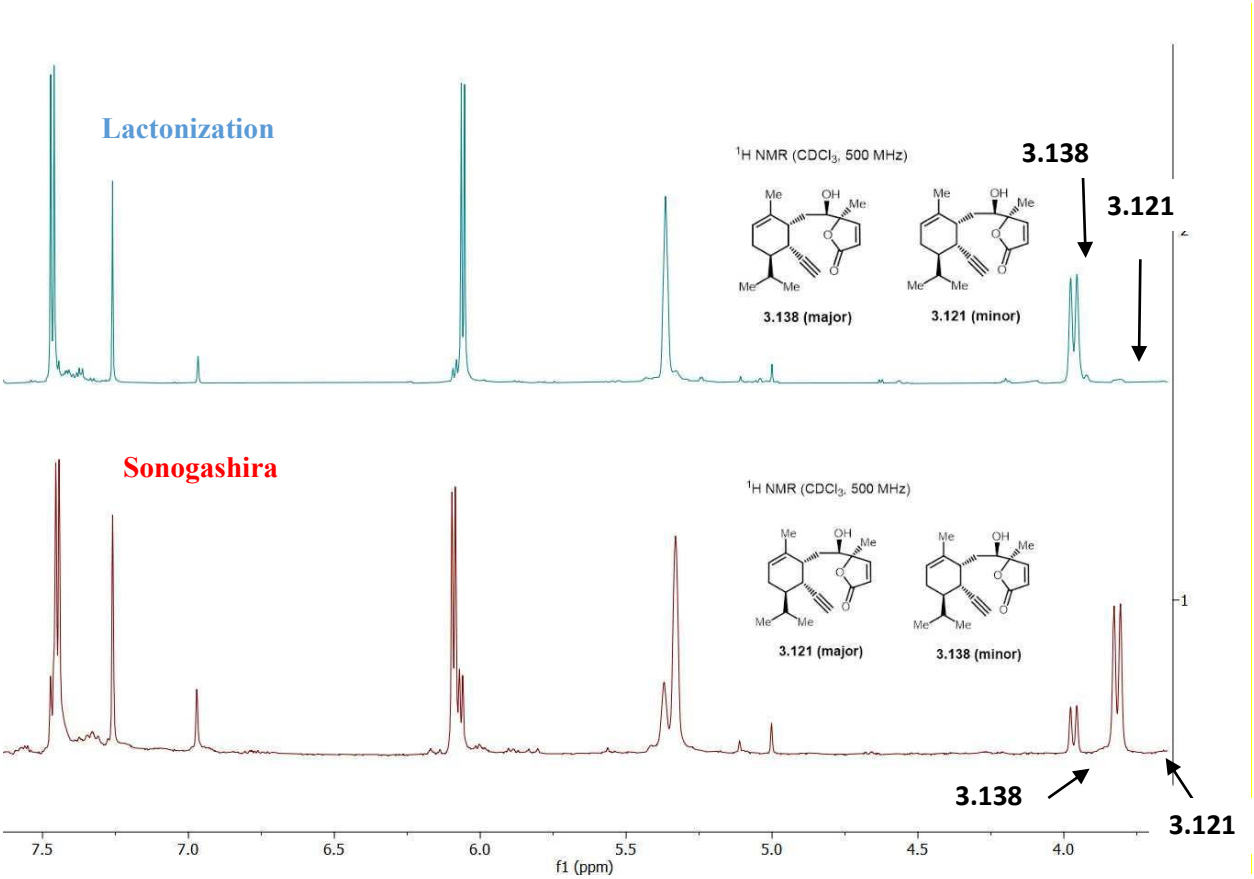
the title compounds (0.94 g, 2.5 mmol, 72% yield, 4:1 dr, 7:1 *Z:E*, containing 17% aldehyde) as colorless oil. (Note: characterization was conducted as a mixture, cannot fully identify the chemical shift, see the attached spectrum for ^{1}H NMR and ^{13}C NMR information.) **3.137**: IR (neat) ν_{max} 1733 (s), 1371 (s), 1252 (s), 1090 (s).; HRMS (DART) for $C_{23}H_{35}O_4$ $[M+H]^+$ calculated: 375.253, found: 375.253. $[\alpha]^{20}_D$: 49.2 (c = 1.00, $CHCl_3$, l = 50 mm).

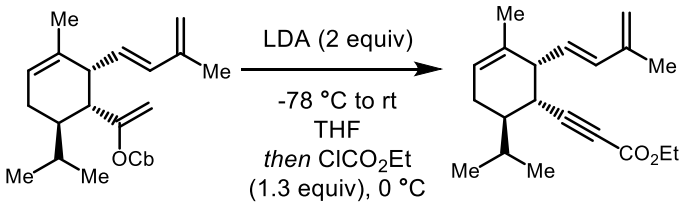


(S)-5-((S)-2-((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)-1-hydroxyethyl)-5-methylfuran-2(5H)-one (3.138) and **(R)-5-((R)-2-((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)-1-hydroxyethyl)-5-methylfuran-2(5H)-one (3.121)**. To a stirred solution of Methyl (Z)-3-((4S,5S)-5-(((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)acrylate (70 mg, 0.18 mmol, 1 equiv) in mathanol (1.5 mL) was added *p*-Toluenesulfonic acid monohydrate (6.9 mg, 0.036 mmol, 0.2 equiv) at rt, and the resulting mixture was allowed to stir for 12 h. The mixture was concentrated in vacuo and purified by silica gel column chromatography with 10-20% EtOAc/hexane (R_f = 0.6 in 30% EtOAc/hexane) as the eluent to yield the title compounds (40mg, 0.13 mmol, 73% yield, 11:1 dr) as white solid. (Note: NMR data is tentatively assigned due to the diastereomeric mixture, NMR data of the minor diastereomer is not clear enough to be fully

identified.) **3.138**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 5.7 Hz, 1H), 6.06 (d, *J* = 5.7 Hz, 1H), 5.36 (s, 1H), 3.97 (d, *J* = 10.8 Hz, 1H), 2.72 – 2.66 (m, 1H), 2.42 – 2.37 (m, 1H), 2.27 – 2.22 (m, 1H), 2.12 – 2.06 (m, 1H), 2.02 (d, *J* = 2.7 Hz, 1H), 1.86 – 1.75 (m, 2H), 1.68 (d, *J* = 2.0 Hz, 3H), 1.60 – 1.53 (m, 2H), 1.47 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 159.2, 135.1, 121.5, 121.4, 92.0, 86.0, 77.4, 77.2, 76.9, 74.4, 71.6, 39.1, 36.9, 33.2, 33.2, 27.9, 24.2, 21.9, 20.8, 18.6, 17.5.; HRMS (DART) for $C_{19}H_{27}O_3$ $[M+H]^+$ calculated: 303.195, found: 303.195. $[\alpha]^{20}_D$: -6.50 (c = 1.00, $CHCl_3$, l = 50 mm). (Note: NMR Spectral data are in accordance with the minor diastereomer isolated from the Sonogashira cross coupling, see Figure 3.1.)

Figure 3.1. ^{1}HNMR of Two Diastereomers.

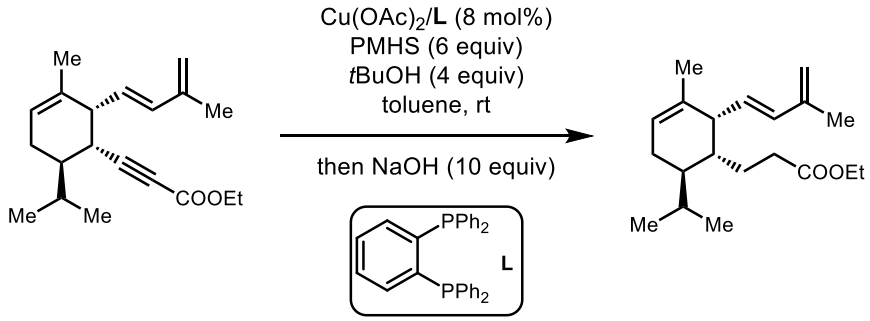




Note: Preparation of LDA: diisopropylamine (9.7 mL, 68.7 mmol) was dissolved in THF (36 mL) and cooled to -78 °C, then nBuLi (2.5 M, 24.1 mL) was added. The reaction was allowed to stir at 0 °C for 30 minutes, then used directly (~0.86 M).

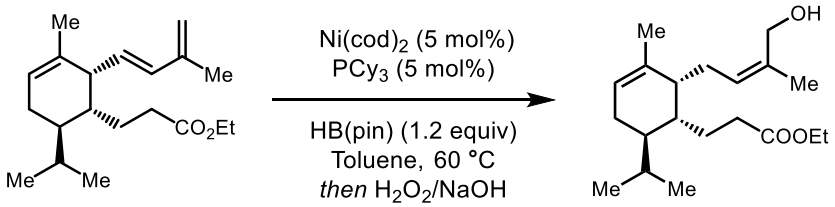
Ethyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)propiolate (3.152). The title compound was prepared according to a modified literature procedure.[42] 1-((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1- yl)cyclohex-3-en-1-yl)vinyl diisopropylcarbamate (5.4 g, 14.46 mmol) was added to a 100 mL round bottom flask, and dissolved in THF (15 mL). At -78 °C, LDA (0.86 M, 33.6mL, 2.0 equiv) was added, then the reaction was allowed to stir at RT for 1 hour. Next, the reaction was cooled to 0 °C and ethyl chloroformate (1.8 mL, 18.8 mmol, 1.3 equiv) was added, and the reaction was allowed to stir at 0 °C for 1 hour. The reaction was diluted with Et_2O (100 mL) and transferred to a separatory funnel, then extracted with H_2O (2x100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. The crude product was purified by silica gel column chromatography with 0-50% toluene/hexane as the eluent to yield the title compound (2.7 g, 9.0 mmol, 62% yield) as a pale-yellow oil. **3.152**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (d, *J* = 15.6 Hz, 1H), 5.68 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.49 (s, 1H), 4.93 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 1H), 2.72 (dd, *J* = 10.9, 5.0 Hz, 1H), 2.20 – 2.12 (m, 1H), 2.03 – 1.95 (m, 1H), 1.86 (s, 3H), 1.85 – 1.80 (m, 1H), 1.78 – 1.68 (m, 2H), 1.63 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J*

= 7.0 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 142.1, 136.1, 133.5, 128.7, 122.4, 115.7, 90.1, 76.9, 61.8, 46.3, 36.7, 35.7, 28.4, 24.0, 22.4, 20.9, 18.9, 15.5, 14.2.; IR (neat) ν_{max} 2961 (w), 2231 (w), 1711 (s), 1246 (s), 1082(w).; HRMS (DART) for $C_{20}H_{29}O_2$ $[M+H]^+$ calculated: 301.216, found: 301.218. $[\alpha]^{20}_D$: 246 (c = 1.00, $CHCl_3$, l = 50 mm).



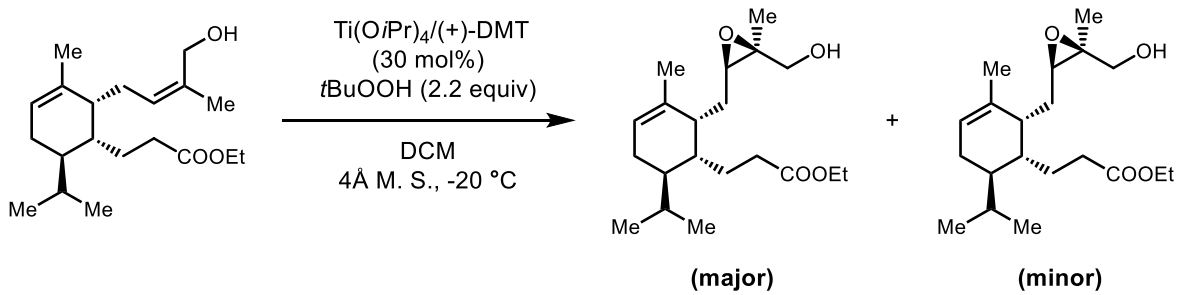
Ethyl 3-((1R,2R,6R)-2-((Z)-4-hydroxy-3-methylbut-2-en-1-yl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (3.155). The title compound was prepared according to a modified literature procedure.[70] Copper acetate (98 mg, 0.54 mmol, 0.06 equiv) and bis(diphenylphosphino)benzene (241 mg, 0.54 mmol, 0.06 equiv) are combined in a 100 mL flame-dried round bottom flask under argon. The reagents are dissolved in degassed *tert*-butanol (2.54 mL, 27.0 mmol, 3 equiv) and toluene (15 mL). The mixture was allowed to stir for 20 min at rt under an argon atmosphere. Polymethylhydrosiloxane (2.42 mL, 40 mmol, 4.5 equiv) is added via syringe whereupon the solution changes color from blue to yellow over a 10 min period. Then this solution was added to Ethyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)propiolate (2.7 g, 9.0 mmol, 1 equiv) via syringe. After 16 hours, the solvent was evaporated in vacuo and the residue was quickly purified with 10% EtOAc/hexane to yield a mixture of product and mono reduction alkenyl ester (incomplete reduction, usually 7:1 ratio). (**Note: condition is not optimized, if the reaction does reach full completion, please**

ignore the resubjecting process) The mixture was then resubjected to the condition described above with Copper acetate (33 mg, 0.18 mmol, 0.02 equiv), bis(diphenylphosphino)benzene (80 mg, 0.18 mmol, 0.02 equiv), *tert*-butanol (8.5 mL, 18.0 mmol, 1 equiv), polymethylhydrosiloxane (0.80 mL, 13.3 mmol, 1.5 equiv), and toluene (5 mL). After 16 hours, 100 mL of ether was added followed by 3N NaOH (30 mL, 10 equiv) was added and allowed to stir vigorously for 24 hours. Then, the organic layer was separated and washed with H_2O (2x100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography with 0-8% EtOAc/hexane (R_f = 0.3 in 9% EtOAc/hexane) as the eluent to yield the title compounds (2.5g, 8.2 mmol, 91%, containing trace "silane" residue) as colorless oil. **3.155**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (d, *J* = 15.6 Hz, 1H), 5.47 – 5.41 (m, 2H), 4.9 (d, *J* = 4.7 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.65 (d, *J* = 9.6 Hz, 1H), 2.42 (ddd, *J* = 16.0, 9.0, 5.2 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.03 – 1.89 (m, 3H), 1.83 (s, 3H), 1.80 – 1.74 (m, 1H), 1.59 (s, 3H), 1.55 – 1.51 (m, 2H), 1.33 – 1.27 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 142.2, 135.1, 134.6, 129.2, 122.2, 115.0, 60.3, 46.0, 38.9, 37.5, 31.7, 26.5, 24.6, 24.1, 22.3, 21.3, 19.0, 14.7, 14.4. IR (neat) ν_{max} 2959 (m), 1736 (s), 1164 (m), 1057 (m).; HRMS (DART) for $C_{20}H_{33}O_2$ $[M+H]^+$ calculated: 305.248, found: 305.247. $[\alpha]^{20}_D$: 230 (c = 0.65, $CHCl_3$, l = 50 mm).



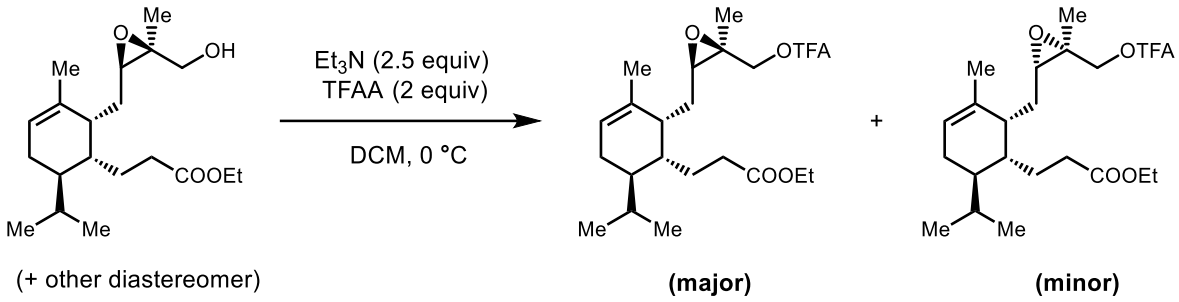
Ethyl 3-((1R,2R,6R)-2-((Z)-4-hydroxy-3-methylbut-2-en-1-yl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (3.156). The title compound was prepared according to a modified literature procedure.[46] To an oven-dried 50 mL RBF was added $Ni(cod)_2$ (110 mg, 0.40 mmol, 0.05 equiv), PCy_3 (112 mg, 0.40 mmol, 0.05 equiv), ethyl 3-((1R,2R,6R)-2-((Z)-4-hydroxy-3-methylbut-2-en-1-yl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (2.4 g, 8.0 mmol, 1 equiv), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.39 mL, 9.60 mmol, 1.2 equiv.), and toluene (8 mL). The reaction was allowed to stir at 60 °C overnight. The reaction solution was diluted with Et_2O (10 mL), transferred to a separatory funnel and the organic layer was washed with H_2O (2x10 mL) then brine (10 mL). The organic layer was dried over sodium sulfate, then filtered, and concentrated. The crude product was was dissolved in THF (12 mL) and cooled to 0 °C. To this was added NaOH (3 M in H_2O, 8.0 mL, 24 mmol, 3 equiv) and H_2O_2 (30% aqueous solution, 4.0 mL, 38.8 mmol, 4.85 equiv), and the reaction was allowed to stir at RT for 1 hour. The reaction was cooled to 0 °C and quenched with saturated aqueous sodium thiosulfate (20 mL) (caution: exothermic, gas evolution), then transferred to a separatory funnel. The aqueous layer was removed, and the organic layer was washed with H_2O (2x10 mL) then brine (1x20mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. The crude product was purified by silica gel column chromatography with 0-10% EtOAc/hexane (R_f = 0.3 in 17% EtOAc/hexane) as the eluent, to yield the title compound (1.65 g, 5.1 mmol, 63% yield) as colorless oil. **3.157**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (s, 1H), 5.27 (t, *J* = 7.9 Hz, 1H), 4.30 (d, *J* = 12.1 Hz, 1H), 4.12 (qd, *J* = 7.2, 1.8 Hz, 2H), 3.97 (d, *J* = 12.0 Hz, 1H), 2.35 – 2.22 (m, 2H), 2.21 – 2.08 (m, 3H), 1.98 – 1.91 (m, 1H), 1.85 – 1.82 (m, 1H), 1.81 (s, 3H), 1.79 – 1.73 (m, 1H), 1.71 – 1.63 (m, 4H), 1.61 – 1.51 (m, 2H), 1.38 (p, *J* = 6.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 136.3, 134.9, 127.7,

121.5, 61.6, 60.6, 39.5, 38.6, 37.1, 32.2, 27.5, 27.1, 24.3, 23.1, 22.8, 21.5, 21.0, 17.9, 14.4. IR (neat) ν_{max} 2958 (m), 2928 (m), 1734 (s), 1162 (m), 1005 (m).; HRMS (DART) for $C_{20}H_{35}O_3$ $[M+H]^+$ calculated: 323.258, found: 323.257. $[\alpha]^{20}_D$: 63.0 (c = 1.00, $CHCl_3$, l = 50 mm).



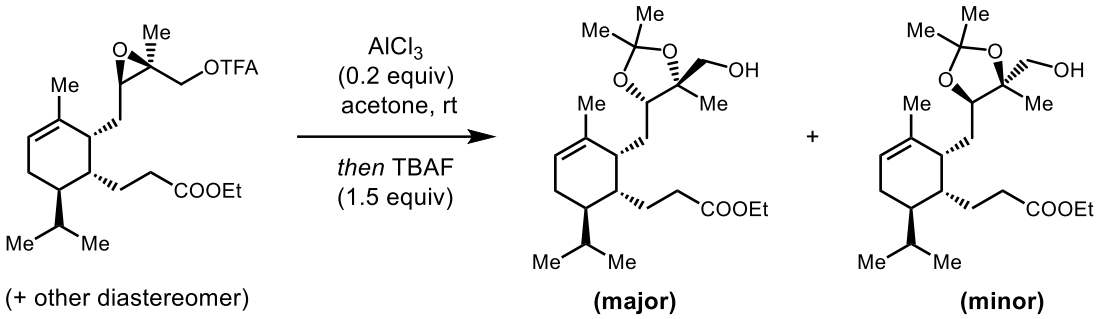
Ethyl 3-((1R,2R,6R)-2-(((2R,3S)-3-(hydroxymethyl)-3-methyloxiran-2-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (3.157 (major)) and **ethyl 3-((1R,2R,6R)-2-(((2S,3R)-3-(hydroxymethyl)-3-methyloxiran-2-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (3.157 (minor))**. The title compounds were prepared according to a modified literature procedure.[57] To a stirred suspension of powdered (+) dimethyl tartrate (321 mg, 1.80 mmol, 0.36 equiv) and 4Å molecular seives (0.4 g) in dry DCM (10 ml) was added Ti(O*i*Pr)$_4$ (0.45 mL, 1.50 mmol, 0.3 equiv) at -25 °C (dry ice bath) and allowed to stir vigorously for 25 min, *t*BuOOH (5.5 M in decane, anhydrous, 2.0 mL, 2.2 equiv) was added and the mixture allowed to stir for 25 min. Ethyl 3-((1R,2R,6R)-2-((Z)-4-hydroxy-3-methylbut-2-en-1-yl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (1.6 g, 5.0 mmol, 1 equiv) in DCM (10 mL) was added and mixture was allowed to stir for 25 mins. The flask was then put into a freezer (-20 °C) and kept for 16 hours before diluting with Et_2O (20 ml), and filtering through a pad of Celite, washing thoroughly with Et_2O. The filtrate is washed with brine (50 mL) and the organic layer was dried over sodium sulfate, then filtered and concentrated in vacuo. The crude material was purified by silica gel column chromatography with 0-15% EtOAc/hexane (R_f = 0.2 in 17% EtOAc/hexane) as

the eluent to yield the title (1.51g, 4.5 mmol, 89% yield, 15:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric mixture, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.157 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 2H), 2.93 (dd, *J* = 7.2, 5.6 Hz, 1H), 2.39 (ddd, *J* = 15.2, 9.7, 5.4 Hz, 1H), 2.28 – 2.16 (m, 2H), 2.00 – 1.90 (m, 2H), 1.88 – 1.77 (m, 4H), 1.70 (s, 3H), 1.58 (td, *J* = 10.4, 4.8 Hz, 1H), 1.54 – 1.45 (m, 2H), 1.38 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 136.6, 122.4, 64.6, 63.8, 61.5, 60.3, 38.0, 37.8, 37.8, 31.9, 27.8, 26.8, 24.2, 23.5, 23.2, 20.9, 20.2, 16.0, 14.2. IR (neat) ν_{max} 2959 (m), 2930 (m), 1733 (s), 1164 (m), 1035 (m).; HRMS (DART) for $C_{20}H_{35}O_4$ $[M+H]^+$ calculated: 339.253, found: 339.254. $[\alpha]^{20}_D$: 96.0 (c = 1.00, $CHCl_3$, l = 50 mm).



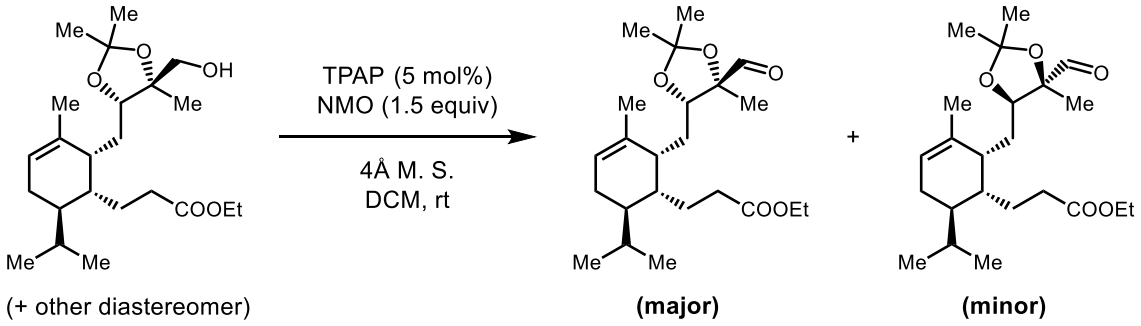
Ethyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-(((2R,3S)-3-methyl-3-((2,2,2-trifluoroacetoxy)methyl)oxiran-2-yl)methyl)cyclohex-3-en-1-yl)propanoate (3.159 (major)) and **ethyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-(((2S,3R)-3-methyl-3-((2,2,2-trifluoroacetoxy)methyl)oxiran-2-yl)methyl)cyclohex-3-en-1-yl)propanoate (3.159 (minor))**. To a 100 mL round bottom flask equipped with a stir bar, was added Ethyl 3-((1R,2R,6R)-2-(((2R,3S)-3-(hydroxymethyl)-3-methyloxiran-2-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (1.48 g, 4.37 mmol, 1 equiv) followed by dichloromethane (12 mL) under N_2.

The reaction was cooled to 0 °C in an ice bath and charged with Et_3N (1.52 mL, 10.9 mmol, 2.5 equiv) followed by dropwise addition of trifluoroacetic anhydride (1.24 mL, 8.7 mmol. 2.0 equiv). The reaction was allowed to stir in the cold room (4 °C) for 16 hours. The reaction was then diluted with deionized water (20 mL) and extracted twice with diethyl ether (20 mL), the organic layers were combined and washed with 1M HCl (2 x 20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuo. The crude material was purified by silica gel column chromatography with 0-7% EtOAc/hexane (R_f = 0.3 in 9% EtOAc/hexane) as the eluent to yield the title compounds (1.45 g, 3.3 mmol, 76% yield, 15:1 dr) as colorless oil. (Note: Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.159 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 1H), 4.39 (d, *J* = 11.7 Hz, 2H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.97 (dd, *J* = 6.8, 5.7 Hz, 1H), 2.37 (ddd, *J* = 15.2, 9.4, 5.7 Hz, 1H), 2.24 (ddt, *J* = 29.0, 11.8, 6.7 Hz, 2H), 1.99 – 1.91 (m, 1H), 1.89 – 1.73 (m, 4H), 1.69 (d, *J* = 1.8 Hz, 3H), 1.62 (tdd, *J* = 9.6, 5.8, 4.2 Hz, 1H), 1.55 – 1.43 (m, 2H), 1.40 (s, 3H), 1.39 – 1.34 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 157.5, 157.2, 135.5, 122.8, 68.9, 64.1, 60.5, 58.4, 38.1, 37.9, 37.8, 32.0, 28.0, 27.0, 24.3, 23.5, 23.2, 21.1, 19.9, 16.4, 14.4. IR (neat) ν_{max} 2961 (w), 1788 (m), 1732 (m), 1220 (m), 1147 (s), 1034 (w).; HRMS (DART) for $C_{22}H_{34}O_5F_3$ $[M+H]^+$ calculated: 435.235, found: 435.235. $[\alpha]^{20}_D$: 132 (c = 1.00, $CHCl_3$, l = 50 mm).



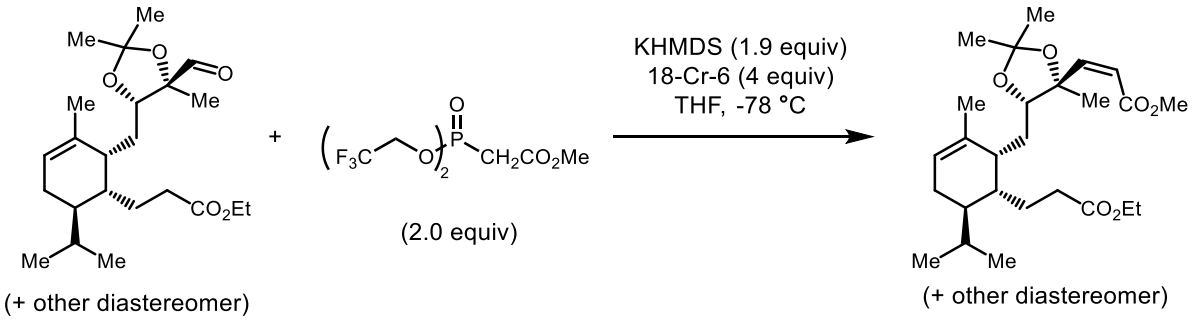
Ethyl 3-((1R,2R,6R)-2-(((4S,5S)-5-(hydroxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (3.160 (major)) and **ethyl 3-((1R,2R,6R)-2-(((4R,5R)-5-(hydroxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (3.160 (minor))**. The title compounds were prepared according to a modified literature procedure.[61] To a solution of aluminum trichloride (87 mg, 0.65 mmol, 0.2 equiv) in acetone (10 mL) was slowly added ethyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-(((2R,3S)-3-methyl-3-((2,2,2-trifluoroacetoxy)methyl)oxiran-2-yl)methyl)cyclohex-3-en-1-yl)propanoate (1.42 g, 3.3 mmol, 15:1 dr, 1 equiv) at RT under N_2. The mixture was neutralized with a solution of $NaHCO_3$ (5%) and extracted with EtOAc (2 x 20 mL). The combined organic layers washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. TBAF (1 M, 3.3 mL, 4.9 mmol, 1.5 equiv) was added to the residue and the mixture was allowed to stir at rt for 2 hours before diluting with Et_2O (30 mL). Then, the mixture was washed with water (2 x 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude material was purified by silica gel column chromatography with 10-25% EtOAc/hexane (R_f = 0.2 in 20% EtOAc/hexane, minor diastereomer R_f = 0.3 in 20% EtOAc/hexane) as the eluent to yield the title compounds (0.8 g, 2.0 mmol, 62% yield, 8:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.160 (major)**: ^{1}H NMR

(500 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.16 – 4.08 (m, 3H), 3.57 (d, *J* = 11.8 Hz, 1H), 3.46 (d, *J* = 11.8 Hz, 1H), 2.41 – 2.35 (m, 1H), 2.32 (td, *J* = 7.3, 2.2 Hz, 2H), 2.00 – 1.93 (m, 1H), 1.91 – 1.82 (m, 1H), 1.78 – 1.68 (m, 3H), 1.67 (s, 3H), 1.61 – 1.55 (m, 2H), 1.46 – 1.40 (m, 4H), 1.36 – 1.31 (m, 4H), 1.25 (td, *J* = 7.2, 0.9 Hz, 3H), 1.07 (s, 3H), 0.86 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 135.5, 121.2, 107.1, 82.7, 75.5, 66.2, 60.6, 38.9, 35.3, 32.0, 28.8, 28.2, 27.5, 26.5, 24.3, 22.2, 22.1, 20.5, 19.6, 18.9, 14.4.; IR (neat) ν_{max} 2960 (br), 1733 (s), 1376 (w), 1217 (w), 1180 (w).; HRMS (DART) for $C_{23}H_{41}O_5$ $[M+H]^+$ calculated: 397.295, found: 397.295. $[\alpha]^{20}_D$: 7.80 (c = 1.00, $CHCl_3$, l = 50 mm).



Ethyl 3-((1R,2R,6R)-2-(((4S,5R)-5-formyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (3.161 (major)) and **Ethyl 3-((1R,2R,6R)-2-(((4R,5S)-5-formyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (3.161 (minor))**. The title compounds were prepared according to a modified literature procedure.[79] In an oven-dried 25 mL round bottom flask under argaon, ethyl 3-((1R,2R,6R)-2-(((4S,5S)-5-(hydroxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (0.72g, 1.8 mmol, 1 equiv) was dissolved in DCM (8 mL) containing both the molecular sieves (0.32 g) and N-methyl morpholine N-oxide (319 mg, 2.7 mmol, 1.5 equiv). After stirring the mixture for 10 min, tetrapropyl

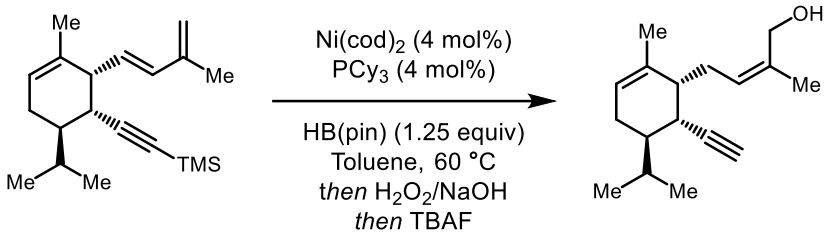
ammonium perruthenate (32 mg, 0.091 mmol, 0.05 equiv) was added and the reaction was allowed to stir for 6 hours. When complete, the mixture was diluted with Et_2O and filtrated through a pad of silica gel, washing thoroughly with Et_2O. The filtrate was then concentrated in vacuo and purified by silica gel column chromatography with 0-10% EtOAc/hexane (R_f = 0.2 in 9% EtOAc/hexane) as the eluent to yield the title compounds (0.49 g, 1.24 mmol, 68% yield, 13:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.161 (major)：** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 5.30 (s, 1H), 4.19 (dd, *J* = 10.9, 2.0 Hz, 1H), 4.15 – 4.07 (m, 2H), 2.38 – 2.22 (m, 3H), 1.98 – 1.91 (m, 1H), 1.88 – 1.80 (m, 1H), 1.76 – 1.66 (m, 3H), 1.64 (s, 3H), 1.61 – 1.54 (m, 1H), 1.49 (s, 3H), 1.47 – 1.42 (m, 2H), 1.41 (s, 3H), 1.36 – 1.32 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 173.8, 135.1, 121.6, 109.4, 86.1, 74.2, 60.4, 38.5, 35.1, 31.8, 28.4, 27.4, 27.3, 26.2, 24.2, 22.1, 22.1, 20.6, 16.2, 14.4.; IR (neat) ν_{max} 2961 (m), 1734 (s), 1375 (m), 1210 (m), 1179 (m).; HRMS (DART) for $C_{23}H_{39}O_5$ $[M+H]^+$ calculated: 395.279, found: 395.280. $[\alpha]^{20}_D$: 39 (c = 0.80, $CHCl_3$, l = 50 mm).



Methyl (Z)-3-((4S,5S)-5-(((1R,5R,6R)-6-(3-ethoxy-3-oxopropyl)-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)acrylate (3.162 (major))

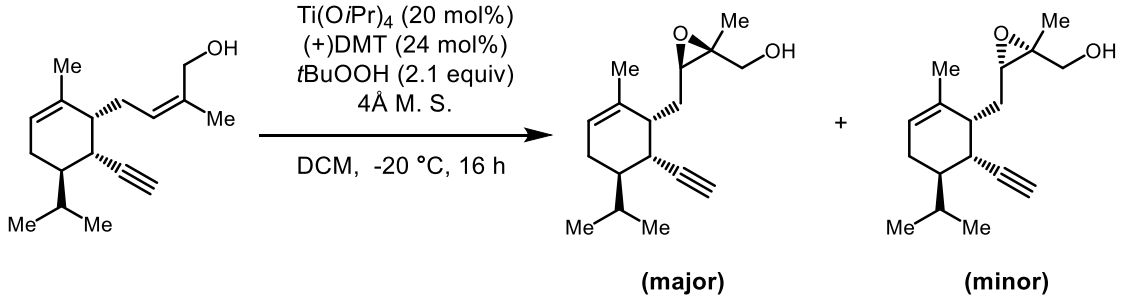
and **methyl (Z)-3-((4R,5R)-5-(((1R,5R,6R)-6-(3-ethoxy-3-oxopropyl)-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)acrylate (3.162 (minor))**. The title compounds were prepared according to a modified literature procedure.[63] A solution of methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (0.71 g, 2.23 mmol, 2.0 equiv) and 18-Crown-6 (1.18 g, 4.46 mmol, 4 equiv) in THF (6 mL) was allowed to stir at - 78°C under N_2, then a solution of KHMDS (0.5 M, 4.24 mL, 1.9 equiv) in THF was added. This was allowed to stir for 10 minutes at -78 °C. Then a solution of Ethyl 3-((1R,2R,6R)-2-(((4S,5R)-5-formyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propanoate (0.44 g, 1.12 mmol, 1 equiv) in THF (6 mL) was introduced at -78°C. The reaction was allowed to stir at -78 °C for 1 hour and it was quenched with sat. NH_4Cl (20 mL). The aqueous layer was extracted twice with Et_2O (10 mL) and the combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude material was purified by silica gel column chromatography with 0-7% EtOAc/hexane (Rf = 0.2 in 9% EtOAc/hexane) as the eluent to yield the title compounds (0.45 g, 1.0 mmol, 90% yield, 11:1 dr, 18:1 *Z:E*) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.162 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (d, *J* = 12.6 Hz, 1H), 5.78 (d, *J* = 12.7 Hz, 1H), 5.30 (s, 1H), 4.13 – 4.06 (m, 3H), 3.69 (s, 3H), 2.39 (s, 1H), 2.30 (t, *J* = 7.8 Hz, 2H), 1.98 (ddd, *J* = 18.1, 6.0, 2.9 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.78 – 1.68 (m, 3H), 1.67 (s, 3H), 1.64 – 1.59 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 167.3, 146.2, 135.4, 121.1, 119.5, 107.7, 83.1, 79.5, 60.1, 38.7, 35.0, 32.1, 28.8, 28.2, 27.3, 26.2, 24.1, 22.1, 22.0, 20.5, 14.3.; IR (neat) ν_{max} 2960 (w), 1733 (s), 1376

(m), 1255 (m), 1102 (m).; HRMS (DART) for $C_{26}H_{43}O_6$ $[M+H]^+$ calculated: 431.305, found: 431.305. $[\alpha]^{20}_D$: 21.2 (c = 1.00, $CHCl_3$, l = 50 mm).



