DEVELOPMENT OF CATALYTIC CONJUNCTIVE CROSS-COUPLING REACTIONS AND PROGRESS TOWARDS THE TOTAL SYNTHESIS OF THE SARCODICTYINS

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DEVELOPMENT OF CATALYTIC CONJUNCTIVE CROSS-COUPLING REACTIONS AND PROGRESS TOWARDS THE TOTAL SYNTHESIS OF THE SARCODICTYINS

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Abstract: This dissertation describes the development of a method for the stereoselective synthesis of organoboronates and the applications of these products to target-oriented synthesis. The first chapter discusses an investigation of the palladium-catalyzed conjunctive cross-coupling reaction by kinetic analysis. This reaction enables the asymmetric synthesis of organoboronates by utilizing the 1,2-metallate rearrangement of borates as a mechanistic step in a cross-coupling reaction. The second chapter describes the application of the conjunctive cross-coupling reaction to the asymmetric synthesis of tertiary boronic esters. In chapter three, the conjunctive cross-coupling reaction of 1,2-disubstituted alkenyl boronates is presented. Such a substrate class is susceptible to the undesired Suzuki-Miyaura cross-coupling reaction, and this challenge led to the development of a novel diol ligand for boron as an effective solution. The final chapter details the progress toward the total synthesis of the sarcodictyin natural products, which display promising anti-cancer activity. The synthetic route utilizes reactions of organoboronates for powerful C–C bond formations; the construction of a fully-cyclyzed advanced intermediate is achieved in eight steps.

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To my family

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Å: angstrom

Ac: acetyl

acac: acetylacetonyl

atm: atmosphere(s)

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

9-BBN: 9-borabicylco[3.3.1]nonane

BHT: 2,6-di-*t*-butyl-4-methylphenol

Bn: benzyl

Boc: *tert*-butoxycarbonyl

Bu: butyl

cat: catechol

CAN: ceric ammonium nitrate

cod: 1,5-cyclooctadiene

conv.: conversion

CPME: cyclopentyl methyl ether

CSA: camphorsulfonic acid

CuTC: copper(I) thiophene-2-carboxylate

Cy: cyclohexyl

d: day(s)

DABCO: 1,4-diazabicyclo[2.2. 2]octane

DART: direct analysis in real time

dba: dibenzylideneacetone

DCE: dichloroethane

DCM: dichloromethane

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

DET: diethyl tartrate

DFT: density functional theory

DI: deionized

DIBAL: diisobutylaluminum hydride

DMA: *N,N*-dimethylacetamide

DMAP: 4-dimethylaminopyridine

DMDO: dimethyldioxirane

DME: dimethoxyethane

DMF: *N,N*-dimethylformamide

DMSO: dimethylsulfoxide

DMP: Dess-Martin periodinane

DPPB: 1,4-bis(diphenylphosphino) butane

DPPBz: 1,2-bis(diphenylphosphino) benzene

DPPE: 1,2-bis(diphenylphosphino) ethane

DPPF: 1,1’-bis(diphenylphosphino)

ferrocene

DPPM: 1,1-bis(diphenylphosphino) methane

DPPP: 1,3-bis(diphenylphosphino) propane

d.r.: diastereomeric ratio

e.e.: enantiomeric excess

eg: ethylene glycol

eq: equation(s)

equiv.: equivalent(s)

e.r.: enantiomeric ratio

ESI: electrospray ionization

Et: ethyl

EtOAc: ethyl acetate

GC: gas chromatography

h: hour(s)

HMDS: 1,1,1,3,3,3-hexamethyldisilazide

HPLC: high performance liquid chromatography

HRMS: high resolution mass spectrometry

Hz: hertz

IPA: isopropanol

IR: infrared spectroscopy

KDA: potassium diisopropylamide

LDA: lithium diisopropylamide

LLS: longest linear sequence

M: molar

mac: 1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol

MALDI: matrix-assisted laser desorption/ionization

mCPBA: *meta*-chloroperoxybenzoic acid

Me: methyl

MeCN: acetonitrile

min: minutes

MOM: methoxymethyl

Ms: methanesulfonyl

MS: molecular sieves

MTBE: methyl *t*-butyl ether

Na-naphth: sodium naphthalenide

nbd: 2,5-norbornadiene

NBS: *N*-bromosuccinimide

NHC: N-heterocyclic carbene

NMO: *N*-methylmorpholine *N*-oxide

NMR: nuclear magnetic resonance

neo: neopentylglycol

NOESY: Nuclear Overhauser Effect Spectroscopy

N.R: no reaction

N.D: not determined

Ph: phenyl

pin: pinacol

Piv: pivaloyl

PMA: phosphomolybdic acid

PMB: *para*-methoxybenzyl

PMP: *para*-methoxyphenyl

ppm: parts per million

PPTS: pyridinium *para*-toluenesulfonate

Pr: propyl

pybox: pyridine 2,6-(bis)oxazoline

rac: racemic

RCM: ring-closing metathesis

RPKA: reaction progress kinetic analysis

r.r.: regioisomeric ratio

rt: room temperature

RT: room temperature

SAR: structure-activity relationship

SFC: supercritical fluid chromatography

Sia: siamyl

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

TBAF: tetrabutylammonium fluoride

TBDPS: *t*-butyldiphenylsilyl

TBS: *t*-butyldimethylsilyl

temp: temperature

TES: triethylsilyl

Tf: trifluoromethanesulfonyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TIB: 2,4,6-triisopropylbenzenecarbonyl

TIPS: triisopropylsilyl

TLC: thin layer chromatography

TMEDA: *N,N,N',N'*-Tetramethylenediamine

TMP: 2,2,6,6-tetramethylpiperidide

TMS: trimethylsilyl

tol: toluene

TPAP: tetrapropylammonium perruthenate

Ts: *p*-toluenesulfonyl

UV: ultraviolet

xylyl: dimethylphenyl

Chapter 1

Kinetic Analysis of the Palladium-Catalyzed Conjunctive Cross-Coupling Reaction

1.1. Introduction

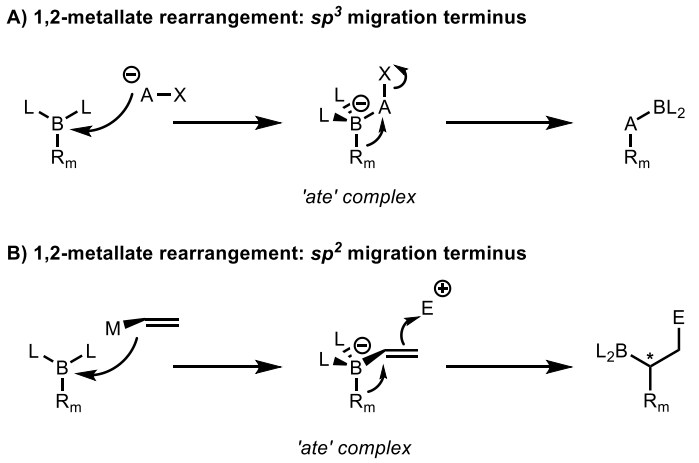
Organoboronates are valuable synthetic intermediates.[1] Like other organometallic reagents, organoboronates are used as nucleophilic reagents, but they offer many advantages over their counterparts. Boronic esters are typically stable to air and moisture, which allows them to be isolated and handled under ambient conditions. Furthermore, they are non-toxic, environmentally benign, and readily available from simple, inexpensive starting materials.[1] In terms of synthetic utility, organoboronates undergo a variety of useful transformations in which the boron atom is converted into a heteroatom or a carbon-based functional group.[2] For stereodefined α-boryl stereocenters, the carbon–boron bond is configurationally stable and subsequent transformations generally occur with high levels of stereospecificity. Therefore, the catalytic, asymmetric synthesis of organoboronates is desirable.[3]

In terms of reaction mechanism, synthetic transformations of organoboronates often occur through the intermediacy of a four-coordinate boron species, known as a boron 'ate' complex or borate.[2] The boron 'ate' complex, which is a relatively high-energy intermediate, is generated by the addition of a strong nucleophile to the vacant *p* orbital of a three-coordinate boron atom. Thus, the reactivity of organoboronates is dominated by shifts between three- and four-coordinate boron compounds. For example, if one of the groups on boron has a leaving group attached, then the

[1] Hall, D. G. Ed., Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials (Wiley-VCH, Weinheim, Germany, 2011).
[2] Sandford, C.; Aggarwal, V. K. *Chem. Commun*. **2017**, *53*, 5481–5494.
[3] Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11700–11733.

'ate' complex can undergo a rearrangement, known as a 1,2-metallate rearrangement (Scheme 1.1.A). In this reaction, a migrating group (R_m) displaces a leaving group (X) on the migration terminus (A). A 1,2-metallate rearrangement also occurs if the boron 'ate' complex contains an alkenyl group in the presence of an electrophile (E^+) to activate the π-electrons of the alkene (Scheme 1.1.B). This transformation results in the addition of the migrating group and the electrophile across the alkene in a regioselective manner.

Scheme 1.1. 1,2-Metallate rearrangement

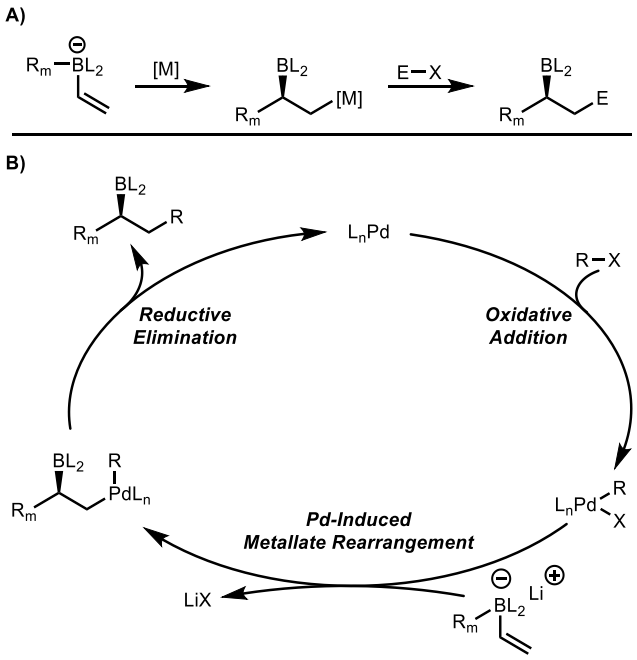


Recently, our research group has investigated the use of a transition metal catalyst to induce a 1,2-metallate rearrangement with a vinyl boron 'ate' complex (Scheme 1.2.A). Specifically, a Pd catalyst was found to effectively promote this type of reaction, such that the Pd-induced 1,2-metallate rearrangement replaces the transmetallation step in the Suzuki-Miyaura cross-coupling reaction (Scheme 1.2.B).[4] This reaction is termed "conjunctive cross-coupling" because two nucleophilic reagents are incorporated into the reaction product rather than one. The following

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

chapter will discuss an investigation into the kinetic profile of the Pd-catalyzed conjunctive cross-coupling reaction.

Scheme 1.2. The conjunctive cross-coupling reaction



1.2. Background

1.2.1. Reactivity of organoboronates

The reactivity of organoboronates is highly dependent on the ligands on boron.[3] Boranes, which contain three carbon ligands attached to boron, are highly electrophilic due to the low-energy vacant *p* orbital of boron. The corresponding borane-derived 'ate' complexes are highly nucleophilic because the formal negative charge resides heavily on the carbon ligands, leading to partial carbanionic character.[5] On the other hand, boronic esters, which contain two oxygen ligands and one carbon ligand attached to boron, have reduced electrophilicity due to the delocalization of the oxygen lone pair electrons into the *p* orbital of boron.[1] Accordingly, the

[5] Based on the Pauling electronegativity of C (2.55) compared to B (2.04).

corresponding 'ate' complexes have attenuated nucleophilicity because the negative charge resides mostly on the electronegative oxygen ligands rather than the carbon ligand(s).[6] We thus chose to study transformations of boronic esters rather than boranes since the former are more widely accessible due to their increased stability, and have practical synthetic advantages. Notably, symmetric boranes, which contain three identical carbon ligands, typically only utilize one of the ligands for synthetic transformations. A more atom economical strategy involves the use of mixed borane reagents with one migrating group and two nonmigrating/blocking substituents.[7] However, the relative reactivity of different substituents on boron is often difficult to predict, such that the blocking substituents can participate in undesired reactions.[7]

1.2.2. 1,2-Metallate rearrangement of boronic esters

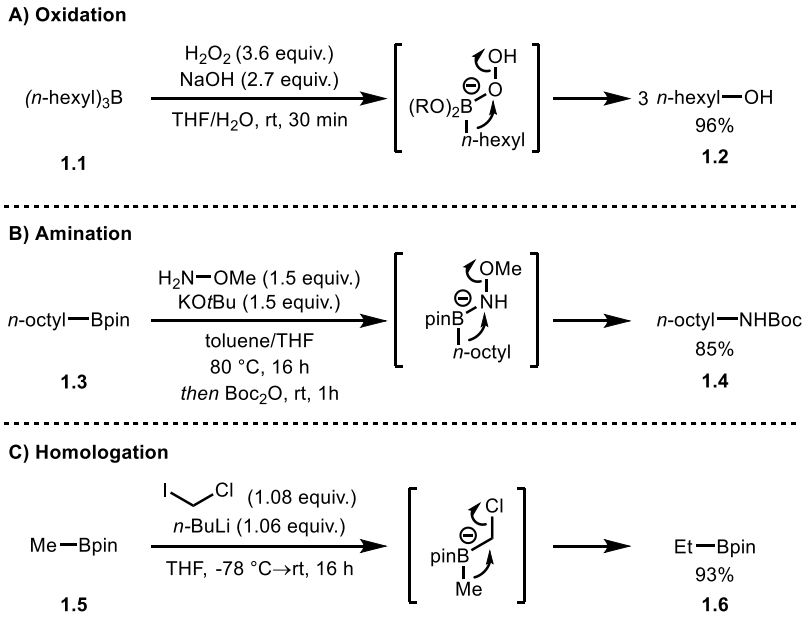
1.2.2.1. 1,2-Metallate rearrangement with an sp^3 migration terminus

The 1,2-metallate rearrangement, with boron being considered a metal, is a common mechanistic step in many reactions of organoboronates.[2] The most widely-used example of this reactivity is the replacement of the boron atom with an oxygen atom, which is referred to as oxidation (Scheme 1.3.A). To accomplish this transformation, a nucleophilic oxygen atom appended to a leaving group is used as the reagent. In one example, the Brown group oxidizes tri-*n*-hexylborane (**1.1**) into *n*-hexanol (**1.2**) using aqueous hydrogen peroxide and sodium hydroxide in THF.[8] Notably, each of the three *n*-hexyl ligands on boron are oxidized, so the intermediate borinic and boronic esters must also undergo the oxidation reaction. The corresponding reaction to form a C–N bond is also known, though there are only a few examples for the direct amination

[6] Based on the Pauling electronegativity of O (3.44) compared to B (2.04) and C (2.55).
[7] Aggarwal, V. K.; Fang, G. Y.; Ginesta, X.; Howells, D. M.; Zaja, M. *Pure Appl. Chem.* **2006**, *78*, 215–229.
[8] Brown, H. C.; Snyder, C.; Subba Rao, B. C.; Zweifel, G. *Tetrahedron* **1986**, *42*, 5505–5510.

of boronic esters (Scheme 1.3.B). Boronic ester **1.3** undergoes the amination reaction with methoxyamine [9] to yield **1.4** after protection of the free amine; a recently-developed aminoazanium reagent accomplishes a similar transformation.[10] Lastly, the C–B bond can be transformed into a C–C bond by a homologation reaction through the intermediacy of an α-halo boron 'ate' complex (Scheme 1.3.C). This convenient method for methylene insertion into the C–B bond was popularized by the Matteson group using (chloromethyl)lithium, which is generated *in situ* from *n*-butyllithium and chloroiodomethane.[11] Under these conditions, methyl–B(pin) (**1.5**) is converted into ethyl–B(pin) (**1.6**) in high yield.

Scheme 1.3. 1,2-metallate rearrangement from boron to an sp³ migration terminus

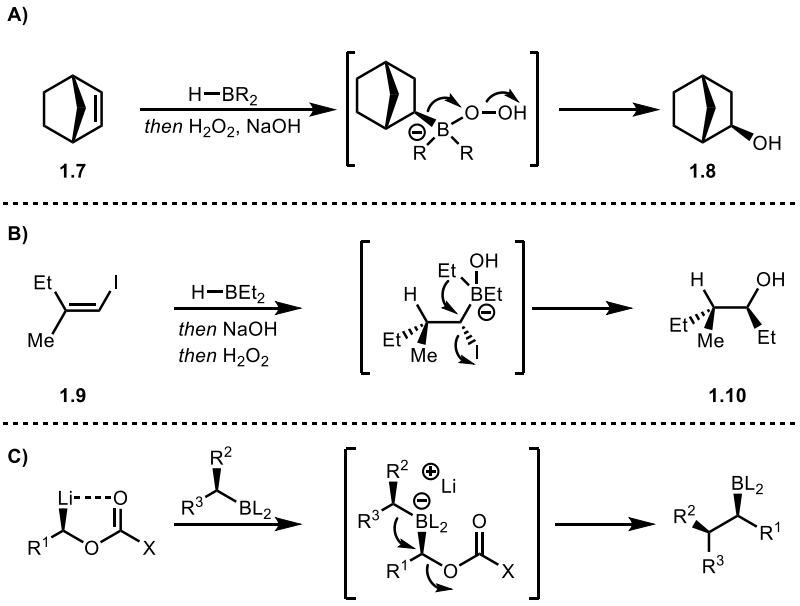


In terms of synthetic utility, it is important to note the stereochemical outcome of the reactions involving a 1,2-metallate rearrangement. The Brown group found that the hydroboration

[9] (a) Mlynarski, S. N; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc*. **2012**, *134*, 16449–16451. (b) Edelstein, E. K.; Grote, A. C.; Palkowitz, M. D.; Morken, J. P. *Synlett* **2018**, *29*, 1749–1752.
[10] Liu, X.; Zhu, Q.; Chen, D.; Wang, L.; Jin, L.; Liu, C. *Angew. Chem. Int. Ed.* **2020**, *59*, 2745–2749.
[11] Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687–1689.

product of **1.7** undergoes oxidation to alcohol **1.8** in a stereoretentive manner with respect the migrating group (Scheme 1.4.A).[12] Furthermore, the Midland group found that the 1,2-metallate rearrangement is stereoinvertive at the migration terminus (Scheme 1.4.B).[13] Hydroboration of alkenyl iodide **1.9** and subsequent S_N2-like displacement of the leaving group by the migrating group yields alcohol **1.10** after boron oxidation. These stereochemical outcomes can be generalized for all 1,2-metallate rearrangement reactions, and because of this predictability, α-chiral boron 'ate' complexes have been used extensively in organic synthesis.[14] For example, lithiated carbamate and benzoate derivatives react with chiral organoboronates for powerful C–C bond forming reactions (Scheme 1.4.C).[15]

Scheme 1.4. Stereochemistry of the 1,2-metallate rearrangement



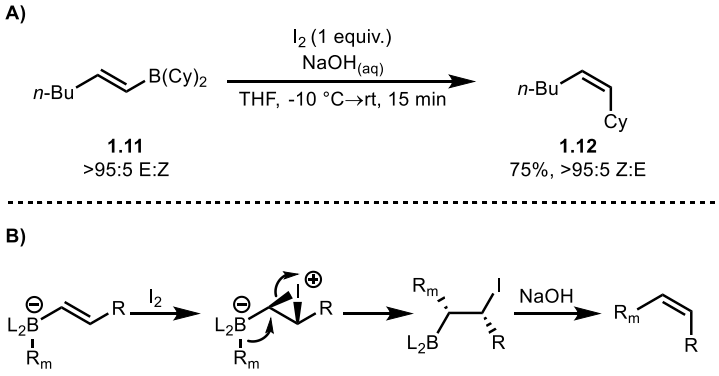
[12] Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 2544–2551.
[13] Midland, M. M.; Zolopa, A. R.; Halterman, R. L. *J. Am. Chem. Soc*. **1979**, *101*, 248–249.
[14] Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res*. **2014**, *47*, 3174–3183.
[15] (a) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, *13*, 2275–2280. (b) Mykura, R. C.; Veth, S.; Varela, A.; Dewis, L.; Farndon, J. J.; Myers, E. L.; Aggarwal, V. K. J. *Am. Chem. Soc.* **2018**, *140*, 14677–14686.

1.2.2.2. 1,2-Metallate rearrangement with an sp^2 migration terminus

The electrophile-induced 1,2-metallate rearrangement of C(sp^2)-substituted boron 'ate' complexes enables a variety of synthetic transformations.[16] One of the earliest examples of this reactivity was reported by the Zweifel group,[17] whereby treatment of alkenyl borane **1.11** with molecular iodine and sodium hydroxide leads to **1.12** as the final product (Scheme 1.5.A). This reaction was subsequently modified for boronic ester substrates by the Matteson group[18] and the Evans group[19] independently, whereby the reactive boron 'ate' complexes are generated by addition of alkenyllithium reagents to boronic esters. Recently, this method was expanded upon by the Aggarwal group by using Grignard reagent-derived boronic ester 'ate' complexes as substrates.[20] The mechanism for this reaction involves an iodine-induced metallate rearrangement, followed by base-induced antiperiplanar deiodoboration (Scheme 1.5.B). The stereochemical outcome of the reaction is consistent with an *anti*-periplanar alignment of the migrating group and the electrophile for the 1,2-metallate rearrangement.

[16] Namirembe, S.; Morken, J. P. *Chem. Soc. Rev.* **2019**, *48*, 3464–3474.
[17] Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, 89, 3652–3653.
[18] Matteson, D. S.; Jesthi, P. K. *J. Organomet. Chem*. **1976**, *110*, 25–37.
[19] (a) Evans, D. A.; Thomas, R. C.; Walker, J. A. *Tetrahedron Lett.* **1976**, *17*, 1427–1430. (b) Evans, D. A.; Crawford, T. C.; Thomas, R. C.; Walker, J. A. *J. Org. Chem.* **1976**, *41*, 3947–3953.
[20] Armstrong, R. J.; Niwetmarin, W.; Aggarwal, V. K. *Org. Lett*. **2017**, *19*, 2762–2765.

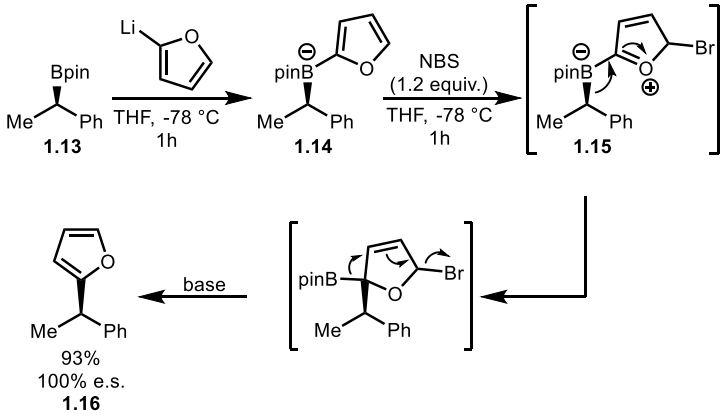
Scheme 1.5. The Zweifel olefination reaction



Additionally, the Aggarwal group has utilized the strategy of halogen-induced 1,2-metallate rearrangement followed by elimination for a variety of metal-free C(sp^3)–C(sp^2) coupling reactions (Scheme 1.6).[21] For example, enantioenriched organoboronate **1.13** is treated with 2-furyllithium to generate 'ate' complex **1.14**, and subsequent electrophilic aromatic bromination by NBS leads to transient intermediate **1.15**. Subsequent 1,2-metallate rearrangement and base-induced dehaloboration reestablishes aromaticity to generate **1.16**. The scope of aryl coupling partners includes a wide variety of aromatic and heteroaromatic groups; the reactions proceed in good yield and with excellent stereospecificity. This method represents a significant advancement in C(sp^3)–C(sp^2) coupling reactions, as the corresponding metal-catalyzed cross-coupling reactions of secondary and tertiary organoboronates are not broadly applicable.

[21] (a) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nat. Chem*. **2014**, *6*, 584–589. (b) Llaveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2015**, *137*, 10958–10961. (c) Odachowski, M.; Bonet, A.; Essafi, S.; Conti-Ramsden, P.; Harvey, J. N.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2016**, *138*, 9521–9532. (d) Ganesh, V.; Odachowski, M.; Aggarwal V. K. *Angew. Chem. Int. Ed*. **2017**, *56*, 9752–9756. (e) Wilson, C. M.; Ganesh, V.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 16318–16322. (f) Bigler, R.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2018**, *57*, 1082–1086.

Scheme 1.6. C(sp^3)–C(sp^2) coupling reactions by 1,2-metallate rearrangement

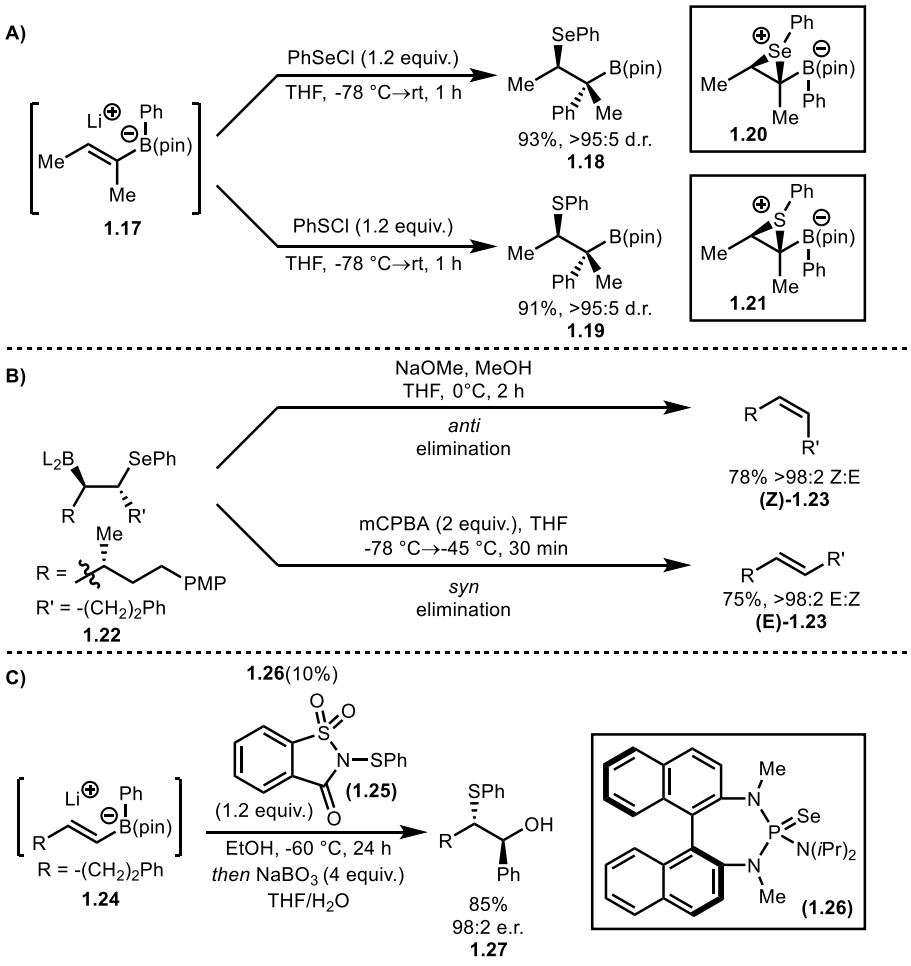


One drawback of using halogen electrophiles for the 1,2-metallate rearrangement is that the β-halo boronate intermediates readily undergo dehaloboration such that boron functional group handle is not maintained. To address this limitation, the Aggarwal group has demonstrated the ability of other π-acids, such as selenium- and sulfur-based electrophiles, to induce a diastereoselective 1,2-metallate rearrangement such that the boronate products are isolable (Scheme 1.7.A).[22] Alkenyl boron 'ate' complex **1.17** is transformed into either β-seleno boronate **1.18** or β-thio boronate **1.19** in good yield and with excellent diastereoselectivity. A possible reaction mechanism for these transformations involves the intermediacy of transient seleniranium zwitterionic complex **1.20** or the analogous thiiranium **1.21**. The product of this reaction is synthetically useful, as the β-seleno boronate **1.22** undergoes *syn* elimination in the presence of sodium methoxide, or *anti* elimination under oxidative conditions to selectively generate either **(Z)-1.23** or **(E)-1.23** with complete stereocontrol (Scheme 1.7.B).[23] Recently, the Denmark group has utilized a sulfur-based electrophile (**1.25**) in conjunction with a catalytic amount of a phosphine

[22] Armstrong, R. J.; Sandford, C.; García-Ruiz, C.; Aggarwal, V. K. *Chem. Commun*. **2017**, *53*, 4922–4925.
[23] Armstrong, R. J.; García-Ruiz, C.; Myers, E.L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 786–790.

selenide (**1.26**) to promote the enantioselective 1,2-metallate rearrangement of an alkenyl boron 'ate' complex (**1.24**) (Scheme 1.7.C).[24] A possible mechanism for this transformation involves the activation of electrophile **1.25** with the catalyst (**1.26**) to facilitate formation of the reactive thiiranium intermediate. In summary, the 1,2-metallate rearrangement of C(sp^2)-substituted boron 'ate' complexes can be induced by many electrophiles in a stoichiometric fashion for useful synthetic transformations.

Scheme 1.7. Se- and S-induced 1,2-metallate rearrangement



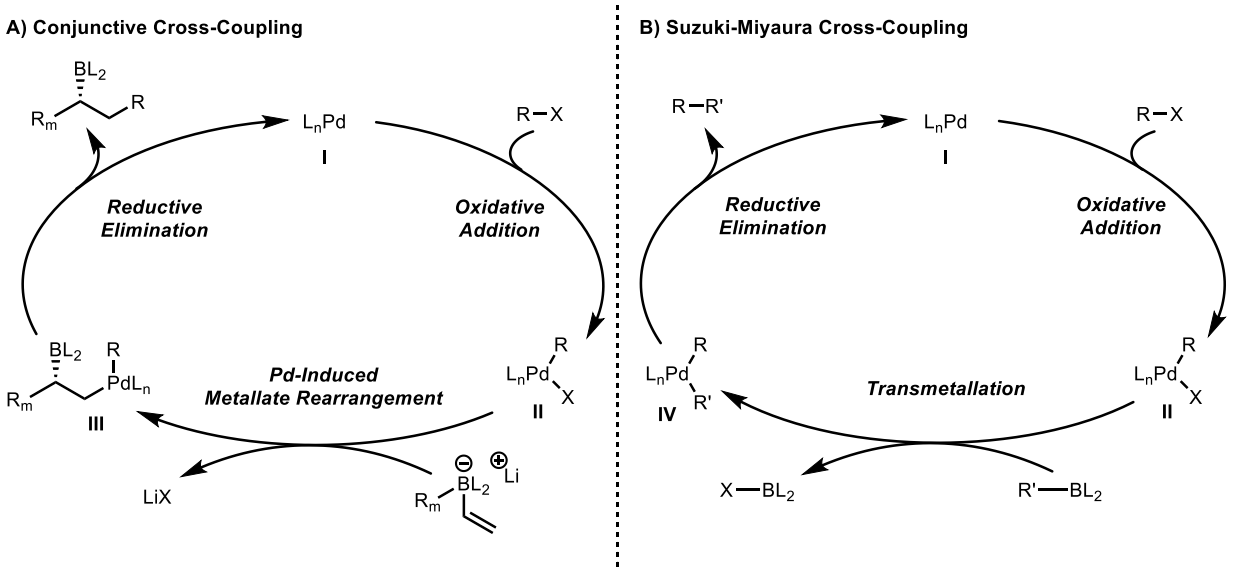
[24] Tao, Z.; Robb, K. A.; Panger, J. L.; Denmark, S. E. *J. Am. Chem. Soc.* **2018**, *140*, 15621–15625.

1.2.3. The conjunctive cross-coupling reaction

In contrast to the reactions with stoichiometric electrophiles, our research group has investigated the use of a transition metal catalyst as the electrophile to induce a 1,2 metallate rearrangement with vinyl boron 'ate' complexes.[16] Specifically, a cationic Pd^{II} complex was found to effectively promote the 1,2-metallate rearrangement.[4] As shown in Scheme 1.8.A, the catalytic cycle for this transformation occurs by the following steps: Pd^0 undergoes oxidative addition with the electrophile to generate a Pd^{II} intermediate (**I→II**). Next, Pd^{II} activates the alkene of the boron 'ate' complex to induce the metallate rearrangement, which generates a Pd^{II} intermediate possessing two organic ligands (**II→III**). Finally, reductive elimination generates the reaction product and regenerates the Pd^0 catalyst (**III→I**). This reaction shares two mechanistic steps with the Suzuki-Miyaura cross-coupling reaction, namely oxidative addition and reductive elimination (Scheme 1.8.B). The two reactions differ with respect to the reaction between the Pd^{II} oxidative addition adduct (**II**) and the boron 'ate' complex: the conjunctive cross-coupling reaction involves a Pd-induced 1,2-metallate rearrangement step, whereas the Suzuki-Miyaura cross-coupling reaction involves a transmetallation step.[25]

[25] A detailed discussion of the chemoselectivity between these reactions is found in Chapter 3.

Scheme 1.8. The catalytic cycles of A) the conjunctive cross-coupling reaction and B) the Suzuki-Miyaura cross-coupling reaction



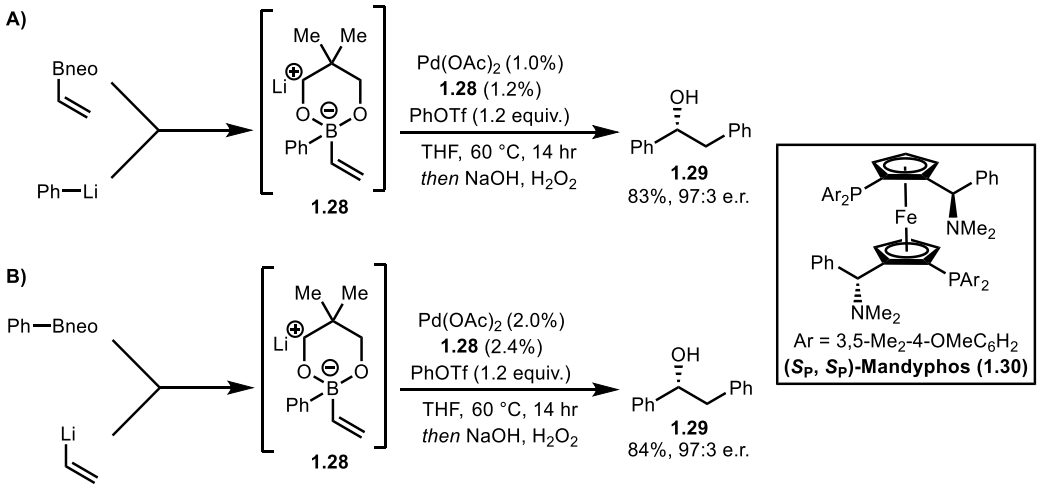
While oxidative addition and reductive elimination are ubiquitous in cross-coupling reactions, the Pd-induced metallate rearrangement of boron 'ate' complexes does not have extensive precedent.[26] A mechanistic analogy can be made between the Pd-induced metallate rearrangement and the alkene hydroxypalladation step of the Wacker oxidation,[27] which can operate either by a *syn*- or *anti*-addition pathway.[28] Related Pd-induced nucleometallation reactions have been utilized for C–C and C–heteroatom bond-forming reactions, and thus, this class of reaction represents a powerful tool for organic synthesis.[29] In terms of the Pd-induced metallate

[26] Echavarren, A. M.; Homs, A. In *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A., Bräse, S., Oestreich, M., Eds.; Wiley-VCH: Weinheim, Germany, **2013**, *1*, 1-64.
[27] (a) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem. Int. Ed.* **1962**, 1, 80–88. (b) Jira, R. *Angew. Chem. Int. Ed.* **2009**, 48, 9034–9037.
[28] Keith, J. A.; Henry, P. M. Angew. Chem., Int. Ed. 2009, 48, 9038–9049.
[29] McDonald, R. I., Liu, G., Stahl, S. S. *Chem. Rev.* **2011**, 111, 2981–3019.

rearrangement of a boron 'ate' complex, reactions of alkynyl[30] and indoyl[31] borane 'ate' complexes with catalytic Pd^{II} species have been reported. However, the Pd-induced 1,2-metallate rearrangement step is not necessarily the definitive mechanistic pathway.

Thus, the conjunctive cross-coupling reaction was relatively novel with respect to employing the Pd-induced 1,2-metallate rearrangement as a step in the catalytic cycle. The first generation of the conjunctive cross-coupling reaction between phenyl triflate and 'ate' complex **1.28** was found to benefit from the following features: a) The use of THF solvent; b) A neopentyl glycol (neo) ligand on boron; and c) $Pd(OAc)_2$ and Mandyphos ligand **1.30** as the catalyst (Scheme 1.9).[4] The vinyl boron 'ate' complex **1.28** is generated either by the addition of an organolithium reagent to a vinyl boron reagent (Scheme 1.9.A) or by addition of vinyllithium to a boronic ester (Scheme 1.9.B). Organotriflate electrophiles are uniquely effective because of the non-coordinating nature of the triflate counterion; halide ions strongly inhibit the reaction.

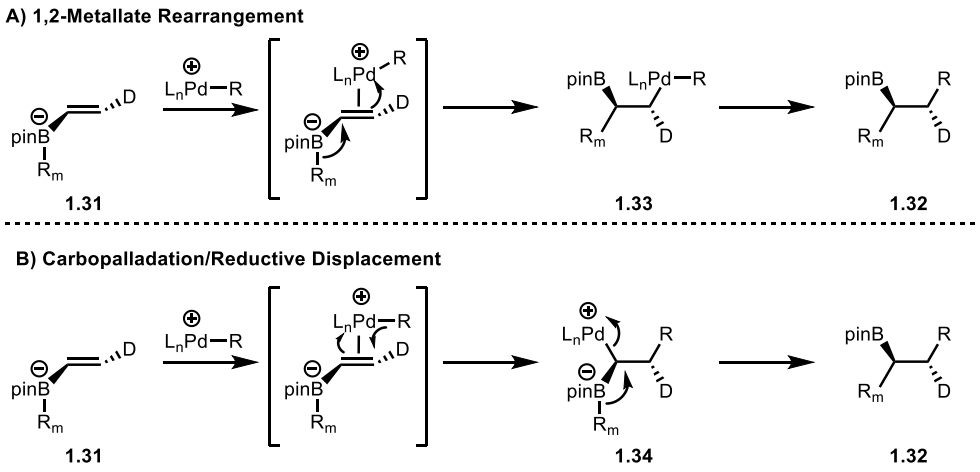
Scheme 1.9. Reaction conditions for the conjunctive cross-coupling reaction



[30] (a) Chen, Y.; Li, N. S.; Deng, M. Z. *Tetrahedron Lett.* **1990**, 31, 2405–2406. (b) Ishida, N.; Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 42, 4381–4383. (c) Ishida, N.; Narumi, M.; Murakami, M. *Org. Lett.* **2008**, 10, 1279–1281. (d) Ishida, N.; Narumi, M.; Murakami, M. *Helvetica Chimica Acta* **2012**, 95, 2474–2480. (e) Shimamoto, Y.; Sunaba, H.; Ishida, N.; Murakami, M. *Eur. J. Org. Chem.* **2013**, 8, 1421–1424.
[31] (a) Ishikura, M.; Kato, H. *Tetrahedron* **2002**, 58, 9827–9838. (b) Panda, S.; Ready, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 6038–6041. (c) Panda, S.; Ready, J. M.; *J. Am. Chem. Soc.* **2018**, *140*, 13242–13252.

Due to the rarity of the Pd-induced 1,2-metallate rearrangement in catalytic reactions, the conjunctive cross-coupling reaction provides an opportunity to investigate this novel elementary step. When the reaction is conducted using a deuterium label on the vinyl group of the 'ate' complex (**1.31**, Scheme 1.10.A), the stereochemical configuration of the product (**1.32**) is consistent with an *anti*-periplanar alignment of the migrating group and the electrophile, *via* intermediate **1.32** (Scheme 1.10.A). However, an alternative mechanism cannot be ruled out whereby the Pd^{II} oxidative addition adduct undergoes a β-migratory insertion with alkene to generate intermediate **1.34**; subsequent reductive displacement of Pd by the migrating group yields **1.32** (Scheme 1.10.B). Of note, the β-migratory insertion pathway is favored by Murakami *et al*,[30b] but the 1,2-metallate rearrangement pathway is proposed to operate according to DFT calculations conducted within our research group.[32] Experimentally, these mechanisms are both consistent with the Pd^{II} oxidative addition adduct, rather than a different palladium species, interacting with the alkene in the stereochemistry-determining step because the enantioselectivity of the reaction depends on the identity of the electrophile.

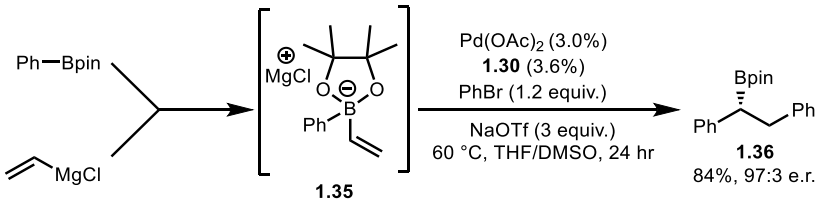
Scheme 1.10. Possible mechanisms of the conjunctive cross-coupling reaction



[32] Lovinger, G. J. Enantioselective Multi-Component Reactions: Conjunctive Coupling and Related Processes. Ph.D. Thesis, Boston College. October 2019.

Subsequent developments to the conjunctive cross-coupling include the use of 'ate' complexes derived from Grignard reagents as milder alternatives to organolithium reagents (Scheme 1.11).[33] The reaction with organomagnesium nucleophiles suffers from ineffective boron 'ate' complex formation due to the attenuated nucleophilicity of Grignard reagents relative to organolithium reagents. Furthermore, the catalytic reaction is inhibited by the halide ions which are present in Grignard reagents or organohalide electrophiles. Both of these problems are overcome by using alkali metal triflates as stoichiometric additives in the reaction. The triflate salt enables complete boron 'ate' complex formation with the Grignard reagent, and also acts as a halide scavenger due to the poor solubility of alkali metal halides in the reaction medium. The reaction is also improved by using a THF/DMSO solvent mixture, so that 'ate' complex **1.35** is very efficiently converted into organoboronate **1.36**.

Scheme 1.11. The conjunctive cross-coupling reaction with a Grignard reagent-derived 'ate' complex

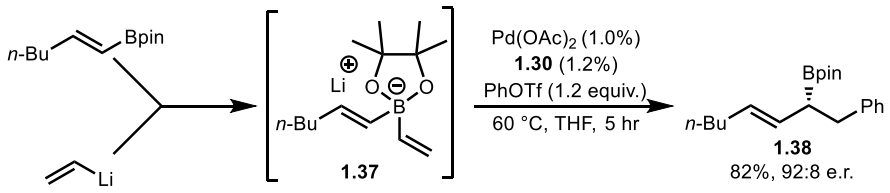


Another development for the conjunctive cross-coupling reaction is the use of alkenyl migrating groups for the synthesis of versatile allylic boronate products (Scheme 1.12).[34] This reaction occurs through the intermediacy of a non-symmetric bis(alkenyl) 'ate' complex (**1.37**), in which there are two potential sites for Pd to induce the 1,2 metallate rearrangement. In spite of

[33] Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153–3160.
[34] Edelstein, E. K.; Namirembe, S.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 5027–5030.

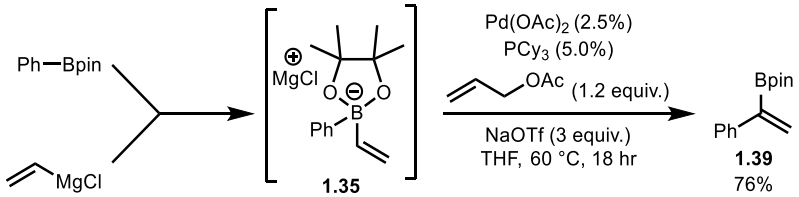
the two potential sites for Pd binding, this reaction is highly chemoselective, and Pd only activates the least hindered alkene to yield **1.38**.

Scheme 1.12. The conjunctive cross-coupling reaction with a bis(alkenyl) 'ate' complex



The Pd-induced 1,2-metallate rearrangement is also a key step in the vinylidenation of organoboronates (Scheme 1.13).[35] In this process, Grignard reagent-derived boron 'ate' complex **1.35** reacts with a Pd catalyst and allyl acetate as a stoichiometric oxidant to yield alkenyl boronate **1.39**. With the allyl electrophile, the expected conjunctive cross-coupling reaction does not form when using a bidentate ligand for Pd because the η^3 binding mode of the allyl group prevents the Pd^{II} intermediate from interacting with the vinylboron 'ate' complex. However, the use of a monodentate phosphine ligand in this reaction results in significant formation of the vinylidenation product.

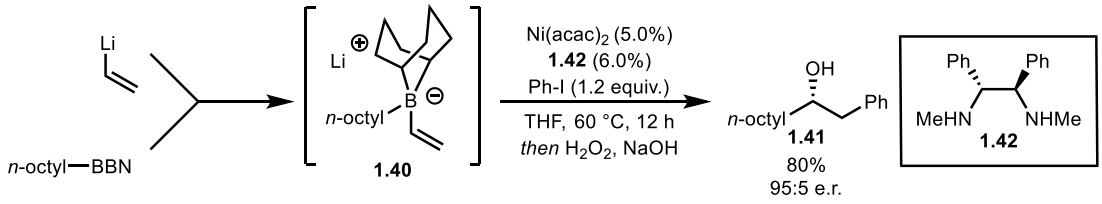
Scheme 1.13. Vinylidenation reaction by Pd-induced 1,2-metallate rearrangement



[35] Aparece, M. D.; Gao, C.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 592–595.

Nickel-based catalytic systems are also effective in promoting a conjunctive cross-coupling reaction (Scheme 1.14).[36] In the presence of a nickel complex with a chiral diamine supporting ligand (**1.42**), the 9-BBN borane-derived 'ate' complex **1.40** and an aryl iodide electrophile yield alcohol **1.41** after boron oxidation. Of note, the use of an aryl iodide instead of an aryl triflate is optimal for the reaction. Mechanistic experiments support that the reaction occurs by a mechanism that is analogous to the Pd-catalyzed conjunctive cross-coupling reaction, namely by a sequence of oxidative addition, Ni-induced metallate rearrangement, and reductive elimination.[36]

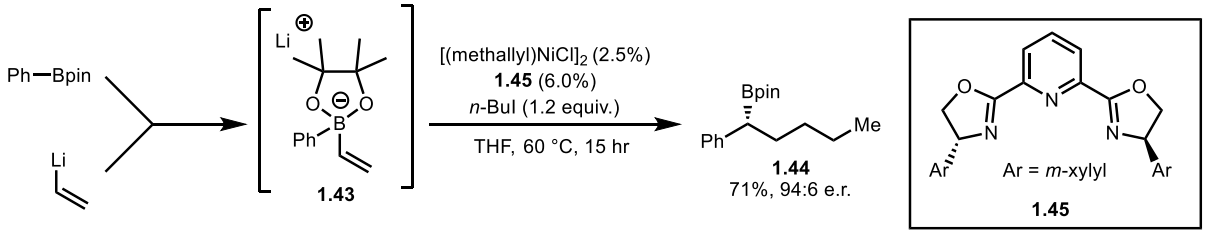
Scheme 1.14. The Ni-catalyzed conjunctive cross-coupling reaction of 9-BBN borates



A Ni-derived catalyst was developed for the conjunctive cross-coupling reaction of alkyl electrophiles with a vinylboron 'ate' complex (Scheme 1.15).[37] As an example of this process, a nickel complex bearing pybox ligand **1.45** catalyzes the coupling between **1.43** and *n*-butyl iodide to yield **1.44**. In contrast to the previous Ni-catalyzed conjunctive cross-coupling reaction, boronic ester 'ate' complexes are viable substrates for the reaction, whereas borane 'ate' complexes are not. The electrophilic coupling partner can be a primary or secondary alkyl iodide. Mechanistic studies suggest that the reaction operates by a similar mechanism to the previous conjunctive cross-coupling reactions.[37]

[36] Chierchia, M. P.; Law, C.; Morken, J. P. *Angew. Chem. Int. Ed.* **2017**, *56*, 11870–11874.
[37] Lovinger, G. J.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 17293–17296.

Scheme 1.15. Ni-catalyzed conjunctive cross-coupling reaction of with alkyl electrophiles



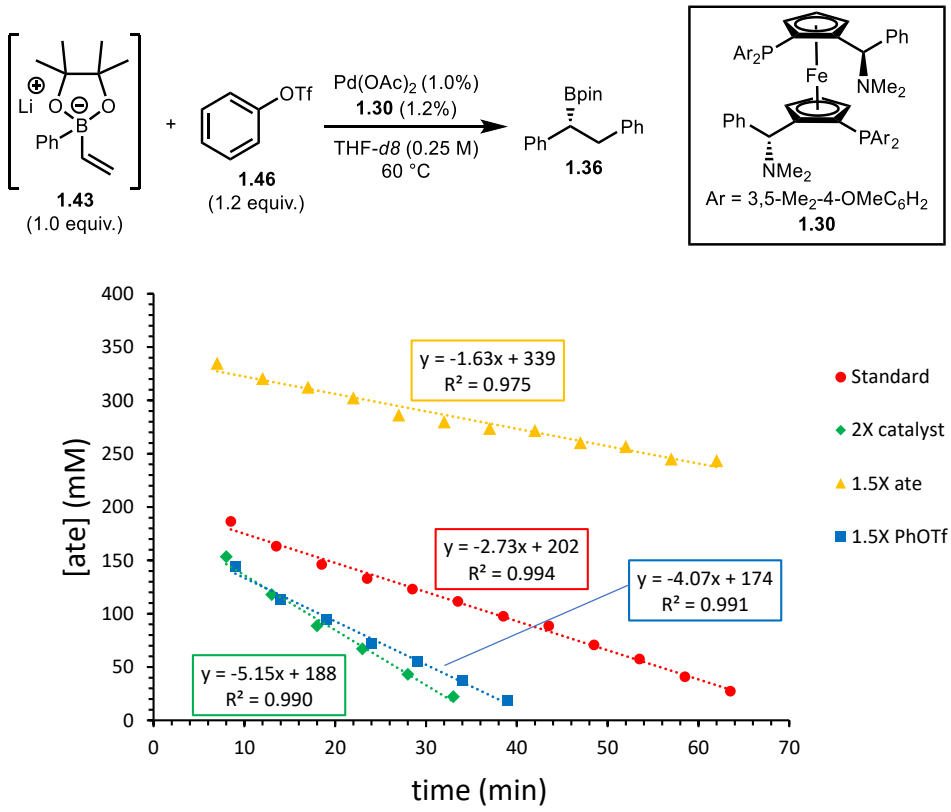
1.3. Mechanistic studies on the palladium-catalyzed conjunctive cross-coupling reaction[38]

1.3.1. Reaction progress kinetic analysis

A detailed understanding of the kinetics of the conjunctive cross-coupling reaction can facilitate reaction development by identifying the challenging steps in the catalytic cycle.[39] Reaction progress kinetic analysis of the reaction between boron 'ate' complex **1.43** and phenyltriflate (**1.46**) under standard catalytic reaction conditions was studied by ^{1}H NMR spectroscopy. The reaction proceeds with minimal formation of byproducts (<5%) and is almost complete within 1 hour at 60 °C. Based on the plot of ['ate'] vs. time (Figure 1.1, 'standard'), the rate of reaction is constant over the course of the reaction, which is characteristic of an apparent zero-order process. It can be assumed that the reaction is not decelerated by product inhibition or catalyst decomposition, as the reaction proceeds to near-completion without change in kinetic behavior.

[38] Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed*. **2018**, *57*, 12799–12803.
[39] Blackmond, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 10852–10866.

Figure 1.1. Reaction progress kinetic analysis of the conjunctive cross-coupling reaction



Next, the effect of the concentration of the individual reaction components on the rate of reaction was investigated by a series of *different excess* experiments. These experiments were run in triplicate (see Section 1.4.2.1), and the order of each reaction component was calculated by the average of the order over the three experiments. The *different excess* experiments were conducted at the following concentrations for each component: 2X [catalyst], 1.5X [PhOTf], and 1.5X ['ate' complex]. Attempts to conduct the reaction at higher [PhOTf] or ['ate'] led to complicated reaction kinetics, the origin of which is discussed later in this section.

When the concentration of catalyst is doubled (Figure 1.1, '2X catalyst'), the rate of reaction increases in a roughly first-order fashion (order = 1.1). An increase in the concentration of PhOTf (Figure 1.1, '1.5X PhOTf') also results in a rate acceleration in a roughly first-order fashion (order

= 1.4),[40] and an increase in the concentration of 'ate' complex (Figure 1.1, '1.5X ate') results in a decrease in the reaction rate in a roughly inverse-first-order fashion (order = –0.9). Therefore, the rate law for reaction can be approximated as shown in Equation 1. This rate law is consistent with an apparent zero-order process because [catalyst] does not change over the course of the reaction, and the order of this component does not factor into the effective reaction order. Furthermore, if [electrophile] and ['ate'] are roughly equivalent and decrease at the same rate over the reaction, then their orders cancel out such that the overall reactions appears to be zero-order.[41]

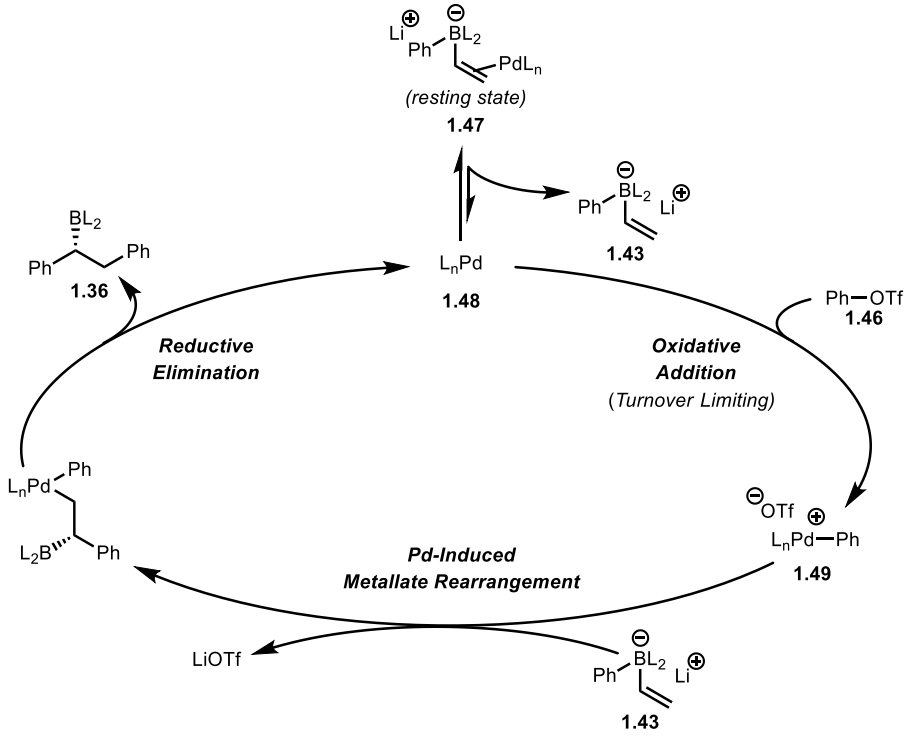
$$\text{rate} = \frac{k_{obs}\bullet[\text{catalyst}]\bullet[\text{electrophile}]}{[\text{'ate'}]} \qquad \text{(eq. 1)}$$

A catalytic cycle that is consistent with the kinetic profile of the reaction is presented in Scheme 1.16. The first-order relationship with respect to [PhOTf] suggests that the electrophile is involved in the turnover-limiting step of the reaction, and the inverse-first-order ['ate'] suggests that the 'ate' complex inhibits the reaction. Oxidative addition must be turnover-limiting because this is the only step in which the catalyst reacts with the electrophile (**1.46**). Therefore, the 'ate' complex (**1.43**) inhibits the reaction by competitively binding to the active Pd^0 catalyst (**1.48**) and forming an inactive Pd complex (**1.47**). While the nature of the bonding interaction between Pd^0 and the 'ate' complex cannot be definitively assigned, experimental evidence suggests Pd^0–alkene complex (**1.47**) as a possibility. Notably, other Pd-catalyzed cross-coupling reactions with alkenyl nucleophiles have been observed to have decreased rates of oxidative addition due to inhibitory

[40] The non-integer order can be explained as follows: for reactions in which [electrophile]>['ate'], the reaction rate is accelerated over the course of the reaction, and data was not collected at the beginning of the reaction.
[41] Attempts to conduct the reaction with [PhOTf] >> ['ate'] led to a deviation from zero-order kinetics; the rate of reaction increases over time. Attempts to conduct the reaction with ['ate'] >> [PhOTf] resulted in a greatly diminished rate of reaction.

Pd^0–alkene binding.[42] Furthermore, (Mandyphos)Pd^0 complexes appear to be stable in the presence of a vinylboron 'ate' complex (**1.43**), but not in the presence of an 'ate' complex which lacks an alkene (see Section 1.3.2). The kinetic data for the conjunctive cross-coupling reaction is also inconsistent with any other step being turnover-limiting. If the 1,2-metallate rearrangement is turnover-limiting, then the reaction would be zero-order with respect to both ['ate'] and [PhOTf], assuming that the prerequisite Pd^{II}–alkene binding is fast. Similarly, if reductive elimination is turnover-limiting, then the reaction would also be zero-order with respect to ['ate'] and [PhOTf].

Scheme 1.16. The catalytic cycle of the Pd-catalyzed conjunctive cross-coupling reaction



[42] (a) Amatore, C.; Bucaille, A.; Fuxa, A.; Jutand, A; Meyer, G.; Ndedi Ntepe, A. *Chem. Eur. J.* **2001**, *7*, 2134–2142. (b) Amatore, C.; Carré, E.; Jutand, A.; Medjour, Y. *Organometallics* **2002**, *21*, 4540–4545.

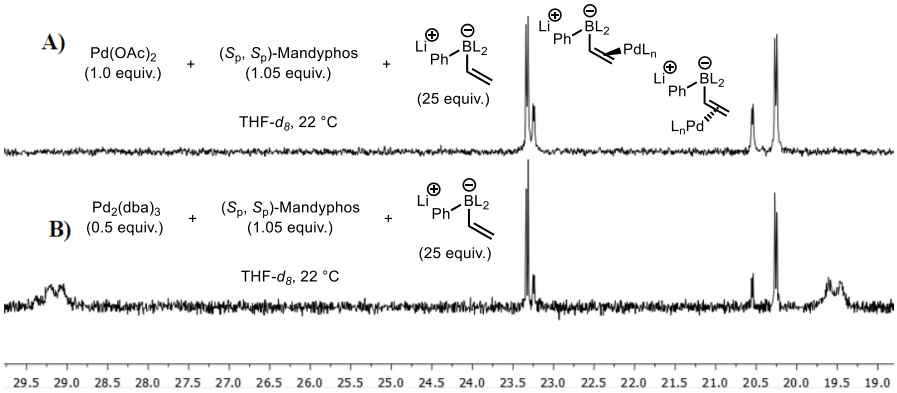
1.3.2. Determination of the catalyst resting state

According to the proposed mechanism, the catalyst resting state is complex **1.47**. Since, complexes of Pd^0 coordinated to electron-rich alkenes have rarely been reported, this hypothesis was tested experimentally. A mixture of Pd(II) acetate, Mandyphos ligand **1.30**, and vinylboron 'ate' complex **1.43** were allowed to react in THF-d_8. The resulting ^{31}P NMR spectrum (Figure 1.2.A) indicates the presence of two unique bis(phosphine)palladium species in which Pd^0 is associated with the boron 'ate' complex. Of note, when an 'ate' complex lacking an alkene substituent is mixed with $Pd(OAc)_2$ and ligand **1.30**, the ^{31}P NMR spectrum indicates no interaction between the 'ate' complex and the catalyst, and Pd black precipitates from the reaction mixture almost immediately. This observation suggests that in the case of 'ate' complex **1.43**, the alkene likely ligates to Pd^0 and prevents precipitation, resulting in complex **1.47**. Related bisphosphine-ligated Pd^0–alkene complexes have been characterized and exhibit a similar ^{31}P NMR splitting pattern due to the prochiral alkene rendering the phosphine atoms inequivalent.[43] Furthermore, two diastereomeric Pd^0 complexes arise as a result of the chiral bisphosphine ligand and prochiral alkene, hence the two sets of peaks observed by ^{31}P NMR spectroscopy (Figure 1.2.A). Overall, the experimental data is consistent with the putative catalyst resting state (**1.47**) in which Pd^0 interacts with the 'ate' complex by alkene association. The coordination geometry of this structure at the Pd center has not been definitively assigned, but a configuration is required in which the phosphorous atoms are spectroscopically distinct. Further structural information about the resting state structure might be obtained by ^1H NMR analysis or X-ray crystallographic structure determination, but efforts towards this were not extensively pursued.

[43] (a) Herrmann, W. A.; Thiel, W. R.; Broβmer, C.; Öfele, K.; Priermeier, T.; Scherer, W. *J. Organomet. Chem*. **1993**, *461*, 51–60. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 7215–7216. (c) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc*. **1997**, *119*, 5176–5185. (d) Reid, S. M.; Mague, J. T.; Fink, M. J. *J. Organomet. Chem*. **2000**, *616*, 10–18.

The observation of Pd^0 complex **1.47** upon mixing a Pd^{II} source with 'ate' complex **1.43** suggests that the 'ate' complex effectively reduces the $Pd(OAc)_2$ precatalyst to a Pd^0 species. In order to test this hypothesis, an analogous reaction was conducted using $Pd_2(dba)_3$ as a Pd^0 source; the same resonances were observed in the ^{31}P NMR spectrum (Figure 1.2.B). Notably, the reaction from $Pd_2(dba)_3$ to **1.47** proceeds sluggishly, and the ^{31}P NMR spectrum contains other resonances (~19.5 ppm, ~29 ppm), possibly due to the strong interaction between dba and Pd^0. Overall, complex **1.47** is prepared either from a Pd^0 or Pd^{II} source, so the 'ate' complex reduces Pd^{II} to Pd^0.

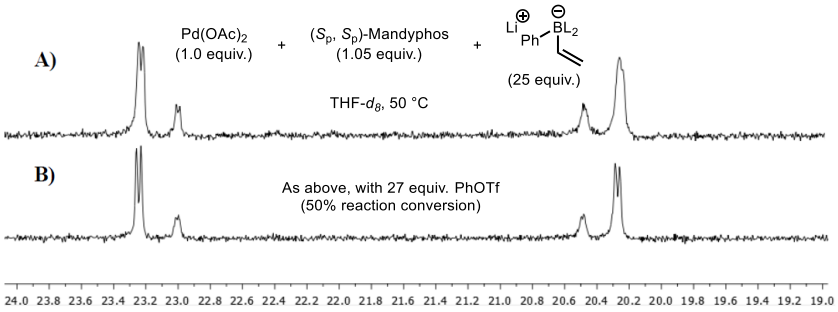
Figure 1.2. ^{31}P NMR spectra of palladium-alkene complexes



For the determination of the catalyst resting state in the Pd-catalyzed conjunctive cross-coupling reaction, the reaction was monitored by ^{31}P NMR spectroscopy to identify the catalytic complexes present during the reaction. For comparison, the Pd^0–alkene complex (**1.47**) was heated to 50 °C, at which temperature a catalytic conjunctive cross-coupling reaction can proceed. The ^{31}P NMR spectrum at 50 °C is relatively unchanged compared to the spectrum acquired at room temperature (Figure 1.3.A). Next, phenyltriflate (**1.46**) was added to this mixture and heating was continued at 50 °C while the reaction progress was monitored by ^1H NMR spectroscopy. At 50% reaction conversion, the only species observed by ^{31}P NMR spectroscopy is **1.47** (Figure 1.3.B), thus supporting the hypothesis that this species is the catalyst resting state. In summary, the

catalyst resting state is proposed to be an off-cycle Pd^0–alkene complex (**1.47**) based on ^{31}P NMR analysis.

Figure 1.3. ^{31}P NMR spectra of palladium–alkene complexes during catalytic conjunctive cross-coupling reaction



1.3.3. Conclusion

The reaction mechanism of the palladium-catalyzed conjunctive cross-coupling was studied by kinetic analysis. The reaction is an apparent zero-order process, and is accelerated by an increased concentration of the electrophile, but inhibited by the boron 'ate' complex. It is proposed that oxidative addition is the turnover-limited step in the catalytic cycle, and that the catalyst resting state is an inactive Pd^0 species in which palladium coordinates to the alkene of the 'ate' complex (**1.47**). Future optimization of the catalytic efficiency should focus on accelerating the oxidative addition step. This might be achieved by modifying the ligand on palladium or by conducting the reaction with slow addition of the 'ate' complex to minimize its inhibitory effect. Furthermore, the conjunctive cross-coupling reaction with a disubstituted alkenylboron 'ate' complex might proceed readily if the inhibitory effect of the alkene is diminished.

1.4. Experimental section

1.4.1. 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 ($CDCl_3$: 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 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 ($CDCl_3$: 77.2 ppm). ^{11}B NMR spectra were recorded on a Varian Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer. 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. 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, and cerium(IV) sulfate in ethanol with sulfuric acid (Seebach).

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

methanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. 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 argon. Palladium (II) acetate, (S_p,S_p)-Mandyphos (**1.30**) was purchased from Strem Chemicals, Inc. and used without further purification. Vinyl boronic acid pinacol ester was purchased from CombiBlocks and purified by distillation prior to use. Phenyl trifluoromethanesulfonate was purchased from Oakwood Chemicals and used without further purification. All other reagents were purchased from Aldrich, Alfa Aesar, or Acros and used without further purification.

1.4.2. Experimental procedures

1.4.2.1. Kinetic analysis: representative procedure for ^{1}H NMR experiments

All reagents were prepared as stock solutions by dilution in volumetric flasks immediately prior to the experiment.

A) Preparation of the 'ate' complex solution

To an oven-dried 2-dram vial with stir bar in an Ar-filled glovebox was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (169.4 mg, 1.1 mmol, 1.0 equiv.) and 0.8 mL Et_2O. The vial was sealed with a septum cap removed from the glovebox. The vial was cooled to 0 ºC under N_2, and phenyllithium solution (1.9 M in dibutyl ether, 0.58 mL, 1.1 mmol, 1.0 equiv.) was added via syringe. This mixture was allowed to stir at room temperature for 20 minutes, then the solvent

was carefully removed under vacuum. The vial was returned to the glovebox, and diluted to 1.1 mL with THF-*d8* (1.0 M solution).

B) Preparation of the PhOTf solution

To a volumetric flask in an Ar-filled glovebox was added phenyl trifluoromethanesulfonate (273.7 mg, 1.21 mmol). This was then diluted to 1.1 mL with THF-*d8* (1.1 M solution).

C) Preparation of the catalyst solution

To an oven-dried 2-dram vial with stir bar in an Ar-filled glovebox was added Palladium (II) acetate (2.7 mg, 12 μmol) and 1.2 mL THF-*d8*. To this solution was added **1.30** (15.2 mg, 14.4 μmol), and the solution was stirred for 20 minutes in the glovebox prior to using it.

D) General procedure for conducting the reaction

To an oven-dried J. Young tube in the glovebox was added 'ate' complex solution (0.2 mL, 0.2 mmol, 1.0 equiv.), PhOTf solution (0.2 mL, 0.22 mmol, 1.1 equiv.), catalyst solution (0.2 mL, 2.0 μmol, 0.01 equiv.), and THF-*d8* (0.2 mL). The tube was sealed with a screw cap and placed into an NMR probe which was preheated to 60 ºC (calibrated with ethylene glycol standard). A ^{1}H NMR spectrum was then obtained every 5 minutes for 1 hour.

1.5X 'ate' complex experiment was conducted according to General Procedure with 'ate' complex solution (0.3 mL, 0.3 mmol), PhOTf solution (0.2 mL, 0.22 mmol), catalyst solution (0.2 mL, 2.0 μmol), and THF-*d8* (0.1 mL).

1.5X PhOTf experiment was conducted according to General Procedure with 'ate' complex solution (0.2 mL, 0.2 mmol), PhOTf solution (0.3 mL, 0.33 mmol), catalyst solution (0.2 mL, 2.0 μmol), and THF-*d8* (0.1 mL).

2X catalyst experiment was conducted according to General Procedure with 'ate' complex solution (0.2 mL, 2.0 mmol), PhOTf solution (0.2 mL, 0.22 mmol), and catalyst solution (0.4 mL, 4.0 μmol).

Figure 1.4. Sample ^{1}H NMR spectra from kinetics experiments.

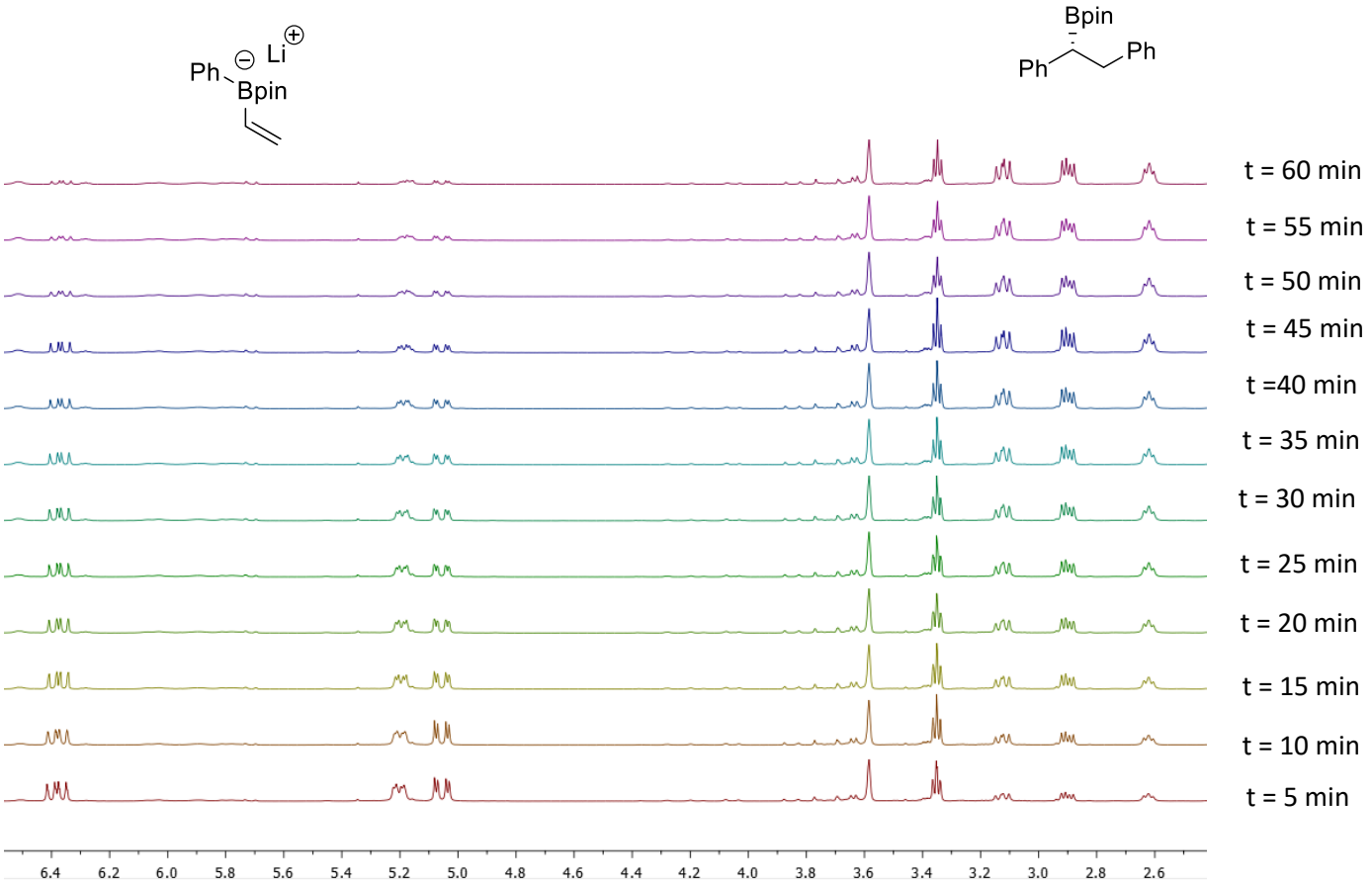
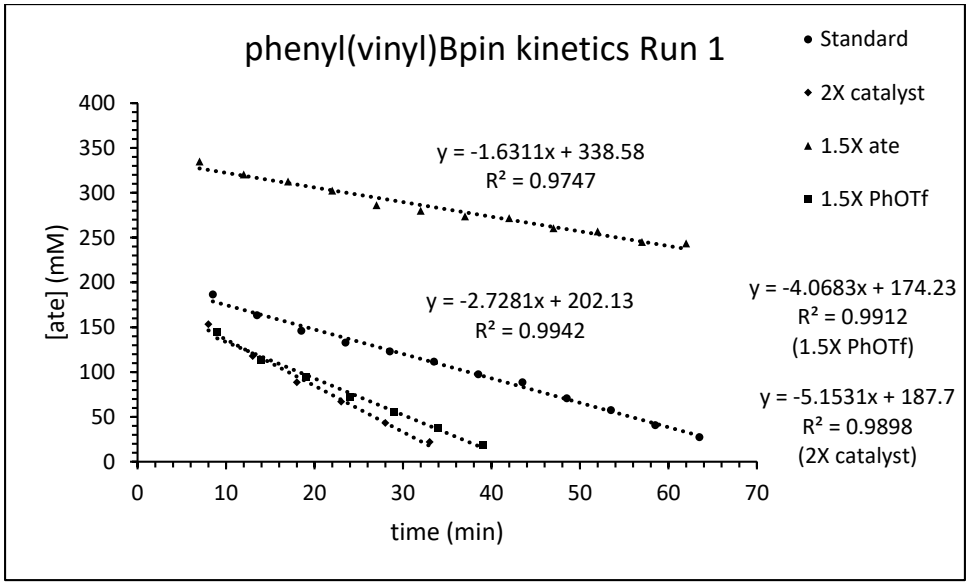
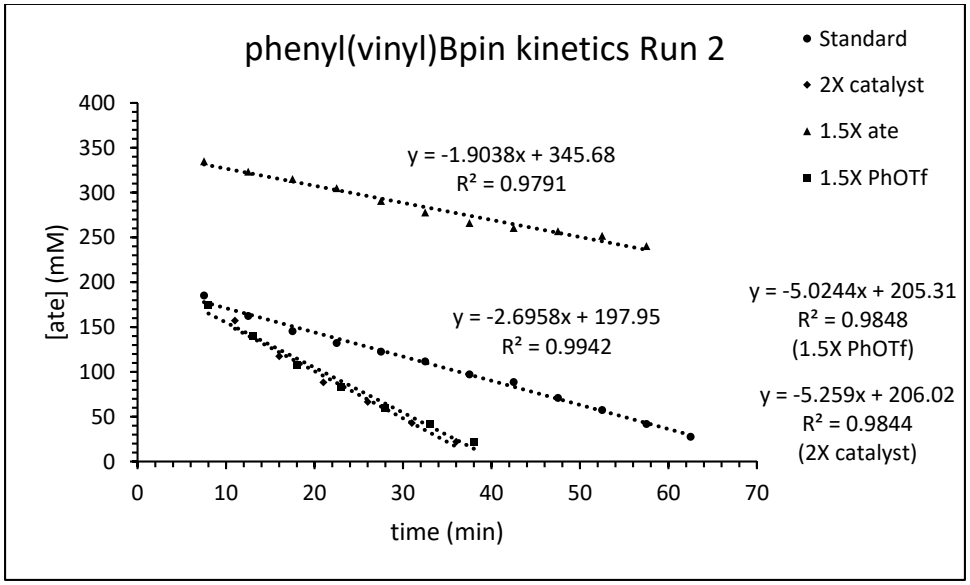
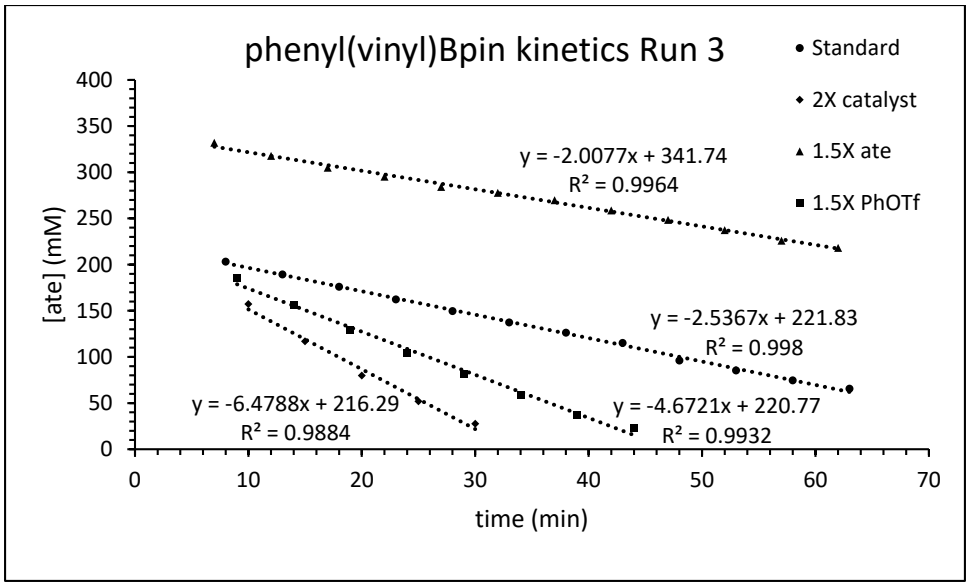


Figure 1.5. Plot of [‘ate’] vs. time for the conjunctive coupling with phenyl(vinyl)Bpin and phenyltriflate (run in triplicate).







1.4.2.2. Observation of (Mandyphos)Pd(0)-'ate' by ^{31}P NMR

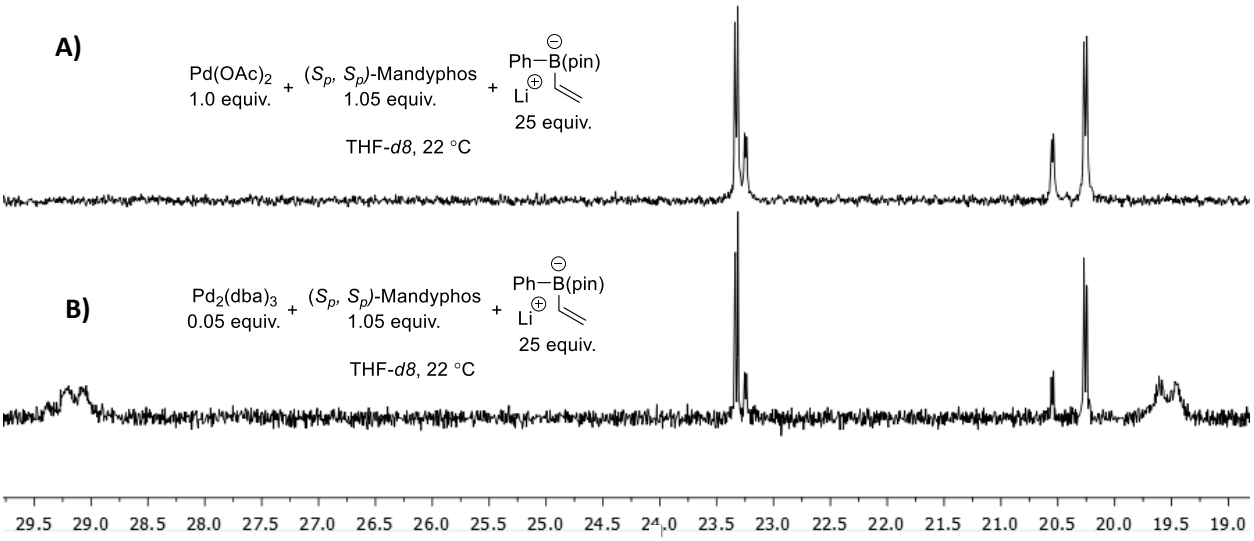
A) Preparation from $Pd(OAc)_2$

To an oven-dried 2-dram vial with stir bar in an Ar-filled glovebox was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.) and 0.2 mL Et_2O. The vial was sealed was a septum cap and removed from the glovebox. The reaction was cooled to 0 ºC, then phenyllithium (1.9 M in dibutyl ether, 0.11 mL, 0.2 mmol, 1.0 equiv.) was added dropwise via syringe. The reaction was allowed to stir at room temperature for 20 minutes then the solvent was carefully removed under vacuum. The vial was returned to the glovebox. To a separate 2-dram vial with stir bar in the glovebox was added palladium (II) acetate (1.80 mg, 8.0 µmol, 0.04 equiv.), 0.8 mL THF-*d8*, and **1.30** (8.9 mg, 8.4 µmol, 0.042 equiv.). This solution was allowed to stir for 20 min, then added to the 'ate' complex vial, and this mixture were transferred to an NMR tube, which was sealed with a cap. A ^{31}P NMR spectrum was obtained (Figure 1.6.A). ^{31}P NMR (202 MHz, THF-d8) δ 34.21 (not resolved), 23.33 (d, J = 5.1 Hz), 23.25 (d, J = 3.5 Hz), 20.55 (d, J = 3.8 Hz), 20.26 (d, J = 5.1 Hz), 16.85 (not resolved).

B) Preparation from $Pd_2(dba)_3$

To an oven-dried 2-dram vial with stir bar in an Ar-filled glovebox was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.) and 0.2 mL Et_2O. The vial was sealed was a septum cap and removed from the glovebox. The reaction was cooled to 0 ºC, then phenyllithium (1.9 M in dibutyl ether, 0.11 mL, 0.2 mmol, 1.0 equiv.) was added dropwise via syringe. The reaction was allowed to stir at room temperature for 20 minutes then the solvent was carefully removed under vacuum. The vial was returned to the glovebox. To a separate 2-dram vial with stir bar in the glovebox was added tris(dibenzylideneacetone)dipalladium(0) (3.66 mg, 4.00 umol, 0.02 equiv.) 0.8 mL THF-d_8, and **1.30** (8.9 mg, 8.4 µmol, 0.042 equiv.). This solution was allowed to stir for 20 min, then added to the 'ate' complex vial, and this mixture was transferred to an NMR tube, which was sealed with a septum cap. After 6 hours at room temperature, a ^{31}P NMR spectrum was obtained (Figure 1.6.B). ^{31}P NMR (202 MHz, THF-d_8) δ 29.14 (not resolved), 23.32 (d, J = 4.8 Hz), 23.24 (d, J = 3.3 Hz), 20.55 (d, J = 3.8 Hz), 20.26 (d, J = 4.8 Hz), 19.60 (not resolved), -21.94 (s).

Figure 1.6. ^{31}P NMR spectra of A) 4% $Pd(OAc)_2$ / Mandyphos stirred with 0.2 mmol ate complex in THF-d_8 for 15 minutes at room temperature, and B) 2% $Pd_2(dba)_3$ / Mandyphos stirred with 0.2 mmol 'ate' complex in THF-d8 for 6 h at room temperature.

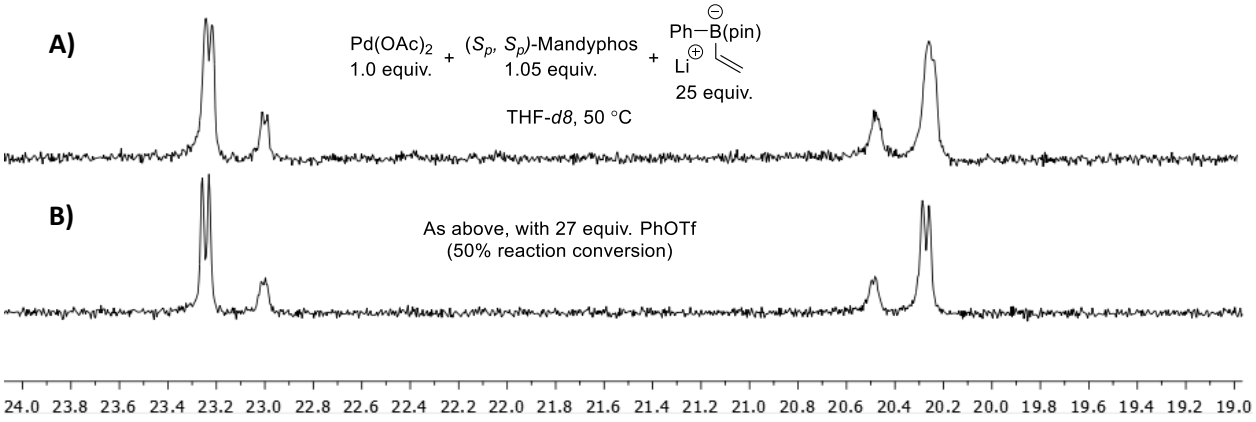


1.4.2.3. Observation of the catalyst resting state

To an oven-dried 2-dram vial with stir bar in an Ar-filled glovebox was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.) and 0.2 mL Et_2O. The vial was sealed was a septum cap and removed from the glovebox. The reaction was cooled to 0 ºC, then phenyllithium (1.9 M in dibutyl ether, 0.11 mL, 0.2 mmol, 1.0 equiv.) was added dropwise via syringe. The reaction was allowed to stir at room temperature for 20 minutes then the solvent was carefully removed under vacuum. Vial was brought back into the glovebox. To a separate 2-dram vial with stir bar in the glovebox was added palladium (II) acetate (1.80 mg, 8.0 µmol, 0.04 equiv.), 0.8 mL THF-d_8, and **1.30** (8.9 mg, 8.4 µmol, 0.042 equiv.). This solution was allowed to stir for 20 min, then added to the 'ate' complex vial, and this mixture was transferred to an NMR tube, which was sealed with a septum cap. A ^{31}P NMR spectrum was obtained at 50 ºC (Figure

1.7.A). ^{31}P NMR (202 MHz, THF-d_8) δ 23.23 (d, J = 5.6 Hz), 23.00 (d, J = 4.1 Hz), 20.48 (not resolved), 20.26 (not resolved). Phenyl trifluoromethanesulfonate (0.036 mL, 0.22 mmol, 1.1 equiv.) was added via syringe through the septum cap. The NMR tube was placed back into the NMR probe at 50 ºC for 30 minutes, and the ^{1}H NMR spectrum indicated approximately 50% conversion of 'ate' complex to the conjunctive cross-coupling product, before another ^{31}P NMR spectrum was obtained (Figure 1.7.B). ^{31}P NMR (202 MHz, THF-d_8) δ 23.25 (d, J = 5.8 Hz), 23.01 (not resolved), 20.50 (not resolved), 20.28 (d, J = 5.6 Hz).

Figure 1.7. ^{31}P NMR spectra of A) 0.2 mmol ate complex with 4% Pd(OAc)$_2$ / Mandyphos at 50 C in 0.8 mL THF-d8, and B) the same mixture after 0.22 mmol PhOTf (NMR at 50% conversion).



Chapter 2

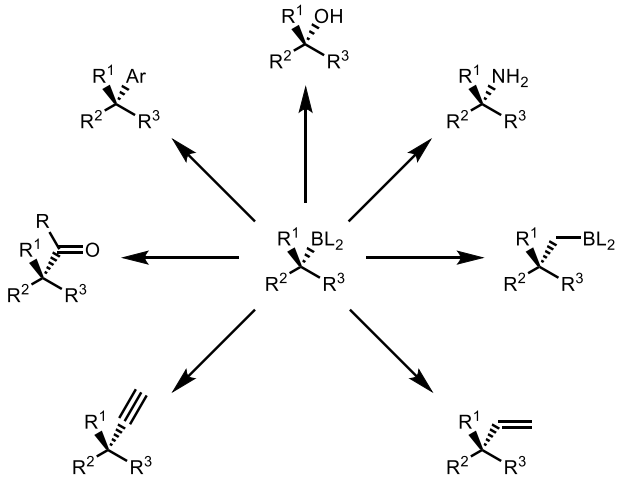
The Enantioselective Construction of Tertiary Boronic Esters by Conjunctive Cross-Coupling

2.1. Introduction

The enantioselective synthesis of fully-substituted stereocenters remains a challenge in organic synthesis.[1] The bond-forming reaction is inherently difficult due to the steric encumbrance in the transition state, and the lack of structural bias in the substrate often results in poor enantioselectivity for the reaction.[2] A practical solution to this problem is to utilize tertiary boronates as intermediates for the synthesis of a variety of fully-substituted stereocenters.[3] Due to the array of transformations available to tertiary organoboronates, these motifs offer an efficient inroad to the asymmetric synthesis of tertiary alcohols, α-tertiary amines, and all-carbon quaternary centers (Scheme 2.1).[4]

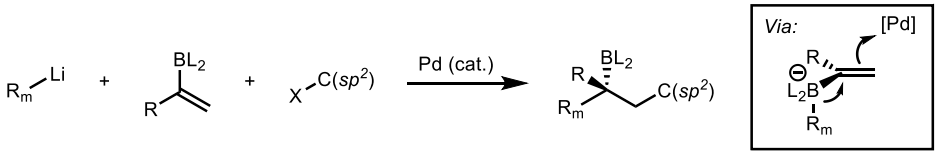
[1] Liu, Y.; Han, S.; Liu, W.; Stoltz, B. M. *Acc. Chem. Res*. **2015**, *48*, 740–751. b) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181–191.
[2] Christoffers, J.; Baro, A. Eds., Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis (John Wiley & Sons, 2006).
[3] Scott, H. K.; Aggarwal, V. K. *Chem. Eur. J.* **2011**, *17*, 13124–13132.
[4] Sandford, C.; Aggarwal, V. K. *Chem. Commun*. **2017**, *53*, 5481–5494.

Scheme 2.1. Transformations of tertiary boronates



Current methods for the asymmetric synthesis of tertiary boronates are limited to a few classes of transformations.[5] While these reactions provide efficient access to certain tertiary boronates, the transformations are often limited in scope. The synthesis of tertiary boronates by the conjunctive cross-coupling reaction (Scheme 2.2) would complement the current synthetic methods by providing access to structural motifs which are not attainable by current synthetic methods. Furthermore, the starting materials for this process are relatively simple, such that a broad array of products can be obtained in minimal synthetic steps.

Scheme 2.2. Synthesis of tertiary boronates by the conjunctive cross-coupling reaction



The mechanism of the conjunctive cross-coupling reaction is proposed to involve a Pd-induced 1,2-metallate rearrangement step (Scheme 2.2, inset). Such a reaction bears resemblance

[5] Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11700–11733.

to other *anti*-nucleopalladation reactions, which are not effective for 1,1-disubstituted alkene substrates.[6] Based on the kinetic data presented in Chapter 1, the 1,2-metallate rearrangement occurs by a relatively low energetic barrier, presumably due to its intramolecular nature. Therefore, the added alkene substitution may not completely inhibit the reaction, insofar as the competing transmetallation between the Pd^{II} oxidative addition adduct and the boron 'ate' complex does not occur instead. The following chapter will discuss the development of the conjunctive cross-coupling reaction for the synthesis of tertiary boronates, and its application to target-oriented synthesis.

2.2. Background

2.2.1 Synthesis of enantioenriched tertiary boronic esters

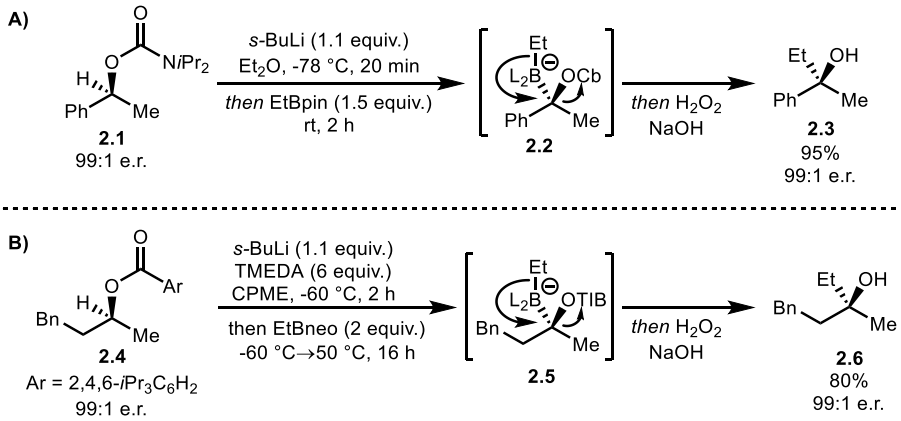
2.2.1.1 Lithiation–borylation

Addressing the challenge of tertiary boronate construction, the Aggarwal group has used a lithiation–borylation strategy.[7] Readily-available enantioenriched secondary alcohols are converted into the corresponding *N*,*N*-diisopropylamino carbamate, which enables lithiation of the α-proton of **2.1** and also imparts configurational stability on the corresponding chiral organolithium species (Scheme 2.3.A). Subsequent addition of the organolithium reagent to an organoboronic ester forms a boron 'ate' complex (**2.2**), and upon warming the reaction to room temperature, the 1,2-metallate rearrangement yields the tertiary alcohol **2.3** after oxidation. The lithiation-borylation reaction was subsequently improved by adding magnesium bromide and methanol to the reaction.[8] A limitation of this method is that the lithiation of secondary

[6] Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, 102, 4973–4979.
[7] Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature*, **2008**, *456*, 778–782.
[8] Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5142–5145.

carbamates only occurs for substrates with an anion-stabilizing (i.e. phenyl) group to activate the acidic proton. However, modifying the deprotonation conditions allows for the use of unactivated secondary TIB benzoates (**2.4**) as substrates for the lithiation–borylation procedure to yield tertiary alcohol **2.6** (Scheme 2.3.B).[9] Of note, the 1,2-metallate rearrangement with a TIB-benzoate leaving group requires elevated temperatures.

Scheme 2.3. Synthesis of tertiary boronates by lithiation–borylation



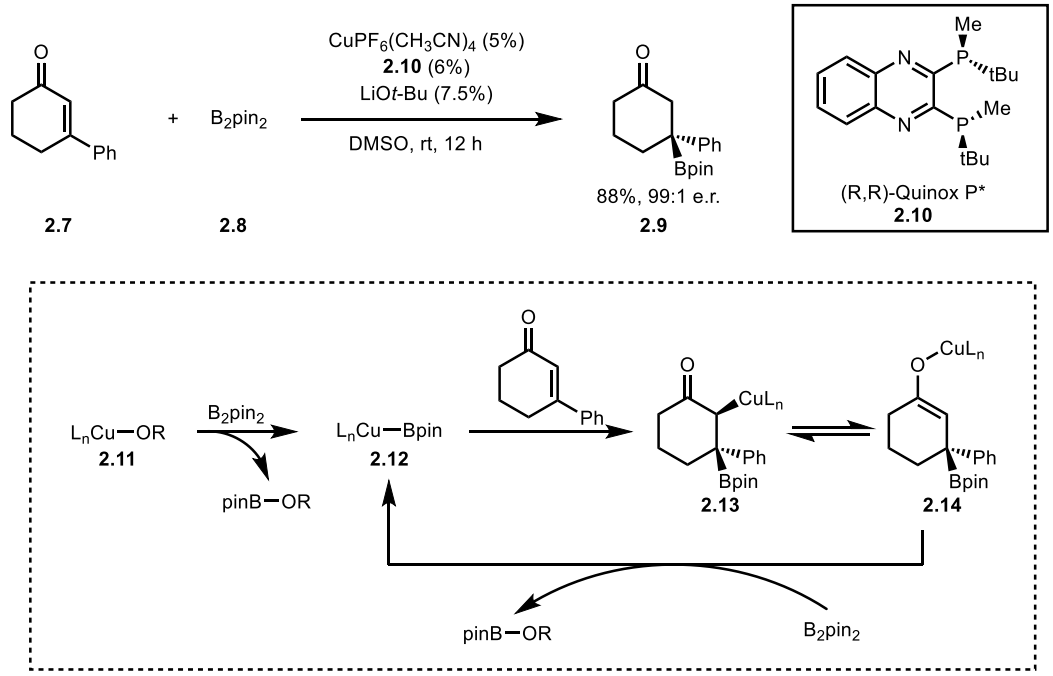
2.2.1.2 Conjugate borylation

An alternative approach for synthesis of nonracemic tertiary organoboronates is by catalytic, asymmetric methods. This is appealing because either enantiomer of the product is selectively accessed from the same set of starting materials depending on the choice of the chiral ligand. The first example of the catalytic, asymmetric synthesis of tertiary boronates was reported by the Shibasaki group by a borylative addition to an α,β-unsaturated ketone (Scheme 2.4).[10] Cyclic enone **2.7** undergoes conjugate borylation in the presence of a copper-based catalyst with QuinoxP* (**2.10**) as the chiral ligand, and B_2pin_2 (**2.8**) as the boron source to yield protoboration

[9] Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054–16057.
[10] Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2009**, *131*, 11664–11665.

product **2.9**. The reaction proceeds by the formation of a Cu^{I} alkoxide (**2.11**) which transmetallates with B_2pin_2 to form boryl–copper intermediate **2.12**, and subsequent β-migratory insertion into the α,β-unsaturated ketone to generates a copper enolate **2.13** or **2.14**. Next, the Cu^{I}–enolate transmetallates with B_2pin_2 to regenerate boryl–copper intermediate **2.12** along with the product as a boron enolate. The reaction is most efficient in polar, aprotic solvents such as DMF or DMSO; protic additives such as methanol are detrimental. The presence of a lithium cation is also beneficial for the reaction, as lithium *tert*-butoxide leads to higher yields than the corresponding sodium or potassium salts. Lastly, the use of $CuPF_6(CH_3CN)_4$ as a precatalyst is optimal due to the *in situ* formation of $LiPF_6$, which accelerates the reaction.

Scheme 2.4. Conjugate borylation reaction of cyclic enone substrates

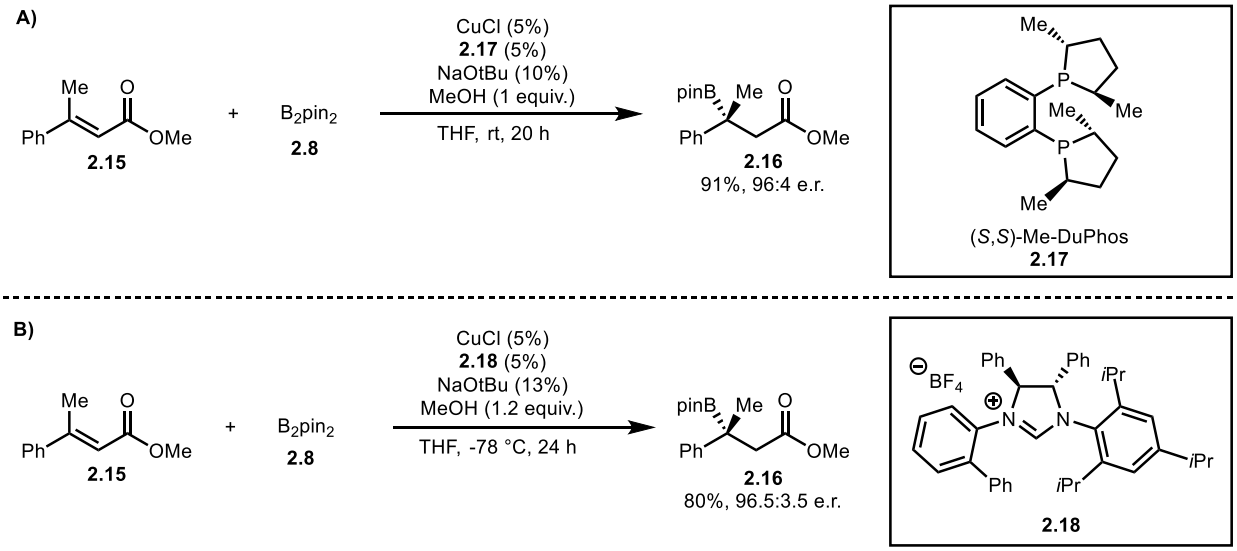


Shortly after Shibasaki's studies, the asymmetric conjugate borylation of acyclic α,β-unsaturated ester substrates was reported by the Yun group (Scheme 2.5.A).[11] Substrate **2.15** is transformed to β-boryl ester **2.16** using a combination of CuCl and a DuPhos supporting ligand (**2.17**). THF is the best solvent for this reaction, and sodium *tert*-butoxide is used as the catalytic base. Notably, this reaction employs methanol as a protic additive, which facilitates catalyst turnover by protonating the copper enolate intermediate to form a more-reactive copper alkoxide.

A similar method to Yun's was developed contemporaneously by the Hoveyda group (Scheme 2.5.B).[12] The reaction conditions are almost identical to the those of the previous example, with the exception that a N-heterocyclic carbene (**2.18**) is used rather than a bis(phosphine) as the ancillary ligand ligand. The reaction is typically conducted at –78 °C, but can proceed in the absence of methanol at 4 °C, yielding the boron enolate as the reaction product. In addition to ester substrates, ketone and thioester substrates also effectively participate in the reaction. Sterically hindered alkene substrates are not tolerated in the reaction and the major byproduct is the conjugate reduction product.

[11] Feng, X.; Yun, J. *Chem.-Eur. J.* **2010**, *16*, 13609–13612.
[12] O'Brien, J. M.; Lee, K. S.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2010**, 132, 10630-10633.

Scheme 2.5. Conjugate borylation reaction of acyclic alkene substrates

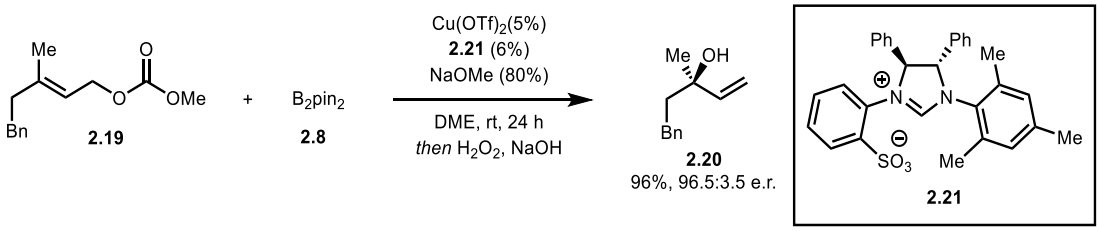


2.2.1.3 Allylic borylation

Tertiary organoboronates have also been synthesized by the borylative substitution of allylic carbonates, as developed by the Hoveyda group (Scheme 2.6).[13] Similar to the conjugate borylation reaction, the allylic borylation of **2.19** employs a Cu and NHC (**2.21**) catalytic system, along with an alkoxide base and B_2pin_2 (**2.8**). Tertiary alcohol **2.20** is isolated in excellent yield and enantiopurity after the allylic substitution reaction and subsequent oxidation. Notably, the reaction employs a Cu^{II} precatalyst which is reduced *in situ* to Cu^{I} under the reaction conditions. The overall reaction proceeds with exclusive S_N2' regioselectivity, and in excellent yield and enantioselectivity for a variety of substrates. For substrates that are sterically hindered, the enantioselectivity of the reaction is diminished and a significant amount of the regioisomeric S_N2 product is observed. The change in regioselectivity for the reaction is possibly due to an alternative mechanism in which Cu^{III}–π-allyl intermediate is formed, as suggested by the authors.

[13] Guzman-Martinez, A.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2010**, 132, 10634–10637.

Scheme 2.6. Allylic borylation reaction

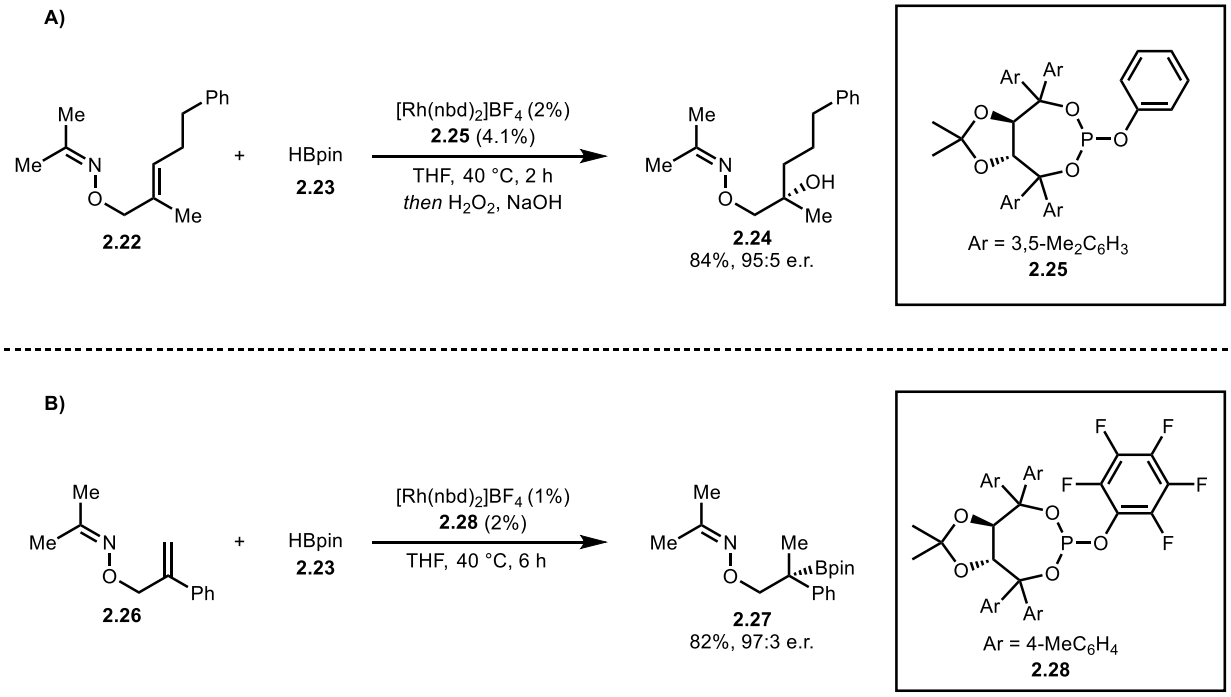


2.2.1.4 Hydroboration

The catalytic, asymmetric hydroboration reaction has emerged as a useful method for the synthesis of tertiary boronates. In this regard, the Takacs group has used a Rh-based catalytic system to develop an oxime-directed asymmetric hydroboration of substrates with alkyl-[14] and aryl-substituted[15] alkenes (Scheme 2.7). Alkene **2.22** is converted into tertiary alcohol **2.24** by hydroboration with a cationic Rh^I catalyst in a regio- and enantioselective manner followed by oxidation. The chiral ligand is a TADDOL-based phosphite (**2.25**), and pinacolborane (**2.23**) is used as the hydroborating reagent. Using a modified phosphite ligand (**2.28**) under similar reaction conditions, 1,1-disubstituted alkene **2.26** is converted into tertiary boronate **2.27**. The predominant byproducts of this reaction result from alkene hydrogenation or the undesired regioisomeric hydroboration reaction. Notably, the regioselectivity for the reaction is highly sensitive to the nature of the phosphite ligand and the directing group.

[14] Shoba, V. M.; Thacker, N. C.; Bochat, A. J.; Takacs, J. M. *Angew. Chem., Int. Ed*. **2016**, *55*, 1465–1469.
[15] Bochat, A. J.; Shoba, V. M.; Takacs, J. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 9434–9438.

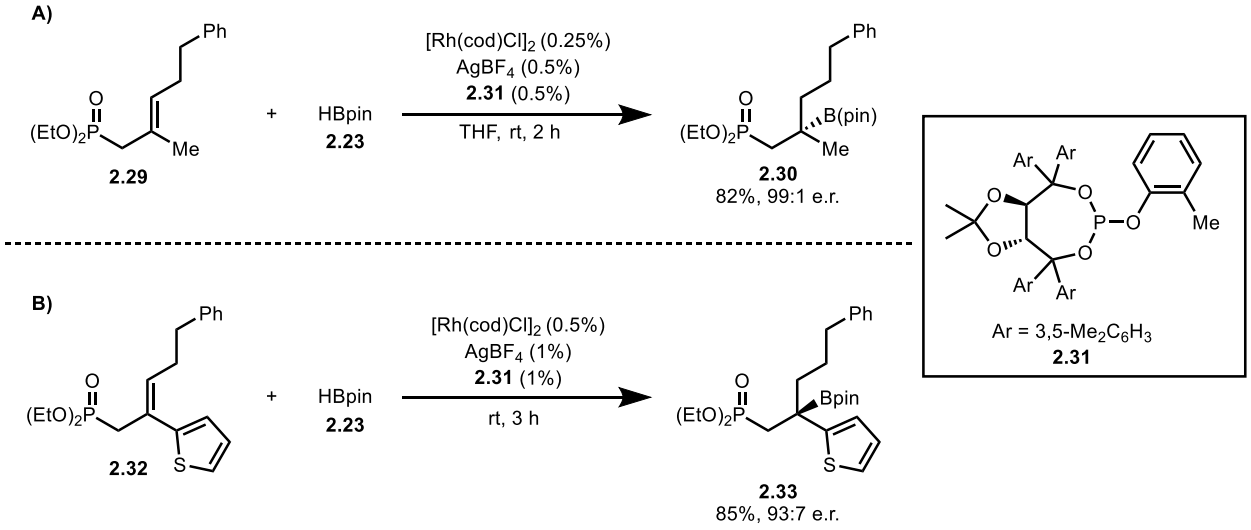
Scheme 2.7. Oxime-directed catalytic asymmetric hydroboration reaction



The catalytic, asymmetric hydroboration of alkyl-[16] and aryl-substituted[17] alkene substrates is also enabled by a phosphonate group directing group (Scheme 2.8). This reaction employs very similar reaction conditions to the oxime-directed hydroboration reactions, albeit with a different phosphite ligand (**2.31**). Alkene **2.29** is converted into tertiary boronate **2.30**, and alkene **2.32** is converted into **2.33**. As in the oxime-direct hydroboration reactions, the major byproducts are the regioisomeric hydroboration product and the alkene hydrogenation product.

[16] Chakrabarty, S.; Takacs, J. M. *J. Am. Chem. Soc*. **2017**, *139*, 6066–6069.
[17] Chakrabarty, S.; Takacs, J. M. *ACS Catal*. **2018**, *8*, 10530–10536.

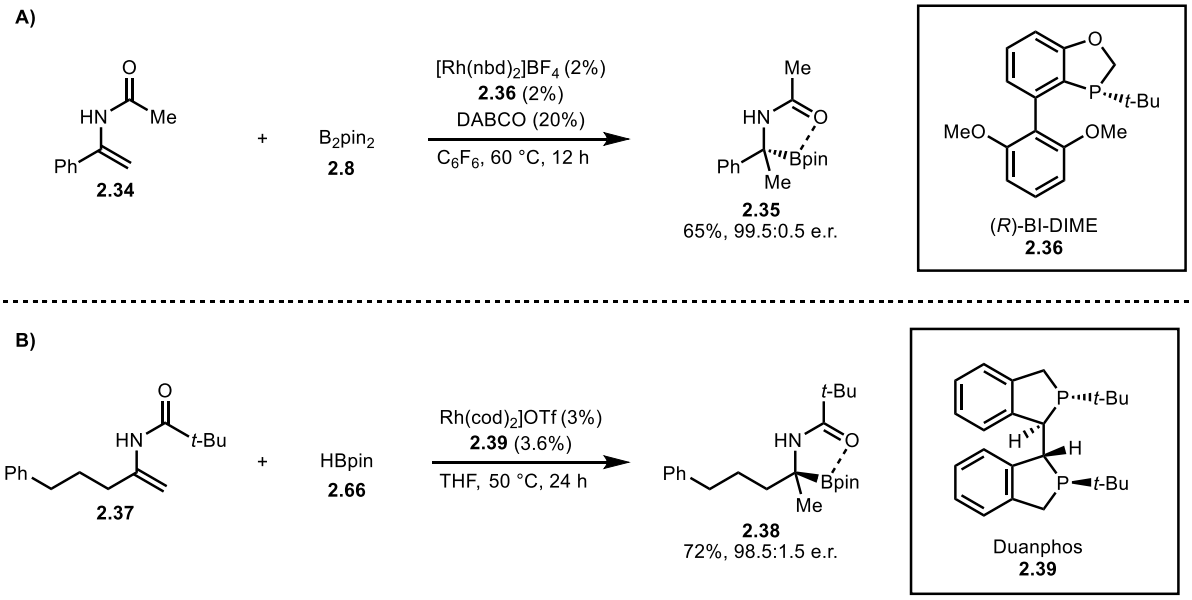
Scheme 2.8. Phosphonate-directed catalytic, asymmetric hydroboration reaction



The Tang group developed an asymmetric hydroboration reaction of aryl-substituted enamide substrates to generate α-amino tertiary boronates with high levels of enantiopurity (Scheme 2.9.A).[18] Enamide (**2.34**) is converted into tertiary boronate (**2.35**) using a cationic rhodium catalyst with a P-chiral, monodentate phosphine ligand (**2.36**). The boron reagent is B_2pin_2 (**2.8**), and the N–H bond of the amide is necessary for the reaction to occur. Additionally, only aryl-substituted enamides participate in the reaction. The major byproducts of the reaction are the diboration product, reduction product, and regioisomeric hydroboration product. The addition of a Lewis base, such as DABCO, improves the chemoselectivity of the reaction.

[18] Hu, N.; Zhao, G.; Zhang, U.; Liu, X.; Li, G.; Tang, W. *J. Am. Chem. Soc*. **2015**, *137*, 6746–6749.

Scheme 2.9. Catalytic, asymmetric hydroboration of enamides



A similar enamide hydroboration reaction was recently reported by the Li group (Scheme 2.9.B).[19] In this reaction, both alkyl- and aryl-substituted enamides are tolerated as substrates, and the reaction is highly enantioselective. A cationic rhodium complex with a Duanphos ligand (**2.39**) catalyzes the hydroboration of **2.37** in the presence of pinacolborane (**2.23**), yielding tertiary boronate **2.38**. The pivaloyl amide directing group is optimal in terms of yield and regioselectivity, and the free N–H of the amide is necessary for the desired reaction to occur.

2.3. Conjunctive cross coupling reaction to generate tertiary boronates[20]

2.3.1. Conjunctive cross-coupling reaction development

The enantioselective synthesis of tertiary boronates can be achieved by the conjunctive cross-coupling reaction using an α-substituted alkenyl boron 'ate' complex. Based on the kinetics

[19] Bai, X.-Y.; Zhao, W.; Sun, X. Li, B.-J. *J. Am. Chem. Soc*. **2019**, *141*, 19870–19878.
[20] Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed*. **2018**, *57*, 12799–12803.

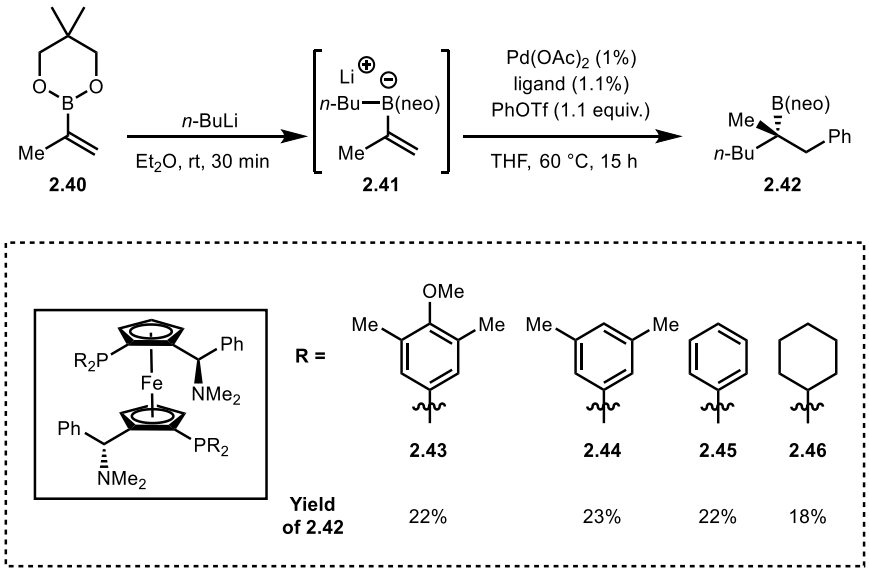
of this reaction as discussed in Chapter 1, the additional alkene substituent is not expected to decrease the catalytic efficiency, as oxidative addition is the turnover-limited step. In fact, the disubstituted alkene substrate might experience increased catalytic efficiency due to the less-favorable formation of the inactive Pd^0–alkene complex resting state. However, some challenges were anticipated in developing this reaction. Related *anti* nucleopalladation reactions through the intermediacy of Pd^{II}–alkene complexes are not effective for 1,1-disubstituted alkenes.[6] Furthermore, even if palladium can activate the alkene, steric hindrance at the migration terminus can disfavor the 1,2-metallate rearrangement[8] and allow other reaction pathways, such direct transmetallation to predominate. Lastly, the added alkene substituent might decrease the ability of the catalyst to distinguish the prochiral faces of the alkene, resulting in diminished enantioselectivity.

Since the neopentyl glycol (neo) ligand on boron is optimal for the reaction with unsubstituted vinylboron 'ate' complexes,[21] the 'ate' complex **2.41**, derived from isopropenylB(neo) (**2.40**) and *n*-BuLi, was subjected to the standard conjunctive cross-coupling conditions (Scheme 2.10). Treatment with $Pd(OAc)_2$ (1%), **2.43** (1.1%), and phenyltriflate at 60 °C for 15 hours delivered the conjunctive coupling product **2.42** in 22% isolated yield. The reaction proceeds to full conversion of the boron 'ate' complex, and the low yield is due to poor chemoselectivity for the reaction. Specifically, the Suzuki–Miyaura cross-coupling products with either organic group on boron coupled to the electrophile are obtained in 70% combined yield. Therefore, the α-substituent of the alkene likely disfavors the necessary activation of the alkene by the catalytic Pd^{II} oxidative addition adduct. To solve this problem, Mandyphos ligands with different substituents on phosphorous were investigated (Scheme 2.10). However, ligands **2.44**,

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

2.45, and **2.46** did not improve the chemoselectivity of the reaction and resulted in similar levels of reactivity.

Scheme 2.10. Mandyphos ligand investigation for B(neo) 'ate' complex

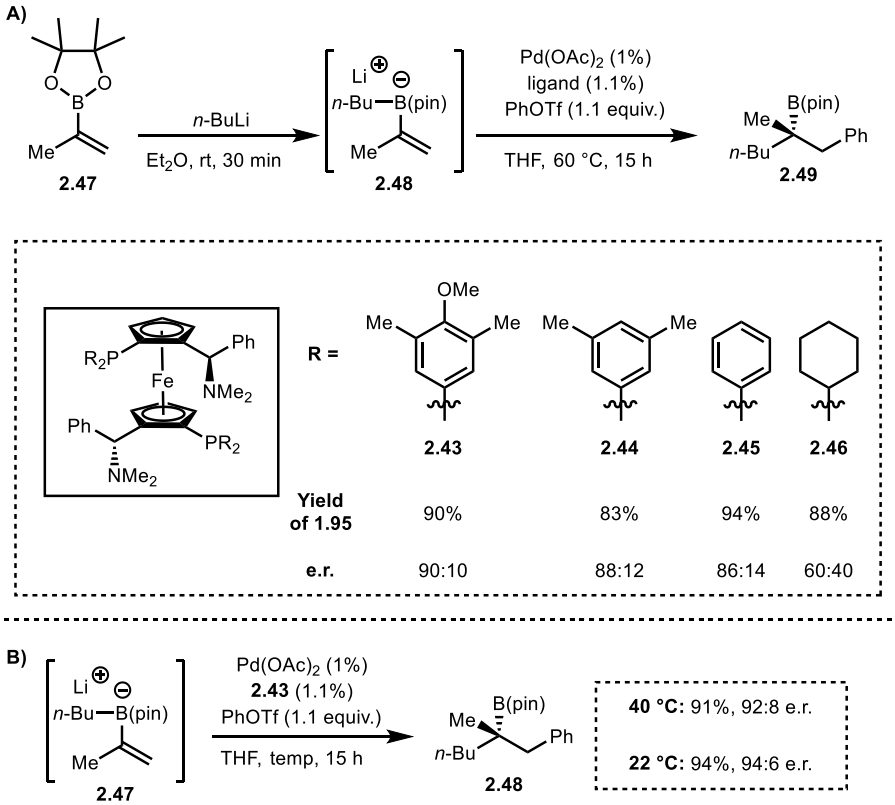


Next, we considered that the Suzuki–Miyaura reaction might occur via an intermediate in which Pd^{II} coordinates to the oxygen atom of the boron ligand in the 'ate' complex,[22] as this sort of intermediate has been implicated in recent studies.[23] This hypothesis was tested by switching from a neopentyl glycol ligand on boron to a bulkier pinacol ligand in which the oxygen atoms have diminished Lewis basicity due to steric hindrance. Thus, the 'ate' complex **2.48** was employed in the conjunctive cross-coupling reaction, resulting in high levels of chemoselectivity, with the desired product (**2.49**) being isolated in 90% yield and 90:10 enantiomeric ratio (Scheme 2.11). In order to improve the enantioselectivity of the reaction, other Mandyphos ligands (**2.44**, **2.45**, and **2.46**) were investigated, but none increased the enantioselectivity of the reaction

[22] See Chapter 3 for a detailed discussion.
[23] (a) Thomas, A. A.; Denmark, S. E. *Science* **2016**, *352,* 329–332. (b) Thomas, A. A.; Wang, H.; Zahrt, A. F.; Denmark, S. E. *J. Am. Chem. Soc.* **2017**, *139,* 3805–3821. (c) Thomas, A. A.; Zahrt, A. F.; Delaney, C. P.; Denmark, S. E. *J. Am. Chem. Soc.* **2018**, *140,* 4401–4416.

(Scheme 2.11.A). On the other hand, conducting the reaction at a lower temperature was effective in increasing the enantioselectivity of the reaction; at room temperature (22 °C) the reaction is sluggish, but the product was isolated in 94% yield and 94:6 e.r. after 15 hours (Scheme 2.11.B). Notably, at lower temperatures, the chemoselectivity of the reaction improves, and the reaction pathway favors the conjunctive cross-coupling product rather than the Suzuki–Miyaura cross-coupling product.

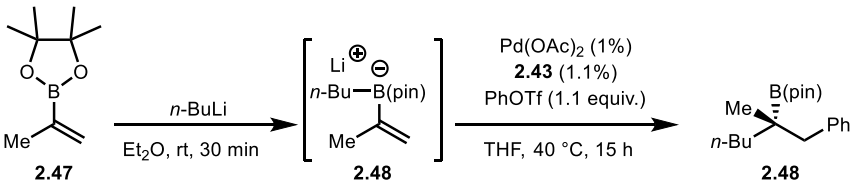
Scheme 2.11. Reaction optimization for B(pin) 'ate' complex



Further reaction optimization focused on investigating solvent effects for the reaction. The reactions in certain solvents did not proceed to completion at room temperature, and thus, all reactions were conducted at 40 °C to ensure an effective comparison between the solvents. According to the data presented in Table 2.1, there is an approximate relationship between the

yield of the product and the Lewis basicity of the solvent.[24] Solvents such as THF and dioxane are highly effective (Table 2.1, Entry 1–2), whereas both less-coordinating ethereal solvents (Table 2.1, Entry 3–5) and highly Lewis basic solvents (Table 2.1, Entry 9–12) result in diminished product yields. Non-coordinating solvents (Table 2.1, Entry 6–8) are particularly ineffective. The enantioselectivity of the reaction is relatively insensitive to solvent effects, with all solvents resulting in 76–84% enantiomeric excess. Overall, THF is the optimal solvent in terms of yield (91%) and enantioselectivity (92:8 e.r.) at 40 °C.

Table 2.1. Solvent optimization



Entry	Solvent	Yield	e.r.
1	THF	91%	92:8
2	Dioxane	84%	92:8
3	Et_2O	50%	88:12
4	CPME	35%	92:8
5	MTBE	24%	88:12
6	DCM	17%	91:9
7	Toluene	<5%	ND
8	Ph-CF_3	<5%	ND
9	MeCN	20%	91:9
10	DMSO	45%	90:10
11	DMF	70%	92:8
12	DMA	61%	91:9

In summary, the use of pinacol as a ligand on boron rather than neopentyl glycol results in a highly chemoselective conjunctive cross-coupling reaction. The optimal catalyst for the

[24] Maria, P.-C.; Gal, J.-F. *J. Phys. Chem*. **1985**, *89*, 1296–1304.

reaction is $Pd(OAc)_2$ (1%) with Mandyphos **2.43** (1.1%), and THF is the best reaction solvent. Lower temperatures result in increased chemoselectivity and enantioselectivity for the reaction; for certain substrates, conducting the reaction at room temperature is optimal. However, for the majority of substrates, the reaction at 40 °C is optimal in order to achieve full conversion within 15 hours. Lastly, for reactions that contain halide salts, the addition of potassium triflate (either 1 or 2 equivalents) is necessary for optimal results.[25]

2.3.2. Substrate Scope

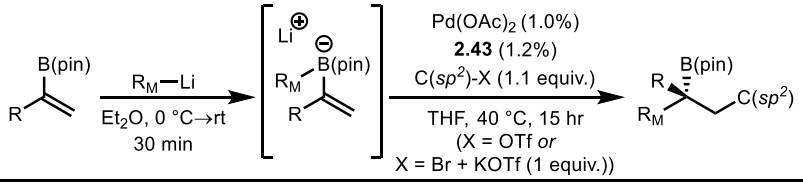
To explore the scope of this reaction, 'ate' complexes (prepared from an organolithium reagent an α-substituted alkenyl boronate) were subjected to the standard reaction conditions (Scheme 2.12). Alkyl migrating groups with varying substitution patterns are tolerated in the reaction with an isopropenyl migration terminus (**2–4**). Notably, even a highly hindered 'ate' complex with a *t*-butyl migrating group is formed efficiently, and the subsequent conjunctive cross-coupling reaction generates a product with contiguous fully-substituted carbon centers (**5**) in excellent yield. Substituted aryl groups are also competent migrating groups in the reaction (**6–8**). In addition to an isopropenyl migration terminus, other α-substituted boronic ester 'ate' complexes can be employed (**10–13**). Notably, functionalized *n*-alkyl substituents are tolerated, but an isopropyl substituent was ineffective in this reaction (not shown). In terms of the electrophile, a variety of aryl and heteroaryl groups with varying steric and electronic profiles can be incorporated into the reaction products (**9, 14–25**). Both electron-donating and electron-withdrawing groups are effective, and the reaction with an electron-deficient arene electrophile proceeds efficiently at room temperature (**20**). Sterically-hindered ortho-substituted arene

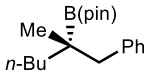
[25] For complete reaction optimization see: Zhang, L. Catalytic Conjunctive Cross-Coupling and Catalytic Diboration Reactions. Ph.D. Thesis, Boston College. May 2017.

electrophiles are also tolerated as well (**22, 24**). Lastly, highly-substituted alkenyl electrophiles (**26**) and migrating groups (**27**) can be incorporated in the products. For all these reactions, halide impurities can be tolerated if potassium triflate is added as a halide scavenger.[26]

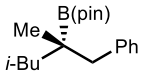
[26] Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc*. **2017**, *139*, 3153–3160.

Scheme 2.12. Substrate scope using an alkenyl boronate reagent

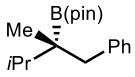




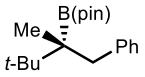
X = OTf: **2**
94%, 94:6 er[a]



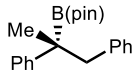
X = OTf: **3**
94%, 93:7 er



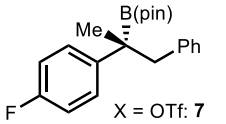
X = OTf: **4**
96%, 86:14 er



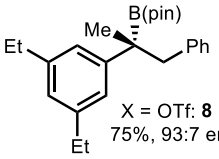
X = OTf: **5**
88%, 96:4 er



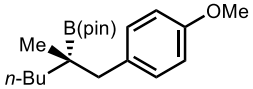
X = OTf: **6**
90%, 91:9 er



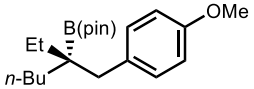
X = OTf: **7**
82%, 88:12 er



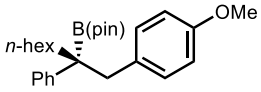
X = OTf: **8**
75%, 93:7 er



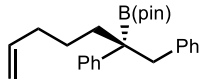
X = OTf: **9**
95%, 92:8 er



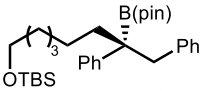
X = OTf: **10**
72%, 84:16 er



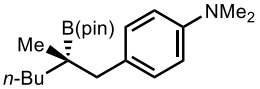
X = OTf: **11**
86%, 92:8 er[b]



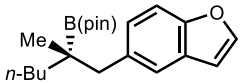
X = OTf: **12**
87%, 91:9 er[b]



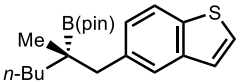
X = OTf: **13**
73%, 91:9 er[b]



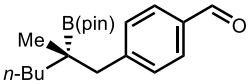
X = Br: **14**
82%, 92:8 er



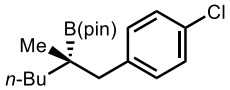
X = Br: **15**
85%, 90:10 er



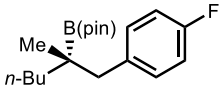
X = Br: **16**
85%, 91:9 er



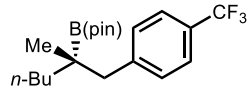
X = Br: **17**
81%, 90:10 er



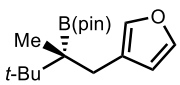
X = Br: **18**
96%, 86:14 er[b]



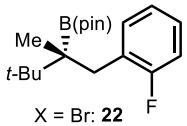
X = Br: **19**
92%, 90:10 er



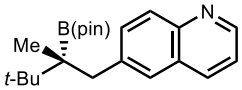
X = Br: **20**
89%, 91:9 er[a]



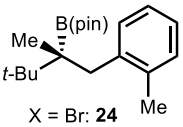
X = Br: **21**
83%, 84:16 er



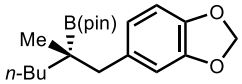
X = Br: **22**
55%, 83:17 er[a]



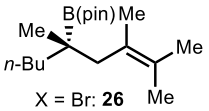
X = Br: **23**
52%, 86:14 er



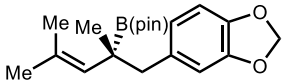
X = Br: **24**
70%, 92:8 er



X = Br: **25**
96%, 90:10 er



X = Br: **26**
75%, 88:12 er[b]

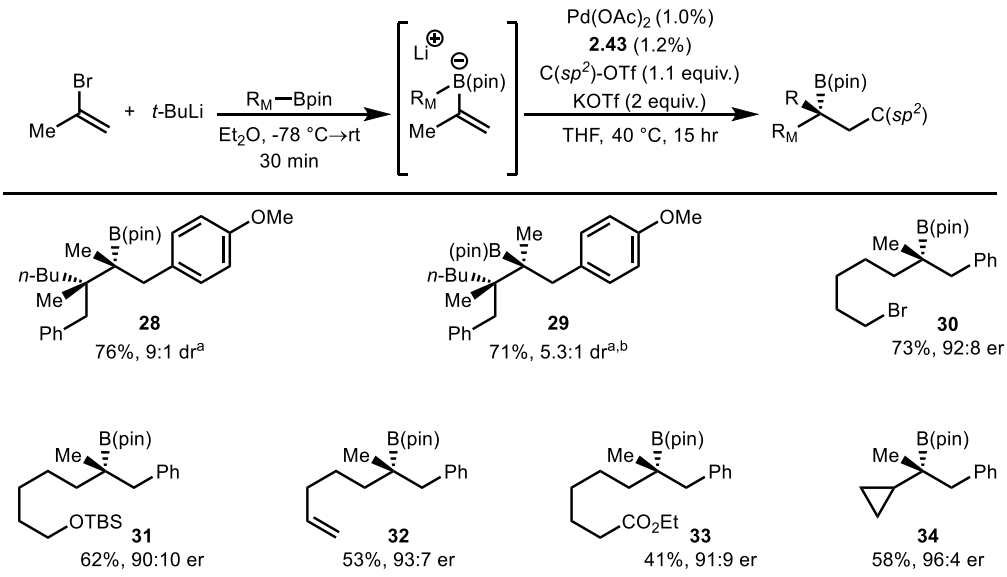


X = Br: **27**
87%, 91:9 er

[a]Reaction was conducted at 23 °C
[b]Reaction was conducted at 60 °C

In an effort to improve the synthetic utility of this method, the reaction was performed using 'ate' complexes prepared by the addition of an alkenyllithium reagent to a boronic ester (Scheme 2.13). Due to the high availability of functionalized boronic esters, this presents the opportunity to utilize a variety of migrating groups in the conjunctive cross-coupling reaction. The nonracemic tertiary boronate **2** was subjected to a consecutive conjunctive cross-coupling reaction to obtain a product with two contiguous fully-substituted carbon stereocenters (**28, 29**). Additionally, a variety of functional groups are incorporated into the migrating group, such as an alkyl bromide (**30**), a protected alcohol (**31**), an alkene (**32**), and an ester (**33**). A cyclopropyl group is also a good migrating group for this reaction (**34**). Notably, the yields of the reactions of *in situ* prepared organolithium reagents are slightly diminished, as they contain lithium halide salts which inhibit the catalyst. Overall, the conjunctive cross-coupling reaction should be a valuable tool for the efficient synthesis of functionalized tertiary boronates.

Scheme 2.13. Substrate scope using alkenyllithium reagent



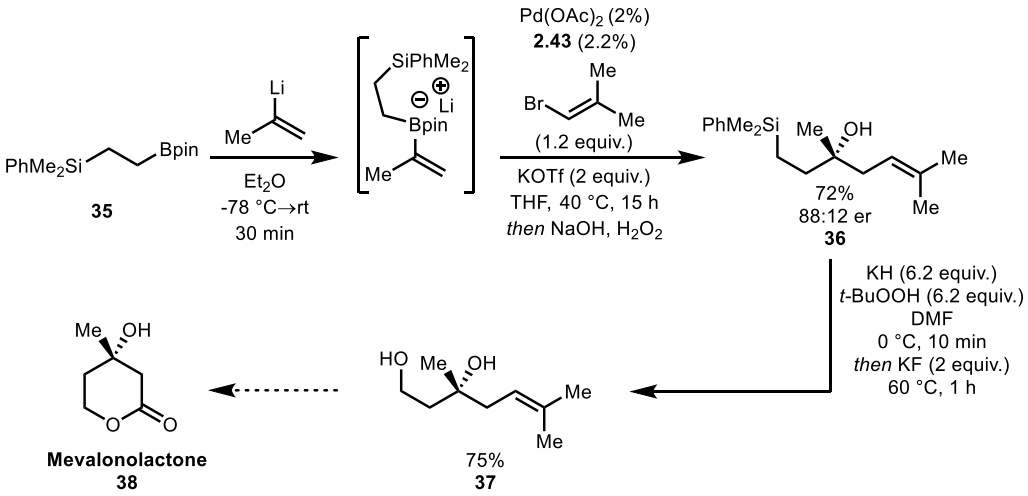
[a]Yield is overall, after two successive conjunctive cross-coupling reactions
[b]ent-**2.43** was used as the ligand

2.3.3. Target-oriented synthesis

The application of the conjunctive cross-coupling reaction is demonstrated by the construction of the biologically-active molecule mevalonolactone [27] (**38**) which contains a stereogenic tertiary alcohol (Scheme 2.14). The 1,3 diol motif of **38** can be constructed by the conjunctive cross-coupling reaction using a β-hydroxyethyl migrating group and subsequent boron oxidation. However, employing such a migrating group does not yield any desired product in the conjunctive cross-coupling reaction, possibly due the decomposition of the 'ate' complex by β-elimination.[28] An effective solution is using the 'ate' complex derived from compound **35**, which contains a silyl group as a masked hydroxyl group.[29] The conjunctive cross-coupling reaction with this 'ate' complex and an alkenyl electrophile under standard catalytic reaction conditions delivers intermediate **36** after boron oxidation in good yield and enantiomeric ratio. Next, conversion of the silyl group to a hydroxyl group by modified Tamao–Fleming oxidation[30] delivers intermediate **37**, a known precursor to **38**.[31]

[27] Scopel, M.; Abraham, W. R.; Antunes, A. L.; Terezinha Henriques, A.; Macedo, J.; Jose, A. *Med. Chem.* **2014**, 10, 246–251.
[28] (a) Matteson, D. S. *J. Organomet. Chem*. **1999**, *581*, 51–65. (b) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165–168. (c) Millán, A.; Grigol Martinez, P. D.; Aggarwal, V. K. *Chem. Eur. J.* **2018**, *24*, 730–735.
[29] Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc. Perkin Trans. 1* **1995**, 317–337.
[30] (a) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem*. **1996**, *61*, 6044–6046. (b) Reddy, P. V.; Smith, J.; Kamath, A.; Jamet, H.; Veyron, A.; Koos, P.; Philouze, C.; Greene, A. E.; Delair, P. *J. Org. Chem*. **2013**, *78*, 4840–4849.
[31] Mori, K.; Okada, K. *Tetrahedron* **1985**, *41*, 557–559.

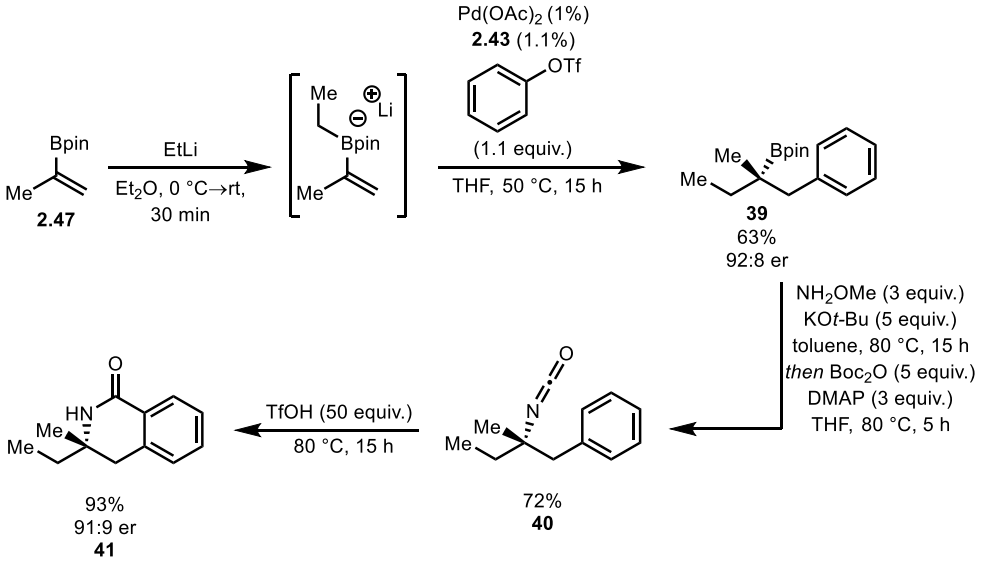
Scheme 2.14. Formal synthesis of mevalonolactone



Next, lactone **41**, which contains a stereogenic α-tertiary amine, was synthesized as an application of the conjunctive cross-coupling reaction (Scheme 2.15). This isoquinolone derivative has moderate anti-inflammatory and analgesic properties.[32] Notably, this molecule was synthesized racemically, and an enantioselective synthesis might be challenging due to the lack of steric bias between the substituents of the stereogenic center. The α-tertiary amine can be constructed by a conjunctive cross-coupling reaction, followed by amination of the resulting tertiary boronate.[33] Indeed this is accomplished using an ethyl migrating group and phenyltriflate as the electrophile in the conjunctive cross-coupling reaction to yield **39**. Subsequent boron amination and isocyanate formation efficiently constructed intermediate **40**. Lastly, **41** is synthesized by acid-promoted aromatic substitution[34] in high yield and enantiospecificity.

[32] Vikharev, Y. B.; Shklyaev, Y. V.; Anikina, L. V.; Kolla, V. É.; Tolstikov, A. G. *Pharm. Chem. J.* **2005**, *39*, 405–408.
[33] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc*. **2012**,*134*, 16449–16451.
[34] Kurouchi, H.; Kawamoto, K.; Sugimoto, H.; Nakamura, S.; Otani, Y.; Ohwada, T. *J. Org. Chem*. **2012**, *77*, 9313–9328.

Scheme 2.15. Synthesis of analgesic agent 41



2.3.4. Conclusion

The conjunctive cross-coupling reaction of an α-substituted alkenyl boron 'ate' complex was investigated, and it was found that the Suzuki-Miyaura cross-coupling reaction is the dominant reaction pathway for this substrate class. However, the conjunctive cross-coupling reaction can be favored by using a bulky diol ligand on boron, such as pinacol, in order to obtain tertiary boronate products in good yield and enantiopurity. Overall, this method has been applied to the synthesis of a broad array of tertiary boronates, which can potentially be used as intermediates for the asymmetric synthesis of complex molecules containing sterically encumbered stereocenters.

2.4. Experimental section

2.4.1. 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 ($CDCl_3$: 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 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 ($CDCl_3$: 77.2 ppm). ^{11}B NMR spectra were recorded on a Varian Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer. 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. 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, and cerium(IV) sulfate in ethanol with sulfuric acid (Seebach's Stain).

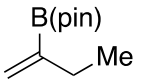
Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector with isopropanol or methanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. 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 argon. Palladium (II) acetate, Mandyphos ligands, and 1,1′-Bis(dicyclohexyl-phosphino)ferrocene were purchased from Strem Chemicals, Inc. and used without further purification. 2-isopropenyl boronic acid pinacol ester was purchased from Combi Blocks and used without further purification. 4-Methoxyphenyltrifluoromethanesulfonate, phenyl trifluoromethanesulfonate, trifluoromethansulfonic acid, and trifluoromethansulfonic anhydride were purchased from Oakwood Chemicals and used without further purification. All other reagents were purchased from Aldrich, Alfa Aesar, or Acros and used without further purification.

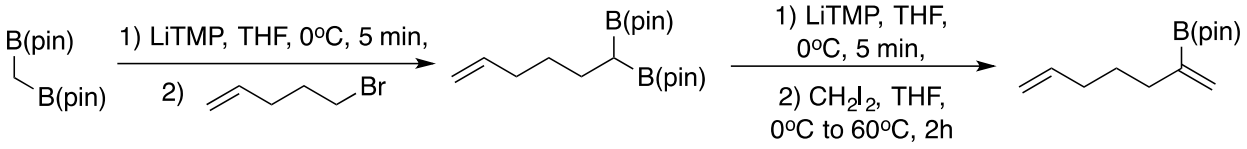
2.4.2. Experimental Procedures

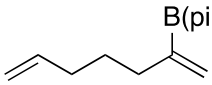
2.4.2.1. Procedures for Preparation of Boronic Esters



2-(but-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S-1). To an oven-dried round bottom flask equipped with a magnetic stir bar under N_2, 2-bromobut-1-ene (5.0 mmol, 1.0 equiv.) and diethyl ether (10.0 mL) were added, and the flask was cooled to -78 °C. Then, a tert-butyl lithium solution (10.0 mmol, 2.0 equiv.) was added at -78 °C dropwise, and the reaction mixture was allowed to stir at -78 °C for 20 minutes. The result solution was transferred to a syringe, and was added to a separated flask with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7.5 mmol, 1.5 equiv.) in diethyl ether (10.0 mL) solution by syringe pump over 40 minutes at -78 °C under N_2. Upon completion, the reaction mixture was allowed to warm to room temperature and stir for 1 hour. Then the reaction mixture was cooled to 0 °C, and a 1M HCl (aq.) solution (10.0 mL) was added and stir for additional 1 hour. The reaction mixture was allowed to warm to room temperature and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under

reduced pressure, and subsequently purified via silica gel column chromatography to afford the desired product (630.6 mg, 69% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 (s, 1H), 5.58 (s, 1H), 2.14 (q, J = 7.2 Hz, 2H), 1.25 (s, 12H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 127.9, 83.4, 28.4, 24.9, 13.8. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.2; IR (neat) ν_{max} 2977.6 (m), 2932.4 (m), 1443.3 (m), 1425.6 (m), 1304.4 (s), 1272.8 (m), 1112.3 (s), 1051.9 (m), 967.3 (m), 737.6 (m), 670.5 (m) cm^{-1}. HRMS (DART) for $C_{10}H_{20}BO_2$ $[M+H]^+$ calculated: 183.1556, found: 183.1554.

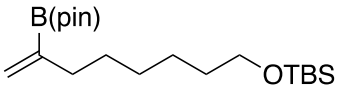




2-(hepta-1,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S-2). The title compound was prepared according to the literature procedure.[35] In the glove box, an oven-dried round bottom flask with magnetic stir bar was charged with LiTMP (4.15 mmol, 1.10 equiv), sealed with a septum, and removed from the glovebox. The reaction flask was cooled to 0 °C, and THF (6.0 mL), and solution of 2,2'-(hex-5-ene-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (prepared according to the literature precedence [36] with bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane and 5-bromopent-1-ene) (3.77 mmol, 1.00 equiv) in THF (6.0 mL) were added. The reaction mixture was allowed to stir for 5 minutes at 0 °C. Next, a solution of diiodomethane (7.54 mmol, 2.00 equiv) in THF (3.0 mL) was added dropwise at 0 °C. The reaction vial was allowed to warm to 60 °C and stir for additional 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude

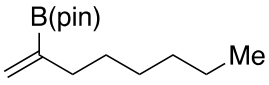
[35] Coombs, J. R.; Zhang, L.; Morken, J. P. *Org Lett*. **2015**, *17*, 1708–1711.
[36] Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc*. **2014**, *136*, 10581–10854.

mixture was purified by silica gel chromatography to afford the title compound (687.2 mg, 82% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 13.2, 10.2, 6.2 Hz1H), 5.75 (d, *J* = 3 Hz, 1H), 5.58 (s, 1H), 4.98 (dd, *J* = 16.8, 1.8 Hz, 1H), 4.91 (dd, *J* = 10.8, 1.2 Hz, 1H), 2.14 (t, *J* = 7.28 Hz, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.50 (p, *J* = 7.2 Hz, 2H), 1.24 (s, 12H. ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.3, 129.3, 114.4, 83.5, 35.0, 33.6, 28.6, 24.9. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.1; IR (neat) ν_{max} 2978.1 (m), 2928.7 (m), 1615.4 (w), 1426.2 (m), 1368.4 (s), 1306.5 (s), 1272.2 (m), 1198.1 (s), 1111.9 (m), 990.9 (m), 861.3 (m), 670.4 (w) cm^{-1}. HRMS (DART) for $C_{13}H_{24}BO_2$ $[M+H]^+$ calculated: 223.1869, found: 223.1881.



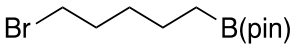
***tert*-butyldimethyl((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-7-en-1-yl)oxy)silane (S-3).** The title compound was prepared according to a literature procedure with slight modifications.[35] In an Ar-filled glovebox, LiTMP (475.99 mg, 3.23 mmol, 1.0 equiv.) was added to a 50 mL round bottom flask equipped with a magnetic stir bar. The flask was sealed with a rubber septum and removed from the glovebox. Dry THF (8.2 mL, 0.4 M) was added to the reaction vial, and cooled to 0 °C, before a solution of 7,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptoxy-tert-butyl-dimethyl-silane (prepared according to the literature precedence[36] with bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane and ((6-bromohexyl)oxy)(*tert*-butyl)-dimethylsilane) (1.56 g, 3.23 mmol, 1.0 equiv.) in THF (9.7 mL, 0.33 M) was added. The reaction mixture was allowed to stir for 5 minutes at 0 °C. Next, a solution of diiodomethane (0.52 mL, 6.47 mmol, 2.0 equiv.) in THF (6.5 mL) was added dropwise at 0 °C. The reaction vial was warmed to 60 °C and stirred for additional 2 hours. Upon completion, the reaction mixture filtered through a plug of silica gel with diethyl ether, then concentrated under reduced pressure. The crude mixture was purified by silica gel

chromatography (2 % ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (830 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (s, 1H), 5.58 (s, 1H), 3.59 (t, *J* = 6.7 Hz, 2H), 2.13 (t, *J* = 7.6 Hz, 2H), 1.56-1.46 (m, 2H), 1.46-1.37 (m, 2H), 1.37-1.23 (m, 16H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 128.7, 83.2, 63.3, 35.3, 32.9, 29.2, 29.1, 26.0, 25.7, 24.7, 18.4, -5.3. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.2. IR (neat): ν_{max} 2978.0 (m), 2928.7 (m), 2856.7 (m), 1462.9 (m), 1427.8 (m), 1407.6 (m), 1387.6 (m), 1307.9 (m), 1254.3 (m), 1141.9 (s), 1100.25 (m), 969.1 (m), 834.9 (s), 811.4 (m), 774.5 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{42}BO_3Si[M+H]^+$: calculated: 369.2996, found: 369.3001.

