Platnium-Catalyzed 1,2-Diboration of Cis-Substituted 1,3-Dienes: A Route to Enantioenriched Bifunctional Allylboration Reagents

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PLATINUM-CATALYZED 1,2-DIBORATION OF *CIS*-SUBSTITUTED 1,3-DIENES: A ROUTE TO ENANTIOENRICHED BIFUNCTIONAL ALLYLBORATION REAGENTS

a dissertation

by

GRACE ELIZABETH FERRIS

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GRACE ELIZABETH FERRIS

Dissertation Advisor:

Professor James P. Morken

ABSTRACT: This dissertation describes the first enantioselective 1,2-diboration of *cis*-substituted 1,3-dienes. In the presence of a platinum catalyst and TADDOL-derived phosphonite ligands, both 4,4-disubstituted and mono-*cis*-substituted 1,3-dienes undergo regioselective 1,2-diboration to afford the corresponding 1,2-diols upon oxidation in up to 98:2 er and high yield. By achieving enantioselective 1,2-diboration of 1,3-dienes, a new synthetic route to α-chiral (*Z*)-allylboronate reagents has been developed. In the presence of an aldehyde, these allyl bis(boronate) esters undergo highly diastereoselective allylboration reaction to afford enantioenriched 1,5-homoallylic alcohols bearing all-carbon quaternary centers or *syn*-propionate motifs. In the presence of 1,4-dicarbonyl compounds, the (*Z*)-allylboronates undergo a double allylation reaction to afford cyclohexanols with four contiguous stereocenters in good yield and moderate to excellent diastereoselectivity. The tandem diboration/double allylation has been applied to the total synthesis of pumilaside B aglyon, and the partial synthesis 1β-hydroxy arbusculin A and bromophycolide F.

Dedicated to:

My mother, Robin A. Briggs, for her inspiring strength and perseverance.

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List of Abbreviations

atm: atmosphere

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

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

BDSB: bromodiethylsulfonium bromopentachloroantimonate

BINOL: binapthol

Bn: benzyl

cat: catechol

COD: cyclooctadiene

COSY: correlation spectroscopy

Cy: cyclohexyl

dba: dibenzylidene acetone

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane

DFT: density functional theory

DMAP: 4-dimethylaminopyridine

DMAPP: dimethylallyl diphosphate

DMF: dimethylformamide

dppm: diphenylphosphinomethane

dr: diastereomer ratio

EtOAc: ethyl acetate

ee: enantiomeric excess

eq: equation

equiv: equivalent(s)

er: enantiomer ratio

es: enantiospecificity

G-I: Grubbs' first generation catalyst

G-II: Grubbs' second generation catalyst

GC: gas chromatography

h: hour

HG-II: Hoveyda-Grubbs' second generation catalyst

HRMS: high resolution mass spectroscopy

IPC: *iso*-pinocamphenyl

IPP: isopentenyl disphosphate

IR: infrared spectroscopy

kcal: kilocalorie

L: ligand

LA: Lewis acid

LAH: lithium aluminum hydride

LDA: lithium diisopropylamide

LG: leaving group

M: molar

m-CPBA: *meta*-chloroperbenzoic acid

MEM: methoxyethyoxymethyl

mol: mole

MOM: methoxymethyl

Ms: methanesulfonic acid

nbd: norbornadiene

ND: not determined

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

NMR: nuclear magnetic resonance

NOESY: nuclear overhauser effect spectroscopy

Nuc: nucleophile

o-FBn: *ortho*-fluorobenzyl

PCy_3: tricyclohexyl phosphine

Ph: phenyl

pin: pinacol

PMA: phosphomolybdic acid

PMB: *para*-methoxybenzyl

PPTS: pyridinium toluene-4-sulfonate

p-TsOH: *para*-toluene sulfonic acid

QUINAP: 1-(2-diphenylphosphino-1-napthyl)isoquinoline

RCM: ring-closing metathesis

ROM: ring-opening metathesis

rr: regioisomer ratio

SFC: supercritical fluid chromatography

SiO_2: silica gel

TADDOL: (4*R*,5*R*)-(-)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol

tart: tartaric acid

TBAF: tetra-*n*-butylammonium fluoride

TBDPS: *tert*-butyldiphenylsilyl

TBS: *tert*-butyldimethylsilyl

TEMPO: 2,2,6,6-tetramethy-1-piperidinyloxyl

TES: triethylsilyl

THF: tetrahydrofuran

Tf: trifluoromethanesulfonyl

TFA: trifluoroacetyl

TFAA: trifluoroacetic acid

TMEDA: tetramethylethylenediamine

TON: turnover number

TPAP: tetrapropylammonium perruthenate

TS: transition state

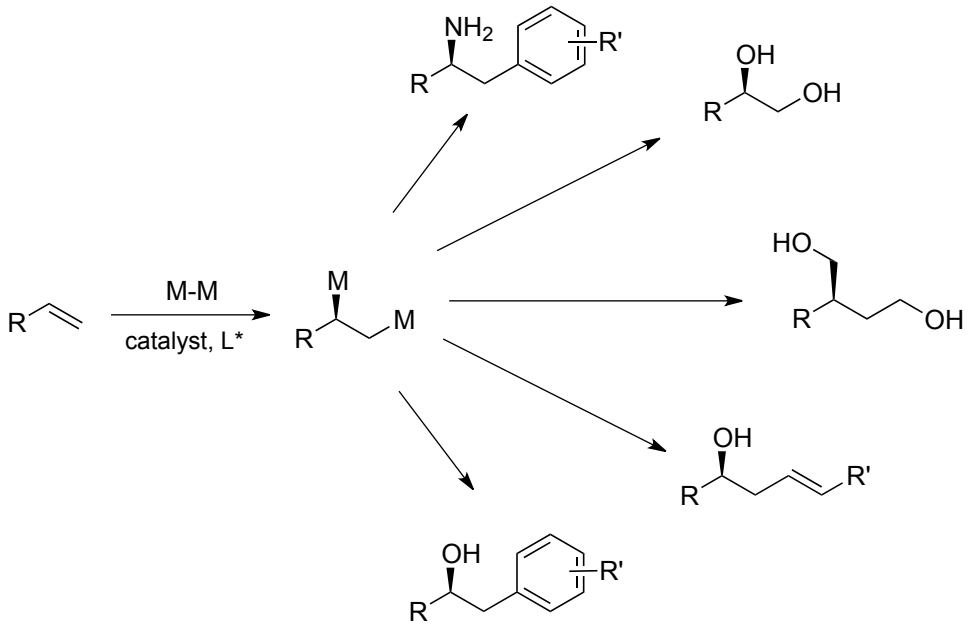
Chapter 1

Development of Enantioselective 1,2-Diboration of *Cis*-Substituted 1,3-Dienes and Tandem Diboration/Allylboration Strategy

1.1. Introduction

The development of catalytic, enantioselective methods for functionalizing molecules has revolutionized organic chemistry. Methods of this type have enabled the synthesis of biologically and medicinally relevant compounds, agrochemicals, and natural products in enantiopure form. Most commonly, asymmetric reactions transform a singular class of prochiral starting material compounds into a specific, more functionalized group of products. Using this strategy, a diverse array of products can only be produced if a unique catalyst system is developed for every desired functional group interconversion. Alternatively, we aim to develop a single method wherein olefin-containing starting materials are converted to enantioenriched, bis(metallated) intermediates by a chiral transition metal complex. The dimetallation products can then be manipulated by taking advantage of previously developed transformations to access a variety of functional group patterns (Scheme 1.1). Thus, the development of a single, catalytic, enantioselective method provides access to a diverse array of products.

Scheme 1.1. Dimetallation of Olefins to Access a Diverse Array of Products



A number of dimetallation reagents have been employed to effect bisfunctionalization of olefins, including: disilanes, distannanes, silylboranes, silylgermanes, and borylstannanes.[1] Unfortunately, direct manipulations of C-Sn, C-Ge, and C-Si bonds are somewhat limited. Furthermore, these bimetallic reagents can be toxic and/or cost prohibitive. Diboron compounds offer several advantages over alternative dimetallation reagents. First, the reactions of organoboronates are both expansive and extremely well developed. In addition, diboron compounds are significantly less toxic and less expensive than their Sn, Ge, and Si counterparts, making them ideal for both academic and industrial settings. Lastly, the ligands on diboron reagents may be readily tuned to achieve the desired balance of stability and reactivity.

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[1] (a) Burks, H. E.; Morken, J. P. *Chem. Comm.* **2007**, 4717. (b) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. (c) Obora, Y.; Tsuji, Y.; Kakehi, T.; Kobayashi, M.; Shinkai, Y.; Ebihara, M.; Kawamura, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 599. (d) Onozawa, S. Y.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389.

The reactivity profile of organoboranes makes them extremely valuable intermediates in organic synthesis. Trivalent boron compounds are capable of acting as Lewis acids due to their empty p-orbital, which allows for coordination with a Lewis basic nucleophile. If the nucleophile has a pendant leaving group, the intermediate "ate" complex can undergo a stereoretentive 1,2-metallate rearrangement with concomitant leaving group expulsion to reveal the nucleophile-inserted product (Scheme 1.2, eq. 1). Using this method, organoboron compounds have successfully been converted to the corresponding alcohols,[2] amines,[3] phosphines and sulfides.[4] When carbon nucleophiles are employed, the corresponding homologated products can also be synthesized.[5] Alternatively, the nucleophilic "ate" complex can be trapped with an external electrophile (eq. 2). This method gives rise to the stereoinverted product and has been successfully used to install halogen, diamide, and carbon functionality.[6] In addition to the metallate-rearrangement mode of reactivity, organoboron compounds also participate in transmetallation reactions and thus are used extensively in transition-metal catalyzed cross-coupling reactions (eq. 3).[7]

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[2] (a) Zweifel, G.; Brown, H. C. *Org. React.* **1963**, *13*, 1. (b) Brown, H. C.; Snyder, C.; Subba Rao, B. C.; Zweifel, G. *Tetrahedron* **1986**, *42*, 5505. (c) Kabalka, G. W.; Wadgaonkar, P. P.; Shoup, T. M. *Organometallics* **1990**, *9*, 1316.

[3] (a) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1973**, *95*, 2394. (b) Brown, H. C.; Kim, K. W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761. (c) Knight, F. I.; Brown, J. M.; Lazzari, D.; Ricci, A.; Blacker, A. J. *Tetrahedron* **1997**, *53*, 11411. (d) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J.* **2000**, *6*, 1840. (e) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449. (f) Zhu, C.; Li, G.; Ess, D. H.; Falk, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253.

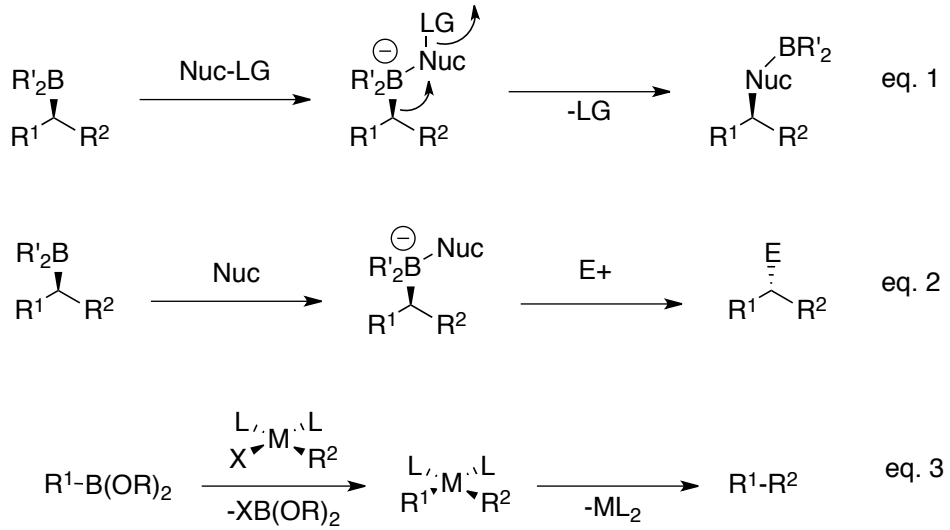
[4] Draper, P. M.; Chan, T. H.; Harpp, D. N. *Tetraherdon Lett.* **1970**, *11*, 1687.

[5] (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Chen, A.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, *64*, 9704. (c) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec.* **2009**, *9*, 24.

[6] (a) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16794. (b) Kabalka, G. W. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 888.

[7] (a) Suzuki, A.; Miyaura, N.; Abiko, S.; Itoh, M.; Brown, H. C.; Sinclair, J. A.; Midland, M. M. *J. Am. Chem. Soc.* **1973**, *95*, 3080. (b) Leung, T.; Zweifel, G. *J. Am. Chem. Soc.* **1974**, *96*, 5620. (c) Yamada, K.; Miyaura, N.; Itoh, M.; Suzuki, A. *Synthesis* **1997**, 679. (d) Hara, S.; Dojo, H.; Kato, T.; Suzuki, A. *Chem. Lett.* **1983**, 1125.

Scheme 1.2. Reactivity Modes of Carbon-Boron Bonds



When the boron atom is adjacent to an alkene, a new reactivity pattern is available. These so-called "allylboron" reagents are well known to undergo addition to aldehydes, giving the corresponding homoallylic alcohols (Scheme 1.3).[8] This reaction proceeds with formation of a new carbon-carbon bond and up to two new stereocenters. While this type of allylmetallation reaction can be accomplished with chromium, silicon, indium, potassium, aluminum, magnesium, lithium, zinc, and tin reagents,[9] allylboronic esters are superior because they are generally less toxic and more stable.

The stereochemical outcome for crotylmetal addition to carbonyl compounds is dependent on the Lewis acidity of the metal center. Highly Lewis acidic metals, such as boron, chromium, magnesium, aluminum, and iridium, react through a closed chair-like transition state (Scheme 1.3, eq. 1) and are classified at Type I allylation reagents.[9] With these compounds, the nucleophilicity of the crotylmetal species is enhanced upon

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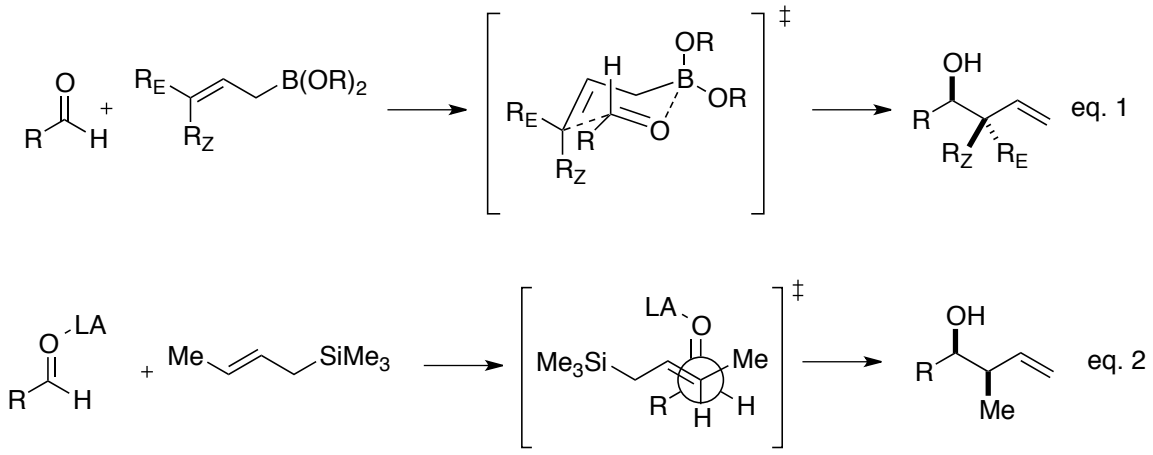
[8] Lachance, H.; Hall, D. G., *Org. React.* **2008**, *73*, 1.
[9] Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

coordination of the Lewis basic carbonyl lone pair with the Lewis acidic metal center. This coordination also enhances the electrophilicity of the carbonyl. Type II reagents possess metals that are unable to directly coordinate the carbonyl oxygen. These reagents include silicon and tin compounds, and require the addition of an external Lewis acid to activate the electrophile. Resulting allylation reactions generally occur through an open, synclinal transition state (eq. 2) and predominantly lead to the *syn* diastereomer of product.[9] The stability of the allylmetal species also has a significant consequence on the stereochemical outcome for crotylmetallations of carbonyl compounds. With careful selection of the ligands on boron, configurationally stable crotylboron reagents can by synthesized in a highly selective fashion. The geometric integrity of the olefin, combined with the closed-chair transition state, make the stereochemical outcome of carbonyl allylborations highly predictable. As such, this reaction has become one of the most widely used methods for carbon-carbon bond formation in organic synthesis.

Scheme 1.3. Stereochemical Outcomes of Closed and Open Transition States in Allylmetallation of Aldehydes



A number of strategies have been developed to synthesize stereodefined allyl- and crotylboron reagents. Some of the most commonly used are illustrated in Scheme 1.4.[10] In the presence of boron-based electrophiles, nucleophilic allymetal reagents (M = Li, K, or Mg) have been shown to undergo addition to provide the corresponding allylboron compound (eq. 1). The utility of this method is sometimes hampered by the stability of the allylic metal precursor, which may undergo metallotropic rearrangement and thereby lead to an isomeric mixture of products. Alternatively, allylic boronates can be generated by addition of stereodefined vinylmetal reagents to halomethyl boronic esters (eq. 2). Unfortunately, some alkenylmetal species exhibit poor nucleophilicity and thus are less effective vinylation reagents. Rather than employing a nucleophilic vinylmetal species, one can also synthesize allylboronates by homologation of electrophilic vinylboronic esters (eq. 3). Recently, the Hoveyda group has disclosed a tungsten-catalyzed cross-metathesis strategy for accessing *Z*-(pinacolato)allylboron reagents from terminal alkenes and (pinacolato)allylboron (eq. 4).[11] Finally, hydroboration of 1,3-dienes has also been demonstrated as a useful method for accessing allylboronates (eq. 5).

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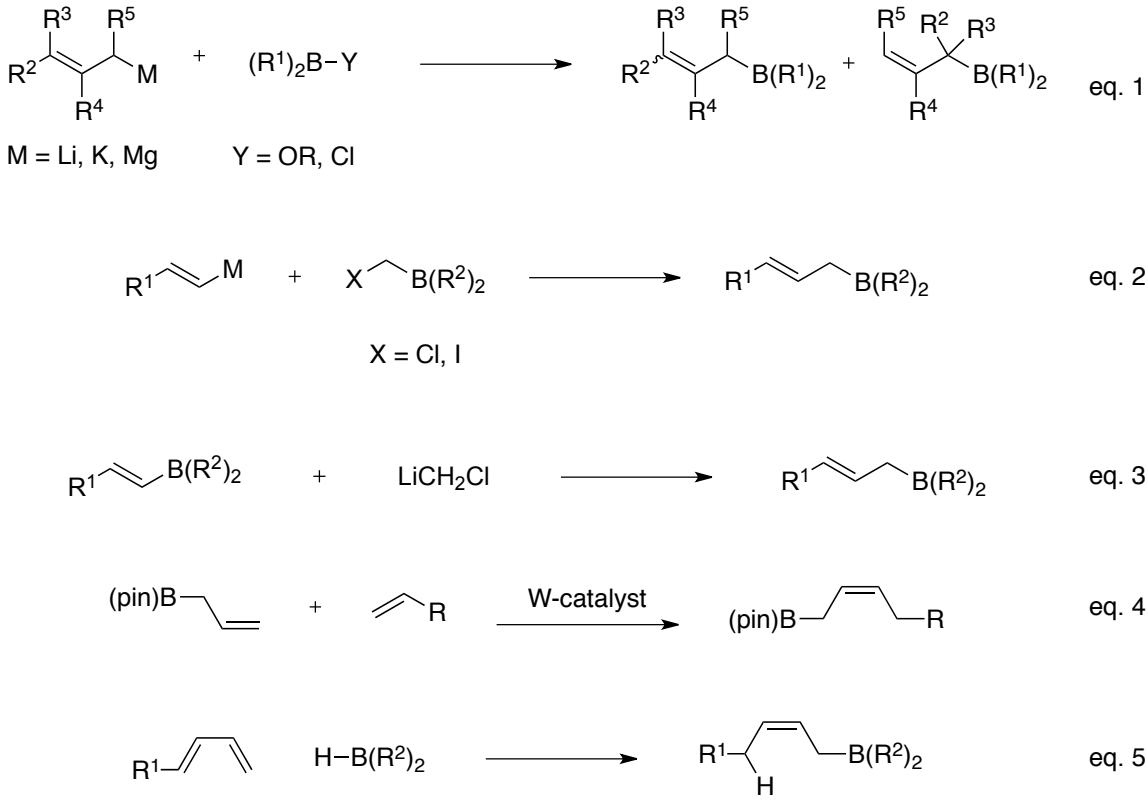
[10] Kennedy, J. W. J.; Hall, D. G. In *Boronic Acids;* Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005, pp 241 - 277.
[11] Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026.

Scheme 1.4. General Methods for Allylboronate Synthesis

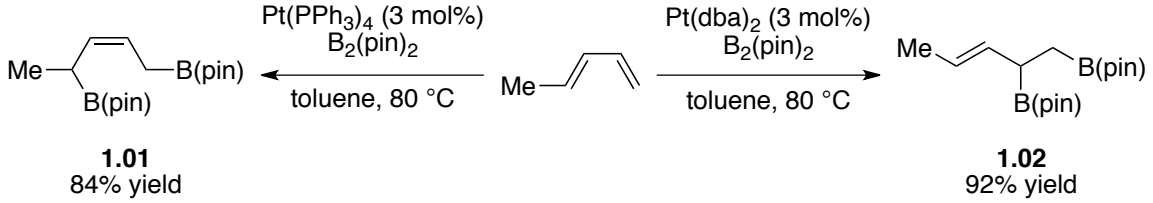


Like diene hydroboration, diene diboration can also be used to synthesize allylboronates. The advantage of diboration is that it allows installation of a second functional group in the product. Transition-metal catalyzed diboration of 1,3-dienes was first realized by Miyaura.[12] In the presence of bis(pinacolato)diboron [$B_2(pin)_2$] and Pt $(PPh_3)_4$, a series of 1,3-dienes underwent selective 1,4-diboration to yield the corresponding (*Z*)-1,4-bis(boronate)esters in high yield (Scheme 1.5). Interestingly, divergent reactivity was observed in the absence or presence of phosphine ligands. In the presence of 3 mol% $Pt(PPh_3)_4$, *trans*-penta-1,3-diene was converted to the (*Z*)-1,4-bis (boronate) ester **1.01** in 84% yield. However, when 3 mol% of $Pt(dba)_2$ was employed,

[12] (a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Comm.* **1996**, 2073. (b) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Comm.* **1997**, 689.

the 1,2-diboration pathway predominated and 1,2-bis(boronate) ester **1.02** was isolated in 92% yield.

Scheme 1.5. Discovery of Platinum-Catalyzed 1,2- and 1,4-Diboration of 1,3-Dienes

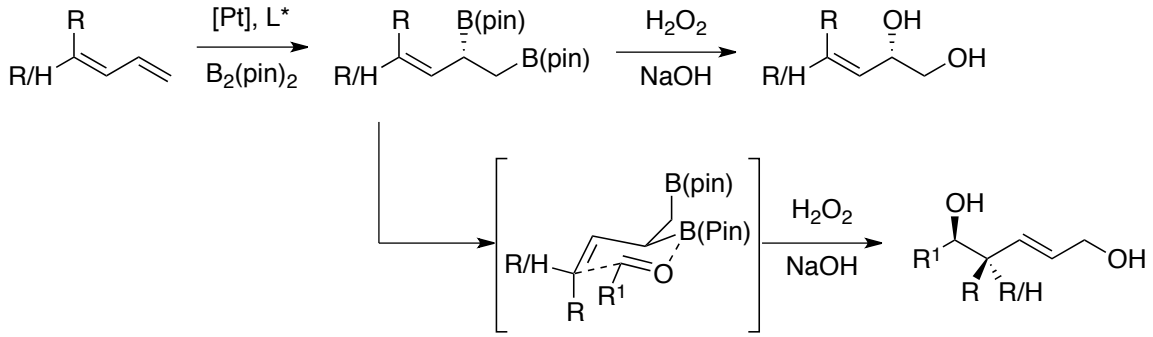


1.01
84% yield

1.02
92% yield

While a number of 1,4-diene diboration methods have been developed since Miyaura's initial discovery, 1,2-diboration is much less studied. In this chapter, I will describe the development of enantioselective 1,2-diboration of *cis*-substituted 1,3-dienes. In addition to providing a complimentary route to enantioenriched 1,2-diols, this method is a powerful means to access stereodefined α-chiral allylboration reagents (Scheme 1.6). The allylboronate generated upon 1,2-diboration can undergo a highly diastereoselective allylboration to produce the corresponding 1,5-homoallylic alcohol. Importantly, the allylboration product bears an additional boronic ester, which can serve as a handle for product manipulation.

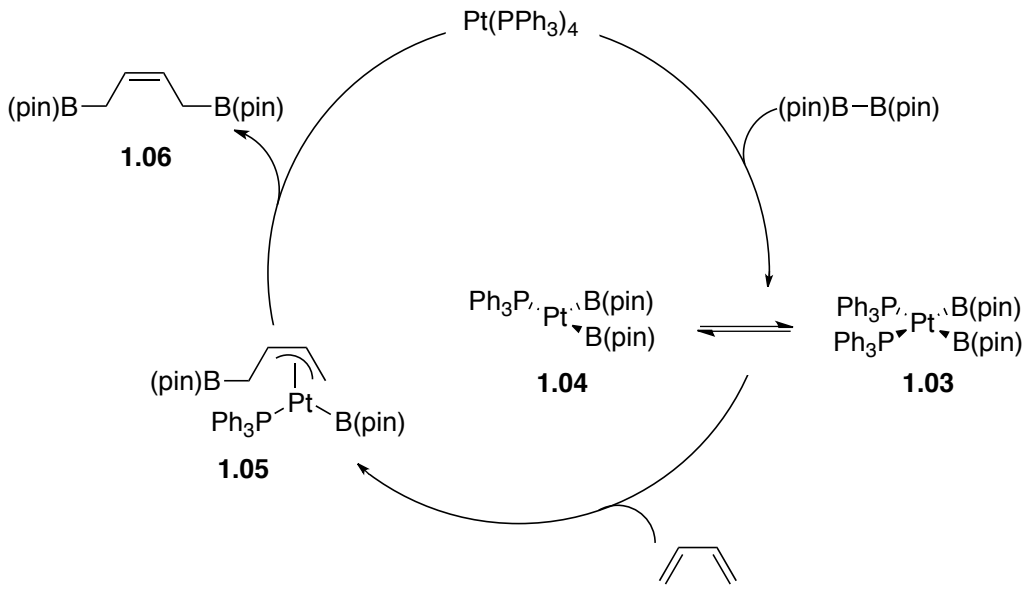
Scheme 1.6. Enantioselective 1,2-Diboration of 1,3-Dienes



1.2. Diene Diboration Background

When Miyaura reported 1,4-diboration of 1,3-dienes, the following mechanism was proposed (Scheme 1.7). First, Pt(0) undergoes oxidative addition into the B-B bond of the diboron reagent to generate bis(boryl)platinum (II) species **1.03**. After ligand dissociation to give the tri-coordinate Pt-II complex **1.04**, the diene coordinates and inserts into the Pt-B bond to generate Pt-π-allyl complex **1.05**. Reductive elimination ultimately occurs on the less-substituted carbon to give the 1,4-bis(boronate)ester **1.06**.

Scheme 1.7. Miyaura's Proposed Mechanism for Platnium-Catalyzed 1,4-Diboration of 1,3-Dienes

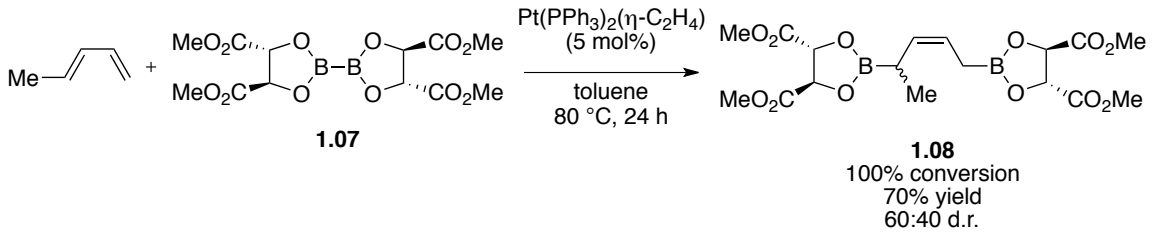


The development of racemic diboration of 1,3-dienes set the stage for the development of enantioselective variants. Just two years after Miyaura's first report, Marder and co-workers[13] realized the first diastereoselective diene diboration reaction

[13] Clegg, W.; Johann, T. R. F.; Marder, T. B.; Normal, N. C.; Orpen, A. G.; Peakman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem. Soc., Dalton Trans.* **1998**, 1431.

by employing optically active diboron compounds bearing chiral diolate backbones. The most selective of these reagents was **1.07**, derived from tartaric acid. In the presence of **1.07** and 5 mol% $Pt(PPh_3)_2(\eta\text{-}C_2H_4)$ at elevated temperature, *trans*-penta-1,3-diene completely converted to 1,4-bis(boronate) ester **1.08**, isolated in 70% yield as a 60:40 ratio of diastereomers (Scheme 1.8).

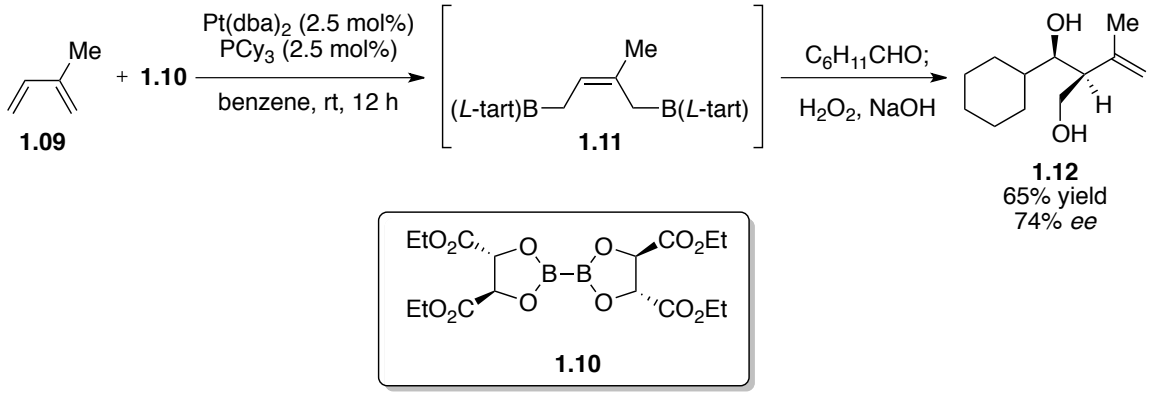
Scheme 1.8. Diastereoselective 1,4-Diboration of 1,3-Dienes with Tartrate-Derived Diboron Reagent



In 2003, the Morken group published a complimentary method for diastereoselective diene diboration with chiral diboron reagents.[14] A series of tartrate-derived boronic esters were examined; ultimately the ethyl ester derivative **1.10** proved to be the most selective for this reaction. Rather than isolating the direct diboration product, the allylbis(boronate)ester **1.11** was treated with an aldehyde, followed by oxidative workup, to yield the the corresponding enantioenriched homoallylic alcohols. Under the optimized conditions, isoprene underwent diboration with **1.10** in the presence of $Pt(dba)_2$ (2.5 mol%) and PCy_3 (2.5 mol%), followed by allylboration to cyclohexanecarboxyaldehyde and subsequent oxidation, to afford 1,3-diol **1.12** in 65% yield and 74% *ee* (Scheme 1.9).

[14] Morgan, J. B.; Morken, J. P. *Org. Lett.* **2003**, *5*, 2573.

Scheme 1.9. Tandem Diastereoselective Diene Diboration/Allylation/Oxidation

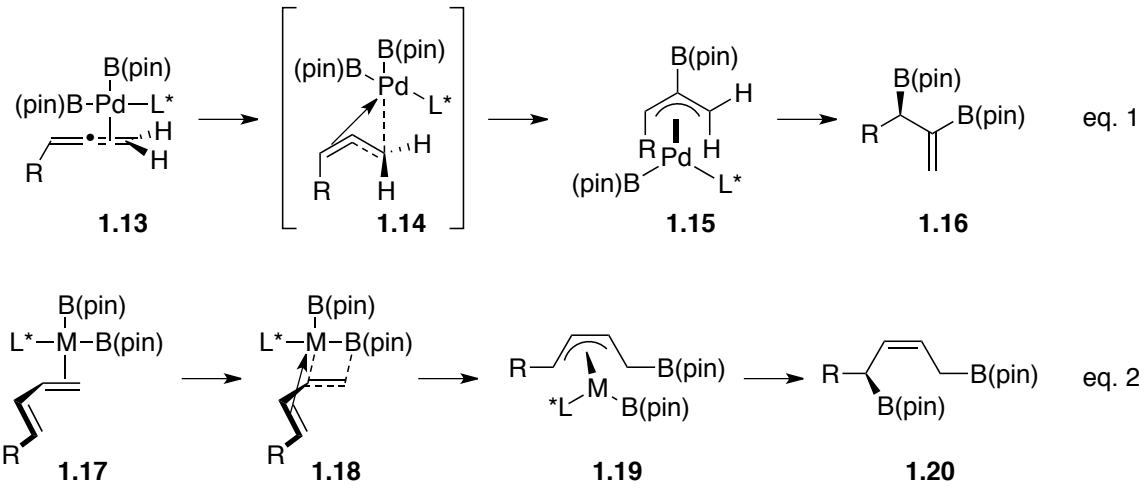


The above-described efforts to effect an enantioselective diene diboration relied on chiral diboron reagents. While this allowed access to synthetically useful intermediates, it was largely achieved with only moderate stereoinduction and required the use of a stoichiometric chirality source. A more efficient enantioselective diene diboration would instead be achieved through the use of a chiral transition metal catalyst and an achiral diboron reagent. In 2004, the Morken group disclosed enantioselective diboration of prochiral allenes in the presence of $B_2(pin)_2$, Pd(0), and chiral TADDOL-derived phosphoramadite ligands.[15] Mechanistic studies and DFT calculations led to the proposal of the following mechanism: after oxidative addition of Pd(0) with $B_2(pin)_2$, the *cis*-bis(boryl) complex coordinates with the least hindered olefin of the allene (Scheme 1.10, **1.13**). Migratory insertion of the terminal olefin into a Pd-B bond with concomitant rotation of the internal alkene directly produces coordinatively saturated η^3-allyl Pd-complex **1.15**. This alkene rotation allows for π-bonding from the adjacent olefin to develop and stabilize transition state **1.14**. The Pd-allyl intermediate

[15] (a) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328. (b) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.

can then undergo reductive elimination to afford the internal 1,2-diboration product **1.16** (eq. 1). Following this insight, it was hypothesized that 1,3-dienes might also participate in enantioselective diboration under similar conditions due to their potential for transition-state stabilization by the adjacent alkene (eq. 2).

Scheme 1.10. Mechanism for Pd-Catalyzed Enantioselective Allene Diboration and Proposal for Transition-Metal Catalyzed Enantioselective 1,3-Diene Diboration

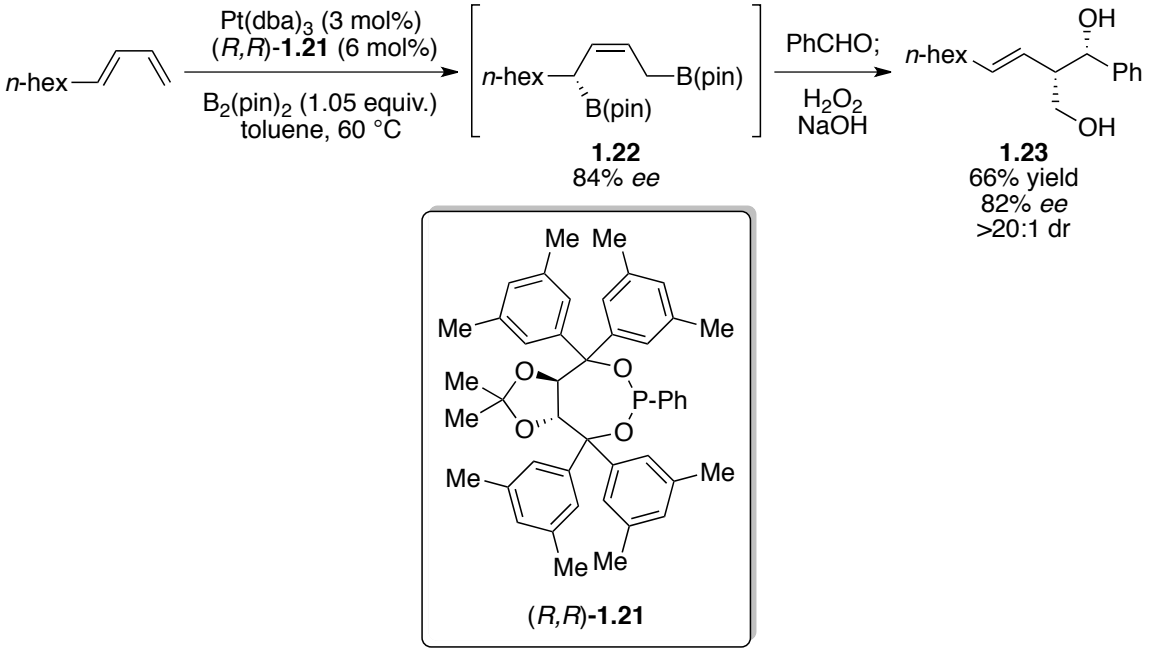


In 2009, the Morken group realized this goal under slightly modified conditions from their Pd-catalyzed enantioselective allene diboration. In the presence of Pt(0), 3,5-xylylTADDOL(phenylphosphonite) **1.21** and $B_2(pin)_2$, *trans*-substituted 1,3-dienes underwent enantioselective diboration in high yield and with excellent levels of enantioselectivity.[16] The chiral allylboronates generated in this process also participate in diastereoselective allylboration of benzaldehyde with good levels of chirality transfer (Scheme 1.11). Platinum-catalyzed diboration of cyclic 1,3-dienes has also been reported

[16] (a) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134. (b) Burks, H. E.; Kliman, L. T., Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 13949.

by the Morken group (Scheme 1.12).[17] Extensive optimization of the ligand scaffold revealed that phosphonite ligand (*R,R*)-**1.24** was superior in effecting high levels of enantioselectivity in the 1,4-diboration of cyclic 1,3-dienes. With this ligand, an array of 2-alkyl- and 2-aryl-substituted 1,3-cyclohexa- and 1,3-cycloheptadienes underwent smooth diboration and oxidation to the corresponding cyclohexenediols in good yield and excellent enantioselectivity. It is worth noting that Ni-catalyzed 1,4-diboration of 1,3-dienes has also been reported,[18] although attempts to develop an asymmetric variant of this reaction is yet to be realized.

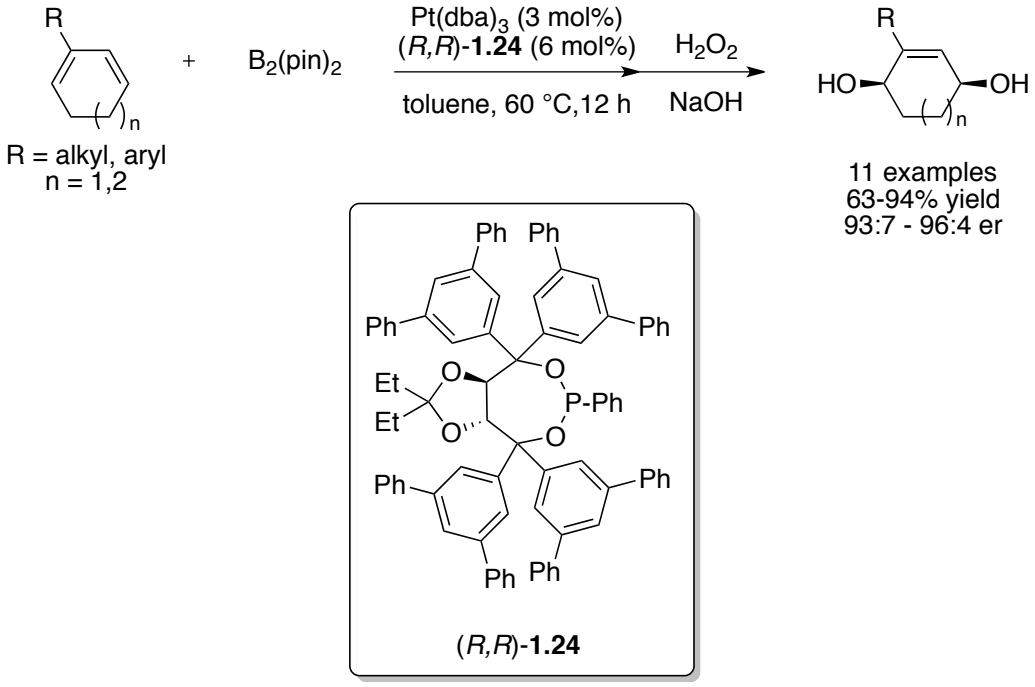
Scheme 1.11. Platinum-Catalyzed Enantioselective 1,4-Diboration of *trans*-Substituted 1,3-Dienes



[17] Hong, K.; Morken, J. P. *J. Org. Chem.* **2011**, *76*, 9102.

[18] Ely, R. J.; Morken, J. P. *Org. Lett.* **2010**, *12*, 4348.

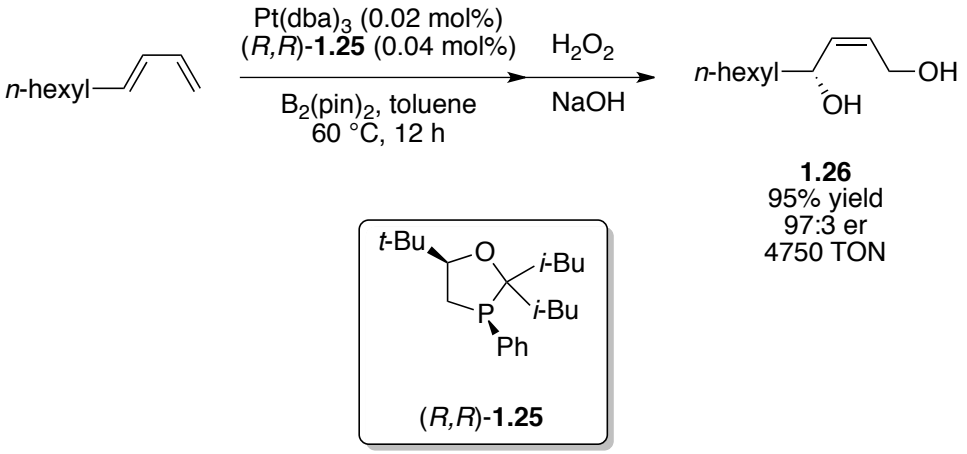
Scheme 1.12. Pt-Catalyzed Enantioselective 1,4-Diboration of Cyclic 1,3-Dienes



After the initial development of enantioselective 1,4-diboration of 1,3-dienes, the Morken group improved on this work by implementing a novel, chiral oxaphospholane ligand **1.25** (Scheme 1.13).[19] This catalyst system proved to be both more selective and more reactive than the previously-developed Pt/TADDOL-phosphonite system. As demonstrated by the diboration of *trans*-deca-1,3-diene, 1,4-diol **1.26** can be isolated in 95% yield and 97:3 er with only 0.02 mol% catalyst loading.

[19] Schuster, C. H.; Li, B.; Morken, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 7906.

Scheme 1.13. Enantioselective 1,4-Diboration of 1,3-Dienes with Platinum-Oxaphospholane Complex



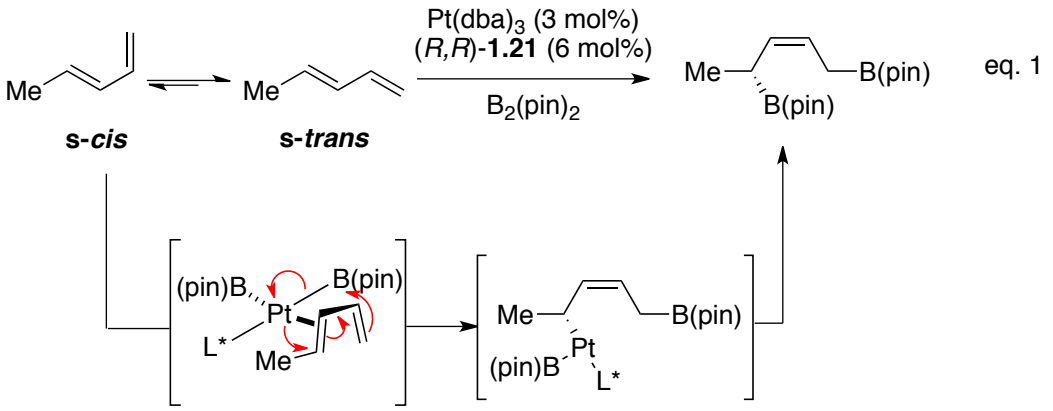
An intriguing observation was made when *cis*-penta-1,3-diene was subjected to the Pt/TADDOL-catalyzed diboration conditions:[16] while <10% of the desired 1,4-diboration product was observed, the regioisomeric 1,2-diol could be isolated in a 54% yield. This turnover in selectivity may be explained by the preferred conformation of the diene isomer. Conjugated butadienes can adopt two different planar conformations; the *s*-cis and the *s*-trans. In the case of buta-1,3-diene, the equilibrium between the two conformers lies 4.0 kcal/mol in favor of the *s*-trans isomer due to steric interactions in the *s*-cis isomer.[20] In the initial mechanistic hypothesis, it was postulated that the diene must adopt the *s*-cis conformation in order for 1,4-diboration to occur;[21] for *trans*-1,3-dienes the *s*-cis conformation is energetically accessible under the reaction conditions (Scheme 1.14, eq. 1). However, in the case of *cis*-penta-1,3-diene, $A^{1,3}$-strain contributes

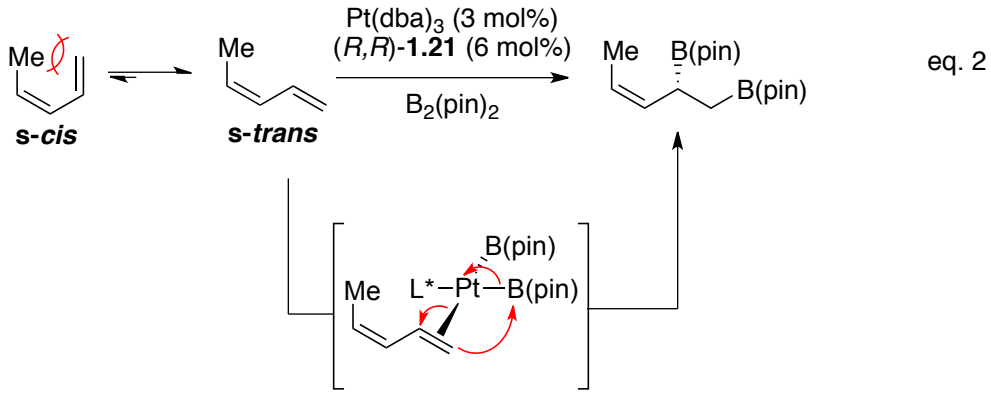
[20] Anslyn, E. V.; Dougherty, A. D. *Modern Physical Organic Chemistry;* Mudzek, J., Ed.; University Science Books: California, 2006: p 115.

[21] (a) Hughes, R. P.; Powell, J. *J. Am. Chem. Soc.* **1972**, *94*, 7723. (b) Hughes, R. P.; Powell, J. *J. Organometal. Chem.* **1972**, *34*, C51.

an additional 4 kcal/mol penalty for the *s*-cis conformer, rendering the *s*-trans conformer largely inaccessible. As a result, 1,2-diboration predominates when *cis*-substituted dienes are employed to generate a motif reminiscent of the products of alkene diboration (eq. 2).

Scheme 1.14. Proposed Insertion Mechanism for Pt-Catalyzed Diboration of *Trans*- and *Cis*-1,3-Dienes

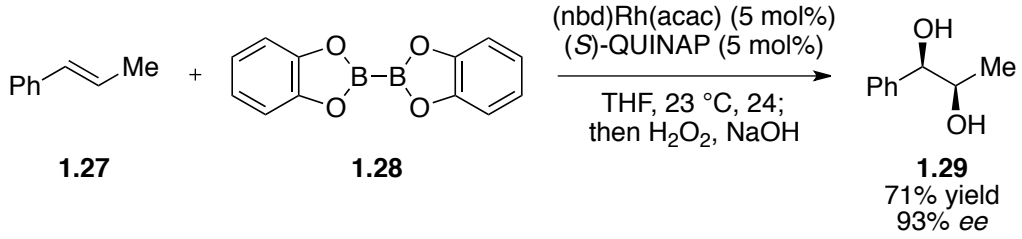




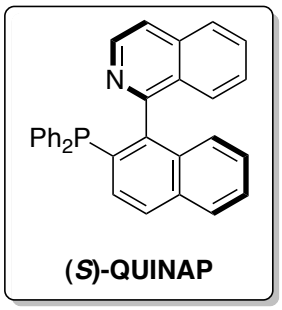
1.3. Enantioselective Alkene Diboration Background

The first enantioselective diboration of alkenes was developed by the Morken group.[22] In the presence of a Rh(I)-QUINAP complex and $B_2(cat)_2$ (**1.28**), a number of internal and terminal alkenes underwent diboration to afford the corresponding enantioenriched 1,2-diols after oxidation (Scheme 1.15). While this catalyst/diboron system accomplished the desired asymmetric transformation, the process was impractical due to the cost of both $B_2(cat)_2$ and the QUINAP ligand. Furthermore, this system was ineffective for highly enantioselective diboration of most α-olefins.

Scheme 1.15. Rh-QUINAP Catalyzed Alkene Diboration with $B_2(cat)_2$



1.27 **1.28** **1.29**
71% yield
93% *ee*



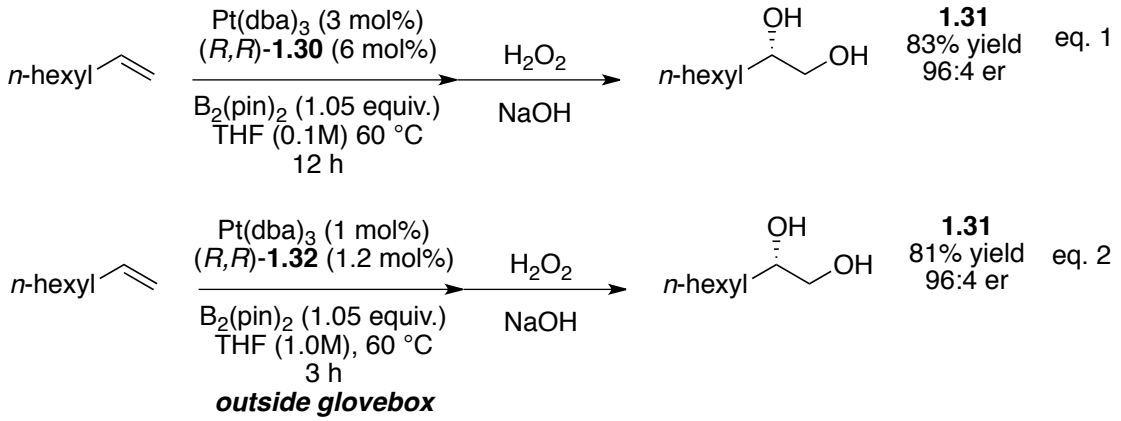
A platinum-catalyzed variant provided enhanced selectivity in the diboration of α-olefins.[23] In the presence of $Pt(dba)_3$ and TADDOL-phosphonite ligand **1.30**, 1-octene underwent facile diboration with $B_2(pin)_2$ to afford diol **1.31** in 83% yield and 92% *ee* (Scheme 1.16, eq. 1). This reaction was a significant improvement on the Rh-catalyzed

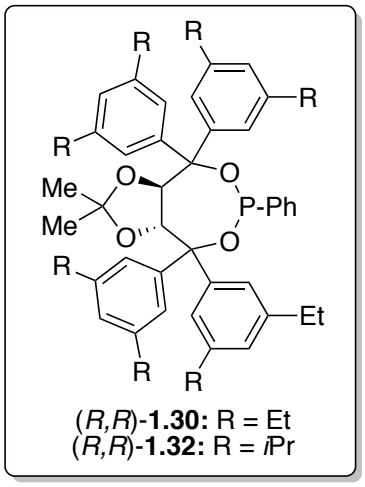
[22] (a) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702. (b) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538.
[23] Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc. 131*, **2010,** 13210.

alkene diboration because lower catalyst loadings and shorter reaction times were needed. Furthermore, the diboron reagent is substantially less expensive compared to $B_2(cat)_2$. More recently, extensive optimization of the catalyst system and reaction conditions revealed that alkene diboration can be achieved in just three hours with excellent levels of enantioselectivity using only 1 mol% $Pt(dba)_3$ and 1.2 mol% **1.32**.[24] It is particularly noteworthy that alkene diboration can now be performed without the use of the glovebox, greatly enhancing the applicability of this method to usage in both academic and industrial settings. Organocatalytic diboration of alkenes has been recently reported by the Fernández group, albiet with only mild stereoinduction.[25]

[24] Coombs, R. J.; Kliman, L. T.; Morken, J. P. *Manuscript submitted for publication.*
[25] Gulyas, H.; Bonet, A.; Sole, C.; Fernández, E. *Org. Biomol. Chem.* **2012**, *10*, 6621.

Scheme 1.16. Platinum-Catalyzed Diboration of Alkenes with $B_2(pin)_2$



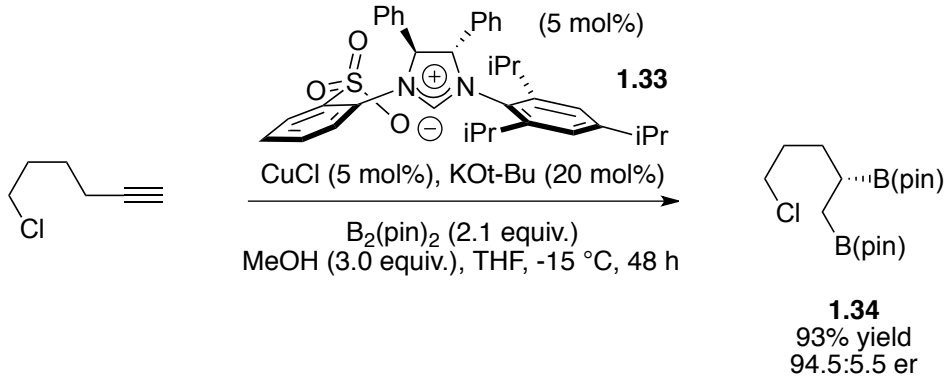


An alternative route to vicinal bis(boronate) esters has been developed by the Hoveyda group.[26] Terminal alkynes were shown to undergo Cu-catalyzed tandem double-hydroboration with $B_2(pin)_2$ with chiral N-heterocyclic carbene (NHC) ligand **1.33** to produce enantioenriched 1,2-bisboronates (Scheme 1.17).[27] The scope of this reaction was proven to tolerate halides, ethers, Boc-protected amines, and propargylic

[26] Jang, W.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859.
[27] (a) Hoveyda, A. H.; Lee, Y.; Jang, H., *J. Am. Chem. Soc.* **2009**, *131*, 18234. (b) Hoveyda, A. H.; Lee, Y., *J. Am. Chem. Soc.*, **2009**, *131*, 3160.

heteroatoms, as well as α- and β-branching. These transformations were highly selective, with enantioselectivities ranging from 93:7 - 97.5:2.5 er.

Scheme 1.17. NHC-Copper-Catalyzed Bis(hydroboration) of Terminal Alkynes



1.4. Asymmetric Allylmetallation Background

Despite the similarity in the product motifs arising from alkene diboration and 1,2-diboration of 1,3-dienes, the diene diboration method is particularly attractive because it generates α-chiral allylboronates. Enantioselective allylmetallation reactions have become one of the most widely employed methods for constructing propionate-type stereodyads and triads.[28] With judicious choice of the metal and fine tuning of the ligand scaffold, highly diastereoselective carbonyl allylmetallations have been achieved. A particularly useful feature of this reaction in the context of target-oriented synthesis is that the products of carbonyl allylation have two useful functional groups (the alcohol and olefin) that can be used to add further complexity to the molecular structure. As such, number of research groups have focused on developing new stereoselective carbonyl allylation reagents and methodologies.[29]

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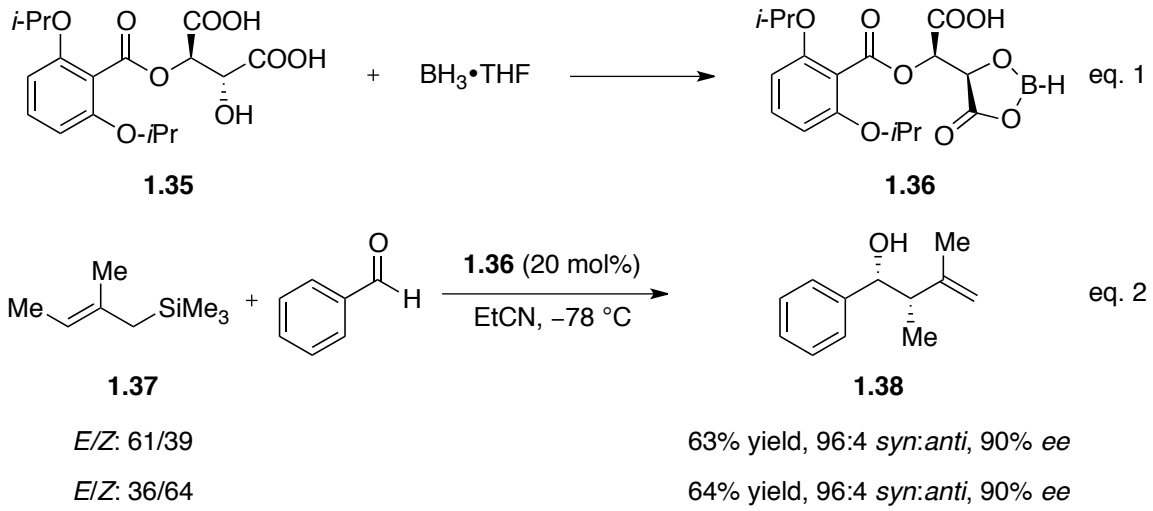
[28] Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013,** DOI: 10.1021/cr400008h
[29] Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

The first catalytic, enantioselective allylmetallation was developed by Yamamoto in 1991, wherein a chiral (acyloxy)borane (CAB, **1.36**) was used to catalyzed the reaction between allylsilanes and aldehydes (Scheme 1.18, eq. 1).[30] Originally developed as a chiral modifier and activator for α,β-unsaturated carboxcylic acids in Diels-Alder reactions,[31] these tartaric-acid derived catalysts proved to be extremely effective for rendering allylsilane addition to achiral aldehydes enantioselective. In the presence of 20 mol% **1.36**, a number of allylsilanes underwent smooth nucleophilic addition to aldehydes in moderate to good yields and good enantioselectivity. Allyltrimethylsilane required increased reaction temperatures in order to achieve full conversion, resulting in lower enantioselectivity of the product homoallylic alcohol (55% *ee* with benzaldehyde.) More electron-rich methyl-substituted crotylsilane **1.37** afforded the desired homoallylic alcohol **1.38** in higher enantioselectivities under less forcing reaction conditions (eq. 2). Regardless of the olefin geometry of the crotylsilane employed, the *syn*-diastereomer of product was favored in all reactions.

[30] Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561.
[31] (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254. (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.

Scheme 1.18. Catalytic Enantioselective Allylsilation of Aldehydes with Chiral (Acyloxy)Borane Catalysts

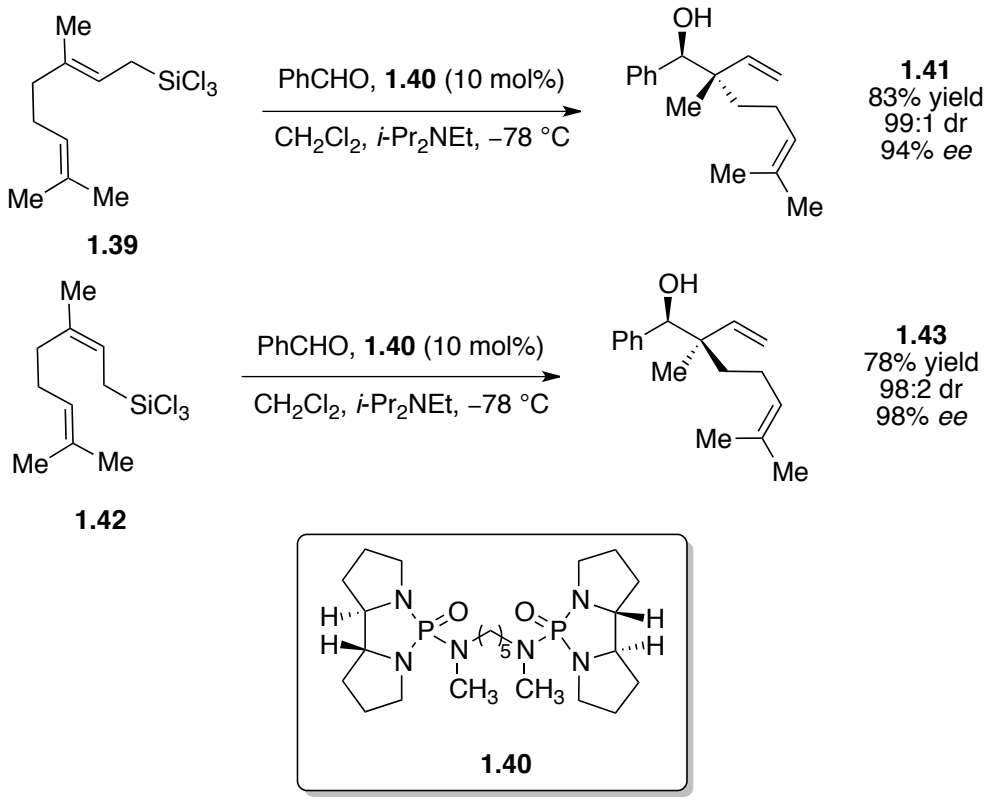


An alternative catalytic aldehyde allylation reaction, developed by the Denmark group in 1994, utilized chiral Lewis bases to render the addition of allyltrichlorosilanes to aldehydes enantioselective.[32] Prior to this development, Kobayashi had reported that DMF could act as a Lewis basic ligand to promote the addition of crotyltrichlorosilane to aldehydes.[33] Denmark discovered that chiral phosphoramide catalysts could also promote addition of allyl- and crotyltrichlorosilanes to aryl aldehydes in good yield, but moderate enantioselectivity (40-60% *ee*). It was also demonstrated that substoichiometric amounts (25 mol%) of the phosphoramide could be used to promote the reaction with only a slight loss in yield and enantiopurity. Extensive optimization of the phosphoramide structure led to a second generation bisphosphoramide catalyst **1.40** (Scheme 1.19).[34] With this catalyst, geraniol-derived crotylsilane **1.39** undergoes highly

[32] Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Gridel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.
[33] (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453. (b) Kobayashi, S.; Nishio, K. *Synthesis* **1994**, 457.
[34] Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488.

selective addition to benzaldehyde, and the corresponding homoallylic alcohol **1.41** bearing an all-carbon stereocenter was isolated in 83% yield, 99:1 *anti:syn* diastereomer ratio, and 94% *ee*. Similarly, the isomeric crotyltrichlorosilane **1.42**, upon addition to benzaldehyde, produced the *syn* isomer in 78% yield, 98:2 diastereomer ratio, and 98% *ee*. Unfortunately, this reaction is incompatible with aliphatic aldehydes and requires the use of excess Hunig's base in order to facilitate catalyst turnover.[35]

Scheme 1.19. Chiral Bisphosphoramide Catalyzed Allylsilation of Benzaldehyde with Isomeric Crotyltrichlorosilanes



Due to the associative nature of the transition state in Type I allylation reactions,[9] it was long thought that the addition of Lewis or Brønsted acids would be disruptive to

[35] Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6419.

this typically highly diastereoselective reaction. Dennis Hall beautifully demonstrated that this was not the case when he revealed that significant rate enhancement can be achieved when allylboronic pinacol esters react with aldehydes in the presence of Sc $(OTf)_3$.[36] Hall postulated that activation occurs through coordination of a pinacol oxygen lone pair to scandium, thereby enhancing the Lewis acidity of the boron and encouraging tighter coordination of the carbonyl lone pair. Since this discovery, both chiral and achiral Lewis and Brønsted acids have been examined for promotion of allylboration reactions.

Hall and co-workers[37] employed Yamamoto's chiral diol-$SnCl_4$ complexes[38] to achieve the first highly enantioselective, Lewis acid-catalyzed allylboration of aldehydes. To highlight the catalyst control exhibited in this reaction, *cis*-crotyl (pinacolboronic ester) **1.45** was reacted with α-methyl aldehyde **1.44** under three different reaction conditions (Scheme 1.20). In the presence of only $SnCl_4$, crotylation proceeds in an 81% yield with a 66:34 dr favoring the *anti-syn* stereotriad (**1.47**). In the presence of 11 mol% (*R,R*)-diol **1.46**, the diastereoselectivity was significantly enhanced; the homoallylic alcohol was isolated in 77% yield and now in a 95:5 *anti-syn*:*syn-syn* ratio. When the mismatched enantiomer (*S,S*)-diol **1.46** was employed, little to no change from the ligandless conditions was observed (68:32 a*nti-syn*:*syn-syn* ratio), although the diol mixture was isolated in diminished yield.

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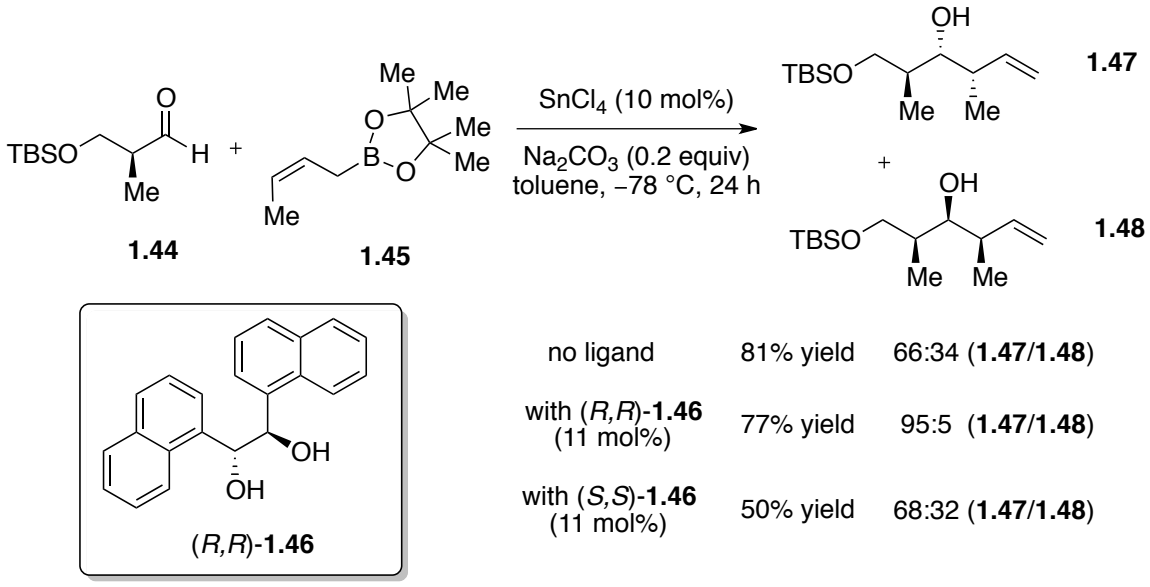
[36] Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586.
[37] Rauniyar, V.; Hall, D. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2426.
[38] Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.

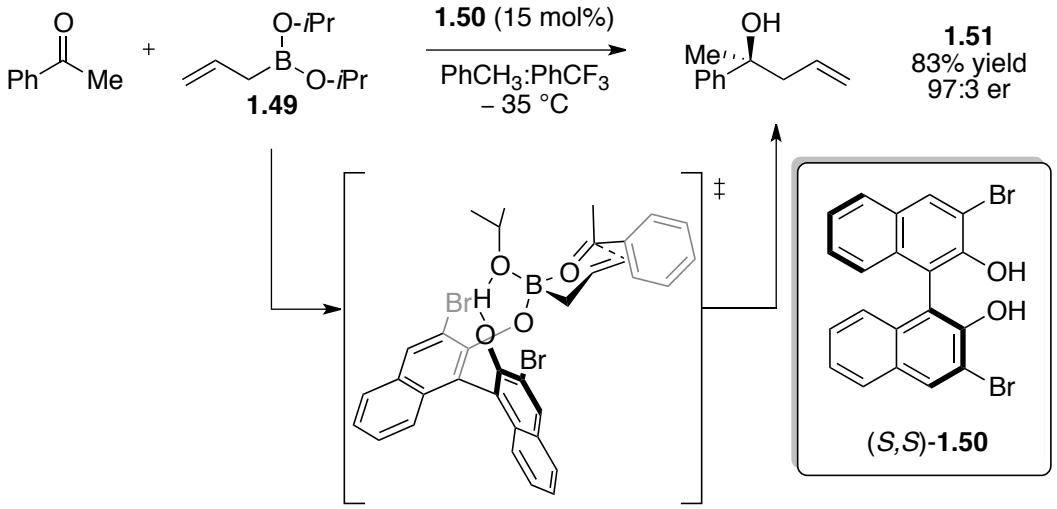
Scheme 1.20. Lewis-Acid Catalyzed Enantioselective Crotylboration of α-Chiral Aldehydes



Chiral diols were also used by Schaus and co-workers, but as Brønsted acid catalysts for the enantioselective allylboration of ketones.[39] Asymmetric ketone allylmetallation is notoriously more challenging than their aldehyde counterpart due to the significantly diminished steric difference between the enantiotopic faces. With allylboronic ester **1.49**, benzophenone undergoes facile allylboration in the presence of 15 mol% enantiopure BINOL-derived catalyst **1.50** to the corresponding tertiary alcohol **1.51** in 83% yield and 97:3 er (Scheme 1.21). In the proposed transition state model, after ligand exchange on the boronic ester, the remaining isopropoxy ligand participates in hydrogen bonding with the naptholic proton, thereby promoting the reaction and directing the facial selectivity.

[39] Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.

Scheme 1.21. Asymmetric Brønsted Acid-Catalyzed Ketone Allylboration

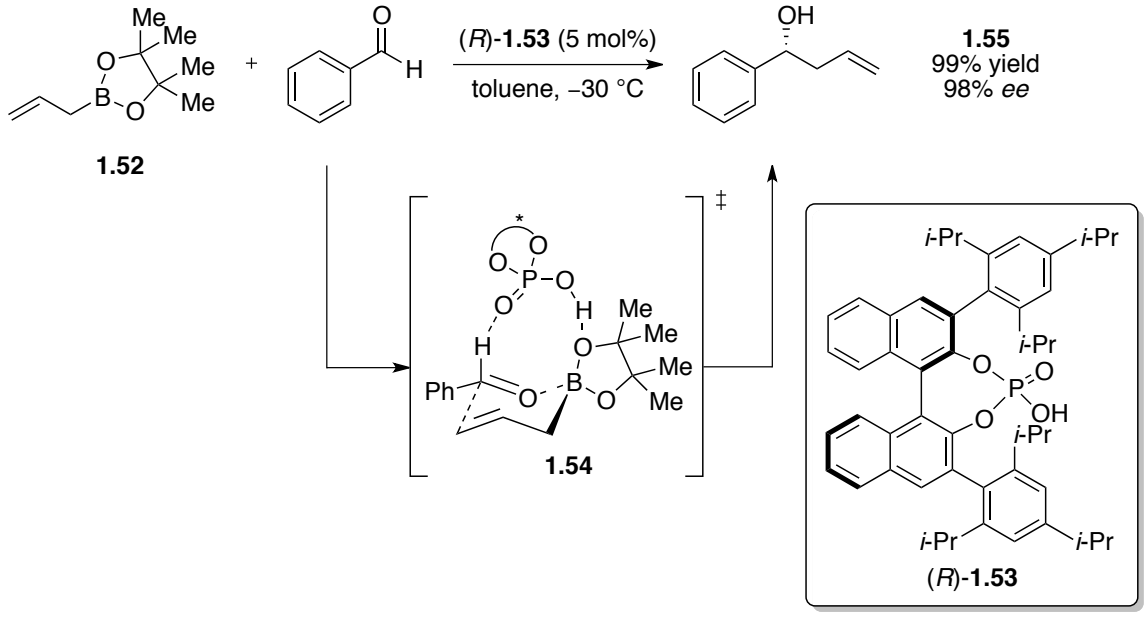


Antilla and co-workers have also developed a highly enantioselective Brønsted acid-catalyzed allylboration reaction which utilizes BINOL-derived phosphoric acid to impart facial selectivity.[40] In the presence of **1.53**, benzaldehyde undergoes allylation with allylB(pin) (**1.52**) to afford homoallylic alcohol **1.55** in near quantitative yield and 98% *ee* (Scheme 1.22). In their initial transition state model, it was proposed that the phosphoric acid participates in a hydrogen bonding interaction with the pseudoequitorial boronate oxygen, thereby enhancing the Lewis acidity of boron and inducing enantiocontrol. Goodman proposed an alternative model where the phosphoric acid stabilizes the transition state by forming two hydrogen bonds: one with the the pseudoaxial oxygen of the boronate, and a second with formyl hydrogen of the aldehyde (**1.53**).[41] This two-point binding motif rigidifies the transition state structure, possibly accounting for the high enantioselectivity observed in the allylboration reaction. DFT

[40] Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884.
[41] Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 2716.

studies published more recently by Antilla and Houk were in agreement with Goodman's hydrogen bonding model.[42]

Scheme 1.22. Chiral Phosphoric Acid-Catalyzed Allylboration of Benzaldehyde



Catalytic enantioselective allylboration of isatins has recently been described by the Hoveyda group.[43] In the presence of only 0.5 mol% chiral amino alcohol **1.57** and 1.5 equivalents of allylB(pin), N-protected isatin **1.56** undergoes allylboration in 1.5 hours to afford homoallylic alcohol **1.59** in 94% yield and 98:2 enantiomer ratio after amide deprotection (Scheme 1.23). To account for the high enantioselectivity observed in this reaction, they propose an allylation transition state in which the substrate is bound to the catalyst through both a hydrogen bond and a Lewis acid/Lewis base coordination (**1.58**). The homoallylic alcohols generated from isatin allylation can potentially be applied to the synthesis of medicinally relevant indolines.

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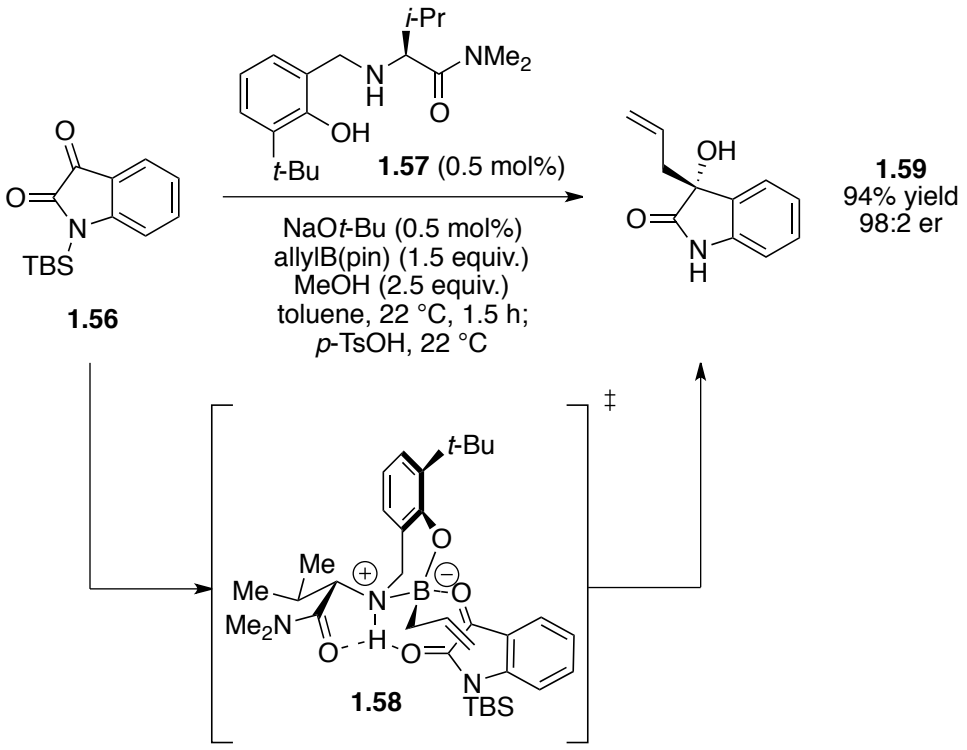
[42] Wang, H.; Jain, P.; Anilla, J. C.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 1208.

[43] Silverio, D.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216.

Scheme 1.23. Enantioselective Isatin Allylboration



α-Substituted allyl- and crotylboronic esters remain a challenge to engage in enantio- and diastereoselective allylboration reactions. The homoallylic alcohols produced with these allylboration reagents often contain a mixture of *E*/*Z* alkene isomers. While high *E*/*Z* selectivity has been achieved with very small[44] and very large[45] diolate ligands on boron, the commonly employed pinacolboronic ester generally results in poor alkene selectivity (Scheme 1.24).[46] A creative solution to this problem was recently developed by Aggarwal,[38] who demonstrated that high diastereoselectivity could be achieved when α-substituted crotyl boronic esters of the type **1.60** (prepared

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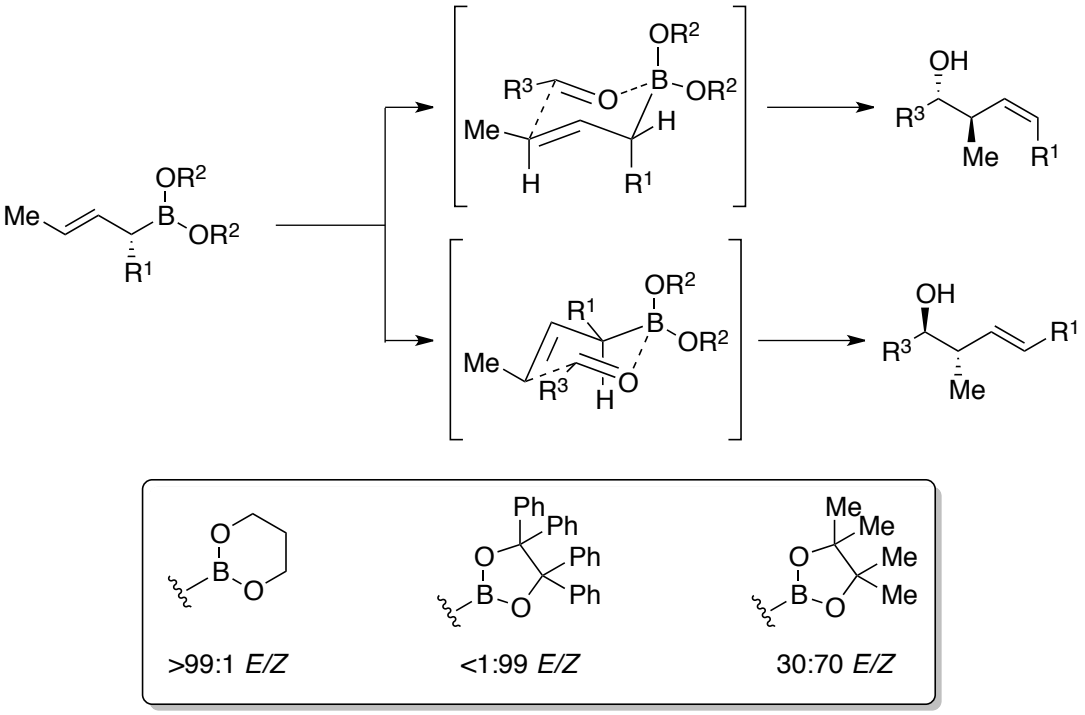
[44] (a) Althaus, M.; Mahmood, A.; Suarez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025. (b)Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644.

[45] (a) Pietruszka, J.; Schone, N. *Eur. J. Org. Chem.* **2004**, 5011. (b) Pietruska, J.; Schone, N. *Synthesis* **2006**, 24. (c) Cmrecki, V.; Eichenaur, N. C.; Frey, W.; Pietruska, J. *Tetrahedron* **2010**, *66*, 6550.

[46] Scheme adapted from: Chen, J. L.-Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 4316.

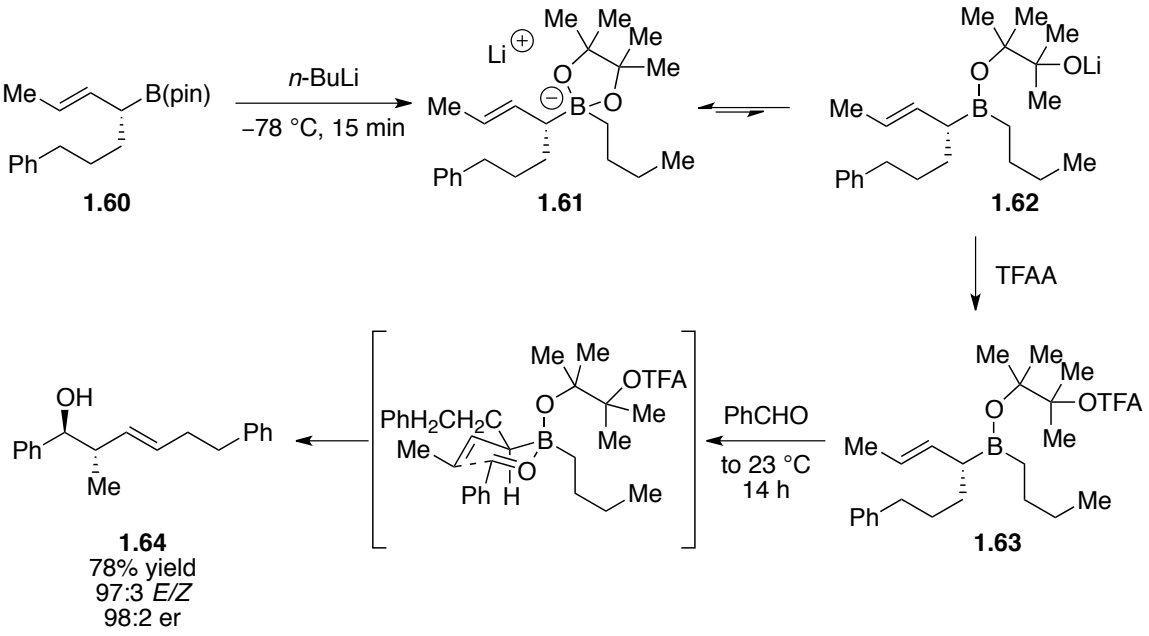
from their previously developed lithiation-borylation strategy)[47] are converted to the corresponding borinic ester **1.62** *in situ* with *n*-butyl lithium (Scheme 1.25). These more reactive, Lewis acidic crotylation reagents undergo facile addition to aldehydes to yield the corresponding homoallylic alcohols in high *E*-selectivity. High *E*-selectivity was only accomplished when the borinic ester intermediate was trapped with TFAA to arrive at allylation-active borinic ester **1.63**.

Scheme 1.24. Diastereoselectivity in Allylboration of α-Chiral Crotyl Boronic Esters



[47] (a) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, 2275. (b) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarawal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491. (c) Webster, M. P.; Partridge, B.; Aggarwal, V. K. *Org. Synth.* **2011**. *88*, 247. (d) Larouche-Gauthier, R.; Fletcher, C. J.; Couto, I.; Aggarwal, V. K. *Chem. Commun.* **2011**, *47*, 12592. (e) Zschage, O.; Hoppe, D. *Angew. Chem. Int. Ed.* **1989**, *28*, 69.

Scheme 1.25. Diastereoselective Allylation with Enantioenriched α-Substituted Crotyl Pinacol Boronic Esters *via* Borinic Ester Intermediate



Each of the above-described examples are significant additions to enantioselective- and diastereoselective allylmetallation technology. We recognized that the 1,2-bis(boronate) esters generated from Pt-catalyzed diene diboration are perfectly situated to participate in an allylboration reaction with carbonyl electrophiles. The direct allylboration product contains a terminal allylboronate, which could be oxidized to the corresponding alcohol or could participate in alternative chain-extending reactions. While traditional allylation reactions generate terminal olefins, this strategy would offer a new platform for product diversification. Furthermore, this method would offer a *syn*-selective, catalytic, asymmetric route to propionate motifs. As such, we were motivated to expand the scope of 1,2-diboration of *cis*-substituted 1,3-dienes and apply the bis

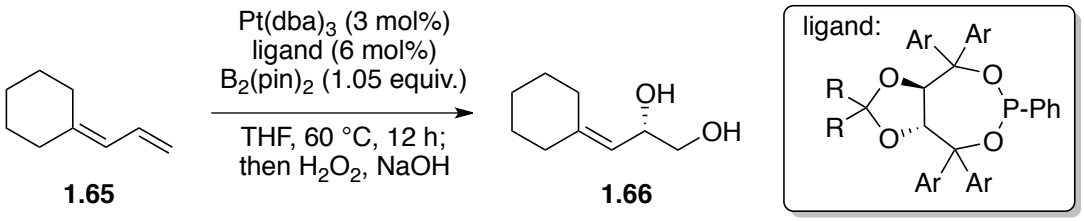
(boronate) intermediates in a tandem diboration/allylation/functionalization reaction sequence for rapid access to polyketide-like products.

1.5. Development of Enantioselective 1,2-Diboration of *cis*-Substituted 1,3-Dienes

We expected that 4,4-disubstituted 1,3-dienes would be competent substrates for 1,2-diboration because, like *cis*-penta-1,3-diene, they contain a *cis*-substituent on the diene terminus. Given the different steric environments between this substrate class and monosubstituted *cis*-dienes, we anticipated that slight modification to the ligand structure might be required to achieve the highest enantioselectivity. As such, an extensive ligand screen was performed on symmetrically substituted diene **1.65**. During the initial studies, a clear correlation was observed between the steric bulk of the ligand and the enantioselectivity of the reaction. It is noteworthy that more sterically hindered 4,4-disubstituted dienes converted solely to the desired 1,2-diboration regioisomer, regardless of the ligand employed for this reaction. This is likely due to the steric strain associated in generating a tertiary Pt-C species in the boryl insertion step of the 1,4-diboration mechanism. With the relatively small 3,5-dimethyl-TADDOL-phenylphosphonite **1.21** (Table 1.1, entry 2), good enantioselectivity (90:10 er) was observed for 1,2-diol **1.66**, albeit with incomplete conversion of the diene and only a 75% isolated yield. We were pleased to find that rigidifying the catalyst structure by increasing the steric bulk on the 3- and 5-substituents of the TADDOL-aryl rings enhanced the enantioselectivity of the diboration reaction (entries 3-6). However, when *t*-butyl-TADDOL-phenylphosphonite (**1.68**) was employed, reaction conversion was

diminished. The decrease in reactivity was likely observed because the bulkiness of ligand inhibited substrate binding and/or olefin insertion (entries 6 & 7). Modifications to the dioxolane backbone improved the enantioselectivity from 97:3 er with acetonide **1.68** up to 99:1 with geminal *i*-propyl substitution **1.70**. Unfortunately, the reaction conversion suffered significantly with the increase in size of the dioxolane. This TADDOL-phosphonite ligand screen revealed that both the *t*-butyl and *i*-propyl ligands exhibited excellent enantioselectivity for 4,4-disubstituted diene diboration, but only **1.32** adequately balanced enantioselectivity and reactivity.

Table 1.1. Ligand Screen for Platinum-Catalyzed Diboration of 4,4-Disubstituted Dienes



1.65 **1.66**

entry	ligand	R	Ar	%conv	%yield	er
1	PCy_3	-	-	81	64	-
2	(*R,R*)-**1.21**	Me	3,5-dimethylphenyl	78	75	90:10
3	(*R,R*)-**1.30**	Me	3,5-diethylphenyl	93	78	95:5
4	(*R,R*)-**1.67**	Me	3,5-diphenylphenyl	90	85	93:7
5	(*R,R*)-**1.32**	Me	3,5-di-*i*Pr-phenyl	90	78	97:3
6	(*R,R*)-**1.68**	Me	3,5-di-*t*Bu-phenyl	75	70	97:3
7[a]	(*R,R*)-**1.68**	Me	3,5-di-*t*Bu-phenyl	80	76	97:3
8	(*R,R*)-**1.69**	Et	3,5-di-*t*Bu-phenyl	65	63	98:2
9[a]	(*R,R*)-**1.69**	Et	3,5-di-*t*Bu-phenyl	64	58	98:2
10	(*R,R*)-**1.70**	*i*-Pr	3,5-di-*t*Bu-phenyl	50	46	99:1

[a] 2.0 equiv $B_2(pin)_2$ were employed.

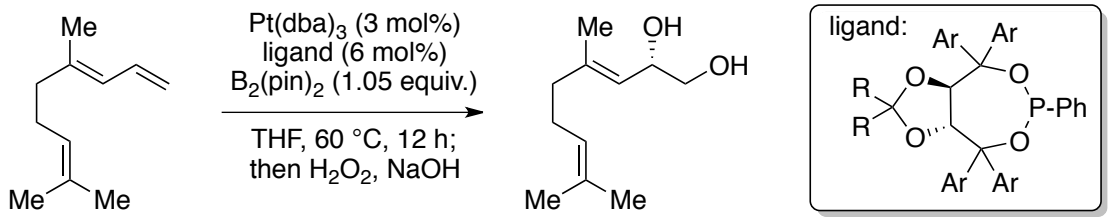
Provided that the end goal of developing an enantioselective 1,2-diboration of *cis*-1,3-dienes was to use the resulting organoboronates in carbonyl allylation reactions, it was pertinent to examine the viability of both symmetrical and unsymmetrical 4,4-disubstituted dienes in the diboration reaction. To this end, geraniol-derived diene **1.71** was examined using an array of phosphine ligands (Table 1.2). Surprisingly, a survey of achiral phosphorous-based ligands revealed that only PCy_3 was minimally effective in the Pt-catalyzed 1,2-diboration of 4,4-disubstituted dienes; only 19% conversion and 12%

isolated yield of the desired product **1.72** could be achieved. Despite significant changes to both the electronic and steric properties of the phosphine ligands, no commercially available monodentate achiral phosphine ligands performed better than PCy_3 (entries 3-7). Much to our delight, the chiral TADDOL-phosphonite ligands previously examined provided efficient formation of **1.72**. As observed with the symmetrical 4,4-disubstituted diene, both the *i*-propyl and *t*-butyl ligands **1.32** and **1.68** were equally effective in rendering this reaction highly enantioselective (98:2 er, entries 8 & 9). Ligand **1.32** proved optimal as it produced higher conversions than **1.68**, a likely result of the steric bulkiness in the 3- and 5-positions on the aryl rings (95% versus 83%, respectively.) Analogous to symmetrically substituted 1,3-dienes, none of the undesired 1,4-diboration regioisomer was observed in these reactions. The difference in reactivity between the achiral monodentate phosphine ligands and TADDOL ligands might be explained by the equilibrium between monoligated and bisligated Pt-phosphine complexes. It is possible that a L_2Pt complex (**I**) was formed with monodentante phosphine ligands (Scheme 1.26). In order for the diene to coordinate, one phosphine ligand must therefore dissociate (**II**). If phosphine re-association is more favorable than binding of the bulky 4,4-disubstituted diene, then diboration cannot occur. Alternatively, the TADDOL ligands examined (with a cone angle >180° as indicated by X-ray crystallographic data)[48] produce a significantly more encumbered ligand sphere when bound to platinum. As a result, it might be more likely for the diene to coordinate rather than a second equivalent from ligand (**III**). It is possible that the bulky, monodentate PCy_3 ligand might also

[48] Kliman, L. T. *Enantioselective Platinum-Catalyzed Diboration of Unsaturated Hydrocarbons: A Versatile Tool for Synthesis.* Doctoral Dissertation, Boston College, Chestnut Hill, MA, 2011.

slightly perturb the equilibrium toward the monoligated complex, thereby allowing diboration to occur to a small extent.

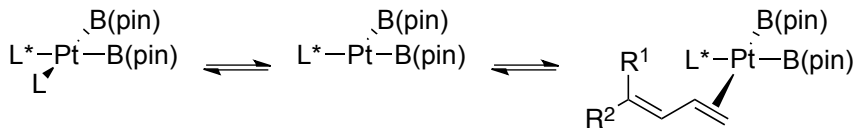
Table 1.2. Ligand Analysis for Platinum-Catalyzed 1,2-Diboration of Unsymmetrical 4,4-Disubstituted Dienes



1.71 **1.72**

entry	ligand	%conv	%yield	er
1	none	0	0	-
2	PCy_3	19	12	-
3	PBn_3	0	0	-
4	$P(NMe_2)_3$	0	0	-
5	$P(OEt)_3$	0	0	-
6	PPh_3	0	0	-
7	PPh_2(*o*-tolyl)	trace	0	-
8	(*R,R*)-**1.32**	95	86	98:2
9	(*R,R*)-**1.68**	83	77	98:2

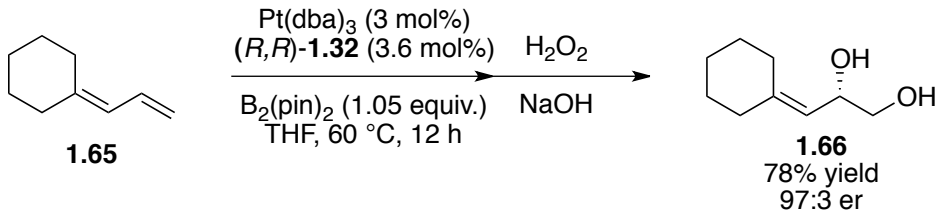
Scheme 1.26. Possible Phosphine-Ligated Platinum Bis(boryl) Complexes



I **II** **III**

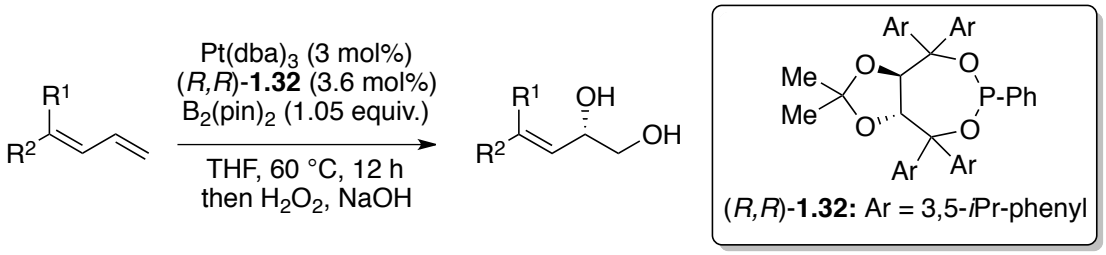
With the optimal ligand in hand, the metal-to-ligand ratio was examined. When the ligand loading was decreased from 6 mol% to 3.6 mol%, **1.65** underwent exclusive 1,2-diboration to give the corresponding 1,2-diol **1.66** in 78% yield and 97:3 er. (Scheme 1.27). In addition, the regioselectivity was unchanged under these reaction conditions.

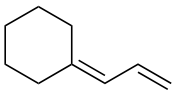
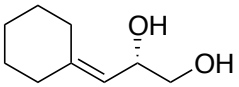
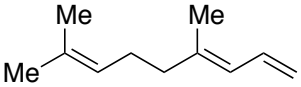
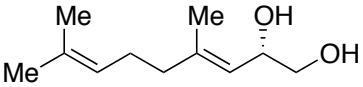
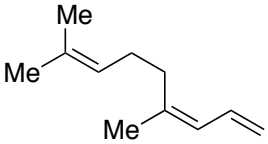
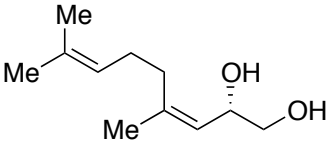
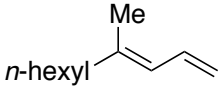
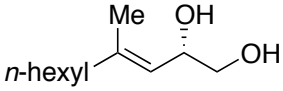
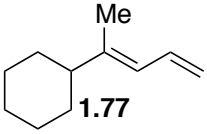
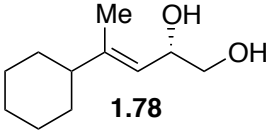
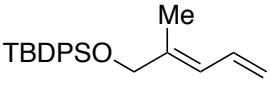
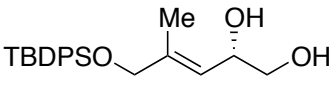
Scheme 1.27. Decreased Metal:Ligand Ratio for 4,4-Disubstituted 1,3-Diene Diboration



With the use of (*R,R*)-**1.32**, a variety of 4,4-disubstituted dienes underwent regioselective 1,2-diboration with high enantioselectivity for all substrates examined (Table 1.3). Isomeric dienes **1.71** and **1.73** (derived from geraniol and nerol, respectively) undergo smooth diboration to give the corresponding 1,2-diols in high yield (78% and 86%) and near perfect enantiocontrol (98:2 er). Furthermore, these substrates demonstrate that remote trisubstituted alkenes embedded within the diene substrate are well tolerated; no diboration of the internal olefin was observed. Both linear and branched aliphatic dienes perform well under the standard reaction conditions (entries 4 & 5). As demonstrated by the diboration of **1.79**, silyl ether functionality is tolerated under the reaction conditions and diol **1.80** can be isolated in 87% yield and 96:4 er.

Table 1.3. Platinum-Catalyzed Enantioselective 1,2-Diboration of 4,4-Disubstituted Dienes

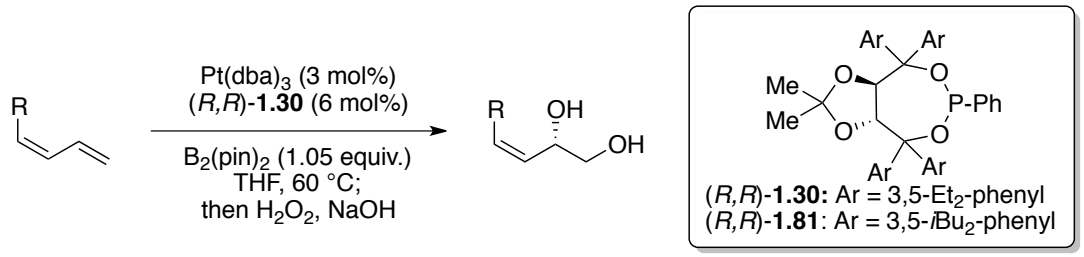


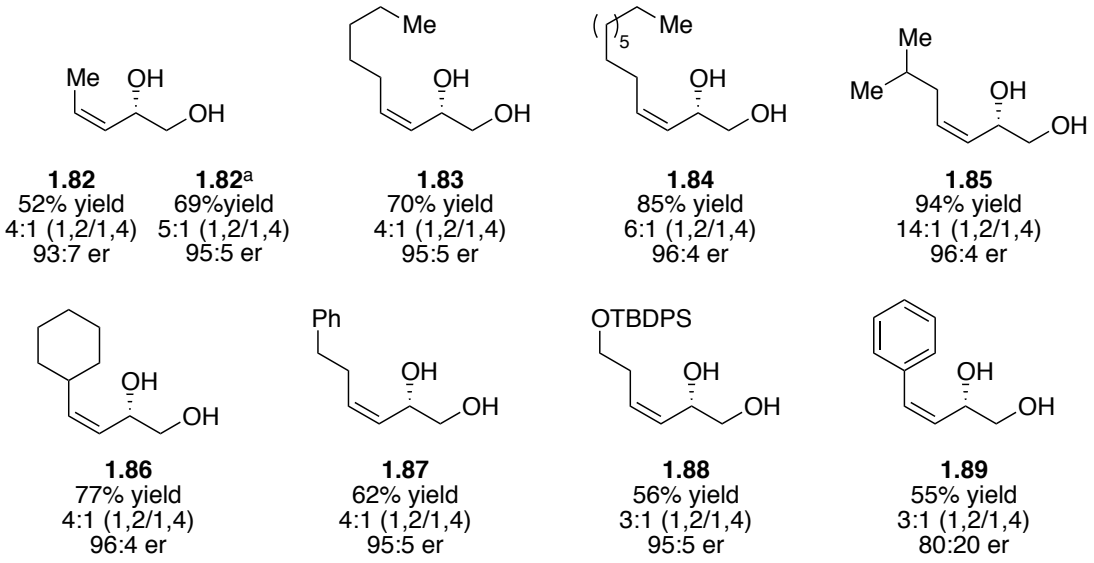
entry	diene	product	%yield	er
1	 **1.65**	 **1.66**	78	97:3
2	 **1.71**	 **1.72**	78	98:2
3	 **1.73**	 **1.74**	86	98:2
4	 **1.75**	 **1.76**	76	97:3
5	 **1.77**	 **1.78**	78	97:3
6	 **1.79**	 **1.80**	87	96:4

Yields reported are of the 1,2-diol; average of two experiments. Enantioselectivity determined by GC analysis of a derivative employing a chiral stationary phase.

With slight modification to the reaction conditions, monosubstituted *cis*-1,3-dienes also participate well in the diboration reaction, albiet with lower regioselectivity (Scheme 1.28). Both ligands (*R,R*)-**1.30** and (*R,R*)-**1.81** proved competent for effecting a highly enantioselective diboration of *cis*-substituted 1,3-dienes. However, given the relative ease of synthesis of **1.30** compared to **1.81**, this ligand was used to more broadly examine the substrate scope of 1,2-diboration of monosubstituted *cis*-1,3-dienes (Scheme 1.28). Under the optimal reaction conditions, it was observed that both the yield and the 1,2-regioselectivity were enhanced as the length of the alkyl chain increased from methyl (52%, 4:1) to pentyl (70%, 4:1) to nonyl (85% yield, 6:1). This trend in regioselectivity may be due to the alkyl chain blocking the catalyst from approaching or prohibiting formation of the s-cis conformation. In addition to linear alkyl chains, those bearing α- and β-branching were well tolerated (**1.86**, 96:4 er, 77% and **1.85**, 94% yield respectively.) Excellent regioselectivity was observed with the *i*-butyl substituted diene, with a 14:1 preference for the 1,2-diol **1.85**. Silyl ethers are compatible with the reaction conditions, although diminished yield and regioselectivity was observed as compared to disubstituted diene **1.79** (**1.88**, 56% yield, 3:1 rr). Planar substrates, such as **1.89**, exhibit poor enantiocontrol in this reaction (80:20 er); this is likely due to decreased facial differentiation by the chiral catalyst. If the phenyl ring is moved out of conjugation with the 1,3-diene, as in **1.87**, high enantioselectivity is restored.

Scheme 1.28. Enantioselective 1,2-Diboration/Oxidation of *Cis*-1,3-Dienes





1.82	**1.82**[a]	**1.83**	**1.84**	**1.85**
52% yield	69%yield	70% yield	85% yield	94% yield
4:1 (1,2/1,4)	5:1 (1,2/1,4)	4:1 (1,2/1,4)	6:1 (1,2/1,4)	14:1 (1,2/1,4)
93:7 er	95:5 er	95:5 er	96:4 er	96:4 er

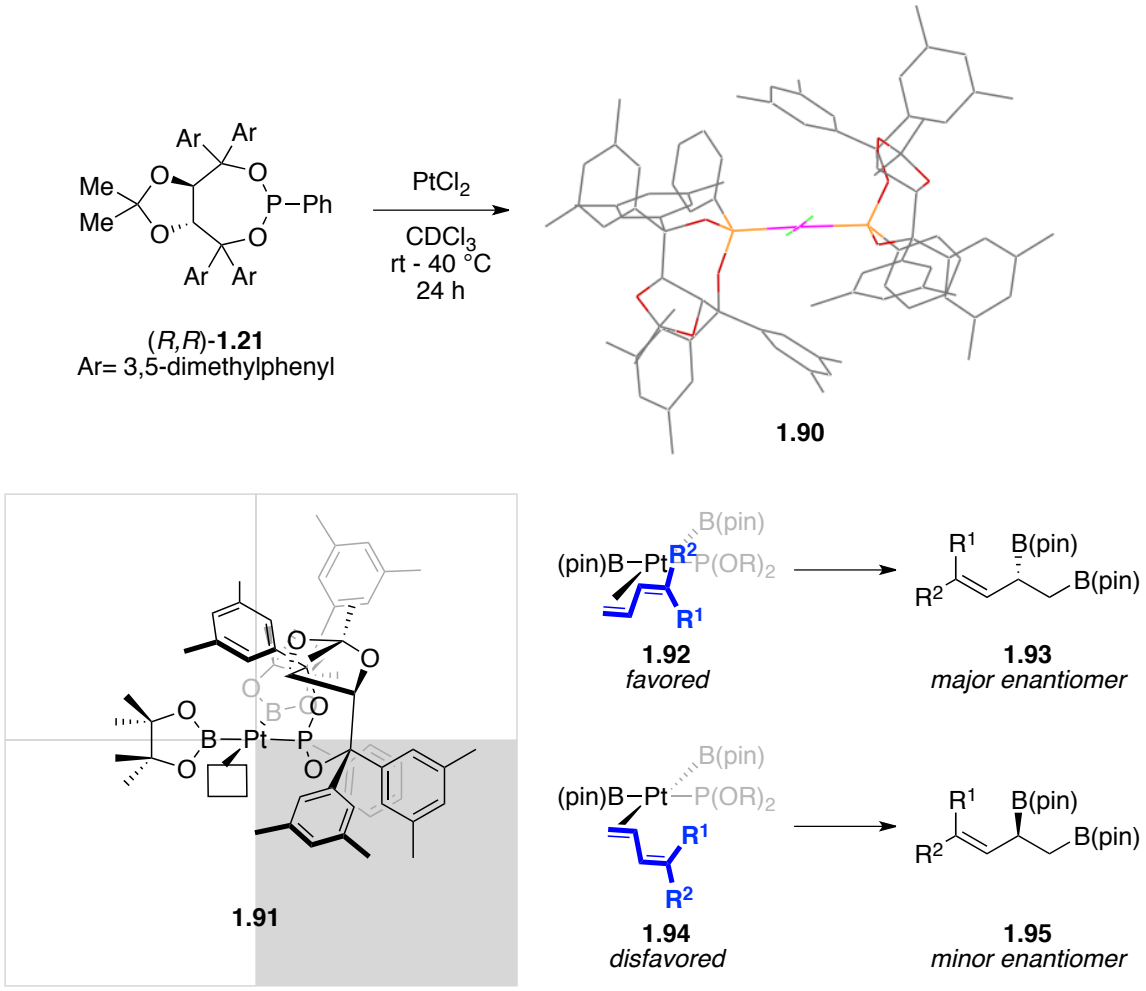
1.86	**1.87**	**1.88**	**1.89**
77% yield	62% yield	56% yield	55% yield
4:1 (1,2/1,4)	4:1 (1,2/1,4)	3:1 (1,2/1,4)	3:1 (1,2/1,4)
96:4 er	95:5 er	95:5 er	80:20 er

Regioselectivity determined from the crude ^{1}H NMR. Yields reported are of the isolated 1,2-diol; average of two experiments. Enantioselectivity determined by GC analysis of a derivative employing a chiral stationary phase. [a] Ligand (*R,R*)-**1.56** was employed in this reaction.

Although limited crystallographic information has been obtained at this time, a stereochemical model has been hypothesized. What is known is that $PtCl_2$ will bind with TADDOL-derived ligand **1.21** to form a bis(ligated) complex **1.90** (Scheme 1.29).[48] In addition, it is well documented that Pt(0)-phosphine complexes undergo oxidative addition with diboron compounds to give the *cis*-bis(boryl) species. In order for substrate binding to occur, only one ligand may be bound to the Pt-complex (a structure that is likely favored compared to the bis(ligated) complex due to the size of the bulky ligand). With this information, we propose that square-planar Pt-II complex **1.91** is

representative of the monoligated, bis(boryl) phosphine complex in solution prior to diene coordination. In order to avoid the aryl ring in the bottom right quadrant of the platinum-phosphonite complex, insertion occurs *via* **1.92** where the majority of the diene is oriented up and away from the protruding aryl ring. Because insertion of the substrate into the Pt-B bond is the stereochemical determining step, this pathway ultimately affords the major enantiomer observed after reductive elimination (**1.93**). If the opposite face of the diene were to bind in the open coordination site on platinum, a penalizing steric interaction would occur (**1.94**). Given the positioning of the diene within the ligand pocket, **1.92** also explains why substitution at the 3- and 5-positions on the aryl ring and the diolate backbone dramatically influenced the enantioselectivity of the diboration.

Scheme 1.29. Proposed Stereochemical Model for Enantioselective 1,2-Diboration of *Cis*-1,3-Dienes



1.6. Development of Tandem Diboration/Allylboration Strategy

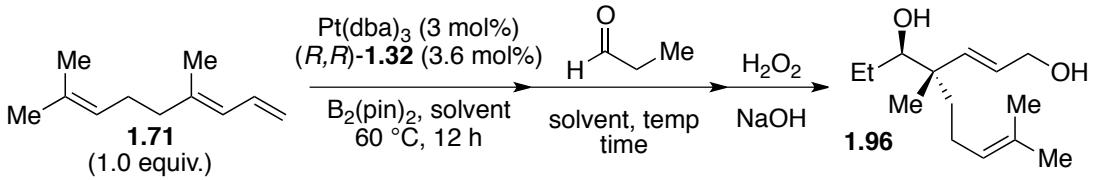
The development of the first catalytic, enantioselective 1,2-diboration of 1,3-dienes provided a new route to α-chiral substituted (*Z*)-allylboration reagents. It was hypothesized that a single-pot diboration/allylation/oxidation sequence might be possible if the diboration intermediate was treated with an aldehyde. If successful, this reaction sequence would provide rapid access to enantioenriched homoallylic alcohols.

4,4-Disubstituted-1,3-dienes would furnish an all-carbon quaternary center adjacent to the alcohol stereocenter when utilized in this tandem strategy. Alternatively, *cis*-1,3-dienes would deliver *syn*-polyketide motifs that are currently difficult to access by asymmetric catalysis. Prior to oxidation, the allylboration product from both substrate classes would contain a newly unveiled allylboronate that could be used to further elaborate the product.

Investigations into the diboration/allylation/oxidation reaction sequence began with geraniol-derived diene **1.71** (as the allyboronate precursor) and propionaldeyde (Table 1.4). When the 1,2-bis(boronate) was stirred with one equivalent of propionaldehyde in CH_2Cl_2 at 40 °C for 8.5 hours, only 38% conversion in the allylation step was observed (entry 1). If the reaction time was extended to 24 hours, conversion improved slightly to 54% (entry 2). Rather than continuing to increase the reaction time, we examined the effect of increasing the temperature in the allylation reaction. To do so, the solvent for both the diboration and allylation was switched to toluene because of its non-coordinating nature and high boiling point. This change also improved the operational simplicity of this reaction. At elevated reaction temperature, even after prolonged reaction times, incomplete conversion for the allylation was observed (entries 3-5). When the aldehyde was added in a three- and four-fold excess to the bis(boronate), high conversions of 90% and 98% were observed (entries 6 & 7). Although the three-fold excess provided the desired conversion in the allylation step, using excess of a valuable aldehyde may not be efficient if this method were to be used in a synthesis context. We were pleased to find that increasing the reaction concentration from 0.3 M to

1.0 M with only one equivalent of propionaldehyde provided 78% conversion in the allylation step (entry 8).

Table 1.4. Optimization of Tandem Diboration/Allylation/Oxidation of 4,4-Disubstituted-1,3-Dienes



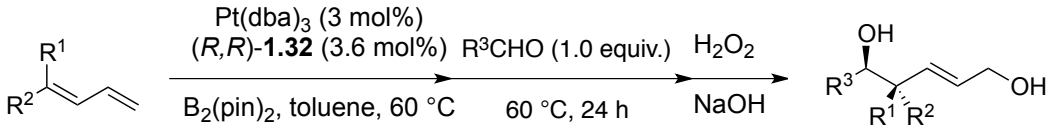
entry	diboration solvent (concentration)	adehyde equiv.	allylation solvent (concentration)	temp. (°C)	time (h)	conversion[a]
1	THF (0.1 M)	1.0	DCM (0.25 M)	40	8.5	38%
2	THF (0.1 M)	1.0	DCM (0.25 M)	40	24	54%
3	toluene (0.3 M)	1.0	toluene (0.3 M)	60	10	29%
4	toluene (0.3 M)	1.0	toluene (0.3 M)	60	24	47%
5	toluene (0.3 M)	1.0	toluene (0.3 M)	100	24	48%
6	toluene (0.3M)	3.0	toluene (0.3 M)	60	24	90%
7	toluene (0.3M)	4.0	toluene (0.3 M)	60	24	>98%
8	toluene (1.0M)	1.0	toluene (1.0 M)	60	24	78%

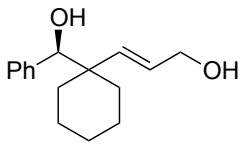
[a] Reaction conversion based on diene.

We next examined the generality of the tandem diboration/allylation strategy for constructing all-carbon quaternary centers (Scheme 1.30). Aromatic aldehydes were excellent reaction partners in this sequence and the corresponding 1,5-diols were isolated in 80-87% yield and ≥96:4 enantiopurity. Products derived from α,β-unsaturated aldehydes were also produced in high yield and enantioselectivity (**1.100** & **1.101**), although aliphatic aldehydes did not react completely in the allylation step and thus

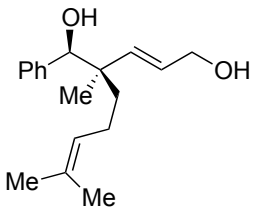
were isolated in diminished, yet synthetically useful, yields (**1.102**, **1.013, 1.95, 1.04, 1.105**). In order to achieve a moderate yield of 58% of **1.105**, the reaction of sterically hindered *i*-butyraldehyde necessitated a 3:1 aldehyde:diene ratio. Nearly every substrate combination that was examined, with the exception of **1.97**, produced the homoallylic alcohol as a single diastereomer. A noteworthy feature of the tandem diboration/ allylation/oxidation sequence when 4,4-disubstituted 1,3-dienes are employed is that either diastereomer of the homoallylic alcohol can be obtained by judicious choice of the alkene geometry in the diene starting material (**1.96** vs. **1.104**, **1.98** vs. **1.99**).

Scheme 1.30. Tandem Diboration/Allylation/Oxidation Sequence of 4,4-Disubstituted-1,3-Dienes: Access to Enantioenriched All-Carbon Quaternary Centers

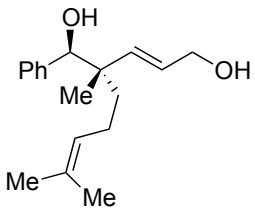




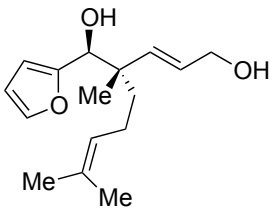
1.97
62% yield
97:3 er



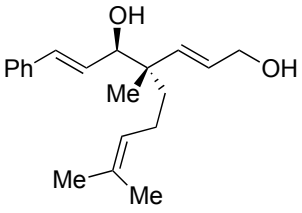
1.98
85% yield
9:1 dr
96:4 er



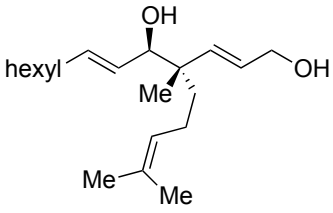
1.99
87% yield
>20:1 dr
97.5:2.5 er



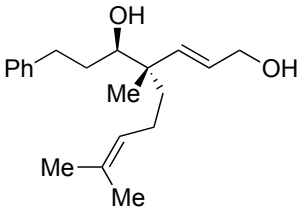
1.100
80% yield
>20:1 dr
96:4 er



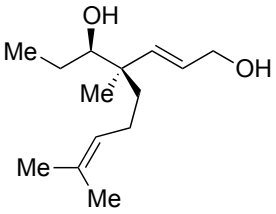
1.101
87% yield
>20:1 dr
98:2 er



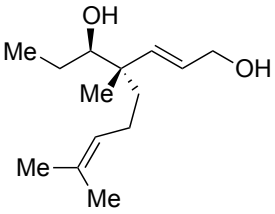
1.102
75% yield
>20:1 dr
97:3 er



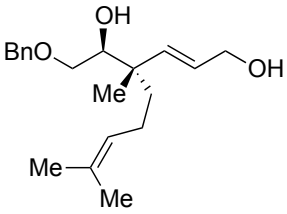
1.103
72% yield
>20:1 dr
97.5:2.5 er



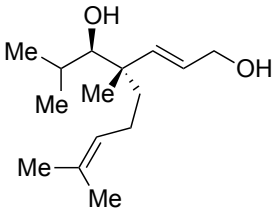
1.104
67% yield
>20:1 dr
96:4 er



1.96
67% yield
>20:1 dr
95:5 er



1.105
74% yield
>20:1 dr
97:3 er

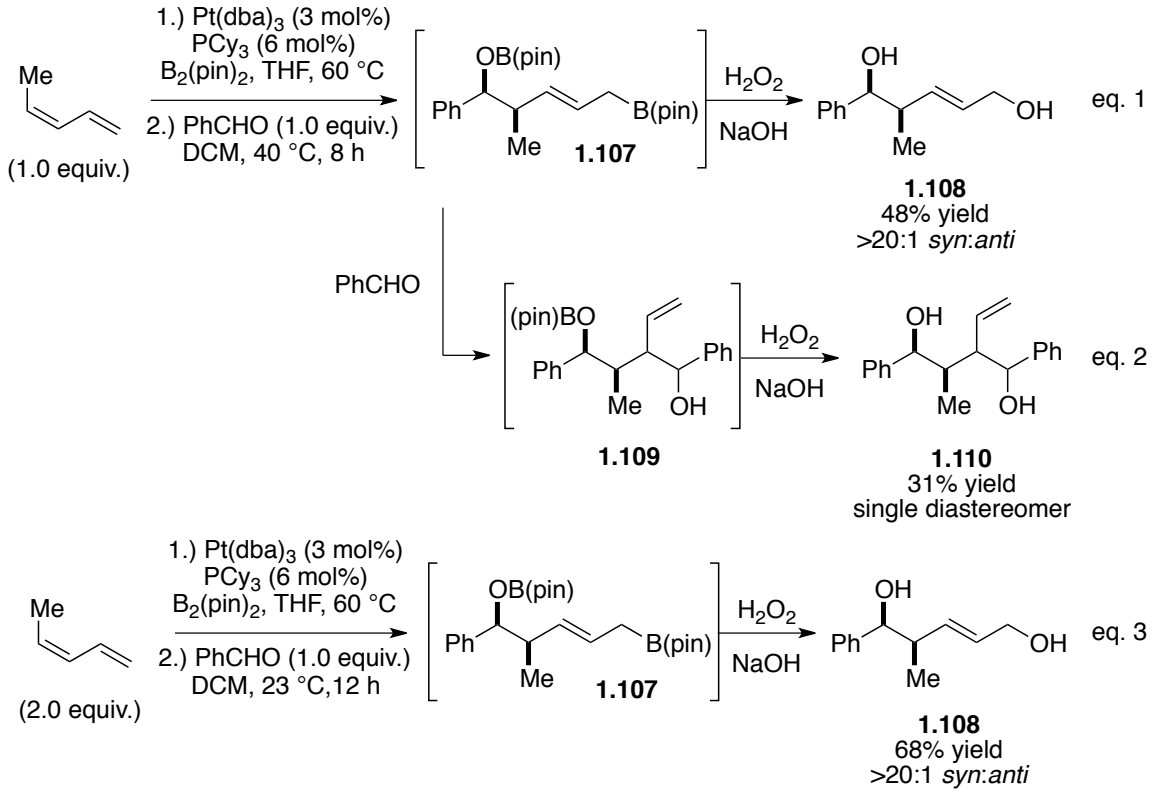


1.106[a]
58% yield
>20:1 dr
97:3 er

Yields reported are of the isolated yields (average of at least two experiments.) Diastereomer ratio determined by analysis of the crude ^{1}H NMR. Enantiomer ratios determiend using SFC analysis with a chiral stationary phase. [a] 3.0 equivalents of *i*-PrCHO.

When *cis*-penta-1,3-diene was subjected to similar diboration/allylation/oxidation conditions, the desired homoallylic alcohol **1.108** was isolated in 48% yield as a single diastereomer (Scheme 1.31, eq. 1). Unfortunately, a significant amount of the bis-allylation side product **1.110** was also isolated (31% yield, eq. 2). Interestingly, this compound too appeared to be a single diastereomer of product, although the relative configuration was not determined. Adjustments to the reaction stoichiometry revealed that a 2:1 bis(boronate):aldehyde was required to maximize the yield of the desired homoallylic alcohol (eq. 3). If one were to implement this method in the context of total synthesis, the aldehyde might be the product of a multi-step sequence and therefore be most valuable. If so, this reaction stoichiometry will maximize the yield of the desired product without sacrificing the precious electrophilic partner.

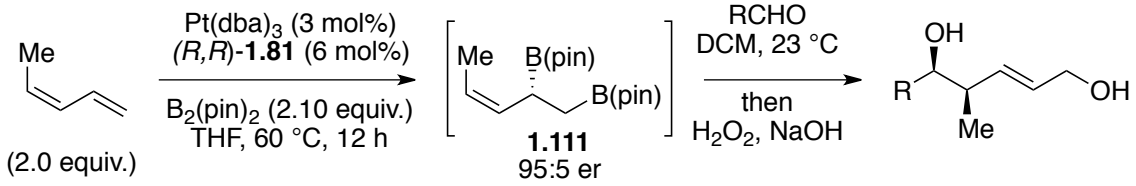
Scheme 1.31. Initial Results for Iterative Diboration/Allylation/Oxidation Sequence

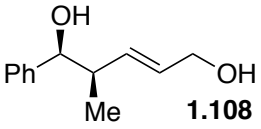
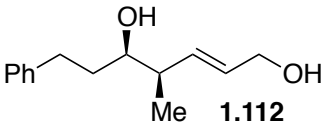
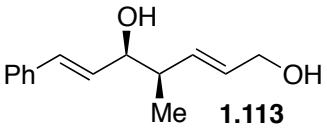
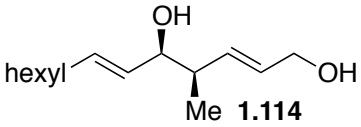
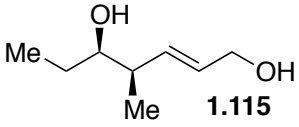
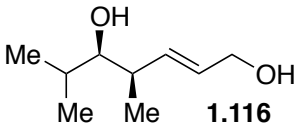
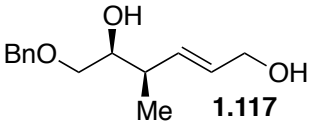


With the optimized conditions in hand, a series of aldehydes were examined in the tandem diboration/allylation/oxidation reaction sequence with *cis*-penta-1,3-diene (Table 1.5). As was anticipated, the (*Z*)-crotylboronate intermediate **1.111** generated from 1,2-diboration gave rise solely to the *syn* diastereomer of product containing the (*E*)-alkene. Aromatic and α,β-unsaturated aldehydes performed well under these reaction conditions; the desired homoallylic alcohols were obtained in 64-71% yield and with excellent transfer of chirality (entries 1, 3 and 4). Despite their lower electrophilicity, both linear and α-substituted aliphatic aldehydes were suitable reaction partners in this chemistry. However, the isobutryaldehyde-derived product **1.116** was isolated with a minor loss in optical purity (entry 6, 93:7 er, 96% es). As demonstrated by entry 7, α-

oxygenation in the aldehyde was also well tolerated. All of the described diboration/ allylation/oxidation reactions were performed in a single flask operation without isolation or purification of the diboration or allylation intermediates, saving time and minimizing purification solvent waste.

Table 1.5. Tandem Enantioselective Diboration/Allylation/Oxidation of *Cis*-penta-1,3-Diene

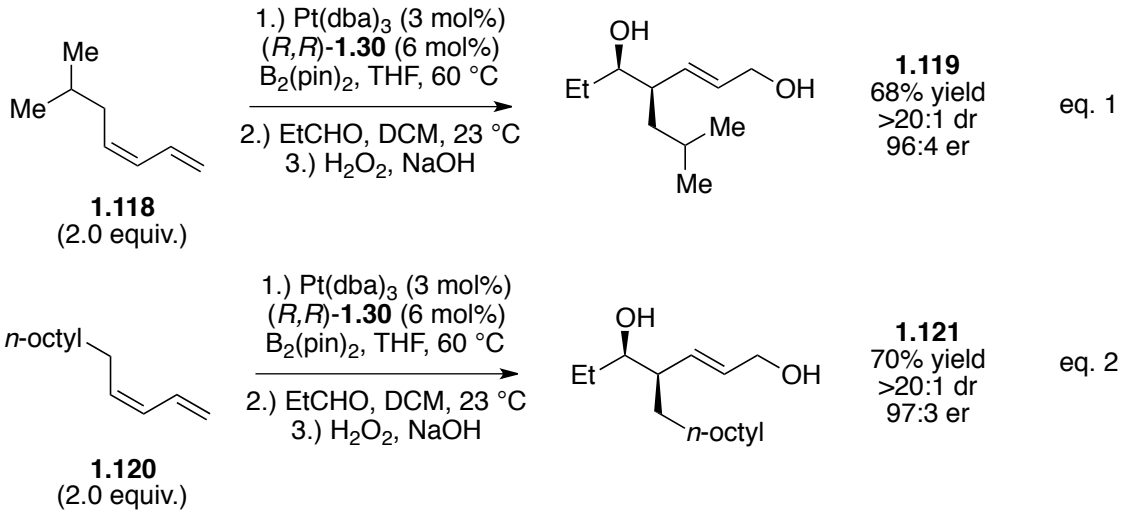


entry	product	%yield[a]	dr[b]	er[c]	es[d]
1	 **1.108**	71	>20:1	94:6	98
2	 **1.112**	66	>20:1	94:6	98
3	 **1.113**	64	>20:1	95:5	>99
4	 **1.114**	68	>20:1	96:4	>99
5	 **1.115**	72	>20:1	94:6	98
6	 **1.116**	62	>20:1	93:7	96
7	 **1.117**	72	>20:1	94:6	98

[a] Percent yield of purified material; average of at least two experiments. [b] Diastereoselectivity determined by analysis of the crude ^{1}H NMR spectrum. [c] Enantioselectivity determined by GC or SFC analysis employing a chiral stationary phase. [d] Enantiospecificity (es) calculated as follows: (%*ee* allylation product/%*ee* diboration product)*100; value ≥ 100% for entries 3 and 4 likely a result of error in the measurement of er.

While employing *cis*-penta-1,3-diene in the enantioselective diboration/allylation strategy gives rise to *syn*-propionate motifs, other dienes may be used to access more diverse products. To this end, we evaluated the performance of more substituted *cis*-1,3-dienes with propionaldehyde (Scheme 1.32). When (*Z*)-6-methylhepta-1,3-diene (**1.118**) was subjected to the tandem diboration/allylation/oxidation conditions, homoallylic alcohol **1.119** was isolated in 68% yield and 96:4 er as a single diastereomer (eq. 1). Diene **1.120** performed equally well, and the corresponding 1,5-diol **1.121** was obtained in a 70% isolated yield and 97:3 er as a single diastereomer (eq. 2).

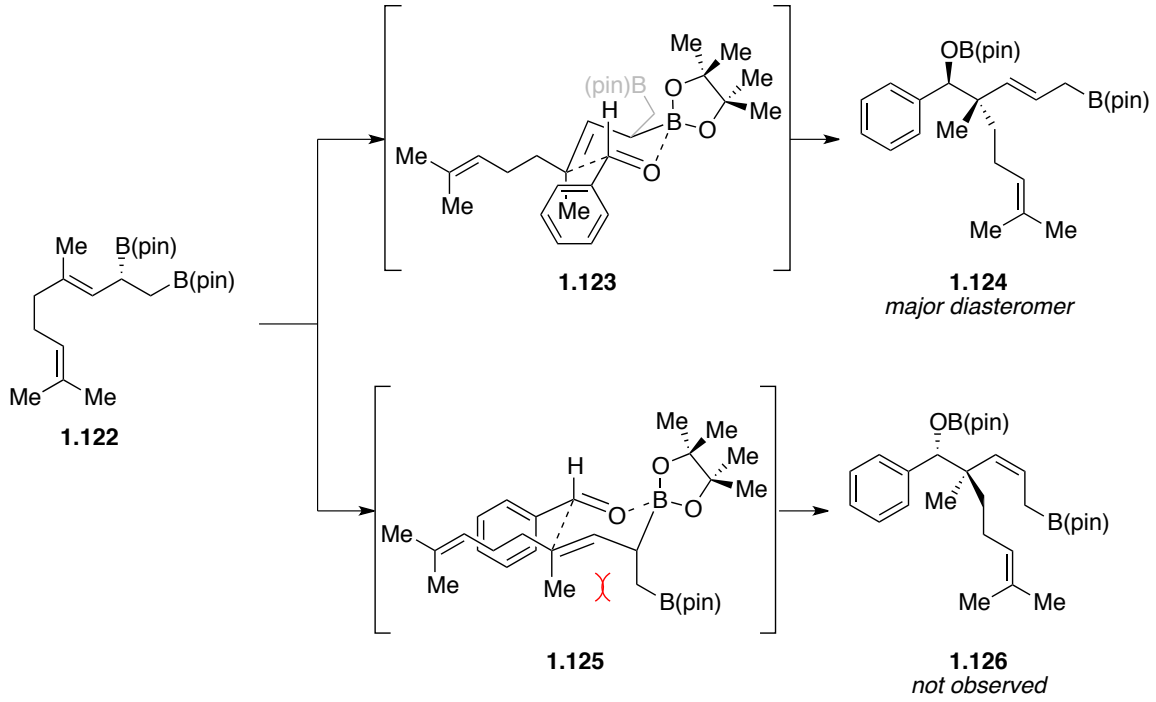
Scheme 1.32. Tandem Diboration/Allylation/Oxidation with Alkyl Substituted *cis*-1,3-Dienes



Although (*E*)-crotylboronic acid pinacol esters with α-substitution suffer from low diastereoselectivity in allylation reactions, the α-substituted (*Z*)-allylboronic esters generated through 1,2-diboration of *cis*-substituted 1,3-dienes are highly selective allylboration reagents. The stereochemical outcome of this process can be explained through the following model. In the presence of benzaldehyde, allylboronate **1.122** reacts

via transition state is **1.123** because transition state **1.125** suffers from destabilizing $A^{1,3}$-strain (Scheme 1.33). The penalizing interaction in the disfavored transition state is present for both 4,4-disubstituted and monosubstituted *cis*-1,3-dienes, therefore both reagent classes are highly diastereoselective.

Scheme 1.33. Diastereoselectivity Model for Allylboration with α-Substituted (*Z*)-Allylboronic Esters

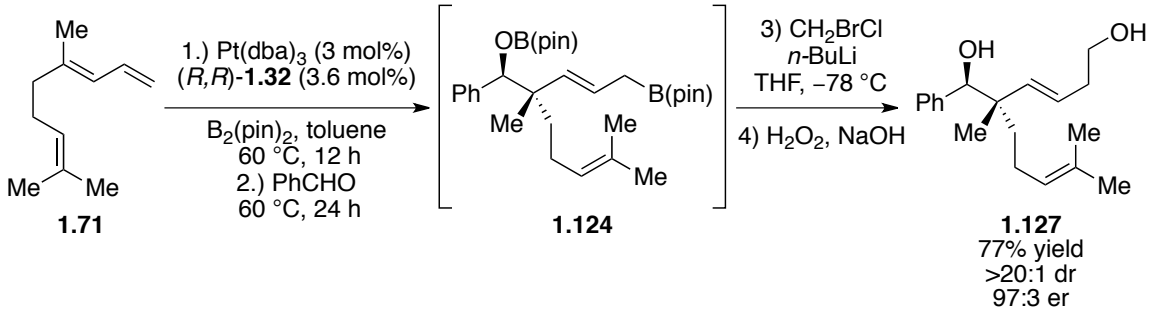


1.7. Elaboration of Diboration/Allylboration Intermediates in Single-Flask Operation

The vast majority of allylmetallation reactions described in the literature furnish a homoallylic alcohol bearing a terminal olefin. However, when α-chiral allylboron reagents are used, the alkene produced is 1,2-disubstituted. The allylboronates generated by 1,2-diboration of 1,3-dienes bear a methylboronic ester at the α-position, which is

translated to the alkene terminus *via* the allylboration reaction. This modified olefin (as compared to traditional allylation products) provides a platform for chain-extending reactions. To this end, it was demonstrated that the terminal allylboronate can be homologated[49] to afford enantioenriched 1,6-diols. Geraniol-derived diene **1.71** underwent successive enantioselective diboration, allylation with benzaldehyde, homologation with chloromethyllithium, and oxidation to produce 1,6-diol **1.127** in an overall 58% yield (Scheme 1.34). Notably, this tandem reaction sequence was performed as a single flask operation. The enantiomeric purity of the product, established in the diboration step, was conserved through all of the subsequent functionalization reactions.

Scheme 1.34. Single-Flask Enantioselective Diene Diboration/Allylation/ Homologation/Oxidation



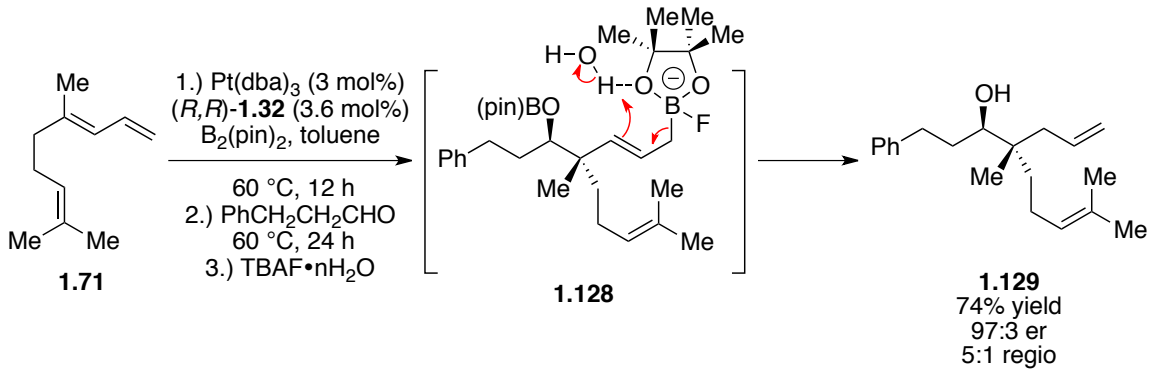
To further illustrate the versatility of the terminal allylboronate generated in this method, we subjected the allylation intermediate to fluoride-promoted protodeboronation (Scheme 1.35).[50] In the presence of tetrabutylammonium fluoride (TBAF), γ-selective protodeboronation occurs on the diboration/allylation intermediate to afford the corresponding terminal bishomoallylic alcohol **1.129** in a 74% yield and 97:3

[49] (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Chen, A. C.; Ren, L.; Crudden, C. M. *Chem. Commun.* **1999**, 611. (c) Chen, A. C.; Crudden, C. M. *Chem. Commun.* **2000**, 721.

[50] Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096.

er. The observed regioselectivity in the protodeboronation may be accounted for by hydrogen bonding of water with one of the pinacol oxygen lone pairs (**1.128**), which have enhanced Lewis basicity after fluoride binds to boron.

Scheme 1.35. Single-Flask Enantioselective Diene Diboration/Allylation/γ-Selective Protodeboronation



1.8. Conclusions

Using a platnium-catalyst in the presence of TADDOL-derived phenylphosphonite ligands, the first enantioselective 1,2-diboration of *cis*- and 4,4-disubstituted 1,3-dienes was achieved. Upon oxidation, a variety of optically active 1,2-diols were synthesized in excellent yield and enantiopurity. The 1,2-selectivity for diboration of this substrate class lies in the inability for *cis*-substituted 1,3-dienes to readily adopt the *S*-cis conformation. While the direct 1,2-diboration product can be directly oxidized to the corresponding 1,2-diols, they also contain an embedded allylboronate moiety which can be engaged in allylboration reactions. In the presence of an aldehyde, highly diastereoselective allylboration occurs to produce 1,5-homoallylic alcohols bearing an all-carbon quaternary center or a *syn*-propionate motif upon

oxidation. The diboration/allylation/oxidation sequence tolerates a wide range of diene/aldehyde combinations, including aliphatic, aromatic, heteroaromatic, and α,β-unsaturated aldehydes. Finally, the latent allylboronate generated after the diboration/allylation sequence serves as a useful handle for further elaborating the reaction product. The terminal allylboronic ester underwent facile homologation or fluoride-promoted protodeboronation to give the corresponding 1,6-diol or bishomoallylic alcohols, respectively. Each of these products, isolated after single-flask, multi-step sequences, was obtained in remarkably high yield, and with excellent levels of enantio- and diastereopurity. This method demonstrates that valuable α-chiral (*Z*)-allylboronates can be generated with ease using readily accessible diene starting materials, a non-toxic diboron reagent, and tartaric-acid derived Pt-ligand complexes.

1.9 Experimental

1.9.1. General Information.

^{1}H NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), a Varian Gemini-500 (500 MHz), a Varian Inova-500 (500 MHz), or a Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants (to the nearest 0.5 Hz). ^{13}C NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), a Varian Gemini-500 (125 MHz), or a Varian Gemini-600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, ν_{max} cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, or phosphomolybdic acid (PMA) in ethanol. Analytical chiral gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supelco β-Dex 120 column with helium as the

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

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran, dichloromethane, acetonitrile, and diethyl ether were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon. Triethylamine was distilled from calcium hydride. Potassium tetrachloroplatinate(II) was purchased from Acros Organics. Dibenzylideneacetone was purchased from Oakwood Chemicals. Tetrabutylammonium chloride was purchased from Fluka. Sodium acetate was purchased from Fisher Scientific. Norbornene was purchased from Aldrich and was sublimed prior to use. Bis (pinacolato)diboron was generously donated by Allychem Co., Ltd. and was recrystallized from pentane prior to use. Dichlorophenylphosphine, tris (dibenzylidenacetone) dipalladium (0), and tri-*t*-butylphosphine, were purchased from Strem Chemicals, Inc. and used without further purification. (*Z*)-penta-1,3-diene was purchased from ChemSampCo and was used without purification. 1,3,5-Tribromobenzene was purchased from Alfa Aesar. Benzaldehyde, hydrocinnamaldehyde, cinnamaldehyde, nonenal, propionaldehyde, *iso*-butyraldehyde, and benzyloxyacetaldehyde were purchased from Aldrich and distilled prior to use. All other reagents were purchased from Aldrich and used without further purification.

1.9.2. Preparation of $Pt(dba)_3$.

Tris(dibenzylideneacetone)platinum was prepared using the literature procedure[51] with slight modification. To a three-neck 500 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser was added dibenzylideneacetone (3.95 g, 16.80 mmol), tetrabutylammonium chloride (2.00 g, 7.20 mmol), and sodium acetate (3.55 g, 43.30 mmol). Methanol (210.0 mL) was added and the solution was warmed to 70 °C in an oil bath until the solids dissolved (5 minutes). In a separate 50 mL pear-shaped flask was added potassium tetrachloroplatinate (1.00 g, 2.41 mmol) and water (8.0 mL), and the mixture gently warmed until solids dissolved. The contents of the pear shaped flask were transferred to the three-neck flask and the reaction was allowed to stir at 70 °C for 3 h. After 3 h, the reaction was cooled to ambient temperature, transferred to a one-neck 500 mL round-bottom flask and concentrated by rotary evaporation to half the volume. The reaction mixture was then filtered on a Büchner funnel and the remaining solids were washed with copious amounts of water and methanol until all yellow dibenzylideneacetone crystals were removed. The resulting solid residue was placed under high vacuum for 24 hours to remove residual methanol and water. This procedure furnished a dark brown solid (1.84 g, 85%) consistent with $Pt(dba)_3$. Anal Calc'd for $C_{51}H_{42}O_3Pt$: C, 68.22; H, 4.71. Found: C, 67.09; H, 4.49 (average of two experiments). Platinum analysis was performed by ICP Optical Emission Spectroscopy; calculated for $Pt(dba)_3$: 21.73% Pt; found 21.92% (average of two experiments.)

[51] Lewis, L. N.; Krafft, T. A.; Huffman, J. C. *Inorg. Chem.* **1992**, *31*, 3555.

1.9.3. Ligand Synthesis

The following TADDOL-derived phosphonite ligands were prepared according to the literature procedure and the spectral data are in accordance with the literature: (*R,R)*-**1.21**,[52] (*R,R*)-**1.30** and (*R,R*)-**1.68**.[53]

Preparation of 1,1′-(5-bromo-1,3-phenylene)bis(2-methylpropan-1-ol.)[54]

To a flame-dried 1 L round-bottomed flask equipped with magnetic stir bar was added 1,3,5-tribromobenzene (4.00 g, 12.71 mmol) and diethyl ether (500.0 mL) under N_2. The reaction was cooled to -78 °C and *tert*-butyllithium (33.2 mL, 1.7 M solution in pentane) was added dropwise *via* syringe. After stirring at -78 °C for 2 h, *iso*-butyraldehyde (4.6 mL, 50.82 mmol) was added and the reaction was allowed to warm to 0 °C before being quenched with saturated aqueous ammonium chloride (20 mL). The organic and aqueous layers were separated and the aqueous layer was washed with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (100% dichloromethane, then 100% ethyl acetate) to afford a brown solid (3.64 g, 95%).

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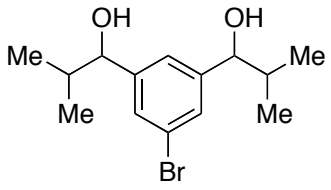
[52] Seebach, D.; Hayakawa, M.; Sakaki, J.-i.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711

[53] Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.

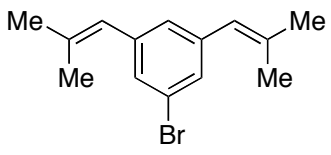
[54] Matsuda, K.; Nakamura, N.; Takahashi, K.; Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1995**, *117*, 5550.



4,4'-(5-bromo-1,3-phenylene)bis(2-methylpropan-1-ol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (6H, d, *J* = 7.0 Hz), 0.94 (6H, d, *J* = 6.5 Hz), 1.86 (2H, d, *J* = 2.5 Hz), 1.91 (2H, m), 4.36 (2H, dd, *J* = 6.5 Hz, 2.5 Hz), 7.14 (1H, ddd, *J* = 5.5 Hz, 5.5 Hz 1.5 Hz), 7.35 (2H, dd, *J* = 2.5 Hz, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.05, 19.15, 19.17, 35.55, 79.41, 122.49, 123.65, 123.71, 128.72, 128.74, 145.93, 145.96; IR (neat): 3364.1 (m), 2960.1 (s), 2872.8 (m), 1572.7 (w), 1467.5 (m), 1156.8 (w), 1033.1 (s), 710.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{25}BrNO_2$ [M $+NH_4$]: calculated: 318.1068, found: 318.1057.

Preparation of 1-bromo-3,5-bis(2-methylprop-1-en-1-yl)benzene.

To a flame-dried 250 mL 3-neck round-bottomed flask equipped with magnetic stir bar and reflux condenser was added 4,4'-(5-bromo-1,3-phenylene)bis(2-methylpropan-1-ol) (3.64 g, 12.08 mmol) and *p*-TsOH•H_2O (1.62 g, 8.55 mmol). The reaction apparatus was purged with N_2 and toluene (120.0 mL) was added. The reaction mixture was brought to reflux and stirred for 36 h. After completion, the reaction was cooled to room temperature and diluted with ethyl acetate (60 mL). The organics were washed with saturated aqueous sodium bicarbonate (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (100% hexanes) to afford a colorless oil (2.36 g, 74%).

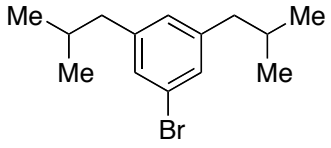


1-bromo-3,5-bis(2-methylprop-1-en-1-yl)benzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83 (6H, d, *J* = 1.0 Hz), 1.86 (6H, d, *J* = 1.5 Hz), 6.16 (2H, br s), 6.96 (1H, s), 7.15 (2H, d, *J* = 1.0 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.66, 27.03, 122.00, 124.19, 128.07, 129.14, 137.06, 140.49; IR (neat): 2969.6 (m), 2911.6 (m), 1655.8 (w), 1589.1 (m), 1555.2 (s), 1444.5 (m), 873.7 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{18}Br$ [M+H]: calculated: 265.0592, found: 265.0603.

Preparation of 1-bromo-3,5-di-iso-butylbenzene.[55]

To a flame-dried 250 mL round-bottomed flask equipped with magnetic stir bar was added 1-bromo-3,5-bis(2-methylprop-1-en-1-yl)benzene (2.36 g, 8.89 mmol) and dichloromethane (88.0 mL) under N_2. The reaction was cooled to -78 °C and $HBF_4 \bullet OEt_2$ (4.7 mL, 34.70 mmol) was added. After stirring at -78 °C for 3 h, triethylsilane (11.1 mL, 69.40 mmol) was added and the reaction was allowed to stir overnight while slowly warming to roomtemperature. Saturated aqueous sodium bicarbonate (50 mL) was added and the organic and aqueous layers were separated. The aqueous layer was washed with ethyl acetate (3 x 25 mL). The combined organics were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The crude material was purified by column chromatography on silica gel (100% hexanes) to afford a colorless oil (2.32 g, 97%).



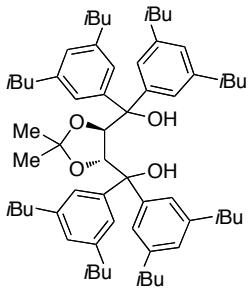
1-bromo-3,5-di-*iso*-butylbenzene. ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (12H, d, J = 7.0 Hz), 1.82 (2H, m), 2.39 (4H, d, J = 7.5 Hz), 6.18 (1H, d, J = 1.5 Hz), 7.09 (2H, d, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.52, 30.39, 45.25, 122.09, 129.01, 129.54, 143.80; IR (neat):

[55] Stadler, D.; Mühlthau, F.; Rubenbauer, P.; Herdtweck, E.; Bach, T. *Synlett*, **2006**, *16*, 2573.

2954.0 (s), 2923.5 (m), 1601.7 (w), 1568.5 (s), 1440.9 (m), 1167.4 (w), 865.4 (m), 700.1 (m) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{22}Br$ [M+H]: calculated 269.0905, found: 269.0899.

Preparation of 3,5-di-iso-butylphenylTADDOL.

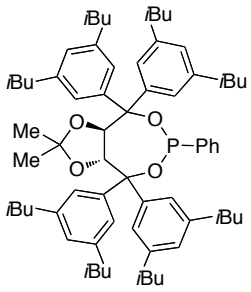
3,5-Di-*iso*-butylphenylTADDOL was prepared according to the literature procedure[53] with slight modification. To a flame-dried 100 mL 2-neck round-bottomed flask equipped with magnetic stir bar and reflux condenser was added crushed magnesium turnings (439.0 mg, 18.05 mmol) under N_2. The apparatus was flame-dried again, a single crystal of I_2 was added and the reaction mixture was diluted with tetrahydrofuran (29.0 mL). To another flame dried 25 mL pear-shaped flask was added 1-bromo-3,5-di-*iso*-butylbenzene (4.37 g, 16.25 mmol) and tetrahydrofuran (12.0 mL). The solution of 1-bromo-3,5-diethylbenzene in tetrahydrofuran was slowly added to the magnesium mixture at room temperature *via* syringe. The reaction was heated to reflux at 80 °C in an oil bath for 3 h, at which time the reaction was cooled to 0 °C, and a solution of (4*R*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (788.0 mg, 3.61 mmol) in tetrahydrofuran (4.0 mL) was added slowly *via* syringe. The reaction was allowed to reflux for 12 h, after which it was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (10 mL). The organic and aqueous layers were separated and the aqueous layer was washed with ethyl acetate (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1-5% ethyl acetate/hexanes) to afford the title compound as a yellow solid (1.79 g, 55%).



3,5-Di-*iso*-butylphenylTADDOL. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (24H, d, *J* = 6.5 Hz), 0.84 (24H, dd, *J* = 6.5 Hz, 3.5 Hz), 1.68 (4H, m), 1.81 (4H, m), 2.32 (8H, d, *J* = 7.0 Hz), 2.40 (8H, d, *J* = 7.0 Hz), 3.52 (2H, s), 4.68 (2H, s), 6.74 (2H, s), 6.81 (2H, s), 6.89 (4H, d, *J* = 1.5 Hz), 7.10 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.24, 22.29, 22.34, 22.42, 27.00, 30.14, 30.33, 31.32, 45.41, 45.52, 77.32, 78.10, 81.28, 109.14, 125.81, 126.89, 128.70, 129.07, 139.97, 140.69, 142.60, 145.52, 148.20; IR (neat): 3320.1 (w), 2953.2 (s), 2923.4 (m), 2867.7 (m), 1601.1 (w), 1464.5 (m), 1166.8 (w), 881.7 (w) cm^{-1}; HRMS-(TOF MS ES+) for $C_{63}H_{94}O_4Na$ [M+Na]: calculated:937.7050, found: 937.7065.

Preparation of (*R*,*R*)-3,5-di-iso-butylphenylTADDOLPPh (1.81).

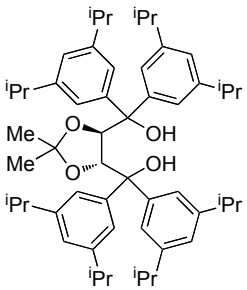
To a flame-dried 50 mL round-bottomed flask equipped with magnetic star bar was added 3,5-di-*iso*-butylphenylTADDOL (1.79 g, 1.95 mmol) and tetrahydrofuran (19.5 mL) under N_2. Triethylamine (0.9 mL, 6.60 mmol) was added *via* syringe and the reaction mixture was cooled to 0 °C in an ice bath. Dichlorophenylphosphine (0.3 mL, 2.14 mmol) was added dropwise *via* syringe at 0 °C, the reaction was brought to room temperature and was allowed to stir for 2 h. The reaction was diluted with Et_2O (20 mL) under N_2, quickly filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (5% ethyl acetate/hexanes) to afford the title compound as a white solid (1.85 g, 93%).



(*R,R*)-3,5-di-*iso*-butylphenylTADDOLPPh (1.81). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (3H, s), 0.70 (24H, t, J = 6.8 Hz), 0.74 (24H, d, *J* = 6.0 Hz), 1.37 (3H, s), 1.58-1.71 (8H, m), 2.25 (8H, d, *J* = 6.8 Hz), 2.290 (8H, d, *J* = 7.2 Hz), 4.76 (1H, d, *J* = 8.8 Hz), 5.50 (1H, dd, *J* = 8.4 Hz, 4.4 Hz), 6.58 (1H, s), 6.63 (2H, s), 6.71 (1H, s), 6.83 (2H, s), 6.92 (1H, s), 7.01 (2H, s), 7.14 (1H, s), 7.34 (5H, br s), 7.69 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.20, 22.24, 22.25, 22.36, 22.42, 24.79, 27.76, 30.16, 30.17, 30.23, 30.55, 45.38, 45.50, 45.64, 77.20, 82.41, 82.45, 82.49, 82.72, 83.36, 83.44, 84.18, 84.23, 110.79, 125.82, 125.89, 127.17, 127.20, 127.75, 128.08, 128.14, 128.80, 128.89, 128.91, 129.03, 129.95, 130.19, 130.32; ^{31}P NMR (202 MHz, $CDCl_3$): δ 156.11; IR (neat): 2952.7 (s), 2921.9 (m), 2867.5 (w), 1600.2 (w), 1464.4 (m), 1161.9 (m), 1038.2 (m), 802.7 (m) cm^{-1}; HRMS-(TOF MS ES+) for $C_{69}H_{98}O_4P$ [M+H]: calculated: 1021.7203, found: 1021.7190.

