Regio- and stereoselective Ni-catalyzed 1,4-hydroboration and diboration of 1,3-dienes: Access to stereodefined (Z)-allyboron reagents and application towards the total synthesis of discodermolide

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REGIO- AND STEREOSELECTIVE NI-CATALYZED 1,4-HYDROBORATION AND DIBORATION OF 1,3-DIENES: ACCESS TO STEREODEFINED (Z)-ALLYLBORON REAGENTS AND APPLICATION TOWARDS THE TOTAL SYNTHESIS OF DISCODERMOLIDE

a dissertation

by

ROBERT J. ELY

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ABSTRACT

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REGIO- AND STEREOSELECTIVE HYDROBORATION AND DIBORATION OF 1,3-DIENES: ACCESS TO STEREODEFINED (Z)-ALLYLBORON REAGENTS AND STUDIES TOWARD THE TOTAL SYNTHESIS OF DISCODERMOLIDE

Under the direction of Professor James P. Morken

Detailed within this dissertation are the developments of novel hydroboration and diboration methodologies to access allylboron reagents and efforts towards the application of these methods to the total synthesis of discodermolide. Chapter 1 describes the development of Ni-catalyzed 1,4-hydroboration of 1,3-dienes with pinacolborane. This method provides synthetically useful allylboron intermediates which can be oxidized to stereodefined (*Z*)-allylic alcohols or used in stereoselective carbonyl addition reactions. Chapter 2 details the development of Ni-catalyzed 1,4-diboration of 1,3-dienes with bis(pinacolato)diboron. This reaction broadens the scope of 1,4-diboration reactions by reacting with high 1,4- and (*Z*)-selectivity with internal and sterically hindered dienes. The intermediate allylborons can be oxidized to stereodefined 1,4-diols. Chapter 3 describes the development of diastereoselective Ni-catalyzed 1,4-hydroboration of chiral 1,3-dienols. The reaction provides *syn*-propionate homoallylic alcohols with stereodefined trisubstituted allylborons that can be utilized for the synthesis of polyketide structures. This methodology, among others, was applied towards the total synthesis of discodermolide.

ACKNOWLEDGMENTS

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I could not have made it through my five years here without working next to the great people that I did. I deeply appreciate the friendships I acquired while here. I specifically want to thank Dr. Laura Brozek, Dr. Laura Kliman, and Dr. Ping Zhang for their friendship and constant guidance. Dr. Bob Kyne has been an especially good friend and colleague during my time here and helped make my time at work fun. I would like to thank Zhiyong Yu for his contributions to our joint project, and the rest of the Morken group for making it such an enjoyable lab to be a part of.

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LIST OF ABBREVIATIONS

Ac: acetyl

Bn: benzyl

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

Cb: carbamate

cod: cyclooctadiene

Cy: cyclohexyl

dba: dibenzylidene acetone

DCM: dicholoethane

DMF: dimethylformamide

dr: diastereomeric ratio

eq: equation

equiv: equivalent(s)

er: enantiomeric ratio

Et_2O: diethyl ether

EtOAc: ethyl acetate

HB(pin): pinacolborane

h: hour(s)

HMPT: hexamethylphosphorous triamide

KO*t*-Bu: potassium *tert*-butoxide

L: ligand

M: metal

$NaIO_4$: sodium periodate

NEt_3: triethylamine

Ni: nickel

NMO: N-methylmorpholino N-oxide

NMR: nuclear magnetic resonance

PCy_3: tricyclohexylphosphine

pin: pinacol

SFC: supercritical fluid chromatography

TBDPS: *tert*-butyldiphenylsilyl

TBS: *tert*-butyldimethylsilyl

TBSOTf: *tert*-Butyldimethylsilyl trifluoromethanesulfonate

TES: triethylsilyl

THF: tetrahydrofuran

TPAP: tetrapropylammonium perruthenate

Chapter 1

Regio- and Stereoselective Nickel-Catalyzed 1,4-Hydroboration of 1,3-Dienes: Access to (*Z*)-Allylboron Reagents and Derived Allylic Alcohols

1.1. Introduction

Organoboron reagents are an extremely important class of reagents in organic chemistry, and tremendous advances in their utility in catalysis have been made since the discovery of their palladium-catalyzed cross-coupling with carbon halides by Suzuki and Miyaura in 1979.[1] These reagents are relatively non-toxic and can participate in a wide variety of bond-forming reactions, making them attractive intermediates for the synthesis of natural products, biologically active compounds, and materials.[2] Their unique reactivity is due to an empty p-orbital on the boron atom: nucleophilic addition to this orbital generates an ate complex, rendering it susceptible to cross-coupling reactions (eq. 1, Scheme 1), nucleophilic additions (eq. 2, Scheme 1), and, if an appropriate leaving group is attached, 1,2-migrations (eq. 3, Scheme 1).

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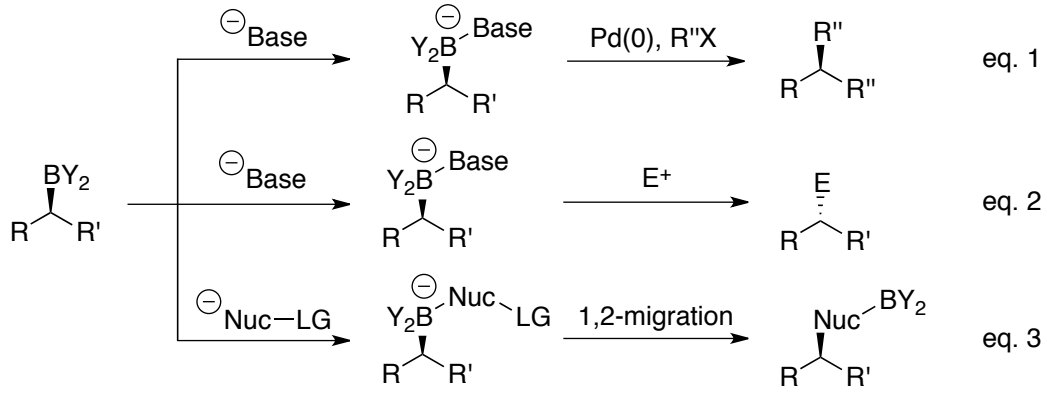
[1] Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun*. **1979**, 866.

[2] (a) Hall, D. G. Boronic Acid-based Receptors and Sensors for Saccharides. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH:Weinheim, Germany, 2005; pp 441-475. (b) Yang, W.; Gao, X.; Wang, B. Biological and Medicinal Applications of Boronic Acids. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH:Weinheim, Germany, 2005; pp 481–512.

Scheme 1.1. Reactivity Patterns of Organoboranes



Allylboron reagents are a uniquely versatile subset of organoborons because of the nucleophilicity of the γ-alkenic carbon. In addition to Suzuki-Miyaura couplings,[3] nucleophilic additions,[4] and 1,2-migrations such as oxidation,[5] amination,[6] and

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[3] (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* **1977**, 679. (d) Hara, S.; Dojo, H.; Kato, T.; Suzuki, A. *Chem. Lett*. **1983**, 1125.

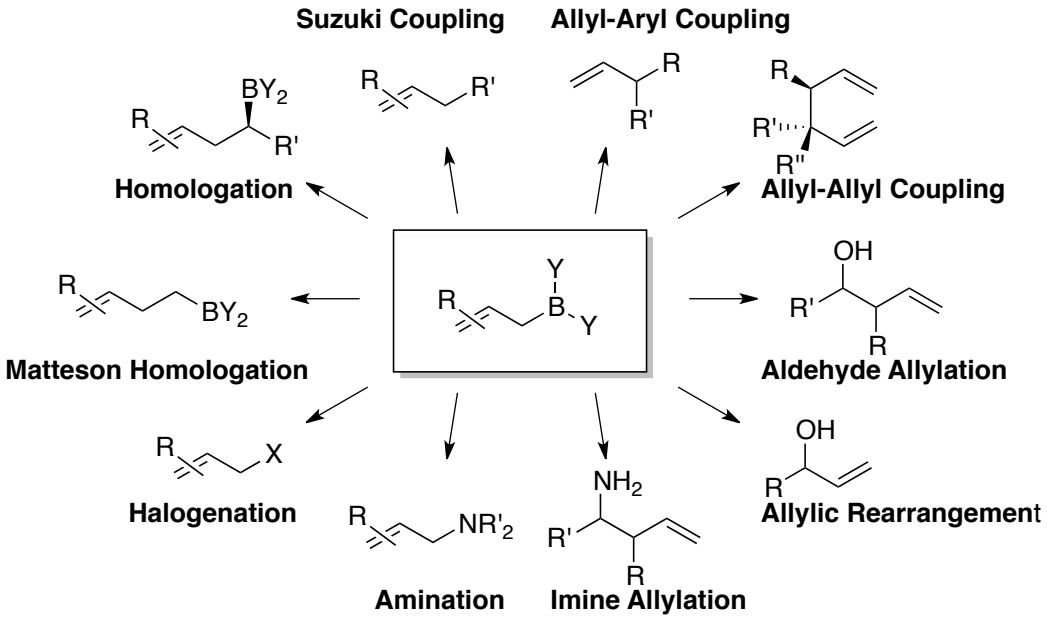
[4] For halogenations, see: (a) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456. (b) Brown, H. C.; Lane, C. F. *Tetrahedron* **1988**, *44*, 2763. (c) Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567. For examples of halogenation, amination, and carbon-carbon bond formation, see: (d) Laroucher-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2011**, *133*, 16794.

[5] (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.

[6] (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) Bagutski, V.; Elford, T. G.; Aggarwal, V. K. *Angew. Chem. Int., Ed*. **2011**, *50*, 1080.

homologation,[7] allylborons participate in a variety of carbonyl[8] and imine[9] allylations. More recently, they have also been found to be excellent nucleophiles in allyl-allyl cross-coupling reactions (Scheme 1.2).[10]

Scheme 1.2. Utility of Allylboron Reagents



[7] For a review, see: (a) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chemical Record* **2009**, *9*, 24. (b) 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) Sonawane, R. P.; Jheengut, V.; Rabalakos, R.; Larouche-Gautheir, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem., Int. Ed*. **2011**, *50*, 3760.

[8] For a reveiw see: (a) Lachance, H.; Hall, D. G. In *Organic Reactions*; Denmark, S. E., Ed.; Wiley: New York, 2009; Vol. 73. For selected examples see: (b) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884. (c) Rauniyar, V.; Hall, D. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2426. (d) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (e) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.

[9] For a review, see: (a) Ramadhar, T. R.; Batey, R. A. *Synthesis* **2011**, *9*, 1321. For representative examples, see: (b) Viera, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2011**, *133*, 3332. (c) Lou, L.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc*. **2006**, *129*, 15398. (d) Wada, R.; Shibaguichi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2006**, *128*, 7687. (e) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 9646. (f) Itsuno, S.; Watanabo, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 109.

[10] (a) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 10686. (b) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc*. **2011**, *133*, 9716. (c). Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778.

The electrophilicity of boron compounds, a feature which figures prominently in rates of carbonyl allylations, is very sensitive to the nature of the ligands on the boron atom. [11] Allylboranes (Y = alkyl, Scheme 1.2) are very reactive but are not stable to air or moisture and generally must be used directly after they are generated. Allylboronic esters (Y = OR, Scheme 1.2), however, are stable to air and water but are less reactive. Many allylboronic pinacol esters (Y = pinacol, Scheme 1.2) are even stable to silica gel chromatography. This is due to a stabilizing oxygen lone-pair donation into the empty p-orbital on boron. The broad utility of allylboronic esters and their stability to common purification techniques has made them attractive targets for synthetic methodologies. This introduction will focus on the methods to generate substituted allylboronic esters.

Several strategies exist to synthesize crotylboronic esters including reaction of a borate ester with a metallated organic fragment, homologation of a vinylboronic ester, addition of further substitution to an allylboronic ester, or transition metal-catalyzed addition of organoboronic esters to allylic electrophiles. The addition of an allyl-metal to a boronate ester electrophile is one of the most common methods to form allylboronic esters. For example, the (*E*)- and (*Z*)-crotylboronic esters, **1.1** and **1.2**, are commonly synthesized *via* this approach (Scheme 1.3). This method requires Schlosser's base[12] to deprotonate either *trans*-2-butene (eq. 4) or *cis*-2-butene (eq. 5) and generate a configurationally stable crotylpotassium anion, which after addition to a boronic ester electrophile, generates the crotylboronic ester in excellent selectivity. This method is

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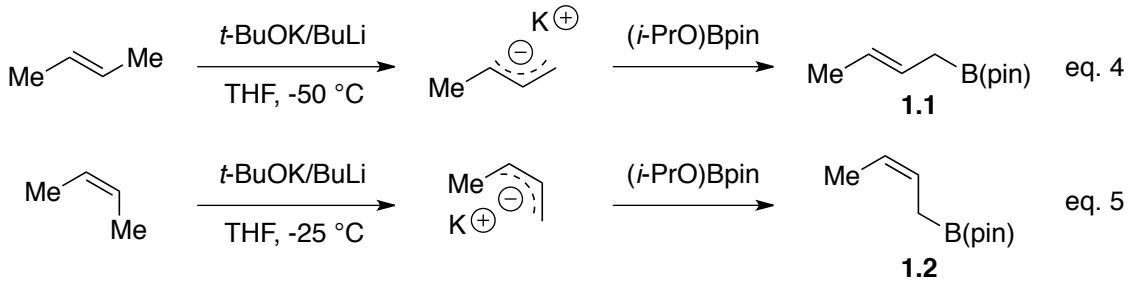
[11] Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868.
[12] Frujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *47*, 2751.

reliable for simple, symmetrical alkenes but can lead to poor regioselectivities with more substituted examples. The harsh conditions required for the generation of reactive allylmetals are also not compatible with many functional groups.

Scheme 1.3. Synthesis of (*E*)- and (*Z*)-Crotylboronic Esters



Alkenylmetals are generally more configurationally stable than allymetals, and thus are good precursors to generate allylboronic esters *via* alkylation reactions (Scheme 1.4).[13] The low reactivity of many vinylmetals limits these reactions, typically requiring the use of either lithium or magnesium anions for broad utility.[14] Optically active α-alkyl allylboronic esters can be accessed from α-chloroalkyl boronic esters in a procedure developed by Matteson (Scheme 1.4, eq 7).[15] The nucleophile displaces the chloride *via* a 1,2-migration resulting in net inversion of the stereocenter in high diastereoselectivity.

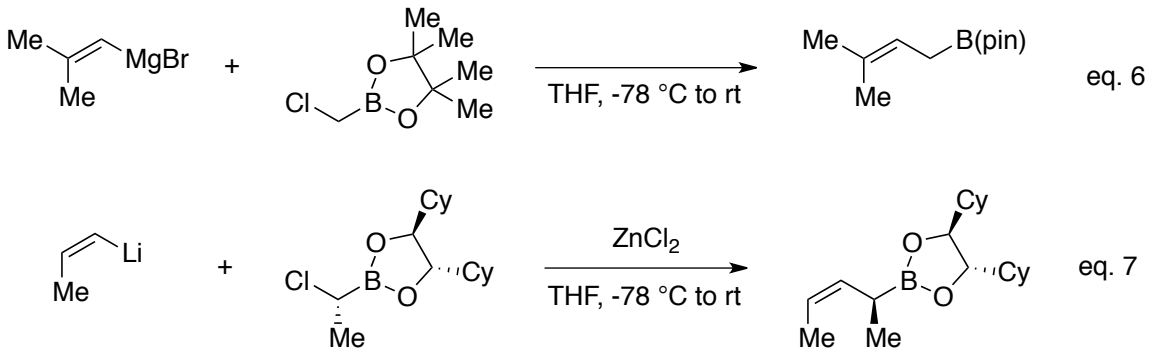
---

[13] (a) Wuts, P. G. M.; Thompson, A. P.; Callen, G. R. *J. Org. Chem.* **1983**, *48*, 5398. (b) Hoffman, R. W.; Schlapbach, A. *Tetrahedron* **1992**, *48,* 1959. (c) Hoffman, R. W.; Schlapbach, A. *Liebigs Ann. Chem.* **1990**, 1243.

[14] For examples of other useful metals, see: for alkenylaluminum (a) Nyzam, V.; Belaud, C.; Villiéras, J. *Tetrahedron* **1993**, *43*, 6899. (b) Nyzam, V.; Belaud, C.; Zammattio, F.; Villiéras, *J. Bull. Chem. Soc. Chim. Fr.* **1997**, *134*, 583. For alkenylcopper (c) Kennedy, J. W. J.; Hall, D. G.; *J. Am. Chem. Soc*. **2002**, *124*, 898. (d) Zhu, N.; Hall, D. G.; J. Org. Chem. **2003**, *68*, 6066.

[15] (a) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555. (b) Matteson, D. S. *Chem. Rev*. **1989**, *89*, 1535.

Scheme 1.4. Alkenylmetals for the Synthesis of Allylboronic Esters



The one-carbon homologation of vinylboronic esters, also developed by Matteson,[16] has been used to synthesize allylboronic esters. The starting materials can be conveniently accessed by hydroboration of terminal alkynes, selectively furnishing *trans*-vinylboronic esters. Addition of CH_2ClLi yields the allylboronic ester after 1,2-migration (eq. 8, Scheme 1.5). This method has been expanded by Aggarwal[17] to synthesize α-alkyl allylboronic esters in high optical purity through the addition of Hoppe's lithiated carbamates[18] to vinylboronic esters (eq. 9, Scheme 1.5). The allylboronic esters are not isolated; rather they are used directly in highly diastereoselective aldehyde allylation reactions.

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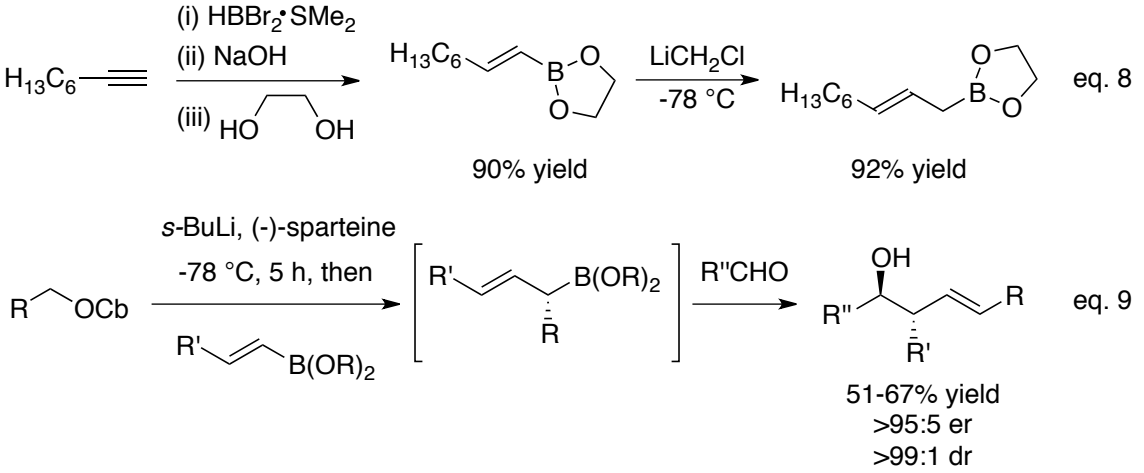
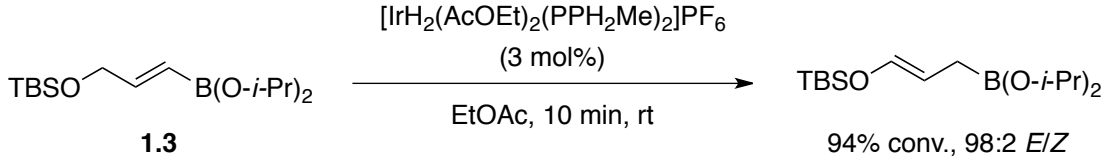
[16] see reference 5a and Thadani, A, N.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 8051.
[17] Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132,* 4025.
[18] For a review, see: Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282.

Scheme 1.5. Matteson Homologation Applied to the Synthesis of Allyboronic Esters



Vinylboronic esters can also be isomerized to allylboronic esters if there is a sufficient thermodynamic driving force for isomerization. Examples include 3-siloxy-vinylboronic ester **1.3** that, in the presence of an Ir catalyst, will isomerize to the corresponding (*E*)-allylboronic ester in good yield and selectivity (Scheme 1.6).[19] This reaction proceeds because of oxygen-alkene conjugation in the resulting enol ether.

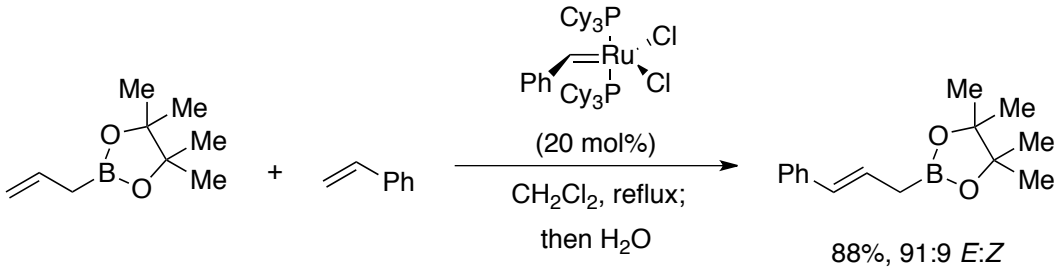
Scheme 1.6. Isomerization of Vinylboronic Esters to Allylboronic Esters



[19] Yamamoto, Y.; Miyaira, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem*. **1999**, *64*, 296.

Cross-metathesis, an invaluable tool for generating functionalized alkenes, has also been applied to the synthesis of allylboronic esters (Scheme 1.7). Starting from an allylboronic ester, the metathesis installs further substitution, resulting in a crotylboronic ester. Often utilizing the 1st generation Grubb's catalyst, these metatheses furnish 3-substituted allylboronic esters in good yields.[20] The reaction is also very functional-group tolerant, but suffers from moderate to low (*E*):(*Z*) selectivities.

Scheme 1.7. Cross-Metathesis to Synthesize 3-Substituted Allylboronic Esters



More recently, palladium-catalysis has been used to generate (*E*)-allylboronic esters from allylic electrophiles and bis(pinacolato)diboron ($B_2(pin)_2$, **1.4**). Miyaura first developed this elegant methodology utilizing allylic acetates or halides as electrophiles in DMSO with $Pd(dba)_2$ as the catalyst (eq. 10, Scheme 1.8).[21] Addition of boron occurs to the least hindered carbon and exclusively provides the (*E*)-isomer even if the electrophile is not isomerically pure. Unfortunately, the product is often contaminated with a 1,5-

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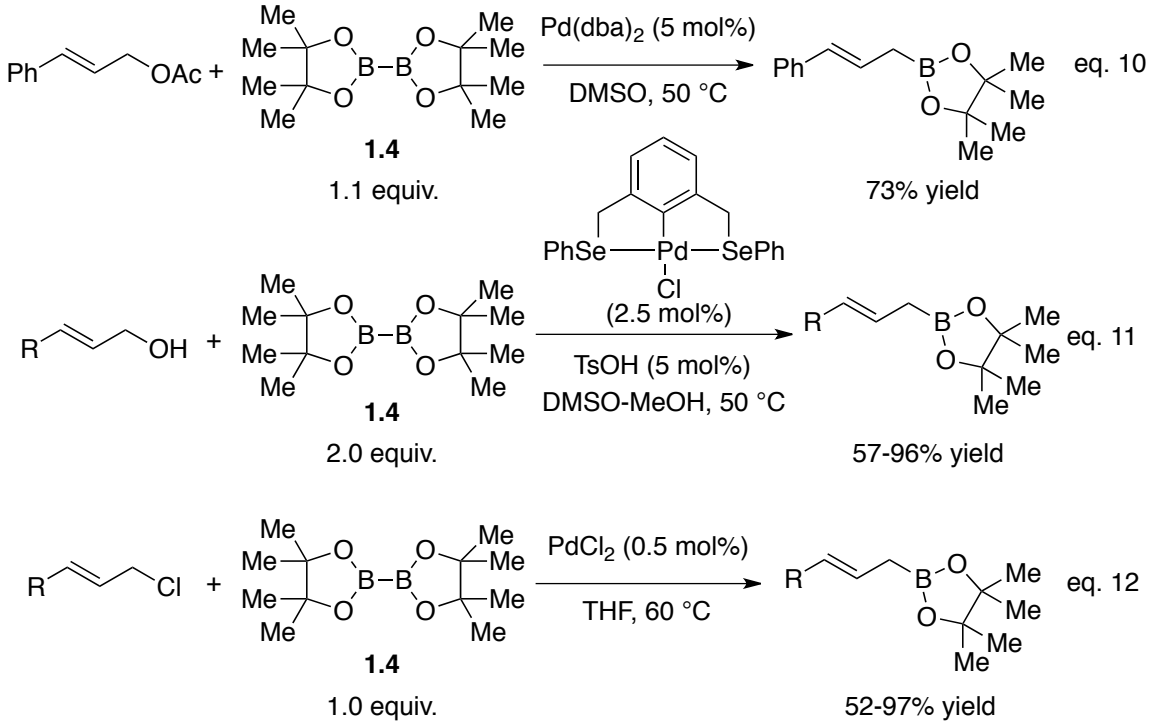
[20] (a) Yamamoto, Y.; Takahashi, M.; Miyaura, N. *Synlett* **2002**, 128. (b) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807.
[21] Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett*. **1996**, *37*, 6889.

hexadiene byproduct that can complicate purification. To remedy this problem Aggarwal, in collaboration with Szabó, used a palladium pincer complex with two equivalents of $B_2(pin)_2$ in a DMSO-MeOH solvent system to convert allylic alcohols to the (*E*)-allylboronic esters in good yields and selectivities without problematic byproducts (eq. 11, Scheme 1.8).[22] Most recently, a similar reaction was developed by Morken which employs allylic chlorides in THF with only one equivalent of $B_2(pin)_2$ (eq. 12, Scheme 1.8).[23] Allylic acetates could also be used with $Ni(cod)_2$ as catalyst. This method avoids the use of excess $B_2(pin)_2$ and difficult-to-remove solvents.

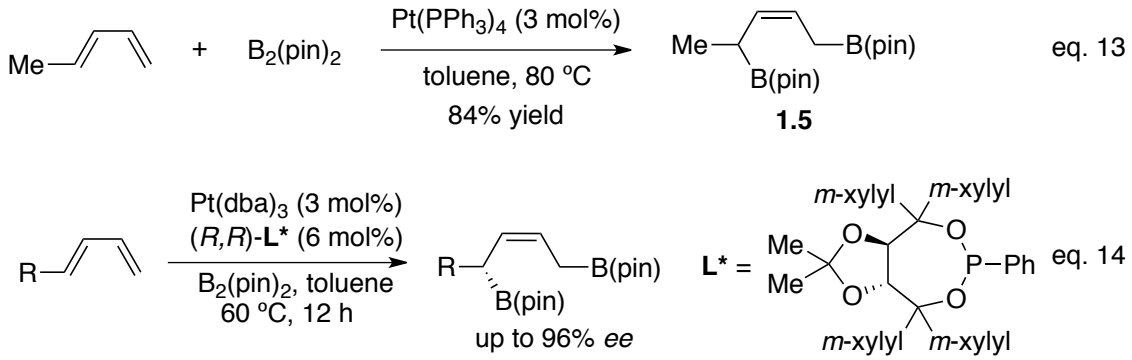
Scheme 1.8. Pd-Catalyzed Cross-Coupling to Access Allylboronic Esters



[22] Dutheuil, G.; Selander, N.; Szabo, K. J.; Aggarwal, V. K. *Synthesis* **2008**, *14*, 2293.
[23] Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

The methods surveyed thus far for the synthesis of allylboronic esters have either been (*E*)-selective or have required the stoichiometric synthesis of (*Z*)-allyl- or vinylmetal reagents. A catalytic approach to selectively prepare (*Z*)-allylboronic esters would be very attractive; such methods were developed after it was discovered that platinum catalysts could oxidatively insert into $B_2(pin)_2$ and subsequently add across unsaturated compounds.[24] One example is the diboration of 1,3-dienes first developed by Miyaura. The reaction is 1,4-selective with monodentate phosphine ligands, and selectively produces the (*Z*)-allyl(bis)boronic ester **1.5** (eq. 13, Scheme 1.9).[25] The Morken group was the first to demonstrate that this diboration could be done with high enantioselectivity using a TADDOL-derived phosphonite ligand (eq. 14, Scheme 1.9).[26]

Scheme 1.9. Pt-Catalyzed 1,4-Diboration of Dienes



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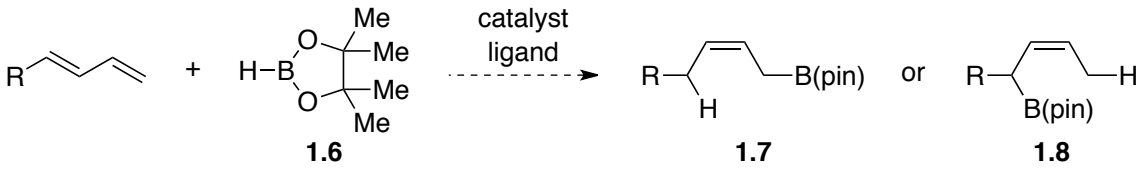
[24] For recent reviews see: Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (b) M. Suginome, Y. Ito, *Chem. Rev*. **2000**, *100*, 3221. For selected examples see: (c) Lesley, G.; Nguyen, P.; Taylor, N. J.; Marder, T. B. *Organometallics* **1996**, *15*, 5137. (d) Iverson, C. N. Smith, M. R. III *Organometallics*, **1996**, *15*, 5155. (e) T. Ishiyama, N. Miyaura, *J. Organomet. Chem*. **2000**, *611*, 392.

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

[26] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.

During the development of the enantioselective 1,4-diboration of dienes in our group, it was postulated that pinacolborane (HB(pin), **1.6**)[27] could react in a similar manner with 1,3-dienes as $B_2(pin)_2$ and result in a 1,4-hydroboration of a diene (Scheme 1.10). This could provide a catalytic and stereoselective route to (*Z*)-allylboronic esters like **1.7** or **1.8** from simple unsaturated starting materials. In this chapter, I will describe the first Ni-catalyzed 1,4-hydroboration of 1,3-dienes.

Scheme 1.10. Hydroboration as a Method to Synthesize (*Z*)-Allylboronic Esters



1.6 **1.7** **1.8**

1.2. Background

The catalytic hydroboration of alkenes has been an invaluable synthetic tool since its discovery by Manning and Noth in 1985.[28] Subsequently, the transition metal-catalyzed hydroboration of alkenes[29] and alkynes[30] has been throughly studied; however, the hydroboration of dienes has remained relatively unexplored. The catalytic hydroboration of dienes could provide alternate chemo- and regioselectivities than

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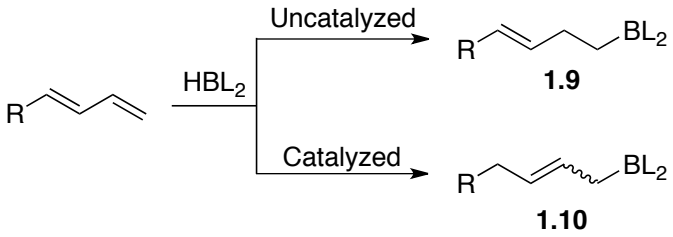
[27] Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.
[28] Männig, D.; Nöth, H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 878.
[29] Reviews: (a) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695. (b) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957. (c) Burgess, K.; Ohlmeyer, M. J. *Chem. Re*V. **1991**, *91*, 1179.
[30] See reference 25 and for representative examples : (a) Periera, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127. (b) He, X. Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 1696. (c) Periera, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283. (d) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990.

uncatalyzed hydroboration. While the uncatalyzed hydroboration of acyclic dienes provides the homoallylic boronic ester **1.9**, catalyzed variants could proceed through a different mechanism to the complimentary regioisomer **1.10**, the product of a 1,4-hydroboration (Scheme 1.11).[31]

Scheme 1.11. Uncatalyzed vs. Catalyzed Hydroboration of 1,3-Dienes



The first example of catalytic hydroboration of dienes was described by Suzuki and Miyaura using Pd-catalysis.[32] Butadiene and 2,3-disubstituted dienes were excellent substrates with catecholborane (HB(cat), **1.11**) as the hydroborating reagent and $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ as catalyst (Scheme 1.12). Allylboronic catechol esters **1.12** are not stable to water or silica gel, and thus were reacted directly with benzaldehyde to provide homoallylic alcohols **1.13**. The hydroboration reaction showed excellent 1,4-and (*Z*)-selectivity as determined by the *syn*-stereochemistry of the homoallylic alcohol isolated from the crotylation reaction.

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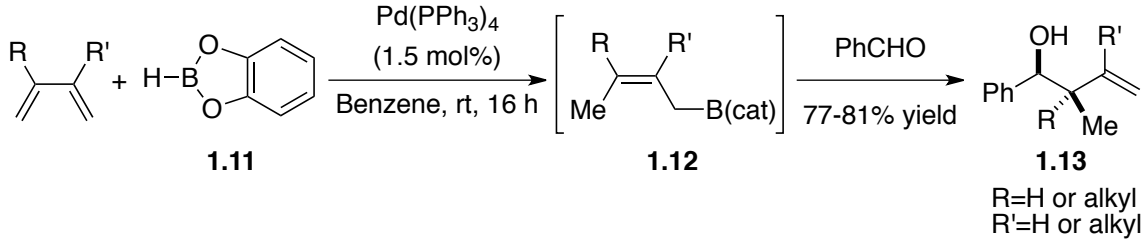
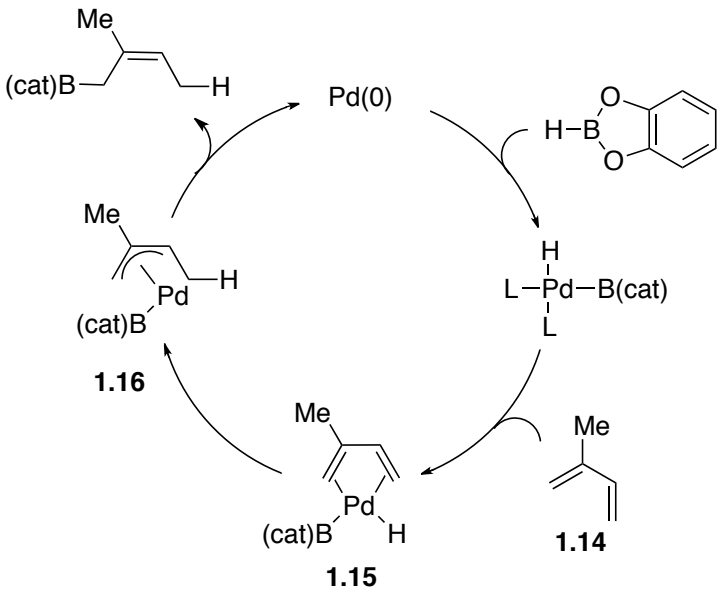
[31] Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Org. Chem.* **1978**, *43*, 1058.
[32] Satoh, M.; Nomoto, Y.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett*. **1989**, *30*, 3789.

Scheme 1.12. Pd-Catalyzed Hydroboration of 1,3-Dienes



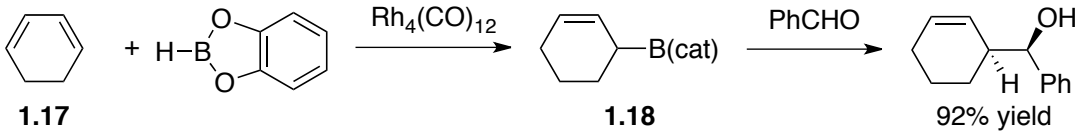
The reaction was remarkably stereoselective for isoprene (**1.14**, Scheme 1.13) suggesting a very selective alkene insertion into the Pd-H bond (**1.15** to **1.16**, Scheme 1.13) that results from oxidative addition of Pd(0) to catecholborane. Subsequent reductive elimination produces the product, and releases Pd(0).

Scheme 1.13. Proposed Mechanism for Pd-Catalyzed Hydroboration of 1,3-Dienes



The palladium-catalyzed hydroboration of 1-substituted or cyclic dienes was very sluggish; however, $Rh_4(CO)_{12}$ was found to catalyze the hydroboration of 1,3-cyclohexadiene (**1.17**) with catecholborane to provide the allylboronic ester **1.18** in good yield (Scheme 1.14). It is not clear whether this reaction is a 1,4- or 1,2-selective hydroboration, as 1,2 hydroboration is favored for several uncatalyzed hydroborations of cyclohexadiene.[33]

Scheme 1.14. Rh-Catalyzed Hydroboration of Cyclohexadiene



1.17 **1.18** 92% yield

Hayashi demonstrated the use a rhodium catalyst to effect the double hydroboration of 1-phenyl-1,3-butadiene (**1.19**) with catecholborane (Scheme 1.15).[34] Wilkinson's catalyst promoted the double hydroboration of **1.19** using 2.5 equivalents of catecholborane, providing the 1,3-diol after oxidation in a 10:1 *anti*:*syn* ratio. No monohydroboration product was isolated, even when only 1.0 equivalent of catecholborane was used.

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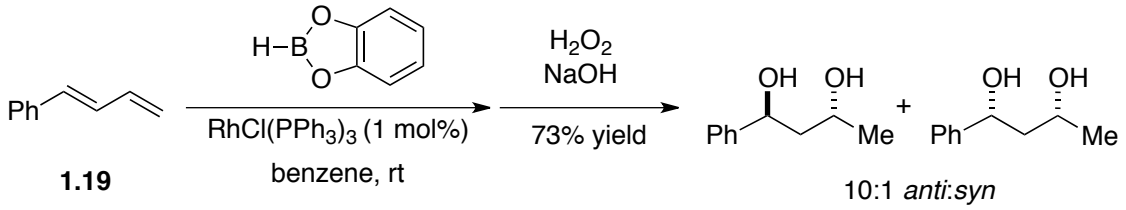
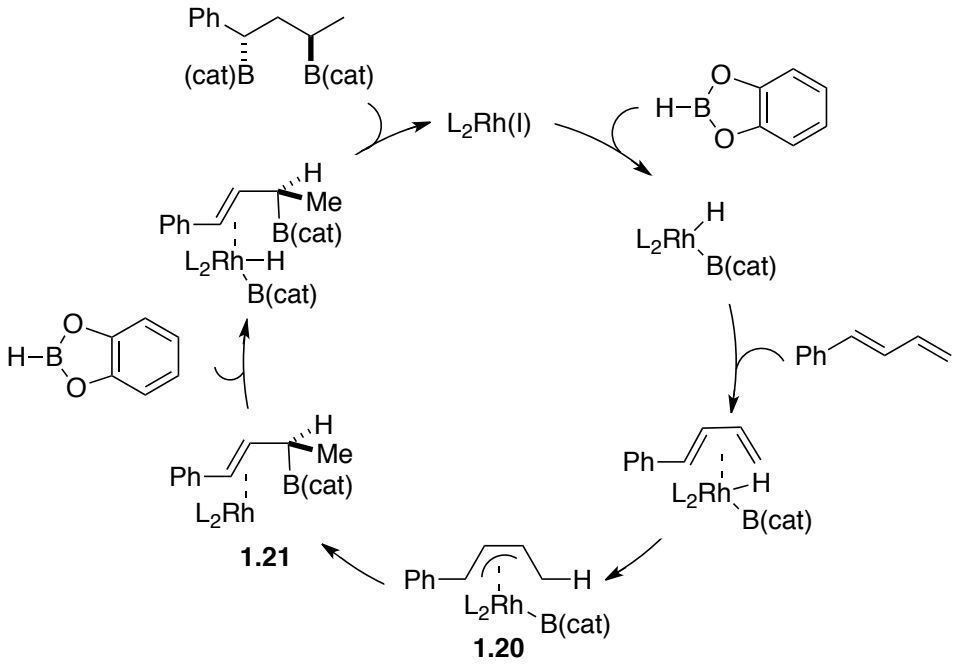
[33] Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564.
[34] Matsumoto, Y.; Hayashi, T. *Tetrahedron Lett.* **1991**, *32*, 3387.

Scheme 1.15. Rh-Catalyzed Hydroboration of 1-Phenyl-1,3-Butadiene



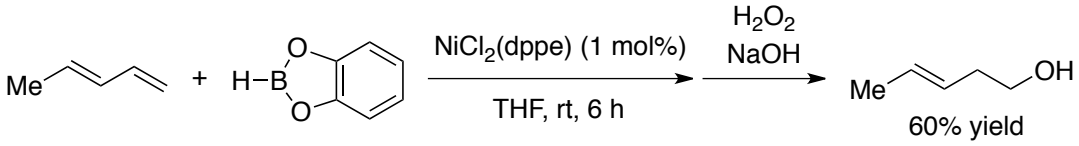
The proposed mechanism consists of two 1,2-hydroborations (Scheme 1.16). After oxidative addition of catecholborane to Rh(I) and complexation to the diene, the terminal alkene inserts into the Rh-H bond forming Rh π-allyl complex **1.20**. Reductive elimination provides the styrene adduct **1.21**, which undergoes another regioselective hydroboration, providing the 1,3-bis(boryl) product.

Scheme 1.16. Mechanism of Rh-Catalyzed Hydroboration of 1-Phenyl-1,3-Butadiene



Ni(II) has also been found to catalyze the hydroboration of terminal dienes with the same regioselectivity as uncatalyzed hydroboration, providing the homoallylic alcohol after oxidation (Scheme 1.17).[35] This reaction, studied by Zaidlewicz, employed $Ni(Cl)_2$(dppe) as catalyst for the hydroboration of several acyclic and cyclic dienes. All hydroborations were 1,2-selective, but the reaction was found to proceed faster than the hydroboration of terminal alkenes, demonstrating a reactivity trend opposite to that of the uncatalyzed process.

Scheme 1.17. Ni(II)-Catalyzed Hydroboration of 1,3-Dienes



Most recently, Ritter described an iron-catalyzed 1,4-hydroboration of 2-substituted dienes.[36] The reaction employed an iminopyridine-iron(II) complex that was reduced *in situ* with magnesium. In the presence of HB(pin), this Fe-catalyst provided linear 1,4-(*E*)-allylboronic esters **1.22** in excellent yields and regioselectivities (Scheme 1.18.). This was the first example of catalytic hydroboration of dienes that utilized HB (pin) as the hydroboration reagent, and the resulting allylboronic esters are stable to air, moisture, and silica gel chromatography.

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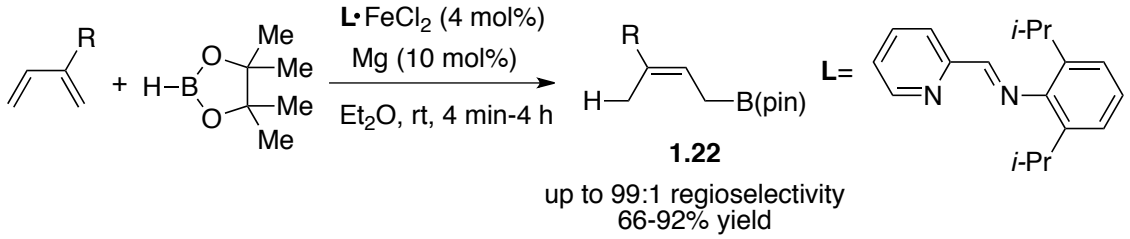
[35] Zaidlewicz, M.; Meller, J. *Tetrahedron Lett.* **1997**, *38*, 7279.
[36] Wu, J. Y.; Moreau, B.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 12915.

Scheme 1.18. Iron-Catalyzed 1,4-Hydroboration of 2-Substituted Dienes

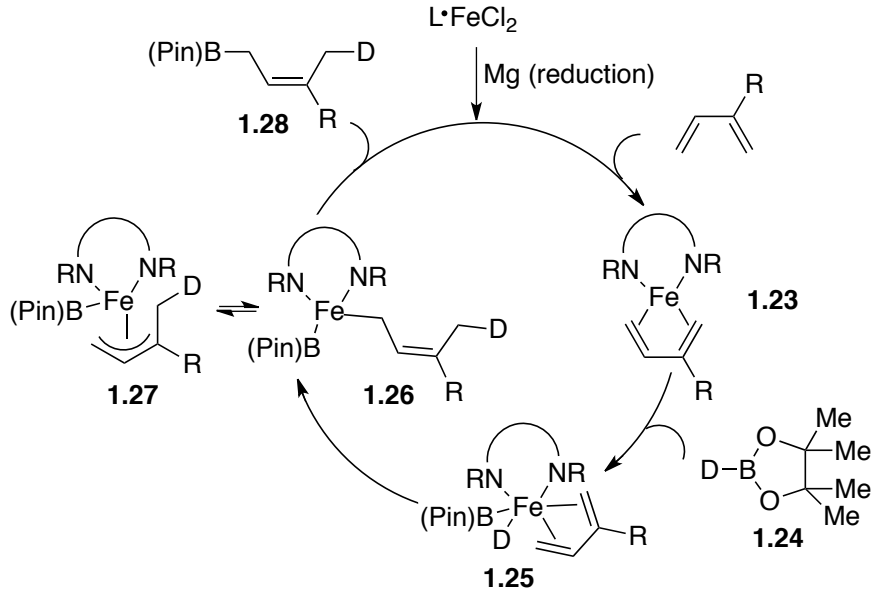


up to 99:1 regioselectivity
66-92% yield

To elucidate the mechanism of iron-catalyzed hydroboration of dienes, a labeling experiment was performed using deuterated-pinacolborane (DB(pin), **1.24**) (Scheme 1.19). Deuterium incorporation was observed exclusively at the branched methyl position to give **1.28**, suggesting that the insertion is likely irreversibly, a feature that is in contrast to Rh-catalyzed hydroboration of alkenes.[37] The alkene geometry of the product was rationalized by a mechanism involving catalyst binding to the *S*-cis conformation of the diene **1.25**, followed by a bond migration to form Fe-π-allyl complex **1.27**. Reductive elimination from the terminal, least hindered Fe-carbon bond **1.26** results in the (*E*)-allylboronic ester. The mechanistic data cannot determine whether Fe-boron or Fe-hydrogen bond migration occurs first.

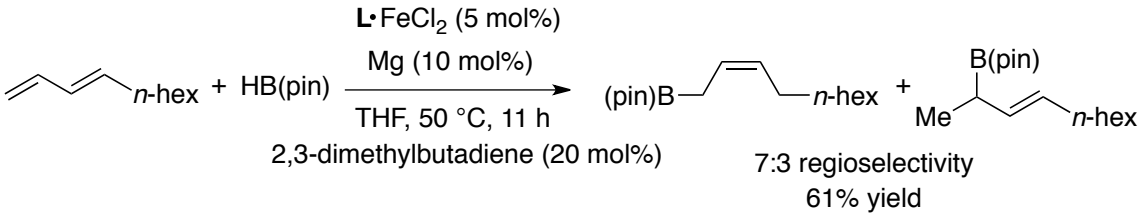
[37] Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671.

Scheme 1.19. Mechanism of Iron-Catalyzed Hydroboration of 2-Substituted Dienes



The iron-catalyzed hydroboration is only selective with 2-substituted dienes. For example, decadiene provides a 7:3 mixture of regioisomers in 61% yield (Scheme 1.20). While this limits the scope of the reaction, it still provides a powerful method to make difficult-to-access trisubstituted allylboronic esters and alcohols.

Scheme 1.20. Iron-Catalyzed Hydroboration of Decadiene



Of all the above diene hydroboration examples, none can selectively provide a range of variously substituted, bench-top stable (*Z*)-allylboronic esters. Due to the broad synthetic utility of these reagents, it was of great interest to develop diene hydroboration conditions that could provide these valuable reagents in high chemo- and regioselectivity.

1.3. Development of the Nickel-Catalyzed 1,4-Hydroboration of 1,3-Dienes[38,39]

When I joined the Morken group, the enantioselective Pt-catalyzed 1,4-diene diboration was being developed.[24] It had been discovered by Miyaura that $Pt(dba)_3$, in the presence of a monodentate phosphine ligand, added $B_2(pin)_2$ across a terminal 1,3-diene in a 1,4-fashion.[23] In our group's studies, the electron-rich monodentate phosphine ligand tricyclohexylphosphine (PCy_3), was found to be the best achiral ligand for this process (eq. 15, Scheme 1.21). We believed that simply exchanging $B_2(pin)_2$ with HB(pin) might result in the catalytic 1,4-hydroboration of a 1,3-diene. The reaction might provide either (*Z*)-allylboronic ester **1.26** or **1.27** selectively (eq. 16, Scheme, 1.21), either of which would be useful for asymmetric synthesis.

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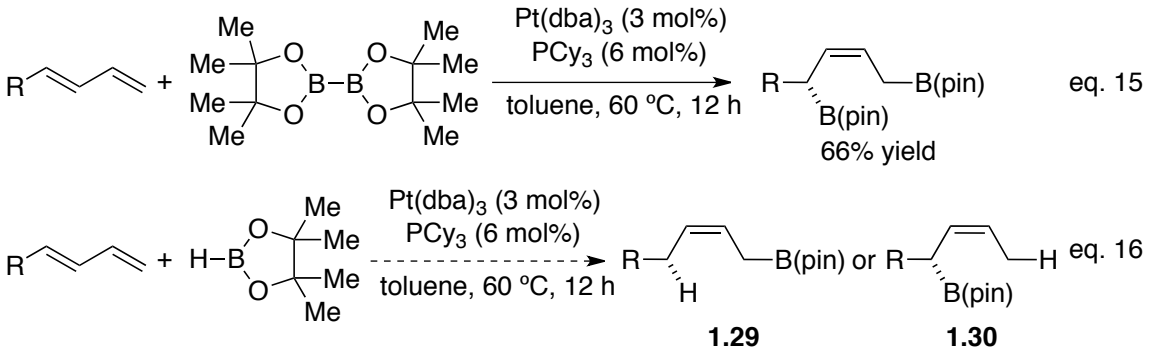
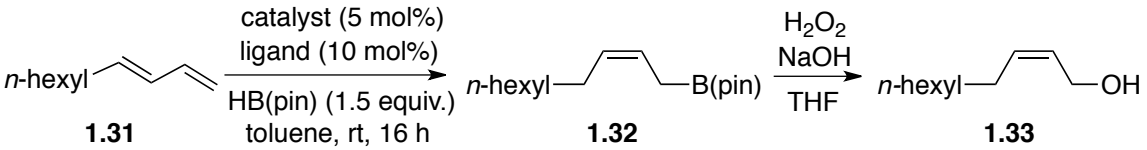
[38] Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534.
[39] Ely, R. J.; Morken, J. P. *Org. Synth*. **2011**, *88*, 342.

Scheme 1.21. Inspiration for Catalyzed 1,4-Hydroboration of Dienes



My initial survey of conditions was based on those for the Pt-catalyzed diene diboration of 1,3-decadiene (**1.31**). Unfortunately, with HB(pin) in place of $B_2(pin)_2$, no conversion of starting material was observed (entries 1-3, Table 1.1). The more reactive HB(cat) was then employed (entry 4), but again only starting material was isolated. Other monodentate phosphine ligands with different electronic properties were then evaluated. $P(NMe_2)_3$ (entry 5), a slightly less electron rich ligand than PCy_3, did not provide any product, nor did PPh_3 (entry 6) or $P(OEt)_3$ (entry 7). Palladium catalysis, shown to be successful as a diene hydroboration catalyst by Suzuki,[31] gave only starting material (entry 8). While Pt- and Pd-catalysts were ineffective for the hydroboration of **1.31**, another d^{10}-metal catalyst, $Ni(cod)_2$, cleanly converted the diene to the terminal (*Z*)-allylboronic ester **1.32**, which was oxidized to **1.33** for ease of isolation and characterization (entry 9).

Table 1.1. Catalyst Evaluation for Diene Hydroboration[a]



1.31 **1.32** **1.33**

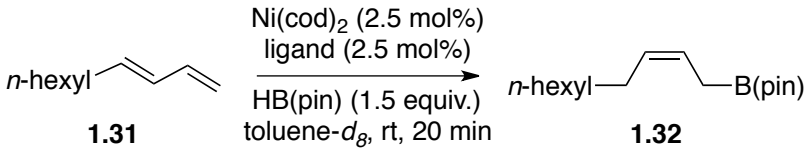
entry	catalyst	ligand	% conversion[b]
1	$Pt(dba)_3$	PCy_3	0
2	$Pt(dba)_3$	PCy_3	0[c]
3	$Pt(dba)_3$	PCy_3	0[d]
4	$Pt(dba)_3$	PCy_3	0[e]
5	$Pt(dba)_3$	$P(NMe_2)_3$	0
6	$Pt(dba)_3$	PPh_3	0
7	$Pt(dba)_3$	$P(OEt)_3$	0
8	$Pd_2(dba)_3$	PCy_3	0
9	**$Ni(cod)_2$**	**PCy_3**	**100**

[a] Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Determined by ^1H NMR. [c] Reaction at 60 °C. [d] Reaction in THF. [e] Reaction run with catecholborane.

After discovering the optimal metal for the 1,4-hydroboration of 1,3-decadiene, other phosphine ligands were surveyed in the reaction (Table 1.2). Toluene-d_8 was used as solvent in order to easily monitor the conversion by ^1H NMR. The reaction with PCy_3 and $P(NMe_2)_3$ was very efficient, giving 100% conversion to **1.32** in only 20 minutes (entries 1 and 2). PPh_3, a less electron-donating ligand than PCy_3 did promote the reaction, but proceeded slowly (entry 3). $P(OEt)_3$, the least electron-donating ligand examined, did not promote the reaction (entry 4), nor did a bidentate phosphine ligand (entry 5). 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), a N-heterocyclic

carbene (NHC), known for being a strong σ-donating ligand,[40] was employed in the hydroboration of **1.31** (entry 7). Unlike electron-donating phosphine ligands, no product was observed. Of note, the reaction without added ligand goes to 50% conversion after longer reaction time (entry 6).

Table 1.2. Ligand Survey for Ni-Catalyzed 1,4-Hydroboration of Dienes[a]



1.31 **1.32**

entry	ligand	% conversion[b]
1	**PCy_3**	**100**
2	$P(NMe_2)_3$	100
3	PPh_3	30
4	$P(OEt)_3$	0
5	dppb	0
6	–	0
7	IMes•HCl/KO*t*-Bu	0

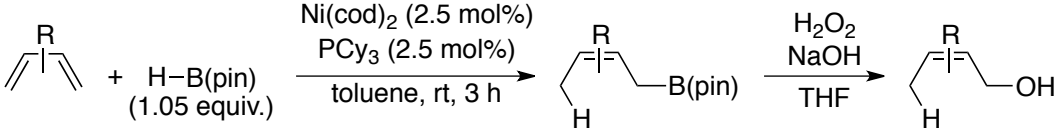
[a] Reactions conducted at [substrate] = 0.25 M. [b] Determined by ^{1}H NMR. [c] 50% conversion after 16 h.

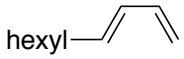
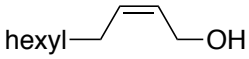
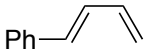
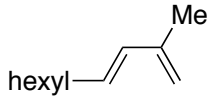
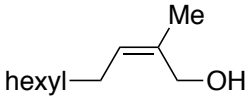
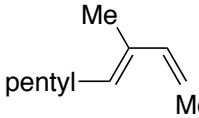
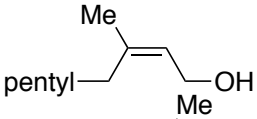
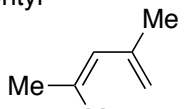
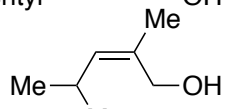
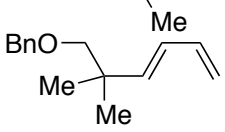
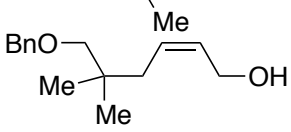
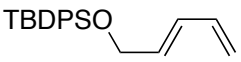
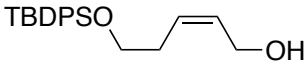
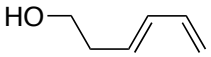
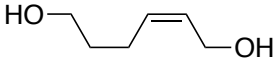
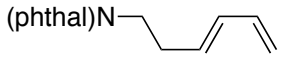
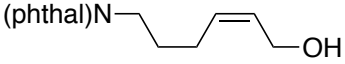
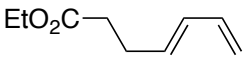
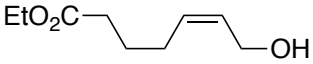
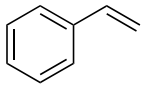
With optimal conditions for the Ni-catalyzed 1,4-hydroboration in hand, a variety of acyclic, terminal 1,3-dienes were synthesized and their reactivity in the hydroboration reaction was examined (Table 1.3). A phenyl substituted 1,3-diene was found to work equally as well as one with a simple alkyl group (entries 1 and 2). Importantly, multiply substituted dienes reacted with complete stereocontrol, providing trisubstituted allylic

[40] For a review, see: Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009,** *109,* 3612.

alcohols with difficult-to-access substitution patterns after oxidation (entries 3-5). Dienes containing a variety of synthetically common functional groups including benzyl-and silyl-protected alcohols, an unprotected alcohol, a phthalimide, and an ester were tolerated in the reaction (entries 6-10). Two equivalents of HB(pin) were required for the reaction with the free hydroxyl (entry 8), as the first equivalent deprotonates the alcohol (bubbling of H_2 observed upon addition). No reaction was observed with styrene, suggesting that the reaction was likely to be generally selective for dienes over alkenes (entry 11). All reactions were completely regio- and stereoselective.

Table 1.3. Ni-Catalyzed 1,4-Hydroboration of Terminal 1,3-Dienes[a]

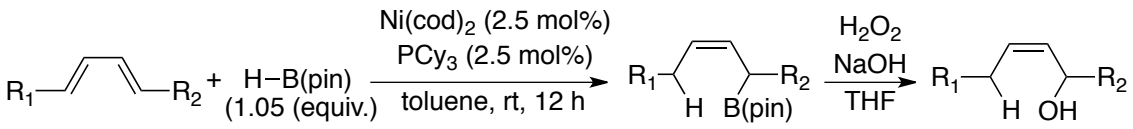


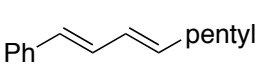
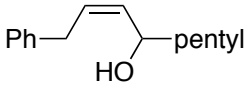
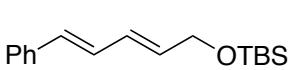
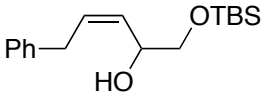
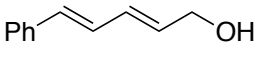
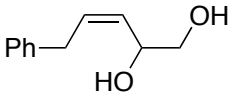
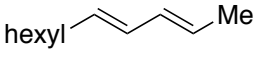
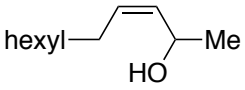
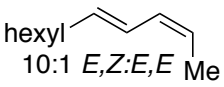
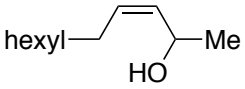
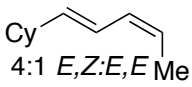
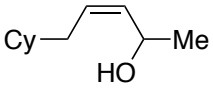
Entry	Substrate	Product	% Yield[b]
1			85%
2			91%
3			93%
4			81%
5			63%
6			89%
7			56%
8			61%[c]
9			72%[d]
10			81%[d]
11		NR	-[e]

[a] Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Value is an average of two experiments. [c] 2.1 equiv. of HB(pin) used. [d] Oxidized with buffered (pH=7) H_2O_2. [e] Reaction at 60 °C for 12 h.

After discovering that borylation occurred selectively at the terminal carbon in the Ni-catalyzed 1,4-hydroboration of terminal dienes, it was of interest to determine if the reaction would proceed with selectivity when internal dienes were employed. A variety of internal dienes were synthesized and submitted to the reaction conditions. It was found that the hydroboration not only proceeded with internal dienes, but was remarkably sensitive to the diene substituents. Borylation occurred at the least hindered carbon with high selectivities (Table 1.4, entries 1-3). Notably, the regioselectivity was moderate even when discrimination was required between a methyl and a *n*-alkyl group (entry 4). Interestingly, high regiocontrol could still be obtained when mixtures of stereoisomers were used (entries 5 and 6).

Table 1.4. Ni-Catalyzed Hydroboration of Internal Dienes[a]



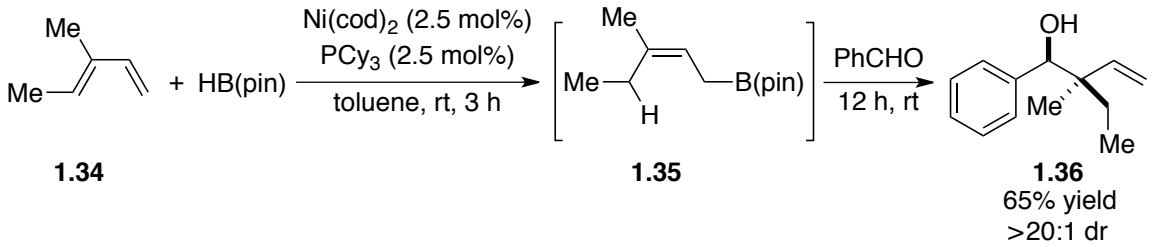
entry	substrate	product	regioselection	% yield[b]
1			10:1	84
2			>20:1	91[c]
3			>20:1	54[d]
4			5:1	61
5			>20:1	82
6			>20:1	83

[a] Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Values are an average of two experiments. [c] $Ni(cod)_2$ (1 mol%) and PCy_3 (1 mol%) employed for the experiment. [d] HB(pin) (2.1 equiv. employed).

In addition to its utility as a reliable method to make (*Z*)-allylic alcohols, diene hydroboration provides access to useful allylboronic esters that would be difficult to prepare otherwise. To demonstrate the utility of the allylboronic ester intermediate, a one-pot Ni-catalyzed hydroboration-allylation reaction was developed using commercially available 3-methyl-1,3-pentadiene (**1.34)** (Scheme 1.22). After the formation of **1.35** was

complete, benzaldehyde was added to the reaction mixture to produce the quaternary center-containing allylation product **1.36** in good yield and excellent diastereoselectivity.

Scheme 1.22. Utility of Diene Hydroboration Products in Allylation Reaction

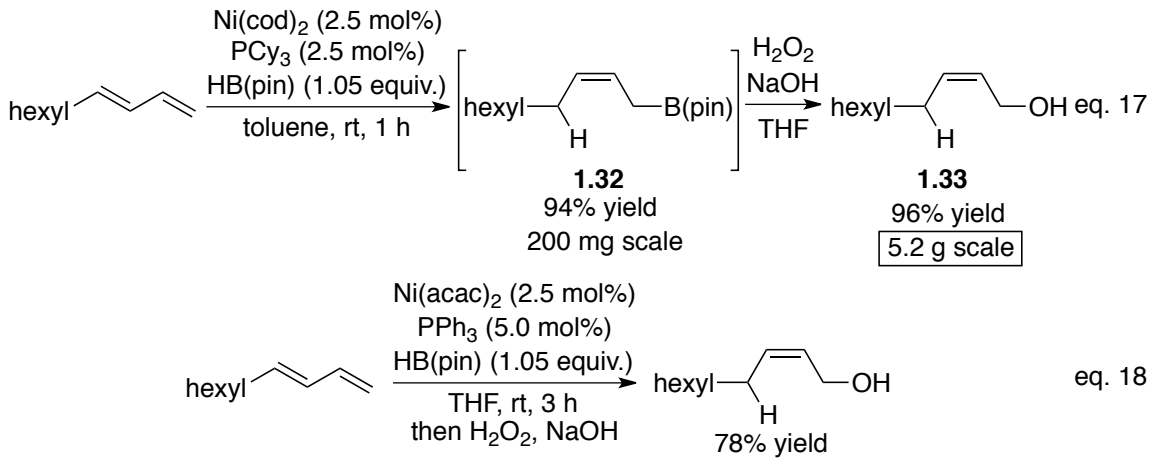


1.34 **1.35** **1.36**
65% yield
>20:1 dr

Ni-catalyzed 1,4-hydroboration of dienes was also amenable to multi-gram scale synthesis. 1,3-Decadiene was submitted to the hydroboration reaction conditions on a 5.0 g scale and, after oxidation, the resulting (*Z*)-allylic alcohol **1.33** was isolated in 96% yield (eq. 17, Scheme 1.23). The efficiency of the reaction allows the (*Z*)-allylboronic ester to be isolated in excellent purity on a 200 mg scale by simply concentrating the reaction mixture and filtering it through a short plug of silica gel. It was also found that the Ni-catalyzed hydroboration was efficient when conveniently set up outside the dry-box. This experiment employed $Ni(acac)_2$ and PPh_3 as the catalyst, both of which are stable to air and moisture (eq. 18, Scheme 1.23).[41]

[41] Unpublished results with Meredith Eno.

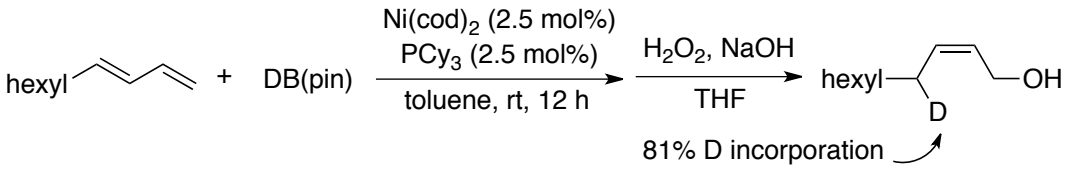
Scheme 1.23. Multi-Gram Scale and Ni(II)-Catalyzed Diene Hydroboration



1.4. Mechanistic Investigations for the Ni-Catalyzed 1,4-Hydroboration of 1,3-Dienes

To understand the mechanistic features of the Ni-catalyzed hydroboration of 1,3-dienes, in particular issues that result in 1,4-selectivity, the (*Z*)-alkene, and regioselectivity with internal dienes, several experiments were carried out. First, the hydroboration was conducted with DB(pin), and the oxidation product was analyzed by ^{1}H NMR (Scheme 1.24). Deuterium was observed only at the C4 carbon in 81% incorporation. The lack of scrambling and high incorporation suggests a very selective hydride insertion.[34]

Scheme 1.24. Deuterium Labeling Experiment

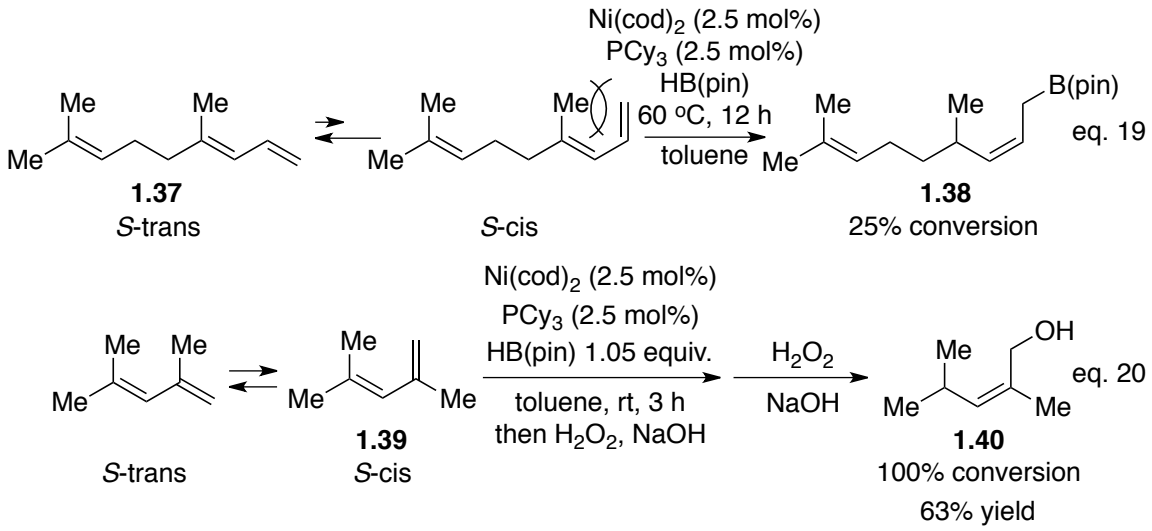


In Pt-catalyzed diene diboration, only dienes that can adopt the *S*-cis conformation will react with 1,4-selectivity.[42] Suspecting this also may be true for Ni-catalyzed diene hydroboration, **1.37**, a compound which suffers an unfavorable $A^{1,3}$-strain in the *S*-cis conformation, was synthesized and submitted to the reaction conditions (eq. 19, Scheme 1.25). After 12 h at room temperature, only starting material was observed, and after 12 h at elevated temperatures only 25% conversion to **1.38** was achieved. However, **1.39**, which suffers offsetting $A^{1,3}$-interactions in the *S*-trans and *S*-cis conformation, reacted smoothly at room temperature in 3 h to provide **1.40** in excellent 1,4- and (*Z*)-selectivity (eq. 20, Scheme 1.25). It is interesting that internal *cis*-dienes react so efficiently since these structures should also suffer similar $A^{1,3}$-strain in the *S*-cis conformation compared to **1.38** (Table 1.4). It is unlikely that isomerization of the internal *cis*-dienes to *trans*-dienes is occurring since different regioselectivities are observed.

---

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

Scheme 1.25. Effects of $A^{1,3}$-Strain on the Ni-Catalyzed 1,4-Hydroboration of Dienes



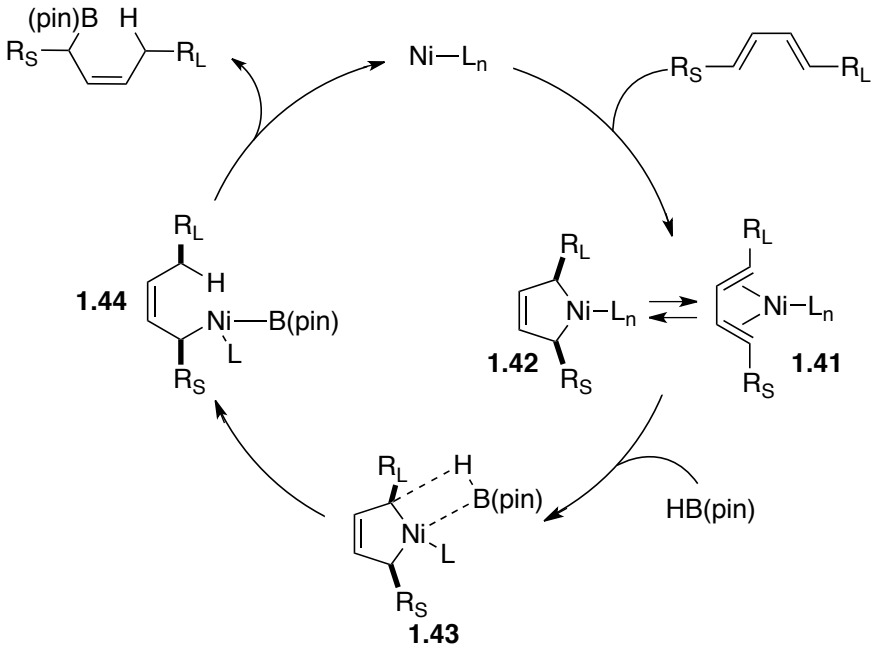
These outcomes, along with the observation that the hydroboration was ineffective with styrene, points to several possible mechanisms. Ni(0) could first coordinate either to the *S*-cis form of the diene as shown in structure **1.41** (Scheme 1.26), or oxidatively add to the diene to form nickelacycle **1.42**. While $L_2Ni(0)$ complexes have been shown to bind to butadiene as shown in **1.41**,[43] structures like **1.42** have been observed with heterobutadienes,[44] and are proposed to account for the coupling of 1,3-dienes with organoboronates.[45] HB(pin) could then approach the nickelacycle placing the hydrogen near the large diene substituent (R_L) and the phosphine ligand near the small diene substituent (R_S) as shown in **1.45**. σ-bond metathesis (**1.43**) occurs such that the

---

[43] Benn, R.; Betz, P.; Goddard, R.; Jolly, P. W.; Kokel, N.; Kruger, C.; Topalovic, I. Z. *Naturforsch*. **1991**, *46*, 1395.
[44] Karsch, H. H.; Leithe, A. W.; Reisky, M.; Witt, E. *Organometallics* **1999**, *18*, 90.
[45] Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun*. **2002**, 2210.

least hindered Ni-carbon bond is formed, as seen in **1.44.** Reductive elimination provides the product. This mechanism rationalizes both the 1,4- and (*Z*)-selectivity in addition to the observation that simple alkenes are not reactive.

Scheme 1.26. Proposed Nickelacycle Mechanism for Ni-Catalyzed Diene Hydroboration

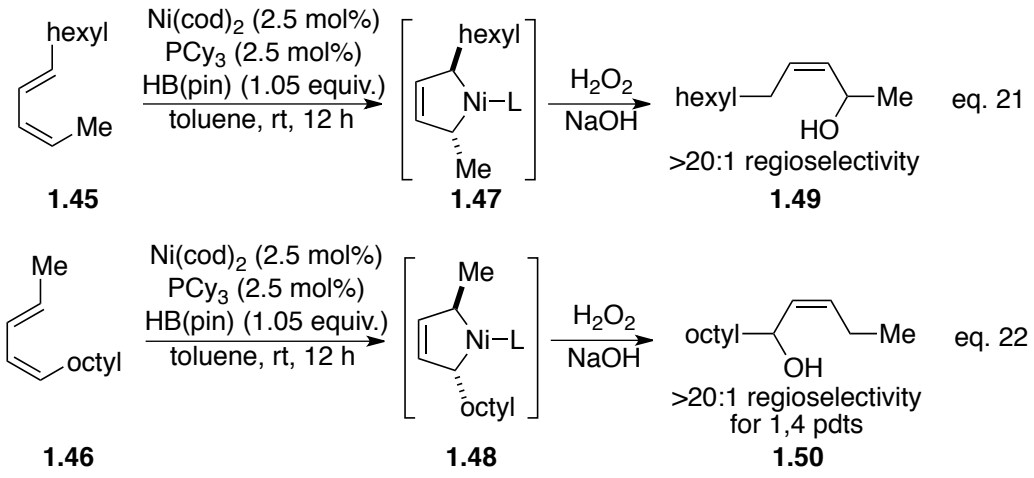


To test whether oxidative addition of the diene to Ni(0) results in **1.42**, dienes **1.45** and **1.46** were synthesized and subjected to the Ni-catalyzed hydroboration conditions (Scheme 1.27). If a nickelacycle were formed, both dienes would result in approximately equivalent nickelacycles, **1.47** and **1.48**. HB(pin) should approach each intermediate at the same position, and result in the same product. Borylation, however, occurred

exclusively at the *cis*-substituent of each diene, resulting in two different products: **1.49** and **1.50**. This result suggests an alternate mechanism maybe operative.

While the hydroboration of **1.46** produced **1.50** as the sole 1,4-hydroboration product, 1,2-hydroboration of the *trans*-alkene to produce an allylboronic ester also occurred. Attempts to selectively produce **1.50** or the 1,2-hydroboration product with various phosphine ligands were unsuccessful. 1,2-Hydroboration to produce an allylic boronic ester is also observed in the hydroboration of **1.37**. It is unclear why these products arise.

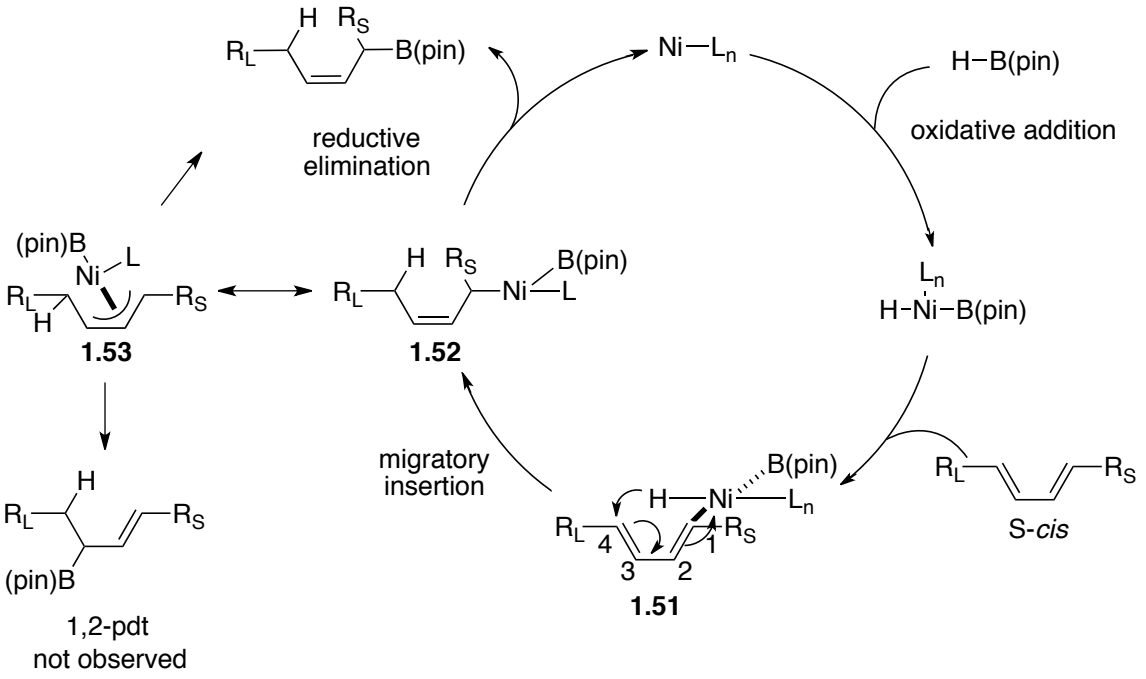
Scheme 1.27. Regioselectivity Differences in Internal *Cis*-Dienes



A more probable mechanism starts with oxidative addition of Ni(0) into HB(pin), followed by coordination of the diene in the *S*-cis conformation with the least hindered olefin binding to Ni(II) (Scheme 1.28). Carbon-hydrogen bond formation then occurs at

C4 of the diene, remote from the metal center, as shown in **1.51**, forming a (*Z*)-olefin and the least hindered Ni-carbon bond (**1.52**). Reductive elimination subsequently provides the product. It is unlikely that **1.52** would isomerize to π-allyl **1.53** since this intermediate would appear to have little steric or electronic preference for reductive elimination to provide either the 1,4- or 1,2-hydroboration product for internal dienes.

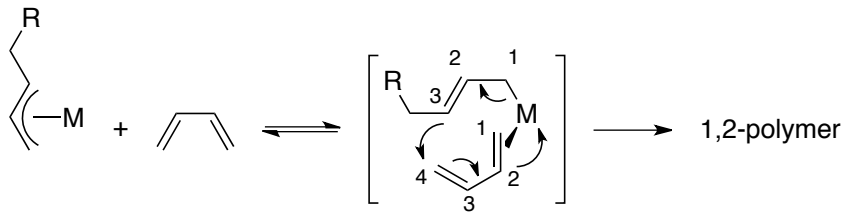
Scheme 1.28. Proposed Mechanism for the Ni-Catalyzed 1,4-Hydroboration of Dienes



A similar electrocyclic-like transition state to **1.51** has been proposed for the polymerization of Pd-allyl structures with 1,3-dienes by Hughes and Powell in the early

1970's (Scheme 1.29).[46] The *S*-cis conformation is required for carbon-carbon bond formation between C_3 of the Pd-π-allyl and C_4 of the diene.

Scheme 1.29. Proposed Mechanism for Pd-Catalyzed Polymerization of Pd-Allyl Complexes and 1,3-Dienes



The mechanism of Ni-catalyzed 1,4-hydroboration of dienes proposed in Scheme 1.28 also explains why internal dienes with a *cis*-substituent gave higher regioselectivity than the *trans*-isomer. For a *trans*-diene, the regioselectivity is dependent on the steric differences of the two carbon groups on the diene, R_L and R_S (**1.54**, Scheme 1.30). In entry 5 of Table 1.4 a 5:1 regioselectivity arises when R_L = hexyl and R_S = Me. However, when a *cis*-diene is in the *S*-cis conformation, shown in **1.55**, the steric discrimination is between R_L and hydrogen, as R_S is pointed down, away from the ligand. Thus, in entry 6 of Table 1.4 when R_L = hexyl and R_S = Me in the *cis*-position, the regioselectivity is >20:1.

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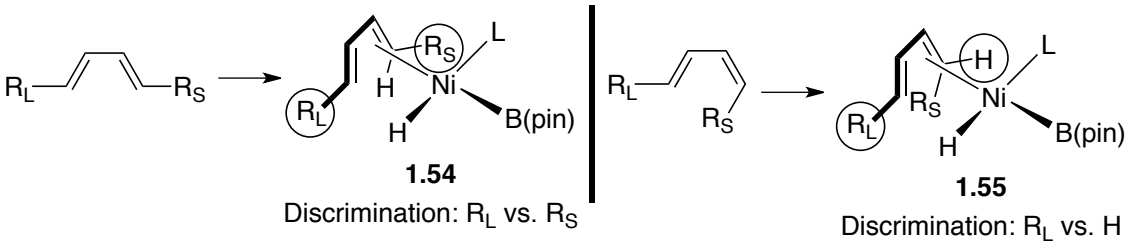
[46] (a) Hughes, R. P.; Powell, J. *J. Am. Chem. Soc.* **1972**, *94*, 7723. (b) Hughes, R. P.; Powell, J. *J. Organometal. Chem.* **1972**, *34*, C51.

Scheme 1.30. Proposed Binding of *Trans*- and *Cis*-Dienes to NiL_n



1.5 Conclusions

A novel nickel-catalyzed 1,4-hydroboration of 1,3-dienes has been developed that produces (*Z*)-allylboronic esters in high yields and excellent regio- and stereoselectivities. The products can be directly oxidized to provide stereodefined substituted allylic alcohols that can be difficult to access by other methods. The (*Z*)-allylboronic ester can be isolated in excellent yields and purity or can be used in *syn*-selective aldehyde crotylation reactions. Furthermore, the reaction can be carried out on multi-gram scale or conveniently on the bench top using a Ni(II)-catalyst.

1.6. Experimental Procedures

I. General Information

^{1}H NMR spectra were recorded on Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. $^{13}C\{^{1}H\}$NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) and Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). Infrared (IR) spectra were recorded on a Bruker a-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (ESI) was performed at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 mm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA), and potassium permanganate ($KMnO_4$).

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene, tetrahydrofuran, methylene chloride, 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. Benzene and toluene-d_8 were distilled from calcium hydride. Bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$), tricyclohexylphosphine (PCy_3), tetrapropylammonium perruthenate, and tetrakis(triphenylphosphine) palladium(0) were purchased from Strem Chemicals, Inc. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (pinacolborane) was purchased from Aldrich and used without further purification. Triphenylphosphine was purchased from Aldrich and recrystallized from hexanes before use. 2,4-dimethyl-1,3-pentadiene was purchased from Acros and distilled before use. 3-methyl-1,3-pentadiene was purchased from ChemSampCo and used without further purification. Styrene and benzaldehyde were purchased from Aldrich and distilled before use. Potassium phthalamide was purchased from Eastman and used without further purification. All other reagents were purchased from Aldrich or Fisher and used without further purification.

II. Representative Procedure for Ligand Screen (Scheme 2).

In the dry-box, an oven-dried 6-dram vial equipped with a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.2 mL of a 18.2 μM solution of $Ni(cod)_2$ in toluene-d_8, 3.60 μmol), PCy_3 (0.2 mL of a 44.0 μM solution of PCy_3 in toluene-d_8, 8.70 μmol), pinacolborane (27.8 mg, 0.22 mmol), and (*Z*)-dec-2-en-1-ol (0.18 mL of a 0.80 mM solution of (*Z*)-dec-2-en-1-ol in toluene-d_8 , 0.14 mmol). The vial was sealed and allowed to stir in the dry-box for 5 min at room temperature then transferred by syringe into a J-Young tube. The reaction was analyzed by ^1H NMR 20 minutes after the addition of the diene. Conversion was determined by integration of the alkene protons of the product

relative to the starting material.

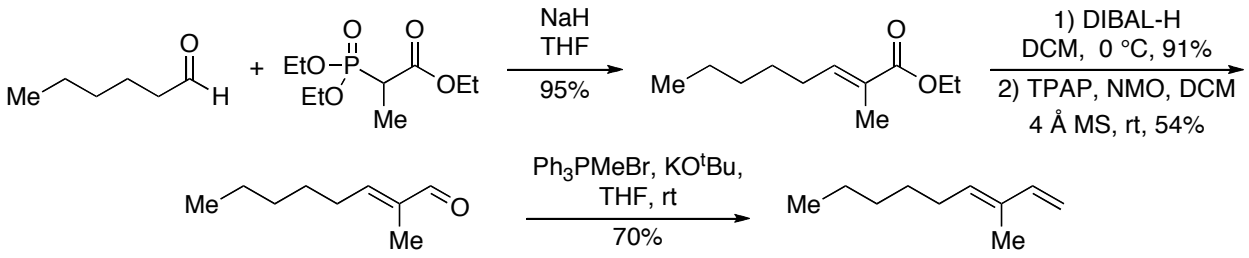
III. Preparation of Starting Material.

A. The following dienes were prepared by Wittig olefination of the commercially available α,β-unsaturated aldehydes with methyltriphenylphosphonium bromide and potassium *tert*-butoxide in tetrahydrofuran: *trans*-1,3-decadiene (**1.31**),[47] *trans*-1-phenyl-1,3-butadiene (Table 1.3, entry 2),[48]

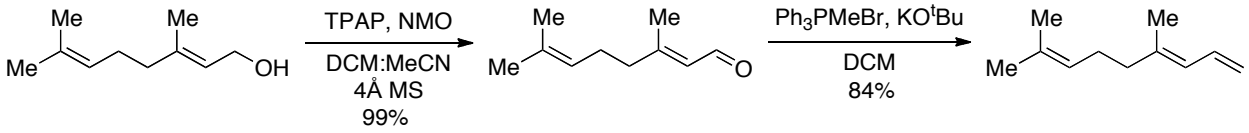
The following dienes were prepared by the literature procedure: (*E*)-2-methyldeca-1,3-diene[49] (Table 1.3, entry 3), (*E*)-*tert*-butyl(penta-2,4-dienyloxy)diphenylsilane[3] (Table 1.3, entry 7), (*E*)-((2,2-dimethylhexa-3,5-dienyloxy)methyl)benzene[3] (Table 1.3, entry 6), (*E*)-ethylhepta-4,6-dienoate[50] (Table 1.3, entry 10), (*E*)-hepta-4,6-dien-1-ol[51] (Table 1.3, entry 8), and (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol[52] (Table 1.4, entry 3). Spectral data are in accordance with the literature references.

[47] Meyers, A. I.; Ford, M. E. *J. Org. Chem.* **1976**, *41*, 1735.
[48] Yeh, K. L.; Liu, B.; Lo, C. Y.; Huang, H. L.; Liu, R. S. *J. Am. Chem. Soc.* **2002**, *124*, 6510.
[49] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 9134.
[50] Crawford, J.; Bishop, J.; Spino, C. *J. Org. Chem*. **1995**, *60*, 844.
[51] Ware Jr., R. W.; Day, C. S.; King, S. B. *J. Org Chem*. **2002**, *67*, 6174.
[52] Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc*. **2001**, *123*, 12168.

B. Preparation of (E)-3-methylnona-1,3-diene (Table 1.3, entry 4). The title compound was synthesized as shown below. The spectral data was in accordance with the literature.[53]



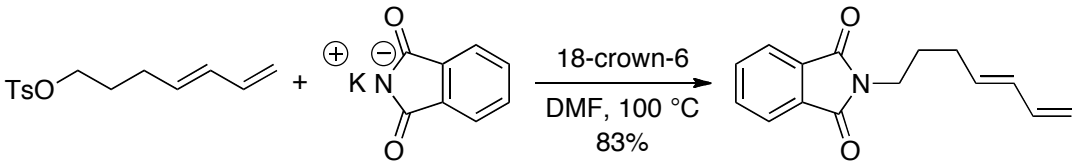
C. Preparation of (E)-4,8-dimethylnona-1,3,7-triene (1.37). The title compound was synthesized as shown below. The spectral data was in accordance with the literature.[54]

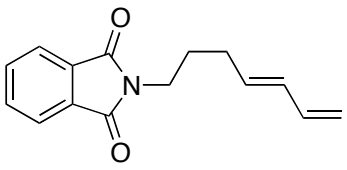


D. Preparation of (E)-2-(hepta-4,6-dienyl)isoindoline-1,3-dione. To a flame-dried round-bottom flask equipped with a reflux condenser and a magnetic stir bar was added (*E*)-hepta-4,6-dienyl 4-methylbenzenesulfonate (1.6 g, 5.9 mmol) in DMF (19.8 mL) under nitrogen. Potassium phthlamide (3.31 g, 17.9 mmol) and 18-crown-6 (4.70 g, 17.9 mmol) were added, and the reaction was allowed to stir at 100 °C for 10 h. After being cooled to room temperature, the reaction was quenched with the addition of water (20 mL)

[53] Pospíšil, J.; Markó, I. E. *Org. Lett*. **2006**, *8*, 5983.
[54] Davies, H. M. L.; Loe, Ø; Stafford, D. G. *Org. Lett*. **2005**, *7*, 5561.

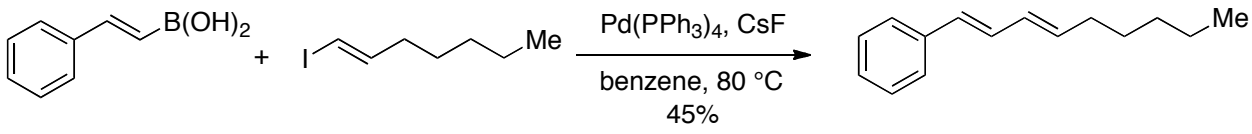
and DCM (20 mL) and the layers were separated. The organic layer was washed with water (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford the title compound as a clear, yellow liquid (1.20 g, 83%). R_f=0.26 (10:1 hexanes:ethyl acetate, stain with $KMnO_4$).



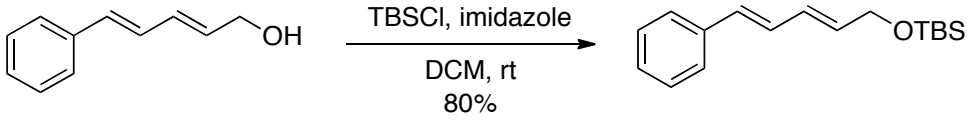


(*E*)-2-(hepta-4,6-dienyl)isoindoline-1,3-dione (Table 1.3, entry 9). ^{1}H NMR (400 MHz, $CDCl_3$): d 1.80 (2H, ddd, *J* = 15 Hz, 8.0 Hz, 8.0 Hz, $CH_2C\mathbf{H_2}CH_2$), 2.16 (2H, ddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz, $NCH_2CH_2C\mathbf{H_2}$), 3.70 (2H, t, *J* = 7.0 Hz, $NC\mathbf{H_2}$), 4.95 (1H, d, *J* = 10.5 Hz, $CH{=}CH_tC\mathbf{H_c}$), 5.08 (1H, d, *J* = 17.5 Hz, $CH{=}C\mathbf{H_t}CH_c$), 5.69 (1H, ddd, J=15.0 Hz, 6.5 Hz, 6.5 Hz, $CH_2C\mathbf{H}{=}CH$), 6.08 (1H, dd, J=15.0 Hz, 10.5 Hz, $CH_2CH{=}C\mathbf{H}$), 6.26 (1H, ddd, *J* = 17.5 Hz, 10.5 Hz, 10.5 Hz, $C\mathbf{H}{=}CH_2$), 7.71 (2H, dd, *J* = 5.0 Hz, 2.4 Hz, Ar**H**), 7.84 (2H, dd, *J* = 5.5 Hz, 3.5 Hz, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 137.1, 134.0, 133.5, 132.3, 131.9, 123.3, 115.4, 37.7, 30.0, 28.0; IR (neat): 2928 (w), 2919 (w), 2849 (w), 1711 (s), 1396 (m), 719 (m); HRMS-(ESI+) for $C_{15}H_{19}N_2O_2$ [M+NH_4]: calculated: 259.14465, found: 259.14554.