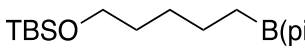


4,4,5,5-tetramethyl-2-(oct-1-en-2-yl)-1,3,2-dioxaborolane (S-4). The title compound was prepared according to a literature procedure with slight modifications.[35] In an Ar-filled glovebox, LiTMP (911 mg, 6.19 mmol, 1.0 equiv.) was added to a 100 mL round bottom flask equipped with a magnetic stir bar. The flask was sealed with a rubber septum and removed from the glovebox. Dry THF (15.5 mL, 0.4 M) was added to the reaction vial, and cooled to 0 °C, before a solution of 2,2'-(heptane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (2.18 g, 6.19 mmol, 1.0 equiv.) (prepared according to the literature precedence[36] with bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane and 1-bromohexane) in THF (18.8 mL, 0.33 M) was added. The reaction mixture was allowed to stir for 5 minutes at 0 °C. Next, a solution of diiodomethane (1.00 mL, 12.4 mmol, 2.0 equiv.) in THF (12.0 mL) was added dropwise at 0 °C. The reaction vial was warmed to 60 °C and stirred for additional 2 hours. Upon completion, the reaction mixture filtered through a plug of silica gel with diethyl ether, then concentrated under reduced pressure. The crude mixture was purified by silica gel

chromatography (2 % ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (830 mg, 54% yield). All spectral data was in accordance with the literature.[35]



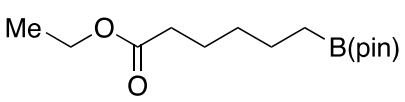
2-(5-bromopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S-5). The title compound was prepared according to the literature precedence.[37] To an oven-dried 6-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added 5-bromo-penten (5.0 mmol, 1.00 equiv.), pinacolborane (6.0 mmol, 1.20 equiv.), $[Ir(cod)Cl]_2$ (0.05 mmol, 0.01 equiv.), 1,1-Bis(diphenylphosphino)methane (0.10 mmol, 0.02 equiv.), and dichloromethane (5.0 mL). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at room temperature for 24 hours. The reaction was quenched with methanol (1.0 mL) and water (3.0 mL), and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and subsequently purified via silica gel column chromatography to afford the desired product (1.116 g, 80% yield). All spectral data was in accordance with the literature.[38]



***tert*-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)silane (S-6).** The title compound was prepared according to the literature precedence.[37] To an oven-dried 6-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added *tert*-butyldimethyl(pent-4-en-1-yloxy)silane (5.0 mmol, 1.00 equiv.), pinacolborane (6.0 mmol, 1.20 equiv.), $[Ir(cod)Cl]_2$ (0.05 mmol, 0.01 equiv.), 1,1-Bis(diphenylphosphino)methane (0.10 mmol, 0.02 equiv.), and dichloromethane (5.0 mL). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where

[37] Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2014**, *60*, 10695–10700.
[38] Molander, G. A.; Ham, J. *Org. Lett.* **2006**, *8*, 2031–2034.

it was allowed to stir at room temperature for 24 hours. The reaction was quenched with methanol (1.0 mL) and water (3.0 mL), and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and subsequently purified via silica gel column chromatography to afford the desired product (1.548 g, 94% yield). All spectral data was in accordance with the literature.[39]



ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanoate (S-7). The title compound was prepared according to a literature procedure with slight modifications.[40] In an Ar-filled glovebox, B_2pin_2 (1.90 g, 7.50 mmol, 1.5 equiv.), lithium methoxide (379.7 mg, 10.00 mmol, 2.0 equiv.), and copper (I) iodide (95.2 mg, 0.50 mmol, 0.10 equiv.) were added to a 100 mL round bottom flask equipped with a magnetic stir bar. The flask was sealed with a rubber septum and removed from the glovebox. Ethyl 6-bromohexanoate (0.89 mL, 5.00 mmol, 1.0 equiv) was added via syringe, followed by DMF (15.00 mL, 0.33 M). Reaction was stirred at room temperature for 15 hours. Then, reaction mixture was passed through a plug of silica gel with diethyl ether. The filtrate was then poured into separatory funnel containing aqueous saturated sodium chloride. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). Combined organic layers washed with aqueous saturated sodium chloride, dried over sodium sulfate, then filtered through a plug of cotton and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (2% - 5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (906.0 mg, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.10 (q, J = 7.2 Hz,

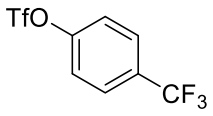
[39] Bedford, R. B.; Brenner, P. B.; Carter, E.; Gallagher, T.; Murphy, D. M.; Pye, D. R. *Organometallics* **2014**, *33*, 5940–5943.
[40] Yang, C.; Zhang, Z.; Tajuddin, H.; Wu, C.; Liang, J.; Liu, J.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu. L. *Angew. Chem. Int. Ed*. **2012**, *51*, 528–532.

2H), 2.31-2.22 (m, 2H), 1.67-1.56 (m, 2H), 1.47-1.36 (m, 2H), 1.36-1.27 (m, 2H), 1.27-1.18 (m, 15H), 0.76 (t, J = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 82.8, 60.1, 34.3, 31.8, 31.3, 24.8, 24.8, 23.6, 14.2. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.2. IR (neat): ν_{max} 2977.9 (m), 2931.2 (m), 2863.6 (m), 1734.6 (s), 1463.7 (m), 1407.9 (s), 1370.8 (m), 1271.4 (m), 1214.5 (m), 1183.6 (m), 1144.1 (s), 968.2 (m), 873.0 (m), 673.2 (m) cm^{-1}. HRMS (DART) for $C_{14}H_{28}BO_4$ $[M+H]^+$: calculated: 271.2081, found: 271.2081.

2.4.2.2. Procedures for preparation of aryl trifluoromethanesulfonates

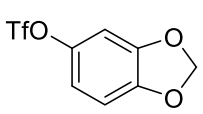
General procedure for the synthesis of aryl trifluoromethanesulfonates

Aryl trifluoromethansulfonates were made according to literature procedure with slight modification. To a solution of the corresponding phenol and pyridine in CH_2Cl_2 at 0 °C, a solution of trifluoromethanesulfonic anhydride in CH_2Cl_2 was added dropwise. The mixture was then warmed to room temperature and allowed to stir for 1 hour. The mixture was diluted with Et_2O, quenched with 3M HCl *(aq)* and washed successively with $NaHCO_3$ *(aq, sat.)* and brine. The solution was dried over Na_2SO_4, filtered with Et_2O, and the solvent was removed under reduced pressure. The residue was purified on silica gel chromatography to afford aryl trifluoromethanesulfonates.



4-(trifluoromethyl)phenyl trifluoromethanesulfonate (S-8). Prepared according to the general procedure above with 4-trifluoromethylphenol (0.630 g, 3.8 mmol), trifluoromethanesulfonic anyhydride (0.774 mL, 4.6 mmol), pyridine (0.615 mL, 7.6 mmol), and CH_2Cl_2 (6.0 mL). The crude residue was purified on silica gel chromatography

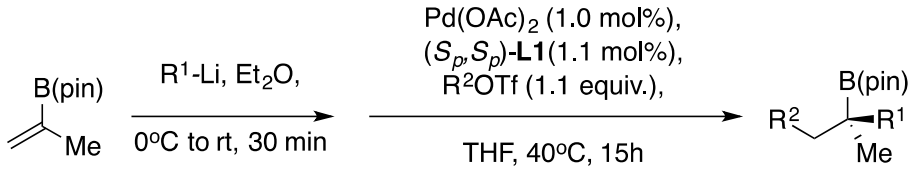
(10% ethyl acetate in hexanes) to afford the product as a colorless oil (1.180 g, 98% yield). All spectral data was in accordance with the literature.[41]



benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate (S-9). Prepared according to the general procedure above with sesamol (1.04 g, 7.5 mmol), trifluoromethansulfonic anhydride (1.5 mL, 9.0 mmol), pyridine (1.2 mL, 15.0 mmol), and CH_2Cl_2 (13.0 mL). The crude residue was purified with silica gel chromatography (5% ethyl acetate in hexanes) to afford the product as colorless oil (1.89 g, 94%). All spectral data as in accordance with the literature.[42]

2.4.2.3. Procedures for the conjunctive cross-coupling reaction

Method A:

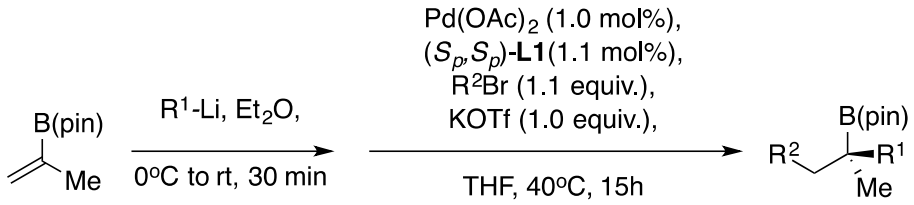


To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added 2-isopropenyl boronic acid pinacol ester (0.20 mmol, 1.00 equiv.) and diethyl ether (0.2 mL), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0 °C, and an alkyl/aryllithium solution (0.20 mmol, 1.0 equiv.) was added at 0 °C. The reaction vial was allowed to warm to room temperature and stirred for 30 minutes. Then, the solvent was carefully removed under reduced pressure (residual ether and hexane results in diminished yield), and the reaction vial was brought back into the glovebox. To a separate oven-dried 2-dram vial

[41] Gill, D.; Hester, A. J.; Lloyd-Jones, G. C. *Org. Biomol. Chem*. **2004**, *2*, 2547–2548.
[42] Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc*. **1987**, *109*, 5478–5486.

equipped with a magnetic stirbar in the glovebox was added $Pd(OAc)_2$ (0.002 mmol, 0.01 equiv.), **2.43** (0.0022 mmol, 0.011 equiv.), and THF (0.2 mL). The $Pd(OAc)_2$/**2.43** solution was allowed to stir for 20 minutes at room temperature. Then the $Pd(OAc)_2$/**2.43** solution was transferred into the reaction vial, followed by THF (0.6 mL), and aryl/alkenyl triflate (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 15 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, concentrated under reduced pressure, and subsequently purified via silica gel column chromatography to afford the desired products.

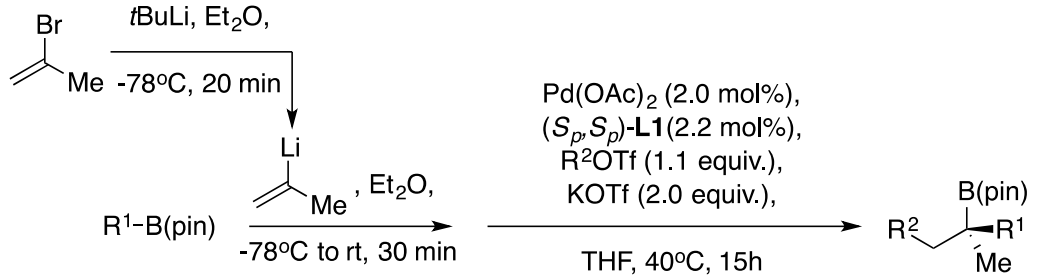
Method B:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added 2-isopropenyl boronic acid pinacol ester (0.20 mmol, 1.00 equiv.) and diethyl ether (0.2 mL), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0 °C, and an alkyl/aryl lithium solution (0.20 mmol, 1.0 equiv.) was added at 0 °C. The reaction vial was allowed to warm to room temperature and stirred 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 $Pd(OAc)_2$ (0.002 mmol, 0.01 equiv.), **2.43** (0.0022 mmol, 0.011 equiv.), and THF (0.2 mL). The $Pd(OAc)_2$/**2.43** solution was allowed to stir for 20 minutes at room temperature. Then the

$Pd(OAc)_2$/**2.43** solution was transferred into the reaction vial, followed by THF (0.6 mL), potassium trifluoromethanesulfonate (0.20 mmol, 1.0 equiv.) and aryl/alkenyl bromide (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 15 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, concentrated under reduced pressure, and subsequently purified via silica gel column chromatography to afford the desired products.

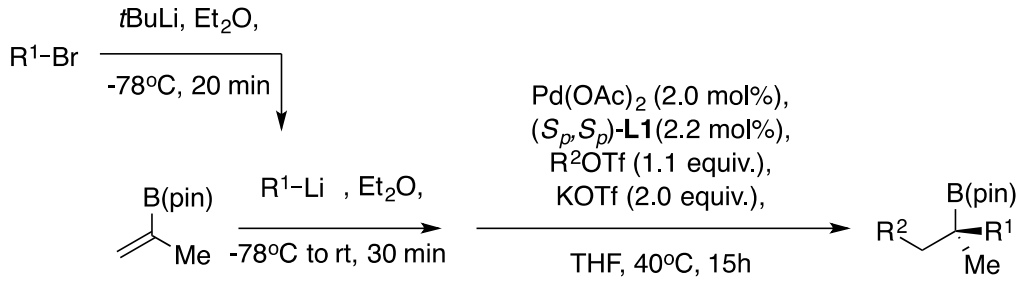
Method C:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added 2-isopropenyl bromide (0.20 mmol, 1.00 equiv.) and diethyl ether (0.2 mL), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to -78 °C, and a *tert*-butyl lithium solution (0.40 mmol, 2.0 equiv.) was added at -78 °C. The reaction vial was allowed to stir at -78 °C for 20 minutes. Then an alkyl/aryl boronic acid pinacol ester solution was added at -78 °C. The reaction vial was allowed to warm to room temperature and stirred 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 $Pd(OAc)_2$ (0.004 mmol, 0.02 equiv.), **2.43** (0.0044 mmol, 0.022 equiv.), and THF (0.4 mL). The $Pd(OAc)_2$/**2.43** solution was allowed to stir for 20 minutes at room

temperature. Then the $Pd(OAc)_2$/**2.43** solution was transferred into the reaction vial, followed by THF (0.4 mL), potassium trifluoromethanesulfonate (0.40 mmol, 2.0 equiv.) and aryl/alkenyl triflate (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 15 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, concentrated under reduced pressure, and subsequently purified via silica gel column chromatography to afford the desired products.

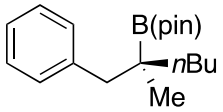
Method D:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added aryl bromide (0.20 mmol, 1.00 equiv.) and diethyl ether (0.2 mL), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to -78 °C, and a *tert*-butyl lithium solution (0.40 mmol, 2.0 equiv.) was added at -78 °C. The reaction vial was allowed to stir at -78 °C for 20 minutes. Then a 2-isopropenyl boronic acid pinacol ester solution was added at -78 °C. The reaction vial was allowed to warm to room temperature and stirred 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 $Pd(OAc)_2$ (0.004 mmol, 0.02 equiv.), **2.43** (0.0044 mmol, 0.022 equiv.), and THF (0.4 mL). The $Pd(OAc)_2$/**2.43** solution was allowed to stir for 20 minutes at room

temperature. Then the $Pd(OAc)_2$/**2.43** solution was transferred into the reaction vial, followed by THF (0.4 mL), potassium trifluoromethanesulfonate (0.40 mmol, 2.0 equiv.) and aryl/alkenyl triflate (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 15 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, concentrated under reduced pressure, and subsequently purified via silica gel column chromatography to afford the desired products.

2.4.2.4. Characterization of conjunctive cross-coupling products and analysis of stereochemistry



(*R*)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylhexan-2-yl)-1,3,2-dioxaborolane (2). The reaction was performed according to the general procedure ***(Method A)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (56.6 mg, 94% yield at room temperature; 54.8 mg, 91% yield at 40 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31-7.02 (m, 5H), 2.78 (d, J = 13.1 Hz, 1H), 2.46 (d, J = 13.1 Hz, 1H), 1.51-1.37 (m, 1H), 1.37-1.13 (m, 17H), 0.94-0.82 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 140.4, 130.6, 127.8, 125.8, 83.3, 45.0, 39.4, 28.4, 25.3, 25.0, 23.8, 21.4, 14.4; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.5; IR (neat): ν_{max} 2927.2 (m), 2859.5 (w), 1494.5 (m), 1378.9 (m), 1307.2 (m), 1218.5 (m), 1137.7 (s), 968.1 (m), 852.1 (m), 747.1 (m), 701.6 (m) cm^{-1}.

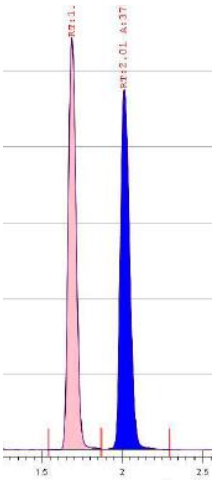
HRMS (DART) for $C_{19}H_{35}BO_2N$ $[M+NH_4]^+$: calculated: 320.2761, found: 320.2763. $[\alpha]^{20}_D$: -5.03 (c = 2.310, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexyl-phosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

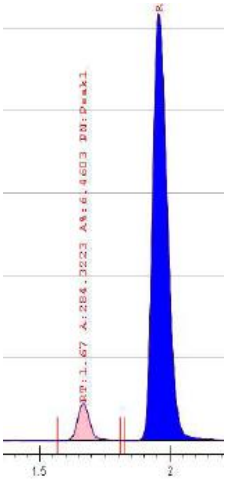
Chiral SFC (Chiralcel ODR-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylhexan-2-yl)-1,3,2-dioxaborolane.

Racemic Material



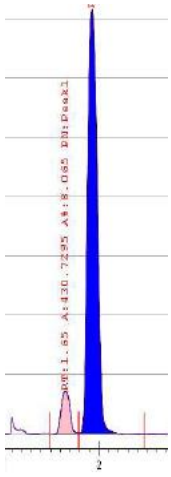
Peak No	% Area	Area	RT (min)
1	49.4079	3701.4525	1.69
2	50.5921	3790.1679	2.01
Total:	100	7491.6204	

Standard Conditions (room temperature)

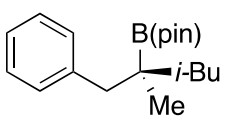


Peak No	% Area	Area	RT (min)
1	6.4603	284.3223	1.67
2	93.5397	4116.729	1.96
Total:	100	4401.0513	

Standard Conditions (40 °C)



Peak No	% Area	Area	RT (min)
1	8.065	430.7295	1.65
2	91.935	4909.9976	1.93
Total:	100	5340.7271	



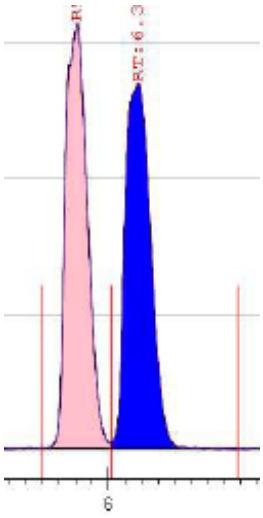
(*R*)-2-(2,4-dimethyl-1-phenylpentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3). The reaction was performed according to the general procedure ***(Method A)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), isobutyl lithium (0.12 mL, 1.72 M in heptane, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (56.8 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.10 (m, 5H), 2.80 (d, *J* = 13.1 Hz, 1H), 2.47 (d, *J* = 13.0 Hz, 1H), 1.78-1.65 (m, 1H), 1.52-1.42 (m, 1H), 1.24-1.16 (m, 13H), 1.00-0.86 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.8, 130.6, 127.5, 125.7, 83.2, 48.4, 45.8, 25.8, 25.3, 24.9, 24.7, 24.2, 21.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.5. IR (neat) ν_{max} 3062.1 (m), 3028.6 (m), 2954.4 (m), 1602.8 (m), 1467.8 (m), 1378.8 (s), 1371.1 (s), 1336.2 (m), 1307.6 (s), 1250.4 (m), 1136.2 (s), 1084.8 (m), 1031.5 (m), 849.3 (m), 790.8 (m), 701.9 (s), 597.4 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{32}BO_2$ $[M+H]^+$: calculated: 303.2495, found: 303.2291. $[\alpha]^{20}_D$: +4.23 (c = 1.773, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

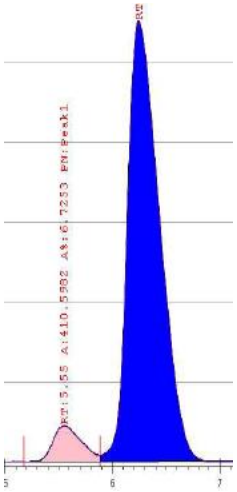
Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds see compounds **6-OH, 37** and **39**).

Chiral SFC (Chiralcel OD-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(2,4-dimethyl-1-phenylpentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

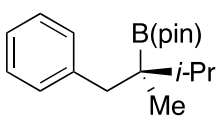
Racemic Material



Standard Conditions



Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	50.1177	5739.4388	5.62	1	6.7253	410.5982	5.55
2	49.8823	5712.4912	6.36	2	93.2747	5694.6624	6.25
Total:	100	11451.93		Total:	100	6105.2606	



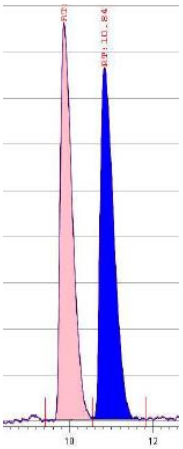
(*S*)-2-(2,3-dimethyl-1-phenylbutan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4). The reaction was performed according to the general procedure ***(Method A)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), isopropyl lithium (0.36 mL, 0.56 M in pentane, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (54.0 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.19 (m, 4H), 7.18-7.11 (m, 1H), 2.89 (d, *J* = 12.9 Hz, 1H), 2.46 (d, *J* = 12.9 Hz, 1H), 1.71 (h, *J* = 6.9 Hz, 1H), 1.18 (d, *J* = 54.1 Hz, 12H), 0.97 (dd, *J* = 31.0, 6.9 Hz, 6H), 0.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.9, 130.5, 127.6, 125.6, 83.0, 43.3, 35.2, 25.5, 24.8, 19.9, 17.7, 17.3. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.3. IR (neat) ν_{max} 2975.5 (m), 2929.6 (m), 2873.5 (m), 1495.0 (m), 1467.6 (m), 1370.7 (s), 1306.9 (s), 1269.1 (m), 1209.4 (m), 1142.2 (s), 1126.5 (m), 1084.1 (m), 967.9 (m), 848.2 (m) cm^{-1}. HRMS (DART) for $C_{18}H_{33}BO_2N$ $[M+NH_4]^+$: calculated: 306.2604, found: 306.2596. $[\alpha]^{20}_D$: -3.83 (c = 1.200, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

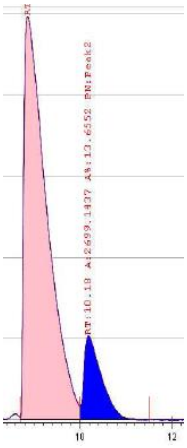
Chiral SFC (Chiralcel AD-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2,3-dimethyl-1-phenylbutan-2-ol.

Racemic Material

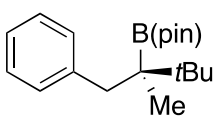


Peak No	% Area	Area	RT (min)
1	49.9738	1729.7895	9.86
2	50.0262	1731.6052	10.84
Total:	100	3461.3947	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	86.3448	17067.2797	8.86
2	13.6552	2699.1437	10.18
Total:	100	19766.4234	



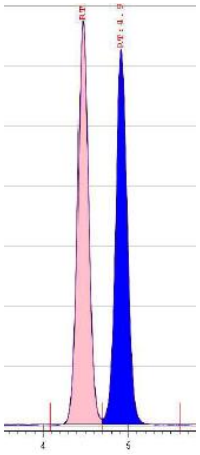
(*S*)-4,4,5,5-tetramethyl-2-(2,3,3-trimethyl-1-phenylbutan-2-yl)-1,3,2-dioxaborolane (5). The reaction was performed according to the general procedure ***(Method A)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.12 mL, 1.7 M in pentane, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (53.4 mg, 88% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 3.09 (d, *J* = 12.5 Hz, 1H), 2.31 (d, *J* = 12.5 Hz, 1H), 1.18 (d, *J* = 85.1 Hz, 12H), 1.01 (s, 9H), 0.82 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 144.1, 133.5, 130.1, 128.1, 85.8, 42.1, 37.7, 29.6, 28.5, 27.3, 19.9. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.4. IR (neat) ν_{max} 3028.4 (m), 2973.9 (m), 2874.3 (m), 1603.7 (m), 1495.1 (m), 1475.1 (m), 1455.6 (m), 1398.9 (m), 1302.8 (s), 1271.1 (m), 1209.5 (m), 1143.8 (s), 1115.5 (m), 872.3 (m), 804.6 (m), 673.5 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{32}BO_2$ $[M+H]^+$: calculated: 303.2495, found: 303.2490. $[\alpha]^{20}_D$: -22.58 (c = 1.500, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure for 72 hours at room temperature, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

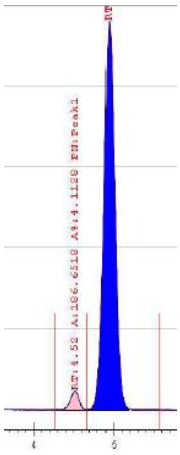
Chiral SFC (Chiralcel OJ-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2,3,3-trimethyl-1-phenylbutan-2-ol.

Racemic Material

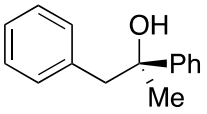


Peak No	% Area	Area	RT (min)
1	49.1983	5781.3223	4.46
2	50.8017	5969.7503	4.91
Total:	100	11751.0726	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	4.1128	186.6518	4.52
2	95.8872	4351.6184	4.94
Total:	100	4538.2702	



(*R*)-1,2-diphenylpropan-2-ol (6-OH). The reaction was performed according to the *conjunctive cross-coupling (**Method A**)/oxidation* procedure with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), phenyl lithium (0.11 mL, 1.9 M in dibutyl ether, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (8.0 % ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (35.7 mg, 84% yield at room temperature; 54.8 mg, 91% yield at 40 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29-7.23 (m, 4H), 7.03-7.02 (m, 2H), 3.16 (d, *J* = 13.8 Hz, 1H), 3.06 (d, *J* = 13.2 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 147.7, 136.9, 130.8, 128.2, 126.8, 125.1, 74.6, 50.7, 29.6; IR (neat): ν_{max} 3445.6 (br), 3060.1 (m), 3027.5 (m), 2974.3 (m), 2922.5 (m), 2850.4 (m), 1602.1 (m), 1446.7 (m), 1347.0 (m), 1179.0 (m), 1067.5 (m), 946.0 (m), 770.3 (s), 698.9 (s), 573.6 (m) cm^{-1}. HRMS (DART) for $C_{15}H_{15}$ $[M+H-H_2O]^+$: calculated: 195.1174, found: 195.1174. $[\alpha]^{20}_D$: +51.80 (c = 0.905, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

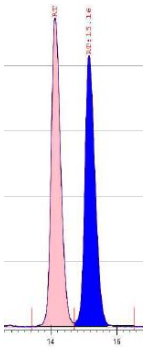
Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexyl-phosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was determined by comparison of optical rotation of the product before the oxidation to the literature[43] (assigned by analogy to previous work – stereochemistry determined by comparison of products to known alcohols[44]) (Measured: $[\alpha]^{20}_D$: -51.2 (c = 1.105, $CHCl_3$, l =50 mm), literature: $[\alpha]^{24}_D$: -63.9 (c =

[43] Bagutski, V.; Ros, A.; Aggarwal, V. K. *Tetrahedron* **2009**, *65*, 9956–9960.
[44] Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491–7494.

6.2, CH_2Cl_2), 99 % *e.e* for (*S*)-2-(1,2-diphenylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane). (And the absolute stereochemistry was assigned to be (*S*)-2-(1,2-diphenylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

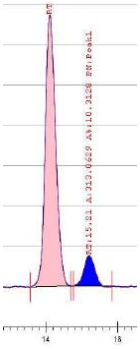
Chiral SFC (Chiralcel OD-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1,2-diphenylpropan-2-ol.

Racemic Material

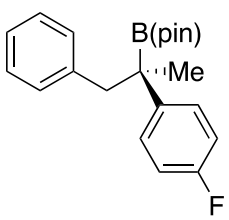


Peak No	% Area	Area	RT (min)
1	51.3279	4756.4478	14.12
2	48.6721	4510.334	15.16
Total:	100	9266.7818	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	89.6872	2722.619	14.1
2	10.3128	313.0629	15.21
Total:	100	3035.6819	



(*S*)-2-(2-(4-fluorophenyl)-1-phenylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7). The reaction was performed according to the general procedure ***(Method D)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.24 mL, 1.7 M in pentane, 0.40 mmol, 2.00 equiv.), 1-bromo-4-fluorobenzene (35.0 mg, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (75.2 mg, 0.40 mmol, 2.00 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (55.0 mg, 81% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28-7.23 (m, 2H), 7.18-7.13 (m, 3H), 7.00-6.94 (m, 4H), 3.15 (d, J = 13.2 Hz, 1H), 2.95 (d, J = 13.1 Hz, 1H), 1.28 (s, 3H), 1.22 (d, J = 17.9 Hz, 12H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 163.56 (d, $^{1}J_{C–F}$ = 243.3 Hz), 144.60, 141.89, 133.05, 131.28 (d, $^{3}J_{C–F}$ = 7.9 Hz) 130.1, 128.5, 117.3 (d, $^{2}J_{C–F}$ = 20.8 Hz) 86.3, 48.5, 27.5, 27.4, 27.2, 23.3. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 33.8. ^{19}F NMR: (564 MHz, $CDCl_3$) δ -118.6. IR (neat) ν_{max} 2977.0 (m), 2930.9 (m), 1602.5 (m), 1507.4 (s), 1460.1 (m), 1372.2 (m), 1317.7 (s), 1229.6 (m), 1142.8 (s), 1100.9 (m), 1014.4 (m), 966.9 (m), 850.6 (m), 754.7 (m), 579.2 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{30}BFO_2N$ $[M+NH_4]^+$: calculated: 358.2354, found: 358.2350. $[\alpha]^{20}_D$: -39.91 (c = 1.430, $CHCl_3$, l = 50 mm).

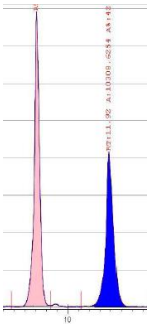
Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on the

corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

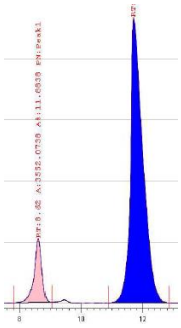
Chiral SFC (Chiralcel OJ-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(4-fluorophenyl)-1-phenylpropan-2-ol.

Racemic Material

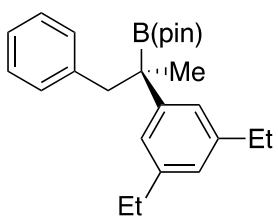


Peak No	% Area	Area	RT (min)
1	57.2278	13792.5788	8.54
2	42.7722	10308.6254	11.92
Total:	100	24101.2042	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	11.8838	3552.0738	8.62
2	88.1162	26337.9331	11.7
Total:	100	29890.0069	



(*S*)-2-(2-(3,5-diethylphenyl)-1-phenylpropan-2-yl)-4,4,5,5-tetra-methyl-1,3,2-dioxaborolane (8). The reaction was performed according to the general procedure ***(Method D)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.24 mL, 1.7 M in pentane, 0.40 mmol, 2.00 equiv.), 1-bromo-3,5-diethylbenzene (42.6 mg, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (75.2 mg, 0.40 mmol, 2.00 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (56.8 mg, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22-7.09 (m, 3H), 7.09-6.99 (m, 2H), 6.95 (s, 2H), 6.83 (s, 1H), 3.21 (d, *J* = 13.0 Hz, 1H), 2.87 (d, *J* = 13.0 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 4H), 1.32-1.13 (m, 21H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.5, 143.6, 139.9, 130.5, 127.4, 125.6, 124.5, 124.0, 83.4, 45.8, 29.1, 24.9, 24.4, 20.7, 15.7. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 36.6. IR (neat) ν_{max} 2964.7 (m), 2929.4 (m), 2871.9 (m), 1597.5 (m), 1460.2 (m), 1377.9 (m), 1350.5 (m), 1312.6 (s), 1271.2 (m), 1212.0 (m), 1145.0 (s), 1098.7 (m), 966.9 (m), 750.7 (m) cm^{-1}. HRMS (DART) for $C_{25}H_{36}BO_2$ $[M+H]^+$: calculated: 379.2808, found: 379.2798. $[\alpha]^{20}_D$: -15.71 (c = 0.60, $CHCl_3$, *l* = 50 mm).

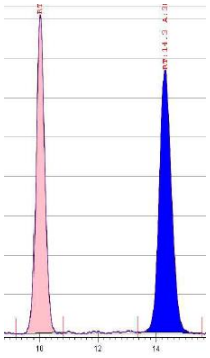
Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on the

corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

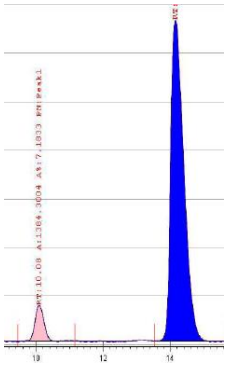
Chiral SFC (Chiralcel OJ-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(3,5-diethylphenyl)-1-phenylpropan-2-ol.

Racemic Material

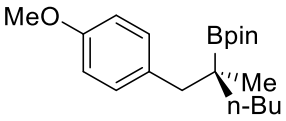


Peak No	% Area	Area	RT (min)
1	45.5526	3254.9697	10
2	54.4474	3890.55	14.3
Total:	100	7145.5197	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	7.1833	1384.3004	10.08
2	92.8167	17886.7192	14.14
Total:	100	19271.0196	



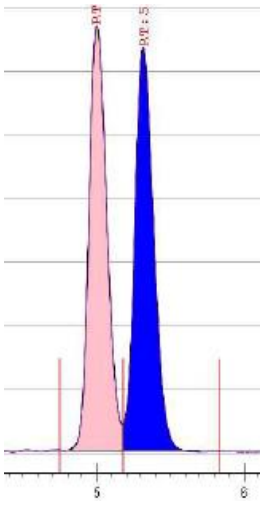
(*R*)-2-(1-(4-methoxyphenyl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9). The reaction was performed according to the general procedure ***(Method A)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), and **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (63.1 mg, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.5 Hz, 2H), 6.77 (t, *J* = 8.5 Hz, 2H), 3.77 (s, 3H), 2.73 (d, *J* = 13.3 Hz, 1H), 2.42 (d, *J* = 13.2 Hz, 1H), 1.48-1.36 (m, 1H), 1.37-1.10 (m, 17H), 0.95-0.79 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.3, 134.9, 133.9, 115.6, 85.7, 57.8, 46.5, 41.8, 30.9, 27.7, 27.5, 26.3, 23.8, 16.8. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.6. IR (neat) ν_{max} 2975.6 (m), 2955.1 (m), 2927.6 (m), 2858.6 (m), 1611.1 (m), 1510.6 (s), 1465.2 (m), 1370.8 (m), 1301.6 (m), 1246.4 (s), 1177.3 (m), 1138.4 (s), 1038.8 (m), 853.2 (m), 823.2 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{34}BO_3$ $[M+H]^+$: calculated: 333.2601, found: 333.2600. $[\alpha]^{20}_D$: -4.66 (c = 0.840, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

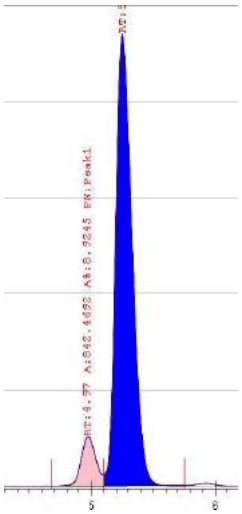
Chiral SFC (Chiralcel OD-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(1-(4-methoxyphenyl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Racemic Material

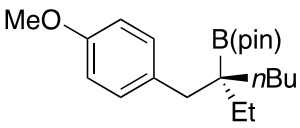


Peak No	% Area	Area	RT (min)
1	49.9848	2823.0389	5
2	50.0152	2824.759	5.32
Total:	100	5647.7979	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	8.9245	842.4692	4.97
2	91.0755	8597.4971	5.25
Total:	100	9439.9663	



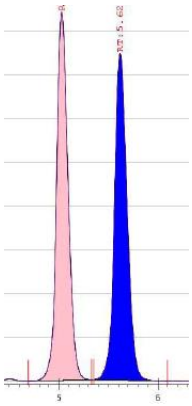
(*R*)-2-(3-(4-methoxybenzyl)heptan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10). The reaction was performed according to the general procedure ***(Method A)*** with 2-(but-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (36.4 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (49.7 mg, 72% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 3H), 2.62 (d, *J* = 3.0 Hz, 2H), 1.38-1.14 (m, 20H), 0.95-0.81 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 157.8, 132.4, 131.3, 113.2, 83.2, 55.4, 38.8, 33.9, 27.3, 26.5, 25.3, 25.3, 23.8, 14.4, 9.5; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.5; IR (neat): ν_{max} 2957.5 (m), 2928.9 (m), 2858.5 (w), 1511.3 (m), 1459.8 (m), 1404.2 (m), 1301.3 (m), 1246.7 (s), 1136.9 (s), 1039.3 (m), 837.0 (m), 687.7 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{36}BO_3$ $[M+H]^+$: calculated: 347.2758, found: 347.2745. $[\alpha]^{20}_D$: -1.09 (c = 0.655, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with 2-(but-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexyl-phosphino)ferrocene (6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the conjunctive cross-coupling/oxidation procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

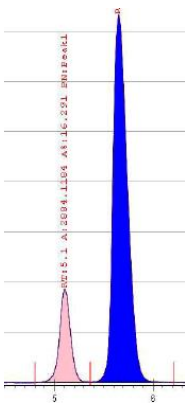
Chiral SFC (Chiralcel OJ-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-3-(4-methoxybenzyl)heptan-3-ol.

Racemic Material

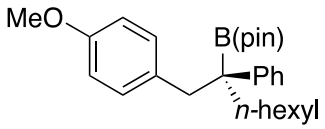


Peak No	% Area	Area	RT (min)
1	50.5891	6807.0834	5.03
2	49.4109	6648.554	5.62
Total:	100	13455.6374	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	16.291	2884.1184	5.1
2	83.709	14819.6338	5.65
Total:	100	17703.7522	



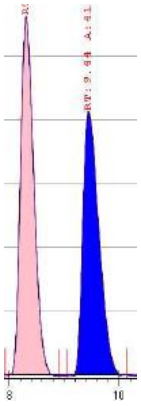
(*R*)-2-(1-(4-methoxyphenyl)-2-phenyloctan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11). The reaction was performed according to the general procedure ***(Method A)*** with 4,4,5,5-tetramethyl-2-(oct-1-en-2-yl)-1,3,2-dioxaborolane (47.6 mg, 0.20 mmol, 1.00 equiv.), phenyl lithium (0.11 mL, 1.9 M in dibutyl ether, 0.20 mmol, 1.00 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (72.7 mg, 86% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.20 (m, 2H), 7.20-7.14 (m, 2H), 7.11 (td, *J* = 7.0, 1.3 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 3.71 (s, 3H), 3.04 (d, *J* = 6.9 Hz, 2H), 1.82-1.64 (m, 2H), 1.33-1.15 (m, 22H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 157.8, 145.6, 131.6, 131.3, 128.1, 128.0, 125.3, 112.9, 83.6, 55.3, 41.1, 33.6, 32.0, 30.3, 25.6, 25.0, 24.9, 22.8, 14.3; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.1; IR (neat): ν_{max} 2976.5 (m), 2929.3 (m), 2857.3 (w), 1511.0 (s), 1464.4 (m), 1371.2 (m), 1301.6 (m), 1247.7 (s), 1144.4 (s), 1037.8 (m), 852.5 (m), 700.0 (m) cm^{-1}. HRMS (DART) for $C_{27}H_{40}BO_3$ $[M+H]^+$: calculated: 423.3071, found: 423.3078. $[\alpha]^{20}_D$: -28.96 (c = 1.410, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with 4,4,5,5-tetramethyl-2-(oct-1-en-2-yl)-1,3,2-dioxaborolane, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

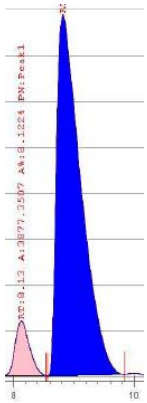
Chiral SFC (Chiralcel ODR-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1-(4-methoxyphenyl)-2-phenyloctan-2-ol.

Racemic Material

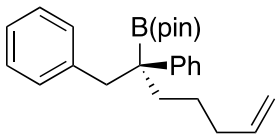


Peak No	% Area	Area	RT (min)
1	52.9461	4708.6986	8.3
2	47.0539	4184.6851	9.44
Total:	100	8893.3837	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	8.1224	3877.3507	8.13
2	91.8776	43859.2344	8.82
Total:	100	47736.5851	



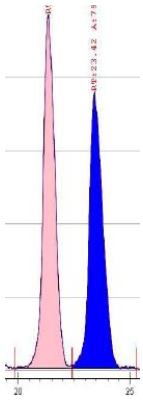
(*S*)-2-(1,2-diphenylhept-6-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12). The reaction was performed according to the general procedure ***(Method A)*** with 2-(hepta-1,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (44.4 mg, 0.20 mmol, 1.00 equiv.), phenyl lithium (0.11 mL, 1.9 M in dibutyl ether, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M) at 60 °C. The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (67.5 mg, 89% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.20 (m, 4H), 7.20-7.10 (m, 4H), 6.87 (dd, *J* = 6.3, 2.9 Hz, 2H), 5.94-5.73 (m, 1H), 5.01 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.95 (dd, *J* = 10.3, 2.0 Hz, 1H), 3.16 (s, 2H), 2.16-1.99 (m, 2H), 1.92-1.72 (m, 2H), 1.54-1.39 (m, 2H), 1.24 (d, *J* = 16.2 Hz, 12H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 145.3, 139.5, 139.1, 130.4, 128.1, 128.0, 127.6, 125.9, 125.4, 114.5, 83.7, 41.8, 34.6, 33.3, 25.0, 25.0, 24.9; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 33.71; IR (neat): ν_{max} 2977.4 (m), 2932.5 (m), 2862.5 (w), 1496.1 (m), 1454.8 (m), 1371.0 (m), 1313.6 (m), 1142.7 (s), 909.6 (m), 856.4 (m), 700.4 (s) cm^{-1}. HRMS (DART) for $C_{25}H_{34}BO_2$ $[M+H]^+$: calculated: 377.2652, found: 377.2657. $[\alpha]^{20}_D$: -22.05 (c = 1.110, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with 2-(hepta-1,6-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the conjunctive cross-coupling/oxidation procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

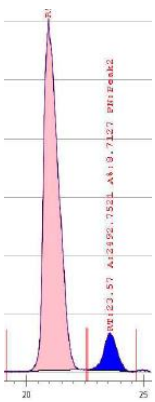
Chiral SFC (Chiralcel AD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1,2-diphenylhept-6-en-2-ol.

Racemic Material

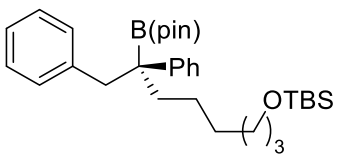


Peak No	% Area	Area	RT (min)
1	52.308	8699.9302	21.36
2	47.692	7932.2036	23.42
Total:	100	16632.1338	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	91.2873	26117.8526	20.94
2	8.7127	2492.7521	23.57
Total:	100	28610.6047	



(*S*)-*tert*-butyl((7,8-diphenyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl)oxy)dimethylsilane (13). The reaction was performed according to the general procedure ***(Method A)*** with *tert*-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)oxy)silane (68.1 mg, 0.20 mmol, 1.00 equiv.), phenyl lithium (0.11 mL, 1.9 M in dibutyl ether, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M) at 60 °C. The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (79.0 mg, 76% yield). ^{1}H NMR (600 MHz, $CDCl_3$): 7.27-7.21 (m, 2H), 7.21-7.17 (m, 2H), 7.16-7.11 (m, 1H), 7.11-7.07 (m, 3H), 6.84-6.80 (m, 2H), 3.65-3.52 (m, 2H), 3.12 (s, 2H), 1.83-1.65 (m, 2H), 1.55 -1.44 (m, 3H), 1.36-1.14 (m, 17H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): 147.9, 142.0, 132.9, 131.4, 130.5, 130.0, 128.3, 127.8, 86.1, 65.9, 44.3, 36.1, 35.5, 32.8, 28.7, 28.4, 28.1, 27.5, 27.4, 27.4, 21.0, -2.6. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.1. IR (neat) ν_{max} 2977.8 (m), 2929.6 (m), 2856.6 (m), 1496.3 (m), 1370.9 (m), 1311.3 (m), 1254.5 (m), 1212.9 (m), 1143.1 (s), 1100.1 (s), 1005.8 (m), 835.4 (s), 774.5 (m), 700.7 (m) cm^{-1}. HRMS (DART) for $C_{32}H_{52}BO_3Si$ $[M+H]^+$: calculated: 523.3779, found: 523.3779. $[\alpha]^{20}_D$: -16.61 (c = 0.650, $CHCl_3$, *l* = 50 mm).

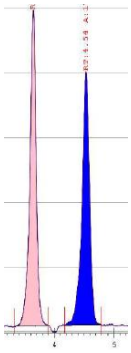
Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with *tert*-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)oxy)silane, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation*

procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

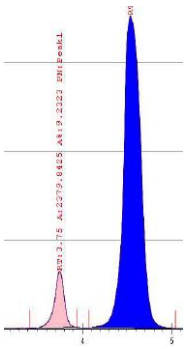
Chiral SFC (Chiralcel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-6-((tert-butyldimethylsilyl)oxy)-1,2-diphenylhexan-2-ol.

Racemic Material

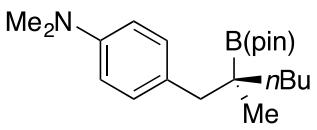


Peak No	% Area	Area	RT (min)
1	50.8847	1836.1111	3.64
2	49.1153	1772.267	4.54
Total:	100	3608.3781	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	9.2323	2379.8425	3.75
2	90.7677	23397.4572	4.54
Total:	100	25777.2997	



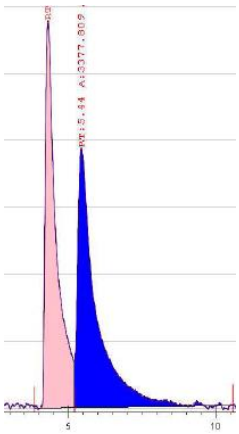
(*R*)-*N,N*-dimethyl-4-(2-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl)aniline (14). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 4-bromo-*N,N*-dimethylaniline (44.0 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (57.5 mg, 83% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 2.88 (s, 6H), 2.68 (d, *J* = 13.4 Hz, 1H), 2.38 (d, *J* = 13.3 Hz, 1H), 1.49-1.37 (m, 1H), 1.34-1.12 (m, 17H), 0.94-0.80 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.1, 131.2, 128.7, 112.6, 83.2, 43.9, 41.1, 39.2, 28.5, 25.3, 25.0, 23.8, 21.3, 14.4; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.3; IR (neat): ν_{max} 2925.8 (m), 2858.4 (w), 1614.7 (m), 1519.7 (s), 1465.5 (m), 1378.1 (m), 1370.3 (m), 1342.8 (m), 1305.5 (s), 1214.9 (m), 1137.2 (s), 948.1 (m) cm^{-1}. HRMS (DART) for $C_{27}H_{37}BNO_2$ $[M+H]^+$: calculated: 346.2917, found: 346.2905. $[\alpha]^{20}_D$: -3.67 (c = 2.875, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

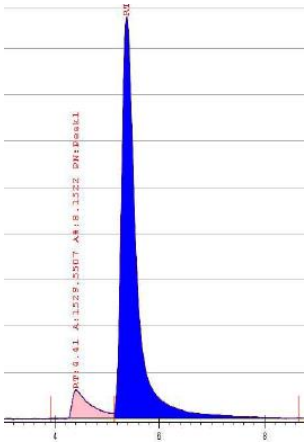
Chiral SFC (Chiralcel OJ-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-N,N-dimethyl-4-(2-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl)aniline.

Racemic Material

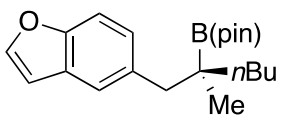


Peak No	% Area	Area	RT (min)
1	47.5159	3058.0657	4.3
2	52.4841	3377.809	5.44
Total:	100	6435.8747	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	8.1522	1529.5507	4.41
2	91.8478	17232.7821	5.37
Total:	100	18762.3328	



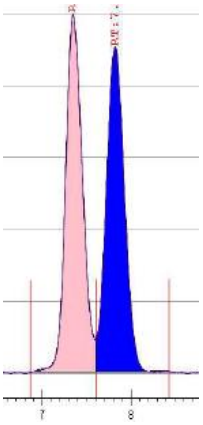
(*R*)-2-(1-(benzofuran-5-yl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 5-bromobenzofuran (43.3 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (63.0 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.42 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.68 (s, 1H), 2.91 (d, *J* = 13.2 Hz, 1H), 2.56 (d, *J* = 13.2 Hz, 1H), 1.50 (t, *J* = 11.6 Hz, 1H), 1.41-1.13 (m, 17H), 0.96-0.87 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 156.2, 147.4, 137.3, 129.6, 129.5, 125.0, 112.8, 109.0, 85.7, 47.4, 42.0, 30.9, 27.8, 27.5, 26.3, 23.8, 16.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 34.2. IR (neat) ν_{max} 2975.3 (m), 2956.5 (m), 2927.1 (m), 1466.9 (m), 1379.1 (m), 1340.9 (s), 1308.0 (s), 1261.8 (m), 1110.6 (s), 1032.2 (m), 968.4 (m), 851.9 (m), 734.3 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{32}BO_3$ $[M+H]^+$: calculated: 343.2445, found: 343.2436. $[\alpha]^{20}_D$: -8.46 (c = 0.835, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

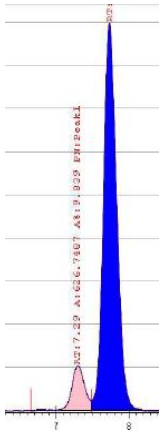
Chiral SFC (Chiralcel OD-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(1-(benzofuran-5-yl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Racemic Material

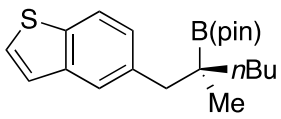


Peak No	% Area	Area	RT (min)
1	50.6292	3309.6612	7.34
2	49.3708	3227.3976	7.82
Total:	100	6537.0588	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	9.839	626.7487	7.29
2	90.161	5743.3208	7.74
Total:	100	6370.0695	



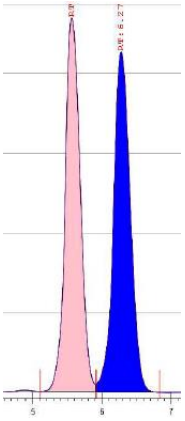
(*R*)-2-(1-(benzo[*b*]thiophen-5-yl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (16). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 5-bromobenzo[*b*]thiophene (46.9 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (61.0 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.38 (d, *J* = 5.4 Hz, 1H), 7.30-7.17 (m, 2H), 2.94 (d, *J* = 13.1 Hz, 1H), 2.60 (d, *J* = 13.1 Hz, 1H), 1.54-1.46 (m, 1H), 1.43-1.13 (m, 17H), 0.97-0.85 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.5, 137.2, 136.4, 127.3, 126.0, 124.9, 123.6, 121.4, 83.1, 44.7, 39.3, 28.2, 25.1, 24.8, 23.6, 21.2, 14.2. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.5. IR (neat) ν_{max} 2974.8 (m), 2956.3 (m), 2927.0 (m), 2858.5 (m), 1466.4 (m), 1420.5 (m), 1379.0 (m), 1348.0 (m), 1308.7 (s), 1272.7 (m), 1163.4 (m), 1140.3 (s), 1087.8 (m), 968.4 (m), 832.6 (m), 768.2 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{32}BO_2S$ $[M+H]^+$: calculated: 359.2216, found: 359.2225. $[\alpha]^{20}_D$: -4.10 (c = 1.000, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

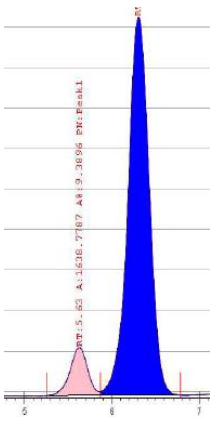
Chiral SFC (Chiralcel OJ-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(1-(benzo[b]thiophen-5-yl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Racemic Material

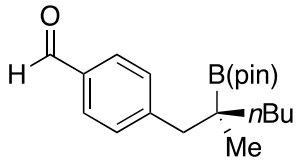


Peak No	% Area	Area	RT (min)
1	49.6956	35515.3238	5.56
2	50.3044	35950.4448	6.27
Total:	100	71465.7686	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	9.3896	1638.7787	5.63
2	90.6104	15814.3513	6.3
Total:	100	17453.13	



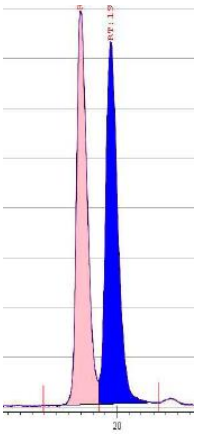
(*R*)-4-(2-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl)benzaldehyde (17). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 4-bromobenzaldehyde (40.7 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (53.4 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR 9.96 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 2.87 (d, *J* = 12.8 Hz, 1H), 2.54 (d, *J* = 12.8 Hz, 1H), 1.54-1.37 (m, 1H), 1.37-1.12 (m, 17H), 0.95-0.82 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.3, 148.3, 134.5, 131.2, 129.4, 83.5, 45.1, 39.5, 28.3, 25.3, 25.0, 23.7, 21.5, 14.3; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.3; IR (neat): ν_{max} 2975.7 (m), 2928.5 (m), 2858.5 (w), 1700.8 (s), 1605.7 (m), 1466.8 (m), 1380.8 (m), 1309.0 (m), 1214.0 (m), 1139.0 (s), 968.3 (w), 851.4 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{32}BO_3$ $[M+H]^+$: calculated: 331.2445, found: 331.2457. $[\alpha]^{20}_D$: -3.53 (c = 1.090, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(diphenylphosphino)ferrocene (6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

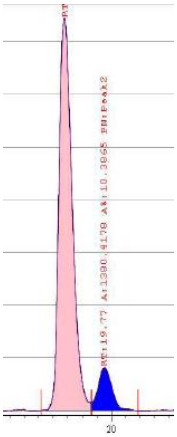
Chiral SFC (Chiralcel OD-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-4-(2-hydroxy-2-methylhexyl)benzaldehyde.

Racemic Material

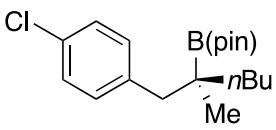


Peak No	% Area	Area	RT (min)
1	49.0217	12179.4416	18.48
2	50.9783	12665.5684	19.74
Total:	100	24845.01	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	89.6135	11910.1133	18.39
2	10.3865	1380.4178	19.77
Total:	100	13290.5311	



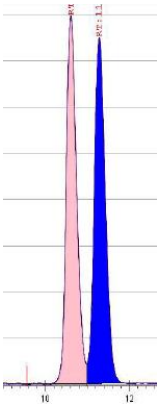
(*R*)-2-(1-(4-chlorophenyl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 1-bromo-4-chlorobenzene (42.1 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M) at 60 °C. The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (64.6 mg, 96% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 2.76 (d, *J* = 13.1 Hz, 1H), 2.43 (d, *J* = 13.2 Hz, 1H), 1.43 (td, *J* = 12.1, 3.6 Hz, 1H), 1.36-1.13 (m, 17H), 1.00-0.78 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 141.4, 134.3, 134.0, 130.3, 85.8, 46.7, 41.8, 30.8, 27.7, 27.5, 26.2, 23.8, 16.8. ^{11}B NMR: (160 MHz, Chloroform-*d*) δ 34.5. IR (neat) ν_{max} 2976.5 (m), 2957.2 (m), 2859.1 (m), 1490.8 (m), 1466.4 (m), 1378.7 (s), 1309.3 (s), 1272.4 (m), 1164.7 (s), 1092.1 (m), 968.1 (m), 853.4 (m), 787.1 (m), 727.7 (m), 579.2 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{31}BClO_2$ $[M+H]^+$: calculated: 337.2105, found: 337.2114. $[\alpha]^{20}_D$: -3.60 (c = 0.855, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(diisopropylphosphino)-ferrocene (6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the conjunctive cross-coupling/oxidation procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

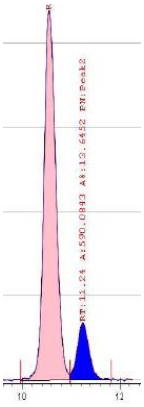
Chiral SFC (Chiralcel OD-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-chlorophenyl)-2-methylhexan-2-ol.

Racemic Material

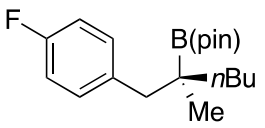


Peak No	% Area	Area	RT (min)
1	49.8201	6885.3541	10.61
2	50.1799	6935.0792	11.28
Total:	100	13820.4333	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	86.3548	3734.3985	10.55
2	13.6452	590.0843	11.24
Total:	100	4324.4828	



(*R*)-2-(1-(4-fluorophenyl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (19). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 1-bromo-4-fluorobenzene (38.5 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (58.8 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (dd, J = 8.3, 5.5 Hz, 2H), 6.91 (dd, J = 10.0, 7.6 Hz, 2H), 2.77 (d, J = 13.3 Hz, 1H), 2.43 (d, J = 13.2 Hz, 1H), 1.43 (dt, J = 12.0, 5.9 Hz, 1H), 1.37-1.12 (m, 17H), 1.01-0.77 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.3 (d, $^{1}J_{C–F}$ = 243.1 Hz), 135.8, 131.6 (d, $^{3}J_{C–F}$ = 7.6 Hz), 114.2 (d, $^{2}J_{C–F}$ = 20.7 Hz) 83.1, 43.9, 39.2, 28.1, 25.1, 24.8, 23.6, 21.1, 14.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.5. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -118.3. IR (neat) ν_{max} 2977.1 (m), 2957.6 (m), 2928.3 (m), 2859.8 (m), 1602.9 (m), 1508.8 (s), 1466.6 (m), 1379.1 (s), 1309.1 (s), 1157.9 (s), 1112.3 (m), 1093.1 (m), 968.3 (m), 852.98 (m), 767.4 (m), 669.9 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{31}BFO_2$ $[M+H]^+$: calculated: 321.2401, found: 321.2408. $[\alpha]^{20}_D$: -4.21 (c = 1.615, $CHCl_3$, l = 50 mm).

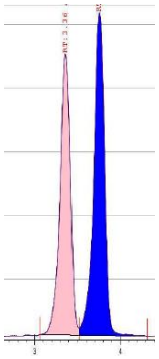
Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation procedure*, and the enantioselectivity was determined on the

corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

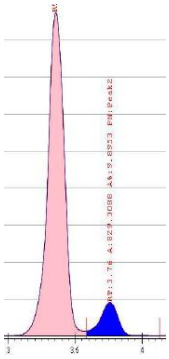
Chiral SFC (Chiralcel OJ-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(4-fluorophenyl)-2-methylhexan-2-ol.

Racemic Material

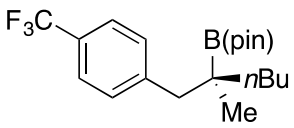


Peak No	% Area	Area	RT (min)
1	44.9309	1850.1542	3.36
2	55.0691	2267.624	3.75
Total:	100	4117.7782	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	90.1047	7551.4868	3.35
2	9.8953	829.3088	3.76
Total:	100	8380.7956	



(*R*)-4,4,5,5-tetramethyl-2-(2-methyl-1-(4-(trifluoromethyl)phenyl)-hexan-2-yl)-1,3,2-dioxaborolane (20). The reaction was performed according to the general procedure ***(Method A)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 4-(trifluoromethyl)phenyl trifluoro-methanesulfonate (64.7 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (67.4 mg, 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 2.85 (d, *J* = 13.0 Hz, 1H), 2.52 (d, *J* = 12.9 Hz, 1H), 1.44 (td, *J* = 11.9, 3.5 Hz, 1H), 1.37-1.10 (m, 17H), 1.01-0.77 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.5, 130.5, 128.0 (partially buried, q, $^{2}J_{C–F}$ = 32.4 Hz), 124.5 (partially buried, q, $^{1}J_{C–F}$ = 271.3 Hz), 124.4 (q, $^{3}J_{C–F}$ = 3.8 Hz), 83.2, 44.4, 39.2, 28.1, 25.0, 24.8, 23.5, 21.2, 14.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.4. ^{19}F NMR: ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.3 IR (neat) ν_{max} 2958.8 (m), 2929.4 (m), 2860.9 (m), 1617.9 (m), 1467.6 (m), 1380.4 (m), 1322.7 (s), 1273.4 (m), 1118.7 (s), 1066.7 (s), 1019.7 (m), 968.1 (m), 826.7 (m), 696.3 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{34}BF_3O_3N$ $[M+NH_4]^+$: calculated: 388.2635, found: 388.2656. $[\alpha]^{20}_D$: -1.96 (c = 2.100, $CHCl_3$, *l* = 50 mm).

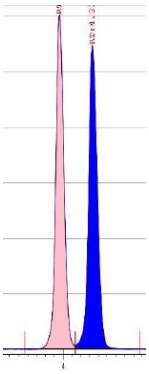
Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst.. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on

the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

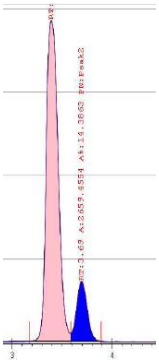
Chiral SFC (Chiralcel OD-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-2-methyl-1-(4-(trifluoromethyl)phenyl)hexan-2-ol.

Racemic Material



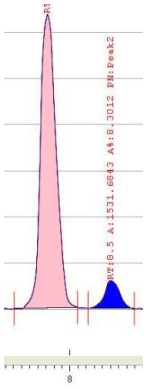
Peak No	% Area	Area	RT (min)
1	50.4514	7738.8905	3.96
2	49.5486	7600.4205	4.33
Total:	100	15339.311	

Standard Conditions (40 °C)

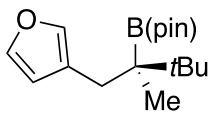


Peak No	% Area	Area	RT (min)
1	85.6137	15826.53	3.39
2	14.3863	2659.4554	3.69
Total:	100	18485.9854	

Standard Conditions (room temperature)



Peak No	% Area	Area	RT (min)
1	91.6988	16919.7418	7.72
2	8.3012	1531.6843	8.5
Total:	100	18451.4261	



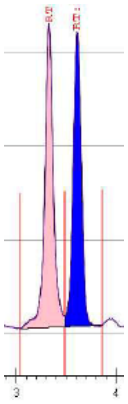
(*S*)-2-(1-(furan-3-yl)-2,3,3-trimethylbutan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (21). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.12 mL, 1.7 M in pentane, 0.20 mmol, 1.00 equiv.), 3-bromofuran (32.3 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M) at 60 °C. The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (50.0 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.22 (s, 1H), 6.31 (s, 1H), 2.85 (d, J = 13.3 Hz, 1H), 2.11 (d, J = 13.3 Hz, 1H), 1.17 (d, J = 47.5 Hz, 12H), 0.97 (s, 9H), 0.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.50, 140.66, 123.47, 113.38, 83.06, 34.72, 28.53, 26.95, 25.70, 24.47, 17.40. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.3. IR (neat) ν_{max} 2974.6 (m), 2874.2 (m), 1501.0 (m), 1460.8 (m), 1399.6 (m), 1370.5 (m), 1303.4 (s), 1264.5 (m), 1209.8 (m), 1144.0 (s), 1110.9 (m), 1024.9 (m), 967.1 (m), 851.4 (m), 723.0 (m), 635.5 (m) cm^{-1}. HRMS (DART) for $C_{17}H_{30}BO_3$ $[M+H]^+$: calculated: 293.2288, found: 293.2305. $[\alpha]^{20}_D$: -38.79 (c = 1.053, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

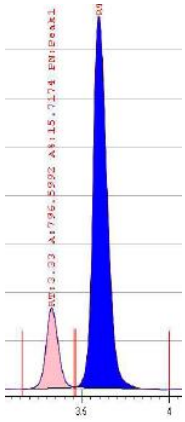
Chiral SFC (Chiralcel OD-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1-(furan-3-yl)-2,3,3-trimethylbutan-2-ol.

Racemic Material

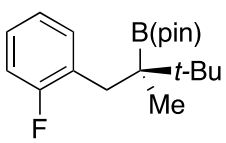


Peak No	% Area	Area	RT (min)
1	52.5426	992.3582	3.33
2	47.4574	896.3136	3.61
Total:	100	1888.6718	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	15.7174	796.5992	3.33
2	84.2826	4271.6557	3.6
Total:	100	5068.2549	



(*S*)-2-(1-(2-fluorophenyl)-2,3,3-trimethylbutan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 1-bromo-2-fluorobenzene (37.6 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M) at 60 °C. The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a white solid (52.0 mg, 81% yield). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.43 (td, J = 7.7, 1.8 Hz, 1H), 7.12 (tdd, J = 7.1, 5.0, 1.9 Hz, 1H), 7.06-6.86 (m, 2H), 2.89 (d, J = 13.6 Hz, 1H), 2.66 (d, J = 13.6 Hz, 1H), 1.21 (d, J = 58.2 Hz, 12H), 1.03 (s, 9H), 0.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.8 (d, $^{1}J_{C–F}$ = 244.6 Hz), 132.6 (d, $^{3}J_{C–F}$ = 4.8 Hz) 128.7 (d, $^{2}J_{C–F}$ = 15.6 Hz) 127.2 (d, $^{3}J_{C–F}$ = 8.2 Hz), 123.2, 114.9 (d, $^{2}J_{C–F}$ = 23.4 Hz) 83.2, 35.2, 31.4, 26.9, 25.8, 24.6, 16.1. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.3. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -114.6. IR (neat) ν_{max} 2974.3 (m), 2873.8 (m), 1584.0 (m), 1475.9 (m), 1400.1 (m), 1369.3 (m), 1303.3 (s), 1228.1 (m), 1181.7 (m), 1143.9 (s), 1120.2 (s), 1035.0 (m), 945.3 (m), 754.9 (s), 663.3 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{31}BFO_2$ $[M+H]^+$: calculated: 321.2401, found: 321.2418. $[\alpha]^{20}_D$: -15.88 (c = 2.250, $CHCl_3$, l = 50 mm).

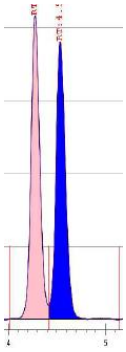
Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on

the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

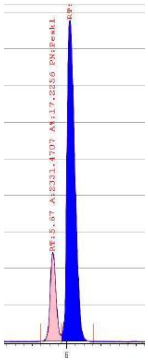
Chiral SFC (Chiralcel OD-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1-(2-fluorophenyl)-2,3,3-trimethylbutan-2-ol.

Racemic Material

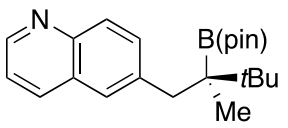


Peak No	% Area	Area	RT (min)
1	50.1737	2607.4373	4.27
2	49.8263	2589.3855	4.53
Total:	100	5196.8228	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	17.2256	2331.4707	5.67
2	82.7744	11203.4438	6.07
Total:	100	13534.9145	



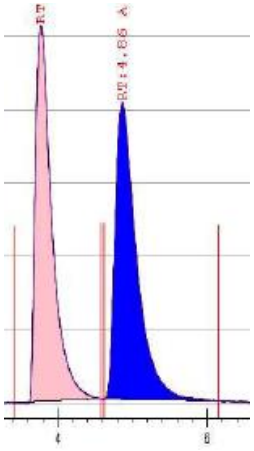
(*S*)-6-(2,3,3-trimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)quinolone (23). The reaction was performed according to the general procedure ***(Method A)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.12 mL, 1.7 M in pentane, 0.20 mmol, 1.00 equiv.), quinolin-6-yl trifluoromethanesulfonate (61.0 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.) in THF (0.8 mL, 0.25 M) at 60 °C. The crude mixture was purified by silica gel chromatography (5-20% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a white solid (39.0 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.09 – 7.98 (m, 1H), 7.95 (dt, *J* = 8.6, 0.7 Hz, 1H), 7.76-7.61 (m, 2H), 7.34 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.28 (d, *J* = 12.5 Hz, 1H), 2.50 (d, *J* = 12.5 Hz, 1H), 1.25 (s, 6H), 1.12-1.01 (m, 15H), 0.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.5, 147.0, 140.3, 135.4, 133.6, 128.7, 128.1, 127.8, 120.8, 83.2, 39.4, 35.1, 27.0, 25.8, 24.7, 17.3. ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.9. IR (neat) ν_{max} 2973.3(m), 2874.1 (m), 1593.7 (m), 1500.3 (m), 1459.4 (m), 1370.6 (m), 1304.5 (s), 1266.8 (m), 1226.9 (m), 1209.5 (m), 1164.4 (m), 1143.3 (s), 1115.8 (m), 841.1 (s), 784.2 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{33}BNO_2$ $[M+H]^+$: calculated: 354.2604, found: 354.2610. $[\alpha]^{20}_D$: -21.96 (c = 0.750, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(diisopropylphosphino)-ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

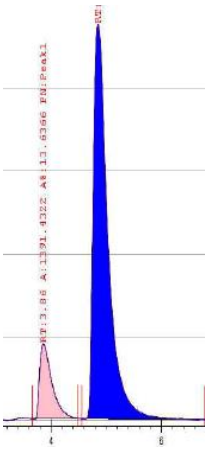
Chiral SFC (Chiralcel OJ-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-6-(2,3,3-trimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)quinolone.

Racemic Material

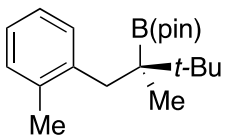


Peak No	% Area	Area	RT (min)
1	49.4414	3945.7417	3.77
2	50.5586	4034.8982	4.86
Total:	100	7980.6399	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	13.6366	1391.4322	3.86
2	86.3634	8812.2584	4.85
Total:	100	10203.6906	



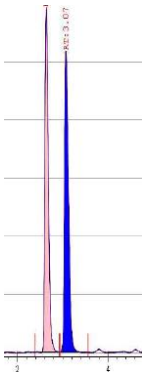
(*S*)-4,4,5,5-tetramethyl-2-(2,3,3-trimethyl-1-(o-tolyl)butan-2-yl)-1,3,2-dioxaborolane (24). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.12 mL, 1.7 M in pentane, 0.20 mmol, 1.00 equiv.), 1-bromo-2-methylbenzene (37.6 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (45.3 mg, 71% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 6.8, 2.3 Hz, 1H), 7.10-6.97 (m, 3H), 2.98 (d, *J* = 13.3 Hz, 1H), 2.51 (d, *J* = 13.3 Hz, 1H), 2.32 (s, 3H), 1.18 (d, *J* = 63.8 Hz, 12H), 1.02 (s, 9H), 0.81 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 140.6, 137.6, 130.5, 130.3, 125.6, 125.4, 83.3, 35.7, 35.0, 27.2, 26.0, 24.8, 20.9, 16.5; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.5; IR (neat): ν_{max} 2973.1 (m), 2874.5 (w), 1460.2 (m), 1398.4 (m), 1370.1 (m), 1301.9 (s), 1208.9 (m), 1144.5 (s), 1124.1 (m), 967.5 (m), 852.2 (m), 741.9 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{34}BO_2$ $[M+H]^+$: calculated: 317.2652, found: 317.2661. $[\alpha]^{20}_D$: -13.59 (c = 1.385, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexyl-phosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

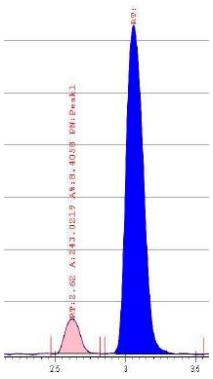
Chiral SFC (Chiralcel ODR-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-4,4,5,5-tetramethyl-2-(2,3,3-trimethyl-1-(o-tolyl)butan-2-yl)-1,3,2-dioxaborolane.

Racemic Material

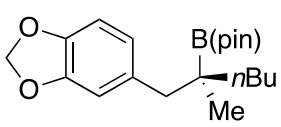


Peak No	% Area	Area	RT (min)
1	50.079	6484.4311	2.63
2	49.921	6463.9835	3.07
Total:	100	12948.4146	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	8.4058	243.0219	2.62
2	91.5942	2648.1033	3.06
Total:	100	2891.1252	



(*R*)-2-(1-(benzo[*d*][1,3]dioxol-5-yl)-2-methylhexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 5-bromobenzo[*d*][1,3]dioxole (38.5 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (66.4 mg, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (s, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.9, 1H), 5.89 (s, 2H), 2.72 (d, *J* = 13.2 Hz, 1H), 2.37 (d, *J* = 13.2 Hz, 1H), 1.44 (td, *J* = 11.8, 3.5 Hz, 1H), 1.35-1.15 (m, 17H), 0.97-0.82 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.9, 145.4, 134.1, 123.1, 110.8, 107.5, 100.6, 83.1, 44.6, 39.2, 28.2, 25.1, 24.8, 23.6, 21.2, 14.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.5. IR (neat) ν_{max} 2956.5 (m), 2927.3 (m), 2870.7 (m), 1503.3 (s), 1488.1 (s), 1467.2 (m), 1440.0 (m), 1371.1 (m), 1274.9 (m), 1246.2 (s), 1164.4 (s), 968.2 (s), 851.3 (m), 770.8 (m), 669.9 (m), 608.6 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{32}BO_4$ $[M+H]^+$: calculated: 347.2394, found: 347.2383. $[\alpha]^{20}_D$: -4.83 (c = 1.61, $CHCl_3$, *l* = 50 mm).

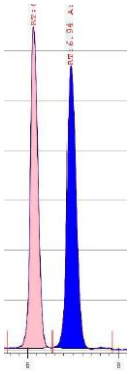
Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(diisopropylphosphino)-ferrocene (6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on the

corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

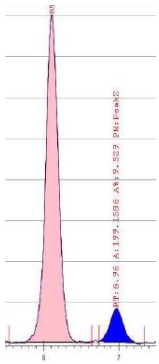
Chiral SFC (Chiralcel OJ-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-1-(benzo[d][1,3]dioxol-5-yl)-2-methylhexan-2-ol.

Racemic Material

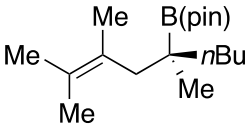


Peak No	% Area	Area	RT (min)
1	50.1598	3855.4563	6.12
2	49.8402	3830.8983	6.94
Total:	100	7686.3546	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	90.471	1890.8774	6.11
2	9.529	199.1586	6.96
Total:	100	2090.036	



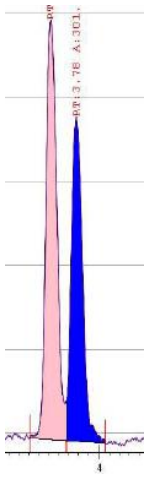
(*R*)-4,4,5,5-tetramethyl-2-(2,3,5-trimethylnon-2-en-5-yl)-1,3,2-dioxaborolane (26). The reaction was performed according to the general procedure ***(Method B)*** with isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *n*-butyl lithium (0.08 mL, 2.5M in hexane, 0.20 mmol, 1.00 equiv.), 2-bromo-3-methylbut-2-ene (32.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (37.6 mg, 0.20 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M) at 60 °C. The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (44.1 mg, 75% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.14 (d, *J* = 13.4 Hz, 1H), 2.08 (d, *J* = 13.4 Hz, 1H), 1.72-1.55 (m, 9H), 1.51-1.42 (m, 1H), 1.36-1.09 (m, 17H), 0.93-0.79 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 126.9, 126.0, 83.1, 43.7, 41.0, 28.5, 25.4, 25.1, 25.0, 23.9, 21.4, 21.2, 21.0, 20.2, 14.3; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.2; IR (neat): ν_{max} 2926.7 (m), 2860.1 (w), 1466.4 (w), 1370.6 (m), 1305.6 (m), 1141.0 (s), 968.6 (w), 850.7 (w) cm^{-1}. HRMS (DART) for $C_{18}H_{36}BO_2$ $[M+H]^+$: calculated: 295.2808, found: 295.2804. $[\alpha]^{20}_D$: -4.12 (c = 1.055, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the *conjunctive cross-coupling/oxidation* procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

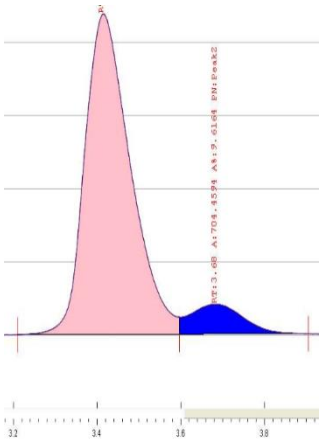
Chiral SFC (Chiralcel OD-H, 0% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-2,3,5-trimethylnon-2-en-5-ol.

Racemic Material



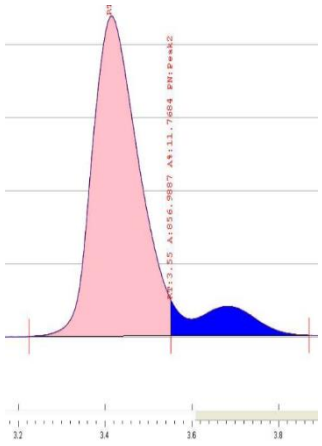
Peak No	% Area	Area	RT (min)
1	55.7398	379.8018	3.52
2	44.2602	301.5819	3.78
Total:	100	681.3837	

Standard Conditions

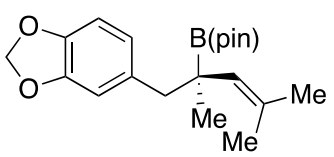


Peak No	% Area	Area	RT (min)
1	90.3836	6621.136	3.41
2	9.6164	704.4594	3.68
Total:	100	7325.5954	

Lower Limit



Peak No	% Area	Area	RT (min)
1	88.2316	6425.1414	3.41
2	11.7684	856.9887	3.55
Total:	100	7282.1301	



(*S*)-2-(1-(benzo[*d*][1,3]dioxol-5-yl)-2,4-dimethylpent-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (27). The reaction was performed according to the general procedure ***(Method D)*** with modification. Using isopropenyl boronic acid pinacol ester (33.6 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.24 mL, 1.7 M in pentane, 0.40 mmol, 2.00 equiv.), 1-bromo-2-methylprop-1-ene (27.0 mg, 0.20 mmol, 1.00 equiv.), benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate (59.4 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **2.43** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (75.2 mg, 0.40 mmol, 2.00 equiv.) in THF (0.8 mL, 0.25 M). The reaction mixture was allowed to warm to room temperature after adding the *tert*-butyl lithium. The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (60 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75-6.65 (m, 2H), 6.62 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.94-5.85 (m, 2H), 5.01 (p, *J* = 1.4 Hz, 1H), 2.74 (d, *J* = 13.2 Hz, 1H), 2.64 (d, *J* = 13.2 Hz, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.55 (d, *J* = 1.4 Hz, 3H), 1.24 (d, *J* = 16.6 Hz, 12H), 1.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.4, 133.6, 131.8, 123.6, 111.1, 107.3, 100.5, 83.2, 44.2, 30.7, 26.5, 25.0, 24.7, 23.5, 20.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.1. IR (neat): ν_{max} 2976.0 (m), 2924.6 (m), 1503.0 (m), 1488.4 (s), 1458.0 (m), 1379.4 (m), 1336.9 (m), 1275.6 (m), 1212.0 (s), 1143.4 (m), 1101.9 (s), 1040.3 (m), 933.5 (m), 811.2 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{30}BO_4$ $[M+H]^+$: calculated: 345.2237, found: 345.2249. $[\alpha]^{20}_D$: -48.84 (c = 1.000, $CHCl_3$, *l* = 50 mm).

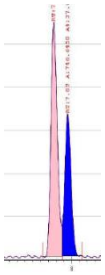
Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. The product was oxidized with NaOH, and H_2O_2 according to the

conjunctive cross-coupling/oxidation procedure, and the enantioselectivity was determined on the corresponding alcohol. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

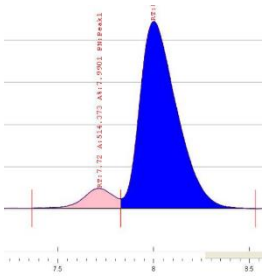
Chiral SFC (Chiralcel ODR-H, 1% IPA, 3 mL/min, 100 bar, 25 °C, 210-270 nm) – analysis of (R)-1-(benzo[d][1,3]dioxol-5-yl)-2,4-dimethylpent-3-en-2-ol.

Racemic Material



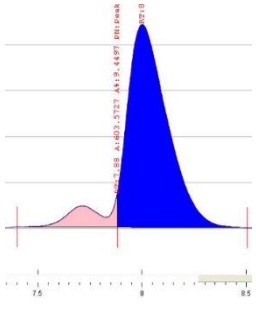
Peak No	% Area	Area	RT (min)
1	62.3105	1234.4004	7.54
2	37.6895	746.6458	7.89
Total:	100	1981.0462	

Standard Conditions

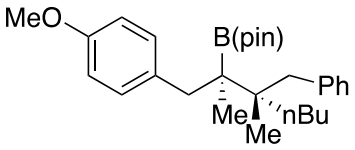


Peak No	% Area	Area	RT (min)
1	7.9901	514.373	7.72
2	92.0099	5923.2916	8
Total:	100	6437.6646	

Lower Limit



Peak No	% Area	Area	RT (min)
1	9.4497	603.5727	7.88
2	90.5503	5783.6134	8
Total:	100	6387.1861	

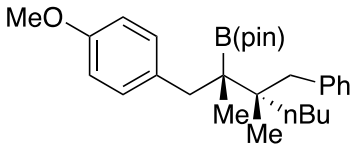


2-((*2S*,*3S*)-3-benzyl-1-(4-methoxyphenyl)-2,3-dimethylheptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (28). The target product was synthesized according to the General procedure (***Method C***): To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added 2-isopropenyl bromide (0.30 mmol, 1.00 equiv.) and diethyl ether (0.3 mL), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to -78 °C, and a *tert*-butyl lithium solution (0.60 mmol, 2.00 equiv.) was added at -78 °C. The reaction vial was allowed to stir at -78 °C for 20 minutes. Then an (*R*)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylhexan-2-yl)-1,3,2-dioxaborolane (prepared according to the conjunctive cross coupling general procedure ***Method A***, the crude material was passed through a silica gel plug with diethyl ether, concentrated under reduced pressure, and used without further purification.) diethyl ether solution (0.30 mmol, 1.00 equiv.) was added at -78 °C. The reaction vial was allowed to warm to room temperature and stirred 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 $Pd(OAc)_2$ (0.006 mmol, 0.02 equiv.), (S_p, S_p)-**2.44** (0.0066 mmol, 0.022 equiv.), and THF (0.6 mL). The $Pd(OAc)_2$/(S_p, S_p)-**2.44** solution was allowed to stir for 20 minutes at room temperature. Then the $Pd(OAc)_2$/(S_p, S_p)-**2.44** solution was transferred into the reaction vial, followed by THF (0.6 mL), potassium trifluoromethanesulfonate (0.60 mmol, 2.0 equiv.) and 4-methoxyphenyl trifluoromethanesulfonate (0.33 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 15 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, concentrated under reduced pressure, and subsequently purified via silica

gel column chromatography to afford the desired product (102.7 mg, 76% yield, 9:1 *d.r.*). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.16 (m, 6H), 6.81 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.13 (d, *J* = 12.7 Hz, 1H), 3.04 (d, *J* = 13.1 Hz, 1H), 2.67 (d, *J* = 13.0 Hz, 1H), 2.44 (d, *J* = 12.7 Hz, 1H), 1.62-1.49 (m, 1H), 1.43-1.08 (m, 17H), 1.03-0.97 (m, 6H), 0.80 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 157.9, 140.9, 133.3, 132.2, 131.1, 131.0, 127.8, 125.7, 113.1, 83.3, 55.4, 41.6, 38.7, 36.2, 27.6, 26.2, 26.1, 24.9, 24.0, 17.7, 14.3; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.9; IR (neat): ν_{max} 2956.1 (m), 2930.4 (m), 2869.9 (w), 1610.1 (w), 1510.5 (s), 1463.8 (m), 1371.6 (m), 1299.2 (m), 1246.4 (s), 1143.0 (s), 1037.9 (m), 967.9 (m), 833.2 (m), 702.5 (m) cm^{-1}. HRMS (DART) for $C_{29}H_{44}BO_3$ $[M+H]^+$: calculated: 451.3384, found: 451.3391. $[\alpha]^{20}_D$: -32.31 (c = 2.060, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The diastereomer ratio was determined by ^{1}H NMR. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

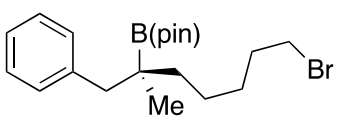


2-((*2R*,*3S*)-3-benzyl-1-(4-methoxyphenyl)-2,3-dimethylheptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (29). The target product was synthesized according to the General procedure (***Method C***): To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added 2-isopropenyl bromide (0.30 mmol, 1.00 equiv.) and diethyl ether (0.3 mL), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to -78 °C, and a *tert*-butyl lithium solution (0.60 mmol, 2.00 equiv.) was added at -78 °C. The reaction vial was allowed to stir at -78 °C for 20 minutes. Then an (*R*)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylhexan-2-yl)-1,3,2-dioxaborolane (prepared according to the conjunctive cross coupling general procedure ***Method A***, the crude material was passed through a silica gel plug with diethyl ether, concentrated under reduced pressure, and used without further purification.) diethyl ether solution (0.30 mmol, 1.00 equiv.) was added at -78 °C. The reaction vial was allowed to warm to room temperature and stirred 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 $Pd(OAc)_2$ (0.006 mmol, 0.02 equiv.), (R_p, R_p)-**2.44** (0.0066 mmol, 0.022 equiv.), and THF (0.6 mL). The $Pd(OAc)_2$/(R_p, R_p)-**2.44** solution was allowed to stir for 20 minutes at room temperature. Then the $Pd(OAc)_2$/(R_p, R_p)-**2.44** solution was transferred into the reaction vial, followed by THF (0.6 mL), potassium trifluoromethanesulfonate (0.60 mmol, 2.0 equiv.) and 4-methoxyphenyl trifluoromethanesulfonate (0.33 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 15 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, concentrated under reduced pressure, and subsequently purified via silica

gel column chromatography to afford the desired product (99.1 mg, 73% yield, 5.3:1 *d.r.* diastereoselectivity was determined by ^{1}H NMR). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.18 (m, 7H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 3.15 (d, *J* = 12.7 Hz, 1H), 2.89 (s, 2H), 2.53 (d, *J* = 12.7 Hz, 1H), 1.52-1.09 (m, 18H), 1.07-0.88 (m, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 157.9, 140.7, 133.3, 132.2, 131.1, 131.0, 127.8, 125.7, 113.1, 113.0, 83.3, 55.4, 41.3, 38.7, 28.2, 26.2, 26.1, 24.9, 24.2, 17.9, 14.4; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.0; IR (neat): ν_{max} 2955.9 (m), 2930.8 (m), 2869.9 (w), 1610.3 (w), 1510.3 (s), 1463.9 (m), 1387.1 (m), 1299.3 (m), 1246.4 (s), 1142.9 (s), 1038.2 (m), 967.9 (m), 833.4 (m), 702.5 (m) cm^{-1}. HRMS (DART) for $C_{29}H_{44}BO_3$ $[M+H]^+$: calculated: 451.3384, found: 451.3387. $[\alpha]^{20}_D$: +29.71 (c = 3.745, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The diastereomer ratio was determined by ^{1}H NMR. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).



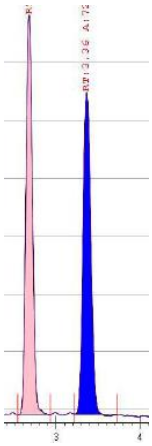
(*R*)-2-(7-bromo-2-methyl-1-phenylheptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30). The reaction was performed according to the general procedure ***(Method C)*** with 2-bromopropene (24.2 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.24 mL, 1.7 M in pentane, 0.40 mmol, 2.00 equiv.), 2-(5-bromopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (55.4 mg, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **2.43** (4.60 mg, 0.0044 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (75.2 mg, 0.40 mmol, 2.00 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (57.4 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.04 (m, 5H), 3.40 (t, J = 6.9 Hz, 2H), 2.77 (d, J = 13.0, 1H), 2.49 (d, J = 13.0 Hz, 1H), 1.96-1.75 (m, 2H), 1.49-1.12 (m, 18H), 0.88 (s, 3H). ^{13}C NMR (MHz, $CDCl_3$): (151 MHz, $CDCl_3$) δ 142.6, 133.0, 130.3, 128.3, 85.8, 47.4, 41.7, 36.6, 35.4, 31.6, 27.74, 27.71, 27.5, 23.9. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.6. IR (neat) ν_{max} 3028.0 (m), 2976.6 (m), 2929.9 (m), 2857.5 (m), 1494.3 (m), 1380.1 (s), 1371.0 (s), 1309.4 (s), 1250.4 (m), 1228.6 (m), 1164.5 (s), 1109.8 (m), 967.8 (m), 748.1 (m), 670.2 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{33}BBrO_2$ $[M+H]^+$: calculated: 395.1757, found: 395.1751. $[\alpha]^{20}_D$: -7.28 (c = 0.965, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with 2-(5-bromopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

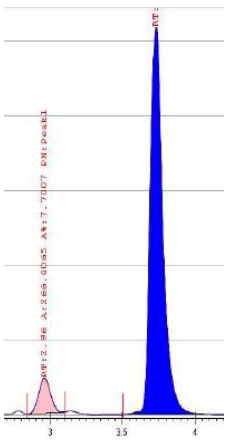
Chiral SFC (Chiralcel ODR-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(7-bromo-2-methyl-1-phenylheptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Racemic Material

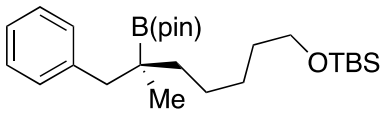


Peak No	% Area	Area	RT (min)
1	50.7099	748.9426	2.67
2	49.2901	727.9746	3.36
Total:	100	1476.9172	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	7.7007	266.4065	2.96
2	92.2993	3193.0848	3.73
Total:	100	3459.4913	



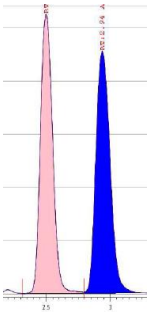
(*R*)-*tert*-butyldimethyl((6-methyl-7-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptyl)oxy)silane (31). The reaction was performed according to the general procedure ***(Method C)*** with 2-bromopropene (24.2 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.24 mL, 1.7 M in pentane, 0.40 mmol, 2.00 equiv.), *tert*-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)silane (65.7 mg, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **2.43** (4.60 mg, 0.0044 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (75.2 mg, 0.40 mmol, 2.00 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (55.2 mg, 62% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24-7.08 (m, 5H), 3.59 (t, *J* = 6.7 Hz, 2H), 2.79 (d, *J* = 13.1 Hz, 1H), 2.47 (d, *J* = 13.1 Hz, 1H), 1.54-1.48 (m, 2H), 1.38-1.12 (m, 20H), 0.94-0.84 (m, 12H), 0.04 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 142.8, 133.0, 130.2, 128.3, 85.8, 66.0, 47.4, 42.2, 35.6, 29.4, 28.6, 28.5, 27.7, 27.5, 27.4, 23.8, -2.6. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.3. IR (neat) ν_{max} 2976.0 (m), 2929.4 (m), 2856.9 (m), 1469.9 (m), 1380.5 (m), 1371.1 (m), 1254.2 (m), 1212.4 (m), 1099.7 (s), 968.2 (m), 834.7 (s), 813.3 (m), 775.0 (m), 702.3 (m) cm^{-1}. HRMS (DART) for $C_{26}H_{48}BO_3Si$ $[M+H]^+$: calculated: 447.3466, found: 447.3480. $[\alpha]^{20}_D$: -2.28 (c = 0.800, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with *tert*-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)silane, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexylphosphino)-ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

Chiral SFC (Chiralcel ODR-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-tert-butyldimethyl((6-methyl-7-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptyl)oxy)silane.

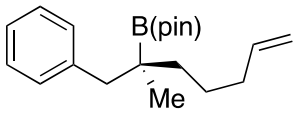
Racemic Material



Peak No	% Area	Area	RT (min)
1	49.771	1738.422	2.5
2	50.229	1754.4185	2.94
Total:	100	3492.8405	

Standard Conditions

Peak No	% Area	Area	RT (min)
1	9.6843	418.206	2.5
2	90.3157	3900.2017	2.93
Total:	100	4318.4077	



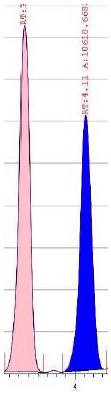
(*R*)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylhept-6-en-2-yl)-1,3,2-dioxaborolane (32). The reaction was performed according to the general procedure ***(Method C)*** with 2-bromopropene (24.2 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.24 mL, 1.7 M in pentane, 0.40 mmol, 2.00 equiv.), 4,4,5,5-tetramethyl-2-(pent-4-en-1-yl)-1,3,2-dioxaborolane (39.2 mg, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **2.43** (4.60 mg, 0.0044 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (75.2 mg, 0.40 mmol, 2.00 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (33.4 mg, 53% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30-7.08 (m, 5H), 5.90-5.72 (m, 1H), 5.00 (dd, *J* = 17.5, 1.7 Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 2.80 (d, *J* = 13.1 Hz, 1H), 2.49 (d, *J* = 13.1 Hz, 1H), 2.11-1.97 (m, 2H), 1.54-1.33 (m, 3H), 1.31-1.17 (m, 13H), 0.90 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 142.7, 141.8, 133.0, 130.2, 128.3, 116.8, 85.8, 47.4, 41.7, 37.3, 28.0, 27.8, 27.5, 23.9. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.4. IR (neat) ν_{max} 3062.1 (m), 3028.1 (m), 2929.2 (m), 2861.9 (m), 1640.3 (m), 1494.6 (m), 1380.7 (s), 1371.0 (s), 1349.6 (m), 1309.0 (s), 1212.9 (m), 1142.6 (s), 1031.3 (m), 967.6 (m), 748.4 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{32}BO_2$ $[M+H]^+$: calculated: 315.2495, found: 315.2489. $[\alpha]^{20}_D$: -10.15 (c = 0.650, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with 4,4,5,5-tetramethyl-2-(pent-4-en-1-yl)-1,3,2-dioxaborolane, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

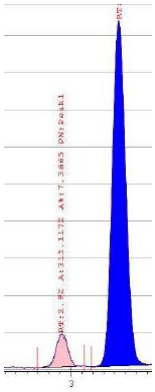
Chiral SFC (Chiralcel OD-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylhept-6-en-2-yl)-1,3,2-dioxaborolane.

Racemic Material

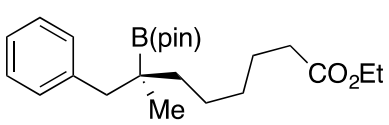


Peak No	% Area	Area	RT (min)
1	54.2936	12604.1579	3.45
2	45.7064	10610.6683	4.11
Total:	100	23214.8262	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	7.3665	315.1172	2.92
2	92.6335	3962.5782	3.44
Total:	100	4277.6954	



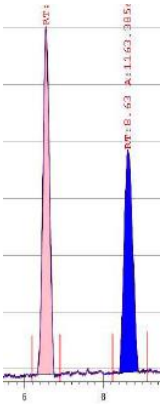
ethyl (*R*)-7-methyl-8-phenyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octanoate (33). The reaction was performed according to the general procedure ***(Method C)*** with 2-bromopropene (24.2 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.24 mL, 1.7 M in pentane, 0.40 mmol, 2.00 equiv.), ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanoate (54.0 mg, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **2.43** (4.60 mg, 0.0044 mmol, 0.011 equiv.), potassium trifluoromethanesulfonate (75.2 mg, 0.40 mmol, 2.00 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (34.0 mg, 44% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25-7.09 (m, 5H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.77 (d, *J* = 13.1 Hz, 1H), 2.48 (d, *J* = 13.1 Hz, 1H), 2.28 (t, *J* = 7.6 Hz, 3H), 1.71-1.60 (m, 2H), 1.45 (td, *J* = 12.5, 3.4 Hz, 1H), 1.40-1.13 (m, 19H), 0.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.5, 142.7 133.0, 130.2, 128.3, 85.8, 62.8, 47.4, 41.9, 37.0, 32.7, 28.3, 27.7, 27.6, 27.4, 23.8, 16.9. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.8. IR (neat) ν_{max} 3027.8 (m), 2977.3 (m), 2929.9 (m), 2858.6 (m), 1735.0 (s), 1602.9 (m), 1494.4 (m), 1349.0 (s), 1308.4 (s), 1251.8 (m), 1211.5 (m), 1143.1 (s), 1061.4 (m), 968.2 (m), 748.3 (m), 597.6 (m) cm^{-1}. HRMS (DART) for $C_{23}H_{38}BO_4$ $[M+H]^+$: calculated: 389.2863, found: 389.2866. $[\alpha]^{20}_D$: -8.26 (c = 0.690, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanoate, and $Pd(OAc)_2$ (1.0 mol%), (S_p, S_p)-**2.44** (0.6 mol%), and (R_p, R_p)-**2.44** (0.6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

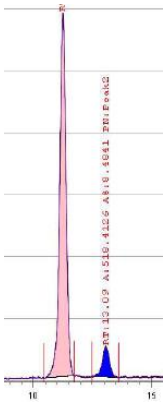
Chiral SFC (Chiralcel OD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of ethyl (R)-7-methyl-8-phenyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octanoate.

Racemic Material

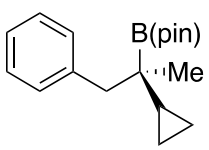


Peak No	% Area	Area	RT (min)
1	55.1931	1433.0577	6.55
2	44.8069	1163.3856	8.63
Total:	100	2596.4433	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	91.5159	5592.0214	11.25
2	8.4841	518.4126	13.09
Total:	100	6110.434	



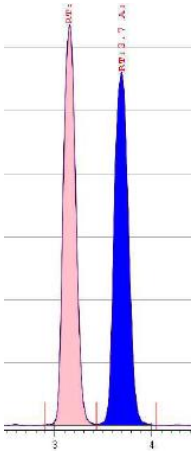
(*S*)-2-(2-cyclopropyl-1-phenylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34). The reaction was performed according to the general procedure ***(Method C)*** with 2-bromopropene (24.2 mg, 0.20 mmol, 1.00 equiv.), *tert*-butyl lithium (0.24 mL, 1.7 M in pentane, 0.40 mmol, 2.00 equiv.), 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (33.6 mg, 0.20 mmol, 1.00 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **2.43** (4.60 mg, 0.0044 mmol, 0.022 equiv.), and potassium trifluoromethanesulfonate (75.2 mg, 0.40 mmol, 2.00 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (34.8 mg, 60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.21 (m, 4H), 7.21-7.13 (m, 1H), 2.89 (d, *J* = 12.9 Hz, 1H), 2.62 (d, *J* = 12.9 Hz, 1H), 1.22 (d, *J* = 26.6 Hz, 12H), 0.79 (s, 3H), 0.76-0.69 (m, 1H), 0.47-0.19 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 140.5, 130.6, 127.7, 125.7, 83.3, 45.4, 25.1, 24.91, 24.86, 19.5, 19.2, 1.8, 1.0; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 33.7; IR (neat): ν_{max} 2977.3 (m), 2926.8 (w), 1454.4 (m), 1388.2 (m), 1307.8 (m), 1211.7 (m), 1143.8 (s), 861.0 (m), 701.7 (m) cm^{-1}. HRMS (DART) for $C_{18}H_{28}BO_2$ $[M+H]^+$: calculated: 287.2182, found: 287.2172. $[\alpha]^{20}_D$: -15.27 (c = 0.780, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(dicyclohexyl-phosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

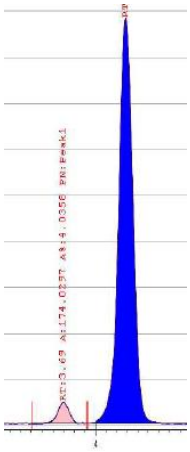
Chiral SFC (Chiralcel OD-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-2-(2-cyclopropyl-1-phenylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Racemic Material



Peak No	% Area	Area	RT (min)
1	49.9977	2852.9164	3.15
2	50.0023	2853.1799	3.7
Total:	100	5706.0963	

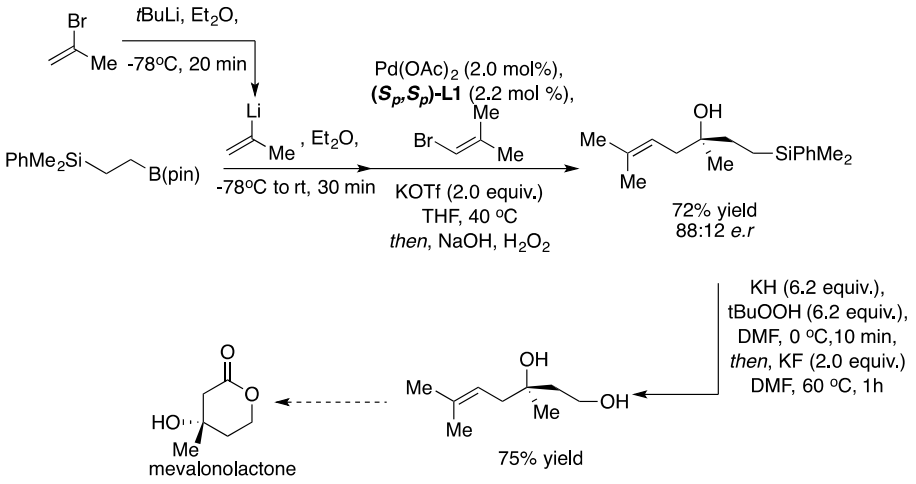
Standard Conditions

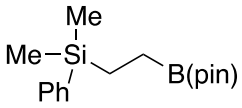


Peak No	% Area	Area	RT (min)
1	4.0358	174.0297	3.69
2	95.9642	4138.1398	4.28
Total:	100	4312.1695	

2.4.2.5. Target synthesis

Enantioselective synthesis of (S)-mevalonolactone

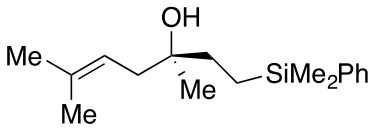




dimethyl(phenyl)(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-silane (35). The title compound was prepared according to a literature procedure with slight modification[45]. In an Ar-filled glovebox, B_2pin_2 (1.27 g, 5.00 mmol, 1.0 equiv.), copper (I) chloride (24.8 mg, 0.25 mmol, 0.05 equiv.) 1,1′-bis(diisopropylphosphino)ferrocene (112.1 mg, 0.25 mmol, 0.05 equiv.), and potassium tert-butoxide (673 mg, 6.00 mmol, 1.2 equiv.) were added to 50 mL round bottom flask equipped with a magnetic stir bar. The flask was sealed with a rubber septum and removed from the glovebox. Dry THF (10.00 mL, 0.5 M) was added and reaction mixture was cooled to 0 C before dimethyl-phenyl-vinyl-silane (0.91 mL, 5.00 mmol, 1.0 equiv.) was slowly added, followed by anhydrous methanol (0.81 mL, 20.00 mmol, 4.0 equiv.). Reaction was allowed to warm to room temperature and stirred for 3 hours. Reaction mixture was filtered through a plug of silica gel with diethyl ether, then concentrated to afford a yellow oil. The crude mixture was purified by silica gel

[45] Kubota, K.; Yamamoto, E.; Ito. H. *Adv. Synth. Catal*. **2013**, **355**, 3527–3531.

chromatography (1% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (1.21 g, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56-7.45 (m, 2H), 7.39-7.29 (m, 3H), 1.23 (s, 12H), 0.89-0.68 (m, 4H), 0.26 (d, J = 2.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.4, 133.7, 128.7, 127.6, 82.9, 24.8, 8.5, -3.5. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.1. IR (neat): ν_{max} 2977.7 (m), 2955.3 (m), 1426.0 (m), 1412.8 (s), 1358.9 (m), 1319.1 (m), 1237.7 (m), 1144.6 (m), 1112.8 (m), 996.2 (m), 879.5 (m), 832.9 (s), 811.9 (m), 771.8 (m) cm^{-1}. HRMS (DART) for $C_{16}H_{31}BNO_2Si$ $[M+NH_4]^+$: calculated: 308.2217, found: 308.2217.



(*R*)-1-(dimethyl(phenyl)silyl)-3,6-dimethylhept-5-en-3-ol (36). Prepared according to ***Method C***. Upon completion of the reaction, the mixture was cooled to 0 °C, then 3 M aq. NaOH (0.5 mL) was added followed by 30% aq. H_2O_2 (0.5 mL). This solution was stirred vigorously for 3 hours at room temperature then diluted with diethyl ether, cooled to 0 °C and quenched with sat. sodium thiosulfate (0.5 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether 3 times. Combined organic layers were dried over sodium sulfate, then filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (2% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (80.0 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.58-7.46 (m, 2H), 7.41-7.31 (m, 3H), 5.15 (t, 1H), 2.16 (t, J = 8.1 Hz, 2H), 1.73 (s, 3H), 1.63 (s, 3H), 1.52-1.42 (m, 2H), 1.13 (s, 3H), 0.85-0.71 (m, 2H), 0.28 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.1, 135.0, 133.5, 128.9, 127.7, 119.4, 73.7, 39.4, 35.6, 26.2, 26.1, 18.0, 9.4, -3.2, -3.3. IR (neat) ν_{max} 3419.9 (br), 3068.7 (m), 2963.7 (m), 2924.3 (m), 2858.1 (m), 1452.9 (m), 1375.2 (m), 1248.0 (m), 1192.4 (m), 1113.1 (s), 1025.3

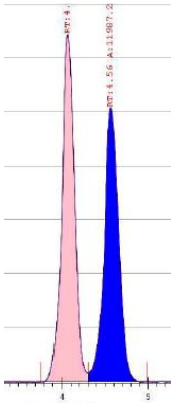
(m), 878.9 (m), 837.5 (s), 816.2 (s), 699.5 (s), 633.5 (m) cm^{-1}. HRMS (DART) for $C_{17}H_{27}Si$ $[M+H-H_2O]^+$: calculated: 259.1882, found: 259.1870. $[\alpha]^{20}_D$: +3.96 (c = 0.910, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the general procedure (***Method C***) with $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(diisopropyl-phosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

Chiral SFC (Chiralcel OJ-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1-(dimethyl(phenyl)silyl)-3,6-dimethylhept-5-en-3-ol.

Racemic Material



Peak No	% Area	Area	RT (min)
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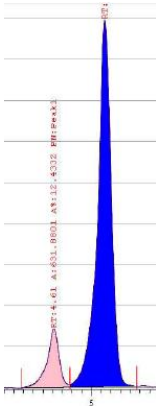
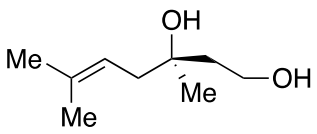
2	47.6388	11987.2052	4.56
Total:	100	25162.6717	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	12.4332	631.8801	4.61
2	87.5668	4450.302	5.14
Total:	100	5082.1821	

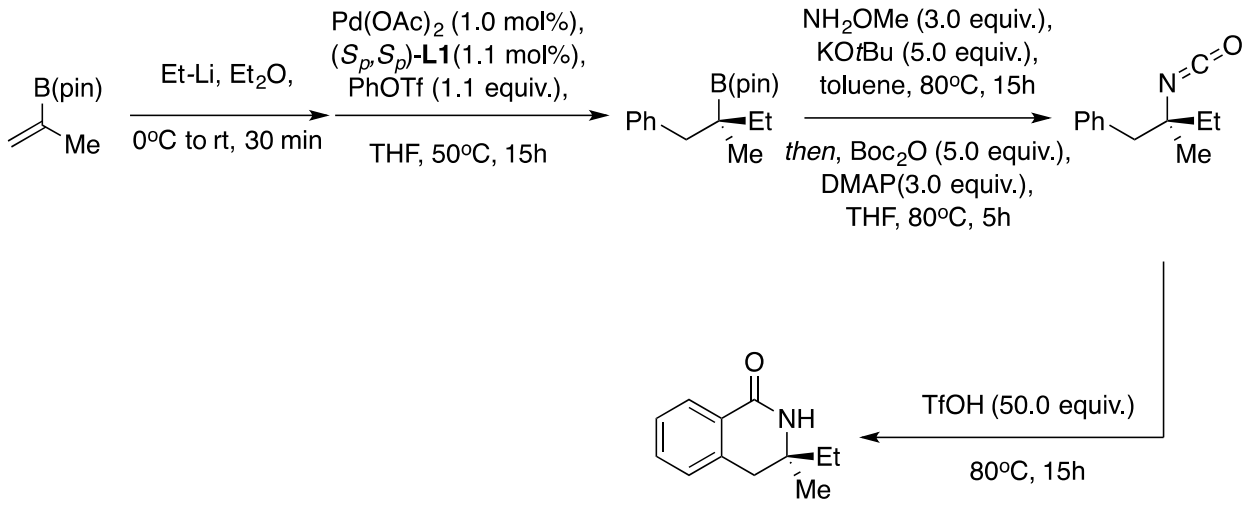


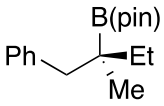
(*R*)-3,6-dimethylhept-5-ene-1,3-diol (37). The title compound was prepared according to a literature procedure with slight modification.[30b] In an Ar-filled glove-box, neat potassium hydride (79.15 mg, 1.97 mmol, 6.2 equiv.) was added to 20 mL scintillation vial equipped with a magnetic stir bar. The vial was sealed with a rubber septum, and dry DMF (3.8 mL) was added. This solution was cooled to 0 C, then *tert*-butyl hydroperoxide (5.5 M in decane, 358.8 uL, 1.97 mmol, 6.2 equiv.) was added slowly and reaction mixture was stirred for 10 min at 0 °C. Next, (*R*)-1-[dimethyl(phenyl)silyl]-3,6-dimethyl-hept-5-en-3-ol (87.0 mg, 0.32 mmol, 1.0 equiv.) as a solution in DMF (2.5 mL) was added, followed by potassium fluoride (37.0 mg, 0.63 mmol, 2.0 equiv.) in one portion. Reaction was warmed to 60 °C and stirred for 2 hour (caution: gas evolution). Reaction mixture was diluted with ethyl acetate and quenched with H_2O, then poured into a separatory funnel. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over sodium sulfate, then filtered through a plug of cotton, and concentrated under reduced pressure to yield a pale-yellow oil. The crude mixture was purified by silica gel chromatography (20-50% ethyl acetate in hexanes, stain in Seebach's Stain) to afford a colorless oil (38.0 mg, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 5.27-5.15 (m, 1H), 3.97-3.77 (m, 2H), 2.79 (br s, 1H), 2.35-2.13 (m, 3H), 1.89-1.71 (m, 4H), 1.71-1.60 (m, 4H), 1.23 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 138.2, 121.6, 77.0, 62.5, 44.1, 43.7, 29.3, 28.7, 20.7. IR (neat) ν_{max} 3336.6 (br), 2968.2 (m), 2917.5 (m), 1451.3 (m), 1375.6 (s), 1296.5 (m), 1252.1 (m), 1125.7 (m), 1096.9 (m), 1056.5 (s), 967.6 (m), 925.4 (m), 880.9 (m), 559.7 (m) cm^{-1}. HRMS (DART) for $C_9H_{19}O_2$ $[M+H]^+$: calculated: 159.1380, found: 159.1380. $[\alpha]^{20}_D$: +1.83 (c = 0.800, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Absolute stereochemistry was determined by comparison of optical rotation to the literature (stereochemistry assigned by conversion to the natural product mevalonolactone)[31] (Measured: $[\alpha]^{20}_{D}$: +1.830 (c = 1.300, $CHCl_3$, l =50 mm), literature: $[\alpha]^{20.5}_{D}$: -2.52 (c = 1.11, $CHCl_3$), 98:2 *e.r* for (*S*)-3,6-dimethylhept-5-ene-1,3-diol). And the absolute stereochemistry was assigned to be (*R*)-3,6-dimethylhept-5-ene-1,3-diol.

Enantioselective synthesis of (S)-3-ethyl-3-methyl-3,4-dihydroisoquinolin-1(2H)-one





(*R*)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylbutan-2-yl)-1,3,2-dioxaborolane (39). The title compound was synthesized according the general procedure (***Method A***) with 2-isopropenyl boronic acid pinacol ester (100.8 mg, 0.60 mmol), ethyllithium (1.20 mL, 0.5M in benzene/cyclohexane, 0.60 mmol), phenyltrifluoromethanesulfonate (149.8 mg, 0.66 mmol), palladium (II) acetate (1.350 mg, 0.006 mmol), **2.43** (6.90 mg, 0.0066 mmol) in THF (2.4 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2.5% ethyl acetate in hexanes) to afford the desire product as a colorless oil. (104.1 mg, 63% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22-7.17 (m, 4H), 7.15-7.12 (m, 1H), 2.77 (d, J = 12.6 Hz, 1H), 2.47 (d, J = 13.2 Hz, 1H), 1.54-1.47 (m, 1H), 1.26-1.17 (m, 13H), 0.90 (t, J = 7.2 Hz, 3H), 0.86 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 140.3, 130.5, 127.7, 125.8, 83.3, 44.6, 31.9, 25.3, 25.0, 20.9, 10.5. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 34.7; IR (neat) ν_{max} 2975.6 (m), 2928.9 (m), 1460.3 (m), 1383.9 (s), 1370.6 (s), 1307.5 (s), 1263.3 (m), 1210.5 (m), 1139.0 (s), 741.7 (m), 701.9 (m), 688.3 (m) cm^{-1}.

HRMS (DART) for $C_{17}H_{28}BO_2$ $[M+H]^+$ calculated: 275.2182, found: 275.2187. $[\alpha]^{20}_D$: -4.745 (c = 1.080, $CHCl_3$, *l* =50 mm)

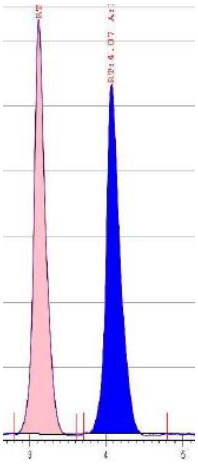
Analysis of Stereochemistry:

Racemic compound was prepared according to the general procedure (***Method A***) with isopropenyl boronic acid pinacol ester, and $Pd(OAc)_2$ (5 mol%) and 1,1′-Bis(diisopropyl-phosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry was determined by comparison of optical rotation to the literature[46] after oxidation (Measured: $[\alpha]^{20}_D$: +3.680 (c = 1.300, $CHCl_3$, l =50 mm), literature: $[\alpha]^{24}_D$: -6.5 (c = 1.97, $CHCl_3$), 80% *e.e* for (*R*)-2-methyl-1-phenylbutan-2-ol). And the absolute stereochemistry was assigned to be (*S*)-2-methyl-1-phenylbutan-2-ol.

[46] Doyle, A. G.; Jacobson, E. N. *Angew. Chem. Int. Ed*. **2007**, *46*, 3701–3705.

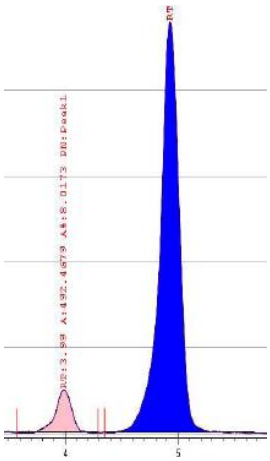
Chiral SFC (Chiralcel OD-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylbutan-2-yl)-1,3,2-dioxaborolane.

Racemic Material

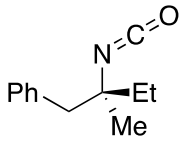


Peak No	% Area	Area	RT (min)
1	50.0153	3407.6911	3.12
2	49.9847	3405.6128	4.07
Total:	100	6813.3039	

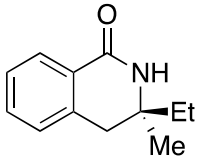
Standard Conditions



Peak No	% Area	Area	RT (min)
1	8.0173	492.4679	3.99
2	91.9827	5650.0971	4.93
Total:	100	6142.565	



(*S*)-(2-isocyanato-2-methylbutyl)benzene (40). To an oven-dried 6-dram vial equipped with a magnetic stir bar was added NH_2OMe solution (1.70 mmol, 3.00 equiv.) in THF[1] under N_2. The vial was brought into the glovebox, potassium *tert*-butoxide (2.84 mmol, 5.00 equiv.) was added, followed by the (*R*)-4,4,5,5-tetramethyl-2-(2-methyl-1-phenylbutan-2-yl)-1,3,2-dioxaborolane (0.56 mmol, 1.00 equiv.) in toluene (3.6 mL). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 80 °C for 15 hours. The reaction mixture was allowed to cool to room temperature, and Boc_2O (2.84 mmol, 5.00 equiv.) solution in THF was added, followed by 4-dimethylaminopyridine (1.70 mmol, 3.00 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and heated 80 °C for 5 hours. Then the reaction mixture was allowed to cool to room temperature and diluted with 5% ethyl acetate in hexanes, and passed through a silica gel plug with 5% ethyl acetate in hexanes. The result solution was concentrated under reduced pressure, and subsequently purified via silica gel column chromatography (1% ethyl acetate in hexanes) to afford the desired product as a colorless oil (76.3 mg, 72% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 2.76 (d, *J* = 13.8 Hz, 1H), 2.66 (d, *J* = 13.8 Hz, 1H), 1.58-1.46 (m, 2H), 1.18 (s, 3H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.7, 130.8, 128.3, 127.0, 61.8, 48.1, 35.2, 27.0, 8.8. IR (neat) ν_{max} 3030.6 (m), 2972.8 (m), 2926.9 (m), 2254.3 (s), 1454.5 (m), 1379.9 (m), 1186.9 (m), 1031.0 (m), 754.3 (m), 619.4 (m) cm^{-1}. HRMS (DART) for $C_{12}H_{16}ON$ $[M+H]^+$ calculated: 190.1232, found: 190.1230. $[\alpha]^{20}_D$: +7.61 (c = 0.680, $CHCl_3$, *l* =50 mm).



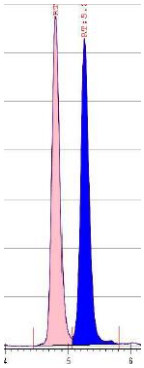
(*S*)-3-ethyl-3-methyl-3,4-dihydroisoquinolin-1(*2H*)-one (41). To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (*S*)-(2-isocyanato-2-methylbutyl)benzene (0.19 mmol, 1.00 equiv.). The vial was sealed with a septum cap, and purged with N_2. The reaction vial was cooled to 0 °C, and TfOH (9.5 mmol, 50.0 equiv.) was added dropwise under N_2. The reaction vial was heated to 80 °C and allowed to stir for 24 hours, then the reaction mixture was poured into ice-water (20.0 mL), and extracted with dichloromethane (20 mL x3). The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure, and subsequently purified via silica gel column chromatography (40 % ethyl acetate in hexanes) to afford the desired product as a white solid (33.6 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 5.82 (brs, 1H), 2.95 (d, *J* = 16.0 Hz, 1H), 2.85 (d, *J* = 16.0 Hz, 1H), 1.65-1.51 (m, 2H), 1.23 (s, 3H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.6, 137.7, 132.5, 128.1, 127.1, 54.8, 39.7, 34.1, 26.2, 8.4. IR (neat) ν_{max} 3182.7 (m), 3063.4 (m), 2922.5 (m), 2852.9 (m), 1658.6 (s), 1604.4 (m), 1460.8 (s), 1395.3 (s), 1168.1(m), 820.6 (m), 778.4 (m), 581.7 (m) cm^{-1}. HRMS (DART) for $C_{12}H_{16}ON$ $[M+H]^+$ calculated: 190.1232, found: 190.1233. $[\alpha]^{20}_D$: -11.16 (c = 0.650, $CHCl_3$, *l* =50 mm)

Analysis of Stereochemistry:

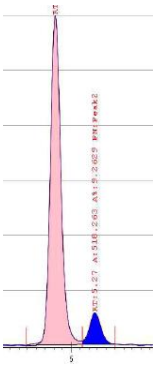
Racemic compound was prepared according to the same procedure with racemic (2-isocyanato-2-methylbutyl)benzene. Absolute stereochemistry was assigned by analogy (see compounds 6-OH, 37 and 39).

Chiral SFC (Chiralcel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (*S*)-3-ethyl-3-methyl-3,4-dihydroisoquinolin-1(*2H*)-one.

Racemic Material Standard Conditions



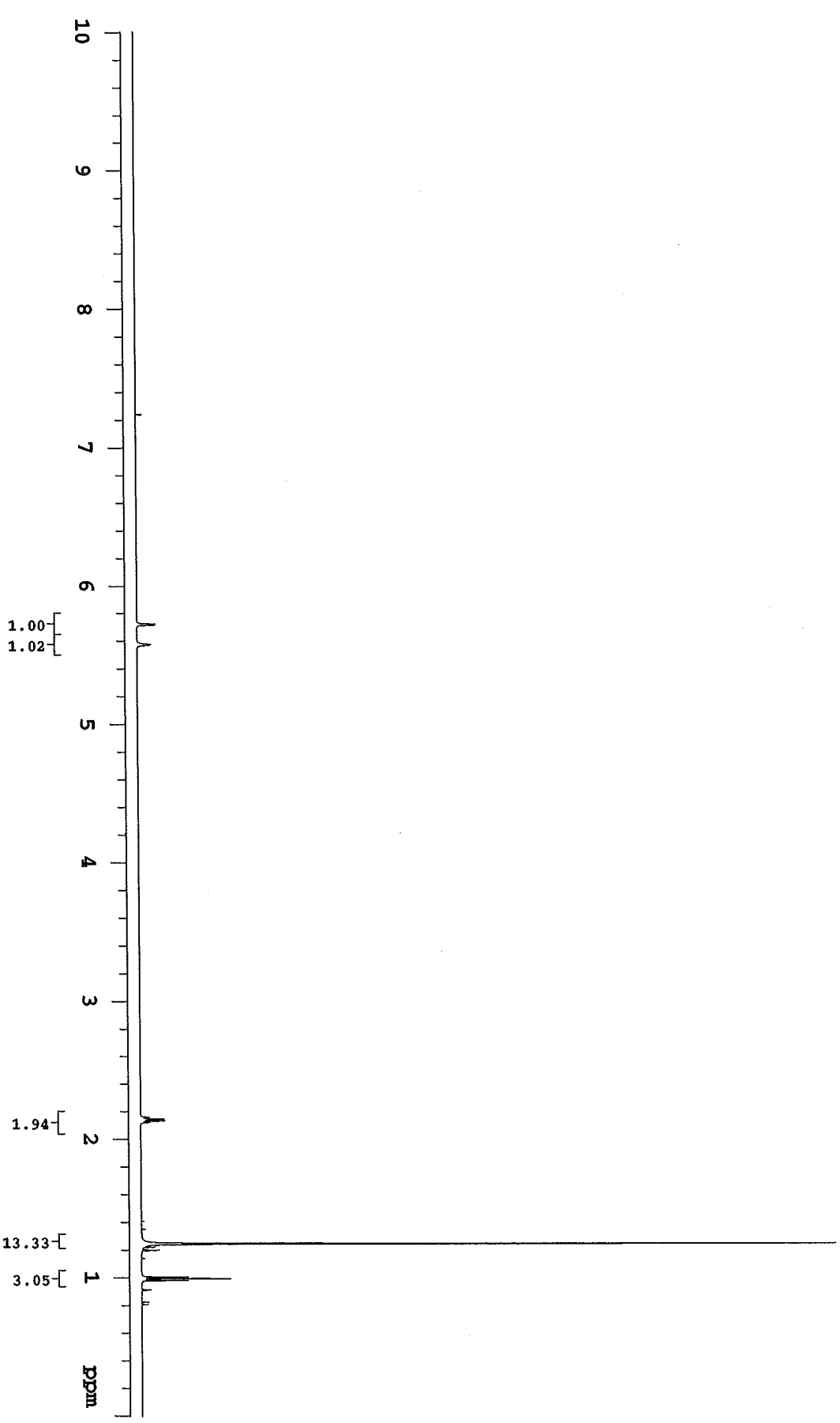
Peak No	% Area	Area	RT (min)
1	49.6255	2981.1745	4.81
2	50.3745	3026.1642	5.25
Total:	100	6007.3387	



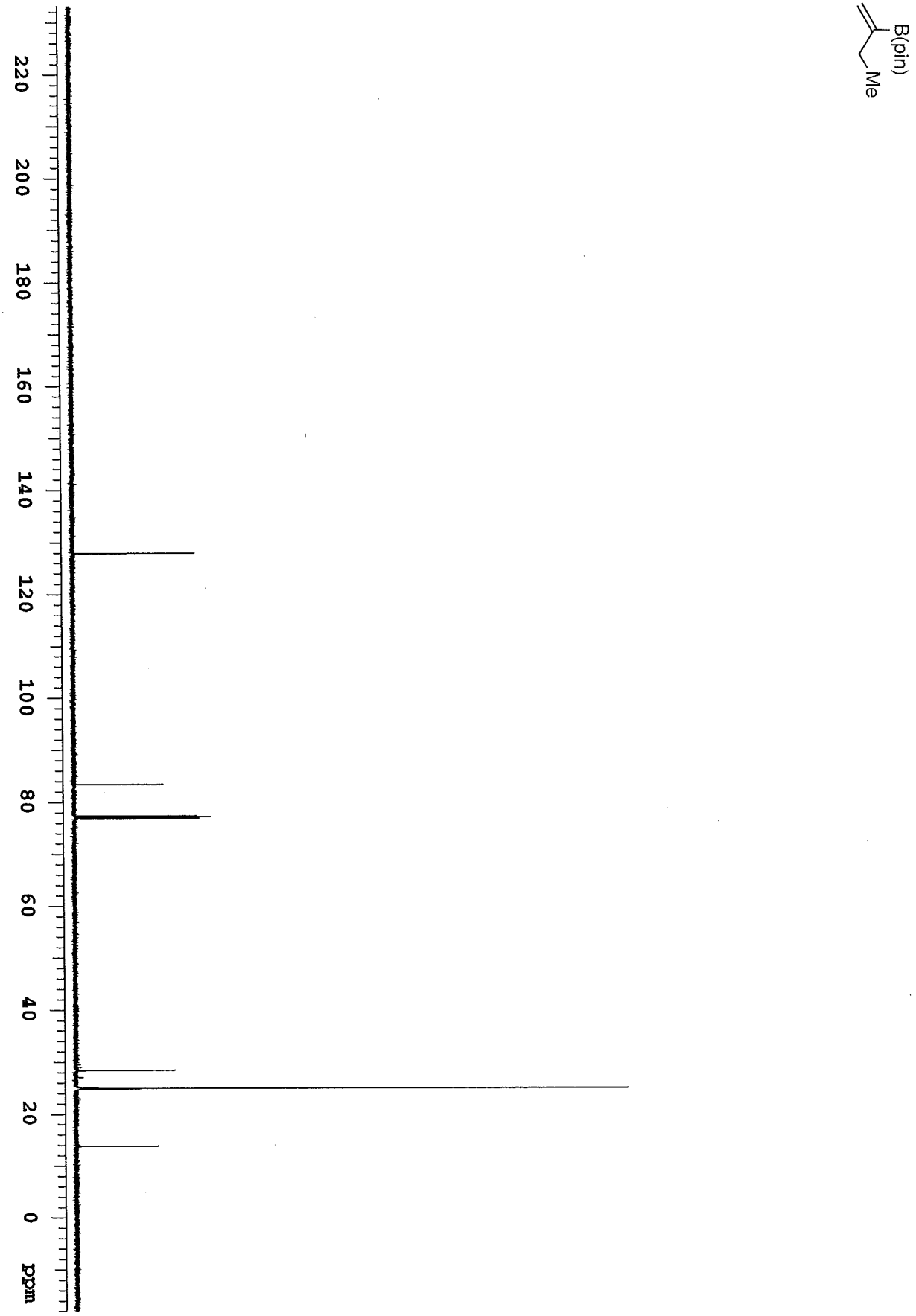
Peak No	% Area	Area	RT (min)
1	90.7371	5076.7806	4.82
2	9.2629	518.263	5.27
Total:	100	5595.0436	

2.4.3. NMR spectra

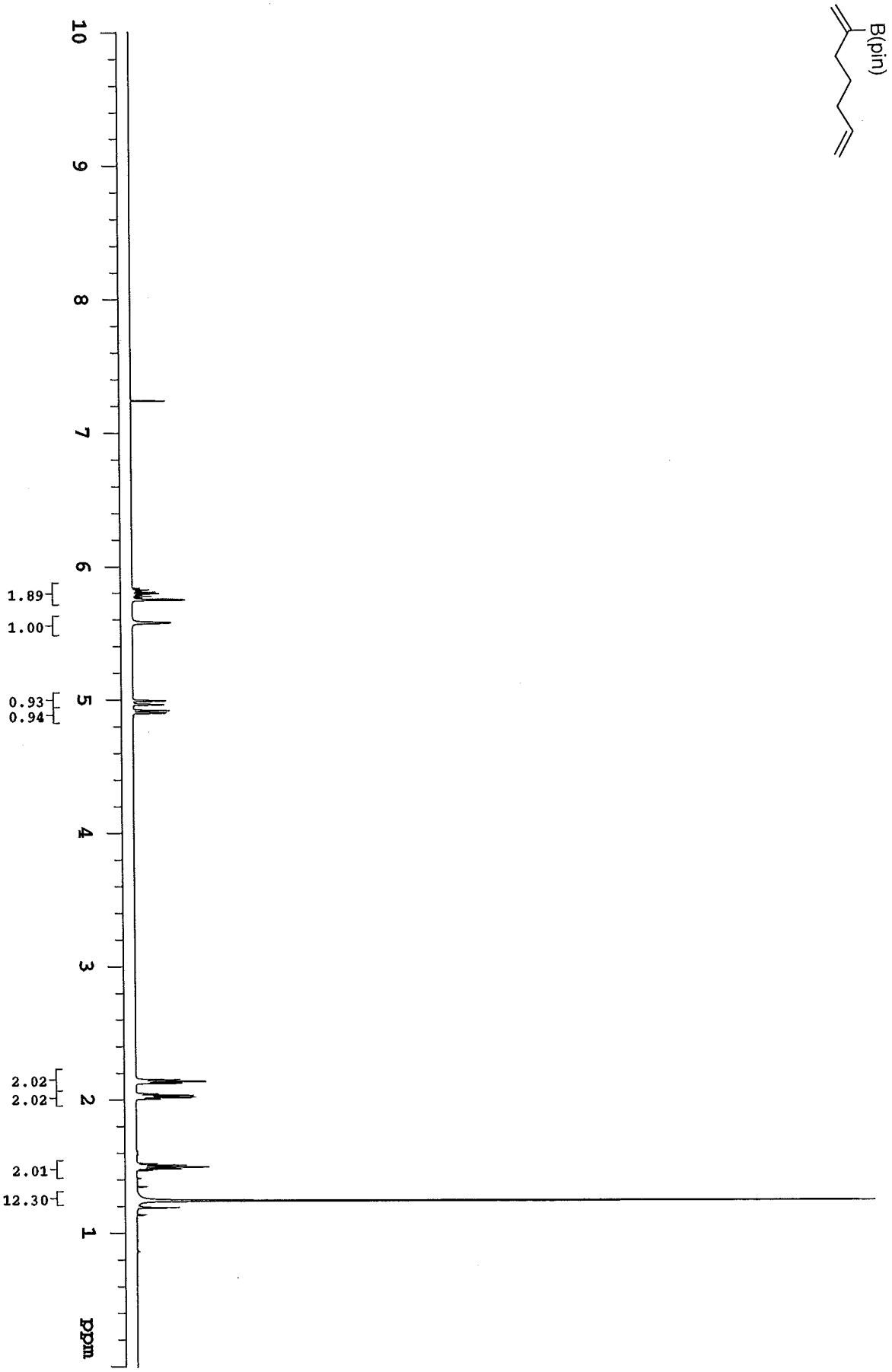
Compound S-1



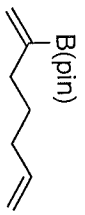
Compound S-1

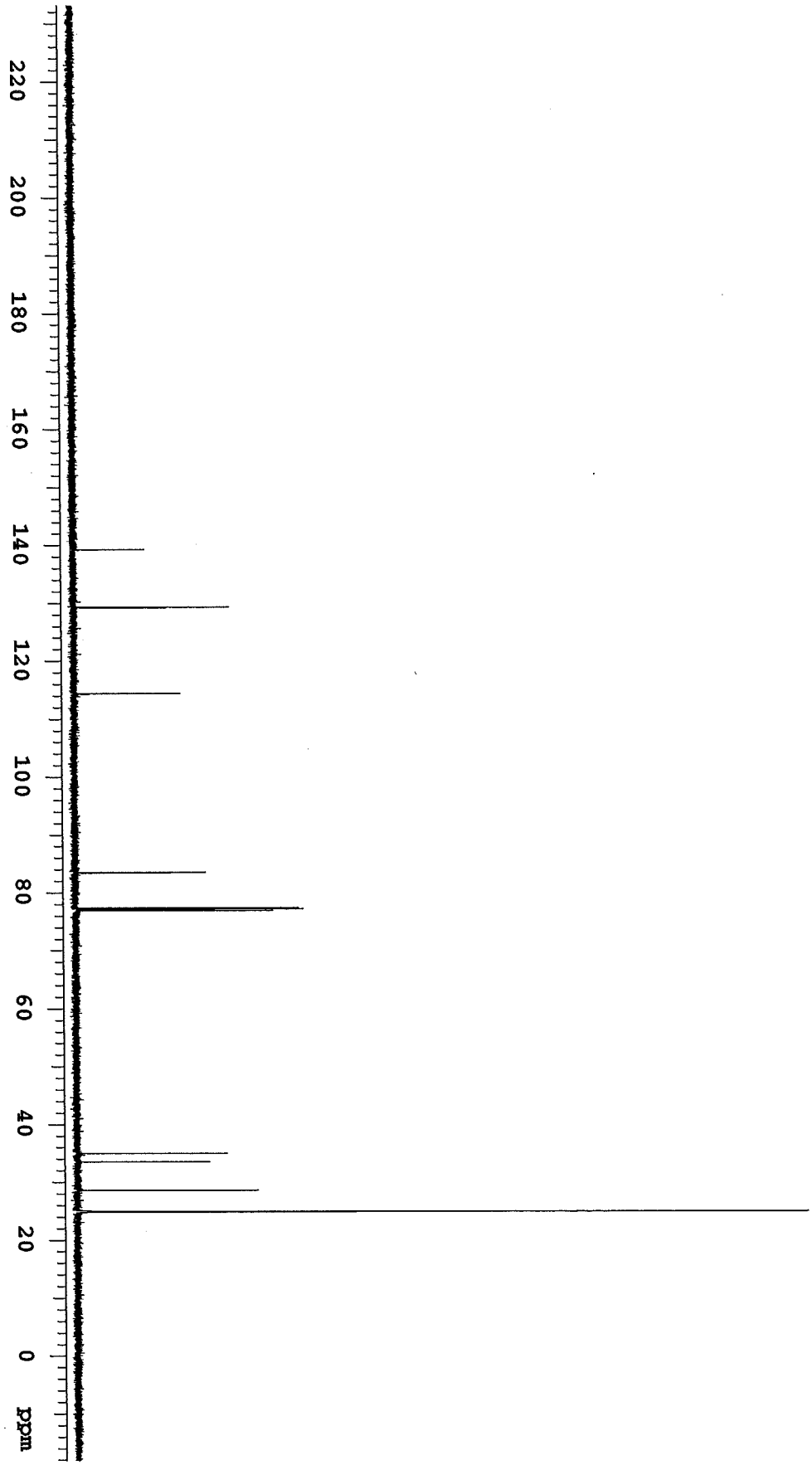


Compound S-2

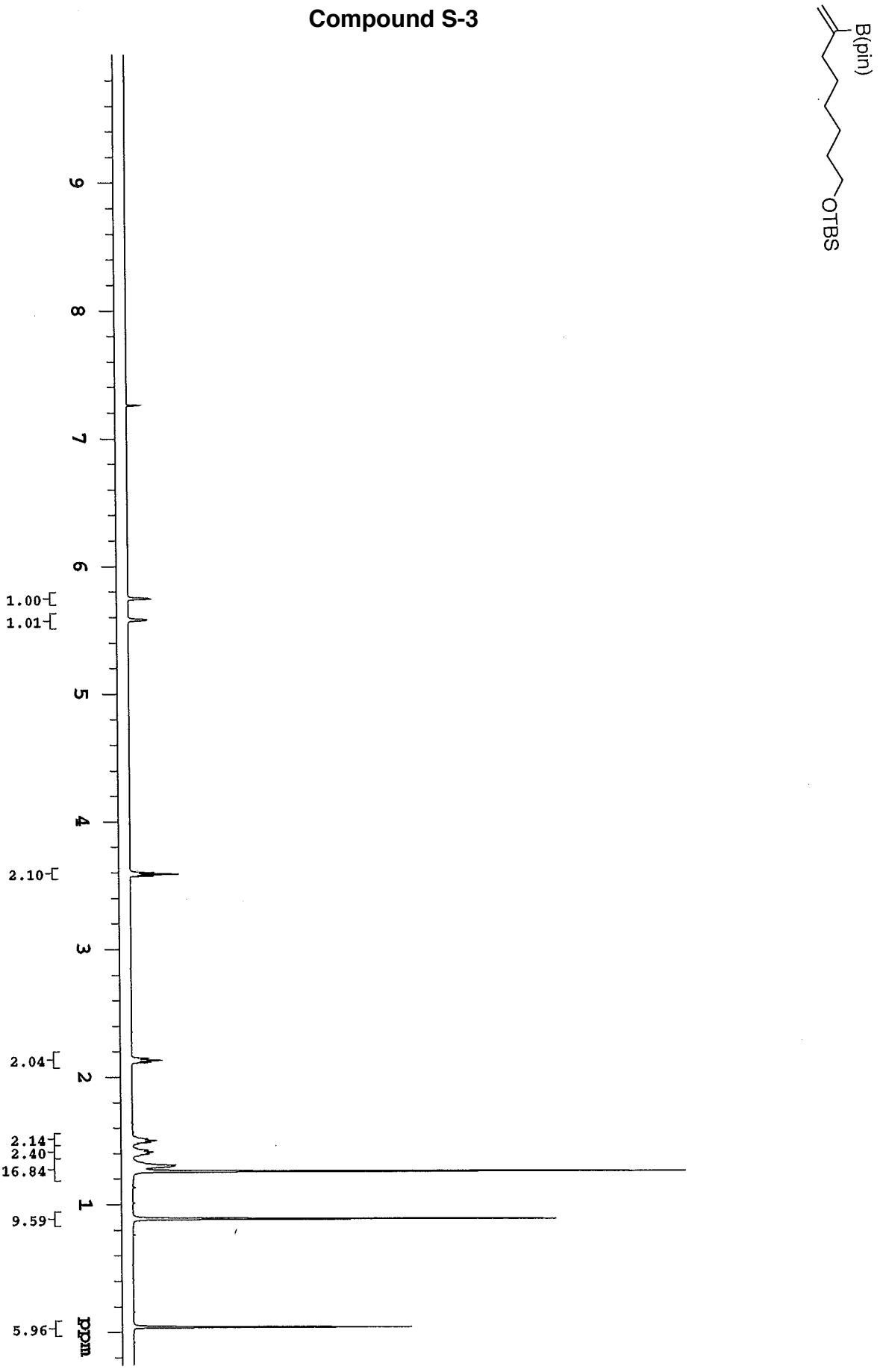


Compound S-2

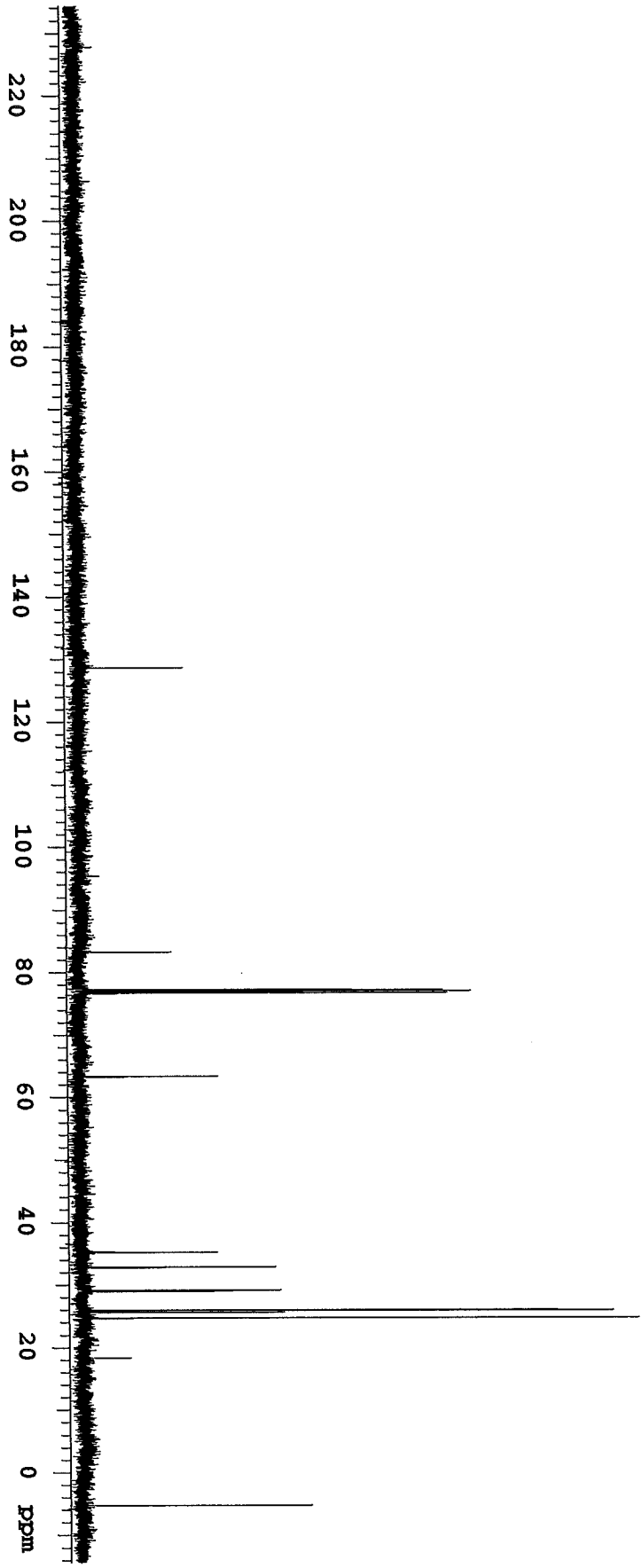


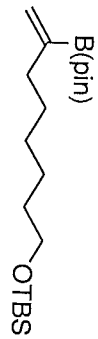


Compound S-3

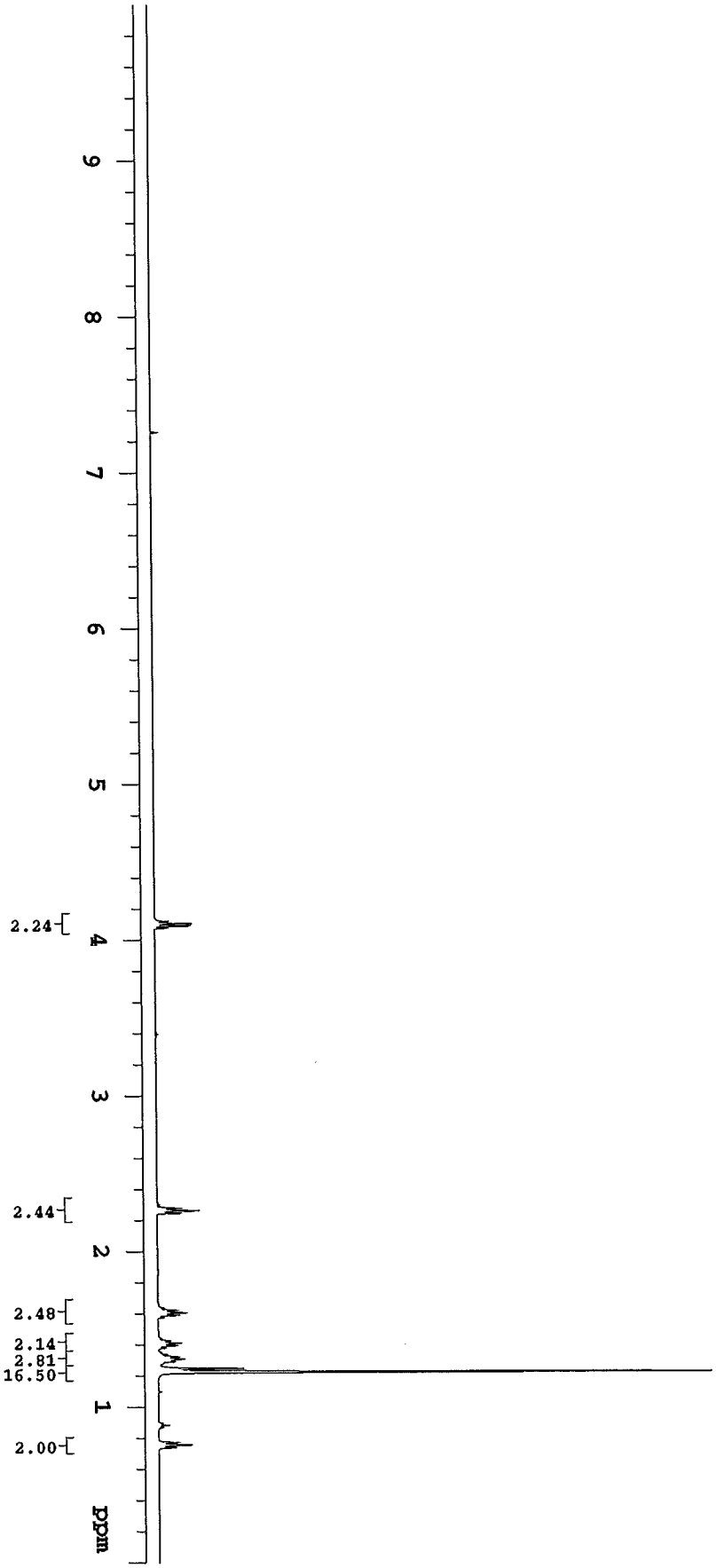


Compound S-3

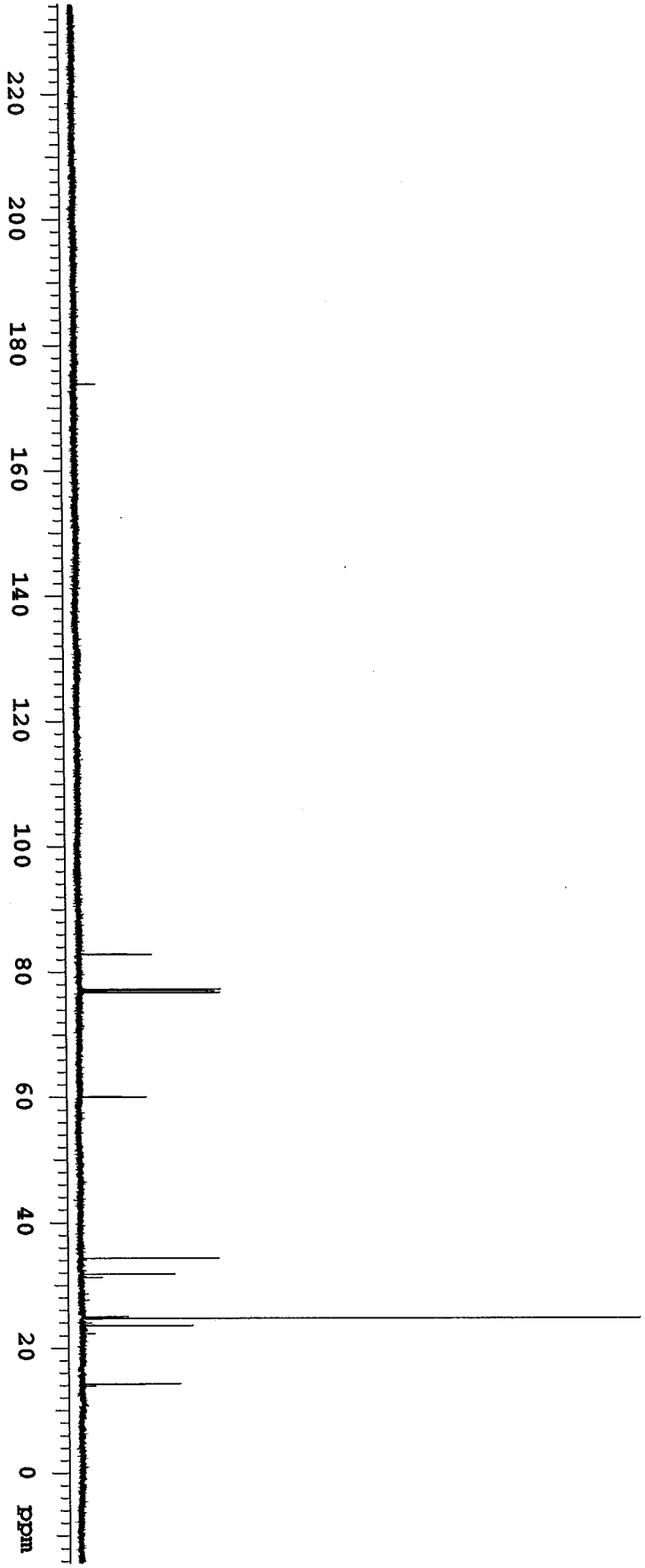




Compound S-7



Compound S-7



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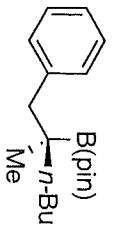
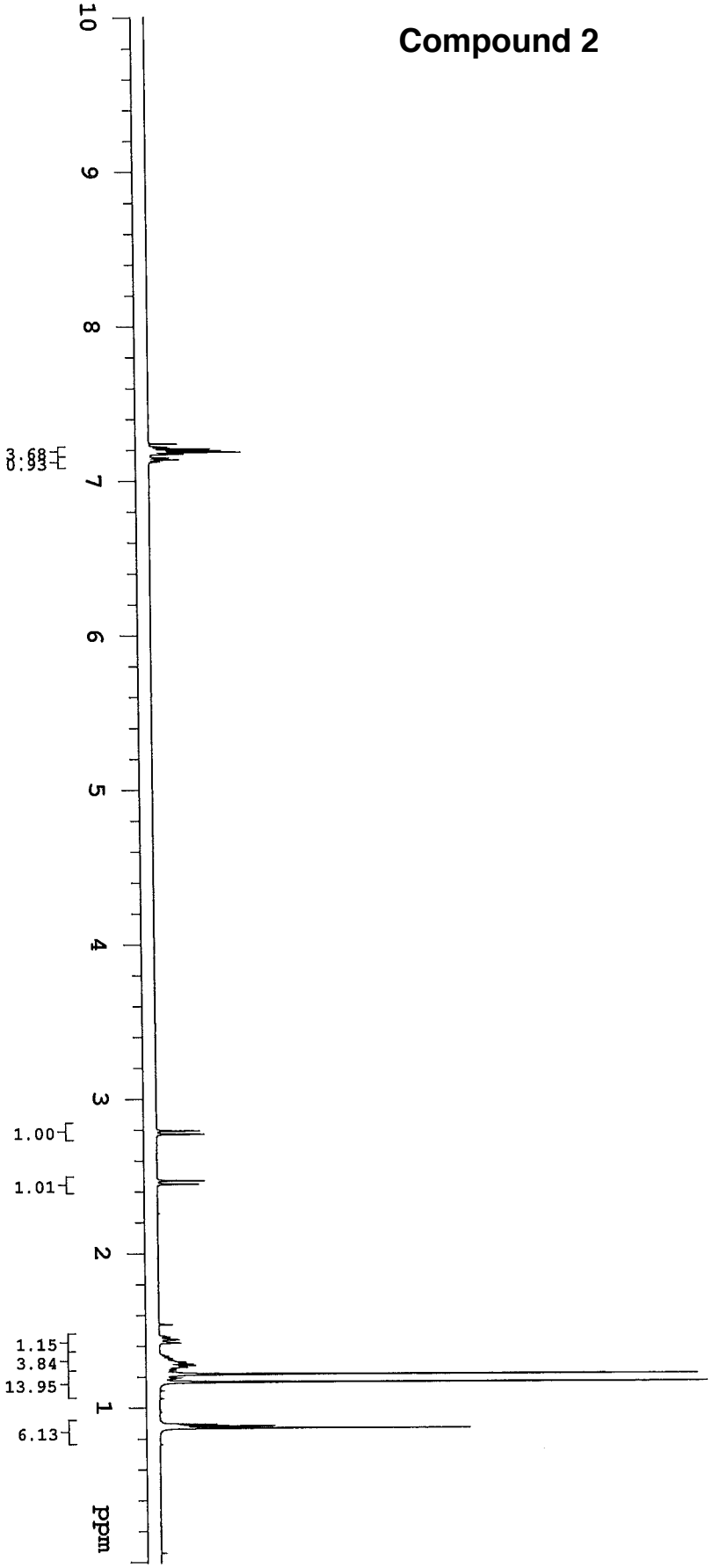
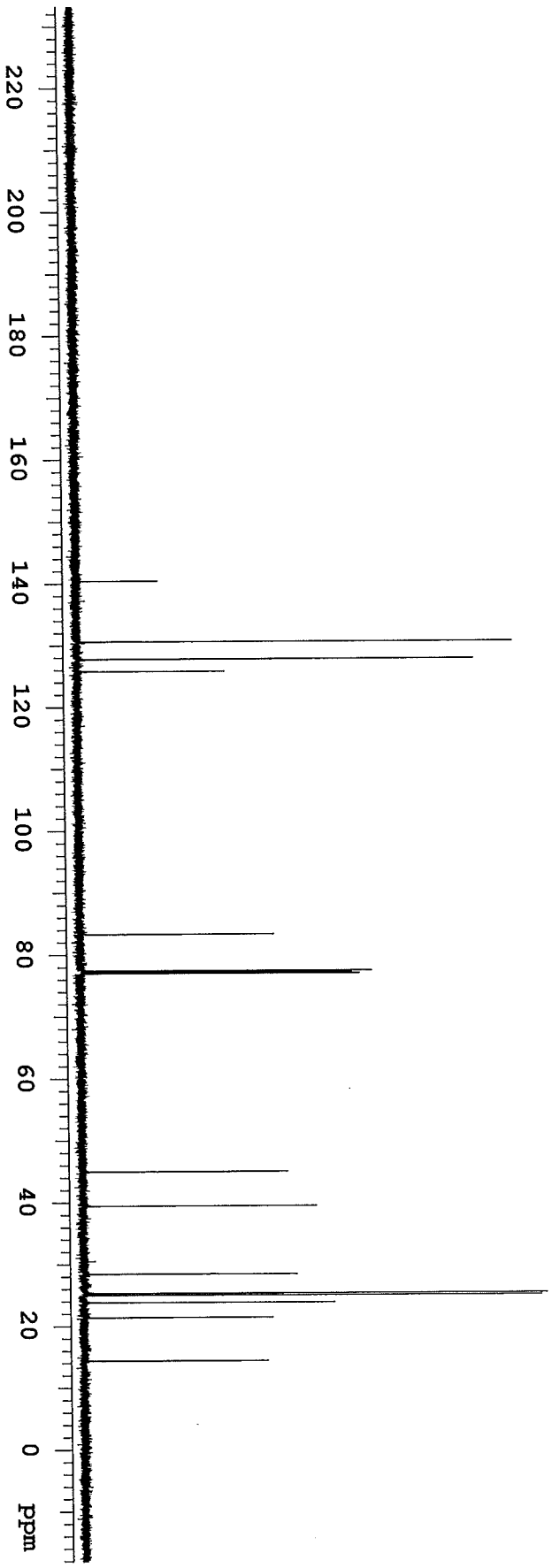
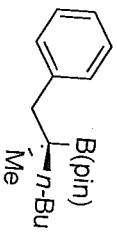