Preparation of 3,5-di-iso-propylphenylTADDOL.

3,5-Di-*iso*-propylphenylTADDOL was prepared according to the procedure described above for 3,5-di-*iso*-butylphenylTADDOL using 1-bromo-3,5-di-*iso*-propylbenzene, which was prepared according to the literature procedure from 2,6-diisopropylaniline as shown below.[56]



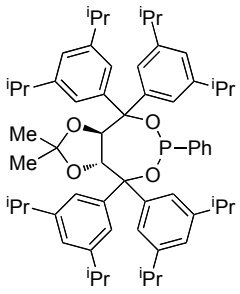
3,5-di-*iso*-propylphenylTADDOL. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (6H, s), 1.06 (24H, dd, *J* = 7.5 Hz, 7.0 Hz), 1.16 (24H, dd, *J* = 7.0 Hz, 1.5 Hz), 2.72 (4H, dddd, *J* = 7.0 Hz, 7.0H Hz, 7.0 Hz, 7.0 Hz), 2.81 (4H, dddd, *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz, 7.0 Hz), 3.63 (2H, s), 4.61

[56] Diemer, V.; Chaumeil, H.; Defoin, A.; Fort, A.; Boeglin, A.; Carré, C. *Eur. J. Org. Chem.* **2006**, *12*, 2727.

(2H, s), 6.86 (2H, s), 6.92 (2H, s), 6.95 (4H, d, J = 1.5 Hz), 7.16 (4H, d, J = 1.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.87, 23.96, 24.00, 24.39, 26.95, 30.32, 34.16, 34.33, 78.50, 81.23, 108.9, 123.2, 123.4, 123.5, 124.5, 142.5, 145.8, 147.3, 148.0; IR (neat): 3235.4 (w), 2967.2 (s), 2868.4 (m), 1599.3 (m), 1463.7 (m), 1073.2 (m), 872.4 (s), 739.8 (s), 709.6 (m) cm^{-1}; HRMS-(+MALDI) for $C_{55}H_{78}O_4Na$ [M+Na]: calculated 825.5792, found: 825.5770. $[\alpha]_D^{25}$ = +19.88 (c = 0.97, $CHCl_3$, l = 50 mm).

Preparation of (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (1.32).

To a flame dried 50 mL round bottom flask equipped with magnetic star bar was added 3,5-di-*iso*-propylphenylTADDOL (1.09 g, 1.36 mmol) and tetrahydrofuran (13.6 mL, 0.1 M) under N_2. Triethylamine (0.65 mL, 4.64 mmol) was added via syringe and the reaction mixture was brought to 0 °C in an ice bath. Dichlorophenylphosphine (0.20 mL, 1.50 mmol) was added dropwise via syringe at 0 °C. The reaction was brought to room temperature and was allowed to stir for 2 h. The reaction was diluted with Et_2O (20 mL), filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (3% ethyl acetate/hexanes, with 1% Et_3N to prevent hydrolysis) to afford the title compound as a white solid (1.03 g, 83%).

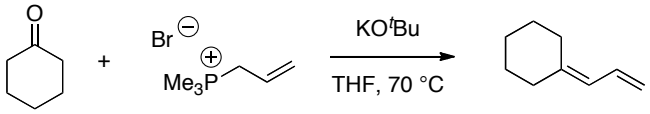


(*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (1.32). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.11 (3H, s), 1.10-1.25 (48H, m), 1.51 (3H, s), 2.78-2.84 (8H, m), 4.91 (1H, d, J = 8.5 Hz), 5.58 (1H, dd, J = 8.5 Hz, 4.0 Hz), 6.83 (1H, s), 6.91 (2H, s), 6.94 (1H, s), 6.98 (2H, d, J = 2.0 Hz), 7.18 (2H, br s), 7.34 (2H, s), 7.44-7.47 (3H, m), 7.51 (2H, s), 7.86-7.90 (2H, m); ^{13}C

NMR (125 MHz, $CDCl_3$): δ 23.86, 23.90, 23.98, 24.12, 24.19, 27.99, 34.03, 34.12, 34.16, 34.43, 82.76, 82.83, 83.22, 83.39, 83.84, 83.89, 84.31, 84.34. 110.4, 123.1, 123.3, 123.4, 123.5, 123.6, 124.7, 124.8, 125.1, 128.1, 128.2, 129.9, 130.1, 130.4, 141.4, 141.7, 142.1, 142.2, 146.2, 146.3, 146.8, 147.1, 147.3, 147.8, 147.9; ^{31}P NMR (202 MHz, $CDCl_3$): δ 155.41; IR (neat): 2957.6 (s), 2868.3 (w), 1598.6 (w), 1464.9 (m), 1162.7 (w), 1027.6 (m), 877.8 (s), 799.7 (m), 735.3 (s), 693.3 (m) cm^{-1}. $[\alpha]_D^{25}$ = -50.40 (*c* = 0.34, $CHCl_3$, *l* = 50 mm).

1.9.4. Preparation of 4,4-Disubstituted 1,3-Dienes

Preparation of allylidenecyclohexane (1.65).

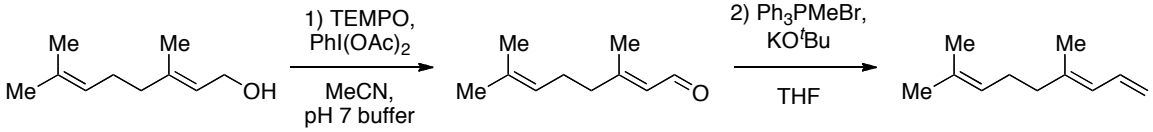


The title compound was prepared according to the literature procedure with slight modification.[57] To a flame-dried, round-bottomed flask in the glove box was added the phosphonium salt (3.00 g, 15.22 mmol) and potassium *t*-butoxide (1.71 g, 15.22 mmol). The flask was sealed, brought to the bench, and THF (51 mL) was added via syringe under N_2. The reaction mixture was cooled to 0 °C in an ice bath and charged with cyclohexanone (1.3 mL, 12.69 mmol, freshly distilled from $MgSO_4$). The flask was then fitted with a flame-dried reflux condenser and was heated to 70 °C in an oil bath for 14 h. The reaction mixture was then cooled to rt and diluted with diethyl ether (50 mL) and the layers were separated. The organic layer was washed with DI H_2O (2 x 25 mL) then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified

[57] Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723.

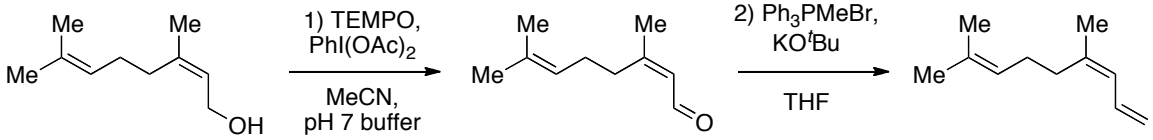
by column chromatography on SiO_2 (100% hexanes) to give the title compound as a clear, colorless oil (1.36 g, 88%). All spectral data were in accordance with the literature.[58]

Preparation of (E)-4,8-dimethylnona-1,3,7-triene (1.71).



The title compound was prepared from geraniol according to the procedure described below for (*Z*)-4,8-dimethylnona-1,3,7-triene. The crude product was purified by column chromatography on SiO_2 (100% hexanes, R_f = 0.56 in 5:1 hexanes:ethyl acetate, stain in PMA) to afford the title compound as a clear, colorless oil (918.8 mg, 95%). All spectral data were in accordance with the literature.[49]

Preparation of (Z)-4,8-dimethylnona-1,3,7-triene (1.73).

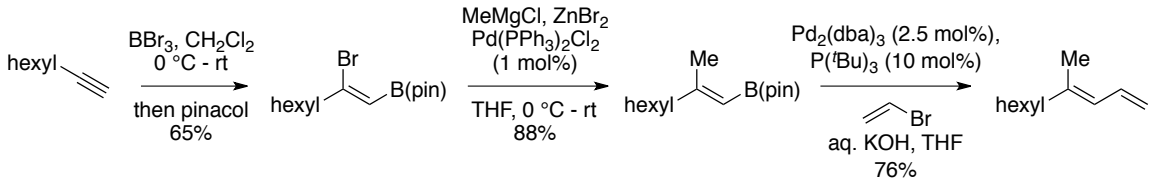


To a 50 mL round-bottomed flask equipped with a stir bar was added iodobenzene diacetate (2.30 g, 7.13 mmol) and TEMPO (101.3 mg, 0.65 mmol). Acetonitrile (6.5 mL) and pH 7 buffer (1.6 mL) were then added, and the reaction mixture was cooled to 0 °C in an ice bath. Nerol (1.00 g, 6.48 mmol) was added via syringe at 0 °C and the reaction was allowed to stir for 3 h (slowly warming to rt). The reaction was then quenched with saturated aqueous sodium thiosulfate (5 mL) and the

[58] Meagher, T. P.; Yet, L.; Hsiao, C. N.; Shechter, H. *J. Org. Chem.* **1998**, *63*, 4181.

layers were separated. The aqueous layer was washed with DCM (3 x 20 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (2-5% ethyl acetate/ hexanes, R_f = 0.45 in 5:1 hexanes:ethyl acetate, stain in PMA) to afford the aldehyde as a clear, colorless oil (987.4 mg, 100%). To a flame-dried, round-bottomed flask in the glove box was added triphenylphosphonium bromide (2.76 g, 7.78 mmol) and potassium *t*-butoxide (873.4 mg, 7.78 mmol). The flask was sealed, brought to the bench, and charged with THF (20 mL) under N_2. The aldehyde (987.4 mg, 6.49 mmol) was then added as a solution in THF (6 mL). The reaction mixture was allowed to stir at rt for 30 min and was then diluted with Et_2O (30 mL). The solution was filtered over a pad of silica gel and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (100% hexanes, R_f = 0.60 in 5:1 hexanes:ethyl acetate, stain in PMA) to afford the title compound as a clear, colorless oil (821.3 mg, 84%). All spectral data were in accordance with the literature.[59]

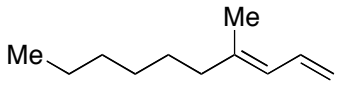
Preparation of (E)-4-methyldeca-1,3-diene (1.75).



The title compound was prepared as shown above from 1-octyne according to the literature procedure.[11] The Suzuki-Miyaura cross coupling was carried out as described above for (*E*)-penta-2,4-dien-2-ylcyclohexane with slight modification as follows: To a

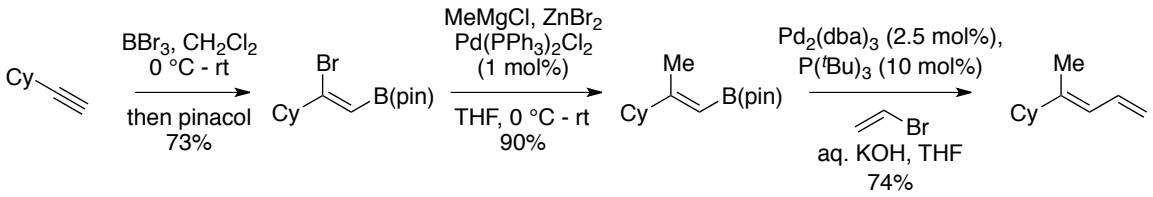
[59] Davi, M.; Lebel, H. *Org. Lett.* **2009**, *11*, 41.

flame-dried, round-bottomed flask equipped with a stir bar in the glove box was added $Pd_2(dba)_3$ (132.0 mg, 144.2 μmol) and $P(^tBu)_3$ (117.0 mg, 578.3 μmol). The reaction mixture was removed from the glove box and the vinylboronic acid pinacol ester (1.45 g, 5.77 mmol) was added under N_2 via syringe as a solution in THF (95 mL). Degassed aqueous KOH (3.0 M, 5.8 mL, 17.31 mmol) was then added to the reaction, followed by vinyl bromide (1.0 M in THF, 17.3 mL, 17.31 mmol). The reaction was allowed to stir at rt for 12 hours under N_2, at which time the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the layers were separated. The aqueous layer was washed with dichloromethane (3 x 100 mL) and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (100% hexane, R_f = 0.69, stain in PMA) to afford a clear, colorless oil as an inseparable mixture of the desired diene and homodimer product (716.0 mg, 24:1 product:homodimer, 76%). The diene mixture can be further purified (to remove the homodimer) by Kugelrohr distillation under N_2 at 225 °C to afford the title compound as a clear, colorless oil (235.0 mg, 27%).



(*E*)-4-methyldeca-1,3-diene (1.75). ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.0 Hz); 1.23-1.30 (6H, m); 0.87 (3H, t, *J* = 6.5 Hz), 1.23-1.30 (6H, m), 1.37-1.43 (2H, m), 1.73 (3H, s), 2.02 (2H, t, *J* = 7.0 Hz), 4.95 (1H, dd, *J* = 10.0 Hz, 2.0 Hz), 5.06 (1H, dd, *J* = 17.0 Hz, 2.5 Hz), 5.83 (1H, dd, *J* = 11.0 Hz, 1.9 Hz), 6.56 (1H, ddd, *J* = 17.0 Hz, 11.0 Hz, 11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 16.5, 22.6, 27.8, 29.0, 31.8, 39.8, 114.3, 125.3, 133.5, 140.0; IR (neat): 2956.8 (m), 2926.5 (s), 2885.9 (m), 1651.4 (w), 1457.5 (w), 1418.6 (w), 1379.2 (w), 986.0 (m), 896.0 (s), 657.1 (w); HRMS-(ESI+) for $C_{11}H_{21}$ [M+H]: calculated: 153.1643, found: 153.1646.

Preparation of (E)-penta-2,4-dien-2-ylcyclohexane (1.77).



The title compound was prepared as shown above from cyclohexylacetylene according to the literature procedure.[60] The Suzuki-Miyaura cross coupling was carried out according to the literature procedure[61] with slight modification as follows: To a flame-dried 250 mL round-bottomed flask equipped with a stir bar in the glove box was added $Pd_2(dba)_3$ (173.0 mg, 189.0 μmol) and $P(^tBu)_3$ (153.0 mg, 754.0 μmol). The reaction mixture was removed from the glove box and the vinylboronic acid pinacol ester (1.89 g, 7.54 mmol) was added under N_2 via syringe as a solution in THF (125 mL). Degassed aqueous KOH (3.0 M, 7.5 mL, 22.63 mmol) was then added to the reaction, followed by vinyl bromide (1.0 M in THF, 22.6 mL, 22.63 mmol). The reaction was allowed to stir at rt for 12 hours under N_2, at which time the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the layers were separated. The aqueous layer was washed with dichloromethane (3 x 100 mL) and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (100% hexane, $R_f = 0.67$, stain in CAM) to afford an inseparable heterogeneous mixture of a colorless oil and a white solid (913.5 mg, 30:1 product:homodimerized diene, 74%). The diene mixture can be further purified (to remove the homodimer) by Kugelrohr distillation under N_2 at 200 °C to afford the title compound as a clear, colorless oil (323.0 mg, 29%).

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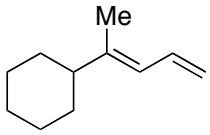
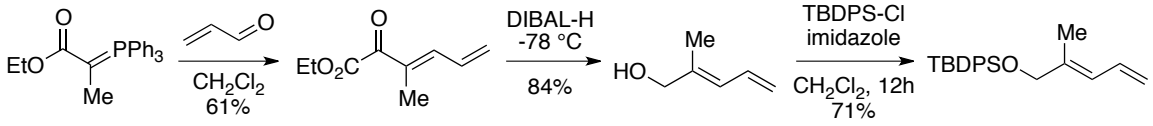
[60] Wang, C.; Tobrman, T.; Xu, Z.; Negishi, E. *Org. Lett.* **2009**, *11,* 4092.
[61] Posner, G. H.; Tang, P. *J. Org. Chem.* **1978**, *43*, 4131.

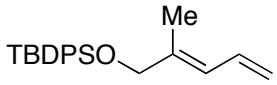


(*E*)-penta-2,4-dien-2-ylcyclohexane (1.77). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09-1.30 (5H, m), 1.64-1.70 (3H, m), 1.72 (3H, s), 1.72-1.77 (2H, m), 1.88 (1H, dddd, *J* = 11.5 Hz, 11.5 Hz, 3.0 Hz, 3.0 Hz), 4.96 (1H, dd, *J* = 10.0 Hz, 2.0 Hz), 5.08 (1H, dd, *J* = 16.5 Hz, 2.0 Hz), 5.84 (1H, d, *J* = 11.0 Hz), 6.59 (1H, ddd, *J* = 16.5 Hz, 10.0 Hz, 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 26.3, 26.6, 31.6, 47.5, 114.5, 123.4, 133.6, 144.8; IR (neat): 3082.7 (w), 2924.1 (s), 2852.1 (s), 1646.7 (w), 1448.1 (m), 1019.4 (w), 985.1 (m), 890.3 (s), 657.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{19}$ [M +H]: calculated: 151.1487, found: 151.1482.

Preparation of (E)-tert-butyl((2-methylpenta-2,4-dien-1-yl)oxy)diphenylsilane (1.79).



(*E*)-*tert*-butyl((2-methylpenta-2,4-dien-1-yl)oxy)diphenylsilane.

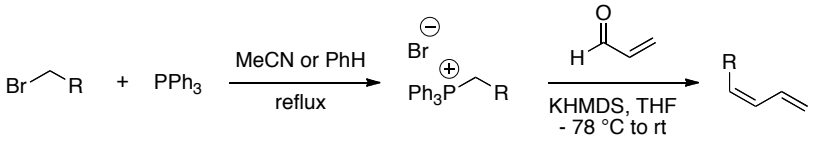


The title compound was prepared as shown above using standard procedures. The crude product was purified by column chromatography on SiO_2 (2% ethyl acetate/hexanes, R_f = 0.37, stain in $KMnO_4$) to afford a viscous, clear, colorless oil (715.0 mg, 71%, 20:1 *E*:*Z*). ^{1}H NMR (500 MHz, $CDCl_3$): 1.06 (9H, s), 1.70 (3H, s), 4.09 (2H, d, *J* = 0.5 Hz), 5.06 (1H, dd, *J* = 10.5 Hz, 1.0 Hz), 5.17 (1H, dd, *J* = 17.0 Hz, 1.5 Hz), 6.17 (1H, dd, *J* = 11.0 Hz, 0.5 Hz), 6.61 (1H, ddd, *J* = 17.0 Hz, 10.5 Hz, 10.5 Hz), 7.35-7.43 (6H, m), 7.66-7.68 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 19.3, 26.8, 68.3, 116.2, 124.2, 127.6, 129.6, 132.8, 133.6, 135.5, 137.5; IR (neat): 2958.2 (w), 2930.5 (m), 2893.2 (w), 2856.3 (m), 1471.8 (w), 1462.0 (w), 1427.1 (m), 1380.4 (w), 1362.1 (w), 1207.9 (w),

1187.5 (w), 1148.4 (w), 1106.3 (s), 1066.6 (m), 1028.8 (m), 989.9 (m), 939.8 (w), 900.1 (m), 823.0 (m), 739.0 (m), 699.3 (s), 659.1 (w), 615.8 (m), 596.5 (m), 573.5 (w), 503.1 (s), 488.1 (s), 431.0 (w) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{29}OSi$ [M+H]: calculated: 337.1988, found: 337.1997.

1.9.5. Preparation of Monosubstituted *Cis*-1,3-Dienes

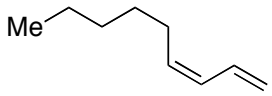
A. Representative Procedure for *cis*-Selective Wittig Olefination.[62]



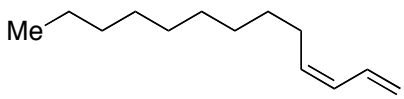
To a flame-dried 2-neck round-bottomed flask equipped with a reflux condenser was added triphenylphosphine (16.68 g, 63.61 mmol) under N_2, followed by acetonitrile (42.4 mL). 1-Bromohexane (7.00 g, 42.41 mmol) was then added *via* syringe and the reaction mixture was heated to 90 °C in an oil bath for 24 h. The reaction mixture was then cooled to room temperature and the solvent was removed by rotary evaporation to give the phosphonium salt as a white solid (17.83 g, 98%). To a flame-dried round bottomed flask was added potassium bis(trimethylsilyl)amide (3.27, 16.38 mmol) and the phosphonium salt (7.00 g, 16.38 mmol) in the glove box. The flask was sealed and brought to the bench. THF (227.0 mL) was added *via* syringe under N_2 and the solution was cooled to -78 °C (dry ice/acetone). The reaction mixture was allowed to stir at -78 °C for 1 h. To a second flame-dried round-bottomed flask was added acrolein (1.64 mL, 24.57 mmol) and THF (100.0 mL). The acrolein solution was cooled to -78 °C and was then slowly transferred *via* cannula to the ylide solution. The reaction mixture was stirred at -78 °C for 1 h, and then at room temperature for 1 h. The solvent was then removed by rotary evaporation

[62] Chen, A.; Vaultier, M.; Carriê, R. *Tetrahedron Lett.* **1989**, *30*, 4953.

to $^1/_4$ of the original volume. The crude mixture was diluted with pentane (150 mL) and washed with H_2O (3 x 100 mL). The layers were separated and the combined organics were dried with Na_2SO_4, filtered, and carefully concentrated (due to product volatility). The crude product was purified by column chromatography on silica gel (100 % pentane, $R_f = 0.83$, stain in $KMnO_4$) to provide a clear, colorless liquid (1.69 g, 83%).

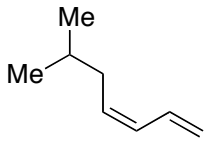


(*Z*)-nona-1,3-diene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, t, *J* = 6.0 Hz), 1.26-1.34 (4H, m), 1.38 (2H, dddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz, 7.5 Hz), 2.17 (2H, dt, *J* = 8.0 Hz, 8.0 Hz), 5.07 (1H, d, *J* = 10.0 Hz), 5.17 (1H, d, *J* = 16.5 Hz), 5.45 (1H, dt, *J* = 10.5 Hz, 7.5 Hz), 5.98 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.63 (1H, ddd, *J* = 17.0 Hz, 11.0 Hz, 11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.5, 27.7, 29.3, 31.4, 116.6, 129.1, 132.3, 133.0; IR (neat): 2954.3 (m), 2925.4 (s), 2858.6 (m), 1465.3 (m), 1363.3 (w), 1076.4 (w), 967.4 (s), 726.5 (w) cm^{-1}; HRMS-(ESI+) for C_9H_{17} [M+H]: calculated: 125.1330, found: 125.1331.

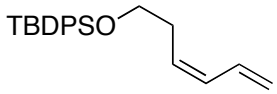


(*Z*)-trideca-1,3-diene. The title compound was prepared according to the representative procedure with the following modifications: The phosphonium salt was made using 1-bromodecane as the electrophile, and benzene as the solvent. The phosphonium salt was a viscous oil, and was used without purification. The olefination reaction was performed without modification to provide a clear, colorless liquid (1.15 g, 54%, $R_f = 0.70$ in 100% hexanes, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 7.0 Hz), 1.24-1.31 (10H, m), 1.36 (2H, dddd, *J* = 6.5 Hz, 6.5 Hz, 6.5 Hz, 6.5 Hz), 2.16

(2H, dtd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz), 5.06 (1H, d, J = 10.0 Hz), 5.15 (1H, d, J = 17.0 Hz), 5.44 (1H, dt, J = 10.5 Hz, 8.0 Hz), 5.98 (1H, dd, J = 11.0 Hz, 11.0 Hz), 6.62 (1H, ddd, J = 17.0 Hz, 11.0 Hz, 11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 27.7, 29.25, 29.33, 29.5, 29.58, 29.62, 31.9, 116.6, 129.1, 132.3, 133.1; IR (neat): 2955.6 (w), 2922.4 (s), 2853.4 (m), 1464.8 (w), 1434.4 (w), 1377.3 (w), 995.4 (m), 900.3 (s), 783.9 (w), 721.5 (w), 653.6 (w) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{25}$ [M+H]: calculated: 181.1956, found: 181.1948.

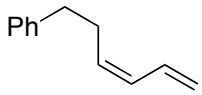


(*Z*)-6-methylhepta-1,3-diene. The title compound was prepared according to the representative procedure with the following modifications: The phosphonium salt was purchased from Aldrich. The olefination reaction was performed without modification to provide a clear, colorless liquid (1.45 g, 55%, R_f = 0.82 in 100% pentane, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (6H, d, J = 7.0 Hz), 1.64 (1H, m), 2.06 (2H, dd, J = 7.5 Hz, 7.5 Hz), 5.06, (1H, d, J = 10.0 Hz), 5.16 (1H, d, J = 17.0 Hz), 5.46 (1H, dt, J = 10.5 Hz, 8.0 Hz), 6.03 (1H, dd, J = 11.0 Hz, 11.0 Hz), 6.62 (1H, ddd, J = 17.0 Hz, 11.5 Hz, 11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3, 28.7, 36.8, 116.7, 129.9, 131.8, 132.5; IR (neat): 2955.5 (s), 2925.8 (s), 2869.9 (m), 1696.9 (w), 1466.7 (m), 1367.4 (m), 1150.3 (w), 1078.3 (w), 969.6 (s) cm^{-1}; HRMS-(ESI+) for C_8H_{15} [M+H]: calculated: 111.1174, found: 111.1174.



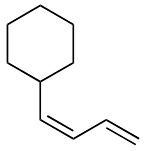
(*Z*)-*tert*-butyl(hexa-3,5-dien-1-yloxy)diphenylsilane. The title compound was prepared according to the representative procedure with the following modifications: 3-bromopropan-1-ol was protected as the silyl ether and used as the electrophile to make the phosphonium

salt with acetonitrile as the solvent. The phosphonium salt was an off-white solid, and was used without purification. The olefination reaction was performed without modification to provide a clear, colorless liquid (953 mg, 61%, R_f = 0.40 in 100% hexanes, stain in $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.03 (9H, s), 2.43 (2H, ddd, *J* = 8.0 Hz, 8.0 Hz, 8.0 Hz), 3.68 (2H, t, *J* = 7.0 Hz), 5.06 (1H, d, *J* = 10.0 Hz), 5.16 (1H, d, *J* = 16.5 Hz), 5.46 (1H, dt, *J* = 10.5 Hz, 8.0 Hz), 6.04 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.52 (1H, ddd, *J* = 17.0 Hz, 10.0 Hz, 10.0 Hz), 7.34-7.41 (6H, m), 7.65 (2H, d, *J* = 1.5 Hz), 7.66 (2H, d, *J* = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 26.8, 31.3, 63.4, 117.2, 127.60, 128.6, 129.6, 130.9, 132.3, 133.9, 135.6; IR (neat): 2857.4 (w), 1427.5 (w), 1107.6 (m), 822.9 (w), 700.7 (s), 505.3 (m) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{29}OSi$ [M+H]: calculated 337.1987, found: 337.1975.



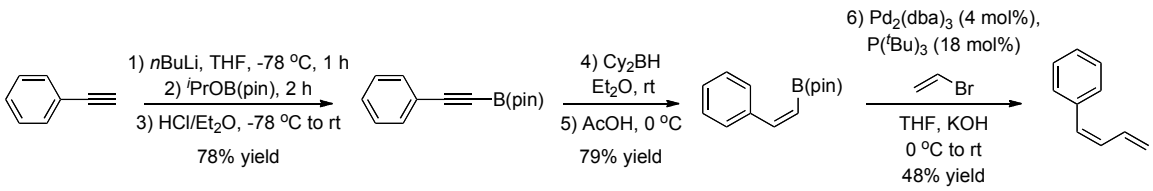
(*Z*)-hexa-3,5-dien-1-ylbenzene. The title compound was prepared according to the representative procedure with the following modifications: The phosphonium salt was made using (3-bromopropyl)benzene as the electrophile, and acetonitrile as the solvent. The phosphonium salt was a white solid, and was used without purification. The olefination reaction was performed without modification to provide a clear, colorless liquid (930.0 mg, 53%, R_f = 0.50 in 100% hexanes, stain in $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ 2.51 (2H, ddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz), 2.70 (2H, t, *J* = 7.5 Hz), 5.08 (1H, d, *J* = 10.0 Hz), 5.18 (1H, d, *J* = 17.0 Hz), 5.49 (1H, dt, *J* = 10.5 Hz, 7.5 Hz), 6.01 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.60 (1H, ddd, *J* = 16.5 Hz, 10.5 Hz, 10.5 Hz), 7.17-1.20 (3H, m), 7.30 (2H, t, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 35.8, 117.2, 125.9, 128.3, 128.4, 129.7, 131.6, 132.1, 141.7;

IR (neat): 2923.9 (w), 1495.5 (m), 1453.8 (m), 969.3 (s), 745.9 (m), 698.4 (s) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{15}$ [M+H]: calculated: 159.1174, found: 159.1179.



(*Z*)-buta-1,3-dien-1-ylcyclohexane. The title compound was prepared according to the representative procedure with the following modifications: The phosphonium salt made using (bromomethyl) cyclohexane as the electrophile and acetonitrile as the solvent. The phosphonium salt was isolated as a white solid (8.26 g, 71%). The olefination reaction was performed without modification to provide a clear, colorless liquid (1.06 g, 83%, R_f = 0.58 in 100% hexanes, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03-1.12 (2H, m), 1.13-1.20 (1H, m), 1.23-1.33 (3H, m), 1.51-1.73 (4H, m), 2.40-2.46 (1H, m), 5.05 (1H, d, *J* = 10.5 Hz), 5.16 (1H, d, *J* = 16.5 Hz), 5.29 (1H, dd, *J* = 10.0 Hz, 10.0 Hz), 5.88 (1H, dd, *J* = 10.5 Hz, 10.5 Hz), 6.64 (1H, ddd, *J* = 17.0 Hz, 10.5 Hz, 10.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.8, 26.0, 33.2, 36.8, 116.6, 127.2, 132.6, 138.9; IR (neat): 2922.2 (s), 2851.0 (m), 1697.0 (w), 1448.8 (w), 1361.0 (w), 970.6 (w), 890.2 (w) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{17}$ [M+H]: calculated: 137.1330, found: 137.1330.

Preparation of (*Z*)-buta-1,3-dien-1-ylbenzene.



The borylation of phenylacetylene was performed following the literature procedure without modification. [63]The resulting alkynyl pinacolboronate was subjected to hydroboration/protodeboronation according to the literature procedure.[64] The resulting (*Z*)-alkenyl pinacolboronate was then subjected to a Suzuki cross-coupling with vinyl bromide as follows: To a flame-dried, round-bottomed flask equipped with magnetic stir bar was added $Pd_2(dba)_3$ (99.0 mg, 0.11 mmol) and $P(^tBu)_3$ (87.9 mg, 0.44 mmol) in the glove box. The flask was sealed and brought to the bench. (*Z*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (1.0 g, 2.47 mmol) was added as a solution in THF (10.0 mL) *via* syringe under N_2. The reaction mixture was then charged with THF (62.0 mL), and aqueous potassium hydroxide (4.3 mL, 13.04 mmol). The flask was cooled to 0 °C and vinyl bromide (13.0 mL of 1.0 M solution in THF, 13.0 mmol) was added dropwise *via* syringe. The reaction was allowed to slowly warm to room temperature while stirring overnight. Saturated ammonium chloride (20 mL) was added to the reaction and the aqueous and organic layers were separated. The aqueous layer was washed with ethyl acetate (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (100% hexanes, R_f = 0.57, visualize by UV) to provide a clear, colorless liquid (270 mg, 48%).

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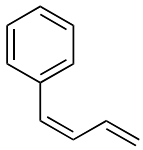
[63] Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K.; Nishihara, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12634.
[64] Ellis, N. M.; Molander, G. A. *J. Org. Chem.* **2008**, *73*, 6841.

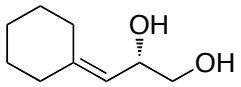


(*Z*)-buta-1,3-dien-1-ylbenzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.22 (1H, d, *J* = 10.5 Hz), 5.36 (1H, d, *J* = 17.0 Hz), 6.26 (1H, dd, *J* = 11.5 Hz, 11.5 Hz), 6.46 (1H, d, *J* = 11.5 Hz), 6.88 (1H, ddd, *J* = 17.0 Hz, 11.0 Hz, 11.0 Hz), 7.22-7.25 (1H, m), 7.31-7.36 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.6, 127.0, 128.4, 129.0, 130.4, 130.8, 133.2, 137.4; IR (neat): 29.18.6 (w), 1629.6 (m), 1450.1 (m), 968.1 (s), 694.3 (s), 638.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{11}$ [M+H]: calculated 131.0861, found: 131.0865.

1.9.6. Representative Procedure for Diboration/Oxidation

To an oven-dried 6-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (8.7 mg, 10.0 μmol), (*R,R*)-3,5-diethylphenyl-TADDOLPPh (**1.30**) (15.4 mg, 19.3 μmol), $B_2(pin)_2$ (85.9 mg, 338.1 μmol) and tetrahydrofuran (3.2 mL, [substrate] = 0.1 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (Z)-nona-1,3-diene (40.0 mg, 322.0 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (2 mL) was added dropwise over 5 min. The reaction mixture was diluted with ethyl acetate (5 mL) and the aqueous and organic layers were separated. The aqueous layer was washed with ethyl acetate (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes) to afford a clear, colorless oil (35.7 mg, 70%).

1.9.7. Characterization and Proof of Stereochemistry of 1,2-Diols

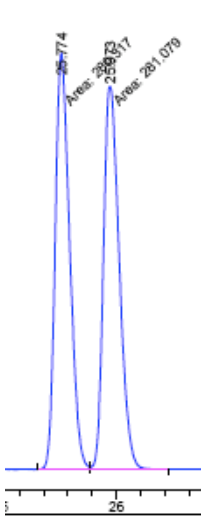


(*S*)-3-cyclohexylidenepropane-1,2-diol (1.66). The diboration was performed according to the representative procedure with allylidenecyclohexane (50.0 mg, 409.1 μmol), $Pt(dba)_3$ (11.0 mg, 12.3 μmol), (*R*,*R*)-3,5-diethylphenylTADDOLPPh (**1.32**) (13.4 mg, 14.7 μmol), and $B_2(pin)_2$ (109.1 mg, 429.6 μmol) in tetrahydrofuran (4.0 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.18 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a white solid (49.8 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44-1.57 (6H, m), 2.07 (2H, t, *J* = 6.0 Hz), 2.14-2.21 (2H, m), 2.27 (2H, br s), 3.44 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.52 (1H, dd, *J* = 11.0 Hz, 3.5 Hz), 4.48 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.0 Hz), 5.06 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.5, 27.9, 28.4, 29.5, 37.0, 66.7, 68.6, 119.9, 145.7; IR (neat): 3379.4 (br m), 2925.8 (s), 2853.2 (m), 1447.4 (w), 1070.8 (w), 1025.2 (w) cm^{-1}; HRMS-(ESI+) for $C_9H_{15}O$ [M+H-H_2O]: calculated: 139.1123, found: 139.1120. $[\alpha]_D^{20}$ = +9.46 (*c* = 1.51, $CHCl_3$, *l* = 50 mm).

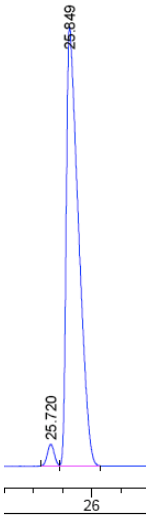
Analysis of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid to afford the acetonide for GLC analysis as shown below. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry be assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 90 °C for 5 min, ramp 3 °C/min to 160 °C, 20 psi, s/r = 35:1) - analysis of 4-(cyclohexylidenemethyl)-2,2-dimethyl-1,3-dioxolane.

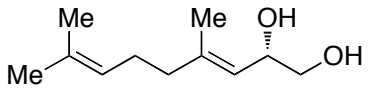


racemic



derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	25.720	BV	0.0524	30.27500	8.96470	2.80138
2	25.849	VB	0.0781	1050.44067	180.07285	97.19862



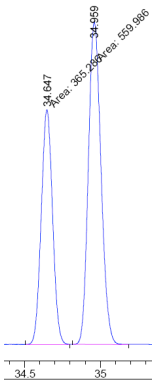
(*S*,*E*)-4,8-dimethylnona-3,7-diene-1,2-diol (1.71). The diboration was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499.1 μmol), $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R*,*R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (16.3 mg, 18.0 μmol), and $B_2(pin)_2$ (133.1 mg, 524.1 μmol) in tetrahydrofuran (5.0 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (20-40% ethyl acetate/hexanes, R_f = 0.13 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil that was inseparable from pinacol (80.4 mg, 9.7:1 product:pinacol = 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58

(3H, s), 1.66 (3H, s), 1.69 (3H, s), 1.99-2.02 (2H, m), 2.06-2.10 (2H, m), 3.46 (1H, dd, J = 11.0 Hz, 8.0 Hz), 3.53 (1H, dd, J = 11.0 Hz, 4.0 Hz), 4.46 (1H, ddd, J = 8.0 Hz, 8.0 Hz, 3.5 Hz), 5.05 (1H, t, J = 6.0 Hz), 5.13 (1H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.8, 17.7, 25.6, 26.3, 39.5, 66.4, 69.4, 123.0, 123.7, 131.9, 141.3; IR (neat): 3349.0 (br m), 2967.7 (w), 2916.0 (m), 2857.6 (w), 1444.1 (w), 1377.9 (w), 1074.75 (m), 1021.0 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{19}O$ [M+H-H_2O]: calculated: 167.1436, found: 167.1442. $[\alpha]_D^{20}$ = +25.95 (c = 0.33, $CHCl_3$, l = 50 mm).

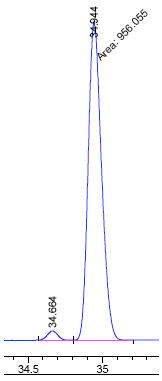
Analysis of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid to afford the acetonide for GLC analysis as shown below. The analogous racemic material was prepared by mixing approximate equimolar amounts of the product made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 90 °C for 5 min, ramp 2 °C/min to 160 °C, 20 psi, s/r = 35:1) - analysis of (E)-4-(2,6-dimethylhepta-1,5-dien-1-yl)-2,2-dimethyl-1,3-dioxolane.



mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**



derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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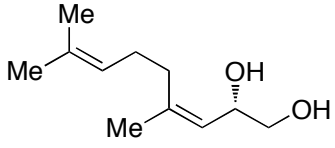
2	34.944	MM	0.1041	956.05499	153.13448	97.80977



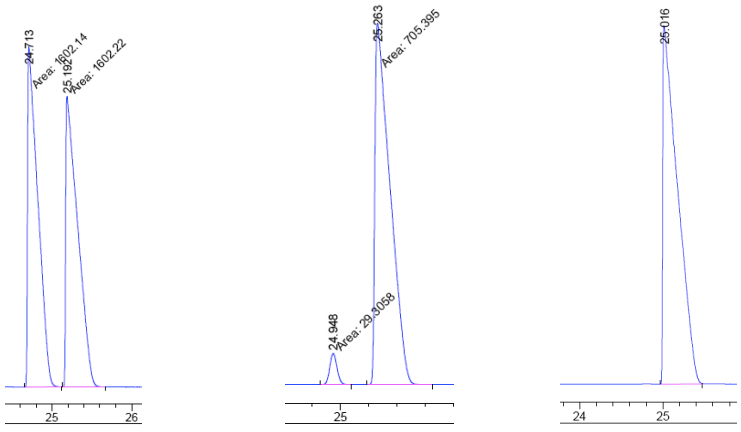
(*S,Z*)-4,8-dimethylnona-3,7-diene-1,2-diol (1.74). The diboration was performed according to the representative procedure with (*Z*)-4,8-dimethylnona-1,3,7-triene (30.0 mg, 199.7 μmol), $Pt(dba)_3$ (5.4 mg, 6.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (6.5 mg, 7.2 μmol), and $B_2(pin)_2$ (53.2 mg, 209.7 μmol) in tetrahydrofuran (2.0 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (20-50% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil that was inseparable from pinacol (40.7 mg, 2.2:1 product:pinacol = 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (3H, s), 1.67 (3H, s), 1.73 (3H, d, *J* = 1.0 Hz), 1.99 (2H, br s), 2.02-2.13 (4H, m), 3.45 (1H, dd, *J* = 11.5 Hz, 8.0 Hz), 3.54 (1H, dd, *J* = 11.5 Hz, 4.0 Hz), 4.42 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.0 Hz), 5.06-5.10 (1H, m),

5.16 (1H, dd, J = 9.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 23.4, 25.6, 26.5, 32.5, 66.6, 68.9, 123.7, 124.1, 132.6, 141.5; IR (neat): 3362.7 (br m), 2967.2 (m), 2917.8 (s), 2858.5 (m), 1668.5 (w), 1446.4 (m), 1376.4 (m), 1152.5 (w), 1075.0 (s), 1021.4 (s), 873.0 (m), 835.1 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{19}O$ [M+H-H_2O]: calculated: 167.1436, found: 167.1442. $[\alpha]_D^{20}$ = +13.25 (c = 2.10, $CHCl_3$, l = 50 mm).

Proof of Stereochemistry.

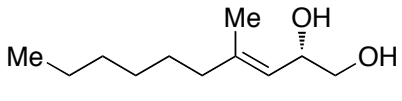
The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.948	MM	0.0595	29.30579	8.21093	3.98881
2	25.263	MM	0.1234	705.39478	95.27135	96.01119

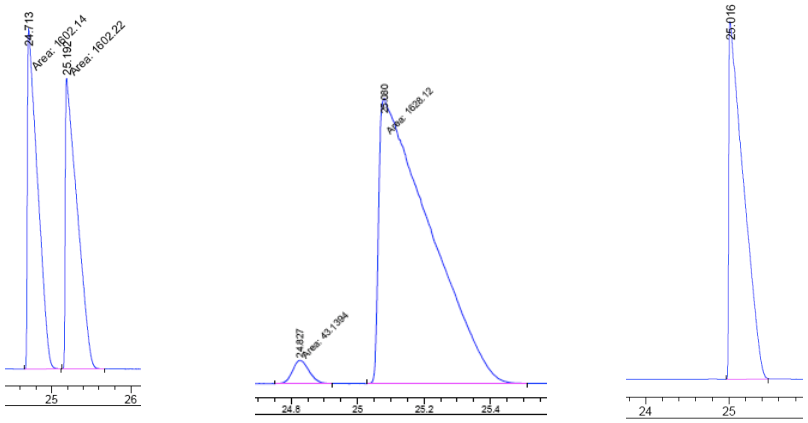


(*S*,*E*)-4-methyldec-3-ene-1,2-diol (1.76). The diboration was performed according to the representative procedure with (*E*)-4-methyldeca-1,3-diene (50.0 mg, 328.3 μmol), $Pt(dba)_3$ (8.9 mg, 9.9 μmol), (*R*,*R*)-3,5-di-*iso*-propylTADDOLPPh (**1.32**) (10.8 mg, 11.9 μmol), and $B_2(pin)_2$ (88.0 mg, 346.5 μmol) in tetrahydrofuran (3.3 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (35-75% ethyl acetate/hexane, R_f = 0.18 in 50% ethyl acetate/hexane, stain in PMA) to afford a clear, colorless oil that was inseparable from pinacol (89.1 mg, 1:1.5 product:pinacol = 76%). ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (3H, t, *J* = 7.0 Hz), 1.22-1.29 (6H, m), 1.33-1.39 (2H, m), 1.67 (3H, d, *J* = 1.0 Hz), 1.97 (2H, t, *J* = 7.0 Hz), 1.92 (2H, br s), 3.44 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.53 (1H, dd, *J* = 11.0 Hz, 3.5 Hz), 4.45 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.5 Hz), 5.11 (1H, dd, *J* = 8.5 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 16.7, 22.6, 27.6, 28.9, 31.7, 39.6, 66.4, 69.4, 122.6, 141.7; IR (neat): 3362.7 (br m), 2995.7 (m), 2926.3 (s), 2856.8 (m), 1458.0 (m), 1379.0 (m), 1075.2 (m), 1027.1 (m), 873.6 (w) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{26}NO_2$ $[M+NH_4]$: calculated: 204.1964, found: 204.1962. $[\alpha]_D^{20}$ = +8.27 (*c* = 0.94, ethyl acetate, *l* = 50 mm).

Proof of Stereochemistry.

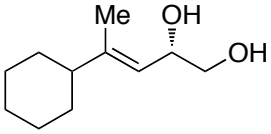
The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.827	MM	0.0570	43.13941	12.60305	2.58124
2	25.080	MM	0.1765	1628.12439	153.72232	97.41876



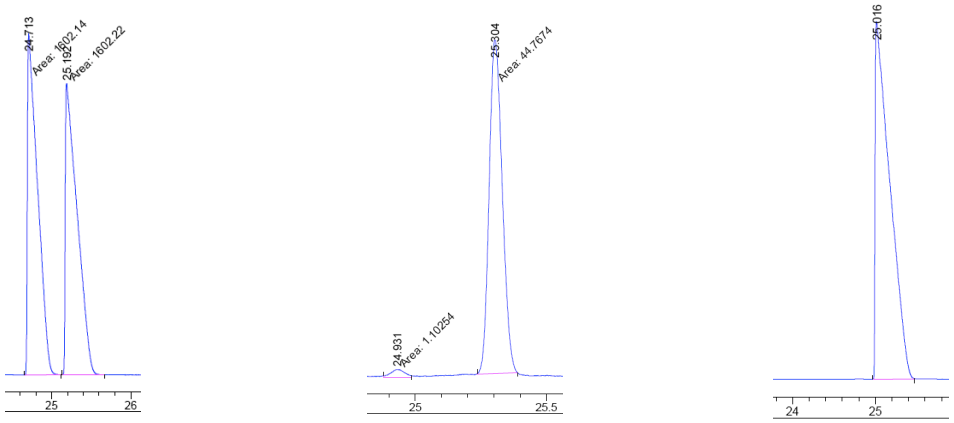
(*S*,*E*)-4-cyclohexylpent-3-ene-1,2-diol (1.78). The diboration was performed according to the representative procedure with (*E*)-penta-2,4-dien-2-ylcyclohexane (50.0 mg, 332.7 μmol), $Pt(dba)_3$ (8.9 mg, 9.9 μmol), (*R*,*R*)-3,5-di-*iso*-propylTADDOLPPh (**1.32**) (10.8 mg, 12.0 μmol), and $B_2(pin)_2$ (88.7 mg, 349.3 μmol) in tetrahydrofuran (3.3 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (40-65% ethyl acetate/ hexane, R_f = 0.18 in 50% ethyl acetate in hexane, stain in PMA) to afford a white solid (50.1 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06-1.28 (6H, m), 1.64-.167 (2H, m), 1.66 (3H, s), 1.73 (2H, d, *J* = 13.0 Hz), 1.82 (1H, dddd, *J* = 11.0 Hz, 11.0 Hz, 2.5 Hz, 2.5 Hz), 2.16 (1H, br s), 2.26 (1H, br s), 3.43 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.53 (1H, dd, *J* = 11.5 Hz, 3.5 Hz), 4.46 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 4.0 Hz), 5.11 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (125

MHz, $CDCl_3$): δ 15.1, 26.2, 26.55, 26.56, 31.67, 31.69, 47.2, 66.4, 69.4, 121.0, 146.4; IR (neat): 3405.5 (m), 3287.9 (br m), 2920.5 (s), 2848.2 (m), 1461.8 (w), 1444.6 (m), 1384.4 (w), 1343.4 (w), 1264.0 (w), 1214.3 (w), 1103.3 (m), 1079.1 (m), 1057.6 (m), 1026.7 (s), 978.2 (w), 990.7 (m), 876.4 (m), 827.2 (m), 704.5 (br m), 641.0 (m), 550.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{24}NO_2$ [M+NH_4]: calculated: 202.1807, found: 202.1813. $[\alpha]_D^{20}$ = +17.65 (*c* = 2.12, $CHCl_3$, *l* = 50 mm).

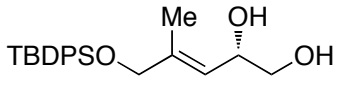
Proof of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.931	MM	0.0619	1.10254	2.96929e-1	2.40363
2	25.304	MM	0.0580	44.76743	12.87476	97.59637



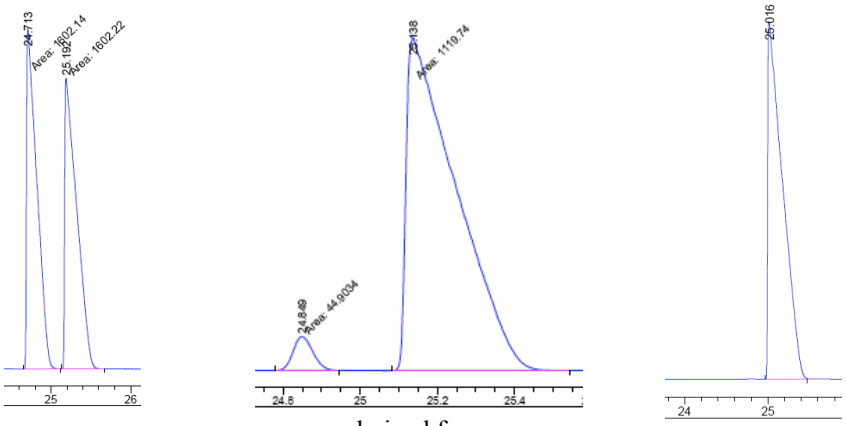
(*S*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-3-ene-1,2-diol (1.80). The diboration was performed according to the representative procedure with (*E*)-tert-butyl(2-methylpenta-2,4-dienyloxy)diphenylsilane (100.0 mg, 297.1 μmol), $Pt(dba)_3$ (8.0 mg, 8.9 μmol), (*R*,*R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (9.7 mg, 10.7 μmol), and $B_2(pin)_2$ (79.0 mg, 311.1 μmol) in tetrahydrofuran (3.0 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (35-65% ethyl acetate/hexanes, R_f = 0.20 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil that was inseparable from pinacol (127.8 mg, 1:1 product:pinacol = 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (9H, s), 1.63 (3H, s), 1.92 (2H, br s), 3.46 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.53 (1H, dd, *J* = 10.5 Hz, 3.0 Hz), 4.04 (2H, s), 4.49 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 4.0 Hz), 5.45 (1H, ddd, *J* =

8.5 Hz, 1.5 Hz, 1.5 Hz), 7.34-7.43 (6H, m), 7.62-7.66 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 19.2, 26.8, 66.3, 68.0, 69.1, 122.2, 127.6, 129.7, 133.5, 133.6, 135.52, 135.53, 139.5; IR (neat): 3361.5 (br m), 2929.9 (m), 2856.5 (m), 1471.8 (w), 1427.4 (m), 1389.4 (w), 1362.0 (w), 1109.3 (s), 1070.1 (s), 1028.0 (m), 823.9 (m), 740.0 (m), 700.9 (s), 614.9 (w), 503.9 (s), cm^{-1}. HRMS-(ESI+) for $C_{22}H_{34}NO_3Si$ [M+NH_4]: calculated: 388.2299, found: 388.2303. $[\alpha]_D^{20}$ = +13.72 (*c* = 2.85, $CHCl_3$, *l* = 50 mm).

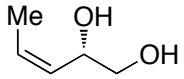
Proof of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



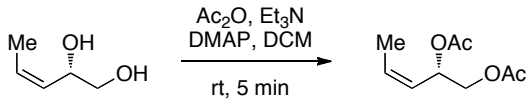
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.849	MM	0.0588	44.90338	12.72177	3.85554
2	25.138	MM	0.1499	1119.74133	124.50630	96.14446



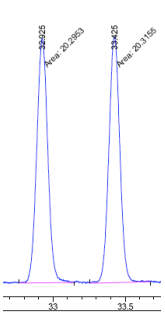
(S,Z)-pent-3-ene-1,2-diol (1.82). The diboration was performed according to the representative procedure with (Z)-penta-1,3-diene (40.0 mg, 587.2 μmol), $Pt(dba)_3$ (15.8 mg, 17.6 μmol), (R,R)-3,5-di-iso-butylphenylTADDOLPPh (**1.56**) (35.9 mg, 35.2 μmol), and $B_2(pin)_2$ (156.5 mg, 616.4 μmol) in tetrahydrofuran (5.8 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (40-75% ethyl acetate/hexanes, R_f = 0.11 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (41.3 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.68 (3H, dd, J = 6.5 Hz, 1.5 Hz), 2.46 (2H, br s), 3.47 (1H, dd, J = 11.0 Hz, 8.0 Hz), 3.56 (1H, dd, J = 11.5 Hz, 3.5 Hz), 4.56 (1H, ddd, J = 8.5 Hz, 8.5 Hz, 3.5 Hz), 5.36 (1H, ddd, J = 10.5 Hz, 8.5 Hz, 1.5 Hz), 5.65 (1H, dqd, J = 10.5 Hz, 7.0 Hz, 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 66.2, 68.3, 128.7, 128.8; IR (neat): 3333.5 (s), 2921.0 (m), 1441.3 (m), 1067.3 (s), 1024.6 (s), 718.1 (m) cm^{-1}; HRMS-(ESI+) for $C_5H_{14}NO_2$ [M+NH_4]: calculated: 120.1024, found: 120.1021. $[\alpha]^{25}_D$ = +24.91 (c = 0.58, $CHCl_3$, l = 50 mm).

Proof of Stereochemistry:

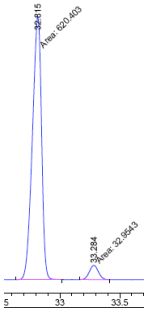
The enantioselectivity was determined by treating the resulting 1,2-diol with acetic anhydride and triethylamine to afford the bis(acetate) for GLC analysis as shown below. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction.



Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 2 °C/min to 130 °C, 20 psi, s/r = 35:1) - analysis of (Z)-pent-3-ene-1,2-diyl diacetate.



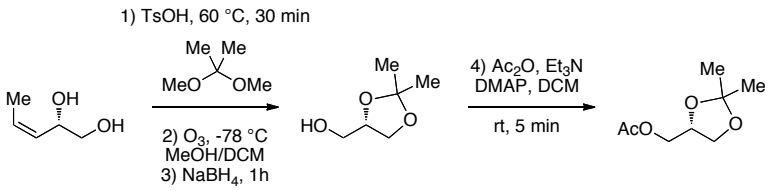
racemic



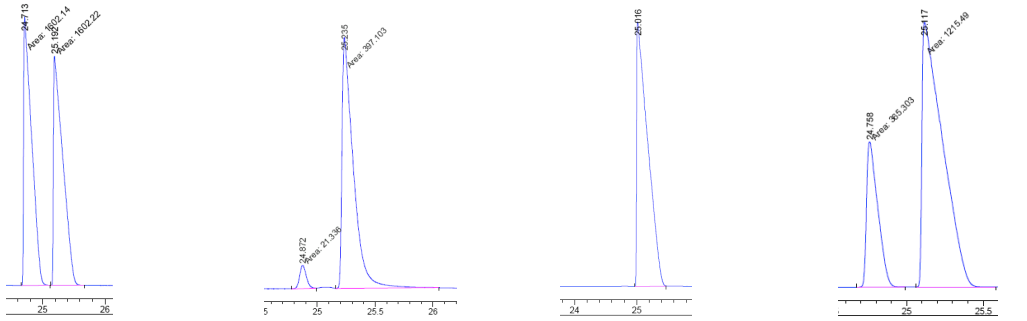
derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.815	MM	0.0885	620.40283	116.85755	94.95616
2	33.284	MM	0.0868	32.95425	6.32439	5.04384

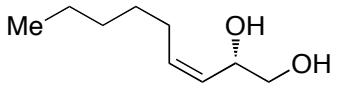
The absolute configuration was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol (below). The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.



Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.872	MM	0.0660	21.33599	5.39037	5.09895
2	25.235	MM	0.1126	397.10287	58.80334	94.90105



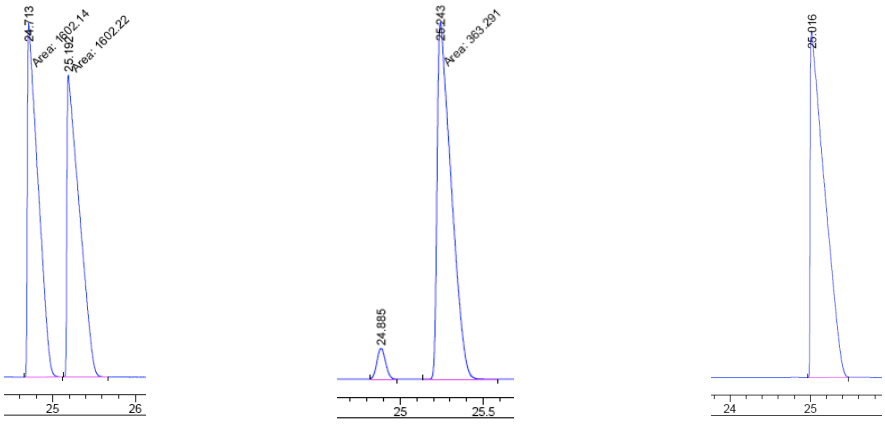
(*S*,*Z*)-non-3-ene-1,2-diol (1.83). The diboration was performed according to the representative procedure with (Z)-nona-1,3-diene (40.0 mg, 322.0 μmol), $Pt(dba)_3$ (8.7 mg, 10.0 μmol), (*R*,*R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (15.4 mg, 19.3 μmol), and $B_2(pin)_2$ (85.9 mg, 338.1 μmol) in tetrahydrofuran (3.2 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.18 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (35.7 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.2 Hz), 1.24-1.31 (4H, m), 1.32-1.38 (2H, m), 1.52 (2H, br s), 2.03-2.13 (2H, m), 3.48 (1H, dd, *J* = 11.4 Hz, 7.8 Hz), 3.57 (1H, dd, *J* = 11.4 Hz, 3.6 Hz), 4.54 (1H, dddd, *J* = 11.4 Hz, 7.8 Hz, 3.6 Hz, 1.0 Hz), 5.35 (1H, dd, *J* = 10.2 Hz, 10.2 Hz), 5.58 (1H, ddd, *J* = 10.8 Hz, 7.2 Hz, 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.5, 27.9, 29.3, 31.4, 66.4, 68.6, 127.8, 135.0; IR (neat): 3479.53 (br w),

2955.8 (s), 2928.7 (s), 2858.7 (m), 2361.9 (w), 1734.0 (s), 1458.3 (m), 1376.6 (m), 1230.2 (s), 1176.0 (s), 1121.3 (s), 1093.4 (s), 1041.3 (s) cm^{-1}; HRMS-(ESI+) for $C_9H_{22}N_1O_2$ [M+NH_4]: calculated: 176.1651, found: 176.1644. $[\alpha]^{25}_D$ = +12.37 (*c* = 0.91, $CHCl_3$, *l* = 50 mm).

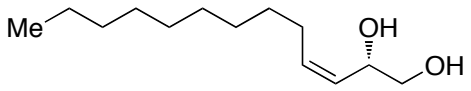
Proof of Stereochemistry:

The enantioselectivity was determined by treating the resulting 1,2-diolenantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.885	BB	0.0564	19.32054	5.31722	5.04965
2	25.243	MM	0.0984	363.29132	61.50985	94.95035

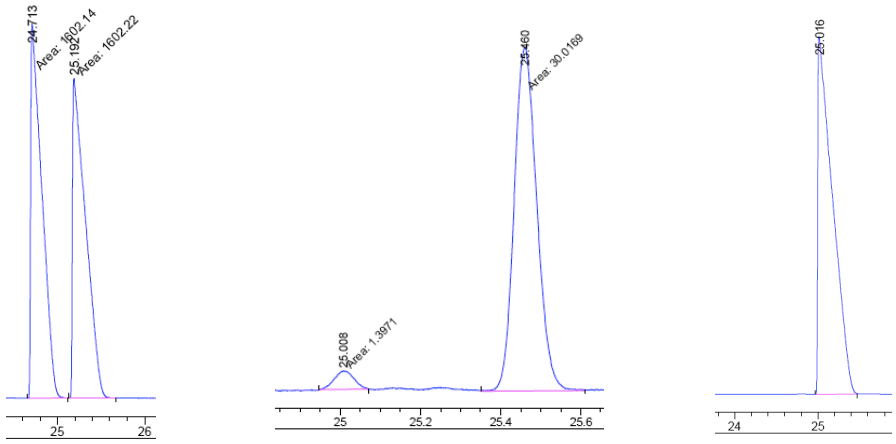


(*S*,*Z*)-tridec-3-ene-1,2-diol (1.84). The diboration was performed according to the representative procedure with (*Z*)-trideca-1,3-diene (40.0 mg, 221.8 μmol), $Pt(dba)_3$ (6.1 mg, 5.5 μmol), (*R*,*R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (10.6 mg, 13.3 μmol), and $B_2(pin)_2$ (59.1 mg, 232.9 μmol) in tetrahydrofuran (2.2 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.25 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (40.4 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.5 Hz), 1.24-1.30 (12H, m), 1.31-1.38 (2H, m), 1.89 (2H, br s), 2.04-2.14 (2H, m), 3.48 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.56 (1H, dd, *J* = 11.0 Hz, 3.5 Hz), 4.54 (1H, ddd, *J* = 7.5 Hz, 7.5 Hz, 3.0 Hz), 5.34 (1H, dd, *J* = 7.5 Hz, 7.5 Hz), 5.58 (1H, ddd, *J* = 12.0 Hz, 7.5 Hz, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 28.0, 29.26, 29.30, 29.47, 29.53, 29.6, 31.9, 66.4, 68.6, 127.8, 135.0; IR (neat): 3363.4 (br m), 2955.2 (m), 2922.9 (s), 2858.8 (m), 1464.6 (w), 1376.8 (m), 1180.4 (m), 1154.8 (m), 1112.1 (w), 1075.2 (m), 1025.8 (m), 950.7 (m), 884.2 (m) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{30}N_1O_2$ [M+NH_4]: calculated: 232.2277, found: 232.2271. $[\alpha]^{25}_D$ = +4.70 (*c* = 0.51, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.

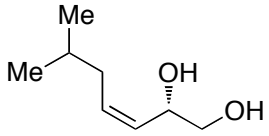


racemic

derived from reaction product

authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	25.008	MM	0.0567	1.39710	4.10396e-1	4.44737
2	25.460	MM	0.0654	30.01688	7.64383	95.55263



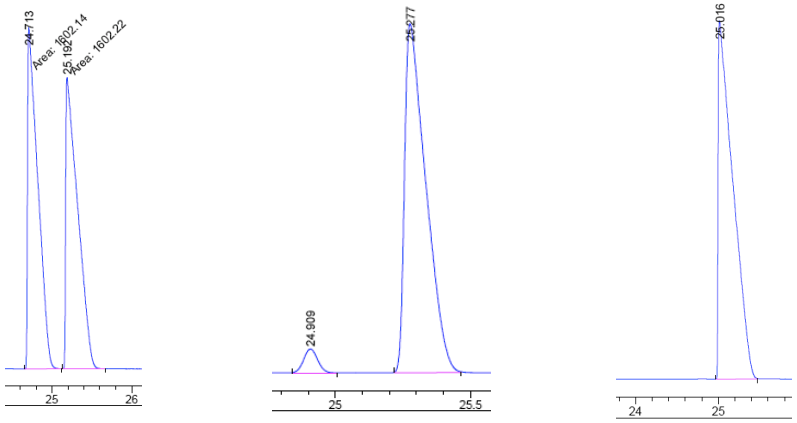
(*S*,*Z*)-6-methylhept-3-ene-1,2-diol (1.85). The diboration was performed according to the representative procedure with (*Z*)-6-methylhepta-1,3-diene (50.0 mg, 453.7 μmol), $Pt(dba)_3$ (12.2 mg, 13.6 μmol), (*R*,*R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (17.4 mg, 21.8 μmol), and $B_2(pin)_2$ (120.9 mg, 476.4 μmol) in tetrahydrofuran (4.5 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (30-70% ethyl acetate/hexanes, R_f = 0.22 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (61.5 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, d, *J* = 5.0 Hz), 0.89 (3H, d, *J* = 4.5 Hz), 1.23 (2H, br s), 1.62 (1H, m), 1.93-2.04 (2H, m), 3.47 (1H, dd, *J* = 10.5 Hz, 8.5 Hz), 3.56 (1H, dd, *J* = 11.0 Hz, 3.5 Hz), 4.52 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 3.5 Hz), 5.39 (1H, dd, *J* = 11.0

Hz, 9.0 Hz), 5.59 (1H, ddd, 10.5 Hz, 7.5 Hz, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 22.3, 28.5, 66.3, 68.6, 128.5, 133.5; IR (neat): 3346.2 (br m), 2954.7 (s), 2924.1 (s), 2869.4 (m), 1717.4 (w), 1464.3 (m), 1383.8 (m), 1367.0 (m), 1075.0 (s), 1026.9 (m) 869.8 (w) cm^{-1}; HRMS-(ESI+) for $C_8H_{20}N_1O_2$ [M+NH_4]: calculated: 162.1494, found: 162.1497. $[\alpha]^{25}_D$ = +9.42 (*c* = 0.53, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

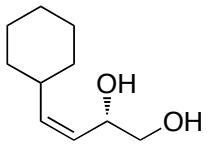
The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.909	BB	0.0559	12.92987	3.59962	4.29653
2	25.277	BB	0.0778	288.00732	52.66652	95.70347

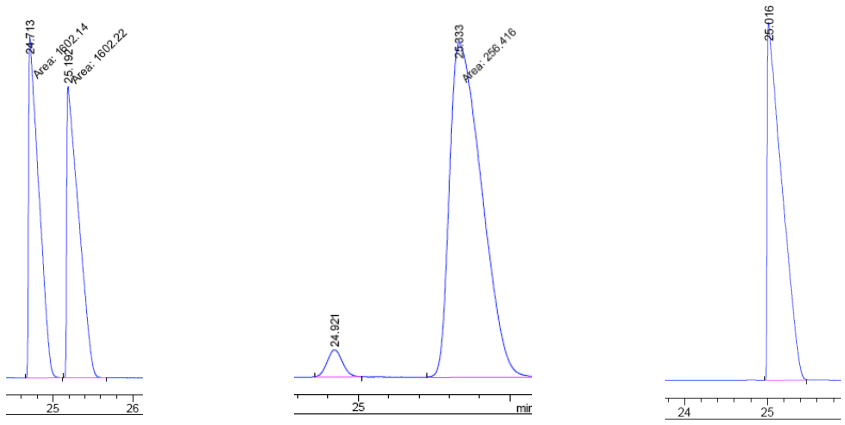


(*S*,*Z*)-4-cyclohexylbut-3-ene-1,2-diol (1.86). The diboration was performed according to the representative procedure with (*Z*)-buta-1,3-dien-1-ylcyclohexane (50.0 mg, 367.0 μmol), $Pt(dba)_3$ (10.0 mg, 9.2 μmol), (*R*,*R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (17.6 mg, 22.0 μmol), and $B_2(pin)_2$ (97.9 mg, 385.4 μmol) in tetrahydrofuran (3.7 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.22 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (48.1 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03-1.18 (3H, m), 1.22-1.31 (3H, m), 1.62-1.72 (4H, m), 1.9 (2H, br s), 2.25-2.33 (1H, m), 3.48 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.55 (1H, dd, *J* = 11.0 Hz. 4.0 Hz), 4.55 (1H, ddd, *J* = 8.5 Hz, 8.0 Hz, 4.0 Hz), 5.24 (1H, dd, *J* = 11.0 Hz, 9.0 Hz), 5.43 (1H, dd, *J* = 10.5 Hz, 10.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.66, 25.74, 25.8, 33.3, 33.5, 37.1, 66.7, 68.8, 125.8, 140.8; IR (neat): 3361.9 (br m), 2921.2 (s), 2849.7 (m), 1447.5 (m), 1373.0 (w), 1324.5 (w), 1146.9 (w), 1069.1 (m), 1025.5 (m), 947.9 (w), 889.6 (w), 744.7 (w) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{22}N_1O_2$ [M+NH_4]: calculated: 188.1651, found: 188.1643. $[\alpha]^{25}_D$ = +9.50 (*c* = 0.52, $CHCl_3$, *l* = 50 mm).

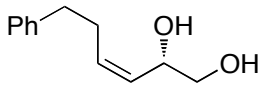
Proof of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.921	BB	0.0532	9.94366	2.81709	3.73317
2	25.333	MM	0.1224	256.41574	34.92316	96.26683



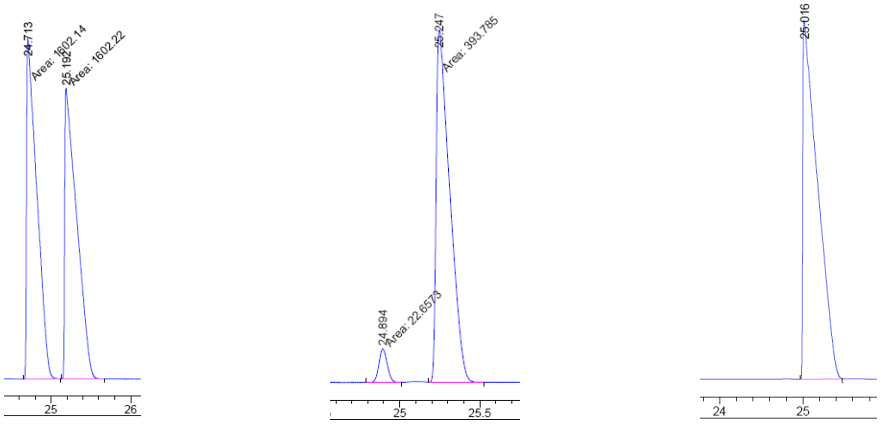
(*S,Z*)-6-phenylhex-3-ene-1,2-diol (1.87). The diboration was performed according to the representative procedure with (Z)-hexa-3,5-dien-1-ylbenzene (30 mg, 189.5 μmol), $Pt(dba)_3$ (5.1 mg, 5.7 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (9.1 mg, 11.3 μmol), and $B_2(pin)_2$ (50.5 mg, 199.1 μmol) in tetrahydrofuran (1.9 mL, 0.1 M). The crude reaction mixture was purified on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.21 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear colorless oil (22.6 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34-2.51 (2H, m), 2.65 (1H, ddd, *J* = 13.6 Hz, 7.2 Hz, 7.2 Hz), 2.72 (1H, ddd, *J* = 14.0 Hz, 7.2 Hz, 7.2 Hz), 3.43 (2H, d, *J* = 6.0 Hz), 4.31 (1H, m), 5.35 (1H, dd, *J* =

9.2 Hz, 9.2 Hz), 5.60 (1H, ddd, J = 10.8 Hz, 8.0 Hz, 8.0 Hz), 7.15-7.20 (3H, m), 7.26-7.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.85, 35.56, 66.09, 68.28, 126.12, 128.35, 128.70, 128.92, 133.11, 141.33; IR (neat): 3361.9 (m), 2923.4 (m), 2855.5 (w), 1453.6 (m), 1074.3 (s), 1028.3 (m), 738.6 (m), 698.7 (s) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{20}NO_2$ [M+NH_4^+]: calculated: 210.1494, found: 210.1496. $[\alpha]_D^{25}$ = +6.20 (c = 0.69, $CHCl_3$, l = 50 mm).

Proof of Stereochemistry.

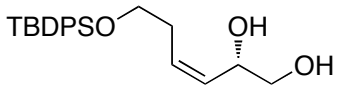
The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.894	MM	0.0596	22.65732	6.33500	5.44069
2	25.247	MM	0.0982	393.78497	66.81371	94.55931

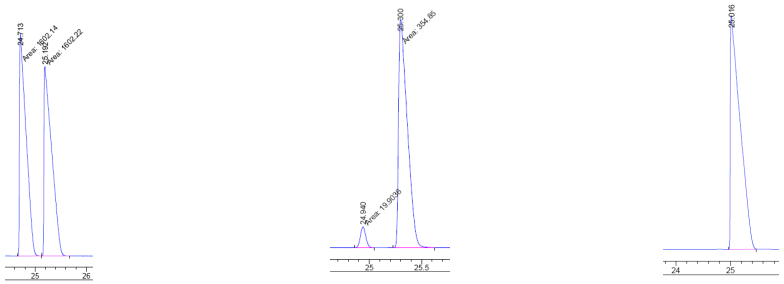


(*S*,*Z*)-6-((*tert*-butyldiphenylsilyl)oxy)hex-3-ene-1,2-diol (1.88). The diboration was performed according to the representative procedure with ((*Z*)-*tert*-butyl(hexa-3,5-dien-1-yloxy)diphenylsilane (60.0 mg, 178.3 μmol), $Pt(dba)_3$ (4.8 mg, 5.3 μmol), (*R*,*R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (8.5 mg, 10.7 μmol), and $B_2(pin)_2$ (47.5 mg, 187.2 μmol) in tetrahydrofuran (1.8 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (20-50% ethyl acetate/hexanes, R_f = 0.44 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear colorless oil that was inseparable from the 1,4-diol and pinacol (58.3 mg, 6.1:1.6:1 product:1,4-diol:pinacol = 56%). ^{1}H NMR (500 MHz, $CDCl_3$): **1,2-diol:** δ 1.03 (9H, s), 1.96 (1H, br s), 2.32 (1H, ddd, *J* = 13.0 Hz, 6.0 Hz, 6.0 Hz), 2.36 (1H, br s), 2.44 (1H, ddd, *J* = 14.5 Hz, 7.0 Hz, 7.0 Hz), 3.46 (1H, dd, *J* = 11.0 Hz, 7.5 Hz), 3.55 (1H, d, *J* = 9.5 Hz), 3.62-3.69 (2H, m), 4.45 (1H, m), 5.53 (1H, dd, *J* = 10.5 Hz, 8.0 Hz), 5.62 (1H, ddd, *J* = 10.5 Hz, 8.0 Hz, 8.0 Hz), 7.36-7.43 (6H, m), 7.63-7.66 (4H, m); **1,4-diol:** δ 1.04 (9H, s), 1.56 (2H, br s), 1.65 (1H, dddd, *J* = 13.5 Hz, 4.0 Hz, 4.0 Hz, 4.0 Hz), 1.86 (1H, dddd, *J* = 19.0 Hz, 8.5 Hz, 8.5 Hz, 5.0 Hz), 3.83 (1H, ddd, *J* = 10.5 Hz, 4.0 Hz, 4.0 Hz), 3.86 (1H, ddd, *J* = 10.5 Hz, 5.0 Hz, 5.0 Hz), 4.17 (1H, dd, *J* = 13.0 Hz, 5.5 Hz), 4.27 (1H, dd, *J* = 13.0 Hz, 6.5 Hz), 4.76 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.0 Hz), 5.57 (1H, m), 5.73 (1H, ddd, *J* = 11.5 Hz, 6.0 Hz, 6.0 Hz), 7.36-7.43 (6H, m), 7.63-7.66 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): **mixture of diols** δ 9.0, 19.2, 26.8, 29.7, 31.3, 38.7, 58.9, 62.7, 63.2, 66.2, 67.9, 68.3, 127.7, 127.8, 129.7, 129.90, 129.92, 130.4, 130.4, 131.0, 133.4, 134.4, 135.56, 135.59; IR (neat): 3354.6 (m), 2928.9 (m), 1471.6 (w), 1427.4 (m), 1108.6 (s), 700.9 (s), 504.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{30}O_3Si$ [M+H]: calculated: 371.2042, found: 371.2059. $[\alpha]^{25}_D$ = +10.18 (*c* = 0.45, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

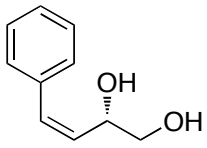
The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.940	MM	0.0596	19.99112	5.59125	5.32877
2	25.300	MM	0.0969	355.16321	61.06040	94.67123



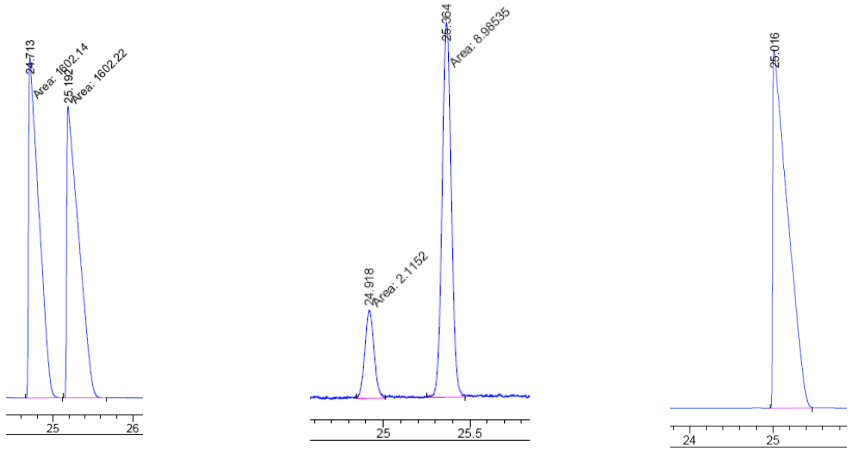
***S,Z*)-4-phenylbut-3-ene-1,2-diol (1.89).** The diboration was performed according to the representative procedure with (*Z*)-buta-1,3-dien-1-ylbenzene (30 mg, 230.4 μmol), $Pt(dba)_3$ (6.2 mg, 6.9 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (11.0 mg, 13.8 μmol), and $B_2(pin)_2$ (61.4 mg, 241.9 μmol) in tetrahydrofuran (2.3 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford a white solid (20.8 mg, 55%). ^1H NMR

(500 MHz, $CDCl_3$): δ 2.25 (2H, br s), 3.54 (1H, dd, *J* = 10.5 Hz, 8.0 Hz), 3.67 (1H, d, *J* = 9.5 Hz), 4.63 (1H, ddd, *J* = 8.5 Hz, 8.0 Hz, 3.0 Hz), 5.59 (1H, dd, *J* = 11.5 Hz, 9.5 Hz), 6.60 (1H, d, *J* = 11.5 Hz), 7.20-7.23 (3H, m), 7.27-7.30 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 66.2, 68.7, 127.6, 128.3, 128.7, 129.7, 133.4, 136.2; IR (neat): 3350.7 (s), 2925.7 (w), 1493.4 (w), 1071.1 (s), 1020.4 (m), 699.4 (s) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{16}NO_2$ [M+NH_4]: calculated: 182.1181, found: 182.1173. $[\alpha]^{25}_D$ = +9.12 (*c* = 0.49, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

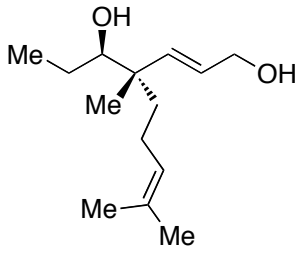
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.918	MM	0.0611	2.11520	5.76821e-1	19.05490
2	25.364	MM	0.0613	8.98535	2.44295	80.94510

1.9.8. Representative Procedure for Diboration/Allylation/Oxidation with 4,4-Disubstituted 1,3-Dienes

To an oven-dried 2-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (**1.32**) (16.4 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) and toluene (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499.1 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The

reaction mixture was then cooled to ambient temperature, returned to the glove box and charged with freshly distilled cinnamaldehyde (66.0 mg, 499.1 μmol). The reaction was brought to the bench and heated to 60 °C in and oil bath and was allowed to stir for 24 h. The reaction mixture was then cooled to 0 °C (ice/water) and charged with tetrahydrofuran (2.0 mL), 3 M sodium hydroxide solution (2 mL), and 30 wt % hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (2 mL) was carefully added dropwise. The reaction mixture was diluted with ethyl acetate (5 mL) and the aqueous and organic layers were separated. The aqueous layer was rinsed with ethyl acetate (3 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.32 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (129.8 mg, 87%).

1.9.9. Characterization and Proof of Stereochemistry



(4*S*,5*R*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)hept-2-ene-1,5-diol (1.96). The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465.9 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R*,*R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled propionaldehyde (27.0 mg, 465.9 μmol). The crude reaction mixture

was purified on silica gel (30-60% ethyl acetate/hexanes) to afford an inseparable mixture of the product, pinacol, and 1,2-diol (129.4 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.44 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (70.7 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, s), 0.96 (3H, t, *J* = 7.5 Hz), 1.16-1.26 (1H, m), 1.28-1.40 (2H, m), 1.51-1.59 (1H, m), 1.55 (3H, s), 1.64 (3H, d, 1.0 Hz), 1.75-1.83 (1H, m), 1.85-1.92 (1H, m), 2.03 (2H, br s), 3.17 (1H, dd, *J* = 10.0 Hz, 1.5 Hz), 4.12 (2H, d, *J* = 2.5 Hz), 5.05 (1H, ddd, *J* = 7.0Hz, 7.0 Hz, 1.5 Hz), 5.58-5.61 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.5, 17.59 17.64, 22.7, 23.9, 25.6, 37.7, 44.0, 63.8, 79.3, 124.7, 129.2, 131.3, 138.1; IR (neat): 3340.5 (br m), 2964.8 (m), 2927.6 (m), 2874.3 (m), 1665.2 (w), 1454.9 (m), 1377.5 (m), 1313.7 (w), 1243.7 (w), 1100.1 (m), 1047.7 (w), 974.5 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{30}NO_2$ [M+NH_4]: calculated: 224.2277, found: 244.2274; $[\alpha]_D^{20}$ = +6.78 (*c* = 1.75, $CHCl_3$, *l* = 50 mm).

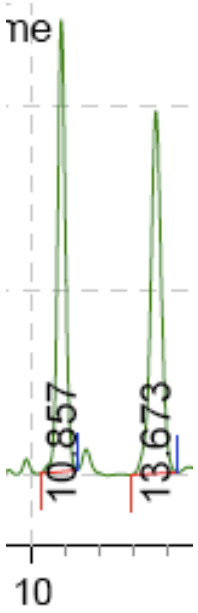
Analysis of Stereochemistry:

The olefin geometry of the 1,5-diol was determined to be *trans* by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in d6-benzene: ^{1}H NMR (500 MHz, C_6D_6): δ 0.89 (3H, s), 1.00 (3H, t, *J* = 7.5 Hz), 1.19 (1H, dddd, *J* = 14.5 Hz,

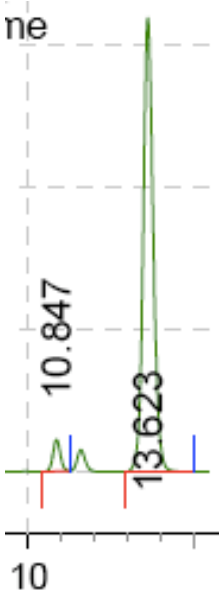
10.5 Hz, 7.5 Hz, 7.5 Hz), 1.31-1.44 (3H, m), 1.56 (3H, s), 1.68 (3H, s), 1.87-2.02 (2H, m), 3.03 (1H, dd, *J* = 10.5 Hz, 2.0 Hz), 3.84 (2H, d, *J* = 5.5 Hz), 5.19 (1H, ddd, *J* = 7.5 Hz, 7.5 Hz, 1.0 Hz), 5.44 (1H, ddd, *J* = 16.0 Hz, 5.0 Hz, 5.0 Hz), 5.52 (1H, d, *J* = 16.0 Hz).

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for HPLC analysis. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

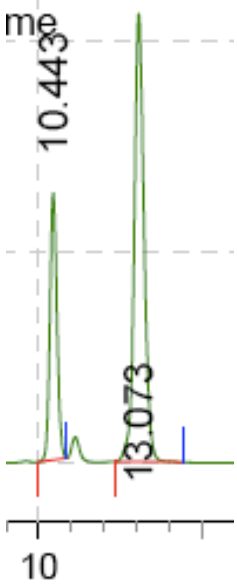
Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 1% IPA, 220 nm) - analysis of (S,E)-4-((R)-1-hydroxypropyl)-4,8-dimethylnona-2,7-dien-1-yl benzoate.



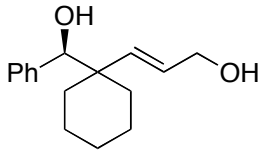
mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**



derived from reaction product using (*R,R*)-**1.32**



reaction product spiked with "rac"

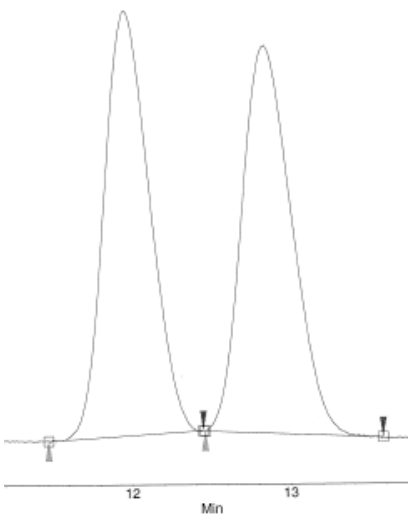


(*S*,*E*)-3-(1-(hydroxy(phenyl)methyl)cyclohexyl)prop-2-en-1-ol (1.97). The diboration was preformed according to the representative procedure with the following modifications: The diboration was carried out in tetrahydrofuran (2.5 mL) with allylidenecyclohexane (30.0 mg, 245.6 μmol), $Pt(dba)_3$ (6.7 mg, 7.4 μmol), (*R*,*R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (**1.32**) (13.4 mg, 14.7 μmol), and $B_2(pin)_2$ (65.5 mg, 257.9 μmol) for 8 h at 60 °C. The reaction mixture was then cooled to ambient temperature and the solvent was removed *in vacuo*. The vial was sealed, returned to the glove box and charged with dichloromethane (0.5 mL) and freshly distilled benzaldehyde (27.4 mg, 257.9 μmol). The allylation was allowed to stir at rt for 14 h, at which time the reaction was subjected to the standard oxidation conditions. The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.33 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (37.5 mg, 62%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.05 (2H, m), 1.19-1.49 (8H, m), 1.82 (1H, s), 1.84 (1H, s), 4.12 (2H, d, *J* = 5.5 Hz), 4.29 (1H, s), 5.35 (1H, d, *J* = 16.5 Hz), 5.55 (1H, ddd, *J* = 16.5 Hz, 6.0 Hz, 6.0 Hz), 7.14-7.16 (2H, m), 7.17-7.24 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 22.1, 26.2, 31.8, 33.1, 44.6, 64.0, 127.3, 127.4, 128.0, 131.5, 135.6, 140.8; IR (neat): 3364.6 (m), 2927.6 (s), 2853.5 (m), 1450.9 (m), 1156.5 (w), 1016.6 (m), 981.1 (m), 702.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{21}O$ [M+H-H_2O]: calculated: 229.1592, found: 229.1600. $[\alpha]_D^{25}$ = -53.17 (*c* = 0.40, $CHCl_3$, *l* = 50 mm).

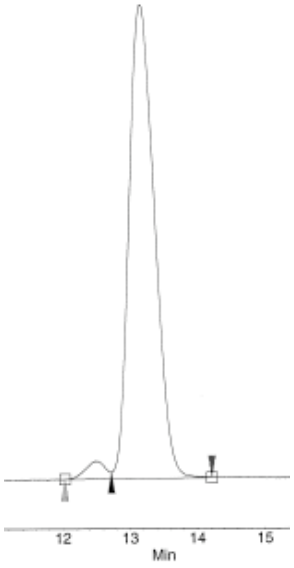
Analysis of Stereochemistry:

The enantioselectivity was determined SFC analysis of the reaction product. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AS-H, Chiraldex, 150 bar, 3 mL/min, 3% MeOH, 50 °C)- analysis of reaction product.

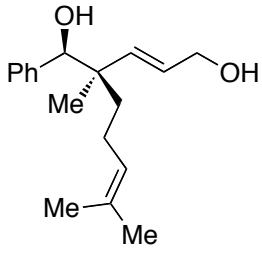


racemic



reaction product

Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
12.03	12.49	12.72	0.00	2.89	176.8	61.8	2.891
12.72	13.13	14.21	0.00	97.11	4760.1	2077.4	97.109



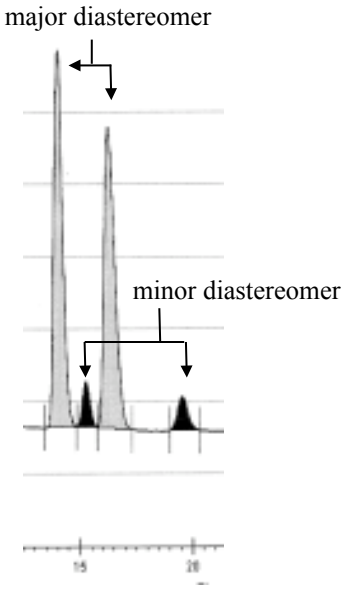
(4*R*,5*S*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)-5-phenylpent-2-ene-1,5-diol (1.98). The diboration/allylation was performed according to the representative procedure with (*Z*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465.9 µmol), $Pt(dba)_3$ (12.6

mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled benzaldehyde (49.5 mg, 465.9 μmol). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes) to afford an inseparable mixture of the product and pinacol (171.9 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.44 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) and the layers were separated. The aqueous layer was washed with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.33 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil as a mixture of diastereomers (108.0 mg, 85%, 9:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (3H, s), 1.32-1.39 (2H, m), 1.53 (3H, s), 1.63 (3H, s), 1.76-1.92 (2H, m), 2.15 (1H, br s), 4.12 (2H, d, *J* = 6.0 Hz), 4.42 (1H, s), 5.00 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.55 (1H, ddd, *J* = 15.5 Hz, 5.5 Hz, 5.5 Hz), 5.66 (1H, dd, *J* = 16.0 Hz, 1.0 Hz), 7.22-7.30 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 19.5, 22.8, 25.7, 36.5, 44.2, 63.9, 81.1, 124.7, 127.4, 127.5, 127.8, 129.4, 131.2, 136.9, 141.2; IR (neat): 3364.0 (m br), 3029.5 (w), 2967.0 (m), 2925.7 (m), 2857.2 (m), 1493.3 (w), 1452.1 (m), 1376.7 (m), 1197.7 (w), 1080.0 (m), 1044.6 (m), 1011.7 (s), 980.0 (s), 745.3 (m), 703.1 (s); HRMS-(ESI+) for $C_{18}H_{30}NO_2$ [M+NH_4]: calculated: 292.2277, found: 292.2278; $[\alpha]_D^{20}$ = -24.17 (*c* = 3.81, $CHCl_3$, *l* = 50 mm).

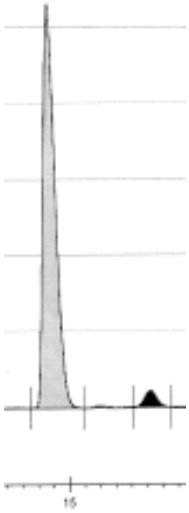
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the product made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

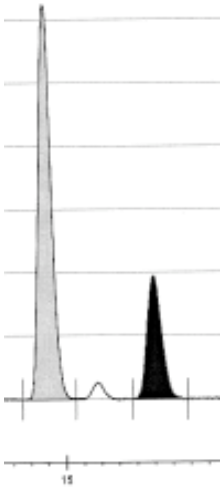
Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C)- analysis of reaction product.



mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**

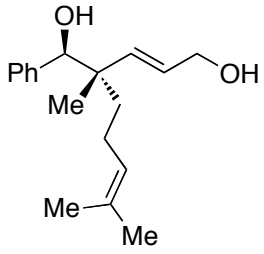


derived from reaction product using (*R,R*)-**1.32**



reaction product spiked with "rac"

Peak No	% Area	Area	RT (min)	Height (mV)
1	96.1313	14209.2633	14.25	529.634
2	3.8687	571.8425	17.64	21.1354



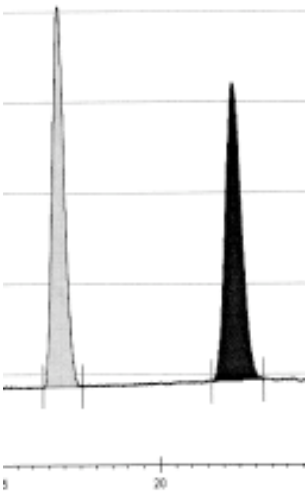
(4*S*,5*S*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)-5-phenylpent-2-ene-1,5-diol (1.99). The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465.9 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled benzaldehyde (49.5 mg, 465.9 μmol). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes) to afford an inseparable mixture of the product and pinacol (160.2 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.44 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.28 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (111.5 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22-1.30 (1H, m), 1.38-1.44 (1H, m), 1.53 (3H, s), 1.63 (3H, d, *J* = 1.0 Hz), 1.77-1.89 (2H, m), 4.15 (2H, m), 4.42 (1H, s), 5.02 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.0 Hz), 5.61 (1H, ddd, *J* = 15.5 Hz, 5.0 Hz, 5.0 Hz), 5.72 (1H, dd, *J* = 16.0 Hz, 1.0 Hz), 7.22-7.30 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.0, 17.6, 22.8, 25.7, 37.8, 44.8, 63.8, 80.5, 124.6, 127.51, 127.53, 128.0, 130.0, 131.3, 137.6, 140.6; IR (neat): 3376.9 (br s), 3085.8 (w), 3061.3 (w), 3028.8 (w), 2968.5 (s), 2922.4 (s), 2856.9 (s), 1666.4 (w), 1493.3 (w),

1452.8 (s), 1377.4 (m), 1195.6 (w), 1082.4 (m), 1046.0 (m), 1011.6 (s), 979.7 (s), 903.5 (w), 839.6 (w), 702.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{30}NO_2$ [M+NH_4]: calculated: 292.2277, found: 292.2271; $[\alpha]_D^{20}$ = -25.07 (*c* = 3.00, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

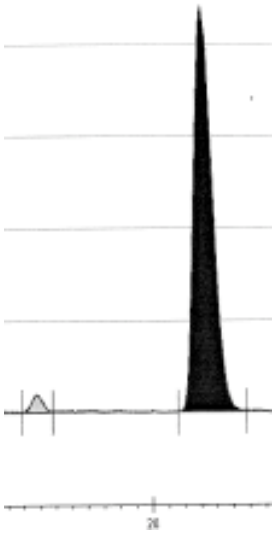
The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C)- analysis of reaction product.



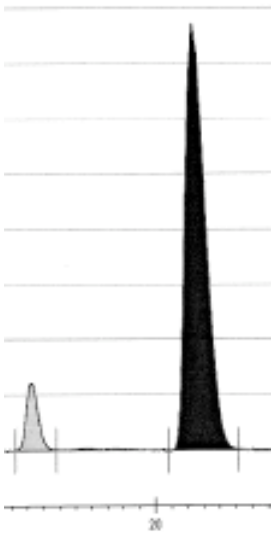
mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**

Peak No	% Area
1	2.4924
2	97.5076



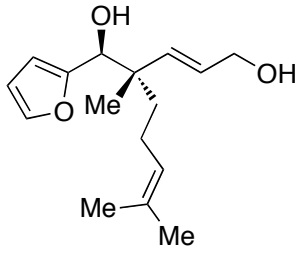
derived from reaction product using (*R,R*)-**1.32**

Area	RT (min)
221.3811	16.4
8660.7138	21.5



reaction product spiked with "rac"

Height (mV)
9.5035
220.0133



(4*S*,5*S*,*E*)-5-(furan-2-yl)-4-methyl-4-(4-methylpent-3-en-1-yl) pent-2-ene-1,5-diol (1.100). The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465.9 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R*,*R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled 2-furfural (44.8 mg, 465.9 μmol). The crude material was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, yellow oil (99.0 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (3H, s), 1.23-1.31 (1H, m), 1.35-1.41 (1H, m), 1.54 (3H, s), 1.63 (3H, s), 1.85 (2H, ddd, *J* = 17.5 Hz, 17.5 Hz, 9.0 Hz), 2.11 (1H, br s), 2.40 (1H, br s), 4.13 (2H, d, *J* = 4.5 Hz), 4.45 (1H, s), 5.02 (1H, t, *J* = 7.0 Hz), 5.63-5.71 (2H, m), 6.20 (1H, d, *J* = 3.5 Hz), 6.31 (1H, dd, *J* = 3.0 Hz, 1.5 Hz), 7.33 (1H, dd, *J* = 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 17.7, 22.6, 25.6, 37.5, 44.5, 63.7, 74.4, 107.8, 110.1, 124.6, 129.7, 131.4, 137.2, 141.5, 154.5; IR (neat): 3356.4 (m br), 2967.3 (m), 2921.9 (m), 2856.6 (m), 1665.2 (w), 1502.2 (w), 1452.5 (m), 1377.0 (m), 1277.4 (w), 1223.4 (w), 1146.9 (m), 1077.5 (m), 1050.5 (m), 1007.1 (s), 976.4 (s), 946.9 (w), 932.8 (w), 902.7 (w), 884.4 (w), 838.7 (w), 808.4 (m), 731.9 (s) cm^{-1}; HRMS-(ESI+): for $C_{16}H_{28}NO_3$ [M+NH_4]: calculated: 282.2069, found: 282.2080; $[\alpha]_D^{20}$ = +6.78 (*c* = 1.75, $CHCl_3$, *l* = 50 mm).

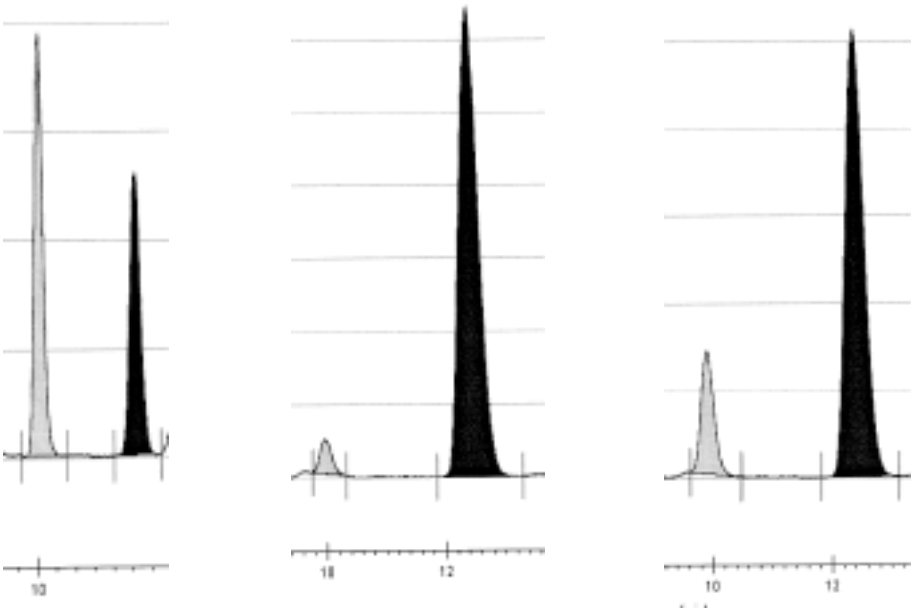
Analysis of Stereochemistry:

The olefin geometry of the 1,5-diol was determined to be *trans* by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in benzene: ^{1}H NMR (500 MHz, C_6D_6): δ 1.04 (3H, s), 1.41-1.55 (2H, m), 1.53 (3H, d, *J* = 1.0 Hz), 1.64 (3H,

d, *J* = 1.0 Hz), 1.96 (2H, ddd, *J* = 15.0 Hz, 15.0 Hz, 8.0 Hz), 2.43 (1H, br s), 3.93 (2H, d, *J* = 5.0 Hz), 4.42 (1H, s), 5.15 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.54 (1H, m), 5.68 (1H, dd, *J* = 16.0 Hz, 1.0 Hz), 6.07 (1H, dd, *J* = 3.0 Hz, 1.5 Hz), 6.15 (1H, d, *J* = 3.0 Hz), 7.04 (1H, dd, *J* = 2.0 Hz, 1.0 Hz).

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C)- analysis of reaction product.

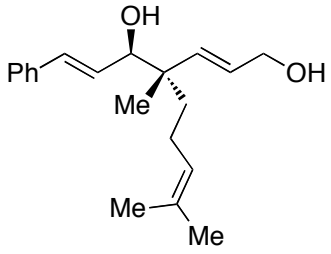


mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**

derived from reaction product using (*R,R*)-**1.32**

reaction product spiked with "rac"

Peak No	% Area	Area	RT (min)	Height (mV)
1	4.2533	648.2372	9.95	46.8904
2	95.7467	14592.4269	12.33	643.2522



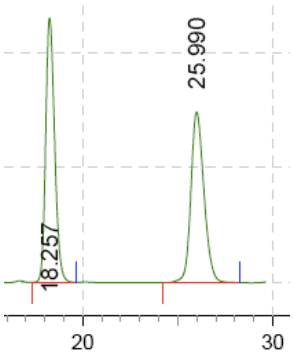
(2*E*,4*S*,5*R*,6*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)-7-phenylhepta-2,6-diene-1,5-diol (1.101). The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499.1 μmol), $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (16.4 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) in toluene (0.50 mL, 1.0 M), and freshly distilled cinnamaldehyde (66.0 mg, 499.1 μmol). The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.32 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (129.8 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (3H, s), 1.40 (2H, t, *J* = 9.0 Hz), 1.55 (3H, s), 1.64 (3H, s), 1.82-1.96 (2H, m), 3.99 (1H, dd, *J* = 7.5 Hz, 1.0 Hz), 4.18 (2H, d, *J* = 4.5 Hz), 5.05 (1H, t, *J* = 7.0 Hz), 5.66-5.74 (2H, m), 6.19 (1H, dd, *J* = 16.0 Hz, 7.5 Hz), 6.56 (1H, d, *J* = 16.0 Hz), 7.21-7.24 (1H, m), 7.30 (2H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 7.36 (2H, dd, *J* = 7.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 17.7, 22.7, 25.7, 37.8, 44.3, 63.8, 78.9, 124.6, 126.5, 127.7, 128.3, 128.6, 129.9, 131.4, 132.8, 136.7, 137.5; IR (neat): 3365.3 (m), 2923.9 (s), 2855.5 (m), 1448.9 (m), 1073.8 (m), 970.3 (s), 748.2 (m), 693.1 (m) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{27}O$ [M+H-H_2O]: calculated: 283.2062, found: 283.2055. $[\alpha]_D^{25}$ = +14.91 (*c* = 0.59, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

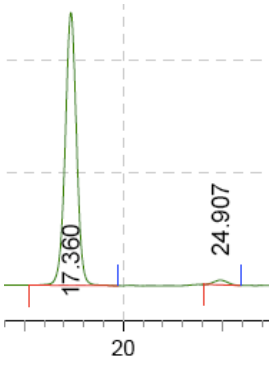
The enantioselectivity was determined by HPLC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-

di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

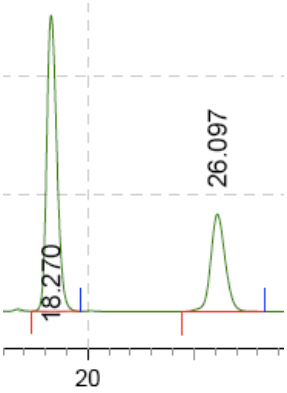
Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 5% IPA, 254 nm) - analysis of the reaction product.



mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**

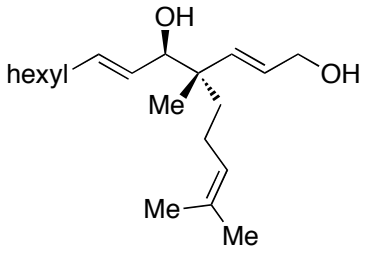


reaction product from (*S,S*)-**1.32**



reaction product spiked with "rac"

Retention Time	Area	Area %	Height	Height %
17.360	810071808	97.96	20281394	98.30
24.907	16853753	2.04	350658	1.70



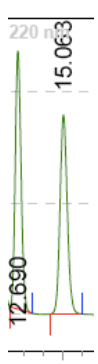
(2*E*,4*S*,5*R*,6*E*)-4-methyl-4-(4-methylpent-3-en-1-yl) trideca-2,6-diene-1,5-diol (1.102). The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465.9 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled *trans*-2-nonenal (65.3 mg, 465.9 μmol). The crude material was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.37 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (107.7 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86

(3H, t, *J* = 6.5 Hz), 0.95 (3H, s), 1.22-1.38 (10H, m), 1.55 (3H, s), 1.58 (2H, br s), 1.64 (3H, d, *J* = 1.0 Hz), 1.77-1.93 (2H, m), 2.02 (2H, ddd, *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz), 3.76 (1H, d, *J* = 7.5 Hz), 4.16 (2H, dd, *J* = 3.0 Hz, 1.5 Hz), 5.05 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.41 (1H, dddd, *J* = 15.0 Hz, 9.0 Hz, 1.5 Hz, 1.5 Hz), 5.61-5.69 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 17.5, 17.6, 22.58, 22.60, 25.6, 28.8, 29.1, 31.7, 32.4, 37.9, 43.7, 63.8, 79.1, 124.8, 128.5, 129.5, 131.2, 134.9, 137.9; IR (neat): 3348.7 (br w), 2959.4 (m), 2023.3 (m), 2854.5 (m), 1665.7 (w), 1455.3 (m), 1376.7 (m), 1302.5 (w), 1079.0 (m), 1004.8 (m), 970.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{35}O$ [M+H–H_2O]: calculated: 291.2688, found: 291.2694; $[\alpha]_D^{20}$: -1.11 (*c* = 1.98, $CHCl_3$, *l* = 50 mm).

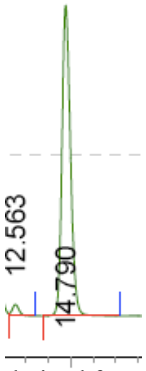
Analysis of Stereochemistry:

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et3N to make the mono(benzoate) for HPLC analysis. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R*,*R*)-3,5-di-*iso*-propylTADDOLPPh and (*S*,*S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

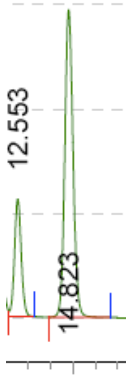
Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 1% IPA, 220 nm) - analysis of (S,E)-4-((R)-1-hydroxypropyl)-4,8-dimethylnona-2,7-dien-1-yl benzoate.



mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**

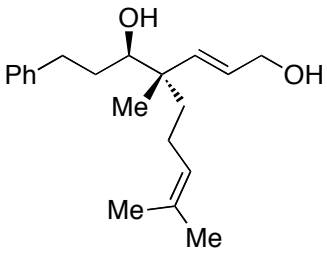


derived from reaction product using (*R,R*)-**1.32**



reaction product spiked with "rac"

Retention Time	Area	Area %	Height	Height %
12.563	12638941	2.89	590139	3.52
14.790	424218119	97.11	16172744	96.48



(4*S*,5*R*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)-7-phenylhept-2-ene-1,5-diol (1.103). The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465.9 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled hydrocinnamaldehyde (62.5 mg, 465.9 μmol). The crude reaction mixture was purified on silica gel (30-60% ethyl acetate/ hexanes) to afford an inseparable mixture of the product, pinacol, and 1,2-diol (152.6 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.44

mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.33 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a white solid (101.9 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, s), 1.21-1.38 (2H, m), 1.51-1.60 (1H, m), 1.54 (3H, s), 1.64 (3H, s), 1.74-1.81 (2H, m), 1.82- 1.90 (1H, m) 1.96 (2H, br s), 2.58 (1H, ddd, *J* = 14.0 Hz, 9.5 Hz, 7.0 Hz), 2.90 (1H, ddd, 14.0 Hz, 10.0 Hz, 5.0 Hz), 3.30 (1H, dd, *J* = 10.5 Hz, 1.5 Hz), 4.12 (2H, d, *J* = 4.0 Hz), 5.03 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.57-5.65 (2H, m), 7.14-7.19 (3H, m), 7.22-7.27 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 17.6, 22.7, 25.6, 32.9, 33.2, 37.6, 44.0, 63.7, 76.7, 124.6, 125.8, 128.3, 128.4, 129.4, 131.4, 137.9, 142.3; IR (neat): 3328.2 (br m), 3025.6 (w), 2963.6 (m), 2923.9 (m), 2857.1 (m), 1603.3 (w), 1495.8 (w), 1453.4 (m), 1377.8 (m), 1304.2 (w), 1153.2 (w), 1081.9 (m), 1065.7 (m), 1043.0 (m), 1008.1 (m), 977.7 (s), 935.2 (m), 838.0 (w), 747.6 (m), 699.0 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{34}NO_2$ [M+NH_4]: calculated: 320.2590, found: 320.2598; $[\alpha]_D^{20}$ = +20.52 (*c* = 2.59, $CHCl_3$, *l* = 50 mm).

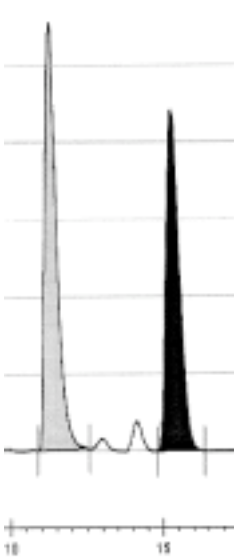
Proof of Stereochemistry:

The olefin geometry of the 1,5- diol was determined to be *trans* by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in pyridine: ^{1}H NMR (500 MHz, C_5D_5N): δ 1.19 (3H, s), 1.56 (3H, s), 1.67 (3H, s), 1.75 (2H, dd, *J* = 10.5 Hz, 8.5 Hz), 1.88-1.96 (1H, m), 2.00-2.08 (2H, m), 2.09-2.18 (1H, m) 2.83 (1H, ddd, *J* = 13.5 Hz, 10.0 Hz, 6.5 Hz), 3.24 (1H, ddd, *J* = 14.5 Hz, 10.5 Hz, 4.5 Hz), 3.66 (1H, dd, *J* = 10.0

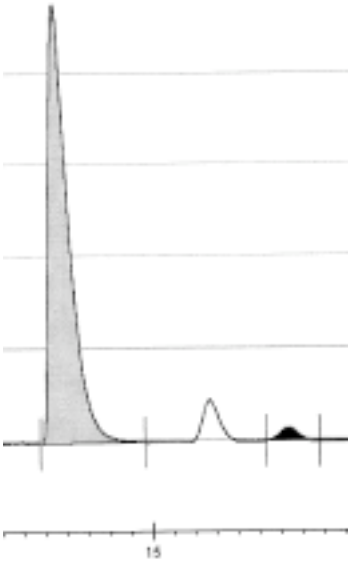
Hz, 3.5 Hz), 4.49 (2H, d, *J* = 4.0 Hz), 5.21 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.93 (1H, ddd, *J* = 16.0 Hz, 5.5 Hz, 5.5 Hz), 6.22 (1H, ddd, *J* = 16.0 Hz, 1.5 Hz, 1.5 Hz), 7.22-7.25 (2H, m), 7.29-7.34 (3H, m).

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C) - analysis of the reaction product.



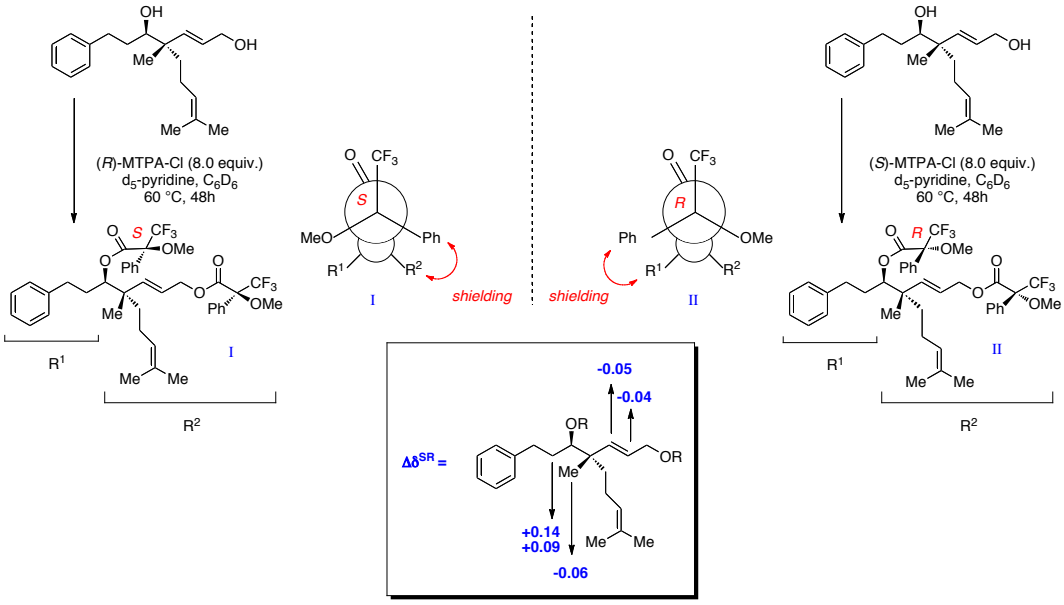
mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**



reaction product from (*S,S*)-**1.32**

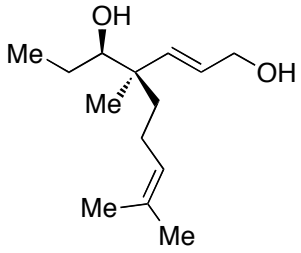
Peak No	% Area	Area	RT (min)	Height (mV)
1	97.4544	15459.5538	12.68	478.3297
2	2.5456	403.8223	18.18	14.4624

The absolute stereochemistry was determined using Mosher Ester analysis under the following procedure[65]: To an oven-dried NMR tube with a septum under N_2 was added diol **32** (6.0 mg, 0.02 mmol) as a solution in C_6D_6:pyridine-d_5 (5:1, 0.6 mL). The (*R*)-MTPA-Cl (29 μL, 0.16 mmol) was added under N_2 via microsyringe and the reaction was heated to 60 °C in an oil bath and allowed to stir for 48 hours until full bis(acylation) was detected by ^{1}H NMR. The reaction was cooled to ambient temperature and was quenched with *N*,*N*-dimethylethylene diamine (30 μL, 0.16 mmol). The mixture was diluted with Et_2O (10 mL) and washed with dilute HCl (1 x 10 mL) at 0°C, saturated aqueous sodium carbonate (1 x 10 mL) at 0°C, and brine (1 x 10 mL). The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude oil was then analyzed by ^{1}H NMR to determine chemical shift data of the resulting (*S*)-Mosher ester. An analogous procedure was performed on diol **32** with (*S*)-MTPA-Cl to synthesize the (*R*)-Mosher Ester.



[65] a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. b) Hoye, T. R.; Jeffery, C. S.; Shao, F. *Nat. Protocols* **2007**, *2*, 2451. c) Brand, D. J.; Steenkamp, J. A. Brandt, E. V.; Takeuchi, Y. *Tet. Lett.* **2007**, *48*, 2769.

As described by Takeuchi,[17c] the most stable conformer of the Mosher Ester requires that the $-CF_3$ and methine proton of the secondary alcohol be *syn*-coplanar. In this conformation, the phenyl substituent of the ester will impose an anisotropic, magnetic shielding effect on protons above and below the plane of the phenyl ring. This shielding results in an upfield shift for the affected protons in the ^1H NMR spectra. When the alcohol has been acylated with both enantiomers of the Mosher acid chloride (or carboxylic acid), then the relative chemical shifts in ^1H NMR can be used to determine the absolute stereochemistry of the stereocenter in question. By convention, $\Delta\delta^{SR}$ (δS-δR) is positive for R^1 and negative for R^2. Upon Mosher Ester analysis, it was determined that the (*R,R*)-enantiomer of ligand produces the (*R*)-enantiomer of the corresponding secondary alcohol in the diboration/allylation/oxidation sequence of 4,4-disubstituted dienes. This conclusion is in accordance with the proven absolute stereochemistry of the 1,2-diboration/oxidation products, assuming the allylation proceeds in a closed-chair transition state as is typically observed for allyl(boronate) additions to aldehydes.



(4*R*,5*R*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)hept-2-ene-1,5-diol (1.104). The diboration/allylation was performed according to the representative procedure with (*Z*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465.9 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled propionaldehyde (27.0 mg, 465.9 μmol). The crude reaction mixture was purified on silica gel (30-65% ethyl acetate/hexanes) to afford an inseparable

mixture of the product, pinacol, and 1,2-diol (118.2 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.44 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.29 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (70.7 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.5 Hz), 1.00 (3H, s), 1.20 (1H, dddd, *J* = 14.5 Hz, 10.5 Hz, 7.5 Hz, 7.5 Hz), 1.38 (2H, t, *J* = 8.5 Hz), 1.52-1.60 (2H, m), 1.56 (3H, s), 1.81-1.90 (2H, m), 3.17 (1H, d, *J* = 10.5 Hz), 4.12-4.13 (2H, m), 5.06 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.0 Hz), 5.56-5.64 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6, 17.6, 18.6, 22.6, 24.6, 25.7, 37.5, 43.9, 63.9, 80.0, 124.8, 128.8, 131.4, 137.6; IR (neat): 3353.8 (br m), 2965.9 (m), 2929.0 (m), 2874.7 (m), 1665.3 (w), 1455.1 (m), 1376.7 (m), 1312.9 (w), 1242.1 (w), 1102.2 (m), 1047.6 (w), 1010.9 (m), 975.5 (s), 940.5 (w) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{30}NO_2$ [M+NH_4]: calculated: 244.2277, found: 244.2287. $[\alpha]_D^{20}$ = +22.17 (*c* = 1.52, $CHCl_3$, *l* = 50 mm).

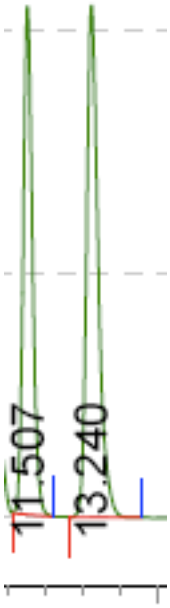
Analysis of Stereochemistry:

The olefin geometry of the 1,5-diol was determined to be *trans* by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in benzene: ^{1}H NMR (500 MHz, C_6D_6): δ 0.94 (3H, t, *J* = 7.5 Hz), 0.96 (3H, s), 1.12 (1H, dddd, *J* = 15.0 Hz, 11.0 Hz, 7.5 Hz, 7.5 Hz), 1.39-1.47 (3H, m), 1.56 (3H, s), 1.68 (3H, s), 1.94-1.98 (2H, m),

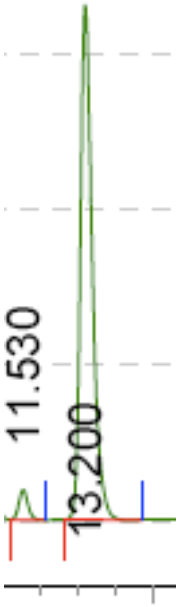
3.03 (1H, dd, *J* = 10.5 Hz, 1.5 Hz), 8.84-8.90 (2H, m), 5.20 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.0 Hz), 5.44 (1H, ddd, *J* = 16.0 Hz, 4.5 Hz, 4.5 Hz), 5.49 (1H, d, *J* = 16.5 Hz).

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for HPLC analysis. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

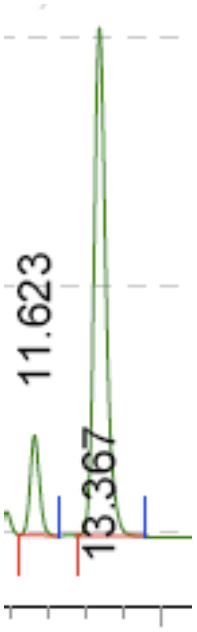
Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 1% IPA, 220 nm) - analysis of (R,E)-4-((R)-1-hydroxypropyl)-4,8-dimethylnona-2,7-dien-1-yl benzoate.



mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**

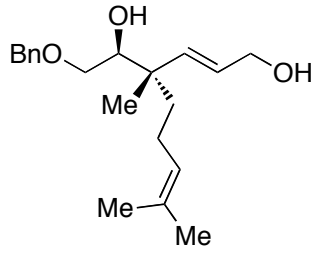


derived from reaction product using (*R,R*)-**1.32**



reaction product spiked with "rac"

Retention Time	Area	Area %	Height	Height %
11.530	27547574	4.29	1610403	5.49
13.200	613910926	95.71	27748826	94.51



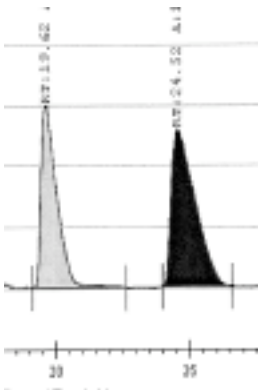
(4*S*,5*S*,*E*)-6-(benzyloxy)-4-methyl-4-(4-methylpent-3-en-1-yl) hex-2-ene-1,5-diol (1.105). The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499.1 μmol), Pt $(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (16.4 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) in toluene (0.50 mL, 1.0 M), and freshly distilled benzyloxyacetaldehyde (75.0 mg, 499.1 μmol). The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.19 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (117.6 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (3H, s), 1.33-1.46 (2H, m), 1.55 (3H, s), 1.64 (3H, s), 1.77-1.84 (1H, m), 1.87-1.94 (1H, m), 3.34 (1H, t, *J* = 9.5 Hz), 3.58 (1H, dd, *J* = 9.5 Hz, 2.5 Hz), 3.63 (1H, dd, *J* = 9.0 Hz, 2.5 Hz), 4.10 (2H, d, *J* = 5.5 Hz), 4.51 (2H, dd, *J* = 17.0 Hz, 12.0 Hz), 5.05 (1H, ddd, *J* = 6.0 Hz, 6.0 Hz, 1.5 Hz), 5.58 (1H, ddd, *J* = 16.0 Hz, 6.0 Hz, 6.0 Hz), 5.70 (1H, d, *J* = 16.0 Hz), 7.26-7.34 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 18.7, 22.4, 25.6, 37.6, 41.9, 63.9, 71.0, 73.3, 75.7, 124.6, 127.66, 127.74, 128.4, 131.3, 137.3, 137.9; IR (neat): 3412.8 (m), 2921.9 (s), 2859.4 (m), 1453.6 (m), 1092.4 (s), 982.7 (m), 736.4 (m), 698.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{34}NO_3$ [M+NH_4]: calculated: 336.2539, found: 336.2542. $[\alpha]_D^{25}$ = +7.63 (*c* = 0.72, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

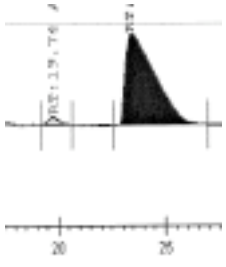
The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-

di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

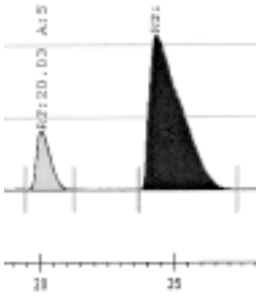
Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C) - analysis of the reaction product.



mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**

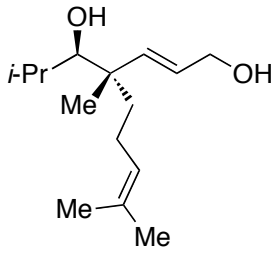


reaction product from (*R,R*)-**1.32**



reaction product spiked with "rac"

Peak No	% Area	Area	RT (min)	Height (mV)
1	3.0359	1340.8172	19.74	41.1508
2	96.9641	42824.4476	23.33	451.6391



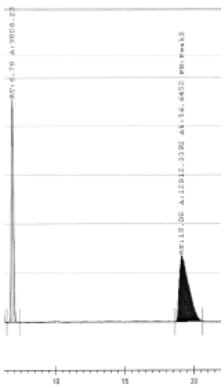
(4*S*,5*R*,*E*)-4,6-dimethyl-4-(4-methylpent-3-en-1-yl)hept-2-ene-1,5-diol (1.106). The diboration/allylation was performed according to the representative procedure with the following modifications: (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499.1 μmol), $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**1.32**) (16.4 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) in toluene (0.50 mL, 1.0 M), and freshly distilled isobutyraldehyde (108.0 mg, 1.50 mmol). The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.38 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (69.6 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84

(3H, d, J = 7.0 Hz), 0.96 (3H, d, J = 7.0 Hz), 0.99 (3H, s), 1.35-1.44 (2H, m), 1.55 (3H, s), 1.64 (3H, s), 1.75-1.83 (1H, m), 1.85-1.94 (2H, m), 3.19 (1H, s), 4.12 (2H, d, J = 5.5 Hz), 5.05 (1H, t, J = 6.0 Hz), 5.58 (1H, ddd, J = 16 Hz, 5.5 Hz, 5.5 Hz), 5.69 (1H, d, J = 15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.6, 17.6, 18.8, 22.7, 23.5, 25.6, 28.6, 38.5, 44.4, 63.9, 81.4, 124.8, 128.3, 131.3, 138.5; IR (neat): 3375.5 (m), 2964.6 (s), 2871.8 (m), 1465.2 (m), 1378.4 (m), 1077.2 (w), 980.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{27}O$ [M+H-H_2O]: calculated: 223.2062, found: 223.2070. $[\alpha]_D^{25}$ = -3.80 (c = 1.21, $CHCl_3$, l = 50 mm).

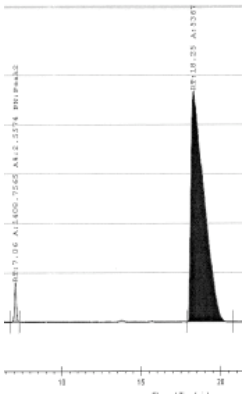
Analysis of Stereochemistry:

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for SFC analysis. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C)- analysis of (S,E)-4-((R)-1-hydroxy-2-methylpropyl)-4,8-dimethylnona-2,7-dien-1-yl benzoate.



mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**



reaction product from (*R,R*)-**1.32**

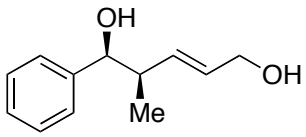
Peak No	% Area	Area	RT (min)	Height (mV)
1	2.5574	1408.7565	7.06	160.6432
2	97.4426	53676.012	18.25	934.6718

1.9.10. Representative Procedure for Diboration/Allylation/Oxidation of Monosubstituted *Cis*-1,3-Dienes

To an oven-dried 6-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (12.7 mg, 14.1 μmol), (*R,R*)-3,5-di-*i*-butylphenyl-TADDOLPPh (**1.81**) (28.8 mg, 28.3 μmol), $B_2(pin)_2$ (119.7 mg, 471.2 μmol) and tetrahydrofuran (4.7 mL, [substrate] = 0.1 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*Z*)-penta-1,3-diene (32.0 mg, 471.2 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was then cooled to ambient temperature and the solvent was removed *in vacuo*. The vial was sealed, returned to the glove box and charged with

dichloromethane (1.0 mL) and freshly distilled benzaldehyde (25.0 mg, 235.6 μmol). The reaction was brought to the bench and allowed to stir at room temperature for 12 h at which time the reaction mixture was cooled to 0 °C (ice/water) and charged with tetrahydrofuran (2.0 mL), 3 M sodium hydroxide solution (2 mL), and 30 wt % hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 12 h at which time the vial was cooled to 0 °C (ice/water). Saturated aqueous sodium thiosulfate (2 mL) was carefully added dropwise. The reaction mixture was diluted with ethyl acetate (5 mL) and the aqueous and organic layers were separated. The aqueous layer was rinsed with ethyl acetate (3 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.23 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (32.6 mg, 72%).

1.9.11. Characterization and Proof of Stereochemistry.

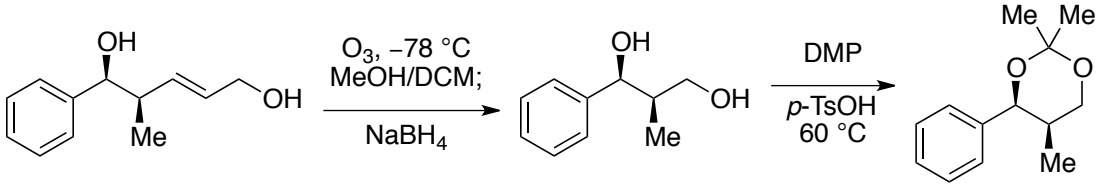


(4*R*,5*S*,*E*)-4-methyl-5-phenylpent-2-ene-1,5-diol (1.108). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.01 (3H, d, *J* = 6.6 Hz), 1.23 (2H, br s), 2.56-2.60 (1H, m), 4.05 (2H, d, *J* = 3.6 Hz), 4.60 (1H, d, *J* = 5.4 Hz), 5.61-5.62 (2H, m), 7.26-7.30 (3H, m), 7.31-7.33 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.5, 43.4, 63.6, 77.6, 126.5, 127.5, 128.1, 130.1, 134.3, 142.6; IR (neat): 3355.9 (br m), 2967.3 (w), 2929.1 (w), 2873.0 (w), 1719.7 (w), 1452.3 (m), 1370.6 (w), 1259.5 (w), 1055.1

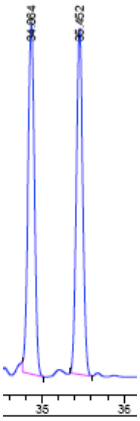
(w), 973.2 (s), 755.1 (m), 700.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{20}NO_2$ [M+NH_4]: calculated: 210.1494, found: 210.1492. $[\alpha]^{25}_D$ = -14.00 (*c* = 0.90, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

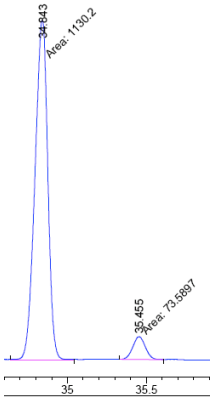
The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/ reduction, followed by acetonide protection (as shown below) for GLC analysis. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The major diastereomer was determined by measuring the coupling constant of the carbinol hydrogen in the six-membered ring ketal below by ^1H NMR: *J* = 4.0 Hz, proving *syn* stereochemistry.



Chiral GLC (β-Dex 120, Supelco, 90 °C for 5 min, ramp 2 °C/min to 150 °C, 20 psi, s/r = 35:1) - analysis of 2,2,5-trimethyl-4-phenyl-1,3-dioxane.



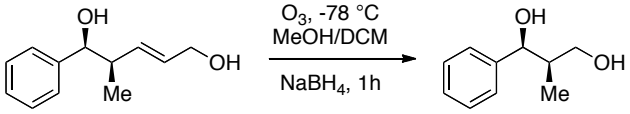
racemic



derived from reaction

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	34.843	MM	0.0941	1130.20166	200.08630	93.88684
2	35.455	MM	0.0918	73.58967	13.36460	6.11316

The absolute stereochemistry was determined by subjecting the 1,5-diol to ozonolysis/reduction. The specific rotation of the resulting 1,3-diol ($[\alpha]^{24}_D$ = -57.20 (*c* = 0.16, $CHCl_3$, *l* = 50 mm)) was compared to literature values ($[\alpha]^{24}_D$ = -51.60 (c = 0.15, $CHCl_3$)).[66]

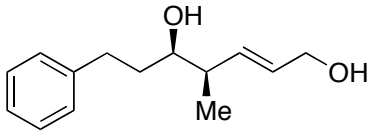


$[\alpha]^{24}_D$ = -57.2 (c=0.16, $CHCl_3$)

The olefin geometry of the 1,5-diol was determined to be *trans* by measuring the coupling constants of the vinylic hydrogens from the ^1H NMR taken in benzene: ^1H

[66] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.

NMR (500 MHz, C_6D_6): δ 0.97 (3H, d, *J* = 6.5 Hz), 2.42 (1H, ddq, *J* = 13.0 Hz, 13.0 Hz, 7.0 Hz), 3.79 (2H, dd, *J* = 5.5 Hz, 1.0 Hz), 4.38 (1H, d, *J* = 5.5 Hz), 5.44 (1H, ddd, *J* = 16.0 Hz, 5.5 Hz, 5.5 Hz), 5.54 (1H, dd, *J* = 15.5 Hz, 7.5 Hz), 7.06-7.10 (1H, m), 7.18-7.23 (3H, m).

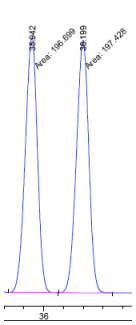


(4*R*,5*R*,*E*)-4-methyl-7-phenylhept-2-ene-1,5-diol (1.112). The diboration/allylation was performed according to the representative procedure with (*Z*)-penta-1,3-diene (40.6 mg, 596.2 μmol), $Pt(dba)_3$ (16.1 mg, 17.9 μmol), (*R*,*R*)-3,5-di-*i*-butylphenylTADDOLPPh (**1.81**) (36.5 mg, 35.8 μmol), $B_2(pin)_2$ (151.9 mg, 596.2 μmol) in tetrahydrofuran (6.0 mL, 0.1 M), freshly distilled hydrocinnamaldehyde (40.0 mg, 298.1 μmol) and dichloromethane (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.19 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (45.9 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.02 (3H, d, *J* = 6.6 Hz), 1.64-1.70 (1H, m), 1.76-1.82 (1H, m), 2.30 (1H, dd, *J* = 12.0 Hz, 6.6 Hz), 2.63 (1H, ddd, *J* = 13.8 Hz, 9.6 Hz, 6.6 Hz), 2.83 (1H, ddd, *J* = 13.8 Hz, 9.6 Hz, 4.8 Hz), 3.50 (1H, ddd, *J* = 9.0 Hz, 5.4 Hz, 3.0 Hz), 4.11 (2H, d, *J* = 5.4 Hz), 5.61-5.71 (2H, m), 7.15-7.19 (3H, m), 7.23-7.29 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.7, 32.5, 35.9, 42.4, 63.6, 74.3, 125.9, 128.41, 128.44, 130.0, 134.5, 142.1 ; IR (neat): 3350.7 (br m), 3024.3 (w), 2920.9 (m), 2855.7 (w), 1718.7 (w), 1495.8 (w), 1453.3 (m), 1377.1 (w), 1315.7 (w), 1259.9 (w), 1066.4 (s), 1028.2 (s), 973.4 (m), 920.0 (w), 870.4 (w), 746.6 (m), 699.8 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{24}NO_2$ [M+NH_4]: calculated: 238.1807, found: 238.1801. $[\alpha]^{25}_D$ = +26.52 (*c* = 0.98, $CHCl_3$, *l* = 50 mm).

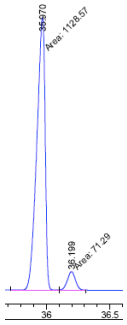
Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/ reduction, followed by acetonide protection. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The major diastereomer was determined by measuring the coupling constant of the carbinol hydrogen in the six-membered ring ketal below by ^1H NMR: J = 3.5 Hz, proving *syn* stereochemistry. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 90 °C for 5 min, ramp 3 °C/min to 180 °C, 20 psi, s/r = 35:1) - analysis of 2,2,5-trimethyl-4-phenethyl-1,3-dioxane.

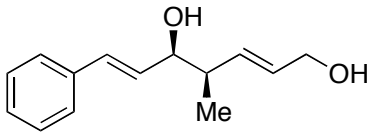


racemic



derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	35.970	MM	0.0765	1128.57434	245.91464	94.05849
2	36.199	MM	0.0724	71.29002	16.40378	5.94151



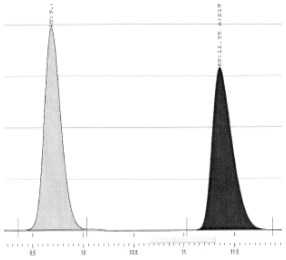
(2*E*,4*R*,5*R*,6*E*)-4-methyl-7-phenylhepta-2,6-diene-1,5-diol (1.113). The diboration/allylation was performed according to the representative procedure with (*Z*)-penta-1,3-diene (31.0 mg, 454.0 μmol), $Pt(dba)_3$ (12.2 mg, 13.6 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh **(1.81)** (27.8 mg, 27.2 μmol), $B_2(pin)_2$ (115.3 mg, 454.0 μmol) in

tetrahydrofuran (4.5 mL, 0.1 M), freshly distilled cinnamaldehyde (30 mg, 227.0 μmol), and dichloromethane (0.9 mL). The crude reaction mixture was purified by column chromatography on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.16 in 50% ethyl acetate/hexanes, stain in PMA) to afford a white solid (32.7 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.07 (3H, d, *J* = 6.6 Hz), 1.22 (2H, br s), 2.46-2.51 (1H, m), 4.12 (2H, d, *J* = 4.2 Hz), 4.20 (1H, dd, *J* = 5.4 Hz, 5.4 Hz), 5.69-5.76 (2H, m), 6.20 (1H, dd, *J* = 15.6 Hz, 6.6 Hz), 6.57 (1H, d, *J* = 15.6 Hz), 7.21-7.23 (1H, m), 7.29-7.33 (2H, m), 7.35-7.38 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.2, 42.5, 63.6, 76.0, 126.5, 127.7, 128.6, 129.8, 130.6, 131.4, 133.7, 136.7; IR (neat): 3362.1 (br m), 2957.9 (w), 2924.8 (m), 2869.3 (w), 2854.6 (w), 1715.4 (w), 1494.7 (w), 1450.5 (m), 1377.4 (w), 1070.1 (w), 968.8 (s), 750.0 (m), 695.1 (m); HRMS-(ESI+) for $C_{14}H_{22}NO_2$ [M+NH_4]: calculated: 236.1651, found: 236.1653. $[\alpha]^{25}_D$ = -17.40 (*c* = 0.70, $CHCl_3$, *l* = 50 mm).

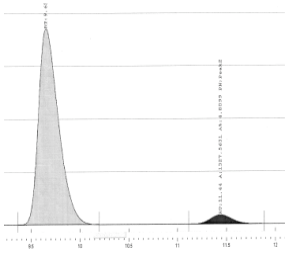
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy. The olefin geometry of the 1,5-diol was determined to be *trans* by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in benzene: ^{1}H NMR (500 MHz, C_6D_6): δ 1.01 (3H, d, *J* = 9.0 Hz), 2.29 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 8.5 Hz), 3.83 (2H, d, *J* = 7.0 Hz), 3.97 (1H, ddd, *J* = 8.0 Hz, 2.0 Hz, 2.0 Hz), 5.53 (1H, ddd, *J* = 20.0 Hz, 5.5 Hz, 5.5 Hz), 5.63 (1H, dd, *J* = 19.5 Hz, 9.0 Hz), 6.13 (1H, dd, *J* = 20.0 Hz, 7.0 Hz), 6.51 (1H, d, *J* = 20.0 Hz), 7.03-7.09 (1H, m), 7.11-7.13 (2H, m), 7.26-7.28 (2H, m).

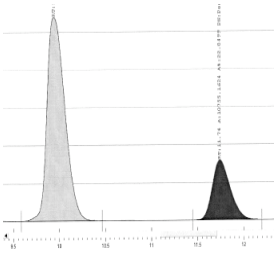
Chiral SFC (AD-H, Chiraldex, 5 mL/min, 5% MeOH, 100 bar, 35 °C) - analysis of reaction product.



racemic

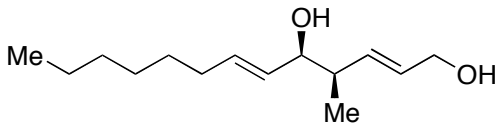


reaction product



coinjection of diboration product + racemic

Peak No	% Area	Area	RT (min)	Height (mV)
1	95.1901	26272.8013	9.65	1850.4523
2	4.8099	1327.5631	11.44	86.6913



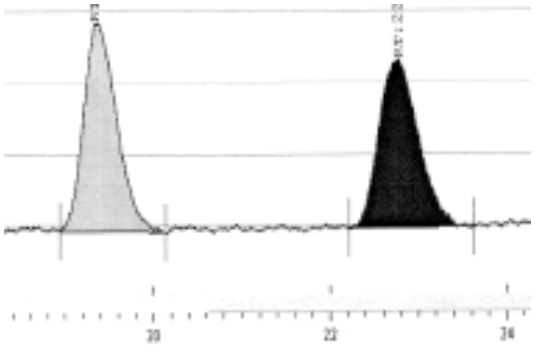
(2*E*,4*R*,5*R*,6*E*)-4-methyltrideca-2,6-diene-1,5-diol (1.114). The diboration/allylation was performed according to the representative procedure with (*Z*)-1,3-pentadiene (30.0 mg, 440.4 μmol), $Pt(dba)_3$ (11.8 mg, 13.2 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh (**1.81**) (27.0 mg, 26.4 μmol), $B_2(pin)_2$ (117.4 mg, 462.4 μmol) in tetrahydrofuran (4.4 mL, 0.1 M), freshly distilled nonenal (31.0 mg, 220.2 μmol) and dichloromethane (0.9 mL). The crude reaction mixture was purified by column chromatography on silica gel (25-40% ethyl acetate/hexanes, R_f = 0.37 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (32.7 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.5 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 1.23-1.34 (6H, m), 1.47 (2H, br s), 2.02 (2H, ddd, *J* = 14.0 Hz, 7.0 Hz, 7.0 Hz), 2.36 (1H, m), 3.95 (1H, br s), 4.11 (2H, br s), 5.42 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 5.60-5.72 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.5. 22.8, 29.0, 29.4, 31.9, 32.5, 42.5, 64.0, 76.5, 130.3, 130.4, 133.7,

134.3; IR (neat): 3355.2 (m), 2924.7 (s), 2854.7 (m), 1456.9 (w), 1003.2 (m), 968.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{30}NO_2$ [M+NH_4]: calculated: 244.2276, found: 244.2271. $[\alpha]^{25}_D$ = +12.73 (*c* = 0.54, $CHCl_3$, *l* = 50 mm).

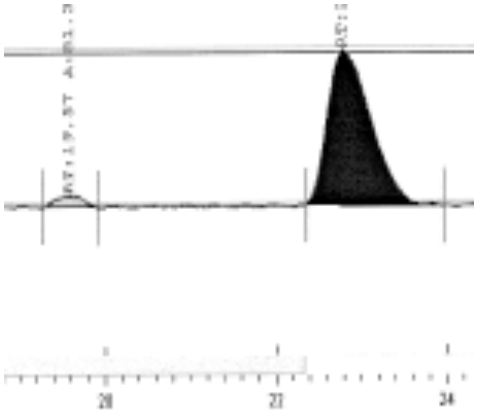
Analysis of Stereochemistry:

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for SFC analysis. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 3 mL/min, 3% MeOH, 100 bar, 35 °C) - analysis of the mono (benzoate) of the reaction product.

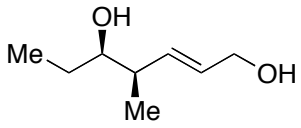


racemic



derived from reaction product

Peak No	% Area	Area	RT (min)	Height (mV)
1	4.3907	81.3506	19.57	3.7672
2	95.6093	1771.4541	22.78	50.2873



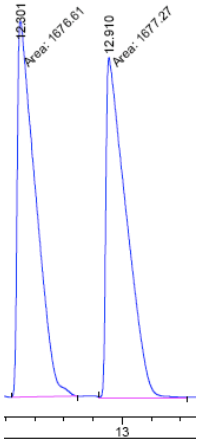
(4*R*,5*R*,*E*)-4-methylhept-2-ene-1,5-diol (1.115). The diboration/allylation was performed according to the representative procedure with (*Z*)-penta-1,3-diene (58.6 mg, 860.8 μmol), $Pt(dba)_3$ (23.2 mg, 25.8 μmol), (*R*,*R*)-3,5-di-*i*-butylphenylTADDOLPPh (**1.81**)

(52.7 mg, 51.6 μmol), $B_2(pin)_2$ (218.6 mg, 860.8 μmol) in tetrahydrofuran (2.9 mL, 0.3 M), freshly distilled propionaldehyde (25.0 mg, 430.4 μmol), and dichloromethane (1.7 mL). The crude reaction mixture was purified by column chromatography on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.15 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (45.3 mg, 73%**).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* = 7.0 Hz), 1.00 (3H, d, *J* = 7.0 Hz), 1.32-1.41 (1H, m), 1.48-1.56 (1H, m), 1.69 (2H, br s), 2.25-2.31 (1H, m), 3.39 (1H, dddd, *J* = 4.5 Hz, 4.5 Hz 4.5 Hz, 4.5 Hz), 4.10 (2H, d, *J* = 4.5 Hz), 5.62-5.71 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.4, 14.3, 26.9, 41.7, 63.6, 76.4, 129.6, 135.1; IR (neat): 3333.4 (br m), 2962.8 (w), 2931.0 (w), 2874.7 (w), 1457.3 (w), 1376.1 (w), 1081.6 (w), 1022.8 (w), 1003.9 (m), 971.9 (s), 704.7 (w) cm^{-1}; HRMS-(ESI+) for $C_8H_{20}NO_2$ [M+NH_4]: calculated: 162.1494, found: 162.1499. $[\alpha]^{25}_D$ = +26.74 (*c* = 0.50, $CHCl_3$, *l* = 50 mm).

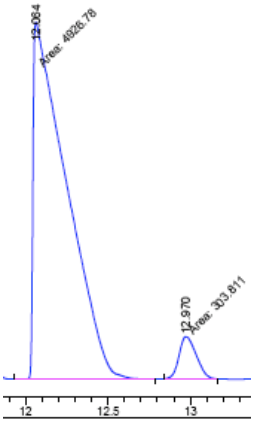
Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/ reduction, followed by acetonide protection. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 70 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of 4-ethyl-2,2,5-trimethyl-1,3-dioxane.

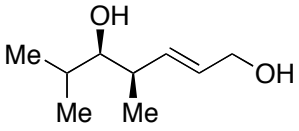


racemic



derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	12.064	MM	0.2343	4926.78467	350.49905	94.19166
2	12.970	MM	0.1209	303.81058	41.88768	5.80834



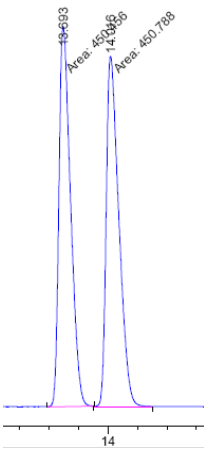
(4*R*,5*R*,*E*)-4,6-dimethylhept-2-ene-1,5-diol (1.116). The diboration/allylation was performed according to the representative procedure with (*Z*)-1,3-pentadiene (56.6 mg, 830.8 μmol), $Pt(dba)_3$ (22.4 mg, 24.9 μmol), (*R*,*R*)-3,5-di-*i*-butylphenylTADDOLPPh (**1.81**) (50.9 mg, 49.8 μmol), $B_2(pin)_2$ (221.5 mg, 872.4 μmol) in tetrahydrofuran (8.3 mL, 0.1 M), freshly distilled isobutyraldehyde (30.0 mg, 415.4 μmol) and dichloromethane (1.6 mL). The crude reaction mixture was purified by column chromatography on silica gel (25-40% ethyl acetate/hexanes, R_f = 0.28 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (40.8 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (6H, dd, *J* = 8.5 Hz, 6.5 Hz), 1.02 (3H, d, *J* = 8.0 Hz), 1.39 (2H, br s), 1.73 (1H, m), 2.36 (1H, m), 3.15

(1H, dd, J = 7.0 Hz, 7.0 Hz), 4.10 (2H, d, J = 5.5 Hz), 5.62-5.71 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 17.0, 19.7, 30.6, 39.3, 63.7, 79.8, 129.1, 135.8; IR (neat): 3330.8 (m), 2959.2 (m), 2924.8 (s), 1459.0 (m),1085.5 (m), 970.6 (s) cm^{-1}; HRMS-(ESI+) for $C_9H_{22}NO_2$ [M+NH_4]: calculated: 176.1650, found: 176.1649. $[\alpha]^{25}_D$ = +10.54 (c = 0.57, $CHCl_3$, l = 50 mm).

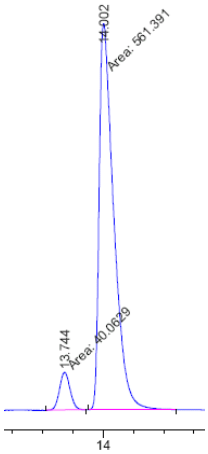
Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/ reduction, followed by acetonide protection. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 70 °C for 5 min, ramp 3 °C/min to 140 °C, 20 psi, s/r = 35:1) - analysis of 4-isopropyl-2,2,5-trimethyl-1,3-dioxane.



racemic



derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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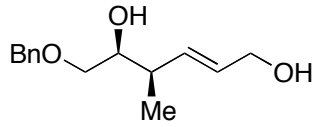
2	14.002	MM	0.1108	561.39105	84.41213	93.33899

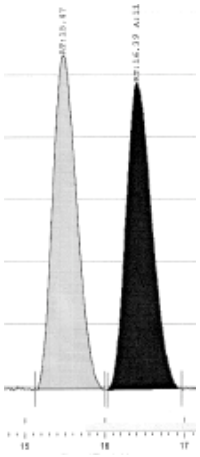


(4*R*,5*S*,*E*)-6-(benzyloxy)-4-methylhex-2-ene-1,5-diol (1.117). The diboration/allylation was performed according to the representative procedure with (*Z*)-1,3-pentadiene (30.0 mg, 440.4 μmol), $Pt(dba)_3$ (11.8 mg, 13.2 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh (**1.56**) (27.0 mg, 26.4 μmol), $B_2(pin)_2$ (117.4 mg, 462.4 μmol) in tetrahydrofuran (4.4 mL, 0.1 M), freshly distilled benzyloxyacetaldehyde (33.0 mg, 220.2 μmol) and dichloromethane (0.9 mL). The crude reaction mixture was purified by column chromatography on silica gel (35-50% ethyl acetate/hexanes, R_f = 0.19 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (37.5 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (3H, d, *J* = 7.0 Hz), 1.23 (2H, br s), 2.34 (1H, m), 3.37 (1H, dd, *J* = 9.5 Hz, 7.5 Hz), 3.52 (1H, dd, *J* = 9.5 Hz, 3.0 Hz), 3.63 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 3.5 Hz), 4.07 (2H, d, *J* = 4.5 Hz), 4.50 (1H, d, *J* = 11.5 Hz), 4.54 (1H, d *J* = 11.5 Hz), 5.64-5.66 (2H, m), 7.26-7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9, 39.6, 63.6, 72.6, 73.4, 73.6, 127.6, 127.8, 128.5, 129.7, 134.1, 137.9; IR (neat): 3380.3 (s), 2924.6 (s), 2858.7 (s), 1719.1 (w), 1453.9 (m), 1078.9 (s), 974.3 (s), 698.6 (m) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{24}NO_2$ [M+NH_4]: calculated: 254.1756, found: 254.11755. $[\alpha]^{25}_D$ = +13.59 (*c* = 0.48, $CHCl_3$, *l* = 50 mm).