E. Preparation of (1E,3E)-nona-1,3-dienylbenzene (Table 1.4, entry 1). The title compound was synthesized as shown below. The spectral data was in accordance with the literature.[55]



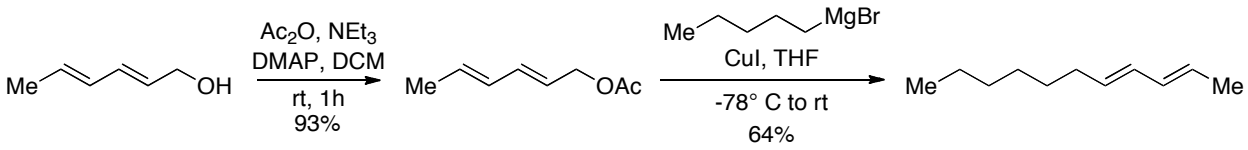
***F. Preparation of tert*-butyldimethyl((2*E*,4*E*)-5-phenylpenta-2,4-dienyloxy)silane (Table 1.3, entry 2).** The title compound was synthesized as shown below. The spectral data was in accordance with the literature.[56]

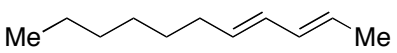


G. Prepartion of (2E,4E)-undeca-2,4-diene. To a 100 mL flame-dried round-bottom flask equipped with a magnetic stir bar was added CuI (4.7 g, 25 mmol), THF (25 mL), and (2*E*,4*E*)-hexa-2,4-dien-1-yl acetate (3.5 g, 25 mmol). The flask was flushed with nitrogen then cooled to -78 °C. Pentyl magnesiumbromide (35 mL of a 0.72 M solution in THF, 25 mmol) was then added drop-wise. The reaction was allowed to stir at -78 °C for 1 h, then allowed to warm to room temperature overnight. The reaction was quenched with the addition of aqueous ammonium chloride, diluted with pentane (20 mL) and

[55] Choi, J. Y.; Denmark, S. E. *J. Am. Chem. Soc*. **1999**, 121, 5821.
[56] Chin, L.; Gu, Y.G.; Burnett, F. N.; Wang, K. K. *J. Org. Chem*. **1991**, 56, 1914.

water (30 mL) and the layers were separated. The aqueous layer was extracted with pentane (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (pentane) to afford the title compound as a clear, colorless liquid (1.90 g, 50%). R_f=0.8 (pentane, stain with $KMnO_4$).

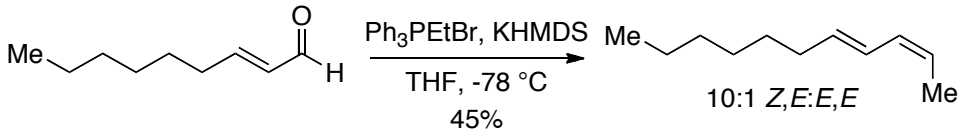


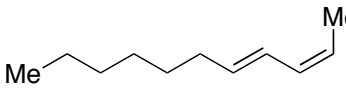


(2*E*,4*E*)-undeca-2,4-diene (Table 1.4 entry 4). ^{1}H NMR (400 MHz, CDCl3): δ 0.89 (3H, t, *J* = 6.8 Hz, $CH_2C\mathbf{H_3}$), 1.24-1.40 (8H, m, $(C\mathbf{H_2})_\mathbf{4}$), 1.74 (3H, d, *J* = 6.8 Hz, $CH{=}CHC\mathbf{H_3}$), 2.06 (2H, ddd, *J* = 6.8 Hz, 6.8 Hz, 6.8 Hz, $C\mathbf{H_2}CH{=}CH$), 5.50-5.64 (2H, m, C**H**=C**H**), 5.96-6.08 (2H, m, C**H**=C**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.4, 132.0, 130.4, 126.8, 32.8, 32.0, 29.7, 29.1, 22.9, 18.2, 14.3; IR (neat): 3016 (w), 2958 (m), 2925 (s), 2855(m), 985(m); HRMS-(ESI+) for $C_{11}H_{21}$ [M+H]: calculated: 153.16433, found: 153.16404.

H. Preparation of (2Z,4E)-undeca-2,4-diene. In the dry-box, to a flame-dried 250 mL round-bottom flask equipped with a magnetic stir bar was added potassium bis(trimethylsilyl)amide (2.65 g, 7.13 mmol) and ethyltriphenylphosphonium bromide (1.46 g, 14.3 mmol). The reaction flask was removed from the dry-box and a nitrogen

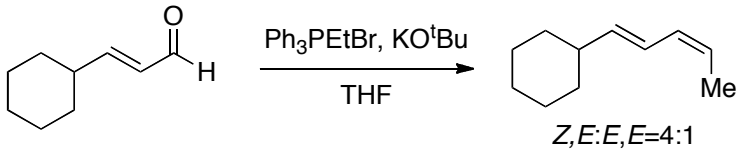
line was attached. The flask was cooled to -78 °C and THF (143 mL) was added. The reaction was allowed to stir for 1 h at -78 °C, then (*E*)-2-nonenal (0.59 mL, 3.57 mmol in 10 mL THF) was added drop-wise. The reaction was allowed to stir at -78 °C for 1 h, then warmed to room temperature and stirred for 5 h. The solvent was removed by rotary evaporation, and the residue was then taken up in diethyl ether, filtered through silica gel, and washed with diethyl ether. The filtrate was concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (pentane) to afford the title compound with a 10:1 *Z*,*E*:*E*,*E* ratio (490 mg, 45%). R_f=0.8 (pentane, stain with $KMnO_4$).



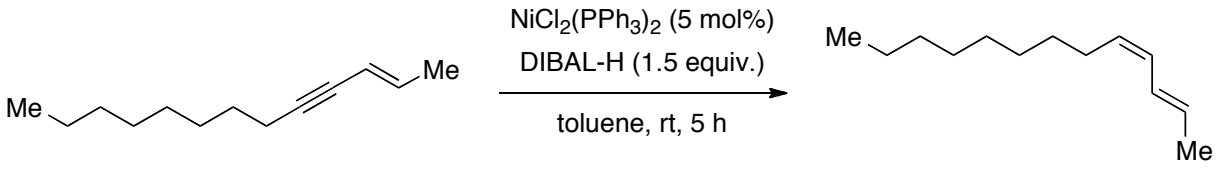


(2*Z*,4*E*)-undeca-2,4-diene (Table 1.4, entry 5.) ^{1}H NMR (400 MHz, CDCl3): δ 0.90 (3H, t, *J* = 7.0 Hz, $CH_2C\mathbf{H_3}$), 1.27-1.42 (8H, m, $(C\mathbf{H_2})_4$), 1.75 (3H, dd, *J* = 6.8 Hz, 1.6 Hz, $CH{=}CHC\mathbf{H_3}$), 2.11 (2H, ddd, *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz, $C\mathbf{H_2}CH{=}CH$), 5.38 (1H, dddd, *J* = 10.8 Hz, 6.8 Hz, 6.8 Hz, 6.8 Hz, $CH{=}C\mathbf{H}CH_3$), 5.67 (1H, ddd, *J* = 14.6 Hz, 7.0 Hz, 7.0 Hz, $CH_2C\mathbf{H}{=}CH$), 5.98 (1H, ddd, *J* = 10.8 Hz, 10.8 Hz, 1.6 Hz, $C\mathbf{H}{=}CHCH_3$), 6.33 (1H, ddd, *J* = 14.6 Hz, 10.8 Hz, 1.2 Hz, $CH_2CH{=}C\mathbf{H}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.8, 129.8, 125.5, 124.0, 33.1, 32.0, 29.6, 29.2, 22.9, 14.3, 13.5; IR (neat): 3019 (w), 2957 (m), 2924 (s), 2855 (m), 943 (m), 709 (m); HRMS-(ESI+) for $C_{11}H_{21}$ [M+H]: calculated: 153.16433, found: 153.16404. R_f=0.8 (pentanes, stain in $KMnO_4$).

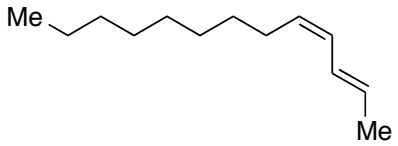
I. Prepartion of (1E,3Z)-penta-1,3-dien-1-ylcyclohexane (Table 1.4, entry 6). The title compound was synthesized as shown below. The spectral data was in accordance with the literature.[57]



J. Preparation of (2E,4Z)-trideca-2,4-diene (1.46). To a flame-dried 5 mL round-bottom flask equipped with a magnetic stir bar was added $NiCl_2(PPh_3)_2$ (18.3 mg, 0.028 mmol) and then the flask was purged with N_2. Toluene (2.8 mL) was then added, followed by the addition of DIBAL-H (0.15 mL, 0.84 mmol). The reaction was allowed to stir for 10 min followed by the addition of (*E*)-tridec-2-en-4-yne.[58] The reaction was allowed to stir at room temperature for 5 h and was then quenched with H_2O. The reaction mixture was diluted with EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (pentane) to afford the title compound as a clear, colorless liquid (836 mg, 59%). R_f=0.8 (pentane, stain with $KMnO_4$).



[57] Morgan, I. T.; Sarkar, A. K.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 2749.
[58] Kasatkin, A.; Whitby, R. J. *J. Am. Chem. Soc*. **1999**, *121*, 7039.



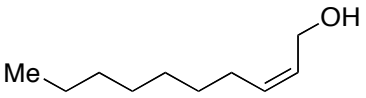
(2E,4Z)-trideca-2,4-diene (1.46). ^{1}H NMR (500 MHz, CDCl3): δ 0.79 (3H, t, *J* = 7.0 Hz), 1.17-1.29 (14H, m), 1.68 (3H, d, *J* = 6.5 Hz), 2.06 (2H, dt, J = 6.5 Hz, 6.5 Hz), 5.29 (1H, dt, *J* = 11.0 Hz, 7.5 Hz), 5.66 (1H, dq, *J* = 13.5 Hz, 6.5 Hz), 5.94 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.32 (1H, ddd, *J* = 13.5 Hz, 11.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 130.2, 129.1, 128.7, 127.3, 32.1, 30.0, 29.8, 29.8, 29.6, 29.5, 27.9, 22.9, 18.5, 14.3; IR (neat): 3018 (w), 2956 (s), 2852 (s), 1453 (s), 9080 (s), 944 (s), 818 (m), 722 (m); HRMS-(ESI+) for $C_{14}H_{27}$ [M+H]: calculated: 195.2113, found: 195.2119. R_f=0.8 (pentanes, stain in $KMnO_4$).

IV. Representative Procedure for Diene Hydroboration/Oxidation.

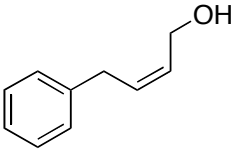
In the dry-box, an oven-dried 6-dram vial equipped with a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.2 mL of a 54.5 μM solution of $Ni(cod)_2$ in toluene, 10.9 μmol), PCy_3 (0.2 mL of a 54.5 μM solution of PCy_3 in toluene, 10.9 μmol), toluene (1.33 mL, 0.25M), pinacolborane (58.4 mg, 0.456 mmol), and *trans*-1,3-decadiene (60 mg, 0.434 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, and allowed to stir at room temperature for 3 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with THF (1.5 mL), 3 M sodium hydroxide (1 mL), and 30% hydrogen peroxide (0.75 mL). The reaction was allowed to gradually warm to room temperature and stir for 12 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (1 mL) added drop-wise. The reaction mixture was

diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted 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 on silica gel (7:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.6 mg, 85%).

V. Full Characterization and Proof of Stereochemistry.



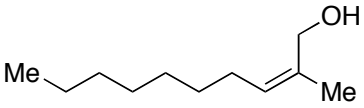
(*Z*)-dec-2-en-1-ol (1.33).[59] Spectral data is in accordance with the literature.



(*Z*)-4-phenylbut-2-en-1-ol (Table 1.3, entry 2). The reaction was performed with the general procedure, but with 1 mol % $Ni(cod)_2$ and 1 mol % PCy_3. ^{1}H NMR (400 MHz, CDCl3): δ 3.45 (2H, d, J = 5.6 Hz, PhC**H$_2$**), 4.32 (2H, d, J = 4.4 Hz, C**H$_2$**OH), 5.75 (2H, m, C**H**=C**H**), 7.20-7.30 (5H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ140.3, 131.2, 129.5, 128.7, 128.4, 126.3, 58.8, 33.9; IR (neat): 3322 (br w), 3024 (w), 2919 (w), 1494 (m), 1453 (m), 1018 (s), 697 (s); HRMS-(ESI+) for $C_{10}H_{11}$ [M-H_2O+H]: calculated: 131.08608, found:131.08591. The crude reaction mixture was purified on silica gel (8:1 hexanes:ethyl acetate) to afford a clear, colorless oil (62.8 mg, 91%). R_f=0.24 (8:1 hexanes:ethyl acetate, stain in PMA).

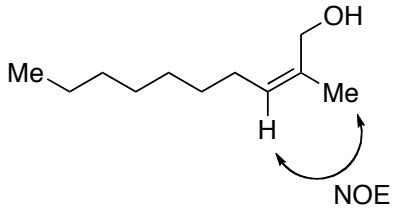
Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by analogy to entry 1.

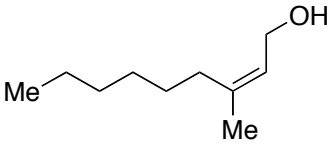
[59] Mayer, S. F.; Steinreiber, A.; Orru, R. V. A.; Faber, K. *J. Org. Chem*. **2002**, *67*, 9115.



(*Z*)-2-methyldec-2-en-1-ol (Table 1.3, entry 3). ^{1}H NMR (400 MHz, CDCl3): δ 0.88 (3H, t, *J* = 6.0 Hz, C**H$_3$**CH$_2$), 1.15-1.40 (10 H, m, CH$_3$(C**H$_2$**)$_5$), 1.8 (3H, d, *J* = 1.6 Hz, CH=CC**H$_3$**), 2.03 (2H, ddd, J = 8.0 Hz, 8.0 Hz, 8.0 Hz, CH$_2$C**H$_2$**CH=CH), 4.13 (2H, d, *J* = 2.0 Hz, C**H$_2$**OH), 5.30 (1H, t, *J* = 8.0 Hz, C**H**=C); ^{13}C NMR (100 MHz, CDCl$_3$): δ134.2, 129.1, 61.8, 32.1, 30.3, 29.5, 29.4, 27.8, 22.9, 21.5, 14.3; IR (neat): 3311 (br w), 2956 (m), 2922 (s), 2854 (m), 1456 (w), 1005 (s); HRMS-(ESI+) for $C_{11}H_{21}$ [M-H_2O+H]: calculated: 153.16433, found: 153.16462. The crude reaction mixture was purified on silica gel (13:1 hexane:ethyl acetate) to afford a clear, colorless oil (62.4 mg, 93%). R_f=0.13 (13:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry proven by NOE correlation as shown below.

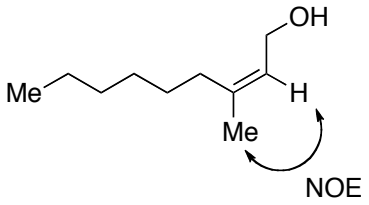


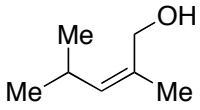


(*Z*)-3-methylnon-2-en-1-ol (Table 1.3, entry 4). ^{1}H NMR (400 MHz, CDCl3): δ 0.87 (3H, t, J = 7.4 Hz, CH$_2$C**H$_3$**), 1.24-1.38 (8H, m, CH$_2$(C**H$_2$**)$_4$CH$_3$), 1.72 (3H, d, *J* = 1.6 Hz, CH=CHC**H$_3$**), 2.05 (2H, t, *J* = 7.6 Hz, C**H$_2$**C=CH), 4.11 (2H, d, *J* = 7.2 Hz, C**H$_2$**OH), 5.4 (1H, t, *J* = 6.8 Hz, C=C**H**);

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 124.2, 59.3, 32.2, 32.0, 29.4, 28.5, 23.7, 22.8, 14.3; IR (neat): 3326 (br w), 2925 (s), 2856 (m), 1448 (w), 1067 (m); HRMS-(ESI+) for $C_{10}H_{19}$ [M-H_2O+H]: calculated: 139.14868, found: 139.1482. The crude reaction mixture was purified on silica gel (7:1 hexanes:ethyl acetate) to afford a clear, colorless oil (54.9 mg, 81%). R_f=0.18 (7:1 hexanes:ethyl acetate, stain in PMA).

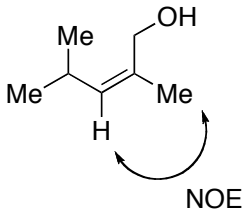
Proof of Stereochemistry: : (*Z*)-alkene stereochemistry proven by NOE correlation as shown below.

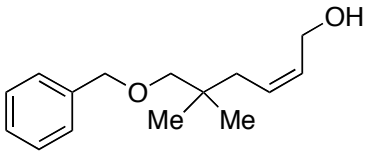




(*Z*)-2,4-dimethylpent-2-en-1-ol (1.40). The reaction was performed with the general procedure, but allowed to stir for 12 h. ^{1}H NMR (400 MHz, CDCl3): δ 0.93 (6H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$), 1.76 (3H, d, *J* = 1.6 Hz, CH=CC**H**$_3$), 2.58 (1H, dddd, *J* = 13.2 Hz, 9.6 Hz, 6.8 Hz, 6.8 Hz, C**H**(CH$_3$)$_2$), 4.12 (2H, s, C**H**$_2$OH), 5.11 (1H, d, *J* = 9.2 Hz, C**H**=C); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 132.0, 62.0, 27.1, 23.8, 21.4; IR (neat): 3319 (br w), 2957 (s), 2868 (m), 1466 (w), 1007 (s); HRMS-(ESI+) for C_7H_{13} [M-H_2O+H]: calculated: 97.10173, found: 97.10101. The crude reaction mixture was purified on silica gel (7:1 hexanes:ethyl acetate) to afford a clear, colorless oil (44.9 mg, 63%). R_f=0.24 (7:1 hexanes:ethyl acetate, stain in PMA).

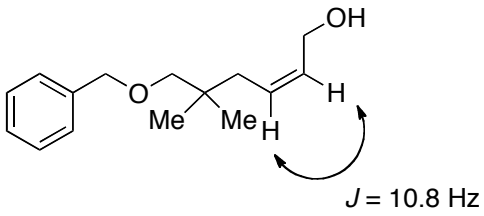
Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by NOE correlation as shown below.

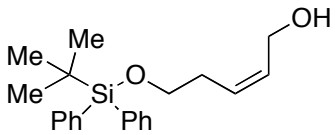




(*Z*)-6-(benzyloxy)-5,5-dimethylhex-2-en-1-ol (Table 1.3, entry 6). ^{1}H NMR (400 MHz, CDCl3): δ 0.93 (6H, s, (C**H**$_3$)$_2$), 2.11 (2H, d, *J* = 8.0 Hz, CH=CHC**H**$_2$C(CH$_3$)$_2$), 3.14 (2H, s, OC**H**$_2$C), 4.15 (2H, d, *J* = 6.8 Hz, C**H**$_2$OH), 4.51 (2H, s, PhC**H**$_2$O), 5.59 (1H, ddd, *J* = 10.8 Hz, 7.8 Hz, 7.8 Hz, C**H**=CHCH$_2$OH), 5.74 (1H, ddd, *J* = 10.8 Hz, 6.6 Hz, 6.6 Hz, CH=C**H**CH$_2$OH), 7.27-7.34 (5H, m, Ar**H**); ^{13}C NMR (100 MHz, CDCl$_3$): δ 138.8, 130.6, 129.5, 128.5, 127.7, 127.6, 78.5, 73.5, 58.5, 36.5, 35.5, 24.9; IR (neat): 3372 (br w), 2956 (m), 2868 (m), 1454 (w), 1099 (s), 1029 (s), 697 (s); HRMS-(ESI+) for C$_{15}$H$_{23}$O$_2$ [M+H]: calculated: 235.16980, found: 235.17019. The crude reaction mixture was purified on silica gel (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (58.4 mg, 89%). R$_f$=0.14 (10:1 hexanes:ethyl acetate, stain in PMA).

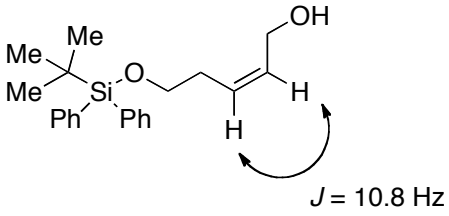
Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.

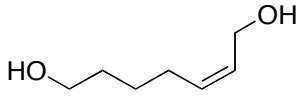




(*Z*)-5-(*tert*-butyldiphenylsilyloxy)pent-2-en-1-ol (Table 1.3, entry 7). ^{1}H NMR (400 MHz, CDCl3): δ 1.06 (9H, s, OSiC(C**H$_3$**)$_3$), 1.6 (1H, s br, O**H**), 2.37 (2H, ddd, *J* = 6.4 Hz, 6.4 Hz, 6.4 Hz, SiOCH$_2$C**H$_2$**), 3.67 (2H, t, *J* = 6.4 Hz, SiOC**H$_2$**CH$_2$), 4.15 (2H, d, *J* = 6.4, C**H$_2$**OH), 5.59 (1H, ddd, *J* = 10.8 Hz, 8.0 Hz, 8.0 Hz, C**H**=CHCH$_2$OH), 5.77 (1H, ddd, *J* = 10.8 Hz, 6.8 Hz, 6.8 Hz, CH=C**H**CH$_2$OH), 7.37-7.46 (6H, m, Ar**H**), 7.67-7.69 (4H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 133.8, 130.8, 129.8, 129.6, 127.8, 63.4, 58.7, 31.1, 27.1, 19.4; IR (neat): 3363 (br w), 3070 (w), 3017 (m), 2858 (m), 1389 (m), 1110 (s), 701 (s), 505 (m); HRMS-(ESI+) for $C_{21}H_{29}O_2Si$ [M+H]: calculated: 341.19368, found: 341.19268. The crude reaction mixture was purified on silica gel (7:1 hexanes:ethyl acetate) to afford a clear, colorless oil (38.0 mg, 56%). R_f=0.20 (7:1 hexanes:ethyl acetate, stain in PMA).

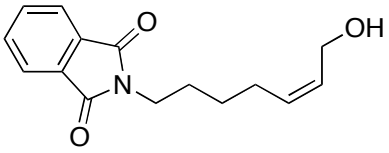
Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.





(*Z*)-hept-2-ene-1,7-diol (Table 1.3, entry 8). The reaction was performed with the general procedure, but 2.1 equiv. of pinacolborane was used.^{1}H NMR (400 MHz, CDCl3): δ 1.42 (2H, dddd, *J* = 14.4 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, C**H$_2$**CH$_2$CH$_2$OH), 1.55 (2H, dddd, *J* = 13.2 Hz, 7.2 Hz, 7.2 Hz, 7.2

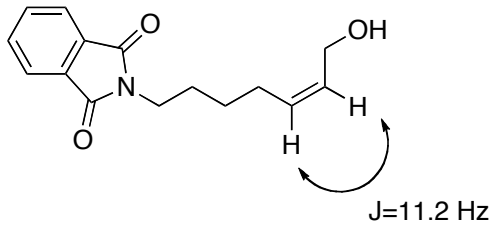
Hz, $CH_2C\mathbf{H_2}CH_2OH$), 2.09 (2H, ddd, *J* = 7.6 Hz, 7.6 Hz, 7.6 Hz, $CH{=}CHC\mathbf{H_2}CH_2$), 2.53 (1H, s br, O**H**), 3.60 (2H, t, *J* = 6.4 Hz, $CH_2C\mathbf{H_2}OH$), 4.15 (2H, d, *J* = 6.4 Hz, $C\mathbf{H_2}OH$), 5.47-5.53 (1H, m, $C\mathbf{H}{=}CHCH_2OH$), 5.56-5.62 (1H, m, $CH{=}C\mathbf{H}H_2OH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.7, 129.0, 62.6, 58.4, 32.1, 27.2, 25.9; IR (neat): 3287 (br m), 2928 (s), 2859 (m), 1431 (w), 1006 (s); HRMS-(ESI+) for $C_7H_{18}NO_2$ [M+NH_4]: calculated: 148.13375, found: 148.13360. The crude reaction mixture was purified on silica gel (1:2 hexanes:ethyl acetate) to afford a clear, colorless oil (50.1 mg, 72%). R_f=0.12 (1:2 hexanes:ethyl acetate, stain in PMA).

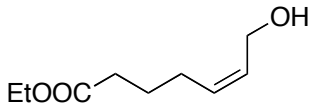


(*Z*)-2-(7-hydroxyhept-5-enyl)isoindoline-1,3-dione (Table 1.3, entry 9). The reaction was performed with the general procedure, but upon oxidation, pH=7 phosphate buffer (1 mL) was used instead of a 3.0 M solution of sodium hydroxide. ^{1}H NMR (400 MHz, CDCl3): δ 1.43 (2H, dddd, *J* = 7.2 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, $CH{=}CHCH_2C\mathbf{H_2}$), 1.67 (2H, dddd, *J* = 7.2 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, $NCH_2C\mathbf{H_2}$), 2.14 (2H, ddd, *J* = 7.6 Hz, 7.6 Hz, 1.6 Hz, $CH{=}CHC\mathbf{H_2}$), 3.67 (2H, t, *J* = 9.5 Hz, $NC\mathbf{H_2}$), 4.20 (2H, dd, *J* = 6.8 Hz, 1.2 Hz, $HOC\mathbf{H_2}$), 5.48 (1H, dddd, *J* = 11.2 Hz, 7.6 Hz, 7.6 Hz, 0.8 Hz, $C\mathbf{H}{=}CHCH_2OH$), 5.63 (1H, dddd, *J* = 11.2 Hz, 6.8 Hz, 6.8 Hz, 1.6 Hz, $CH{=}C\mathbf{H}CH_2OH$), 7.67 (2H, dd, *J* = 5.2 Hz, 3.2 Hz, Ar**H**), 7.79 (2H, dd, *J* = 5.2 Hz, 3.2 Hz, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 133.9, 132.1, 132.0, 129.2, 123.2, 58.4, 37.6, 27.7, 26.5, 26.4; IR (neat): 3466 (w br), 3013 (w), 2929 (m), 1706 (s), 1438 (m), 719 (m); HRMS-(ESI+) for $C_{15}H_{21}N_2O_3$ [M+NH_4]: calculated: 277.15522, found:

277.15531. The crude reaction mixture was purified on silica gel (3:1 hexanes:ethyl acetate) to afford a clear, colorless oil (39.4 mg, 61% (after subtraction of inseparable pinacol and unknown impurity)). R_f=0.16 (3:1 hexanes:ethyl acetate, stain in PMA).

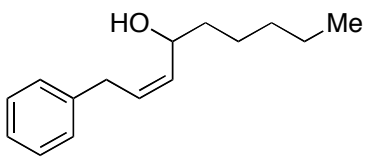
Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.





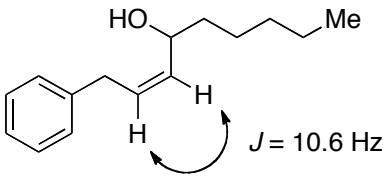
(*Z*)-ethyl-7-hydroxyhept-5-enoate (Table 1.3, entry 10). The reaction was performed with the general procedure, but allowed to stir for 12 h. Upon oxidation, pH=7 phosphate buffer (1 mL) was used instead of a 3.0 M solution of sodium hydroxide. ^{1}H NMR (400 MHz, CDCl3): δ 1.23 (3H, t, *J* = 7.6 Hz, $CH_2C\mathbf{H_3}$), 1.66-1.73 (2H, m, $CH_2C\mathbf{H_2}CH_2COOEt$), 2.11 (2H, ddd, *J* = 7.2 Hz, 7.2 Hz, 7.2 Hz, $CH{=}CHC\mathbf{H_2}$), 2.28 (2H, t, *J* = 7.6 Hz, $C\mathbf{H_2}COOEt$), 4.11 (2H, q, *J* = 7.3 Hz, $COOC\mathbf{H_2}CH_3$), 4.14 (2H, d, *J* = 7.2 Hz, $HOC\mathbf{H_2}$), 5.47 (1H, m, $HOCH_2C\mathbf{H}{=}CH$), 5.64 (1H, m, $HOCH_2CH{=}C\mathbf{H}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 131.6, 129.9, 60.5, 58.4, 33.7, 26.7, 24.8, 14.4; IR (neat): 3421 (br w), 2926 (m), 1734 (s), 1031 (m); HRMS-(ESI+) for $C_9H_{17}O_3$ [M+H]: calculated: 173.11777, found: 341.11815. The crude reaction mixture was purified on silica gel (3:1 hexanes:ethyl acetate) to afford a clear, colorless oil (53.9 mg, 81%). R_f=0.23 (3:1 hexanes:ethyl acetate, stain in PMA).

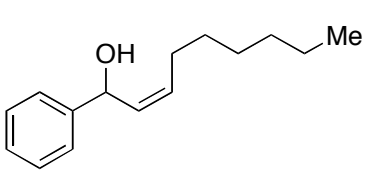
Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by analogy.



(*Z*)-1-phenylnon-2-en-4-ol (Table 1.4, entry 1). The reaction was performed with the general procedure, but allowed to stir for 12 h.^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9 (3H, t, *J* = 6.8 Hz, C**H$_3$**CH$_2$), 1.26-1.58 (6H, m, (C**H$_2$**)$_3$CH$_3$), 1.6-1.68 (2H, m, C**H$_2$**CHOH), 3.40-3.54 (2H, m, PhC**H$_2$**), 4.56 (1H, dddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz, 1.0 Hz, C**H**OH), 5.52 (1H, dddd, *J* = 10.6 Hz, 3.2 Hz, 1.6 Hz, 1.6 Hz, HC=C**H**CHOH), 5.69 (1H, dddd, *J* = 10.6 Hz, 7.6 Hz, 7.6 Hz, 1Hz, PhCH$_2$C**H**=CH), 7.19-7.23 (3H, m, Ar**H**), 7.28-7.32 (2H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 133.8, 130.4, 128.5, 127.7, 126.3, 67.9, 37.8, 34.1, 32.0, 25.3, 22.9, 14.3; IR (neat): 3342 (br w), 3063 (w), 3026 (m), 2857 (m), 1602 (w), 1453 (m), 1052 (m), 739 (s), 696 (s); HRMS-(ESI+) for $C_{15}H_{26}NO$ [M+NH_4]: calculated: 236.20144, found: 236.20211. The crude reaction mixture was purified on silica gel (20:1 hexanes:ethyl acetate) to afford a clear, colorless oil (29.9 mg, 85%). R_f=0.11 (20:1 hexanes:ethyl acetate, stain in PMA). Regioselectivity was determined by the mass of the collected products.

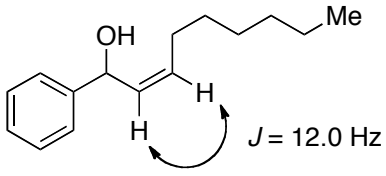
Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.

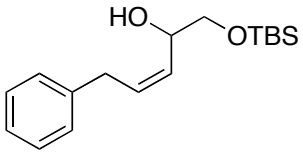




(*Z*)-1-phenylnon-2-en-1-ol (Table 1.4, entry 1 minor regioisomer). The reaction was performed with the general procedure, but allowed to stir for 12 h. ^{1}H NMR (400 MHz, C_6D_6): δ 0.89 (3H, t, *J* = 8.0 Hz, C**H$_3$**), 1.20-1.36 (8 H, m, $CH_3(C\mathbf{H_2})_4$), 2.02 (2H, dddd, *J* = 16 Hz, 16 Hz, 8 Hz, 8 Hz, CH=CHC**H$_2$**), 5.35-5.41 (1H+1H, m, PhC**H**OH+CHC**H**=CH), 5.61 (1H, dddd, *J* = 12 Hz, 4 Hz, 3.8 Hz, 3.8 Hz CH=C**H**CH_2), 7.09-7.2 (3H, m, Ar**H**), 7.41 (2H, d, 8 Hz, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 132.7, 132.0, 128.7, 127.6, 126.1, 69.7, 31.9, 29.9, 29.2, 28.0, 22.8, 14.3; IR (neat): 3354 (br w), 3062 (w), 2955 (s), 2854 (m), 1453 (w), 1023 (w), 698 (m); HRMS-(ESI+) for $C_{15}H_{21}$ [M-H_2O+H]: calculated: 201.16433, found: 201.16497. The crude reaction mixture was purified on silica gel (20:1 hexanes:ethyl acetate) to afford a clear, colorless oil (3.0 mg, 9%). R_f=0.12 (20:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.

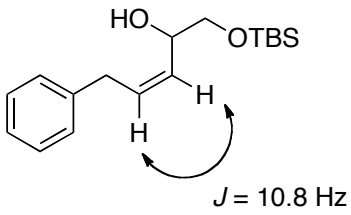


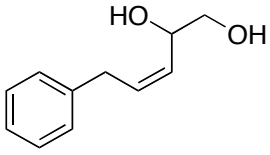


(*Z*)-1-(*tert*-butyldimethylsilyloxy)-5-phenylpent-3-en-2-ol (Table 1.4, entry 2). The reaction was performed with the general procedure, but with 1 mol % $Ni(cod)_2$ and 1 mol % PCy_3. ^{1}H NMR (400 MHz, CDCl3): δ 0.095 (6H, s, $OSi(C\mathbf{H_3})_2CH(CH_3)_3$), 0.92 (9H, s,

$OSi(CH_3)_2CH(C\mathbf{H_3})_3$), 2.63 (1H, br s, CHO**H**), 3.41-3.65 (2H + 1H, m, $PhCH_AC\mathbf{H_B}$ + $C\mathbf{H_2}OSi$), 3.63 (1H, dd, *J* = 10.2 Hz, 3.8 Hz, $PhC\mathbf{H_A}CH_B$), 4.61 (1H, ddd, *J* = 8.4 Hz, 8.4 Hz, 3.6 Hz, C**H**OH), 5.49 (1H, dd, *J* = 10.8 Hz, 8.4 Hz, CH=C**H**COH), 5.77 (1H, ddd, *J* = 10.8 Hz, 8.0 Hz, 8.0 Hz, $CH_ACH_BC\mathbf{H}$=CH), 7.19-7.32 (5H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 132.4, 129.0, 128.7, 128.5, 126.3, 68.6, 67.1, 34.4, 26.1, 18.6, -5.1; IR (neat): 3412 (br w), 3026 (w), 2953 (w), 2856 (w), 1253 (w), 1104 (m), 884 (s); HRMS-(ESI+) for $C_{17}H_{32}NO_2Si$ [M+NH_4]: calculated: 310.22023, found: 196.22011. The crude reaction mixture was purified on silica gel (15:1 hexanes:ethyl acetate) to afford a clear, colorless oil (58.0 mg, 91%). R_f=0.22 (15:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.

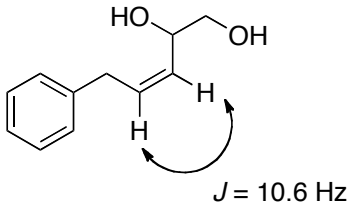


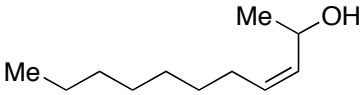


(*Z*)-5-phenylpent-3-ene-1,2-diol (Table 1.4, entry 3). The reaction was performed with the general procedure, but with 1 mol % $Ni(cod)_2$, 1 mol % PCy_3, and 2.1 equiv. pinacolborane. ^{1}H NMR (400 MHz, CDCl3): δ 2.30 (1H, br s, O**H**), 3.44-3.48 (2H+1H, m, $PhCH_AC\mathbf{H_B}$ + $C\mathbf{H_2}OH$), 3.56 (1H, dd, *J* = 11.2 Hz, 3.6 Hz, $PhC\mathbf{H_A}CH_B$), 4.60 (1 H, ddd, *J* = 8.0 Hz, 8.0

Hz, 3.6 Hz, C**H**OH), 5.43 (1H, dd, *J* = 10.6 Hz, 8.4 Hz, CH_2CH=C**H**COH), 5.71 (1H, ddd, *J* = 10.6 Hz, 7.6 Hz, 7.6 Hz, CH_2C**H**=CH), 7.16 (5H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 132.8, 129.0, 128.8, 128.4, 126.4, 68.8, 66.6, 34.3; IR (neat): 3344 (br, w), 3025 (w), 2921 (w), 1452 (w), 1072 (s), 1026 (s), 738 (s), 697 (s); HRMS-(ESI+) for $C_{11}H_{18}N_1O_2$ [M+NH_4]: calculated: 196.13375, found: 196.13433. The crude reaction mixture was purified on silica gel (1:1 hexanes:ethyl acetate) to afford a clear, colorless oil (36.1 mg, 54%). R_f=0.18 (1:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.

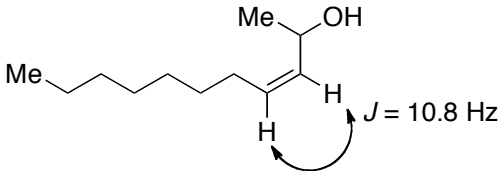




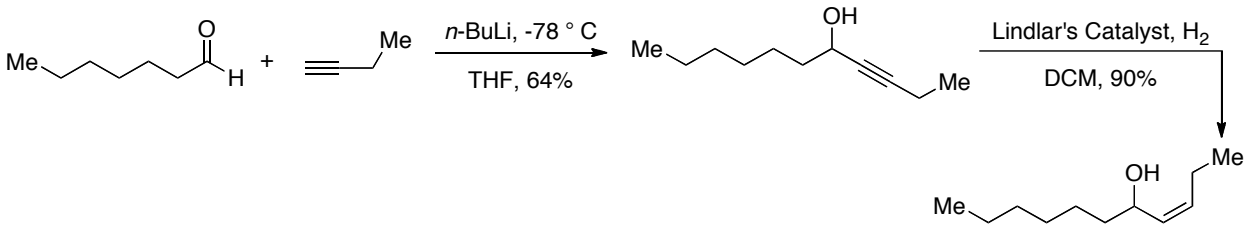
(*Z*)-undec-3-en-2-ol (Table 1.4, entry 4 and 5). The reaction was performed with the general procedure, but allowed to stir for 12 h. ^{1}H NMR (400 MHz, C_6D_6): δ 0.90 (3H, t, *J* = 6.8 Hz, C**H$_3$**), 1.20-1.34 (10H, m, (C**H$_2$)$_5$**), 1.76 (3H, d, *J* = 6.4 Hz, CHOHC**H$_3$**), 1.91-2.01 (2H, m, C**H$_2$**CH=CH), 4.52 (1H, br dddd, *J* = 6.4 Hz, 6.4 Hz, 6.4 Hz, 6.4 Hz, C**H**OH), 5.31 (1H, dddd, *J* = 10.8 Hz, 7.2 Hz, 7.2Hz, 1.2 Hz, CH_2C**H**=CH), 5.44 (1H, ddd, *J* = 10.8 Hz, 8.4 Hz, 1.2 Hz, CH=C**H**CHOH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9, 131.6, 64.1, 32.0, 29.9, 29.4, 29.3, 27.7, 23.8, 22.9, 14.3; IR (neat): 3331 (br w), 3008 (m), 2924 (s), 2855 (m), 1459 (w), 1058 (m); HRMS-(ESI+) for $C_{11}H_{21}$ [M-H_2O+H]: calculated: 153.16433,

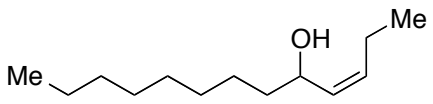
found: 153.16455. The crude reaction mixture was purified on silica gel (15:1 hexanes:ethyl acetate) to afford a clear, colorless oil (40.9 mg, 61% for entry 4; 50.0 mg, 82% for entry 5). R_f=0.23 (15:1 hexanes:ethyl acetate, stain in PMA). Product from Table 2, entry 5 contained a small amount of (*Z*)-undec-2-en-1-ol (isomerization / hydroboration product) could not be separated.

Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.



Proof of Regioselectivity: The regioisomeric 1,4-hydroboration product **1.49B** was synthesized as shown below, and compared to the crude reaction product. It was detected in a 5:1 ratio as determined by crude ^{1}H NMR for Table 2 entry 4, but not detected for Table 2 entry 5.

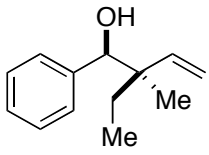




(Z)-tridec-3-en-5-ol (1.50). The reaction was performed with the general procedure, but allowed to stir for 12 h. The crude product was assigned by analogy to the ^{1}H NMR of **1.49B** and was further compared to the hydroboration product from Table 1.4, entry 5.

VI. Procedure for Hydroboration/Allylation (Scheme 1.22).

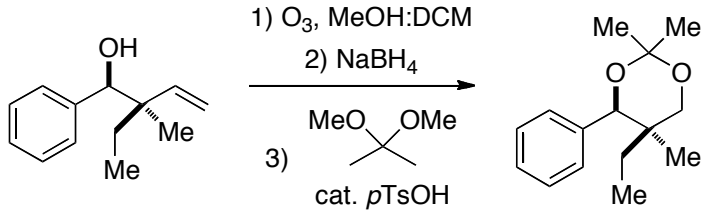
In the dry-box, an oven-dried 6-dram vial equipped with magnetic stir bar was charged successively with $Ni(cod)_2$ (0.5 mL of a 36.3 μM solution of $Ni(cod)_2$ in toluene, 18.3 μmol), PCy_3 (0.5 mL of a 56.3 μM solution of PCy_3 in toluene, 18.3 μmol), toluene (1.9 mL, 0.25M), pinacolborane (98.2 mg, 0.77 mmol), and (*E*)-3-methylpenta-1,3-diene (60 mg, 0.73 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, and allowed to stir at room temperature for 3 h. The solvent was then removed by rotary evaporation, and DCM (0.73 mL) and benzaldehyde (0.08 mL, 0.77 mmol) were added. The reaction mixture was allowed to stir at room temperature for 16 h. The solvent was removed by rotary evaporation and the crude reaction mixture was purified on silica gel (100:1 hexanes:ethyl acetate) to afford a clear, colorless oil (90.3 mg, 65%). R_f=0.32 (100:1 hexanes:ethyl acetate, stain in $KMnO_4$).



2-ethyl-2-methyl-1-phenylbut-3-en-1-ol (1.36). ^{1}H NMR (400 MHz, CDCl3): δ 0.8 (3H, t, *J* = 7.6 Hz, $CH_2C\mathbf{H_3}$), 1.06 (3H, s, $C\mathbf{H_3}$), 1.36-1.43 (2H, m, $C\mathbf{H_2}CH_3$), 2.13 (1H, d, *J* = 4.8 Hz, O**H**), 4.45 (1H, d, *J* = 4.4 Hz, C**H**OH), 5.02 (1H, dd, *J* = 17.6 Hz, 1.2 Hz, CH=C$\mathbf{H_t}H_c$), 5.22 (1H, dd, *J* = 10.8,

J=1.6 Hz, CH=CH$_t$**H**$_c$), 5.76 (1H, dd, *J* = 17.6 Hz, 11.2 Hz, C**H**=CH$_2$), 7.25-7.34 (5H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 141.5, 128.0, 127.6, 115.6, 80.9, 45.7, 29.0, 18.6, 8.5; IR (neat): 3473 (br w), 3063 (w), 2968 (s), 1453 (m), 1022 (m), 725 (s); HRMS-(ESI+) for $C_{13}H_{18}ONa$ [M+Na]: calculated: 213.1255, found: 213.1266.

Proof of stereochemistry. The relative configuration was assigned by comparison of the ^{1}H NMR spectrum with that reported in the literature,[60] after conversion of the title compound into the protected-1,3-diol by ozonolysis/reduction/acetonide formation as shown below.

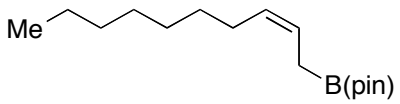


VII. Procedure for Five Gram Hydroboration (Scheme 1.23, eq. 16).

In the dry-box, a flame-dried 500-mL round-bottom flask equipped with a magnetic stir bar is sequentially charged with Ni(cod)$_2$ (259 mg, 0.94 mmol), PCy_3 (264 mg, 0.94 mmol), toluene (120 mL), HB(pin) (5.73 mL, 39.5 mmol), and *(E)*-deca-1,3-diene (5.2 g, 37.6 mmol). The flask containing the diene is rinsed with toluene (30 mL). The resulting red homogeneous solution is capped with a septum, removed from the glove box, and placed under a nitrogen atmosphere. The mixture is allowed to stir at room temperature for 1 h. The mixture is concentrated by rotary evaporation (20 mmHg, 40 ˚C) to a black

[60] Burke, E. D.; Gleason, G. L. *Org. Lett***. 2004**, *6*, 405.

oil. The intermediate allylic boronate ester (**132**) can be easily purified or oxidized in the same flask using the standard oxidation procedure. To isolate **132**, the brown residue is filtered through a short SiO_2 plug eluting with 40:1 hexanes:EtOAc. The filtrate is then concentrated by rotary evaporation to provide the boronate as a clear, colorless oil (336 mg, 94% yield). For **133**, after oxidation, the crude oil is purified by flash chromatography on SiO_2 eluting with 7:1 hexanes:EtOAc to afford **133** as a clear, colorless oil (5.51 g, 96% yield).



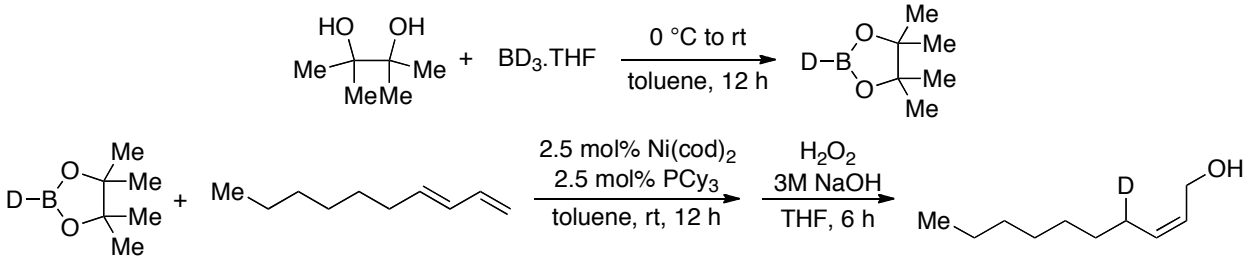
(*Z*)-2-(dec-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (132). ^{1}H NMR (500 MHz, $CDCl_3$: 7.26 ppm): d 0.87 (3H, t, *J* = 7.0 Hz, $CH_2C\mathbf{H_3}$), 1.19-1.34 (22H, m, $(C\mathbf{H_2})_5$ + $(C\mathbf{H_3})_4$), 1.65 (2H, d, *J* = 8.0 Hz, $C\mathbf{H_2}B$), 2.00 (2H, dt, *J* = 7.0 Hz, 7.0 Hz, $C\mathbf{H_2}CH{=}CH$), 5.38 (1H, dtd, *J* = 8.5 Hz, 7.0 Hz, 1.0 Hz, $CH{=}C\mathbf{H}CH_2B$), 5.48 (1H, dtd, *J* = 9.5 Hz, 8.0 Hz, 1.5 Hz, $C\mathbf{H}{=}CHCH_2B$); ^{13}C NMR (125 MHz, $CDCl_3$: 77.23 ppm): δ 14.2, 22.8, 24.9, 27.2, 29.4, 29.4, 29.7, 32.0, 83.2, 124.1, 130.1; IR (neat): 2978 (m), 2957 (s), 2855 (m), 1324 (s), 1145 (s), 968 (w), 848 (w); HRMS-(ESI+) for $C_{16}H_{32}BO_2$ [M+H]: calculated: 267.2495, found: 267.2505.

VIII. Procedure for Ni(II)-Catalyzed Hydroboration (Scheme 1.23, eq. 17).[41]

To a flame-dried 20-dram vial equipped with a magnetic stir bar was added $Ni(acac)_2$ (4.6 mg, 0.018 mmol) and PPh_3 (5.8 mg, 0.36 mmol). The vial was capped with a septum and purged with N_2, followed by the addition of **1.31** (100 mg, 0.72 mmol) in THF (2.81

mL). Pinacolborane (0.11 mL, 0.76 mmol) was then added and the reaction was allowed for 3 h at room temperature. The reaction mixture was cooled to 0 °C (ice/water) and charged with THF (1.5 mL), 3 M sodium hydroxide (1 mL), and 30% hydrogen peroxide (0.75 mL). The reaction was allowed to gradually warm to room temperature and stir for 12 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (1 mL) added drop-wise. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted 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 on silica gel (7:1 hexanes:ethyl acetate) to afford a clear, colorless oil (88.0 mg, 78%).

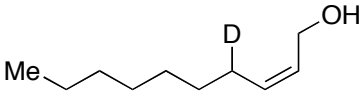
IX. Deuterium Labeling Experiment (Scheme 1.24).



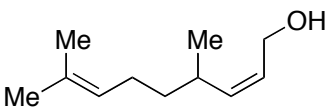
Deuterated pinacolborane was made in accordance with the literature[61] with a slight modification. To a solution of freshly recrystallized pinacol (59 mg, 0.5 mmol) in toluene (0.1 mL) in a 5 mL round-bottom flask equipped with a magnetic stir bar was added borane-d_3-THF 1.0 M complex (0.5 mL, 0.5 mmol) under nitrogen at 0 °C. The reaction was allowed to stir and warm to room temperature overnight. The solution was taken into

[61] Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.*, **2009**, *131*, 9612.

the dry-box and added to a oven-dried 6-dram vial equipped with a magnetic stir bar charged with $Ni(cod)_2$ (2.6 mg, 9.52 μmol), PCy_3 (2.6 mg, 9.52 μmol), (*E*)-deca-1,3-diene (69 mg, 0.5 mmol), and toluene (1.0 mL). The vial was sealed with a polypropylene cap, removed from the dry-box, and allowed to stir at room temperature for 12 h. The reaction was oxidized and worked-up in accordance with the representative procedure. The crude reaction mixture was purified on silica gel (7:1 hexanes:ethyl acetate) to afford a clear, colorless oil (10 mg, 13%). R_f=0.17 (7:1 hexanes:ethyl acetate, stain in PMA). The deuterium incorporation was determined to be 81% at C-4 by integration of the proton resonance at 1.91 ppm in C_6D_6 as assigned by HSQC of (*Z*)-dec-2-en-1-ol.



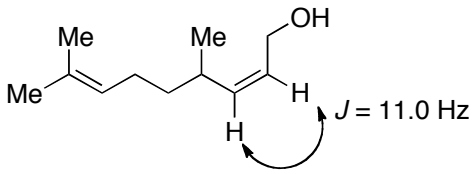
(*Z*)- dec-2-en-1-ol-4-d$_1$. ^{1}H NMR (500 MHz, C_6D_6): δ 0.90 (3H, t, *J* = 6.8 Hz, $CH_2C\mathbf{H_3}$), 1.21-1.36 (10 H, m, $(C\mathbf{H_2})_5$), 1.89-1.93 (1H, m, C**H**DCH=CH), 3.99 (2H, d, *J* = 6.4 Hz, $C\mathbf{H_2}OH$), 5.37-5.42 (1H, m, CHDC**H**=CH), 5.56 (1H, dddd, *J* = 10.8 Hz, 6.6 Hz, 6.6 Hz, 1.6 Hz, CH=C**H**CH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.5, 128.5, 58.9, 32.0, (29.8-non-deuterated), 29.7, (29.4-non-deuterated), 29.4, 29.4, (27.6-non-deuterated), 27.3 (t, J=15.3 Hz), 22.9, 14.3; IR (neat): 3314 (br w), 2956 (w), 2923 (m), 2855 (m), 1264 (s), 908 (m), 729 (s); HRMS-(ESI+) for $C_{10}H_{18}D$ [M-H_2O+H]: calculated: 140.15495, found: 140.15491.

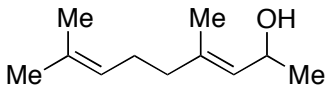


(*Z*)-4,8-dimethylnona-2,7-dien-1-ol (1.38-OH). The reaction was performed with the general procedure, but

allowed to stir for 12 h at 60 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (3H, d, *J* = 6.5 Hz, CHC**H$_3$**), 1.60 (3H, s, C**H$_3$**), 1.69 (3H, s, C**H$_3$**), 1.88-1.97 (2H, m, C**H$_2$**), 2.08-2.14 (2H, m, C**H$_2$**), 2.42-2.52 (1H, m, C**H**CH_3), 4.18 (2H, ddd, *J* = 7.0 Hz, 3.5 Hz, 1.5 Hz, C**H$_2$**OH), 5.07-5.13 (1H, m, C=C**H**CH_2CH_2), 5.31 (1H, dddd, *J* = 11.0 Hz, 10.0 Hz, 1.5 Hz, 1.5 Hz, C**H**=$CHCH_2OH$), 5.57 (1H, dddd, *J* = 11.0 Hz, 7.0 Hz, 7.0 Hz, 1.0Hz, CH=C**H**CH_2OH)); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.4, 131.8, 127.4, 124.6, 59.0, 37.5, 31.9, 25.9, 25.8, 21.6, 17.9; IR (neat): 3328 (br w), 2962 (s), 2925 (s), 1454 (w), 1006 (w); HRMS-(ESI+) for $C_{11}H_{19}$ [M-H_2O+H]: calculated: 151.14868, found: 151.14873. The crude reaction mixture contained a 1:1 inseparable mixture of (*Z*)-4,8-dimethylnona-2,7-dien-1-ol and (*E*)-4,8-dimethylnona-3,7-dien-2-ol. The two products were purified on silica gel (15:1 hexanes:ethyl acetate) to afford a clear, colorless oil (39.6 mg, 58%). R_f=0.23 (15:1 hexanes:ethyl acetate, stain in PMA). Product was separated from (*E*)-4,8-dimethylnona-3,7-dien-2-ol by selective protection of the primary alcohol with TBDPSiCl, followed by deprotection with TBAF.

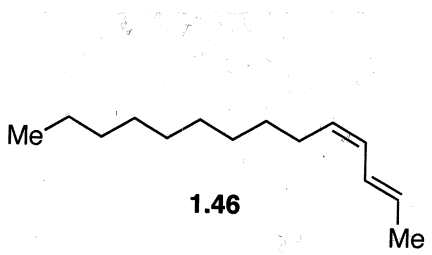
Proof of Stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below.



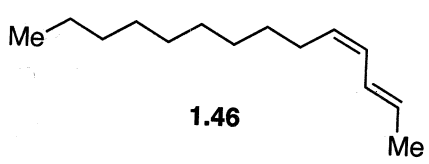


(*E*)-4,8-dimethylnona-3,7-dien-2-ol (1.38-OH-B). The reaction was performed with the general procedure, but

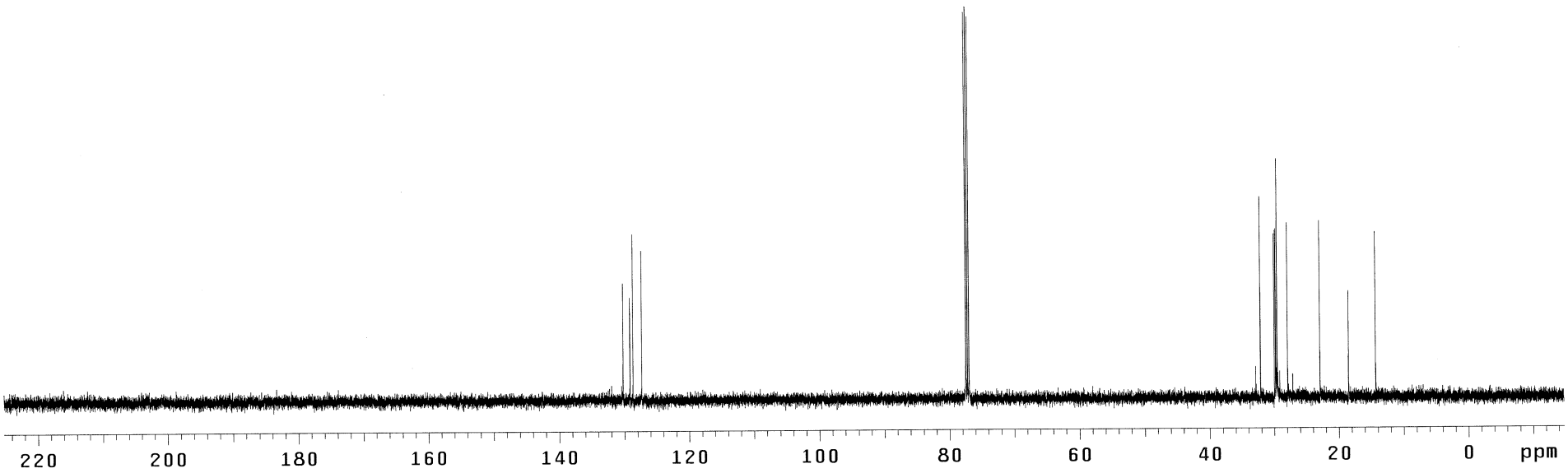
allowed to stir for 12 h at 60 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (3H, d, *J* = 6.0 Hz, CHOHC**H$_3$**), 1.33 (1H, br, O**H**), 1.61 (3H, s, C**H$_3$**), 1.69 (6H, d, *J* = 1.5 Hz, C**H$_3$**+C**H$_3$**), 1.99-2.02 (2H, m, C**H$_2$**), 2.08-2.40 (2H, m, C**H$_2$**), 4.59 (1H, dddd, *J* = 8.5 Hz, 6.0 Hz, 6.0 Hz, 6.0 Hz, C**H**OH), 5.08-5.11 (1H, m, C=C**H**CH_2), 5.23 (1H, ddd, *J* = 8.5 Hz, 1.5 Hz, 1.0 Hz, C=C**H**CHOH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 131.9, 129.3, 124.1, 65.0, 39.7, 32.8, 26.6, 25.9, 17.9, 16.6; IR (neat): 3328 (br w), 2962 (s), 2925 (s), 1454 (w), 1006 (w); HRMS-(ESI+) for $C_{11}H_{19}$ [M-H_2O+H]: calculated: 151.14868, found: 151.14873. The crude reaction mixture contained a 1:1 inseparable mixture of (*Z*)-4,8-dimethylnona-2,7-dien-1-ol and (*E*)-4,8-dimethylnona-3,7-dien-2-ol. The two products were purified on silica gel (15:1 hexanes:ethyl acetate) to afford a clear, colorless oil (39.6 mg, 58%). R_f=0.23 (15:1 hexanes:ethyl acetate, stain in PMA). Product was separated from (*Z*)-4,8-dimethylnona-2,7-dien-1-ol by selective protection of the primary alcohol with TBDPSiCl.

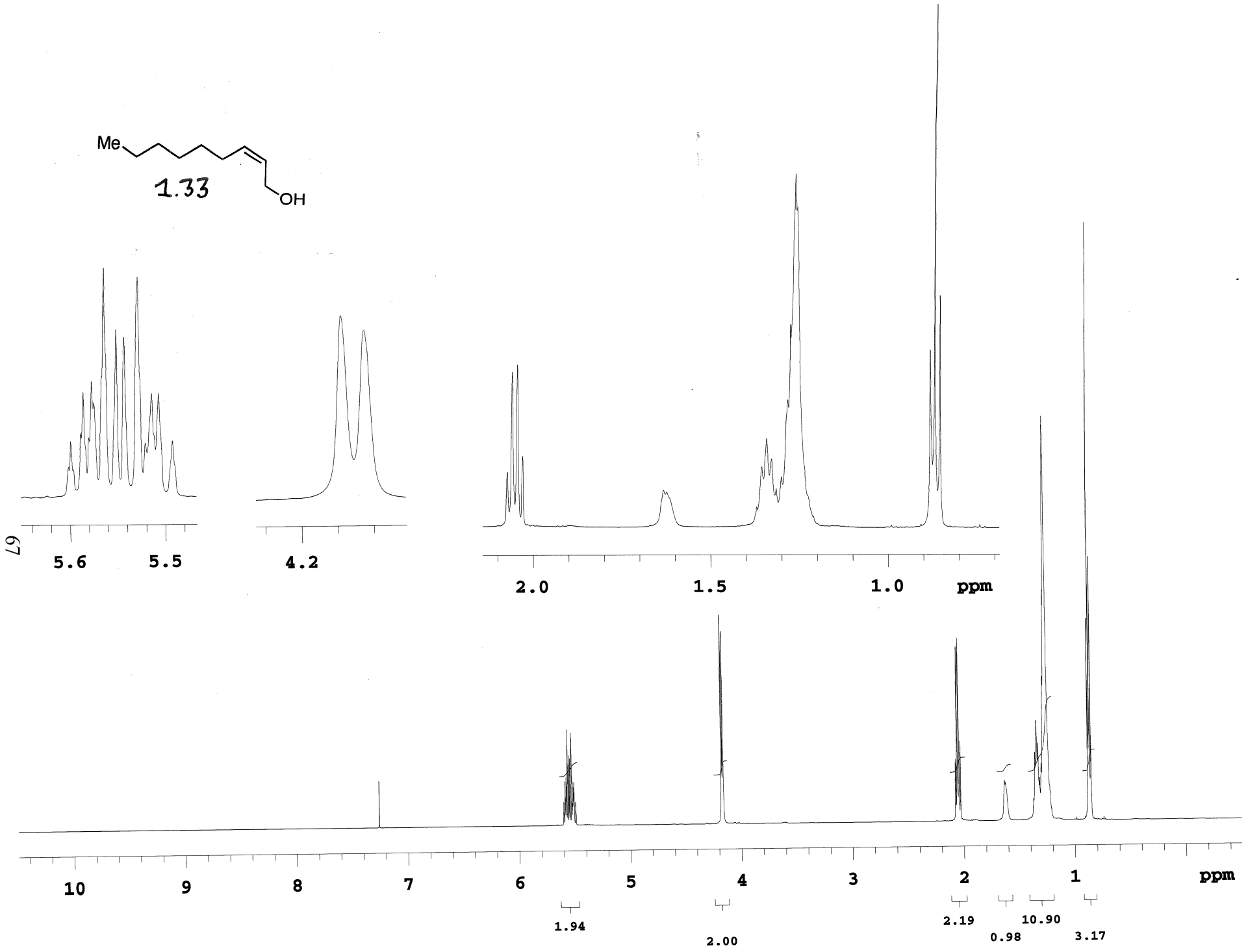


1.46



1.46

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1.33
OH
67
5.6
5.5
4.2
2.0
1.5
1.0
ppm
10
9
8
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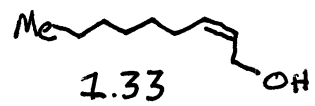
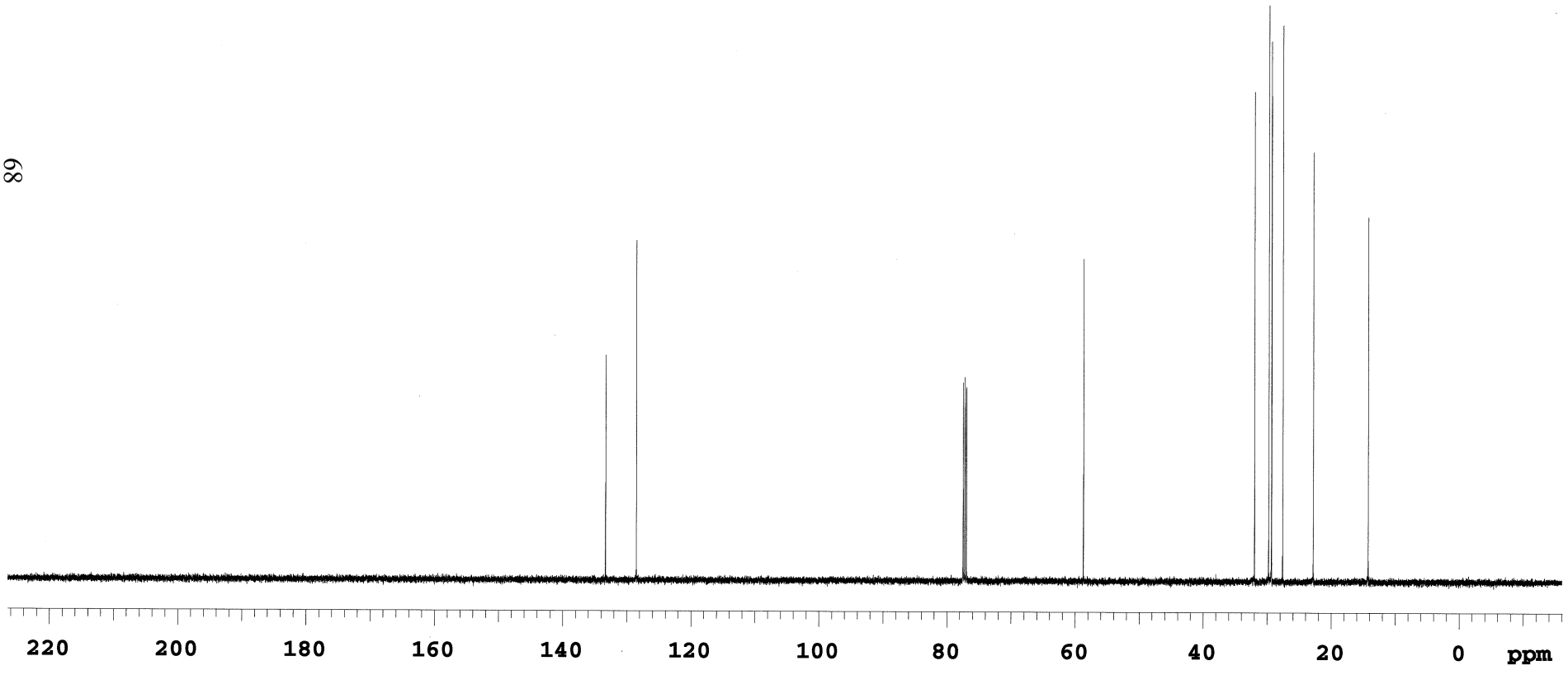
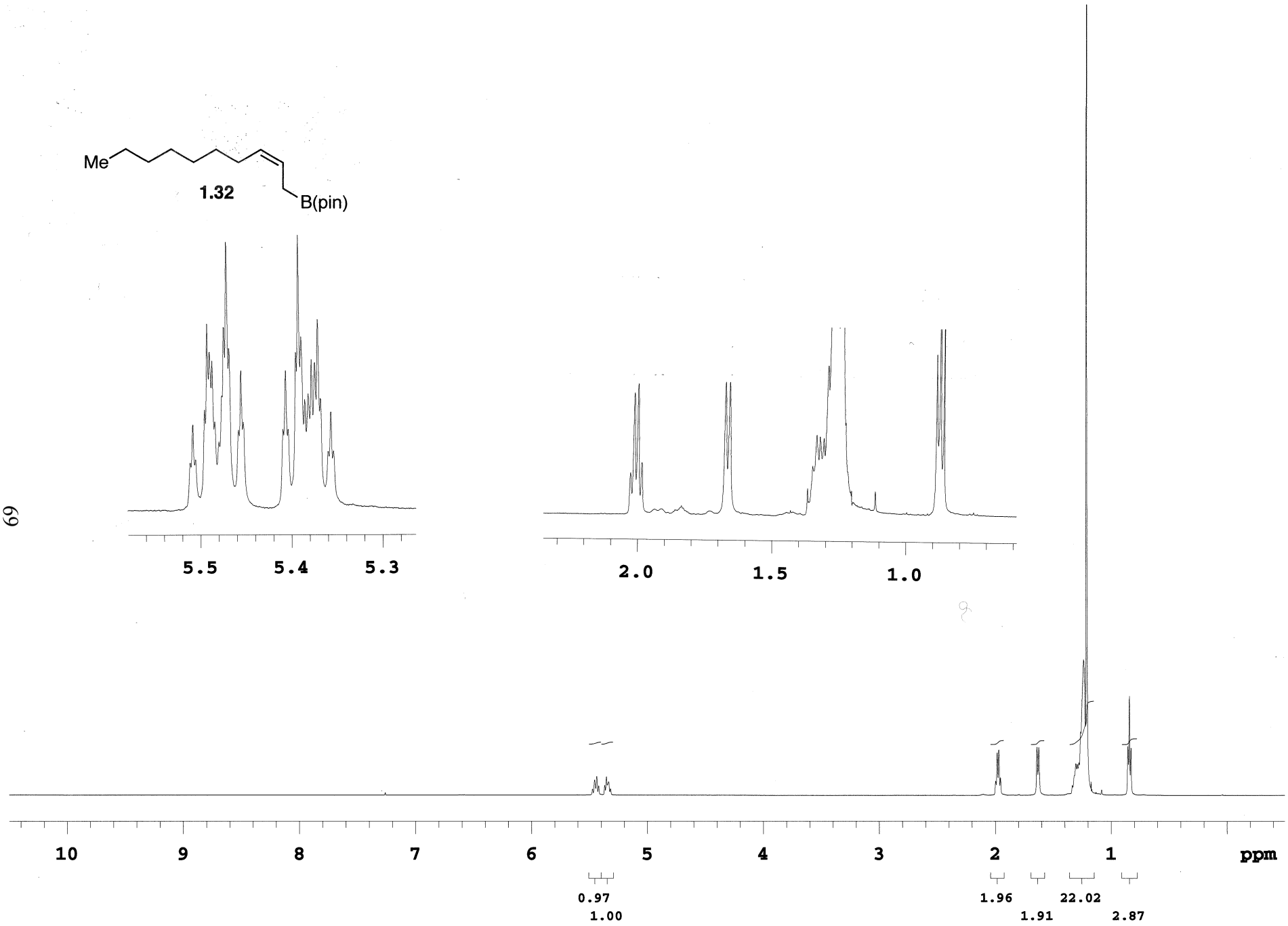
1.94
2.00
2.19
0.98
10.90
3.17

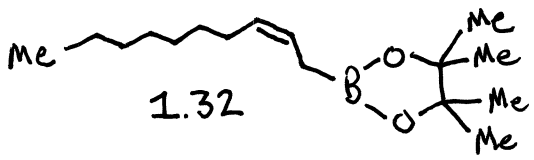


1.33

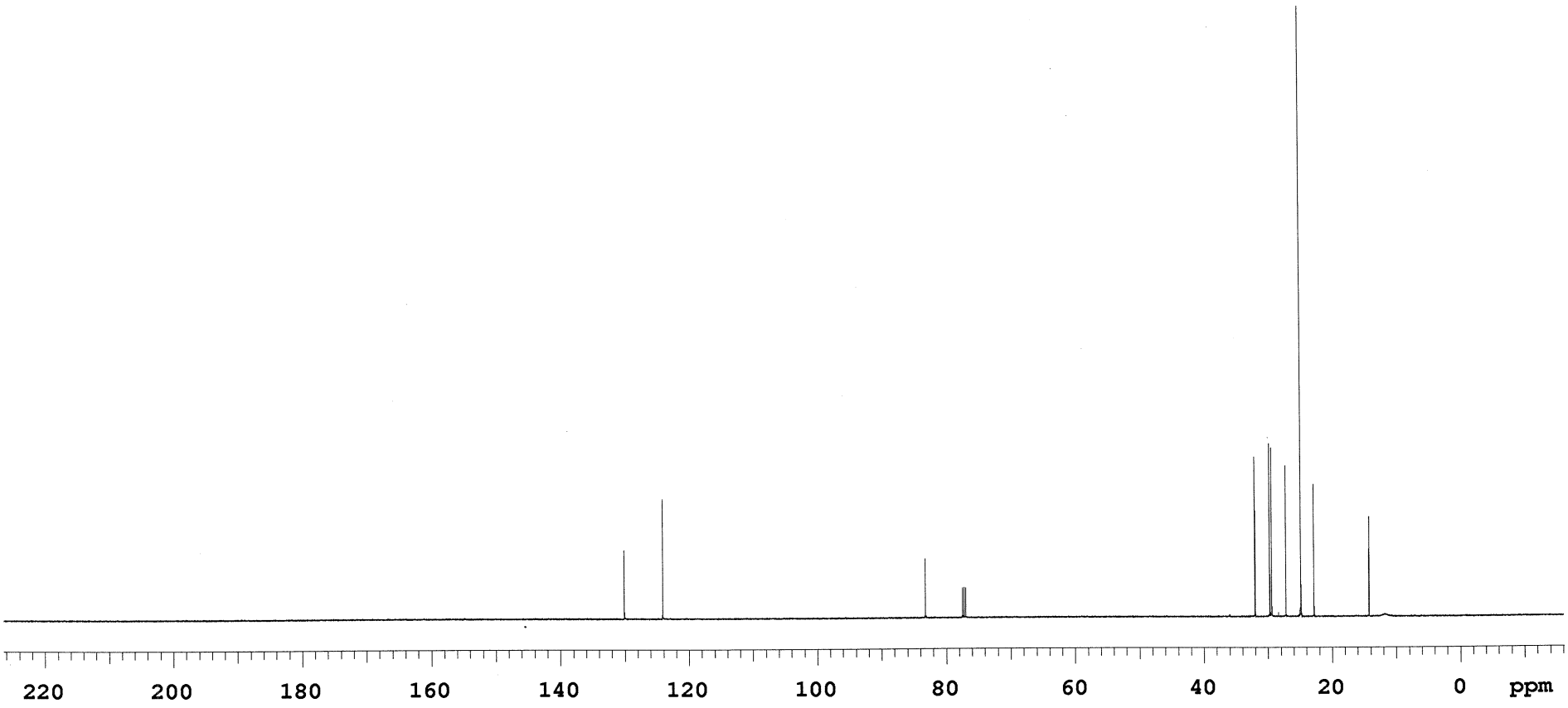
89




Me
1.32
B(pin)
5.5
5.4
5.3
2.0
1.5
1.0
10
9
8
7
6
5
4
3
2
1
ppm
0.97
1.00
1.96
1.91
22.02
2.87



1.32



Chapter 2

Development, Scope, and Utility of Nickel-Catalyzed 1,4-Diboration of 1,3-Dienes

2.1. Introduction

Conjugated dienes have had a rich history in Ni-catalysis. The Ni-catalyzed dimerization, oligomerization, and Diels-Alder reactions of butadiene and isoprene have been throughly studied.[1] More recently, a variety of Ni-catalyzed addition reactions across 1,3-dienes have been developed including hydrocyanation,[2] addition of activated methylenes,[3] hydroamination,[4] hydroarylation,[5] hydrovinylation,[6] carbostannylation,[7] and hydroboration.[8] While all of these transformations are Ni(0)-catalyzed, most were developed with a single transformation in mind, require different reaction conditions and have varying substrate limitations. Our research group has focused on the dimetallation

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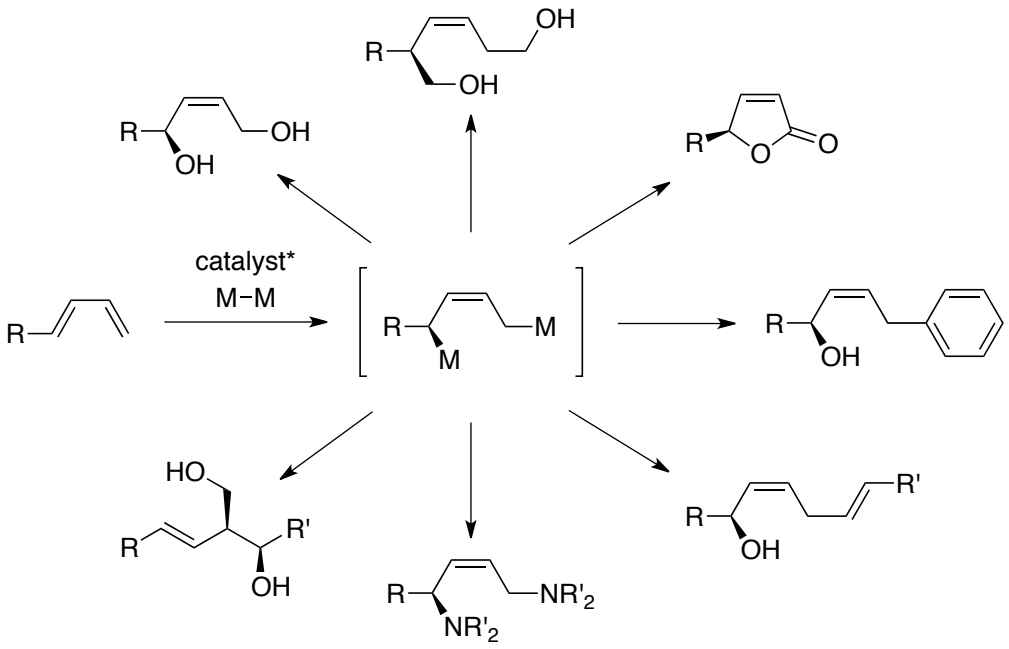
[1] Kimura, M.; Tamaru, Y. Reaction of Dienes and Allenes. In Modern Organonickel Chemistry; Tamaru, Y., Ed; Wiley-VCH: Weinheim, Germany, 2005; pp 137-170.
[2] (a) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313. (b) Tolman, C. A.; McKinney, R. J.; Seidel, W. C.; Druliner, J. D.; Stevens, W. R. Homogeneous Nickel Catalyzed Olefin Hydrocyanation. *Adv. Catal.* **1985**, *33*, 1. (c) Saha, B.; RajanBabu, T. V. *Org. Lett*. **2006**, *8*, 4657.
[3] Andell, O. S.; Bäckvall, J.-E.; Moberg, C. *Acta Chem. Scand. B*. **1986**, *40*, 184.
[4] Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc*. **2001**, *123*, 4366.
[5] Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, T. *Chem. Commun*. **2002**, 2210
[6] See ref. 5 and Page, J. P.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2012**, 134, 6556.
[7] Shirakawa, E.; Nakao, Y.; Yoshida, H.; Hiyama, T. J. *Am. Chem. Soc*. **2000**, *122*, 9030.
[8] (a) Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 2534. (b) Zaidlewicz, M.; Meller, J. *Tetrahedron Lett.* **1997**, *38*, 7279.

of 1,3-dienes to generate reactive dimetallated intermediates that can be used to access a diverse range of different products in a single step (Scheme 2.1). Specifically, the first enantioselective Pt-catalyzed 1,4-diboration of 1,3-dienes was developed in our laboratory to generate (*Z*)-bis(allyl)boronic esters. Despite the wealth of Ni-catalyzed additions to dienes, the addition of dimetallated reagents has been scarce. In this chapter, I will the describe development of the first nickel-catalyzed 1,4-diboration of 1,3-dienes.

Scheme 2.1. Dimetallation of Dienes to Access a Variety of Products



2.2. Background

The first example of a Ni-catalyzed dimetallation of a 1,3-diene was reported by Kumada in 1973, which described the 1,4-addition of *sym*-tetramethyldisilane (**2.1**)

across butadienes in low to moderate yields (eq. 1, Scheme 2.2).[9] The low yields were attributed to hydrosilyation byproducts. The authors did not describe the stereoselectivity of the reaction or the synthetic utility of the products. More recently, Suginome and Ito described the Ni-catalyzed addition of silylborane **2.2** across 1,3-dienes in a 1,4-fashion (eq. 2, Scheme 2.2).[10] The silaboration requires two equivalents of the diene, but generates (*Z*)-4-boryl-1-silyl-2-alkenes in excellent stereoselectivities and yields. Unfortunately, unsymmetrical dienes gave mixtures of regioisomers. Additionally, acyclic internal 1,3-dienes and 1,1-disubstituted dienes did not react. The silylboration of cyclic dienes, however, proceeded in the presence of the sterically congested ligand cyclohexyl (diphenyl)phosphine to provide *cis*-4-boryl-1-silyl-2-cycloalkenes in high yield and stereoselectivity (eq. 3, Scheme 2.2). Silaboration of dienes can also be catalyzed by Pt (0),[11] and has been accomplished in a non-racemic fashion on cyclohexadiene by Moberg.[12] These products have been utilized in stereo- and chemoselective allylborations of aldehydes.

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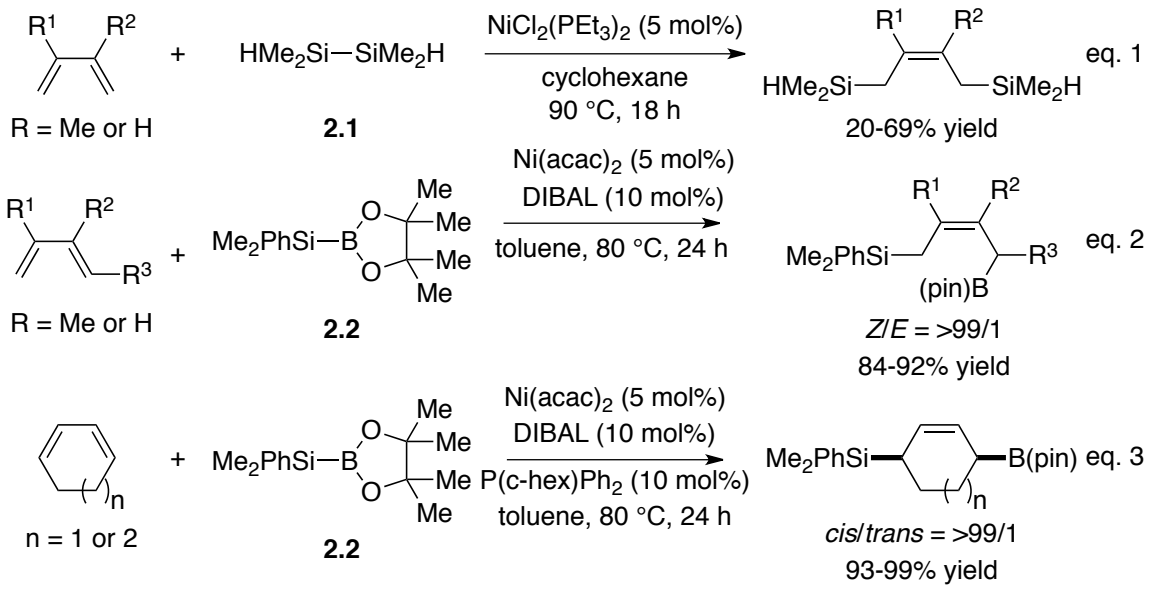
[9] (a) Okinoshima, H.; Yamamoto, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9263. (b) Jzang, T. T.; Liu, C.-S. *Main Group Met. Chem.* **1987**, *10*, 373. (c) Ishikawa, M.; Nishihara, Y.; Sakamoto, H.; Ono, T.; Oshita, J. *Organometallics* **1992**, 11, 483. (d) Obora, Y.; Tsuji, Y.; Kakehi, T.; Kobayashi, M.; Shinkai, Y.; Ebihara, M.; Kawamura, T. J. Chem. Soc., Perkin Trans. 1 **1995**, 599.

[10] (a) Suginome, M.; Matsuda, T.; Yoshimoto, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1567. (b) Suginome, M.; Ito, Y. *J. Organomet. Chem.* **2003**, *680*, 43.

[11] (a) Suginome, M.; Nakamura, H.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4248.

[12] (a) Gerdin, M.; Moberg, C. *Adv. Synth. Catal.* **2005**, *347*, 749. (b) Gerdin, M.; Penhoat, M.; Zalubovskis, R.; Pétermann, C.; Moberg, C. *J. Organomet. Chem.* **2008**, *693*, 3519.

Scheme 2.2. Ni-Catalyzed Silaboration of 1,3-Dienes



A variety of other transition metal-catalyzed dimetallations of 1,3-dienes have been reported in the literature that employ distannanes, silylgermanes, and borylstannanes as dimetallating agents.[13] The known transformations of silicon,[14] tin,[15] and germanium,[16] however, are limited to protonation, oxidation, and a few examples of cross coupling. In order for dimetallation to be a synthetic tool, the carbon-metal bond must be easily

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

[14] For a review see: (a) Jones G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599. (b) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809; (c) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett*. **2005**, *7*, 2405; (c) Honda, M.; Mikami, Y.; Sanjyo, T.; Segi, M.; Nakajima, T. *Chem. Lett.* **2005**, *34*, 1432.

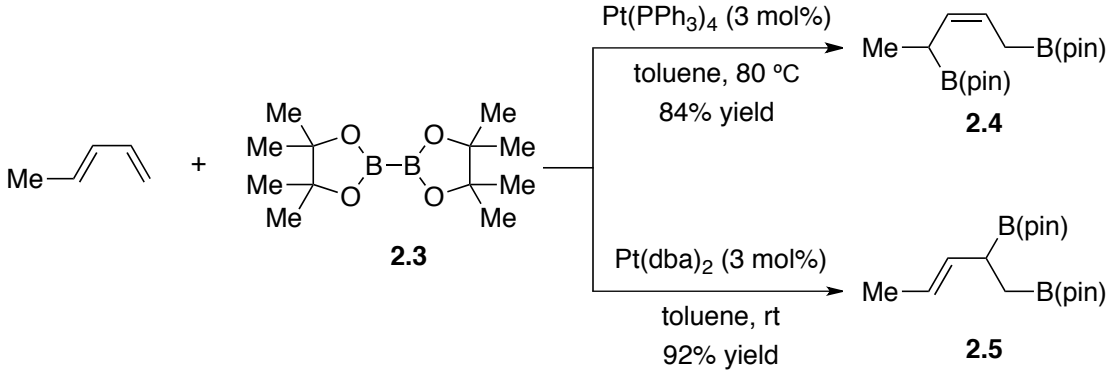
[15] (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. "Tin in Organic Synthesis," Butterworth, London (1987). (b) Davies, A. G. "Organotin Chemistry," VCH, Weinheim (1997).

[16] (a) *The Chemistry of Organic Germanium, Tin and Lead Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1995; Vol. 1 and 2002; Vol 2. (b) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth*. **2004**, *1*, 211(c) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P.; Tseng, C.-C.; de Fraine, P.; Parr, N. J.; Scicinski, J. *J. Appl. Organomet. Chem*. **2007**, *21*, 572.

transformed to a variety of functional groups. For example, diboron reagents allow for a wide array of further transformations, and are both non-toxic and inexpensive.[17]

The first example of the addition of a diboron reagent to 1,3-dienes was reported by Miyaura and co-workers utilizing bis(pinacolato)diboron (**2.3**).[18] The regioselectivity of the Pt-catalyzed reaction was highly dependent on the ligand, as shown in Scheme 2.3. The diboration of *trans*-1,3-pentadiene with 3 mol% $Pt(PPh_3)_4$ selectively added **2.3** across the diene in a 1,4-fashion providing the (*Z*)-1,4-bis(boronic)ester, **2.4**, in 84% yield. In the absence of a phosphine ligand, 1,2-diboration of the terminal alkene was the predominant pathway, providing **2.5** in 92% yield.

Scheme 2.3. Non-Enantioselective Diboration of 1,3-Dienes

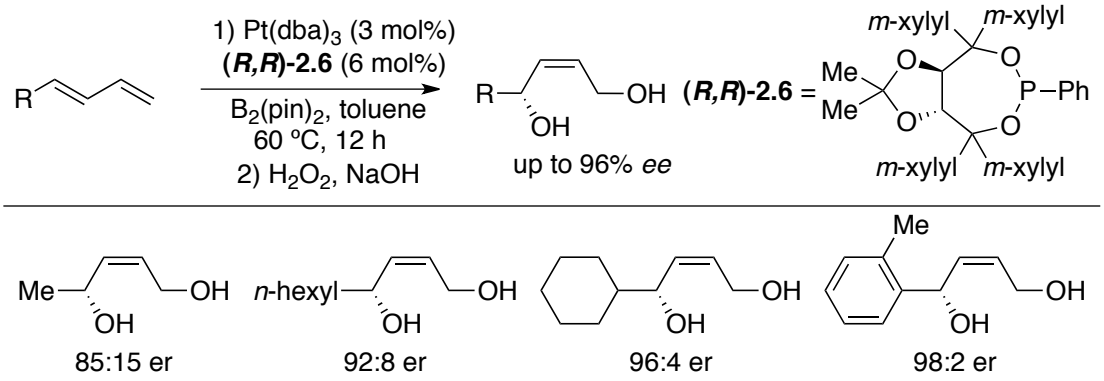


The first enantioselective Pt-catalyzed 1,4-diboration of 1,3-dienes was developed in our laboratory, utilizing $Pt(dba)_3$ and TADDOL-derived phosphonite ligands (**2.6**,

[17] See Chapter 1, section 1.1 and references within for a thorough discussion.
[18] (a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1996**, 2073. (b) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689.

Scheme 2.4).[19] The 1,4-diol products that result after oxidation represent the first example of synthetically useful enantioselectivities in the 1,4-dihydroxylation of 1,3-dienes.[20] The enantioselectivities ranged from 85:15-98:2 er for terminal acyclic- and cyclic dienes. The lower enantioselectivities were observed with acyclic straight-chained alky-substituted dienes.

Scheme 2.4. Enantioselective Pt-Catalyzed 1,4-Diboration of 1,3-Dienes



In order to increase the enantioselectivities for straight-chain alkyl-dienes in the Pt-catalyzed 1,4-diboration, a new phosphine ligand scaffold was developed in our

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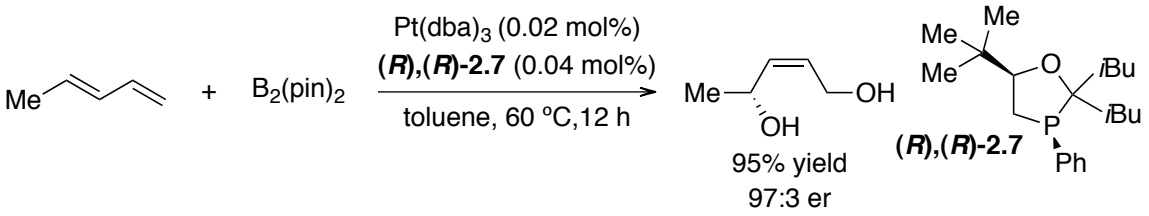
[19] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.