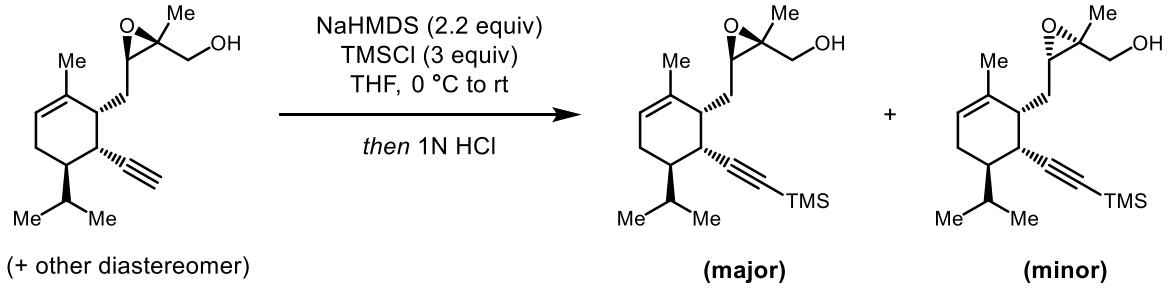
(Z)-4-((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)-2-methylbut-2-en-1-ol (3.169). The title compound was prepared according to a modified literature procedure.[46] To an oven-dried 100 mL RBF was added $Ni(cod)_2$ (206 mg, 0.75 mmol, 0.04 equiv), PCy_3 (210 mg, 0.75 mmol, 0.04 equiv), (((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1- yl)ethynyl)trimethylsilane (5.6 g, 18.7 mmol, 1 equiv), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.4 mL, 23.4 mmol, 1.25 equiv), and toluene (19 mL). The reaction was allowed to stir at 60 °C overnight. The reaction solution was transferred to a separatory funnel and the organic layer was washed with H_2O (2x20 mL) then brine (20 mL). The organic layer was dried over sodium sulfate, then filtered, and concentrated. The crude product was was dissolved in THF (28 mL) and cooled to 0 °C. To this was added NaOH (3 M in H_2O, 18.7 mL, 3 equiv) and H_2O_2 (29% aqueous solution, 8.8 mL, 82.5 mmol, 4.4 equiv), and the reaction was allowed to stir at RT for 1 hour. The reaction was cooled to 0 °C and quenched with saturated aqueous sodium thiosulfate (20 mL) (caution: exothermic, gas evolution), then transferred to a separatory funnel. The aqueous layer was removed, and the organic layer was washed with H_2O (2x20 mL) then brine (1x30 mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. TBAF (1 M, 24.3 mL, 1.3 equiv) was then added to the residue and the mixture was allowed to stir at rt

for 1 hours before diluting with Et_2O (30 mL). Then, the mixture was washed with water (2 x 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with 5-10% EtOAc/hexane (R_f = 0.2 in 10% EtOAc/hexane) as the eluent, to yield the title compound (4.14 g, 16.8 mmol, 90% yield) as colorless oil. **3.169**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.34 (t, *J* = 7.6 Hz, 1H), 4.14 (qd, *J* = 11.8, 6.1 Hz, 2H), 2.62 (ddd, *J* = 9.4, 4.9, 2.5 Hz, 1H), 2.51 – 2.37 (m, 2H), 2.22 – 2.17 (m, 1H), 2.15 (d, *J* = 2.5 Hz, 1H), 2.11 – 1.99 (m, 2H), 1.84 – 1.76 (m, 1H), 1.80 (s, 3H), 1.70 – 1.64 (m, 1H), 1.68 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 134.9, 127.6, 121.7, 86.3, 71.2, 61.7, 41.5, 38.5, 34.2, 28.9, 28.0, 24.2, 22.6, 21.6, 20.7, 16.7.; IR (neat) ν_{max} 3307 (m), 2859 (s), 2931 (m), 1451 (w), 1002 (m), 628 (m).; HRMS (DART) for $C_{17}H_{27}O$ $[M+H]^+$ calculated: 247.206, found: 247.205. $[\alpha]^{20}_D$: 125 (c = 1.00, $CHCl_3$, l = 50 mm).



((2S,3R)-3-(((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.170 (major)) and **((2R,3S)-3-(((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.170 (minor))**. Starting from (Z)-4-((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)-2-methylbut-2-en-1-ol (4.1g, 16.6 mmol) and following an identical procedure to that described

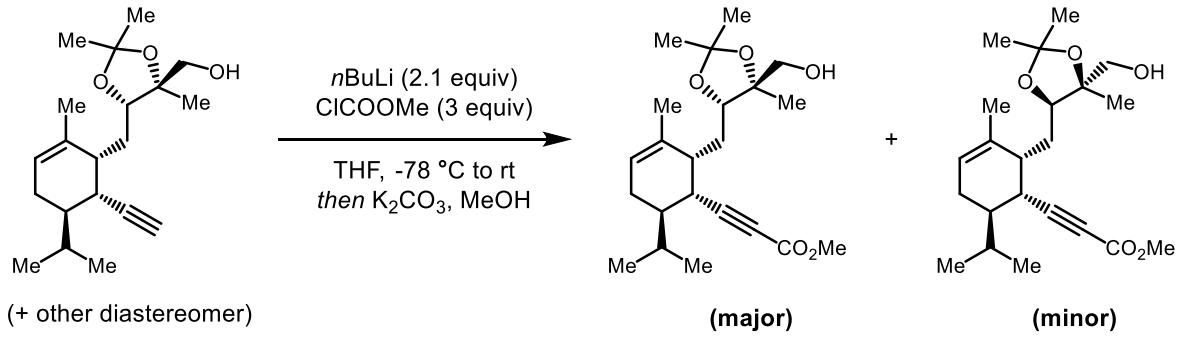
for the preparation of **3.102**, title compounds were isolated (3.74g, 14.2 mmol, 86%, 10:1 dr). (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.170 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (s, 1H), 3.65 (s, 2H), 2.97 (dd, *J* = 8.5, 4.2 Hz, 1H), 2.62 (ddd, *J* = 11.0, 4.9, 2.5 Hz, 1H), 2.34 (q, *J* = 5.7 Hz, 1H), 2.25 – 2.13 (m, 3H), 2.10 (s, 1H), 2.01 – 1.93 (m, 1H), 1.82 – 1.73 (m, 2H), 1.71 (s, 3H), 1.61 (tdd, *J* = 10.3, 6.1, 4.3 Hz, 1H), 1.38 (s, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.6, 122.6, 85.6, 72.2, 63.9, 63.8, 61.7, 40.3, 37.4, 34.8, 28.5, 28.2, 23.9, 22.6, 20.7, 20.0, 15.4.; IR (neat) ν_{max} 3305 (br), 2960 (s), 2929 (m), 1042 (m).; HRMS (DART) for $C_{17}H_{27}O_2$ $[M+H]^+$ calculated: 263.201, found: 263.202. $[\alpha]^{20}_D$: 153 (c = 1.00, $CHCl_3$, l = 50 mm).



((2S,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.102 (major)) and **((2R,3S)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.102 (minor))**. The title compounds were prepared according to a modified literature procedure.[78] Under a positive pressure of N_2, a solution ((2S,3R)-3-(((1R,5R,6R)-6-

(78) Yang, Q.; Draghici, C.; Njardarson, J. T.; Li, F.; Smith, B. R.; Das, P. *Organic & biomolecular chemistry* **2014**, *12*, 330–344.

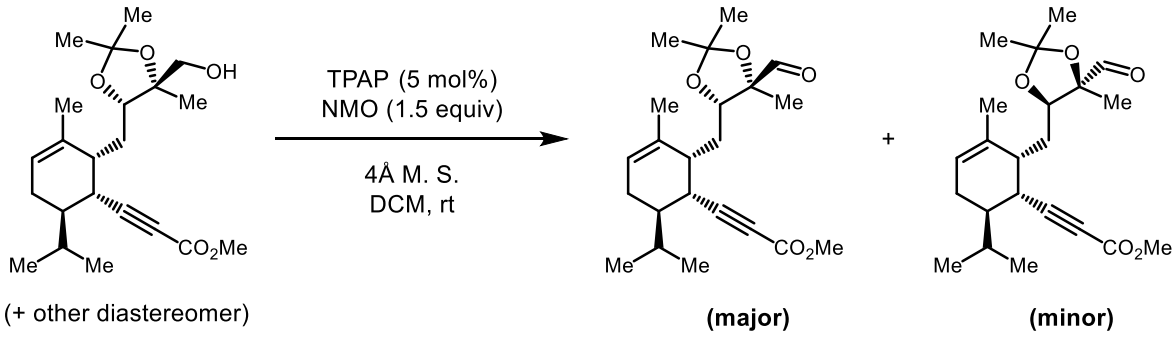
ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2-methyloxiran-2-yl)methanol (3.67g, 14 mmol) in THF (56 mL) was cooled to 0 °C, and NaHMDS (2 M in THF, 15.4 mL, 2.2 equiv) was added. After stirring for 30 min at 0 °C, chlorotrimethylsilane (5.33 mL, 42.0 mmol, 3 equiv) was added dropwise. Once the addition was completed, the cold bath was removed, and the reaction was allowed to stir at RT for 1 h. The reaction was cooled to 0 °C, quenched by water (18 mL), then hydrochloric acid (1 M, 28.0 mL, 2 equiv) was added to the crude reaction mixture and allowed to stir at RT for 1.5 h. The complete consumption of the TMS ether was observed by TLC. The reaction mixture was poured into a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na2SO4, filtered, and concentrated. The crude material was purified by silica gel column chromatography with 0-10% EtOAc/hexane (R_f = 0.2 in 10% EtOAc/hexane) as the eluent to yield the title compounds (4.16 g, 12.4 mmol, 89% yield, 10:1 dr) as colorless oil. Spectral data are in accordance with the literature.[40]



Methyl 3-((1R,2R,6R)-2-(((4S,5S)-5-(hydroxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (3.174 (major)) and **methyl 3-((1R,2R,6R)-2-(((4R,5R)-5-(hydroxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (3.174 (minor))**. Under a positive pressure of

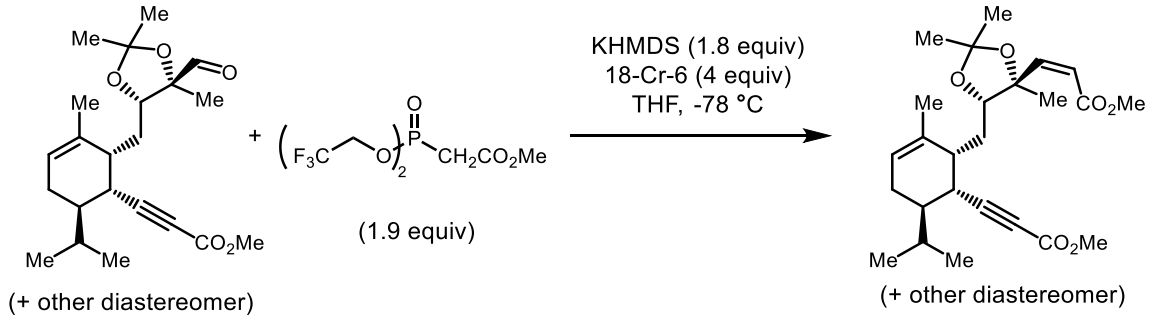
N_2, a solution of ((4S,5S)-5-(((1R,5R,6R)-6-Ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methanol (186 mg, 0.58 mmol) in THF (1.2 mL) was cooled to -78 °C, and *n*BuLi (2.47M in hexane, 0.49 mL, 2.1 equiv) was added dropwise. After stirring for 1 hour at -78 °C, methyl chloroformate (0.13 mL, 1.7 mmol, 3 equiv) was added dropwise. Once the addition was completed, the cold bath was removed, and the reaction was allowed to stir at RT for 1 h. The reaction was quenched with sat. NH_4Cl (3 mL) and extracted with Et_2O (3x3 mL). The combined organic layer was washed with H_2O (5 mL) then brine (5 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in MeOH (1.8 mL) and potassium carbonate (78mg, 0.23 mmol, 0.4 equiv) was added. The mixture was allowed to stir at RT for 2 hours and monitored by TLC (product R_f = 0.3 in 20% EtOAc/hexane, while R_f of **3.175** is 0.5 in 20% EtOAc/hexane). Once complete, the reaction was diluted with Et_2O (20 mL) and transferred to a separatory funnel, then extracted with H_2O (2x10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. The crude product was purified by silica gel column chromatography with 10-20% EtOAc/hexane as the eluent to yield the title compounds (135 mg, 0.36 mmol, 61% yield, 3.5:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers) **3.174 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) 5.32 (s, 1H), 4.23 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.73 (s, 3H), 3.54 – 3.34 (m, 2H), 2.81 (dd, *J* = 8.9, 4.9 Hz, 1H), 2.53 – 2.37 (m, 1H), 2.09 – 1.94 (m, 2H), 1.86 – 1.78 (m, 1H), 1.69 (s, 3H), 1.68 – 1.62 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.05 (s, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 135.4, 120.8, 107.1, 91.5, 82.6, 77.9, 75.6, 66.2, 52.8, 38.6, 37.9, 34.0, 31.6, 28.8, 28.0, 26.7, 24.1, 21.8, 20.7, 18.9, 17.3.; **3.174 (minor)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (s, 1H), 4.19 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.73 (s, 3H), 3.54 – 3.34 (m, 2H), 2.75 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.53 – 2.37 (m, 1H), 2.09

– 1.94 (m, 2H), 1.86 – 1.78 (m, 1H), 1.72 (s, 3H), 1.68 – 1.62 (m, 2H), 1.42 (s, 3H), 1.34 (s, 3H), 1.05 (s, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 135.7, 121.9, 107.2, 91.3, 83.0, 76.6, 76.1, 65.5, 52.5, 38.9, 37.5, 35.5, 28.7, 28.5, 26.7, 26.3, 24.0, 23.3, 20.7, 16.0, 14.1.; IR (neat) ν_{max} 2959 (w), 2230 (w), 1715 (s), 1435 (w), 1252 (s), 1093 (m).; HRMS (DART) for $C_{22}H_{35}O_5$ $[M+H]^+$ calculated: 379.248, found: 379.247. $[\alpha]^{20}_D$: 37.4 (c = 1.00, $CHCl_3$, l = 50 mm).



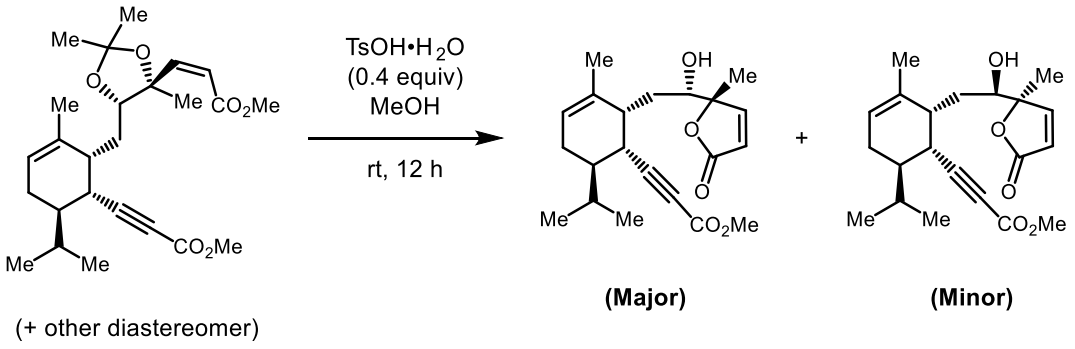
Methyl 3-((1R,2R,6R)-2-(((4S,5R)-5-formyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (3.176 (major)) and **methyl 3-((1R,2R,6R)-2-(((4R,5S)-5-formyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (3.176 (minor))**. Starting from **3.174** (130 mg, 0.34 mmol) and following an identical procedure to that described for the preparation of **3.161**, title compounds were isolated (82 mg, 0.22 mmol, 63%, 4:1 dr). (Note: NMR data is tentatively assigned due to the diastereomeric isomers) **3.174 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 5.35 (s, 1H), 4.41 (dd, J = 10.4, 2.4 Hz, 1H), 2.65 (ddd, J = 9.3, 4.9, 2.5 Hz, 1H), 2.34 (s, 1H), 2.10 – 2.05 (m, 2H), 2.04 (d, J = 2.5 Hz, 1H), 1.86 – 1.77 (m, 1H), 1.69 (s, 3H), 1.66 – 1.53 (m, 2H), 1.49 (s, 3H), 1.43 (s, 3H), 1.19 (s, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4, 135.4, 121.3, 109.5, 86.0, 85.5, 76.6, 71.7, 38.7, 37.9, 33.6, 30.6, 28.5, 27.9,

26.5, 24.1, 21.9, 20.8, 17.1, 16.0.; **3.174 (minor)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 5.35 (s, 1H), 4.31 (dd, *J* = 10.3, 3.7 Hz, 1H), 2.59 (ddd, *J* = 10.7, 4.6, 2.5 Hz, 1H), 2.34 (s, 1H), 2.19 – 2.15 (m, 2H), 2.13 (d, *J* = 2.6 Hz, 1H), 1.86 – 1.77 (m, 1H), 1.74 (s, 3H), 1.66 – 1.53 (m, 2H), 1.51 (s, 3H), 1.41 (s, 3H), 1.22 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.3, 135.6, 122.5, 109.5, 86.4, 85.9, 75.8, 71.8, 66.0, 37.3, 35.1, 31.2, 28.5, 28.3, 24.0, 23.6, 20.8, 16.3, 15.8, 15.4.; IR (neat) ν_{max} 1735 (m), 1714 (s), 1248 (s), 1223 (m), 751 (w).; HRMS (DART) for $C_{22}H_{33}O_5$ $[M+H]^+$ calculated: 377.232, found: 377.231. $[\alpha]^{20}_D$: 63.0 (c = 1.00, $CHCl_3$, l = 50 mm).



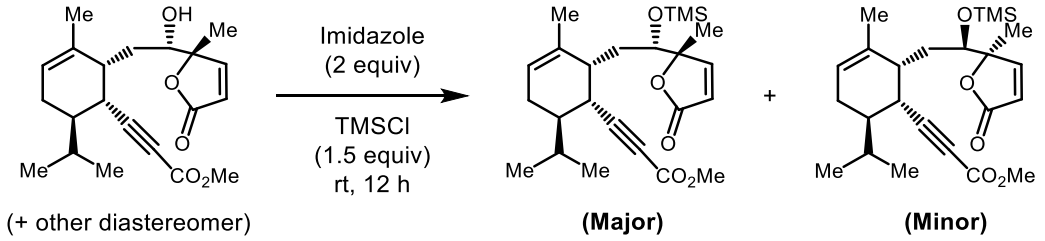
Methyl (Z)-3-((4S,5S)-5-(((1R,5R,6R)-5-isopropyl-6-(3-methoxy-3-oxoprop-1-yn-1-yl)-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)acrylate (3.177 (major)) and **methyl (Z)-3-((4S,5S)-5-(((1R,5R,6R)-5-isopropyl-6-(3-methoxy-3-oxoprop-1-yn-1-yl)-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)acrylate (3.177 (minor))**. Starting from **3.176** (1.91 g, 5.1 mmol) and following an identical procedure to that described for the preparation of **3.137**, title compounds were isolated (2.17 g, 5.0 mmol, 99%, 4.6:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, ^{13}C NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.177 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (d, *J* = 12.7 Hz, 1H), 5.74 (d, *J* = 12.5 Hz, 1H), 5.34 (s, 1H), 4.21 (dd,

J = 10.9, 2.0 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.83 (dd, *J* = 8.6, 4.8 Hz, 1H), 2.42 (s, 1H), 2.13 – 2.07 (m, 1H), 2.02 – 1.95 (m, 1H), 1.85 (ddd, *J* = 14.6, 8.3, 2.2 Hz, 2H), 1.73 – 1.66 (m, 2H), 1.69 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H), 1.29 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 154.1, 146.5, 143.4, 135.3, 121.1, 119.6, 107.9, 91.1, 82.8, 80.7, 75.8, 52.6, 51.4, 38.8, 37.5, 33.7, 31.0, 28.7, 28.1, 26.0, 24.3, 21.8, 21.0, 17.6.; **3.177 (minor)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (d, *J* = 12.6 Hz, 1H), 5.76 (d, *J* = 10.6 Hz, 1H), 5.34 (s, 1H), 4.17 (dd, *J* = 11.2, 2.6 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.76 (dd, *J* = 10.0, 4.5 Hz, 1H), 2.50 – 2.45 (m, 1H), 2.13 – 2.07 (m, 1H), 2.03 – 1.93 (m, 1H), 1.85 (ddd, *J* = 14.6, 8.3, 2.2 Hz, 2H), 1.73 – 1.66 (m, 2H), 1.73 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H).; IR (neat) ν_{max} 2958 (w), 2230 (w), 1716 (s), 1253 (s), 1223 (m).; HRMS (DART) for $C_{25}H_{37}O_6$ $[M+H]^+$ calculated: 433.259, found: 433.261.; $[\alpha]^{20}_D$: 29.6 (c = 1.00, $CHCl_3$, l = 50 mm).



Methyl 3-((1R,2R,6R)-2-((S)-2-hydroxy-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (3.178 (major)) and **methyl 3-((1R,2R,6R)-2-((S)-2-hydroxy-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (3.178 (minor))**. Starting from **3.177** (1.14 g,

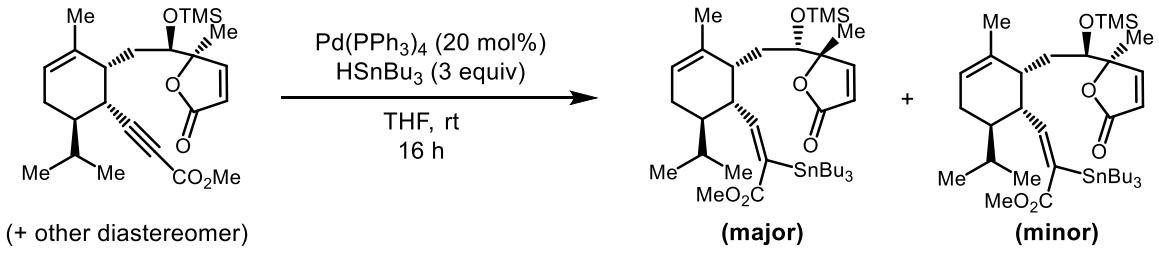
2.6 mmol), *p*-Toluenesulfonic acid monohydrate (201 mg, 1.05 mmol, 0.4 equiv) and following an identical procedure to that described for the preparation of **3.138**, title compounds were isolated (0.86 g, 2.4 mmol, 90%, 4.6:1 dr) as white solid. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.178 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 5.7 Hz, 1H), 6.02 (d, *J* = 5.7 Hz, 1H), 5.35 (s, 1H), 3.95 – 3.89 (m, 1H), 3.72 (s, 3H), 2.81 (dd, *J* = 8.7, 5.0 Hz, 1H), 2.54 – 2.45 (m, 2H), 2.12 – 2.03 (m, 1H), 2.00 – 1.93 (m, 1H), 1.88 – 1.79 (m, 1H), 1.76 – 1.57 (m, 6H), 1.46 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 159.0, 153.9, 134.7, 121.3 (d, *J* = 8.9 Hz), 91.8, 91.1, 75.7, 74.0, 52.6, 38.8, 36.4, 33.4, 33.1, 27.9, 24.0, 21.6, 20.6, 18.3, 17.4, 15.4.; IR (neat) ν_{max} 2959 (w), 2230 (w), 1753 (m), 1714 (s), 1255 (s), 1082 (w).; HRMS (DART) for $C_{21}H_{29}O_5$ $[M+H]^+$ calculated: 361.201, found: 361.202.; $[\alpha]^{20}_D$: 2.60 (c = 1.00, $CHCl_3$, l = 50 mm).



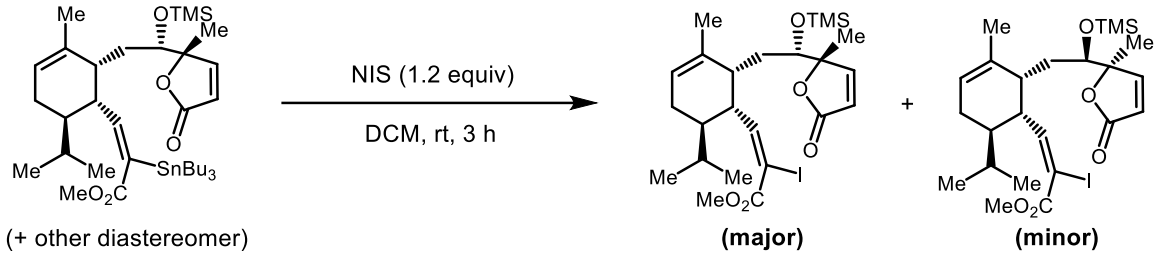
Note: reaction was conducted under open atmosphere.

Methyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((S)-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-((trimethylsilyl)oxy)ethyl)cyclohex-3-en-1-yl)propiolate (3.179 (major)) and **methyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((R)-2-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-((trimethylsilyl)oxy)ethyl)cyclohex-3-en-1-yl)propiolate (3.179 (minor))**. In a 2-dram vial was added methyl 3-((1R,2R,6R)-2-((S)-2-hydroxy-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-

yl)ethyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (78 mg, 0.22 mmol, 1 equiv), imidazole (29.5 mg, 0.43 mmol, 2 equiv), chlorotrimethylsilane (0.04 mL, 0.32 mmol, 1.5 equiv) and DCM (1 mL). The mixture was allowed to stir for 12 hours and quenched with H_2O (5 mL). The mixture was extracted with Et_2O (3x5 mL) and the combined organic layer was washed with H_2O (5 mL) then brine (5 mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. The crude product was purified by silica gel column chromatography with 0-7% EtOAc/hexane as the eluent to yield the title compounds (82 mg, 0.19 mmol, 87% yield, 5:1 dr) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.179 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 21.4, 5.7 Hz, 1H), 5.96 (d, *J* = 5.7 Hz, 1H), 5.31 (s, 1H), 4.01 (dd, *J* = 10.9, 1.7 Hz, 1H), 3.68 (s, 3H), 2.65 (dd, *J* = 10.4, 4.9 Hz, 1H), 2.25 (t, *J* = 6.2 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.96 – 1.89 (m, 1H), 1.78 – 1.70 (m, 1H), 1.61 (s, 3H), 1.60 – 1.57 (m, 1H), 1.45 – 1.40 (m, 1H), 1.37 (s, 3H), 0.88 (dd, *J* = 11.2, 7.0 Hz, 34H), 0.77 (d, *J* = 6.8 Hz, 3H), 0.15 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 158.6, 153.9, 135.6, 121.9, 121.1, 92.0, 90.5, 77.0, 52.7, 37.8, 37.4, 35.7, 34.4, 28.2, 23.8, 21.6, 21.0, 17.8, 16.0, 0.9.; IR (neat) ν_{max} 1760 (s), 1715 (s), 1250 (s), 1114 (m), 842 (m).; HRMS (DART) for $C_{24}H_{37}O_5Si$ $[M+H]^+$ calculated: 433.240, found: 433.240.; $[\alpha]^{20}_D$: 47.8 (c = 1.00, $CHCl_3$, l = 50 mm).



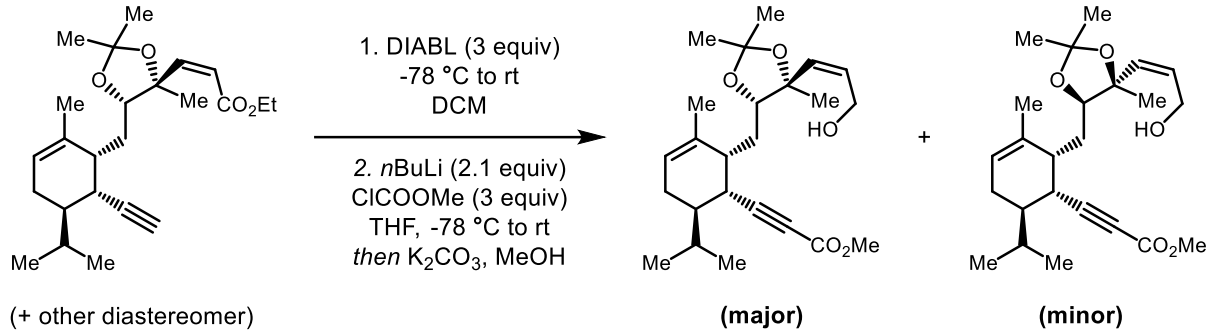
Methyl (E)-3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((S)-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-((trimethylsilyl)oxy)ethyl)cyclohex-3-en-1-yl)-2-(tributylstannyl)acrylate (3.185 (major)) and **Methyl (E)-3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((R)-2-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-((trimethylsilyl)oxy)ethyl)cyclohex-3-en-1-yl)-2-(tributylstannyl)acrylate (3.185 (minor))**. **))**. Starting from **3.179** (0.19 g, 0.43 mmol) and following an identical procedure to that described for the preparation of **3.117**, title compounds (0.26 g, 0.35 mmol, 80%, 12:1 dr) were purified by silica gel column chromatography with 0-5% EtOAc/hexane (R_f = 0.5 in 9% EtOAc/hexane, minor diastereomer R_f = 0.4 in 9% EtOAc/hexane) as the eluent as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.185 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (d, *J* = 5.7 Hz, 1H), 6.02 (d, *J* = 5.7 Hz, 1H), 5.93 (d, *J* = 10.3 Hz, J_{Sn-H} = 30 Hz, 1H), 5.32 (s, 1.7 Hz, 1H), 3.65 (s, 3H), 2.95 (td, *J* = 9.8, 4.8 Hz, 1H), 2.27 (s, 1H), 1.94 – 1.86 (m, 1H), 1.83 – 1.75 (m, 1H), 1.72 – 1.65 (m, 2H), 1.62 (s, 3H), 1.53 – 1.44 (m, 8H), 1.41 (s, 3H), 1.31 (dq, *J* = 14.6, 7.2 Hz, 8H), 0.96 – 0.91 (m, 5H), 0.91 – 0.87 (m, 13H), 0.67 (d, *J* = 6.7 Hz, 3H), 0.16 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 171.6, 158.3, 154.0, 137.4, 136.2, 121.9, 121.0, 91.6, 76.3, 51.1, 42.5, 33.4, 28.9, 28.2, 27.3, 23.7, 21.6, 21.2, 19.5, 16.3, 13.7, 10.3, 0.8.; IR (neat) ν_{max} 2956 (s), 2929 (m), 1765 (s), 1707 (m), 1114 (s), 844 (s).; HRMS (DART) for $C_{36}H_{65}O_5SiSn$ $[M+H]^+$ calculated: 725.362, found: 725.362.; $[\alpha]^{20}_D$: 42 (c = 0.90, $CHCl_3$, l = 50 mm).



Note: reaction was conducted under open atmosphere.

Methyl (E)-2-iodo-3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((S)-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-((trimethylsilyl)oxy)ethyl)cyclohex-3-en-1-yl)acrylate (3.187 (major)) and **methyl (E)-2-iodo-3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((S)-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-((trimethylsilyl)oxy)ethyl)cyclohex-3-en-1-yl)acrylate (3.187 (minor))**. NIS (90 mg, 0.40 mmol, 1.2 equiv) was added to a cold solution of methyl (E)-3-((1R,2R,6R)-6-isopropyl-3-methyl-2-((S)-2-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-((trimethylsilyl)oxy)ethyl)cyclohex-3-en-1-yl)-2-(tributylstannyl)acrylate (240 mg, 0.33 mmol, 1 equiv) in dry DCM (3 mL). Upon completion (TLC, 3 h), the reaction was quenched by the addition of sat aqueous solution of $Na_2S_2O_3$ (3 mL). The aqueous phase extracted with DCM (2x5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography with 0-7% EtOAc/hexane as the eluent to yield the title compounds (160 mg, 0.29 mmol, 86%) as white solid. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.187 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (d, J = 5.7 Hz, 1H), 6.68 (d, J = 11.2 Hz, 1H), 6.12 (d, J = 5.7 Hz, 1H), 5.35 (s, 1H), 3.75 (s, 3H), 3.55 – 3.51 (m, 1H), 3.22 (ddd, J = 11.2, 9.1, 5.1 Hz, 1H), 2.25 (d, J = 6.4 Hz, 1H), 1.95 – 1.79 (m, 2H), 1.63 (s, 4H), 1.56 – 1.48 (m, 1H), 1.43 (s, 3H), 1.42 – 1.39 (m, 2H), 0.91 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H), 0.16 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ

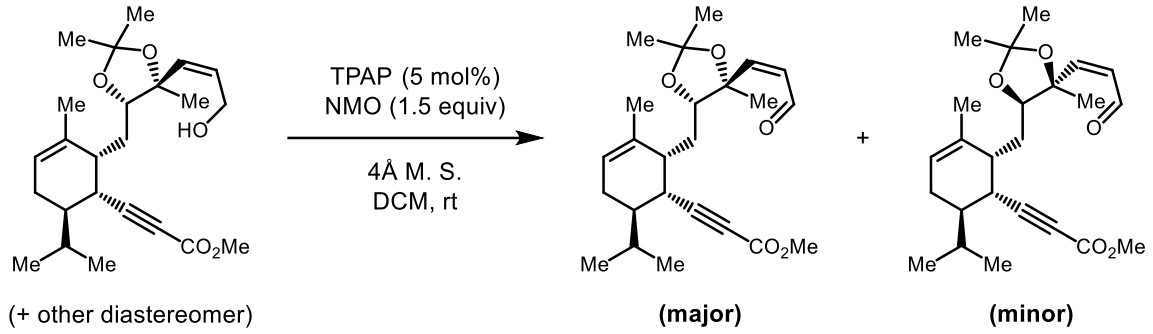
172.1, 164.1, 159.0, 158.2, 135.3, 122.5, 121.5, 91.6, 83.9, 76.6, 53.2, 43.6, 39.4, 37.9, 33.9, 28.7, 24.0, 21.6, 21.2, 18.7, 16.9, 0.8.; IR (neat) ν_{max} 1756 (s), 1214 (s), 1111 (s), 840 (s), 735 (s); HRMS (DART) for $C_{24}H_{38}O_5SiI$ $[M+H]^+$ calculated: 561.153, found: 561.155.; $[\alpha]^{20}_D$: -23.0 (c = 1.00, $CHCl_3$, l = 50 mm).



Note: Due to the shortage of DIBAL in hexane, DIABL in cyclohexane is used. Condition is not optimized.

Methyl 3-((1R,2R,6R)-2-(((4S,5S)-5-((Z)-3-hydroxyprop-1-en-1-yl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (3.188 (major)) and **methyl 3-((1R,2R,6R)-2-(((4R,5R)-5-((Z)-3-hydroxyprop-1-en-1-yl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)propiolate (3.188 (minor))**. Under a positive pressure of N_2, to a solution of isolated as a mixture and used directly into the next step without further purification. Methyl (Z)-3-((4S,5S)-5-(((1R,5R,6R)-6-ethynyl-5-isopropyl-2-methylcyclohex-2-en-1-yl)methyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)acrylate (900 mg, 2.4 mmol, 1 equiv) in DCM (7 mL) was added Diisobutylaluminum hydride (1M solution in cyclohexane, 7.21 mL, 3 equiv) at -78 °C. The solution was allowed to stir at -78 °C for 0.5 hour and was slowly warmed to rt over 1 hour. Then, methanol (0.49 mL) was added, and the resulted solution was quenched by sat. NH_4Cl (10 mL). The reaction was extracted with Et_2O (2x10 mL) and the combined organic layer was washed with water (20 mL) and brine (20 mL) and was then

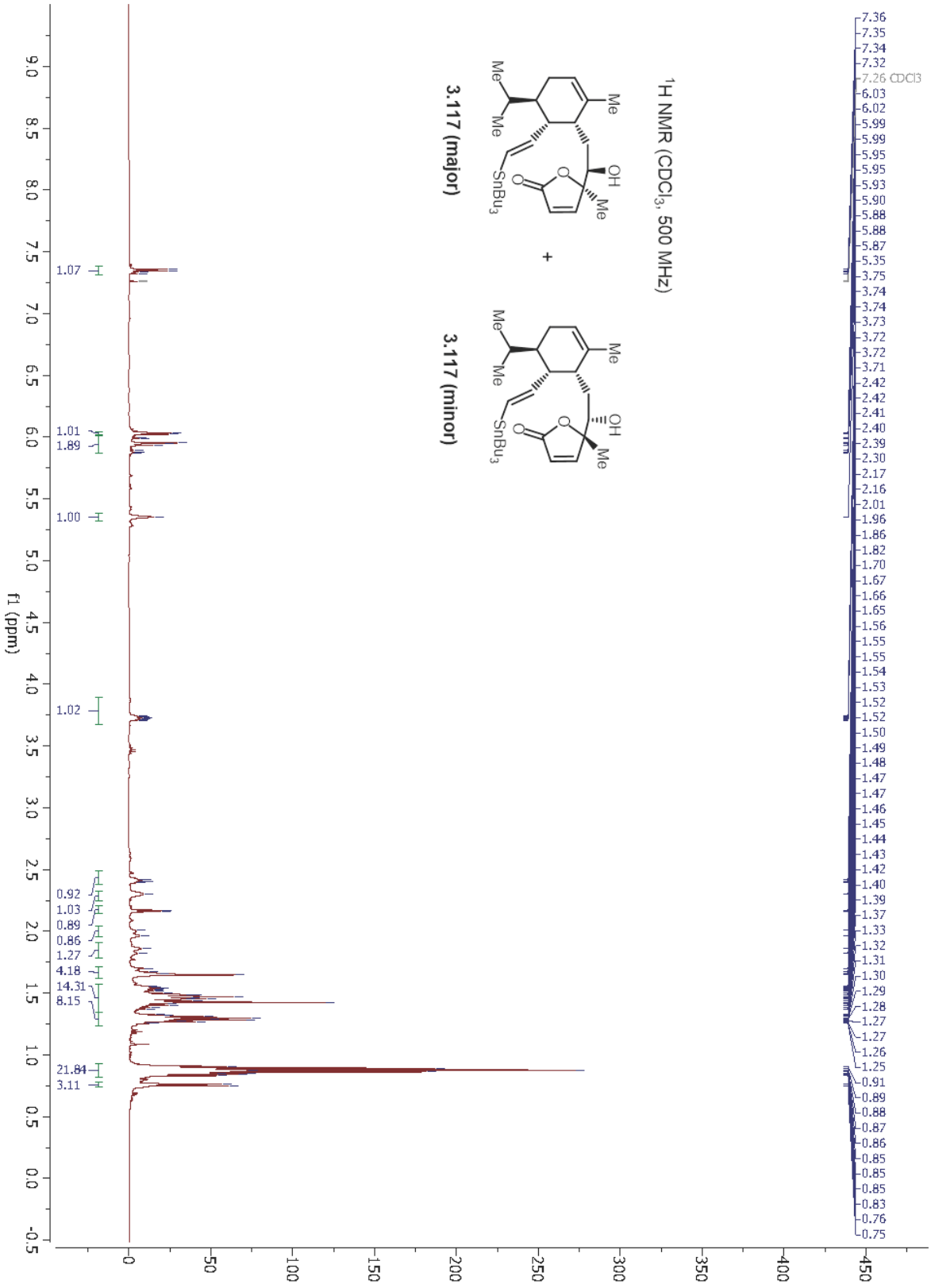
dried over sodium sulfate, filtered, and concentrated. The resulting residue was quickly purified by silica gel column chromatography with 15% EtOAc/hexane as the eluent. The post-column mixture was directly used in the next reaction following an identical procedure to that described for the preparation of **3.174** based on the crude mass. Finally, the resulting residue was purified by silica gel column chromatography with 0-15% EtOAc/hexane (Rf = 0.6 in 30% EtOAc/hexane) as the eluent to yield the title compounds (133 mg, 0.33 mmol, 14%) as colorless oil. (Note: NMR data is tentatively assigned due to the diastereomeric isomers, ^{1}H NMR data of the minor diastereomer is not clear enough to be fully identified.) **3.188 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) 5.62 (ddt, *J* = 18.2, 12.1, 6.0 Hz, 1H), 5.47 (d, *J* = 12.2 Hz, 1H), 5.33 (s, 1H), 4.33 – 4.19 (m, 2H), 4.08 (dd, *J* = 9.8, 2.9 Hz, 1H), 3.71 (s, 3H), 2.80 (dd, *J* = 8.7, 4.8 Hz, 1H), 2.39 (s, 1H), 2.12 – 2.01 (m, 1H), 1.97 (q, *J* = 6.7 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.67 (s, 3H), 1.65 – 1.61 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H), 1.17 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 135.1, 132.6, 129.9, 121.0, 107.7, 90.9, 82.9, 81.2, 75.8, 59.0, 52.6, 38.7, 37.5, 33.8, 30.6, 28.6, 28.0, 26.2, 24.2, 22.4, 21.8, 20.6, 17.4.; **3.188 (minor)**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 135.6, 132.5, 130.3, 122.0, 107.9, 91.0, 83.2, 81.3, 76.2, 58.9, 52.5, 38.8, 37.3, 35.5, 31.2, 28.5, 28.4, 26.2, 24.0, 23.3, 22.4, 20.7, 15.8.; IR (neat) ν_{max} 2958 (m), 2922 (s), 2851 (m), 1716 (s), 1253 (s); HRMS (DART) for $C_{24}H_{37}O_5$ $[M+H]^+$ calculated: 405.263, found: 405.263.; $[\alpha]^{20}_D$: 6 (c = 0.10, $CHCl_3$, l = 50 mm).