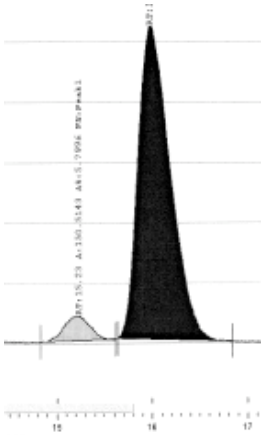
Analysis of Stereochemistry:

The enantioselectivity was determined SFC analysis of the reaction product. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

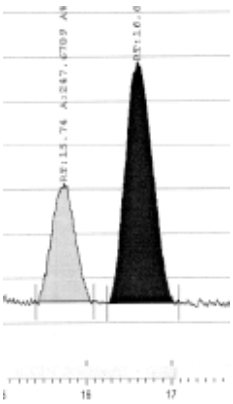
Chiral SFC (AD-H, Chiraldex, 100 bar, 5 mL/min, 4% MeOH, 35 °C)- analysis of reaction product.



racemic

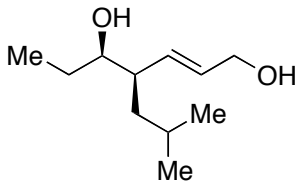


reaction product



coinjection of diboration product + racemic

Peak No	% Area	Area	RT (min)	Height (mV)
1	5.7996	150.5143	15.23	8.1557
2	94.2004	2444.7506	15.98	103.8991



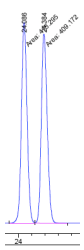
(4*R*,5*R*,*E*)-4-isobutylhept-2-ene-1,5-diol (1.119). The diboration/allylation was performed according to the representative procedure with (*Z*)-6-methylhepta-1,3-diene (75.9 mg, 688.7 μmol), $Pt(dba)_3$ (18.6 mg, 20.7 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (32.9 mg, 41.3 μmol), $B_2(pin)_2$ (174.9 mg, 688.7 μmol) in tetrahydrofuran (2.3 mL, 0.3 M), distilled propionaldehyde (20.0 mg, 344.3 μmol), and dichloromethane (1.4 mL), followed by oxidation to afford an inseparable 1:1 mixture of the 1,2-diol and diboration/allylation product. To facilitate purification, the crude reaction mixture was dissolved in THF:Et_2O:H_2O (1:1:1) and $NaIO_4$ (4 equiv) was added at room temperature (oxidative cleavage of both the 1,2-diboration product and pinacol). The reaction mixture

was stirred for 2h, after which time it was diluted with ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (20-40% ethyl acetate/hexanes, R_f = 0.23 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (46.3 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.81 (3H, d, *J* = 6.6 Hz), 0.87 (3H, d, *J* = 6.6 Hz), 0.94 (3H, t, *J* = 7.2 Hz), 1.19-1.25 (2H, m), 1.26-1.33 (1H, m), 1.50-1.57 (2H, m), 1.73 (2H, br s), 2.22 (1H, dddd, *J* = 9.6 Hz, 9.6 Hz, 5.4 Hz, 5.4 Hz), 3.36 (1H, ddd, *J* = 8.4 Hz, 4.8 Hz, 3.0 Hz), 4.10 (2H, d, *J* = 5.4 Hz), 5.47 (1H, dd, *J* = 15.6 Hz, 9.6 Hz), 5.67 (1H, ddd, *J* = 15.6 Hz, 6.0 Hz, 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.5, 21.4, 23.9, 25.3, 26.5, 39.2, 46.5, 63.5, 76.5, 131.3, 133.2; IR (neat): 3351.3 (br m), 2954.7 (m), 2927.4 (m), 2869.3 (w), 1464.6 (w), 1382.8 (w), 1367.0 (w), 1074.2 (m), 1021.7 (m), 972.6 (s), 869.9 (w), 828.3 (w) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{26}NO_2$ [M+NH_4]: calculated: 204.1964, found: 204.1970. $[\alpha]^{25}_D$ = -21.07 (*c* = 0.58, $CHCl_3$, *l* = 50 mm).

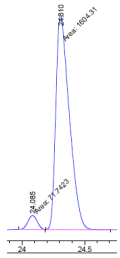
Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/ reduction, followed by acetonide protection. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 70 °C for 5 min, ramp 2 °C/min to 150 °C, 20 psi, s/r = 35:1) - analysis of 4-ethyl-5-isobutyl-2,2-dimethyl-1,3-dioxane.

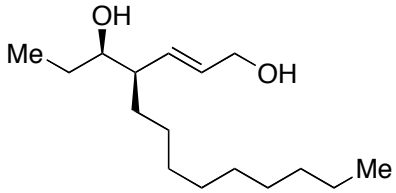


racemic



derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.085	MM	0.0856	71.74227	13.96429	4.28043
2	24.310	MM	0.1246	1604.31128	214.56406	95.71957



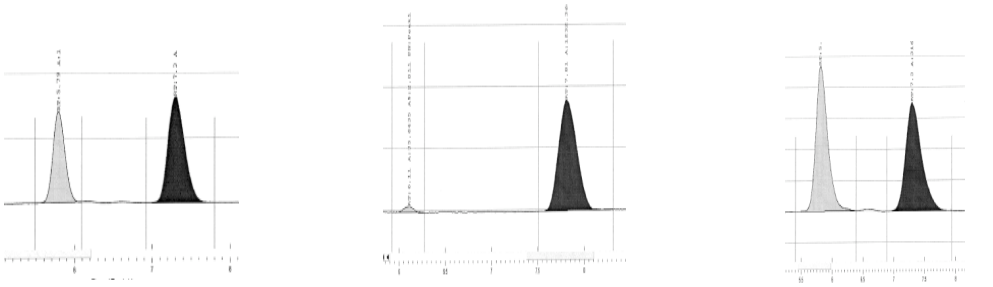
(4*R*,5*R*,*E*)-4-nonylhept-2-ene-1,5-diol (1.121). The diboration/allylation was performed according to the representative procedure with (*Z*)-trideca-1,3-diene (124.2 mg, 688.7 μmol), $Pt(dba)_3$ (18.6 mg, 20.7 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (**1.30**) (32.9 mg, 41.3 μmol), $B_2(pin)_2$ (174.9 mg, 688.7 μmol) in tetrahydrofuran (2.3 mL, 0.3 M), distilled propionaldehyde (20.0 mg, 344.3 μmol), and dichloromethane (1.4 mL), followed by oxidation to afford an inseparable 1:1 mixture of the 1,2-diol and diboration/allylation product. To facilitate purification, the crude reaction mixture was dissolved in THF:Et_2O:H_2O (1:1:1) and $NaIO_4$ (4 equiv) was added at room temperature (oxidative cleavage of both the 1,2-diboration product and pinacol). The reaction mixture was stirred for 2h, after which time it was diluted with ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and

concentrated in vacuo. The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.33 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (61.7 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.5 Hz), 0.94 (3H, t, *J* = 7.5 Hz), 1.22-1.33 (14H, m), 1.48-1.62 (2H, m), 2.07-2.13 (1H, m), 3.38 (1H, ddd, *J* = 9.0 Hz, 5.5 Hz, 3.0 Hz), 4.12 (2H, dd, 6.0 Hz, 1.5 Hz), 5.47 (1H, dd, *J* = 15.5 Hz, 9.5 Hz), 5.67 (1H, ddd, *J* = 15.5 Hz, 6.0 Hz, 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.4, 14.1, 22.7, 26.8, 27.4, 29.3, 29.59, 29.62, 29.7, 30.1, 31.9, 48.9, 63.6, 76.1, 131.4, 133.2; IR (neat): 3355.5 (br m), 2955.8 (w), 2922.5 (s), 2853.5 (m), 1463.3 (w), 1377.5 (w), 1078.2 (w), 1019.5 (w), 973.0 (m), 721.2 (w) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{36}NO_2$ [M +NH_4]: calculated: 274.2746, found: 274.2751. $[\alpha]^{25}_D$ = -10.42 (*c* = 0.84, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/ reduction. The resulting 1,3-diol was treated with benzoic anhydride and Et_3N to make the mono(benzoate) for SFC analysis. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 5 mL/min, 5% MeOH, 100 bar, 35 °C) - analysis of 2-(1-hydroxypropyl)undecyl benzoate.



racemic

derived from reaction product

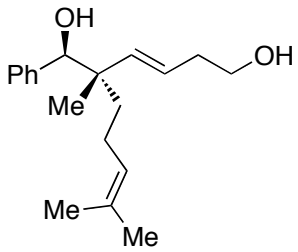
coinjection of diboration product + racemic

Peak No	Area	RT (min)	Height (mV)
1	2.811	6.11	4.7413
2	97.189	7.81	89.8004

1.9.12. Diboration/Allylation/Homologation/Oxidation, Procedure, Characterization and Proof of Stereochemistry.

To an oven-dried 2-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (**1.32**) (16.3 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) and toluene (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499.1 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was then cooled to ambient temperature, returned to the glove box and charged with freshly distilled benzaldehyde (53.0 mg, 499.1 μmol). The reaction was heated to 60 °C in and oil bath and was allowed to stir for 24 h. The reaction mixture was then cooled to ambient temperature and the vial cap was exchanged for a septum. After the vial was

purged with N_2, tetrahydrofuran (2.5 mL) was added via syringe, followed by bromochloromethane (84 μL, 1.25 mmol). The reaction mixture was then cooled to -78 °C (dry ice/acetone) and *n*-BuLi (0.50 mL, 1.25 mmol, 2.48 M in hexane) was added dropwise under N_2. The reaction was allowed to stir at 78 °C for 10 min, and was then allowed to warm to rt and stir for 7 h. The reaction mixture was then transferred to a scintillation vial using tetrahydrofuran (2 x 1 mL) to rinse the reaction vial. The reaction mixture was then cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide solution (2 mL) and 30 wt % hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (2 mL) was carefully added dropwise. The reaction mixture was diluted with ethyl acetate (5 mL) and the aqueous and organic layers were separated. The aqueous layer was rinsed with ethyl acetate (3 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.32 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (119.5 mg, 83%).



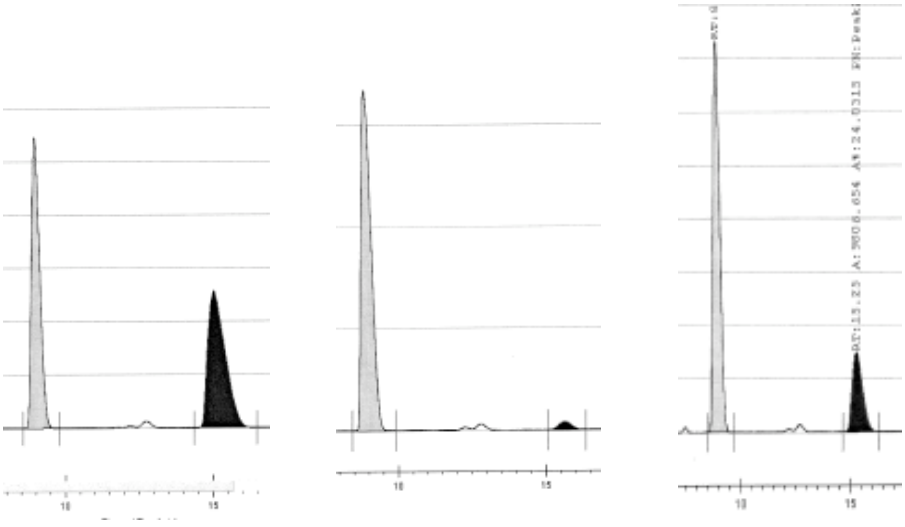
(1*S*,2*S*,*E*)-2-methyl-2-(4-methylpent-3-en-1-yl)-1-phenylhex-3-ene-1,6-diol (1.127). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, s), 1.21-1.28 (1H, m), 1.38-1.43 (1H, m), 1.53 (3H, s), 1.64 (3H, s), 1.84 (2H, ddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz), 2.33 (2H, ddd, *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz), 3.58-3.67 (2H, m), 4.37 (1H, s), 5.03 (1H, t, *J* = 7.0 Hz), 5.37 (1H, ddd, *J* = 16.0 Hz, 7.0 Hz, 7.0 Hz), 5.55 (1H, d, *J* = 16.0 Hz), 7.22-7.30

(5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.0, 17.6, 22.9, 25.7, 36.2, 37.9, 45.3, 61.8, 80.3, 124.7, 127.1, 127.4, 127.5, 130.0, 131.2, 139.1, 140.7; IR (neat): 3378.7 (m), 2966.2 (m), 2925.7 (s), 2855.9 (m), 1452.6 (m), 1376.7 (w), 1046.3 (s), 982.3 (m), 745.6 (m), 702.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{32}NO_2$ [M+NH_4]: calculated: 306.2433, found: 306.2419. $[\alpha]_D^{25}$ = -55.77 (*c* = 0.34, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 5 mL/min, 5% MeOH, 35 °C)- analysis of reaction product.



mixture of products from (*R,R*)-**1.32** and

derived from reaction

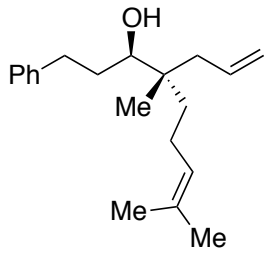
reaction product spiked

Peak No	% Area	Area	RT (min)	Height (mV)
1	97.1166	39804.9326	8.8	1668.4574
2	2.8834	1181.817	15.65	40.7109

1.9.13. Diboration/Allylation/Protodeboronation, Procedure, Characterization and Proof of Stereochemistry

To an oven-dried 2-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (**1.32**) (16.3 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) and toluene (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499.1 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was then cooled to ambient temperature, returned to the glove box and charged with freshly distilled hydrocinnamaldehyde (67.0 mg, 499.1 μmol). The reaction was heated to 60 °C in and oil bath and was allowed to stir for 24 h. The reaction mixture was then cooled to ambient temperature, TBAF•nH_2O (521.9 mg, 2.00 mmol) was added and the vial was quickly sealed with a septum and purged with N_2. The reaction mixture was then transferred via syringe to a separate 25 mL flame-dried round-bottomed flask containing oven-dried 4 Å molecular sieves. The original vial was washed with toluene (2 x 1 mL), and the mixture was allowed to stir at rt for 10 min (to remove excess water from TBAF•nH_2O). The reaction mixture was then cannula transferred to an oven-dried scintillation vial fitted with a septum, and the flask was rinsed with toluene (2.5 mL, final [substrate] = 0.1 M). The reaction mixture was then heated to 60 °C in an oil bath for 6 h, at which time it was cooled to rt and the volatiles were removed *in vacuo* and the residue was filtered over a silica plug (10% ethyl acetate/hexanes). The crude material was then purified by column chromatography on silica gel (2-8% ethyl acetate/hexanes,

R_f = 0.33 in 10% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (105.8 mg, 74%, 5:1 terminal:internal alkene).

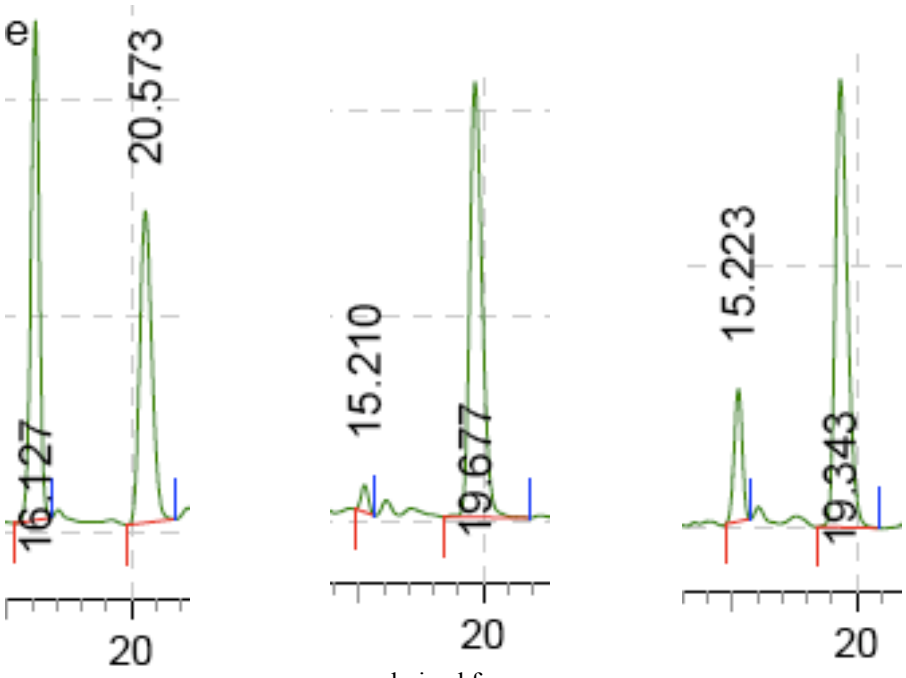


(3*R*,4*S*)-4-allyl-4,8-dimethyl-1-phenylnon-7-en-3-ol (1.109). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, s), 1.17-1.24 (2H, m), 1.32 (1H, ddd, *J* = 14.5 Hz, 14.5 Hz, 6.0 Hz) 1.51 (1H, br s), 1.57 (3H, s), 1.58-1.63 (1H, m), 1.65 (3H, s), 1.76-1.84 (1H, m), 1.86-1.94 (1H, m), 2.06 (1H, dd, *J* = 14.0 Hz, 7.0 Hz), 2.15 (1H, dd, *J* = 14.0 Hz, 8.0 Hz), 2.58 (1H, ddd, *J* = 16.0 Hz, 9.5 Hz, 6.5 Hz), 2.91 (1H, ddd, 14.5 Hz, 9.5 Hz, 4.0 Hz), 3.40 (1H, dd, *J* = 11.0 Hz), 5.01-5.09 (3H, m), 5.83 (1H, dddd, *J* = 17.0 Hz, 7.5 Hz, 7.5 Hz, 7.5 Hz), 7.15-7.20 (3H, m), 7.24-7.28 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 20.3, 22.1, 25.7, 33.2, 33.4, 36.4, 40.3, 40.8, 76.7, 117.1, 124.8, 125.8, 128.4, 128.5, 131.3, 135.6, 142.4; IR (neat): 3444.9 (br w), 3063.0 (w), 3026.7 (w), 2924.6 (s), 2924.6 (s), 2859.0 (m), 1637.8 (w), 1602.7 (w), 1495.4 (w), 1454.2 (s), 1378.0 (m), 1076.7 (m), 1040.5 (m), 913.1 (m), 748.5 (m), 699.5 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{31}O$ [M+H]: calculated: 287.2375, found: 287.2377. $[\alpha]_D^{25}$ = +40.54 (*c* = 0.69, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by HPLC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 0.5% IPA, 254 nm)- analysis of reaction product.

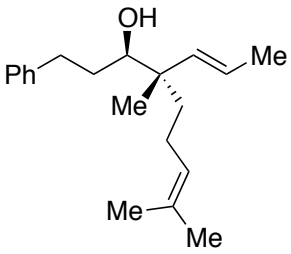


mixture of products from (*R,R*)-**1.32** and (*S,S*)-**1.32**

derived from reaction product using (*R,R*)-**1.32**

reaction product spiked with "rac"

Retention Time	Area	Area %	Height	Height %
15.210	1083144	3.39	54466	5.78
19.677	30853081	96.61	887157	94.22



(3*R*,4*S*)-4,8-dimethyl-1-phenyl-4-((*E*)-prop-1-en-1-yl)non-7-en-3-ol. Purified by column chromatography on silica gel (2-8% ethyl acetate/hexanes, R_f = 0.38 in 10% ethyl acetate/hexanes, stain in PMA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, s), 1.20-1.27 (2H, m), 1.28- 1.35 (1H, m), 1.53-1.61 (1H, m), 1.55 (3H, d, *J* = 0.5 Hz), 1.65 (3H, d, *J* = 1.0 Hz), 1.75-1.81 (1H, m), 1.82-1.88 (1H, m), 2.59 (1H, ddd, *J* = 14.0 Hz, 10.0 Hz, 7.0 Hz), 2.92 (1H, ddd, *J* = 14.0 Hz, 10.5 Hz, 5.0 Hz), 3.24 (1H, dd, *J* = 10.5 Hz, 1.5 Hz), 5.05 (1H, ddd, *J* = 6.0 Hz, 6.0 Hz, 1.5 Hz), 5.31 (1H, dq, *J* = 15.5 Hz, 1.5 Hz), 5.48 (1H, dq, *J* = 15.5 Hz, 6.0 Hz), 7.13-7.21 (3H, m), 7.24-7.28 (2H, m); ^{13}C NMR (125

MHz, $CDCl_3$): δ 17.2, 17.6, 18.3, 22.8, 25.7, 32.8, 33.4, 37.8, 44.3, 76.6, 124.9, 125.7, 125.9, 128.3, 128.5, 131.3, 136.8, 142.6; HRMS-(ESI+) for $C_{20}H_{29}$ [M+H-H_2O]: calculated: 269.2269, found: 269.2260.

Chapter 2

Development of Catalytic Enantioselective Tandem Allylation Strategy for the Rapid Construction of Highly Functionalized 1,4-Cyclohexanediols

2.1. Introduction

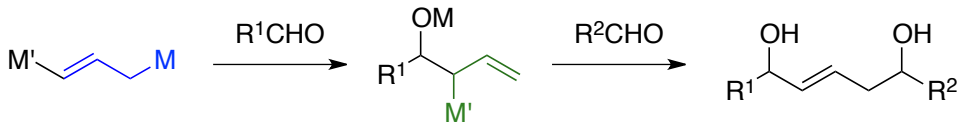
Given the enormous impact that diastereo- and enantioselective allylmetallation reactions have had on synthetic organic chemistry, it is not surprising that allylmetal reagents that would allow for iterative carbon-carbon bond forming reactions have also been developed. In order to accomplish a double allylation, two reactive metals must be correctly positioned about an alkene such that the first allylmetallation reaction unveils a second allylmetal species (Scheme 2.1).[67] While such double allylation reagents are extremely useful in the synthesis of polyhydroxylated natural products, they also introduce many synthetic challenges. Three different techniques can be used to render allylmetallations stereoselective: 1) installation of a chiral ligand on the metal, 2) design of a substrate in which chirality is present at the metal-bound carbon, or 3) implementation of a chiral catalyst to bias the allylboration transition state. As compared to simple allylation reagents, new diastereoselectivity issues arise because these allylation reagents will be used to form two new carbon-carbon bonds. Furthermore, fine tuning the reactivity of the metal centers must be achieved in order to perform a

[67] Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070.

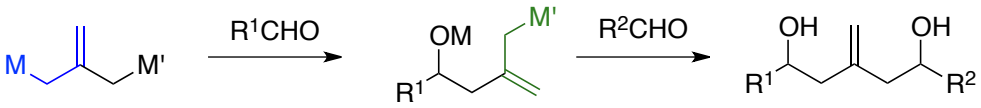
chemoselective addition to two different electrophilic species. To date, several double allylation reagents have been synthesized, and they are categorized into three classes (Scheme 2.1). The development of each will be described in the following sections.

Scheme 2.1. Classes of Bimetallic Double Allylation Reagents

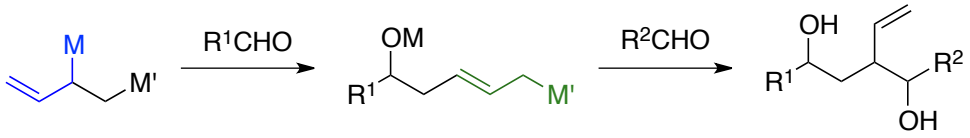
Type 1:



Type 2:



Type 3:



2.2. Background

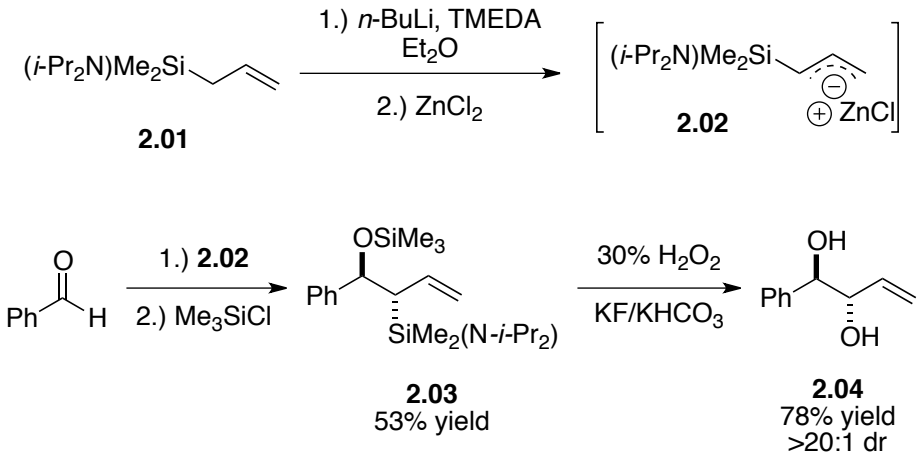
2.2.1. Early Development of Compounds with Double Allylation Motifs

The earliest silcon- and boron-based double allylation reagents were not, in fact, used to effect tandem allylation reactions. Instead, they were used to access 1,2-diols in high diastereomeric purity. As early as 1987, Ito and co-workers discovered that allyl (diisopropylamino)dimethylsilane **2.01** underwent lithiation with *n*-butyllithium in the presence of TMEDA, followed by the addition of $ZnCl_2$, to give heterobimetallic reagent **2.02** (Scheme 2.2).[68] In the presence of an aldehyde, allylzinconation gives the

[68] Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987,** *52*, 957.

corresponding 1,2-*anti*-diol **2.04** after silyl trapping with TMS-Cl and oxidation. This reaction was compatible with aromatic, heteroaromatic, and aliphatic aldehydes to give the corresponding racemic 1,2-diols in good yield and diastereoselectivity.

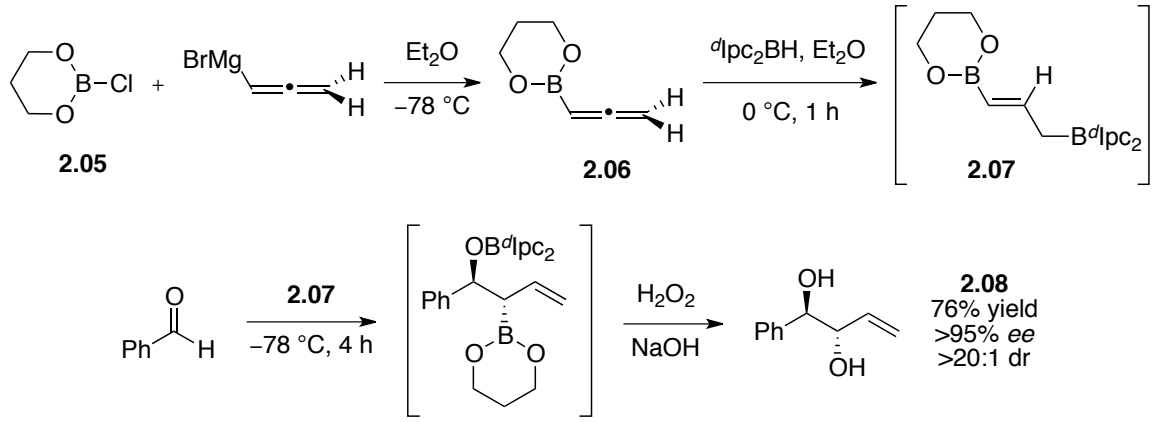
Scheme 2.2. Stereoselective α-Hydroxylallylation of Aldehydes



In the mid-1990's, Brown and co-workers synthesized enantiomerically enriched boron-based reagents analogous to Ito's silylation species through an entirely different synthetic route.[69] *B*-Allenyl-(1,3,2-dioxaborinane) **2.06** was prepared *via* the reaction of allenylmagenesium bromide and boronic ester **2.05**. The allenylboronate then underwent *E*-selective hydroboration with $B^d(Ipc)_2$ in ethereal solvent to generate mixed boronate/ borane reagent **2.07**,[70] which was then used without isolation or purification. When reacted with benzaldehyde, **2.07** underwent smooth allylboration to provide 1,2-diol **2.08** in 76% yield, >95% *ee*, and >20:1 diastereoselectivity for the *anti*-isomer after alkaline oxidation.

[69] Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686.
[70] Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.

Scheme 2.3. Enantioselective Synthesis of *Anti*-1,2-Diols *via* Boronic Ester Substituted Chiral Allylboronates



These synthetic routes to access the first Si- and B-based double allylation reagents laid the ground work for future development of these multifunctional species. By subjecting these reagents to >1 equivalent of an aldehyde electrophile, new and synthetically useful polyhydroxylated motifs can be accessed with ease in high stereoselectivity.

2.2.2. Type I Double Allylation Reagents

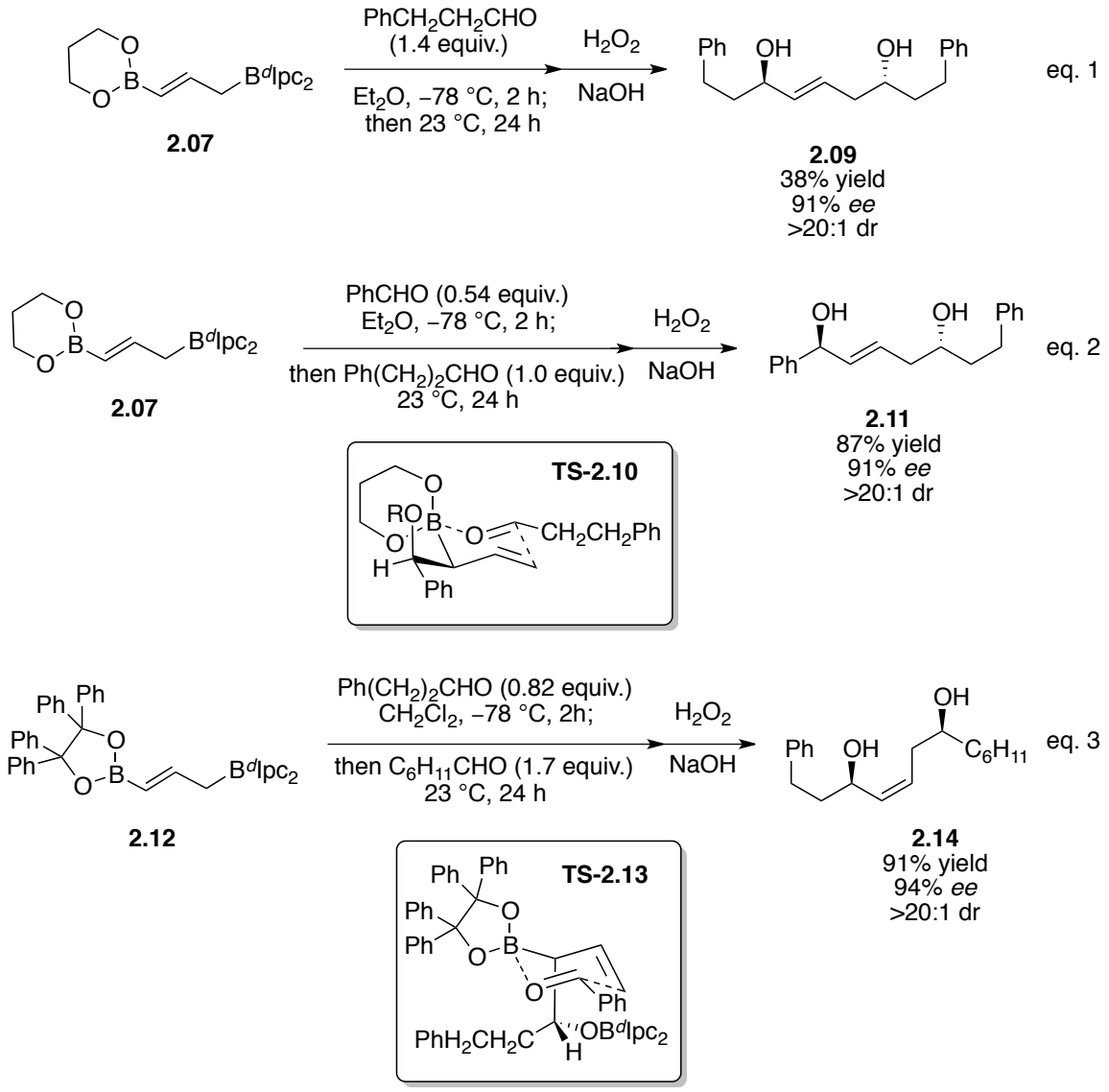
Type I bimetallic double allylation reagents were pioneered by William Roush, who spent over 10 years improving the synthesis and utility of various silicon, boron, and mixed Si/B-allyl reagents for the generation of *anti*-1,2-diols.[71] In 2002, he recognized the potential for Brown's 1,3-bifunctionalized allylation reagent **2.07** to be used in the stereoselective synthesis of *anti*-1,5-diols *via* a bisallylation pathway (Scheme 2.4).[72] When reacted with 1.4 equivalents of hydrocinnamaldehyde, the corresponding

[71] (a) Roush, W. R.; Grover, P. T. *Tetrahedron Lett.* **1990**, *31*, 7567. (b) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981. (c) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **199**, *62*, 1112. (d) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413.
[72] Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644.

1,5-diol **2.09** bearing an (*E*)-alkene was isolated in 38% yield and 91% *ee* (eq. 1). In order to achieve successful heterocoupling with two distinct aldehydes, the temperature and reagent stoichiometry had to be carefully controlled (eq. 2). With a small diolate ligand on boron, the second allylboration reaction proceeded through **TS-2.10** to afford *anti*-1,5-diol **2.11** in 87% yield and 91%*ee* as a single diastereomer with less than 5% of the the undesired homocoupled product. By increasing the steric bulk of the diolate backbone of the boronic ester, the (*Z)*-1,5-*syn*-diol could also be accessed in high diastereoselectivity *via* **TS-2.13** (eq. 3).[73] Roush later extended this methodology to the synthesis of 2-methyl-1,2-*syn*- and 2-methyl-1,2-*anti*-3-butenediols using double allylboration reagents derived from hydroboration of methyl-substituted allenyl boronates.[74]

[73] Winbush, S. M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 4344.
[74] Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *1312*, 14602.

Scheme 2.4. Enantioselective Synthesis of *anti*- and *syn*-1,5-Diols Using Double Allylboration Strategy



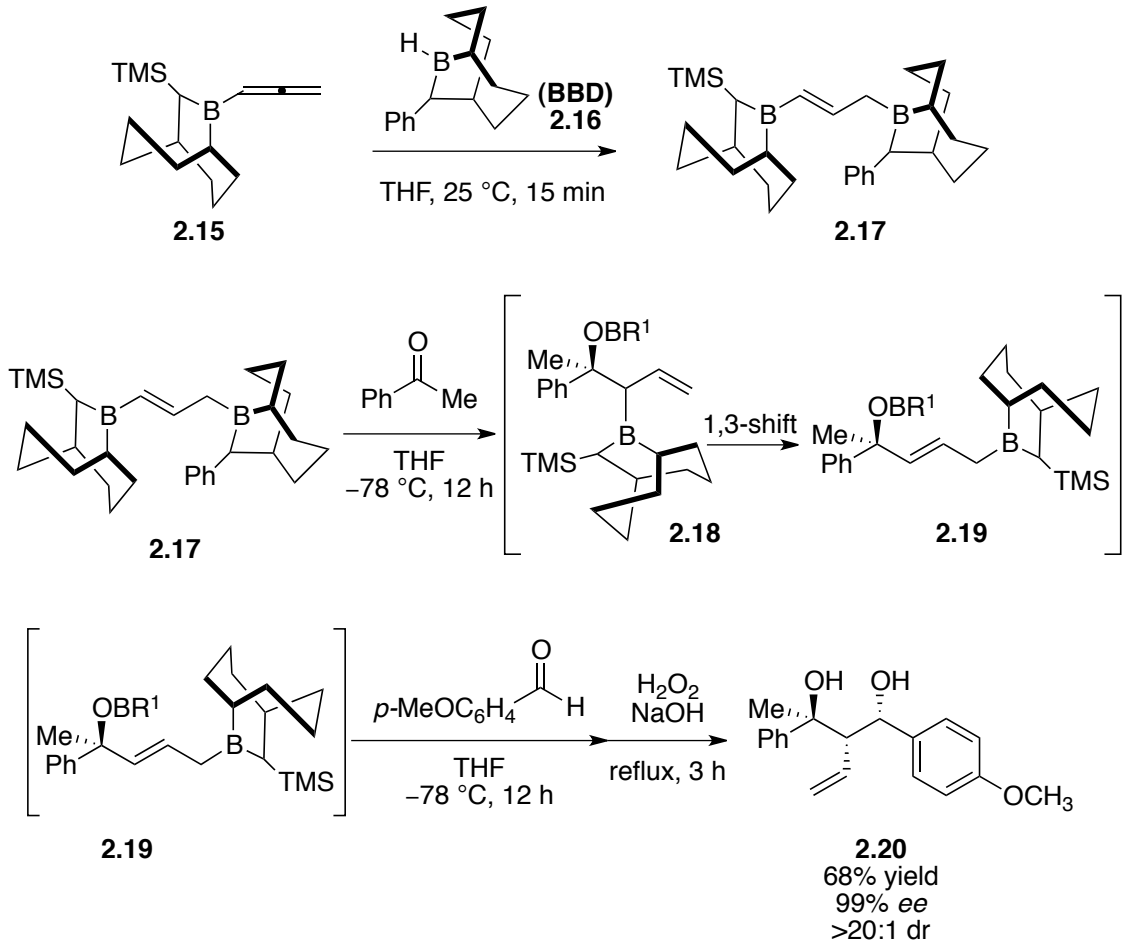
Soderquist also developed a family of Type I bimetallic double allylation reagents that utilize mixed borabicyclo[3.3.2]decanes (BBD, Scheme 2.5).[75] These bimetallic reagents (**2.17**) were synthesized by hydroboration of alleneylborane **2.15** with phenyl-substituted 9-BBD derivative **2.16**. In the presence of **2.17**, benzaldehyde allylboration

[75] González, A. Z.; Román, J. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1269.

occurs to afford intermediate **2.18**, which rapidly undergoes a suprafacial 1,3-borotropic rearrangement to form allylborane **2.19**. The driving force for this rearrangement is to eliminate sterically penalizing interactions between the 10-TMS-9-BBD moiety and the adjacent alkoxyborane. Upon addition of *p*-anisaldehyde, a second allylboration occurs to yield enantioenriched 1,3-diol **2.20** in 68% yield and 99% *ee* as a single diastereomer. In addition to the good chemoselectivity observed in these reactions, the ability to selectively establish three stereogenic centers is an important feature of this methodology. Roush later combined his strategy for synthesizing (*Z*)-*syn*-1,5-diols with Soderquist's 9-BBD reagents to develop a complimentary route to 1,5-*anti*-diols.[76]

[76] Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *13*, 14174.

Scheme 2.5. Soderquist's Type I Bis(borabicyclo[3.3.2]decane) Strategy for Accessing 1,3-Diol Stereotriads



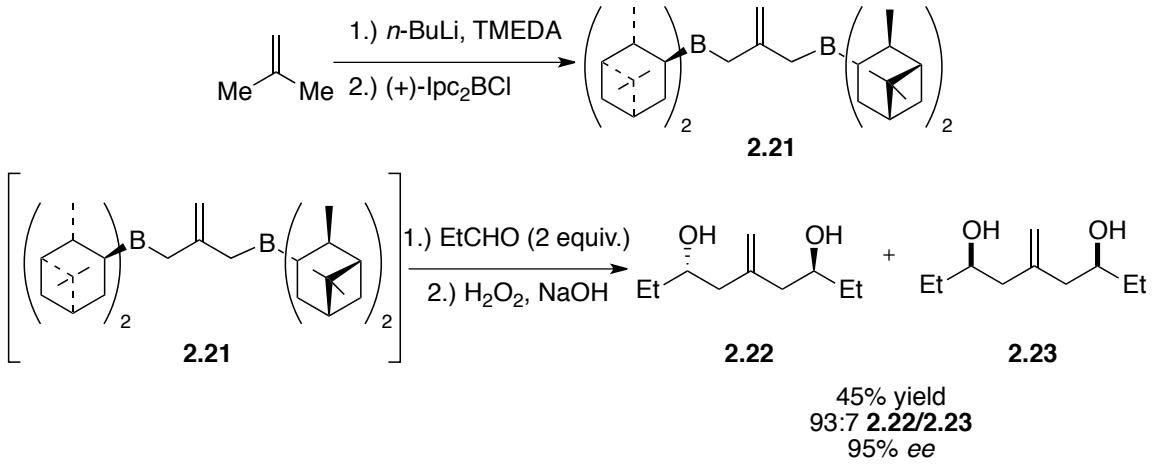
2.2.3. Type II Double Allylation Reagents

Given their symmetrical nature, Type II double allylation reagents have limited synthetic use. However, as demonstrated by Barrett, they do address a long-standing problem in the construction of C_2-symmetric 3-methylenepentane-1,5-diols.[77] Traditional methods to access this motif have resulted in a 1:1 mixture of the C_2-symmetric and

[77] (a) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D. *Chem. Commun.* **1999**, 459. (b) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375.

racemic isomers. Barrett took inspiration from the Brown allylboration to synthesize **2.21** from a double deprotonation of 2-methylpropene with *n*-butyllithium, followed by electrophilic trap with *B*-chlorodiisopinocampheylborane (Scheme 2.6). Upon mixing propionaldehyde with **2.21,** double allylation occured to produce diastereomeric 1,5-diols **2.22** and **2.23** in a combined 45% yield and 93:7 diastereoselectivity in favor of the *anti*-diol. Although the reaction was low yielding, the enantiopurity of the 1,5-*anti*-diol was 95%. One of the shortcomings of this method that the second allylation step did not proceed to completion. The utility of **2.21** would be expanded if this reagent could be used to make unsymmetrical diols by enlisting two different aldehyde partners. Unfortunately, attempts to accomplish this transformation with benzaldehyde and isobutyraldehyde revealed that the second allylation reaction occurs at a faster rate than the first; therefore, the mixed allylboration product was never isolated in synthetically useful yields.

Scheme 2.6. Synthesis of Enantioenriched C_2-Symmetric 1,5-Diols Using 1,3-Bis (Diisopinocampheylboryl)-2-Methylenepropanes

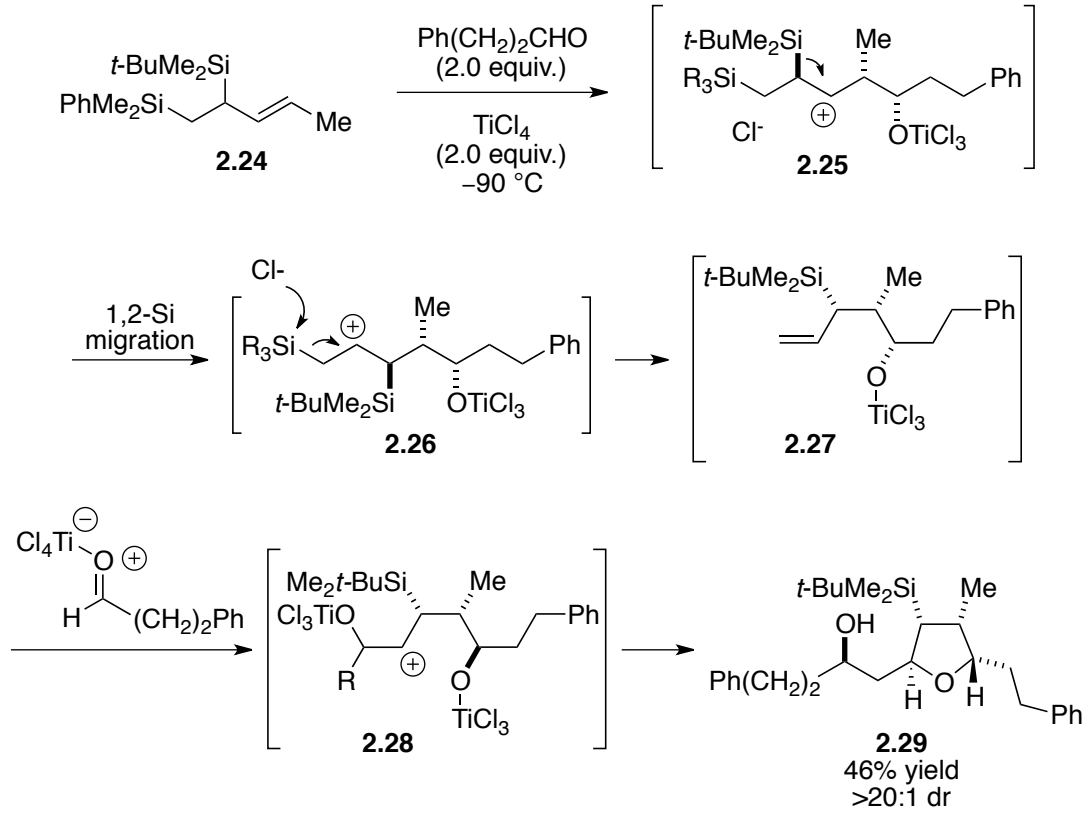


2.2.4. Type III Double Allylation Reagents

Type III bimetallic double allylation reagents hold great promise for achieving "ideal" reagent status because a stoichiometric chiral ligand on the metal is not required. Instead, these reagents could rely on chirality present in the carbon framework to induce an enantioselective double allylation. The first examples of these reagents were developed in a racemic fashion by Woerpel, who demonstrated that allylic silanes bearing a silylmethyl group at the allylic position could react with two equivalents of an aldehyde (Scheme 2.7).[78] He recognized that the stereochemistry in the starting allylsilane could impact the allylation to generate three new stereogenic centers in high diastereomer purity. In the presence of hydrocinnamaldehyde, silane **2.24** undergoes allylsilation to form cation **2.25**. Rapid 1,2-silylmigration occurs to generate double-β-Si-stabilized intermediate **2.26**. After base-promoted silicon elimination, the newly unveiled silane participates in the second allylsilation event to afford **2.26**. Upon intramolecular trap, tetrahydrofuran **2.27** is produced in 46% yield as a single diastereomer.

[78] Smitrovich, J. H.; Woerpel, K. A. *Synthesis* **2002**, 2778.

Scheme 2.7. Synthesis of Silyl-Substituted Tetrahydrofurans with Silylmethyl Allylic Silanes as Double Allylation Reagents

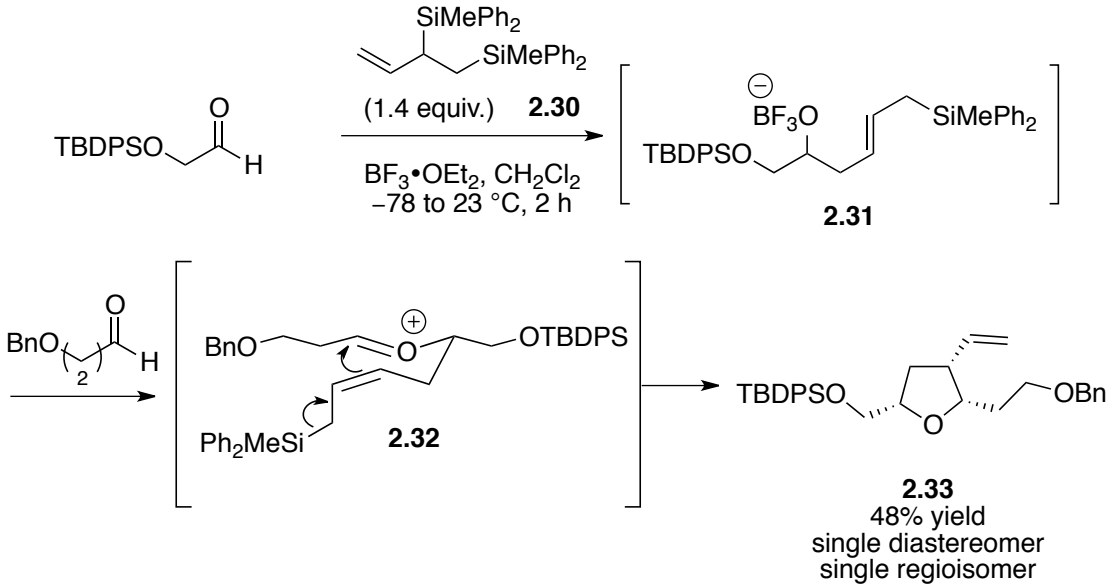


Shortly after Woerpel's discovery, Sarkar and co-workers devised a similar strategy in which racemic 2,3,5-trisubstituted tetrahydrofurans were synthesized from β-alkoxy aldehydes and disilane **2.30** (Scheme 2.8).[79] This reaction proceeds by a different mechanism than the 1,2-silyl-migration reported by Woerpel. Instead, the direct allylsilation product of **2.30** and (*tert*-butyldiphenylsilyloxy)ethanal undergoes Si-elimination to produce allylsilane **2.31**. After exchange with a 3-benzyloxypropanal, ring closure by intramolecular allylsilation of oxocarbenium **2.32** produced tetrahydrofuran **2.33** in 48% yield as a single stereo- and regioisomer. High regioselectivity could be

[79] Sarkar, T. K.; Haque, S. A.; Basak, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1417.

obtained when both aldehydes were present at the outset of the reaction. This is possible because (*tert*-butyldiphenylsilyloxy)ethanal is significantly more electrophilic than 3-(benzyloxy)propanal due to the inductive effect from the neighboring silyoxy substituent.[80] While the substrate scope examined in this study was extremely narrow, this method demonstrates that divergent reactivity is obtainable with bis(silyl)allyl reagents. Despite the presence of chiral centers in both Woerpel's and Sarkar's reagents, neither research group synthesized their bimetallic reagents in enantioenriched form. This may have been due, in part, to difficulties in trying to synthesize the allylsilanes, even in racemic form.

Scheme 2.8. Synthesis of Alkyl-2,3,5-Substituted Tetrahydrofurans with 1,2-Disilyl-3-Butene *via* Double Allylsilation Reaction



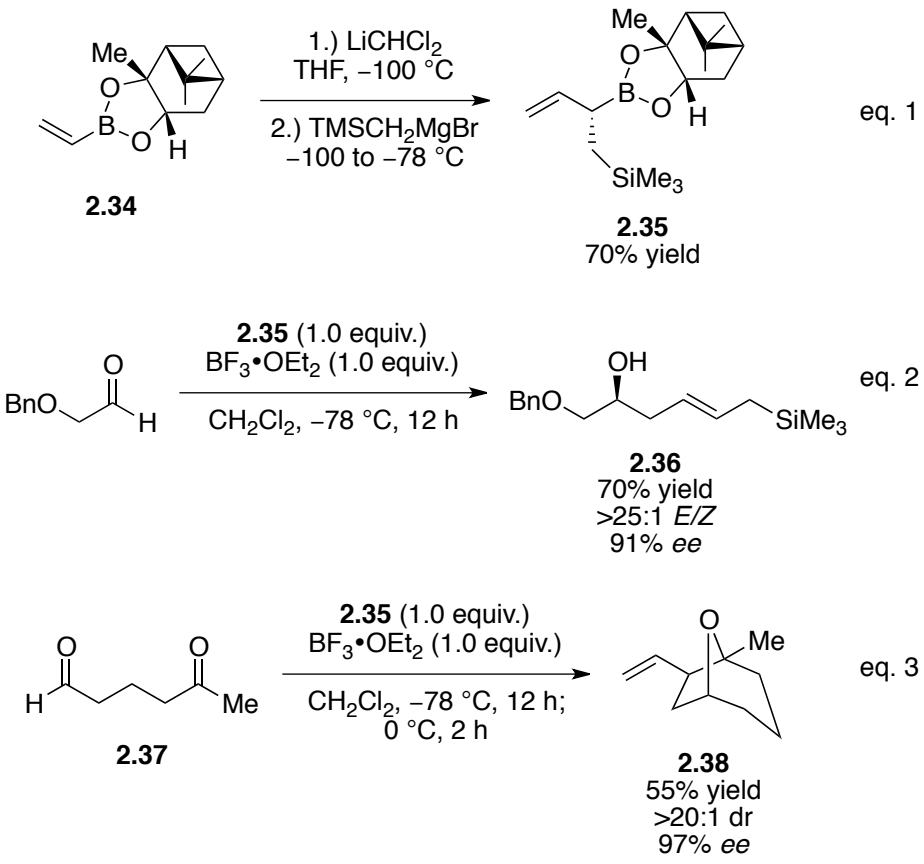
In 2007, Dennis Hall realized the first synthesis and utilization of non-racemic mixed boron/silicon Type III bimetallic double allylation reagent, revealing the true

[80] Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868.

synthetic potential of this reagent class.[69] In addition to significantly simplifying and generalizing the synthesis, the use of two different metals allows for chemodivergent reactivity. Allylboronic ester **2.35** was prepared in a straightforward manner by homologation of pinanedioxy ethylene boronic ester **2.34**, followed by *in situ* addition of trimethylsilylmethyl magnesium bromide (Scheme 2.9, eq. 1). α-Trimethylsilylmethyl-methyl-substituted allylboronic ester **2.35**, unlike many of the previously developed double allylation regents, is stable to column chromatography and long term storage. The chirality source, pinanediol, is inexpensive and commericially available in both enantiomeric forms. With this reagent, benzyloxyacetaldehyde undergoes smooth allylboration in the presence of $BF_3 \cdot OEt_2$ to furnish the corresponding allylsilane-bearing homoallylic alcohol **2.36** in 70% yield, >25:1 *E:Z* selectivity, and 91% *ee* (Scheme 2.9, eq. 2). Additionally, when ketoaldehyde **2.37** was employed as the electrophile, oxabicycle **2.38** was formed in 55% yield, >20:1 dr, and 97% *ee*. This methodology was later expanded to the synthesis of substituted tetrahydrofurans by utilizing untethered carbonyl electrophiles for the double allylation cascade.[81]

[81] Sivasubramaniam, Y.; Hall, D. G. *Hetereocycles* **2010**, *80*, 1449.

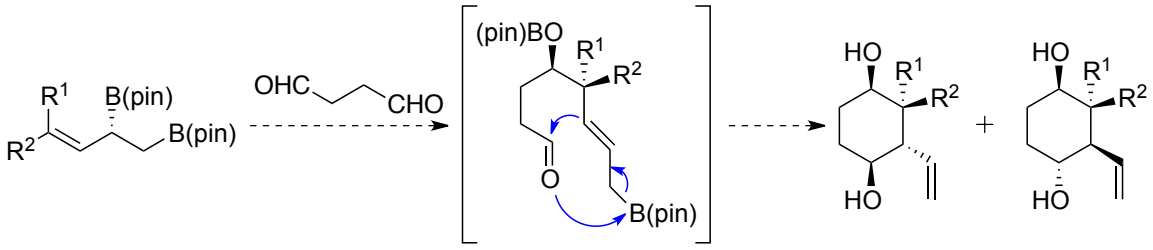
Scheme 2.9. Mixed Non-Racemic Boron-Silicon Double Allylation Reagent for the Synthesis of Hydroxy-Functionalized Allylic Silanes and Oxabicycles



One of the unmet challenges in enantioselective double allylation is the development of reagents that do not require a stoichiometric equivalent of chiral ligand on the metal. A more practical reagent would utilize chirality in the carbon backbone of the allyl fragment to achieve an asymmetric allylmetallation reaction. To accomplish this, we were inspired by our recently developed enantioselective 1,2-diboration of 4,4-disubstituted dienes and *cis*-1,3-dienes, which have the structural motif of Type III double allylation reagents. One distinguishing feature of these reagents is that the chirality is installed through use of a chiral catalyst. During the initial development of

tandem 1,2-diboration/allylation with *cis*-1,3-dienes, the double-allylation pathway was prohibited by altering the reaction stoichiometry. Although double allylation was never observed with 4,4-disubstituted dienes, we wondered if manipulation of the electrophile could render the second allylation pathway more favorable. Specifically, we envisaged taking advantage of entropy[82] by using a 1,4-dicarbonyl electrophile so that the second allylboration would occur in an intramolecular fashion (Scheme 2.10). If successful, this method would generate 1,4-cyclohexanediols with four contiguous stereocenters, and would have potential for high diastereocontrol given the conformational preferences of the cyclic transition state structure. When prenylated dienes are employed, this method would produce carbocyclic products map well onto a number of terpenoid natural products.

Scheme 2.10. Synthesis of Enantioenriched 1,4-Diols *via* Double Allylboration Strategy Enabled by Enantioselective 1,2-Diboration of 1,3-Dienes



[82] Page, M. I.; Jencks, W. P. *Proc. Nat. Acad. Sci.* **1971**, *68*, 1678.

2.3. Development of Enantioselective Tandem Diboration/Double Allylation with 1,4-Dicarbonyl Compounds

2.3.1. Double Allylation with Symmetrical 1,4-Dialdehydes

At the outset of this project, we reasoned that one of the most challenging aspects would be the synthesis and isolation of the proposed 1,4-dialdehyde electrophiles. We investigated two methods for their synthesis: 1) acid-catalyzed hydrolysis of 2,5-dimethoxy-tetrahydfuran **2.39**,[83] and 2) ozonolysis of cyclooctadiene[84] (Scheme 2.11, eq. 1 & 2). Hydrolysis of **2.39** was an appealing route because it is inexpensive and operationally simple to execute. Unfortunately, implementation of this method proved to be problematic because it was difficult to achieve full conversion and the reaction mixture was contaminated with polymeric by-products. Ozonolysis, while more laborious, reliably provided succinaldehyde in high purity. Furthermore, the reduction byproduct, triphenylphosphine oxide, did not effect the outcome of the double allylation reaction and did not need to be separated from the dialdehyde. This method was also appealing because it could be used to synthesize more elaborate dialdehydes from a variety of readily accessible olefin precursors.

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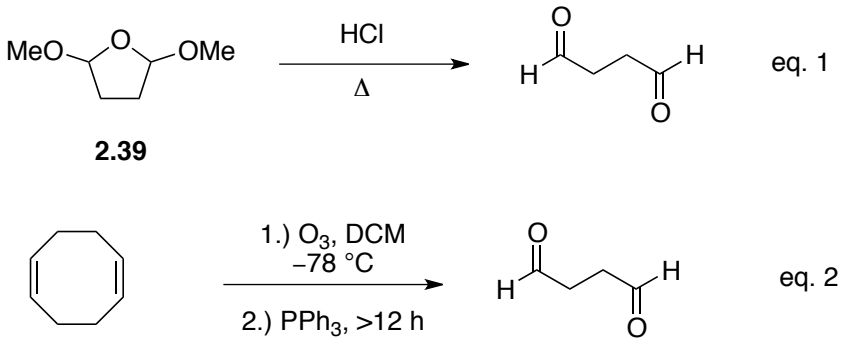
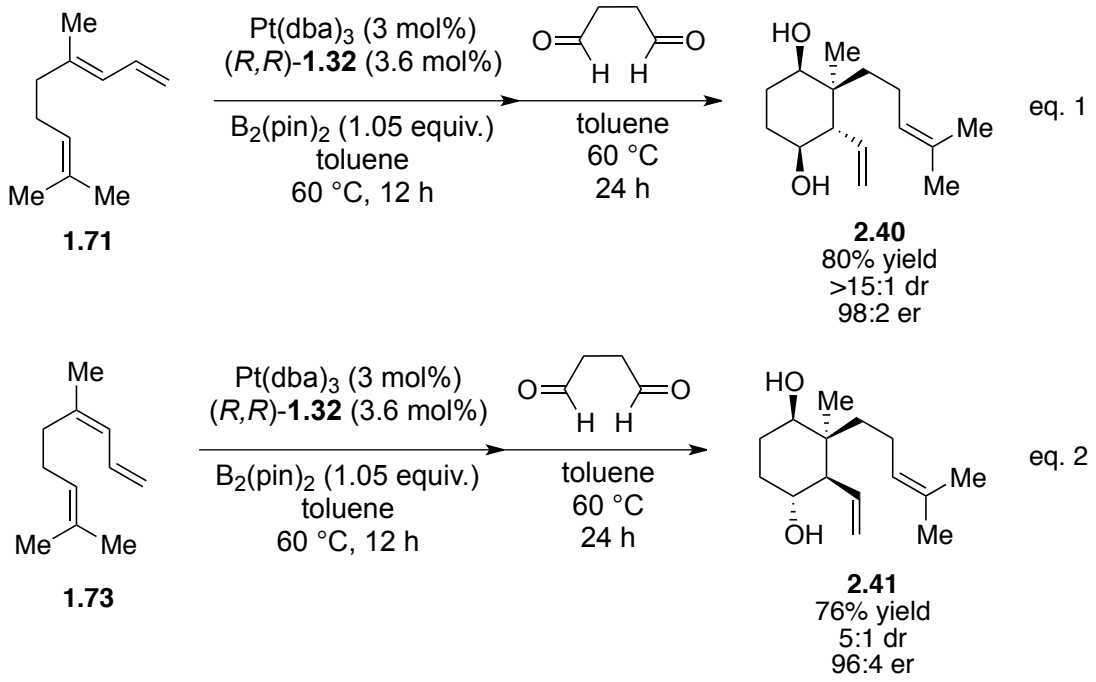
[83] Enkisch, C.; Schneider, C. *Eur. J. Org. Chem.* **2009**, *32*, 5549.
[84] dos Santos, C.; Bahlaouan, Z.; Kassimi K. E.; Troufflard, C.; Hendra, F.; Delarue-Cochin, S.; Zahouily, M.; Cavé, C.; Joseph, D. *Heterocycles* **2007**, *73*, 751.

Scheme 2.11. Preparation of Succinaldehyde



Having determined a viable route to succinaldehyde, the study of tandem diene diboration/dicarbonyl double allylation was begun. Geranial-derived diene **1.71** and neral-derived diene **1.73**, when subjected to the previously developed diboration/ allylation conditions with succinaldehyde as the dicarbonyl electrophile, underwent facile conversion to the corresponding 1,4-diols (Scheme 2.12). Diol **2.40** was isolated in 80% yield, 98:2 er, and a *syn:anti* diol diastereomer ratio of >15:1 for the intramolecular allylboration reaction (eq. 1). Because the intermolecular allylboration was highly diastereoselective, a total of only two diastereomers were observed for the tandem process. Similarly, neral-derived diene **1.73** was converted to diol **2.41** in comparably high yield and enantiopurity (76%, 96:4 er), but with preference for the *anti*-diol diastereomer in a 5:1 ratio (eq. 2).

Scheme 2.12. Tandem Diboration/Double Allylation of Geranial- and Neral-Derived Dienes with Succinaldehyde

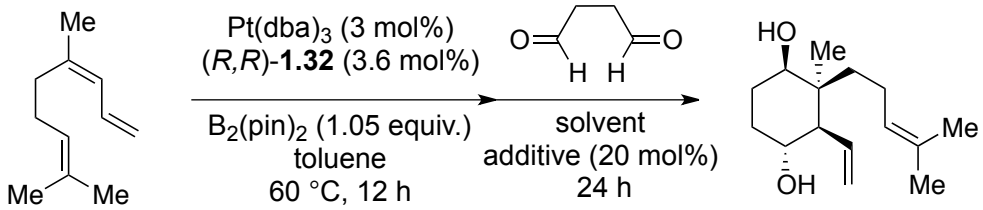


While these initial results were promising, we were interested in shortening the reaction time and improving the diastereoselectivity of the second allylboration reaction (Table 2.1). We hypothesized that the addition of triflate-ligated Lewis acids, which have been shown to promote allylboration reactions,[85,36] might aid in achieving these goals. Unfortunately, the addition of 20 mol% $Sc(OTf)_3$, $Yb(OTf)_3$, and $Cu(OTf)_2$ to double allylations with diene **1.72** and succinaldehyde led to intractable mixtures of products. Because Lewis-acid-catalyzed allylboration reactions are typically performed at lower temperatures, we repeated the reaction with $Sc(OTf)_3$ at 4 °C to exclude the possibility that the observed decomposition was a result of the reaction temperature. In both toluene and CH_2Cl_2, attempted double allylboration in the presence of 20 mol% $Sc(OTf)_3$

[85] Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412.

still did not produce the desired 1,4-diol. Disappointingly, and somewhat surprisingly, the solvent played a minimal role in the diastereoselectivity of the allylation reaction (entries 7-10.) A very small increase in diastereoselectivity was observed with DMF as the solvent; however, due to the impractical nature of using such a high-boiling solvent, toluene remained as the solvent of choice for this reaction.

Table 2.1. Optimization of Double Allylation with Succinaldehyde and (*Z*)-4,4-Disubstituted Diene Bis(boronate) Ester

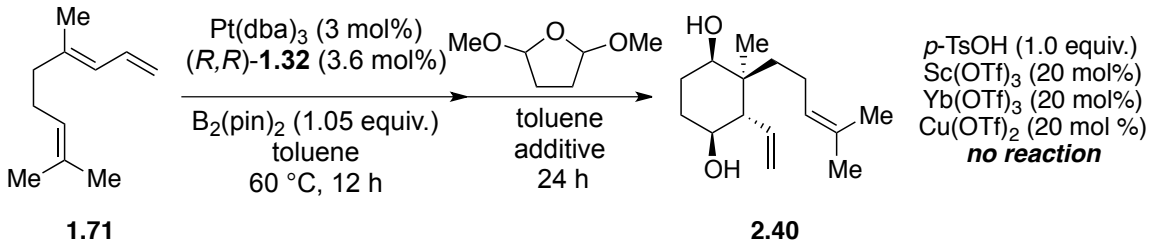


1.73 **2.41**

entry	solvent	additive	temp (°C)	*anti:syn*
1	toluene	-	60	5:1
2	toluene	$Sc(OTf)_3$	60	decomp
3	toluene	$Yb(OTf)_3$	60	decomp
4	toluene	$Cu(OTf)_2$	60	decomp
5	toluene	$Sc(OTf)_3$	4	decomp
6	DCM	$Sc(OTf)_3$	4	decomp
7	THF	-	60	4.9:1
8	DCM	-	60	4.4:1
9	IPA	-	60	4.3:1
10	DMF	-	60	5.3:1

We also investigated whether acidic additives could convert the extremely stable, 2,5-dimethoxytetrahydrofuran to the reactive dialdehyde *in situ*. This would preclude the need to synthesize unstable dialdehydes at the outset of every double allylation reaction. Unfortunately, in the presence of both protic organic acid (*p*-toluene sulfonic acid) and Lewis acids ($Sc(OTf)_3$, $Yb(OTf)_3$, and $Cu(OTf)_2$), double allylation did not occur, suggesting that 2,5-dimethoxytetrahydrofuran was not converted to succinaldehyde *in situ* (Scheme 2.13).

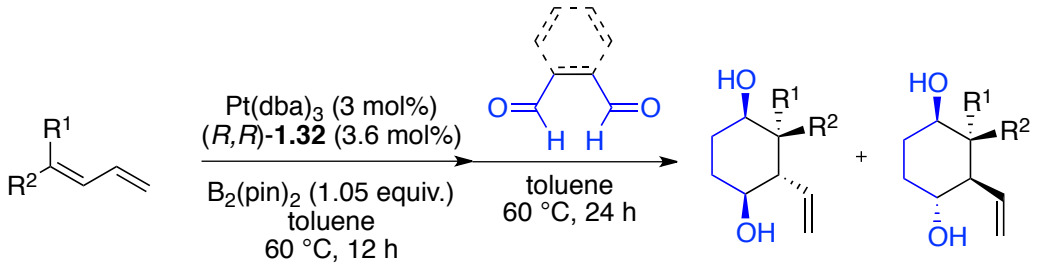
Scheme 2.13. Acid-Catalyzed *in situ* Synthesis of Succinaldehyde in Diboration/ Double Allylation Reaction

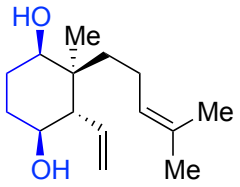


With optimized conditions for both dialdehyde synthesis and double allylation in hand, the scope of the diboration/double allylation with symmetrical dialdehydes was examined (Scheme 2.14). When phthalaldehyde was used as the electrophile, the double allylation reaction could be performed at ambient temperature (likely due to the enhanced accessibility of the carbonyl as compared to succinaldehyde.) With this aldehyde, a similar trend in diastereoselectivity was observed with isomeric dienes. When (*E*)-diene **1.71** was employed, diol **2.43** was isolated in 83% yield, 96:4 er, and 2.8:1 dr in favor of the *syn*-diol. Alternatively, usage of (*Z*)-diene **1.73** produced diol **2.44** in 72% yield, 97:3 er, and a low diastereomer ratio of 1.2:1 in favor of the *anti*-diol. The

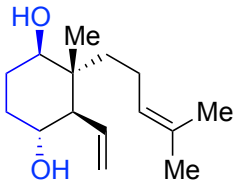
product obtained from silyl ether-containing diene **1.79** was isolated in 71%, 97:3 er and 10:1 *syn*:*anti* ratio. Spirocycles could also be synthesized using this method; **2.45** was isolated in 72% yield and 9:1 dr, but with considerably lower enantiomeric purity. Unfortunately, attempts to synthesize 7- and 8-membered rings using glutaraldehyde and adipaldehyde as the electrophiles resulted in complex mixtures of products most closely resembling the mono-allylation product. Despite this shortcoming, tandem enantioselective 1,2-diboration/double allylation with 1,4-dialdehyde electrophiles is an extremely effective and efficient method for generating 1,4-cyclohexanediols with four contiguous stereocenters in high yield and good diastereo- and enantiopurity. It is noteworthy that in nearly all cases, the *syn*- and *anti*-diastereomers are readily separable by silica gel chromatography. Having access to a single diastereomer of these highly substituted 1,4-cyclohexane diols renders even reactions with moderate diastereoselectivity useful in total synthesis.

Scheme 2.14. Tandem Diboration/Double Allylation of 4,4-Disubstituted 1,3-Dienes with Symmetrical 1,4-Dialdehydes

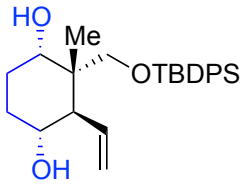




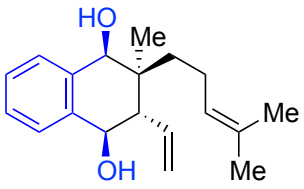
2.40[a]
80%
>15:1 dr
98:2 er



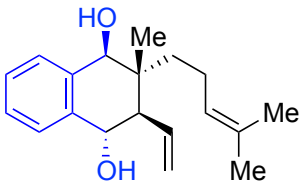
2.41[a]
76%
5:1 dr
96:4 er



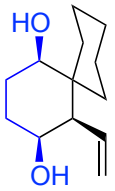
2.42[a]
71%
10:1 dr
97:3 er



2.43[b,c]
83%
2.8:1 dr
96:4 er



2.44[b,c]
72%
1.2:1 dr
97:3 er



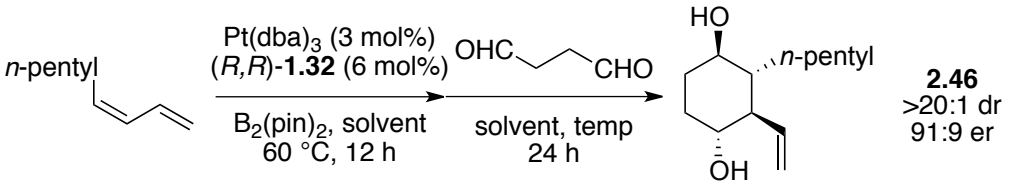
2.45[a]
72%
9:1 dr
88:12 er

Reported yields are an average of at least two experiments. Diastereoselectivity determined by analysis of crude ^{1}H NMR. Absolute stereochemistry determined by either X-ray crystallography or NOESY analysis. Enantiomeric purity determined by SFC analysis on a chiral stationary phase. [a] Allylation performed with two equivalents of succinaldehdye. [b] Allylation performed with one equivalent of phthalaldehyde. [c] Allylation performed at room temperature.

Given the utility of 4,4-disubstituted-1,3-dienes in this reaction, we expected that the monosubstituted *cis*-1,3-diene-derived allyl bis(boronate) esters would be extremely effective double allylboration reagents as well. This hypothesis was supported by earlier

evidence that the products from diboration/monoallylation with *cis*-1,3-dienes underwent facile intermolecular allylation to a second equivalent of aldehyde. We anticipated that the lower 1,2/1,4-regioselectivity in the diboration reaction with this substrate class would slightly diminish the overall yield for this process. Unfortunately, achieving the desired double allylation with *cis*-1,3-dienes proved to be especially challenging (Table 2.2). Under the previously optimized conditions for double allylation with 4,4-disubstituted dienes, reactions were conducted at both room temperature and 60 °C. 1,4-Diol **2.46** was isolated in only 36% and 29% yield, respectively (entries 1 & 2). We reasoned that the low yield might be due to double intermolecular allylation that was competitive with the desired double allyation. Consequently, we increased the diene:aldehyde ratio from 1:2 to 1:1.5; unfortunately, the isolated yield of **2.46** was not improved under these reaction conditions (entries 3 & 4). Mild improvement was finally achieved when the diboration was performed in THF and the allylation solvent was replaced with CH_2Cl_2. These were the reaction conditions used in the previously developed *cis*-diene diboration/monoallylation reaction. From this experiment, *anti*-diol **2.46** was isolated in a 39% yield as a single diastereomer with a 91:9 er (entry 5).

Table 2.2. Optimization of *Cis*-1,3-Diene Diboration/Double Allylation with Succinaldehyde



entry	diboration solvent	diene:aldehyde	allylation solvent	temperature	%yield
1	toluene	1:2	toluene	23 °C	36
2	toluene	1:2	toluene	60 °C	29
3	toluene	1:1.5	toluene	23 °C	27
4	toluene	1:1.5	toluene	60 °C	30
5	THF	1:3	DCM	23 °C	39

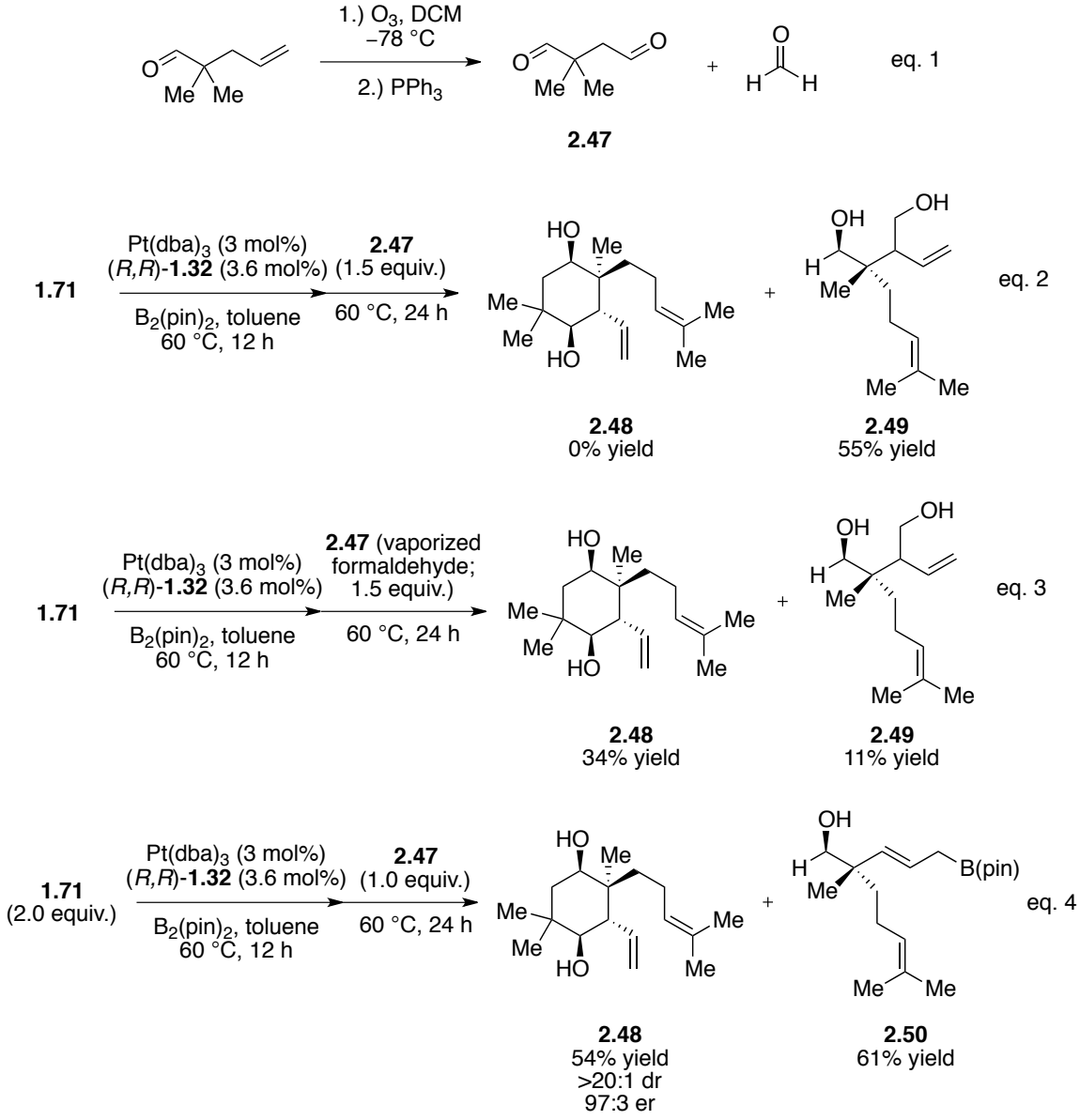
Isolated yield of purified product. In all cases, a single diastereomer was isolated. Enantioselectivity was determined by SFC analysis employing a chiral stationary phase.

2.3.2. Double Allylation with Unsymmetrical 1,4-Dicarbonyl Compounds

It was also of interest to study how unsymmetrical dicarbonyl compounds performed in double allylation reaction. To begin, we examined whether steric differences in dicarbonyl **2.47** would effect a regioselective double allylation (Scheme 2.15). We imagined that the first allylation might occur at the least hindered aldehyde, followed by ring closure at the α-geminally substituted aldehyde. Dialdehyde **2.47** was synthesized *via* the ozonolysis of 2,2-dimethylpent-4-enal (Scheme 2.15, eq. 1). This route to 2,2-dimethylsuccinaldehyde also generates a stoichiometric equivalent of formaldehyde, which unfortunately also proved to be an extremely competent electrophile. When dialdehyde **2.47** was used in a 1.5:1 ratio with respect to the diene starting material, the sole product observed was the double allylation with

formaldehyde to give product **2.49** (eq. 2). Attempts to remove formaldehyde from the ozonolysis solution using aqueous extraction, purging with nitrogen, and by addition of 4Å molecular sieves were unsuccessful. Fortunately, heating the dialdehyde solution to vaporize formaldeyde was met with mild success; cyclic diol **2.48** was isolated in 34% yield and formation of the formaldehyde double allylation product was reduced to 11% (eq. 3). Still unsatisfied with this low yielding reaction, the reaction stoichiometry was then altered. When geraniol-derived diene **1.71** was used in a two-fold excess to the dialdehyde, **2.48** was isolated as a single diastereomer in a 54% yield (relative to the dialdehyde) and 97:3 er. Note that the excess allyl bis(boronate) did undergo monoallylation to formaldehyde to form **2.50** in a 61% yield.

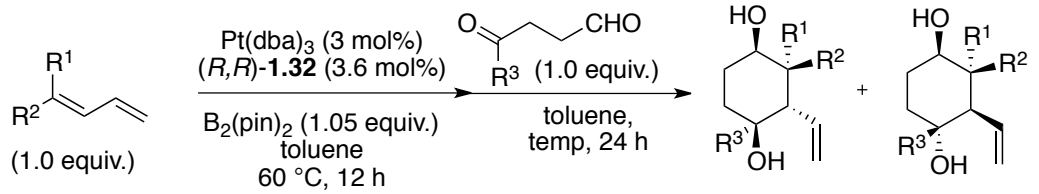
Scheme 2.15. Double Allylation of 2,2-Dimethylsuccinaldehyde: Synthesis and Reaction Optimization

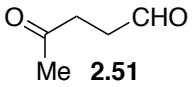
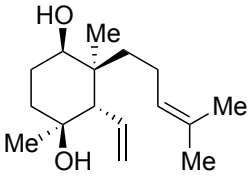
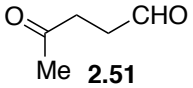
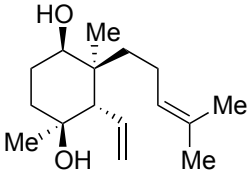
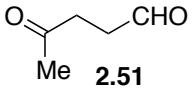
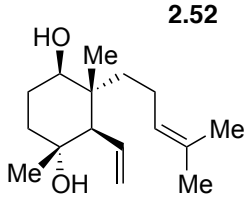
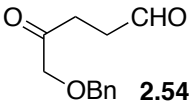
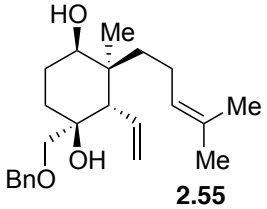
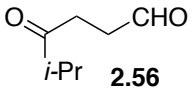
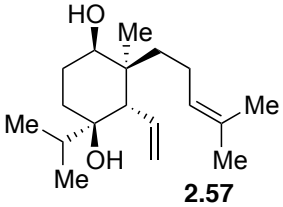


We also hoped to take advantage of electrophilicity differences to perform a regioselective double-allylation of 1,4-ketoaldehydes. As such, a number of ketoaldehydes with different substitution at the ketone center were subjected to the diboration/double allylation conditions (Table 2.3). When 4-oxopentanal (**2.51**) was

stirred with the geranial-derived allylboronate at 60 °C for 24 hours, tertiary alcohol **2.52** was isolated in a 61% yield, 97:3 er, and 11:1 diastereomer ratio favoring the *syn*-diol. Given the increased steric hindrance at the ketone center, we reasoned that an elevated reaction temperature might facilitate ring closure. Indeed, when the double allyation with **1.71** and 4-oxopentenal was performed at 80 °C, the isolated yield of **2.52** increased to 77% while maintaining high levels of diastereoselectivity and no erosion of enantioselectivity. 4-Oxopentenal is also a competent reaction partner with isomeric diene **1.73**. As observed previously with this diene, the *anti*-diol **2.52** was favored in a 5:1 diastereomer ratio, and the mixture of diols was isolated in a 61% yield and 96:4 er. Oxygenated ketoaldehyde **2.54** exhibited comparable reactivity to 4-oxo-pentanal, but gave rise to only the *syn* diastereomer in 60% yield and 97:3 er (entry 4). More hindered ketoaldehyde **2.55** proved too encumbered for effective ring closure to occur. When this electrophile was subjected to the diboration/double allylation conditions, only products derived from monoallylation of the aldehyde were isolated (**2.56**). As was the case with symmetrical dialdehydes, the diastereomeric diols resulting from ketoaldehydes and sterically-desymmetrized 1,4-dicarbonyl electrophiles can be readily separated by column chromatography.

Table 2.3. Regioselective Diene Diboration/Double Allylation with Ketoaldehyde Electrophiles



entry	diene	aldehyde	temperature	product	%yield[a]	*syn:anti* [b]	er[c]
1	**1.71**	 **2.51**	60 °C	 **2.52**	61	11:1	97:3
2	**1.71**	 **2.51**	80 °C	 **2.52**	77	11:1	97:3
3	**1.73**	 **2.51**	80 °C	 **2.53**	61	1:5	96:4
4	**1.71**	 **2.54**	80 °C	 **2.55**	60	>20:1	97:3
5	**1.71**	 **2.56**	80 °C	 **2.57**	mono-allylation	-	-

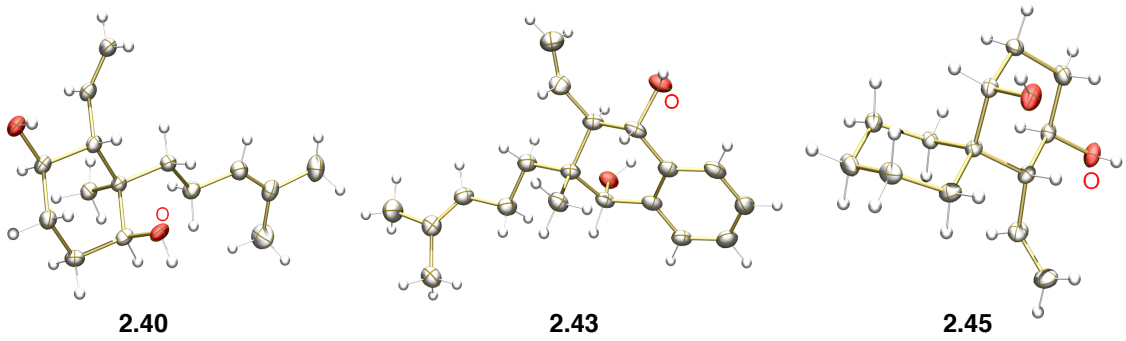
[a] Percent yield of purified material; average of at least two experiments. [b] Diastereoselectivity determined by analysis of the crude ^{1}H NMR spectrum. [c] Enantioselectivity determined by SFC analysis employing a chiral stationary phase.

2.4. Intramolecular Allylboration Transition State Analysis

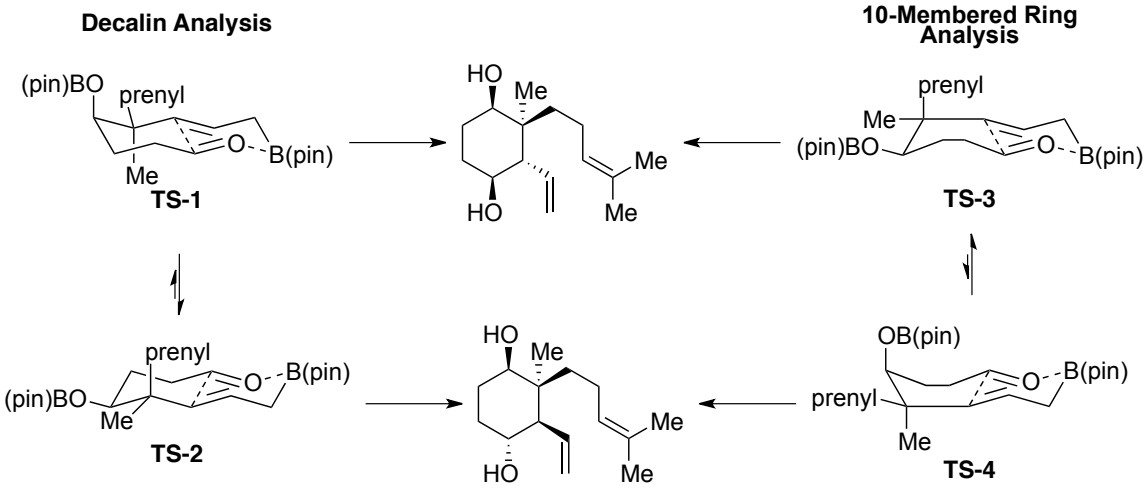
From the outset of the development of the tandem diboration/double allylation, we were very curious to elucidate the origins of the reaction diastereoselectivity. X-ray crystallographic data indicated that the *syn* diastereomer predominated when the (*E*)-configured dienes were employed (Figure 2.1). In developing an initial stereochemical model, we anticipated that the *anti*-diastereomer would predominate with (*E*)-dienes: if the second allylboration with succinaldehyde and geranial-derived diene **1.71** reacted through a *trans*-decalin-like transition-state, minimization of 1,3-diaxial interactions would predict that **TS-2** would be preferred (Scheme 2.16, *vs*. **TS-1**). Alternatively, we considered that the transition state might be influenced by the conformational preferences of 10-membered rings, where a boat-chair conformation is typically more stable.[86] Two boat-chair conformations can be considered for the allylboration transition state: one in which the large OB(pin) group is equatorial (**TS-3**), and one in which it is axial (**TS-4**). Equatorial positioning of the large boronic ester should be more favorable. Using this initial analysis, the *syn* diastereoselectivity observed with *E*-dienes is accurately predicted.

[86] Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

Figure 2.1. X-Ray Crystallography Structures of *Syn*-Diol Products



Scheme 2.16. Initial Transition-State Analysis for Second Allylboration



While this conformational analysis helped to explain the observed diastereoselectivity with (*E*)-configured diene **1.71**, it did not explain the turnover in selectivity observed with isomeric diene **1.73**. The difference in A-value for a methyl group (1.74 kcal/mol) versus an ethyl group (used to approximate the prenyl chain, 1.79 kcal/mol) is only 0.05 kcal/mol.[87] Even when newly introduced *syn*-pentane interactions

[87] Eliel, E. L., Wilen, S. H., Mander, L. N. (1994). *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York.

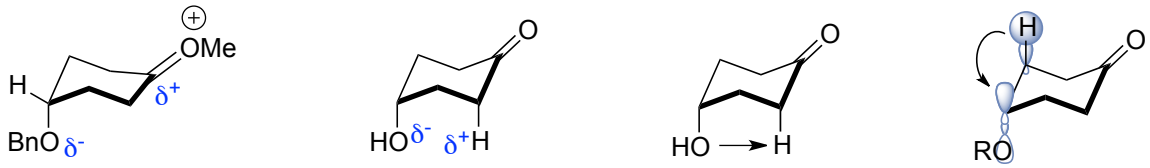
are accounted for (3.0 kcal/mol), minimization of steric interactions with the substituents at the quaternary center cannot account for the observed turnover in diastereoselectivity. To determine what other factors might be affecting diastereoselectivity, we looked to the diboration/double allylation with symmetrical diene **1.65**, where the only stereogenic center resides at the C5 carbinol. The diboration/ double allylation reaction of **1.65** and succinaldehyde produced the corresponding *syn* diol in a 9:1 ratio. From this observation, we concluded that there must be a stabilizing effect for placing the OB(pin) group in the axial position if the allylboration was proceeding through a *trans*-decalin state.

It has been previously observed that cyclohexanone derivatives with C4-alkoxy groups prefer the axial C-O bond conformer. Four different hypotheses have been proposed to explain preference. During his studies on nucleophilic additions to 4-alkoxy-substituted cyclohexanone oxocarbenium ions, Woerpel observed that the alkoxy group exerted a strong influence on the conformational preference of the cyclohexanone (Figure 2.2, **I**).[88] He reasoned that this preference is driven by an electrostatic attraction between the alkoxy substituent (bearing a partial negative charge) and the cationic carbon of the oxocarbenium ion. Computational studies indicated that the axial conformer was preferred by 4.6 kcal/mol when the C4-substituent is a benzyloxy group. These studies revealed a distortion of the cyclohexanone ring to minimize the distance between the dipoles. An alternative stabilizing electrostatic interaction put forth by Rittner and co-workers might occur between the δ- axial oxygen and δ+ axial hydrogens

[88] Baghdasarian, G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 6851. (b) Dibble, D. J.; Ziller, J. A.; Woerpel, K. A. *J. Org. Chem.* **2011**, *76*, 7706.

at C2 and C5, adjacent to the carbonyl (**II**).[89] Takahashi, through the use of *ab initio* MO calculations, found evidence of hydrogen bonding between the acidic axial α-hydrogens and axial heteroatoms (**III**).[90] The calculations revealed a decrease in bond distance from that predicted by the van der Waals radii between the axial C-X substituent and carbonyl α-hydrogens. The fourth explanation that has been proposed is similar to the anomeric effect; that is, a hyperconjugative interaction by the adjacent axial C-H σ-orbital donating into the antiperiplanar C-O σ* orbital stabilizes the axial C-O conformation (**IV**).[91]

Figure 2.2. Previous Proposals for Observed Conformational Preference of Axial C-O Bonds in Cyclohexanone Derivatives



I **II** **III** **IV**

A clear analogy can be drawn between the two proposed chair-chair transition states for the intramolecular allylboration and alkoxy-substituted cyclohexanone derivatives, and has allowed for development of a new diastereoselectivity model. The predominant driving force for the conformational preferences in the transition state is the stabilizing effect of axial C-OB(pin) bond orientation (Figure 2.3, **TS-5**, entry 1). When the steric environment at the adjacent stereocenter reinforces this preference (that

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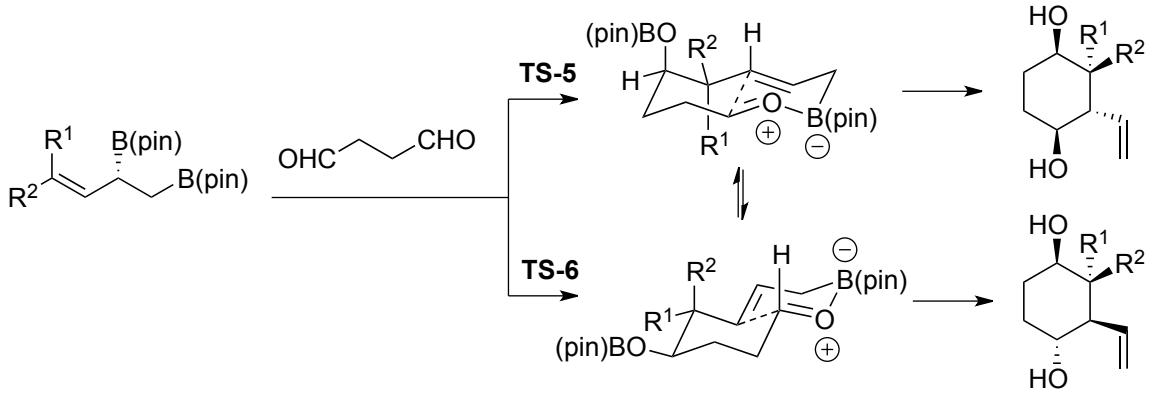
[89] Freitas, M. P.; Tormena, C. F.; Olivira, P. R.; Rittner, R. *J. Mol. Struc. (Theochem)* **2002**, *589-590*, 147.
[90] Takahashi, O.; Yamasaki, K.; Kohno, Y.; Ueda, K.; Suezawa, H.; Nishio, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 272.
[91] (a) Kihara, M.; Iwai, Y.; Nagao, Y. *Hetereocycles* **1995**, *41*, 2279. (b) Nagao, Y.; Goto, M. *Hetereocycles* **1995**, *41*, 883.

is, the smaller of the two groups occupies the axial position and the larger occupies the equatorial position,) *syn*-diastereoselectivity is enhanced (entry 2). However, when (*Z*)-configured dienes are employed, the steric preferences of the quaternary center conflict with those of positioning the C-O bond axial; therefore, the reaction proceeds by **TS-6** and the *anti*-diol predominates (entry 3.) If the size difference between R_{ax} and R_{eq} is exaggerated, as is the case when monosubstituted *cis*-1,3-dienes are employed, then high *anti*-diastereoselectivity can be achieved.

Figure 2.3. **Improved Diastereoselectivity Model for Second Allylboration**



entry	R^1	R^2	*syn:anti*
1	-$(CH_2)_5$		9:1
2	Me	prenyl	15:1
3	prenyl	Me	1:5
4	*n*-pentyl	H	<1:20

While the electronic arguments for positioning the C-O bond axially helped to clarify our understanding of the diastereoselectivity, the observed trends are still somewhat puzzling. Although this effect may be the predominant driving force for the

conformational preferences of the cyclic transition state in (*E*)-configured dienes, it appears as though the steric interactions with the quaternary center override this preference with (*Z*)-configured dienes. One plausible explanation is that rather than the reaction proceeding through two competing chair transition states (as in Figure 2.3), it might be the case that *anti*-diastereomer comes about by allylboration *via* boat-chair **TS-4** (where the C-O bond remains in the axial position.) The steric and electronic preferences that predominated in the chair-chair conformer may be disrupted in the boat-chair conformer, which could explain the conflicting data. An alternative explanation could be that the prenyl group is a poorer hyperconjugative stabilizer than the methyl group because of the electron withdrawing nature of the sp^2-hybridized carbons, thereby allowing 1,3-diaxial interactions with the quaternary center to govern the conformational preferences of the transition state.

Analysis of the transition state can also shed light on why double allylation on 5- and 6-carbon dialdehydes were unsuccessful. By inserting additional methylene units between the carbonyls, a higher entropic cost must be paid to bring the allylboronate and aldehyde termini together with the proper orbital alignment for allylation to occur. Furthermore, distortion of the decalin-like framework might disrupt stabilizing interactions, thereby increasing the energy of the transition state and prohibiting intramolecular allylboration.

2.5. Conclusion

Coupling of 1,3-dienes and 1,4-dicarbonyl compounds to synthesize enantioenriched, highly substituted 1,4-cyclohexane-diols has been made possible by the recent development of the Pt-catalyzed enantioselective diene diboration/double

allylation strategy. When symmetrical 1,4-dialdehydes are used as the electrophile, *syn* and *anti* diols can be accessed in high yield, excellent enantiopurity, and synthetically useful levels of diastereoselectivity. This method is also compatible with *cis*-1,3-dienes, although lower isolated yields are reported compared to 4,4-disubstituted 1,3-dienes. Regioselective double allylation has been achieved for both sterically differentiated 1,4-dialdehydes and electronically differentiated ketoaldehydes. In both cases, the first allylboration reaction occurs at the more reactive aldehyde site, followed by ring closure *via* intramolecular allylboration into the less electrophilic carbonyl center. The diastereoselectivity for the second allylboration in this tandem reaction sequence can be explained through two competing *trans*-decalin-like transition states. In the favored transition state, the C-O bond is oriented in the axial position, a preference which could potentially be explained through electrostatic, hydrogen bonding, or hyperconjugative interactions. When the steric bias of the adjacent quaternary center opposes that of the inherent C-O axial preference, turnover in diastereoselectivity is observed. An appealing attribute of the tandem diboration/double allylation is that separation of the *syn*- and *anti*-diastereomers is possible by silica gel chromatography, which is particularly useful in the context of total synthesis. Even though the diastereoselectivity is sometimes low, this feature allows rapid access to highly substituted carbocycles from simple, readily accessible starting materials.

2.6. Experimental

2.6.1.General Information

^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), a Varian Inova-500 (500 MHz), or a Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants. ^{13}C NMR spectra were recorded on either a Varian Gemini-500 (125 MHz), a Varian Inova-500 (125 MHz), or a Varian Gemini-600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$ 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, νmax cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

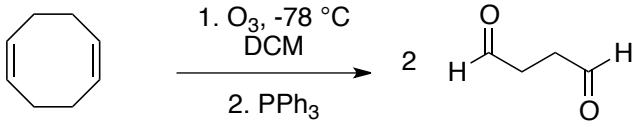
Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230x450 mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate (KMnO4) in water, or phosphomolybdic acid (PMA) in ethanol. Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector. Optical rotations were measured on a Atago AP-300 Polarimeter. Melting point determination was performed with Digimelt MPA160.

All reactions were conducted in oven- or flamed-dried glassware under an inert atmosphere of nitrogen or argon, unless otherwise noted. Tetrahydrofuran (THF), toluene (PhMe), and dichloromethane (DCM) were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing through two activated alumina columns after being purged with argon. Triethylamine was distilled from calcium hydride. Bis(pinacolato)diboron was generously donated by Allychem Co., Ltd. and was recrystallized from pentane prior to use. Cyclooctadiene was purchased from Aldrich and distilled over sodium metal prior to use. All other reagents were purchased from either Aldrich, Alfa-Aesar or Acros and used without further purification.

2.6.2. Preparation of 1,4-Dicarbonyl Compounds

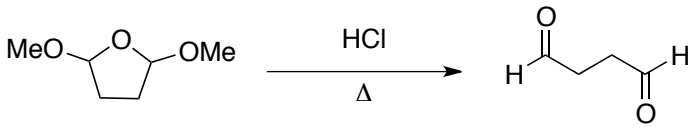
Preparation of succinaldehyde.

The following two procedures can be used interchangeably for the diboration/double allylation reaction (although ozonolysis is the preferred method.)



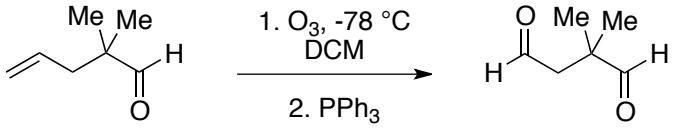
a) The title compound was prepared according to the literature procedure[84] with slight modification. To a 2-dram vial equipped with a stir bar was added cyclooctadiene (40.6 μL, 0.33 mmol) and DCM (6.6 mL, 0.05 M). The solution was cooled to -78 °C, and ozone was bubbled through until the reaction solution was blue in color. The mixture was then purged with N_2 until the blue color dissipated. Next,

triphenylphosphine (173 mg, 0.66 mmol) was added in a single portion. The vial was sealed and allowed to warm to room temperature and stir overnight. The solution was carefully concentrated until triphenylphosphine oxide began to precipitate.



b) The title compound was prepared according to the literature procedure[83] with slight modification. To a 6-dram vial equipped with a stir bar was added 2,5-dimethoxytetrahydrofuran (0.5 mL, 3.83 mmol) and 1.0 M hydrochloric acid (2.0 mL, 2.0 mmol). The solution was stirred and heated with in an oil bath at 60 °C for 30 minutes. Upon cooling, solid powdered $NaHCO_3$ was added until a pH = 6 was reached. The aqueous solution was extracted 3 x 5 mL EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated carefully on the rotary evaporator. Due to the mild evaporation conditions, the dialdehyde was isolated as a mixture with ethyl acetate, starting material and polymeric byproduct; the typical weight percent of product was between 30-40%.

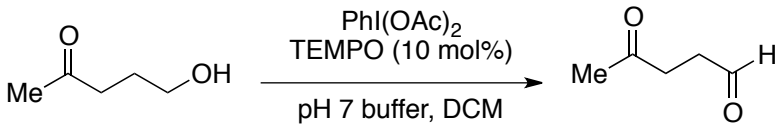
Preparation of 2,2-dimethylsuccinaldehyde



To a 2-dram vial equipped with a stir bar was added 2,2-dimethyl-4-pentenal (34 uL, 0.25 mmol) and DCM (1.5 mL). The solution was cooled to -78 °C and ozone was bubbled through until the reaction solution was blue in color. The mixture was then

purged with N_2 until the blue color dissipated. Next, triphenylphosphine (0.275 mmol, 72.1 mg) was added as a single portion. The vial was sealed and allowed to warm to room temperature and stir overnight, then carefully concentrated until triphenylphosphine oxide began to precipitate.

Preparation of 4-oxopentanal.



The title compound was prepared from 5-hydroxy-2-pentanone according to the literature procedure[92] with slight modification. To an aluminum foil-covered round bottom flask equipped with a stir bar was added $PhI(OAc)_2$ (17.467 g, 54.23 mmol) and TEMPO (770.3 mg, 4.93 mmol). The flask was sealed with a septum and purged with N_2. The solids were dissolved in DCM (50 mL, 1.0 M), and 5-hydroxy-2-pentanone (5.0 mL, 49.30 mmol) and pH 7 buffer (12 mL) were added in succession *via* syringe. The solution was allowed to stir at room temperature for 1 hour. Upon completion, the reaction was quenched with the addition of 15 mL saturated aqueous sodium thiosulfate. The mixture was transferred to a separatory funnel and washed with DCM (3 x 30 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by column chromatography on SiO_2 (100% pentane, then 1:1 - 3:1 Et_2O:pentane, R_f = 0.18 in 1:1 Et_2O:pentane, stain in $KMnO_4$) to afford the ketoaldehyde as a yellow-brown oil. The title compound was then distilled with the Kugelrohr under vacuum at 65 °C to afford a colorless oil (2.907 g, 59% yield).

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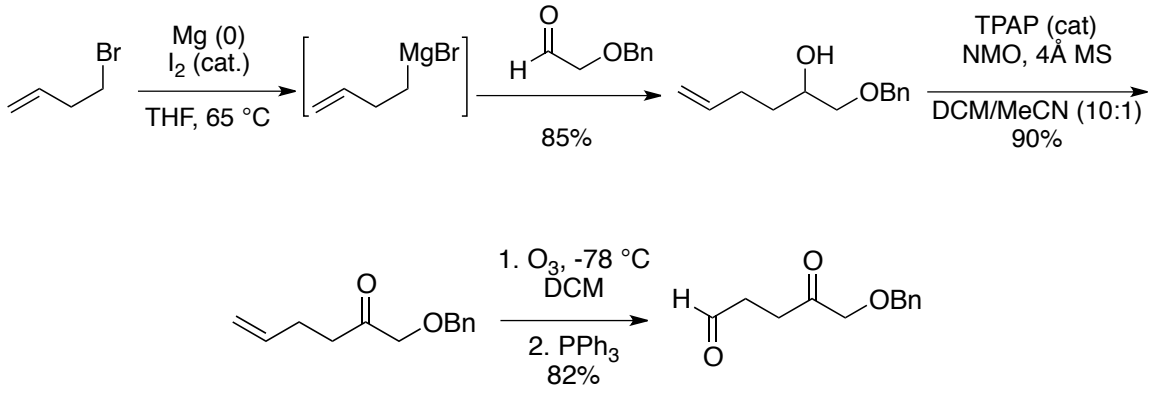
[92] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem., Int. Ed*. **2012**, *51*, 521.

Preparation of 5-(benzyloxy)-4-oxopentanal.



To a flame-dried 2-neck round bottom flask equipped with a reflux condenser and a stir bar was added ground magnesium turnings (148 mg, 6.1 mmol). The apparatus was flamed dried three times and put under positive N_2 pressure. A crystal of I_2 was added, and the magnesium was suspended in THF (6 mL, 1.0 M). Next, 1-bromobutene (0.61 mL, 6.0 mmol) was added slowly, and the reaction was warmed to 65 °C and refluxed for 2 hours. Of this stock solution, 4.9 mL was transferred to a flame-dried round bottom flask equipped with a stir bar. The solution was cooled to 0 °C, and benzyloxyacid aldehyde (0.5 mL, 3.56 mmol) was added dropwise as a solution in THF (7.12 mL, 0.5 M). The solution was stirred at 0 °C for 2 hours, then quenched with saturated aqueous ammonium chloride solution (5 mL). The mixture was transferred to a separatory funnel and washed with 3 x 20 mL EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The bis-homoallylic alcohol was purified by column chromatography on SiO_2 (5:1 hexanes/ethyl acetate, R_f = 0.19 in 5:1 hexanes/ethyl acetate, stain in $KMnO_4$) to afford 1-(benzyloxy)hex-5-en-2-ol as a clear, colorless oil (625 mg, 85%).

To a round bottom flask equipped with a stir bar was added 4Å MS. The apparatus was flamed dried and placed under positive pressure of N_2. Dichloromethane (5 mL) was charged to the flask, followed by the addition of 1-(benzyloxy)hex-5-en-2-ol (550 mg, 2.67 mmol). The remaining DCM (5 mL) and acetonitrile (1 mL) were then added to the solution. *N*-Methylmorpholine *N*-oxide (468.7 mg, 4.0 mmol) was added in a single portion. The flask was sealed with a septum, purged with N_2, and allowed to stir at room temperature for 20 minutes. Upon the addition of NMO, the solution changed color from cloudy white to black. Next, TPAP (46.8 mg, 0.133 mmol) was added as a single portion, followed by a N_2 purge of the flask atmosphere. The reaction was allowed to stir at room temperature until complete by TLC. The solution was then concentrated until acetonitrile was removed, redissolved in DCM, filtered over SiO_2, and concentrated *in vacuo*. The resulting oil was used in the next step without further purification (492.2 mg, 90%).

To a round bottom flask equipped with a stir bar was added 1-(benzyloxy)hex-5-en-2-one (417 mg, 2.0 mmol) and DCM (8.0 mL, 0.25 M). The flask was loosely closed with a plastic yellow cap with a N_2 source and a vent needle. Next, solution was cooled to – 78 °C, the N_2 needle removed, and ozone was bubbled through until a blue color persisted. The solution was purged with N_2 until the blue color dissipated, then triphenylphosphine (642 mg, 2.45 mmol) was added in a single portion. The reaction was sealed and allowed to warm to room temperature and stir for 14 hours. The solution was then the concentrated *in vacuo*. The resulting mixture was purified by column chromatography on SiO_2 (3:1 Et_2O/pentane, R_f = 0.21 in 3:1 Et_2O/pentane, stain in PMA)

to afford a clear, colorless oil (372.6 mg, 82% yield). The ^{1}H and ^{13}C spectra were in accordance with the literature.[93]

2.6.3. Representative Procedure for Diboration/Oxidation I - Ozonolysis-Derived Dicarbonyls.

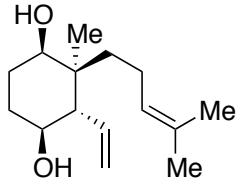
To an oven-dried 2-dram vial equipped with a magnetic stir bar in the glove box was added $Pt(dba)_3$ (3 mol%), (*R,R*)-3,5-di-*iso*-propylphenyl-TADDOL-PPh (3.6 mol%), $B_2(pin)_2$ (1.05 equiv), and toluene ([substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the glove box and charged with diene (1.0 equiv.) The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 hours. After cooling to room temperature, the dicarbonyl compound (2.0 equiv.) was transferred quantitatively to the flask using minimal toluene. The vial was purged with N_2 , sealed and heated to 60 °C for 24 hours. The reaction mixture was then cooled to room temperature, transferred to a 6-dram scintillation vial with THF (2 mL), and stirred with 2mL of 3M NaOH for 3 hours. The reaction mixture was diluted with ethyl acetate (5 mL), transferred to a separatory funnel and washed with ethyl acetate (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on SiO_2.

[93] Silva, N. R.; de Magalhaes, G. C. *Synth. Commun.* **1999**, *29*, 1477.

2.6.4. Representative Procedure for Diboration/Double Allylation II - Neat Dicarbonyl Addition.

To an oven-dried 2-dram vial equipped with a magnetic stir bar in the glove box was added $Pt(dba)_3$ (3 mol%), ((*R,R*)-3,5-di-*iso*-propylphenyl-TADDOL-PPh (3.6 mol%), $B_2(pin)_2$ (1.05 equiv), and toluene ([substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the glove box and charged with diene (1.0 equiv.) The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 hours. After cooling to room temperature, the dicarbonyl compound (1.0 equiv.) was added by mass. The vial was purged with N_2 , sealed and heated to 60 °C for 24 hours. The reaction mixture was then cooled to room temperature, transferred to a 6-dram scintillation vial with THF (2 mL), and stirred with 2 mL of 3M NaOH for 3 hours. The reaction mixture was diluted with ethyl acetate (5 mL), transferred to a separatory funnel and washed with ethyl acetate (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on SiO_2.

2.6.5. Characterization and Proof of Stereochemistry

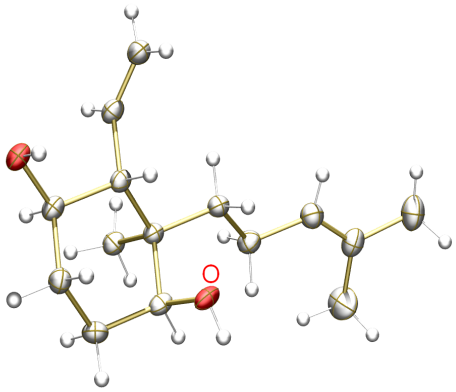


(1*R*,2*S*,3*S*,4*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclohexane-1,4-diol (2.40). The diboration was performed according to Representative Diboration/Double Allylation Procedure I with (*E*)-4,8-dimethylnona-1,3,7-triene (50.0 mg, 0.33

mmol), $Pt(dba)_3$ (8.9 mg, 9.9 μmol), (*R,R*)-di-*iso*-propylTADDOL-PPh (10.8 mg, 11.9 μmol), $B_2(pin)_2$ (87.9 mg, 0.35 mmol), toluene (0.33 mL, 1.0 M) and succinaldehyde (56.8 mg, 0.66 mmol). The crude reaction mixture was purified by column chromatography on SiO_2 (75:25 - 60:40 hexanes/ethyl acetate, R_f = 0.21 in 50:50 hexanes/ethyl acetate, stain in PMA) to afford a white solid (64.0 mg, 81%, d.r. >15:1 *syn*:*anti* diol). ^1H NMR (500 MHz, $CDCl_3$): δ 5.65 (1H, dt, *J* = 17.1 Hz, 10.1 Hz), 5.27 (1H, dd, *J* = 10.0 Hz, 2.2 Hz), 5.19 (1H, ddd, *J* = 17.1 Hz, 2.2 Hz, 0.5 Hz), 5.11-5.07 (1H, m), 3.63 (1H, br s), 3.56 (1H, dt, *J* = 4.6 Hz, 10.5 Hz), 2.04 (1H, t, *J* = 10.0 Hz), 2.00-1.84 (3H, m), 1.79-1.70 (3H, m), 1.69-1.60 (1H, m), 1.65 (3H, d, *J* = 1.0 Hz), 1.58 (3H, s), 1.45-1.39 (2H, m), 1.23-1.17 (1H, m), 0.86 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.1, 131.7, 124.8, 120.7, 70.6, 67.9, 55.2, 40.5, 38.6, 27.2, 27.0, 25.7, 21.3, 18.3, 17.6; IR (neat): 3382.9 (br), 2966.7 (m), 2931.3 (s), 1444.7 (m), 1378.2 (m), 1263.1 (w), 1036.5 (m), 995.6 (m), 914.9 (m) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{27}O_2$ [M+H]: calculated: 239.2011, found: 239.2005. $[\alpha]_D^{23}$: +10.98 (*c* = 0.91, $CHCl_3$, *l* = 10 mm).

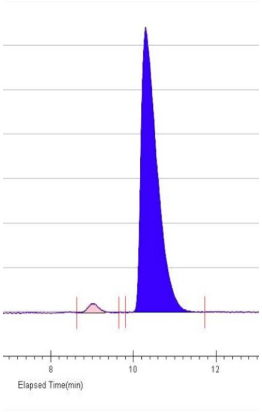
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the bis(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by crystallography using anomalous dispersion. Flack parameter = 0.03.

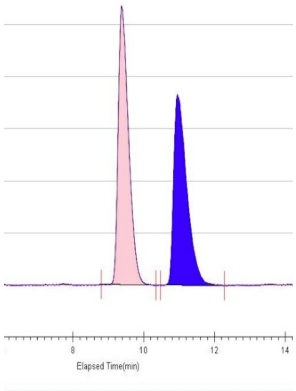


(*S,S*)-*i*Pr$_2$TADDOL-PPh used when this crystal structure was obtained

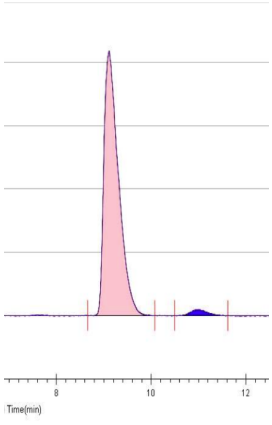
Chiral SFC (AD-H, Chiraldex, 5 mL/min, 3% i-PrOH, 100 bar, 35 °C)-analysis of the bis (benzoate) of the reaction product ***2.40****.*



Product from (*R,R*)-*i*Pr$_2$TADDOL-PPh



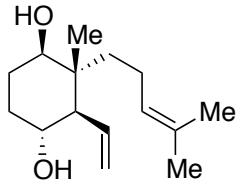
Mixture of products from (*R,R*)- and (*S,S*)-ligands



Product from (*S,S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	2.2257	194.0318	9.02	10.0518	0.0087
2	97.7743	8523.8557	10.3	320.1263	0.0099
Total:	100	8717.8875			

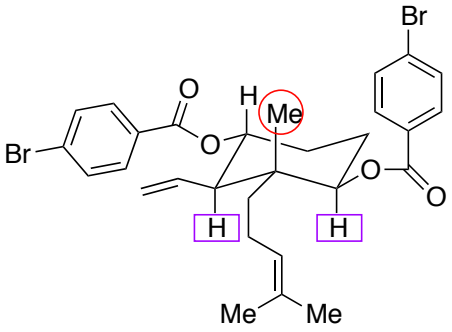


(1*R*,2*R*,3*R*,4*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclohexane-1,4-diol (2.41). The diboration was performed according to Representative Diboration/Double Allylation Procedure I with (*Z*)-4,8-dimethylnona-1,3,7-triene (50.0 mg, 0.33 mmol), $Pt(dba)_3$ (8.9 mg, 9.9 μmol), (*R*,*R*)-di-*iso*-propylTADDOL-PPh (10.8 mg, 11.9 μmol), $B_2(pin)_2$ (87.9 mg, 0.35 mmol), toluene (0.33 mL, 1.0 M) and succinaldehyde (56.8 mg, 0.66 mmol). The crude reaction mixture was purified by column chromatography on SiO_2 (67:33–50:50 hexanes/ethyl acetate, R_f = 0.22 in 50:50 hexanes/ethyl acetate, stain in PMA) to afford a colorless oil (82.3 mg, 5:1:1 d.r., mixture of three diastereomers and pinacol, combined yield 73%). The major diastereomer was isolated after the second column chromatography purification (80:1 dichloromethane/methanol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71 (1H, dt, *J* = 17.1 Hz, 10.0 Hz), 5.31 (1H, dd, *J* = 10.3 Hz, 2.0 Hz), 5.22 (1H, ddd, *J* = 17.1 Hz, 2.0 Hz, 0.5 Hz), 5.07-5.03 (1H, m), 3.59 (1H, dd, *J* = 11.5 Hz, 4.4 Hz), 3.54 (1H, dt, *J* = 4.6 Hz, 10.8 Hz), 2.10-2.05 (1H, m), 1.96-1.91 (2H, m), 1.89 (1H, t, *J* = 9.8 Hz), 1.81-1.75 (1H, m), 1.65 (3H, d, *J* = 1.0 Hz), 1.63-1.55 (1H, m), 1.57 (3H, s), 1.46-1.39 (1H, m), 1.35-1.27 (1H, m), 1.25-1.18 (1H, m), 0.84 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 131.6, 124.5, 120.5, 72.2, 67.6, 55.2, 41.0, 37.3, 31.6, 28.4, 25.7, 20.8, 17.6, 15.0; IR (neat): 3385.9 (br), 2969.5 (m), 2930.5 (s), 1448.9 (m), 1376.7 (w), 1115.7 (w), 1044.2 (s), 1011.3 (m), 954.1 (m), 915.3 (w) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{27}O_2$ [M+H]: calculated: 239.2011, found: 239.2017. $[\alpha]_D^{23}$ = −24.10 (*c* = 0.93, $CHCl_3$, *l* = 10 mm**).**

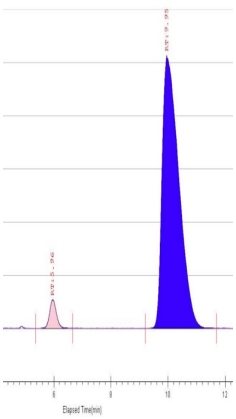
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the bis(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic

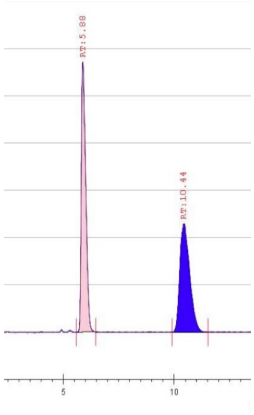
DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis of the bis-4-bromobenzoate of the reaction product (prepared using 4-bromobenzoyl chloride, triethylamine, and DMAP). The following NOEs were observed:



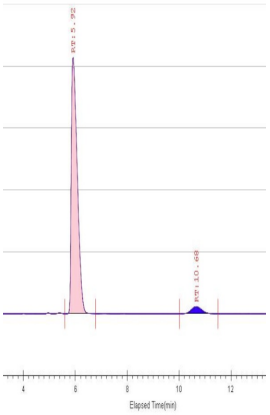
Chiral SFC (AD-H, Chiraldex, 3 mL/min, 5% MeOH, 100 bar, 35 °C)-analysis of the bis (benzoate) of reaction product ***2.41****.*



Product from
(*R,R*)-*i*Pr$_2$TADDOL-PPh



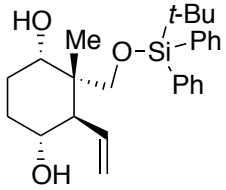
Mixture of products from
(*R,R*)- and (*S,S*)-ligands



Product from
(*S,S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	4.126	1796.7898	5.96	107.404	0.0057
2	95.874	41751.6838	9.95	1026.2145	0.0095
Total:	100	43548.4736			



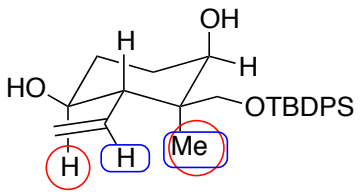
(1*R*,2*R*,3*S*,4*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methyl-3-vinylcyclohexane-1,4-diol (2.42). The diboration was performed according the Representative Procedure I with slight modification using (*E*)-*tert*-butyl((2-methylpenta-2,4-dien-1-yl)oxy)diphenylsilane (111.0 mg, 0.33 mmol), Pt(dba)$_3$ (8.9 mg, 9.0 μmol), (*S,S*)-3,5-di-*iso*-propylphenyl-PPh (10.8 mg, 12.0 μmol), B$_2$(pin)$_2$ (88.0 mg, 0.35 mmol), toluene (0.33 mL, 1.0M), and succinaldehyde (56.8 mg, 0.66 mmol). Upon completion of the double allylation, the mixture was transferred to a 6-dram scintillation vial with 2 mL of THF and cooled to 0 °C. To the solution was then added 2 mL pH 7 buffer, followed by the dropwise addition

of 30% H_2O_2. The mixture was allowed to stir and warmed to room temperature over 6 hours, then quenched with a saturated solution of sodium thiosulfate (2 mL). The reaction mixture was then diluted with ethyl acetate (5 mL) and isolated as previously described. The crude reaction mixture was purified by column chromatography on SiO_2 (70:30 - 40:60 hexanes/ethyl acetate, R_f = 0.28 in 50:50 hexanes/ethyl acetate, stain in PMA) to afford a clear, colorless oil (99.5 mg, 71%, d.r. = 10:1 *syn:anti* diol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 - 7.62 (4H, m), 7.45 - 7.35 (6H, m), 5.56 (1H, dt, *J* = 17.1 Hz, 10.0 Hz), 5.23 - 5.16 (2H, m), 4.07 (1H, br s), 3.82 (1H, t, *J* = 2.7 Hz), 3.60 (1H, dt, *J* = 9.8 Hz, 6.9 Hz), 3.51 (1H, d, *J* = 10.3 Hz), 3.44 (1H, d, *J* = 10.3 Hz), 2.58 (1H, dd, *J* = 10.0 Hz, 9.8 Hz), 1.87 - 1.82 (2H, m), 1.80 - 1.66 (3H, m), 1.06 (9H, s), 0.69 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.8, 135.7, 135.61, 135.48, 135.55, 135.4, 132.3, 132.1, 130.0, 129.90, 127.82, 127.76, 127.74, 120.9, 77.2, 74.0, 71.5, 68.3, 49.0, 42.0, 27.2, 26.91, 26.86, 26.82, 19.1, 16.4; IR (neat): 3424.6 (br w), 3071.2 (w), 29292 (m), 2856.7 (w), 1784.4 (w), 1470.5 (2), 1442.5 (w), 1427.4 (m), 1390.2 (w), 1361.5 (w), 1264.8 (w), 1109.7 (w), 1078.1 (s), 1031.9 (m), 999.4 (m), 966.3 (w), 938.7 (w), 822.0 (m), 740.8 (m), 701.4 (s), 614.0 (m), 504.2 (s) cm^{-1}; HRMS-(ESI+) for $C_{26}H_{37}O_3Si$ [M+H]: calculated: 425.2512, found: 245.2515; $[\alpha]_D^{22}$: -10.37 (*c* = 2.890, $CHCl_3$, *l* = 10 mm).

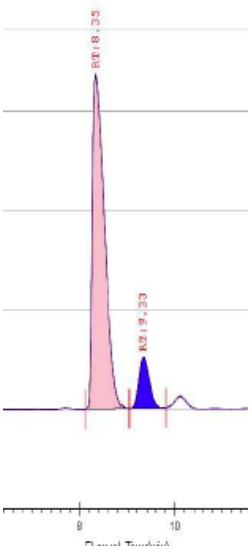
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the reaction product. A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by analogy to other

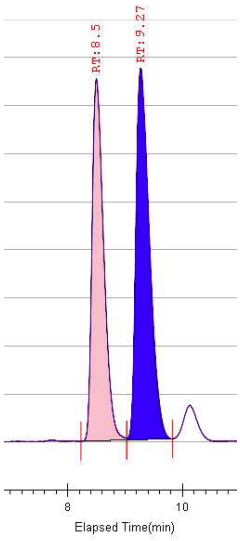
products derived from (*S,S*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry was assigned by NOESY analysis. The following NOEs were observed:



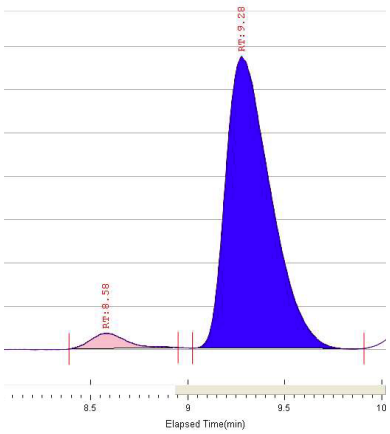
Chiral SFC (AD-H, Chiraldex, 3 mL/min, 8% i-PrOH, 100 bar 35 °C) - analysis of reaction product ***2.42.***



Product from (*R,R*)-*i*Pr$_2$TADDOL-PPh



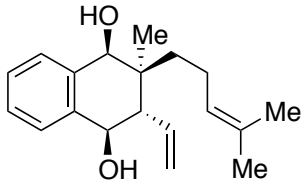
Mixture of products from (*R,R*)- and (*S,S*)-ligands



Product from (*S,S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	**% Area**	**Area**	**RT (min)**	**Height (mV)**	**K'**
1	3.9127	438.6183	8.58	34.5948	0.0091
2	96.0873	10771.5411	9.28	672.8939	0.0098
Total:	100	11210.1594			

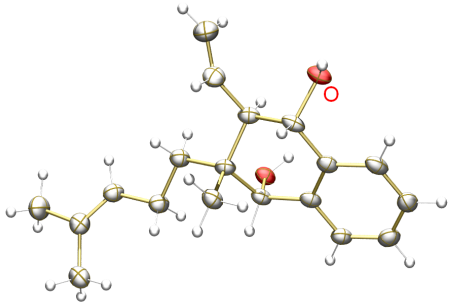


(1*S*,2*S*,3*S*,4*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinyl-1,2,3,4-tetrahydronaphthalene-1,4-diol (2.43). The diboration was performed according to Representative Diboration/Double Allylation Procedure II with (*E*)-4,8-dimethylnona-1,3,7-triene (50.0 mg, 0.33 mmol), $Pt(dba)_3$ (8.9 mg, 9.9 μmol), (*R,R*)-di-*iso*-propylTADDOL-PPh (10.8 mg, 11.9 μmol), $B_2(pin)_2$ (87.9 mg, 0.35 mmol), toluene (0.33 mL, 1.0 M) and phthalaldehyde (44.3 mg, 0.33 mmol). The crude reaction mixture was purified by column chromatography on SiO_2 (80:20 hexanes/ethyl acetate, R_f = 0.22 in 75:25 hexanes/ethyl acetate, stain in PMA) to afford a white solid (78.9 mg, 83% combined yield, d.r. = 2.8:1 *syn*:*anti* diol). The two diastereomers was separated after a purification by column chromotography (85:15–75:25 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (1H, d, *J* = 7.6 Hz), 7.36-7.33 (1H, m), 7.30-7.26 (2H, m), 5.81 (1H, dt, *J* = 16.9 Hz, 9.8 Hz), 5.33 (1H, dd, *J* = 10.3 Hz, 2.0 Hz), 5.30 (1H, ddd, *J* = 16.9, 2.0, 0.5 Hz), 5.16-5.12 (1H, m), 4.48 (1H, d, *J* = 9.5 Hz), 4.35 (1H, s), 2.54 (1H, t, *J* = 9.8 Hz), 2.20-2.13 (1H, m), 2.06-1.98 (1H, m), 1.68 (3H, s), 1.63 (3H, s), 1.61-1.55 (1H, m), 1.28-1.22 (1H, m), 0.81 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.0, 136.9, 136.2, 131.5, 129.9, 128.7, 128.1, 127.9, 124.8, 120.2, 73.8, 69.2, 52.4, 39.5, 37.8, 25.7, 21.2, 17.7, 16.4; IR (neat): 3374.0 (br), 2966.1 (m), 2921.7 (m), 1453.5 (w), 1380.0 (m), 996.9 (s), 918.1 (w), 765.0 (m), 745.8 (s) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{25}O_1$ [M+H-H_2O]: calculated: 269.1905, found: 269.1909. $[\alpha]_D^{23}$: -14.37 (*c* = 1.39, $CHCl_3$, *l* = 10 mm).

Analysis of Stereochemistry:

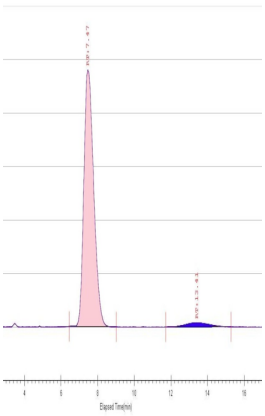
The enantioselectivity was determined by SFC analysis of the bis(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic

DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh, and reconfirmed by anomalous dispersion effects in diffraction measurements on the crystal.

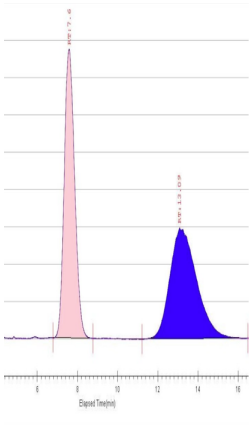


(*S,S*)-*i*Pr$_2$TADDOL-PPh used when this crystal structure was obtained

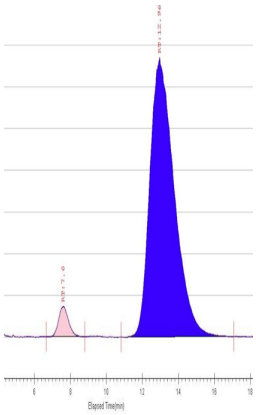
Chiral SFC (AD-H, Chiraldex, 3 mL/min, 5% MeOH, 100 bar, 35 °C)-analysis of the bis (benzoate) of reaction product ***2.43****.*



Product from (*R*,*R*)-*i*Pr$_2$TADDOL-PPh



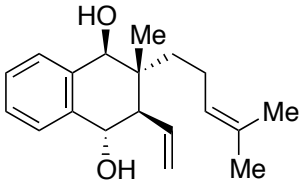
Mixture of products from (*R*,*R*)- and (*S*,*S*)-ligands



Product from (*S*,*S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	95.9863	35913.7946	7.47	960.8472	0.006
2	4.0137	1501.7331	13.41	16.884	0.0108
Total:	100	37415.5277			

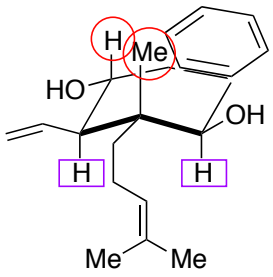


(1*S*,2*R*,3*R*,4*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinyl-1,2,3,4-tetrahydronaphthalene-1,4-diol (2.44). The diboration was performed according to Representative Diboration/Double Allylation Procedure II with (*Z*)-4,8-dimethylnona-1,3,7-triene (50.0 mg, 0.33 mmol), Pt(dba)$_3$ (8.9 mg, 9.9 μmol), (*R*,*R*)-di-*iso*-propylTADDOL-PPh (10.8 mg, 11.9 μmol), B$_2$(pin)$_2$ (87.9 mg, 0.35 mmol), toluene (0.33 mL, 1.0 M) and phthalaldehyde (44.3 mg, 0.33 mmol). The crude reaction mixture was purified by column chromatography on SiO$_2$ (75:25–60:40 hexanes/ethyl acetate, stain in PMA) to afford a heterogeneous mixture (77.5 mg, 82% combined yield, d.r. = 1.2:1 *anti*:*syn* diol [with 8% of minor diastereomer from first allylation]). A second purification

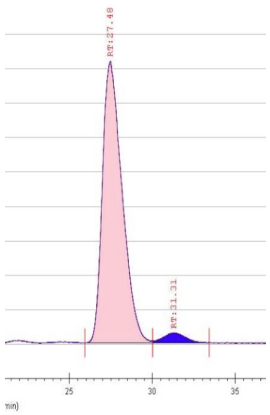
was used to separate the two major diastereomers (85:15–75:25 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60-7.55 (2H, m), 7.32-7.27 (2H, m), 5.88 (1H, dt, *J* = 16.9 Hz, 10.0 Hz), 5.38 (1H, dd, *J* = 10.5 Hz, 2.0 Hz), 5.34 (1H, ddd, *J* = 17.1 Hz, 2.0 Hz, 0.5 Hz), 5.10-5.07 (1H, m), 4.79 (1H, d, *J* = 4.6 Hz), 4.58 (1H, d, *J* = 9.8 Hz), 2.34 (1H, t, *J* = 9.8 Hz), 2.03 (2H, q, *J* = 7.9 Hz), 1.67 (3H, d, *J* =0.7 Hz), 1.64-1.58 (1H, m), 1.59 (3H, s), 1.38-1.32 (1H, m), 0.81 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 136.1, 135.3, 131.7, 128.0, 127.4, 127.3, 126.1, 124.3, 120.1, 72.3, 69.3, 53.9, 41.3, 37.1, 25.7, 21.0, 17.7, 14.9; IR (neat): 3383.9 (br), 2967.6 (m), 2921.7 (s), 1452.2 (m), 1380.2 (m), 1129.0 (w), 1027.2 (m), 1010.3 (s), 918.0 (w), 762.1 (s), 680.7 (w), 668.1 (w) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{25}O_1$ [M +H-H_2O]: calculated: 269.1905, found: 269.1902. $[\alpha]_D^{23}$= +16.63 (*c* = 0.60, $CHCl_3$, *l* = 10 mm). R_f = 0.32 in 75:25 hexanes/ethyl acetate.

Analysis of Stereochemistry:

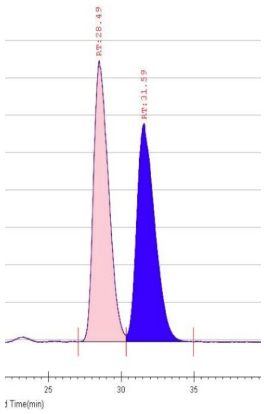
The enantioselectivity was determined by SFC analysis of the bis(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis. The following NOEs were observed:



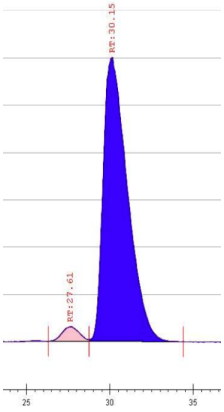
Chiral SFC (AD-H, Chiraldex, 1.5 mL/min, 4% MeOH, 100 bar, 35 °C)-analysis of the bis (benzoate) of reaction product ***2.44****.*



Product from
(*R*,*R*)-*i*Pr$_2$TADDOL-PPh



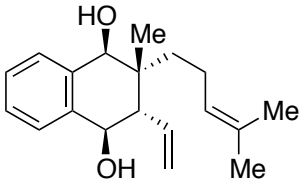
Mixture of products from
(*R*,*R*)- and (*S*,*S*)-ligands



Product from
(*S*,*S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	96.3551	33728.0439	27.48	409.9959	0.0374
2	3.6449	1275.8455	31.31	14.4836	0.0427
Total:	100	35003.8894			

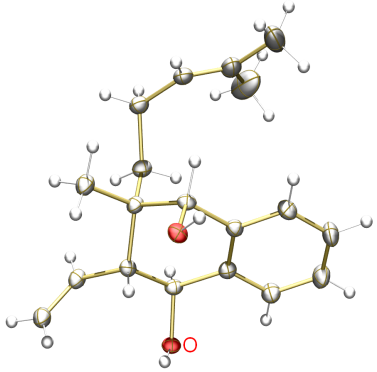


(1*S*,2*R*,3*S*,4*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinyl-1,2,3,4-tetrahydronaphthalene-1,4-diol (*syn* diastereomer from reaction producing **2.44**). R_f = 0.27 in 67:33 hexanes/ethyl acetate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (1H, d, *J* = 7.3 Hz), 7.37-7.33 (1H, m), 7.30-7.28 (2H, m), 5.88 (1H, dt, *J* = 16.9 Hz, 9.9 Hz), 5.34-5.29 (2H, m), 4.92-4.88 (1H, m), 4.57 (1H, dd, *J* = 9.5 Hz, 4.7 Hz), 4.47 (1H, s), 2.66 (1H, t, *J* = 9.7 Hz), 2.02-1.93 (1H, m), 1.89-1.81 (1H, m), 1.58 (3H, d, *J* = 0.7 Hz), 1.46 (3H, s), 1.41-1.35 (1H, m), 1.13-1.01 (1H, m), 1.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.2, 136.8, 136.2, 131.6, 129.8, 128.7, 128.2, 128.1, 124.4, 120.2, 74.2, 69.2, 52.6, 40.2, 32.7, 25.6, 22.3, 21.8, 17.4; IR (neat): 3301.5 (br s), 2966.1 (s), 2923.5 (m), 2864.7 (w), 1453.9 (w), 1040.8 (m), 1005.5 (s), 987.2 (s), 926.8 (m), 765.8 (w), 743.7 (w) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{25}O_1$

[M+H-H_2O]: calculated: 269.1905, found: 269.1902. $[\alpha]_D^{23}$= −108.00 (*c* = 0.37, $CHCl_3$, *l* = 10 mm).

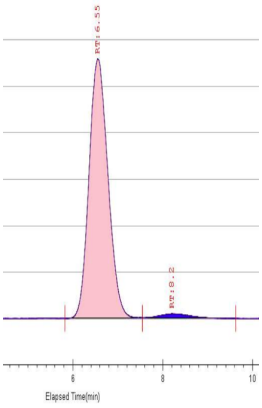
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the bis(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by crystallography using anomalous dispersion. Flack parameter = 0.34.

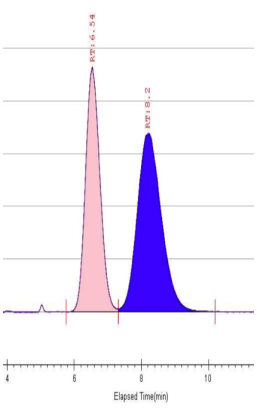


(*S,S*)-*i*Pr_2TADDOL-PPh used when this crystal structure was obtained

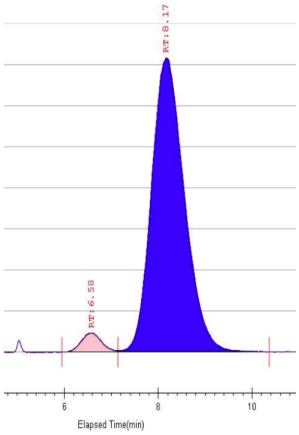
Chiral SFC (AD-H, Chiraldex, 3 mL/min, 5% MeOH, 100 bar, 35 °C)-analysis of the bis (benzoate) of reaction product ***2.44*** *minor diastereomer.*



Product from
(*R*,*R*)-*i*Pr$_2$TADDOL-PPh



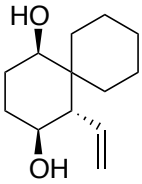
Mixture of products from
(*R*,*R*)- and (*S*,*S*)-ligands



Product from
(*S*,*S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	97.1229	16401.5583	6.55	559.9962	0.0064
2	2.8771	485.8737	8.2	10.1418	0.008
Total:	100	16887.432			

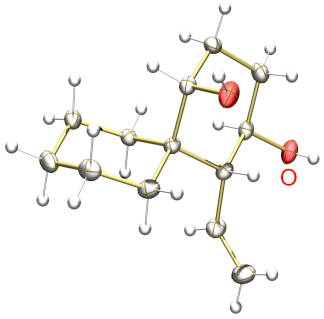


(1R,4S,5S)-5-vinylspiro[5.5]undecane-1,4-diol (2.45). The diboration was performed according to Representative Diboration/Double Allylation Procedure I with allylidenecyclohexane[3] (40.3 mg, 0.33 mmol), Pt(dba)$_3$ (8.9 mg, 9.9 μmol), (*R*,*R*)-di-iso-propylTADDOL-PPh (10.8 mg, 11.9 μmol), $B_2(pin)_2$ (87.9 mg, 0.35 mmol), toluene (0.33 mL, 1.0 M) and and succinaldehyde (56.8 mg, 0.66 mmol). The crude reaction mixture was purified by column chromatography on SiO_2 (67:33–50:50 hexanes/ethyl acetate) to afford a colorless oil (4.8 mg, 7%, *anti* diol) and a white solid (44.0 mg, 63%, *syn* diol, R_f = 0.14 in 50:50 hexanes/ethyl acetate, stain in PMA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (1H, dt, *J* = 16.9 Hz, 10.3 Hz), 5.31 (1H, dd, *J* = 10.0 Hz, 2.2 Hz), 5.18 (1H, ddd, *J* = 16.9 Hz, 2.2 Hz, 0.5 Hz), 4.20 (1H, t, *J* = 2.9 Hz), 3.59

(1H, dt, J = 4.5 Hz, 10.8 Hz), 2.05 (1H, t, J = 10.0 Hz), 1.90-1.83 (1H, m), 1.81-1.77 (1H, m), 1.76-1.08 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.1, 121.1, 67.5, 65.8, 55.0, 40.9, 32.1, 28.6, 27.4, 26.33, 26.29, 21.2, 21.1; IR (neat): 3320.4 (br), 2923.0 (s), 2858.2 (m), 1451.1 (m), 1089.6 (w), 1064.7 (m), 1023.9 (m), 993.9 (s), 970.5 (m), 912.6 (m), 634.2 (m) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{21}O_1$ [M+H-H_2O]: calculated: 193.1592, found: 193.1596. $[\alpha]_D^{23}$ = −46.83: (c = 0.64, $CHCl_3$, l = 10 mm).

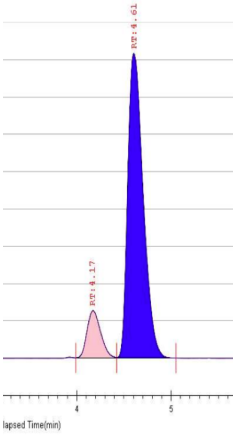
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the bis(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by crystallography using anomalous dispersion. Flack parameter = 0.18.

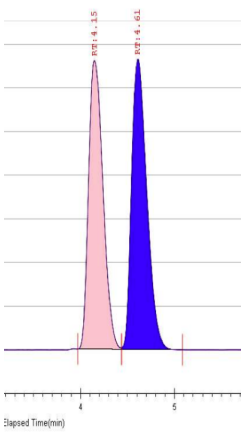


(*S,S*)-*i*Pr_2TADDOL-PPh used when this crystal structure was obtained

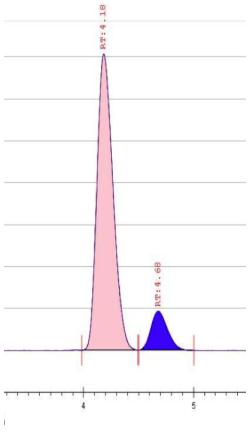
Chiral SFC (AD-H, Chiraldex, 3 mL/min, 10% MeOH, 100 bar, 35 °C)-analysis of the bis (benzoate) of reaction product ***2.45****.*



Product from (*R,R*)-*i*Pr$_2$TADDOL-PPh



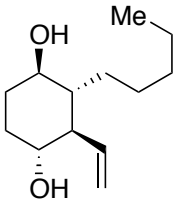
Mixture of products from (*R,R*)- and (*S,S*)-ligands



Product from (*S,S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	11.9326	2514.401	4.17	253.2321	0.0034
2	88.0674	18557.3147	4.61	1631.3881	0.0037
Total:	100	21071.7157			



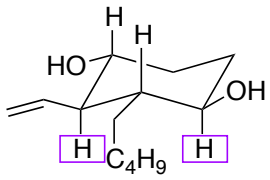
(1*R*,2*R*,3*S*,4*S*)-2-pentyl-3-vinylcyclohexane-1,4-diol (2.46). The diboration was performed according to Representative Diboration/ Double Allylation Procedure I with slight modification using (*Z*)-nona-1,3-diene (41.0 mg, 0.33 mmol), Pt(dba)$_3$ (8.9 mg, 9.9 μmol), (*R,R*)-di-*iso*-propylTADDOL-PPh (10.8 mg, 19.8 μmol), B$_2$(pin)$_2$ (87.9 mg, 0.35 mmol), and THF (0.66 mL, 0.5 M). After cooling to room temperature, the diboration reaction solvent was removed *in vacuo*. The reaction mixture was transferred to a vial containing succinaldehyde (85.2 mg, 0.99 mmol) with 0.5 mL DCM (0.5 M), purged with N$_2$, sealed and stirred at room temperature for 24 hours. Upon completion, the reaction mixture

was warmed to room temperature, transferred to a 6-dram scintillation vial with THF (2 mL), and stirred with 2 mL of 3M NaOH for 3 hours. the reaction mixture was diluted with ethyl acetate (5 mL), transferred to a separatory funnel and washed with ethyl acetate (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified twice by column chromatography on silica gel (70:30 - 40:60 hexanes/ethyl acetate, then 30:1 - 20:1 DCM/methanol. R_f = 0.19 in 25:1 DCM/methanol, stain in PMA) to afford a single diastereomer of the title compound as a white solid (27.0 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (1H, dt, *J* = 17.1 Hz, 10.0 Hz), 5.24 (1H, dd, *J* = 10.0 Hz, 1.7 Hz), 5.17 (1H, dd, *J* = 17.1 Hz, 2.0 Hz), 3.44 (1H, dt, *J* = 10.3 Hz, 4.7 Hz), 3.26 - 3.21 (1H, m), 2.05 - 1.98 (2H, m), 1.96-1.95 (1H, m), 1.81 (1H, ddd, *J* = 9.5 Hz, 9.5 Hz, 9.5 Hz), 1.61 - 1.54 (1H, m), 1.41 - 1.31 (3H, m), 1.30 - 1.16 (9H, m), 0.85 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 119.2, 71.4, 71.3, 53.6, 45.8, 33.0, 32.4, 31.0, 28.2, 23.8, 22.6, 14.0; IR (neat): 3344.0 (m br), 3075.9 (2), 2921.1 (s), 2873.4 (s), 2859.6 (s), 1643.0 (2), 1456.7 (m), 1354.3 (m), 1151.0 (w), 1113.7 (w), 1069.7 (m), 1032.4 (s), 990.0 (m), 915.2 (m), 724.9 (2), 682.8 (m), 567.2 (w); HRMS-(ESI+) for $C_{13}H_{23}O_1$ [M+1-H_2O]: calculated: 195.1749, found: 195.1746. $[\alpha]_D^{23}$: -11.04 (*c* = 0.905, $CHCl_3$, *l* = 10 mm).

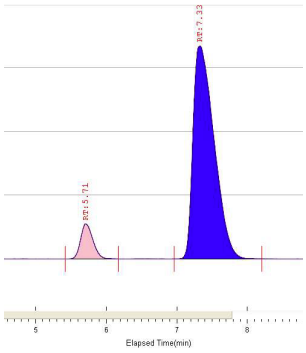
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the bis(benzoate) of the reaction product prepared using benzoic anhydride, triethylamine, and catalytic DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by analogy

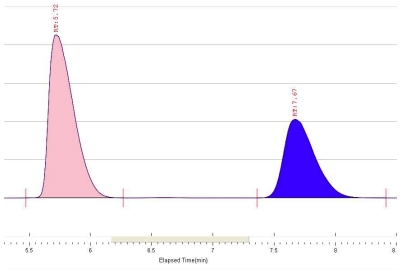
to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry was assigned by 2D-NMR analysis. A COSY was used to elucidate the identity of the carbinol signals, and the following NOE was observed during NOESY analysis:



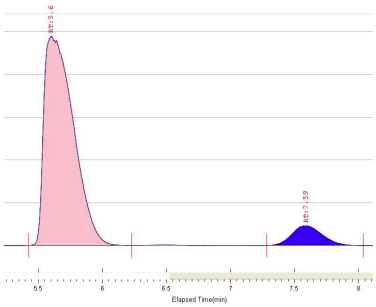
Chiral SFC (AD-H, Chiraldex, 3 mL/min, 5% MeOH, 100 bar, 35 °C) - analysis of reaction product ***2.46****-bisbenzoate.*



Product from (*R,R*)-*i*Pr$_2$TADDOL-PPh



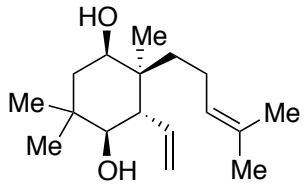
Mixture of products from (*R,R*)- and (*S,S*)-ligands



Product from (*S,S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

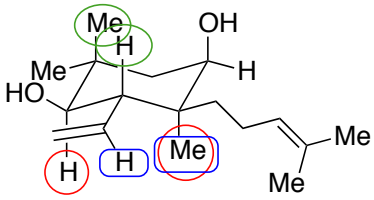
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	8.7479	3307.7824	5.71	274.7333	0.0053
2	91.2521	34504.479	7.33	1666.1093	0.0069
Total:	100	37812.2614			

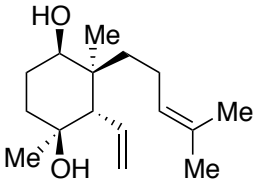


(1*R*,2*S*,3*S*,4*R*)-2,5,5-trimethyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclohexane-1,4-diol (2.48): The diboration was performed according to Representative Diboration/Double Allylation Procedure I with slight modification using (*E*)-4,8-dimethylnona-1,3,7-triene (75.1 mg, 0.50 mmol), $Pt(dba)_3$ (13.5 mg, 15.0 μmol), (*R*,*R*)-di-*iso*-propylTADDOL-PPh (16.4 mg, 18.0 μmoll), $B_2(pin)_2$ (133.3 mg, 0.525 mmol), and toluene (0.5 mL, 1.0 M). After cooling to room temperature, the reaction mixture was transferred to a vial containing 2,2-dimethylsuccinaldehyde (28.5 mg, 0.25 mmol) using minimal toluene. The crude reaction mixture was purified on SiO_2 (10:1 - 30:70 hexanes/ethyl acetate, R_f = 0.24 in 6:1 hexanes/ethyl acetate, stain in PMA) to afford a single diastereomer of the title compound as a yellow oil (36.4 mg, 54% yield, >20:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65 (1H, dt, *J* = 16.9 Hz, 10.0 Hz), 5.28 (1H, dd, *J* = 9.2 Hz, 2.0 Hz), 5.19 (1H, dd, *J* = 16.9 Hz, 2.0 Hz), 5.10 (1H, dt, *J* = 7.1 Hz, 1.2 Hz), 3.63 (1H, t, *J* = 2.9 Hz), 3.34 (1H, d, *J* = 10.8 Hz), 2.23 (1H, t, *J* = 10.3 Hz), 1.99 - 1.86 (2H, m), 1.65 (3H, s), 1.63 - 1.54 (2H, m), 1.58 (3H, s), 1.46 - 1.39 (2H, m), 1.23 - 1.17 (2H, m), 1.09 (3H, s), 1.02 (3H, s), 0.88 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.6, 131.7, 124.8, 120.7, 74.8, 72.6, 50.9, 41.5, 41.1, 38.5, 34.8, 30.9, 25.7, 22.0, 21.3, 18.2, 17.6; IR (neat): 3477.0 (br m), 3072.6 (w), 2965.6 (s), 2922.1 (s), 1636.5 (w), 1452.4 (m), 1377.6 (m), 1363.9 (m), 1260.0 (m), 1092.3 (m), 1037.8 (s), 1019.4 (s), 1000.5 (s), 965.6 (m), 919.8 (m), 882.7 (w), 811.0 (w), 743.3 (w), 663.7 (w), 539.5 (w), 522.6 (w), 455.7 (w), 445.4 (w), 416.5 (w); HRMS-(ESI+) for $C_{17}H_{29}O_1$ [M+H-H_2O]: calculated: 249.2218, found: 249.2228; $[\alpha]_D^{22}$: -88.65 (*c* = 1.465, $CHCl_3$, *l* = 10 mm).