[20] For recent applications of the singlet oxygen [4+2] cycloaddition in synthesis, see: (a) Lee, J. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2005**, *127*, 13122. (b) Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901. (c) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2020. (d) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811. (e) Zhou, G.; Gao, X.; Li, W. Z.; Li, Y. *Tetrahedron Lett.* **2001**, *42*, 3101. (f) Izzo, I.; Meduri, G.; Avallone, E.; De Riccardis, F.; Sodano, G. *Eur. J. Org. Chem.* **2000**, 439. (g) For recent reviews, see: (h) Clennan, E. L.; Pace, A. *Tetrahedron* **2005**, *61*, 6665. For a recent review on diacetoxylation: Bäckvall, J.-E. Palladium-Catalyzed 1,4-Additions to Conjugated Dienes. In *Metal Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 479-529.

laboratory by Christopher Schuster.[21] The 1,3-oxaphospholanes (termed OxaPhos) are readily available from enantiopure epoxides, primary phosphines, and ketones or ketals. The optimized ligand **2.7** increases the enantioselectivity of the Pt-catalyzed 1,4-diboration of *trans*-1,3-pentadiene from 85:15 er with the TADDOL-phosphonite to 97:3 er. The enantioselectivities for a variety of acyclic terminal dienes were >96:4 er, and the catalyst loading could be dropped to as low as 0.02 mol% without erosion of enantioselectivity or yield (Scheme 2.5).

Scheme 2.5. Pt-Catalyzed 1,4-Diboration of 1,3-Dienes with OxaPhos Ligand

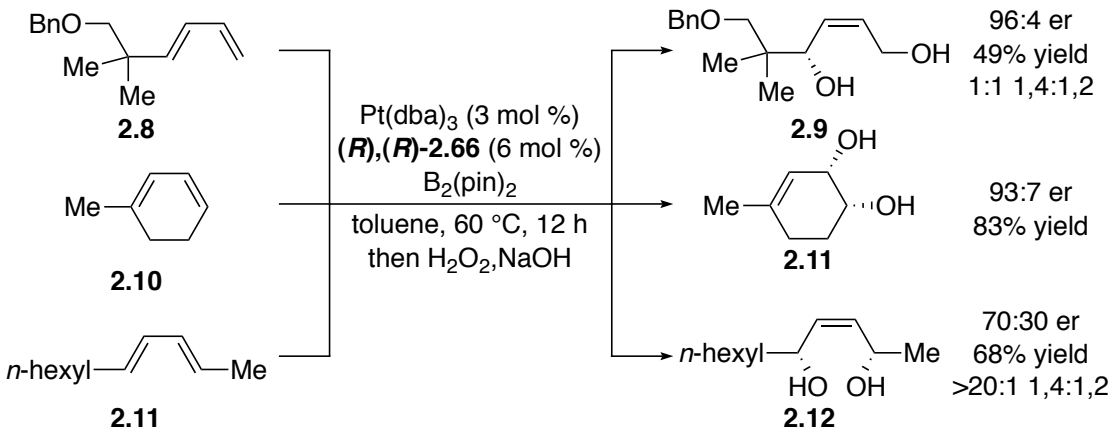


There are still unresolved problems with the Pt-catalyzed 1,4-diboration of 1,3-dienes. The diboration of 1,3-dienes containing sterically encumbered centers adjacent to the diene suffer lower 1,4-selectivities due to a 1,2-diboration pathway that starts to compete. For example, when diene **2.8** was submitted to the optimized diboration conditions, the 1,4-diol **2.9** was isolated with excellent enantioselectivity but in only 48% yield because the 1,4:1,2-selectivity was 1:1 (Scheme 2.6). The increased steric size adjacent to C4 of the diene makes carbon-boron bond formation more difficult, resulting

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

in competing 1,2-diboration. This was also the case with cyclic dienes that contain disubstitution at one end of the diene, as observed in the diboration of **2.10**. While the 1,2-diol **2.11** was isolated in good enantioselectivity and yield, the 1,4-product was not observed (Scheme 2.6). Internal dienes present an interesting class of substrates that have just begun to be studied in detail in our laboratory. It was recently discovered that diboration of internal diene **2.11** was completely 1,4-selective, and provided the internal 1,4-diol **2.12** in moderate yield upon oxidation. Unfortunately, the enantioselectivity was not synthetically useful (Scheme 2.6).[22]

Scheme 2.6. Problematic Dienes in Pt-Catalyzed 1,4-Diboration

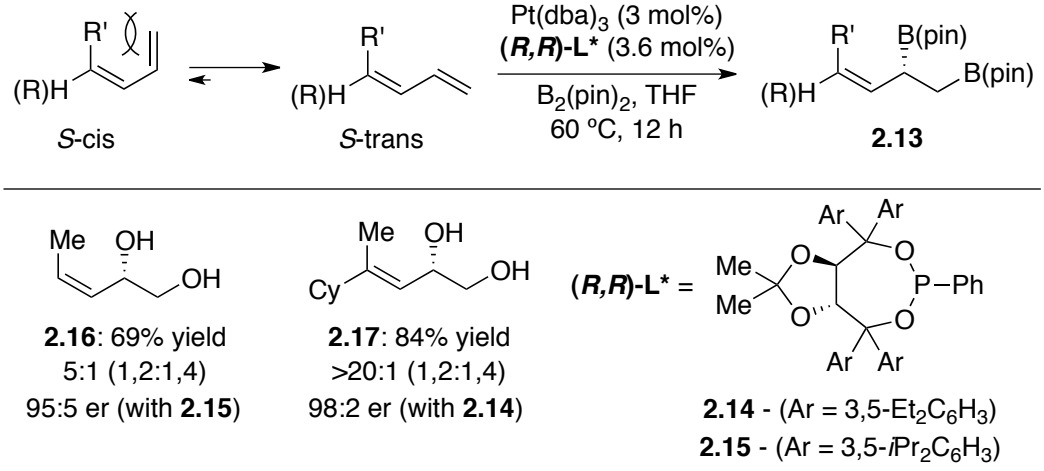


During the studies of the Pt-catalyzed 1,4-diboration of 1,3-dienes it was found that the diboration of *cis*-dienes and 1,1-disubstituted dienes did not provide the 1,4-

[22] Unpublished results by Dr. Laura T. Kliman and John R. Coombs.

diboration product, but instead, were 1,2-selective.[23] These dienes suffer $A^{1,3}$-strain in the *S*-cis conformation; thus, these substrates predominantly exist in the *S*-trans conformation (Scheme 2.7). The proposed mechanism for the Pt-catalyzed 1,4-diboration of dienes requires the diene to adopt the *S*-cis conformation for 1,4-selectivity. The 1,2-diboration of *cis*- and 1,1-disubstituted dienes was further studied and high enantioselectivity for the diboration of *cis*-1,3-pentadiene (**2.16**) was achieved with ligand **2.14**, while ligand **2.15** was optimal for 1,1-disubstituted dienes. The 1,2-bis(boronic)ester intermediates (**2.13**) are excellent aldehyde allylation reagents, or can be oxidized to allylic 1,2-diols. While these substrates are very valuable for polyketide synthesis, the development of a catalyst that remains 1,4-selective for sterically hindered- or *c*is-1,3-dienes would compliment the 1,2-diboration reactions and further broaden the scope of diene diboration.

Scheme 2.7. Pt-Catalyzed 1,2-Diboration of *Cis*-and 1,1-Disubstituted Dienes



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

The first example of a Ni-catalyzed 1,4-diboration of a diene was discovered in our laboratory by Hee Yeon Cho. During her studies on the borylative coupling of aldehydes and dienes, she found that $Ni(cod)_2$ in the presence of PCy_3, could couple an aldehyde, a 1,3-diene, and $B_2(pin)_2$ to form 1,5-diols (**2.18**, upon oxidation) with high diastereoselectivity (eq. 4, Scheme 2.8).[24] The diastereo- and regioselectivity of this reaction could arise from a Ni-catalyzed 1,2-diboration of the 1,3-diene (**2.19)**, followed by aldehyde allylation (**2.20**) and oxidation (eq. 4, Scheme 2.8). To determine if this was the operative mechanism, the aldehyde was omitted from the reaction, and it was discovered that $Ni(cod)_2$ catalyzed the 1,4-diboration of *trans*-1,3-pentadiene (**2.21**), not 1,2-diboration, suggesting another mechanistic pathway for the 3-component borylative coupling (eq. 5, Scheme 2.8). Further studies were warranted considering that the reaction resulted in a single regio- and stereoisomer, and employed commercially available, inexpensive starting materials.

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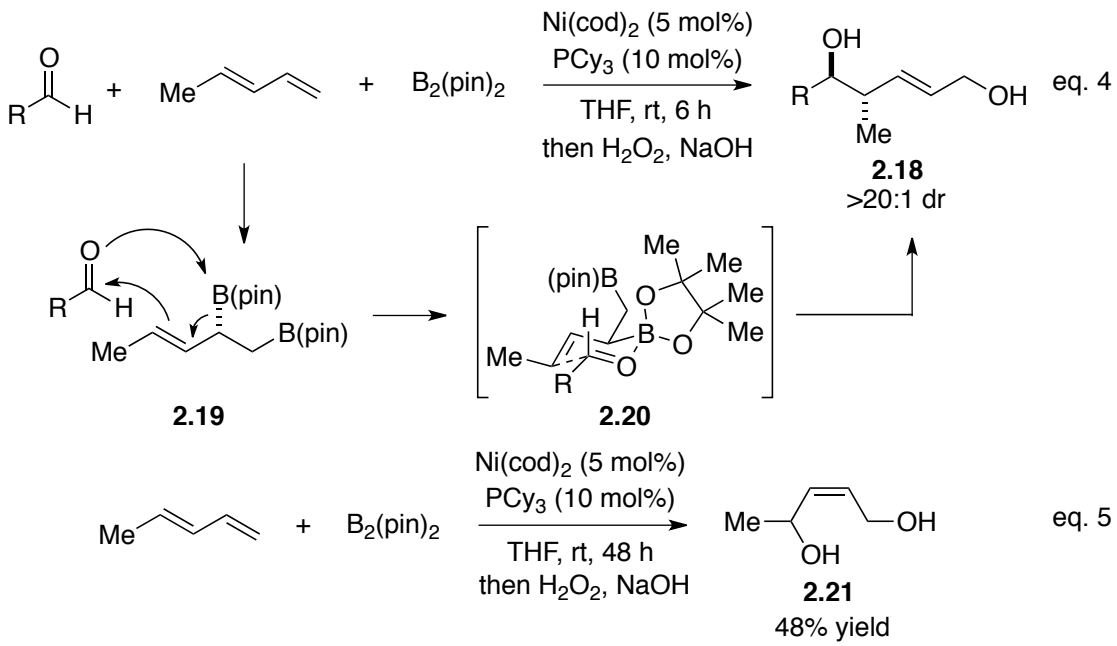
[24] (a) Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc.* **2008***, 130,* 16140. (b) Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc.* **2010***, 132,* 7576.

Scheme 2.8. First Example of Ni-Catalyzed 1,4-Diboration of 1,3-Dienes



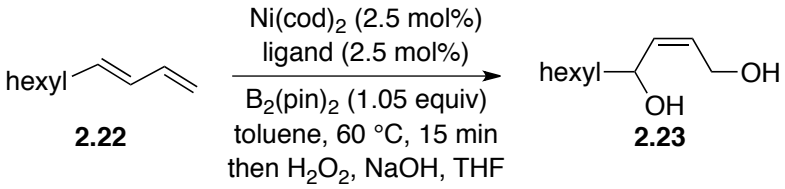
2.3. Development of Nickel-Catalyzed 1,4-Diboration of 1,3-Dienes[25]

The discovery that $Ni(cod)_2$ catalyzed the 1,4-diboration of 1,3-dienes prompted me to further investigate the reaction and determine if this new diboration catalyst could be complimentary to the Pt-catalyzed variants developed in our laboratory. My investigation began with analyzing ligand effects on the diboration reaction. As depicted in Scheme 2.9, the diboration of *trans*-1,3-decadiene (**2.22**) was examined in the presence of 2.5 mol% $Ni(cod)_2$ and a near-stoichiometric quantity of $B_2(pin)_2$. It was found that strongly donating monodentate phosphine ligands, including tricyclohexylphosphine (PCy_3) and hexamethylphosphorous triamide (HMPT), catalyze complete conversion to

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

the 1,4-bis(boronic)ester at 60 °C in only 15 min; oxidation delivered the (*Z*)-1,4-diol (**2.23**) in good yields (entries 1 and 2, Scheme 2.9). Less donating ligands such as triphenylphosphine (PPh_3), triethyl phosphite ($P(OEt)_3$), and cyclooctadiene (cod), were ineffective (entries 3-5, Scheme 2.9).

Scheme 2.9. Ligand Effects in the Ni-Catalyzed 1,4-Diboration of 1,3-Dienes



entry	ligand	% yield[b]
1	**PCy_3**	**83**
2	$P(NMe_2)_3$	83
3	PPh_3	8
4	$P(OEt)_3$	<5
5	-	<5

[a] Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Value is an average of two experiments.

A variety of terminal 1,3-dienes were submitted to the optimal reaction conditions with PCy_3 as ligand (Table 2.1). As represented in entries 1 and 2, substrates with alkyl and phenyl substitution were converted to the 1,4-diol, after oxidation, in high yield and stereoselectivity. Multiply substituted dienes react to provide the (*Z*)-trisubstituted alkene in excellent stereocontrol (entries 3-5). In contrast to Pt-catalyzed 1,4-diboration of dienes, the multiply substituted diene in entry 5 was converted exclusively to the 1,4-diol

in good yield (no reaction is observed with Pt-catalysis).[26] Notably, benzyl- and silyl ethers are well tolerated in the reaction (entries 6 and 7); however, an allylic silyl ether was incompatible with the reaction conditions (entry 8). The known proclivity for Ni(0) to form π-allyl complexes with allylic ethers may explain this result.[27] As shown in entry 6, complete 1,4-selectivity was maintained even when a quaternary center was adjacent to the diene, and the 1,4-diol was isolated in excellent yield (Pt-catalyzed diboration resulted in a 1:1 mixture of 1,4- and 1,2-diol, see Scheme 2.6).[13]

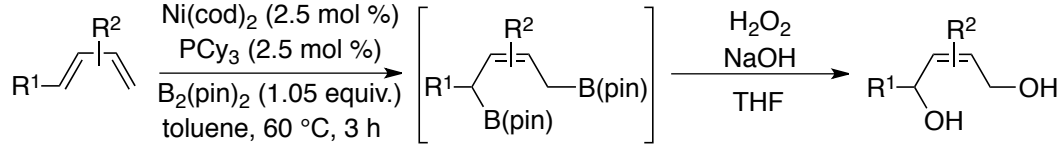
Similar to Pt-catalyzed diboration, only dienes able to adopt the *S*-cis conformation participate in 1,4-diboration. An $A^{1,3}$-interaction destabilizes the *S*-cis conformation of the substrate in entry 9 and the reaction does not proceed. Unlike Pt-catalyzed diboration, no 1,2-diboration was observed.[16,17] 1,2-Diboration was also not observed with styrene as substrate in the Ni-catalyzed diboration, suggesting that the reaction is selective for 1,3-dienes. Interestingly, the highly substituted diene in entry 5 possesses offsetting $A^{1,3}$-interactions in the *S*-cis and *S*-trans conformations allowing the diene to react efficiently.

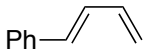
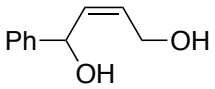
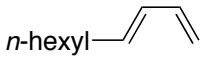
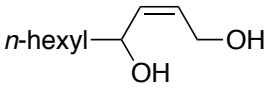
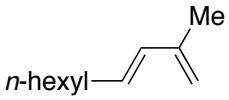
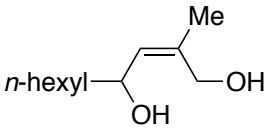
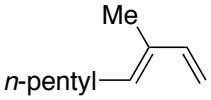
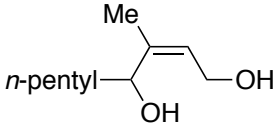
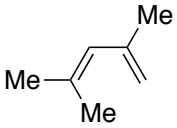
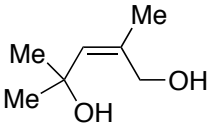
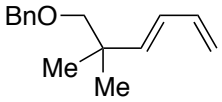
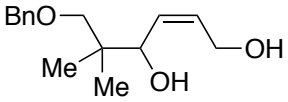
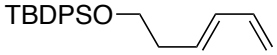
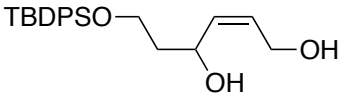
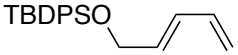
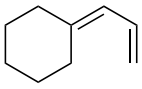
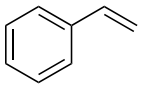
---

[26] Unpublished results with Dr. Laura T. Kliman.

[27] For early examples: (a) Eisch, J. J.; Im, K. R. *J. Organomet. Chem.* **1977**, *139*, C45. (b) Hayashi, T.; Konishi, M.; Yokota, K.; Humada, M. *Chem. Commun.* **1981**, 313. (c) Yamamoto, T.; Ishizu, J.; Yamamoto, A. *J. Am. Chem. Soc*. **1981**, *103*, 6863.

Table 2.1. Ni-Catalyzed Diboration Substrate Scope: Terminal Dienes

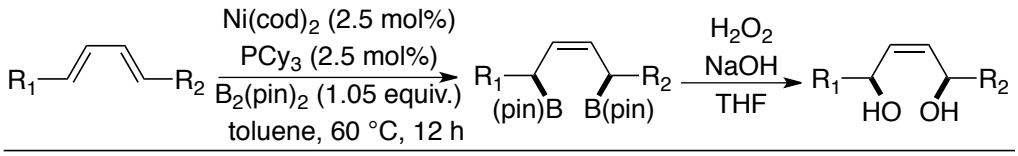


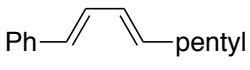
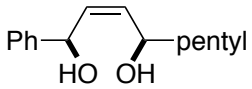
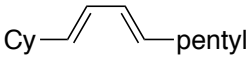
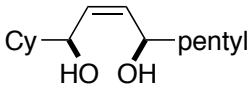
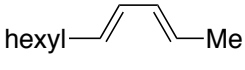
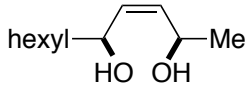
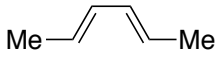
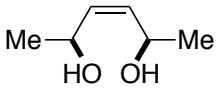
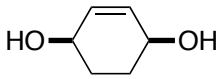
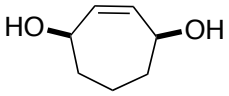
entry	diene	product	% yield[b]
1			84[c]
2			84
3			88
4			94
5			71[e]
6			88
7			95[d]
8		N.R.	-
9		N. R.	-[e]
10		N.R.	-[e]

[a] Reactions were conducted at a concentration of 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Values are an average of two experiments. [c] 1 Mol % $Ni(cod)_2$ and 1 mol % PCy_3 employed for this reaction. [d] Oxidation carried out with 30% H_2O_2 and pH=7 phosphate buffer. [e] Reaction time of 12 hours.

At the time I was investigating Ni-catalyzed diboration, the diboration of internal dienes had not yet been studied. To learn if Ni-catalysis could effectively expand the scope of diene diboration, a series of internal dienes were submitted to the Ni-catalyzed diene diboration conditions. It was quickly determined that longer reaction times were required to obtain full conversion, but with this modification, a series of internal acyclic dienes proved to be active participants in the diboration (Table 2.2). The reaction was completely regio- and stereoselective, providing the (*Z*)-*syn*-1,4-diol in good yields for substrates with aliphatic and aromatic substituents (entries 1-4). Cyclic dienes, known to be excellent substrates for enantioselective Pt-catalyzed 1,4-diboration,[16] also participated in the Ni-catalyzed diboration, but with moderate yields (entries 5 and 6).

Table 2.2. Ni-Catalyzed Diboration Substrate Scope: Internal/Cyclic Dienes



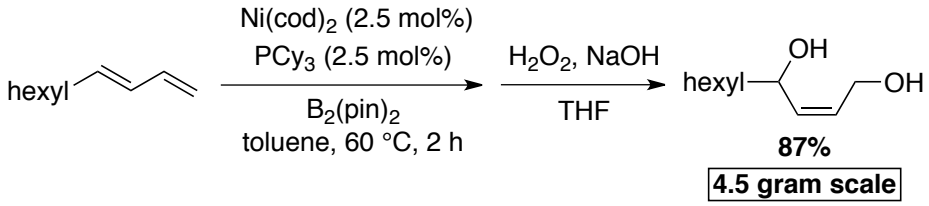
entry	diene	product	% yield[b]
1			77
2			66
3			72
4			74
5			47
6			44

[a] Reactions were conducted at a concentration of 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Values are an average of two experiments.

An advantage of the Ni-catalyzed diboration compared to other diboration systems is the commercial availability of the reagents and the relatively low price of the catalyst ($Ni(cod)_2$ = \$6/mmol vs. K_2PtCl_4 (Pt-catalyst precursor) = \$25/mmol). This renders large scale diboration reactions practical. To test the feasibility of a multi-gram scale Ni-catalyzed diboration, 4.5 grams of 1,3-decadiene was submitted to the optimized

diboration conditions (Scheme 2.10). The reaction proceeded efficiently and delivered the 1,4-diol, after oxidation, in excellent yield. Purification of the product on multi-gram scale was greatly aided by subjection of the crude reaction mixture to three equivalents of sodium periodate ($NaIO_4$); this procedure effectively removes pinacol, which was the only byproduct of the reaction.

Scheme 2.10. Multi-Gram Scale Ni-Catalyzed Diene Diboration

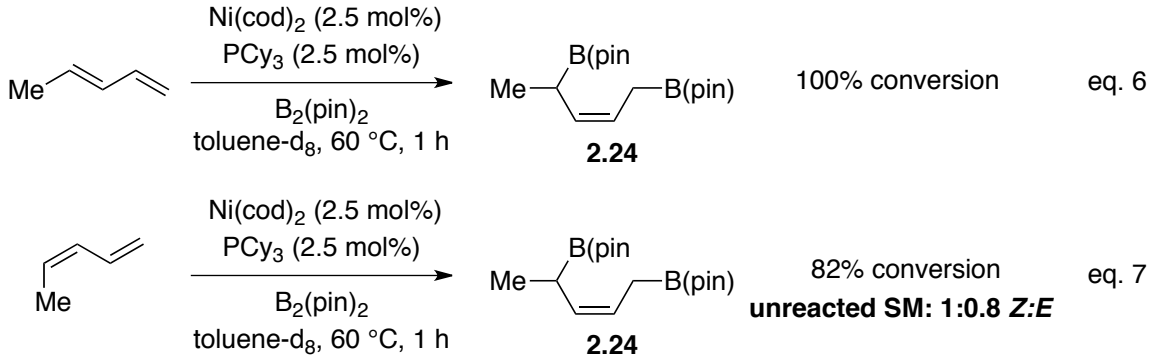


2.4. Mechanistic Discussion for the Ni-Catalyzed 1,4-Diboration of 1,3-Dienes

The Ni-catalyzed diboration of 1,3-dienes has proven to be a great compliment to the Pt-catalyzed diboration developed in our laboratory, providing higher 1,4-diboration selectivities for several substrates. It has been of interest to determine the mechanism of the reaction, specifically, why the reaction was 1,4- and (*Z*)-selective. The lack of reactivity of the 1,1-disubstituted diene from Table 2.1, entry 9, suggested that only dienes that can access the *S*-cis conformation can react. To further probe this hypothesis, the progress of the diboration of *cis*- and *trans*-1,3-pentadiene was followed by ^{1}H NMR. After 1 hr, the diboration of *trans*-1,3-pentadiene had gone to complete conversion to the

1,4-bis(boronic)ester **2.24** (eq. 6, Scheme 2.11). In contrast, the diboration of *cis*-1,3-pentadiene only went to 82% conversion to **2.24**, and the remaining starting material was a 1:0.8 mixture of *cis*- and *trans*-1,3-pentadiene (eq. 7, Scheme 2.11). This result suggests that *cis*-dienes can participate in 1,4-diboration under Ni-catalysis, but they do so at a slower rate and might involve prior Ni-catalyzed isomerization to the *trans*-isomer before diboration occurs.

Scheme 2.11. Comparison of the Diboration of *Cis*- and *Trans*-1,3-Pentadiene

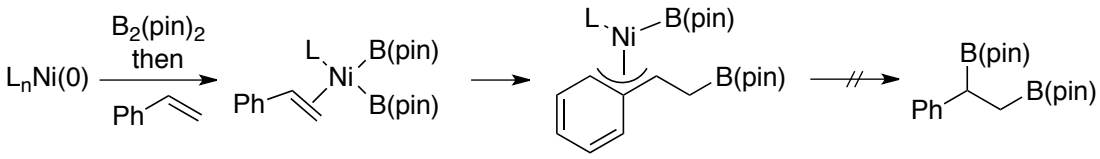


The commonly accepted mechanism for diboration of unsaturated hydrocarbons for group 10 metals involves initial oxidative addition of the diboron reagent, followed by alkene coordination. Subsequent insertion into the metal-boron bond with concomitant π-allyl formation, followed by reductive elimination provides the product.[28] The observation that styrene was unreactive suggests that this pathway may not be operative

[28] (a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1996**, 2073. (b) Clegg, W.; Thorsten, J.; Marder, T. B.; Norman, N. C.; Orpen, A. G.; Peakman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem.* Soc., Dalton Trans. **1998**, 1431. (c) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.

for Ni-catalyzed diboration since a Ni-π-benzyl complex could be formed and subsequently deliver the 1,2-bis(boronic ester) (Scheme 2.12).[29]

Scheme 2.12. Mechanism for Diboration of Vinylarenes



A mechanism that could explain the reactions selectivity for dienes involves initial coordination or oxidative addition of Ni(0) to the diene to form either η4-nickel diene complex **2.25** [30] or nickelacycle **2.26**. [31] Subsequent reaction with $B_2(pin)_2$ would result in formation of the least hindered nickel-carbon bond (**2.28)** and reductive elimination provides the 1,4-bis(boronic)ester. This mechanism would account for the high 1,4- and (*Z*)-selectivity and the lack of reactivity with styrene.

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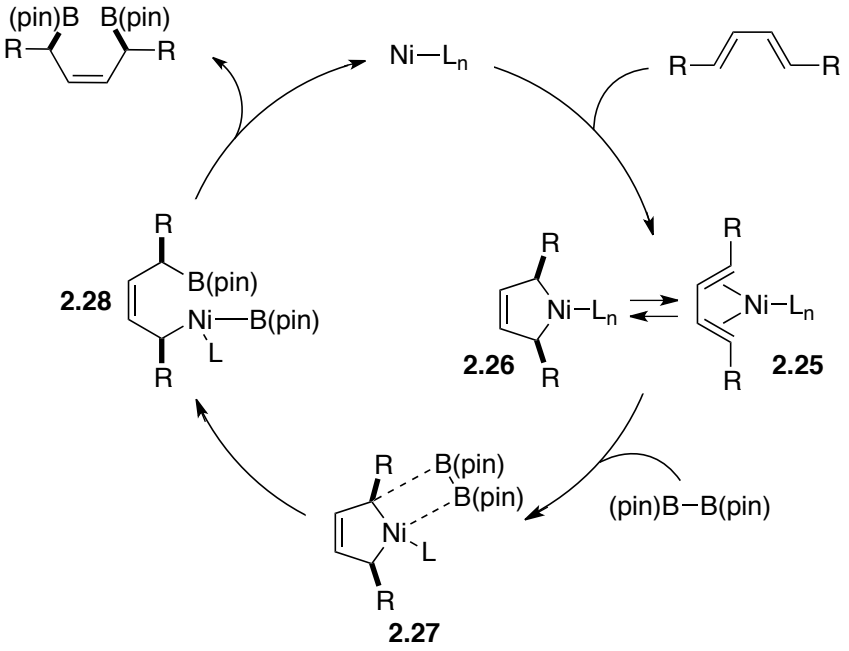
[29] The reaction with 2-vinylnaphthalene occurred with <25% conversion to a mixture of products, none of which appeared to be a diboration product.
[30] Benn, R.; Betz, P.; Goddard, R.; Jolly, P. W.; Kokel, N.; Kruger, C.; Topalovic, I. Z. *Naturforsch*. **1991**, *46*, 1395.
[31] Karsch, H. H.; Leithe, A. W.; Reisky, M.; Witt, E. *Organometallics* **1999**, *18*, 90.

Scheme 2.13. Proposed Mechanism for Ni-Catalyzed Diene Diboration



A mechanism similar to one proposed for the Pt-catalyzed 1,4-diboration would also explain the high 1,4- and (*Z*)-selectivity (Scheme 2.14).[32] The Ni(0)-catalyst first oxidatively adds to $B_2(pin)_2$ to form the Ni(II) structure **2.29**. Although the oxidative addition of $B_2(pin)_2$ to Ni(0) is not known, it is well precedented for other group 10 metals.[33] Coordination of **2.29** to the least hindered alkene of the diene in the *S*-cis conformation sets up carbon-boron bond formation at C4 of the diene, remote from the metal center, as shown in **2.30**.[34] This provides the least hindered nickel-carbon bond

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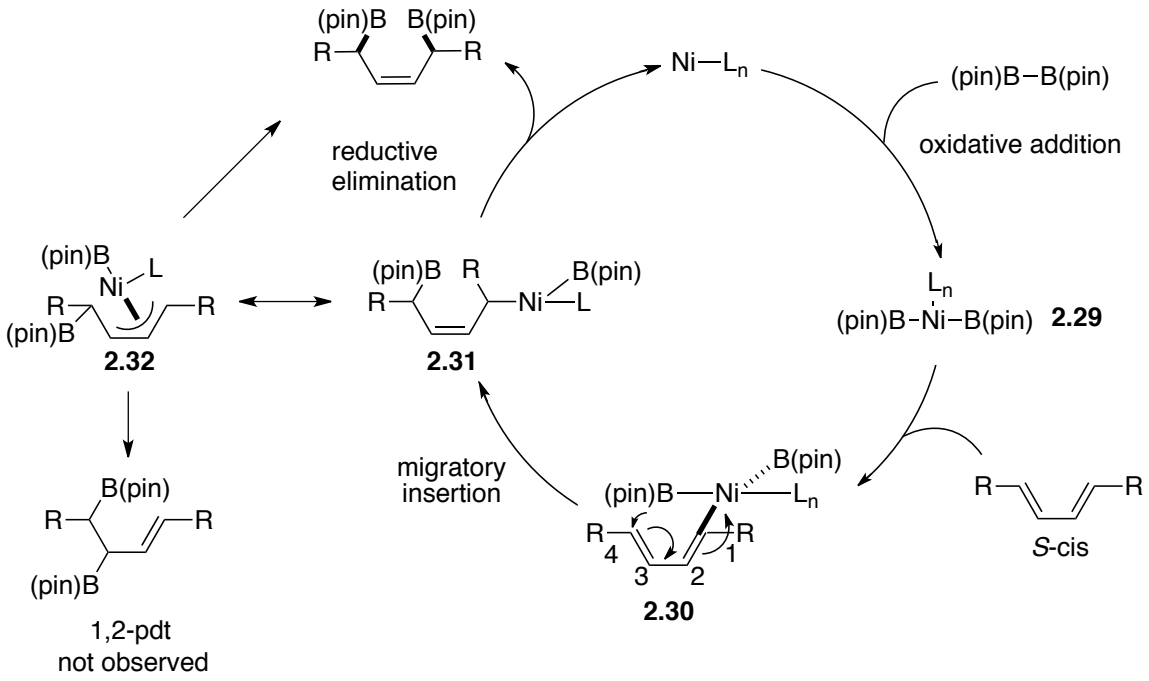
[32] See Chapter 1.5 of Dr. Laura T. Kliman's graduate thesis.

[33] For recent reviews see: Miyaura, N. *Bull. Chem. Soc. Jpn*. **2008**, *81*, 1535. (b) M. Suginome, Y. Ito, *Chem. Rev*. **2000**, *100*, 3221. For selected examples with Pt(0) see: (c) Lesley, G.; Nguyen, P.; Taylor, N. J.; Marder, T. B. *Organometallics* **1996**, *15*, 5137. (d) Iverson, C. N. Smith, M. R. III *Organometallics*, **1996**, *15*, 5155. (e) T. Ishiyama, N. Miyaura, *J. Organomet. Chem*. **2000**, *611*, 392. For examples with Pd, see ref. 28c.

[34] See Chapter 1.4 for a more in-depth discussion for this step.

(**2.31**), and reductive elimination provides the product. Concomitant π-allyl formation after carbon-boron bond formation to form **2.32** seems unlikely since this intermediate would appear to have little steric or electronic preference for the 1,4- or 1,2-diboration product for internal dienes.

Scheme 2.14. Alternate Proposed Mechanism for Ni-Catalyzed Diboration of Dienes



2.5. Conclusions

The first Ni-catalyzed 1,4-diboration of 1,3-dienes was developed to produce 1,4-(*Z*)-bis(boronic)esters in good yields and stereoselectivities. The direct oxidation of the bis(boryl) intermediates provides rapid access to 1,4-diols using inexpensive and commercially available reagents. The reaction was amendable to multi-gram scale and

was 1,4-selective for both *cis*- or *trans*-1,3-dienes. 1,4-Selectivites were also obtainable for several dienes that were not 1,4-selective with Pt-catalysis.

2.6. Experimental Procedures

I. General Information

^{1}H NMR spectra were recorded on Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. $^{13}C\{^{1}H\}$NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) and Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). Infrared (IR) spectra were recorded on a Bruker a-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (ESI) was performed at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 mm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA), and potassium permanganate ($KMnO_4$).

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene, tetrahydrofuran, methylene chloride, and diethyl ether were purified using a Pure Solv MD-4 solvent purification system, from

Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon. Benzene and toluene-d_8 were distilled from calcium hydride. Bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$), tricyclohexylphosphine (PCy_3), and tetrakis(triphenylphosphine) palladium(0) ($Pd(PPh_3)_4$) were purchased from Strem Chemicals, Inc. and used without further purification. Bis(pinacolato)diboron ($B_2(pin)_2$) was obtained from Allychem Co., Ltd. and recrystallized from pentane prior to use. Triphenylphosphine (PPh_3) was purchased from Aldrich and recrystallized from hexanes before use. 2,4-dimethyl-1,3-pentadiene was purchased from Acros and distilled before use. Styrene, cyclohexadiene, and cycloheptadiene were purchased from Aldrich and distilled before use. (2*E*,4*E*)-hexa-2,4-diene was purchased from Aldrich as a mixture of isomers, and used without further purification. All other reagents were purchased from Aldrich or Fisher and used without further purification.

II. Representative Procedure for Ligand Evaluation **(Scheme 2.9).**

In the dry box, an oven-dried 6-dram vial with magnetic stir bar was charged successively with $Ni(cod)_2$ (0.12 mL of a 46.2 mM solution of $Ni(cod)_2$ in toluene, 5.54 μmol), PCy_3 (0.12 mL of a 46.2 mM solution of PCy_3 in toluene, 5.54 μmol), toluene (0.63 mL, 0.25 M), $B_2(pin)_2$ (58.0 mg, 0.23 mmol), and (*E*)-deca-1,3-diene (30 mg, 0.22 mmol). The vial was sealed and removed from the dry box and allowed to stir at 60 °C in an oil bath for 15 min. The reaction mixture was cooled to 0 °C (ice/water) and charged with THF (1.5 mL), 3 M sodium hydroxide (1 mL), and 30 wt % hydrogen peroxide (0.75 mL). The reaction was allowed to warm to rt and stir for 12 h, at which time the

vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (1 mL) was added drop-wise. The reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified on silica gel (1:1 hexanes:ethyl acetate, R_f = 0.20, stain in PMA) to afford a clear, colorless oil (31.0 mg, 83%).

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III. Preparation of Starting Material.

A. The following dienes were prepared by Wittig olefination of the commercially available α,β-unsaturated aldehydes with methyltriphenylphosphonium bromide and potassium *tert*-butoxide in tetrahydrofuran: *trans*-1-phenyl-1,3-butadiene[35] (Table 2.1, entry 1), *trans*-1,3-decadiene[36] (Table 2.1, entry 2).

The following dienes were prepared by the literature procedure: (*E*)-2-methyldeca-1,3-diene[37] (Table 2.1, entry 3), (*E*)-3-methylnona-1,3-diene[38] (Table 2.1, Entry 4), (*E*)-*tert*-butyl(penta-2,4-dienyloxy)diphenylsilane[37] (Table 2.1, entry 7), (*E*)-((2,2-dimethylhexa-3,5-dienyloxy)methyl)benzene[37] (Table 2.1, entry 8), (1*E*,3*E*)-nona-1,3-dienylbenzene[38] (Table 2.2, entry 1), (2*E*,4*E*)-undeca-2,4-diene[38] (Table 2.2, entry 3). Spectral data are in accordance with the literature references.

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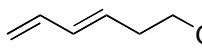
[35] Yeh, K. L.; Liu, B.; Lo, C. Y.; Huang, H. L.; Liu, R. S. *J. Am. Chem. Soc.* **2002**, *124*, 6510.
[36] Meyers, A. I.; Ford, M. E. *J. Org. Chem.* **1976**, *41*, 1735.
[37] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 9134.
[38] Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 2534.

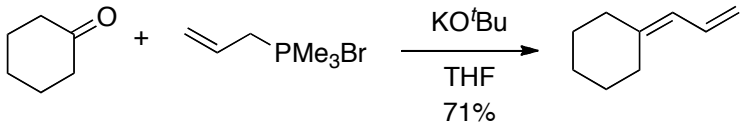
B. Preparation of (E)-tert-butyl(hexa-3,5-dienyloxy)diphenylsilane . To a flame-dried round-bottom flask equipped with a magnetic stir bar was added imidazole (7.3 g, 26.7 mmol) and the flask was purged with N_2. A solution of (*E*)-hexa-3,5-dien-1-ol[39] (874.0 mg, 8.9 mmol) in DCM (18 mL, 0.5 M) was added, followed by TBDPSCl (1.5 mL, 5.9 mmol), and triethylamine (0.82 mL, 5.88 mmol). The reaction was allowed to stir for 14 h at room temperature, and was then diluted with DCM and water, and the layers were separated. The aqueous layer was washed with DCM (3 x 30 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified on silica gel (200:1 hexanes:ethyl acetate, R_f = 0.26, stain in $KMnO_4$) to afford a clear, colorless oil (2.6 g, 86%).



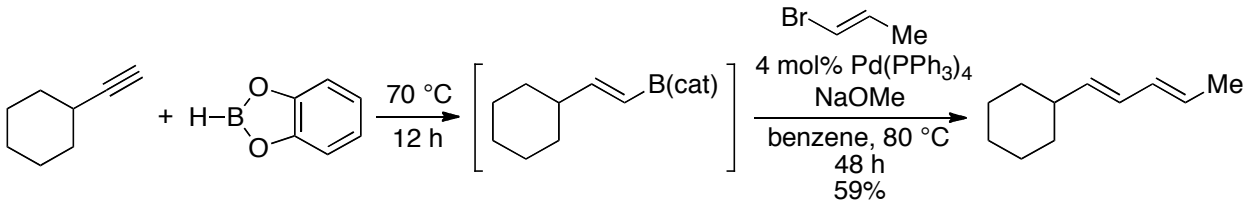
(*E*)-*tert*-butyl(hexa-3,5-dienyloxy)diphenylsilane (Table 2.1, entry 7). ^{1}H NMR (400 MHz, CDCl3): 1.10 (9H, s, C(C**H$_3$**)$_3$), 2.39 (2H, dt, *J* = 6.8 Hz, 6.8 Hz, C**H$_2$**CH$_2$OSi), 3.76 (2H, t, *J* = 5.2 Hz, CH$_2$C**H$_2$**OSi), 5.02 (1H, d, *J* = 10.4 Hz, C**H$_c$**H$_t$=CH), 5.14 (1H, d, *J* = 16.8 Hz, CH$_c$**H$_t$**=CH), 5.74 (1H, ddd, *J* = 14.4 Hz, 6.8 Hz, 6.8 Hz, CH=C**H**CH$_2$CH$_2$), 6.13 (1H, dd, *J* = 14.4 Hz, 10.4 Hz, C**H**=CHCH$_2$CH$_2$), 6.34 (1H, ddd, *J* = 16.8 Hz, 10.0 Hz, 10.0 Hz, C**H**=CH$_2$), 7.40-7.48 (6H, m, Ar**H**), 7.72 (4H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): 137.4, 135.8, 134.2, 133.0, 131.7, 129.8, 127.8, 115.4, 63.7, 36.2, 27.1, 19.4; IR (neat): 3071 (w), 2930 (m), 1472 (m), 1110 (s), 737 (s), 504 (m); HRMS-(ESI+) for $C_{22}H_{29}OSi$ [M+H]: calculated: 337.1987, found: 337.2002.

[39] Habrant, D.; Stengel, B.; Meunier, S.; Mioskowski, C. *Chem. Eur. J.* **2007**, *13*, 5433.

C. Preparation of allylidenecyclohexane (Table 2.1, entry 9). The title compound was synthesized from cyclohexanone and allyltrimethylphosphonium bromide,[39] as shown below. The spectral data was in accordance with the literature.[40]



D. Preparation of (1E,3E)-penta-1,3-dien-1-ylcyclohexane (Table 2, Entry 3). The title compound was synthesized as shown below. The spectral data was in accordance with the literature.[41]



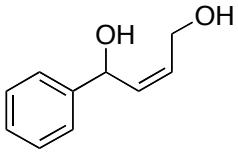
IV. Representative Procedure for Diene Diboration/Oxidation.

In the dry-box, an oven-dried 6-dram vial equipped a with magnetic stir bar was charged successively with $Ni(cod)_2$ (0.23 mL of a 46.2 mM solution of $Ni(cod)_2$ in toluene, 10.8

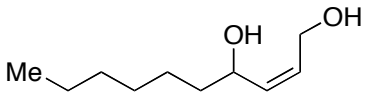
[39] Saegusa, K.; Kakihana, M.; Oda, D.; Tamura, R. *J. Org. Chem*. **1988**, *53*, 2723.
[40] Pospíšil, J.; Markó, I. E. *Org. Lett*. **2006**, *8*, 5983.
[41] Morgan, I. T.; Sarkar, A. K.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, *17*, 2749.

μmol), PCy_3 (0.23 mL of a 46.2 mM solution of PCy_3 in toluene, 10.8 μmol), toluene (1.25 mL, 0.25 M), $B_2(pin)_2$ (116.0 mg, 0.45 mmol), and (*E*)-deca-1,3-diene (60 mg, 0.43 mmol). The vial was sealed and removed from the dry box and allowed to stir at 60 °C in an oil bath for 3 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with THF (1.5 mL), 3 M sodium hydroxide (1 mL), and 30 wt % hydrogen peroxide (0.75 mL). The reaction was allowed to warm to room temperature and stir for 12 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (1 mL) was added drop-wise. The reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified on silica gel (1:1 hexanes:ethyl acetate, R_f = 0.20, stain in PMA) to afford a clear, colorless oil (62.8 mg, 84%).

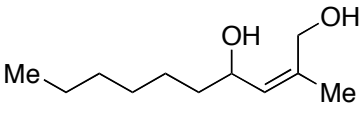
V. Full Characterization and Proof of Stereochemistry.



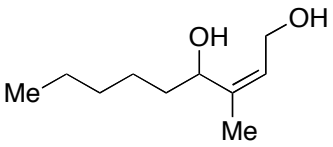
(*Z*)-dec-2-ene-1,4-diol (Table 2.1, entry 1). Spectral data is in accordance with the literature.[37]



(*Z*)-dec-2-ene-1,4-diol (Table 2.1, entry 2). Spectral data is in accordance with the literature.[37]

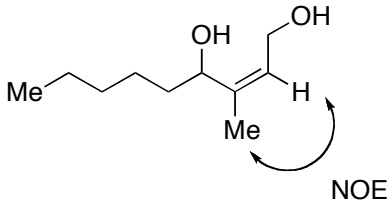


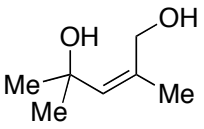
(*Z*)-2-methyldec-2-ene-1,4-diol (Table 2.1, entry 3). Spectral data is in accordance with the literature.[37]



(*Z*)-3-methylnon-2-ene-1,4-diol (Table 2.1, entry 5). ^{1}H NMR (400 MHz, CDCl3): 0.87 (3H, t, J = 6.8 Hz, $CH_2C\mathbf{H_3}$), 1.11-1.28 (6H, m, $C\mathbf{H_2}C\mathbf{H_2}C\mathbf{H_2}CH_3$), 1.38-1.43 (1H, m, $C\mathbf{H_A}H_BCHOH$), 1.55-1.60 (1H, m, $CH_AC\mathbf{H_B}CHOH$), 2.08 (3H, s, $CC\mathbf{H_3}$), 2.97 (2H, s br, 2 x O**H**), 3.99 (1H, dd, J = 12.4 Hz, 5.6 Hz, $HOC\mathbf{H_A}CH_B$), 4.24 (1H, dd, J = 12.4 Hz, 8.6 Hz, $HOCH_AC\mathbf{H_B}$), 5.86 (1H, dd, J = 7.1 Hz, 7.1 Hz, C=C**H**); ^{13}C NMR (100 MHz, $CDCl_3$): 141.6, 126.1, 69.6, 57.6, 34.7, 32.0, 25.6, 22.8, 18.0, 14.2; IR (neat): 3317 (br m), 2930 (s), 2858 (m), 1451 (w), 1001 (s); HRMS-(ESI+) for $C_{10}H_{19}O$ [M-H_2O+H]: calculated: 155.1436, found:155.1442. The crude reaction mixture was purified on silica gel (1.5:1 hexanes:ethyl acetate, R_f = 0.16, stain in PMA) to afford a clear, colorless oil (70.6 mg, 94%).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry proven by NOE correlation as shown below.

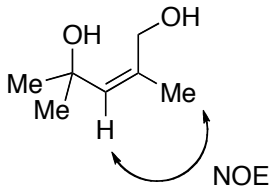


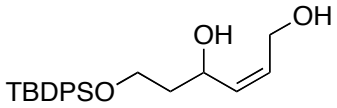


(*Z*)-2,4-dimethylpent-2-ene-1,4-diol (Table 2.1, entry 5). ^{1}H NMR (400 MHz, CDCl3): 1.37 (6H, s, 2 x $C\mathbf{H_3}COH$), 1.73 (3H, s,

C**H$_3$**C=CH), 4.20 (2H, s, C**H$_2$**OH), 5.39 (1H, s, C**H**=C); ^{13}C NMR (100 MHz, $CDCl_3$): 135.4, 134.5, 71.4, 62.8, 31.9, 24.0; IR (neat): 3342 (br m), 2973 (s), 1449 (w), 1376 (s), 1143 (s), 1005 (s), 952 (s); HRMS-(ESI+) for $C_7H_{13}O$ [M+H-H_2O]: calculated: 113.0966, found: 113.0964. The crude reaction mixture was purified on silica gel (1:1.5 hexanes:ethyl acetate, R_f = 0.19, stain in PMA) to afford a clear, colorless oil which contains a small amount of inseparable pinacol byproduct (63.3 mg, 71% after adjustment for pinacol impurity).

Proof of Stereochemistry: **(***Z***)**-alkene stereochemistry proven by NOE correlation as shown below.

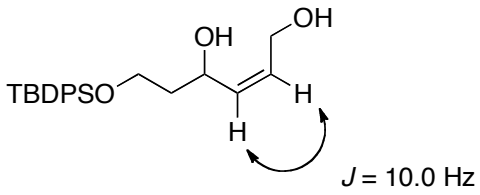


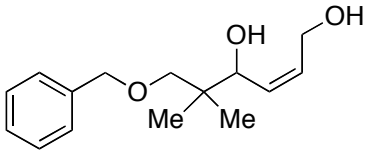


(*Z*)-6-(*tert*-butyldiphenylsilyloxy)hex-2-ene-1,4-diol (Table 2.1, entry 7). ^{1}H NMR (400 MHz, CDCl3): 1.09 (9H, s, C(C**H$_3$**)$_3$), 1.69 (1H, dddd, *J* = 10.2 Hz, 4.2 Hz, 3.0 Hz, 3.0 Hz, C**H$_A$**$CH_B$$CH_2$OSi), 1.87-1.94 (1H, m, CH_AC**H$_B$**CH_2OSi), 3.85-3.93 (2H, m, C**H$_2$**OSi), 4.21 (1H, ddd, *J* = 10.6 Hz, 5.4 Hz, 1.2 Hz, HOC**H$_A$**CH_B), 4.32 (1H, ddd, *J* = 10.6 Hz, 5.4 Hz, 1.2 Hz, HOCH_AC**H$_B$**), 4.81 (1H, ddd, *J* = 6.8 Hz, 6.8 Hz, 3.2 Hz, C**H**OH), 5.62 (1H, ddd, J = 10.0 Hz, 6.0 Hz, 1.2 Hz, C**H**=CHCH_2OH), 5.78 (1H, dddd, *J* = 10.0 Hz, 5.6 Hz, 5.6 Hz, 1.2 Hz,

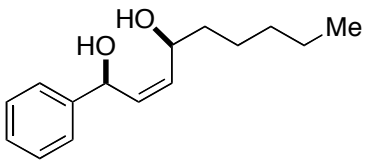
CH=C**H**CH_2OH), 7.41-7.50 (6H, m, Ar**H**), 7.69-7.72 (4H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): 135.8, 134.6, 133.2, 130.7, 130.1, 128.0, 67.8, 62.8, 58.9, 38.9, 27.0, 19.2; IR (neat): 3370 (br m), 3071 (w), 2931 (m), 1427 (m), 1111 (s), 702 (s), 504 (m); HRMS-(ESI+) for $C_{22}H_{31}O_3Si$ [M+H]: calculated: 371.2043, found: 371.2037. The crude reaction mixture was purified on silica gel (2:1 hexanes:ethyl acetate, R_f = 0.18, stain in PMA) to afford a clear, colorless oil (55.4 mg, 84%).

Proof of stereochemistry: **(***Z***)**-alkene stereochemistry determined by coupling constants as shown below.





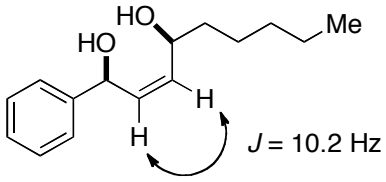
(*Z*)-6-(benzyloxy)-5,5-dimethylhex-2-ene-1,4-diol (Table 1, entry 8). Spectral data is in accordance with the literature.[37]

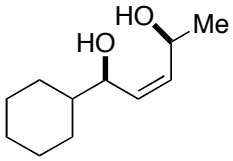


(*Z*)-1-phenylnon-2-ene-*syn*-1,4-diol (Table 2.2, entry 1). ^1H NMR (500 MHz, CDCl3): 0.77 (3H, t, *J* = 6.8 Hz, C**H$_3$**), 1.14-1.24 (6H, m, C**H$_2$**C**H$_2$**C**H$_2$**CH_3), 1.31-1.41 (1H, m, HOCHC**H$_A$**H_B), 1.46-1.54 (1H, m, HOCHCH_A**H$_B$**), 4.51 (1H, ddd, *J* = 6.4 Hz, 6.4 Hz,

6.4 Hz, HOC**H**CH_2), 5.45-5.50 (1H+1H, m, PhC**H**OH + PhCHOHCH=C**H**), 5.65 (1H, dd, *J* = 10.2 Hz, 8.8 Hz, PhCHOHC**H**=CH), 7.17-7.29 (5H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): 143.1, 134.6, 134.1, 128.8, 127.8, 126.2, 69.9, 67.8, 37.4, 31.9, 25.3, 22.8, 14.2; IR (neat): 3341 (br w), 2928 (m), 2857 (w), 1493 (m), 1015 (s), 743 (m), 697 (s); HRMS-(ESI+) for $C_{15}H_{26}NO_2$ [M+NH_4]: calculated: 252.1964, found: 252.1961. The crude reaction mixture was purified on silica gel (2:1 hexanes:ethyl acetate, R_f = 0.11, stain in PMA) to afford a white solid (mp 53-56 °C) (54.1 mg, 77%).

Proof of stereochemistry: **(***Z***)**-alkene stereochemistry determined by coupling constants as shown below. *Syn*-stereochemistry determined by analogy to (*Z*)-hex-3-ene-2,5-diol (Table 2.2, entry 4).

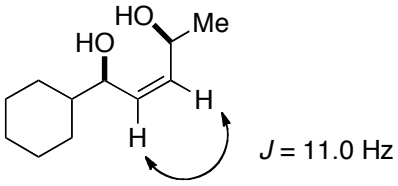


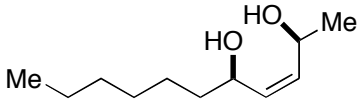


(*Z*)-1-cyclohexylpent-2-ene-*syn*-1,4-diol (Table 2.2, entry 2). ^{1}H NMR (500 MHz, CDCl3): 0.85-1.00 (2H, m, C**H$_2$**), 1.09-1.39 (4H, m, C**H$_2$**C**H$_2$**), 1.24 (3H, d, *J* = 6.5 Hz, C**H$_3$**), 1.60-1.78 (4H, m, C**H$_2$**C**H$_2$**), 1.89-1.91 (1H, m, C**H**CHOH), 2.67 (2H, br s, 2 x O**H**), 4.15 (1H, dd, *J* = 8.0 Hz, 8.0 Hz, HOC**H**Cy), 4.63 (1H, dddd, *J* = 8.0 Hz, 6.5 Hz, 6.5 Hz, 6.5 Hz, HOC**H**CH_3), 5.47 (1H, ddd, *J* = 10.1 Hz, 9.0 Hz, 1.0 Hz, C**H**=CH), 5.58 (1H, ddd, *J* = 11.0 Hz, 9.0 Hz, 1.0 Hz, CH=C**H**); ^{13}C NMR (100 MHz, $CDCl_3$): 136.4, 132.5, 72.0, 63.7, 43.7, 29.0, 28.8,

26.7, 26.2, 26.1, 23.4; IR (neat): 3320 (br m), 2966 (s), 2851 (m), 1450 (w), 1060 (m); HRMS-(ESI+) for $C_{11}H_{19}O_1$ [M+H-H_2O]: calculated: 167.1436, found: 167.1432. The crude reaction mixture was purified on silica gel (1:1 hexanes:ethyl acetate, R_f = 0.11, stain in PMA) to afford a clear, colorless oil (47.7 mg, 66%).

Proof of stereochemistry: (*Z*)-alkene stereochemistry determined by coupling constants as shown below. *Syn*-stereochemistry determined by analogy to (*Z*)-hex-3-ene-2,5-diol (Table 2.2, entry 4).

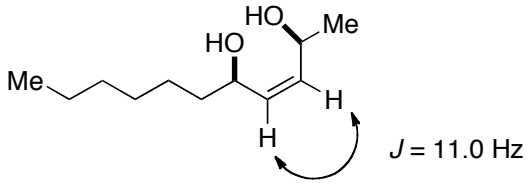


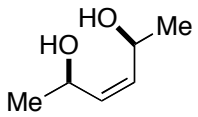


(*Z*)-undec-3-ene-*syn*-2,5-diol (Table 2.2, entry 3). ^{1}H NMR (500 MHz, CDCl3): 0.87 (3H, t, *J* = 6.0 Hz, $CH_2C\mathbf{H_3}$), 1.22 (3H, d, *J* = 6.0 Hz, $C\mathbf{H_3}CHOH$), 1.22-1.32 (8H, m, $(C\mathbf{H_2})_4$), 1.36-1.44 (1H, m, $C\mathbf{H_A}H_BCHOH$), 1.54-1.62 (1H, m, $CH_A\mathbf{H_B}CHOH$), 4.40 (1H, ddd, *J* = 8.5 Hz, 7.0 Hz, 7.0 Hz, $HOC\mathbf{H}CH_2$), 4.61 (1H, dddd, *J* = 8.0, 6.0 Hz, 6.0 Hz, 6.0 Hz, $HOC\mathbf{H}CH_3$), 5.39 (1H, dd, *J* = 11.0 Hz, 9.0 Hz, C**H**=CH), 5.49 (1H, dd, *J* = 11.0 Hz, 9.0 Hz, CH=C**H**); ^{13}C NMR (100 MHz, $CDCl_3$): 135.7, 133.9, 67.5, 63.5, 37.3, 32.0, 29.4, 25.5, 23.4, 22.8, 14.2; IR (neat): 3335 (br w), 2927 (s), 2857 (m), 1456 (w), 1058 (s); HRMS-(ESI+) for $C_{11}H_{21}O_1$ [M+H-H_2O]: calculated: 169.1592, found: 169.1589. The

crude reaction mixture was purified on silica gel (2:1 hexanes:ethyl acetate, R_f=0.09, stain in PMA) to afford a clear, colorless oil (54.3 mg, 74%).

Proof of stereochemistry: **(***Z***)**-alkene stereochemistry determined by coupling constants as shown below. *Syn*-stereochemistry determined by analogy to (*Z*)-hex-3-ene-2,5-diol (Table 2.3, entry 4).

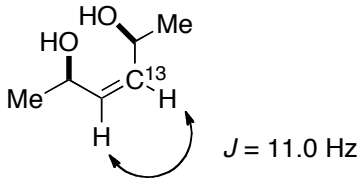




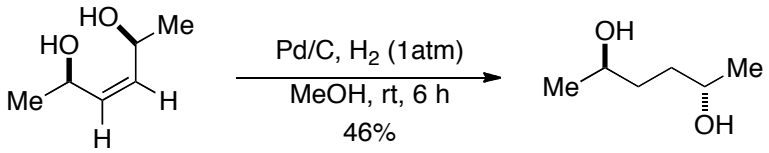
(*Z*)-hex-3-ene-*syn*-2,5-diol (Table 2.2, entry 4). ^{1}H NMR (500 MHz, CDCl3): 1.24 (6H, d, *J* = 6.0 Hz, 2 x C**H$_3$**), 3.17 (2H, s br, 2 x O**H**), 4.65 (2H, dddd, *J* = 12.5 Hz, 6.5 Hz, 6.5 Hz, 6.5 Hz, 2 x CH_3C**H**OH), 5.47 (2H, dd, *J* = 7.5 Hz, 1.5 Hz, C**H**=C**H**); ^{13}C NMR (100 MHz, $CDCl_3$): 134.9, 64.6, 23.5; IR(neat): 3309 (br s), 2970 (s), 2926 (s), 1370 (w), 1065 (s); HRMS-(ESI+) for $C_6H_{16}NO_2$ [M+NH_4]: calculated: 134.1181, found: 134.1180. The starting material (purchased from Aldrich) contains ~40% of (2*Z*,4*E*)-hexa-2,4-diene. The *cis*-isomer is converted to the terminal 1,4-bis(boronate)ester during the reaction, and results in ~40% of the terminal 1,4-diol after oxidation which is inseparable from the internal 1,4-diol. The crude reaction mixture was purified on silica gel (1:2 hexanes:ethyl acetate, R_f = 0.06, stain in PMA) to afford a

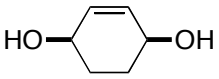
clear, colorless oil (61.0 mg, 72% based on mass of combined diols). The product was separated from (*Z*)-hex-2-ene-1,4-diol by selective protection with TBDPSCl.

Proof of stereochemistry: **(***Z*)-stereochemistry of the meso-diol was determined by the *J*-value of the ^{13}C satellite peaks in the ^{1}H NMR.



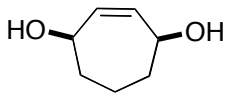
Proof of stereochemistry: *Syn*-diol relationship was confirmed after hydrogenation to the known saturated diol, and comparison of the ^{13}C NMR spectrum.





cyclohex-2-ene-1,4-diol (Table 2, entry 5). Spectral data is in accordance with the literature.[42]

[42] Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876.



cyclohept-2-ene-1,4-diol (Table 2, entry 6). Spectral data is in accordance with the literature.[43]

VI. Procedure for Multi-Gram Diboration of Decadiene (Scheme 2.10).

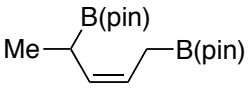
In the dry-box, a flame-dried 250-mL round-bottom flask equipped with a magnetic stir bar was charged successively with $Ni(cod)_2$ (224 mg, 0.81 mmol), PCy_3 (228 mg, 0.81 mmol), toluene (130 mL, 0.25 M), $B_2(pin)_2$ (8.68 g, 34.18 mmol), and (*E*)-deca-1,3-diene (4.50 g, 32.55 mmol). The flask was sealed with a septum, removed from the dry box, attached to a nitrogen inlet, and allowed to stir at 60 °C in an oil bath for 2 h. The reaction mixture was concentrated *in vacuo* to half the original volume, cooled to 0 °C (ice/water) and charged with THF (60 mL), 3 M sodium hydroxide (15 mL), and 30 wt % hydrogen peroxide (15 mL). The reaction was allowed to warm to room temperature and stir for 12 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (15 mL) was added drop-wise. The reaction mixture was diluted with ethyl acetate (30 mL) and water (60 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 60 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a clear, colorless oil. The crude oil was taken up in THF (10 mL), Et_2O (10 mL), and H_2O (10 mL), followed by the addition of $NaIO_4$ (20.80 g, 97.65 mmol) at 0 °C (ice/water). The reaction was allowed to warm to rt and stir for 5 h. The reaction mixture was then quenched with saturated

[43] Pinkerton, A. A.; Lu, W.; Lai, Y.; Pearson, A. J. *J. Org. Chem*. **1989**, *54*, 3882.

aqueous sodium thiosulfate (10 mL). The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a clear, yellow oil. The crude reaction mixture was purified on silica gel (1:1 hexanes:ethyl acetate, R_f = 0.20, stain in PMA) to afford a clear, colorless oil (4.91 g, 87%).

VII. Procedure/Results for cis-Pentadiene Isomerization ^{1}H NMR study **(Scheme 2.11).**

In the dry-box, an oven-dried 6-dram vial equipped with a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.20 mL of a 27.1 mM solution of $Ni(cod)_2$ in toluene-d_8, 5.5 μmol), PCy_3 (0.20 mL of a 27.1 mM solution of PCy_3 in toluene-d_8, 5.5 μmol), toluene-d_8 (0.48 mL, 0.25 M), $B_2(pin)_2$ (58.7 mg, 0.23 mmol), and *cis*-pentadiene (15 mg, 0.22 mmol). The mixture was allowed to stir until the solution was homogenous (approximately 2 min), then syringed into an NMR tube. The tube was capped, sealed with parafilm, removed from the dry-box, and heated to 60 °C in an oil bath. The reaction was monitored by ^{1}H NMR. As the reaction progressed, *trans*-pentadiene along with 1,4-bis(boronate)ester was observed along with the disappearance of *cis*-pentadiene. After 1 h, the reaction contained an 1:0.8 mixture of *cis*-pentadiene and *trans*-pentadiene: 1,4-bis(boronate)ester was produced in 82% conversion, and >99% conversion for *trans*-pentadiene. In the control experiment, in which no $B_2(pin)_2$ was added, no isomerization was observed.



(Z)-2,2'-(pent-2-ene-1,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (Scheme 2.11). ^{1}H NMR (500 MHz, CDCl3): 0.98 (3H, t, *J* = 7.0 Hz, C**H$_3$**CH), 1.16-1.20 (24H, m, (C**H$_3$**)$_8$), 1.56 (1H, dd, *J* = 7.5 Hz, 7.5 Hz, C**H$_A$**H$_B$), 1.64 (1H, dd, *J* = 8.0 Hz, 7.5 Hz, CH$_A$**H$_B$**), 2.03 (1H, dq, *J* = 15.0 Hz, 7.0 Hz, CH$_3$C**H**), 5.29 (1H, br dd, *J* = 10.0 Hz, 10.0 Hz, CHC**H**=CH), 5.38 (1H, br ddd, 8.5 Hz, 8.5 Hz, 8.5 Hz, CH=C**H**CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): 16.0, 24.7, 24.7, 24.8, 24.9, 83.0, 83.1, 122.7, 132.4; IR (neat): 2978 (m), 2931 (w), 2873 (w), 1320 (s), 1143 (s), 849 (m), 549 (m); HRMS-(ESI+) for $C_{17}H_{33}B_2O_4$ [M+H]: calculated: 323.2565, found: 323.2575.

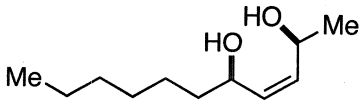


Table 2.2, entry 3

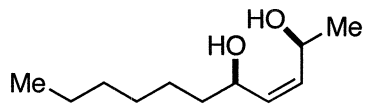
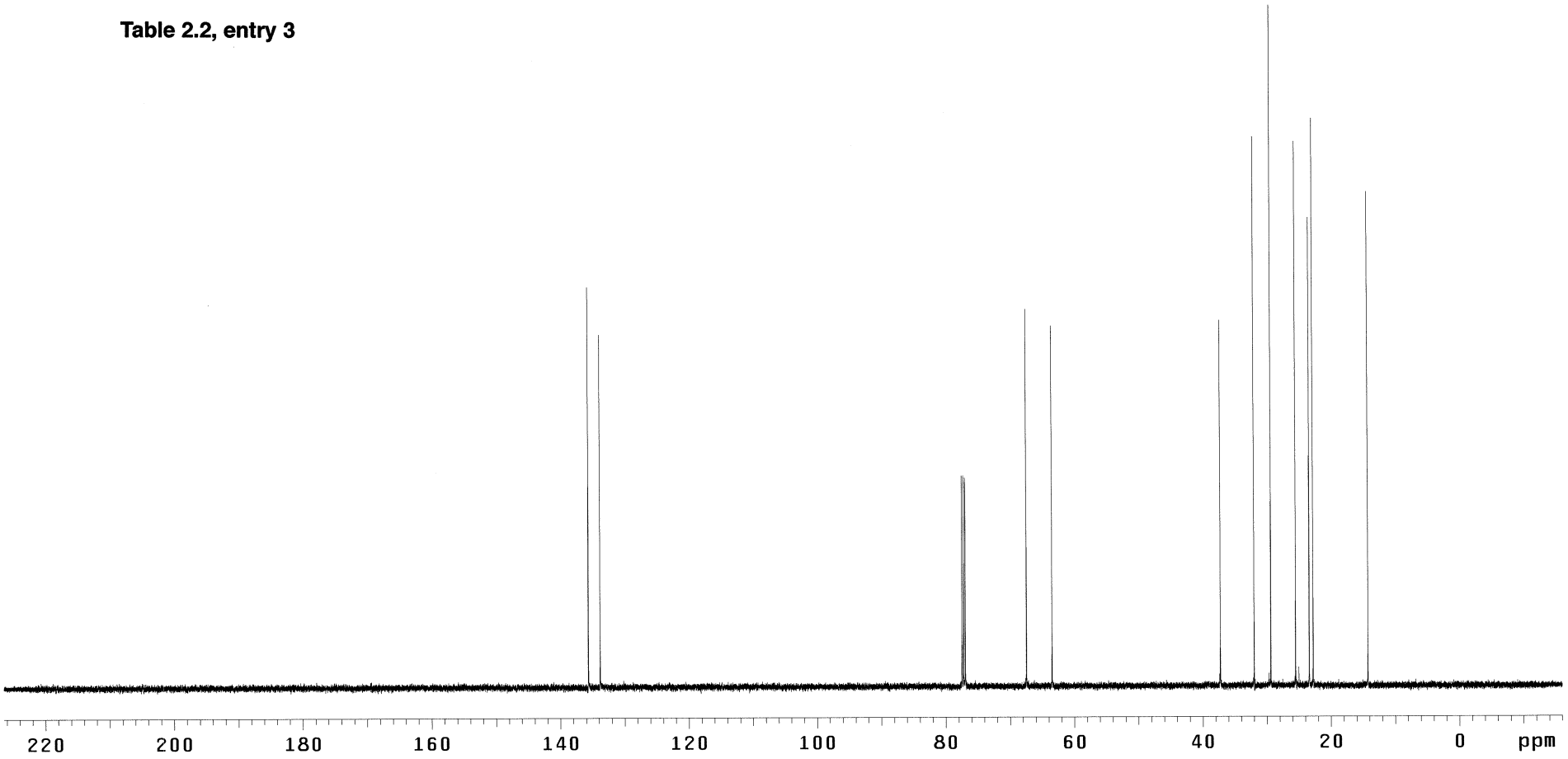


Table 2.2, entry 3



Chapter 3

Development, Scope, and Utility of Diastereoselective Nickel-Catalyzed 1,4-Hydroboration of Chiral 1,3-Dienols: Application to the Synthesis of (+)-Discodermolide

3.1. Introduction

Polyketides are an important class of natural products that often exhibit potent biological activity and useful pharmacological properties.[1] Compounds containing polyketide functionality are five times more likely to possess medicinally relevant activity compared to other families of natural products,[2] and account for roughly 20% of top-selling small molecule therapeutics.[1c,d] Accordingly, significant efforts have been directed toward their efficient construction.[3] Several examples of medicinally valuable and synthetically challenging polyketides are shown in Figure 3.1.

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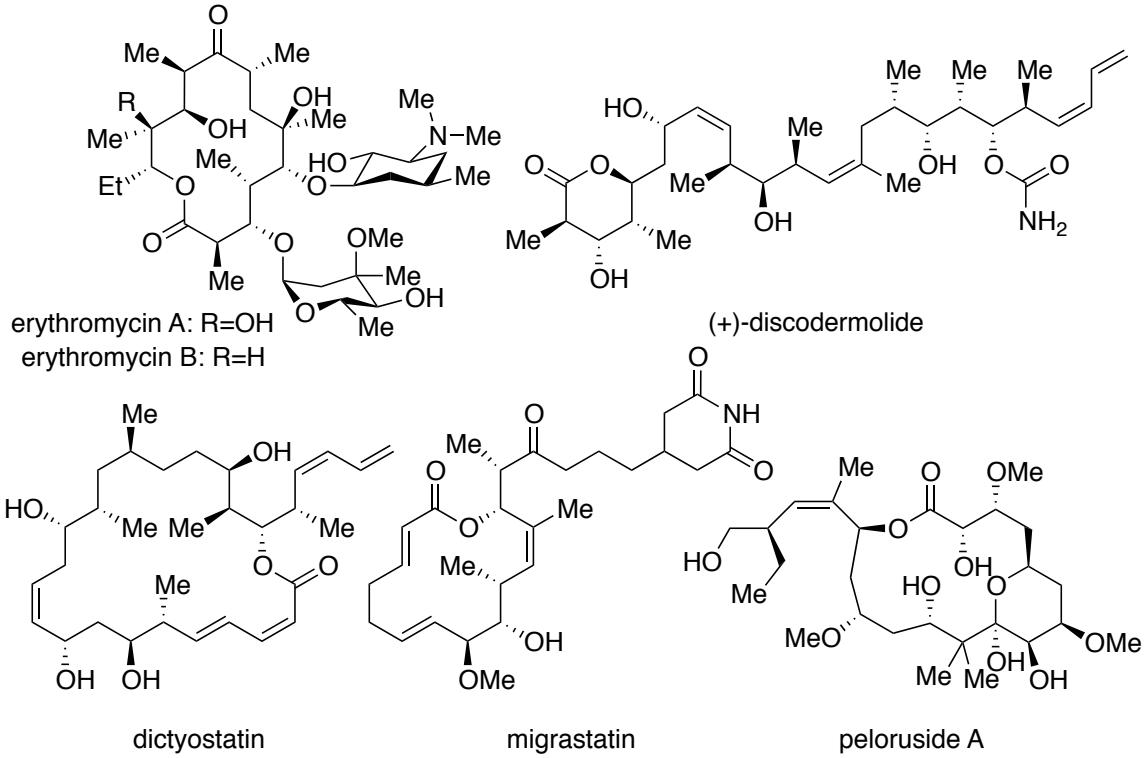
[1] (a) *Macrolide Antibiotics. Chemistry, Biology, and Practice*, 2nd ed.; Omura, S., Ed.; Academic Press: New York, 2002. (b) Polyketides Biosynthesis, Biological Activity, and Genetic Engineering; Rimando, A. M., Baerson, S. R., Eds.; ACS Symposium Series 955; American Chemical Society: Washington, DC, 2007. (c) Newman, D. J.; Cragg, G. M. *J. Nat. Prod*. **2007**, *70,* 461. (d) Newman,D. J.; Grothaus, P.G.; Cragg, G. M. *Chem. Rev***. 2009**, *109*, 3012. (e) O'Hagan, D. *The Polyketide Metabolites*; Ellis Horwood: Chichester, U.K., 1991.

[2] Rohr, J. *Angew. Chem., Int. Ed*. **2000**, *39*, 2847.

[3] Reviews: (a) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev*. **2005**, *34*, 677. (b) Morris, J. C.; Nicholas, G. M.; Phillips, A. J. *Nat. Prod. Rep.* **2007**, *24*, 87.

Figure 3.1. Selected Medicinally Relevant Polyketide Natural Products



Erythromycin is one of the most studied polyketide structures and has been used as a potent antibiotic for the past 60 years.[4] As a synthetic challenge in 1956, R. B. Woodward said of erythromycin A, "*looks at present time quite hopelessly complex, particularly in view of its plethora of asymmetric centers.*"[5] Subsequently, the methods for asymmetric C-C bond formation have expanded such that erythromycin derivatives

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[4] a) *Polyketides: Biosynthesis, Biological Activity, and Genetic Engineering* (Eds.:Baerson, S. R.; Rimando, A. M.), American Chemical Society, Washington, DC, **2006**; b) Staunton, J.; Wilkinson, J. *Chem. Rev*. **1997**, *97*, 2611 c) Floss, H. G.; Yu, T. *Chem. Rev*. **2005**, *105*, 621.

[5] R. B. Woodward in *Perspectives in Organic Chemistry* (Ed.: A. Todd), Wiley-Interscience, New York, **1956**, p. 160.

are now considered test structures for new methodologies.[6] The most commonly used methods to construct polyketides are the aldol reaction, crotyl-metal addition to prochiral electrophiles, and hydroboration of allylic alcohols or ethers.

3.2. Background

While the aldol reaction can efficiently construct fully saturated ketide subunits[7] such as those present in erythromycin, separate olefination reactions are required to install unsaturated sites found in polyketides such as discodermolide, dictyostatin, migrastatin, and peloruside A (Figure 3.1). The vinylogous aldol reaction was developed to address these issues. This method reacts extended enolate based nucleophiles (**3.1**) with aldehydes to generate versatile structural motifs (**3.2**, Scheme 3.1). Unfortunately, these reactions are generally *anti*-selective and only highly enantioselective with aromatic and α-β-unsaturated aldehydes.[8]

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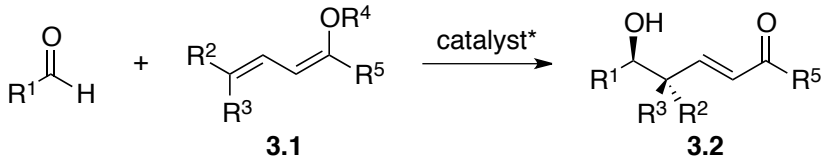
[6] (a) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed*. **2006**, *45*, 7506. For the first synthesis of erythromycin A see: (b) Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3215. For selected examples of related syntheses, see: (c) Martin, S. F.; Hida, T.; Kym, P. R.; Loft, M.; Hodgson, A. *J. Am. Chem. Soc*. **1997**, *119*, 3193. (d) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc*. **1978**, *100*, 4620. (e) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **1987**, *109*, 1565. (f) Myles, D. C.; Danishefsky, S. J. *J. Org. Chem*. **1990**, *55*, 1636. (g) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc*. **1998**, *120*, 5921. (h) Stang, E. M.; White, M. C. *Nat. Chem*. **2009**, *1*, 547. (i) Chandra, B.; Fu, D.; Nelson, S. G. *Angew. Chem., Int. Ed*. **2010**, *45*, 2591.

[7] (a) Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; p 249. (b) Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; p 279. (c) Yeung, K.-S.; Paterson, I. *Chem. Rev*. **2005**, *105*, 4237. (d) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed*. **2006**, *45*, 7506. (e) Morris, J. C.; Nicholas, G. M.; Phillips, A. *J. Nat. Prod. Rep*. **2007**, *24*, 87. (f) Paterson, I. In *Asymmetric Synthesis*, 2nd ed.; Christmann, M., Bräse, S., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2008; pp 293. (g) Paterson, I.; Findlay, A. D. *Aust. J. Chem*. **2009**, *62*, 624.

[8] (a) Denmark, S. E.; Heemstra Jr., J. R.; Beutner, G. L. *Angew. Chem., Int. Ed*. **2005**, *44*, 4682. (b) Brodmann, T.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174.

Scheme 3.1. General Vinylogous Aldol Reaction



The addition of crotyl-metal reagents (**3.3**) to prochiral aldehydes is a highly developed methodology to assemble polyketide substructures with excellent diastereo- and enantiocontrol (Scheme 3.2).[9] The homoallylic alcohols generated in this reaction (**3.4**) generally contain a terminal olefin that can require several synthetic manipulations to install further functionality (**3.5**). An alternative pathway utilizes chiral crotylation reagents (**3.6**) that contain embedded functional groups allowing for facile elaboration of the reaction products. Thus, methods to synthesize functionalized chiral crotylation reagents are valuable for the construction of polyketide fragments.

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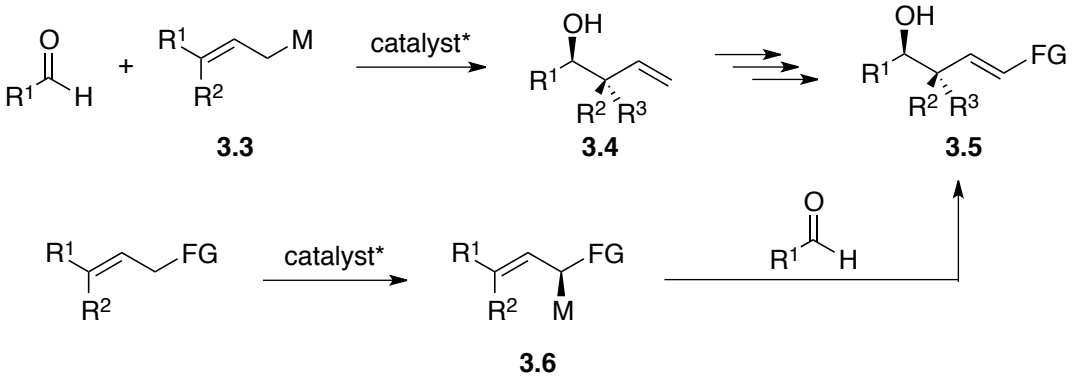
[9] Reviews on catalytic asymmetric carbonyl allylation: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis, Supplement* Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer-Verlag, Berlin, **2004**, *Vol. 2*, 97. (c) For selected recent examples: (e) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884. (f) Rauniyar, V.; Hall, D. G. *Angew.Chem., Int. Ed.* **2006**, *45*, 2426. (g) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (h) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (i) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (j) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.

Scheme 3.2. General Crotylation Strategy Toward Functionalized Homoallylic Alcohols



The enantioselective deprotonation of allylic carbamates, followed by addition to electrophilic metal sources, pioneered by Hoppe, has been a valuable tool for the synthesis of α-chiral crotylation reagents.[10] Ardisson has utilized this method to access enantioenriched crotyltitanium reagent **3.9** *via* a sparteine-mediated deprotonation of allylic carbamate **3.8** with *n*-BuLi.[11] Transmetallation with titanium, followed by addition of propionaldehye provided the (*Z*)-*anti*-homoallylic alcohol **3.10** containing a synthetically versatile vinylcarbamate in excellent yield and with high diastereo- and enantioselectivity (Scheme 3.3). The vinylcarbamate can be transformed into a terminal alkyne or used in nickel-catalyzed cross couplings as highlighted in the total syntheses of the natural products tyonolide[11] and discodermolide;[12] however, this method is restricted

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[10] For reviews, see: (a) Hoppe, D.; Christoph, G. Z.; Marek, I. (Eds.), *The Chemistry of Functional Groups Part 1*; Wiley: Chichester **2004**, 1055-1164. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed*. **1997**, *36*, 2282.

[11] Berque, I.; Le Ménez, P. L.; Razon, P.; Mahuteau, J.; Férézou, J.-P.; Pancrazi, A.; Ardisson, J.; Brion, J.-D. *J. Org. Chem*. **1999**, *64*, 373.

[12] de Lemos, E.; Porée, F.-H.; Commerçon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Angew., Chem. Int. Ed*. **2007**, *46*, 1917.

to *anti*-selective crotylation reactions due to the stereochemical instability of allyl-titanium reagents.

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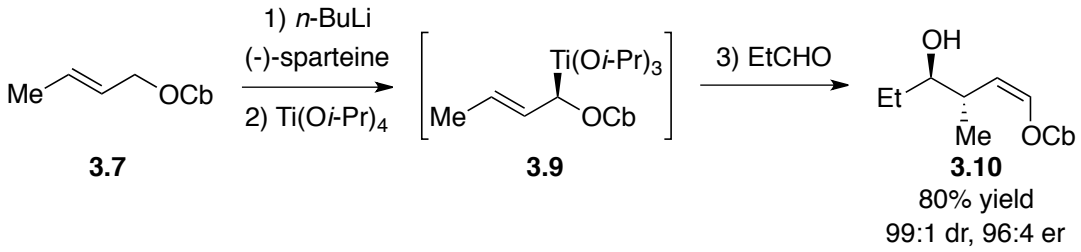
Scheme 3.3. Chiral Allyl-Titanium Reagents for the Synthesis of Homoallylic Vinylcarbamates



Similar to Ardisson, Aggarwal has also taken advantage of enantioenriched lithiated carbamates to prepare chiral crotylation reagents.[13] The sparteine-mediated deprotonation of alkyl carbamates (**3.11**) with *s*-BuLi generates enantioenriched nucleophiles with the ability to homologate vinylborons (**3.12**; see Chapter 1, Section 1.1) to chiral crotylborons (**3.13**, Scheme 3.4). Upon the addition of an aldehyde, these reagents participate in allylboration to produce homoallylic alcohols (**3.14**) with high diastereoselectivities and with excellent chirality transfer. Additionally, the product alkene geometry can be rendered either *cis* or *trans* by tuning the ligands on boron, and

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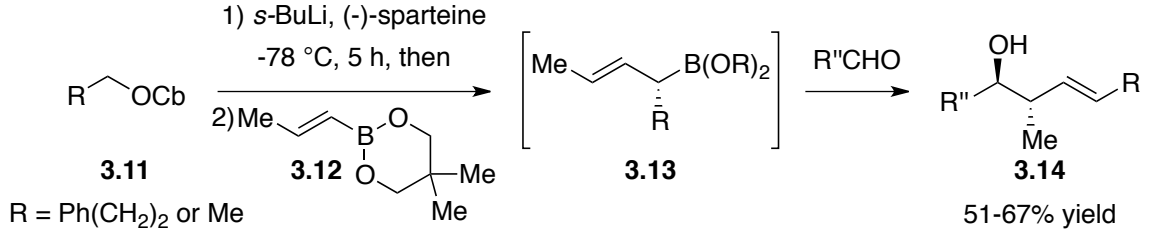
[13] Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2010**, *132*, 4025.

the *anti*- or *syn*-selectivity is ultimately controlled by the alkene geometry of the vinyl boron. While the only examples have simple alkyl chains appended to the alkene, this method has great promise for attaching further functionality.[14]

Scheme 3.4. Homologation of Vinylborons to Produce Chiral Allylborons



Although lithiated carbamate utilization has been successful at generating α-chiral crotylmetal reagents, it requires the use of stoichiometric amounts of base and metal. A catalytic synthesis to obtain similar reagents would be desirable. One such method, developed by Panek and co-workers, utilizes an enantioselective Rh(II)- or Cu(I)-catalyzed Si-H insertion to α-diazo vinyl esters to produce chiral crotylsilane reagents (Scheme 3.5).[15] The Cu-catalyzed silane insertion into **3.15** proceeds with moderate enantioselectivity and produces crotylsilane reagent **3.16**, a compound that must be

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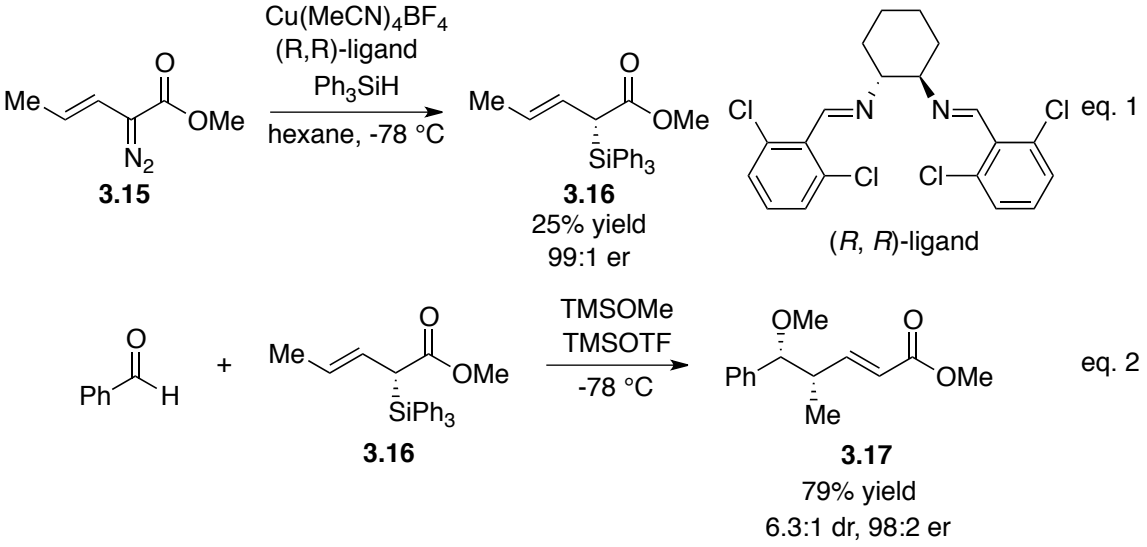
[14] For a review see: Thomas, S. P. T; French, R. M.; Jheengut, V.; Aggarwal, V. K. *The Chemical Record* **2009**, *9*, 24.
[15] Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett*. **2010**, *12*, 2112.

recrystallized to obtain high optical purity. The Lewis acid promoted crotylation to benzaldehyde generates the vinylogous aldol product **3.17** in good yield and enantioselectivity but with only modest diastereoselectivity. Unfortunately, only aromatic aldehydes give synthetically useful enantio- and diastereoselectivities.

Scheme 3.5. Synthesis of Crotylsilane Reagents to Generate Vinylogous Aldol Products



As demonstrated in Hoffmann's studies, α-chiral crotylboron reagents react with a wide range of aldehydes with high diastereoselectivity and with excellent chirality transfer;[16] thus, a catalytic method to synthesize these reagents is extremely valuable. Recently, Morken and co-workers disclosed a Pt-catalyzed enantioselective 1,2-

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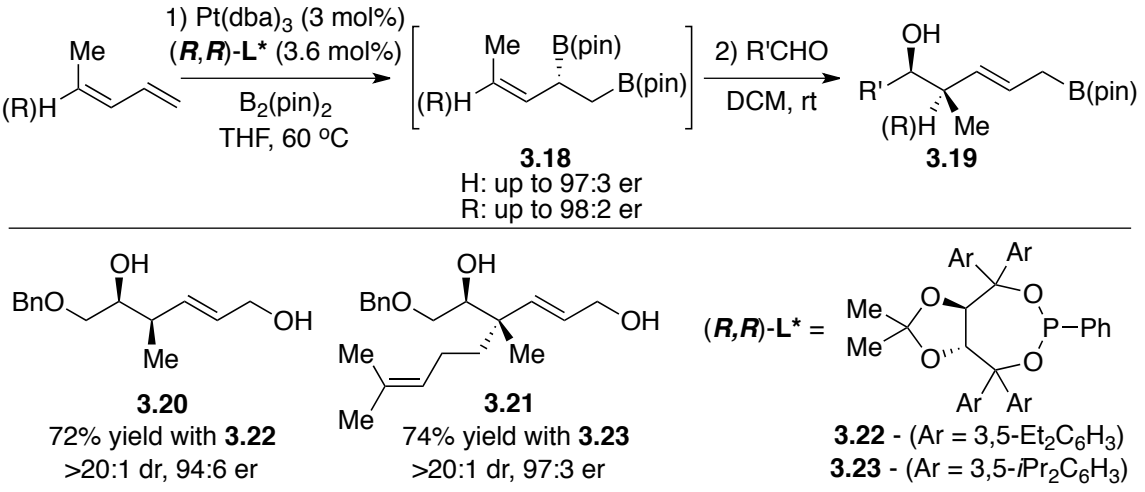
[16] (a) Hoffmann, R. F. *Pure Appl. Chem*. **1988**, *60*, 123. (b) Hoffmann, R. W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem*. **1990**, *62*, 1993. (c) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem*. **1981**, *46*, 1309. (d) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed*. **1979**, *18*, 306.

diboration of *cis*- and 1,1-disubstituted-terminal dienes (see Chapter 2, Section 2.2)[17] that produces 1,2-diboron products **3.18**. These compounds are excellent crotylation reagents that provide *syn*-selective (or quaternary carbon centers for 1,1-disubstituted dienes) homoallylic alcohols containing a terminal allylboronic ester (**3.19**) with good enantio- and diastereoselectivities (Scheme 3.6). The allylboronic ester provides a synthetic handle for a variety of further transformations (see Chapter 1, Section 1.1) including direct oxidation to allylic alcohols **3.20** and **3.21**. Since 1,2-diboration is only favored for *cis*- and 1,1-disubstituted dienes, only the *syn*-homoallylic alcohol can be accessed with this methodology.

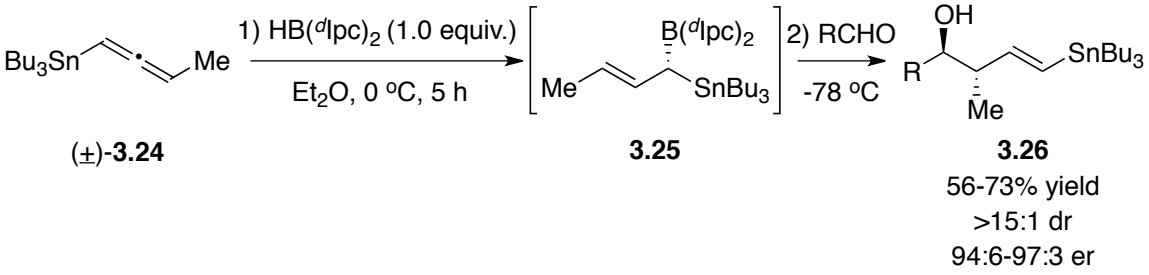
Scheme 3.6. Catalytic *Cis*-and 1,1-Disubstituted Diene Diboration to Provide α-Chiral Crotylboron Reagents



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

A method to access functionalized *anti*-homoallylic alcohols was developed by Roush and co-workers *via* an enantioconvergent hydroboration of racemic allenylstannane (±)-**3.24** with Brown's *d*-diisopinocampheylborane ($(^{d}Ipc)_2BH$).[18] The hydroboration of one enantiomer of **3.24** directly provides **3.25** while the hydroboration of the other enantiomer provides **3.25** after a 1,3-boratropic shift. The α-chiral allylborane reacts with aldehydes to provide enantioenriched *anti*-homoallylic alcohols in good yields and diastereoselectivities (**3.26**, Scheme 3.7). Although the vinylstannane in the products can be used for efficient cross coupling reactions,[19] the toxicity of tin and the use of stoichiometric chiral modifier limits the utility of this method.