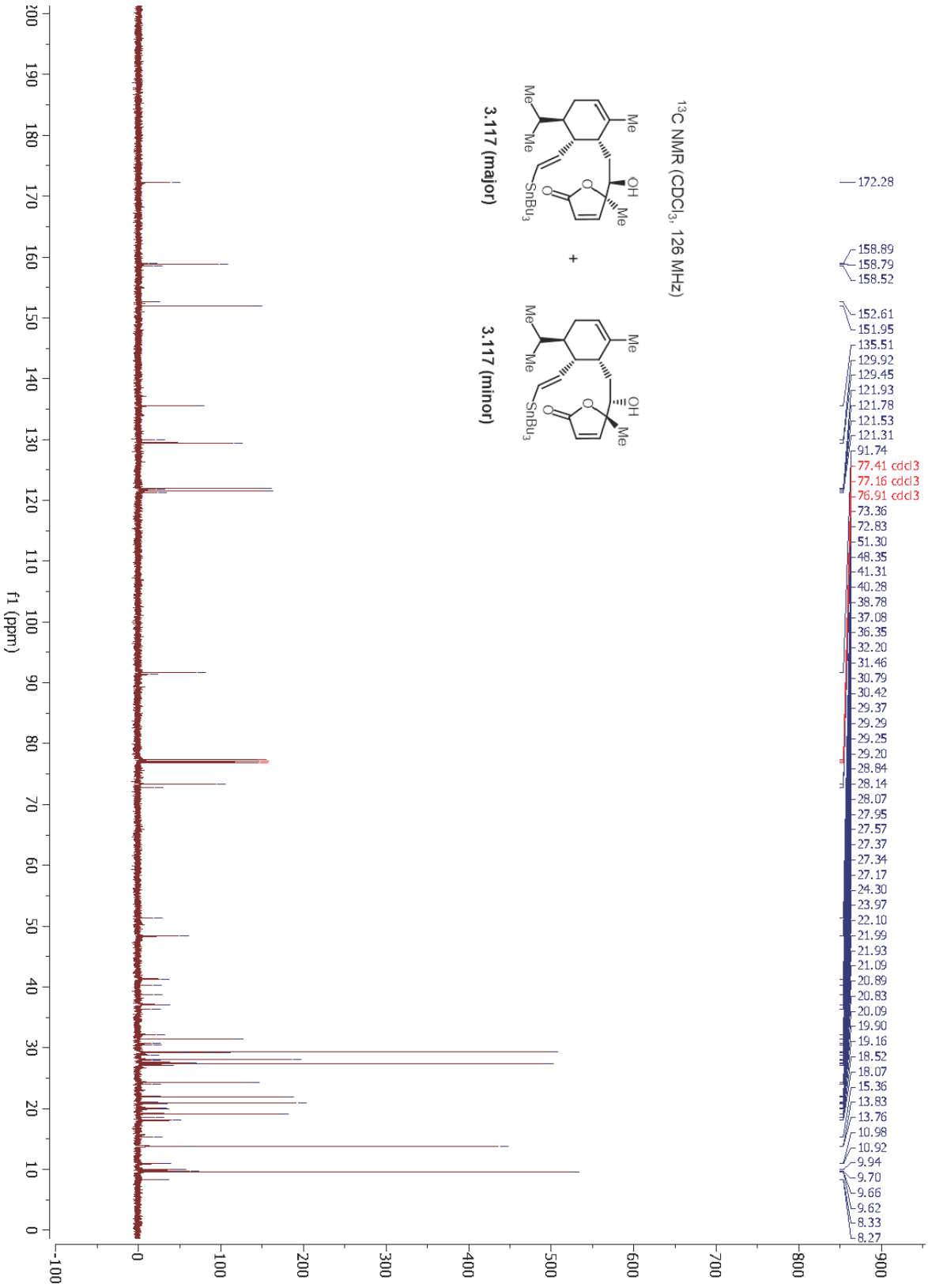


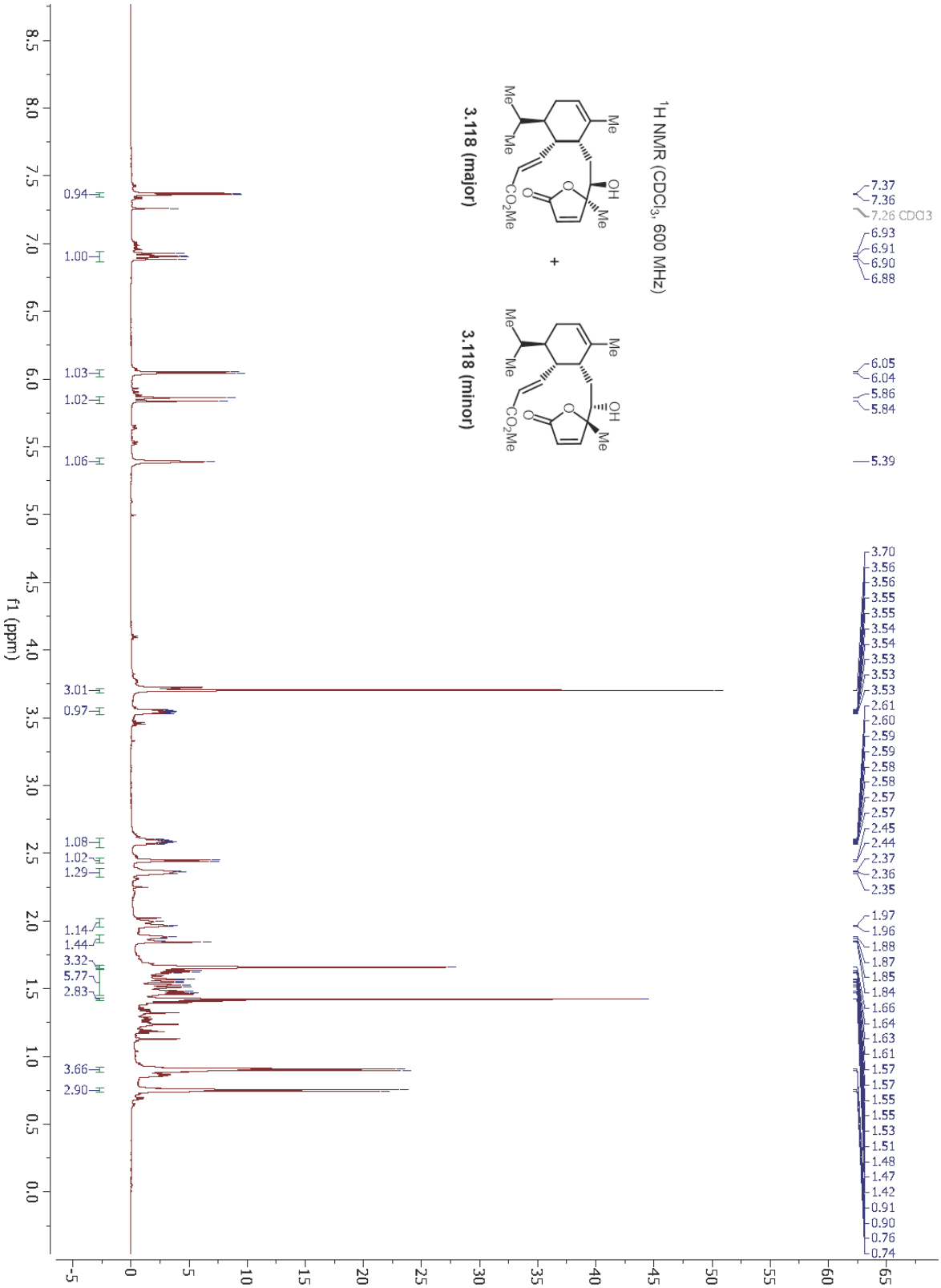
Methyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-(((4S,5S)-2,2,5-trimethyl-5-((Z)-3-oxoprop-1-en-1-yl)-1,3-dioxolan-4-yl)methyl)cyclohex-3-en-1-yl)propiolate (3.189 (major)) and **methyl 3-((1R,2R,6R)-6-isopropyl-3-methyl-2-(((4R,5R)-2,2,5-trimethyl-5-((Z)-3-oxoprop-1-en-1-yl)-1,3-dioxolan-4-yl)methyl)cyclohex-3-en-1-yl)propiolate (3.189 (minor))**. Starting from **3.188** (130 mg, 0.32 mmol) and following an identical procedure to that described for the preparation of **3.161**, title compounds were isolated (80 mg, 0.20 mmol, 62%). (Note: NMR data is tentatively assigned due to the diastereomeric isomers) **3.189 (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.55 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 12.1 Hz, 1H), 5.79 (dd, *J* = 12.1, 7.8 Hz, 1H), 5.37 (s, 1H), 4.17 (dd, *J* = 9.9, 2.6 Hz, 1H), 3.71 (s, 3H), 2.81 (dd, *J* = 9.0, 4.9 Hz, 1H), 2.41 (s, 1H), 2.17 – 1.97 (m, 2H), 1.88 – 1.81 (m, 1H), 1.77 – 1.63 (m, 6H), 1.47 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.1, 153.9, 149.2, 135.0, 129.4, 121.2, 108.4, 90.7, 84.1, 80.8, 76.0, 52.7, 38.5, 37.9, 34.0, 30.9, 28.5, 28.0, 26.1, 24.1, 22.5, 21.7, 20.7, 17.1.; **3.189 (minor)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1H NMR (500 MHz, cdcl3) δ 10.56 (d, *J* = 7.7 Hz, 1H), 6.32 (d, *J* = 12.1 Hz, 1H), 5.82 (dd, *J* = 12.1, 7.7 Hz, 1H), 5.39 (s, 1H), 4.04 (dd, *J* = 10.9, 2.7 Hz, 1H), 3.74 (s, 3H), 2.76 (dd, *J* = 10.5, 4.6 Hz, 1H), 2.49 – 2.45 (m, 1H), 2.17 – 1.97 (m, 2H), 1.88 – 1.81 (m, 1H), 1.77 – 1.63 (m, 6H), 1.47 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.9, 153.9, 148.8, 135.3, 129.7, 122.3, 108.5, 90.8, 84.5, 80.6, 76.4, 53.5, 52.5,

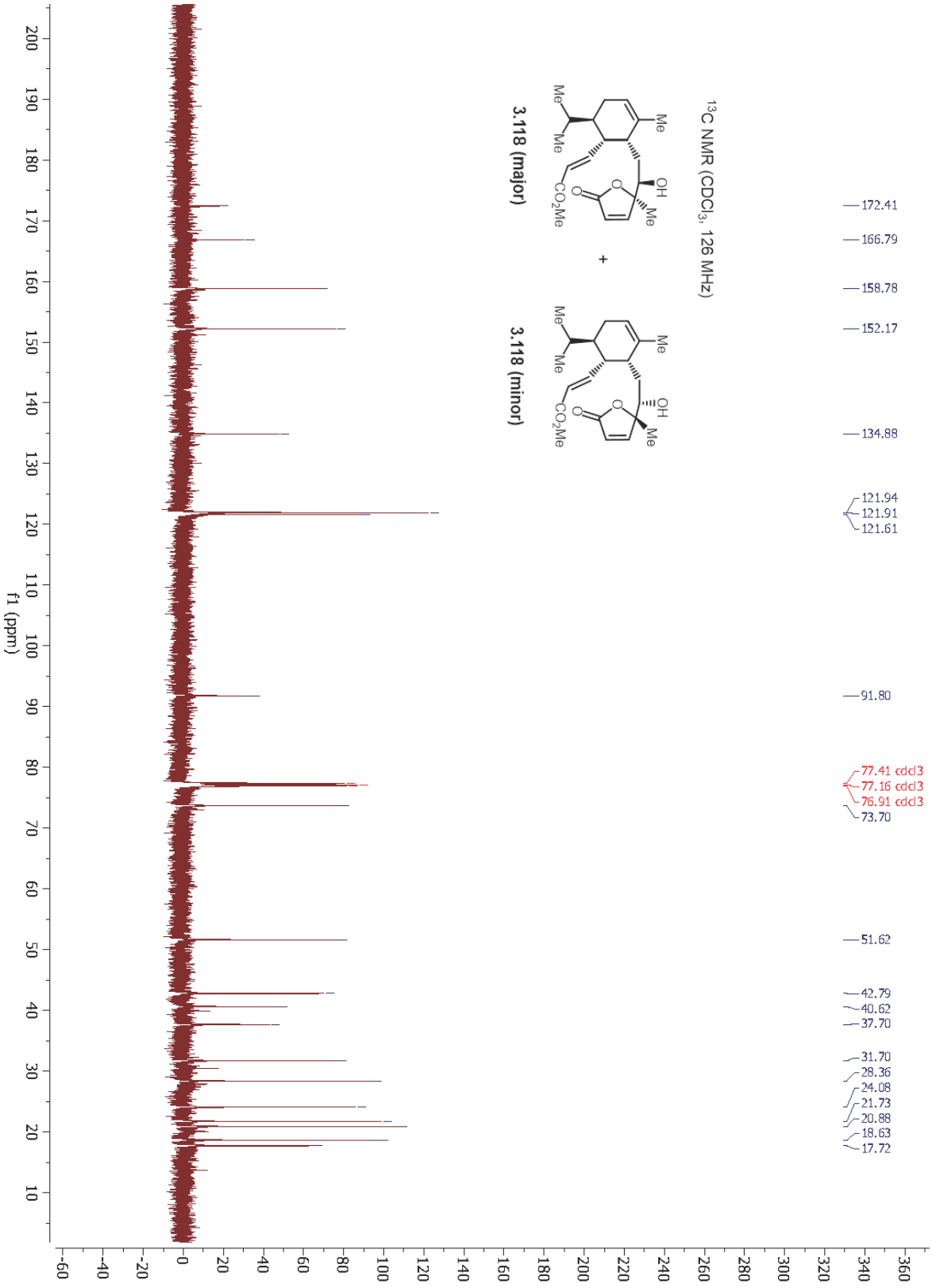
38.9, 37.3, 35.5, 31.4, 29.8, 28.5, 28.4, 24.0, 20.7, 15.7.; IR (neat) ν_{max} 2924 (w), 1715 (s), 1694 (m), 1677 (m), 1253 (s), 1224 (w).; HRMS (DART) for $C_{24}H_{35}O_5$ $[M+H]^+$ calculated: 403.248, found: 403.248. $[\alpha]^{20}_D$: 12 (c = 0.20, $CHCl_3$, l = 50 mm).

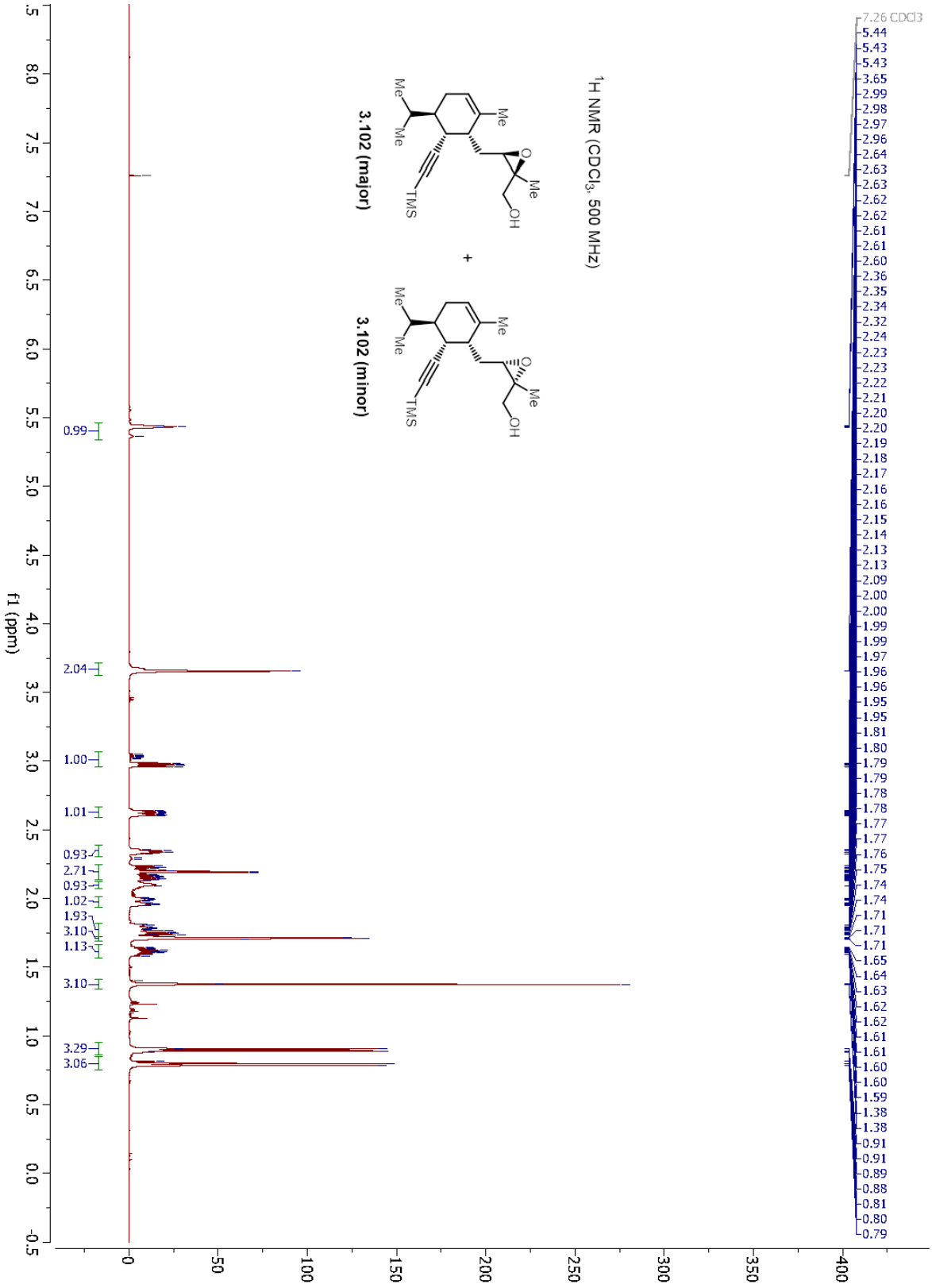
3.7.3 ^{1}H NMR and ^{13}C NMR Spetra

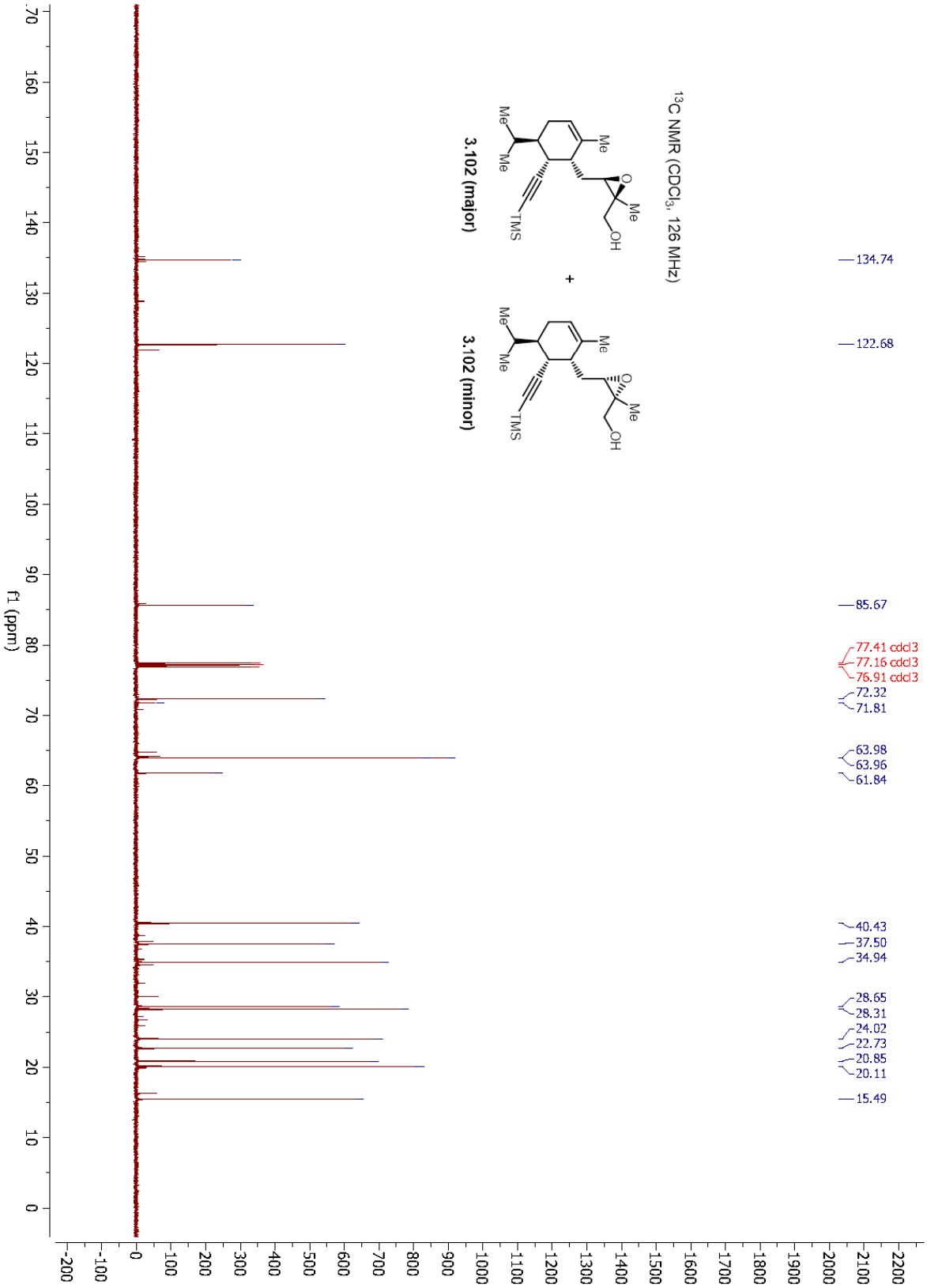

^{1}H NMR ($CDCl_3$, 500 MHz)
3.117 (major)
3.117 (minor)
f1 (ppm)
7.26 CDCl3

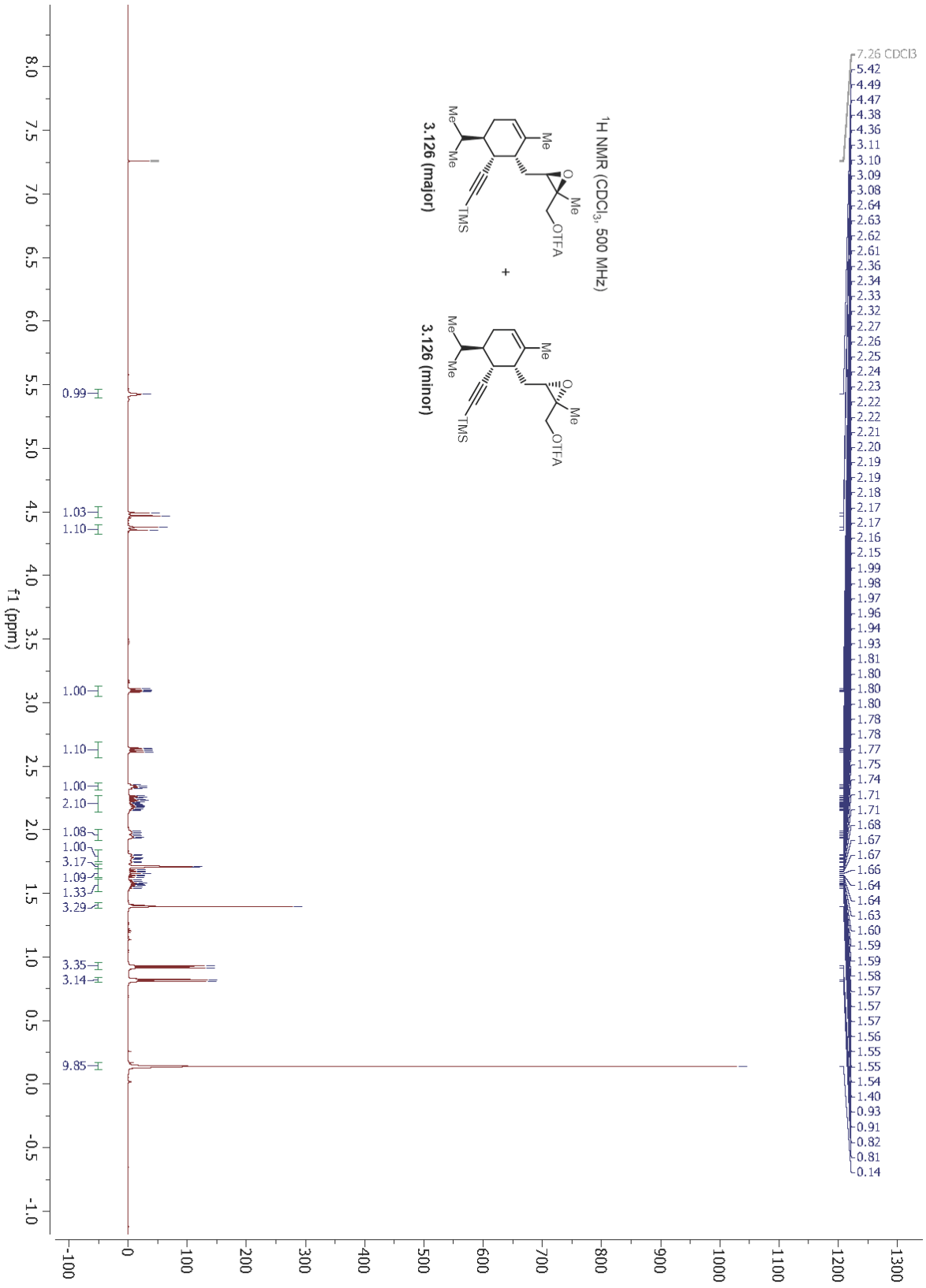

^{13}C NMR ($CDCl_3$, 126 MHz)
3.117 (major)
+
3.117 (minor)
Me
Me
OH
Me
SnBu3
f1 (ppm)
172.28
158.89
158.79
158.52
152.61
151.95
135.51
129.92
129.45
121.93
121.78
121.53
121.31
91.74
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
73.36
72.83
51.30
48.35
41.31
40.28
38.78
37.08
36.35
32.20
31.46
30.79
30.42
29.37
29.29
29.25
29.20
28.84
28.14
28.07
27.95
27.57
27.37
27.34
27.17
24.30
23.97
22.10
21.99
21.93
21.09
20.89
20.83
20.09
19.90
19.16
18.52
18.07
15.36
13.83
13.76
10.98
10.92
9.94
9.70
9.66
9.62
8.33
8.27

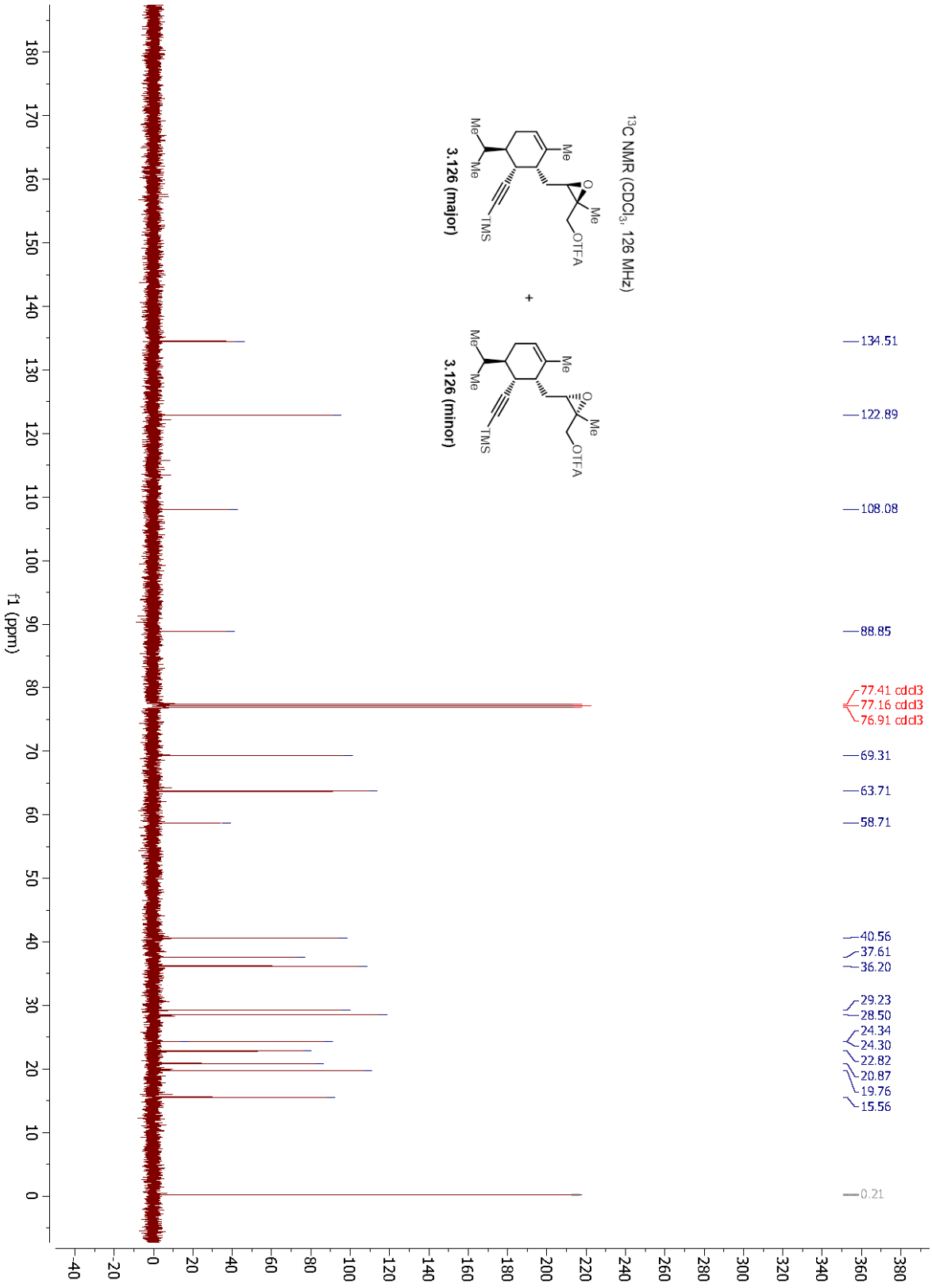

^{1}H NMR (CDCl$_3$, 600 MHz)
3.118 (major)
3.118 (minor)
+
f1 (ppm)
7.37
7.36
7.26 CDCl3
6.93
6.91
6.90
6.88
6.05
6.04
5.86
5.84
5.39
3.70
3.56
3.56
3.55
3.55
3.54
3.54
3.53
3.53
3.53
2.61
2.60
2.59
2.59
2.58
2.58
2.57
2.57
2.45
2.44
2.37
2.36
2.35
1.97
1.96
1.88
1.87
1.85
1.84
1.66
1.64
1.63
1.61
1.57
1.57
1.55
1.55
1.53
1.51
1.48
1.47
1.42
0.91
0.90
0.76
0.74
0.94
1.00
1.03
1.02
1.06
3.01
0.97
1.08
1.02
1.29
1.14
1.44
3.32
5.77
2.83
3.66
2.90

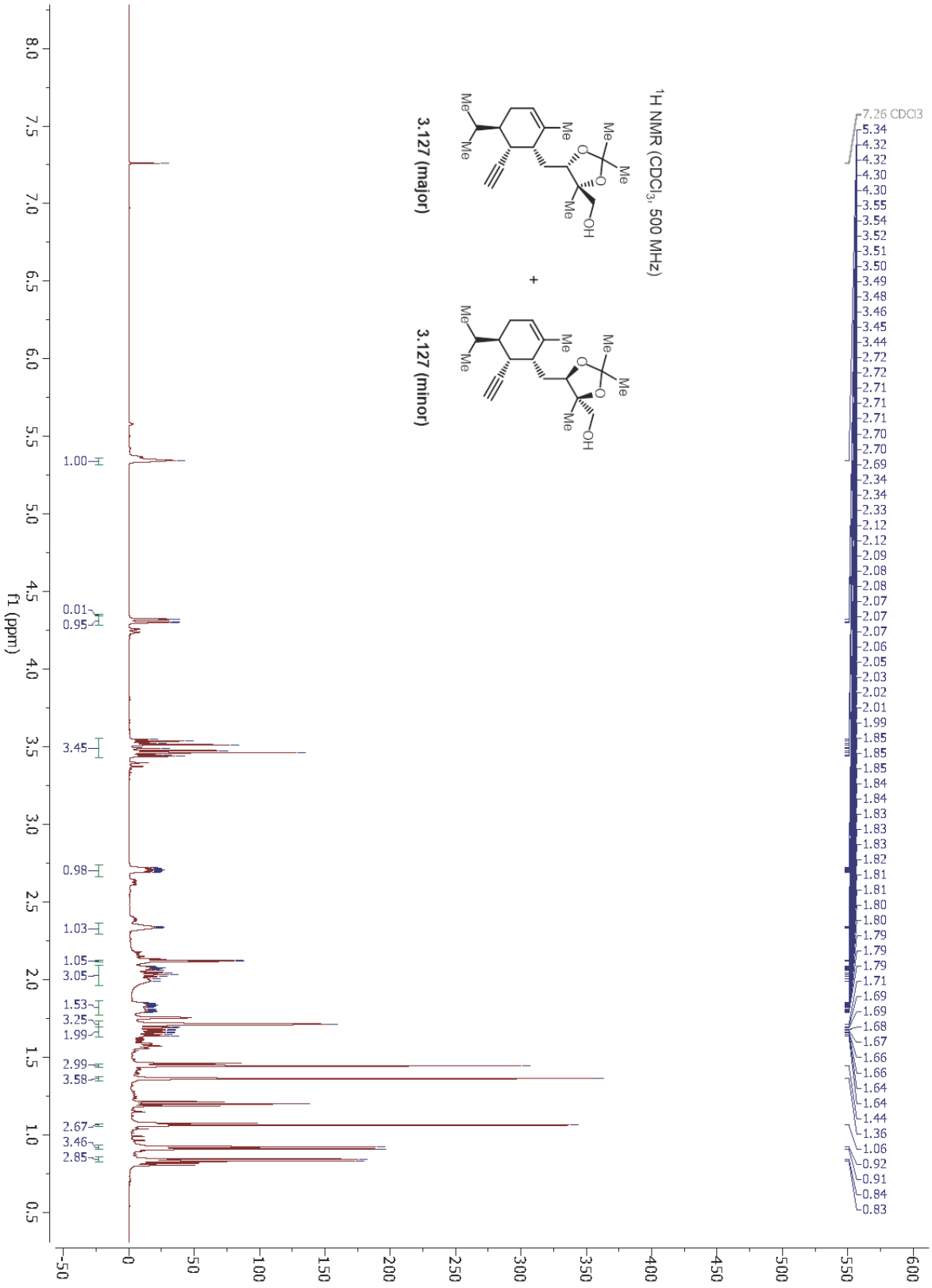

^{13}C NMR ($CDCl_3$, 126 MHz)
3.118 (major)
+
3.118 (minor)
Me
Me
OH
Me
CO_2Me
O
172.41
166.79
158.78
152.17
134.88
121.94
121.91
121.61
91.80
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
73.70
51.62
42.79
40.62
37.70
31.70
28.36
24.08
21.73
20.88
18.63
17.72
f1 (ppm)