Analysis of Stereochemistry:

Due to difficulties in derivitizing the title compound with a chromophore, the enantioselectivity was assigned by analogy to diboration/double allylation products derived from the geranial-diene and (*R,R*)-*i*Pr$_2$TADDOL-PPh. The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-di-*iso*-propylTADDOL-PPh. The relative stereochemistry was assigned by NOESY analysis. The following NOEs were observed:



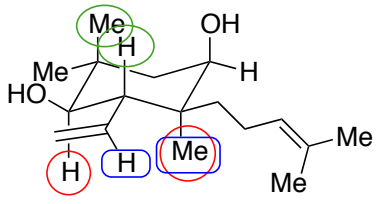


(1*S*,2*S*,3*S*,4*R*)-1,3-dimethyl-3-(4-methylpent-3-en-1-yl)-2-vinylcyclohexane-1,4-diol (2.52): The diboration/double allyation was performed according to Representative Diboration/ Double Allylation Procedure II using (*E*)-4,8-dimethylnona-1,3,7-triene (50 mg, 0.33 mmol), Pt(dba)$_3$ (8.9 mg, 9.0 μmol), (*R,R*)-di-*iso*-propylTADDOL-PPh (10.8 mg, 12.0 μmol), B$_2$(pin)$_2$ (88.0 mg, 0.35 mmol), toluene (0.33 mL, 1.0 M), and 4-oxopentenal (33.0 mg, 0.33 mmol). The crude reaction mixture was purified twice on SiO$_2$ (first purification: 70:30 - 40:60 hexanes/ethyl acetate, R_f = 0.26 in 25:1 DCM/ methanol, stain in PMA) to afford a clear, colorless oil (64.9 mg, 78%, 11:1 *syn:anti* diol). A second purification on SiO$_2$ (25:1 DCM/methanol) was used to separate the diastereomers. ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.73 (1H, dt, *J* = 16.9 Hz, 10.3 Hz), 5.23 (1H, dd, *J* = 10.3 Hz, 2.4 Hz), 5.14 (1H, dd, *J* = 16.9 Hz, 2.2 Hz), 5.11 - 5.07 (1H, m), 3.61 (1H, t, *J*

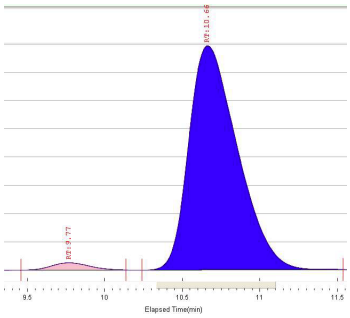
= 3.4 Hz), 2.18 (1H, d, *J* = 10.5 Hz), 1.99 - 1.92 (2H, m), 1.89 - 1.81 (2H, m), 1.76 - 1.72 (2H, m), 1.65 (3H, s), 1.59 - 1.55 (1H, m), 1.59 (3H, s), 1.43 (1H, br s), 1.39 (1H, br s), 1.34 - 1.29 (2H, m), 1.18 (3H, s), 0.91 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.0, 131.6, 124.9, 120.4, 71.4, 71.3, 57.7, 39.9, 38.5, 33.5, 26.6, 25.7, 25.6, 21.6, 19.1, 17.6; IR (neat): 3416.7 (m br), 3072.0 (w), 2965.8 (m), 2924.9 (s), 1634.8 (w), 1451.3 (m), 1419.2 (w), 1381.8 (s), 1328.1 (w), 1279.5 (w), 1197.2 (m), 1107.7 (m), 1062.9 (s), 1039.9 (m), 1017.4 (s), 974.0 (m), 910.0 (s), 883.8 (w), 833.5 (w), 809.4 (w), 651.9 w), 548.3 (w), 448.1 (w); HRMS-(ESI+): for $C_{16}H_{27}O_1$ [M+1-H_2O]: calculated: 235.20619, found: 235.20727. $[\alpha]_D^{22}$: -52.58 (*c* = 0.95, $CHCl_3$, *l* = 10 mm).

Analysis of Stereochemistry:

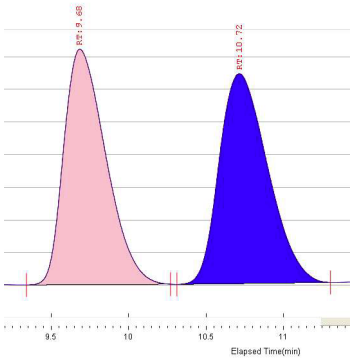
The enantioselectivity was determined by SFC analysis of the mono(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry was assigned by NOESY analysis. The following NOEs were observed:



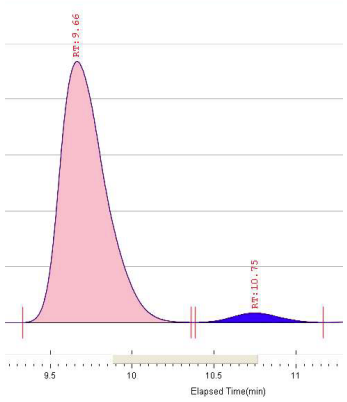
Chiral SFC (AD-H, Chiraldex, 1.5 mL/min, 5% MeOH, 100 bar, 35 °C)- analysis of reaction the mono(benzoate) of reaction product **2.52**.



Product from (*R*,*R*)-*i*Pr$_2$TADDOL-PPh



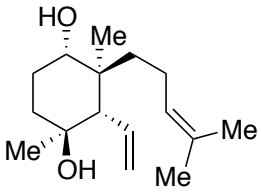
Mixture of products from (*R*,*R*)- and (*S*,*S*)-ligands



Product from (*S*,*S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	2.4744	437.3655	9.77	25.9145	0.012
2	97.5256	17238.2324	10.66	792.2277	0.0131
Total:	100	17675.5979			

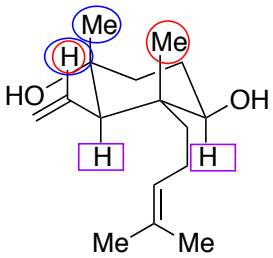


(1*S*,2*S*, 3*R*,4*R*)-1,3-dimethyl-3-(4-methylpent-3-en-1-yl)-2-vinylcyclohexane-1,4-diol (2.53): The diboration/double allyation was performed according to Representative Diboration/ Double Allylation Procedure II with slight modification using (*Z*)-4,8-dimethylnona-1,3,7-triene (1.476 g, 9.822 mmol) Pt(dba)$_3$ (88.2 mg, 98.2 μmol), (*R*,*R*)-di-*iso*-propylTADDOL-PPh (107.2 mg, 117.8 μmol), B$_2$(pin)$_2$ (2.619 g, 10.31 mmol), toluene (9.8 mL, 1.0 M), and 4-oxopentenal (1.18 g, 11.79 mmol) in a large pressure vessel. The crude reaction mixture was purified twice on SiO$_2$ (first purification: 70:30 - 40:60 hexanes/ethyl acetate, second purification: 30:1 - 20:1 DCM/methanol, R_f = 0.25 in 25:1 DCM/methanol, stain in PMA) to afford a clear, colorless oil (1.66 g, 67%, d.r. = 5:1

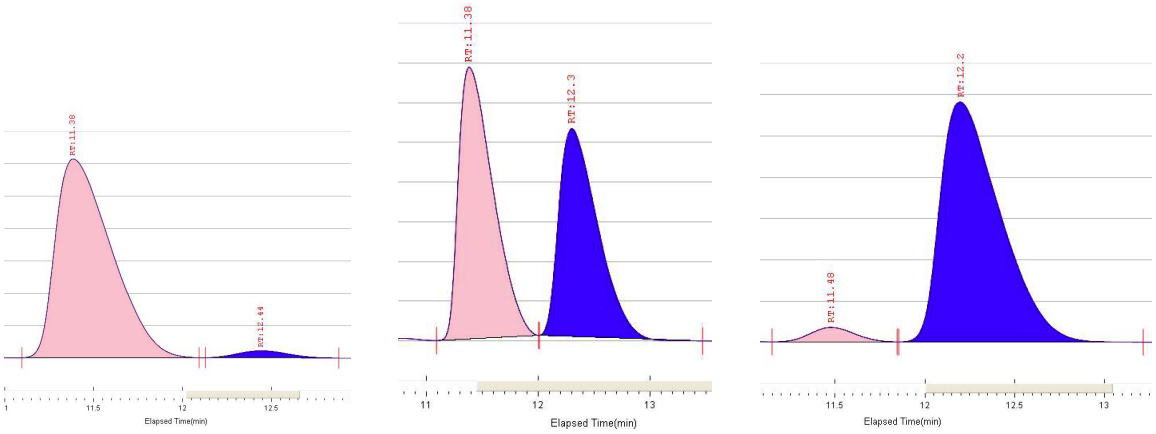
anti:syn diol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (1H, dt, *J* = 17.1 Hz, 10.3 Hz), 5.29 (1H, dd, *J* = 10.3 Hz, 2.2 Hz), 5.19 (1H, dd, *J* = 17.1 Hz, 2.4 Hz), 5.02 (1H, dt, *J* = 7.1 Hz, 1.0 Hz), 3.56 (1H, dd, *J* = 10.8 Hz, 3.4 Hz), 2.05 (1H, d, *J* = 10.5 Hz), 2.00 (1H, br s), 1.91 (2H, dd, *J* = 7.8 Hz, 7.6 Hz), 1.80 - 1.75 (2H, m), 1.64 (3H, s), 1.62 - 1.47 (2H, m), 1.56 (3H, s), 1.42 - 1.36 (2H, m), 1.23 - 1.17 (1H, m), 1.18 (3H, s), 0.89 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.7, 131.5, 124.5, 120.5, 72.9, 71.1, 57.3, 40.5, 38.7, 38.0, 28.2, 25.7, 25.1, 21.2, 17.6, 16.0; IR (neat): 3420.2 (br m), 3072.3 (w), 2968.6 (m), 2924.9 (s), 2872.4 (m), 1634.7 (w), 1555.5 (m), 1450.1 (m), 1381.7 (m), 1312.5 (w), 1130.2 (m), 1075.3 (s), 1037.0 (s), 1001.3 (m), 951.8 (s), 916.0 (s), 879.2 (w), 832.1 (w), 812.0 (w), 670.6 (m), 558.0 (w), 437.3 (w); HRMS-(ESI+): for $C_{16}H_{27}O_1$ [M+H-H_2O]: calculated 235.2062, found: 235.2070. $[\alpha]_D^{23}$: +6.70 (c = 1.490, $CHCl_3$, *l* = 10 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the mono(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic DMAP). A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions.The relative stereochemistry was assigned by NOESY analysis. The following NOEs were observed:



Chiral SFC (AD-H, Chiraldex, 1.5 mL/min, 5% MeOH, 100 bar , 35 °C)- analysis of mono (benzoate) of reaction product* ***2.53****.*



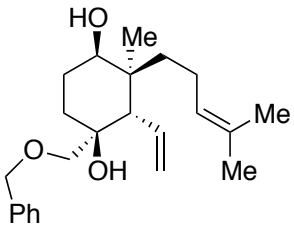
Product from (*R,R*)-*i*Pr$_2$TADDOL-PPh

Mixture of products from (*R,R*)- and (*S,S*)-ligands

Product from (*S,S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	4.2653	1199.9207	11.48	70.2127	0.0152
2	95.7347	26932.0117	12.2	1163.3115	0.0162
Total:	100	28131.9324			

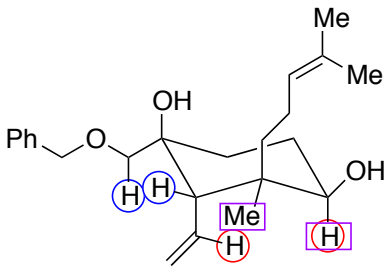


(1*R*,2*R*,3*S*,4*R*)-1-((benzyloxy)methyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-2-vinylcyclohexane-1,4-diol (2.55): The diboration/double allyation was performed according to Representative Diboration/Double Allylation Procedure II using 5-(benzyloxy)-4-oxopentanal (50 mg, 0.33 mmol) Pt(dba)$_3$ (8.9 mg, 9.0 μmol), (*R,R*)-di-*iso*-propylTADDOL-PPh (10.8 mg, 12.0 μmol)), $B_2(pin)_2$ (88.0 mg, 0.35 mmol), toluene (0.33 mL, 1.0 M), and 4-oxopentenal (68.0 mg, 0.33 mmol). The crude reaction mixture was purified on SiO_2 (5:1 - 3:1 hexanes/ethyl acetate, R_f = 0.26 in 1:1 hexanes/ethyl acetate, stain in PMA) to afford a colorless oil (71.0 mg, 60%, d.r. = > 20:1 *syn:anti* diol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 - 7.31 (2H, m), 7.29 - 7.25 (3H, m), 5.60 (1H, dt, *J* = 16.6

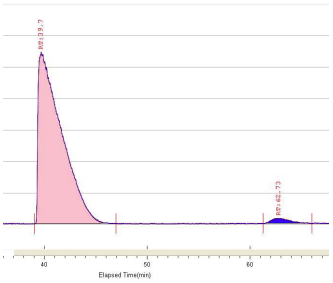
Hz, 10.0 Hz), 5.13 (1H, tt, *J* = 7.1 Hz, 1.5 Hz), 5.07 - 5.01 (2H, m), 4.50 (1H, d, *J* = 12.0 Hz), 4.45 (1H, d, *J* = 12.0 Hz), 3.59 (1H, dd, *J* = 10.0 Hz, 3.7 Hz), 3.32 (1H, d, *J* = 9.1 Hz), 3.18 (1H, d, *J* = 8.8 Hz), 2.66 (1H, s), 2.41 (1H, d, *J* = 10.0 Hz), 2.07 - 1.98 (2H, m), 1.95 - 1.85 (2H, m), 1.75 - 1.70 (1H, m), 1.66 (3H, s), 1.65 - 1.53 (2H, m), 1.60 (3H, s), 1.38 (1H, br s), 1.32 - 1.26 (1H, m), 0.87 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 135.7, 131.0, 128.3, 127.6, 127.5, 125.4, 118.2, 76.9, 74.9, 73.4, 72.8, 54.0, 39.9, 33.7, 30.2, 26.2, 25.7, 23.9, 22.4, 17.6; IR (neat): 3444.4 (br w), 3069.4 (w), 3029.0 (w), 2961.9 (m), 2928.8 (m), 2859.1 (m), 1496.4 (w), 1452.8 (m), 1375.4 (m), 1252.1 (w), 1202.2 (w), 1092.4 (s), 1058.7 (s), 1028.5 (m), 998.5 (m), 915.4 (m), 839.7 (w), 735.9 (s), 697.5 (s), 579.1 (w), 357.4 (w), 412.5 (m); HRMS-(ESI+): for $C_{23}H_{33}O_2$ [M+H-H_2O]: calculated: 342.2481, found: 341.2475. $[\alpha]_D^{22}$: -52.58 (*c* = 0.95, $CHCl_3$, *l* = 10 mm).

Analysis of Stereochemistry:

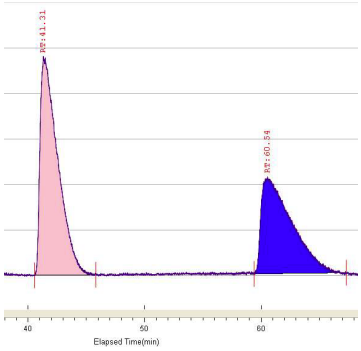
The enantioselectivity was determined by SFC analysis of the reaction product. A mixture of the products made using (*R,R*)-di-*iso*-propylTADDOL-PPh and (*S,S*)-di-*iso*-propylTADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-di-*iso*-propylTADDOL-PPh. The relative stereochemistry was determined by NOESY analysis. The following NOEs were observed:



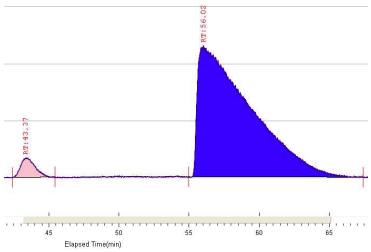
Chiral SFC (AD-H, Chiraldex, 3.0 mL/min, 5% i-PrOH, 100 bar, 35 °C) - analysis of reaction product ***2.55.***



Product from
(*R*,*R*)-*i*Pr$_2$TADDOL-PPh



Mixture of products from
(*R*,*R*)- and (*S*,*S*)-ligands



Product from
(*S*,*S*)-*i*Pr$_2$TADDOL-PPh

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	97.9452	43039.9397	39.7	272.5994	0.0412
2	2.0548	902.9478	62.73	8.087	0.0651
Total:	100	43942.8875			

Chapter 3

Applications of Diboration/Double Allylation Strategy to the Total Synthesis of Terpenoid Natural Products

3.1. Introduction

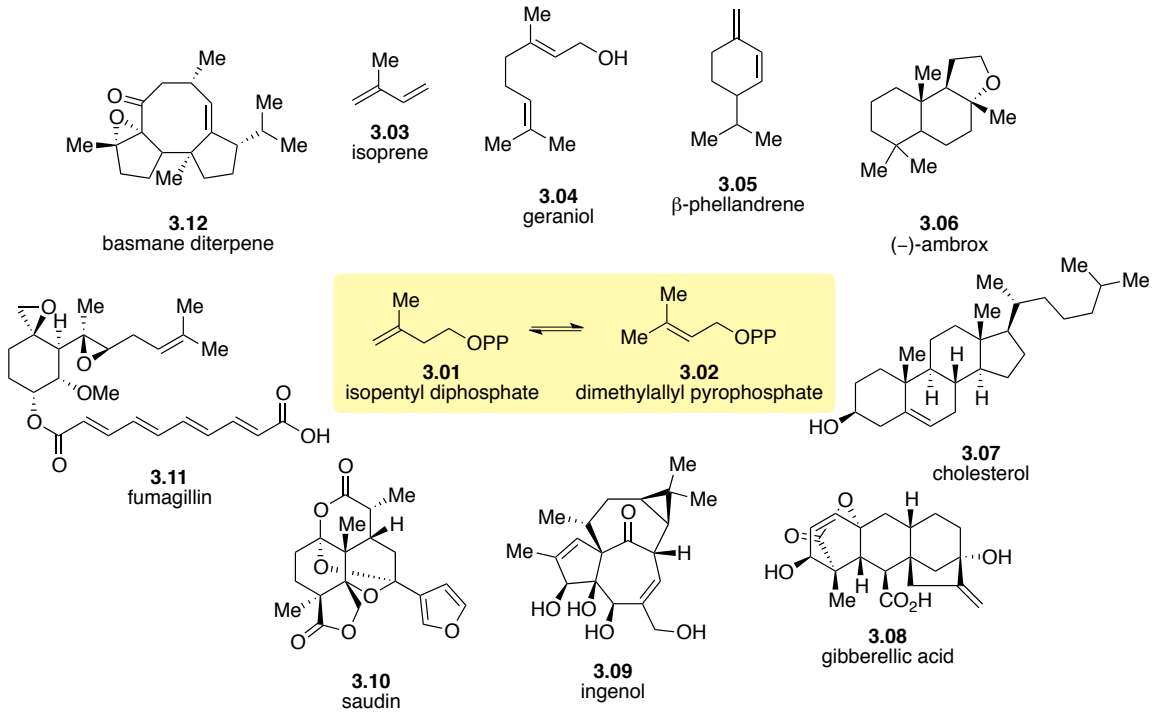
3.1.1. Terpenoid Natural Products

The largest, and arguably most diverse, class of secondary metabolites are terpenes. By 2007, more than 55,000 terpenoid structures had been isolated. Fascinatingly, the defining feature of this diverse class of compounds is that they are all synthesized from two 5-carbon isomeric species: isopentenyl diphosphate (IPP, **3.01,** Figure 3.1) and dimethylallyl diphosphate (DMAPP, **3.02**). These isoprene units are combined, rearranged, cyclized and oxidized by terpene synthases to create a plethora of intriguing structures, both simple (**3.03** - **3.05**) and complex (**3.06** - **3.13**).[94] Plants, animals, and microorganisms, despite their phylogenetic differences, have all been found to generate terpene secondary metabolites. It is thought that these metabolites are used primarily for defense and signaling across nearly all species.[95] Given their diverse structural and biological properties, terpenes have found use in medicine, fragrance,

[94] Chen, F.; Tholl, D.; Bohlmann, J.; Pichersky, E. *Plant J.* **2011**, *66*, 212.
[95] Gershenzon, J.; Dudareva, N. *Nature Chem. Bio.* **2007**, *3*, 408.

flavor, hormones and materials.[96] As such, research in terpene isolation, characterization, synthesis, and applications has received great attention from scientists worldwide.

Figure 3.1. Examples of Terpene Natural Products and Isopentenyl Precursors



The natural function of terpenes can generally be divided into two classes: defense and signaling. For example, drimane sesquiterpenes (which are prevalent in plants and some marine organisms)[97] have been found to have potent antibacterial[98] and antifungal activity.[99] This class of isoprenoids is also toxic to insects,[100] nematodes,[101] mollusks and fish.[102] In some cases, they deter insects from feeding on plants[103] and fish

[96] Breitmaier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones* (Wiley-VCH, Weinheim, Germany, 2006.)
[97] Jansen, B. J. M.; de Groot, A. *Nat. Prod. Rep.* **2004**, *21*, 449.
[98] Rastogi, N. *et al. Immunol. Med. Microbiol.* **1998**, *20*, 267.
[99] Lunde, C. S.; Kubu, I. *Antimicrob. Agents Chemother.* **2000**, *44*, 1943.
[100] Justicia, J. *Eur. J. Org. Chem.* **2005**, 712.
[101] Lorimer, S. D.; Perry, N. B.; Foster, L M.; Burgess, E. J. *J. Agric. Food Chem.* **1996,** *44*, 2842.
[102] Ito, H.; Muranaka, T.; Mori, K.; Jin, Z. X.; Yoshida, T. *Chem. Pharm. Bull.* **1997**, *45*, 1720.
[103] Messchendorp, L.; Gols, G. J. Z.; van Loon, J. A. A. *Entomol. Exp. Appl.* **2000**, *95*, 217.

from feeding on mollusks.[104] While the drimane sesquiterpenes only represent a subset of the terpene natural product class, they demonstrate the versatility of roles they can play as defense agents in plants and animals. The lipophilicity of most terpenoid structures suggests that a possible mode of action is to disrupt chemiosmotic control in cell membranes.[105] Pyrethroids, for instance, attack the nervous system of insects by disrupting the voltage-sensitive sodium channel in nervous cell membranes.[106] Alternatively, it has been proposed that terpenes work in synergy with other toxins by acting as a non-polar solvent to expedite membrane invasion.[107] As signaling chemicals, terpenes are extremely effective at sending specific messages because of their chemical diversity combined with their characteristic low molecular weight, liphophilic nature, and high vapor pressure. For immobile organisms, such as plants, terpenes have been shown to play a vital role in attracting pollinating insects.[108]

3.1.2. Classic Strategies for the Synthesis of Terpenoid Natural Products

Because of their structural diversity and complexity, as well as their array of useful characteristics for medicine, agriculture, and materials, terpene secondary metabolites are highly attractive targets for natural product total synthesis. In 1953, Ružička laid the groundwork for the biogenesis of mono-, sesqui-, di- and triterpenes when he put forth the "biogenetic isoprene rule" and the squalene hypothesis.[109] Since then, a number of general strategies for terpene construction have been reported in the

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[104] Paul, V. J. *J. Nat. Prod.* **1997**, *60*, 1115.
[105] (a) Cox, S. D. *J. Appl. Microbiol.* **2000**, *88*, 170. (b) Inoue, Y. *FEMS Microbiol. Lett.* **2004**, *237*, 325.
[106] Soderlund, D. M. in *Pyrethrum Flowers: Production, Chemistry, Toxicology, and Uses* (eds. Casida, J. E. & Quistad, G. B.) 297-233 (Oxford University Press, New York, 1995.)
[107] (a) Guillet, G.; Belanger, A.; Arnason, J. T. *Phytochemistry* **1998**, *49*, 423. (b) Kang, R. *J. Agric. Food. Chem.* **1992**, *40, 2328.*
[108] Raguso, R. A.; Light, D. M. *Entomol. Exp. Appl.* **1998**, *86*, 287.
[109] (a) Ružička, L. *Experentia* **1953,** *9, 357.* (b) Eschenmoser, A.; Ružička, O. J.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (b) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta.* **2005**, *88*, 3011.

literature, including (but not limited to): polyolefin carbocyclizations,[110] the Diels-Alder reaction,[111] ring-closing metathesis,[112] [2+2] photocycloadditions,[113] and the Claisen rearrangement.[114]

Often times, synthetic chemists aim to access challenging natural product targets by mimicking enzymatic pathways. Polyolefin carbocyclization is the premier example of biomimetic synthesis. In nature, steroid biosynthesis from squalene and squalene-derivatives occurs *via* a two step process: 1) enzyme-catalyzed carbocyclization and proton-loss termination (with or without atom/group rearrangements) and 2) side chain modification. Through the enzyme-catalyzed process, several new quaternary and tertiary stereocenters, as well as ring junctions, are formed in a single, impressive, highly selective step. Replicating this mastery of stereochemistry and control of C-C bond formation in the laboratory is not trivial. In 1994, Johnson reported the first nonenzymatic, biomimetic polyene pentacyclization.[115] By using fluorine as a cation-stabilizing group,[116] acid-catalyzed pentacyclization of **3.13** afforded **3.14** in 31% yield (Scheme 3.1). After oxidative cleavage and regiospecific dehydrofluorination, **3.16** was reduced with DIBAl-H to furnish to sophoradiol in 87% yield as a 4:1 mixture of diastereomers.

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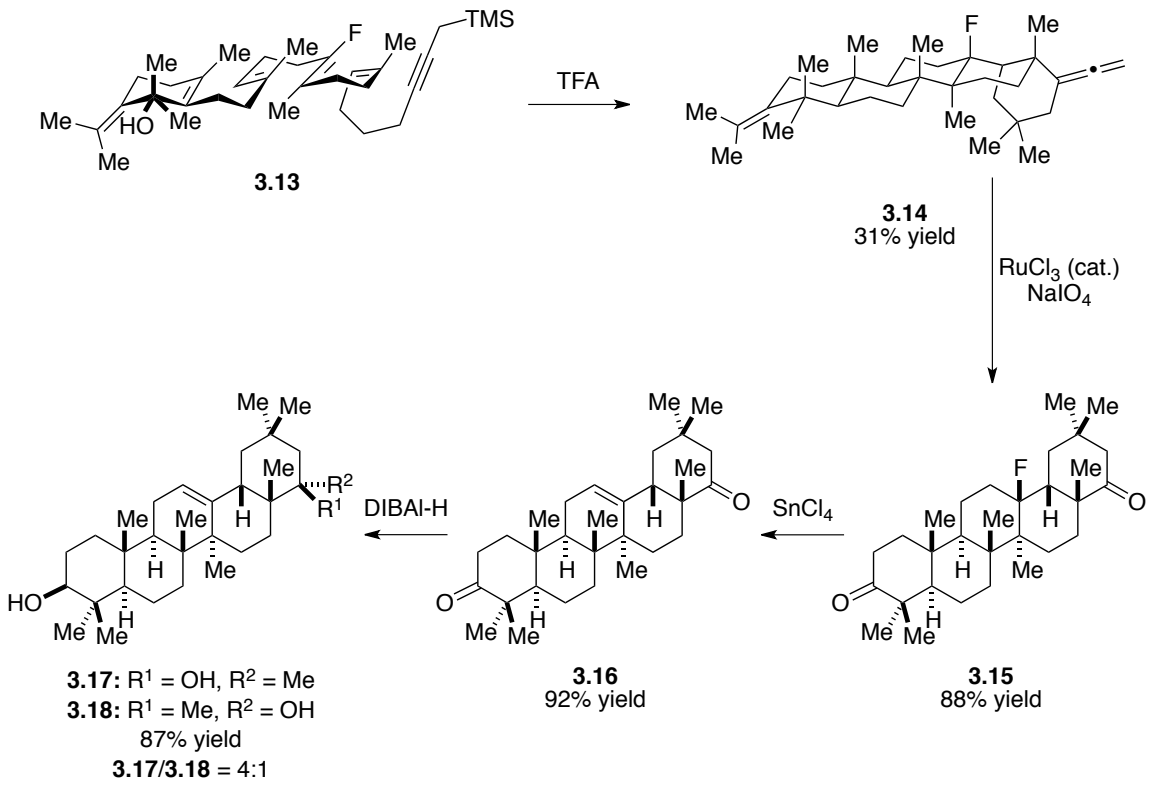
[110] Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.
[111] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.
[112] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.
[113] Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.
[114] Martín Castro, A. *Chem. Rev.* **2004**, *104*, 2939.
[115] Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324.
[116] Nicolaou, K. C.; Sorenen, E. J. *Classics in Total Synthesis;* VCH Publishers: Weinheim, Germany, 1996; p 83.

Scheme 3.1. Synthesis of Sophoradiol by Nonenzymatic, Biomimetic Polyene Pentacyclization

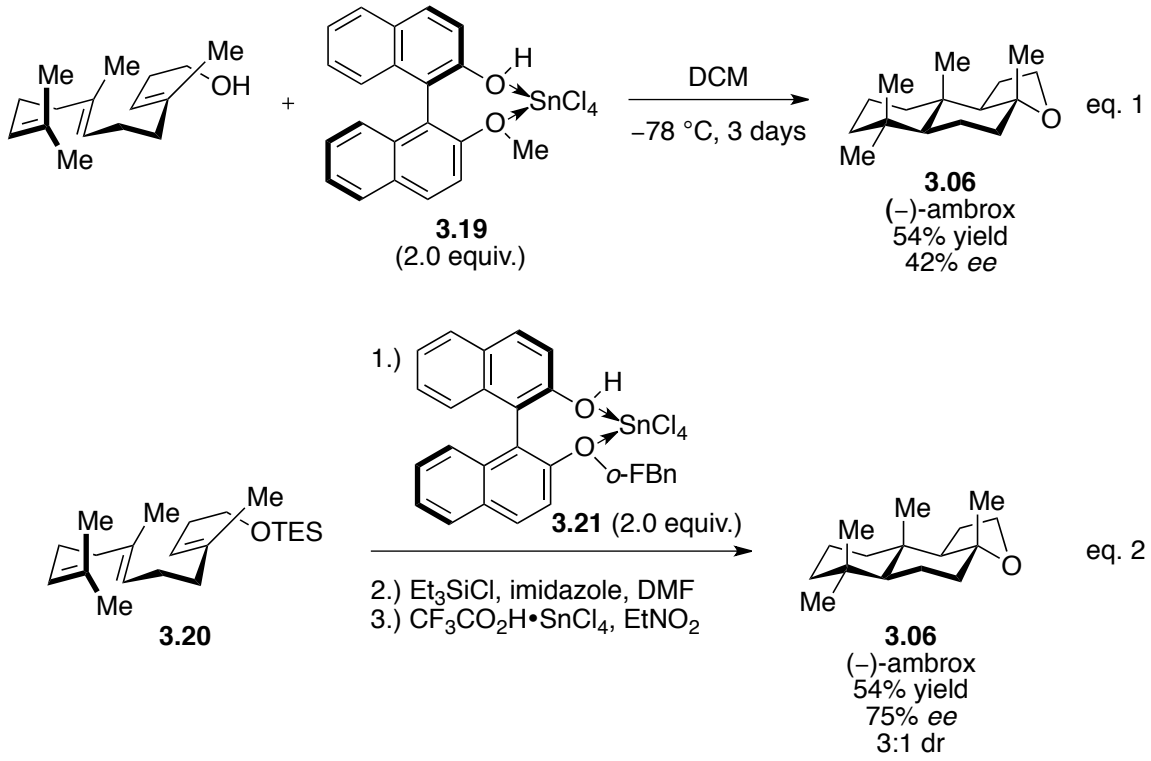


In 1999, Yamamoto and co-workers reported the first enantioselective cyclization of polyprenoids in their synthesis of (-)-ambrox (**3.06**).[117] To accomplish this transformation, Yamamoto employed a combined superstoichiometric amount of Lewis acid/chiral Brønsted acid **3.19** with homofarnesol to generate ambrox in 42% *ee* (Scheme 3.2, eq. 1). They later improved this method by implementing a three-step sequence from silylated homofarnesol **3.20** to afford **3.06** in 54% yield and 75% *ee* as a 3:1 ratio of diastereomers (eq. 2).[118] This work was fundamental for the development of a number of

[117] Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.
[118] Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647.

classic terpenoid total syntheses, many of which employed epoxide-opening as the termination step to imitate epoxysqualene polycyclization.

Scheme 3.2. First Enantioselective Biomimetic Carbocycliation of Polyprenoids

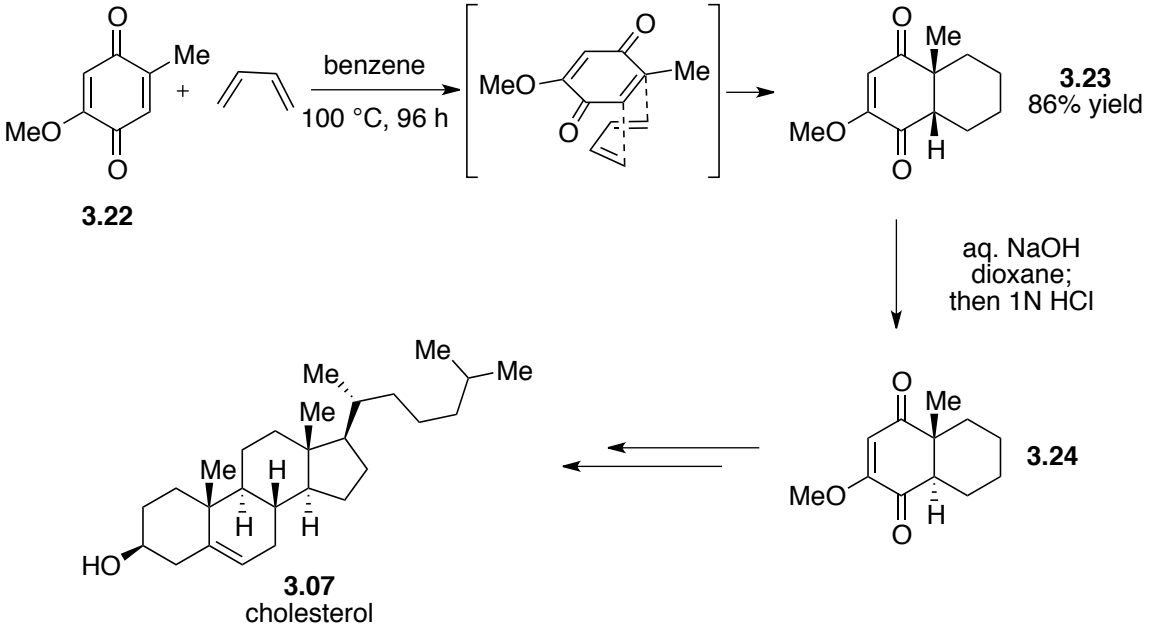


The potential application of the Diels-Alder [4+2] cycloaddition to terpene synthesis was clear even in the nascent stages of reaction development. In their pioneering paper, Diels and Alder stated, "Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps even alkaloids, has been moved to the near prospect."[119] However, it was not until 1952 that Woodward creatively used the Diels-Alder reaction to combine quinone **3.22** and butadiene en route to cortisone and

[119] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

cholesterol (Scheme 3.3).[120] When stirred together for for 96 hours at 100 °C, bicycle **3.23** was formed in 86% yield *via* an *endo*-transition state. The *cis*-decalin underwent facile epimerization to the corresponding *trans*-decalin **3.24** before being elaborated to the target hormone steroidal products. It is of particular note that during these studies, Woodward revealed that regioselective Diels-Alder reactions could be effected by taking advantage of nonsymmetrical dienophiles.

Scheme 3.3. Woodward's Synthesis of Cholesterol Utilizing the Diels-Alder Reaction

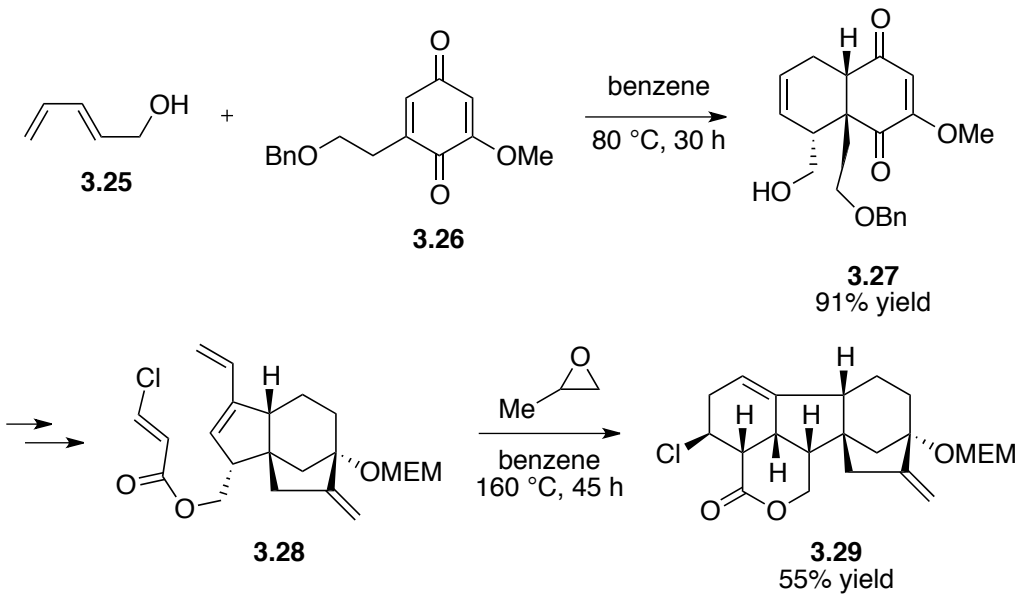


Another classic application of the Diels-Alder reaction in target-oriented terpene synthesis was Corey's route to gibberellic acid (**3.08**).[121] A chemo- and regioselective [4+2] cycloaddition was used to join diene **3.25** and quinone **3.26** to afford *cis*-fused bicycle **3.27** in 91% yield as a single adduct (Scheme 3.4). After elaboration of this

[120] Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223.
[121] (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8034.

intermediate, an intramolecular Diels-Alder reaction was performed on **3.28**. At 160 °C in the presence of proplyene oxide, pentacycle **3.29** was formed and, after recrystallization, was isolated in 55% yield. While forcing conditions are required for the described Diels-Alder reactions, Corey's gibberellic acid synthesis demonstrates the utility of this cycloaddition reaction for simultaneous construction of multiple fused rings, as are found in the majority of terpenoid natural products.

Scheme 3.4. Synthesis of Gibberelic Acid Enabled by Both Inter- and Intramolecular Diels-Alder Reactions



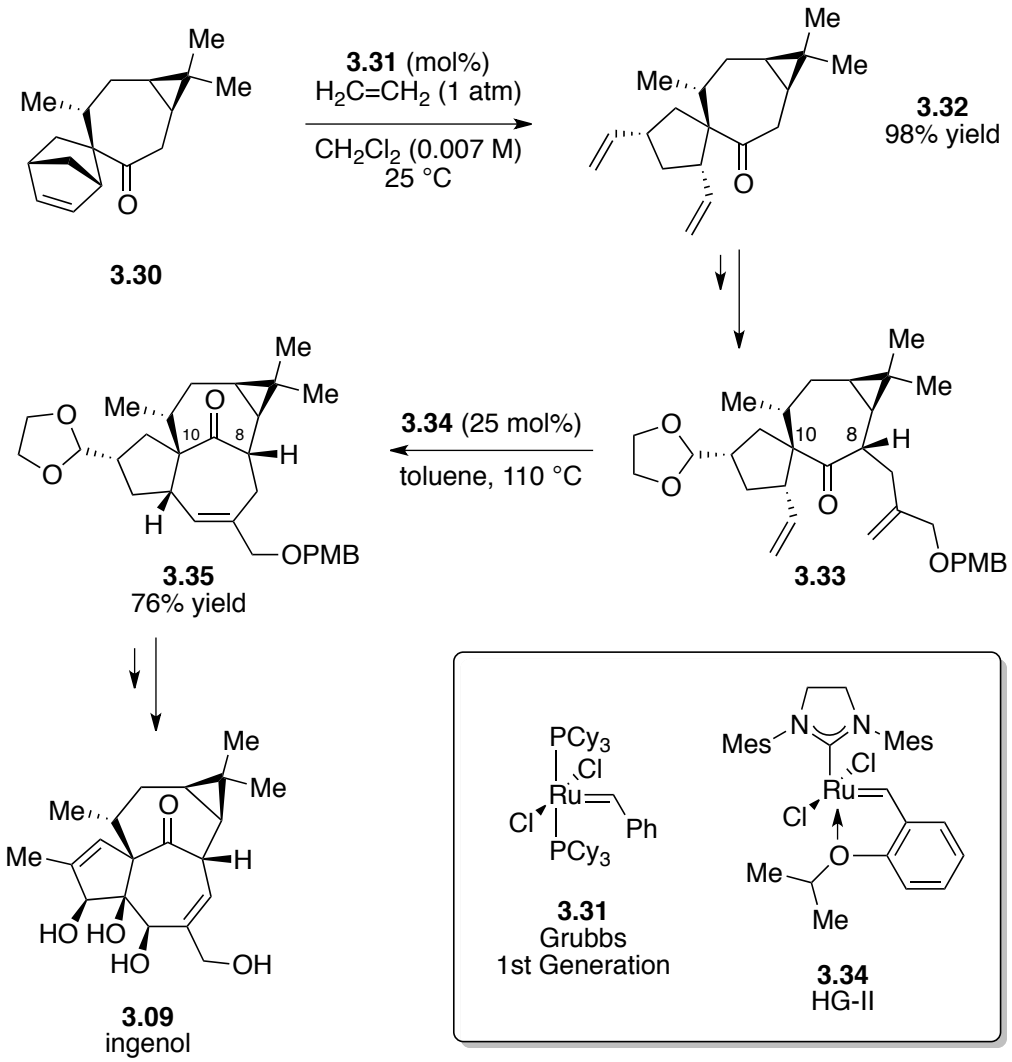
Olefin metathesis has also played a crucial role in the total synthesis of isoprenoid natural products. In 2004, Wood and co-workers used both ring-opening metathesis (ROM) and ring-closing metathesis (RCM) in their total synthesis of ingenol, the parent member of ingenane diterpene natural products.[122] Given its highly

[122] Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P D.; Greene, B. Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.

oxygenated, polycyclic structure, in conjunction with its demonstrated biological activity,[123] ingenol has been an appealing target for synthetic chemists for over 25 years.[124] A formidable challenge in the synthesis of ingenol is establishing the strained "inside-outside" (*trans*) intrabridgehead stereochemistry in the BC-ring system. To accomplish this, Wood first performed ring-opening/cross-metathesis on cyclohexene **3.30** with 2 mol% of Grubbs first generation catalyst (**3.31**) and ethylene to afford spirocycle **3.32** in quantitative yield (Scheme 3.5). In order to suppress ROM polymerization and other metathesis pathways, high dilution and an ethylene atmosphere were required. After careful installation of the olefin-containing sidechain at C8, RCM was then accomplished using 25 mol% HG-II (**3.34**) to form **3.35** in 76% yield, thereby elegantly accessing the cycloheptenone with the pivotal *trans*-ring fusion at C8 and C10 bridgehead positions. Further elaboration of metathesis product finally afforded ingenol (**3.09**).

[123] Blanco-Molina, M.; Tron, G. C.; Macho, A.; Lucena, C.; Calzado, M. A.; Muñoz, E.; Appendino, G. *Chem. Biol.* **2001**, *8*, 767 (and references therein.)
[124] Kim, S.; Winkler, J. *Chem. Soc. Reg.* **1997**, *26*, 387.

Scheme 3.5. Olefin Metathesis in the Total Synthesis of Ingenol

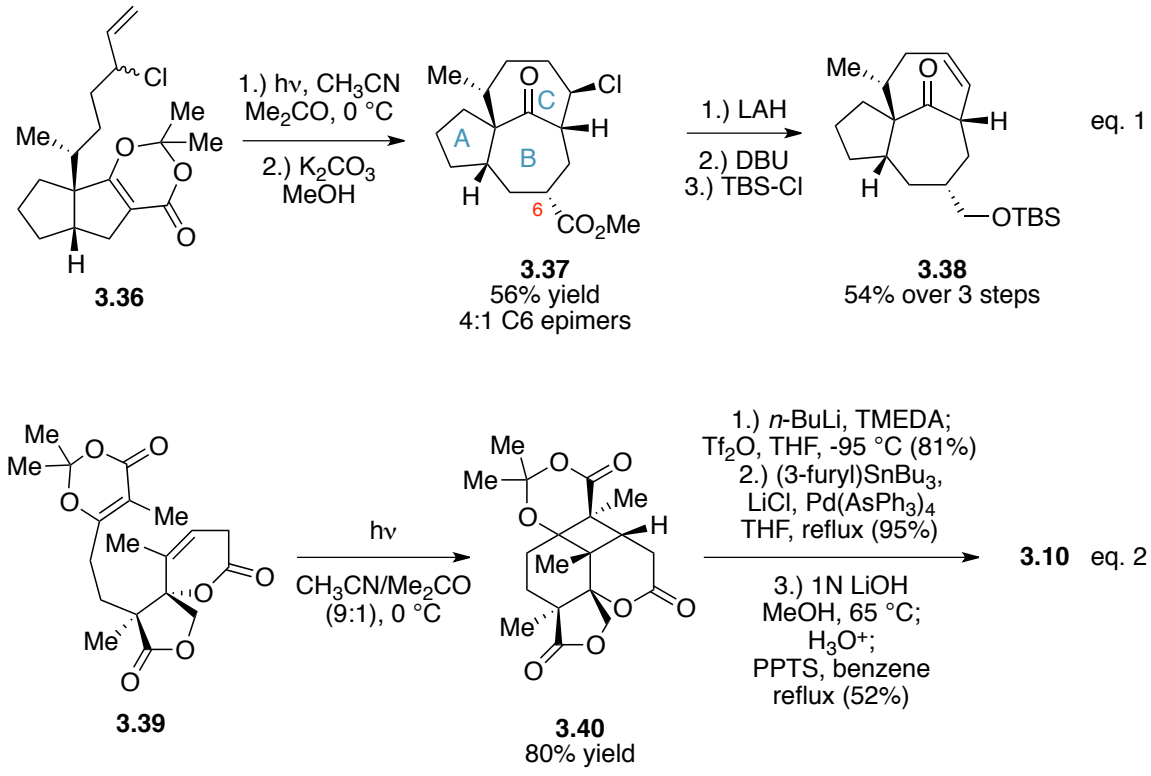


The De Mayo reaction, characterized by a tandem [2+2] photoaddition/retro-aldol fragmentation, has been used extensively in the context of terpenoid synthesis. In an alternative strategy to (±)-ingenol, Winkler relied on the De Mayo reaction to establish the inside-outside bridgehead stereochemistry (Scheme 3.6, eq. 1).[125] Irradiation of allylic chloride **3.36** proceeded in 60% yield to the corresponding cyclobutane, which then underwent retro-aldol fragmentation in the presence of potassium carbonate and

[125] Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726.

methanol to afford methyl ester **3.37**. Hydride reduction of the ester, base-promoted chloride elimination, and silylation of the primary alcohol produced ketone **3.38** in 54% yield. Previously, Winkler[126] had also used the De Mayo reaction in the synthesis of racemic saudin (**3.10**), a potent hypoglycemia agent.[127] When late stage intermediate **3.39** was subjected to irradiation, photocycloaddition proceeded smoothly to afford cycloadduct **3.40** in 80% yield as a single diastereomer (eq. 2). The highly strained pentacycle was converted to the enol silane with *n*-BuLi and Tf_2O in the presence of TMEDA, followed by Stille coupling with 3-furyltributylstannane and retro-Michael/ cyclization, to afford (±)-saudin.

Scheme 3.6. Winkler's Application of the De Mayo Reaction in the Total Synthesis of Ingenol and Saudin



[126] Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425.
[127] Kozlowski, J. F.; Main, P. J. *J. Org. Chem.* **1985**, *50*, 916.

Another method that has been used extensively in terpene total synthesis is the Claisen rearrangement. This strategy for C-C bond formation is ideal for targeted synthesis because the allyl vinyl ether starting materials can be accessed through simple procedures from commercially available compounds, and the sigmatropic rearrangement can be performed in a chemo-, regio-, diastereo- and enantioselective fashion. Buchi employed the Claisen rearrangement to synthesize a viable intermediate for the terpenoid antibiotic fumagillin (**3.11**).[128] When 3,4-dihydro-2H-pyranylethylene **3.41** was heated to 190 °C, a [3,3]-sigmatropic rearrangement occurred and the corresponding aldehyde **3.42** was isolated in 67% yield (Scheme 3.7). It is notable that these substrates generate cyclohexene products with substitution patterns that are difficult to access by the Diels-Alder [4+2] cycloaddition. Paquette[129] has also demonstrated that the Claisen rearrangement can be used as a general strategy for accessing basmane diterpenes, a class of tricyclic isoprenoids found in tobacco.[130] Allyl vinyl ether **3.43**, accessed in enantiopure form from limonene, underwent thermal rearrangement at 180 °C through a chair-like transition state to the corresponding octadienenone **3.44** as a 15:1 ratio of C4 epimers in a combined 34-60% isolated yield (Scheme 3.8). With careful planning, the Clasien rearrangement can be an extremely powerful tool in terpene synthesis to convert more readily accessible intermediates to highly substituted carbocycles bearing multiple stereocenters.

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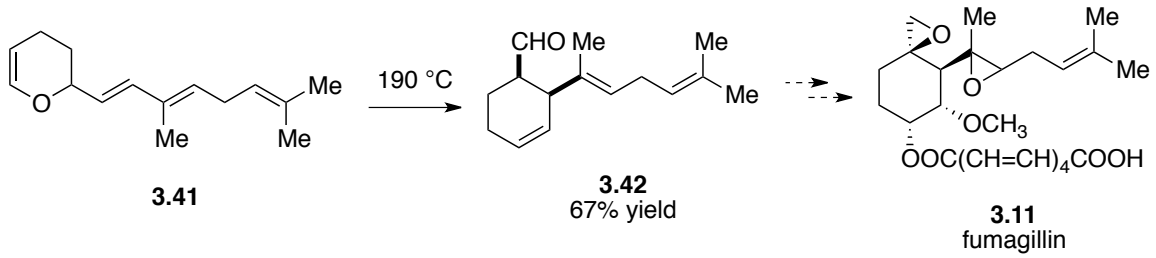
[128] Büchi, G.; Powel, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126.
[129] Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252.
[130] Wahlberg, I.; Eklund, A. -M.; Nishida, T.; Enzell, C. R.; Berg, J. -E. *Tetrahedron Lett.* **1983**, *24*, 843.

Scheme 3.7. Synthesis of Fumagillin Intermediate Enabled by Claisen Rearrangement

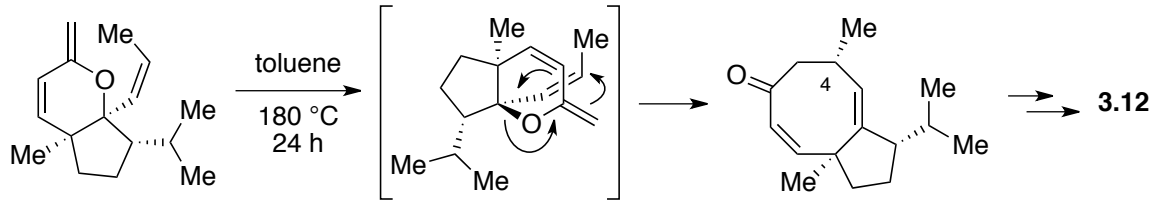


3.41

3.42
67% yield

3.11
fumagillin

Scheme 3.8. Claisen Rearrangement Route to Basmane Diterpenes



3.43

3.44
15:1 dr
34-60% yield

3.1.3. Diboration/Double Allylation as a New Strategy for Terpenoid Total Synthesis

At the outset of developing the diene diboration/double allylation tandem reaction, we were hopeful that this strategy would be a new entry into methods for synthesizing terpenoid natural products. Specifically, the cyclic 1,4-diol with four contiguous stereocenters is representative of the substitution pattern found in a number of sesquiterpenoid natural products (Figure 3.2).[131] The advantage of employing the

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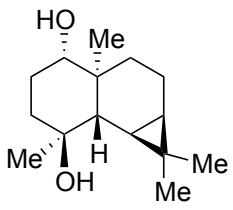
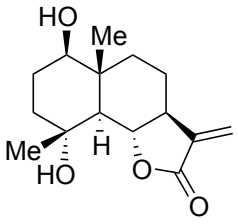
[131] (a) Kitajima, J.; Kimizuka, K.; Tanaka, Y. *Chem. Pharm. Bull.* **2000**, *48*, 777. (b) Choi, J. Y.; Na, M.; In, H.; Lee, S. H.; Bae, E. Y.; Kim, B. Y.; Ahn, J. S. *Molecules* **2009**, *14*, 266. (c) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalbersberg, W.; Hay, M. E. *J. Nat. Prod.* **2006**, *69*, 731. (d) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Trivellone, E.; Uris, M. J. *Tetrahedron Lett.* **1990**, *31*, 6565. (e) Wu, Z.-J.; Xu, X.-K.; Zeng, H.-W.; Shen, Y.-H.; Tian, J.-M.; Su, J.; Li, H.-L.; Shan, L.; Liu, R.-H.; Zhang, W.-D. *Planta. Med.* **2011**, *77*, 1545. (f) Hoffman, J. J.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Kriek, G. R. *J. Org. Chem.* **1978**, *43*, 1254. (g) Akihisa, T.; Arai, K.; Kimura, Y.; Koike, K.; Kokke, W. C. M. C.; Shibata, T.; Nikaido, T. *J. Nat. Prod.* **1999**, *62*, 265. (h) Jain, S.; Abraham, I.; Carvalho, P.; Kuag, Y.-H.; Shaala, L. A.; Youssef, D. T. A.; Avery, M. A.; Chen, Z.-S.; El Sayed, K. A. *J. Nat. Prod.* **2009**, *72*, 1291. (i) Xie, W.-D.; Niu, Y.-F.; Lai, P.-X.; Row, K.-H. *Chem. Pharm. Bull.* **2010**, *58*(7), 991.

double allylation method in terpene synthesis are as follows: 1) the diene starting materials can be readily accessed in two high-yielding, well-precedented steps from isomerically pure terpenols, 2) the diols are generated in high enantiopurity *via* a chiral catalyst in the diene diboration reaction, 3) both *cis*- and *trans*- 1,4-diols can be accessed by judicious choice of diene isomer, 4) some diene/dialdehyde pairings give rise to a highly diastereoselective reaction; in nearly all cases, the diastereomers are separable by silica gel chromatography, and 5) with two hydroxyl groups and a number of olefins, the diboration/double allylation products can be elaborated with ease. To demonstrate the viability of our method in terpene synthesis, we set out to synthesize pumilaside B aglycon (**3.45**), 1β-hydroxy arbusculin A (**3.46**), and bromophycolide F (**3.47**).

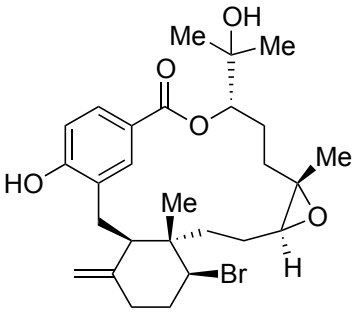
Figure 3.2. Terpenoid Natural Products Potentially Accessible Through Diboration/ Double Allylation Strategy



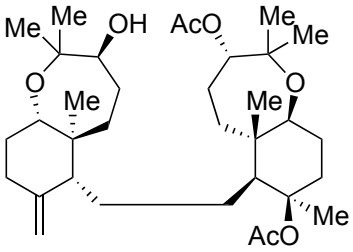
3.45
pumilaside B aglycon



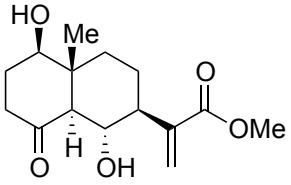
3.46
1β-hydroxy arbusculin A



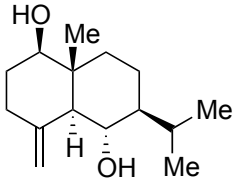
3.47
bromophycolide F



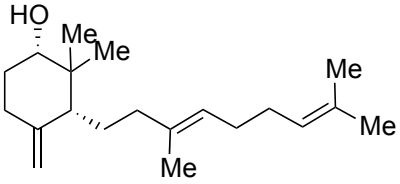
3.48
raspacionin A



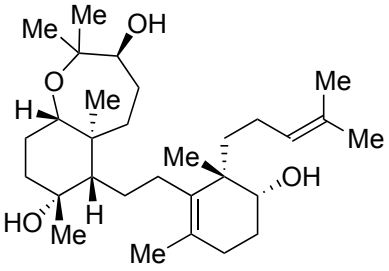
3.49
ainsliatone B



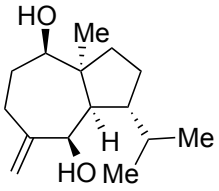
3.50
volenol



3.51
achilleol



3.52
siphonellinol



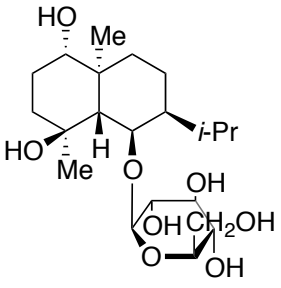
3.53
artabarrol

3.2. Total Synthesis of Pumilaside B Aglycon

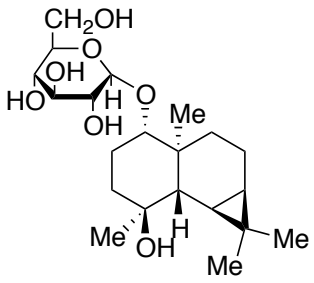
3.2.1. Background, Isolation and Retrosynthetic Analysis

The fruit of *Ficus pumila* has been used in Chinese folk medicine as an anti-tumor, anti-inflammatory, and tonic medicament.[132] Despite its long-standing use in Chinese folk medicine, it was not until 1998 that any of the constituents from the fruit had been isolated, characterized, or analyzed.[133] Of the eighteen compounds isolated, two new sterols, two new cycloartane-type triterpenoids, and a new euphane-type terpenoid were isolated. A year later, Kitajima and co-workers isolated three new glucoside sesquiterpenes from the *F. pumila* fruit (Figure 3.3). Because of its intriguing tricyclic structure, the aglycon of pumilaside B (**3.45**) was an attractive target. In addition, four of the six stereocenters present in the molecule could be installed using the above-described diboration/double allylation strategy.

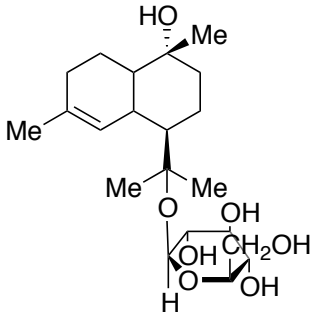
Figure 3.3. Glycosides Isolated from *Ficus Pumila*



3.54
pumilaside A



3.55
pumilaside B



3.56
pumilaside C
(rel. config.)

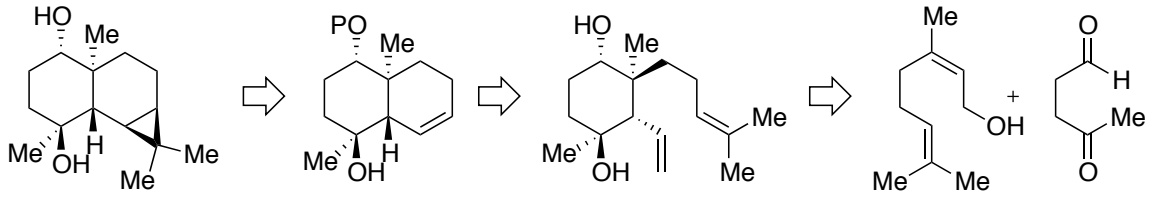
---

[132] (a) Kimura, S., Konoshima, M. (ed.), "Coloured Illustrations of Chinese Medicinal Plants," Yuhgonsha, Kyoto, 1986, pp. 412-413. (b) Miyata, S. (ed.), "Antitumoral Crude Drugs and Their Prescriptions," Kagaku, Shoin, Tokyo, 1981, pp. 25-27.

[133] Kitajima, J.; Kimizuka, K.; Tanaka, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1408.

The synthesis strategy we envisioned is depicted below (Scheme 3.9). We imagined installing the cyclopropane unit by a carbenoid insertion reaction from the corresponding cyclohexene **3.57**. Synthesis of the cyclohexene might come about from ring-closing metathesis of the two olefins in the diboration/double allylation product *ent*-**2.53**. The coupling partners for the diboration/double allylation would ultimately arise from nerol and 4-oxopentanal.

Scheme 3.9. Retrosynethetic Analysis for Pumilaside B Aglycon

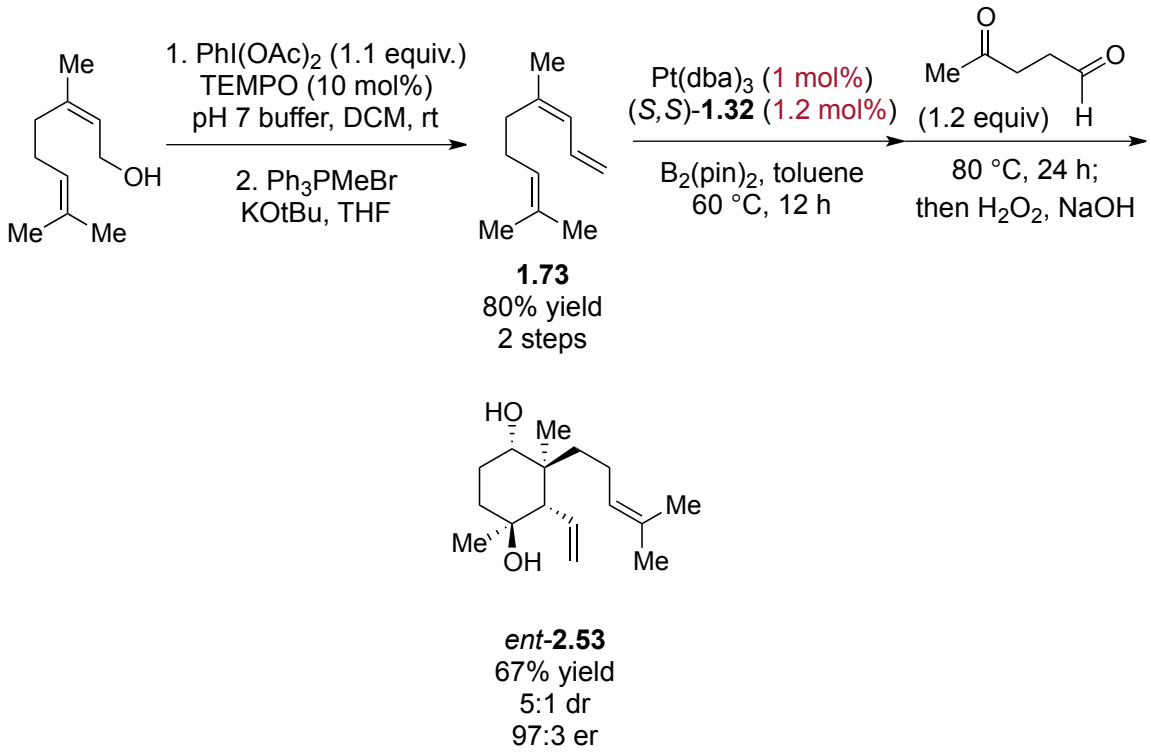


3.46 **3.57** *ent*-**2.53**

3.2.2. Complete Total Synthesis of Pumilaside B Aglycon

To begin, diene **1.73** was synthesized from commercially available nerol by oxidation to the corresponding aldehyde with hypervalent iodine and catalytic TEMPO, followed by Wittig olefination, in an 80% yield over two steps (Scheme 3.10). The neral-derived diene was then subjected to optimized Pt-catalyzed diboration/double allylation conditions. When performed on large scale, the catalyst loading for the diboration reaction could be reduced to 1 mol% $Pt(dba)_3$ and 1.2 mol% (*S,S*)-**1.32**. To achieve the highest yield, 1.2 equivalents of 4-oxopentenal were employed in the double allylation reaction. Under these conditions, diol *ent*-**2.53** was isolated in 67% yield, 97:3 er, and a 5:1 *anti:syn* ratio.

Scheme 3.10. Route from Nerol to 1,4-Diol-*ent*-2.53

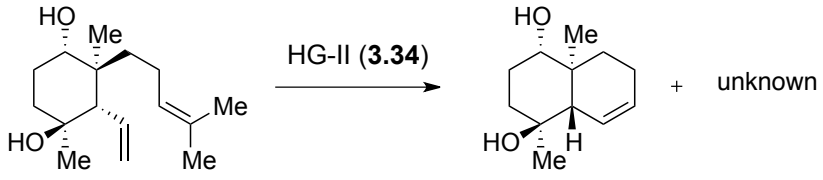


At this point in time, the two diastereomers were separated by column chromatography and pure *anti-ent*-**2.53** was subjected to a number of ring-closing metathesis[134] conditions (Table 3.1). In the presence of 10 mol% Hoveyda-Grubbs second generation catalyst (HG-II, **3.34**) at 60 °C in a sealed vial, the RCM reaction proceeded in 100% conversion, but to a mixture of **3.58** and an unidentified compound (entry 1). When the reaction temperature was increased to 100 °C, the unknown product predominated in a 2.5:1 ratio (entry 2). Interestingly, we observed that the nature of the reaction vessel had a significant effect on the outcome of the reaction. When the reaction was performed with a sealed vial with a larger headspace volume, the product ratio was improved to 11:1 desired **3.58**/unknown, but full conversion was not achieved. If

[134] Garber, S. B.; Kingsbury, J. S.; Gray, B. L. Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

instead, the reaction was performed in a a round bottom flask equipped with a reflux condenser and a nitrogen inlet (entry 4), the ratio of **3.58**/unknown decreased to 4:1. These observations led us to believe that the unidentifiable byproduct may be related to the isopropylene released over the course of the reaction. In support of this hypothesis, we observed that longer reaction times produced more byproduct, whereas shorter reaction times resulted in a lesser amount of byproduct formation (entries 5-6). Selective cyclohexene formation was achieved with shorter reaction times or higher dilution, but at the expense of reaction conversion (entry 7). The optimal product ratio and conversion was accomplished when, by accident, the solvent slowly evaporated over the course of the reaction (entry 8). When the initial concentration was 0.05 M in benzene, and then the solvent was slowly purged over an 18 hour period until only a neat oil remained, 93% conversion to solely the desired cyclohexene product was realized. If the initial reaction concentration was increased to 0.1M, but the entire solvent volume was evaporated over the course of the reaction, comparable results were obtained (entry 9). This serendipitous discovery proved to be reproducible; under reducing solvent conditions, in the presence of 12 mol% HG-II, cyclohexene **3.58** was isolated in near quantitative yield as the sole product.

Table 3.1. Optimization of Ring-Closing Metathesis with Hoveyda-Grubbs Second Generation Catalyst



ent-**2.53** **3.58**

entry	catalyst loading	temp/solvent	time (h)	[M]	%conversion	RCM:unknown
1[a]	10%	60 °C/C_6H_6	16.5	0.1	100	8:1
2[a]	10%	100 °C/toluene	16.5	0.1	100	1:2.5
3[a]	10%	60 °C/C_6H_6	18	0.1	85	11:1
4[b]	12%	60 °C/C_6H_6	19	0.1	100	4:1
5[b]	12%	60 °C/C_6H_6	21.5	0.1	100	1.5:1
6[b]	12%	60 °C/C_6H_6	6	0.1	45	>20:1
7[b]	12%	60 °C/C_6H_6	13	0.05	41	>20:1
8[b,c]	12%	60 °C/C_6H_6	18	0.05	93	>20:1
9[b,c]	12%	60 °C/C_6H_6	18	0.10	100	>20:1

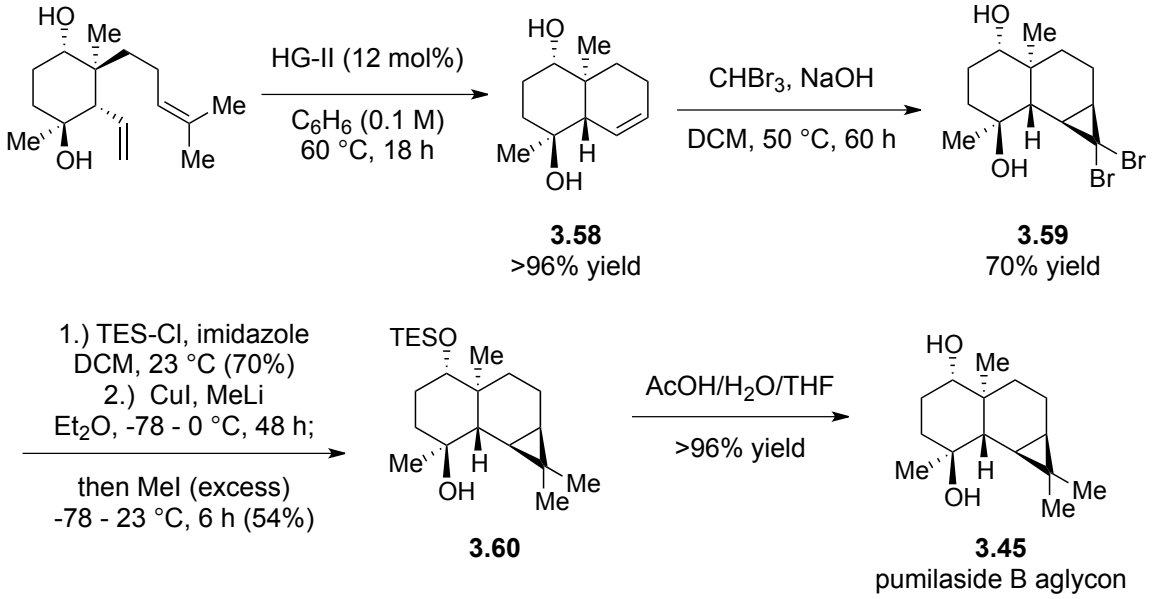
[a] Reaction performed in sealed vessel. [b] Reaction performed in round bottom flask with reflux condensor. [c] Solvent evaporated overnight.

The remainder of the synthesis of pumilaside B aglycon proceeded quite smoothly. Ring-closing metathesis product **3.58**, in the presence of *in situ* generated dibromocarbene, underwent facile conversion to dibromocyclopropane **3.59** in 70% yield as a single diastereomer (Scheme 3.11).[135] The high facial selectivity observed in the cyclopropanation can be accounted for by assuming the carbene approaches from the

[135] Thamapipol, S.; Kündig, E. P. *Org. Biomol. Chem.* **2011**, 9, 7564.

least-hindered face of the *trans*-decalin bicycle. After protection of the secondary alcohol with TES-Cl, methylation with lithium dimethyl cuprate and methyl iodide[136] afforded tricycle **3.60** in 40% yield over two steps. Finally, pumilaside B aglycon was unveiled by deprotection of the silyl ether in a heterogenous acetic acid/water/THF mixture[137] in quantitative yield.

Scheme 3.11. Synthesis of Pumilaside B Aglycon from Diboration/Double Allylation Intermediate



By employing the recently developed diene diboration/double allylation method with nerol-derieved diene and 4-oxo-pentanal, the first total synthesis of pumilaside B aglycon was achieved. The entire synthesis was completed in 9 steps and 14% overall yield from readily available starting materials. Four contiguous stereocenters were installed in the correct configuration in a single flask, three-step operation, highlighting

[136] Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4349.
[137] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

the efficiency of the diboration/double allylation method for building up molecular complexity. The remaining two stereogenic centers were installed with ease by taking advantage of the conformational preferences of the decalin core. This total synthesis serves as a proof of concept for the utility of this method in terpene synthesis.

3.3. Progress Towards the Total Synthesis of 1β-Hydroxy Arbusuclin A

3.3.1. Background, Isolation and Retrosynthetic Analysis

Protein tyrosine phosphatases (PTPases), which are found in the liver, muscle, and adipose tissue, play a critical role in the regulation of insulin.[138] As such, inhibitors of some PTPases have the potential to treat type II diabetes and obesity.[139] One possible source for new PTP inhibitors are the roots of *Saussurea lappa*, which have been used as folk medicaments to treat gastric and abdominal pain, distention, lack of appetite, anorexia, nausea, and vomiting.[140] Choi *et al.* conducted an activity-guided fractionation of a methanol extract of *S. lappa* roots and isolated ten terpenoid natural products.[141] While 1β-hydroxy arbusculin A (**3.46**) showed little inhibition of PTP1B at 30 μg/mL, compounds with this exocyclic enone motif frequently exhibit biological activity, likely due to the electrophilicity of this functional group.

We envisioned a route to **3.46** that would take advantage of both the diboration/ double allylation and the Morken group's previously developed 1,4-diboration of 1,3-

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[138] Schultz, L. D.; Schweitzer, P. A.; Rajan, T. V.; Yi, T.; Ihle, J. N.; Matthews, R. J.; Thomas, M. L.; Beier, D. R. *Cell* **1993**, *73*, 1445.

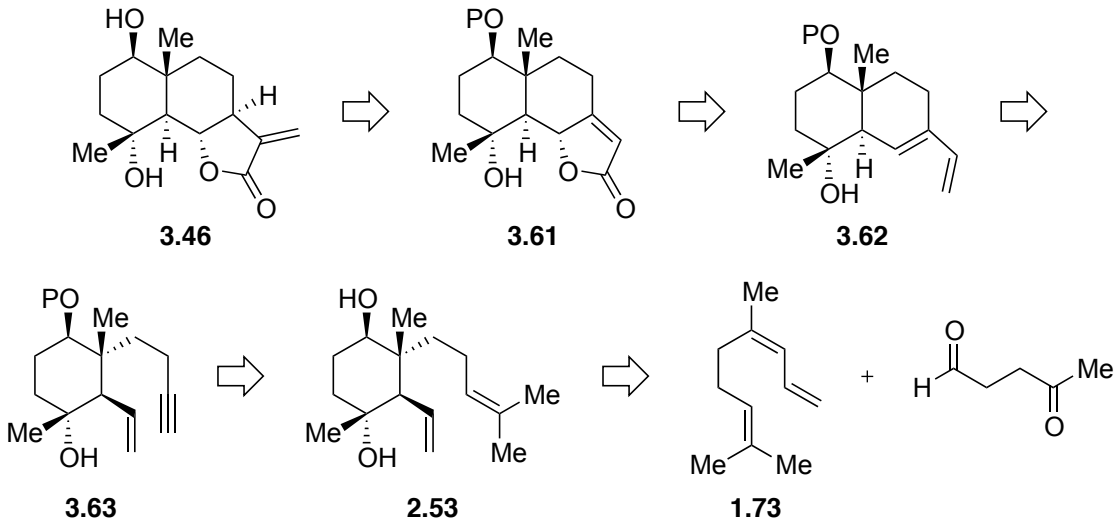
[139] Johnson, T. O.; Ermolieff, J.; Jirousek, M. R. *Nat. Rev. Drug. Discov.* **2002**, *1*, 696.

[140] (a) Jiangsu New Medical College. Zhong Yao Da Ci Dian (Dictionary of Chinese Material Medica); Shanghai Scientific and Technological Publishers: Shanghai, P. R. China, **1988**; pp. 353-366. (b) Zhu, Y. P. Chinese Material Medica; Chemistry, Pharmacology and Applications, Hardwood Academic Publishers: New York, USA, **1998**; pp. 379-380.

[141] Choi, J. Y.; Na, M.; In, H.; Lee, S. H.; Bae, E. Y.; Kim, B. Y.; Ahn, J. S. *Molecules* **2009**, *14*, 266.

dienes methodologies (Scheme 3.12). The exocyclic olefin of **3.46** could be installed by hydrogenation of butenolide **3.61**, followed by subjection of the reduced compound to Eschenmoser's salt.[142] Platinum-catalyzed 1,4-diboration of 1,3-diene **3.62** would accomplish the required oxidation and provide access to the lactone in an enantioselective fashion, hopefully under catalyst-controlled conditions. Diene **3.62** could be readily prepared from enyne **3.63** employing enyne ring-closing metathesis, which ultimately would be accessed from the diboration/double allylation product **2.53**.

Scheme 3.12. Retrosynthetic Analysis of 1β-Hydroxy Arbusculin A



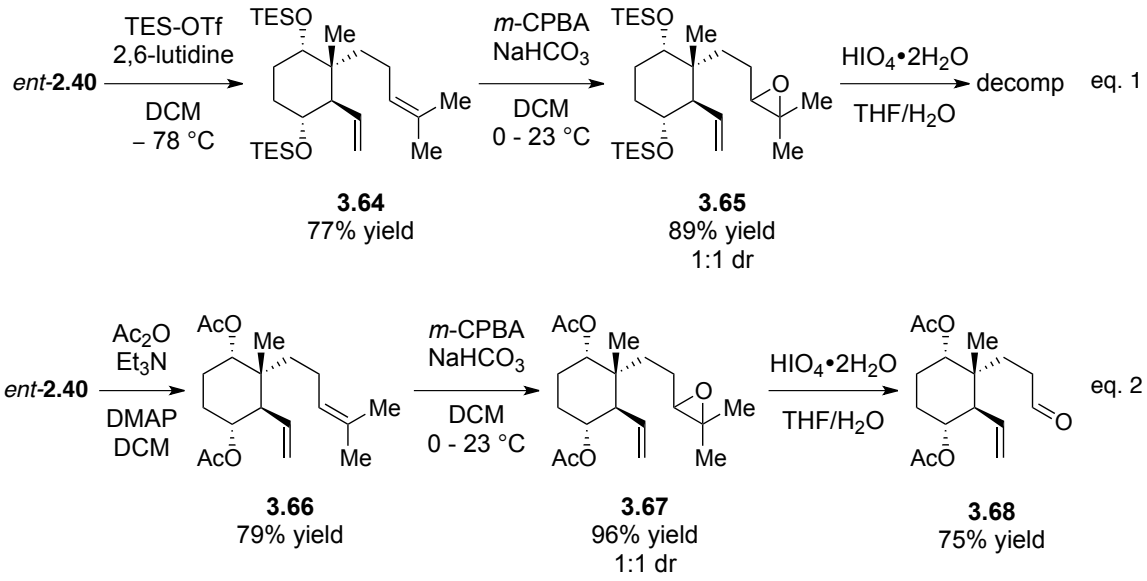
3.3.2. Progress Towards 1β-Hydroxy Arbusculin A

We began effords towards 1β-Hydroxy Arbusculin A with diol *ent*-**2.40** to serve as a model for diol **2.53** because the diboration/double allylation synthesis was higher-yielding and more selective than that producing **2.53**. We hoped to access alkyne **3.63** by converting the trisubstituted olefin to an aldehyde, which could then undergo Seyferth-Gilbert homologation to afford the corresponding terminal alkyne. In anticipation of the

[142] Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* **1971**, *10*(5), 330.

free secondary alcohol being incompatible with our hypothesized route, we explored how best to protect the alcohols. Silyl protection with triethylsilyl triflate proceeded smoothly to afford bis(silyl)ether **3.64** in 77% yield (Scheme 3.13, eq. 1). Epoxidation[143] of the electron-rich trisubstituted olefin with *m*-CPBA led to **3.65**, isolated in 89% yield as a 1:1 mixture of diastereomers. Unfortunately, cleavage of the epoxide mixture with periodic acid[144] only lead to decomposition of the starting material; none of the desired aldehyde was observed. Much to our delight, the acyl protecting group was compatible with both the epoxidation and epoxide-cleavage reactions; aldehyde **3.68** was isolated in 57% yield over three steps (eq. 2).

Scheme 3.13. Protecting Group Strategy

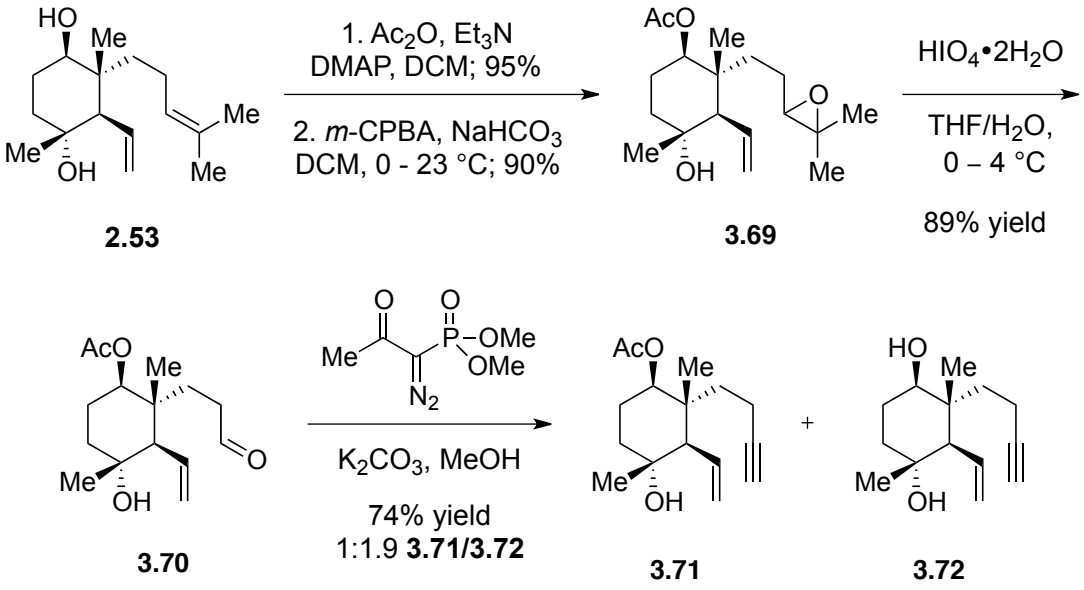


After determining a suitable protecting group, we proceeded forward with the synthesis using the the diboration/double allylation product **2.53** (Scheme 3.14). As with the model substrate, sequential acylation and *m*-CPBA epoxidation occured in high

[143] Cha, J. Y.; Yeoman, J. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964.
[144] Lu, K.; Huang, M.; Xiang, Z.; Liu, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2006**, *8*, 1193.

yield: 95% and 90%, respectively. Mono-acylated epoxide **3.69** underwent facile cleavage with periodic acid to afford aldehyde **3.70** in 89% yield without complications from the hindered tertiary alcohol. Alkyne **3.71** was then accessed by subjecting the aldehyde to Seyferth-Gilbert homologation with the Ohira-Bestman reagent[145] in a combined 74% yield as a 1:1.9 mixture with the deacylated product. Deacylation occurred due the basicity of the reaction mixture and might be avoided with a more robust acyl protecting group (such as a pivolate.)

Scheme 3.14. Conversion of Alkene to Alkyne Towards 1β-Hydroxy Arbusculin A

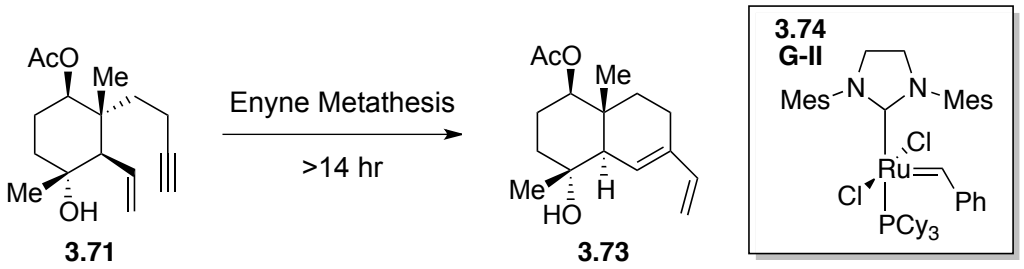


In order to form the second ring of 1β-hydroxy arbusculin A, ring closing enyne metathesis was performed on **3.71** (Table 3.2). With 10 mol% of both Grubbs' second generation catalyst (G-II, **3.74**) or Hoveyda-Grubbs' second generation catalyst (HG-II, **3.34**), little conversion was achieved, even under prolonged reaction times (entires 1-2). Unfortunately, an increase in reaction temperature to 50 °C with 5 mol% of **3.34** afforded

[145] Mueller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

only mild improvement on the isolated yield of diene **3.73**. Efficient cyclization was finally achieved when the reaction atmosphere was changed from nitrogen to ethylene. In intramolecular enyne metathesis with unsubstituted alkynes, it is thought that ethylene prevents side reactions between the ruthenium catalyst and the vinyl group of the product diene that, in turn, decreases catalyst activity.[146] With 5 mol% **3.74** at room temperature, the desired diene was isolated in a 57% yield (entry 4). When the catalyst loading was dropped to 3.5 mol%, enyne metathesis was significantly less efficient (entry 5).

Table 3.2. Optimization of Intramolecular Enyne Metathesis



entry	catalyst (mol%)	solvent	atmosphere	temp (°C)	%yield
1	G-II (10%)	DCM	N_2	23	10
2	HG-II (10%)	DCM	N_2	23	-
3	HG-II (5%)	toluene	N_2	50	15
4	G-II (5%)	DCM	CH_2CH_2	23	49
5	G-II (3.5%)	DCM	CH_2CH_2	23	17

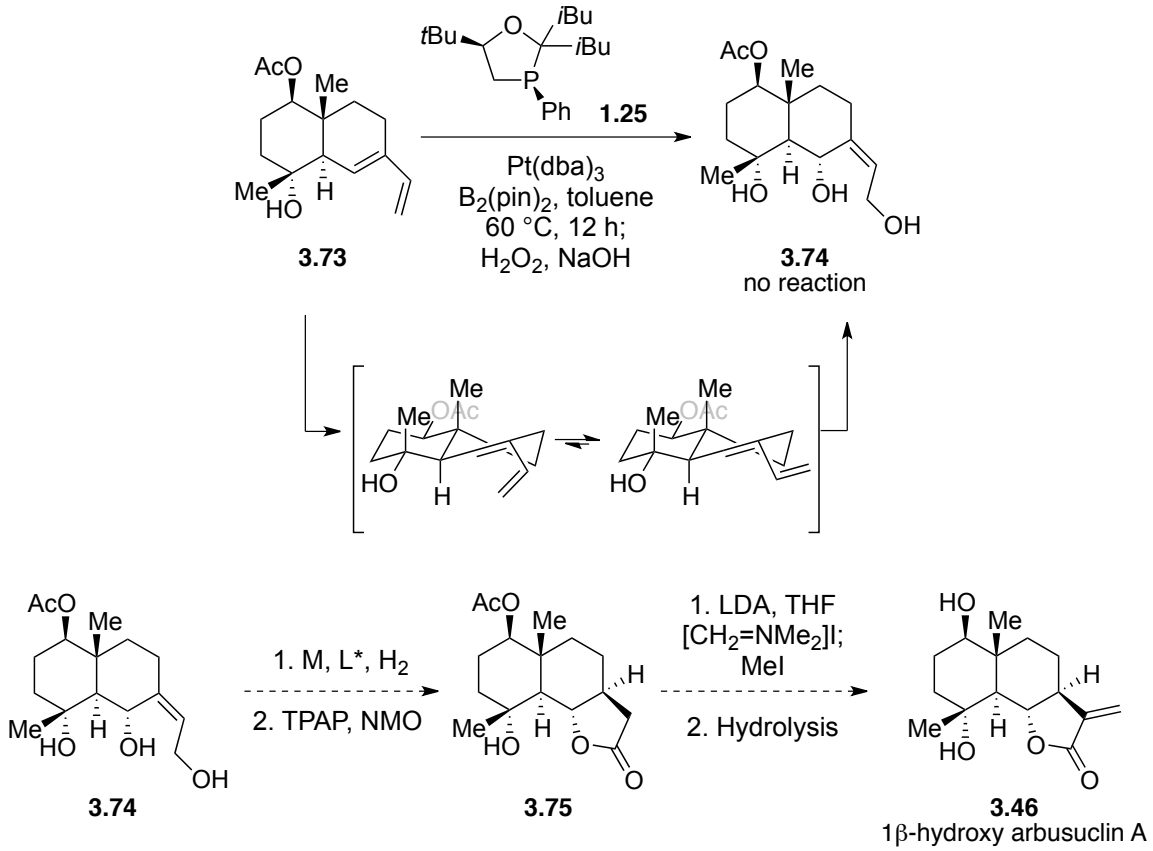
Having successfully performed ring-closure, we envisioned completing the synthesis of 1β-hydroxy arbusculin A as depicted in Scheme 3.15. Diene **3.67** should

[146] (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (b) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488.

undergo 1,4-diboration with oxaphospholane ligand **1.25** to afford diol **3.69** after oxidation.[19] Unfortunately, all attempts to perform diboration on this diene have been unsuccessful. This may be due to $A^{1,3}$-strain prohibiting formation of the s-cis conformer, or that the approach path for the Pt-catalyst is too hindered. It might be possible access the desired oxygenation and olefin substitution pattern by performing a Diels-Alder reaction with singlet oxygen,[147] or by transition-metal catalysis with an achiral phosphine ligand. Should the diboration route be successful, we hoped to complete this synthesis in the following manner. A two step hydrogenation-oxidation procedure could be used to access lactone **3.69**. Hydrogenation of the *cis*-olefin may occur in a diastereoselective fashion under substrate-controlled conditions, as has previously been demonstrated by Tada in the synthesis of a similarly-substituted eudesmanolide natural product.[148] If unselective, a chiral catalyst could potentially be used to override the inherent selectivity in this butenolide hydrogentation. Finally, insertion of the exocyclic olefin can likely be accomplished using Eshenmoser's salt, which, after hydrolysis of the acetate protecting group, would afford 1β-hydroxy arbusculin A.

[147] Ficini, J.; Barbara, C.; Ourfelli, O. *Heterocycles* **1989**, *28*, 547.
[148] Tada, M.; Kanamori, A. *Chem. Lett.* **1989**, *18*(6), 1085.

Scheme 3.15. Proposed Completion of 1β-Hydroxy Arbusculin A



While incomplete at this time, significant progress has been made towards the total synthesis of 1β-hydroxy arbusculin A. Rapid access to the substituted core of this sesquiterpenoid natural product was made possible by the diboration/double allylation strategy. Hopefully, an additional diene diboration will install the remaining two stereocenters in a diastereoselective fashion under catalyst control. Together, these two strategies demonstrate the utility of enantioseletive 1,2- and 1,4-diene diboration in the context of total synthesis.

3.4. Progress Towards the Total Synthesis of Bromophycolide F

3.4.1. Background, Isolation and Retrosynthetic Analysis

The above-described syntheses of sesquiterpene natural products pumilaside B aglycon and 1β-hydroxy arbusculin A exemplify the power of the diboration/double allylation strategy to convert simple, prochiral 1,3-diene and dicarbonyl compounds to highly substituted, enantioenriched diols reminiscent of sesquiterpene natural product cores. After learning about how to functionalize these products, we sought to synthesize a more ambitious and biologically relevant natural product with our method. Bromophycolide F (**3.40**) is one of many in the class of bromophycolide macrolides that have been isolated from *Callophycus serratus,* a red macroalgae found on Pacific ocean cave floors (Scheme 3.16).[149] Unique to this natural product class is the 15-membered macrolide ring with a halogenated diterpene-benzoate framework. In addition to their intriguing carbon skeletons, Kubanek has also demonstrated that some members of the bromophycolide natural product family exhibit growth inhibition of MRSA and VREF bacterial strains, as well as anti-tumor and anti-malarial activity. When the pharmacological activity was examined, bromophycolide F had an average IC_{50} of 41.3 μM across 11 cancer cell lines, and exhibited antifungal activity against amphotericin B-resistant *Candida albicans* (IC_{50} of 240 μM).[150]

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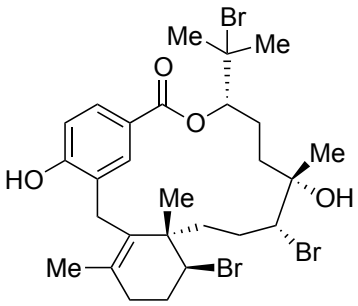
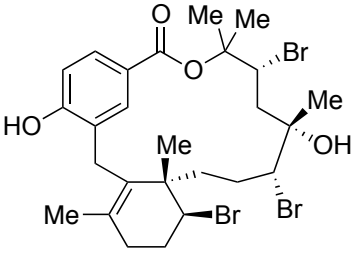
[149] (a) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Hardcastle, K. I.; Fairchild, C. R.; Aalbersberg, W.; Raventos-Suarez, C.; Hay, M. E. *Org. Lett.* **2005**, *7*, 5261. (b) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalbersberg, W.; Hay, M. E. *J. Nat. Prod.* **2006**, *69*, 731. (c) Lane, A. L.; Stout, E. P.; Lin, A.-S.; Prudhomme, J.; Le Roche, K.; Fairchild, C. R.; Franzblau, S. G.; Hay, M. E.; Aalbersberg, W.; Kubanek, J. *J. Org. Chem.* **2009**, *74*, 2736. (d) Lin, A.-S.; Stout, E. P.; Prudhomme, J.; Le Roche, K.; Fairchild, C. R.; Franzblau, S. G.; Aalbersberg, W.; Hay, M. E.; Kubanek, J. *J. Nat. Prod.* **2010**, *73*, 275.

[150] Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalbersberg, W.; Hay, M. E. *J. Nat. Prod.* **2006**, *69*, 731.

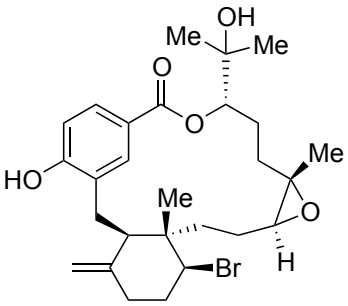
Scheme 3.16. Representative Members of Bromophycolide Natural Products



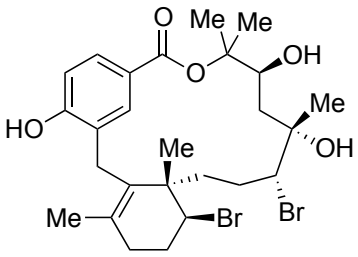
3.76
bromophycolide A



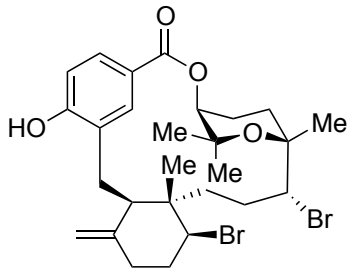
3.77
bromophycolide B



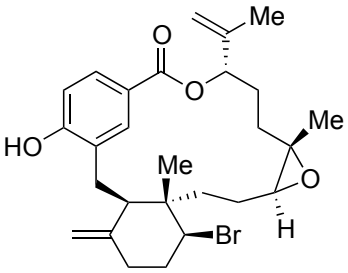
3.40
bromophycolide F



3.78
bromophycolide G



3.79
bromophycolide P



3.80
bromophycolide R

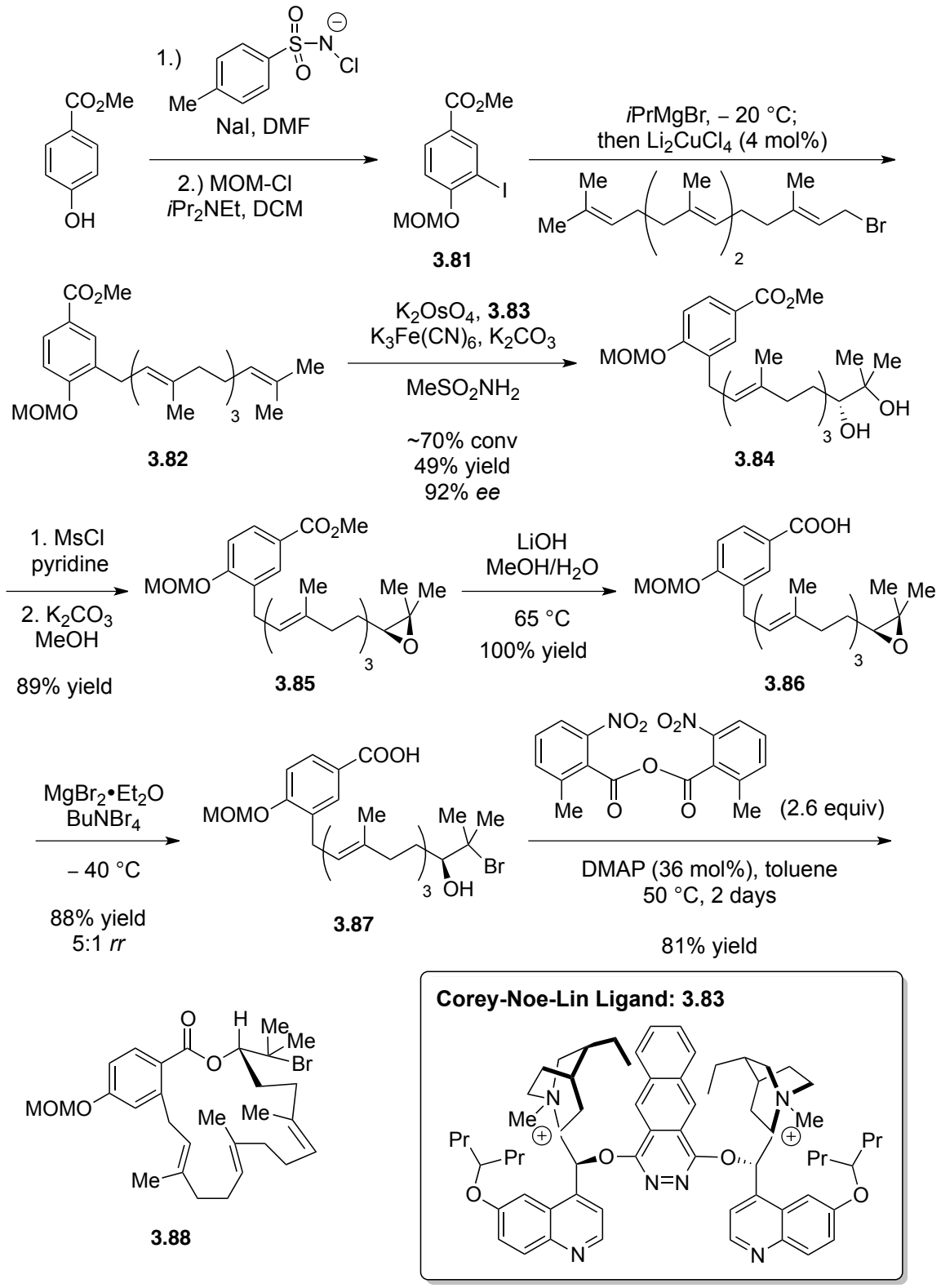
Currently, only one asymmetric route to the skeleton of bromophycolide A and D has been reported (Scheme 3.17).[151] Krauss demonstrated that the majority of the carbon framework could be installed early in the synthesis by coupling geranylgeranyl bromide with phenyl iodide **3.81**. Next, asymmetric, regioselective dihydroxylation of the terminal trisubstituted olefin was accomplished with cinchona alkaloid ligand **3.83** developed by Corey and Noe.[152] When run to approximately 70% conversion, the desired regioisomer **3.84** was isolated in 49% yield and 92% enantiopurity. After a series of relatively simple functional group manipulations, bromohydrin **3.87** was synthesized in 88% yield in a 5:1 regioisomer ratio by subjecting epoxide **3.86** to $MgBr_2 \bullet Et_2O$. Finally,

[151] Lin, H.; Pochapsky, S. S.; Krauss, I. J. *Org. Lett.* **2011**, *13*, 1222.
[152] Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741.

the base-sensitive bromohydrin **3.87** underwent smooth macrolactonization under Shiina's conditions[153] to afford bromophycolide intermediate **3.88** in an impressive 81% yield.

[153] (a) Shiina, I.; Fukui, H.; Sasaki, A. *Nat. Protoc.* **2007**, *2*, 2312. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822.

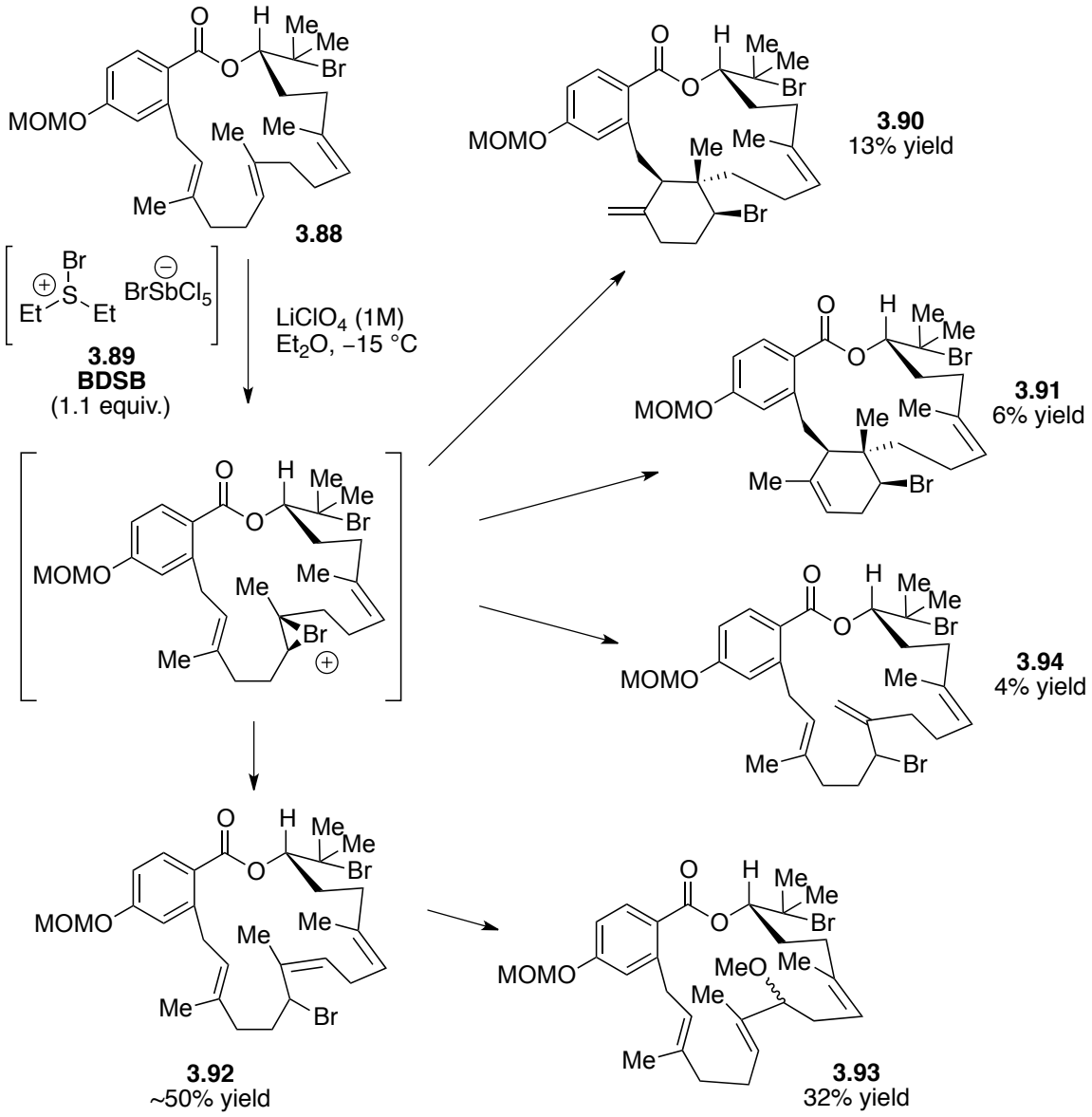
Scheme 3.17. Krauss's Enantioselective Synthesis of Bromophycolide A & D Core



In order to form the highly substituted cyclohexane core, Krauss and co-workers attempted a bromonium-initiated transannular cyclization (Scheme 3.18). After subjecting **3.88** to bromodiethylsulfonium bromopentachloroantimonate (BDSB, **3.89**)[154] in 1 M $LiClO_4/Et_2O$, only 19% of the desired cyclization occurred in ~2:1 ratio of **3.90** and **3.91**. The majority of the material isolated was uncyclized elimination product **3.92**, which was converted to **3.93** when subjected to methanolysis conditions (~50% and 32% yield, respectively.) An additional 4% elimination/bromonium-opening product **3.94** was found in the mixture. While creative, the bromonium-initiated transannular cyclization was met with only mild success, limiting the utility of this method for accessing the bromophycolide natural product class.

[154] (a) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc*. **2010**, *132*, 14303. (b) Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899.

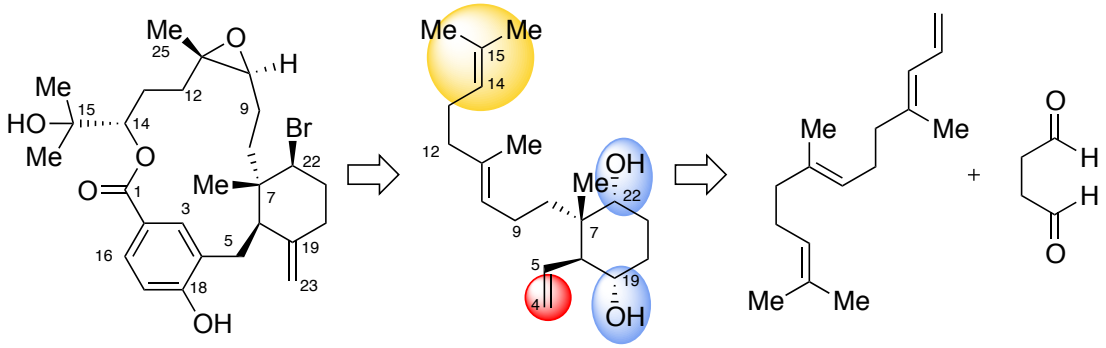
Scheme 3.18. Bromonium-Initiated Transannular Cyclization



We recognized that the diene diboration/double allylation strategy might be a viable alternative to the synthesis of the bromophycolides. Specifically, we envisaged synthesizing bromophycolide F from the *trans,trans*-farnesol-derived diene **3.96** and succinaldehyde (Scheme 3.19). To complete the synthesis, a number of formidable challenges would have to be addressed. First and foremost, the terminal carbon of the

vinyl group generated in the double allylation process (C4) would either need to be excised or converted into one of the aryl carbons in the benzoate ring. As Krauss reported, regioselective oxidation of the trisubstituted olefin at C14/C15 would need to be accomplished in order to eventually access the desired macrocyclic core. Finally, selective functionalization of the two secondary alcohols at C19 and C22 would need to be investigated. Given the steric bulk of the adjacent quaternary center at C7, we anticipated that large protecting groups would be part of our strategy in differentiating the two alcohols.

Scheme 3.19. Proposed Retrosynthesis of Bromophycolide F

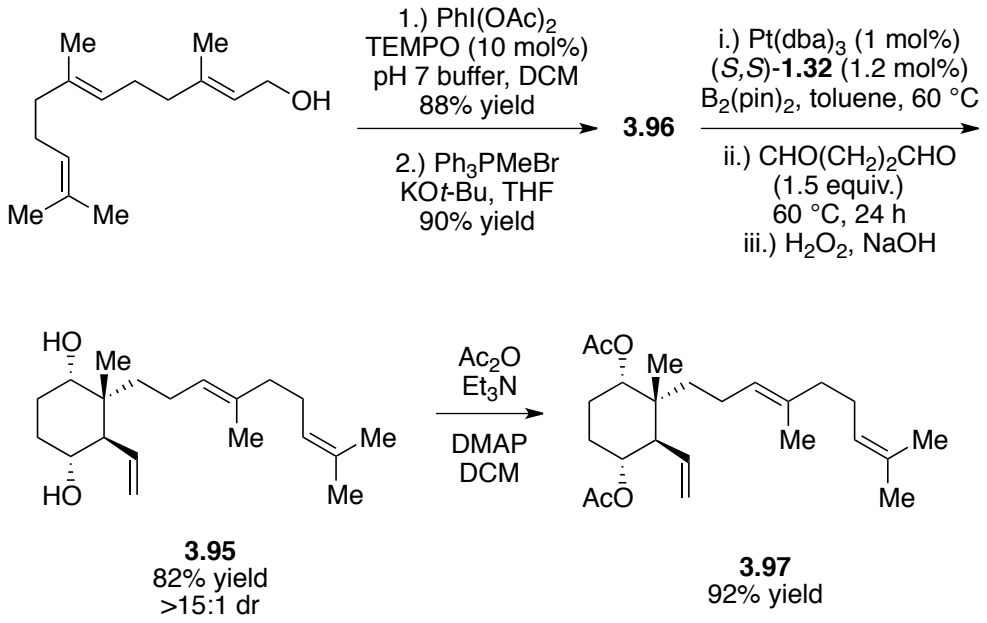


3.40 **3.95** **3.96**

3.4.2. Progress Towards Bromophycolide F

Our route to bromophycolide F began with the synthesis of diene **3.96** from *trans,trans*-farnesol by a two- step oxidation-Wittig olefination sequence (Scheme 3.20). When subjected to the diboration/double allylation conditions using 1 mol% $Pt(dba)_3$, 1.2 mol% **1.32**, and 1.5 equivalents of succinaldehyde, diol **3.95** was isolated in 82% yield and >15:1 diastereomer ratio in favor of the *syn*-1,4-diol. Cyclohexanol **3.95** was acylated with ease in the presence of acetic anhydride and catalytic DMAP to afford **3.97** in a 92% yield.

Scheme 3.20. Diboration/Double Allylation of Farnesol-Derived Diene

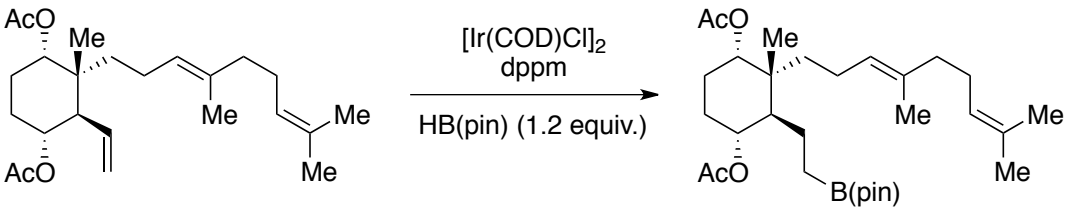


At this point, we explored how to functionalize the terminal olefin generated in the diboration/double allylation sequence. Not surprisingly, many of the manipulations attempted on the sterically hindered monosubstituted olefin were unsuccessful. Fortunately, iridium-catalyzed hydroboration[155] with pinacol borane [HB(pin)] met with some success (Table 3.3). With 3 mol% $[Ir(COD)Cl]_2$ and 6 mol% dppm, hydroboration product **3.98** was isolated in 61% yield (entry 1). It is noteworthy that the more substituted alkenes were inert under the reaction conditions. A number of perturbations to the reaction conditions were performed in order to improve conversion in the hydroboration reaction. When the reaction time was extended to 48 hours, full conversion was achieved and **3.98** was isolated in 92% yield. Increasing the reaction temperature to 50 °C, as well as increasing the catalyst loading to 10 mol%, also afforded

[155] Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695.

the desired diol in high yield (87% and 86%, respectively.) Given the comparability of these results, we ultimately chose to perform the hydroboration at elevated temperatures in order to minimize the amount of time and catalyst required to accomplish this transformation.

Table 3.3. Optimization of Iridium-Catalyzed Hydroboration of Hindered Terminal Olefin



3.97 **3.98**

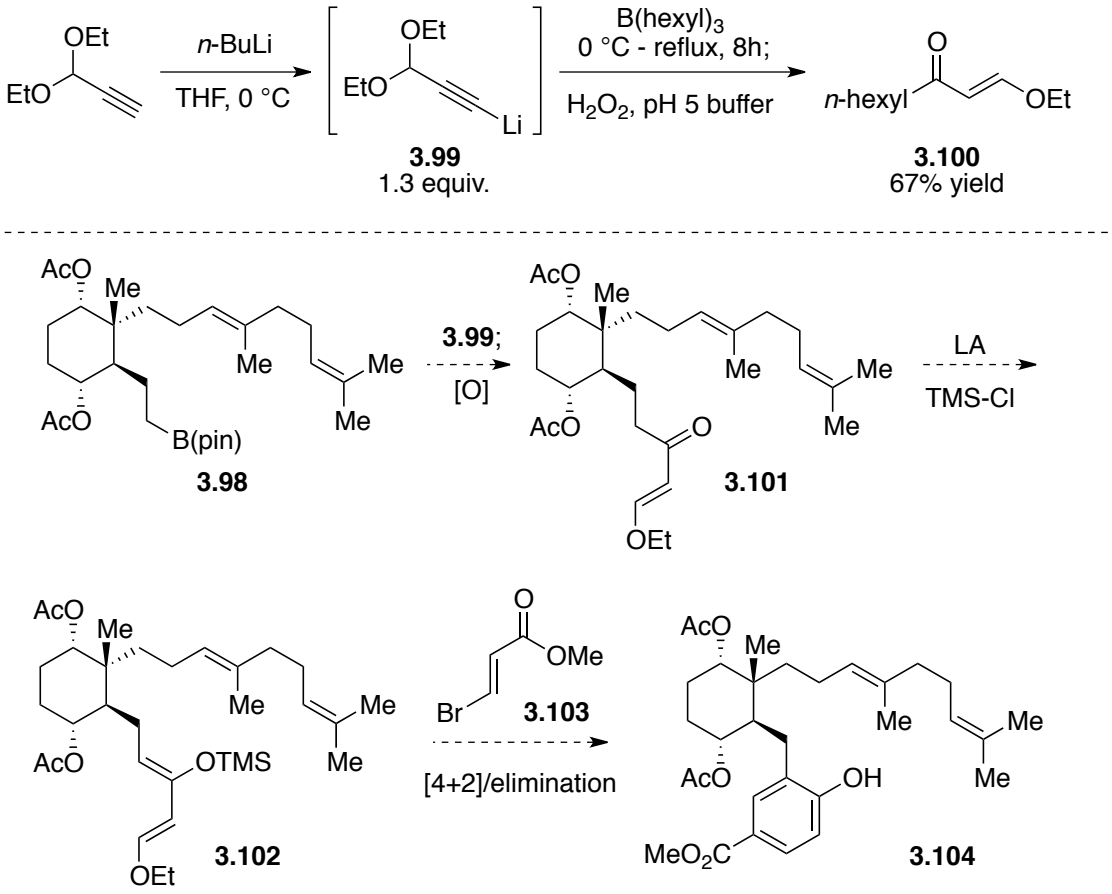
entry	$[Ir]_2$ (mol%)	dppm (mol%)	solvent	temp (°C)	time (h)	%yield
1	3	6	DCM	23	24	61
2	3	6	DCM	23	48	92
3	3	6	toluene	50	24	87
4	5	10	DCM	23	24	86

We were excited to successfully install a boronic ester on the alkene terminus because it could serve as a versatile platform for building up the aryl ester of bromophycolide F. To accomplish this, we were inspired by a method reported by Suzuki,[156] wherein trialkylboranes underwent homologation with lithium acetylides (**3.99**) to afford β -alkoxy-substituted α,β-unsaturated ketones after oxidation (Scheme 3.21, **3.100**). If this procedure could be applied to boronic esters, we imagined using it to

[156] Hara, S.; Dojo, H.; Kato, T.; Suzuki, A. *Chem. Lett.* **1983**, *7*, 1125.

convert the terminal boronic ester in **3.98** to the corresponding enone **3.101**. After silyl enol ether formation, Danishefsky's Diene-type intermediate **3.102** may undergo [4+2] cycloaddition-elimination with bromoacrylate **3.103** to access the aryl ring with the desired oxidation pattern (**3.104**). Unfortunately, addition of **3.99** to model pinacol boronic esters was unsuccessful, even under Lewis-acid-catalyzed conditions with Sc $(OTf)_3$. This may be due to the decreased electrophilicity of boronic esters with respect to boranes.

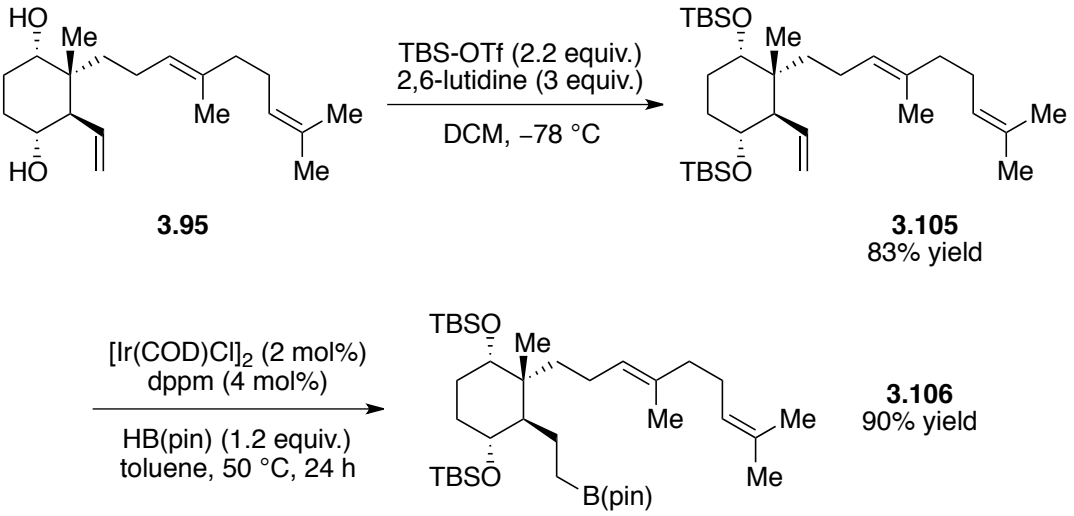
Scheme 3.21. Potential Homologation Route to Danishefky's Diene-Like Intermediate



While the acetylide homologation route to **3.90** was ultimately unsuccessful, we are still hopeful that the [4+2] cycloaddition would be an efficient route to installing the

aryl ring. If, alternatively, the boronic ester bearing carbon could be rendered nucleophilic, it should be possible to trap a carbonyl electrophile that could then be functionalized to mimic **3.102**. In order for this strategy to be successful, a change in the diol protection groups would be required. Bis(silyl) ether **3.105** was isolated in 83% yield after protection of **3.95** with TBS-OTf in the presence of 2,6-lutidine (Scheme 3.22). Iridium-catalyzed hydroboration again proceeded smoothly at 50 °C in the presence of 4 mol% catalyst, despite the significantly bulkier protecting group, to afford boronic ester **3.106** in 90% yield.

Scheme 3.22. Silyl Ether Protecting Group Strategy



With terminal boronic ester **3.106** in hand, we then explored a variety of functionalization reactions that might be viable for accessing the Danishefsky's diene intermediate. The most direct route we imagined was to convert the boronic ester-bearing-carbon into Grignard reagent **3.108** by a boron/magensium exchange procedure recently developed by Breit.[157] This organomagnesium species could then be trapped

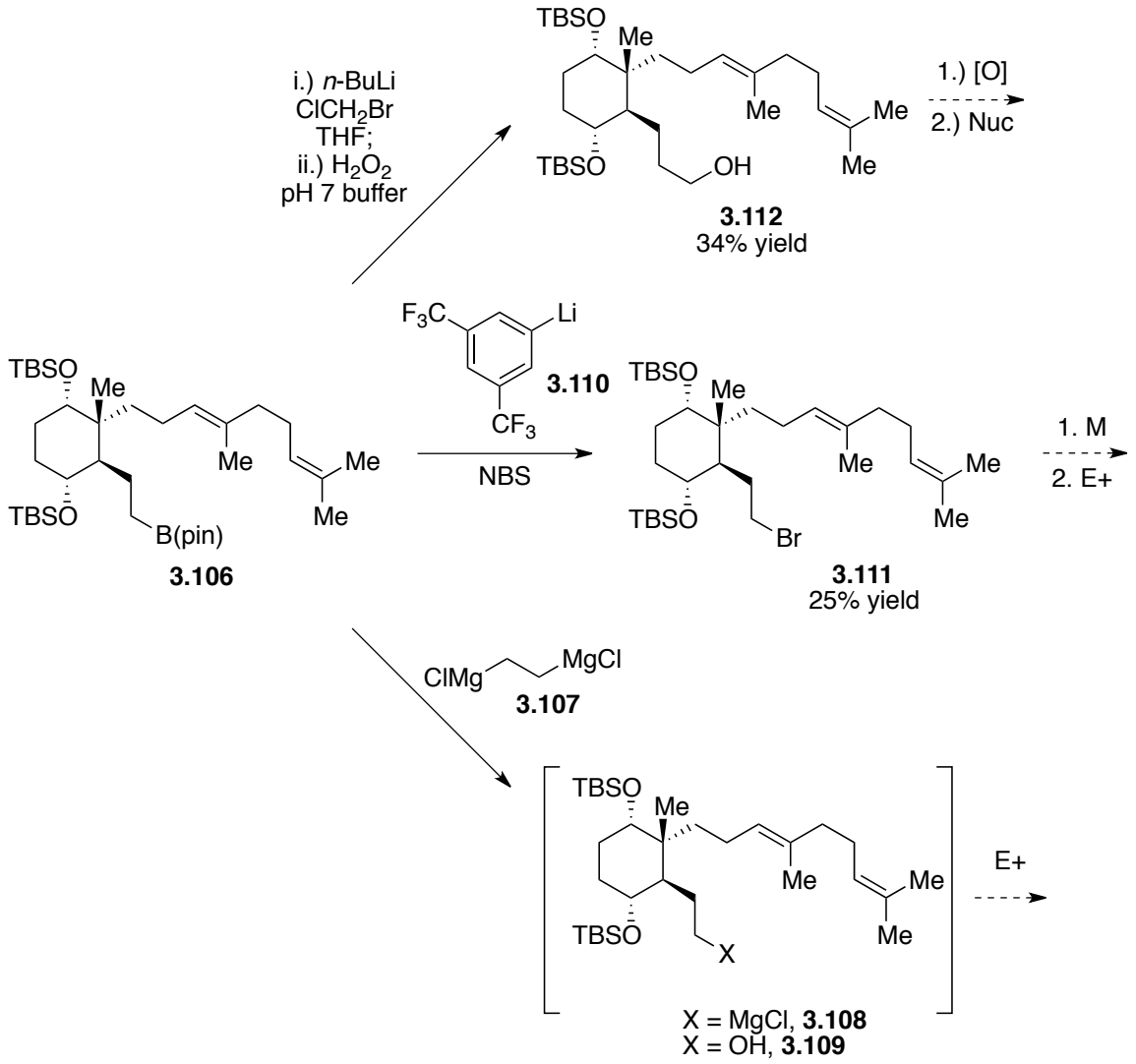
[157] Reichle, M. A.; Breit, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 5730.

with a carbonyl electrophile to install the remainder of the carbons in the diene fragment (Scheme 3.23). When **3.106** was mixed with alkylmagnesium reagent **3.107**, followed by the addition of benzaldehyde, no electrophilic trapping was observed. The only product isolated was the corresponding alcohol **3.109** from direct oxidation of the C-Mg bond, evidence that boron/magnesium exchange was achieved. A less direct, but more promising, route to a similar intermediate was accomplished by reacting **3.106** with aryl lithium **3.110**; the "ate" complex generated was then quenched with an electrophilic bromine source to produce **3.111** in 25% yield. While Aggarwal initially developed this method to functionalize enantioenriched secondary boronic esters into stereoinverted products,[158] it also has the potential to be used as an organometallic precursor for building the aromatic ring in bromophycolide F.

Rather than installing oxygenation at C18 *via* a carbonyl electrophile, one could alternatively imagine extending the functionality of the boronic ester through a homologation-oxidation technique. Boronic ester **3.106,** when subjected to chloromethyllithium followed by buffered oxidation, was readily converted to **3.112**, albeit in only a 34% isolated yield. Although this route would add considerably more steps to the overall sequence, it serves as a proof-of-concept for possibilities available to convert hydroboration product **3.106** into the target terpenoid.

[158] Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16794.

Scheme 3.23. Functionalization of the Terminal Boronic Ester



Considerable work remains in order to complete the first total synthesis of bromophycolide F. What has been demonstrated is that by utilizing the diboration/ double allylation strategy with farnesol-derived diene **3.96** and succinaldehyde, the majority of the carbon framework, including the highly substituted cyclohexane core, can be accessed in high yield. Furthermore, a number of potential routes have been explored for constructing the benzoate from the key terminal olefin hydroboration product. The remaining challenges left so solve are: 1.) carrying out the Diels-Alder/

elimination sequence to build the aromatic ring, 2.) selective oxidation of the trisubstituted olefins, 3.) macrolactonization, and 4.) differentiation of the secondary alcohols.

3.5. Experimentals

3.5.1. General Information

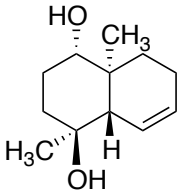
^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), a Varian Inova-500 (500 MHz), or a Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants. ^{13}C NMR spectra were recorded on either a Varian Gemini-500 (125 MHz), a Varian Inova-500 (125 MHz), or a Varian Gemini-600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$ 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, νmax cm-1. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230x450 mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, or phosphomolybdic acid (PMA) in ethanol. Optical rotations were measured on a Atago AP-300 Polarimeter. Melting point determination was performed with Digimelt MPA160.

All reactions were conducted in oven- or flamed-dried glassware under an inert atmosphere of nitrogen or argon, unless otherwise noted. Tetrahydrofuran (THF),

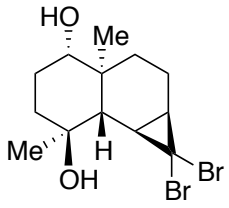
toluene (PhMe), and dichloromethane (DCM) were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing through two activated alumina columns after being purged with argon. Triethylamine was distilled from calcium hydride. Bis(pinacolato)diboron was generously donated by Allychem Co., Ltd. and was recrystallized from pentane prior to use. Cyclooctadiene was purchased from Aldrich and distilled over sodium metal prior to use. All other reagents were purchased from either Aldrich, Alfa-Aesar or Acros and used without further purification.

3.5.2. Pumilaside B Aglycon: Experimental Procedures and Characterization



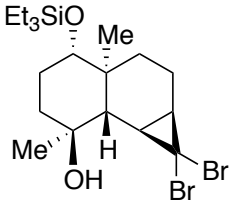
(1*S*,4*S*,4a*S*,8a*S*)-1,4a-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-1,4-diol (3.58): To a flame-dried 3-neck round bottom flask equipped with a stir bar and a reflux condenser was added the diol from the previous step (48 mg, 0.19 mmol). The flask was purged with N_2, and benzene (1.9 mL, 0.1 M) was added. Hoveyda-Grubbs Catalyst second generation (14.3 mg, 22.8 μmol) was added in a single portion, and the flask was resealed with a septum and purged with N_2. The reaction was then heated to 60 °C for 12 hours, slowly purging the entire solvent volume over the reaction time. Upon completion, the mixture was transferred to a 6-dram scintillation vial with diethyl ether and concentrated. The crude reaction mixture was purified on SiO_2 (25:1 DCM/ methanol, R_f = 0.18 in 25:1 DCM/MeOH, stain in PMA) to afford an off-white foamy solid (37.0 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.73 - 5.68 (2H, m), 3.38 (1H, dd, *J* = 11.3 Hz, 4.2 Hz), 2.08 - 2.06 (3H, m), 1.83 - 1.75 (3H, m), 1.70 - 1.61 (1H, m), 1.53 -

1.47 (1H,m), 1.34 - 1.28 (2H, m), 1.23 (1H, s), 1.12 (3H, s), 0.86 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 127.1, 124.8, 77.9, 71.5 52.4, 40.7, 37.9, 35.7, 28.9, 22.6, 22.5, 12.2; IR (neat): 3352.5 (br m), 3024.5 (w), 2970.8 (w), 2925.1 (m), 2857.0 (m), 1455.5 (m), 1381.3 (m), 1337.2 (m), 1235.6 (w), 1183.1 (m), 1159.7 (m), 1117.3 (m), 1069.7 (s), 1046.3 (s), 1031.1 (m), 1010.4 (m), 996.3 (m), 973.6 (m), 952.5 (m), 912.2 (s), 854.5 (w), 826.9 (m), 784.0 (m), 658.6 (s), 636.6 (s), 581.6 (m), 454.2 (w); HRMS-(ESI+) for $C_{12}H_{19}O_1$ [M+H-H_2O]: calculated: 179.1436, found: 179.1442; $[\alpha]_D^{24}$: +28.04 (*c* = 1.425, $CHCl_3$, *l* = 10 mm).



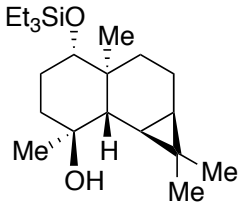
(1a*R*,3a*S*,4*S*,7*S*,7a*S*,7b*S*)-4,4-dibromo-3a,7-dimethyldecahydro-1*H*-cyclopropa[*a*]naphthalene-4,7-diol (3.59): The title compound was prepared according to the literature procedure.[135] To a 6-dram scintillation vial equipped with a stir bar was added the diol from the previous step (232.0 mg, 1.182 mmol), DCM (2.3 mL, 0.5 M), and bromoform (4.1 mL, 47.28 mmol). Finely powdered NaOH (804.0 mg, 20.09 mmol) was then added in a single portion. The vial was sealed with a teflon-lined cap and heated to 50 °C for 64 hours. Upon cooling, the solution was diluted with water (10 mL) and washed with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified on SiO_2 (25:1 - 20:1 DCM/methanol, R_f = 0.28 in 25:1 DCM/methanol, stain in PMA) to afford a foamy white solid (325.3 mg, 70% yield, single diastereomer). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.27 (1H, dd, *J* = 10.5 Hz, 3.9 Hz), 1.91 - 1.81 (3H, m), 1.79 - 1.74 (3H, m), 1.65 - 1.51 (4H, m), 1.28 (3H, s), 1.23 (1H, s), 1.20 (1H, d, *J* = 5.4 Hz), 0.95 (1H, dt, *J* = 12.7 Hz, 7.6 Hz), 0.81 (3H, s) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 77.6, 72.0, 51.1, 40.6, 40.4, 37.3, 34.1, 28.8, 27.9, 26.6, 23.3, 16.6, 14.0; IR

(neat): 3675.3 (br m), 2970.4 (m), 2934.5 (m), 2870.3 (m), 1559.4 (w), 1458.0 (w), 1438.4 (w), 1384.0 (m), 1338.9 (w), 1279.3 (w), 1279.3 (w), 1247.5 (w), 1162.3 (w), 1112.3 (m), 1085.2 (m), 1075.0 (m), 1058.1 (m), 1033.3 (s), 1002.6 (w), 951.8 (w), 911.8 (w), 859.0 (w), 835.8 (w), 722.0 (m), 709.7 (s), 668.8 (m), 643.4 (m), 571.8 (w), 495.8 (w), 452.5 (w); HRMS-(ESI +) for $C_{13}H_{24}N_1Br_2O_2$ [M+NH_4]: calculated: 384.0174, found: 384.0169. $[\alpha]_D^{23}$: +8.72 (*c* = 1.145, $CHCl_3$, *l* = 10 mm).



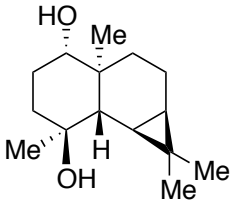
(1a*R*,3a*S*,4*S*,7*S*,7a*S*,7b*S*)-4,4-dibromo-3a,7-dimethyl-4-((triethylsilyl)oxy)decahydro-1*H*-cyclopropa[*a*]naphthalen-7-ol: To a round bottom flask equipped with a stir bar was added the diol from the previous step (92 mg, 0.25 mmol) and imidazole (20.4 mg, 0.299 mmol). The flask was sealed with a septum and purged with N_2. Next, imidazole was added as a single portion, and the solution changed from clear and colorless to cloudy white. The reaction was allowed to stir at room temperature for 2.5 hours. Upon completion, the solution was diluted with water (15 mL), transferred to a separatory funnel and washed with DCM (3x15 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (5:1 - 2:1 pentane/ether, R_f = 0.33 in 5:1 pentane/ether, stain in PMA) to afford a foamy white solid (89.0 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.26 - 3.19 (1H, m), 1.89 - 1.78 (3H, m), 1.76 - 1.70 (2H, m), 1.66 - 1.59 (2H, m), 1.55 - 1.47 (2H, m), 1.31 (1H, br s), 1.27 (3H, s), 1.16 (1H, d, *J* = 5.5 Hz), 0.91 (9H, t, *J* = 8.0 Hz), 0.82 (1H, dt, *J* = 12.5 Hz, 7.5 Hz), 0.76 (3H, s), 0.57 - 0.49 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.2, 72.0, 51.2, 41.0, 40.5, 37.9, 34.4, 29.3, 28.2, 26.9, 23.3, 16.8, 14.4, 6.9, 5.2; IR (neat): 3360.0 (br w), 2947.5 (m),

2912.1 (m), 2874.2 (m), 1458.4 (m), 1412.7 (w), 1385.0 (m), 1356.2 (w), 1332.6 (w), 1237.9 (w), 1163.0 (2), 1096.8 (s), 1067.4 (s), 1052.2 (m), 1004.0 (m), 972.2 (w), 956.1 (w), 935.4 (w), 913.8 (w), 878.0 (w), 859.7 (w), 840.8 (m), 825.1 (m), 771.3 (m), 740.0 (s), 724.9 (s), 711.1 (s), 670.9 (m), 550.7 (2), 520.3 (w), 488.4 (w), 415.8 (w); HRMS-(ESI+): for $C_{19}H_{33}Br_2O_1Si$ [M +H-H_2O]: calculated: 463.0667, found: 463.0661; $[\alpha]_D^{24}$: +18.54 (*c* = 2.155, $CHCl_3$, *l* = 10 mm)



(1a*R*,3a*S*,4*S*,7*S*,7a*S*,7b*R*)-4,4,3a,7-tetramethyl-4-((triethylsilyl)oxy) decahydro-1*H*-cyclopropa[*a*]naphthalen-7-ol (3.60): The title compound was prepared according to the literature procedure.[136] with slight modification. To an aluminum foil-wrapped flame-dried round bottom flask equipped with a stir bar was added CuI (748 mg, 3.93 mmol), and the flask was purged with N_2. The CuI was suspended in anhydrous Et_2O (2.0 mL) and cooled to – 78 °C. Upon cooling, a 1.71 M solution of MeLi (4.61 mL, 7.88 mmol) was added slowly over 30 minutes, then slowly warmed to –20 °C and stirred for an additional 10 minutes. The solution was then re-cooled to – 78 °C, and the dibromide from the previous step (190 mg, 0.393 mmol) was added as a solution in anhydrous Et_2O (0.6 mL, 0.66 M). The flask was sealed with parafilm and kept at 4 °C in the cold room for 28 hrs. The solution was then re-cooled to – 20 °C and iodomethane (0.98 mL, 15.72 mmol) was added slowly. The reaction was allowed to warm to room temperature and stir for 6 hours. The reaction was then diluted with $CHCl_3$ (5 mL) and Cu-salts precipitated as a white solid. The heterogeneous mixture was filtered over SiO_2 and concentrated *in vacuo*. The crude reaction mixture was purified on SiO_2 (8:1 - 4:1

pentane/Et_2O, R_f = 0.36 in 4:1 pentane/Et_2O, stain in PMA) to afford a white solid (75.2 mg, 54%). ^1H NMR (500 MHz, $CDCl_3$): δ 3.22 - 3.14 (1H, m), 1.79 - 1.70 (2H, m), 1.63 - 1.58 (3H, m), 1.52 (1H, dd, *J* = 14.9 Hz, 7.6 Hz), 1.48 - 1.37 (2H, m), 1.24 (3H, s), 1.03 (3H, s), 0.94 - 0.90 (13H, m), 0.80 (3H, s), 0.61 - 0.49 (8H, m), 0.45 (1H, dd, *J* = 9.3 Hz, 6.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.9, 72.3, 48.0, 40.0, 38.2, 37.3, 29.3, 29.2, 23.1, 19.5, 18.8, 17.6, 15.5, 15.3, 13.5, 7.0, 5.2; IR (neat): 3447.1 (br w), 2936.9 (m), 2874.7 (m), 1468.6 (w), 1413.9 (w), 1381.8 (w), 1355.5 (w), 1332.1 (w), 1310.9 (w), 1237.3 (w), 1191.7 (w), 1162.6 (w), 1091.1 (s), 1057.0 (w), 1041.5 (w), 1002.9 (m), 983.8 (w), 956.6 (w), 933.8 (2), 915.3 (2), 868.3 (w), 828.3 (w), 797.3 (w), 741.7 (m), 725.8 (m), 688.2 (w); HRMS-(ESI+): for $C_{21}H_{41}O_2Si$ [M+H]: calculated: 335.2770, found: 355.2763; $[\alpha]_D^{23}$: +12.89 (*c* = 0.775, $CHCl_3$, *l* = 10 mm)



Pumilaside B aglycon (3.45): The title compound was prepared according to the literature procedure[137] with slight modification. To a 6-dram scintillation vial equipped with a stir bar was added the silyl ether from the previous step (61.7 mg, 0.175 mmol), followed by a 3:1:1 mixture of glacial acetic acid, water, and THF (1.0 mL, 0.35 mL, 0.35 mL, total concentration 0.1M). The reaction was stirred at room temperature for 3 hours until complete by TLC. The solution was diluted with water (15 mL) and transferred to a separatory funnel and washed with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (25:1 DCM/methanol, R_f = 0.25 in 25:1 DCM/methanol, stain in PMA) to afford a white solid (41 mg, 98%). ^1H NMR (500 MHz, $CDCl_3$): δ 3.20 (1H, dd, *J* = 11.0

Hz, 4.2 Hz), 1.80 (1H, dt, *J* = 12.2 Hz, 2.9 Hz), 1.77 - 1.70 (2H, m), 1.65 - 1.61 (1H, m), 1.59 - 1.53 (2H, m), 1.50 - 1.44 (2H, m), 1.25 (3H, s), 1.03 (3H, s), 0.96 (1H, d, *J* = 6.1 Hz), 0.91 (3H, s), 0.83 (3H, s), 0.67 (1H, dt, *J* = 13.0 Hz, 7.6 Hz), 0.62 (1H, t, *J* = 9.1 Hz), 0.47 (1H, dd, *J* = 9.3 Hz, 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.4, 72.2, 47.9, 39.9, 37.6, 36.9, 29.2, 28.7, 23.1, 19.3, 18.6, 17.6, 15.4, 15.1, 13.2; IR (neat): 3397.5 (br m), 2928.3 (s), 2861.5 (m), 1708.0 (w), 1673.1 (w), 1458.7 (m), 1381.6 (m), 1343.3 (w), 1285.9 (w), 1257.4 (w), 1185.7 (2), 1161.3 (m), 1122.3 (w), 1103.8 (w), 1077.9 (m), 1037.4 (m), 1014.2 (w), 1000.0 (m), 982.8 (m), 953.4 (w), 928.1 (w), 882.0 (w), 832.0 (w), 798.0 (w), 751.6 (w), 643.0 (m); HRMS-(ESI +) for $C_{15}H_{25}O_1$ [M+1-H_2O]: calculated: 221.1905, found: 221.1912. $[\alpha]_D^{23}$: +49.95 (*c* = 0.200, MeOH, *l* = 10 mm); melting point: 108.6 - 110.4 °C.

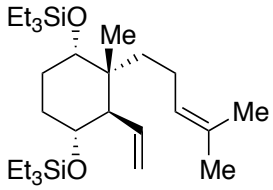
Pumilaside B aglycon ^{1}H NMR (d_5-pyridine):

Reported (ppm)	Found (ppm)	Δδ (ppm)	ΔHz
0.64 (3H, t) J = 6.5Hz	0.65 (3H, t) J = 8.6 Hz	+0.01	+2.1
0.91 (1H, dd) J = 9.0 Hz, 6.0 Hz	0.90-0.98 (2H, m)		
1.05 (3H, s)	1.06 (3H, s)	+0.01	
1.10 (3H, s)	1.10 (3H, s)	0	
1.22 (3H, s)	1.22 (3H, s)	0	
1.42 (1H, d) J = 6.0 Hz)	1.42 (1H, d) J = 5.9 Hz	0	-0.01
1.53 (3H, s)	1.54 (3H, s)	+0.01	
nd	1.67 (1H, dd) J = 14.7, 7.1 Hz		
nd	1.98-1.87 (2H, m)		
nd	2.07-2.00 (3H, m)		
nd	2.18 (1H, dd) J = 13.0, 8.3 Hz		
3.59 (1H, t) J = 7.0 Hz	3.59 (1H, t) J = 6.6 Hz	0	-0.4

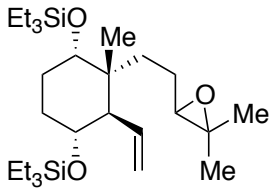
Pumilaside B aglycon ^{13}C NMR (d_5-pyridine):

Reported (ppm)	Found (ppm)	Δδ (ppm)
78.12	78.15	+0.03
71.63	71.64	+0.01
48.63	48.67	+0.04
41.89	41.93	+0.04
38.51	38.54	+0.03
37.83	37.86	+0.03
30.09	30.13	+0.04
29.61	29.64	+0.03
23.74	23.78	+0.04
21.08	21.12	+0.04
18.99	19.04	+0.05
17.53	17.55	+0.02
16.02	16.05	+0.03
15.74	15.76	+0.02
14.45	14.45	0

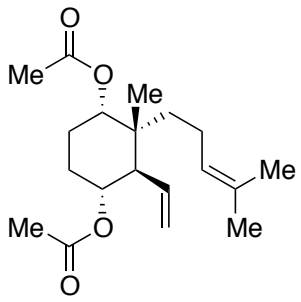
3.5.3. 1β-Hydroxy Arbusculin A: Experimental Procedures and Characterization



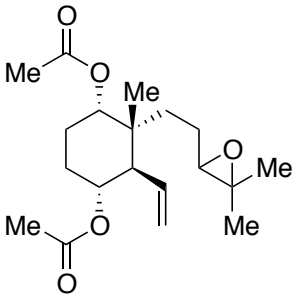
(((1*S*,2*R*,3*R*,4*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclohexane-1,4-diyl)bis(oxy))bis(triethylsilane) (3.64): To a flame-dried round bottom flask equipped with a stir bar was added *ent*-**2.40** (100 mg, 0.420 mmol.) The flask was sealed with a septum, purged with N_2, and 2,6-lutidine (0.15 mL, 1.259 mmol) and DCM (2.1 mL, 0.20 M) were added. The solution was cooled to -78 °C and TES-OTf (0.21 mL, 0.93 mmol) was added. The solution was stirred at this temperature for 2 hours before quenching with water. The heterogenous mixture was transferred to a separatory funnel and extracted 3x20 mL DCM. The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude mixture was purified on SiO_2 (100:1 - 50:1 hexanes/ ethyl acetate, R_f = 0.72 in 100:1 hexane/ethyl acetate, stain in PMA) to afford a colorless oil (151.2 mg, 77% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (1H, dt, *J* = 16.6 Hz, 9.8 Hz), 5.05 (1H, dd, *J* = 10.3 Hz, 2.5 Hz), 5.03 - 4.99 (2H, m), 3.62 (1H, dt, *J* = 10.8 Hz, 4.4 Hz), 3.57 (1H, d, *J* = 2.9 Hz), 2.16 (1H, t, *J* = 10.3 Hz), 1.90 - 1.71 (3H, m), 1.64 (3H, s), 1.62 - 1.58 (3H, m), 1.56 (3H, s), 1.48 (1H, dt, *J* = 12.2 Hz, 5.4 Hz), 1.13 (1H, dt, *J* = 12.2 Hz, 5.9 Hz), 0.93 (18 H, dt, *J* = 13.7 Hz, 8.3 Hz), 0.77 (3H, s), 0.61 - 0.52 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.6, 130.5, 125.4, 118.3, 71.6, 70.4, 54.2, 41.2, 37.7, 29.7, 29.6, 27.8, 25.7, 21.5, 18.5, 17.7, 7.1, 7.0, 5.3, 5.2; IR (neat): 2951.7 (s), 2876.1 (s), 1458.4 (w), 1238.0 (w), 1074.6 (s), 1007.3 (s), 910.8 (m), 791.5 (s), 724.3 (s) cm^{-1}; HRMS-(ESI+) for $C_{27}H_{55}O_2Si_2$ [M+H]: calculated: 467.3751, found: 467.3743; $[\alpha]_D^{24}$= -16.99 (*c* = 1.175, $CHCl_3$, *l* = 10 mm).



(((1*S*,2*R*,3*R*,4*R*)-2-(2-(3,3-dimethyloxiran-2-yl)ethyl)-2-methyl-3-vinylcyclohexane-1,4-diyl)bis(oxy))bis(triethylsilane) (3.65): The title compound was prepared according to the literature procedure.[143] To a solution of the **3.64** in DCM (3.2 mL, 0.1 M) at 0 °C was added $NaHCO_3$ (46 mg, 0.549 mmol), then *m*-CPBA (72.4 mg, 0.323 mmol, 77% weight by mass.) The solution was allowed to warm to room temperature and stir for 1 hour. Next, the mixture was diluted with $Na_2S_2O_3$ (2 mL) and aqueous saturated $NaHCO_3$ (2 mL) and stirred for an additional 20 minutes. The layers were separated the organics were washed 1x1:1 $Na_2S_2O_3$:$NaHCO_3$ (15 mL total.) The combined aqueous extracts were washed 3x15 mL DCM, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified on SiO_2 (30:1 pentane/ethyl acetate, R_f = 0.26 in 30:1 pentane:ethyl acetate, stain in PMA) to afford a colorless oil (138.1 mg, 89% yield, 1:1 mixture of diastereomers.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 - 5.47 (2H, m), 5.09 - 5.06 (2H, m), 5.05 - 5.01 (2H, m), 3.65 - 3.59 (2H, m), 3.52 (2H, s), 2.63 - 2.59 (2H, m), 2.21 - 2.16 (2H, m), 1.8 - 1.69 (2H, m), 1.65 - 1.59 (8H, m), 1.57 - 1.50 (4H, m), 1.49 - 1.43 (2H, m), 1.35 - 1.29 (2H, m), 1.27 (6H, m), 1.26 - 1.15 (2H, m), 1.23 (6H, s), 1.21 (6H, s), 0.97 - 0.90 (32H, m), 0.76 (3H, s), 0.75 (3H, s), 0.63 - 0.52 (24H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 137.3, 118.5, 72.1, 71.6, 70.33, 70.28, 65.2, 64.9, 58.3, 58.0, 54.21, 54.16, 41.0, 34.4, 29.7, 29.52, 29.50, 27.7, 27.6, 25.0, 24.9, 22.8, 22.7, 18.9, 18.7, 18.5, 18.4, 7.1, 6.9, 6.7, 5.4, 5.3, 5.20, 5.18, 4.4; IR (neat): 2953.2 (s), 2876.2 (s), 1459.1 (w), 1377.7 (w), 1238.7 (w), 1076.7 (s), 1010.2 (m), 911.3 (w), 792.2 (m), 738.7 (s), 725.0 (s) cm^{-1}; HRMS-(ESI+) for $C_{27}H_{55}O_3Si_2$ [M+H]: calculated: 483.3690, found: 483.3689; $[\alpha]_D^{23}$= -17.13 (*c* = 2.330, $CHCl_3$, *l* = 10 mm).

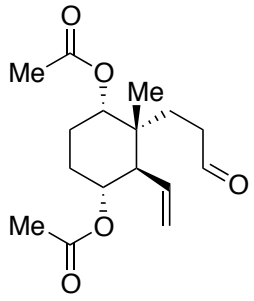


(1*S*,2*R*,3*R*,4*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclohexane-1,4-diyl diacetate (3.66): To a vial equipped with a stir bar was added diol **ent-2.40** (100 mg, 0.42 mmol), DMAP (2.5 mg, 0.021 mmol), and DCM (2.0 mL, 0.2 M.) Next, triethylamine (0.18 mL, 1.26 mmol) and acetic anhydride (0.12mL, 1.26 mmol) were added sequentially. The mixture was allowed to stir at room temperature for 17 hours before quenching with water. The mixture was extracted 3x20 mL DCM, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude mixture was purified on SiO_2 (10:1 - 8:1 hexanes/ethyl actetate, R_f = 0.21 in 10:1 hexanes/ethyl acetate, stain in PMA) to afford a colorless oil (107.2 mg, 79% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (1H, dt, *J* = 17.1 Hz, 10.3 Hz), 5.10 (1H, dd, *J* = 10.3 Hz, 2.0 Hz), 5.05 (1H, dd, *J* = 16.6 Hz, 2.0 Hz), 5.01-4.96 (2H, m), 4.77 (1H, t, *J* = 2.5 Hz), 2.26 (1H, t, *J* = 10.3 Hz), 2.06 (3H, s), 1.96 (3H, s), 1.89 - 1.70 (6H, m), 1.63 (3H, s), 1.61 - 1.54 (1H, m), 1.52 (3H, s), 1.31 - 1.20 (3H, m), 0.95 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.1, 135.3, 131.3, 124.4, 119.1, 73.0, 71.0, 52.7, 40.0, 38.0, 25.7, 25.6, 24.1, 21.23, 21.20, 21.1, 17.9, 17.4; IR (neat): 2930.5 (br w), 1730.9 (s), 1445.6 (w), 1373.3 (m), 1234.0 (s), 1023.1 (m), 915.2 (m) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{34}N_1O_4$ [M + NH_4]: calculated: 340.2488; found: 340.2496; $[\alpha]_D^{24}$= -117.95 (*c* = 1.100, $CHCl_3$, *l* = 10 mm).



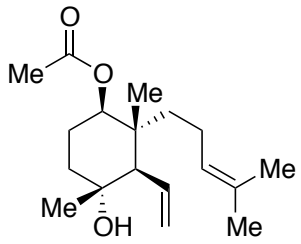
(1*S*,2*R*,3*R*,4*R*)-2-(2-(3,3-dimethyloxiran-2-yl)ethyl)-2-methyl-3-vinylcyclohexane-1,4-diyl diacetate (3.67): The title compound was prepared according to the literature procedure.[143] To a solution of the **3.66** (107.0 mg, 0.33 mmol) in DCM (3.3 mL, 0.1 M) at 0 °C was added $NaHCO_3$ (47.1 mg, 0.561 mmol), then *m*-CPBA (74.0 mg, 0.33 mmol, 77% weight by mass.) The solution was allowed to warm to room temperature and stir for 1 hour. Next, the mixture was diluted with $Na_2S_2O_3$ (2 mL) and aqueous saturated $NaHCO_3$ (2 mL) and stirred for an additional 20 minutes. The layers were separated the organics were washed 1x1:1 $Na_2S_2O_3$:$NaHCO_3$ (15 mL total.) The combined aqueous extracts were washed 3x15 mL DCM, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified on SiO_2 (5:1 hexanes/ethyl acetate, R_f = 0.22, 0.18 in 5:1 hexanes:ethyl acetate, stain in PMA) to afford two colorless oils in a combined 96% yield. **Diastereomer 1:** R_f = 0.22 in 5:1 hexanes:ethyl acetate, 52.2 mg, 47% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (1H, dt, *J* = 16.6 Hz, 9.8 Hz), 5.12 (1H, dd, *J* = 10.3 Hz, 2.0 Hz), 5.08 (1H, dd, *J* = 17.1 Hz, 2.0 Hz), 4.98 (1H, dt, *J* = 11.3 Hz, 4.9 Hz), 4.72 (1H, t, *J* = 2.4 Hz), 2.58 (1H, dd, *J* = 7.8 Hz, 4.4 Hz), 2.30 (1H, t, *J* = 10.3 Hz), 2.07 (3H, s), 1.96 (3H, s), 1.87 - 1.80 (2H, m), 1.77 - 1.70 (1H, m), 1.64 - 1.58 (1H, m), 1.57 - 1.50 (1H, m), 1.45 - 1.39 (1H, m), 1.37 - 1.31 (1H, m), 1.26 (3H, s), 1.21 - 1.13 (1H, m), 1.18 (3H, s), 0.93 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.3, 135.1, 119.4, 72.5, 70.9, 64.5, 58.5, 52.7, 39.9, 34.5, 25.7, 24.8, 24.3, 22.1, 21.2, 21.1, 18.6, 17.9; IR (neat): 2960.9 (br w), 1732.8 (m), 1455.5 (br w), 1374.6 (m), 1238.6 (s), 1025.0 (m) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{31}O_5$ [M+H]: calculated: 339.2172; found: 338.2161; $[\alpha]_D^{23}$= -75.80 (*c* = 1.580, $CHCl_3$, *l* = 10 mm).