Scheme 3.7. Enantioconvergent Hydroboration of Racemic Allenes to Provide α-Chiral Crotylboron Reagents



(±)-**3.24** **3.25** **3.26**
56-73% yield
>15:1 dr
94:6-97:3 er

The diastereoselective hydroboration of allylic alcohols or ethers has been commonly used to install propionate units along with reactive carbon-boron bonds for

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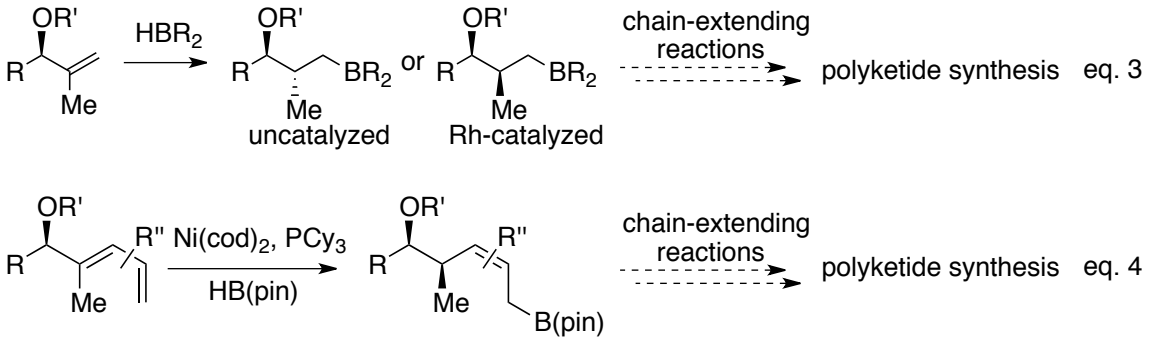
[18] Chen, M.; Roush, W. R. *J. Am. Chem. Soc*. **2011**, *133*, 5744.
[19] (a) Stille, J. K. *Angew. Chem., Int. Ed*. **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. *J. Org. React*. **1997**, *50*, 1.

further synthetic elaboration (eq. 3, Scheme 3.8).[20] However, similar to aldol adducts, several synthetic manipulations are required to construct unsaturated segments. Furthermore, with exception to the example by Ardisson, all the above methodologies provide functionalized homoallylic alcohols with *trans*-alkenes. Many polyketides, including those listed in Figure 1, contain synthetically challenging *cis*-alkenes adjacent to the propionate moiety. As a possible method to construct these common polyketide segments, it was thought that a diastereoselective Ni-catalyzed 1,4-hydroboration of 1,3-dienes could be developed. This strategy could install dehydrated diketide units with an additional allylboronic ester for rapid construction of complex polyketides (eq. 4, Scheme 3.8).[21]

Scheme 3.8. Diastereoselective Hydroboration as a Tool for Polyketide Construction



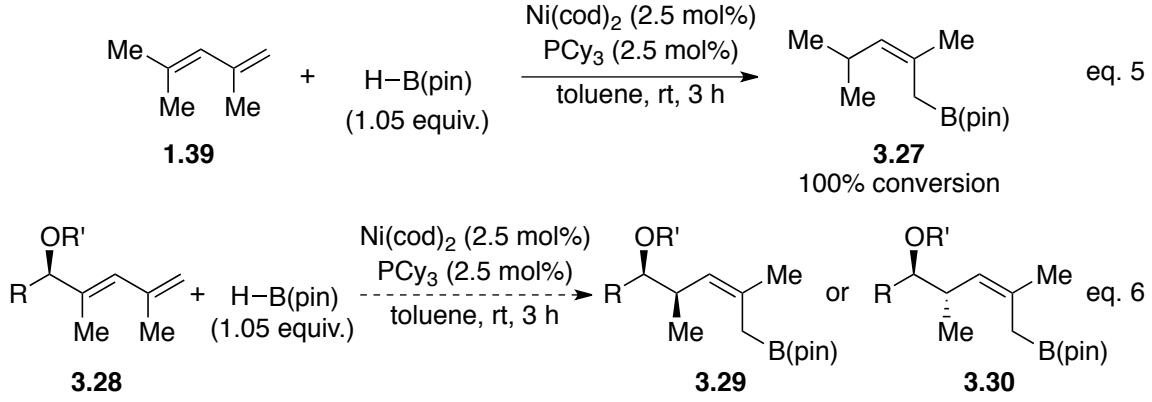
[20] (a) Kishi, Y. *Aldrichimica Acta* **1980**, *13,* 23. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981***, 37, 3873.* (c) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (d) Midland, M. M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725. (e) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Netz, J. T.; Paddon-Row: M. N. *Tetrahedron* **1984**, *40*, 2257.

[21] Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 2534.

3.3. Development of Diastereoselective Nickel-Catalyzed 1,4-Hydroboration of Chiral 1,3-Dienols[22]

During my studies on Ni-catalyzed 1,4-hydroboration of 1,3-dienes, I found that diene **1.39** reacted efficiently under the reaction conditions to produce **3.27**. Complete conversion and high 1,4-and (*Z*)-selectivity were observed (eq. 5, Scheme 3.9). This was an interesting result because the catalytic hydroboration of trisubstituted alkenes is rare,[23] and it presented an opportunity to study a diastereoselective reaction if a chiral center were adjacent to the diene (eq. 6, Scheme 3.9). Specifically, it was envisioned that a neighboring oxygenated functional group (**3.28**) may serve to control the configuration of the propionate product and deliver high *syn*- or *anti*-selectivity (**3.29** and **3.30**, eq. 6, Scheme 3.9).

Scheme 3.9. Inspiration for Ni-Catalyzed Diastereoselective Hydroboration



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[22] Ely, R. J.; Yu, Z.; Morken, J. P. Manuscript in preparation.

[23] (a) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc*. **2010**, *132*, 1740. (b) Smith, S. M.; Thacker, M. C.; Takacs, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 3734. (c) Hadebe, S. W.; Robinson, R. S. *Tetrahedron Lett.* **2006**, *47*, 1299. (d) Edwards, D. R.; Crudden, C. M.; Yam, K. *Adv. Synth. Catal.* **2005**, *347*, 50. (e) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671. (f) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc*. **1992**, *114*, 6679.

To initiate studies on the diastereoselective hydroboration of dienes, TBS-protected **3.31** was synthesized and subjected to the Ni-catalyzed hydroboration conditions. Encouragingly, the reaction was efficient at room temperature in toluene and, after oxidation, provided the *syn*-diastereomer **3.33** in 10:1 dr and 86% yield (entry 1, Table 3.1). To determine if the ligand had an effect on the diastereoselectivity, the smaller ligands P(cyclopentyl)$_3$ and P(*n*-Bu)$_3$ were tested and resulted in diminished selectivity (entries 2 and 3). The use of THF as solvent improved the diastereoselectivity of the reaction (entry 4), as did lowering the temperature to 0 °C (entry 5). Further decreasing the temperature to -20 °C caused incomplete conversion to **3.32**, even with extended reaction time, and did not improve the diastereoselectivity (entry 6). Next, a variety of protecting groups were analyzed as it is known that alcohol protecting groups can dramatically affect the diastereoselective hydroboration of allylic ethers.[24] Utilizing the smaller TES-protecting group provided the product in excellent yield but with slightly diminished diastereoselectivity compared to TBS (entry 7). The reaction with the larger TBDPS-protecting group required a longer reaction time, but furnished the product as a single diastereomer as determined by ^{1}H NMR (entry 8). A benzyl oxy substituted diene also reacted efficiently, as did the unprotected substrate, but with lower selectivities and yield (entries 9 and 10). It should be noted that in all cases the indicated 1,4-

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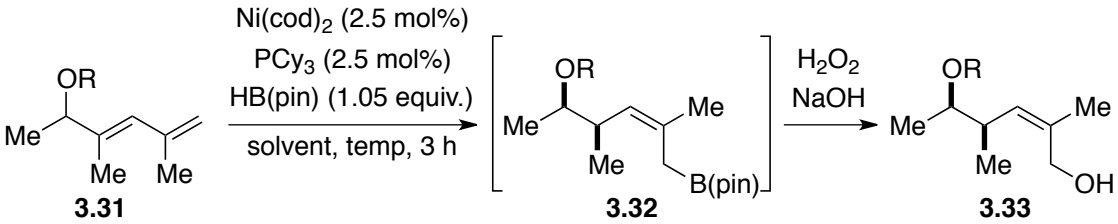
[24] (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1988**, *110*, 6917. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1991**, *114*, 6671. (c) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc*. **1983**, *105*, 2487.

hydroboration product was the only detectable compound; regioisomeric products or those arising from 1,2-hydroboration were not observed.

Table 3.1. Catalytic Hydroboration of Chiral Dienols: Protecting Group Evaluation[a]



3.31 **3.32** **3.33**

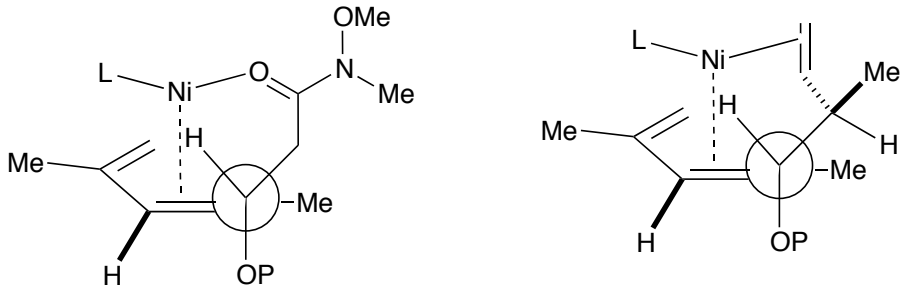
entry	R	solvent	temp °C	dr[b]	yield (%)[c]
1	TBS	toluene	rt	10:1	86
2[d]	TBS	toluene	rt	6:1	82
3[e]	TBS	toluene	rt	2:1	82
4	TBS	THF	rt	12:1	86
5	**TBS**	**THF**	**0**	**14:1**	**89**
6[f]	TBS	THF	-20	14:1	ND
7	TES	THF	0	12:1	93
8[g]	**TBDPS**	**THF**	**rt**	**>20:1**	**80**
9[f]	Bn	THF	0	7:1	72
10[h]	H	THF	0	6:1	56

[a] Reactions were conducted at a concentration of 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of purified material. Values are an average of two experiments. [d] Reaction run with P(cyp)$_3$ as ligand. [e] Reaction run with P(*n*-Bu)^3 as ligand. [f] Reaction run for 12 h. [g] Reaction run for 24 h. [h] Two equiv. HB(pin) employed.

Once optimal reaction conditions were found, a series of TBS-protected substrates were examined in the diastereoselective diene hydroboration (Table 3.2). Enhanced levels of selectivity (relative to substrate **3.31**) were seen with an *n*-alkyl substituent at the carbinol carbon (entry 1, Table 3.2 vs. entry 5, Table 3.1). Dienes with branching

adjacent to the chiral center, including a quaternary center, required longer reaction times but still provided reaction products in good yields and good levels of stereoselection (entries 2 and 3). Dienes with protected oxygen functionality and esters participated in the reaction and provided products with excellent diastereomeric purity (entry 4, 5, and 8). Unfortunately, Weinreb[25] amide- and terminal alkene-derived substrates proved unreactive (entries 6 and 7), most likely due to the basic functional groups coordinating to the metal and prohibiting the oxidative addition of HB(pin) (Figure 3.2). Of note, the optically active diene in entry 8, derived from an Evans' aldol reaction, provided the *syn*, *syn*-stereotriad in excellent yield and good diastereoselectivity.

Figure 3.2. Coordination of Weinreb Amide and Alkene to Nickel Catalyst

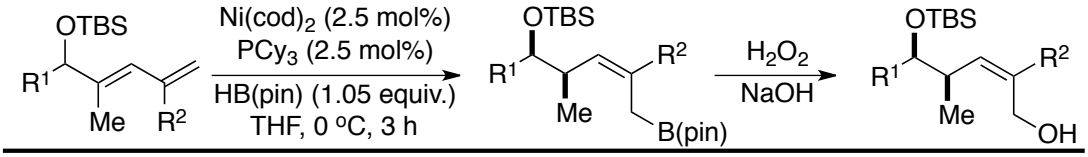


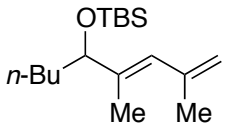
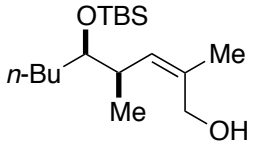
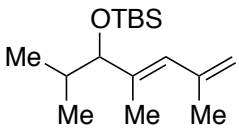
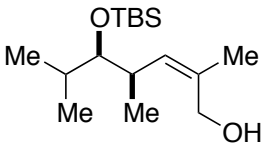
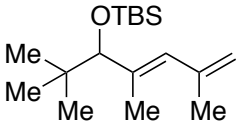
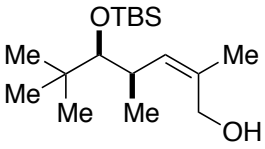
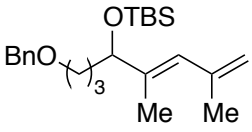
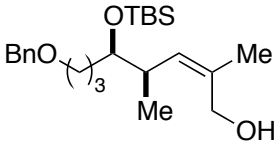
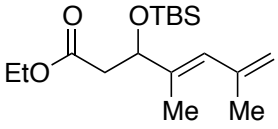
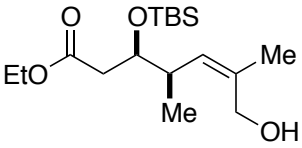
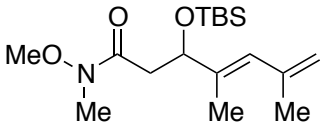
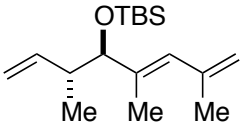
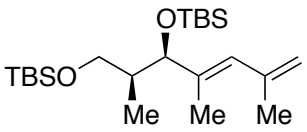
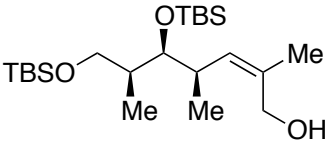
Weinreb Amide as a Ligand

Olefin as a Ligand

[25] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett* **1981**, *22*, 3815.

Table 3.2. Scope of the Ni-Catalyzed Hydroboration of Dieneols[a]



entry	substrate	product	yield(%)[b]	dr
1			90	>20:1
2[c]			98	10:1
3[c,d]			86	6:1
4			88	>20:1
5[e]			80	>20:1
6		NR	-	-
7[c,f]		NR	-	-
8[c]			91	6:1

[a] Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Values are an average of two experiments. [c] Reaction run for 12 h. [d] Reaction run at rt. [e] Oxidation with buffered (pH = 7) H_2O_2. [f] Reaction run at 40 °C.

It was of interest to determine how the geometry and substitution on the diene affected the hydroboration. After extended reaction time at higher temperature a 3:1 (*Z*):(*E*)-diene mixture (entry 1, Table 3.3) gave a high level of stereoselection. Importantly, the (*Z*):(*E*)-diene delivered the same product stereoisomer as obtained from the pure (*E*)-substrate. This observation suggests that high levels of stereocontrol can be obtained even if mixtures of olefin isomers are employed in the reaction. Suspecting that only dienes able to adopt the *S*-cis conformation would react (see chapter 1, section 1.3), the substrate in entry 2 was examined. The lack of reactivity supports the notion that substrates with low concentrations of *S*-cis conformer possess diminished reactivity. The additional methyl group at the 2-postion on the dienes in entries 1-8 of Table 3.2 compared to entry 2 of Table 3.3 allows access to the *S*-cis conformer because the *S*-cis and *S*-trans conformations have offsetting $A^{1,3}$ interactions. Importantly, the substituent required to facilitate the formation of the *S*-cis conformer was not limited to CH_3; indeed both phenyl- and silyl-substituted dienes underwent hydroboration in excellent yield and good diastereoselectivity (entries 3-4). Notably, the $PhMe_2Si$-substituent can offer a convenient handle for additional alkene transformations.[26]

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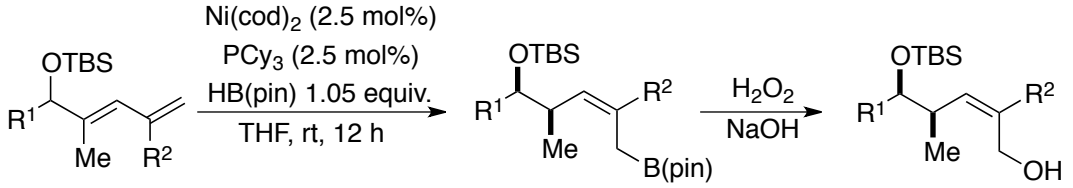
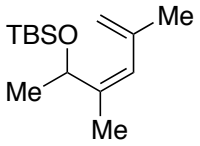
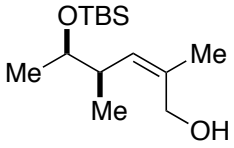
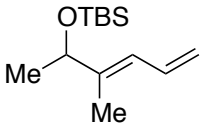
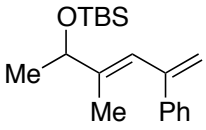
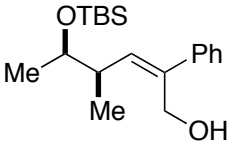
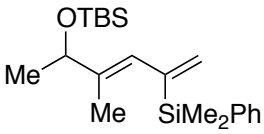
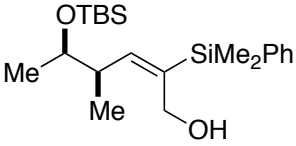
[26] For selected vinylsilane transformations: (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (c) Hiyama, T. in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: Negishi, E-i.), Wiley-Interscience, New York, **2002**, Vol. 1, 285–309; (d) Hiyama, T. in: *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: Diederich, F.; Stang, J. P.), Wiley-VCH, Weinheim, **1998**, pp. 421–452. (e) Colvin, E. W. *Silicon in Organic Sythesis.*, Butterworths, **1981**. (f) Pawluc´, P.; Prukała, W.; Marciniec, B. *Eur. J. Org. Chem.* **2010**, 219. (g) Trost, B.M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.*, **2005**, *127*, 10028. (i) Sore, H. F; Galloway, W. R. J. D.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 1845.

Table 3.3. Hydroboration of (*Z*)-and Differentially Substituted-Dienes[a]



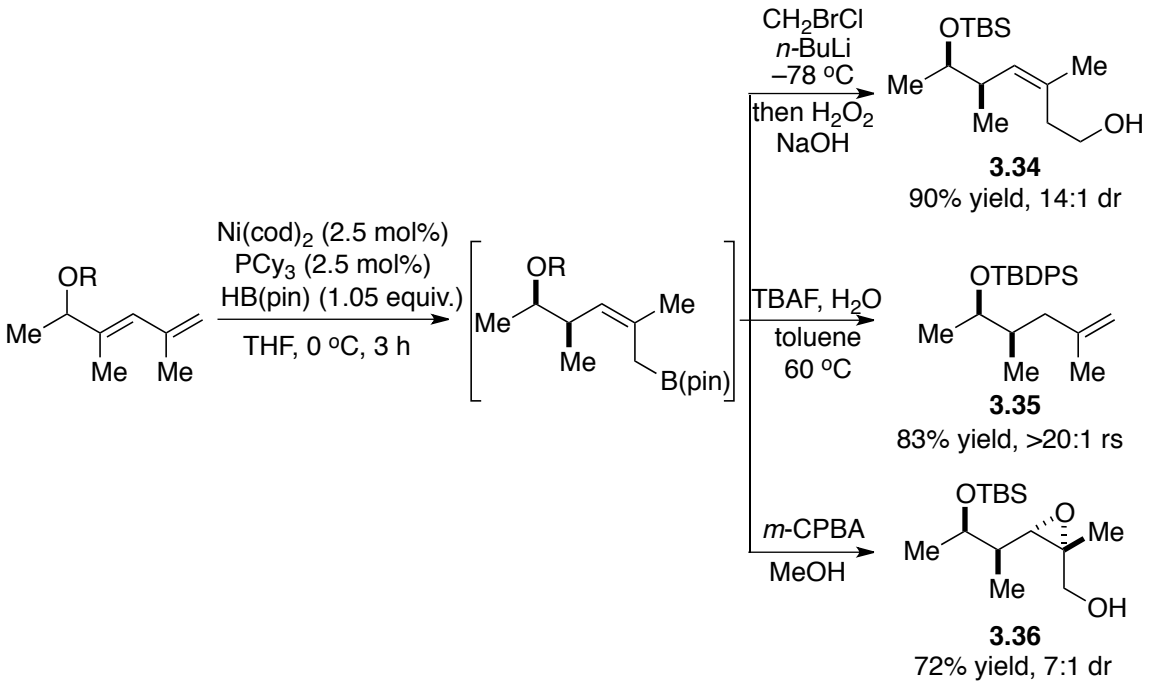
Entry	Substrate	Product	Yield(%)[b]	dr
1[c]			40	17:1
2[d]		NR	-	-
3			91	9:1
4[e]			84	>10:1

[a] Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Values are an average of two experiments. [c] 3:1 (*Z*:*E*)-mixture. [d] Reaction run at 60 °C. [e] Reaction run at 40 °C.

An attractive feature of the diene hydroboration is that the intermediate allylboronic ester provides a useful synthetic handle for further bond-forming reactions (see Chapter 1, Section 1.1). For example, homologation using Matteson's protocol followed by oxidation delivered homoallylic alcohol **3.34** in excellent yield (Scheme

3.10).[27] The terminal alkene **3.35** can be constructed after a selective allylic protonation employing Aggarwal's conditions for protodeboronation.[28] Lastly, diastereoselective alkene epoxidation and boron oxidation occurred concomitantly with the addition of *m*-CPBA to form the functionalized alcohol **3.36** in good yield.[29] In each example, the intermediate allylboronic ester was not isolated, and was transformed in a single-flask reaction.

Scheme 3.10. Utility of Allylboronic Ester Intermediate



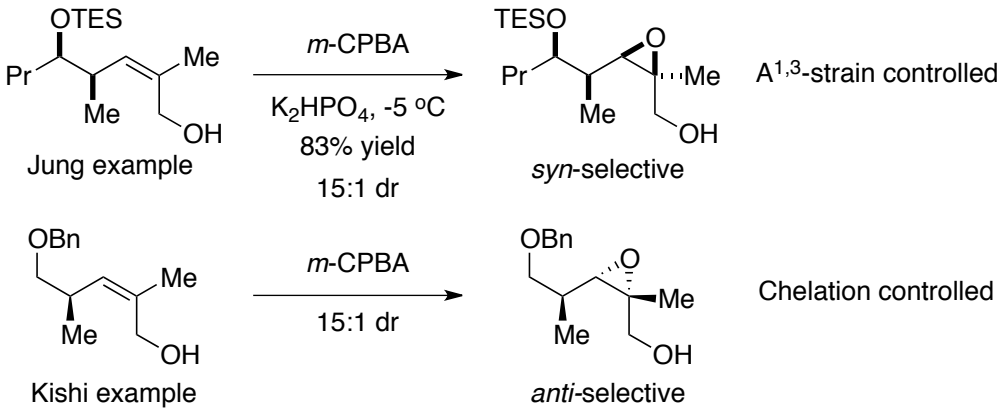
[27] (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Chen, A. C.; Ren, L.; Crudden, C. M. *Chem. Commun.* **1999**, 611. (c) Chen, A. C.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, *64*, 9704. (d) Ren, L.; Crudden, C. M. *Chem. Commun.* **2000**, 721.

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

[29] (a) Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc*. **1997**, *119*, 12150. (c) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett*. **1979**. 4374.

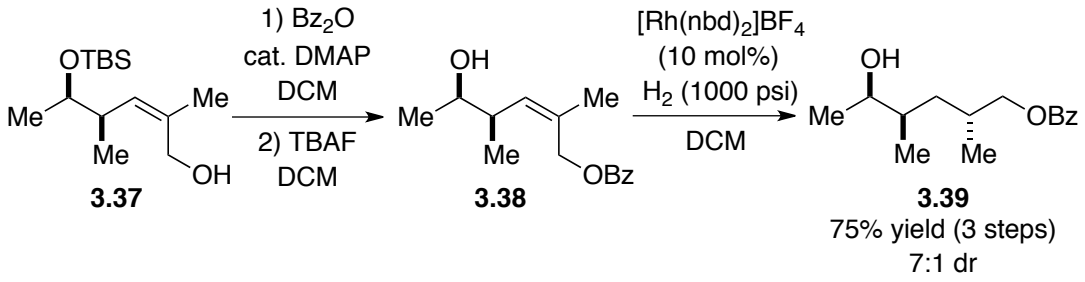
The selectivity of the diastereoselective epoxidation to form **3.36** is an interesting result since it is opposite to what was expected. Running the reaction with only one equivalent of *m*-CPBA resulted in the isolation of the allylic alcohol suggesting that oxidation of the boronic ester is faster than epoxidation of the alkene. Thus, this reaction is very similar to several reports of diastereoselective epoxidation of allylic alcohols (Figure 3.3).[29] Interestingly, an epoxidation example out of the Jung lab,[29b] very similar to our conditions, provided the *syn*-diastereomer, while an example out of the Kishi lab with a substrate without the carbinol stereocenter provided the anti-diastereomer.[29c] In the first example, *m*-CPBA is believed to approach from the least sterically hindered face of the alkene while minimizing $A^{1,3}$-strain. The diastereoselectivity observed in the Kishi example is believed to the result of chelation between the benzyl ether and *m*-CPBA to provide the *anti*-product. The TBS-group in our example should minimize chelation to *m*-CPBA and result in the *syn*-diastereomer similar to Jung's observations.

Figure 3.3. Stereoselective Epoxidation of Acyclic Allylic Alcohols



The trisubstituted alkene formed in the hydroboration reaction can also be functionalized to make fully saturated structures that align well with polyketide frameworks. Using the oxidized hydroboration product **3.37**, a two step protecting group manipulation formed homoallylic alcohol **3.38** that was subjected to directed catalytic hydrogenation (eq. 7, Scheme 3.11). The fully saturated structure **3.39** was formed in good yield and diastereoselectivity representing a skipped methyl fragment that is common in macrolide structures.

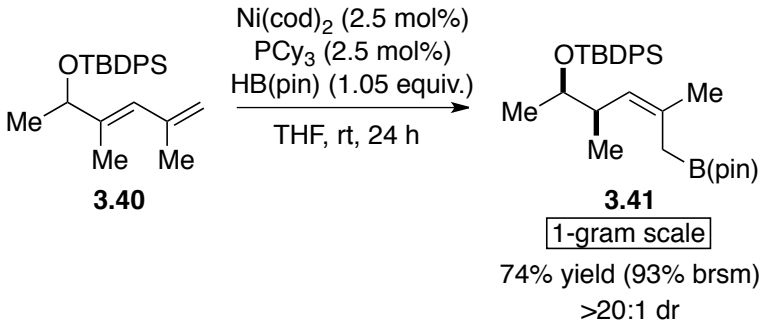
Scheme 3.11. Catalytic Directed Hydrogenation of Oxidized Hydroboration Products



The versatility of the hydroboration products makes it important that the reaction can be executed on large scale so that it can be implemented early in a synthetic route. Thus, one gram of the readily accessible TBDPS-protected dienol **3.40** was subjected to the Ni-catalyzed hydroboration conditions. The reaction with a TBDPS-protected dienol was sluggish compared to other protected substrates (see Table 3.1 entries 5 and 7 vs. entry 8); however, the allylboronic ester **3.41** was easily isolated from the unreacted

starting material as one diastereomer in good yield (Scheme 3.12). Longer reaction times did not improve the conversion presumably due to deactivation of the catalyst.

Scheme 3.12. Gram Scale Ni-Catalyzed Hydroboration

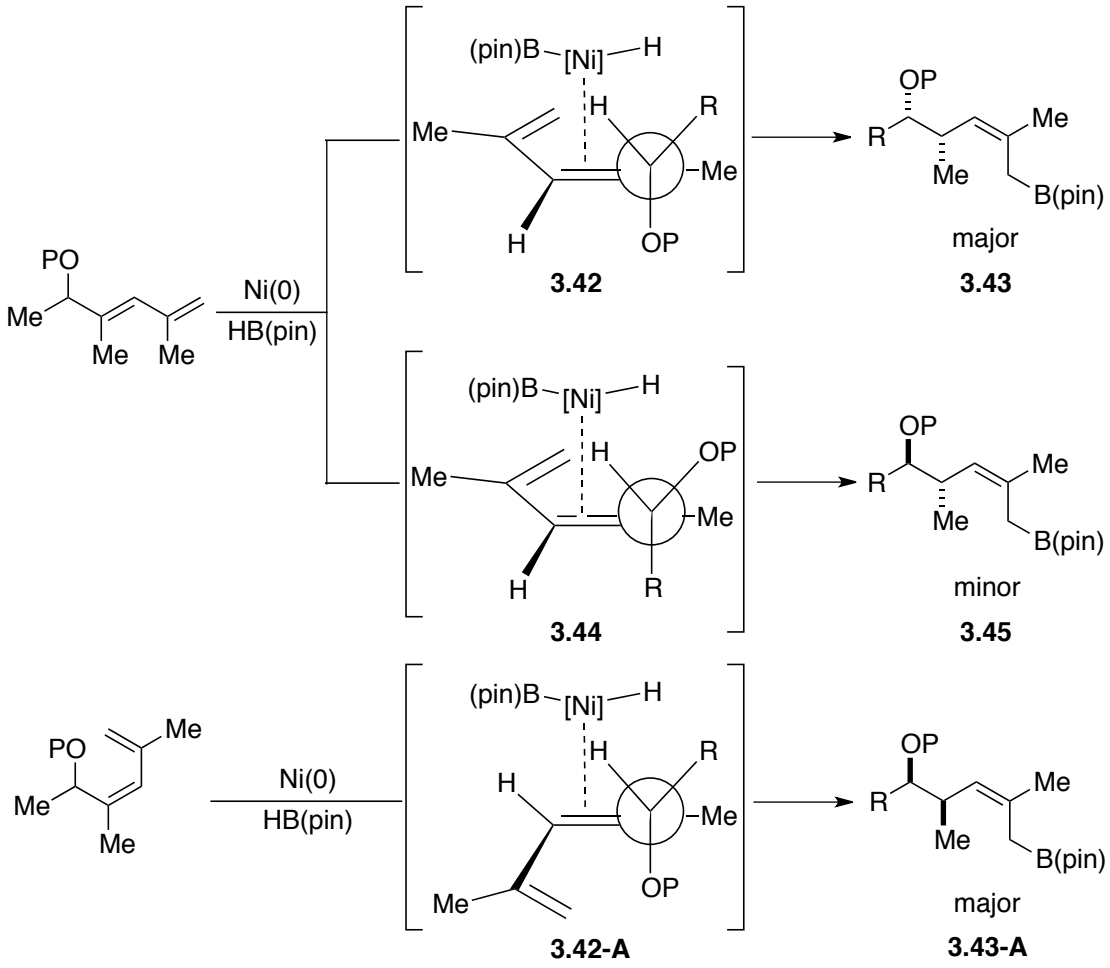


A mechanistic rational explaining the stereochemical outcome of the Ni-catalyzed hydroboration is depicted in Scheme 3.13. Consonant with a hypothesis by Burgess,[30] we suspect that the Ni-complex associates with the diene in a manner that positions the C-O bond, the best π-acceptor, *anti* to the incoming metal. This conformation provides net stabilization of the newly forming bond by mixing the π* of the diene and the σ* of the C-O bond. This interaction lowers the HOMO-LUMO energy gap of the approaching metal nucleophile and the alkene electrophile. As seen in conformation **3.42**, steric interactions are minimized when the carbinol hydrogen is directed toward the metal center and the carbinol substituent is directed away from the metal, producing the observed products **3.43**. This model provides a clear rationale for the observation that

[30] Burgess, K.; van der Donk, W. A.; Jarstifer, M. B.; Ohlmeyer, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 6139.

larger protecting groups serve to enhance the selectivity and why branching substituents at the chiral center lower the selectivity. It also explains why the (*Z*)-dienol (Table 3.3, entry 1) was not only less reactive, but also gave the same diastereomer of product as the (*E*)-dienol (**3.43-A**).

Scheme 3.13. Stereochemical Model for Ni-Catalyzed Diastereoselective Hydroboration



3.4. Application of Ni-Catalyzed Diastereoselective Hydroboration in the Synthesis of Discodermolide

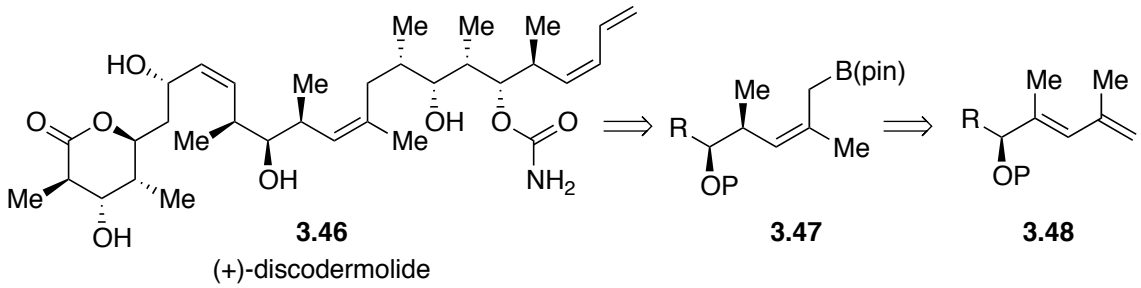
Diastereoselective Ni-catalyzed hydroboration of chiral dienols proved to be a reliable method to generate not only *syn*-propionate motifs but also (*Z*)-trisubstituted allylboronic esters with excellent stereoselectivity. The synthesis of stereodefined trisubstituted olefins has been intensively studied as these structural motifs are ubiquitous in natural products and are valuable substrates for stereoselective synthesis.[31] This is exemplified in the several syntheses of the challenging (*Z*)-trisubstituted olefin present in discodermolide (**3.46**, Scheme 3.14), one of the most thoroughly studied polyketides.[32] We believed that the diastereoselective hydroboration of a chiral dienol **(3.48)** would provide rapid construction of this challenging segment of the molecule, installing the *syn*-propionate unit, the (*Z*)-trisubstituted olefin, and supplying a boronic ester (**3.47**) for the further installation of the right half of the natural product in a single catalytic step.

---

[31] For recent examples of stereocontrolled trisubstituted olefin synthesis, see; (a) Moure, A. L.; Arrayás, A. G.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc*. **2012**, dx.doi.org/10.1021/ja300627s. (b) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419. (c) Rooke, D. A.; Ferreira, E. M.; *J. Am. Chem. Soc*. **2010**, *132*, 11926. (d) Belardi, J. K.; Micalizio, G. C. *J. Am. Chem. Soc*. **2008**, *130*, 16870. (e) Xie, Q.; Denton, R. W.; Parker, K. A. *Org. Lett*. **2008**, *10*, 5345. (f) Prantz, K.; Mulzer, J. *Chem. Eur. J*. **2010**, *16*, 485.

[32] For reviews, see; (a) Paterson, I.; Florence, G. J. *Top. Curr. Chem.* **2009**, *286*, 73. (b) Florence, G. J.; Gardner, N. M.; Paterson, I. *Nat. Prod. Rep.* **2008**, *25*, 342. (c) Smith, A. B.; Freeze, B. S. *Tetrahedron* **2008**, *64*, 261.

Scheme 3.14. Diastereoselective Hydroboration of Chiral Dienols Applied to the Synthesis of Discodermolide



3.46 (+)-discodermolide **3.47** **3.48**

A. Biological Activity of Discodermolide

Discodermolide was first isolated by Gunaskera and co-workers at the Harbor Branch Oceanographic Institution in 1990 from extracts of the rare Caribbean marine sponge *Discodermia dissoluta*.[33] Biological studies have proven discodermolide to be the most potent microtubule stabilizer in human cell lines to date, with IC_{50} values ranging from 3 to 80 nM.[34] Similar in action to paclitaxel,[35] discodermolide causes cell cycle arrest in the G2/M phase by binding and stabilizing mitotic spindle microtubules.[36] Furthermore, discodermolide displays potent activity against paclitaxel-resistant ovarian and colon cancer cell lines, with an IC_{50} of 2.5 nM.[37] For this reason, as well as its

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[33] Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1990**, *55*, 4912. Correction: *J. Org. Chem*. **1991**, *56*, 1346.

[34] Michaelis, M. L.; Ansar, S.; Chen, Y.; Reiff, E. R.; Seyb, K. I.; Himes, R. H.; Audus, K. L.; Georg, G. I. *J. Pharmacol. Exp. Ther*. **2005**, *312*, 659.

[35] Nicolau, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed.* **1994**, *33*, 15.

[36] (a) ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243. (b) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 287.

[37] Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharm.* **1997**, *52*, 613.

challenging structure, discodermolide has generated significant efforts toward its synthesis, culminating in 13 completed total syntheses.[38] Common to all syntheses has been a convergent approach by dividing the molecule into three equally complex fragments. Arguably, the most difficult aspects of the total syntheses of discodermolide have been the successful union of the different fragments and the synthesis of the (*Z*)-trisubstituted olefin.

B. Selected Strategies for the Total Synthesis of Discodermolide

The first total synthesis of (+)-discodermolide was completed by Schreiber and co-workers in 1996.[38d] Schreiber first synthesized the unnatural antipode (-)-discodermolide in 1993,[38a] confirming the relative stereochemistry and establishing the absolute stereochemistry. The key steps in their synthetic strategy involved a Nozaki-Hiyama-Kishi coupling[39] between aldehyde **3.49** and alkynyl iodide **3.50**, followed by an

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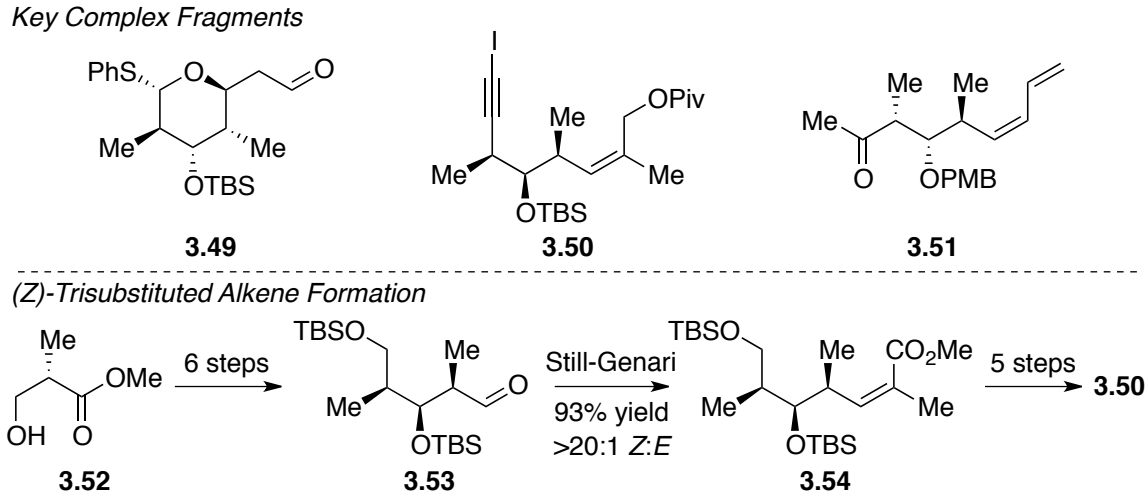
[38] For completed total syntheses of discodermolide, see; (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc*. **1993**, *115*, 12621. (b) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *Chem. Biol*. **1994**, *1*, 67. (c) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (d) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 11054. (e) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem*. **1997**, *62*, 6098. (f) Marshall, J. A.; Johns, B. A. *J. Org. Chem*. **1998**, *63*, 7885. (g) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett*. **1999**, *1*, 1823. (h) Halstead, D. P. Ph.D. Thesis, Harvard University, Cambridge, MA, 1999. (i) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 377. (j) Harried, S. S.; Lee, C. P.; Yang, G.; Lee, T. I. H.; Myles, D. C. *J. Org. Chem*. **2003**, *68*, 6646. (k) Smith, A. B.; Freeze, B. S.; Brouard, I.; Hirose, T. *Org. Lett*. **2003**, *5*, 4405. (l) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett*. **2003**, *5*, 35. (m) Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repic, O.; Wang, R.-M.; Florence, G.; Lyothier, I.; Paterson, I. *Org. Process Res. Dev*. **2004**, *8*, 122 and references cited therein. (n) Arefolov, A.; Panek, J. S. *J. Am. Chem. So*c. **2005**, *127*, 5596. (n) Smith, A. B., III; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett*. **2005**, *7*, 1825. (o) Paterson, I.; Lyothier, I. *Org. Lett*. **2004**, *6*, 4933. (p) See ref. 12.

[39] (a) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn*. **1982**, *55*, 561. (b) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*, 5585. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc*. **1986**, *108*, 6048. (d) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc*. **1986**, *108*, 5644. (e) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett*. **1987**, *28*, 3463.

enolate alkylation to connect **3.51** (Scheme 3.15). All three fragments of Schreiber's synthesis commenced with commercially available Roche ester (**3.52**, ~$20/g from Aldrich) which has served as a starting material for all total syntheses of discodermolide to date. The (*Z*)-trisubstituted olefin in **3.50** was prepared *via* a Still-Genari olefination[40] of aldehyde **3.53** to furnish **3.54** in excellent yield and with high stereoselectivity. Schreiber's total synthesis was completed in a longest linear sequence of 24 steps (36 total) in 3.6% overall yield.

Scheme 3.15. Schreiber's Strategy for the Total Synthesis of (+)-Discodermolide

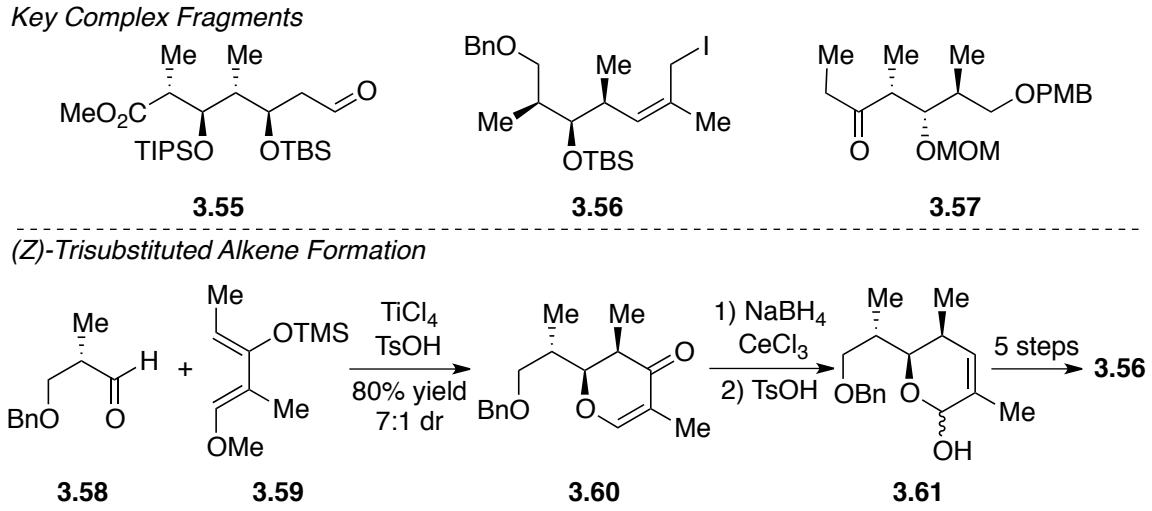


Myles and co-workers reported the total synthesis of (-)-discodermolide in 1997[36e] followed by a synthesis of the natural antipode in 2003.[36j] Similar to Schreiber's strategy, Myles used an enolate alkylation to adjoin **3.56** and **3.57,** followed by a Nozaki-

[40] Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.

Hiyama-Kishi addition to aldehyde **3.55** (Scheme 3.16). An interesting sequence to install the (*Z*)-trisubstituted alkene in **3.56** involved a titanium-mediated diastereoselective hetero-Diels-Alder reaction[41] between aldehyde **3.58** and Danishefsky's diene[42] (**3.59**) to furnish **3.60** in good yield and diastereoselectivity. A Luche reduction[43] followed by a Ferrier rearrangement[44] produced **3.61.** Reductive opening of the lactol, followed by four additional steps provided **3.56**. In a longest linear sequence of 22 steps, Myles synthesis provided (+)-discodermolide in 1.1% overall yield.

Scheme 3.16. Myles' Strategy for the Total Synthesis of (+)-Discodermolide



[41] Springer, J. B.; DeBoard, J.; Corcoran, R. C. *Tetrahedron Lett*. **1995**, *36*, 8733.
[42] Danishefsky, S. J.; Pearson,W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc*. **1985**, *107*, 1256.
[43] Luche, J. L. *J. Am. Chem. Soc*. **1978**, *100*, 2226.
[44] Ferrier, R. J.; Overend, W. G.; Ryan, A. E. *J. Chem. Soc., Abstracts* **1962**, 3667.

To show the utility of their crotylsilane methodology in the synthesis of polypropionate motifs (see section 3.2, Scheme 3.5), Panek and co-workers synthesized (+)-discodermolide in 2005 in 27 steps (42 total) in 2.1% overall yield.[36n] The strategy employed a 1,4-*syn*-1,5-*anti* aldol reaction between ketone **3.62** and aldehyde **3.63** to connect the first two fragments. The (*Z*)-trisubstituted vinyl silane in **3.63** was later converted to a vinyl iodide for use in an established Suzuki-Miyaura coupling[45] with an alkylborane derived from **3.64** to provide the carbon framework of discodermolide. The synthesis of the (*Z*)-trisubstituted olefin began with the synthesis of TMS-alkyne **3.66** which was available in four steps from the α-chiral crotylsilane addition product **3.65**.[15] Hydrozirconation[46] of alkyne **3.66**, followed by iodination, and Negishi coupling[47] afforded vinyl silane **3.67** with the desired (*Z*)-stereochemistry. Further elaboration provided the propargylic aldehyde **3.63** in 4 steps.

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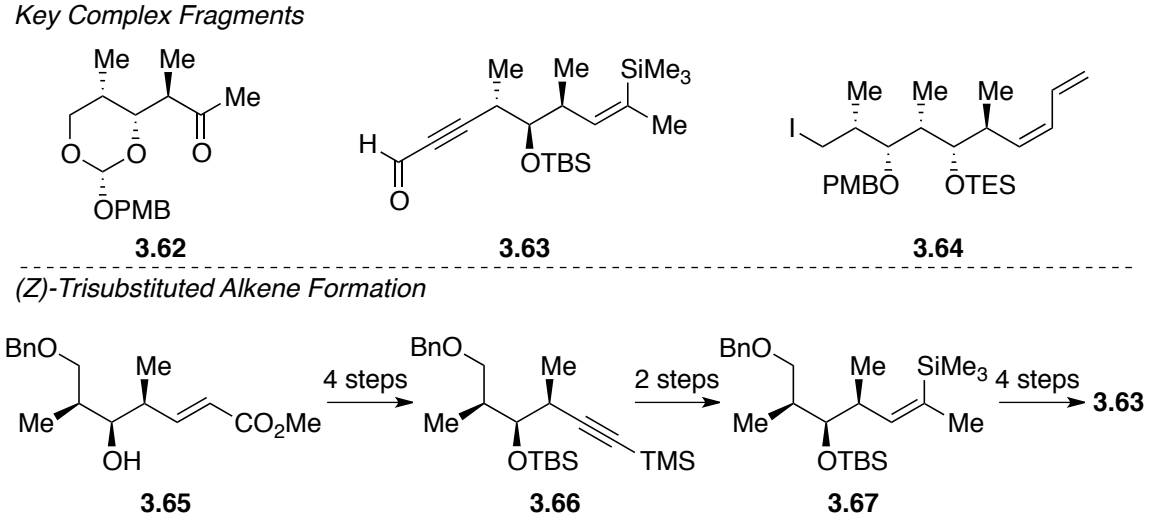
[45] See ref. 36f for the development of the optimal Suzuki-Miyaura cross-coupling conditions in the synthesis of discodermolide.
[46] Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc*. **1974**, *96*, 8115.
[47] King, A. O.; Okukado, K.; Negishi, E. *J. Chem. Soc., Chem. Commun*. **1997**, 683.

Scheme 3.17. Panek's Strategy for the Total Synthesis of (+)-Discodermolide

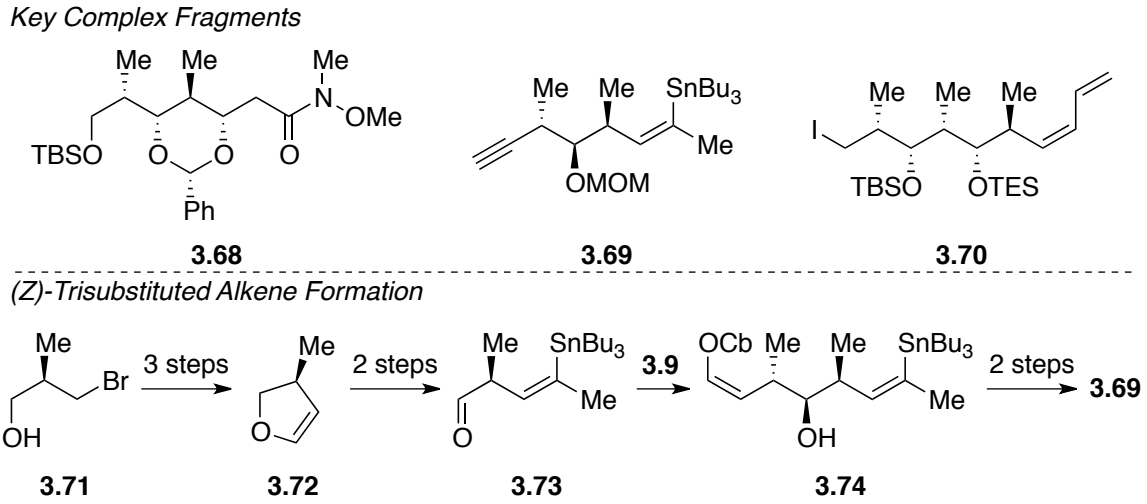


In the most recent synthesis of discodermolide, Ardisson and co-workers highlighted the utility of crotyltitanium reagent (**3.9**, Scheme 3.3) to furnish *anti*-propionate arrays with adjacent vinyl carbamates available for further polyketide construction.[12] The addition of the lithiated alkyne derived from **3.69** to Weinreb amide[48] **3.68**, followed by a Lindlar reduction,[49] provided the left portion of discodermolide. The vinylstannane was later converted to a vinyl iodide for a Suzuki-Miyaura coupling similar to previous syntheses.[45] The required (*Z*)-trisubstituted vinylstannane was available from dihydrofuran **3.72** which is derived from **3.71** in 3 steps. Deprotonation of **3.72** with *t*-BuLi and subsequent addition to $Me_2CuLi{\cdot}LiCN$ resulted in a 1,2-cuprate transfer that provided a homoallylic alcohol after trapping with Bu_3SnCl. Oxidation to the aldehyde

[48] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
[49] Lindlar, H.; Dubuis, R. *Org. Synth*. **1973**, *5*, 880.

3.73 and crotylation with crotyltitanium reagent **3.9** provided the vinyl carbamate **3.74**. Alcohol protection followed by a Fritsch–Buttenberg–Wiechell[50] rearrangement elegantly provided the alkyne **3.69**.

Scheme 3.18. Ardisson's Strategy for the Total Synthesis of (+)-Discodermolide



The most prominent groups involved in the study of discodermolide have been those of Smith and Paterson. Both laboratories have developed several generations of syntheses in order to provide an efficient and practical large scale synthesis. As proof of their success, Novartis Pharmaceuticals undertook a 60 g scale synthesis of (+)-discodermolide for clinical trials (*vide infra*) by combining the best aspects of each groups' strategy.

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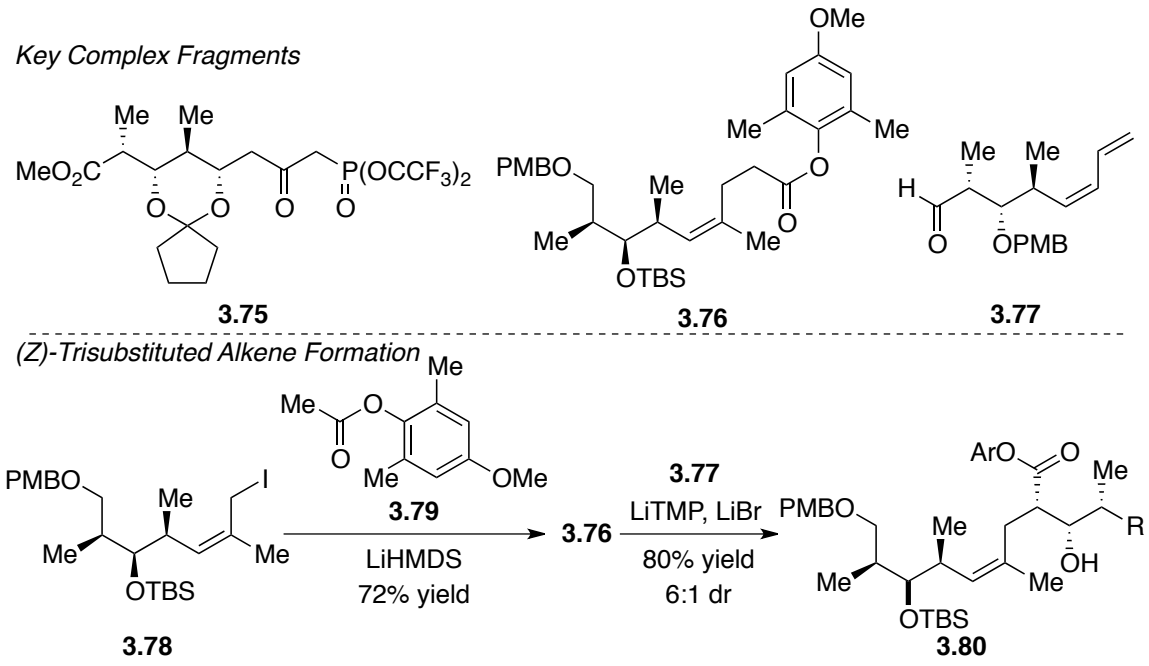
[50] For a review, see; Knorr, R. *Chem. Rev*. **2004**, *104*, 3795.

Paterson and co-workers first synthesized (+)-discodermolide in 2000 using an array of challenging boron- and lithium-mediated aldol reactions.[36i] Since their seminal publication, they have reported second[36l] and third[36o] generation routes in order to overcome technically difficult reactions on large scale, and have provided the highest yielding synthesis to date (11.1% overall yield, 21 longest-linear sequenc). The endgame of the third generation synthesis utilized a highly selective Still-Genari olefination between phosphonate **3.75** and an aldehyde derived from **3.76** (Scheme 3.19). A *syn*-selective aldol reaction between **3.76** and **3.77** constructed the right half of the molecule. The bulky aryl ester of **3.76** was required for high diastereoselectivity in the aldol reaction. The (*Z*)-trisubstituted alkene was produced *via* a Still-Genari olefination similar to that used by Schreiber, followed by three additional steps to provide **3.78**. Enolate alkylation of ester **3.79** with allylic iodide **3.78** provided **3.76,** which reacted with aldehyde **3.77** to furnish **3.80**. The ester in **3.80** was reduced to the required methyl group in a three step sequence.

Scheme 3.19. Paterson's Third Generation Strategy for the Synthesis of Discodermolide

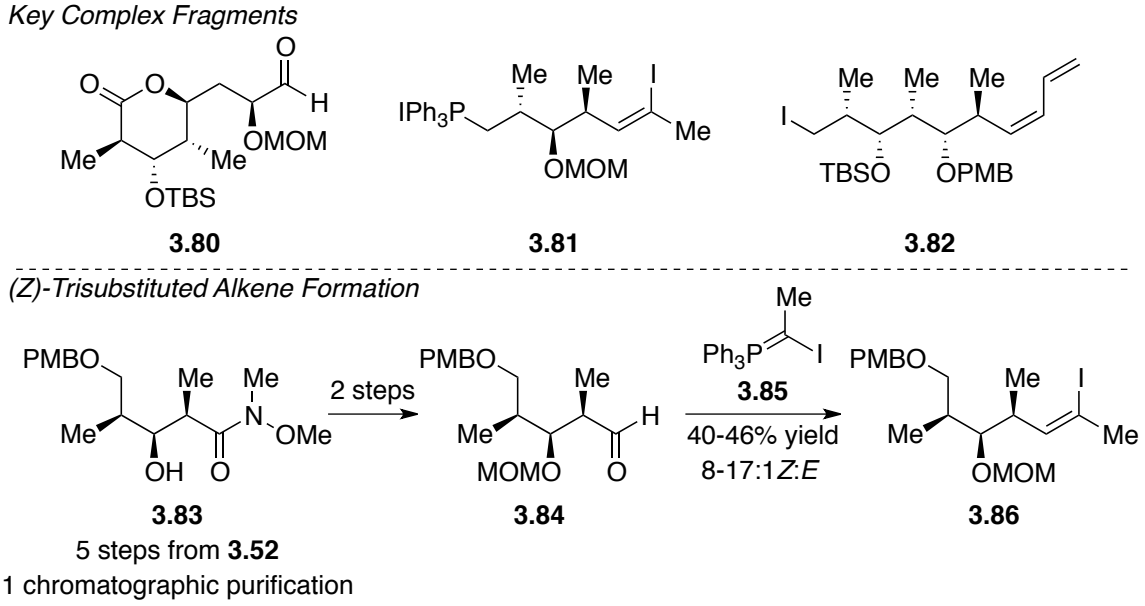


Smith and co-workers first synthesized (-)-discodermolide in 1995, followed by the natural antipode on gram scale in 1999 providing Novartis Pharmaceuticals with sufficient material for preclinical studies.[36g] The gram-scale synthesis was limited by a Wittig olefination requiring ultra-high pressure conditions.[51] As a result, a third generation[36k] effort was developed in 2003, followed by a fourth generation synthesis[36n] in 2005, which at 17 longest-linear sequence of steps is currently the shortest synthesis of (+)-discodermolide (Scheme 3.20). The fourth generation synthesis benefited from the observation that a smaller protecting group on **3.81** (MOM vs. TBS) allowed for much milder conditions in the Wittig olefination between **3.80** and **3.81**, as well as increased

[51] Wittig, G.; Schollkopf, U. *Chem. Ber*. **1954**, *87*, 1318.

the yield of phosphonium salt **3.81** from **3.86** (Scheme 3.20). The endgame utilized the efficient Suzuki-Miyaura coupling between **3.81** and a borane derived from **3.82** that was originally developed by Marshall and co-workers[36f] and adapted by Novartis Pharmaceuticals in their final steps. The largest contribution by Smith's synthesis to Novartis' effort was the route to **3.83**, a common precursor for all three fragments. A *syn*-Evan's aldol[52] reaction was the key to the highly efficient five step synthesis of **3.83**. Only one chromatographic purification was needed as most intermediates could easily be crystallized to give highly pure material. Novartis also utilized a Zhao-Wittig olefination[53] in their scale up effort, which was employed by Smith for the synthesis of the (*Z*)-trisubstituted vinyl iodide **3.86**.

Scheme 3.20. Smith's Fourth Generation Synthesis of (+)-Discodermolide

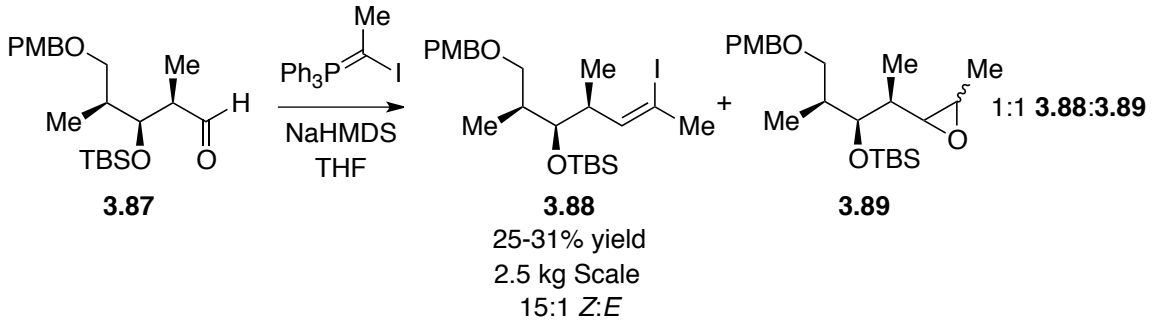


[52] Gage, J. R.; Evans, D. A. *Org. Synth*. **1990**, *68*, 77.
[53] Chen, J.;Wang, T.; Zhao, K. *Tetrahedron Lett*. **1994**, *35*, 2827.

As mentioned previously, Novartis Pharmaceuticals adapted several aspects of both Smith's and Paterson's synthesis to deliver 60 g of (+)-discodermolide in 2004 for clinical trials in a 26 step sequence (39 total, 17 purifications) with an overall yield of 0.65% that took 20 months to complete.[36m] The synthesis of the (*Z*)-trisubstituted vinyl iodide was by far the least efficient step of the synthesis. As shown in Scheme **3.21**, the olefination on a 2.5 kg scale routinely provided **3.88** with good stereoselectivity but in only 25-31% yield. A detailed investigation of this reaction reported by Smith and co-workers[54] found that the poor yield was due to the production of a 1:1 mixture of desired olefin to epoxide **3.89** and instability of the product. It is obvious that a method to synthesize the challenging (*Z*)-trisubstituted olefin in discodermolide is of value, preferably while also establishing the *syn*-propionate and furnishing a synthetic handle for further polyketide construction. We believed that a Ni-catalyzed diastereoselective 1,4-hydroboration of a suitable chiral dienol would meet these challenges and allow for an expedient synthesis of discodermolide.

[54] Arimoto, H.; Kaufman, M. D.; Kobayashi, K.; Qiu, Y.; Smith, A. B., III. *Synlett* **1998**, 765.

Scheme 3.21. Novartis Pharmaceuticals' Synthesis of the (*Z*)-Trisubstituted Vinyl Idodide



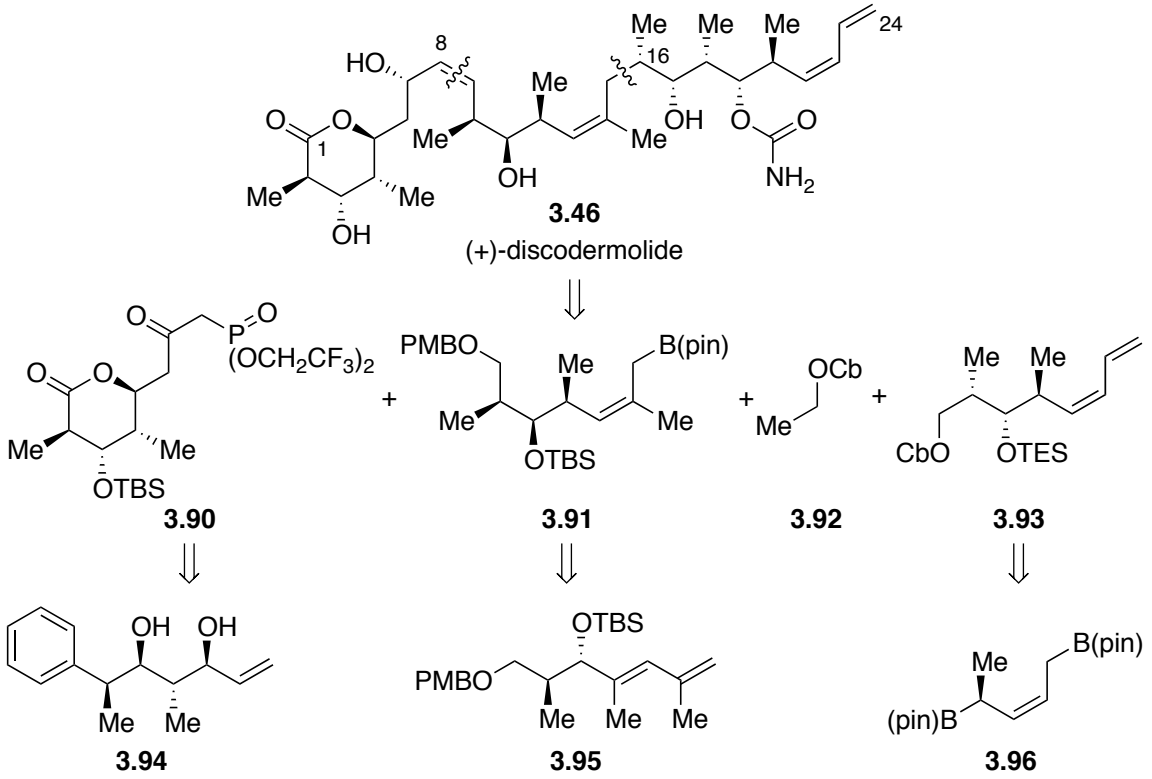
C. Discodermolide Retrosynthesis

Similar to previous syntheses of discodermolide, it was reasoned that the most convergent route would involve breaking the molecule into three equally complex structures (Scheme 3.22). The success of olefination reactions to install the (*Z*)-disubstituted alkene at C8, and the encouraging hydroboration result in Table 3.2, entry 8, identified **3.90** and **3.91** as key intermediates. The phosphonate **3.90** could be elaborated from diol **3.94** by using the aryl group as a masked carboxylic acid.[55] The racemic diol **3.94** has previously been made in our laboratory *via* three component borylative diene-aldehyde coupling.[56] The (Z)-trisubstituted allylboronic ester **3.91** could result from the diastereoselective hydroboration of chiral dienol **3.95**. In order for our synthesis to be competitive with prior syntheses, an efficient construction of **3.95** would be required, as well as an effective strategy to connect the boronic ester **3.91** to the rest of the molecule. An iterative homologation of boronic ester **3.91** with lithiated carbamate **3.92**, followed by **3.93** could accomplish this by installing the C16-C24 fragment in a single flask

[55] For a review, see; Mander, L. N.; Williams, C. M. *Tetrahedron* **2003**, *59*, 1105.
[56] Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 7576.

operation.[57] The carbamate **3.93** could arise from a Pt-catalyzed 1,4-diboration, homologation, oxidation sequence of *trans*-1,3-pentadiene (**3.96**).[58] Notably, our retrosynthetic analysis does not require the use of expensive starting materials such as the Roche ester, and the three principal fragments can be synthesized using methodologies developed in our laboratory.

Scheme 3.22. Retrosynthetic Analysis of (+)-Discodermolide



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[57] For examples of similar strategies in total synthesis, see; (a) Pulis, A. P.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2012**, doi: 10.1021/ja303022d. (b) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed*. **2009**, *48*, 6317. (c) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed*. **2007**, *46*, 7491.

[58] (a) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134. (b) Schuster, C. H.; Li, B.; Morken, J. P. *Angew. Chem., Int. Ed*. **2011**, *50*, 7906.

D. Forward Synthesis of (+)-Discodermolide

The synthesis of diene **3.95** commenced with a high yielding two step sequence involving an olefination reaction between commercially available methacrolein (**3.97**) and stabilized-Wittig reagent **3.98,** followed by $LiAlH_4$ reduction to provide **3.100** (Scheme 3.23). The ester **3.99** was formed with complete (*E*)-selectivity as determined by ^1H NMR. A variety of methods were then considered to install the *anti*-aldol moiety. Unfortunately, very few catalytic *anti*-aldol[8] or -crotylation[9] reactions are highly enantio- and diastereoselective with aliphatic or unsaturated aldehydes.[59] To avoid the use of chiral auxiliary based methodologies,[60] Krische's Ir-catalyzed transfer hydrogenation crotylation[61] was chosen since high diastereo- and enantioselectivities can be achieved with either aliphatic aldehydes or alcohols. This allowed **3.100** to be used directly without prior oxidation to the aldehyde. Thus, catalyst **(*S*)-3.102** was pre-formed from $(Ir(cod)Cl)_2$ and commercially available (*S*)-SEGPHOS, and submitted to the reaction conditions with alcohol **3.100** and crotyl donor **3.101**. After two days at 60 °C the crotylation product **3.103** was isolated in moderate yield and diastereoselectivity but with excellent enantioselectivity.

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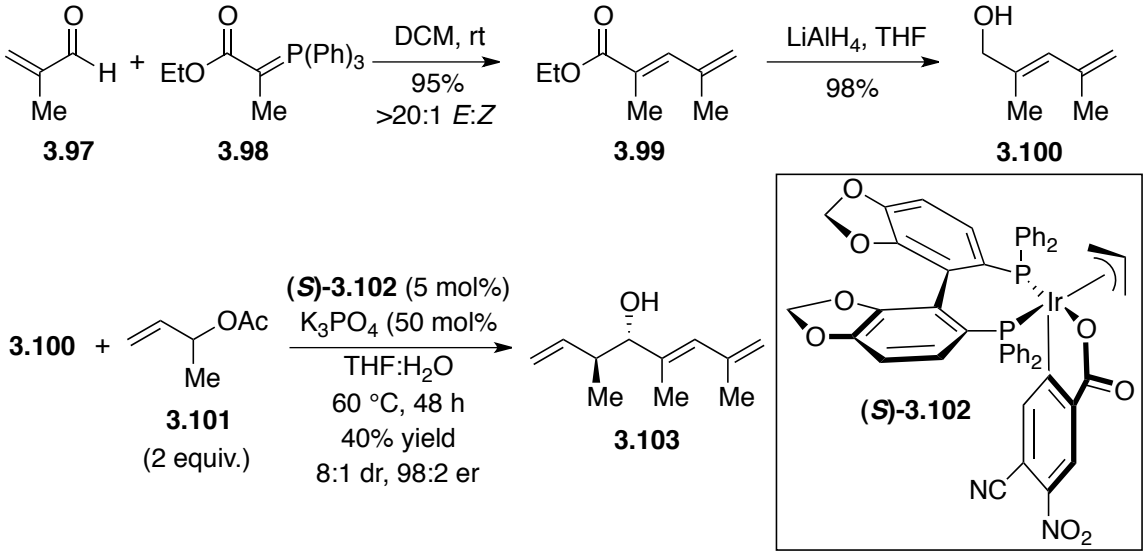
[59] Initial attempts at utilizing the proline catalyzed cross-aldol reaction were unsuccessful, see; Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2002**, *124*, 6798.
[60] (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (c) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (d) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.
[61] See ref 9i and Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem*. **2011**, *76*, 2350.

Scheme 3.23. Synthesis of Chiral Dienol Precursor



After protection of dienol **3.103** as the *t*-butyldimethylsilyl ether, a selective oxidative cleavage of the terminal alkene was required (Scheme 3.24). Differential olefin cleavage using catalytic OsO_4 and NMO[62] produced a complex mixture of products. Employing Sharpless' AD-mix-α reagent,[63] with hopes that the bulky cinchona alkaloid ligand-OsO_4 complex would be selecitive for the terminal olefin,[64] was also unsuccessful as the reaction proceeded slowly and with little selectivity. This problem was overcome by the use of Pt-catalyzed diboration of alkenes with $B_2(pin)_2$.[65] When **3.104** was treated with 1 mol% $Pt(dba)_3$, 1.5 mol% TADDOL-based ligand **(*R*,*R*)-3.105**, and only 1 equiv. of $B_2(pin)_2$, followed by oxidation, the terminal diol **3.106** was isolated as the only

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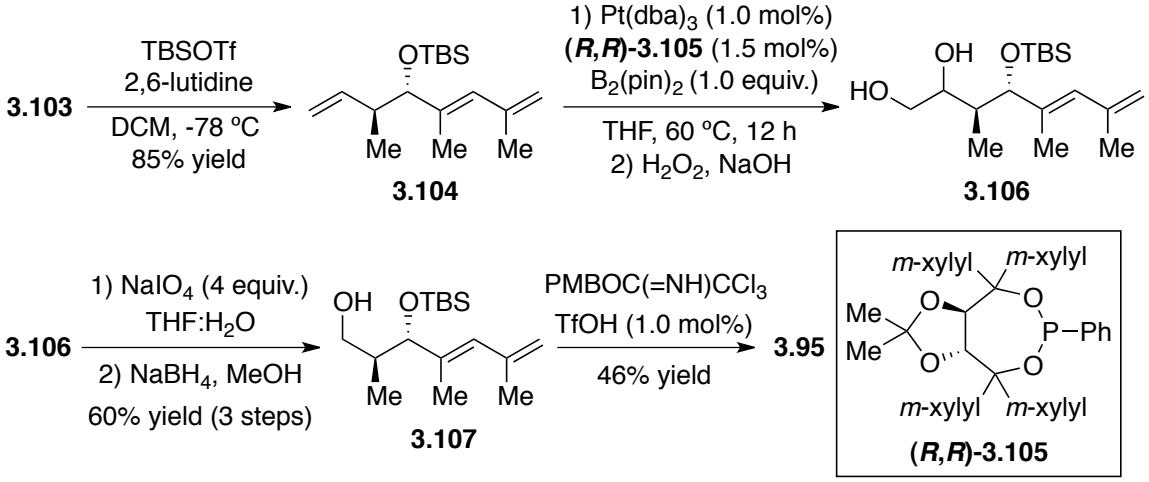
[62] Provencal, D. P.; Gardelli, C.; Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett*. **1995**, *36*, 6033.
[63] Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
[64] Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc*. **1997**, *119*, 2327.
[65] Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 13210.

regioisomer. Metal-free diboration conditions[66] were attempted but produced complex mixtures. Efforts to employ achiral ligands in the Pt-catalyzed diboration conditions surprisingly provided zero conversion. Taking the material forward, the unpurified diol **3.106** was oxidatively cleaved with sodium periodate followed by reduction with sodium borohydride to provide alcohol **3.107** in 60% yield over the three steps. Protection of the primary alcohol as a PMB-ether provided diene **3.95** for the diastereoselective Ni-catalyzed hydroboration.

Scheme 3.24. Synthesis of Chiral Dienol **3.95** for Ni-Catalyzed Hydroboration



Before screening conditions for the diastereoselective Ni-catalyzed hydroboration of **3.95**, the synthesis of carbamate **3.93** was attempted. In order to prepare diol **3.96** with high enantioselectivity, a Pt-catalyzed 1,4-diboration[57b] (see Chapter 2, section 2.2) of

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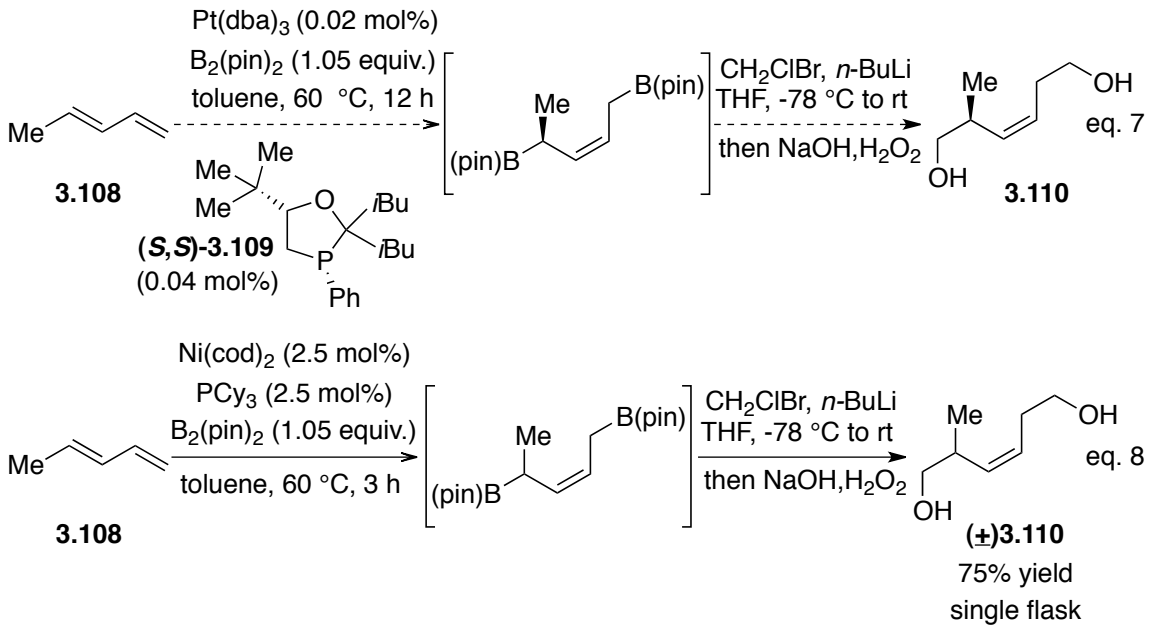
[66] Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 7158.

commercially available **3.108** with ligand **(*S*, *S*)-3.109,** followed by *in situ* double-Matteson homolgation[67] and oxidation (eq. 7, Scheme 3.25) could be performed. Ni-catalyzed 1,4-diboration[68] (see Chapter 2, section 2.3) of **3.108** was first used to provide the desired racemic diol in 75% yield over the three step, single-flask process.

Scheme 3.25. Pt- and Ni- Catalyzed 1,4-Diboration to Provide Diol **3.110**



Once the diol **(±)-3.110** was in hand, a method to selectively eliminate the least hindered alcohol was investigated. It was thought the slight steric bias between the two alcohols might allow for selective protection of the least hindered alcohol. Selective tosylation of **3.110** was attempted utilizing NEt_3 as base in DCM at -78 °C. The reaction

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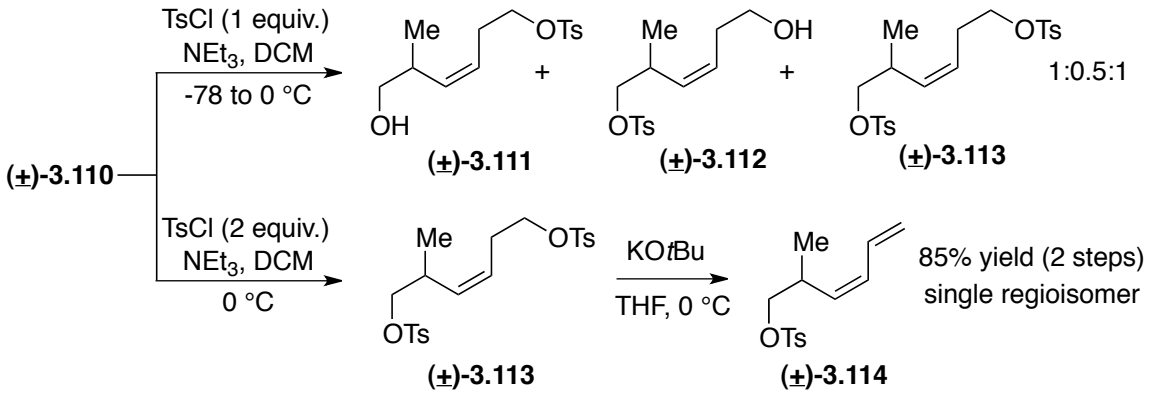
[67] Sadhu, K.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.
[68] Ely, R. J.; Morken, J. P. *Org. Lett*, **2010**, *12*, 4348.

was sluggish at that temperature as monitored by TLC, and was allowed to warm to 0 °C. Unfortunately, the reaction was not selective, providing the desired product **3.111**, the undesired regioisomer **3.112**, and the bis(tosylation) product **3.113** in a 1:0.5:1 ratio (Scheme 3.26). A selective protection of the diol relies on the steric difference of the two alcohols which are both primary; however, if both were activated for an elimination reaction, the reactive site would then be a secondary carbon vs. a tertiary carbon. Therefore, a selective elimination from bis(tosylate) **3.113** seemed much more plausible. To test this hypothesis, bis(tosylate) **3.113** was synthesized, followed by the addition of 1.1 equivalents of KO*t*-Bu at 0 °C. The (*Z*)-diene **3.114** was isolated in excellent yield as a single regioisomer.

Scheme 3.26. Selective Elimination of Bis(Tosylate) to Provide (*Z*)-Diene **3.114**



To complete the synthesis of carbamate **3.93** the tosylate **3.114** needed to be converted to an aldehyde in order to undergo an Evans' aldol reaction to establish the *syn*-

propionate motif. It was hoped that this could be accomplished by the Kornblum oxidation[69] which converts alkyl tosylates or iodides to aldehydes in a single step. Unfortunately, all attempts, including more mild conditions,[70] were unsuccessful as isomerization to the conjugated aldehyde **3.116** was always observed rather than the desired aldehyde **3.115** (eq. 9 and 10, Scheme 3.27). While a one-step conversion of the tosylate to the aldehyde would be more attractive, the oxidation of the alcohol **3.118** to the desired aldehyde is known.[71] Thus, it was thought conversion of the tosylate to the alcohol **3.118** followed by oxidation could provide **3.115**. The tosylate was first smoothy converted to the iodide *via* a Finkelstein reaction,[72] then submitted to silver mediated hydrolysis conditions (eq. 11, Scheme 3.27).[73] These reaction conditions provided a complex mixture of products without isolation of the desired alcohol. Further screening of hydrolysis conditions could provide the desired alcohol; however, this route could possibly be improved by protecting diol **3.110** with different protecting groups, such as acetate or benzoate which are more easily hydrolyzed yet can be selectively eliminated.

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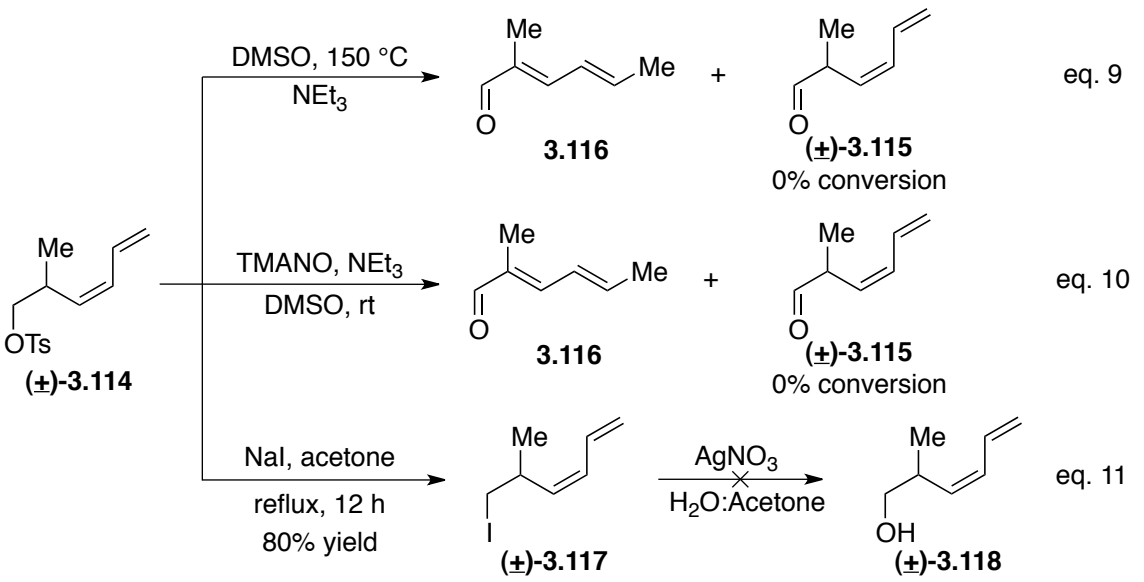
[69] Kornblum, N,; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc*. **1959**, *81*, 4113.
[70] Godfrey, A. G.; Ganem, B. *Tetrahedron Lett*. **1990**, *31*, 4825.
[71] Francavilla, C.; Chen, W.; Kinder, F. R., Jr. *Org. Lett.*, **2003**, *5,* 1233.
[72] Finkelstein, H. *Ber*. **1910**, *43*, 1528.
[73] Reddy, L. R.; Reddy, B. V. S.; Corey, E. J. *Org. Lett*. **2006**, *8*, 2819.

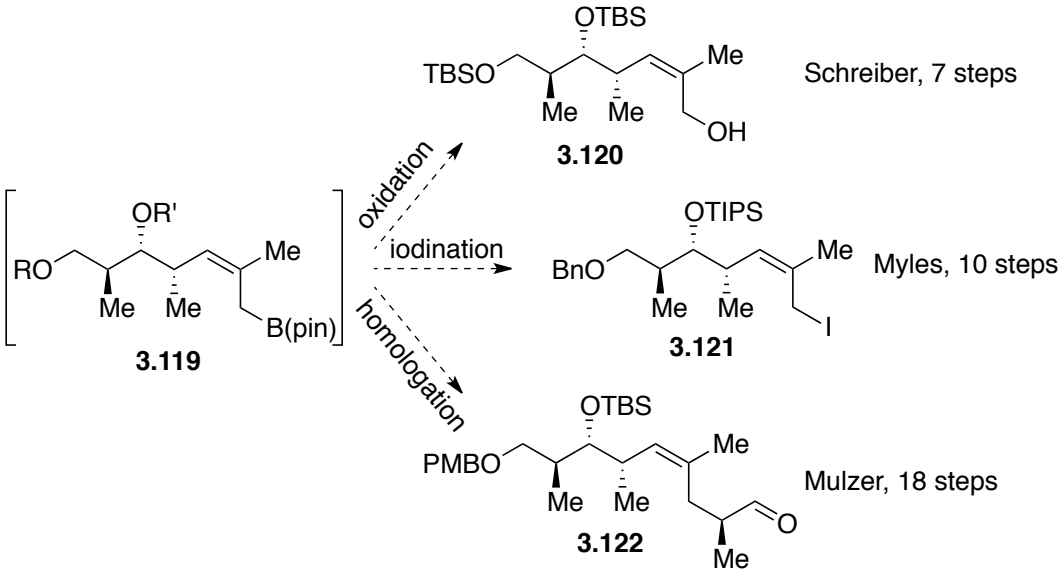
Scheme 3.27. Attempted Oxidation of Tosylate **3.114**



E. Synthesis of the C8-C17 Segment of (+)-Discodermolide

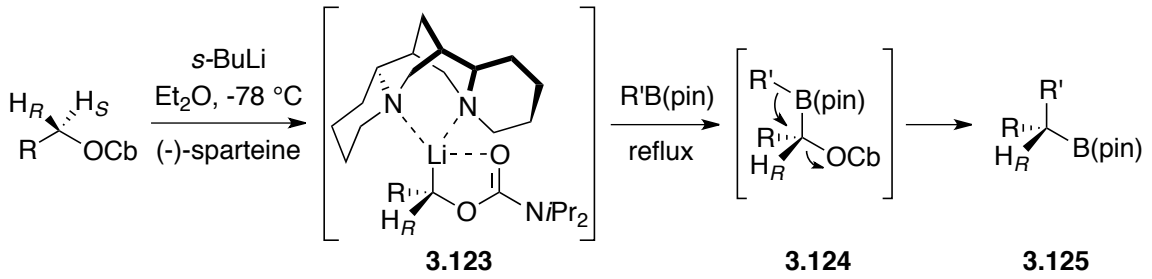
With a plausible route to the C17-C24 segment of (+)-discodermolide in place, the application of the diastereoselective hydroboration to the construction of the C8-C17 segment was investitgated. The synthetic utility of boronic esters allows for flexibility in the synthesis (see Chapter 1, section 1.1) and can provide access to several intermediates previously used in the total synthesis of discodermolide (Scheme 3.28). The Ni-catalyzed hydroboration of a chiral dienol similar to **3.95** would produce **3.119**, which could be then oxidized to allylic alcohol **3.120** used by Schreiber, halogenated to **3.121** used by Myles, or homologated to aldehyde **3.122** used by Mulzer.[31f]

Scheme 3.28. Possible Discodermolide Fragment Synthesis Routes



The conversion of **3.119** to **3.122** could be accomplished by the use of Hoppe-type lithiated carbamates which act as chiral carbenoids that can homologate boronic esters (Scheme 3.29).[10,14,55] The deprotonation of an alkyl carbamate (**3.123**) can be rendered enantioselective by using chiral amine bases such as (-)-sparteine. The lithiated species is configurationally stable and adds to boronic esters with retention of stereochemistry (**3.124**). Upon heating, a 1,2-migration occurs, displacing the carbamate and delivering the enantioenriched alkylboronic ester (**3.125**).

Scheme 3.29. Model for Hoppe-Type Homologation of Boronic Esters



A proposed route to intercept Mulzer's intermediate **3.122** is shown in Scheme 3.30. The homologation of **3.119** to **3.126** would require carbamate **3.92**, which is easily synthesized from ethanol. Unfortunately, the use of commercially available (-)-sparteine for the deprotonation of **3.92** would give the incorrect epimer of product, and (+)-sparteine (**3.128**) is not readily available. As a solution to this long-standing problem, O'Brien designed a (+)-sparteine surrogate (**3.128**) which is available in a few short steps, after isolation of (-)-cytisine from commercially available Laburnum Anagyroides Cytisus seeds.[74] Employing O'Brien's (+)-sparteine surrogate in the homologation of **3.92** and **3.91** would provide the homoallylic boronic ester **3.126** which could be converted to the aldehyde **3.122** by a homologation with dichloromethyllithium.[75]

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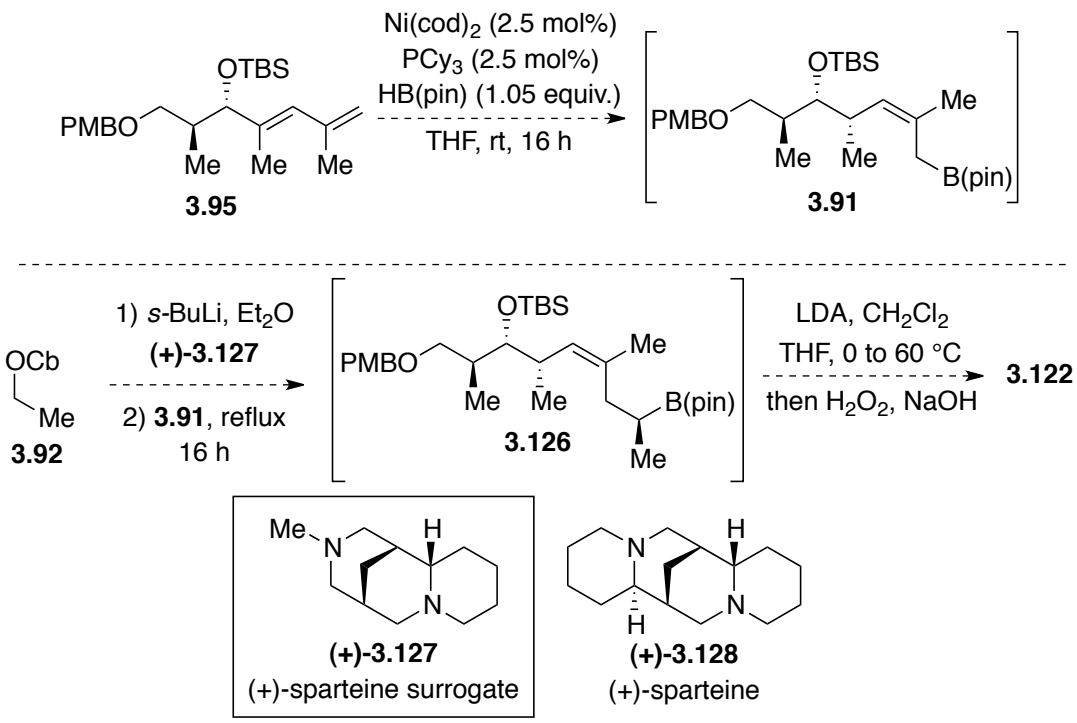
[74] (a) Dearden, M. J.; Firkin, C. R. Hermet, J.-P.; O'Brien, P. *J. Am. Chem. Soc*. **2002**, *124*, 11870. (b) Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Syn*. **2006**, *83*, 141.
[75] (a) Matteson, D. S.; Majumdar, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 7588. (b). Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem*. **1986**, *51*, 3150.