Compound 2





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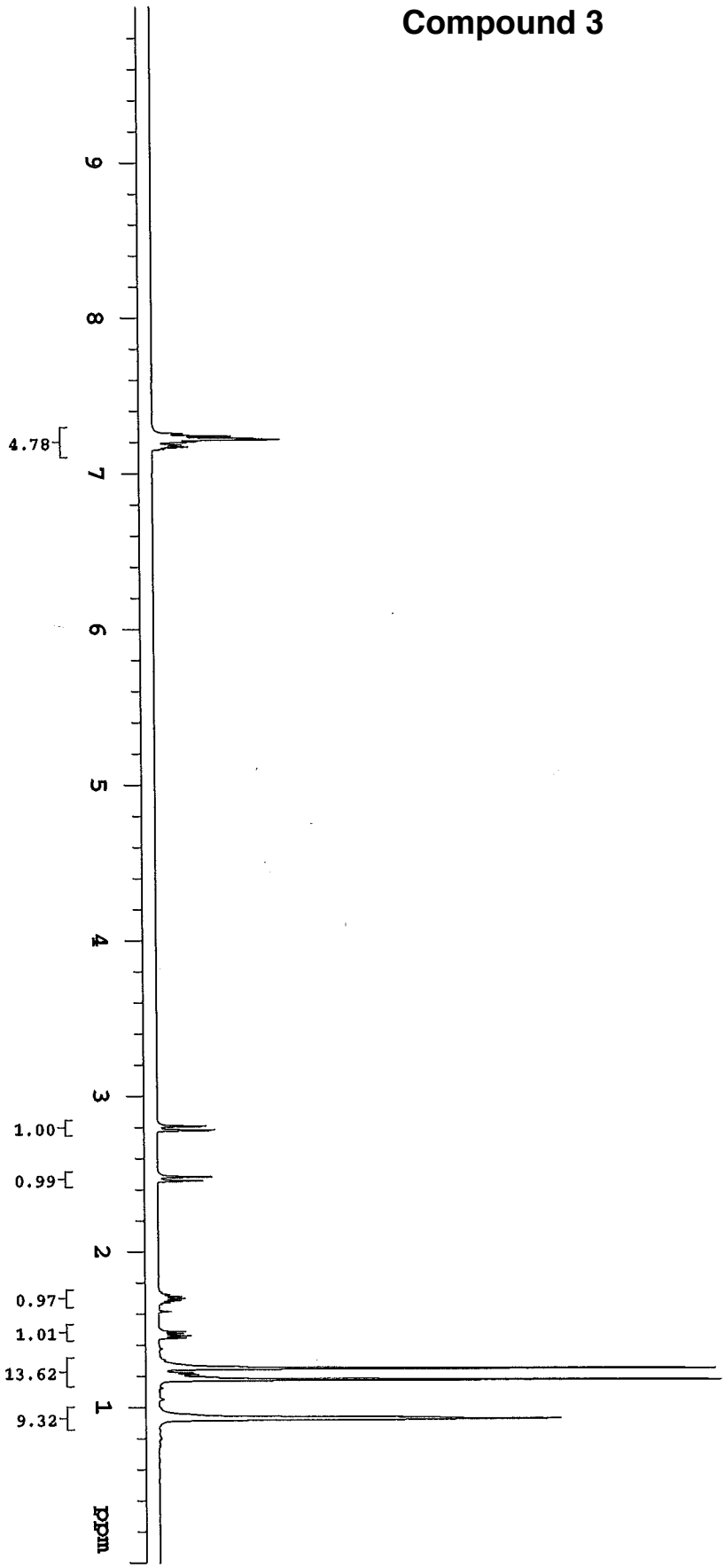

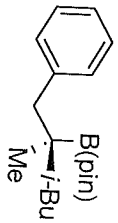

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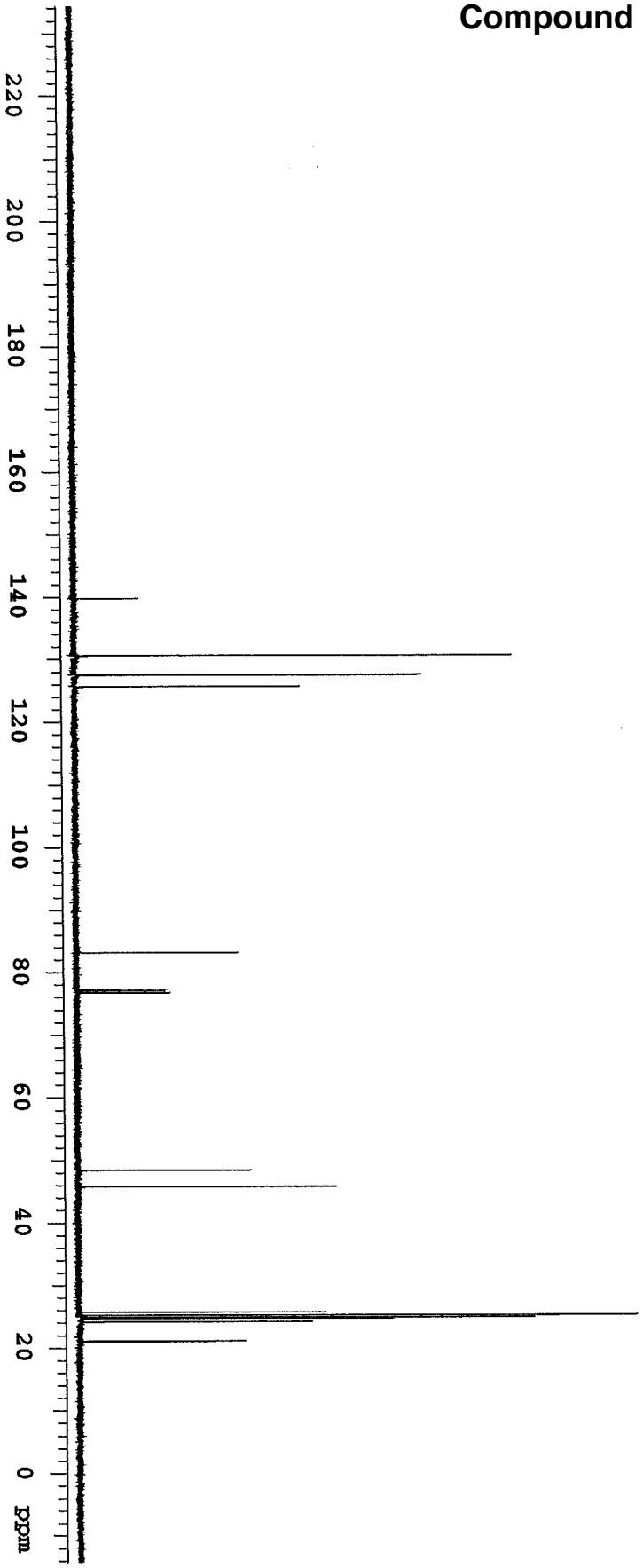
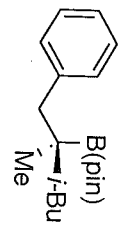
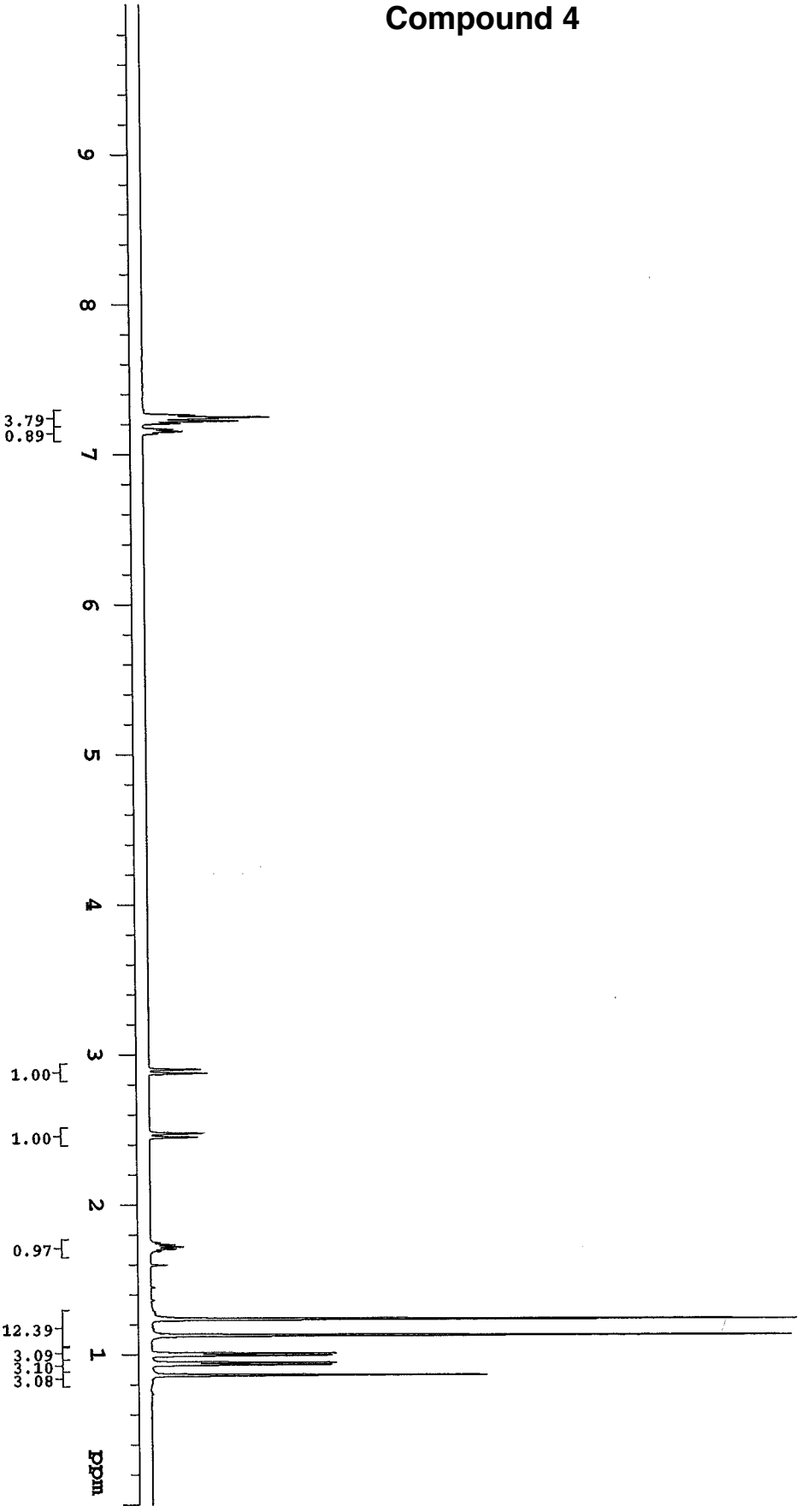
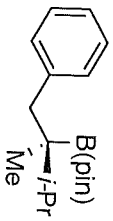


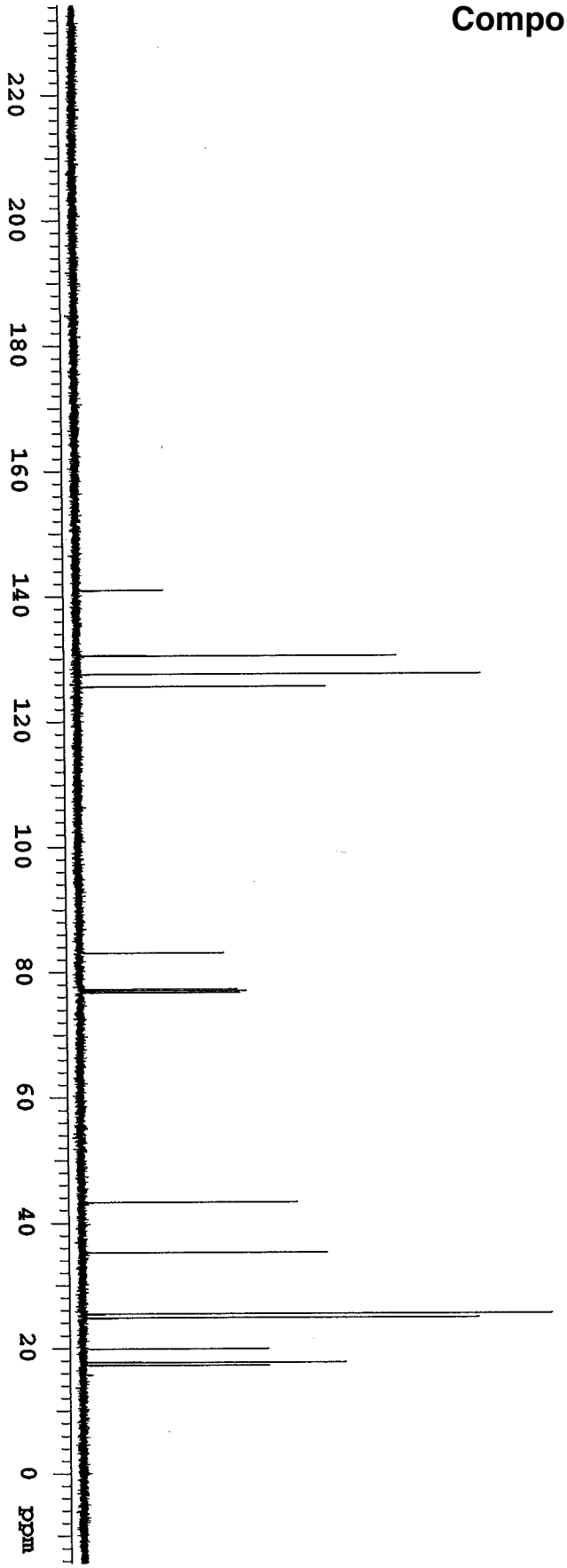


Compound 4



Compound 4





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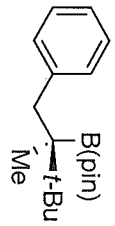
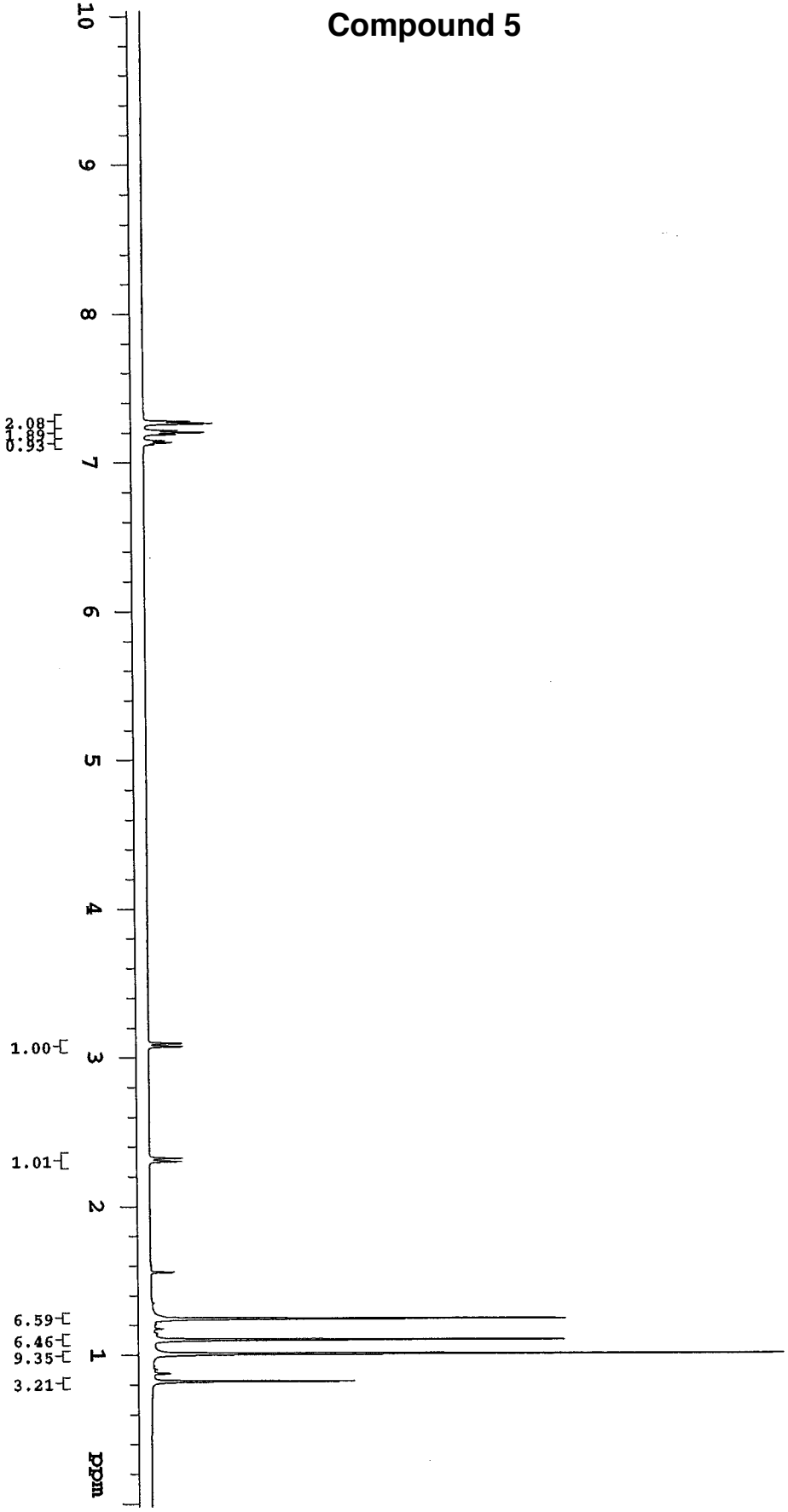

B(pin)
t-Bu
Me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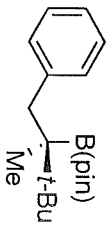
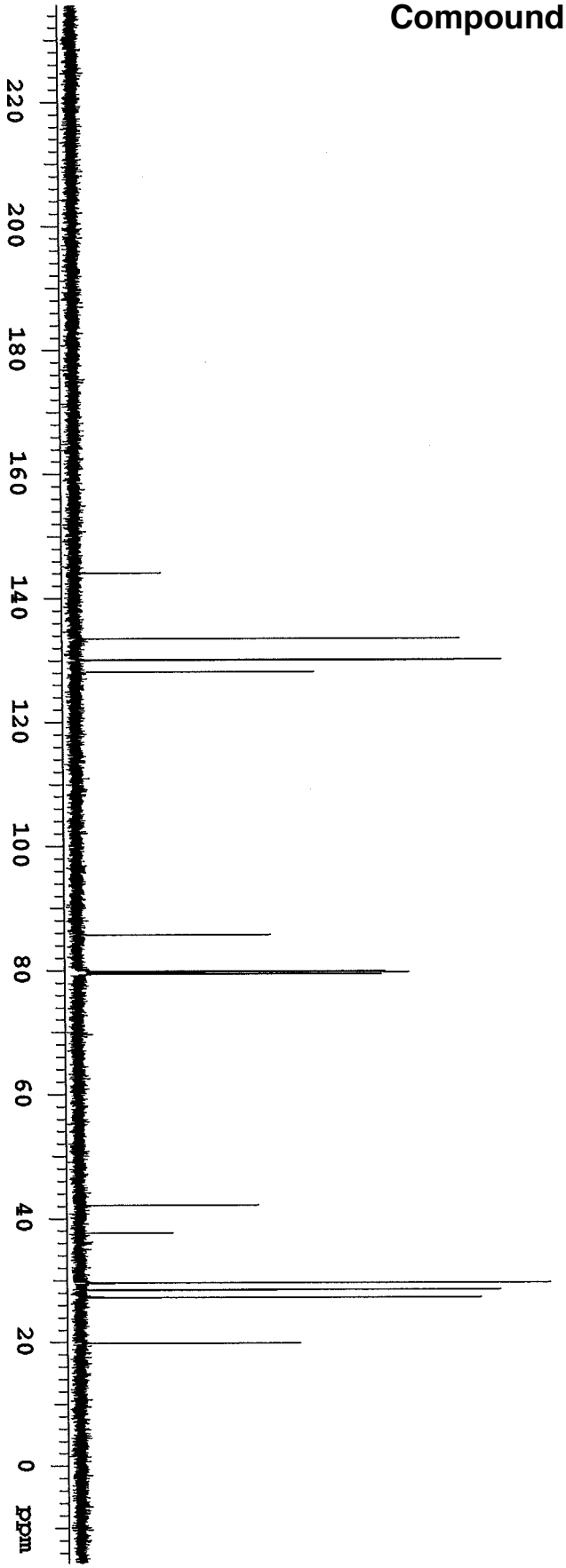
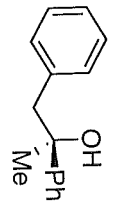
3.21

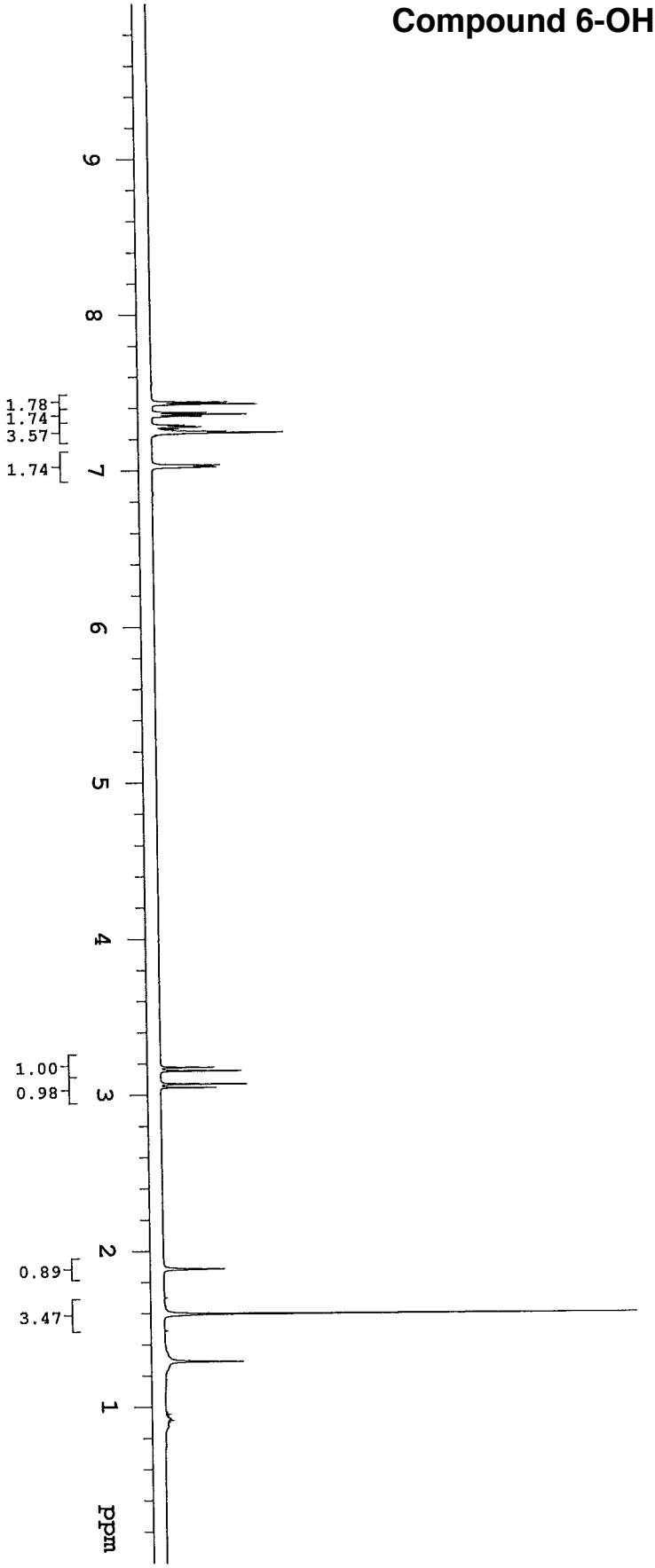
Compound 5



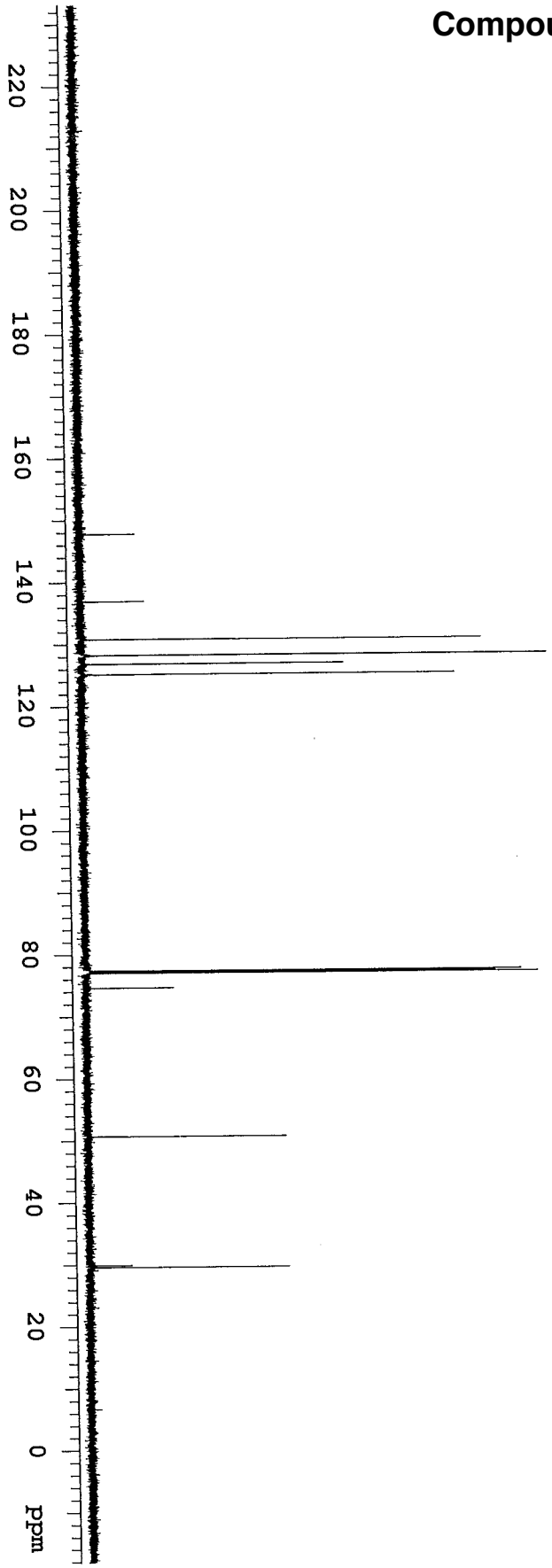


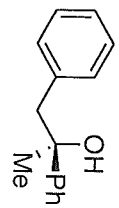
Compound 6-OH



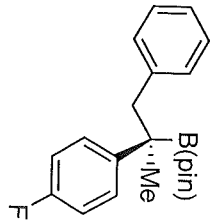


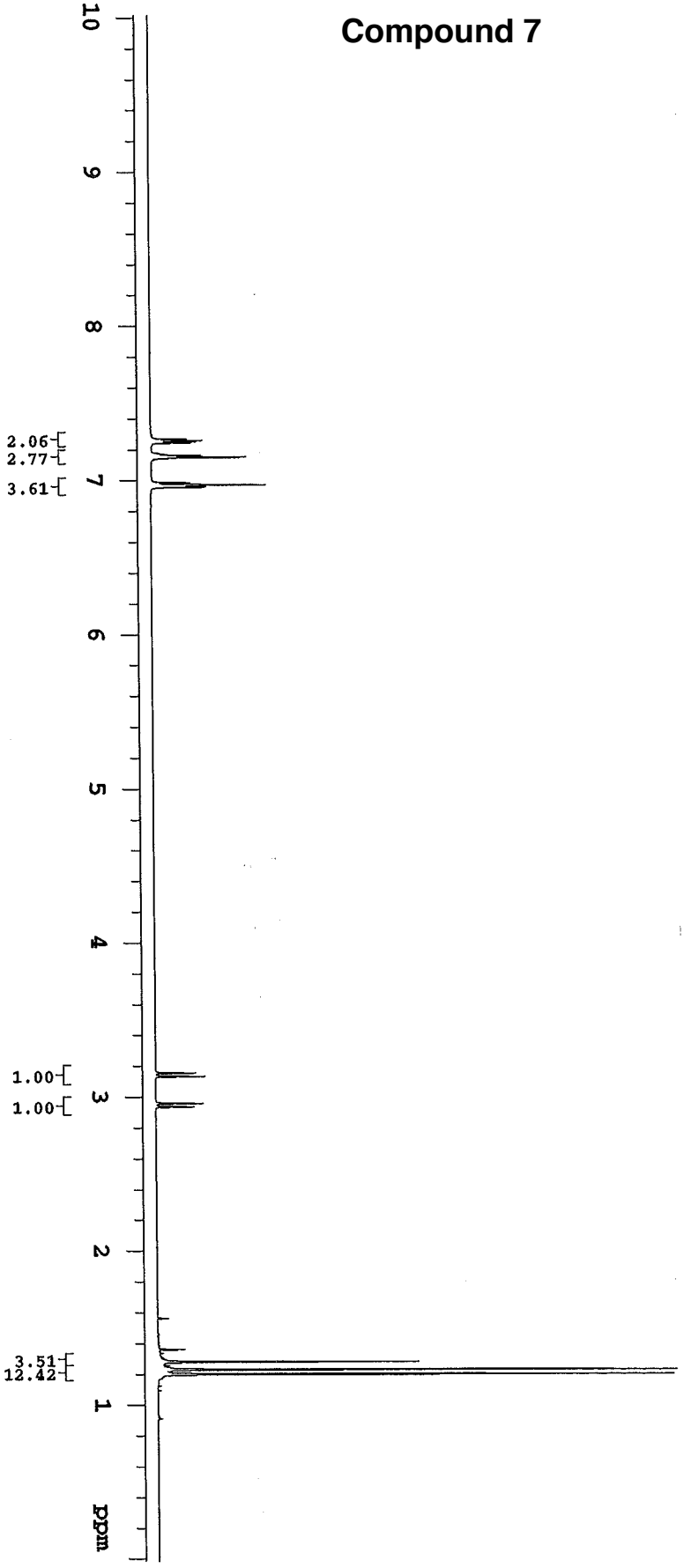
Compound 6-OH



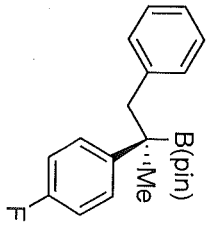


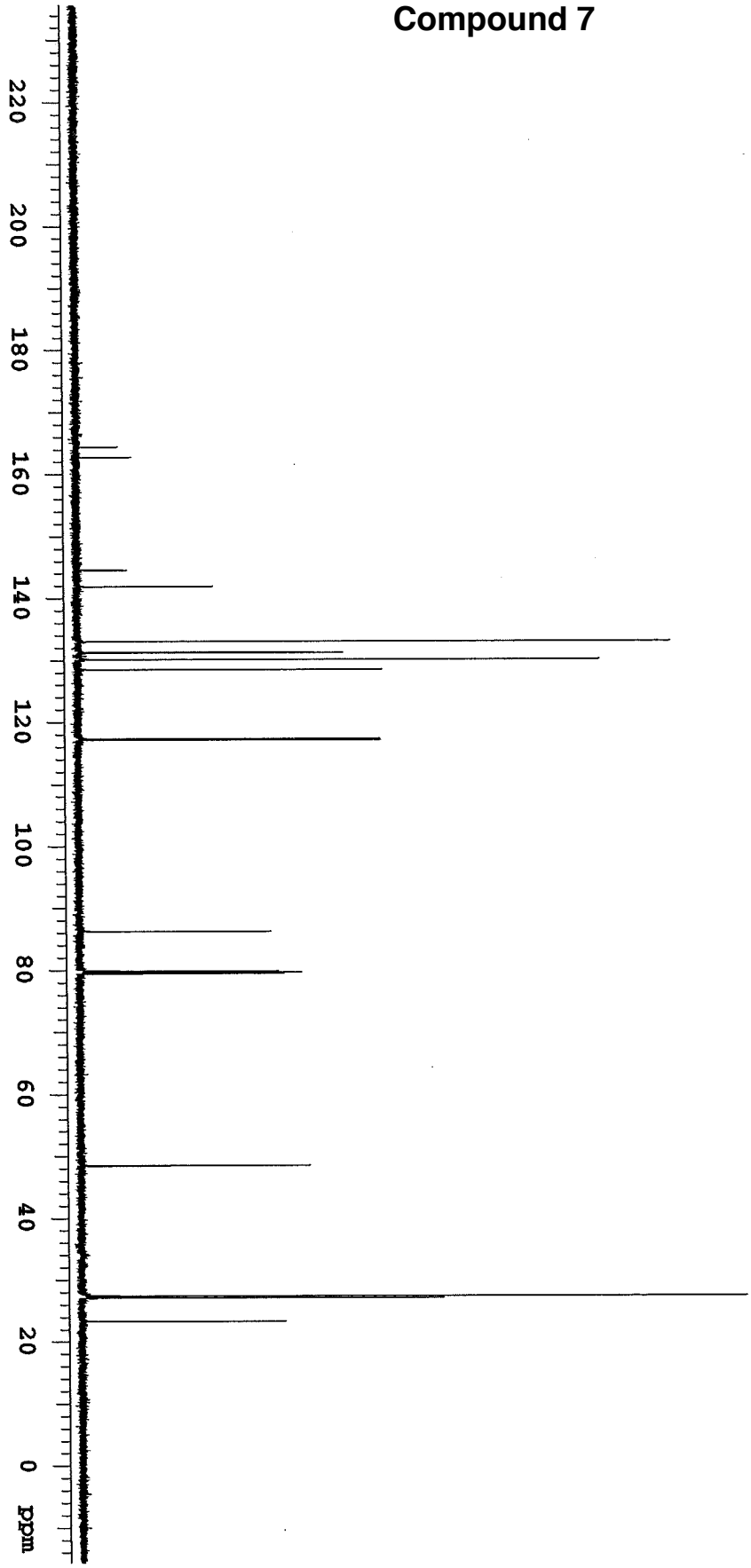
Compound 7



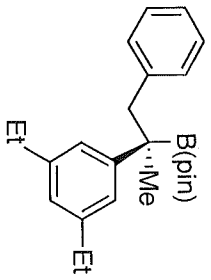


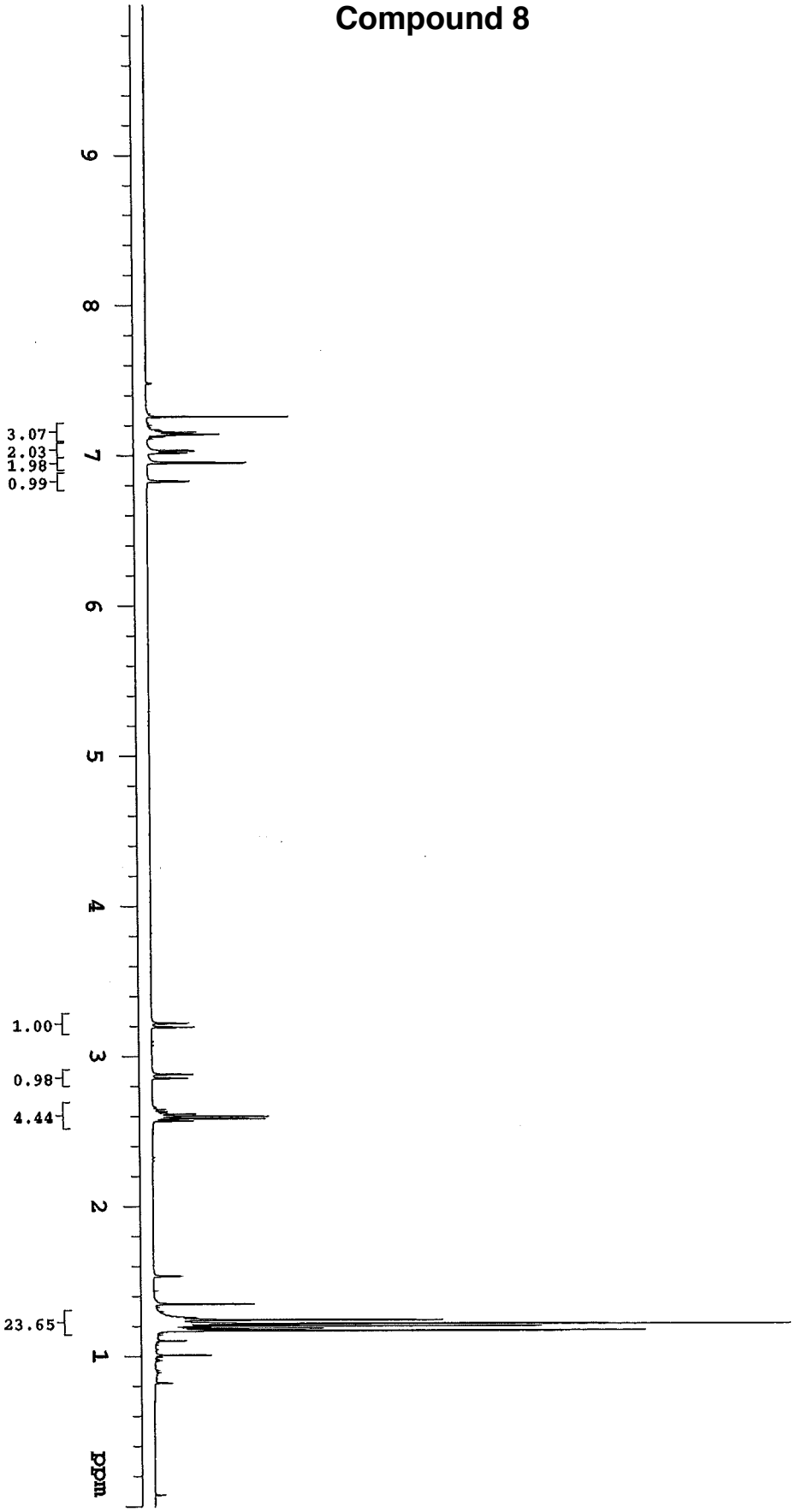
Compound 7



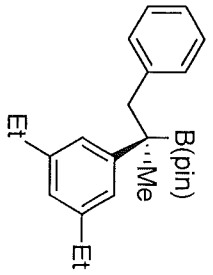


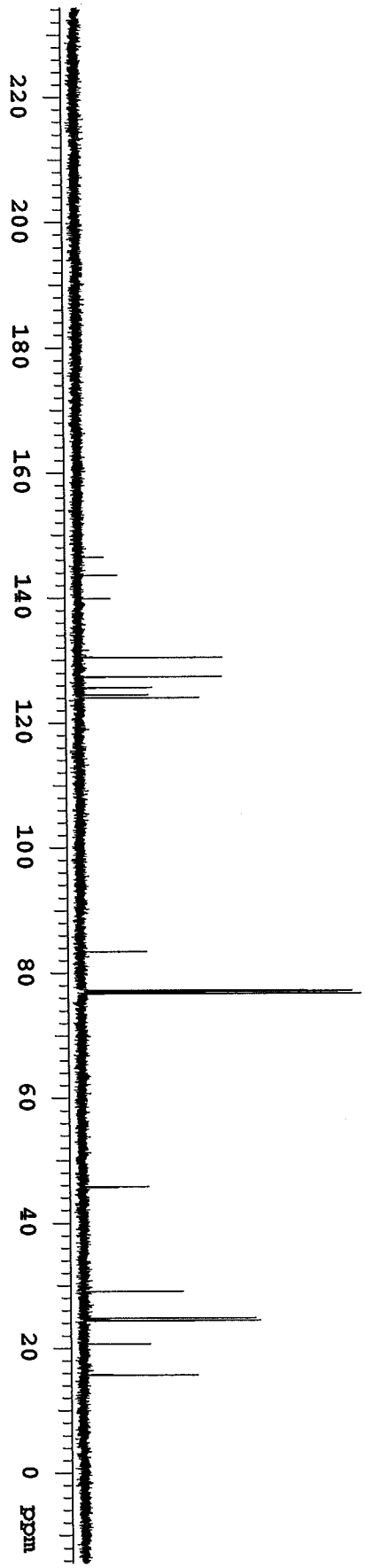
Compound 8



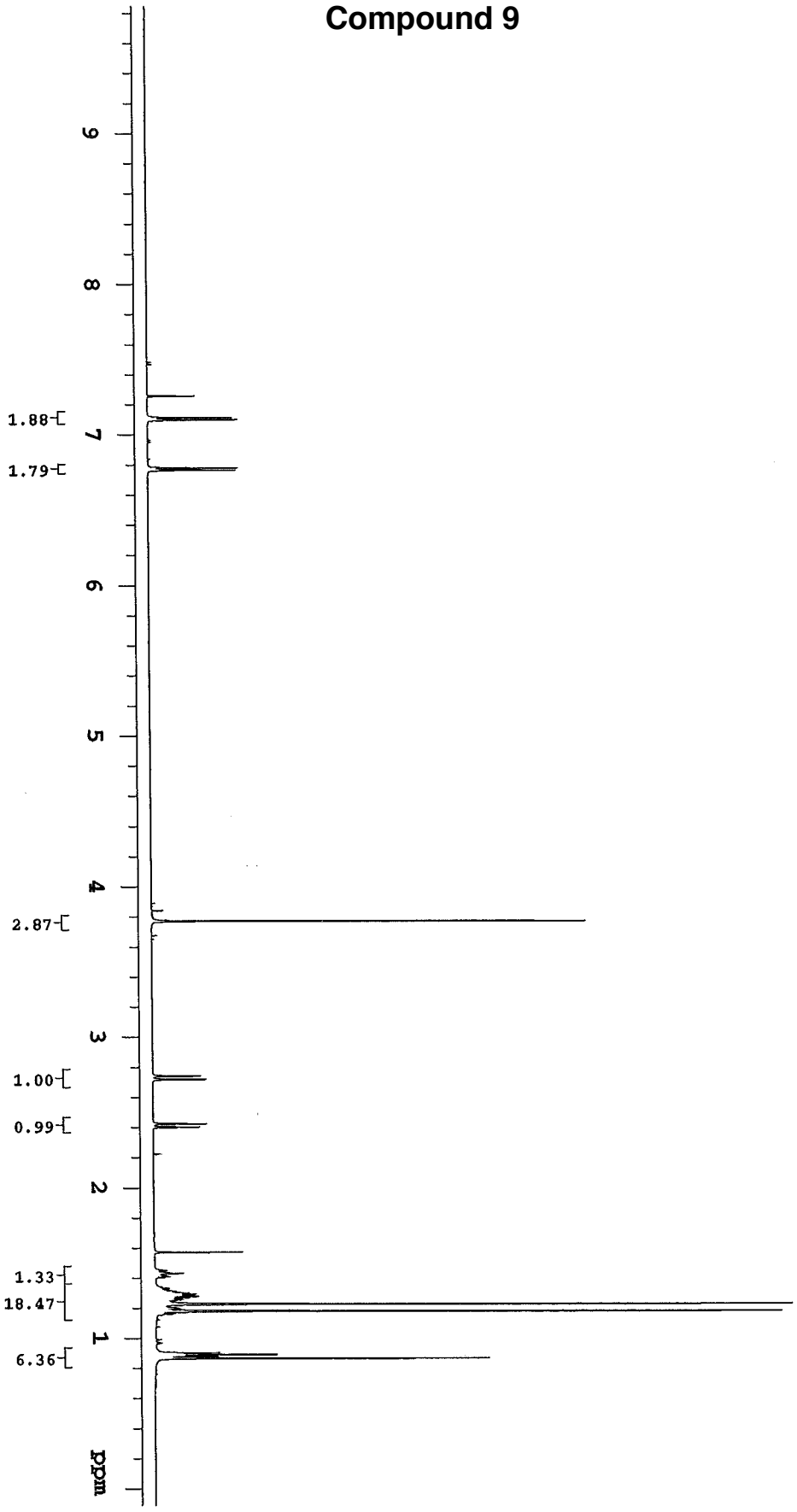


Compound 8

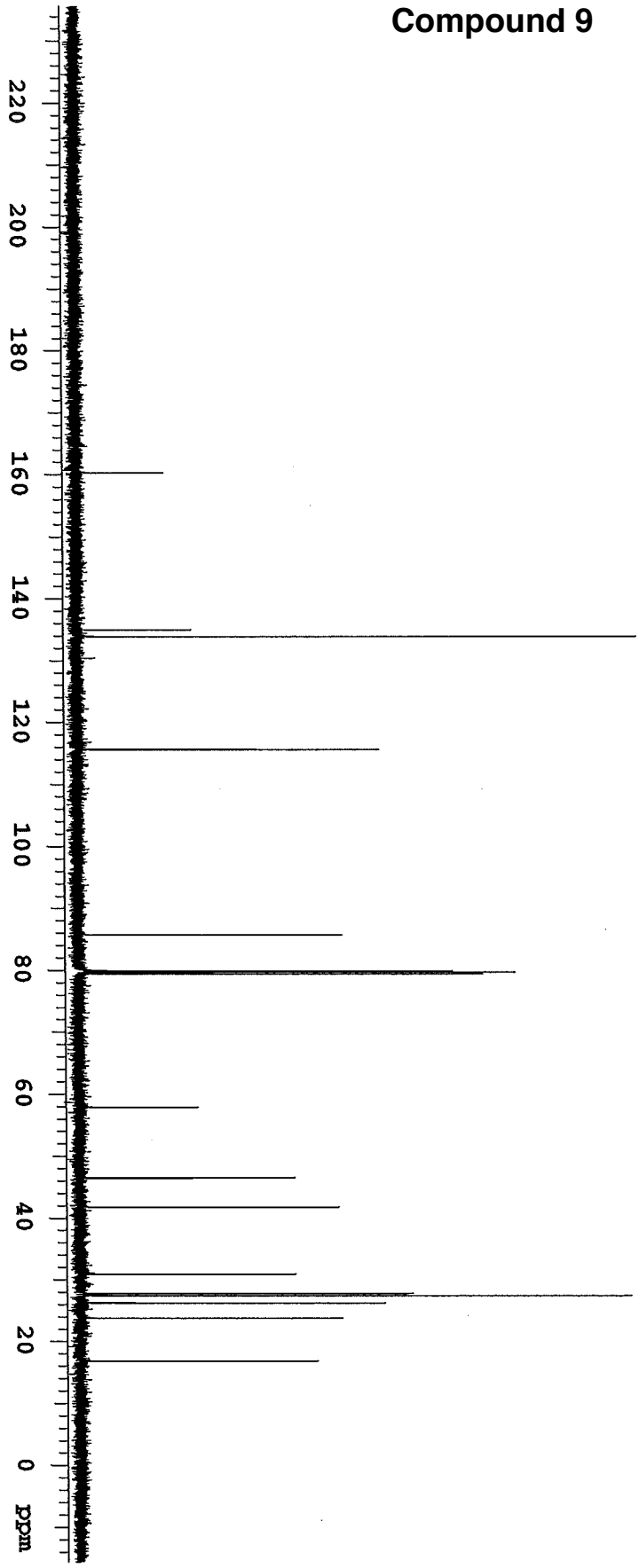


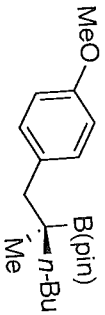


Compound 9

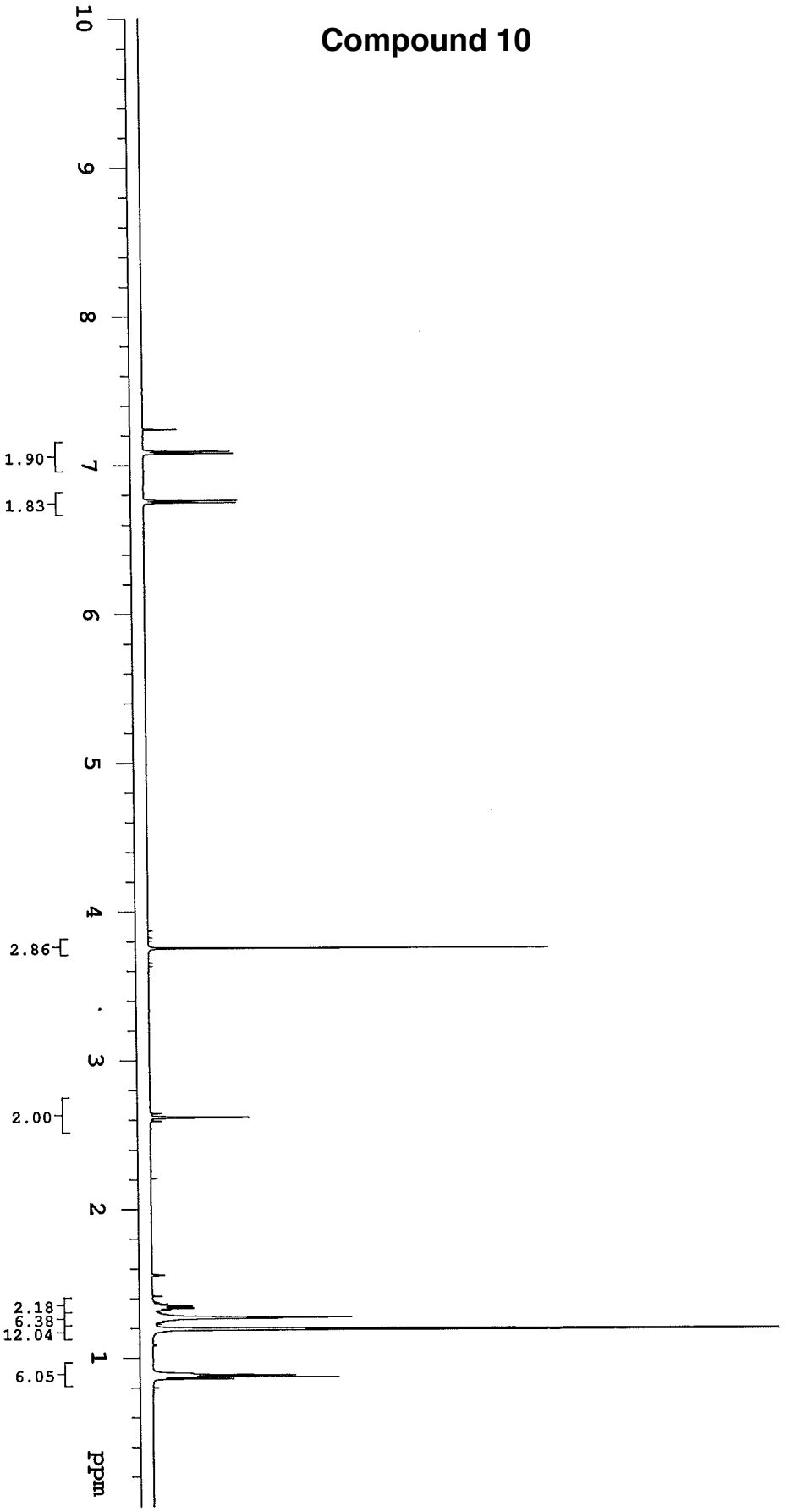


Compound 9





Compound 10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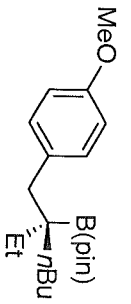
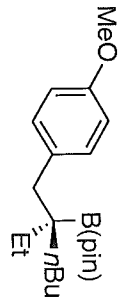
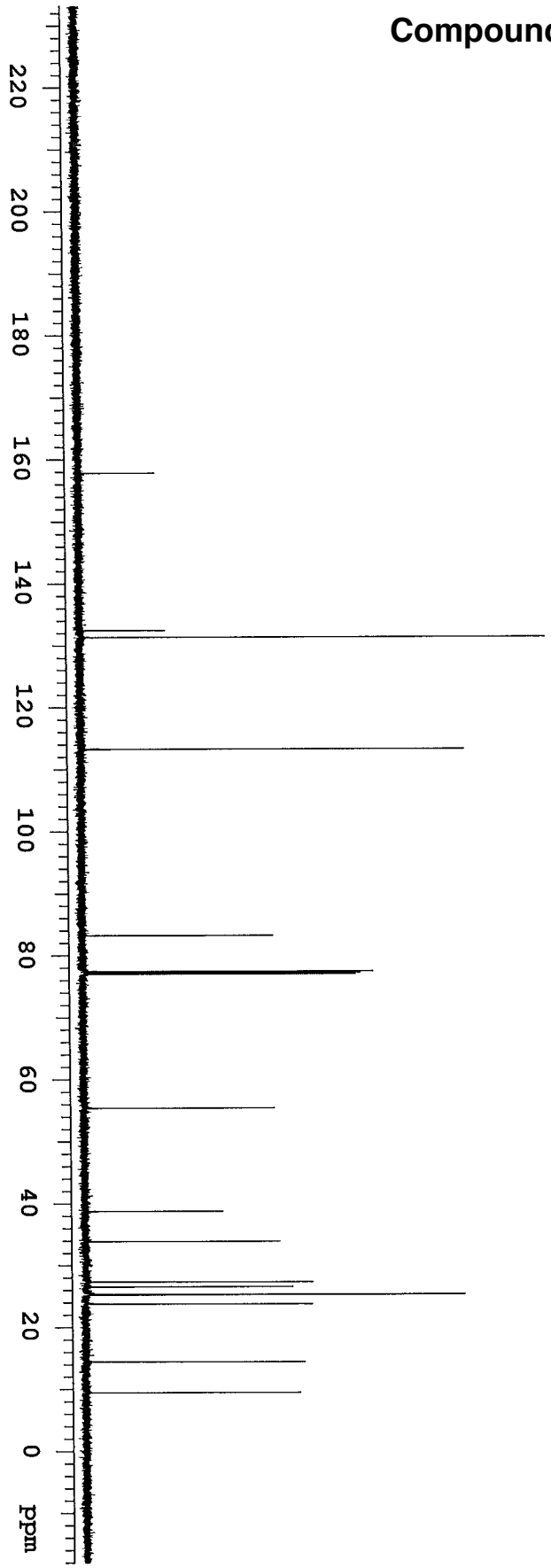
6.05

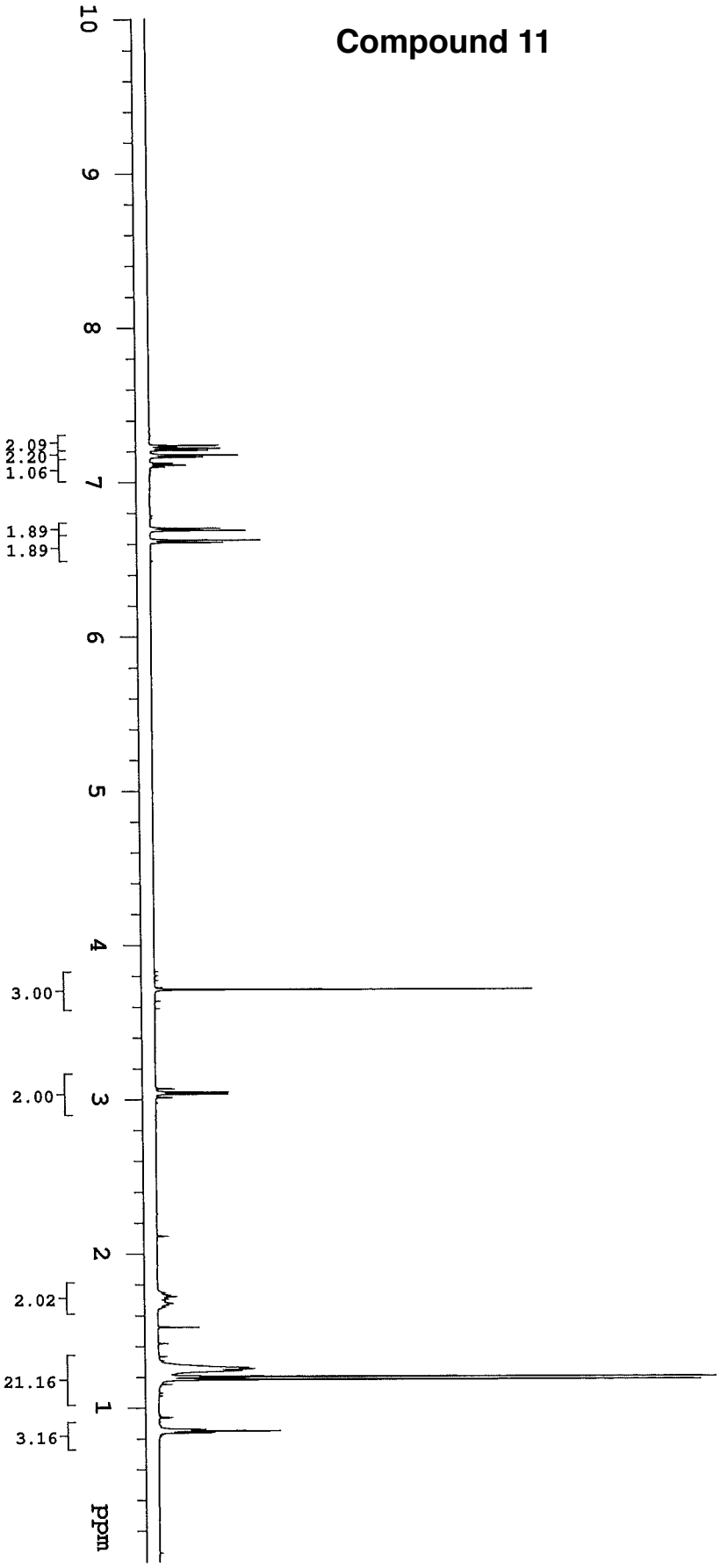

MeO
B(pin)
Et
nBu

Compound 10





Compound 11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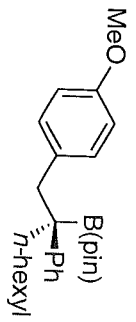
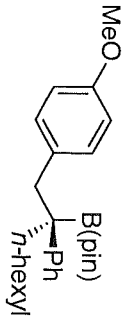
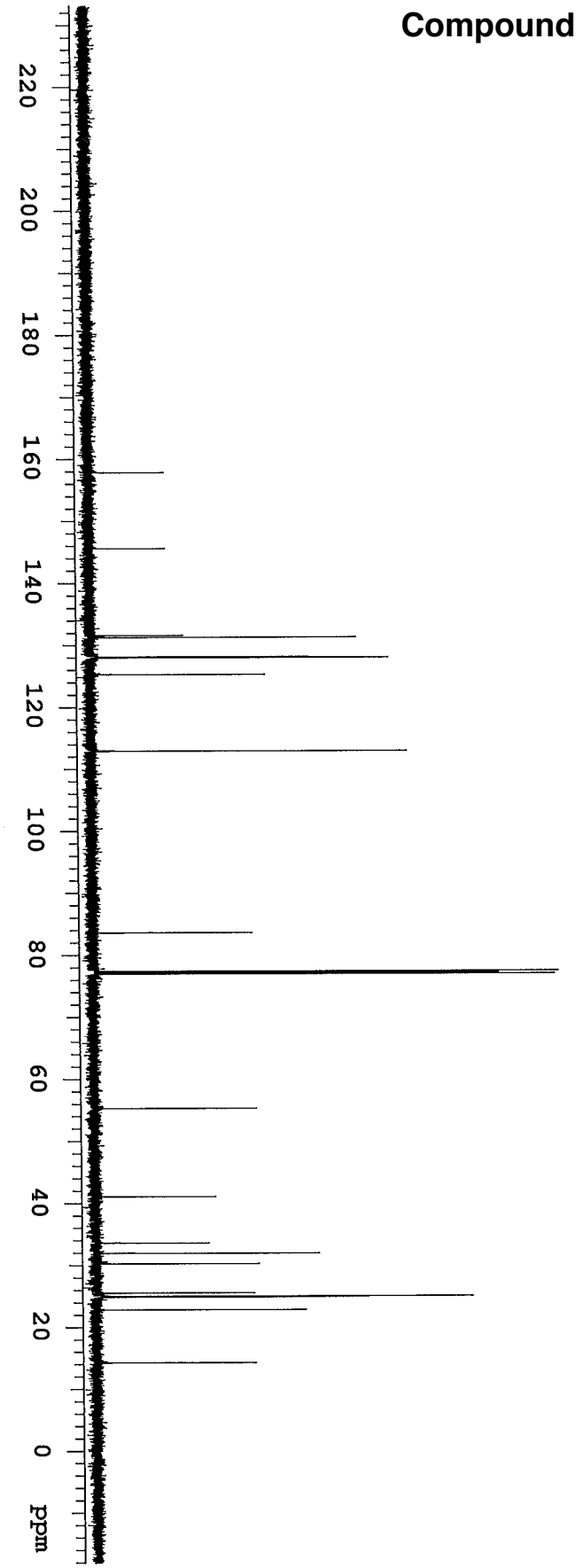
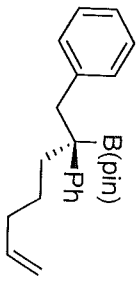

MeO
B(pin)
Ph
n-hexyl

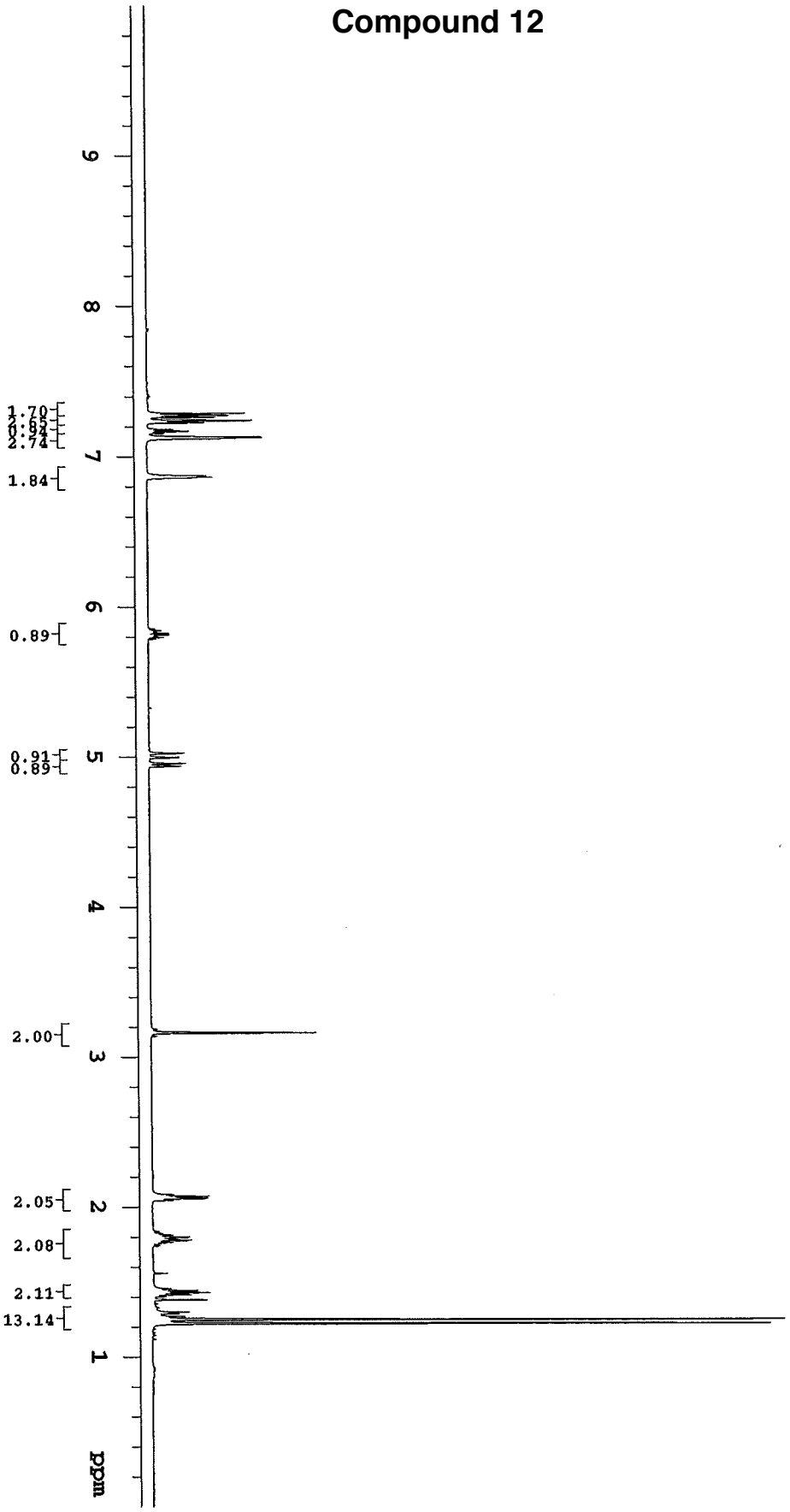
Compound 11





Compound 12


B(pin)
Ph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0.89
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2.11
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8
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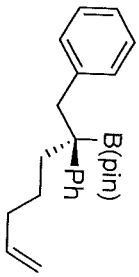
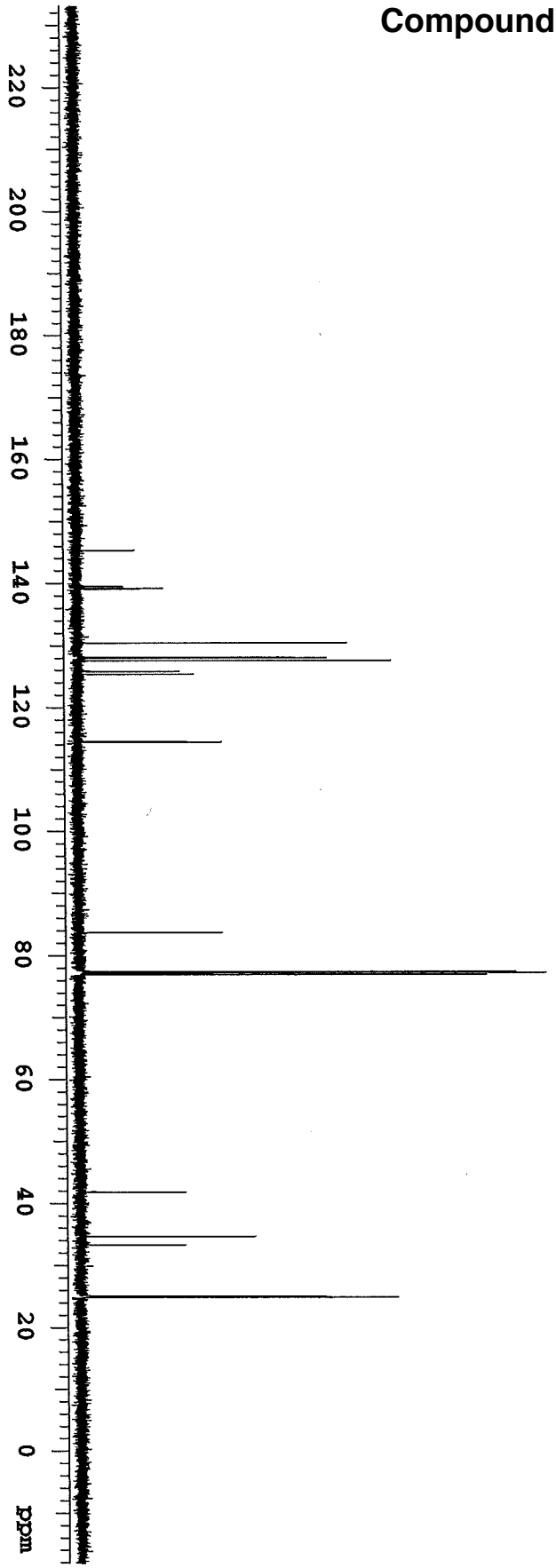
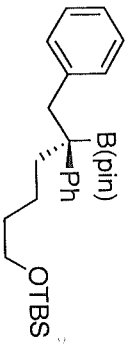
6
5
4
3
2
1
ppm

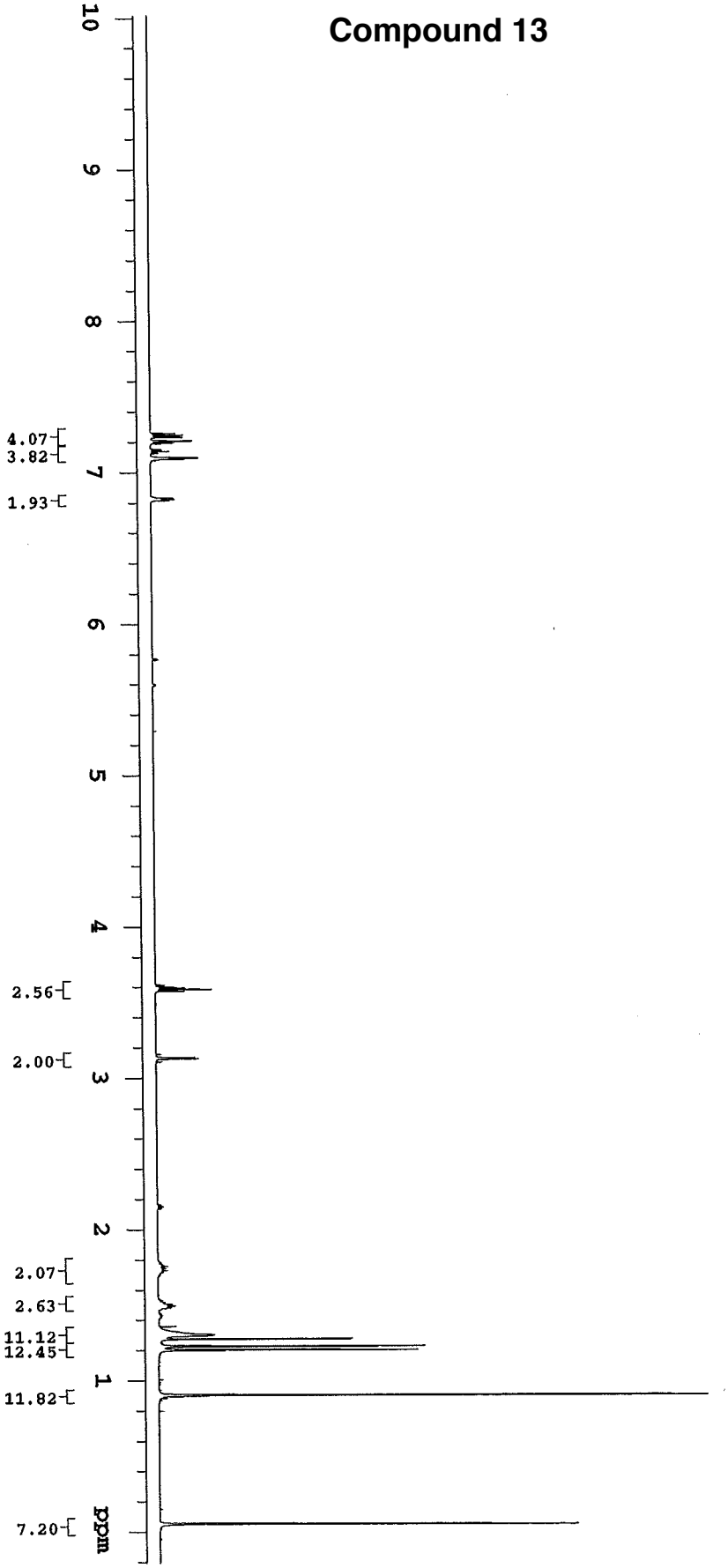
Compound 12



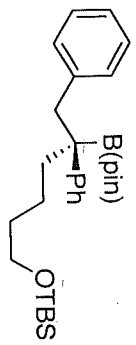


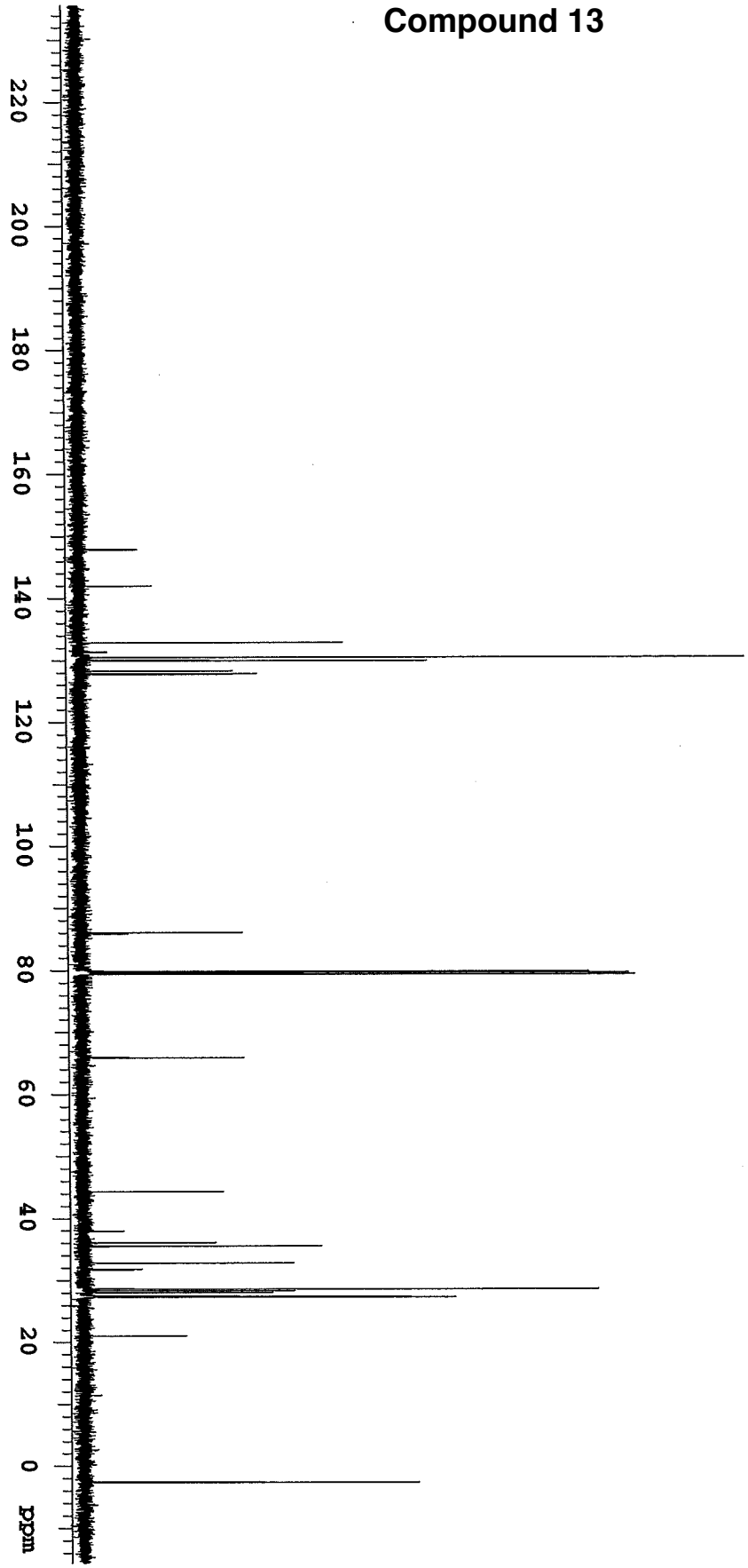
Compound 13


B(pin)
Ph
OTBS

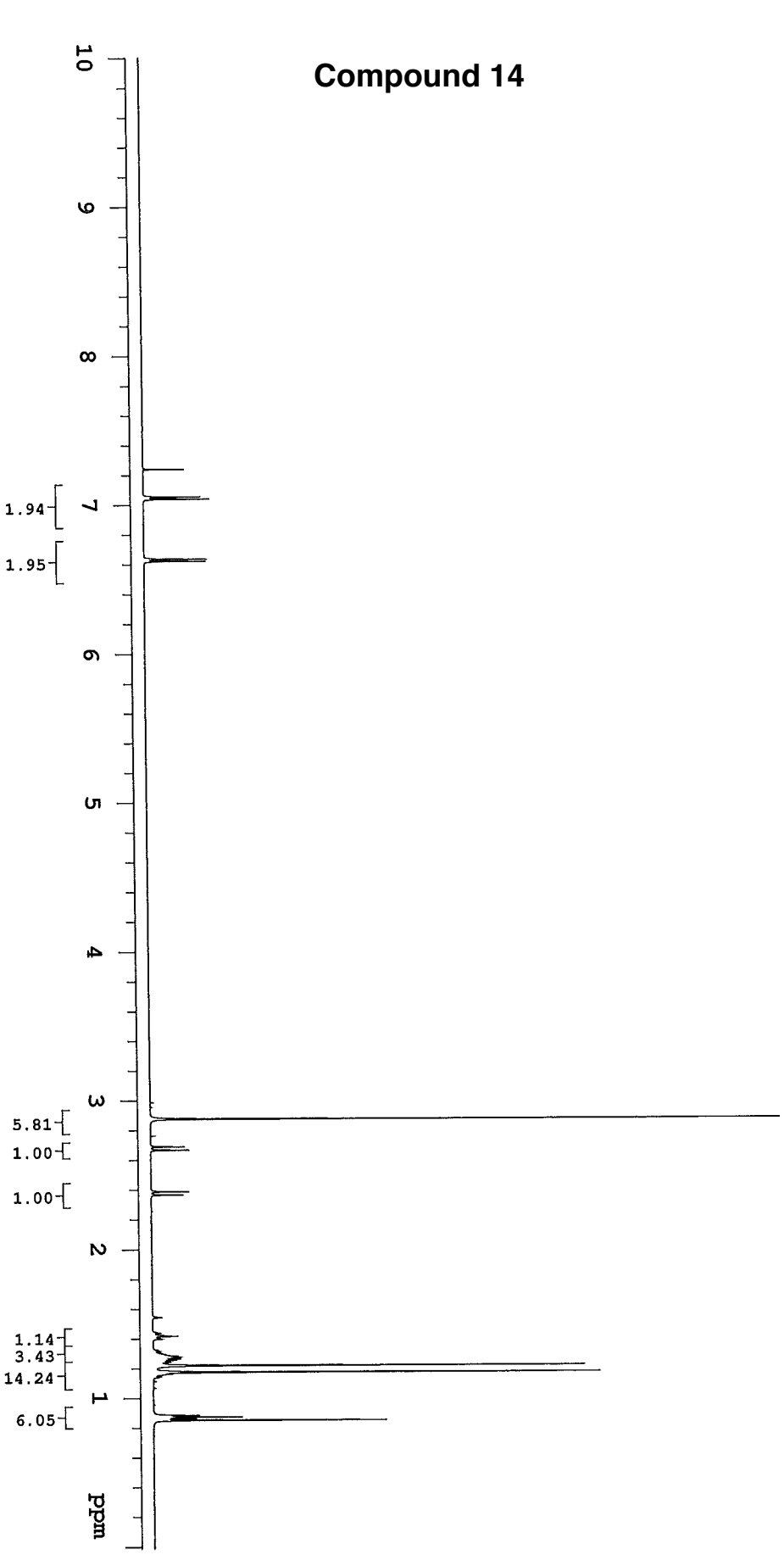

10
9
8
7
6
5
4
3
2
1
ppm
4.07
3.82
1.93
2.56
2.00
2.07
2.63
11.12
12.45
11.82
7.20

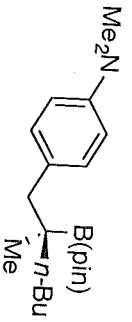
Compound 13



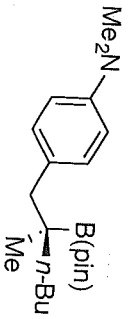


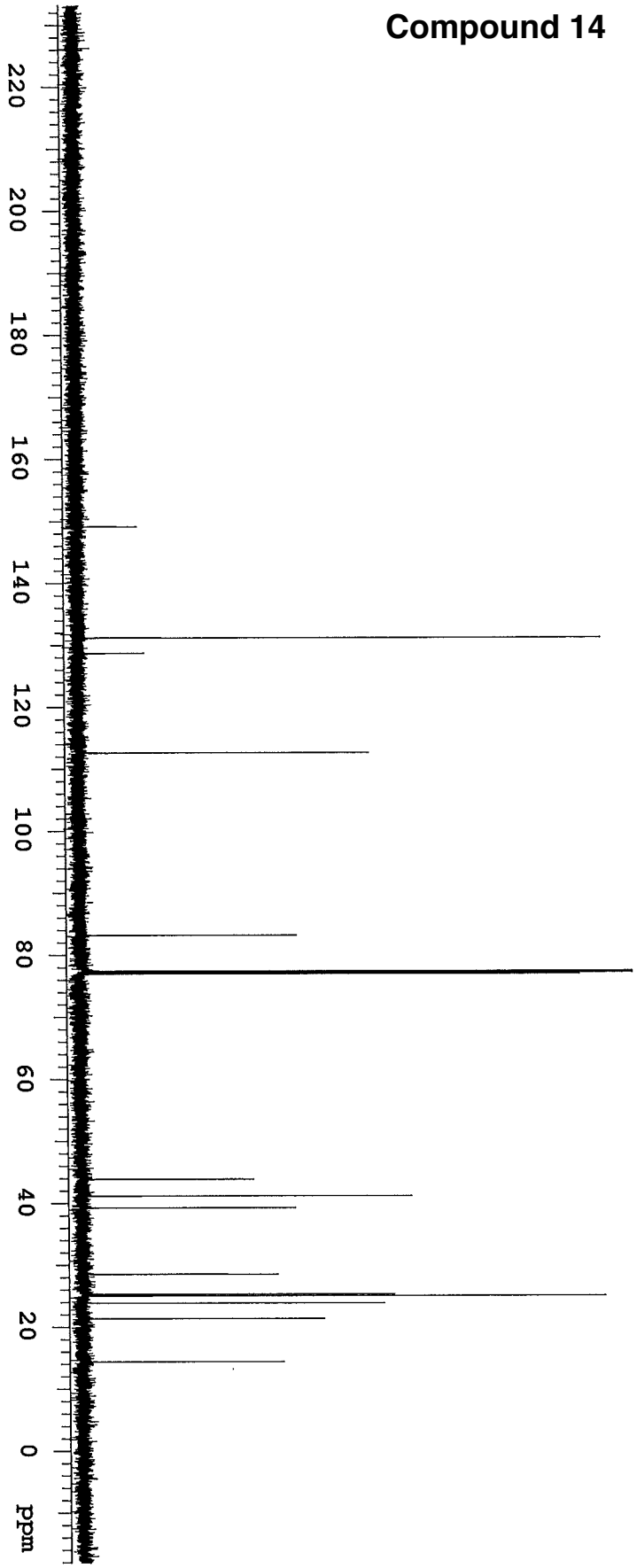
Compound 14


10
9
8
7
6
5
4
3
2
1
ppm
1.94
1.95
5.81
1.00
1.00
1.14
3.43
14.24
6.05

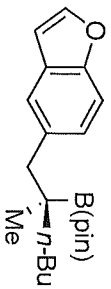

Me2N
B(pin)
n-Bu
Me

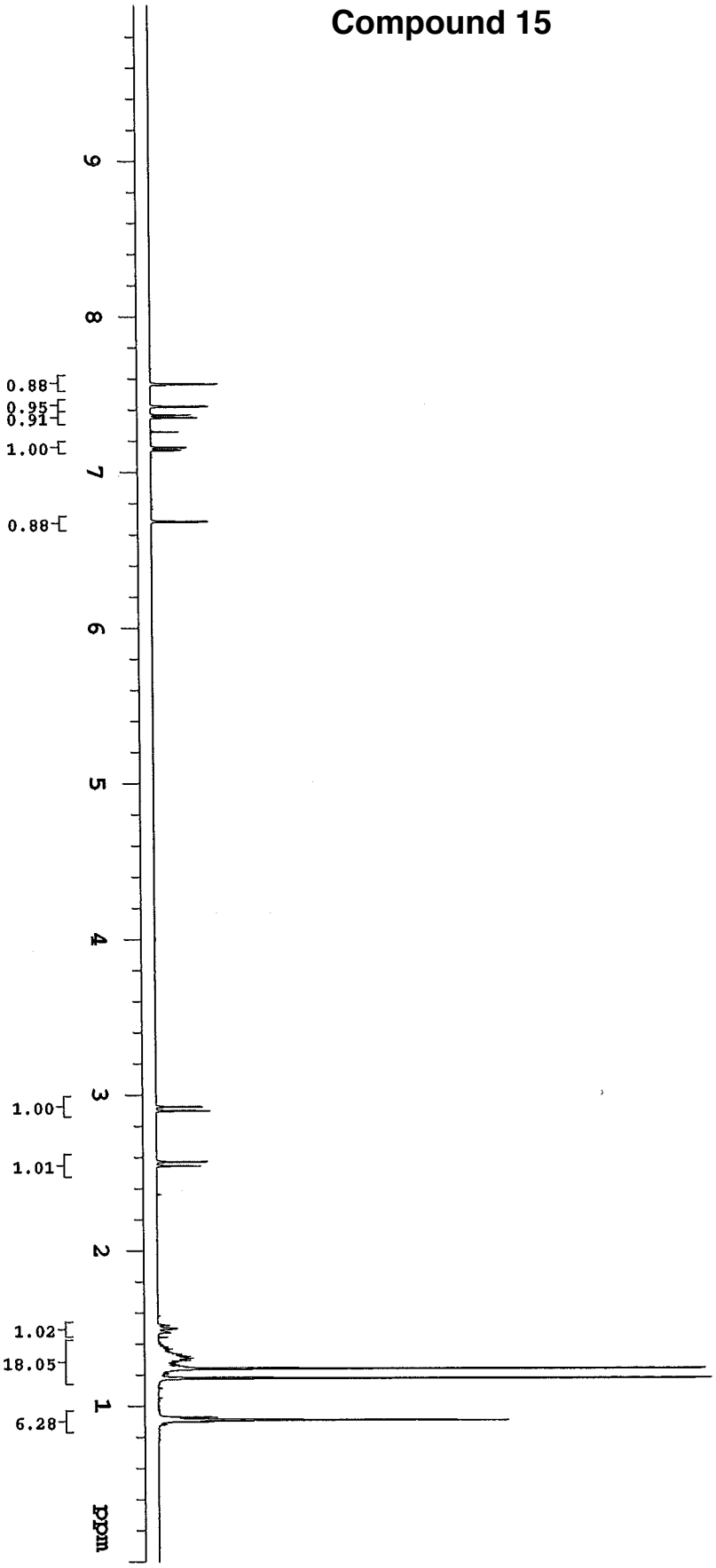
Compound 14



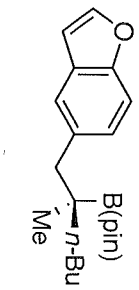


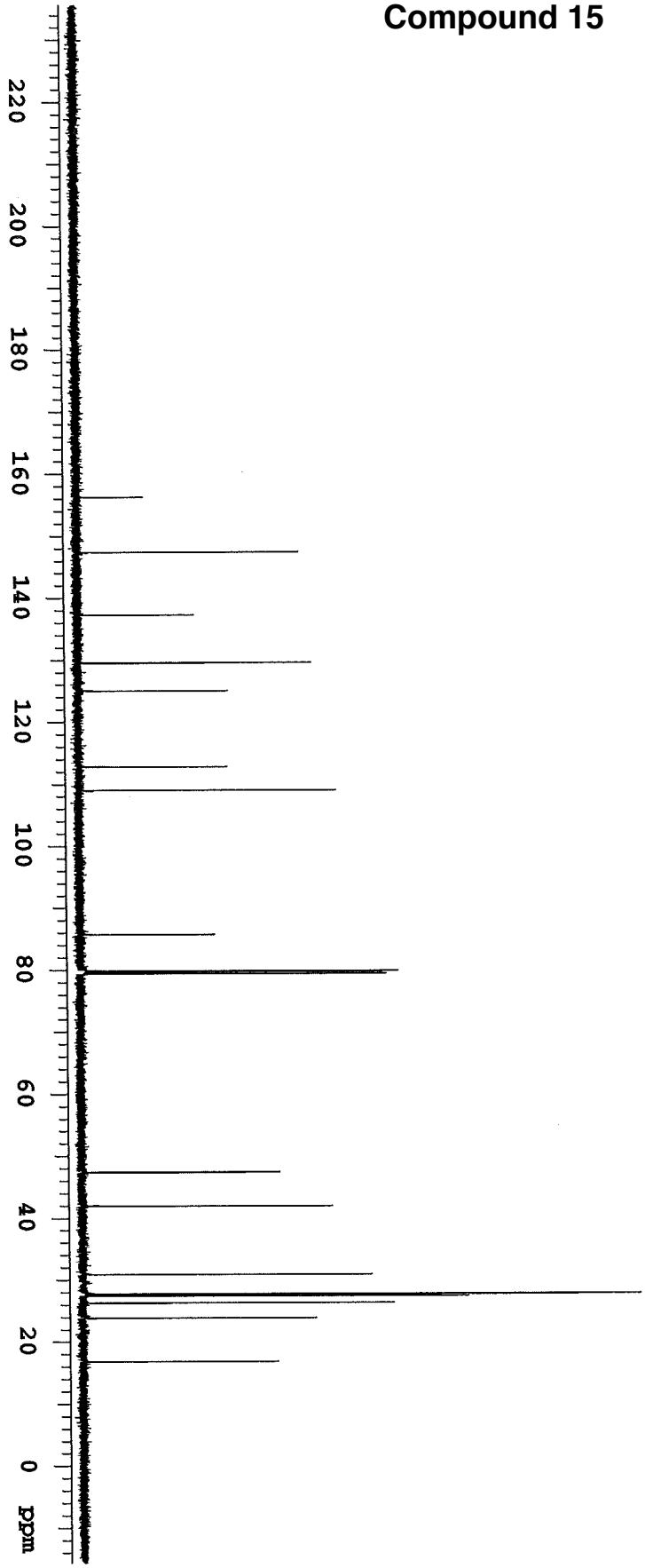
Compound 15


O
B(pin)
n-Bu
Me

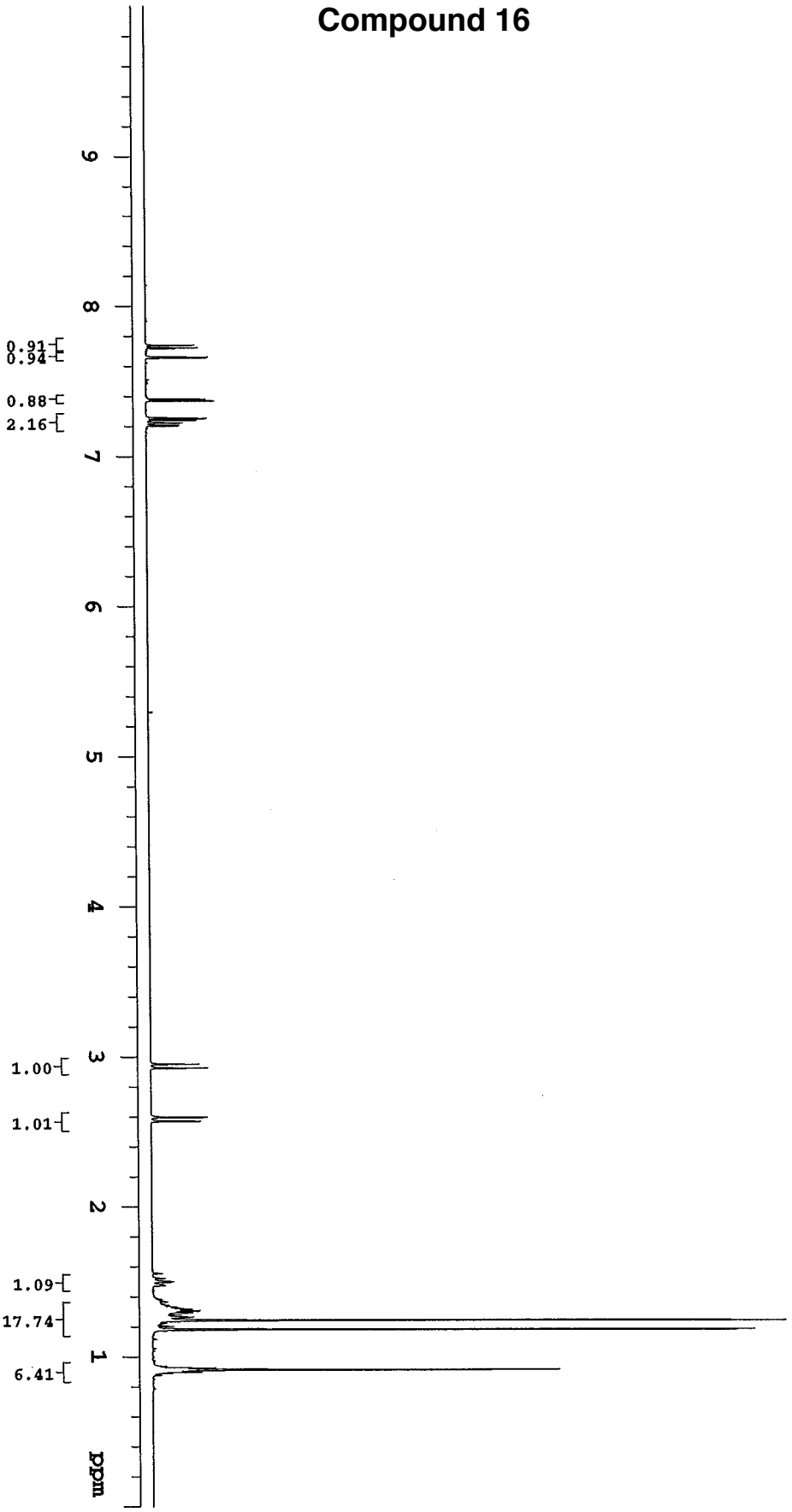

0.88
0.95
0.91
1.00
0.88
1.00
1.01
1.02
18.05
6.28
9
8
7
6
5
4
3
2
1
ppm

Compound 15

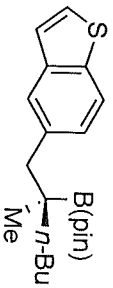


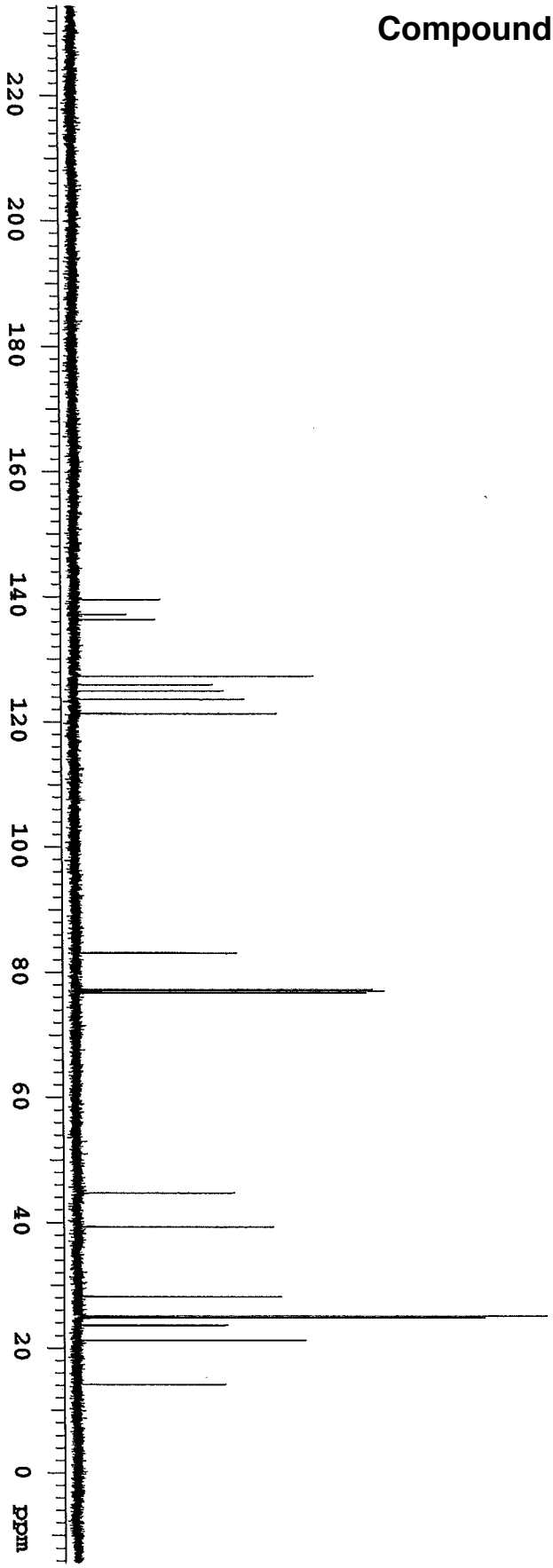


Compound 16

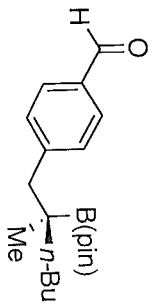

S
B(pin)
n-Bu
Me
9
8
7
6
5
4
3
2
1
ppm
0.91
0.94
0.88
2.16
1.00
1.01
1.09
17.74
6.41

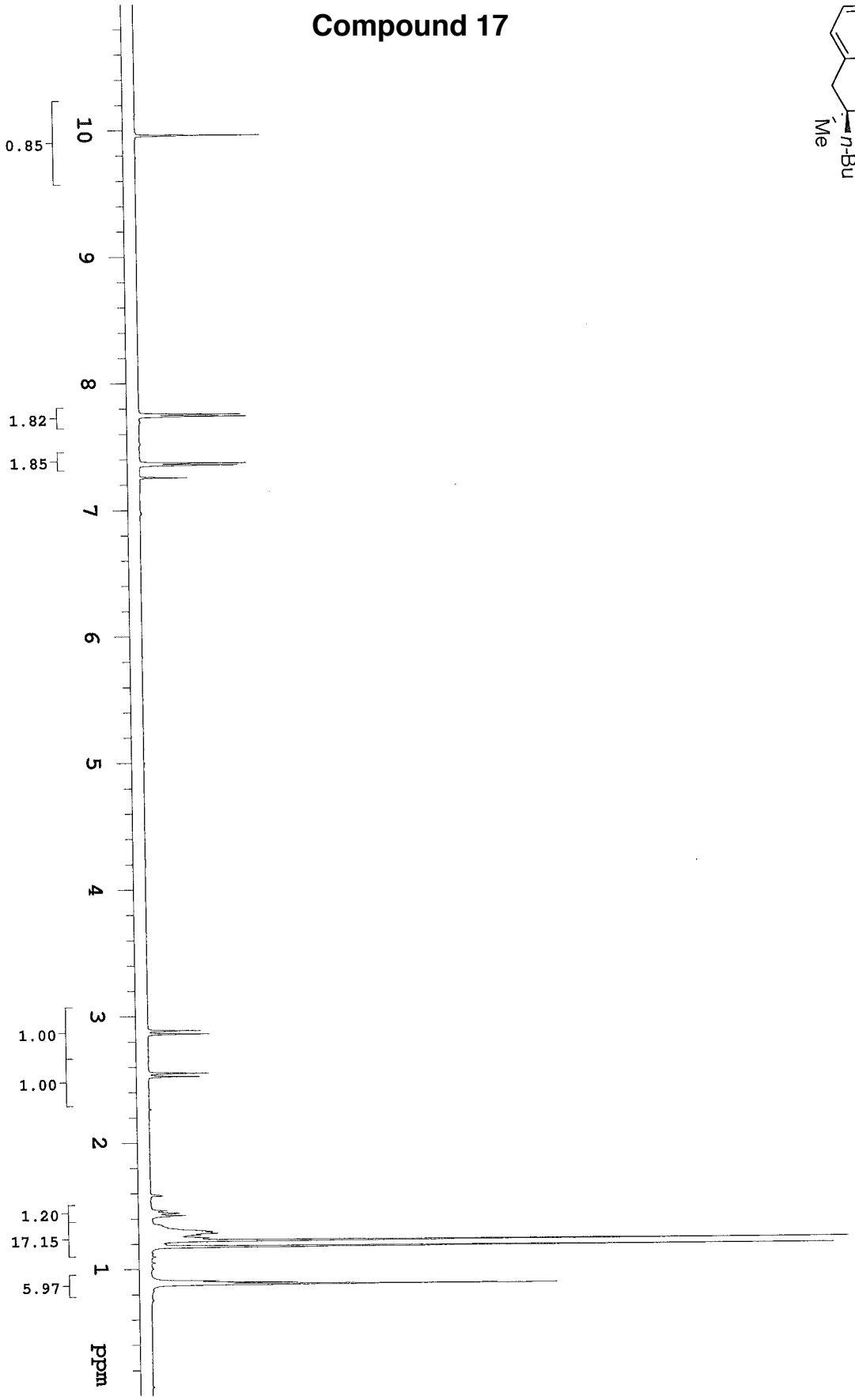
Compound 16



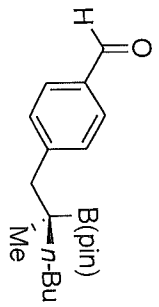


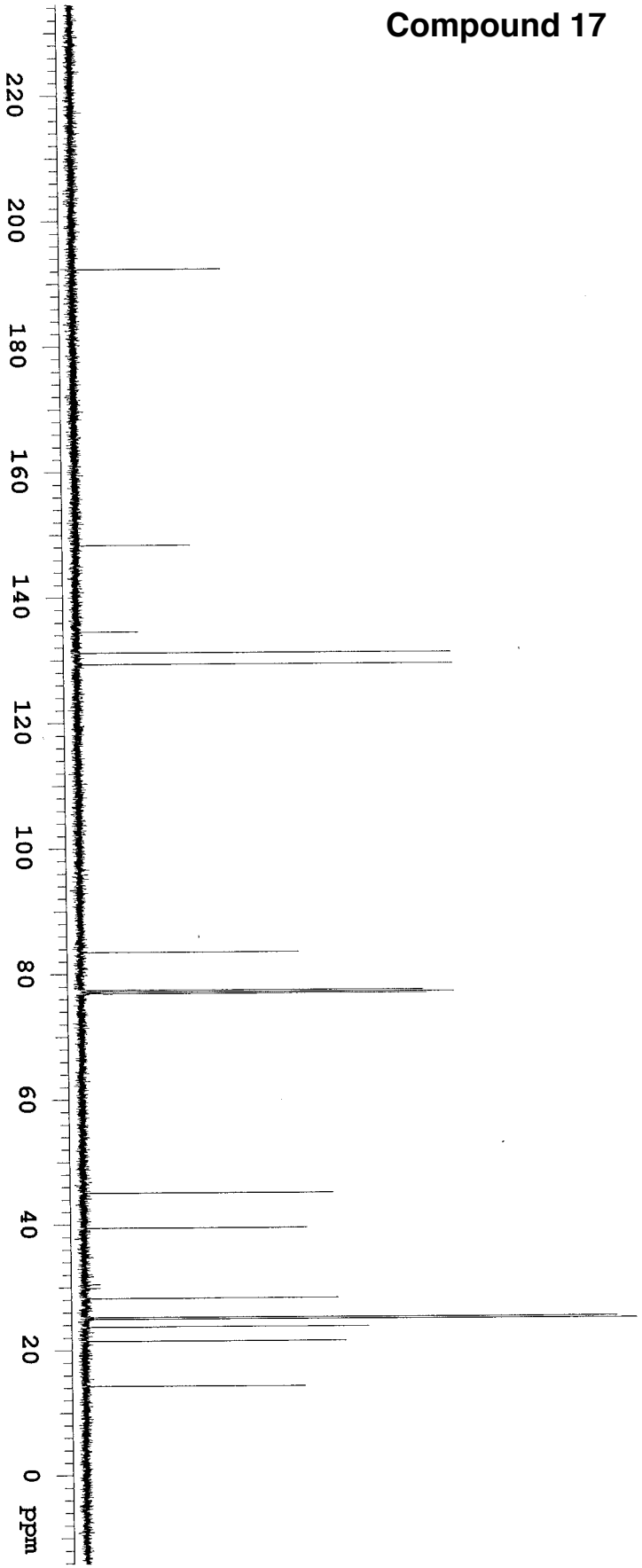
Compound 17


H
O
B(pin)
n-Bu
Me

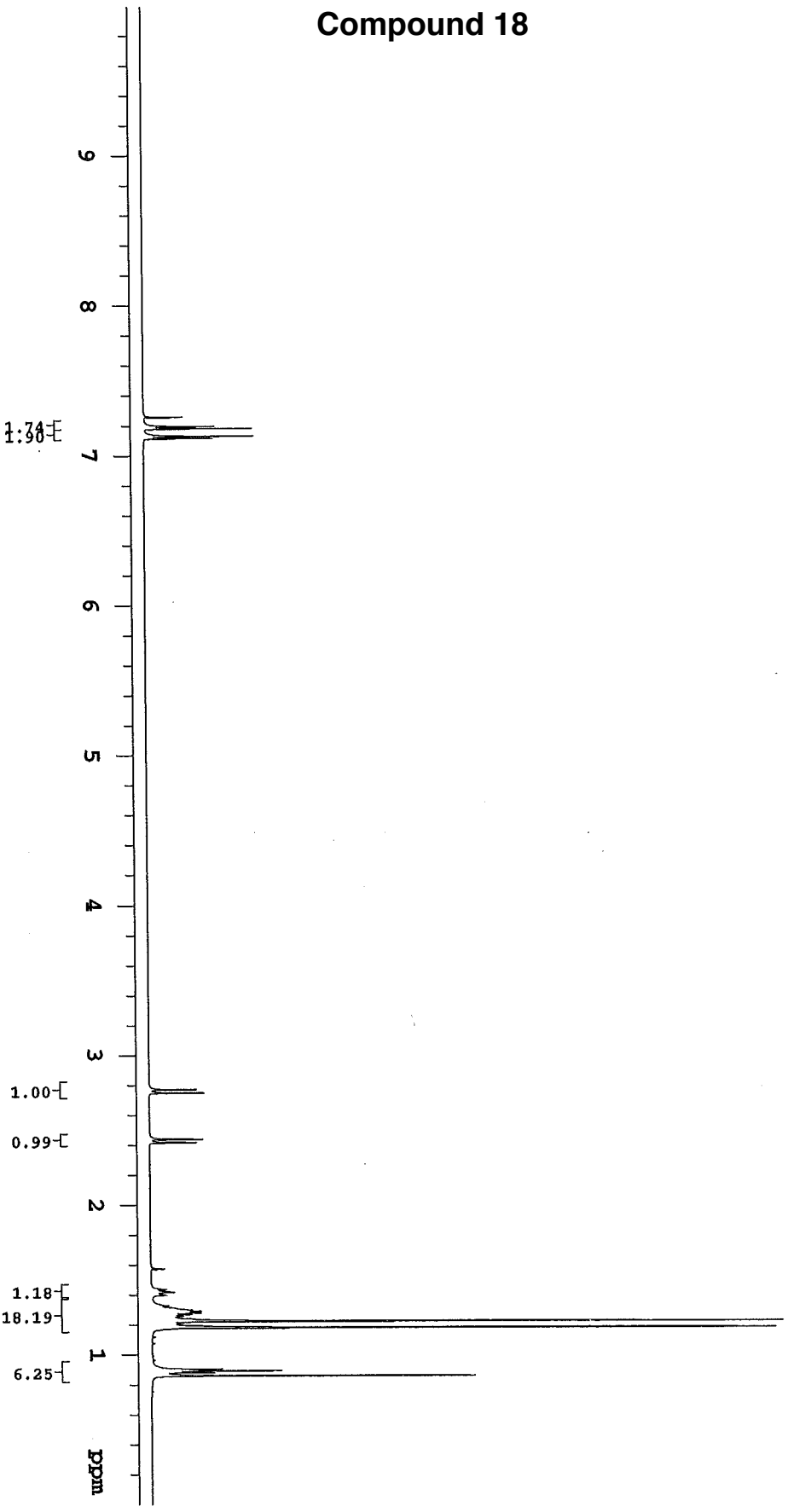

0.85
1.82
1.85
1.00
1.00
1.20
17.15
5.97
10
9
8
7
6
5
4
3
2
1
ppm

Compound 17

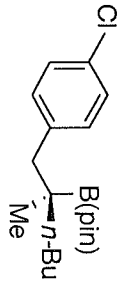


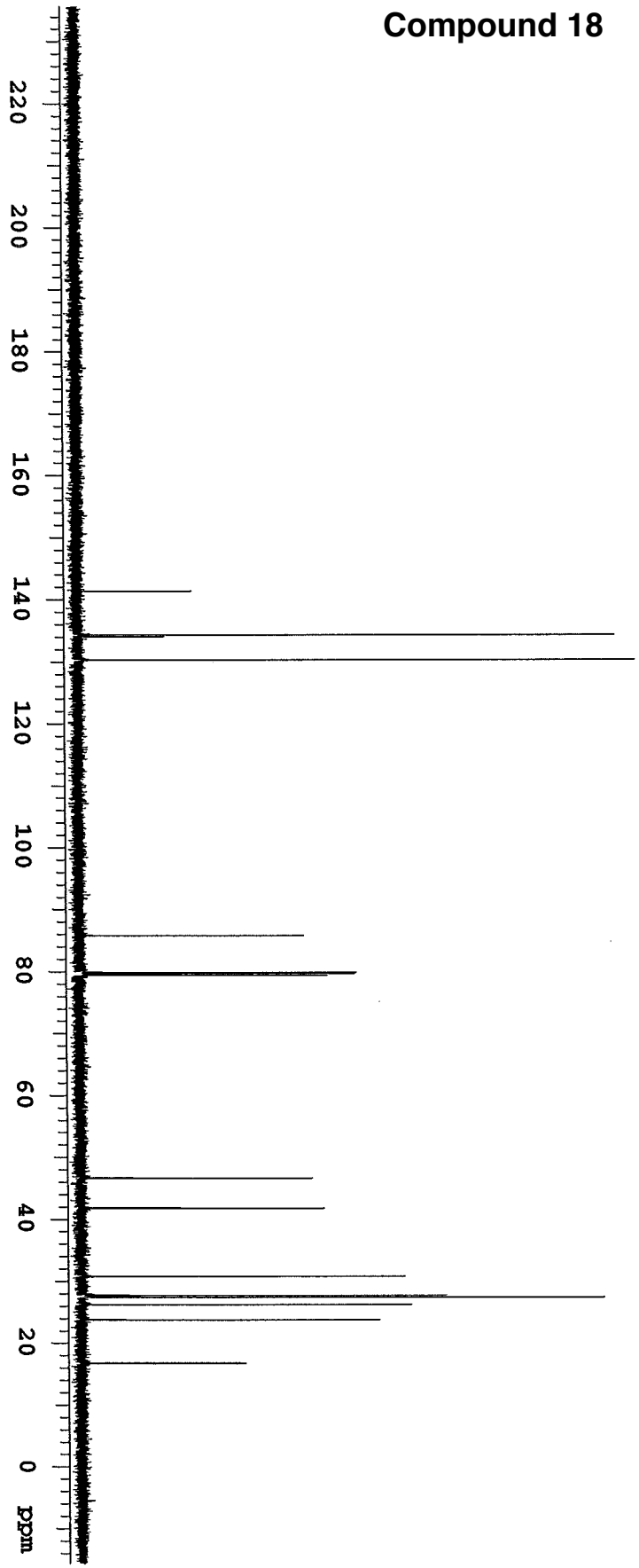


Compound 18

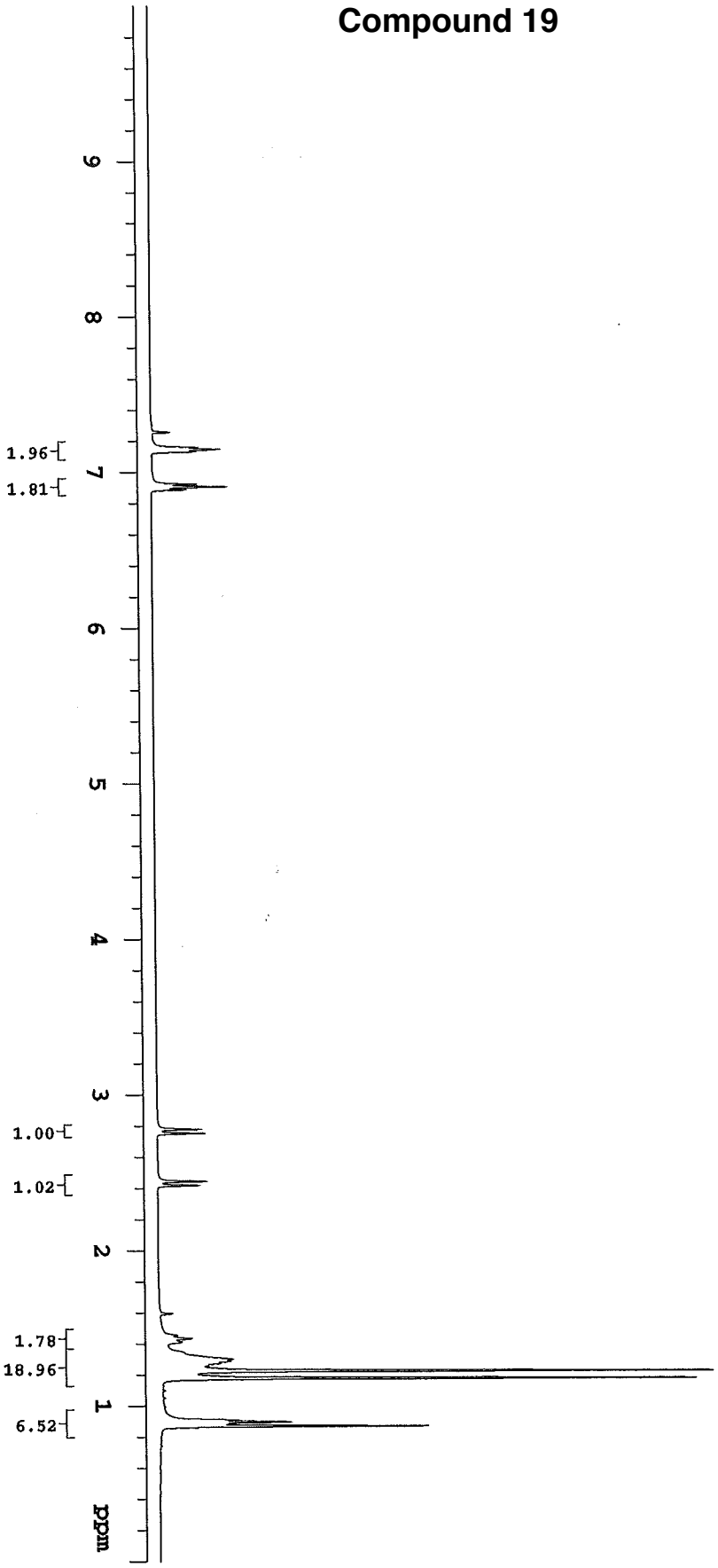


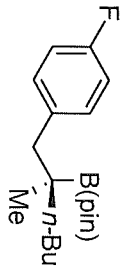
Compound 18



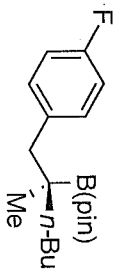


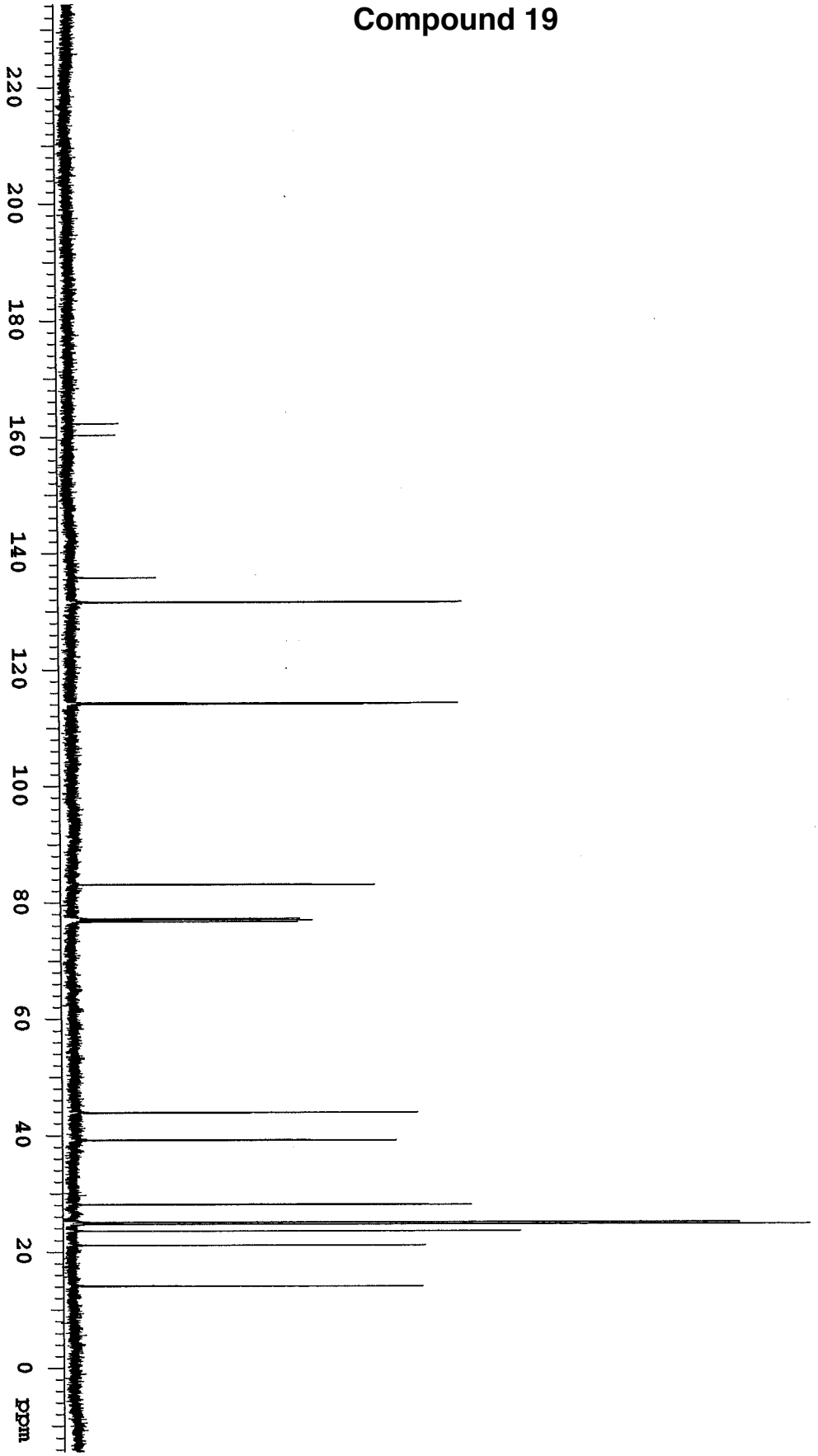
Compound 19



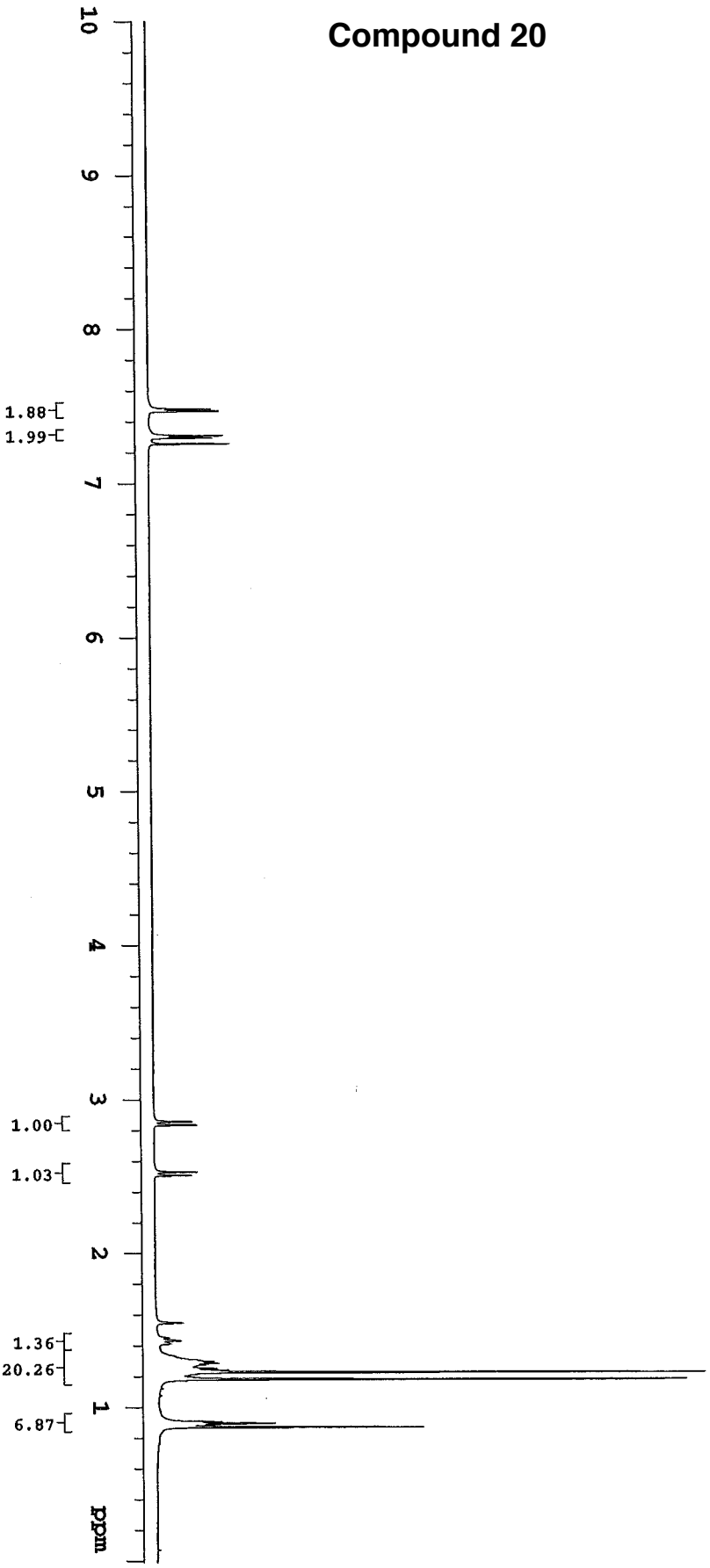


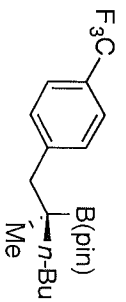
Compound 19



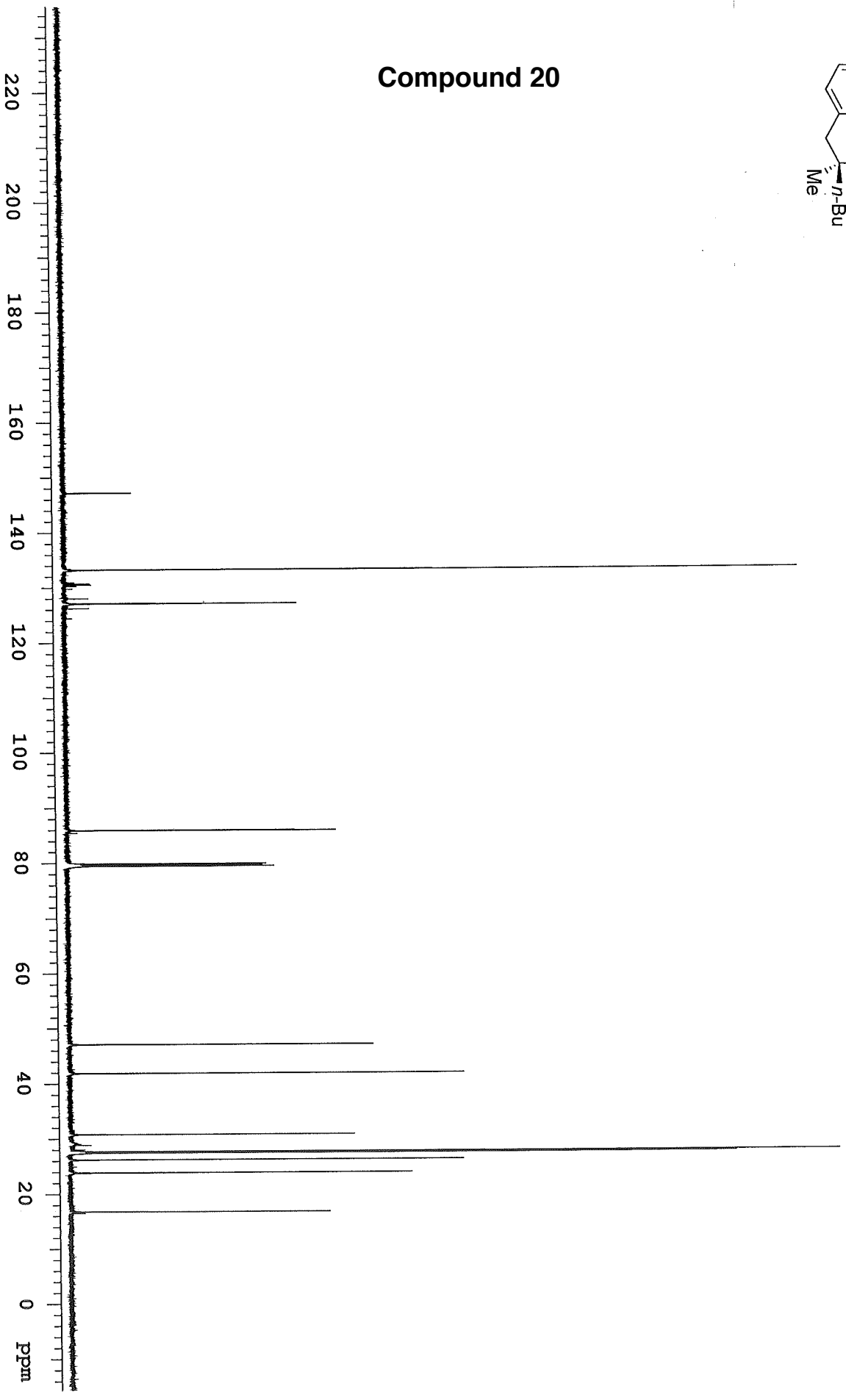


Compound 20

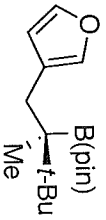


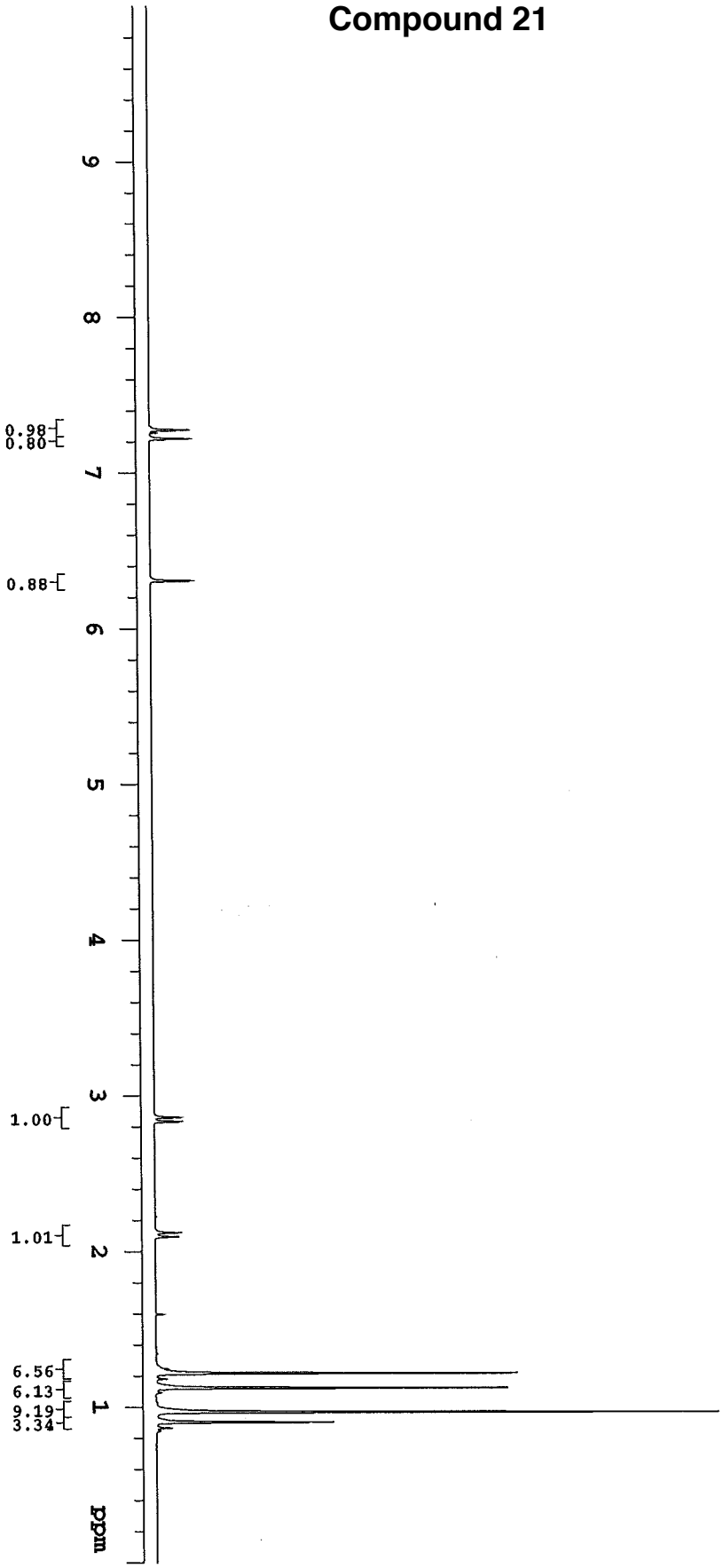


Compound 20

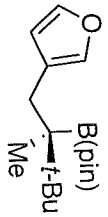


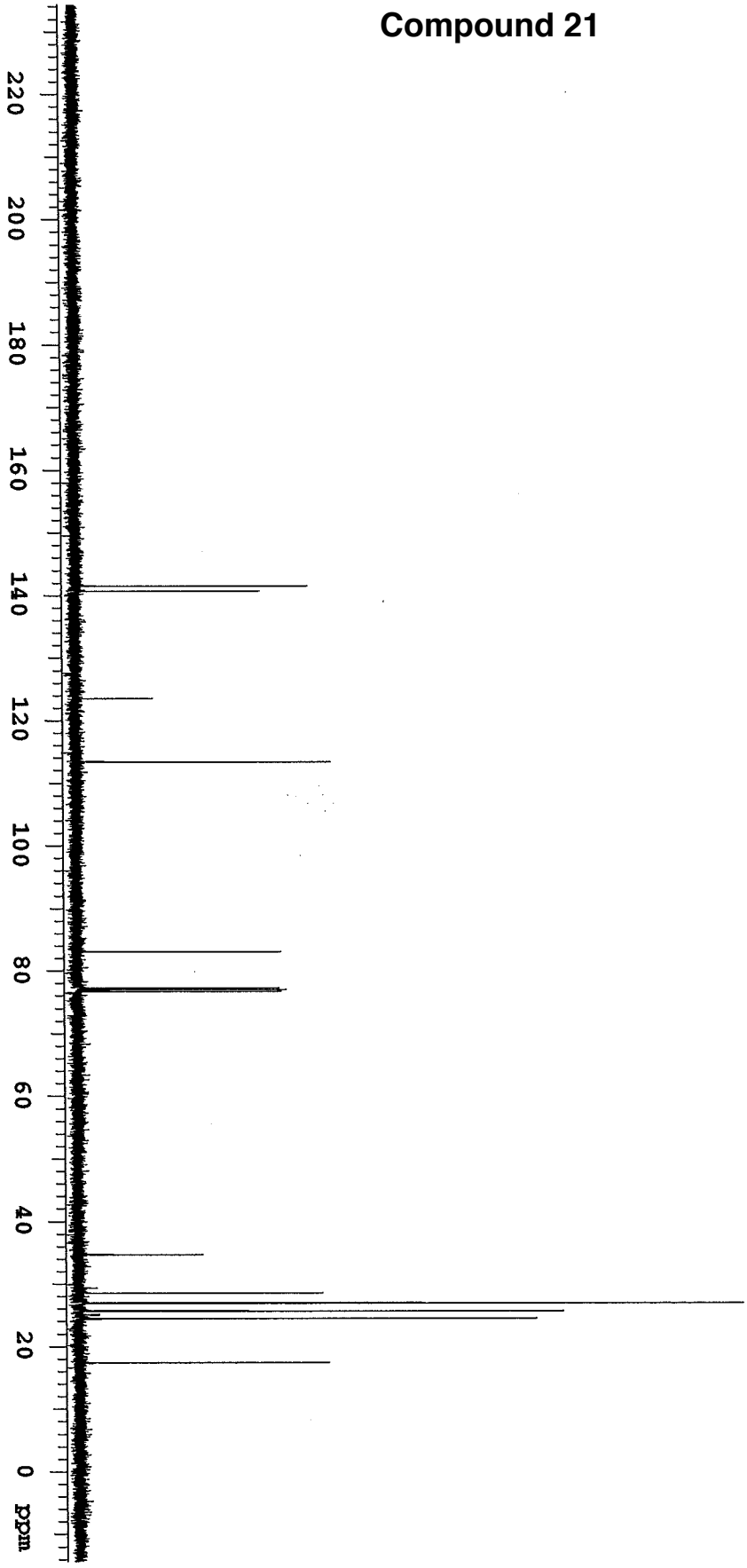
Compound 21



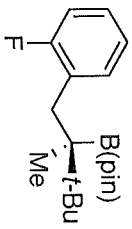


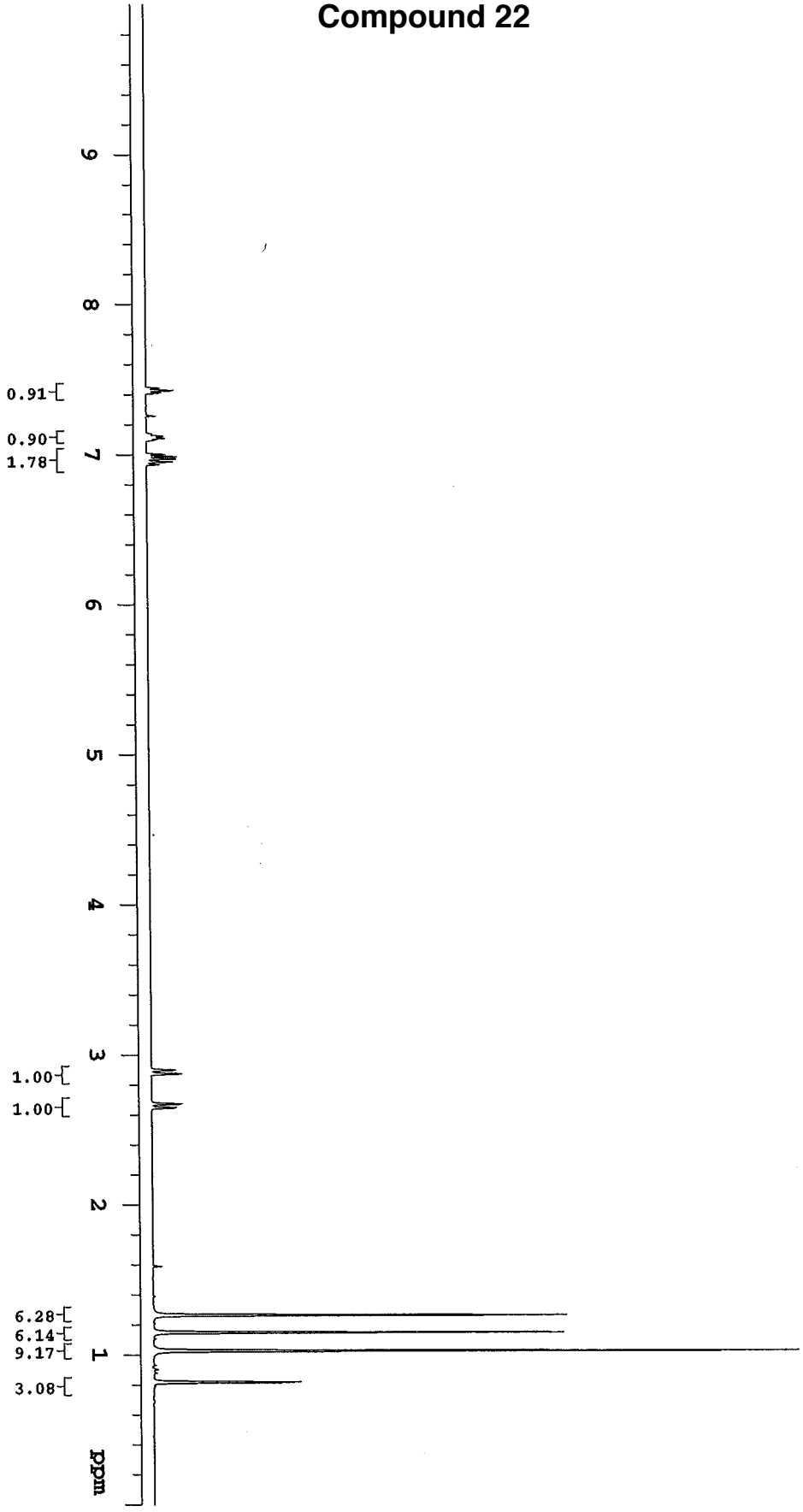
Compound 21



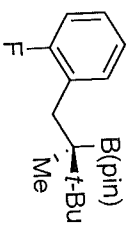


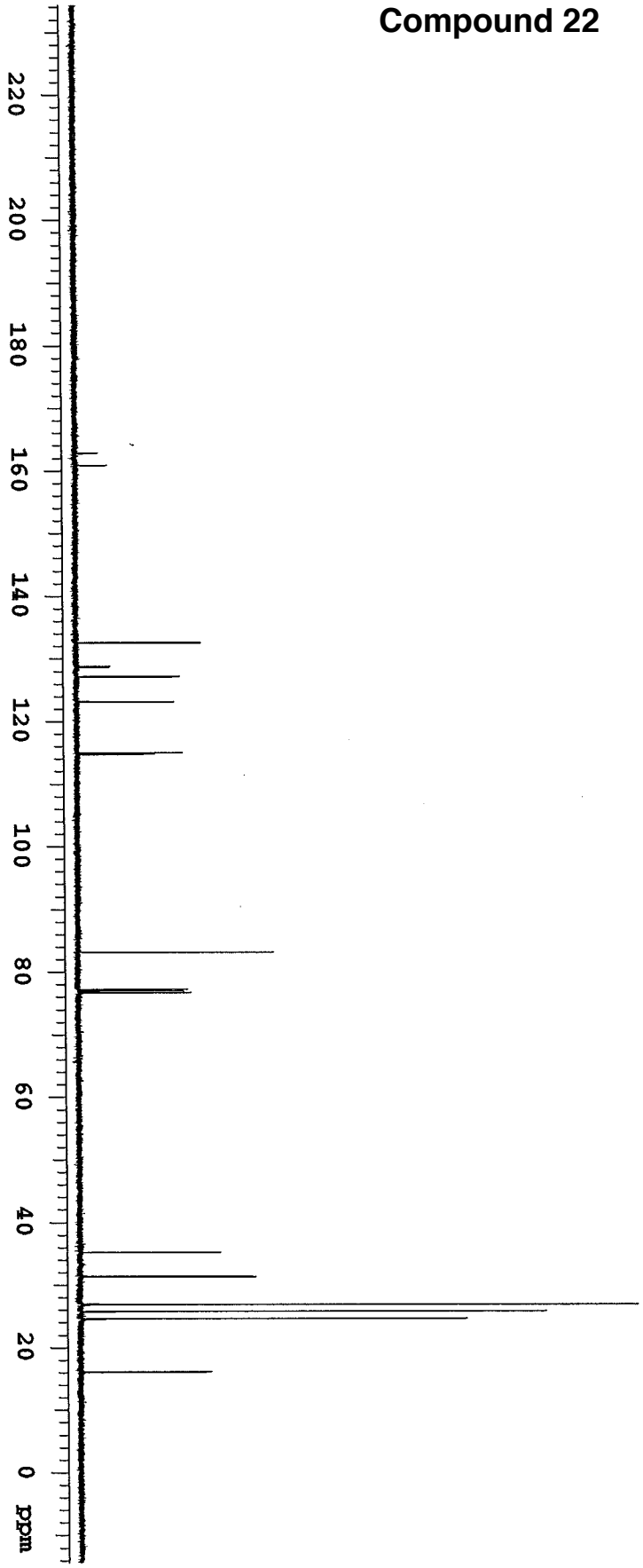
Compound 22



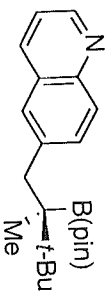


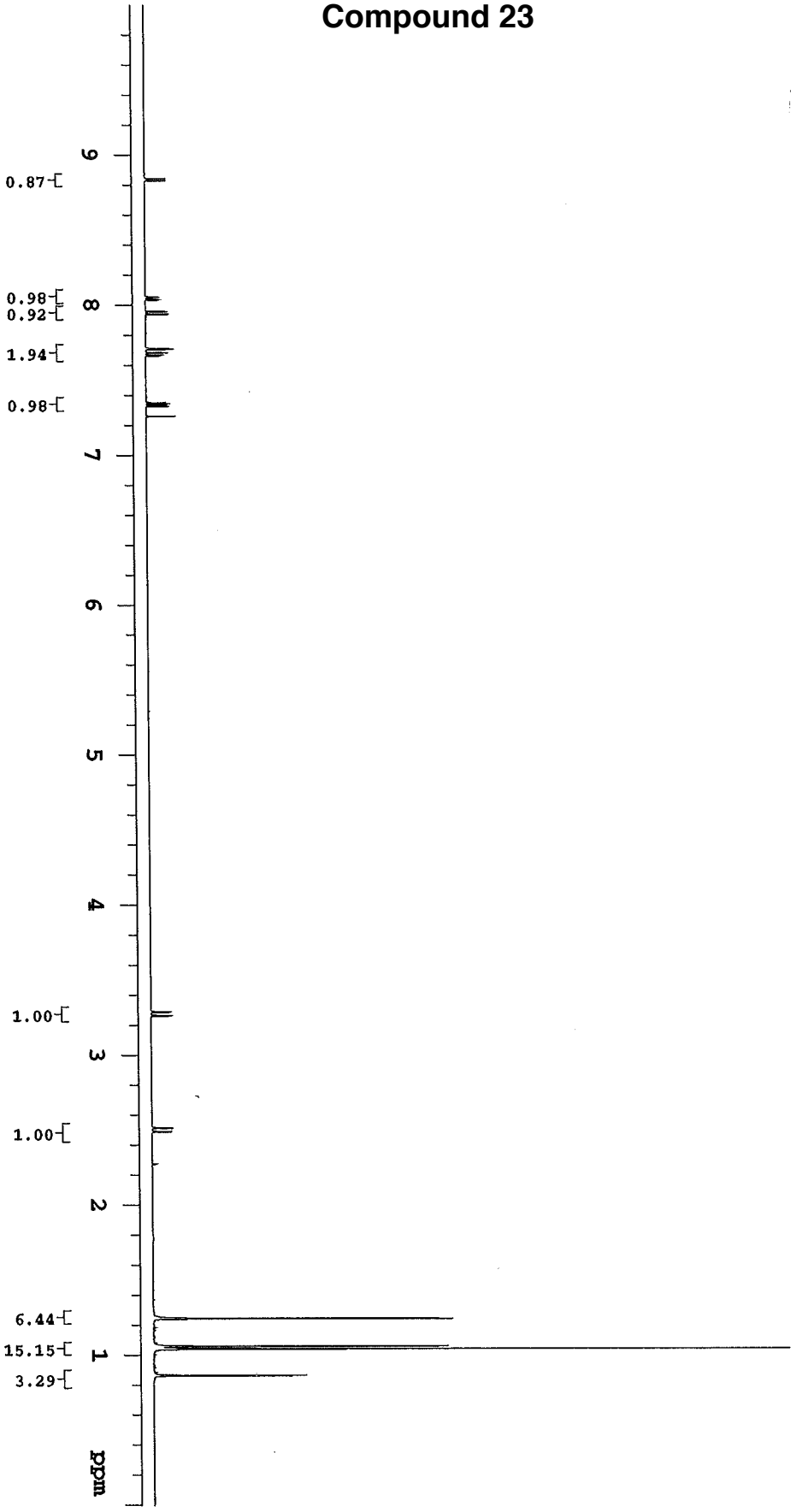
Compound 22



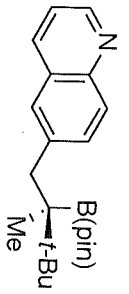


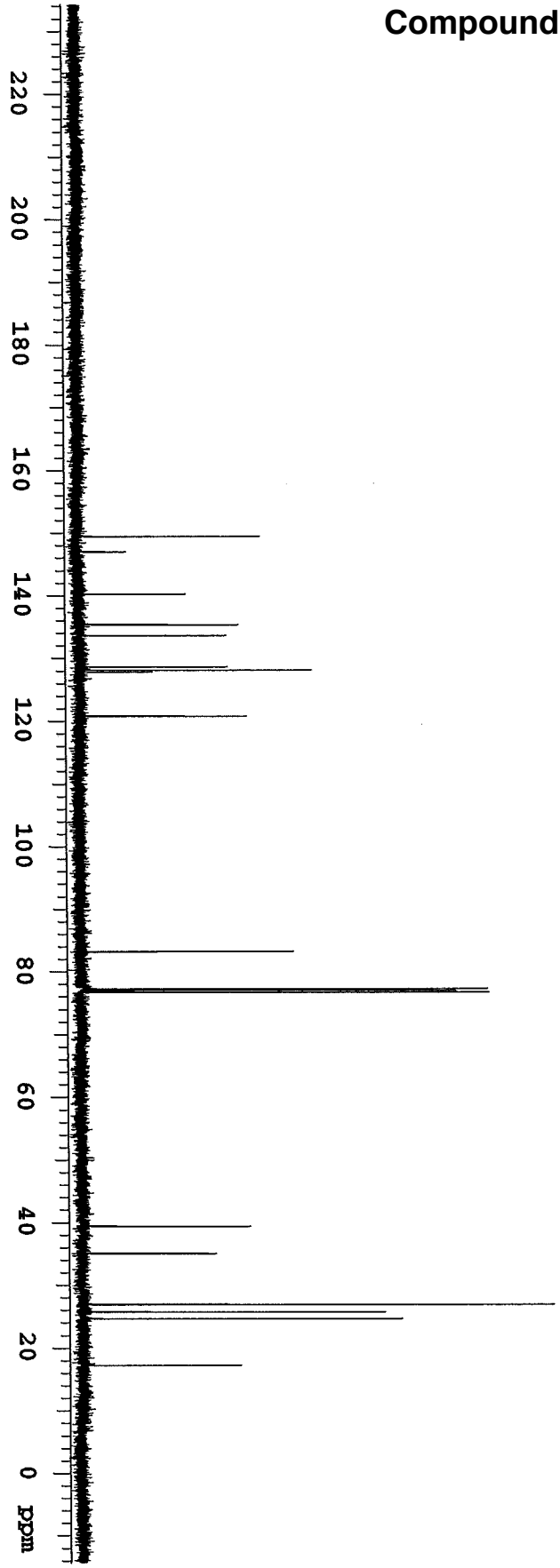
Compound 23


N
B(pin)
t-Bu
Me

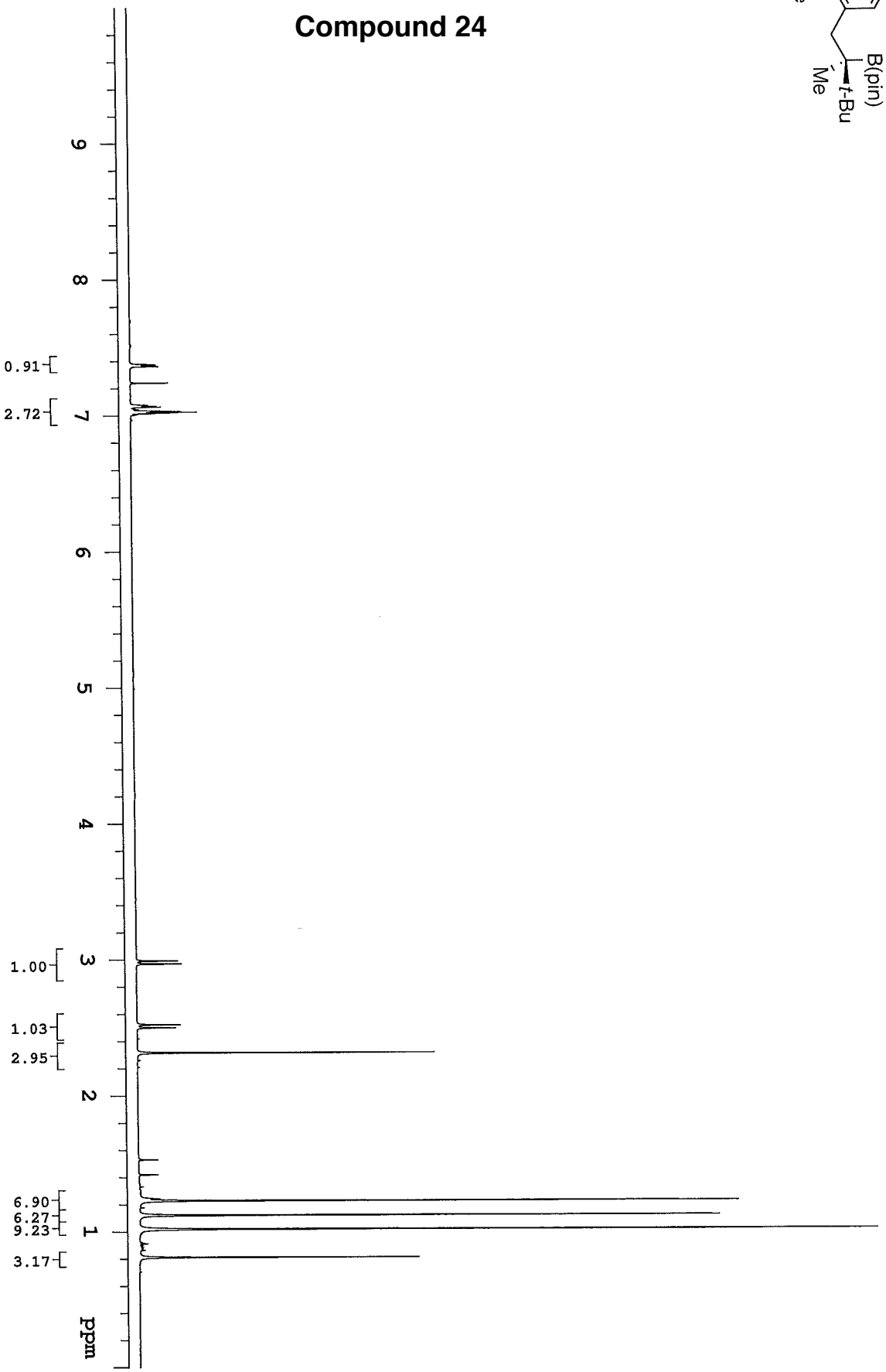

0.87
0.98
0.92
1.94
0.98
1.00
1.00
6.44
15.15
3.29
9
8
7
6
5
4
3
2
1
ppm

Compound 23

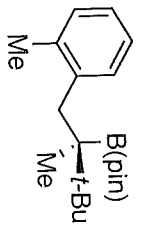


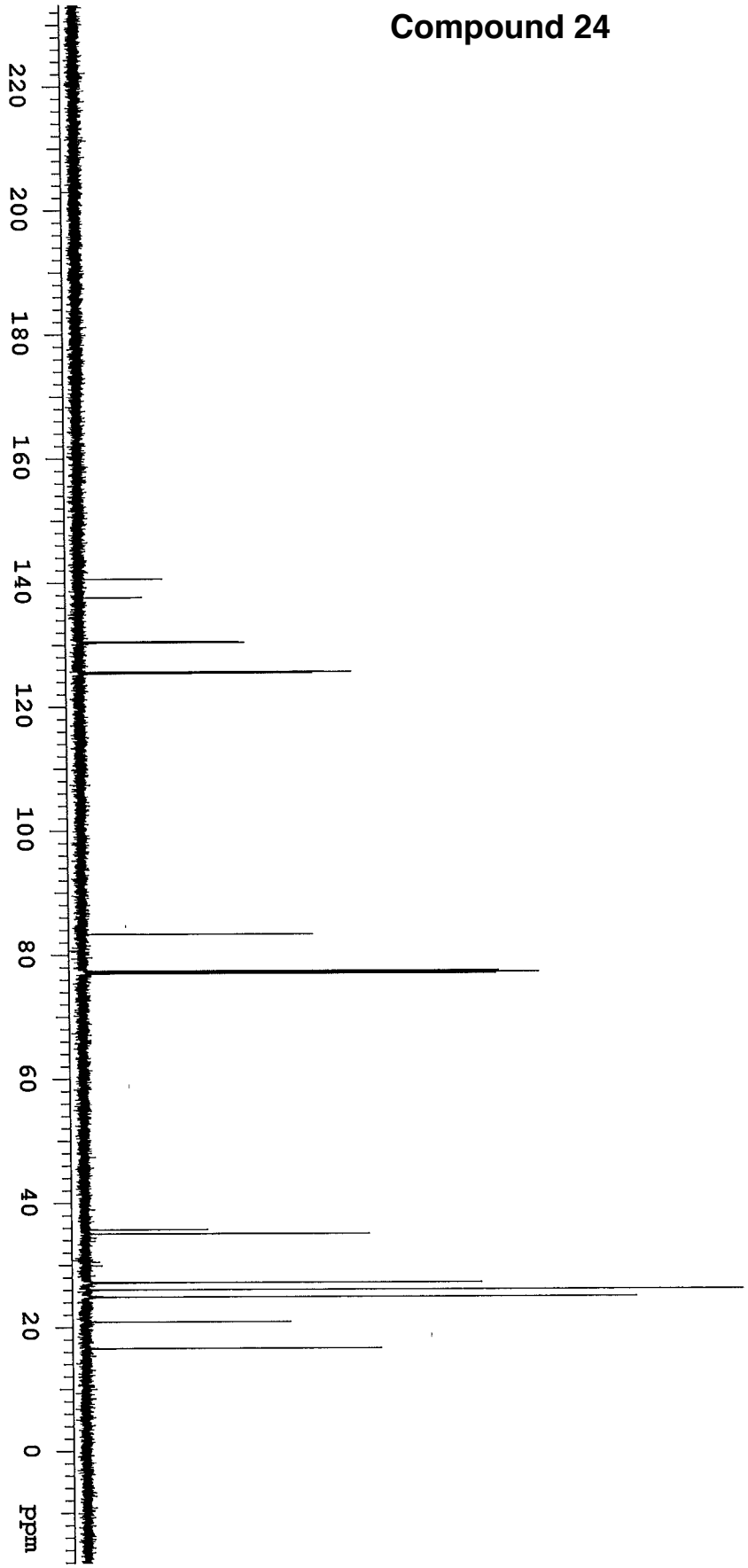


Compound 24

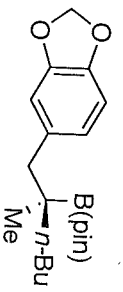

Me
B(pin)
t-Bu
Me
0.91
2.72
1.00
1.03
2.95
6.90
6.27
9.23
3.17
9
8
7
6
5
4
3
2
1
ppm