Diastereomer 2: R_f = 0.18 in 5:1 hexanes:ethyl acetate, 55.5 mg, 50% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (1H, dt, *J* = 16.6 Hz, 9.8 Hz), 5.11 (1H, dd, *J* = 10.3 Hz, 2.0 Hz), 5.07 (1H, dd, *J* = 17.1 Hz, 2.0 Hz), 5.00 (1H, dt, *J* = 11.3 Hz, 4.9 Hz), 4.72 (1H, t, *J* = 2.5 Hz), 2.56 (1H, t, *J* = 5.4 Hz), 2.28 (1H, t, *J* = 11.3 Hz), 2.06 (3H, s), 1.96 (3H, s), 1.88 - 1.80 (2H, m), 1.76 - 1.69 (1H, m), 1.63 - 1.57 (1H, m), 1.49 - 1.43 (1H, m), 1.38 - 1.28 (3H, m), 1.26 (3H, s), 1.18 (3H, s). 0.94 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.3, 135.3, 119.7, 73.2, 71.1, 64.8, 58.6, 52.8, 40.1, 34.6, 25.8, 25.1, 24.4, 22.6, 21.5, 21.4, 18.8, 18.1; IR (neat): 2961.0 (br w), 1731.9 (s), 1456.9 (br w), 1375.2 (m), 1238.3 (s), 1024.8 (m), 915.1 (w); HRMS-(ESI+) for $C_{19}H_{31}O_5$ [M+H]: calculated: 339.2172; found: 339.2181; $[\alpha]_D^{23}$= -68.83 (*c* = 1.450, $CHCl_3$, *l* = 10 mm).



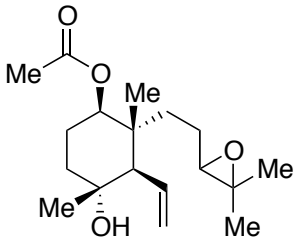
(1*S*,2*R*,3*R*,4*R*)-2-methyl-2-(3-oxopropyl)-3-vinylcyclohexane-1,4-diyl diacetate (3.68): The title compound was synthesized according to the literature procedure[144] with slight modification. To a vial equipped with a stir bar was added **3.67** (107 mg, 0.316 mmol), THF (1.6 mL, 0.2 M with respect to epoxide,) and H_2O (1.5 M with respect to periodic acid.) The solution was cooled to 0 °C and HIO_4-$2H_2O$ (79.3 mg, 0.348 mol) was added in a single portion. The solution was allowed to stir at 0 °C for 4.25 hours. The reaction mixture was quenched with saturated aqueous sodium chloride and extracted 3x20 mL Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified on SiO_2 (4:1 - 2:1 hexanes/ ethyl acetate, R_f = 0.26 in 4:1 hexanes/ethyl acetate, stain in $KMnO_4$) to afford a colorless oil (70.1 mg, 75% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.70 (1H, t, *J* = 1.5 Hz),

5.54 (1H, dt, *J* = 17.1 Hz, 10.3, Hz), 5.14 (1H, dd, *J* = 10.3 Hz, 2.0 Hz), 5.10 (1H, dd, *J* = 17.1 Hz, 2.0 Hz), 4.98 (1H, dt, *J* = 11.3 Hz, 4.4 Hz), 4.71 (1H, t, *J* = 2.5 Hz), 2.37 - 2.24 (3H, m), 2.06 (3H, s), 1.96 (3H, s), 1.86 - 1.81 (2H, m), 1.78 - 1.70 (1H, m), 1.65 - 1.57 (3H, m), 0.92 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 170.5, 170.2, 134.7, 119.8, 72.4, 70.7, 52.4, 39.6, 37.8, 29.2, 25.5, 24.2, 21.2, 21.1, 17.7; IR (neat): 2951.2 (w), 1725.9 (s), 1373.2 (m), 1236.6 (s), 1140.9 (w), 1117.4 (w), 1024.9 (m), 917.7 (w) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{28}N_1O_5$ [M+NH_4]: calculated: 314.1968, found: 314.1953; $[\alpha]_D^{22}$= -67.95 (*c* = 2.350, $CHCl_3$, *l* = 10 mm).



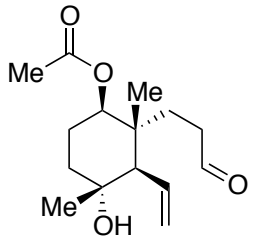
(1*R*,2*R*,3*R*,4*R*)-4-hydroxy-2,4-dimethyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclohexyl acetate: To a vial equipped with a stir bar was added diol **2.53** (400 mg, 1.58 mmol), DMAP (9.7 mg, 0.079 mmol), and DCM (7.9 mL, 0.2 M.) Next, triethylamine (0.26 mL, 1.90 mmol) and acetic anhydride (0.18mL, 1.90 mmol) were added sequentially. The mixture was allowed to stir at room temperature for 3 hours before quenching with water. The mixture was extracted 3x30 mL DCM, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude mixture was purified on SiO_2 (5:1 - 2:1 hexanes/ethyl acetate, R_f = 0.27 in 1:1 hexanes/ethyl acetate, stain in PMA) to afford a colorless oil (436.5 mg, 94% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (1H, dt, *J* = 17.1 Hz, 10.3 Hz), 5.28 (1H, dd, *J* = 10.3 Hz, 2.4 Hz), 5.19 (1H, dd, *J* = 17.1 Hz, 2.5 Hz), 4.94 (1H, dt, *J* = 7.3 Hz, 1.5 Hz), 4.80 - 4.78 (1H, m), 2.10 (1H, d, *J* = 10.3 Hz), 2.01 (3H, s), 1.93 (1H, s), 1.90 - 1.81 (3H, m), 1.78 (1H, dd, *J* = 9.8 Hz, 4.4 Hz), 1.61 (3H, s), 1.59 - 1.54 (2H, m), 1.51 (3H, s),

1.23 - 1.12 (2H, m), 0.94 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 134.3, 131.4, 124.2, 120.6, 75.0, 70.9, 57.2, 39.5, 38.8, 37.4, 25.6, 25.4, 24.7, 21.3, 21.2, 17.4; IR (neat): 3496.2 (w br), 2966.9 (w), 2925.8 (m), 1736.1 (s), 1450.3 (m), 1373.5 (m), 1241.5 (s), 1030.8 (m), 953.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{34}N_1O_3$ [M+NH_4]: calculated: 312.2539, found: 312.2525; $[\alpha]_D^{23}$= -14.01 (*c* = 1.425, $CHCl_3$, *l* = 10 mm).



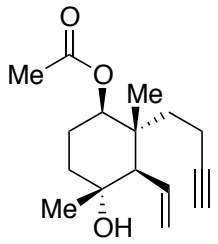
(1*R*,2*R*,3*R*,4*R*)-2-(2-(3,3-dimethyloxiran-2-yl)ethyl)-4-hydroxy-2,4-dimethyl-3-vinylcyclohexyl acetate (3.69): ***As a 1:1 mixture of epoxide diastereomers.*** The title compound was prepared according to the literature procedure.[143] To a solution of acylated **2.53** (604 mg, 2.17 mmol) in DCM (22 mL, 0.1 M) at 0 °C was added $NaHCO_3$ (310.5 mg, 3.70 mmol), then *m*-CPBA (487.2mg mg, 2.17 mmol, 77% weight by mass.) The solution was allowed to warm to room temperature and stir for 1 hour. Next, the mixture was diluted with $Na_2S_2O_3$ (5 mL) and aqueous saturated $NaHCO_3$ (5 mL) and stirred for an additional 20 minutes. The layers were separated the organics were washed 1x $Na_2S_2O_3$:$NaHCO_3$ (1:1 mixture, 30 mL total.) The combined aqueous extracts were washed with 3x40 mL DCM, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified on SiO_2 (1.5:1 hexanes/ethyl acetate, R_f = 0.28 in 1.5:1 hexanes/ethyl acetate, stain in PMA) to afford a colorless oil (604.3 mg, 90% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 -5.74 (2H, m), 5.29 - 5.24 (2H, m), 5.17 - 5.13 (2H, m), 4.76 - 4.72 (2H, m), 2.53 (2H, t, *J* = 6.4 Hz), 2.04 - 2.00 (8H, m), 1.86 - 1.81 (2H, m), 1.79 - 1.75 (2H, m), 1.62 - 1.27 (12H, m), 1.25 - 1.20 (2H, m), 1.23 (6H, s), 1.19 - 1.17 (12H, m), 0.97 (3H, s), 0.96 (3H, s); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 170.3, 134.3, 133.9, 120.9, 120.6, 74.9, 74.8, 70.9, 70.8, 64.5, 64.3, 58.4, 58.2, 57.4, 57.1, 39.4, 39.3, 37.3, 35.10, 35.08, 29.7, 25.5, 24.82, 24.81, 24.63, 24.59, 22.3, 22.2, 21.2, 18.7, 18.6, 17.5; IR (neat): 3467.6 (br w), 2959.2 (m), 2928.9 (m), 1736.1 (s), 1376.5 (m), 1241.7 (s), 1083.5 (m) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{34}N_1O_4$ [M+NH_4]: calculated: 328.2488, found: 328.2482; $[\alpha]_D^{23}$= -6.40 (*c* = 1.560, $CHCl_3$, *l* = 10 mm).



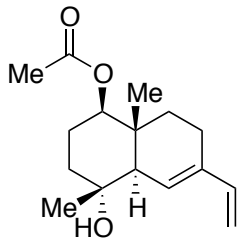
(1*R*,2*R*,3*R*,4*R*)-4-hydroxy-2,4-dimethyl-2-(3-oxopropyl)-3-vinylcyclohexyl acetate (3.70): The title compound was synthesized according to the literature procedure[144] with slight modification. To a vial equipped with a stir bar was added **3.69** (600 mg, 1.93 mmol), THF (9.7 mL, 0.2 M with respect to epoxide,) and H_2O (1.4 mL, 1.5 M with respect to periodic acid.) The solution was cooled to 0 °C and HIO_4-$2H_2O$ (484.6 mg, 2.13 mmol) was added in a single portion. The solution was allowed to stir at 4°C for 13.5 hours. The reaction mixture was quenched with saturated aqueous sodium chloride and extracted 3x50 mL Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified on SiO_2 (1:1 hexanes/ethyl acetate, R_f = 0.31 in 1:1 hexanes/ethyl acetate, stain in PMA) to afford a colorless oil (461.8 mg, 89% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.66 (1H, s), 5.77 (1H, dt, *J* = 17.1 Hz, 10.3 Hz), 5.26 (1H, d, *J* = 10.3 Hz), 5.15 (1H, d, *J* = 16.6 Hz), 4.69 (1H, dd, *J* = 10.3 Hz, 3.9 Hz), 2.46 (1H, ddd, *J* = 17.1 Hz, 11.7 Hz, 4.4 Hz), 2.30 (1H, ddd, *J* = 16.6 Hz, 11.2 Hz, 4.9 Hz), 2.01 (3H, s), 1.95 (1H, d, *J* = 10.3 Hz), 1.93 (1H, br s), 1.84 - 1.76 (2H, m), 1.64 - 1.50 (3H, m), 1.47 - 1.41 (1H, m), 1.18 (3H, s), 0.97 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.8, 170.4, 133.8, 120.9, 74.6, 70.8, 57.4, 39.1, 37.8, 37.1, 30.2, 25.6,

24.6, 21.1, 17.5; IR (neat): 3498.1 (br w), 2932.1 (m), 1722.6 (s), 1372.5 (m), 1241.9 (s), 1165.2 (w), 1141.0 (w), 1083.9 (m), 920.0 (w) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{28}N_1O_4$ [M+NH_4]: calculated: 286.2018, found: 286.2010; $[\alpha]_D^{22}$= -9.47 (*c* = 1.055, $CHCl_3$, *l* = 10 mm).



(1*R*,2*R*,3*R*,4*R*)-2-(but-3-yn-1-yl)-4-hydroxy-2,4-dimethyl-3-vinylcyclohexyl acetate (3.71): The title compound was prepared according the literature procedure with slight modification.[145] To a flame-dried flask equipped with a stir bar was added aldehyde **3.70** (145 mg, 0.54 mmol) and methanol (10.8 mL, 0.05M), then cooled to 0 °C. Next, K_2CO_3 (186.6 mg, 1.35 mmol) and the Ohira-Bestmann reagent (155 mg, 0.81 mmol) were added sequentially. The reaction was fitted with a balloon of nitrogen and stirred at 4 °C for 16 hours. The reaction mixture was then diluted with diethyl ether, washed with H_2O (15 mL) and brine (15 mL.) The organics were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (3:1 - 1:2 hexanes/ethyl acetate, R_f = 0.57 in 1:1 hexanes/ethyl acetate, stain in PMA) to afford the title compound as a colorless oil (38.2 mg, 27% yield) and the deacylated alkyne **3.72** (60.7 mg, 50% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78 (1H, dt, *J* = 17.1 Hz, 10.3 Hz), 5.28 (1H, d, *J* = 9.8 Hz), 5.17 (1H, d, *J* = 16.6 Hz), 4.69 (1H, dd, *J* = 9.8 Hz, 3.9 Hz), 2.19 - 2.12 (1H, m), 2.09 - 2.02 (1H, m), 2.02 (3H, s). 1.93 (1H, d, *J* = 10.8 Hz), 1.89 - 1.87 (3H, m), 1.76 (1H, dd, *J* = 9.8 Hz, 4.9 Hz), 1.62 - 1.45 (4H, m), 1.18 (3H, s), 0.95 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 134.0, 120.9, 84.6, 75.0, 70.8, 68.0, 57.3, 39.5, 38.0, 36.9, 25.8, 24.5, 21.2, 17.3, 12.5; IR (neat): 3503.4 (br w), 3293.4 (w), 2928.9 (m), 1730.6 (s), 1371.6 (m), 1238.2 (s), 1140.2 (m), 1030.3 (m), 916.1 (s), 629.38 (s) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{28}N_1O_3$

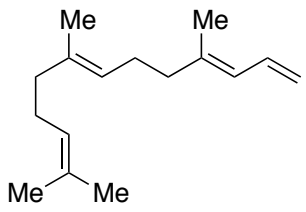
[M+NH_4]: calculated: 282.2069, found: 282.2076; $[\alpha]_D^{22}$= -31.55 (*c* = 0.950, $CHCl_3$, *l* = 10 mm).



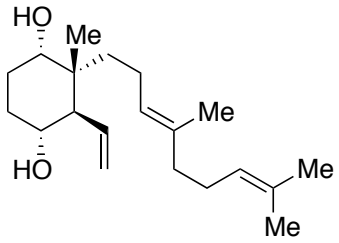
(1*R*,4*R*,4a*R*,8a*R*)-4-hydroxy-4,8a-dimethyl-6-vinyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl acetate (3.73): The title compound was prepared according to the literature procedure with slight modification.[159] To a 50 mL round bottom flask equipped with a stir bar was added enyne **3.71** (91 mg, 0.36 mmol), G-II (15.3 mg, 0.018 mmol), and DCM (12.0 mL, 0.03 M.) The flask was sealed with a septum and purged with ethylene gas, followed by insertion of an ethylene-filled balloon. The reaction was stirred for 18 hours at room temperature, then concentrated *in vacuo*. The crude mixture was purified on SiO_2 (4:1 - 3:1 hexanes/ethyl acetate, R_f = 0.23 in 3:1 hexanes/ethyl acetate, stain in PMA) to afford a colorless oil (42.6 mg, 47% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): 6.38 (1H, dd, *J* = 17.1 Hz, 10.8 Hz), 5.80 (1H, s), 5.06 (1H, d, *J* = 17.6 Hz), 4.92 (1H, d, *J* = 10.8 Hz), 4.63 (1H, dd, *J* = 11.2 Hz, 3.9 Hz), 2.22 - 2.17 (2H, m), 2.14 - 2.08 (1H, m), 2.04 (3H, s), 1.86 - 1.81 (2H, m), 1.73 - 1.64 (2H, m), 1.57 (1H, dt, *J* = 12.2 Hz, 2.9 Hz), 1.33 (1H, dt, *J* = 12.2 Hz, 6.8 Hz), 1.23 (1H, s), 1.14 (3H, s), 0.88 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 139.4, 135.9, 127.0, 110.7, 79.3, 71.2, 53.4, 40.6, 37.6, 35.6, 25.4, 22.6, 21.2, 20.9, 13.5; IR (neat): 3435.8 (br w), 2927.1 (w), 1715.4 (m), 1335.4 (m), 1239.0 (s), 1027.0 (m), 905.6 (s), 732.6 (m) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{23}O_2$ [M+H-H_2O]: calculated: 247.1698, found: 247.1694; $[\alpha]_D^{23}$= +8.36 (*c* =1.195, $CHCl_3$, *l* = 10 mm).

[159] Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63* (18), 6082.

3.4.3. Bromophycolide F: Experimental Procedures and Characterization



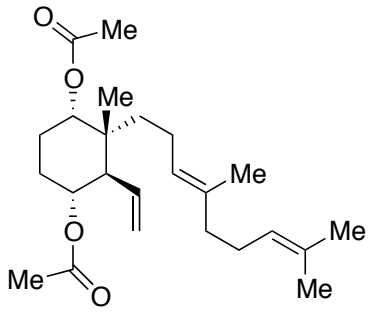
(3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene (3.96): The title compound was prepared from *trans,trans*-farnesol according to the procedure described above for (*Z*)-4,8-dimethylnona-1,3,7-triene. The crude product was purified by column chromatography on SiO_2 (100% hexanes, R_f = 0.44 in 100% pentane, stain in PMA) to afford the title compound as a clear, colorless oil (5.139g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 656 (1H, dt, *J* = 17.1 Hz, 10.8 Hz), 5.85 (1H, d, *J* = 10.8 Hz), 5.11 - 5.06 (3H, m), 4.96 (1H, dd, *J* = 10.3 Hz, 1.5 Hz), 2.14 - 2.09 (2H, m), 2.07 - 2.03 (4H, m), 1.75 (3H, s), 1.67 (3H, s), 1.59 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.4, 135.3, 133.4, 131.2, 125.5, 124.3, 123.9, 114.5, 39.8, 39.7, 26.7, 26.4, 25.7, 17.6, 16.6, 16.0; IR (neat): 2966.5 (w), 2915.7 (m), 2854.2 (w), 1442.0 (m), 1378.2 (m), 985.3 (s), 894.8 (s), 657.3 (w), 487.3 (w) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{27}$ [M+H]: calculated: 219.2113, found: 219.2111.



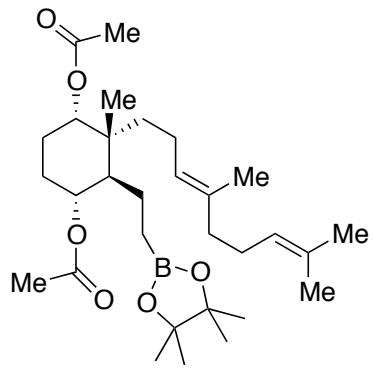
(1*S*,2*R*,3*R*,4*R*)-2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methyl-3-vinylcyclohexane-1,4-diol (3.95): To an oven-dried pressure vessel equipped with a magnetic stir bar in the glove box was added $Pt(dba)_3$ (82.2 mg, 0.0916 mmol), (*S,S*)-3,5-di-*iso*-propylphenyl-TADDOL-PPh (100.0mg, 0.110 mmol), $B_2(pin)_2$ (2.442g, 9.62 mmol), and toluene (9.2 mL, 1.0 M). The vessel was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the glove box and charged with diene (2.0g, 9.158 mmol). The vial was sealed, removed from the glove

box, and stirred at 60 °C for 12 hours. After cooling to room temperature, succinaldehyde (1.18g, 13.74 mmol) was transferred quantitatively to the flask using minimal toluene. The vessel was purged with N_2 , sealed and heated to 60 °C for 24 hours. The reaction mixture was then cooled to room temperature, transferred to a 250 mL round bottom flask with THF (20 mL), and cooled to 0 °C. Upon cooling, 20 mL of 3M NaOH was charged to the flask, followed by the dropwise addition of 10 mL of H_2O_2 (30% wt.), then slowly allowed to warm to room temperature and stir for four hours. The reaction was re-cooled and quenched with the slow addition of 20 mL saturated aqueous sodium thiosulfate solution. The reaction mixture was diluted with ethyl acetate (50 mL), transferred to a separatory funnel and washed with ethyl acetate (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was purified by column chromatography on SiO_2 (70:30 - 30:70 hexanes/ethyl acetate, R_f = 0.35 in 1:1 hexanes/ethyl acetate, stain in PMA) to afford the title compound as a while solid (2.292g, 82% yield, >15:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$): 5.66 (1H, dt, *J* = 17.1 Hz, 9.8 Hz), 5.28 (1H, dd, *J* = 10.3 Hz, 2.5 Hz), 5.20 (1H, dd, *J* = 17.1 Hz, 2.5 Hz), 5.10 (1H, dt, *J* = 6.9 Hz, 1.0 Hz), 5.06 (1H, tt, *J* = 6.9 Hz, 1.5 Hz), 3.64 (1H, s), 3.56 (1H, dt, *J* = 10.8 Hz, 4.9 Hz), 2.07 - 2.00 (3H, m), 1.99 - 1.90 (4H, m), 1.89 - 1.85 (1H, m), 1.74 - 1.72 (2H, m), 1.69 - 1.61 (1H, m), 1.66 (3H, s), 1.58 (3H, s), 1.57 (3H, s), 1.43 (1H, dq, *J* = 14.1 Hz, 5.9 Hz), 1.38 (1H, br s), 1.21 (1H, dq, *J* = 13.3 Hz, 4.9 Hz), 0.87 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.1, 135.2, 131.3, 124.6, 124.2, 120.7, 70.5, 67.9, 55.2, 40.5, 39.6, 38.5, 27.2 27.0, 26.6, 25.6, 21.2, 18.3, 17.7, 15.9; IR (neat): 3406.2 (br m), 2928.5 (s), 1444.5 (m), 1379.8 (m), 1106.8 (w), 1034.8 (s), 995.8 (s), 967.5 (m), 915.3

(m) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{35}O_2$ [M+H]: calculated: 307.2637, found: 307.2637; $[\alpha]_D^{21}$= -7.16 (*c* = 1.395, $CHCl_3$, *l* = 10 mm).

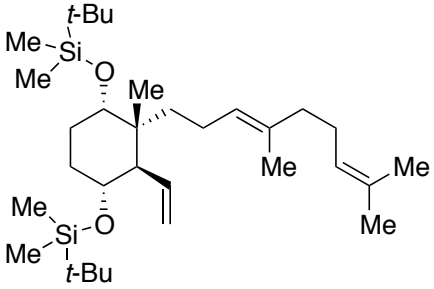


(1*S*,2*R*,3*R*,4*R*)-2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methyl-3-vinylcyclohexane-1,4-diyl diacetate (3.97): To a vial equipped with a stir bar was added **3.85** (148.8 mg, 0.486), DMAP (3.0 mg, 0.0243 mmol), and DCM (1.0 mL, 0.5 M.) Next, triethylamine (0.20 mL, 1.46 mmol) and acetic anhydride (0.14 mL, 1.46 mmol) were added sequentially. The mixture was allowed to stir at room temperature for 4 hours before quenching with water. The mixture was extracted 3x20 mL DCM, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude mixture was purified on SiO_2 (10:1 pentane/ethyl actetate, R_f = 0.26 in 10:1 pentane/ethyl acetate, stain in PMA) to afford a colorless oil (166.9 mg, 88% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (1H, dt, *J* = 17.1 Hz, 9.8 Hz), 5.10 (1H, dd, *J* = 10.3 Hz, 2.4 Hz), 5.07 - 5.03 (2H, m), 5.01 - 4.96 (2H, m), 4.77 (1H, t, *J* = 2.4 Hz), 2.27 (1H, t, *J* = 10.3 Hz), 2.06 (3H, s), 2.04 - 2.00 (2H, m), 1.96 (3H, s), 1.96 - 1.91 (2H, m), 1.89 - 1.70 (5H, m), 1.65 (3H, s), 1.62 - 1.54 (1H, m), 1.57 (3H, s), 1.51 (3H, s), 1.32 - 1.20 (2H, m), 0.95 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.2, 135.3, 134.9, 131.3, 124.3, 124.2, 119.1, 73.0, 71.0, 52.7, 40.0, 39.6, 38.0, 26.6, 25.7, 25.6, 24.2, 21.2, 21.13, 21.11, 17.9, 17.6, 15.7; IR (neat): 2929.5 (w), 1731.2 (s), 1445.3 (w), 1372.7 (m), 1233.2 (s), 1021.9 (s), 914.6 (m), 602.5 (w) cm^{-1}; HRMS-(ESI+) for $C_{24}H_{42}N_1O_4$ [M+NH_4]: calculated: 408.3114, found: 408.3122; $[\alpha]_D^{21}$= +63.94 (*c* = 1.125, $CHCl_3$, *l* = 10 mm).



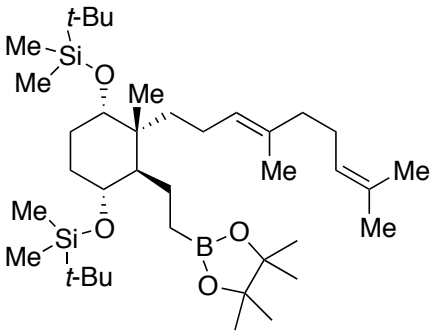
(1*S*,2*R*,3*R*,4*R*)-2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methyl-3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) ethyl)cyclohexane-1,4-diyl diacetate (3.98): The title compound was prepared according to the literature procedure with slight modification.[155] To an oven-dried vial equipped with a stir bar in the glove box was added **3.97** (39.8 mg, 0.102 mmol), $[Ir(COD)Cl)]_2$ (2.1 mg, 3.1 μmol), dppm (2.4 mg, 6.1 μmol), and toluene (0.36 mL, 0.28 M). Pinacol borane (17.7 μL, 0.122 mmol) was then charged to the vessel. After sealing the reaction vial, it was removed from the glove box and stirred at 50 °C for 24 h, then quenched with the addition of methanol (1 mL) and water (1 mL). The mixture was transferred to a separatory funnel and extracted 3 x 20 mL Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (12:1 - 8:1 pentane/ethyl acetate, R_f = 0.23 in 10:1 pentane/ethyl acetate, stain in PMA) to afford a colorless oil (49.1 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 - 5.02 (2H, m), 4.82 (1H, dt, *J* = 10.8 Hz, 3.9 Hz), 4.70 (1H, d, *J* = 2.9 Hz), 2.04 - 2.00 (1H, m), 2.03 (3H, s), 2.02 (3H, s), 1.94 - 1.90 (2H, m). 1.83 - 1.76 (4H, m), 1.71 - 1.66 (1H, m). 1.65 (3H, s), 1.60 - 1.55 (2H, m), 1.57 (3H, s), 1.53 - 1.52 (1H, m), 1.52 (3H, s), 1.46 (1H, ddd, *J* = 16.6 Hz, 12.2 Hz, 4.9 Hz), 1.34 (1H, ddd, *J* = 18.1 Hz, 12.7 Hz, 5.9 Hz), 1.29 - 1.23 (1H, m), 1.20 (12 H, s), 1.19 - 1.13 (1H, m), 0.96 - 0.89 (1H, m), 0.86 (3H, s), 0.84 - 0.78 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 170.3, 134.8, 131.3, 124.44, 124.37, 124.33, 124.28, 82.9, 75.9, 75.8, 74.05, 73.96, 47.6, 41.0, 39.7, 36.8, 29.7, 26.7, 26.2, 25.7, 24.8, 24.0, 22.3, 21.39, 21.38, 21.33, 21.17, 21.15, 17.7, 17.6, 15.8; IR (neat):

2972.6 (w), 2929.7 (w), 1731.3 (s), 1370.7 (m), 1318.5 (m), 1235.4 (s), 1109.7 (m), 1021.5 (m), 967.4 (w) cm^{-1}; HRMS-(ESI+) for $C_{30}H_{55}B_1N_1O_6$ $[M+NH_4]^+$: calculated: 536.4122, found: 536.4123; $[\alpha]_D^{21}$= +27.75 (*c* = 2.520, $CHCl_3$, *l* = 10 mm).



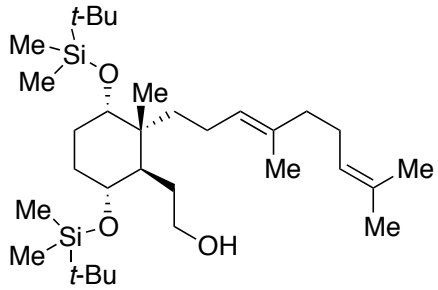
(((1*S*,2*R*,3*R*,4*R*)-2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methyl-3-vinylcyclohexane-1,4-diyl)bis(oxy)) bis(*tert*-butyldimethylsilane) (3.105): To a flame-dried round bottom flask equipped with a stir bar was added **3.95** (153.2 mg, 0.500 mmol.) The flask was sealed with a septum, purged with N_2, and 2,6-lutidine (175 μL, 1.50 mmol) and DCM (2.5 mL, 0.2M) were added. The solution was cooled to -78 °C and TBS-OTf (253 μL, 1.10 mmol) was added. The solution was stirred at this temperature for 4 hours before quenching with water. The heterogenous mixture was transferred to a separatory funnel and extracted 3x20 mL DCM. The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude mixture was purified on SiO_2 (250:1 - 200:1 pentane/ether, R_f = 0.43 in 200:1 hexane/ether, stain in PMA) to afford a colorless oil (222.9 mg, 83% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 5.49 (1H, dt, *J* = 17.1 Hz, 10.3, Hz), 5.08 - 5.04 (2H, m), 5.02 - 4.97 (2H, m), 3.62 (1H, dt, *J* = 10.3 Hz, 4.4 Hz), 3.56 (1H, s), 2.11 (1H, t, *J* = 10.3 Hz), 2.05 - 2.01 (2H, m), 1.95 - 1.92 (2H, m), 1.88 - 1.78 (2H, m), 1.73 - 1.68 (1H, m), 1.65 (3H, s), 1.63 - 1.59 (3H, m), 1.57 (3H, s), 1.55 (3H, s), 1.50 (1H, dt, *J* = 12.2 Hz, 3.4 Hz), 1.16 (1H, dt, *J* = 13.7 Hz, 5.9 Hz), 0.96 (9H, s), 0.83 (9H, s), 0.79 (3H, s), 0.06 (3H, s), 0.03 (3H, s), 0.00 (3H, s), -0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 134.2, 131.2, 125.3, 124.4, 118.4, 71.6, 70.6, 54.6, 41.3, 39.7, 37.4, 29.4, 27.4, 26.7, 26.00, 25.98,

25.7, 21.2, 18.5, 18.3, 18.2, 17.7, 16.1, -3.7, -4.0, -4.2, -5.2; IR (neat): 2928.7 (m), 2856.3 (m), 1253.7 (m), 1074.5 (s), 912.3 (m), 833.5 (s), 772.2 (s), 671.7 (w) cm^{-1}; HRMS-(ESI+) for $C_{32}H_{63}O_2Si_2$ [M+H]: calculated: 535.4367, found: 535.4388; $[\alpha]_D^{23}$= -8.16 (*c* = 1.225, $CHCl_3$, *l* = 10 mm).



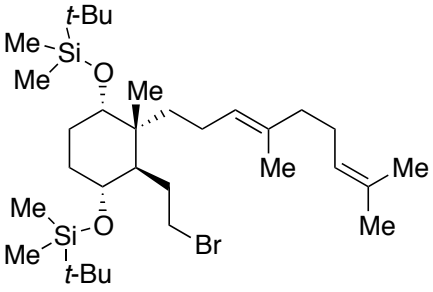
(((1*S*,2*R*,3*R*,4*R*)-2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methyl-3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)cyclohexane-1,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (3.106): The title compound was prepared according to the literature procedure with slight modification.[155] To an oven-dried vial equipped with a stir bar in the glove box was added **3.105** (712.5 mg, 1.33 mmol) $[Ir(COD)Cl)]_2$ (8.9 mg, 13.3 μmol), dppm (10.2 mg, 12.7 μmol) and toluene (5.3 mL, 0.25 M). Pinacol borane (0.23 mL, 1.60 mmol) was then charged. After sealing the reaction vial, it was removed from the glove box and stirred at 50 °C for 24 h, then quenched with the addition of methanol (2 mL) and water (2 mL). The mixture was transferred to a separatory funnel and extracted 3 x 30 mL Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (50:1 - 30:1 pentane/ethyl acetate, R_f = 0.16 in 50:1 pentane/ethyl acetate, stain in PMA) to afford a colorless oil (818.7 mg, 91% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 5.09 - 5.03 (2H, m), 3.56 (1H, dt, *J* = 9.3 Hz, 4.4 Hz), 3.50 (1H, s), 2.06 - 2.00 (2H, m), 1.94 (2H, t, *J* = 7.8 Hz), 1.93 - 1.78 (2H, m), 1.66 (3H, s), 1.58 (3H, s), 1.56 (3H, s), 1.56 - 1.52 (2H, m), 1.52 (3H, s), 1.48 - 1.40 (2H, m), 1.38 - 1.35 (1H, m), 1.32 - 1.25 (2H, m), 1.21

(12H, s), 1.00 - 0.94 (1H, m), 0.87 (9H, s), 0.86 (9H, s), 0.74 (3H, s), 0.03 - 0.01 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.0, 131.2, 125.6, 124.5, 82.6, 73.4, 72.5, 50.2, 42.2, 39.8, 39.7, 35.8, 29.8, 27.1, 26.7, 26.1, 26.0, 25.92, 25.88, 25.84, 25.7, 24.93, 24.85, 22.64, 22.0, 21.4, 18.3, 18.1, 17.7, 16.2, 16.1, -3.7, -4.0, -4.5, -5.2; IR (neat): 2928.6 (m), 2856.3 (m), 1374.8 (m), 1253.2 (m), 1145.8 (m), 1066.9 (m), 833.9 (s), 772.4 (s), 671.5 (w) cm^{-1}; HRMS-(ESI+) for $C_{38}H_{76}B_1O_4Si_2$ [M+H]: calculated: 663.5375, found: 663.5400; $[\alpha]_D^{23}$= +7.90 (*c* = 1.265, $CHCl_3$, *l* = 10 mm).



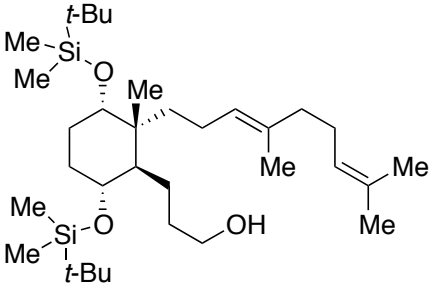
2-((1*R*,2*R*,3*S*,6*R*)-3,6-bis((*tert*-butyldimethylsilyl) oxy)-2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methylcyclohexyl)ethanol (3.109): The title compound was prepared according to the literature procedure[157] with slight modification. To a flame-dried round bottom flask equipped with a stir bar was added **3.106** (87.6 mg, 0.13 mmol) and toluene (0.52 mL, 0.25 M). The solution was cooled to 0 °C and **3.107** (0.43 mL, 0.26 mmol, 0.6 M) was added dropwise. The mixture was allowed to warm to room temperature and stir for 30 minutes before being cooled to - 20 °C. Next, benzaldehyde (11 uL, 0.109 mmol) as a solution in THF (0.82 mL, 0.13 M) was added dropwise to the mixture. The solution was stirred at - 20 °C for one hour, then slowly warmed to room temperature over three hours. To the reaction was added saturated aqueous NH_4Cl (2 mL), and the heterogeneous mixture was transferred to a separatory funnel, and washed 3 x 20 mL Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (20:1 - 10:1 pentane/ethyl

acetate, R_f = 0.23 in 20:1 pentane/ethyl acetate, stain in PMA) to afford a colorless oil (36.6 mg, 51% yield.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.06 (1H, t, *J* = 6.8 Hz), 5.00 (1H, t, *J* = 5.9 Hz), 3.66 - 3.62 (1H, m), 3.56 (1H, s), 3.52 - 3.45 (2H, m), 2.64 (1H, br s), 2.06 - 2.01 (2H, m), 1.96 - 1.76 (4H, m), 1.73 - 1.62 (3H, m), 1.65 (3H, s), 1.59 - 1.57 (5H, m), 1.56 (3H, s), 1.54 - 1.49 (1H, m). 1.48 - 1.41 (1H, m), 1.23 (1H, s), 1.15 (1H, dt, *J* = 12.7 Hz, 4.9 Hz), 0.89 (9H, s), 0.88 (9H, s), 0.75 (3H, s), 0.09 (3H, s), 0.08 (3H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.5, 131.2, 125.0, 124.4, 74.1, 71.3, 64.0, 45.2, 42.7, 40.0, 36.1, 30.9, 29.5, 27.3, 26.7, 26.0, 25.8, 25.7, 21.1, 18.3, 18.1, 17.7, 17.5, 16.2, -3.8, -4.1, -4.2, -5.2; IR (neat): 3422.0 (br w), 2950.7 (m), 2928.5 (m), 2884.6 (m), 2856.4 (m), 1254.7 (m), 1067.2 (m), 1004.1 (w), 833.8 (s), 772.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{32}H_{65}O_3Si_2$ [M+H]: calculated: 553.4472, found: 553.4465; $[\alpha]_D^{27}$= -16.24 (*c* = 1.230, $CHCl_3$, *l* = 10 mm).



(((1*S*,2*R*,3*R*,4*R*)-3-(2-bromoethyl)-2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methylcyclohexane-1,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (3.111): The title compound was prepared according to the literature procedure with slight modification.[158] To a solution of 1,3-bis(trifluoromethyl)-5-bromobenzene (61.5 μL, 0.357 mmol) and THF (3.0 mL, 0.12 M) at - 78 °C was added *n*-butyl lithium (0.16 mL, 2.29 M, 0.347 mmol) dropwise. The solution was allowed to stir for one hour before dropwise addition of **3.106** (200.0 mg, 0.298 mmol). The reaction was allowed to stir at - 78 °C for 30 minutes, then room temperature for 30 minutes. After "ate" complex formation, NBS (63.5 mg, 0.357 mmol) was added dropwise as a solution in

THF (1.5 mL, 0.2M), then continued to stir for one hour. The reaction was quenched upon addition of 20% $Na_2S_2O_3$ and Et_2O. The layers were separated and the aqueous phase was washed 3x 20 mL Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude reaction mixture was purified on SiO_2 (50:1 pentane/ethyl acetate, R_f = 0.23 in 50:1 pentane/ethyl acetate, stain in PMA) to afford the title compound as a colorless oil (45.2 mg, 25% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 (1H, tt, *J* = 6.9 Hz, 1.5 Hz), 5.02 (1H, t, *J* = 6.4 Hz), 3.58 (1H, ddd, *J* = 12.2 Hz, 9.3 Hz, 5.4 Hz), 3.55 - 3.50 (2H, m), 3.28 (1H, ddd, *J* = 11.7 Hz, 9.3 Hz, 6.4 Hz), 2.09 - 2.01 (2H, m), 1.97 - 1.94 (2H, m), 1.93 - 1.88 (2H, m), 1.84 (1H, dt, *J* = 11.2 Hz, 4.9 Hz), 1.72 (1H, ddd, *J* = 12.7 Hz, 8.8 Hz, 5.9 Hz), 1.66 (3H, s), 1.65 - 1.60 (1H, m), 1.59 (3H, s), 1.57 (3H, s), 1.57 - 1.51 (3H, m), 1.31 (1H, ddd, *J* = 9.8 Hz, 5.9 Hz, 2.5 Hz), 1.24 (1H, s), 1.18 (1H, dt, *J* = 12.7 Hz, 4.4 Hz), 0.88 (18 H, s), 0.73 (3H, s), 0.07 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.6, 131.3, 124.9, 124.4, 74.0, 71.5, 48.1, 42.4, 39.7, 36.4, 34.9, 33.5, 29.7, 27.1, 26.7, 25.95, 25.91, 25.7, 21.2, 18.3, 18.0, 17.71, 17.67, 16.2, -3.7, -4.0, -4.4, -5.3; IR (neat): 2952.4 (m); 2928.8 (m), 2856.3 (m), 1254.7 (m), 1066.9 (s), 833.2 (s), 773.0 (s), 671.3 (w) cm^{-1}; HRMS-(ESI+) for [M+H] for $C_{32}H_{64}Br_1O_2Si_2$: calculated: 615.3628, found: 615.3606; $[\alpha]_D^{27}$= +41.20 (*c* = 1.455, $CHCl_3$, *l* = 10 mm).

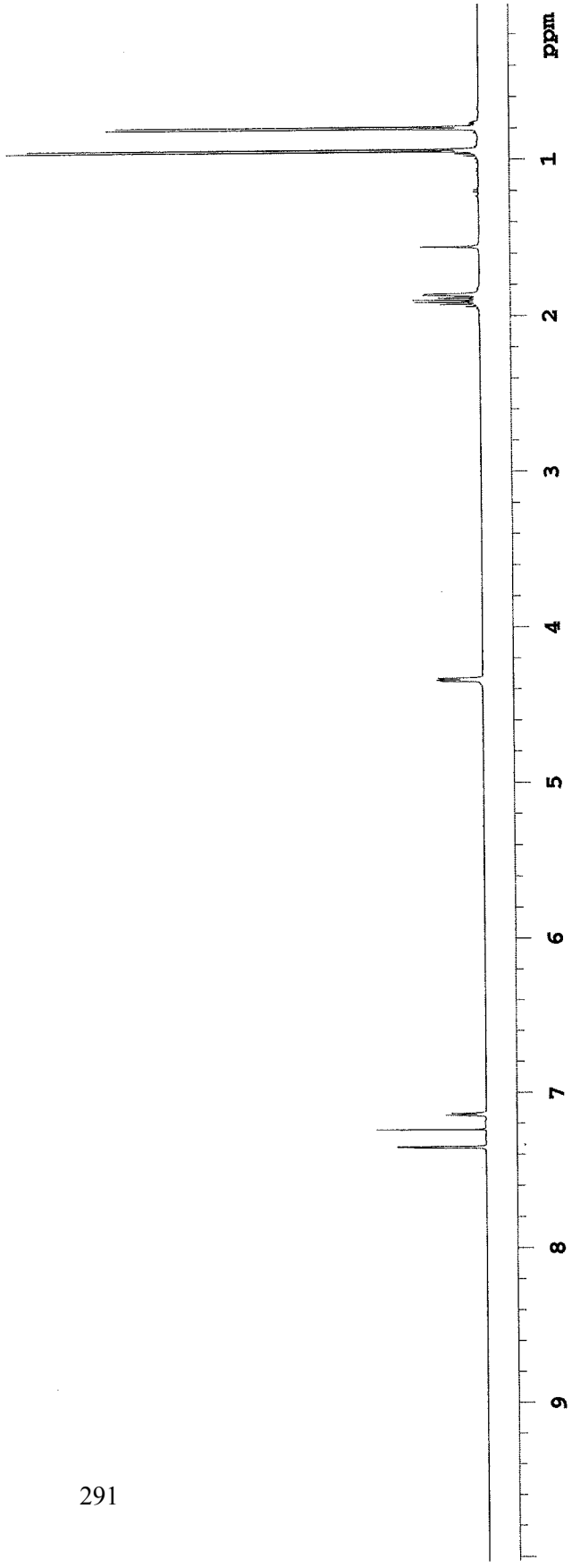


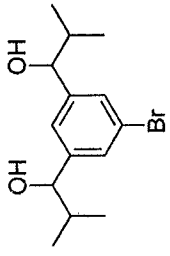
3-((1*R*,2*R*,3*S*,6*R*)-3,6-bis((*tert*-butyldimethylsilyl) oxy)-2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methylcyclohexyl)propan-1-ol (3.112): To a vial equipped with a stir bar was added **3.106** (200 mg, 0.298 mmol) and chlorobromomethane (25 μL, 0.387

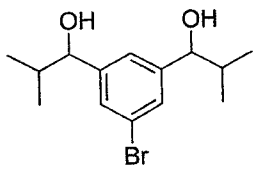
mmol). The vial was sealed with a septum, purged with N_2, and the oils were dissolved in THF (1.5 mL, 0.2 M). The solution was cooled to - 78 °C and *n*-butyllithium (0.17 mL, 2.29 M, 0.387 mmol) was added dropwise. The solution was stirred at this temperature for 10 minutes, then allowed to warm to room temperature and stirred for 12 hours. After cooling to 0 °C, the reaction mixture was oxidized by slow addition of pH 7 buffer (2 mL) and 30% H_2O_2 (1 mL). The mixture was allowed to slowly warm to room temperature and stir for an additional 8 hours. To quench the reaction, the solution was cooled to 0 °C and saturated aqueous sodium thiosulfate (2 mL) was added in a dropwise fashion. The mixture was transferred to a separatory funnel, extracted 3 x 20 mL ethyl acetate, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was purified on SiO_2 (40:1 - 10:1 pentane/ethyl acetate, R_f = 0.08 in 40:1 pentane/ethyl acetate, stain in PMA) to afford a colorless oil (57.7 mg, 34% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 (1H, dddd, *J* = 6.9 Hz, 6.9 Hz, 1.5 Hz, 1.5 Hz), 5.02 (1H, t, *J* = 5.9 Hz), 3.59 (1H, dt, *J* = 6.4 Hz, 2.4 Hz), 3.55 - 3.50 (2H, m), 2.06 - 2.01 (2H, m), 1.96 - 1.93 (2H, m), 1.91 - 1.81 (2H, m), 1.76 - 1.62 (3H, m), 1.66 (3H, s), 1.60 - 1.53 (4H, m), 1.58 (3H, s), 1.56 (3H, s), 1.50 (1H, dt, *J* = 8.3 Hz, 4.4 Hz), 1.43 - 1.36 (1H, m). 1.29 - 1.18 (3H, m), 0.88 (9H, s), 0.87 (9H, s), 0.74 (3H, s), 0.05 (6H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.4, 131.2, 125.2, 124.4, 73.9, 71.8, 63.1, 46.6, 42.8, 39.7, 36.5, 34.7, 29.9, 27.2, 26.7, 26.0, 25.9, 25.7, 23.7, 21.2, 18.1, 18.0, 17.7, 16.2, -3.7, -4.1, -4.3, -5.3 ; IR (neat): 3337.2 (br w), 2928.5 (m), 2856.4 (m), 1461.9 (2), 1254.2 (m), 1066.5 (s). 833.9 (s), 772.3 (s), 670.6 (w) cm^{-1}; HRMS-(ESI+) for $C_{33}H_{67}O_3Si_2$ [M+H] : calculated: 567.4629, found: 567.4622; $[\alpha]_D^{28}$= +4.65 (*c* = 2.150, $CHCl_3$, *l* = 10 mm).

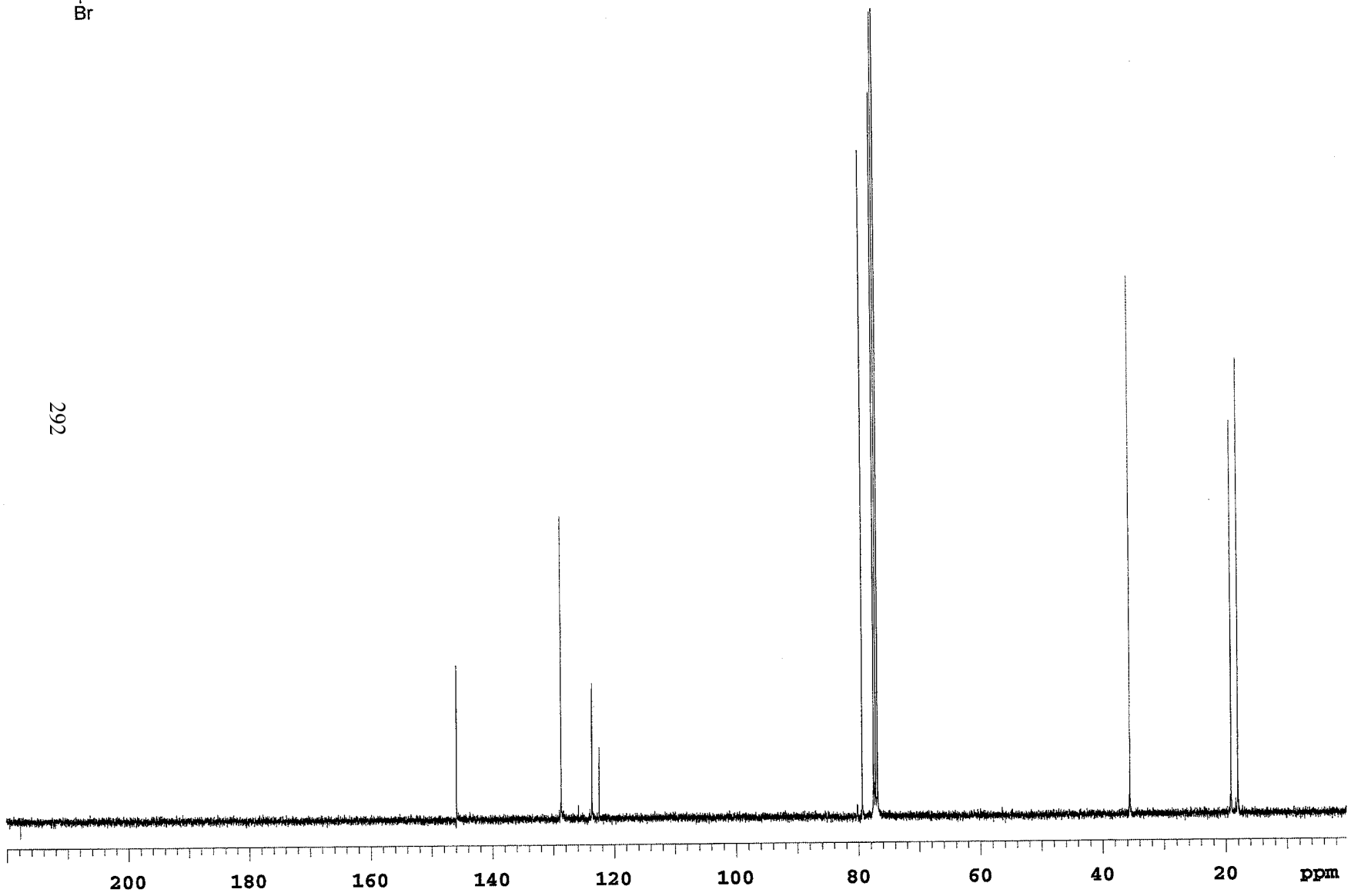
APPENDIX

Representative ^{1}H, ^{13}C, NOESY, and COSY Spectra


ppm
1
2
3
4
5
6
7
8
9


OH
Br
OH


OH
OH
Br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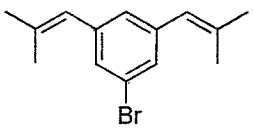
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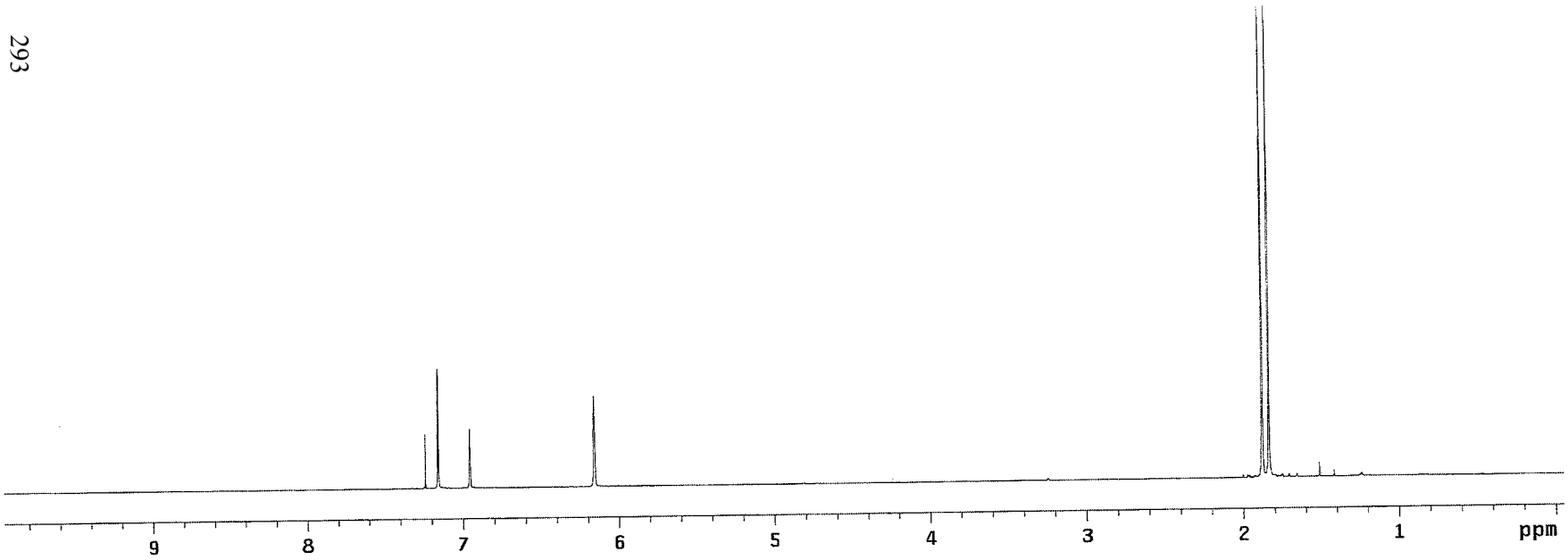
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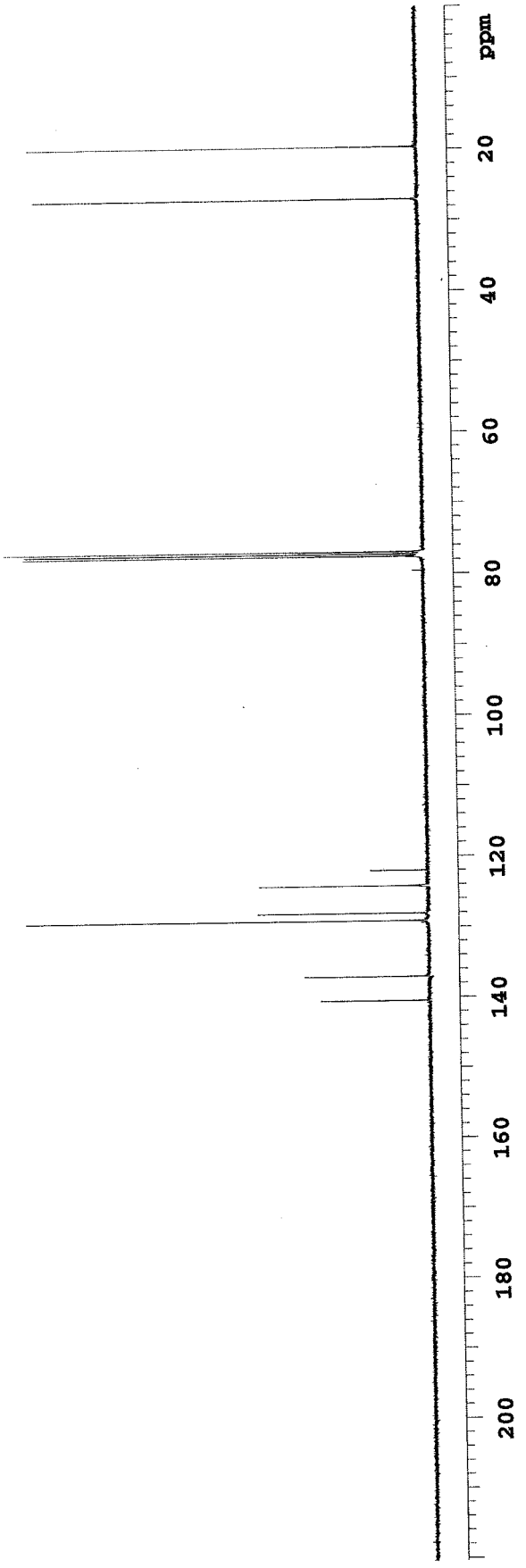
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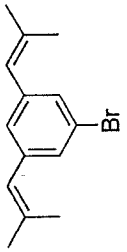
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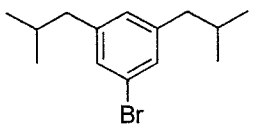
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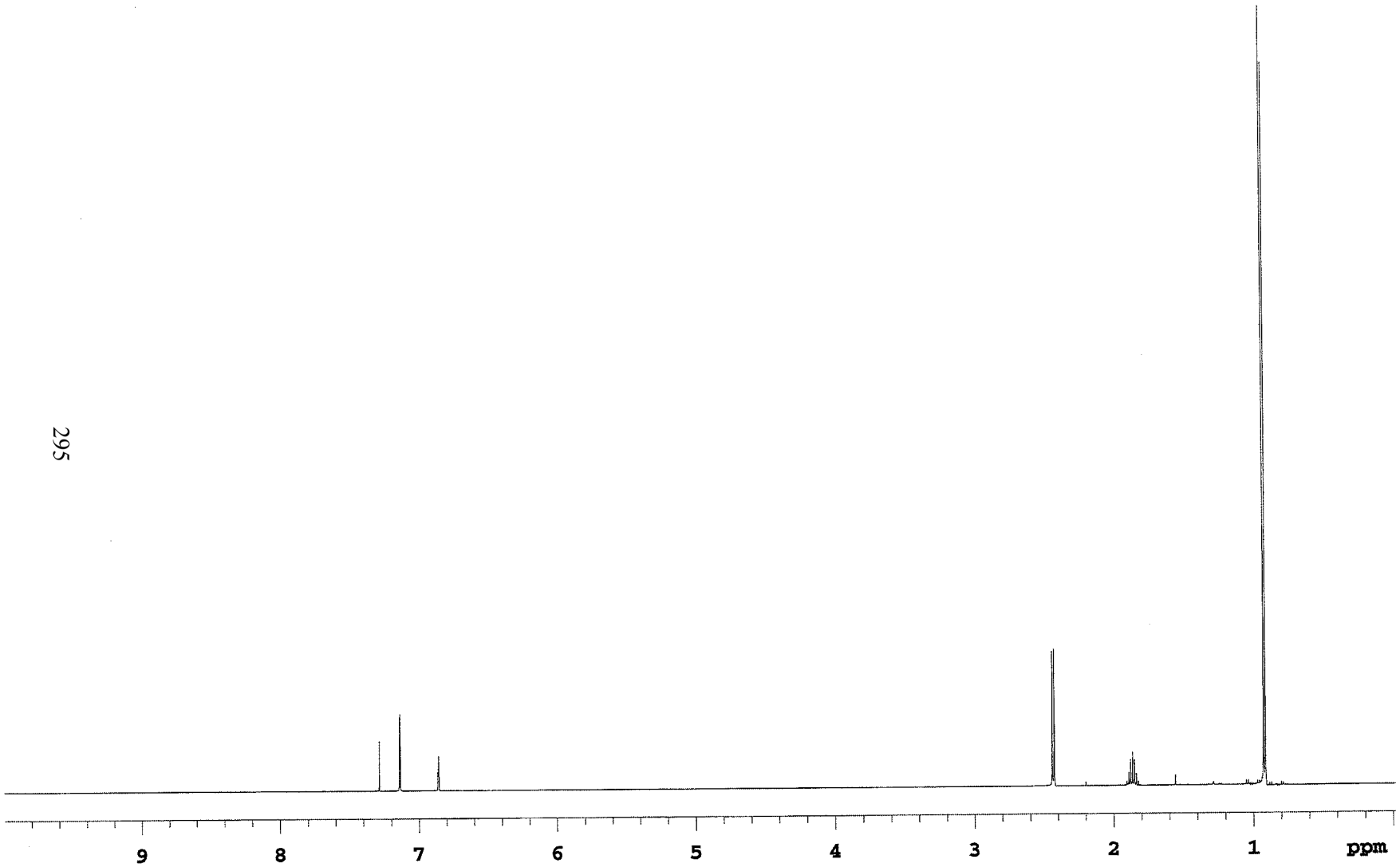
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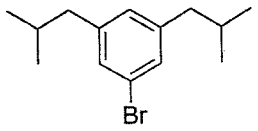
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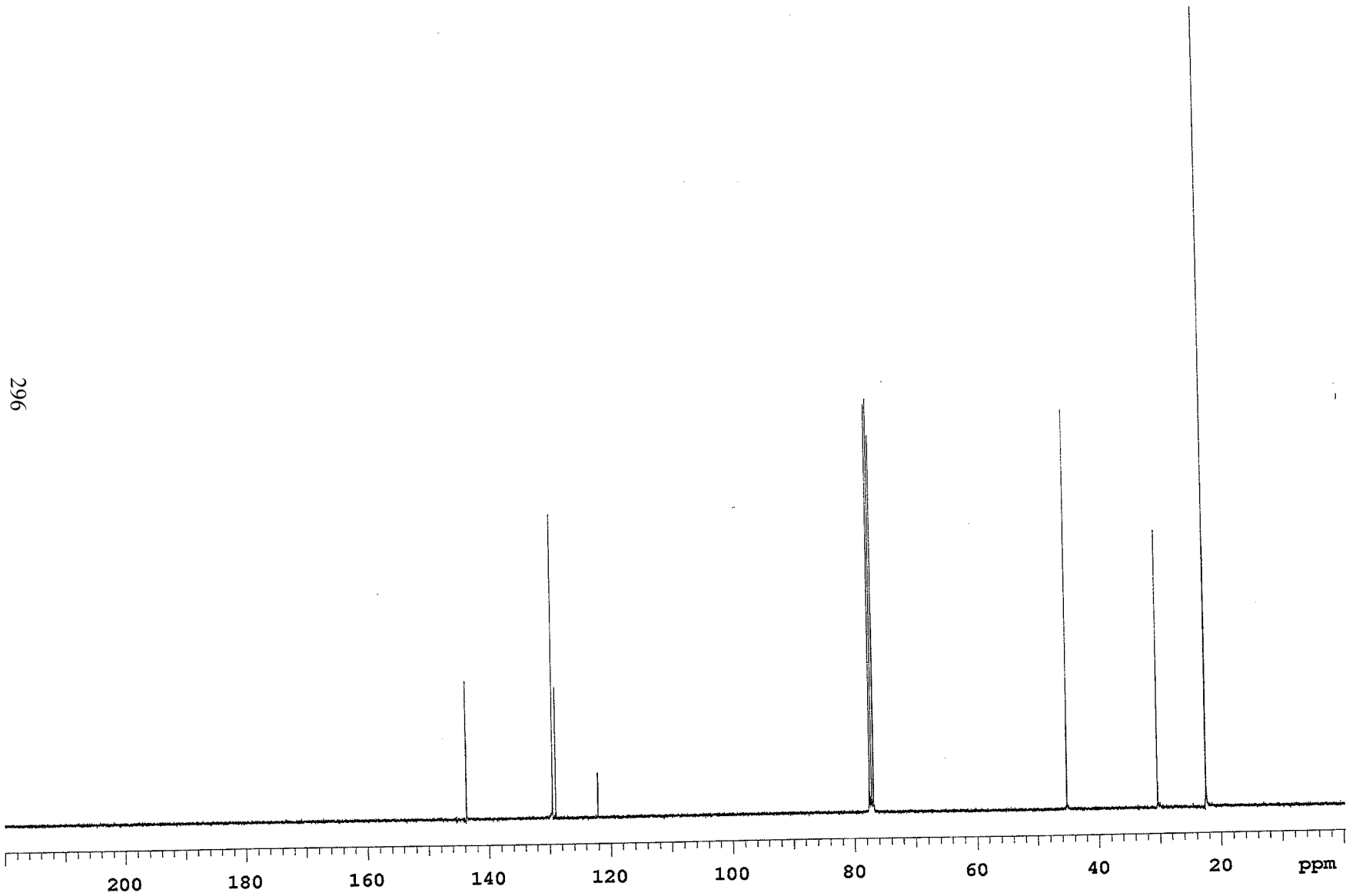
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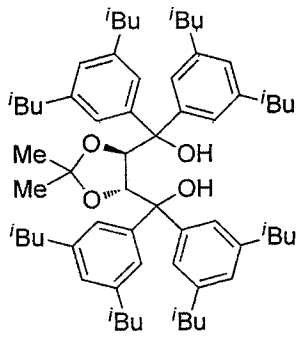
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iBu
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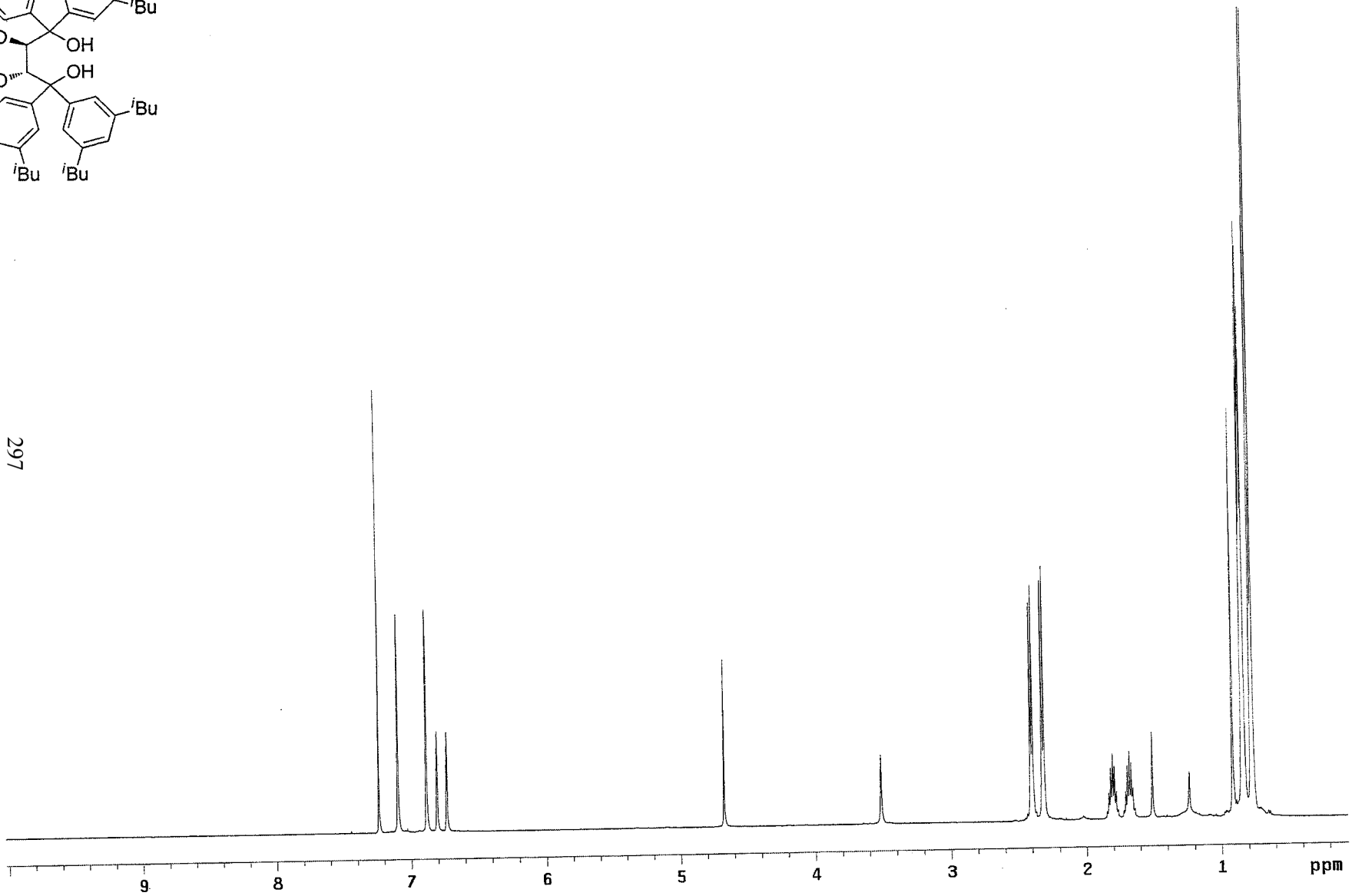
iBu
Me
Me
O
O
OH
OH
iBu
iBu
iBu
iBu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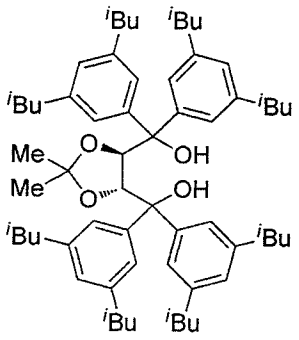
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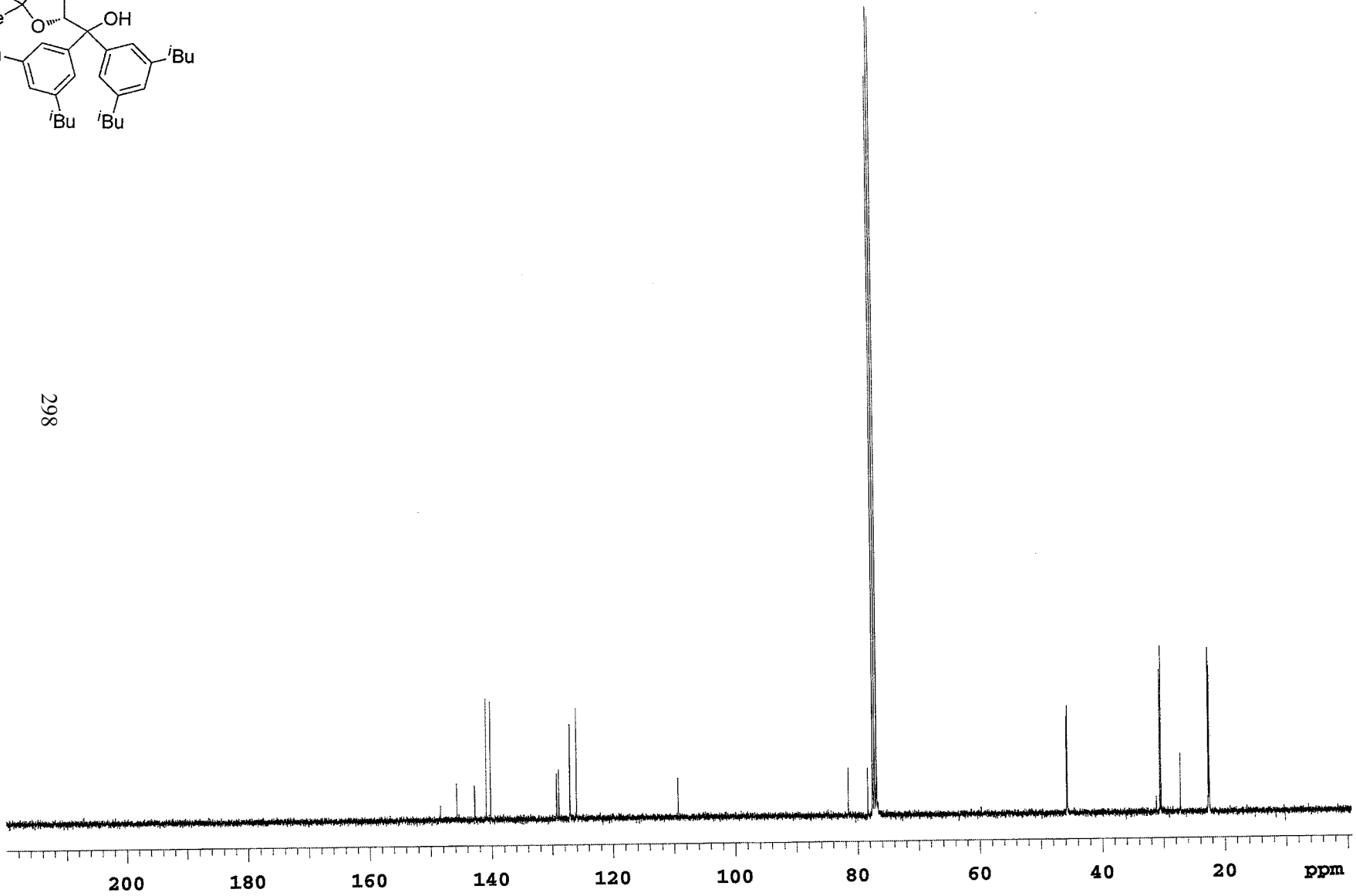
iBu
iBu
iBu
Me
Me
O
O
OH
OH
iBu
iBu
iBu
iBu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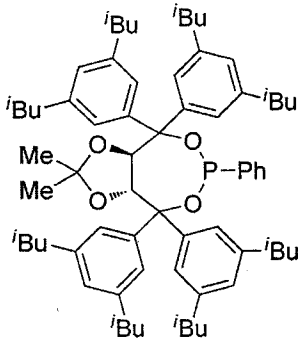
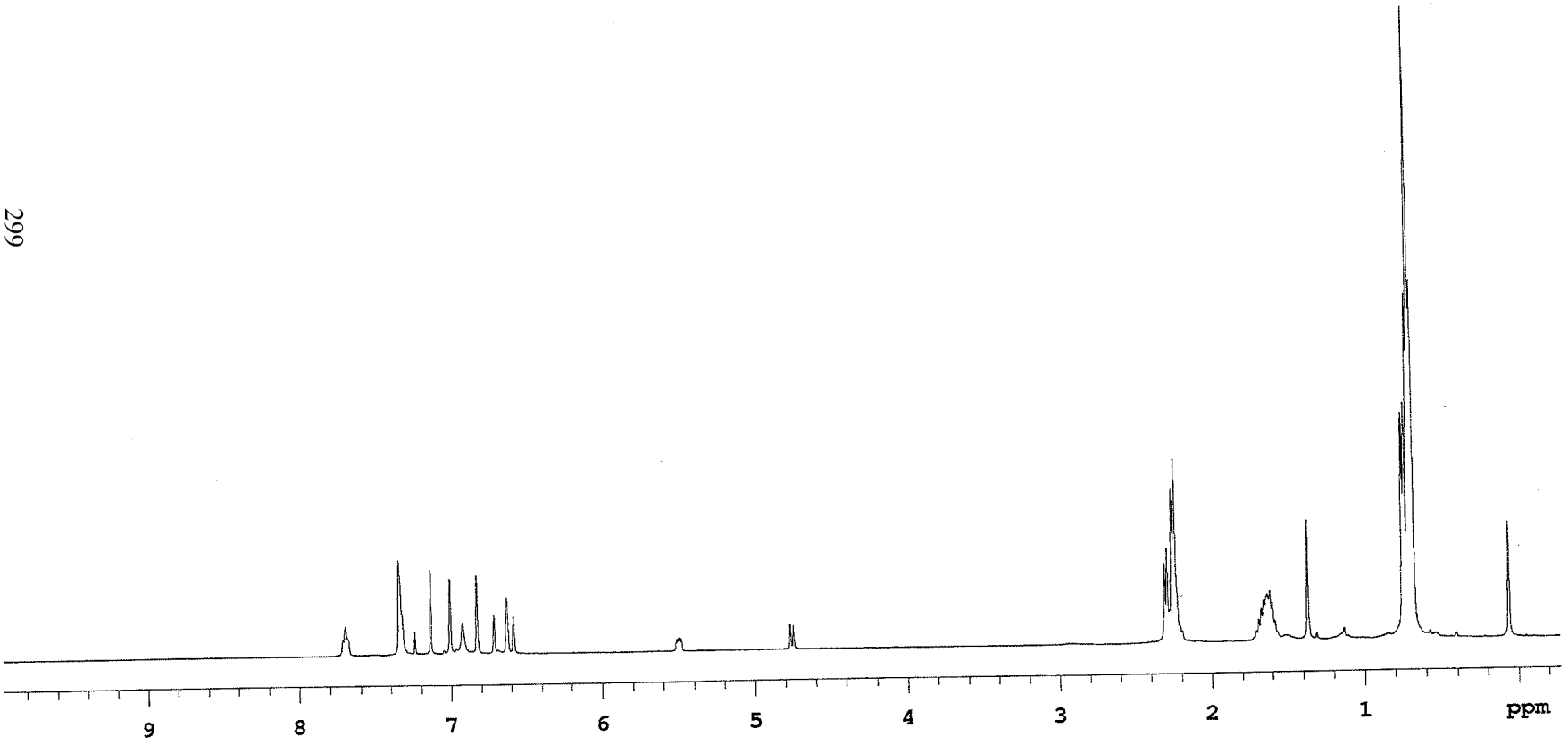

iBu
iBu
iBu
iBu
Me
Me
O
O
O
O
P–Ph
iBu
iBu
iBu
iBu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3
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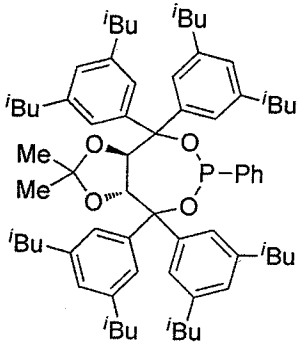
1
ppm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iBu
iBu
iBu
Me
Me
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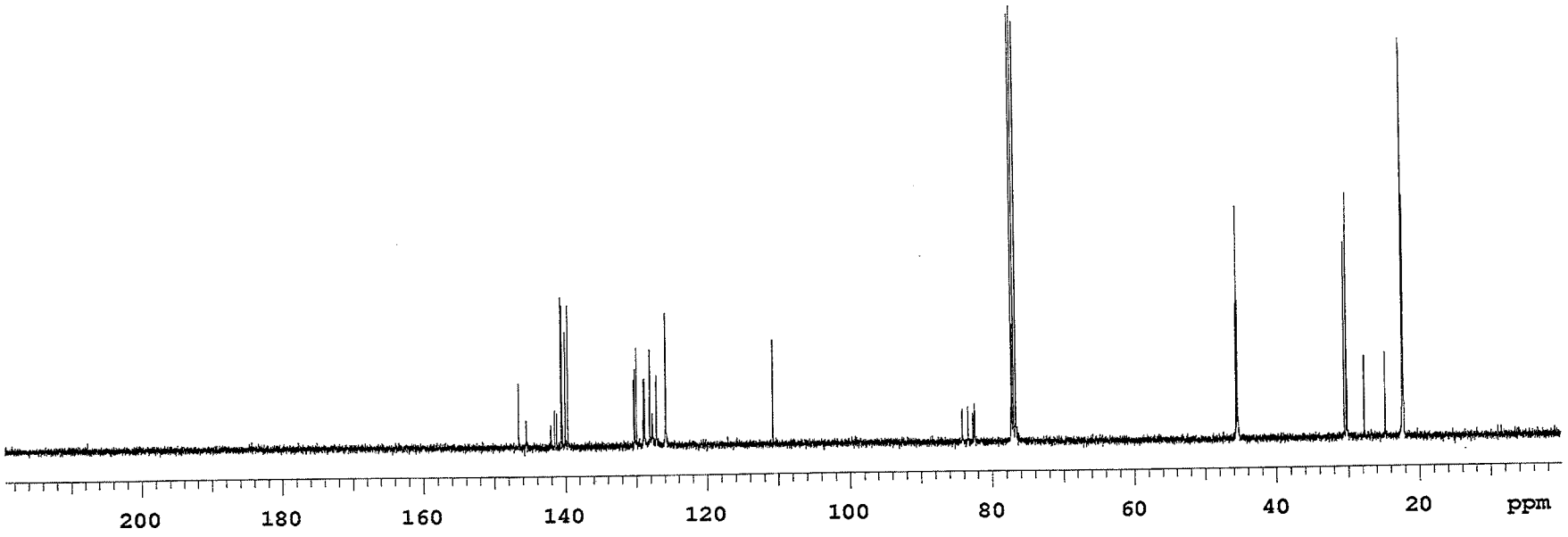
O
O
O
P–Ph
iBu
iBu
iBu
iBu

300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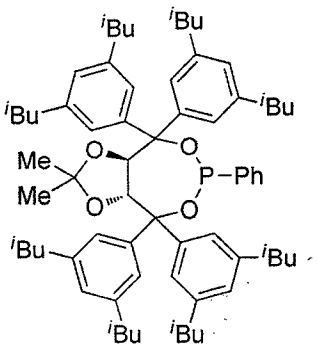
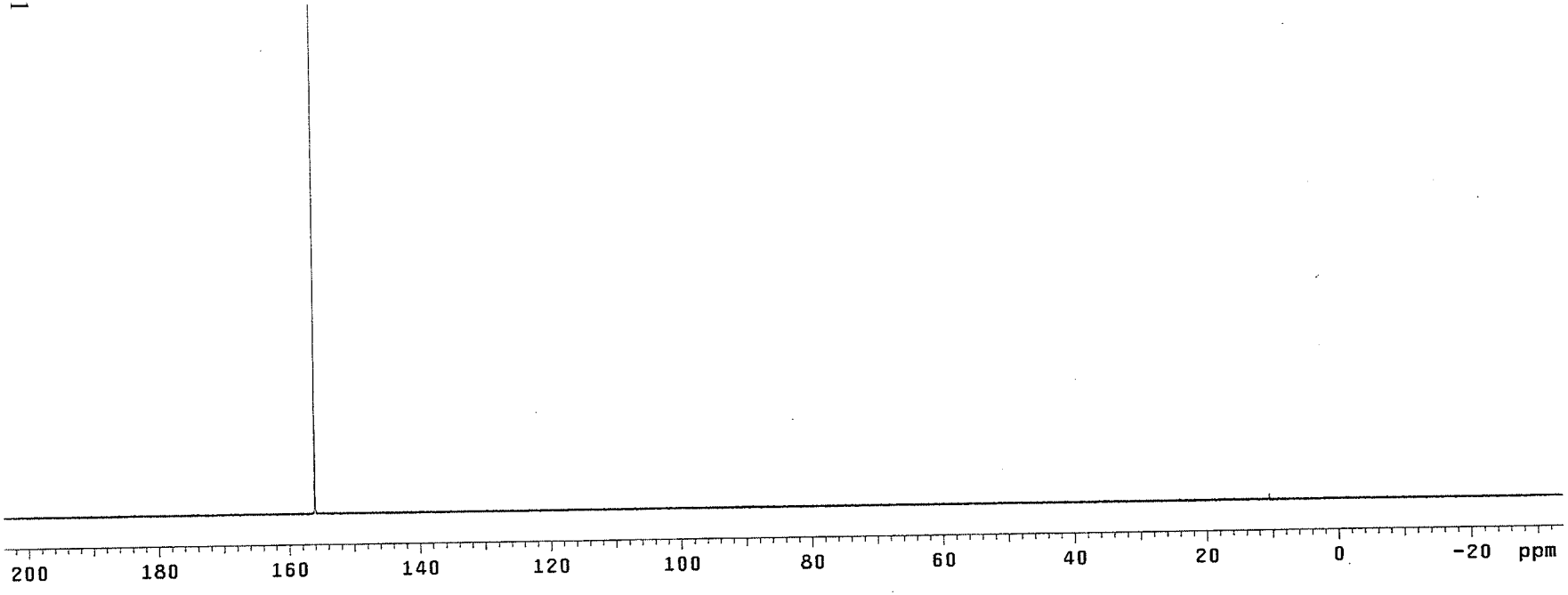
80
60
40
20
ppm


iBu
iBu
iBu
iBu
Me
Me
O
O
O
P–Ph
O
iBu
iBu
iBu
iBu

301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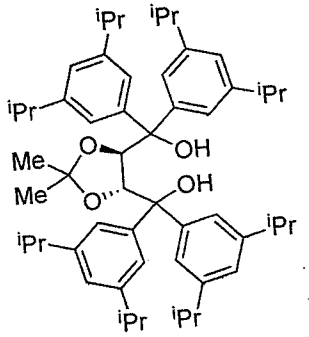
-20
ppm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iPr
iPr
iPr
Me
Me
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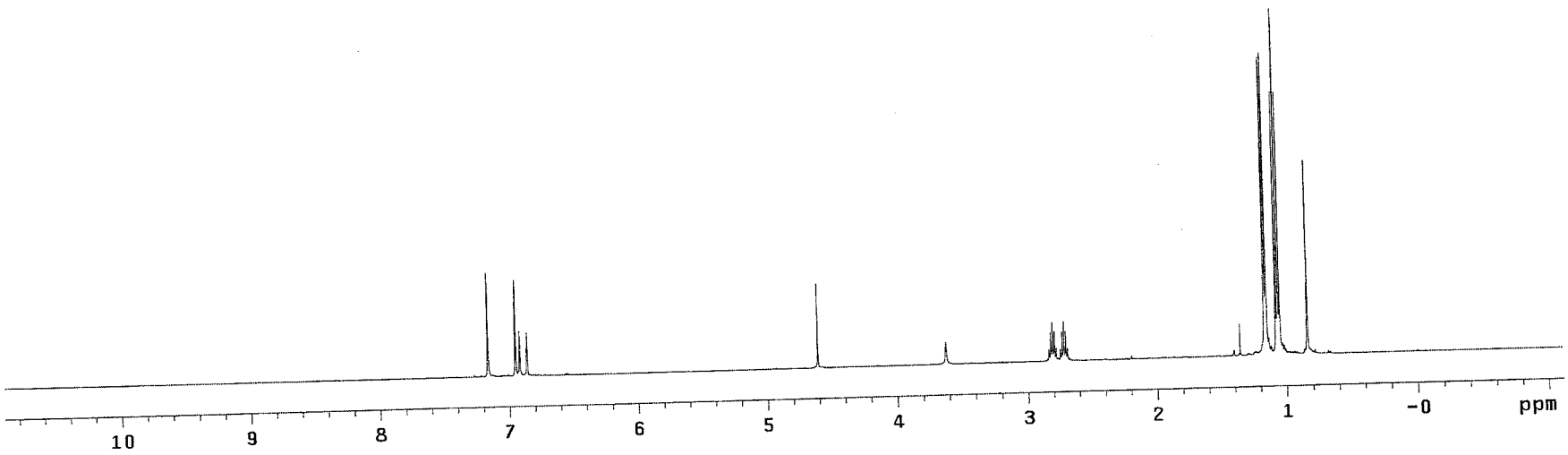
O
OH
OH
iPr
iPr
iPr
iPr
iPr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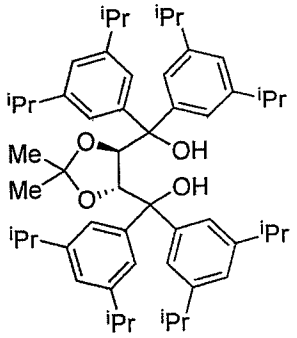
6
5
4
3
2
1
-0
ppm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iPr
iPr
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Me
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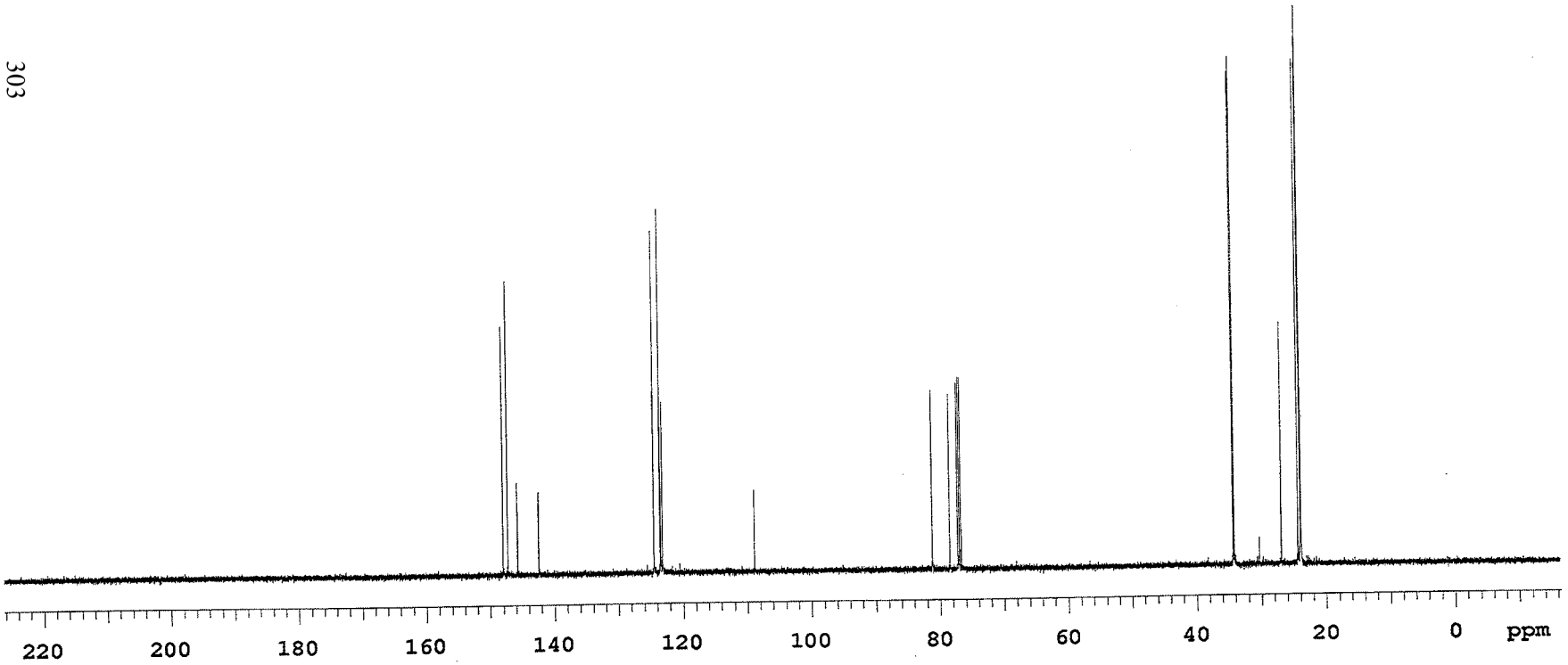
O
OH
OH
iPr
iPr
iPr
iPr

303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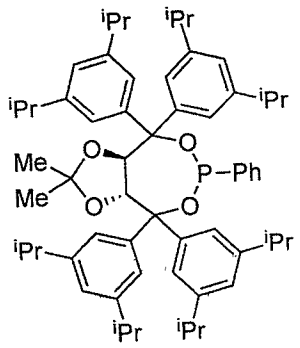
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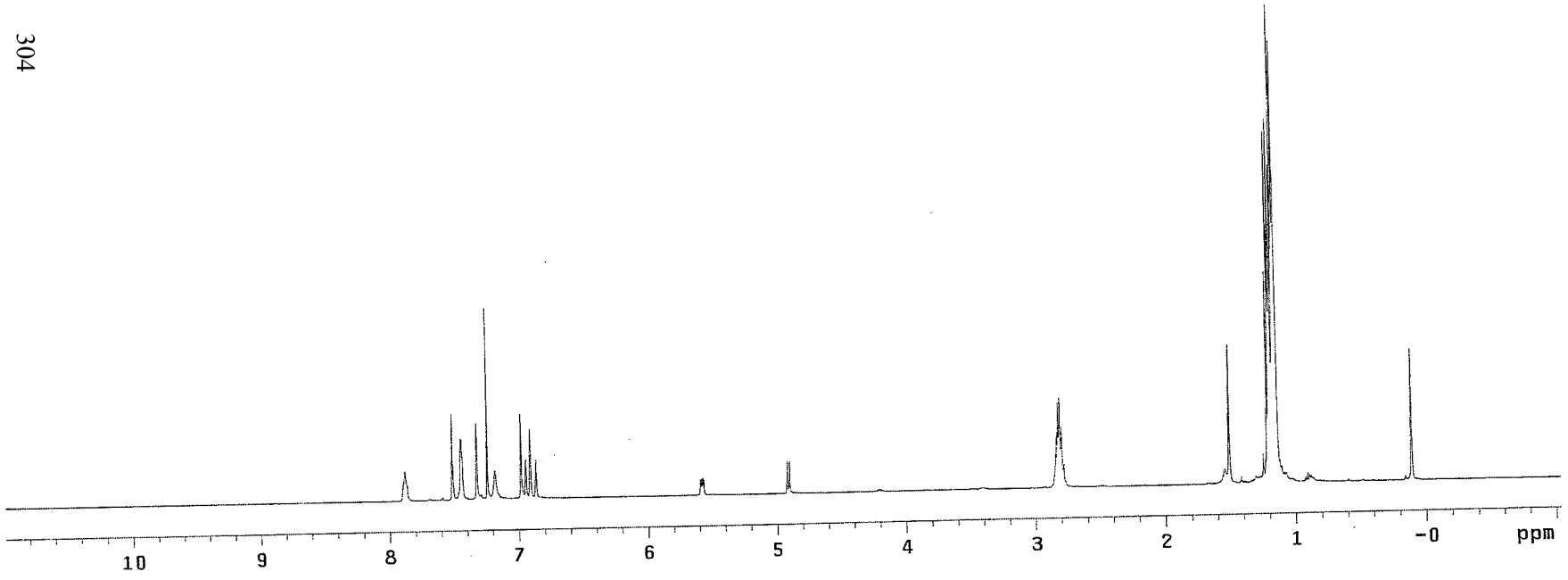
iPr
iPr
iPr
Me
Me
O
O
O
O
P–Ph
iPr
iPr
iPr
iPr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8
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6
5
4
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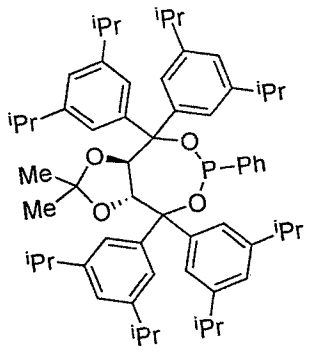
-0
ppm


iPr
iPr
iPr
iPr
Me
Me
O
O
P–Ph
O
O
iPr
iPr
iPr
iPr
iPr

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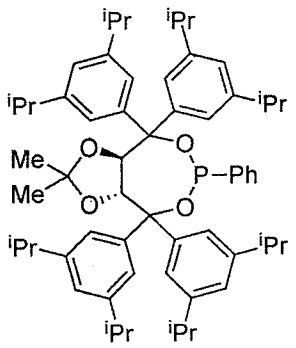
200
180
160
140
120
100
80
60
40
20
0
ppm


iPr
iPr
iPr
iPr
Me
Me
O
O
O
O
P–Ph
iPr
iPr
iPr
iPr

200
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100
80
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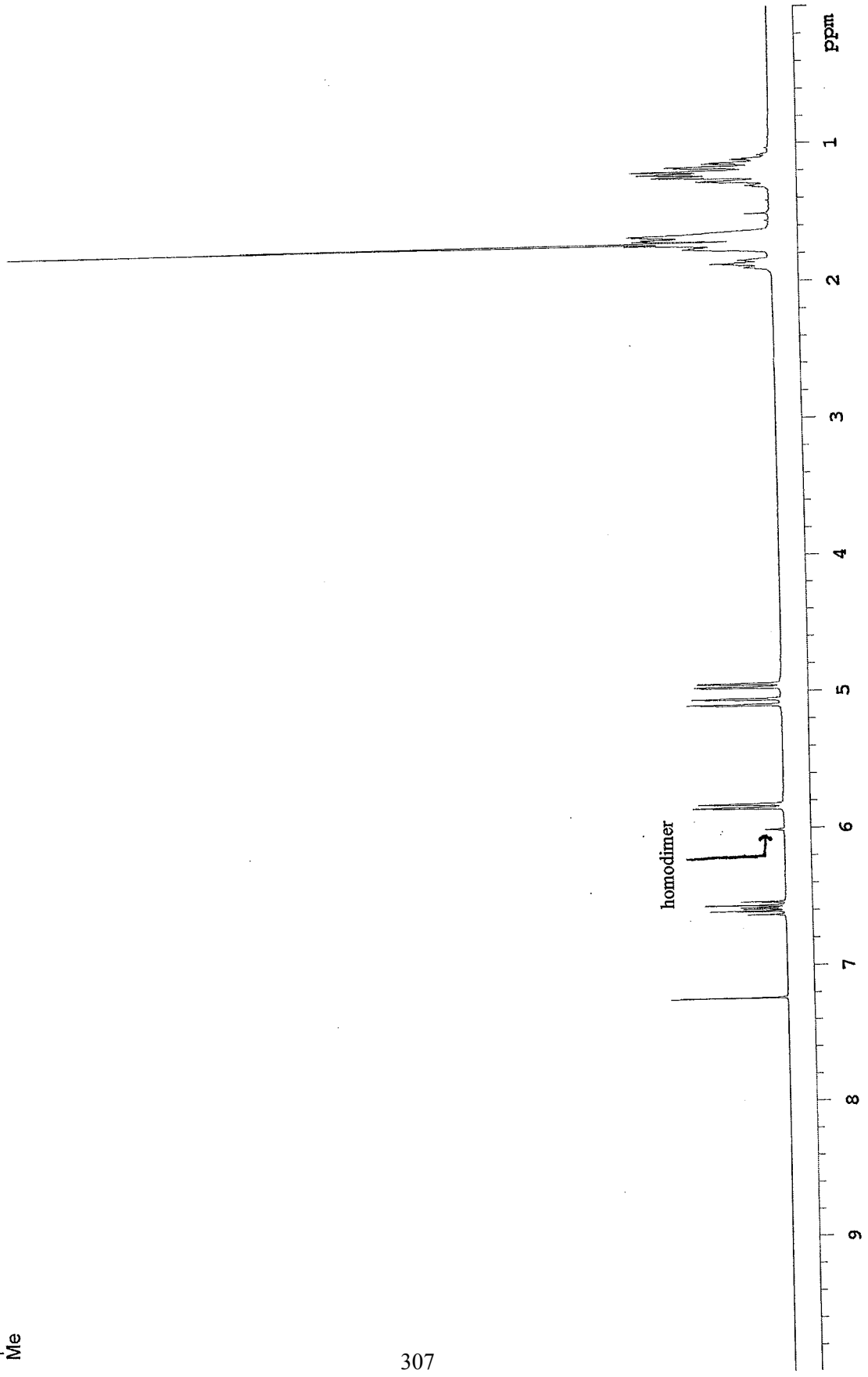
20
0
-20
ppm


homodimer
ppm
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2
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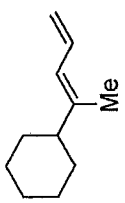
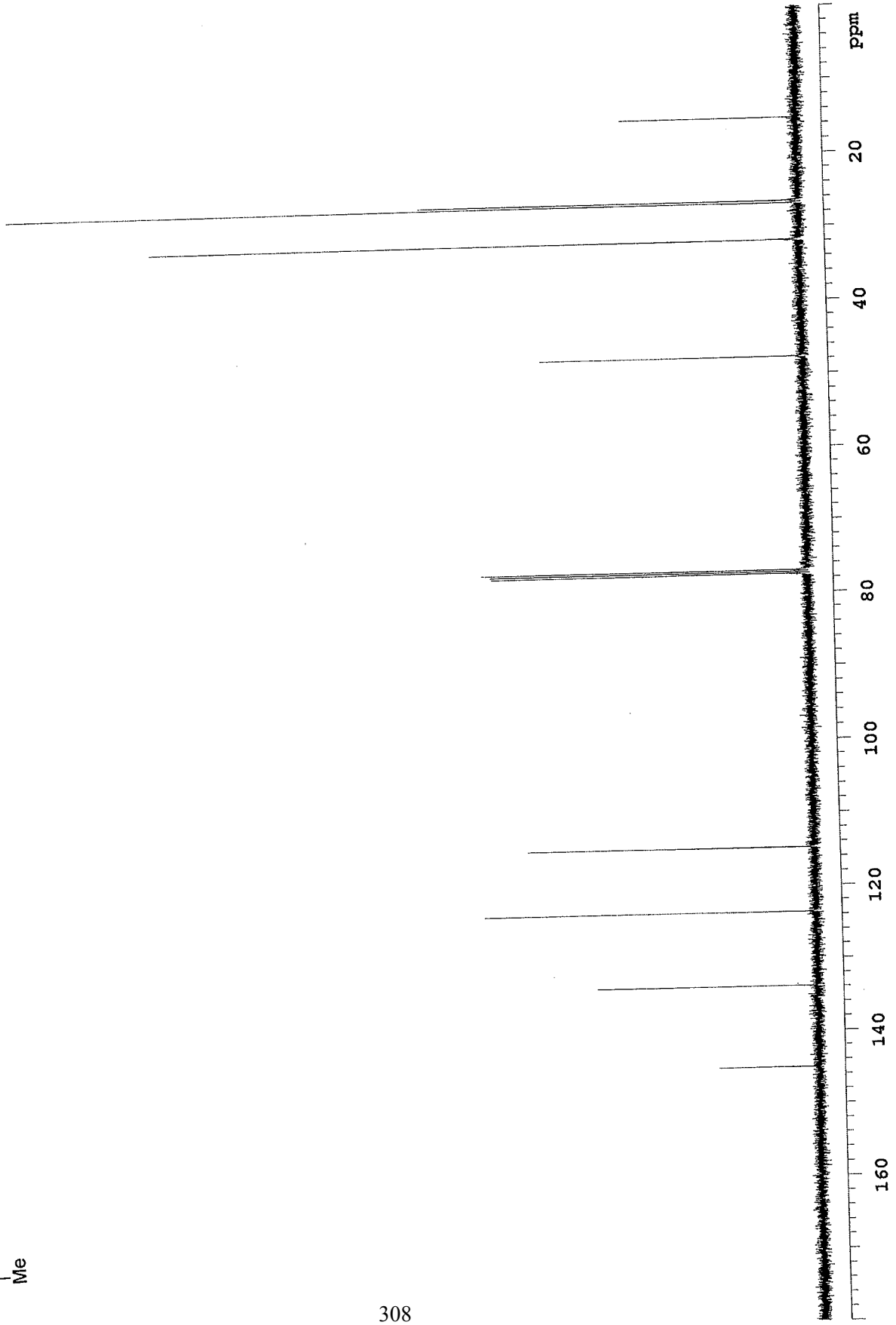
6
7
8
9


Me


ppm
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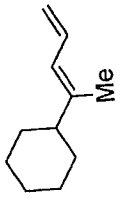
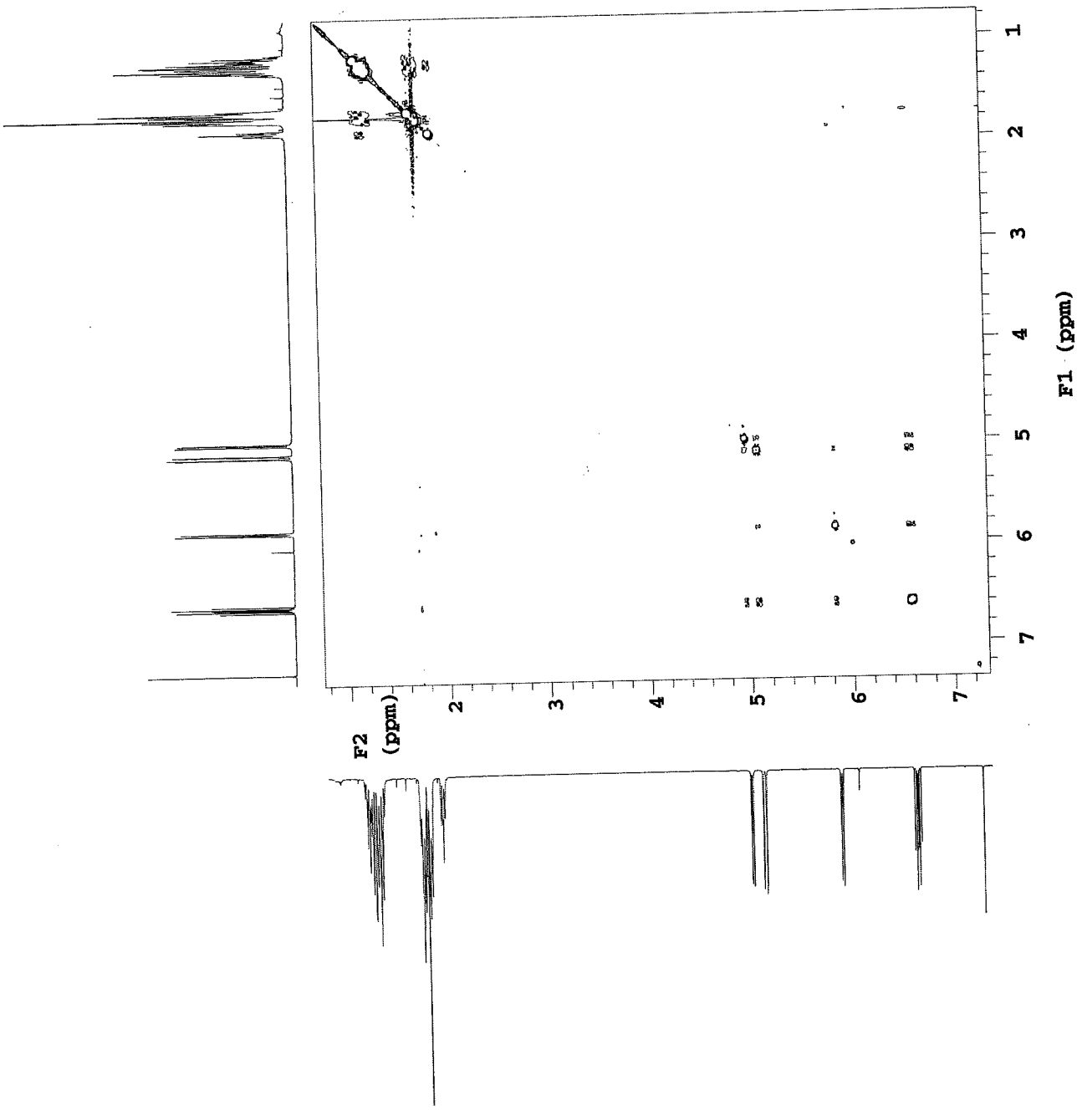
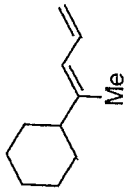
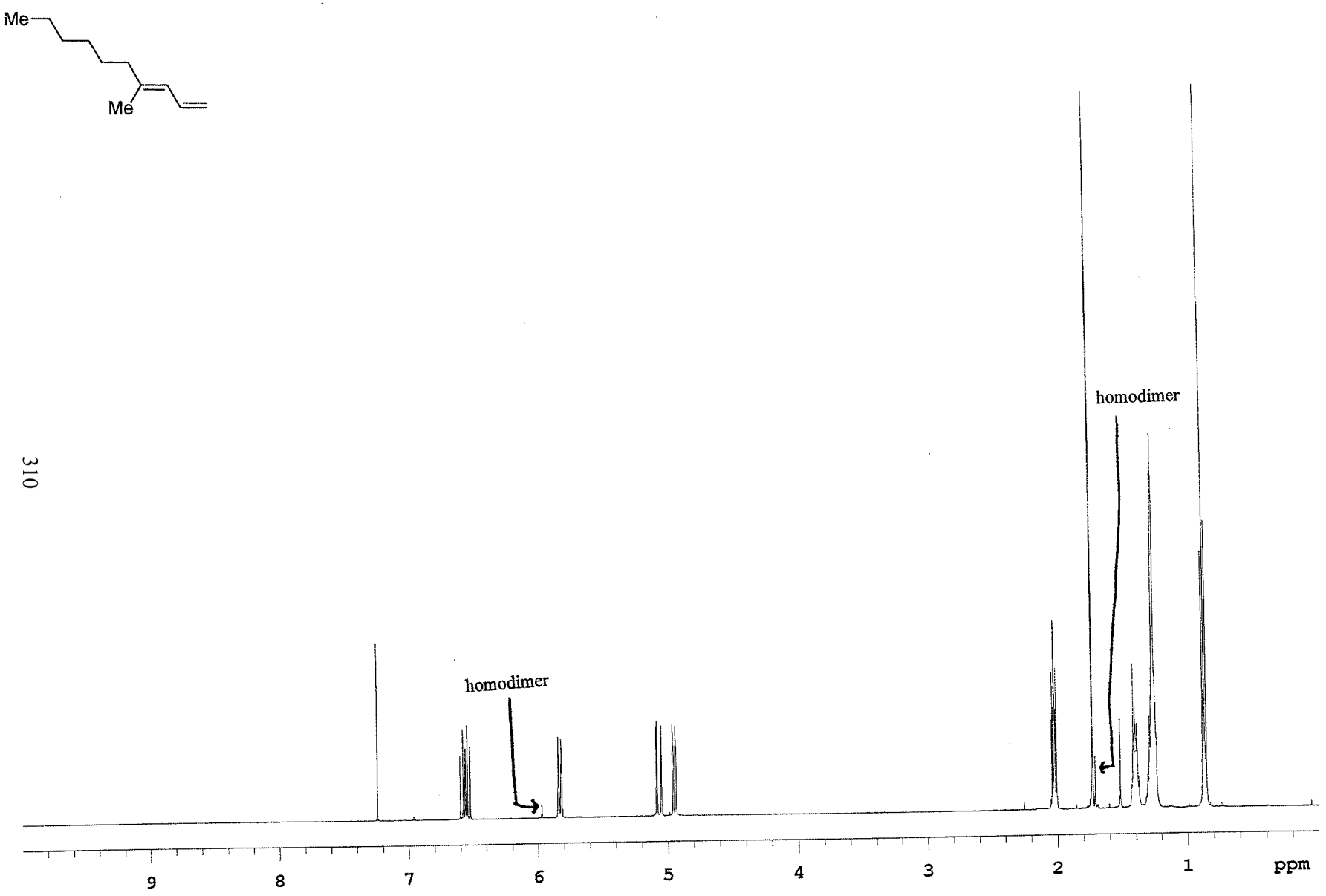
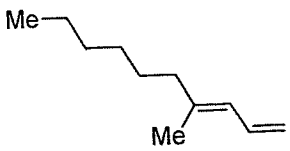
40
60
80
100
120
140
160

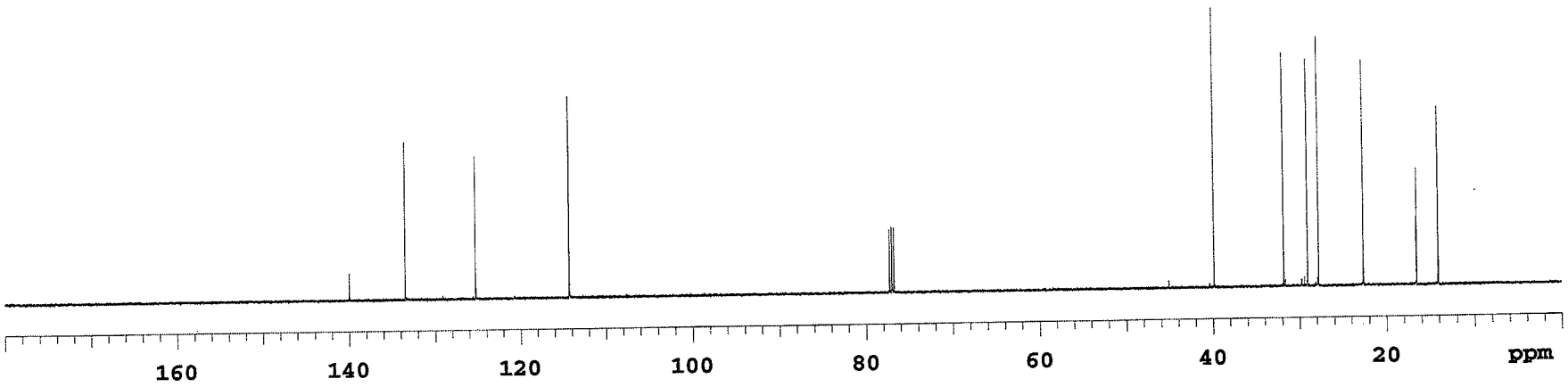

Me


F2 (ppm)
F1 (ppm)


Me


Me
Me
homodimer
homodimer
9
8
7
6
5
4
3
2
1
ppm


Me
Me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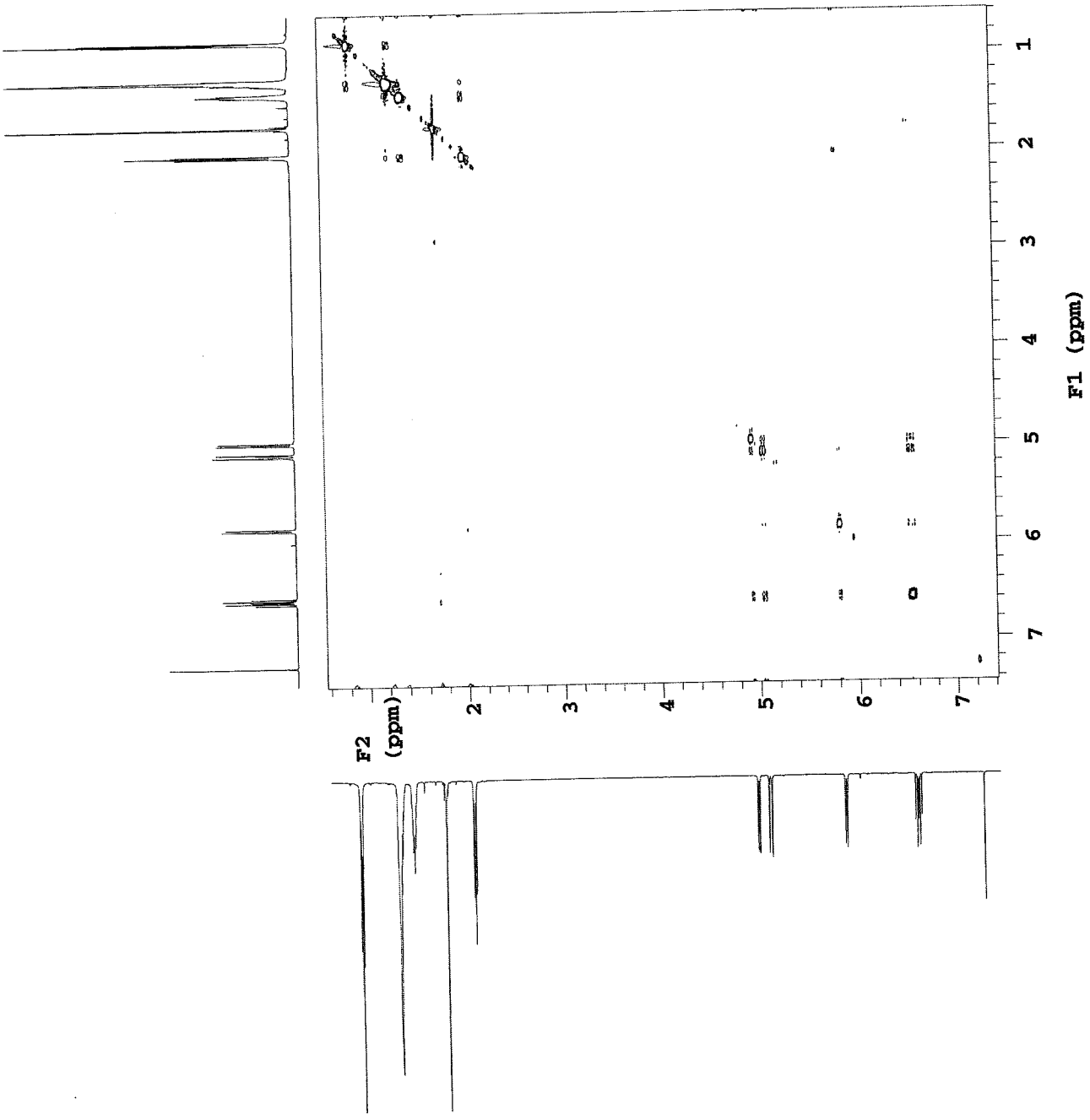
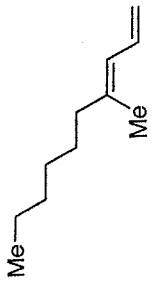
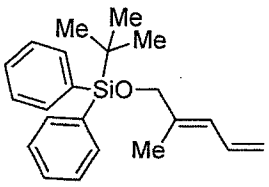
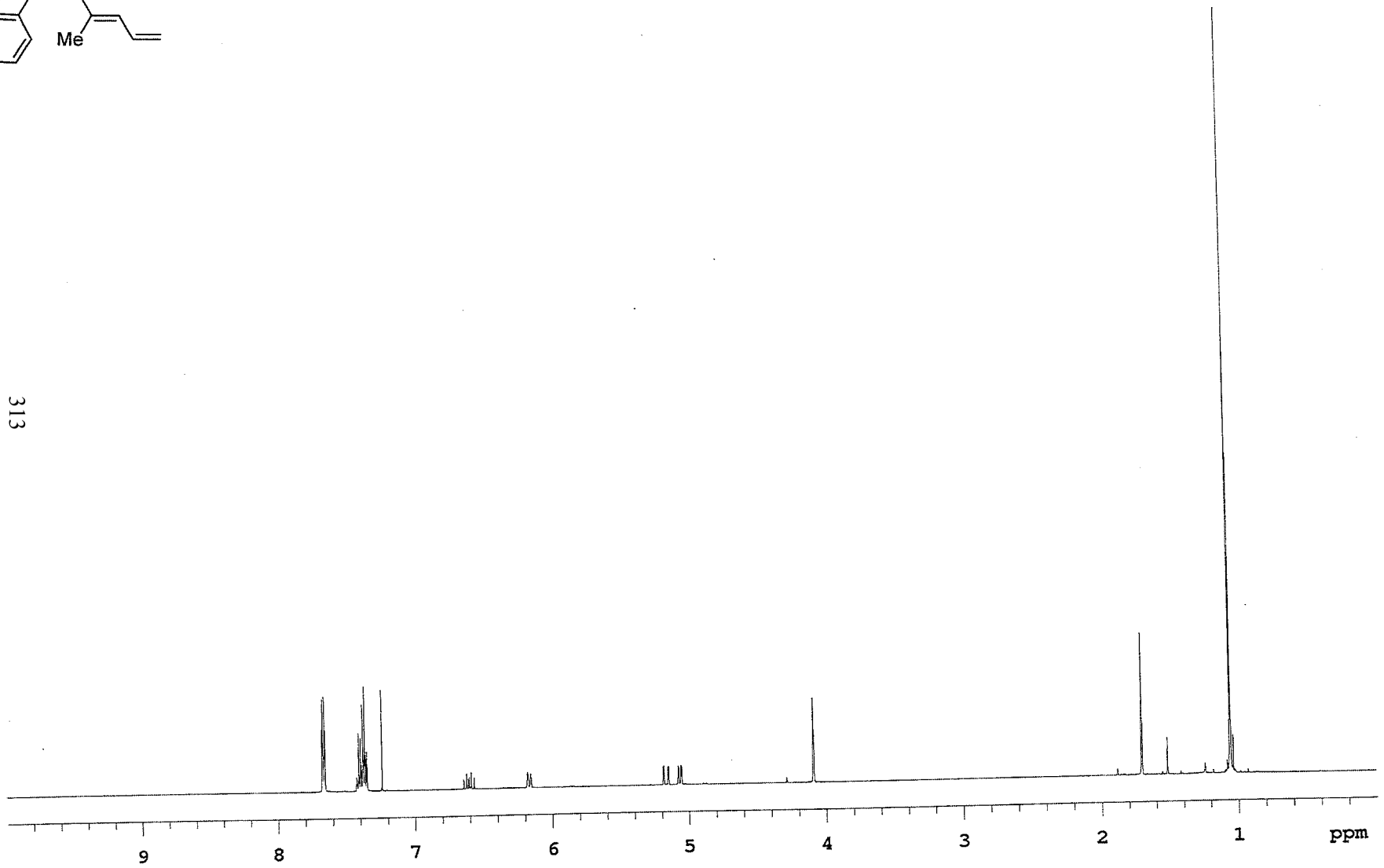
60
40
20
ppm


F2 (ppm)
F1 (ppm)
1
2
3
4
5
6
7


Me
Me


Me
Me
Me
SiO
Me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4
3
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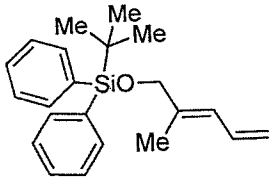
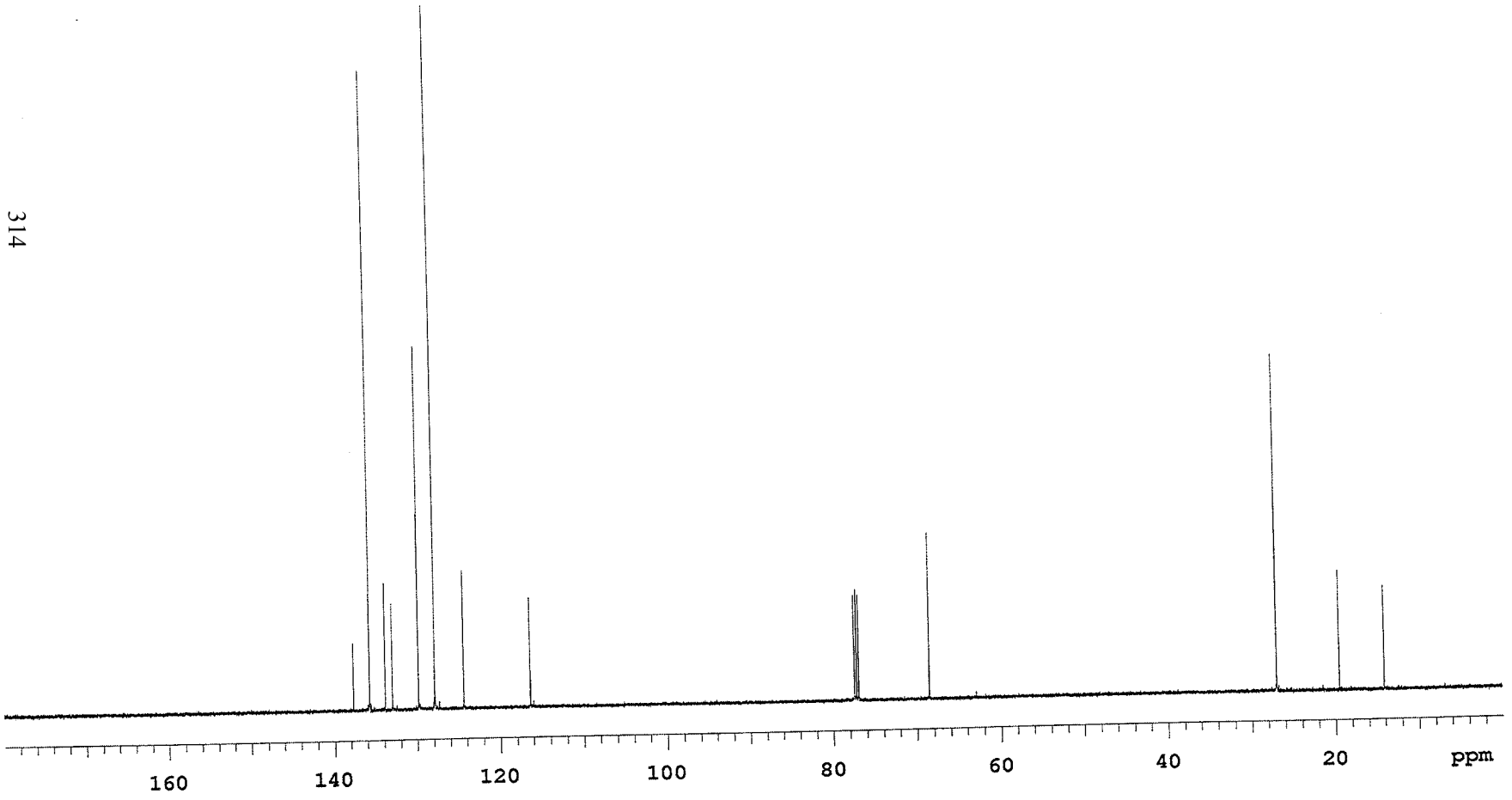
1
ppm


Me
Me
Me
SiO
Me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100
80
60
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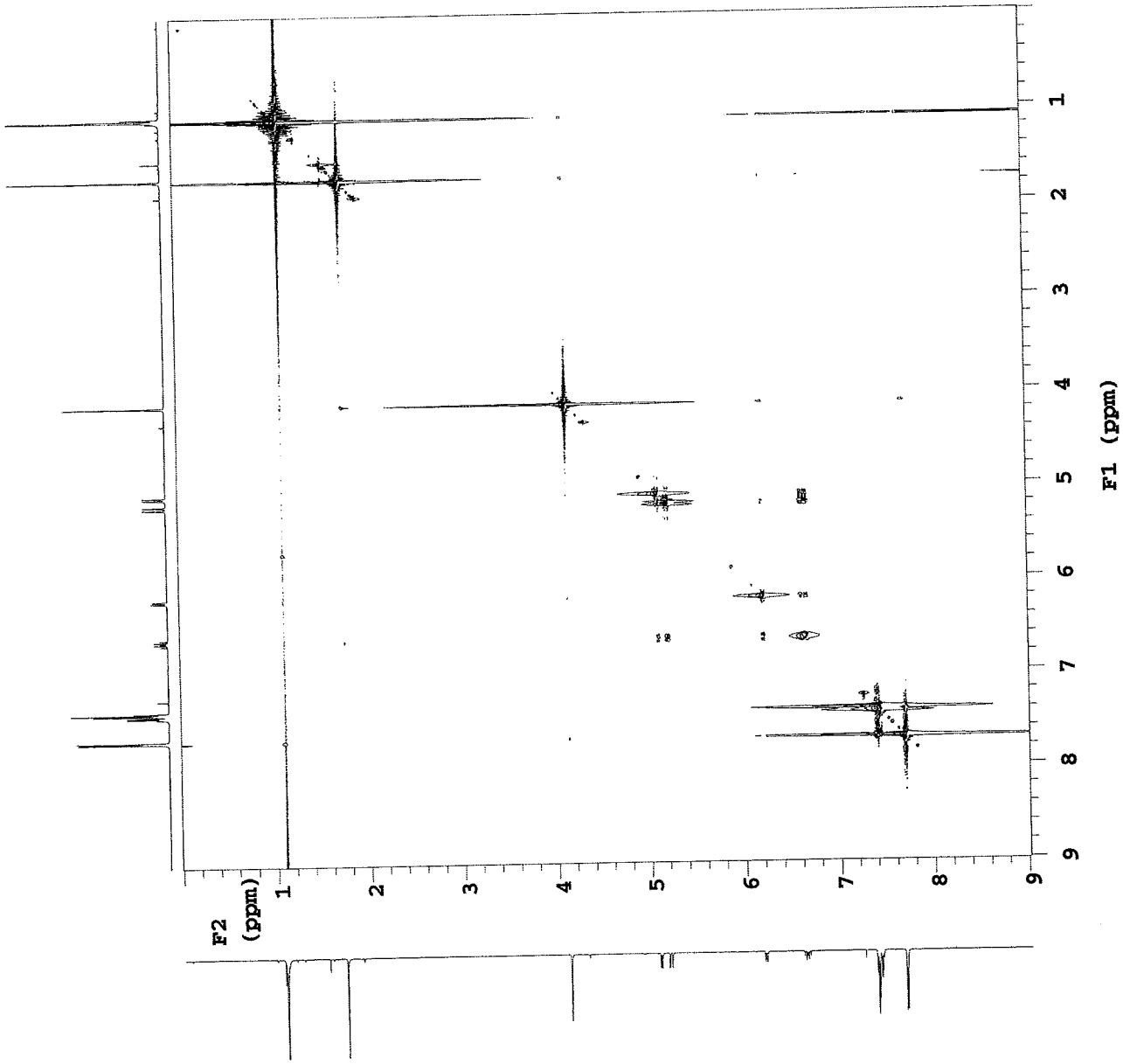
20
ppm


F2 (ppm)
F1 (ppm)
1
2
3
4
5
6
7
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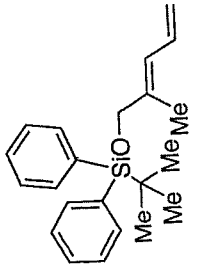
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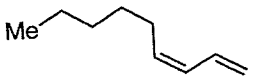
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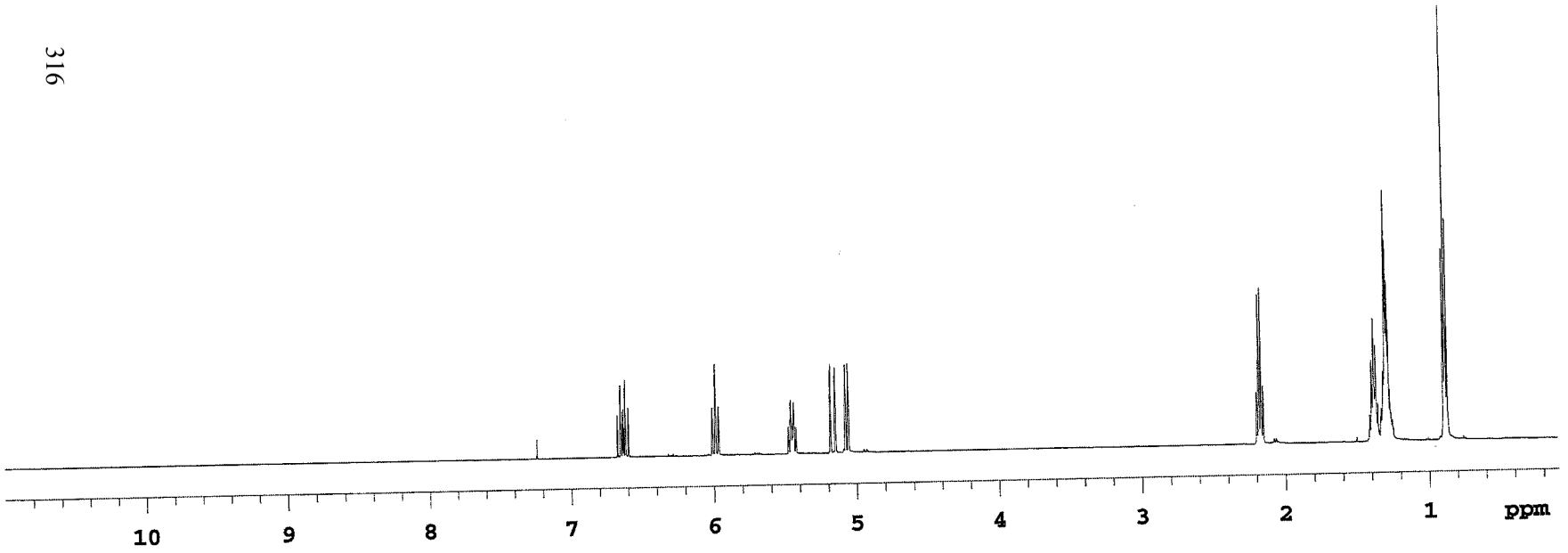
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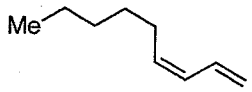
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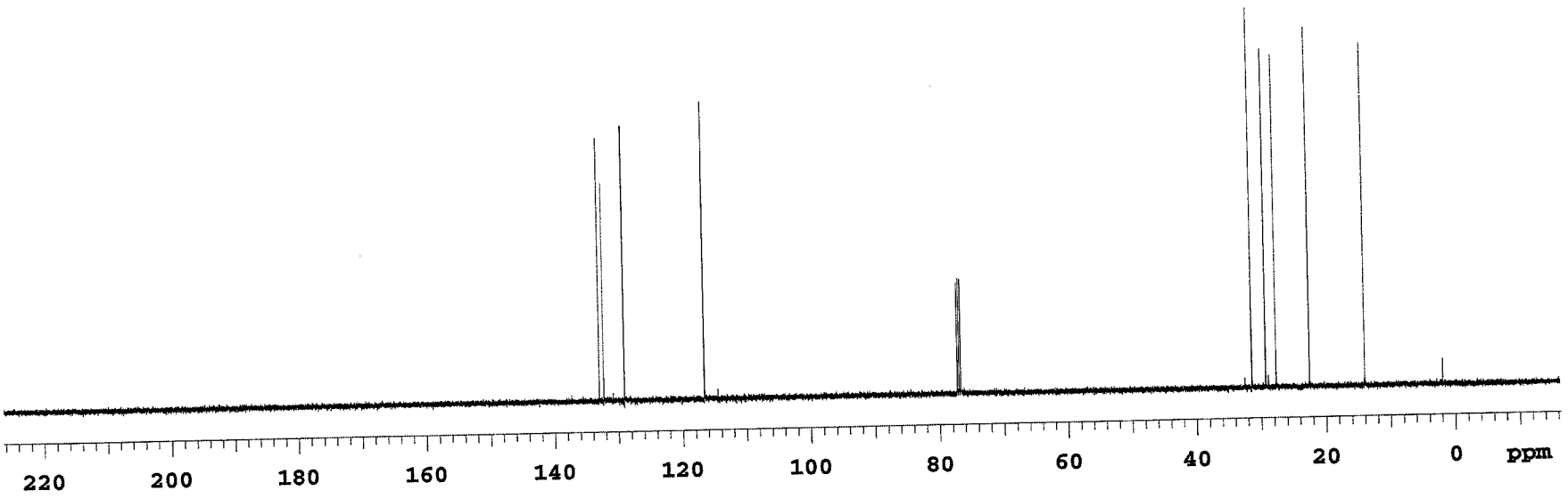
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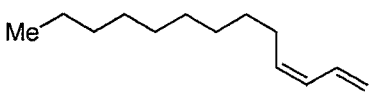
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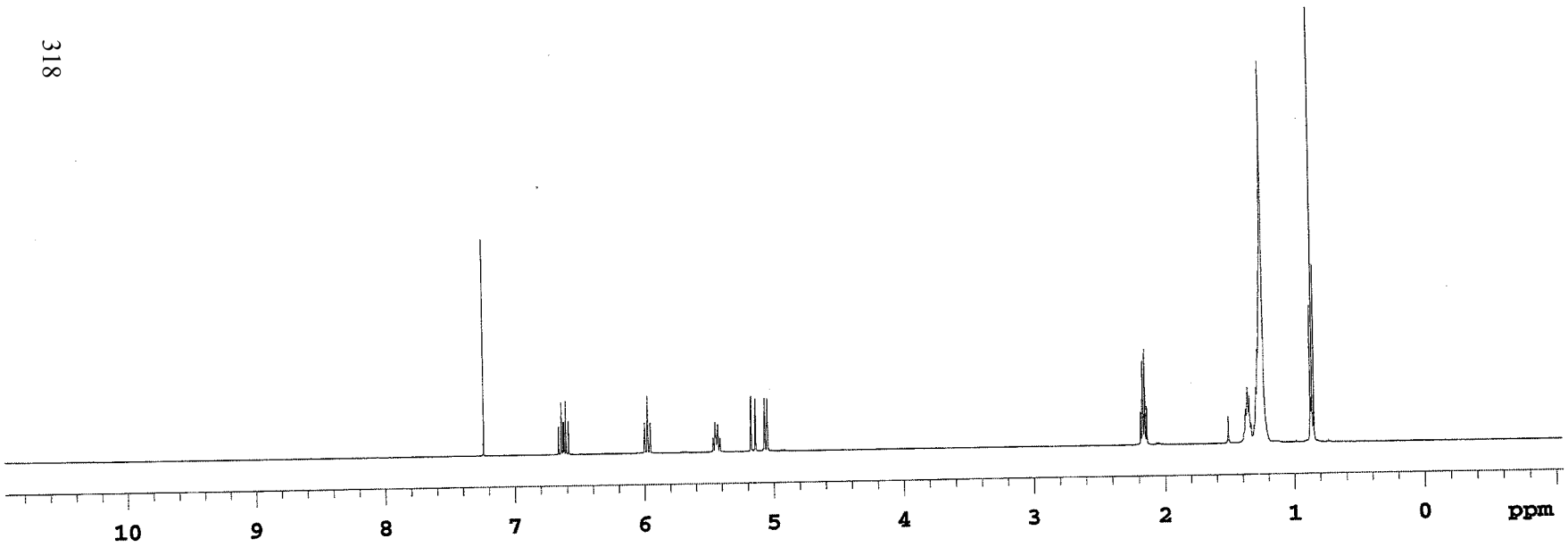
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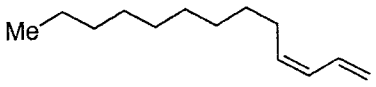
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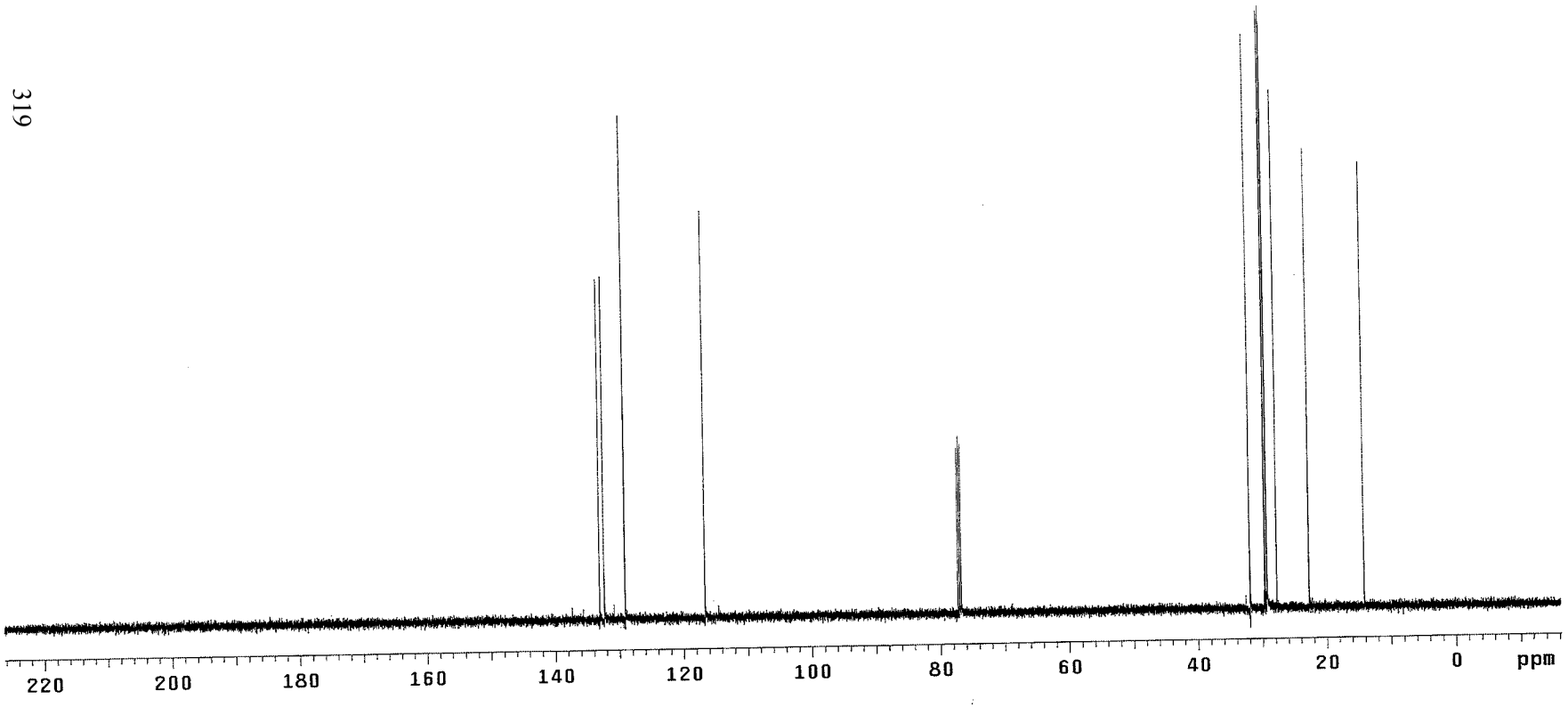
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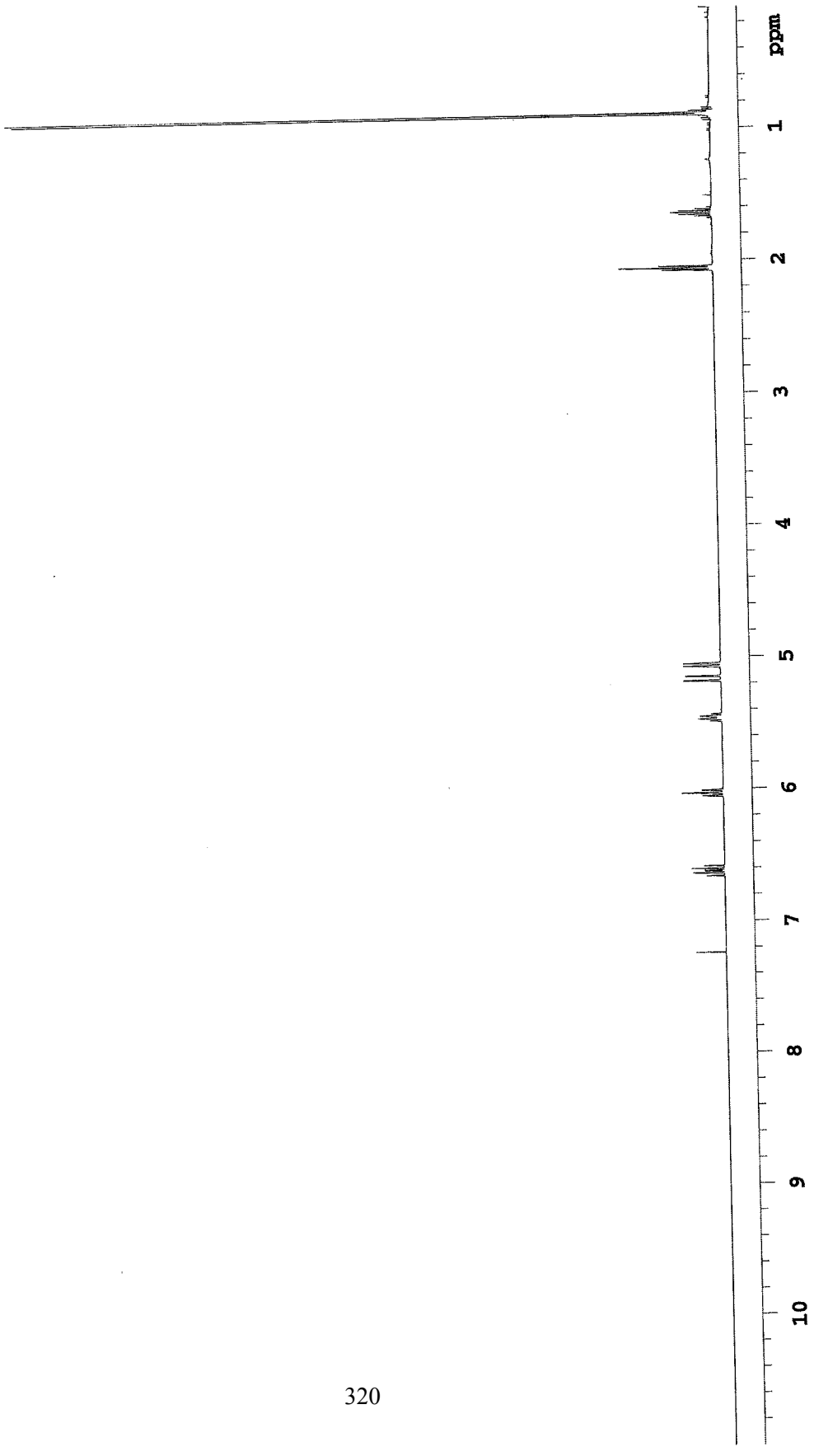
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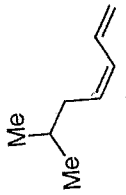
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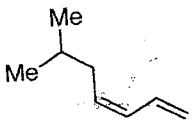
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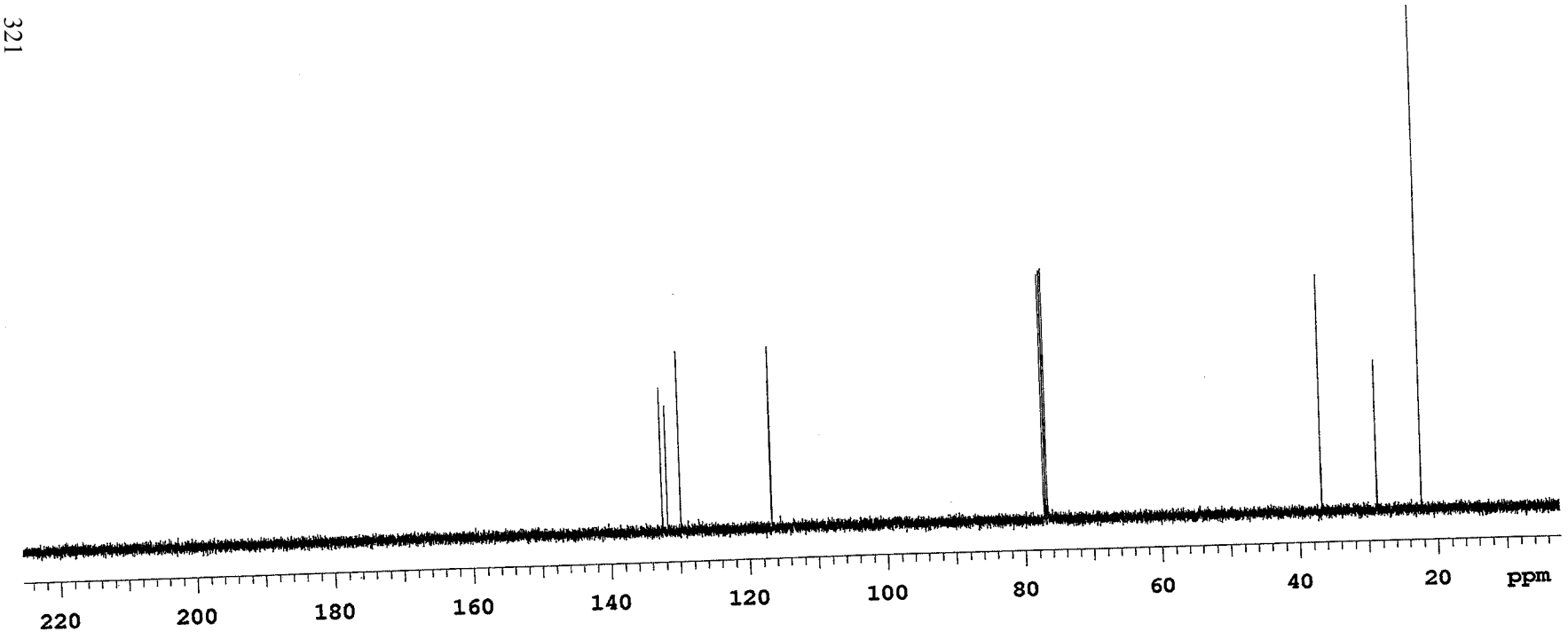
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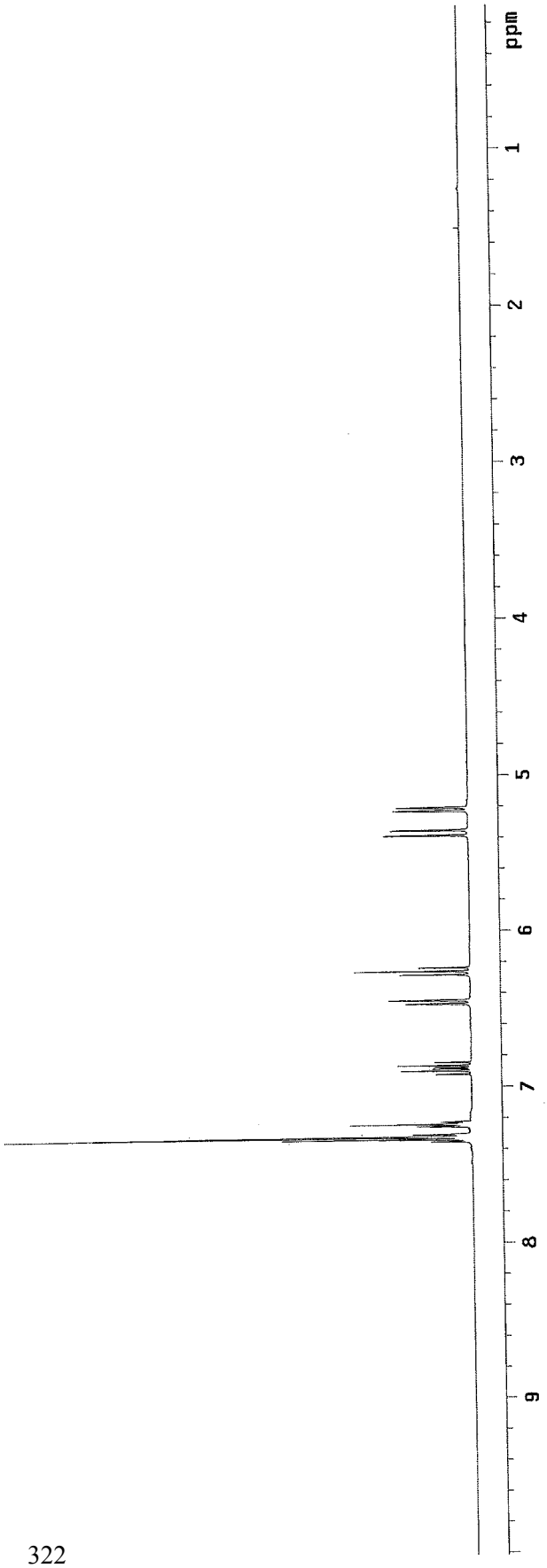
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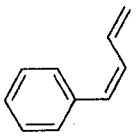

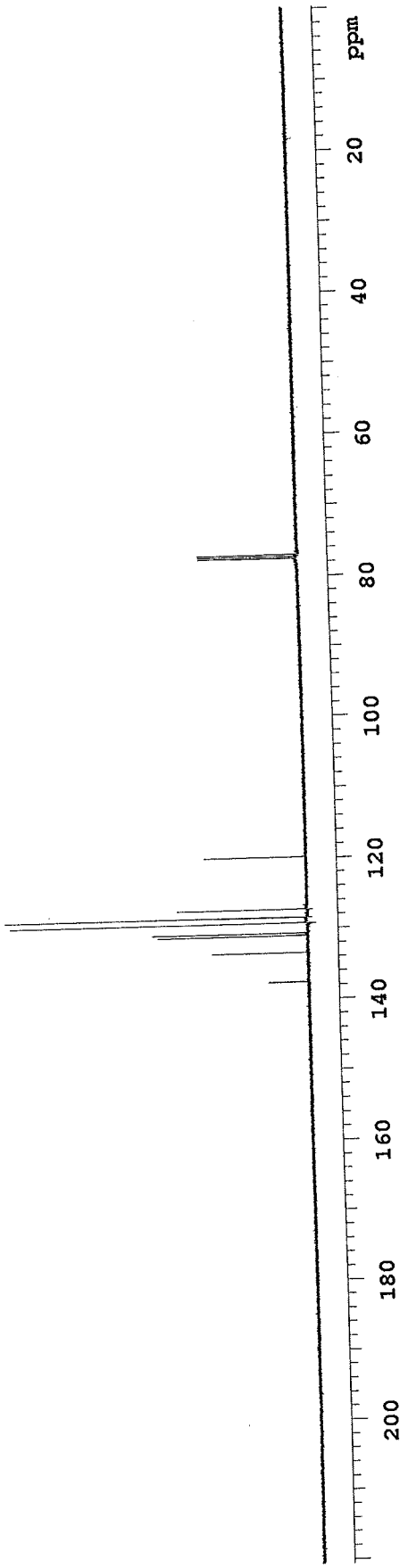
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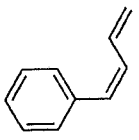