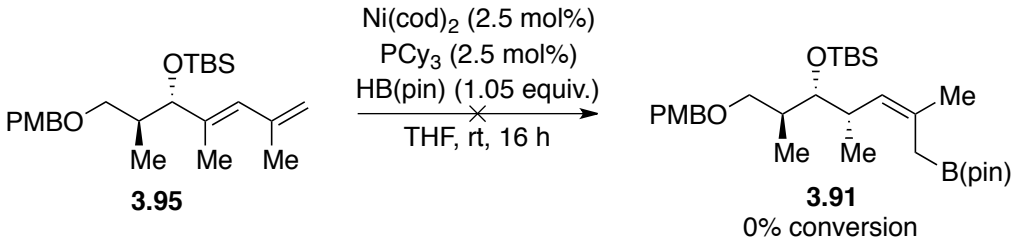
Scheme 3.30. Proposed Synthesis C8-C17 Segment of (+)-Discodermolide



After synthesizing the diamine **(+)-3.127**,[74b] the proposed homologation route commenced with the attempted hydroboration of diene **3.95**. To our surprise, the hydroboration reaction was unsuccessful, returning only starting material (Scheme 3.31). Heating and longer reaction time did not effect the reaction. This outcome could be due to coordination of the PMB-ether to the Ni-catalyst,[76] similar to the Weinreb amide and alkene substrates in Table 3.2 (entries 6 and 7).

[76] For an example of remote directing groups in Ni-catalyzed reductive coupling reactions, see; Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc*. **2004**, *126*, 15342.

Scheme 3.31. Unsuccessful Ni-Catalyzed Hydroboration of PMB-Protected Dienol

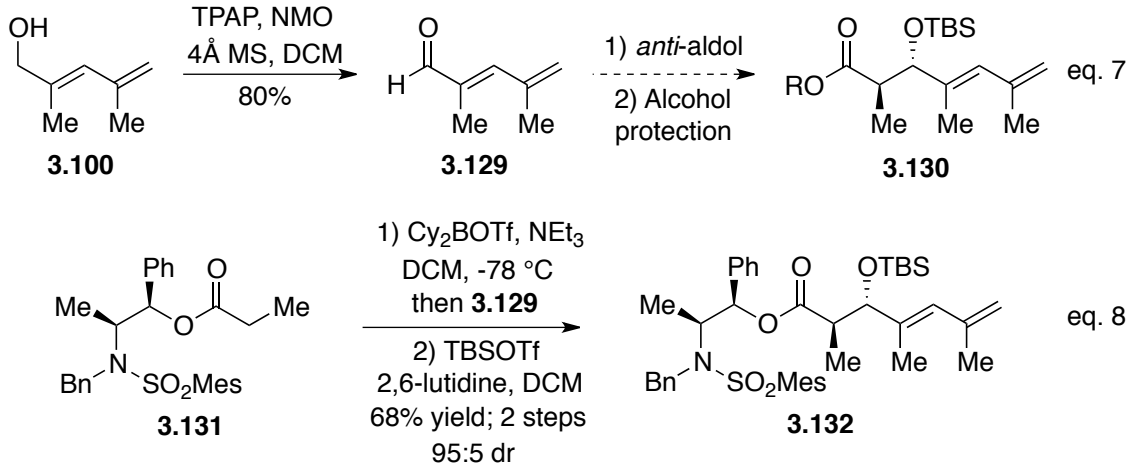


An obvious solution to the lack of reactivity of diene **3.95** in the Ni-catalyzed hydroboration would be to use a different protecting group on the terminal alcohol, such as a TBS-group, which was tolerated in entry 8 of Table 3.2. Esters are also tolerated in the Ni-catalyzed hydroboration (entry 5, Table 3.2), and could be installed *via* an aldol reaction. An *anti*-aldol reaction with aldehyde **3.129**, which is available from the oxidation of alcohol **3.100**, and subsequent alcohol protection would quickly provide a suitable substrate for the Ni-catalyzed hydroboration (eq. 7, Scheme 3.32). The Abiko-Masamune aldol[77] was chosen as it is a highly selective and reliable *anti*-aldol method. Subjection of the chiral auxiliary **3.131**[78] to Cy_2BOTf and NEt_3 generated the (*E*)-enolate and upon addition of **3.129** provided the *anti*-aldol product in good yield and excellent diastereoselectivity (eq. 8, Scheme 3.32). Subsequent TBS-protection provided diene **3.132**.

---

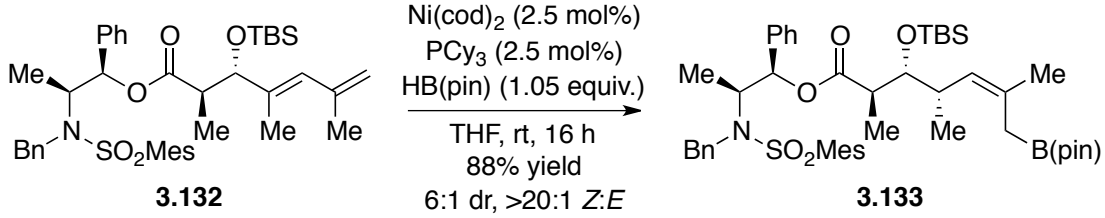
[77] (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc*. **1997**, *119*, 2586. (b) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem*. **2002**, *67*, 5250. (c) Abiko, A. *Org. Syn*. **2002**, *79*, 116.
[78] Abiko, A. *Org. Syn*. **2002**, *79*, 109.

Scheme 3.32. Abiko-Masamune Aldol Strategy



The diene **3.132** was then subjected to the Ni-catalyzed hydroboration conditions (Scheme 3.33). Gratifyingly, the reaction went to full conversion and the allylboronic ester could be isolated in 88% yield with 6:1 diastereoselectivity. Importantly, the reaction was completely (*Z*)-selective, providing an efficient route to the C8-C15 segment of (+)-discodermolide with a boronic ester allowing for further bond construction.

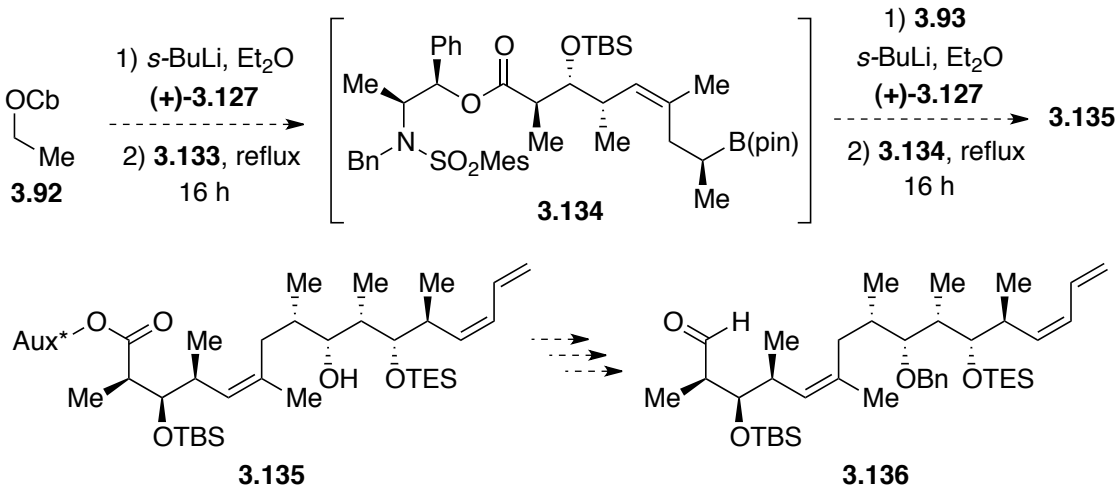
Scheme 3.33. Diastereoselective Hydroboration of **3.132**



F. Future Direction for the Total Synthesis of (+)-Discodermolide

Upon a successful synthesis of carbamate **3.93**, I believe that the Ni-catalyzed hydroboration/homologation strategy could be extended to assemble the C8-C24 segment of (+)-discodermolide. After the hydroboration of diene **3.132**, the resulting allylboron **3.133** could be homologated with **3.92** to afford **3.134** which could be further homologated with carbamate **3.93** to provide **3.135** in a single-flask transformation (Scheme 3.34). The ester **3.135** could then be reduced to the required aldehyde **3.136** for a Still-Genari olefination with **3.90**, in a similar endgame to Paterson's third generation synthesis.

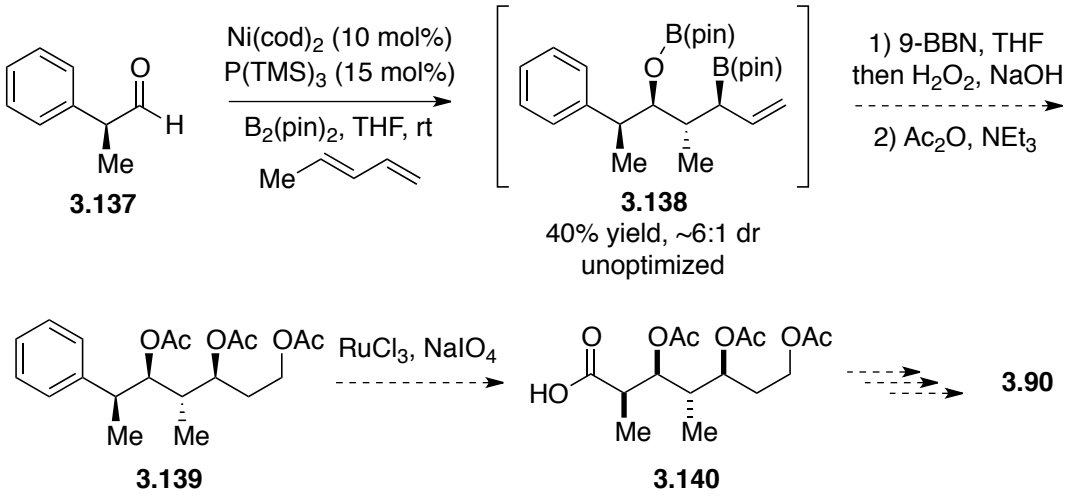
Scheme 3.34. Proposed Synthesis of C8-C24 Segment of (+)-discodermolide



The proposed synthesis of **3.90** shown in Scheme 3.35 was briefly examined. The borylative coupling of aldehyde **3.137** (available from the enantioselective

hydroformylation of styrene)[79] and *trans*-1,3-pentadiene has been accomplished in our laboratory,[55] and proceeded in an unoptimized 40% yield and 6:1 dr (the oxidation product **3.94** was reported). It is possible that the alkene intermediate **3.138** can participate in a hydroboration/oxidation sequence to provide the advanced intermediate **3.139**, after triol protection. A challenging oxidative cleavage of the aryl ring[56] would afford **3.140** which could be further manipulated to give lactone **3.90**. This proposal would be the first synthesis of (+)-discodermolide to begin without the need of the Roche ester as a starting material and compete with Smith's fourth generation synthesis as the most efficient.

Scheme 3.35. Proposed Synthesis for C1-C8 Segment of (+)-Discodermolide



[79] For a review, see: Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007,** *40,* 1251.

3.5. Conclusion

Ni-catalyzed diastereoselective hydroboration of chiral dienols provides a novel method for the synthesis of *syn*-propionate polyketides with adjacent unsaturated sites. The reaction provides a *syn*-propionate unit with moderate to high diastereoselectivity while also generating a (*Z*)-trisubstituted allylboronic ester with high stereoselectivity. The trisubstituted olefin can be used for a variety of stereoselective transformations and the boronic ester serves as a synthetic handle for further polyketide construction. This methodology was developed as a tool to create challenging structural motifs such as the (*Z*)-trisubstituted olefins present in discodermolide. Using the Ni-catalyzed diastereoselective hydroboration, the C9-C15 segment of (+)-discodermolide was achieved in 6 steps with excellent (*Z*)-selectivity for the challenging trisubstituted alkene. The boronic ester produced in the hydroboration provides a synthetic handle for further construction of the molecule.

Unfortunately, clinical trials using discodermolide to treat advanced solid malignancies have been halted due to undesired lung toxicity during chemotherapy. However, it is possible that discodermolide analogues can provide safe alternatives.[80] The flexibility of boronic ester **3.133** could provide access to a variety of discodermolide surrogates in an efficient manner.

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[80] For selected discodermolide analogue syntheses, see: (a) Lemos, E. L; Agouridas, E.; Sorin, G.; Guerreiro, A.; Commerçon, A.; Pancrazi, A.; Betzer, J.-F.; Lannou, M.-I.; Ardisson, J. *Chem. Eur. J.* **2011**, *17*, 10123. b) Paterson, I.; Naylor, G. J.; Gardner, N.M.; Guzman, E.; Wright, A. E. *Chem. Asian J*. **2011**, *6*, 459 c) Paterson, I.; Naylor, G. J.; Fujita, T.; Guzman, E.; Wright, A. E. *Chem. Commun*. **2010**, *46*, 261 d) Fan, Y.; Schreiber, E. M.; Day, B. W. *J. Nat. Prod.* **2009**, *72*, 1748

3.6. Experimental Procedures

I. General Information

^{1}H NMR spectra were recorded on Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling constants (Hz) and assignment. $^{13}C\{^{1}H\}$NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) and Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). Infrared (IR) spectra were recorded on a Bruker α-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (ESI) was performed at Boston College, Chestnut Hill, MA. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar SFC equipped with a Waters 2998 photodiode array detector and an analytical-2-prep column oven with 1:1 hexanes:isopropanol as the modifier.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μm silica gel glass backed plates from Silicycle.

Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA), and potassium permanganate ($KMnO_4$).

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene, tetrahydrofuran, methylene chloride, 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. Bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$), tricyclohexylphosphine (PCy_3), tetrapropylammonium perruthenate, (*S*)-segphos, and tetrakis(triphenylphosphine) palladium(0) were purchased from Strem Chemicals, Inc. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (pinacolborane) was graciously donated by BASF and used without further purification. TBSOTf and TESOTf were purchased from GFS and were distilled prior to use. *Trans*-1,3-pentadiene was purchased from ChemSampCo. Ethyl 2-(triphenylphosphoranylidene)propanoate was purchased from Accela ChemBio or Aldrich. All other reagents were purchased from Aldrich, Acros or Fisher and used without further purification.

II. Preparation of Starting Materials:

The protected dienes **3.31** and dienes in Table 3.2 were prepared from the common aldehyde **SI-1**, which is available from alcohol **3.100** *via* the known ester.[1]

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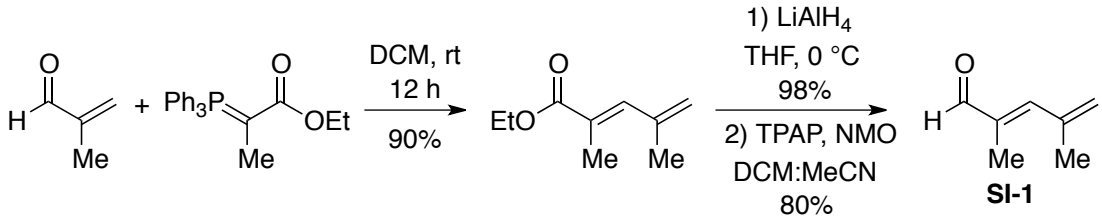
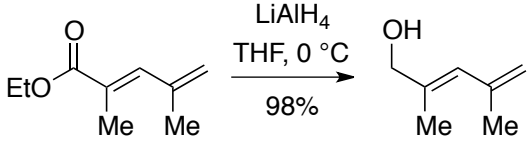
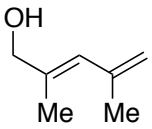
[1] Kemper, J.; Studer, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 4914.

Preparation of (E)-2,4-dimethylpenta-2,4-dien-1-ol (3.100):



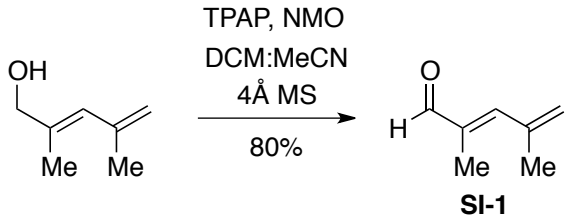
(3.100): In the dry-box, a flame-dried 250 mL round-bottom flask was charged with $LiAlH_4$ (1.30 g, 33.68 mmol). The reaction flask was sealed with a septum, removed from the dry-box, and a nitrogen line was attached. The flask was cooled to 0 °C, followed by the addition of THF (66 mL). (*E*)-ethyl-2,4-dimethylpenta-2,4-dienoate (4.33 g, 28.07 mmol) was added drop-wise, and the reaction was allowed to stir for 1 h. The reaction was quenched with MeOH, followed by the addition of Rochelle's salt (30 mL) and the reaction was allowed to stir vigorously for 2 h. The reaction mixture was diluted with Et_2O and H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford a clear, colorless oil (3.09 g, 98%).



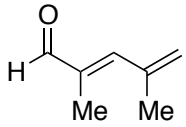


(*E*)-2,4-dimethylpenta-2,4-dien-1-ol (3.100). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (1H, dd, *J* = 1.2 Hz, 1.2 Hz), 4.99 (1H, dd, *J* = 1.6 Hz, 1.6 Hz), 4.84 (1H, s), 4.04 (2H, s), 1.86 (3H, s), 1.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 141.7, 136.5, 127.2, 115.3, 69.3, 23.7, 15.5; IR (neat): 3411 (br, m), 2965 (m), 2927 (m), 2874 (m), 1717 (s), 1376 (s), 1039 (s); HRMS-(ESI+) for $C_7H_{13}O$ [M+H]: calculated: 113.0966, found: 113.0969.

Preparation of (E)-2,4-dimethylpenta-2,4-dienal (SI-1):



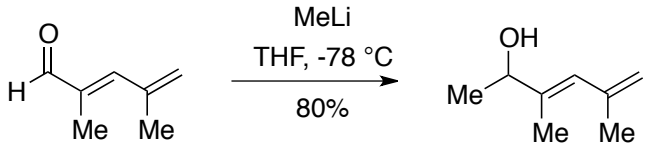
(SI-1). A flame-dried 250 mL round-bottom flask containing a magnetic stir bar was charged with 4Å MS, 4-methylmorpholine N-oxide (4.90 g, 42.00 mmol), DCM (130 mL), MeCN (10 mL), and **3.100** (3.09 g, 27.54 mmol). The reaction was allowed to stir for 20 min, then cooled to 0 °C and tetrapropylammonium perruthenate (295 mg, 0.84 mmol) was added. The reaction was allowed to stir for 2 h while warming to room temperature. The reaction mixture was concentrated by rotary evaporation, then filtered through a pad of silica gel, washing with Et_2O. The solution was concentrated to provide a clear, light yellow oil (2.43 g, 80%).



(*E*)-2,4-dimethylpenta-2,4-dienal (SI-1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (1H, s), 6.71 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 5.32 (1H, dd, *J* = 2.0 Hz, 2.0 Hz), 5.26 (1H, s), 2.02 (3H, s), 1.91 (3H, d, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.1, 152.0, 141.0, 137.8, 123.4, 22.6, 10.6; IR (neat): 3406 (br, w), 2980 (m), 2934 (m), 2875 (m), 1689 (s), 1445 (m), 1376 (m), 1023 (s); HRMS-(ESI +) for $C_7H_{11}O$ [M+H]: calculated: 111.0810, found: 111.0811.

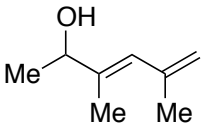
Representative procedure for organometallic nucleophile addition to aldehyde SI-2:

Preparation of (E)-3,5-dimethylhexa-3,5-dien-2-ol (3.31-H, Table 3.1):



(3.31-H): A flame-dried 100 mL round-bottom flask containing a magnetic stir bar, under an atmosphere of nitrogen, was charged with MeLi (3.12 mL of a 1.6 M solution in Et_2O, 4.99 mmol), and Et_2O (20 mL). The reaction flask was cooled to -78 °C, and **SI-1** (500.0 mg, 4.54 mmol) was added drop-wise. The reaction was allowed to stir at -78 °C for 1 h or until the reaction was complete by TLC. The reaction was quenched with water, and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 15 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated by rotary

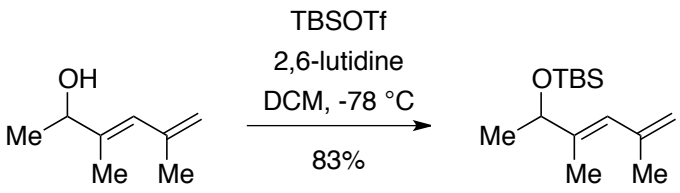
evaporation. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (458.0 mg, 80%). R_f = 0.24 (10:1 hexanes:ethyl acetate, stain in $KMnO_4$).



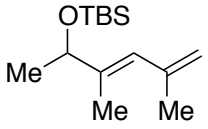
(*E*)-3,5-dimethylhexa-3,5-dien-2-ol (3.31-H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (1H, d, *J* = 1.0 Hz), 4.98 (1H, ddd, *J* = 1.5 Hz, 1.5 Hz, 1.5 Hz), 4.81 (1H, dd, *J* = 1.0 Hz, 1.0 Hz), 4.21 (1H, q, *J* = 6.5 Hz), 1.83 (3H, s), 1.81 (3H, s), 1.26 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 140.5, 126.4, 115.2, 73.9, 23.8, 21.8, 13.4; IR (neat): 3339 (br, m), 2972 (m), 2932 (w), 2874 (w), 1443 (m), 1370 (m), 1103 (s), 954 (s); HRMS-(ESI+) for $C_8H_{15}O$ [M+H]: calculated: 127.1123, found: 127.1123. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (458.0 mg, 80%). R_f = 0.24 (10:1 hexanes:ethyl acetate, stain in $KMnO_4$).

Representative procedure for TBS-protection of dienols:

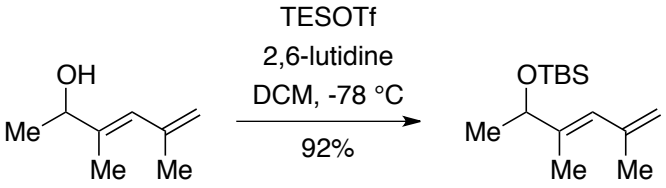
Preparation of (E)-tert-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (3.31-TBS, Table 3.1):

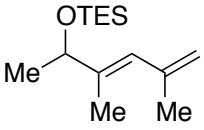


(3.31-TBS): A flame-dried round-bottom flask containing a magnetic stir bar, under an atmosphere of nitrogen, was charged wtih (*E*)-3,5-dimethylhexa-3,5-dien-2-ol (88.0 mg, 0.70 mmol) in DCM (4 mL) and 2,6-lutidine (0.13 mL, 1.05 mmol). The reaction flask was cooled to -78 °C, followed by drop-wise addition of freshly distilled TBSOTf (0.19 mL, 0.84 mmol). The reaction was allowed to stir for 1 h or until done by TLC, then quenched with water. The layers were separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (136.0 mg, 81%). R_f = 0.53 (hexanes, stain in $KMnO_4$).



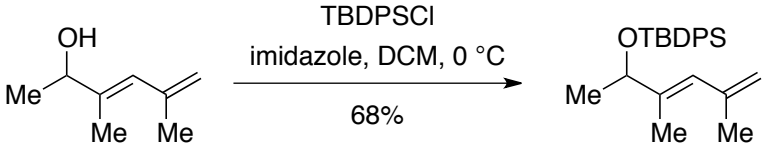
(*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (3.31-TBS, Table 3.1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (1H, s), 4.96 (1H, s), 4.79 (1H, s), 4.17 (1H, q, *J* = 6.5Hz), 1.85 (3H, s), 1.76 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz), 0.89 (9H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2, 131.0, 125.6, 114.6, 74.5, 26.1, 23.9, 23.5, 18.5, 13.5, -4.6, -4.7; IR (neat): 3084 (m), 2958 (m), 2887 (m), 1462 (w), 1443 (w), 1369 (w), 1254 (m), 1082 (m), 1030 (m), 995 (m), 978 (m), 864 (s), 773 (s), 549 (m); HRMS-(ESI$^+$) for $C_{14}H_{28}OSi$ [M+H$^+$]: calculated: 241.1988, found: 241.1977. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (530.0 mg, 83%). R_f=0.53 (hexanes, stain in $KMnO_4$).



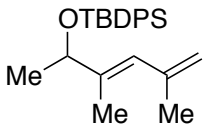


(*E*)-((3,5-dimethylhexa-3,5-dien-2-yl)oxy)triethylsilane (3.31-TES, Table 3.1). The title compound was synthesized according to the representative procedure for the TBS-protection of dienols but with TESOTf. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (1H, d, *J* = 1.0 Hz), 4.96 (1H, ddd *J* = 1.5 Hz, 1.5 Hz, 1.5 Hz), 4.79 (1H, dd, *J* = 1.0 Hz, 1.0 Hz), 4.17 (1H, dq, *J* = 6.0 Hz, 1.0 Hz), 1.85 (3H, s), 1.77 (3H, d, *J* = 1.5 Hz), 1.23 (3H, d, *J* = 6.5 Hz), 0.95 (9H, t, *J* = 7.5 Hz), 0.59 (6H, q, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 140.9, 125.7, 114.6, 74.2, 23.9, 23.5, 13.4, 7.1, 5.0; IR (neat): 2955 (m), 2912 (m), 2877 (m), 1457 (w), 1238 (m), 1056 (s), 1004 (s), 724 (s); HRMS-(ESI+) for $C_{14}H_{29}OSi$ [M+H]: calculated: 241.1988, found: 241.1996. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (263.0 mg, 92%). R_f = 0.42 (hexanes, stain in $KMnO_4$).

Preparation of (E)-tert-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)diphenylsilane (3.31-TBDPS, Table 3.1)



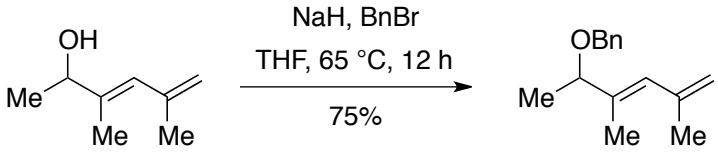
(3.31-TBDPS): A flame-dried round-bottom flask containing a stir bar was charged with (*E*)-3,5-dimethylhexa-3,5-dien-2-ol (30.0 mg, 0.24 mmol), imidazole (19.6 mg, 0.29 mmol), and DCM (1.2 mL). The reaction flask was cooled to 0 °C, then TBDPSCl (0.07 mL, 0.29 mmol) was added drop-wise and the reaction was allowed to stir at 0 °C for 4 h. The reaction was diluted with water and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (60.0 mg, 68%). R_f = 0.28 (hexanes, stain in $KMnO_4$).



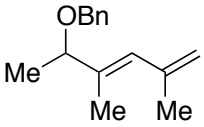
(*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)diphenylsilane (3.31-TBDPS, Table 3.1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (1H, t, *J* = 1.5 Hz), 7.65 (1H, t, *J* = 1.5 Hz), 7.45-7.33 (6H, m), 5.69 (1H, s), 4.94 (1H, s), 4.73 (1H, s), 4.19 (1H, q, *J* = 6.5 Hz), 1.79 (3H, s), 1.78 (3H, t, *J* = 1.5 Hz), 1.19 (3H, dd, *J* = 6.5 Hz, 1.5 Hz), 1.08 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 140.3, 136.2, 136.1, 134.9, 134.4, 129.7, 129.6, 127.7, 127.6, 126.3, 114.5, 75.4, 27.2, 23.8, 23.3, 19.5, 13.4; IR (neat): 3071 (w), 2965 (m), 2932 (m), 2892 (w), 2858 (m), 1473 (w), 1461 (w), 1428 (m), 1389 (w), 1470 (w), 1189 (s), 1110 (s), 1079 (m), 1054 (w), 1027 (m), 891 (w), 764 (m), 739 (m), 701 (s), 506 (s), 485 (m); HRMS-(ESI$^+$) for $C_{24}H_{33}OSi$ [M+H]: calculated: 365.2303, found: 365.2301. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (60.0

mg, 68%). Rf = 0.28 (hexanes, stain in $KMnO_4$).

Preparation of (*E*)-(((3,5-dimethylhexa-3,5-dien-2-yl)oxy)methyl)benzene (3.31-Bn, Table 3.1).

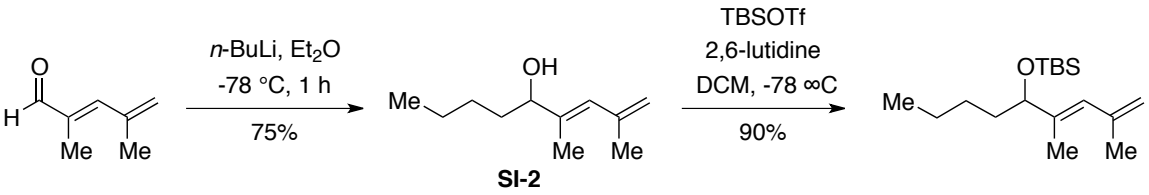


(3.31-Bn): In the dry-box, a flamed-dried 25 mL 2-neck round-bottom flask was charged wtih NaH (45.0 mg, 1.90 mmol). The reaction flask was sealed with a septum, removed from the dry-box, and a nitrogen line was attached. The flask was cooled to 0 °C, followed by the addition of THF (8 mL). (*E*)-3,5-dimethylhexa-3,5-dien-2-ol (200 mg, 1.59 mmol) was then added in THF (1 mL) drop-wise, and the reaction was allowed to stir for 15 min. Benzyl bromide (0.21 mL, 1.75 mmol) was then added drop-wise, and the reaction was refluxed for 12 h. The reaction was diluted with water and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (256.0 mg, 75%). R_f = 0.27 (100:1 hexanes:ethyl acetate, stain in $KMnO_4$).

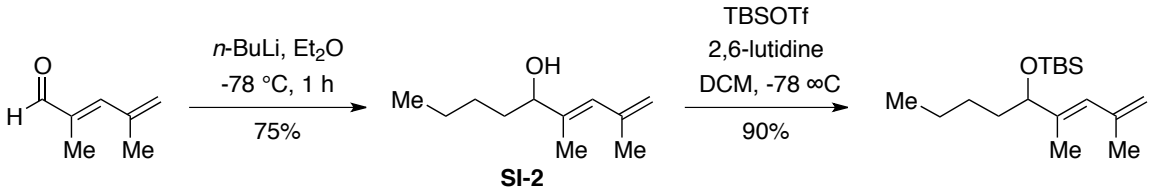


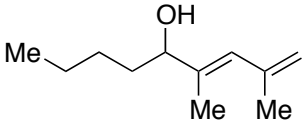
(*E*)-(((3,5-dimethylhexa-3,5-dien-2-yl)oxy)methyl)benzene (3.31-Bn, Table 3.1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.33 (4H, m), 7.29-7.26 (1H, m), 5.88 (1H, s), 5.03 (1H, ddd, *J* = 1.5 Hz, 1.5 Hz, 1.5 Hz), 4.89 (1H, dd, *J* = 1.0 Hz, 1.0 Hz), 4.48 (1H, d, *J* = 11.5 Hz), 4.28 (1H, d, *J* = 12.0 Hz), 3.88 (1H, q, *J* = 6.4 Hz), 1.92 (3H, s), 1.83 (3H, d, *J* = 1.5 Hz), 1.31 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 139.1, 137.9, 129.1, 128.5, 127.9, 127.6, 115.5, 81.3, 70.0, 23.9, 20.5, 12.5; IR (neat): 3032 (m), 2980 (m), 2874 (m), 1718 (s), 1452 (s), 1269 (s), 1093 (s), 698 (s); HRMS-(ESI+) for $C_{15}H_{21}O$ [M+H]: calculated: 217.1592, found: 217.1585. The crude reaction mixture was purified by silica gel chromatography (100:1 hexanes:ethyl acetate) to afford a clear, colorless oil (256.0 mg, 75%). R_f = 0.27 (100:1 hexanes:ethyl acetate, stain in $KMnO_4$).

Preparation of (E)-tert-butyl((2,4-dimethylnona-1,3-dien-5-yl)oxy)dimethylsilane:

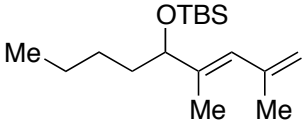


(Entry 1, Table 3.2): The title compound was synthesized as shown below following the representative organometallic nucleophile addition procedure with *n*-BuLi (2.5 M solution in hexanes), followed by protection using the representative TBSOTf protection procedure.





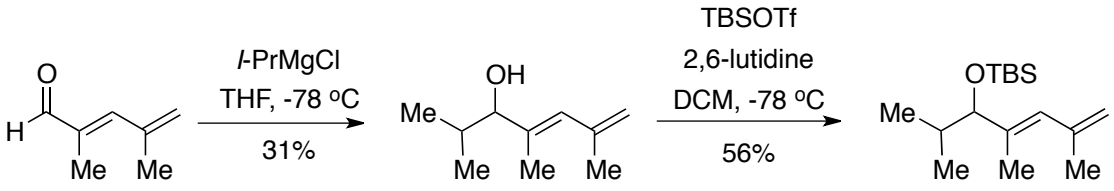
(*E*)-2,4-dimethylnona-1,3-dien-5-ol (SI-2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (1H, s), 5.00 (1H, ddd, *J* = 1.5 Hz, 1.5 Hz, 1.5 Hz), 4.83 (1H, dd, *J* = 1.0 Hz, 1.0 Hz), 4.02 (1H, dd, *J* = 6.5 Hz, 6.5 Hz), 1.86 (3H, s), 1.71 (3H, d, *J* = 1.5 Hz), 1.59-1.54 (2H, m), 1.37-1.32 (4H, m), 0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 139.3, 127.8, 115.3, 78.5. 34.9, 28.2, 23.8, 22.8, 14.2, 13.2; IR (neat): 3353 (br, m), (2957 (s), 2930 (s), 2860 (s), 1448 (m), 1000 (s), 891 (s); HRMS-(ESI+) for $C_{11}H_{21}O$ [M+H]: calculated: 169.1592, found: 169.1590. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (200 mg, 75%). R_f = 0.32 (10:1 hexanes:ethyl acetate, stain in $KMnO_4$).



(*E*)-*tert*-butyl((2,4-dimethylnona-1,3-dien-5-yl)oxy) dimethylsilane (entry 1, Table 3.2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78 (1H, s), 4.96 (1H, ddd, *J* = 1.5 Hz, 1.5 Hz, 1.5 Hz), 4.79 (1H, dd, *J* = 1.0 Hz, 1.0 Hz), 3.94 (1H, dd, *J* = 6.0 Hz, 6.0 Hz), 1.85 (3H, s), 1.73 (3H, d, *J* = 1.5 Hz), 1.56-1.42 (2H, m), 1.33-1.27 (4H, m), 0.91-0.86 (12H, m), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 140.0, 127.1, 114.5, 79.2,

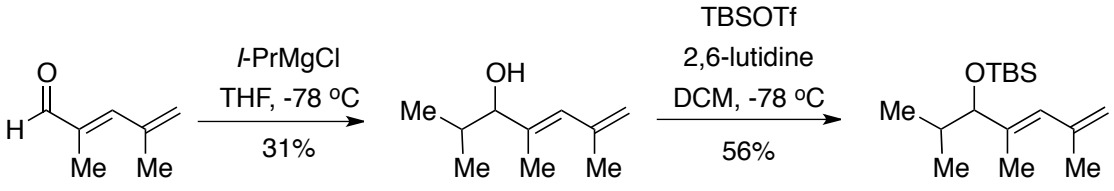
36.3, 28.2, 25.9, 23.9, 22.9, 18.5, 14.3, 13.2, -4.3, -4.8; IR (neat): 2956 (s), 2930 (s), 2857 (s), 1716 (w), 1462 (m), 1254 (s), 1075 (s), 892 (s), 774 (s); HRMS-(ESI+) for $C_{17}H_{35}OSi$ [M+H]: calculated: 282.2457, found: 282.2453. The crude reaction mixture was purified on silica gel (hexanes) to afford a clear, colorless oil (197 mg, 90%). R_f = 0.27 (hexanes, stain in $KMnO_4$).

Preparation of (*E*)-2,4,6-trimethylhepta-4,6-dien-3-ol.

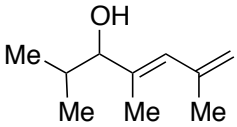


SI-3

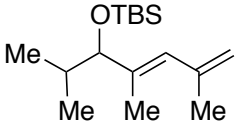
(Entry 2, Table 3.2): The title compound was synthesized as shown below following the representative organometallic nucleophile addition procedure with isopropylmagnesium chloride (2.0 M solution in THF), followed by protection using the representative TBSOTf protection procedure.



SI-3

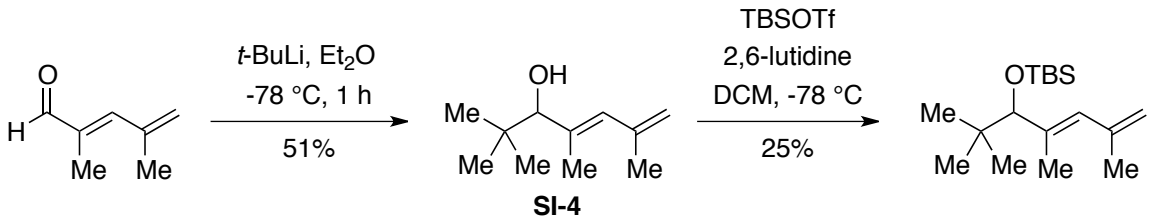


(*E*)-2,4,6-trimethylhepta-4,6-dien-3-ol (SI-3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (1H, s), 4.98 (1H, s), 4.81 (1H, s), 3.60 (1H, d, *J* = 13.0 Hz), 1.84 (3H, s), 1.78 (1H, m), 1.76 (3H, s), 0.97 (3H, d, *J* = 6.5 Hz), 0.80 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 138.5, 129.0, 115.2, 84.5, 31.4, 23.8, 19.7, 18.6, 13.3; IR (neat): 3397 (w), 2956 (s), 2929 (s), 2859 (m), 1632 (w), 1461 (m), 1382 (m), 1297 (w), 1252 (m), 1179 (w), 1064 (s), 1015 (s), 891 (s), 836 (s), 774 (s), 670 (s), 551 (m); HRMS-(ESI$^+$) for $C_{10}H_{19}O$ [M+H]: calculated: 155.1436, found: 155.1436. The crude reaction mixture was purified by silica gel chromatography (8:1 hexanes:diethyl ether) to afford a clear, colorless oil (190.0 mg, 31%). R_f = 0.43 (4:1 hexanes: diethyl ether, stain in $KMnO_4$).

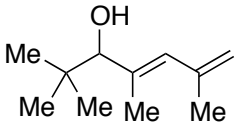


(*E*)-*tert*-butyldimethyl((2,4,6-trimethylhepta-4,6-dien-3-yl)oxy) silane (entry 2, Table 3.2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (1H, s), 4.97 (1H, ddd, *J* = 1.0 Hz, 1.0 Hz, 1.0 Hz), 4.79 (1H, d, *J* = 1.0 Hz), 3.52 (1H, d, *J* = 7.5 Hz), 1.84 (3H, s), 1.74-1.72 (4H, m), 0.91 (3H, d, *J* = 6.5 Hz), 0.90 (9H, s), 0.76 (3H, d, *J* = 7.0 Hz), 0.02 (3H, s), -0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.0, 138.9, 128.6, 114.5, 85.3, 32.4, 26.1, 23.9, 19.7, 19.2, 18.5, 13.4, -4.3, -4.8; IR (neat): 2956 (m), 2929 (m), 2857 (m), 1470 (m), 1251 (s), 1061 (s), 890 (s), 834 (s); HRMS-(ESI+) for $C_{16}H_{33}OSi$ [M+H]: calculated: 269.2301, found: 269.2303. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (38.0 mg, 56%). R_f = 0.60 (hexanes, stain in $KMnO_4$).

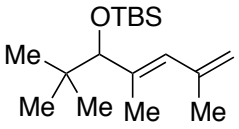
Preparation of (*E*)-*tert*-butyldimethyl((2,2,4,6-tetramethylhepta-4,6-dien-3-yl)oxy) silane.



(Entry 3, Table 3.2) The title compound was synthesized as shown below following the representative organometallic nucleophile addition procedure with *t*-BuLi (1.6 M solution in pentane), followed by protection using the representative TBSOTf protection procedure.

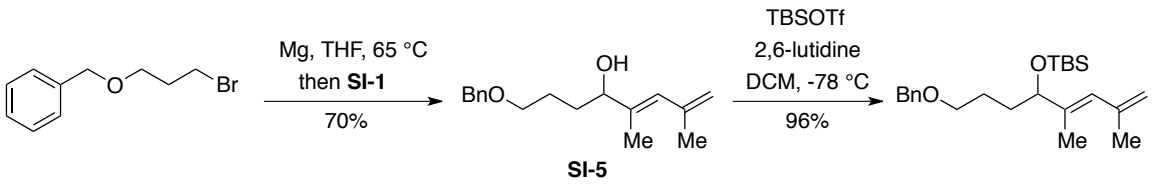


(*E*)-2,2,4,6-tetramethylhepta-4,6-dien-3-ol (SI-4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (1H, s), 5.01 (1H, ddd, *J* = 1.5 Hz, 1.5 Hz, 1.5 Hz), 4.83 (1H, dd, *J* = 1.0 Hz, 1.0 Hz), 3.77 (1H, s), 1.86 (3H, d, *J* = 1.0 Hz), 1.85 (3H, d, *J* = 1.5 Hz), 0.94 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 138.3, 130.0, 115.2, 85.6, 26.9, 25.3, 24.0, 16.4; IR (neat): 3453 (br, w), 2956 (s), 2910 (s), 2871 (s), 1727 (m), 1465 (m), 1365 (s), 1059 (s); HRMS-(ESI+) for $C_{11}H_{21}O$ [M+H]: calculated: 169.1592, found: 169.1597. The crude reaction mixture was purified by silica gel chromatography (20:1 hexanes:ethyl acetate) to afford a clear, colorless oil (207.0 mg, 51%). R_f = 0.30 (20:1 hexanes:ethyl acetate, stain in $KMnO_4$).



(*E*)-*tert*-butyldimethyl((2,2,4,6-tetramethylhepta-4,6-dien-3-yl) oxy)silane (entry 3, Table 3.2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (1H, s), 4.98 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.79 (1H, dd, *J* = 1.0 Hz, 1.0 Hz), 3.63 (1H, d, *J* = 1.0 Hz), 1.84 (3H, s), 1.77 (3H, d, *J* = 1.5 Hz), 1.08 (9H, s), 0.88 (9H, s), 0.03 (3H, s), -0.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 138.8, 129.9, 115.6, 86.4, 36.7, 27.1, 26.1, 25.9, 23.9, 18.5, -4.4, -5.2; IR (neat): 2955 (s), 2929 (m), 2858 (m), 1462 (m), 1361 (m), 1250 (m). 1076 (s), 835 (s), 774 (s); HRMS-(ESI+) for $C_{17}H_{35}OSi$ [M+H]: calculated: 283.2457, found: 283.2454. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (87.0 mg, 25%). R_f = 0.73 (hexanes, stain in $KMnO_4$).

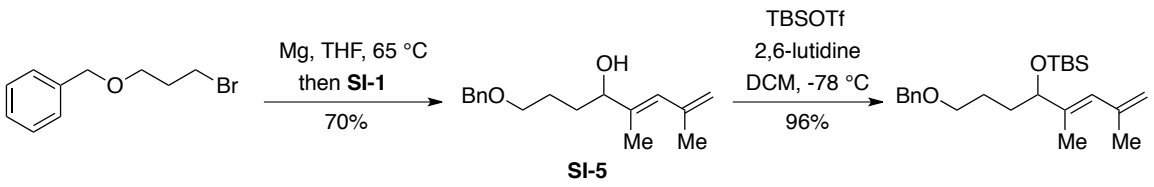
Preparation of (E)-1-(benzyloxy)-5,7-dimethylocta-5,7-dien-4-ol:

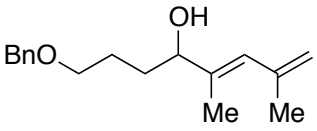


(Entry 4, Table 3.2): The title compound was synthesized by adding the known Grignard reagent[2] to aldehyde **SI-1** following the representative organometallic nucleophile addition procedure, followed by protection using the representative TBSOTf protection

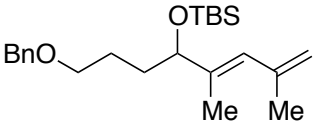
[2] Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2004**, *126*, 9536.

procedure.





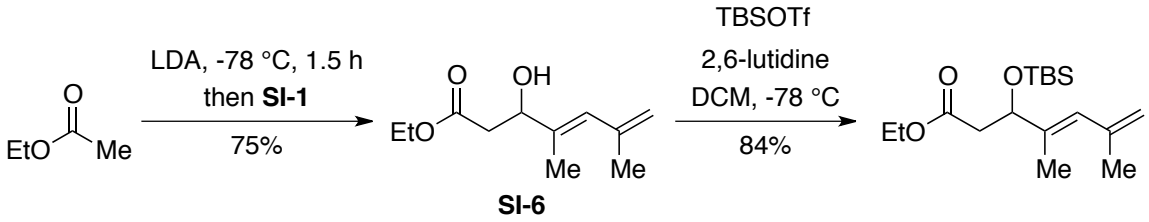
(*E*)-1-(benzyloxy)-5,7-dimethylocta-5,7-dien-4-ol (SI-5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.33 (4H, m), 7.30-7.26 (1H, m), 5.88 (1H, s), 4.82 (1H, s), 4.52 (2H, s), 4.03 (1H, br, s), 3.53-3.50 (2H, m), 2.17-2.16 (1H, m), 1.86 (3H, s), 1.79 (3H, s), 1.73-1.64 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 139.1, 138.5, 128.6, 127.9, 127.8, 127.7, 115.3, 78.0, 73.2, 70.6, 32.5, 26.4, 23.9, 13.6; IR (neat): 3417 (w), 2938 (m), 2857 (m), 1495 (m), 1362 (m), 1309 (w), 1259 (w), 1204 (w), 1097 (s), 1054 (s) 1027 (s), 998 (s), 890 (s), 734 (s), 696 (s), 611 (m), 555 (m), 520 (m); HRMS-(ESI$^+$) for $C_{17}H_{25}O_2$ [M+H]: calculated: 261.1855, found: 261.1846. The crude reaction mixture was purified by silica gel chromatography (5:1 hexanes:diethyl ether) to afford a clear, colorless oil (400.0 mg, 70%). R_f = 0.33 (5:1 hexanes:ethyl acetate, stain in $KMnO_4$).



(*E*)-((1-(benzyloxy)-5,7-dimethylocta-5,7-dien-4-yl)oxy) (*tert*-butyl)dimethylsilane (entry 4, Table 3.2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.32 (4H, m), 7.32-7.25 (1H, m), 5.78 (1H, s), 4.96 (1H, s), 4.78 (2H, s), 4.50 (2H, s), 3.97 (1H, dd, *J* = 6.0 Hz, 6.0 Hz),

3.49-3.44 (2H, m), 1.84 (3H, s), 1.73 (3H, s), 1.69-1.65 (1H, m), 1.60-1.53 (3H, m), 0.87 (9H, s), 0.03 (3H, s), -0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 139.6, 138.9, 128.6, 127.9, 127.7, 127.3, 114.7, 78.9, 73.1, 70.1, 33.1, 26.3, 26.1, 23.9, 18.4, 13.3, -4.4, -4.8; IR (neat): 2953 (m), 2929 (m), 2855 (m), 1472 (w), 1454 (w), 1361 (w), 1254 (m), 1204 (w), 1096 (s), 1070 (s), 1028 (m), 1004 (m), 893 (m), 835 (s), 774 (s), 734 (m), 697 (m); HRMS-(ESI^+) for $C_{23}H_{39}O_2Si$ [M+H]: calculated: 375.2719, found: 375.2722. The crude reaction mixture was purified by silica gel chromatography (40:1 hexanes:diethyl ether) to afford a clear, colorless oil (289.0 mg, 96%). R_f = 0.41 (20:1 hexanes:diethyl ether, stain in $KMnO_4$).

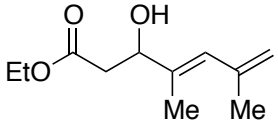
Preparation of (E)-ethyl 3-((tert-butyldimethylsilyl)oxy)-4,6-dimethylhepta-4,6-dienoate:



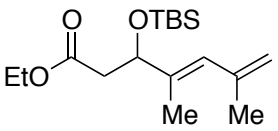
SI-6

(Entry 5, Table 3.2): A flame-dried two-neck round-bottom flask containing a magnetic stir bar and internal thermometer was charged with dry diisopropylamine (0.28mL, 2.00 mmol) and THF (3.0 mL). The flask was cooled to -78 °C and *n*-BuLi (0.84mL, 2.00 mmol) was added drop-wise . The solution was allowed to warm to 0 °C and stir for 15 min. The reaction flask was then cooled to -78 °C, and ethyl acetate (0.20 mL, 2.0 mmol,

distilled) in THF (1.0 mL) was added drop-wise, maintaining an internal temperature below -70 °C. The reaction was allowed to stir at -78 °C for 1.5 h, then a solution of **SI-1** (213 mg, 1.82 mmol) in THF (1.0 mL) was added drop-wise at -78 °C. The reaction was allowed to stir at -78 °C for 40 min. The reaction was quenched with water (3.0 mL), diluted with ethyl acetate (10 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (3:1 hexanes:diethyl ether) to afford the title compound as a clear, colorless oil (288.0 mg, 75%). R_f = 0.51 (3:1 hexanes:ethyl acetate, stain with $KMnO_4$).

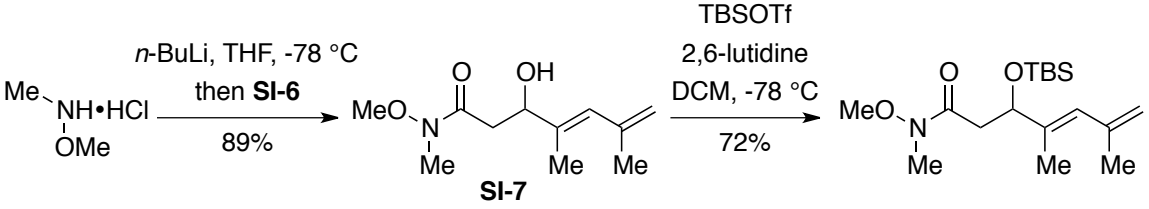


(*E*)-ethyl 3-hydroxy-4,6-dimethylhepta-4,6-dienoate (SI-6). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.97 (1H, s), 5.01 (1H, p, *J* = 1.5 Hz), 4.83 (1H, t, *J* = 1.0 Hz), 4.46 (1H, dt, *J* = 4.0 Hz), 4.18 (2H, q, *J* = 7.0 Hz), 2.85 (1H, d, *J* = 3.5 Hz), 2.58 (1H, d, *J* = 4.0 Hz), 2.56 (1H, d, *J* = 1.0 Hz), 1.85 (3H, s), 1.82 (3H, d, *J* = 1.5 Hz), 1.27 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 141.5, 137.0, 128.1, 115.6, 73.9, 61.0, 40.4, 23.7, 14.4, 13.9; IR (neat): 3466 (m), 3082 (w), 2981 (m), 2938 (m), 1734 (s), 1719 (s), 1445 (m), 1371 (m), 1300 (m), 1272 (s), 1178 (s), 1160 (s), 1019 (s), 894 (s), 522 (m); HRMS-(ESI$^+$) for $C_{11}H_{27}O_2$ [M-H_2O+H]: calculated: 181.1229, found: 181.1231.

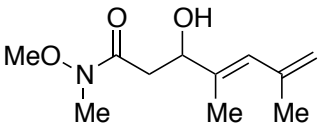


(*E*)-ethyl-3-((*tert*-butyldimethylsilyl)oxy)-4,6-dimethylhepta-4,6-dienoate (entry 5, Table 3.2). The compound was synthesized from **SI-6** following the representative TBS-protection procedure**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (1H, s), 4.98 (1H, s), 4.80 (1H, s), 4.50 (1H, dd, *J* = 9.0Hz, 4.5 Hz), 4.12 (2H, qd, *J* = 7.5 Hz, 7.5 Hz), 2.56 (1H, dd, *J* = 14.0 Hz, 9.0 Hz), 2.42 (1H, dd, *J* = 13.5 Hz, 4.0 Hz), 1.84 (3H, s), 1.77 (3H, s), 1.26 (3H, t, *J* = 7.0 Hz), 0.86 (9H, s), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 141.6, 138.2, 115.3, 76.2, 60.6, 42.8, 25.9, 23.7, 18.3, 14.5, 13.0, -4.5, -5.1; IR (neat): 2956 (m), 2930 (m), 2857 (m), 1738 (s), 1472 (w), 1463 (w), 1445 (w), 1371 (m), 1273 (m), 1252 (s), 1165 (s), 1078 (s), 1024 (s), 1007 (s), 954 (m), 832 (s), 812 (m), 777 (s), 700 (m), 666 (w); HRMS-(ESI$^+$) for $C_{17}H_{33}O_3Si$ [M+H]: calculated: 313.2199, found: 313.2201. The crude reaction mixture was purified by silica gel chromatography (40:1 hexanes:diethyl ether) to afford a clear, colorless oil (198.0 mg, 84%). R_f = 0.30 (40:1 hexanes: diethyl ether, stain in $KMnO_4$).

Preparation of (E)-3-((tert-butyldimethylsilyl)oxy)-N-methoxy-N,4,6-trimethylhepta-4,6-dienamide:

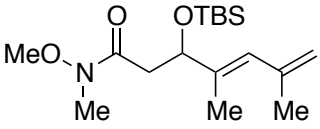


(Entry 6, Table 3.2): A flame- dried two-neck round-bottom flask containing a magnetic stir bar was charged with *N*,*O*-dimethylhydroxylamine hydrochloride (237.0 mg, 2.44 mmol) and THF (3.25 mL). The flask was cooled to -78 °C and *n*-BuLi (2.0 mL, 4.88 mmol in hexanes) was added drop-wise at -78 °C. The reaction was allowed to warm to room temperature and stir for 10 min. The flask was then cooled to -78 °C, and **SI-6** (120.0 mg, 0.61 mmol) in THF (1.0 mL) was added drop-wise at -78 °C and allowed to stir for 2h at -78 °C. The reaction was quenched with saturated NH_4Cl (5.0 mL), diluted with ethyl acetate (10 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (3:1 hexanes:diethyl ether) to afford the title compound as a clear, colorless oil (100.0 mg, 89%). R_f = 0.14 (3:1 hexanes:ethyl acetate, stain with $KMnO_4$).



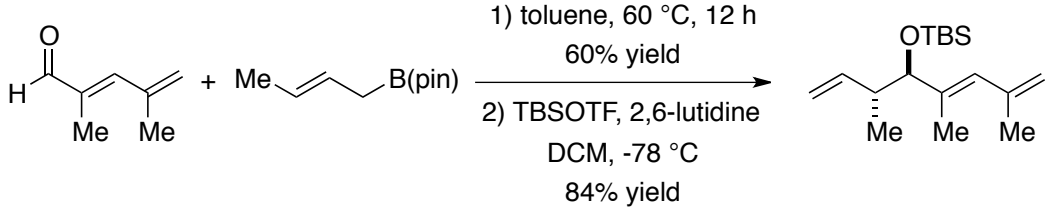
(*E*)-5-hydroxy-2-methoxy-6,8-dimethylnona-6,8-dien-3-one (SI-7). ^1H NMR (500 MHz, $CDCl_3$): δ 5.99 (1H, s), 5.00 (1H, p, *J* = 1.5 Hz), 4.84 (1H, s), 4.46 (1H, d, *J* = 8.5 Hz), 3.86 (1H, s), 3.69 (3H, s), 3.20 (3H, s), 2.71 (1H, d, *J* = 16.0 Hz), 2.61 (1H, dd, *J* = 16.5 Hz, 10.0 Hz), 1.86 (3H, s), 1.83 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 141.7, 137.3, 127.6, 115.4, 73.6, 61.5, 37.3, 32.1, 23.8, 14.3; IR (neat): 3422 (m), 2965 (m), 2921 (m), 2855 (m), 1636 (s), 1440 (s), 1385 (s), 1179 (m), 1105 (m), 997 (m), 939 (s),

890 (s), 603 (m), 524 (m), 485 (m), 432 (s); HRMS-(ESI+) for $C_{11}H_{20}O_3N$ [M+H]: calculated: 214.1443, found: 214.1441.



(*E*)-3-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*,4,6-trimethylhepta-4,6-dienamide (entyr 6, Table 3.2). The compound was synthesized from **SI-7** following the representative TBS-protection procedure**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, s), 4.98 (1H, s), 4.80 (1H, s), 4.59 (1H, dd, *J* = 9.5 Hz, 4.0 Hz), 3.71 (3H, s), 3.81 (3H, s), 2.89 (1H, dd, *J* = 10.0 Hz, 10.0 Hz), 2.33 (1H, dd, *J* = 13.5 Hz, 4.0 Hz), 1.84 (3H, s), 1.80 (3H, s), 0.86 (9H, s), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.8, 138.8, 127.7, 115.1, 77.6, 76.0, 61.6, 39.4, 32.2, 26.0, 23.7, 18.4, 13.5, -4.6, -4.9; IR (neat): 2955 (m), 2930 (m), 2896 (w), 2856 (m), 1664 (s), 1463 (m), 1441 (m), 1383 (s), 1250 (s), 1180 (m), 1004 (m), 972 (w), 947 (m), 892 (m), 812 (s), 777 (s), 668 (w); HRMS-(ESI+) for $C_{17}H_{33}O_3NSi$ [M+H]: calculated: 328.2308, found: 328.2315. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:diethyl ether) to afford a clear, colorless oil (120.0 mg, 72%). R_f = 0.17 (10:1 hexanes: ethyl acetate, stain in $KMnO_4$).

Preparation of (±)-tert-butyldimethyl(((E)-3,5,7-trimethylocta-1,5,7-trien-4-yl)oxy) silane:

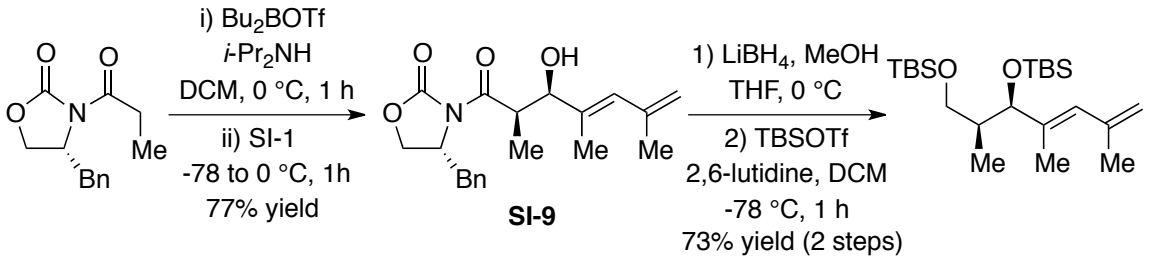


(SI-8): To a flame-dried 20-dram vial with stir bar was added (*E*)-2-(but-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[3] (300 mg, 1.65 mmol) followed by aldehyde **SI-1** (173 mg, 1.57 mmol) in toluene (3.2 mL). The vial was capped and heated to 60 °C and allowed to stir for 12 h. The reaction mixture was cooled to 0 °C, diluted with THF (2 mL), and 3 M NaOH (1 mL) was added. The mixture was allowed to stir for 1 h, then EtOAc (10 mL) and H_2O (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (50:1 hexanes:EtOAc) to afford the title compound as a clear, colorless oil (156.0 mg, 60%). R_f = 0.3 (50:1 hexanes:ethyl acetate, stain with $KMnO_4$).

(Entry 7, Table 3.2). The compound was synthesized from **SI-8** following the representative TBS-protection procedure. For characterization data for this compound and **SI-8**, see **3.103** and **3.104** below.

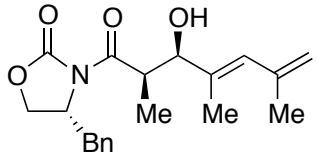
[3] Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

Preparation of (5R,6S)-2,2,3,3,6,9,9,10,10-nonamethyl-5-((E)-4-methylpenta-2,4-dien-2-yl)-4,8-dioxa-3,9-disilaundecane:



(SI-9): To a flame-dried 100 mL round-bottom flask with magnetic stir bar was added (*R*)-4-benzyl-3-propionyloxazolidin-2-one then was purged with N_2. The flask was cooled to 0 °C and DCM (20 mL) and diisopropylethylamine (1.33 mL, 7.62 mmol) were added, followed by the dropwise addition of dibutylboryl trifluoromethanesulfonate (6.5 mL of a 1.0 M solution in DCM, 6.54 mmol). The reaction mixture was allowed to stir at 0 °C for 1 h then cooled to -78 °C. Aldehyde **SI-1** (600 mg, 5.45 mmol) was then added and the reaction was allowed to stir for 30 min. The reaction mixture was warmed to 0 °C and allowed to stir for an additional 1 h, followed by the addition of pH 7 buffer (5 mL), MeOH (5 mL), and H_2O_2 (5 mL). The reaction mixture was allowed to stir for 1 h, warming to room temperature, then diluted with EtOAc (50 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (4:1 hexanes:EtOAc) to afford the title compound as a clear, yellow oil (1.44 g, 77%). $R_f = 0.1$

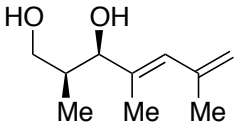
(4:1 hexanes:ethyl acetate, stain with $KMnO_4$).



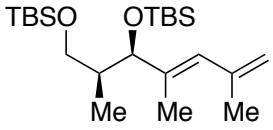
(*R*)-4-benzyl-3-((2*R*,3*R*,*E*)-3-hydroxy-2,4,6-trimethylhepta-4,6-dienoyl)oxazolidin-2-one (SI-9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.32 (2H, m), 7.30-7.28 (1H, m), 7.22-7.20 (2H, m), 6.05 (1H, d, *J* = 1.0 Hz), 5.00 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.82 (1H, dd, *J* = 1.0 Hz), 4.70 (1H, m), 4.40 (1H, s, br), 4.24-4.17 (2H, m), 4.02 (1H, dddd, *J* = 7.0 Hz, 3.5 Hz, 3.5 Hz, 3.5 Hz), 3.27 (1H, dd, *J* = 13.5 Hz, 3.5 Hz), 2.93 (1H, d, *J* = 3.0 Hz), 2.80 (1H, dd, *J* = 13.5 Hz, 9.5 Hz), 1.86 (3H, s), 1.79 (3H, d, *J* = 0.50 Hz), 1.21 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1, 152.9, 141.5, 135.0, 129.6, 129.2, 128.0, 127.7, 115.2, 75.4, 66.2, 55.3, 40.3, 37.8, 23.7, 15.2, 10.4; IR (neat): 3508 (w), 3083 (w), 3028 (w), 2972 (w), 1776 (s), 1696 (s), 1382 (s), 1209 (s), 1108 (s), 702 (s). HRMS-(ESI+) for $C_{20}H_{24}NO_3$ [M+H-H_2O]: calculated: 326.1756, found: 326.1753. $[\alpha]_D$ = -33.9 (*c* = 1.2, $CHCl_3$, *l* = 50 mm).

(SI-10) A 20-dram vial containing a magnetic stir bar was charged with **SI-9**, MeOH (0.02 mL), and THF (1.8 mL) then sealed with a septum and cooled to 0 °C. Lithium borohydride (0.22 mL of a 2.0 M solution in tetrahydrofuan, 0.44 mmol) was added drop-wise and the reaction was allowed to stir for 1 h. The reaction was quenched with H_2O (2 mL) followed by the addition of saturated potassium sodium tartrate solution (5 mL) and the reaction mixture was allowed to stir for 3 h. The reaction was diluted with EtOAc (10

mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (1:1 hexanes:EtOAc) to afford the title compound as a clear, yellow oil (73 mg, 98%). $R_f = 0.2$ (1:1 hexanes:ethyl acetate, stain with $KMnO_4$).



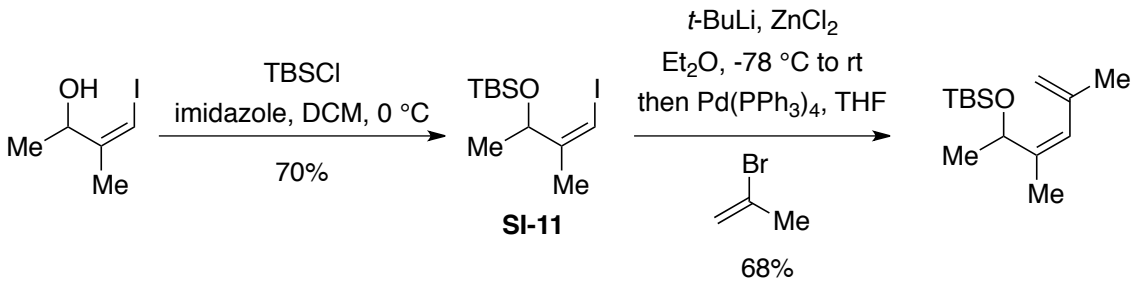
(2*S*,3*R*,*E*)-2,4,6-trimethylhepta-4,6-diene-1,3-diol (SI-10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, d, *J* = 1.0 Hz), 4.99 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.80 (1h, dd, *J* = 1.5 Hz, 1.5 Hz), 4.16 (1H, d, *J* = 4.0 Hz), 3.65 (2H, d, *J* = 5.5 Hz), 2.56 (1H, s, br), 2.02 (3H, s), 1.90 (1H, dqd, *J* = 7.0 Hz, 5.5 Hz, 4.0 Hz), 1.85 (3H, s), 1.75 (3H, d, *J* = 1.5Hz), 0.88 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 137.8, 127.1, 115.0, 78.9, 66.9, 37.8, 24.0, 15.2, 10.5; IR (neat): 3373 (s), 2966 (s), 2932 (s), 2876 (s), 1743 (m), 1629 (w), 1450 (s), 1375 (s), 1030 (s), 892 (s). HRMS-(ESI+) for $C_{10}H_{19}O_2$ [M+H]: calculated: 171.1385, found: 171.1390. $[\alpha]_D = +18.4$ (*c* = 1.0, $CHCl_3$, *l* = 50 mm).



(5*R*,6*S*)-2,2,3,3,6,9,9,10,10-nonamethyl-5-((*E*)-4-methylpenta-2,4-dien-2-yl)-4,8-dioxa-3,9-disilaundecane (Entry 8, Table 3.2). The compound was synthesized from **SI-10** following the representative TBS-protection procedure**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (1H, s), 4.96 (1H, dd, *J* = 2.0 Hz, 2.0 Hz), 4.77 (1H, s), 3.98 (1H, d, *J* = 5.5 Hz),

3.47 (1H, dd, *J* = 10.0 Hz, 6.0 Hz), 3.51 (1H, dd, *J* = 10.0 Hz, 6.0 Hz), 1.81 (3H, s), 1.75-1.70 (1H, m), 1.71 (3H, d, *J* = 1.5 Hz), 0.90 (9H, s), 0.89 (9H, s), 0.04 (3H, s), 0.02 (3H, s), 0.02 (3H, s), -0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 138.3, 127.8, 114.3, 78.4, 65.5, 40.1, 26.1, 26.1, 24.1, 18.5, 14.5, 12.0, -4.3, -4.95, -5.2, -5.2; IR (neat); 2956 (s), 2928 (s), 2857 (s), 1471 (m), 1388 (w), 1252 (s), 1060 (s), 835 (s), 774 (s). HRMS-(ESI+) for $C_{22}H_{47}O_2Si_2$ [M+H]: calculated: 399.3115, found: 399.3119. $[\alpha]_D$ = +10.0 (*c* = 1.0, $CHCl_3$, *l* = 50 mm). The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (104.0 mg, 35%). R_f = 0.47 (hexanes, stain in $KMnO_4$).

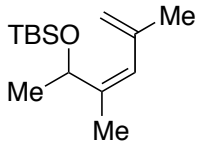
Preparation of (Z)-tert-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane: The title compound was synthesized as shown in the scheme below from the known alcohol.[4]



(Entry 1, Table 3.3). A flame-dried 6-dram vial containing a magnetic stir bar, under nitrogen, was charged with *t*-BuLi (1.6 mL of a 1.6 M solution in pentane, 2.56 mmol) and Et_2O (1.5 mL). The vial was cooled to -78 °C and 2-bromopropene (0.20 mL, 1.28

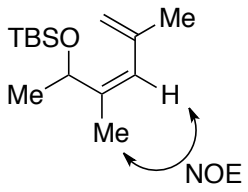
[4] Skepper, C. K.; Quach, T.; Molinski, T. F. *J. Am. Chem. Soc*. **2010**, *132*, 10286.

mmol) was added drop-wise. The reaction was allowed to stir for 30 min at -78 °C, then $ZnCl_2$ (174.5 mg, 1.28 mmol) in THF (3 mL) was added. The reaction was allowed to warm to room temperature and stir for 30 min. The reaction mixture was then transferred *via* cannula to a separate flame-dried 6-dram vial, with a magnetic stir bar, containing Pd $(PPh_3)_4$ (37 mg, 0.032 mmol), **SI-11** (209.0 mg, 0.64 mmol), and THF (2 mL). The reaction was allowed to stir at room temperature for 12 h, followed by filtration through a pad of silica gel, washing with Et_2O. The solution was concentrated by rotary evaporation and the crude reaction mixture was purified by silica gel chromatography (400:1 hexanes:ethyl acetate) to afford a clear, colorless oil (104.0 mg, 68%). R_f = 0.50 (400:1 hexanes:ethyl acetate, stain in $KMnO_4$). The product contains ~10% (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane.

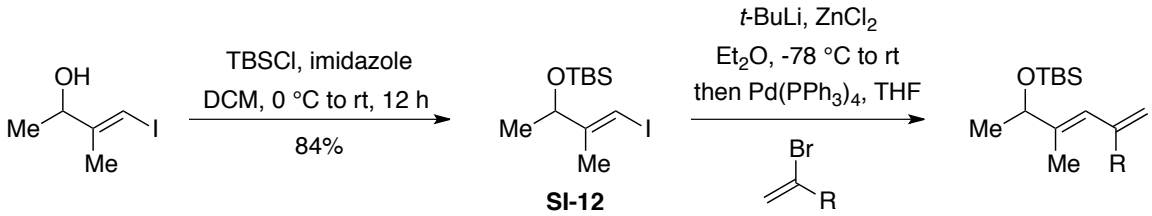


(*Z*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (entry 1, Table 3.3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (1H, dd, *J* = 1.0 Hz, 1.0 Hz), 4.97 (1H, q, *J* = 6.5 Hz), 4.95 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.61 (1H, ddd, *J* = 1.5 Hz, 1.5 Hz, 1.5 Hz), 1.79 (3H, dd, *J* = 1.0 Hz, 1.0 Hz), 1.75 (3H, d, *J* = 1.5 Hz), 1.23 (3H, d, *J* = 6.5 Hz), 0.87 (9H, s), 0.00 (3H, s), -0.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 141.6, 126.5, 113.9, 66.4, 26.1, 24.0, 23.4, 18.4, 17.5, -4.8, -4.8; IR (neat): 2955 (m), 2929 (m), 2857 (m), 1471 (m), 1252 (s), 1078 (s), 832 (s), 773 (s); HRMS-(ESI+) for $C_{14}H_{29}OSi$ [M+H]: calculated: 241.1988, found: 241.1998.

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below.



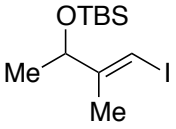
Preparation of Dienes in Table 3.3: The dienes in Table 3.3 (entries 2-4) were prepared from the common vinyl iodide SI-12, which is available from the known alcohol.[5]



(SI-12). A flame-dried 50 mL round-bottom flask containing a magnetic stir bar was cooled to 0 °C and charged wtih (*E*)-4-iodo-3-methylbut-3-en-2-ol (1.07 g, 5.05 mmol), DCM (16 mL), imidazole (378.0 mg, 5.55 mmol), and TBSCl (837.0 mg, 5.55 mmol). The reaction was allowed to stir for 12 h, warming to room temperature. The reaction was diluted with water and the layers were separated. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel

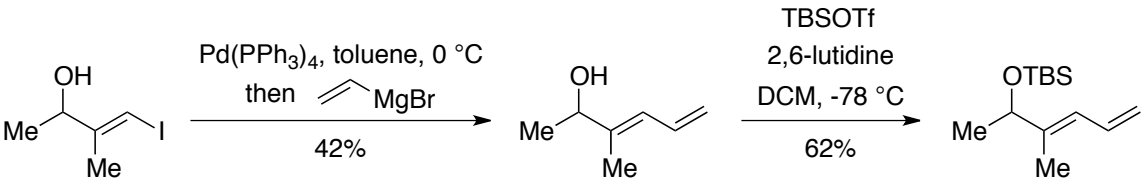
[5] Alvarez, R.; Herrero, M.; López, S.; de Lera, A. R. *Tetrahedron* **1998**, *54*, 6793.

chromatography (hexanes) to afford a clear, colorless oil (1.38 g, 84%). R_f = 0.48 (hexanes, stain in $KMnO_4$).



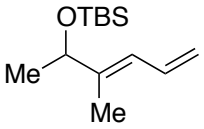
(*E*)-*tert*-butyl((4-iodo-3-methylbut-3-en-2-yl)oxy)dimethylsilane (SI-12). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (1H, s), 4.30 (1H, q, *J* = 6.0 Hz), 1.79 (3H, d, *J* = 1.2 Hz), 1.21 (3H, d, *J* = 6.0 Hz), 0.88 (9H, s), 0.04 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 76.9, 73.3, 26.0, 23.4, 20.1, 18.4, -4.8, -4.8; IR (neat): 2954 (m), 2929 (m), 2857 (m), 1471 (w), 1252 (m), 1088 (s), 834 (s), 775 (s); HRMS-(ESI+) for $C_{11}H_{27}INOSi$ [M+NH_4]: calculated: 344.0907, found: 344.0919. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (1.38 g, 84%). R_f = 0.48 (hexanes, stain in $KMnO_4$).

Preparation of (*E*)-*tert*-butyldimethyl((3-methylhexa-3,5-dien-2-yl)oxy)silane:



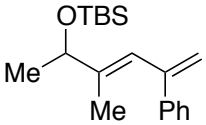
(Entry 2, Table 3.3): In the dry-box, a flame-dried round bottom flask containing a magnetic stir bar, was charged with $Pd(PPh_3)_4$ (54.5 mg, 0.05 mmol). The flask was sealed with a septum, removed from the box and cooled to 0 °C. (*E*)-4-iodo-3-

methylbut-3-en-2-ol (200 mg, 0.94 mmol) in toluene (6.8 mL) was then added and allowed to stir for 20 min, followed by the drop-wise addition of vinyl magnesium bromide (2.82 mL, 1.0 M in THF, 2.82 mmol). The solution was allowed to stir for 1 h at 0 °C, then was warmed to room temperature and allowed to stir for an additional 30 min. The reaction was quenched with a saturated solution of ammonium chloride (5 mL) followed by the addition of water (5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organics were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (44.0 mg, 42%). The representative procedure for TBS-protection of dienols was used to make the titled diene.



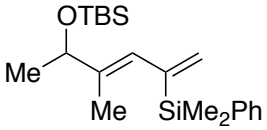
(*E*)-*tert*-butyldimethyl((3-methylhexa-3,5-dien-2-yl)oxy)silane (entry 2, Table 3.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (1H, ddd, *J* = 17.0 Hz, 11.0 Hz, 11.0 Hz), 6.19 (1H, d, *J* = 11.0 Hz), 5.16 (1H, dd, *J* = 17.0 Hz, 2.5 Hz), 5.06 (1H, dd, *J* = 10.0 Hz, 2.0 Hz), 4.20 (1H, q, *J* = 6.5 Hz), 1.73 (3H, d, *J* = 1.0 Hz), 1.21 (3H, d, *J* = 6.5 Hz), 0.89 (9H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.7, 133.3, 124.1, 73.7, 26.1, 26.0, 23.4, 18.5, 12.4, -4.6, -4.7; HRMS-(ESI+) for $C_{13}H_{27}OSi$ [M+H]: calculated: 227.1831, found: 227.1842. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (55.0 mg, 62%). R_f = 0.34 (hexanes, stain in $KMnO_4$).

Representative procedure for Negishi cross-coupling: A flame-dried 6-dram vial containing a magnetic stir bar, under an atmosphere of nitrogen, was charged with *t*-BuLi (2.2 mL of a 1.6 M solution in pentane, 3.50 mmol) and Et_2O (2 mL). The vial was cooled to -78 °C and α–bromostyrene (0.23 mL, 1.75 mmol) was added drop-wise. The reaction was allowed to stir for 30 min at -78 °C, then $ZnCl_2$ (238 mg, 1.75 mmol) in THF (2 mL) was added. The reaction was allowed to warm to room temperature and stir for 30 min. The reaction mixture was then transferred *via* cannula to a separate flame-dried 6-dram vial, containing a magnetic stir bar, $Pd(PPh_3)_4$ (67.0 mg, 0.060 mmol), SI-10 (380.0 mg, 1.16 mmol), and THF (2 mL). The reaction was allowed to stir at room temperature for 12 h, followed by filtration through a pad of silica gel, washing with Et_2O. The solution was concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (248.0 mg, 70%). R_f = 0.38 (hexanes, stain in $KMnO_4$).



(*E*)-*tert*-butyldimethyl((3-methyl-5-phenylhexa-3,5-dien-2-yl)oxy) silane (Table 3.3, entry 3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.37 (2H, m), 7.34- 7.24 (3H, m), 6.17 (1H, s), 5.56 (1H, d, *J* = 1.6 Hz), 5.10 (1H, dd, *J* = 1.6 Hz, 1.6 Hz), 4.30 (1H, q, *J* = 6.4 Hz), 1.66 (3H, d, *J* = 1.2 Hz), 1.28 (3H, d, *J* = 6.4 Hz), 0.92 (9H, s), 0.09 (3H, s), 0.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 144.0, 141.4, 128.4, 127.6, 126.7, 123.5, 114.9, 74.0, 26.1, 23.7, 18.5, 13.8, -4.5, -4.7; IR (neat): 3082 (w), 3026 (m), 2929 (m), 1462 (w), 1250 (m), 1084 (s), 834 (s), 774

(s), 703 (s); HRMS-(ESI+) for $C_{19}H_{31}OSi$ [M+H]: calculated: 303.2144, found: 303.2129. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (248.0 mg, 70%). R_f = 0.38 (hexanes, stain in $KMnO_4$).



(*E*)-*tert*-butyl((5-(dimethyl(phenyl)silyl)-3-methylhexa-3,5-dien-2-yl)oxy)dimethylsilane (Table 3.3, entry 4). The title compound was synthesized following the representative Negishi cross-coupling procedure with (1-bromovinyl)dimethyl(phenyl)silane.[6] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.49 (2H, m), 7.35-7.32 (3H, m), 5.94 (1H, s), 5.60 (1H, dd, *J* = 3.6 Hz, 2.0 Hz), 5.54 (1H, dd, *J* = 3.6 Hz, 1.2 Hz), 4.15 (1H, q, *J* = 6.4 Hz), 1.60 (3H, d, *J* = 1.2 Hz), 1.18 (3H, d, *J* = 6.4 Hz), 0.85 (9H, s), 0.35 (6H, s), 0.00 (3H, s), -0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 140.2, 138.2, 134.2, 129.2, 128.0, 127.9, 125.1, 74.0, 26.1, 23.7, 18.4, 12.9, -3.0, -3.1, -4.6, -4.8; IR (neat): 2955 (m), 2928 (m), 2857 (w), 1471 (w), 1248 (s), 1083 (s), 1053 (s), 832 (s), 773 (s), 773 (s), 698 (s); HRMS-(ESI+) for $C_{21}H_{35}OSi_2$ [M+H]: calculated: 359.2226, found: 359.2231. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (648.0 mg, 95%). R_f = 0.23 (hexanes, stain in $KMnO_4$). The purified product was not reactive in the hydroboration reaction. To further purify, the product was heated with a heat gun while under vacuum to remove any volatiles. The oil was then filtered through a

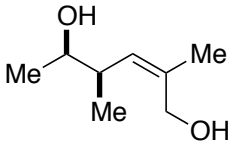
[6] Anderson, J. C.; Smith, S. C.; Swarbrick, M. E. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1517.

pad of silica gel, washing with hexanes. The resulting diene was a 3:1 *E*:*E* to *E*:*Z* mixture.

III. Representative Procedure for Diene Hydroboration/Oxidation.

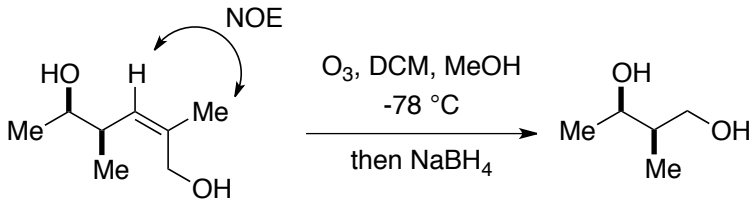
In the dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.20 mL of a 31.30 μM solution of $Ni(cod)_2$ in THF, 6.20 μmol), PCy_3 (0.2 mL of a 31.3 0 μM solution of PCy_3 in THF, 6.20 μmol), THF (1.00 mL, 0.25M), pinacolborane (33.5 mg, 0.26 mmol), and (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (60 mg, 0.25 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, immediately cooled to °C (ice/ water), and allowed to stir for 3 h. The reaction mixture was kept at 0 °C and charged with 3 M sodium hydroxide (1 mL), and 30% hydrogen peroxide (0.75 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 (1 mL) was added drop-wise. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.5 mg, 89%, 14:1 dr).

IV. Full Characterization and Proof of Stereochemistry.

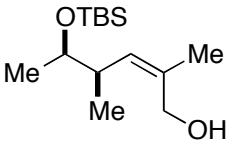


syn-(_Z_)-2,4-dimethylhex-2-ene-1,5-diol (Table 3.1, Entry 10). (^{1}H NMR (500 MHz, $CDCl_3$): δ 5.09 (1H, d, *J* = 11.5 Hz), 4.20 (1H, d, *J* = 11.5 Hz), 3.79 (1H, d, *J* = 11.5 Hz), 3.66 (1H, qd, *J* = 6.5 Hz, 6.5 Hz), 2.66-2.62 (1H, m), 1.80 (3H, s), 1.05 (3H, d, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 129.6, 71.4, 61.5, 38.6, 22.7, 18.3, 17.9; IR (neat): 3315 (m), 2967 (m), 2930 (m), 2873 (m), 1450 (m), 1375 (m), 1316 (w), 1192 (w), 1155 (w), 1087 (m), 1003 (s), 949 (m), 932 (m), 901 (m), 866 (w), 602 (m), 559 (m); HRMS-(ESI) for $C_8H_{18}O_2$ [M+H]: calculated: 145.1229, found: 145.1225. The crude reaction mixture was purified by silica gel chromatography (1:1 hexanes:diethyl ether) to afford a clear, colorless oil (47.0 mg, 56%, 6:1 dr). R_f = 0.19 (1:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to known diol[7] by ozonolysis/reduction.

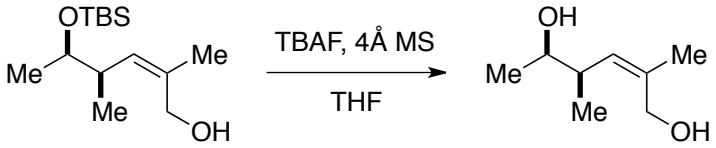


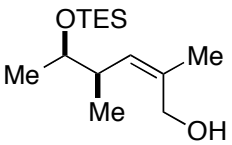
[7] Dandapani, S.; Jeske, M.; Curran, D. P. *J. Org. Chem*. **2005**, *70*, 9447.



***syn*-(*Z*)- 5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhex-2-en-1-ol (Table 3.1, entry 5).** ^{1}H NMR (500 MHz, C_6D_6): δ 5.03 (1H, d, *J* = 10.0 Hz), 4.01 (1H, d, *J* = 12.0 Hz), 3.90 (1H, d, *J* = 11.5 Hz), 3.51 (1H, dq, *J* = 6.0 Hz, 6.0 Hz), 2.48 (1H, ddq, *J* = 10.0 Hz, 7.0 Hz, 5.5 Hz), 1.78 (3H, d, *J* = 1.5 Hz), 1.03 (3H, d, *J* = 6.5 Hz), 0.99 (9H, s), 0.96 (3H, d, *J* = 7.0 Hz), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz, C_6D_6): δ 136.1, 131.1, 73.6, 62.1, 40.5, 26.5, 22.4, 21.4, 18.8, 18.2, -3.9, -4.3; IR (neat): 3334 (br, w), 2957 (m), 2929 (m), 2856 (m), 1462 (w), 1253 (s), 1093 (s), 1005 (s), 959 (s), 834 (s), 773 (s); HRMS-(ESI+) for $C_{14}H_{31}O_2Si$ [M+H]: calculated: 259.2093, found: 259.2089. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.0 mg, 89%, 14:1 dr). R_f = 0.24 (10:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene and *syn*-stereochemistry were proven by comparison to (*Z*)-2,4-dimethylhex-2-ene-1,5-diol (Table 3.1, entry 10) after deprotection as shown below.

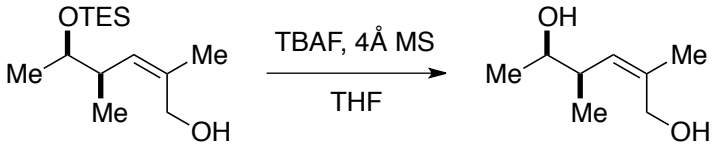


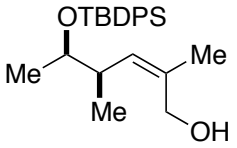


***syn*-(*Z*)-2,4-dimethyl-5-((triethylsilyl)oxy)hex-2-en-1-ol (Table 3.1, entry 7).** ^{1}H NMR (500 MHz, C_6D_6): δ 5.04 (1H, ddd, *J* = 10.0 Hz, 1.5 Hz, 1.0 Hz), 4.12 (1H, d, *J* = 11.5 Hz), 3.89 (1H, d, *J* = 12.0 Hz),

3.56 (1H, dq, J = 6.0 Hz, 5.0 Hz), 2.57 (1H, ddq, J = 10.0 Hz, 7.0 Hz, 5.0 Hz), 1.82 (3H, d, J = 1.5 Hz), 1.03 (3H, d, J = 6.0 Hz), 1.00 (9H, t, J = 8.0 Hz), 0.94 (3H, d, J = 8.0 Hz), 0.61 (6H, q, J = 8.0 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 137.1, 130.4, 73.5, 62.1, 40.4, 22.7, 20.5, 18.4, 7.5, 5.6; IR (neat): 3322 (br, w), 2957 (s), 2930 (s), 2856 m), 1472 (m), 1251 (s), 1085 (s), 1050 (s), 938 (s), 771 (s); HRMS-(ESI+) for $C_{14}H_{31}O_2Si$ [M+H]: calculated: 259.2093, found: 259.2090. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (61.3 mg, 95%, 12:1 dr). R_f = 0.30 (10:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene and *syn*-stereochemistry were proven by comparison to (*Z*)-2,4-dimethylhex-2-ene-1,5-diol (Table 3.1, entry 10) after deprotection as shown below.

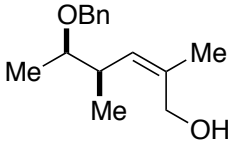




***syn*-(*Z*)-5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylhex-2-en-1-ol (Table 3.1, Entry 8)**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.67 (4H, m), 7.44-7.35 (6H, m), 5.17 (1H, d, J = 10.5 Hz), 4.07 (1H, d, J = 11.5 Hz), 4.00 (1H, d, J = 12.0 Hz), 3.72 (1H, qd, J = 6.5 Hz, 6.5 Hz), 2.55 (1H, dqd, J = 10.0 Hz, 6.5 Hz, 6.5 Hz), 1.79 (3H, s), 1.06 (9H, s), 0.94 (3H, d, J = 6.5 Hz), 0.94 (3H,

d, J =7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2, 136.1, 135.0, 134.7, 134.3, 131.6, 130.0, 129.7, 127.7, 127.6, 74.1, 62.2, 39.7, 27.3, 21.8, 20.4, 19.6, 17.5; IR (neat): 3341 (w), 3071 (w), 2964 (m), 2931 (m), 2858 (m), 1472 (w), 1427 (m), 1376 (w), 1109 (s), 1007 (s), 958 (m), 739 (m), 701 (s), 688 (m), 611 (m), 505 (s), 488 (m); HRMS-(ESI$^+$) for $C_{24}H_{35}O_2Si$ [M+H]: calculated: 383.2406, found: 383.2408. The crude reaction mixture was purified by silica gel chromatography (2:1 hexanes:diethyl ether) to afford a clear, colorless oil (28.0 mg, 80%, >20:1 dr). R_f = 0.48 (1:1 hexanes:diethyl ether, stain in PMA).

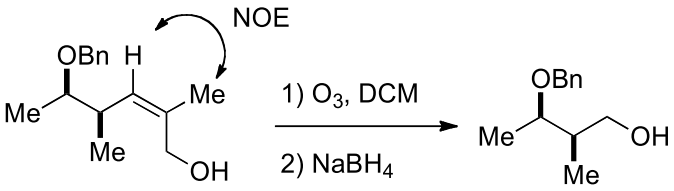
Proof of Stereochemistry: (*Z*)-alkene geometry and *syn*-stereochemistry were proven by comparison to (*Z*)-2,4-dimethylhex-2-ene-1,5-diol (Table 1, entry 1) after deprotection as shown below.

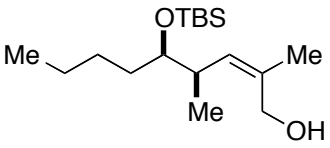


syn-(_Z_)-5-(benzyloxy)-2,4-dimethylhex-2-en-1-ol (Table 3.1, Entry 9). The reaction was performed with the representative procedure but for 12 h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.34 (4H, m), 7.32-7.26 (1H, m), 5.10 (1H, d, J = 10.0 Hz), 4.61 (1H, d, J = 11.5 Hz), 4.46 (1H, d, J = 11.5 Hz), 3.77 (1H, br, d, J = 11.0 Hz), 3.40 (1H, qd, J = 6.5 Hz, 6.5 Hz), 2.8-2.75 (1H, m), 2.50 (1H, br, s), 1.82 (3H, s), 1.11 (3H, d, J = 6.0 Hz), 0.96 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 136.8, 129.9, 128.6, 128.1, 127.9, 79.1, 70.9, 61.8, 37.3, 22.7, 18.3, 14.8; IR (neat): 3395 (m), 2968 (m), 2929 (m), 2870 (m),

1452 (m), 1474 (m), 1203 (w), 1094 (s), 1064 (s), 1005 (s), 947 (w), 929 (w), 865 (w), 735 (s), 697 (s), 610 (w); HRMS-(ESI$^+$) for $C_{15}H_{23}O_2$ [M+H]: calculated: 235.1698, found: 235.1720. The crude reaction mixture was purified by silica gel chromatography (2:1 hexanes:diethyl ether) to afford a clear, colorless oil (46.8 mg, 72%, 7:1 dr). R_f = 0.35 (1:1 hexanes:diethyl ether, stain in PMA).