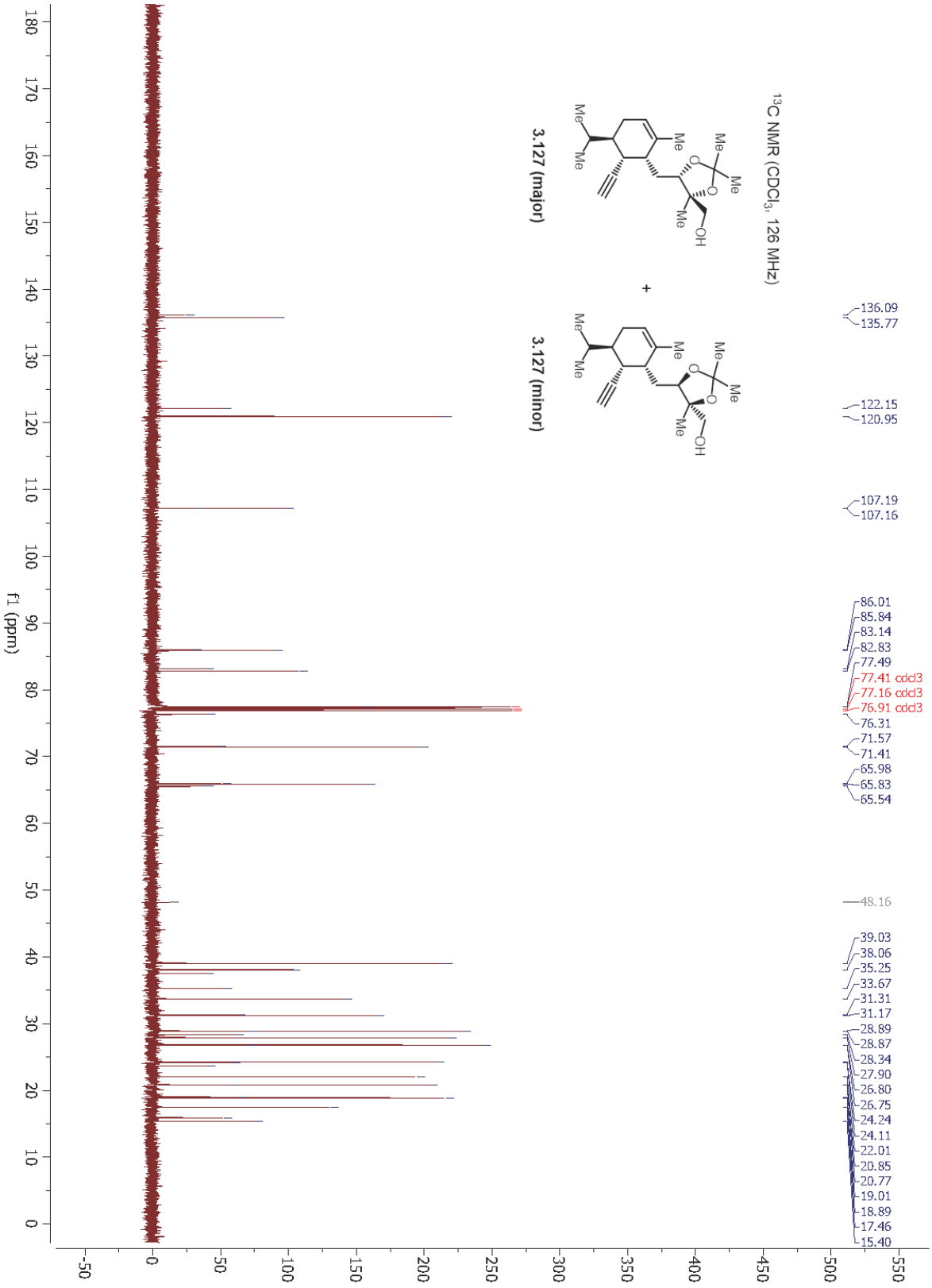

^{1}H NMR (CDCl$_3$, 500 MHz)
3.102 (major)
3.102 (minor)
Me
Me
TMS
O
Me
OH
+
7.26 CDCl3
f1 (ppm)
0.99
2.04
1.00
1.01
0.93
2.71
0.93
1.02
1.93
3.10
1.13
3.10
3.29
3.06


^{13}C NMR (CDCl$_3$, 126 MHz)
3.102 (major)
+
3.102 (minor)
Me
Me
Me
TMS
O
Me
OH
134.74
122.68
85.67
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
72.32
71.81
63.98
63.96
61.84
40.43
37.50
34.94
28.65
28.31
24.02
22.73
20.85
20.11
15.49
f1 (ppm)


^{1}H NMR (CDCl$_3$, 500 MHz)
3.126 (major)
3.126 (minor)
Me
Me
TMS
OTFA
Me
O
+
7.26 CDCl3
f1 (ppm)
0.99
1.03
1.10
1.00
1.10
1.00
2.10
1.08
1.00
3.17
1.09
1.33
3.29
3.35
3.14
9.85


^{13}C NMR ($CDCl_3$, 126 MHz)
3.126 (major)
3.126 (minor)
Me
Me
TMS
Me
O
OTFA
134.51
122.89
108.08
88.85
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
69.31
63.71
58.71
40.56
37.61
36.20
29.23
28.50
24.34
24.30
22.82
20.87
19.76
15.56
0.21
f1 (ppm)


^{1}H NMR ($CDCl_3$, 500 MHz)
3.127 (major)
3.127 (minor)
7.26 CDCl3
f1 (ppm)


^{13}C NMR ($CDCl_3$, 126 MHz)
3.127 (major)
3.127 (minor)
f1 (ppm)
136.09
135.77
122.15
120.95
107.19
107.16
86.01
85.84
83.14
82.83
77.49
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
76.31
71.57
71.41
65.98
65.83
65.54
48.16
39.03
38.06
35.25
33.67
31.31
31.17
28.89
28.87
28.34
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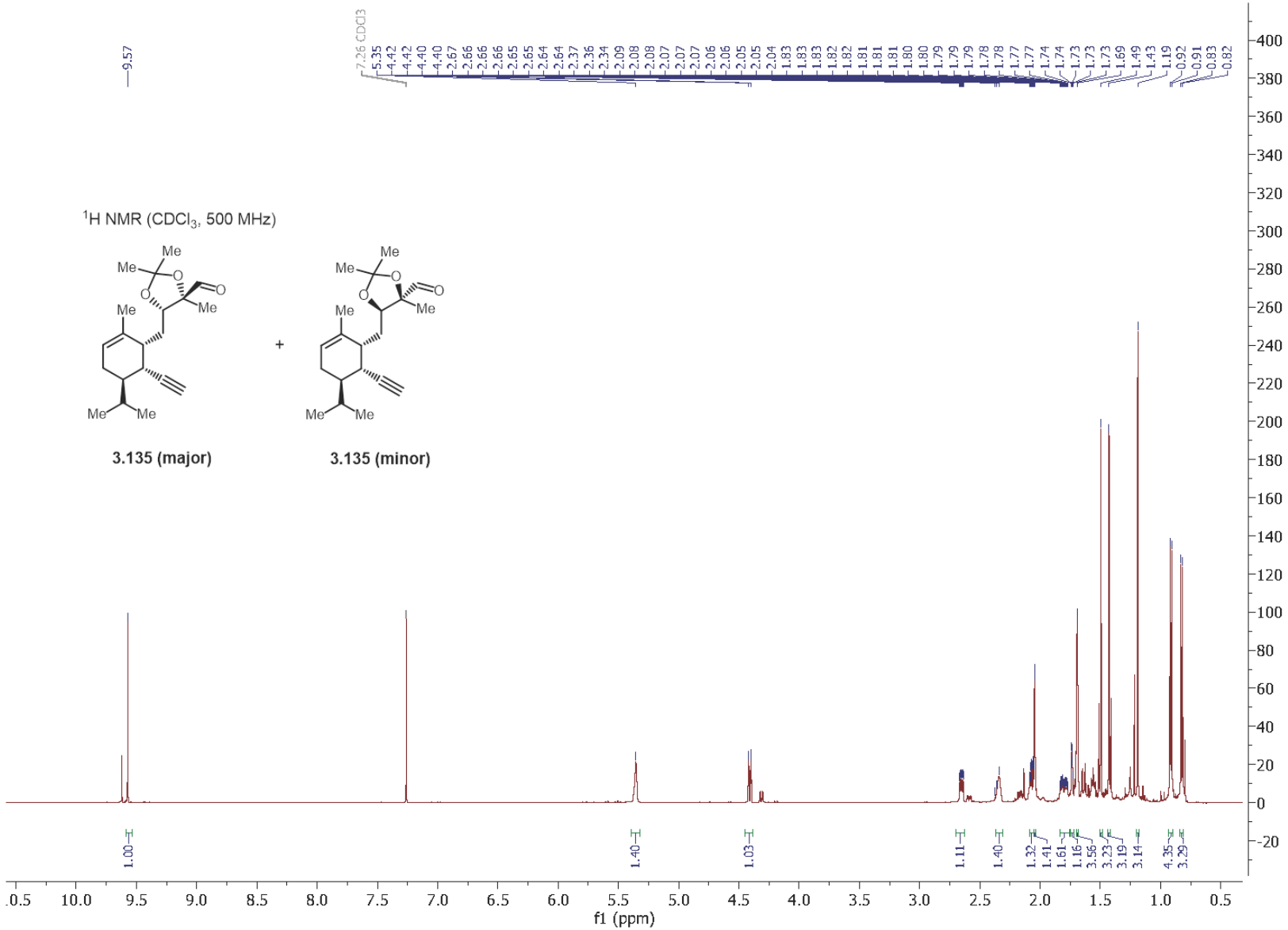
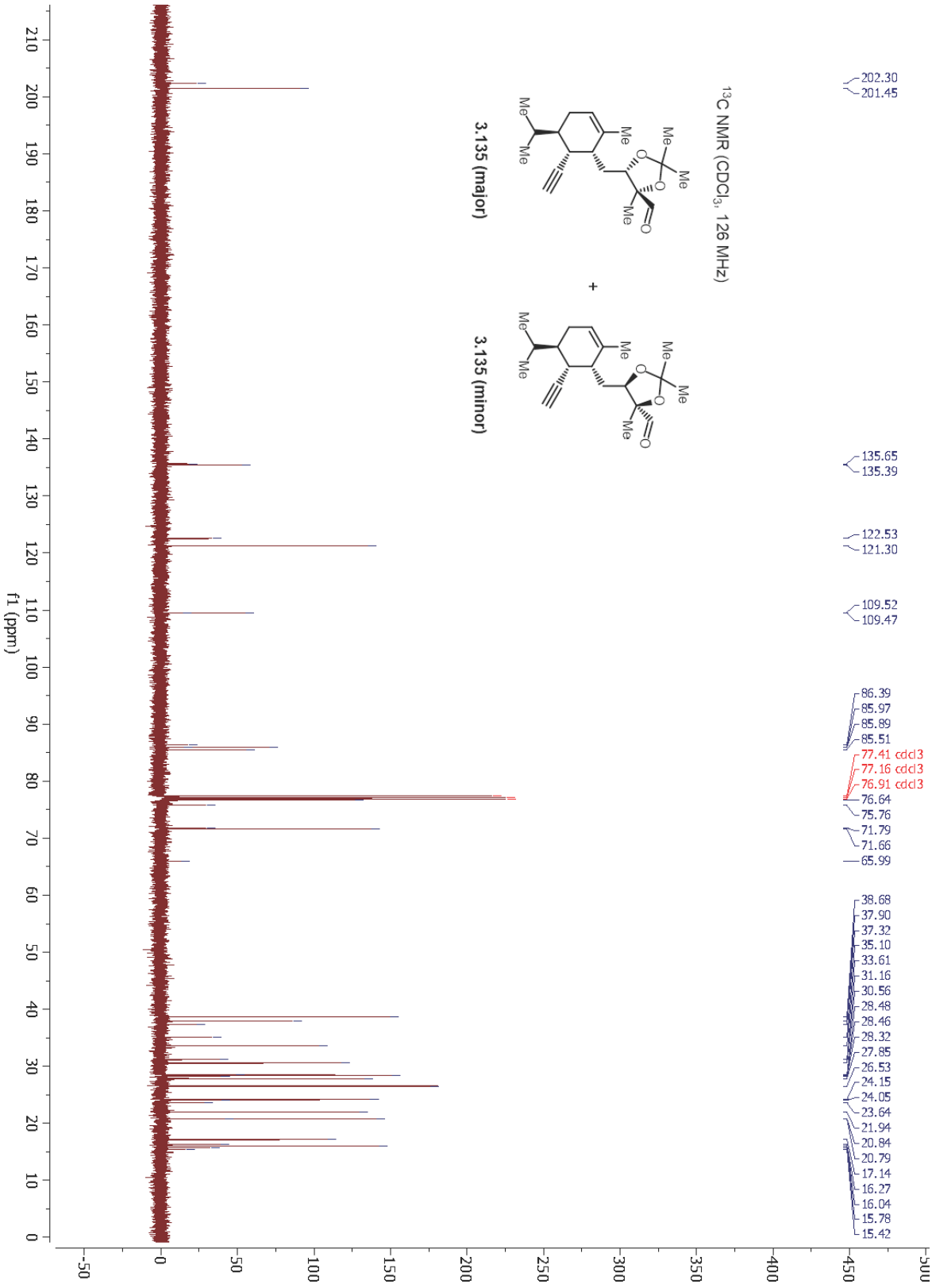
20.85
20.77
19.01
18.89
17.46
15.40


^{1}H NMR ($CDCl_3$, 500 MHz)
3.135 (major)
3.135 (minor)
f1 (ppm)


^{13}C NMR ($CDCl_3$, 126 MHz)
3.135 (major)
3.135 (minor)
+
Me
Me
Me
Me
Me
Me
O
O
O
202.30
201.45
135.65
135.39
122.53
121.30
109.52
109.47
86.39
85.97
85.89
85.51
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
76.64
75.76
71.79
71.66
65.99
38.68
37.90
37.32
35.10
33.61
31.16
30.56
28.48
28.46
28.32
27.85
26.53
24.15
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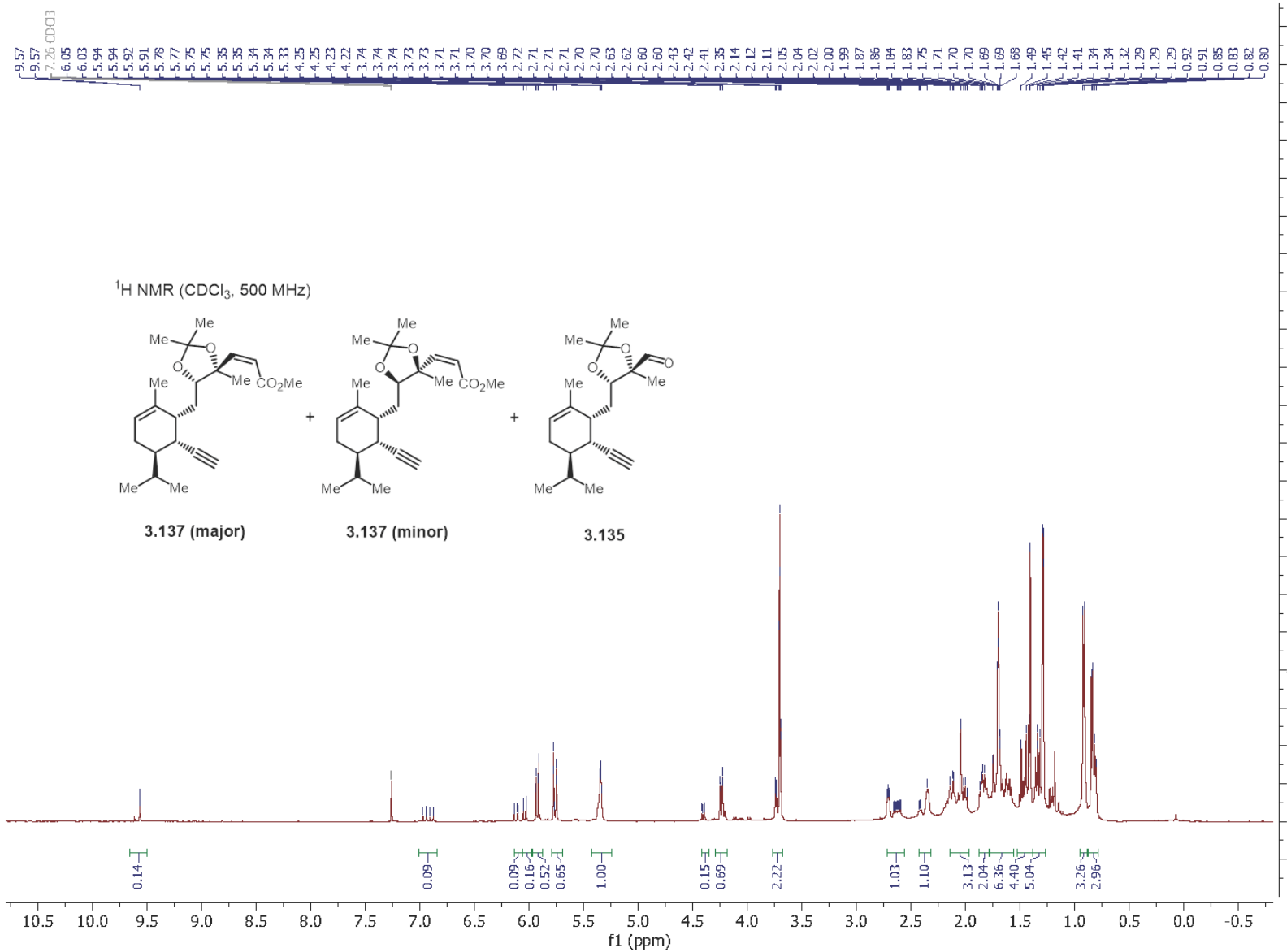
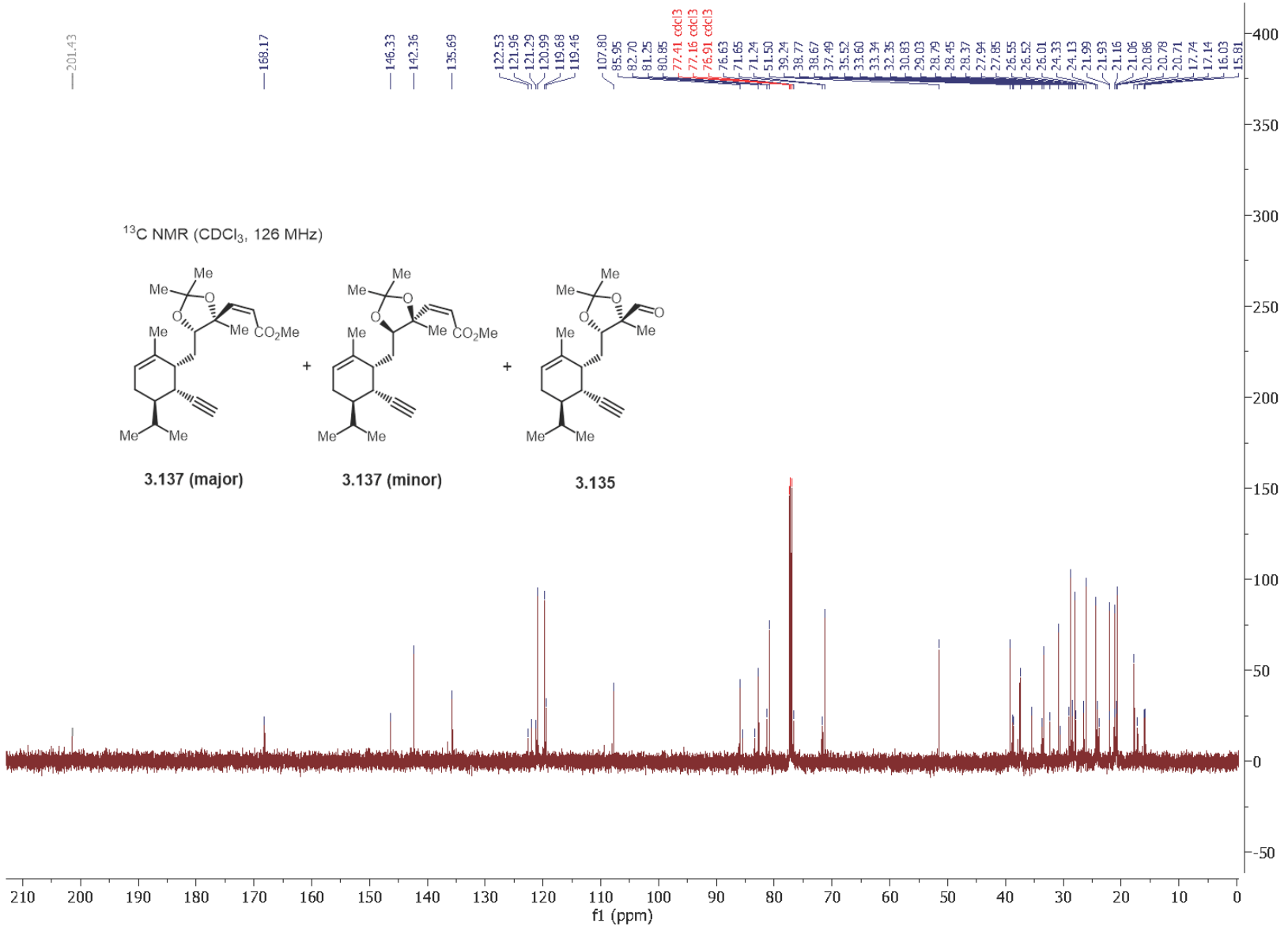
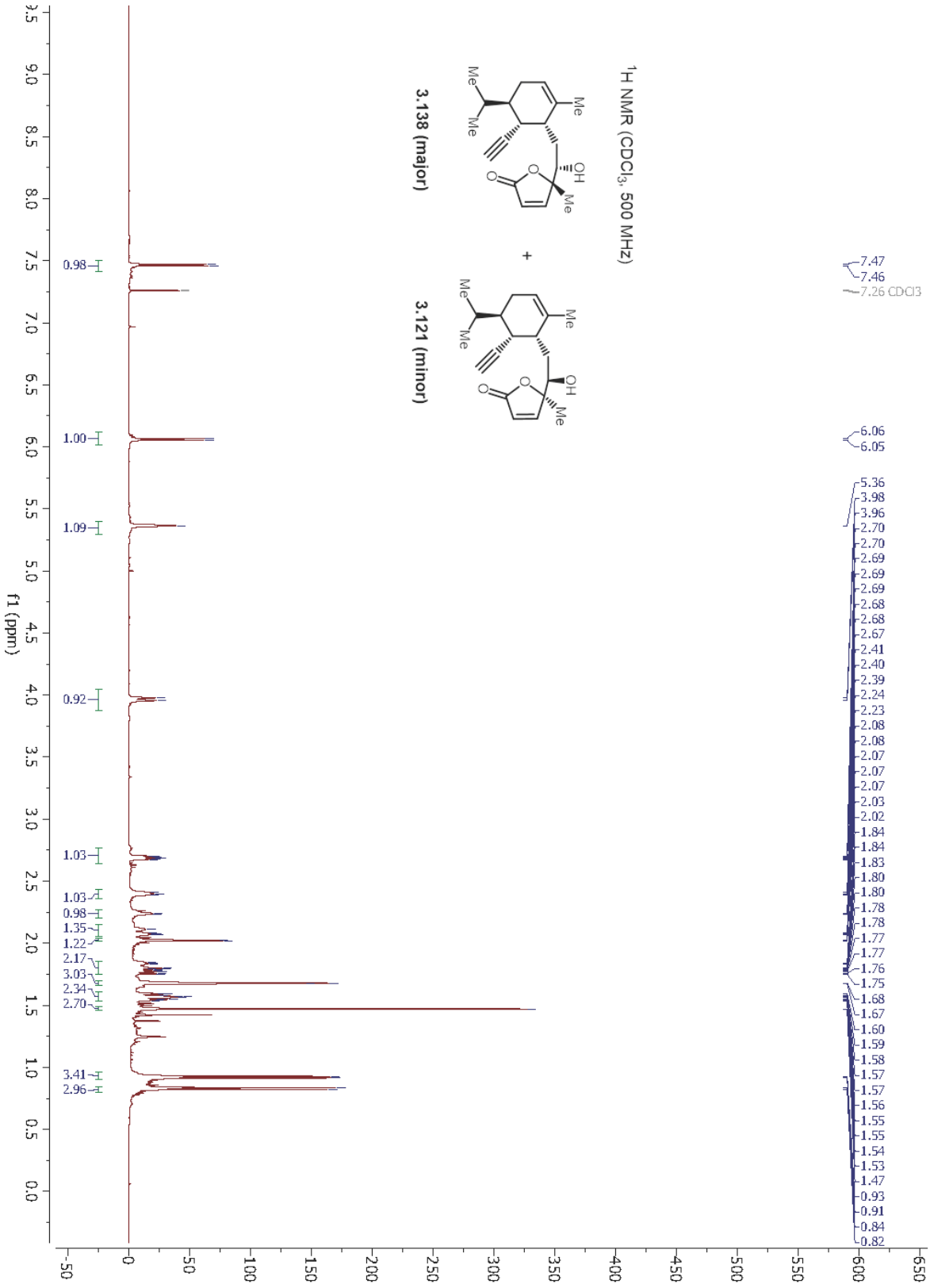
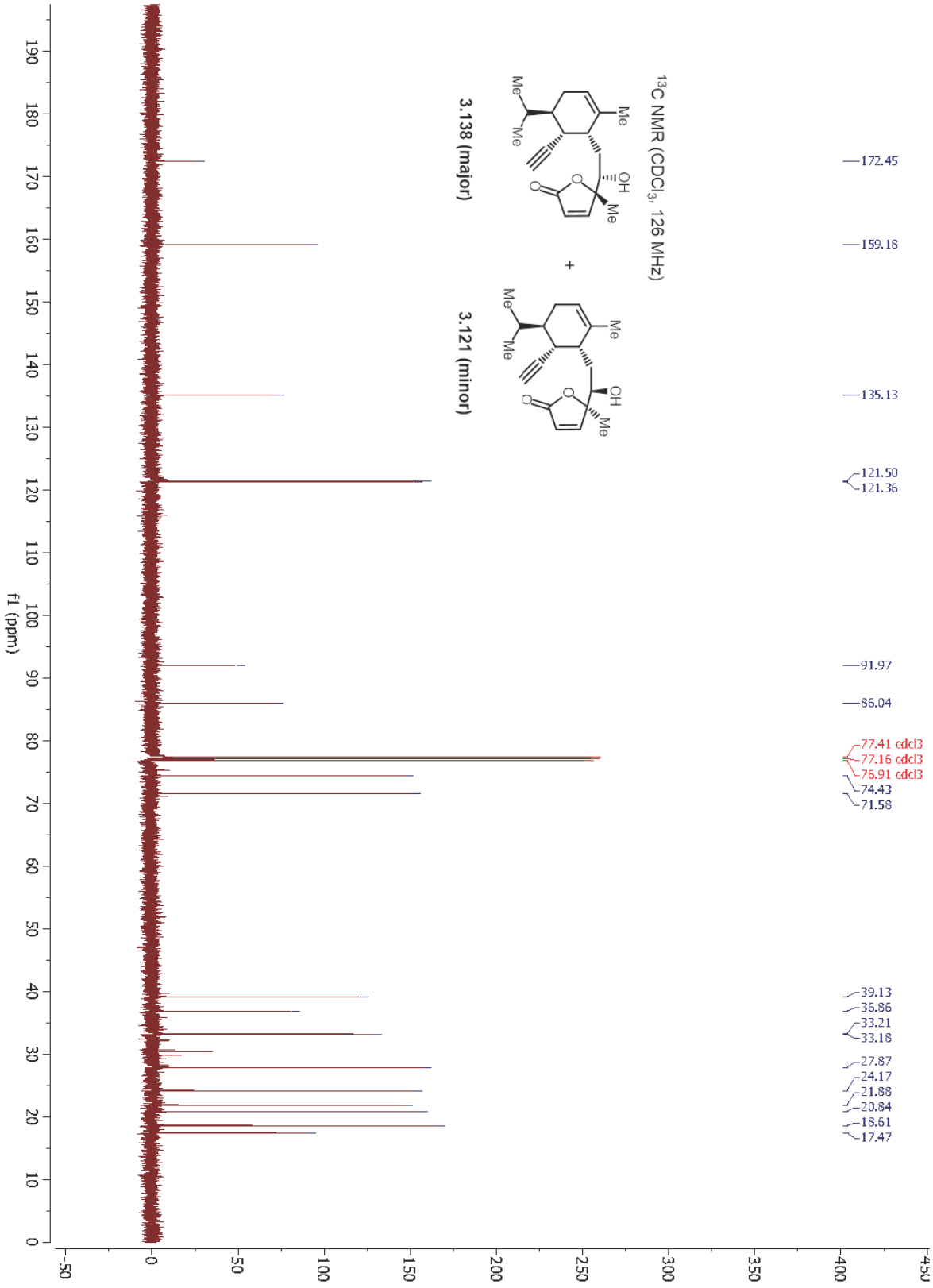
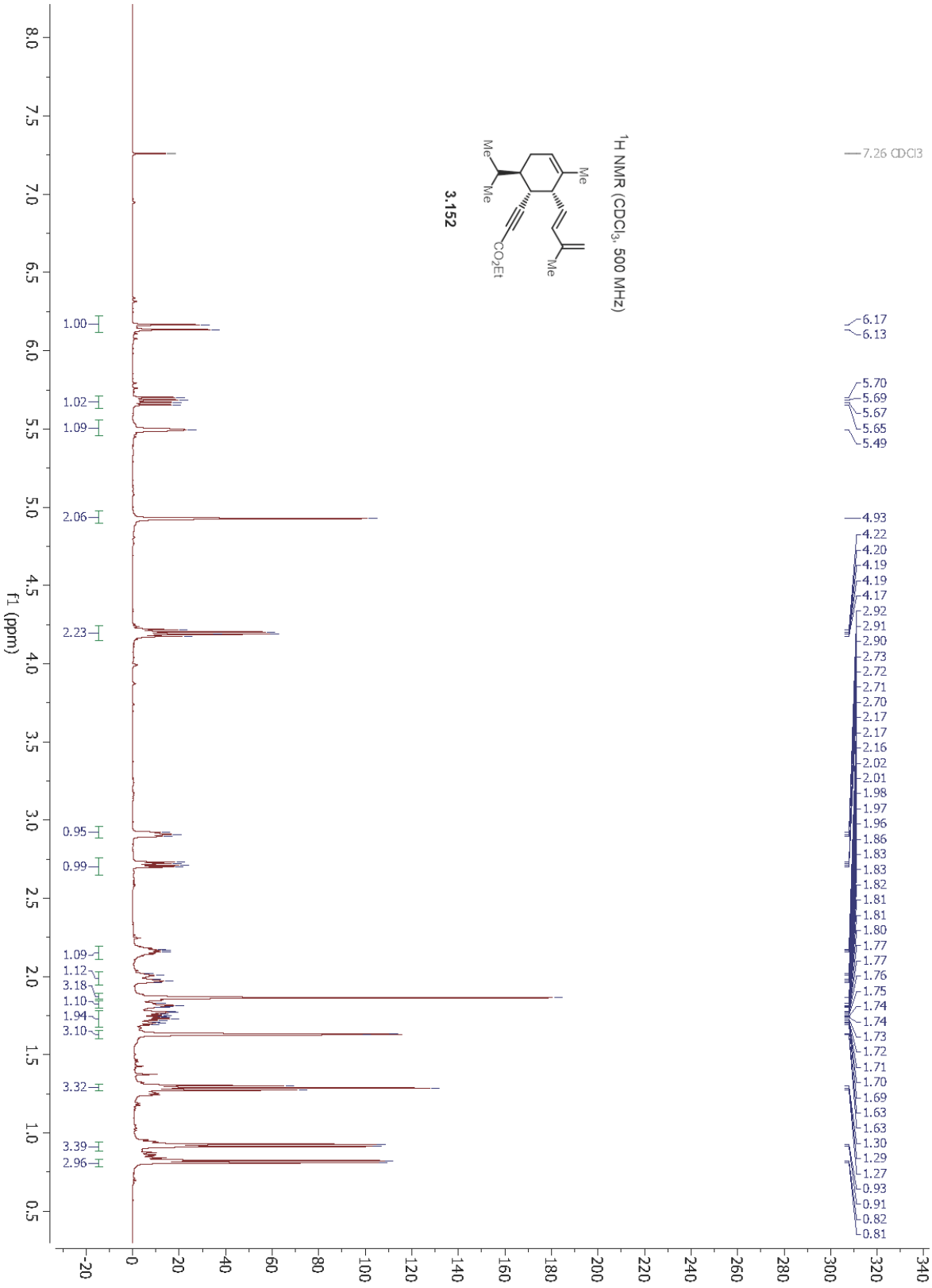
20.84
20.79
17.14
16.27
16.04
15.78
15.42
f1 (ppm)

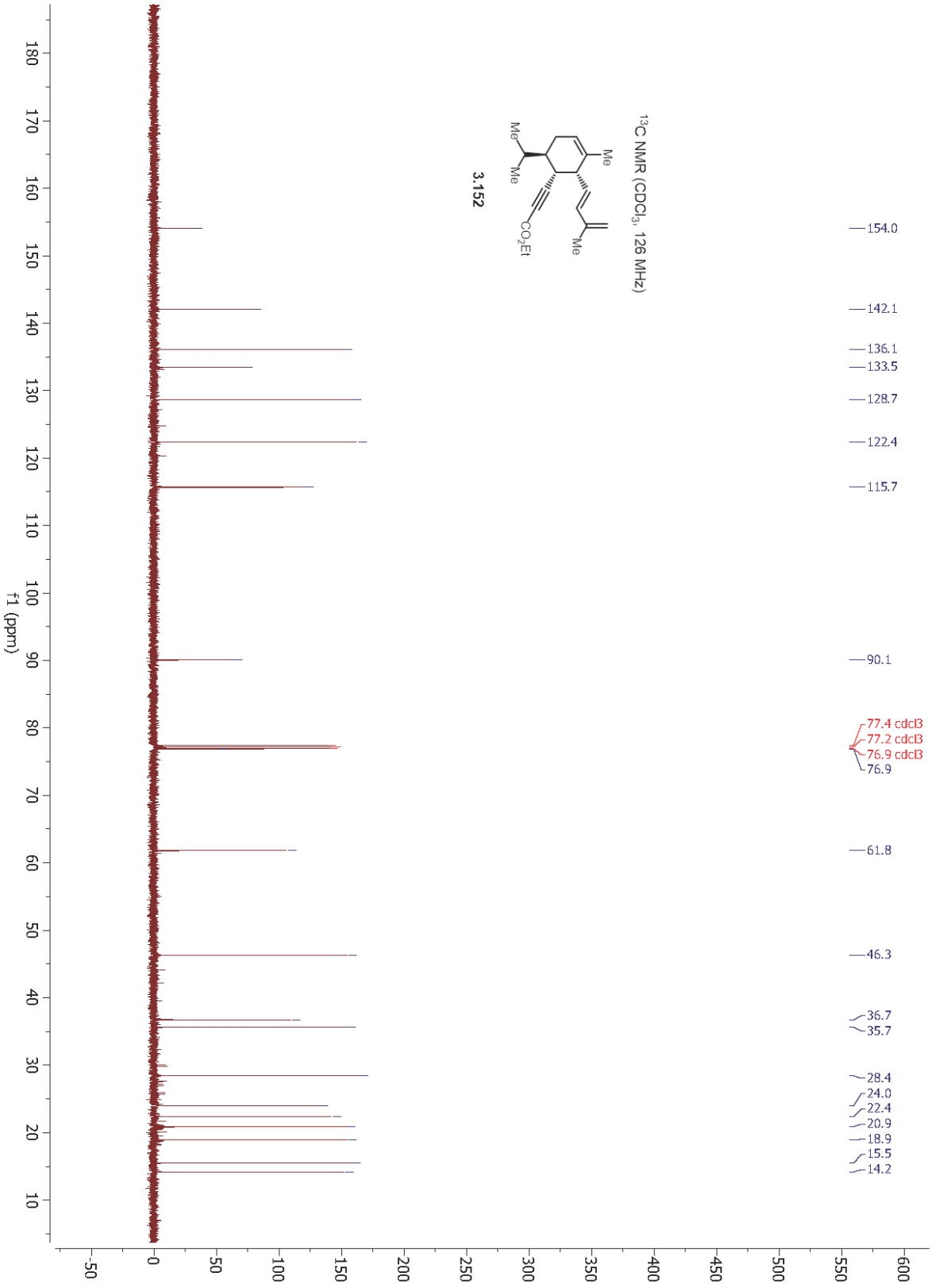

^{1}H NMR ($CDCl_3$, 500 MHz)
3.137 (major)
3.137 (minor)
3.135
f1 (ppm)