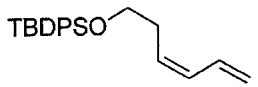
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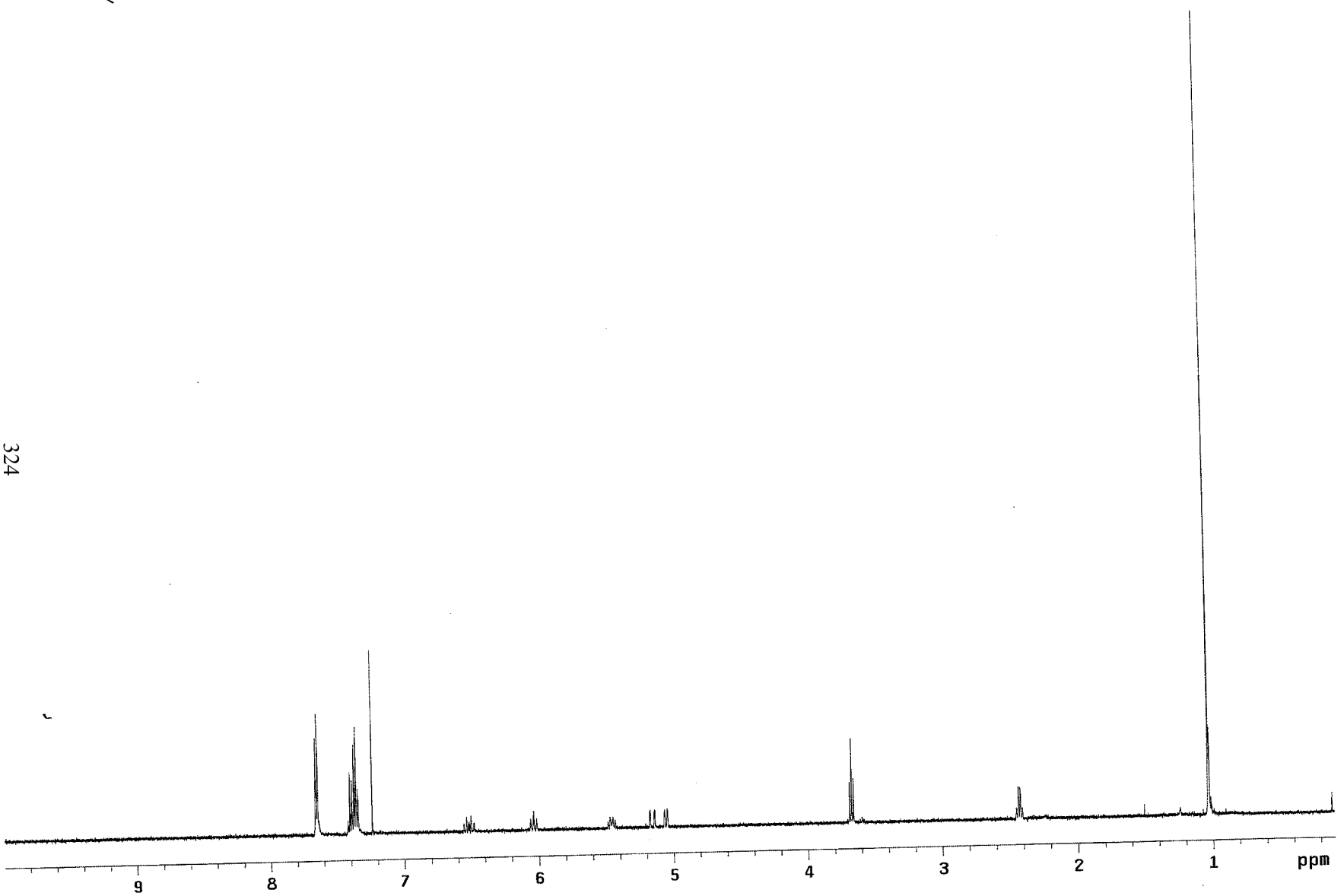
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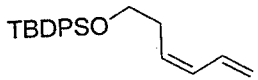
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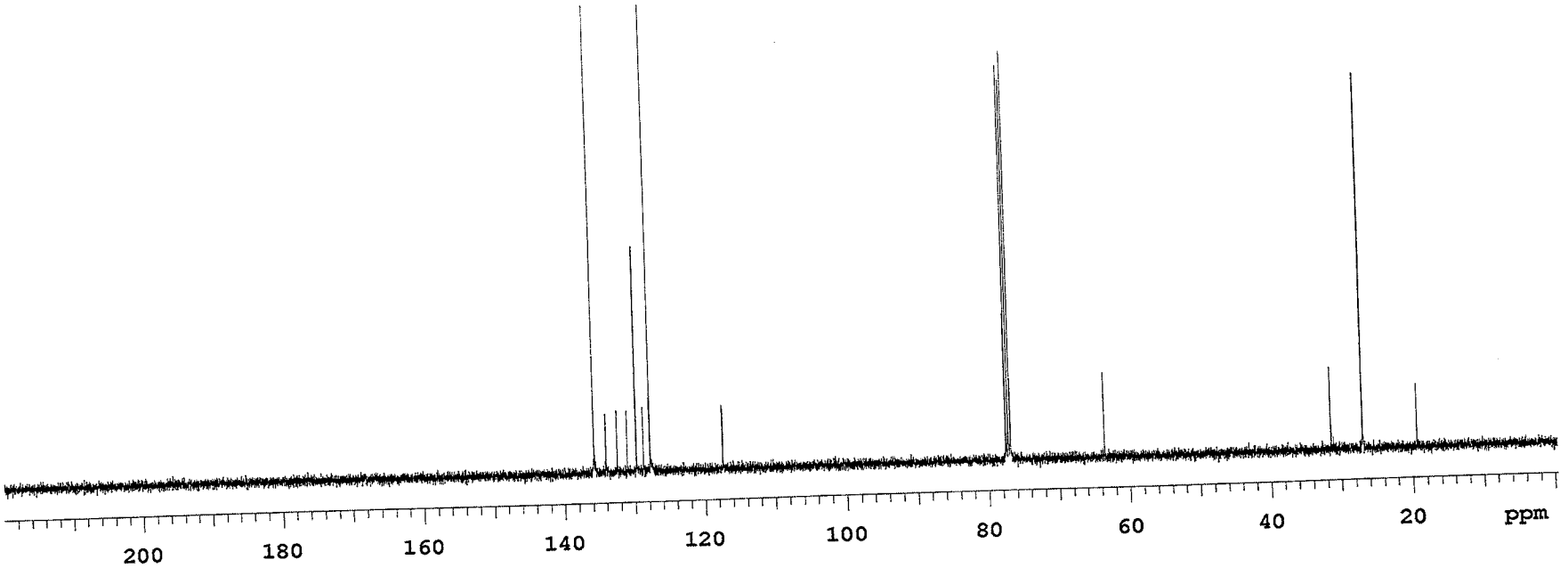
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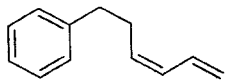

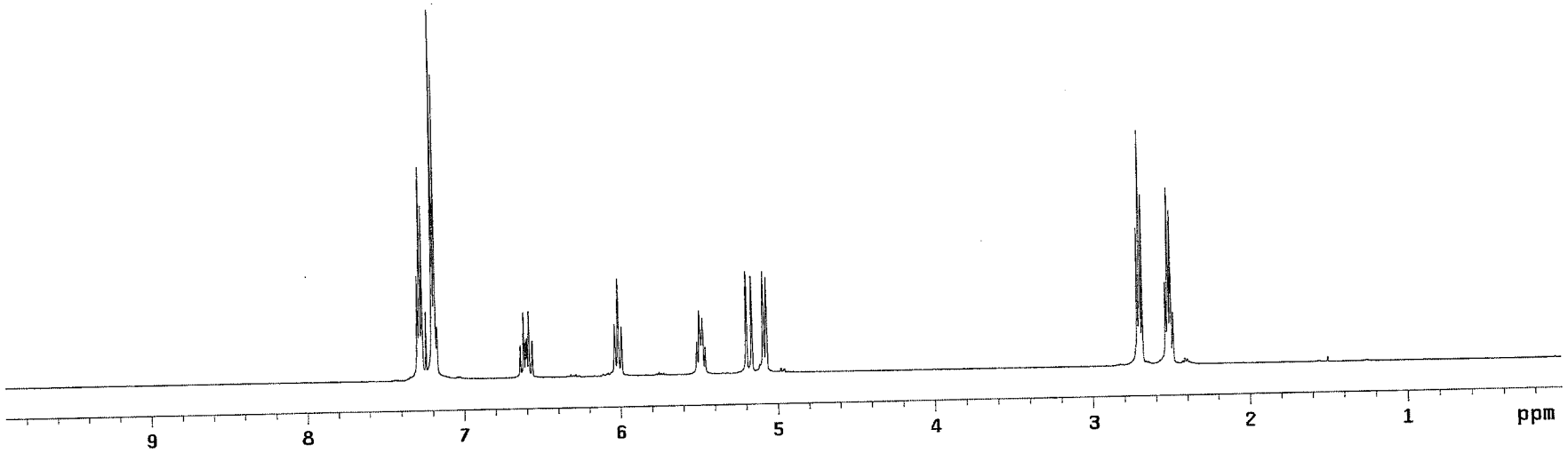
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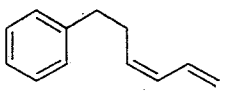

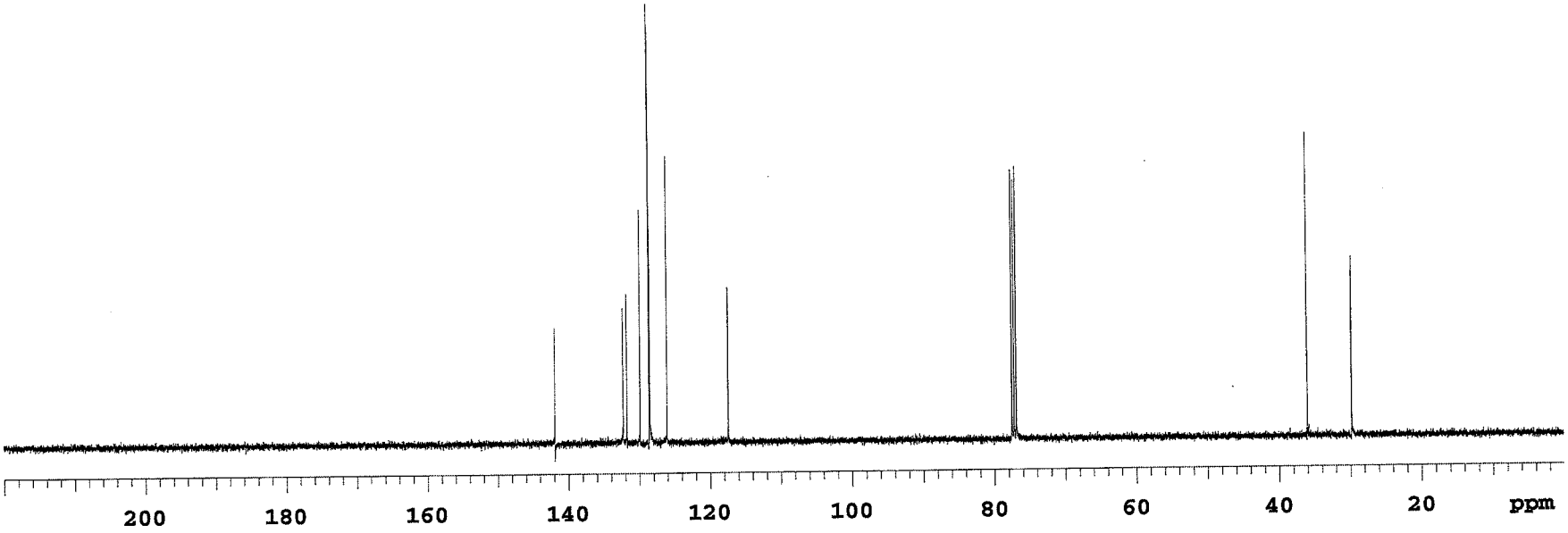
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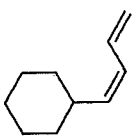

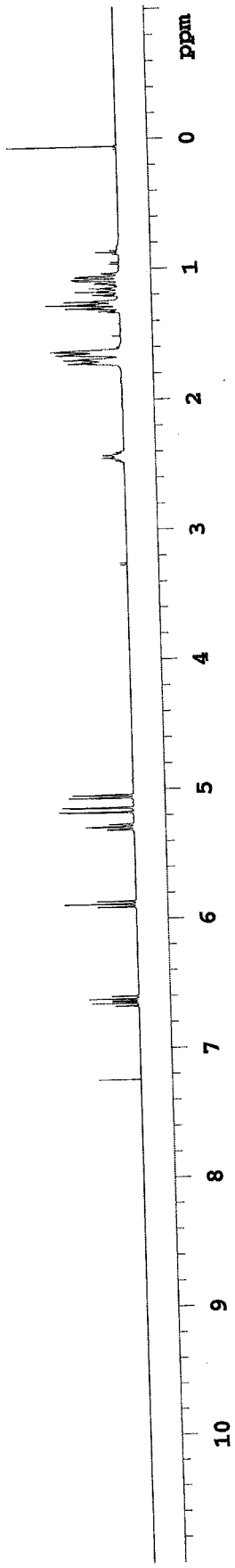
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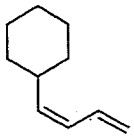

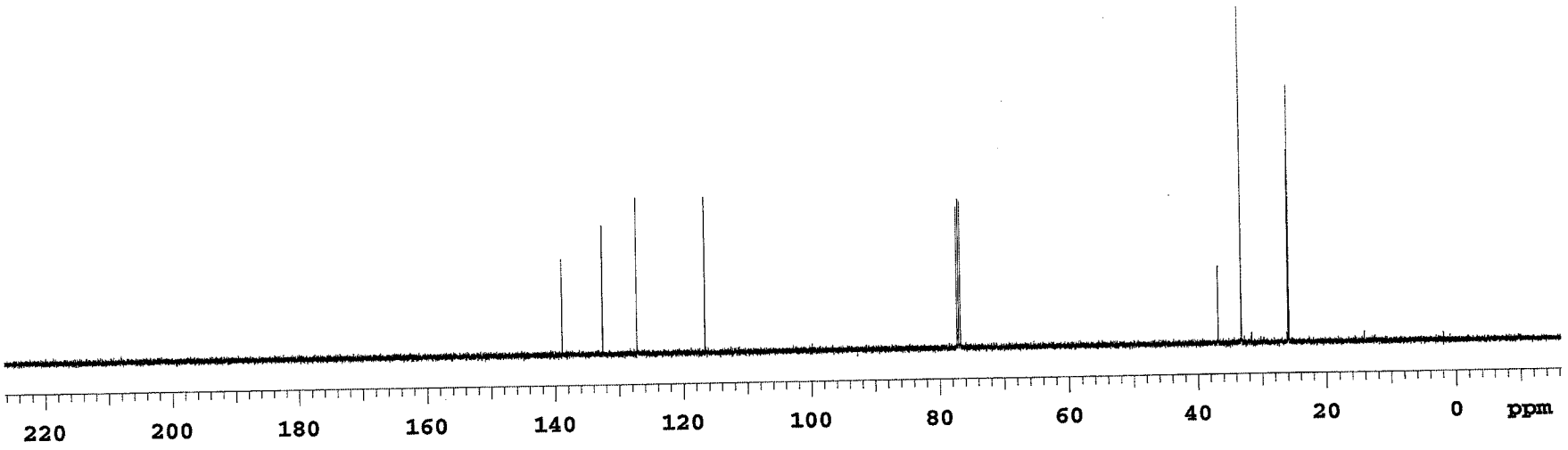
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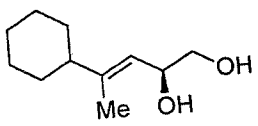
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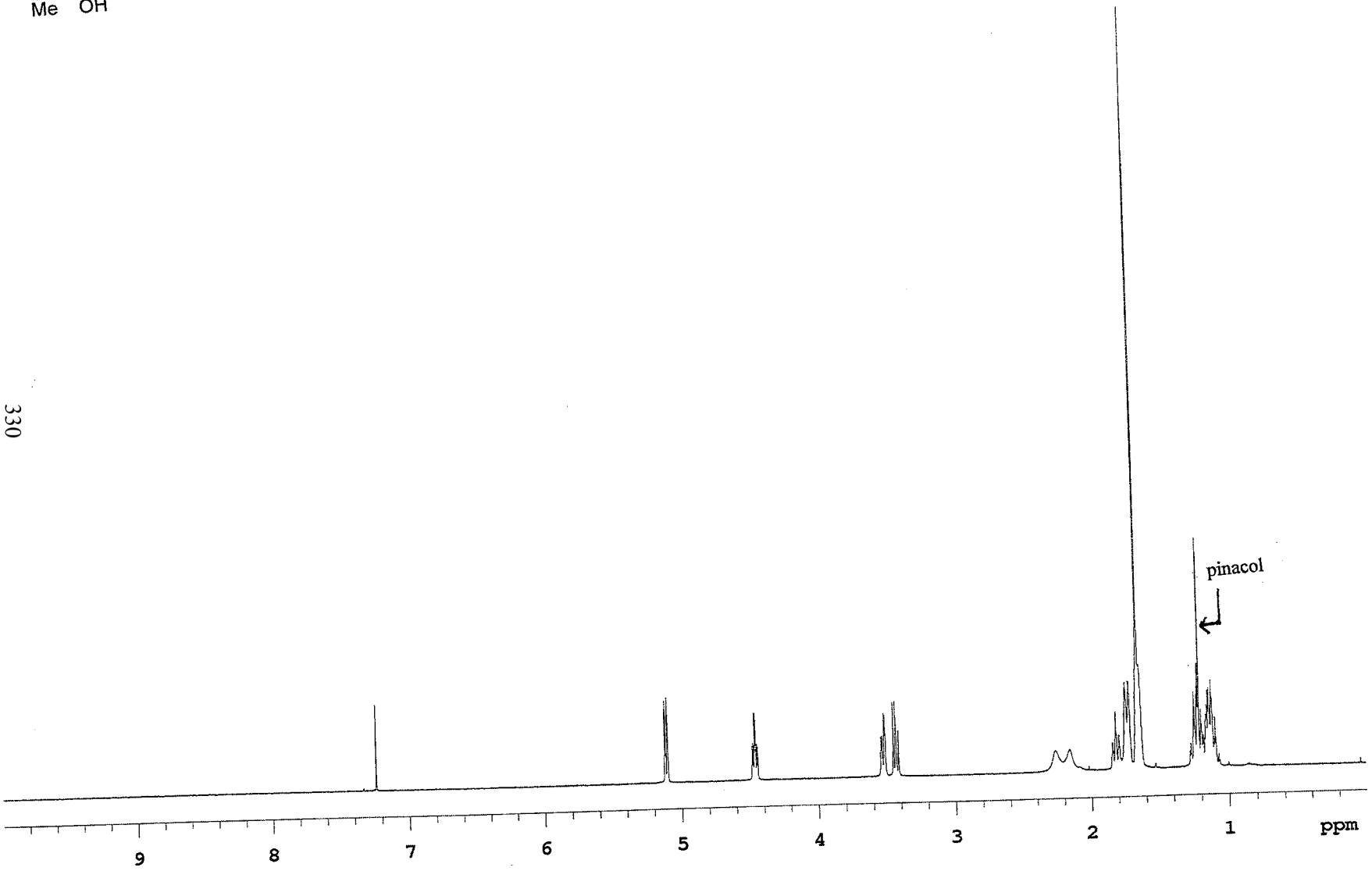
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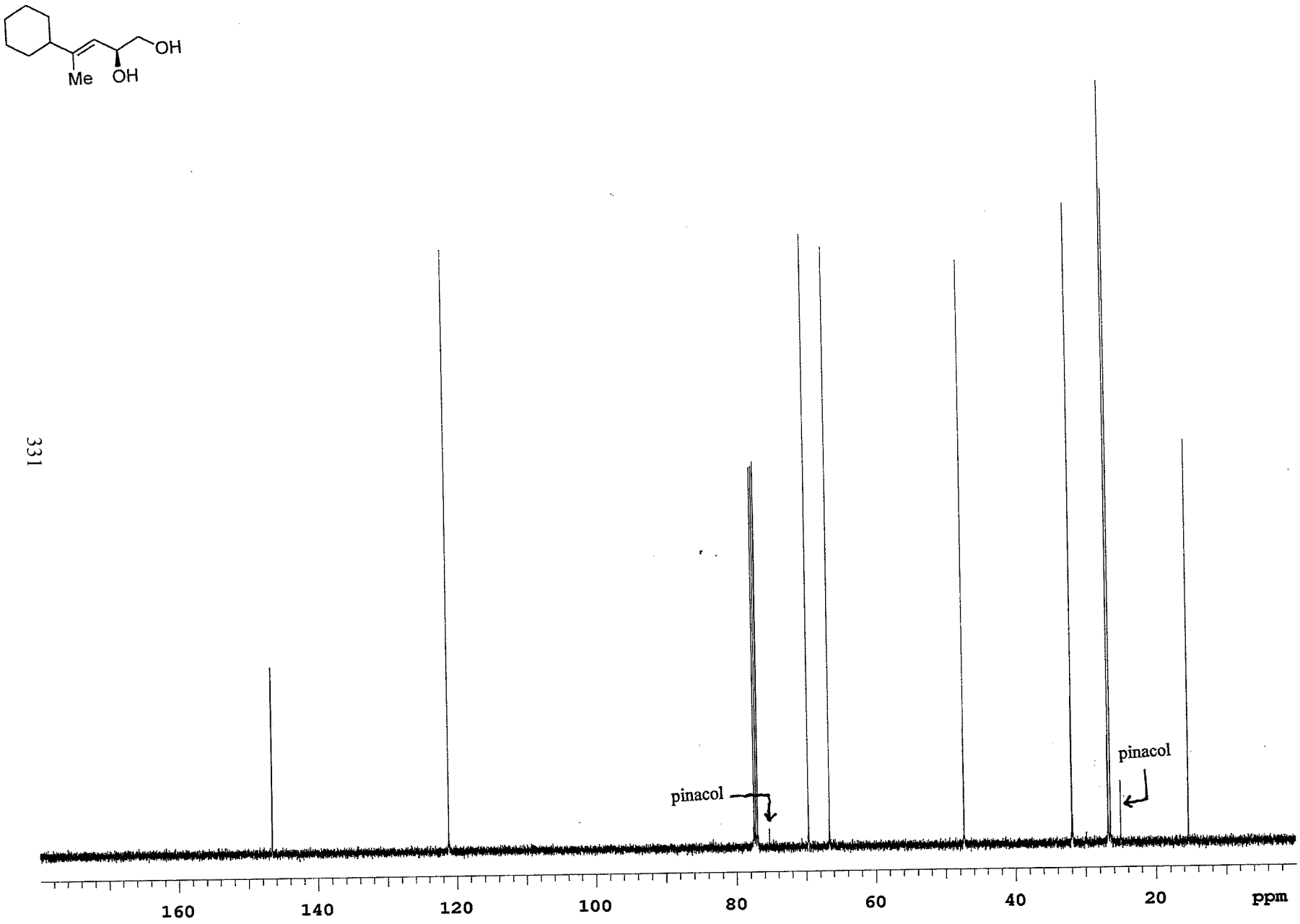
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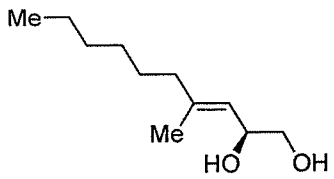
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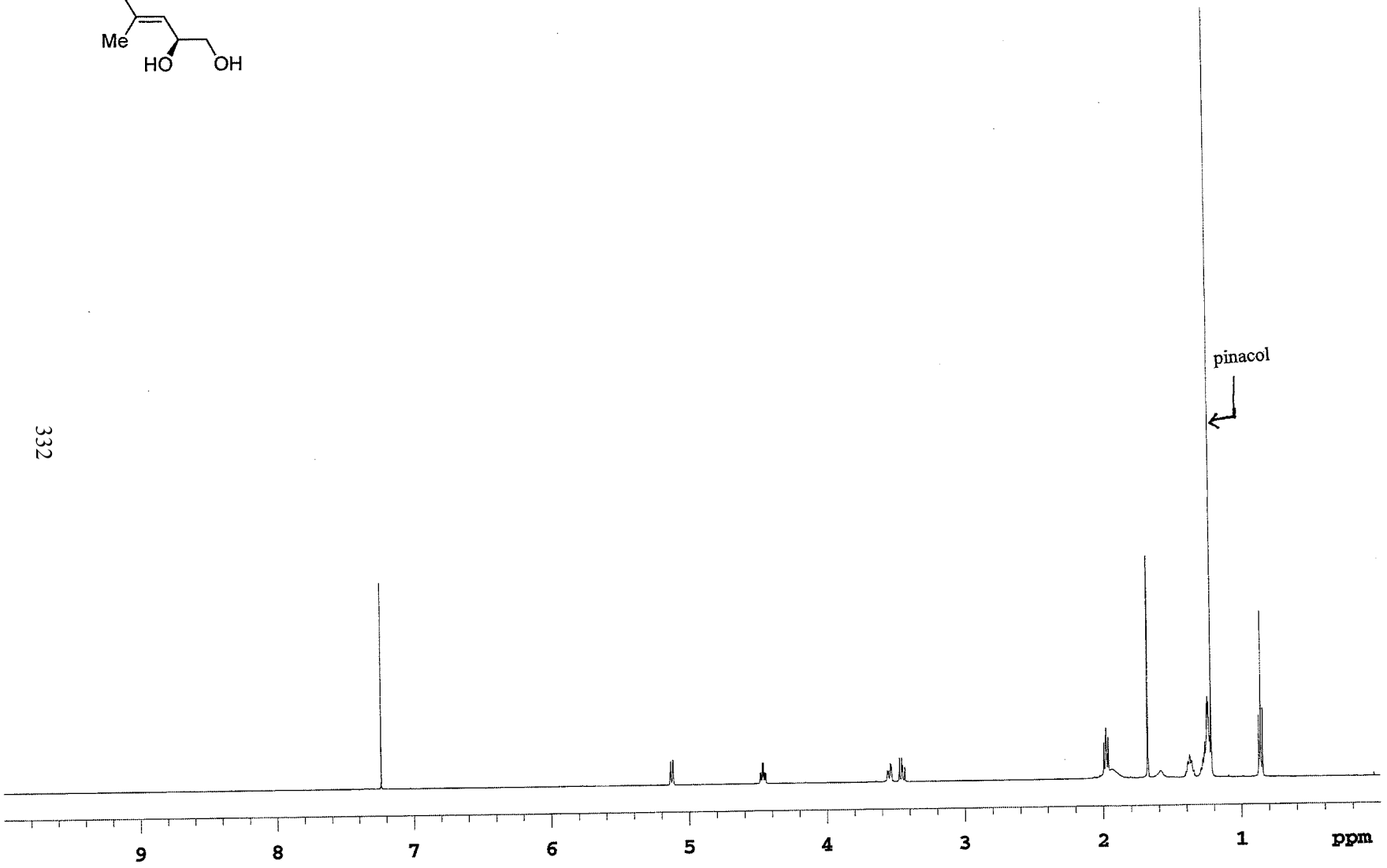
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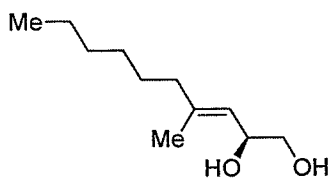
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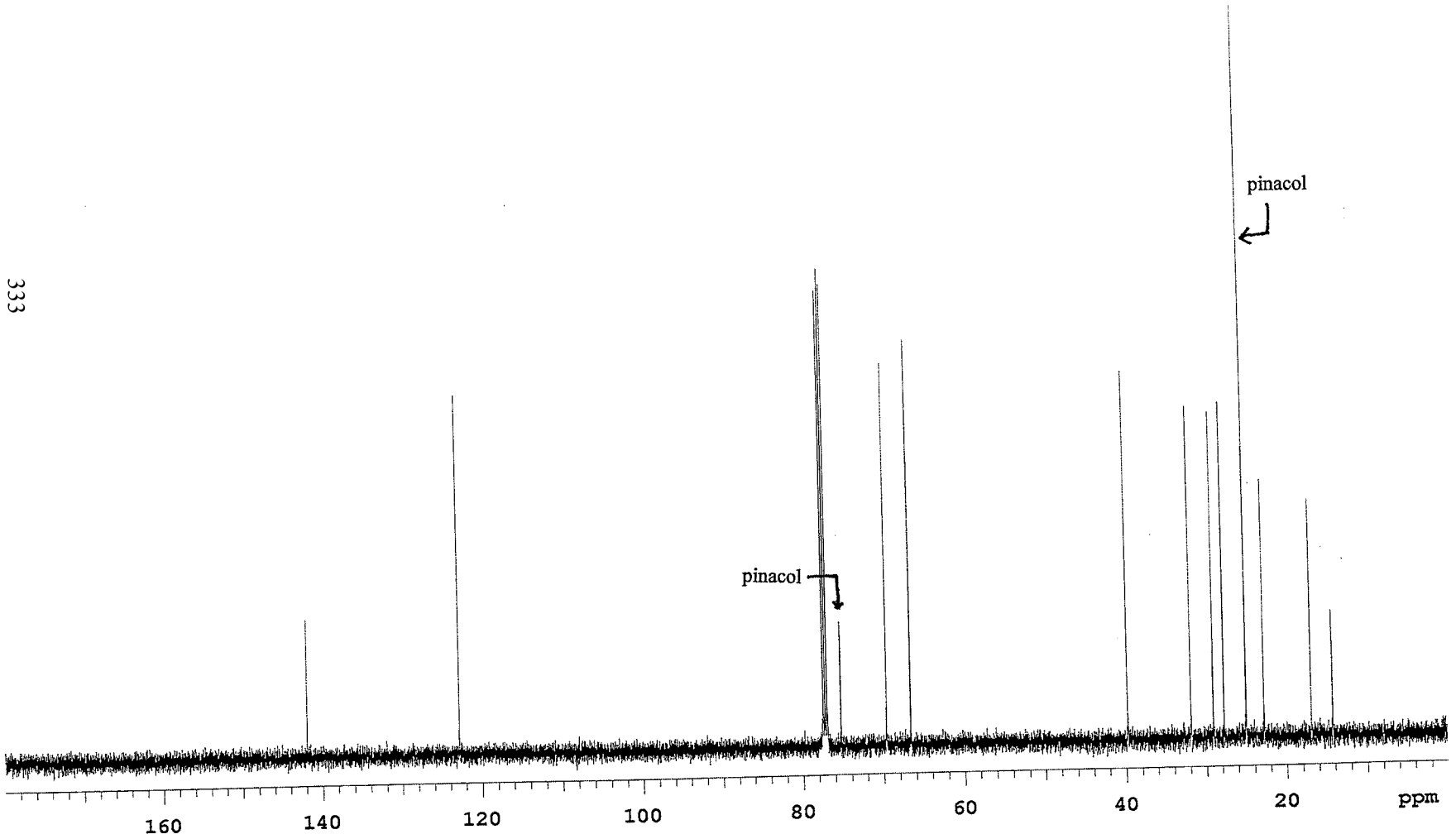
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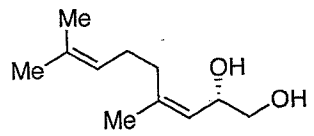
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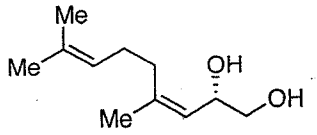
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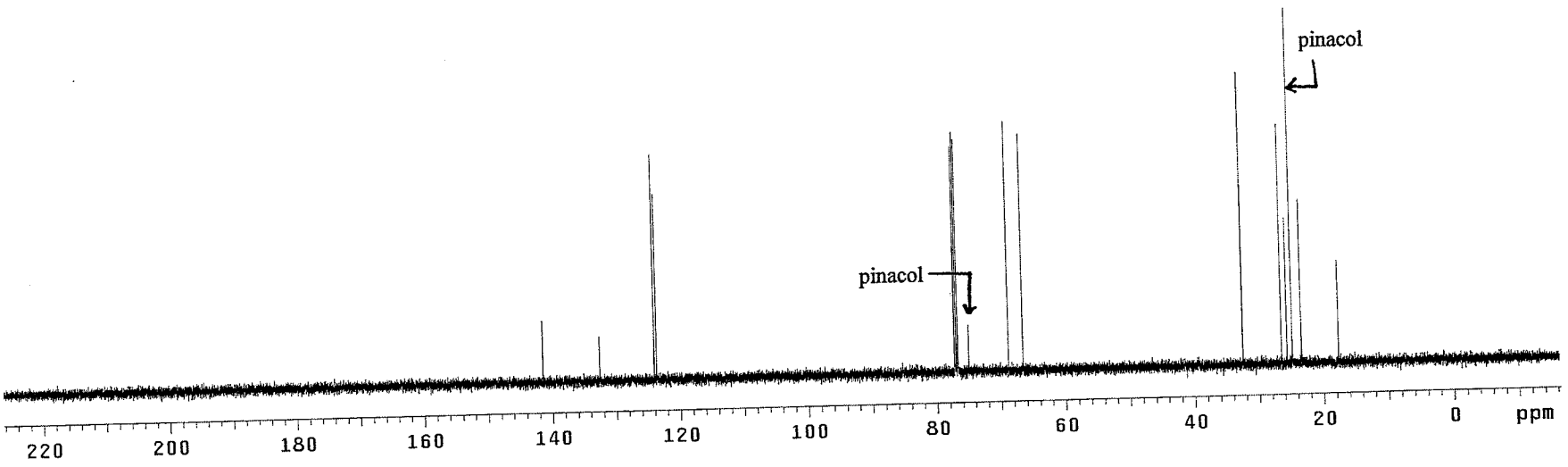
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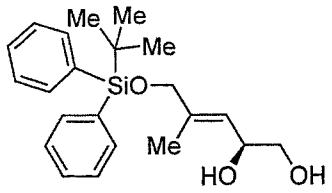
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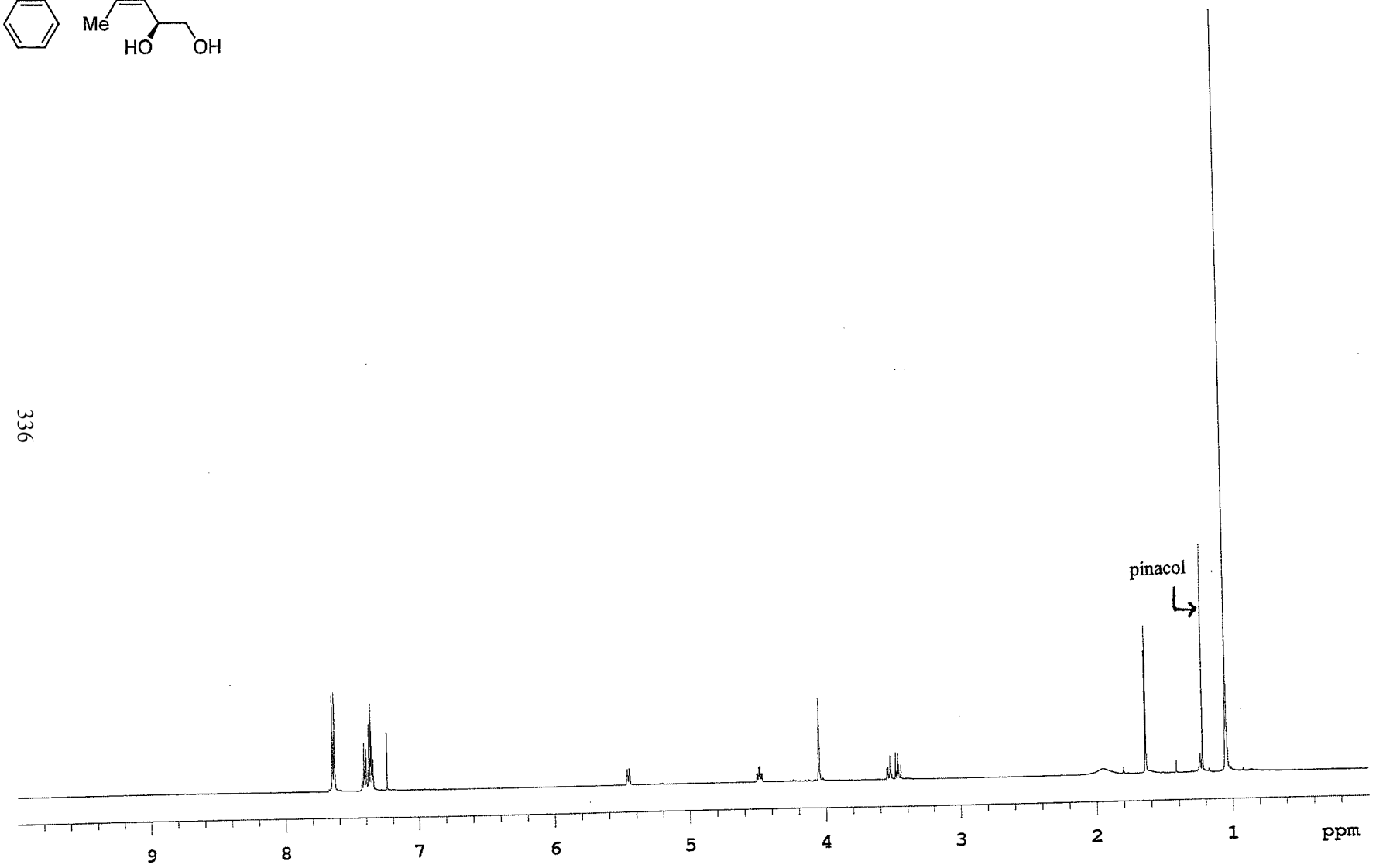
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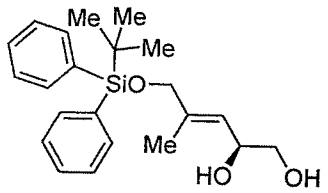
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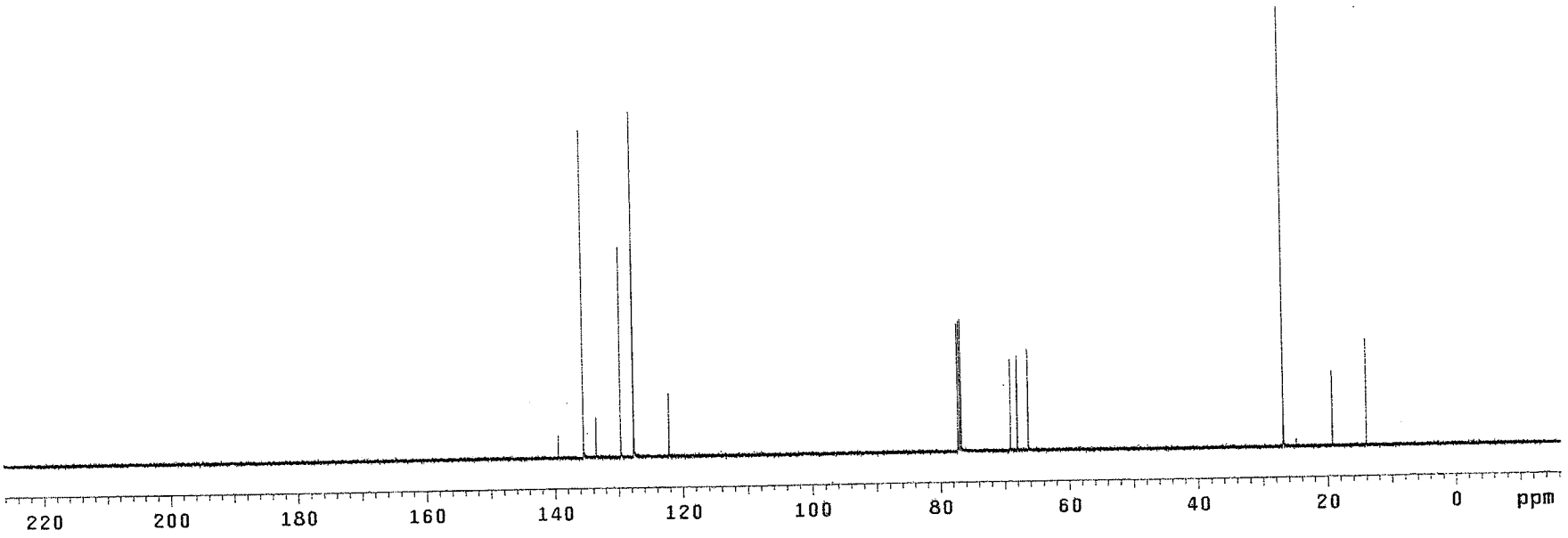
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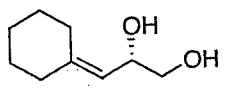
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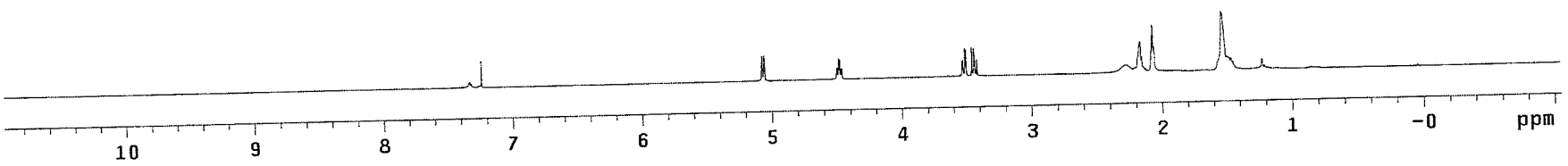
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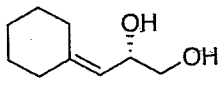
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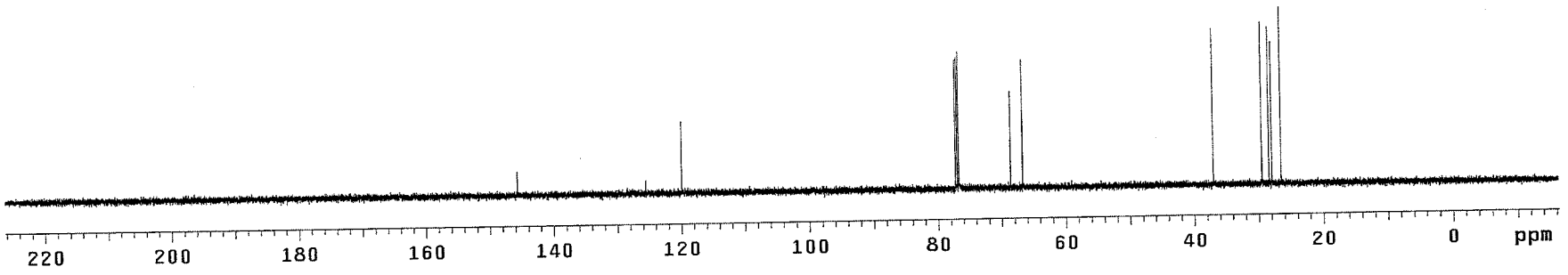
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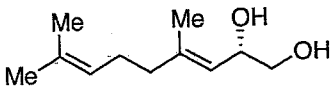
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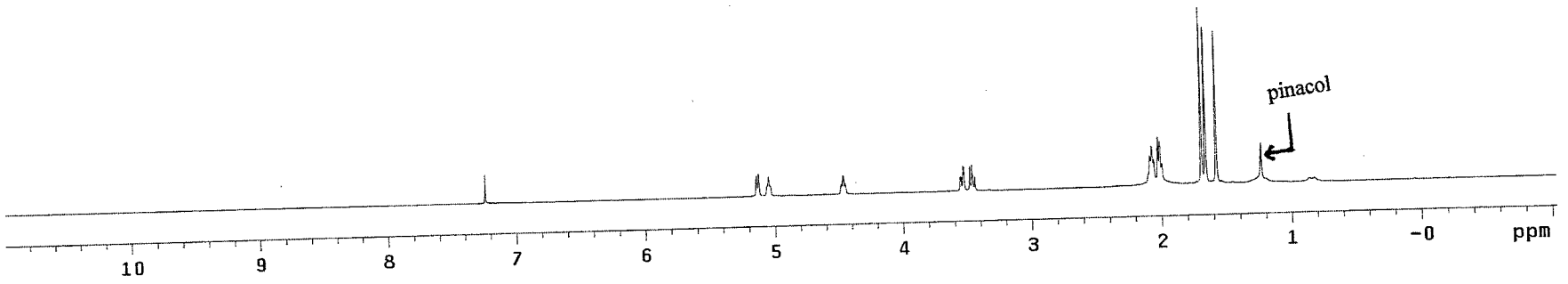
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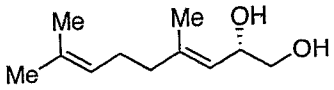
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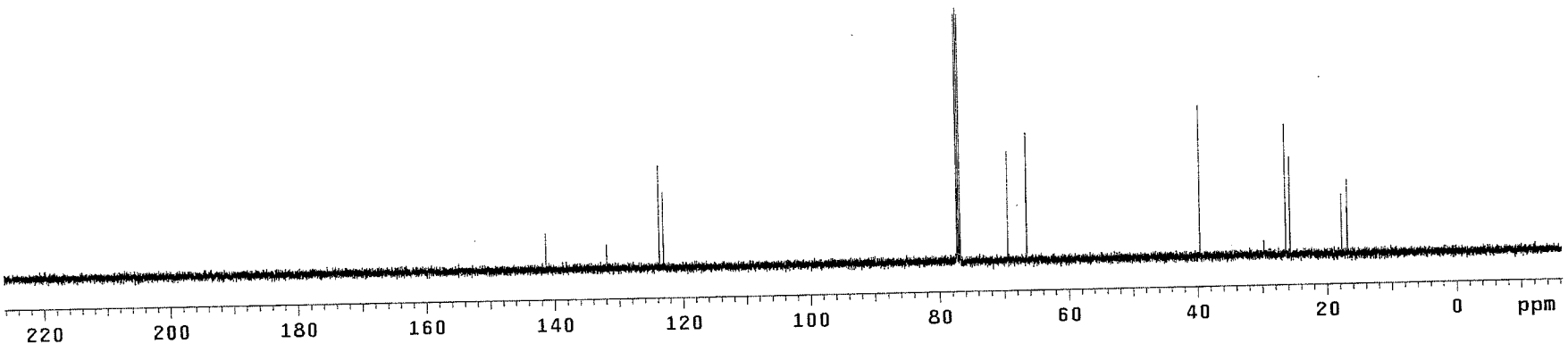
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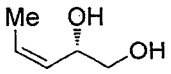

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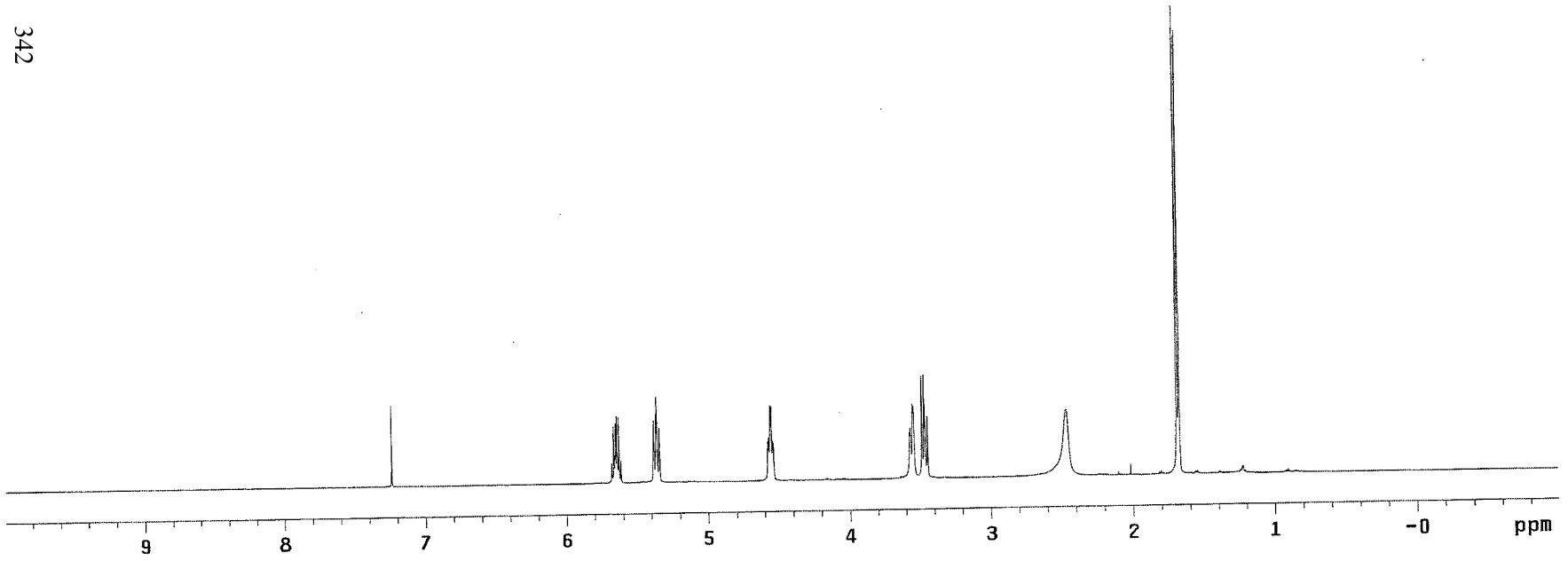

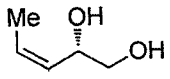
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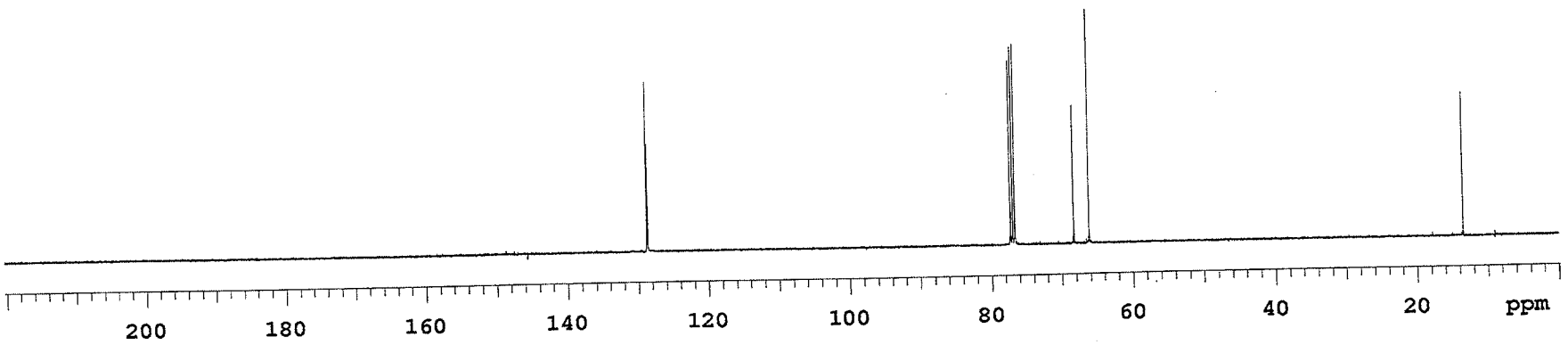
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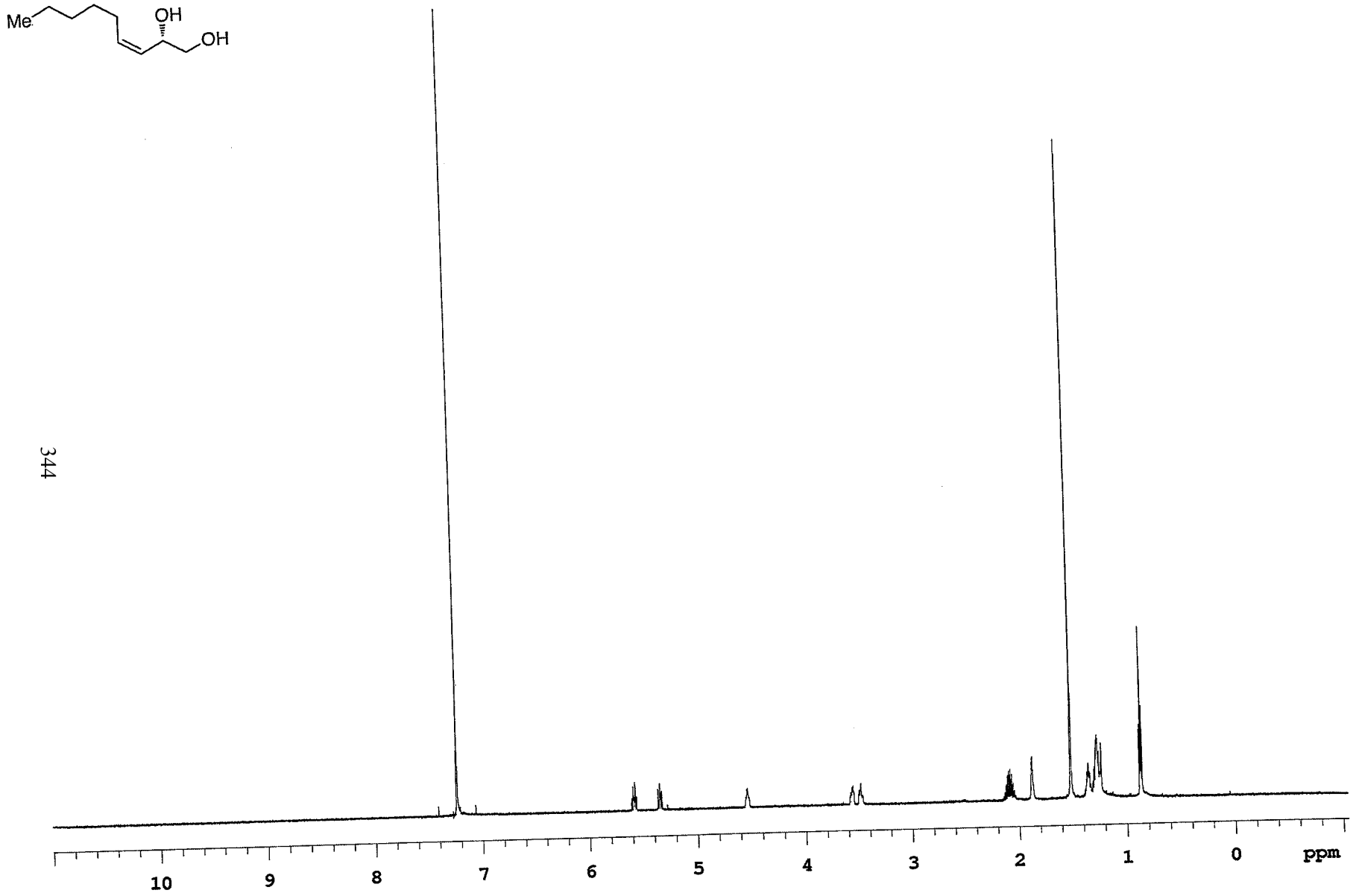
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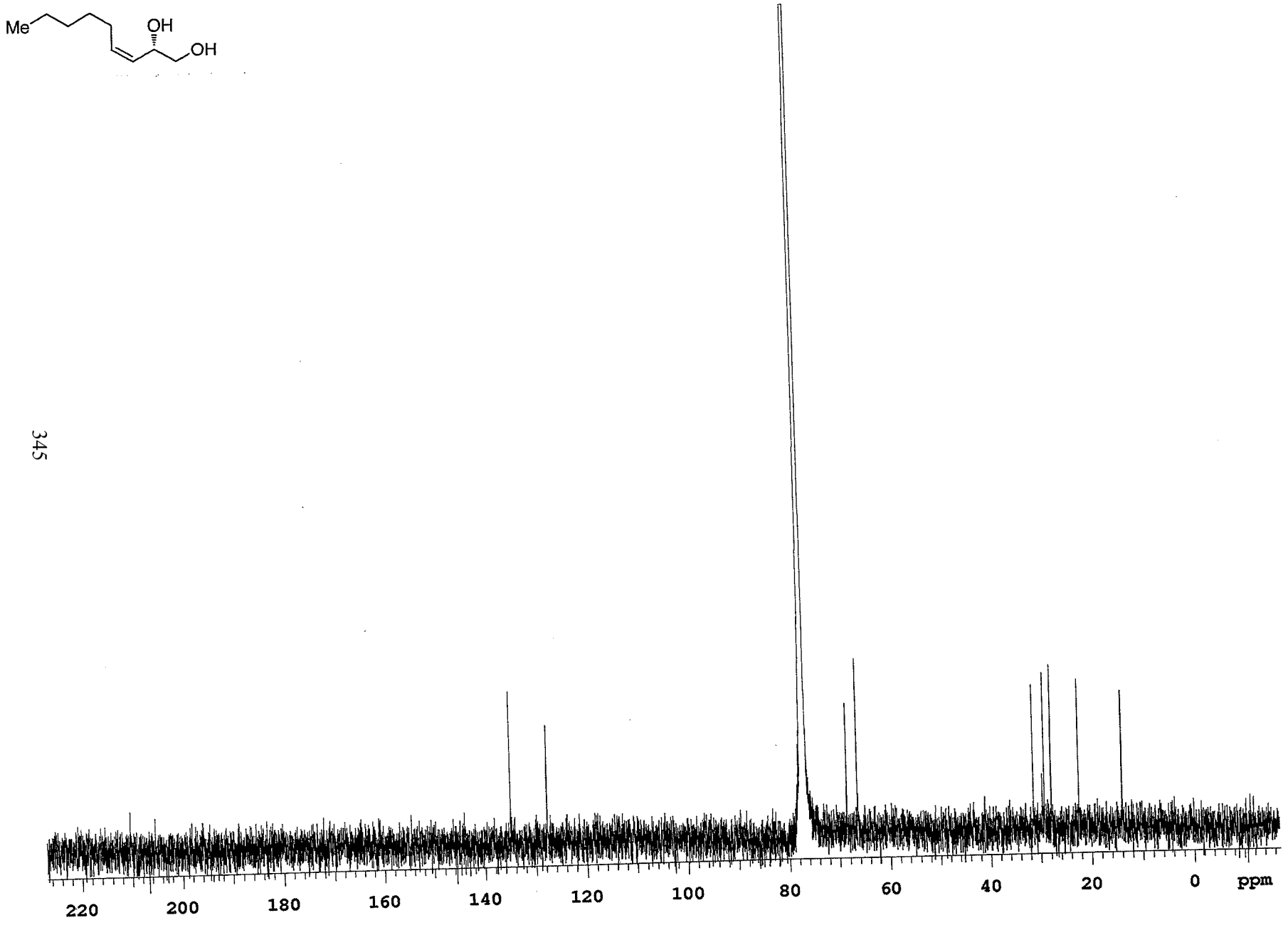
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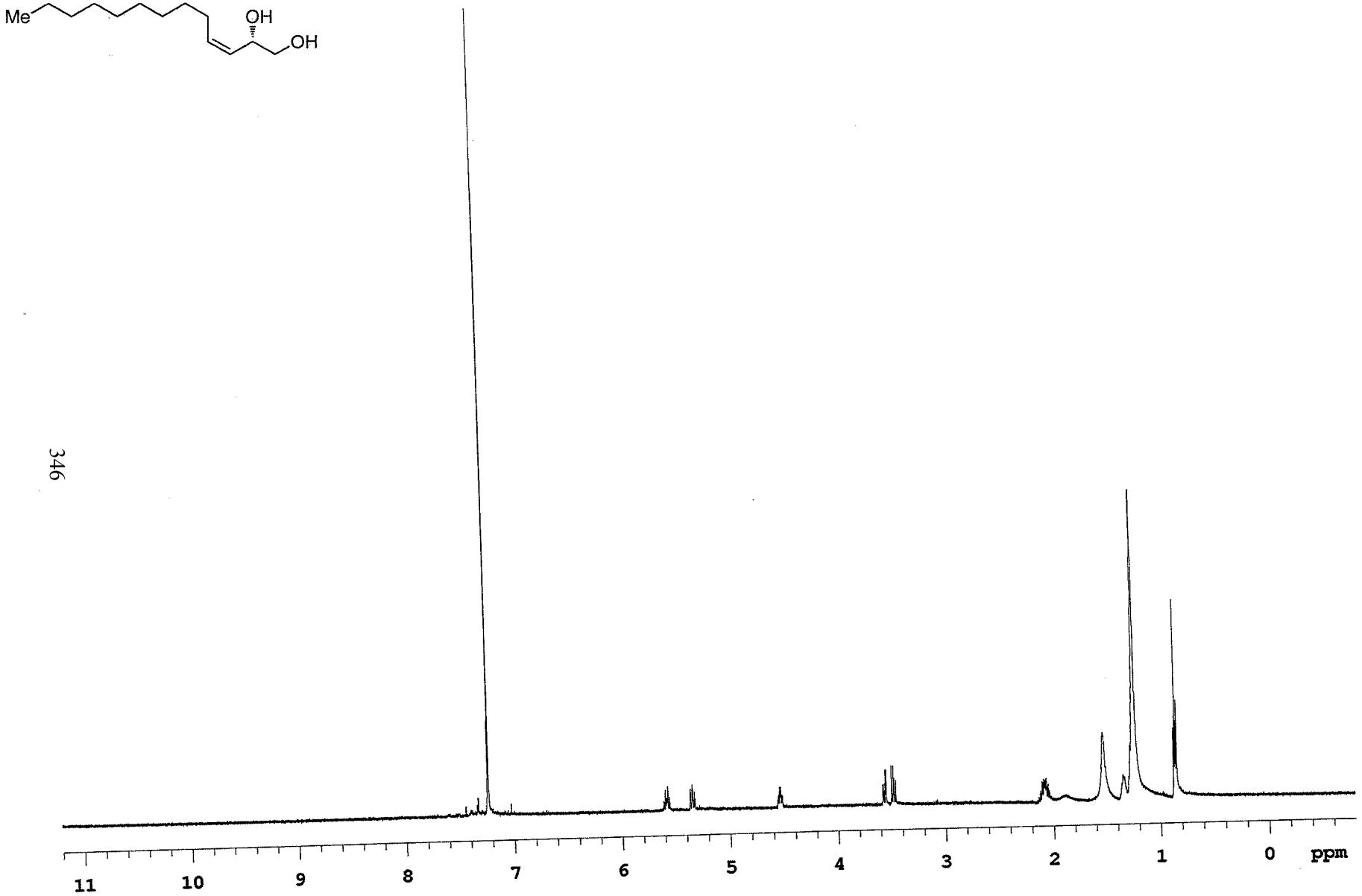
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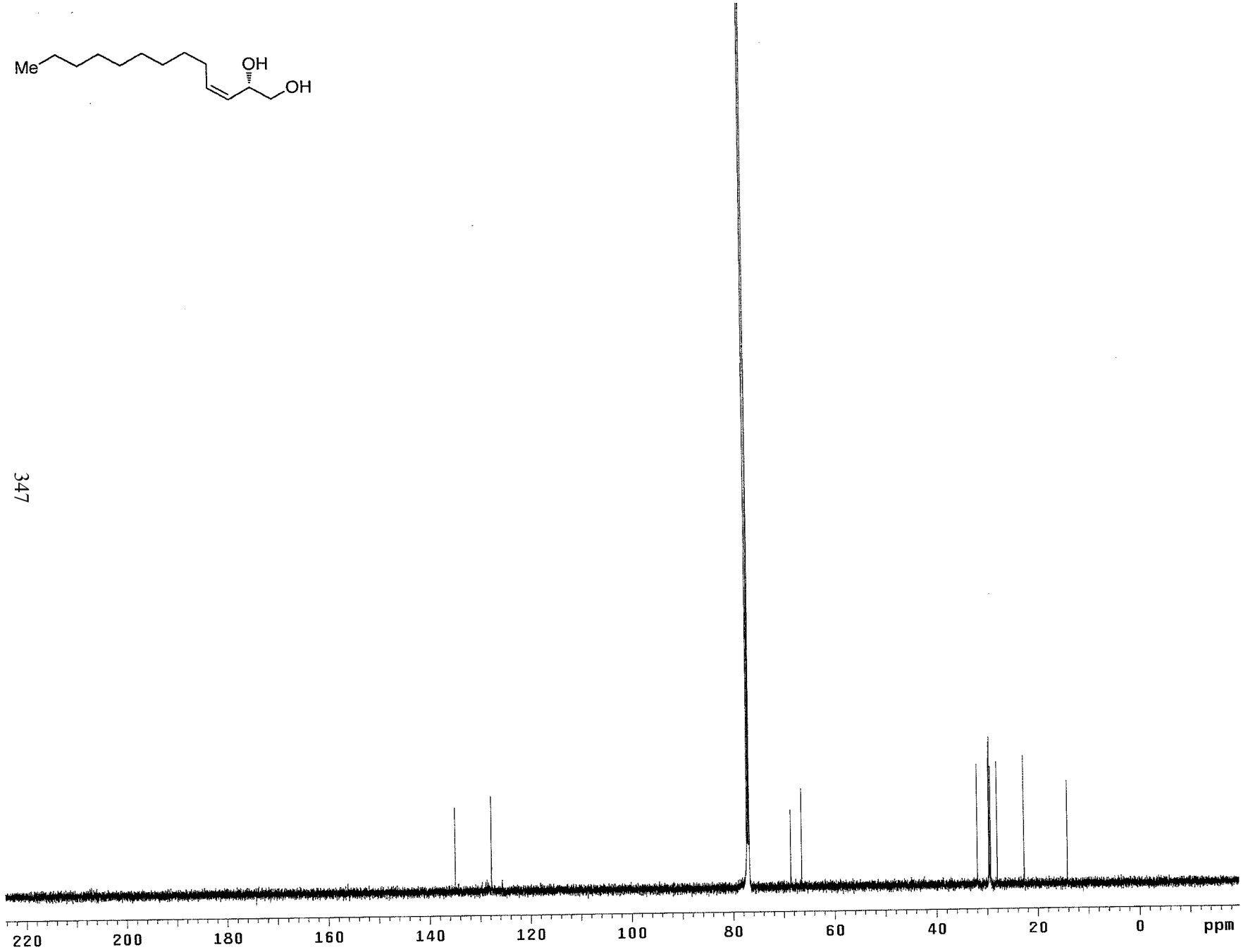
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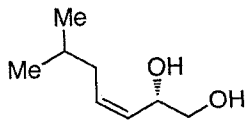
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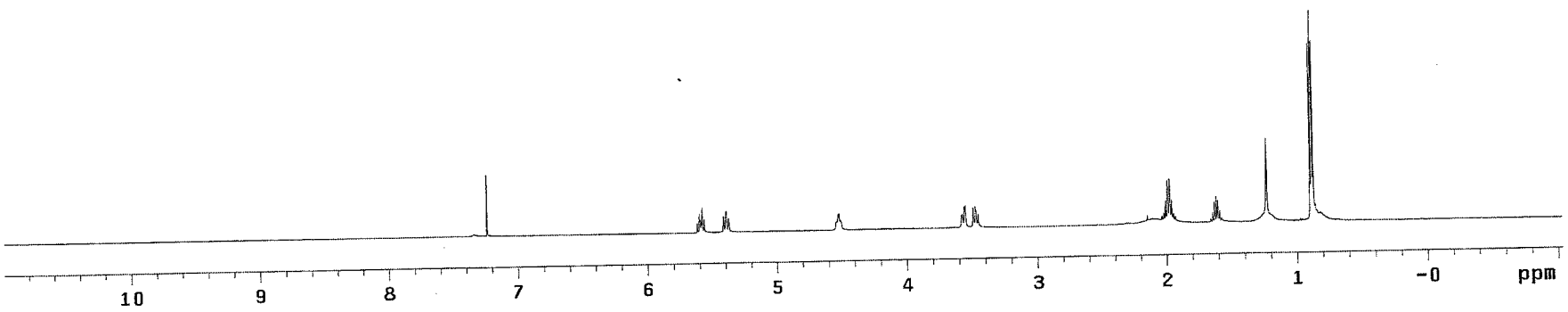
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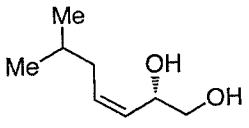
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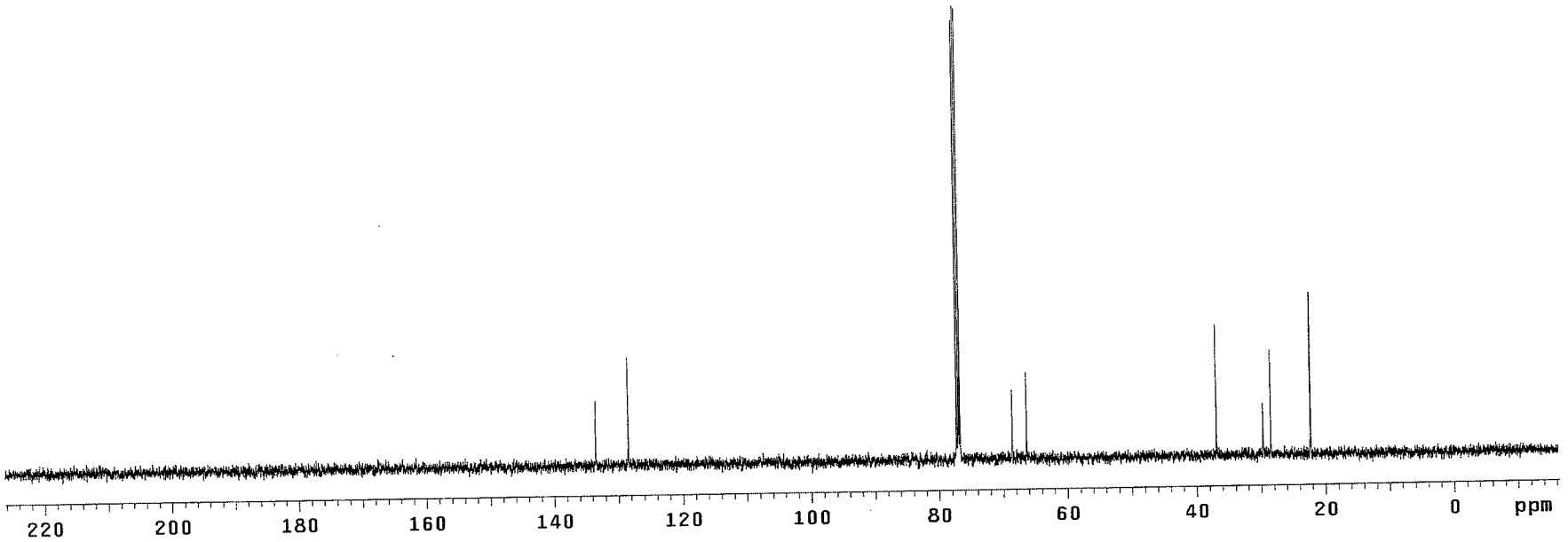
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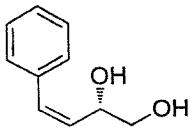
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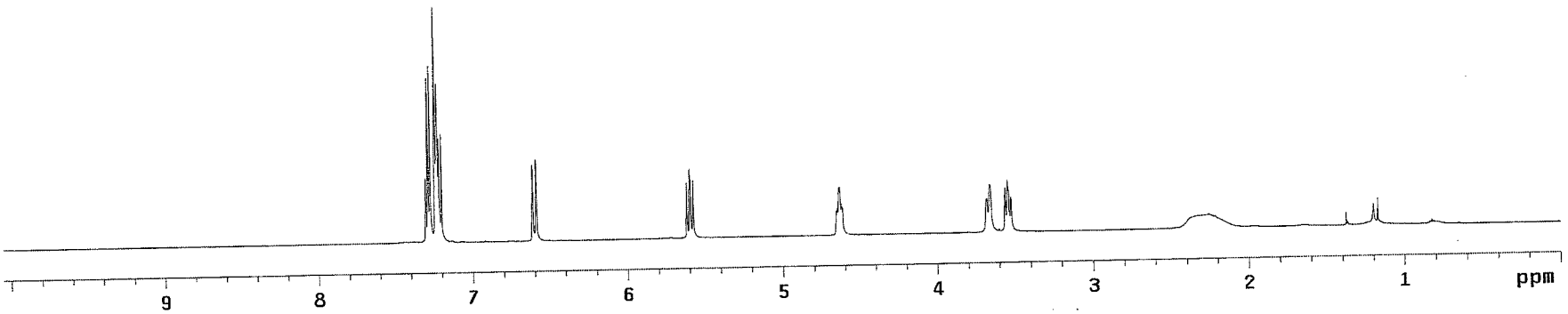
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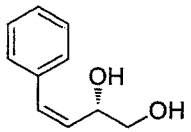
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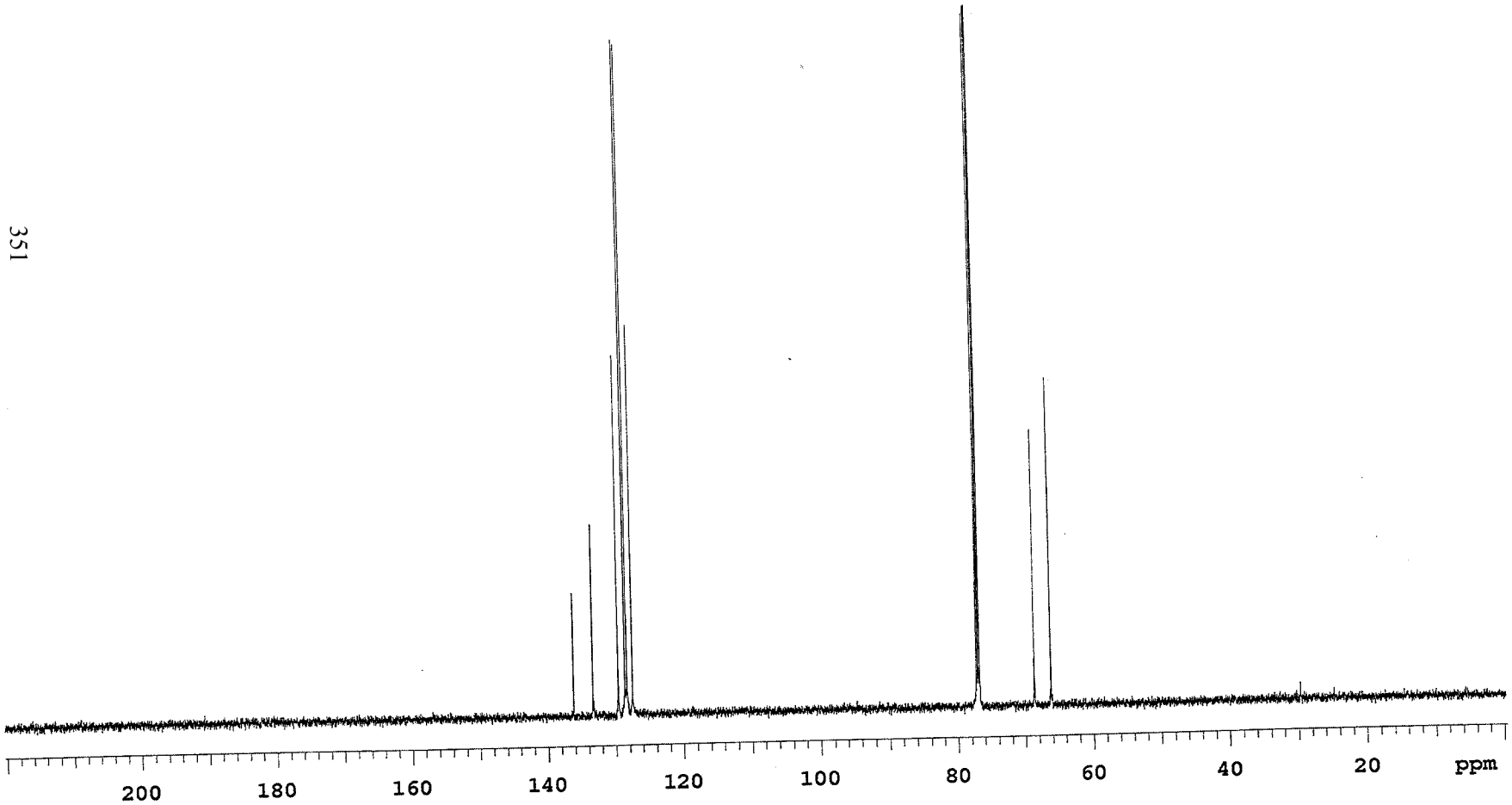
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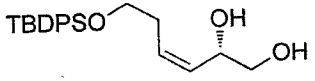
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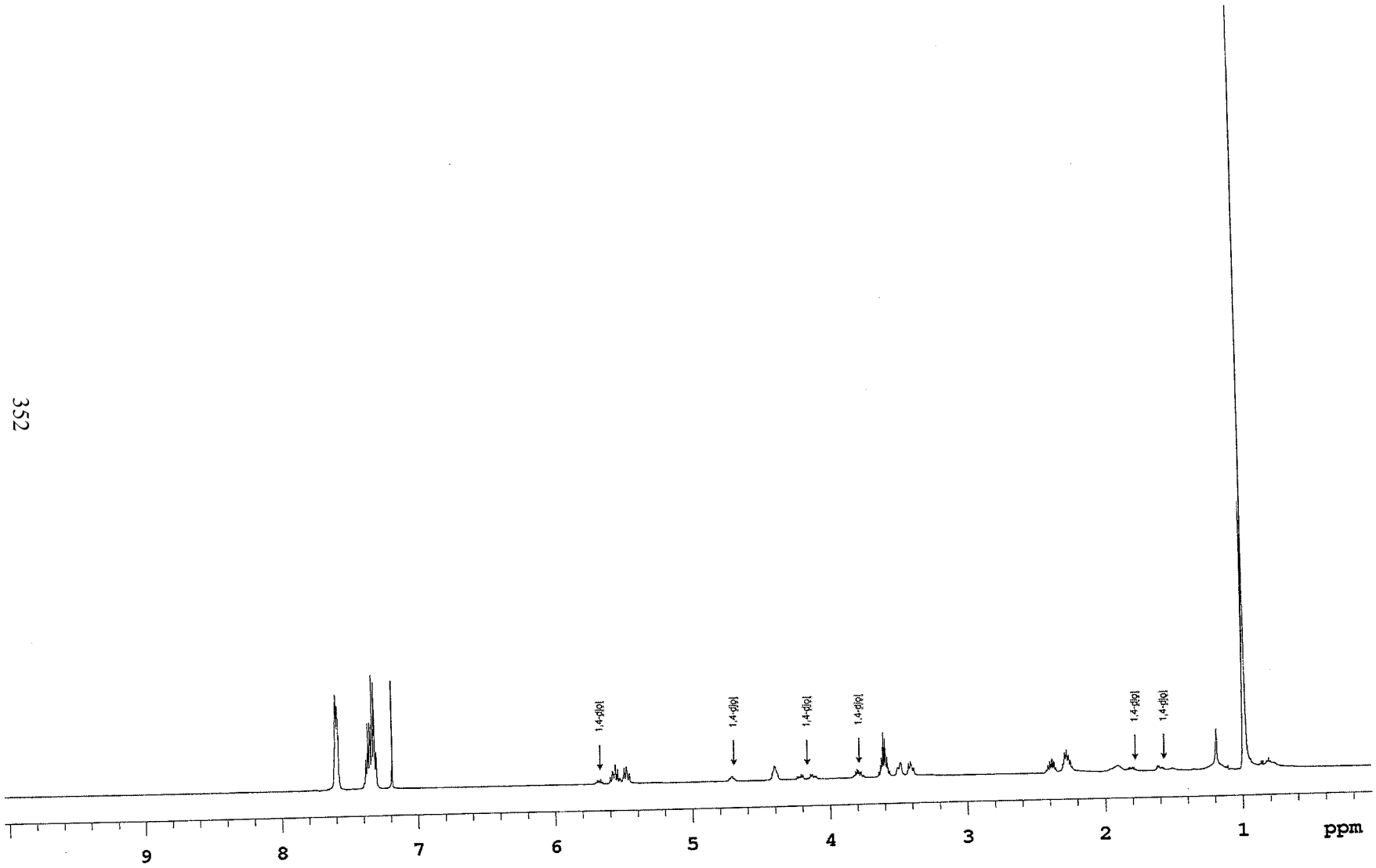
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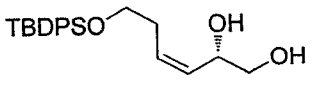
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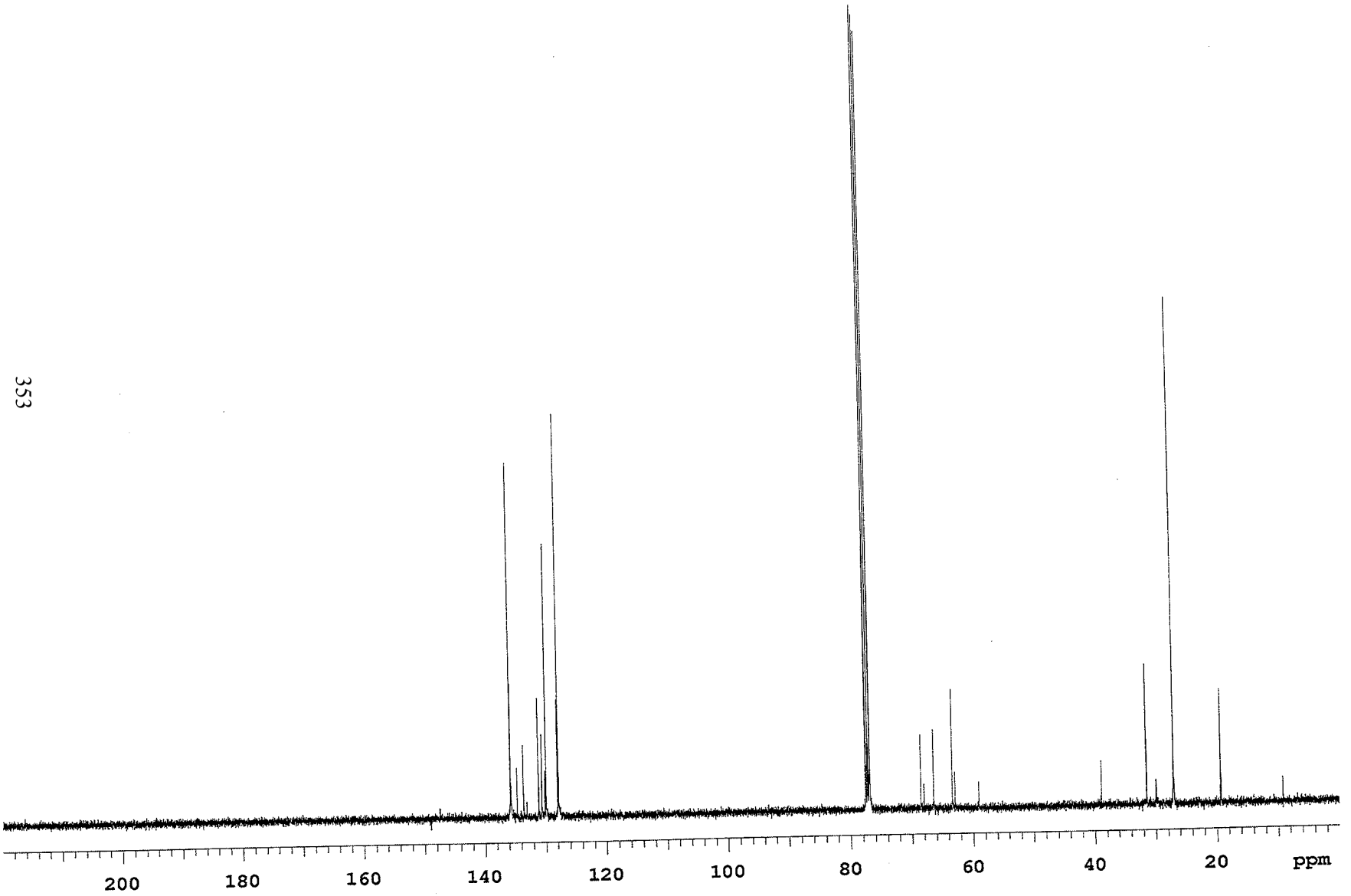
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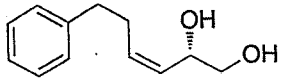
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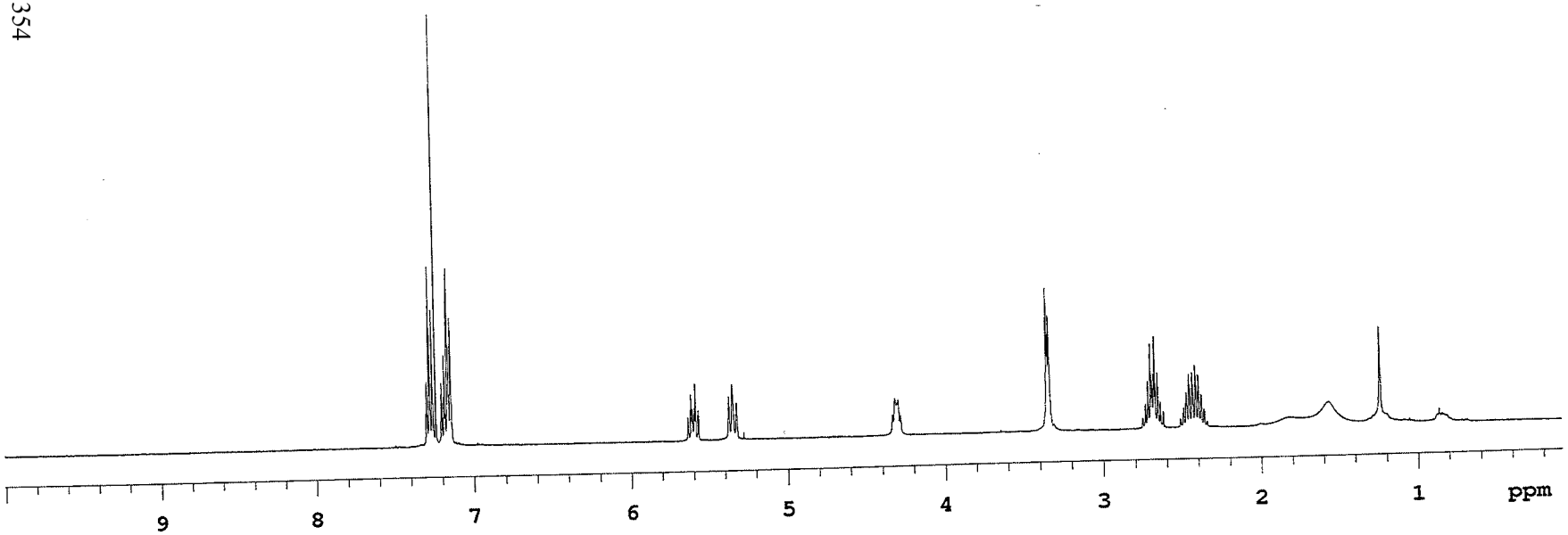
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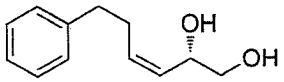
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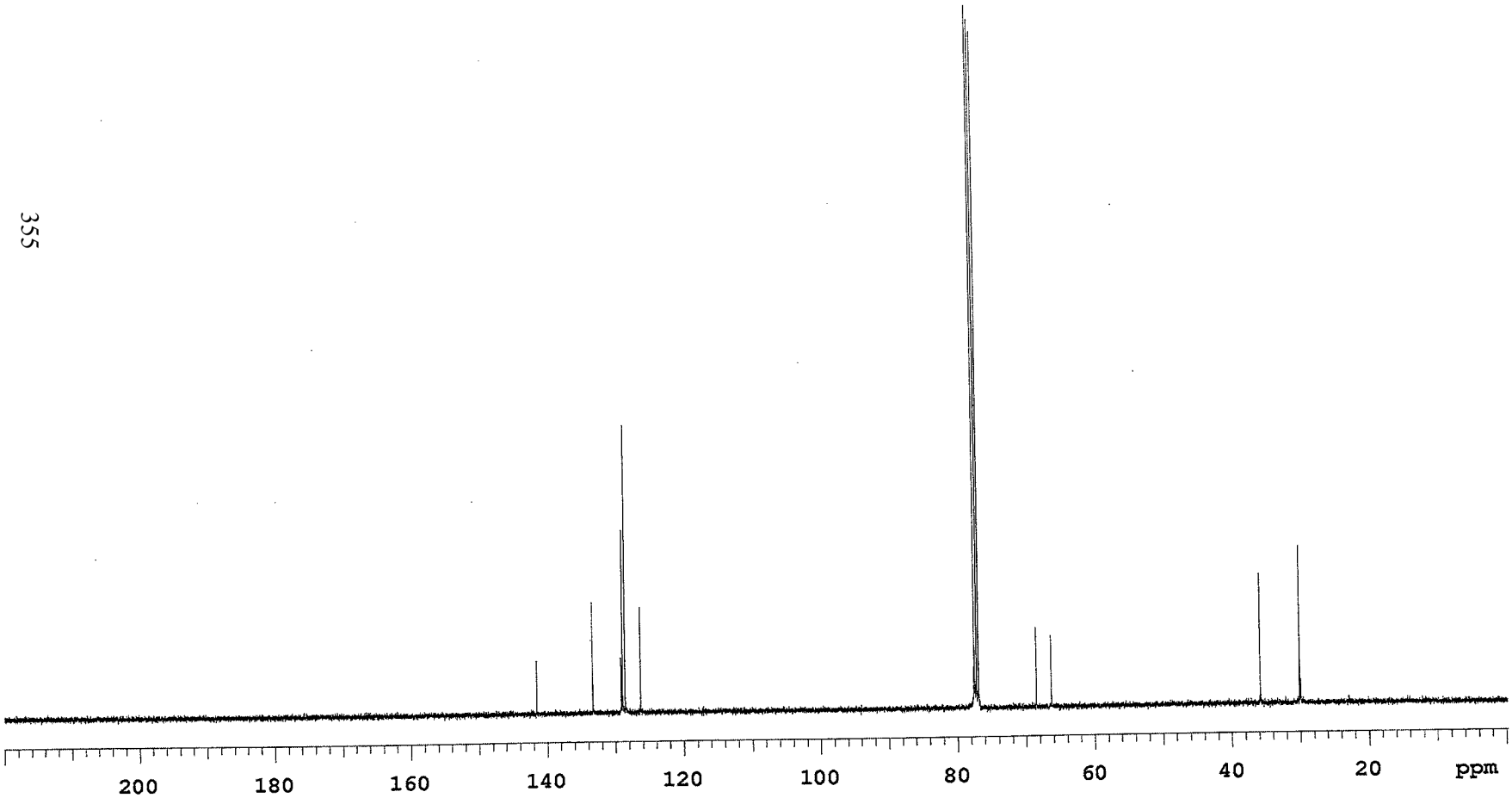
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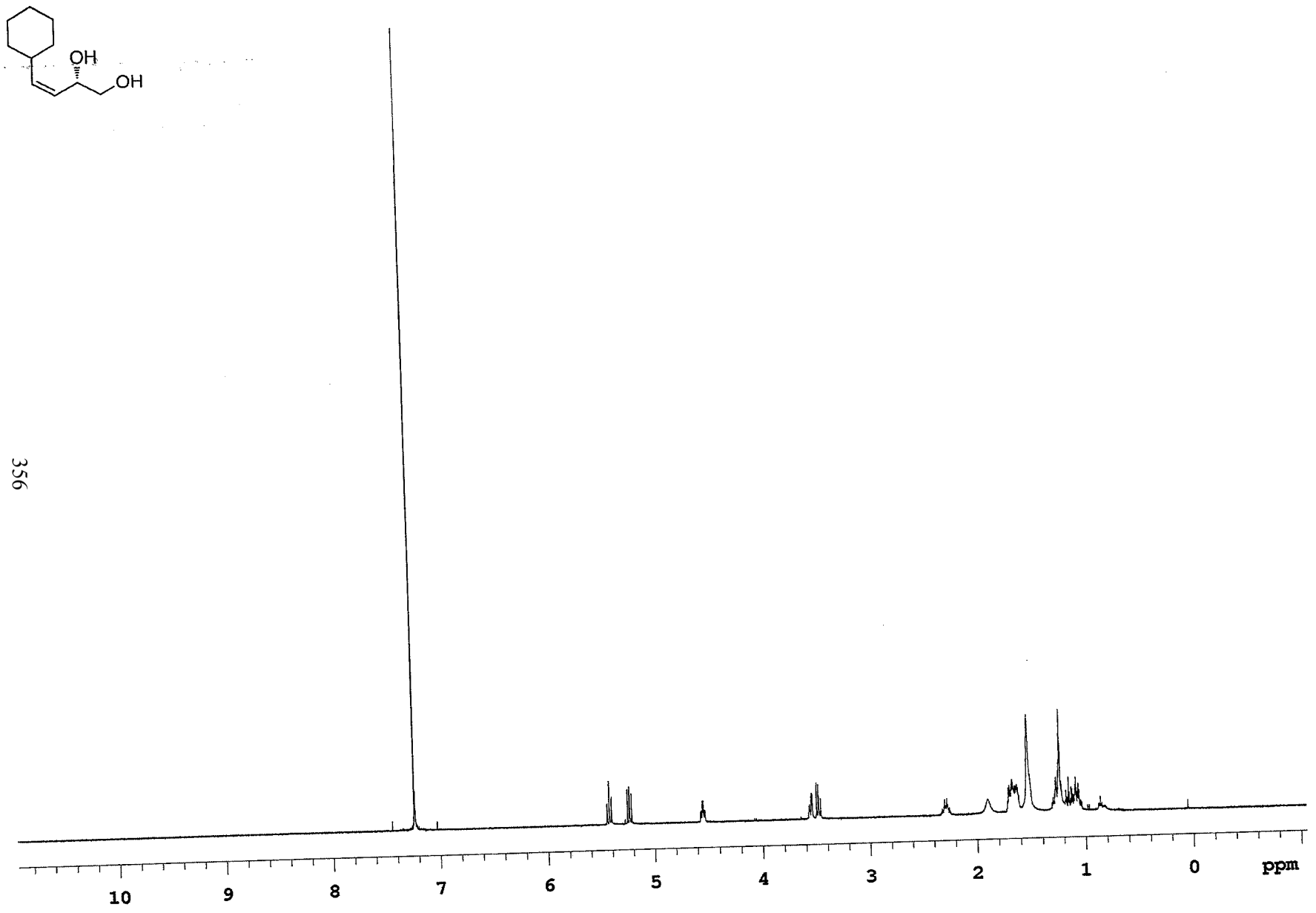
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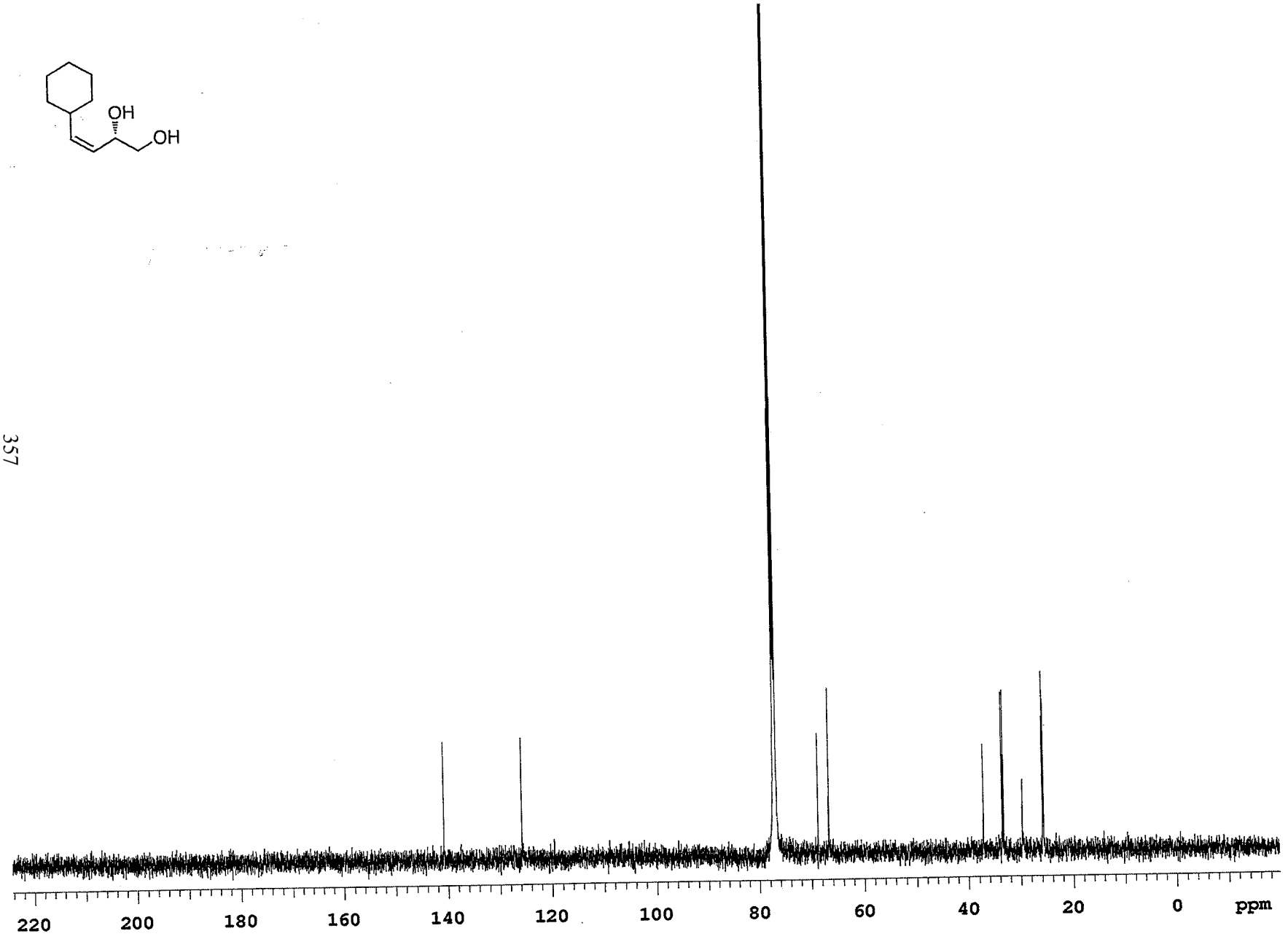
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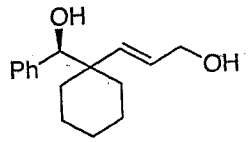
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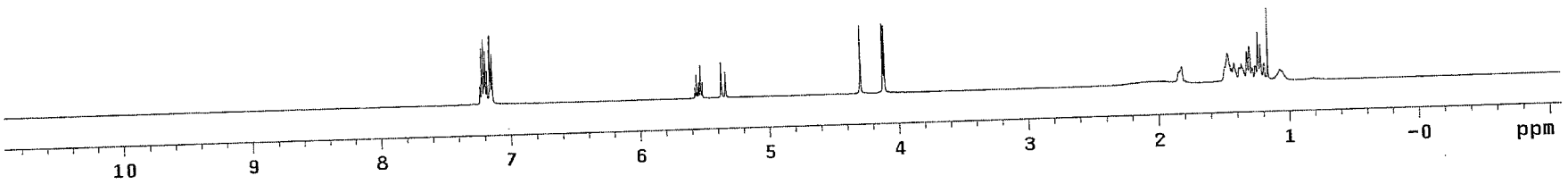
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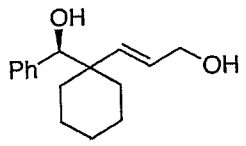
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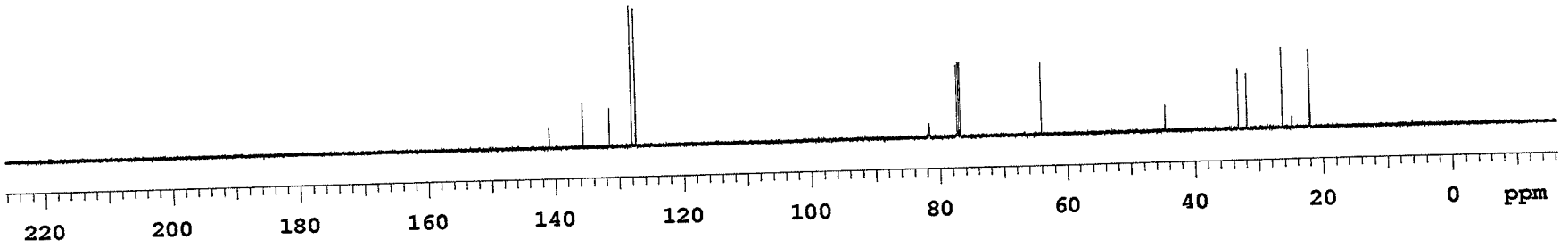
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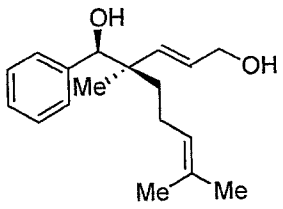
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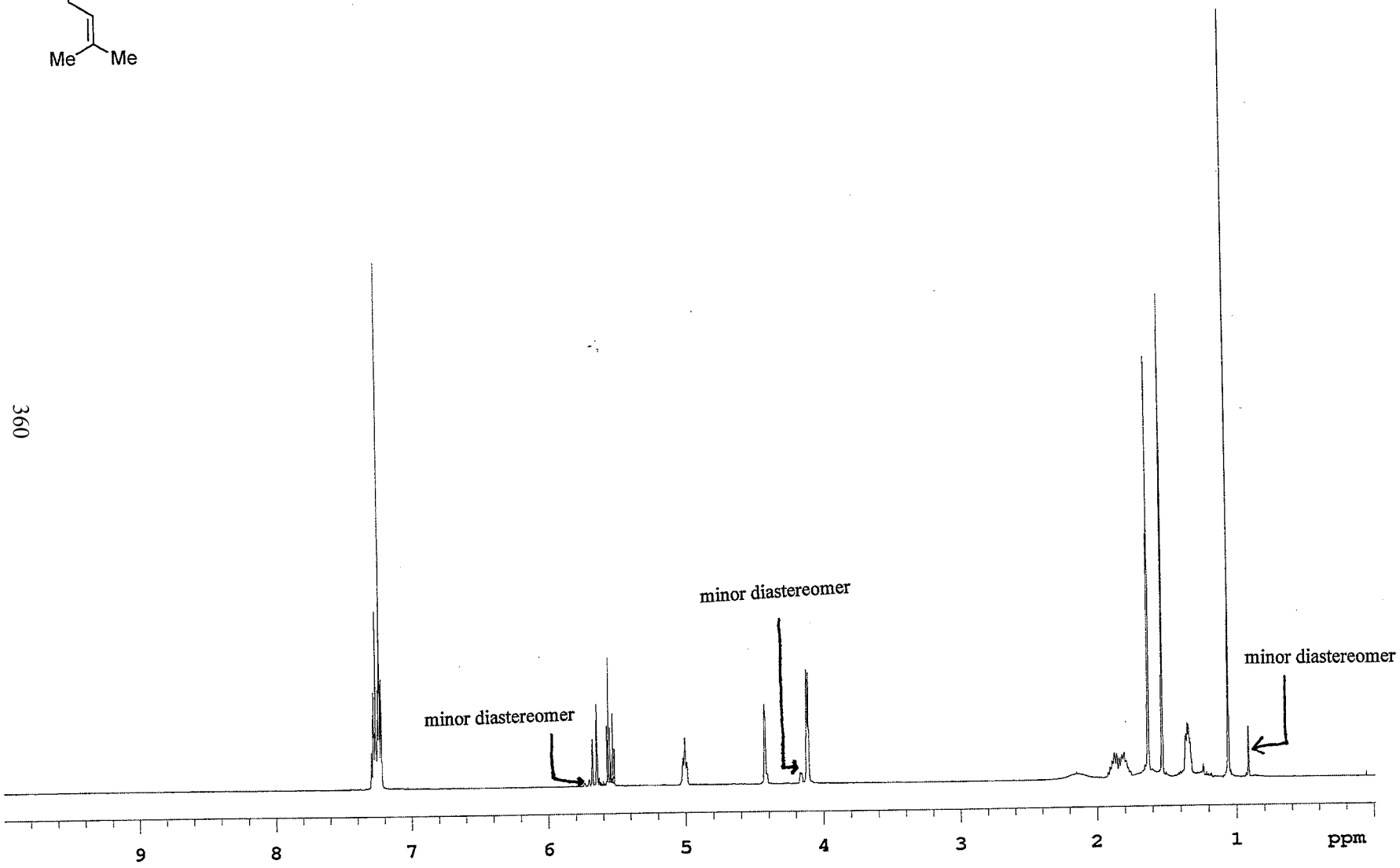
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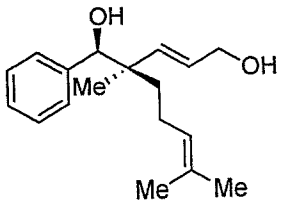
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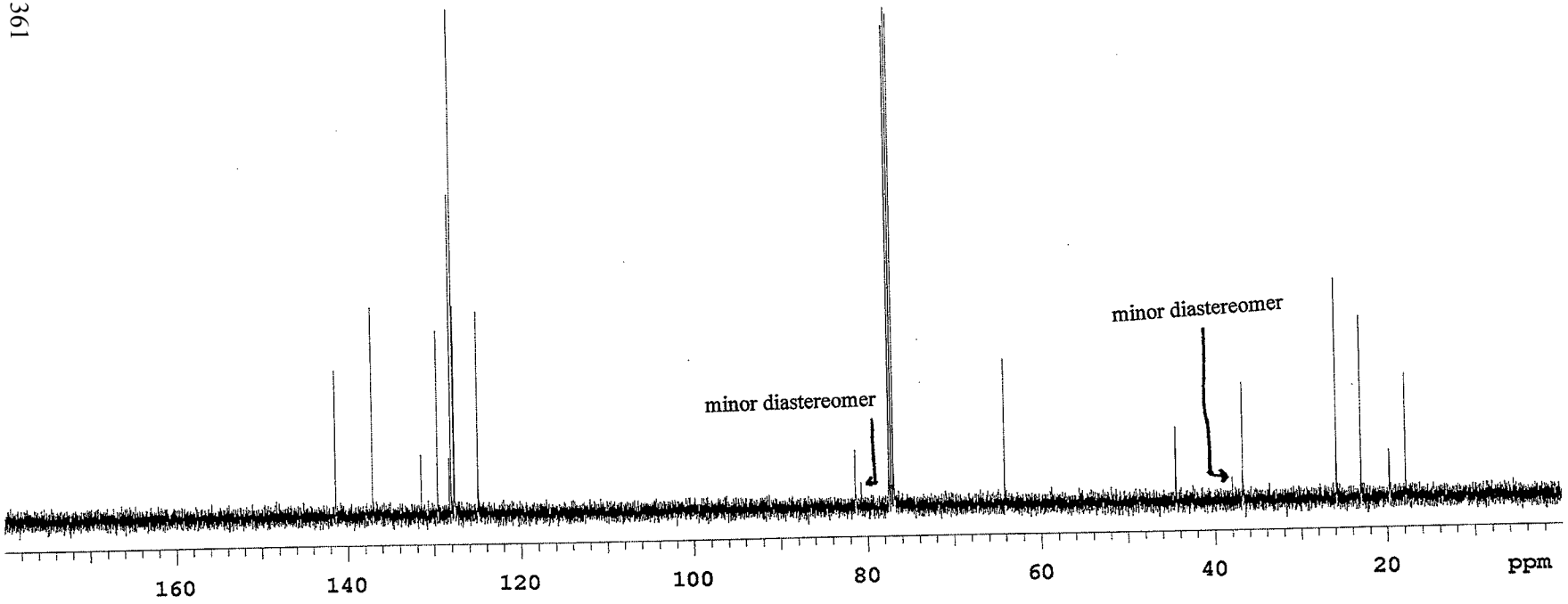
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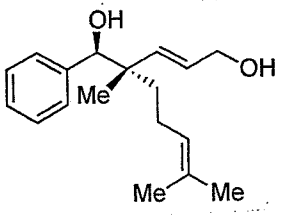
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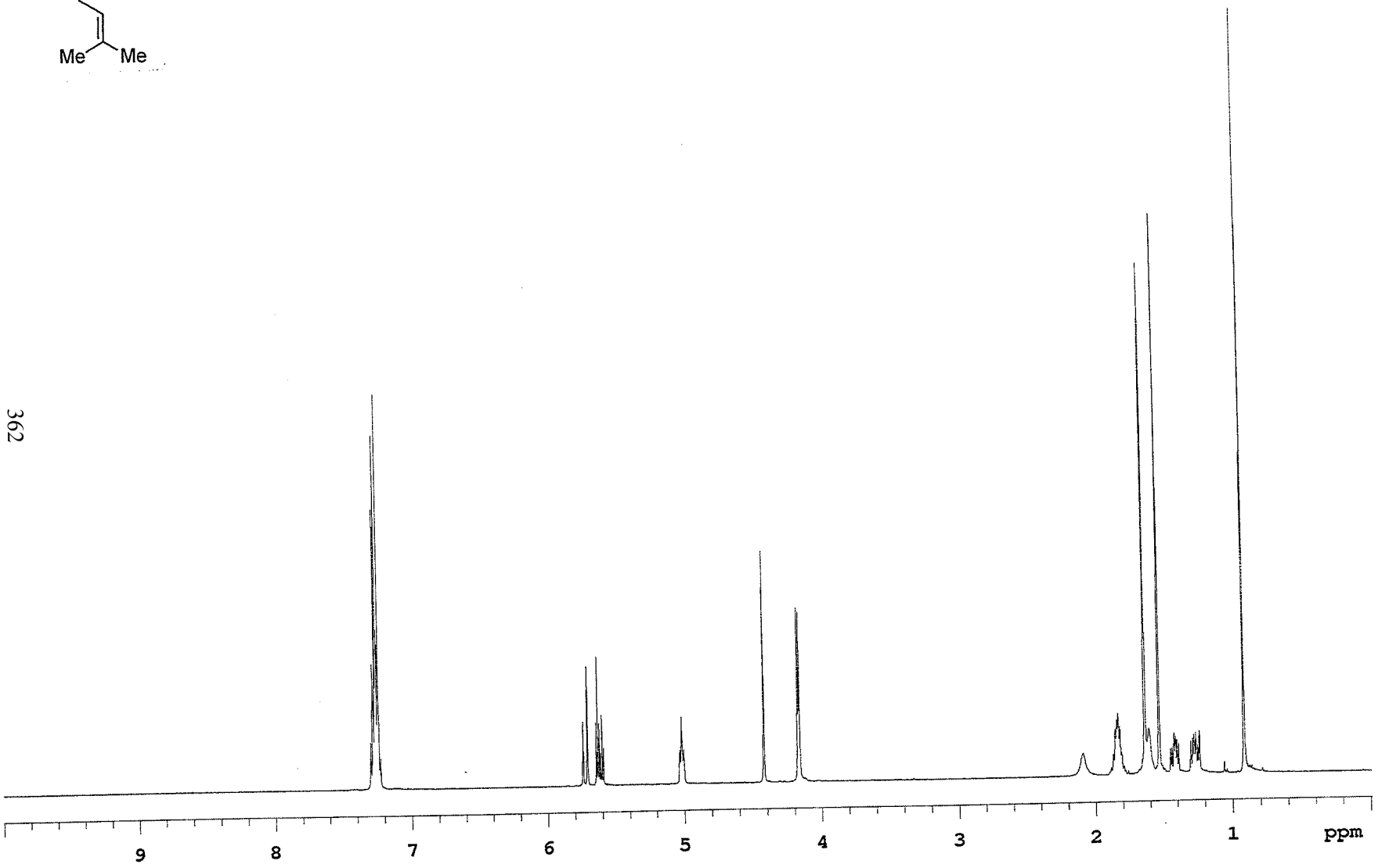
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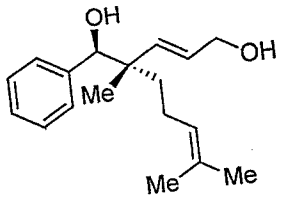
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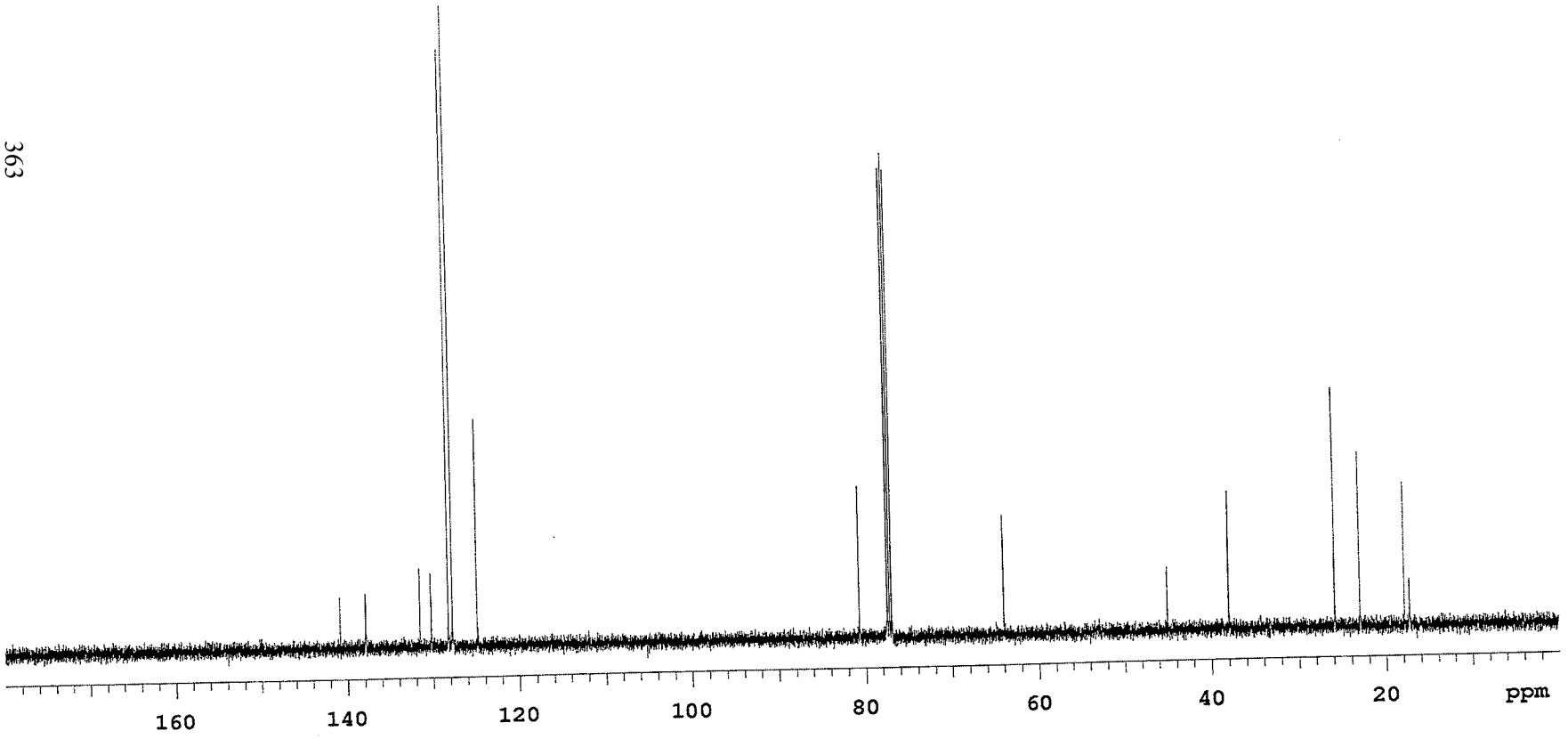
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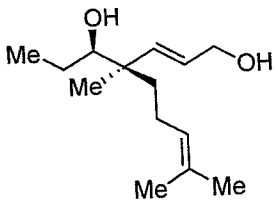
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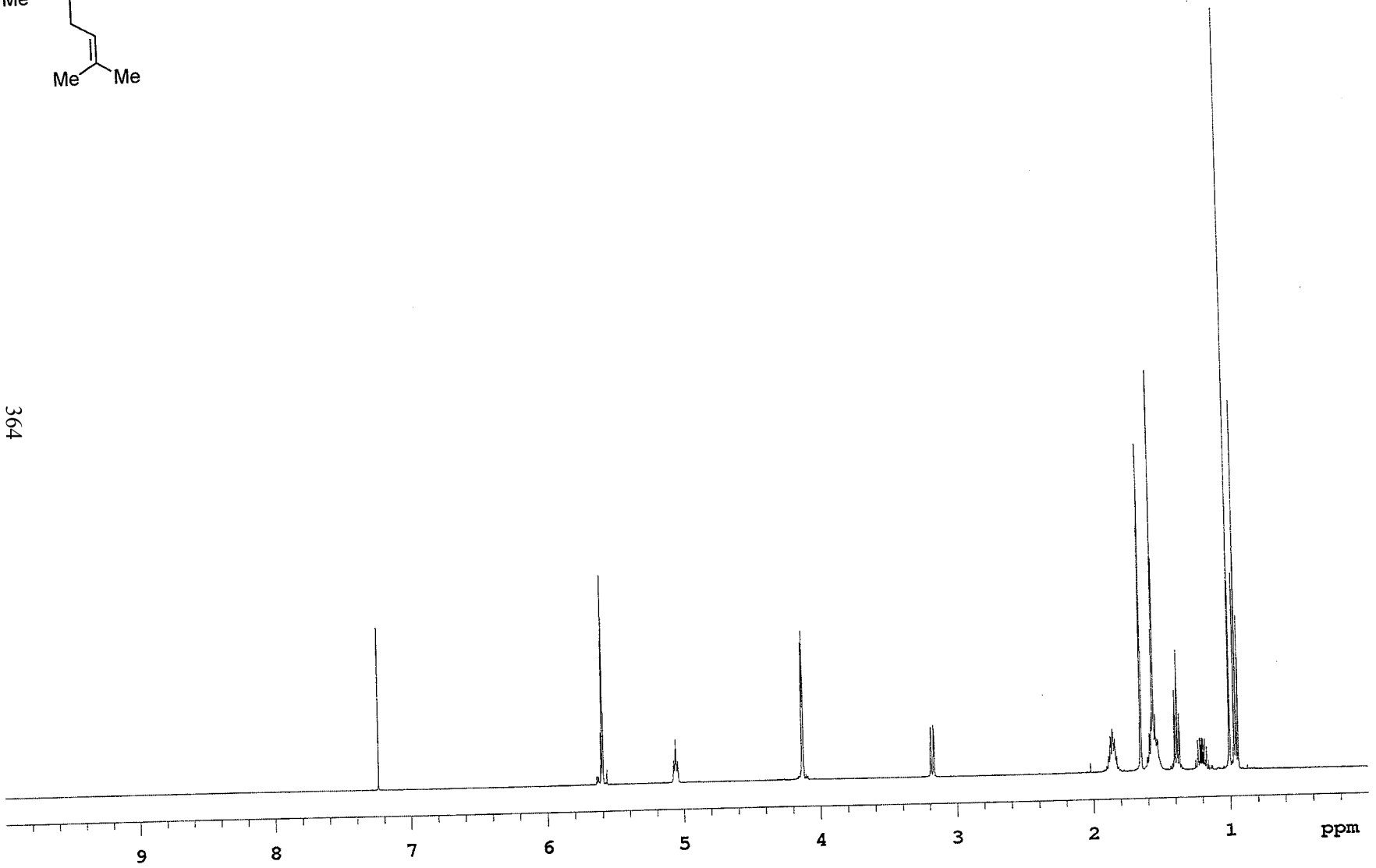
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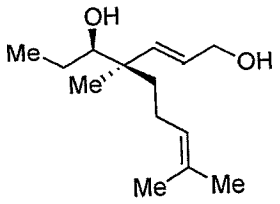
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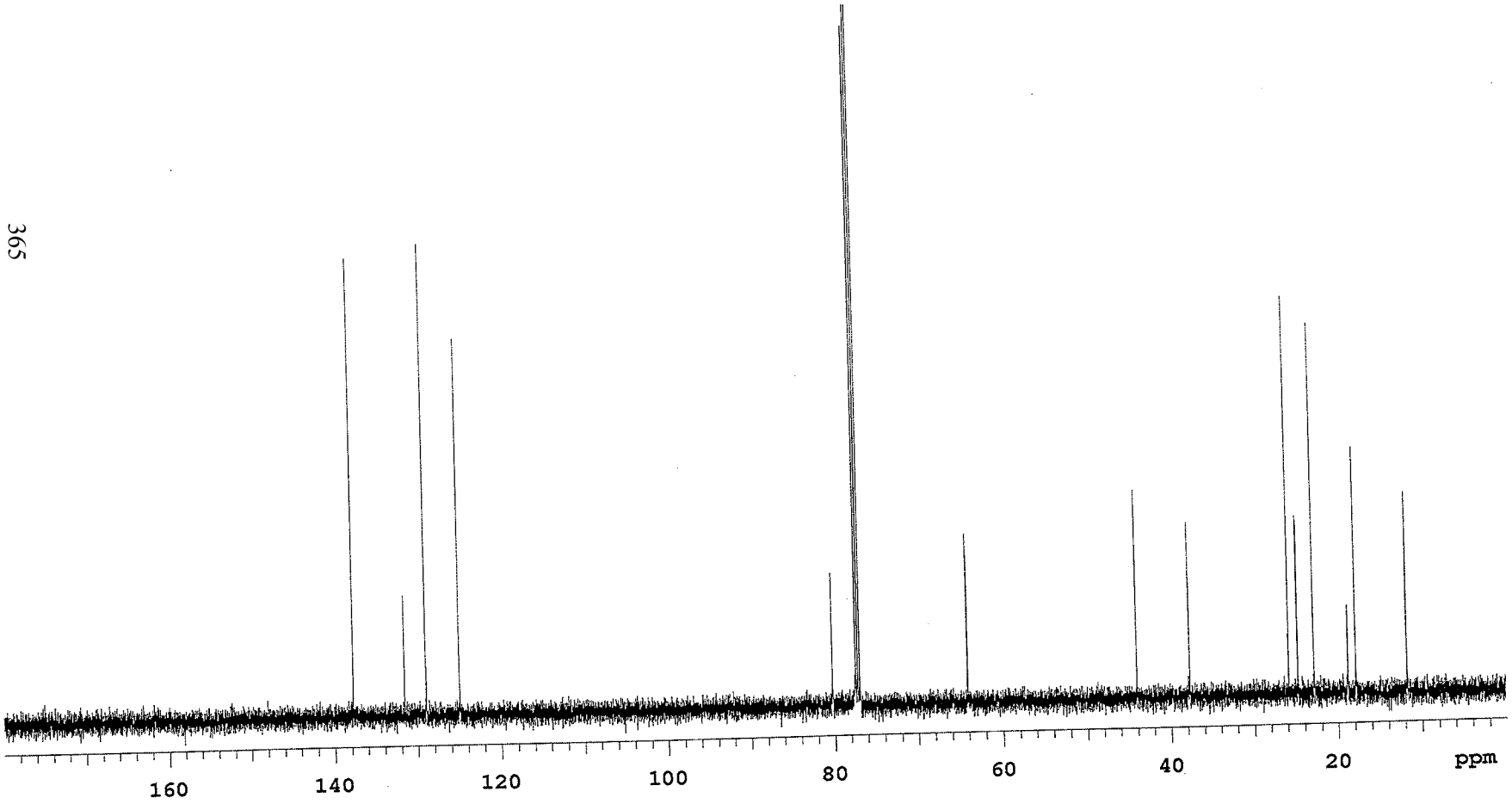
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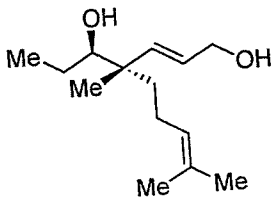
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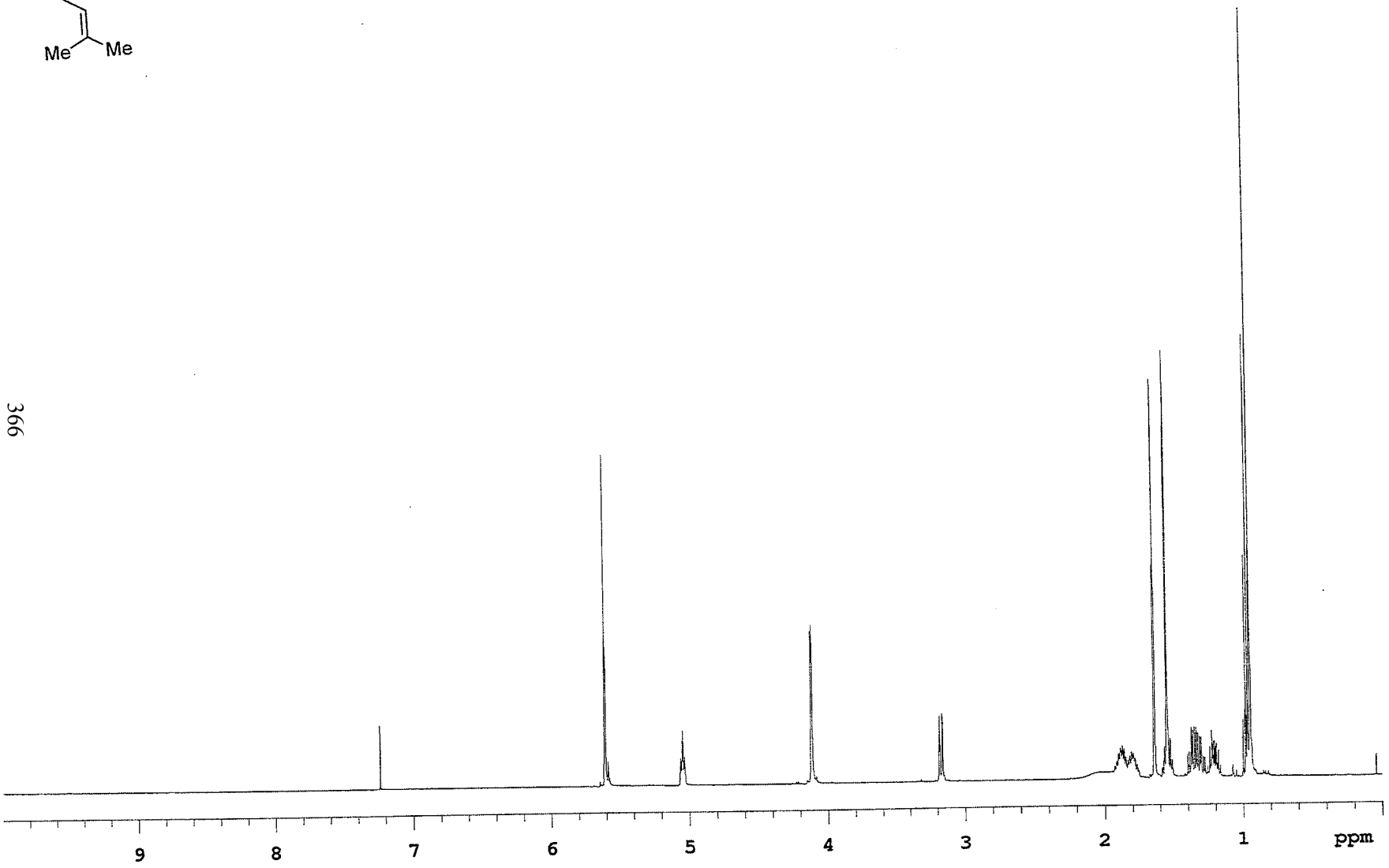
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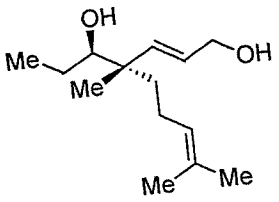
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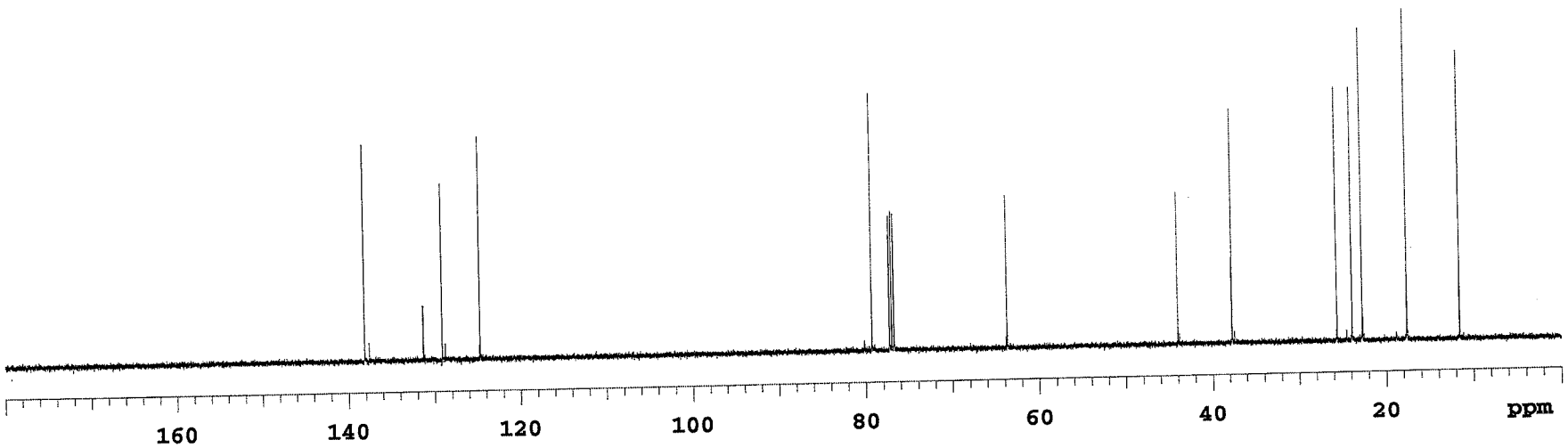
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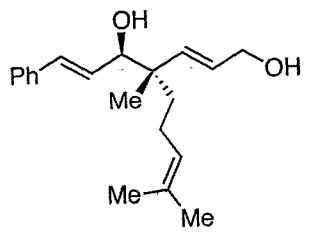
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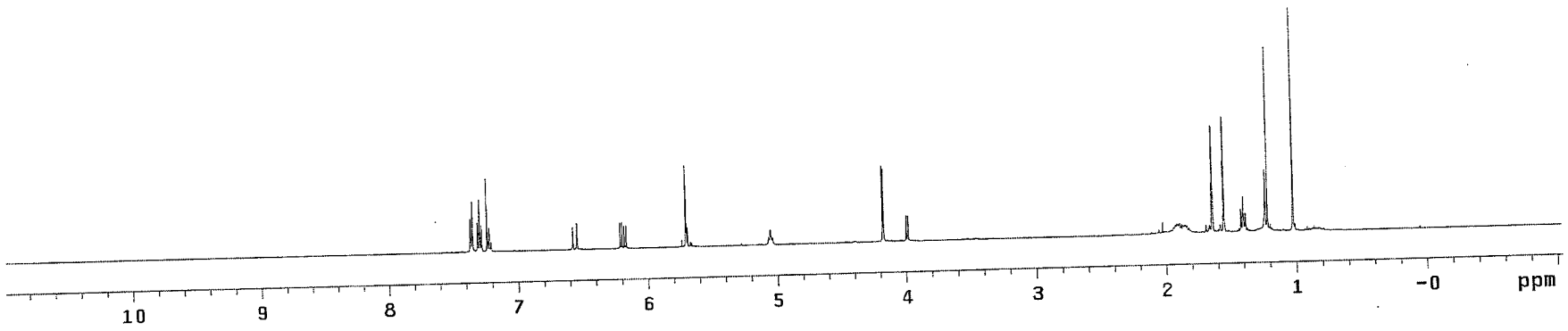
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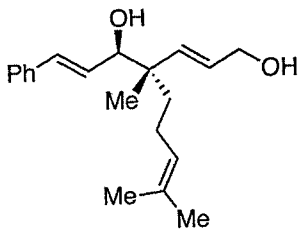
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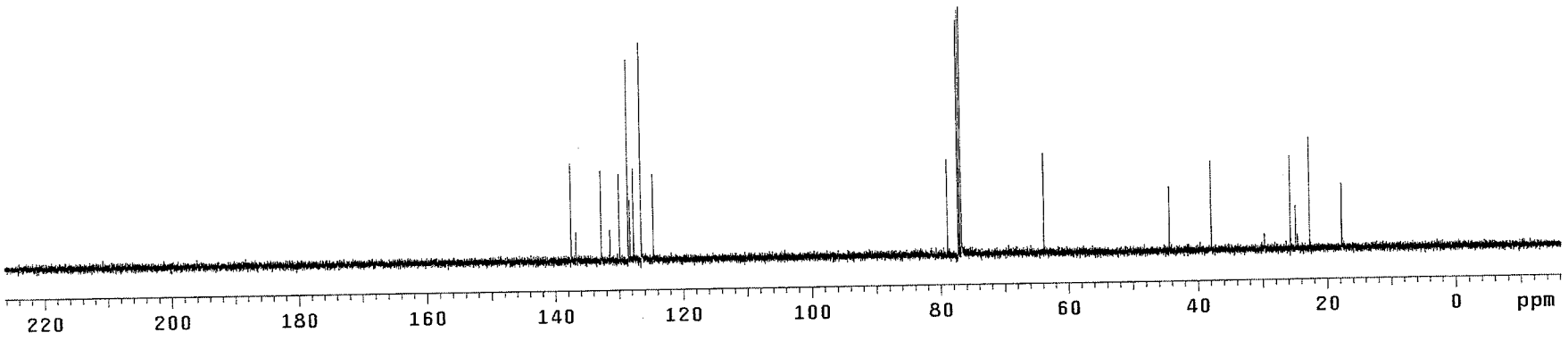
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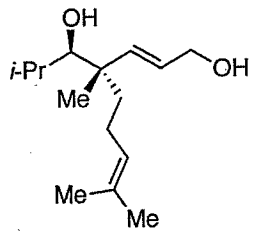
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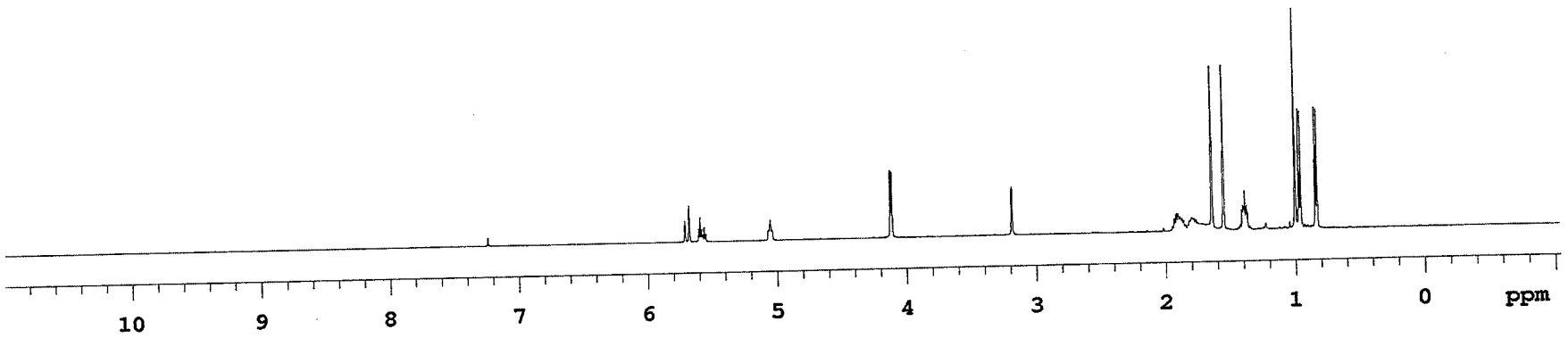
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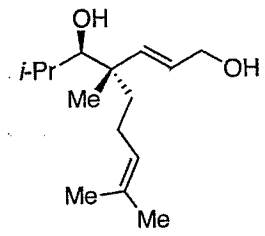
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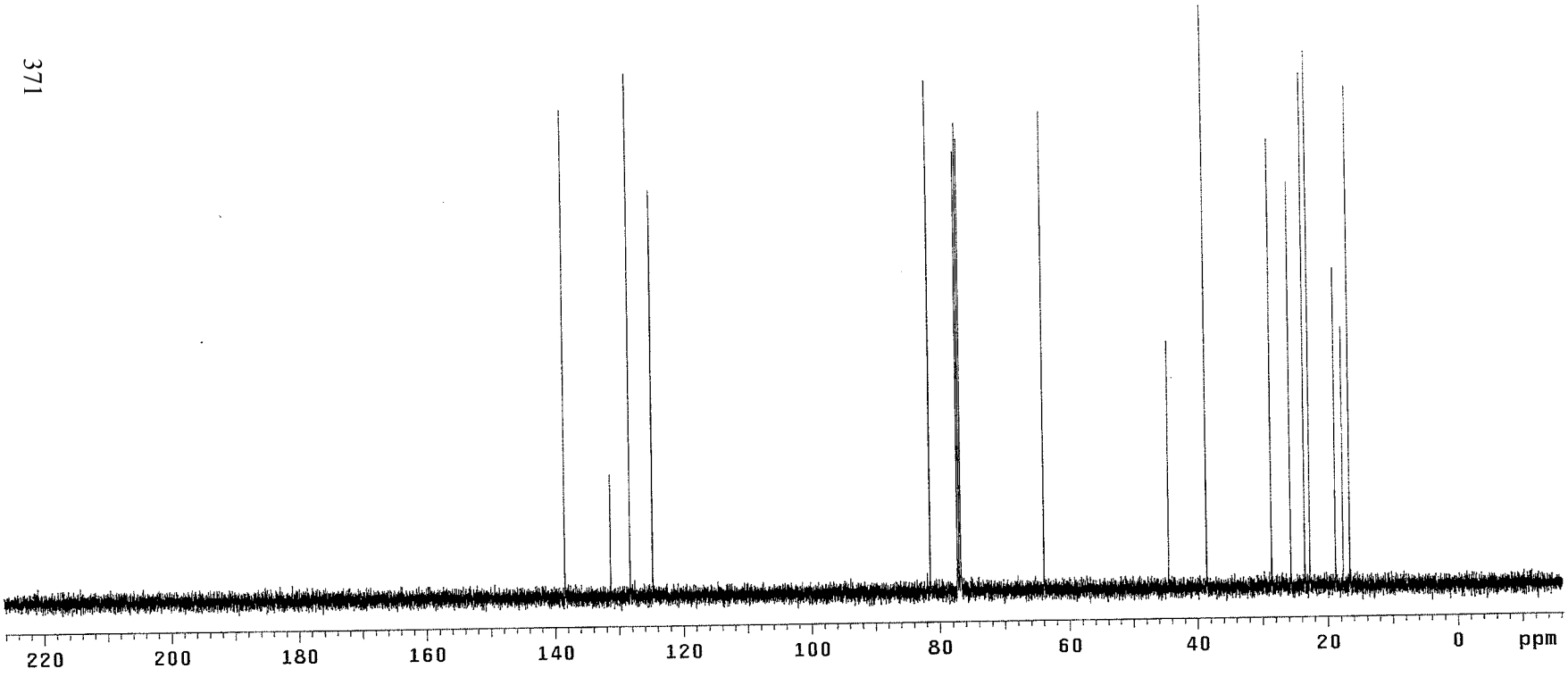
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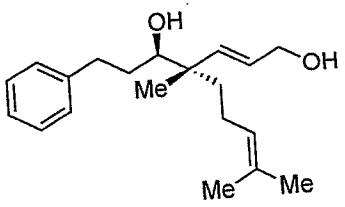

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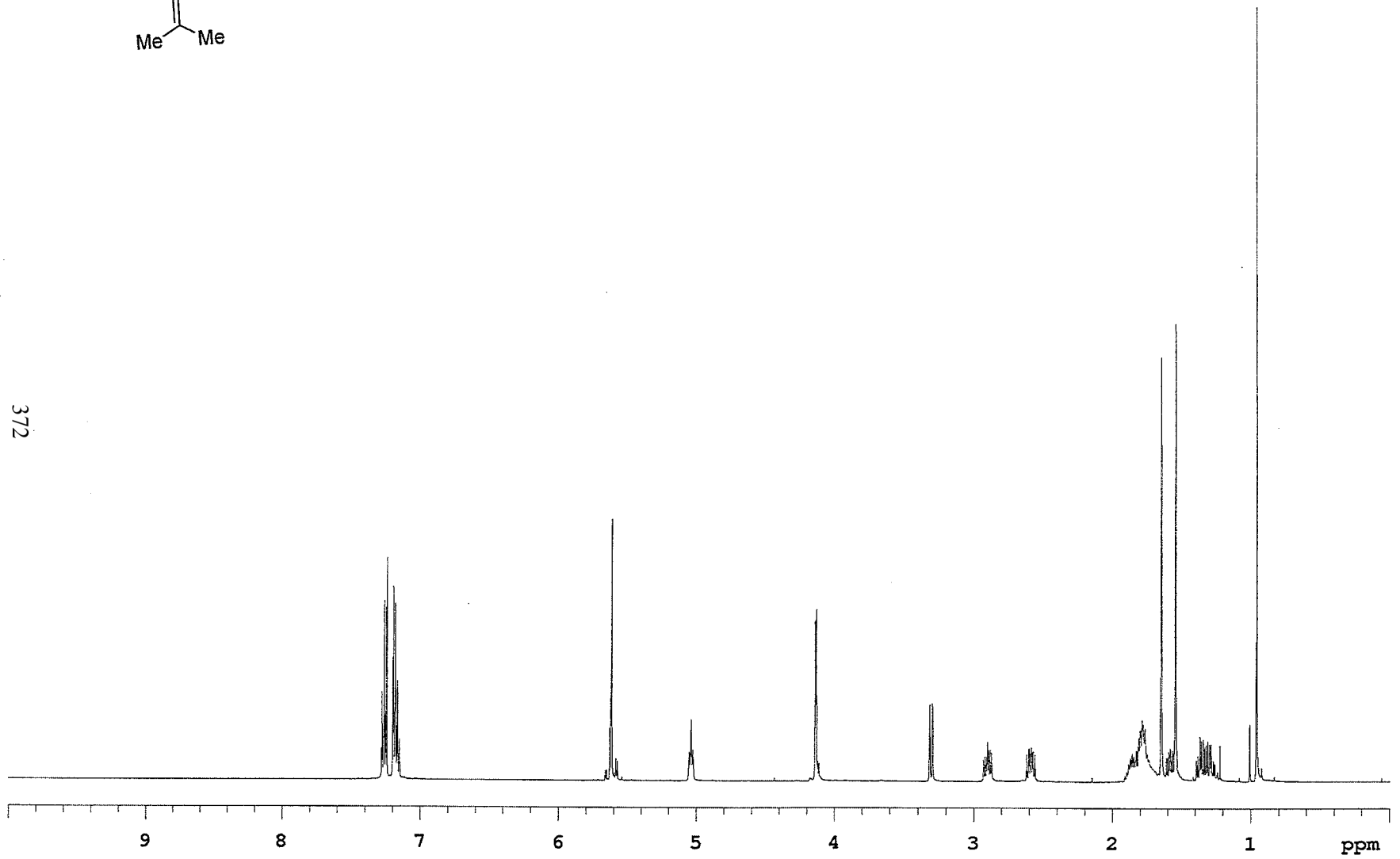

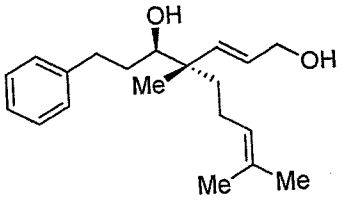
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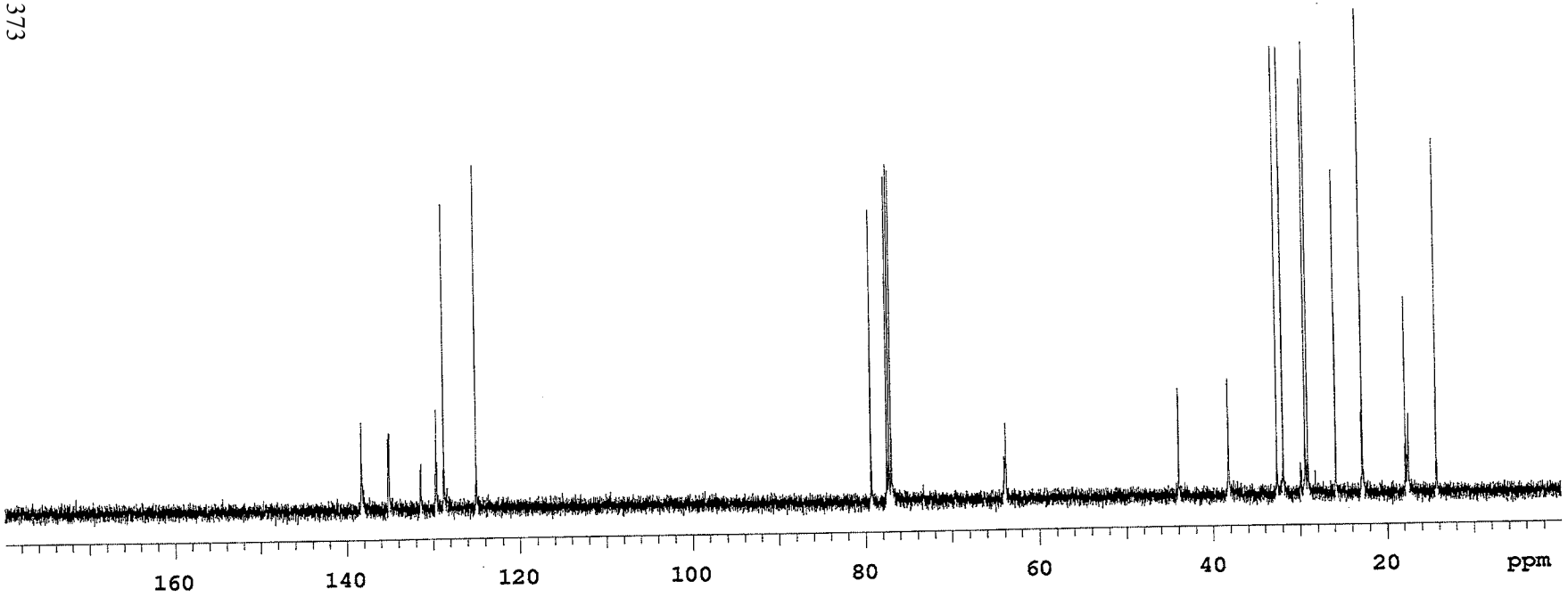
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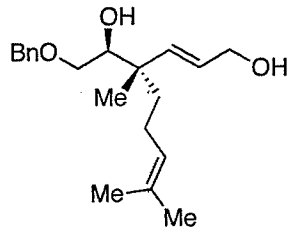
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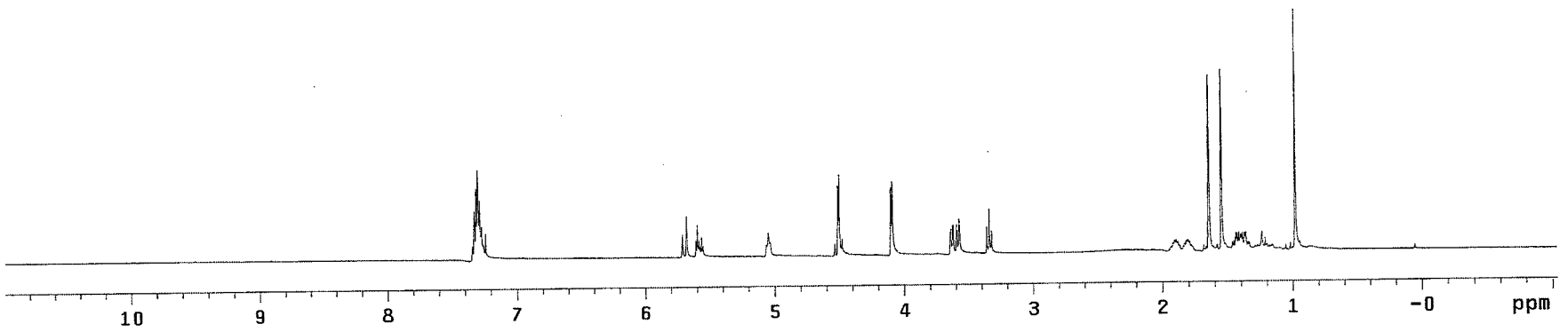
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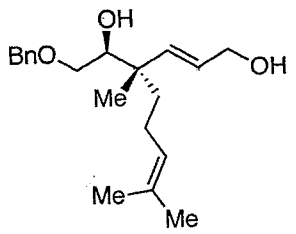
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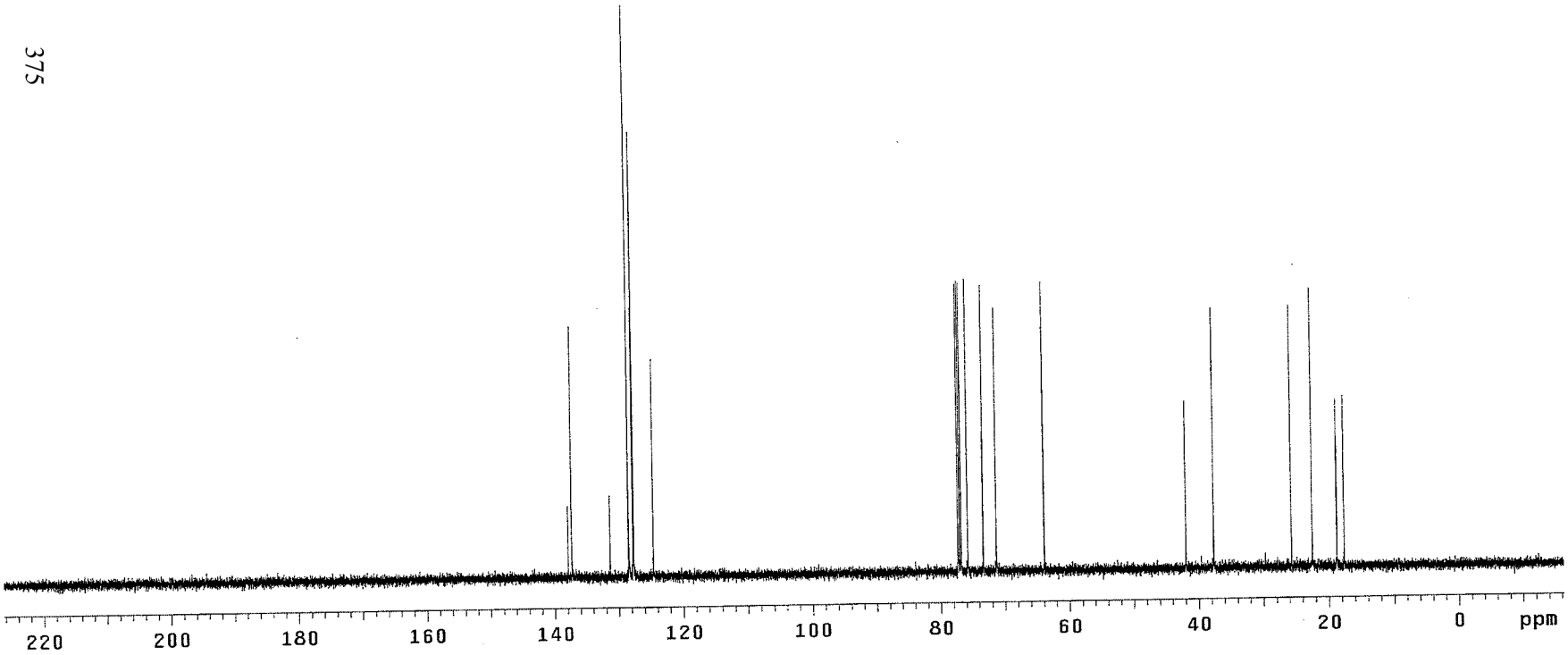
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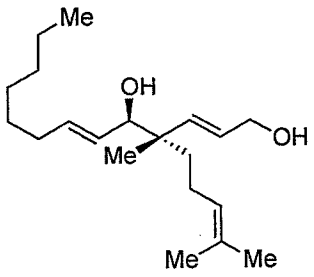
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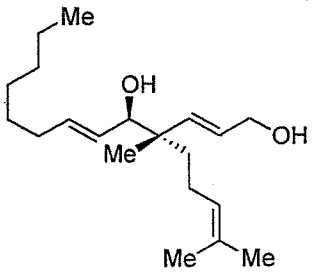
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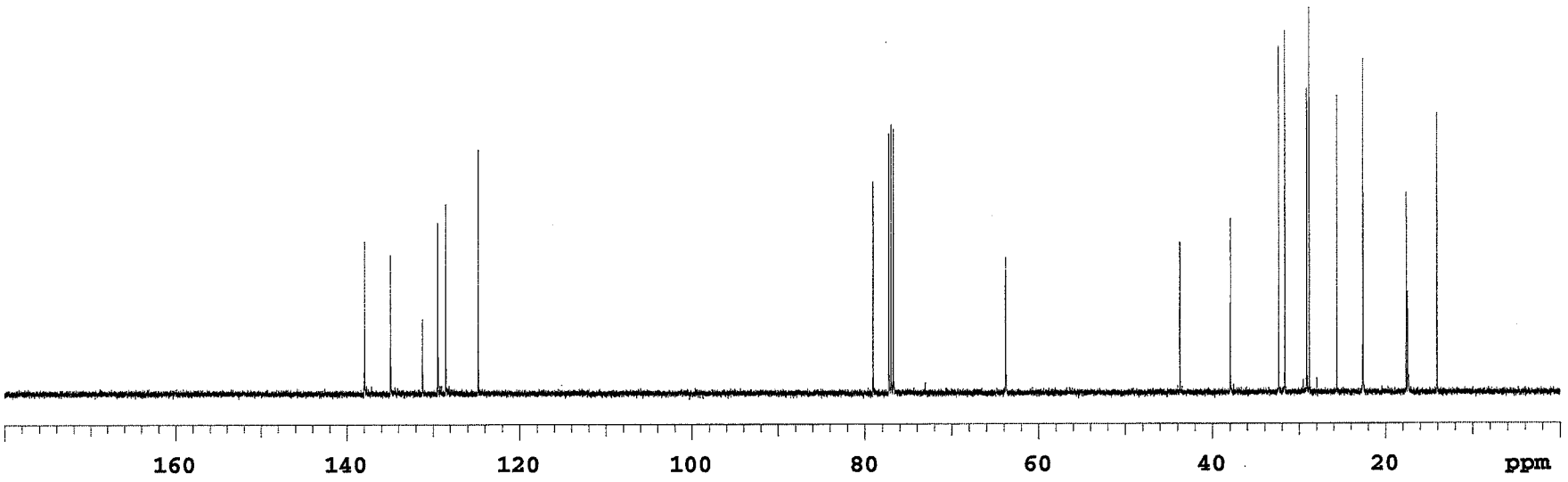
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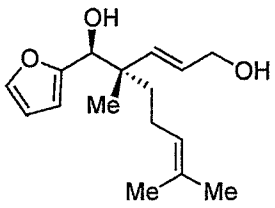
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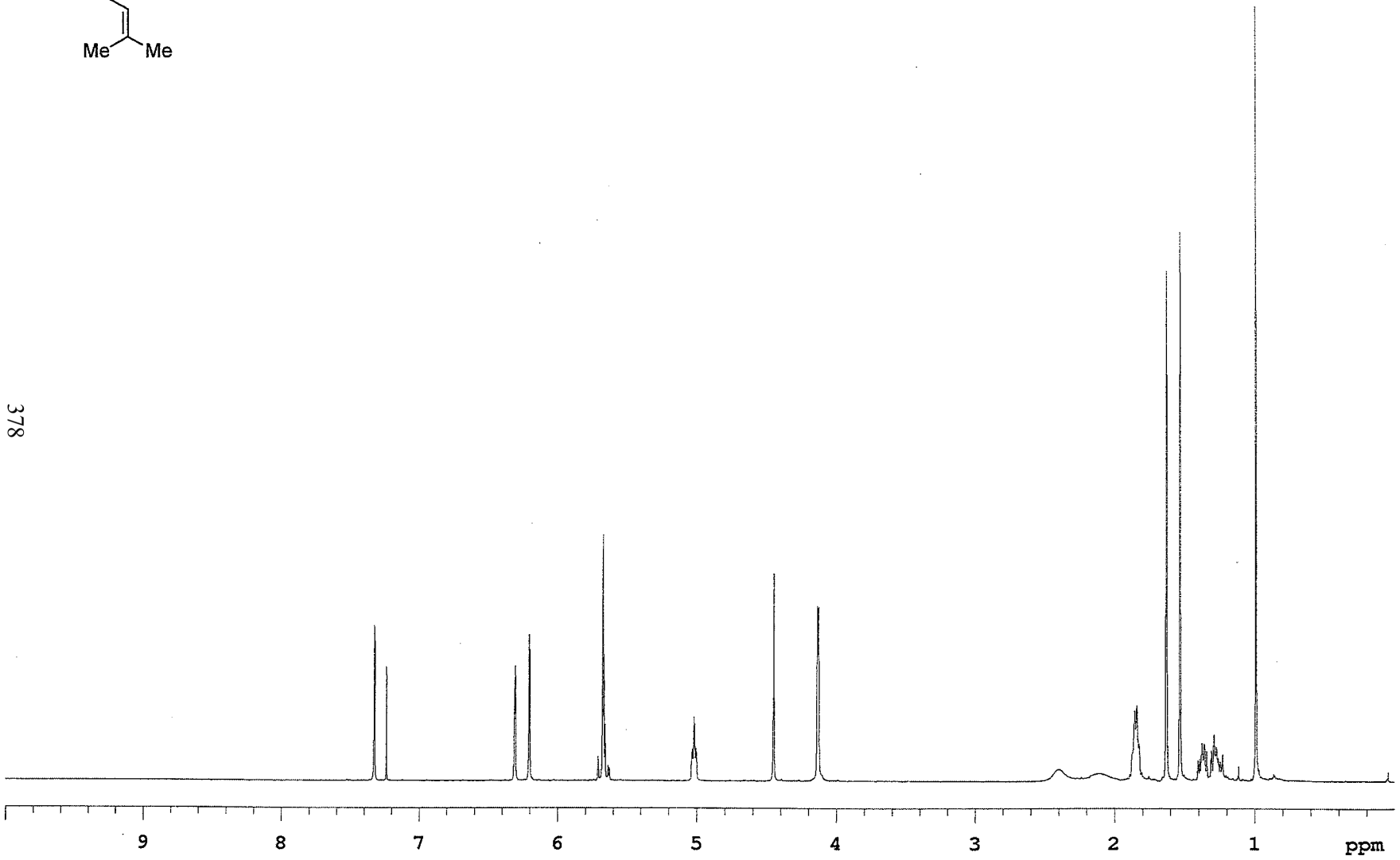
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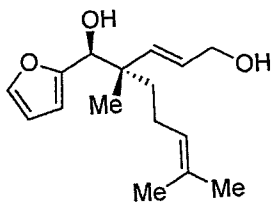