***Proof of Stereochemistry*:** (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to known compound[8] by ozonolysis/reduction.



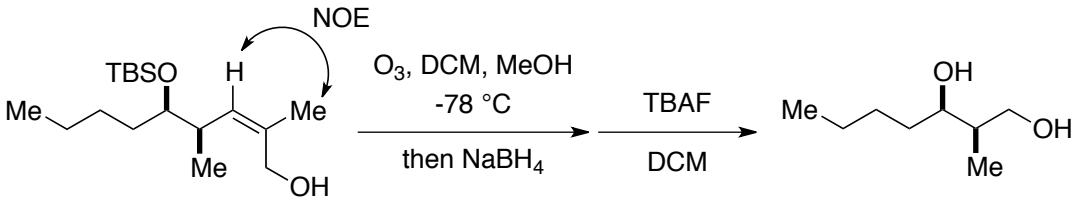


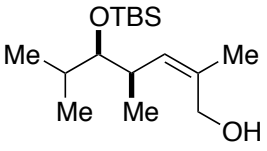
***syn*-(*Z*)- 5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylnon-2-en-1-ol (Table 3.2, entry 1).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.16 (1H, d, *J* = 10.0 Hz), 4.11 (1H, d, *J* = 11.5 Hz), 4.04 (1H, d, *J* = 11.5 Hz), 3.47 (1H, dt, *J* = 6.0 Hz, 4.5 Hz), 2.55 (1H, ddq, *J* = 10.0 Hz, 7.0 Hz, 4.5 Hz), 1.80 (3H, d, *J* = 1.5 Hz), 1.62 (1H, br, s), 1.48-1.34 (2H, m), 1.30-1.23 (4H, m), 0.93 (3H, d, *J* = 7.0 Hz), 0.90 (9H, s), 0.88 (3H, t, *J* = 7.0 Hz), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.1, 132.3, 77.0, 62.0, 37.5, 34.3, 27.7, 26.3, 23.2, 21.9,

[8] Roush, W. R.; Marron, T. G.; Pfeifer, L. A. *J. Org. Chem.* **1997**, *62*, 474.

18.5, 17.2, 14.3, -4.1, -4.2; IR (neat): 3335 (br, w), 2956 (s), 2930 (s), 2858 (s), 1461 (m), 1253 (s), 1005 (s), 834 (s), 773 (s); HRMS-(ESI+) for $C_{17}H_{37}O_2Si$ [M+H]: calculated: 301.2563, found: 301.2570. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.3 mg, 92%, >20:1 dr). R_f = 0.41 (10:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. The relative configuration was assigned by comparison of the ^{1}H NMR spectrum with the known diol,[9] after conversion of the title compound to the known diol by ozonolysis/reduction/deprotection as shown below.



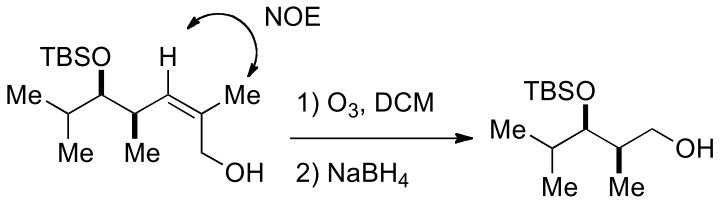


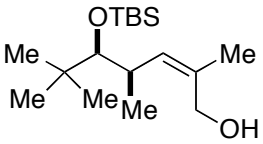
***syn*-(*Z*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhept-2-en-1-ol (Table 3.2, Entry 2).** The reaction was performed with the representative procedure but for 12 h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (1H, d, *J* = 10.0 Hz), 4.10 (2H, s), 3.19 (1H, dd, *J*= 4.5 Hz, 4.5 Hz), 2.58 (1H, qdd, *J* = 12.5Hz, 4.0 Hz, 4.0 Hz), 1.78 (3H, s), 1.76-1.68 (1H, m), 0.93 (3H, d, *J* = 6.0 Hz), 0.91 (9H, s), 0.88 (3H, d, *J* = 7.5 Hz), 0.83 (3H, d, *J* = 6.0 Hz), 0.04 (6H, s); ^{13}C

[9] O'Neil, G. W.; Miller, M. M.; Carter, K. P. *Org. Lett*. **2010**, *12*, 5350.

NMR (125 MHz, $CDCl_3$): δ 133.3, 133.0, 81.8, 62.1, 36.5, 32.1, 26.5, 21.7, 20.7, 18.8, 18.1, 17.7, -3.4, -3.5; IR (neat): 3310 (w), 2957 (m), 2930 (m), 2857 (m), 1472 (m), 1462 (m), 1384 (w), 1252 (m), 1182 (w), 1119 (m), 1086 (m), 1049 (s), 972 (w), 939 (w), 834 (s), 797 (m), 771 (s), 671 (m); HRMS-(ESI^+) for $C_{16}H_{35}O_2Si$ [M+H]: calculated: 287.2406, found: 287.2400. The crude reaction mixture was purified by silica gel chromatography (2:1 hexanes:diethyl ether) to afford a clear, colorless oil (67.0 mg, 98%, 10:1 dr). R_f = 0.51 (1:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to the known compound[10] by ozonolysis/reduction.



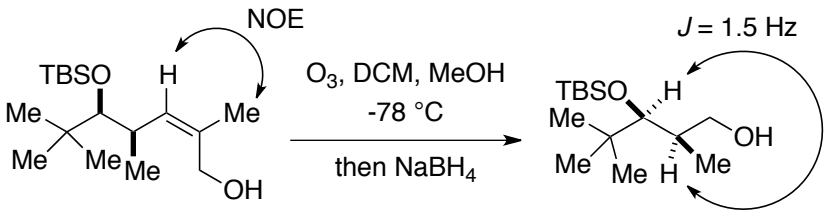


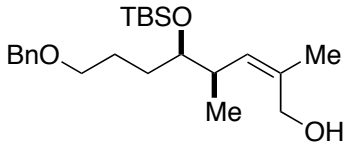
***syn*-(*Z*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4,6,6-tetramethylhept-2-en-1-ol (Table 3.2, entry 3).** The reaction was performed with the representative procedure but ran for 12 h at rt. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (1H, d, *J* = 10.0 Hz), 4.14 (1H, d, *J* = 12.0 Hz), 4.11 (1H, d, *J* = 12.0 Hz), 3.19 (1H, d, *J* = 2.0 Hz), 2.76 (1H, ddq, *J* = 10.0 Hz, 6.5 Hz, 2.0

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

Hz), 1.78 (3H, d, J = 1.5 Hz), 1.3 (1H, br, s), 0.95-0.92 (12H, m), 0.89 (9H, s), 0.08 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 131.3, 83.8, 61.8, 37.2, 33.9, 27.4, 26.6, 21.5, 19.0, 17.0, -2.6, -3.8; IR (neat): 3314 (br, w), 2955 (s), 2930 (s), 2857 (s), 1472 (m), 1252 (s), 1096 (s), 1026 (s), 876 (s), 770 (s); HRMS-(ESI+) for $C_{17}H_{37}O_2Si$ [M+H]: calculated: 301.2563, found: 301.2552. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.0 mg, 89%, 7:1 dr). R_f = 0.35 (10:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by analyzing the chemical shift (3.51 ppm in $CDCl_3$) and J - value (1.5 Hz) between H_3 and H_2 of the diol shown below synthesized by ozonolysis/reduction.[11]





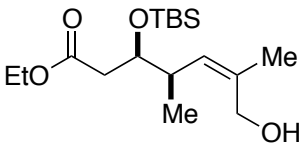
syn-(_Z_)-8-(benzyloxy)-5-((_tert_-butyldimethylsilyl)oxy)-2,4-dimethyloct-2-en-1-ol (Table 3.2, Entry 4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.25 (5H, m), 5.06 (1H, d,

[11] Denmark, S. E.; Ghosh, S. K. Angew. Chem. Int. Ed. 2001, 40, 4759.

J = 10.0 Hz), 4.50 (1H, d, *J* = 12.0 Hz), 4.47 (1H, d, *J* = 12.0 Hz), 4.25 (1H, dd, *J* = 12.0 Hz, 4.0 Hz), 3.87 (1H, dd, *J* = 11.5 Hz, 8.0 Hz), 3.57 (1H, ddd, *J* = 9.0 Hz, 5.0 Hz, 5.0 Hz), 3.49-3.46 (1H, m), 3.37-3.33 (1H, m), 2.60 (1H, qdd, *J* = 10.5 Hz, 6.5 Hz, 6.5 Hz), 2.16 (1H, dd, *J* = 4.0 Hz, 4.0 Hz), 1.77 (3H, s), 1.64-1.62 (3H, m), 1.49-1.43 (1H, m), 0.94 (3H, d, *J* = 6.5Hz), 0.89 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 134.6, 131.7, 128.6, 128.0, 127.8, 76.3, 73.2, 70.6, 61.8, 37.2, 31.3. 26.2, 24.8, 21.8, 18.5, 18.0, -4.1, -4.3; IR (neat): 3395 (m), 1968 (m), 2929 (m), 2870 (m), 1452 (m), 1474 (m), 1203 (w), 1094 (s), 1064 (s), 1005 (s), 947 (w), 929 (w), 865 (w), 735 (s), 697 (s), 610 (w); HRMS-(ESI$^+$) for $C_{23}H_{41}O_3Si$ [M+H]: calculated: 393.2825, found: 393.2813. The crude reaction mixture was purified by silica gel chromatography (6:1 hexanes:diethyl ether) to afford a clear, colorless oil (41.0 mg, 88%, >20:1 dr). R_f = 0.51 (3:1 hexanes:ethyl acetate, stain in PMA).

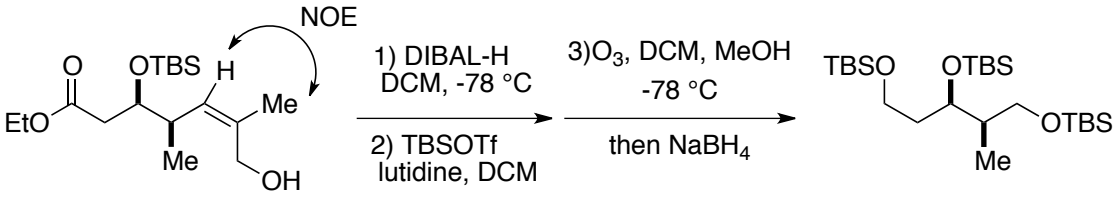
Proof of Stereochemistry (*Z*)-alkene stereochemistry proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to known compound[12] by ozonolysis/reduction.

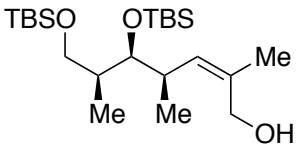
[12] Danishefsky, S. J. Bertinato, P.; Dai-Shi, S.; Fang, M.; Ting-Chao, C.; Kamenecka, T.; Sorensen, E. J.; Balog, A.; Savin, K. A. U.S. Patent 6,369,234, **2002**.



***syn*-(*Z*)-ethyl 3-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-4,6-dimethylhept-5-enoate (Table 3.2, Entry 5).** The reaction was performed with the representative procedure but oxidized with pH 7 buffer instead of 3M NaOH. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.04 (1H, d, *J* = 11.5 Hz), 4.28 (1H, d, *J* = 11.5 Hz), 4.10 (2H, dq, *J* = 8.5Hz, 7.5 Hz), 3.88 (1H, d, *J* = 12.0 Hz), 3.83 (1H, td, *J* = 5.5 Hz, 5.5 Hz), 2.70 (1H, qdd, *J* = 10.5 Hz, 7.0 Hz, 7.0 Hz), 2.46 (2H, d, *J* = 5.5 Hz), 1.79 (3H, s), 1.25 (3H, t, *J* =7.5 Hz), 0.96 (3H, d, *J* = 6.5 Hz), 0.88 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 135.8, 130.9, 73.9, 61.9, 60.8, 41.1, 38.6, 26.0, 22.1, 18.3, 17.8, 14.3, -4.4, -4.5; IR (neat): 2957 (m), 2930 (m), 2857 (m), 1725 (s), 1472 (w), 1462 (w), 1374 (m), 1252 (s), 1175 (m), 1070 (s), 1006 (s), 940 (m), 832 (s), 774 (s), 666 (w); HRMS-(ESI$^+$) for $C_{17}H_{35}O_4Si$ [M+H]: calculated: 331.2305, found: 331.2292. The crude reaction mixture was purified by silica gel chromatography (3:1 hexanes:diethyl ether) to afford a clear, colorless oil (27.0 mg, 80%, >20:1 dr). R_f = 0.57 (3:1 hexanes:ethyl acetate, stain in PMA).

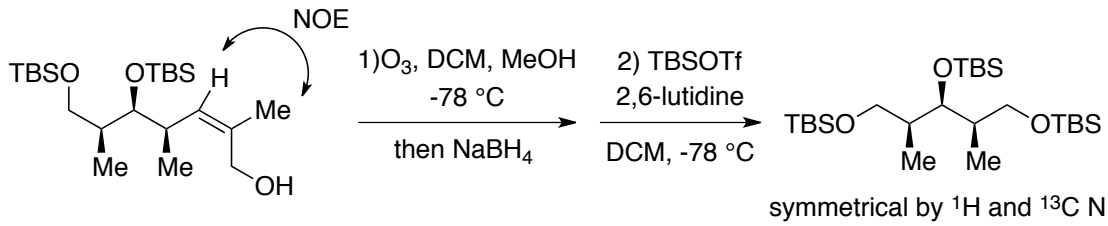
Proof of Stereochemistry (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to the known compound[12] shown below.

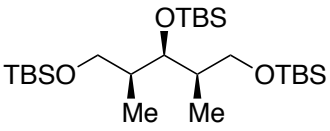




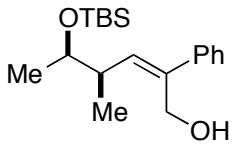
(4*R*,5*S*,6*S*,*Z*)-5,7-bis((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhept-2-en-1-ol (Table 3.2, entry 8). The reaction was performed with the representative procedure but at 0 °C for 12 h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.06 (1H, d, *J* = 10.0 Hz), 4.12 (1H, d, *J* = 11.5 Hz), 3.60 (1H, dd, *J* = 7.0 Hz, 2.5 Hz), 3.41 (1H, dd, *J* = 10.0 Hz, 8.0 Hz), 3.35 (1H, dd, *J* = 10.0 Hz), 2.58 (1H, dqd, *J* = 10.0 Hz, 7.0 Hz, 7.0 Hz), 1.77, (3H, s), 1.71 (1H, dq, *J* = 7.0 Hz, 2.0 Hz), 0.94 (3H, d, *J* = 6.5 Hz), 0.89 (9H, s), 0.87 (9H, s), 0.75 (3H, d, *J* = 7.0 Hz), 0.05 (3H, s), 0.04 (3H, s), 0.02 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.7, 132.8, 75.8, 66.0, 62.1, 39.3, 37.3, 26.5, 26.4, 21.8, 19.0, 18.8, 18.4, 10.8, -3.4, -3.8, -5.0, -5.1; IR (neat): 3345 (w), 2928 (s), 2980 (s), 2857 (s), 1472 (w), 1253 (s), 1089 (s), 835 (s), 774 (s). HRMS-(ESI+) for $C_{22}H_{49}O_3Si_2$ [M+H]: calculated: 417.3220, found: 417.3211. $[\alpha]_D$ = +10.0 (*c* = 1.0, $CHCl_3$, *l* = 50 mm). The crude reaction mixture was purified on silica gel (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.8 mg, 92%, 6:1 dr). R_f = 0.40 (10:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by ozonolysis/reduction/protection to furnish the symmetrical compound as determined by ^{1}H and ^{13}C NMR.





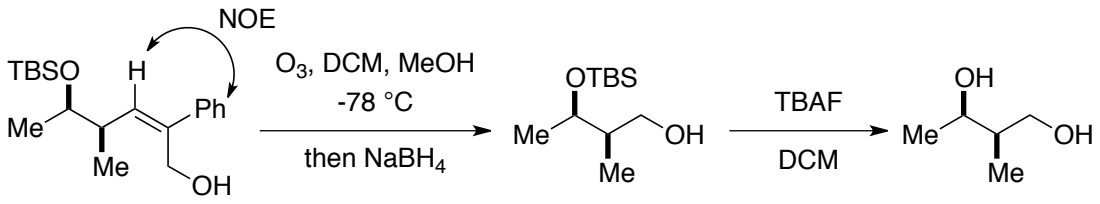
(6*R*,7*r*,8*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,6,8,11,11,12,12-decamethyl-4,10-dioxa-3,11-disilatridecane. Representative ^{1}H and ^{13}C NMR signals: ^{1}H NMR (500 MHz, C_6D_6): δ 3.75 (1H, dd, *J* = 3.5 Hz, 3.5 Hz), 3.52 (2H, dd, *J* = 9.5 Hz, 6.0 Hz), 3.35 (2H, dd, *J* = 9.5 Hz, 7.0 Hz), 1.76 (2H, m), 0.89 (27H, s), 0.86 (3H, d, *J* = 7.0 Hz), 0.04-0.03 (18H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 72.8, 66.1, 40.5, 26.4, 18.7, 18.5, 12.8, -3.8, -5.1, -5.1.

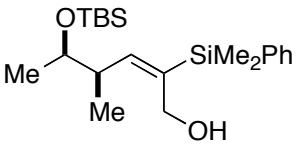


***syn*-(*Z*)- 5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-2-phenylhex-2-en-1-ol (Table 3.3, entry 3).** The reaction was performed with the representative procedure but at rt for 12 h. ^{1}H NMR (500 MHz, C_6D_6): δ 7.52 (2H, dd, *J* = 7.0 Hz, 1.0 Hz), 7.20 (2H, dd, *J* = 7.5 Hz, 7.5 Hz), 7.11 (1H, ddt, *J* = 7.5 Hz, 7.5 Hz, 1.0 Hz), 5.62 (1H, d, *J* = 10.5 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 4.35 (1H, d, *J* = 12.0 Hz), 3.59 (1H, dq, *J* = 11.5 Hz, 5.0 Hz), 2.68 (1H, ddq, *J* = 10.0 Hz, 6.5 Hz, 5.0 Hz), 1.82 (1H, br s), 1.01 (3H, d, *J* = 6.0 Hz), 0.98 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (100 MHz, C_6D_6): δ 142.8, 141.0, 134.7, 129.0, 127.6, 127.2, 73.6, 60.7, 41.2, 26.5, 21.0, 18.9, 18.2, -3.9, -4.3; IR (neat): 3383 (br, w), 2957 (s), 2856 (m), 1462

(m), 1253 (s), 1094 (s), 1005 (s), 834 (s), 772 (s); HRMS-(ESI+) for $C_{19}H_{33}O_2Si$ [M+H]: calculated: 321.2250, found: 321.2249. The crude reaction mixture was purified on silica gel (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (59.0 mg, 93%, 9:1 dr). R_f = 0.38 (10:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to the known diol[7] by ozonolysis/reduction/deprotection as shown below.

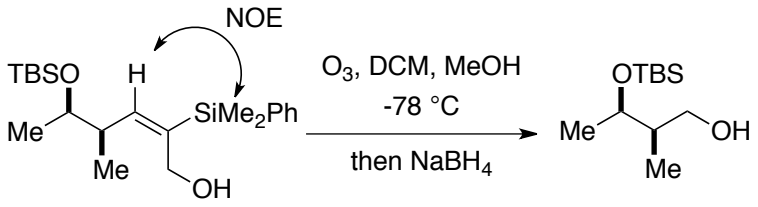




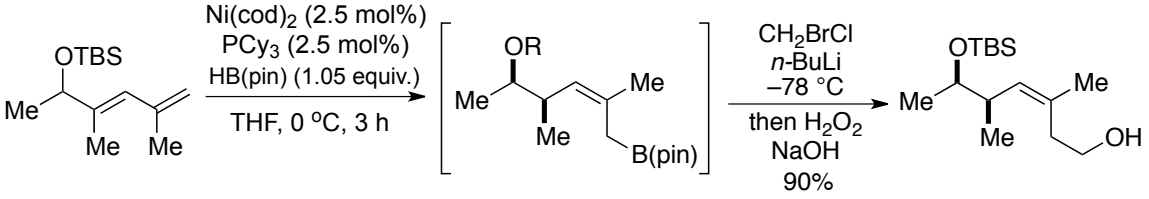
***syn*-(*Z*)- 5-((*tert*-butyldimethylsilyl)oxy)-2-(dimethyl(phenyl) silyl)-4-methylhex-2-en-1-ol (Table 3.3, entry 4).** The reaction was performed with the representative procedure but with 40 mg of diene, and was heated to 40 °C for 12 h. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (2H, m), 7.36-7.34 (3H, m), 5.76 (1H, d, *J* = 9.6 Hz), 4.27 (1H, dd, *J* = 12.0 Hz, 3.0 Hz), 4.18 (1H, dd, *J* = 12.0 Hz, 6.8 Hz), 3.68 (1H, dq, *J* = 6.4 Hz, 6.0 Hz), 2.70 (1H, ddq, *J* = 9.6 Hz, 6.8 Hz, 6.0 Hz), 1.69 (1H, dd, *J* = 4.8 Hz, 4.8 Hz), 1.06 (3H, d, *J* = 6.0 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 0.90 (9H, s), 0.40 (3H, s), 0.40 (3H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 139.5, 139.1, 134.2, 129.1, 128.0, 72.7, 60.7, 40.7, 26.1, 20.6,

18.5, 17.3, -2.3, -2.3, -4.2, -4.5; IR (neat): 3422 (br, w), 2955 (s), 2928 (s), 2855 (s), 1462 (m), 1250 (s), 1111 (s), 1026 (s), 834 (s), 773 (s); HRMS-(ESI+) for $C_{21}H_{39}O_2Si_2$ [M+H]: calculated: 379.2489, found: 379.2476. The crude reaction mixture was purified on silica gel (15:1 hexanes:ethyl acetate) to afford a clear, colorless oil (36.0 mg, 84%, ≥ 10:1 dr). R_f = 0.29 (15:1 hexanes:ethyl acetate, stain in $KMnO_4$). The product contained two impurities in the crude ^{1}H NMR, both in less than 10%, that could not be separated.

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to the known diol[13] by ozonolysis/reduction as shown below.

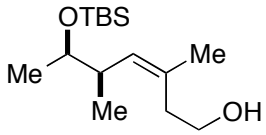


V. ***Procedure for Hydroboration/Matteson Homologation (3.34, Scheme 3.10A):***



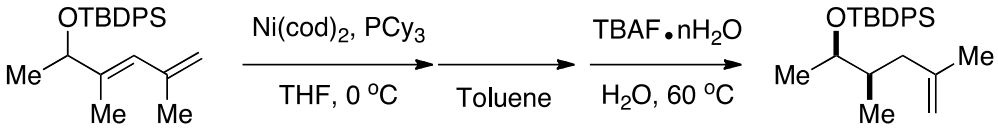
[13] Phukan, P.; Sasmal, S.; Maier, M. E. *Eur. J. Org. Chem*. **2003**, *68*, 1733.

(3.34): In the dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.20 mL of a 31.30 μM solution of $Ni(cod)_2$ in THF, 6.20 μmol), PCy_3 (0.2 mL of a 31.3 0 μM solution of PCy_3 in THF, 6.2 μmol), THF (1.00 mL, 0.25M), pinacolborane (33.5 mg, 0.26 mmol), and (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (60 mg, 0.25 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, immediately cooled to 0 °C (ice/ water), and allowed to stir for 3 h. The cap was then exchanged for a septum, and the vial was flushed with nitrogen. To the vial was added THF (1.5 mL) and bromochloromethane (18.4 μL, 0.27 mmol), at which point the vial was cooled to -78 °C (dry ice/acetone). Freshly titrated *n*-BuLi (0.12 mL of a 2.3 M solution in hexane, 0.27 mmol) was added drop-wise, and the reaction was allowed to stir at -78 °C for 10 min. The reaction was then allowed to warm to room temperature and stir for 16 h. The reaction mixture was cooled to 0 °C and charged with 3 M sodium hydroxide (1 mL) and 30% hydrogen peroxide (0.75 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 (1 mL) was added drop-wise. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (61.2 mg, 90%, 14:1 dr).



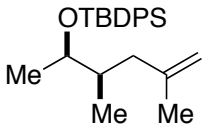
***syn*-(*Z*)- 6-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethylhept-3-en-1-ol (3.34).** ^{1}H NMR (500 MHz, C_6D_6): δ 5.21 (1H, d, *J* = 9.5 Hz), 3.62 (1H, dq, *J* = 6.0 Hz, 4.5 Hz), 3.58 (2H, m), 2.54 (1H, dqd, *J* = 10.0 Hz, 7.0 Hz, 6.5 Hz), 2.27 (2H, m), 1.73 (3H, s), 1.19 (3H, d, *J* = 6.0 Hz), 1.12-1.08 (12H, m), 0.19 (3H, s), 0.18 (3H, s); ^{13}C NMR (100 MHz, C_6D_6): δ 132.2, 131.9, 73.8, 61.2, 41.2, 36.4, 26.7, 24.3, 22.4, 19.0, 18.2, -3.6, -4.1; IR (neat): 3328 (br, w), 2957 (s), 2929 (s), 2857 (s), 1472 (m), 1448 (m), 1254 (s), 1122 (s), 1050 (s), 835 (s), 807 (s); HRMS-(ESI+) for $C_{15}H_{33}O_2Si$ [M+H]: calculated: 273.2250, found: 273.2237. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (61.2 mg, 90%, 14:1 dr). R_f = 0.30 (10:1 hexanes:ethyl acetate, stain in PMA).

VI. ***Procedure for Hydroboration/Protodeboration (3.35, Scheme 3.10B):***



(3.35): In the dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.1 mL of 1.3 μM solution of $Ni(cod)_2$ in THF, 0.13 μmol), PCy_3 (0.1 mL of 1.3 μM solution of PCy_3 in THF, 0.13 μmol), THF (0.05 mL), pinacolborane (7.7 mg, 0.06 mmol), and (*E*)-tert-butyl((3,5-dimethylhexa-3,5-dien-2-yl)

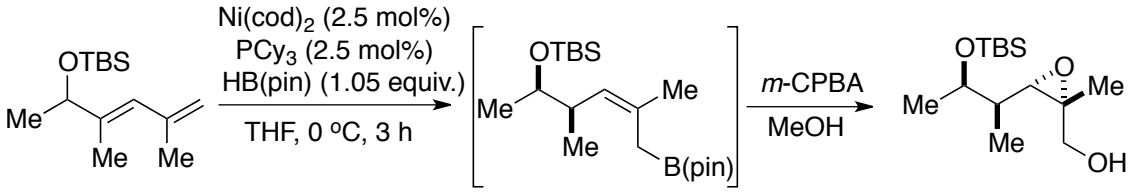
oxy)diphenylsilane (20.0 mg, 0.055 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, and allowed to stir at room temperature for 24 h. The solvent was then removed by rotary evaporation, and TBAF • nH_2O (26 mg, 0.11 mmol) was added. The vial was capped with a septum and purged with nitrogen. Toluene (1.2 mL) was then added, followed by DI water (2.0 μL). The septum was quickly exchanged for a polypropylene cap, and the reaction was allowed to stir at 60 °C for 6 h. The reaction was diluted with diethyl ether and run through a silica pipet column eluting with diethyl ether, followed by concentration by rotary evaporation. The crude material was purified by silica gel chromatography (40:1 hexanes:diethyl ether) to afford the title compound as a clear, colorless oil (17.0 mg, 83%). R_f = 0.84 (20:1 hexanes:diethyl ether, stain with $KMnO_4$).



syn-tert-butyl((-3,5-dimethylhex-5-en-2-yl)oxy)diphenylsilane (3.35). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.68 (4H, m), 7.44-7.40 (2H, m), 7.37 (4H, t, *J* = 7.0 Hz), 4.72 (1H, s), 4.63 (1H, s), 3.83 (1H, qd *J* = 6.0 Hz, 3.0 Hz), 2.34 (1H, dd, *J* = 13.0 Hz, 4.0 Hz), 1.83 (1H, dd, *J* = 13.5 Hz, 10.0 Hz), 1.71-1.68 (1H, m), 1.66 (3H, s), 1.06 (9H, s), 0.97 (3H, d, *J* = 6.0 Hz), 0.77 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 136.2, 136.1, 135.3, 134.6, 129.7, 129.6, 127.7, 127.5, 111.5, 73.0, 40.4, 37.9, 27.3, 22.4, 19.6, 19.4, 14.6; IR (neat): 3071 (w), 2964 (m), 2932 (m), 2858 (m), 1472 (w), 1427 (m), 1380 (m), 1362 (m), 1146 (w), 1106 (s), 1083 (s), 1043 (s), 956 (w), 888 (w), 765 (m), 701 (s); HRMS-(ESI$^+$) for

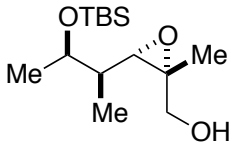
$C_{24}H_{35}OSi$ [M+H]: calculated: 367.2457, found: 367.2475. The crude reaction mixture was purified by silica gel chromatography (20:1 hexanes:diethyl ether) to afford a clear, colorless oil (17.0 mg, 83%, >20:1 dr). R_f = 0.84 (20:1 hexanes: diethyl ether, stain in $KMnO_4$).

VII. ***Procedure for Hydroboration/Epoxidation (3.36, Scheme 3.10C):***



(3.36): In the dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (1.9 mg, 6.80 μmol), PCy_3 (1.9mg, 6.80 μmol), THF (1.08 mL, 0.25M), pinacolborane (35.8 mg, 0.28 mmol), and (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (64 mg, 0.27 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, and allowed to stir at 0 °C for 3 h. The solvent was then removed by rotary evaporation, and K_2HPO_4 (268 mg, 1.08 mmol) was added. The flask was purged with nitrogen and DCM (0.7 mL) and MeOH (86 μL, 2.16 mmol, distilled) were then added, and the flask was cooled to 0 °C. A solution of *m*-CPBA (266.0 mg, 70%, 1.08 mmol) in DCM (2 mL) was added drop-wise at 0 °C and the reaction mixture was allowed to stir at 0 °C for 3 h. The crude reaction mixture was quenched with saturated Na_2CO_3 (2.0 mL), diluted with ethyl acetate (5 mL), and the

layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with saturated Na_2CO_3, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (4:1 hexanes:diethyl ether) to afford the title compound as a clear, colorless oil (53.5 mg, 72%, 7:1 dr). R_f = 0.36 (4:1 hexanes:ethyl acetate, stain with PMA).



(3-3-((*tert*-butyldimethylsilyl)oxy)butan-2-yl)-2-methyloxiran-2-yl)methanol (3.36). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.93 (1H, qd, *J* = 6.0 Hz, 4.5 Hz), 3.92 (1H, qd, *J* = 6.5 Hz, 6.5 Hz), 3.70 (1H, dd, *J* = 11.5 Hz, 7.0 Hz), 3.65 (1H, dd, *J* = 12.0 Hz, 5.0 Hz), 2.75 (1H, d, *J* = 9.5 Hz), 1.40 (3H, s), 1.40-1.35 (1H, m), 1.16 (3H, d, *J* = 6.0 Hz), 0.93 (3H, d, *J* = 6.0 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 69.7, 67.4, 64.2, 60.9, 40.0, 26.1, 22.1, 20.7, 18.3, 10.9, -4.0, -4.8; IR (neat): 3446 (w), 2956 (m), 2930 (m), 2857 (m), 1726 (w), 1472 (m), 1462 (m), 1253 (s), 1149 (m), 1117 (m), 1070 (s), 1023 (s), 960 (s), 892 (m), 835 (s), 801 (s), 773 (s), 707 (m); HRMS-(ESI$^+$) for $C_{14}H_{30}O_3Si$ [M+H]: calculated: 275.2043, found: 275.2052.

Proof of Stereochemistry: The relative configuration was assigned by comparison of the ^{13}C NMR spectrum according to literature reports,[14] after conversion of the product into acetonide **iii**, as shown below.

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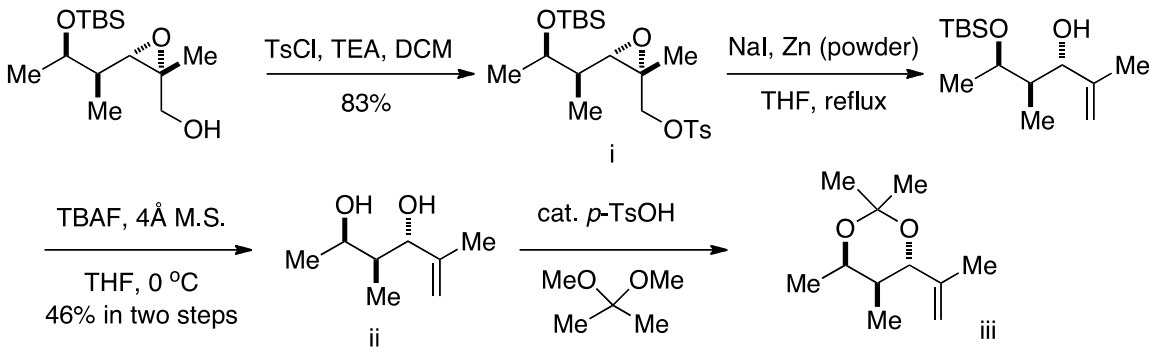
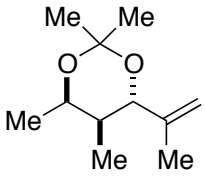
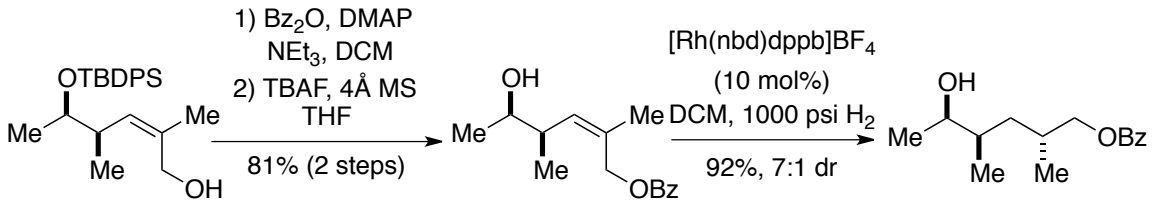
[14] Bestmann, H. J.; Liepold, B.; Kress, A.; Hofmann, A. *Chem. Eur. J.* **1999**, *5*, 2984.



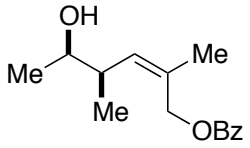


2,2-dimethoxy-4,5-dimethyl-6-(prop-1-en-2-yl)-1,3-dioxane (Scheme 3.10C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (1H, p, *J* = 1.0 Hz), 4.87 (1H, p, *J* = 1.5Hz), 4.09 (1H, qd, *J* = 6.5 Hz, 5.0 Hz), 3.72 (1H, d, *J* = 8.5 Hz), 1.85 (1H, m), 1.77 (3H, s), 1.38 (3H, s), 1.37 (3H, s), 1.11 (3H, d, *J* = 6.5 Hz), 0.84 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 112.6, 100.6, 78.9, 65.5, 37.9, 25.5, 24.4, 18.2, 17.0, 11.9; IR (neat): 2955 (s), 2926 (s), 2863 (s), 1737 (w), 1651 (w), 1622 (w), 1446 (m), 1377 (m), 1225 (m), 1143 (m), 1093 (m), 1022 (m), 895 (w), 861 (w), 817 (w).

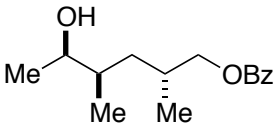
VIII. ***Procedure for Diastereoselective Hydrogenation*** **(3.39,** ***Scheme 3.11):***



(3.39): In the dry-box, an oven-dried 1-dram vial containing a stir bar was charged with (*Z*)-5-hydroxy-2,4-dimethylhex-2-en-1-yl benzoate (20 mg, 0.08 mmol), [Rh(nbd)dppb] BF_4 (5.6mg, 0.008 mmol), and DCM (152μL). The vial was removed from the box and the mixture was stirred under 1000 psi of H_2 gas in a hydrogen bomb for 2 h. The resulting solution was filtered through a short plug of silica gel, washing with diethyl ether. The solution was concentrated by rotary evaporation to afford the title compound as a clear, colorless oil (18.5 mg, 92%, 7:1 dr). R_f = 0.43 (4:1 hexanes: ethyl acetate, stain in PMA).

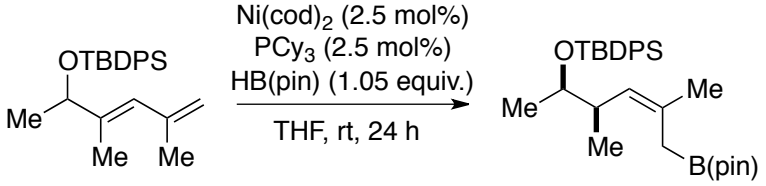


syn-*(Z)*-5-hydroxy-2,4-dimethylhex-2-en-1-yl benzoate (3.38). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, d, *J* = 7.5 Hz), 7.56 (1H, t, *J* = 7.5 Hz), 7.44 (2H, t, *J* = 7.0 Hz), 5.32 (1H, d, *J* = 10.0 Hz), 4.92 (1H, d, *J* = 12.0 Hz), 4.82 (1H, d, *J* = 12.0 Hz), 3.67 (1H, qd, *J* = 6.0 Hz, 6.0 Hz), 2.68 (1H, qdd, *J* = 10.0 Hz, 6.0 Hz, 6.0 Hz), 1.86 (3H, s), 1.15 (3H, d, *J* = 6.5 Hz), 1.02 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 133.2, 132.8, 131.2, 130.4, 129.8, 128.6, 71.9, 64.2, 39.8, 22.0, 20.1, 17.2; IR (neat): 3411 (w), 2968 (m), 2930 (w), 2847 (w), 1717 (s), 1601 (w), 1492 (w), 1451 (m), 1378 (m), 1314 (m), 1266 (s), 1176 (m), 1108 (s), 1025 (s), 902 (m), 709 (s); HRMS-(ESI$^+$) for $C_{15}H_{21}O_3$ [M+H]: calculated: 249.1491, found: 249.1498. The crude reaction mixture was purified by silica gel chromatography (5:1 hexanes:diethyl ether) to afford a clear, colorless oil (78.0 mg, 81%). R_f = 0.28 (5:1 hexanes: ethyl acetate, stain in PMA).



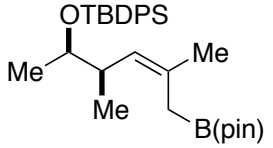
5-hydroxy-2,4-dimethylhexyl benzoate (3.39). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, d, *J* = 8.5 Hz), 7.56 (1H, t, *J* = 2.5 Hz), 7.44 (2H, t, *J* = 2.5 Hz), 4.20 (1H, dd, *J* = 10.5 Hz, 6.0 Hz), 4.12 (1H, dd, *J* = 10.5 Hz, 6.5 Hz), 3.73 (1H, qd, *J* = 6.0 Hz, 4.5 Hz), 2.07-2.00 (1H, m), 1.67-1.58 (1H, m), 1.32 (2H, ddd, *J* = 8.5 Hz, 5.0 Hz, 3.0Hz), 1.17 (3H, d, *J* = 6.5 Hz), 1.01 (3H, d, *J* = 6.0 Hz), 0.90 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 133.1, 130.6, 129.7, 128.6, 71.9, 70.7, 37.0, 36.4, 30.5, 20.4, 16.7, 14.2; IR (neat): 3473 (w), 2966 (m), 2931 (w), 1718 (s), 1379 (w), 1314 (m), 1272 (s), 1113 (s), 1070 (m), 1026 (w), 711 (s), 678 (w), 675 (w); HRMS-(ESI$^+$) for $C_{15}H_{23}O_3$ [M+H]: calculated: 251.1647, found: 251.1644.

IX. Procedure for One gram Hydroboration/Isolation of B(pin) (3.41, Scheme 3.12):



(3.41): In the dry-box, a flame-dried 50 mL round-bottom flask containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (19.3 mg, 0.070 mmol), PCy_3 (19.6 mg, 0.070 mmol), THF (11.2 mL, 0.25M), pinacolborane (0.43 mL, 2.94 mmol), and (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)diphenylsilane (1.02 g, 2.80 mmol). The flask was capped with a septum, removed from the dry-box, and allowed to stir for 24 h at rt.

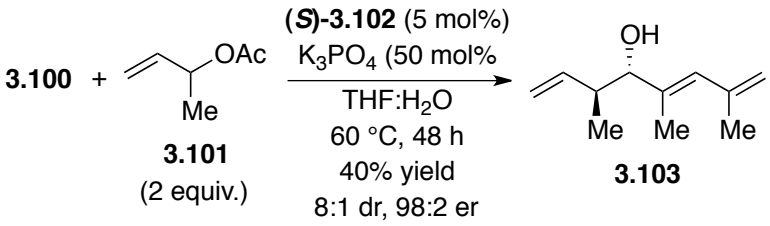
The solvent was then removed by rotary evaporation and the crude reaction mixture was purified by silica gel chromatography (100:1 hexanes:ethyl acetate) to afford the title compound as a clear, light yellow oil (1.01 g, 74% (93% brsm), >20:1 dr). R_f = 0.29 (100:1 hexanes:ethyl acetate, stain with $KMnO_4$).



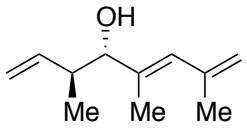
***tert*-butyl((*syn*-*Z*)-3,5-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-2-yl)oxy)diphenylsilane (3.41).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.35 (4H, m), 7.43-7.35 (6H, m), 5.00 (1H, dd, *J* = 9.5 Hz, 1.0 Hz), 3.68 (1H, dq, *J* = 6.5 Hz, 6.5 Hz), 2.34 (1H, ddq, *J* = 10.0 Hz, 6.5 Hz, 6.5 Hz), 1.71 (1H, d, *J* = 15.0 Hz), 1.56 (1H, d, *J* = 15.0 Hz), 1.21 (12H, s), 1.05 (9H, s), 1.00 (3H, d, *J* = 6.5 Hz), 0.95 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2, 136.2, 135.6, 134.7, 131.3, 129.5, 129.4, 127.8, 127.6, 127.5, 83.3, 74.2, 41.1, 27.3, 26.1, 25.0, 24.9, 21.9, 19.7, 16.9; IR (neat): 3071 (w), 3048 (m), 2974 (m), 2891 (m), 1472 (s), 1371 (s), 1323 (s), 1143 (s), 1109 (s), 959 (m), 738 (m), 702 (s), 507 (m); HRMS-(ESI$^+$) for $C_{30}H_{45}O_3BSi$ [M+Na]: calculated: 515.3129, found: 515.3126.

X. Procedures and Full Characterization for the Synthesis of Discodermolide:

Procedure for Krische Crotylation (3.103, Scheme 3.23):[61]



(3.103): In the dry-box, a flame-dried pressure vessel equipped with a magnetic stir bar was sequentially charged with Ir-catalyst **(*S*)-3.102** (170 mg, 0.164 mmol), K_3PO_4 (348 mg, 1.64 mmol), THF (1.64 mL), acetate **3.101** (0.83 mL, 6.56 mmol), and alcohol **3.100** (368 mg, 3.28 mmol). The pressure vessel was sealed with a septum, removed from the dry-box, and placed under an atmosphere of N_2. Degassed H_2O (0.30 mL) was then added *via* syringe and the septum was quickly exchanged for a pressure vessel screw cap. The reaction was allowed to stir for 30 min at room temperature then heated to 60 °C for 48 h. After this time, the reaction mixture was cooled to room temperature, filtered through a pad of silica gel, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (50:1 hexanes:ethyl acetate) to afford the title compound as a clear, colorless oil (229 mg, 42%, 8:1 dr). R_f = 0.30 (50:1 hexanes:ethyl acetate, stain with $KMnO_4$).

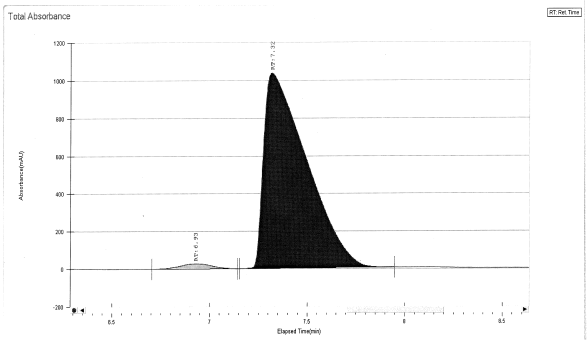


(3*S*,4*S*,*E*)-3,5,7-trimethylocta-1,5,7-trien-4-ol (3.103). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (1H, s), 5.75 (1H, ddd, *J* = 17.5 Hz, 10.0 Hz, 8.5 Hz), 5.21 (1H, ddd, *J* = 17.5 Hz, 2.0 Hz, 1.0 Hz), 5.17 (1H, ddd, 10.0 Hz, 2.0 Hz, 1.0 Hz), 5.01 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.84 (1H, dd, *J* =

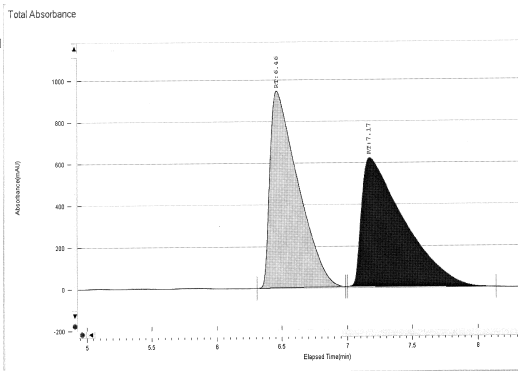
1.0 Hz, 1.0 Hz), 3.67 (1H, dd, *J* = 8.5 Hz, 2.5 Hz), 2.35 (1H, ddq, *J* = 15.0 Hz, 8.0 Hz, 7.0 Hz), 1.88 (3H, s), 1.82 (3H, s), 0.92 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.6, 141.2, 136.8, 130.3, 116.8, 115.4, 81.9, 42.6, 23.8, 17.0, 13.0; IR (neat): 3424 (w), 2963 (s), 2927 (s), 2858 (m), 1637 (m), 1452 (s), 1373 (s), 1011 (s), 893 (s); HRMS-(ESI$^+$) for $C_{11}H_{19}O$ [M+H]: calculated: 167.1436, found: 167.1440. $[\alpha]_D$ = +31.6 (*c* = 1.0, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry: The title compound was directly subjected to SFC analysis and compared to the analogous racemic material **SI-8**.

Chiral SFC (AD-H, Chiralpak, total absorbance, 2.0 mL/min, 0% modifier, 100 bar, 35 °C)-analysis of dienol **3.103**.

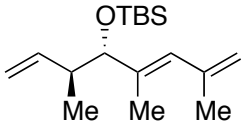


Product derived from crotylation



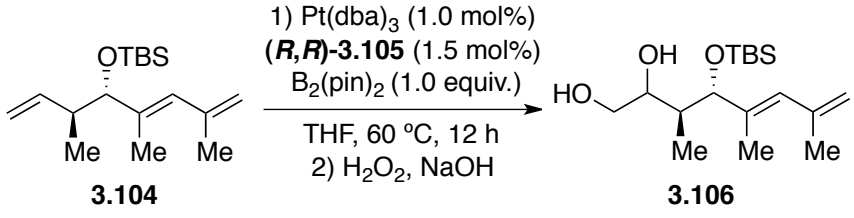
Racemic

Peak No	% Area	Area	RT (min)
1	1.8811	304.8432	6.93
2	98.1189	15900.3754	7.32
Total:	100	16205.2186	



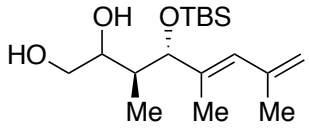
***tert*-butyldimethyl(((3*S*,4*S*,*E*)-3,5,7-trimethylocta-1,5,7-trien-4-yl)oxy)silane (3.104).** The compound was synthesized from **3.103** following the representative TBS-protection procedure**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (1H, ddd, *J* =6 (17.0 Hz, 10.5, HZ, 7.5 Hz), 5.75 (1H, s), 5.00 (1H, ddd, *J* = 10.5 Hz, 2.0 Hz, 2.0 Hz), 4.98-4.96 (1H, m), 4.97 (1H, s), 4.78 (1H, s), 3.67 (1H, d, *J* = 7.5 Hz), 2.31 (1H, ddq, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz), 1.83 (3H, s), 1.74 (3H, s), 0.92-0.83 (12H, m), 0.22 (3H, s), -0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 141.9, 138.4, 128.9, 114.7, 114.0, 83.6, 42.4, 26.1, 23.8, 18.5, 16.8, 13.4, -4.3, -4.8; IR (neat): 2962 (s), 2929 (s), 2858 (s), 1636 (w), 1452 (m), 1252 (m), 1066 (s), 833 (s), 773 (s); HRMS-(ESI$^+$) for $C_{17}H_{33}OSi$ [M+H]: calculated: 281.2301, found: 281.2296. $[\alpha]_D$ = +7.2 (*c* = 1.8, $CHCl_3$, *l* = 50 mm). The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (288 mg, 85%). R_f = 0.40 (hexanes, stain in $KMnO_4$).

Procedure for Diboration/Oxidation (3.106, Scheme 3.24):[65]



3.104 **3.106**

(3.106). In the dry-box, a 2-dram vial equipped with a magnetic stir bar was sequentially charged with $Pt(dba)_3$ (2.0 mg, 0.021 mmol), ligand **(*R,R*)-3.105** (2.0 mg, 0.030 mmol), $B_2(pin)_2$ (57.0 mg, 0.224 mmol), and THF (0.21 mL). The flask was sealed with a polypropylene cap, removed from the dry-box, and heated to 80 °C for 20 min. The vial was brought back into the dry-box and alkene **3.104** (60 mg, 0.21 mmol) was added. The vial was resealed, removed from the dry-box, and allowed to stir at 60 °C for 12 h. The vial was then cooled to 0 °C and charged with 3 M sodium hydroxide (1 mL), and 30% hydrogen peroxide (0.75 mL). The reaction was allowed to gradually warm to room temperature and stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (1 mL) was added drop-wise. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction material was used without further purification.

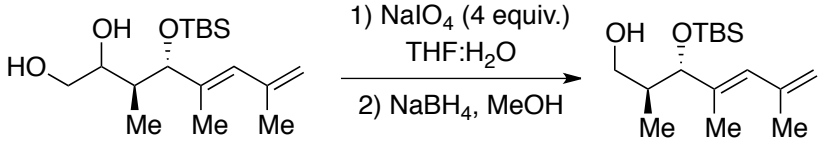


(3*S*,4*S*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-3,5,7-trimethylocta-5,7-diene-1,2-diol (3.106). ^1H and ^{13}C NMR signals: ^1H NMR (500 MHz, $CDCl_3$): δ 5.85 (1H, s), 5.00 (1H, s), 4.80 (1H, s), 3.99 (1H, d, *J* = 6.0 Hz), 3.61 (1H, dd, *J* = 10.5 Hz, 8.5 Hz), 3.48 (1H, dd, *J* = 10.5 Hz, 3.5 Hz), 3.51 (1H, s, br), 1.84 (3H, s), 1.71 (3H, s), 1.25-1.22 (1H, m),

0.9 (12H, m), 0.09 (3H, s), 0.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.4, 136.7, 129.2, 115.2, 82.9, 72.2, 65.4, 37.7, 26.1, 23.8, 18.3, 14.4, 12.3, -4.29, -5.03.

Procedure for Periodate Clevage/Reduction (3.107, Scheme 3.24)

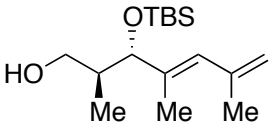
Procedure for Periodate Clevage/Reduction (3.107, Scheme 3.24). To a 20-dram vial equipped with a magnetic stir bar containing crude diol **3.106** was added sodium periodate (163 mg, 0.76 mmol), H_2O (0.5 mL), and THF (0.5 mL). The reaction mixture was allowed to stir for 5 h at room temperature. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation.



3.106 **3.107**

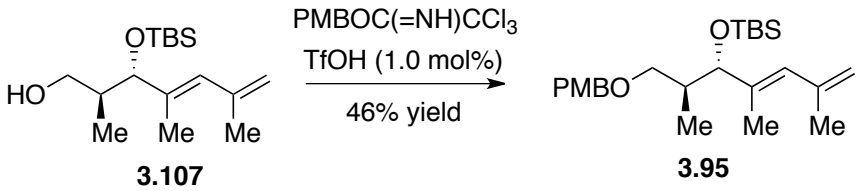
The crude aldehyde was immediately taken up in MeOH (1.0 mL), cooled to 0 °C, and charged with sodium borohydride (15.0 mg, 0.38 mmol). After being allowed to stir for 20 min, the reaction was quenched with saturated sodium bicarbonate (1.0 mL) and diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted 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 silica gel chromatography (10:1 hexanes:ethyl acetate) to afford the title compound as a clear, colorless oil (35.8 mg, 60% over 3 steps). R_f = 0.17 (10:1 hexanes:ethyl acetate, stain with $KMnO_4$).



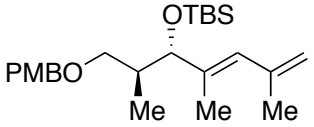
(2*S*,3*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhepta-4,6-dien-1-ol (3.107). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (1H, s), 4.99 (1H, s), 4.79 (1H, s), 3.83 (1H, d, *J* = 8.0 Hz), 3.61 (2H, m), 2.82 (1H, dd, *J* = 4.5 Hz, 4.5 Hz), 1.83 (3H, s), 1.73 (3H, d, 1.9 Hz), 0.89 (12H, s), 0.79 (3H, d, *J* = 6.5 Hz), 0.08 (3H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.5, 137.6, 129.5, 115.2, 85.3, 67.1, 38.7, 26.1, 23.7, 18.3, 14.5, 13.4, -4.16, -4.99; IR (neat): 3421 (w), 2956 (s), 2928 (s), 2856 (s), 1462 (s), 1373 (s), 1061 (s), 835 (s), 775 (s); HRMS-(ESI$^+$) for $C_{16}H_{33}O_2SiNa$ [M+Na]: calculated: 307.2064, found: 307. 2072. $[\alpha]_D$ = -5.8 (*c* = 1.0, $CHCl_3$, *l* = 50 mm).

Procedure for PMB-protection (3.95, Scheme 3.24):



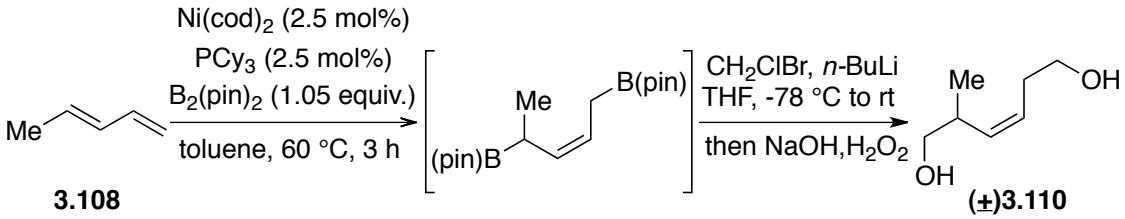
(3.95): To a flame-dried 20-dram vial equipped with a magnetic stir bar was added alcohol **3.107** (80.0 mg, 0.28 mmol) in Et_2O (1.4 mL). The reaction was cooled to 0 °C and 4-methoxybenzyl 2,2,2-trichloroacetimidate (0.18 mL, 0.84 mmol) and

trifluoromethanesulfonic acid (2.0 μL) were added. The reaction was allowed to warm to room temperature and stir for 12 h. the reaction was quenched with saturated sodium bicarbonate (1.0 mL) and diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted 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 silica gel chromatography (10:1 hexanes:ethyl acetate) to afford the title compound as a clear, colorless oil (52.0 mg, 46%). R_f = 0.22 (100:1 hexanes:ethyl acetate, stain with $KMnO_4$).



***tert*-butyl(((2*S*,3*S*,*E*)-1-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-4,6-dien-3-yl)oxy)dimethylsilane (3.95).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (2H, d, *J* = 7.0 Hz), 6.88 (2H, d, *J* = 7.0 Hz), 5.75 (1H, s), 4.98 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.79 (1H, s), 4.45 (1H, d, *J* = 11.5 Hz), 4.39 (1H, d, *J* = 11.5 Hz), 3.81 (3H, s), 3.80 (1H, d, *J* = 13.0 Hz), 3.58 (1H, dd, *J* = 8.5 Hz, 3.5 Hz), 3.37 (1H, dd, *J* = 9.0 Hz, 7.0 Hz), 1.90 (1H, dddq, *J* = 13.5 Hz, 10.0 Hz, 7.0 Hz, 4.0 Hz), 1.84 (3H, s), 1.72 (3H, d, *J* = 1.0 Hz), 0.87 (9H, s), 0.84 (3H, d, *J* = 7.0 Hz), 0.02 (3H, s), -0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 141.8, 138.1, 129.3, 129.3, 114.7, 113.9, 81.1, 72.9, 72.5, 55.5, 38.1, 26.1, 23.8, 18.4, 14.7, 12.9, -4.3, -5.0; IR (neat): 2956 (s), 2929 (s), 2855 (s), 1613 (w), 1513 (s), 1462 (s), 1245 (s), 1062 (s), 836 (s), 775 (s); HRMS-(ESI$^+$) for $C_{24}H_{41}O_3Si$ [M+H]: calculated: 405.2817, found: 405.2817. $[\alpha]_D$ = +4.1 (*c* = 1.0, $CHCl_3$, *l* = 50 mm).

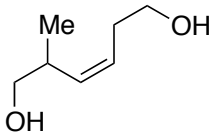
Procedure for Diboration/Homologation/Oxidation (3.110, Scheme 3.25):



3.108 **(±)3.110**

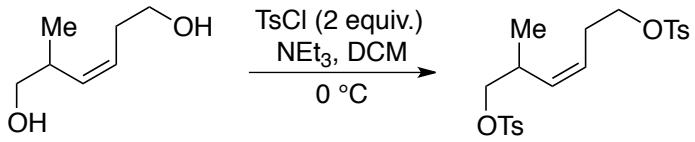
(3.110). In the dry-box, a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged successively with $Ni(cod)_2$ (70.0 mg, 0.25 mmol), PCy_3 (71.0 mg, 0.25 mmol), toluene (34 mL), $B_2(pin)_2$ (2.72 g, 10.79 mmol), and *trans*-1,3-pentadiene (60 mg, 0.43 mmol). The flask was capped with a septum and removed from the dry-box and allowed to stir at 60 °C for 3 h. A majority of the solvent was then removed by rotary evaporation and the flask was purged with N_2. The flask was then charged with THF (51 mL) and bromochloromethane (2.4 mL, 35.7 mmol) and cooled to -78 °C. *n*-BuLi (14.3 mL, 35.7 mmol) was then added drop-wise *via* syringe. After being allowed to stir for 10 min at -78 °C the reaction was allowed to warm to room temperature and stir for 12 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (10 mL), and 30 wt % hydrogen peroxide (5 mL). The reaction was allowed to warm to rt and stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (10 mL) was added dropwise. The reaction mixture was diluted with ethyl acetate (30 mL) and water (30 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 30

mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (1:2 hexanes:ethyl acetate) to afford the title compound as a clear, colorless oil (951 mg, 72%). R_f = 0.10 (1:2 hexanes:ethyl acetate, stain in $KMnO_4$).



(*Z*)-2-methylhex-3-ene-1,6-diol (3.110). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.48 (1H, ddd, *J* = 10.0 Hz, 6.0 Hz, 6.0 Hz), 5.28 (1H, dd, *J* = 10.0 Hz, 10.0 Hz), 3.64 (1H, ddd, *J* = 10.0 Hz, 5.0 Hz, 5.0 Hz), 3.52 (1H, dd, 9.5 Hz, 4.0 Hz), 3.46 (1H, dd, 10.0 Hz, 5.0 Hz), 3.21 (1H, dd, 10.0 Hz, 10.0 Hz), 3.20 (2H, s, br), 2.70-2.64 (1H, m), 2.45-2.34 (1H, m), 2.16-2.10 (1H, m), 0.84 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.1, 127.8, 67.7, 61.8, 34.7, 31.0, 17.2; IR (neat): 3324 (s), 3004 (s), 2956 (s), 2872 (s), 1455 (w), 1035 (s), 744 (s); HRMS-(ESI $^+$) for $C_7H_{15}O_2$ [M+H]: calculated: 131.1078, found: 131.1072.

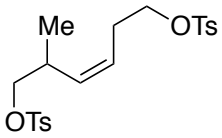
Procedure for Diol Tosylation (3.113, Scheme 3.26):



(±)-3.110 **(±)-3.113**

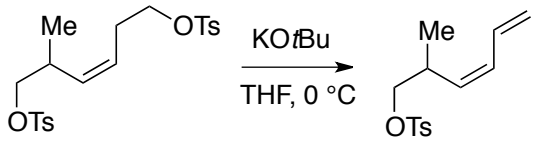
(3.113). To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added diol **3.110** (950 mg, 7.31 mmol) in DCM (15 mL) and NEt_3 (2.34 mL, 15.35

mmol). The flask was cooled to 0 °C and *p*-toluenesulfonyl chloride (2.93 g, 15.35 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stir for 12 h. The crude slurry was then filtered through a plug of silica gel, rinsing with DCM, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (4:1 hexanes:ethyl acetate) to afford a clear, colorless oil (2.62 g, 82%). R_f = 0.30 (4:1 hexanes:ethyl acetate, stain in $KMnO_4$)

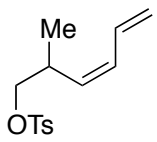


(*Z*)-2-methylhex-3-ene-1,6-diyl bis(4-methylbenzenesulfonate) (3.113). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79-7.75 (4H, m), 7.34-7.33 (4H, m), 5.30 (1H, ddt, *J* = 11.0 Hz, 7.5 Hz, 1.0 Hz), 5.17 (1H, ddd, 11.0 Hz, 11.0 Hz, 1.5 Hz), 4.03 (2H, m), 3.81-3.75 (2H, m), 2.72 (qdddd, *J* = 11.0 Hz, 7.0 Hz, 5.0 Hz, 5.0 Hz, 1.0 Hz), 2.45 (6H, s), 0.91 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 133.8, 133.3, 130.1, 128.1, 125.6, 74.0, 69.6, 32.1, 27.6, 21.9, 17.1; IR (neat): 2964 (w), 2927 (w), 1598 (w), 1357 (m), 1175 (s), 964 (m), 815 (m), 665 (m), 554 (m); HRMS-(ESI$^+$) for $C_{21}H_{27}O_6S_2$ [M+H]: calculated: 439.1236, found: 439.1249.

Procedure for Selective Tosylate Elimination (3.114, Scheme 3.26):

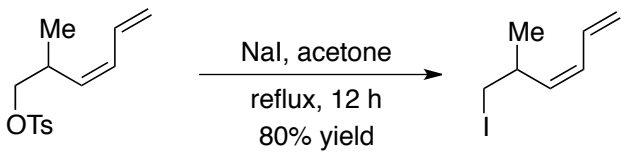


(3.114). To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was added **3.113** (723 mg, 1.65 mmol) in THF (12 mL). The reaction was cooled to 0 °C and KO*t*-Bu (187 mg, 1.67 mmol) was added drop-wise as a solution in THF (3 mL). The reaction was allowed to stir for 4 h at 0 °C then concentrated by rotary evaporation. The crude oil was filtered through a short plug of silica gel, washing with Et_2O, and concentrated to a clear, colorless oil. The material was subsequently without further purification (376 mg, 86%).

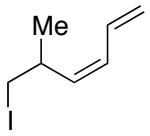


(*Z*)-2-methylhexa-3,5-dien-1-yl 4-methylbenzenesulfonate ((±)-3.114). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (2H, m), 7.34 (2H, m), 6.48 (1H, dddd, *J* = 17.0 Hz, 12.0 Hz, 12.0 Hz, 1.0 Hz), 5.99 (1H, ddd, *J* = 12.0 Hz, 12.0 Hz, 0.5 Hz), 5.21 (1H, ddd, *J* = 17.0 Hz, 1.0 Hz, 0.5 Hz), 5.14 (1H, ddd, *J* = 12.0 Hz, 1.0 Hz, 0.5 Hz), 5.10 (1H, dd, 11.5 Hz, 11.5 Hz), 3.89-3.81 (2H, m), 2.99 (1H, m), 2.45 (3H, s), 1.00 (3H, 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 133.9, 131.9, 131.2, 130.0, 128.1, 128.1, 119.1, 74.1, 32.4, 21.8, 17.4; IR (neat): 3073 (w), 2957 (s), 2871 (m), 1731 (s), 1359 (m), 1267 (m), 1086 (s), 990 (m); HRMS-(ESI$^+$) for $C_{14}H_{22}NO_3Si$ [M+NH_4]: calculated: 284.1320, found: 284.1326.

Procedure for Finkelstein Reaction (3.117, Scheme 3.26):[72]

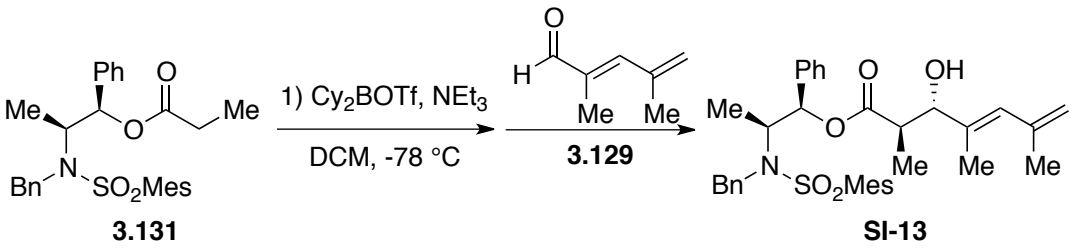


(3.117): A pressure vessel equipped with a magnetic stir bar was charged with tosylate **3.114** (700 mg, 2.63 mmol), sodium iodide (1.97 g, 13.14 mmol), and acetone (13 mL). The vessel was sealed with a pressure vessel screw cap and heated and allowed to stir at 60 °C for 12 h. The resulting white slurry was filtered through silica gel plug, rinsing with hexanes, and concentrated to a yellow oil (467 mg, 80%).



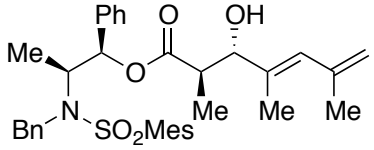
(*Z*)-6-iodo-5-methylhexa-1,3-diene (3.117). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.57 (1H, ddt, *J* = 21.0 Hz, 10.0 Hz, 1.0 Hz), 6.03 (1H, ddd, *J* = 10.0 Hz, 10.0 Hz, 1.0 Hz), 5.20-5.18 (2H, m), 5.16 (1H, dd, *J* = 10.0 Hz, 1.0 Hz), 3.15-3.09 (2H, m), 2.88 (1H, m), 1.22 (3H, d, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.4, 132.1, 130.0, 118.8, 34.8, 21.7, 15.5; IR (neat): 3067 (w), 3025 (w), 2977 (s), 2867 (w), 1494 (m), 1427 (s), 1351 (s), 1248 (s), 1143 (s), 837 (s), 698 (s); HRMS-(ESI$^+$) for $C_7H_{12}I$ [M+H]: calculated:222.9983, found: 222.9988.

Procedure for Abiko-Masamune Aldol (Scheme 3.32):[76]



(**SI-13**): To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added 3.131[77] then the flask was purged with N_2. NEt_3 (1.60 mL, 11.50 mmol) and

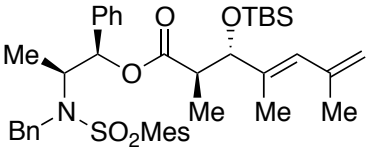
DCM (24 mL) were then added and the flask was cooled to -78 °C. Cy_2BOTf [15] (5.30 mL of a 2.0 M solution in hexanes, 10.55 mmol) was added drop-wise and the reaction was allowed to stir at -78 °C for 30 min. Aldehyde 3.129 (528 mg, 4.80 mmol) was added drop-wise and the reaction was allowed to at -78 °C for 30 min then gradually warm to room temperature and stir for 2 h. MeOH (10 mL), pH 7 buffer (10 mL), and 30 wt % hydrogen peroxide (5 mL) were then sequentially added and the reaction was allowed to stir for 12 h. The reaction mixture was diluted with ethyl acetate (30 mL) and water (30 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (15:1:1 hexanes:ethyl acetate:DCM) to afford the title compound as a clear, colorless oil (2.10 g, 77%). R_f = 0.20 (15:1:1 hexanes:ethyl acetate:DCM, stain in $KMnO_4$).



(2*R*,3*S*,*E*)-(1*R*,2*S*)-2-(*N*-benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 3-hydroxy-2,4,6-trimethylhepta-4,6-dienoate (SI-13): ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (2H, d, *J* = 8.5 Hz), 7.26-7.17 (6H, m), 6.90 (2H, s), 6.85 (2H, dd, *J* = 8.5 Hz, 1.0 Hz), 5.86 (1H, s), 5.83 (1H, d, *J* = 4.0 Hz), 5.03 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.84 (1H, s), 4.82 (1H, d, *J* = 17.0 Hz), 4.61 (1H, d, *J* = 17.0 Hz), 4.11-4.06 (2H, m), 2.64 (1H, dq, *J* = 14.5 Hz, 7.0 Hz), 2.52 (6H, s), 2.45 (1H, d, *J* = 3.5

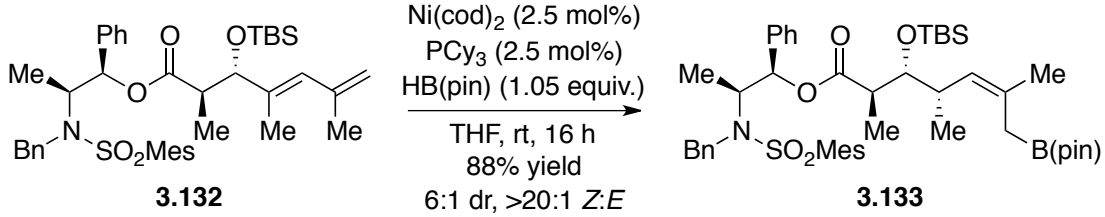
[15] Abiko, A. *Org. Synth*. **2002**, *79*, 103

Hz), 2.29 (3H, s), 1.85 (3H, s), 1.74 (3H, d, *J* = 1.0 Hz), 1.16 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 142.8, 141.3, 140.5, 139.0, 138.5, 135.5, 133.7, 132.5, 131.4, 128.6, 128.5, 128.1, 127.8, 127.3, 126.0, 116.1, 80.8, 78.5, 57.0, 48.5, 43.7, 23.7, 23.2, 21.1, 14.5, 13.6, 12.5; IR (neat): 3546 (w), 2980 (w), 2939 (w), 1746 (s), 1603 (m), 1453 (m), 1323 (s), 1152 (s), 1018 (m), 698 (m); HRMS-(ESI$^+$) for $C_{35}H_{43}NO_5SNa$ [M+Na]: calculated:612.2760, found: 612.2748.

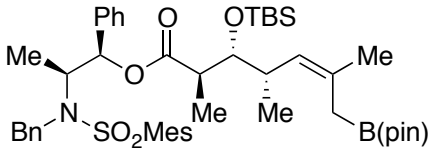


(2*R*,3*S*,*E*)-(1*R*,2*S*)-2-(*N*-benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 3-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhepta-4,6-dienoate (3.132). The compound was synthesized from **SI-8** following the representative TBS-protection procedure but with 3 equiv. of TBSOTf**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (2H, d, *J* = 7.0 Hz), 7.31-7.24 (3H, m), 7.18-7.14 (1H, m), 7.08 (1H, dd, *J* = 7.5 Hz, 7.5 Hz), 6.88 (2H, s), 6.68 (2H, d, *J* = 7.0 Hz), 5.76 (1H, s), 5.68 (1H, d, *J* = 5.5 Hz), 5.00 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.91 (1H, d, *J* = 17.5 Hz), 4.79 (1H, s), 4.40 (1H, d, *J* = 17.5 Hz), 4.12 (1H, d, *J* = 10.0 Hz), 4.01 (1H, dq, *J* = 6.5 Hz, 6.5 Hz), 2.68 (1H, dq, *J* = 7.5 Hz, 7.5 Hz), 2.42 (6H, s), 2.32 (3H, s), 1.82 (3H, s), 1.74 (3H, d, *J* = 7.0 Hz), 1.15 (3H, d, *J* = 7.0 Hz), 0.82 (9H, s), 0.79 (3H, d, *J* = 7.0 Hz), 0.01 (3H, s), -0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 142.6, 141.3, 140.7, 138.9, 138.5, 136.1, 132.4, 131.1, 128.7, 128.6, 128.4, 128.0, 127.7, 126.6, 115.4, 81.4, 77.8, 57.0, 48.5, 45.0, 26.1, 23.6, 23.1, 21.1, 18.4, 15.0, 14.5, 12.4, -4.6, -4.7; IR (neat); 2950 (m), 2936 (m), 2857 (w), 1744 (s), 1455 (m), 1327 (s), 1155 (s), 1066 (s), 837 (s); HRMS-(ESI$^+$) for

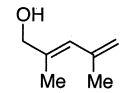
$C_{41}H_{57}NO_5SSiNa$ [M+Na]: calculated: 763.4598, found: 763.4565. $[\alpha]_D$ = +43.5 (*c* = 1.0, $CHCl_3$, *l* = 50 mm). The crude reaction mixture was purified on silica gel (40:1 hexanes:ethyl acetate) to afford the title compound as a clear, colorless oil (238 mg, 75%). R_f = 0.40 (40:1 hexanes:ethyl acetate, stain in $KMnO_4$).



3.132 **3.133**



(**3.133**): The reaction was performed with the representative hydroboration procedure but for 16 h at room temperature. ^{1}H NMR (500 MHz, C_6D_6): δ 7.53 (2H, d, *J* = 7.5 Hz), 7.16-7.10 (2H, m), 7.03-7.00 (2H, m), 7.00-6.93 (4H, m), 6.48 (2H, s), 6.05 (1H, d, *J* = 7.0 Hz), 5.18 (1H, d, *J* = 9.5 Hz), 5.01 (1H, d, *J* = 16.5 Hz), 4.46 (1H, d, *J* = 16.5 Hz), 4.46-4.36 (1H, m), 4.08 (1H, dd, *J* = 5.5 Hz, 5.5 Hz), 2.77-2.70 (2H, m), 2.46 (6H, s), 1.90 (3H, s), 1.87 (1H, d, *J* = 15.0 Hz), 1.80 (3H, d, *J* = 1.0 Hz), 1.71 (1H, d, *J* = 15.0 Hz), 1.45 (3H, d, *J* = 7.0 Hz), 1.14 (3H, d, *J* = 7.0 Hz), 1.05-1.01 (15 H, m), 0.04 (9H, s), 0.22 (3H, s), 0.19 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 142.5, 140.6, 138.6, 138.4, 133.3, 132.3, 132.1, 128.6, 128.4, 128.0, 127.6, 127.0, 126.9, 83.3, 77.7, 56.9, 48.3, 45.7, 36.0, 34.9, 31.8, 26.4, 25.9, 24.9, 23.1, 21.1, 18.6, 16.5, 15.8, 14.3, 12.4, -3.7, -4.2; HRMS-(ESI$^+$) for $C_{47}H_{70}BNO_7SSiNa$ [M+Na]: calculated: 891.5600, found: 891.5586. $[\alpha]_D$ = +20.6 (*c* = 1.0, $CHCl_3$, *l* = 50 mm).



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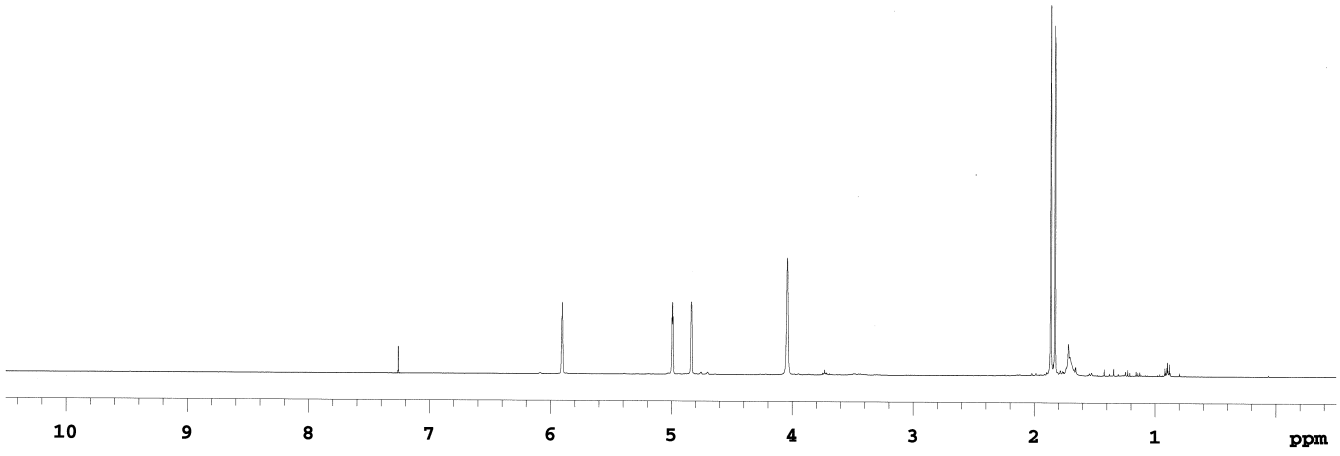

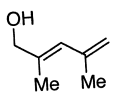

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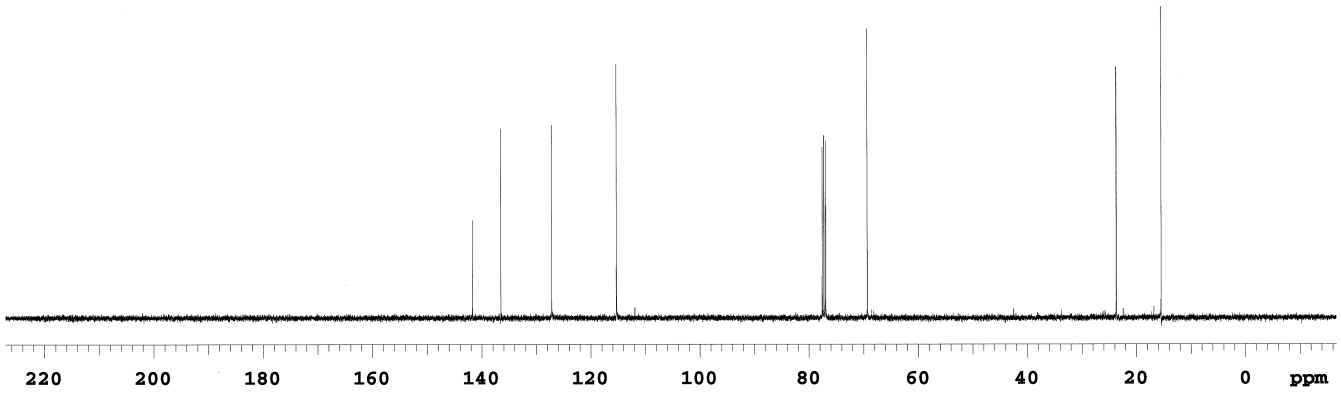

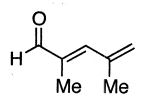

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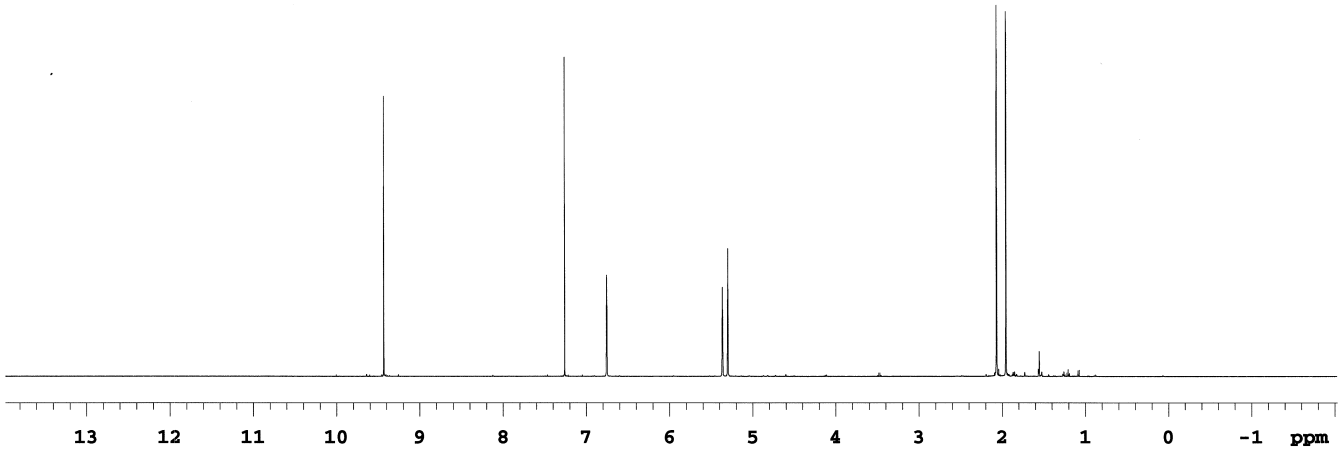
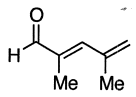
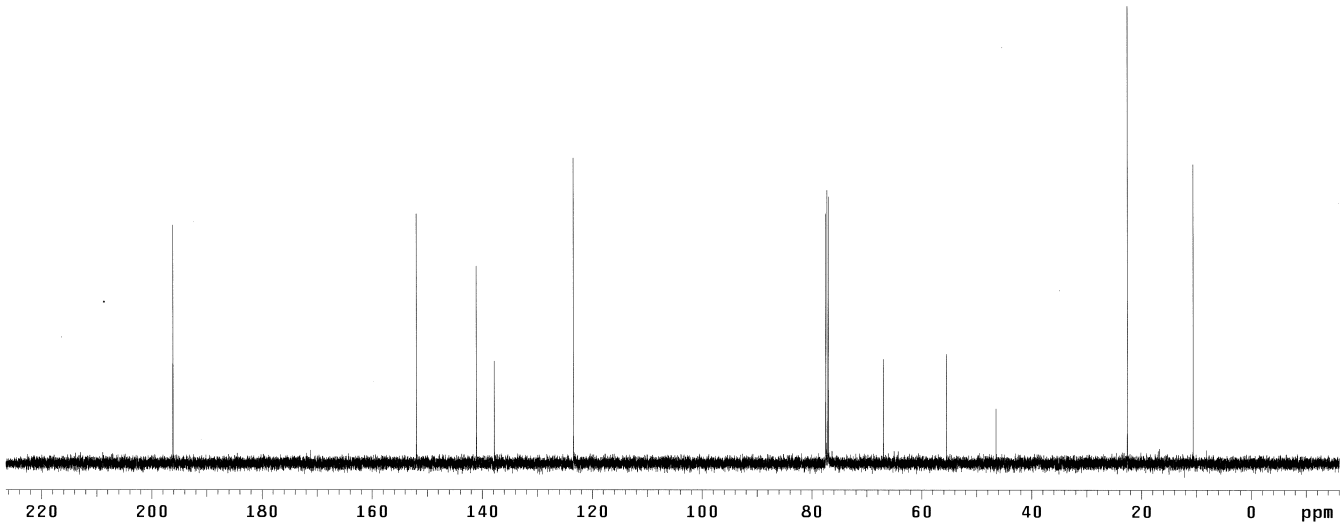
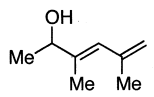




SI-1





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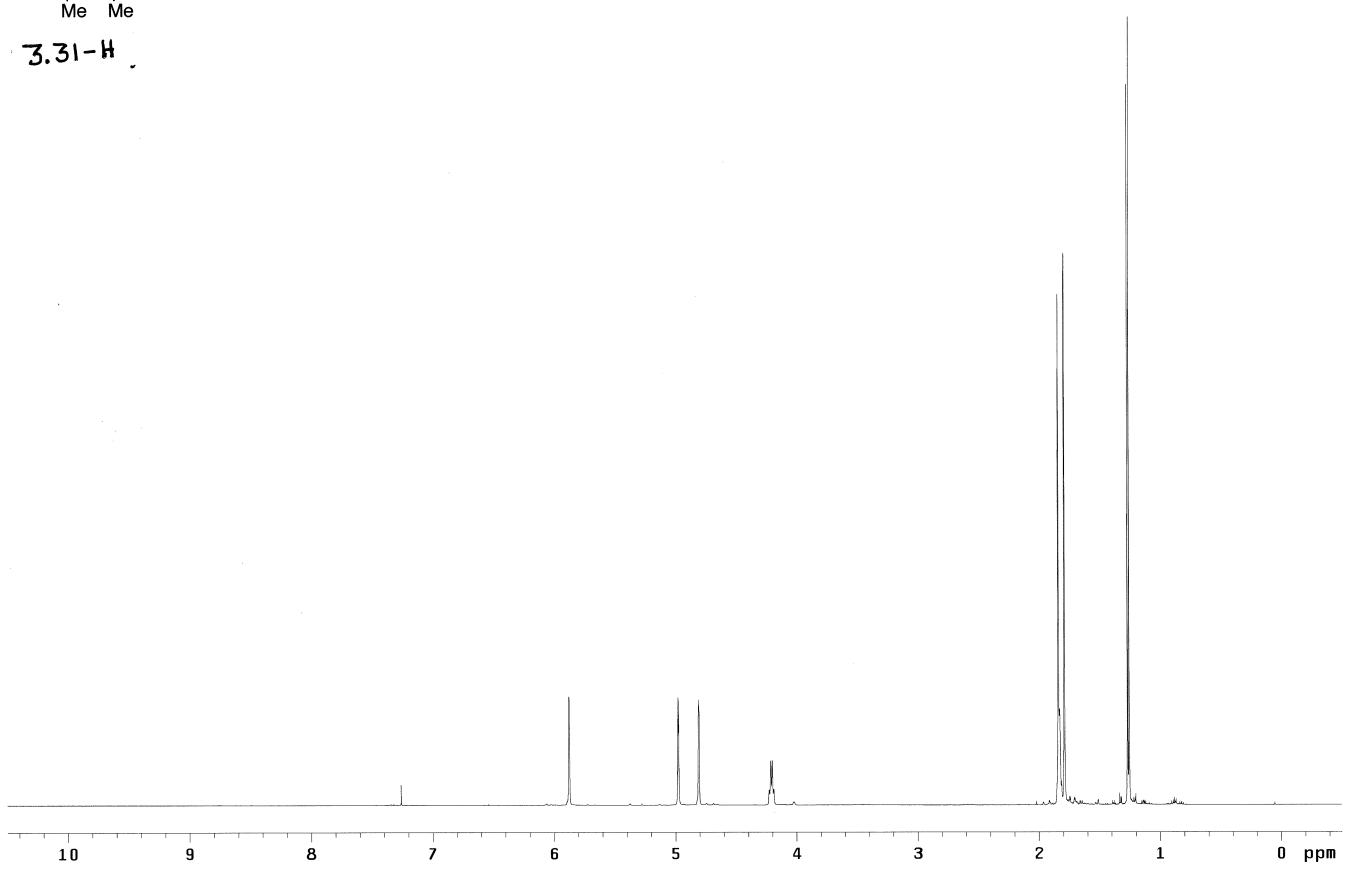
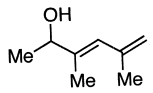
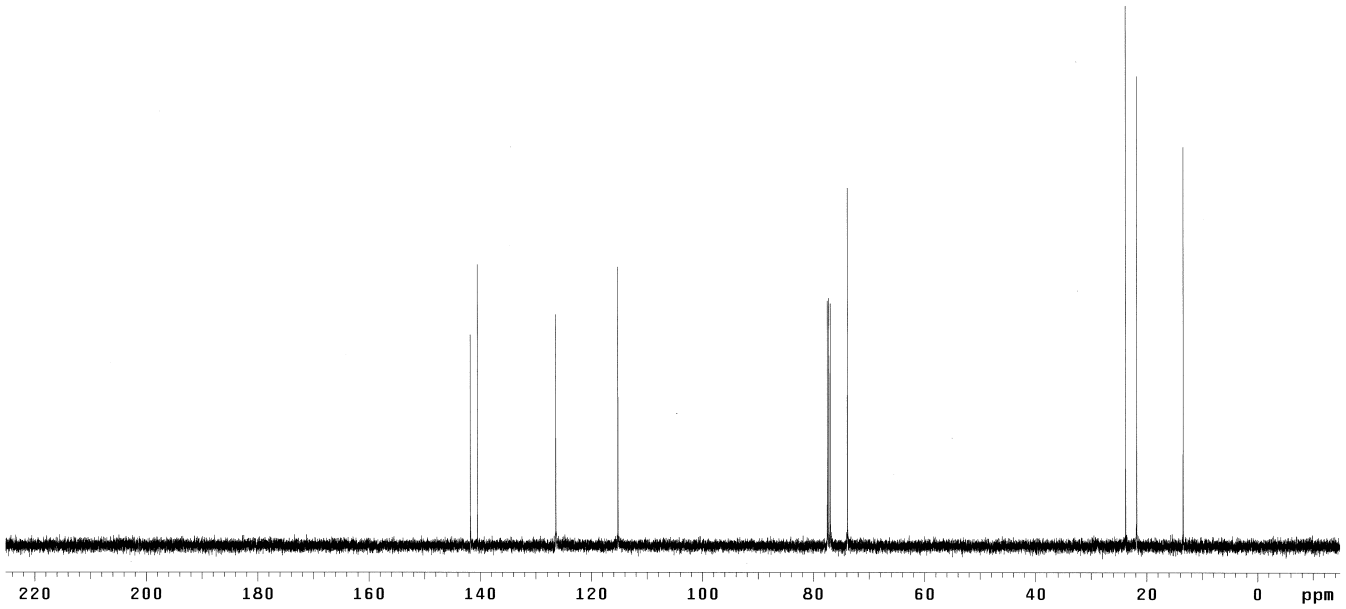
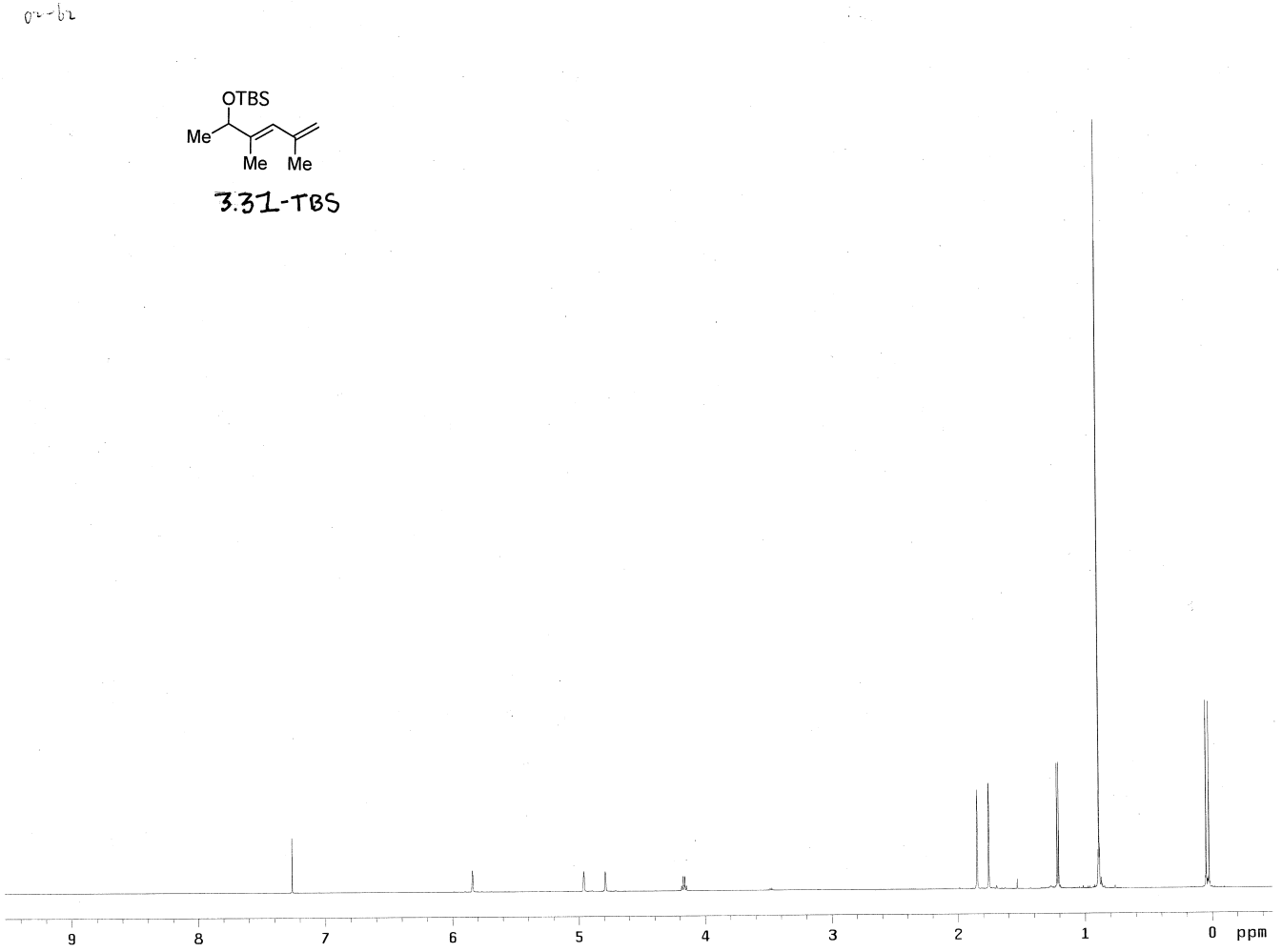