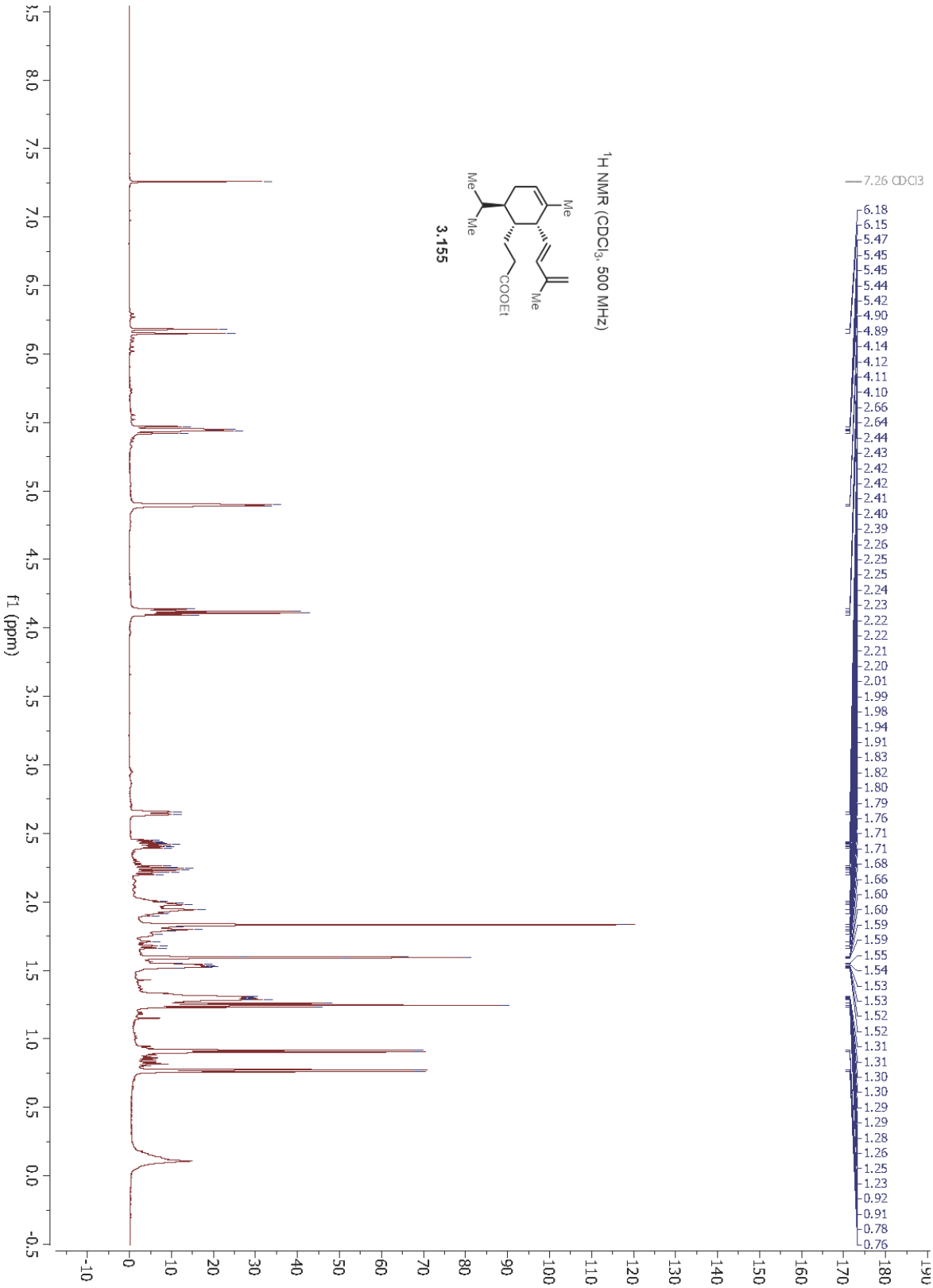

201.43
168.17
146.33
142.36
135.69
122.53
121.96
121.29
120.99
119.68
119.46
107.80
85.95
82.70
81.25
80.85
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
76.63
71.65
71.24
51.50
39.24
38.77
38.67
37.49
35.52
33.60
33.34
32.35
30.83
29.03
28.79
28.45
28.37
27.94
27.85
26.55
26.52
26.01
24.33
24.13
21.99
21.93
21.16
21.06
20.86
20.78
20.71
17.74
17.14
16.03
15.81
13C NMR (CDCl3, 126 MHz)
3.137 (major)
3.137 (minor)
3.135
f1 (ppm)

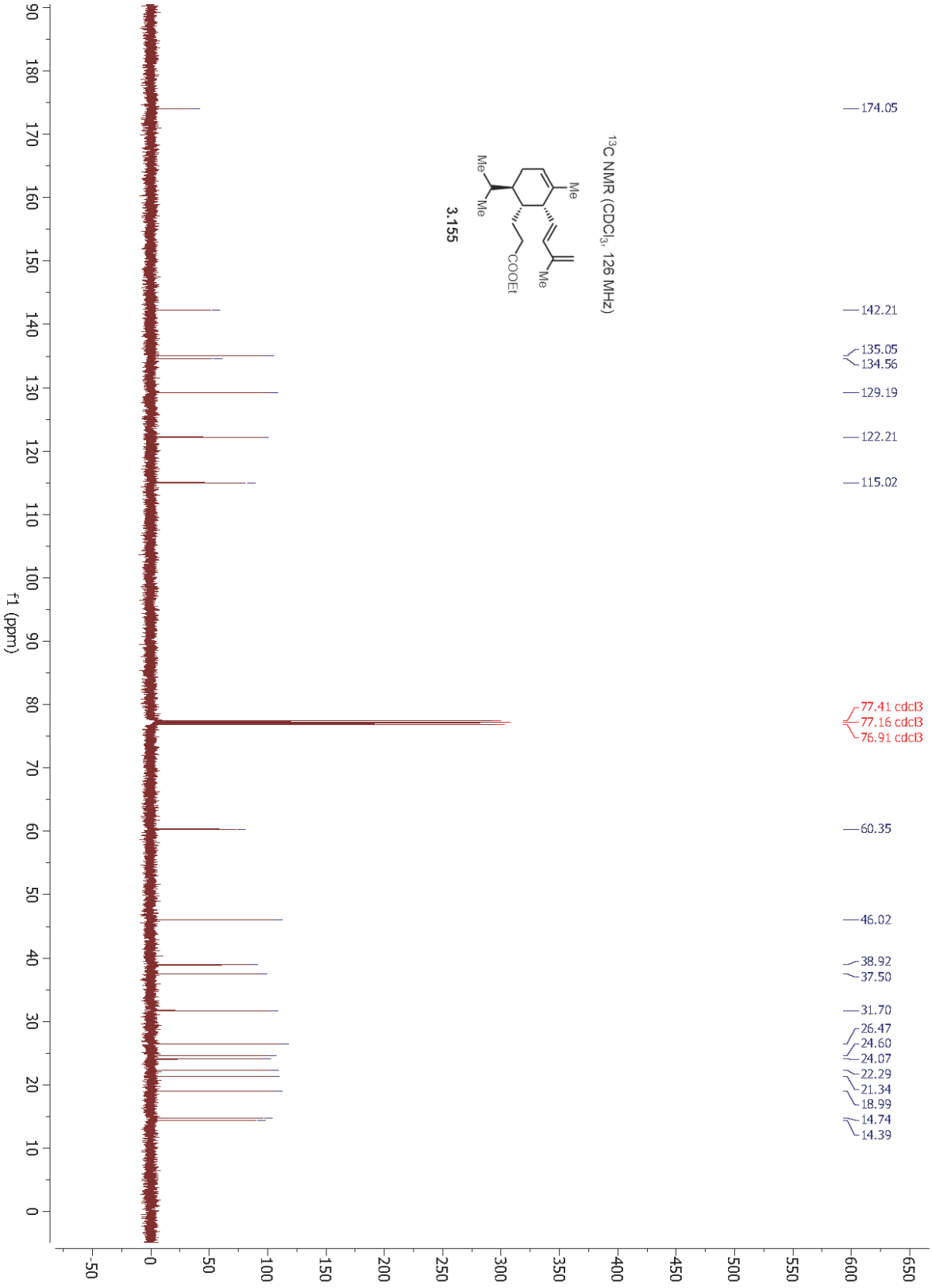

^{1}H NMR (CDCl$_3$, 500 MHz)
3.138 (major)
3.121 (minor)
f1 (ppm)
7.47
7.46
7.26 CDCl3
6.06
6.05
0.98
1.00
1.09
0.92
1.03
1.03
0.98
1.35
1.22
2.17
3.03
2.34
2.70
3.41
2.96

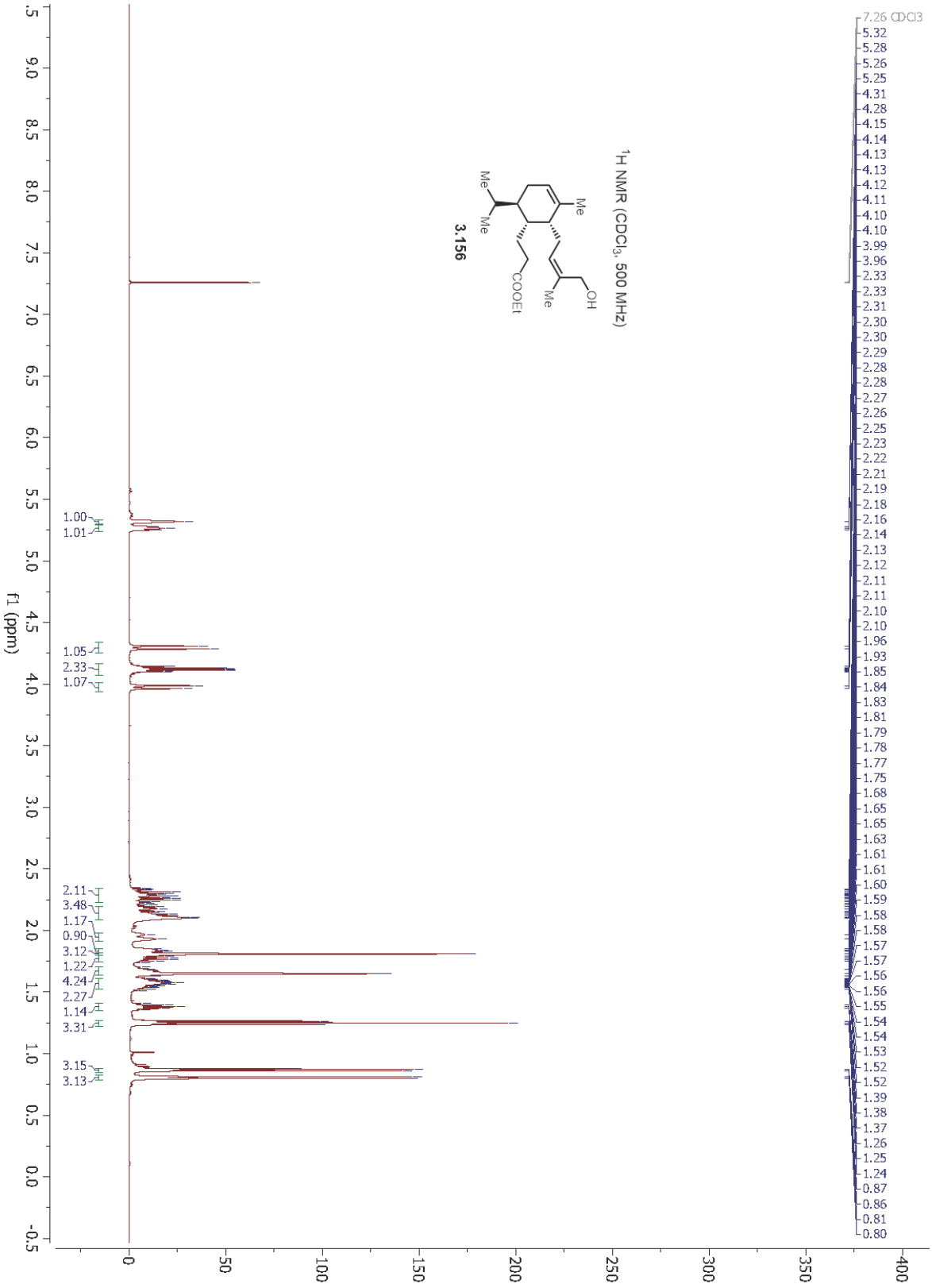

^{13}C NMR ($CDCl_3$, 126 MHz)
3.138 (major)
3.121 (minor)
Me
Me
Me
OH
Me
O
O
+
172.45
159.18
135.13
121.50
121.36
91.97
86.04
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
74.43
71.58
39.13
36.86
33.21
33.18
27.87
24.17
21.88
20.84
18.61
17.47
f1 (ppm)

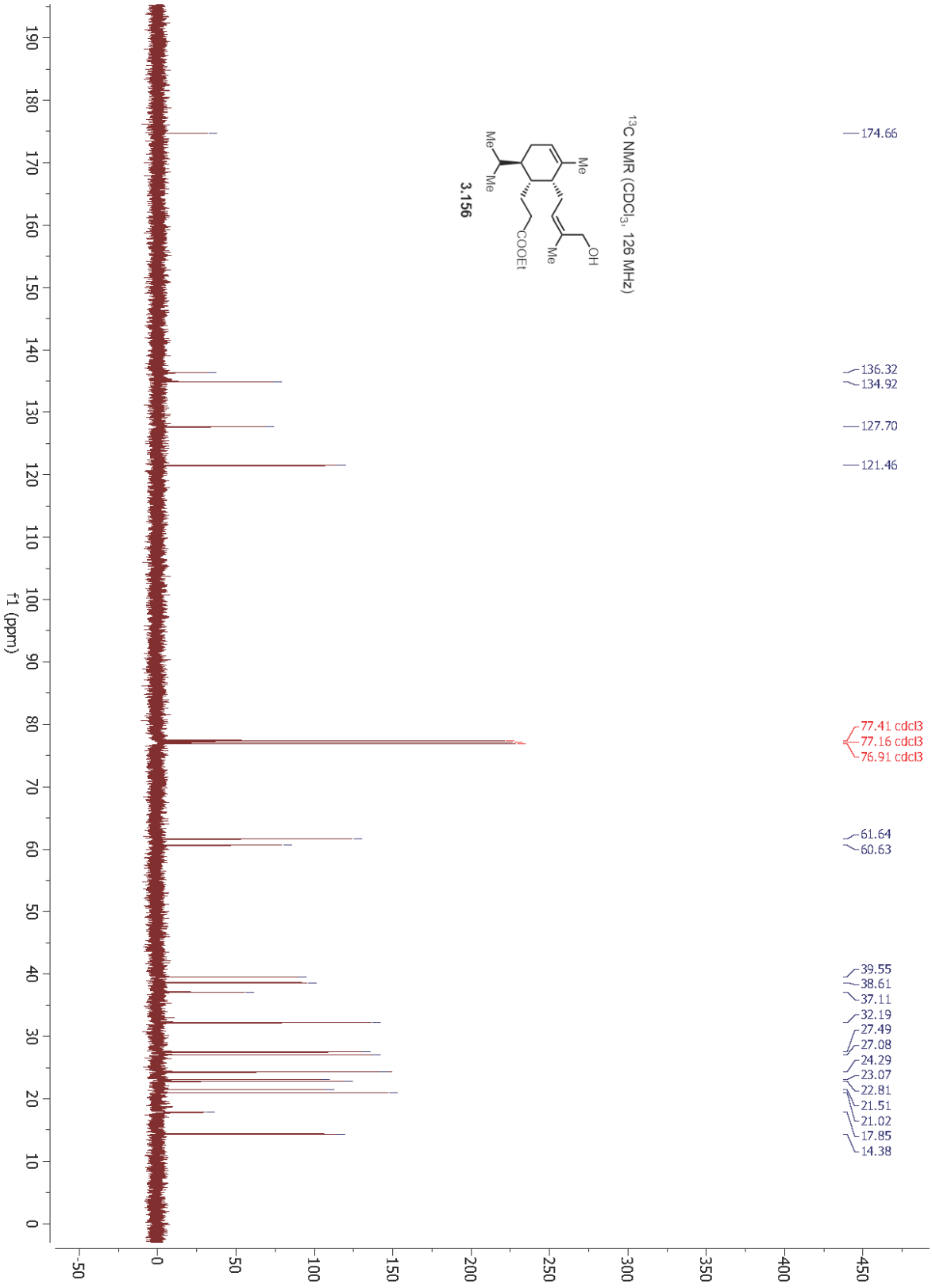

3.152
^{1}H NMR ($CDCl_3$, 500 MHz)
7.26 CDCl3
f1 (ppm)

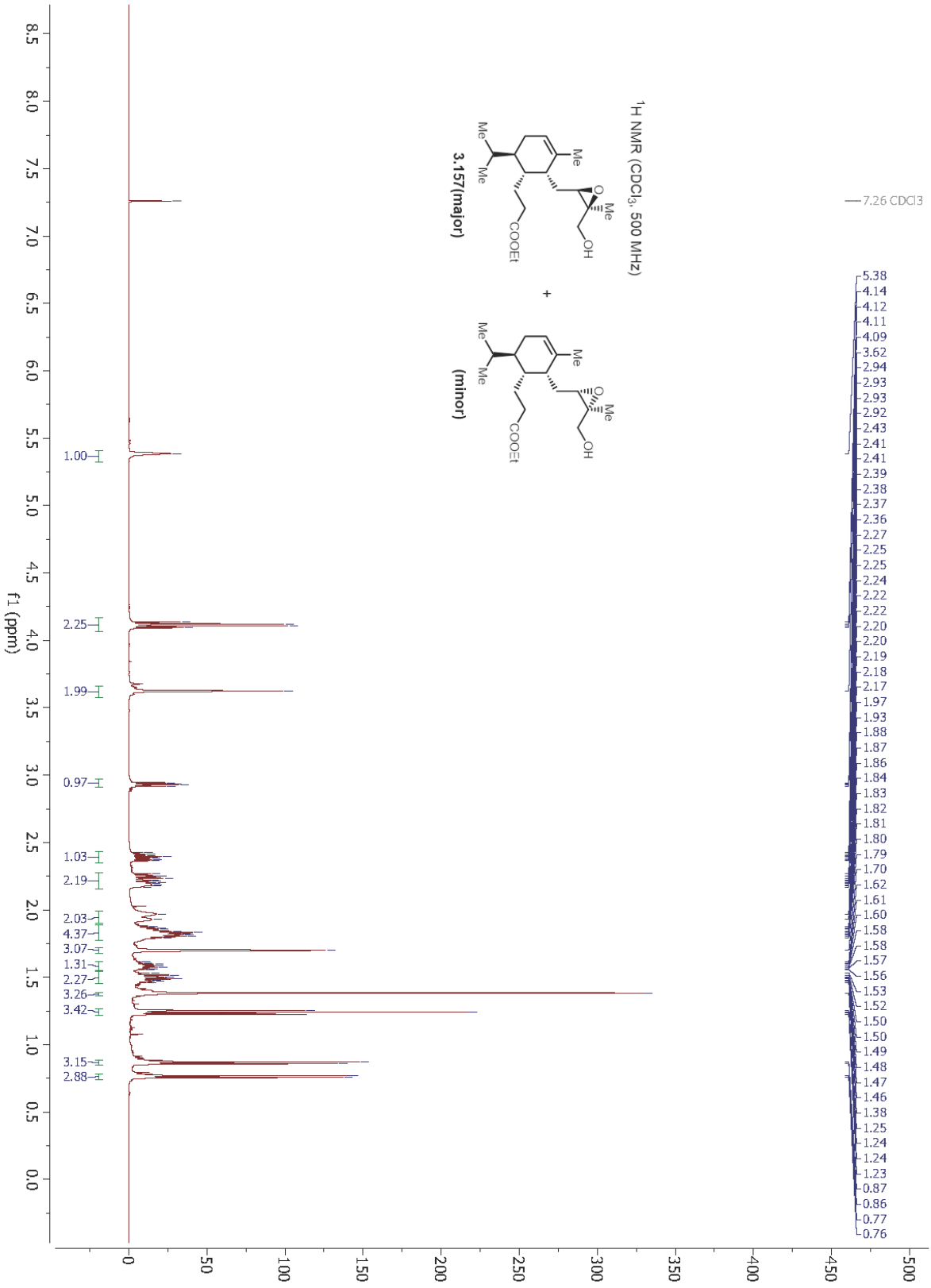

^{13}C NMR ($CDCl_3$, 126 MHz)
3.152
Me
Me
Me
CO_2Et
Me
154.0
142.1
136.1
133.5
128.7
122.4
115.7
90.1
77.4 cdcl3
77.2 cdcl3
76.9 cdcl3
76.9
61.8
46.3
36.7
35.7
28.4
24.0
22.4
20.9
18.9
15.5
14.2
f1 (ppm)

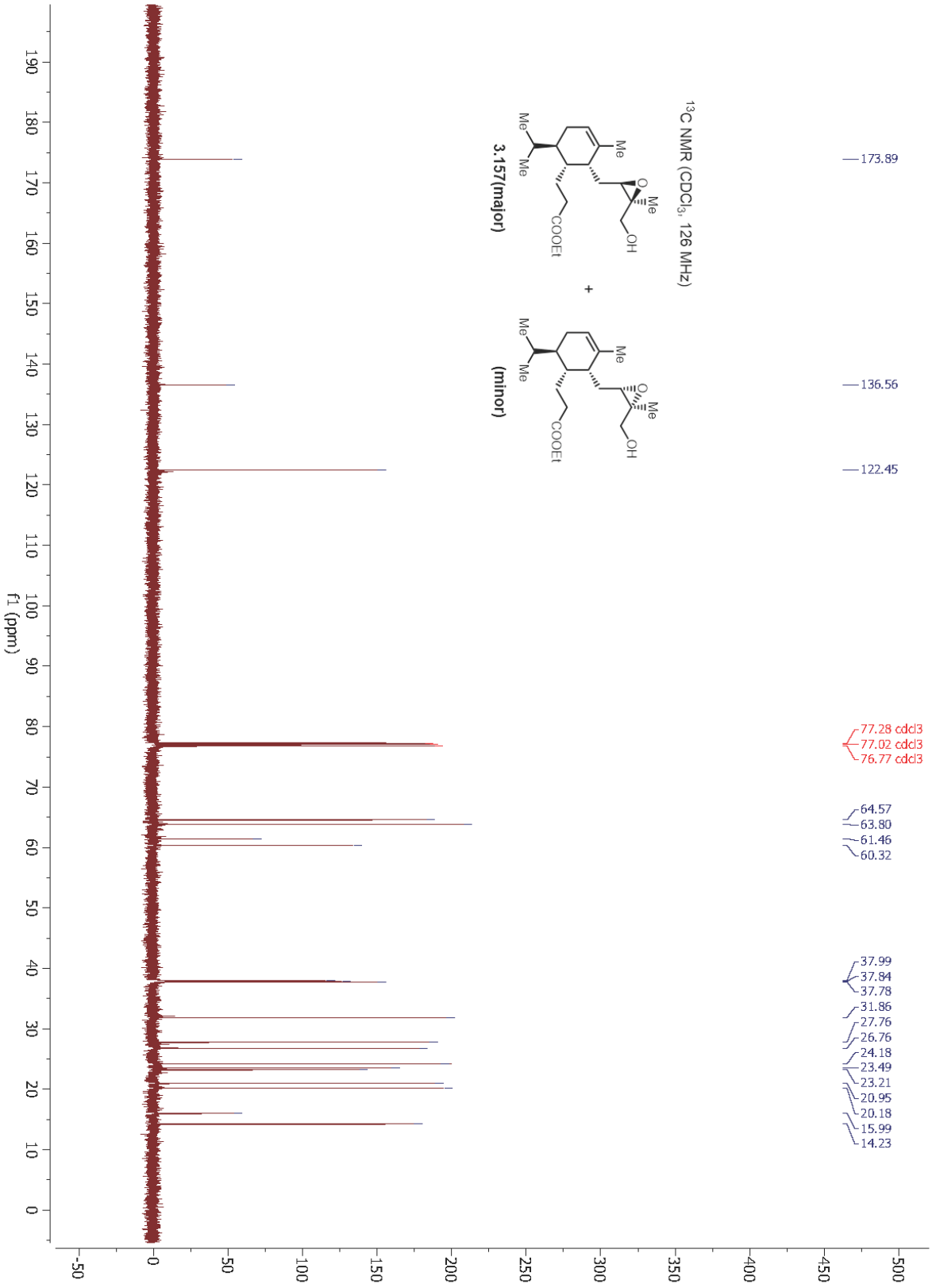

^{1}H NMR (CDCl$_3$, 500 MHz)
3.155
Me
Me
Me
COOEt
Me
7.26 CDCl3
f1 (ppm)

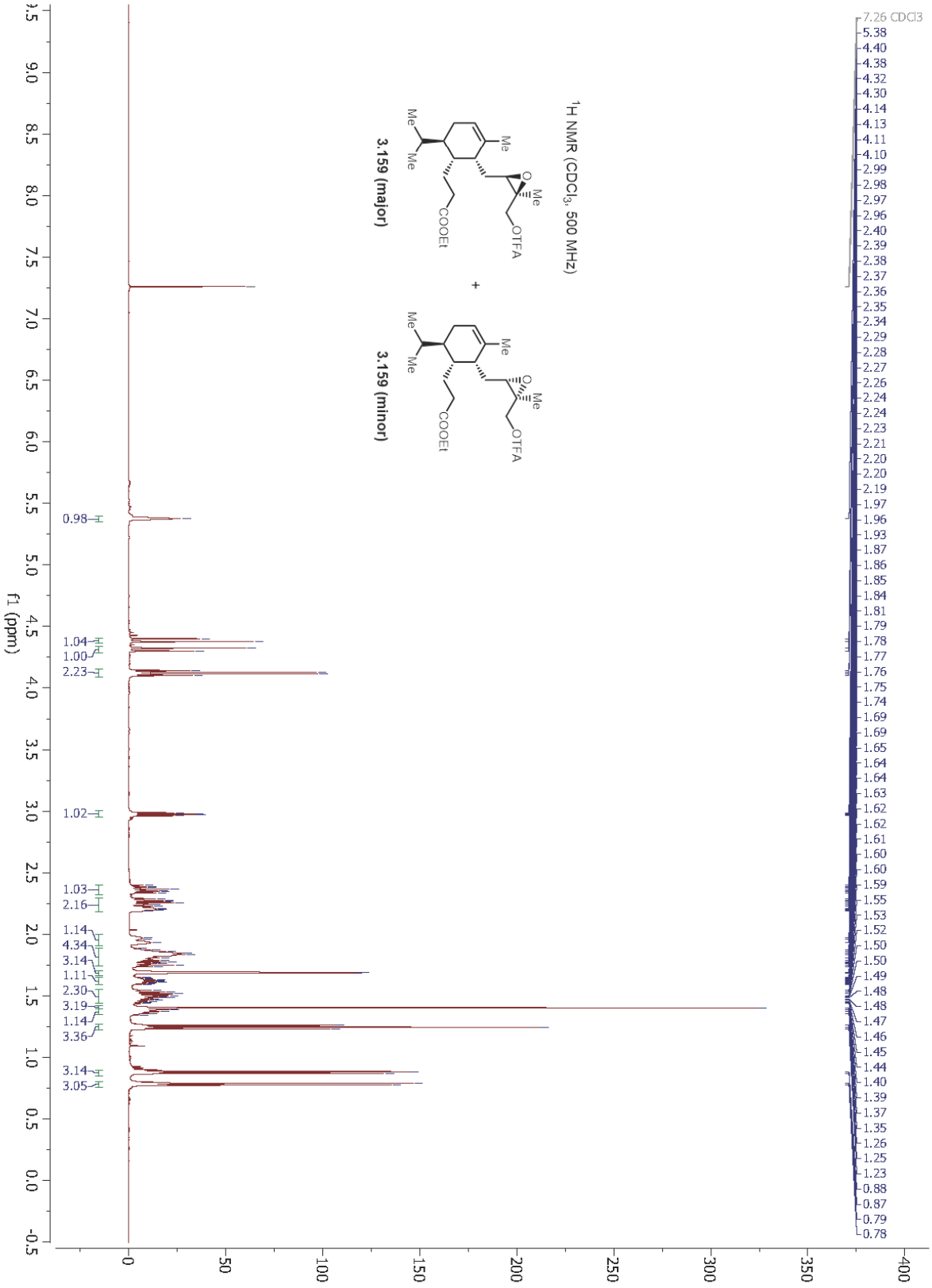

^{13}C NMR ($CDCl_3$, 126 MHz)
3.155
Me
Me
Me
Me
COOEt
174.05
142.21
135.05
134.56
129.19
122.21
115.02
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
60.35
46.02
38.92
37.50
31.70
26.47
24.60
24.07
22.29
21.34
18.99
14.74
14.39
f1 (ppm)

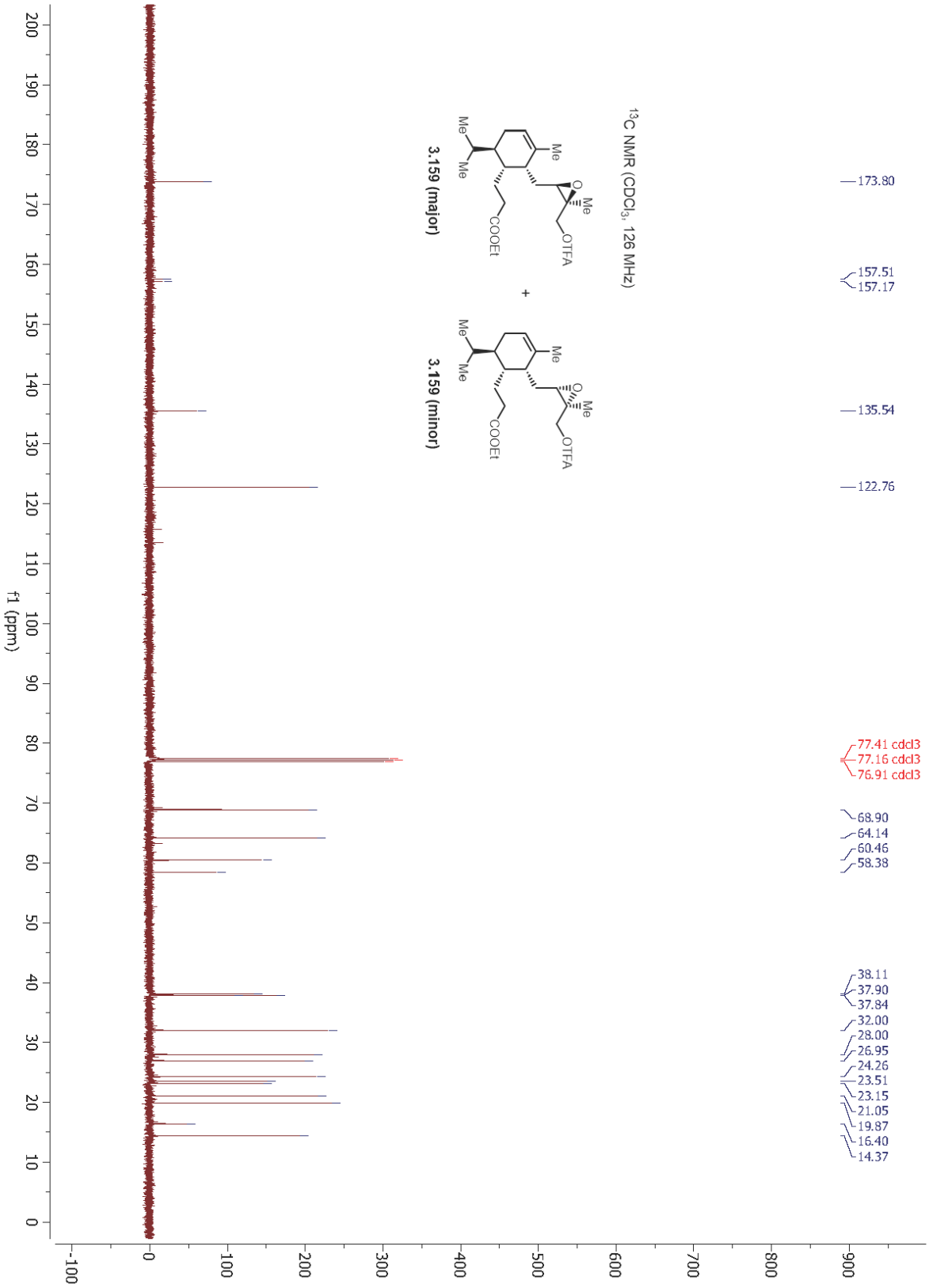

^{1}H NMR (CDCl$_3$, 500 MHz)
3.156
Me
Me
Me
COOEt
Me
OH
f1 (ppm)
7.26 CDCl3
1.00
1.01
1.05
2.33
1.07
2.11
3.48
1.17
0.90
3.12
1.22
4.24
2.27
1.14
3.31
3.15
3.13

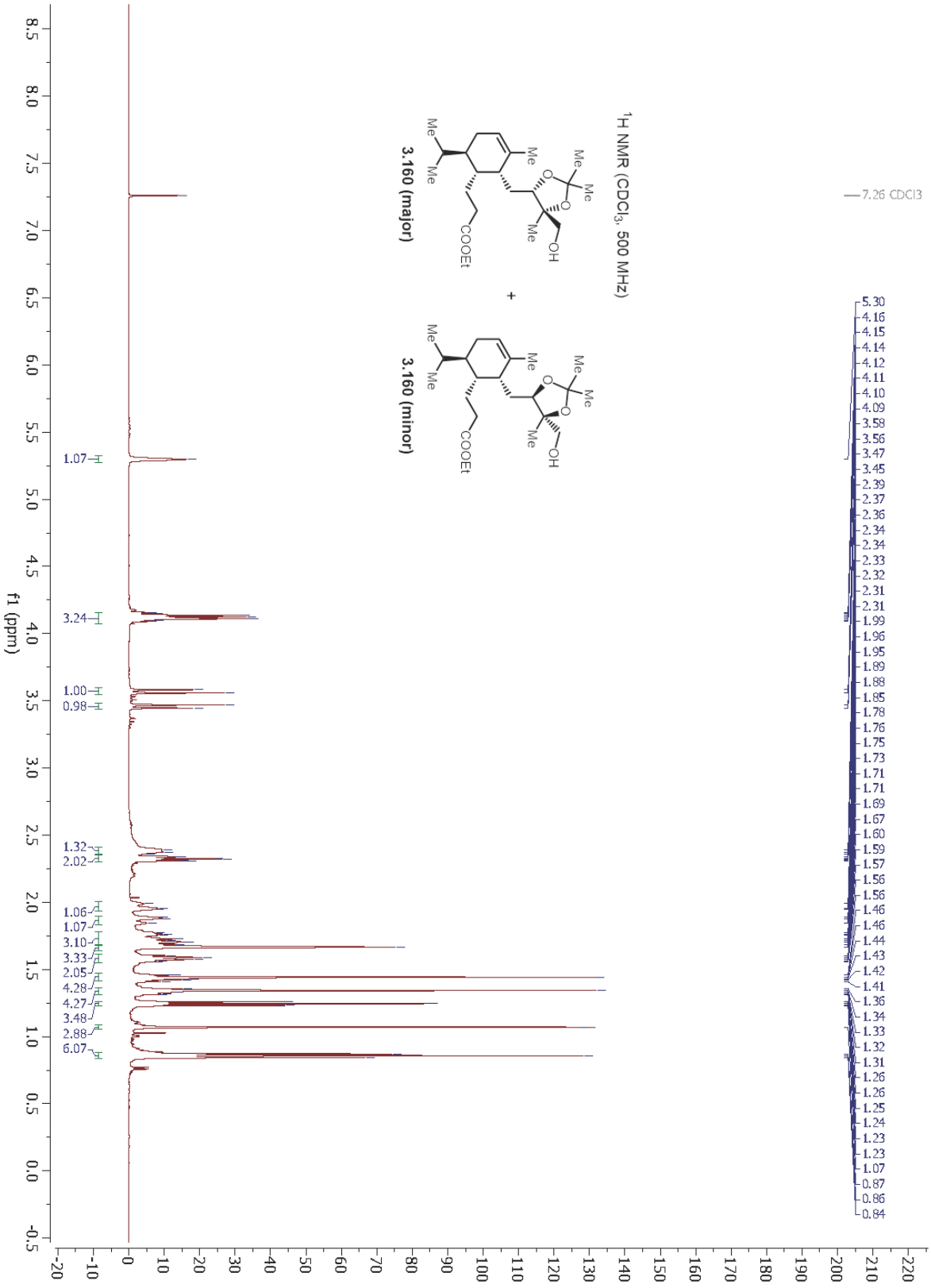

^{13}C NMR ($CDCl_3$, 126 MHz)
3.156
Me
Me
Me
COOEt
Me
OH
174.66
136.32
134.92
127.70
121.46
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
61.64
60.63
39.55
38.61
37.11
32.19
27.49
27.08
24.29
23.07
22.81
21.51
21.02
17.85
14.38
f1 (ppm)