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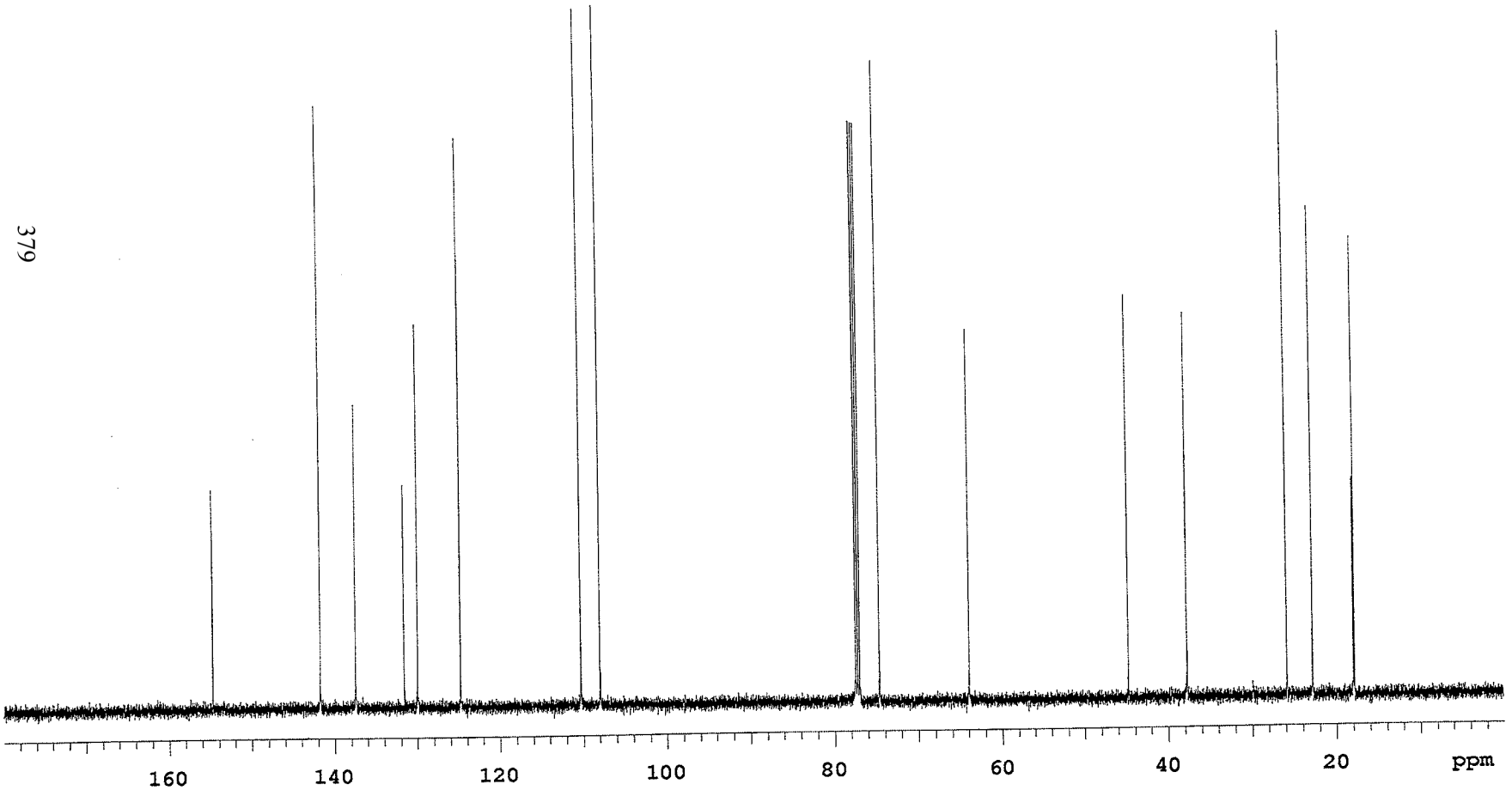

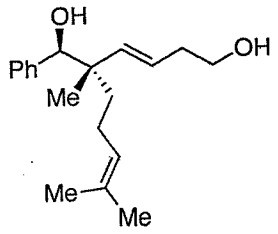
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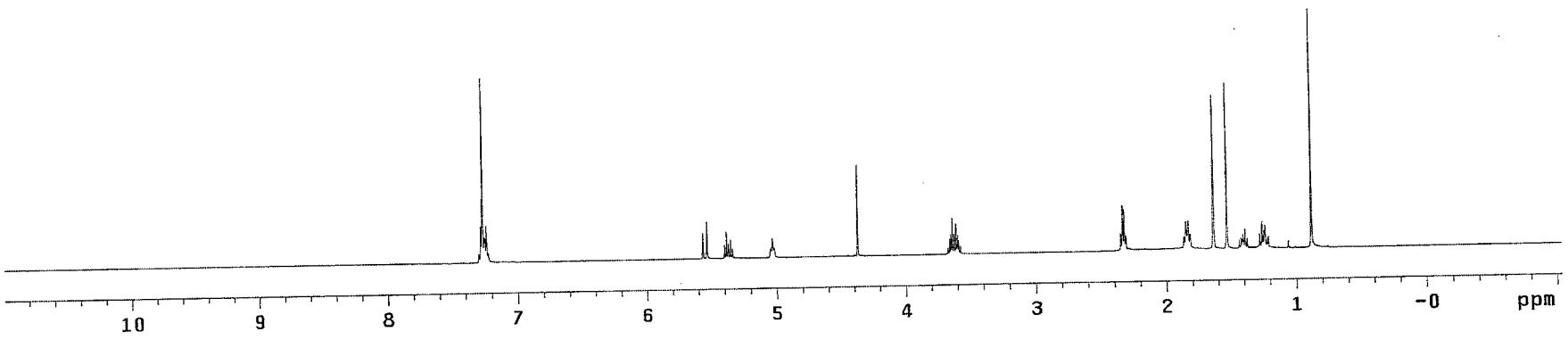
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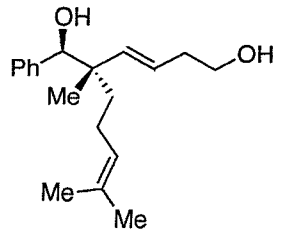
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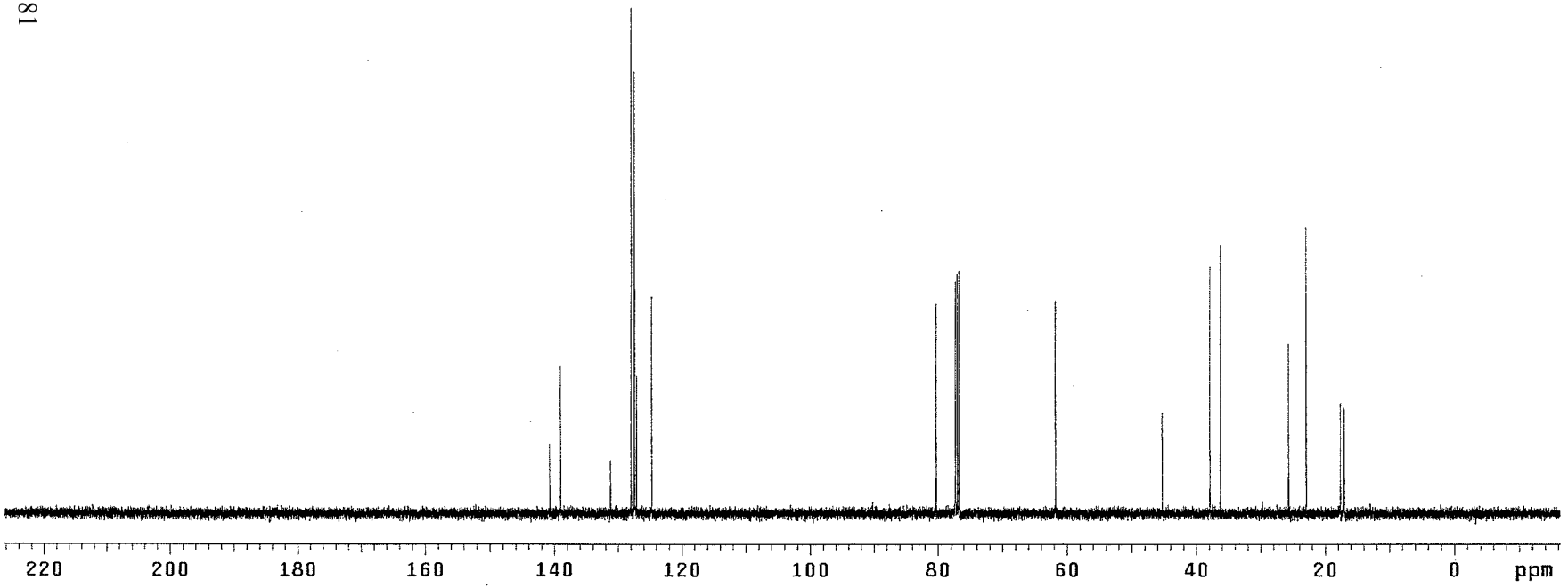
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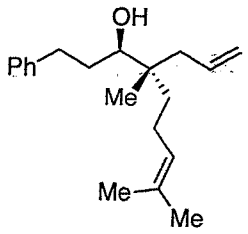
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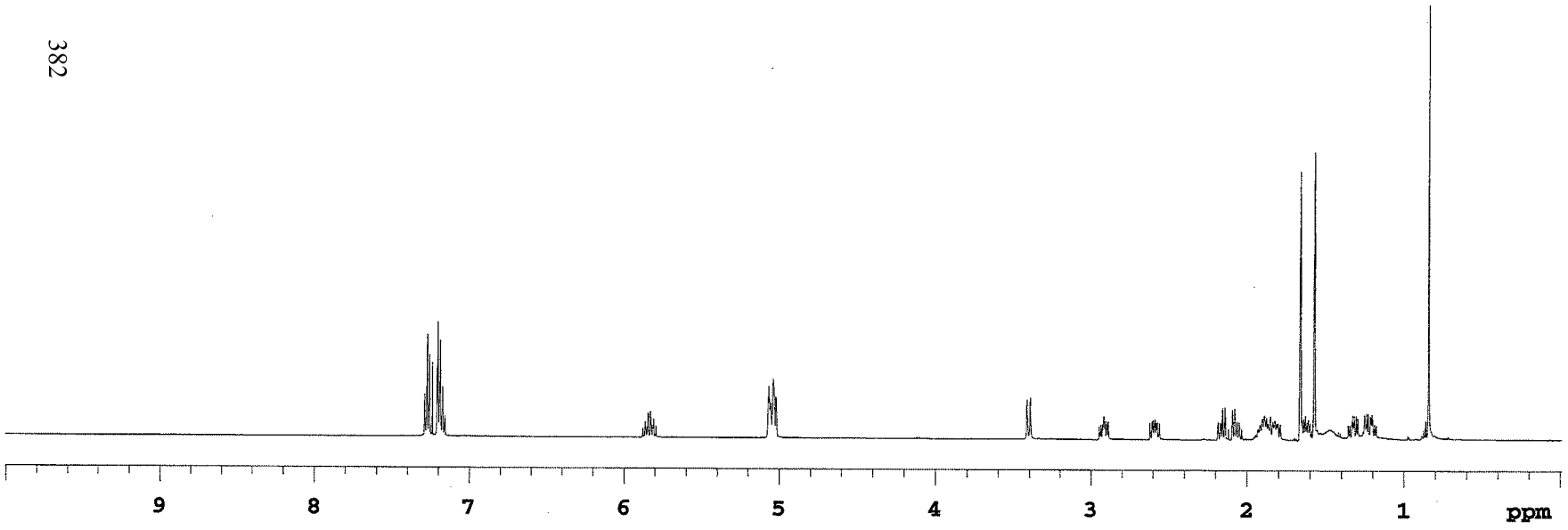
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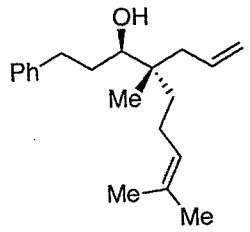
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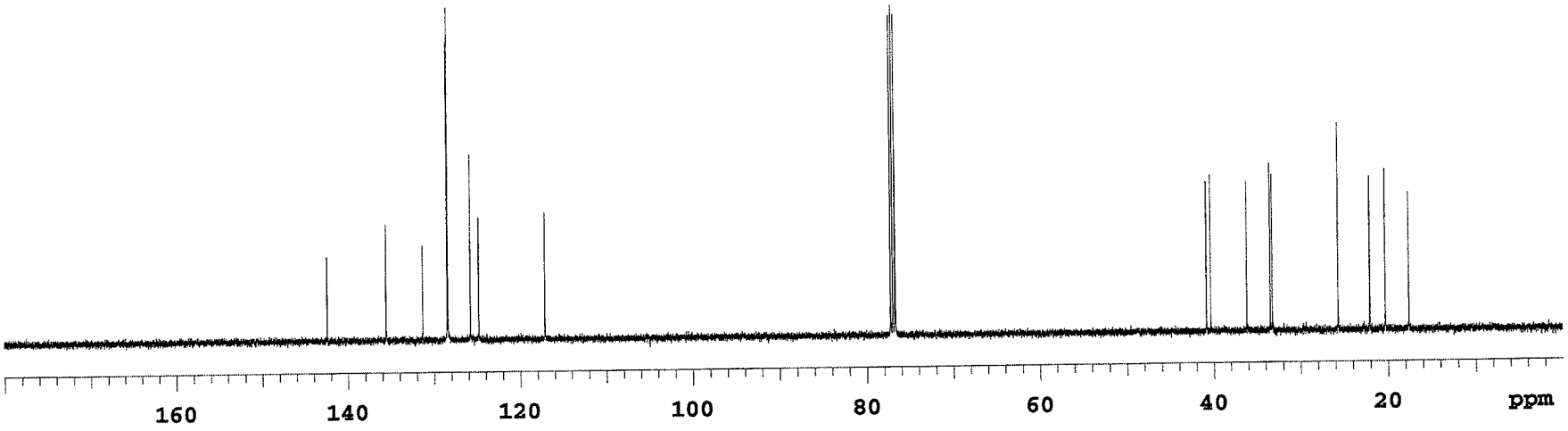
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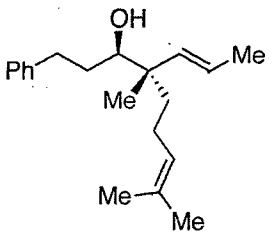
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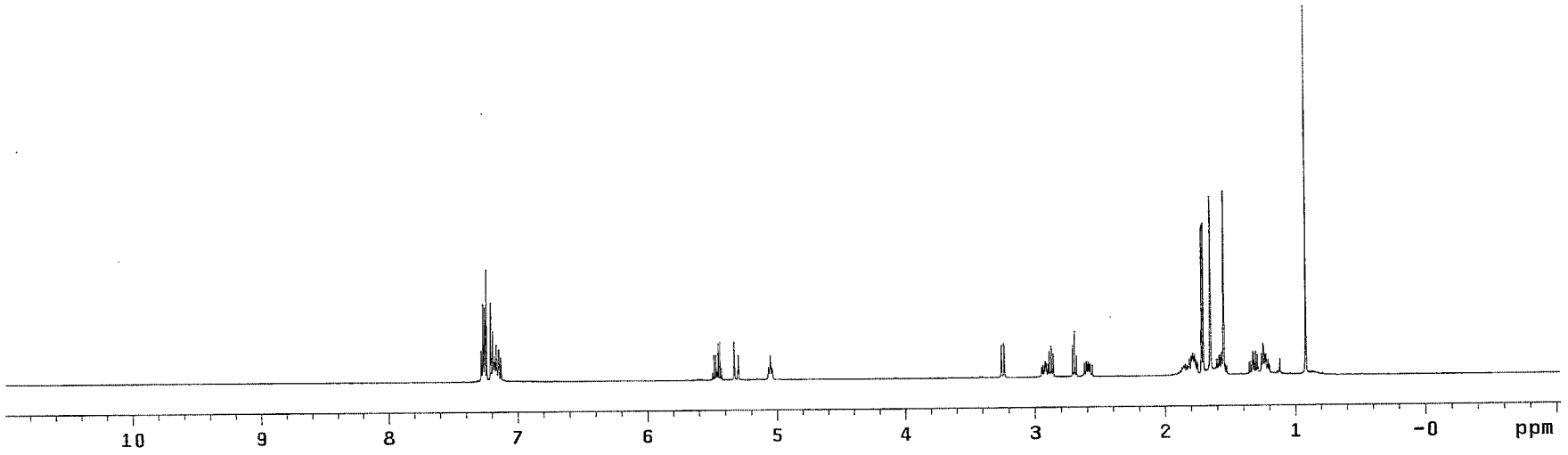
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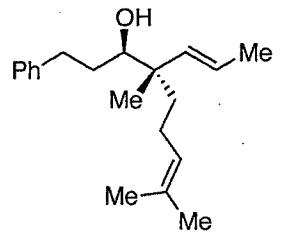
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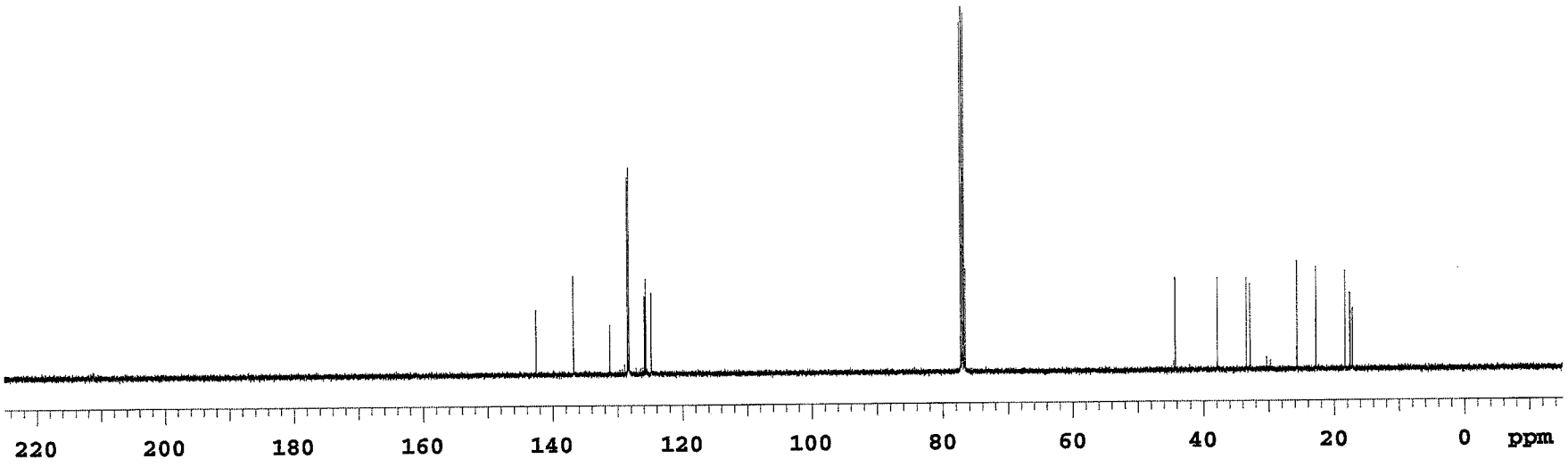
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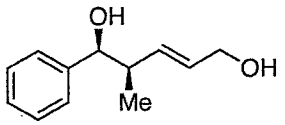
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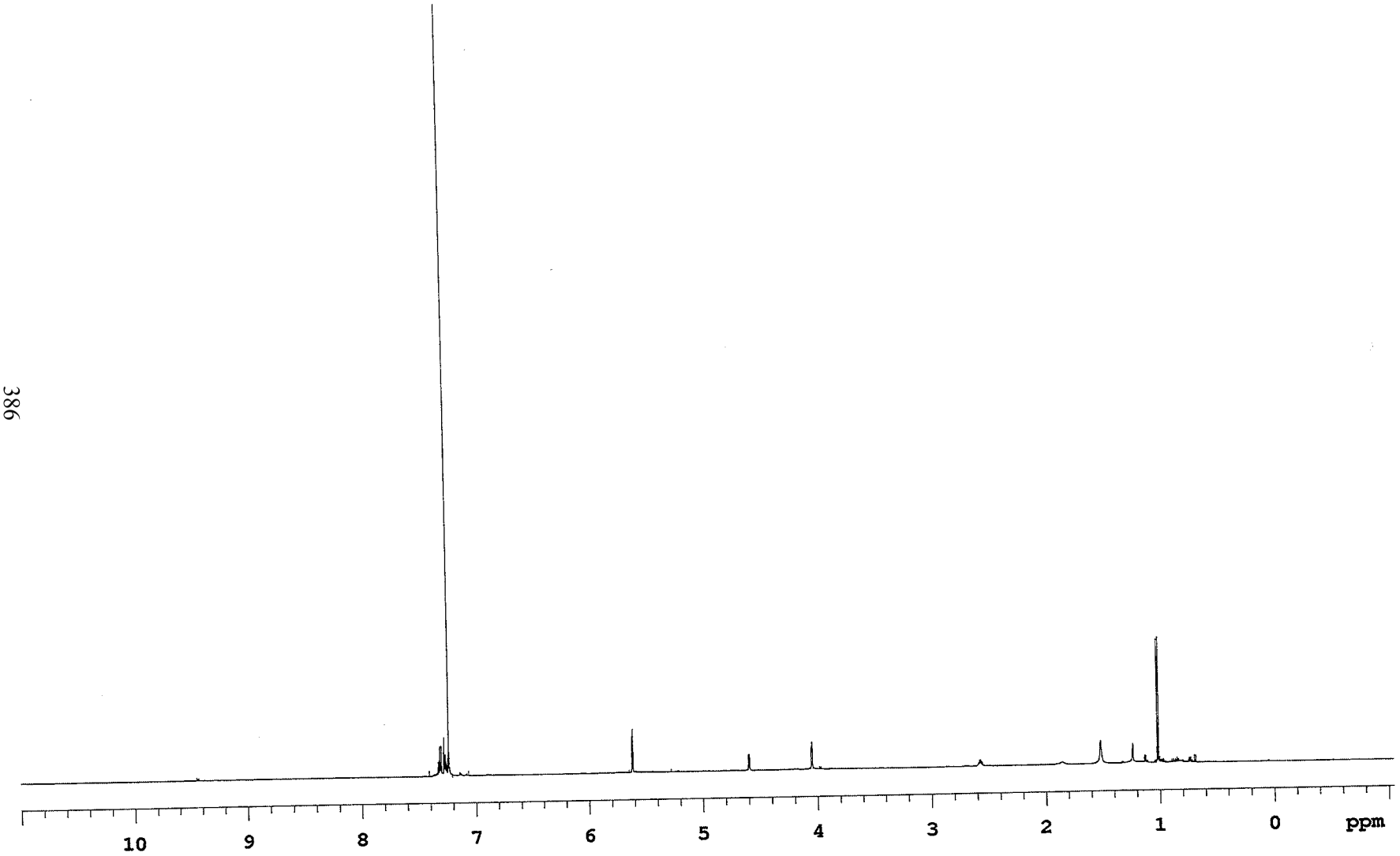
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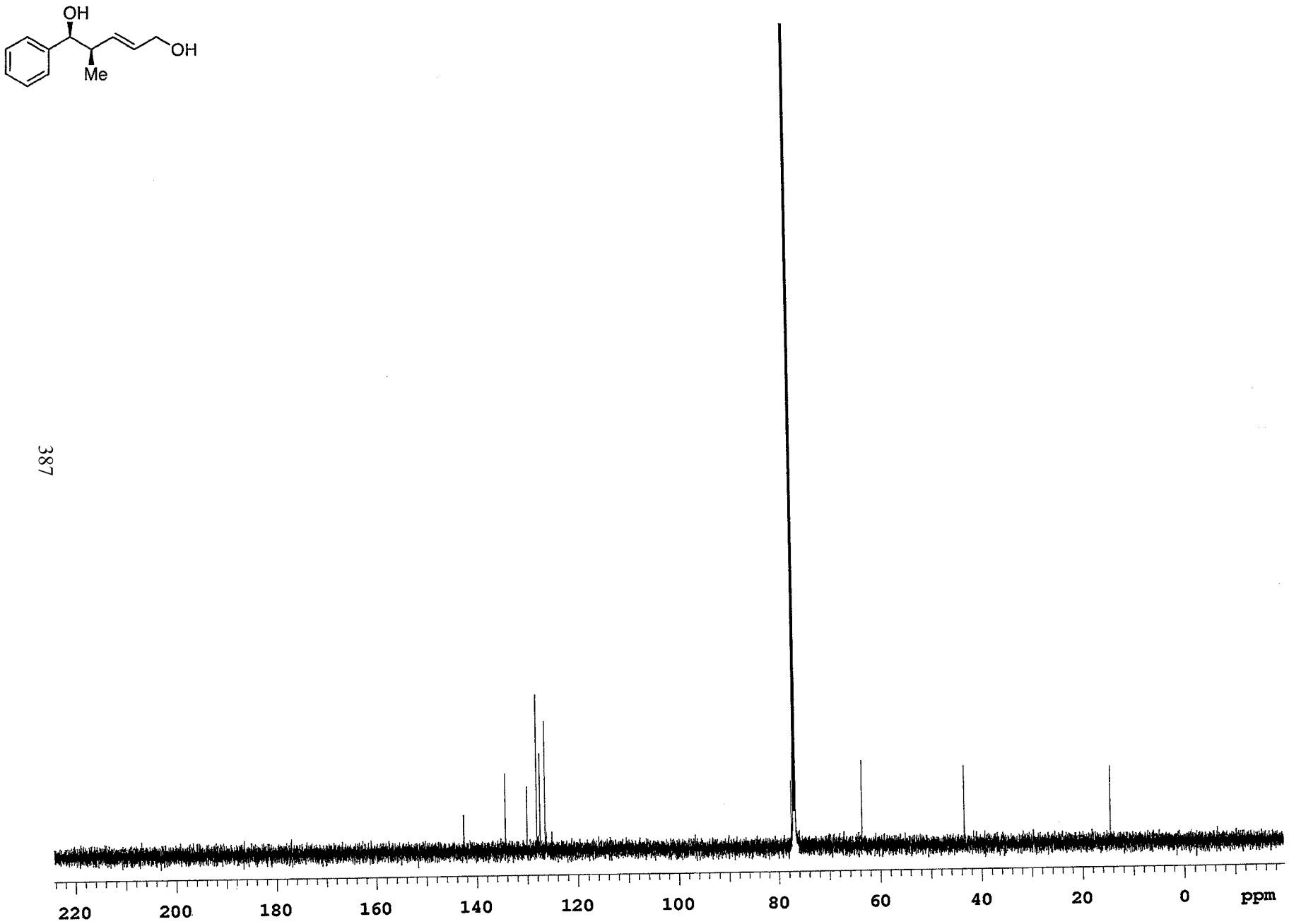
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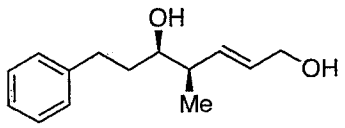
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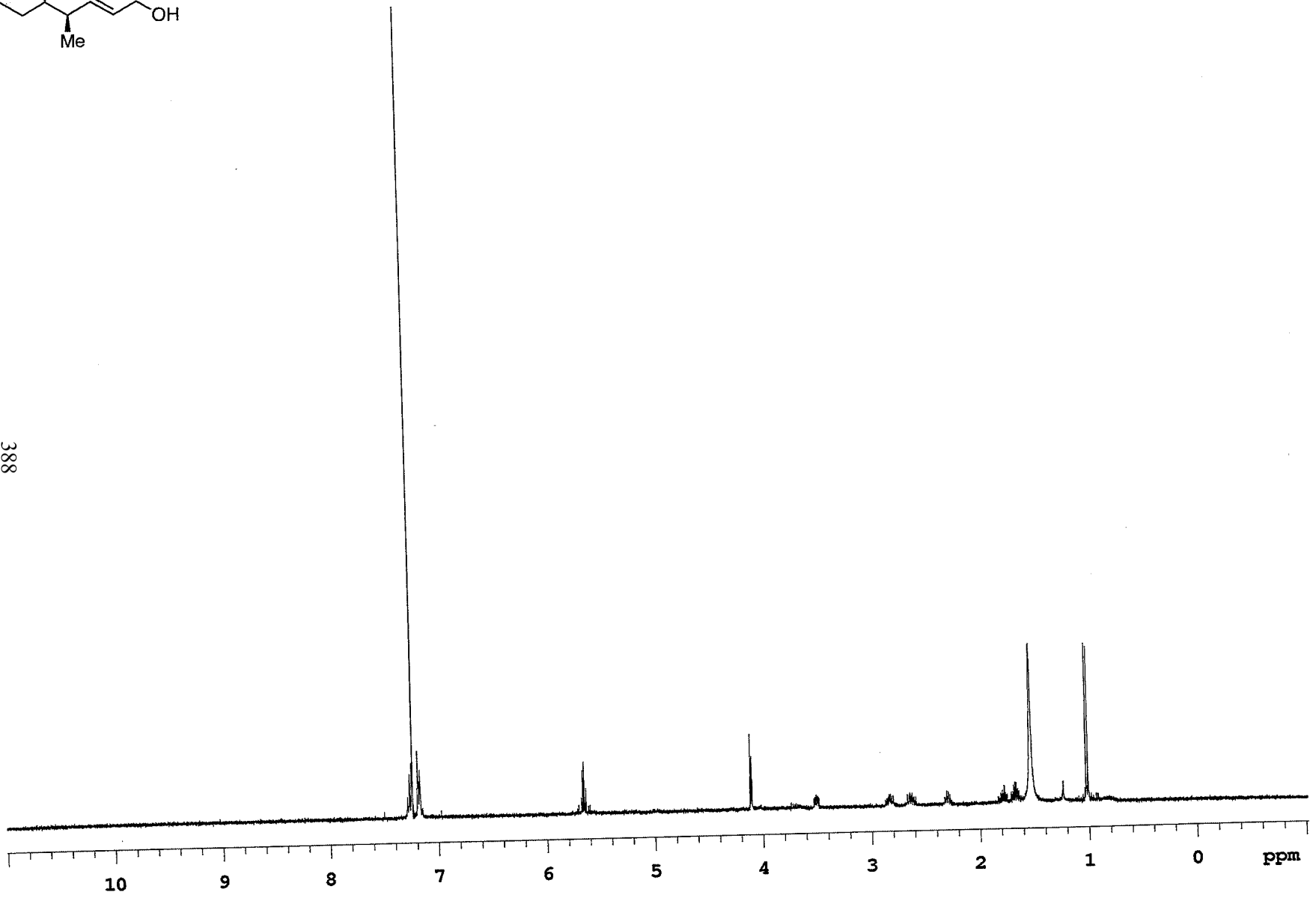
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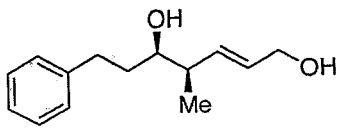
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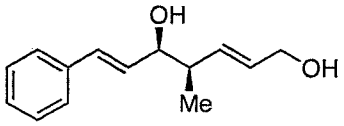
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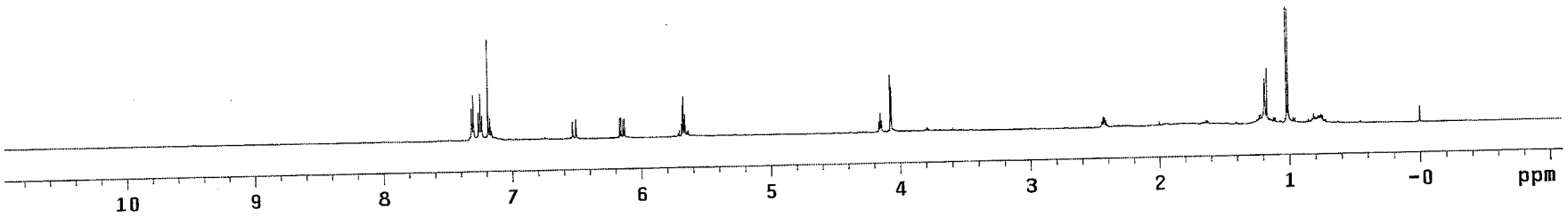
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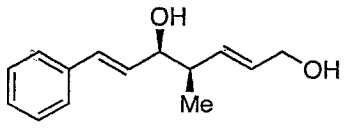
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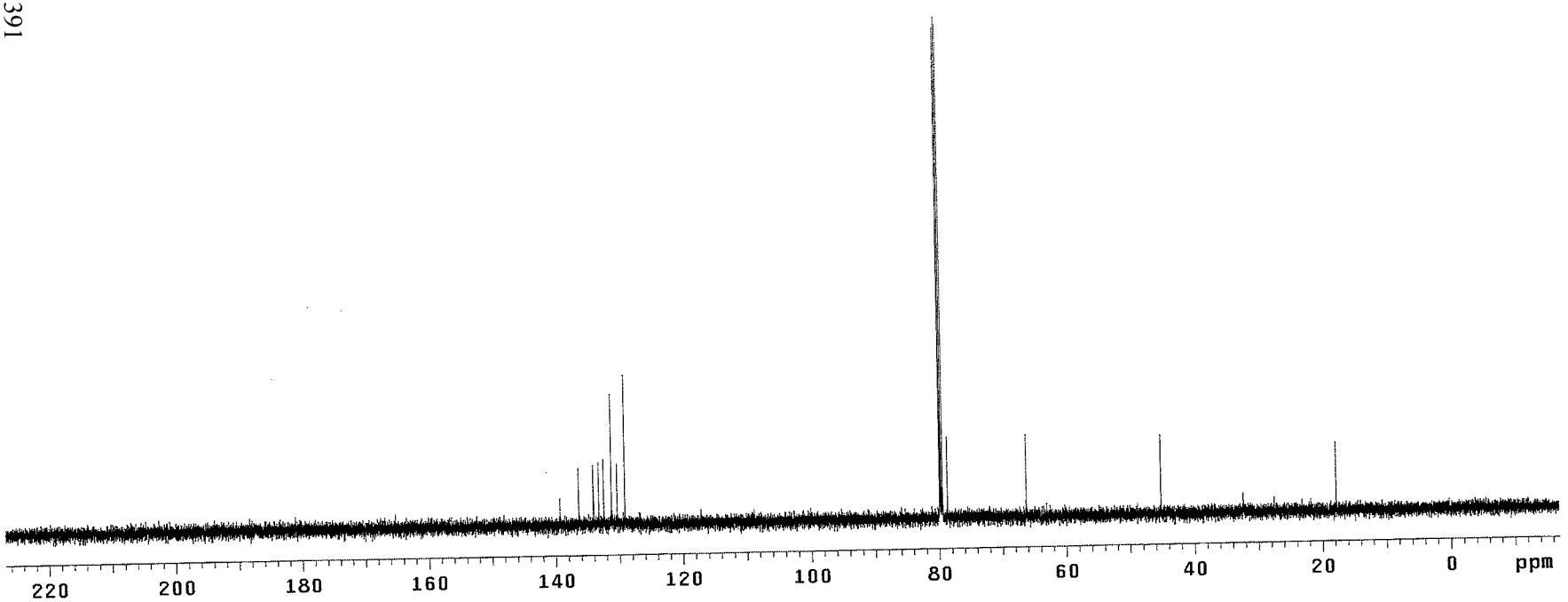
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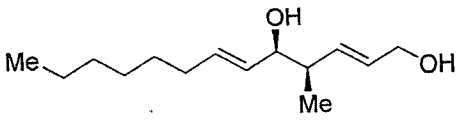

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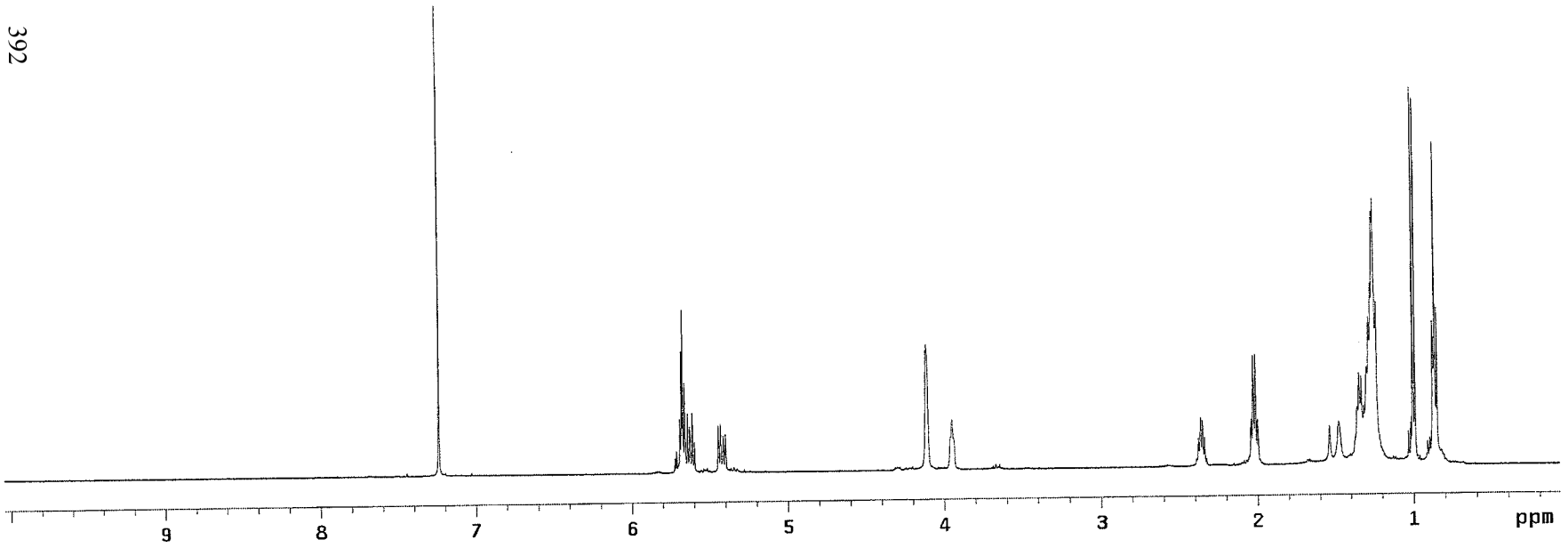

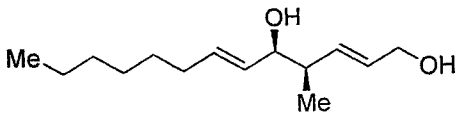
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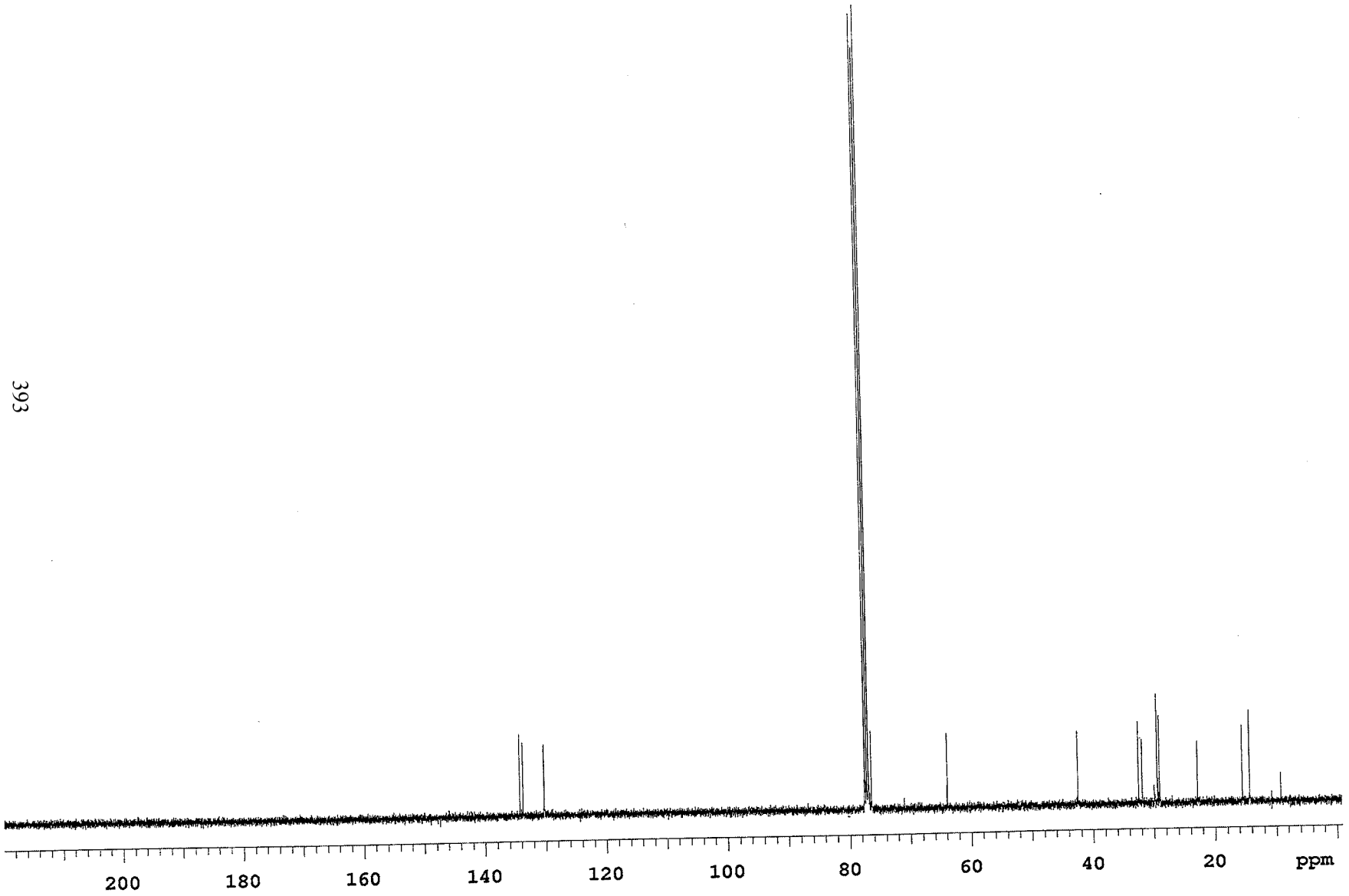
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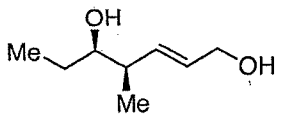
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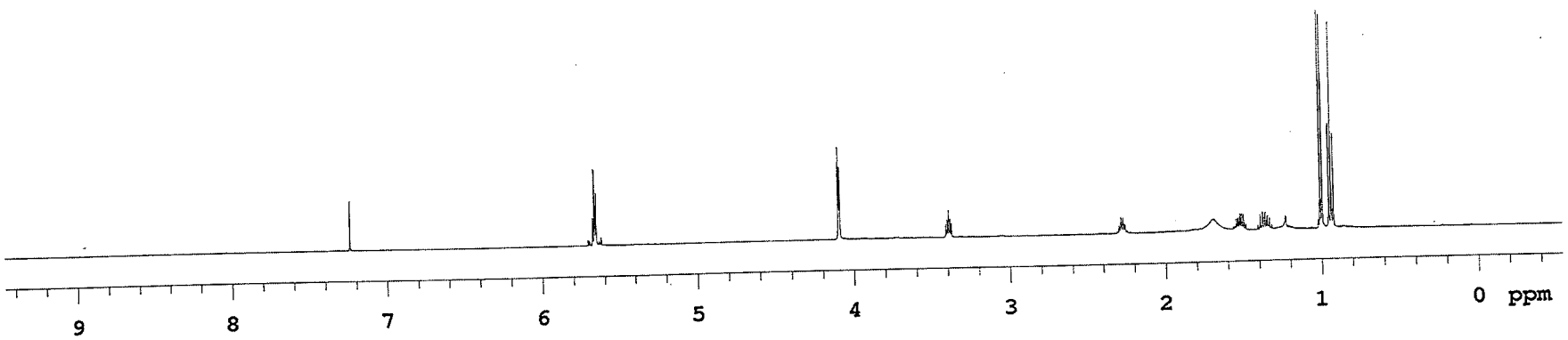
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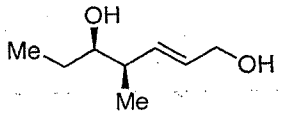
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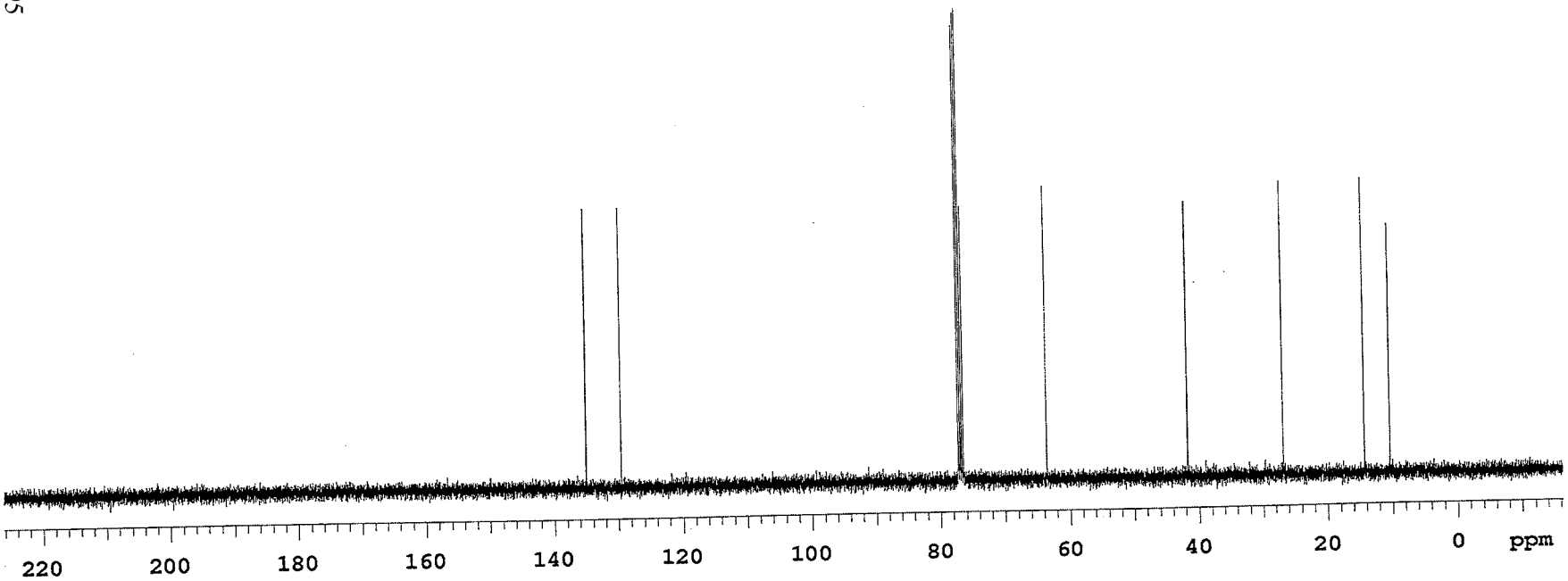
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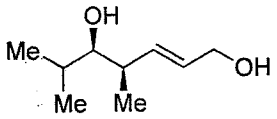
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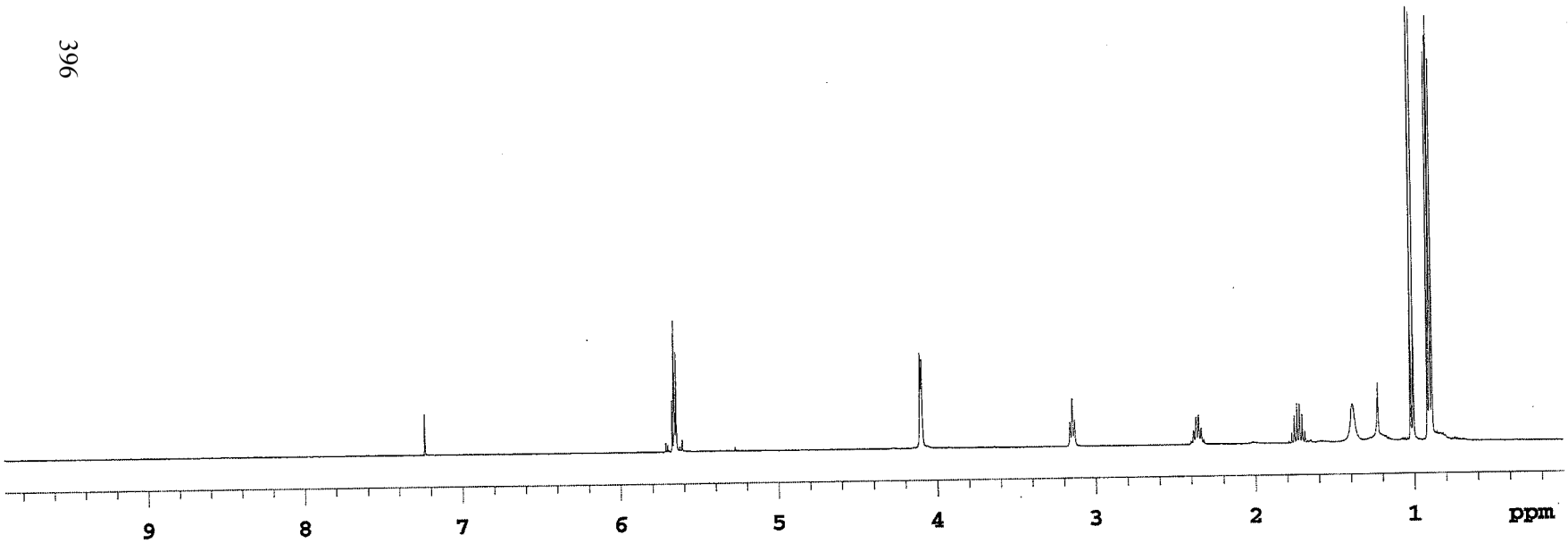
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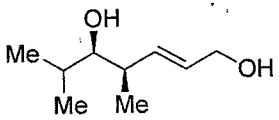
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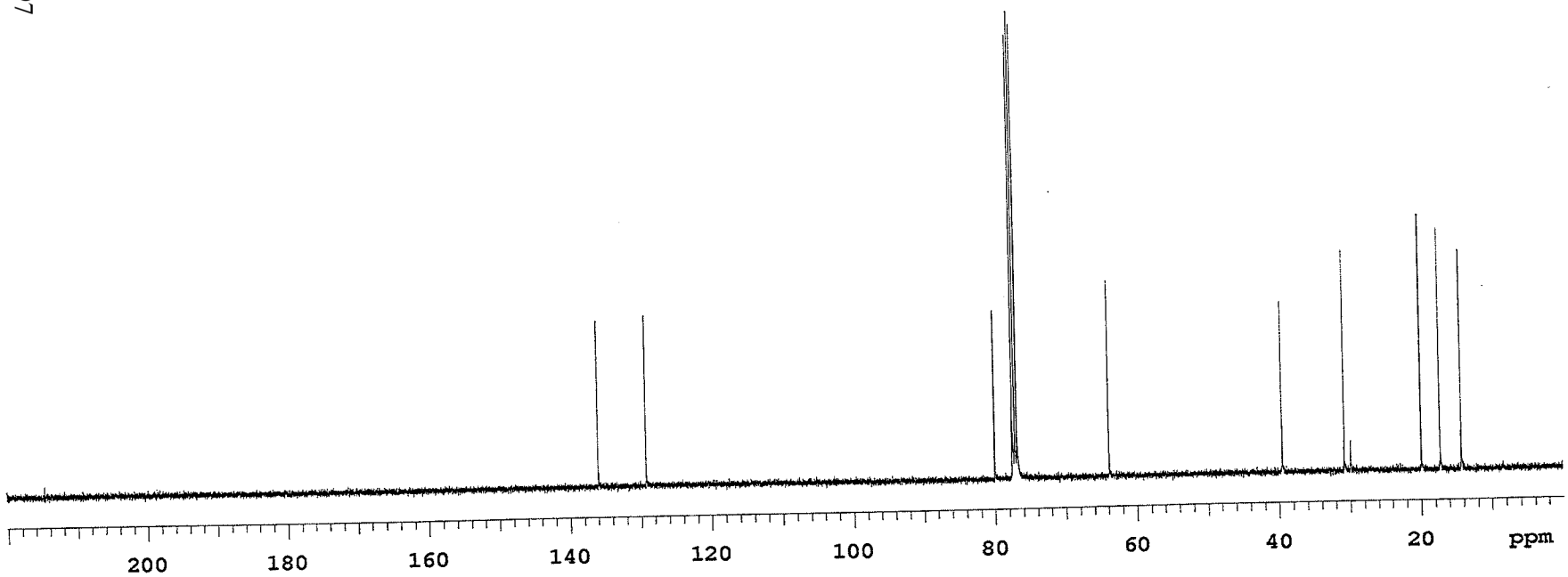
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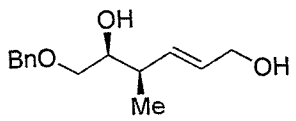
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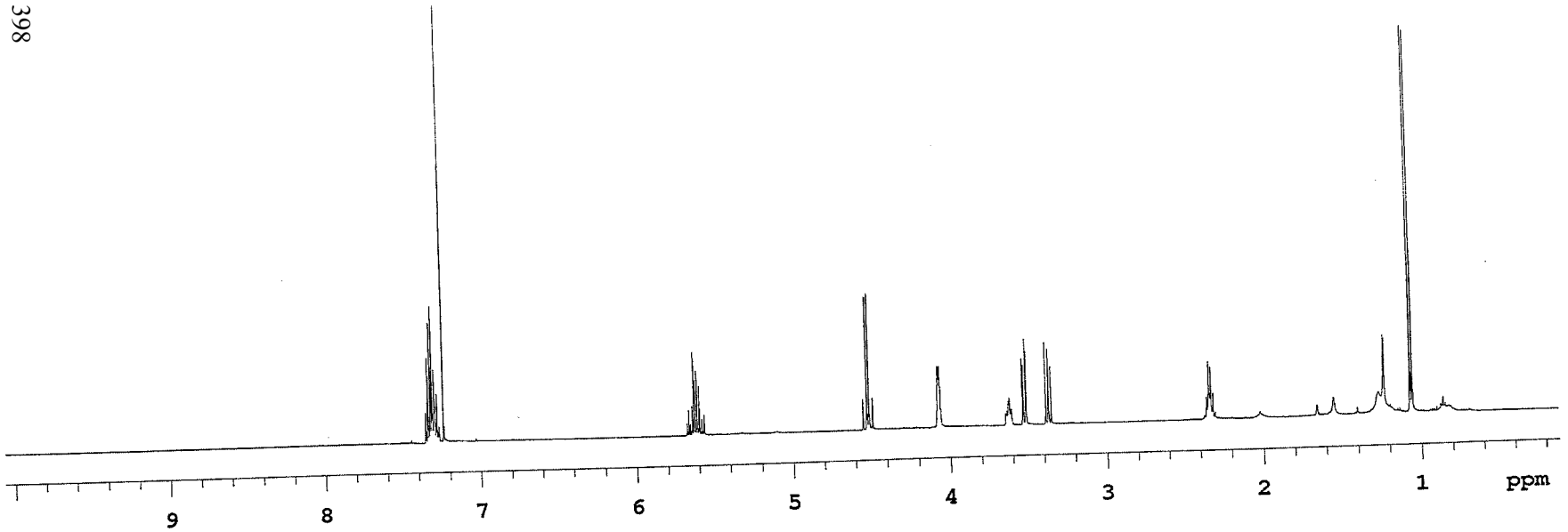
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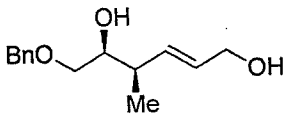
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BnO
OH
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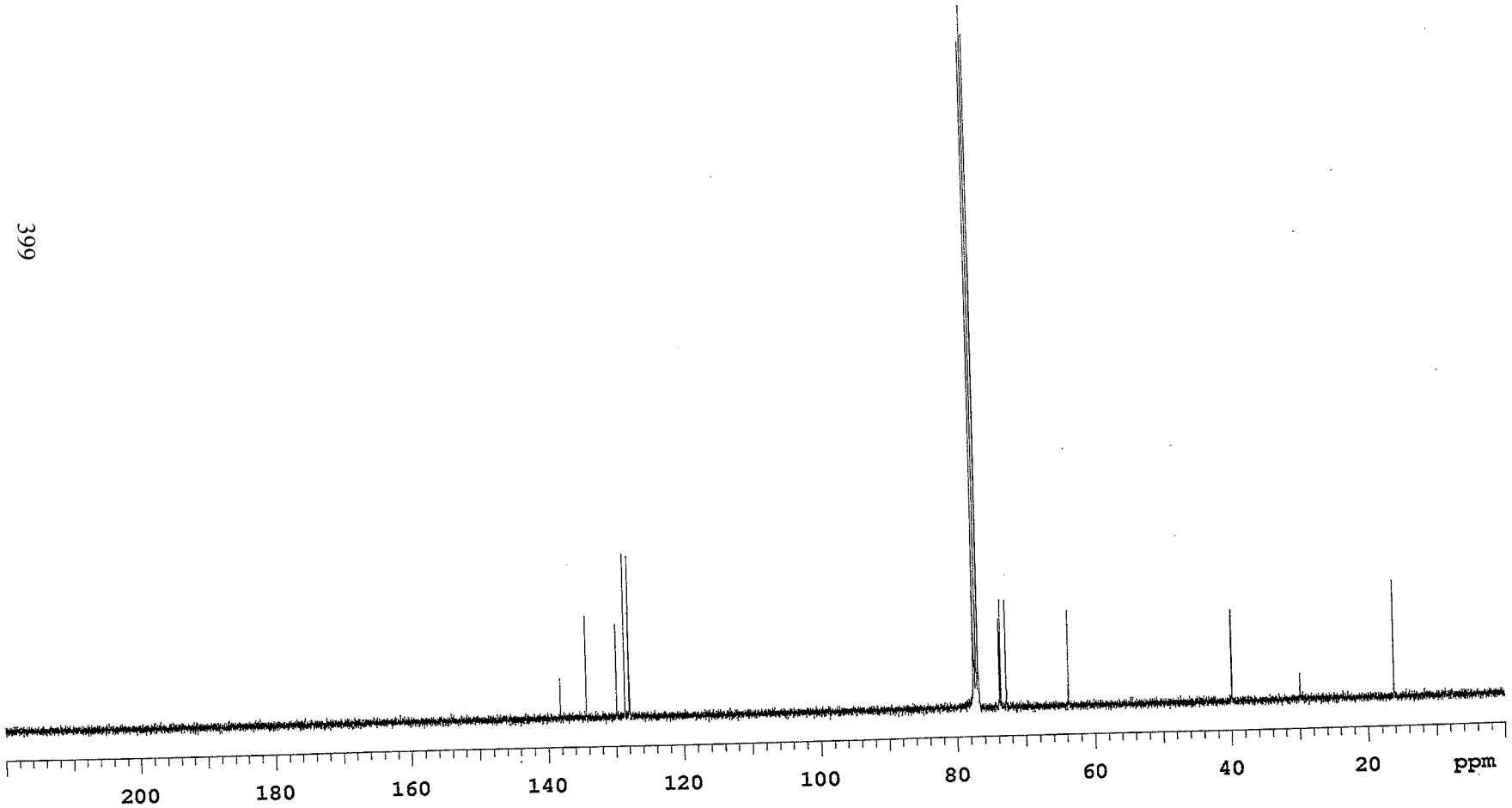
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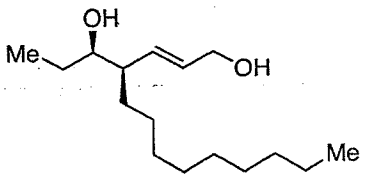
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OH
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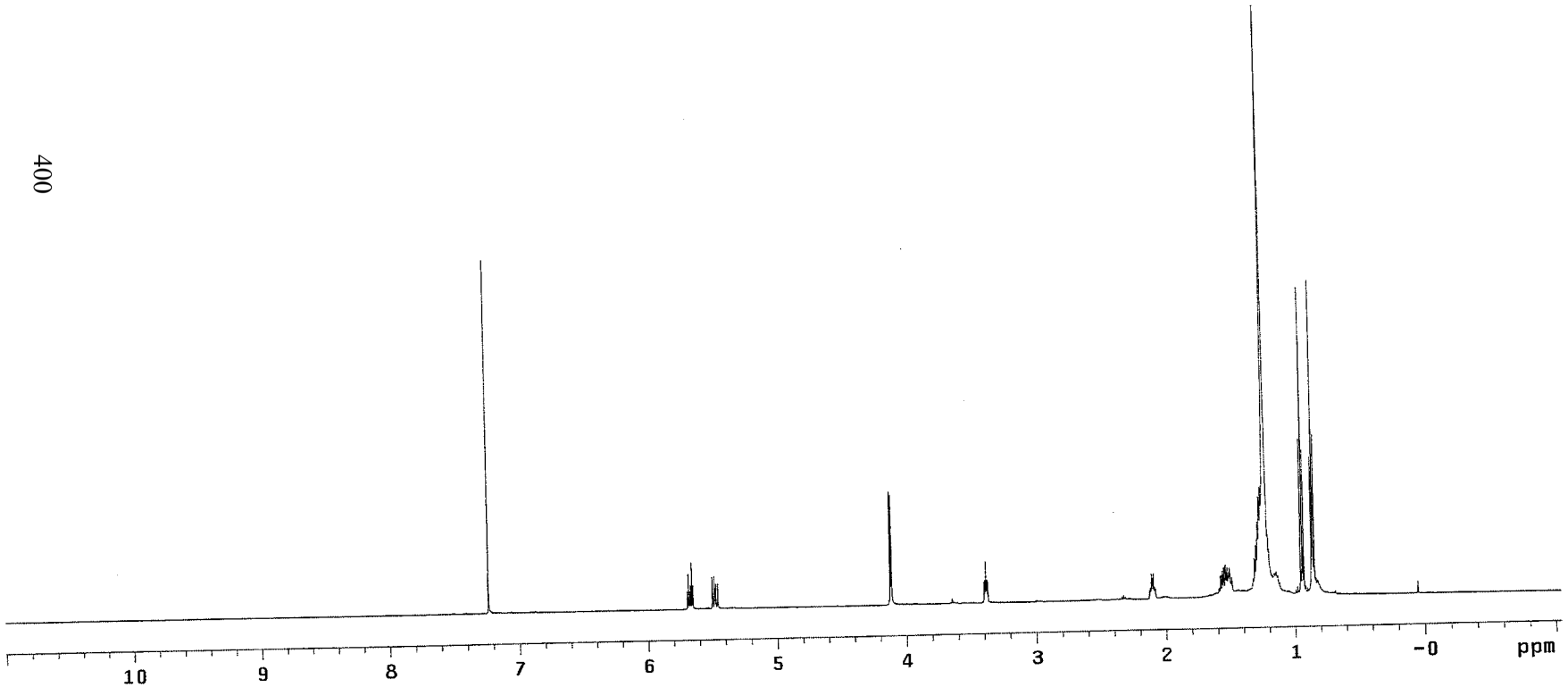
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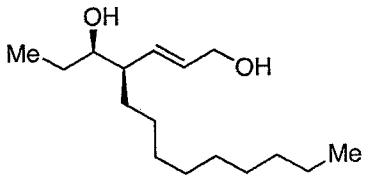
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OH
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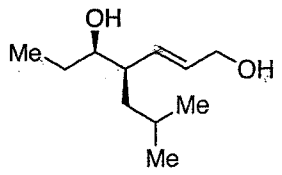

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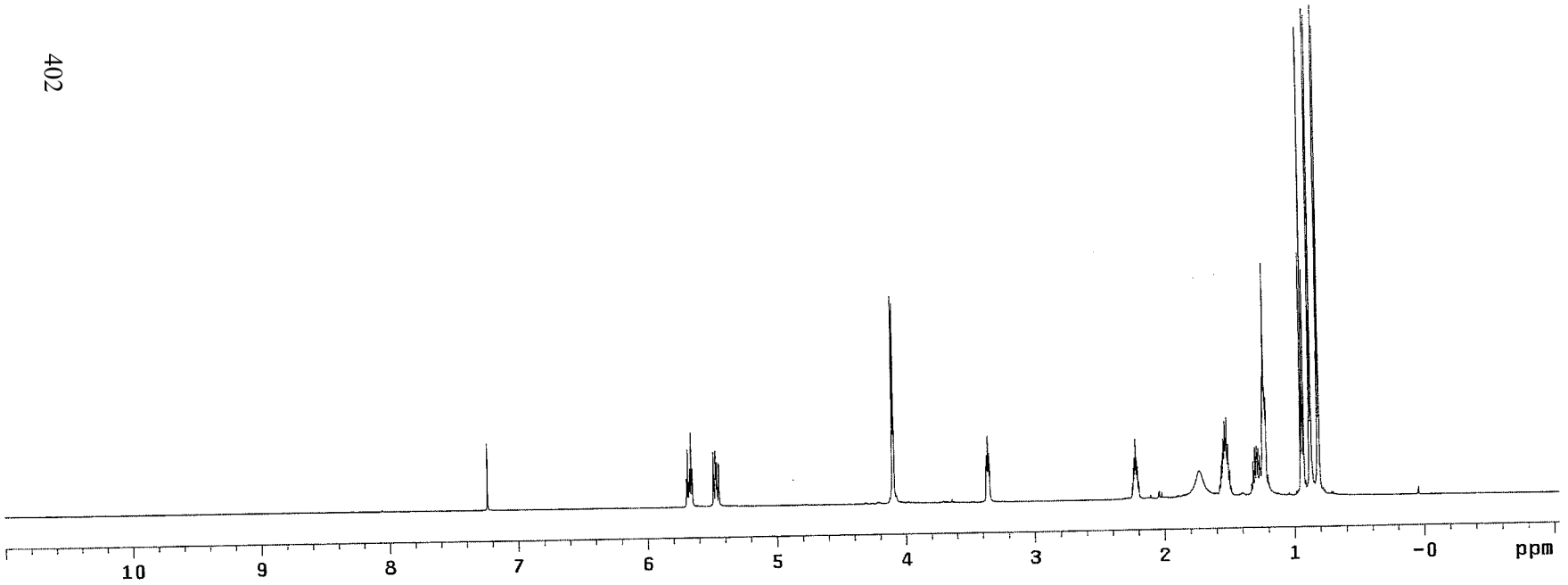

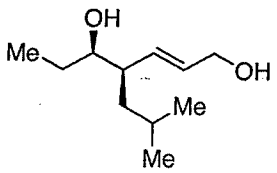
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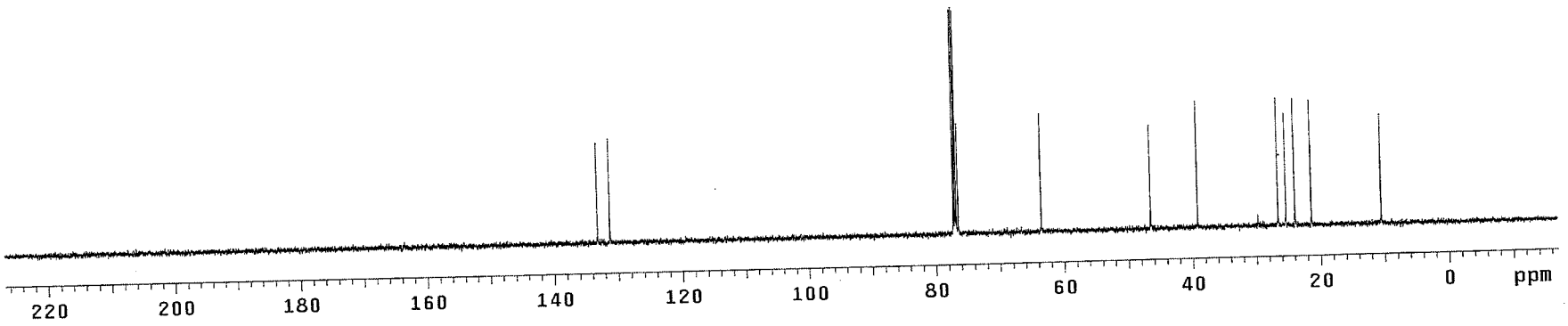
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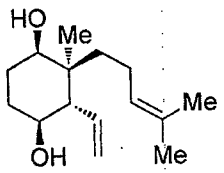
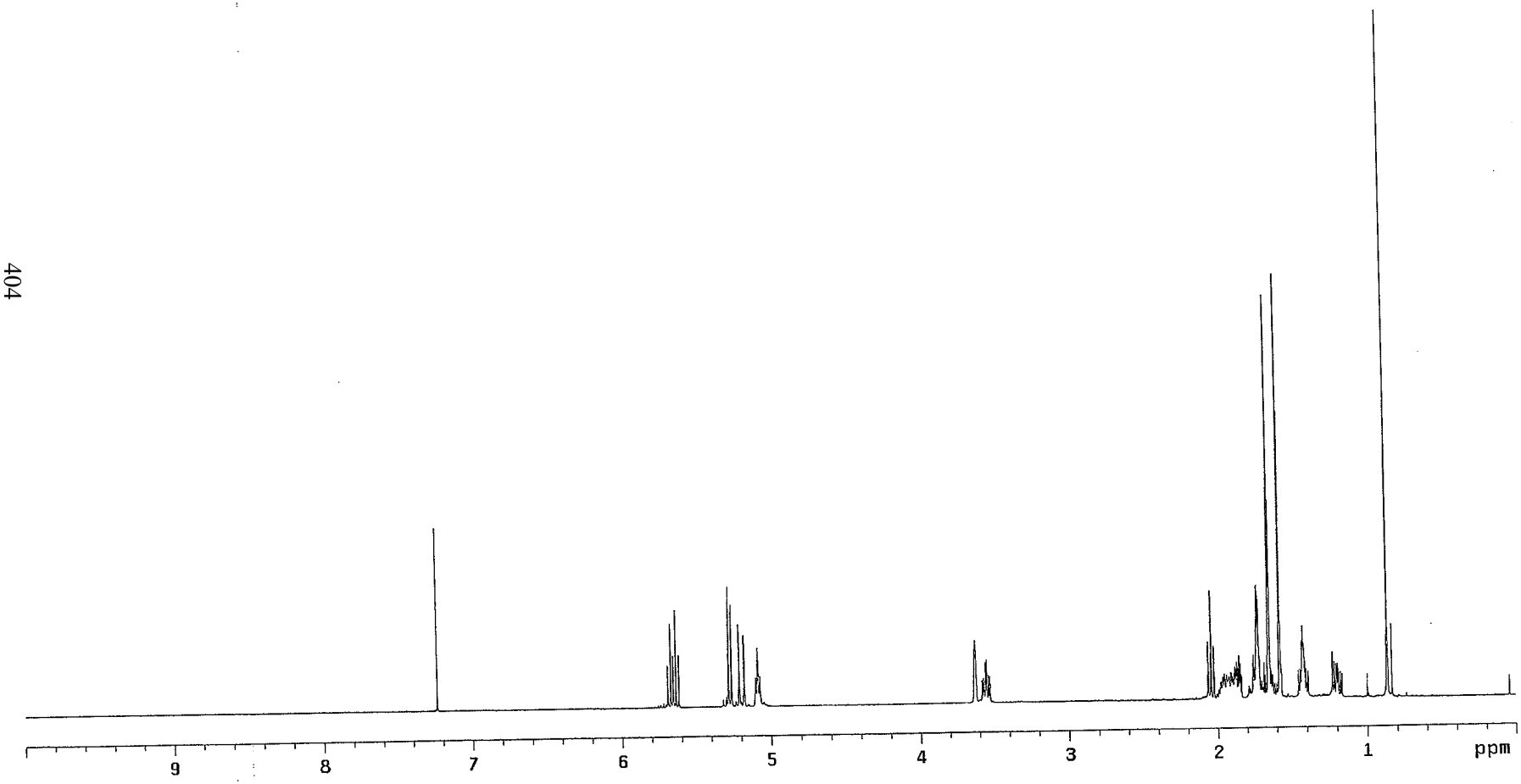
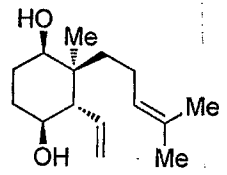
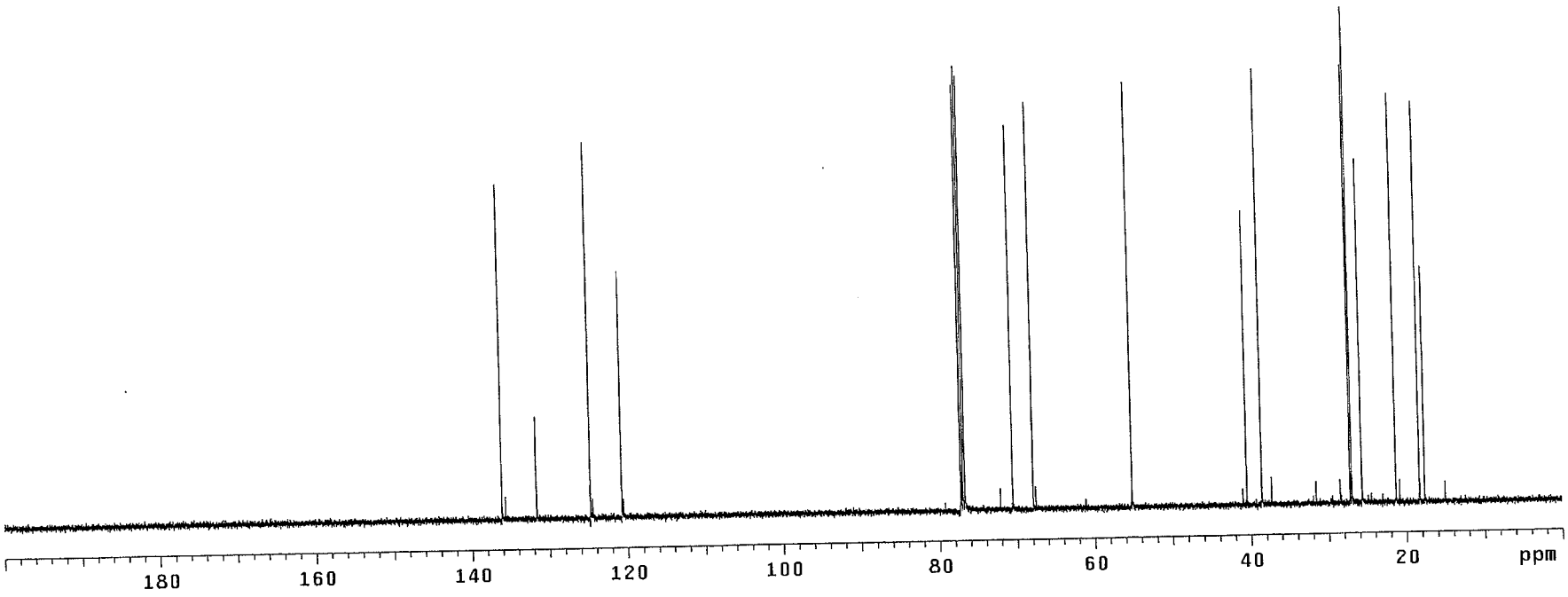


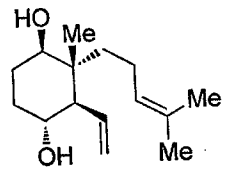
with minor diastereomer





with minor diastereomer

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Me
Me
Me
OH

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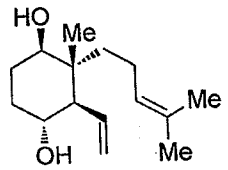
3
2
1
ppm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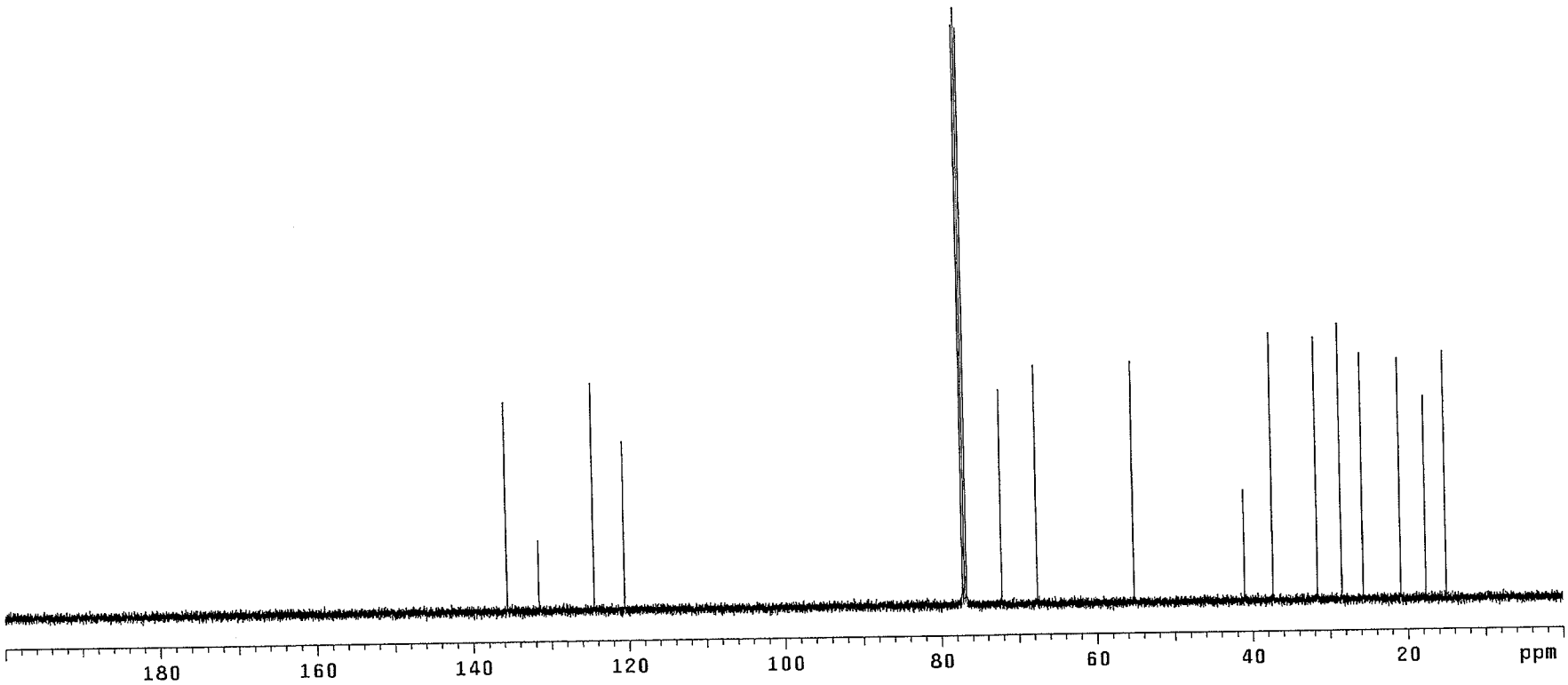
Me
Me
OH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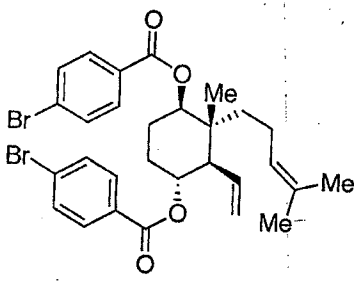
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Me
Br
Br
Me
Me
O
O

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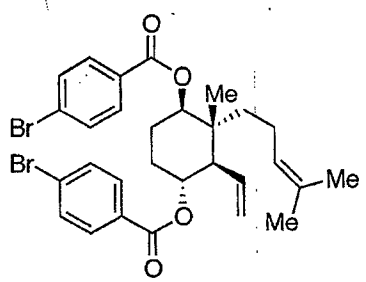
ppm


O
O
Me
Br
Br
Me
Me
O
O

F1
(ppm)
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3
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6
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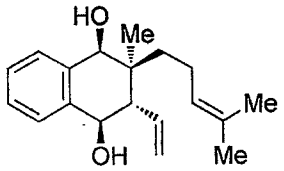
8
7
6
5
4
3
2
1
F2 (ppm)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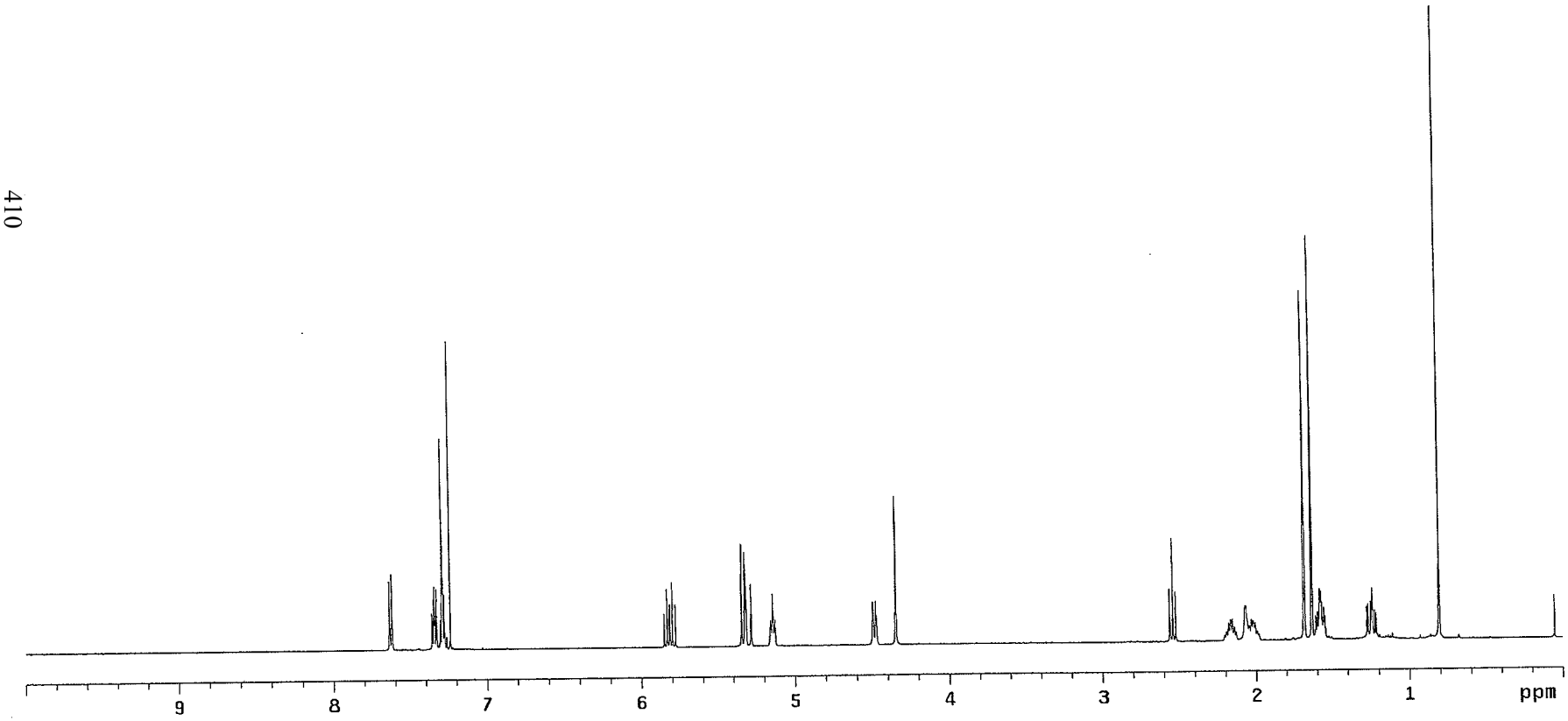
OH
Me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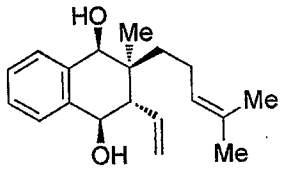
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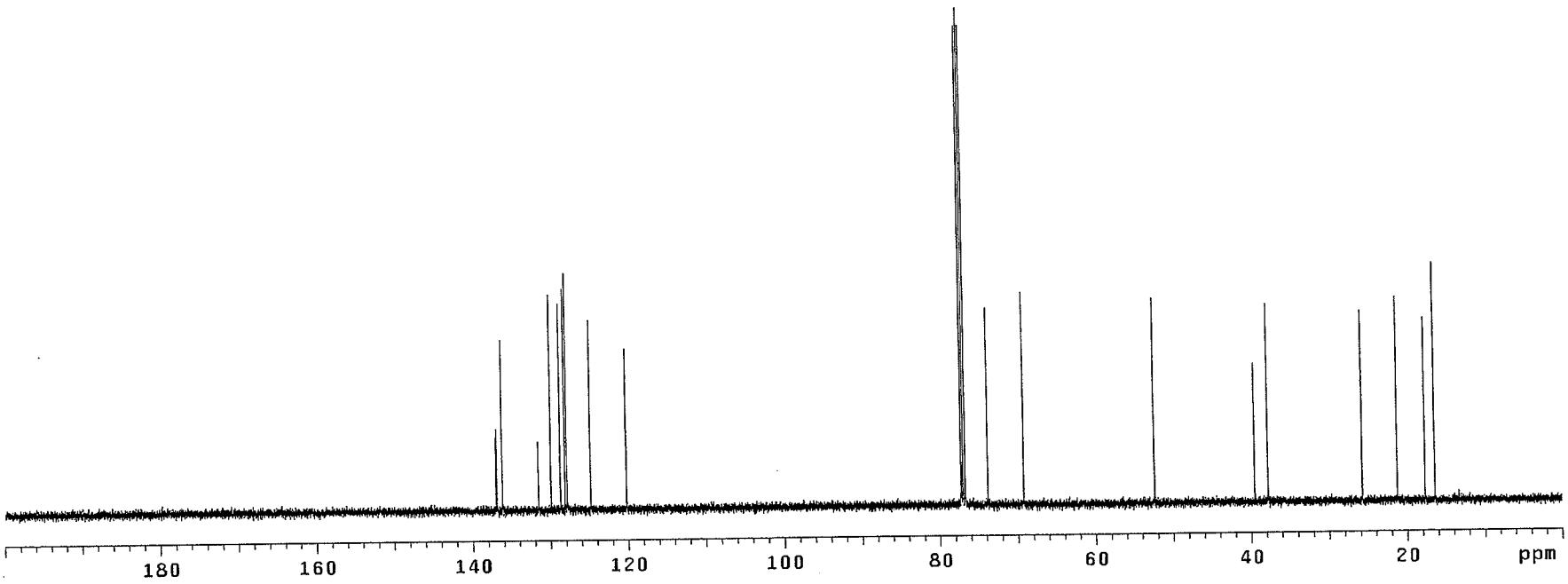
Me
Me
Me
OH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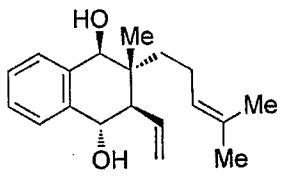
HO
Me
Me
Me
OH

9
8
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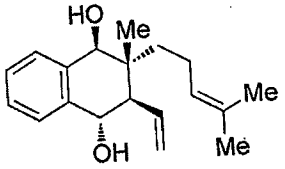
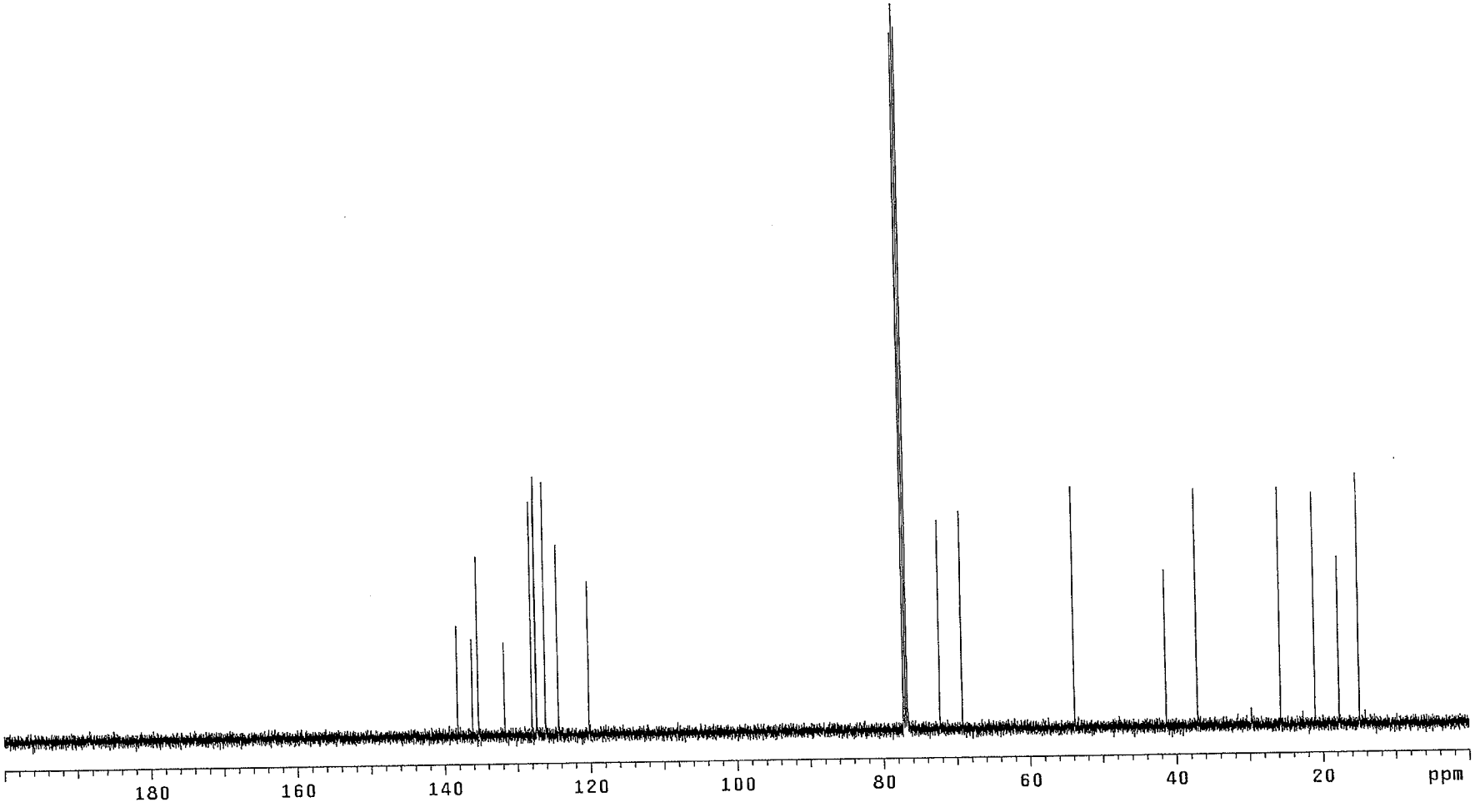
6
5
4
3
2
1
ppm


HO
Me
Me
Me
OH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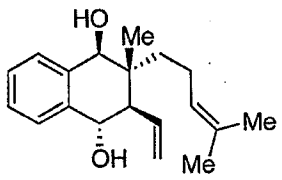
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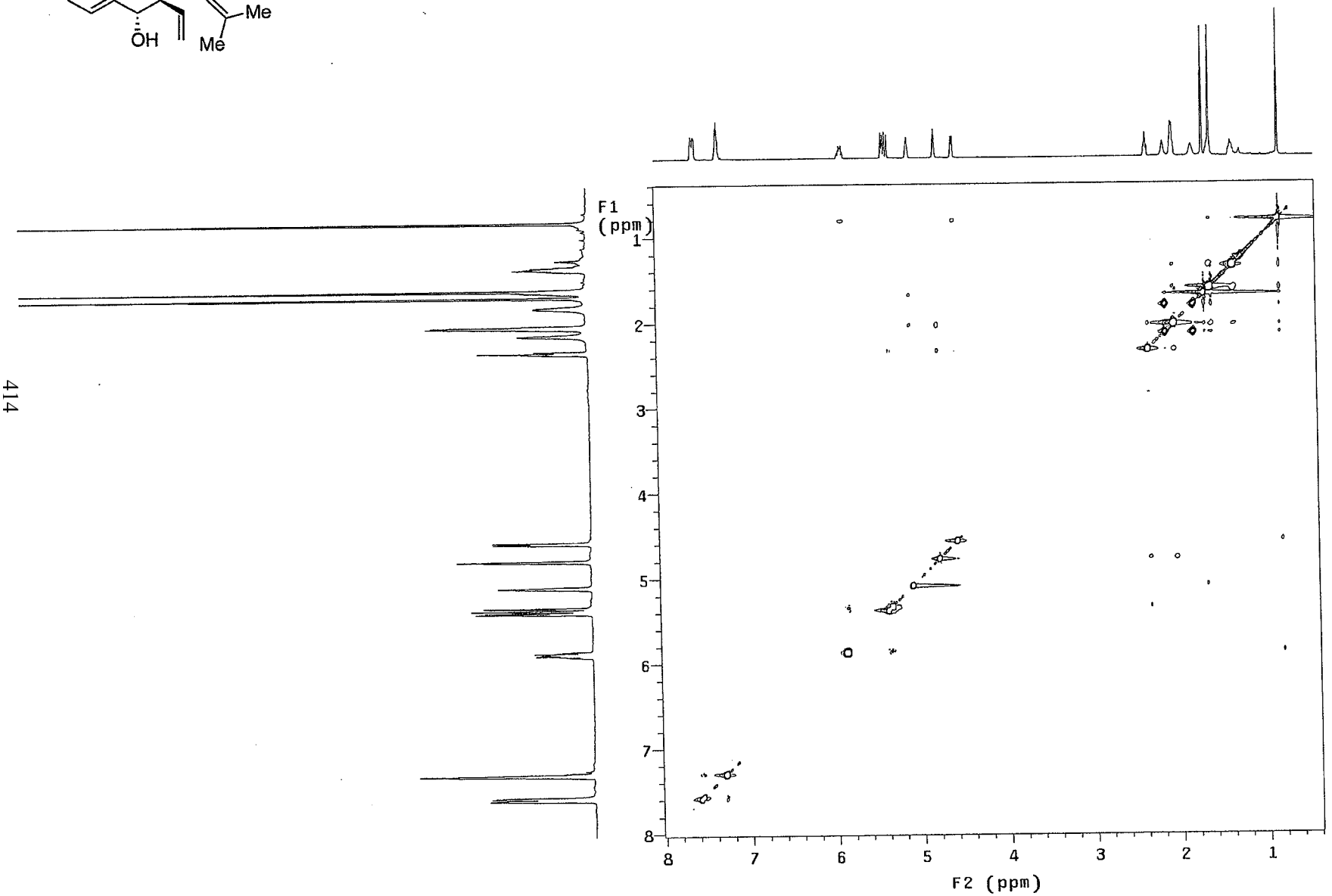
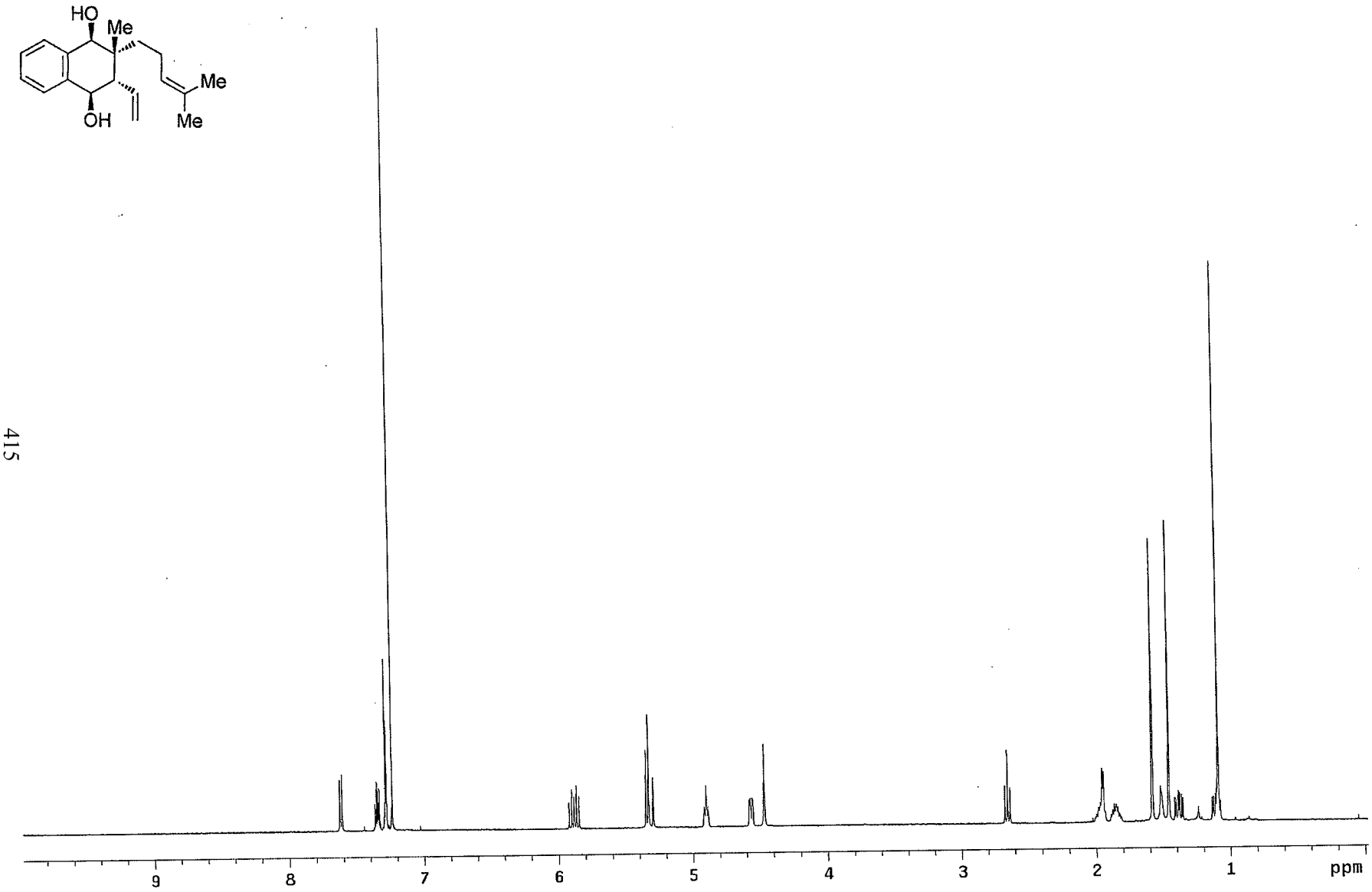
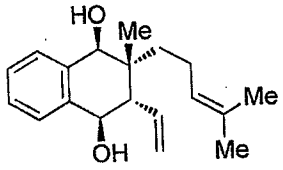
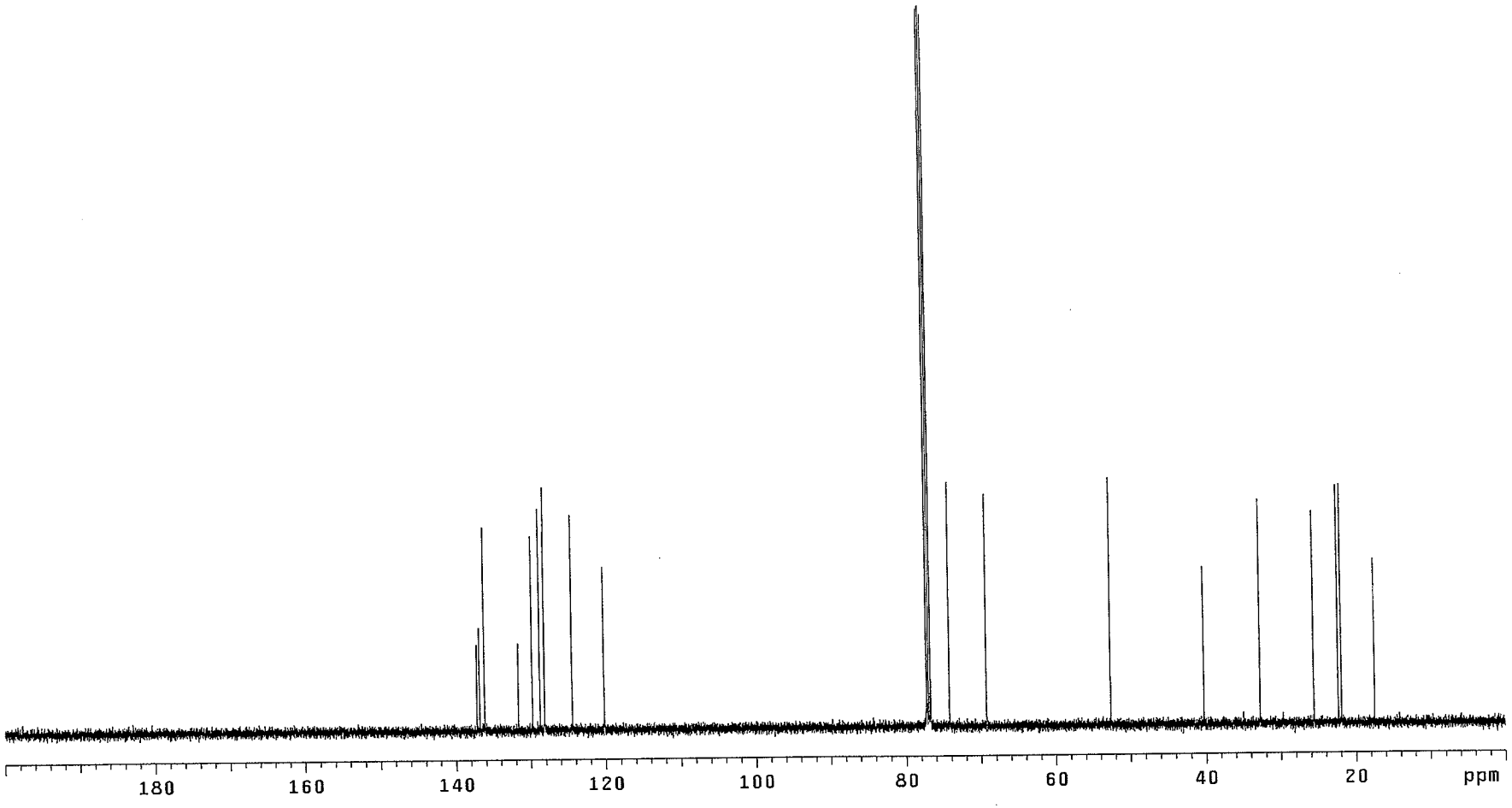
Me
Me
OH
Me


F1
(ppm)
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
F2 (ppm)


HO
Me
Me
Me
OH
9
8
7
6
5
4
3
2
1
ppm


HO
Me
Me
Me
OH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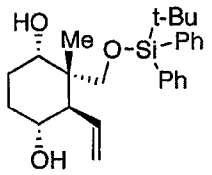
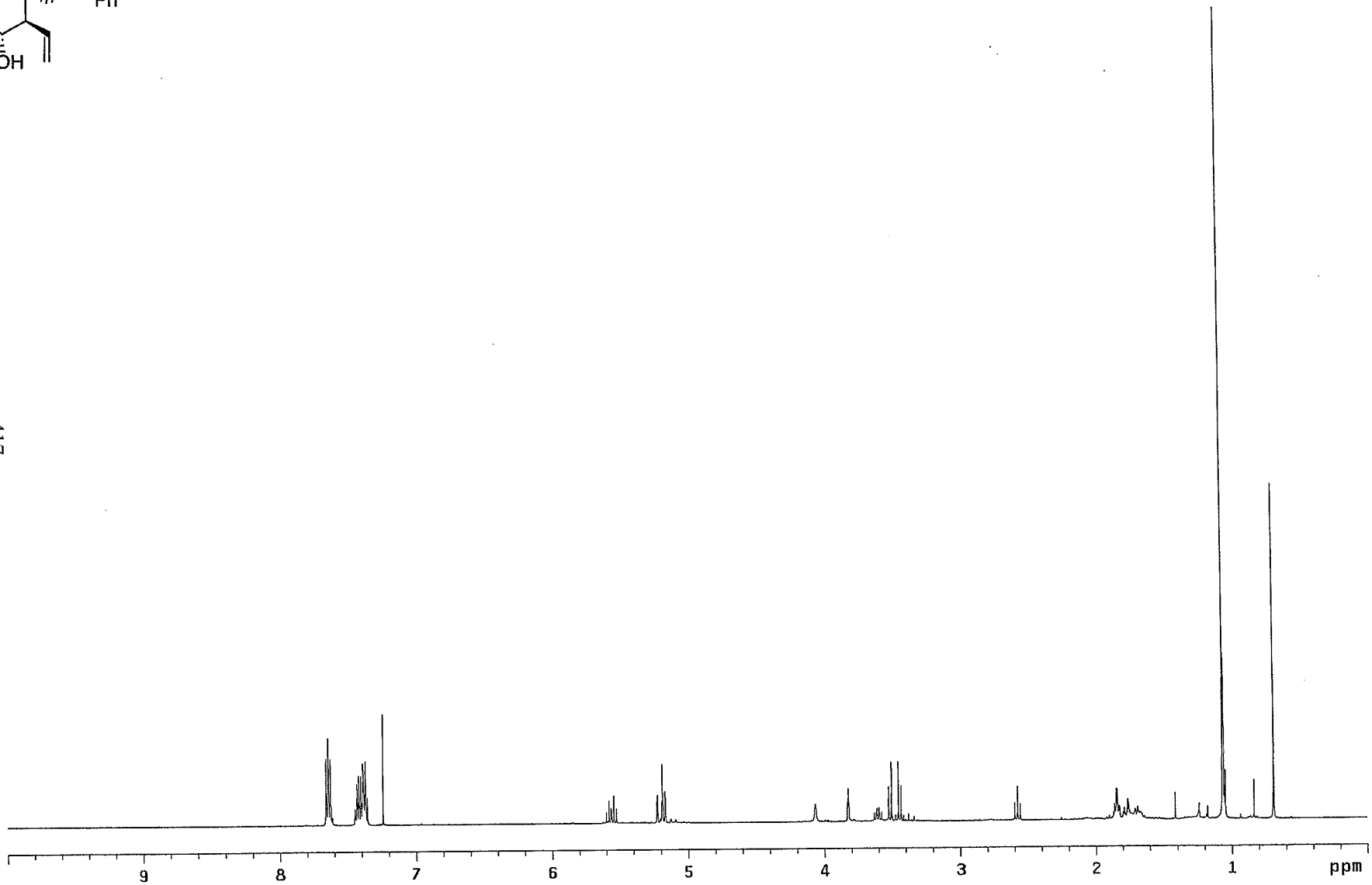
20
ppm


HO
Me
O-Si
t-Bu
Ph
Ph
OH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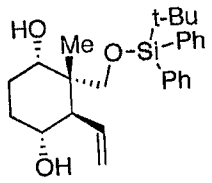
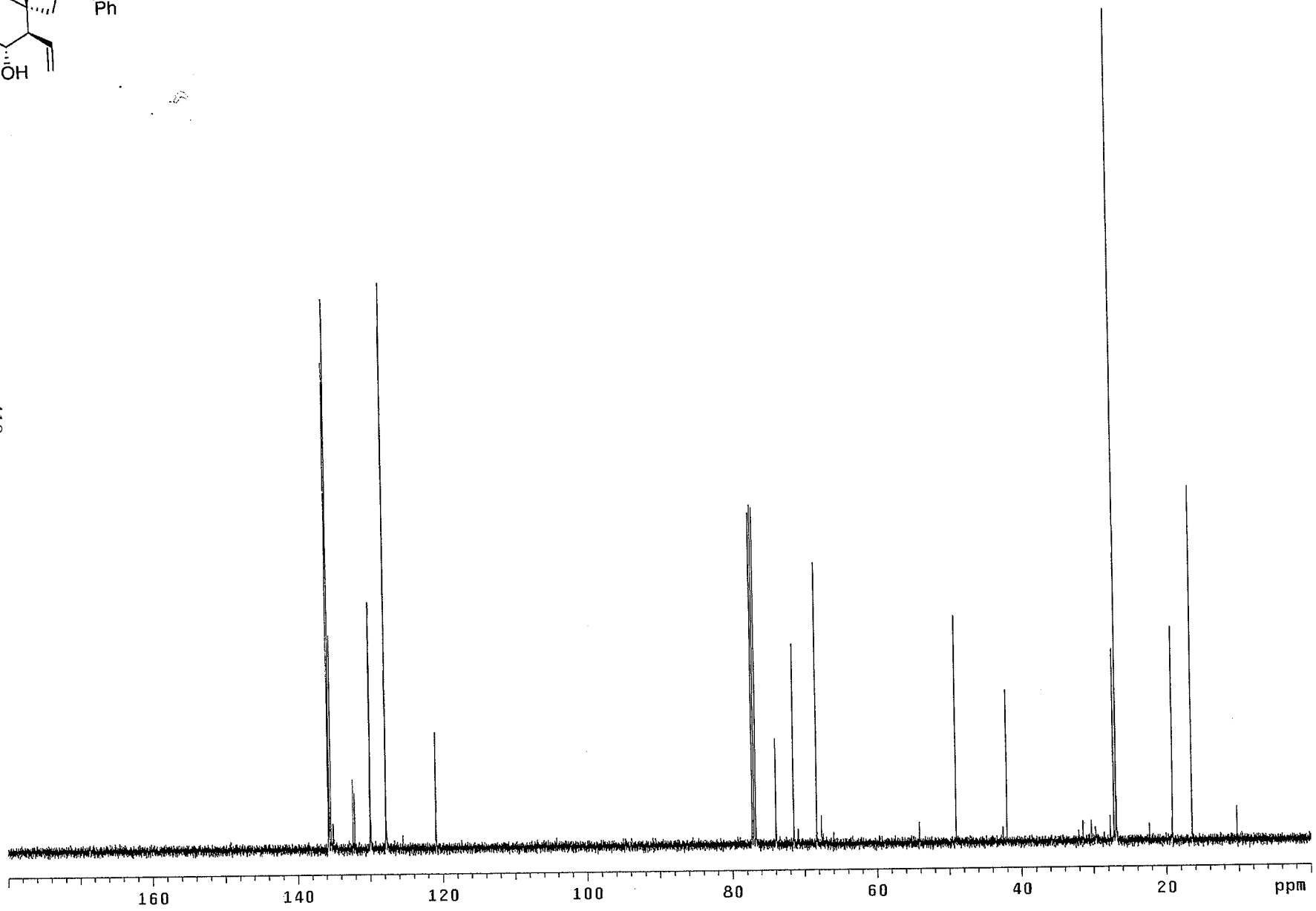
8
7
6
5
4
3
2
1
ppm


HO
Me
O-Si
t-Bu
Ph
Ph
OH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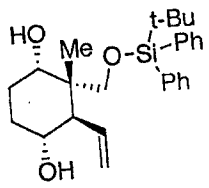
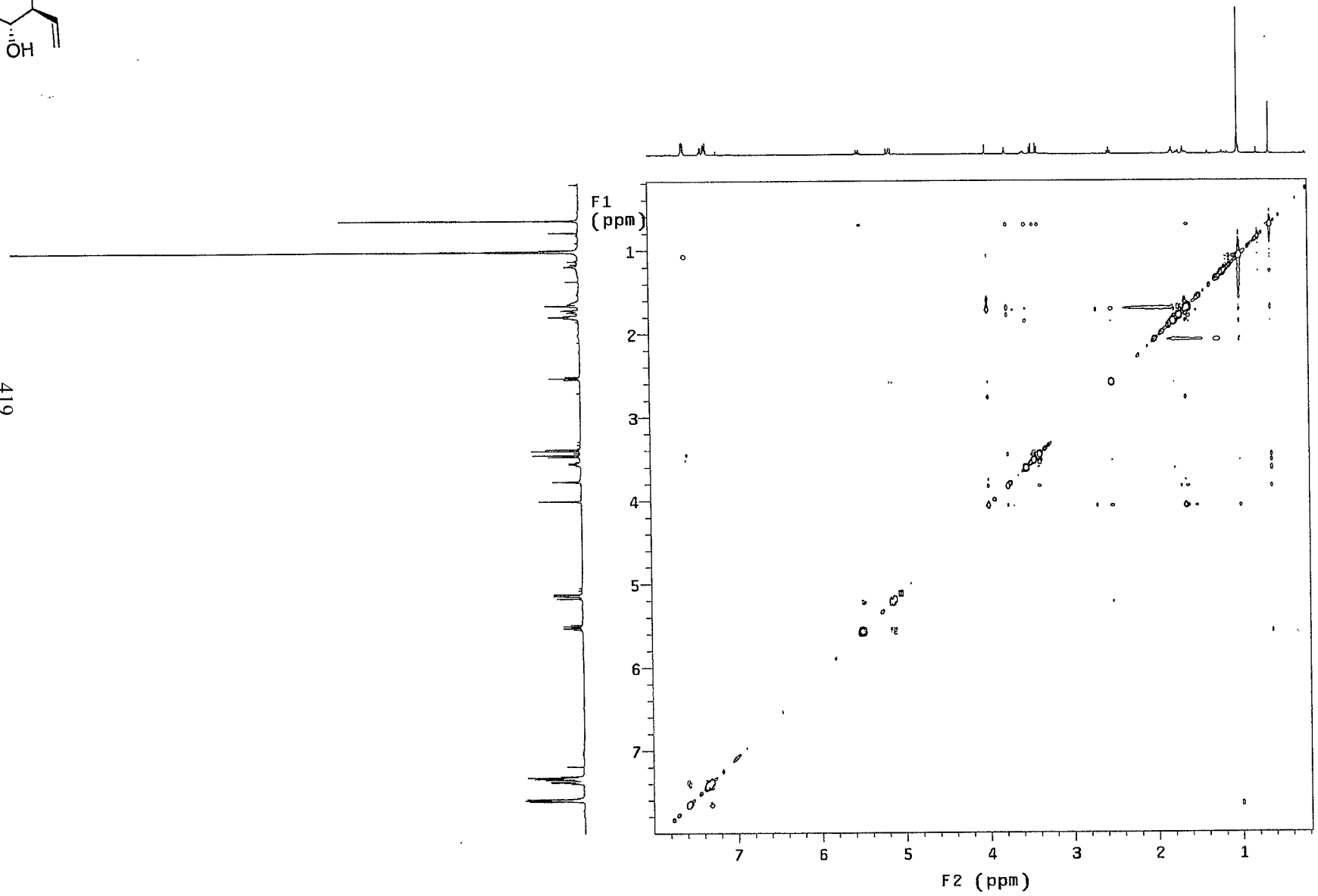
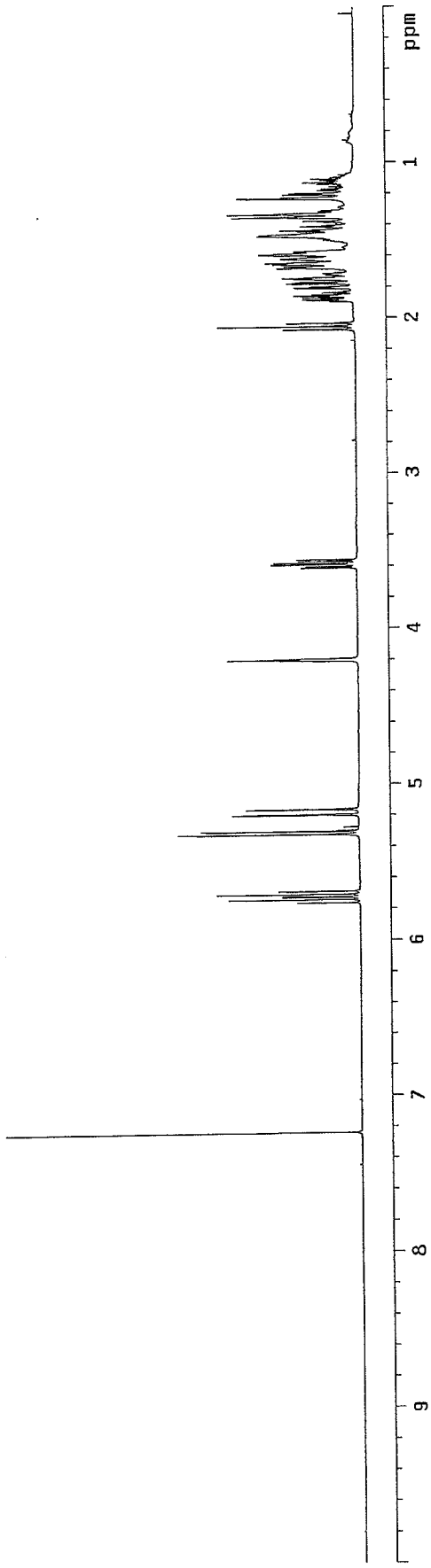
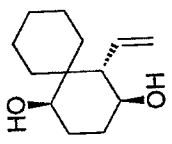
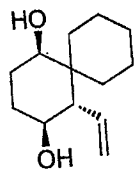
ppm

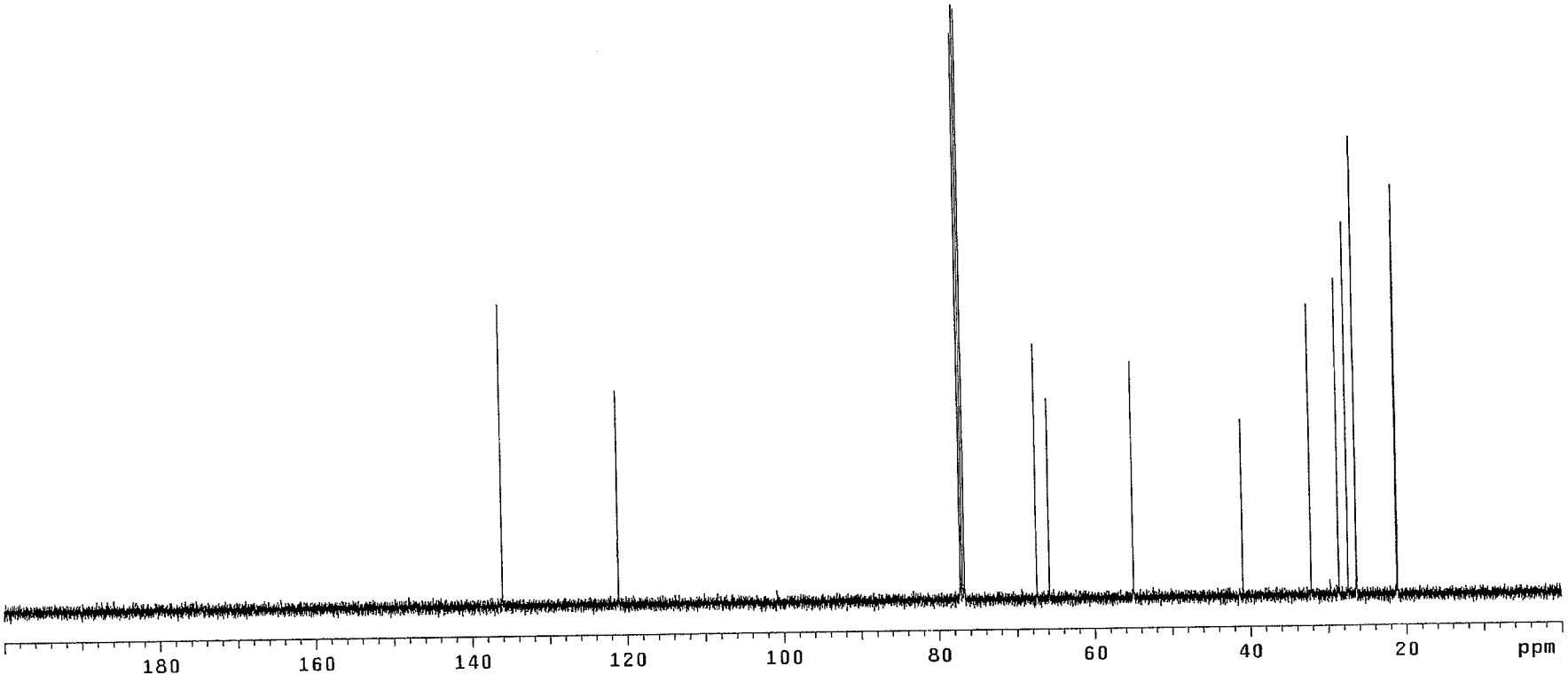

HO
Me
O-Si
t-Bu
Ph
Ph
OH

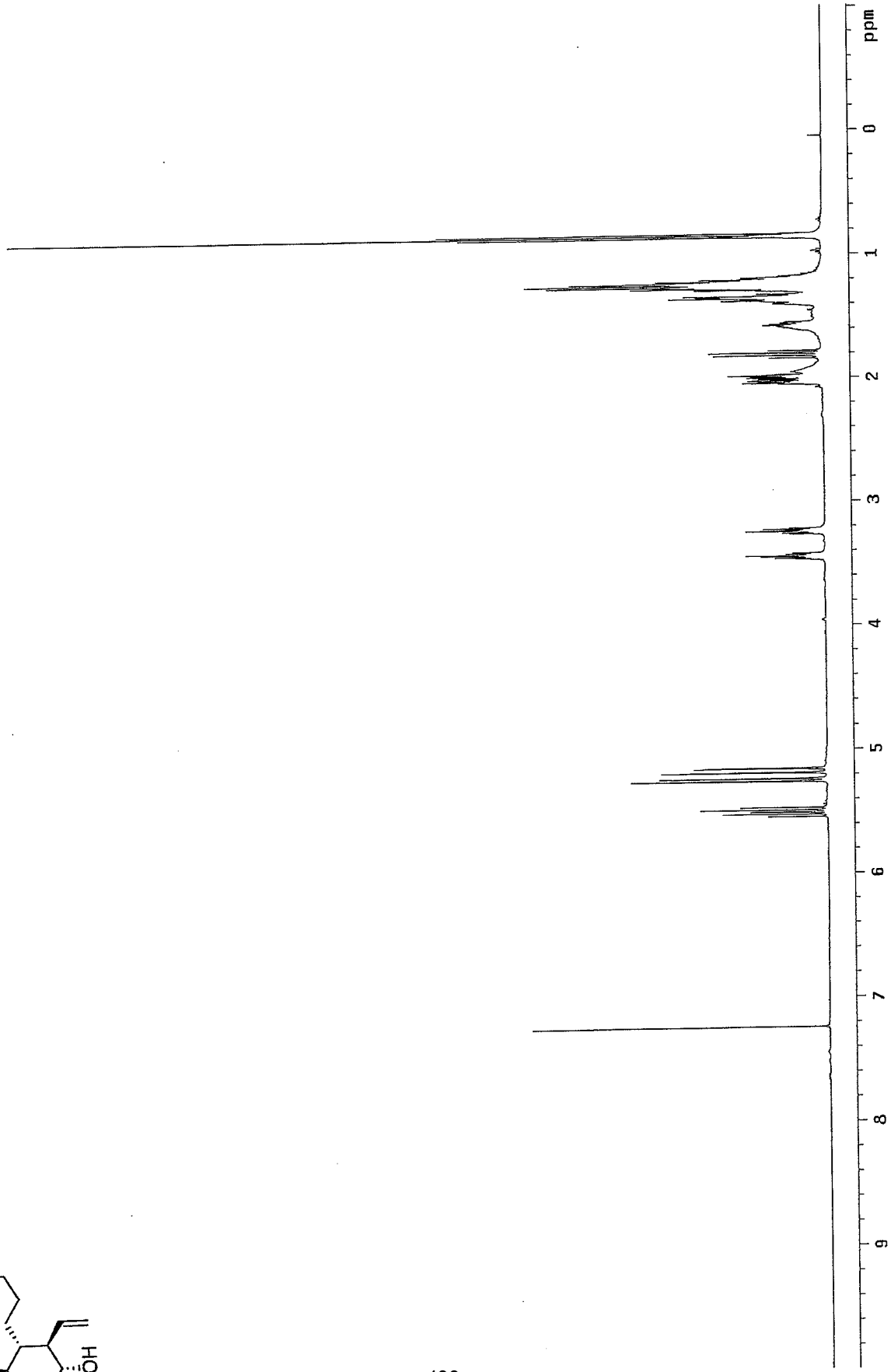

F1
(ppm)
1
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)


ppm
1
2
3
4
5
6
7
8
9

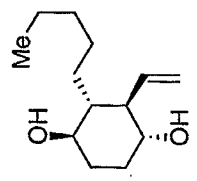

HO
OH

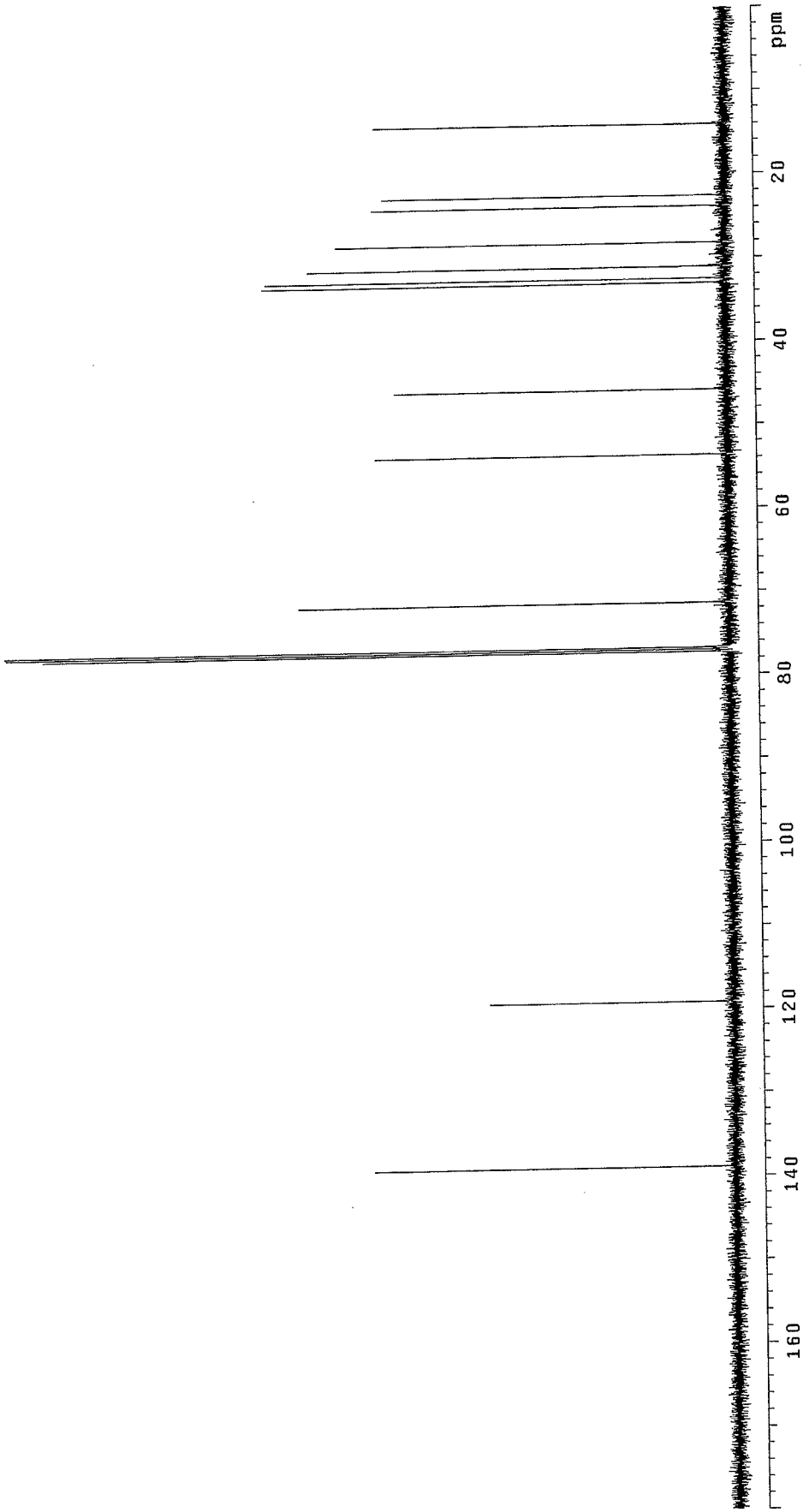

HO
OH

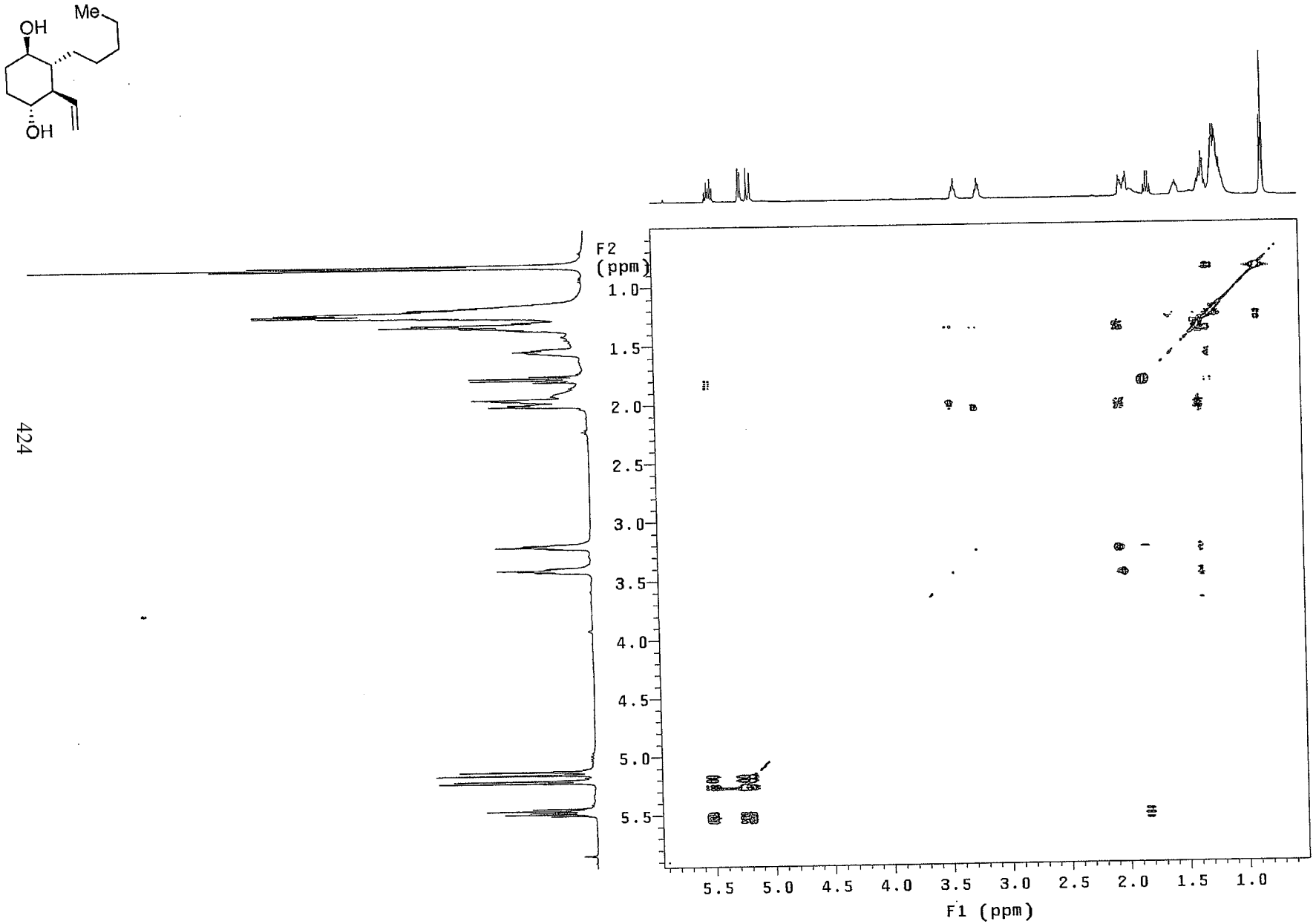

180
160
140
120
100
80
60
40
20
ppm

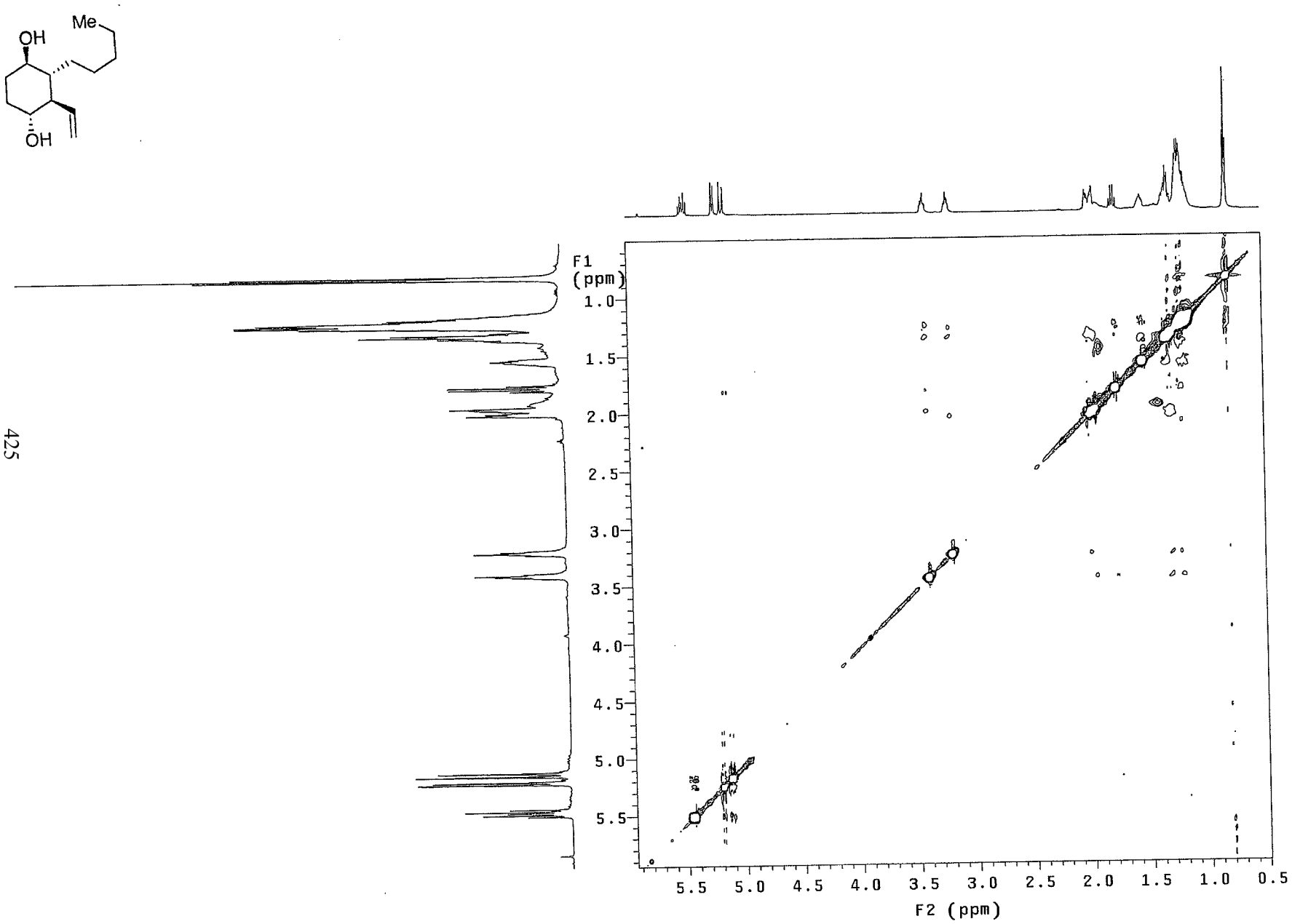

ppm
0
1
2
3
4
5
6
7
8
9

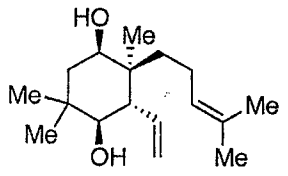
Me
OH
OH

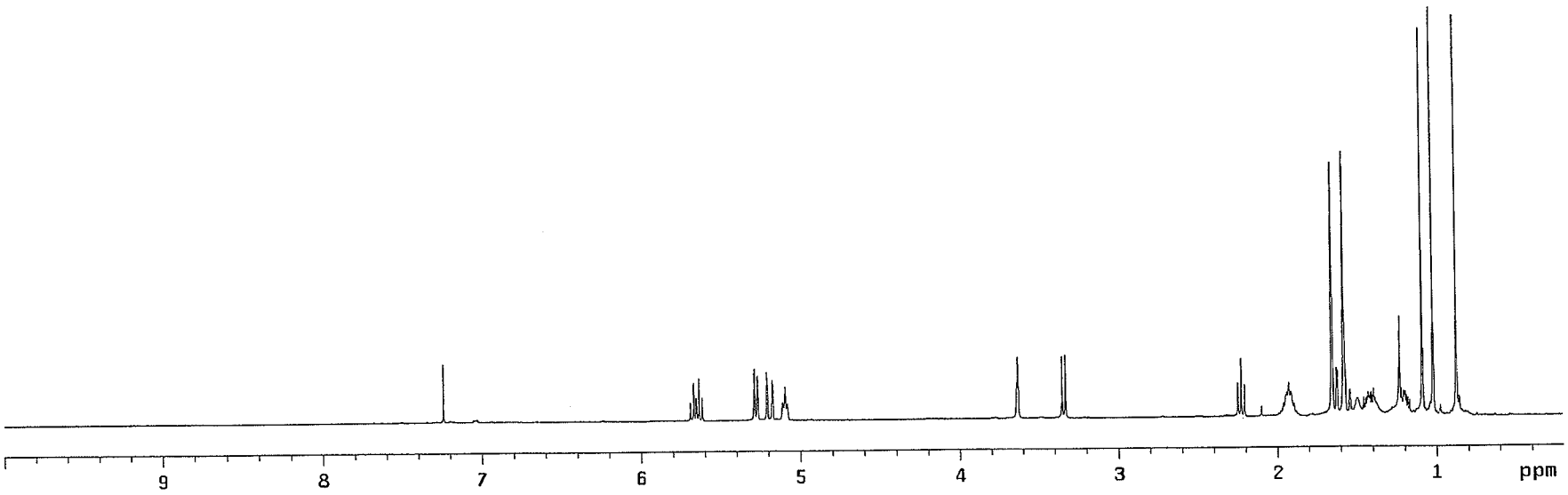

Me
OH
OH

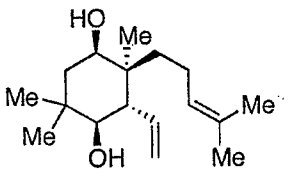

ppm
20
40
60
80
100
120
140
160


Me
OH
OH
F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

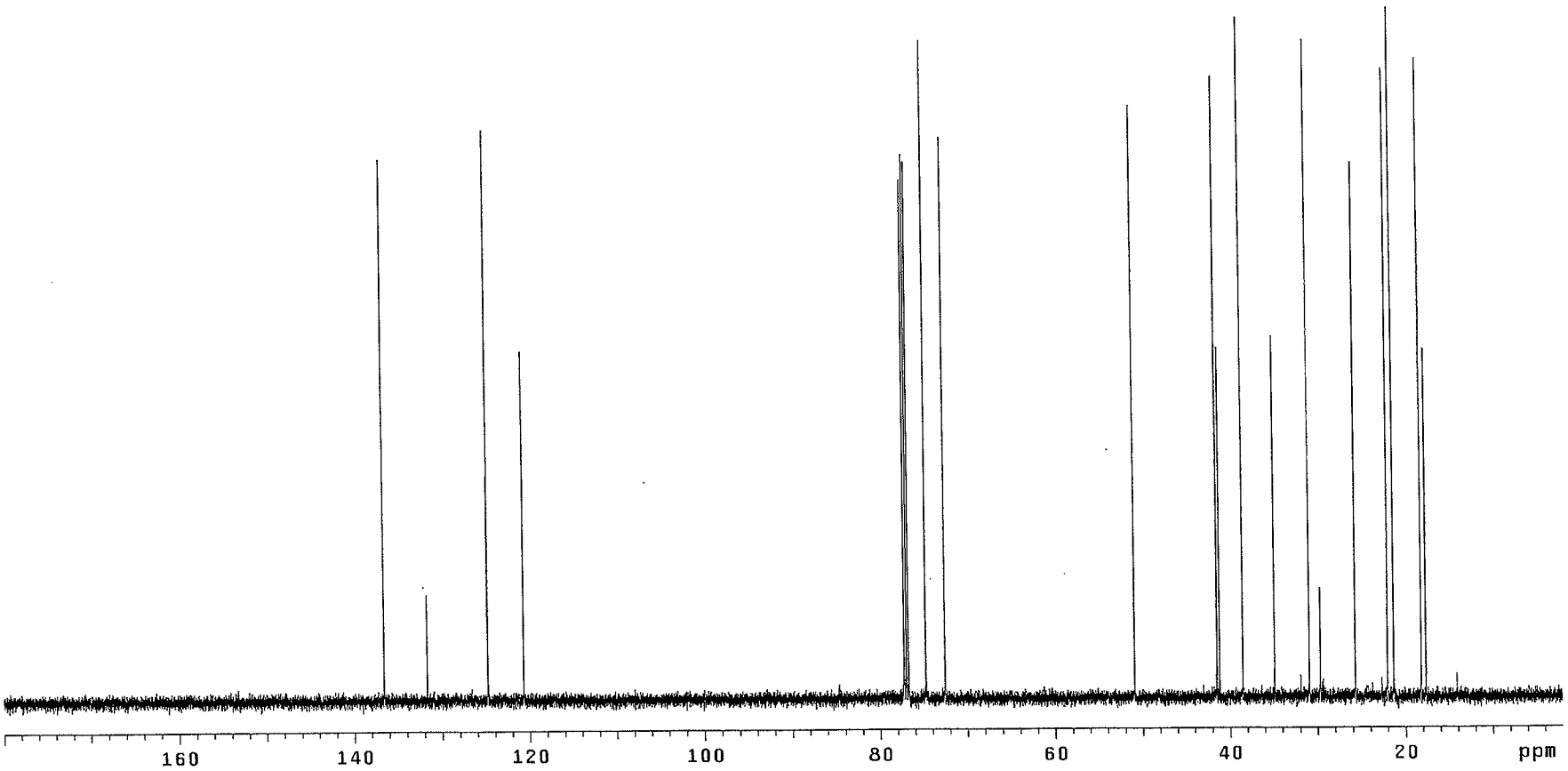

OH
Me
OH
F1
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F2 (ppm)