3.31-H

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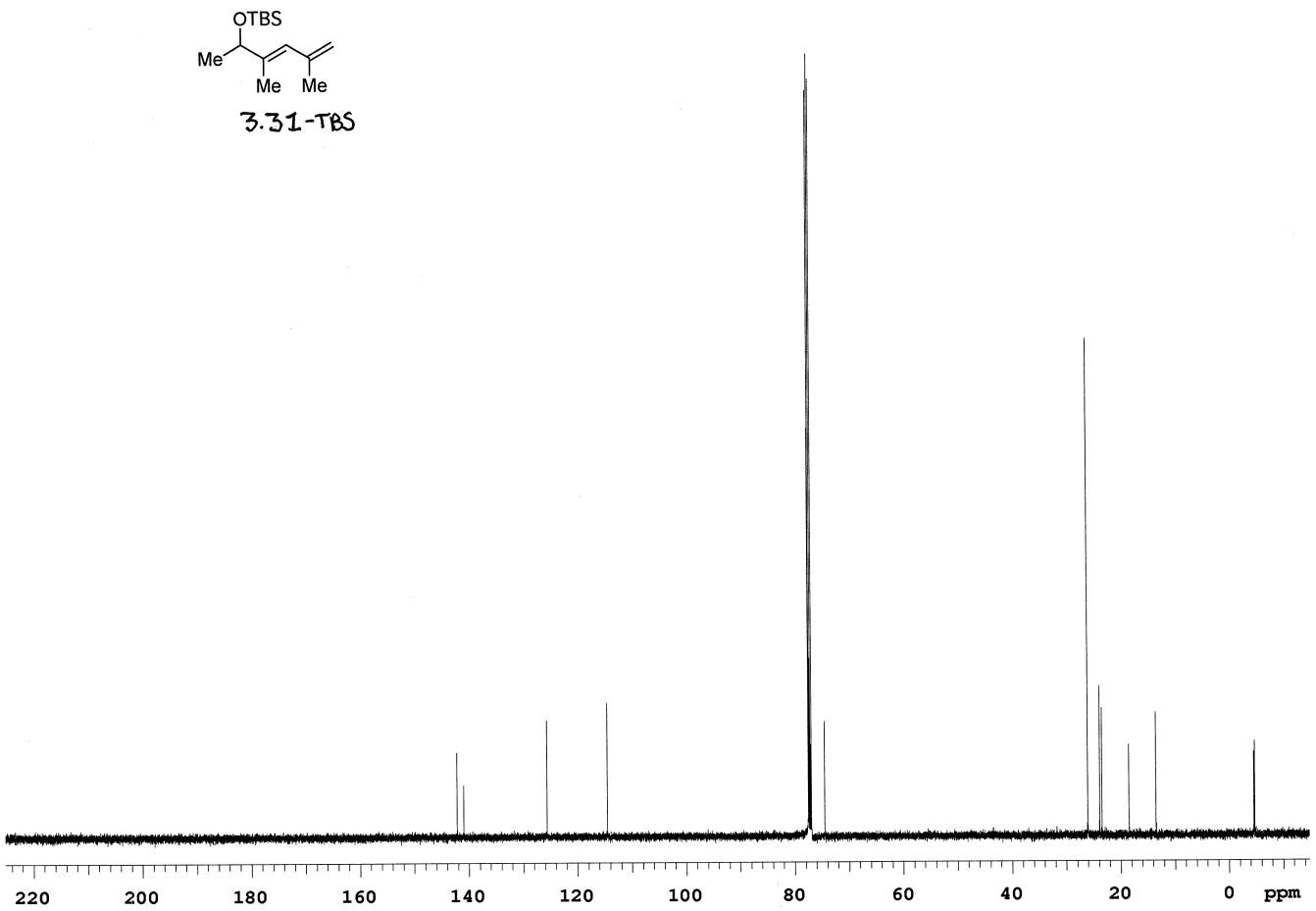
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3.31-TBS
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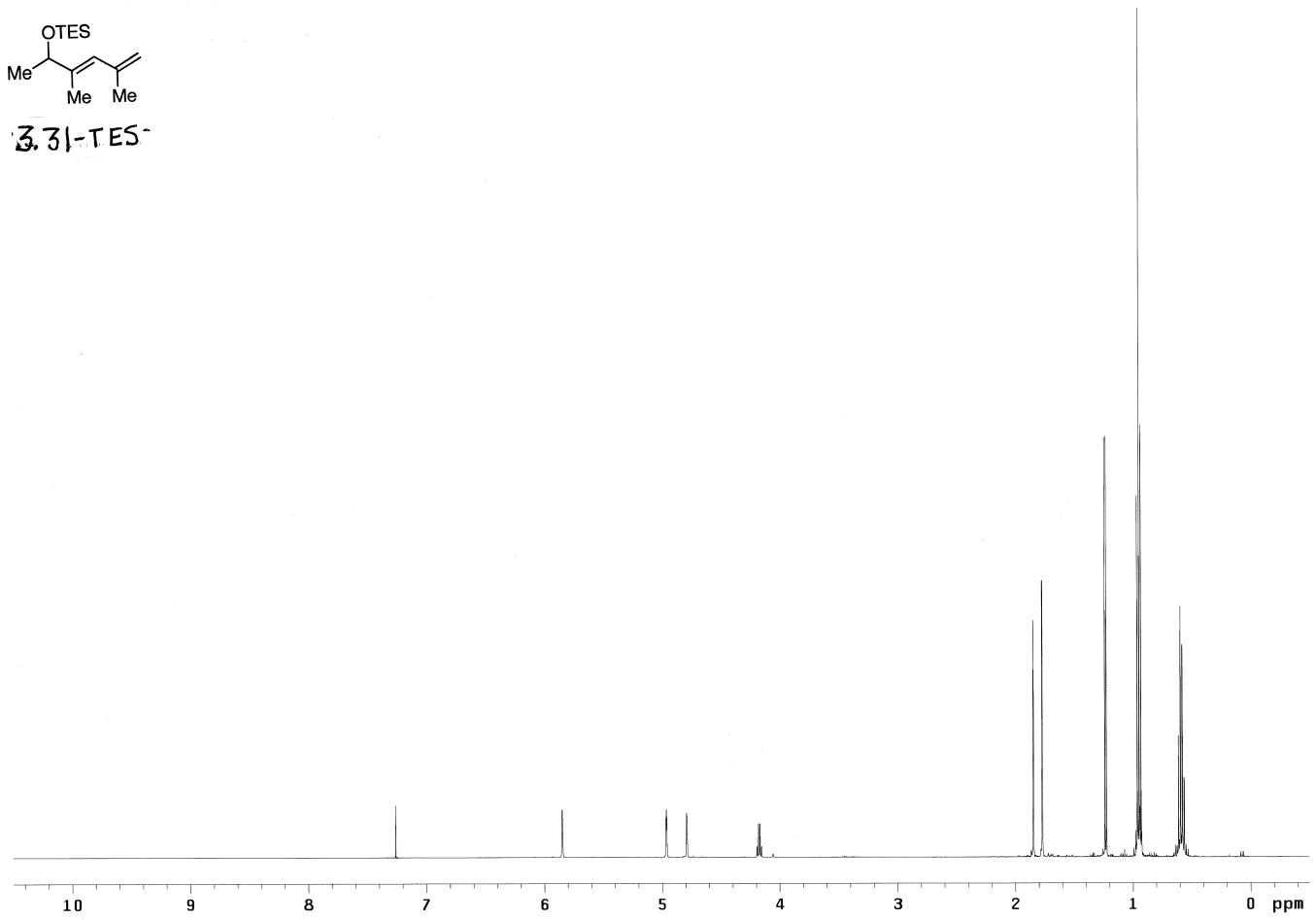
ppm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4
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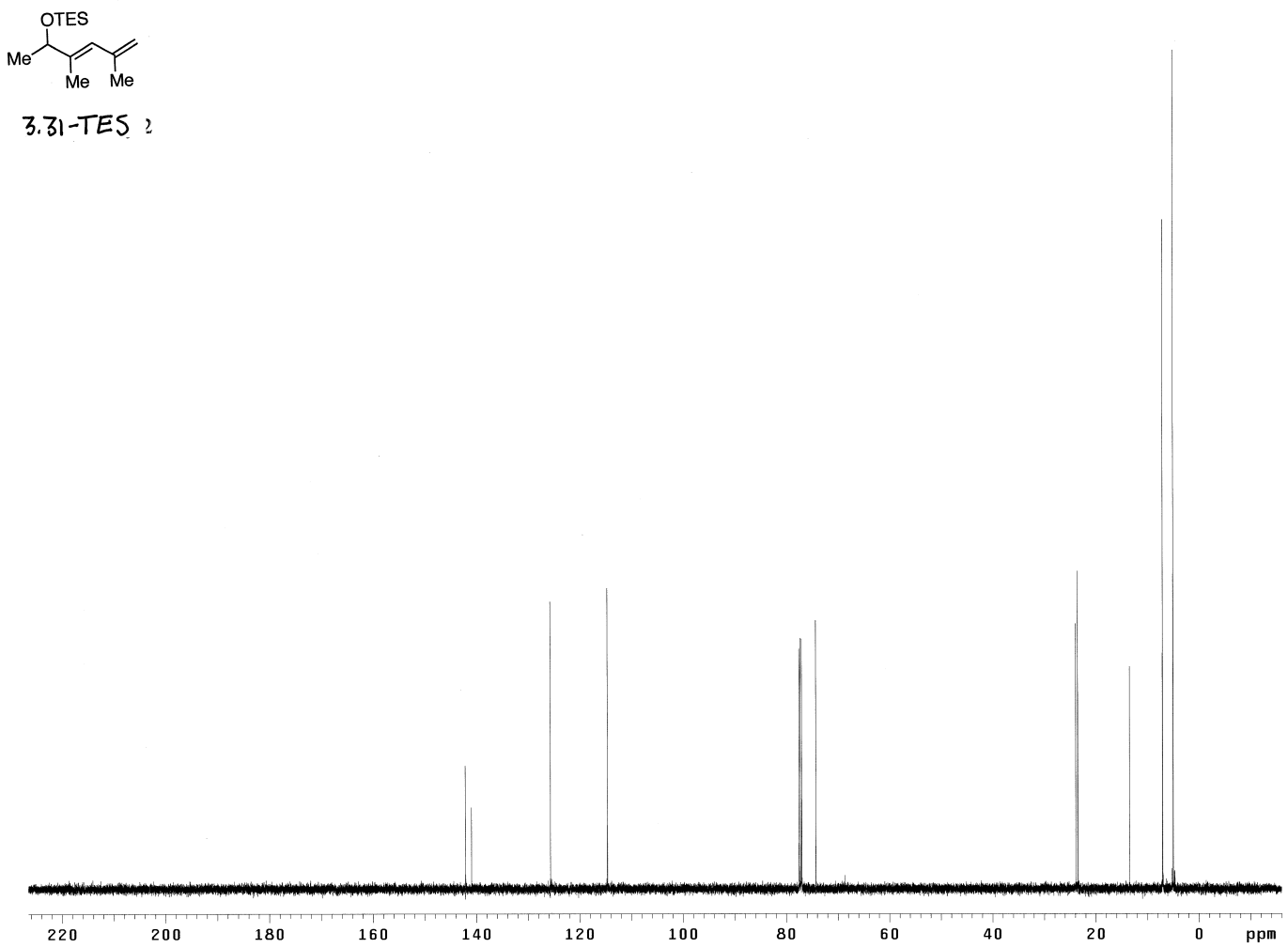
ppm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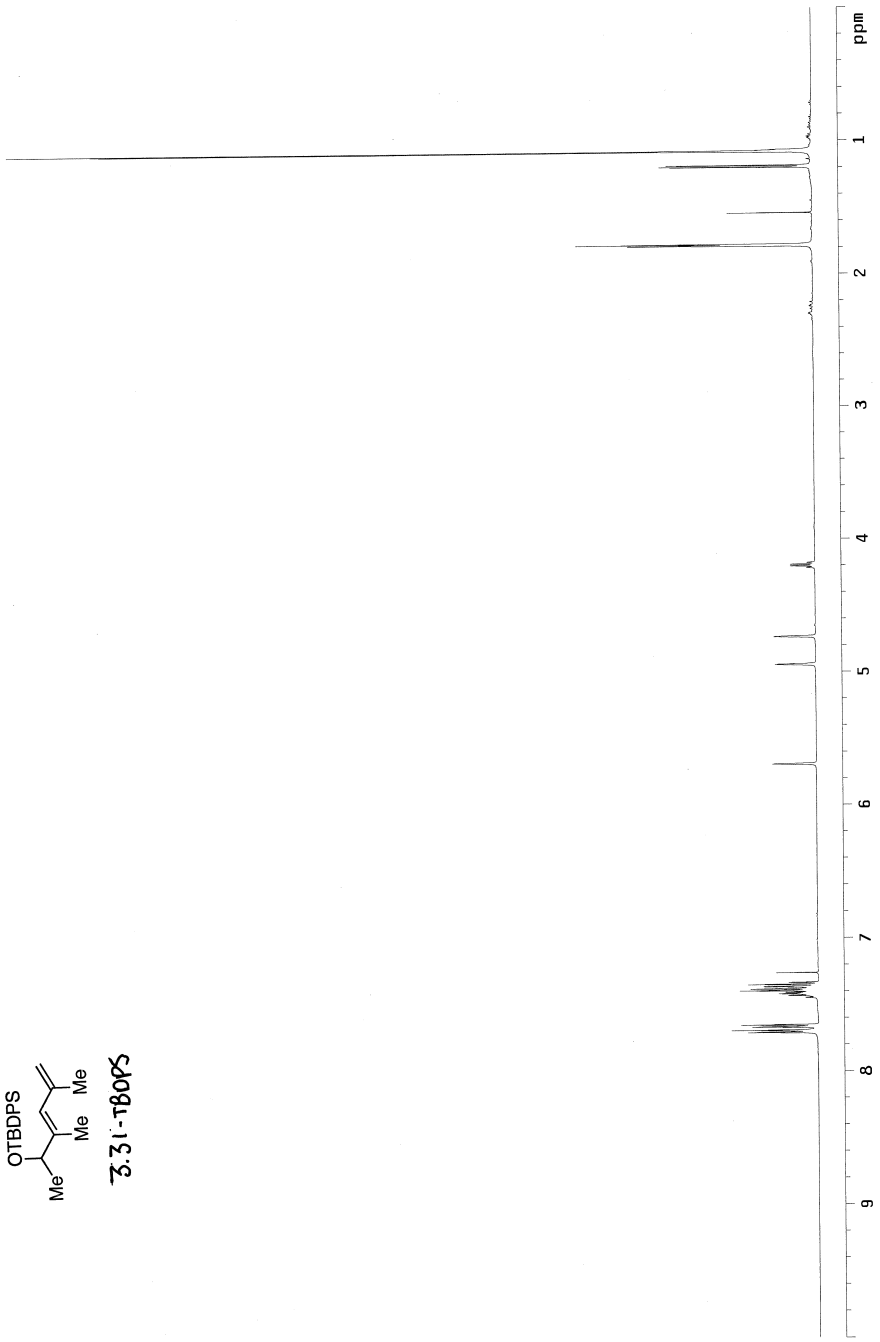
ppm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Me
3.31-TBDPS
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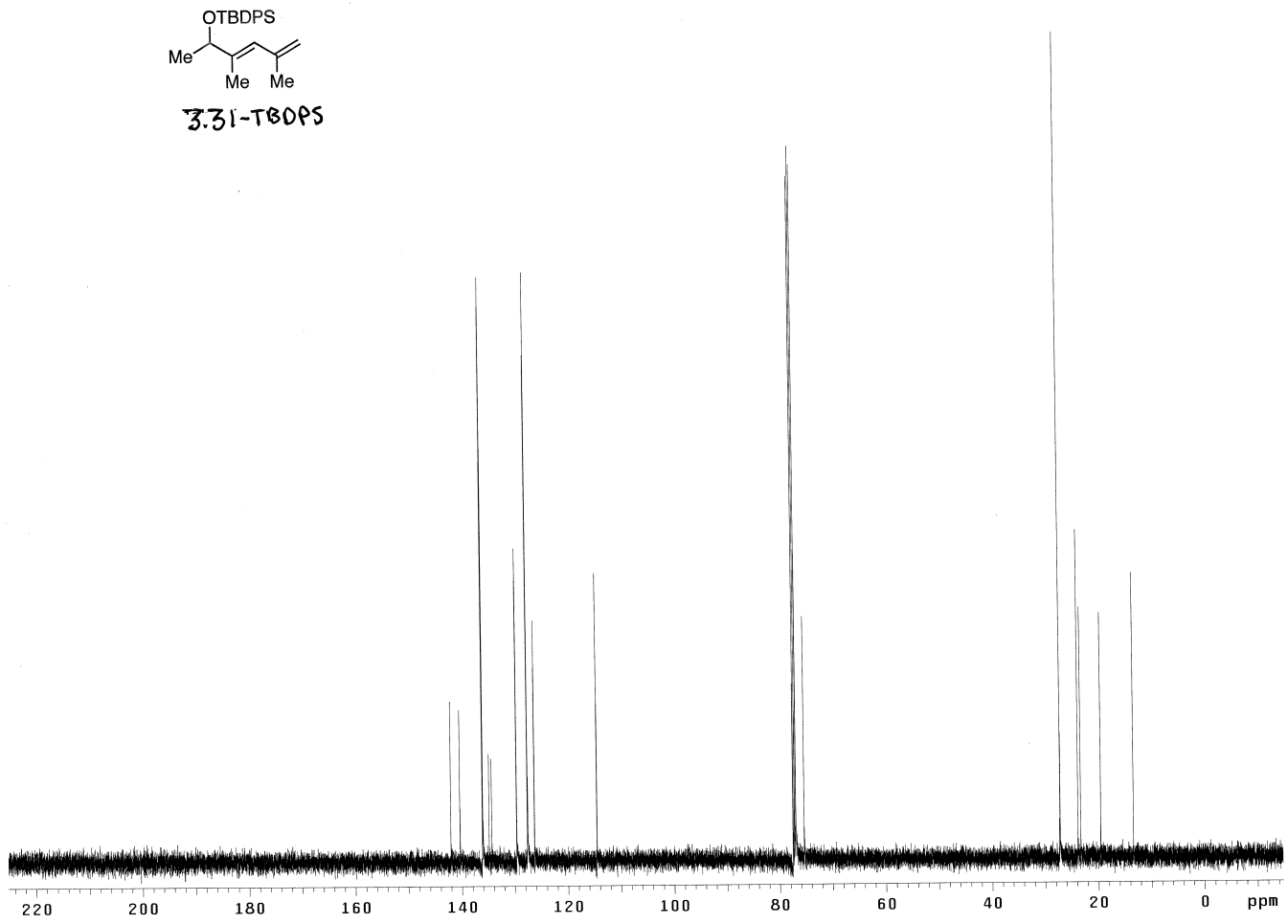
2
3
4
5
6
7
8
9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Me
Me
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120
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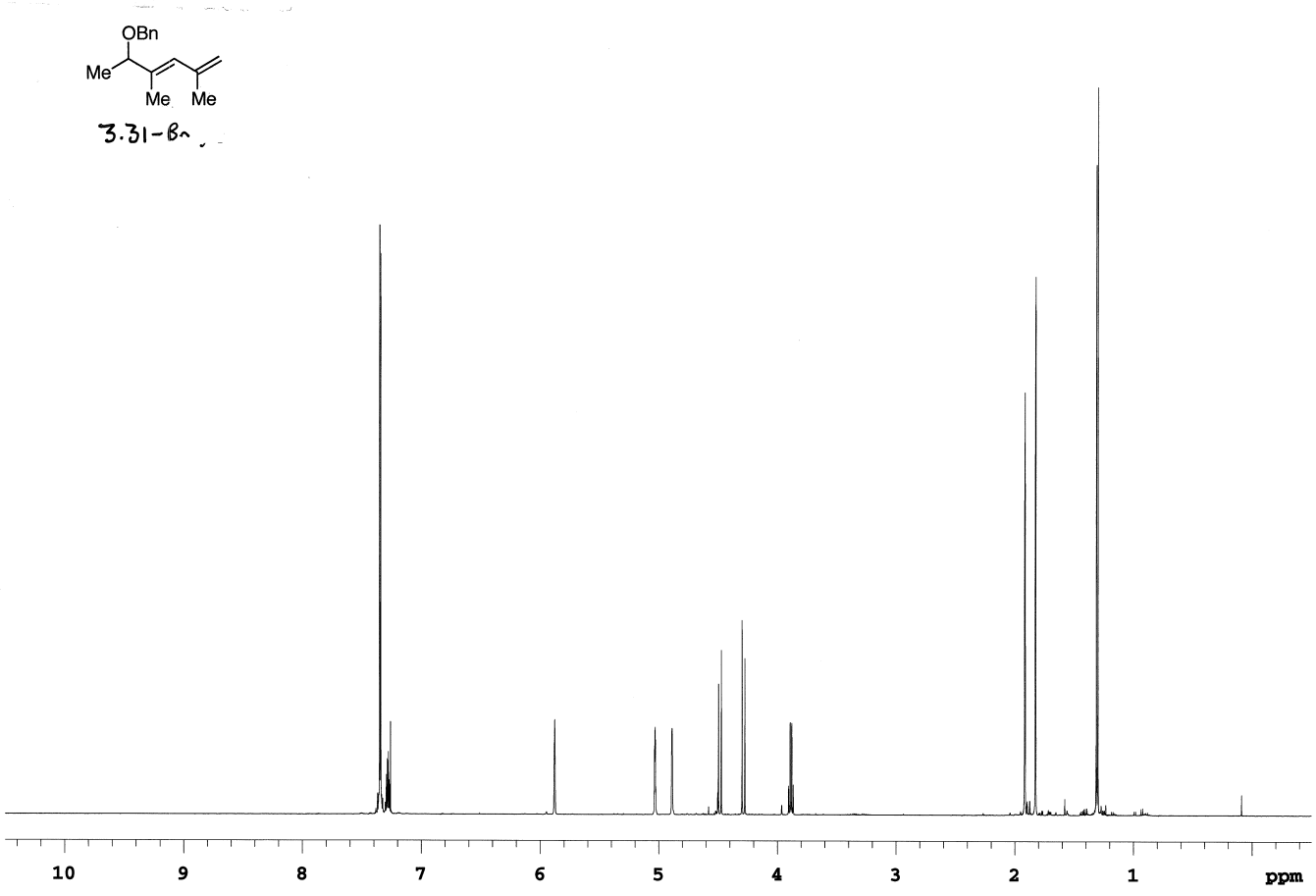
ppm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4
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2
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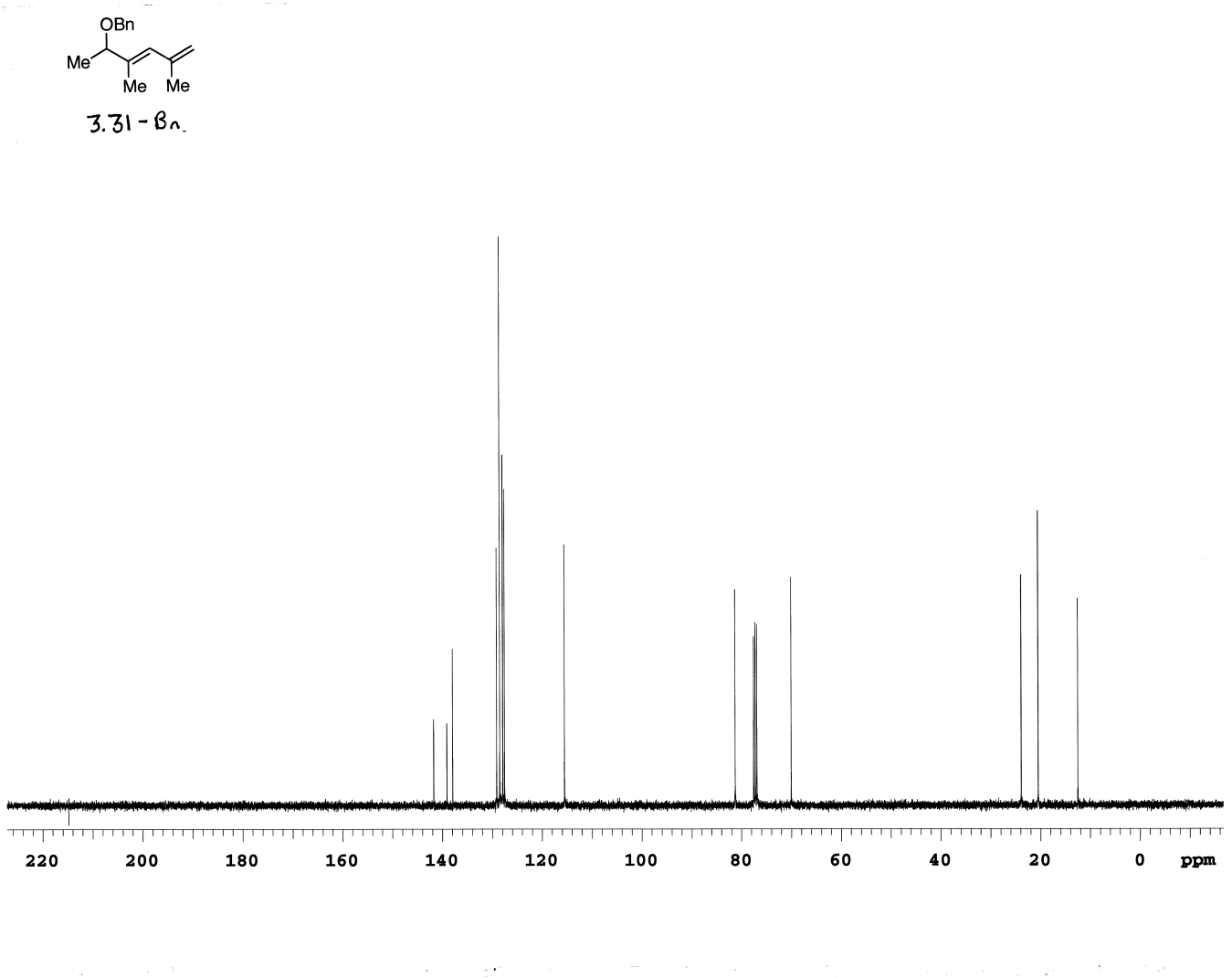
ppm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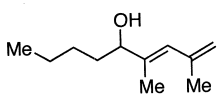
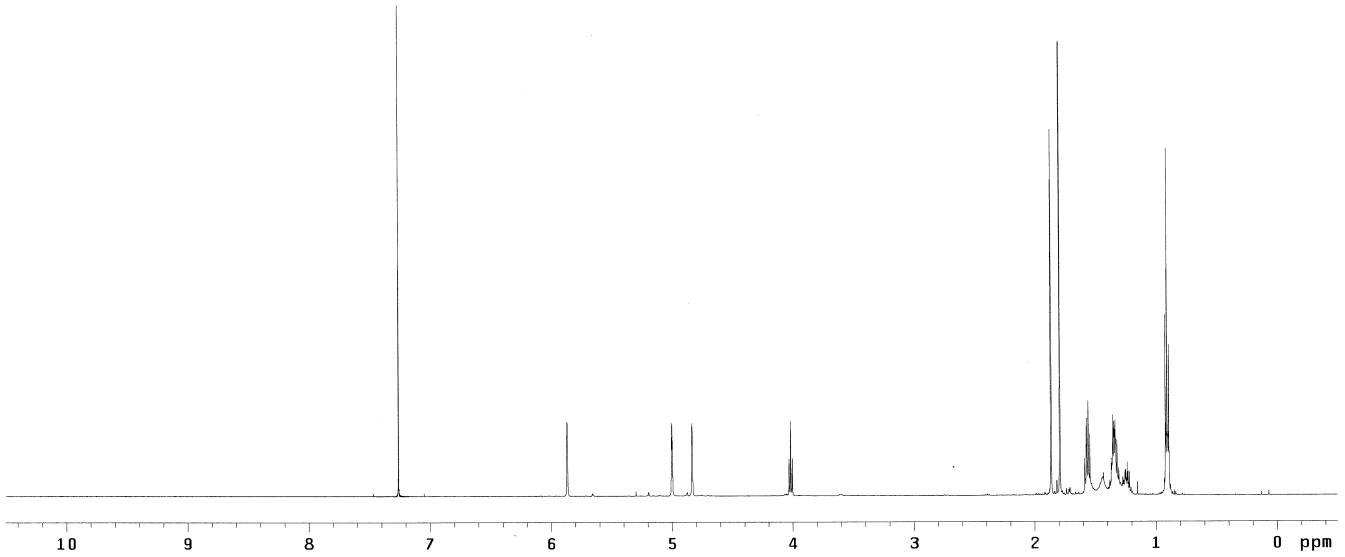
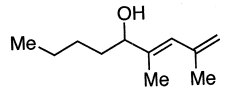
ppm

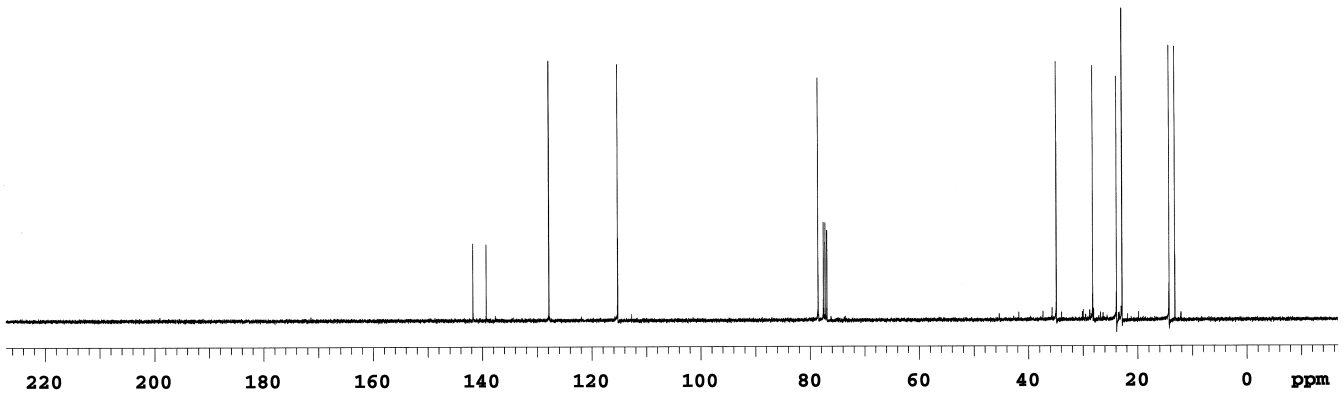


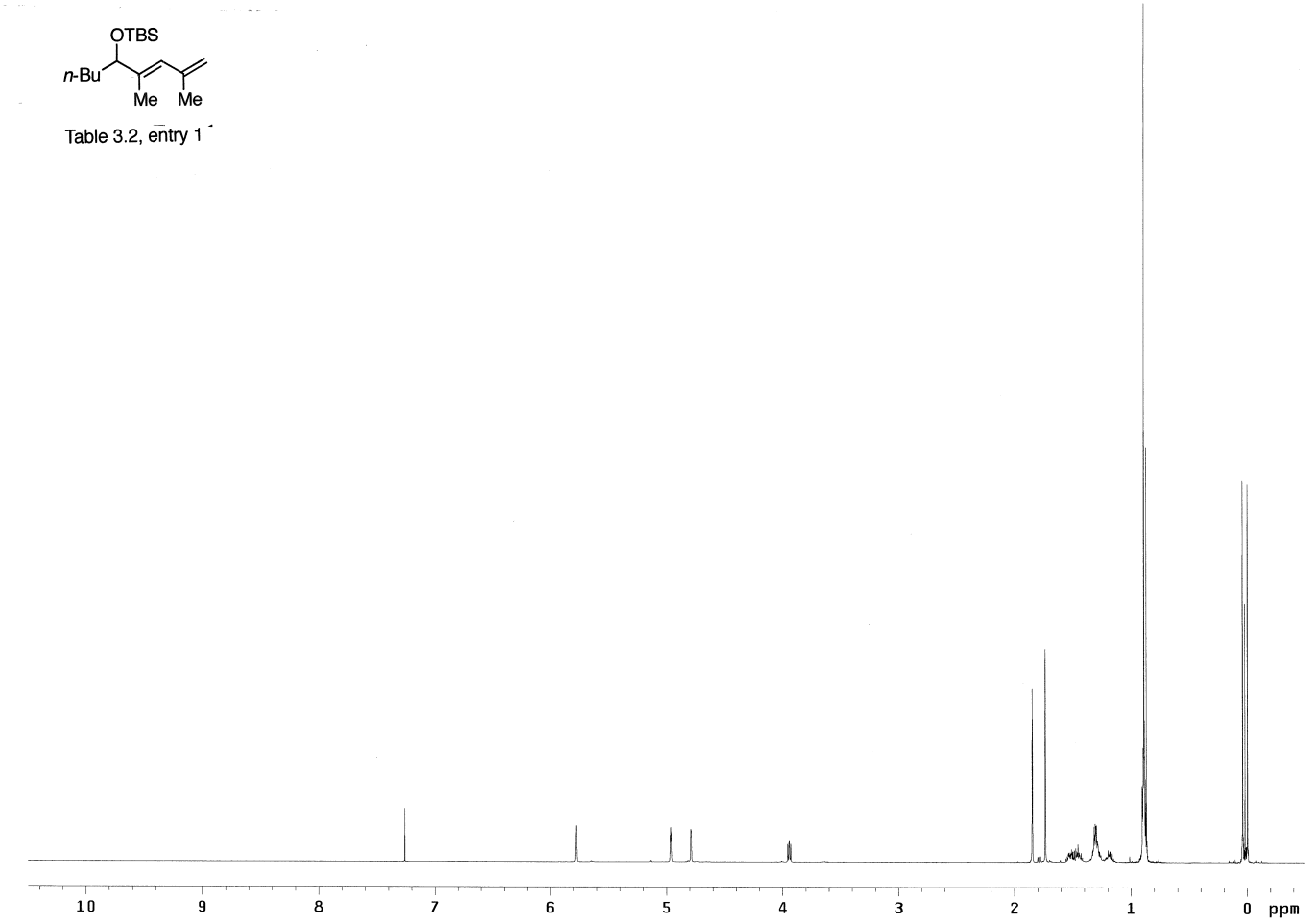
SI-Z





SI-2

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n-Bu
Me
Me
Table 3.2, entry 1
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2
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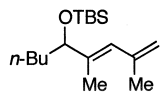
0
ppm



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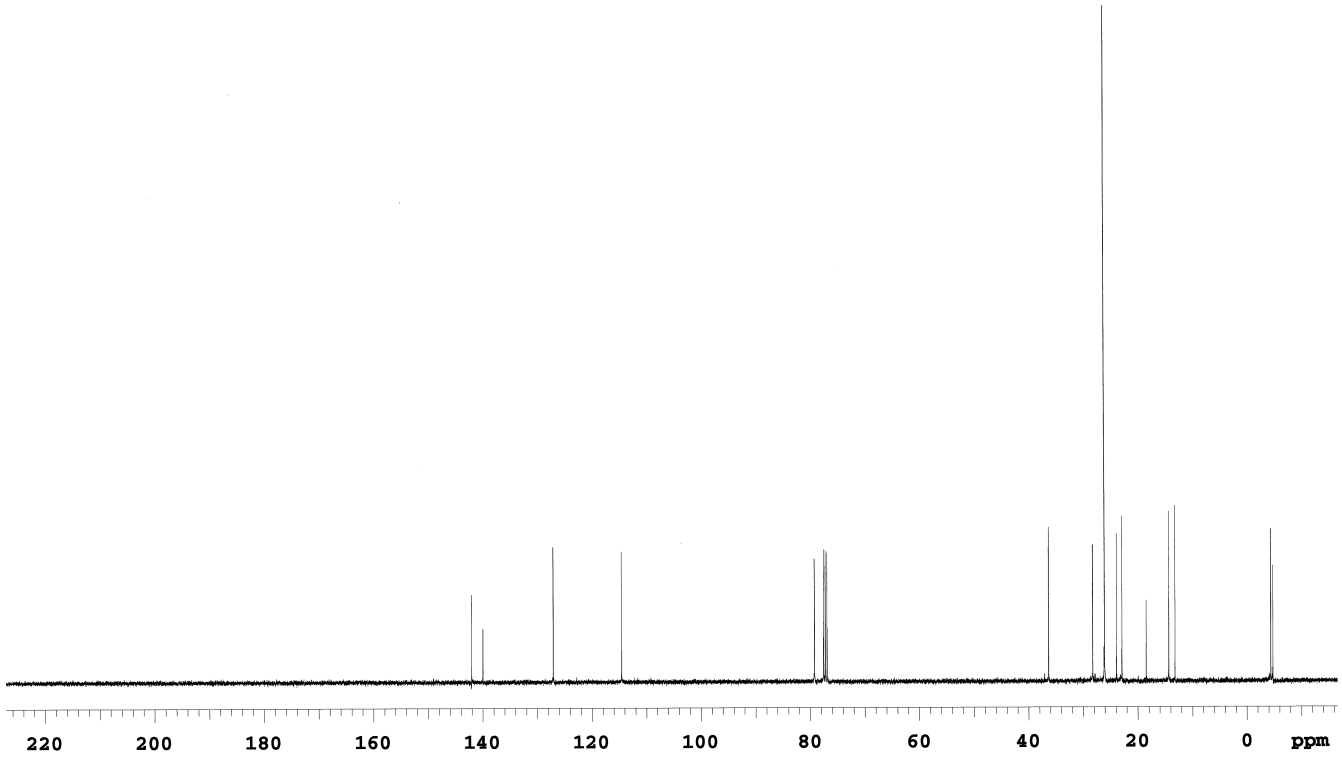
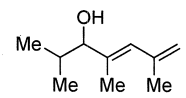
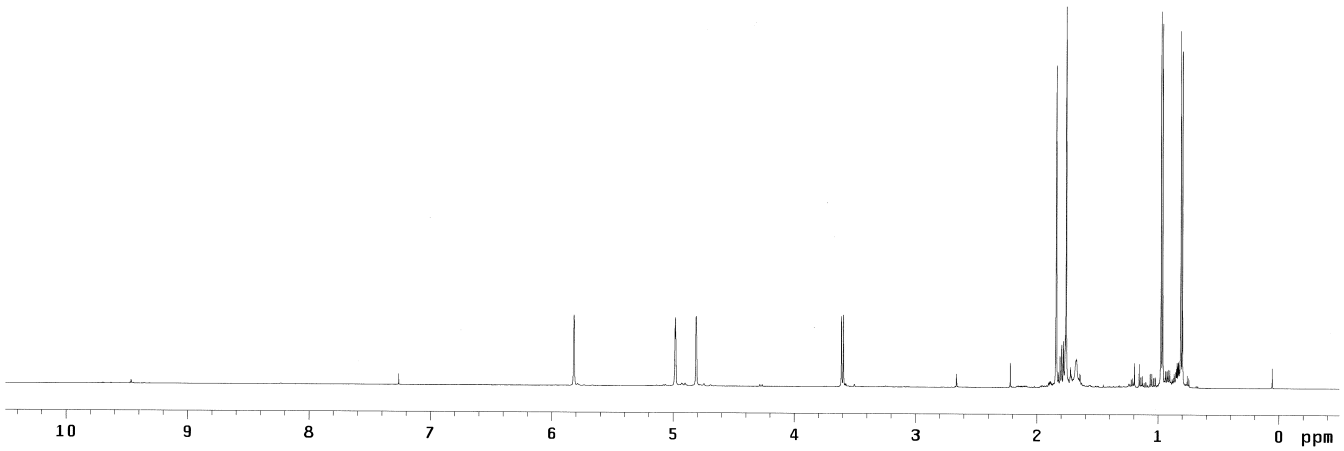
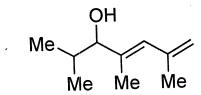




SI-3



182



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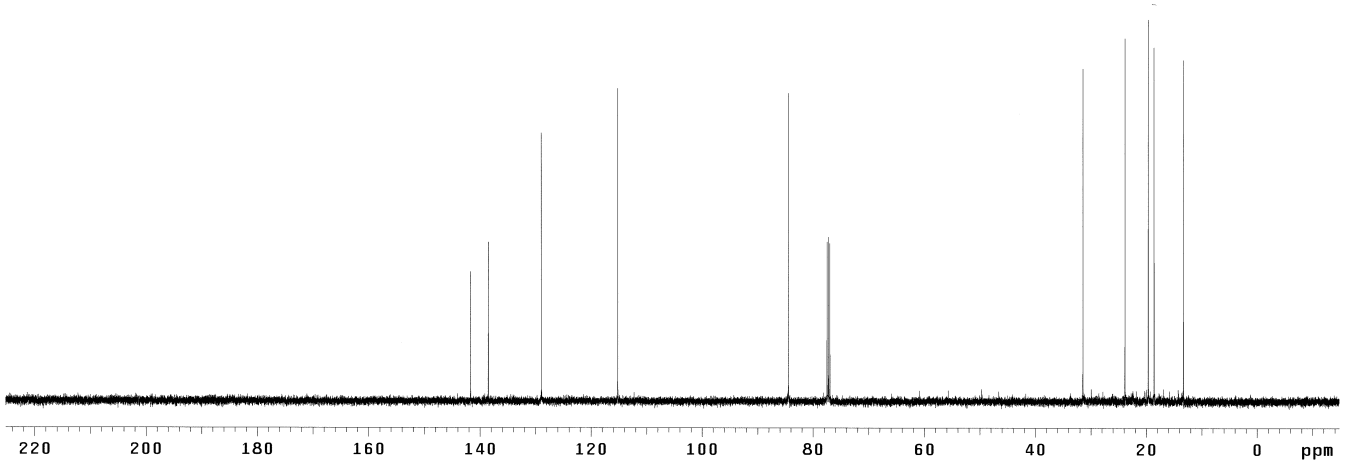

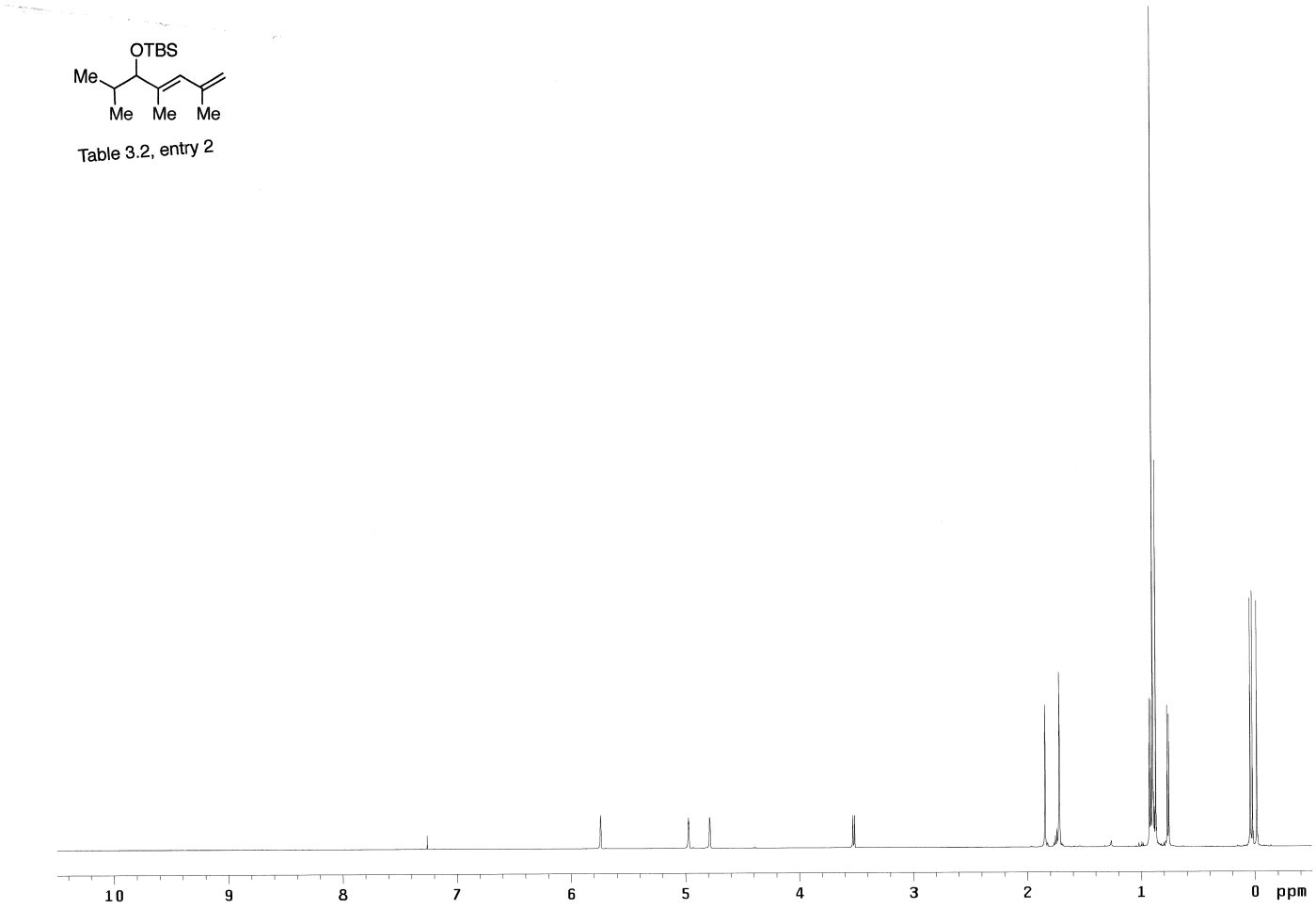

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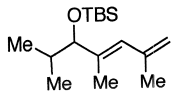

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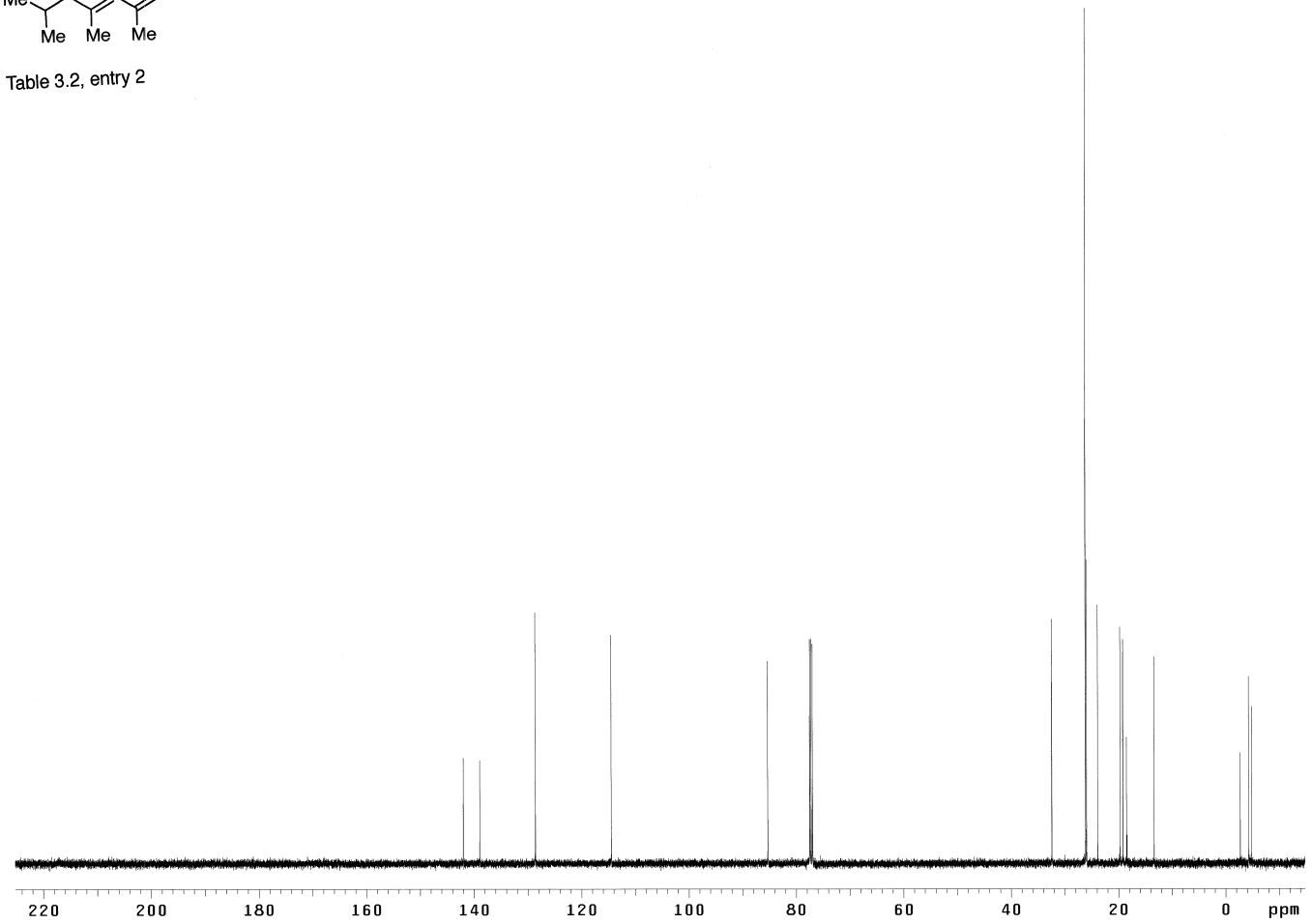

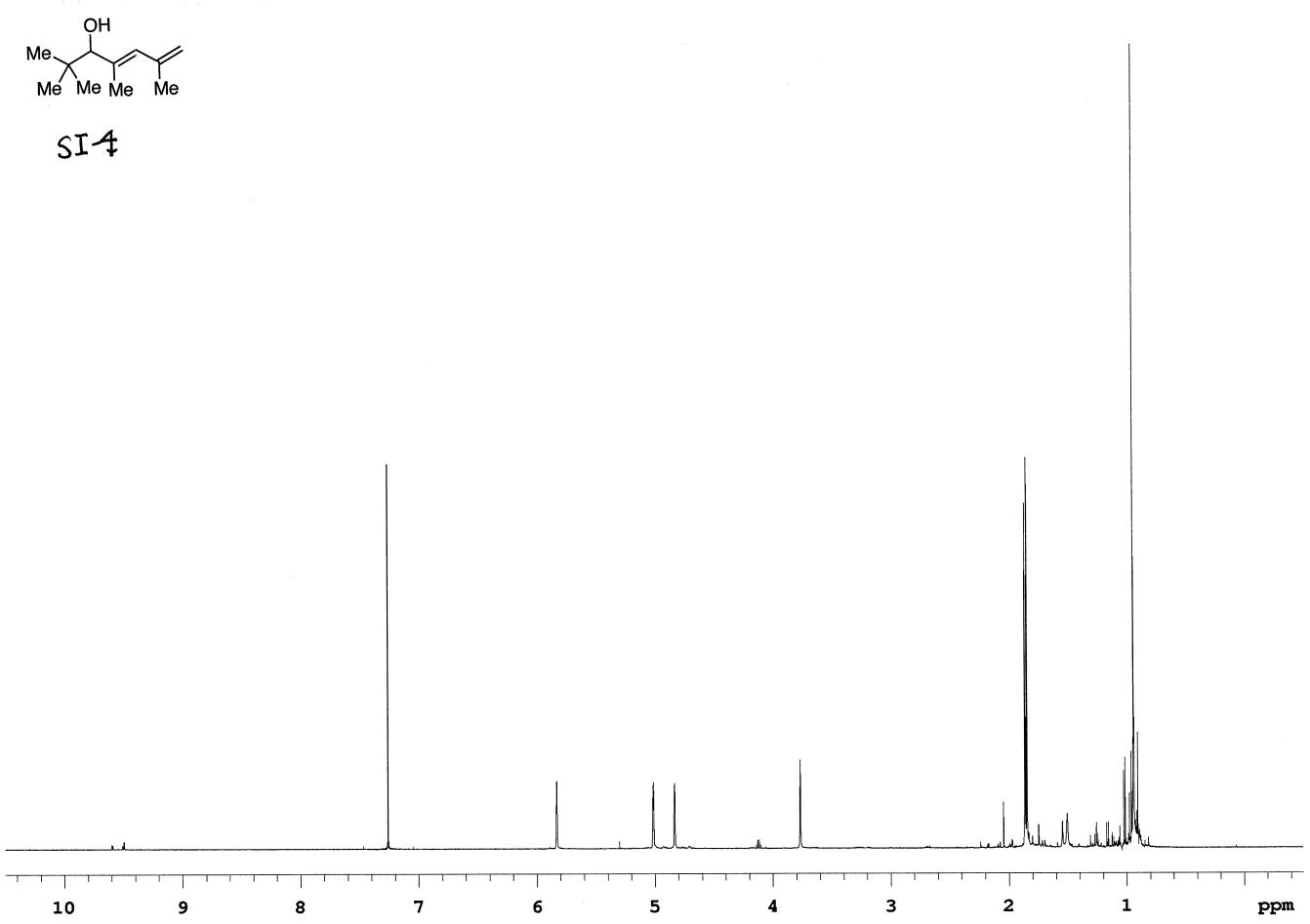
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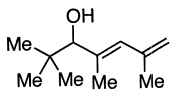

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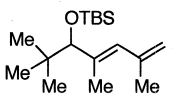

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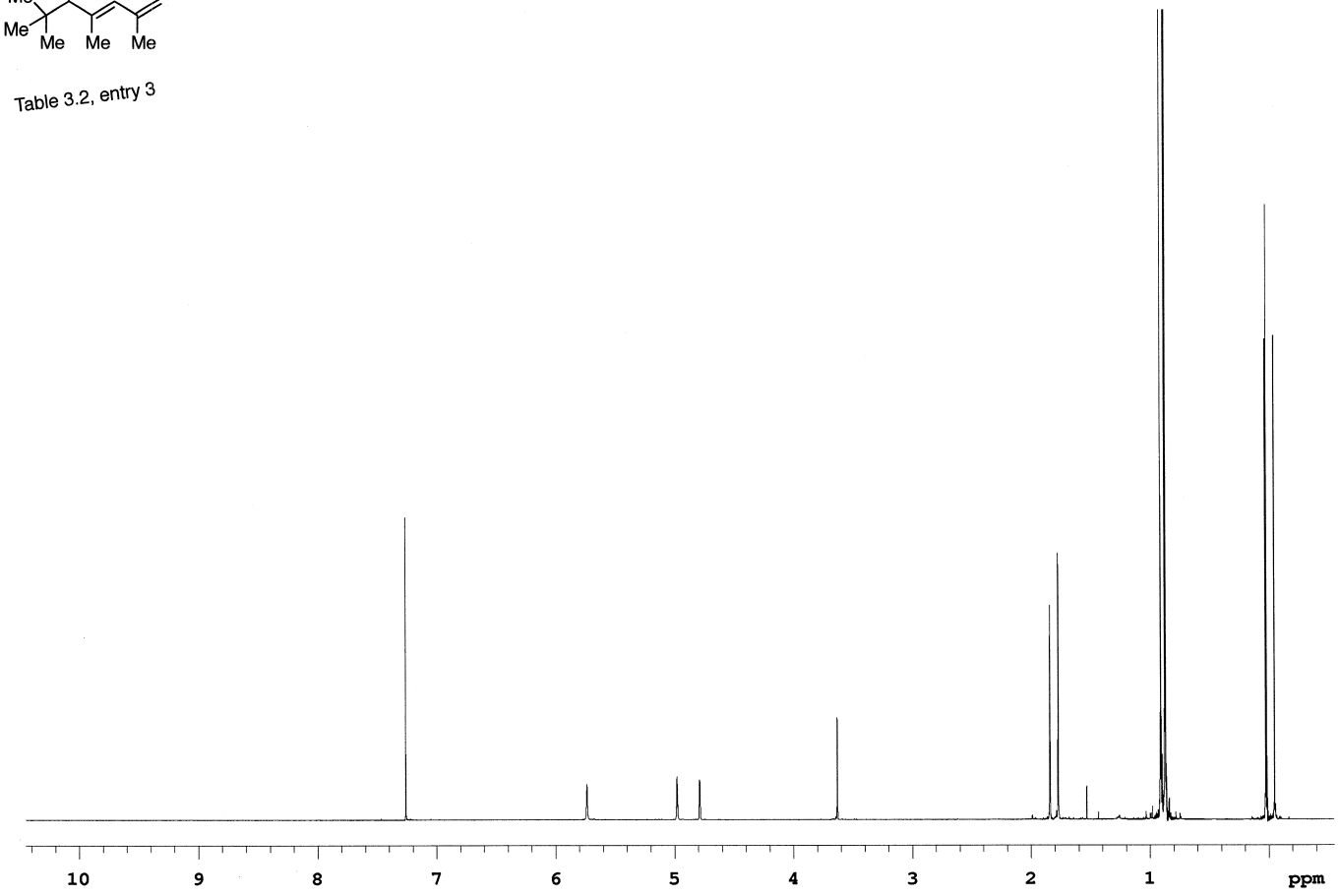

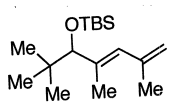

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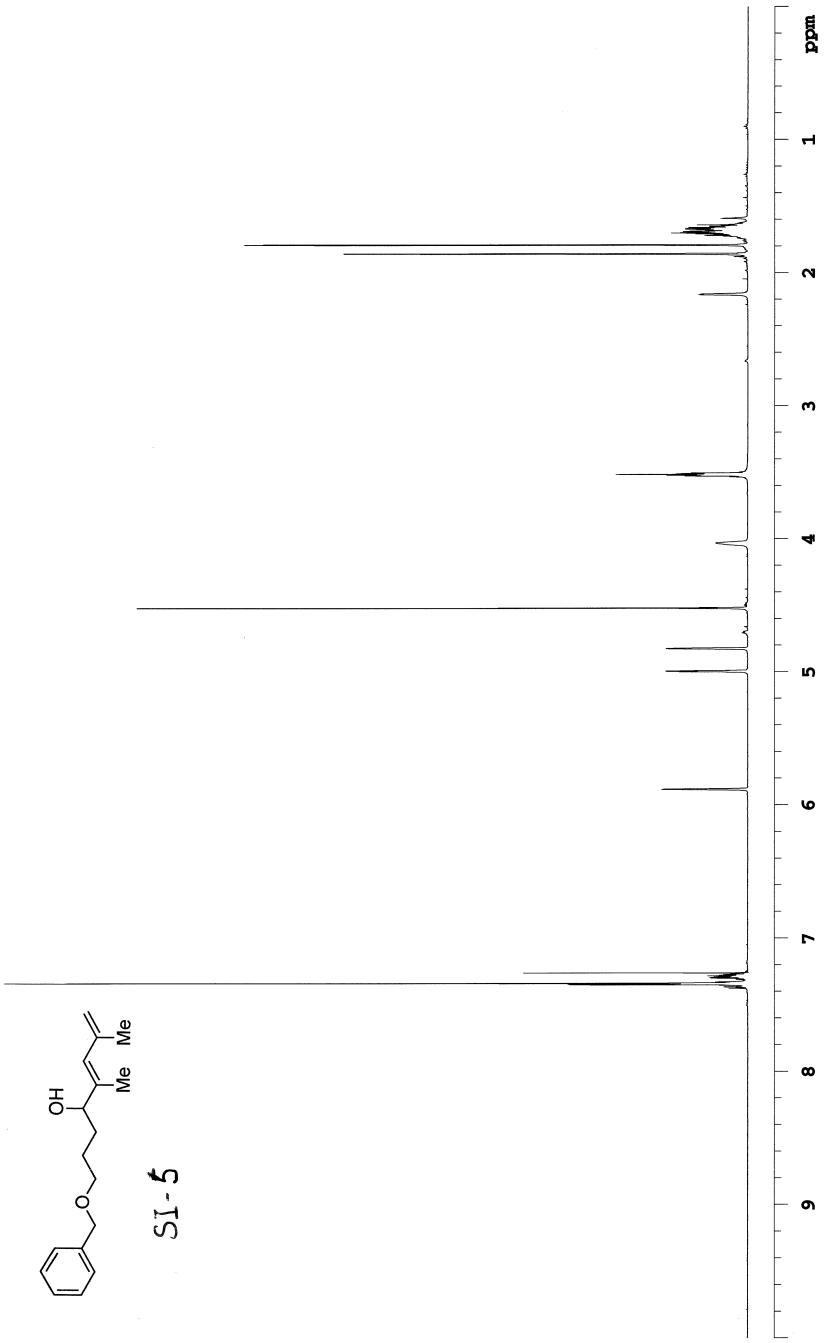
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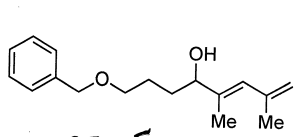

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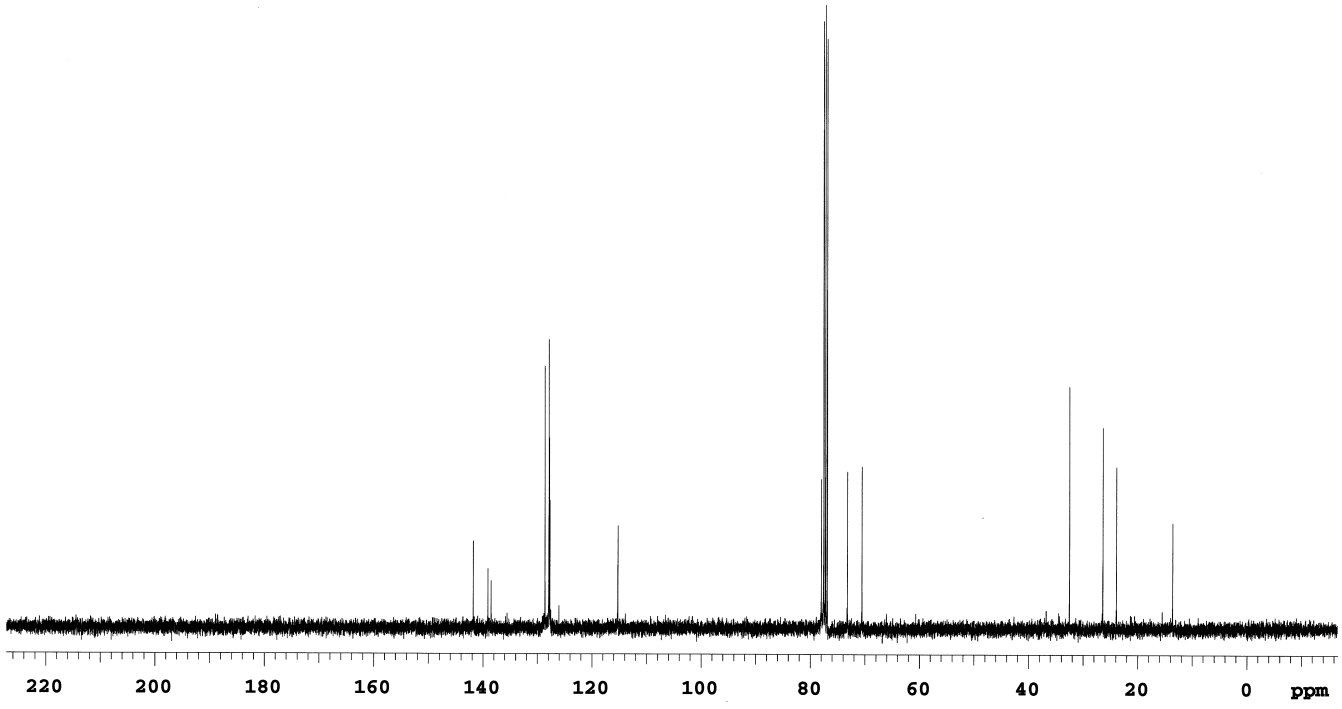

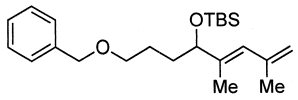

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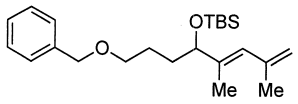

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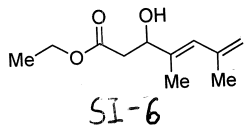

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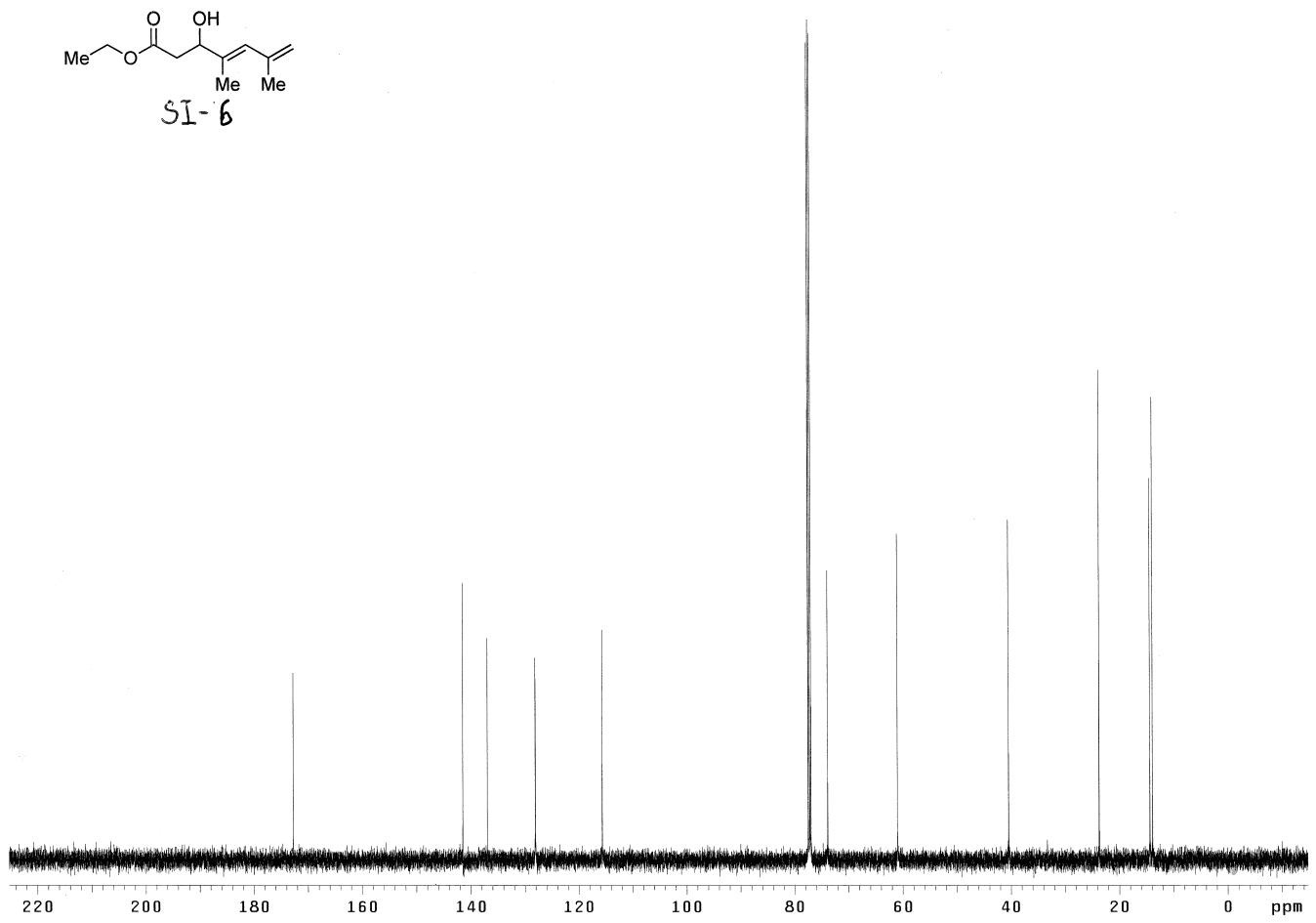
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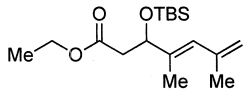

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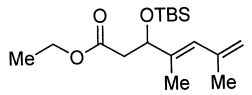

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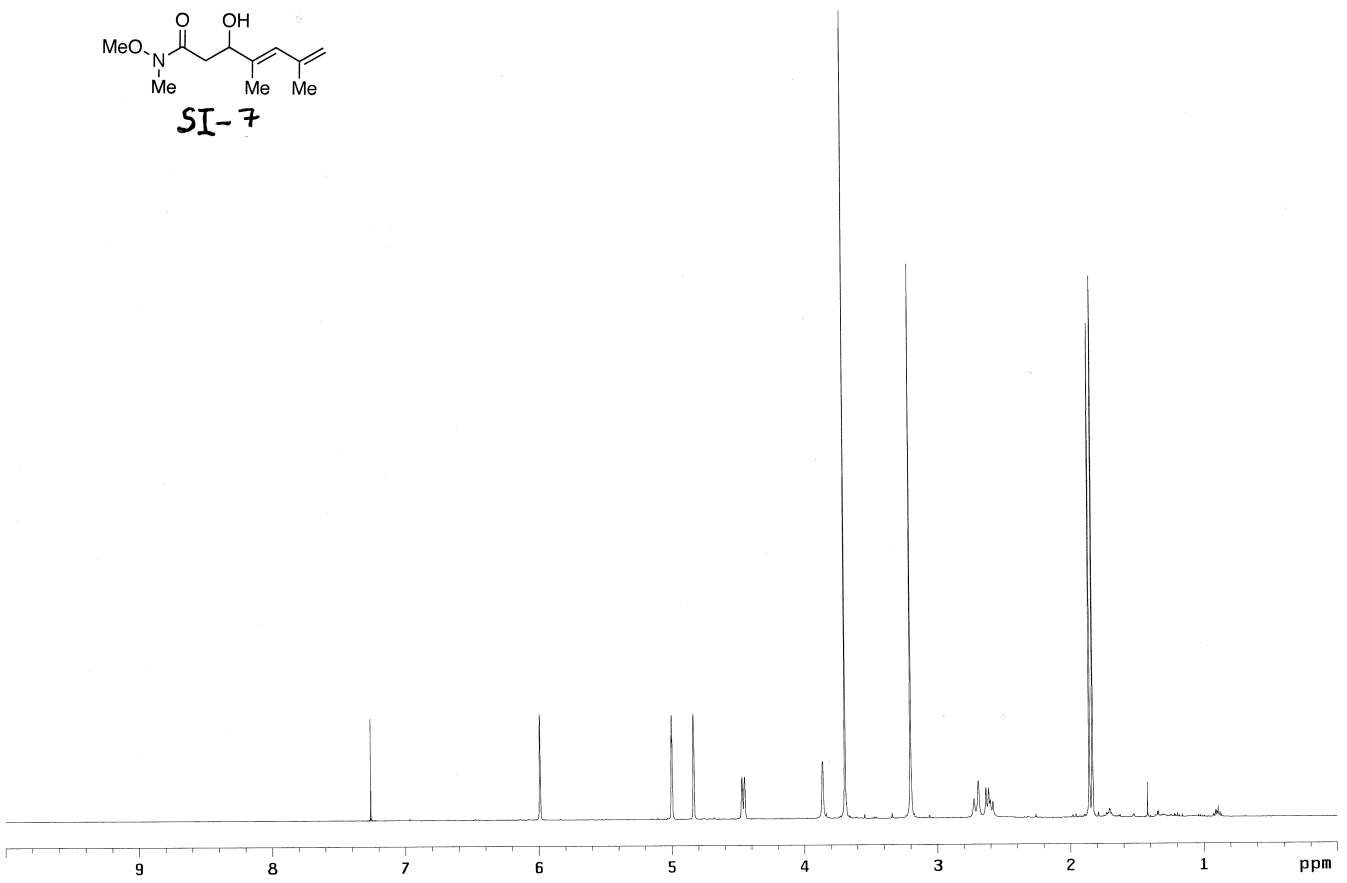
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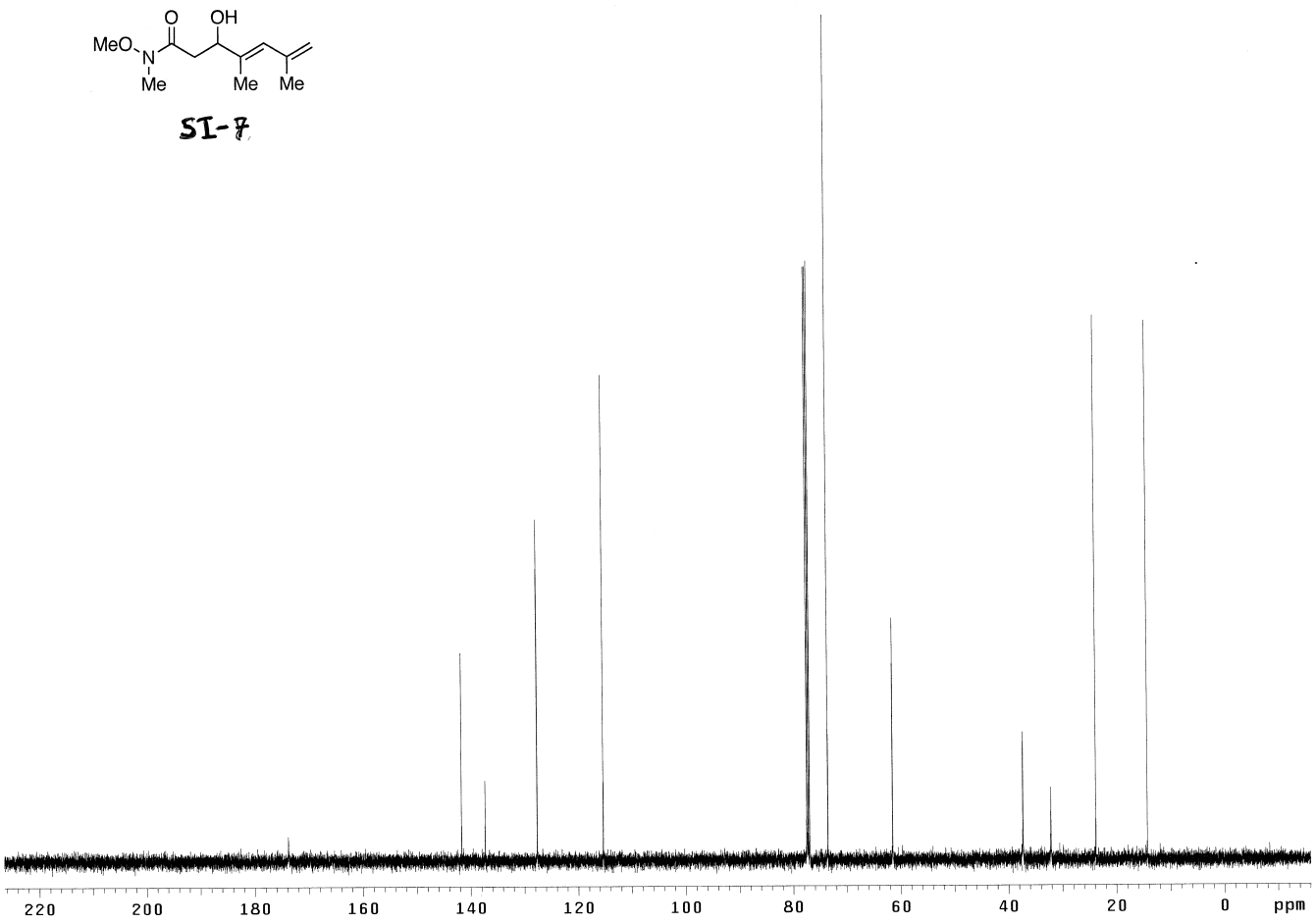

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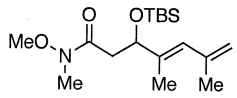

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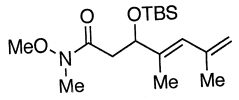

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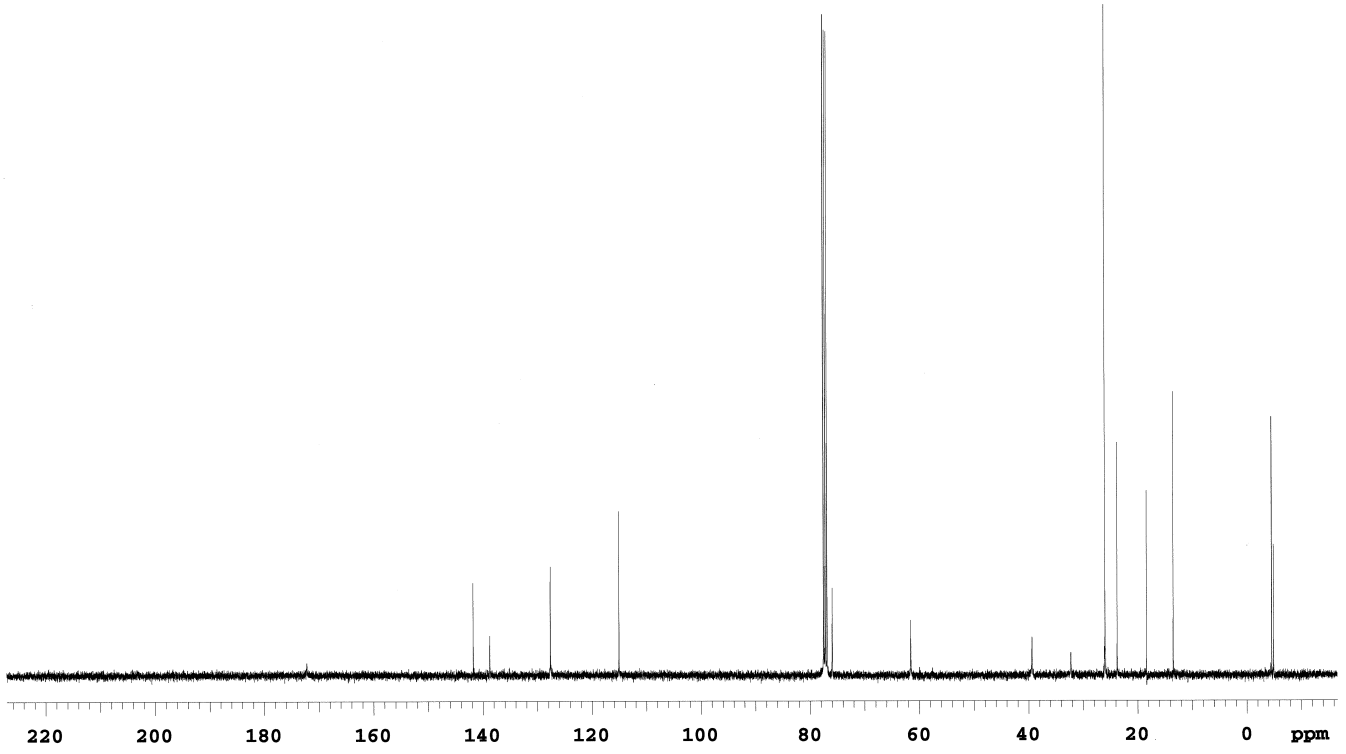

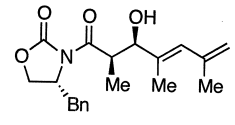

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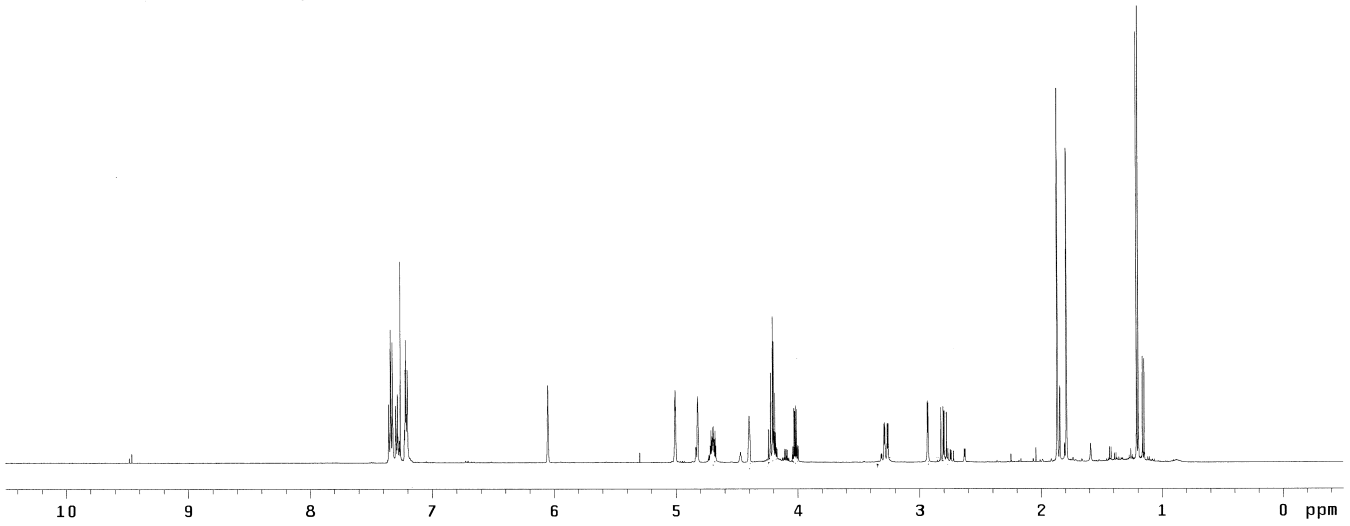

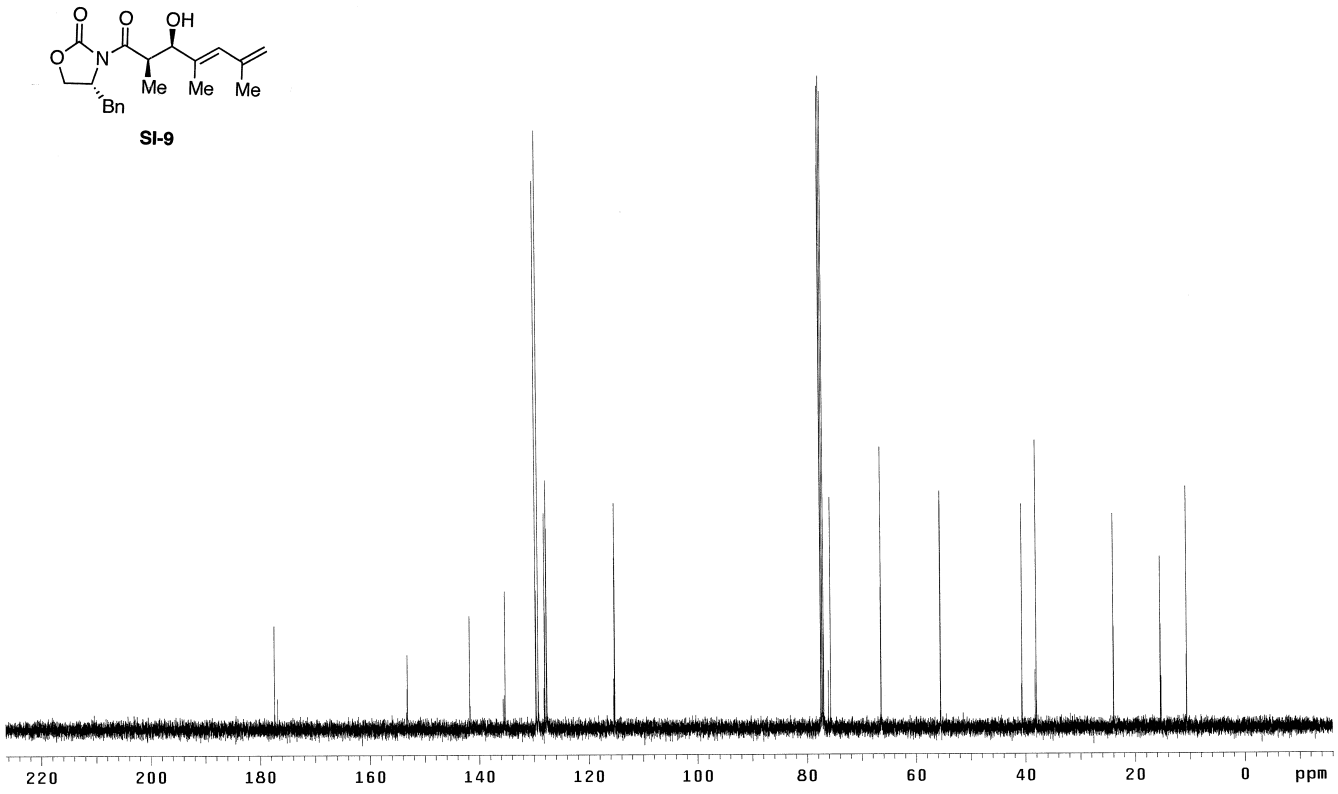

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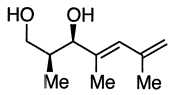

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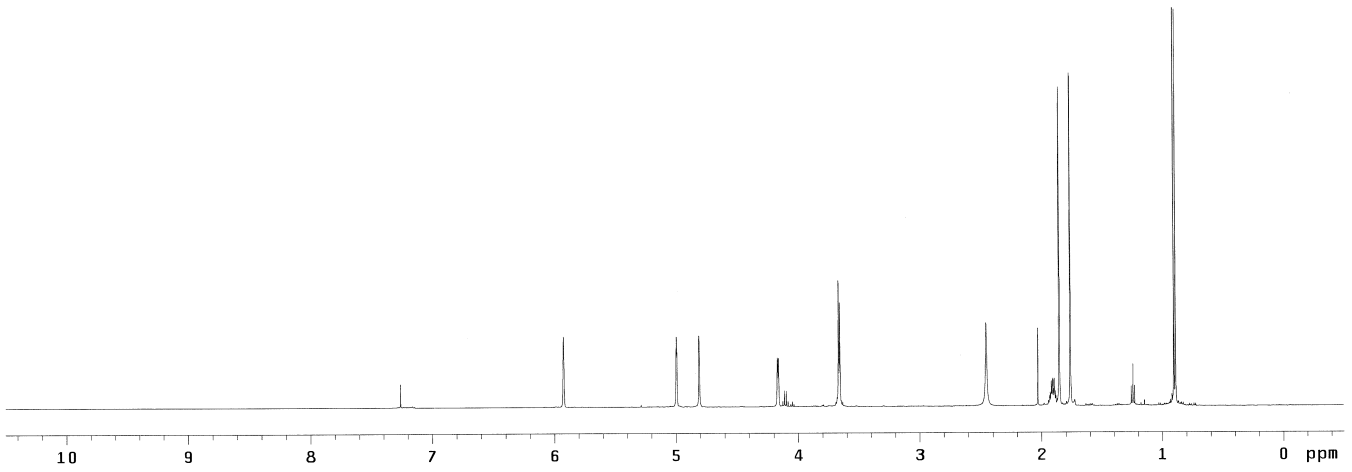

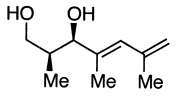

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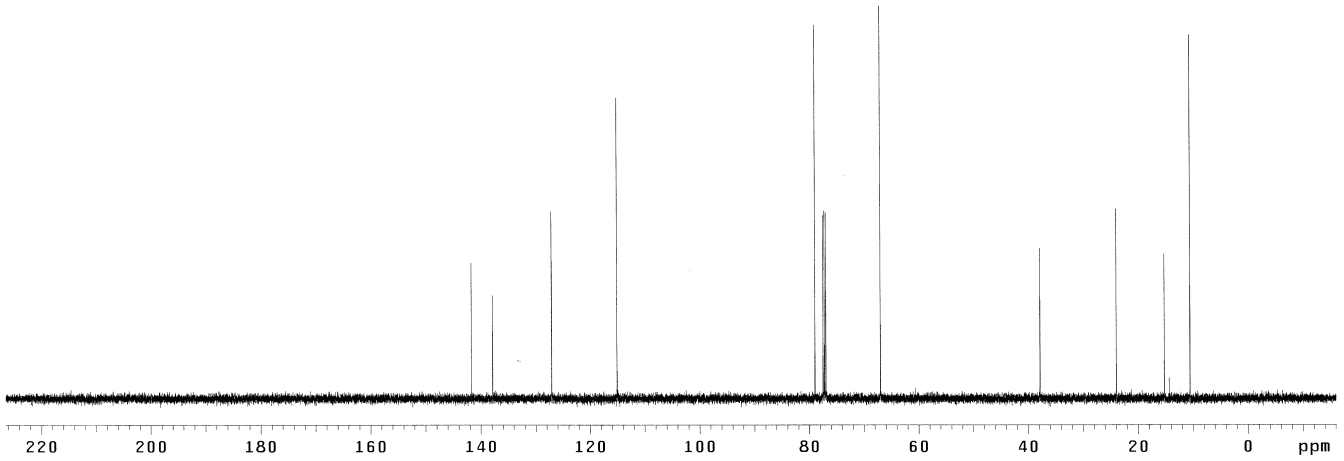