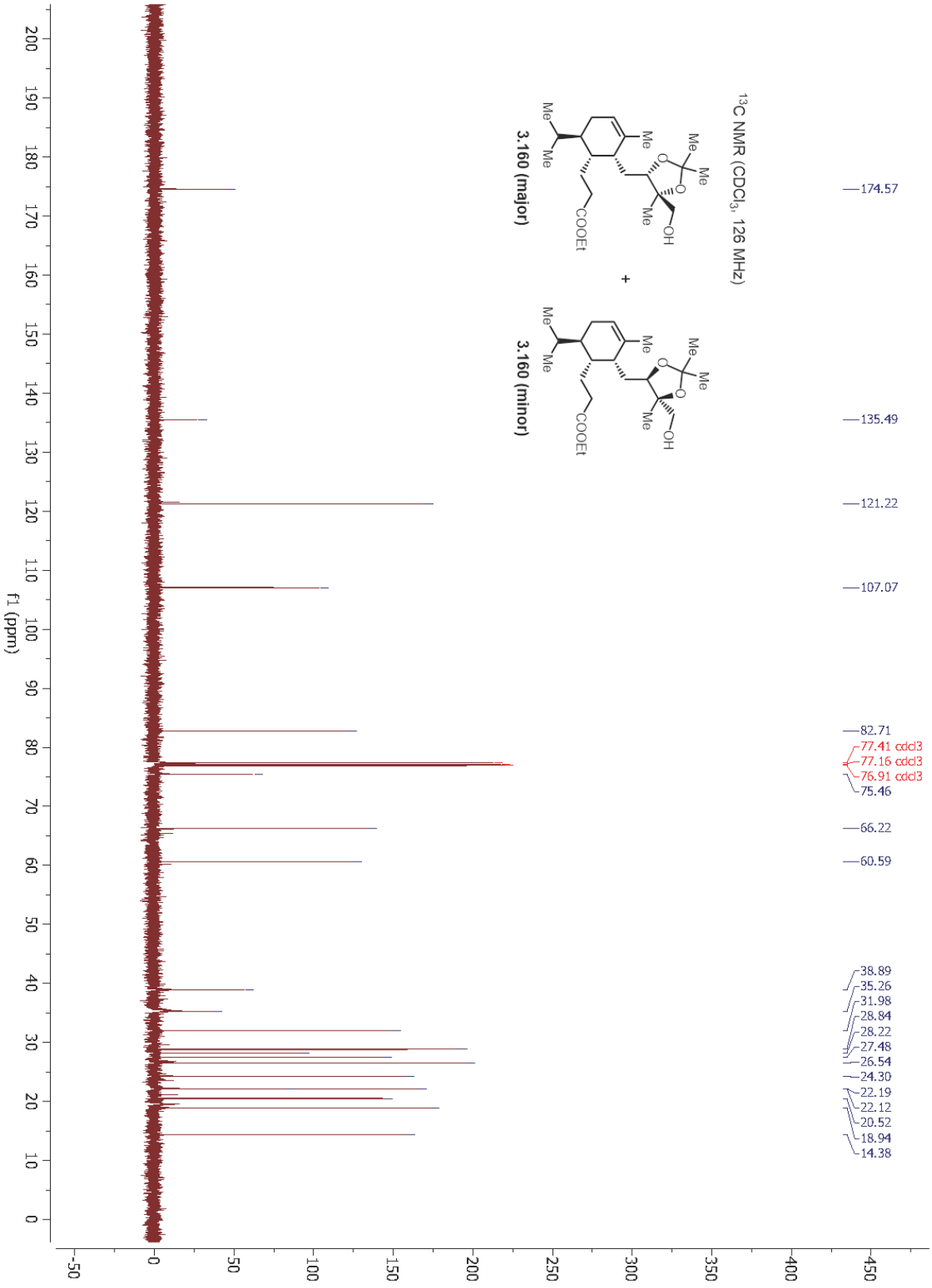

^{1}H NMR (CDCl$_3$, 500 MHz)
3.157(major)
(minor)
7.26 CDCl3
f1 (ppm)
1.00
2.25
1.99
0.97
1.03
2.19
2.03
4.37
3.07
1.31
2.27
3.26
3.42
3.15
2.88

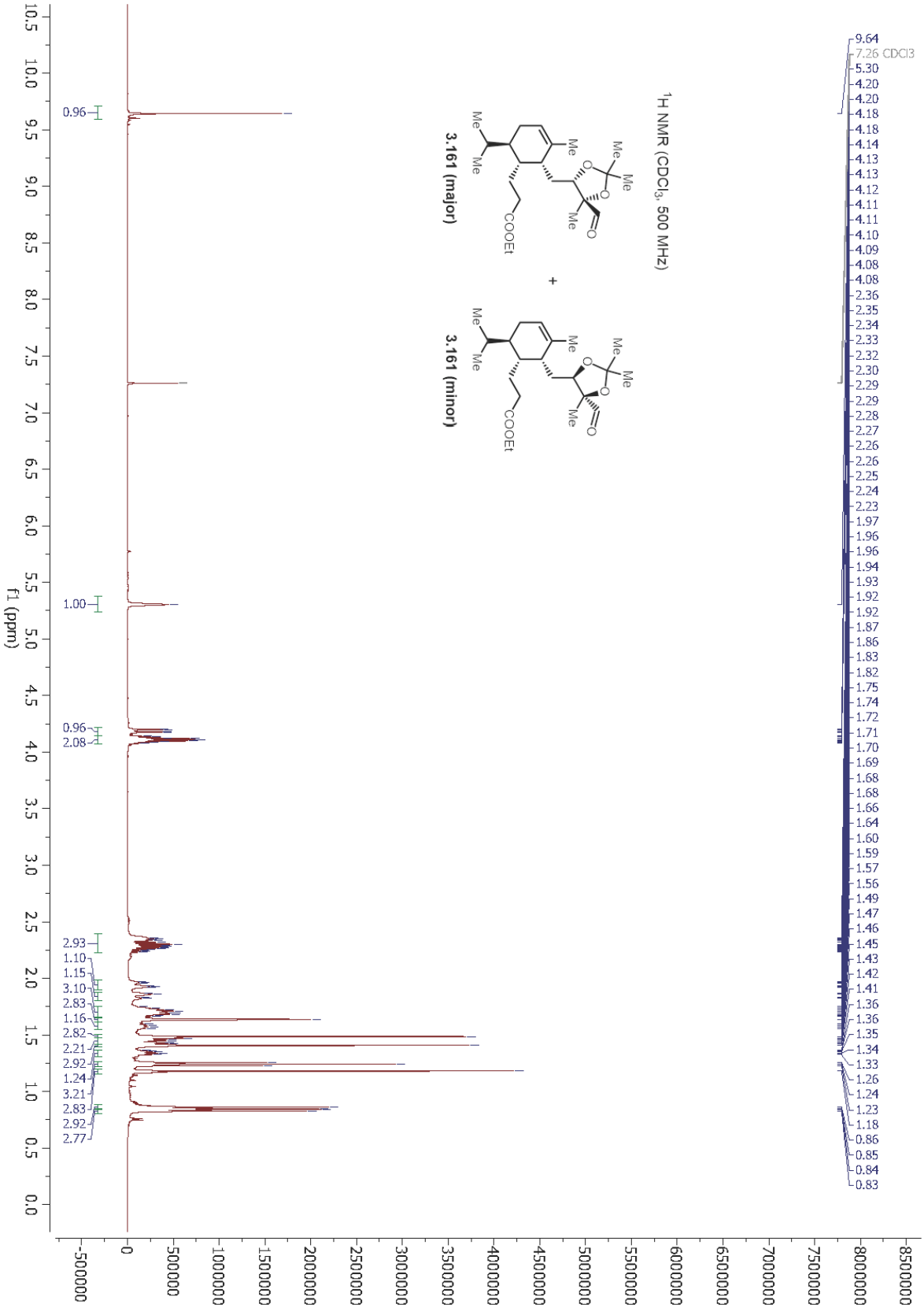

^{13}C NMR ($CDCl_3$, 126 MHz)
3.157(major)
(minor)
Me
Me
Me
Me
O
COOEt
OH
+
173.89
136.56
122.45
77.28 cdcl3
77.02 cdcl3
76.77 cdcl3
64.57
63.80
61.46
60.32
37.99
37.84
37.78
31.86
27.76
26.76
24.18
23.49
23.21
20.95
20.18
15.99
14.23
f1 (ppm)

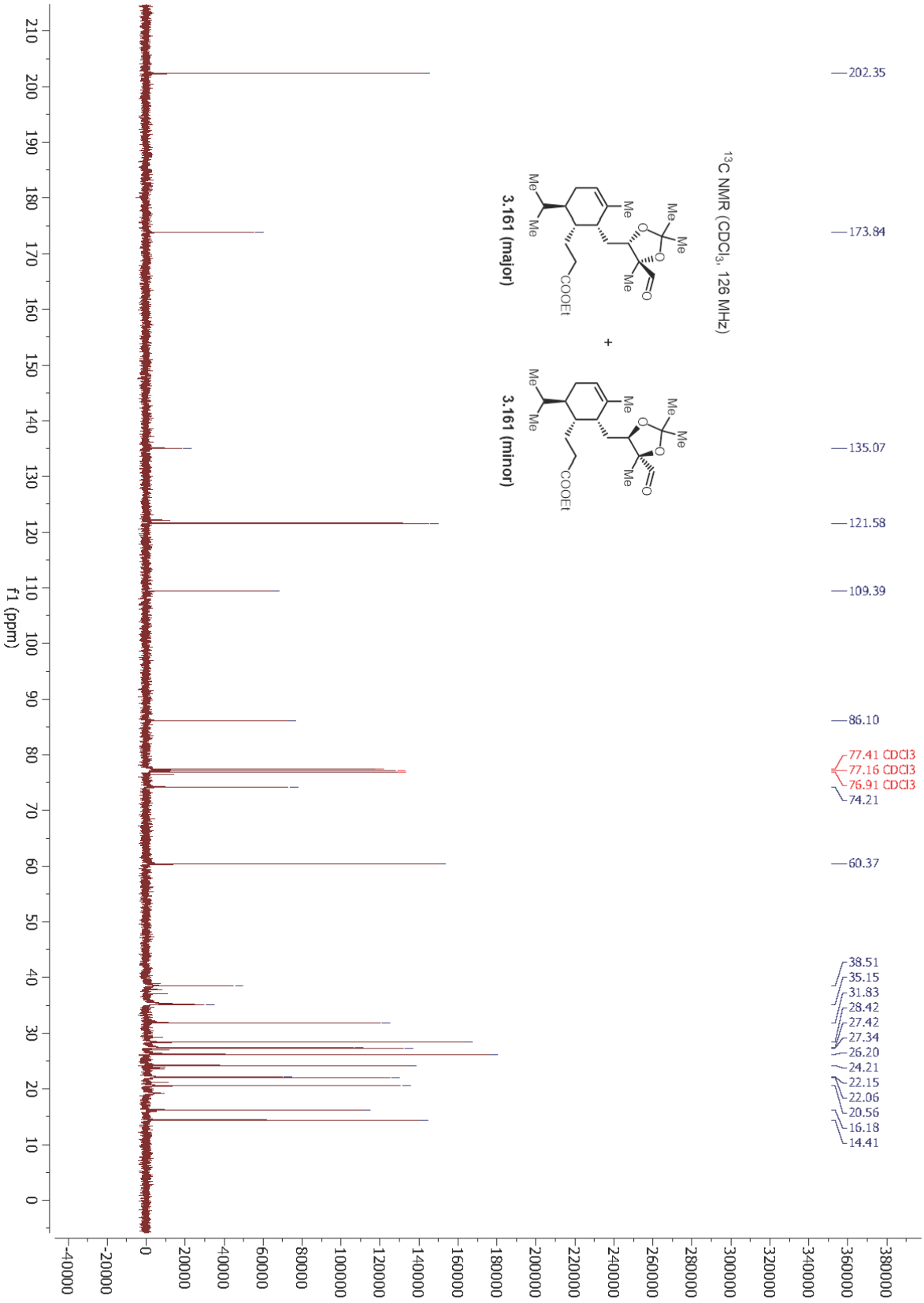

^{1}H NMR (CDCl$_3$, 500 MHz)
3.159 (major)
3.159 (minor)
Me
Me
Me
COOEt
OTFA
+
f1 (ppm)
7.26 CDCl3
0.98
1.04
1.00
2.23
1.02
1.03
2.16
1.14
4.34
3.14
1.11
2.30
3.19
1.14
3.36
3.14
3.05

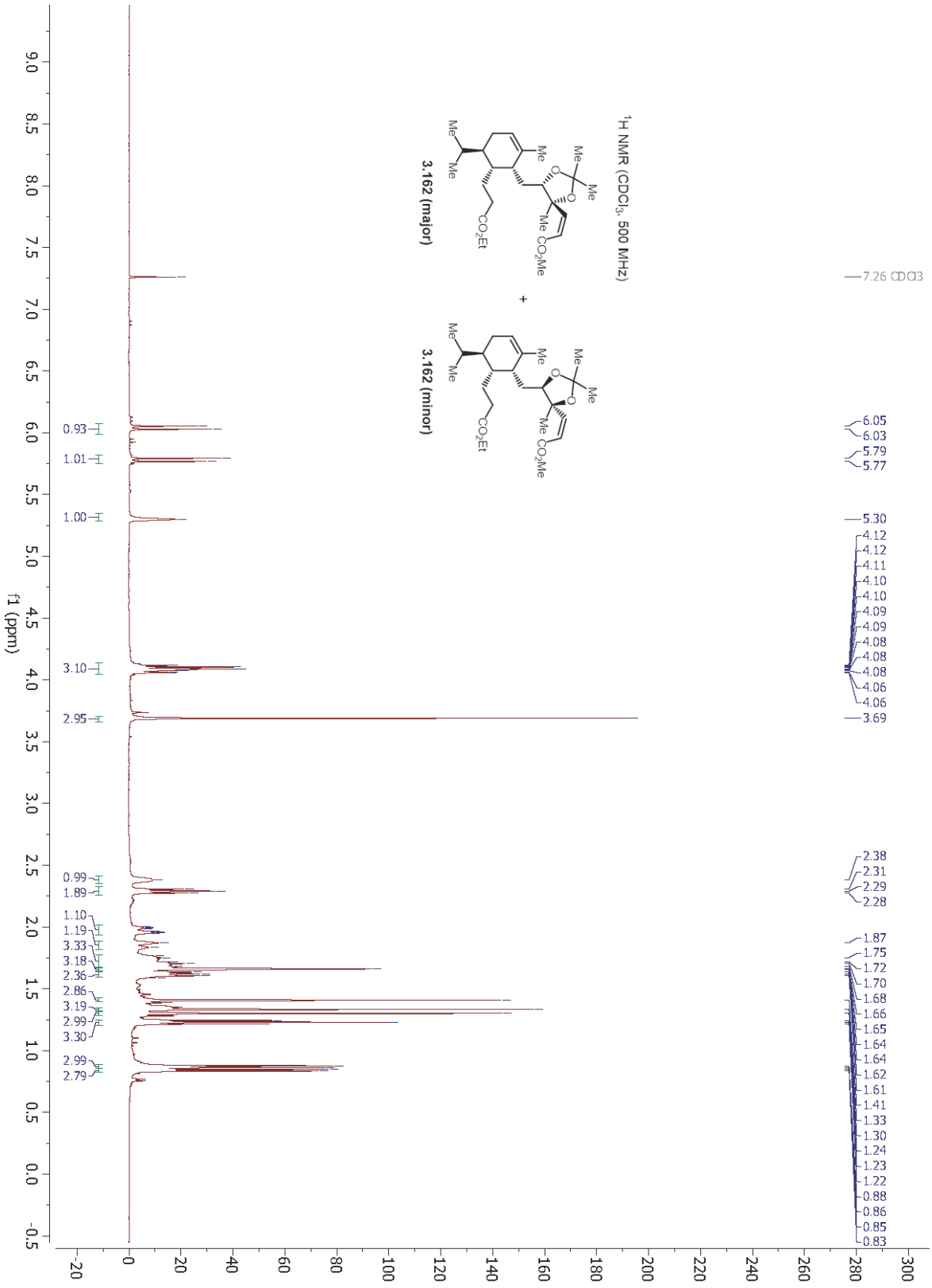

^{13}C NMR (CDCl$_3$, 126 MHz)
3.159 (major)
3.159 (minor)
+
Me
Me
Me
COOEt
OTFA
O
173.80
157.51
157.17
135.54
122.76
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
68.90
64.14
60.46
58.38
38.11
37.90
37.84
32.00
28.00
26.95
24.26
23.51
23.15
21.05
19.87
16.40
14.37
f1 (ppm)

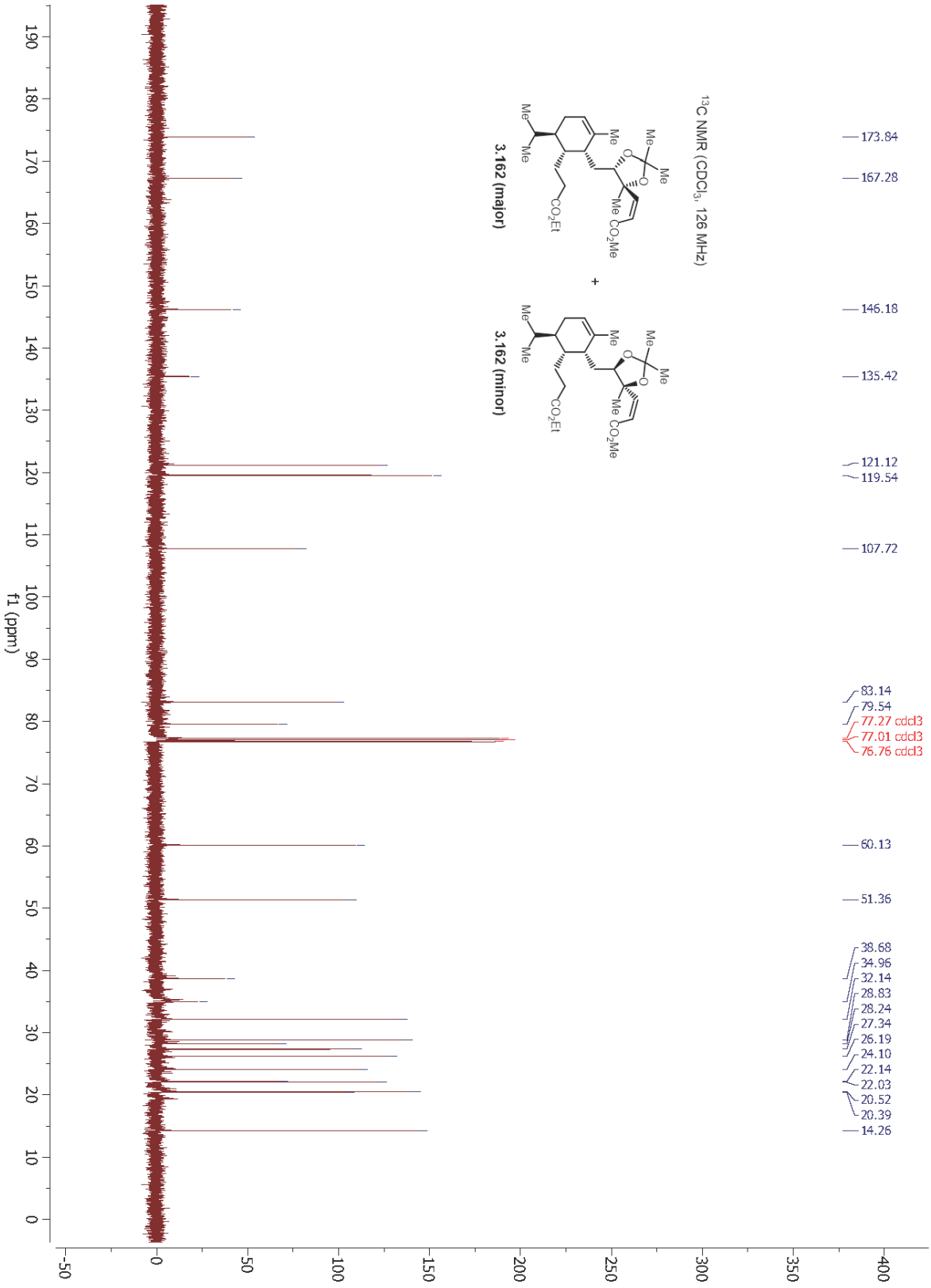

^{1}H NMR ($CDCl_3$, 500 MHz)
3.160 (major)
3.160 (minor)
7.26 CDCl3
f1 (ppm)
1.07
3.24
1.00
0.98
1.32
2.02
1.06
1.07
3.10
3.33
2.05
4.28
4.27
3.48
2.88
6.07

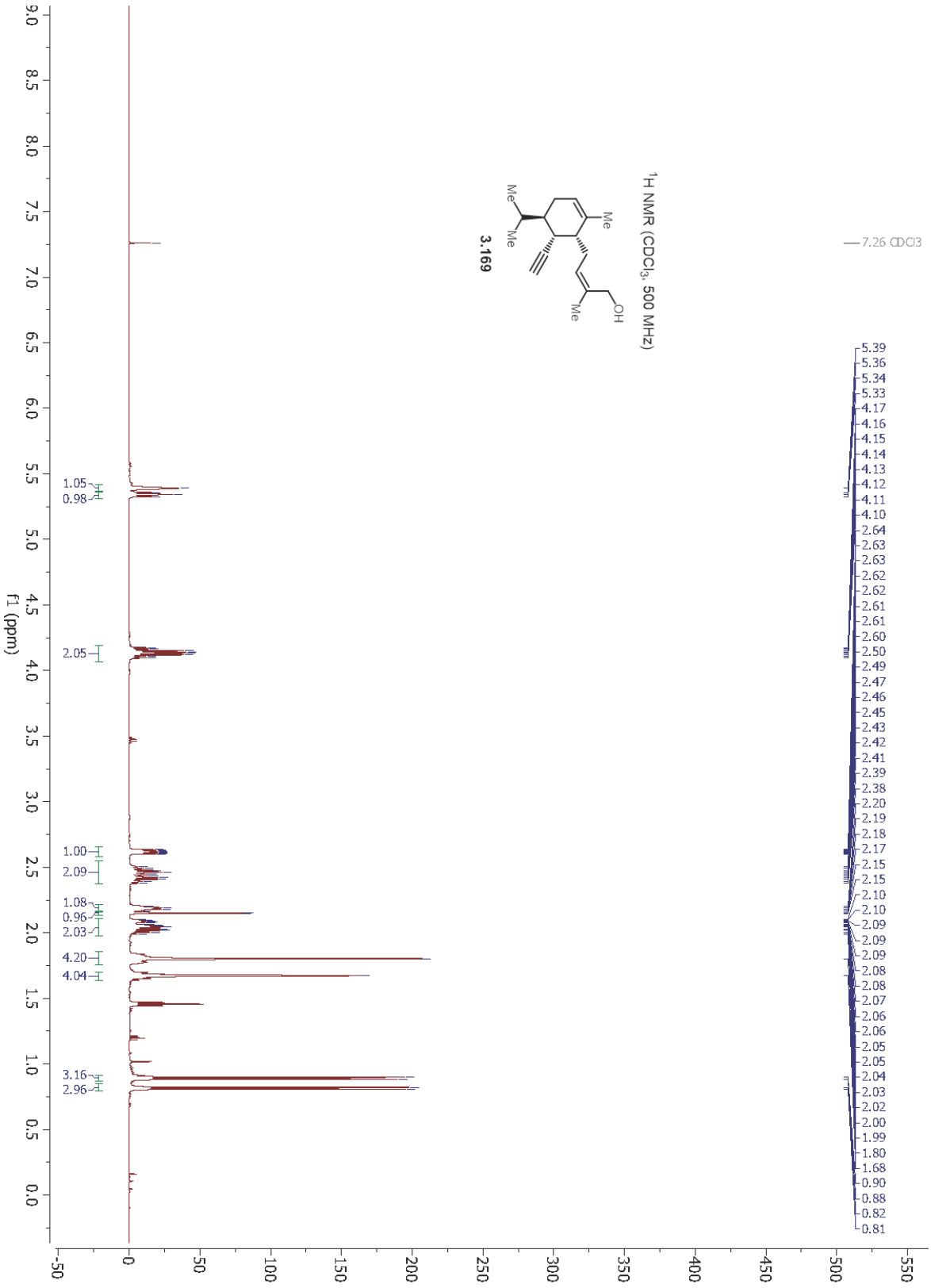

^{13}C NMR ($CDCl_3$, 126 MHz)
3.160 (major)
3.160 (minor)
+
Me
Me
Me
Me
Me
Me
Me
O
O
OH
COOEt
174.57
135.49
121.22
107.07
82.71
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
75.46
66.22
60.59
38.89
35.26
31.98
28.84
28.22
27.48
26.54
24.30
22.19
22.12
20.52
18.94
14.38
f1 (ppm)

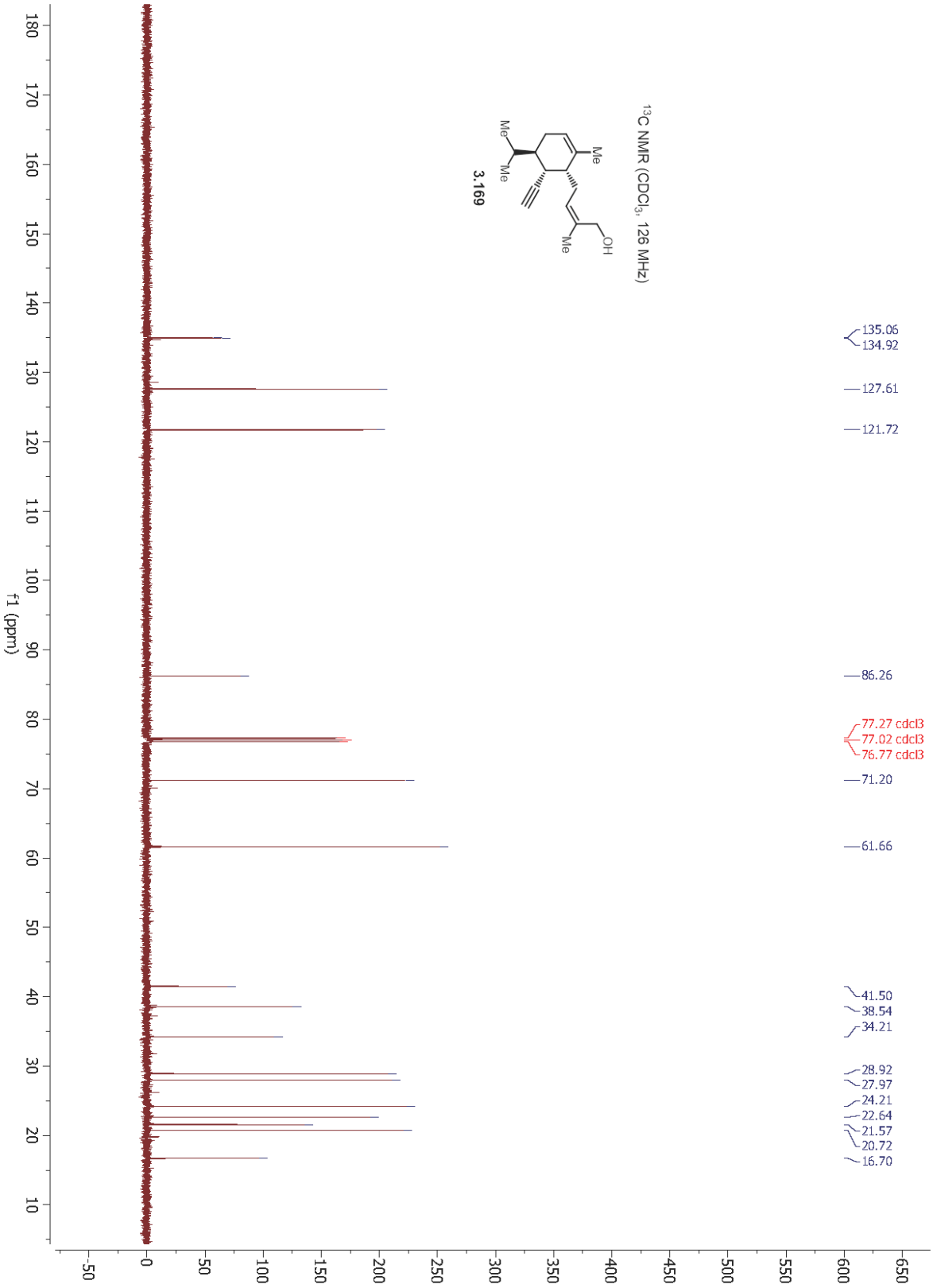

^{1}H NMR (CDCl$_3$, 500 MHz)
3.161 (major)
3.161 (minor)
f1 (ppm)
7.26 CDCl3

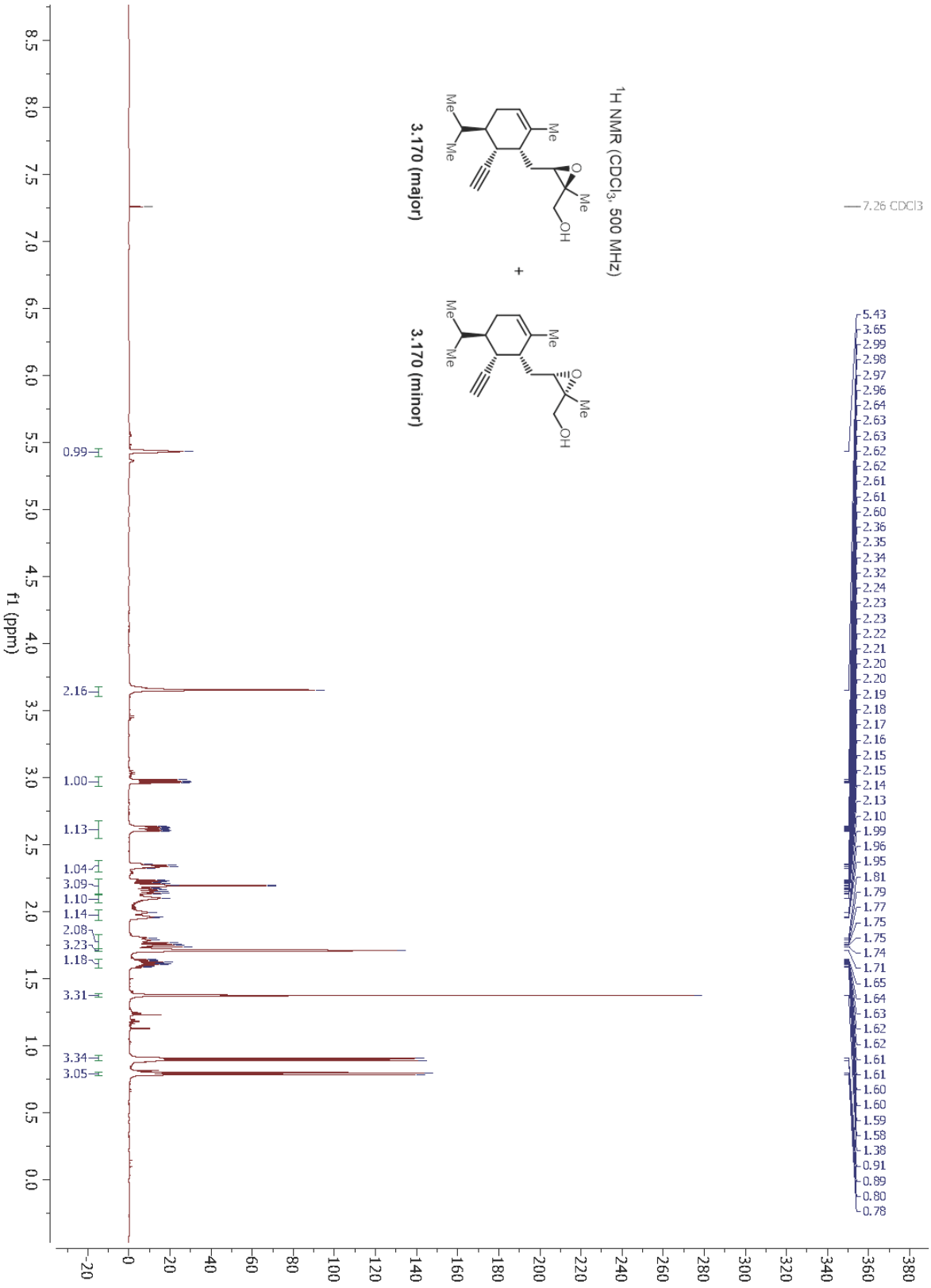

^{13}C NMR ($CDCl_3$, 126 MHz)
3.161 (major)
3.161 (minor)
202.35
173.84
135.07
121.58
109.39
86.10
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
74.21
60.37
38.51
35.15
31.83
28.42
27.42
27.34
26.20
24.21
22.15
22.06
20.56
16.18
14.41
f1 (ppm)

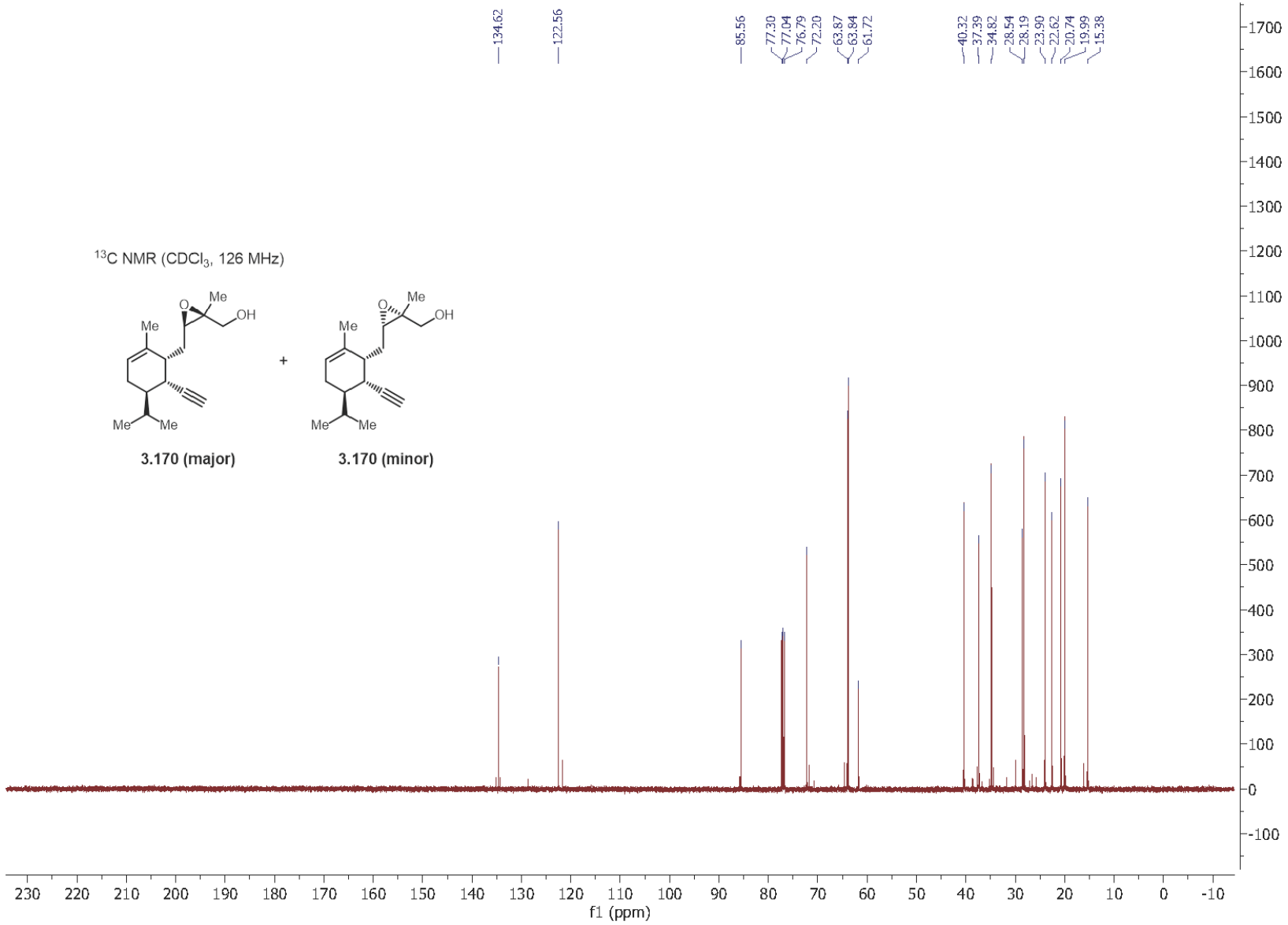

^{1}H NMR (CDCl$_3$, 500 MHz)
3.162 (major)
3.162 (minor)
+
f1 (ppm)
7.26 CDCl3
0.93
1.01
1.00
3.10
2.95
0.99
1.89
1.10
1.19
3.33
3.18
2.36
2.86
3.19
2.99
3.30
2.99
2.79
6.05
6.03
5.79
5.77
5.30
4.12
4.12
4.11
4.10
4.10
4.09
4.09
4.08
4.08
4.08
4.06
4.06
3.69
2.38
2.31
2.29
2.28
1.87
1.75
1.72
1.70
1.68
1.66
1.65
1.64
1.64
1.62
1.61
1.41
1.33
1.30
1.24
1.23
1.22
0.88
0.86
0.85
0.83