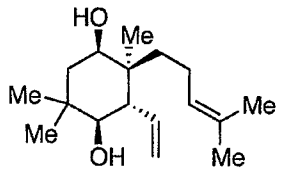

HO
Me
Me
Me
OH
Me
Me

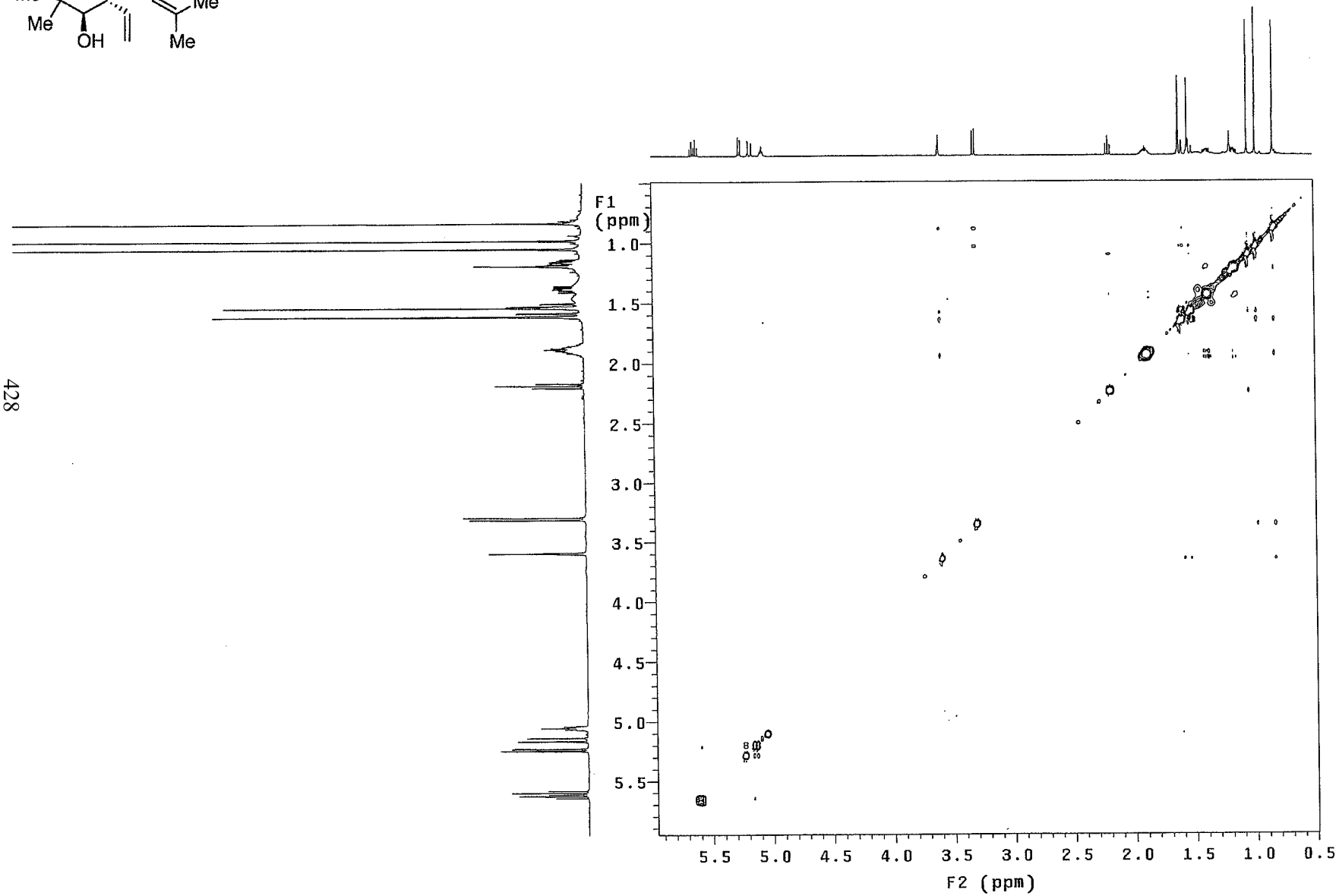

9
8
7
6
5
4
3
2
1
ppm

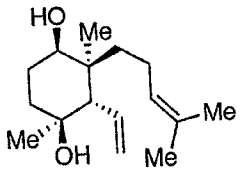


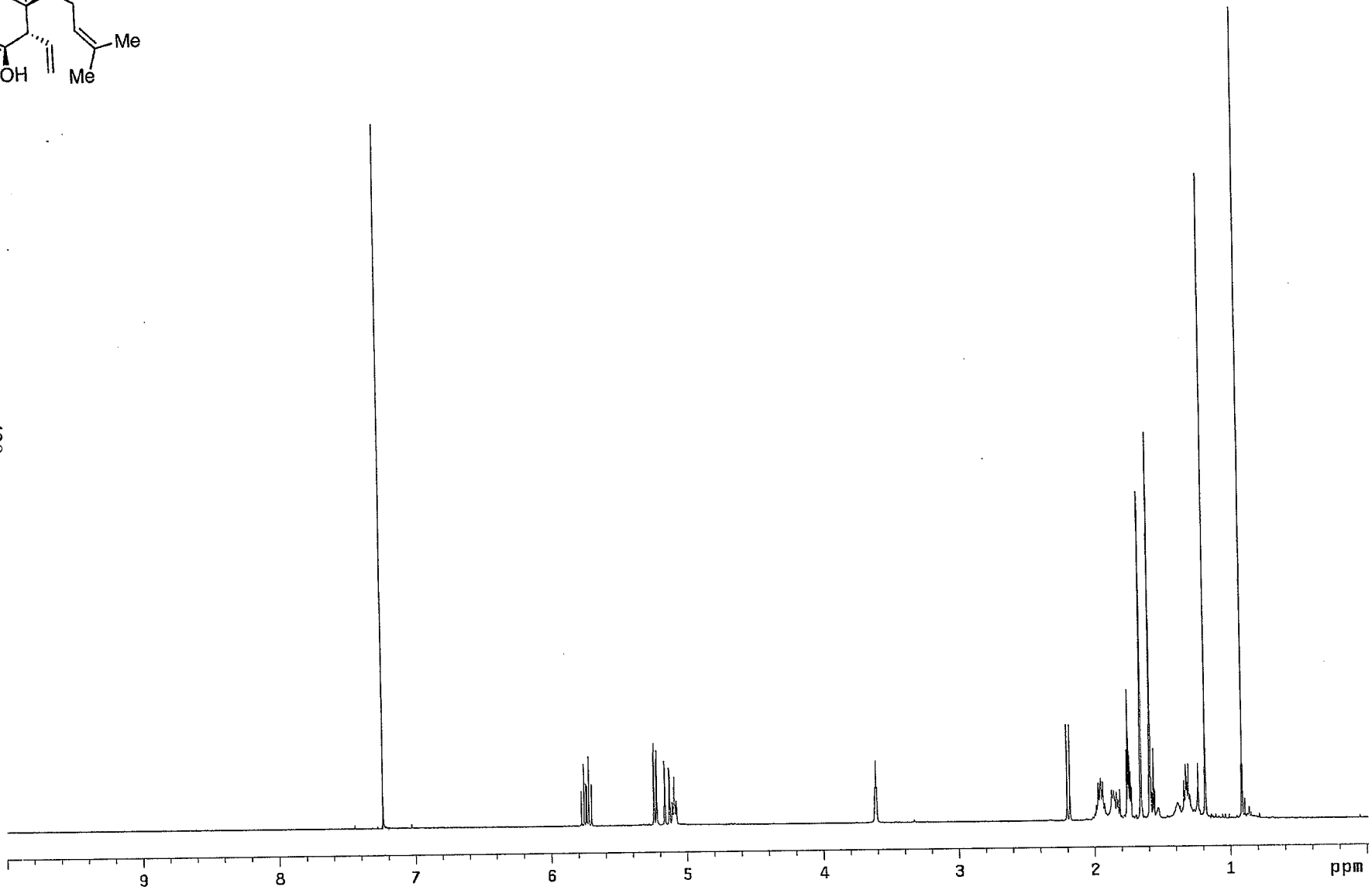
427

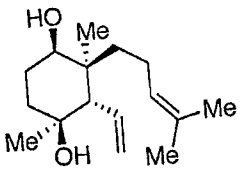


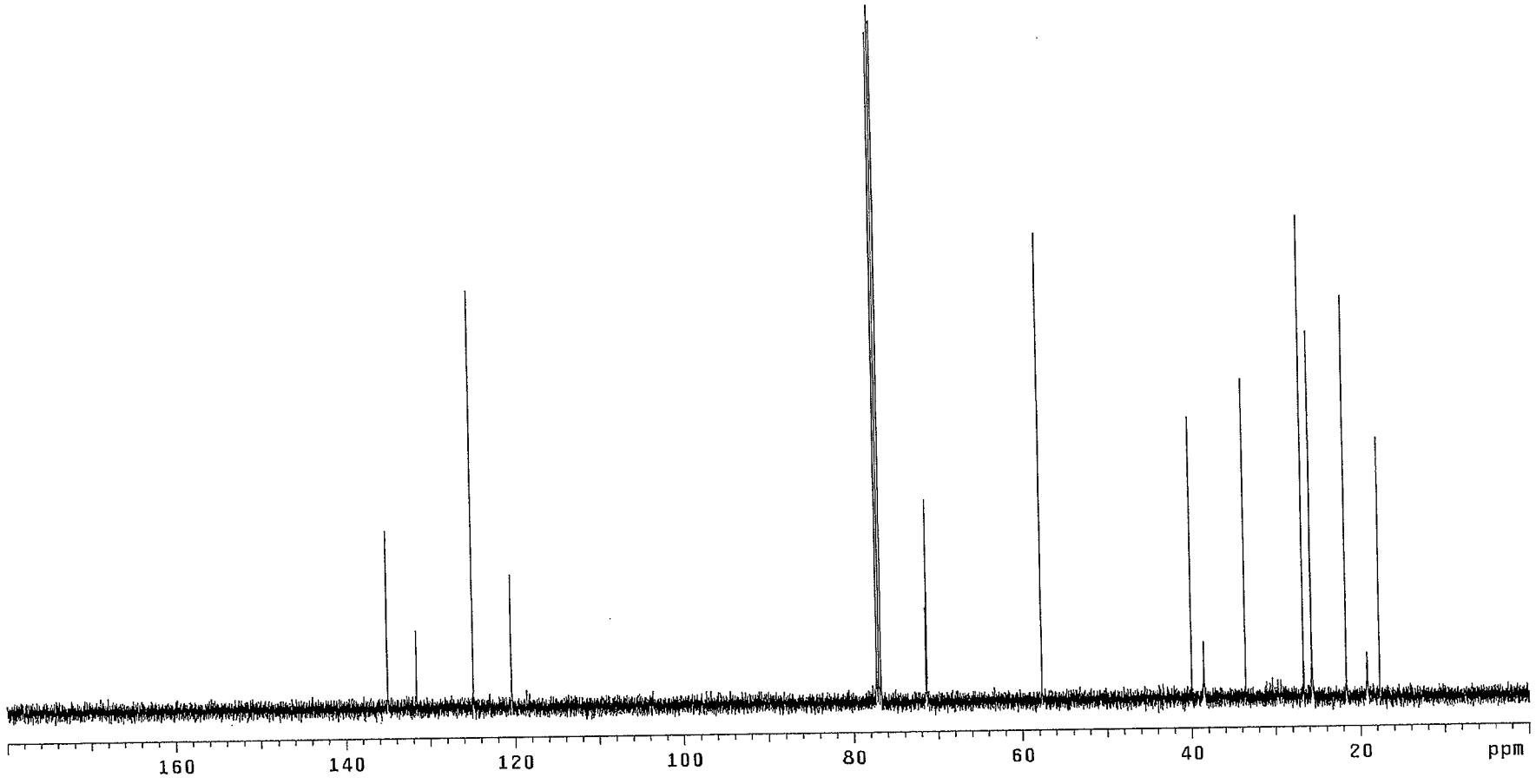

HO
Me
Me
Me
OH
Me
Me


F1
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F2 (ppm)


HO
Me
Me
OH
Me
Me


9
8
7
6
5
4
3
2
1
ppm


HO
Me
Me
Me
OH
Me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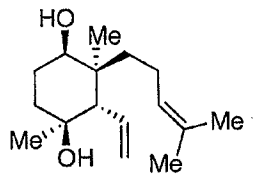
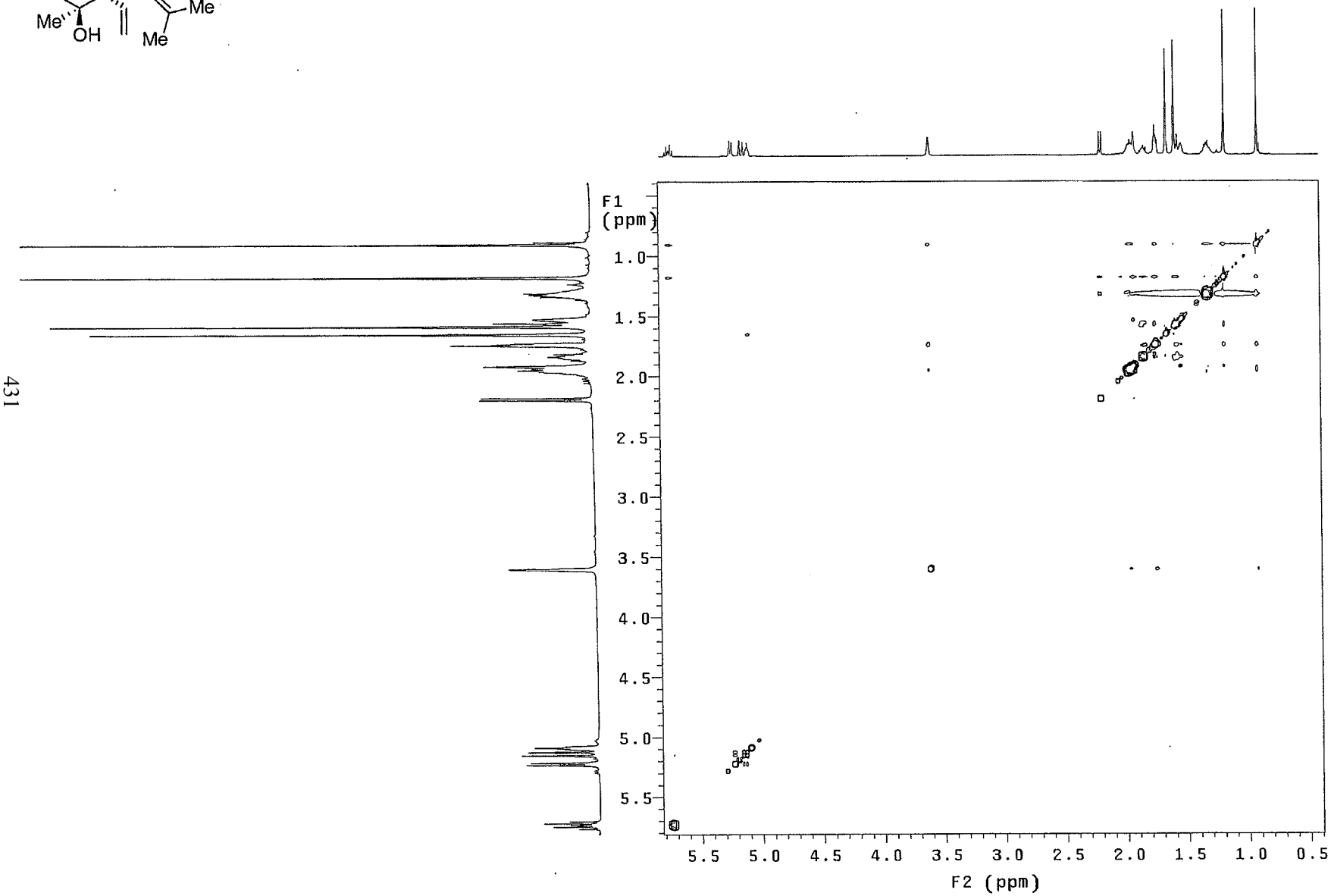
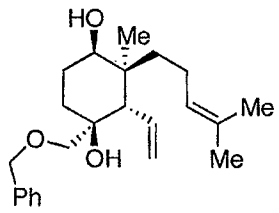
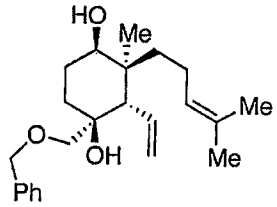
140
120
100
80
60
40
20
ppm

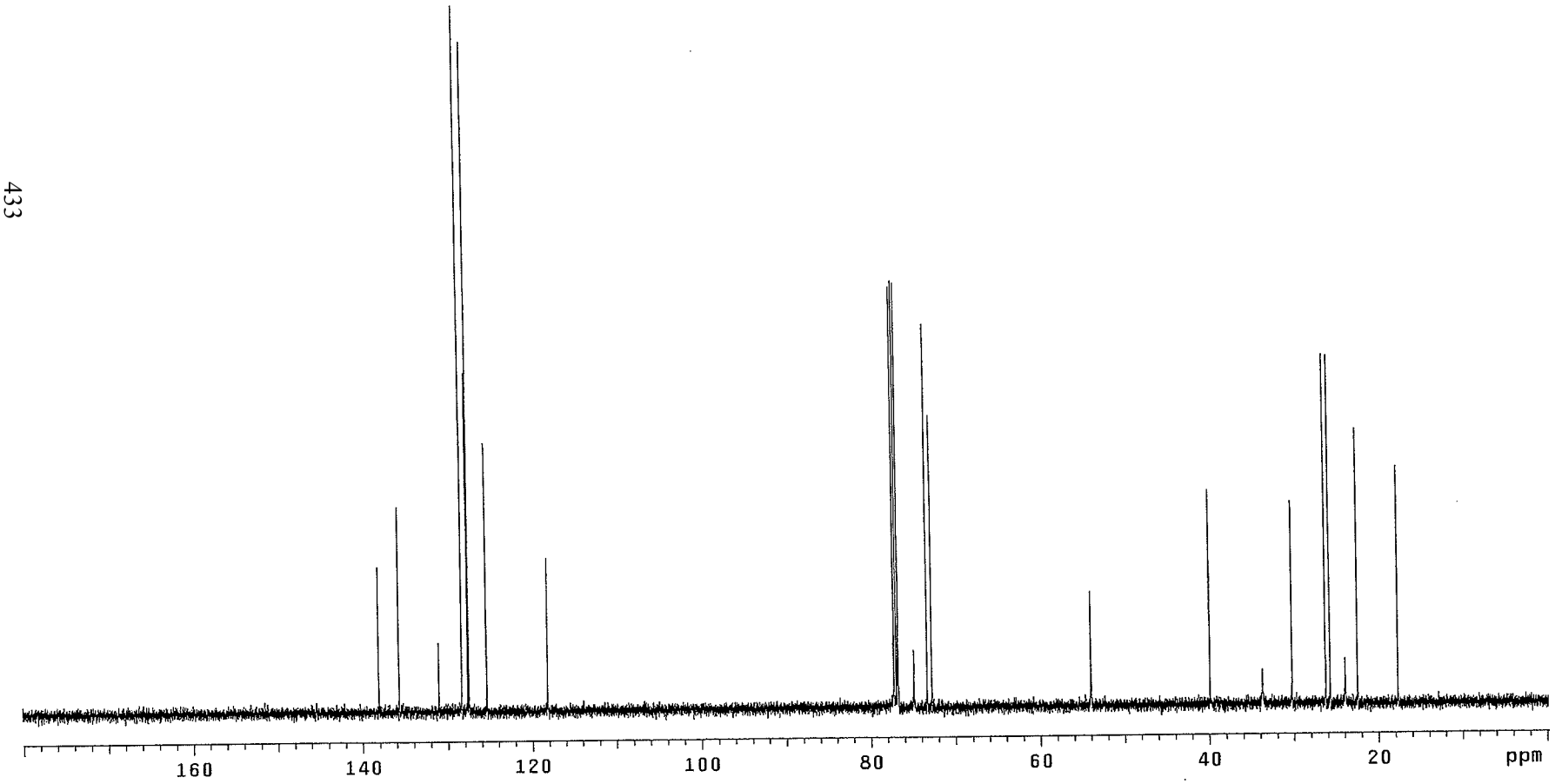

HO
Me
Me
OH
Me
Me


F1
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F2 (ppm)


HO
Me
Me
O
OH
Me
Ph

9
8
7
6
5
4
3
2
1
ppm


HO
Me
Me
O
OH
Me
Ph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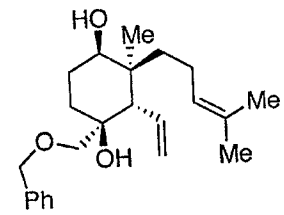
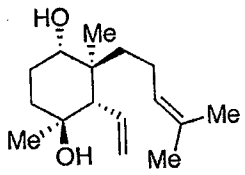
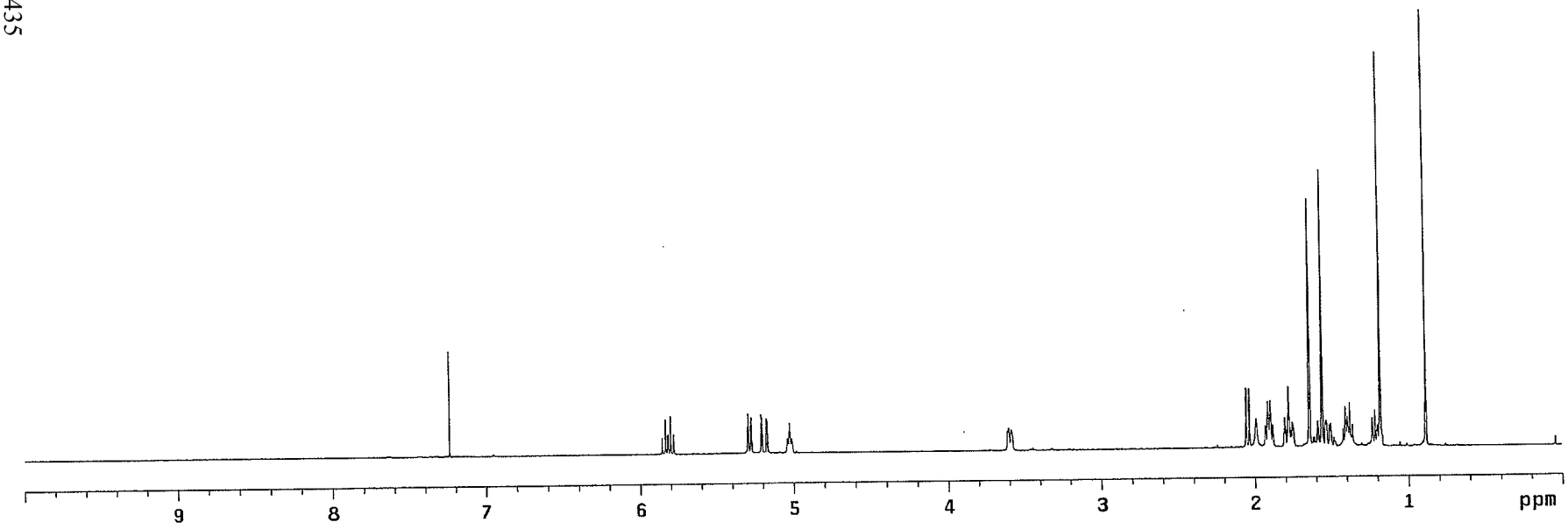
20
ppm


HO
Me
Me
Me
O
OH
Ph

F1
(ppm)
1
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)


HO
Me
Me
Me
OH
Me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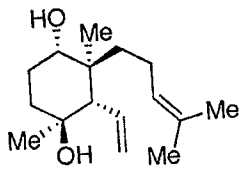
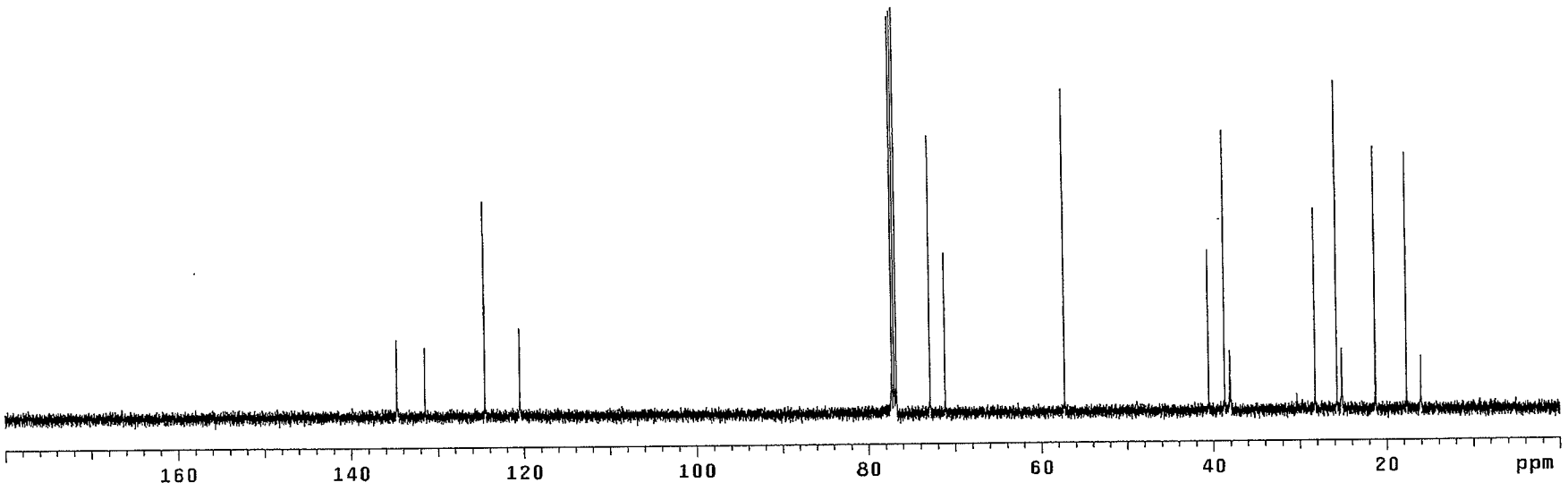
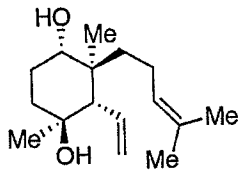
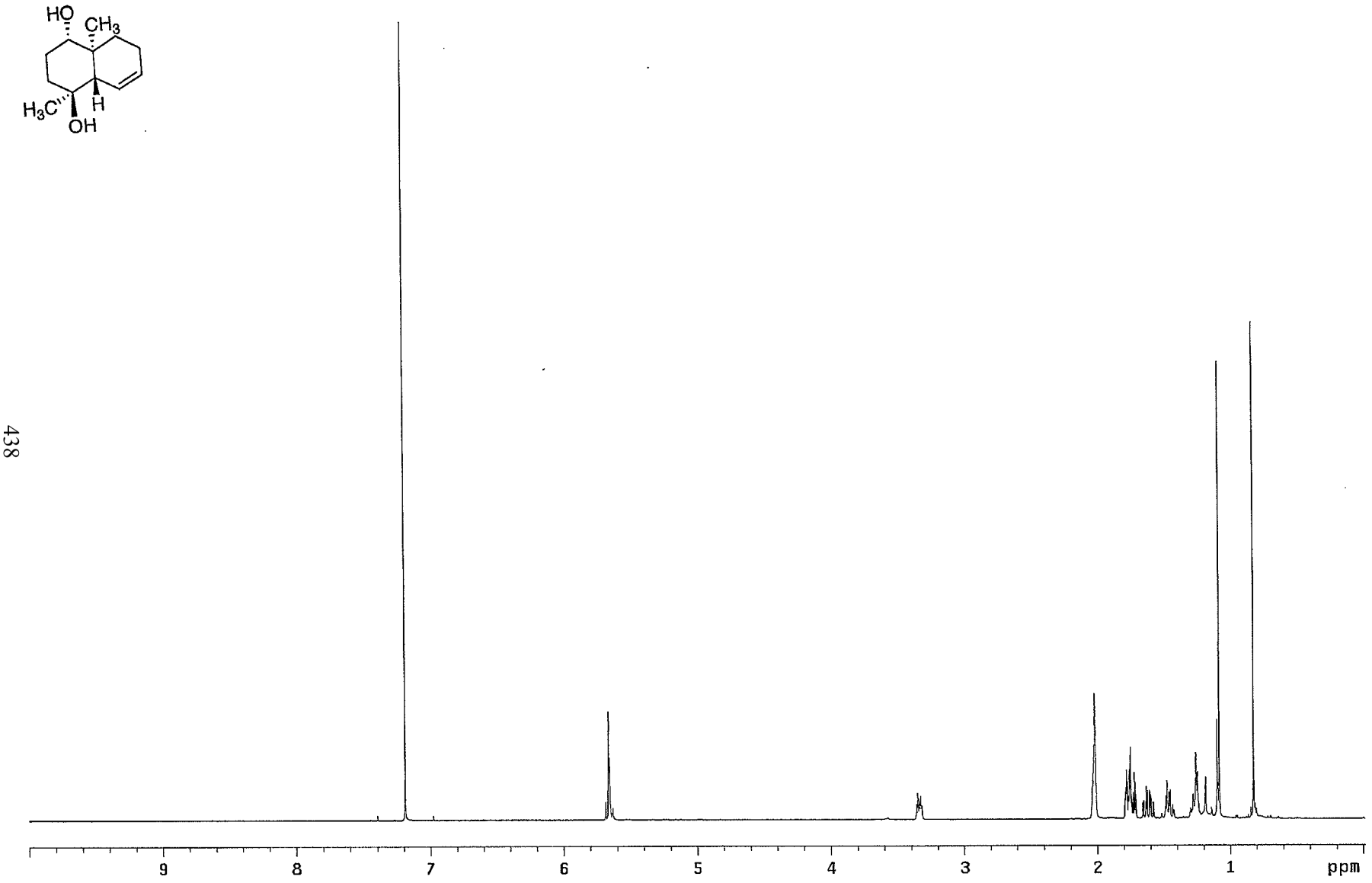
8
7
6
5
4
3
2
1
ppm

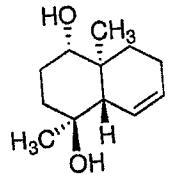

HO
Me
Me
Me
OH
Me

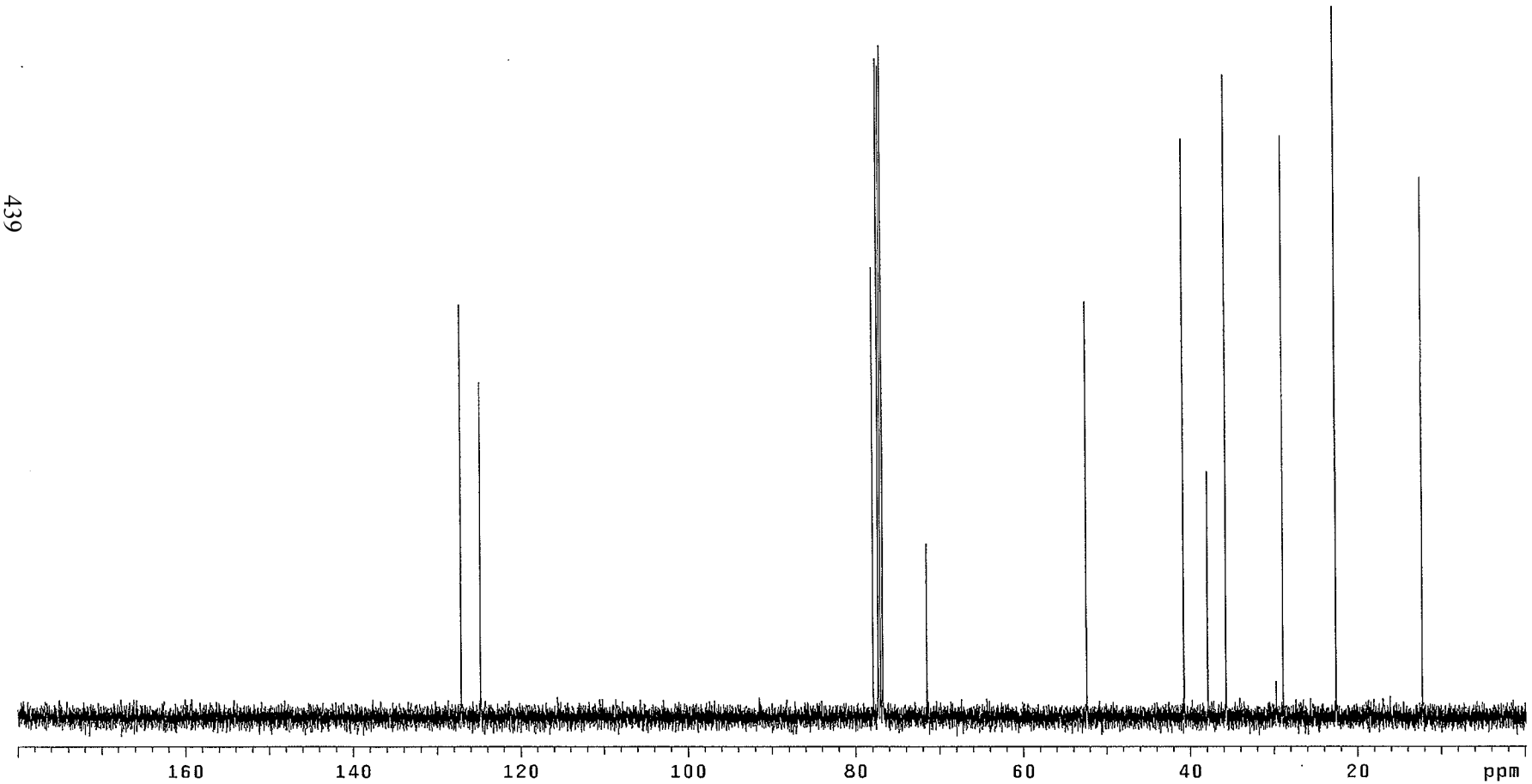

160
140
120
100
80
60
40
20
ppm


HO
Me
Me
Me
OH
Me

F2
(ppm)
1
2
3
4
5
6
7
7
6
5
4
3
2
1
F1 (ppm)


HO
CH3
H3C
H
OH
9
8
7
6
5
4
3
2
1
ppm


HO
CH3
H3C
H
OH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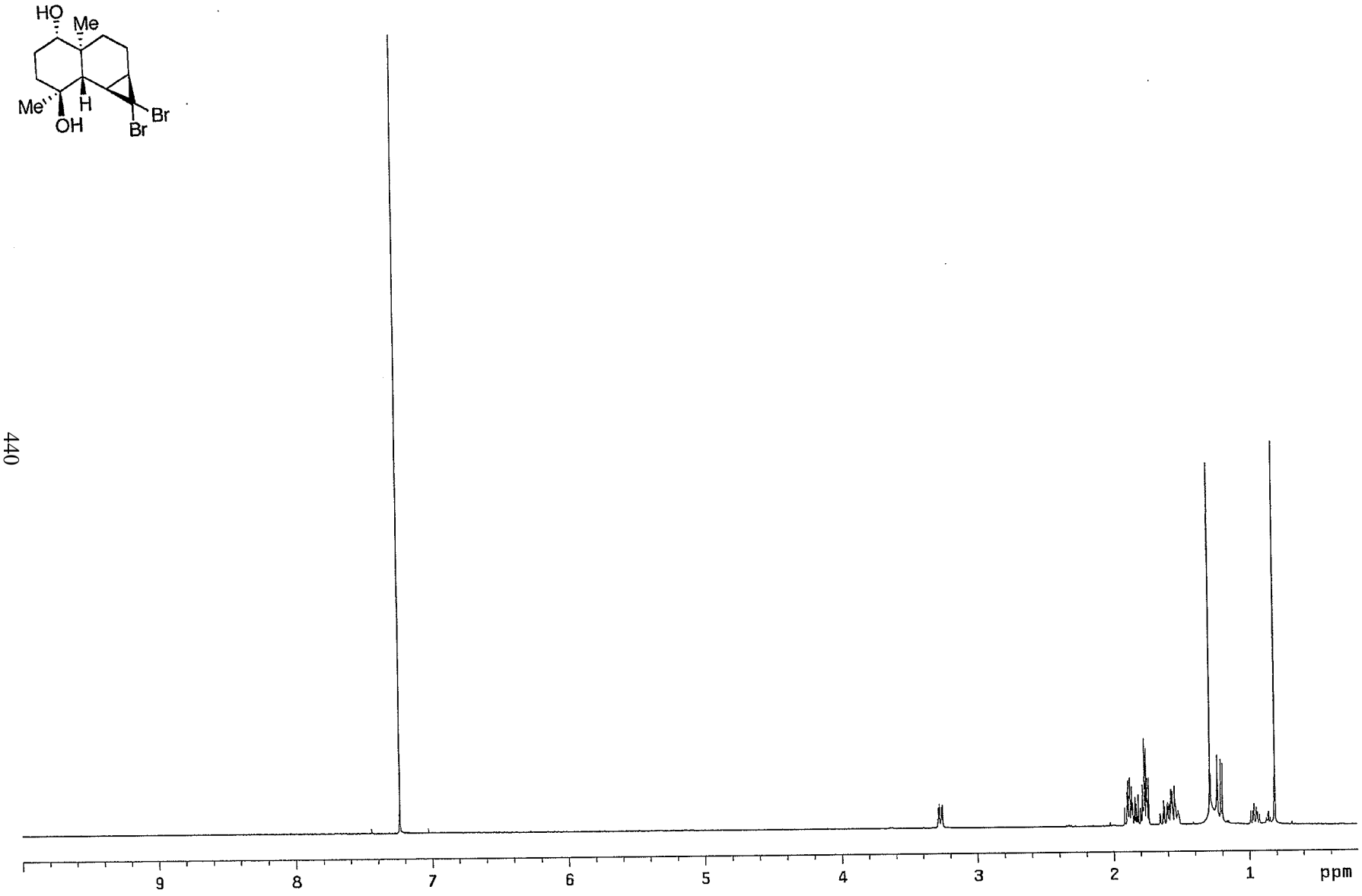
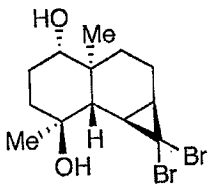
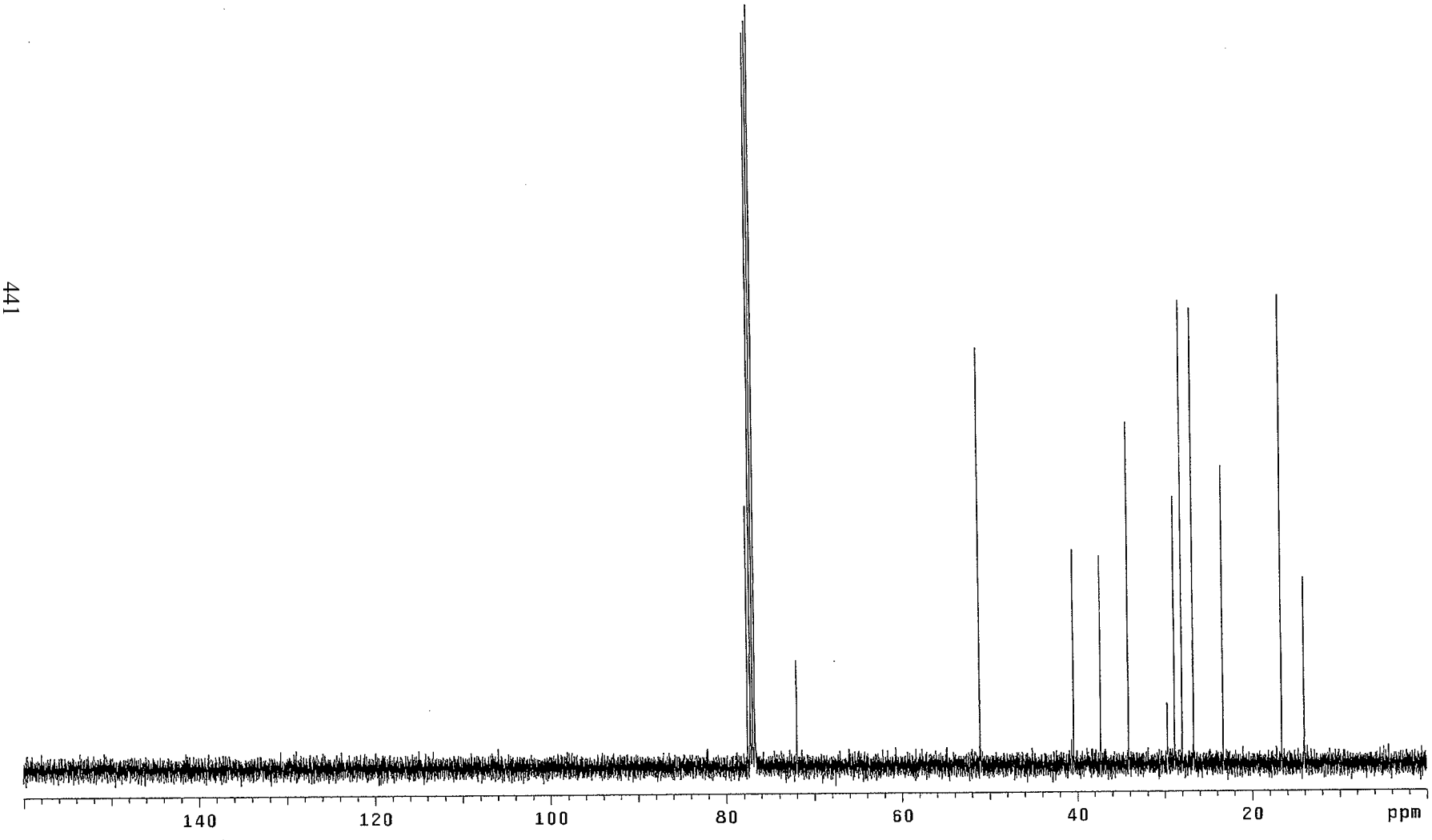
140
120
100
80
60
40
20
ppm


HO
Me
Me
H
OH
Br
Br
9
8
7
6
5
4
3
2
1
ppm


HO
Me
Me
H
OH
Br
Br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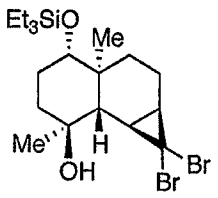
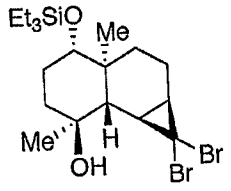
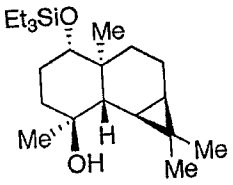
120
100
80
60
40
20
ppm


Et3SiO
Me
Me
H
OH
Br
Br

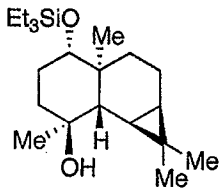
9
8
7
6
5
4
3
2
1
ppm

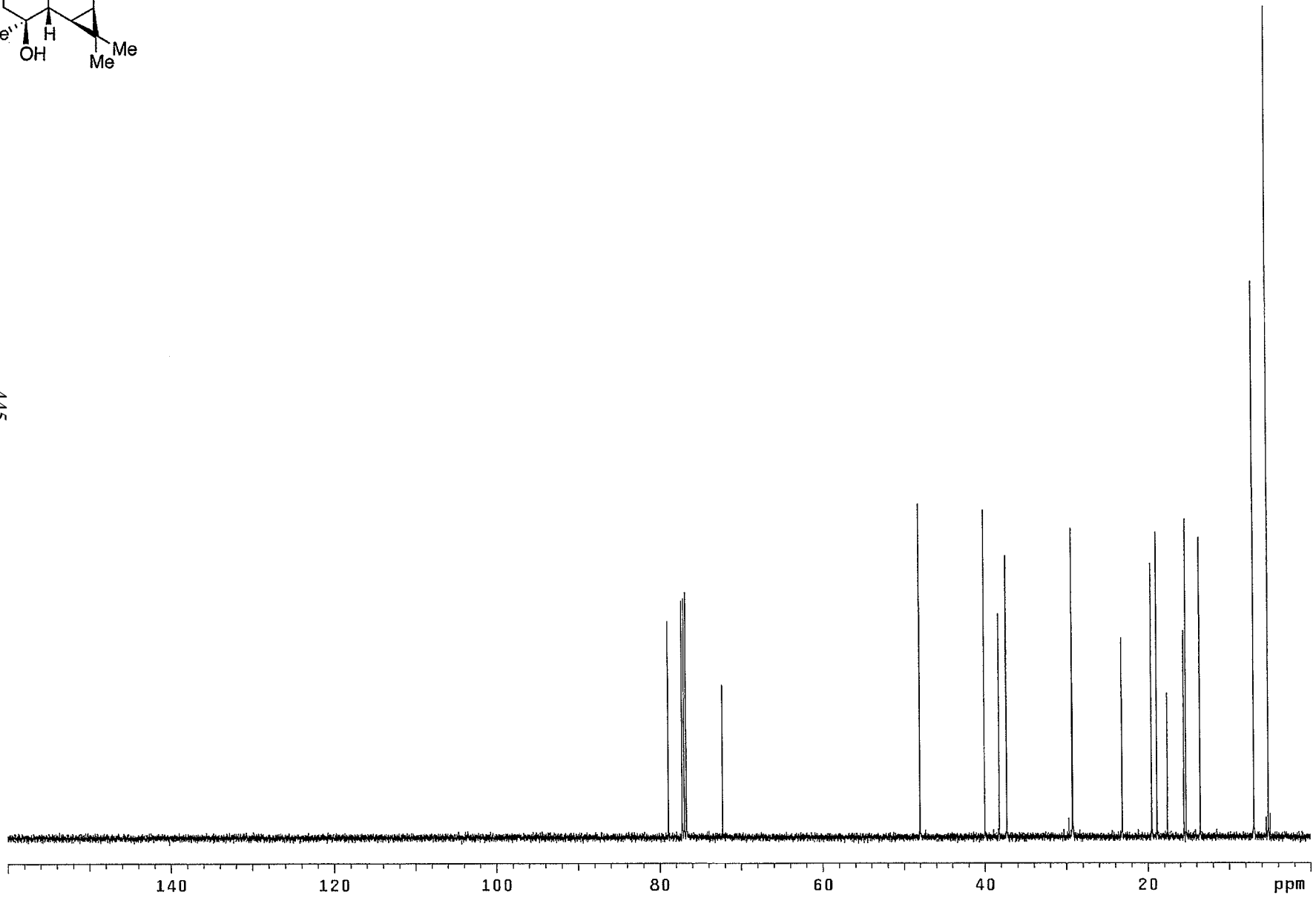

Et3SiO
Me
Me
H
OH
Br
Br

140
120
100
80
60
40
20
0
ppm


Et3SiO
Me
Me
H
OH
Me
Me

9
8
7
6
5
4
3
2
1
ppm


Et3SiO
Me
Me
H
OH
Me
Me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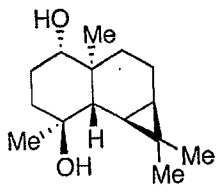
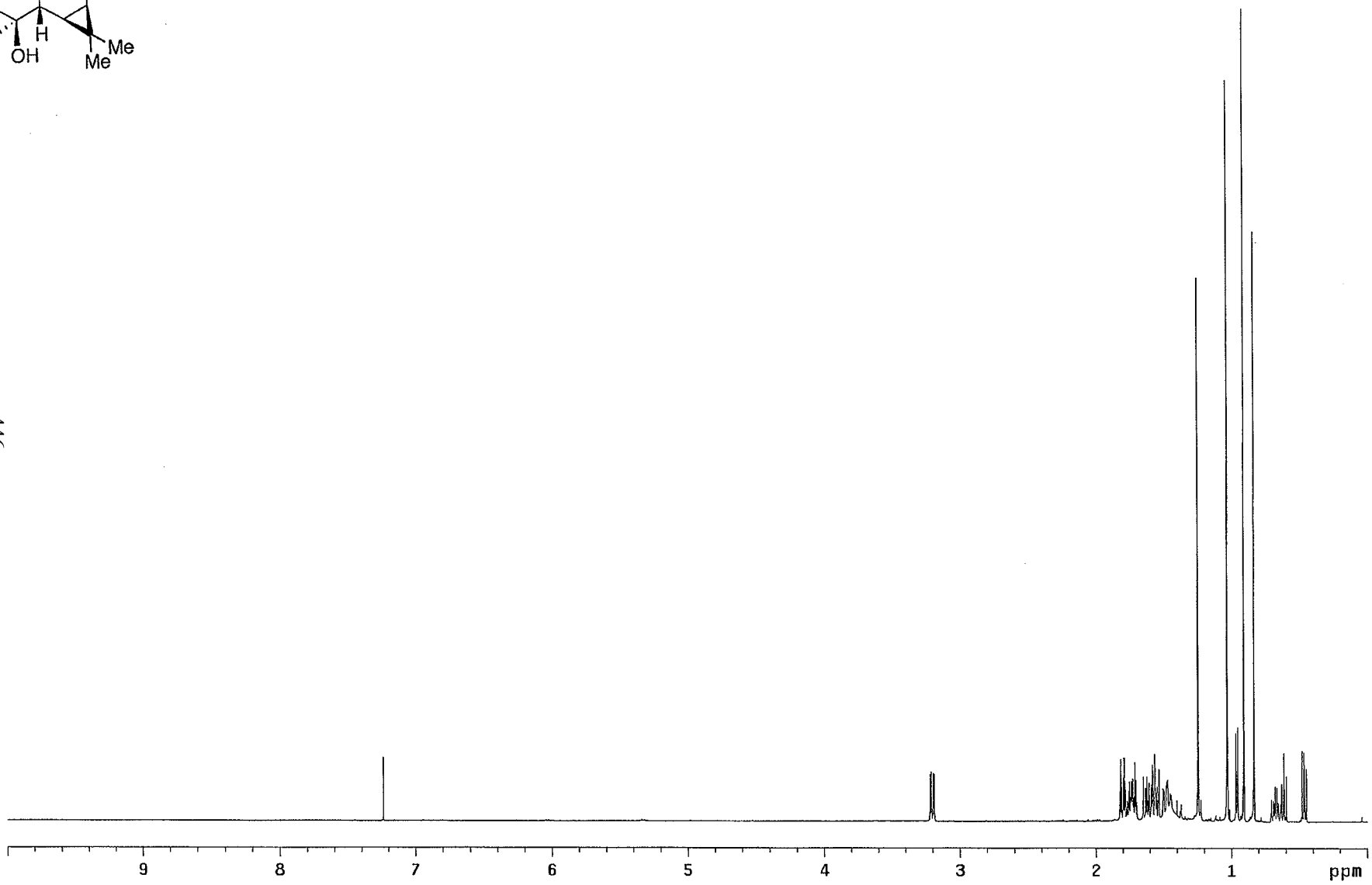
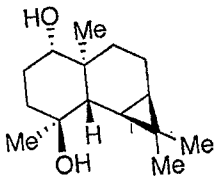
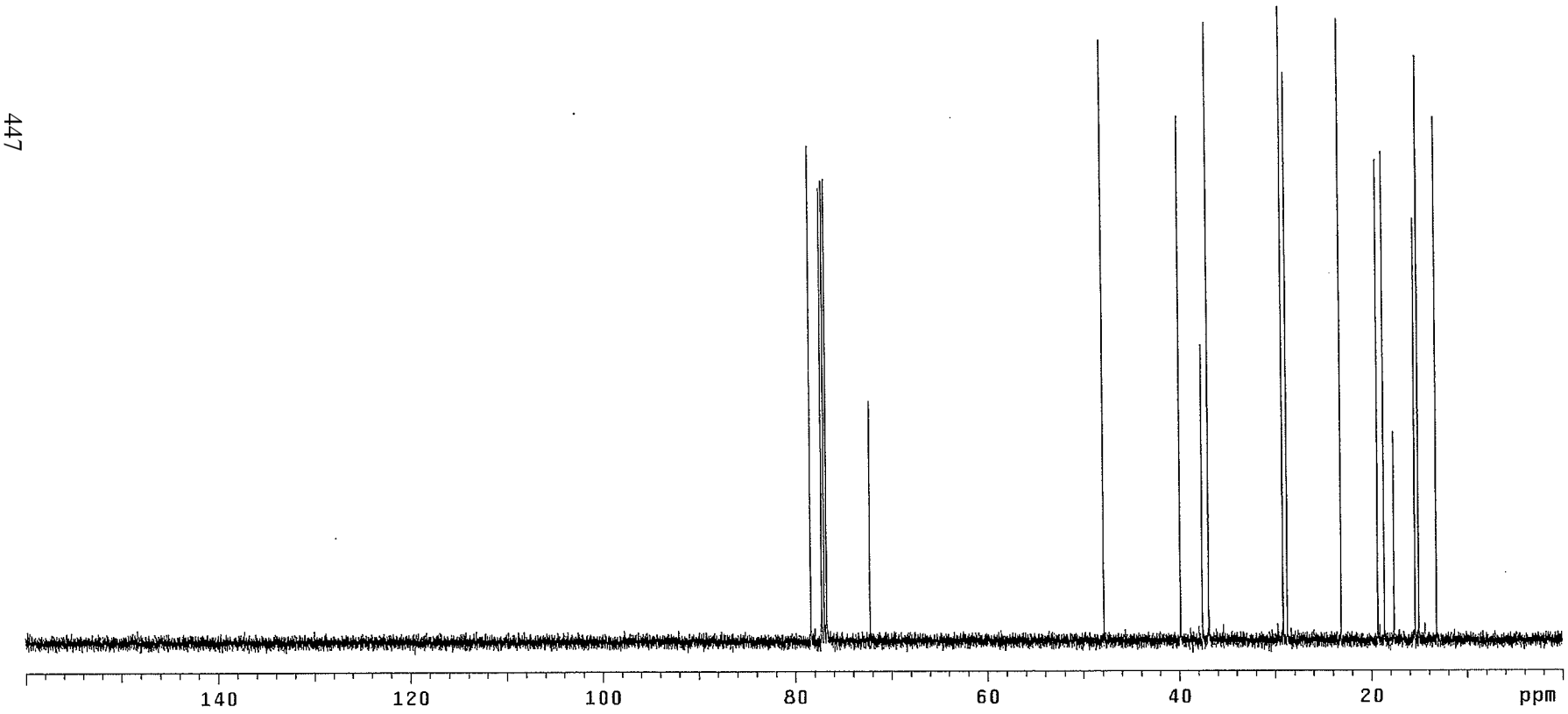
120
100
80
60
40
20
ppm

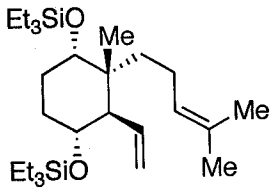

HO
Me
Me
H
OH
Me
Me


9
8
7
6
5
4
3
2
1
ppm

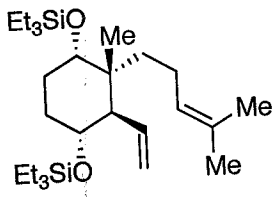


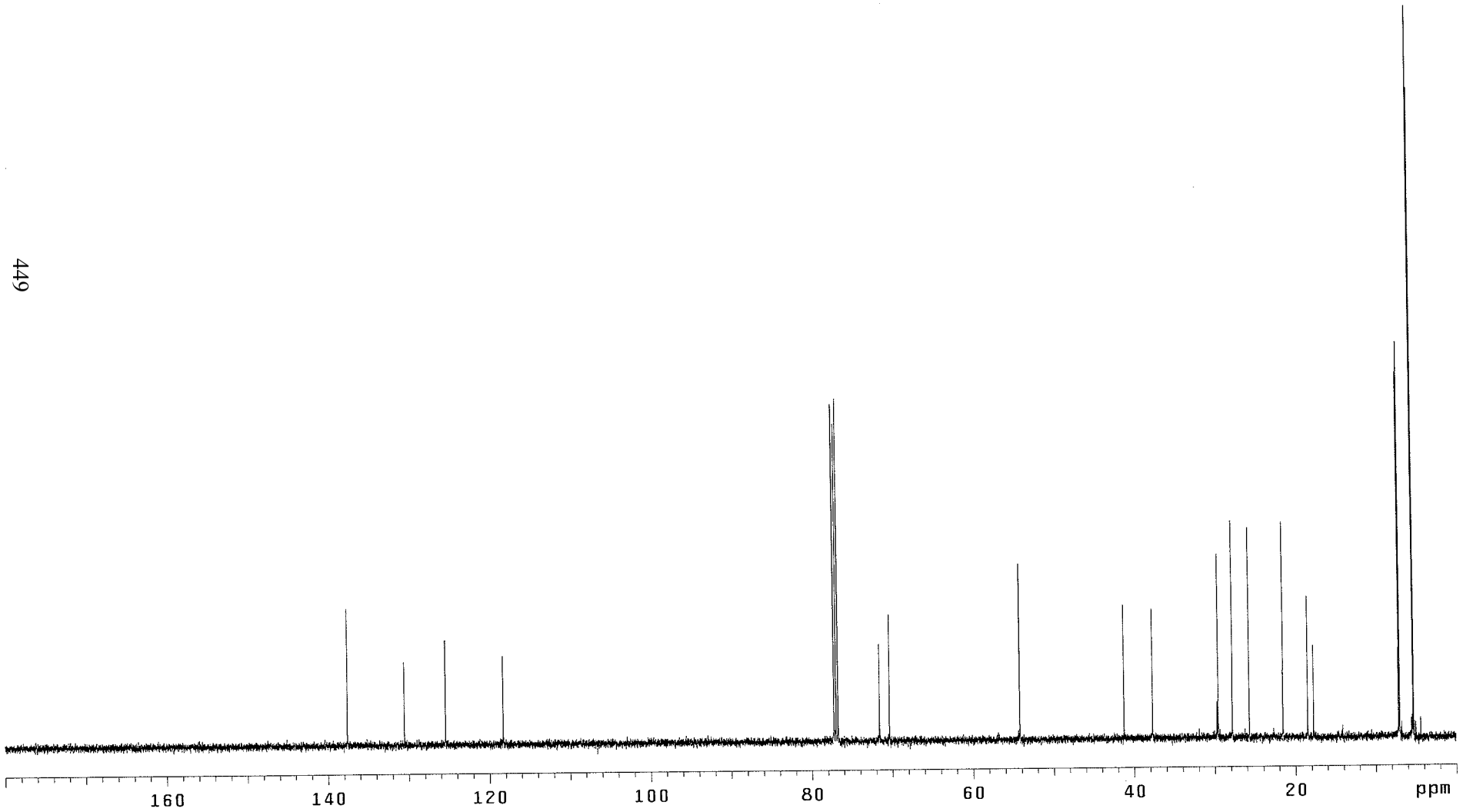
447

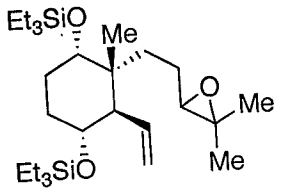



Et3SiO
Me
Me
Me
Et3SiO

9
8
7
6
5
4
3
2
1
ppm


Et3SiO
Me
Me
Me
Et3SiO


160
140
120
100
80
60
40
20
ppm



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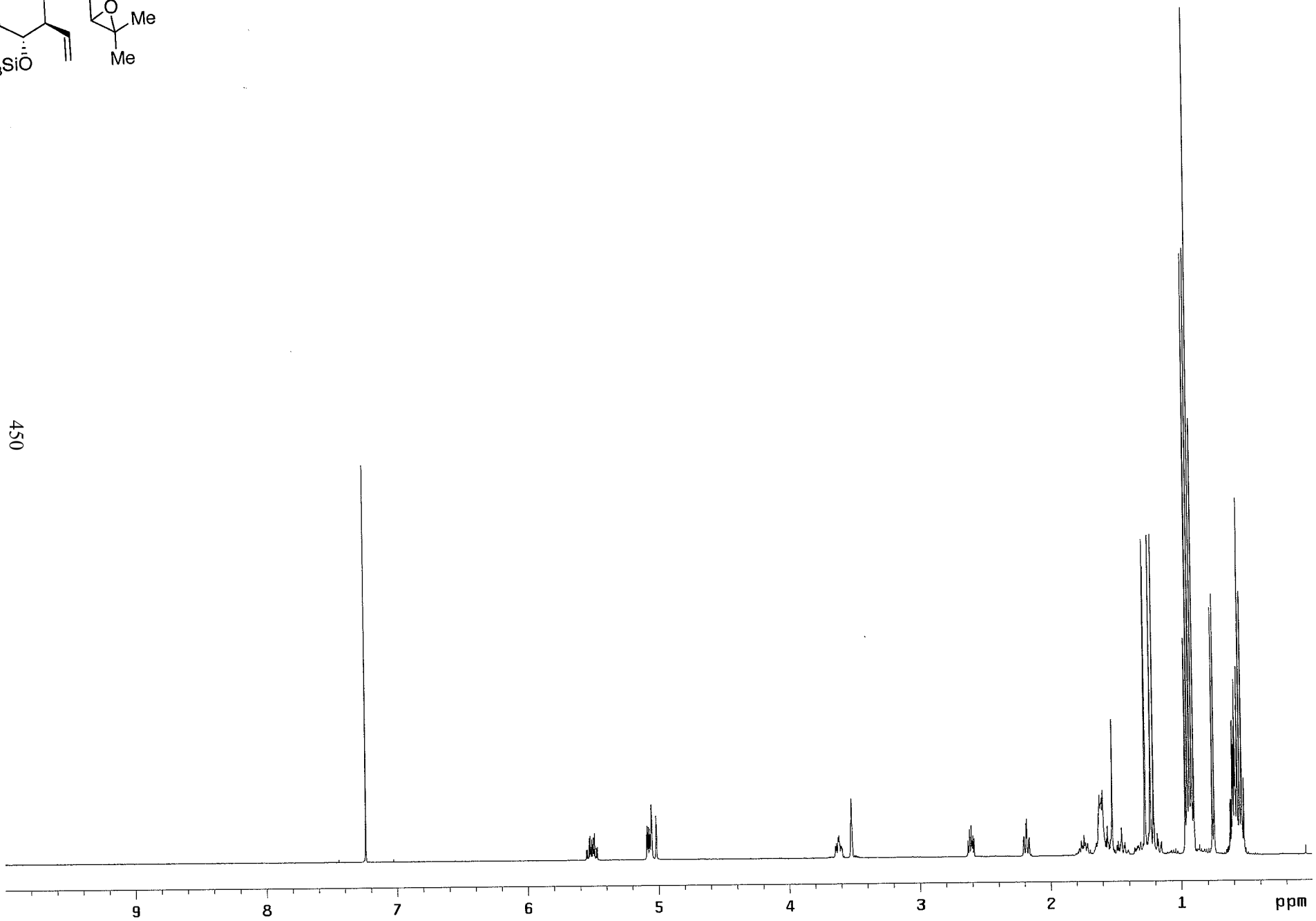
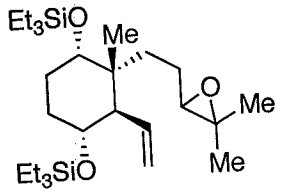
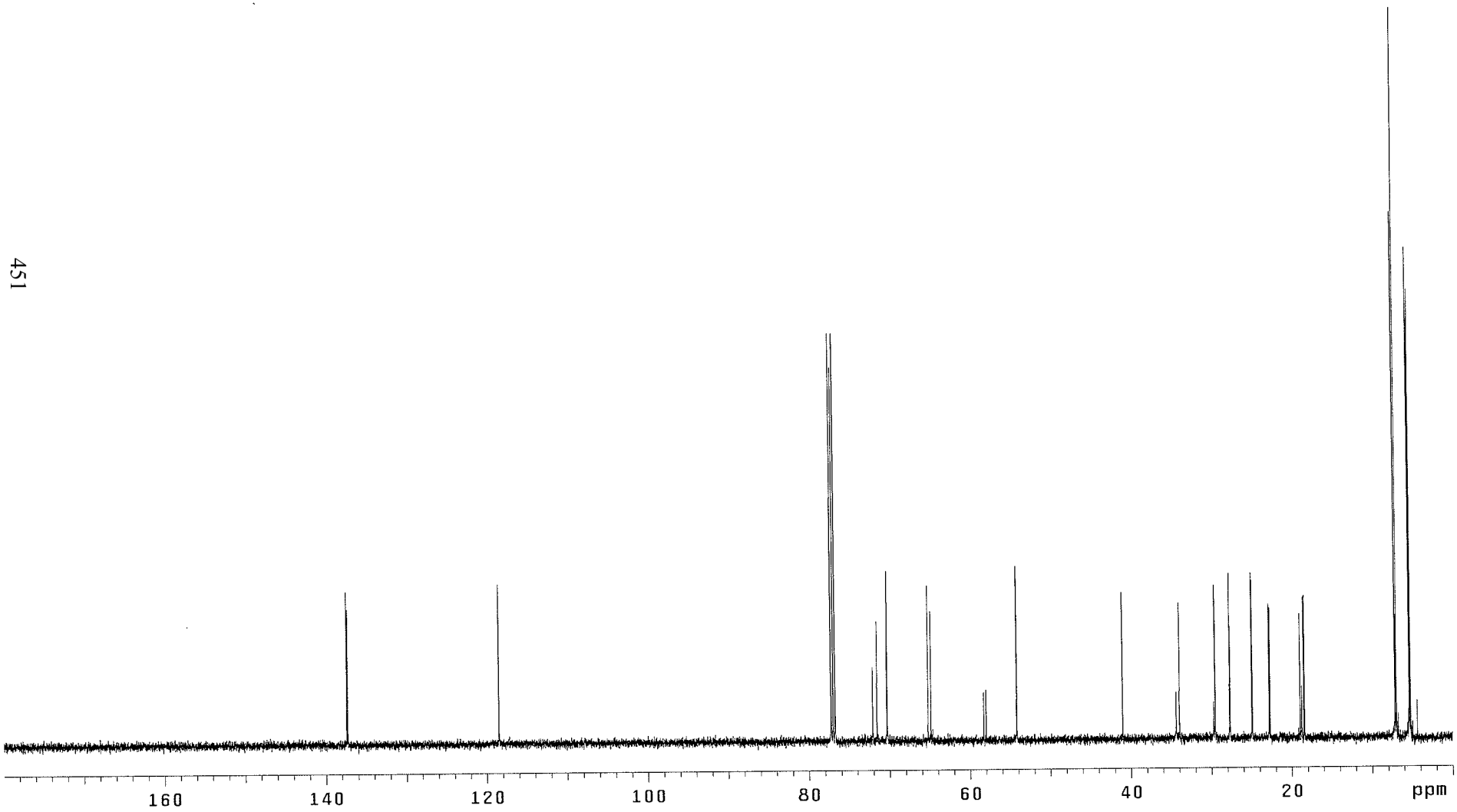



Et3SiO
Me
O
Me
Me
Et3SiO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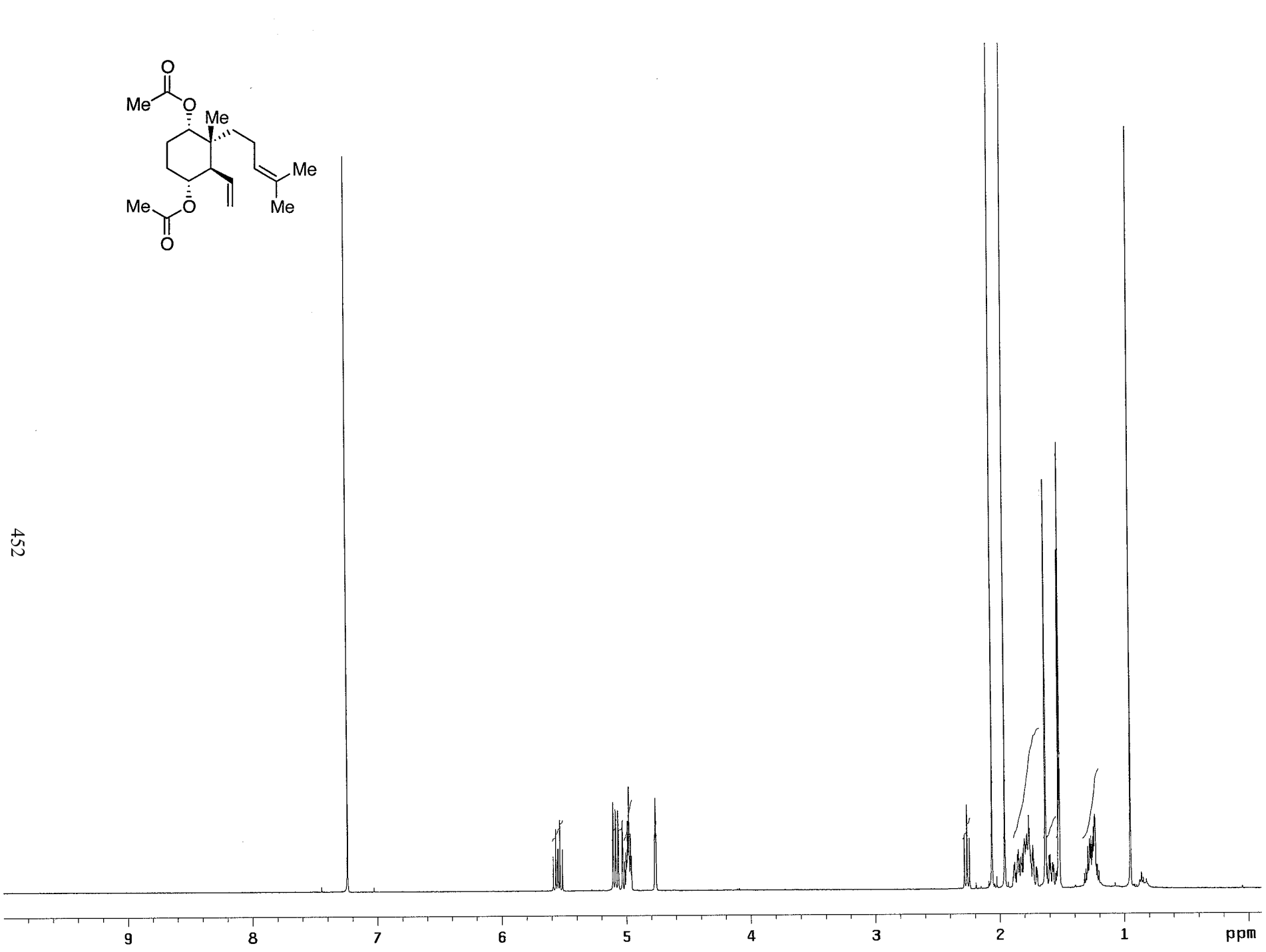
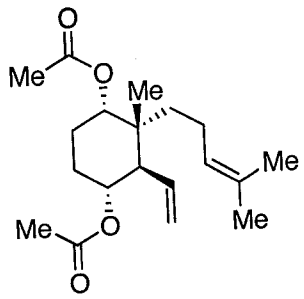
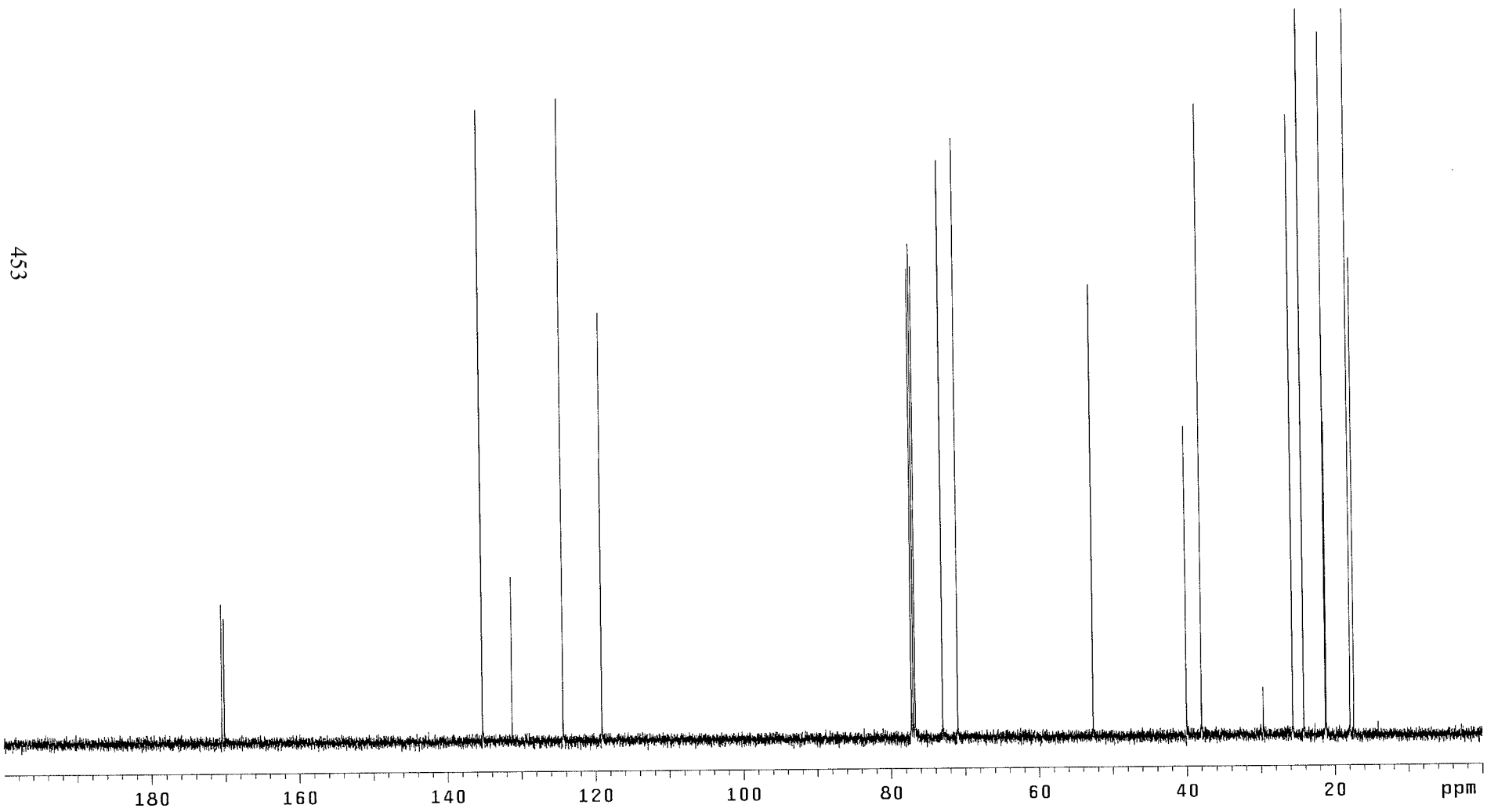
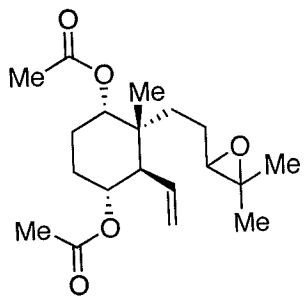
140
120
100
80
60
40
20
ppm


Me
O
Me
Me
Me
Me
O
O
9
8
7
6
5
4
3
2
1
ppm

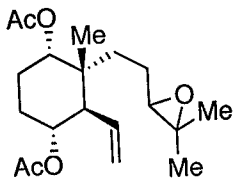


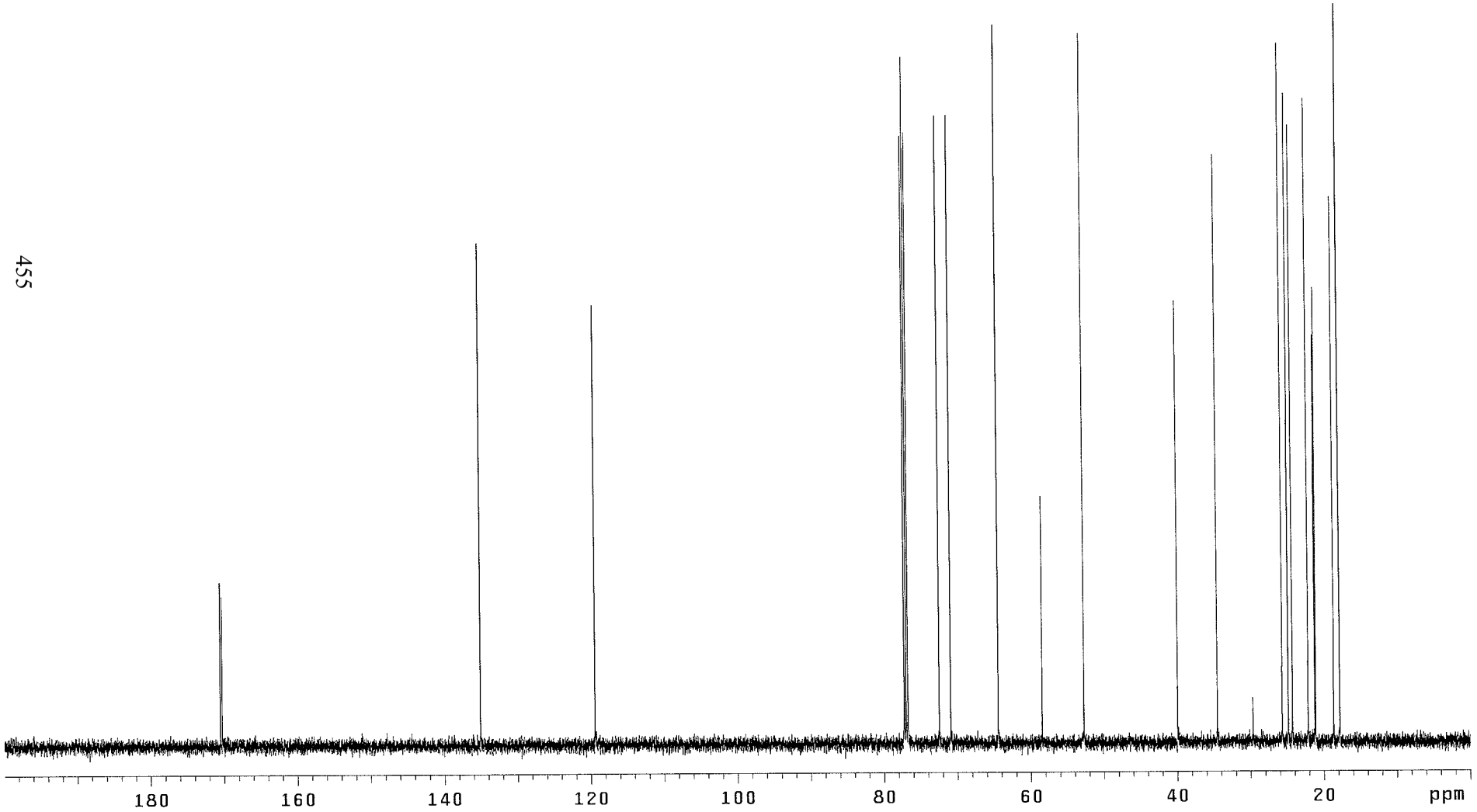
453

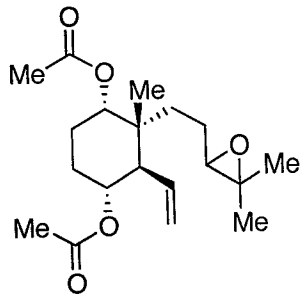



O
Me
O
Me
O
Me
Me
Me
O

9
8
7
6
5
4
3
2
1
ppm


AcO
Me
O
Me
AcO
Me


180
160
140
120
100
80
60
40
20
ppm



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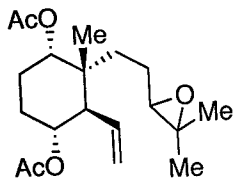

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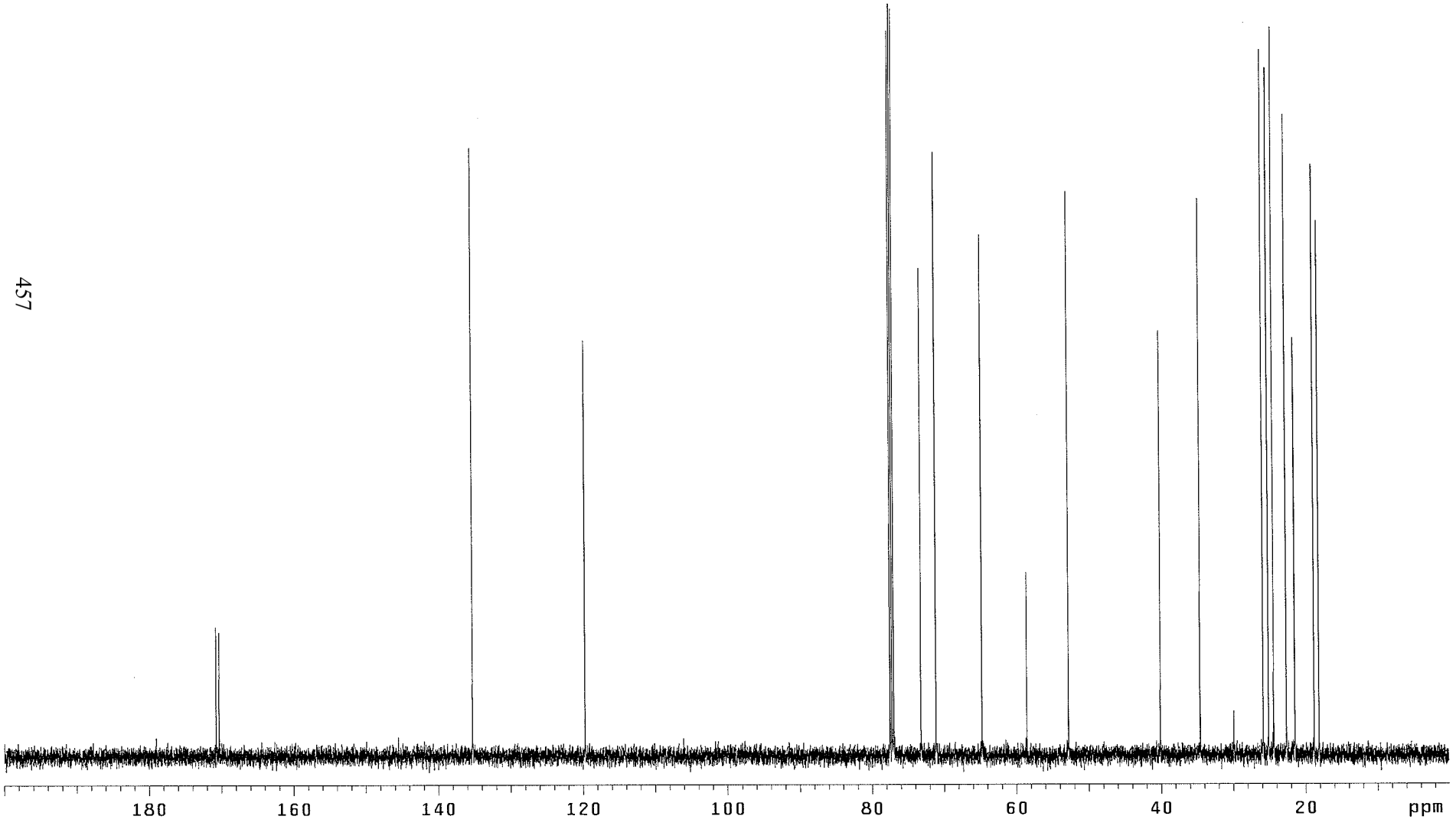
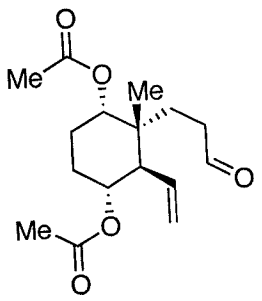
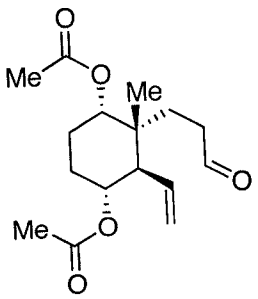
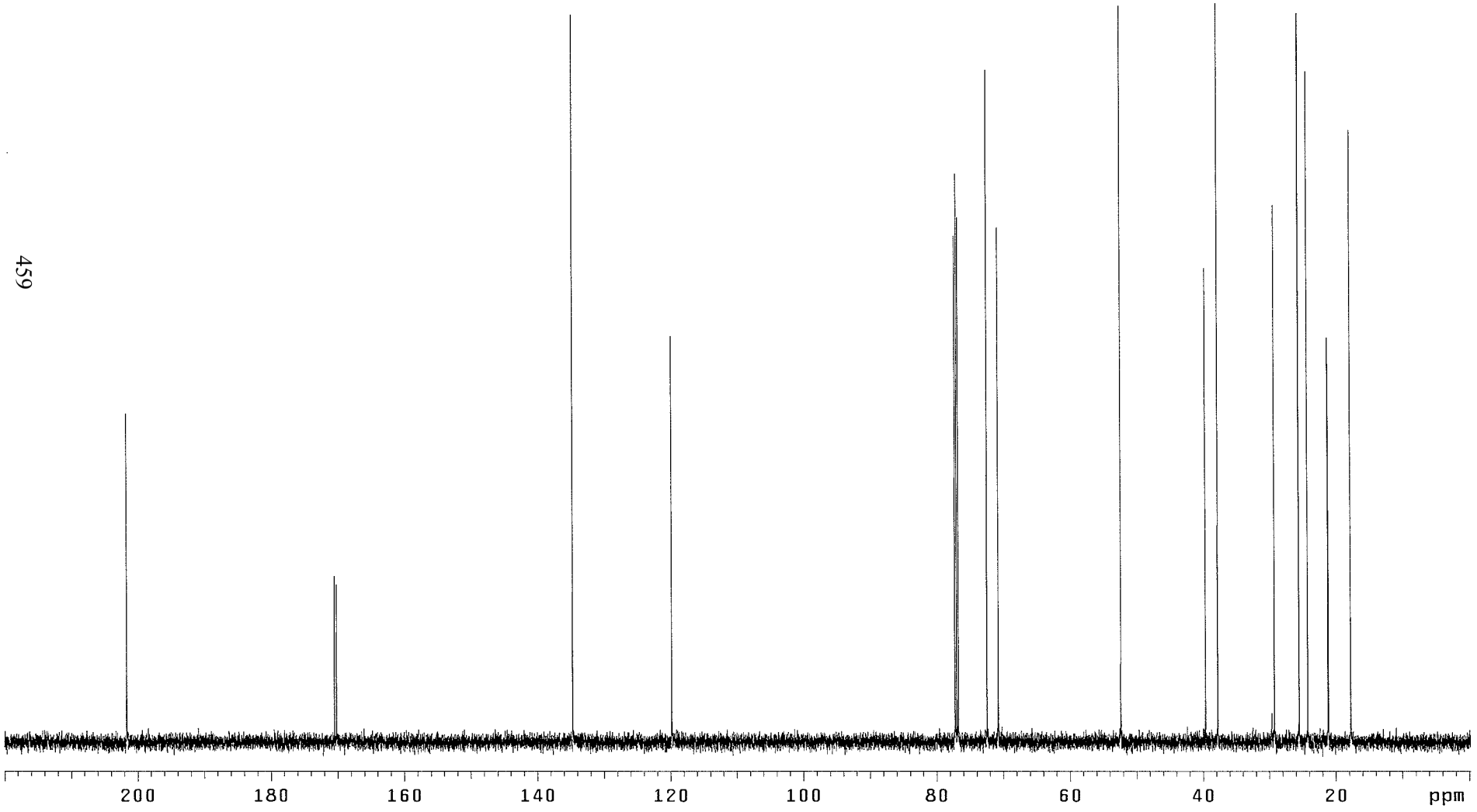


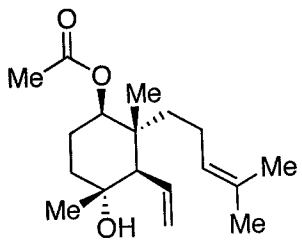

Me
O
O
Me
O
Me
O
O

9
8
7
6
5
4
3
2
1
ppm



459





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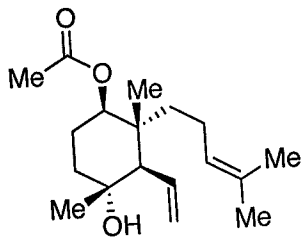

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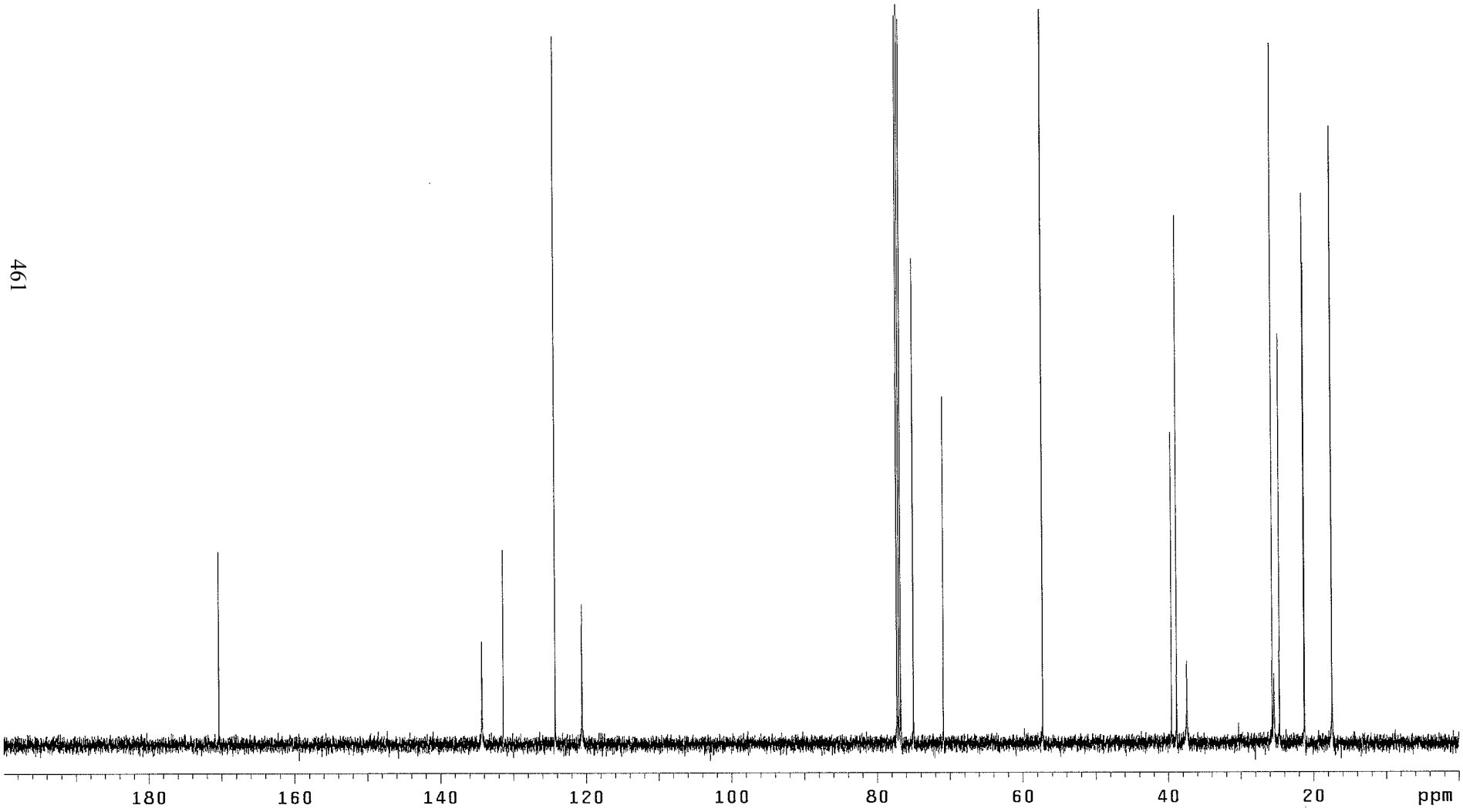

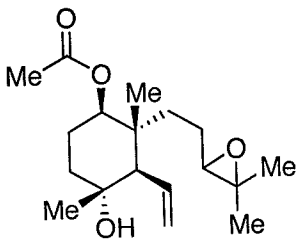

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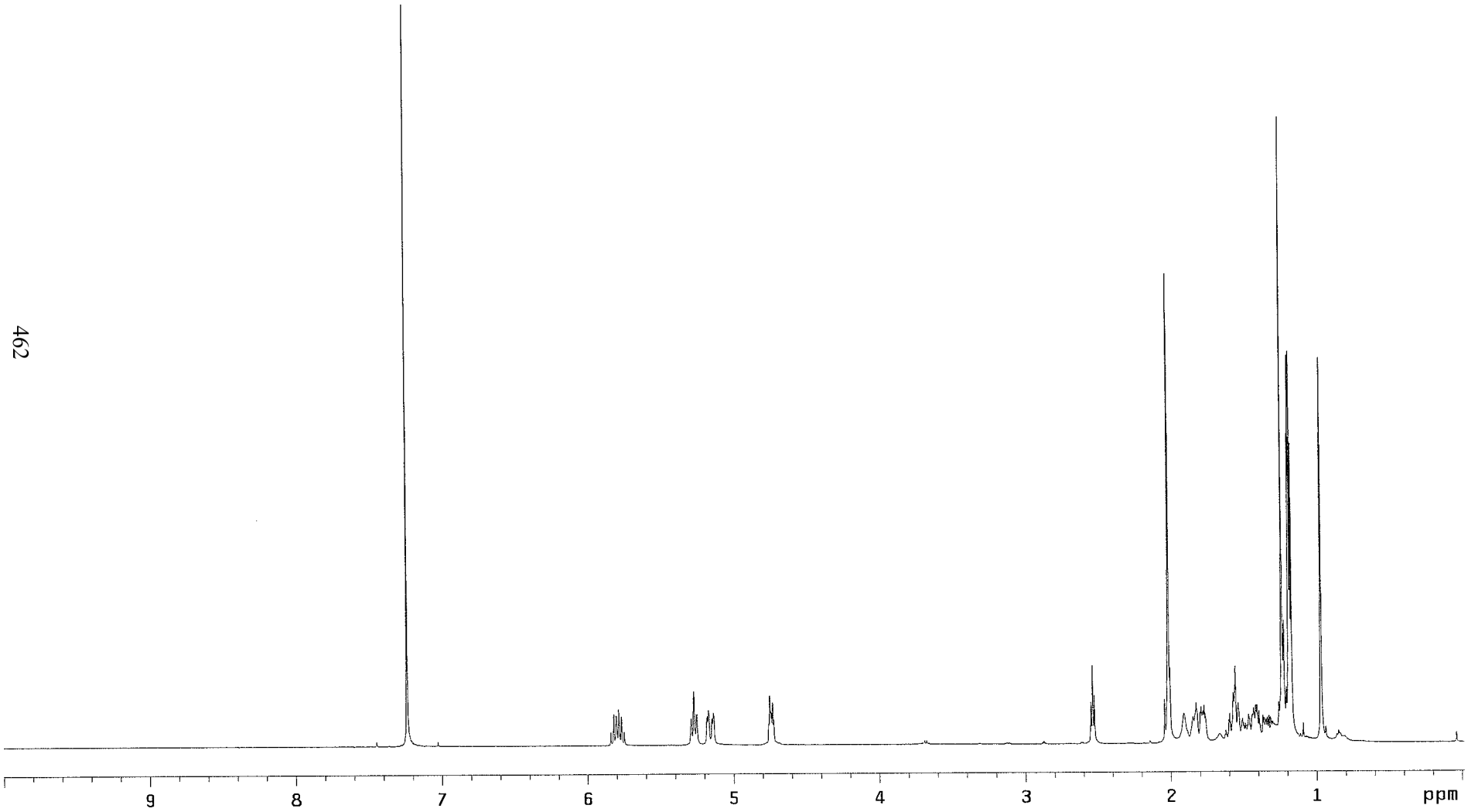

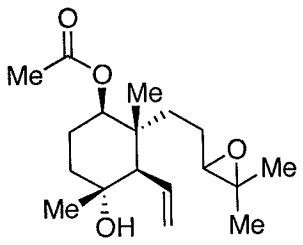

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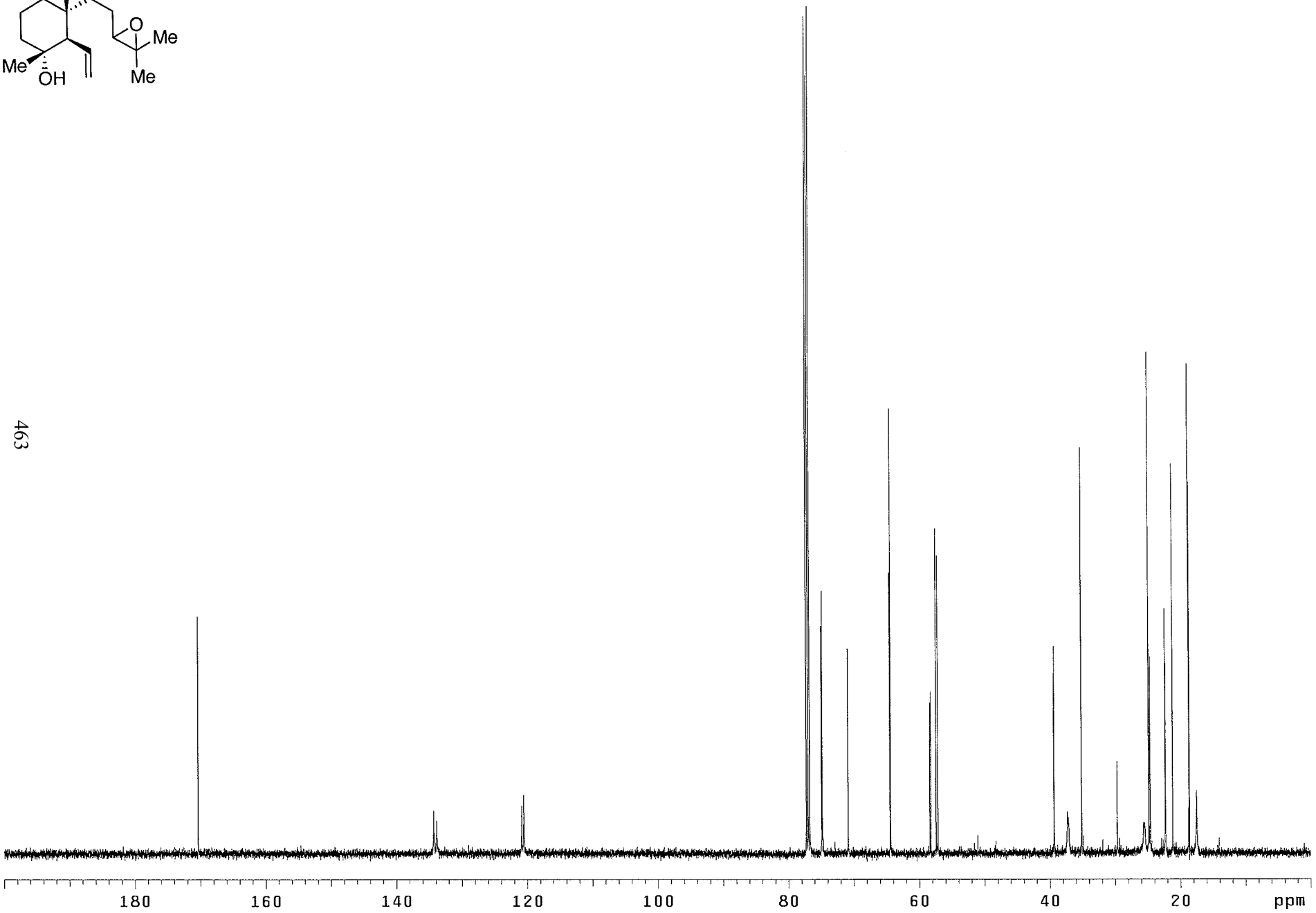
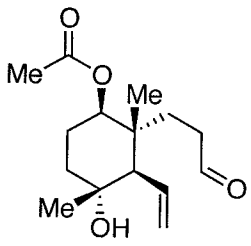
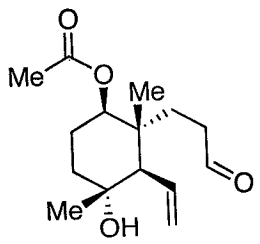
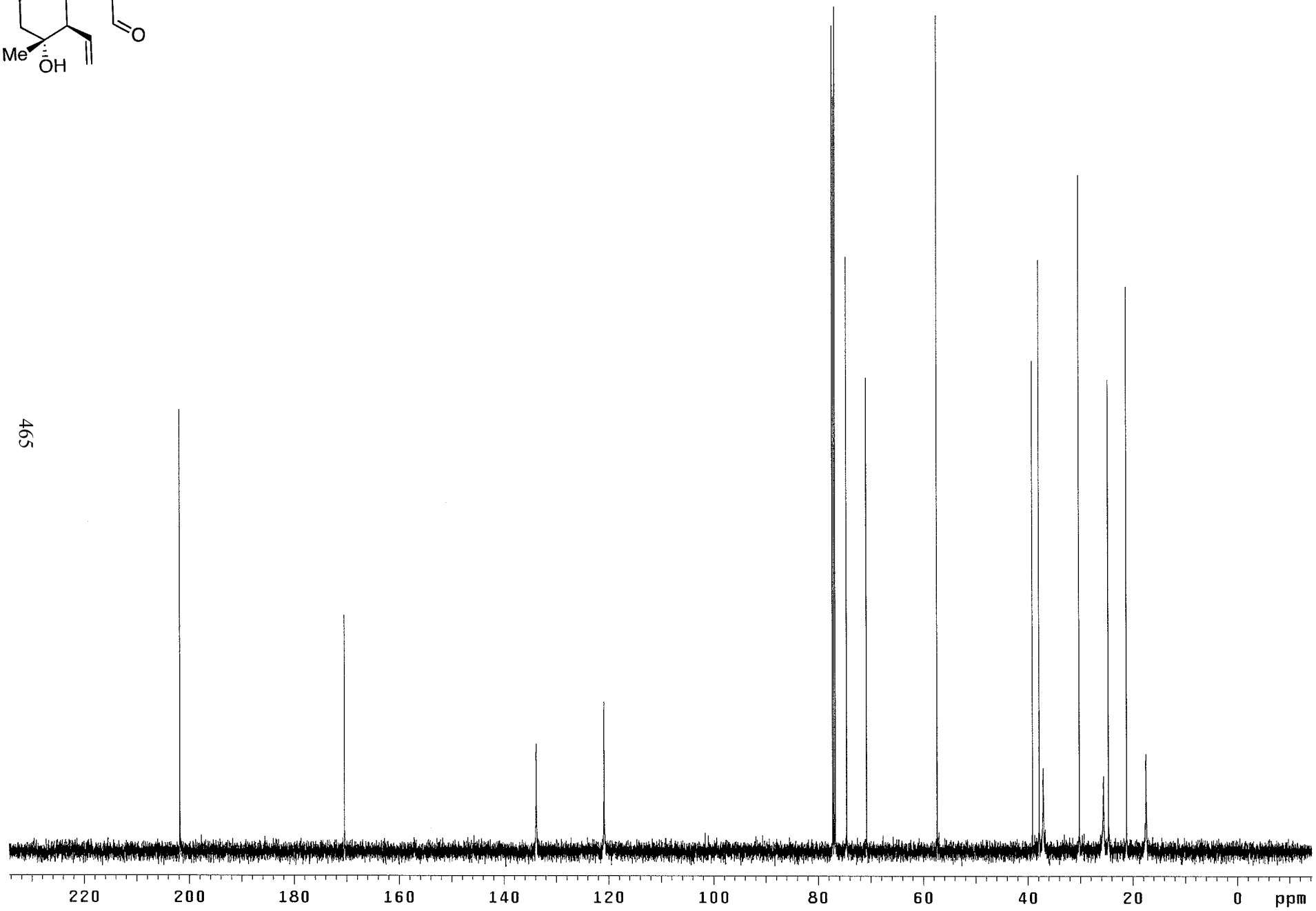



O
Me
O
Me
Me
OH
O

10
9
8
7
6
5
4
3
2
1
ppm


O
Me
O
Me
Me
OH
O


220
200
180
160
140
120
100
80
60
40
20
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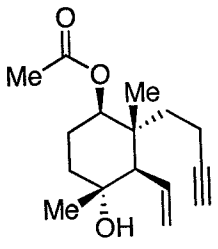

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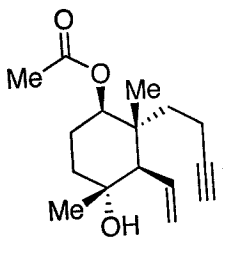

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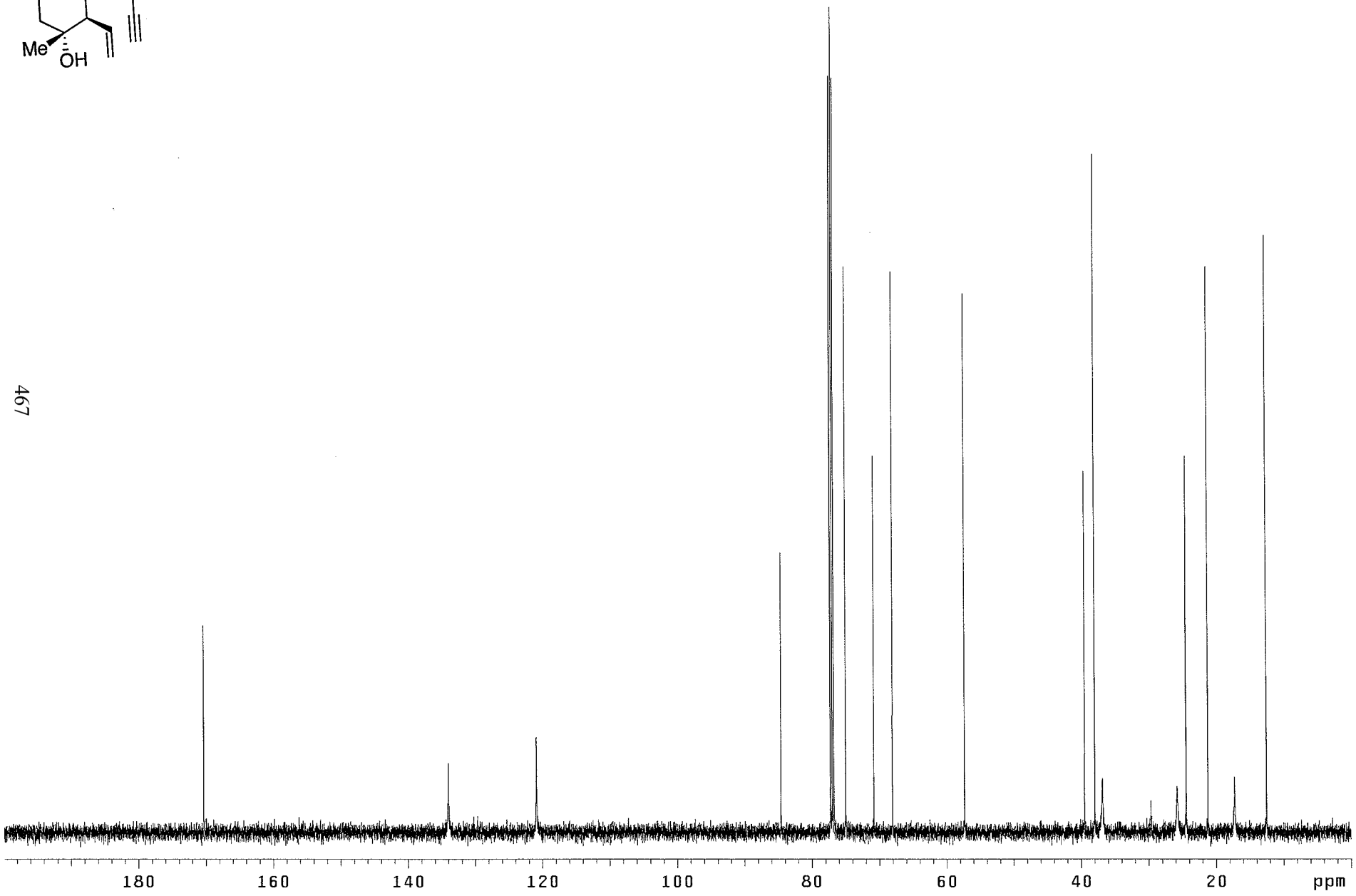

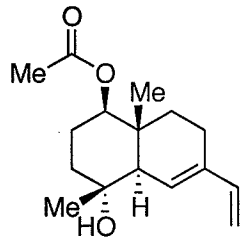
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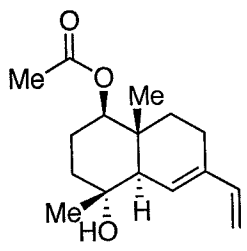

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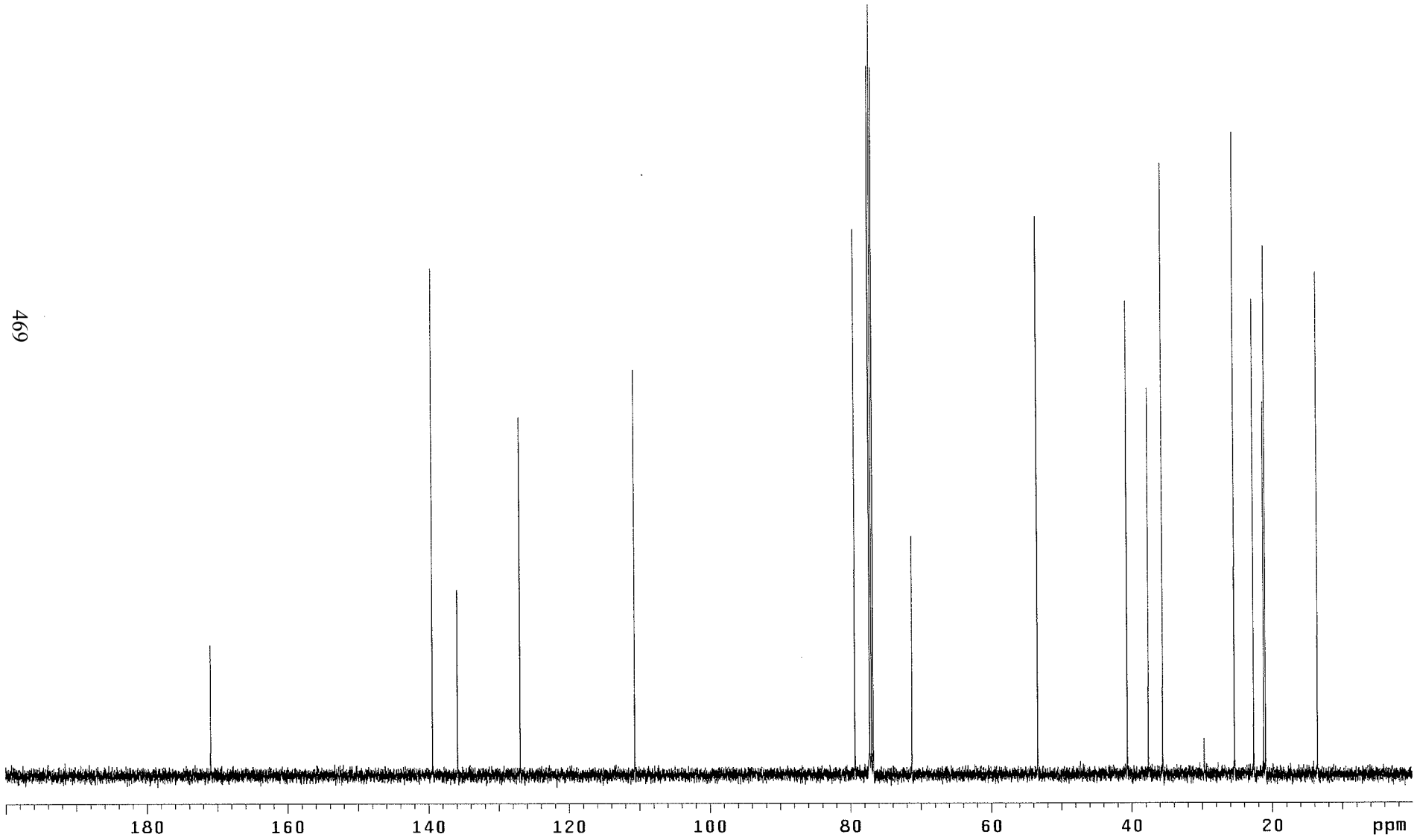

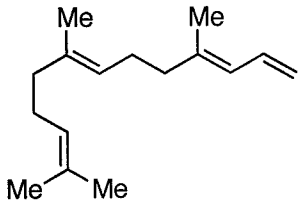

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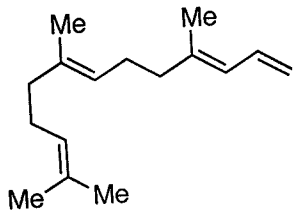

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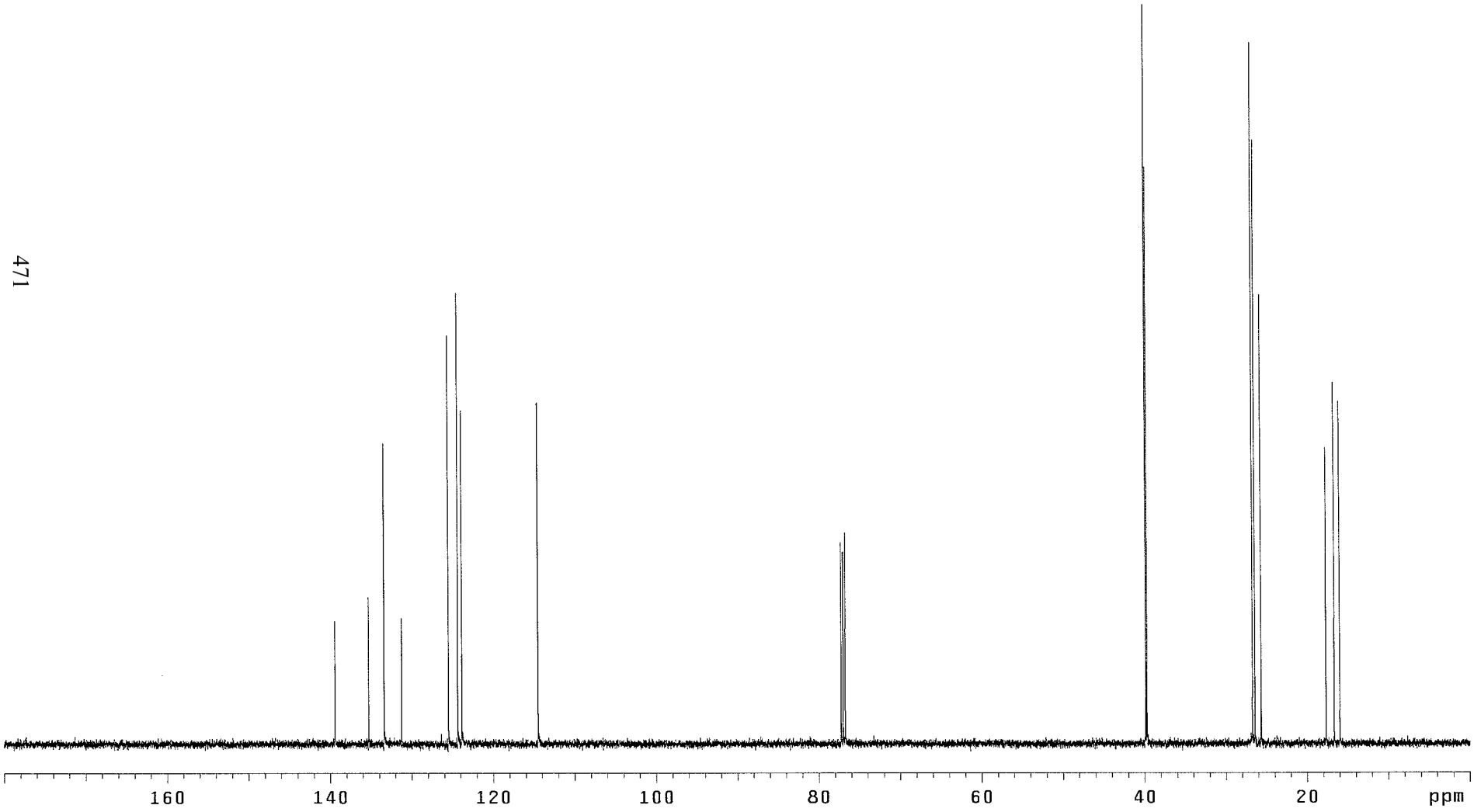

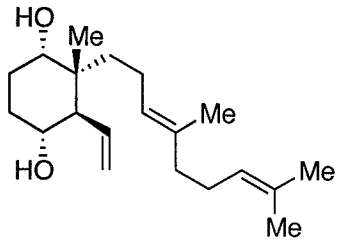

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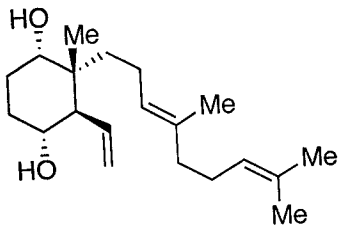

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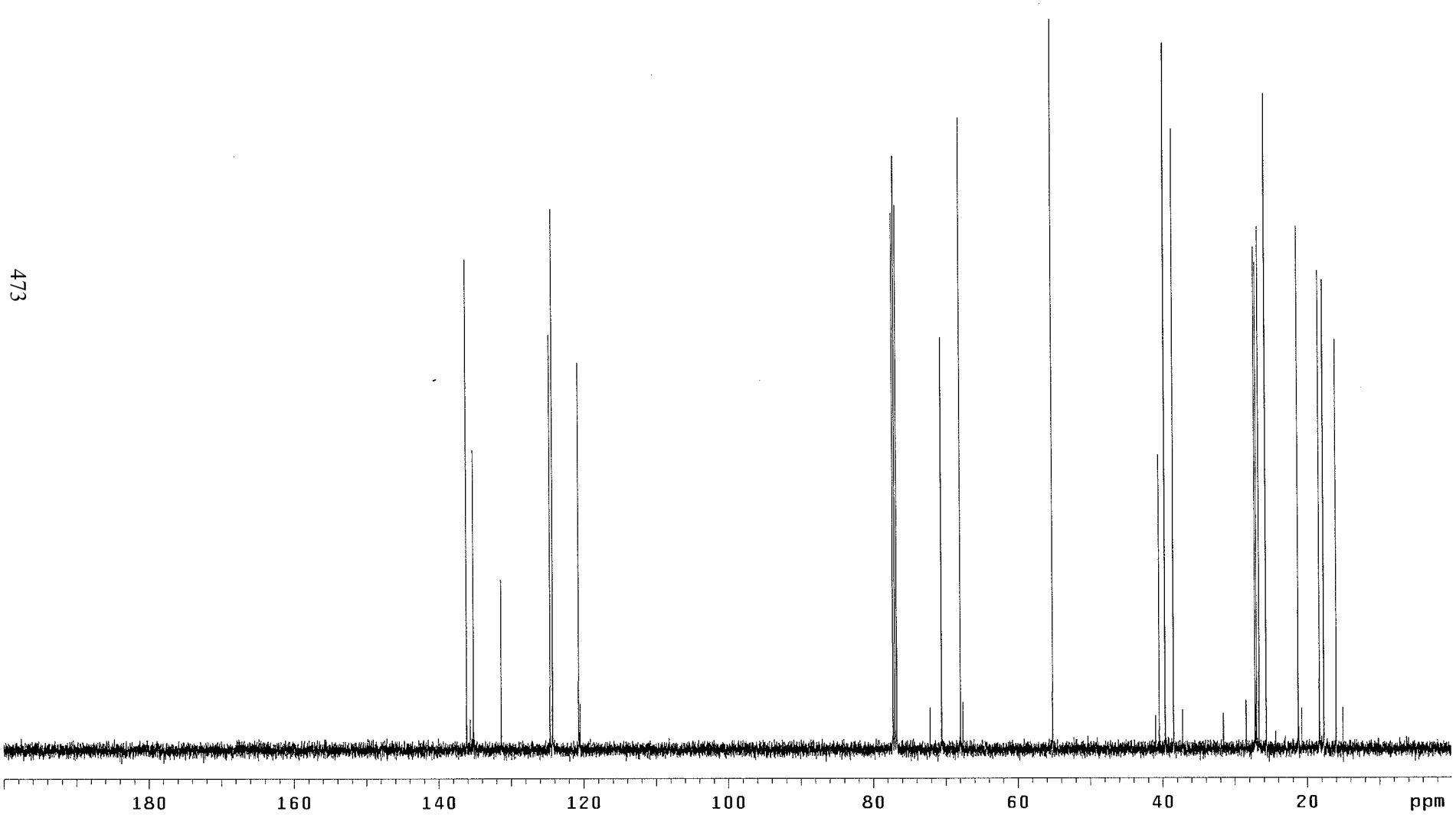

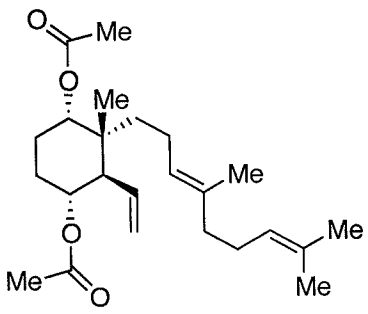

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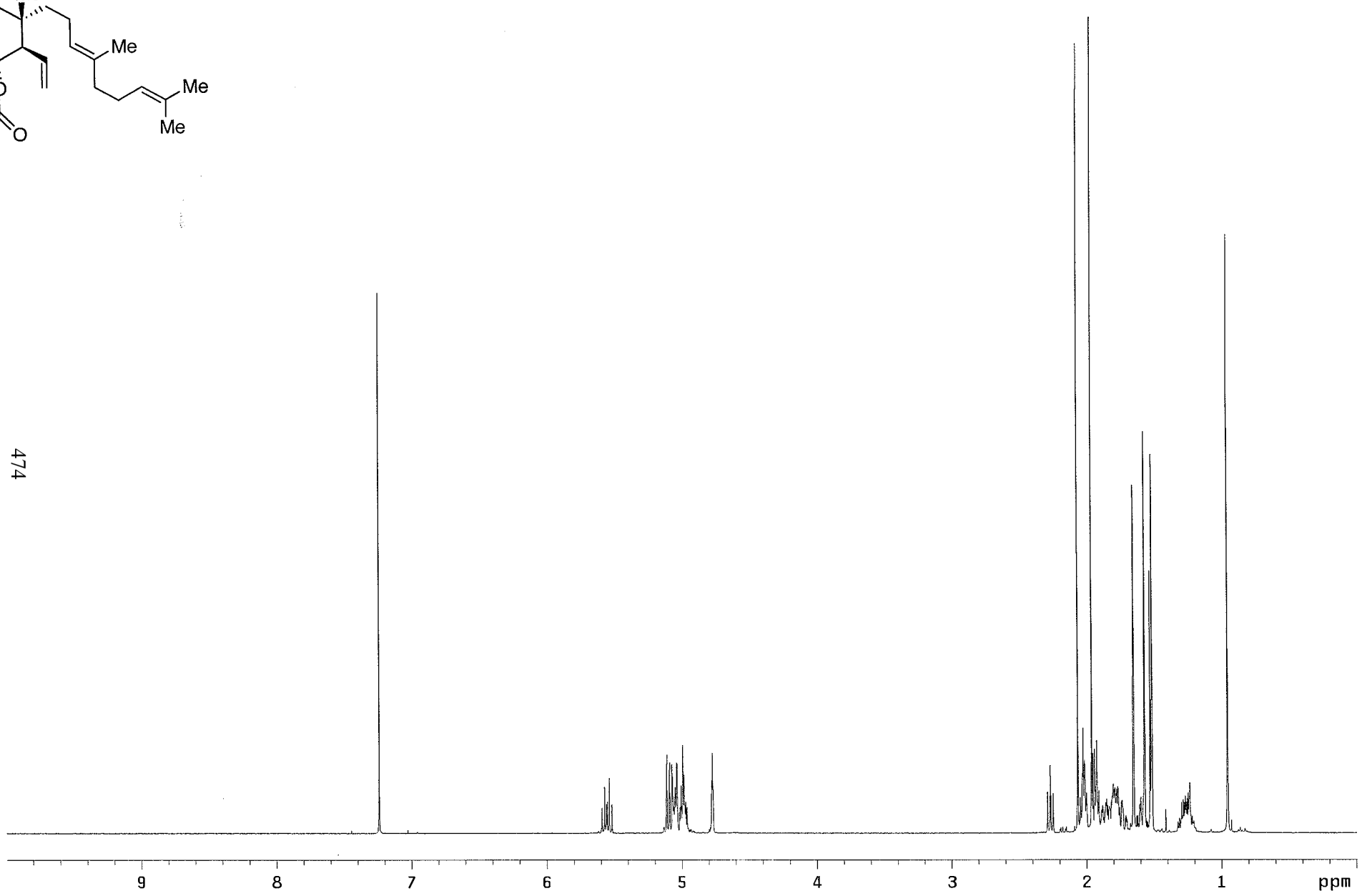

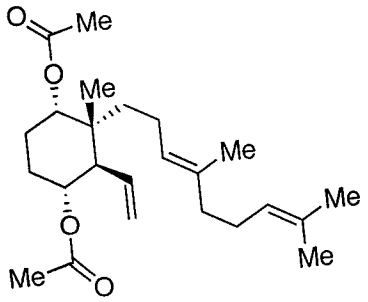

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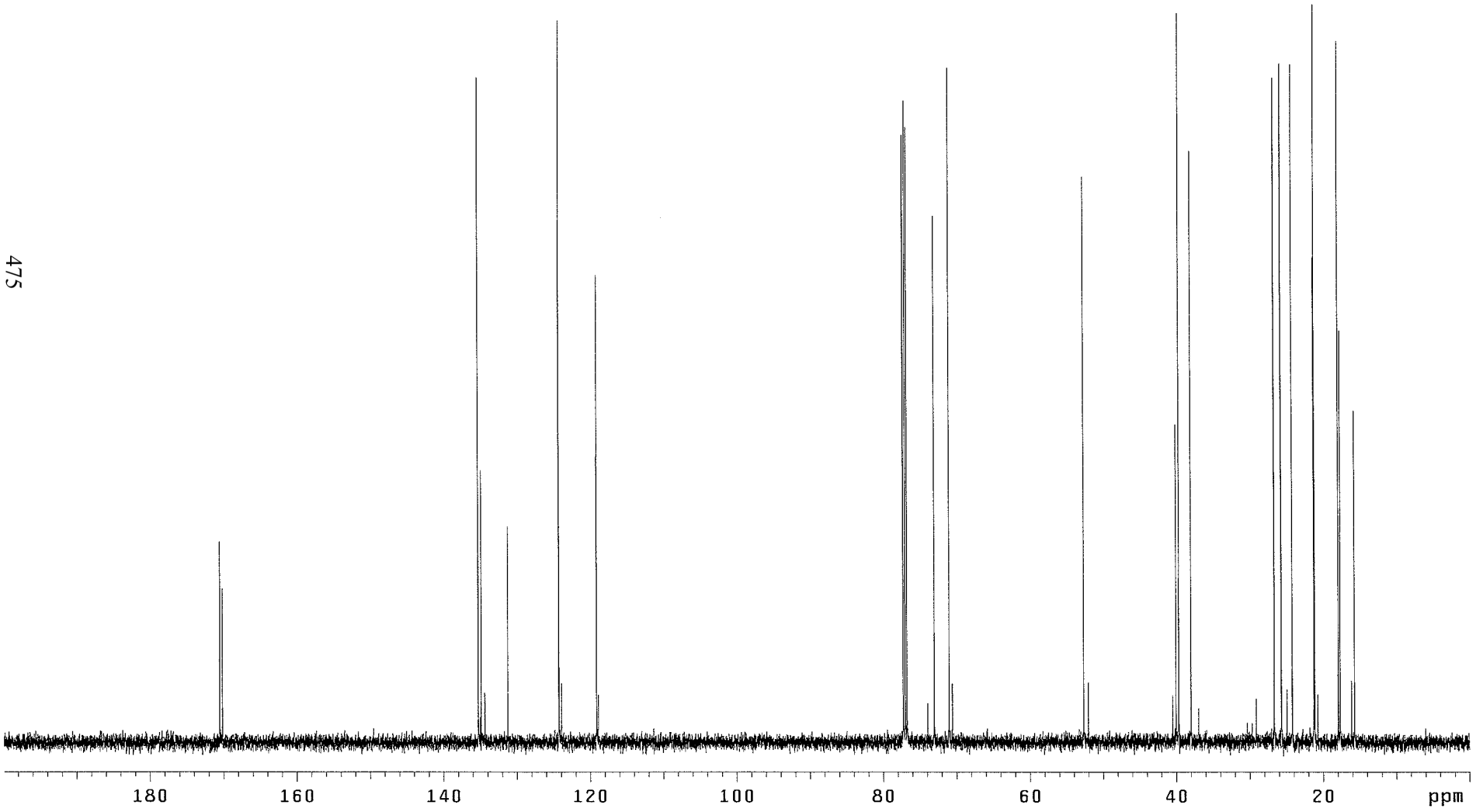

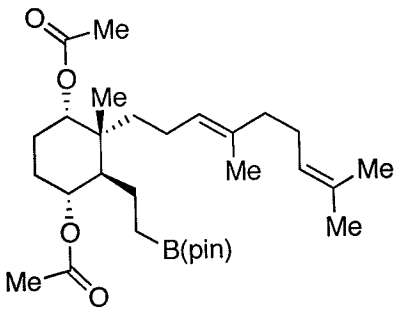

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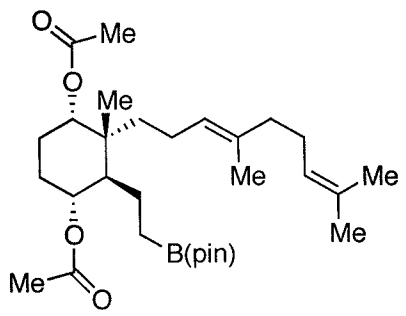

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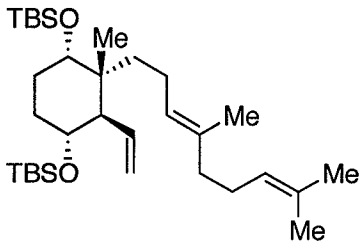

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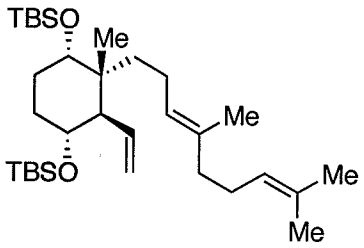
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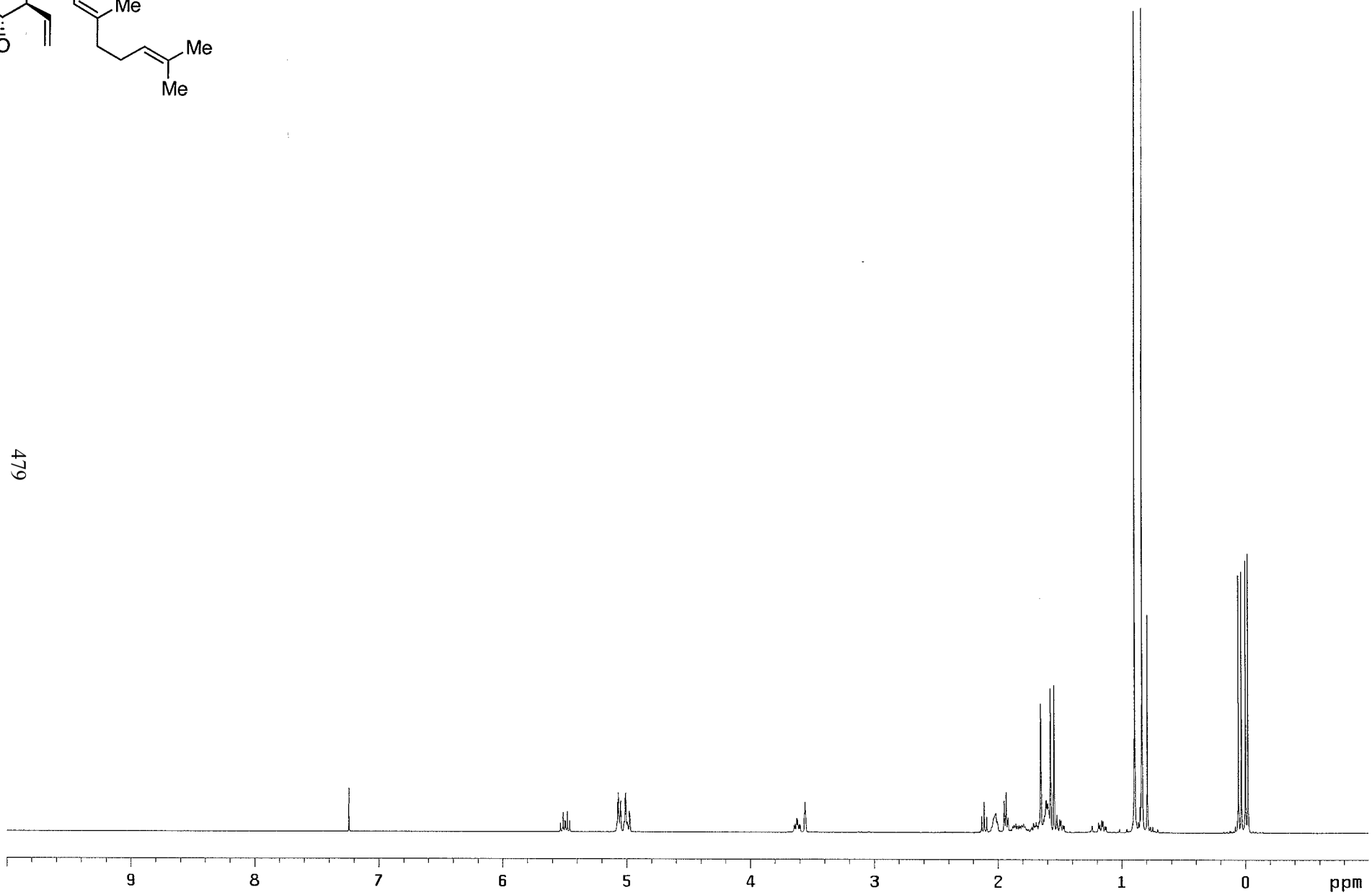
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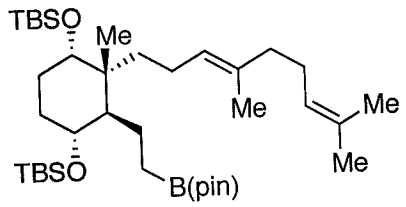

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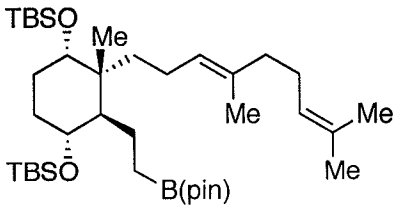
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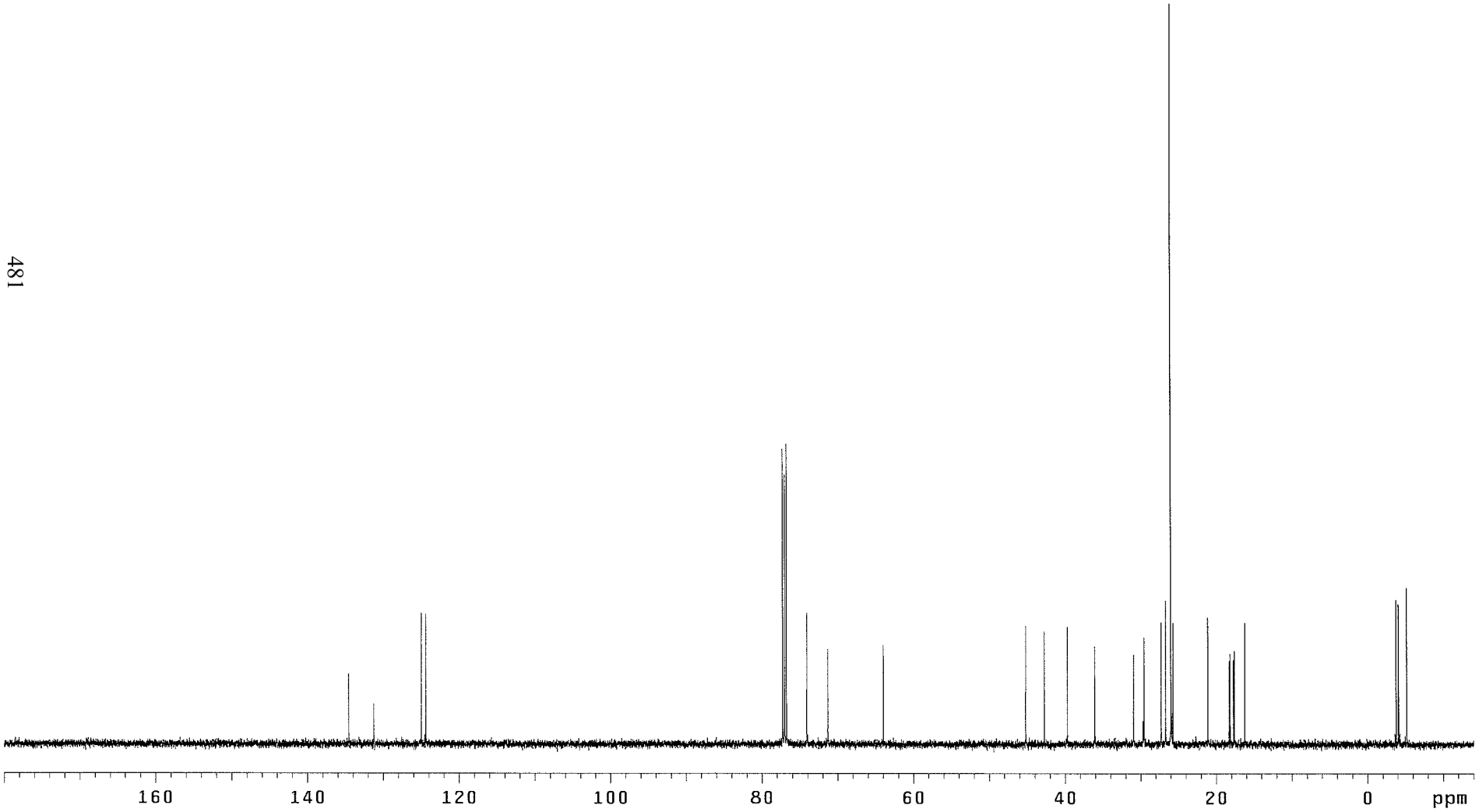
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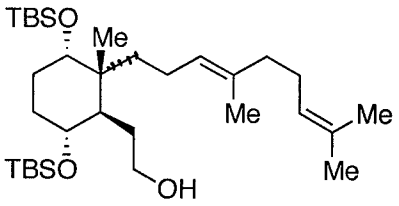
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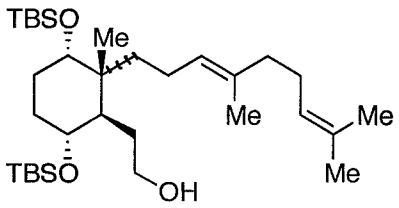
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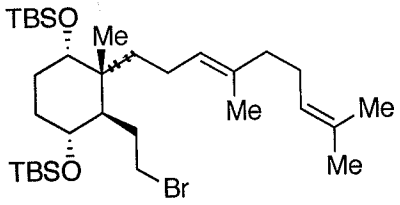

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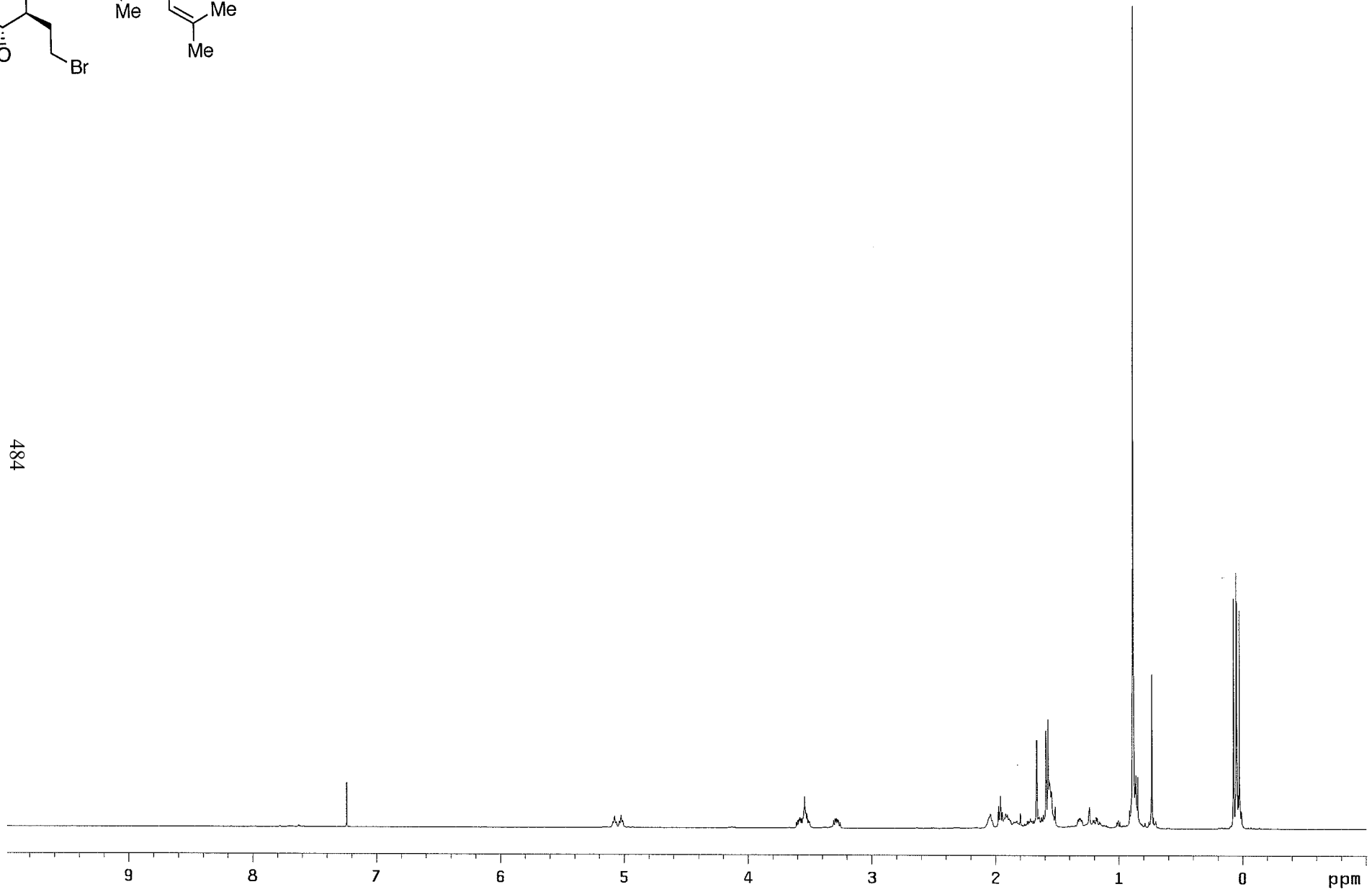

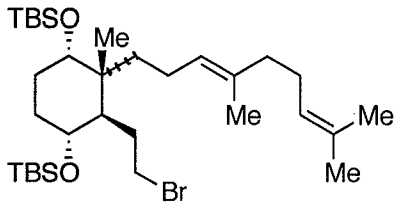
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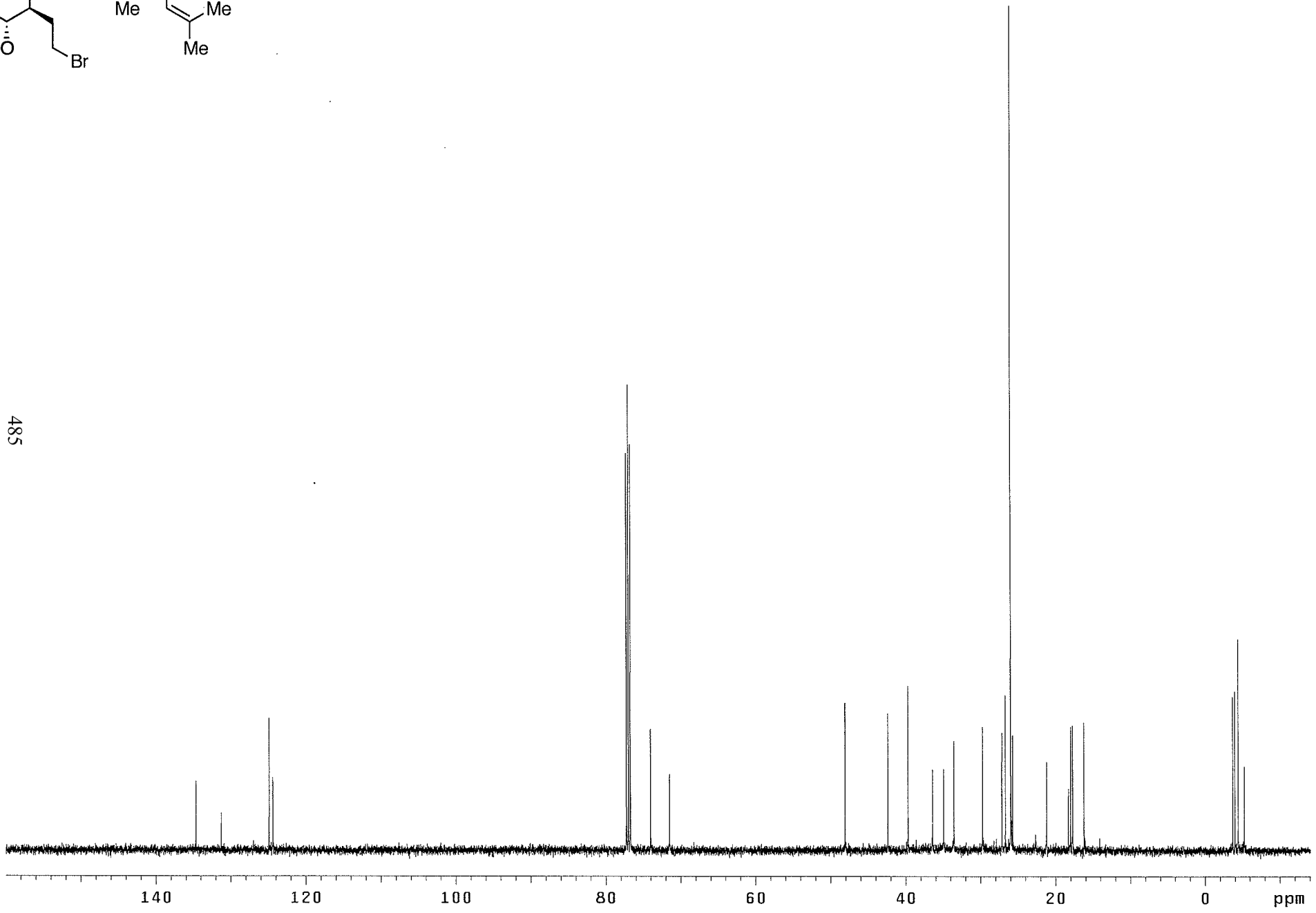
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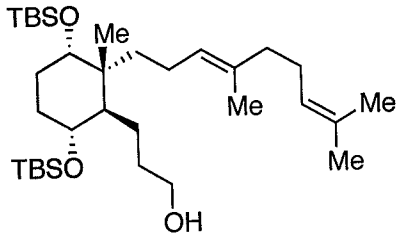
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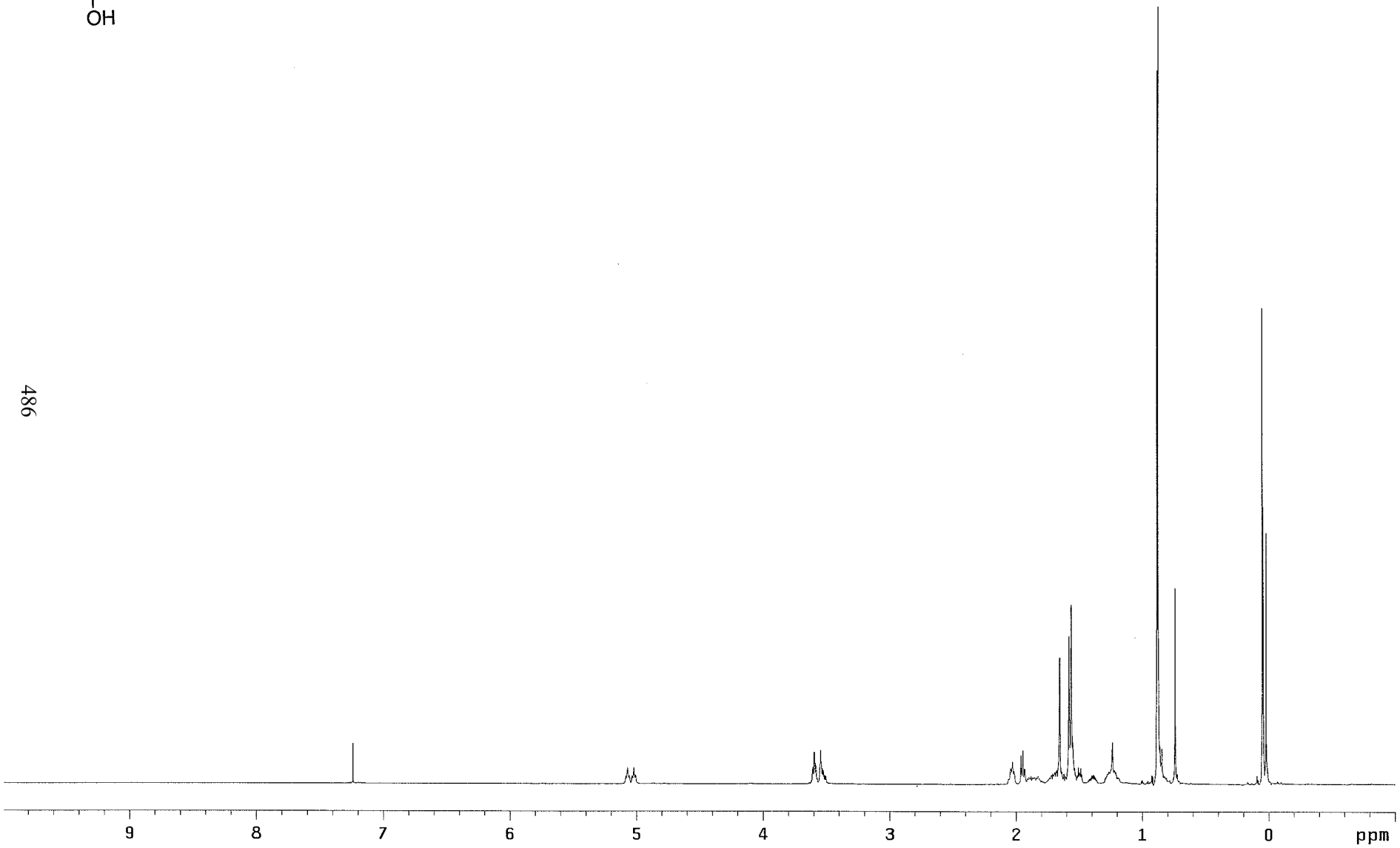
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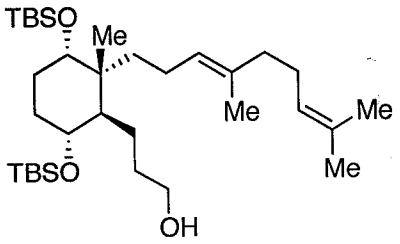
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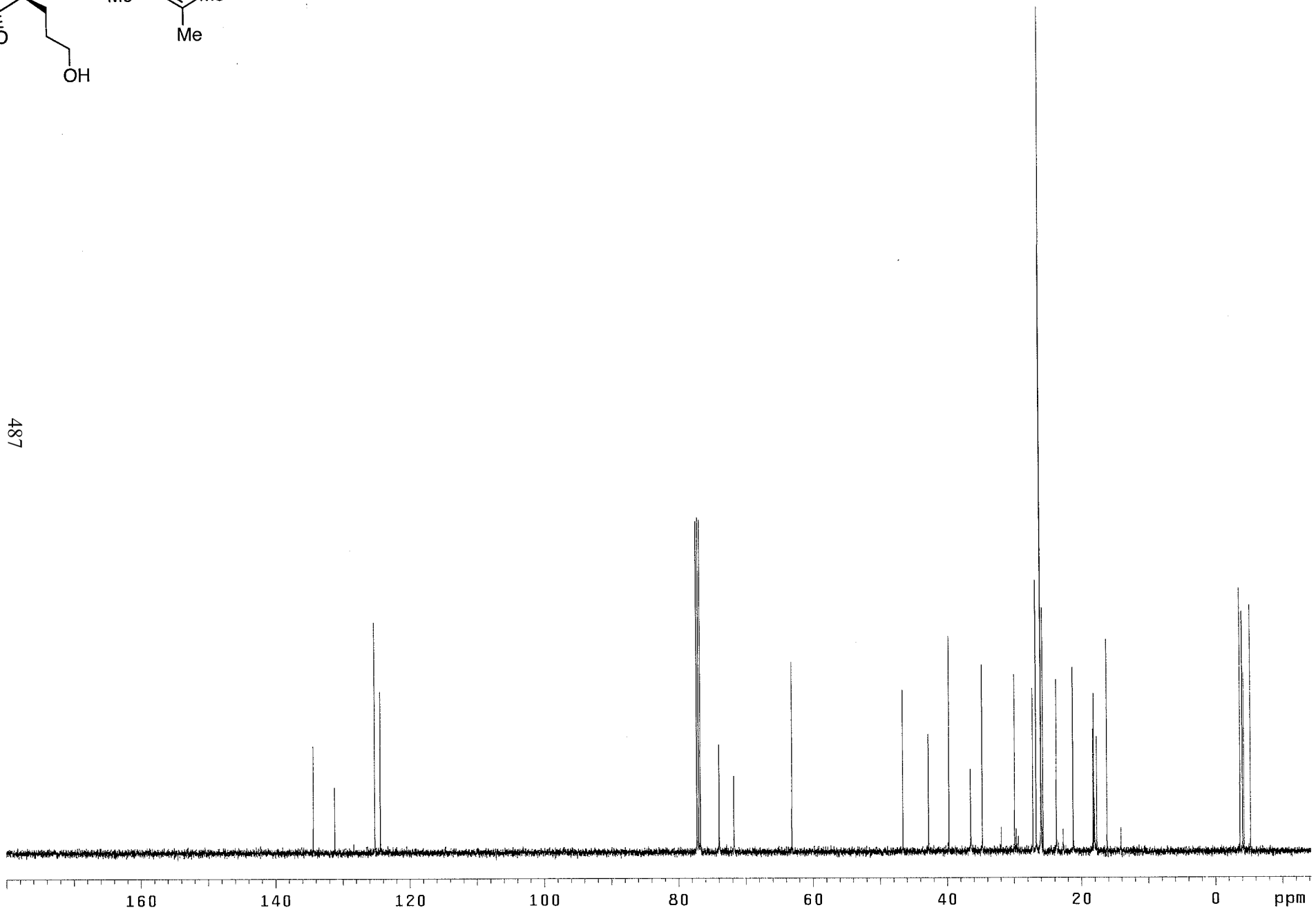
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