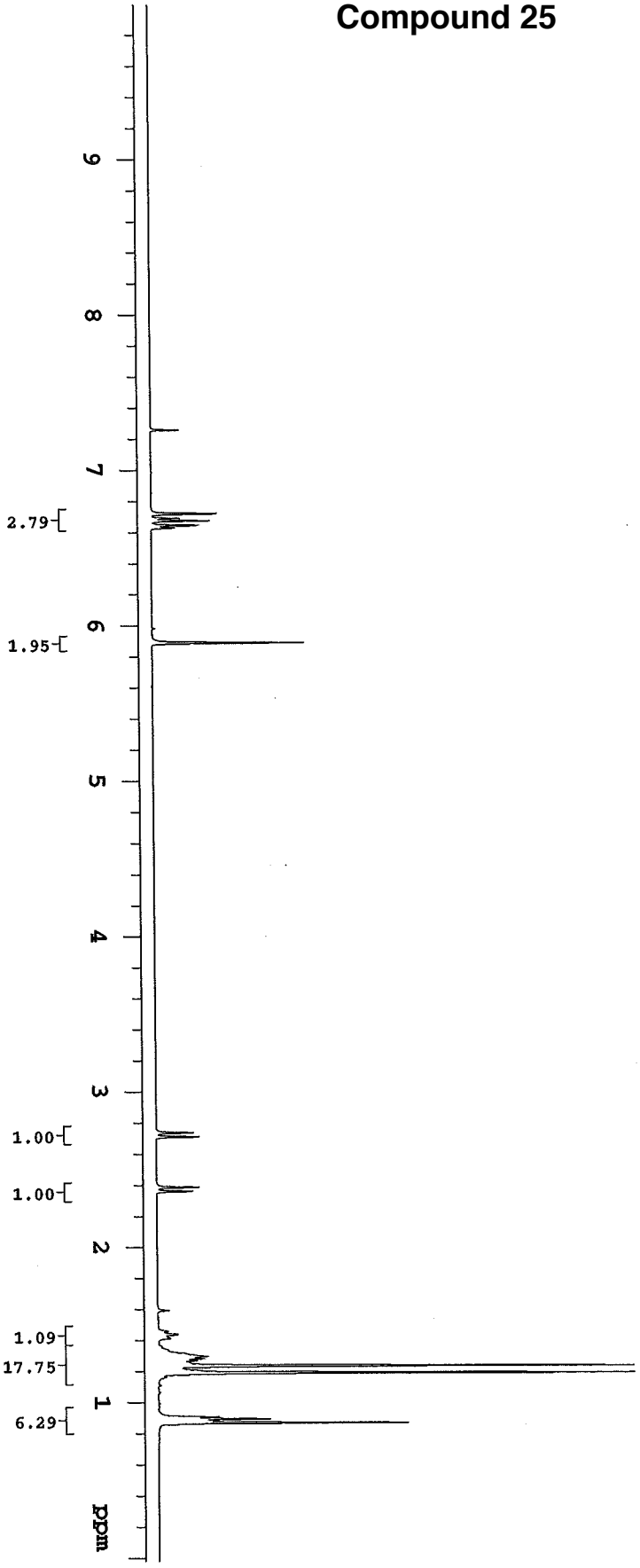
Compound 24



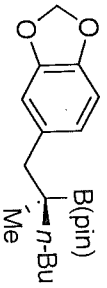


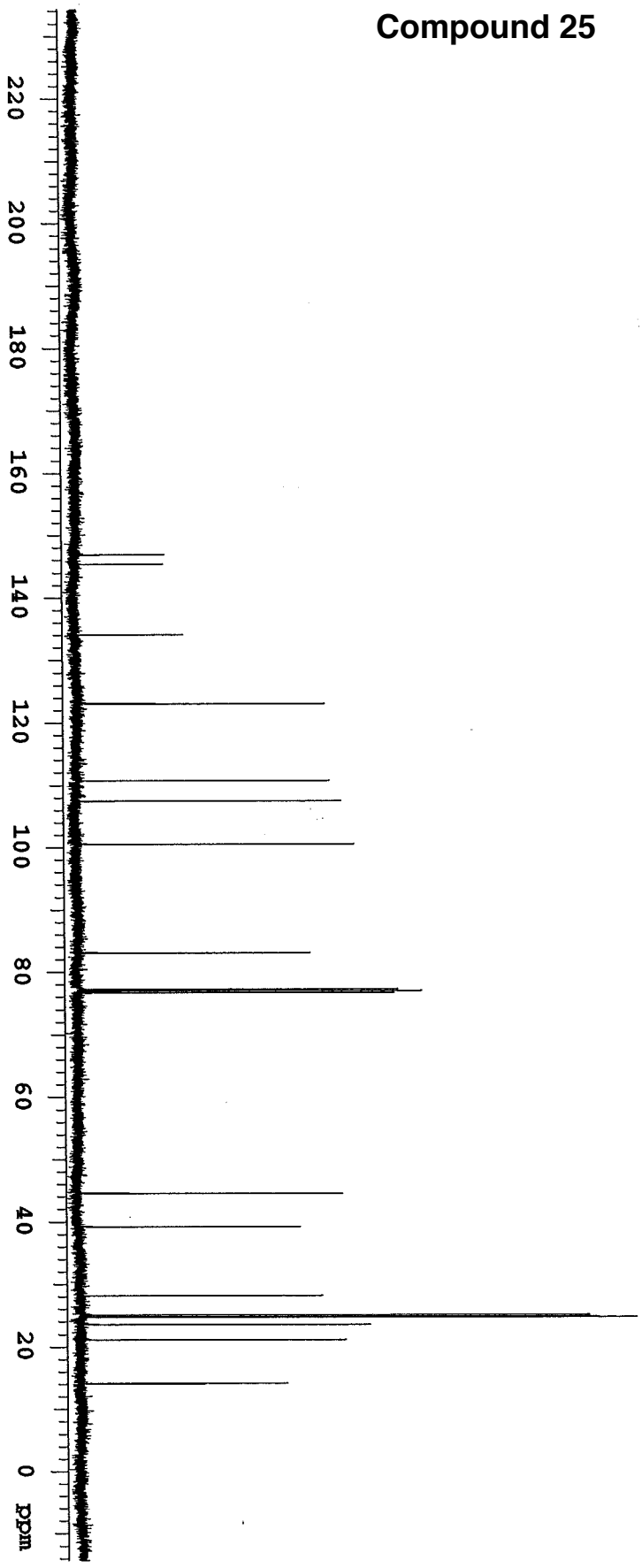
Compound 25



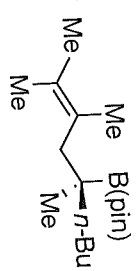


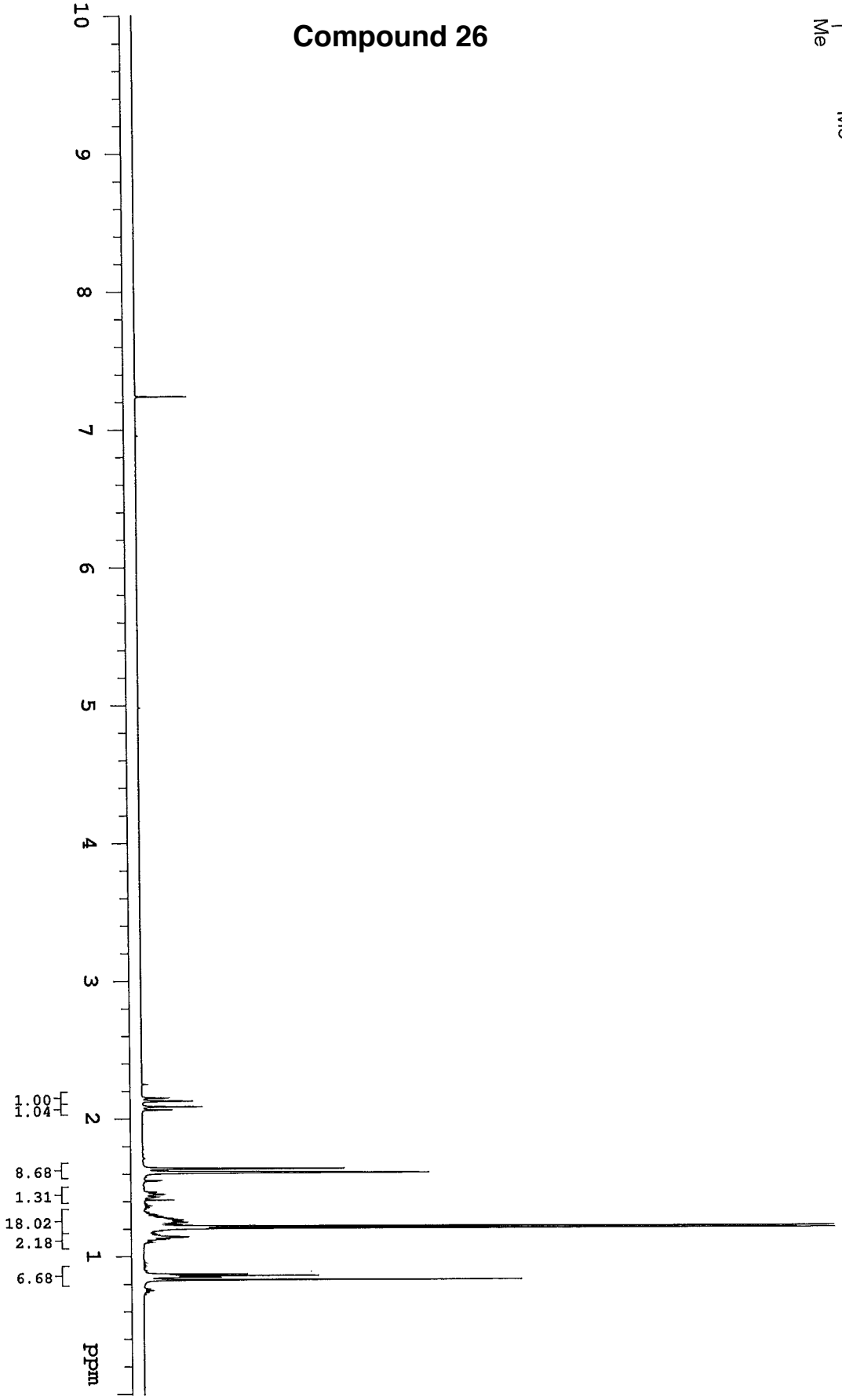
Compound 25





Compound 26


Me
Me
Me
B(pin)
n-Bu
Me


10
9
8
7
6
5
4
3
2
1
ppm
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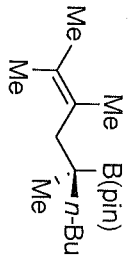
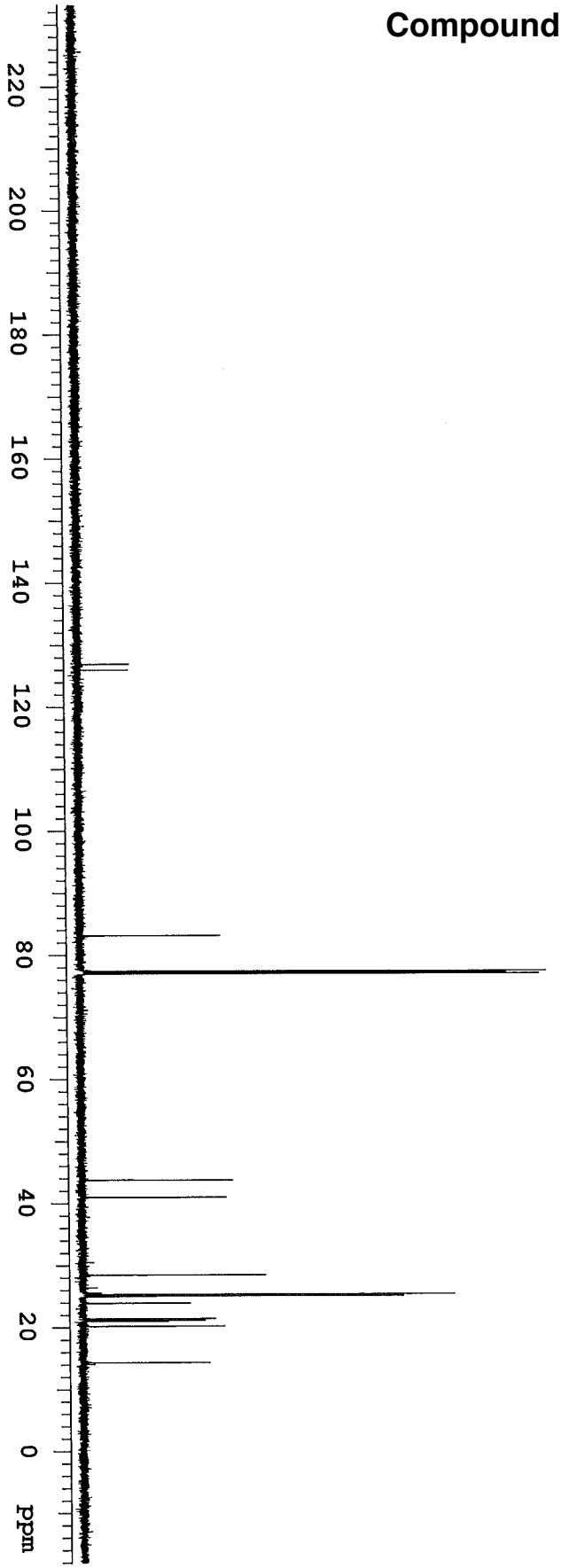
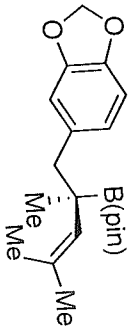
1.04
8.68
1.31
18.02
2.18
6.68

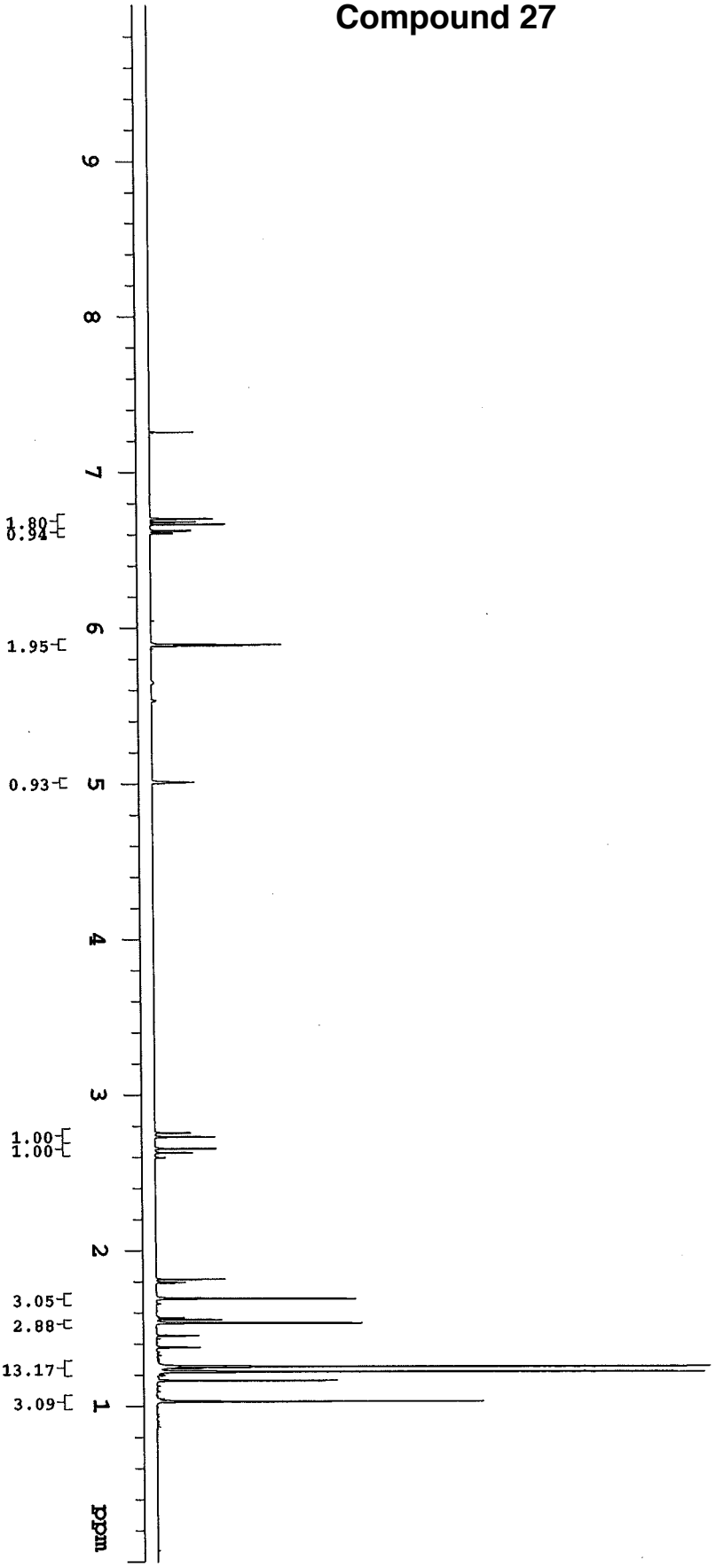
Compound 26



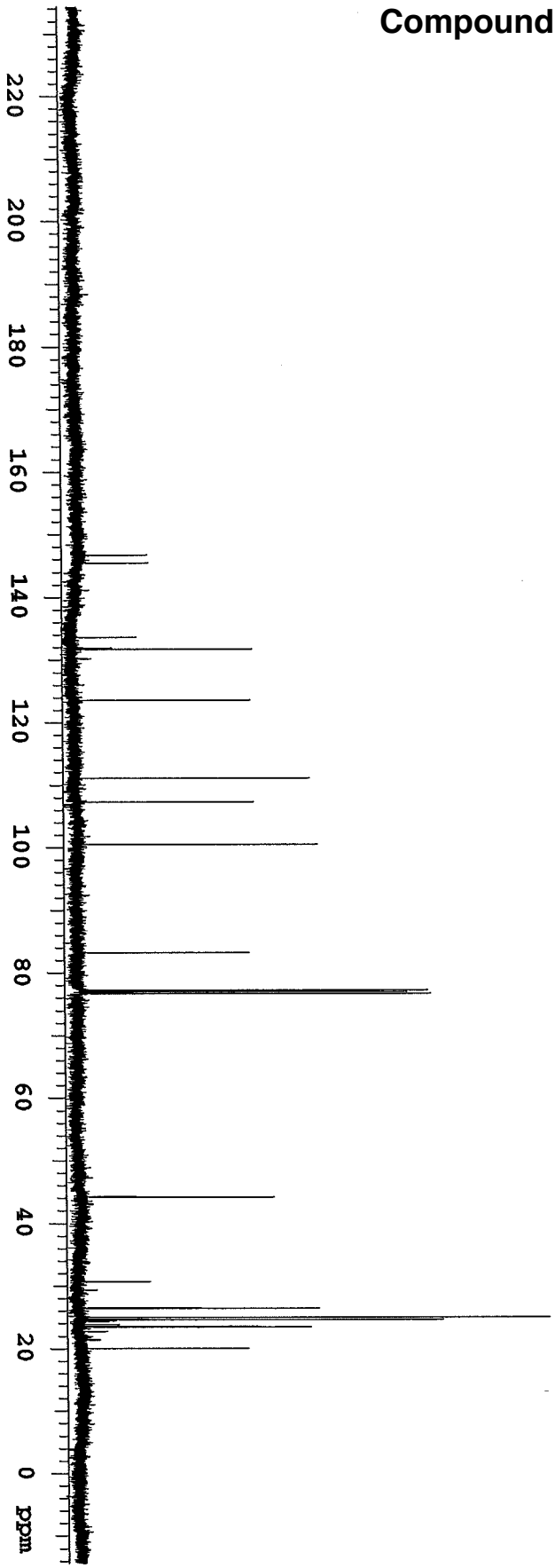


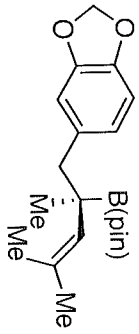
Compound 27


O
O
B(pin)
Me
Me
Me

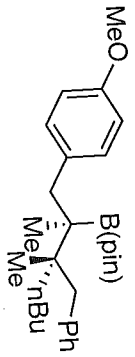

9
8
7
6
5
4
3
2
1
ppm
1.80
0.94
1.95
0.93
1.00
1.00
3.05
2.88
13.17
3.09

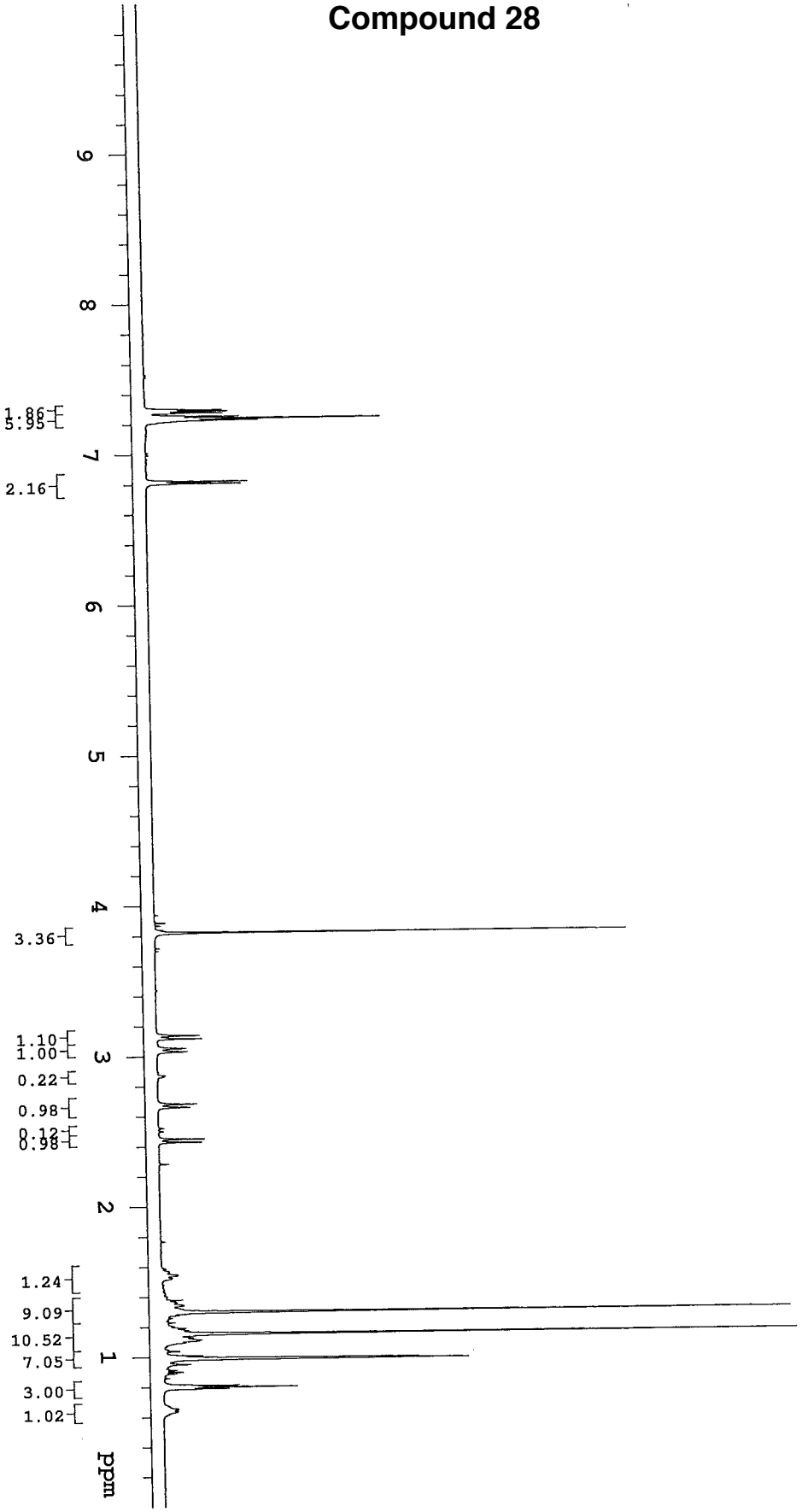
Compound 27



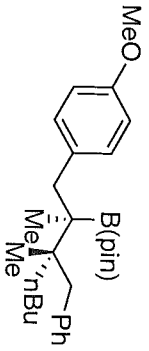


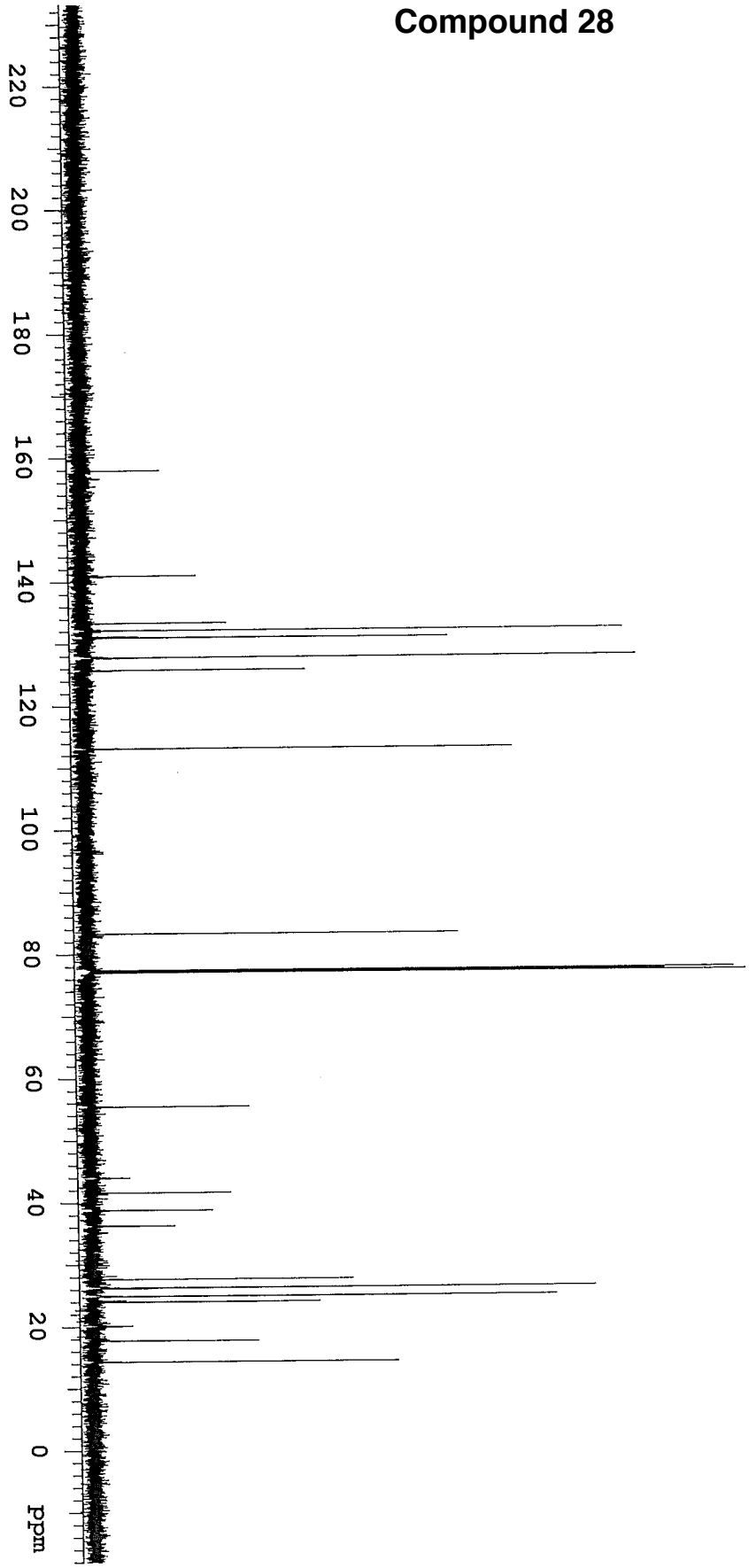
Compound 28


MeO
B(pin)
Me
Me
nBu
Ph

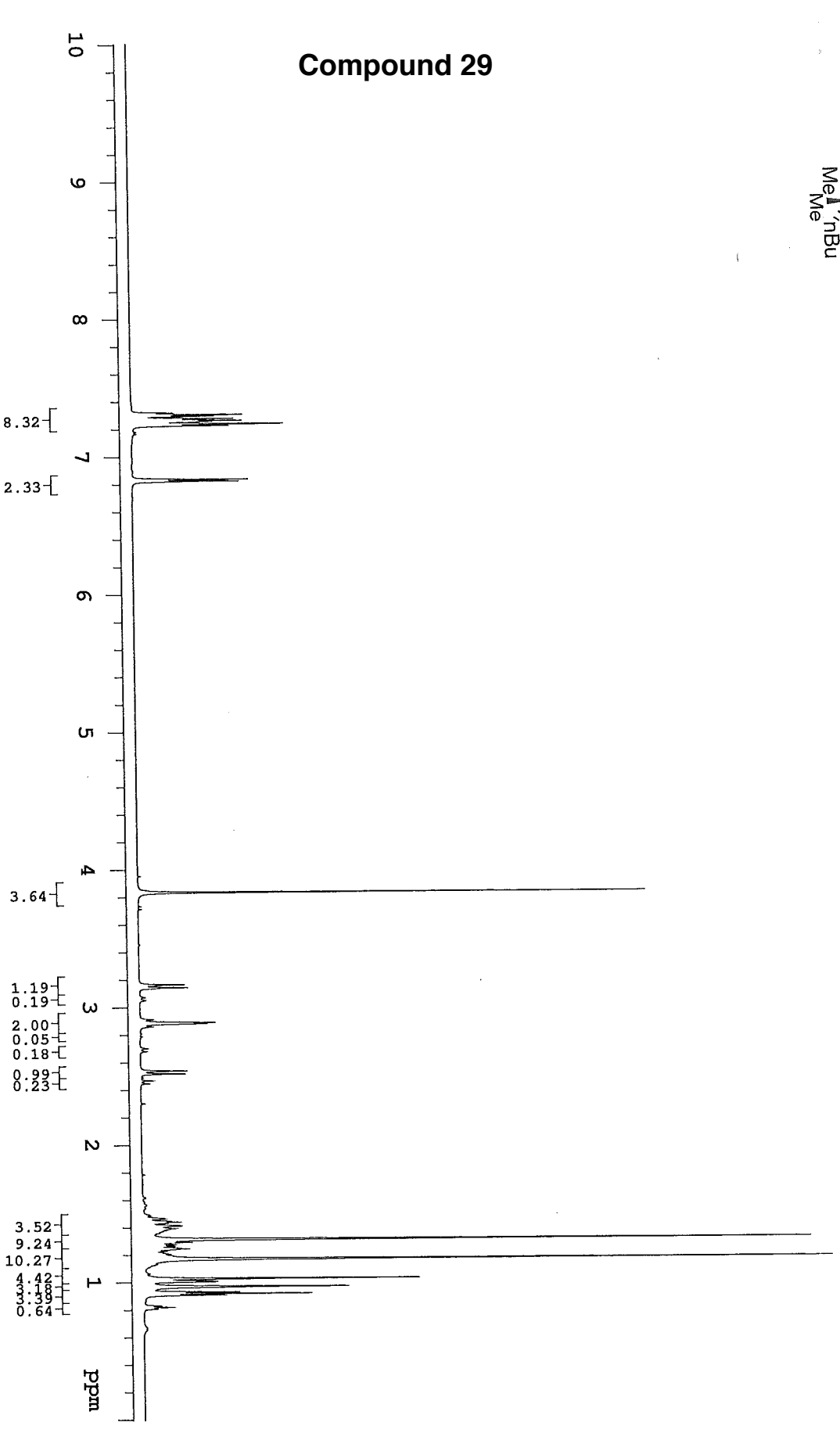

9
8
7
6
5
4
3
2
1
ppm
1.86
5.95
2.16
3.36
1.10
1.00
0.22
0.98
0.12
0.98
1.24
9.09
10.52
7.05
3.00
1.02

Compound 28

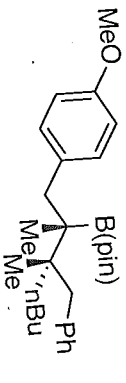


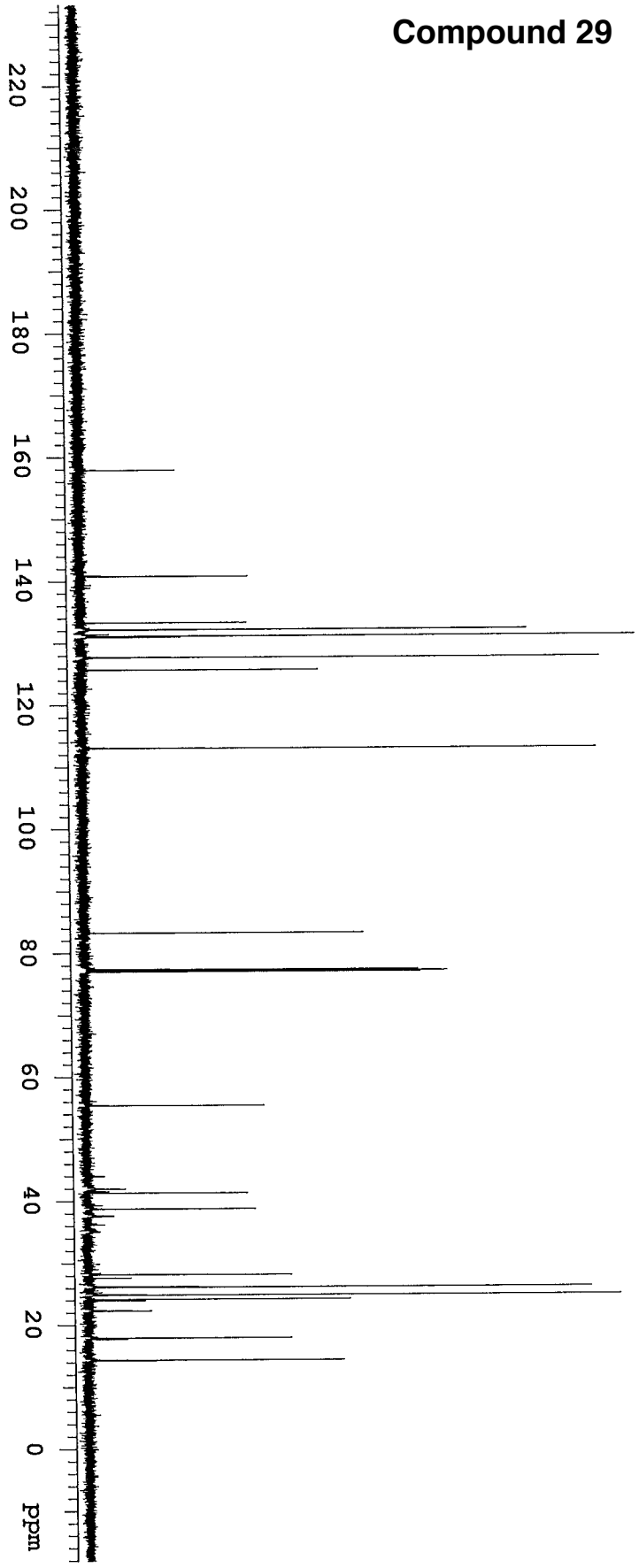


Compound 29

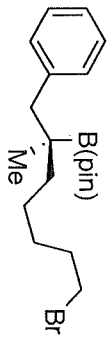

MeO
B(pin)
Me
nBu
Me
Ph
10
9
8
7
6
5
4
3
2
1
ppm
8.32
2.33
3.64
1.19
0.19
2.00
0.05
0.18
0.99
0.23
3.52
9.24
10.27
4.42
3.18
3.39
0.64

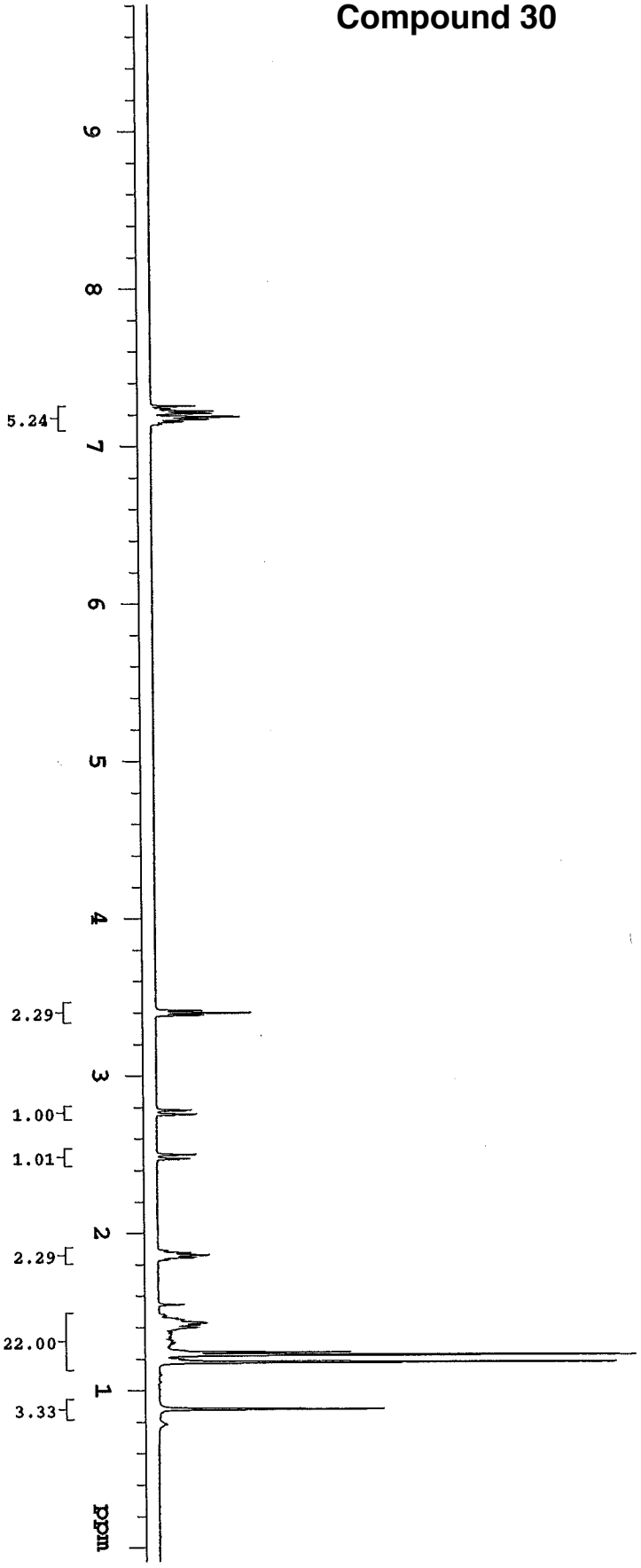
Compound 29



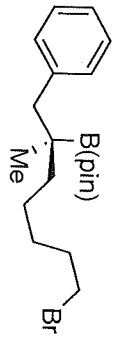


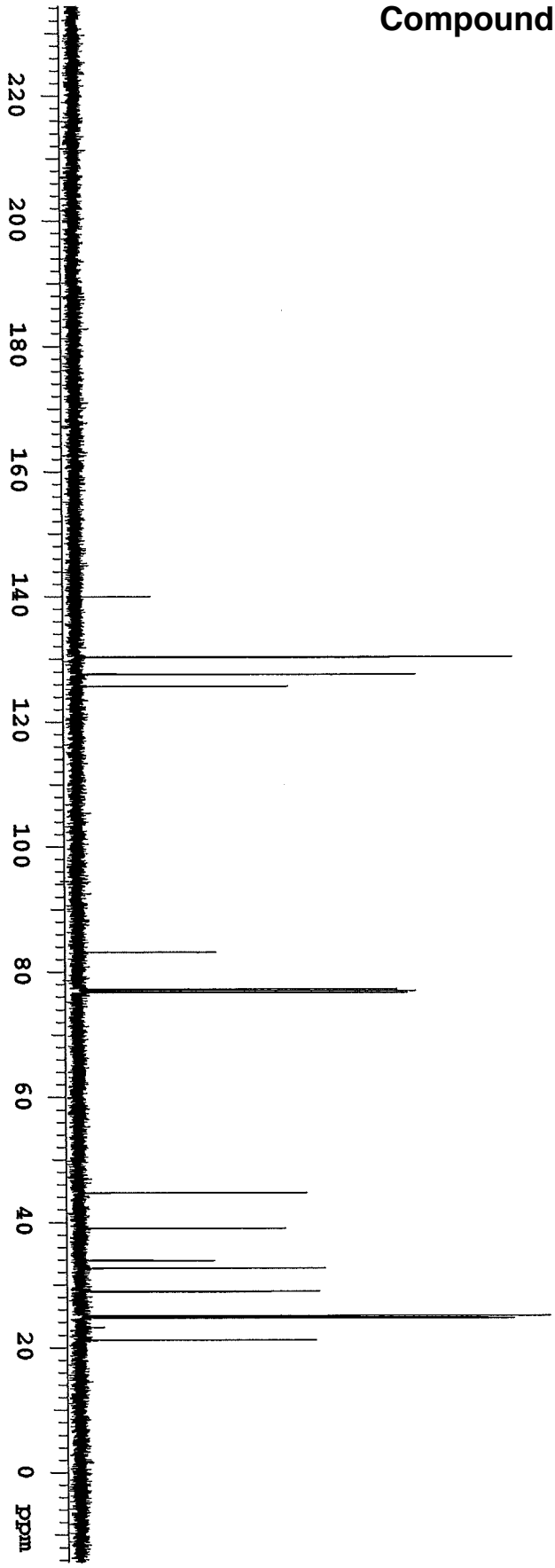
Compound 30



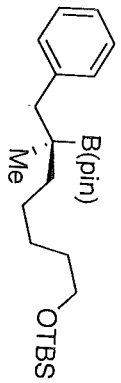


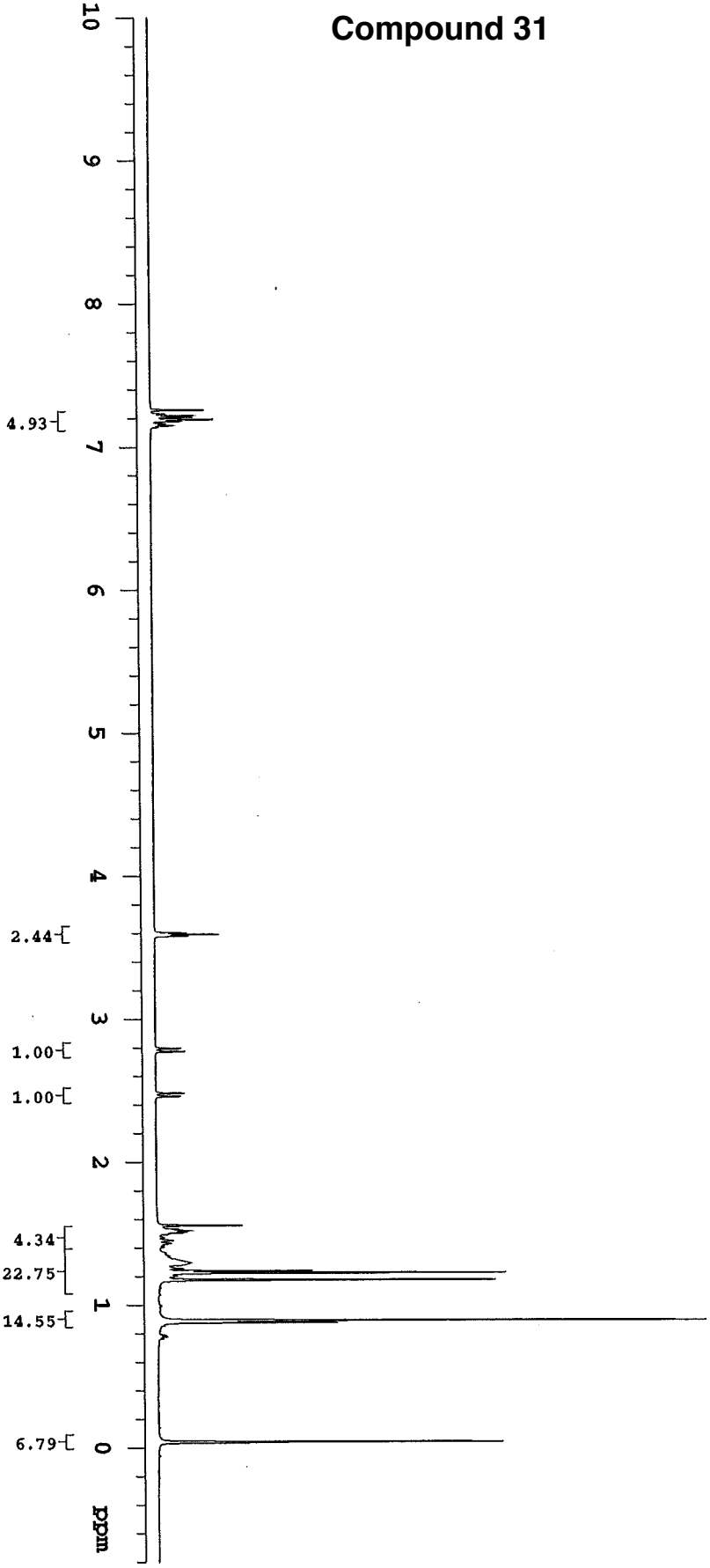
Compound 30





Compound 31


B(pin)
Me
OTBS


10
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8
7
6
5
4
3
2
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0
ppm
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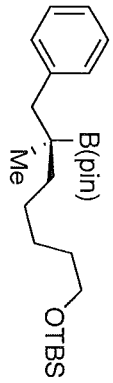
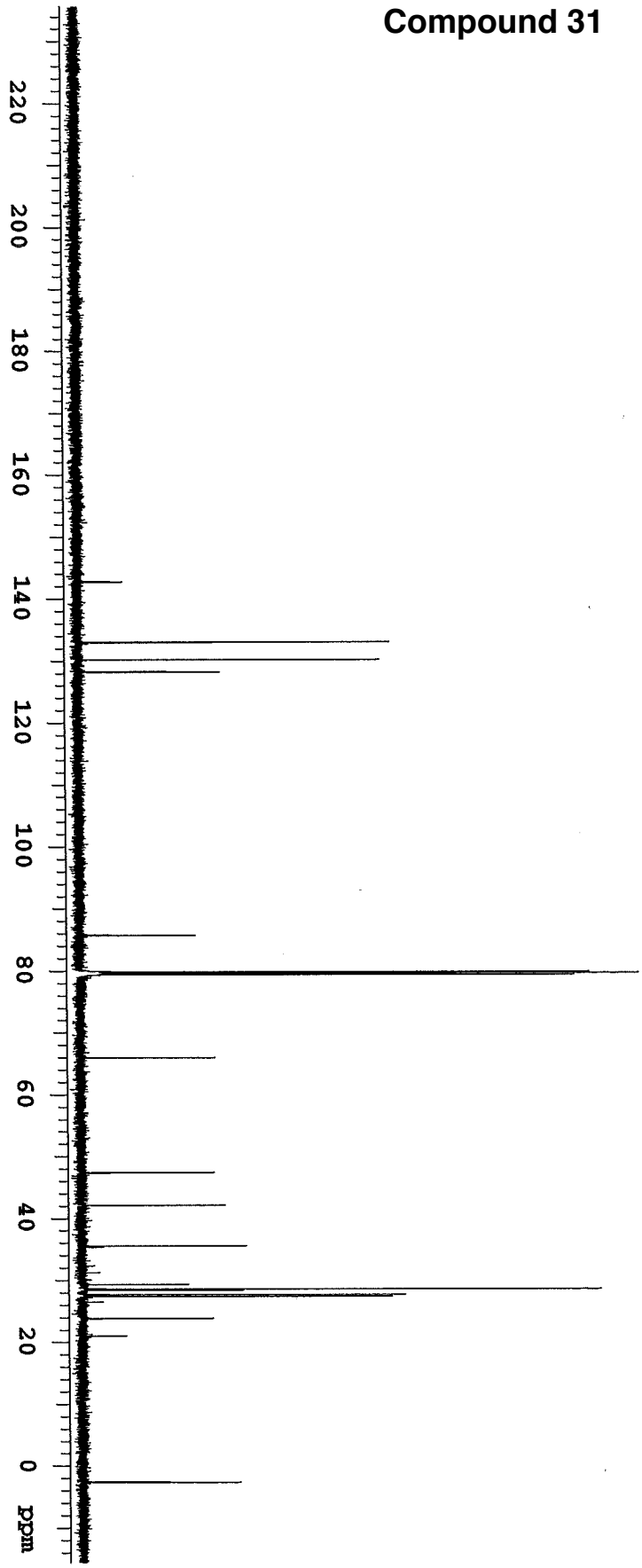
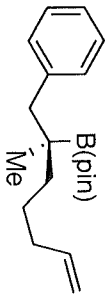
1.00
1.00
4.34
22.75
14.55
6.79

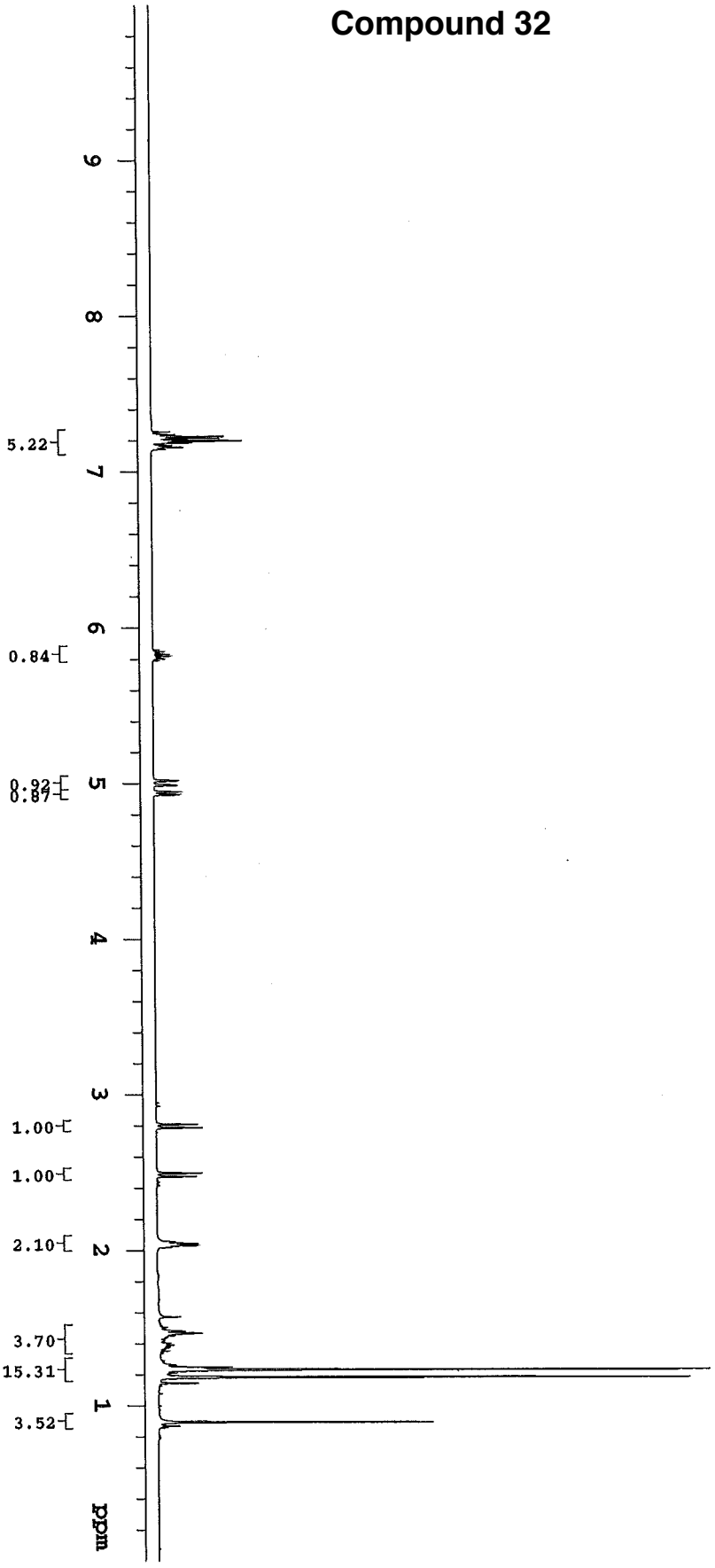
Compound 31



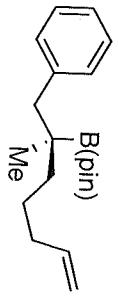


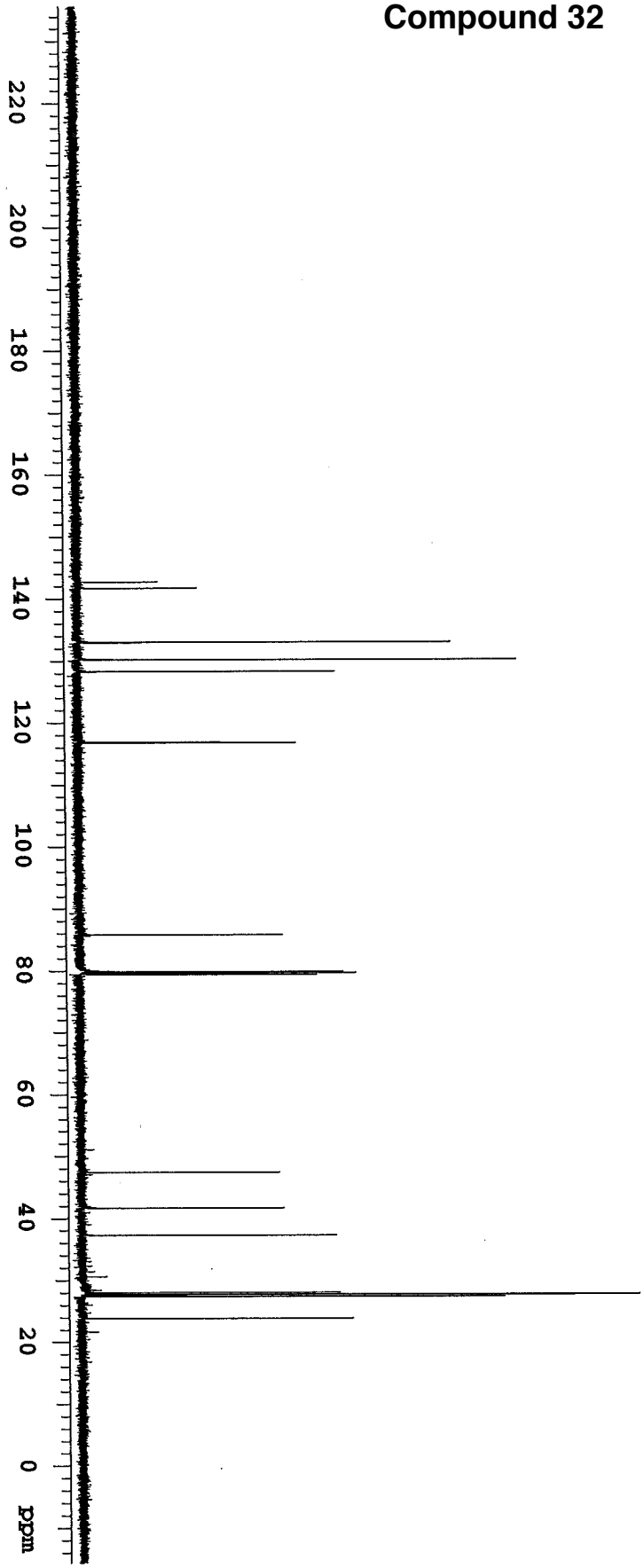
Compound 32



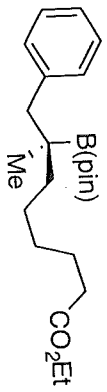


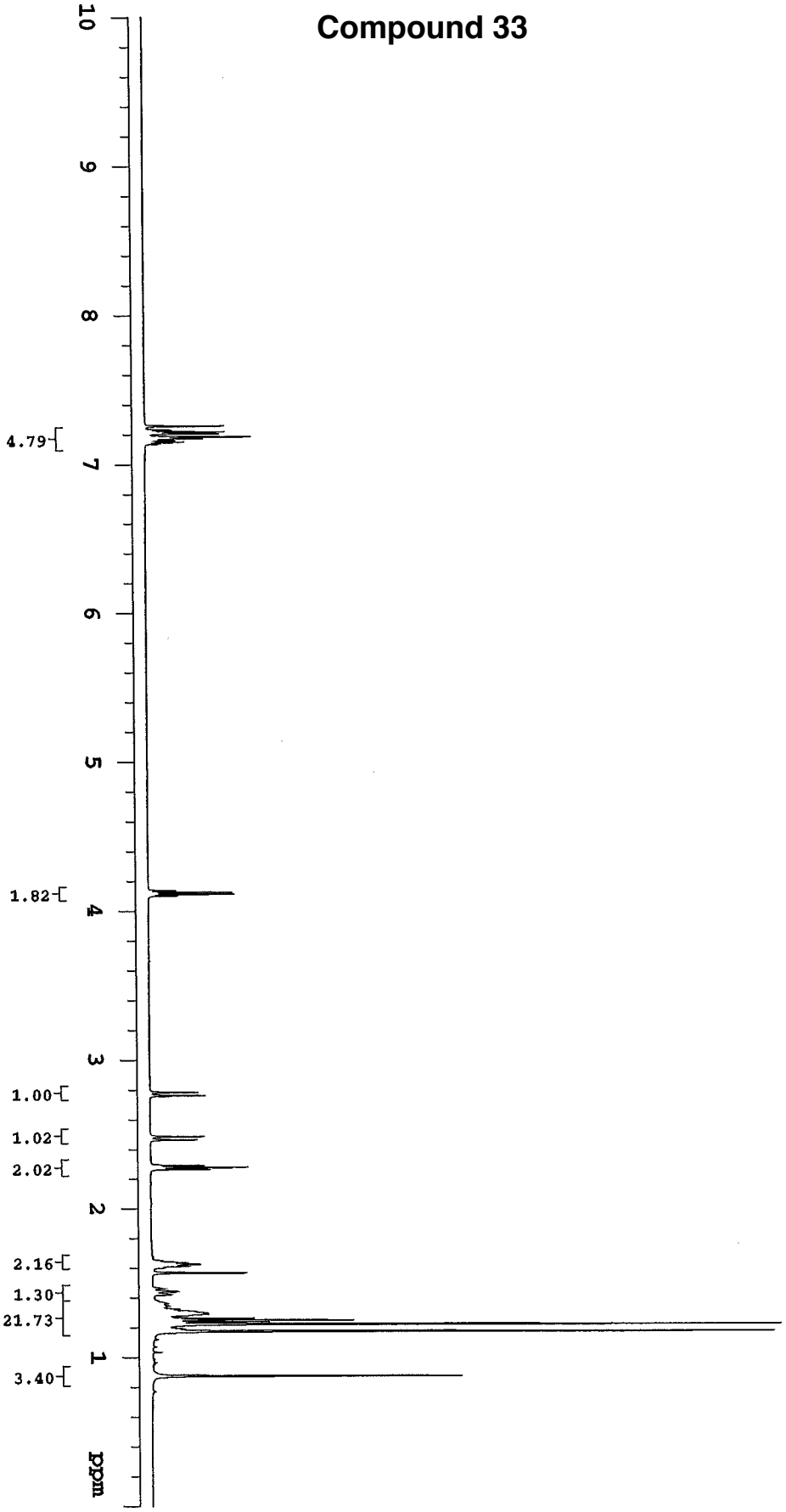
Compound 32





Compound 33


B(pin)
Me
CO2Et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9
8
7
6
5
4
3
2
1
ppm
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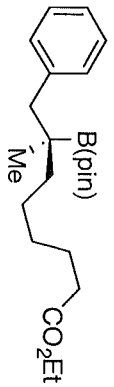
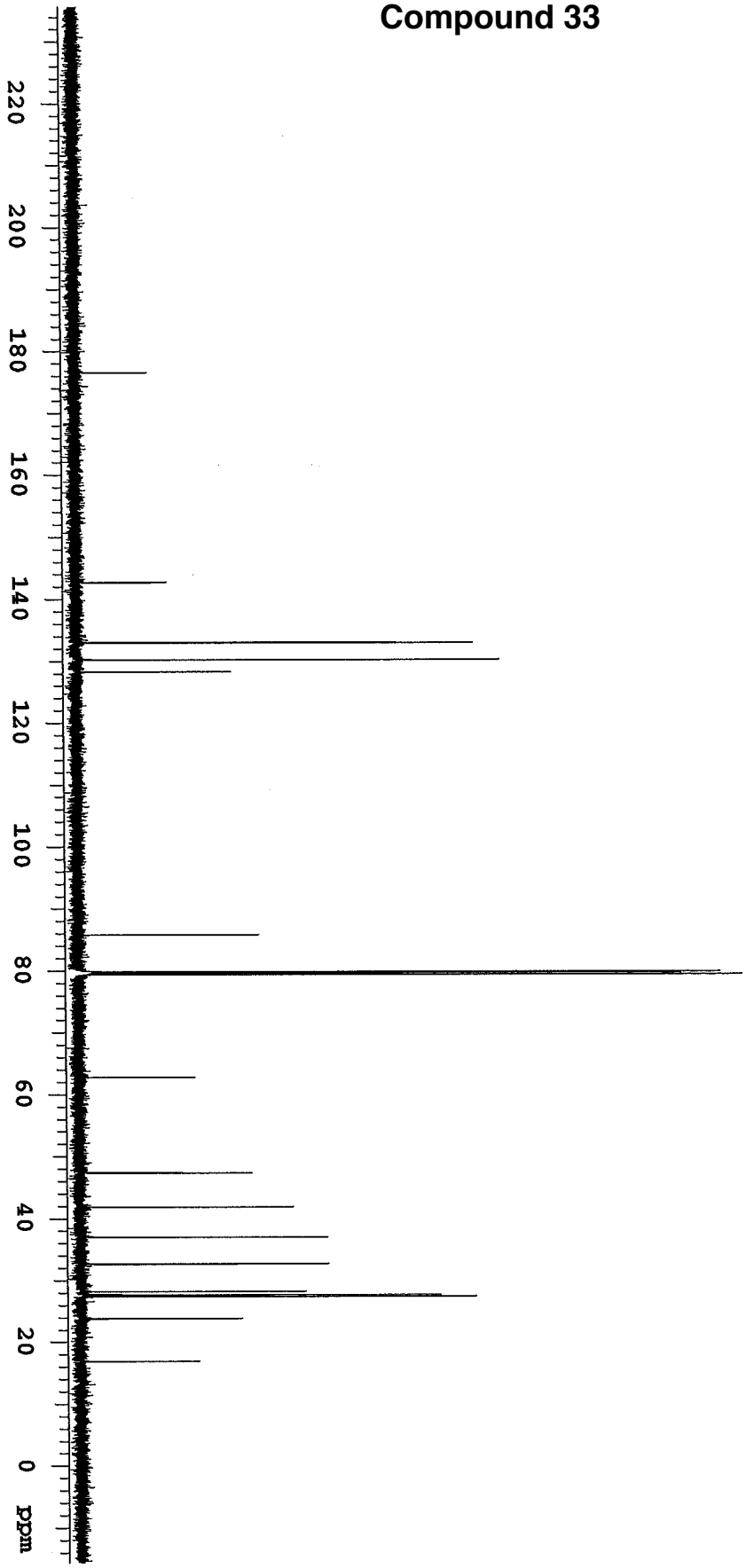
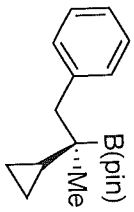
1.00
1.02
2.02
2.16
1.30
21.73
3.40

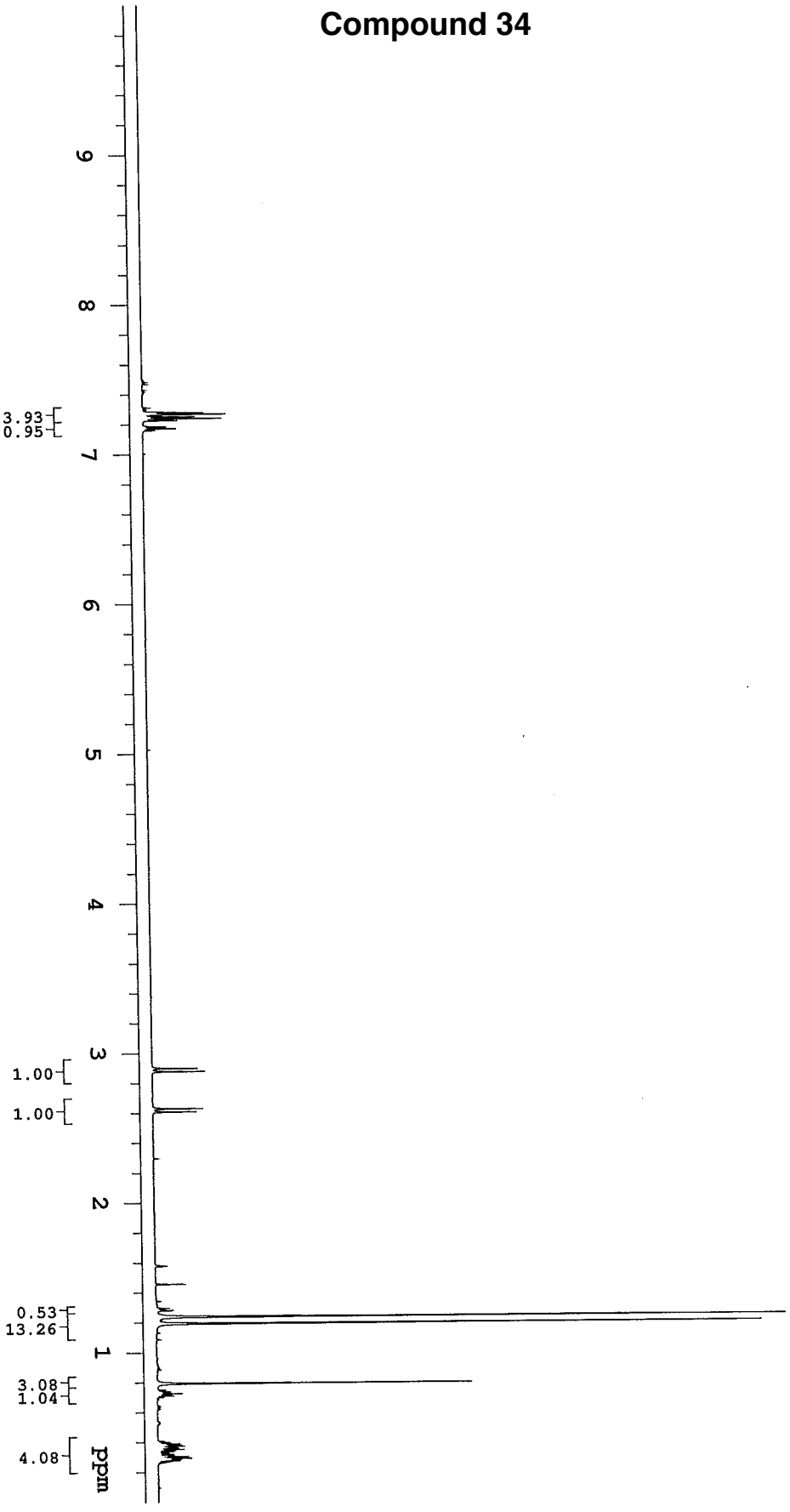
Compound 33



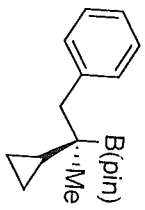


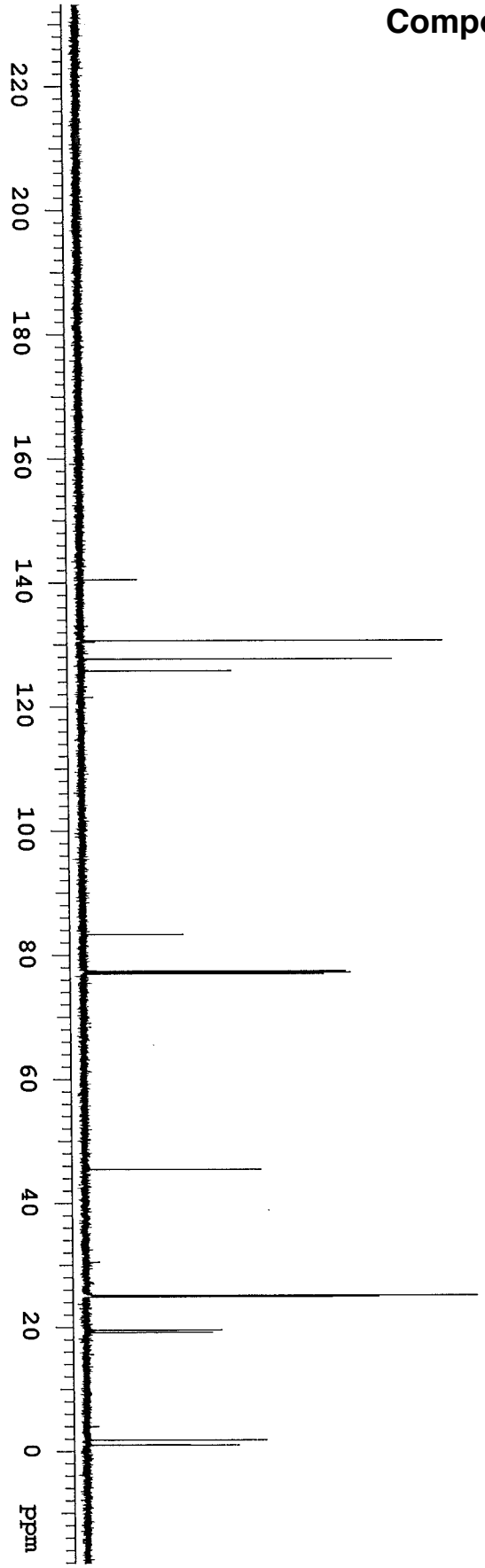
Compound 34



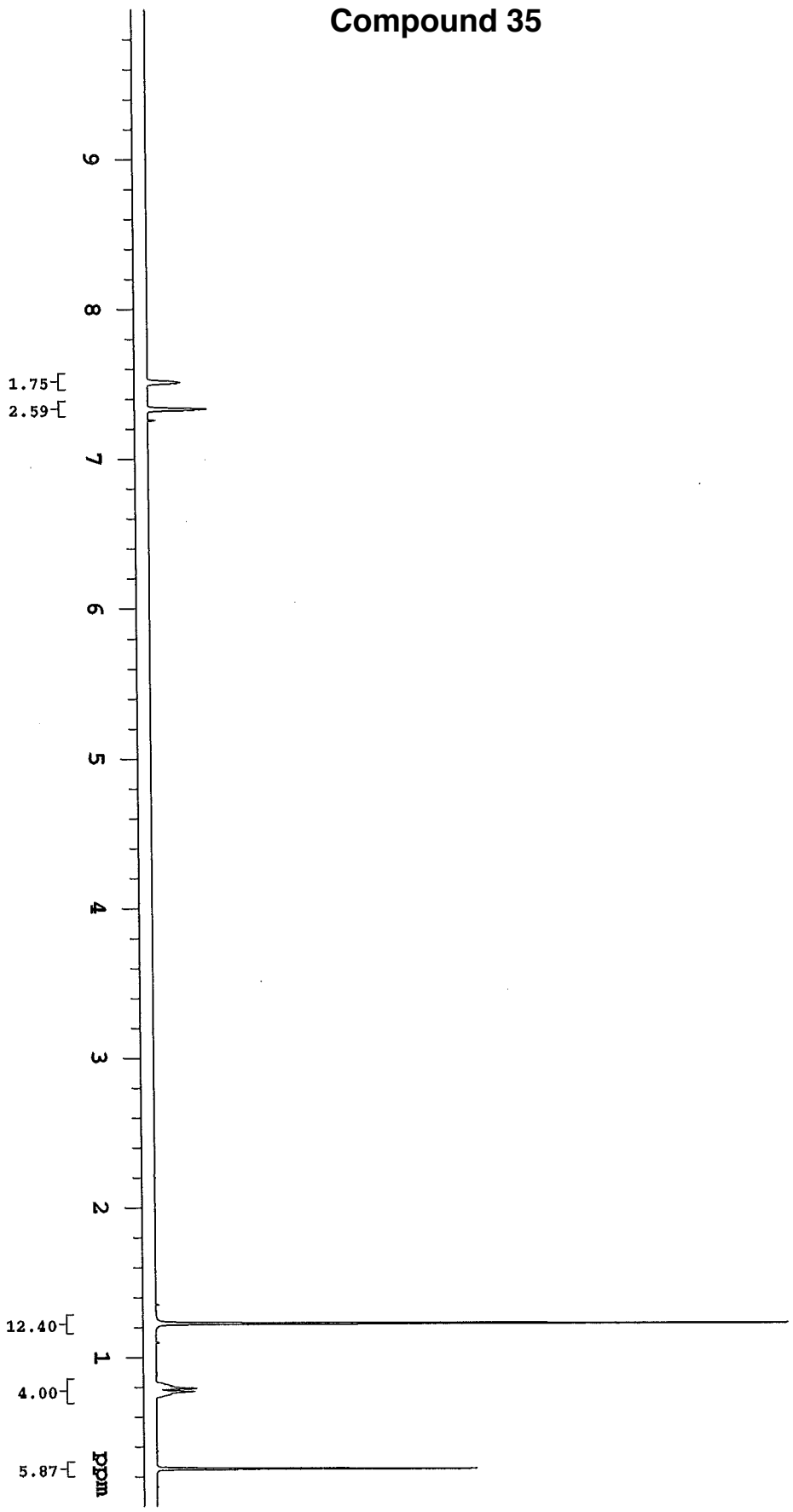


Compound 34

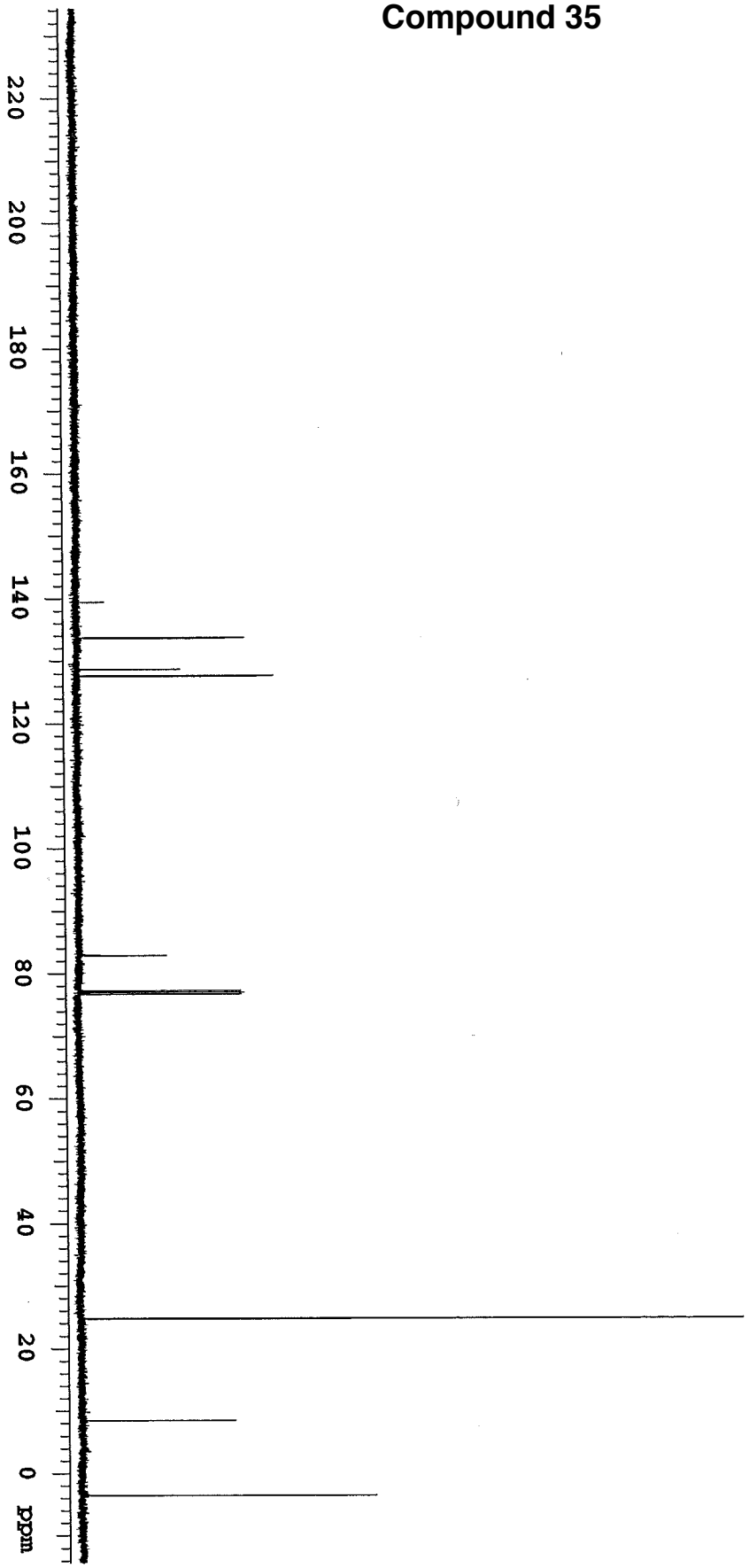




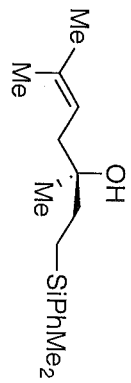
Compound 35

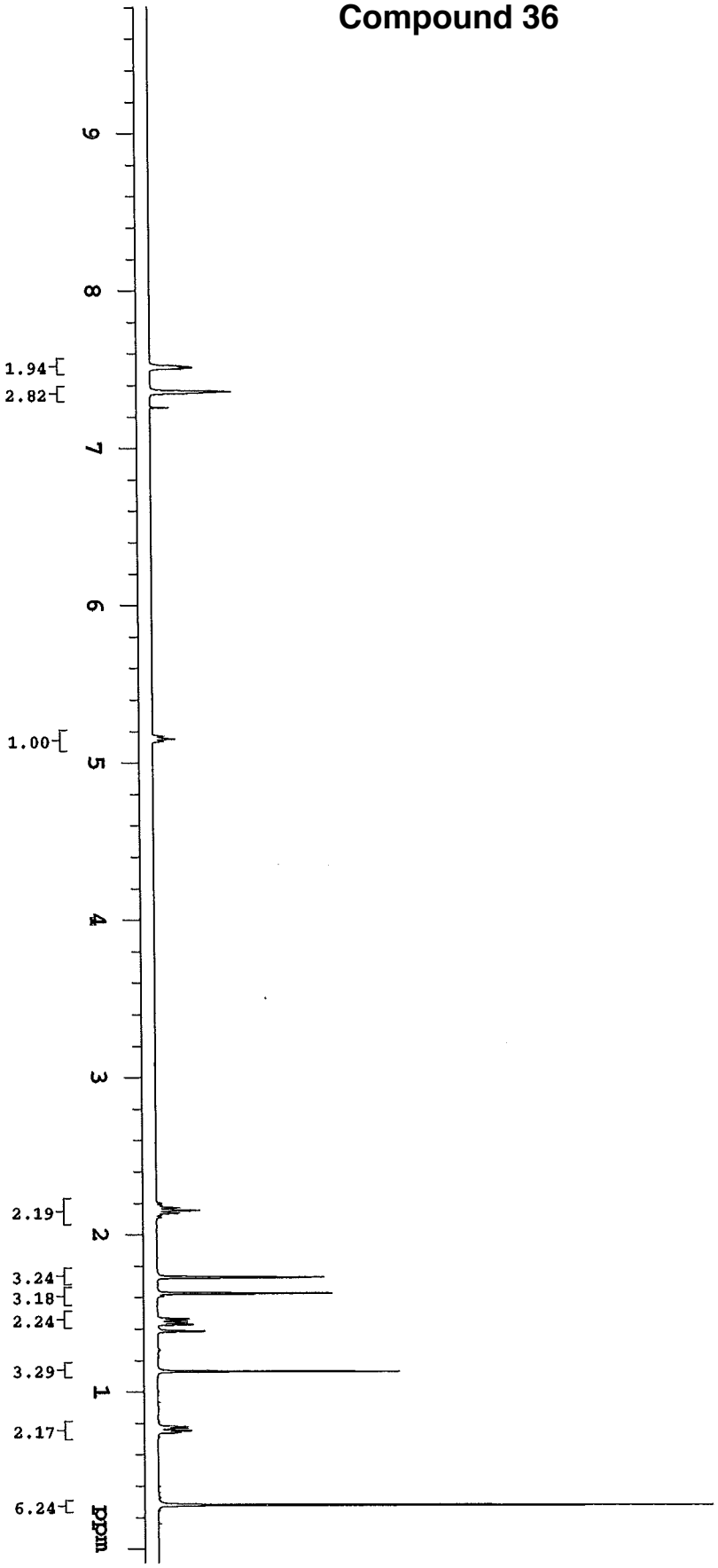


Compound 35

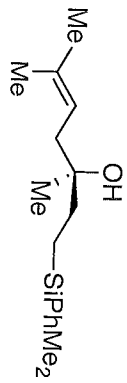


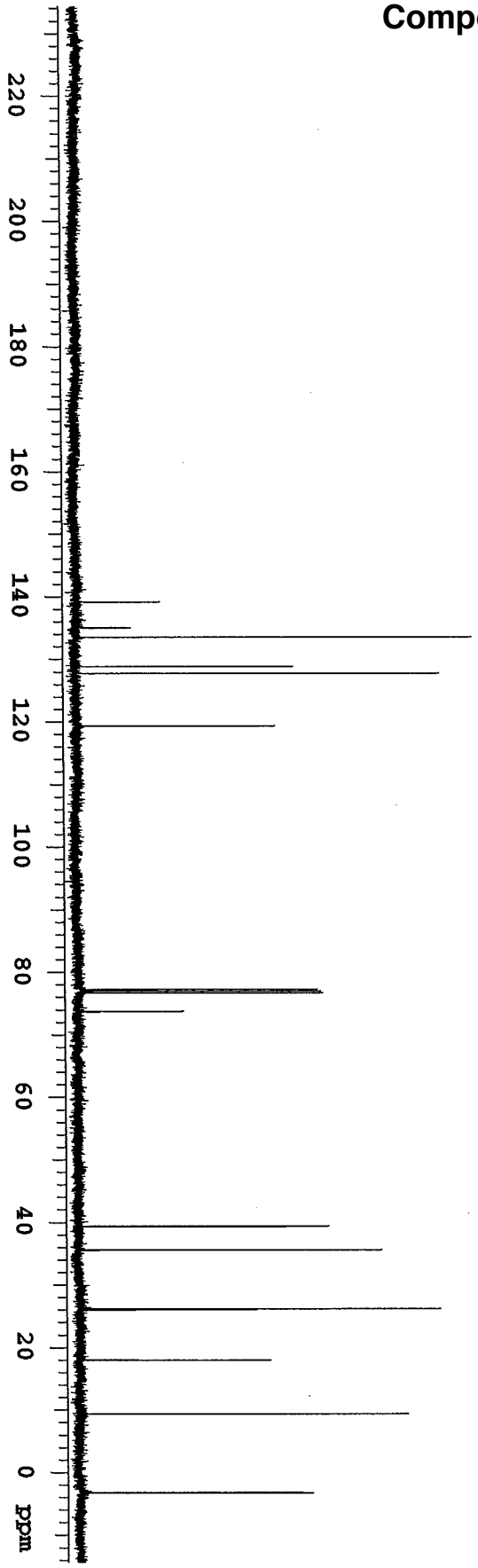
Compound 36



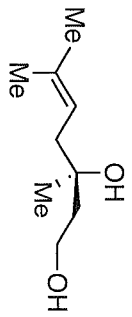


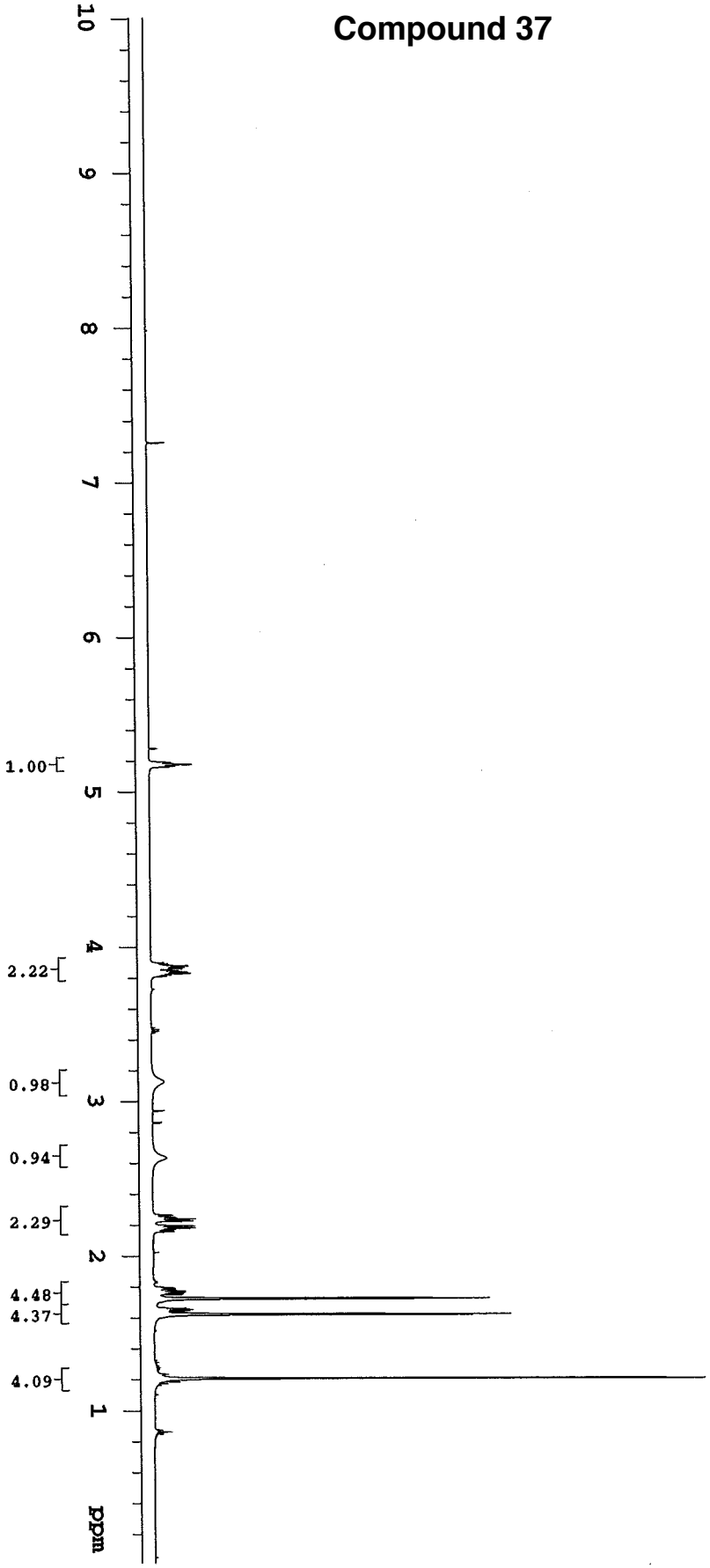
Compound 36



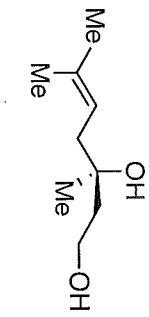


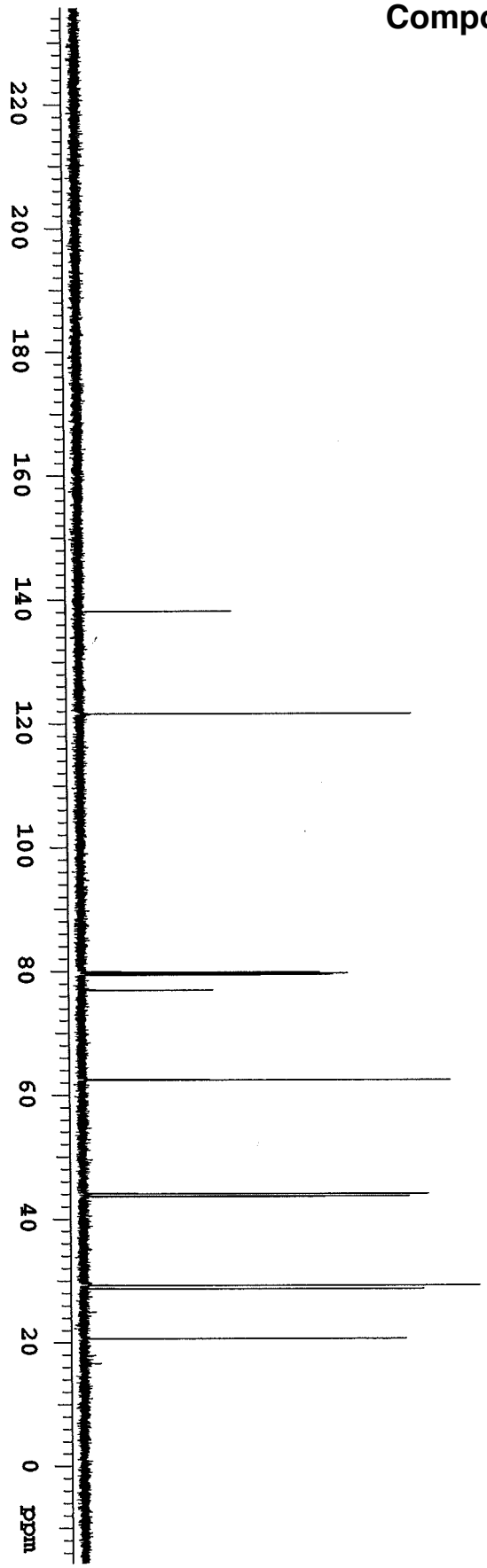
Compound 37



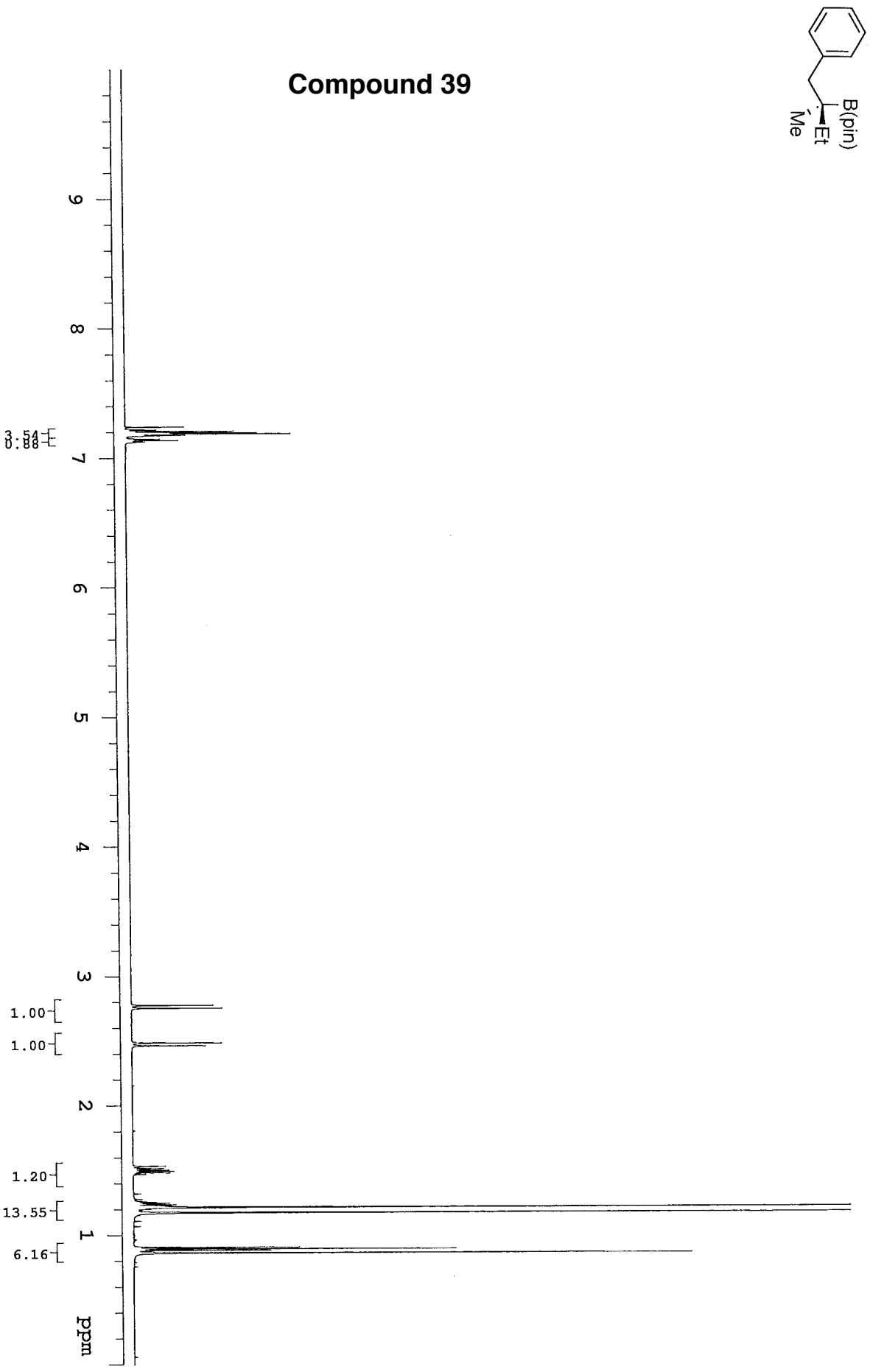


Compound 37

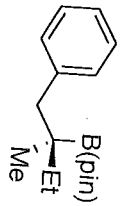


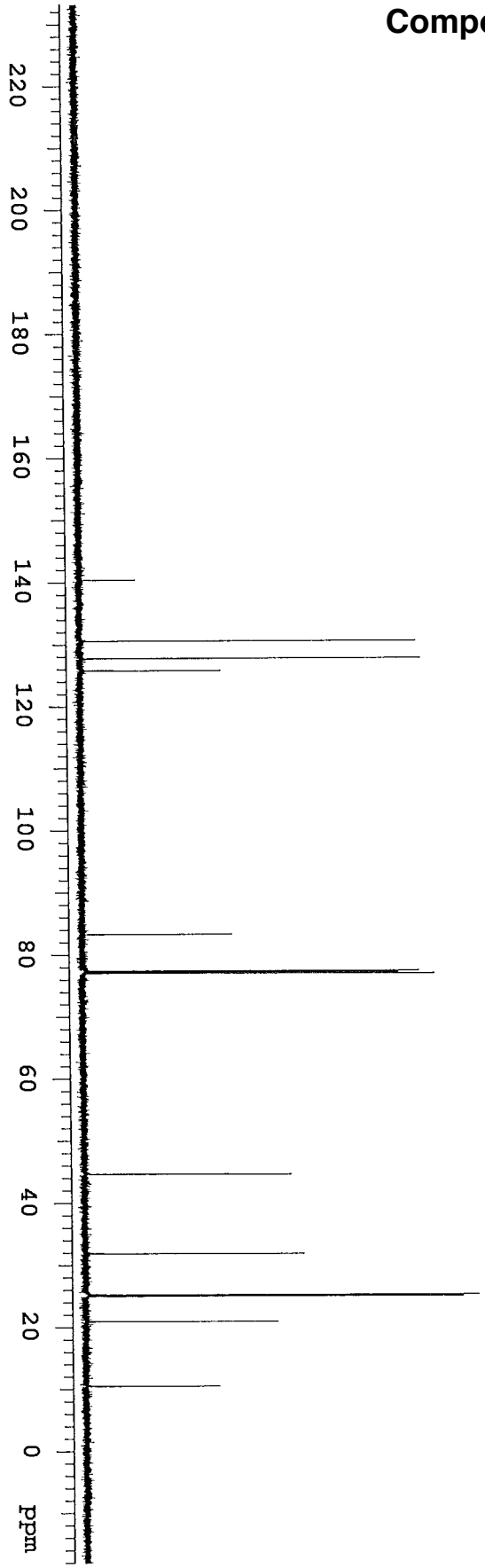


Compound 39

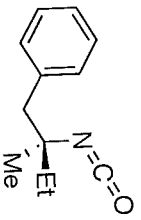


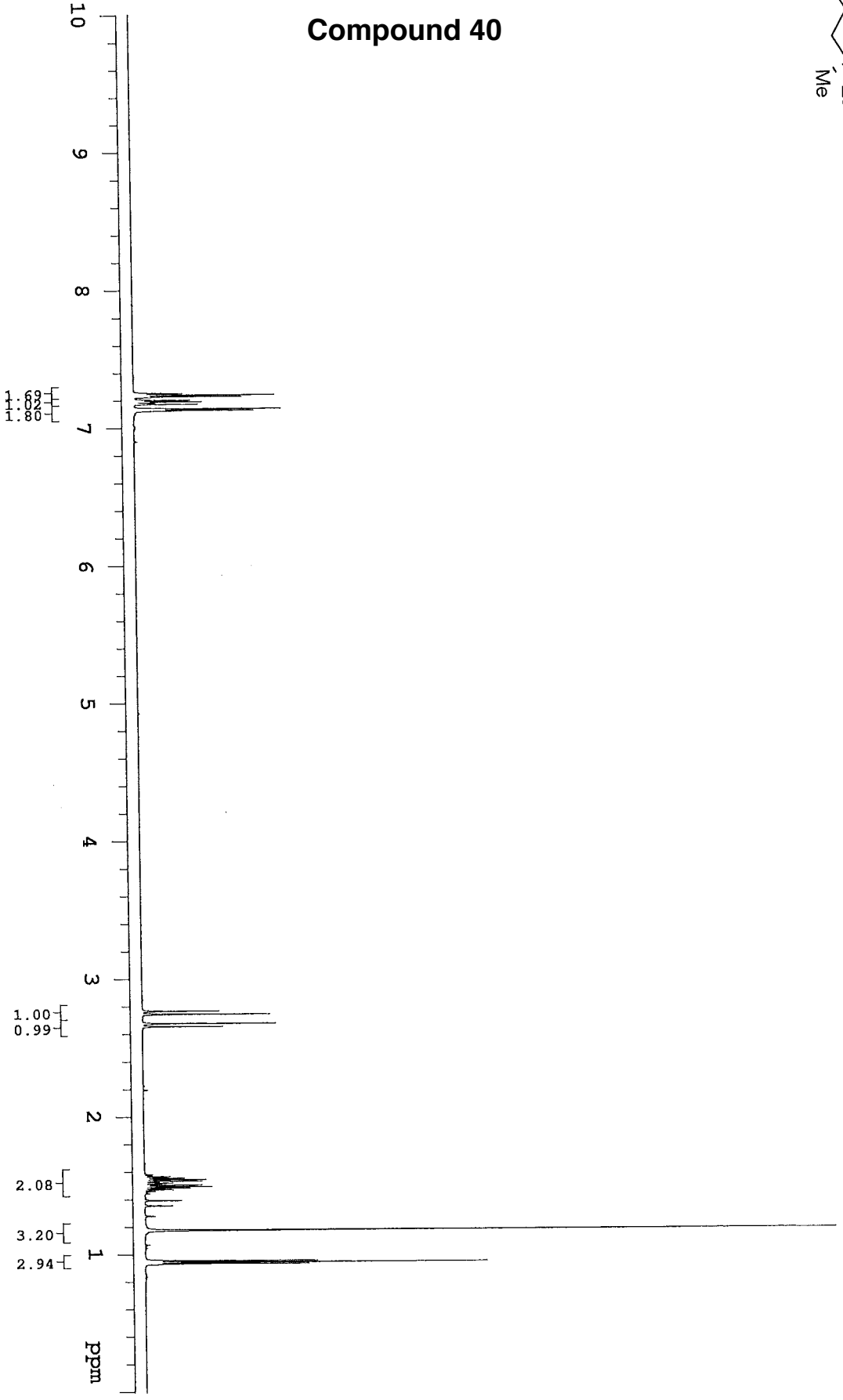
Compound 39



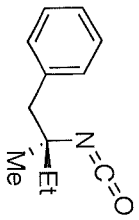


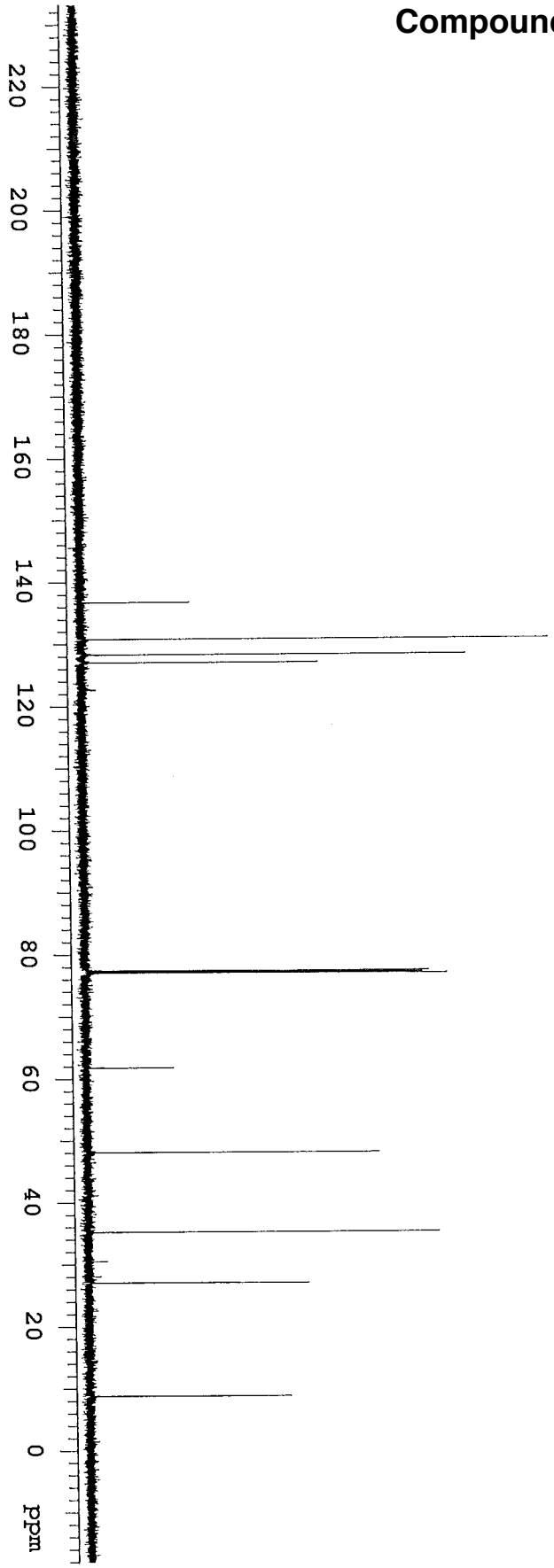
Compound 40



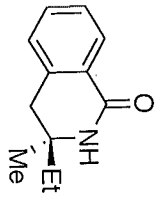


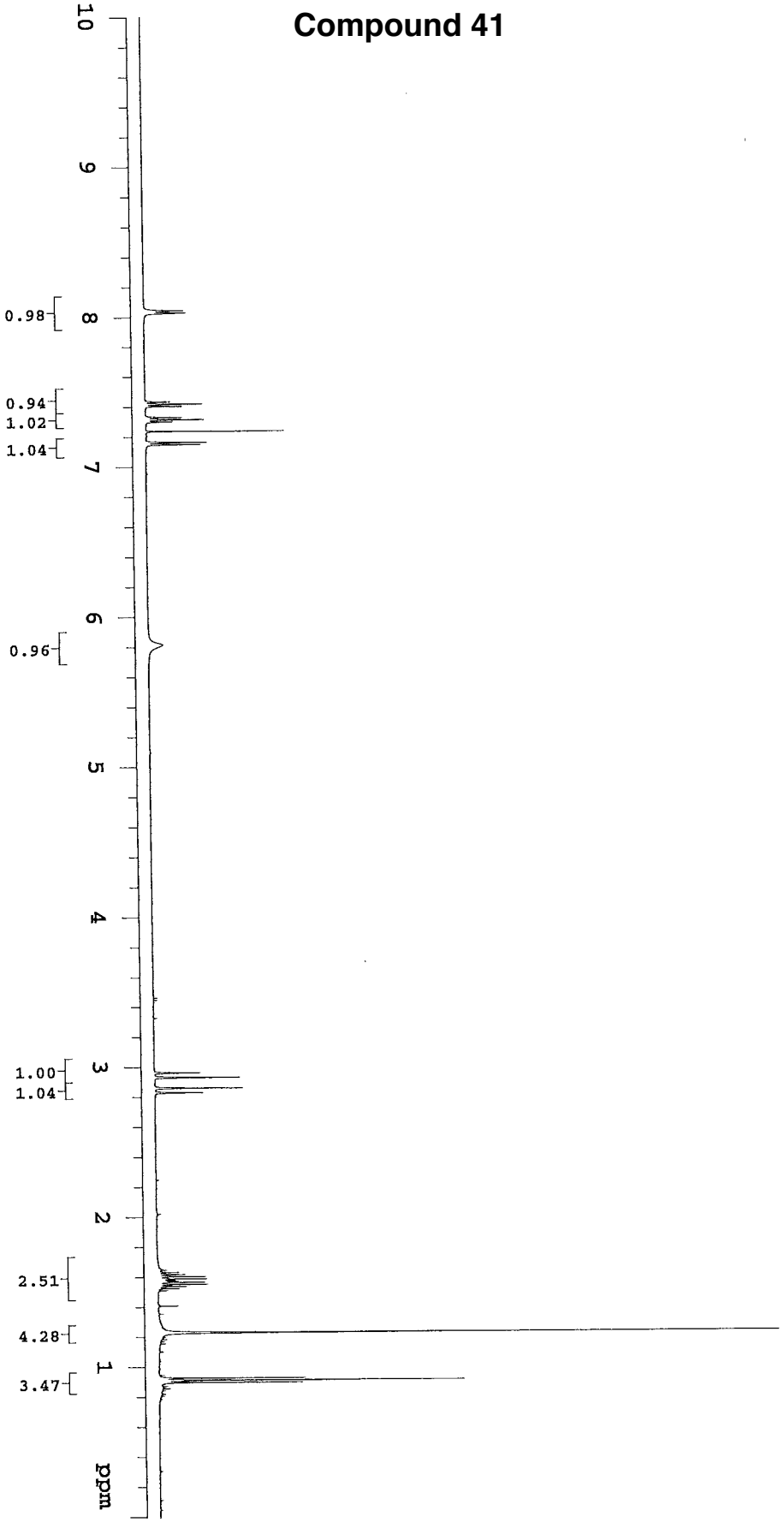
Compound 40



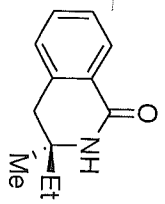


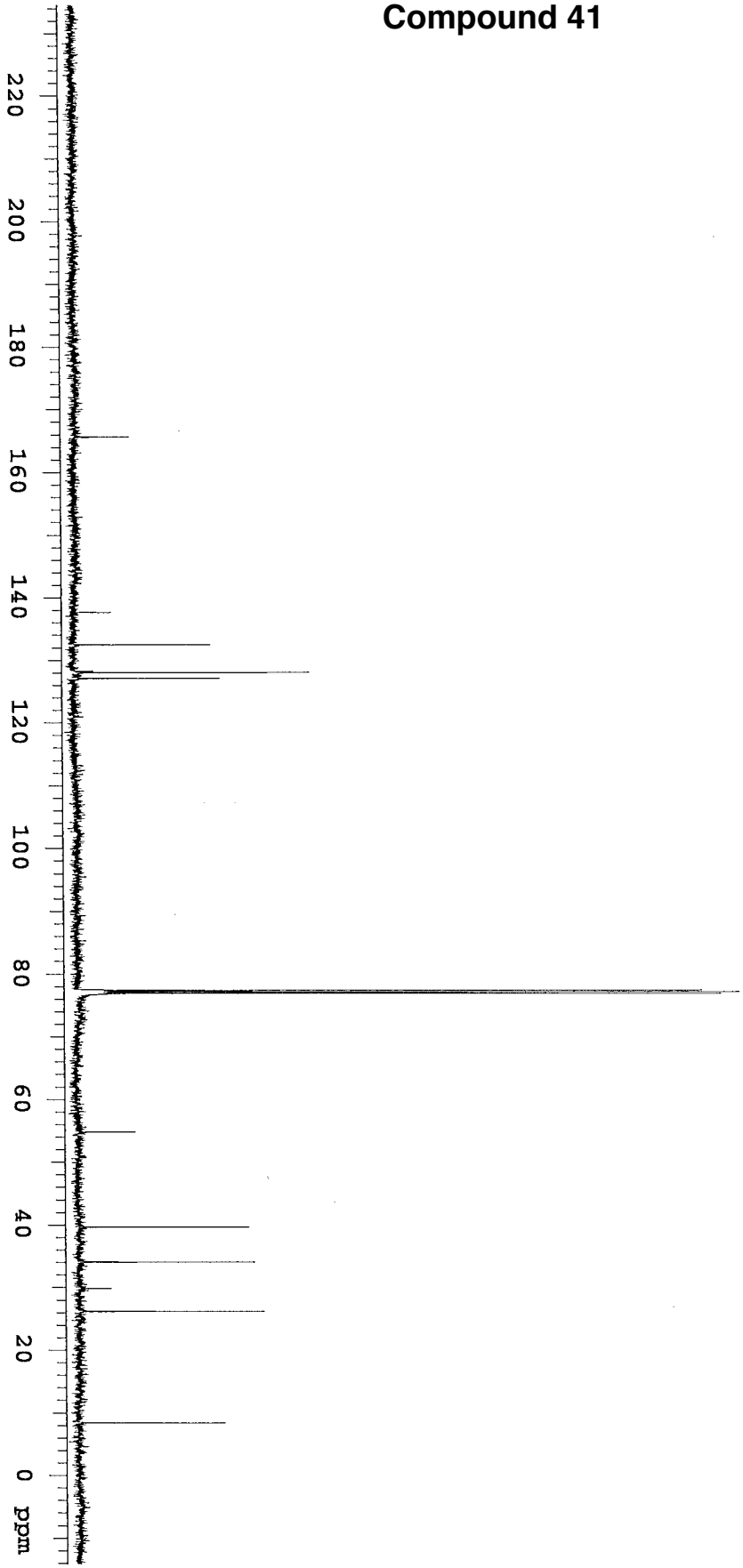
Compound 41


O
NH
Et
Me


10
9
8
7
6
5
4
3
2
1
ppm
0.98
0.94
1.02
1.04
0.96
1.00
1.04
2.51
4.28
3.47

Compound 41





Chapter 3

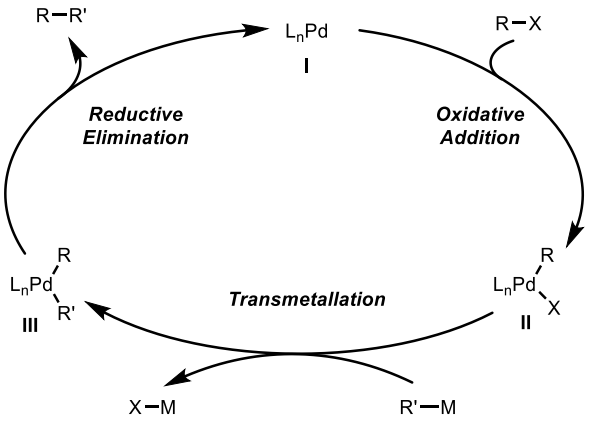
Diastereo- and Enantioselective Synthesis of Organoboronates by Conjunctive Cross-Coupling

3.1. Introduction

Transition metal-catalyzed cross-coupling reactions are of utmost importance for the formation of C–C bonds.[1] Since its first report in 1979,[2] the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction has become the premier cross-coupling reaction for large-scale synthesis.[3] This reaction is particularly appealing due to the mild reaction conditions and broad functional group tolerance.[4] Furthermore, organoboronates are preferred over other organometallic reagents because they are readily available, stable to ambient conditions, and nontoxic.[5] Palladium-catalyzed cross-coupling reactions proceed by a common catalytic cycle (Scheme 3.1), which involves oxidative addition (**I→II**), transmetallation (**II→III**), and reductive elimination (**III→I**) in sequence.[6] The different cross-coupling reactions only diverge mechanistically with respect to the transmetallation step.

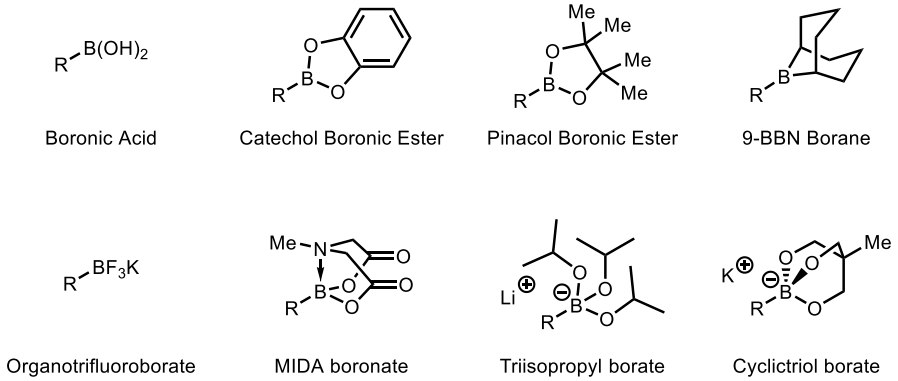
[1] Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. *Chem. Rev.* **2018**, *118*, 2249–2295.
[2] (*a*) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun*. **1979**, 866–867. (*b*) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett*. **1979**, *20*, 3437–3440.
[3] Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177–2250.
[4] Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457–2483.
[5] Pagett, A. B.; Lloyd-Jones, G. C. In *Organic Reactions*, Denmark, S. E., Ed.; John Wiley & Sons, Inc. **2020**, *100*, 547–619.
[6] Echavarren, A. M.; Homs, A. In *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A., Bräse, S., Oestreich, M., Eds.; Wiley-VCH: Weinheim, Germany, **2013**, *1*, 1–64.

Scheme 3.1. Mechanism of Pd-catalyzed cross-coupling reactions



The optimization of the Suzuki-Miyaura cross-coupling reaction has largely focused on accelerating the transmetallation step.[7] Specifically, the interaction of the organoboronate with the base has a pronounced effect on the efficiency this step.[8] Several types of organoboronates have been successfully utilized in cross-coupling reactions, whereby the optimal boron ligands for a particular set of reaction conditions varies (Scheme 3.2). Thus, a detailed understanding of the properties imparted by different boron ligands and their effect on transmetallation is essential for reaction design.

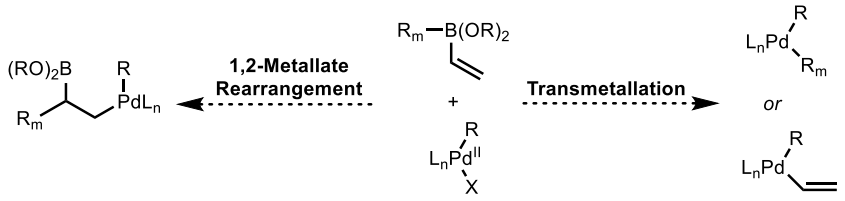
Scheme 3.2. Examples of boronates used in Suzuki-Miyaura cross-coupling reactions



[7] Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 7362–7370.
[8] Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.,* **2014**, 43, 412–443.

The transmetallation of organoboronates is of particular interest to our research group in the context of the conjunctive cross-coupling reaction because it is an undesired reaction pathway. The chemoselectivity in the reaction is dictated by the preference of the Pd^{II} oxidative addition adduct to induce a 1,2-metallate rearrangement with a vinyl boron 'ate' complex, rather than undergoing transmetallation (Scheme 3.3). The following chapter will discuss the Pd-catalyzed conjunctive cross-coupling reaction of β-substituted alkenyl boronates, a substrate class which does not readily undergo the Pd-induced 1,2-metallate rearrangement. Significant reaction optimization was achieved by modifying the ligands on boron to disfavor the competing transmetallation reaction.

Scheme 3.3. 1,2-metallate rearrangement versus transmetallation



3.2. Background

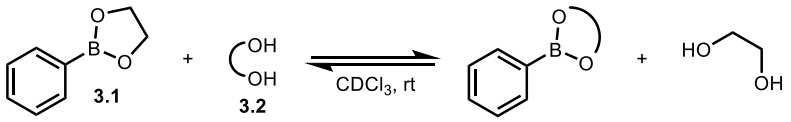
3.2.1. Ligand effects of the stability of organoboronates

In work by H. C. Brown, the stability and reactivity of a series of boronic esters was investigated by monitoring the transesterification between different diols.[9] The rate and extent of transesterification between ethylene glycol (eg) boronic ester **3.1** and a variety of diols (**3.2**) under neutral conditions is shown in Table 3.1. The 1,2-diols with increased steric hindrance around the oxygen atoms result in more-stable boronic esters (Entry 1-3). Diols with less-electron-donating oxygens make for less stable boronic esters (Entry 4-5). For cyclic *syn* diols, 1,2-cyclopentanediol

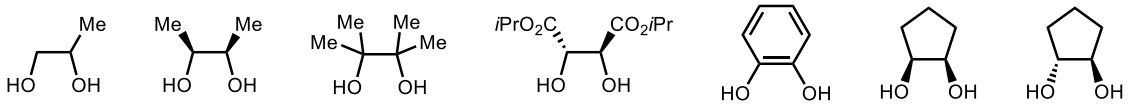
[9] Roy, C.D.; Brown, H.C. *J. Organomet. Chem*. **2007**, *692*, 784–790.

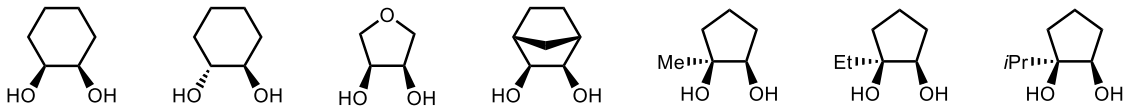
leads to a more stable boronic ester than 1,2-cyclohexanediol (Entry 6, 8), and the corresponding *anti* diols do not ligate to boron (Entry 7, 9). Cyclopentanediol derivatives with rigid ring systems also exchange rapidly and completely (Entry 11, 16), although hindered diols leads to a slower rate of ligand exchange (Entry 12–15). Lastly, the acyclic 1,3 diols are more reactive and form more stable boronates than the analogous 1,2 diols (Entry 17–20).

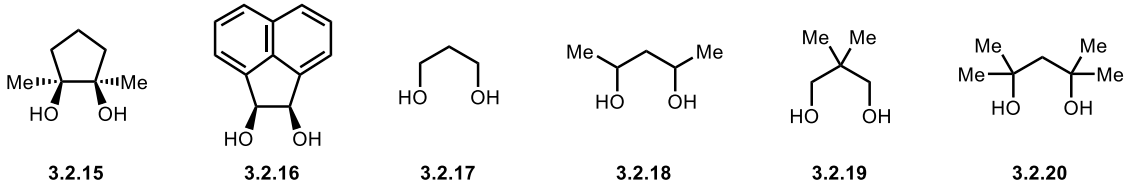
Table 3.1. Boronic ester transesterification reaction[9]



Entry	Diol	% Transesterification	Time (h)
1	3.2.1	68.6	0.1
2	3.2.2	74.7	0.1
3	3.2.3	87.8	94
4	3.2.4	4.5	0.1
5	3.2.5	28	5
6	3.2.6	99	0.1
7	3.2.7	0	47
8	3.2.8	47	0.1
9	3.2.9	0	44
10	3.2.10	97	0.75
11	3.2.11	99.5	0.1
12	3.2.12	99	0.75
13	3.2.13	99	1.5
14	3.2.14	99	1.75
15	3.2.15	99	258
16	3.2.16	97	2.5
17	3.2.17	88.5	0.1
18	3.2.18	98	0.1
19	3.2.19	85	0.1
20	3.2.20	91	67



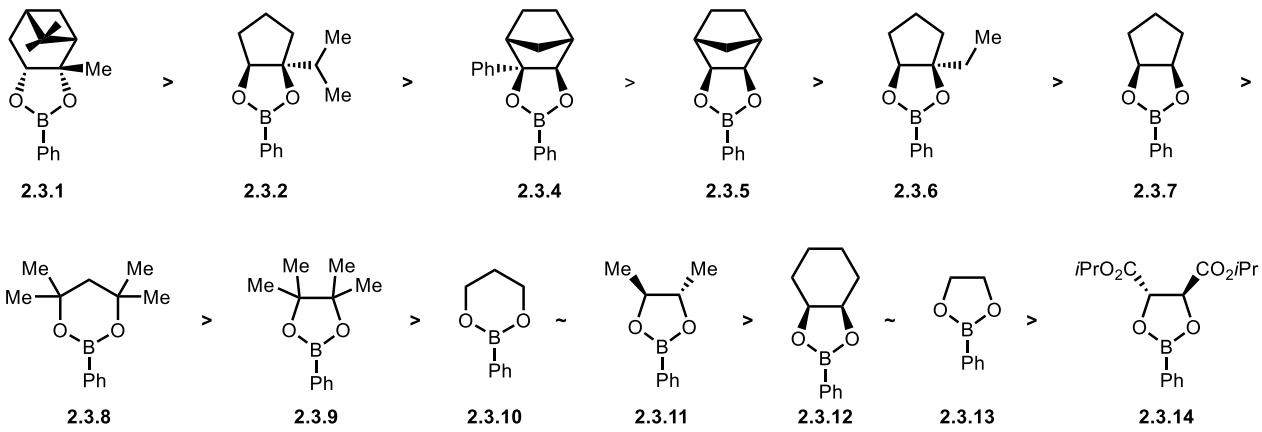




A subsequent study was carried out to further investigate the relationship between diol structure and boronic ester stability.[10] The relative thermodynamic and kinetic stability of a variety of boronic esters was investigated by analyzing the rate and extent of a transesterification reaction for a boronic ester in the presence of an exogenous diol under neutral conditions. The relative kinetic stability can be determined by the amount of time required for the transesterification reaction to reach equilibrium. The thermodynamic stability is determined by the equilibrium ratio between the two different boronic esters in the transesterification reaction; the results are summarized in Scheme 3.4. The diisopropyl tartrate-ligated boronic ester (**3.3.14**), which is relatively unhindered and contains electron-withdrawing substituents on the dioxaborolane ring, is completely and rapidly exchanged with a variety of diols. Comparatively, the sterically-similar *trans*-2,3-butanediol boronic ester (**3.3.11**) is more kinetically and thermodynamically stable. Further increasing the steric profile of diol to the pinacol boronic ester (**3.3.9**) results in increased kinetic and thermodynamic stability. Compared to pinacol, the less-hindered 1,2-cyclopentane diol boronic ester (**3.3.7**) is less kinetically stable, but more thermodynamically stable due to its rigidity (*vide infra*). Lastly, the diols which are both sterically hindered and conformationally rigid, such as **3.3.1** and **3.3.2**, lead to the highest degree of stability.

[10] Roy, C.D.; Brown, H.C. *Monatshefte für Chemie* **2007**, *138*, 879–887.

Scheme 3.4. Relative thermodynamic stability of boronic esters

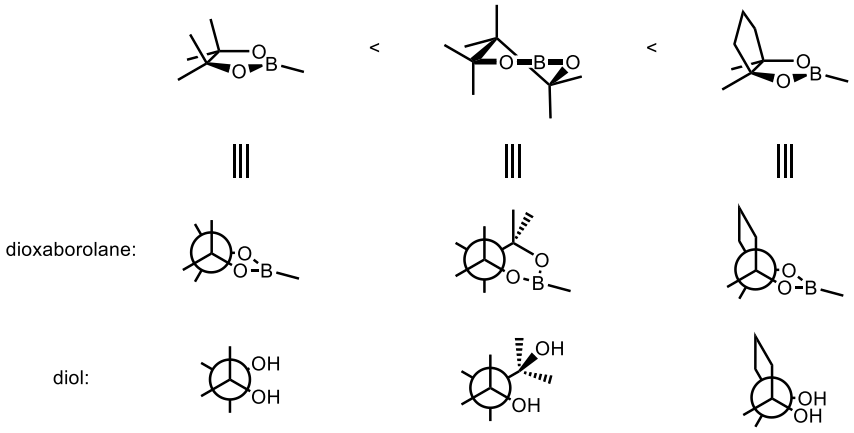


The kinetic stability of boronic esters is inversely related to the electrophilicity of the boron atom; the stability increases with additional steric hindrance and stronger donation of the oxygen lone pairs into the *p* orbital of boron. The thermodynamic stability of boronic esters can be assessed by comparing the conformation of the 1,3-dioxaborolane ring with the low-energy conformation of the free diol.[11] Boronic esters exhibit a nearly planar dioxaborolane ring due in order to achieve a high degree of B–O π-bonding; this introduces steric and torsional strain between the dioxaborolane substituents.[12] The ability to alleviate this strain upon dissociation to the free diol results in decreased thermodynamic stability of the boronic ester. Thus, 5-membered 1,3-dioxaborolanes (from 1,2-diols) are less stable than their 6-membered-ring analogs (from 1,3-diols); the former adopts an unfavorable eclipsed conformation which is avoided in the free diol, whereas the latter has minimal steric strain resulting from the staggered conformation of dioxaborolane substituents (Scheme 3.5). Furthermore, the 5-membered 1,3-dioxaborolanes do not benefit from the gauche effect which stabilizes the corresponding free 1,2-diols.[13] The boronic

[11] Matteson, D. S.; Man, H.-W. *J. Org. Chem.* **1996,** *61,* 6047–6051.
[12] Ho, O. C.; Soundararajan, R.; Lu, J.; Matteson, D. S.; Wang, Z.; Chen, X.; Wei, M.; Willett, R. D. *Organometallics* **1995**, *14*, 2855–2860.
[13] Cabral, B. J. C.; Albuquerque, L. M. P. C.; Fernandes, F. M. S. S. *Theor. Chim. Acta* **1991**, *78*, 271−280.

esters derived from structurally rigid diols, such as 1,2-cyclopentanediol, are particularly stable because the corresponding free diols cannot avoid unfavorable eclipsing interactions due to the constricted rotation. The addition of bulky substituents to these diols leads to increased stability by enforcing a more-staggered conformation in the dioxaborolane ring, which is closer to that of the free diol. Of note, the above trends in thermodynamic stability apply to three-coordinate boronic esters, and a different set of factors govern the stability of four-coordinate boron species.[14]

Scheme 3.5. Conformations of 1,3-dioxaborolanes



3.2.2. Transmetallation in the Suzuki-Miyaura cross-coupling reaction

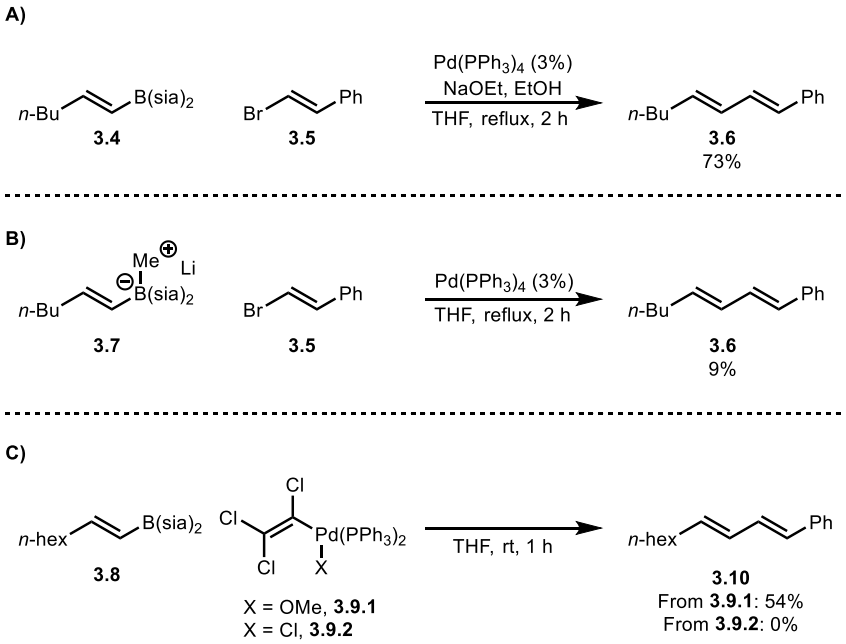
3.2.2.1. Role of base for transmetallation

One feature that distinguishes the Suzuki reaction from other cross-coupling reactions is the necessity of a stoichiometric base to facilitate the transmetallation step.[15] Notably, a similar requirement for a base exists for the transmetallation of organosilicon reagents.[16] The mechanistic role of the base for the transmetallation of organoboronates was first investigated by Suzuki *et al*.[17] The cross-coupling of alkenyl boronate **3.4** and alkenyl bromide **3.5** with a palladium catalyst

[14] Harlow, G. P.; Zakharov, L. N.; Wu, G.; Liu, S.-Y. *Organometallics* **2013**, *32*, 6650−6653.
[15] Miyaura, N. *J. Organomet. Chem*. **2002**, *653*, 54–57.
[16] Denmark, S. E.; Ambrosi, A. *Org. Process Res. Dev.* **2015**, *19*, 982–994.
[17] Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc*. **1985**, *107*, 972–980.

proceeds efficiently in the presence of sodium ethoxide, but not at all in the absence of base (Scheme 3.6.A). It is proposed that the base enables formation of a boron 'ate' complex which is sufficiently nucleophilic to transfer the alkenyl group to palladium. However, the use of an all-carbon borate (**3.7**) does not undergo the cross-coupling reaction as would be expected according to this hypothesis (Scheme 3.6.B). An alternative reaction pathway involves the base reacting with the Pd^{II} oxidative addition adduct to generate a new catalytic species. When alkenyl borane **3.8** is treated with alkoxy–Pd^{II} complex **3.9.1**, the cross-coupling product is formed, but not with chloro–Pd^{II} complex **3.9.2** (Scheme 3.6.C). Thus, the palladium alkoxide species (**3.9.1**) is a competent intermediate in the catalytic cycle.

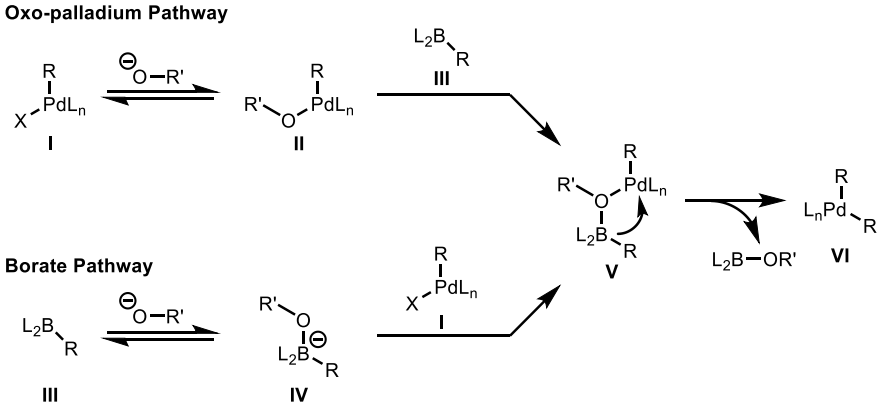
Scheme 3.6. Role of base in the Suzuki reaction



Based on the observations presented above, the mechanism of transmetallation was proposed to involve the nucleophilic addition of oxo-palladium intermediate (**II**, Scheme 3.7) to the 3-coordinate boronate (**III**) to form intermediate **V** (oxo-palladium pathway). In support of

this hypothesis, the reaction efficiency increases for a more nucleophilic alkoxide (R' = Me > Et > *t*-Bu > Ph) and a more electrophilic boronate.[18] However, an alternative reaction pathway was suggested for the cross-coupling of a boronic acid under basic, aqueous conditions.[19] The base reacts with the three-coordinate boron species to form a borate (**IV**), which undergoes a nucleophilic substitution with the Pd^{II} oxidative addition adduct (**I**), leading to the same intermediate (**V**) (borate pathway; Scheme 3.7). This is supported by the conversion of boronic acids to the more-nucleophilic 'ate' complexes in the presence of hydroxide.[20] Overall, the role of base in the transmetallation step is either to activate the palladium complex (oxo-palladium pathway) or to activate the boronate (borate pathway), but the operative pathway depends on the reaction conditions.

Scheme 3.7. Possible transmetallation pathways in the Suzuki-Miyaura cross-coupling

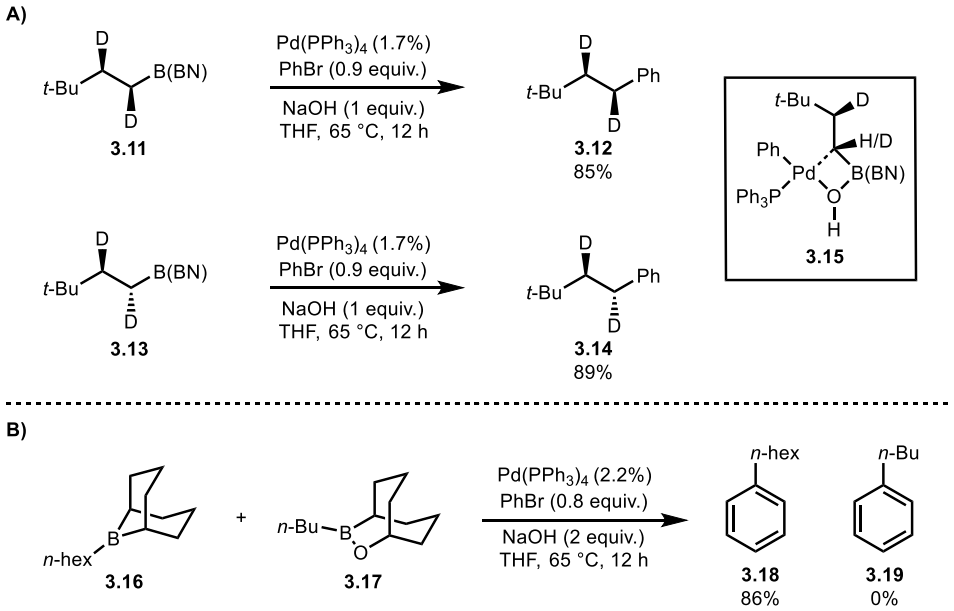


The stereochemical outcome of transmetallation reinforces the important role of the base in this process.[21] The Pd-catalyzed cross-coupling reactions of borane reagents **3.11** and **3.13** in

[18] Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, *2*, 149–151.
[19] Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151–8156.
[20] Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *Can. J. Chem*. **1963**, *41*, 3081–3090.
[21] (a) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458–460. (b) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998,** *63,* 461–470.

the presence of sodium hydroxide yield products **3.12** and **3.14**, respectively, in a stereospecific fashion (Scheme 3.8.A).[21b] Therefore, the transmetallation is stereoretentive with respect to the organoboronate, and a four-centered μ^2-hydroxo transition state model (**3.15**) is invoked. Notably, the frontside S_E2 (cyclic) transmetallation pathway is proposed for alkylsilane nucleophiles as well.[22] Therefore, the importance of the Pd–O–B linkage in the pre-transmetallation complex is established, but the preference for the oxo-palladium pathway versus the borate pathway remains unclear.[21b] In a competition experiment between borane **3.16** and borinate **3.17**, the borane reacts exclusively to yield **3.18** (Scheme 3.8.B). Furthermore, **3.16** forms an 'ate' complex with sodium hydroxide, whereas **3.17** does not. This data suggests that **3.16** reacts via the borate pathway, while **3.17** goes through the slower oxo-palladium pathway. Either way, the pre-transmetallation intermediate contains a Pd–O–B linkage, and the transmetallation occurs via a four-centered transition state.

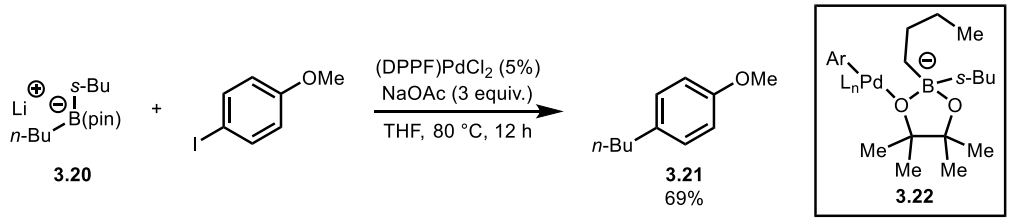
Scheme 3.8. Mechanistic studies of transmetallation



[22] (a) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793–7794. (b) Hatanaka, Y.; Hiyama, T. Synlett **1991**, 845–853.

Further evidence for the feasibility of the borate pathway is that pre-formed boronic ester 'ate' complexes undergo transmetallation in the absence of a base.[23] Borate **3.20** effectively undergoes the cross-coupling reaction with an aryl iodide electrophile to yield **3.21** (Scheme 3.9). Although the optimal reaction conditions employ sodium acetate as an additive for this reaction, it is not required for the catalytic reaction to occur. Thus, borate **3.20** is competent in the transmetallation step; a possible pre-transmetallation intermediate is **3.22**, in which the Pd–O–B linkage is established through the bridging O ligand of the boronic ester.