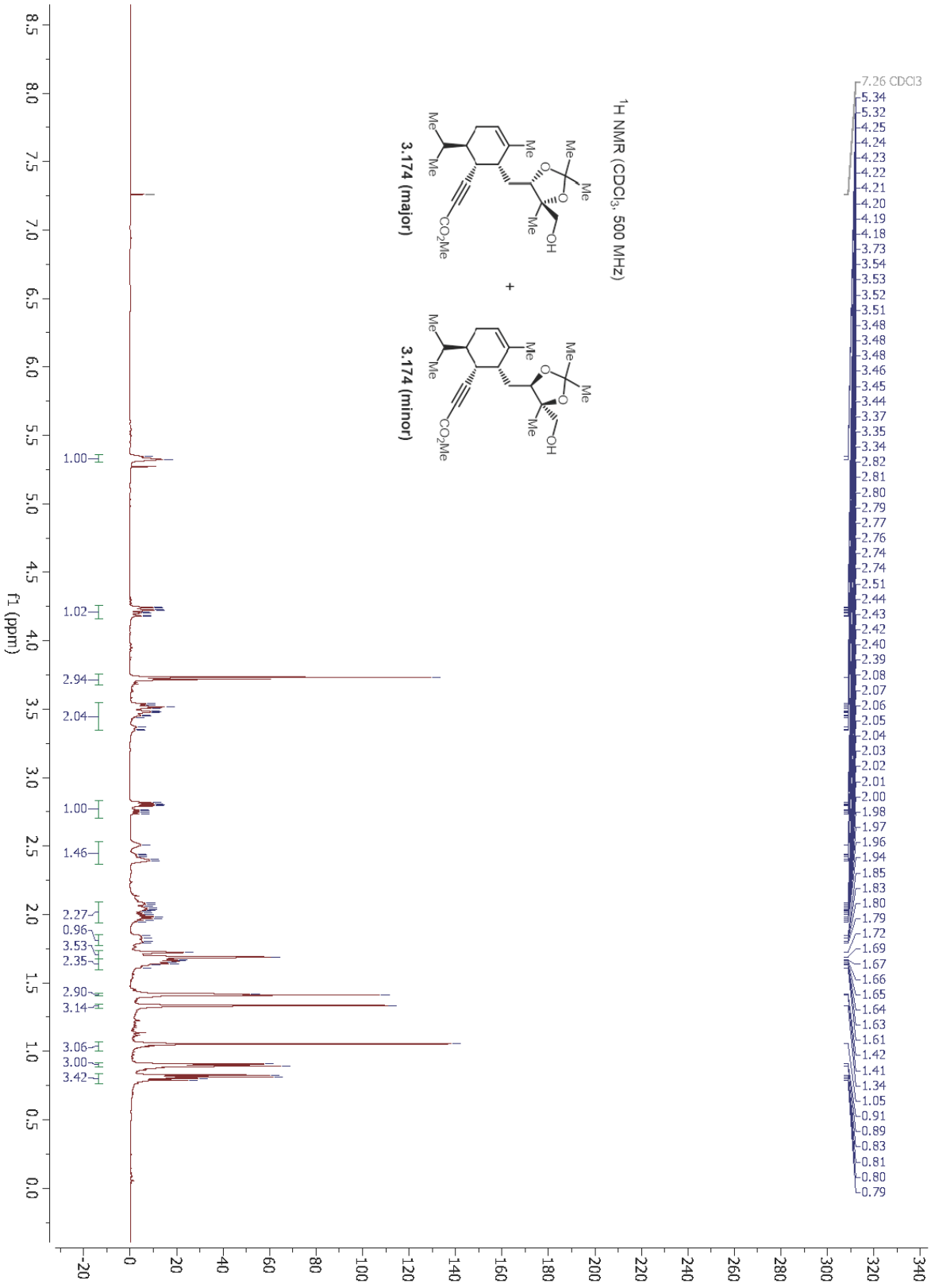

^{13}C NMR ($CDCl_3$, 126 MHz)
3.162 (major)
+
3.162 (minor)
173.84
167.28
146.18
135.42
121.12
119.54
107.72
83.14
79.54
77.27 cdcl3
77.01 cdcl3
76.76 cdcl3
60.13
51.36
38.68
34.96
32.14
28.83
28.24
27.34
26.19
24.10
22.14
22.03
20.52
20.39
14.26
f1 (ppm)

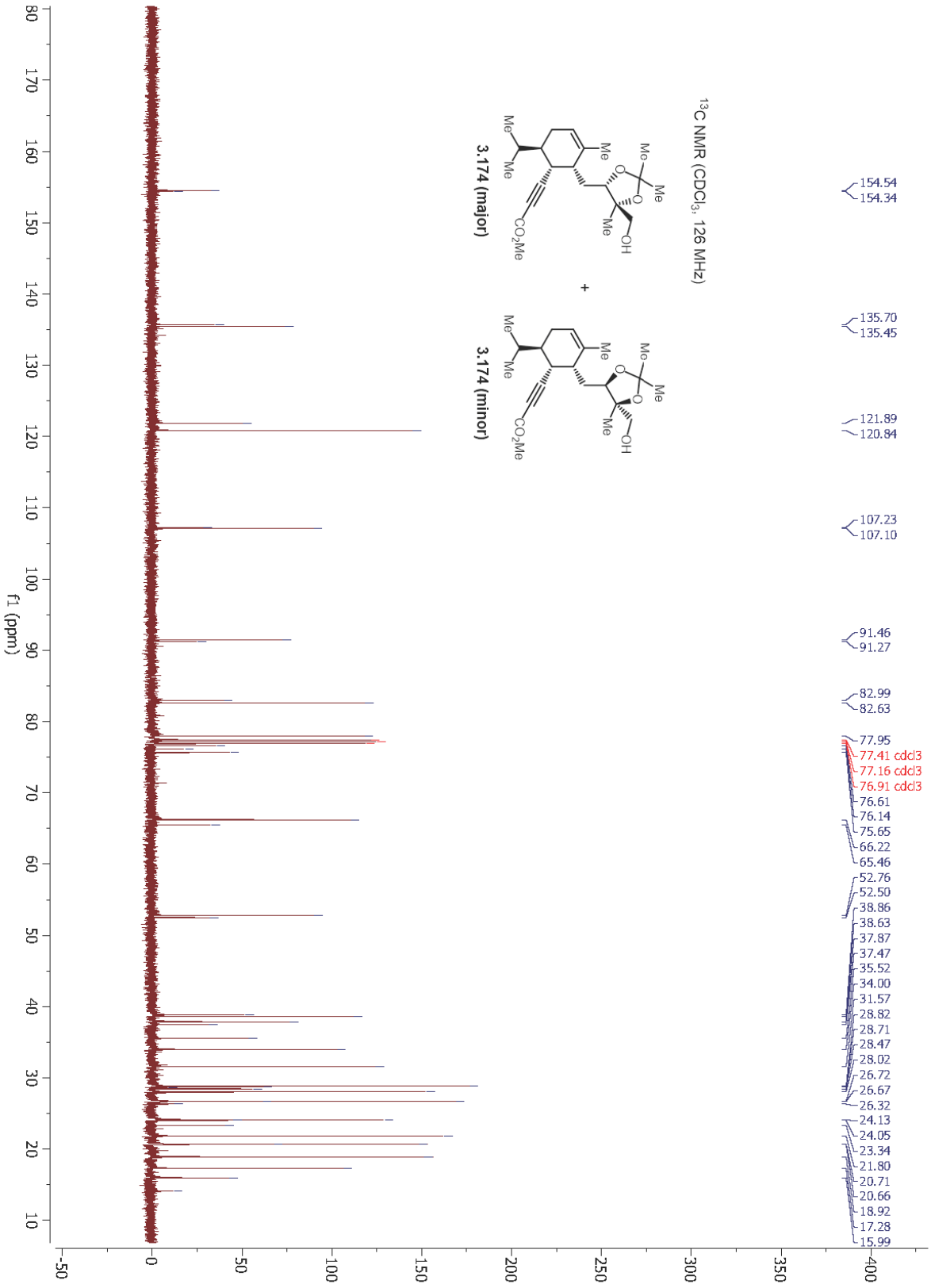

^{1}H NMR ($CDCl_3$, 500 MHz)
3.169
Me
Me
Me
Me
OH
7.26 CDCl3
f1 (ppm)
1.05
0.98
2.05
1.00
2.09
1.08
0.96
2.03
4.20
4.04
3.16
2.96


^{13}C NMR ($CDCl_3$, 126 MHz)
3.169
Me
Me
Me
Me
OH
135.06
134.92
127.61
121.72
86.26
77.27 cdcl3
77.02 cdcl3
76.77 cdcl3
71.20
61.66
41.50
38.54
34.21
28.92
27.97
24.21
22.64
21.57
20.72
16.70
f1 (ppm)


^{1}H NMR (CDCl$_3$, 500 MHz)
3.170 (major)
3.170 (minor)
7.26 CDCl3
f1 (ppm)


134.62
122.56
85.56
77.30
77.04
76.79
72.20
63.87
63.84
61.72
40.32
37.39
34.82
28.54
28.19
23.90
22.62
20.74
19.99
15.38
13C NMR (CDCl3, 126 MHz)
Me
O
OH
Me
Me
Me
3.170 (major)
+
3.170 (minor)
f1 (ppm)


^{1}H NMR ($CDCl_3$, 500 MHz)
3.174 (major)
3.174 (minor)
f1 (ppm)
7.26 CDCl3


^{13}C NMR ($CDCl_3$, 126 MHz)
3.174 (major)
+
3.174 (minor)
f1 (ppm)
154.54
154.34
135.70
135.45
121.89
120.84
107.23
107.10
91.46
91.27
82.99
82.63
77.95
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
76.61
76.14
75.65
66.22
65.46
52.76
52.50
38.86
38.63
37.87
37.47
35.52
34.00
31.57
28.82
28.71
28.47
28.02
26.72
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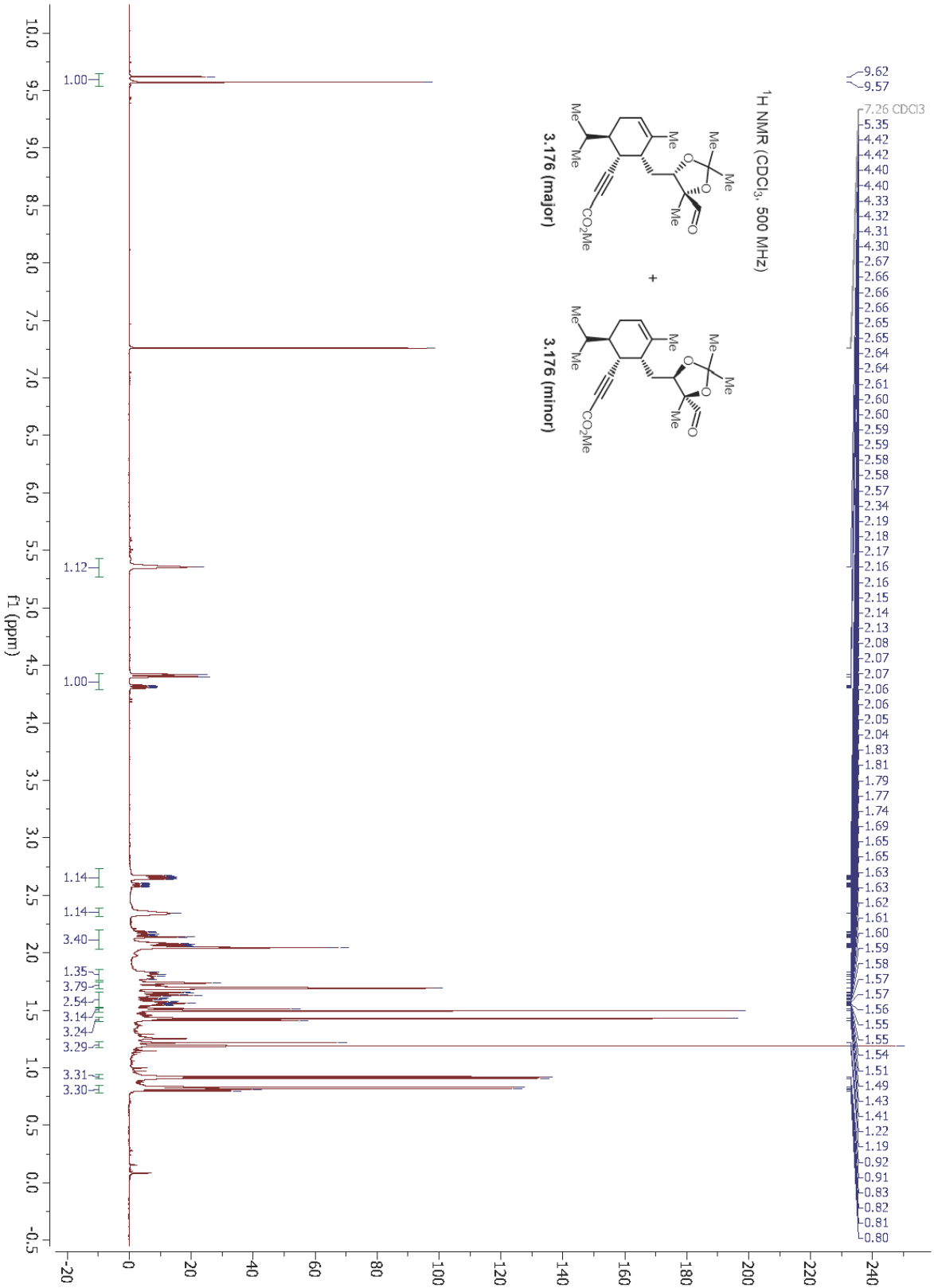
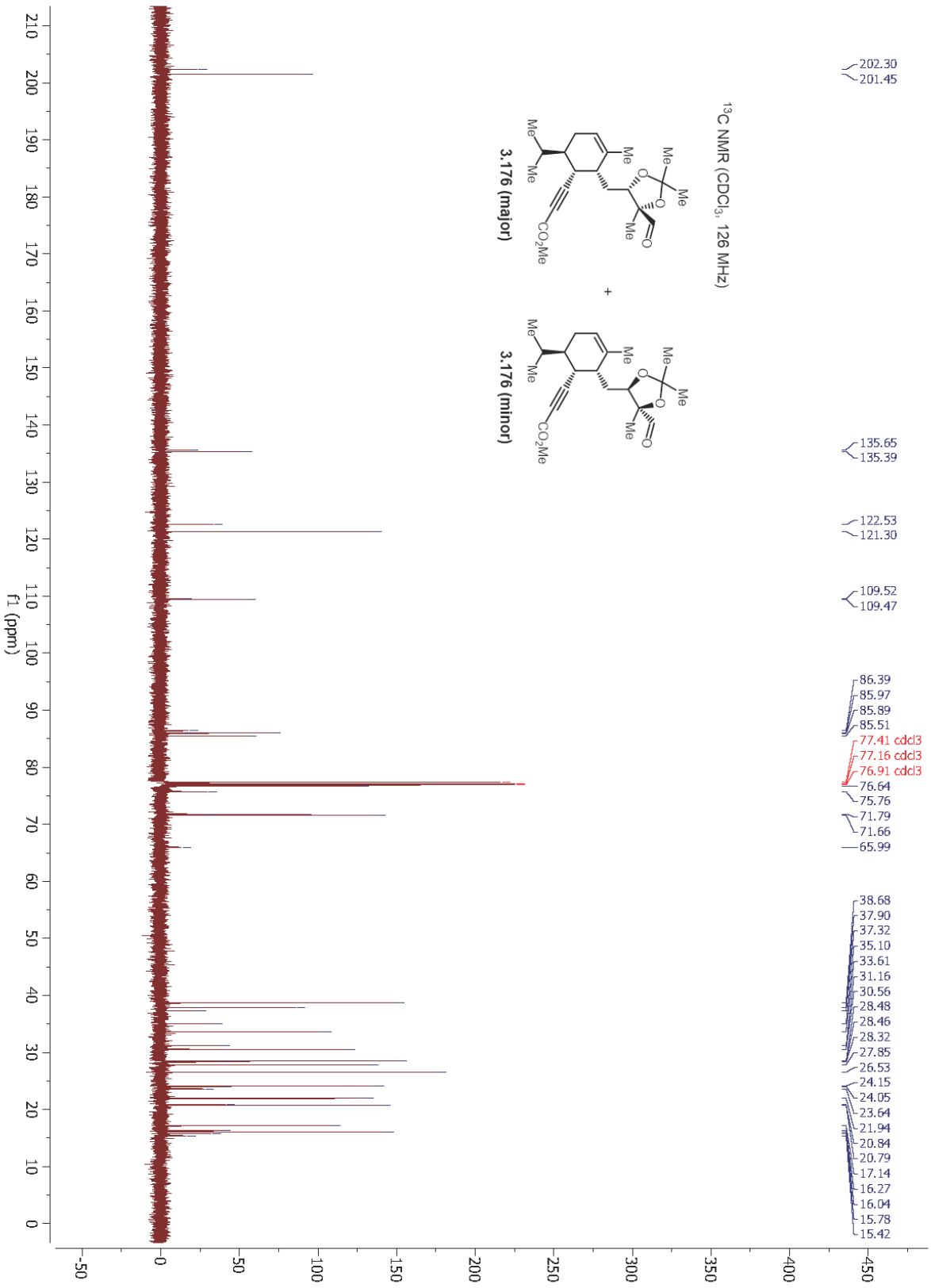
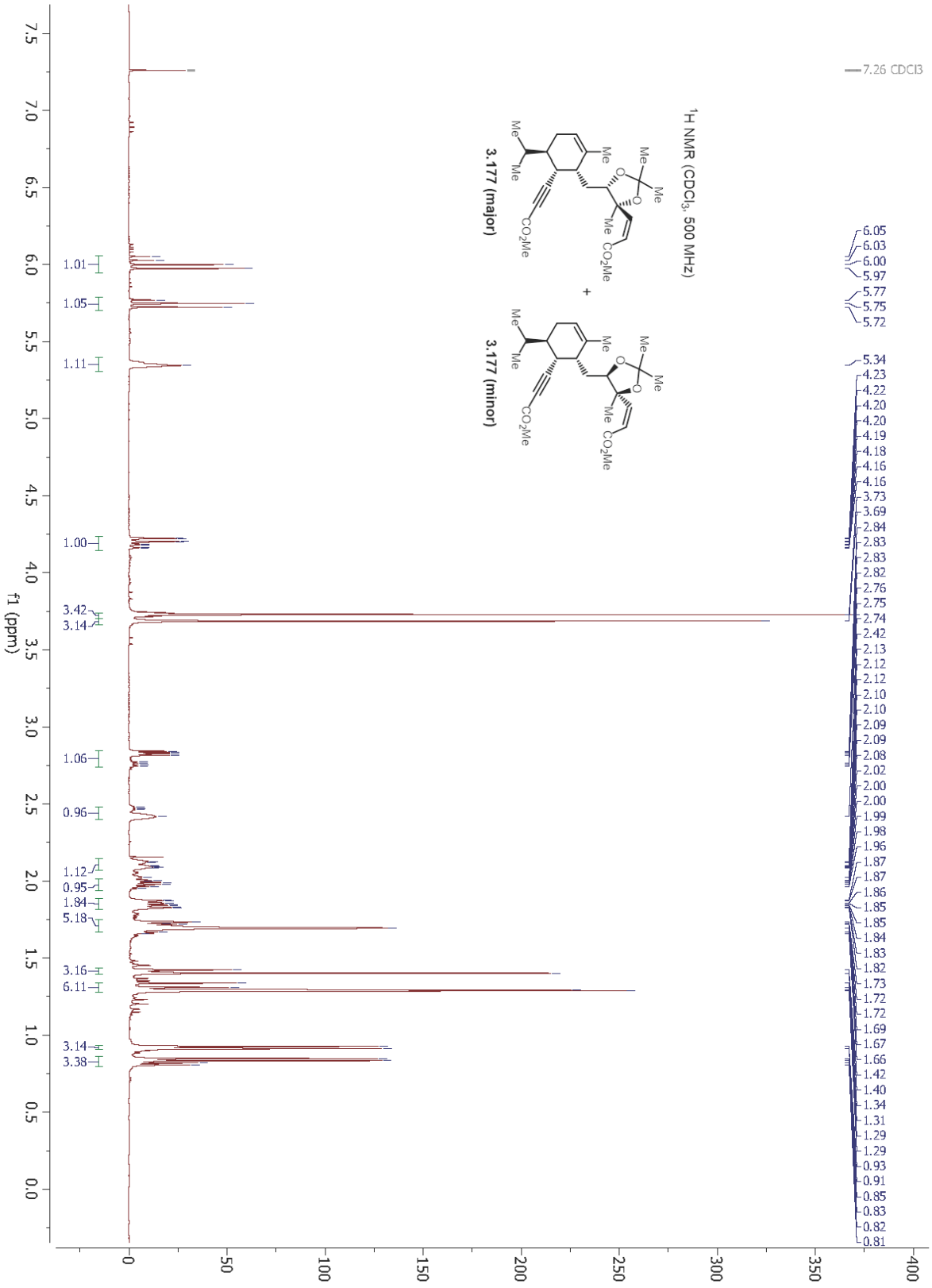
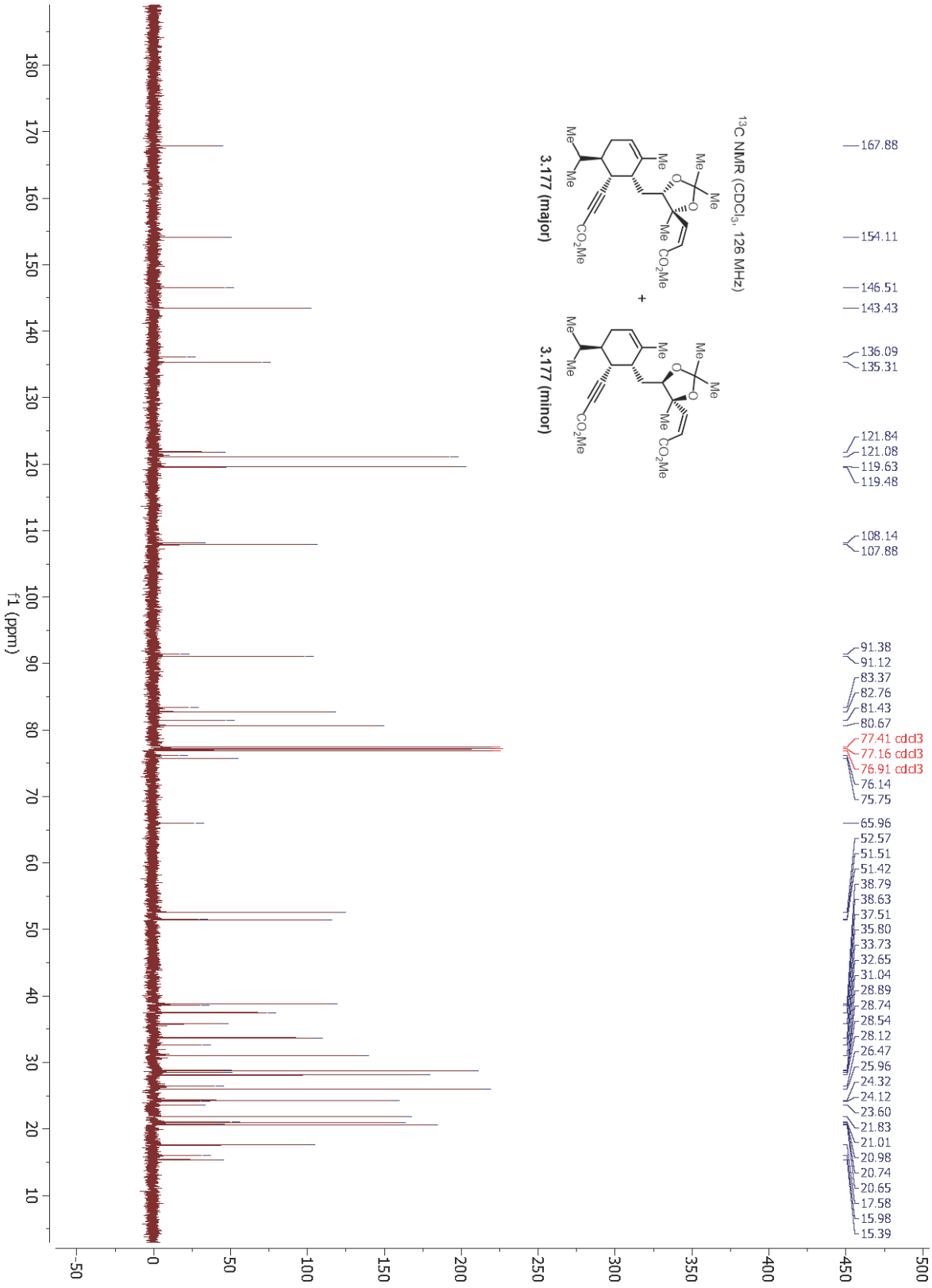
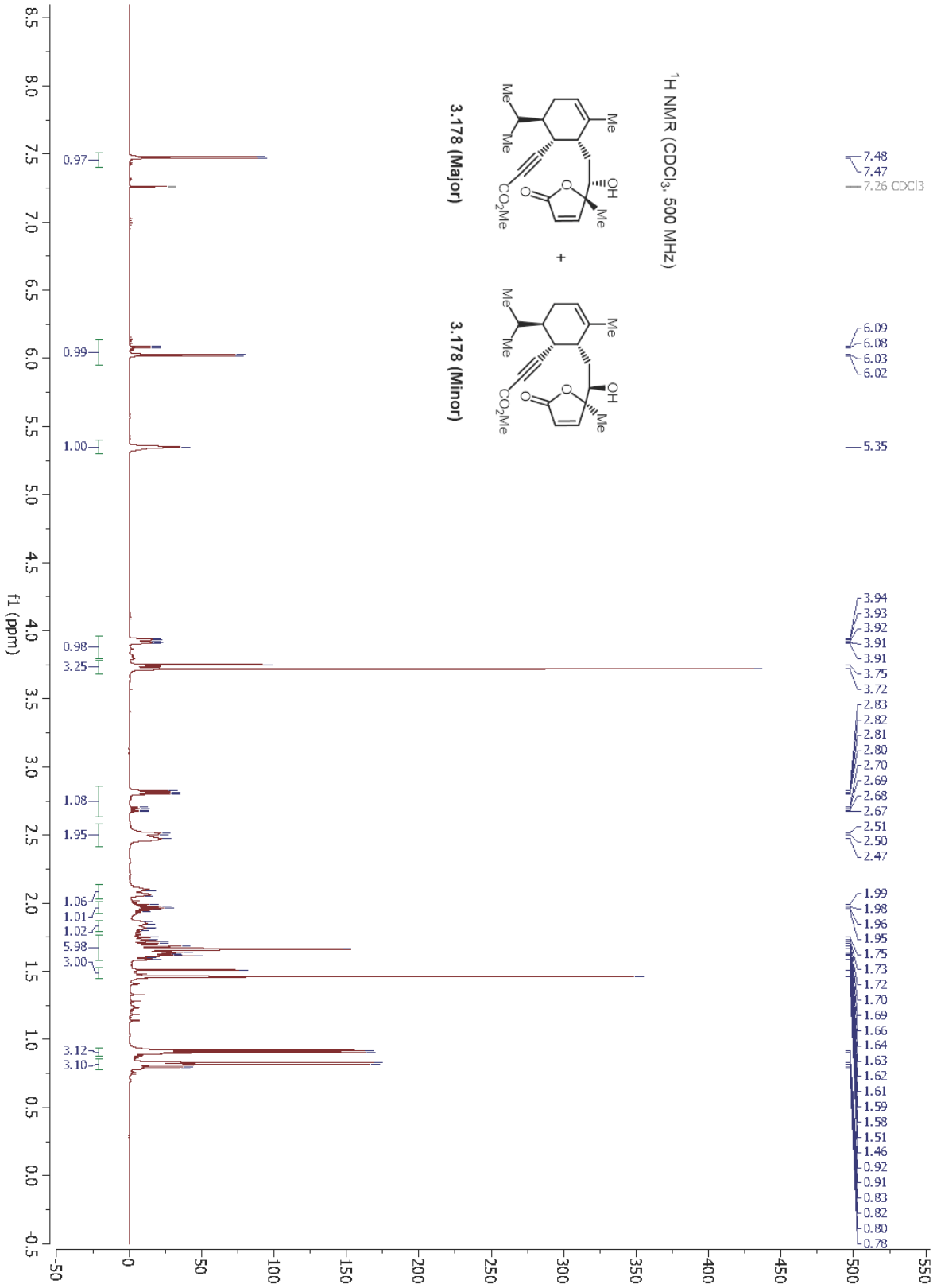
24.13
24.05
23.34
21.80
20.71
20.66
18.92
17.28
15.99

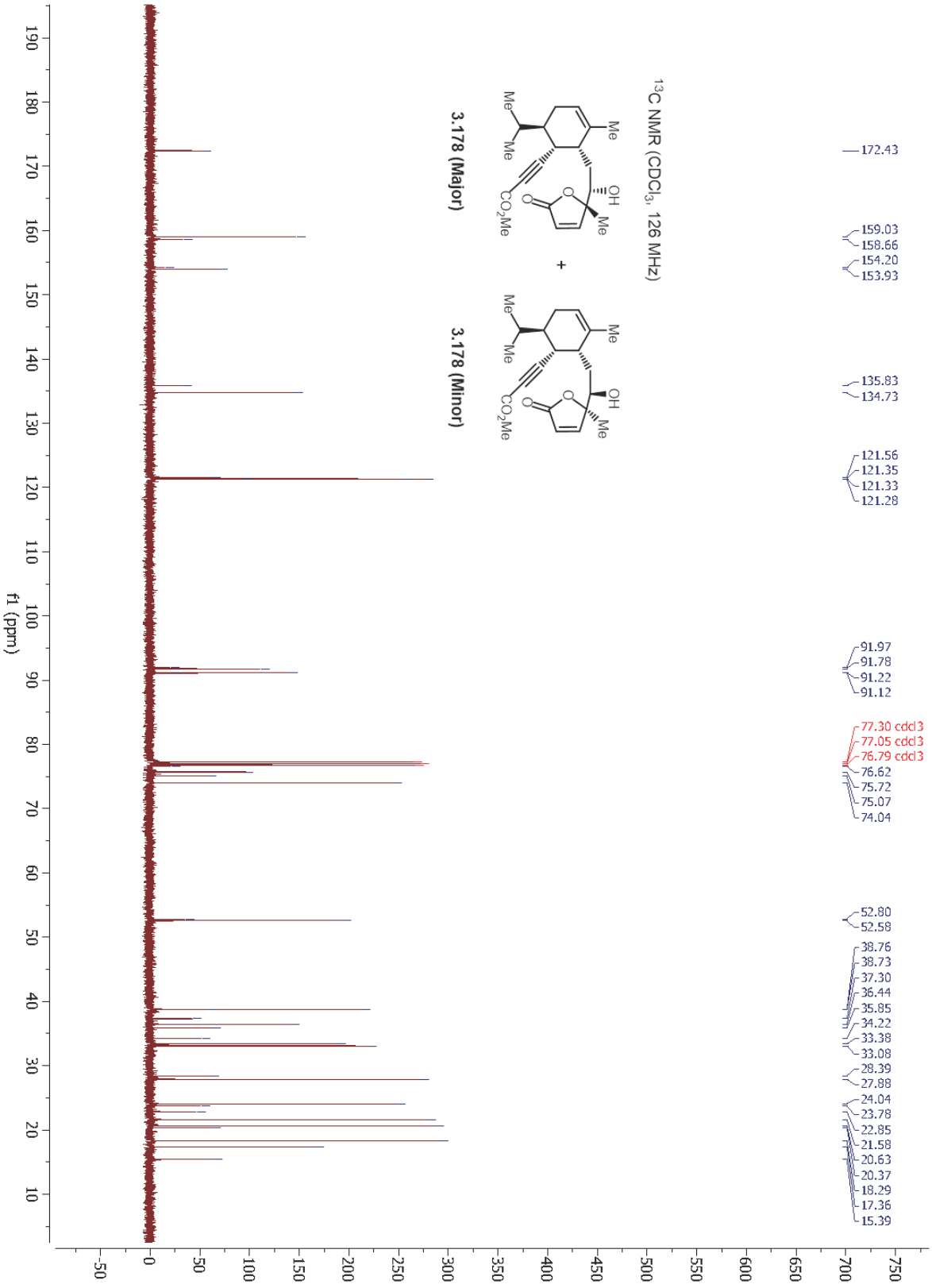

^{1}H NMR (CDCl$_3$, 500 MHz)
3.176 (major)
3.176 (minor)
f1 (ppm)
7.26 CDCl3

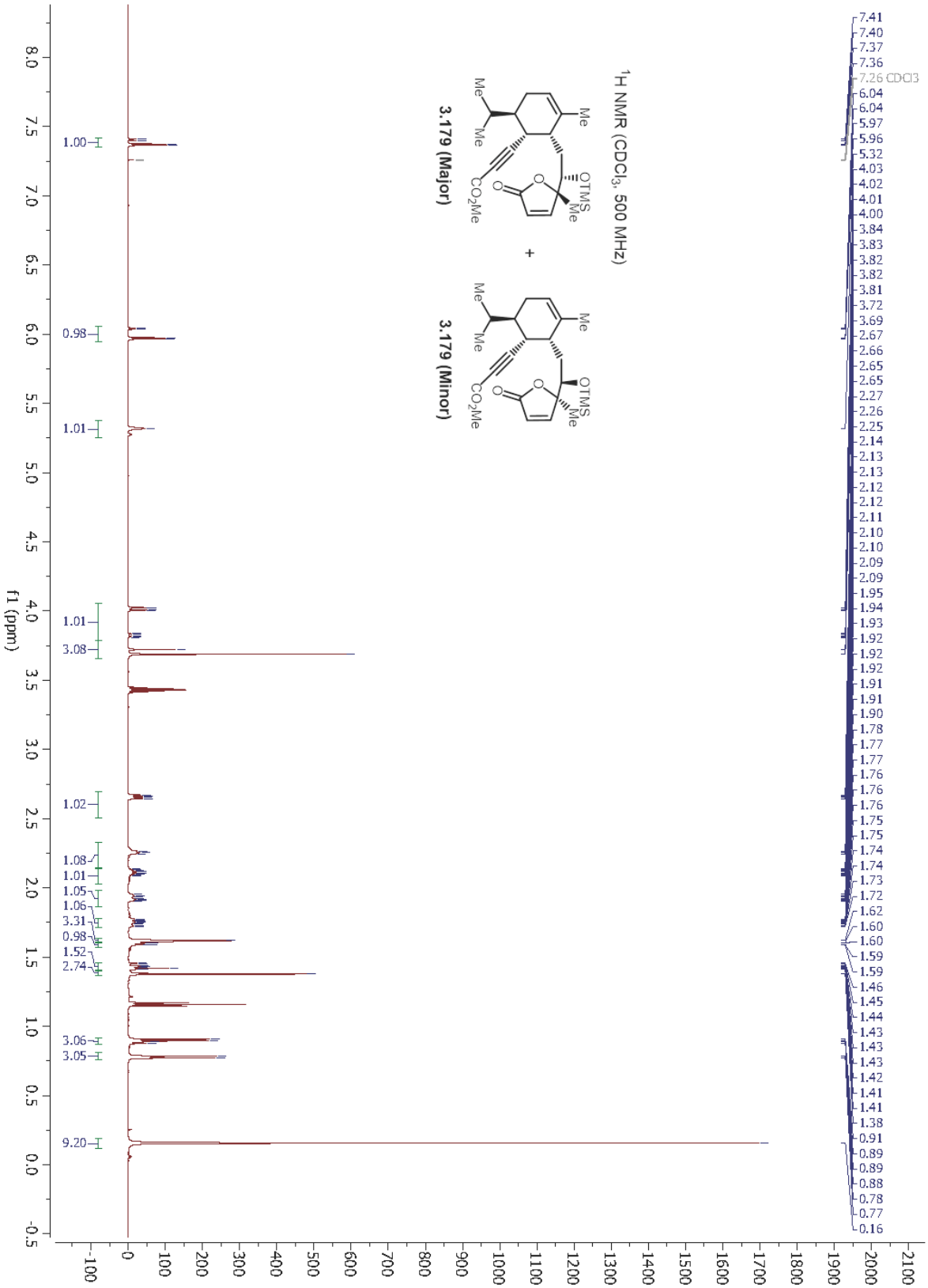

^{13}C NMR ($CDCl_3$, 126 MHz)
3.176 (major)
3.176 (minor)
+
Me
Me
Me
Me
Me
Me
CO_2Me
O
202.30
201.45
135.65
135.39
122.53
121.30
109.52
109.47
86.39
85.97
85.89
85.51
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
76.64
75.76
71.79
71.66
65.99
38.68
37.90
37.32
35.10
33.61
31.16
30.56
28.48
28.46
28.32
27.85
26.53
24.15
24.05
23.64
21.94
20.84
20.79
17.14
16.27
16.04
15.78
15.42
f1 (ppm)

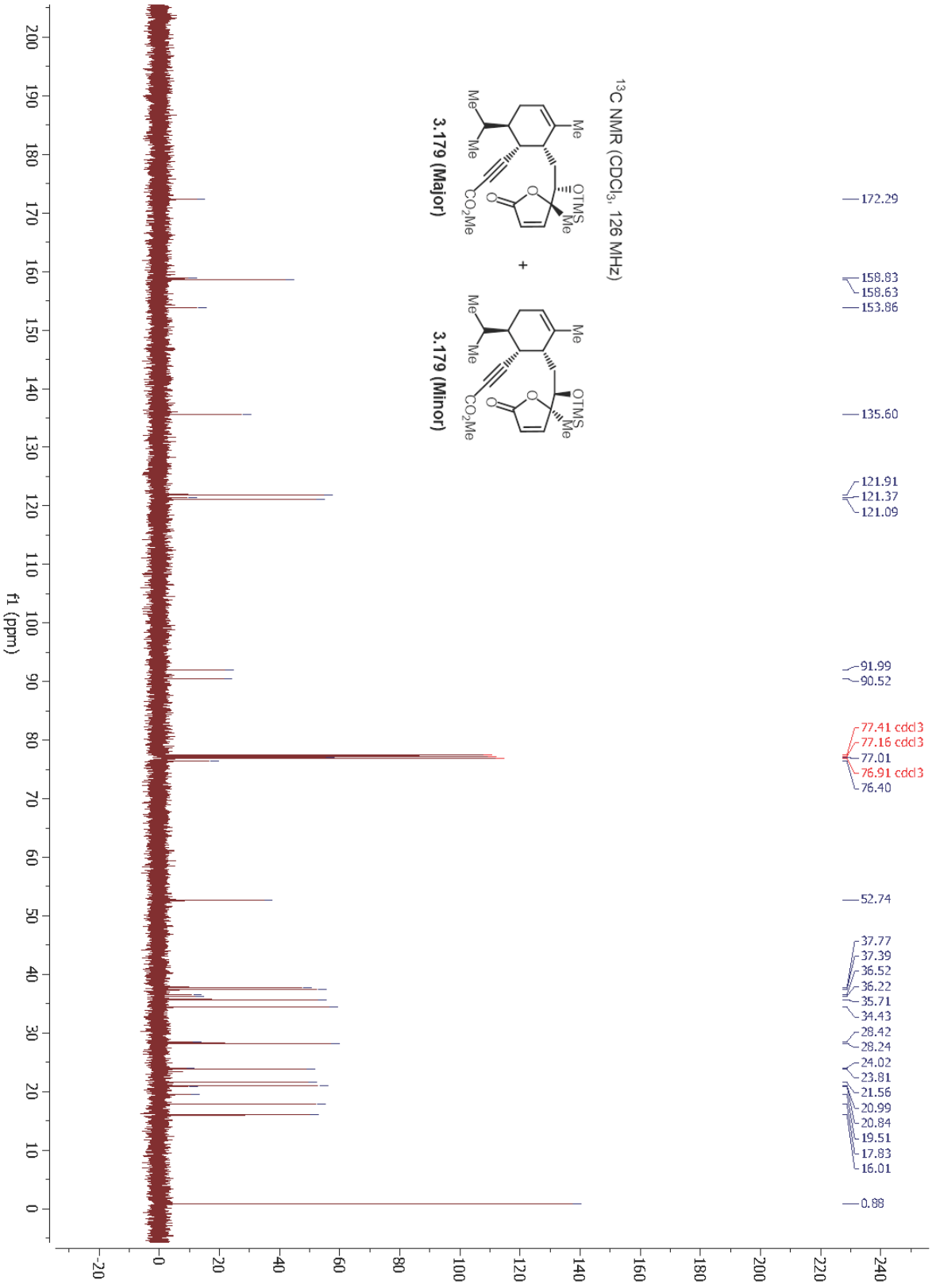

^{1}H NMR ($CDCl_3$, 500 MHz)
3.177 (major)
3.177 (minor)
7.26 CDCl3
f1 (ppm)