Scheme 3.9. Suzuki-Miyaura cross-coupling reaction with a boronic ester 'ate' complex

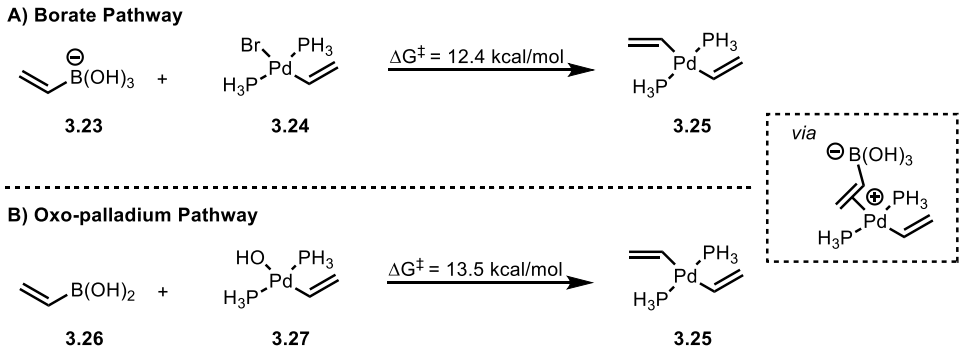


While the oxo-palladium pathway and the borate pathway both converge at a common intermediate, a detailed understanding of the operative mechanism can facilitate reaction optimization. Therefore, the proficiency of the borate pathway versus the oxo-palladium pathway was investigated by DFT calculations.[24] The reaction of interest is the transmetallation from vinyl borate **3.23** to bis(phosphine)Pd^{II} complex **3.24** (Scheme 3.10). The formation of the Pd–O–B adduct in the borate pathway proceeds with a relatively low activation energy of 12.4 kcal/mol, and the same pre-transmetallation intermediate is formed by the reaction of **3.26** and **3.27** (oxo-palladium pathway) with a comparable activation energy of 13.5 kcal/mol. However, the oxo-palladium pathway is ruled out due to the energetically prohibitive formation of the Pd–OH

[23] Zou, G.; Falck, J. R. *Tetrahedron Lett*. **2001**, *42*, 5817–5819.
[24] Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298–9307.

complex from the Pd–Br precursor. A similar conclusion is reached for the cross-coupling of aryl groups as well.[25]

Scheme 3.10. Calculated energies for transmetallation

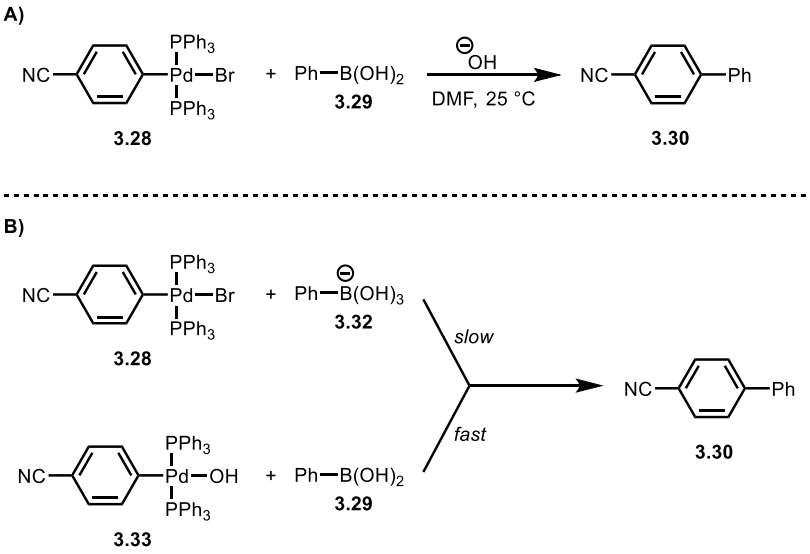


Next, the possible mechanistic pathways were studied experimentally.[26] The rate of reaction of Pd-complex **3.28** with phenylboronic acid (**3.29**) in the presence of hydroxide base was studied (Scheme 3.11.A), and the kinetic competence of possible reactive intermediates (**3.28**, **3.29**, **3.32**, and **3.33**.) was analyzed (Scheme 3.11.B). The rate of the borate pathway when using pre-formed boron 'ate' complex **3.32** with palladium complex **3.28** is slow, whereas the reaction between Pd–OH complex **3.33** and boronic acid **3.29** is fast. Furthermore, Pd complexes **3.28** and **3.33**, as well as boron complexes **3.32** and **3.29**, are in rapid equilibrium under the reaction conditions. The reaction between borate **3.32** and **3.33** is also found to be kinetically insignificant due to the rate deceleration at sufficently high concentrations of hydroxide. Furthermore, the strong inhibitory effect of halide ions (X^-) on transmetallation is consistent with the oxo-palladium pathway, and not the borate pathway; the halide ions favor the formation of the Pd–X complex, which is the active catalytic intermediate for borate pathway, rather the Pd–OH complex, which is

[25] Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Lledós, A.; Maseras, F. *J. Organomet. Chem*. **2006**, *691*, 4459–4466.
[26] (a) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492–2503. (b) Review: Amatore, C.; Le Duc, G.; Jutand, A. *Chem. Eur. J.* **2013**, *19*, 10082–10093.

the active catalytic intermediate in the oxo-palladium pathway. Lastly, transmetallation is accelerated with non-coordinating cations (n-$BuNH_4^+ > Cs^+ > Na^+ > K^+$), since competitive Lewis acid binding to the Pd–OH complex inhibits the reaction.[27] The same preference for the oxo-palladium pathway over the borate pathway is reached in a contemporaneous kinetic study.[28]

Scheme 3.11. Kinetic study on transmetallation

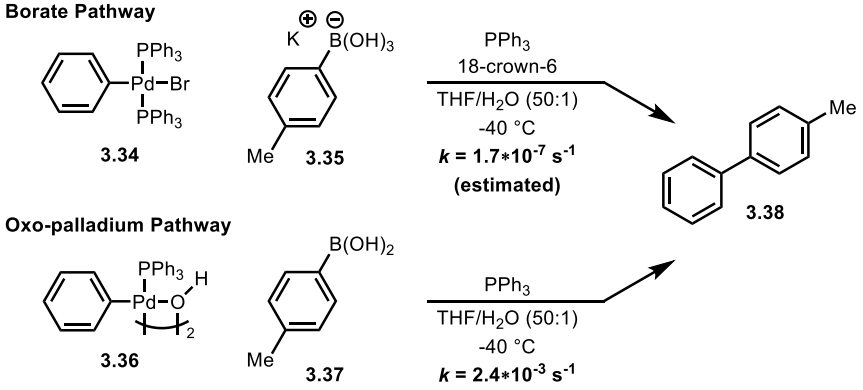


A quantitative determination of the rates of the oxo-palladium pathway and the borate pathway was also performed.[29] As shown in Scheme 3.12, the reaction by the oxo-palladium pathway (**3.36** with **3.37**) is approximately $1.4*10^4$ times faster than the reaction by the borate pathway (**3.34** with **3.35**). This data is applicable to catalytic reaction conditions because of the roughly equivalent concentrations of borate (**3.35**) and boronic acid (**3.37**), as well as Pd–OH complex **3.36** and Pd–Br complex **3.34**. Furthermore, the oxo-palladium pathway is also favored for boronic esters ($(OR)_2$ = cat, neo, pin). Notably, similar kinetic studies have been performed

[27] Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2012**, *18*, 6616–6625.
[28] Schmidt, A. F.; Kurokhtina, A. A.; Larina, E. V. *Russ. J. Gen. Chem*. **2011**, *81*, 1573–1574.
[29] Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119.

for the Ni-catalyzed Suzuki-Miyaura cross-coupling reaction; both the borate pathway and oxo-Ni pathway are possible, but the latter is much faster.[30]

Scheme 3.12. Rate constants for the transmetallation pathways

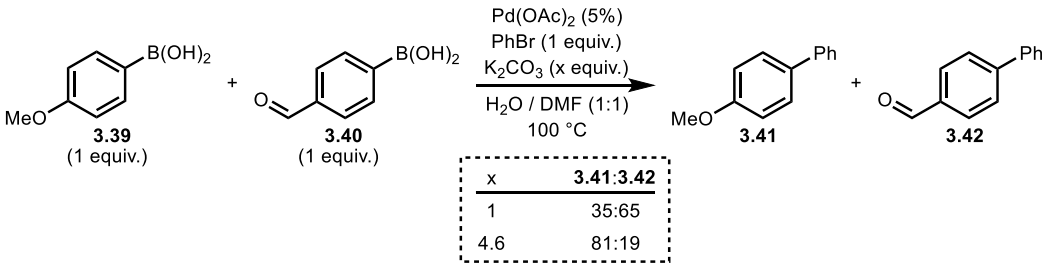


Despite this kinetic evidence, a mechanistic study based on a series of competition experiments seemed to favor the borate pathway.[31] This study investigated the competitive transmetallation between boronic acids of varying acidity (Scheme 3.13). Using equal concentrations of boronic acids **3.39** and **3.40** and a limiting amount of bromobenzene, the more-acidic **3.40** reacts preferentially under low concentration of base (1 equiv. K_2CO_3), but **3.39** reacts faster at high concentrations of base (4.6 equiv. K_2CO_3). The chemoselectivity of the reaction at low concentration of base is dominated by the equilibrium between the boronic acid and the borate, and the substrate that more readily forms the borate (i.e. stronger acid) reacts faster. At high concentration of base, both boronic acids are fully converted to the borate, and the more-nucleophilic complex preferentially transmetallates. This data is consistent with the borate, rather

[30] (a) Christian, A. H.; Müller, P.; Monfette, S. *Organometallics* **2014**, *33*, 2134–2137. (b) Payard, P.-A.; Perego, L. A.; Ciofini, I.; Grimaud, L. *ACS Catal.* **2018**, *8*, 4812–4823.
[31] Lima, C. F. R. A. C.; Rodrigues, A. S. M. C.; Silva, V. L. M.; Silva, A. M. S.; Santos, L. M. N. B. F. *ChemCatChem* **2014**, *6*, 1291–1302.

than the boronic acid, being the active species for transmetallation, which is supported by DFT calculations.[32]

Scheme 3.13. Competition experiment between boronic acids



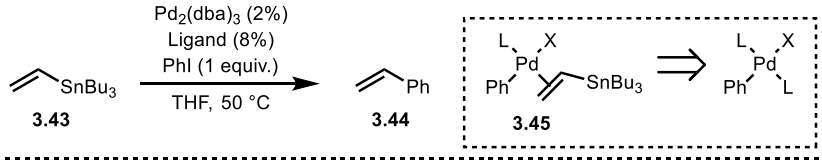
x	3.41:3.42
1	35:65
4.6	81:19

3.2.2.2. Effect of the phosphine ligand

The role of the phosphine ligands on palladium in the transmetallation of organoboronates is likely analogous to that of other nucleophilic coupling partners. The effect of supporting ligands on palladium with respect to the transmetallation of organostannanes was investigated.[33] The reaction between vinyl stannane **3.43** and iodobenzene proceeds with transmetallation being the turnover-limiting step (Table 3.2). Significant rate acceleration is observed for weakly-coordinating ligands such as $AsPh_3$, and thus ligand dissociation to generate Pd complex **3.45** is proposed to precede transmetallation. The dissociative mechanism of L_2PdArX for transmetallation is supported by the fact that bidentate phosphine ligands result in a slower reaction, and a higher concentration of the phosphine ligand exhibits an inhibitory effect. This mechanism is also supported by the rapid transmetallation of stannanes with a stoichiometric mono(phosphine)Pd^{II} complex.[34]

[32] Ortuño, M. A.; Lledós, A.; Maseras, F.; Ujaque, G. *ChemCatChem* **2014**, *6*, 3132–3138.
[33] Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585–9595.
[34] Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **1995**, *117*, 11598–11599.

Table 3.2. Phosphine ligand effects in the Stille cross-coupling reaction[33]



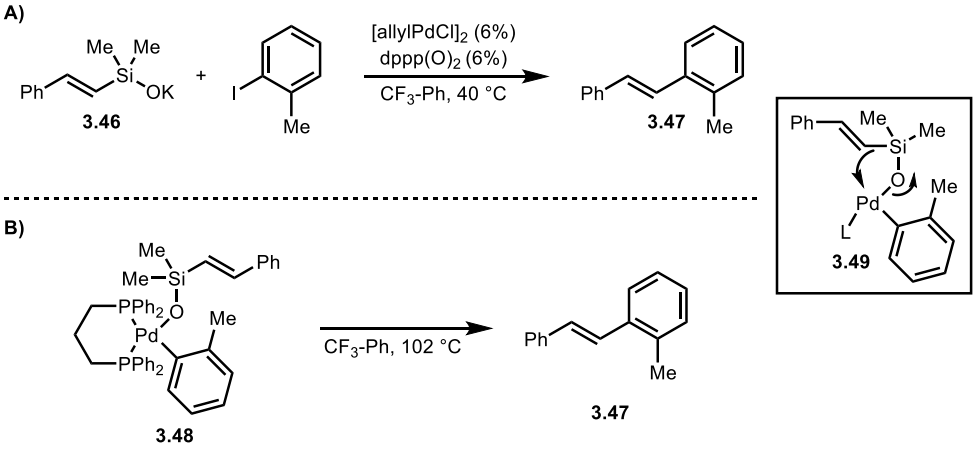
Ligand	k_{rel}
Ph_3P	1.0
$(4\text{-}FC_6H_4)_3P$	0.60
$(4\text{-}ClC_6H_4)_3P$	0.71
$(2\text{-}MeC_6H_4)_3P$	35.2
$(2\text{-furyl})_3P$	105
$(2\text{-thienyl})_3P$	4.8
$Ph_2(C_6F_5)P$	24.3
$Ph(C_6F_5)_2P$	950
$(PhO)_3P$	95.2
$(i\text{PrO})_3P$	42.8
Ph_3As	1100
Ph_3Sb	13.2

Similar to the transmetallation in the Stille cross-coupling reaction, the transmetallation of alkenyl silanolates was shown to be highly sensitive to the phosphine ligands.[35] Under conditions with "ligandless" palladium (i.e. a weakly-coordinating phosphine oxide ligand), the catalytic cross-coupling of potassium silanolate **3.46** and 2-iodo toluene to yield **3.47** proceeds at 40 °C (Scheme 3.14.A). The transmetallation is inhibited by strongly-coordinating phosphine ligands such that the pre-transmetallation intermediate **3.48** is isolable, and the cross-coupling product **3.47** is obtained only upon heating to 102 °C (Scheme 3.14.B). Thus, a possible mechanism for transmetallation involves a coordinatively unsaturated Pd complex with a Pd–O–Si linkage such as **3.49**. Additional evidence which supports a dissociative mechanism of **3.48** is that the

[35] Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Denmark, S. E. *J. Am. Chem. Soc.* **2015**, *137,* 6192–6199.

transmetallation occurs at room tempterature upon treatment with CuTC which facilitates deligation of the phosphine ligand.

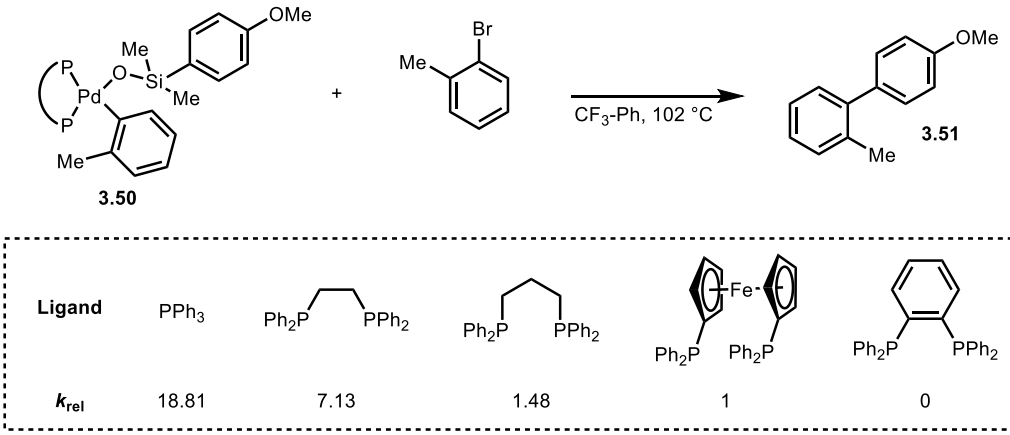
Scheme 3.14. Transmetallation in the Hiyama-Denmark cross-coupling reaction



Next, the rates of transmetallation of an aryl silanolate were investigated with respect to the nature of the phosphine ligand.[36] The decomposition of pre-transmetallation complex **3.50** to **3.51** at 102 °C with different phosphine ligands follows the trend PPh_3 > DPPE > DPPP ~ DPPF >> DPPBz; increasing the lability of the ligand results in a faster transmetallation. Furthermore, additional phosphine ligand inhibits the reaction, and transmetallation with P*t*Bu$_3$ as the ligand proceeds at only 50 °C due to the favorable formation of the mono(phosphine)Pd complex. Overall, kinetic data for the transmetallation of organostannanes and organosilanes supports that a mono(phosphine)- rather than a bis(phosphine)-Pd complex undergoes transmetallation.

[36] Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Ober, M. H.; Wang, H.; Denmark, S. E. *J. Am. Chem. Soc.* **2015**, *137,* 6200–6218.

Scheme 3.15. Effect of the phosphine ligand on the Hiyama-Denmark transmetallation

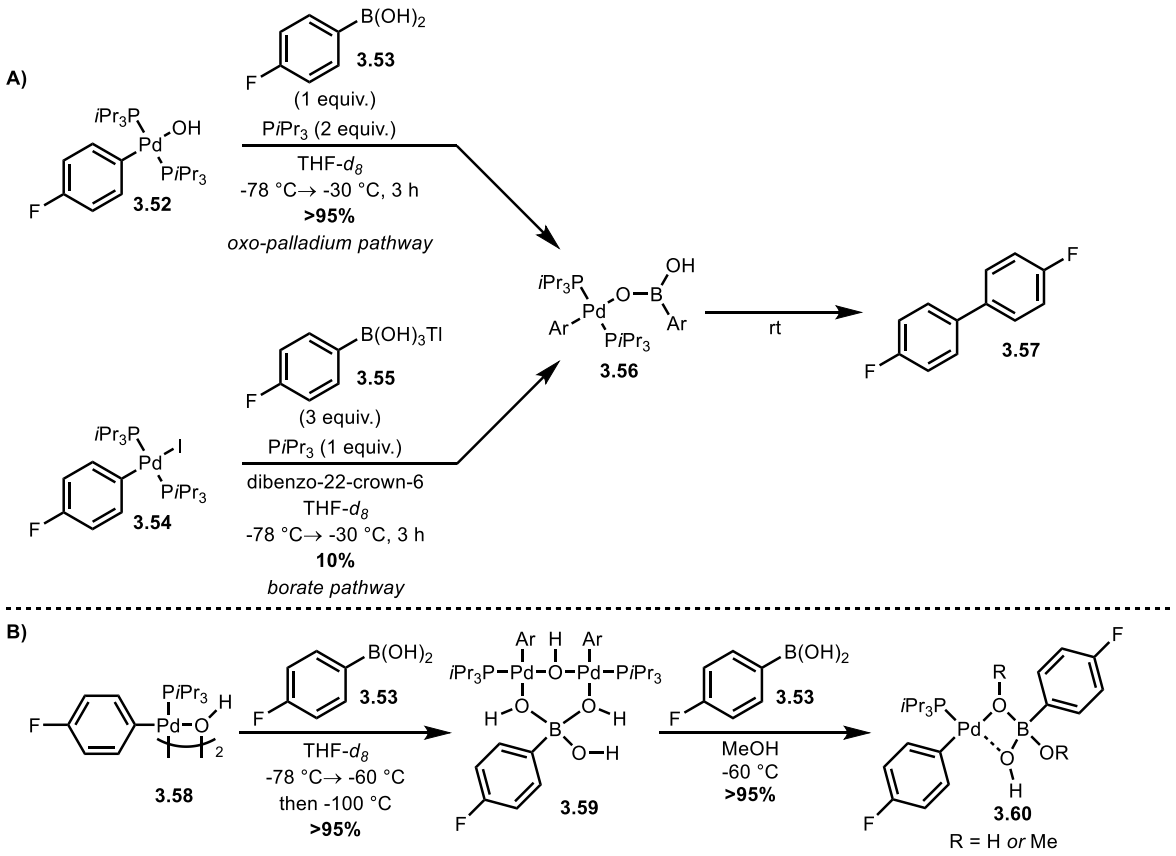


The effect of phosphine ligands in the Suzuki-Miyaura cross-coupling reaction was investigated using similar techniques.[37] The Pd–O–B adduct **3.56** is readily synthesized from hydroxy palladium complex **3.52** and boronic acid **3.53** (oxo-palladium pathway) in the presence of excess phosphine at low temperature (Scheme 3.16.A). Complex **3.56** is also obtained by treatment of Pd–I complex **3.54** with thallium borate **3.55** (borate pathway) albeit with greatly diminished efficiency. Upon warming complex **3.54** to room temperature, the cross-coupling product **3.57** is obtained, thus establishing the chemical competence of this intermediate. Notably, analogous Pt–O–B[38] and Rh–O–B[39] complexes have also been demonstrated as chemically competent intermediates for transmetallation. The decomposition of **3.54** to **3.57** exhibits an inverse dependence on the concentration of the phosphine ligand. This suggests that transmetallation involves a mono(phosphine)Pd complex, as is observed by computational studies.[32, 40] In an attempt to synthesize a pre-transmetallation complex with only one phosphine

[37] (a) Thomas, A. A.; Denmark, S. E. *Science* **2016**, *352,* 329–332. (b) Thomas, A. A.; Wang, H.; Zahrt, A. F.; Denmark, S. E. *J. Am. Chem. Soc.* **2017**, *139,* 3805–3821.
[38] Pantcheva, I.; Nishihara, Y.; Osakada, K. *Organometallics* **2005**, *24*, 3815−3817.
[39] Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc*. **2007**, *129*, 1876−1877.
[40] Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *J. Am. Chem. Soc.* **2005**, *127*, 11102–11114.

ligand on Pd, palladium complex **3.58** is treated with boronic acid **3.53**, yielding adduct **3.59** quantitatively. (Scheme 3.16.B). This 2:1 Pd/B complex (**3.59**) is subsequently converted into the 1:1 Pd/B complex (**3.60**) in the presence of methanol. Upon warming **3.59** to -30 °C, it undergoes first-order decay which coincides with the formation of **3.57** either in the presence or absence of methanol. The first-order kinetics suggest that transmetallation occurs from intermediate **3.60** rather than **3.59**.

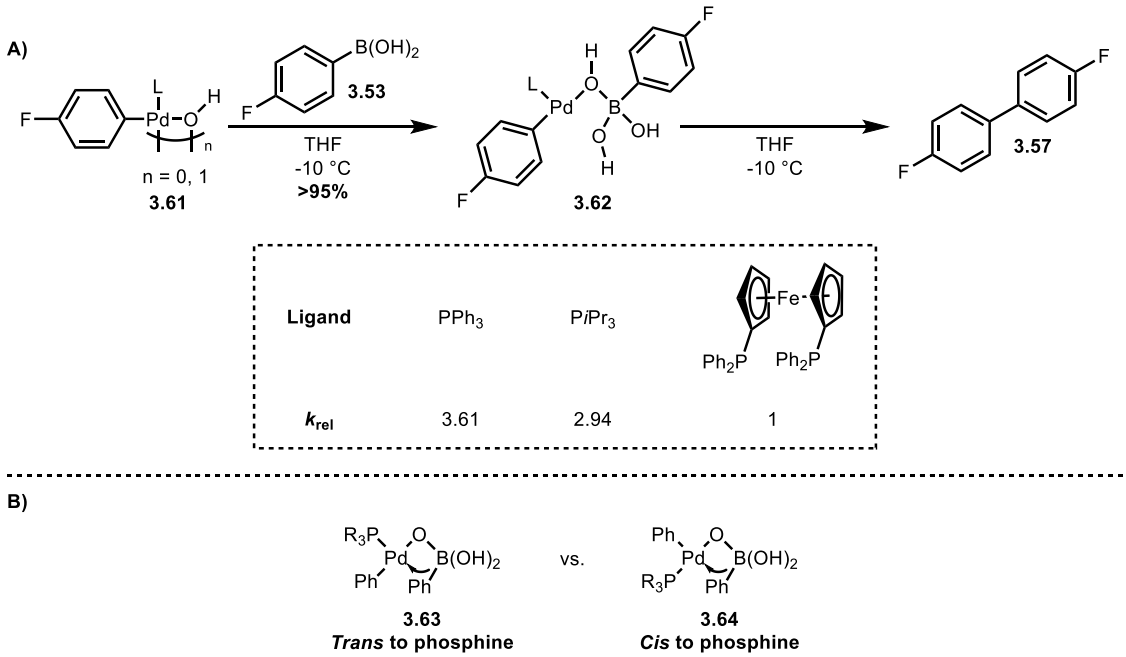
Scheme 3.16. Transmetallation of organoboronates



The effect of different phosphine ligands on the rate of transmetallation of organoboronates was investigated.[37b] The pre-transmetallation complex **3.62** is synthesized by the oxo-palladium complex **3.61** and boronic acid **3.53** for the ligands PPh_3, P*i*Pr$_3$, and DPPF (Scheme 3.17.A). The

monodentate phosphine ligands result in a faster transmetallation, which is consistent with the generation of a coordinatively unsaturated Pd center. In terms of electronic properties, the more electron-deficient PPh_3 reacts faster than P*i*Pr$_3$, suggesting that increasing the electrophilicity of palladium accelerates transmetallation. This is consistent with DFT calculations in which the rate of transmetallation with respect to the phosphine ligand follows the trend: $P(CF_3)_3 > PPh_3 > PMe_3 > P$*t*-Bu$_3$.[41] The rate of transmetallation is affected by the *trans* influence of the phosphine ligand because the transmetallating group on boron is transferred *trans* to the phosphine ligand (**3.63**) rather than *cis* (**3.64**) (Scheme 3.17.B).

Scheme 3.17. Phosphine ligand effect on rate of transmetallation



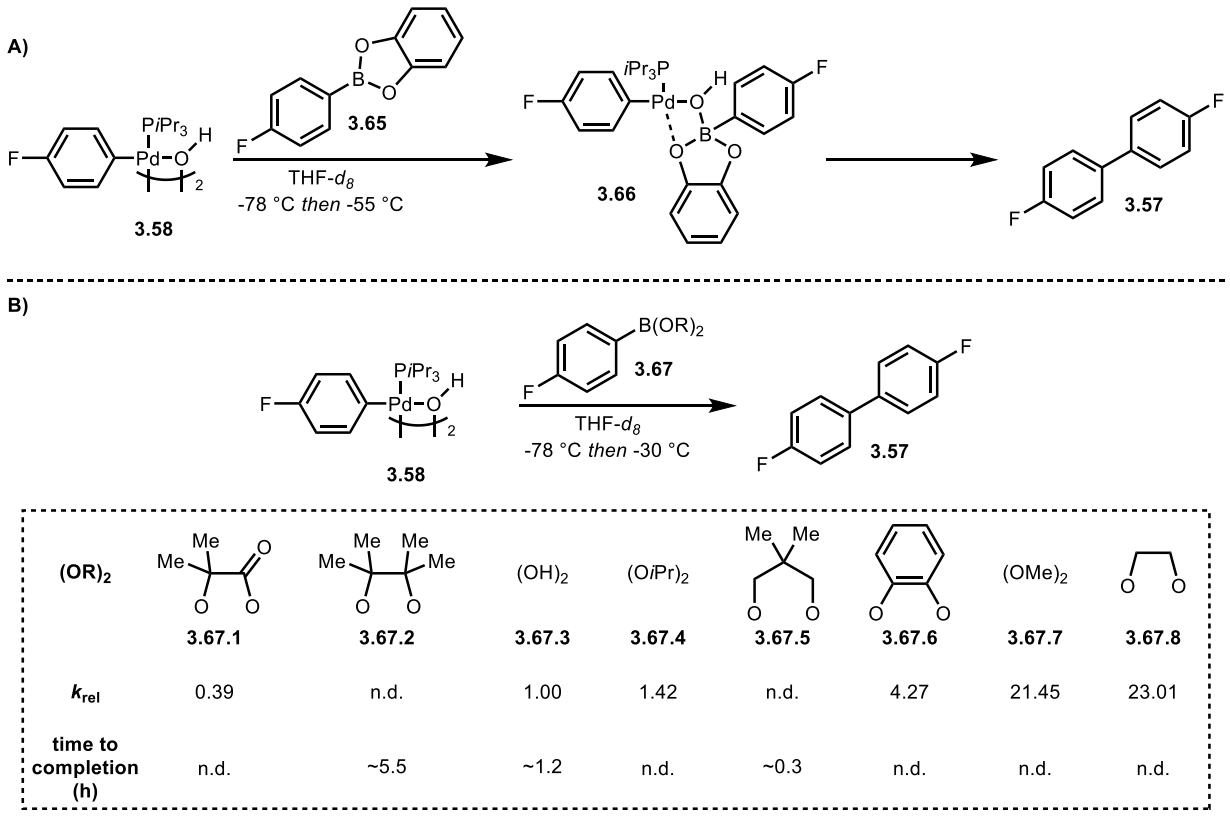
[41] Jover, J.; Fey, N.; Purdie, M.; Lloyd-Jones, G. C.; Harvey, J. N. *J. Mol. Catal. A: Chem*. **2010**, *324*, 39–47.

3.2.2.3. Role of the boronic ester ligand

Based on the proposal that the transmetallation of organoboronates proceeds via a Pd–O–B adduct, the steric and electronic properties of the ligands on boron should have a significant effect on the transmetallation reaction. Thus, the effect of the boronic ester ligand on the rate of transmetallation was investigated.[42] The pre-transmetallation complex **3.66** is synthesized from catechol boronic ester **3.65** and palladium complex **3.58** (Scheme 3.18.A). The complex contains a four-coordinate boron atom, and a *trans* relationship is observed between the phosphine ligand and the diol oxygen rather than the OH group. The rates of transmetallation for a variety of boronic esters are shown in Scheme 3.18.B. The reactions in which a pre-transmetallation intermediate (e.g. **3.66**) is observed exhibit clean, first-order kinetics such that a rate constant can be obtained. For the reactions which exhibit complicated kinetics, the relative rates can be compared by the reaction time to reach completion. Sterically hindered diol ligands **3.67.1** and **3.67.2** react sluggishly compared to the boronic acid **3.67.3**. Boronic esters **3.67.4** and **3.67.5** which are relatively unhindered and contain electron-donating substituents on oxygen react faster than the boronic acid. Notably, **3.67.6** which contains electron-deficient oxygen ligands, also reacts faster than the boronic acid. Lastly, the sterically unhindered boronic esters **3.67.7** and **3.67.8** undergo exceedingly rapid transmetallation. Overall, multiple factors influence the rate of transmetallation due to complex nature of this mechanism.

[42] Thomas, A. A.; Zahrt, A. F.; Delaney, C. P.; Denmark, S. E. *J. Am. Chem. Soc.* **2018**, *140,* 4401–4416.

Scheme 3.18. Transmetallation of boronic esters

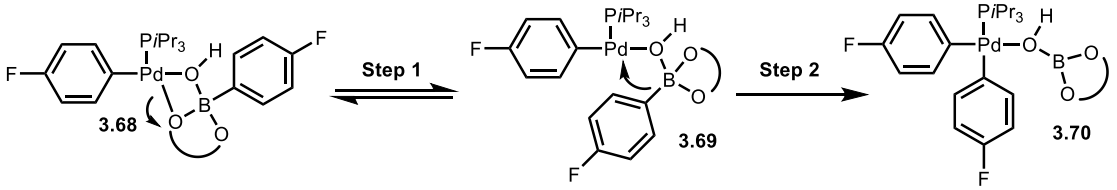


$(OR)_2$			$(OH)_2$	$(OiPr)_2$			$(OMe)_2$	
	3.67.1	**3.67.2**	**3.67.3**	**3.67.4**	**3.67.5**	**3.67.6**	**3.67.7**	**3.67.8**
k_{rel}	0.39	n.d.	1.00	1.42	n.d.	4.27	21.45	23.01
time to completion (h)	n.d.	~5.5	~1.2	n.d.	~0.3	n.d.	n.d.	n.d.

In order to gain more insight into the features of the boron ligands that influence the rate of transmetallation, the mechanism of transmetallation was investigated by DFT calculations.[42] Transmetallation occurs by preliminary formation of the Pd–O–B adduct (i.e. pre-transmetallation intermediate), then formation of a coordinatively unsaturated palladium center (**3.68→3.69**), and finally migration of the organic group from boron to palladium (**3.69→3.70**) (Scheme 3.19). The properties of the boron ligand that influence these steps are demonstrated by comparing a boronic acid, an ethylene glycol ester, and a catechol ester. Step 1 (**3.68→3.69**) is accelerated by decreasing donor ability of the oxygen atom. Therefore, the catechol ligand is optimal for this step due to the electron-withdrawing aryl ring. In terms of sterics, the substrate with an ethylene glycol ligand reacts faster than boronic acid derivative due to the increased steric hindrance of the oxygen

substituents compared to the O–H group. Thus for Step 1, cat > eg > $(OH)_2$. Step 2 (**3.69→3.70**) is accelerated by a more electron-rich oxygen atom because donation of the lone pairs into the $\sigma^*_{B–C}$ orbital (negative hyperconjugation) facilitates the reaction. The electron-deficient catechol ligand is slowest for this step. The ethylene glycol ligand is slower than the boronic acid because of the diminished negative hyperconjugative effect imparted by the dioxaborolane ring. Thus for step 2, $(OH)_2$ > eg > cat. The properties of the boronic ester that favor transmetallation are inversely related for steps 1 and 2, and the optimal boron ligand can depend on the rates of both steps. The experimental results demonstrate that the ethylene glycol boronic ester undergoes the most rapid transmetallation due to the optimal balance between the rate of each step.

Scheme 3.19. Mechanism of transmetallation

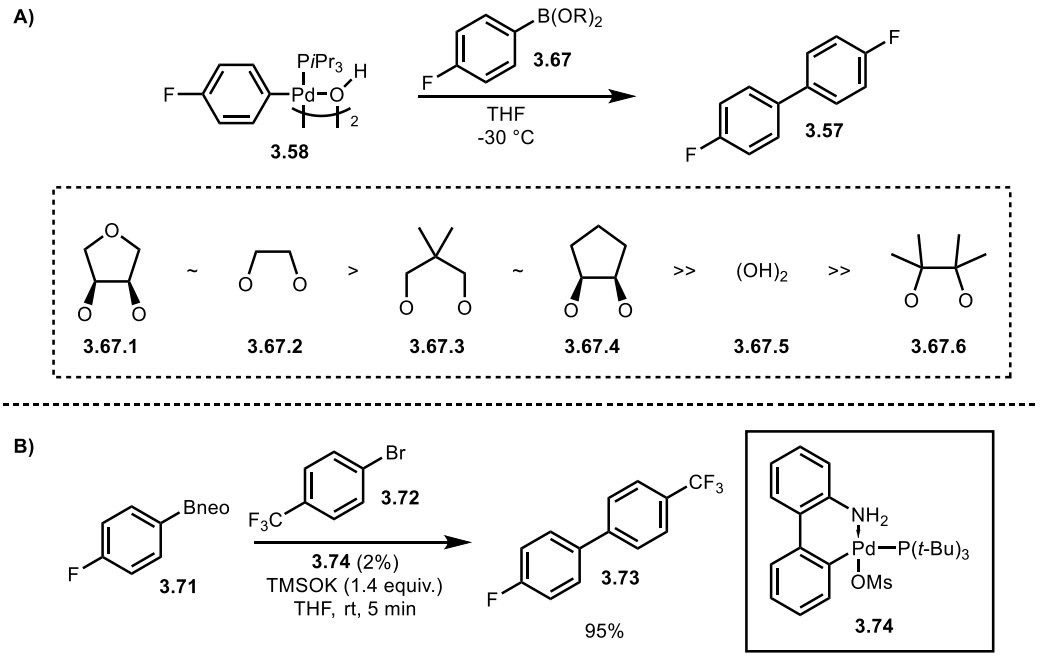


A practical Suzuki-Miyaura cross-coupling reaction of boronic esters was developed based on these results.[43] Under stoichiometric conditions, unhindered boronic esters (**3.67.1**, **3.67.2**, **3.67.3**, and **3.67.4**) give superior rates of transmetallation with Pd complex **3.58** than the corresponding boronic acid (**3.67.4**) (Scheme 3.20.A). For the catalytic reaction, potassium trimethylsilanolate (TMSOK) is an effective base, perhaps due to its high solubility in organic solvent, for the cross-coupling of boronic ester **3.71** with aryl bromide **3.72** in the presence of mono(phosphine) Pd-based catalyst **3.74** (Scheme 3.20.B). Using 2% catalyst loading, the product **3.73** is obtained in quantitative yield within 5 minutes at room temperature. Overall, a complete

[43] Delaney, C. P.; Kassel, V. M.; Denmark, S. E. *ACS Catal.* **2020**, *10*, 73–80.

understanding of the transmetallation step has led to the development of highly efficient Suzuki-Miyaura cross-coupling reactions.

Scheme 3.20. Suzuki-Miyaura cross-coupling of boronic esters



3.3. The conjunctive cross-coupling reaction of β-alkenyl boronates[44]

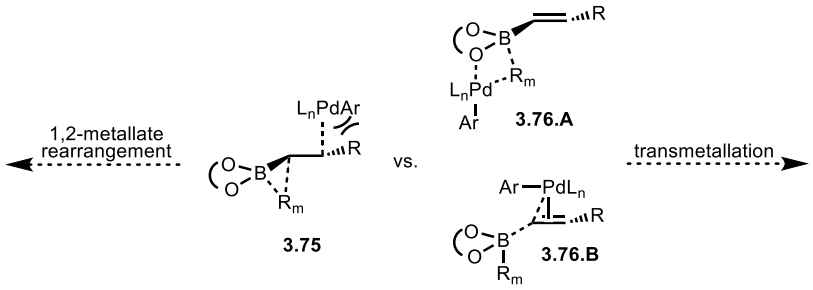
3.3.1. Conjunctive cross-coupling reaction development

The development of the conjunctive cross-coupling reaction of β-substituted alkenyl boronates would allow for synthesis of products containing two contiguous stereocenters in a single reaction. Due to the concerted 1,2-metallate rearrangement, the reaction is expected be highly stereospecific with regard to the stereochemical configuration of the alkene. While this reaction would be a useful synthetic tool, the competing Suzuki-Miyaura cross-coupling reaction is an expected challenge. It is hypothesized that the Pd-induced 1,2-metallate rearrangement transition state (**3.75**, Scheme 3.21) would be greatly penalized by the alkene substituent because

[44] Myhill, J. A.; Wilhelmsen, C. A.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 1518 –15185.

this step requires the formation of a more-hindered secondary alkyl Pd complex. Assuming the transmetallation proceeds by a Pd–O–B linkage (**3.76.A**), this pathway would be unaffected by the distal alkene substituent. However, it is also possible that the transmetallation of the alkenyl group goes through an η^2-Pd–alkene complex (**3.76.B**) rather than a Pd–O–B adduct.[32]

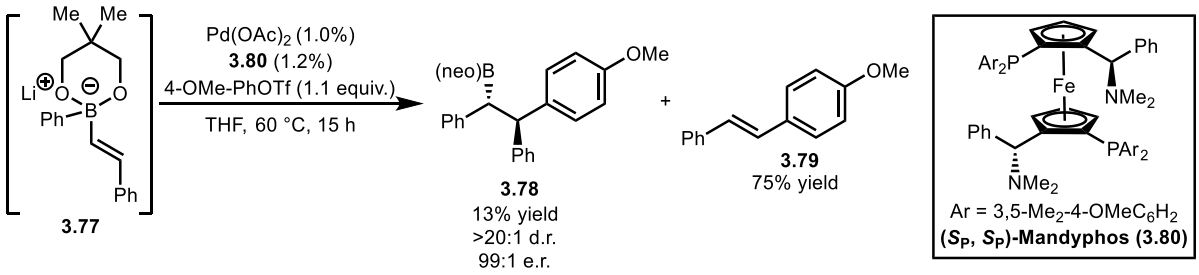
Scheme 3.21. Chemoselectivity in the conjunctive cross-coupling reaction



Initially, the conjunctive cross-coupling reaction with strenylB(neo)-derived 'ate' complex (**3.77**, Scheme 3.22) was investigated according to the optimal reaction conditions for the unsubstituted vinyl boron 'ate' complex.[45] Using 1% $Pd(OAc)_2$ and Mandyphos ligand **3.80** with 4-methoxyphenyltriflate as the electrophile in THF, the desired conjunctive cross-coupling product (**3.78**) is formed in 13% yield after 15 hours. The product **3.78** is obtained as a single diastereomer, and with excellent enantiopurity. However, under these reaction conditions the predominant reaction pathway is the Suzuki-Miyaura cross-coupling reaction, and the stilbene product **3.79** is obtained in 75% yield.

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

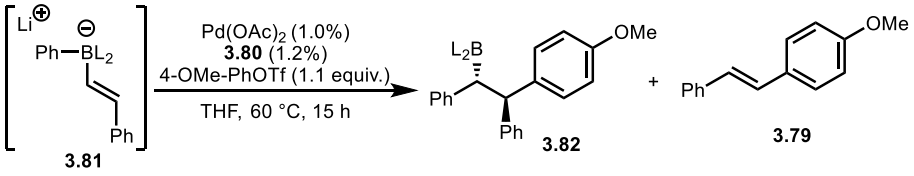
Scheme 3.22. Conjunctive cross-coupling of a β-substituted alkenyl boronate



As described in Chapter 2, the boron ligand may have a remarkable effect on the chemoselectivity of the conjunctive cross-coupling reaction. Specifically, hindered diol ligands disfavor Pd–O binding such that the rate of transmetallation is reduced. Therefore, in order to improve the conjunctive cross-coupling reaction for β-substituted alkenyl boronates, a variety of boron ligands were investigated. 'Ate' complexes **3.81** were subjected to the standard reaction conditions to yield the conjunctive cross-coupling product (**3.82**) and the Suzuki-Miyaura cross-coupling product (**3.79**) (Table 3.3). For neopentyl glycol (**3.81.1**) the Suzuki reaction predominates (Table 3.3, Entry 1), and the rigid cyclopentanediol (**3.81.2**) fails to yield any desired product (Table 3.3, Entry 2). The bulky pinacol boronate (**3.81.3**) results in improved chemoselectivity, and the desired product is obtained in 30% yield (Table 3.3, Entry 3). 1,2-Dimethylcyclopentanediol (**3.81.4**), which has hindered oxygen atoms and a rigid structure, further improves the chemoselectivity; the 1,2-metallate rearrangement is the predominant reaction pathway and the product is isolated in 45% yield (Table 3.3, Entry 4). The steric profile of this ligand is similar to that of pinacol, and the origin of the improved chemoselectivity might be caused by conformational effects imparted by the rigid cyclopentane unit. Along these lines, boronate **3.81.5** was investigated, but led to diminished chemoselectivity compared to **3.81.4** (Table 3.3, Entry 4); this may be attributed to hindered Pd–alkene binding. A similar result is observed for

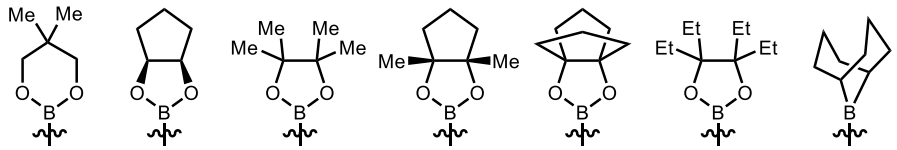
bulky diol **3.81.6**, which led to poor chemoselectivity. The use of a 9-BBN borane-derived 'ate' complex (**3.81.7**) results in excellent chemoselectivity (Table 3.3, Entry 7), which supports the hypothesis that the transmetallation requires a Pd–O–B linkage. Unfortunately, the enantioselectivity for this reaction is low and was unable to be optimized.

Table 3.3. Effect of boron ligand on the conjunctive cross-coupling reaction



Entry	BL_2	**3.82**:**3.79**	**3.82** Yield	d.r.	e.r.
1	**3.81.1**	1:5.8	13% (10%)	>20:1	99:1
2	**3.81.2**	1:>20	<5%	nd	nd
3	**3.81.3**	1:2	35% (30%)	>20:1	98:2
4	**3.81.4**	1.7:1	56% (46%)	>20:1	99:1
5	**3.81.5**	1:2	30%	>20:1	nd
6	**3.81.6**	1:3	20%	>20:1	nd
7	**3.81.7**	>20:1	92% (75%)[a]	>20:1	67:33

[a] Isolated yield after oxidation to the alcohol.

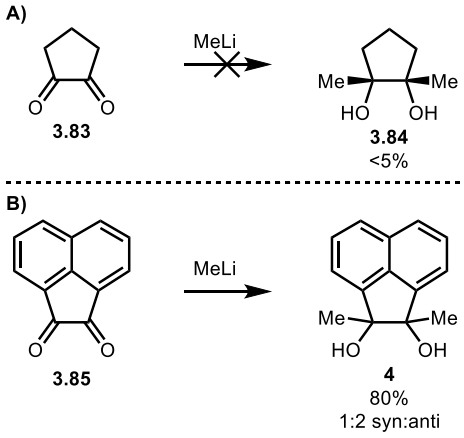


3.81.1 **3.81.2** **3.81.3** **3.81.4** **3.81.5** **3.81.6** **3.81.7**

At this point, further reaction optimization was to be carried out using **3.81.4** as the optimal boronic ester. However, the challenging synthesis of 1,2-dimethylcyclopentanediol (**3.84**) (See section 3.4.2.2), precluded further reaction optimization. Thus, an improved method for the synthesis of **3.84** was proposed to occur by addition of methyllithium to 1,2-cyclopentanedione (**3.83**) (Scheme 3.23.A). The desired product is not obtained from this reaction, likely due to the presence of acidic α-protons of the carbonyl which quench the organolithium reagent. Instead, the

methylation reaction was carried out for a 1,2-dione which lacks α-carbonyl protons, acenaphthoquinone (**3.85**) (Scheme 3.23.B). The methylated acenaphthoquinone product (**4**), referred to as 'mac', is obtained in good yield as a mixture of stereoisomers, with the desired *syn* diastereomer as the minor product (~1:2 d.r.). Notably, the diastereomeric mixture can be enriched to ~1:1 d.r. by treatment with sodium hydride, possibly by equilibration via a reverse pinacol coupling reaction.[46] In order for this diol ligand to enable an investigation of the conjunctive-cross coupling reaction, an improved synthesis had to be developed.

Scheme 3.23. Synthesis of methylated acenaphthoquinone ('mac')

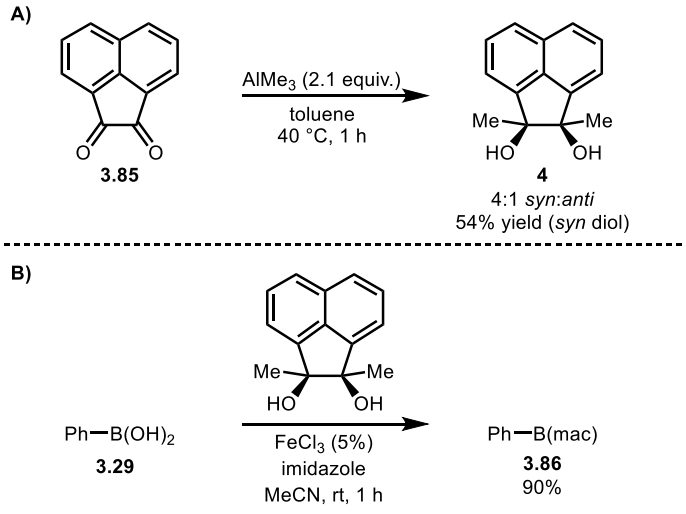


The optimized synthesis of 'mac' diol was achieved by a carbonyl addition reaction of acenaphthoquinone (**3.85**) with trimethylaluminum[47] (4.3:1 *syn*:*anti*) and subsequent recrystallization of the *syn* diol from ethyl acetate (Scheme 3.24.A). The corresponding 'mac' boronate **3.86** is prepared by esterification of boronic acid **3.29** in the presence of a catalytic iron complex within 1 hour at room temperature (Scheme 3.24.B).[48] Based on the results of the boron

[46] Tang, X.; Studer, A. *Org. Lett.* **2016**, *18*, 4448–4450.
[47] Baidossi, W.; Rosenfeld, A.; Wassermann, B. C.; Schutte, S.; Schumann, H.; Blum, J *Synthesis* **1996**, *1996*, 1127–1130.
[48] Wood, J. L.; Marciasini, L. D.; Vaultier, M.; Pucheault, M. *Synlett* **2014**, *25*, 551–555.

ligand investigation described previously, the novel 'mac' diol ligand is expected to perform well in the conjunctive cross-coupling reaction. The rigid, bulky acenaphthene ring hinders the oxygen atoms, while the *syn* methyl groups leave the alkene accessible to facilitate the necessary Pd–alkene binding.

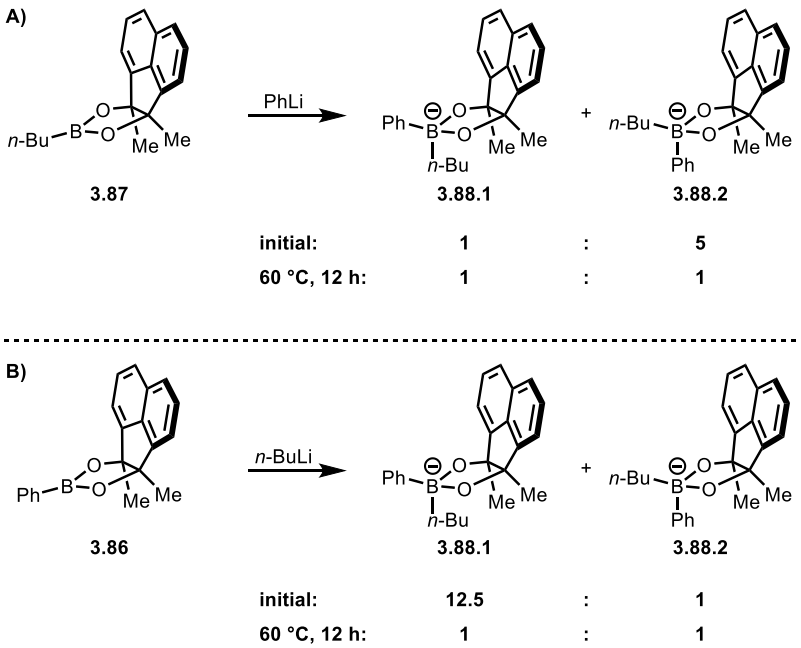
Scheme 3.24. Preparation of 'mac' boronates



Before examining the conjunctive cross-coupling reaction, it was necessary to ensure that such a hindered boronate can effectively form a boron 'ate' complex by treatment with an organolithium reagent. To do this, the 'mac' boronate **3.87** was treated with phenyllithium, which yielded the diastereomeric 'ate' complexes **3.88.1** and **3.88.2** (Scheme 3.25.A). The 'ate' complex formation proceeds to completion as judged by ^{11}B NMR spectroscopy, and the ^{1}H NMR spectrum indicates a 5:1 diastereomer ratio. The major diastereomer (**3.88.2**) arises from addition of the nucleophile *cis* relative to the methyl groups, as determined by NOESY NMR spectroscopy. The opposite diastereomer (**3.88.1**) is favored in a 12.5:1 diastereomer ratio by addition of *n*-butyllithium to phenylB(mac) (**3.86**) (Scheme 3.25.B). Thus, the kinetic product of 'ate' complex formation occurs by addition of the nucleophile *syn* to the methyl groups rather than the bulky

acenaphthene group. The diastereomeric 'ate' complexes might display different reactivity profiles in the conjunctive cross-coupling reaction, thereby leading to unpredictable trends in reactivity based on the method of 'ate' complex formation. However, the 'ate' complexes are not configurationally stable at 60 °C, which is the standard reaction temperature for the conjunctive cross-coupling reaction. Within 12 hours, an equilibrium 1:1 diastereomer ratio is reached for both methods of 'ate' complex formation. Notably, the interconversion is accelerated by Lewis acids, and perhaps occurs by a mechanism in which an oxygen ligand undergoes reversible dissociation from boron. Therefore, the diastereomeric 'ate' complexes are in equilibrium under standard conjunctive cross-coupling reaction conditions, and the initial composition of the 'ate' complex mixture will likely be inconsequential to the subsequent reaction.

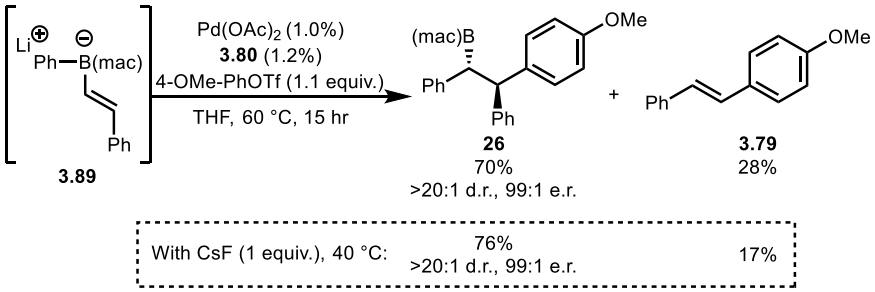
Scheme 3.25. Diastereomeric 'ate' complexes



The B(mac)-derived 'ate' complex **3.89** shows superior performance in the conjunctive cross-coupling reaction under standard conditions, and the desired product (**26**) is obtained in 70%

yield, along with 28% of **3.79** (Scheme 3.26). The chemoselectivity of the reaction is slightly improved by conducting at decreased temperature (40 °C), although the reaction does not reach full conversion. The conversion of the reaction at this temperature is improved in the presence of a stoichiometric amount of cesium fluoride, which is thought to form a more-nucleophilic Cs^+–'ate' complex,[49] delivering **26** in 76% yield.

Scheme 3.26. Conjunctive cross-coupling reaction with a 'mac' boronate



3.3.2. Scope of the conjunctive cross-coupling reaction

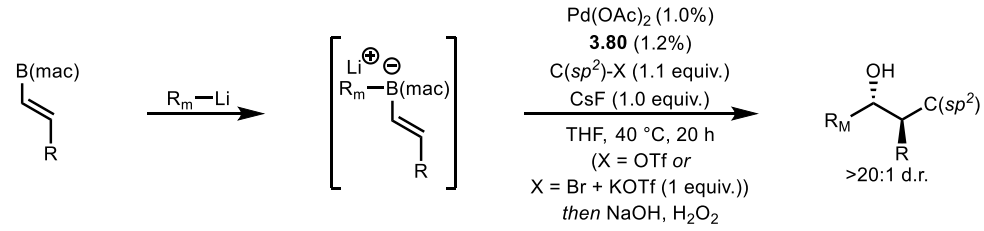
A variety of 'mac' boronic ester 'ate' complexes were examined in the conjunctive cross-coupling reaction. The 'ate' complex is treated with CsF, then subjected to the conjunctive cross-coupling reaction with 1% $Pd(OAc)_2$, 1.2% MandyPhos ligand (**3.80**), and the electrophile in THF at 40 °C for 20 hours (Scheme 3.27). Due to the poor solubility of the reaction products in organic solvents, they were oxidized and then isolated as the corresponding alcohols. The reaction is particularly effective with electron-rich and electron-neutral electrophiles (**2b-OH**, **7**). Electron-withdrawing substituents on the electrophile are tolerated, but result in diminished yield due to the unfavorable chemoselectivity of the reaction (**8–9**). A possible explanation for the observed chemoselectivity trend is that the requisite Pd–alkene binding for the 1,2-metallate rearrangement

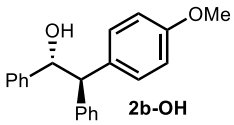
[49] Cation exchange of Li^+ to NMe_4^+ has been reported to improve the reactivity of a boron 'ate' complex in a related process: Ishida, N.; Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 42, 4381–4383

pathway is less favorable for an electron-deficient Pd center due to the diminished backbonding capability. Both aryl triflates and aryl bromides can be employed, provided that potassium triflate is added to counteract the effect of halide byproducts.[50] The reactions of aryl bromides are often more convenient due to the commercial availability of these reagents, but triflates provide superior yield for the reaction. Heteroaryl electrophiles (**10–11**) and alkenyl electrophiles (**12**) are also tolerated. Substituted aryl migrating groups (**13–14**) exhibit good reactivity, but a highly substituted alkenyl migrating group (**15**) results in unusually poor enantioselectivity. Heteroaryl migrating groups are tolerated as well (**16–18**). Notably, alkyl migrating groups are not effective under these conditions, providing the Suzuki-Miyaura cross-coupling product exclusively. The origin for this chemoselectivity has not been determined, but it is thought to be due to electronic rather than steric effects; neither *n*-Bu, *i*Pr, nor *t*-Bu migrating groups participate in the conjunctive cross-coupling reaction despite their range of steric profiles. Perhaps the decreased electronegativity of alkyl groups compared to aryl groups leads to higher partial negative charge on the oxygen atoms, which facilitates transmetallation. Substrates with β-alkyl substituents are effective (**19–20**), and functional groups such as an alkyl chloride (**21**) and a protected alcohol (**22**) can be incorporated. For aromatic alkene substituents, electron-donating groups (**23**) and electron-withdrawing groups (**24–25**) can be tolerated. Notably, the nature of this substituent has a pronounced effect on both the reactivity and chemoselectivity of this process. Electron-rich substituents lead to improved conversion but poorer chemoselectivity compared to their electron-deficient counterparts; the latter substrates react at increased temperature (60 °C) but exhibit more favorable chemoselectivity despite the elevated temperature.

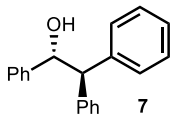
[50] Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc*. **2017**, *139*, 3153–3160.

Scheme 3.27. Scope of the conjunctive cross-coupling reaction

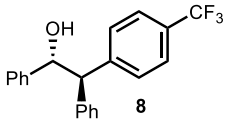




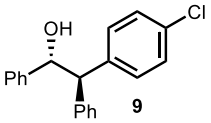
X = OTf: 73%, >99:1 er
X = Br: 59%, >99:1 er



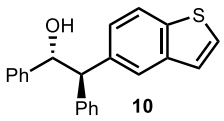
X = OTf: 86%, >99:1 er
X = Br: 43%, >99:1 er



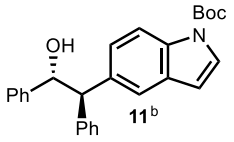
X = OTf: 40% 98:2 er
X = Br: 44%, 98:2 er



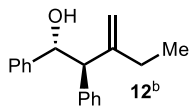
X = Br: 46% 99:1 er



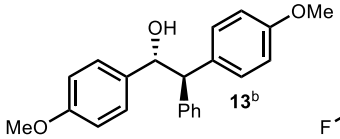
X = Br: 43% 99:1 er



X = Br: 58% 99:1 er



X = Br: 60%, >99:1 er



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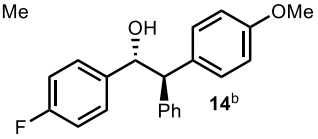
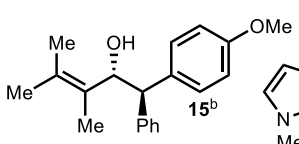


X = OTf: 64%, 99:1 er



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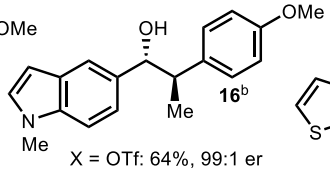

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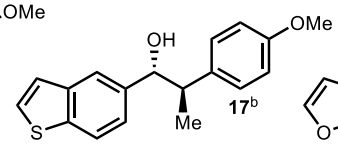
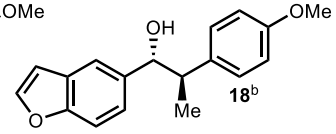
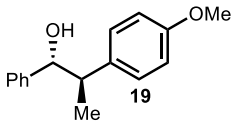


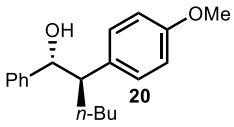
X = OTf: 57%, 99:1 er



X = OTf: 47%, 99:1 er



X = OTf: 65%, 99:1 er



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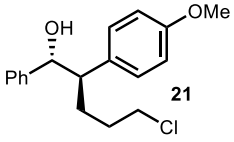

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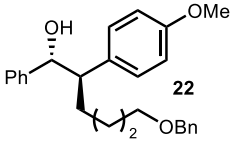
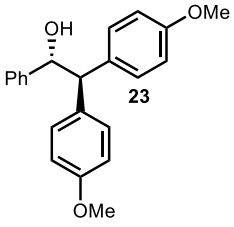
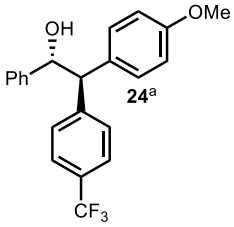


X = OTf: 50%, 99:1 er



X = OTf: 46%, 99:1 er



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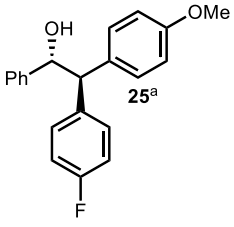


X = OTf: 62%, 99:1 er

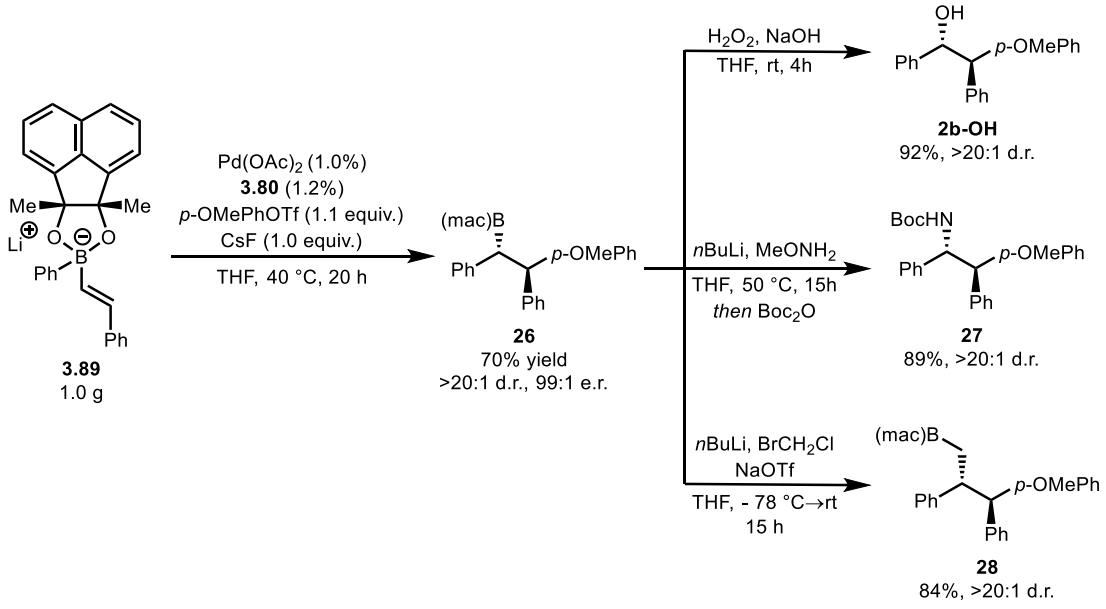
[a]Reaction conducted at 60 °C

[b]Reaction conducted with 2% Pd and 2.2% **3.80**

3.3.3. Synthetic utility of 'mac' boronates

A gram-scale reaction provided 'mac' boronate **26** with similar reaction efficiency and selectivity compared to the small-scale reaction, and this compound was used to investigate transformations of the organoboronate product (Scheme 3.28). The oxidation reaction proceeds in high yield to furnish secondary alcohol **2b-OH**. Amination of the boronate yields carbamate **27** after protection of the free amine.[51] Lastly, the boronate undergoes a modified Matteson homologation reaction to yield **28**.[52] Overall, the reactivity of 'mac' boronates is similar to that of pinacol boronates in terms of 'ate' complex formation and the subsequent 1,2-metallate rearrangement.

Scheme 3.28. Gram scale reaction and product derivatization

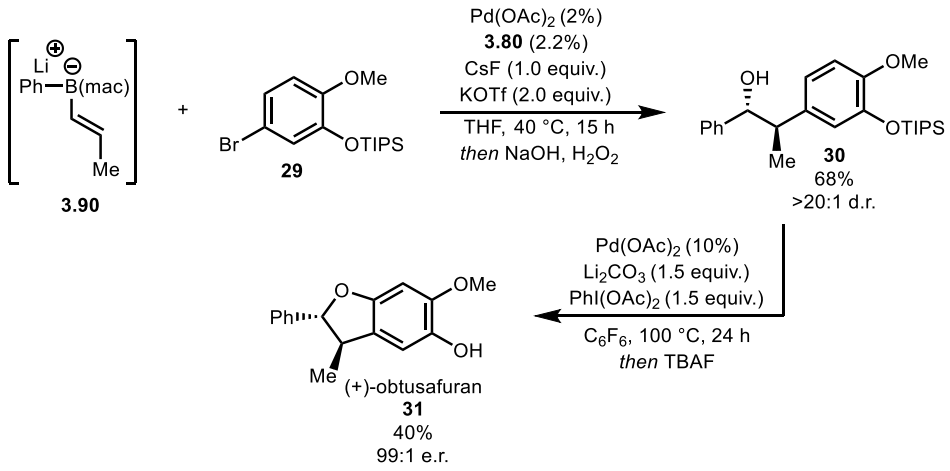


The ability to construct two C–C bonds and establish two contiguous stereocenters in a single reaction allows for the concise synthesis of complex molecules. This is demonstrated by

[51] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc*. **2012**,*134*, 16449–16451.
[52] Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem., Int. Ed*. **2011**, *50*, 3760–3763.

the synthesis of obtusafuran[53] (**31**, Scheme 3.29) in two steps. Obtusafuran is a lignin natural product which displays a wide range of biological activities.[54] The 'ate' complex derived from propenylB(mac) and phenyllithium (**3.90**), undergoes the conjunctive cross-coupling reaction with aryl bromide **29** to rapidly establish intermediate **30**, following oxidation. Next, a C–H oxidation[55] reaction forms the dihydrobenzofuran ring, and then silyl ether deprotection yields the natural product (**31**).

Scheme 3.29. Synthesis of obtusafuran



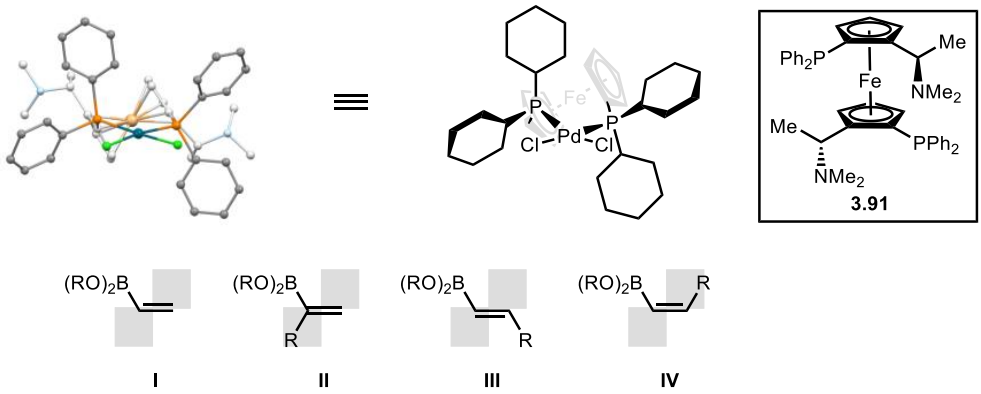
3.3.4. Stereochemical model

A tentative stereochemical model for the Pd-catalyzed conjunctive cross-coupling reaction is shown in Scheme 3.30. Based on the crystal structure of $PdCl_2$ complexed with Mandyphos derivative **3.91**,[56] the chelation of the phosphine ligands with Pd forms a rigid ring system in which the phosphino arene groups are positioned in a pseudo-axial or pseudo-equatorial conformation.

[53] Gregson, M.; Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Dietrichs, H. H.; Gottlieb, O. R. *Phytochemistry* **1978**, *17*, 1395-1400.
[54] Chen, C.-y.; Weisel, M. *Synlett* **2013**, *24*, 189–192.
[55] (a) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc*. **2010**, *132*, 12203–12205. (b) Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc*. **2013**, *135*, 6774–6777.
[56] Hayashi, T.; Yamamoto, A.; Hojo, M.; Kishi, K.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Organomet. Chem.* **1989**, *370*, 129–139.

Based on the C_2 symmetry element of this structure, it can be approximated as a quadrant diagram in which the arenes that are projected forward sterically block opposite quadrants (Scheme 3.30, **I**-**IV**). During the stereochemistry-determining Pd-induced 1,2-metallate rearrangement step of the conjunctive cross-coupling reaction, the alkene of the boronate likely binds to palladium such that the bulky boronate group is situated in a vacant quadrant. For unsubstituted vinylboronates (**I**), the enantioselectivity of the reaction is high (typically ~95% e.e.) because the other prochiral face of the alkene results in steric clash of the boronate with the phosphino substituent. However, for α-substituted alkenyl boronates (**II**), the added substituent must occupy a hindered quadrant such that the bias between the prochiral faces is diminished. These reactions result in diminished levels of enantioselectivity (typically ~90% e.e.). The *trans*-β-substituted alkenyl boronate substrates (**III**) undergo a highly enantioselective reaction (>98% e.e.) because the added substituent occupies the other vacant quadrant in the major transition state. This substituent also reinforces the steric penalty of the disfavored alkene face, such that the bias between the prochiral faces is larger. Lastly, *cis*-β-substituted alkenyl boronates (**IV**) undergo non-selective reactions (<10% e.e.) because unfavorable steric interactions are introduced regardless of which alkene face Pd binds to. It should be noted that these diagrams do not completely reflect the complexity of the conjunctive cross-coupling reaction. Most importantly, the active Pd species involved in 1,2-metallate rearrangement step is not C_2 symmetric, but rather a cationic Pd oxidative addition adduct. Nevertheless, such a model is consistent with the experimentally observed trends in enantioselectivity based on the alkene substitution pattern.

Scheme 3.30. Stereochemical model for the Pd-catalyzed conjunctive cross-coupling reaction



3.3.5. Conclusion

The conjunctive cross-coupling reaction with a β-substituted alkenyl boron 'ate' complex enables the construction of two stereocenters in a single catalytic reaction. Initial experimental results demonstrated that the 1,2-metallate rearrangement reaction pathway is unfavorable relative to the transmetallation reaction pathway. However, the chemoselectivity of this process is altered by modifying the diol ligand on boron. In general, hindered diol ligands favor the 1,2-metallate rearrangement over transmetallation, and a novel 'mac' ligand on boron was developed as a convenient solution to this problem. The 'mac' boronate substrates for this reaction are easily obtained from simple starting materials, and they undergo the conjunctive cross-coupling reaction effectively. Furthermore, 'mac' boronates undergo C–B bond transformations with comparable efficiency to pinacol boronates, which enables a concise synthesis of the natural product (+)-obtusafuran. Further studies on this reaction should focus on a complete model for the origin of chemoselectivity with the 'mac' ligand, as this could enable further reaction optimization.

3.4. Experimental section

3.4.1. General information

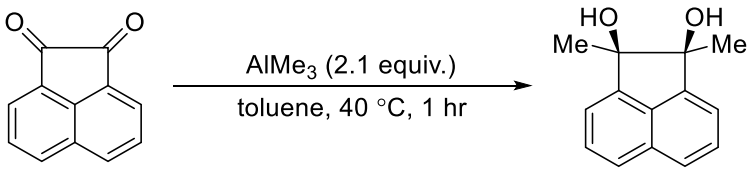
^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), Varian Gemini-600 (600 MHz), or Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, 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 Gemini-500 (126 MHz), Varian Gemini-600 (151 MHz) or a Varian Inova-500 (126 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 Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer. 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. 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, and cerium(IV) sulfate in ethanol with sulfuric acid (magic stain).

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

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. 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 argon. Palladium (II) acetate, Mandyphos **3.80**, and 1,1'-Bis(diisopropylphosphino)ferrocene were purchased from Strem Chemicals, Inc. and used without further purification. 1,3-Bis(diphenylphosphino)propane was purchased from TCI and used without further purification. Acenaphthylene-1,2-dione, 4-methoxyphenyl trifluoromethanesulfonate, phenyl trifluoromethanesulfonate, and cesium fluoride were purchased from Oakwood Chemicals and used without further purification. Potassium trifluoromethanesulfonate was purchased from Oakwood Chemicals and dried by heating (100 ºC) under vacuum overnight. Alkenyl boronic acids were prepared by hydroboration of alkynes with $HBBr_2$ followed by hydrolysis.[57] All other reagents were purchased from Aldrich, Alfa Aesar, Acros, Combi Blocks, or Oakwood Chemicals and used without further purification.

3.4.2. Experimental procedures

3.4.2.1. Preparation of 1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol (mac) (4)

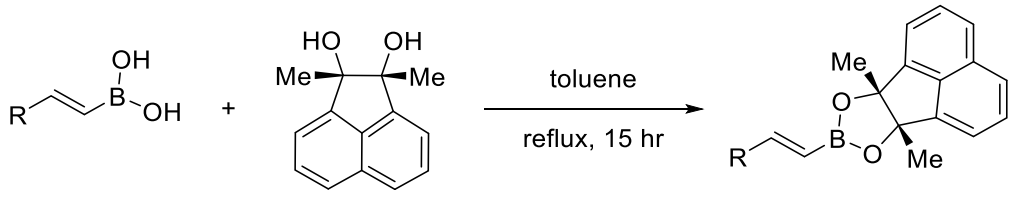


A flame-dried 3-neck 1000 mL RBF was equipped with stir bar, a reflux condenser fitted to the

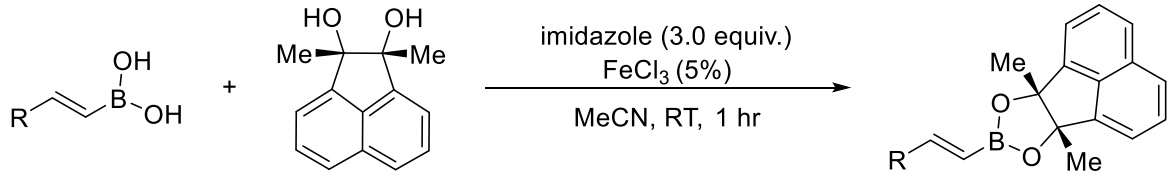
[57] Holt, D.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 7857.

middle neck, and the other two necks were sealed with rubber septa. Acenaphthoquinone (18.22 g, 100 mmol) was added, and the flask was evacuated and backfilled with nitrogen. Dry toluene (100.0 mL, [substrate] = 1.00 M) was added via syringe, and the yellow suspension was stirred at 40 ºC. Trimethyl aluminum (20.1 mL, 210.0 mmol, 2.1 equiv.) was added dropwise via syringe (a 12 mL syringe was used to transfer 5 mL aliquots dropwise). Upon completion of addition, the reaction was allowed to stir for 1 hour at 40 ºC, then cooled to 0 ºC and quenched very slowly with 40 ml H_2O and 20 ml 1M HCl (caution: gas evolution). The reaction was diluted with EtOAc and filtered through a frit funnel, then the filtrate was poured into separatory funnel containing water (200 mL). The organic layer was washed three times with EtOAc (300 mL) then the combined organic layers were washed 3 times with brine, then dried over Na_2SO4, filtered, and concentrated. ^1H NMR analysis of the crude material indicates ~4.3:1 syn:anti diol. The crude product was dissolved in hot EtOAc (750 mL) and stored at -20 ºC overnight. The resulting precipitate was collected by filtration and rinsed with pentane to yield *syn*-1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol as off-white crystals (11.5 g, 53.7 mmol, 54% yield). Suspected losses in yield due to insolubility when transferring between vessels. ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.56 (t, J = 7.5 Hz, 2H), 7.48 (d, J = 6.9 Hz, 2H), 2.97 (s, 2H), 1.63 (s, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.36, 134.51, 131.34, 128.68, 125.07, 119.33, 82.38, 23.53.; HRMS (DART) for $C_{14}H_{13}O$ $[M+H-H_2O]^+$: calculated: 197.0961, found: 197.0956.

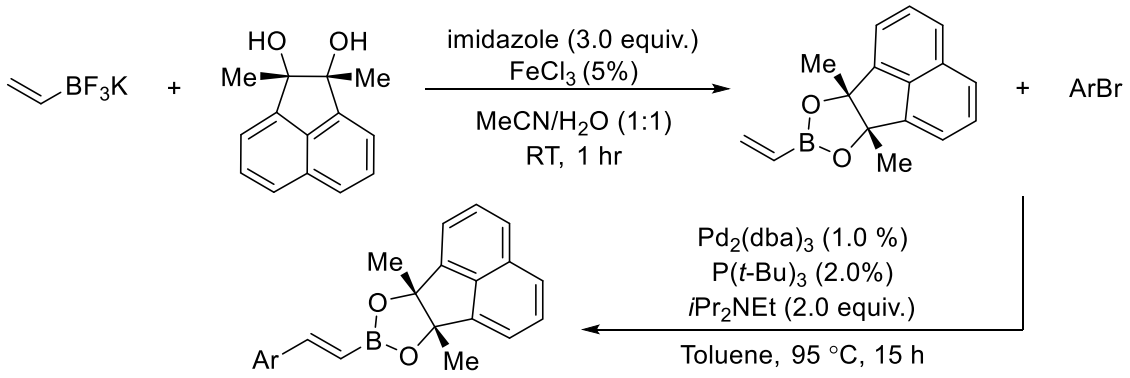
3.4.2.2. Procedures for the preparation of alkenyl boronic esters



Method A: To a 100-mL RBF equipped with a stir bar was added alkenyl boronic acid (3.0 mmol, 1.0 equiv.) and toluene (12 mL). 1,2-Dimethylacenaphthylene-1,2-diol (3.0 mmol, 1.0 equiv.) was added and a Dean-Stark apparatus equipped with a reflux condenser was attached to the flask. The reaction was heated to reflux for 15 hours then concentrated under vacuum. The crude product was purified by silica gel chromatography to afford the desired product. *This method can be used to synthesis boronic esters containing other diol ligands.*



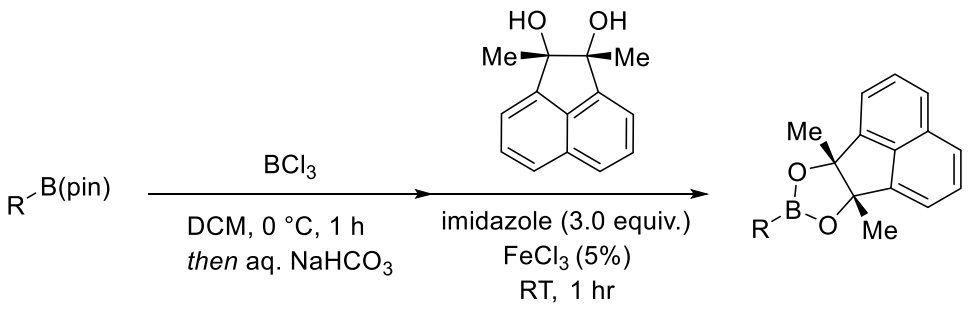
Method B: According to a modified literature procedure.[48] To a scintillation vial equipped with a stir bar was added alkenyl boronic acid (3.0 mmol, 1.0 equiv.) and MeCN (12.00 mL). To this solution was added sequentially 1,2-dimethylacenaphthylene-1,2-diol (3.00 mmol, 1.0 equiv.), imidazole (9.00 mmol, 3 equiv.), and $FeCl_3$ (60.00 μmol, 0.05 equiv.). The reaction was then stirred at room temperature open to air for 1 hour before being filtered through a pad of silica gel with Et_2O. The crude product was purified by silica gel chromatography to afford the desired product. *This method can be used to synthesis boronic esters containing other diol ligands.*



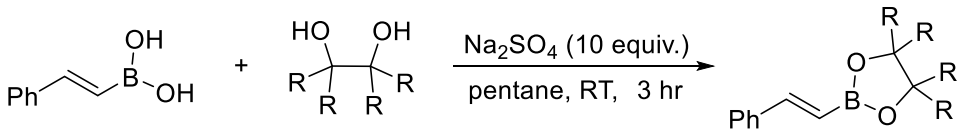
***Method C*:** VinylB(mac) was prepared according to a modified literature procedure, as follows.[48] To a solution of vinyl potassium trifluoroborate (343.9 mg, 2.57 mmol, 1.0 equiv.) in 50% acetonitrile/water (5 mL) was added sequentially open to air at room temperature, 1,2-dimethylacenaphthylene-1,2-diol (550 mg, 2.57 mmol, 1.0 equiv.), imidazole (524.3 mg, 7.70 mmol, 3.0 equiv.), and $FeCl_3$ (20.8 mg, 0.128 mmol, 0.05 equiv.). The reaction was allowed to stir 30 minutes, then filtered through a plug of silica gel with Et_2O and concentrated. The crude material was purified by silica gel column chromatography to affored the desired product (typically 90% yield). The Heck reaction was carried out according to a modified literature procedure.[58] In an argon-filled glovebox, vinylB(mac) (750.30 mg, 3 mmol, 1.0 equiv.), aryl bromide (3.30 mmol, 1.1 equiv.), N,N-diisopropylethylamine (1.05 mL, 6.00 mmol, 2.0 equiv.), tris(dibenzylideneacetone)dipalladium(0) (27.47 mg, 30.00 μmol, 1.0 mol%), tri-*tert*-butylphosphine (10% weight in hexanes, 121.39 mg, 60.00 μmol, 2.0 mol%), and toluene (6.00 mL) were added to an oven-dried scintillation vial equipped with a stir-bar. The vial was sealed and removed from the glovebox. The reaction was then heated to 95 ºC overnight, filtered through a plug of silica gel with Et_2O, and concentrated. The crude product was purified by column

[58] Liu, Z.; Wei, W.; Xiong, L.; Feng, Q.; Shi, Y.; Wang, N.; Yu, L. *New J. Chem.*, **2017**, *41*, 3172.

chromatography with silica gel. *This method can be used to synthesis boronic esters containing other diol ligands.*



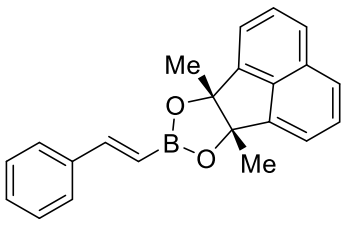
Method D: Boron trichloride (1 M solution in DCM, 17.5 mL, 17.5 mmol, 5.0 equiv.) was added to a solution of boronic acid pinacol ester (3.5 mmol, 1.0 equiv.) in DCM (3.50 mL) at – 78 ºC. The mixture was stirred at 0 ºC for 1 hour, then quenched with saturated aqueous sodium bicarbonate solution (3.5 mL), and the reaction was warmed to room temperature. To this solution was added 1,2-dimethylacenaphthylene-1,2-diol (3.5 mmol, 1.0 equiv.), imidazole (10.5 mmol, 3.0 equiv.), and $FeCl_3$ (0.18 mmol, 0.05 equiv.). The reaction was stirred for 1 hour at room temperature then filtered through a plug of silica gel with Et_2O and concentrated. The crude product was purified by column chromatography with silica gel. *This method can be used to synthesis boronic esters containing other diol ligands.*



Method E: To a 100-mL RBF equipped with a stir bar was added alkenyl boronic acid (3.0 mmol, 1.0 equiv.) and pentane (12 mL, 0.25 M). The diol (3.0 mmol, 1.0 equiv.) was added followed by anhydrous sodium sulfate (30 mmol, 10.0 equiv.). The reaction was allowed to stir at room temperature for 3 hours, then the reaction mixture was filtered through a cotton plug with Et_2O and concentrated. The crude product was purified by silica gel chromatography to afford the desired product.

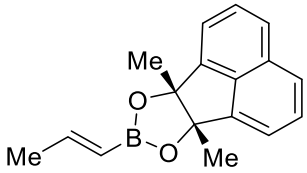
***When to Use Each Method*:**

In instances when boronic acids or potassium trifluoroborates are readily available, Method B is preferred due to operational simplicity, reaction efficiency, and simple product purification. However, if the substrate contains acid-sensitive functionality then Method A or Method E should be used instead. Additionally, if the resulting boronic ester is not stable to silica gel chromatography, then Method E is preferred. In instances when a pinacol boronic ester is more easily obtained than the corresponding boronic acid, Method D is utilized (this method should be avoided if the substrate contains acid-sensitive functionality). Method B is utilized for the synthesis of styrenyl boronic esters as an alternative to the hydroboration of terminal alkynes.



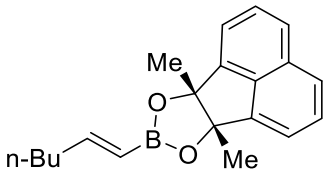
6b,9a-dimethyl-8-((E)-styryl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-1). The title compound was prepared according to Method A with [(E)-styryl]boronic acid (500 mg, 3.38 mmol, 1.0 equiv.), 1,2-dimethylacenaphthylene-1,2-diol (723 mg, 3.38 mmol, 1.0 equiv.), and toluene (15 mL). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (1.05 g, 3.21 mmol, 95% yield) as a white solid.

The title compound was also prepared according to Method B with [(E)-styryl]boronic acid (443.90 mg, 3 mmol, 1.0 equiv.), MeCN (12 mL), $FeCl_3$ (24.33 mg, 150 μmol, 0.05 equiv), imidazole (612.72 mg, 9.00 mmol, 3.0 equiv.), and 1,2-dimethylacenaphthylene-1,2-diol (642.78 mg, 3.00 mmol, 1.0 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (881 mg, 2.70 mmol, 90% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 6.9, 2.1 Hz, 2H), 7.67 – 7.57 (m, 4H), 7.42 (d, J = 7.2 Hz, 2H), 7.36 (d, J = 18.4 Hz, 1H), 7.33 – 7.23 (m, 3H), 6.10 (d, J = 18.4 Hz, 1H), 1.85 (s, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.4, 147.4, 140.1, 137.4, 134.1, 131.5, 131.2, 131.2, 129.7, 128.0, 122.2, 94.7, 79.9, 79.7, 79.5, 24.8.; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.3.; IR (neat) ν_{max} 3024.6 (w), 2972.4 (w), 2932.9 (w), 1622.7 (s), 1450.0 (m), 1433.7 (m), 1313.1 (s), 1139.6 (s), 788.5 (m), 480.5 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{20}BO_2$ $[M+H]^+$ calculated: 327.1556, found: 327.1543.



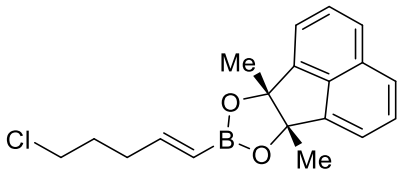
6b,9a-dimethyl-8-((E)-prop-1-en-1-yl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-2). The title compound was prepared according to Method B with [(E)-prop-1-

enyl]boronic acid (379 mg, 4.41 mmol, 1.0 equiv.), MeCN (11 mL), 1,2-dimethylacenaphthylene-1,2-diol (1.35 g, 4.41 mmol, 1.0 equiv.), imidazole (901 mg, 13.2 mmol, 3.0 equiv.), and FeCl3 (36 mg, 221 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (1.12 g, 4.24 mmol, 96% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.65 – 7.52 (m, 4H), 6.69 – 6.56 (m, 1H), 5.40 (d, J = 17.8 Hz, 1H), 1.84 – 1.74 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.98, 144.8, 134.7, 131.3, 128.4, 125.2, 119.4, 91.7, 22.1, 21.6. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 29.9; IR (neat) ν_{max} 3044.5 (w), 2973.6 (m), 2933.7 (w), 1639.4 (s), 1347.6 (m), 1214.4 (m), 1077.7 (m), 777.8 (m) cm^{-1}. HRMS (DART) for for $C17H18BO_2$ $[M+H]^+$: calculated: 265.1400, found: 265.1393.

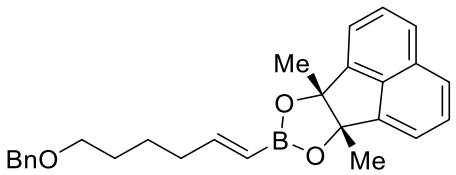


8-((E)-hex-1-en-1-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-3). The title compound was prepared according to Method B with [(E)-hex-1-enyl]boronic acid (213 mg, 1.67 mmol, 1.0 equiv.), MeCN (6.7 mL), 1,2-dimethylacenaphthylene-1,2-diol (357 g, 1.67 mmol, 1.0 equiv.), imidazole (340 mg, 5.00 mmol, 3.0 equiv.), and $FeCl_3$ (13.5 mg, 83 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (465 mg, 1.52 mmol, 91% yield) as a yellow oil which solidified upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.9, 1.1 Hz, 2H), 7.65 – 7.51 (m, 4H), 6.61 (dt, J = 18.0, 6.5 Hz, 1H), 5.38 (d, J = 17.9 Hz, 1H), 2.14 – 2.06 (m, 2H), 1.81 (s, 6H), 1.41 – 1.21 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 144.9, 134.7, 131.3, 128.4, 125.2, 119.4, 91.7, 35.4, 30.3, 22.2, 22.1, 13.9. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.0; IR (neat) ν_{max} 3045.2 (w), 2956.9 (m), 2928.2 (m), 2856.8 (w), 1638.0 (m),

1355.2 (m), 1310.6 (m), 1116.4 (m), 1078.4 (m), 805.8 cm^{-1}. HRMS (DART) for $C_{20}H_{24}BO_2$ $[M+H]^+$: calculated: 307.1869, found: 307.1882.

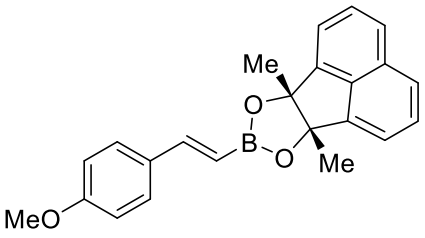


8-((E)-5-chloropent-1-en-1-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-4). The title compound was prepared according to Method B with (E)-(5-chloropent-1-en-1-yl) boronic acid (367 mg, 2.46 mmol, 1.0 equiv.), MeCN (13 mL), 1,2-dimethylacenaphthylene-1,2-diol (527 mg, 2.46 mmol, 1.0 equiv.), imidazole (503 mg, 7.39 mmol, 3.0 equiv.), and $FeCl_3$ (20 mg, 123 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (530 mg, 1.62 mmol, 66% yield) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (dt, J = 8.0, 1.1 Hz, 2H), 7.63 – 7.53 (m, 4H), 6.59 – 6.50 (m, 1H), 5.42 (dq, J = 17.9, 1.5 Hz, 1H), 3.50 – 3.45 (m, 2H), 2.28 – 2.21 (m, 2H), 1.88 – 1.81 (m, 2H), 1.80 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.5, 144.9, 134.8, 131.5, 128.6, 125.4, 119.6, 91.9, 44.4, 32.8, 31.0, 22.2. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 29.73; IR (neat) ν_{max} 3042.8 (w), 2975.0 (w), 2933.3 (w), 1637.7 (m), 1347.5 (m), 1311.14 (m), 1114.9 (m), 1076.1 (m), 825.3 (m), 777.6 (s), 640.4 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{20}BClO_2$ $[M+H]^+$ calculated: 327.1323, found: 327.1334.



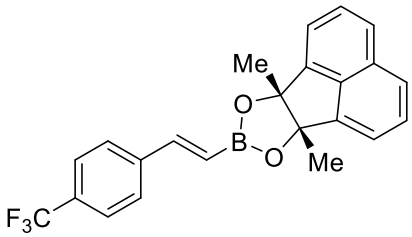
8-((E)-6-(benzyloxy)hex-1-en-1-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-5). The title compound was prepared according to Method B with (E)-(6-(benzyloxy)hex-1-en-1-yl)boronic acid (497 mg, 2.12 mmol, 1.0 equiv.), MeCN (13 ml), 1,2-dimethylacenaphthylene-1,2-diol (453 mg, 2.12 mmol, 1.0 equiv.), imidazole (433 mg,

6.37 mmol, 3.0 equiv.) and $FeCl_3$ (17.2 mg, 106 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (629 mg, 1.53 mmol, 72% yield) as a thick, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 2H), 7.63 – 7.54 (m, 4H), 7.39 – 7.26 (m, 5H), 6.65 – 6.55 (m, 1H), 5.42 – 5.35 (m, 1H), 4.47 (s, 2H), 3.46 – 3.40 (m, 2H), 2.16 – 2.07 (m, 2H), 1.81 (s, 6H), 1.64 – 1.53 (m, 2H), 1.51 – 1.42 (m, 2H) ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5, 144.9, 138.7, 134.7, 131.4, 128.5, 128.4, 127.6, 127.5, 125.3, 119.5, 91.7, 72.9, 70.2, 35.5, 29.3, 24.8, 22.2. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 29.94; IR (neat) ν_{max} 3031.0 (w), 2972.4 (w), 2932.6 (w), 2855.4 (w), 1637.1 (m), 1354.9 (m), 1339.4 (m), 1114.4 (m), 1076.0 (m), 805.8 (m), 777.9 (m), 733.4 (m), 696.6 (m), 641.8 (m) cm^{-1}. HRMS (DART) for $C_{27}H_{29}BO_3$ $[M+H]^+$ calculated: 413.2288, found:413.2304.

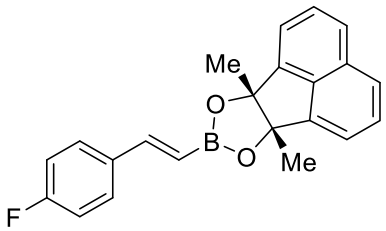


8-((E)-4-methoxystyryl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-6). The title compound was prepared according to Method B with [(E)-2-(4-methoxyphenyl)vinyl]boronic acid (186 mg, 1.04 mmol, 1.0 equiv.), MeCN (4.2 mL), 1,2-dimethylacenaphthylene-1,2-diol (223.49 mg, 1.04 mmol, 1.0 equiv.), imidazole (213 mg, 3.13 mmol, 3.0 equiv.), and $FeCl_3$ (8.5 mg, 52.2 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (353 mg, 0.99 mmol, 95% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 6.7, 2.2 Hz, 2H), 7.65 – 7.56 (m, 4H), 7.40 – 7.35 (m, 2H), 7.32 (d, J = 18.4 Hz, 1H), 6.83 (d, J = 8.5 Hz, 2H), 5.95 (d, J = 18.3 Hz, 1H), 3.79 (s, 3H), 1.85 (s, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 149.2, 144.78, 134.7, 131.4, 130.3, 128.5, 128.4, 125.3, 119.4, 113.9, 91.9, 55.2, 22.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 31.0.; IR (neat) ν_{max} 3041.3 (w),

2972.0 (w), 2932.7 (w), 2836.1 (w), 1623.7 (m), 1603.1 (m), 1509.4 (m), 1312.9 (m), 1252.7 (m), 1116.0 (m), 1077.2 (m), 815.7 (m) cm^{-1}. HRMS (DART) for $C_{23}H_{22}BO_3$ $[M+H]^+$: calculated: 357.1662, found: 357.1664.

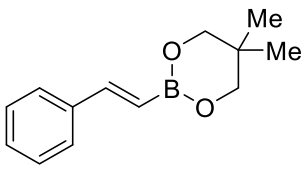


6b,9a-dimethyl-8-((E)-4-(trifluoromethyl)styryl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-7). The title compound was prepared according to Method B with [(E)-2-[4-(trifluoromethyl)phenyl]vinyl]boronic acid (164 mg, 0.76 mmol, 1.0 equiv.), MeCN (3.0 mL), 1,2-dimethylacenaphthylene-1,2-diol (163 mg, 0.76 mmol, 1.0 equiv.), imidazole (155 mg, 2.28 mmol, 3.0 equiv.), and $FeCl_3$ (6.2 mg, 38 μmol). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (276 mg, 0.70 mmol, 92% yield) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (dt, J = 7.2, 1.6 Hz, 2H), 7.70 – 7.59 (m, 4H), 7.56 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 18.3 Hz, 1H), 6.20 (d, J = 18.4 Hz, 1H), 1.87 (s, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 144.5, 140.7, 134.7, 131.4, 130.4 (q, $^2J_{C-F}$ = 32.4 Hz), 128.5, 127.1, 125.5 (q, $^3J_{C-F}$ = 3.8 Hz), 125.4, 124.1 (partially buried, q, $^1J_{C-F}$ = 271.8 Hz), 119.5, 92.2, 29.7, 22.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.3.; ^{19}F NMR (470 MHz, $CDCl_3$) δ 62.7.; IR (neat) ν_{max} 3045.7 (w), 2974.7 (w), 2929.0 (w), 1626.9 (m), 1457.6 (m), 1415.8 (m), 1263.2 (m), 1210.6 (m), 825.1 (m), 778.6 (m) cm^{-1}. HRMS (DART) for $C_{23}H_{19}BO_2F_3$ $[M+H]^+$: calculated: 395.1430, found: 395.1441.



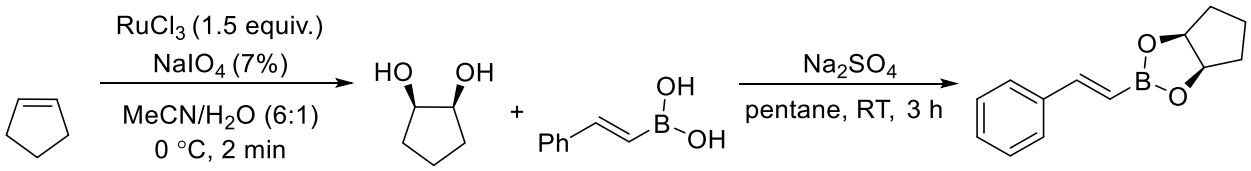
8-((E)-4-fluorostyryl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-8). The title compound was prepared according to Method B with [(E)-2-(4-

fluorophenyl)vinyl]boronic acid (277 mg, 1.67 mmol, 1.0 equiv.), MeCN (6.67 mL), 1,2-dimethylacenaphthylene-1,2-diol (357 mg, 1.67 mmol, 1.0 equiv.), imidazole (304 mg, 5.00 mmol, 3.0 equiv.), and $FeCl_3$ (14 mg, 83.3 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (535 mg, 1.55 mmol, 93% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.1, 1.8 Hz, 2H), 7.66 – 7.56 (m, 4H), 7.46 – 7.36 (m, 2H), 7.32 (d, J = 18.4 Hz, 1H), 7.05 – 6.92 (m, 2H), 6.01 (d, J = 18.4 Hz, 1H), 1.85 (s, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{C-F}$ = 248.5 Hz), 148.3, 144.7, 134.7, 133.7, 133.6, 131.4, 128.6 (d, $^3J_{C-F}$ = 8.2 Hz), 128.5, 125.3, 119.5, 115.5 (d, $^2J_{C-F}$ = 21.6 Hz), 92.0, 22.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.1; ^{19}F NMR: (470 MHz, $CDCl_3$) δ -112.41; IR (neat) ν_{max} 3045.2 (w), 2976.5 (m), 2933.9 (w), 1620.8 (m), 1506.5 (m), 1415.7 (m), 1156.6 (m), 904.0 (m), 778.7 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{19}BO_2F$ $[M+H]^+$: calculated: 345.1462, found: 345.1470.

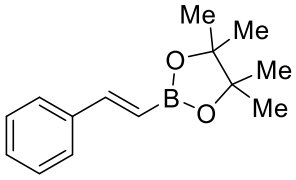


(E)-5,5-dimethyl-2-styryl-1,3,2-dioxaborinane (S-9). The title compound was prepared according to Method E using neopentyl glycol (208 mg, 2.00 mmol, 1 equiv.), (E)-styrylboronic acid (296 mg, 2.00 mmol, 1.0 equiv.), and pentane (20 mL). The crude product was purified by silica gel chromatography with 10% EtOAc / hexanes to yield the title compound (278 mg, 1.29 mmol, 64% yield) as a white solid. Spectral data are in accordance with the literature.[59]

[59] Kobayashi, Y.; Nakayama, Y.; Mizojiri, R. *Tetrahedron* **1998**, *54*, 1053.



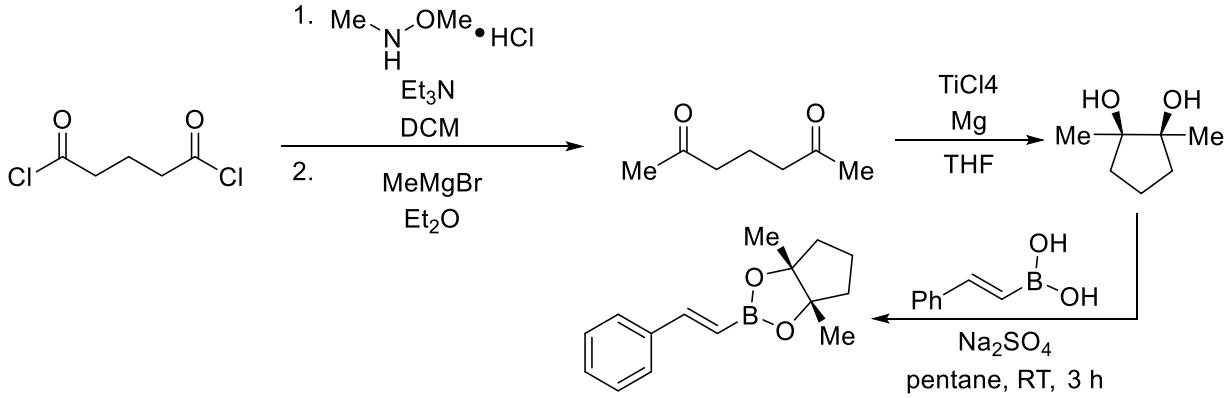
(E)-2-styryltetrahydro-4H-cyclopenta[d][1,3,2]dioxaborole (S-10). The title compound was prepared according to Method E using *syn*-cyclopentane-1,2-diol (prepared using a literature procedure[60]) (109 mg, 1.07 mmol, 1 equiv.) with (E)-styrylboronic acid (158.3 mg, 1.07 mmol, 1 equiv.) and pentane (4 mL). The mixture was allowed to stir overnight in a sealed vial at room temperature. The crude product was purified by silica gel chromatography with 10% EtOAc: hexanes to yield the title compound (174 mg, 0.812 mmol, 76%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.40 (d, J = 18.5 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.32 – 7.28 (m, 1H), 6.17 (d, J = 18.5 Hz, 1H), 4.97 – 4.86 (m, 2H), 2.03 – 1.94 (m, 2H), 1.74 – 1.55 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 137.6, 129.1, 128.7, 127.2, 82.5, 34.9, 21.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.2.; IR (neat) ν_{max} 3025.0 (w), 2960.5 (w), 1622.4 (m), 1357.7 (s), 1032.5 (m), 746.8 (s) cm^{-1}. HRMS (DART) for $C_{13}H_{16}BO_2$ $[M+H]^+$ calculated: 215.1243, found: 215.1252.



(E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (S-11). The title compound was prepared according to a literature procedure[61] using phenylacetylene (2.14 mg, 21.00 mmol, 1.05 equiv.), pinacolborane (2.56 g, 20.0 mmol, 1.0 equiv.) and Bis(cyclopentadienyl)zirconium(IV) chloride hydride (258 mg, 1 mmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-

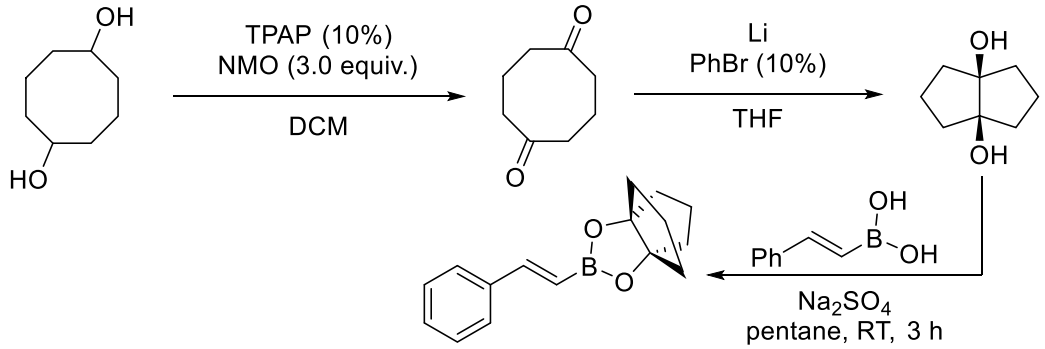
[60] Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.*, **1996**, *2*, 50.
[61] Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.

10% EtOAc / hexanes to yield the title compound (4.25 mg, 18.4 mmol, 92% yield) as a white solid. Spectral data are in accordance with the literature.[62]

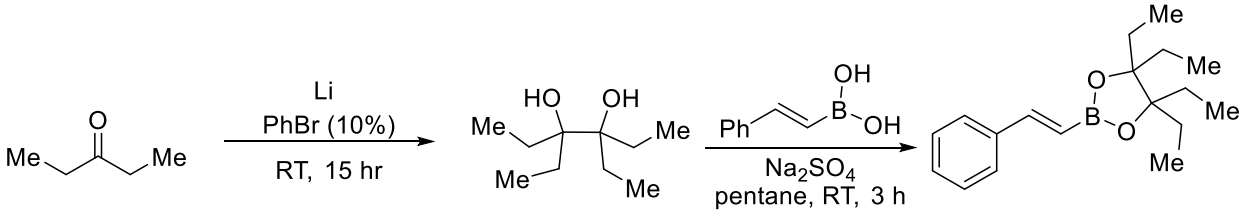


(E)-3a,6a-dimethyl-2-styryltetrahydro-4H-cyclopenta[d][1,3,2]dioxaborole (S-12). The title compound was prepared according to a series of literature reactions[63, 64], then Method E using the cis-1,2-dimethylcyclopentane-1,2-diol (38.6 mg, 296 µmol, 1.0 equiv.) with (E)-styrylboronic acid (43.9 mg, 296 µmol, 1.0 equiv.), and pentane (1 mL). The crude product was purified by silica gel chromatography with 10% EtOAc / hexanes to yield the title compound as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.40 – 7.27 (m, 4H), 6.15 (d, J = 18.4 Hz, 1H), 2.05 (dd, J = 12.9, 5.5 Hz, 2H), 1.69 – 1.50 (m, 4H), 1.37 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.4, 137.7, 129.0, 128.7, 127.2, 90.6, 42.0, 23.4, 21.4. ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.7.; IR (neat) ν_{max} 2966.4 (w), 1623.2 (m), 1353.0 (s). HRMS (DART) for $C_{15}H_{19}BO_2$ $[M+H]^+$ calculated: 243.1556, found: 243.1563.

[62] Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem*. **1992**, *57*, 3482.
[63] Doi, R.; Shibuya, M.; Murayama, T.; Yamamoto, Y.; Iwabuchi, Y. *J. Org. Chem*. **2015**, *80*, 401.
[64] Chanteau, S. H.; Tour, J. M. *J. Org. Chem.*, **2003**, *68,* 8750.

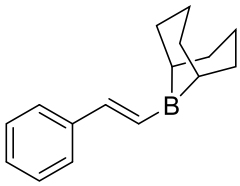


8-((E)-styryl)tetrahydro-1H,4H-3a,6a-(epoxyboranooxy)pentalene (S-13). The title compound was prepared according to Method E with (E)-styrylboronic acid (70.5 mg, 477 µmol, 1.0 equiv.), tetrahydropentalene-3a,6a(1H,4H)-diol (67 mg, 477 µmol, 1.0 equiv.) and 1 mL of pentane. The crude product was purified by silica gel chromatography with 5% EtOAc / hexanes to the yield the title compound (121.1 mg, 338 µmol, 71% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.39 (d, *J* = 18.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.15 (d, *J* = 18.4 Hz, 1H), 2.02 – 1.96 (m, 4H), 1.87 – 1.78 (m, 2H), 1.75 – 1.61 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 137.6, 129.0, 128.7, 127.2, 99.8, 39.0, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7.; IR (neat) ν_{max} 3025.0 (w), 2960.5 (w), 1622.4 (m), 1357.7 (s), 1032.5 (m), 746.8 (m). HRMS (DART) for $C_{16}H_{19}BO_2$ $[M+H]^+$ calculated: 255.1556 found: 255.1552.



(E)-4,4,5,5-tetraethyl-2-styryl-1,3,2-dioxaborolane (S-14). The title compound was prepared according to Method E using 3,4-diethylhexane-3,4-diol (prepared according to a literature

procedure[65]) (79.5 mg, 0.46 mmol, 1.0 equiv.), (E)-styrylboronic acid (67.5 mg, 0.46 mmol, 1.0 equiv.) and pentane (1.5 mL). The crude product was purified by silica gel chromatography with 10% EtOAc / hexanes to yield the title compound (115 mg, 0.40 mmol, 88%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.41 (d, *J* = 18.4 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 6.20 (d, *J* = 18.3 Hz, 1H), 1.80 – 1.67 (m, 8H), 0.96 (t, *J* = 7.5 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 137.8, 128.9, 128.7, 127.2, 88.5, 26.6, 9.0. ^{11}B NMR (192 MHz, $CDCl_3$) δ 29.1.; IR (neat) ν_{max} 2975.3 (w), 2973.5 (w), 2882.9 (w), 1624.2 (m), 1346.2 (s) cm^{-1}. HRMS (DART) for $C_{18}H_{27}BO_2$ $[M+H]^+$ calculated: 287.2182, found: 287.2189.



(E)-9-styryl-9-borabicyclo[3.3.1]nonane (S-15). In an argon-filled glovebox, to an oven-dried scintillation vial was added phenylacetylene (102.13 mg, 1 mmol, 1.0 equiv.), followed by 9-borabicyclo[3.3.1]nonane (0.5 M solution in THF, 2.00 mL, 1.0 mmol, 1.0 equiv.). The solution was allowed to stir for 3 hours at room temperature then used without further purification as a ~0.5 M solution in THF.

3.4.2.3. Procedure for boron 'ate' complex NMR studies

In an argon-filled glovebox, boronic ester (0.2 mmol, 1.0 equiv.) and THF (0.4 mL) were added to an oven-dried 2-dram vial with stir bar. The vial was sealed with a septum cap and removed from the glovebox, then cooled to 0 ºC. The organolithium reagent (0.2 mmol, 1.0 equiv.) was added dropwise and reaction was allowed to stir at room temperature for 15 minutes before the solvent was carefully removed under vacuum. The vial was brought back into the glovebox and the 'ate' complex was dissolved in THF-*d8*, then transferred to an oven-dried NMR tube. The

[65] Zhao, H.; Li, D.-J.; Deng, L. Liu, L.; Guo, Q.-X. *Chem. Commun.* **2003**, 506.

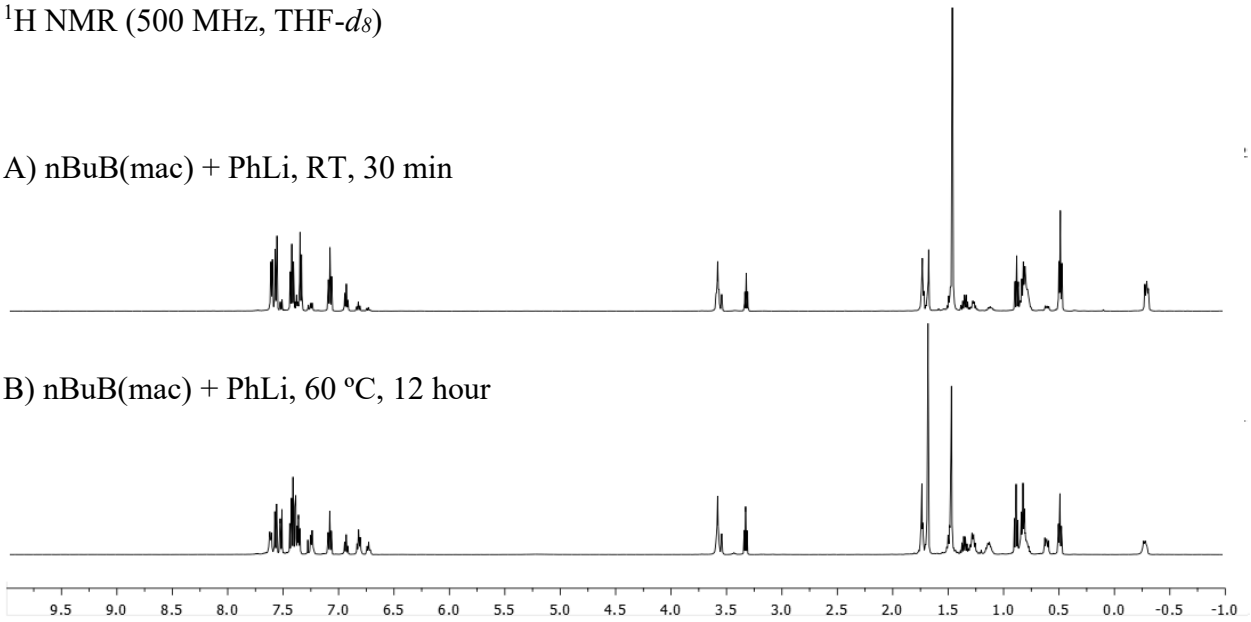
NMR tube was sealed and a ^{1}H NMR spectrum was obtained (Scheme 3.31.A). The NMR tube was then heated to 60 ºC for 12 hours before another ^{1}H NMR spectrum was obtained (Scheme 3.31.B).

Scheme 3.31. ^{1}H NMR spectra of boron 'ate' complex from nBuB(mac)

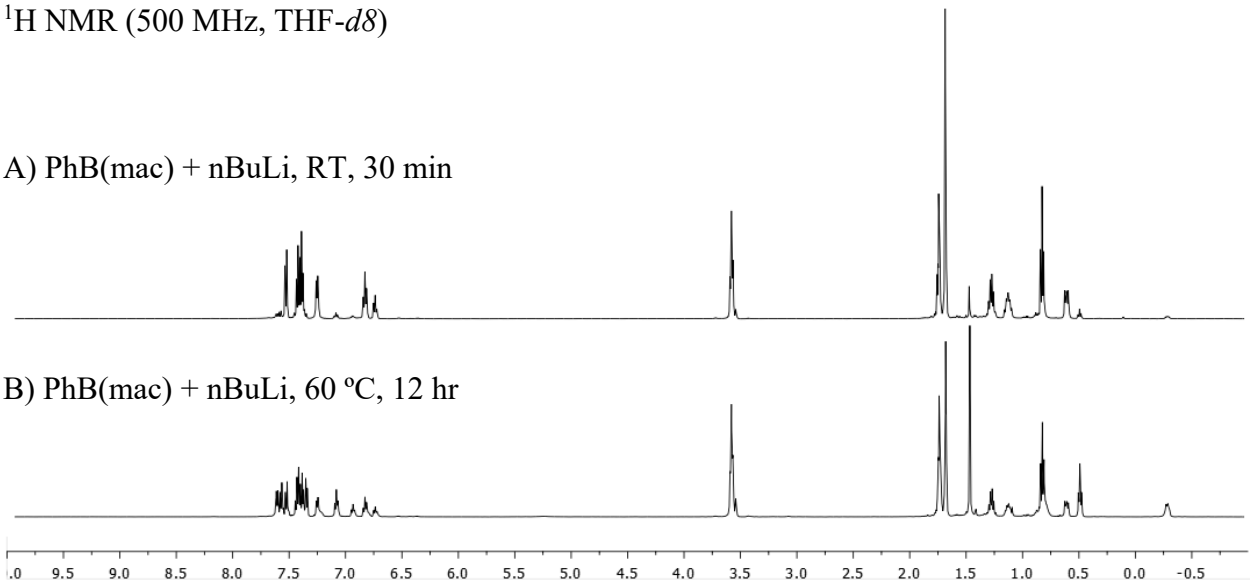
^{1}H NMR (500 MHz, THF-*d*$_{8}$)

A) nBuB(mac) + PhLi, RT, 30 min

B) nBuB(mac) + PhLi, 60 ºC, 12 hour

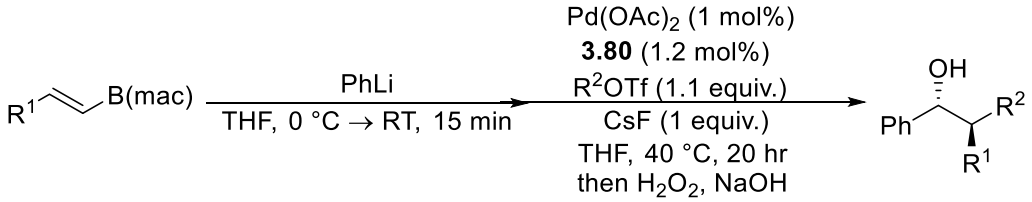


Scheme 3.32. ^{1}H NMR spectra of boron 'ate' complex from PhB(mac)



3.4.2.4. Representative procedure for the conjunctive cross-coupling reaction

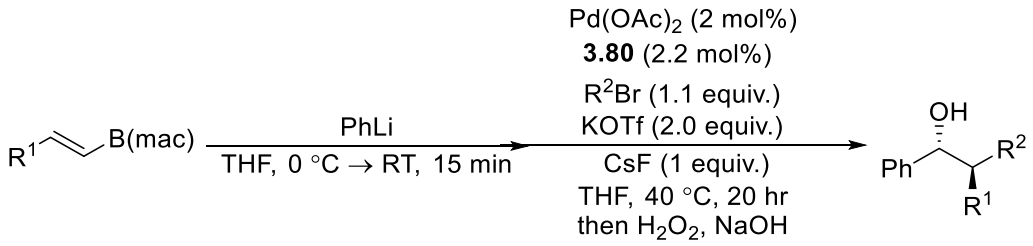
Method A:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added alkenyl boronic acid "mac" ester (0.20 mmol, 1.00 equiv.) and THF (0.4 mL). The vial was sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0 °C, and a phenyllithium solution (1.9 M in dibutyl ether, 0.20 mmol, 1.0 equiv.) was added at 0 °C. The reaction vial was allowed to warm to room temperature and stirred for 15 minutes, then the solvent was carefully removed under reduced pressure, and the reaction vial was brought back into the glovebox. Cesium fluoride (0.20 mmol, 1.0 equiv.) was added to the reaction vial, followed by THF (0.6 mL), and the vial was stirred at room temperature for 5 minutes. To a separate oven-

dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.002 mmol, 0.01 equiv.), **3.80** (0.0024 mmol, 0.012 equiv.), and THF (0.2 mL). The $Pd(OAc)_2$/**3.80** solution was allowed to stir for 15 minutes at room temperature, then it was transferred into the reaction vial, followed by aryl triflate (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 20 hours. The resulting mixture was cooled to room temperature, filtered through a celite plug with diethyl ether, and concentrated under reduced pressure. The crude product was diluted with THF (3 mL) and cooled to 0 °C before 3M NaOH (2 mL) was added, followed by 30% H_2O_2 (1.0 mL) dropwise. The reaction was allowed to warm to room temperature and stirred for 4 hours, then quenched at 0 °C by dropwise addition of saturated aq. $Na_2S_2O_3$ solution (3 mL). This solution was allowed to stir at room temperature for 10 minutes. The mixture was diluted with Et_2O and transferred to a separatory funnel, and the aqueous layer was washed with Et_2O three times. The combined organic layers were washed with brine then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was subsequently purified via silica gel (treated with 2% triethylamine / hexanes prior to use) column chromatography to afford the desired product.

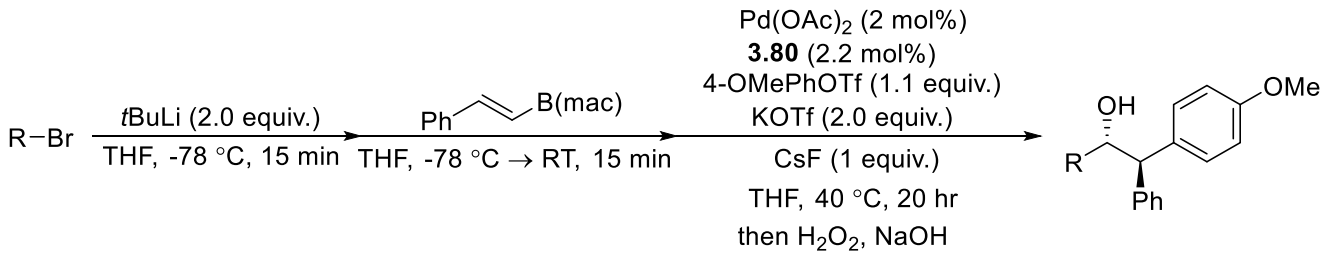
Method B:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added alkenyl boronic acid "mac" ester (0.20 mmol, 1.00 equiv.) and THF (0.4 mL), sealed with

a septum cap, and removed from the glovebox. The reaction vial was cooled to 0 °C, and a phenyllithium solution (1.9M in dibutyl ether, 0.20 mmol, 1.0 equiv.) was added at 0 °C. The reaction vial was allowed to warm to room temperature and stirred for 15 minutes. Then, the solvent was carefully removed under reduced pressure, and the reaction vial was brought back into the glovebox. Cesium fluoride (0.20 mmol, 1.0 equiv.) was added to the reaction vial, followed by THF (0.4 mL), and the vial was stirred at room temperature for 5 minutes, then potassium trifluoromethanesulfonate (0.40 mmol, 2.0 equiv) was added. To a separate oven-dried 2-dram vial equipped with a magnetic stirbar in the glovebox was added $Pd(OAc)_2$ (0.004 mmol, 0.020 equiv.), **3.80** (0.0044 mmol, 0.022 equiv.), and THF (0.4 mL). The $Pd(OAc)_2$/**3.80** solution was allowed to stir for 15 minutes at room temperature, then transferred into the reaction vial, followed by aryl/alkenyl bromide (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 20 hours. The same oxidation and purification procedure was done as in Method A.

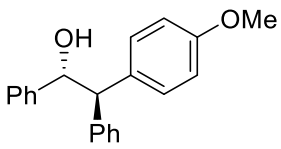
Method C:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added aryl/alkenyl bromide (0.20 mmol, 1.00 equiv.) and THF (0.2 mL), and sealed with a septum cap. To a separate oven-dried 1-dram vial was added styrenyl B(mac) (S-1) (0.2 mmol, 1.0 equiv,) and THF (0.4 mL). Both vials were removed from the glove box. The 2-dram reaction

vial was cooled to -78 °C, and a *tert*-butyllithium solution (0.40 mmol, 2.0 equiv.) was added dropwise at -78 °C and the reaction was allowed to stir at that temperature for 15 minutes. The solution of styrenyl B(mac) (S-1) from the 1-dram vial was then added to the reaction vial slowly, and the reaction was warmed to room temperature and stirred for 15 minutes, then the solvent was carefully removed under reduced pressure, and the reaction vial was brought back into the glovebox. Cesium fluoride (0.20 mmol, 1.0 equiv.) was added to the reaction vial, followed by THF (0.4 mL), and the vial was stirred at room temperature for 5 minutes, then potassium trifluoromethanesulfonate (0.40 mmol, 2.0 equiv) was added. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.004 mmol, 0.02 equiv.), **3.80** (0.0044 mmol, 0.022 equiv.), and THF (0.4 mL). The $Pd(OAc)_2$/**3.80** solution was allowed to stir for 15 minutes at room temperature then transferred into the reaction vial, followed by and 4-methoxyphenyl trifluoromethanesulfonate (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 20 hours. The same oxidation and purification procedure was done as in Method A.

3.4.2.5. Characterization of conjunctive cross-coupling products and analysis of stereochemistry



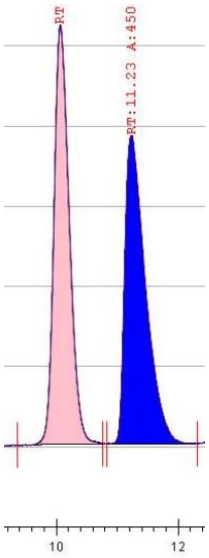
(1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethan-1-ol (2b). The reaction was performed according to the general procedure ***(Method A)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **3.80** (2.5 mg, 2.4 μmol) , 0.012 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (46 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (d, J = 8.2 Hz, 2H), 7.29 – 7.05 (m, 10H), 6.89 (d, J = 8.2 Hz, 2H), 5.36 (d, J = 8.5 Hz, 1H), 4.22 (d, J = 8.5 Hz, 1H), 3.80 (s, 3H), 2.16 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 142.3, 141.9, 132.8, 130.0, 128.5, 128.2, 128.0, 127.5, 126.9, 126.3, 114.2, 76.9, 59.4, 55.2.; IR (neat): ν_{max} 3385.3 (br), 3060.4 (w), 3028.0 (m), 2906.4 (m), 2834.7 (w), 1609.2 (m), 1509.4 (s), 1245.9 (s), 1075.1 (s), 785.0 (m), 697.3 (s), 596.5 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{19}O$ $[M+H-H_2O]^+$: calculated: 287.1436, found: 287.1431. $[\alpha]^{20}_D$: -43.242 (c = 1.200, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

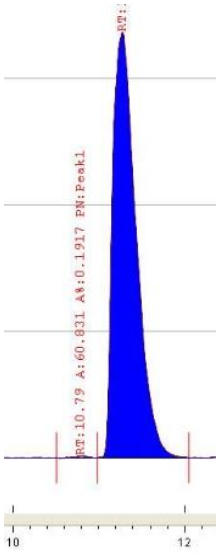
Chiral SFC (OD-H, 12% IPA, 4 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethan-1-ol.

Racemic Material

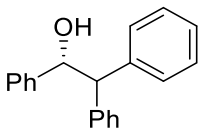


Peak No	% Area	Area	RT (min)
1	50.2496	4554.7092	10.06
2	49.7504	4509.4626	11.23
Total:	100	9064.1718	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.1917	60.831	10.79
2	99.8083	31665.4228	11.27
Total:	100	31726.2538	



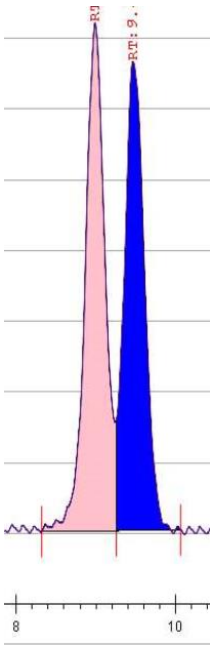
(R)-1,2,2-triphenylethan-1-ol (7). The reaction was performed according to the general procedure ***(Method A)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **3.80** (2.5 mg, 2.4 μmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a white solid (47 mg, 86% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 7.3 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.31 – 7.19 (m, 6H), 7.19 – 7.08 (m, 5H), 5.41 (dd, J = 8.8, 2.7 Hz, 1H), 4.27 (d, J = 8.8 Hz, 1H), 2.13 (d, J = 2.9 Hz, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 142.2, 141.5, 140.9, 128.9, 128.8, 128.6, 128.2, 128.0, 127.6, 127.0, 126.9, 126.4, 76.8, 60.3.; IR (neat): ν_{max} 3341.8 (br), 3060.0 (m), 3027.2 (m), 2908.2 (w), 1598.9 (m), 1493.5 (m), 1451.3 (m), 1301.2 (m), 743.9 (s), 697.0 (s), 598.8 (s) cm^{-1}. HRMS (DART) for $C_{20}H_{17}$ $[M+H-H_2O]^+$: calculated: 257.1325, found: 257.1324. $[\alpha]^{20}_D$: -63.355 (c = 0.960, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

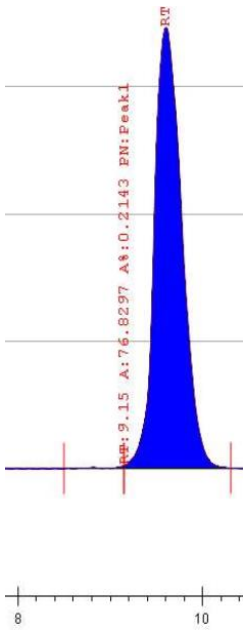
Chiral SFC (Chiralcel OD-H, 10% IPA, 4 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1,2,2-triphenylethan-1-ol.

Racemic Material

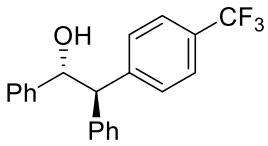


Peak No	% Area	Area	RT (min)
1	51.9085	2512.8466	8.99
2	48.0915	2328.0711	9.47
Total:	100	4840.9177	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.2143	76.8297	9.15
2	99.7857	35770.1731	9.6
Total:	100	35847.0028	



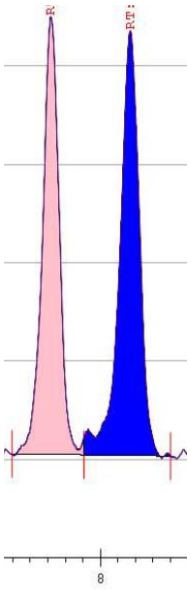
(1R,2R)-1,2-diphenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol (8). The reaction was performed according to the general procedure ***(Method B)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 1-bromo-4-(trifluoromethyl)benzene (49.5 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 µmol, 0.020 equiv.), **3.80** (5.0 mg, 4.8 µmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a pale yellow oil (30 mg, 44% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.28 – 7.08 (m, 10H), 5.44 (d, J = 8.3 Hz, 1H), 4.33 (d, J = 8.3 Hz, 1H), 2.06 (br, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 147.9, 144.8, 143.5, 132.1, 131.6 (q, $^{2}J_{C-F}$ = 32.4 Hz), 131.2, 131.09, 131.06, 130.9, 130.5, 129.4, 129.3, 128.0 (q, $^{3}J_{C-F}$ = 3.7 Hz), 126.9 (partially buried, q, $^{1}J_{C-F}$ = 271.8 Hz), 79.3, 62.3, 33.0.; ^{19}F NMR (470 MHz, $CDCl_3$): δ -62.4.; IR (neat): ν_{max} 3359.1 (br), 3063.1 (w), 3029.7 (m), 2924.1 (w), 1618.8 (m), 1324.7 (s),1163.9 (m), 1113.7 (m), 1068.7 (m), 746.9 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{16}F_3$ $[M+H-H_2O]^+$: calculated: 325.1204, found: 325.1211. $[\alpha]^{20}_D$: -50.989 (c = 1.055, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

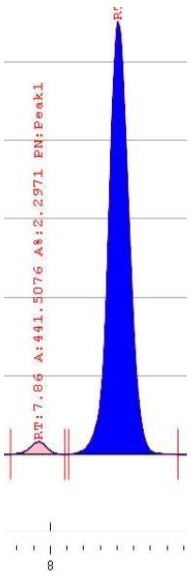
Chiral SFC (Chiralcel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-1,2-diphenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol.

Racemic Material

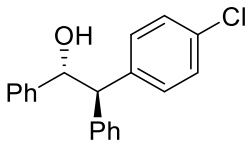


Peak No	% Area	Area	RT (min)
1	46.6539	1187.7833	7.43
2	53.3461	1358.1622	8.34
Total:	100	2545.9455	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	2.2971	441.5076	7.86
2	97.7029	18778.9673	8.81
Total:	100	19220.4749	



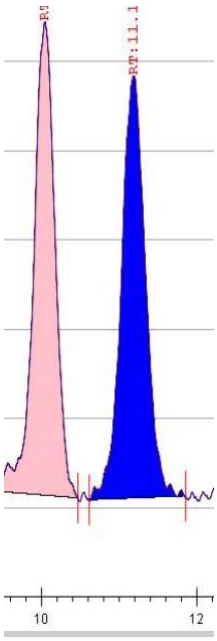
(1R,2R)-2-(4-chlorophenyl)-1,2-diphenylethan-1-ol (9). The reaction was performed according to the general procedure ***(Method B)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 1-bromo-4-chlorobenzene (42.1 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **3.80** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a pale yellow oil (29 mg, 47% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.06 (m, 14H), 5.38 (d, *J* = 8.2 Hz, 1H), 4.24 (d, *J* = 8.2 Hz, 1H), 2.05 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 142.4, 141.4, 139.6, 132.8, 130.6, 128.9, 128.7, 128.54, 128.53, 128.3, 127.9, 126.9, 126.8, 76.9, 59.4.; IR (neat): ν_{max} 3350.5, 3061.4, 3028.4, 2920.9, 1491.2, 1453.2, 1014.8, 799.1, 734.8, 698.5 cm^{-1}. HRMS (DART) for $C_{20}H_{16}Cl$ $[M+H-H_2O]^+$: calculated: 291.0941, found: 291.0930. $[\alpha]^{20}_D$: -32.43 (c = 1.00, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

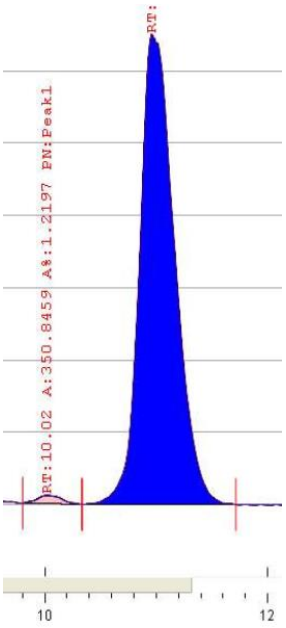
Chiral SFC (Chiralcel OD-H, 10% IPA, 4 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(4-chlorophenyl)-1,2-diphenylethan-1-ol.

Racemic Material

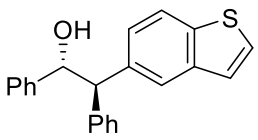


Peak No	% Area	Area	RT (min)
1	50.1967	2046.2136	10.04
2	49.8033	2030.1811	11.19
Total:	100	4076.3947	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	1.2197	350.8459	10.02
2	98.7803	28413.5011	10.96
Total:	100	28764.347	



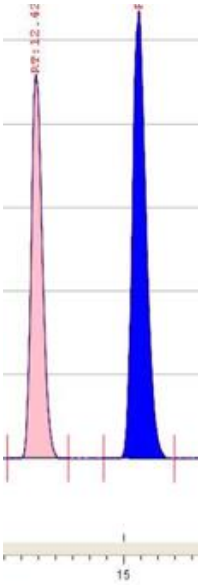
(1R,2R)-2-(benzo[b]thiophen-5-yl)-1,2-diphenylethan-1-ol (10). The reaction was performed according to the general procedure ***(Method B)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.2 mmol, 1 equiv.), phenyllithium in dibutyl ether solution (1.9 M) (0.105 mL, 0.2 mmol, 1 equiv.), 5-bromobenzothiophene (46.9 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **3.80** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium triflate (75.3 mg, 0.4 mmol, 2 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (28.4 mg, 43% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 5.4 Hz, 1H), 7.25 – 7.03 (m, 10H), 5.48 (d, *J* = 8.7 Hz, 1H), 4.40 (d, *J* = 8.6 Hz, 1H), 2.16 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.4, 141.8, 140.2, 138.6, 137.2, 128.7, 128.4, 128.2, 127.7, 127.1, 127.0, 126.5, 125.7, 124.0, 123.8, 122.9, 77.0, 60.3. IR (neat): ν_{max} 3356.7 (bm), 3062.1 (m), 3027.3 (m) 2921.4 (m), 2855.0 (w), 1728.2 (w), 1600.1 (m), 1551.5 (m), 1491.9 (m), 1049.7 (m), 753.0 (s), 696.9 (s), 553.5 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{18}OS$ $[M+H-H2O]^+$: calculated: 313.1051, found: 313.1049. $[\alpha]^{20}_D$: -38.828 (c = 0.855, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with styrenyl B(mac), and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

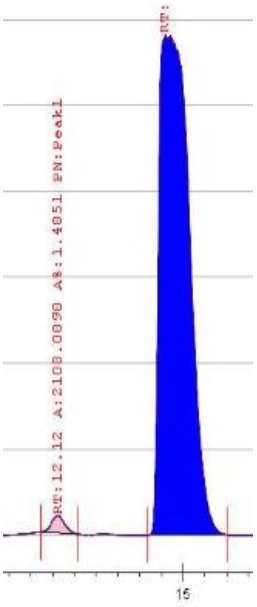
Chiral SFC (Chiralcel ODR-H, 15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(benzo[b]thiophen-5-yl)-1,2-diphenylethan-1-ol

Racemic Material

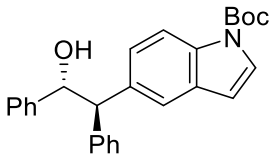


Peak No	% Area	Area	RT (min)
1	41.0665	10437.3868	12.42
2	58.9335	14978.4344	15.44
Total:	100	25415.8212	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	1.4851	2108.0898	12.12
2	98.5149	139837.4666	14.59
Total:	100	141945.5564	



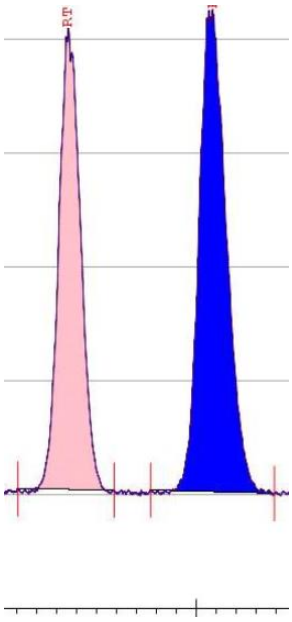
tert-butyl 5-((1R,2R)-2-hydroxy-1,2-diphenylethyl)-1H-indole-1-carboxylate (11). The reaction was performed according to the general procedure ***(Method B)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), tert-butyl 5-bromoindole-1-carboxylate (65.2 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **3.80** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (49 mg, 59% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.04 (m, 10H), 6.55 (d, *J* = 3.7 Hz, 1H), 5.46 (d, *J* = 8.6 Hz, 1H), 4.37 (d, *J* = 8.6 Hz, 1H), 2.23 (s, 1H), 1.68 (s, 9H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.9, 142.5, 142.1, 135.3, 134.4, 131.2, 128.7, 128.4, 128.2, 127.7, 127.1, 126.5, 126.4, 125.4, 121.3, 115.6, 107.5, 83.9, 77.1, 60.4, 28.4.; IR (neat): ν_{max} 3412. 5 (br), 3061.8 (m), 2978.7 (m), 1730.4 (s), 1492.63 (m), 1371.9 (s), 1163.0 (s), 1083.6 (m), 754.3 (s), 698.7 (s) cm^{-1}. HRMS (DART) for $C_{27}H_{26}NO_2$ $[M+H-H_2O]^+$: calculated: 396.1964, found: 396.1953. $[\alpha]^{20}_D$: -45.59 (c = 1.033, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and a 1:1 mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

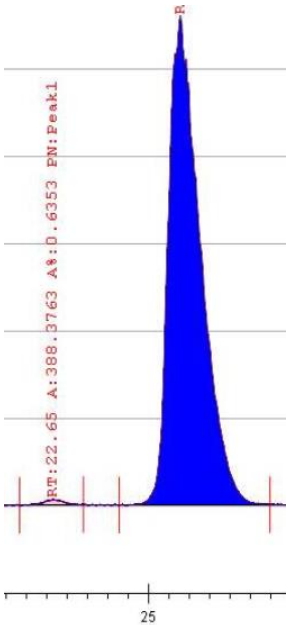
Chiral SFC (Chiralcel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of tert-butyl 5-((1R,2R)-2-hydroxy-1,2-diphenylethyl)-1H-indole-1-carboxylate.

Racemic Material

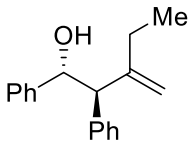


Peak No	% Area	Area	RT (min)
1	43.259	7639.7137	21.79
2	56.741	10020.7002	25.41
Total:	100	17660.4139	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.6353	388.3763	22.65
2	99.3647	60747.6108	25.78
Total:	100	61135.9871	



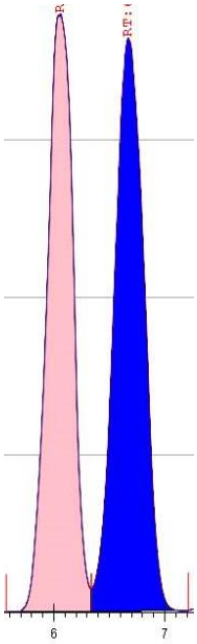
(1R,2S)-3-methylene-1,2-diphenylpentan-1-ol (12). The reaction was performed according to the general procedure ***(Method B)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 2-bromo-1-butene (29.7 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **3.80** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a pale yellow oil (32 mg, 63% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.04 (m, 8H), 6.97 (dt, J = 7.5, 1.4 Hz, 2H), 5.37 (s, 1H), 5.22 (s, 1H), 5.06 (d, J = 9.8 Hz, 1H), 3.54 (d, J = 9.9 Hz, 1H), 2.64 (s, 1H), 2.11 – 1.95 (m, 2H), 1.03 (td, J = 7.4, 1.2 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 154.4, 144.4, 142.2, 131.3, 130.6, 130.5, 130.0, 129.6, 129.2, 111.9, 78.6, 64.0, 31.7, 14.8.; IR (neat): ν_{max} 3440.4 (br), 3062.1 (w), 3028.4 (m), 2964.4 (m), 1641.4 (w), 1492.4 (m), 1453.0 (m), 1218.9 (m), 1074.2 (m), 755.3 (s), 696.9 (s) cm^{-1}. HRMS (DART) for $C_{18}H_{19}$ $[M+H-H_2O]^+$: calculated: 235.1487, found: 235.1481. $[\alpha]^{20}_D$: -209.087 (c = 1.020, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and a 1:1 mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

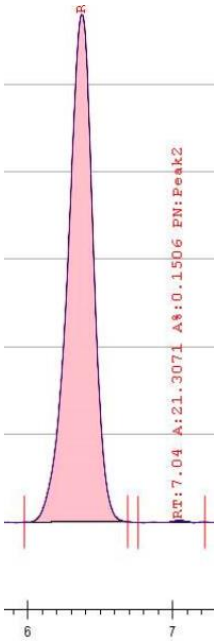
Chiral SFC (Chiralcel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2S)-3-methylene-1,2-diphenylpentan-1-ol.

Racemic Material

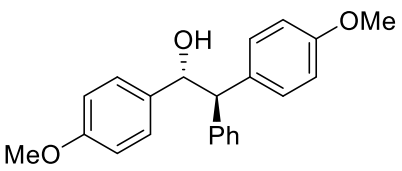


Peak No	% Area	Area	RT (min)
1	47.9207	31092.8311	6.06
2	52.0793	33791.1063	6.67
Total:	100	64883.9374	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	99.8494	14123.3123	6.37
2	0.1506	21.3071	7.04
Total:	100	14144.6194	



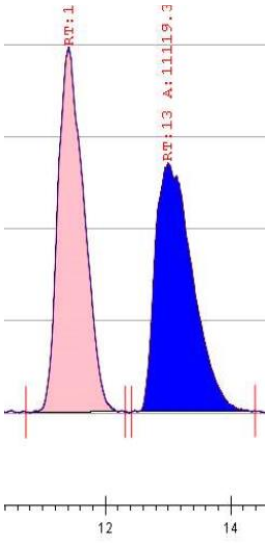
(1R,2R)-1,2-bis(4-methoxyphenyl)-2-phenylethan-1-ol (13). The reaction was performed according to the general procedure ***(Method C)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), 4-bromoanisole (37.4 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **3.80** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (52 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.6 Hz, 2H), 7.19 – 7.03 (m, 6H), 6.89 (d, J = 8.6 Hz, 2H), 6.82 – 6.69 (m, 3H), 5.31 (d, J = 8.7 Hz, 1H), 4.18 (d, J = 8.8 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.08 (br s, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.9, 158.5, 142.0, 134.5, 133.1, 129.9, 128.5, 128.2, 128.0, 126.2, 116.0, 114.8, 114.2, 113.4, 76.5, 59.5, 55.8, 55.24, 55.16.; IR (neat): ν_{max} 3389.0 (b), 3028.0 (w), 3000.8 (m), 2931.9 (m), 2835.0 (m), 1610.7 (m), 1584.3 (s), 1301.9 (w), 1246.2 (s), 1176.8 (m), 1302.9 (m), 828.5 (m), 699.9 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{21}O_2$ $[M+H-H_2O]^+$: calculated: 317.152, found: 317.1547. $[\alpha]^{20}_D$: -37.908 (c = 0.633, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

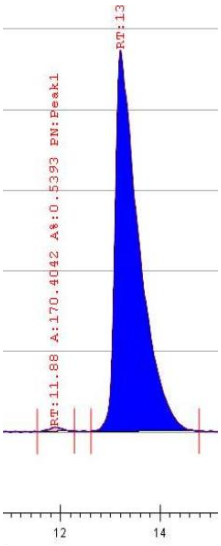
Chiral SFC (Chiralcel OD-H, 15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-1,2-bis(4-methoxyphenyl)-2-phenylethan-1-ol.

Racemic Material

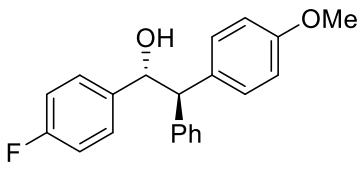


Peak No	% Area	Area	RT (min)
1	50.557	11369.8668	11.42
2	49.443	11119.3306	13
Total:	100	22489.1974	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.5393	170.4042	11.88
2	99.4607	31426.3547	13.2
Total:	100	31596.7589	



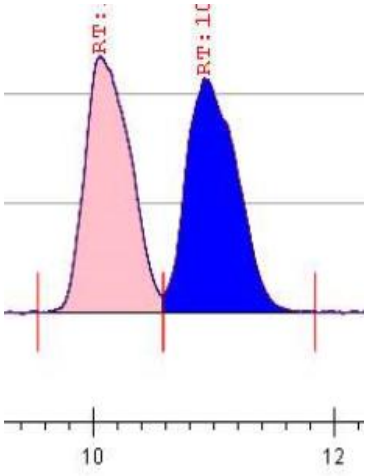
(1R,2R)-1-(4-fluorophenyl)-2-(4-methoxyphenyl)-2-phenylethan-1-ol (14). The reaction was performed according to the general procedure ***(Method C)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), 1-bromo-4-fluorobenzene (35.0 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **3.80** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (45 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.6 Hz, 2H), 7.23 – 7.13 (m, 4H), 7.13 – 7.05 (m, 3H), 6.96 – 6.86 (m, 4H), 5.33 (d, J = 8.8 Hz, 1H), 4.14 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 2.16 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.1 (d, $^{1}J_{C\text{-}F}$ = 245.3 Hz), 158.6, 141.6, 138.01, 137.99, 132.5, 129.9, 128.4 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 128.4, 128.3, 126.4, 114.8 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 114.7, 114.3, 76.3, 59.8, 55.2.; ^{19}F NMR (470 MHz, $CDCl_3$) δ -115.0.; IR (neat): ν_{max} 3378.7 (br), 3060.3 (w), 3029.1 (m), 2908.1 (m), 2835.9 (m), 1605.9 (m), 1508.8 (s), 1220.3 (m), 1178.9 (m), 1033.6 (m),699.4 (m), 567.7 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{18}FO$ $[M+H-H_2O]^+$: calculated: 305.1342, found: 305.1342. $[\alpha]^{20}_D$: -58.335 (c = 0.813, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

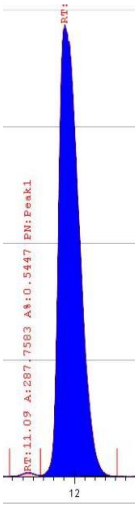
Chiral SFC (Chiralcel OD-H, 12% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-1-(4-fluorophenyl)-2-(4-methoxyphenyl)-2-phenylethan-1-ol.

Racemic Material

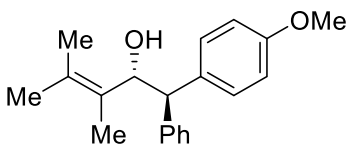


Peak No	% Area	Area	RT (min)
1	49.5931	6149.1124	10.05
2	50.4069	6250.0104	10.92
Total:	100	12399.1228	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.5447	287.7583	11.09
2	99.4553	52539.5337	11.81
Total:	100	52827.292	



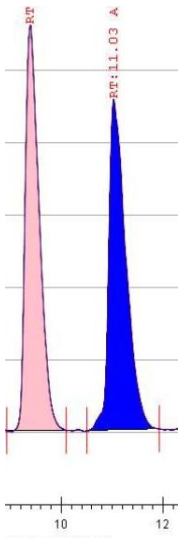
(1R,2R)-1-(4-methoxyphenyl)-3,4-dimethyl-1-phenylpent-3-en-2-ol (15). The reaction was performed according to the general procedure ***(Method C)*** with styrenyl B(mac) (S-1) (65.2 mg, 0.20 mmol, 1.0 equiv.), 2-bromo-3-methyl-but-2-ene (29.8 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **3.80** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (33 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.6 Hz, 2H), 7.23 – 7.15 (m, 4H), 7.15 – 7.10 (m, 1H), 6.90 (d, J = 8.7 Hz, 2H), 5.28 (d, J = 10.2 Hz, 1H), 4.06 (d, J = 10.1 Hz, 1H), 3.79 (s, 3H), 1.66 (s, 3H), 1.60 (s, 1H), 1.54 (s, 3H), 1.51 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 142.1, 133.7, 129.8, 129.7, 128.1, 127.9, 126.8, 126.2, 114.3, 73.1, 55.7, 55.2, 21.0, 20.1, 12.3.; IR (neat): ν_{max} 3448.0 (br), 3027.5 (w), 2993.8 (m), 2928.2 (m), 2858.4 (m), 1609.7 (m), 1510.4 (s), 1248.5 (s), 1178.1 (m), 1034.7 (m), 699.5 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{23}O$ $[M+H-H_2O]^+$: calculated: 279.1749, found: 279.1751. $[\alpha]^{20}_D$: -8.766 (c = 0.920, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

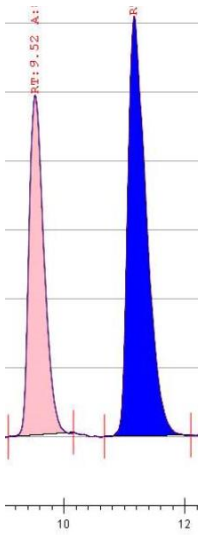
Chiral SFC (Chiralcel ODR-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-1-(4-methoxyphenyl)-3,4-dimethyl-1-phenylpent-3-en-2-ol.

Racemic Material

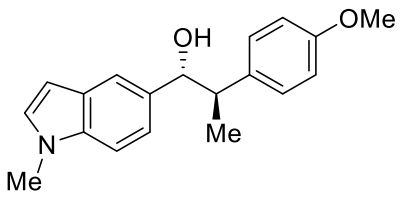


Peak No	% Area	Area	RT (min)
1	50.1135	21398.0761	9.39
2	49.8865	21301.1734	11.03
Total:	100	42699.2495	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	39.509	8442.2713	9.52
2	60.491	12925.7029	11.16
Total:	100	21367.9742	



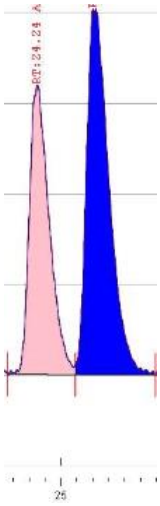
(1R,2R)-2-(4-methoxyphenyl)-1-(1-methyl-1H-indol-5-yl)propan-1-ol (16). The reaction was performed according to the general procedure ***(Method C)*** with (E)-propenyl B(mac) (S-2) (52.8 mg, 0.2 mmol, 1 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2 equiv.), 5-bromo-1-methyl-indole (42.0 mg, 0.20 mmol, 1.0 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **3.80** (5.0 mg, 0.0048 mmol, 0.024 equiv.), potassium triflate (75.3 mg, 0.4 mmol, 2 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (37.8 mg, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 1.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.30 – 7.24 (m, 3H), 7.07 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.49 (d, *J* = 3.0 Hz, 1H), 4.72 – 4.67 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.07 (dq, *J* = 8.9, 7.1 Hz, 1H), 1.86 (d, *J* = 2.1 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 136.7, 136.2, 133.9, 129.3, 129.1, 128.4, 120.7, 119.7, 114.2, 109.3, 101.2, 80.7, 77.4, 77.2, 76.9, 55.4, 47.7, 33.1, 19.0.; IR (neat): ν_{max} 3435.4 (br), 2956.7 (m), 2923.9 (m) 2852.4 (m), 1610.4 (w), 1582.3 (w), 1511.8 (s), 1245.0 (s), 770.3 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{21}NO_2$ $[M+H]^+$: calculated: 296.1645, found: 296.1639. $[\alpha]^{20}_D$: +95.6726 (c = 1.09, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-propenyl B(mac) and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

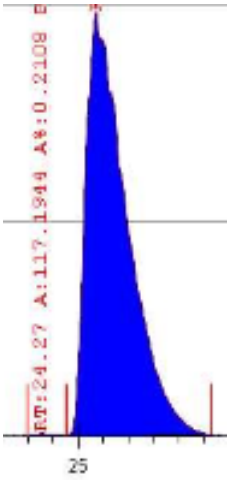
Chiral SFC (Chiralcel ODR-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – (1R,2R)-2-(4-methoxyphenyl)-1-(1-methyl-1H-indol-5-yl)propan-1-ol.