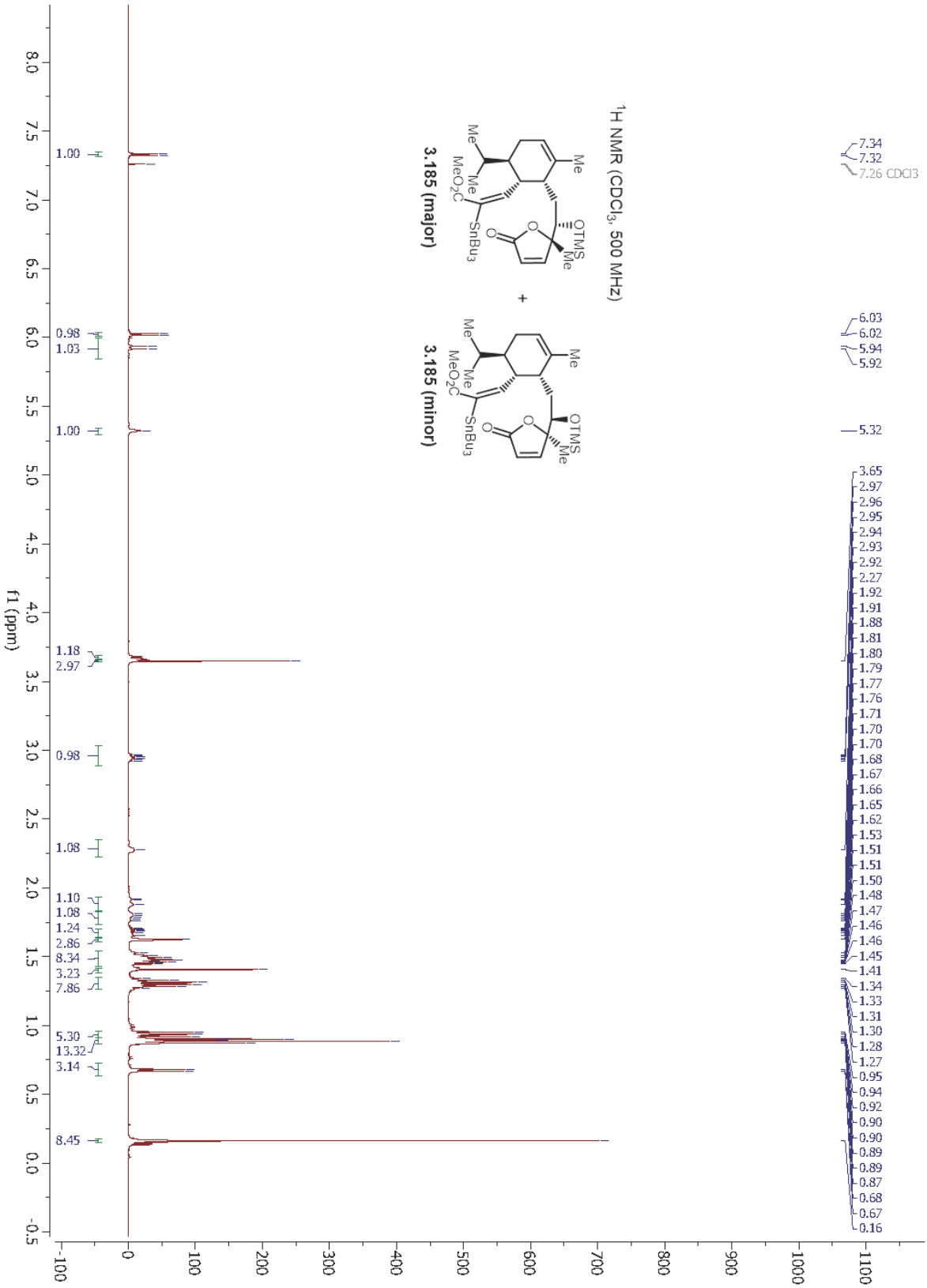

^{13}C NMR ($CDCl_3$, 126 MHz)
3.177 (major)
3.177 (minor)
167.88
154.11
146.51
143.43
136.09
135.31
121.84
121.08
119.63
119.48
108.14
107.88
91.38
91.12
83.37
82.76
81.43
80.67
77.41 cdd3
77.16 cdd3
76.91 cdd3
76.14
75.75
65.96
52.57
51.51
51.42
38.79
38.63
37.51
35.80
33.73
32.65
31.04
28.89
28.74
28.54
28.12
26.47
25.96
24.32
24.12
23.60
21.83
21.01
20.98
20.74
20.65
17.58
15.98
15.39
f1 (ppm)

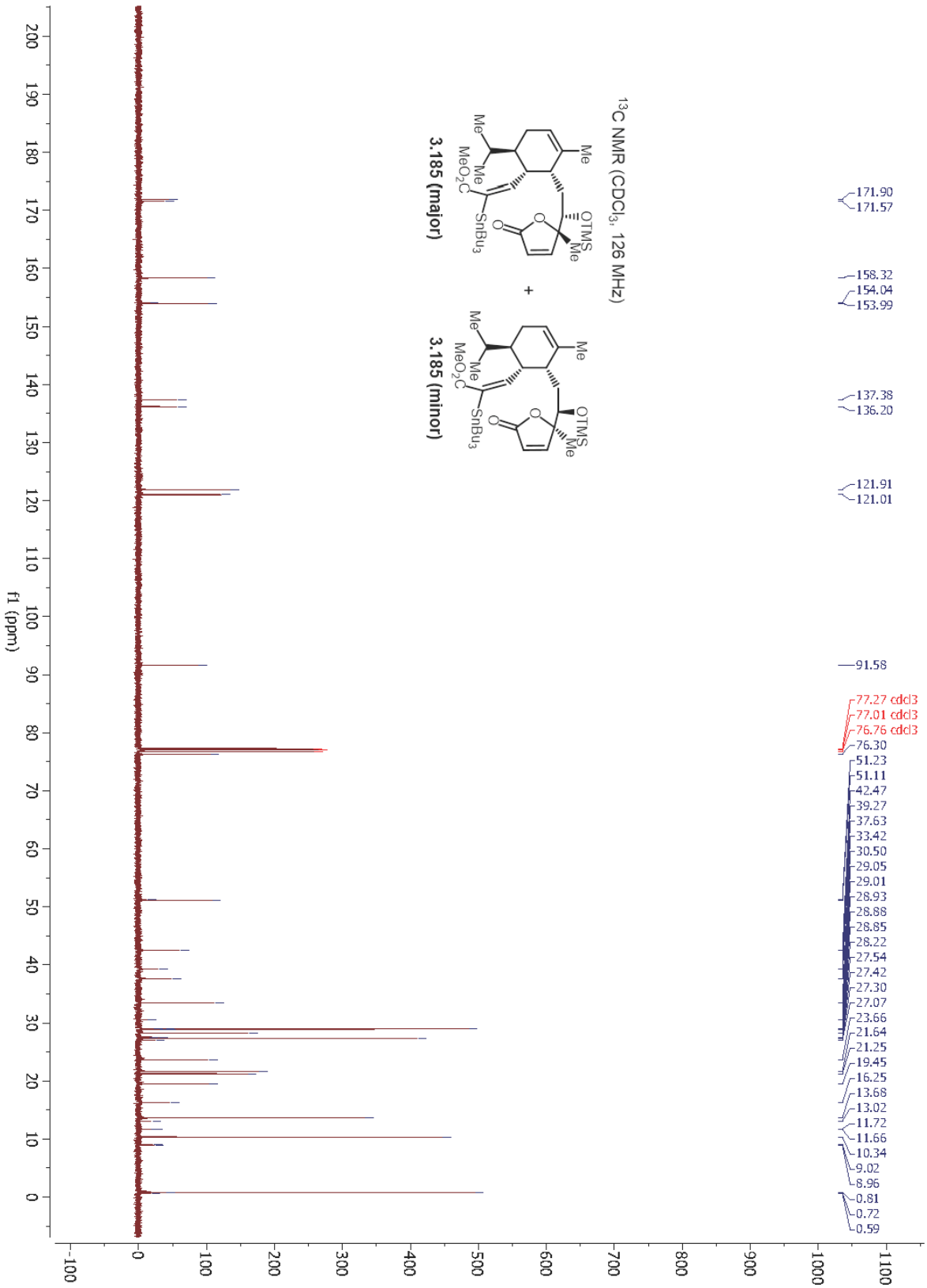

^{1}H NMR (CDCl$_3$, 500 MHz)
3.178 (Major)
3.178 (Minor)
+
Me
Me
Me
OH
Me
CO$_2$Me
f1 (ppm)
7.48
7.47
7.26 CDCl3
6.09
6.08
6.03
6.02
5.35
3.94
3.93
3.92
3.91
3.91
3.75
3.72
2.83
2.82
2.81
2.80
2.70
2.69
2.68
2.67
2.51
2.50
2.47
1.99
1.98
1.96
1.95
1.75
1.73
1.72
1.70
1.69
1.66
1.64
1.63
1.62
1.61
1.59
1.58
1.51
1.46
0.92
0.91
0.83
0.82
0.80
0.78
0.97
0.99
1.00
0.98
3.25
1.08
1.95
1.06
1.01
1.02
5.98
3.00
3.12
3.10

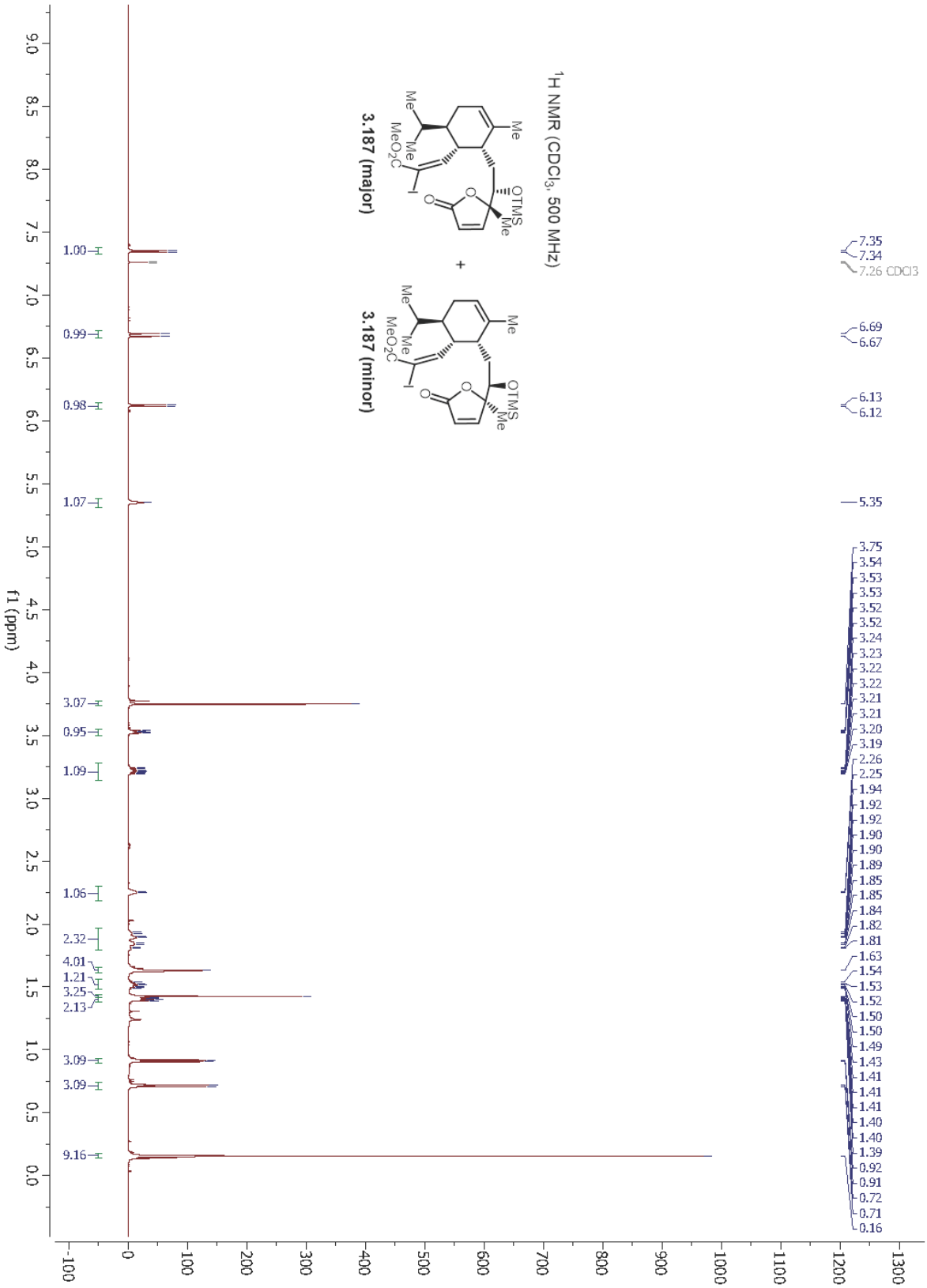

^{13}C NMR ($CDCl_3$, 126 MHz)
3.178 (Major)
3.178 (Minor)
Me
Me
Me
CO_2Me
OH
Me
+
f1 (ppm)
172.43
159.03
158.66
154.20
153.93
135.83
134.73
121.56
121.35
121.33
121.28
91.97
91.78
91.22
91.12
77.30 cdcl3
77.05 cdcl3
76.79 cdcl3
76.62
75.72
75.07
74.04
52.80
52.58
38.76
38.73
37.30
36.44
35.85
34.22
33.38
33.08
28.39
27.88
24.04
23.78
22.85
21.58
20.63
20.37
18.29
17.36
15.39

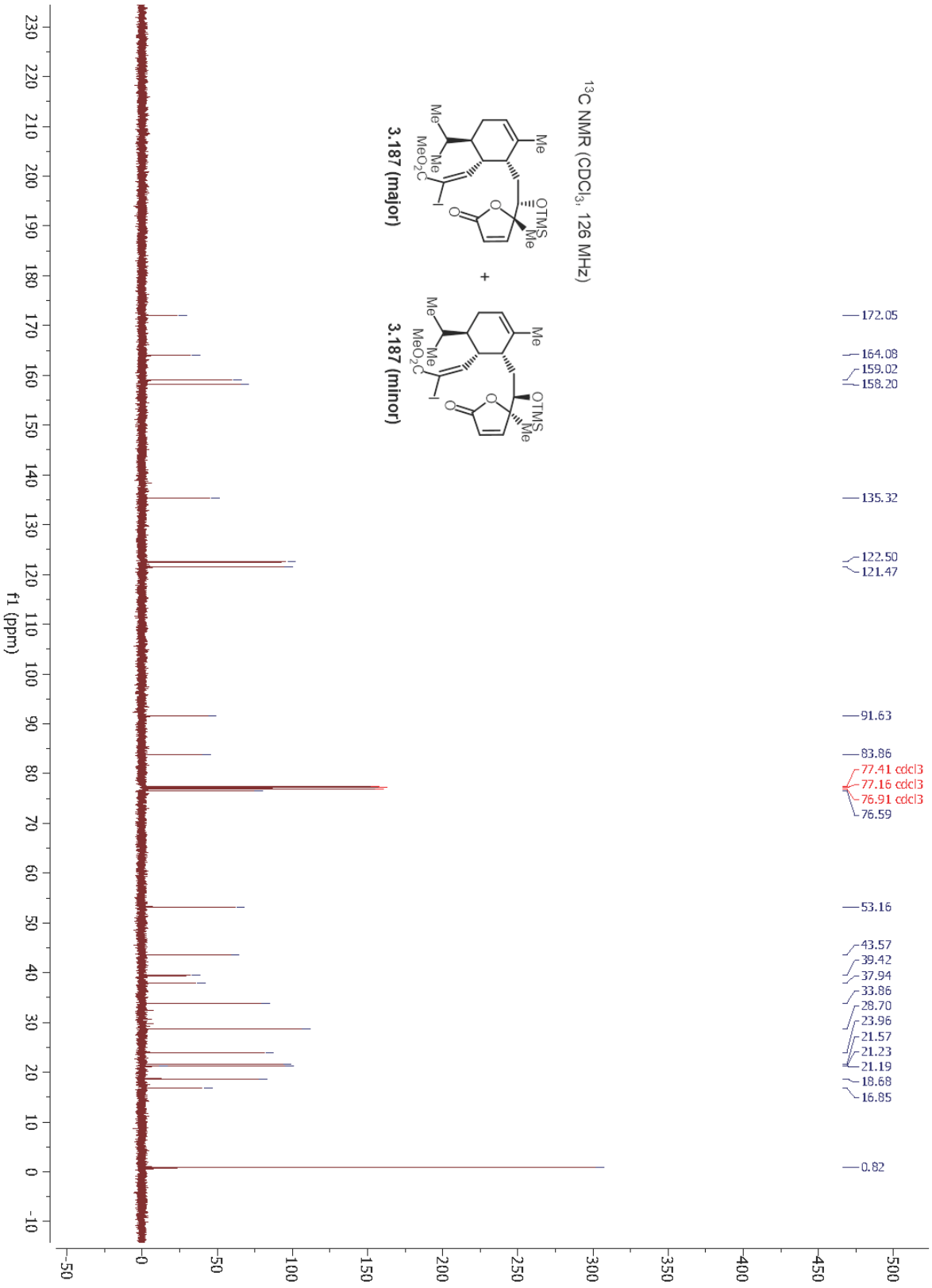

^{1}H NMR ($CDCl_3$, 500 MHz)
3.179 (Major)
3.179 (Minor)
f1 (ppm)
7.26 CDCl3

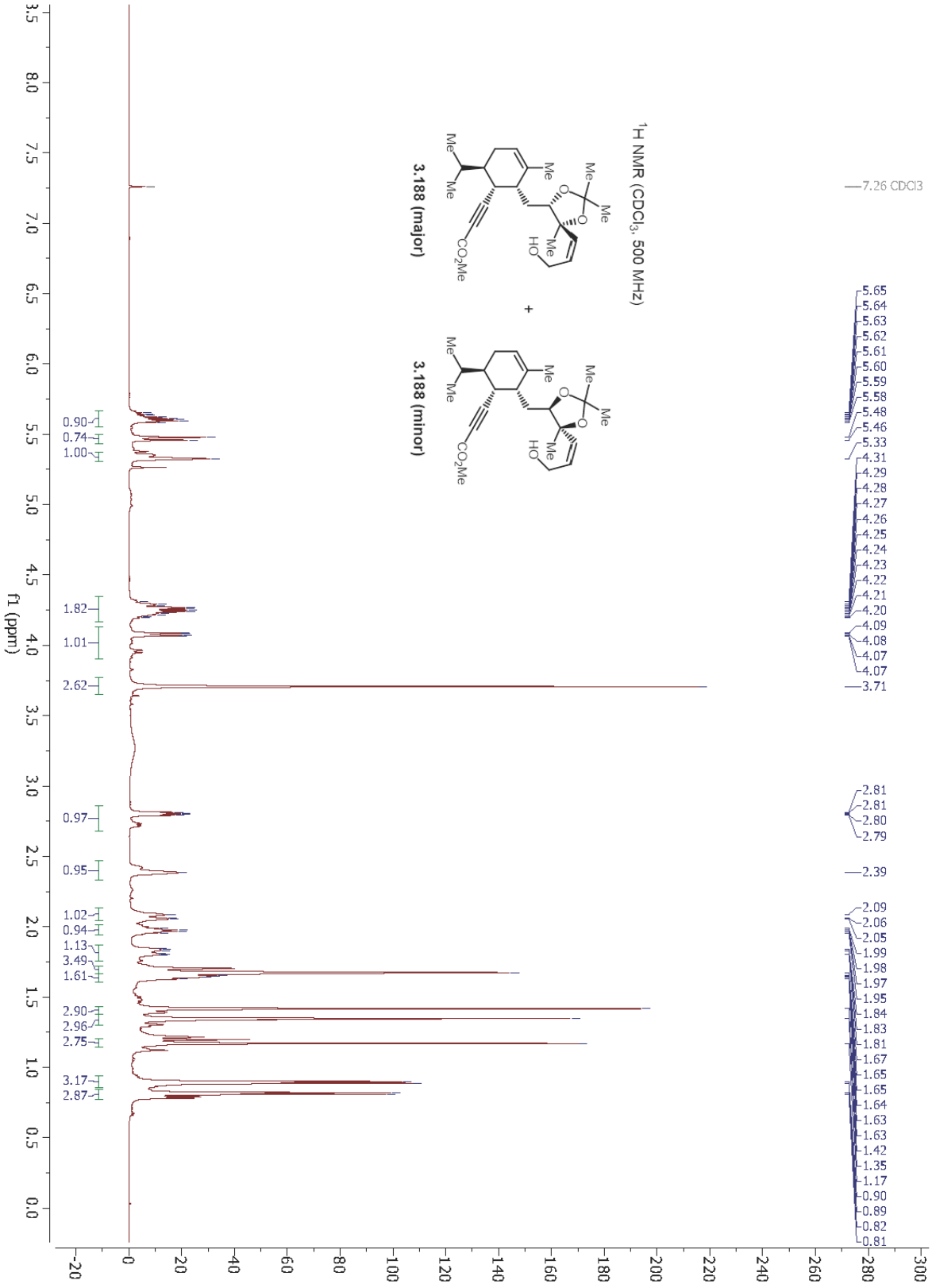

^{13}C NMR ($CDCl_3$, 126 MHz)
3.179 (Major)
3.179 (Minor)
Me
Me
Me
CO_2Me
OTMS
Me
+
172.29
158.83
158.63
153.86
135.60
121.91
121.37
121.09
91.99
90.52
77.41 cdcl3
77.16 cdcl3
77.01
76.91 cdcl3
76.40
52.74
37.77
37.39
36.52
36.22
35.71
34.43
28.42
28.24
24.02
23.81
21.56
20.99
20.84
19.51
17.83
16.01
0.88
f1 (ppm)

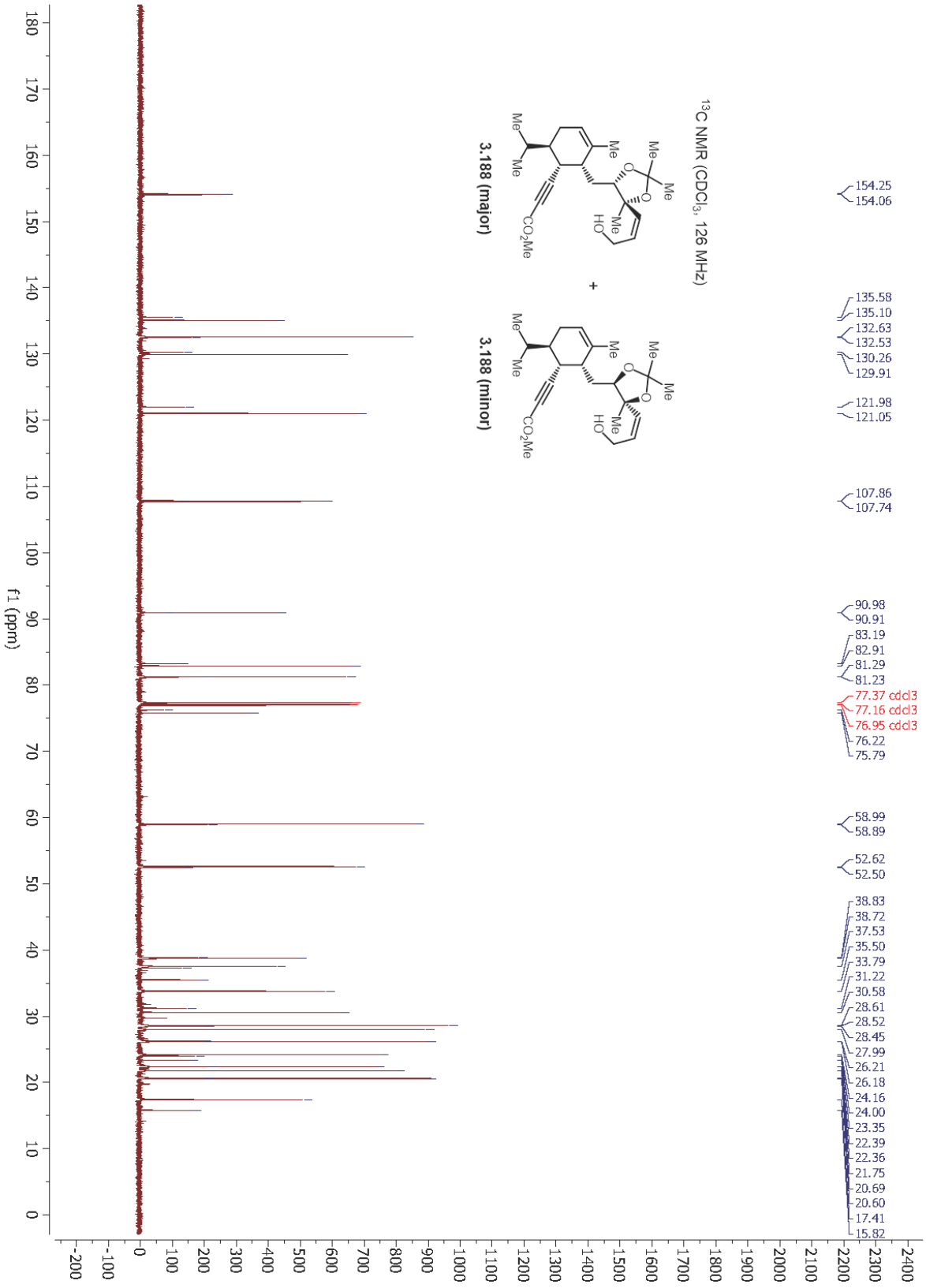

^{1}H NMR ($CDCl_3$, 500 MHz)
3.185 (major)
3.185 (minor)
f1 (ppm)


^{13}C NMR (CDCl$_3$, 126 MHz)
3.185 (major)
3.185 (minor)
f1 (ppm)
171.90
171.57
158.32
154.04
153.99
137.38
136.20
121.91
121.01
91.58
77.27 cdcl3
77.01 cdcl3
76.76 cdcl3
76.30
51.23
51.11
42.47
39.27
37.63
33.42
30.50
29.05
29.01
28.93
28.88
28.85
28.22
27.54
27.42
27.30
27.07
23.66
21.64
21.25
19.45
16.25
13.68
13.02
11.72
11.66
10.34
9.02
8.96
0.81
0.72
0.59


^{1}H NMR (CDCl$_3$, 500 MHz)
3.187 (major)
3.187 (minor)
f1 (ppm)
1.00
0.99
0.98
1.07
3.07
0.95
1.09
1.06
2.32
4.01
1.21
3.25
2.13
3.09
3.09
9.16
7.35
7.34
7.26 CDCl3
6.69
6.67
6.13
6.12
5.35


^{13}C NMR (CDCl$_3$, 126 MHz)
3.187 (major)
+
3.187 (minor)
f1 (ppm)
172.05
164.08
159.02
158.20
135.32
122.50
121.47
91.63
83.86
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
76.59
53.16
43.57
39.42
37.94
33.86
28.70
23.96
21.57
21.23
21.19
18.68
16.85
0.82


^{1}H NMR (CDCl$_3$, 500 MHz)
3.188 (major)
3.188 (minor)
+
7.26 CDCl3
f1 (ppm)


^{13}C NMR ($CDCl_3$, 126 MHz)
3.188 (major)
+
3.188 (minor)
154.25
154.06
135.58
135.10
132.63
132.53
130.26
129.91
121.98
121.05
107.86
107.74
90.98
90.91
83.19
82.91
81.29
81.23
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
76.22
75.79
58.99
58.89
52.62
52.50
38.83
38.72
37.53
35.50
33.79
31.22
30.58
28.61
28.52
28.45
27.99
26.21
26.18
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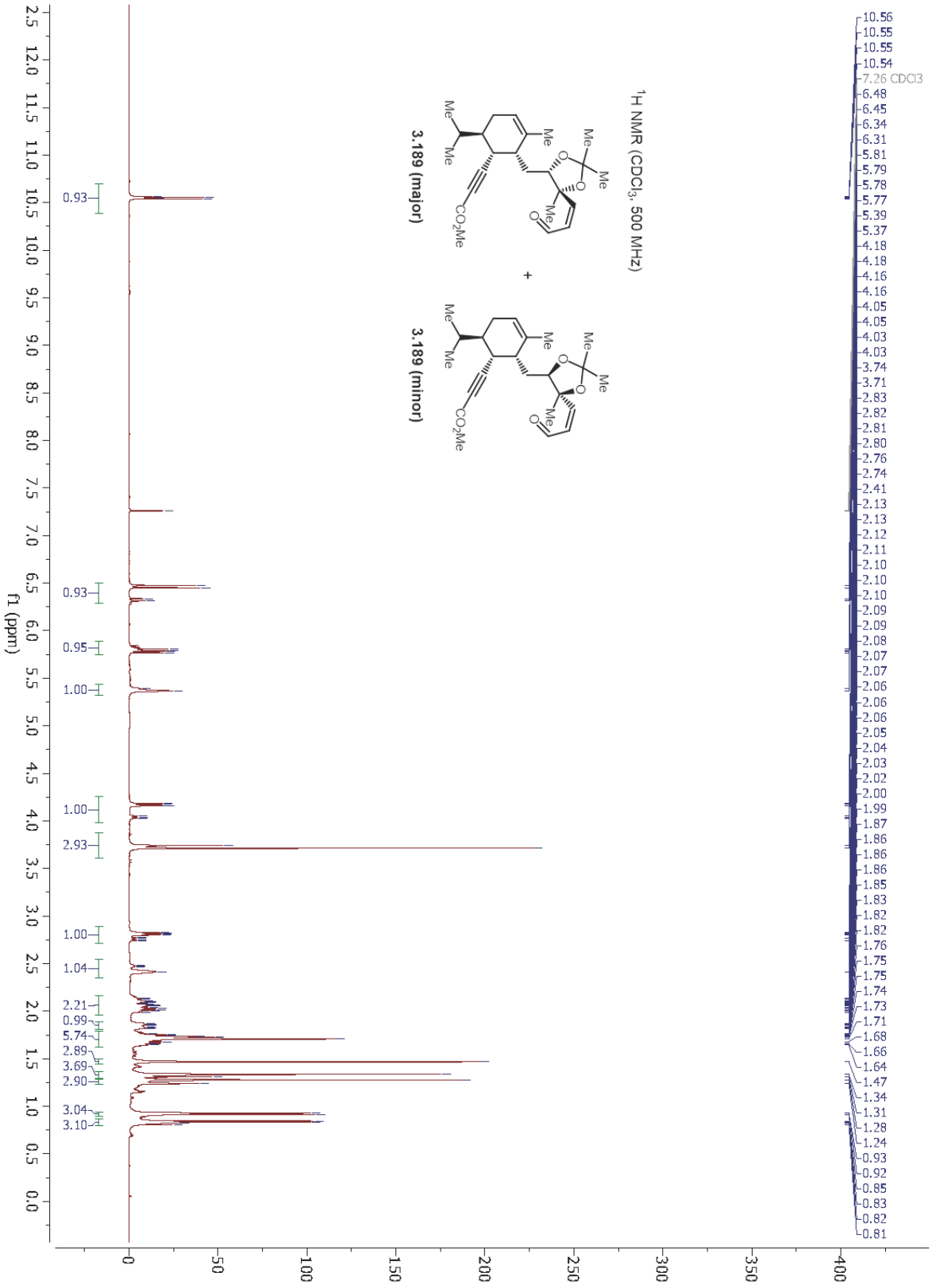
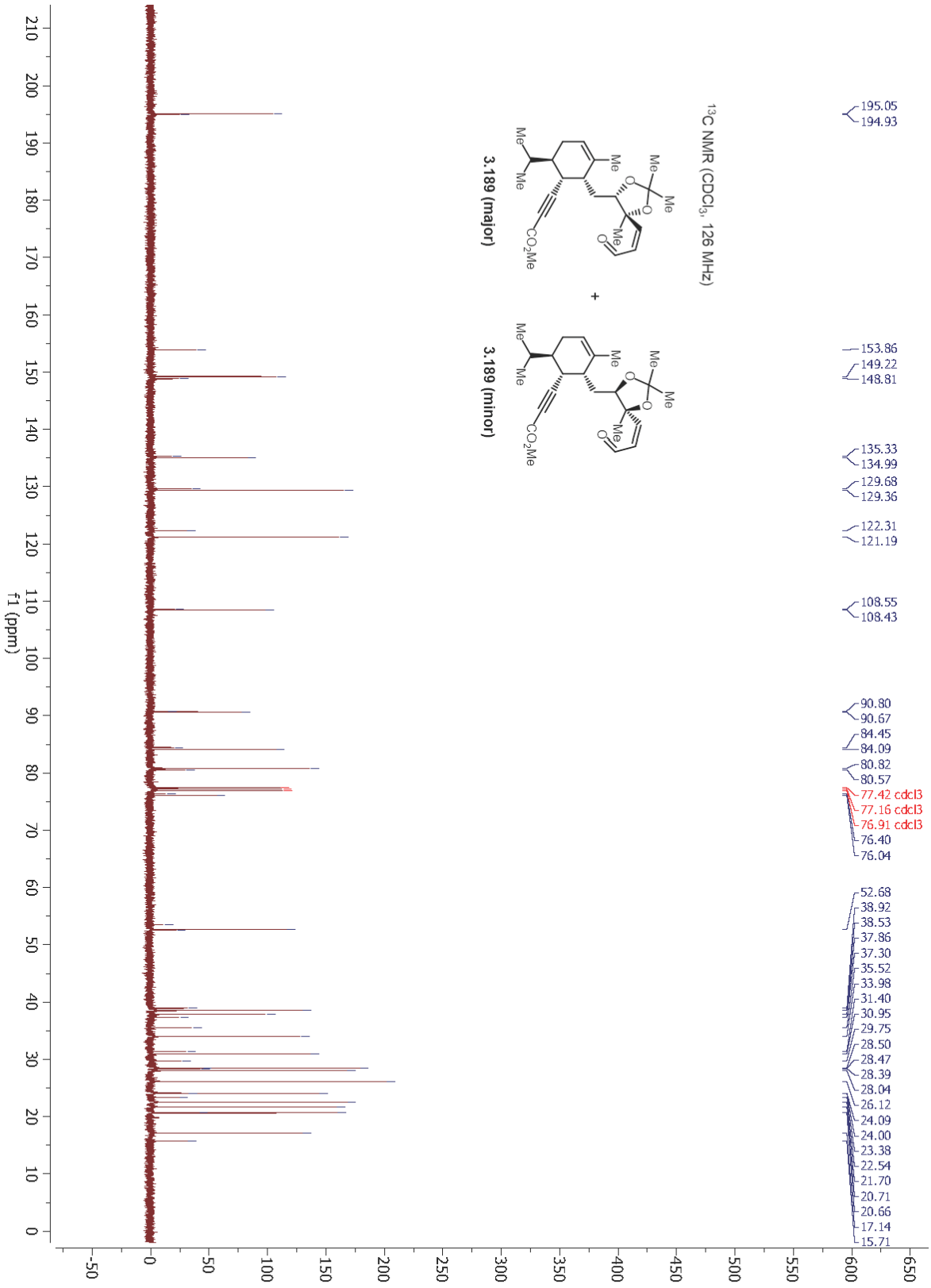
20.69
20.60
17.41
15.82
f1 (ppm)


^{1}H NMR ($CDCl_3$, 500 MHz)
3.189 (major)
3.189 (minor)
f1 (ppm)
7.26 CDCl3


^{13}C NMR ($CDCl_3$, 126 MHz)
3.189 (major)
3.189 (minor)
195.05
194.93
153.86
149.22
148.81
135.33
134.99
129.68
129.36
122.31
121.19
108.55
108.43
90.80
90.67
84.45
84.09
80.82
80.57
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
76.40
76.04
52.68
38.92
38.53
37.86
37.30
35.52
33.98
31.40
30.95
29.75
28.50
28.47
28.39
28.04
26.12
24.09
24.00
23.38
22.54
21.70
20.71
20.66
17.14
15.71
f1 (ppm)