Racemic Material

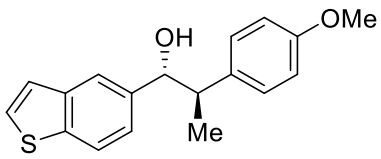


Peak No	% Area	Area	RT (min)
1	41.1283	6949.1704	24.24
2	58.8717	9947.1451	26.01
Total:	100	16896.3155	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.2108	117.1944	24.27
2	99.7892	55478.6465	25.36
Total:	100	55595.8409	



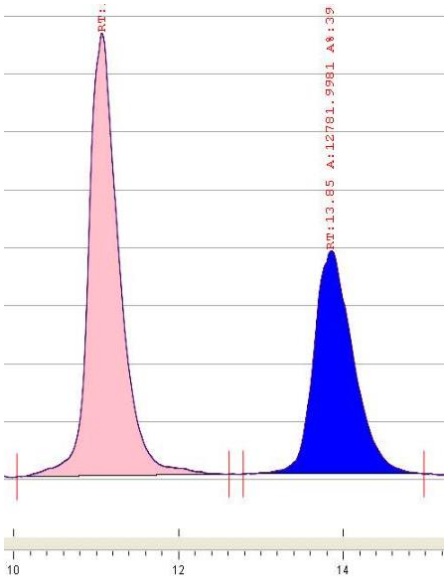
(1R,2R)-1-(benzo[b]thiophen-5-yl)-2-(4-methoxyphenyl)propan-1-ol (17). The reaction was performed according to the general procedure ***(Method C)*** with (E)-propenyl B(mac) (S-2) (52.8 mg, 0.2 mmol, 1 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2 equiv.), 5-bromobenzothiophene (42.6 mg, 0.20 mmol, 1.0 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **3.80** (5.0 mg, 0.0048 mmol, 0.024 equiv.), potassium triflate (75.3 mg, 0.4 mmol, 2 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (35 mg, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.81 (s, 1H), 7.46 (d, *J* = 5.4 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.72 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.09 – 2.97 (m, 1H), 1.95 (br, 1H), 1.07 (d, *J* = 7.1 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7, 139.8, 139.3, 139.1, 135.4, 129.2, 126.9, 124.1, 123.5, 122.5, 122.3, 114.3, 80.1, 55.5, 47.7, 18.7.; IR (neat): ν_{max} 3416 (br), 2961 (m), 2928 (m), 1610 (m), 1583 (w), 1511 (s), 1246 (s), 787 (m) cm^{-1}. HRMS (DART) for $C_{18}H_{17}OS$ $[M+H-H_2O]^+$: calculated: 281.0995, found: 281.1002. $[\alpha]^{20}_D$: +52.99 (c = 1.00, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-propenyl B(mac) and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

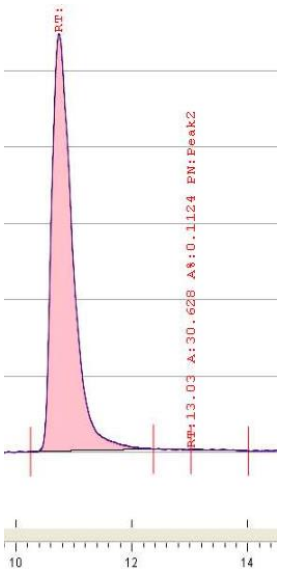
Chiral SFC (Chiralcel AS-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – (1R,2R)-1-(benzo[b]thiophen-5-yl)-2-(4-methoxyphenyl)propan-1-ol

Racemic Material

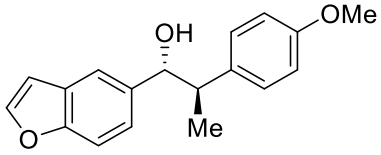


Peak No	% Area	Area	RT (min)
1	60.608	19666.2012	11.07
2	39.392	12781.9981	13.85
Total:	100	32448.1993	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	99.8876	27219.7084	10.74
2	0.1124	30.628	13.03
Total:	100	27250.3364	



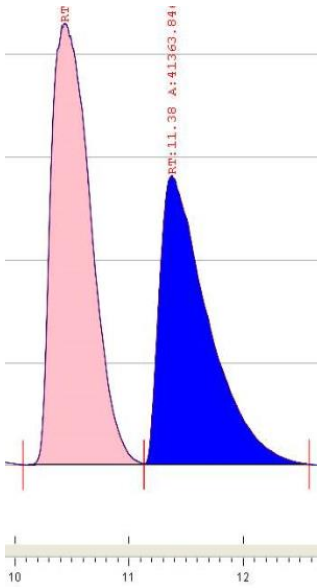
(1R,2R)-1-(benzofuran-5-yl)-2-(4-methoxyphenyl)propan-1-ol (18). The reaction was performed according to the general procedure ***(Method C)*** with (E)-propenyl B(mac) (S-2) (52.8 mg, 0.2 mmol, 1 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2 equiv.), 5-bromobenzofuran (39.4 mg, 0.20 mmol, 1.0 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **3.80** (5.0 mg, 0.0048 mmol, 0.024 equiv.), potassium triflate (75.3 mg, 0.4 mmol, 2 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (28 mg, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.57 (m, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.21 (m, 2H), 6.94 – 6.89 (m, 2H), 6.80 – 6.75 (m, 1H), 4.70 (d, *J* = 8.8 Hz, 1H), 3.82 (s, 3H), 3.08 – 2.94 (m, 1H), 1.93 (br, *J* = 2.1 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7, 154.8, 145.5, 137.5, 135.5, 129.2, 127.5, 123.5, 119.8, 114.3, 111.3, 106.8, 80.2, 55.5, 47.9, 18.8.; IR (neat): ν_{max} 3441(br), 2960 (m), 2927 (m) 1610 (m), 1583 (s), 1467 (m), 1246 (s), 1179 (m), 1032 (s), 741 (m) cm^{-1}. HRMS (DART) for $C_{18}H_{17}O_2$ $[M+H-H_2O]^+$: calculated: 265.1223, found: 265.1232. $[\alpha]^{20}_D$: +48.50 (c = 0.933, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-propenyl B(mac) and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

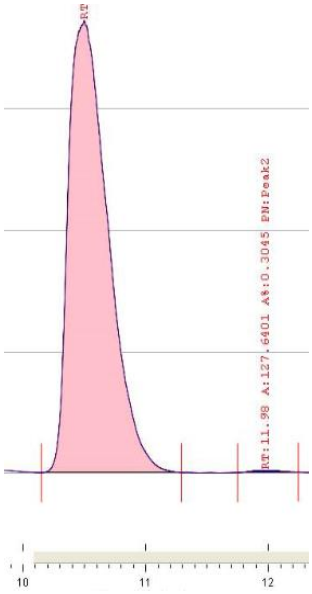
Chiral SFC (Chiralcel ODR-H, 8% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – (1R,2R)-1-(benzofuran-5-yl)-2-(4-methoxyphenyl)propan-1-ol.

Racemic Material

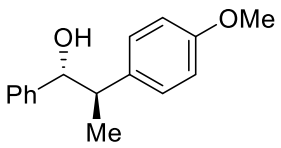


Peak No	% Area	Area	RT (min)
1	55.5182	51626.6428	10.44
2	44.4818	41363.8463	11.38
Total:	100	92990.4891	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	99.6955	41790.8039	10.5
2	0.3045	127.6401	11.98
Total:	100	41918.444	



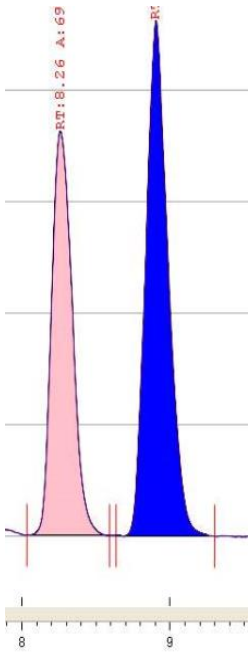
(1R,2R)-2-(4-methoxyphenyl)-1-phenylpropan-1-ol (19). The reaction was performed according to the general procedure (**Method A**) with (E)-propenyl B(mac) (S-2) (52.8 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **3.80** (2.5 mg, 2.4 μmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (1.60 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (34 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 7.22 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 4.61 (d, J = 8.6 Hz, 1H), 3.82 (s, 3H), 3.04 – 2.92 (m, 1H), 1.88 (s, 1H), 1.07 (d, J = 7.1 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 142.6, 135.2, 129.0, 128.2, 127.7, 127.0, 114.1, 79.8, 55.3, 47.3, 18.4.; IR (neat): ν_{max} 3444.8 (br), 3030.4 (w), 2961.7 (m), 2931.5 (m), 2834.8 (w), 1610.5 (w), 1583.1 (s), 1245.5 (s), 1178.3 (m), 1036.7 (m), 724.3 (m) cm^{-1}. HRMS (DART) for $C_{16}H_{17}O$ $[M+H-H_2O]^+$:calculated: 225.1274, found: 225.1270. $[\alpha]^{20}_D$: -69.455 (c = 1.000, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-propenyl B(mac)**,** and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

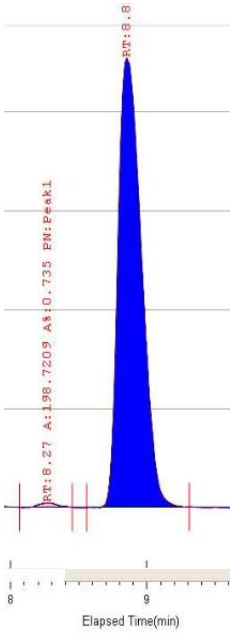
Chiral SFC (Chiralcel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(4-methoxyphenyl)-1-phenylpropan-1-ol.

Racemic Material

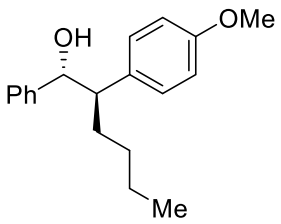


Peak No	% Area	Area	RT (min)
1	42.1696	6987.3301	8.26
2	57.8304	9582.2447	8.9
Total:	100	16569.5748	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.735	198.7209	8.27
2	99.265	26839.1094	8.85
Total:	100	27037.8303	



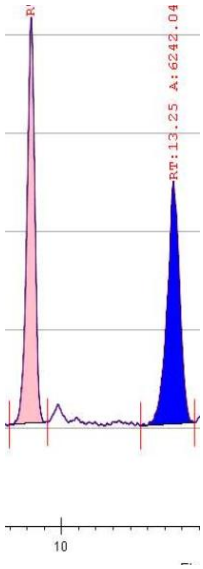
(1R,2R)-2-(4-methoxyphenyl)-1-phenylhexan-1-ol (20). The reaction was performed according to the general procedure (**Method A**) with (E)-hexenyl B(mac) (S-3) (61.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **3.80** (2.5 mg, 2.4 μmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (36 mg, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 5H), 7.16 (dd, J = 8.6, 1.8 Hz, 2H), 6.90 (dd, J = 8.6, 1.7 Hz, 2H), 4.66 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 2.83 – 2.75 (m, 1H), 1.84 (br, 1H), 1.62 – 1.47 (m, 1H), 1.43 – 1.32 (m, 1H), 1.26 – 1.04 (m, 2H), 1.04 – 0.92 (m, 2H), 0.73 (td, J = 7.3, 1.6 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 142.9, 133.1, 129.7, 128.2, 127.6, 127.0, 114.0, 76.8, 55.2, 53.5, 31.7, 29.5, 22.5, 13.9.; IR (neat): ν_{max} 3458.4 (br), 2996.4 (m), 2954.1 (m), 2857.2 (m), 1610.0 (m), 1507.1 (s), 1244.8 (s), 1177.1 (m), 1034.9 (m), 700.2 (s) cm^{-1}. HRMS (DART) for $C_{19}H_{23}O$ $[M+H-H_2O]^+$: calculated: 267.1749, found: 267.1756. $[\alpha]^{20}_D$: +37.172 (c = 1.300, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-hexenyl B(mac),, and $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

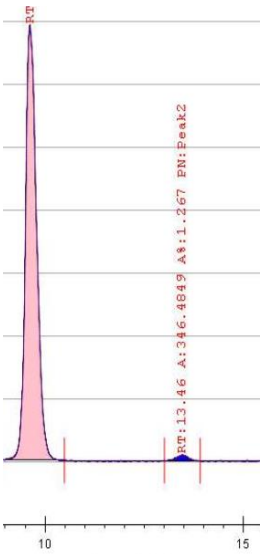
Chiral SFC (Chiralcel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(4-methoxyphenyl)-1-phenylhexan-1-ol

Racemic Material

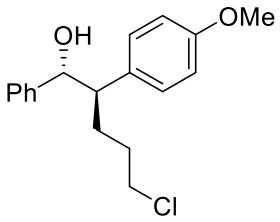


Peak No	% Area	Area	RT (min)
1	51.3895	6598.905	9.12
2	48.6105	6242.0449	13.25
Total:	100	12840.9499	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	98.733	27000.6134	9.62
2	1.267	346.4849	13.46
Total:	100	27347.0983	



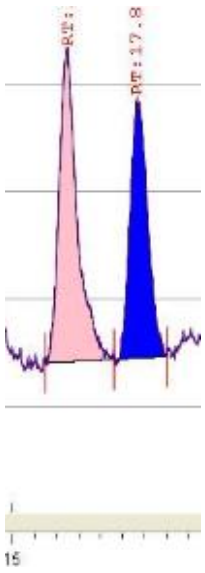
(1R,2R)-5-chloro-2-(4-methoxyphenyl)-1-phenylpentan-1-ol (21). The reaction was performed according to the general procedure ***(Method A)*** with (E)-5-chloro-pentenyl B(mac) (S-4) (65.3 mg, 0.2 mmol, 1.0 equiv.), phenyllithium in dibutyl ether solution (1.9 M) (0.105 mL, 0.2 mmol, 1.0 equiv.), (4-methoxyphenyl) trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **3.80** (2.30 mg, 0.0022 mmol, 0.011 equiv.) and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (31.1 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 7.17 – 7.11 (m, 2H), 6.91 – 6.85 (m, 2H), 4.65 (d, J = 8.2 Hz, 1H), 3.80 (s, 3H), 3.38 – 3.25 (m, 2H), 2.83 – 2.75 (m, 1H), 1.81 (s, 1H), 1.70 – 1.43 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.7, 142.5, 132.2, 129.6, 128.3, 127.8, 126.9, 114.2, 78.8, 55.2, 52.9, 44.8, 30.5, 29.3. IR (neat): ν_{max} 3466.9 (br), 2995.5 (w), 2953.4 (w), 1609.7 (w), 1510.6 (s), 1453.8 (w), 1301.7 (w), 1247.0 (s), 1178.4 (m), 1034.2 (m), 701.56 (m) cm^{-1}. HRMS (DART) for $C_{18}H_{21}ClO_2$ $[M+H-H_2O]^+$: calculated: 287.1203, found:287.1212. $[\alpha]^{20}_D$: +14.145 (c = 0.82, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-5-chloro-pentenyl B(mac), and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

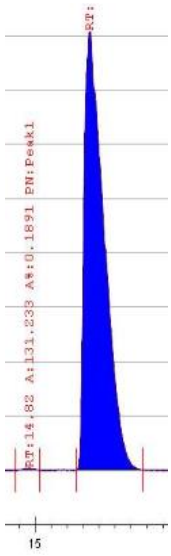
Chiral SFC (Chiralcel ODR-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-5-chloro-2-(4-methoxyphenyl)-1-phenylpentan-1-ol.

Racemic Material

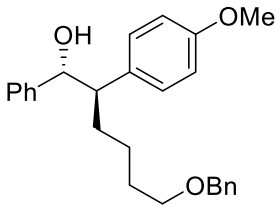


Peak No	% Area	Area	RT (min)
1	55.7361	839.1701	16.25
2	44.2639	666.443	17.83
Total:	100	1505.6131	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.1891	131.233	14.82
2	99.8109	69250.2415	16.72
Total:	100	69381.4745	



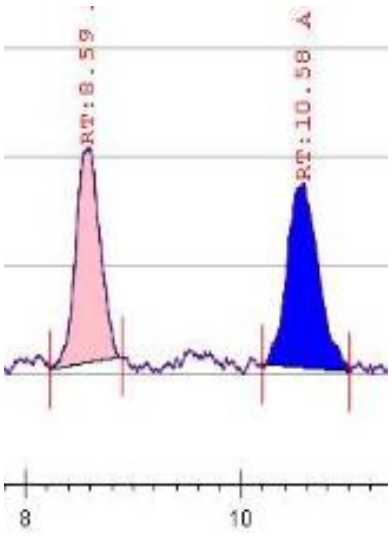
(1R,2R)-6-(benzyloxy)-2-(4-methoxyphenyl)-1-phenylhexan-1-ol (22). The reaction was performed according to the general procedure ***(Method A)*** with (E)-6-(benzyloxy)hexenyl B(mac) (S-5) (82.5 mg, 0.2 mmol, 1.0 equiv.), phenyllithium in dibutylether solution (1.9 M) (0.105 mL, 0.2 mmol, 1.0 equiv.), (4-methoxyphenyl) trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **3.80** (2.30 mg, 0.0022 mmol, 0.011 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (39.1 mg, 50.0% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ. 7.42 – 7.21 (m, 10H), 7.19 – 7.12 (m, 2H), 6.95 – 6.86 (m, 2H), 4.65 (d, J = 8.4, 2.4 Hz, 1H), 4.38 (s, 2H), 3.82 (s, 3H), 3.35 – 3.24 (m, 2H), 2.87 – 2.73 (m, 1H), 1.82 (s, 1H), 1.61 – 1.34 (m, 4H), 1.18 – 1.01 (m, 2H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 142.9, 138.7, 133.0, 129.8, 128.40, 128.37, 127.8, 127.7, 127.6, 127.1, 114.2, 78.9, 72.9, 70.2, 55.3, 53.5, 31.9, 29.6, 24.0.; IR (neat): ν_{max} 3438.8 (br), 3060.1 (w), 3029.9 (w), 2932.3 (m), 2857.5 (m), 1609.6 (m), 1510 (s), 1453.3 (m), 1245.8 (s), 1177.5 (m), 1093.9 (m), 1029.1 (s), 698.4 (s) cm^{-1}. HRMS (DART) for $C_{26}H_{30}O_3$ $[M+H-H_2O]^+$: calculated: 373.2168, found: 373.215. $[\alpha]^{20}_D$: +18.497 (c = 0.955, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-6-(benzyloxy)hexenyl B(mac), and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-3.80** and **3.80** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

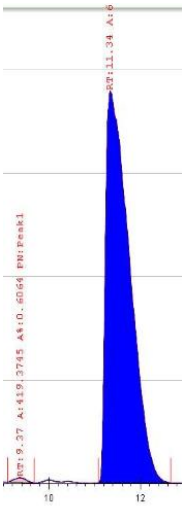
Chiral SFC (Chiralcel ODR-H ,15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-6-(benzyloxy)-2-(4-methoxyphenyl)-1-phenylhexan-1-ol.

Racemic Material

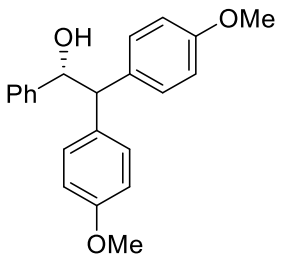


Peak No	% Area	Area	RT (min)
1	47.6343	616.1072	8.59
2	52.3657	677.3049	10.58
Total:	100	1293.4121	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.6064	419.3745	9.37
2	99.3936	68741.3181	11.34
Total:	100	69160.6926	



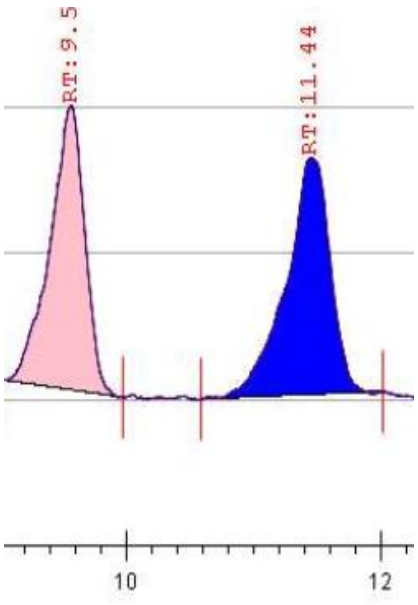
(R)-2,2-bis(4-methoxyphenyl)-1-phenylethan-1-ol (23). The reaction was performed according to the general procedure (**Method A**) with 4-methoxy-styrenyl B(mac) (S-6) (71.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 µmol, 0.010 equiv.), **3.80** (2.5 mg, 2.4 µmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (32 mg, 48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 7.6 Hz, 2H), 7.28 – 7.17 (m, 5H), 7.02 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 5.30 (d, J = 8.6 Hz, 1H), 4.17 (d, J = 8.6 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.13 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 157.9, 142.4, 134.1, 133.1, 129.9, 129.4, 128.0, 127.4, 126.9, 114.2, 113.6, 77.0, 58.6, 55.2, 55.1.; IR (neat): ν_{max} 3429.1 (br), 3060.9 (w), 3030.9 (w), 2932.3 (m), 2834.9 (m), 1608.3 (m), 1508.8 (s), 1245.1 (s), 1176.8 (m), 1032.8 (m), 814.5 (m), 700.5 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{21}O_2$ $[M+H-H_2O]^+$: calculated: 317.1536, found: 317.1535. $[\alpha]^{20}_D$: -51.455 (c = 1.105, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

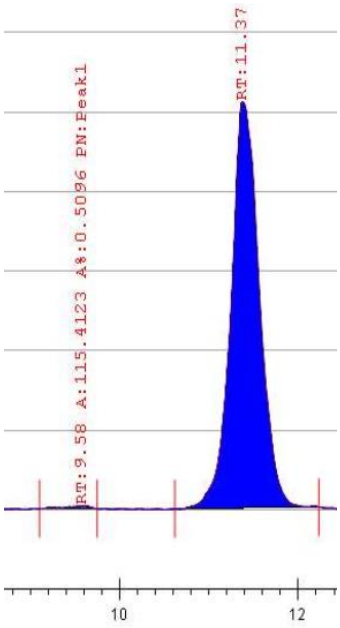
Chiral SFC (Chiralcel OJ-H, 15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2,2-bis(4-methoxyphenyl)-1-phenylethan-1-ol

Racemic Material

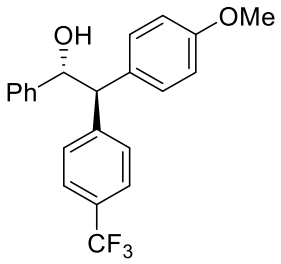


Peak No	% Area	Area	RT (min)
1	48.6093	3676.123	9.57
2	51.3907	3886.4641	11.44
Total:	100	7562.5871	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.5096	115.4123	9.58
2	99.4904	22531.7318	11.37
Total:	100	22647.1441	



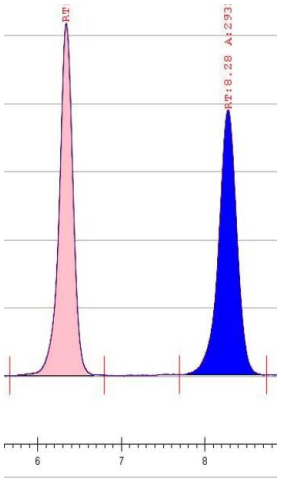
(1R)-2-(4-methoxyphenyl)-1-phenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol (24). The reaction was performed according to the general procedure (**Method A**) at 60 ºC with 4-trifluoromethyl-styrenyl B(mac) (S-7) (78.8 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (1.35 mg, 6.0 μmol, 0.030 equiv.), **3.80** (6.7 mg, 6.4 μmol) , 0.032 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a yellow oil (51 mg, 69% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 2H), 7.34 – 7.12 (m, 9H), 6.90 (d, J = 8.8 Hz, 2H), 5.35 (d, J = 8.4 Hz, 1H), 4.27 (d, J = 8.4 Hz, 1H), 3.80 (s, 3H), 2.16 (s, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 161.4, 148.7, 144.5, 134.5, 132.6, 131.5, 131.2 (q, $^{2}J_{C-F}$ = 32.4 Hz), 130.9, 130.8, 130.5, 129.5, 127.8 (q, $^{3}J_{C-F}$ = 3.9 Hz), 126.8 (q, $^{1}J_{C-F}$ = 271.8 Hz), 117.0, 79.3, 61.8, 57.9.; ^{19}F NMR (564 MHz, $CDCl_3$): δ -62.48.; IR (neat): ν_{max} 3405.1 (br), 3033,4 (w), 2929.2 (m), 2837.9 (w), 1612.4 (m), 1510.8 (s), 1324.0 (s), 1249.5 (s), 1162.8 (s), 1115.1 (s), 1035.4 (s), 814.5 (s), 754.3 (s), 700.4 (s), 605.7 (s) cm^{-1}. HRMS (DART) for $C_{22}H_{18}F_3O$ [M+H-H_2O]$^{+}$: calculated: 355.1310, found: 355.1311. $[\alpha]^{20}_{D}$: -27.50 (c = 1.115, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

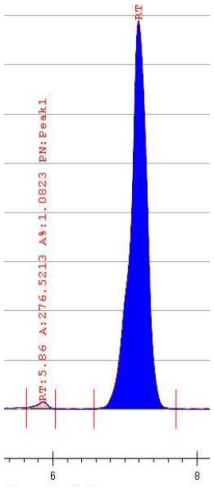
Chiral SFC (Chiralcel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R)-2-(4-methoxyphenyl)-1-phenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol

Racemic Material

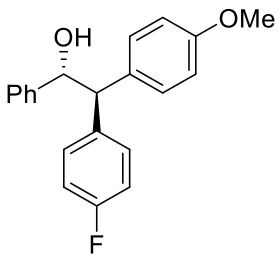


Peak No	% Area	Area	RT (min)
1	50.2702	2965.8056	6.34
2	49.7298	2933.9292	8.28
Total:	100	5899.7348	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	1.0823	276.5213	5.86
2	98.9177	25273.2809	7.19
Total:	100	25549.8022	



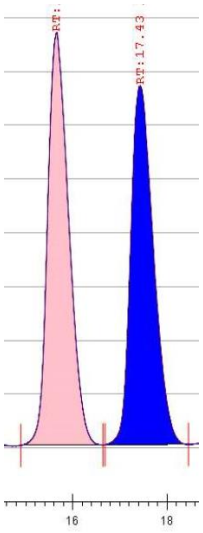
(1R)-2-(4-fluorophenyl)-2-(4-methoxyphenyl)-1-phenylethan-1-ol (25). The reaction was performed according to the general procedure (**Method A**) at 60 ºC with 4-fluoro-styrenyl B(mac) (S-8) (68.8 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 µmol, 0.010 equiv.), **3.80** (2.5 mg, 2.4 µmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a yellow oil (38 mg, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.6 Hz, 2H), 7.26 – 7.17 (m, 5H), 7.08 – 7.03 (m, 2H), 6.90 (d, J = 8.9 Hz, 2H), 6.83 (t, J = 8.6 Hz, 2H), 5.29 (d, J = 8.6 Hz, 1H), 4.19 (d, J = 8.7 Hz, 1H), 3.80 (s, 3H), 2.14 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.3 (d, $^{1}J_{C\text{-}F}$ = 244.7 Hz), 158.6, 142.2, 137.7, 137.7, 132.6, 129.9 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 129.8, 128.1, 127.6, 126.8, 115.0 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz), 114.2, 77.0, 58.7, 55.3.; ^{19}F NMR (470 MHz, $CDCl_3$): δ -116.7.; IR (neat): ν_{max} 3383.7 (br), 3062.4 (w), 3031.9 (w), 2905.6 (w), 2835.8 (w), 1605.4 (s), 1247.9 (m), 1033.8 (m), 819.4 (m), 752.9 (m), 700.4 (m), 576.7 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{18}OF$ $[M+H-H_2O]^+$:calculated: 305.1336, found: 305.1369. $[\alpha]^{20}_D$: -42.020 (c = 1.315, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

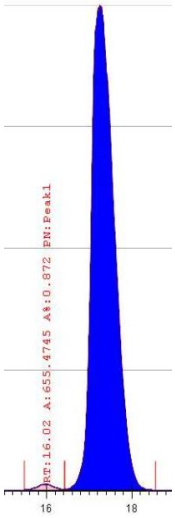
Chiral SFC (Chiralcel OD-H, 9% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R)-2-(4-fluorophenyl)-2-(4-methoxyphenyl)-1-phenylethan-1-ol.

Racemic Material



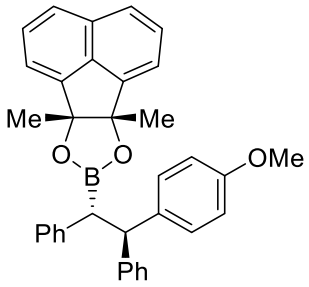
Peak No	% Area	Area	RT (min)
1	51.6168	23769.3094	15.65
2	48.3832	22280.2598	17.43
Total:	100	46049.5692	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.872	655.4745	16.02
2	99.128	74514.8681	17.25
Total:	100	75170.3426	

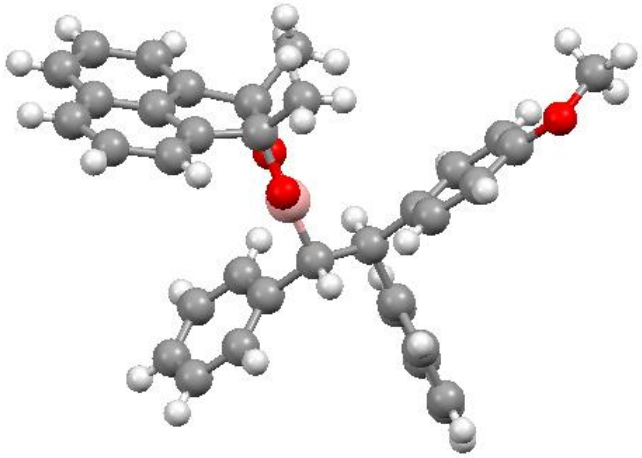
3.4.2.6. Gram-scale reaction and transformations of products



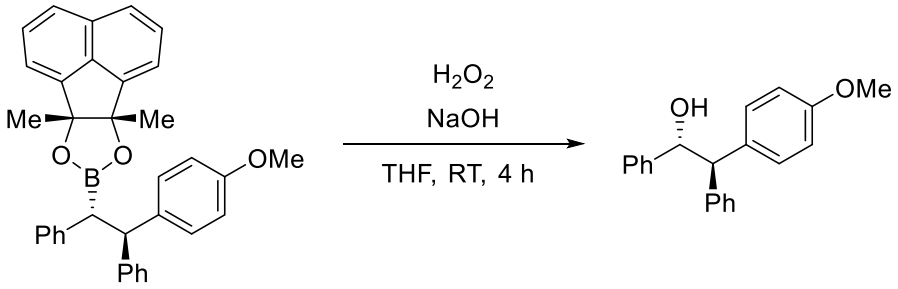
8-((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (26). The reaction was performed according to the general procedure ***(Method A)*** with styrenyl B(mac) (S-1) (1.00 g, 3.07 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 1.6 mL, 3.07 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (864.0 mg, 3.37 mmol, 1.1 equiv.), palladium (II) acetate (6.9 mg, 30 μmol, 0.010 equiv.), **3.80** (38.7 mg, 37 μmol) , 0.012 equiv.), and cesium fluoride (465.7 mg, 3.07 mmol, 1.0 equiv.) in THF (12.3 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a white solid (1.1 g, 70 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.58 – 7.49 (m, 2H), 7.41 (dd, J = 16.5, 6.9 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.09 (t, J = 7.6 Hz, 2H), 7.05 – 6.90 (m, 8H), 6.18 (d, J = 8.7 Hz, 2H), 4.25 (d, J = 12.6 Hz, 1H), 3.61 (s, 3H), 3.15 (d, J = 12.6 Hz, 1H), 1.55 (d, J = 14.6 Hz, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.9, 147.1, 146.9, 146.8, 143.4, 139.0, 137.4, 137.3, 133.9, 131.8, 131.1, 131.0, 130.84, 130.77, 130.66, 130.5, 130.4, 130.3, 128.2, 127.92, 127.89, 127.7, 127.6, 122.2, 121.8, 121.7, 115.5, 94.5, 94.4, 57.5, 56.7, 24.9, 24.40, 24.35.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.2.; IR (neat): ν_{max} 3058.3 (w), 3026.7 (w), 2972.6 (w), 2932.0 (w), 1607.0 (m), 1494.3 (m), 1316.6 (m), 1176.6 (m), 1034.5 (m), 846.8 (m), 699.6 (m) cm^{-1}. HRMS (DART) $C_{35}H_{35}BO_3N$ $[M+H]^+$: calculated: 528.2716, found: 528.2725. $[\alpha]^{20}_D$: -80.816 (c = 0.667, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Enantiomeric ratio was determined by chiral SFC analysis of the corresponding alcohol (see Compound 2b). Absolute stereochemistry was determined by single crystal X-ray diffraction.

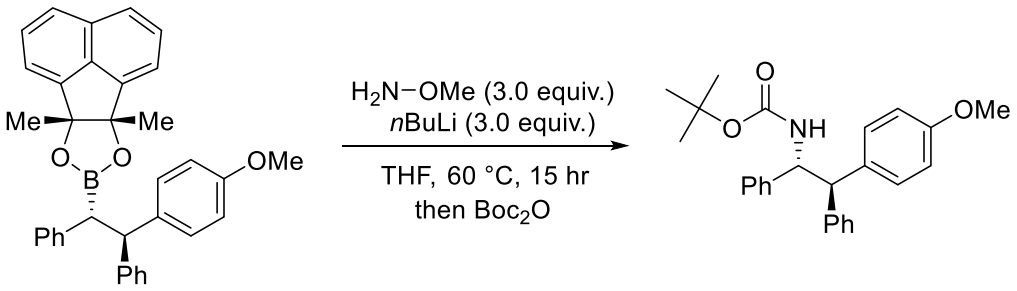


Oxidation



(1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethan-1-ol (2b). 8-((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (26) (51.0 mg, 0.1 mmol, 1.0 equiv.) was dissolved in THF (2 mL) and cooled to 0 °C. 3M NaOH (1.0 mL) was added, followed by 30% H_2O_2 (0.5 mL), dropwise. The reaction mixture was allowed to stir at room temperature for 4 hours. The reaction mixture was cooled to 0 °C and saturated aq. $Na_2S_2O_3$ solution (3 mL) was added dropwise. After stirring at room temperature for 10 minutes, the reaction mixture was poured into a separatory funnel and the aqueous layer was washed three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography with silica gel (silica gel was treated with 2% triethylamine / hexanes prior to use.) (2%-20% EtOAc / hexane, stain in magic stain) to afford the desired product as a white solid (28.0 mg, 92.0% yield).

Amination



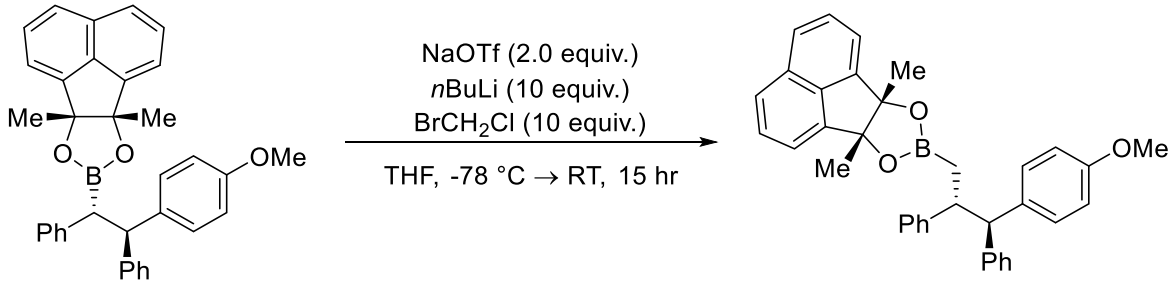
tert-butyl ((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)carbamate (27). The title compound was prepared according to a literature procedure.[51] A flame-dried, 2-dram vial equipped with a magnetic stir bar and septum was purged with N_2. After 5 minutes, O-methylhydroxylamine (2 M in THF, 150.00 uL, 0.3 mmol, 3.0 equiv.) was added and diluted with THF (1 mL). The reaction flask was cooled to -78 °C. A solution of n-butyllithium (2.5 M in hexanes, 120.00 uL, 0.3 mmol, 3.0 equiv.) was added dropwise and the reaction was allowed to stir at -78 °C for 30 min. A separate flame-dried 1-dram vial was charged with 8-((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (26) (51.0 mg, .1 mmol, 1.0 equiv.) and diluted with THF (0.5 mL) under N_2. The solution of boronic ester was then added dropwise to the solution of deprotonated O-methylhydroxylamine dropwise via syringe. The reaction vial was warmed to room temperature and then heated to 60 °C. After stirring at 60 °C for 12 h, the reaction flask was cooled to room temperature and tert-butoxycarbonyl tert-butyl carbonate (1 M in THF, 320.00 uL, 0.32 mmol, 3.2 equiv.) was added and reaction was allowed to stir for 2 h at room temperature. The reaction was filtered through a plug of celite with Et_2O and concentrated in vacuo to give the crude reaction mixture and subsequently purified by silica gel column chromatography (silica gel was treated with 2% triethylamine / hexanes prior to use) (5%-20% EtOAc / hexane, stain in magic stain) to afford the desired product as a white solid (36.0 mg, 89.2% yield). ^1H NMR (500 MHz, $CDCl_3$)

δ 7.23 – 7.01 (m, 12H), 6.87 – 6.80 (m, 2H), 5.35 (br, J = 59.7 Hz, 1H), 4.86 (br, 1H), 4.17 (d, J = 9.3 Hz, 1H), 3.78 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 155.0, 142.0, 129.8, 128.4, 128.2, 128.0, 127.0, 126.9, 126.3, 113.9, 57.3, 55.2, 28.3.; IR (neat): ν_{max} 3402.9 (m), 3029.3 (w), 2975.3 (m), 2934.1 (w), 1682.8 (s), 1511.6 (s), 1248.6 (m), 1169.4 (m), 1015.3 (m), 696.5 (m) cm^{-1}. HRMS (DART) for $C_{26}H_{30}NO_3$ $[M+H]^+$: calculated: 404.2226, found: 404.2226. $[\alpha]^{20}_D$: -66.337 (c = 1.150, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantiospecificity was determined by the diastereomer ratio (>20:1) as detected by ^{1}H NMR.

Homologation



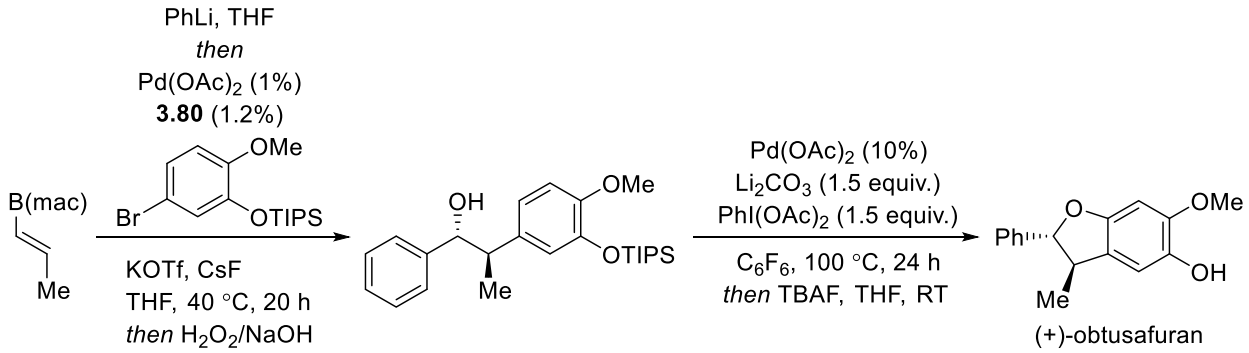
8-((2R,3R)-3-(4-methoxyphenyl)-2,3-diphenylpropyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (28). The title compound was prepared according to a literature procedure with slight modification.[52] In an argon-filled glovebox, an oven-dried 2-dram equipped with magnetic stir bar was charged with 8-((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (26) (51.0 mg, 0.1 mmol, 1.0 equiv.), sodium triflate (34.4 mg, 0.2 mmol, 2.0 equiv.), bromo(chloro)methane (129.4 mg, 1.0 mmol, 10 equiv.), and THF (0.75 mL). The vial was sealed with a septum cap and removed from glovebox. The reaction was cooled to -78 °C and *n*-butyllithium (2.5 M in hexane, 400.00 uL, 1.0 mmol, 10 equiv.) was added dropwise. The resulting mixture was stirred for 1 hour

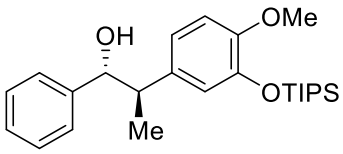
at –78 °C, then allowed to slowly warm to room temperature and stirred overnight. The reaction was filtered through a plug of celite with Et_2O and concentrated in vacuo. The crude product was purified by silica gel column chromatography (2%-5% EtOAc / hexane, stain in magic stain) to afford the desired product as a white solid (44.0 mg, 83.9% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (dd, J = 5.1, 3.1 Hz, 2H), 7.56 (dt, J = 8.2, 7.1 Hz, 2H), 7.46 (ddd, J = 11.0, 6.9, 0.8 Hz, 2H), 7.32 – 7.23 (m, 2H), 7.17 – 7.08 (m, 2H), 7.08 – 7.00 (m, 4H), 6.98 – 6.90 (m, 1H), 6.90 – 6.78 (m, 3H), 6.75 (dd, J = 204.7, 8.8 Hz, 2H), 4.04 (d, J = 11.4 Hz, 1H), 3.72 (s, 3H), 3.62 (td, J = 11.1, 4.6 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.11 (dd, J = 15.0, 4.6 Hz, 1H), 0.99 (dd, J = 15.1, 11.1 Hz, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.5, 147.40, 147.37, 147.32, 146.8, 139.0, 137.2, 134.0, 132.0, 131.0, 130.9, 130.6, 130.5, 130.1, 128.1, 128.1, 127.7, 121.88, 121.85, 116.5, 94.2, 94.1, 79.9, 79.7, 79.5, 61.8, 57.8, 48.7, 24.5, 24.3.; IR (neat): ν_{max} 3059.9 (m), 3027.5 (m), 2970.5 (m), 2931.8 (m), 1608.9 (s), 1582.9 (s), 1357.0 (s), 1250.1 (s), 1175.5 (m), 1077.3 (m), 806.8 (m), 724.7 (s), 667.3 (s) cm^{-1}. HRMS (DART) for $C_{36}H_{37}BO_3N$ $[M+NH_4]^+$: calculated: 542.2866, found: 542.2894. $[\alpha]^{20}_D$: +20.029 (c = 1.000, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantiospecificity was determined by the diastereomer ratio (>20:1) as detected by ^{1}H NMR.

3.4.2.7. Synthesis of (+)-obtusafuran

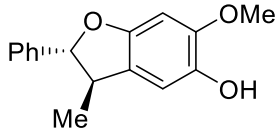




(1R,2R)-2-(4-methoxy-3-((triisopropylsilyl)oxy)phenyl)-1-phenylpropan-1-ol (30). The reaction was performed according to the general procedure ***(Method B)*** with (E)-propenyl B(mac) (S-2) (52.8 mg, 0.2 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, 0.20 mmol, 1.0 equiv.), (5-bromo-2-methoxyphenoxy)triisopropylsilane (79.1 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **3.80** (2.5 mg, 0.0024 mmol, 0.012 equiv.), potassium triflate (37.6 mg, 0.2 mmol, 1.0equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (56 mg, 68% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.31 – 7.23 (m, 1H), 6.86 – 6.76 (m, 3H), 4.57 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 2.91 (q, J = 7.4 Hz, 1H), 1.90 (br, 1H), 1.35 – 1.18 (m, 3H), 1.18 – 0.98 (m, 21H).. ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.1, 145.8, 142.6, 135.5, 128.4, 127.8, 127.13, 121.07, 120.3, 112.4, 79.8, 55.7, 47.7, 18.4, 18.11, 18.08, 18.05, 13.1. IR (neat): ν_{max} 2943, 2866, 1509, 1443, 1278, 1165, 1029, 883, 700 cm^{-1}. HRMS (DART) for $C_{25}H_{39}O_3Si$ $[M+H]^+$: calculated: 415.2663, found: 415.2659. $[\alpha]^{20}_D$: +37.25 (c = 1.02, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Absolute stereochemistry was assigned by analogy (see compounds 26, 31).

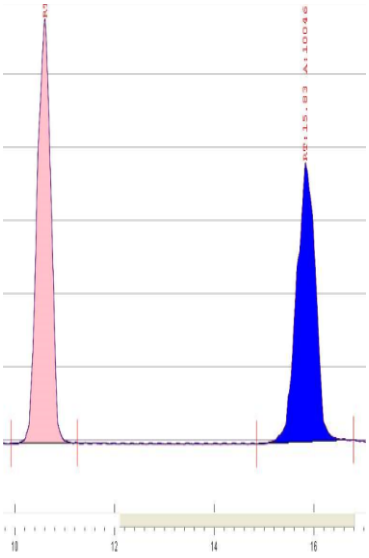


(2R,3R)-6-methoxy-3-methyl-2-phenyl-2,3-dihydrobenzofuran-5-ol ((+)-obtusafuran) (31). The reaction was performed according to a literature procedure.[52a, b] In an argon-filled glovebox, to an oven-dried 1-dram vial was added 2-(4-methoxy-3-triisopropylsilyloxy-phenyl)-1-phenyl-propan-1-ol (56 mg, 135 μmol, 1.0 equiv.), lithium carbonate (14.97 mg, 203 μmol, 1.5 equiv.), diacetoxyiodobenzene (64.84 mg, 203 μmol, 1.5 equiv.), palladium (II) acetate (3mg, 14 μmol, 0.10 equiv.), and hexafluorobenzene (0.14 mL, 1 M). The vial was sealed with a screwcap and placed in a 100 ºC oil bath. After stirring at this temperature for 24 hours, the reaction was cooled down to room temperature and filtered through a plug of silica gel with Et_2O. The crude mixture was concentrated, then dissolved in THF (0.54 mL). Tetrabutylammonium fluoride hydrate (53 mg, 203 μmol, 1.5 equiv.) was added and the reaction was stirred at room temperature for 24 hours then filtered through a plug of silica gel with Et_2O. The solvent was evaporated and the crude product was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (14 mg, 54 μmol, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 5H), 6.73 (s, 1H), 6.51 (s, 1H), 5.28 (s, 1H), 5.12 (d, J = 8.5 Hz, 1H), 3.87 (s, 3H), 3.45 – 3.32 (m, 1H), 1.39 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 146.4, 141.2, 140.1, 128.8, 128.7, 128.3, 126.3, 126.2, 123.1, 109.7, 94.4, 93.0, 56.4, 45.9, 18.6. $[\alpha]^{20}_D$: +56.2 (c = 0.90, MeOH, l = 50 mm).

Analysis of Stereochemistry:

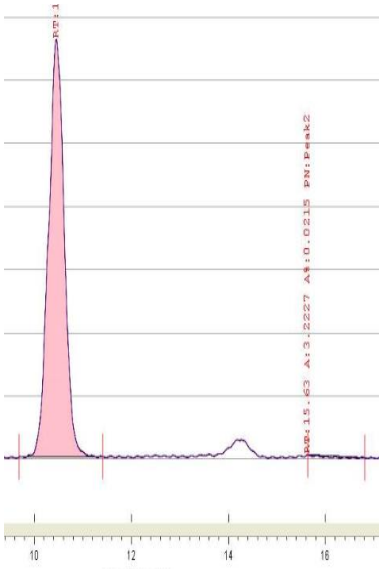
Racemic compound was prepared according to a literature procedure.[66] Absolute stereochemistry was determined by comparison of optical rotation to the literature[54] (Measured: $[\alpha]^{20}_{D}$: +56.2 (c = 0.90, MeOH, *l* = 50 mm), literature: $[\alpha]^{20}_{D}$: +50 (c = 0.33, MeOH), 99:1 *e.r* for (2R,3R)-6-methoxy-3-methyl-2-phenyl-2,3-dihydrobenzofuran-5-ol), and the absolute stereochemistry was assigned to be (2R,3R)-6-methoxy-3-methyl-2-phenyl-2,3-dihydrobenzofuran-5-ol.

Racemic material



Peak No	% Area	Area	RT (min)
1	52.64	11166.1069	10.61
2	47.36	10046.088	15.83
Total:	100	21212.1949	

Standard Conditions

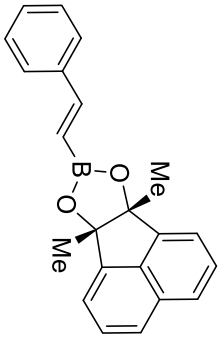


Peak No	% Area	Area	RT (min)
1	99.9785	14956.6731	10.45
2	0.0215	3.2227	15.63
Total:	100	14959.8958	

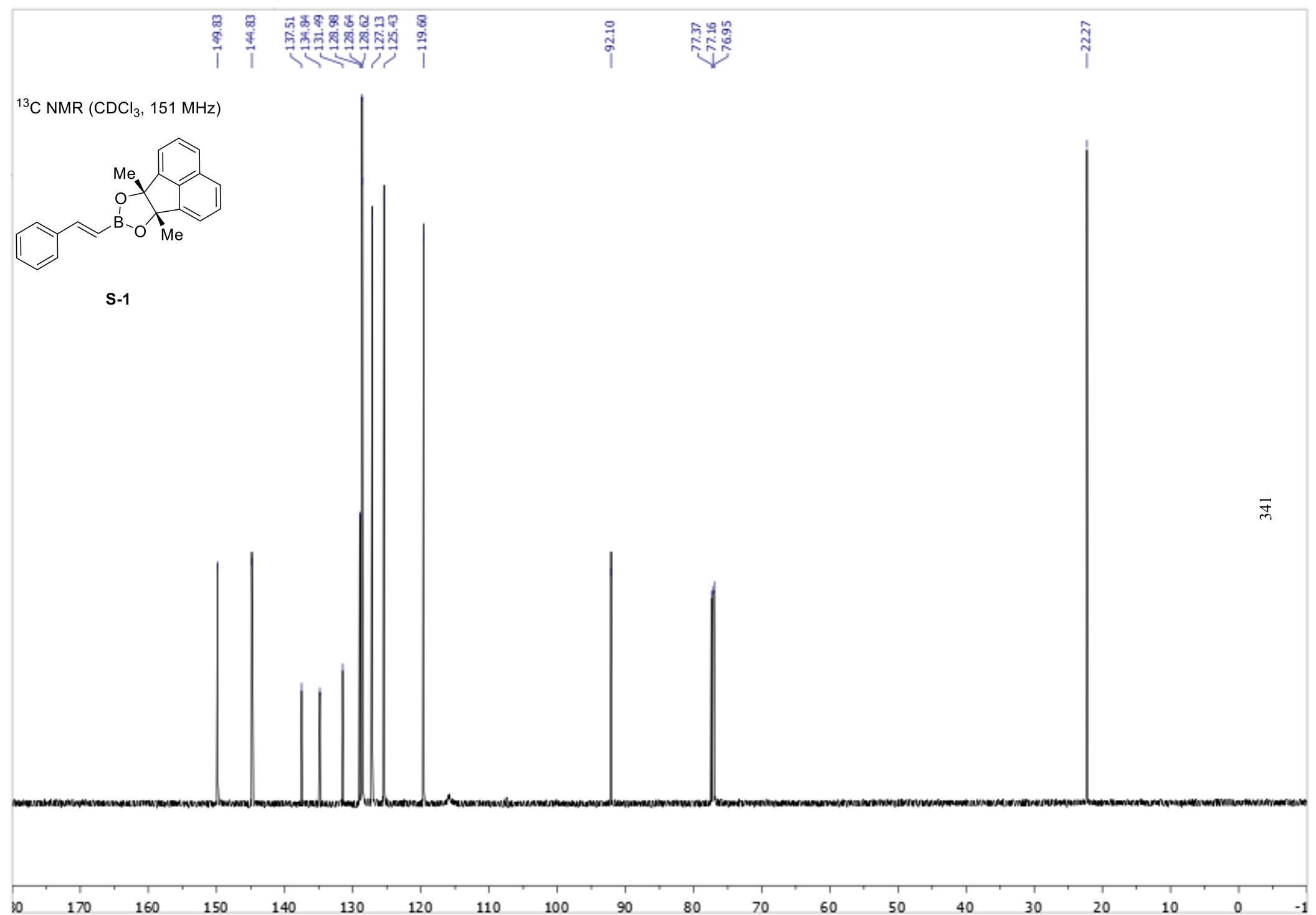
[66] Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch Jr., K. O.; Ray, J. E. *J. Org. Chem*. **1994**, *59*, 6567.

3.4.3. NMR spectra

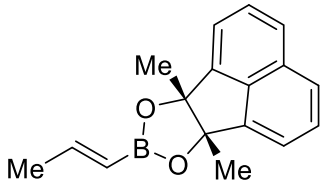
S-1



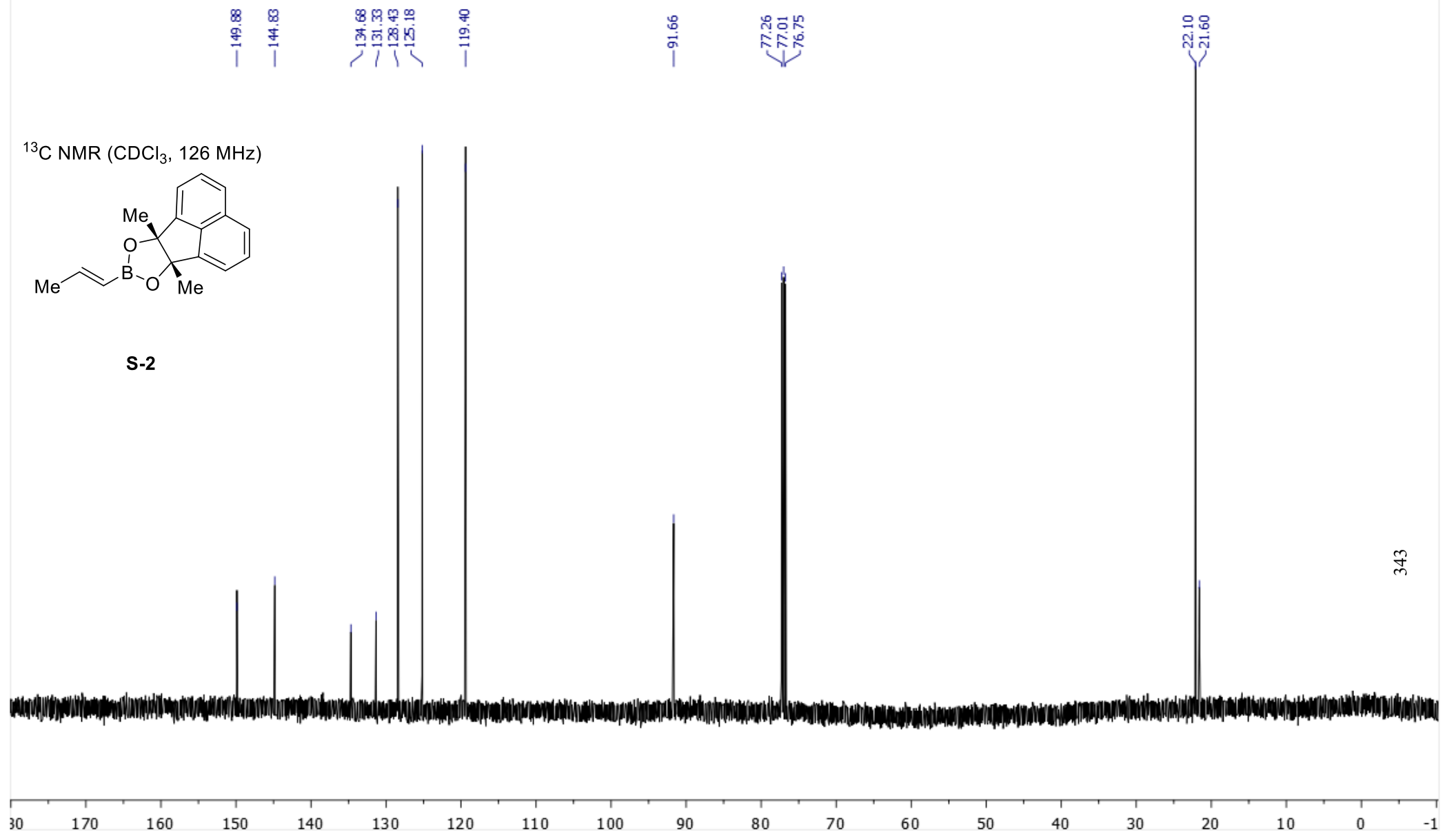
^{1}H NMR ($CDCl_3$, 600 MHz)


149.83
144.83
137.51
134.84
131.49
128.98
128.64
128.62
127.13
125.43
119.60
92.10
77.37
77.16
76.95
22.27
^{13}C NMR ($CDCl_3$, 151 MHz)
Me
O
B
O
Me
S-1
341
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

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



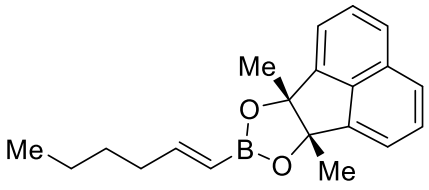
S-2



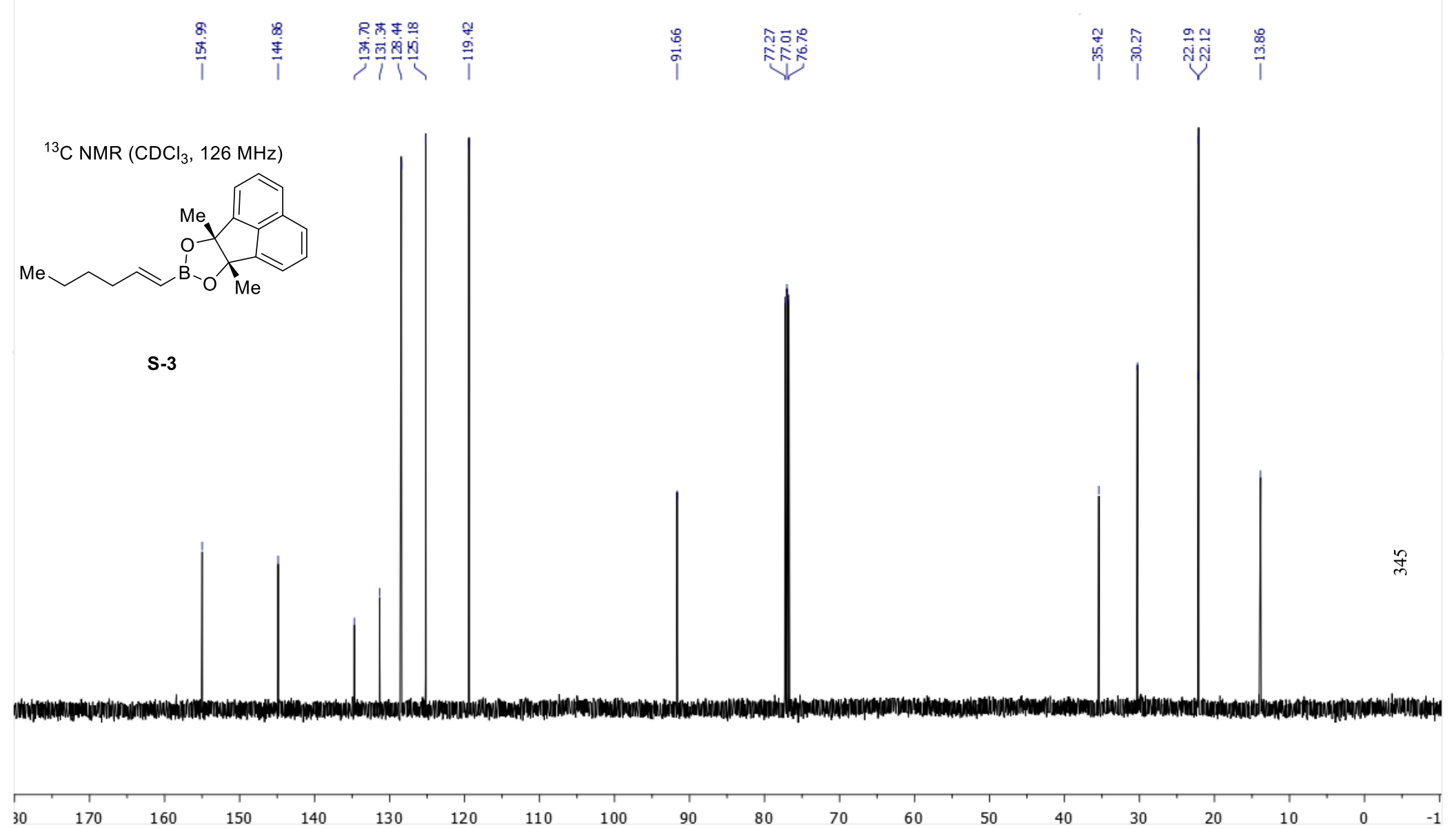
^{13}C NMR ($CDCl_3$, 126 MHz)

S-2

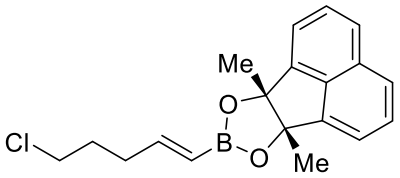
^{1}H NMR ($CDCl_3$, 500 MHz)



S-3

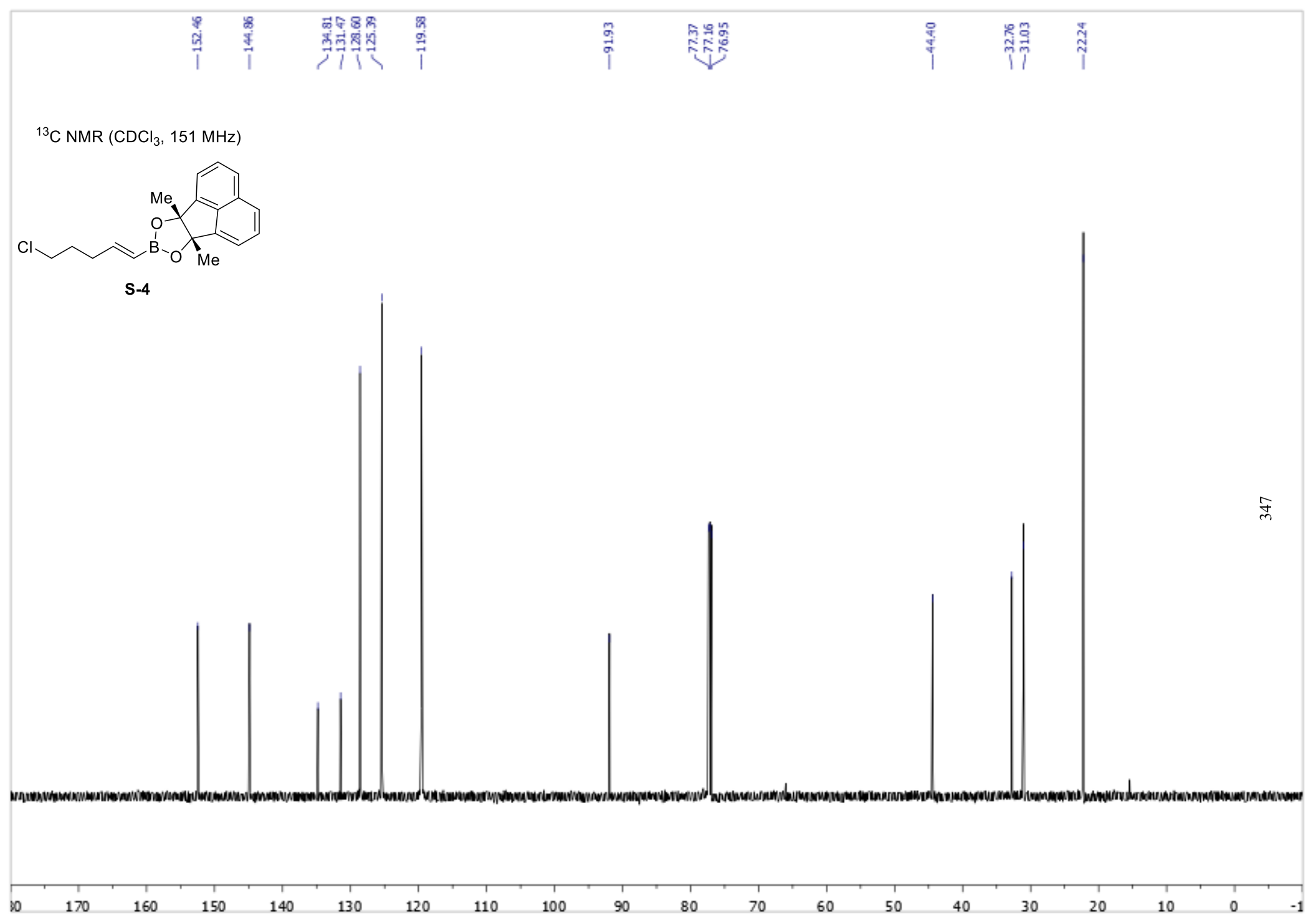

154.99
144.86
134.70
131.34
128.44
125.18
119.42
91.66
77.27
77.01
76.76
35.42
30.27
22.19
22.12
13.86
^{13}C NMR ($CDCl_3$, 126 MHz)
Me
O
B
O
Me
Me
S-3
345
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

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



S-4

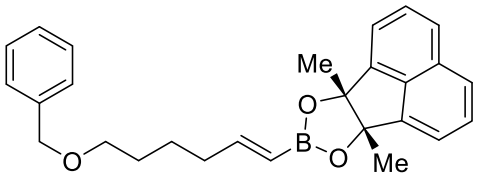
346



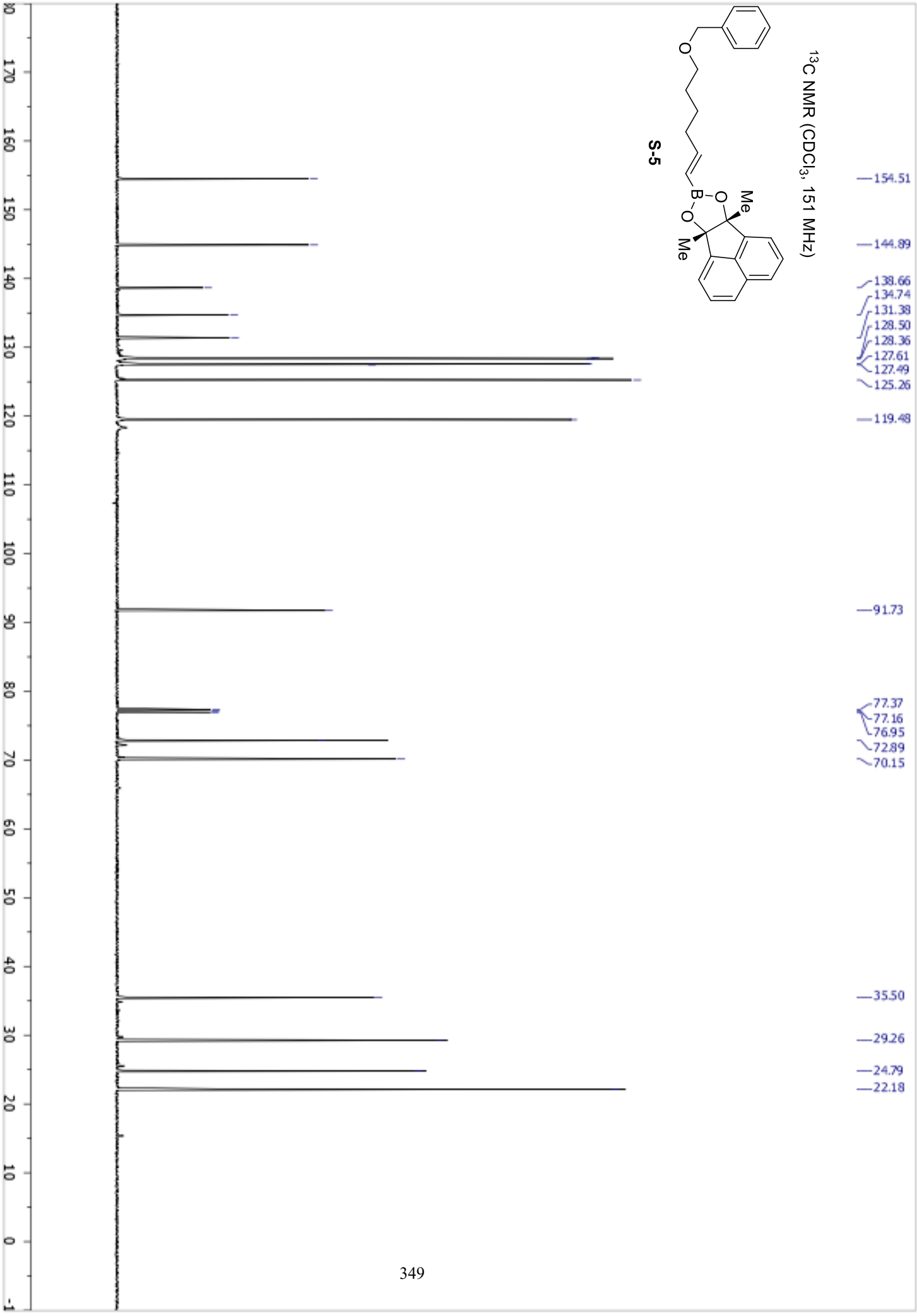
^{13}C NMR ($CDCl_3$, 151 MHz)

S-4

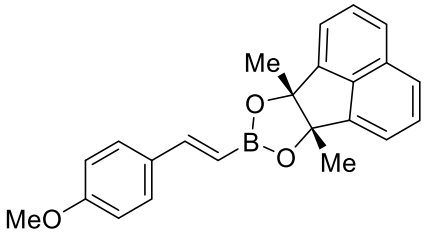
^{13}C NMR ($CDCl_3$, 151 MHz)



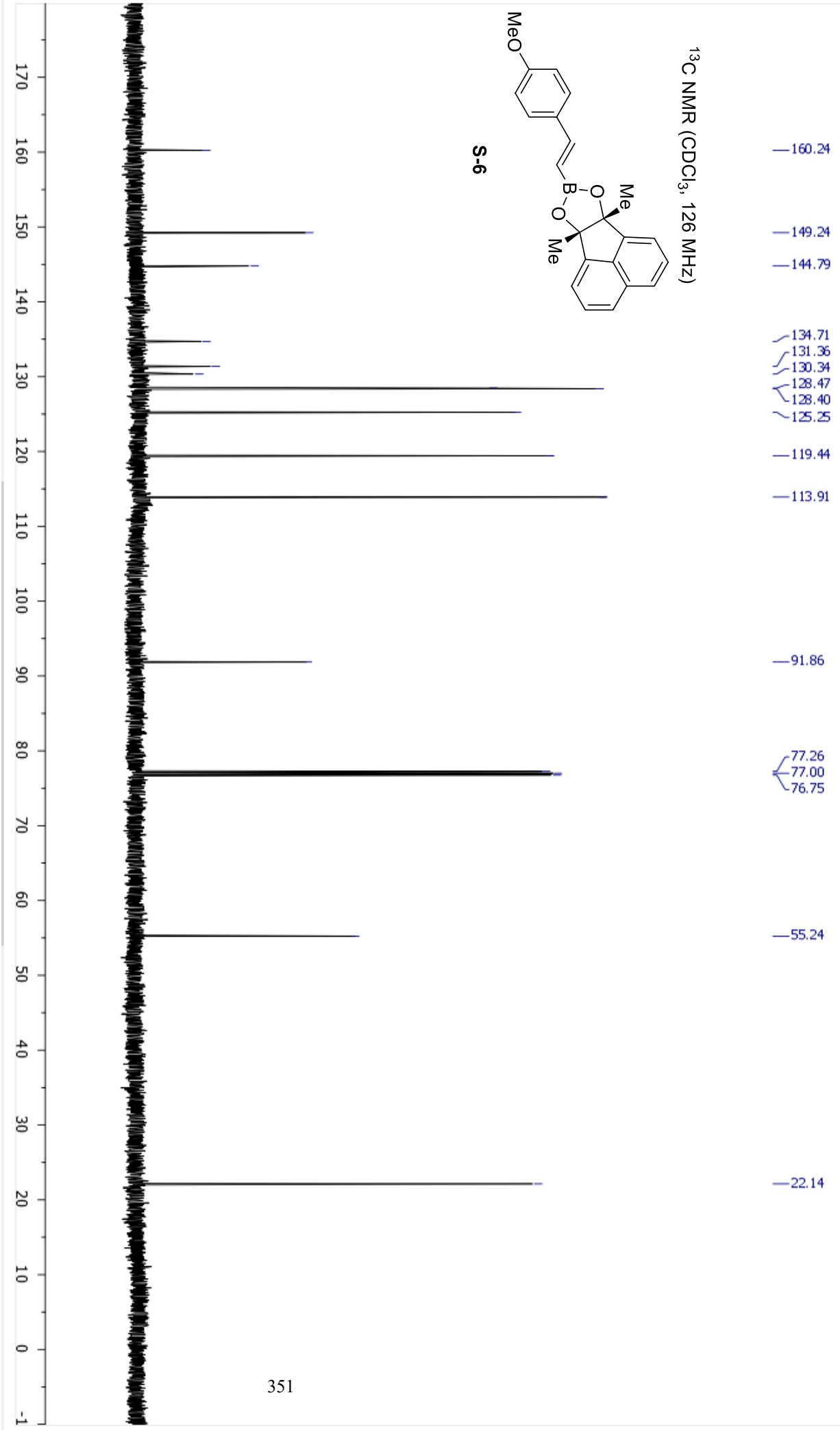
S-5


S-5
^{13}C NMR (CDCl$_3$, 151 MHz)
154.51
144.89
138.66
134.74
131.38
128.50
128.36
127.61
127.49
125.26
119.48
91.73
77.37
77.16
76.95
72.89
70.15
35.50
29.26
24.79
22.18

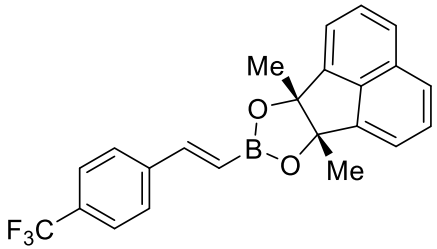
^{1}H NMR ($CDCl_3$, 500 MHz)



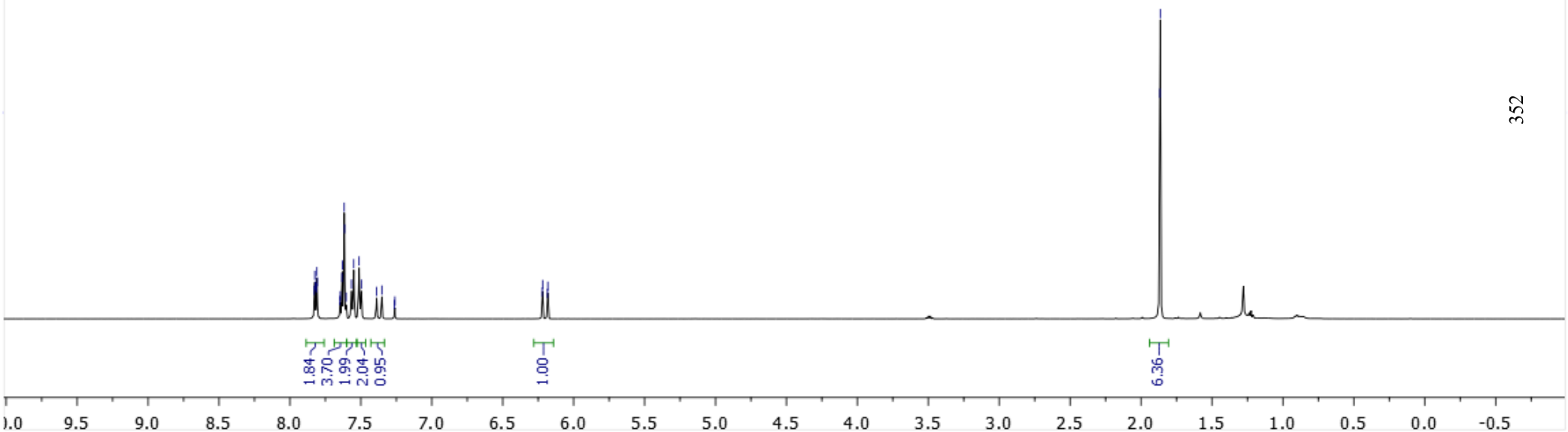
S-6

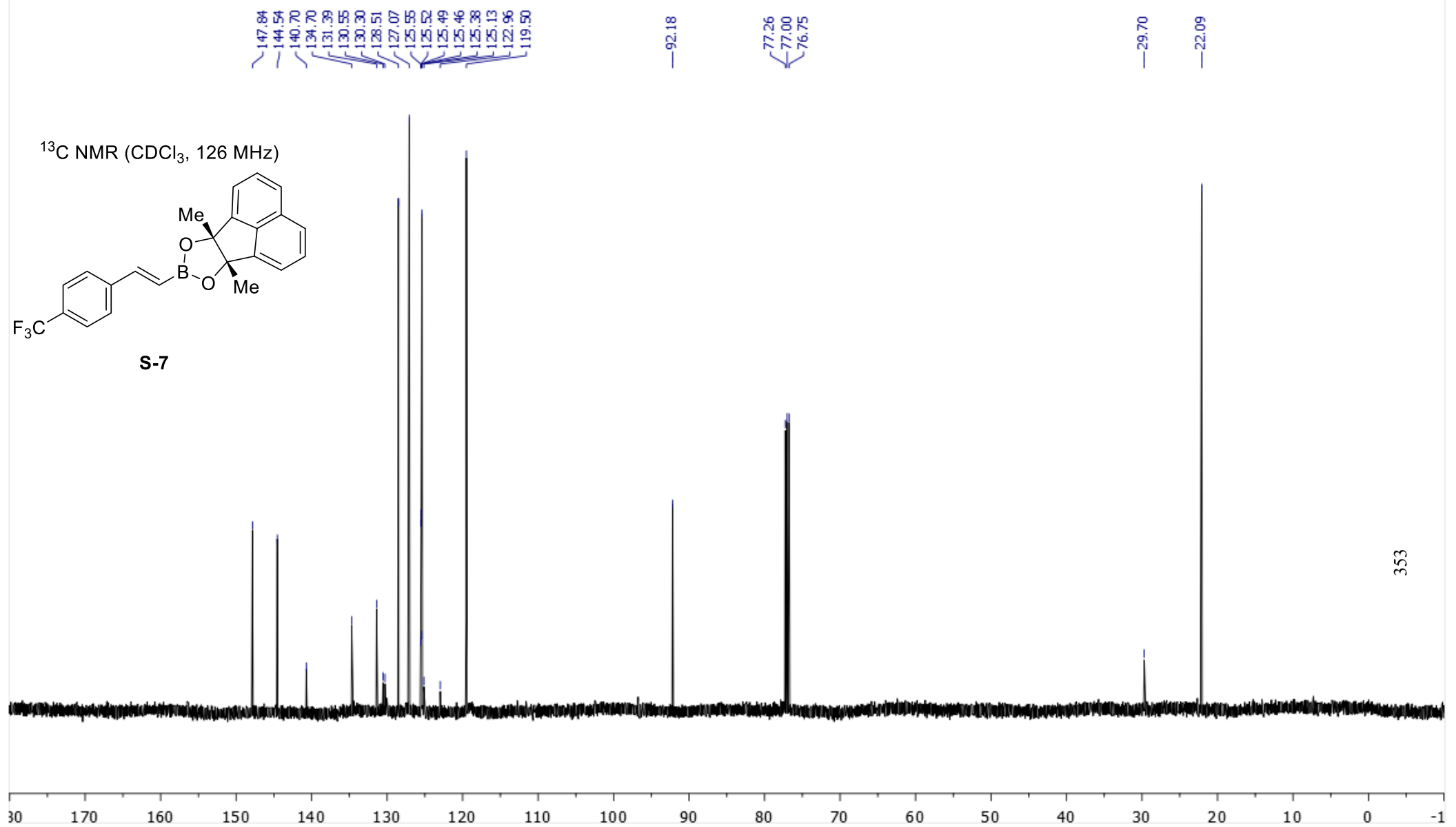

^{13}C NMR (CDCl$_3$, 126 MHz)
S-6
MeO
Me
Me
160.24
149.24
144.79
134.71
131.36
130.34
128.47
128.40
125.25
119.44
113.91
91.86
77.26
77.00
76.75
55.24
22.14

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

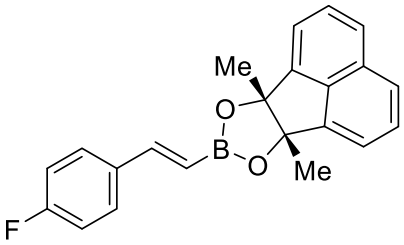


S-7

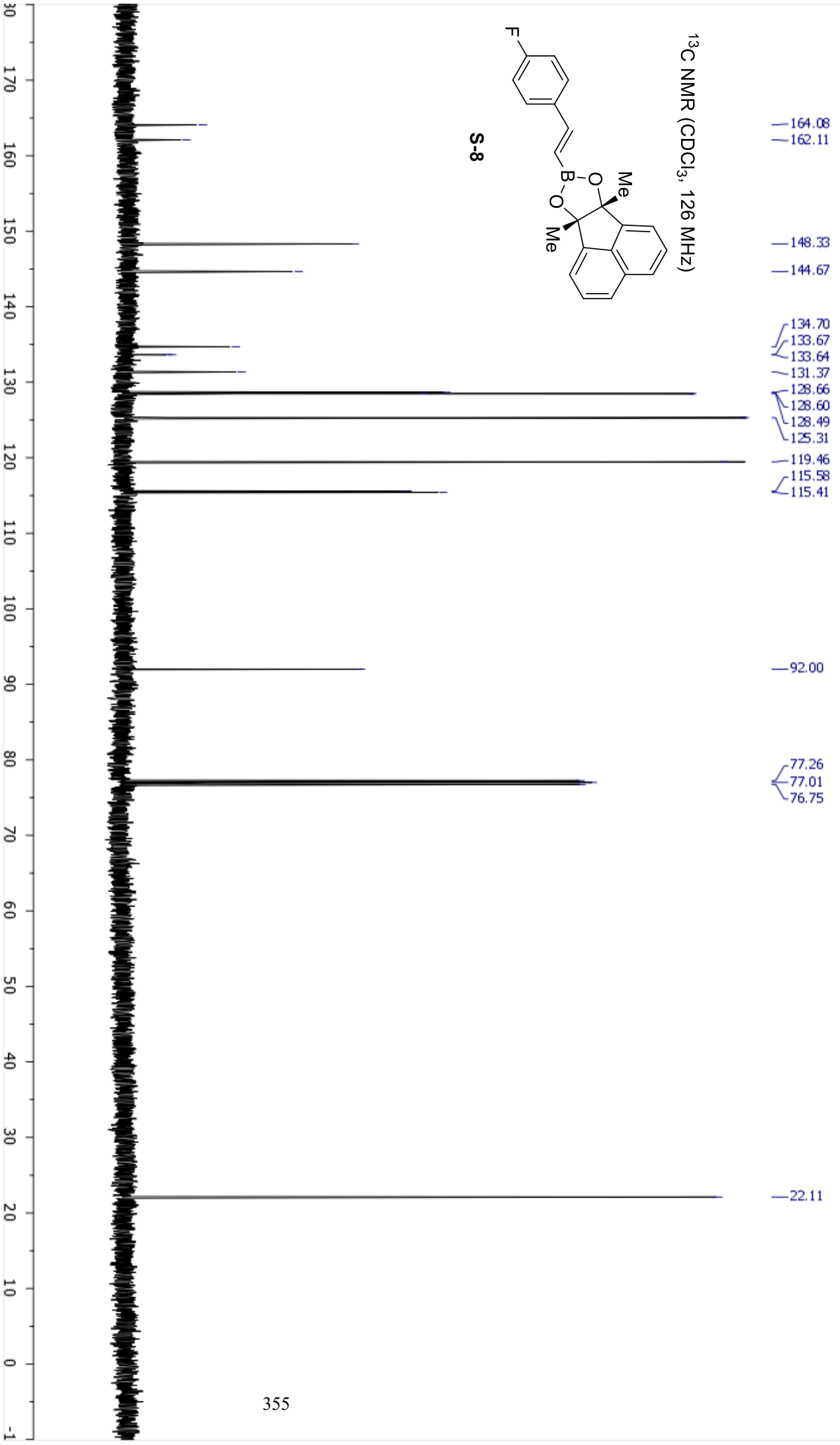


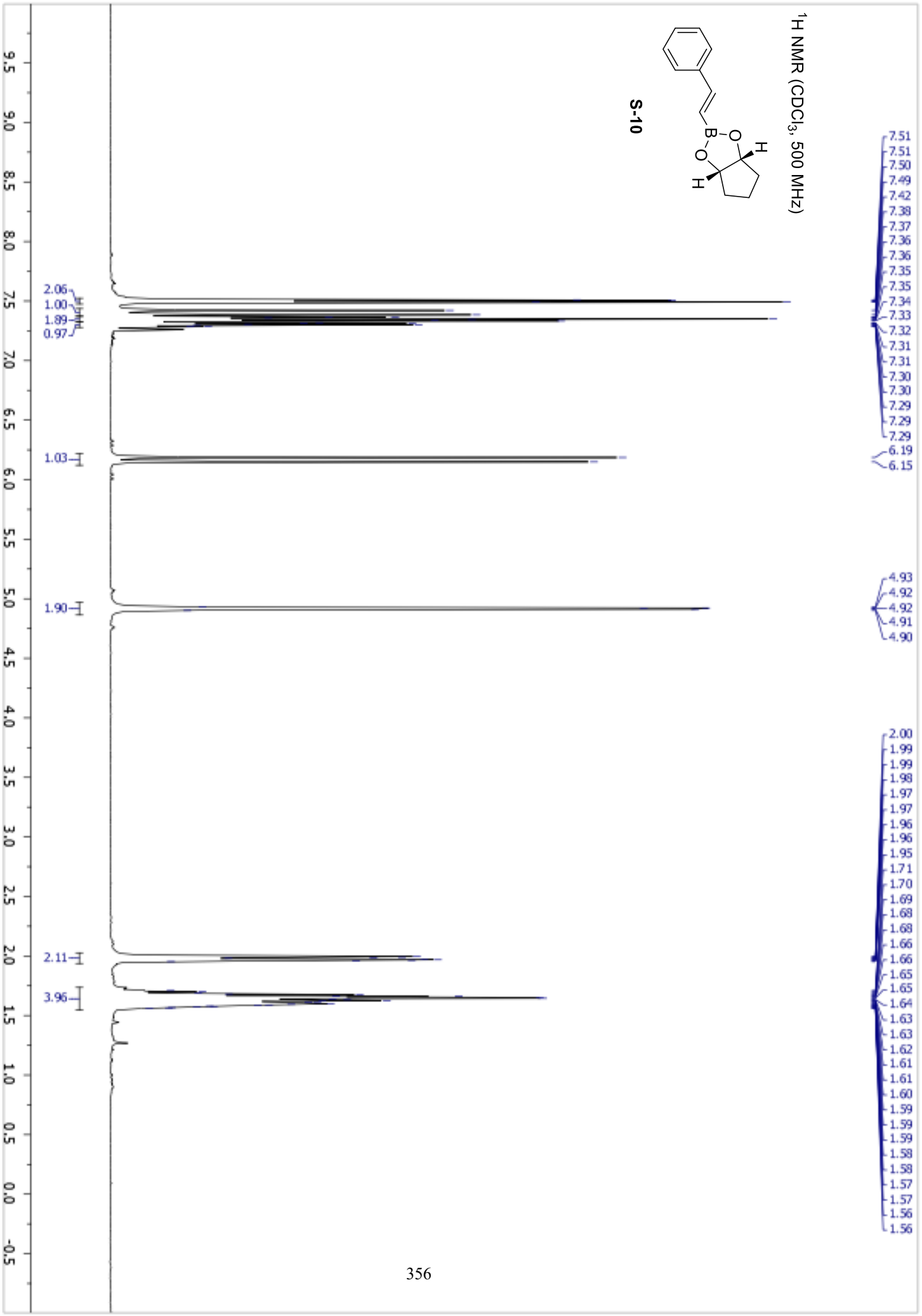

147.84
144.54
140.70
134.70
131.39
130.55
130.30
128.51
127.07
125.55
125.52
125.49
125.46
125.38
125.13
122.96
119.50
92.18
77.26
77.00
76.75
29.70
22.09
353
^{13}C NMR ($CDCl_3$, 126 MHz)
Me
O
B
O
Me
F_3C
S-7
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

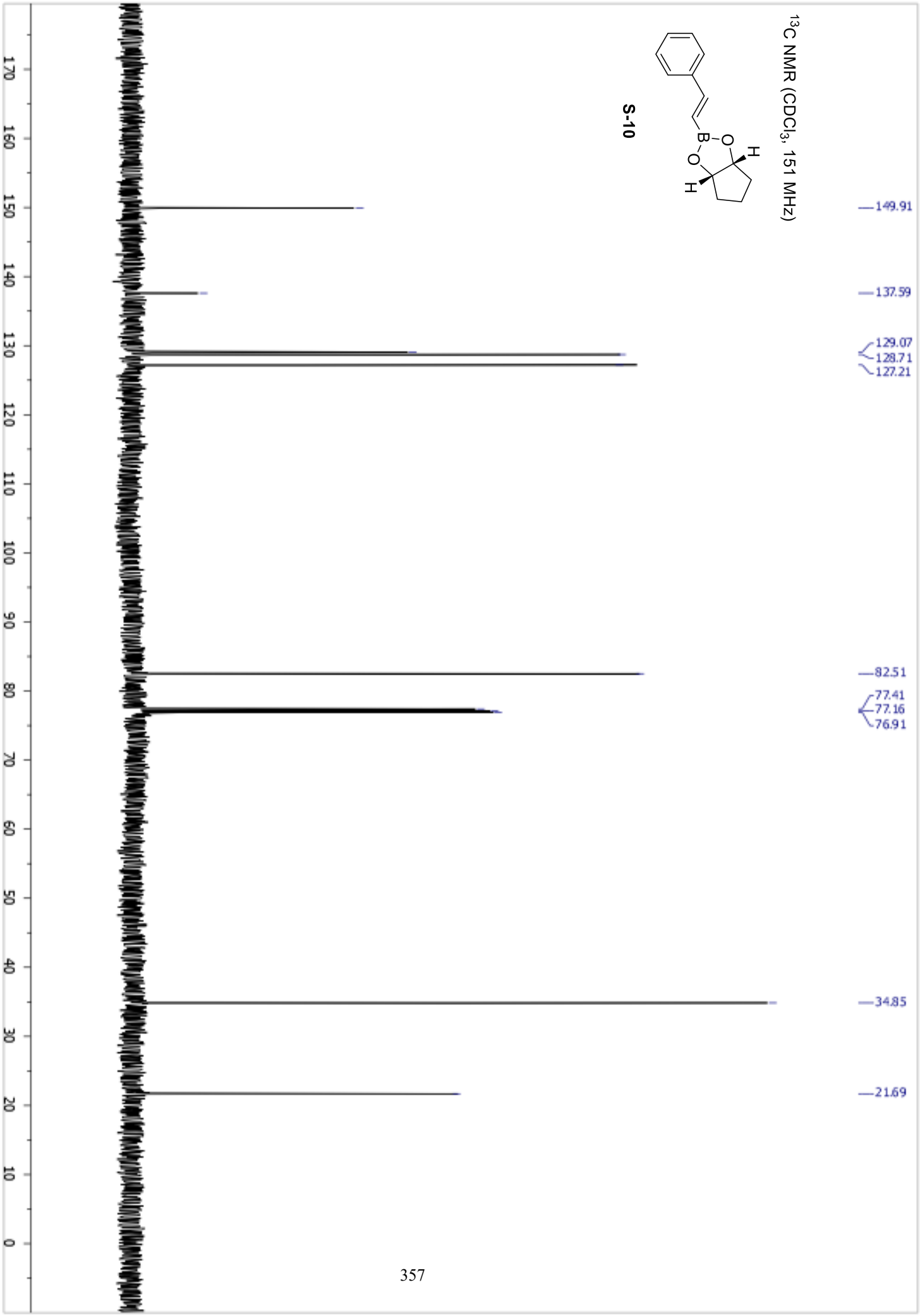
^{1}H NMR ($CDCl_3$, 500 MHz)



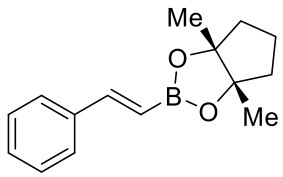
S-8


S-8
^{13}C NMR (CDCl$_3$, 126 MHz)
F
B
O
O
Me
Me
164.08
162.11
148.33
144.67
134.70
133.67
133.64
131.37
128.66
128.60
128.49
125.31
119.46
115.58
115.41
92.00
77.26
77.01
76.75
22.11
30
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

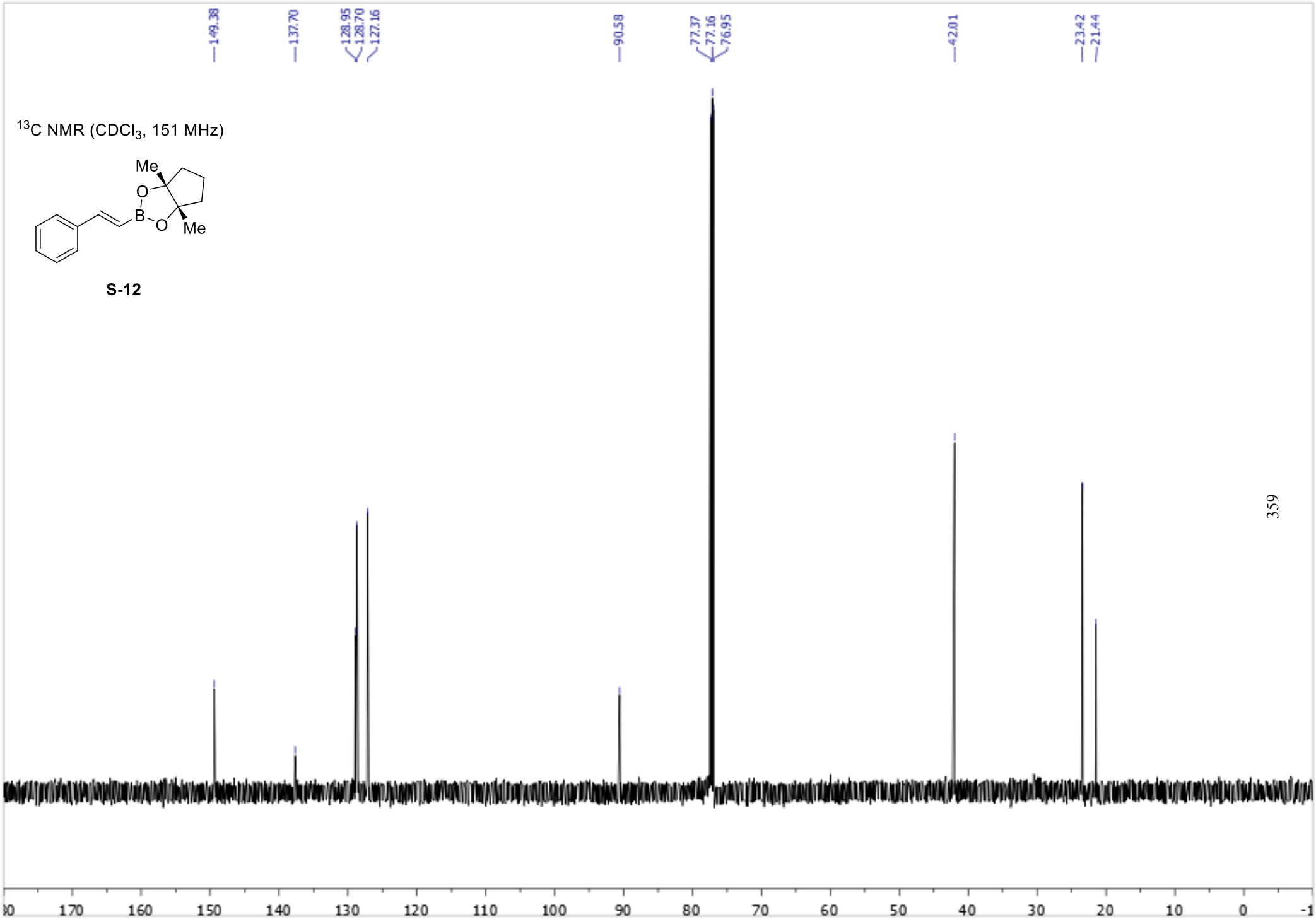

^{1}H NMR ($CDCl_3$, 500 MHz)
S-10
B
O
O
H
H
2.06
1.00
1.89
0.97
1.03
1.90
2.11
3.96
7.51
7.51
7.50
7.49
7.42
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.29
6.19
6.15
4.93
4.92
4.92
4.91
4.90
2.00
1.99
1.99
1.98
1.97
1.97
1.96
1.96
1.95
1.71
1.70
1.69
1.68
1.68
1.66
1.66
1.65
1.65
1.64
1.63
1.63
1.62
1.61
1.61
1.60
1.59
1.59
1.59
1.58
1.58
1.57
1.57
1.56
1.56


^{13}C NMR (CDCl$_3$, 151 MHz)
S-10
149.91
137.59
129.07
128.71
127.21
82.51
77.41
77.16
76.91
34.85
21.69

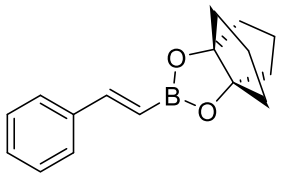
^{1}H NMR ($CDCl_3$, 600 MHz)



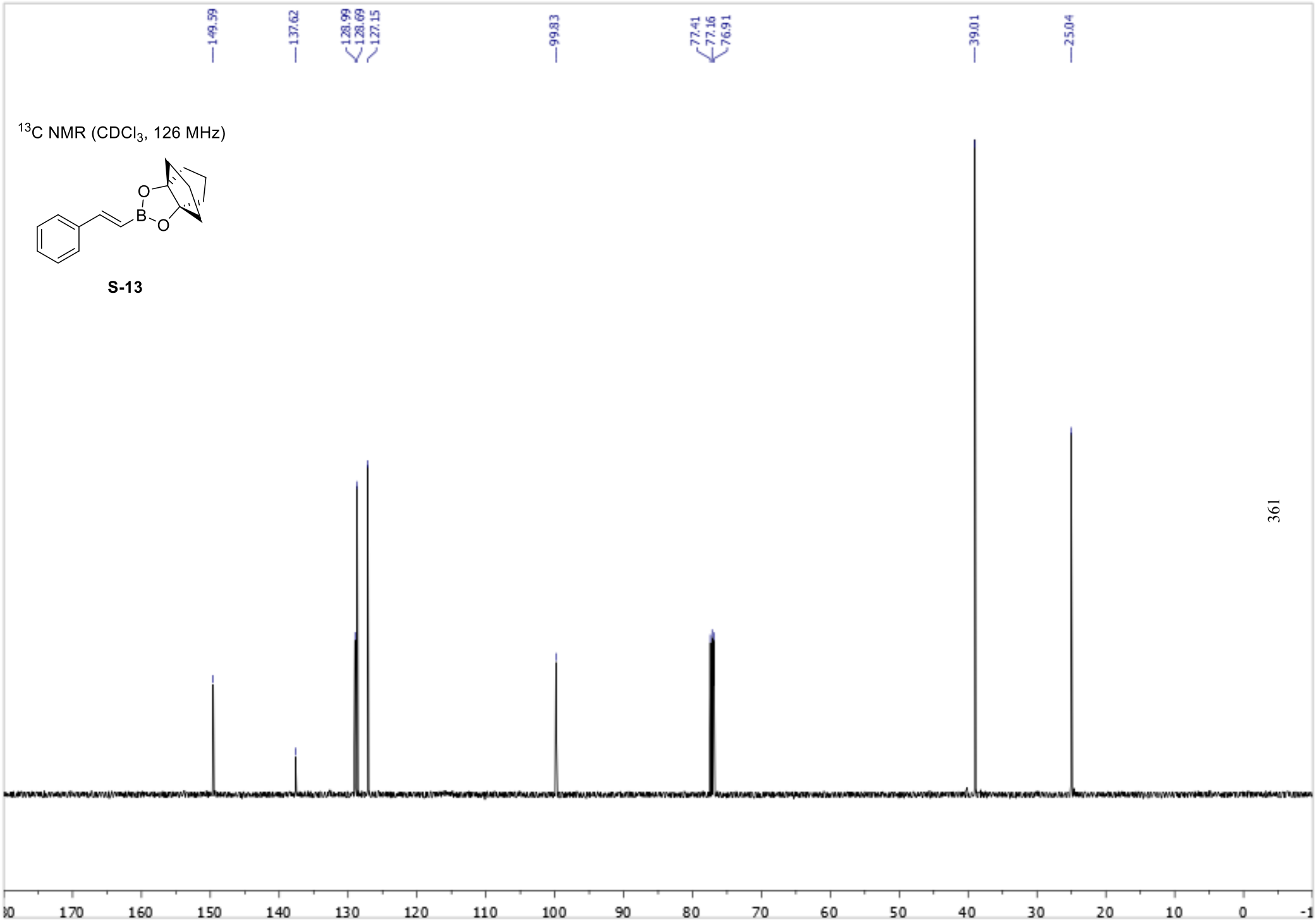
S-12


149.38
137.70
128.95
128.70
127.16
90.58
77.37
77.16
76.95
42.01
23.42
21.44
^{13}C NMR ($CDCl_3$, 151 MHz)
Me
O
B
O
Me
S-12
359
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

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



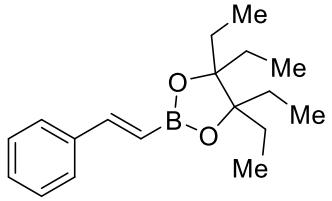
S-13



^{13}C NMR ($CDCl_3$, 126 MHz)

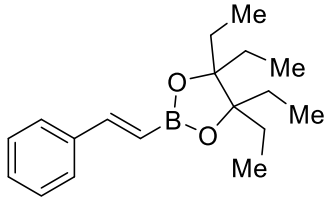
S-13

^{1}H NMR ($CDCl_3$, 600 MHz)



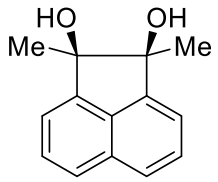
S-14

^{13}C NMR ($CDCl_3$, 126 MHz)



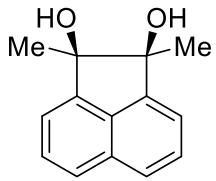
S-14

^{1}H NMR ($CDCl_3$, 600 MHz)



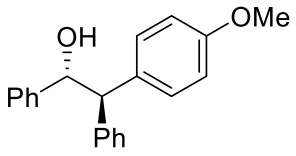
4

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

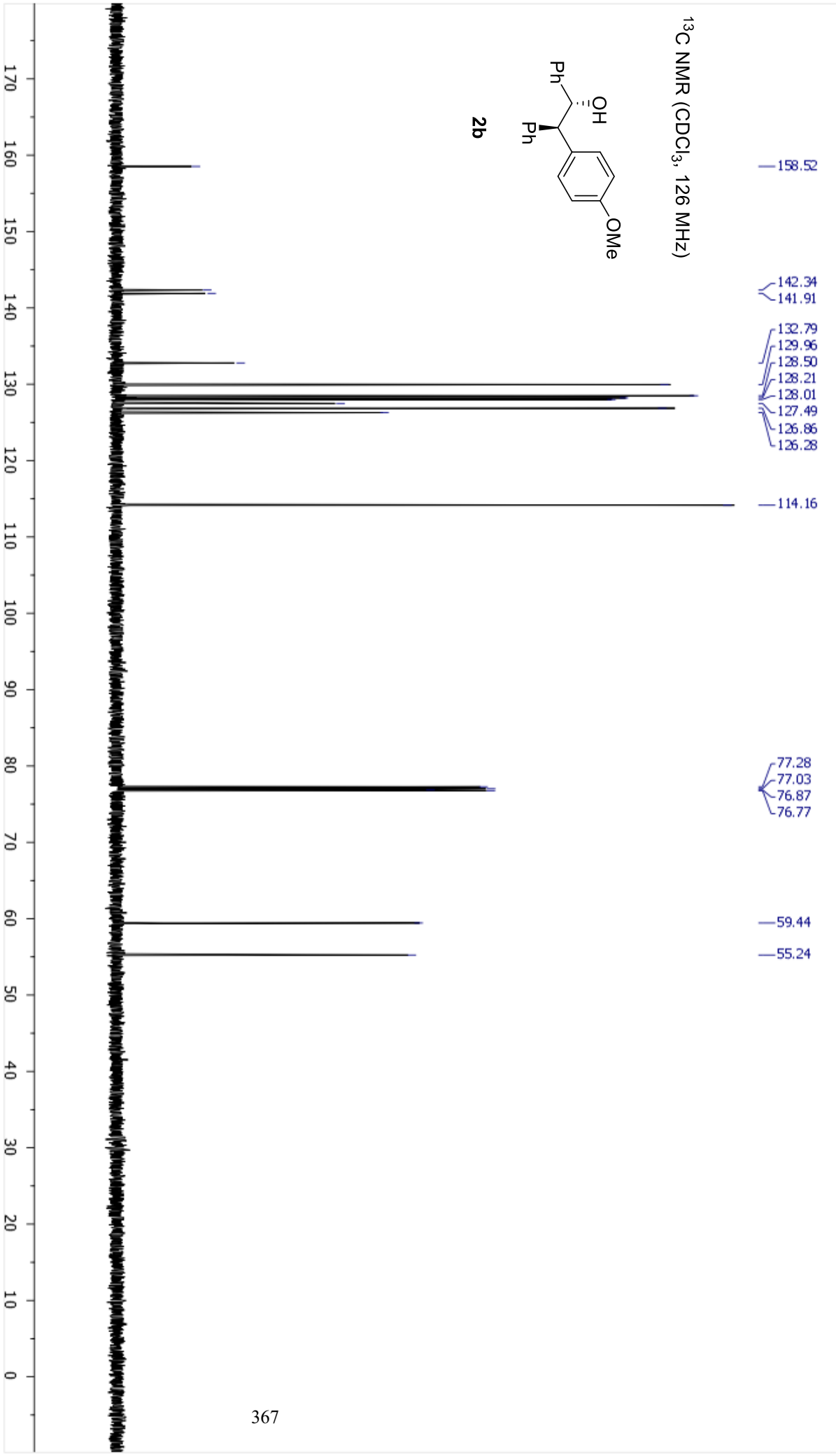


4

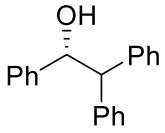
^{1}H NMR ($CDCl_3$, 500 MHz)



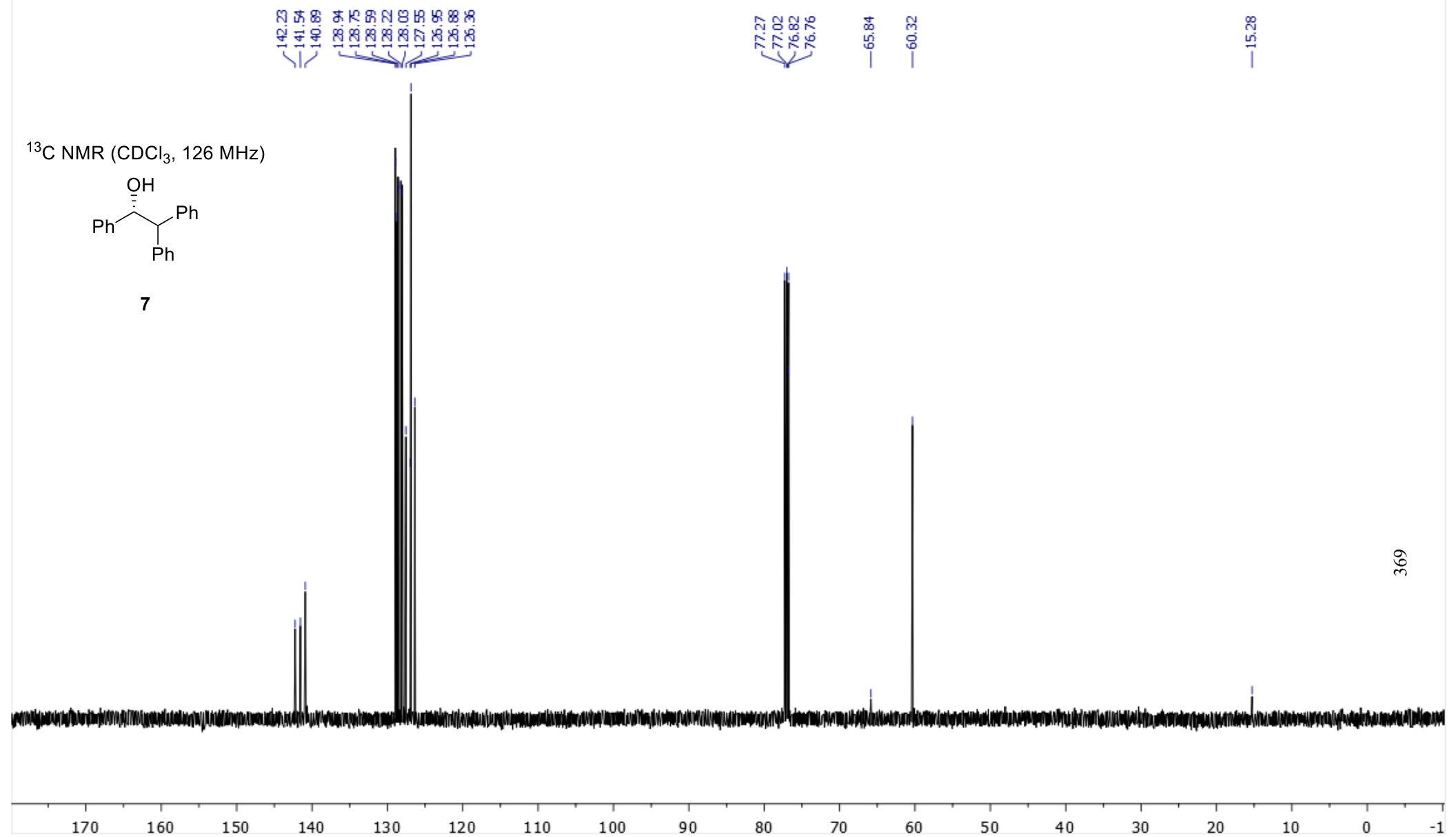
2b


^{13}C NMR (CDCl$_3$, 126 MHz)
2b
Ph
OH
Ph
OMe
158.52
142.34
141.91
132.79
129.96
128.50
128.21
128.01
127.49
126.86
126.28
114.16
77.28
77.03
76.87
76.77
59.44
55.24
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

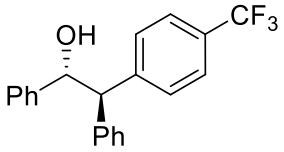
^{1}H NMR ($CDCl_3$, 600 MHz)



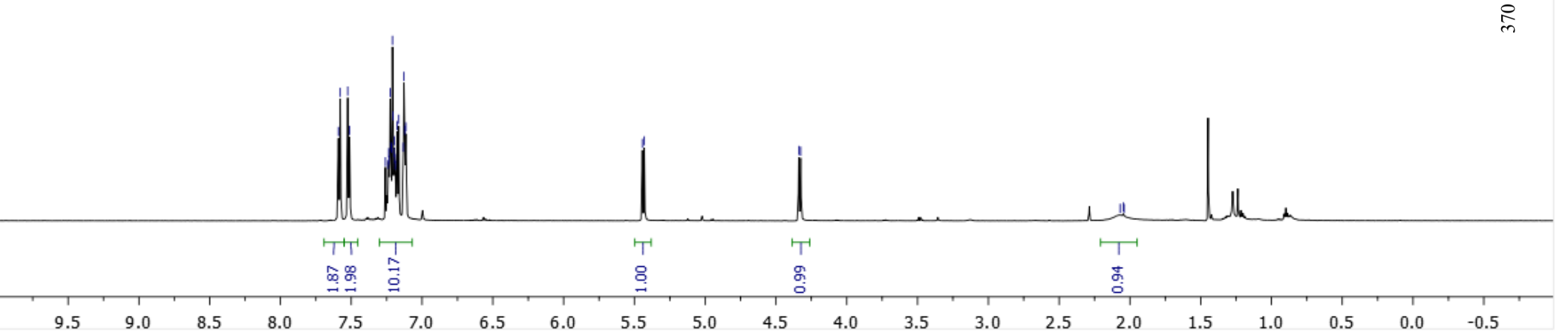
7

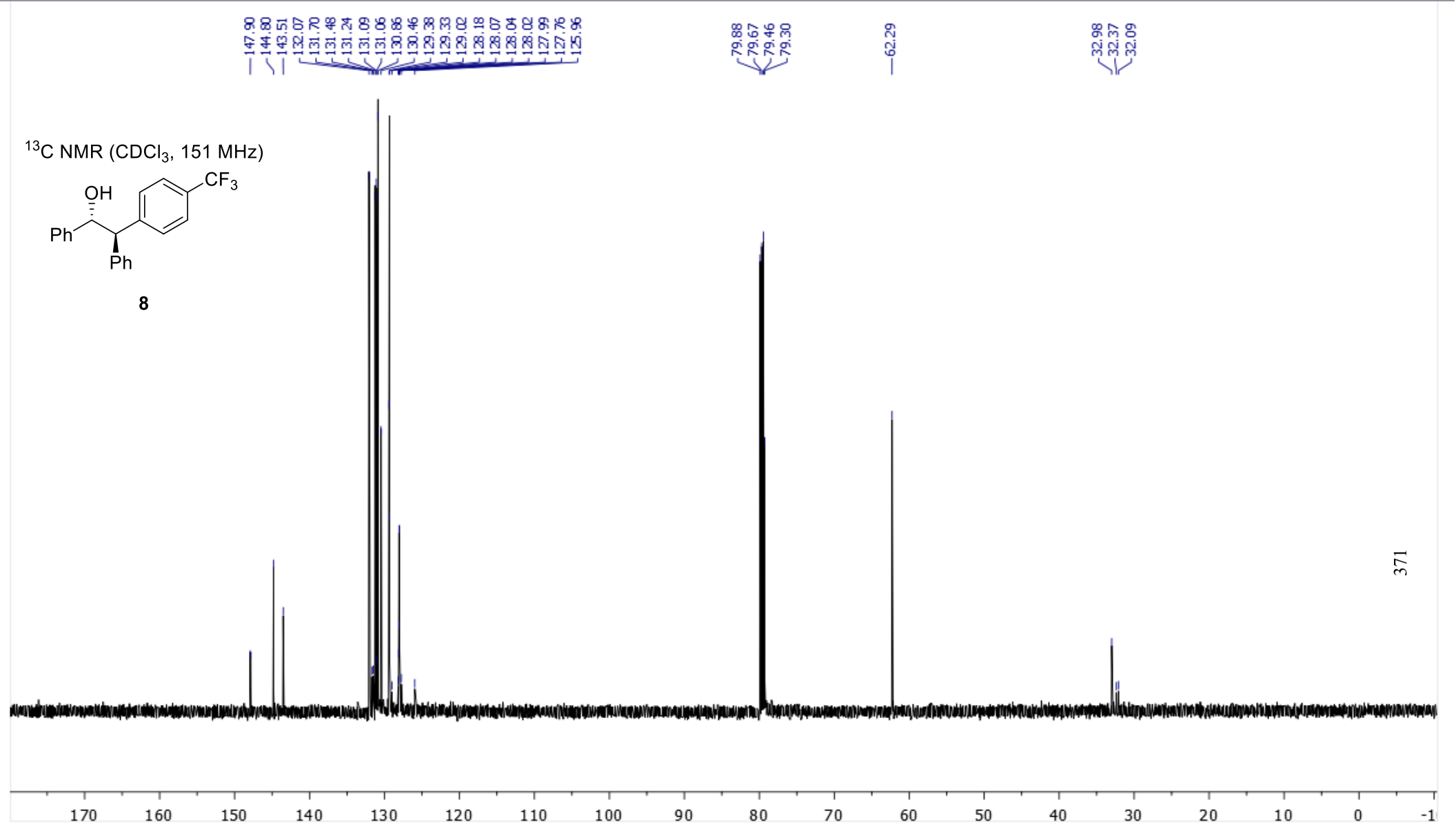

142.23
141.54
140.89
128.94
128.75
128.59
128.22
128.03
127.55
126.95
126.88
126.36
77.27
77.02
76.82
76.76
65.84
60.32
15.28
^{13}C NMR ($CDCl_3$, 126 MHz)
OH
Ph
Ph
Ph
7
369
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

^{1}H NMR ($CDCl_3$, 600 MHz)

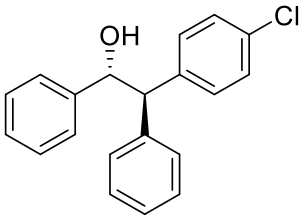


8

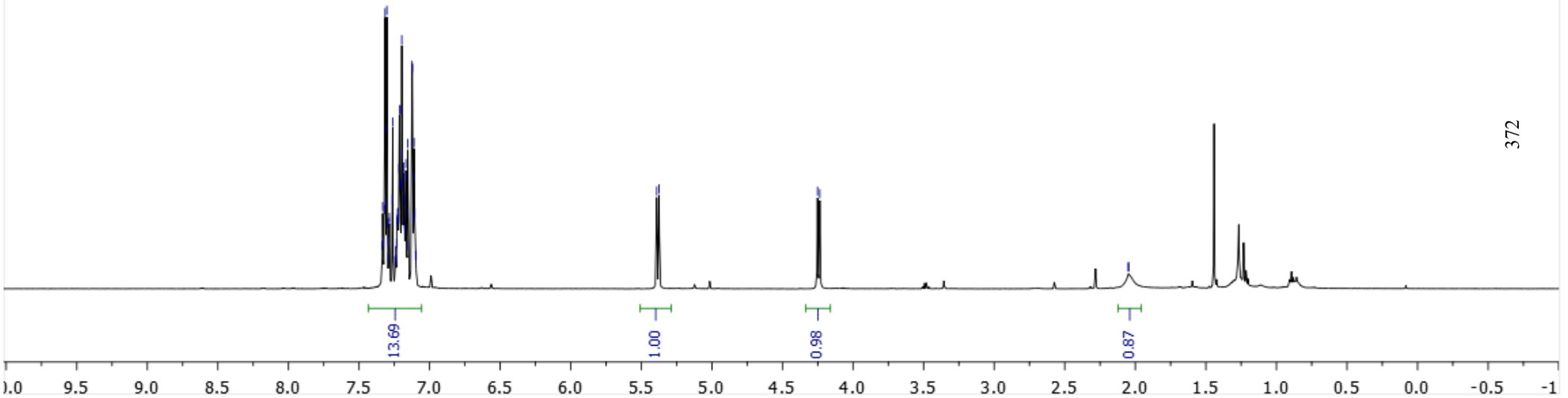


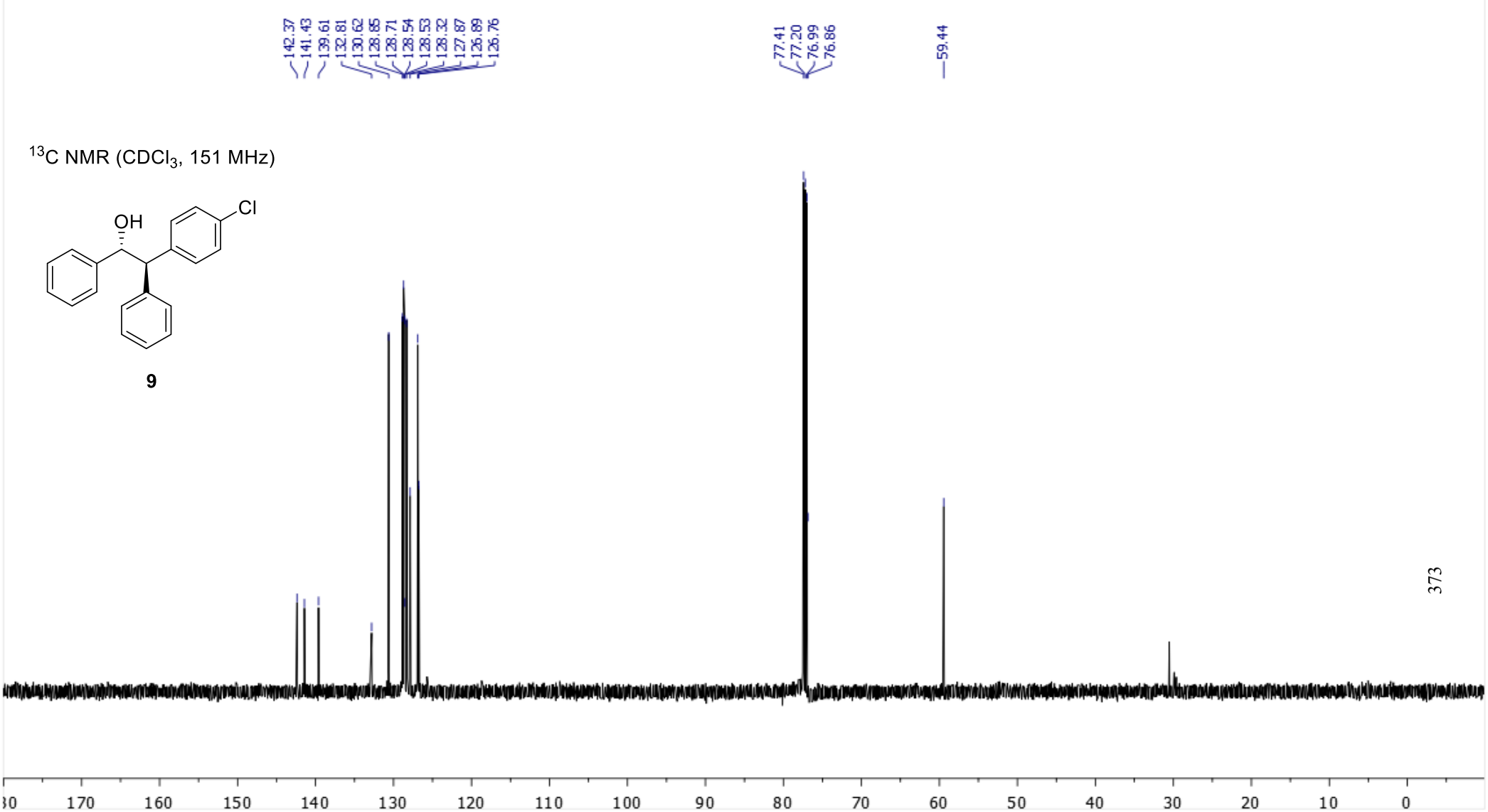

147.90
144.80
143.51
132.07
131.70
131.48
131.24
131.09
131.06
130.86
130.46
129.38
129.33
129.02
128.18
128.07
128.04
128.02
127.99
127.76
125.96
79.88
79.67
79.46
79.30
62.29
32.98
32.37
32.09
^{13}C NMR ($CDCl_3$, 151 MHz)
OH
CF_3
Ph
Ph
8
371
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

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



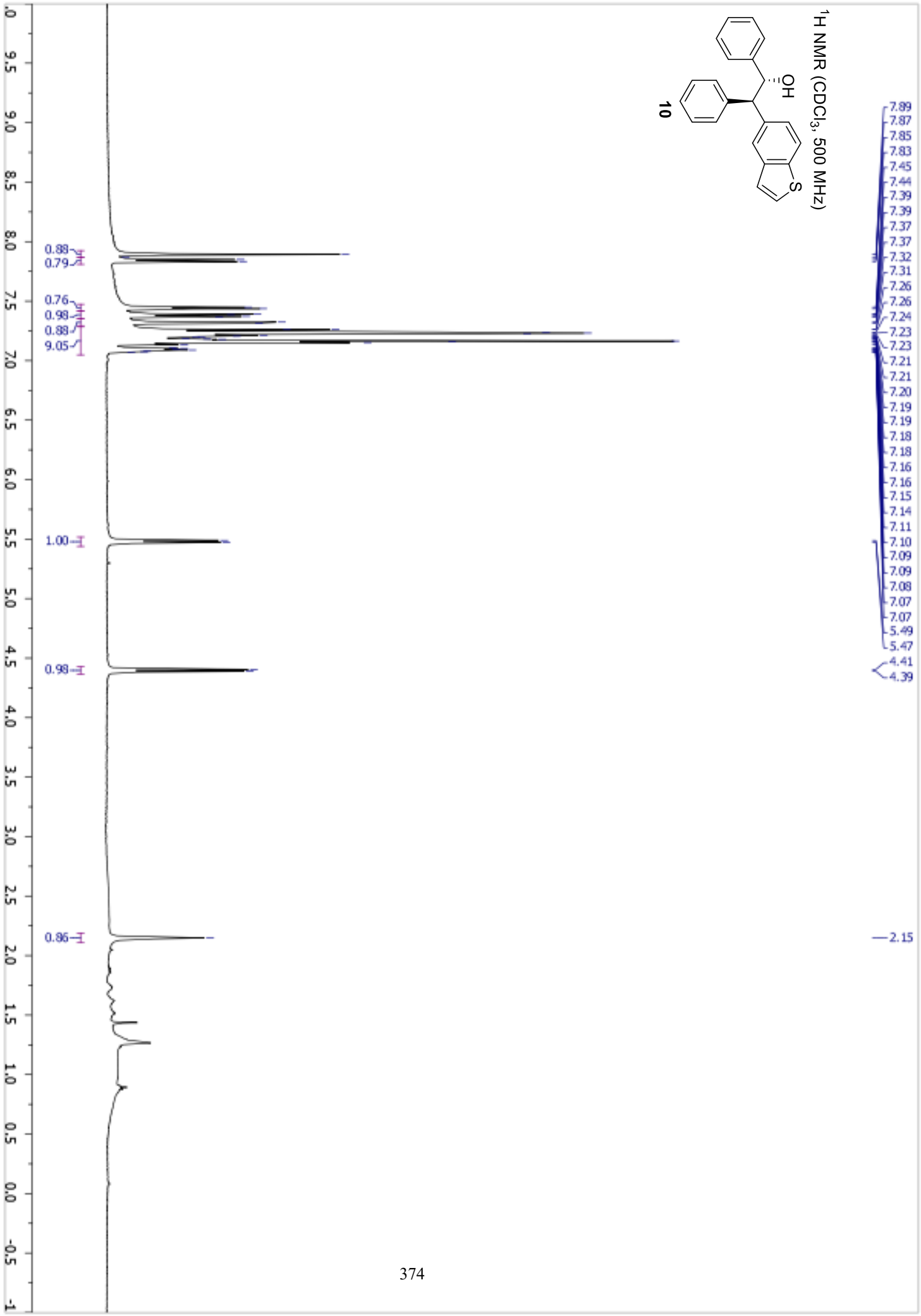
9

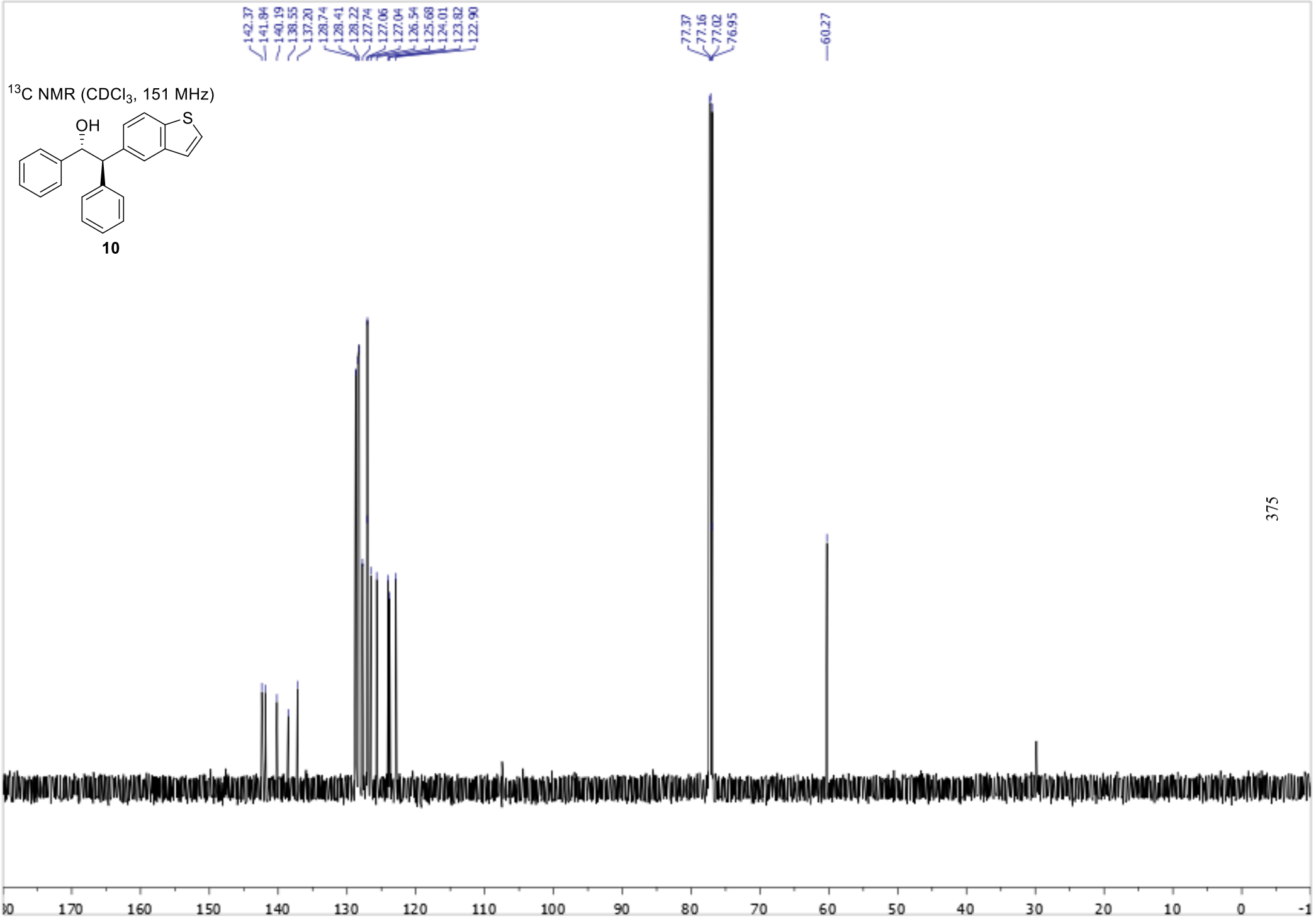




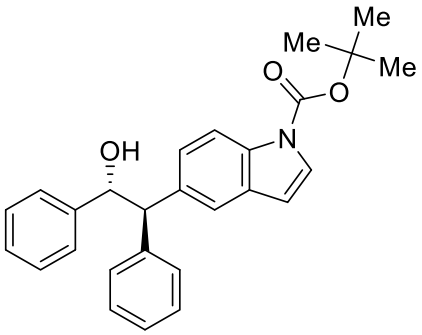
^{13}C NMR ($CDCl_3$, 151 MHz)

9

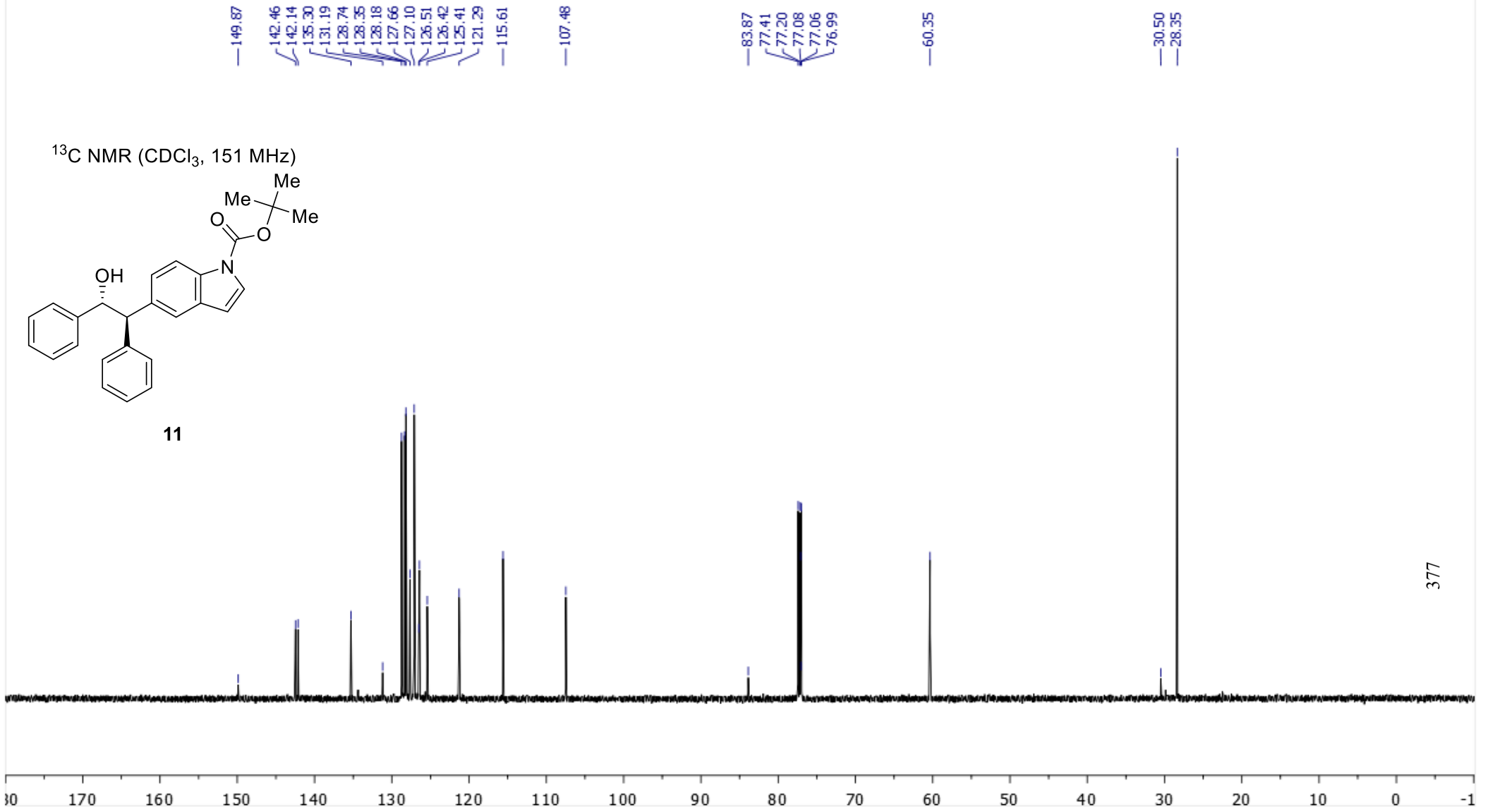

^{1}H NMR (CDCl$_3$, 500 MHz)
10
OH
S
0.88
0.79
0.76
0.98
0.88
9.05
1.00
0.98
0.86
7.89
7.87
7.85
7.83
7.45
7.44
7.39
7.39
7.37
7.37
7.32
7.31
7.26
7.26
7.24
7.23
7.23
7.21
7.21
7.20
7.19
7.19
7.18
7.18
7.16
7.16
7.15
7.14
7.11
7.10
7.09
7.09
7.08
7.07
7.07
5.49
5.47
4.41
4.39
2.15


142.37
141.84
140.19
138.55
137.20
128.74
128.41
128.22
127.74
127.06
127.04
126.54
125.68
124.01
123.82
122.90
77.37
77.16
77.02
76.95
60.27
^{13}C NMR ($CDCl_3$, 151 MHz)
OH
S
10
375
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

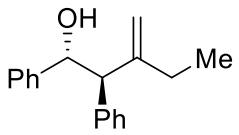
^{1}H NMR ($CDCl_3$, 600 MHz)



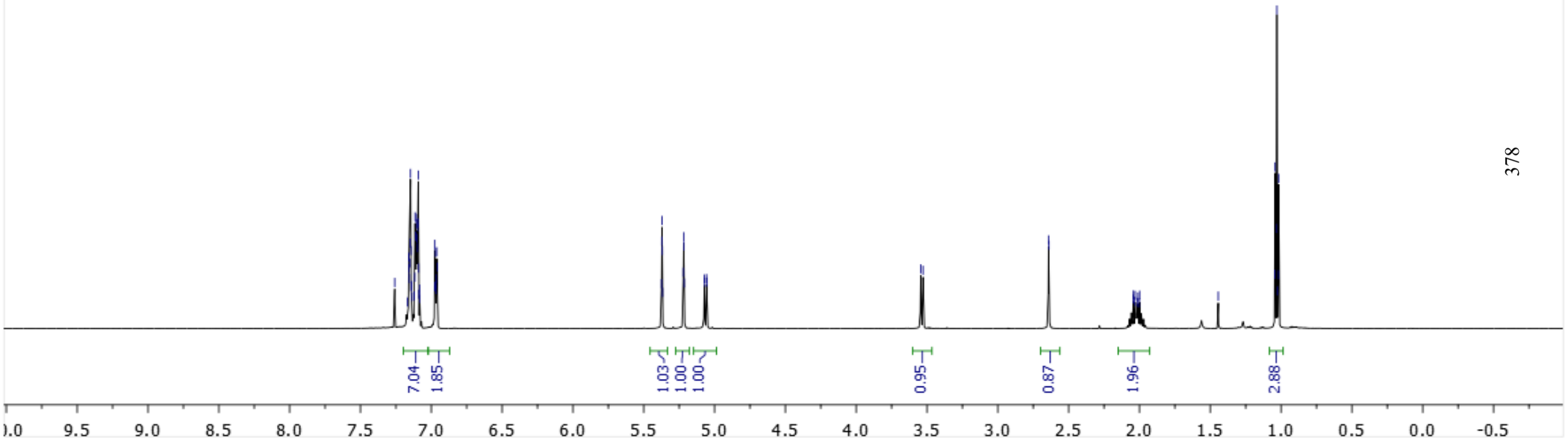
11

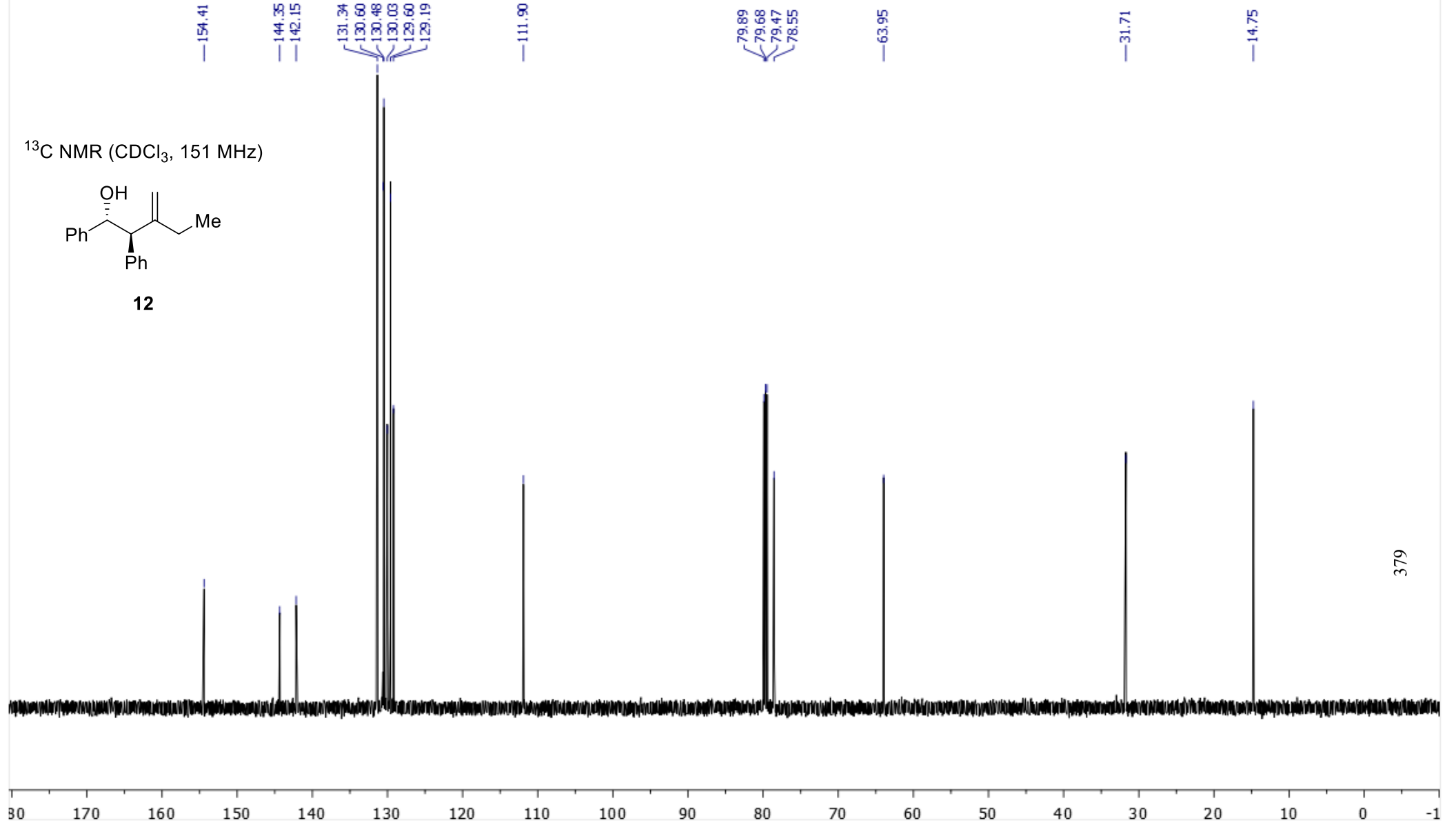

149.87
142.46
142.14
135.30
131.19
128.74
128.35
128.18
127.66
127.10
126.51
126.42
125.41
121.29
115.61
107.48
83.87
77.41
77.20
77.08
77.06
76.99
60.35
30.50
28.35
13C NMR (CDCl3, 151 MHz)
Me
Me
Me
O
O
N
OH
11
377
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

^{1}H NMR ($CDCl_3$, 600 MHz)

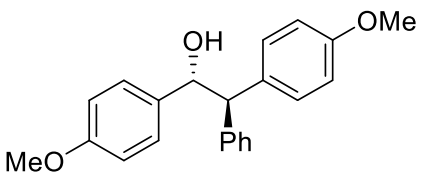


12

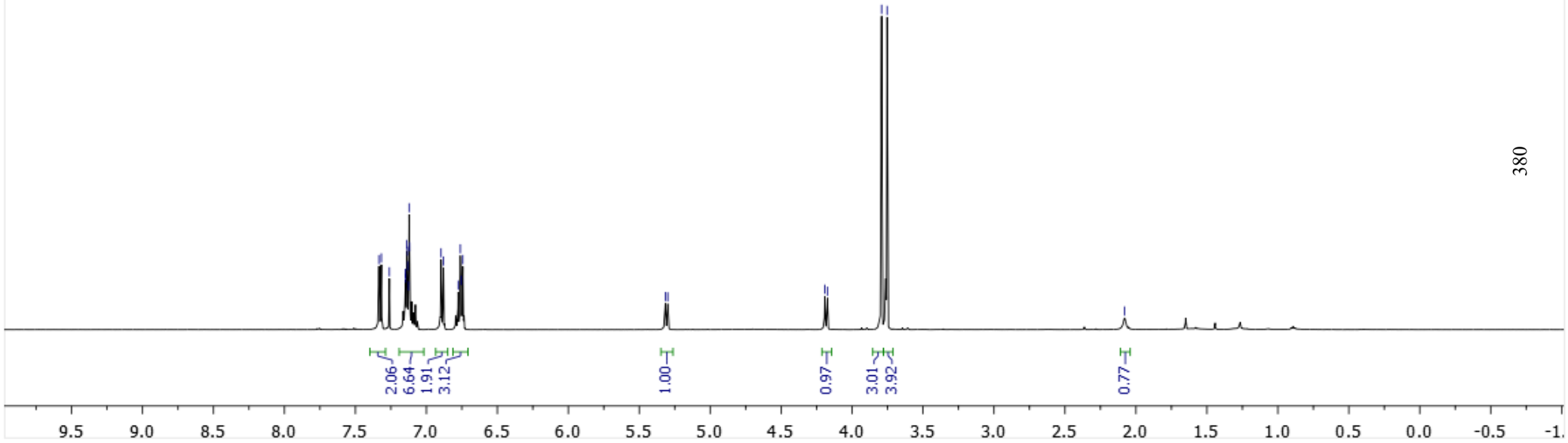


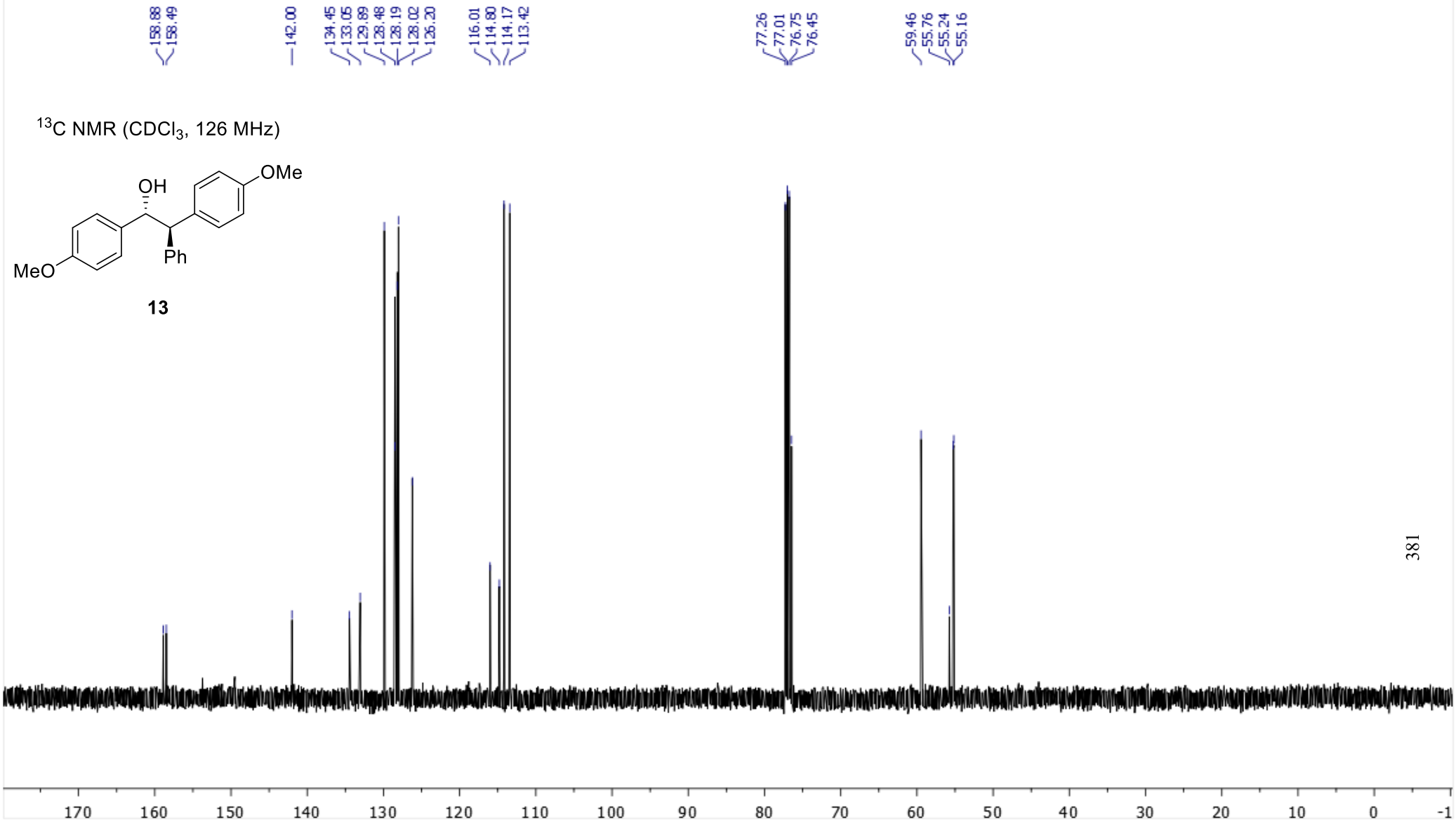

154.41
144.35
142.15
131.34
130.60
130.48
130.03
129.60
129.19
111.90
79.89
79.68
79.47
78.55
63.95
31.71
14.75
^{13}C NMR ($CDCl_3$, 151 MHz)
OH
Ph
Me
Ph
12
379
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

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



13

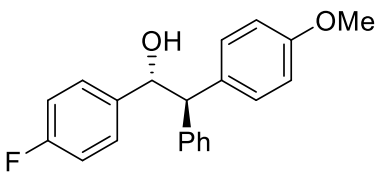




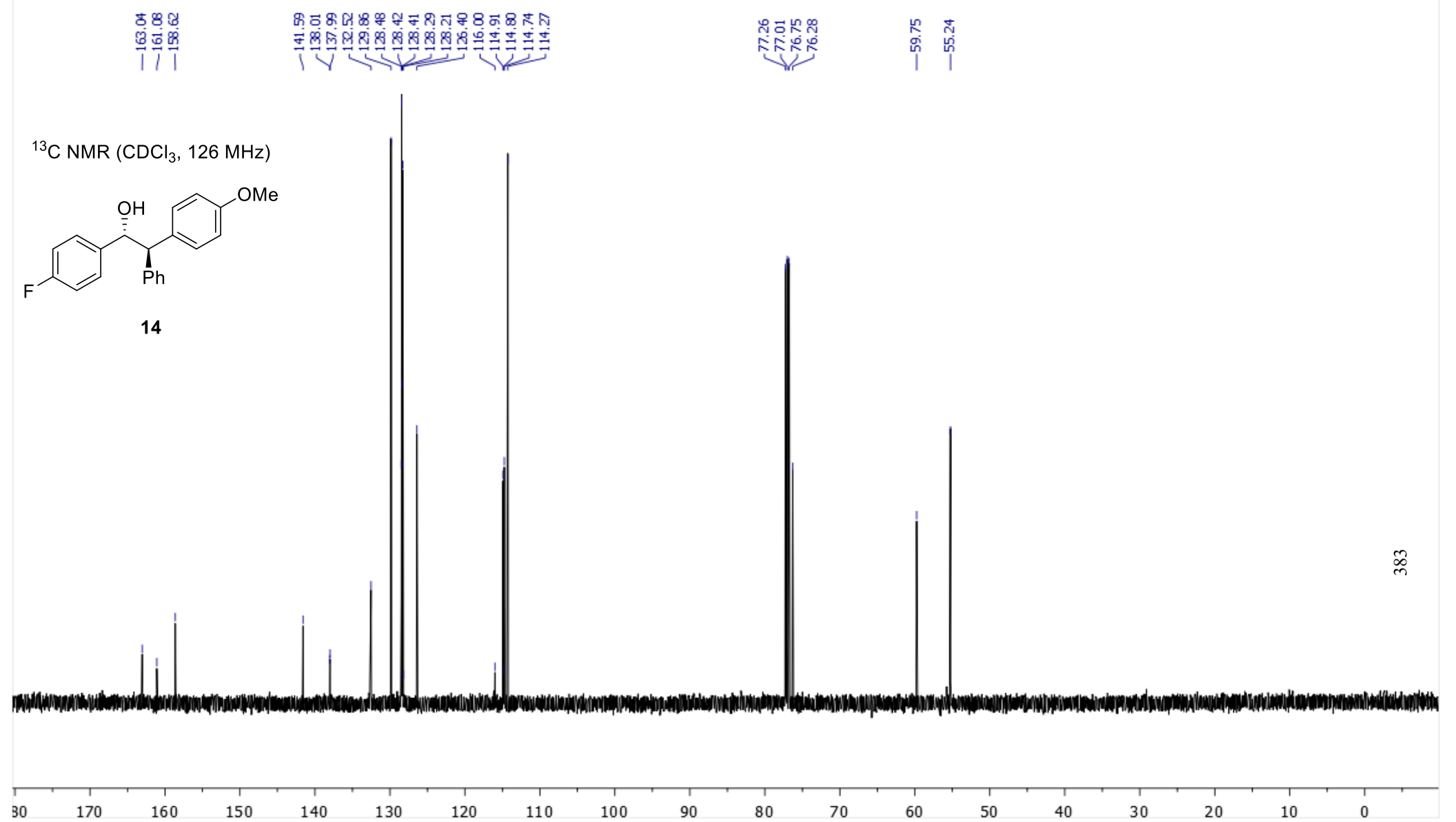
^{13}C NMR ($CDCl_3$, 126 MHz)

13

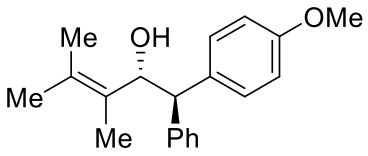
^{1}H NMR ($CDCl_3$, 500 MHz)



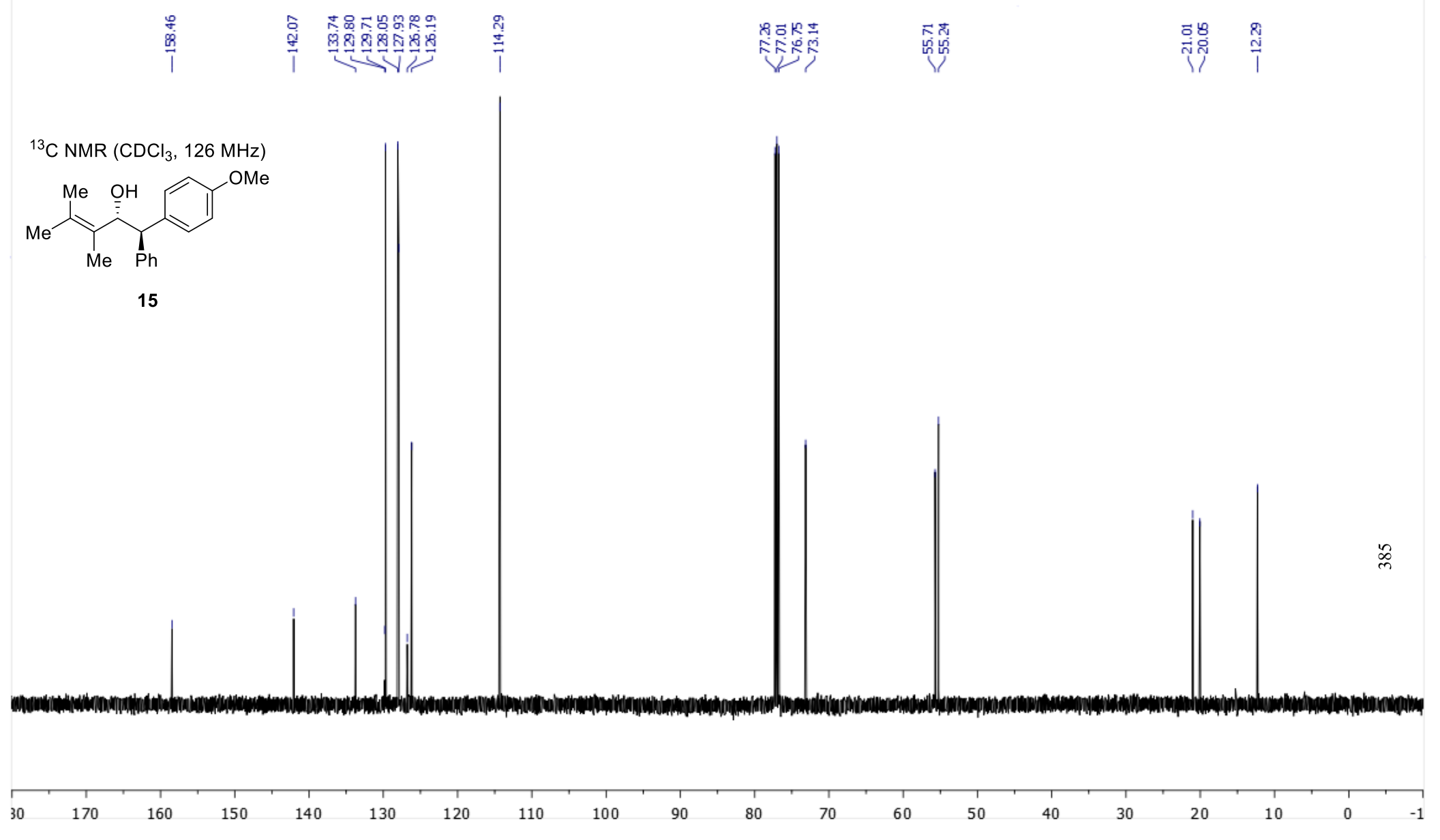
14


163.04
161.08
158.62
141.59
138.01
137.99
132.52
129.86
128.48
128.42
128.41
128.29
128.21
126.40
116.00
114.91
114.80
114.74
114.27
77.26
77.01
76.75
76.28
59.75
55.24
^{13}C NMR ($CDCl_3$, 126 MHz)
OH
OMe
Ph
F
14
383
30
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

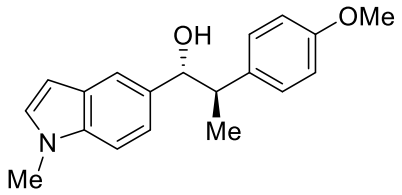
^{1}H NMR ($CDCl_3$, 500 MHz)



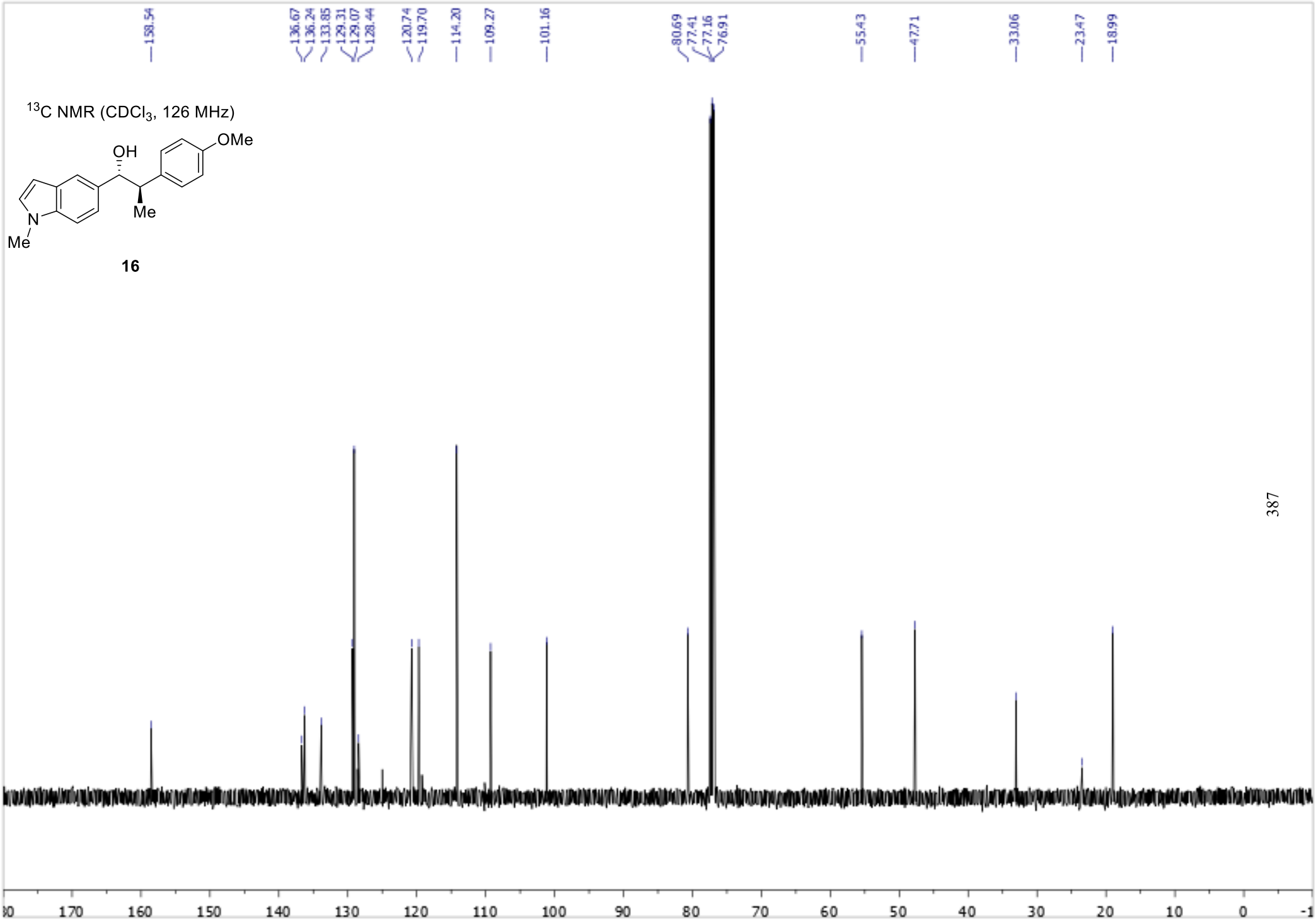
15

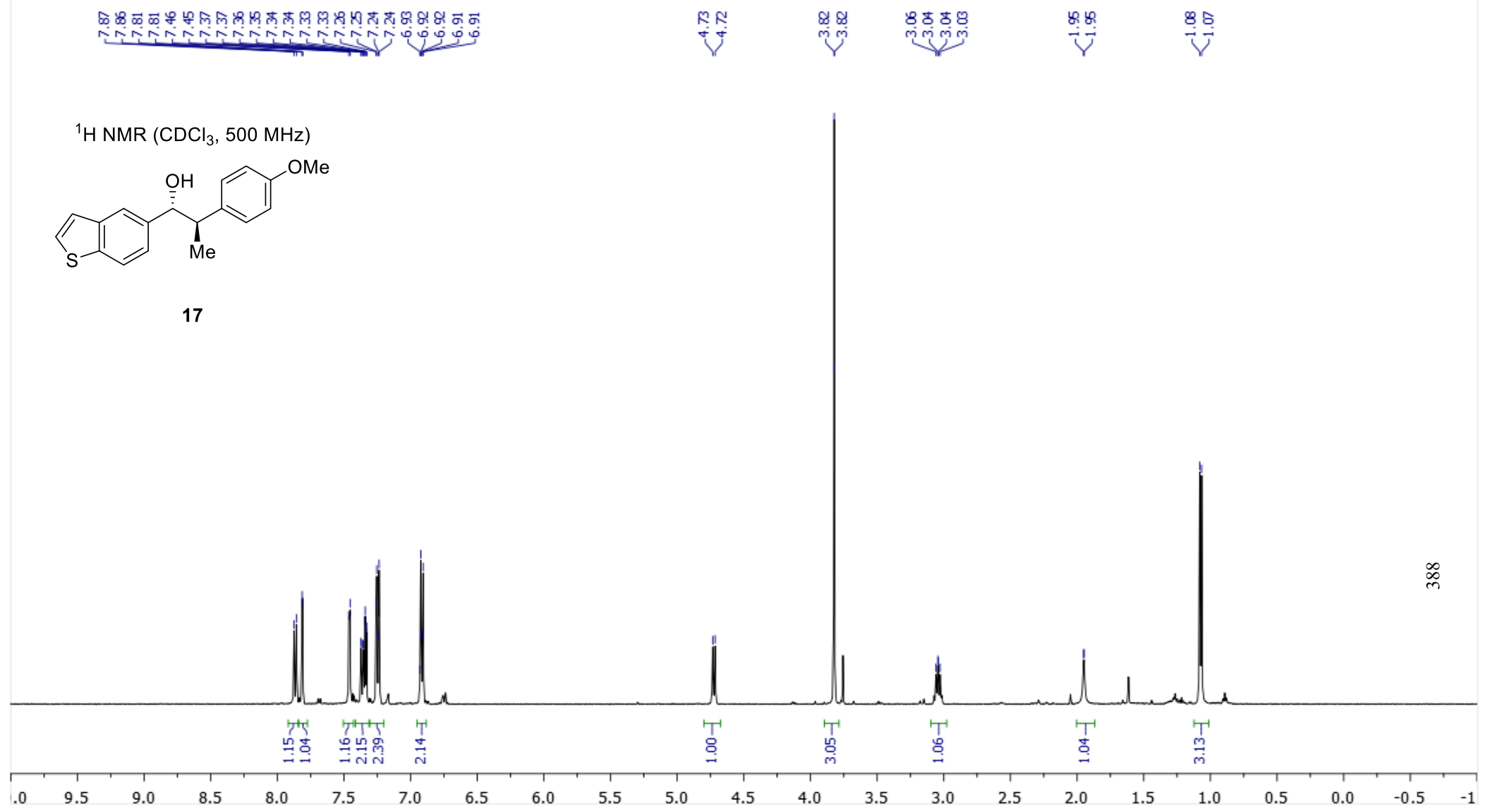

158.46
142.07
133.74
129.80
129.71
128.05
127.93
126.78
126.19
114.29
77.26
77.01
76.75
73.14
55.71
55.24
21.01
20.05
12.29
385
^{13}C NMR (CDCl$_3$, 126 MHz)
Me
OH
OMe
Me
Me
Ph
15
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

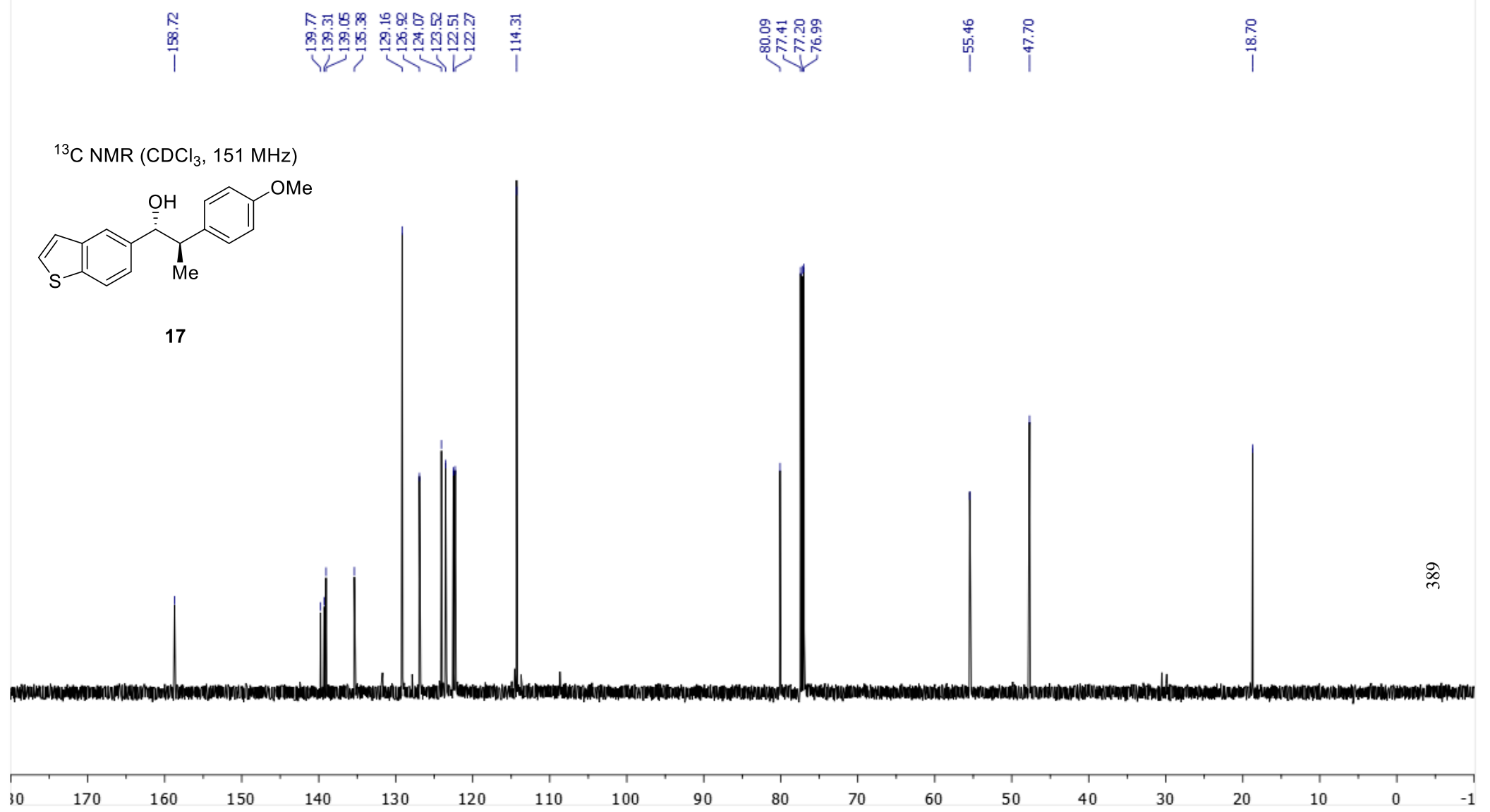
^{1}H NMR ($CDCl_3$, 500 MHz)



16


158.54
136.67
136.24
133.85
129.31
129.07
128.44
120.74
119.70
114.20
109.27
101.16
80.69
77.41
77.16
76.91
55.43
47.71
33.06
23.47
18.99
^{13}C NMR ($CDCl_3$, 126 MHz)
OH
OMe
Me
N
Me
16
387
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

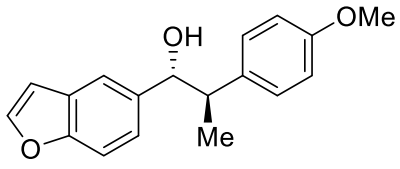

7.87
7.86
7.81
7.81
7.46
7.45
7.37
7.37
7.36
7.35
7.34
7.34
7.33
7.33
7.26
7.25
7.24
7.24
6.93
6.92
6.92
6.91
6.91
4.73
4.72
3.82
3.82
3.06
3.04
3.04
3.03
1.95
1.95
1.08
1.07
^{1}H NMR ($CDCl_3$, 500 MHz)
OH
OMe
Me
S
17
388
1.15
1.04
1.16
2.15
2.39
2.14
1.00
3.05
1.06
1.04
3.13
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1



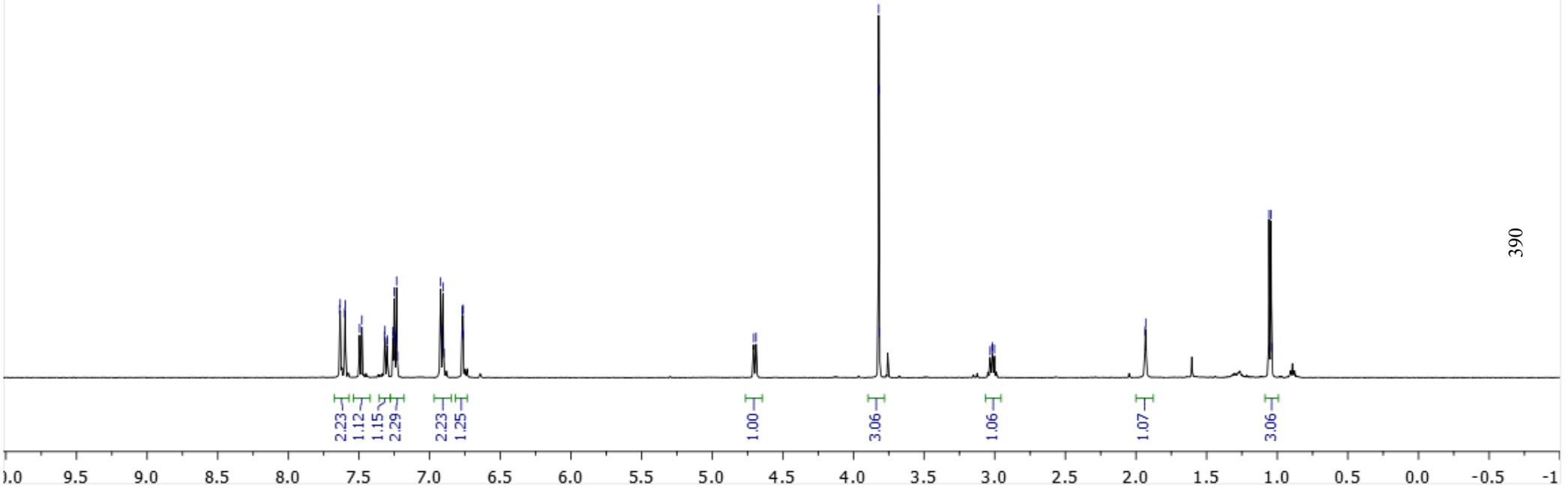
^{13}C NMR ($CDCl_3$, 151 MHz)

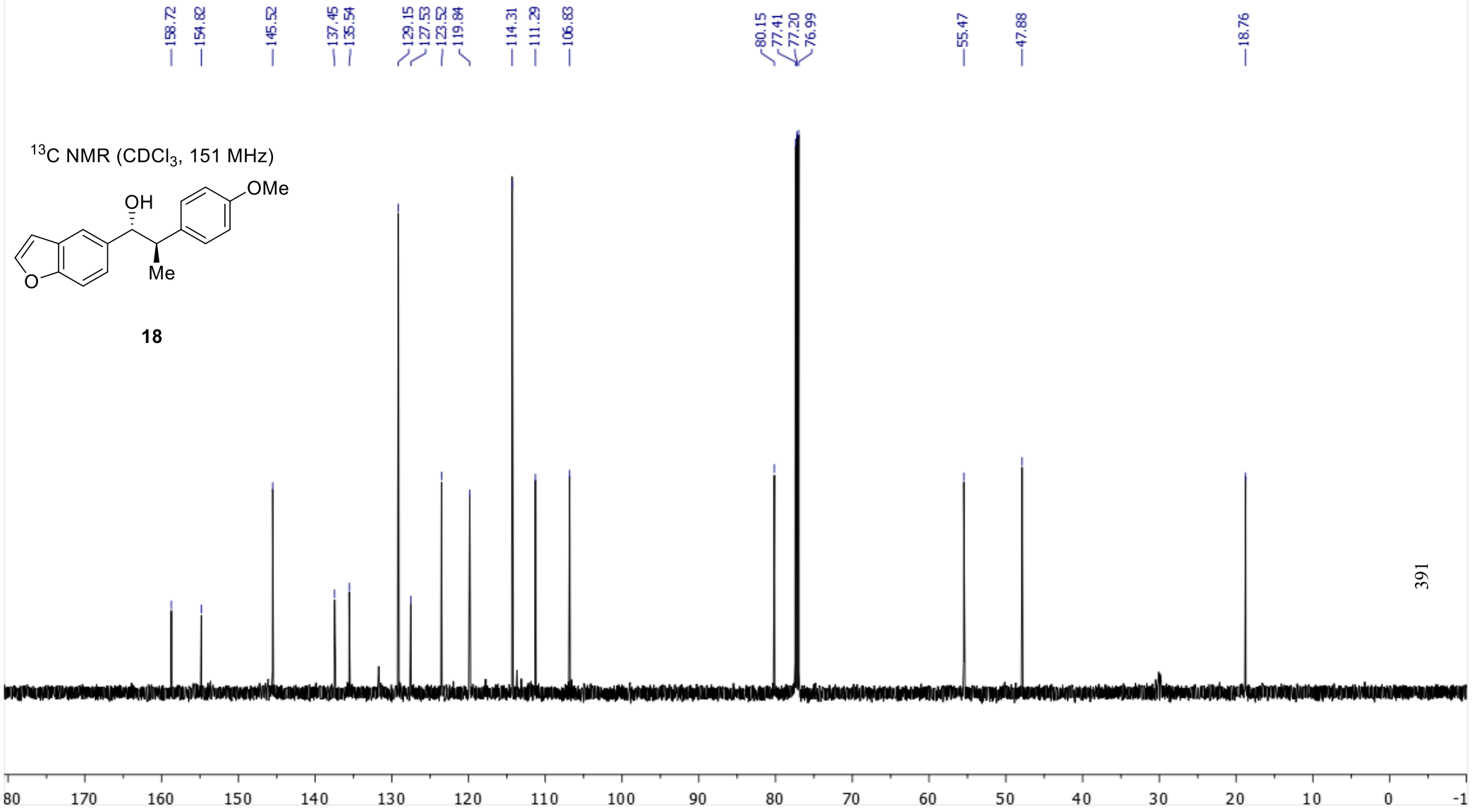
17

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



18

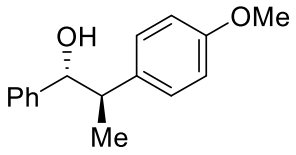




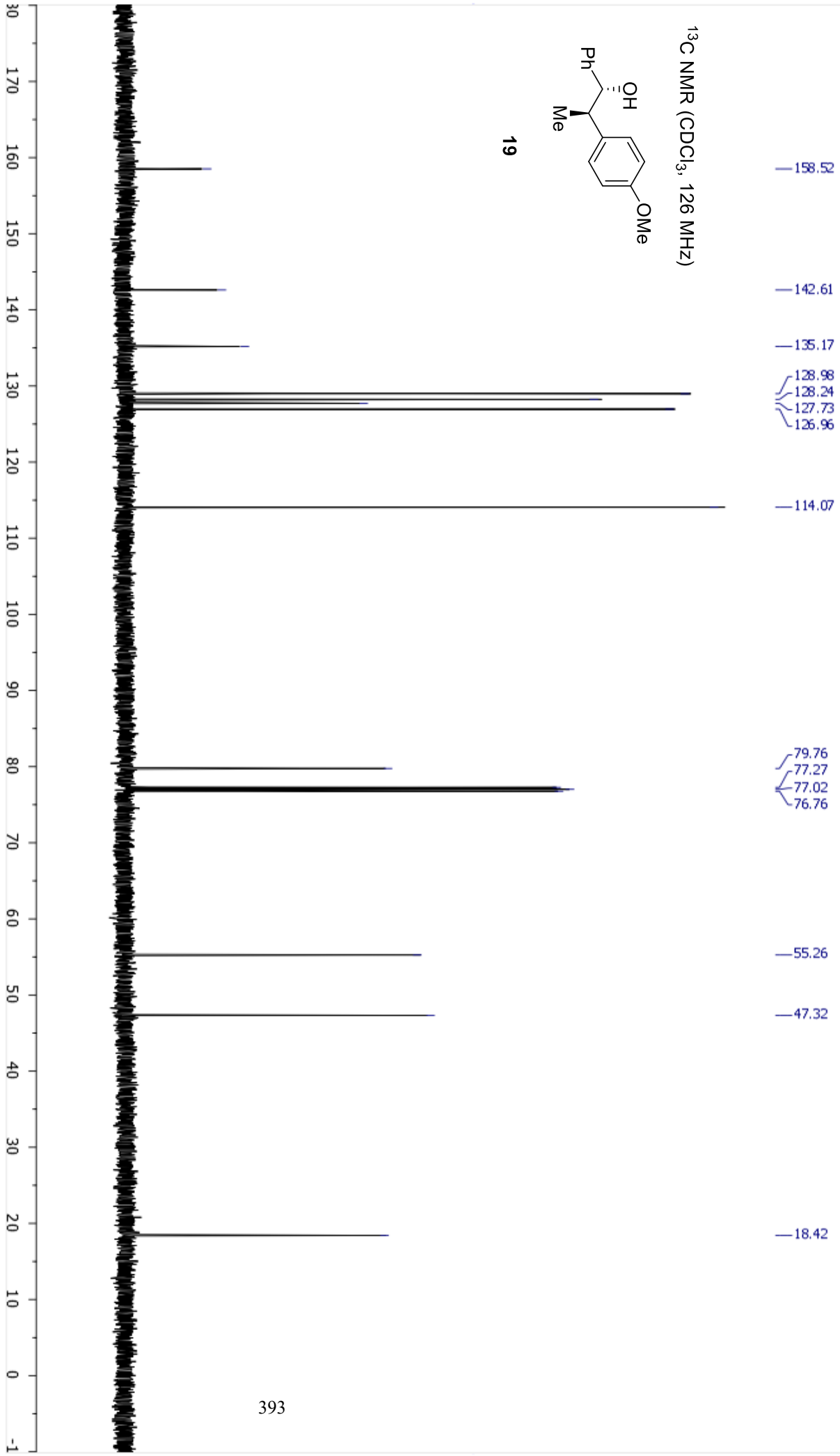
^{13}C NMR ($CDCl_3$, 151 MHz)

18

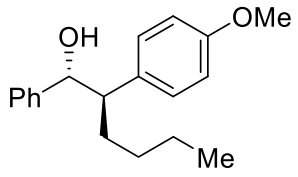
^{1}H NMR ($CDCl_3$, 500 MHz)



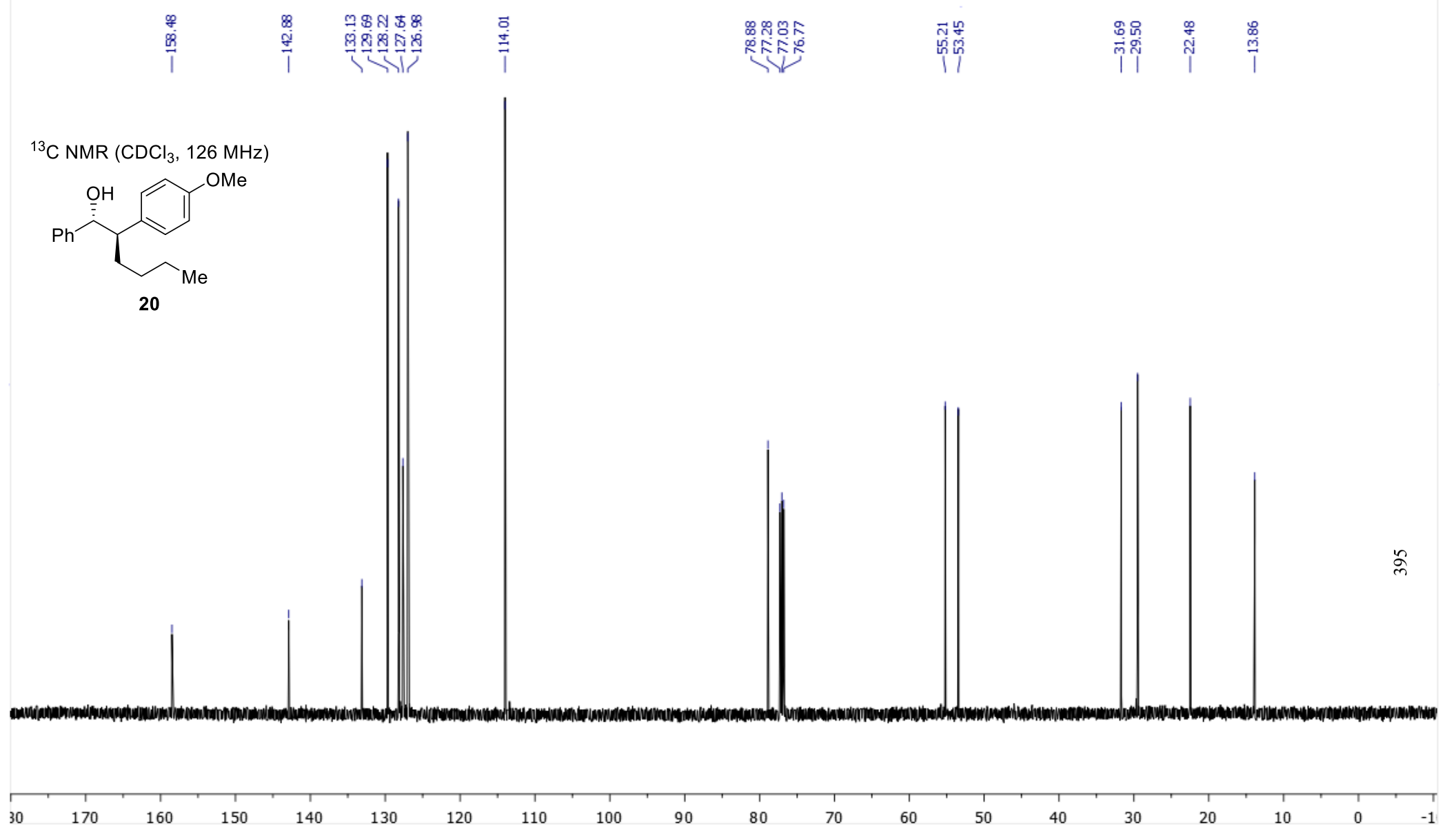
19


^{13}C NMR (CDCl$_3$, 126 MHz)
Ph
OH
Me
OMe
19
158.52
142.61
135.17
128.98
128.24
127.73
126.96
114.07
79.76
77.27
77.02
76.76
55.26
47.32
18.42
30
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

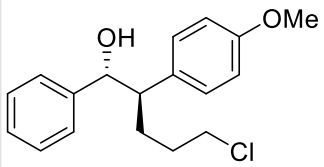
^{1}H NMR ($CDCl_3$, 500 MHz)



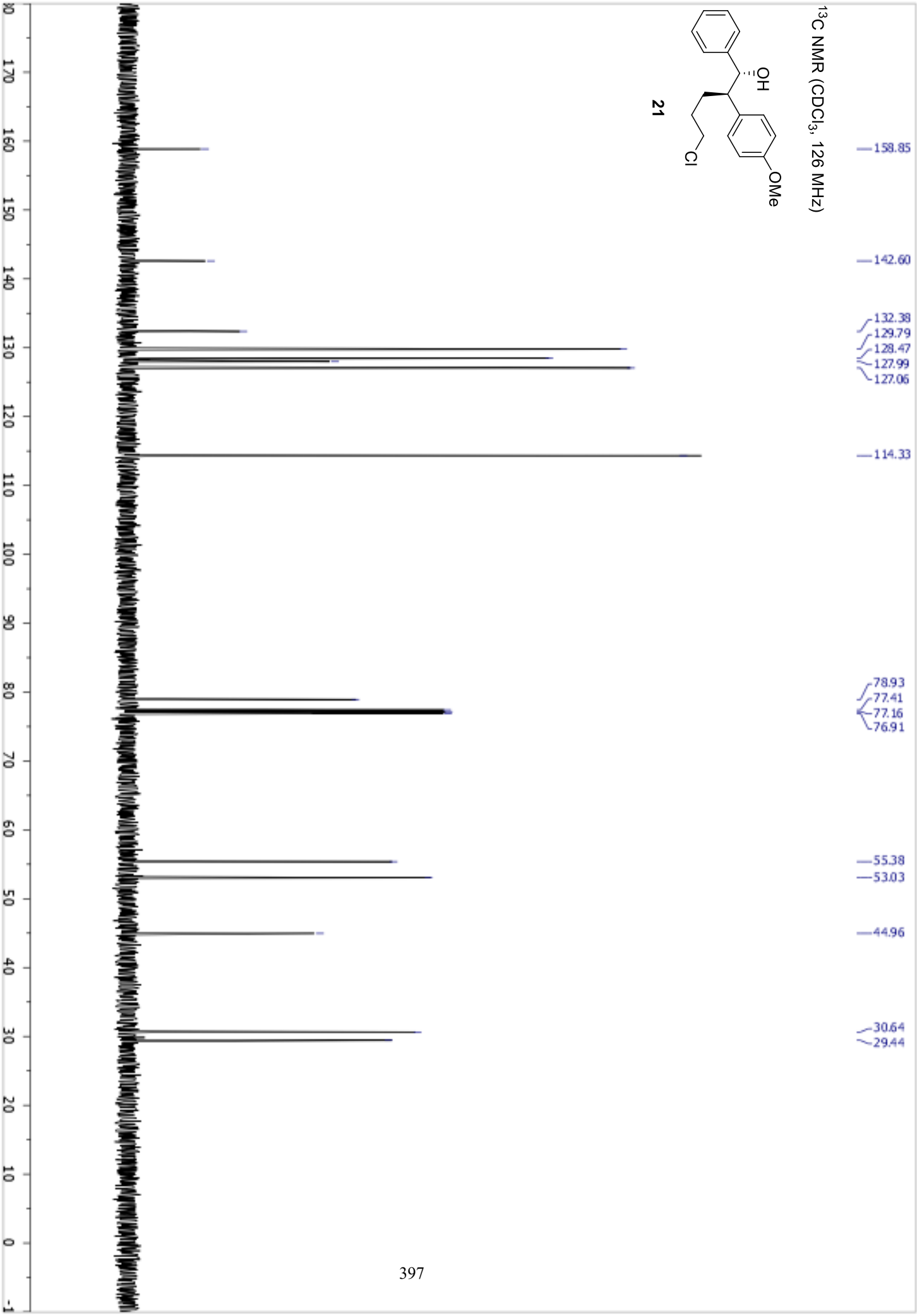
20


158.48
142.88
133.13
129.69
128.22
127.64
126.98
114.01
78.88
77.28
77.03
76.77
55.21
53.45
31.69
29.50
22.48
13.86
^{13}C NMR ($CDCl_3$, 126 MHz)
OH
OMe
Ph
Me
20
395
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

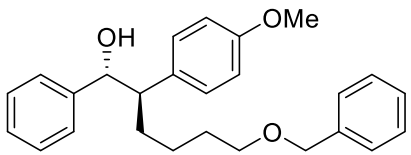
^{1}H NMR ($CDCl_3$, 500 MHz)



21

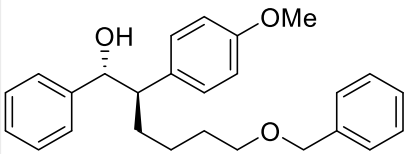

^{13}C NMR (CDCl$_3$, 126 MHz)
OH
Cl
OMe
21
158.85
142.60
132.38
129.79
128.47
127.99
127.06
114.33
78.93
77.41
77.16
76.91
55.38
53.03
44.96
30.64
29.44

^{1}H NMR ($CDCl_3$, 600 MHz)



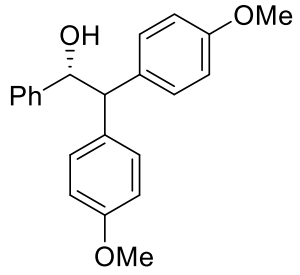
22

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

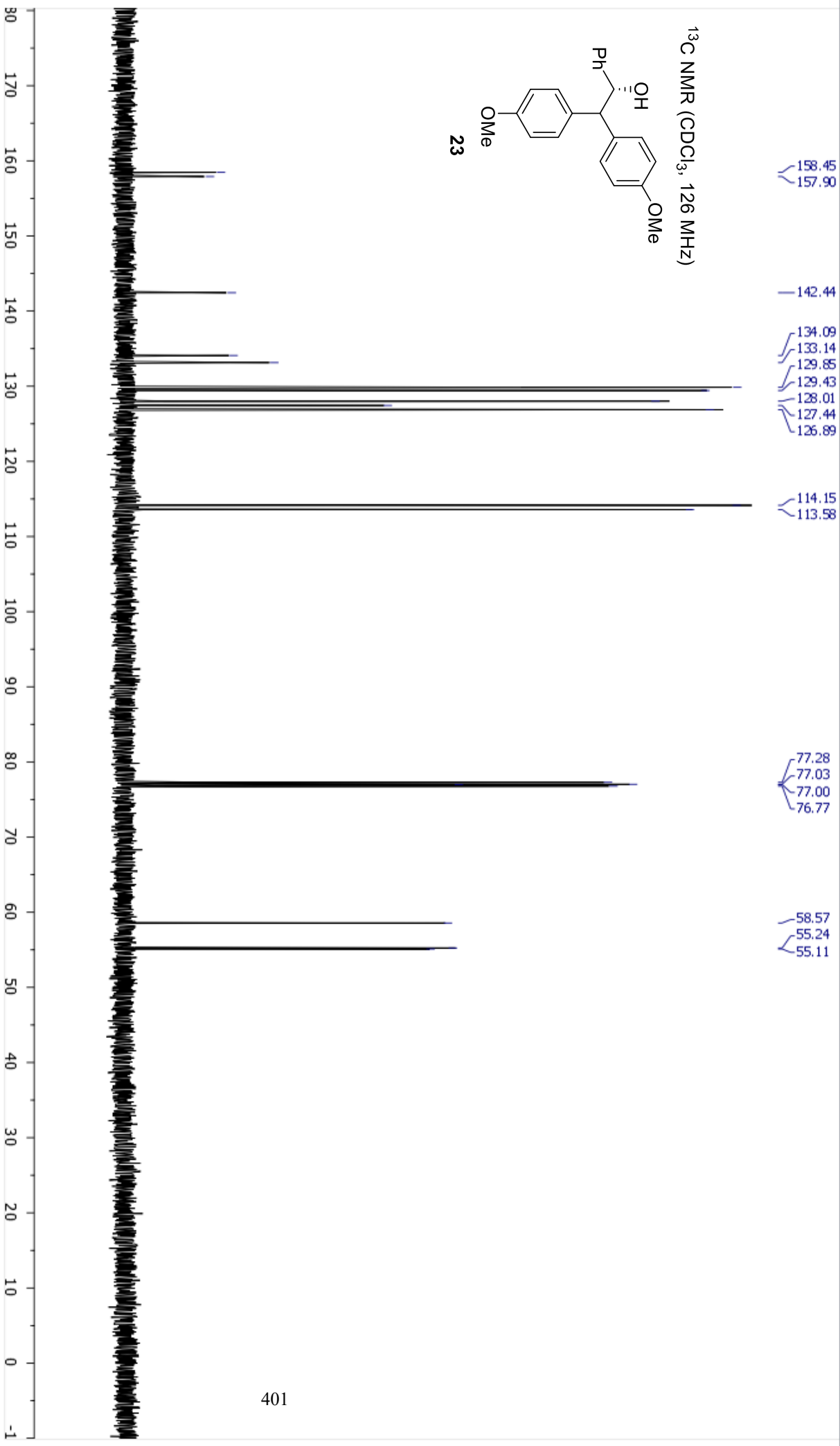


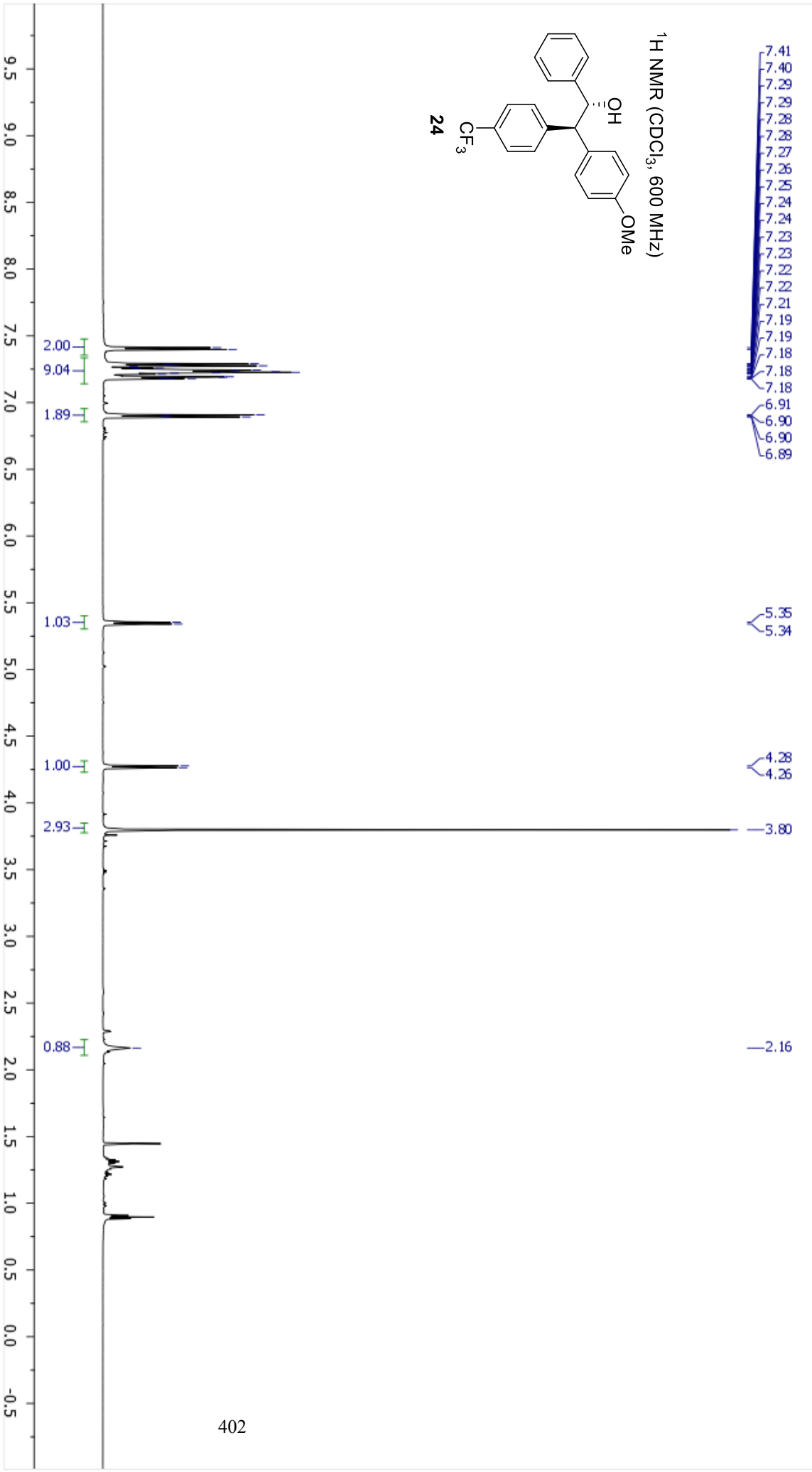
22

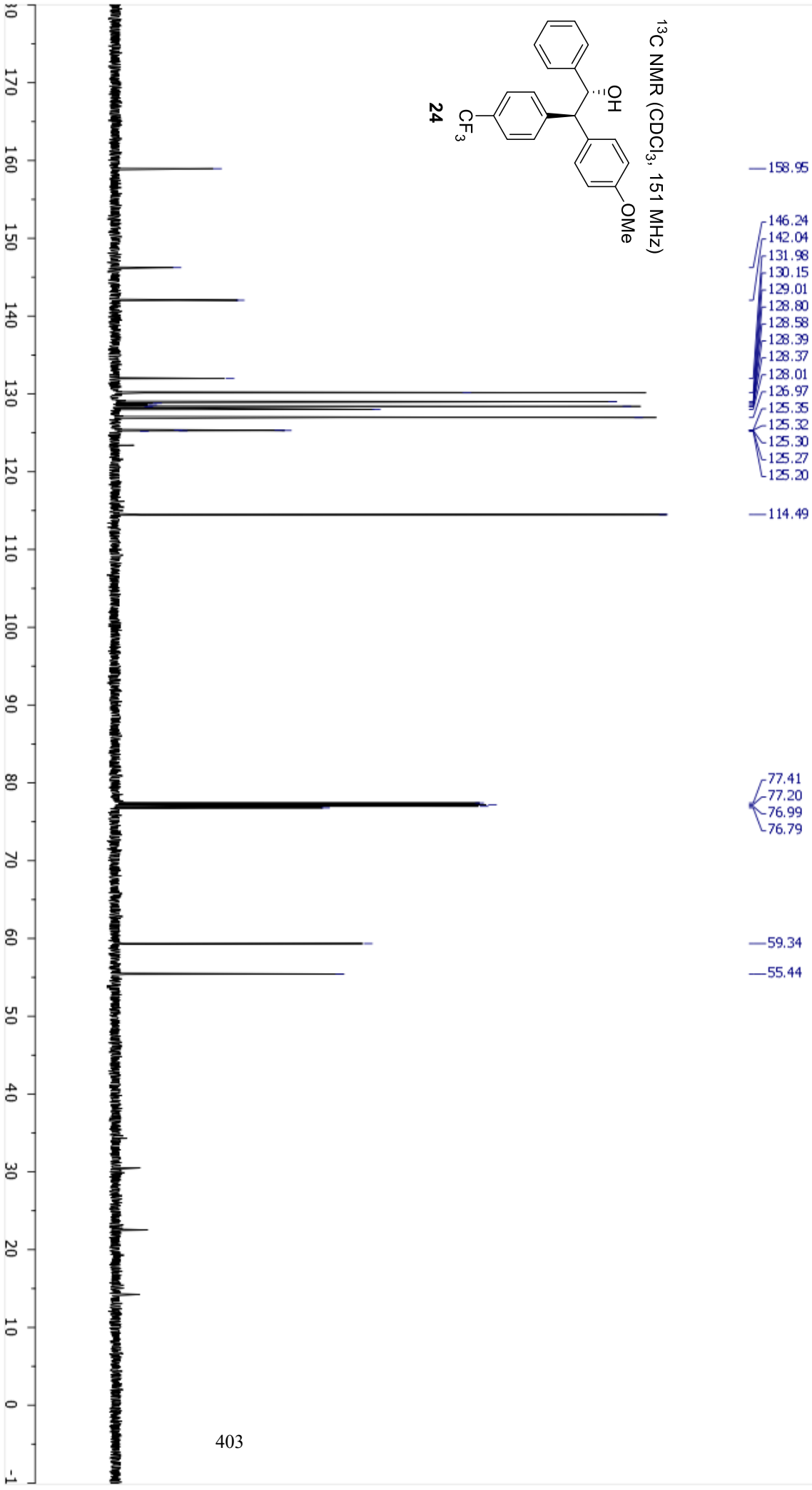
^{1}H NMR ($CDCl_3$, 500 MHz)



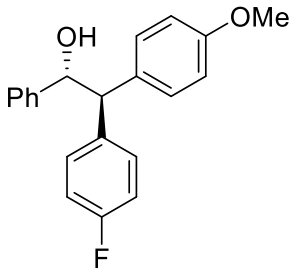
23


^{13}C NMR (CDCl$_3$, 126 MHz)
Ph
OH
OMe
OMe
23
158.45
157.90
142.44
134.09
133.14
129.85
129.43
128.01
127.44
126.89
114.15
113.58
77.28
77.03
77.00
76.77
58.57
55.24
55.11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

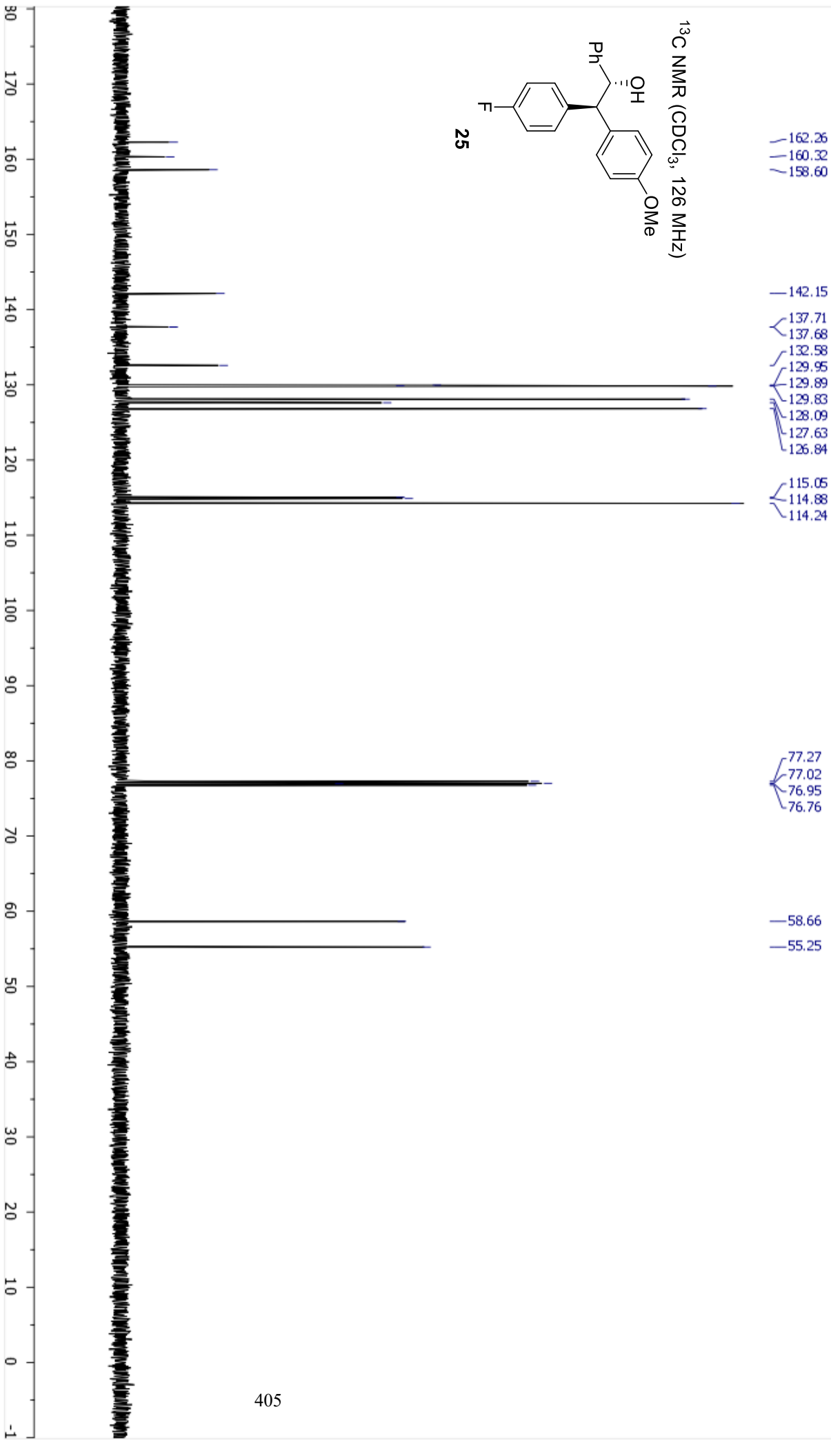

^{1}H NMR ($CDCl_3$, 600 MHz)
24
OH
CF_3
OMe
7.41
7.40
7.29
7.29
7.28
7.28
7.27
7.26
7.25
7.24
7.24
7.23
7.23
7.22
7.22
7.21
7.19
7.19
7.18
7.18
7.18
6.91
6.90
6.90
6.89
5.35
5.34
4.28
4.26
3.80
2.16
2.00
9.04
1.89
1.03
1.00
2.93
0.88


^{13}C NMR (CDCl$_3$, 151 MHz)
OH
CF$_3$
OMe
24
158.95
146.24
142.04
131.98
130.15
129.01
128.80
128.58
128.39
128.37
128.01
126.97
125.35
125.32
125.30
125.27
125.20
114.49
77.41
77.20
76.99
76.79
59.34
55.44
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

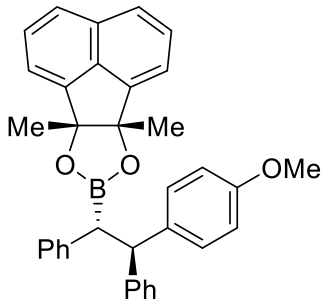
^{1}H NMR ($CDCl_3$, 500 MHz)



25


^{13}C NMR (CDCl$_3$, 126 MHz)
Ph
OH
F
OMe
25
162.26
160.32
158.60
142.15
137.71
137.68
132.58
129.95
129.89
129.83
128.09
127.63
126.84
115.05
114.88
114.24
77.27
77.02
76.95
76.76
58.66
55.25

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



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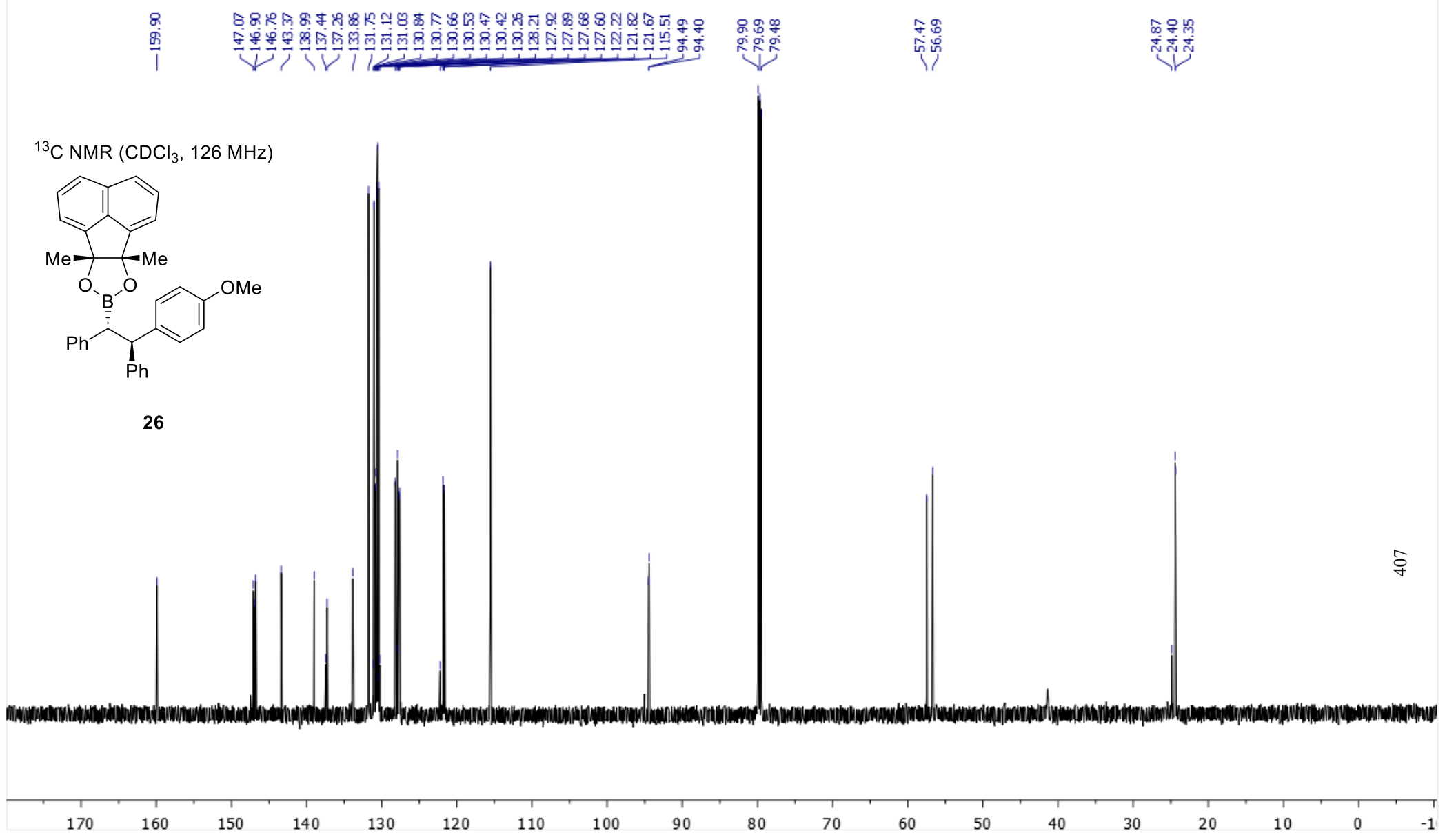
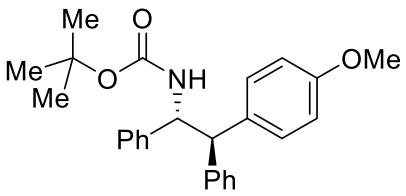


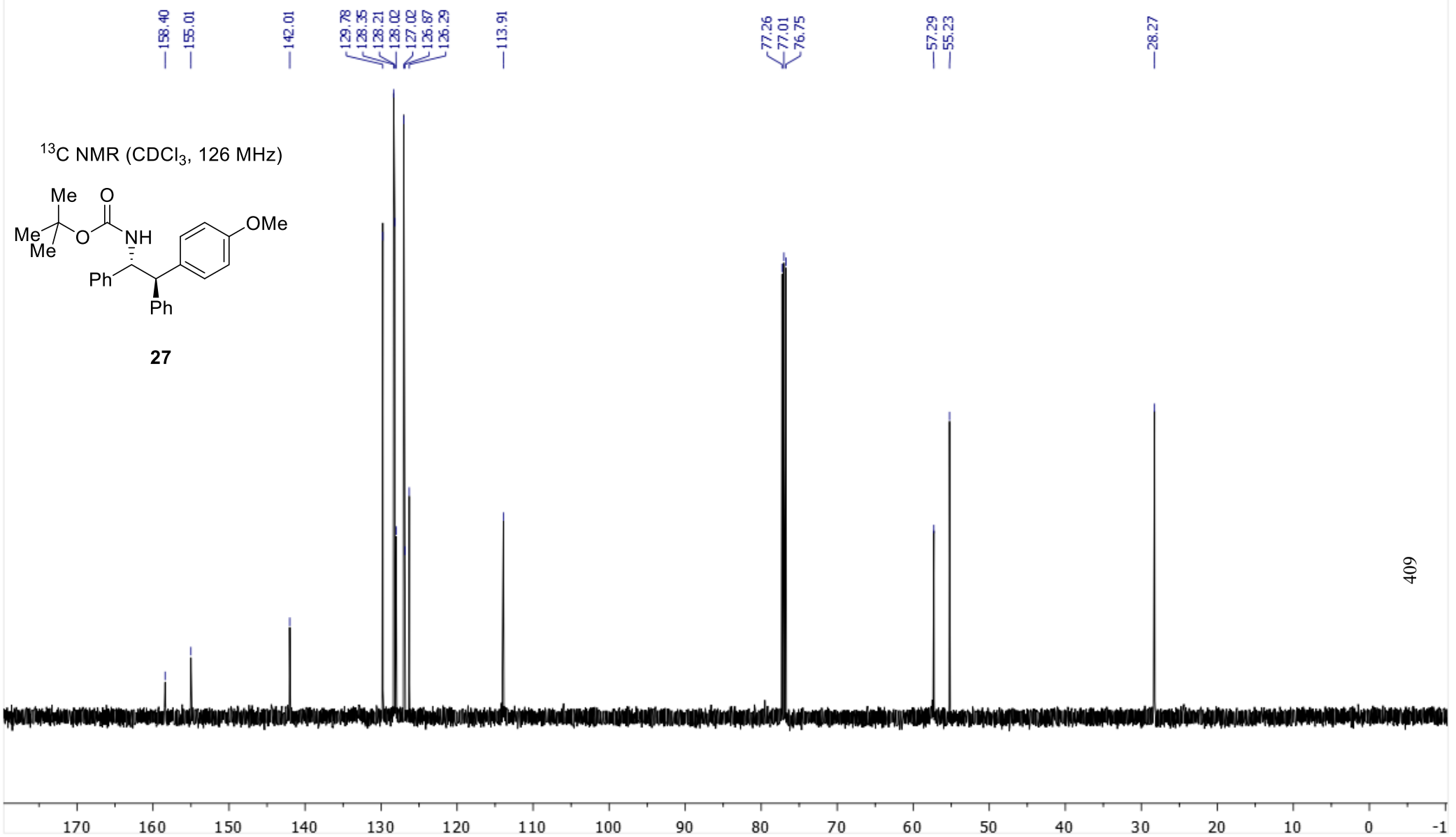
^{13}C NMR ($CDCl_3$, 126 MHz)

26

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



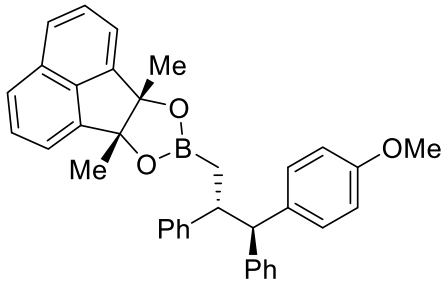
27



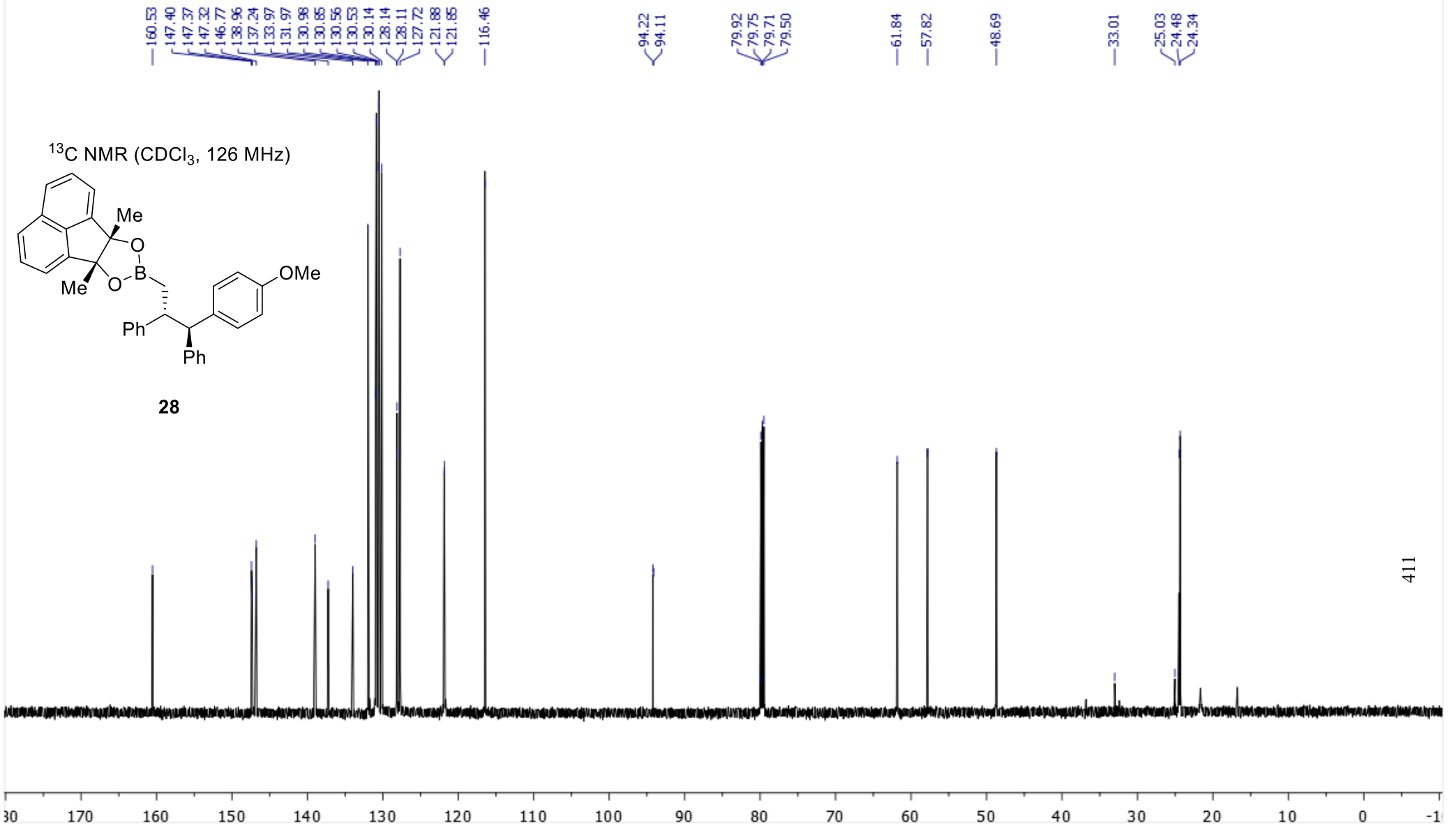
^{13}C NMR ($CDCl_3$, 126 MHz)

27

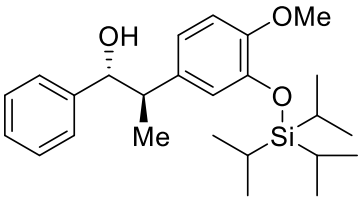
^{1}H NMR ($CDCl_3$, 500 MHz)



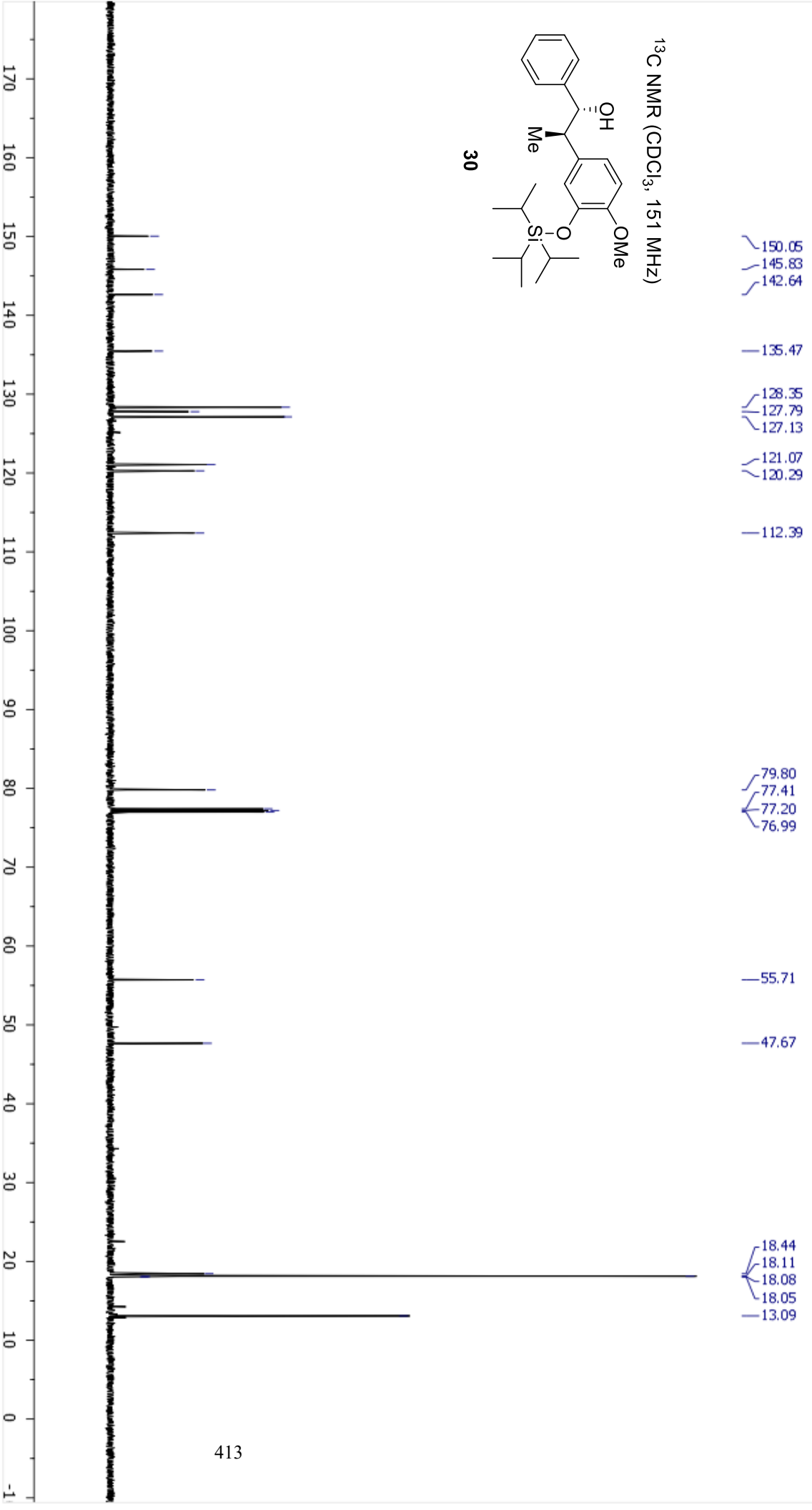
28


160.53
147.40
147.37
147.32
146.77
138.96
137.24
133.97
131.97
130.98
130.85
130.56
130.53
130.14
128.14
128.11
127.72
121.88
121.85
116.46
94.22
94.11
79.92
79.75
79.71
79.50
61.84
57.82
48.69
33.01
25.03
24.48
24.34
^{13}C NMR ($CDCl_3$, 126 MHz)
Me
O
B
O
Me
OMe
Ph
Ph
28
411
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

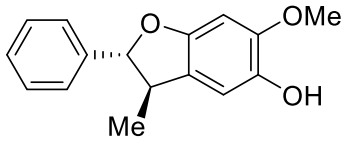
^{1}H NMR ($CDCl_3$, 600 MHz)



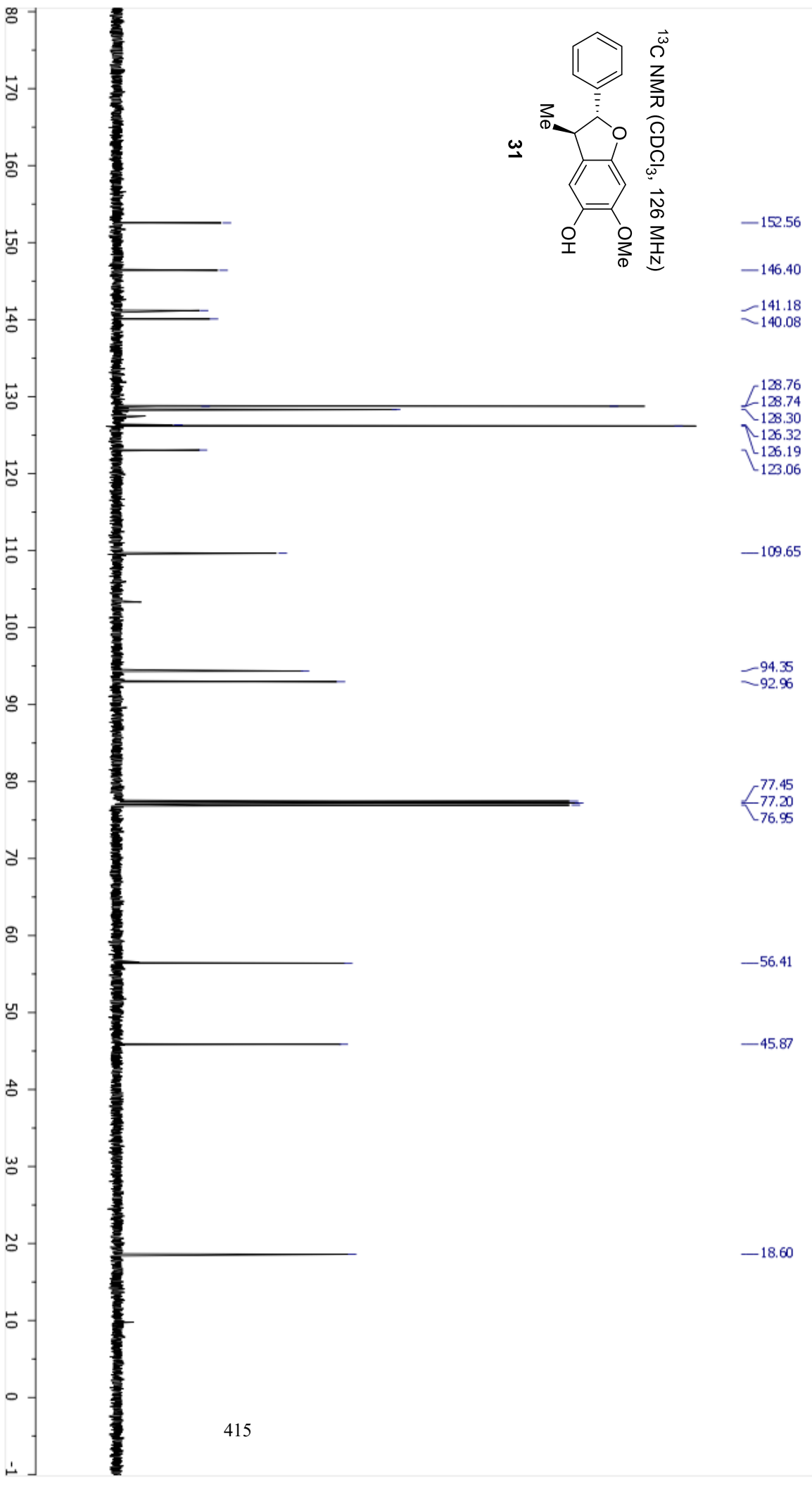
30


^{13}C NMR (CDCl$_3$, 151 MHz)
30
OH
Me
Si
O
OMe
150.05
145.83
142.64
135.47
128.35
127.79
127.13
121.07
120.29
112.39
79.80
77.41
77.20
76.99
55.71
47.67
18.44
18.11
18.08
18.05
13.09

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



31


^{13}C NMR (CDCl$_3$, 126 MHz)
Me
O
OMe
OH
31
152.56
146.40
141.18
140.08
128.76
128.74
128.30
126.32
126.19
123.06
109.65
94.35
92.96
77.45
77.20
76.95
56.41
45.87
18.60
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

Chapter 4

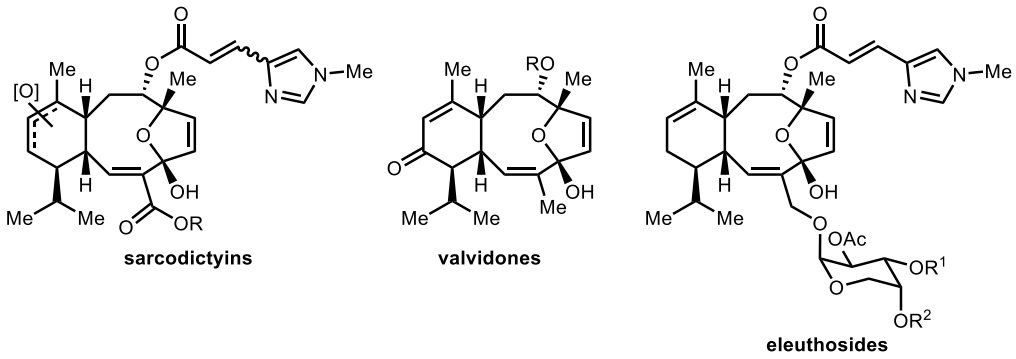
Progress Towards the Total Synthesis of the Sarcodictyins and Related Natural Products

4.1. Introduction

Since their isolation in 1987, the sarcodictyin family of natural products (Scheme 4.1) has attracted the interest of both synthetic and medicinal chemists.[1] These marine natural products are highly cytotoxic against a variety of cancer cell lines, and exhibit a Taxol-like mechanism of action.[2] Despite the promising biological activity, the limited supply of these materials from nature has hindered their possible pharmaceutical development.[1] Therefore, a robust chemical synthesis of the sarcodictyin natural products is highly sought after. Extensive efforts from a variety of research groups have been aimed at synthesizing the sarcodictyin natural products, but only two completed total syntheses of these compounds have been reported thus far.[1] Notably, the Danishefsky group has completed a total synthesis of one member of this class, and the Nicolaou group has achieved the chemical synthesis of a library of natural and unnatural sarcodictyins, which has enabled impactful biological studies.

[1] 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.
[2] Ciomei, M.; Albanese, C.; Pastori, W.; Grandi, M.; Pietra, F.; D'Ambrosio, M.; Guerriero, A.; Battistini, C. *Proc. Am. Ass. Canc. Res*. **1997**, *38*, 5 (Abstract 30).

Scheme 4.1. The sarcodictyin family of natural products



From a synthetic standpoint, the sarcodictyins contain a rigid tricyclic framework. The carbon skeleton is an [8.4.0] ring system, which is rigidified by three endocyclic alkenes, as well as a bridging oxygen atom within the 10-membered ring, forming a γ-lactol. The total synthesis of these natural products is challenging due to the presence of sensitive functionalities such as a hemiketal, a tertiary alcohol, an ester, and multiple alkenes. Therefore, synthetic precursors to the sarcodictyins are often susceptible to decomposition if functional groups are not installed in the proper order. While the previous total syntheses of the sarcodictyins are impressive, they are rather long (>25 steps LLS) due to several protecting group manipulation steps.

The goal of the following work is to develop an efficient and scalable synthetic route to the sarcodictyin family of natural products. It is envisioned that such a route can be enabled by transformations of organoboronates due the broad array of C–C and C–heteroatom bond forming reactions available to these reagents. Furthermore, there exist a variety of methods for C–B bond formations and the boronate functionality is sufficiently robust to be carried through a multi-step synthesis, allowing for their strategic incorporation into the synthetic sequence. The following chapter will discuss the progress towards the total synthesis of the sarcodictyins by the construction of a fully-cyclized advanced intermediate.

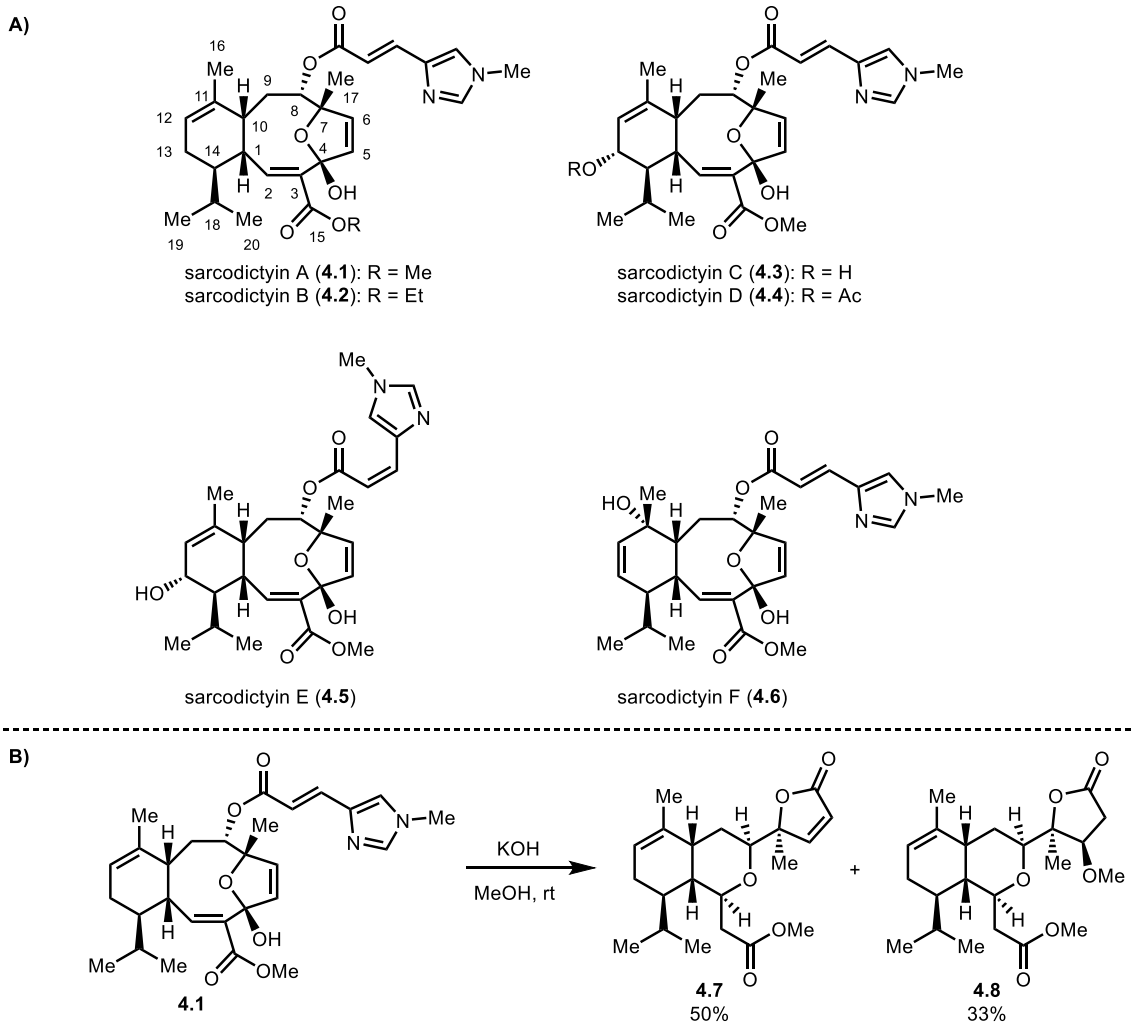
4.2. Background

4.2.1. Isolation of the sarcodictyins

Sarcodictyins A (**4.1**) and B (**4.2**) (Scheme 4.2.A) are marine diterpenoid natural products which were isolated from the ethanol extract of the soft coral *Sarcodictyon roseum* in 1987 by Pietra *et al.*[3] Shortly thereafter, the more-polar sarcodictyins C (**4.3**), D (**4.4**), E (**4.5**), and F (**4.6**), which are oxidized at C-11 or C-13, were isolated from the same source.[4] The structures of the sarcodictyins were determined by 1D and 2D NMR, with the absolute configuration determined by Horeau's method.[5] Of note, sarcodictyin A decomposes to **4.7** and **4.8** in the presence of base by hydrolysis of the urcanoate group followed by structural rearrangements involving the α,β-unsaturated ester and the hemiketal functionality (Scheme 4.2.B).

[3] D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019–2027.
[4] D'Ambrosio, M.; Guerriero, A.; Pietra, R. *Helv. Chim. Acta* **1988**, *71*, 964–976.
[5] Horeau, A. *Tetrahedron Lett*. **1961**, *15*, 506–512.

Scheme 4.2. The sarcodictyins

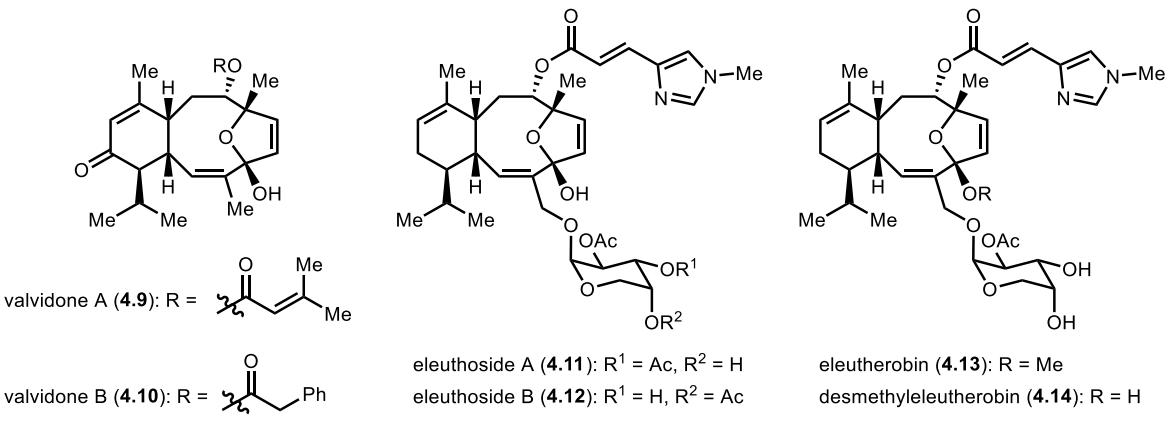


The other members of the sarcodictyin family, valvidones A (**4.9**) and B (**4.10**),[6] Eeuthoside A (**4.11**) and B (**4.12**),[7] and eleutherobin (**4.13**),[8] have been isolated from different species of soft coral (Scheme 4.3). These natural products all share the same carbon skeleton; the 14-membered ring is connected by a C–C bond between C-1 and C-10 (sarcodictyin numbering),

[6] Lin, Y.; Bewley, C. A.; Faulkner, D. J. *Tetrahedron* **1993**, *49*, 7977–7984.
[7] Ketzinel, S.; Rudi, A.; Schleyer, M.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **1996**, *59*, 873-875.
[8] (a) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. H.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744–8745. (b) Long, B. H.; Carboni, J. M.; Wasserman, A. J.; Cornell, L. A.; Casazza, A. M.; Jensen, P. R.; Lindel, T.; Fenical, W.; Fairchild, C. R. *Cancer Res.* **1998**, *58*, 1111–1115.

and a linking oxygen atom between C-4 and C-7. Within the class of natural products, there is variation with respect to the oxidation states at different carbon atoms. The valvidones contain a carbonyl group at C-13 and lack oxygenation at C-15. They also possess a different side chain on the ester at C-8, which differs between valvidones A and B. The eleuthoside natural products only differ from the sarcodictyins by a glycosyloxy group at C-15 instead of an ester, and substituents of the glycoside can vary. An alternative glycoside group is found in eleutherobin and desmethyleleutherobin (**4.14**); the C-4 methyketal of eleutherobin is regarded as an artifact of isolation due to the use of methanol in extracting the product from the natural source, and desmethyleluetherobin is indeed the natural product.[9] Notably, the structure of eleutherobin has been confirmed by crystallographic structure determination.[10]

Scheme 4.3. The valvidone and eleuthoside natural products

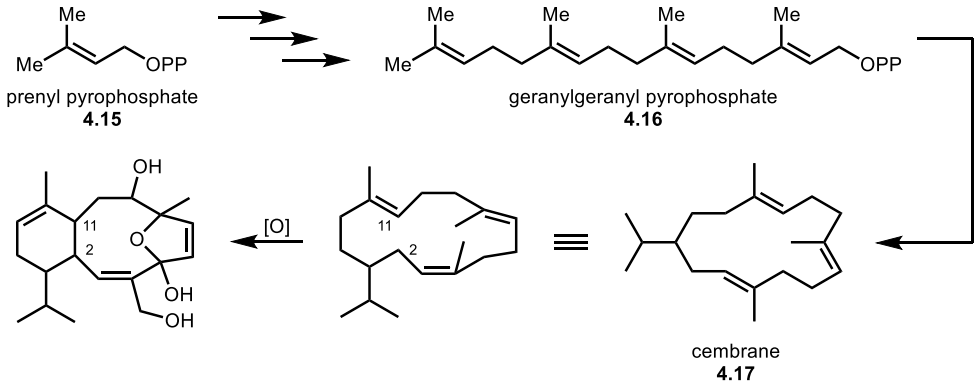


[9] Britton, R.; Roberge, M.; Berisch, H.; Andersen, R. J. *Tetrahedron Lett*. **2001**, *42*, 2953–2956
[10] Cinel, B.; Patrick, B. O.; Roberge, M.; Andersen, R. J. *Tetrahedron Lett.* **2000**, *41*, 2811–2815.

4.2.2. Biosynthesis of the sarcodictyins

The sarcodictyins are diterpene (C_{20}) natural products.[11] As shown in Scheme 4.4, a possible biosynthesis involves the combination of four prenyl pyrophosphate (**4.15**) units to form geranylgeranyl pyrophosphate (**4.16**), and subsequent cyclization to form the cembrane skeleton (**4.17**).[12] This intermediate undergoes another cyclization reaction by C–C bond formation between C-2 and C-11 (cembrane numbering), followed by oxidation of the carbon skeleton to deliver the sarcodictyin natural products.[13] The sarcodictyins are proposed to be a result of over-oxidation at C-15 (sarcodictyin numbering) during the biosynthesis of the eleuthosides, whereas the valvidones are not oxidized at this position.[9] The histidine-derived urcanoic ester at C-8, is likely introduced prior to oxidation at C-15 due to the rapid decomposition of sarcodictyins in the absence of this ester.[9]

Scheme 4.4. Proposed biosynthesis of sarcodictyin natural products



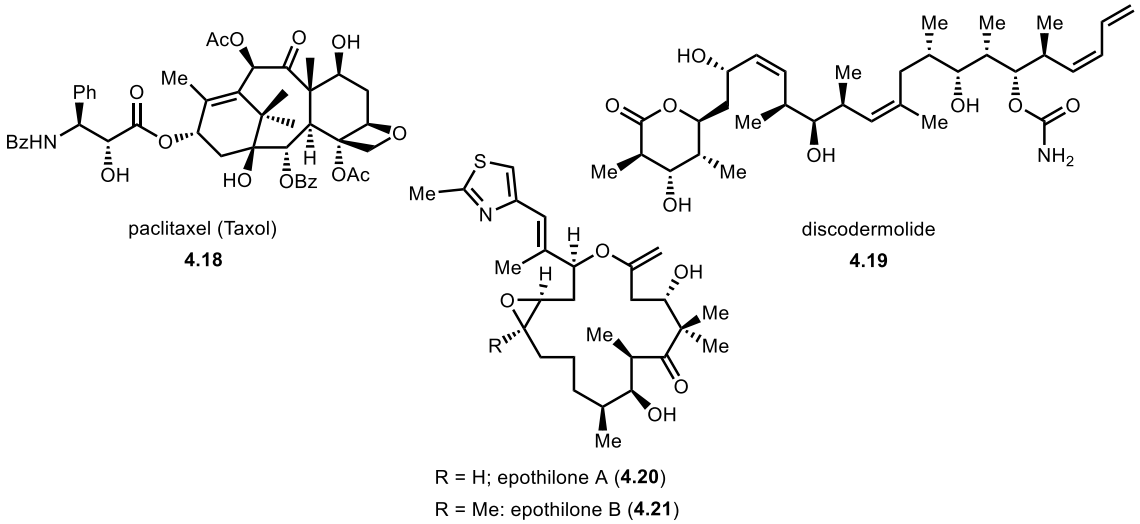
[11] Oldfield, E.; Lin, F.-Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 1124–1137.
[12] Rodríguez, A.D.; Li, Y.; Dhasmana, H. *J. Nat. Prod*. **1993**, *56*, 1101–1113.
[13] Bernardelli, P.; Paquette, L. A. *Heterocycles*. **1998**, *49*, 531–556.

4.2.3. Biological activity of the sarcodictyins

The sarcodictyins display potent anti-tumor activity and a similar mechanism of action to paclitaxel (Taxol, **4.18**).[2] Specifically, these compounds, along with other marine natural products, such as discodermolide (**4.19**)[14] and epothilones A (**4.20**) and B (**4.21**)[15] (Scheme 4.5), exhibit cytotoxicity by the aggregation of microtubules and the stabilization of non-functional tubulin units.[1, 16] Cell division requires both the assembly and disassembly of microtubules, and the disruption of natural microtubule dynamics triggers apoptosis, which is a particularly effective strategy to target cancer cells due to their rapid proliferation.[17] Following the clinical success of Taxol and other marine natural products, the sarcodictyins were pursued as drug-candidates.[18] The development of alternative therapeutic agents to Taxol is necessary due to the emergence of Taxol-resistant cancer cells.[1] The mechanisms of resistance are specific to the Taxol structure, rather than the mechanism of action, and an alternative tubulin-stabilizing agent would likely bypass this resistance.[1] The proposed mechanism of action is supported by the fact that the sarcodictyins A and B compete with Taxol in tubulin binding assays.[1]

[14] (a) Gunasekara, S. P.; Gunasekara, M.; Longley, R. E. *J. Org. Chem.* **1990**, *55*, 4912. (b) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 287.
[15] Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1567.
[16] (a) Horwitz, S. B. *Trends Pharmacol. Sci.* **1992**, *13*, 134. (b) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.
[17] Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. lnt. Ed*. **1994**, *33*, 15–44.
[18] (a) Newman, D. J.; Cragg, G. M. *J. Nat.Prod.* **2004**, *67*, 1216–1238. (b) Simmons, T. L.; Andrianasolo, E.; McPhail, K.; Flatt, P.; Gerwick, W. H. *Mol. Cancer Ther.*, **2005**, *4*, 333.

Scheme 4.5. Examples of microtubule-stabilizing natural products.



A large library of sarcodictyin analogs was synthesized by the Nicolaou group to elucidate the structure activity relationships (SAR) of the molecule.[19] The biological activity for a subset of the analogs is shown in Table 4.1. Sarcodictyin A (**4.1**) is 100-fold less potent than Taxol (**4.18**) against the 1A9 ovarian carcinoma cell line (Entry 2), whereas sarcodictyin B (**4.2**) exhibits similar potency, but does not show improved activity against the Taxol-resistant cell lines 1A9PTX10 and 1A9PTX22 (Entry 3). The modified sarcodictyins **4.22** and **4.23** with a methylketal instead of the hemiketal are more potent against the Taxol-resistant cell lines (Entry 4, 5). Modification of the functional group at C-15 to a free alcohol (Entry 7) or aldehyde (Entry 8) is not tolerated, but the potency is retained for a dimethylacetal (Entry 9) or an amide (Entry 10). The ethylketal (Entry 11) and *n*-propylketal (Entry 12) are tolerated but have slightly decreased activity compared to the methylketal. The modification of the urcanoic ester fragment (Entry 13-16) is not tolerated and results in significant loss of potency. It should be noted that in some cases the tubulin binding

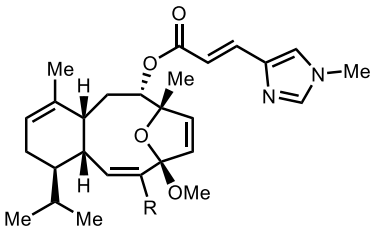
[19] (a) Nicolaou, K. C.; Kim, S.; Pfefferkorn, J.; Xu, J.-Y.; Ohshima, T.; Hosokawa, S.; Vourloumis, D.; Li, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 1418–1421. (b) Nicolaou, K. C.; Winssinger, N.; Vourloumis, D.; Ohshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J.-Y.; Li, T. *J. Am. Chem. Soc.* **1998,** *120,* 10814–10826.

ability is not proportional to the intracellular potency (e.g. Entry 4 vs. Entry 5). The lack of correlation can be attributed to many different factors, and further biological investigations would facilitate drug design.[20]

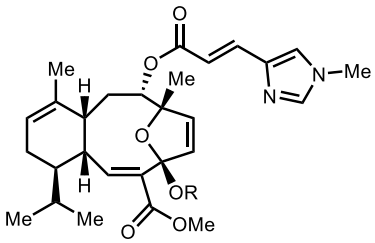
[20] Hamel, E.; Sackett, D. L.; Vourloumis, D.; Nicolaou, K. C. *Biochemistry* **1999**, *38*, 5490–5498.

Table 4.1. Biological activity of sarcodictyin analogs[19]

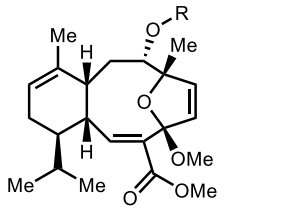
			Inhibition of Carcinoma Cell Growth, IC_{50} (nm)		
Entry	Compound	% Tubulin Polymerization	1A9	1A9PTX10	1A9PTX22
1	Taxol (**4.18**)	65	2	50	40
2	sarcodictyin A (**4.1**)	67	240	140	360
3	sarcodictyin B (**4.2**)	71	2	160	80
4	**4.22**	72	70	4	84
5	**4.23**	46	2	1	60
6	**4.24**	52	25	35	31
7	**4.25**	37	800	>2000	>2000
8	**4.26**	4	600	400	600
9	**4.27**	74	30	45	60
10	**4.28**	52	45	65	60
11	**4.29**	85	110	13	160
12	**4.30**	79	170	>2000	130
13	**4.31**	6	nd	nd	nd
14	**4.32**	18	430	1800	>2000
15	**4.33**	18	300	244	180
16	**4.34**	42	>2000	800	385

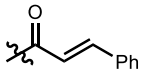


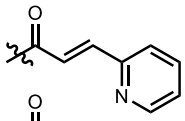
4.22: R = CO_2Me
4.23: R = CO_2Et
4.24: R = CO_2n-Bu
4.25: R = CH_2OH
4.26: R = CHO
4.27: R = $CH(OMe)_2$
4.28: R = CO(NHMe)

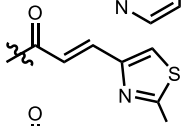


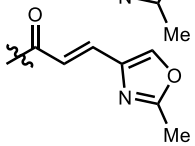
4.29: R = Et
4.30: R = *n*-Pr



4.31: R = 

4.32: R = 

4.33: R = 

4.34: R = 

The sarcodictyins are also potent against other tumor cell lines such as PC3 (prostate carcinoma), LOX-IMV1 (melanoma), and MCF-7 (breast carcinoma).[1] As shown in Table 4.2, the sarcodictyins (**4.1** and **4.2**) are generally less effective than Taxol (**4.18**) and the epothilones (**4.20** and **4.21**) against all cell lines tested. However, the methylketal-containing compounds eleutherobin (**4.13**) and sarcodictyin analog **4.22** have improved potency compared to the sarcodictyins. Thus compounds such as eluetherobin and **4.22** provide a promising starting point for drug discovery efforts.

Table 4.2. Cytotoxicity data for tubulin-stabilizing agents.[1]

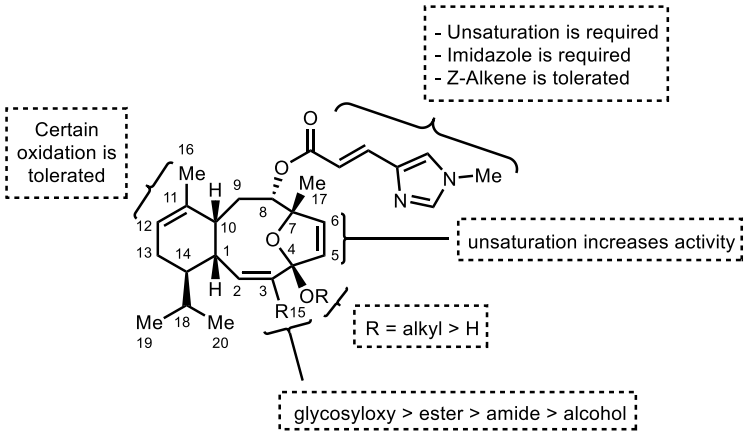
		Inhibition of Carcinoma Cell Growth, IC_{50} (nm)					
Entry	Compound	PC3	LOX-IMV1	MCF-7	1A9	1A9PTX10	1A9PTX22
1	Taxol (**4.18**)	4	6	2	4	60	60
2	epothilone A (**4.20**)	10	10	5	10	40	10
3	epothilone B (**4.21**)	0.9	0.9	0.4	1	3	1
4	sarcodictyin A (**4.1**)	200	400	300	300	200	300
5	sarcodictyin B (**4.2**)	200	500	400	300	300	300
6	eleutherobin (**4.13**)	20	30	10	40	60	30
7	**4.22**	50	80	300	20	20	10

Overall, the pharmacophore of sarcodictyins is summarized in Scheme 4.6.[1] Some oxidative functionalizations are tolerated at C-16 and the C-11/C-12 alkene, based on synthetically modified eleutherobin analogs.[21] Other modifications to the lipophilic region (i.e. cyclohexenyl unit) have not been investigated. The urcanoic ester group is required for cytotoxicity, both with respect to the unsaturation and the imidazole fragment. Notably, an analog of sarcodictyin A with

[21] Britton, R.; de Silva, E. D.; Bigg, C. M.; McHardy, L. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 8632–8633.

a Z-configured urcanoic ester has been isolated and shows similar levels of cytotoxicity against HeLa cells compared to E-configured isomer.[22] The alkene at C-5/C-6 is required for optimal activity.[19a] The C-15 ester is more potent than the corresponding amide, and a free alcohol is significantly less potent. Lastly, a ketal, rather than a hemiketal, at C-4 leads to improved biological activity.

Scheme 4.6. Pharmacophore of the sarcodictyins



4.2.4. Previous syntheses of sarcodictyin natural products

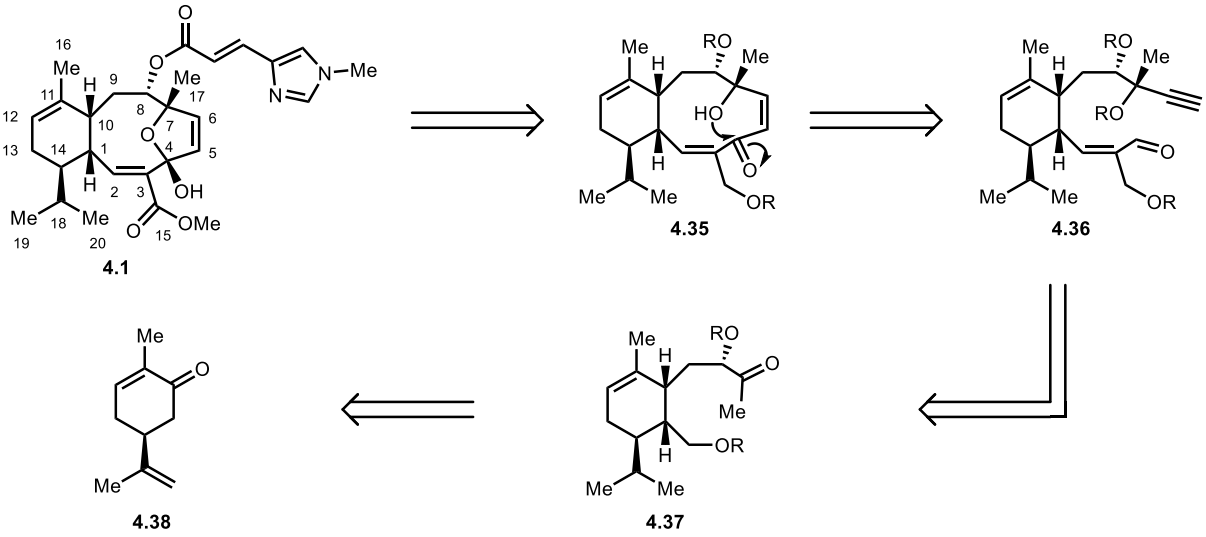
4.2.4.1. Total synthesis of sarcodictyin A and B by the Nicolaou group

Due to the inefficient isolation of sarcodictyins from natural sources, the chemical synthesis of these natural products has been a valuable tool for biological testing.[1] The only total synthesis of sarcodictyin A or B has been reported by the Nicolaou group.[19a, 23] This synthetic route has been particularly important as it enabled preliminary biological testing and SAR studies.[19b] The structure of the sarcodyctins includes a tricyclic framework with a variety of

[22] Nakao, Y.; Yoshida, S.; Matsunaga, S.; Fusetani, N. *J. Nat. Prod.* **2003,** *66,* 524–527.
[23] (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.

oxidation states on the carbon skeleton. The retrosynthetic analysis is shown in Scheme 4.7. The hemiketal at C-4 of the lactol ring can be disconnected into the corresponding alcohol and ketone, which reveals a 10-membered ring (**4.35**). The ring can be closed from the open-chain structure **4.36** by an intramolecular acetylide-aldehyde addition, followed by partial hydrogenation to yield the Z-alkene at C-5/C-6. The tertiary alcohol at C-17 can be synthesized from precursor **4.37** by an acetylide-ketone addition, and the α, β-unsaturated aldehyde can be derived from a Knoevenagel condensation reaction. The structure **4.37** can be derived from (+)-carvone (**4.38**).

Scheme 4.7. Retrosynthesis of Sarcodictyins by the Nicolaou group.

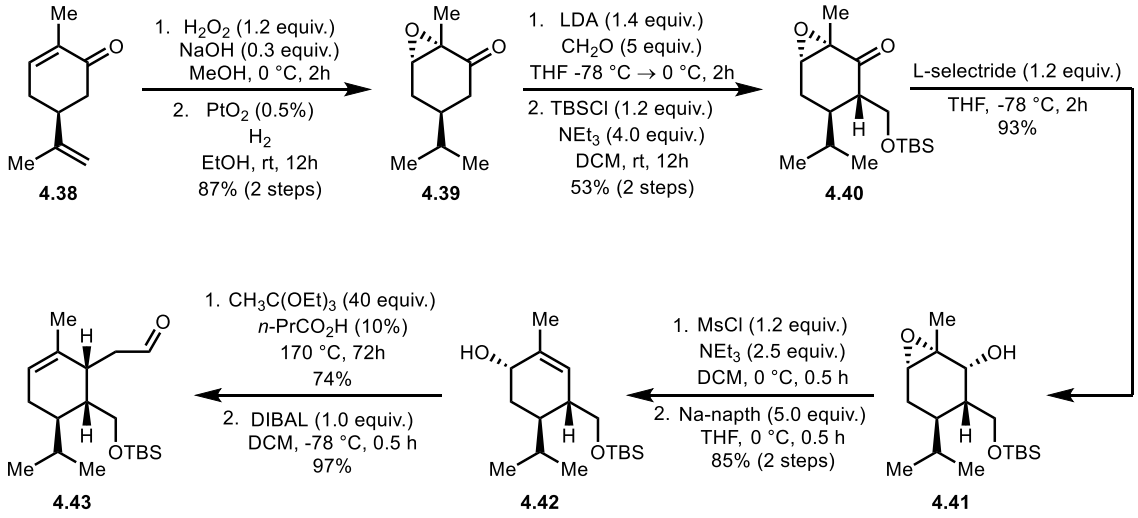


The forward synthesis by Nicolaou group is shown in Scheme 4.8. Intermediate **4.43** is synthesized according to a modified procedure by the Trost group.[24] (+)-Carvone (**4.38**) is subjected to a diastereoselective enone epoxidation with hydrogen peroxide followed by Pt-catalyzed hydrogenation of the isopropenyl group to yield **4.39**. Next, an aldol addition to formaldehyde and TBS protection of the resulting primary alcohol yields **4.40**. The ketone

[24] Trost, B. M.; Tasker, A. S.; Ruther, G.; Brands, A. *J. Am. Chem. Soc*. **1991**, *113*, 670.

functionality is reduced with L-selectride, and the corresponding alcohol (**4.41**) is converted to the mesylate. Next, reductive epoxide opening with sodium naphthalenide and concomitant elimination of the mesylate provides allylic alcohol **4.42**. The alcohol is treated with triethyl orthoacetate and an acid catalyst to promoted a Johnson-Claisen rearrangement, and the resulting ester is reduced to the aldehyde (**4.43**) with DIBAL.

Scheme 4.8. Synthesis of intermediate 4.43 by the Nicolaou group.

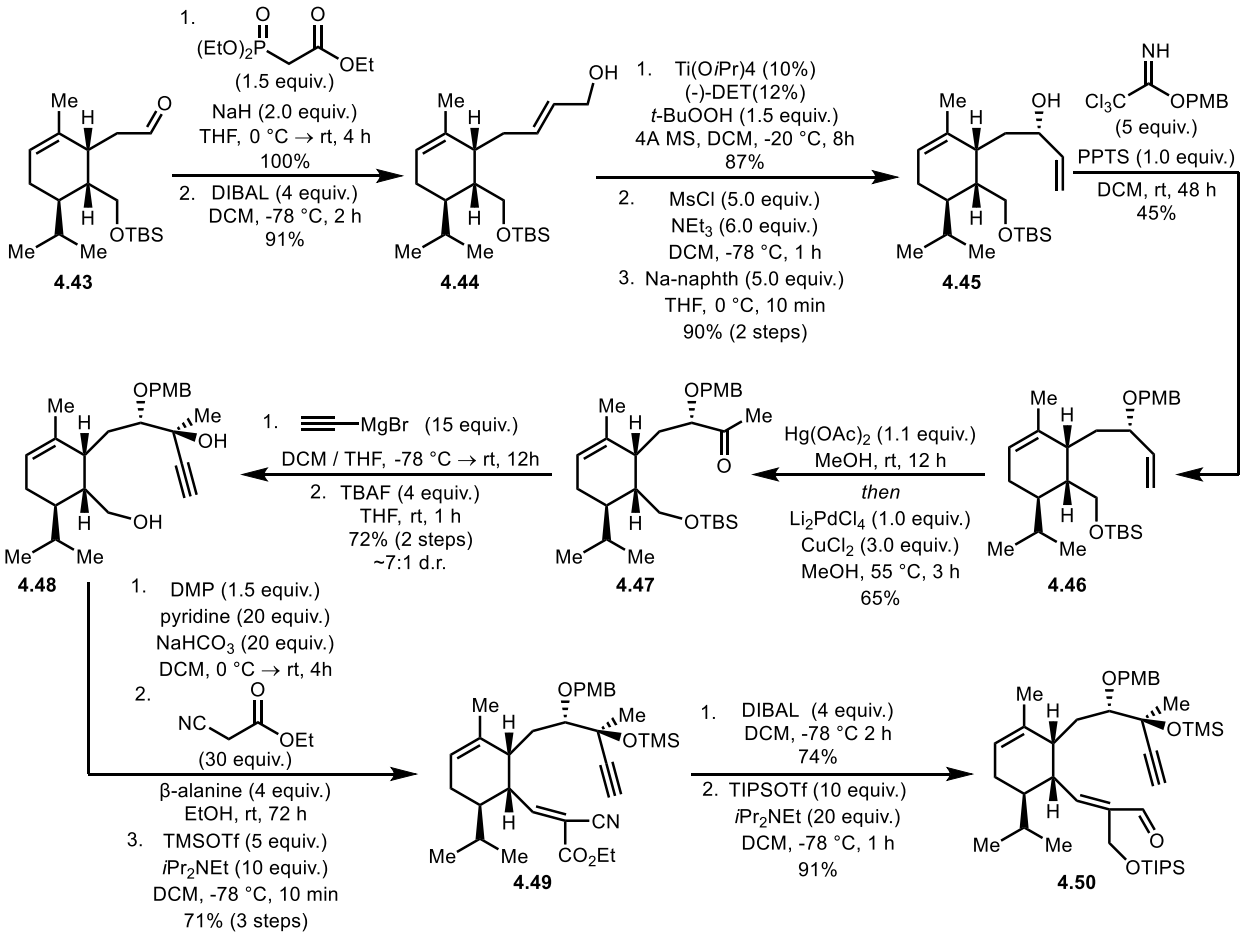


The synthesis of the cyclization precursor is continued as shown in Scheme 4.9. The aldehyde **4.43** undergoes a Horner-Wadsworth-Emmons olefination reaction and the thus-formed ester is reduced to the allylic alcohol **4.44** by DIBAL. Next, the allylic alcohol is isomerized by a sequence of a Sharpless asymmetric epoxidation reaction,[25] mesylation, and reduction with sodium naphthalenide to yield secondary alcohol **4.45**. The protection of the free alcohol with a PMB group yields **4.46** and subsequent oxidation of the alkene to a ketone by sequential oxymercuration and transmetallation to palladium[26] yields **4.47**. The ketone is subjected to a diastereoselective

[25] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974-5976.
[26] Rodeheaver, G. T.; Hunt, D. F. *J. Chem. Soc. D*. **1971**, 818-819.

acetylide addition (~7:1 d.e.), at which point the TBS protecting group is removed to furnish **4.48**. The controlled Dess-Martin oxidation of the primary alcohol to the aldehyde and ensuing Knoevenagel condensation with ethyl cyanoacetate[27] yields **4.49** after TMS protection of the tertiary alcohol. Finally, the single-step DIBAL reduction of both the nitrile to the aldehyde and the ester to the alcohol, followed by TIPS protection of the primary alcohol yields pre-cyclization intermediate **4.50**.

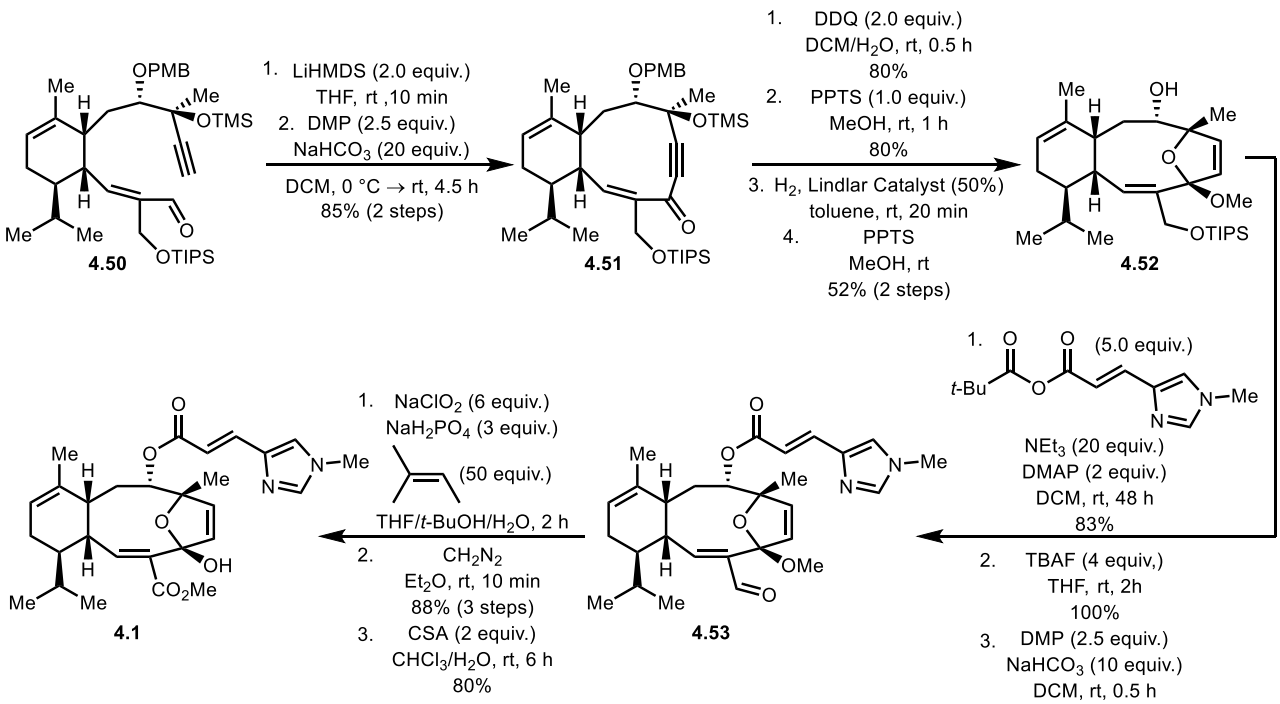
Scheme 4.9. First-generation synthesis of the pre-cyclization intermediate



[27] Anderson, N. H.; Golec, F. A., Jr. *Tetrahedron Lett*. **1977**, 3783-3786.

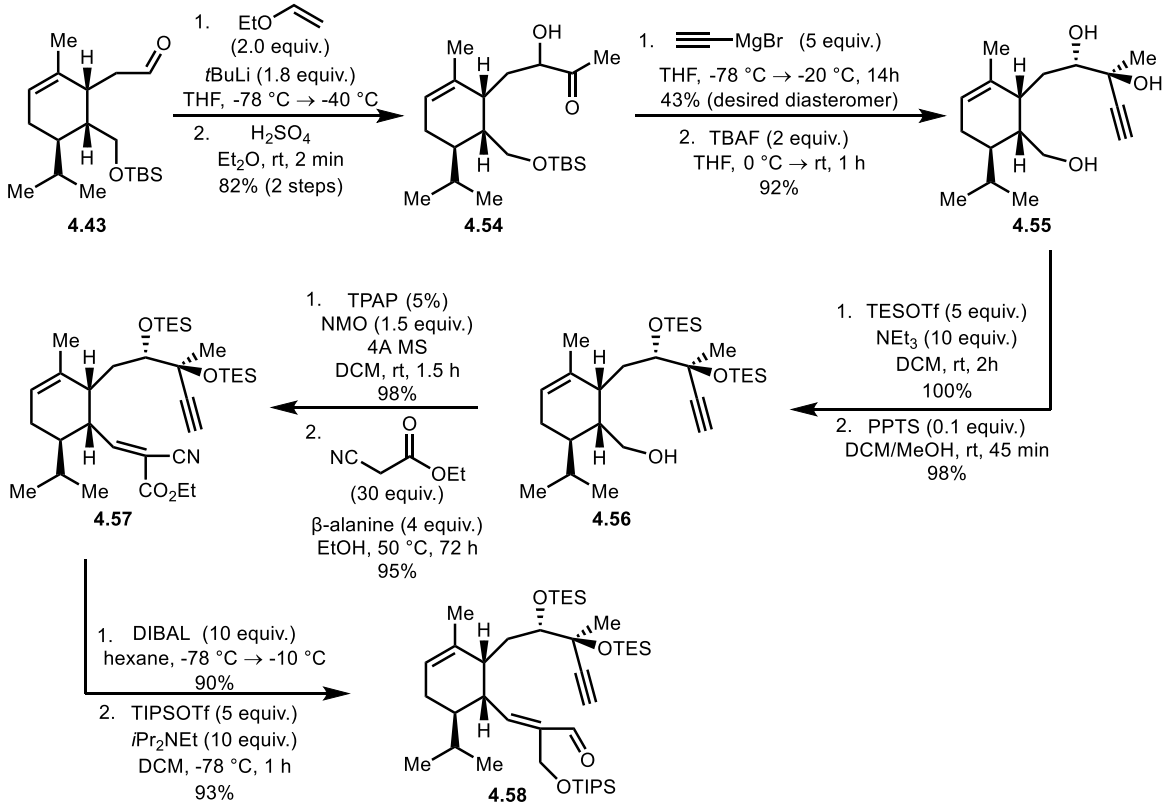
As shown in Scheme 4.10, the synthesis of sarcodictyin A (**4.1**) is continued by an intramolecular acetylide-aldehyde addition of **4.50** with LiHMDS, and Dess-Martin oxidation of the resultant alcohol to yield the cyclic ynone **4.51**. The PMB protecting group is removed by DDQ, and the TMS protecting group by PPTS, then the alkyne is partially hydrogenated with Lindlar's catalyst. The lactol intermediate is protected as the methylketal **4.52** by PPTS in methanol, and the secondary alcohol is esterified with the urcanoic acid mixed anhydride. Subsequent TIPS protecting group removal and Dess-Martin oxidation to the aldehyde yields **4.53**. The synthesis of sarcodictyin A (**4.1**) is completed by sequential Pinnick oxidation of the aldehyde to the carboxylic acid, then esterification with diazomethane, and lastly hydrolysis of the methylketal with CSA and water.

Scheme 4.10. Completion of the synthesis of sarcodictyin A.



The previous synthetic route to sarcodictyin A was later shortened by modifying the synthesis of the pre-cyclization intermediate and altering the protecting groups strategy (Scheme 4.11).[19a, 28] The aldehyde intermediate **4.43** is treated with lithiated vinyl ether then subjected to acid hydrolysis to yield the methyl ketone **4.54**. This mixture of diastereomers is treated with ethynylmagnesium bromide in a diastereoselective manner, and removal of the TBS yields triol **4.55**. This is subjected to global TES protection followed by mono-desilylation of the primary alcohol to yield **4.56**. The primary alcohol is oxidized to the aldehyde by TPAP and NMO, then subjected to the Knoevenagel condensation reaction. Intermediate **4.57** is subjected to a similar DIBAL reduction and TIPS protection sequence as had been utilized previously to arrive at **4.58**.

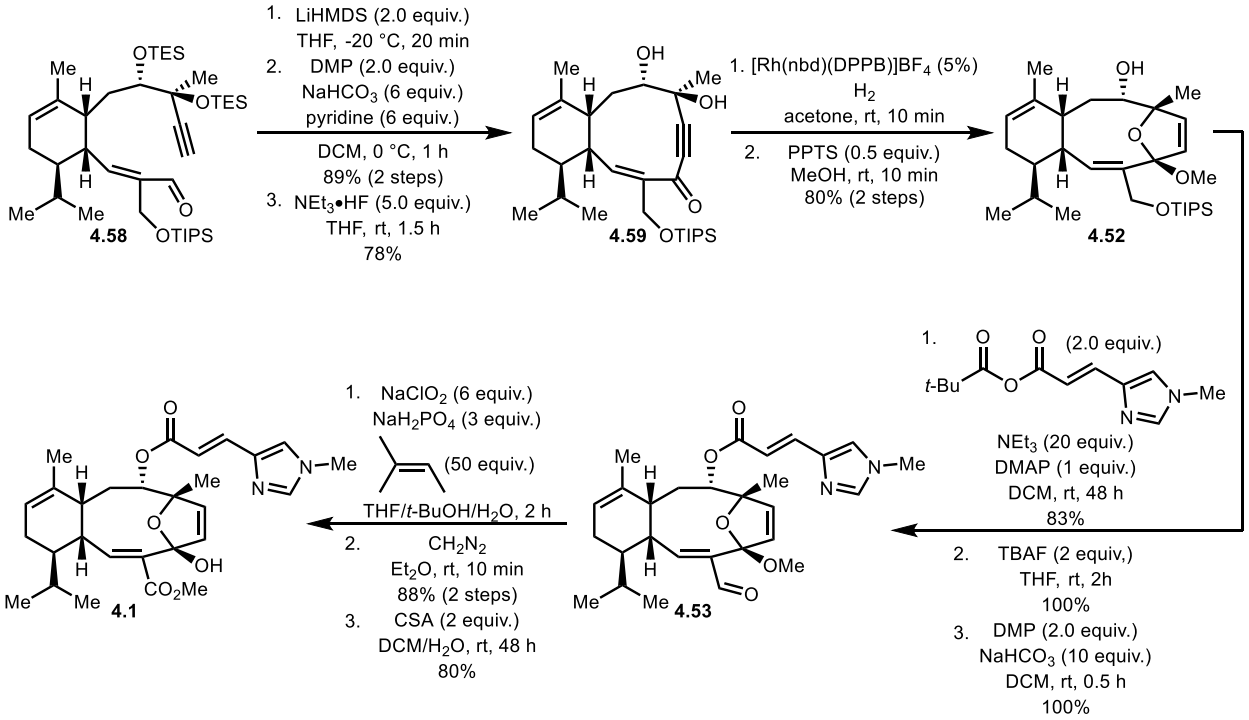
Scheme 4.11. Second-generation synthesis of 4.58



[28] 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.

The completion of the synthesis was also modified and further optimized (Scheme 4.12).[19a] The TES-containing intermediate **4.58** is converted to **4.59** by an acetylide-aldehyde addition reaction followed by Dess-Martin oxidation of the resultant secondary alcohol and removal of the TES protecting groups with HF. The alkyne is partially hydrogenated with a Rh-based catalyst, and the lactol is converted to the methylketal with PPTS in methanol to yield **4.52**. Notably, the Rh-based hydrogenation reaction is more effective than the previous Pd-based system due to suppression of the over-reduction product. From intermediate **4.52**, the completion of the synthesis by conversion to **4.53** then **4.1** is analogous to the previous route. This synthetic route enabled the synthesis of sarcodictyin analogs,[19a] as well as eluetherobin (**4.13**).[28, 29]

Scheme 4.12. Second-generation completion of the synthesis

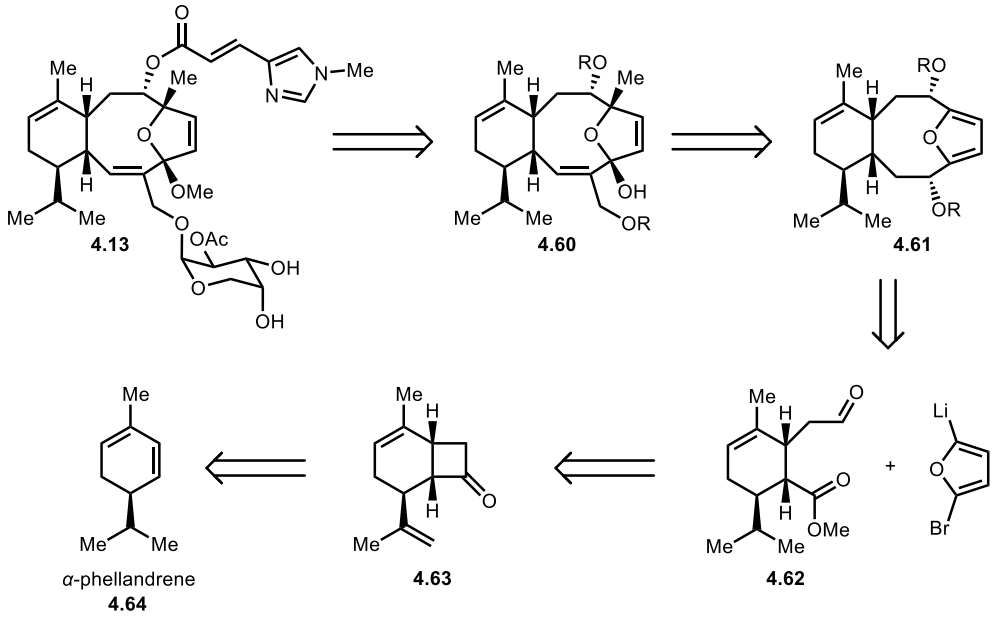


[29] Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**. *120,* 8674–8680.

4.2.4.2. Total synthesis of eluetherobin by the Danishefsky group

The only other completed total synthesis of a member of the sarcodictyin natural products was the synthesis of eleutherobin (**4.13**) by the Danishefsky group.[30] The retrosynthetic analysis involves modifications to the core structure **4.60** (Scheme 4.13). The lactol portion of the molecule comes from the corresponding furan **4.61**, which contains the full carbon skeleton of the natural product. This intermediate is derived from a bifunctional furan reagent and aldehyde **4.62**, which can be traced back to cyclobutanone **4.63**, and then α-phellandrene (**4.64**).

Scheme 4.13. Retrosynthetic analysis of eleutherobin by the Danishefsky group

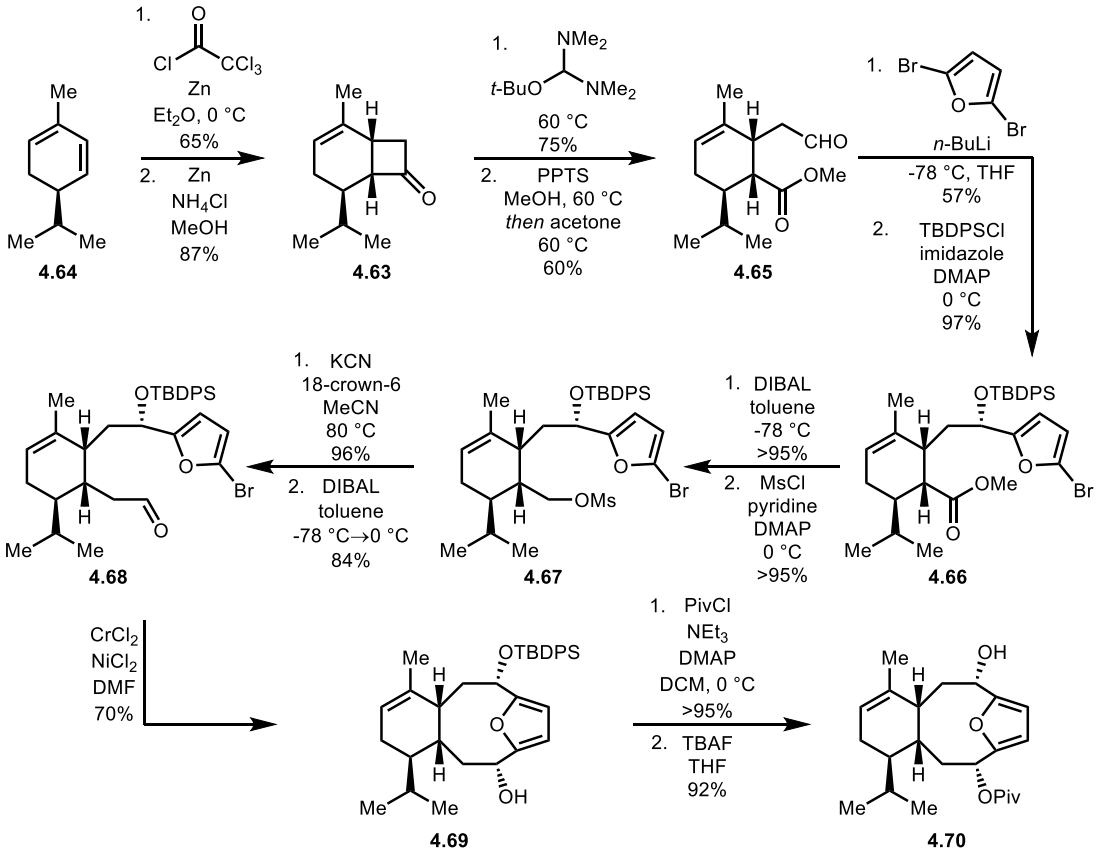


The forward synthesis of **4.1** is shown in Scheme 4.14.[30] α-Phellandrene (**4.64**) undergoes a [2+2] cycloaddition with *in situ*-generated dichloroketene, followed by zinc-mediated protodechlorination to yield cyclobutanone **4.63**. Subsequent enolate addition to Bredereck's

[30] (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.

reagent followed by acid-mediated ring fragmentation yields aldehyde **4.65**. The furanyllithium reagent is added to the aldehyde and the corresponding secondary alcohol is protected with a TBDPS group to yield **4.66**. The ester group is homologated by a sequence of reduction and mesylation to **4.67**, then cyanation, and reduction to **4.68**. The 10-membered ring is closed by an intramolecular Nozaki-Kishi-Hiyama coupling between the bromofuran and the aldehyde, yielding **4.69**. The free secondary alcohol is protected with a pivaloyl group, and the silyl-protected alcohol is deprotected to furnish furan-derivative **4.70**.

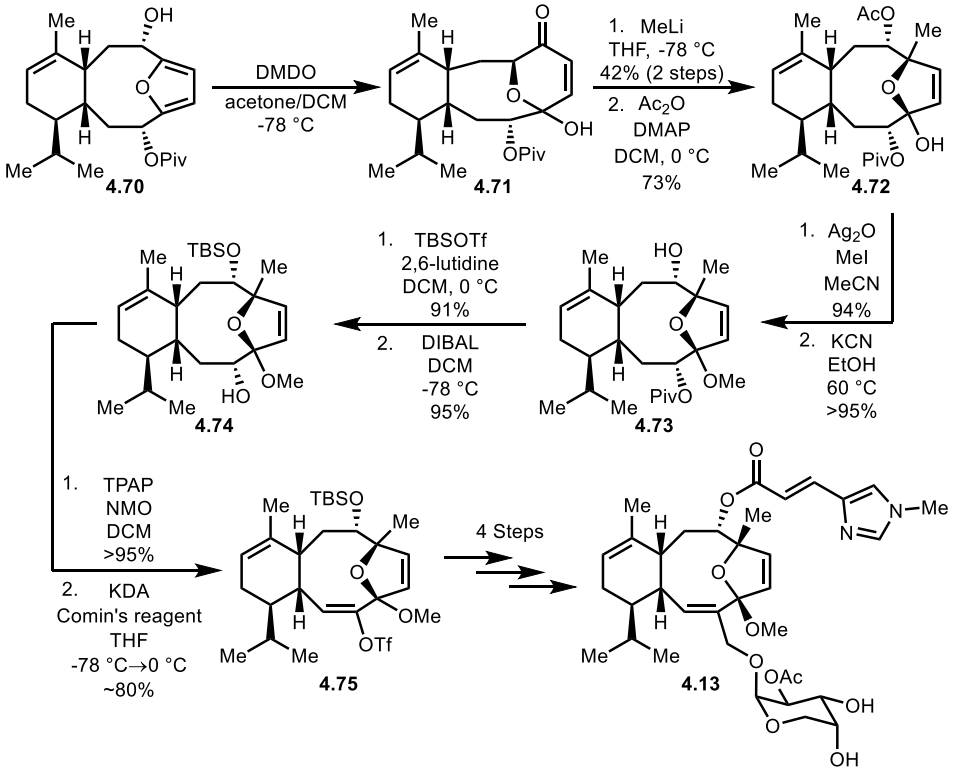
Scheme 4.14. Synthesis of Eleutherobin by the Danishefsky group.



The total synthesis of **4.13** is completed as shown in Scheme 4.15. The furan in **4.70** is transformed by an Achmatowicz reaction to the six-membered lactol **4.71** with DMDO as the

oxidant. Next, the ketone reacts with methyllithium to yield a tertiary alcohol which leads to the five-membered lactol as the more-favorable configuaration, and subsequent acylation of the secondary alcohol yields **4.72**. The alcohol of the lactol is methylated with silver oxide and iodomethane, and the acetyl protecting group is removed to arrive at **4.73**. The free alcohol is protected as a silyl ether, and the pivalyl protecting group is removed from the other secondary alcohol with DIBAL, leading to **4.74**. The alkenyl triflate **4.75** is synthesized by oxidation of the alcohol to the ketone with TPAP/NMO, followed by enolization with KDA and trapping with Comin's reagent. The intermediate **4.75** is converted into the natural product **4.13** after four more steps.

Scheme 4.15. Completion of the total synthesis of eleutherobin by the Danishefsky group.



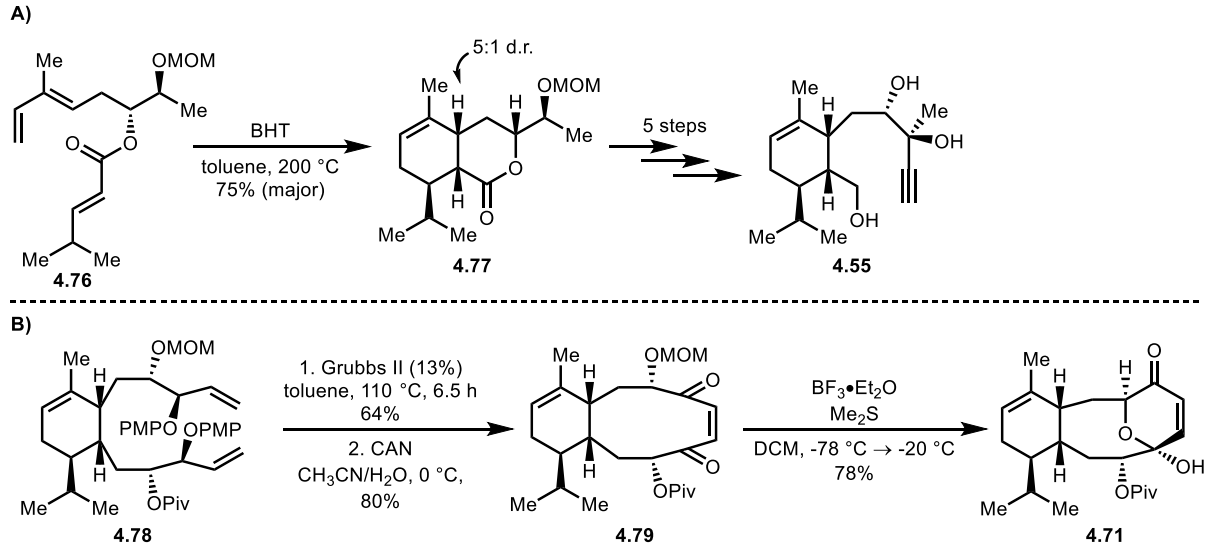
4.2.4.3. Formal synthesis of the sarcodictyins

A formal synthesis of the sarcodictyins was completed by the Metz group in 2003, in which an intermediate along the synthetic route of the Nicolaou group was synthesized.[31] The key step in this synthesis is an intramolecular Diels-Alder (IMDA) cycloaddition to establish the fused ring system in compound **4.77** (Scheme 4.16.A). Subsequent transformations yield the same alkyne **4.55** which has been utilized by the Nicolaou group. Another formal synthesis of the sarcodictyins has been reported by the Gennari group in 2005, along with several reports on the synthesis of many advanced intermediates.[32] The synthetic strategy employs ring-closing metathesis reaction as the key step to synthesize **4.79**, which contains the requisite 10-membered ring (Scheme 4.16.B). Using this strategy, intermediate **4.71** was synthesized, which has been converted to eleutherobin (**4.13**) by the Danishefsky group.

[31] Ritter, N.; Metz, P. *Synlett* **2003**, *15*, 2422–2424.

[32] (a) Ceccarelli, S. M.; Piarulli, U.; Gennari, C. *Tetrahedron Lett*. **1999**, *40*, 153–156. (b) Ceccarelli, S. M.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, *57*, 8531–8542. (c) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Monti, D.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 9187–9190. (d) Beumer, R.; Bayón, P.; Bugada, P.; Ducki, S.; Mongelli, N.; F. Riccardi Sirtori, J. Telser, C. Gennari. *Tetrahedron Lett.* **2003**, *44*, 681 (e) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayón, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913. (f) R. Beumer, P. Bayón, P. Bugada, S. Ducki, N. Mongelli, Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron* **2003**, *59*, 8803. (g) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 588–591. (h) Castoldi, D.; Caggiano, L.; Bayón, P.; Costa, A. M.; Cappella, P.; Sharon, O.; Gennari, C. *Tetrahedron* **2005**, *61*, 2123–2139. (i) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem. Eur. J.* **2006**, *12*, 51–62. (j) Gennari, C.; Castoldi, D.; Sharon, O. *Pure Appl. Chem.* **2007**, *79*, 173–180.

Scheme 4.16. Formal syntheses of sarcodictyin natural products

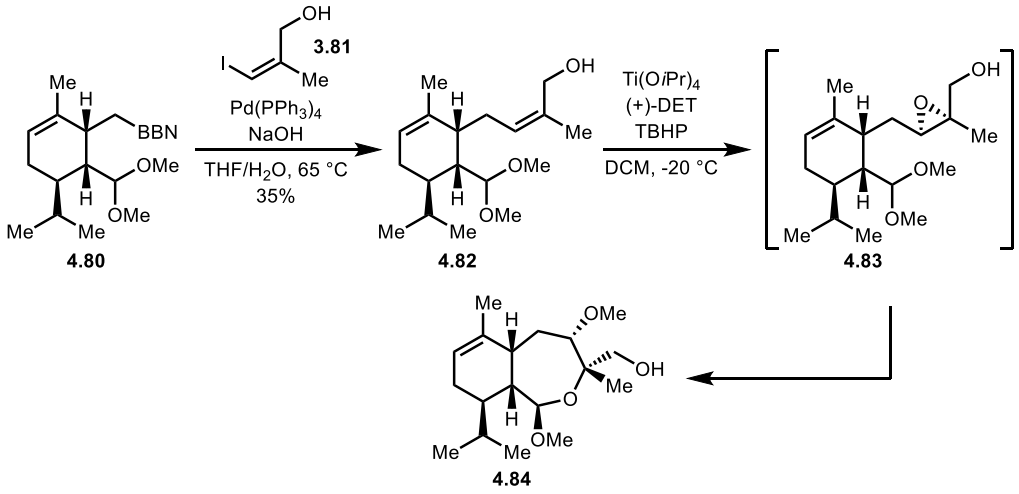


4.2.4.4. Synthesis of sarcodictyin-related intermediates by various groups

The advanced intermediate **4.82** was synthesized by the Magnus group in 2000 (Scheme 4.17).[33] The borane **4.80**, which is derived from carvone, is subjected to a cross-coupling reaction with alkenyl iodide **4.81** to deliver the allylic alcohol product. The main challenge in carrying out subsequent synthetic transformations from **4.82** is the susceptibility of the desired reaction product to decomposition pathways. As an example, when the allylic alcohol **4.82** is epoxidized in the presence of the acetal group, the expected product **4.83** decomposes to **4.84**. Thus, the choice of protecting groups and the order in which functional groups are introduced must be carefully considered when planning a synthetic route.

[33] Carter, R.; Hodgetts, L.; McKenna, J.; Magnus, P.; Wren, S. *Tetrahedron* **2000**, *56*, 4367–4382.

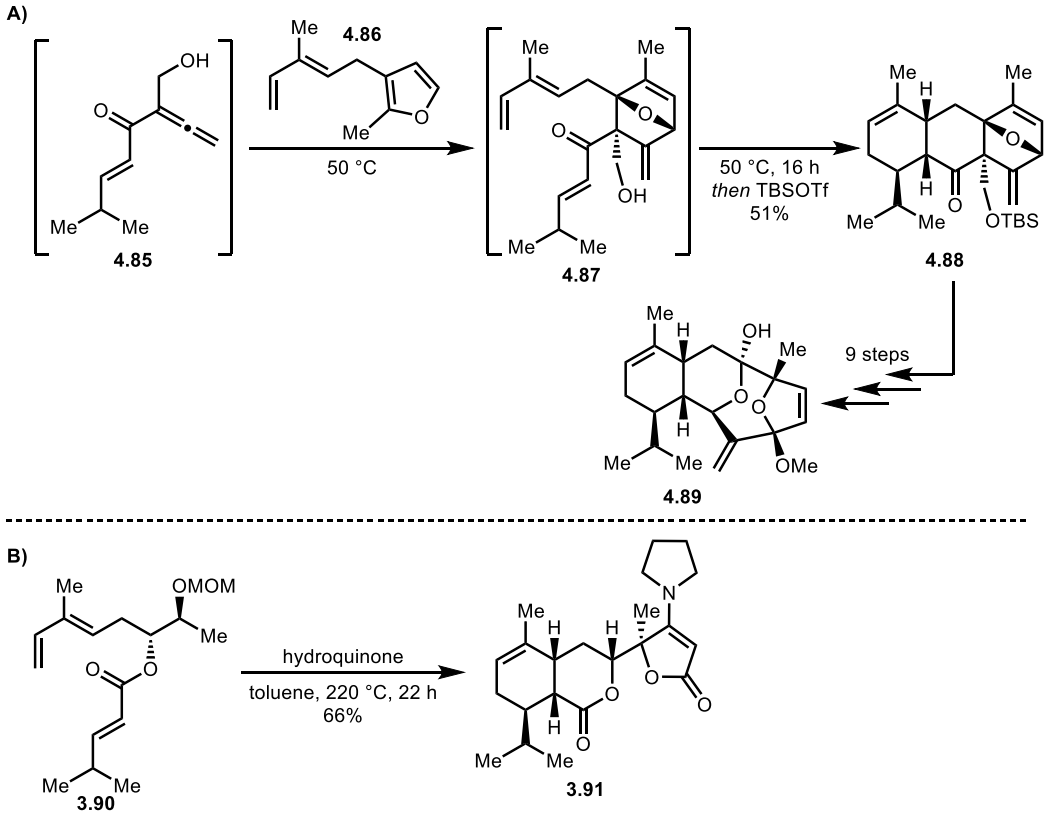
Scheme 4.17. Attempted synthesis of sarcodictyin A by the Magnus group



The Winkler group synthesized an advanced intermediate (**4.88**) by sequential Diels-Alder cycloadditions (Scheme 4.18.A).[34] The allene **4.85** undergoes a [4+2] with furan **4.86**, and the resulting intermediate **4.87** undergoes a consecutive [4+2] reaction to yield **4.88**. This intermediate is converted into **4.89** by a Grob fragmentation strategy, but the completion of the total synthesis by this route has not been reported. Nevertheless, this partial synthesis has introduced strategic bond disconnects that could enable the rapid generation of complex ring systems. A similar synthesis of the 10-membered ring by a Grob fragementation strategy has been proposed in unpublished work by the Britton group (not shown).[35] Additionally, the IMDA strategy is employed by the Royer group for the conversion of **4.90** into **4.91**, which contains the cyclohexene ring of the sarcodictyins (Scheme 4.18.B).[36]

[34] Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.,* **2003**, 5, 1805–1808.
[35] Mowat, J. S. Studies Towards the Total Synthesis of Eleutherobin and Other Marine Natural Products. Ph.D. Thesis, Simon Fraser University. Fall 2012.
[36] (a) Bruyère, H.; Samaritani, S.; Ballereau, S.; Tomas, A.; Royer, J. *Synlett* **2005**, *9*, 1421–1424. (b) Bruyère, H.; Dos Reis, C.; Samaritani, S.; Ballereau, S.; Royer, J. *Synthesis* **2006**, *10*, 1673–1681.

Scheme 4.18. Synthesis of advanced intermediates by an IMDA strategy

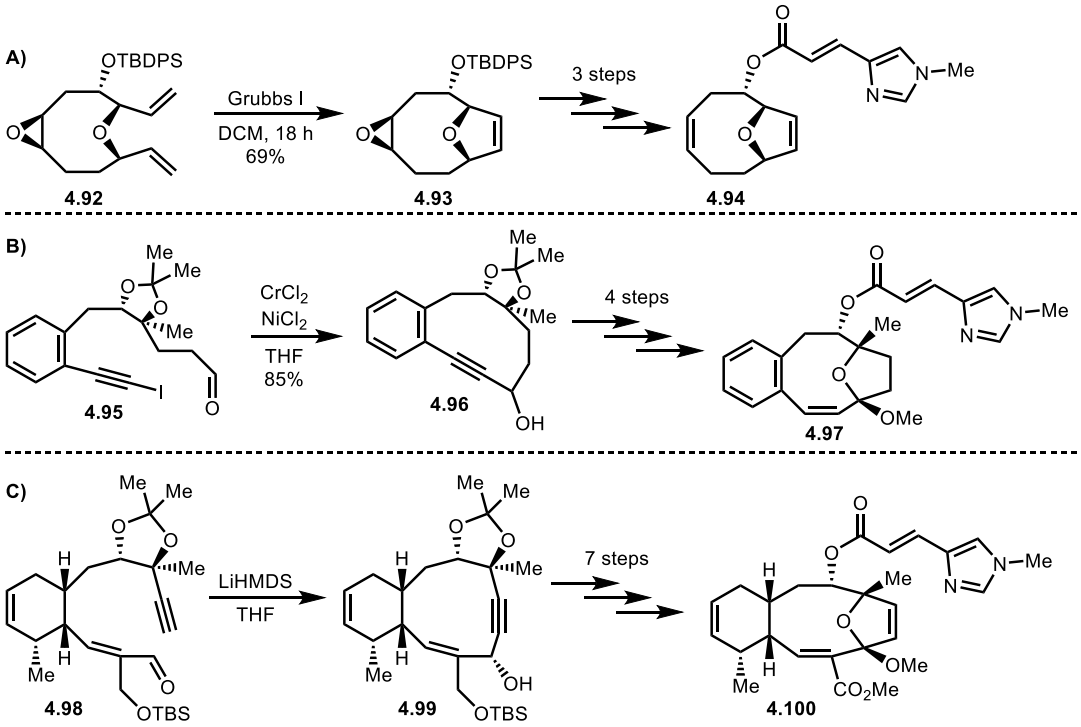


The construction of the synthetically-challenging 10-membered ring system of the sarcodictyins has been studied on simplified model systems (Scheme 4.19). The compound **4.94**, which contains the unsaturated furan functionality and the urcanoic ester group, was synthesized by the Holmes group in 2005 (Scheme 4.19.A).[37] The 10-membered ring is constructed by a ring-closing metathesis reaction to convert **4.92** into **4.93**. Another model structure (**4.97**), which contains a aryl group fused to the 10-membered ring, was synthesized by the Bermejo group in 2007 (Scheme 4.19.B).[38] The ring-closure step to form cyclized structure **4.96** is an intramolecular

[37] (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. *Tetrahedron: Asymmetry* **2009**, *20*, 921–944.
[38] Sandoval, C.; López-Pérez, J. L.; Bermejo, F. *Tetrahedron* **2007**, *63*, 11738–11747.

Nozaki–Kishi–Hiyama coupling between the alkynyl iodide and the aldehyde of **4.95**. A similar acetylide-aldehyde addition strategy was utilized by the Valeev group in the synthesis of an analog of sarcodictyin A (**4.100**), which contains a modified cyclohexenyl unit (Scheme 4.19.C).[39] This synthesis employs a similar strategy to that of the Nicolaou group for the synthesis of precursor **4.98** and the subsequent acetylide addition to form **4.99**.

Scheme 4.19. Synthesis of sarcodictyin analogs by various groups



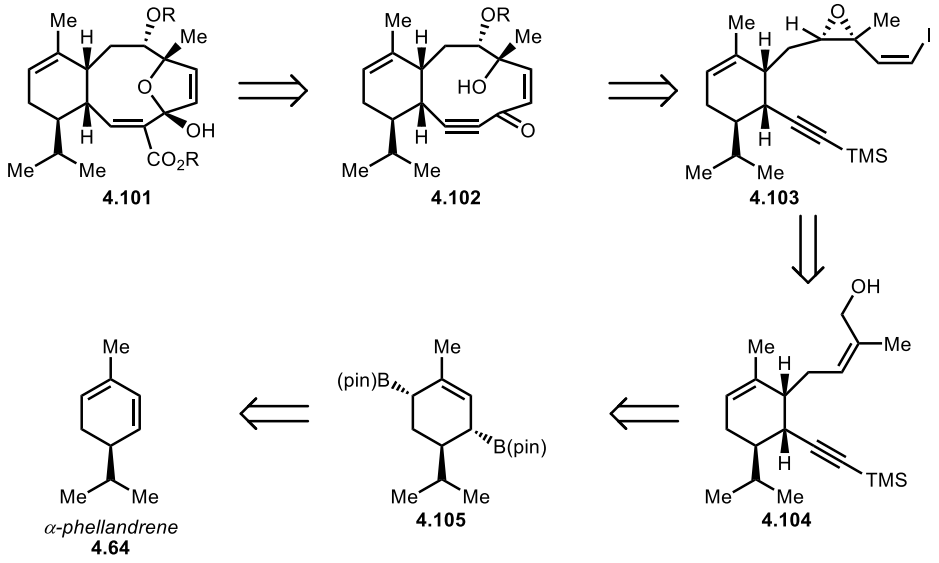
[39] (a) Sharipov, B. T.; Pershin, A. A.; Pilipenko, A. N.; Salikhov, Sh. M.; Valeev, F. A., *Russ. J. Org. Chem*. **2013**, *49*, 1437. (b) Sharipov, B. T.; Pershin, A. A.; Salikhov, Sh. M.; Valeev, F. A.; *Russ. J. Org. Chem*. **2014**, *50*, 1258. (c) Pershin, A. A.; Sharipov, B. T.; Salikhov, Sh. 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.

4.3. Progress toward the total synthesis of sarcodictyins A and B

4.3.1. Retrosynthetic analysis

The goal of this work is to provide a concise synthetic route (~10 steps) to members of the sarcodictyin class of natural products. The synthesis should also employ inexpensive and readily-available reagents to facilitate the large scale (>1g) execution of the synthetic route. In terms of the retrosynthesis, it is envisioned that the natural product core (**4.101**) can be synthesized from strained ynone **4.102** which contains the requisite carbon skeleton. The 10-membered ring can be closed by transformations of the alkynyl silane and alkenyl iodide of **4.103**, which comes from functional group manipulations of allylic alcohol **4.104**. The molecular complexity can be rapidly built up from diboryl intermediate **4.105**, which is derived from α-phellandrene (**4.64**).

Scheme 4.20. Retrosynthetic analysis of sarcodictyins A and B



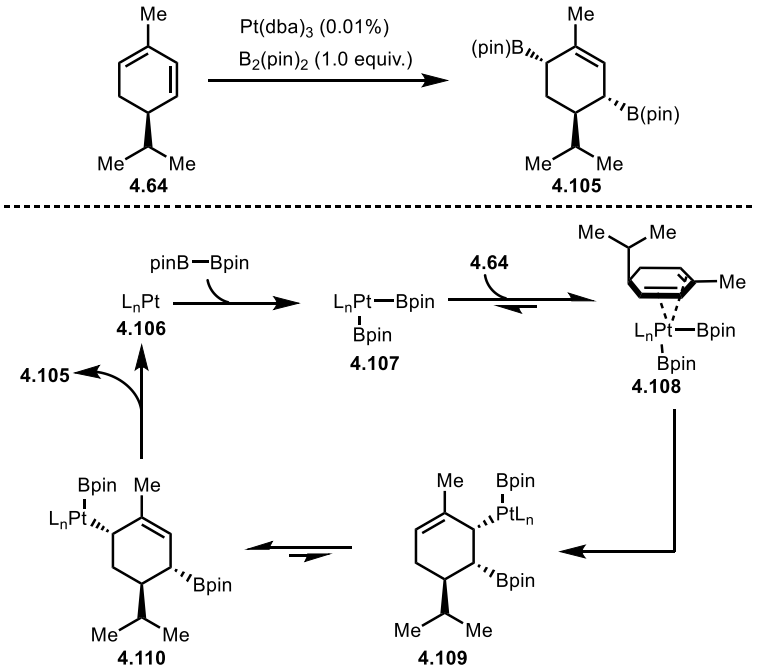
4.3.2. Forward synthesis

In a similar manner to the synthesis of eluetherobin by the Danishefsky group, the functionalized cyclohexenyl unit can be derived from α-phellandrene (**4.64**) which is commercially

available and inexpensive when purchased as an enantiomerically enriched mixture of regioisomers (~80% purity). This starting material is subjected to a Pt-catalyzed 1,4-diboration reaction, which occurs in a diastereoselective manner to furnish **4.105** (Scheme 4.21).[40] A proposed mechanism of the reaction involves oxidative addition of Pt^0 complex (**4.106**) to B_2pin_2 to yield (diboryl)Pt complex **4.107**, then coordination of the diene with the Pt^{II} intermediate (**4.108**). Next, β-migratory insertion generates an allylic Pt species (**4.109**), with a subsequent 1,3 sigmatropic rearrangement forming the less-hindered Pt–C bond (**4.110**) prior to reductive elimination. The facial selectivity of the reaction is controlled by the existing stereocenter in the molecule; the bulky isopropyl group blocks the top face of the cyclohexadiene ring, and the Pt^{II} complex prefers to bind the bottom face of the structure (**4.108**). The stereoselectivity of the reaction has previously been assigned by X-ray analysis of the corresponding diol after boron oxidation.[40]

[40] Poe, S. L.; Morken, J. P. *Angew. Chem. Int. Ed*. **2011**, *50*, 4189.

Scheme 4.21. Proposed mechanism of diboration

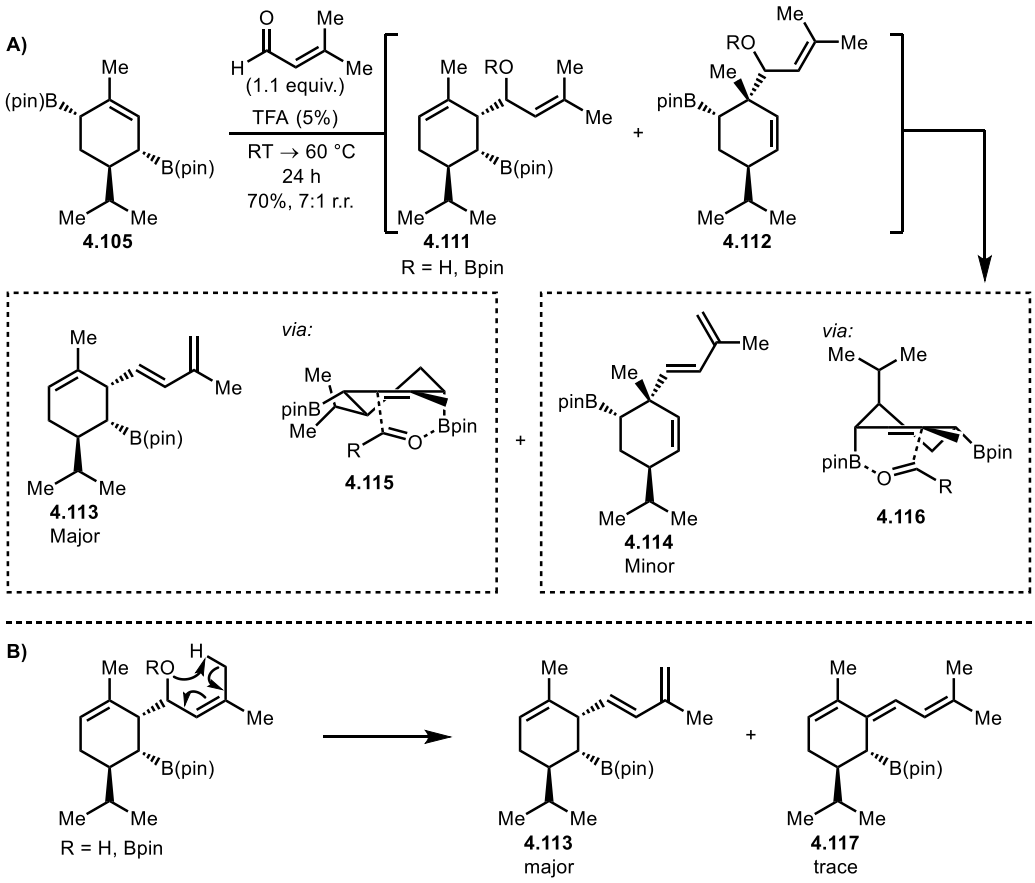


Regarding the diboration reaction conditions, the process is conducted at 60 °C and employs a slight excess of α-phellandrene relative to B_2pin_2. Additional solvent is not required for this reaction, but toluene can be added to improve the solubility of the B_2pin_2 if necessary. Although the reaction conditions have not been optimized, the neat reaction conditions enable an efficient reaction (<16 hours to completion) with a low catalyst loading of 0.01% and without an added ligand. The reaction is tolerant of air and moisture, and can be conveniently conducted in an open flask on ~30g scale. Lastly, the crude product of this reaction can be carried on directly for the following synthetic step in a single-flask operation.

The intermediate allylic boronate **4.105** is treated with 3-methyl-2-butenal and a catalytic amount of acid for a tandem carbonyl allylation and dehydration reaction sequence (Scheme 4.22.A). The allylation reaction is challenging, as there are two allylic boronates in the molecule, which can lead to regioisomeric intermediates **4.111** and **4.112** after the allylation reaction. These

intermediates undergo dehydration to form diene **4.113** as the major product, and the regioisomeric product **4.114** in a ~7:1 ratio. The origin of regioselectivity has not been investigated, but a possible explanation is that the C–C bond formation occurs at the less-hindered carbon. An alternative explanation is that allylation occurs from the chair conformation in which the reactive boronate is in the axial position to achieve the requisite orbital overlap between the alkene and the carbonyl group; the minor transition state **4.116** requires that the bulky isopropyl group be put into an axial position which introduces unfavorable 1,3-diaxial interactions compared to major transition state **4.115**. The dehydration step is also potentially challenging as regioisomeric alkenes can be formed, such as the conjugated triene **4.117** (Scheme 4.22.B). However, due to the preferential formation of **4.113** instead of the more-stable **4.117**, it is proposed that the dehydration occurs by a [3,3]-sigmatropic rearrangement mechanism rather than a stepwise reaction through a carbocation intermediate.

Scheme 4.22. Allylboration and dehydration reaction sequence



Experimentally, the reaction conditions for the allylation reaction employ an acid catalyst to enhance the electrophilicity of the boronate, and thereby promote the allylboration reaction.[41] Under these conditions, the allylation reaction is conducted at room temperature to achieve optimal regioselectivity, and the dehydration reaction requires elevated temperature (60 °C). The acid catalyst is also presumed to accelerate the dehydration, but the isolated dehydration reaction has not been studied due to the instability of the initial allylboration product. Notably, the crude reaction product contains trace amounts of other unidentified alkenyl products, but it was not determined whether these are formed during the reaction or by post-reaction isomerization. The purification of the product is facilitated by heating the crude reaction mixture in the presence of

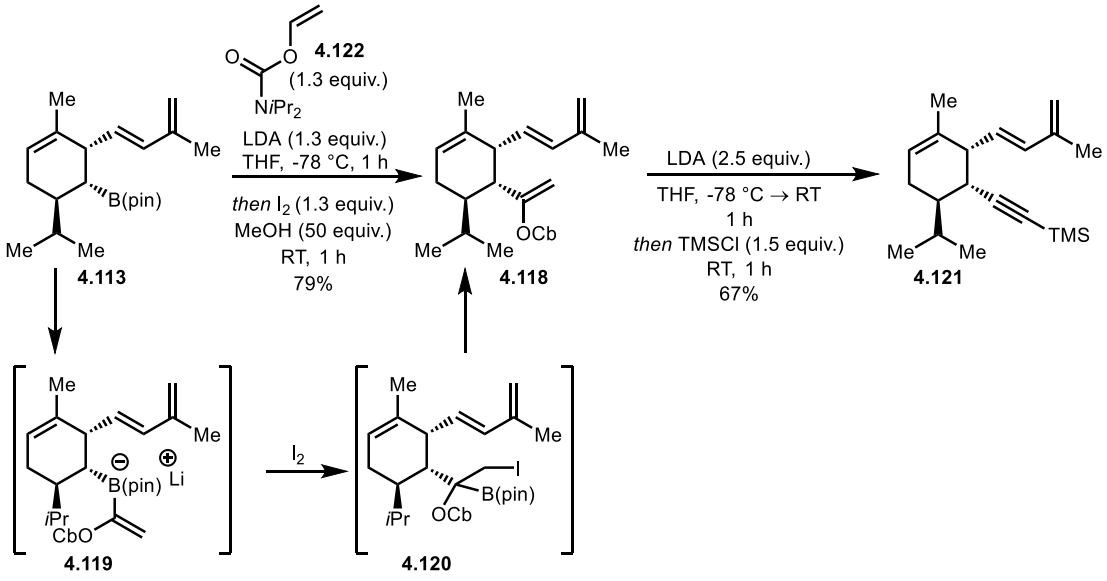
[41] Lachance, H.; Hall, D. G. In *Organic Reactions*, Denmark, S. E., Ed.; John Wiley & Sons, Inc. **2008**, *73*, 1–573.

$NiCl_2$•$6H_2O$ (see Experimental Section) to decompose the pinacol and/or inorganic boron byproducts. The yield for this reaction sequence is ~70%, and the reaction conditions have not been exhaustively optimized. Ideas for improving this reaction are discussed in Section 4.4.1. The regioisomeric products are inseparable by column chromatography and the mixture is carried several steps through the synthesis.

The next step is to transform the remaining boron atom into an alkynyl group by a modified Zweifel olefination reaction which has been developed by the Aggarwal group (Scheme 4.23).[42] In this procedure, *N,N*-diisopropyl vinyl carbamate (**4.122**) undergoes lithiation by LDA, and the resultant alkenyllithium reagent adds to the boron of **4.113** to form 'ate' complex **4.119**. The alkenyl group is activated by I_2 to induce a 1,2-metallate rearrangement, and finally the intermediate β-iodo boronate (**4.120**) undergoes deiodoboronation in the presence of methanol to yield the alkenyl carbamate product (**4.118**). This product can be isolated in 79% yield, or used without chromatographic purification by filtration through a plug of silica gel. The next step in the sequence is an elimination reaction in the presence of LDA, followed by quenching of the thus-formed acetylide with TMSCl to yield the alkynyl silane **4.121**. The purification of the alkynyl silane is facilitated by its non-polar nature; this product can be easily separated from the impurities by elution through a silica gel plug with hexane as the eluent, which facilitates the purification of large quantities of material. This results in 67% yield for the desired product on >10g scale, although higher yields have been achieved for the same reaction on smaller scale.

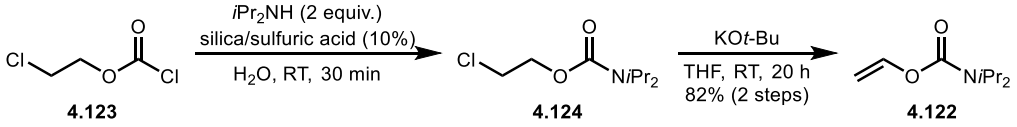
[42] Wang, Y.; Noble, A.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 4270–4274.

Scheme 4.23. Boron alkynylation reaction



This alkynylation procedure can be executed on large scale (>10g) due to the ready availability of **4.122**. It was found that this vinyl carbamate can be easily prepared on >20g scale by a two-step sequence employing commercially available starting materials (Scheme 4.24). The chloroformate **4.123** reacts with diisopropylamine under acidic conditions to yield carbamate **4.124**.[43] This reaction employs water as the solvent, and the crude product (**4.124**) can be extracted with organic solvent and directly subjected to the next step without further purification. The subsequent elimination reaction uses KO*t*Bu as a base to yield **4.122**, which is purified by short-path distillation.[44] The product is obtained in 82% yield over the two steps.

Scheme 4.24. Synthesis of vinyl carbamate

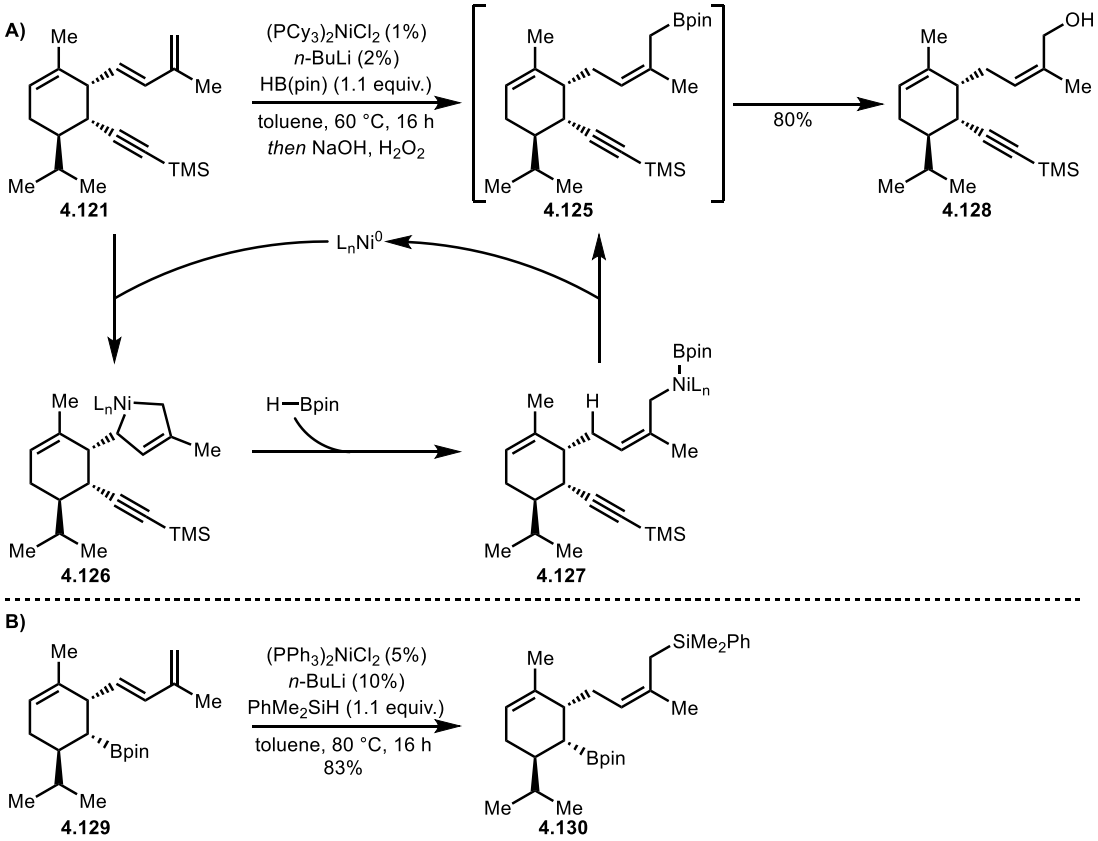


[43] Gawande, M. B.; Polshettiwar, V.; Varmab, R. S.; Jayaram, R. V. *Tetrahedron Lett.* **2007**, *48*, 8170–8173.
[44] Siemer, M.; Fröhlich, R.; Hoppe, D. *Synthesis* **2008**, *14*, 2264–2270.

After the alkynylation, the diene **4.121** is transformed by a 1,4-hydroboration reaction and boron oxidation sequence, which has been developed by our research group, to yield the allylic alcohol **4.128** (Scheme 4.25).[45] This reaction is both highly regioselective and stereoselective with respect to the alkene geometry (>20:1 Z:E). The proposed mechanism involves oxidative cyclization of Ni^0 with the diene to form the metallocyclopentane **4.126**. This intermediate undergoes σ-bond metathesis with HBpin to generate intermediate the Ni-boryl complex **4.127**. Reductive elimination from Ni^{II} regenerates the Ni^0 catalyst and forms the C–B bond of the allylboron product (**4.125**). Notably, the protection of the alkyne with a silyl group is necessary for the diene hydroboration reaction to occur, and the reaction does not work in the presence of a terminal alkyne.

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

Scheme 4.25. Ni-catalyzed 1,4-hydrometallation reactions

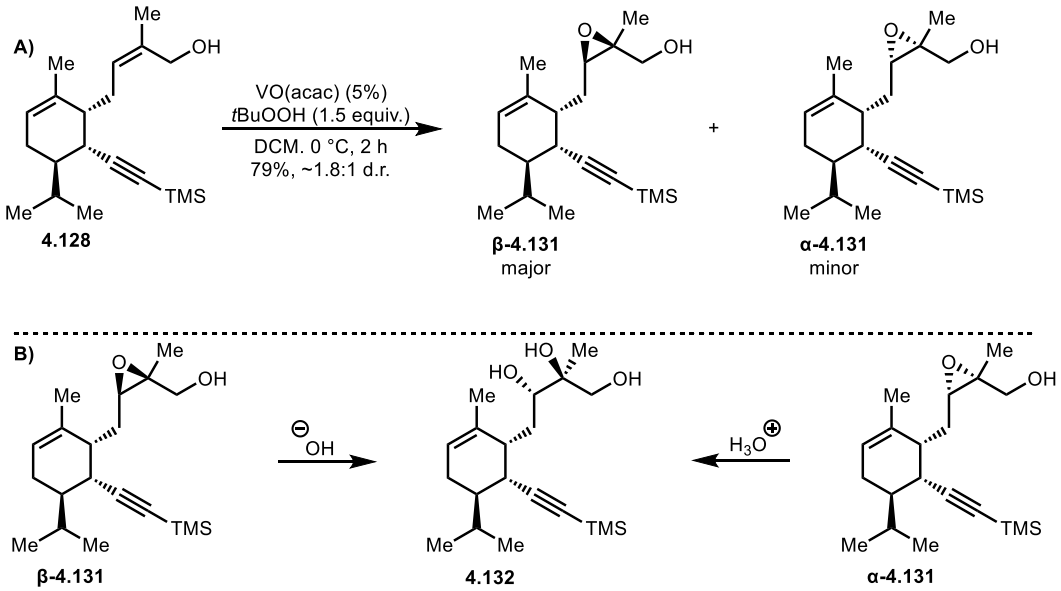


As for the reaction conditions, the 1,4-hydroboration reaction is catalyzed by a Ni complex with a PCy_3 ligand. It is convenient to use $(PCy_3)_2NiCl_2$, rather than $Ni(cod)_2$, as the Ni source due to its stability to air and moisture. The active Ni^0 catalytic species is obtained by *in situ* reduction with *n*BuLi. The reaction occurs at 60 °C and reaches full conversion within 16 hours. The crude allylic boronate product (**4.125**) is subjected to standard boron oxidation conditions with basic aqueous hydrogen peroxide to yield the allylic alcohol (**4.128**) in 80% yield. Notably, an analogous 1,4-hydrosilylation reaction of **4.129** can be achieved with a $PhMe_2SiH$ reagent and a PPh_3-ligated Ni catalyst to yield **4.130** (Scheme 4.25.B). Such a hydrosilation reaction might have useful synthetic applications, but in this case the hydroboration reaction is preferred due to the facile boron oxidation reaction.

After hydroboration and oxidation, the allylic alcohol **4.128** is subjected to a V-catalyzed epoxidation reaction to yield a mixture of **β-4.131** and **α-4.131** (Scheme 4.26.A). The epoxidation occurs in a chemoselective manner at the alkene proximal to the hydroxyl group, although without significant levels of stereocontrol (~1.8:1 d.r.). The major diastereomer (**β-4.131**) is tentatively assigned by comparison of the ^{1}H NMR chemical shifts with those of related structures of known configuration.[32b] Regarding the desired epoxide configuration with respect to the sarcodictyins, it is possible that either diastereomer can lead to the correct stereoisomer of the natural product depending on the regioselectivity of the epoxide hydrolysis (Scheme 4.26.B). Specifically, basic hydrolysis of **β-4.131** at the less-substituted carbon, and acidic hydrolysis of **α-4.131** at the more-substituted carbon lead to the same stereoisomer of **4.132**, which contains the proper alcohol configurations for the natural product. Of note, a similar stereoconvergent epoxide hydrolysis strategy was employed by our research group in the total synthesis of sclerophytin, a structurally similar diterpene natural product.[46] Therefore, the mixture of diastereomers is ideal to carry forward in the synthesis, as the optimal conditions for the later-stage epoxide hydrolysis are yet to be determined.

[46] Wang, B.; Ramirez, A. P.; Slade, J. J.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 16380–16382.

Scheme 4.26. Allylic alcohol epoxidation reaction



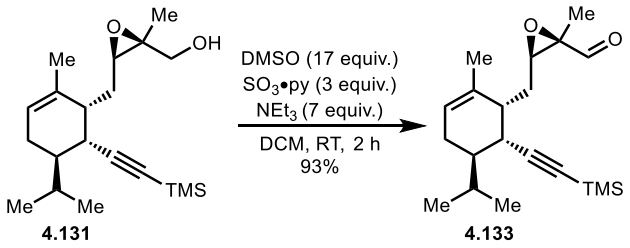
The epoxidation reaction employs $VO(acac)_2$ (5%) as the catalyst and a slight excess of *t*BuOOH as the oxidant. The reaction reaches full conversion within 2 hours at 0 °C, and optimal results are obtained when the reaction is quenched with dimethyl sulfide at that temperature (see Experimental Section).[47] Presumably, when the reaction is not quenched at low temperature, the presence of unreacted peroxide might lead to undesired epoxide-opening reactions upon warming to room temperature. Of note, the diastereomeric products **β-4.131** and **α-4.131** are difficult to separate by silica gel column chromatography and the mixture is carried forward.

After epoxidation, the alcohols **β-4.131** and **α-4.131** are subjected to Parikh-Doering oxidation conditions to yield aldehyde **4.133** (Scheme 4.27). This reaction uses sulfur trioxide-pyridine complex as an activator for DMSO and triethylamine as a base. The oxidation is complete within 2 hours at room tempature, and proceeds with minimal formation of byproducts. Notably, it is necessary to pre-mix the DMSO and sulfur trioxide-pyridine complex in order to avoid

[47] Marshall, J. A.; Van Devender, E. A. *J. Org. Chem*. **2001**, *66*, 8037–8041.

undesired sulfate formation with the alcohol.[48] The aldehyde **4.133** can be isolated in 93% yield by column chromatography or used directly in the next step after simple filtration through a silica gel plug.

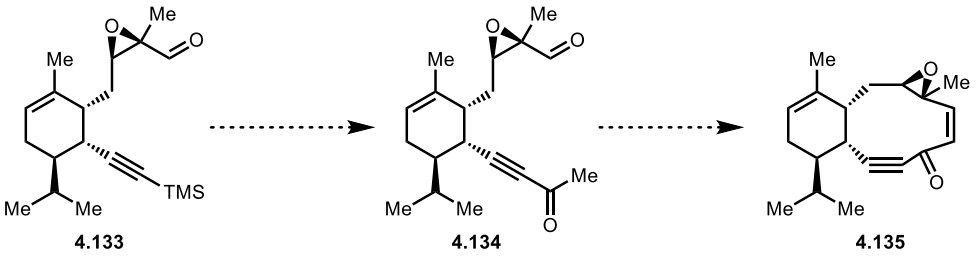
Scheme 4.27. Parikh-Doering oxidation reaction



The construction of the 10-membered ring was envisioned to be accomplished by an intramolecular aldol condensation reaction (Scheme 4.28). Therefore, efforts to convert the alkynyl silane (**4.133**) into an ynone (**4.134**) were carried out. However, the synthesis of intermediate **4.134** was unsuccessful under a variety of reaction conditions. Starting from either aldehyde **4.133** or alcohol **4.131**, attempts to add the TMS-alkyne to acetaldehyde or acetyl chloride were unsuccessful in the presence of either fluoride or alkoxide bases. Additionally, transition-metal catalyzed cross-coupling reactions between **4.133** and acetyl chloride were unsuccessful, possibly due to the β-hydrogen atoms of the oxidative addition adduct. Lastly, Lewis-acid promoted Friedel-Crafts-type substitution reactions with acetyl chloride led to starting material decomposition. Therefore, the aldol condensation reaction could not be attempted, and alternative methods for the synthesis of **4.135** were investigated.

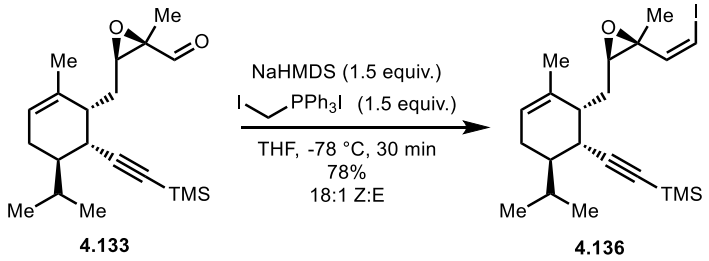
[48] Tojo, G.; Fernández, M. Oxidation of Alcohols to Aldehydes and Ketones. In *Basic Reactions in Organic Synthesis*, Tojo, G., Ed.; Springer Science+Business Media: New York, **2006**, 120–126.

Scheme 4.28. Attempted ring closure by aldol condensation



As an alternative to the aldol reaction, it was anticipated that the 10-membered ring could be closed by an intramolecular cross-coupling reaction. Therefore, the aldehyde **4.133** was converted into Z-alkenyl iodide **4.136** by the Stork-Wittig olefination reaction with (iodomethyl)triphenylphosphonium iodide (Scheme 4.29).[49] The reaction is highly stereoselective (~18:1 Z:E), and is complete within 30 minutes at -78 °C. The reaction mixture contains an unidentified byproduct which cannot be separated from the desired product by chromatography, but the formation of this byproduct is partially suppressed by shortening the reaction time and quenching the reaction at low temperature. Overall, the desired product (**4.136**) is obtained in 78% yield and the inseparable byproducts can be carried on to subsequent reactions.

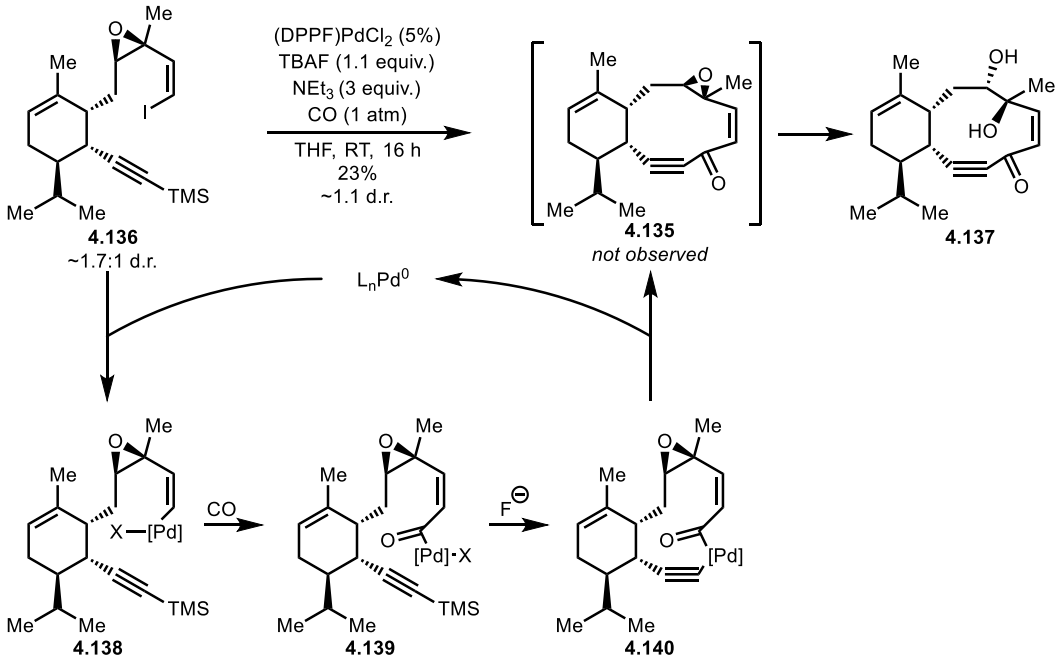
Scheme 4.29. Synthesis of Z-alkenyl iodide by the Stork-Wittig reaction



[49] Stork, G.; Zhao, K. Tetrahedron Lett. **1989**, *30*, 2173–2174.

The formation of the 10-membered ring by a carbonylative cross-coupling reaction between the alkenyl iodide and the alkynyl silane of **4.136** was carried out successfully (Scheme 4.30). Using a Pd-based catalytic system, the diol **4.137** is obtained, such that the expected reaction product, epoxide **4.135**, undergoes hydrolysis. A related Pd-catalyzed carbonylative cross-coupling reaction between an aryl iodide and an alkynyl silane has been reported, but an intramolecular reaction is expected to be challenging due the ring strain imparted by the alkyne.[50] Mechanistically, the reaction involves oxidative addition into the alkenyl iodide to form adduct **4.138**, followed by insertion into CO to generate an acyl-palladium complex (**4.139**). Subsequent fluoride-induced intramolecular transmetallation of the alkynyl silane generates the Pd^{II} complex **4.140**, then reductive elimination delivers the ynone **4.135,** or **4.137** after hydrolysis.

Scheme 4.30. Ring-closure by intramolecular carbonylative cross-coupling

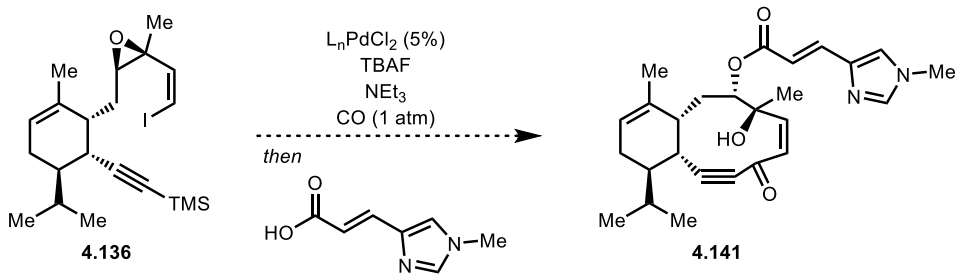


[50] Arcadi, A.; Cacchi, S.; Marinelli, F.; Pace, P.; Sanzi, G. *Synlett* **1995**, *1995*, 823–824.

The carbonylative cross-coupling reaction is effectively catalyzed by a palladium complex with a Xantphos or DPPF ligand. The reaction proceeds to full conversion within 16 h at room temperature under an atmospheric pressure of CO. The reaction requires TBAF in order to activate the silyl group for transmetallation, and trimethylamine is added as a base. The yield of the desired product **4.137** is relatively low (23%), and the remaining mass balance of this reaction has not yet been determined. Attempts to conduct this reaction on scales of >0.1 mmol have led to non-reproducible results, and an improved knowledge of the reaction conditions is necessary for further optimization. Notably, the diastereomeric ratio with respect to the epoxide of the starting material (~1.7:1) is eroded such that the product is obtained in ~1:1 d.r., and the cause of this is yet to be determined.

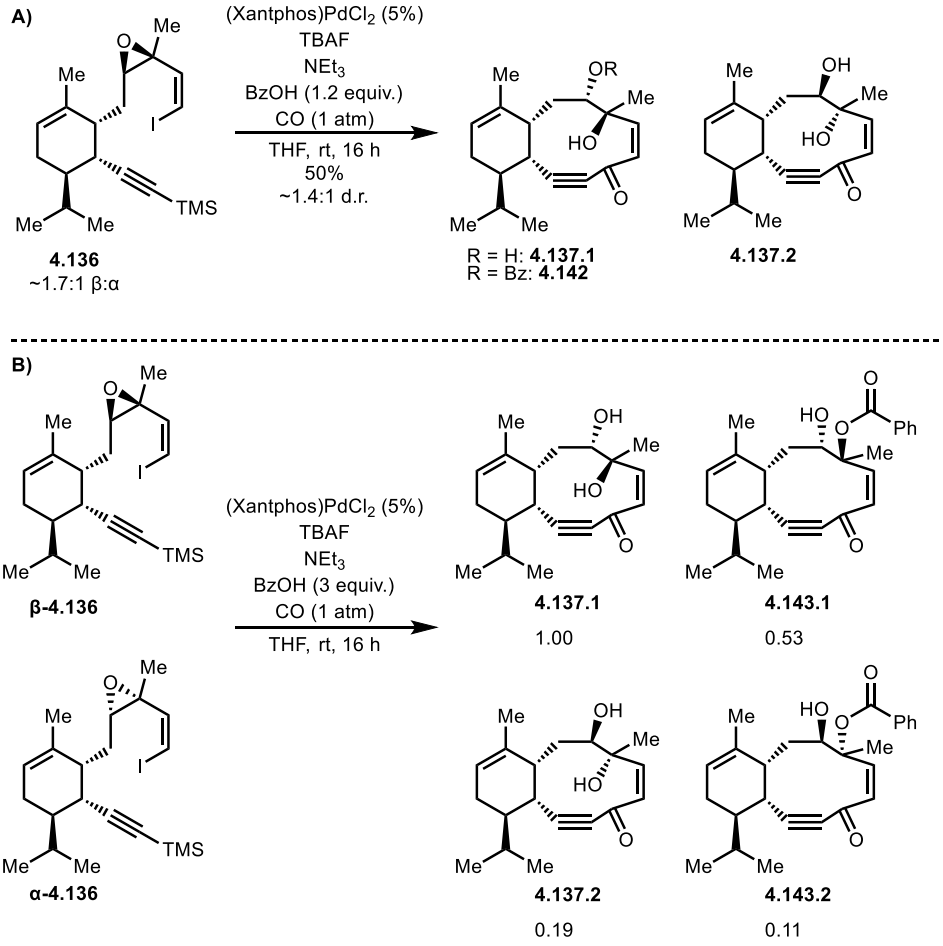
A better understanding of the epoxide hydrolysis step is also necessary for improving the synthetic route. The intermediate epoxide (**4.135**) might be unstable due to the relief of ring string in the 10-membered upon rehybridization of the carbon atoms, resulting in facile hydrolysis. It is suspected that the epoxide hydrolysis does not occur over the course of the reaction due to the anhydrous reaction conditions, but rather during the reaction work-up (i.e. filtration through a plug of silica gel or celite). Additionally, the regiochemistry of the epoxide opening is not known, but is suspected to occur at the less-substituted carbon. Therefore, we tested whether a benzoate nucleophile could open the epoxide (instead of hydroxide) by conducting the reaction in the presence of benzoic acid. If successful, this strategy could shorten the synthetic route by introducing the urcanoic ester in the same step as the ring-closure to synthesize **4.141** directly from **4.136** (Scheme 4.31).

Scheme 4.31. Proposed strategy for epoxide opening



When benzoic acid (1 equivalent) was added to the carbonylative cross-coupling reaction, the benzoate product **4.142** was not obtained in significant quantity, but a serendipitous increase in yield to 50%, and a higher degree of stereospecificity (~1.4:1 d.r. of **4.137**), are observed (Scheme 4.32.A). Upon increasing the amount of benzoic acid (3 equivalents), the products **4.143.1** and **4.143.2**, in which the benzoate opens the epoxide at the tertiary carbon, are obtained along with the hydrolysis products **4.137.1** and **4.137.2** (Scheme 4.32.B). Notably, both sets of products are diastereomerically enriched; the starting material exhibits ~1.7:1 d.r., but both products exhibit ~5:1 d.r. The majority of epoxide **α-4.135** opens by the benzoate under acidic conditions at the more-substituted carbon leading to **4.143.1**, whereas epoxide **β-4.135** preferentially undergoes hydrolytic opening at the less-substituted carbon to yield **4.137.1**. As this relates to the total synthesis of the Sarcodictyins, the benzoate nucleophile does not lead to a desirable intermediate, and a hydroxide nucleophile should be used for this step instead. The optimization of the stereoconvergent epoxide opening strategy has not yet been explored beyond this preliminary result. Additionally, the application of intermediate **4.137** to the completion of the total synthesis has not yet been attempted due to the limited supply of material, but possible transformations are discussed in Section 4.4.2.

Scheme 4.32. Carbonylative cross-coupling in the presence of benzoic acid



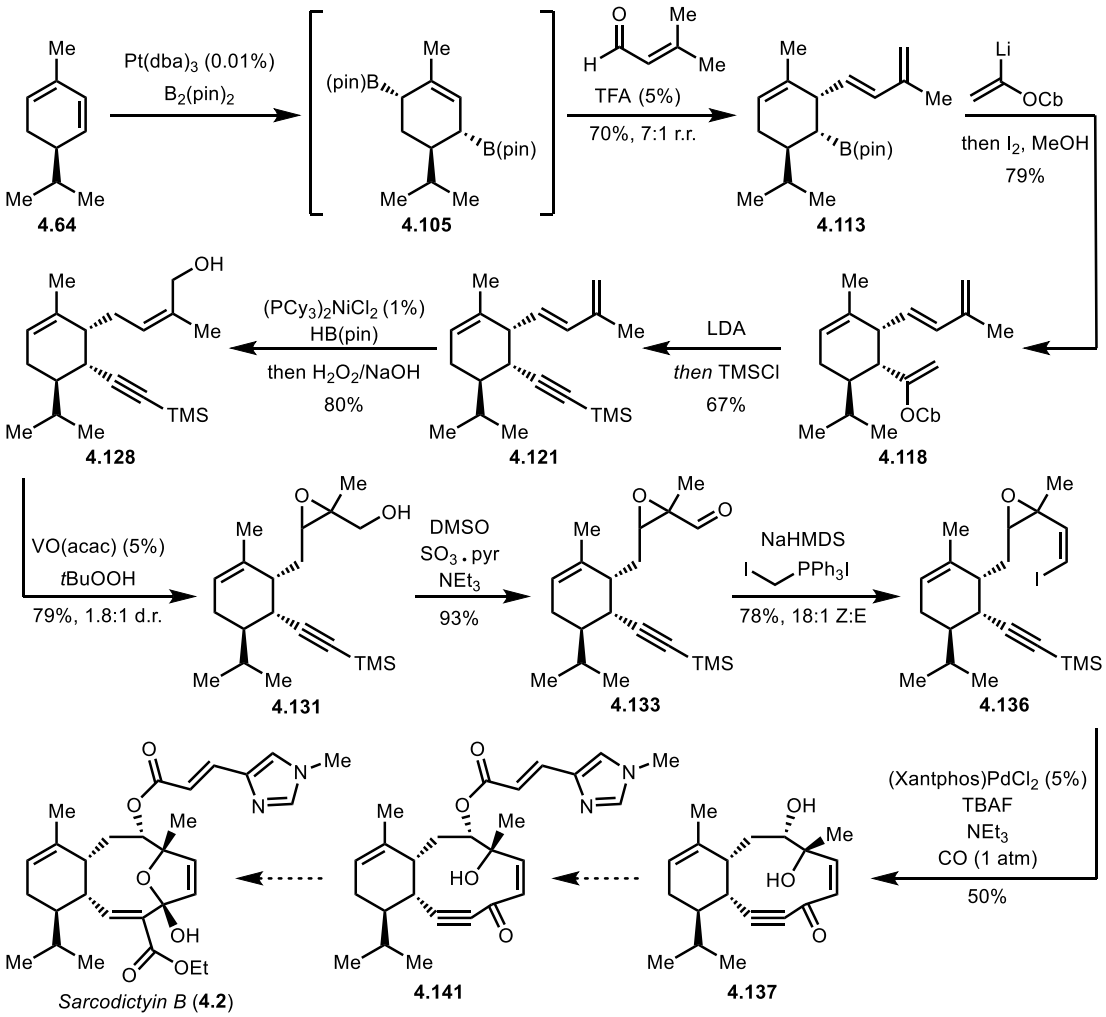
4.4. Future directions

4.4.1. Reaction optimization

In order to achieve a reliable large-scale (>1g) synthesis of the sarcodictyin natural products, further reaction optimization should be completed for each step. The focus of the optimization studies should be on improving the yield of each step, and using smaller amounts of reagents and catalysts. Additionally, the throughput of the material can be improved by shortening reaction times and modifying the post-reaction purification steps. Ideally, column chromatography should be avoided, either by using alternative methods of purification or by eliminating the

formation of byproducts such that purification is not necessary. The current reaction conditions for each step and suggestions for future optimization are described below (Scheme 4.33 and accompanying text).

Scheme 4.33. Summary of the progress towards sarcodictyins A and B



The Pt-catalyzed diboration step is already quite effective, as it employs very low catalyst loading (0.01% Pt) and the intermediate diboron (**4.105**) can be carried forward without further purification. Attempts to further decrease the catalyst loading and shorten the reaction time should be explored. The ensuing allylation reaction can be optimized with respect to the regioselectivity;

this can potentially be achieved by modifying the reaction temperature, amount of catalyst, and reaction concentration. The use of TFA seems to be uniquely effective in catalyzing the allylation-dehydration reaction sequence. Additionally, the possibility of purifying **4.113** by distillation can be investigated.

Next, the alkenylation reaction is complicated by the presence of unreacted vinylcarbamate, which is inseparable from the reaction product (**4.118**). The leftover vinylcarbamate necessitates that additional LDA be added in the subsequent reaction, which may lead to the byproduct formation. Therefore, the possibility of using 1.0 equivalent of vinylcarbamate rather than 1.3 equivalents should be studied. The synthetic route may be optimized by modifying the silyl group on the alkyne of **4.121**; this group can be strategically chosen to impart crystallinity in the molecule to facilitate the purification of the synthetic intermediates.

The Ni-catalyzed hydroboration reaction can benefit from decreasing the catalyst loading and/or the reaction time. The use of alternative solvents to toluene can also be explored, as the high-boiling solvent is difficult to remove after the reaction. A different reaction solvent might also enable a more efficient boron oxidation reaction which can be conducted by a single-flask operation. The subsequent V-catalyzed epoxidation reaction has not been optimized with respect to the catalyst loading. If necessary, the diastereoselectivity of this reaction might be improved by modifying the ligand on vanadium, or using a Ti-based catalytic system.

The Parikh-Doering oxidation reaction does not require extensive optimization, as the cost of reagents and reaction time are already satisfactory. Additionally, the crude product of the reaction is relatively free of byproducts and can be purified by a simple filtration through silica gel. The Stork-Wittig reaction is relatively efficient, but could benefit from decreasing the reaction

time or temperature to suppress the formation of byproducts. The carbonylative cross-coupling reaction may require significant optimization to improve the yield and scalability. In this regard, the use of alternative CO sources, such as *N*-formylsaccharin and $Mo(CO)_6$, has been tested, but the desired reaction product was not detected under these conditions. Preliminary results suggest that benzoic acid as an additive improves the yield of the reaction, but other acids have not yet been investigated. Lastly, the stereoconvergent epoxide opening step seems feasible based on preliminary results, but will likely require carefully chosen reaction conditions. A strategy of epoxide hydrolysis under acidic conditions followed by basic conditions seems promising, but may prove experimentally challenging.

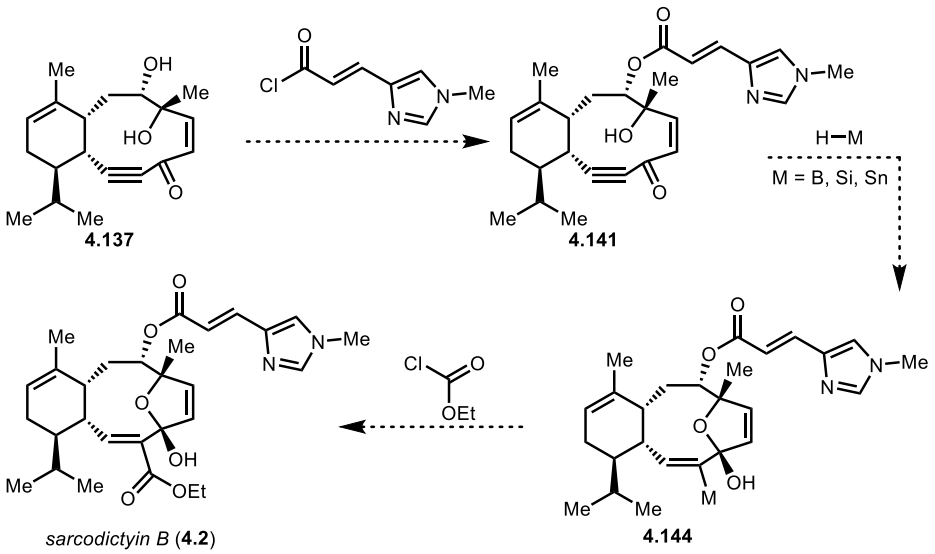
4.4.2. Completion of the synthesis

With a reliable route to diol **4.137**, it is envisioned that the total synthesis can be completed as shown in Scheme 4.34. The secondary alcohol can be acylated in preference to the tertiary alcohol to deliver intermediate **4.141**, as has been demonstrated using benzoic anhydride as a model substrate. Lastly, the hydrometallation of ynone **4.141** to **4.144** and treatment of the alkenyl nucleophile with a chloroformate electrophile would yield **4.2**. The conditions for this hydrometallation reaction will need to be determined experimentally, but examples of ynone hydroboration,[51] hydrosilation,[52] and hydrostannylation[53] have been demonstrated. Additionally,

[51] (a) Kabalka, G. W.; Yu, S.; Li, N.-S.; Lipprandt, U. *Tetrahedron Lett.* **1999**, *40*, 37–40. (b) Yu, S.; Li, N.-S.; Kabalka, G. W. *J. Org. Chem.* **1999,** *64,* 5822–5825. (c) Zi, Y.; Schömberg, F.; Seifert, F.; Görls, H.; Vilotijevic, I. *Org. Biomol. Chem*. **2018**, *16*, 6341–6349.
[52] (a) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11926–11928. (b) Rooke, D. A.; Ferreira, E. M. *Angew. Chem. Int. Ed*. **2012**, *51*, 3225–3230. (c) Rooke, D. A.; Menard, Z. A.; Ferreira, E. M. *Tetrahedron* **2014**, *70*, 4232–4244. (d) Sumida, Y.; Kato, T.; Yoshida, S.; Hosoya, T. *Org. Lett*. **2012**, *14*, 1552–1555.
[53] (a) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem*. **1990**, *55*, 1857–1867. (b) Bellina, F. Carpita, A.; Ciucci, D.; De Santis, M.; Rossi, R. *Tetrahedron* **1993**, *49*, 4677–4698. (b) Leung, L. T.; Leung, S. K.; Chiu, P. *Org. Lett.* **2005**, *7*, 5249–5252. (c) Miao, R.; Li, S.; Chiu, P. *Tetrahedron* **2007**, *63*, 6737–6740.

cross-coupling reactions with chloroformate electrophiles have been reported,[54] and carried out within our group (unpublished results).

Scheme 4.34. Proposed completion of the total synthesis of sarcodictyin B



4.4.3. Conclusion

In summary, the carbon skeleton of the sarcodictyin family of natural products has been synthesized in 8 steps from α-phellandrene. The key steps include 1) a 1,4-diboration and allylation reaction sequence; 2) a Ni-catalyzed 1,4-hydroboration reaction; and 3) an intramolecular carbonylative cross-coupling reaction to establish a strained 10-membered ring. The synthetic route has been executed on multigram scale, with the pre-cyclization alkenyl iodide being obtained in ~5g quantities in a single batch. The reagents and catalysts used for the synthesis are all commercially available or readily prepared from inexpensive materials. The completion of the synthesis of sarcodictyins A and B can ideally be achieved in 2-3 additional steps from the cyclized intermediate. In addition to completing the total synthesis, future efforts should be made

[54] Duan, Y.-Z.; Deng, M.Z. *Synlett* **2005**, *2*, 355–357.

towards optimizing each step and modifying the synthetic route to increase the throughput of material.

4.5. Experimental section

4.5.1. General information

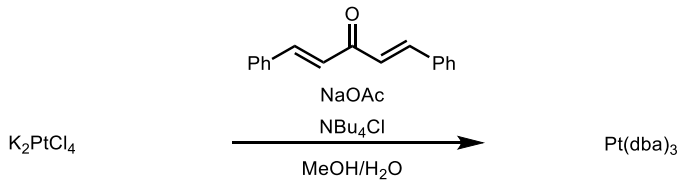
^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), Varian Gemini-600 (600 MHz), or Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, 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 Gemini-500 (126 MHz), Varian Gemini-600 (151 MHz) or a Varian Inova-500 (126 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 Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer. 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. 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, and cerium(IV) sulfate in ethanol with sulfuric acid (magic stain).

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

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. 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 argon. α -phellandrene (≥75%, stabilized) was purchased from Aldrich and used as received. B_2pin_2 was purchased from Oakwood Chemicals or Combi Blocks and used as received (recrystallization from hexane results in improved solubility but does not affect the reaction outcome). 3-Methyl-2-butenal was purchased from Aldrich and used as received. 2-chloroethyl carbonochloridate was purchased from TCI and used as received. Potassium *tert*-butoxide was purchased from Oakwood Chemicals and used as received. *n*-Butyllithium was purchased from Aldrich and used as received. Iodine was purchased from TCI and used as received. Tricyclohexyl phosphine was purchased from Strem Chemicals and used as received. Pinacolborane (containing 0.06% dimethyl sulfide) was purchased from BASF and used as received. Sodium bis(trimethylsilyl)amide (2M in THF) was purchased from Oakwood Chemicals and used as receieved. Triethylamine was distilled over CaH_2 prior to use. All other reagents were purchased from Aldrich, Alfa Aesar, Acros, Combi Blocks, or Oakwood Chemicals and used without further purification.

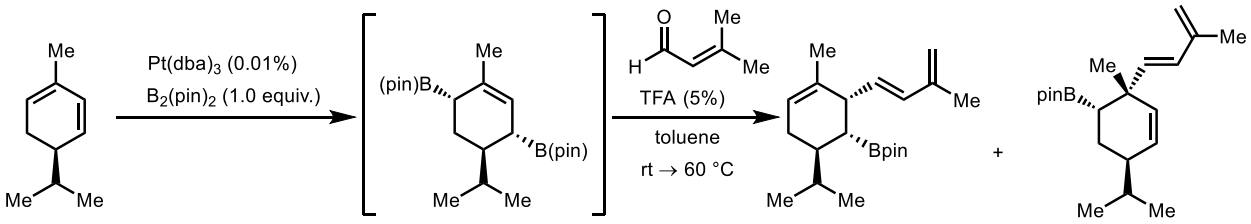
4.5.2. Experimental procedures



Note: reaction is conducted open to air.

$Pt(dba)_3$ (tris-(dibenzylideneacetone)platinum) was prepared according a literature procedure with slight modification.[55] Sodium acetate (2.11 g, 25.72 mmol, 18 equiv.), tetrabutylammoniumchloride (1.19 g, 4.29 mmol, 3 equiv.) and trans, trans-dibenzylideneacetone (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 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 Et2O (1x25 mL). The solid is dried under vacuum to yield $Pt(dba)_3$ as a brown solid (552 mg, 0.61 mmol, 43%). Spectral data are in accordance with the literature.[56]

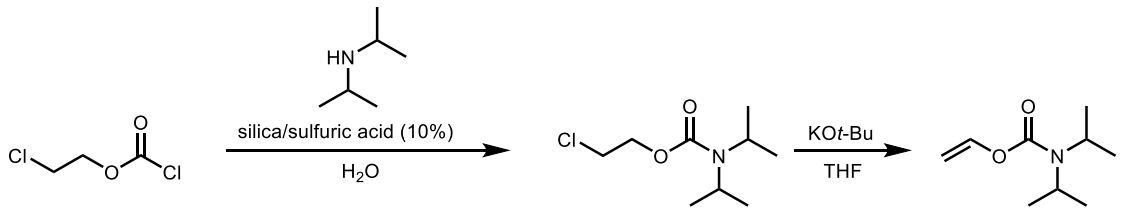
[55] Szymaniak, A. A.; Zhang, C.; Coombs, J. R.; Morken, J. P. *ACS Catal*. **2018**, *8*, 2897.
[56] Lewis, L. N.; Krafft, T. A.; Huffman, J. C. *Inorg. Chem.* **1992**, *31*, 3555–3557.



Note: the reaction is conducted open to air. α-Phellandrene was determined to be ~84% by mass (^{1}H 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 (4.113). The title compound was prepared according to a modified literature procedure.[40] Bis(pinacolato)diboron (15.24 g, 60 mmol, 1 equiv.) was added to round bottom flask with a magnetic stir bar, followed by 5-isopropyl-2-methyl-cyclohexa-1,3-diene (12.26 g, 72.00 mmol, 1.2 equiv.) and tris-(dibenzylideneacetone)platinum (5.4 mg, 0.006 mmol, 0.0001 equiv.). The reaction was heated to 60 °C for 15 hours. The reaction mixture was diluted with toluene (40 mL), then 3-methylbut-2-enal (6.37 mL, 66.00 mmol, 1.1 equiv.) was added. The reaction was cooled to 0 °C and trifluoroacetic acid (0.23 mL, 3.00 mmol, 0.05 equiv.) was added. The reaction was allowed to slowly warm to room temperature over 8 hours, then stirred at 60 °C for 15 hours. Nickel(II) chloride hexahydrate, (1.7 g, 6.0 mmol, 0.1 equiv.) was added to the crude mixture and it was stirred at 80 °C for 1 hour then transferred to a separatory funnel (rinse with hexane). The organic layer was washed with H_2O (50 mL) then brine (50 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated (azeotrope with EtOAc then hexane to remove the residual toluene). The crude product was purified by silica gel column chromatography with 0-5% EtOAc/hexane eluent to yield the title compound (13.9 g, 42.1 mmol, 70% yield) as a colorless oil (~7:1 r.r.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.08 (d, J = 15.5 Hz, 1H), 5.62 (dd, J = 15.4, 9.4 Hz, 1H), 5.49 – 5.44 (br, 1H), 4.88 – 4.82 (m,

2H), 2.72 (dd, J = 9.7, 4.9 Hz, 1H), 2.16 – 2.07 (m, 1H), 1.94 – 1.78 (m, 5H), 1.76 – 1.61 (m, 1H), 1.58 (s, 3H), 1.33 (dd, J = 12.1, 4.9 Hz, 1H), 1.19 (s, 6H), 1.18 (s, 6H), 0.97 – 0.82 (m, 4H), 0.71 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.4, 135.2, 133.6, 132.4, 122.5, 114.6, 83.0, 45.8, 34.3, 29.3, 25.2, 24.9, 24.5, 22.2, 21.6, 19.0, 15.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.4,; IR (neat) ν_{max} 2955 (m), 2927 (m), 1604 (w), 1463 (w), 1399 (s), 1323 (s), 1109 (s), 963 (m), 876 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{36}BO_2$ $[M+H]^+$ calculated: 331.280, found: 331.281. $[\alpha]^{20}_D$: +173.59 (c = 1.10, $CHCl_3$, l = 50 mm).



Silica/sulfuric acid was prepared according to a literature procedure.[57] Silica gel (30g) was added to a 2-neck 250-mL round bottom flask. One neck was fitted with a septum and N_2 inlet, the other neck was fitted with an outlet tube, which was bubbled through H_2O. The reaction flask was cooled to 0 °C, and chlorosulfonic acid (6.7 mL) was added via syringe. The mixture was stirred at RT for 30 minutes, using a spatula to break up chunks of solid, and the resulting powder was used without further purification.

Note: the reaction was conducted open to air.

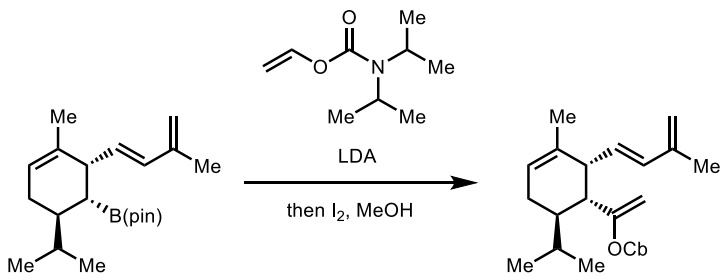
2-chloroethyl diisopropylcarbamate was prepared according to a modified literature procedure.[58] Silica-sulfuric acid (1.5 g) was added to a 250 mL round bottom flask, and suspended in H_2O (75 mL). The reaction mixture was cooled to 0 °C, then diisopropylamine (46.3 mL, 330

[57] Zolfigol, M. A.; Bamoniri, A. *Synlett* **2002**, *10*, 1621–1624.
[58] Gawande, M. B.; Polshettiwar, V.; Varmab, R. S.; Jayaram, R. V. *Tetrahedron Lett*. **2007**, *48*, 8170–8173.

mmol, 2.2 equiv.) was added, followed by 2-chloroethyl carbonochloridate (15.4 mL, 150 mmol, 1 equiv.) (caution: exothermic, gas evolution). The reaction was stirred at RT for 30 minutes then diluted with Et_2O (100 mL) and transferred to a separatory funnel. The organic layer was washed with saturated aqueous $NaHCO_3$ (2x50 mL) then brine (1x50 mL), then dried over sodium sulfate, filtered, and concentrated to yield 2-chloroethyl diisopropylcarbamate as a colorless oil. The crude product was used without further purification.

Vinyl diisopropylcarbamate was prepared according to a modified literature procedure.[59] Potassium *tert*-butoxide (33.7 g, 300 mmol, 2 equiv.) was added to a 1L round bottom flask and dissolved in THF (300 mL). At 0 °C, 2-chloroethyl diisopropylcarbamate (31.2 g, 150 mmol, 1 equiv.) was added, and the reaction was allowed to stir at RT for 24 hours. The reaction was diluted with Et_2O (150 mL) and quenched with H_2O (300 mL) then transferred to a separatory funnel. The aqueous layer was removed, and the organic layer was washed with H_2O (1x300 mL) then brine (1x300 mL). The organic layer was dried over sodium sulfate, then filtered and concentrated. The crude product was purified by a short-path distillation over calcium hydride (house vacuum at 140 °C), to yield vinyl-diisopropylcarbamate (21g, 122.6 mmol, 82%) as a colorless oil. The spectral data are in accordance with the literature.[60]

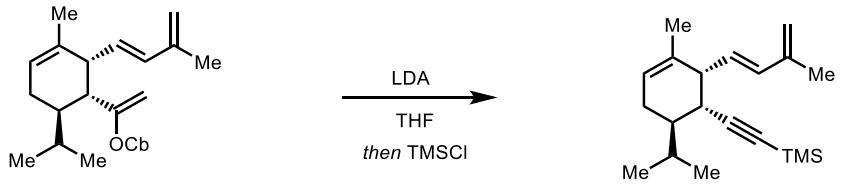
[59] Siemer, M.; Fröhlich, R.; Hoppe, D. *Synthesis* **2008**, *14*, 2264–2270.
[60] Webb, N. J.; Marsden, S. P.; Raw, S. A. *Org. Lett.* **2014**, *16*, 4718–4721.



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 stirred at 0 °C for 30 minutes, then used directly (~0.86 M).

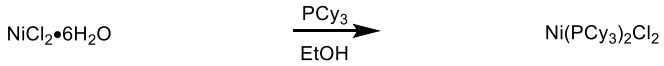
1-((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)vinyl diisopropylcarbamate (4.118). The title compound was prepared according to a modified literature procedure.[42] 2-((1R,2S,6S)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.1 g, 45.7 mmol, 1.0 equiv.) was added to a 500 mL round bottom flask, followed by vinyl-diisopropylcarbamate (10.8 mL, 60.7 mmol, 1.3 equiv.) and anhydrous THF (45.7 mL). To this, freshly prepared LDA (0.86 M, 70.60 mL, 1.3 equiv.) was added at –78 °C, and the resulting solution was stirred for 1 hour at –78 °C. Next, a solution of iodine (15.4 g, 60.7 mmol, 1.3 equiv.) in methanol (92.5 mL, 50 equiv.) was added in one portion, and the reaction was stirred 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 2-4% EtOAc/hexane to yield the title compound (13.5 g, 36.1 mmol, 79% yield) as a colorless oil (contaminated with vinyl-diisopropylcarbamate). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.06 (d, J = 15.6 Hz, 1H), 5.62 (dd, J = 15.6, 8.6 Hz, 1H), 5.49 – 5.43

(m, 1H), 4.87 (d, *J* = 2.2 Hz, 1H), 4.86 – 4.82 (m, 2H), 4.62 (d, *J* = 1.5 Hz, 1H), 3.98 – 3.75 (br, 2H), 2.86 (dd, *J* = 8.6, 4.9 Hz, 1H), 2.44 (dd, *J* = 11.7, 4.8 Hz, 1H), 2.20 – 2.09 (m, 1H), 2.07 – 1.97 (m, 1H), 1.92 – 1.76 (m, 5H), 1.60 (s, 3H), 1.24 – 1.17 (m, 12H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.0, 142.2, 134.7, 134.2, 129.9, 121.8, 114.7, 101.2, 48.3, 48.1, 34.7, 27.12, 24.3, 23.9, 22.4, 22.1, 21.4, 19.21, 15.0.; IR (neat) ν_{max} 3431 (br), 2961 (m), 2930 (m), 1707 (s), 1433 (m), 1368 (m), 1315 (m), 1239 (m), 1145 (m), 1043 (m) cm^{-1}. HRMS (DART) for $C_{24}H_{40}NO_2$ $[M+H]^+$ calculated: 374.305, found: 374.306. $[\alpha]^{20}_D$: +125.51 (c = 1.09, $CHCl_3$, *l* = 50 mm).



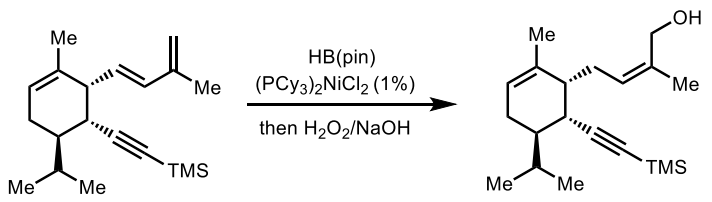
(((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)ethynyl)trimethylsilane (4.121). The title compound was prepared according to a modified literature procedure.[42] 1-((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)vinyl diisopropylcarbamate (13.5 g, 36.14 mmol) was added to a 250 mL round bottom flask, and dissolved in THF (36 mL). At -78 °C, LDA (0.86 M, 105 mL, 2.5 equiv) was added, then the reaction was stirred at RT for 1 hour. Next, the reaction was cooled to 0 °C and chloro(trimethyl)silane (6.9 mL, 54.2 mmol, 1.5 equiv.) was added, and the reaction was stirred at RT 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 to yield the title compound (7.23 g, 24.1 mmol, 67% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.11 (dd, *J* = 15.8, 1.1 Hz,

1H), 5.74 (dd, *J* = 15.7, 7.8 Hz, 1H), 5.51 – 5.45 (br, 1H), 4.91 (s, 2H), 2.86 (t, *J* = 6.5 Hz, 1H), 2.58 (dd, *J* = 11.3, 5.0 Hz, 1H), 2.26 – 2.13 (m, 1H), 2.01 – 1.91 (m, 1H), 1.87 (s, 3H), 1.82 – 1.67 (m, 1H), 1.66 – 1.61 (m, 4H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ142.4, 135.3, 133.9, 130.1, 122.5, 115.0, 108.3, 88.2, 47.1, 37.1, 36.6, 28.4, 24.3, 22.7, 21.0, 19.0, 15.6, 0.4.; IR (neat) ν_{max} 2955 (m), 2871 (w), 2166 (w), 1677 (w), 1451 (w), 1248 (m), 840 (s), 759 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{33}Si$ $[M+H]^+$ calculated: 301.235, found: 301.234. $[\alpha]^{20}_D$: +99.77 (c = 1.02, $CHCl_3$, *l* = 50 mm).



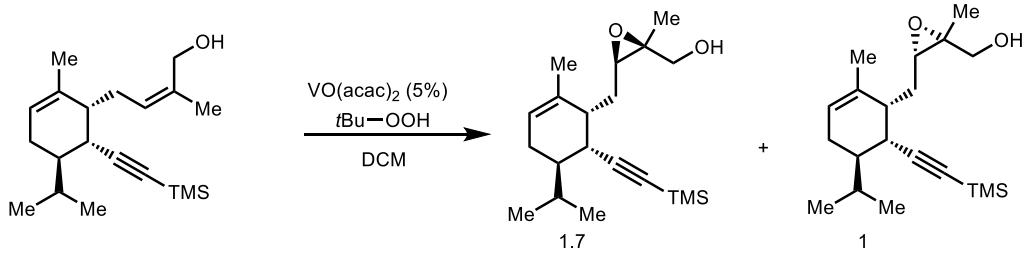
bis(tricyclohexylphosphine)nickel(II) chloride was prepared according to a modified literature procedure.[61] dichloro(hexahydroxy)nickel (2.2 g, 9.26 mmol, 1 equiv.) was added to a 100 mL round bottom flask with EtOH (37 mL). The solution was sparged with N_2 for 15 minutes then tricyclohexylphosphine (5.32 g, 19.0 mmol, 2.05 equiv.) was added. The flask was fitted with reflux condenser, and the reaction was heated to 80 °C for 1 hour. The reaction was cooled to -10 °C, and the solid was transferred to a fritted funnel and collected by vacuum filtration. The solid was washed successively with EtOH (2x10 mL), acetone (2x10 mL), Et_2O (2x10 mL), then pentane (2x 10 mL). The solid was dried under vacuum to yield the title compound (5.3 g, 7.68 mmol, 83% yield) as a pink solid.

[61] Standley, E. A.; Smith, S. J.; Müller, P.; Jamison, T. F. *Organometallics* **2014**, *33*, 2012−2018.



(Z)-4-((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)-2-methylbut-2-en-1-ol (4.128). The title compound was prepared according to a modified literature procedure.[45] To an oven 100 mL RBF was added $Ni(PCy_3)_2Cl_2$ (166 mg, 0.24 mmol, 0.01 equiv.), (((1R,2R,6R)-6-isopropyl-3-methyl-2-((E)-3-methylbuta-1,3-dien-1-yl)cyclohex-3-en-1-yl)ethynyl)trimethylsilane (7.23 g, 24.1 mmol, 1 equiv.), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.84 mL, 26.5 mmol, 1.1 equiv.), and toluene (24 mL). To this was added *n*BuLi (2.5 M in hexane, 0.19 mL, 0.48 mmol, 0.02 equiv.), and the reaction was stirred 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 filtered through a plug of silica gel with 5% EtOAc/hexane as the eluent, then concentrated and subjected to the boron oxidation conditions: The crude product was dissolved in THF (50 mL) and cooled to 0 °C. To this was added NaOH (3 M in H2O, 24 mL, 72 mmol, 3 equiv,) and H_2O_2 (30% aqueous solution, 12 mL, 106 mmol, 4.4 equiv.), and the reaction was stirred at RT for 1 hour. The reaction was cooled to 0 °C and quenched with saturated aqueous sodium thiosulfate (25 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 2-10% EtOAc/hexane as the eluent, to yield the title compound (6.17 g, 19.4 mmol, 80% yield) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 5.39 – 5.36 (br, 1H), 5.34 (d,

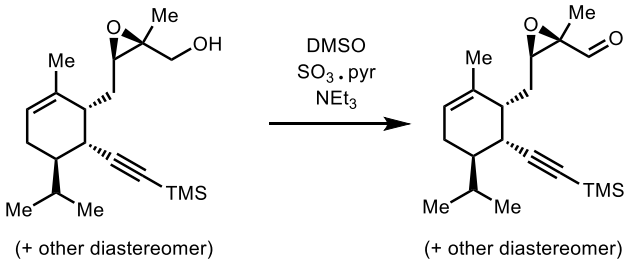
J = 8.6 Hz, 1H), 4.12 (s, 2H), 2.60 (dd, J = 9.7, 4.9 Hz, 1H), 2.47 – 2.38 (m, 2H), 2.21 – 2.12 (m, 1H), 2.07 – 1.96 (m, 2H), 1.83 – 1.71 (m, 5H), 1.72 – 1.63 (m, 4H), 0.88 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H), 0.16 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.1, 135.0, 127.9, 122.0, 109.4, 87.9, 61.7, 42.0, 38.6, 35.7, 29.0, 28.3, 24.6, 22.8, 21.9, 20.9, 16.8, 0.3.; IR (neat) ν_{max} 3347 (br), 2955 (m), 2870 (w), 2163 (w), 1449 (w), 1248 (m), 1000 (m), 840 (s), 759 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{35}OSi$ $[M+H]^+$ calculated: 319.245, found: 319.246. $[\alpha]^{20}_D$: +78.89 (c = 1.02, $CHCl_3$, l = 50 mm).



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 (β-4.131) 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 (α-4.131)**. The title compounds were prepared according to a modified literature procedure.[47] (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 stirred at 0 °C for 2 hours, then dimethyl sulfide (1.4 mL, 19.2 mmol, 1 equiv.) was added to quench the reaction, and stirred 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 as the eluent to yield the title compounds (5.04 g, 15.1 mmol, 79% combined yield, 1.7:1 d.r.) as a colorless oil. (**Note**: NMR data is tentatively assigned due to the diasteromeric mixture and the presence of trace unidentified byproducts in the product mixture.) **β-3.131:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.48 – 5.45 (br, 1H), 3.67 – 3.64 (m, 2H), 2.93 (dd, *J* = 9.5, 3.3 Hz, 1H), 2.64 (d, *J* = 4.9 Hz, 1H), 2.41 – 2.35 (m, 1H), 2.19 – 2.13 (m, 1H), 2.04 (dt, *J* = 14.6, 5.7 Hz, 1H), 1.97 – 1.89 (m, 1H), 1.84 – 1.75 (m, 2H), 1.73 (s, 3H), 1.66 – 1.55 (m, 1H), 1.39 (s, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.16 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 134.4, 123.0, 108.5, 89.2, 63.9, 63.7, 62.0, 40.8, 37.3, 36.4, 28.6, 27.8, 24.2, 22.7, 21.0, 20.2, 15.2, 0.2.; **α-3.131:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.37 – 5.34 (m, 1H), 3.69 (s, 2H), 3.09 (dd, *J* = 6.9, 5.5 Hz, 1H), 2.62 (dd, *J* = 4.8, 1.5 Hz, 1H), 2.31 – 2.25 (m, 1H), 2.24 – 2.19 (m, 2H), 2.14 – 2.07 (m, 1H), 2.00 – 1.93 (m, 1H), 1.84 – 1.74 (m, 2H), 1.71 (d, *J* = 1.8 Hz, 3H), 1.65 – 1.55 (m, 1H), 1.41 (s, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) 135.4, 121.8, 109.0, 88.3, 65.0, 64.1, 61.8, 40.6, 38.1, 35.9, 30.5, 28.4, 24.5, 22.7, 20.9, 20.4, 16.5, 0.3.; IR (neat) ν_{max} 3459 (br), 2956 (m), 2927 (w), 2166 (w), 1463 (w), 1248 (m), 1093 (m), 840 (s), 759 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{35}O_2Si$ $[M+H]^+$ calculated: 335.240, found: 335.240. $[\alpha]^{20}_D$: +67.33 (c = 1.02, $CHCl_3$, *l* = 50 mm).



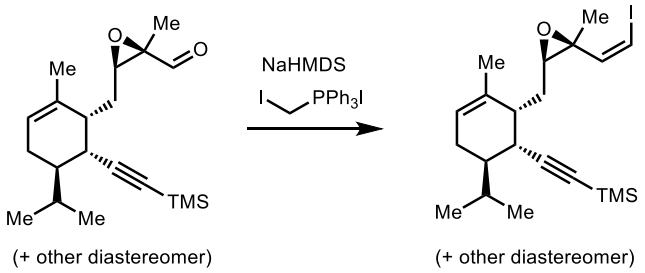
(2R,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxirane-2-carbaldehyde (β-4.133) and **(2S,3S)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxirane-2-carbaldehyde (α-4.133)**. A solution of sulfur trioxide pyridine complex (7.19 g, 45.2 mmol, 3 equiv.) in anhydrous DMSO (18.2 mL, 256 mmol, 17 equiv.) was stirred 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 stirred 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 as the eluent to yield the title compounds (4.65 g, 14.0 mmol, 93% yield) as a colorless oil. (**Note**: NMR data is tentatively assigned due to the diasteromeric mixture and the presence of trace unidentified byproducts in the product mixture.) **β-3.133:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.40 (s, 1H), 5.42 – 5.39 (m, 1H), 3.29 (dd, *J* = 8.6, 4.7 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.41 – 2.34 (m, 1H), 2.34 – 2.28 (m, 1H), 2.17 – 2.09 (m, 1H), 1.96 – 1.89 (m, 1H), 1.89 – 1.81 (m, 1H), 1.80 – 1.72 (m, 1H), 1.66 (s, 3H), 1.54 – 1.46 (m, 1H), 1.39 (s, 3H), 0.89 (d, *J* = 7.4 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.4, 134.0, 123.1, 108.0, 89.0, 65.1, 63.4, 40.6, 37.8,

36.1, 28.8, 28.4, 24.3, 22.7, 20.9, 16.0, 15.6, 0.2.; **α-3.133:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.39 (s, 1H), 5.39 – 5.36 (m, 1H), 3.36 (dd, *J* = 8.4, 4.1 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.34 – 2.28 (m, 1H), 2.24 – 2.17 (m, 1H), 2.17 – 2.09 (m, 1H), 1.99 – 1.92 (m, 1H), 1.81 – 1.72 (m, 2H), 1.71 (s, 3H), 1.62 – 1.54 (m, 1H), 1.41 (s, 3H), 0.90 (d, *J* = 8.1 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.12 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.6, 134.7, 122.5, 108.2, 88.6, 65.7, 63.7, 41.3, 37.6, 35.9, 30.4, 28.4, 24.3, 22.6, 20.9, 16.0, 15.9, 0.3.; IR (neat) ν_{max} 2956 (m), 2871 (w), 2166 (w), 1723 (m), 1439 (w), 1382 (w), 1248 (m), 840 (s), 759 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{33}O_2Si$ $[M+H]^+$ calculated: 333.224, found: 333.224. $[\alpha]^{20}_D$: +108.94 (c = 1.03, $CHCl_3$, *l* = 50 mm).

Note: the reaction is protected from light

(Iodomethyl)-triphenylphosphonium iodide was prepared according to a literature procedure.[62] To a solution of triphenylphosphine (12.01 g, 45.8 mmol, 1 equiv.) in anhydrous toluene (40 mL) in a 200 mL round bottom flask was added diiodomethane (4.91 mL, 61.1 mmol, 1.3 equiv.). The flask was fitted with a reflux condenser and the reaction was heated to 100 °C for 20 hours. The reaction solution was then cooled to 0 °C, and the solid was collected by vacuum filtration, and subsequently washed with hexane (3x50 mL). (iodomethyl)-triphenylphosphonium iodide (23.1 g, 43.6 mmol, 95% yield) was obtained as an off-white solid. Spectral data are in accordance with the literature.[62]

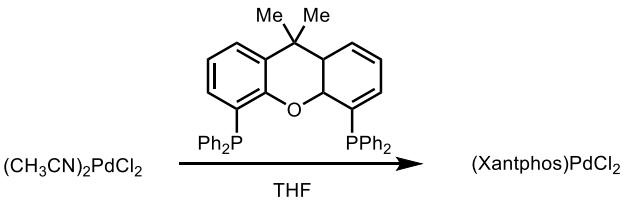
[62] Dias, L. C.; Ferreira, M. A. B. *J. Org. Chem*. **2012**, *77*, 4046−4062.



(((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 (β-4.136) and **(((1R,2R,6R)-2-(((2S,3R)-3-((Z)-2-iodovinyl)-3-methyloxiran-2-yl)methyl)-6-isopropyl-3-methylcyclohex-3-en-1-yl)ethynyl)trimethylsilane (α-4.136)**. The title compounds was prepared according to a modified literature procedure.[63] A solution of (iodomethyl)-triphenylphosphonium iodide (11.9 g, 22.4 mmol, 1.6 equiv.) in THF (84 mL) was stirred at 0 °C then a solution of NaHMDS (2 M in THF, 11.2 mL, 22.4 mmol, 1.6 equiv.) was added. The reaction was stirred for 30 minutes at 0 °C, then cooled to -78 °C and a solution of (2R,3R)-3-(((1R,5R,6R)-5-isopropyl-2-methyl-6-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)methyl)-2-methyloxirane-2-carbaldehyde (+ other diastereomer) (4.65 g, 14.0 mmol, 1 equiv.) in THF (84 mL) was added. The reaction was allowed to stir at -78 °C for 30 minutes then quenched with methanol (1.1 mL, 28.0 mmol, 2 equiv.) at that temperature. The reaction solution was filtered through a fritted funnel and the filtrate was concentrated. The crude product was then filtered through a plug of silica with 10% EtOAc/hexane as the eluent and concentrated. The resulting oil was purified by silica gel column chromatography with 0-2% EtOAc/hexane to yield the title compounds (4.97 g, 10.9 mmol, 78% yield, 18:1 Z:E) as a pale yellow oil. (**Note**: NMR data is tentatively assigned due to the diasteromeric mixture and the presence of trace unidentified byproducts in the product mixture.) **β-3.136:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.3 Hz, 1H), 6.48 (d, *J* = 8.2 Hz, 1H), 5.40 – 5.37 (m, 1H), 3.18 (d, *J*

[63] Stork, G.; Zhao, K. Tetrahedron Lett. **1989**, *30*, 2173–2174.

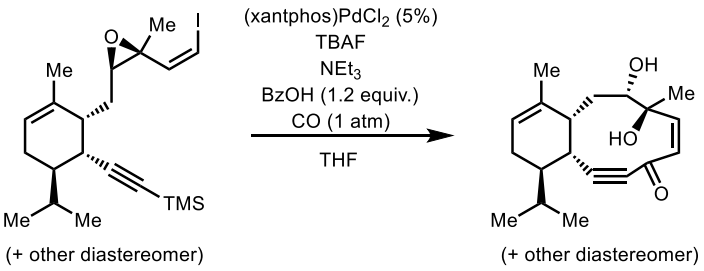
= 6.7 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.39 – 2.32 (m, 1H), 2.20 – 2.12 (m, 2H), 1.81 – 1.70 (m, 5H), 1.65 – 1.55 (m, 1H), 1.51 (s, 3H), 1.36 – 1.16 (m, 1H), 0.93 – 0.90 (m, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.5, 135.5, 122.2, 108.6, 88.3, 82.6, 65.0, 63.7, 62.8, 40.3, 37.6, 36.1, 31.3, 28.4, 24.4, 23.2, 21.6, 21.0, 15.9, 0.4.; **α-3.136:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.2 Hz, 1H), 6.44 (d, *J* = 8.2 Hz, 1H), 5.34 – 5.30 (m, 1H), 3.30 (dd, *J* = 9.4, 2.0 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.41 – 2.31 (m, 1H), 2.21 – 2.11 (m, 1H), 2.01 – 1.90 (m, 1H), 1.81 – 1.74 (m, 2H), 1.67 (s, 3H), 1.65 – 1.57 (m, 1H), 1.51 (s, 3H), 1.35 – 1.17 (m, 1H), 0.93 – 0.91 (m, 3H), 0.82 – 0.80 (m, 3H), 0.15 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.9, 135.8, 121.3, 108.8, 87.9, 82.3, 64.5, 63.2, 61.9, 40.5, 37.7, 35.9, 32.4, 28.3, 24.3, 22.4, 21.6, 21.0, 16.2, 0.5.; IR (neat) ν_{max} 2955 (m), 2923 (w), 2167 (w), 1440 (w), 1372 (w), 1281 (w), 1247 (m), 840 (s), 759 (m), 703 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{34}IOSi$ $[M+H]^+$ calculated: 457.141, found: 457.142. $[\alpha]^{20}_D$: +55.38 (c = 1.00, $CHCl_3$, *l* = 50 mm).



(Xantphos)palladium (II) chloride was prepared according to a modified literature procedure.[64] Bis(acetonitrile)palladium dichloride (393 mg, 1.51 mmol, 1.0 equiv.) and 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (877 mg, 1.51 mmol, 1.0 equiv.) were added to a 200 mL round bottom flask, followed by anhydrous THF (50 mL). The reaction was stirred at RT for 15 hours, then concentrated. The resulting yellow solid was collected by filtration and washed with hexane (3x50 mL). The crude product was recrystallized from dichloromethane

[64] Fujihara, T.; Hosoki, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *Chem. Commun*. **2012**, *48*, 8012–8014.

to yield (Xantphos)palladium (II) chloride (965 mg, 1.28 mmol, 84% yield) as a free-flowing yellow solid. Spectral data are in accordance with the literature.[65]

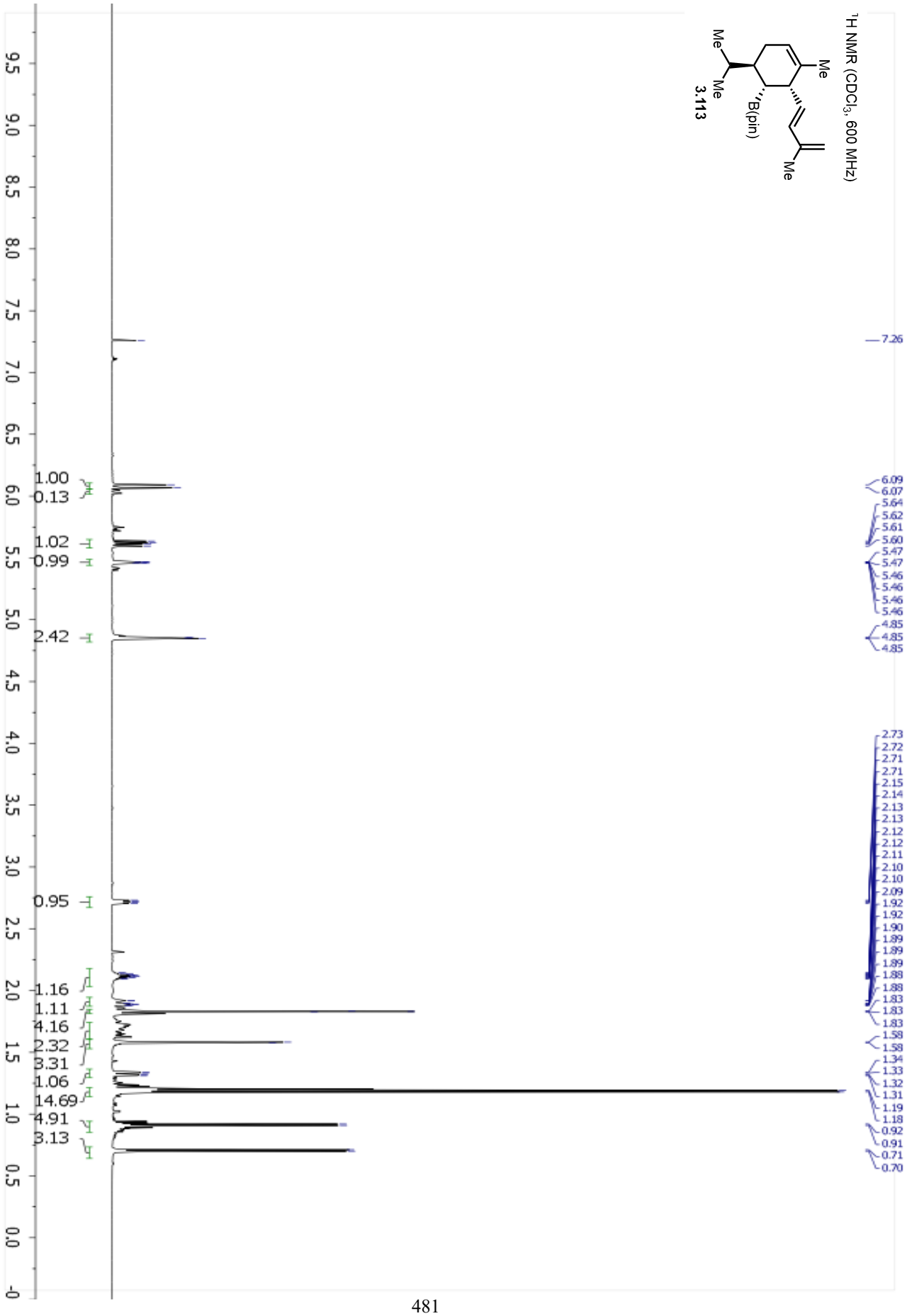


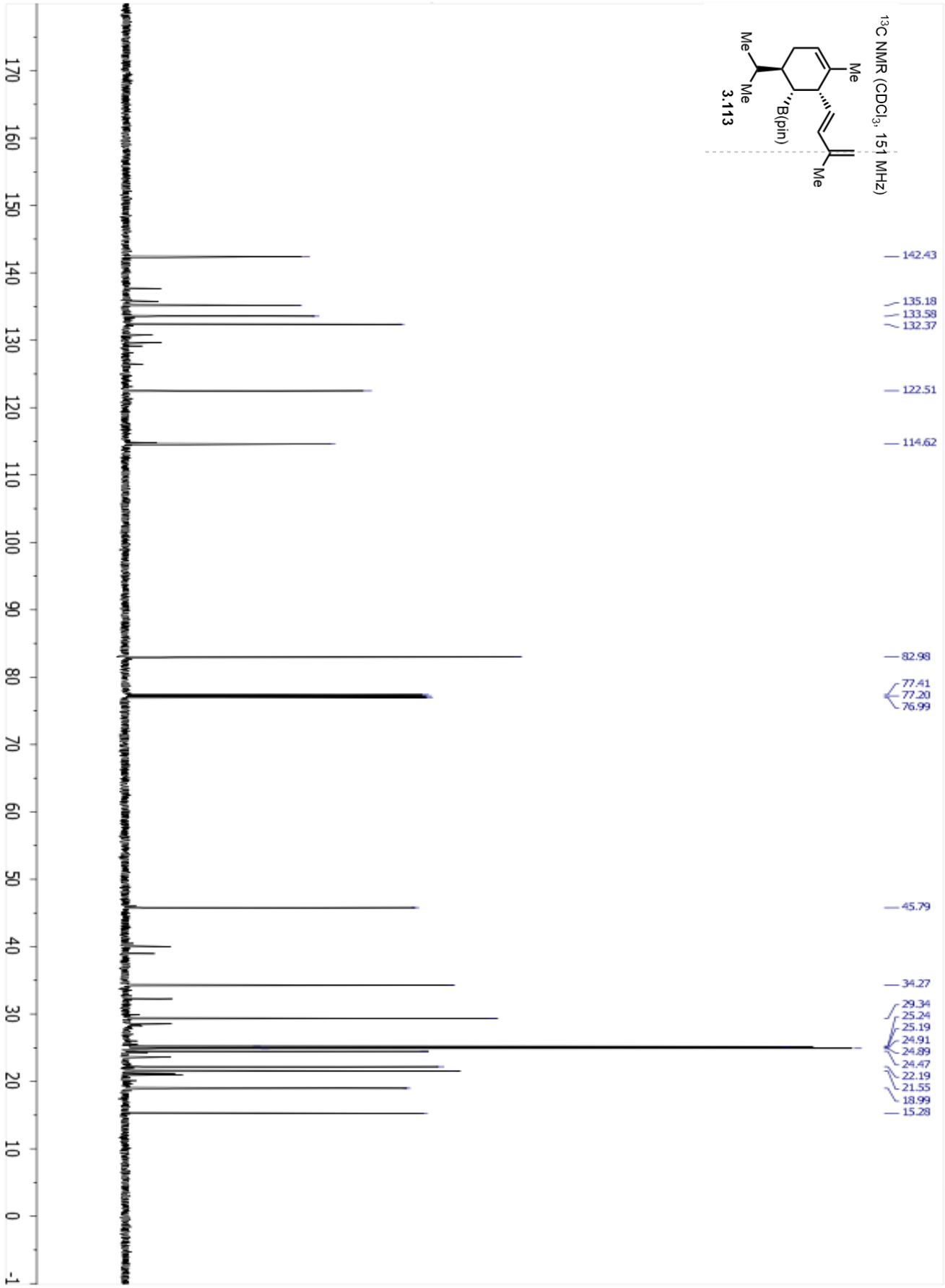
(4R,4aR,8Z,10S,11S,12aR)-10,11-dihydroxy-4-isopropyl-1,10-dimethyl-5,6-didehydro-4,4a,10,11,12,12a-hexahydrobenzo[10]annulen-7(3H)-one (4.137.1) and **(4R,4aR,8Z,10R,11R,12aR)-10,11-dihydroxy-4-isopropyl-1,10-dimethyl-5,6-didehydro-4,4a,10,11,12,12a-hexahydrobenzo[10]annulen-7(3H)-one (4.137.2)**. The title compound was prepared according to a modified literature procedure.[50] To a 1-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 (45 mg, 0.10 mmol, 1 equiv.) , (Xantphos)$PdCl_2$ (3.8 mg, 0.005 mmol, 0.05 equiv.), benzoic acid (14.7 mg, 0.12 mmol, 1.2 equiv.), and THF (0.40 mL). The vial was sealed with a septum cap and placed under a positive pressure of N_2. Next, triethylamine (0.04 mL, 0.30 mmol, 3 equiv.) and TBAF (1 M in THF, 0.12 mL, 0.12 mmol, 1.2 equiv.) were added. The N_2 pressure was removed, and the reaction was stirred under an atmospheric pressure of carbon monoxide (balloon). The reaction was stirred 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 10-30% EtOAc/hexane as the eluent to yield the title compounds (15 mg, 0.049 mmol, 49% yield) as a pale yellow oil.

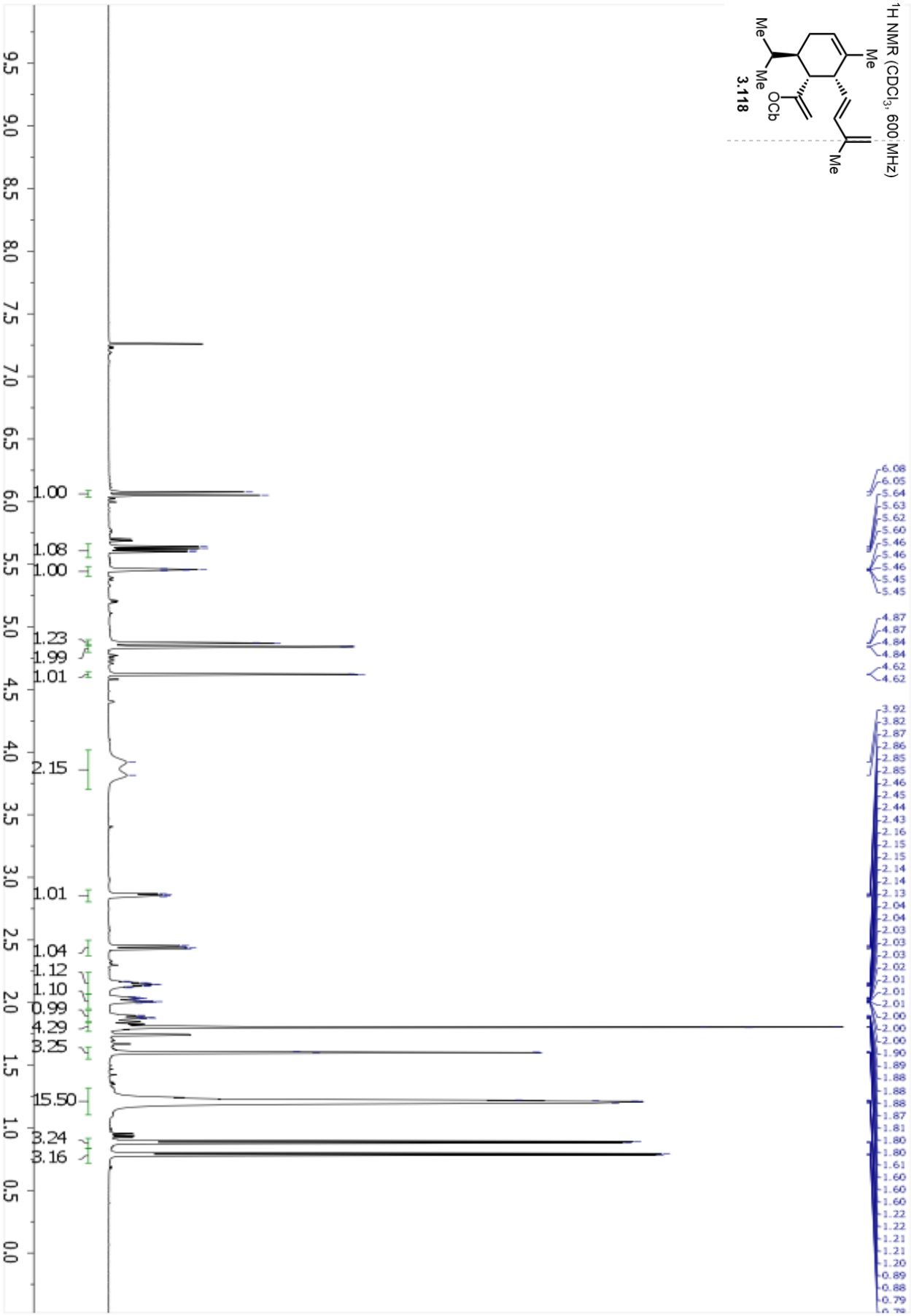
[65] Saikia, K.; Deb, B.; Borah, B. J.; Sarmah, P. P.; Dutta, D. K. *J. Organomet. Chem*. **2012**, *696*, 4293–4297.

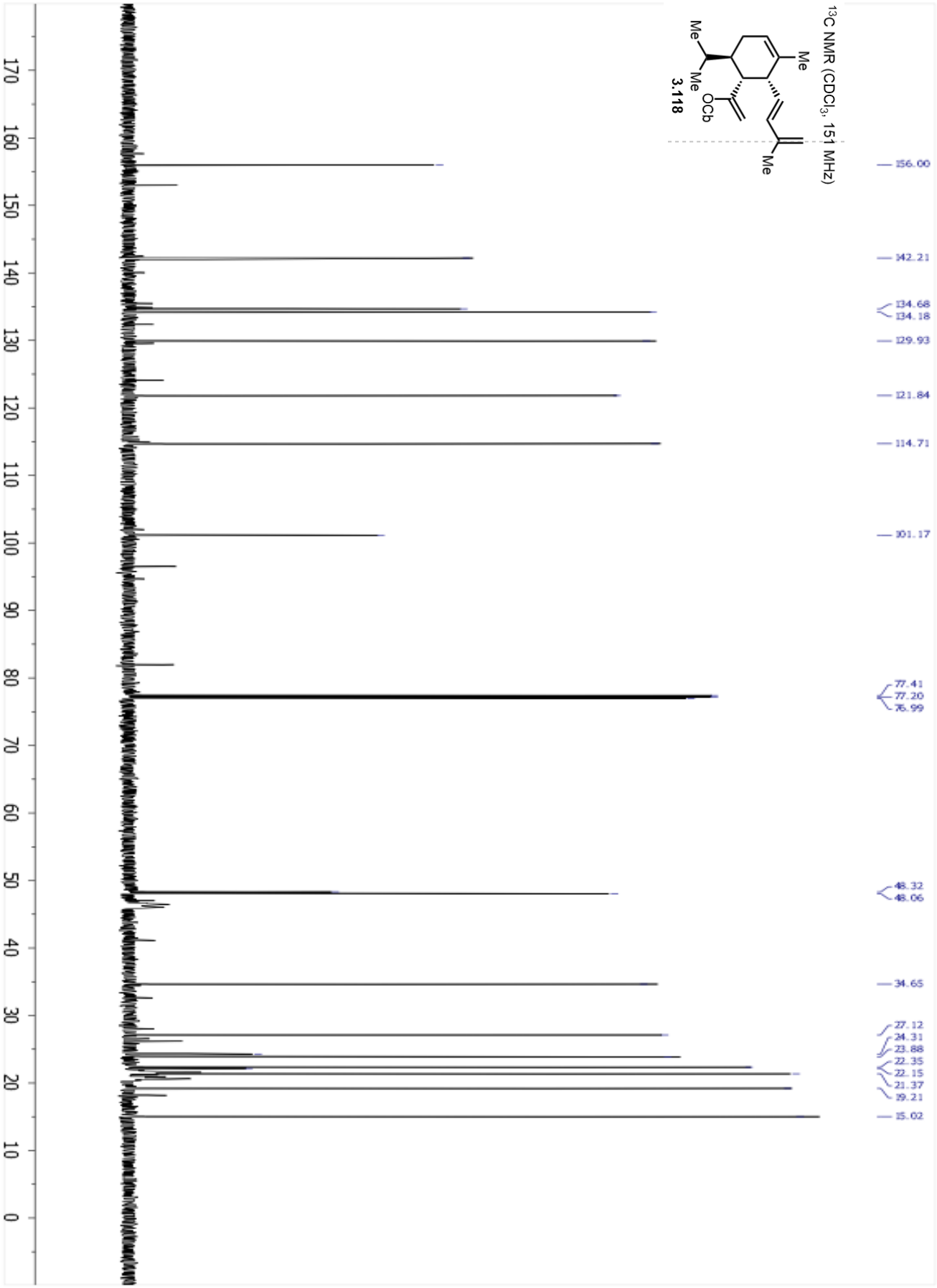
(**Note**: NMR data is tentatively assigned due to the diasteromeric mixture and the presence of trace unidentified byproducts in the product mixture.) **3.137.1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 5.7 Hz, 1H), 6.10 (d, *J* = 5.7 Hz, 1H), 5.36 – 5.32 (m, 1H), 3.82 (ddd, *J* = 11.0, 5.7, 2.3 Hz, 1H), 2.60 (ddd, *J* = 11.3, 4.7, 2.5 Hz, 1H), 2.38 (d, *J* = 18.9 Hz, 1H), 2.27 (d, *J* = 2.4 Hz, 1H), 2.25 – 2.16 (m, 1H), 2.10 – 2.01 (m, 2H), 1.97 – 1.89 (m, 1H), 1.86 – 1.74 (m, 2H), 1.69 (q, *J* = 1.7 Hz, 3H), 1.52 (s, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ **Note:** (C=O) is not apparent because poor S/N ratio, 158.7, 136.4, 121.8, 121.3, 91.1, 87.4, 75.5, 72.9, 39.9, 35.9, 34.1, 33.3, 28.4, 24.0, 22.8, 20.9, 20.7, 15.5.; **3.137.2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 5.7 Hz, 1H), 6.07 (d, *J* = 5.7 Hz, 1H), 5.38 (d, *J* = 3.1 Hz, 2H), 3.97 (ddd, *J* = 10.9, 4.8, 1.9 Hz, 1H), 2.69 (ddd, *J* = 8.9, 4.9, 2.5 Hz, 1H), 2.44 – 2.35 (m, 3H), 2.21 (pd, *J* = 6.8, 3.9 Hz, 2H), 2.09 – 2.03 (m, 1H), 1.98 – 1.88 (m, 1H), 1.71 – 1.67 (m, 3H), 1.48 (s, 3H), 0.94 – 0.92 (m, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ **Note:** (C=O) is not apparent because poor S/N ratio, 159.1, 135.2, 121.6, 121.5, 92.0, 86.1, 74.6, 71.7, 39.1, 37.5, 37.1, 33.4, 28.0, 24.2, 22.0, 20.9, 18.6, 17.5.; IR (neat) ν_{max} 3467 (br), 3289 (br), 2956 (m), 2928 (m), 1752 (s), 1446 (w), 1384 (w), 1113 (m), 1083 (m), 957 (m), 820 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{27}O_3$ $[M+H]^+$ calculated: 303.195, found: 303.195. $[\alpha]^{20}_D$: +122.19 (c = 0.97, $CHCl_3$, *l* = 50 mm).

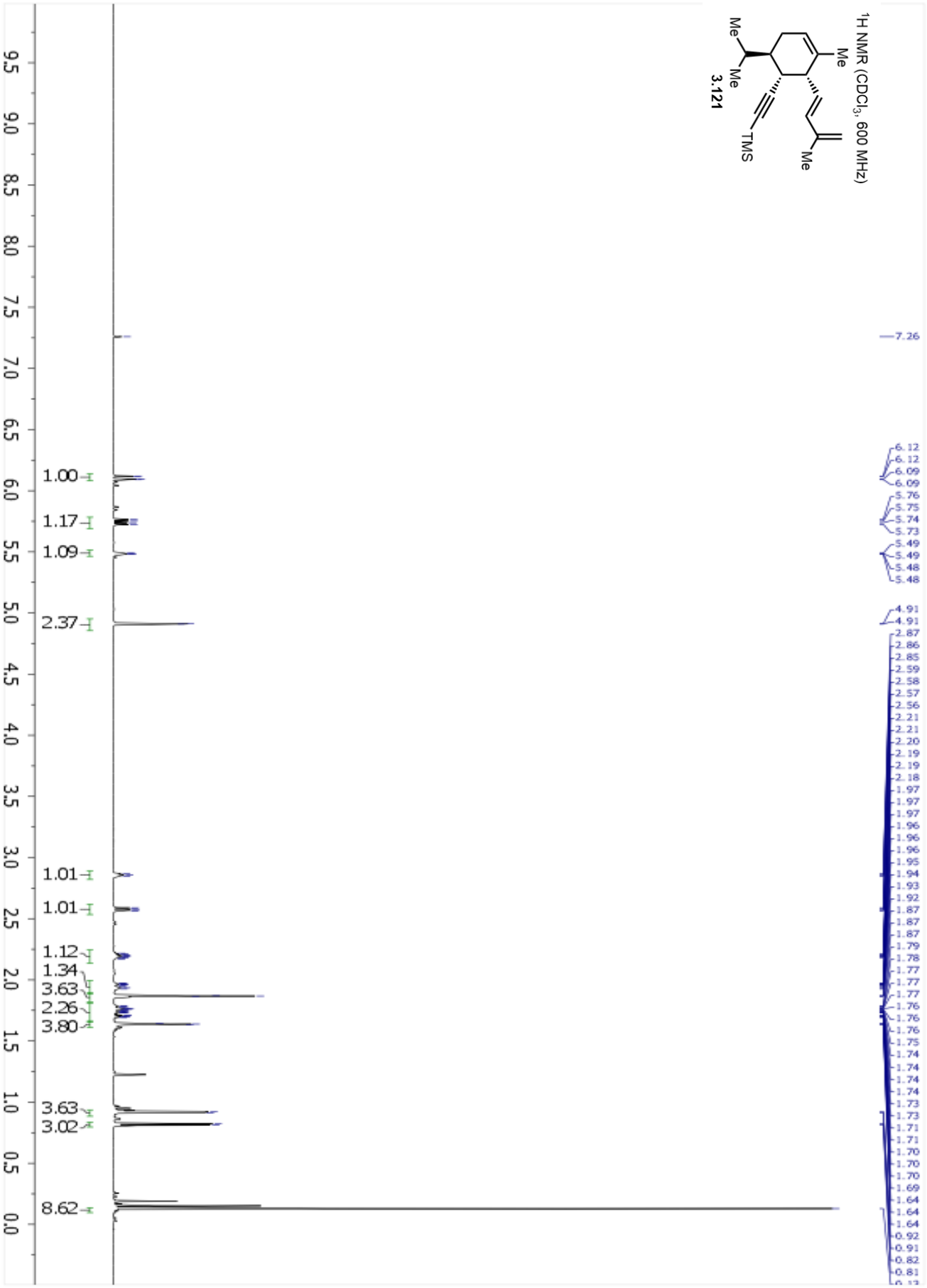
4.5.3. NMR spectra

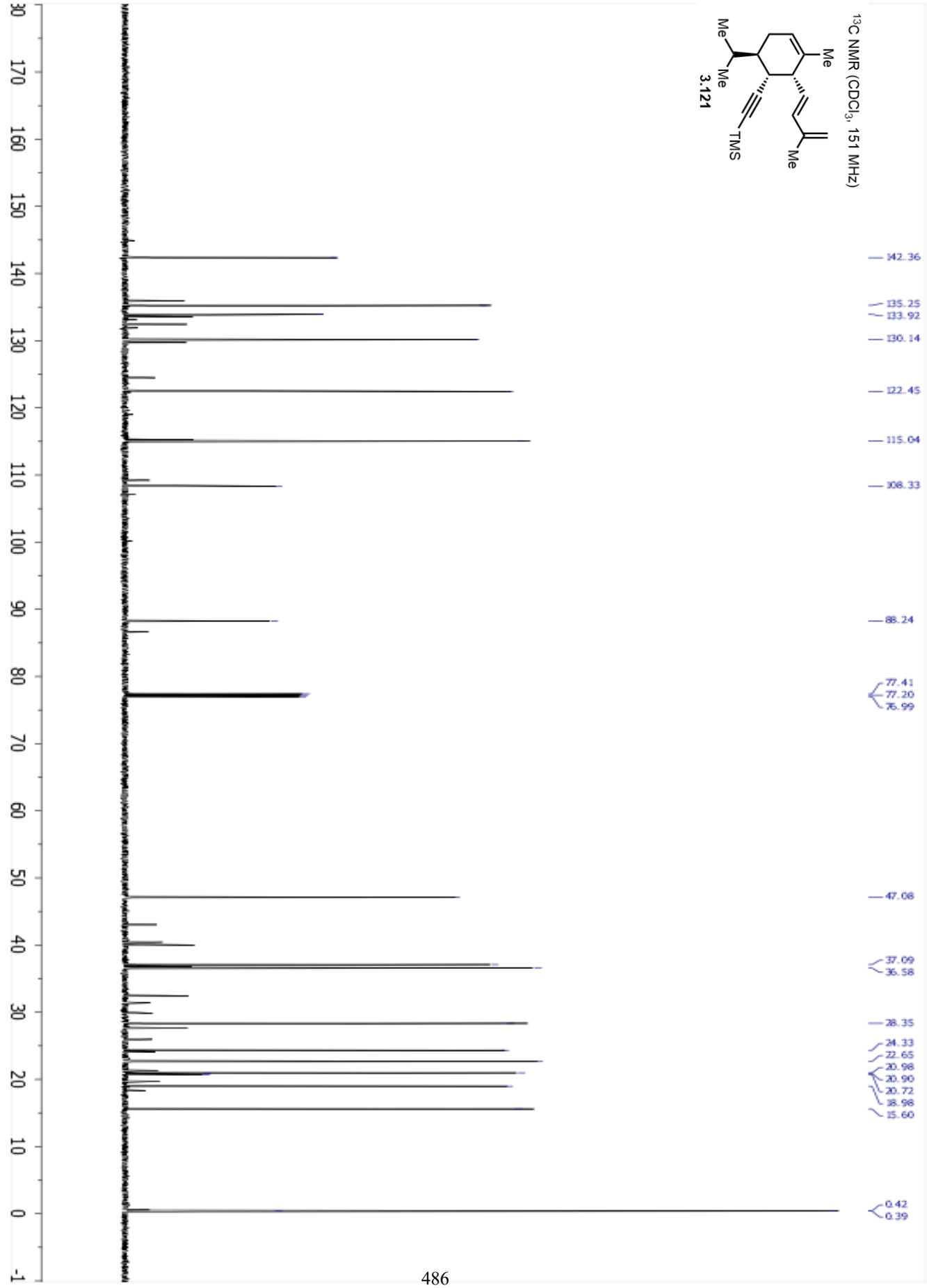


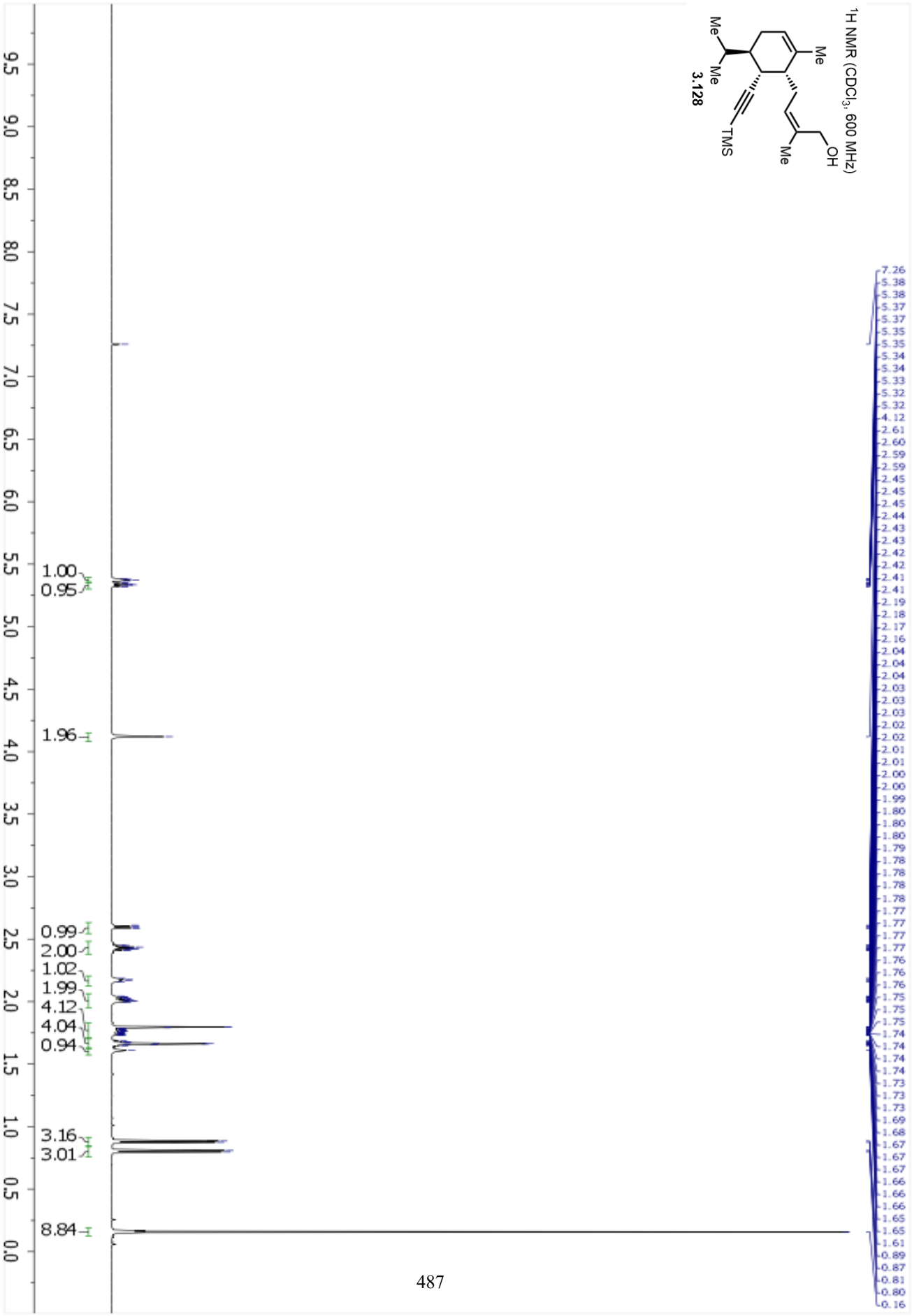

^{13}C NMR ($CDCl_3$, 151 MHz)
Me
Me
B(pin)
Me
Me
3.113
142.43
135.18
133.58
132.37
122.51
114.62
82.98
77.41
77.20
76.99
45.79
34.27
29.34
25.24
25.19
24.91
24.89
24.47
22.19
21.55
18.99
15.28
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1


^{1}H NMR ($CDCl_3$, 600 MHz)
Me
Me
Me
OCb
3.118
Me
1.00
1.08
1.00
1.23
1.99
1.01
2.15
1.01
1.04
1.12
1.10
0.99
4.29
3.25
15.50
3.24
3.16

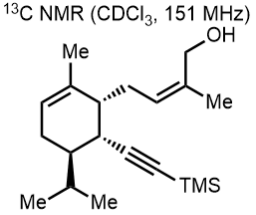

^{13}C NMR ($CDCl_3$, 151 MHz)
Me
Me
Me
OCb
3.118
156.00
142.21
134.68
134.18
129.93
121.84
114.71
101.17
77.41
77.20
76.99
48.32
48.06
34.65
27.12
24.31
23.88
22.35
22.15
21.37
19.21
15.02
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


^{1}H NMR (CDCl$_3$, 600 MHz)
3.121
Me
Me
Me
TMS
Me
7.26
6.12
6.12
6.09
6.09
5.76
5.75
5.74
5.73
5.49
5.49
5.48
5.48
4.91
4.91
2.87
2.86
2.85
2.59
2.58
2.57
2.56
2.21
2.21
2.20
2.19
2.19
2.18
1.97
1.97
1.97
1.96
1.96
1.96
1.95
1.94
1.93
1.92
1.87
1.87
1.87
1.79
1.78
1.77
1.77
1.77
1.76
1.76
1.76
1.75
1.74
1.74
1.74
1.74
1.73
1.73
1.71
1.71
1.70
1.70
1.70
1.69
1.64
1.64
1.64
0.92
0.91
0.82
0.81
1.00
1.17
1.09
2.37
1.01
1.01
1.12
1.34
3.63
2.26
3.80
3.63
3.02
8.62
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

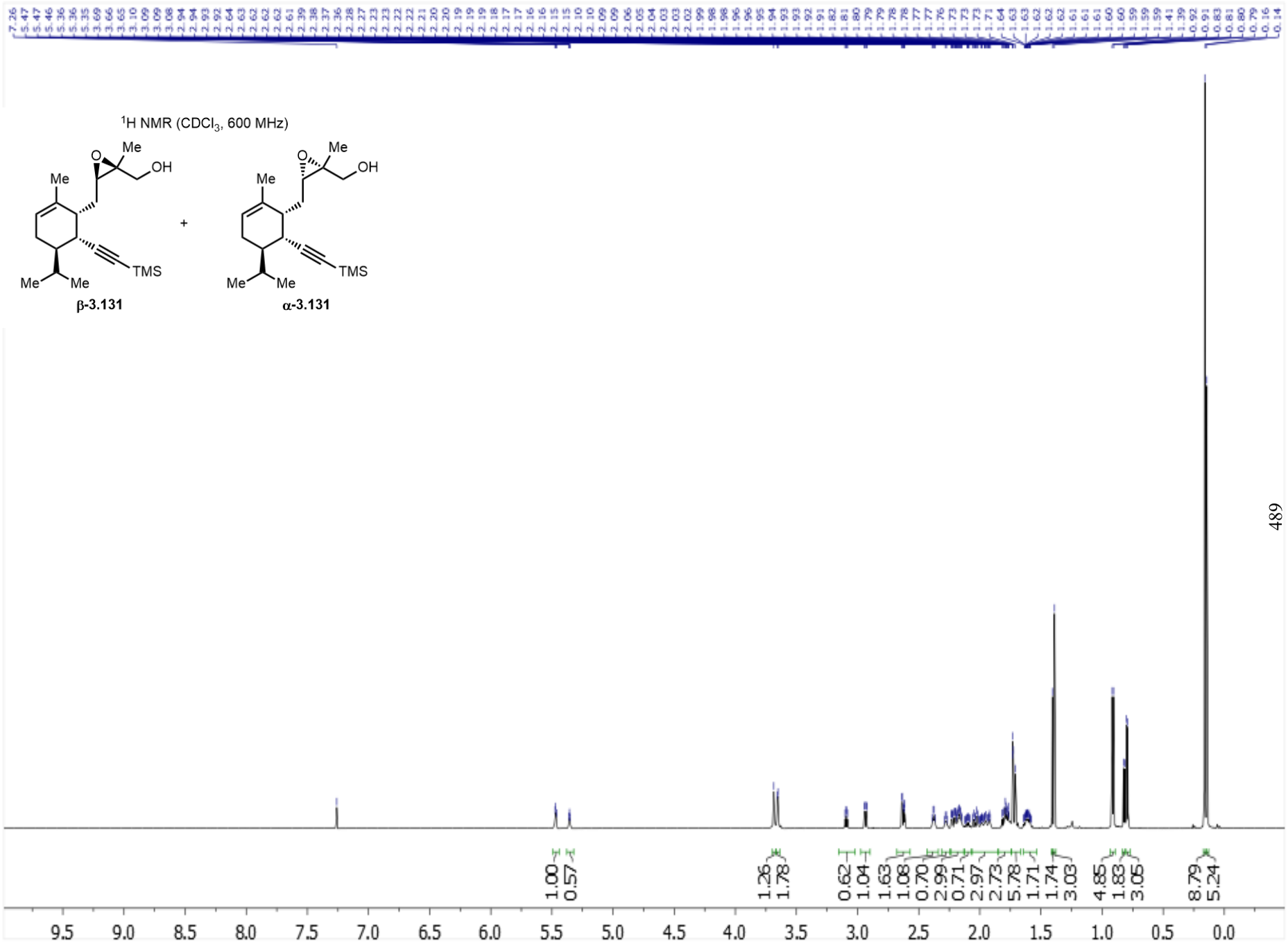

^{13}C NMR ($CDCl_3$, 151 MHz)
Me
Me
Me
TMS
Me
3.121
142.36
135.25
133.92
130.14
122.45
115.04
108.33
88.24
77.41
77.20
76.99
47.08
37.09
36.58
28.35
24.33
22.65
20.98
20.90
20.72
18.98
15.60
0.42
0.39

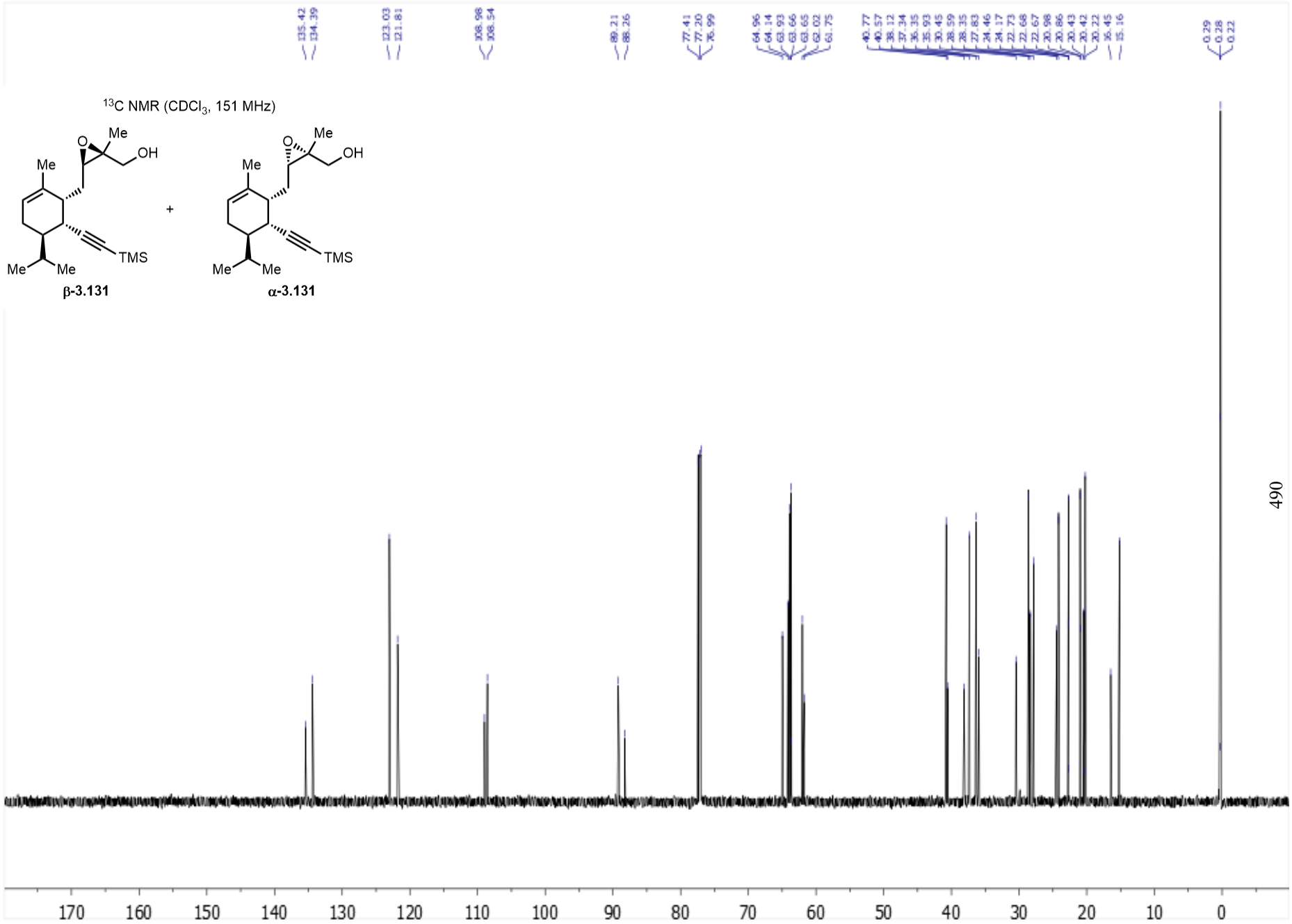

^{1}H NMR ($CDCl_3$, 600 MHz)
Me
Me
Me
TMS
OH
Me
3.128
1.00
0.95
1.96
0.99
2.00
1.02
1.99
4.12
4.04
0.94
3.16
3.01
8.84

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



3.128


^{1}H NMR ($CDCl_3$, 600 MHz)
Me
O
OH
Me
TMS
Me
Me
β-3.131
+
α-3.131
489
1.00
0.57
1.26
1.78
0.62
1.04
1.63
1.08
0.70
2.99
0.71
2.97
2.73
5.78
1.71
1.74
3.03
4.85
1.83
3.05
8.79
5.24
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

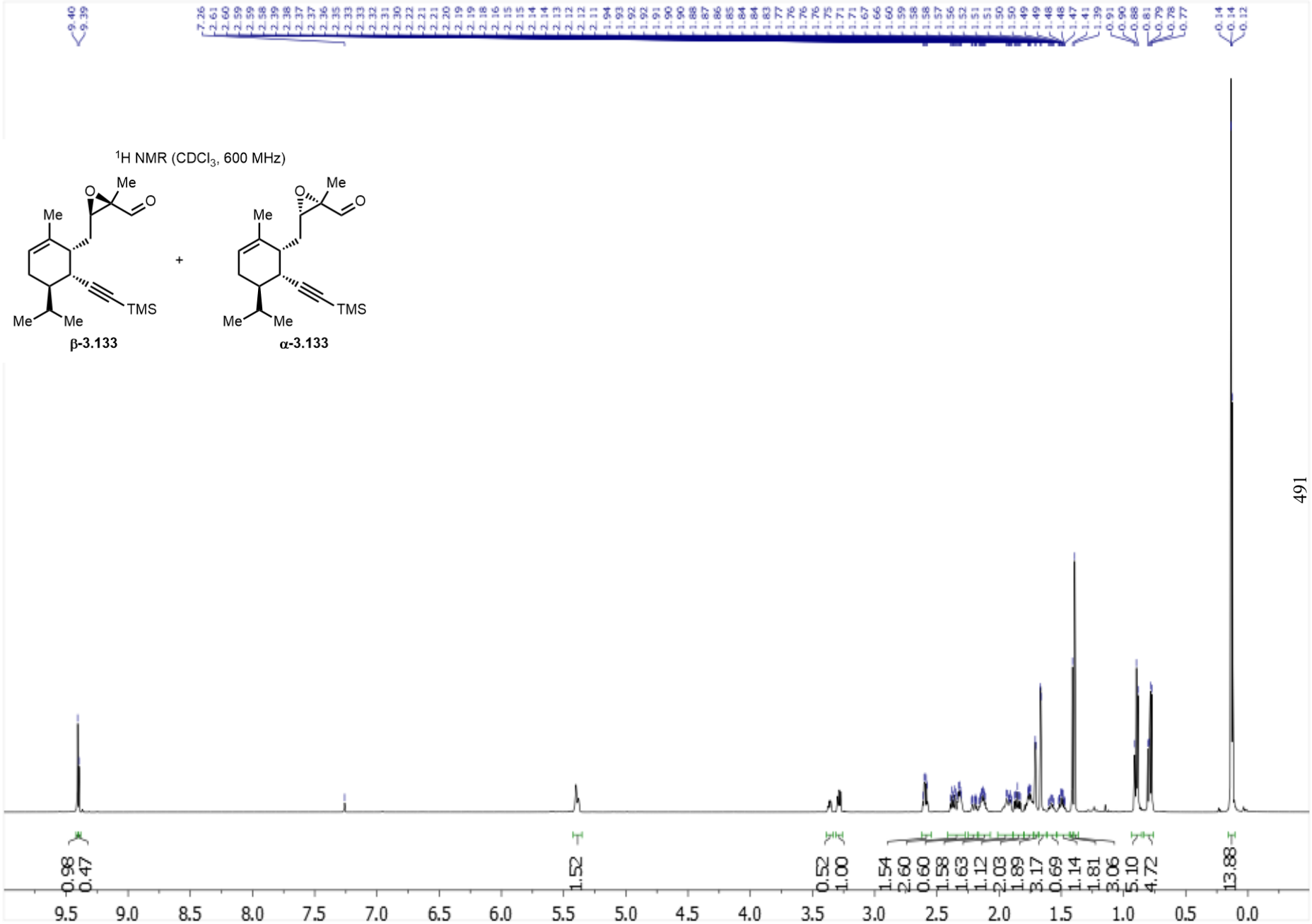


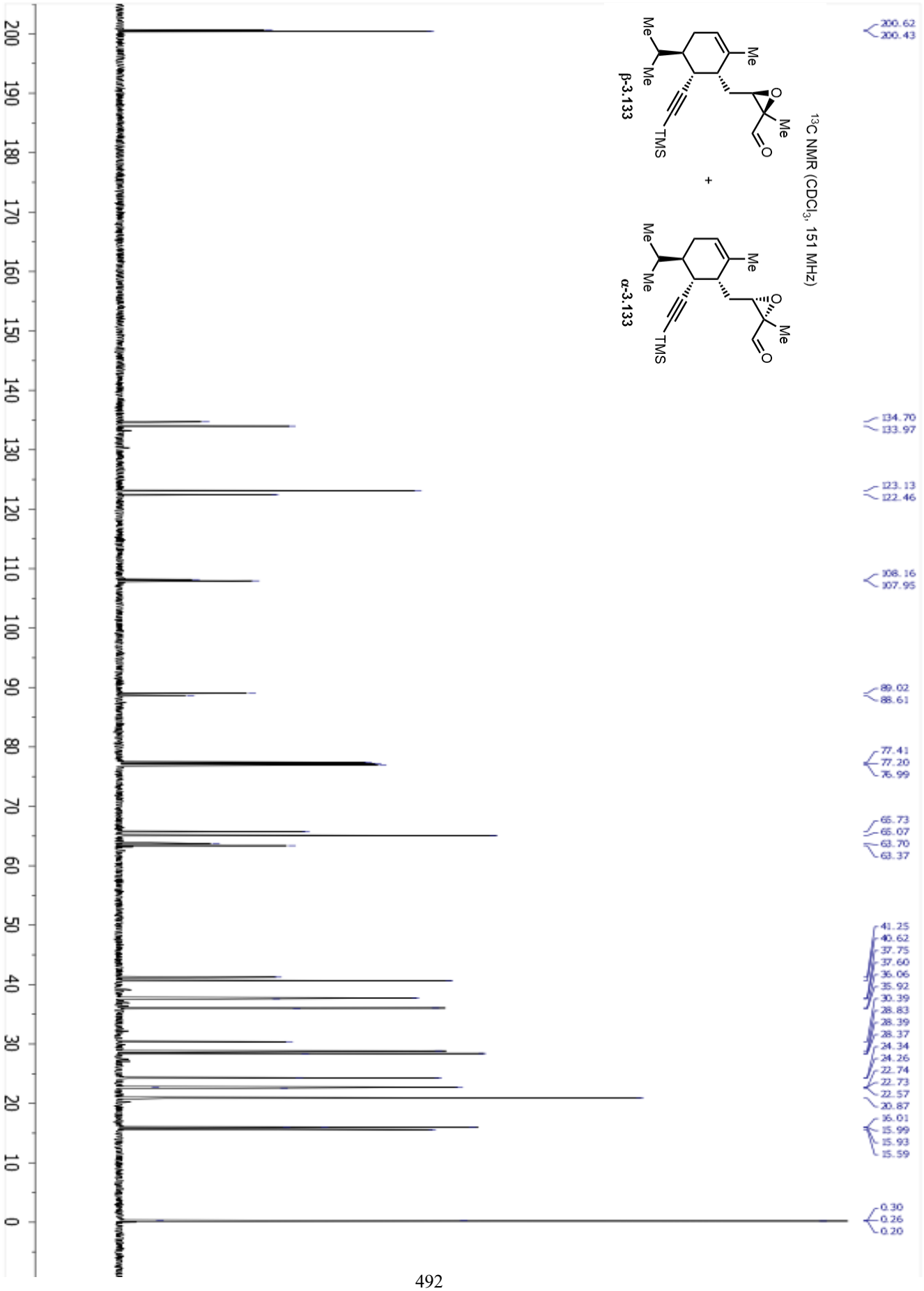
^{13}C NMR ($CDCl_3$, 151 MHz)

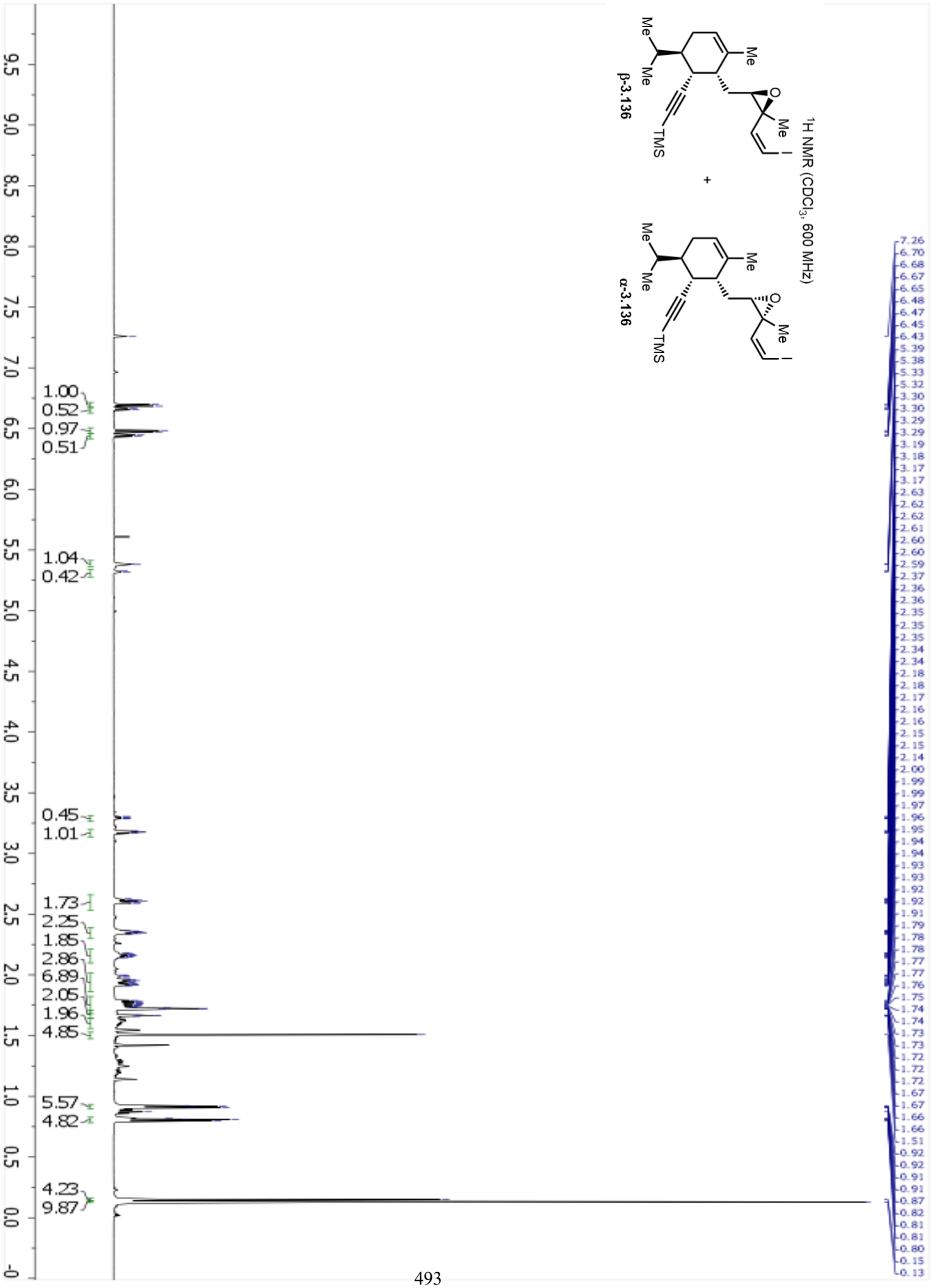
β-3.131

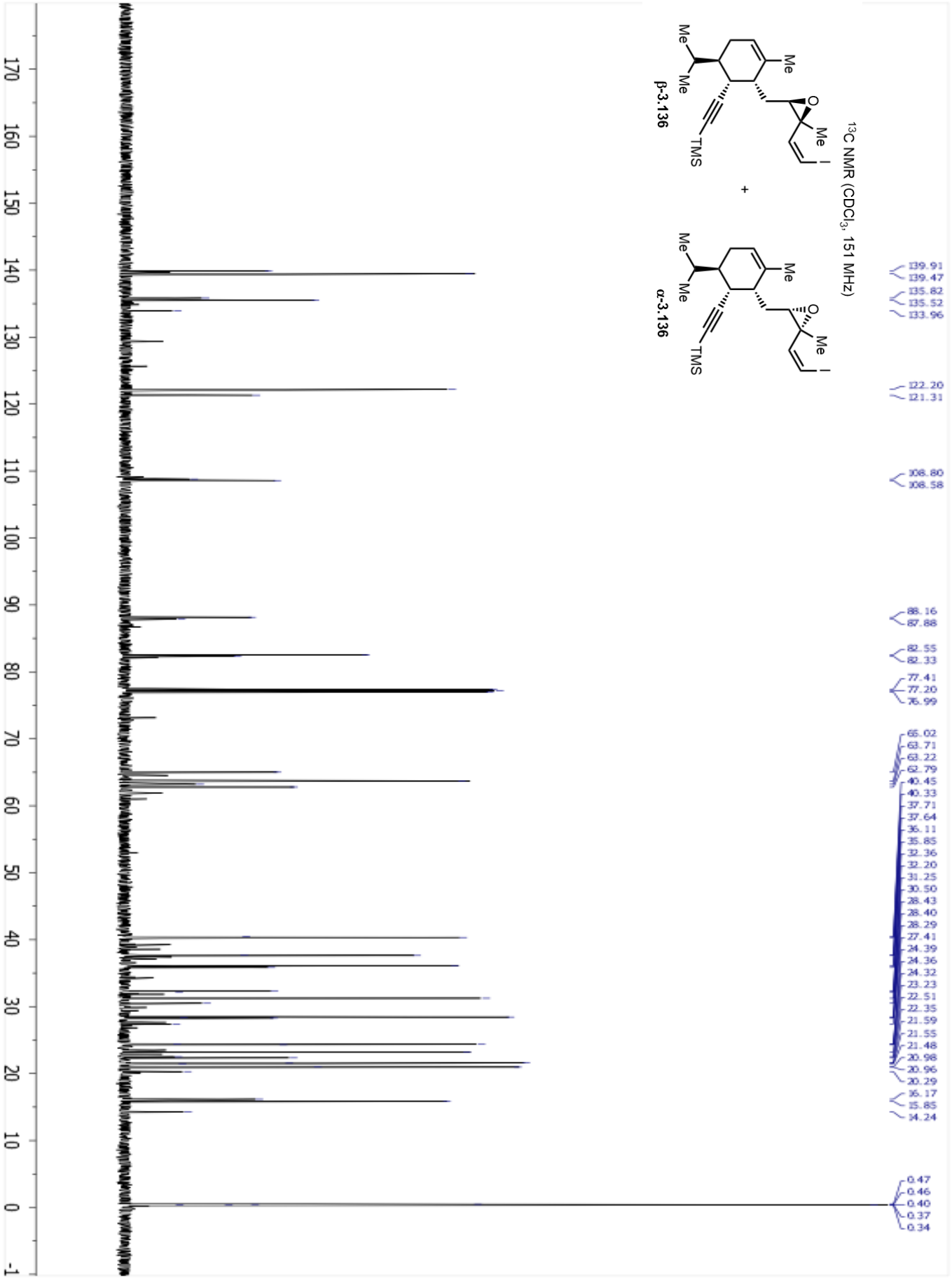
+

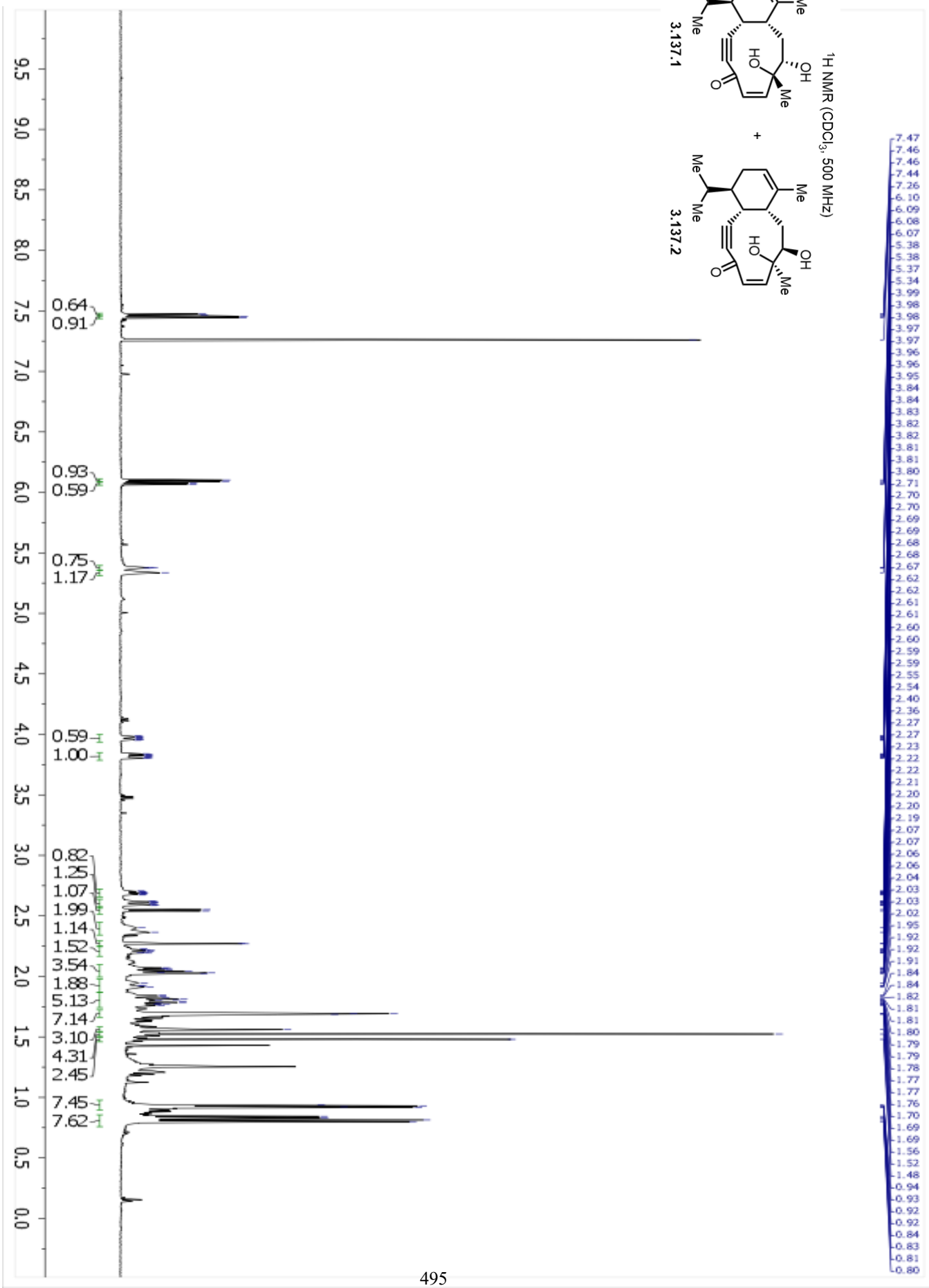
α-3.131

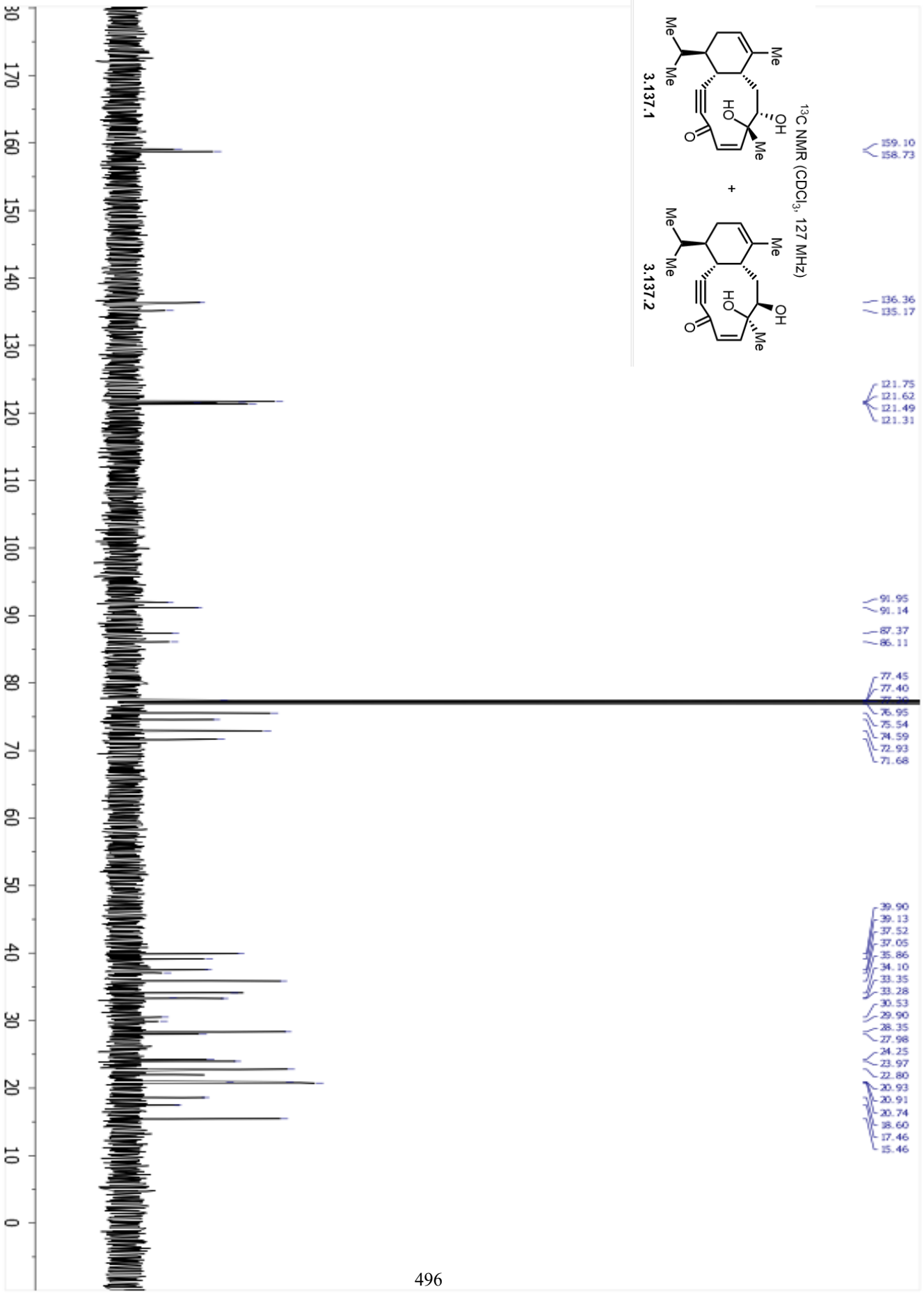

9.40
9.39
7.26
2.61
2.60
2.59
2.59
2.58
2.39
2.38
2.37
2.37
2.36
2.35
2.33
2.32
2.31
2.30
2.22
2.21
2.21
2.20
2.19
2.19
2.18
2.16
2.15
2.14
2.14
2.13
2.12
2.12
2.11
1.94
1.93
1.92
1.92
1.91
1.90
1.90
1.88
1.87
1.86
1.85
1.84
1.84
1.83
1.77
1.76
1.76
1.75
1.71
1.71
1.67
1.66
1.60
1.59
1.58
1.58
1.57
1.56
1.52
1.51
1.51
1.50
1.50
1.49
1.49
1.48
1.48
1.47
1.41
1.39
0.91
0.90
0.88
0.81
0.79
0.78
0.77
0.14
0.14
0.12
^{1}H NMR ($CDCl_3$, 600 MHz)
Me
O
O
Me
Me
TMS
Me
Me
β-3.133
+
Me
O
O
Me
Me
TMS
Me
Me
α-3.133
0.98
0.47
1.52
0.52
1.00
1.54
2.60
0.60
1.58
1.63
1.12
2.03
1.89
3.17
0.69
1.14
1.81
3.06
5.10
4.72
13.88
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
491


β-3.133
α-3.133
Me
Me
Me
TMS
O
Me
O
+
^{13}C NMR ($CDCl_3$, 151 MHz)
200.62
200.43
134.70
133.97
123.13
122.46
108.16
107.95
89.02
88.61
77.41
77.20
76.99
65.73
65.07
63.70
63.37
41.25
40.62
37.75
37.60
36.06
35.92
30.39
28.83
28.39
28.37
24.34
24.26
22.74
22.73
22.57
20.87
16.01
15.99
15.93
15.59
0.30
0.26
0.20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


β-3.136
α-3.136
TMS
Me
Me
Me
Me
O
+
^{1}H NMR ($CDCl_3$, 600 MHz)
1.00
0.52
0.97
0.51
1.04
0.42
0.45
1.01
1.73
2.25
1.85
2.86
6.89
2.05
1.96
4.85
5.57
4.82
4.23
9.87


β-3.136
+
α-3.136
Me
Me
Me
O
TMS
^{13}C NMR ($CDCl_3$, 151 MHz)
139.91
139.47
135.82
135.52
133.96
122.20
121.31
108.80
108.58
88.16
87.88
82.55
82.33
77.41
77.20
76.99
65.02
63.71
63.22
62.79
40.45
40.33
37.71
37.64
36.11
35.85
32.36
32.20
31.25
30.50
28.43
28.40
28.29
27.41
24.39
24.36
24.32
23.23
22.51
22.35
21.59
21.55
21.48
20.98
20.96
20.29
16.17
15.85
14.24
0.47
0.46
0.40
0.37
0.34
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1


3.137.1
+
3.137.2
^{1}H NMR (CDCl$_3$, 500 MHz)
0.64
0.91
0.93
0.59
0.75
1.17
0.59
1.00
0.82
1.25
1.07
1.99
1.14
1.52
3.54
1.88
5.13
7.14
3.10
4.31
2.45
7.45
7.62


^{13}C NMR ($CDCl_3$, 127 MHz)
3.137.1
3.137.2
159.10
158.73
136.36
135.17
121.75
121.62
121.49
121.31
91.95
91.14
87.37
86.11
77.45
77.40
76.95
75.54
74.59
72.93
71.68
39.90
39.13
37.52
37.05
35.86
34.10
33.35
33.28
30.53
29.90
28.35
27.98
24.25
23.97
22.80
20.93
20.91
20.74
18.60
17.46
15.46