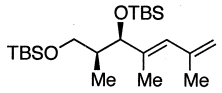

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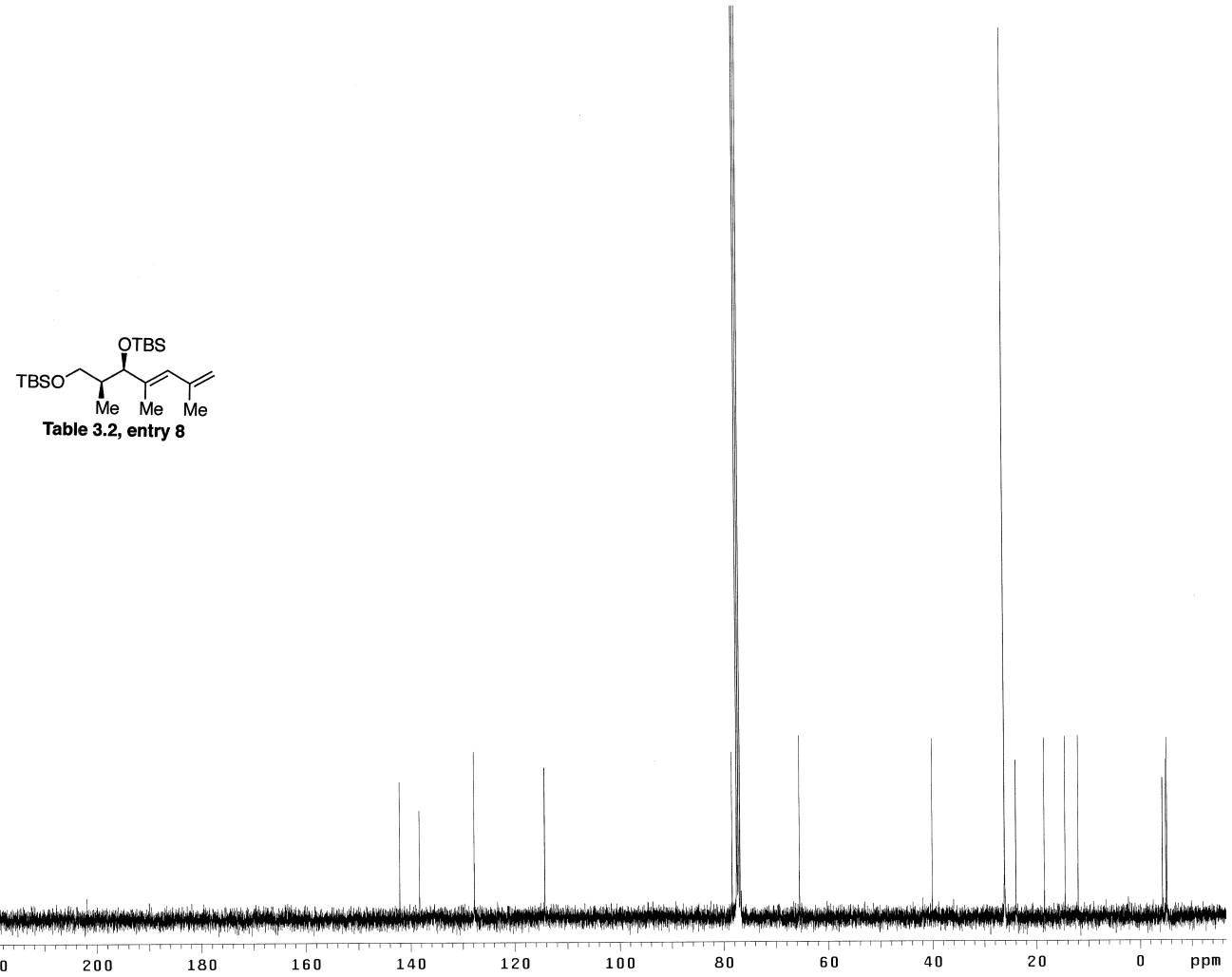

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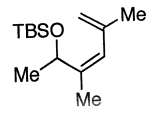

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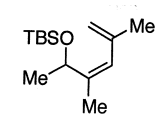

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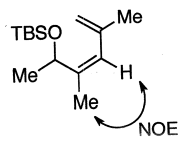

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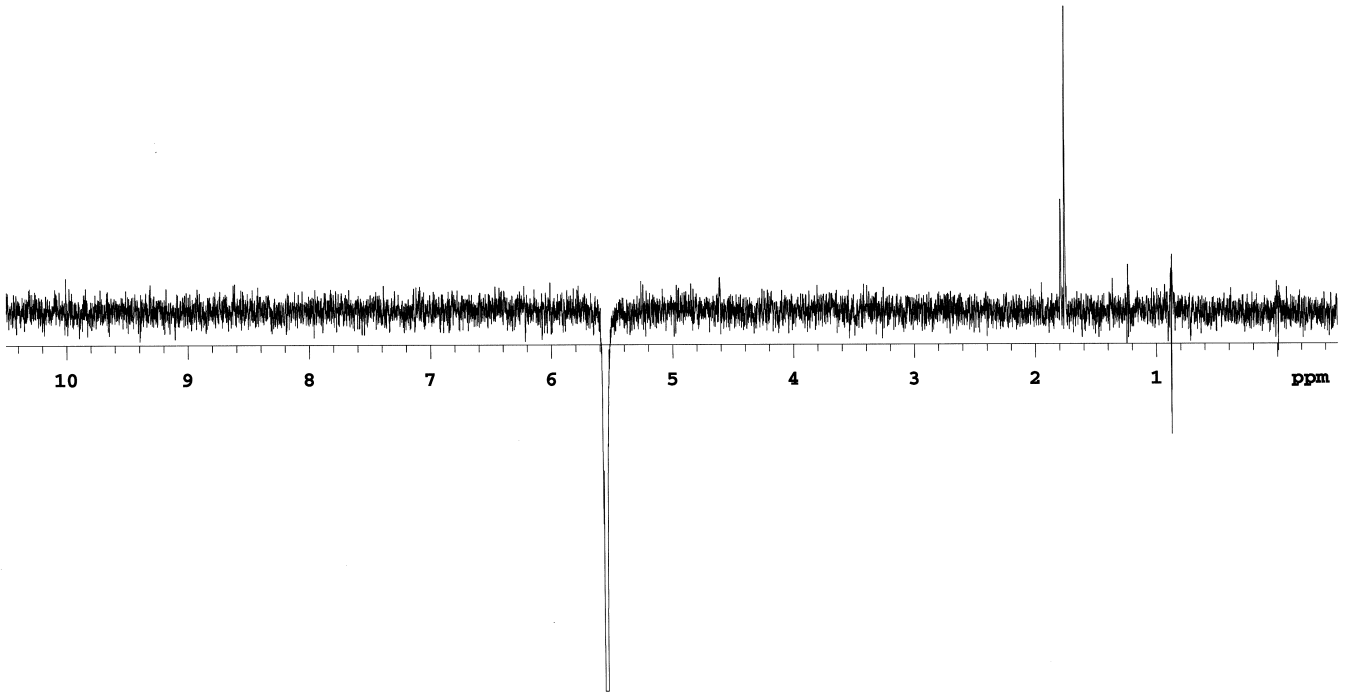

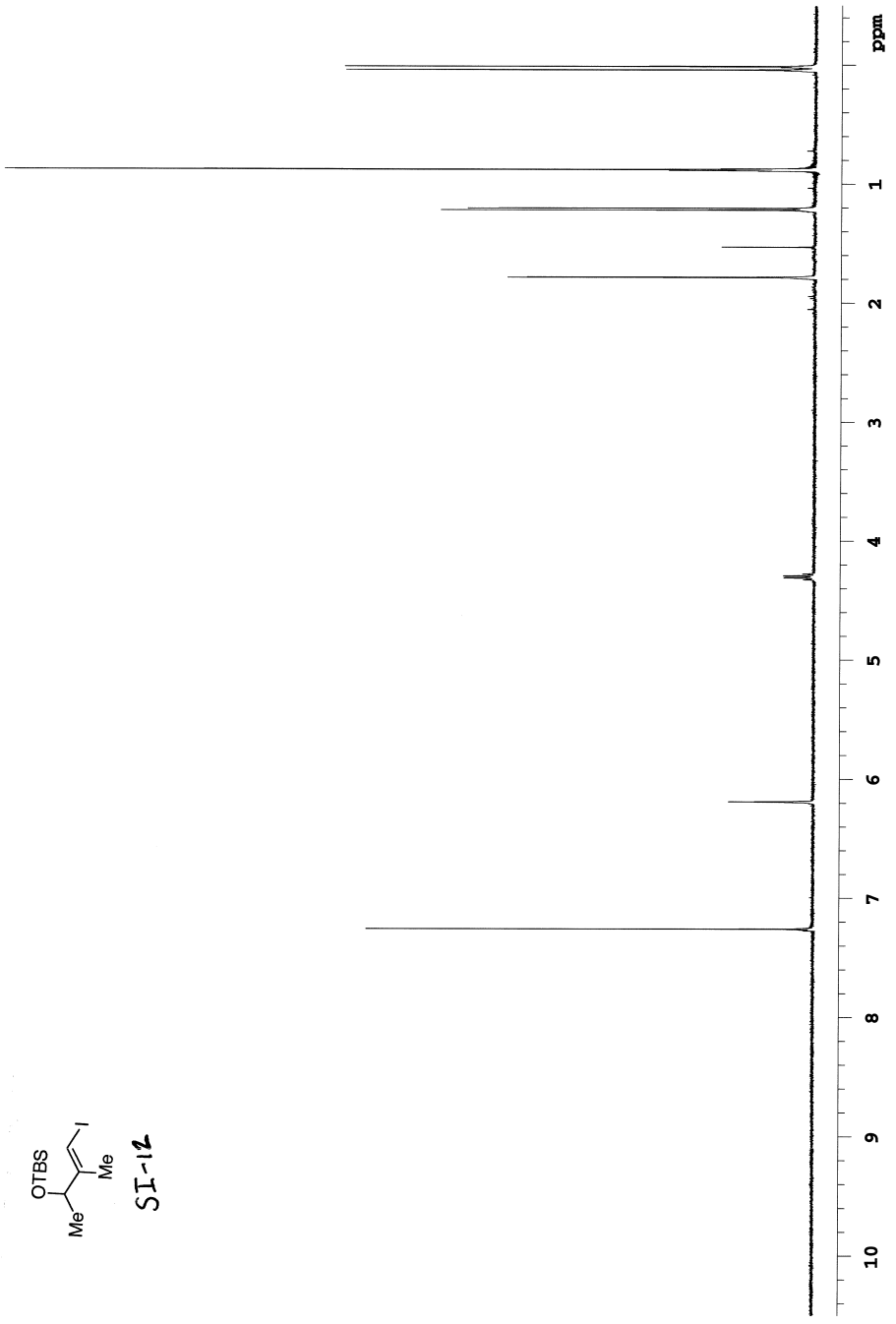
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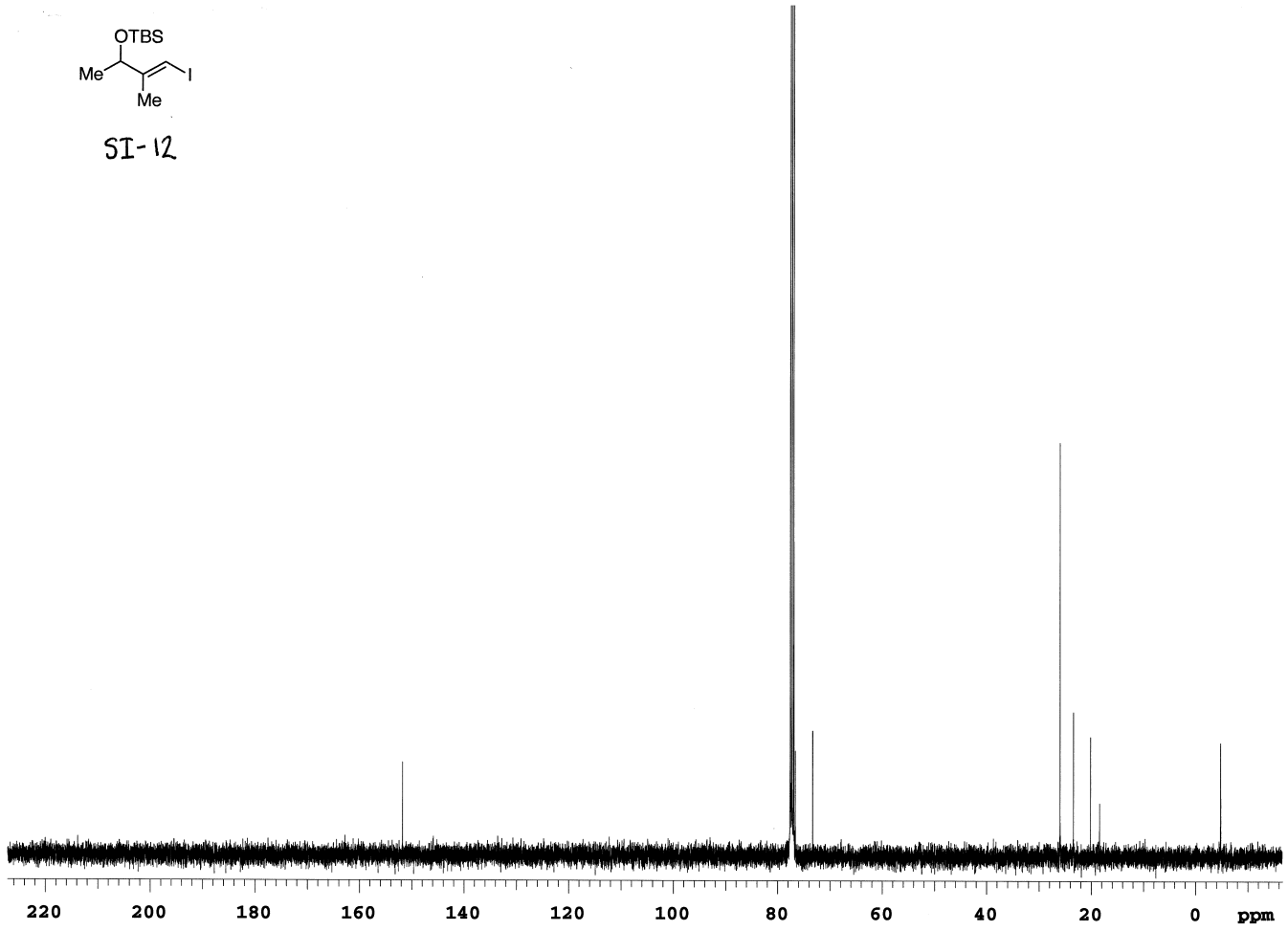
2
1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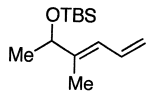

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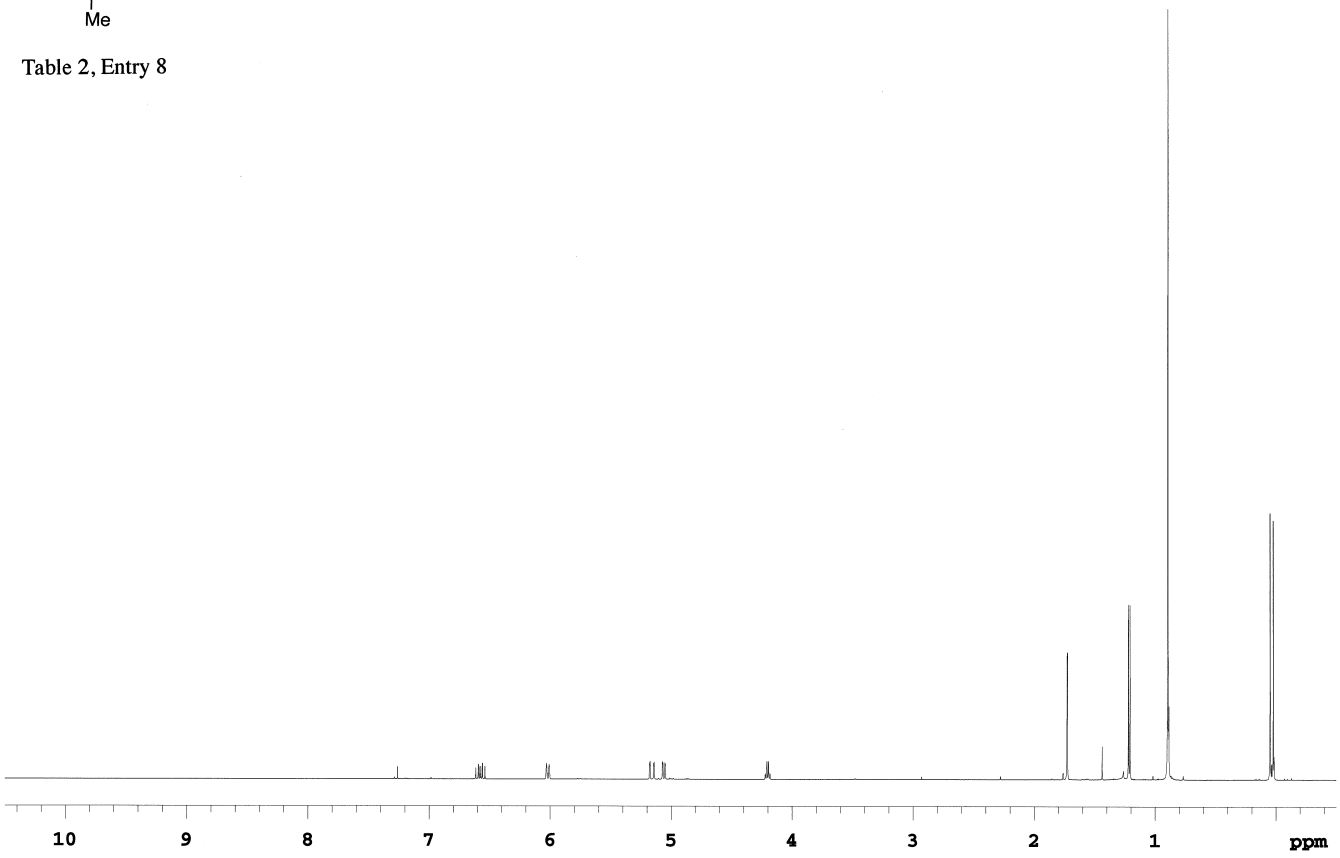

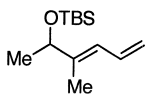

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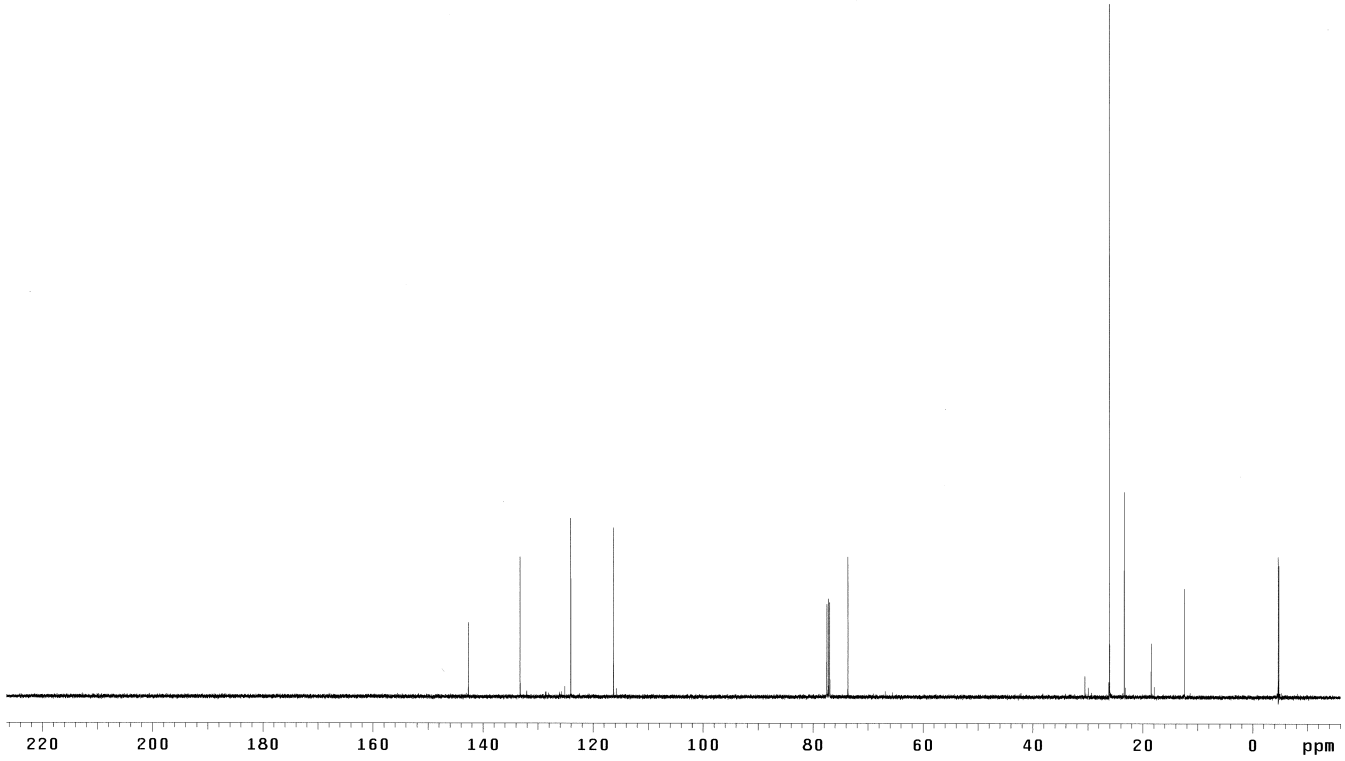

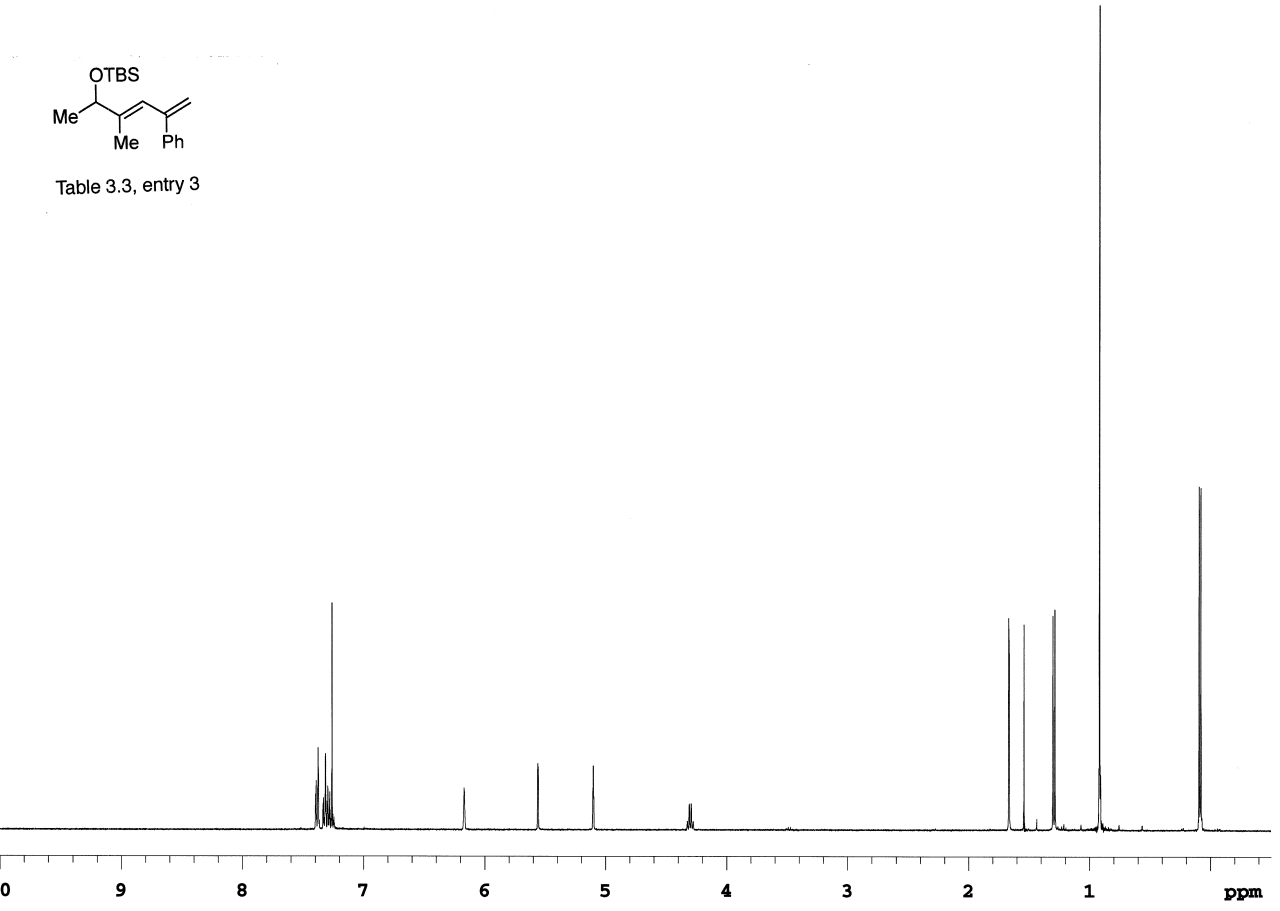
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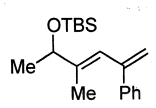

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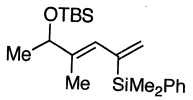

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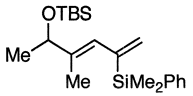

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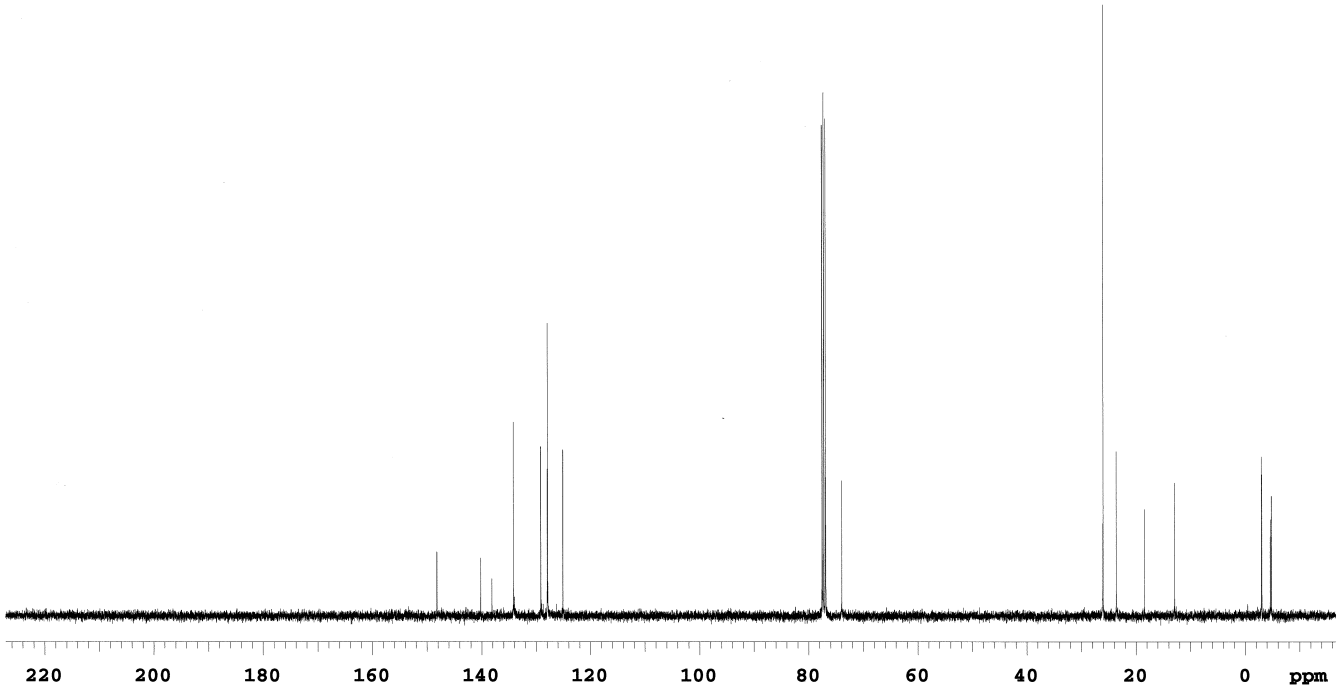

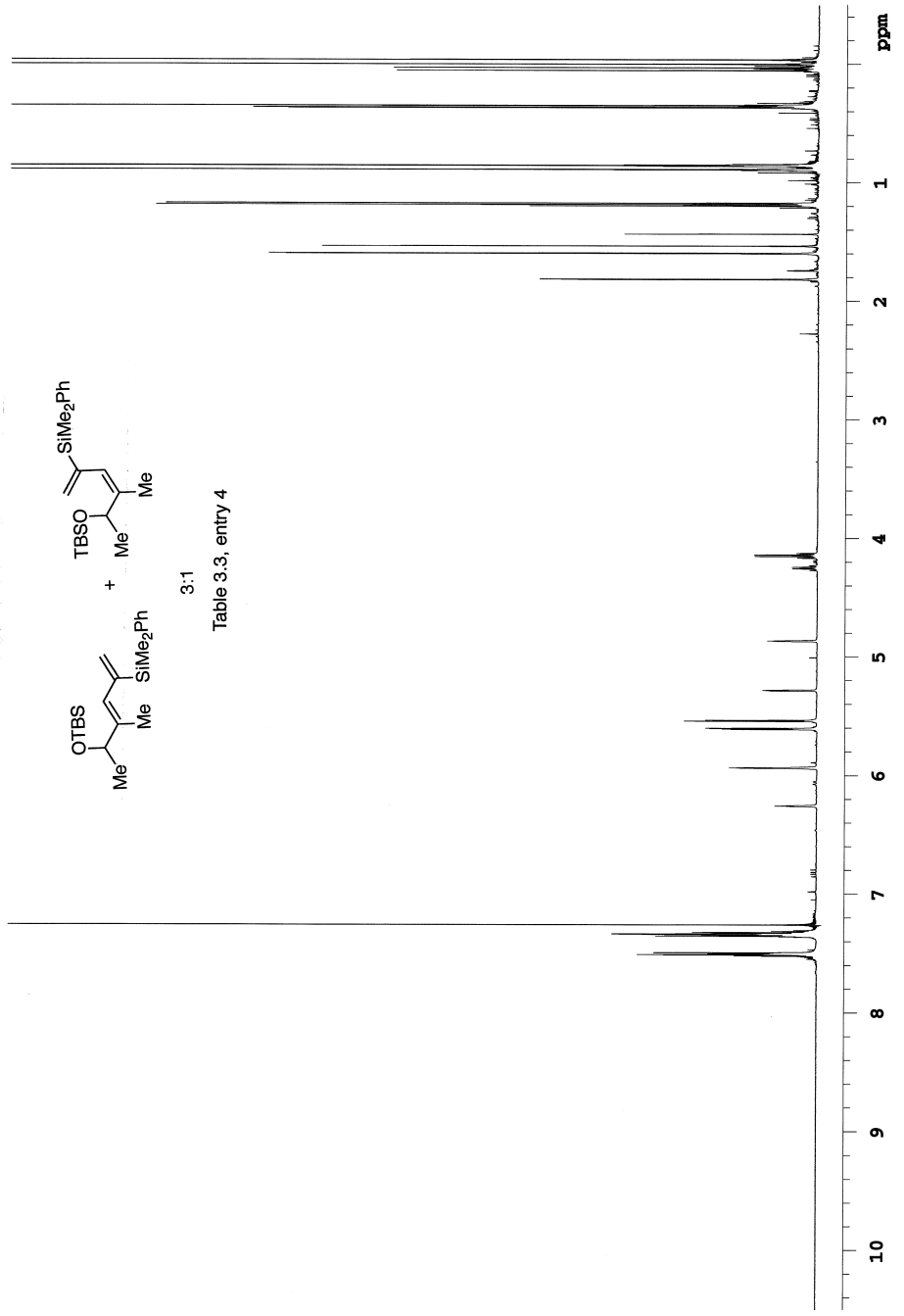
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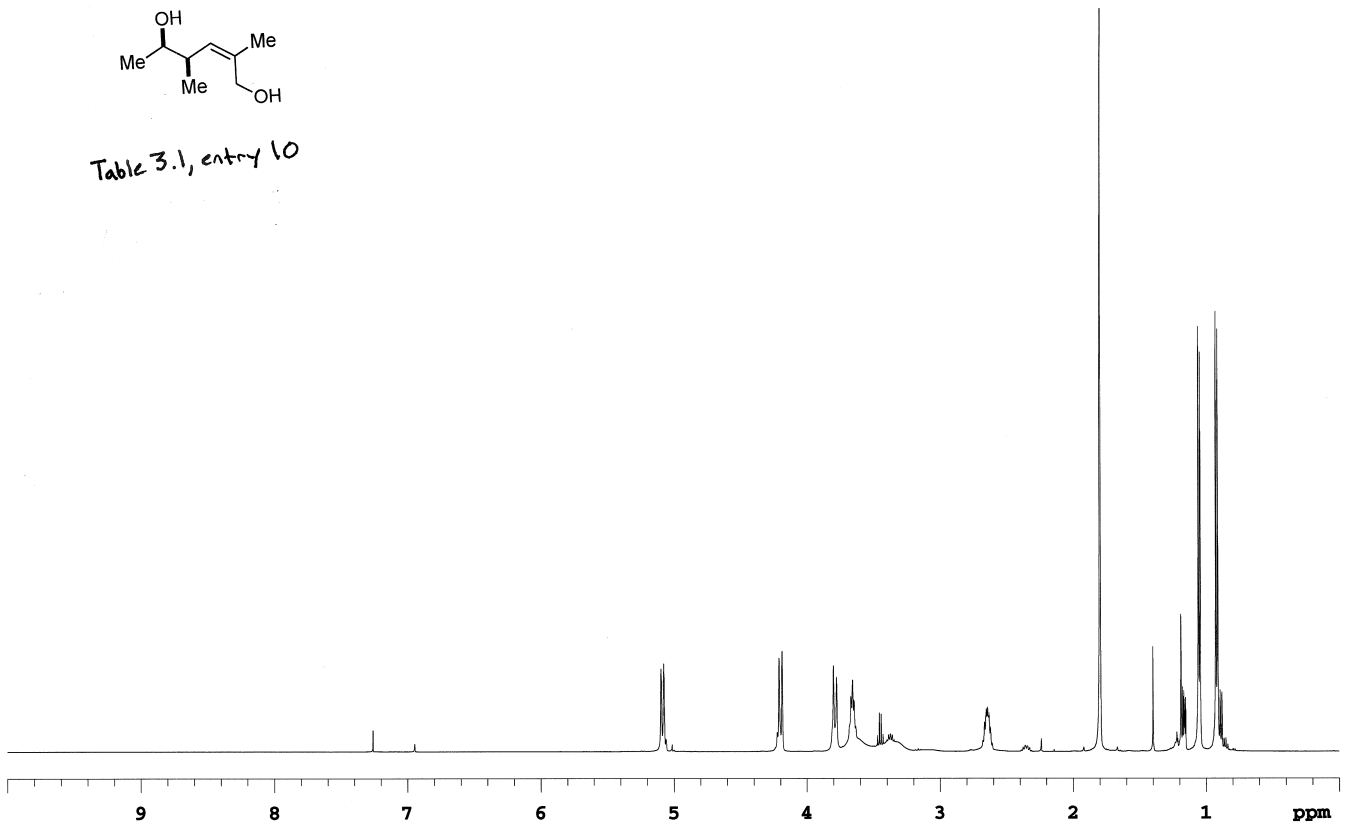
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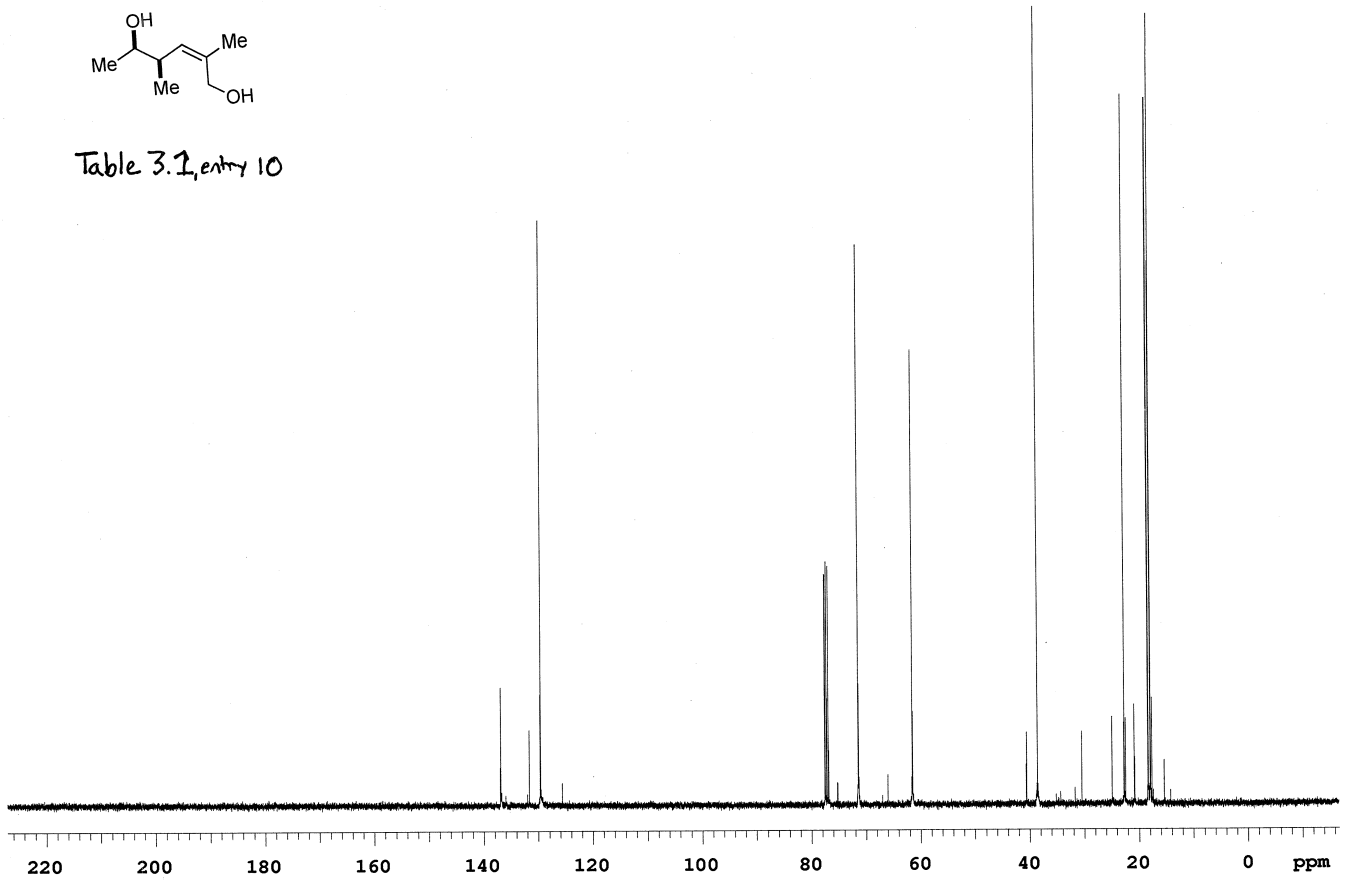
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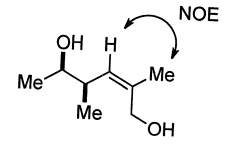
ppm



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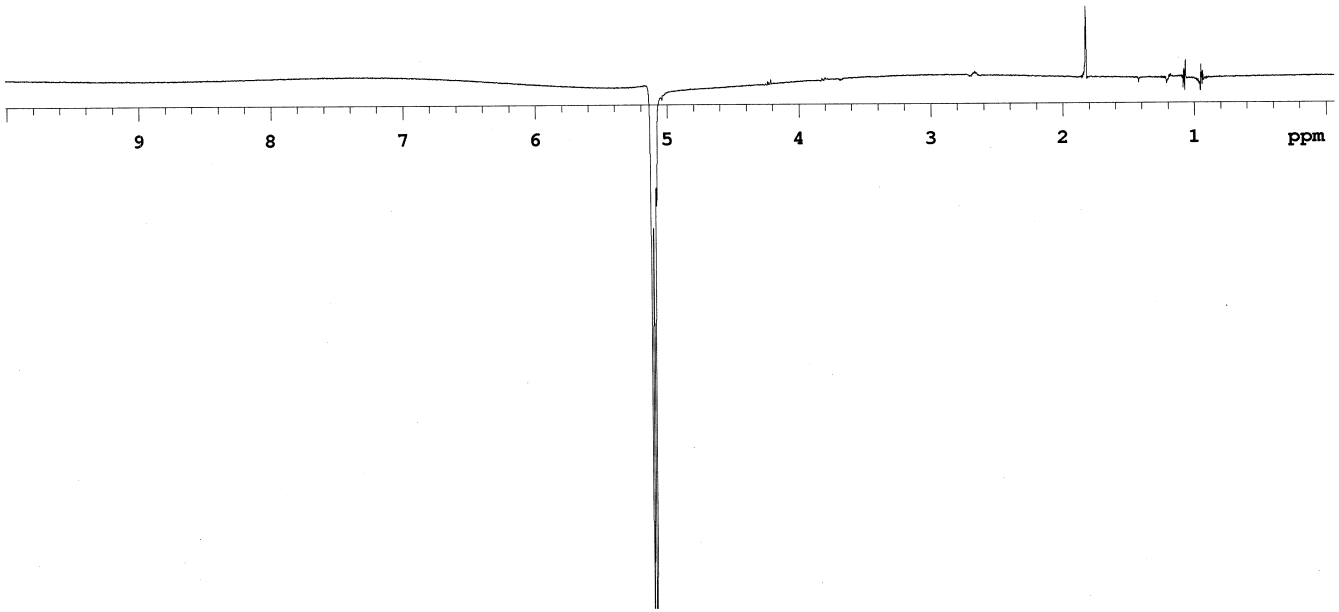

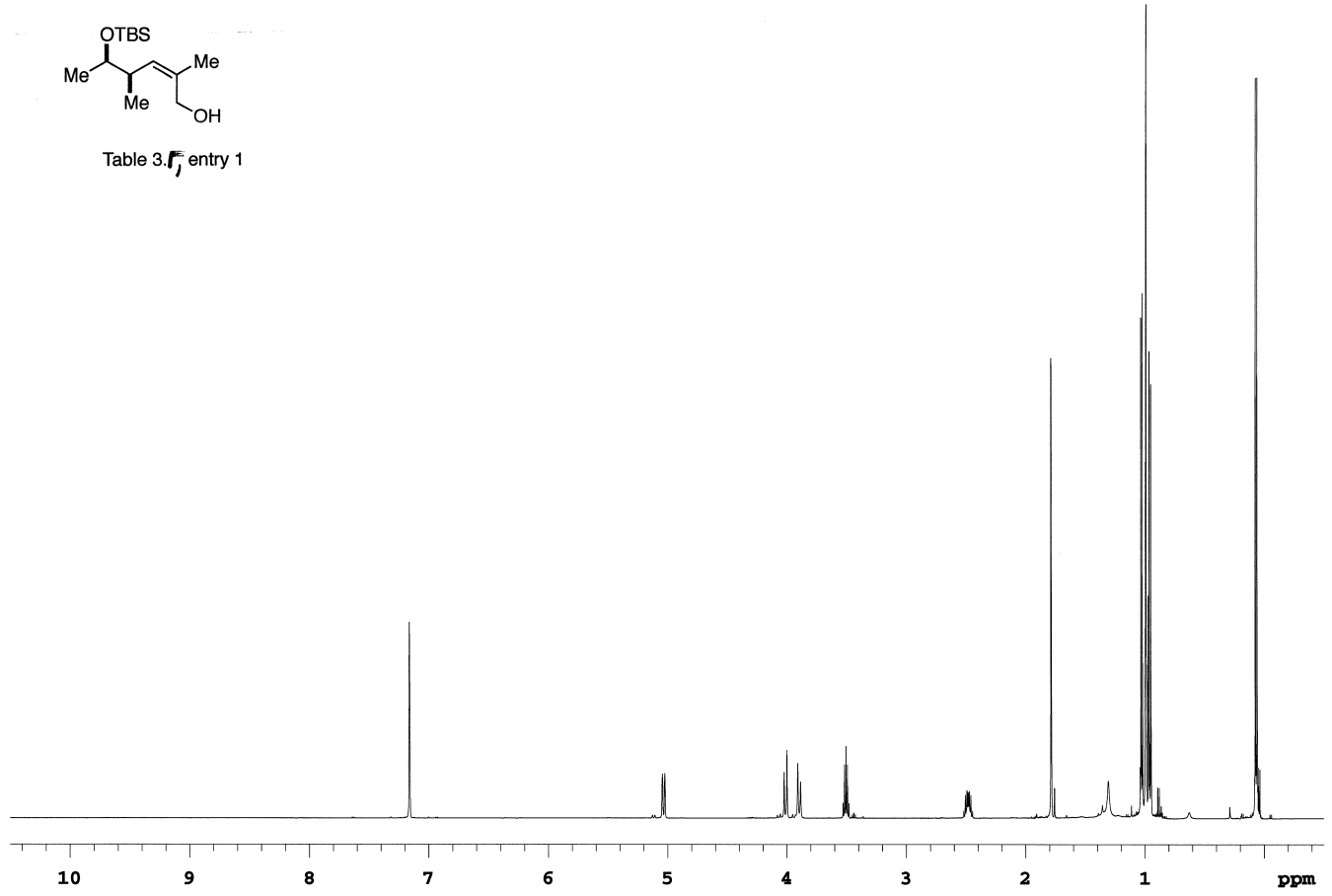

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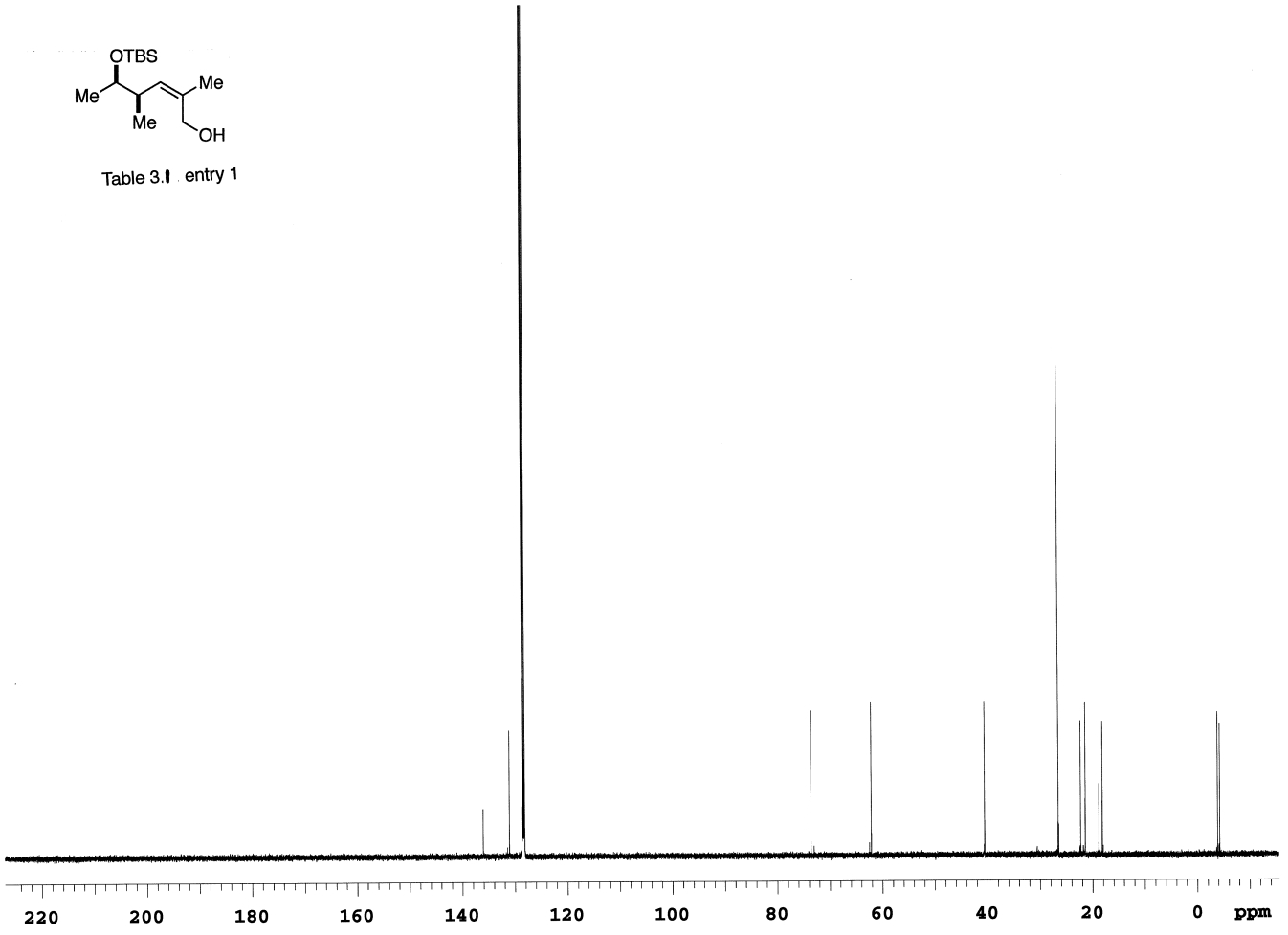
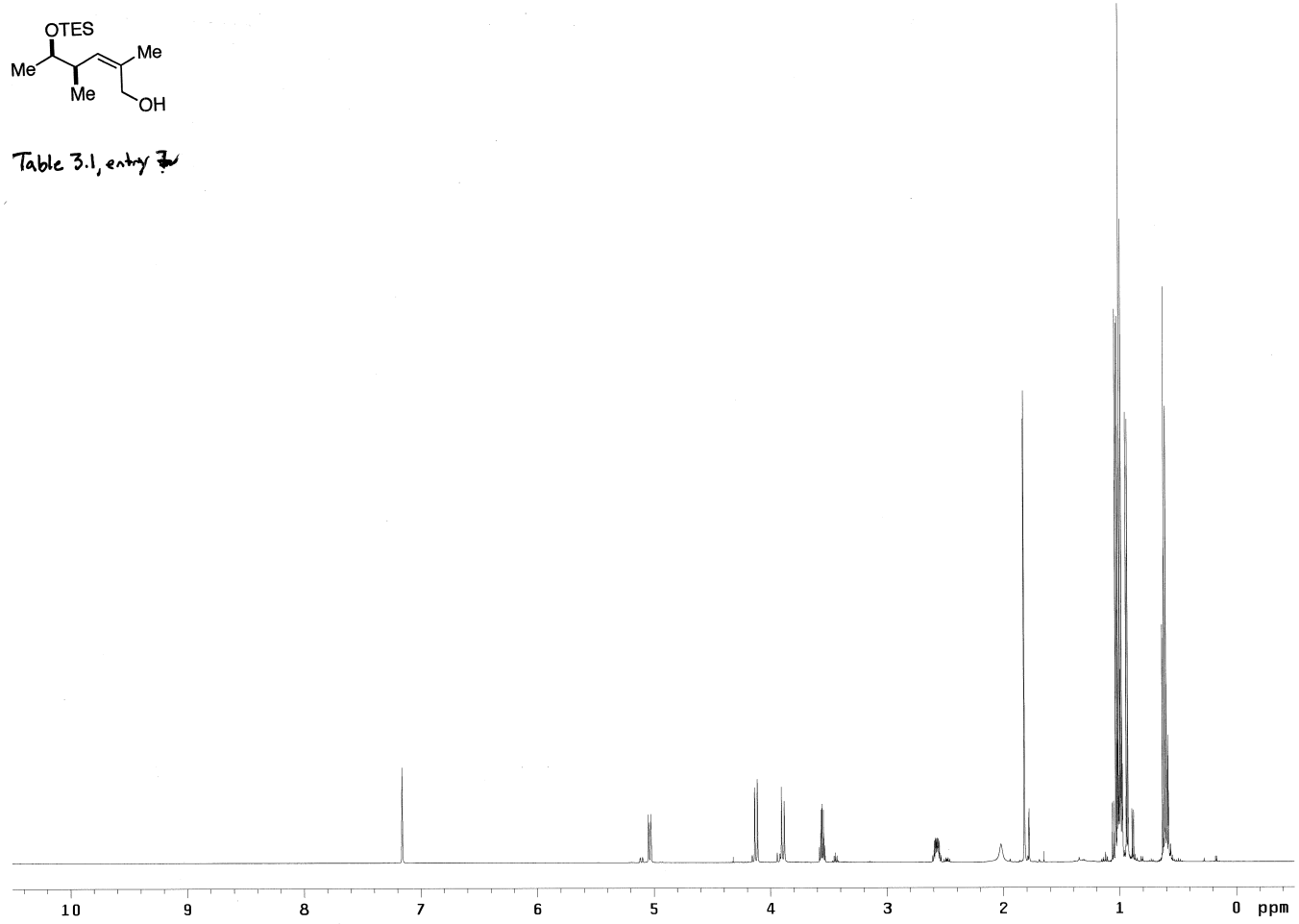

OTBS
Me
Me
Me
OH
Table 3.I entry 1
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Me
Me
OH
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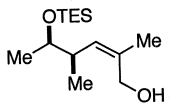
10
9
8
7
6
5
4
3
2
1
0 ppm



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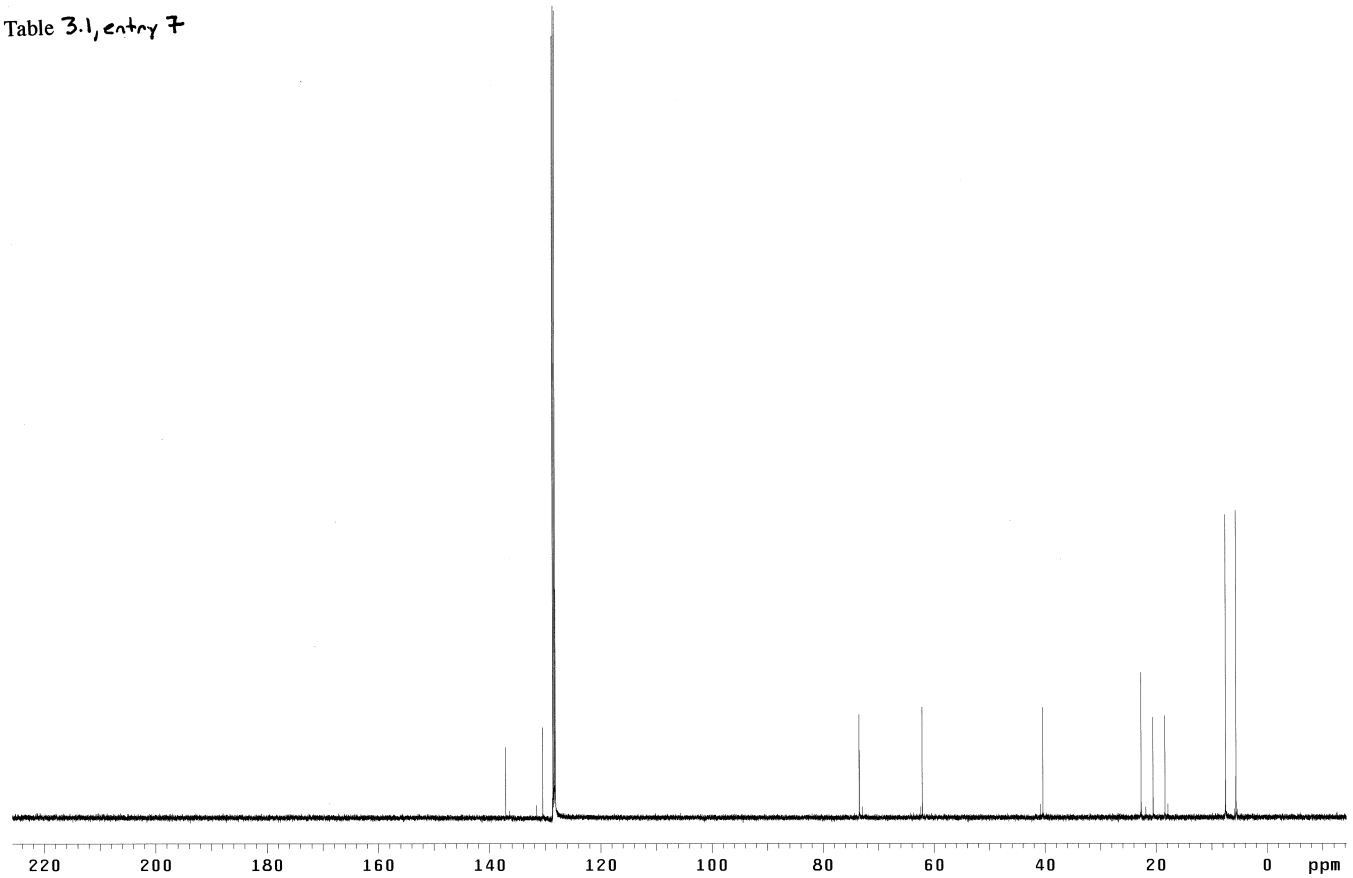


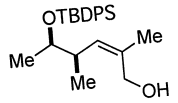
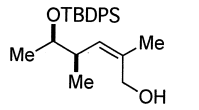


Table 3.1, entry 8



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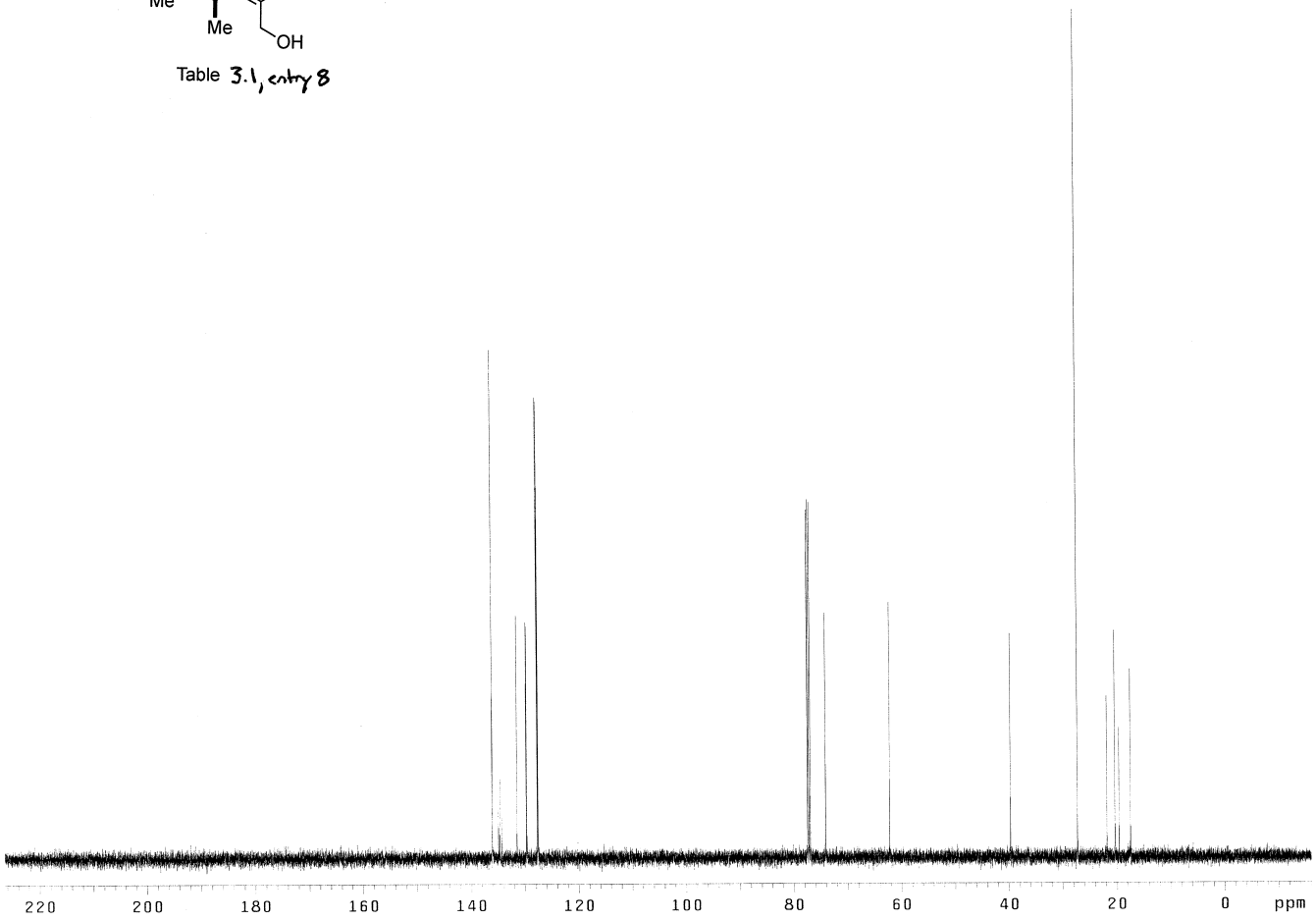
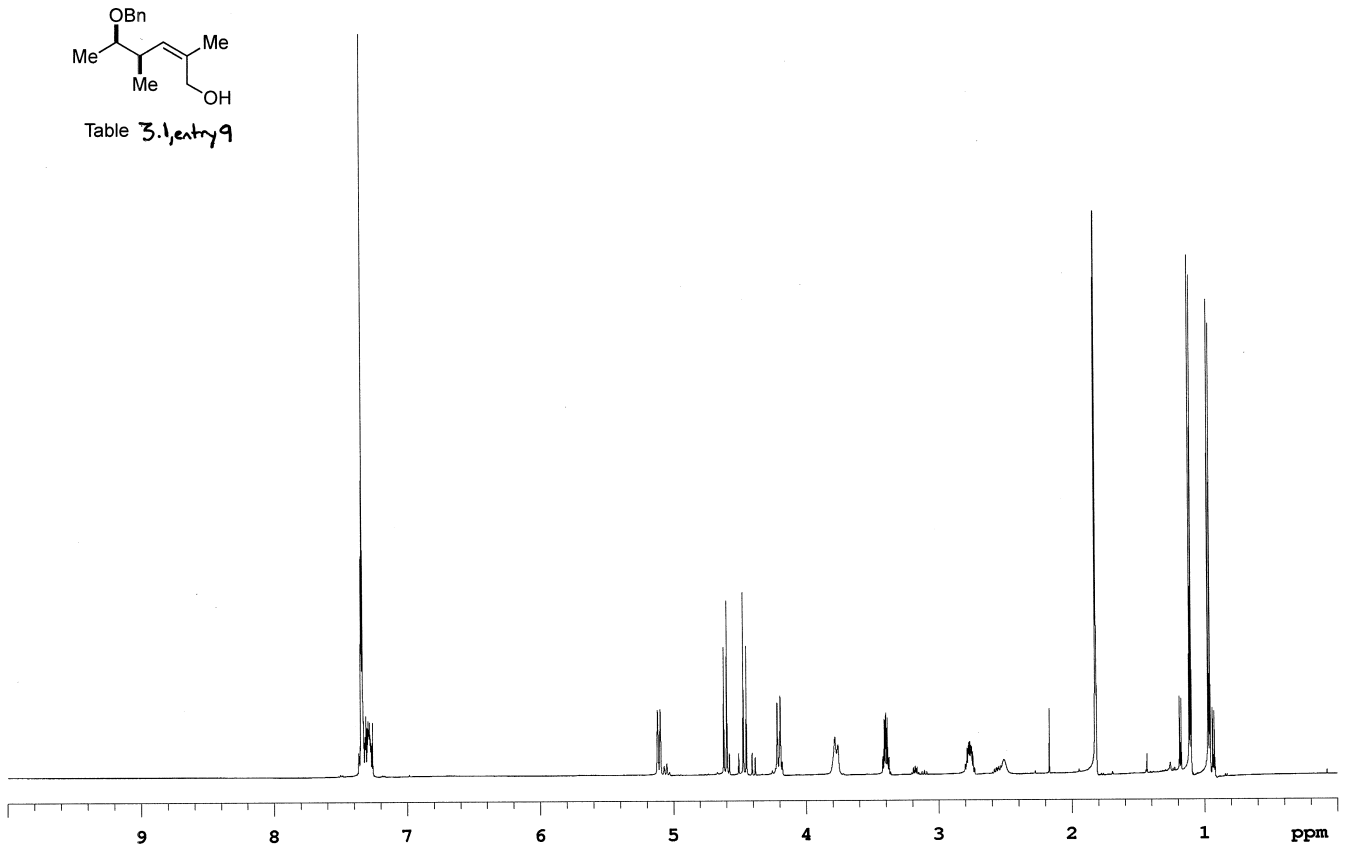
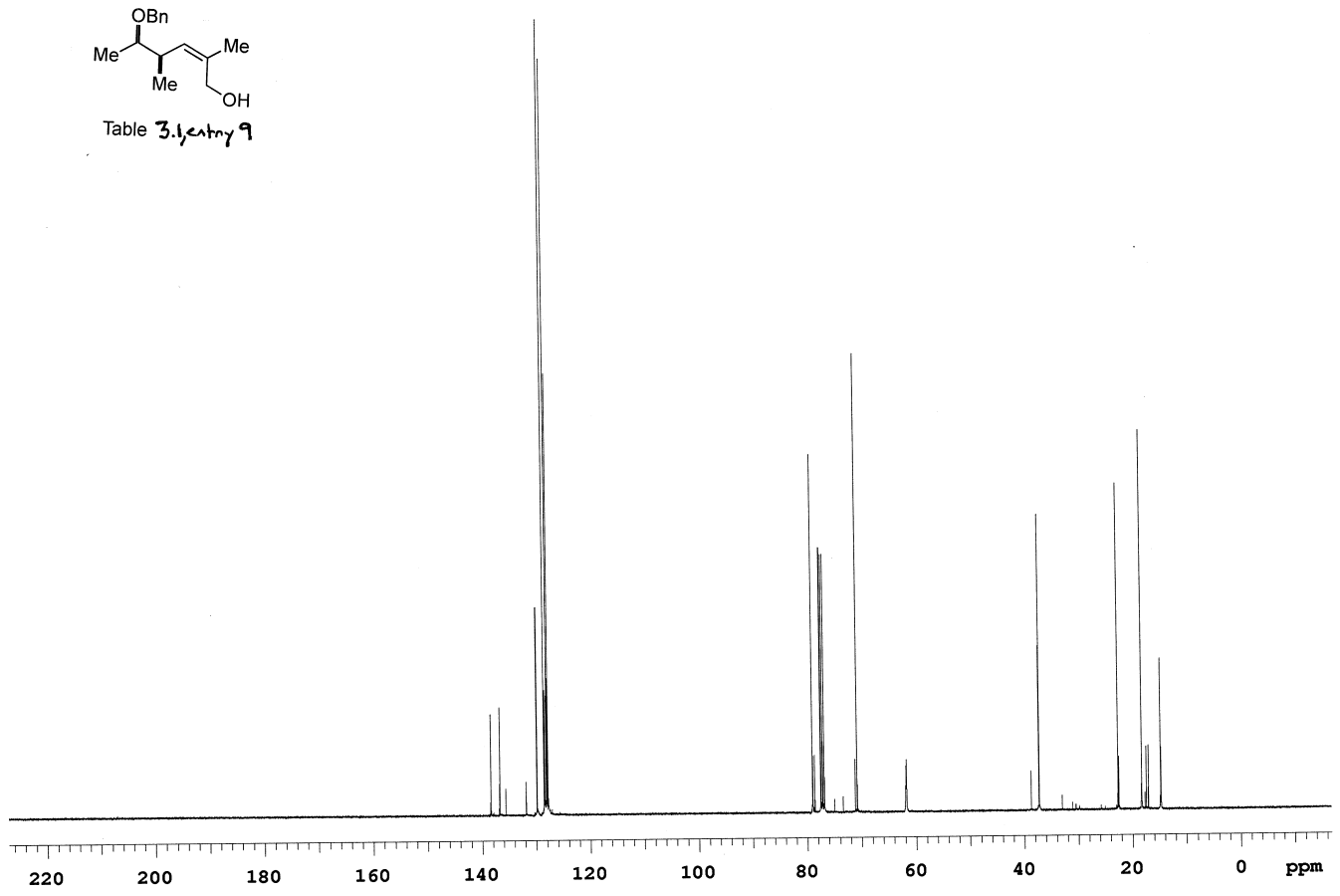



OBn
Me
Me
Me
OH
Table 3.1, entry 9
9
8
7
6
5
4
3
2
1
ppm


OBn
Me
Me
Me
OH
Table 3.1, entry 9
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200
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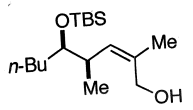
160
140
120
100
80
60
40
20
0
ppm



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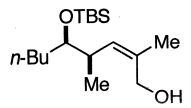

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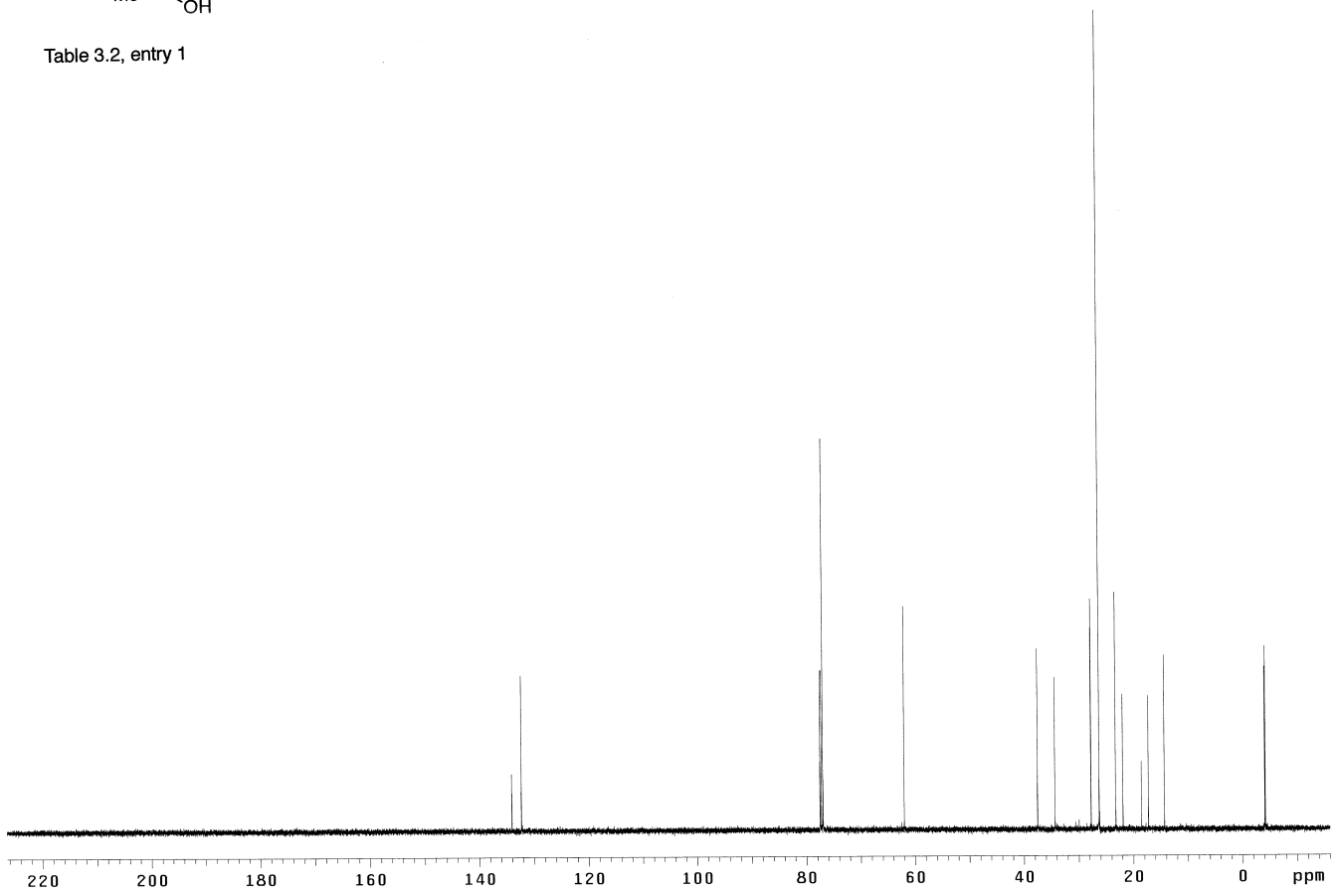

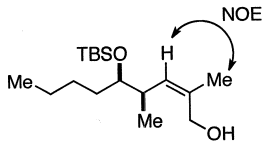

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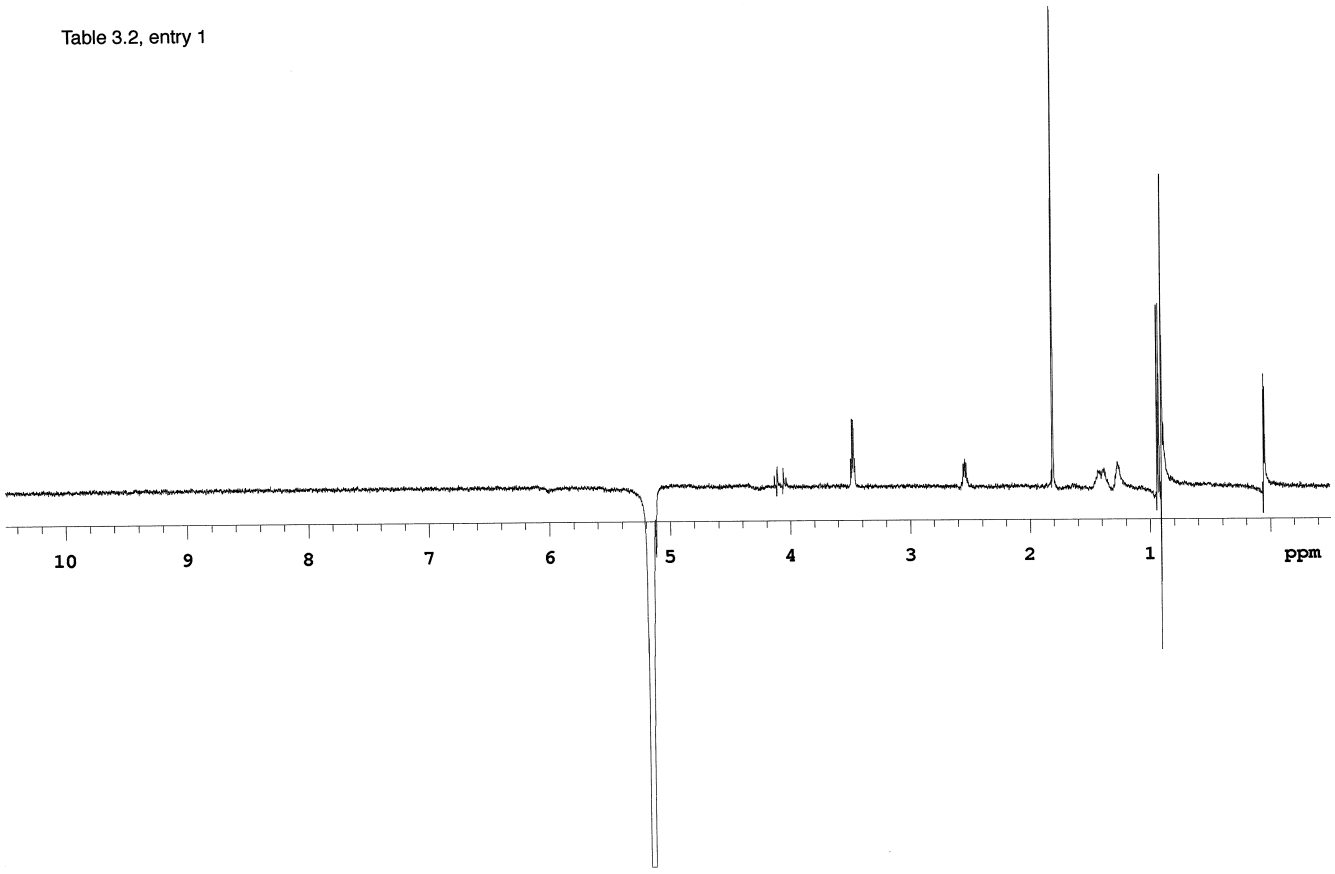

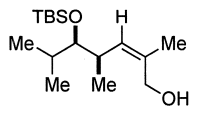

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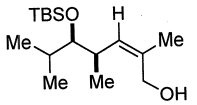

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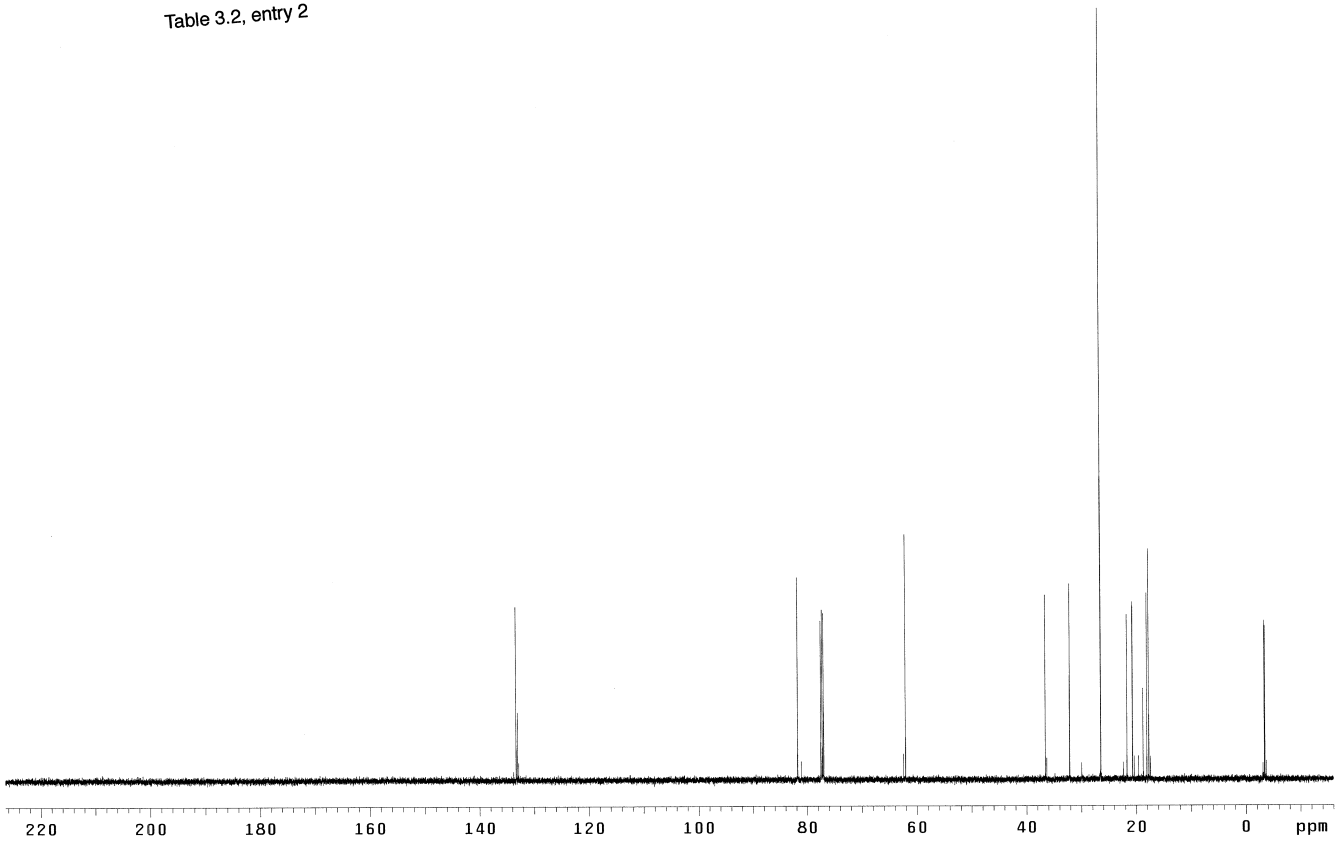

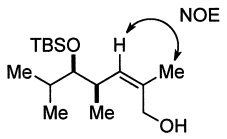

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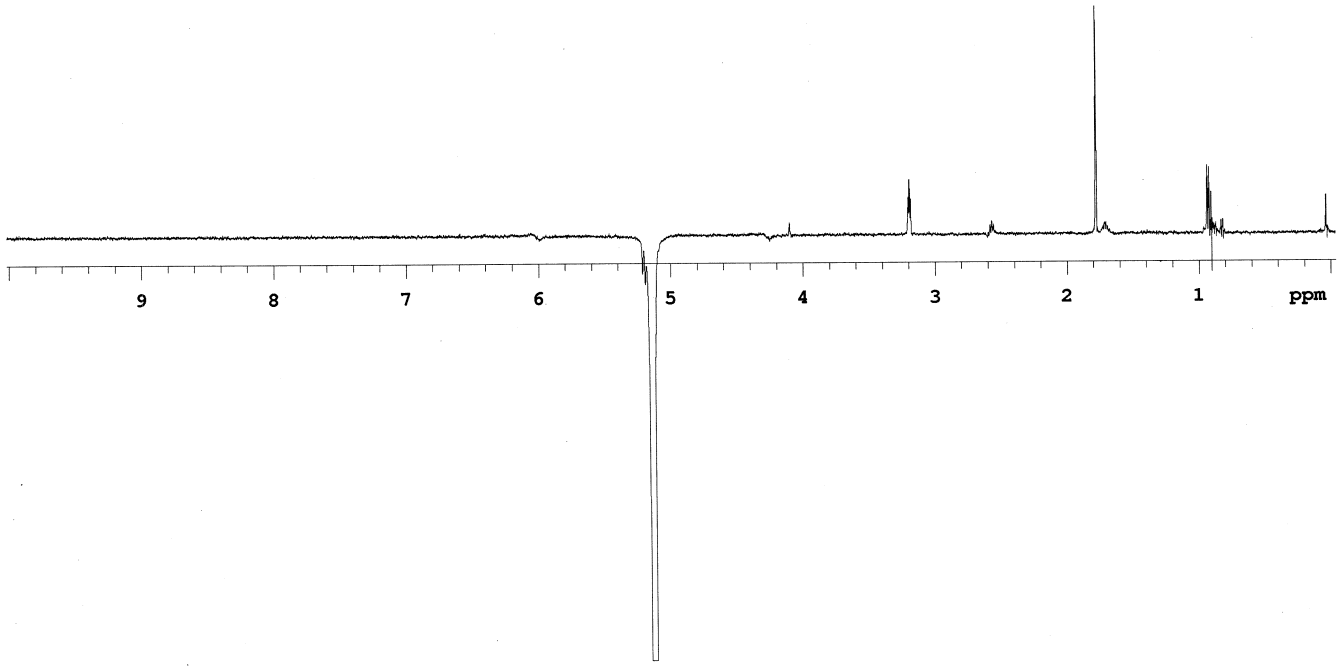

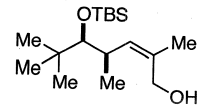

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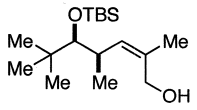

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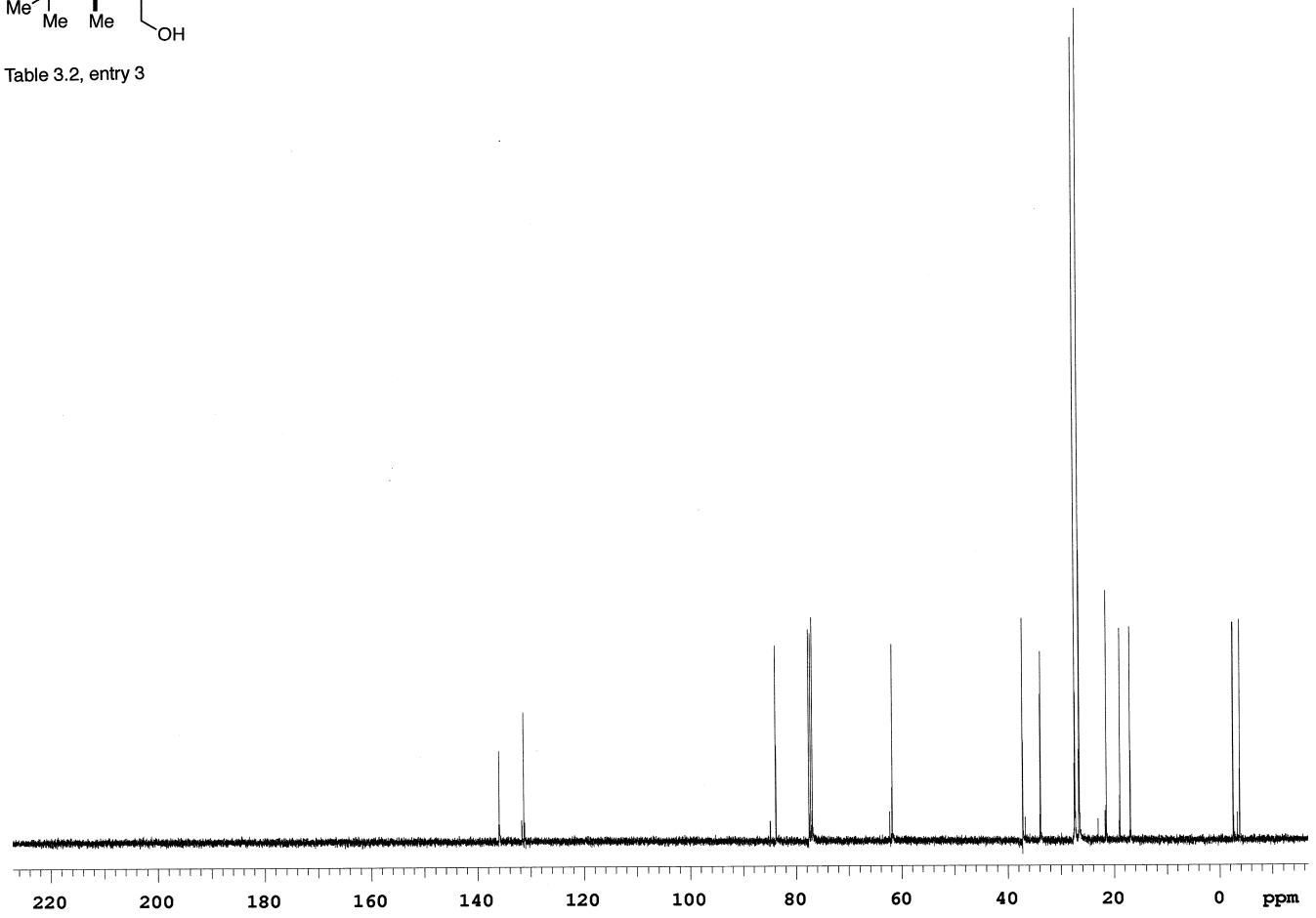

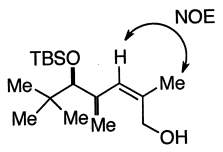

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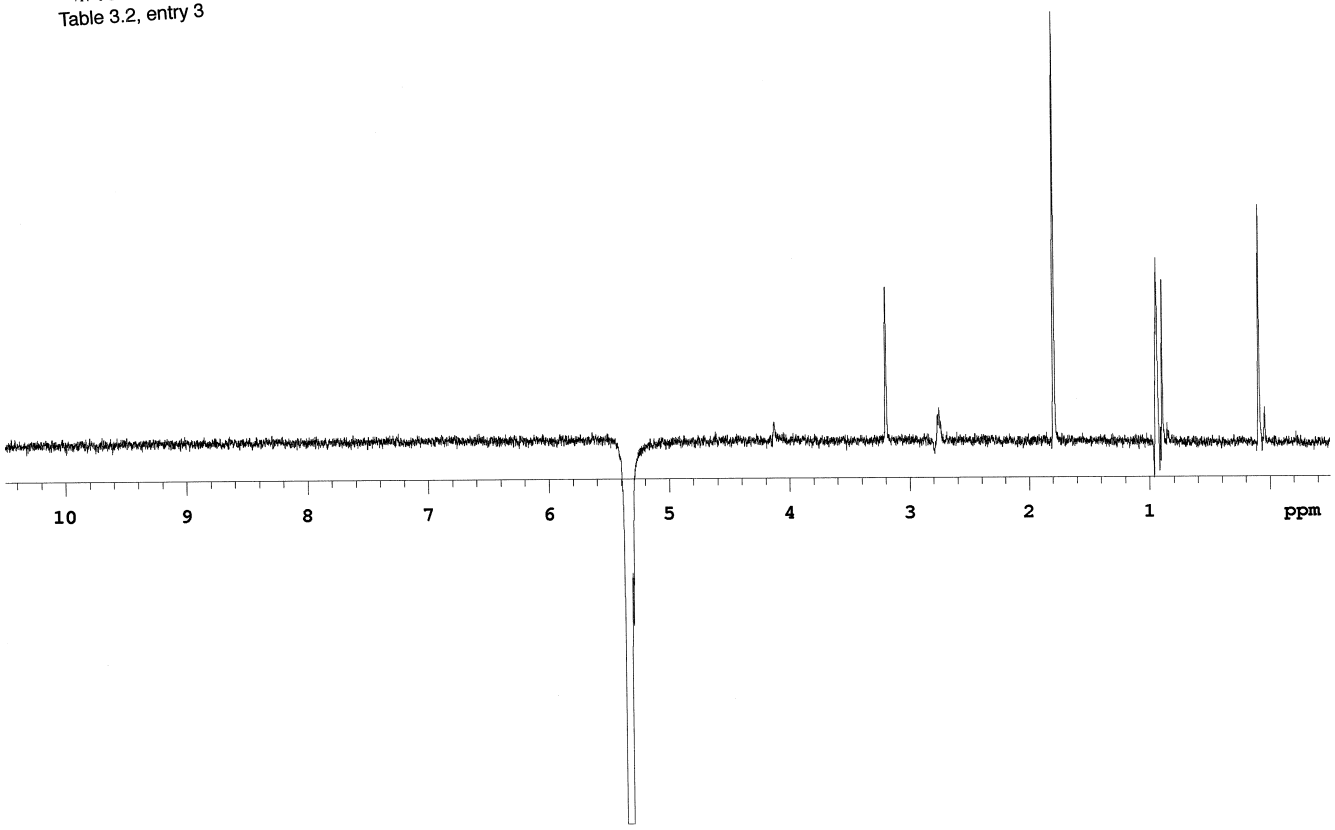

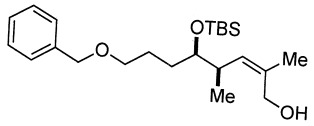

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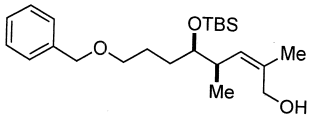

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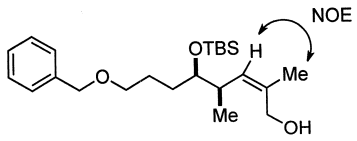
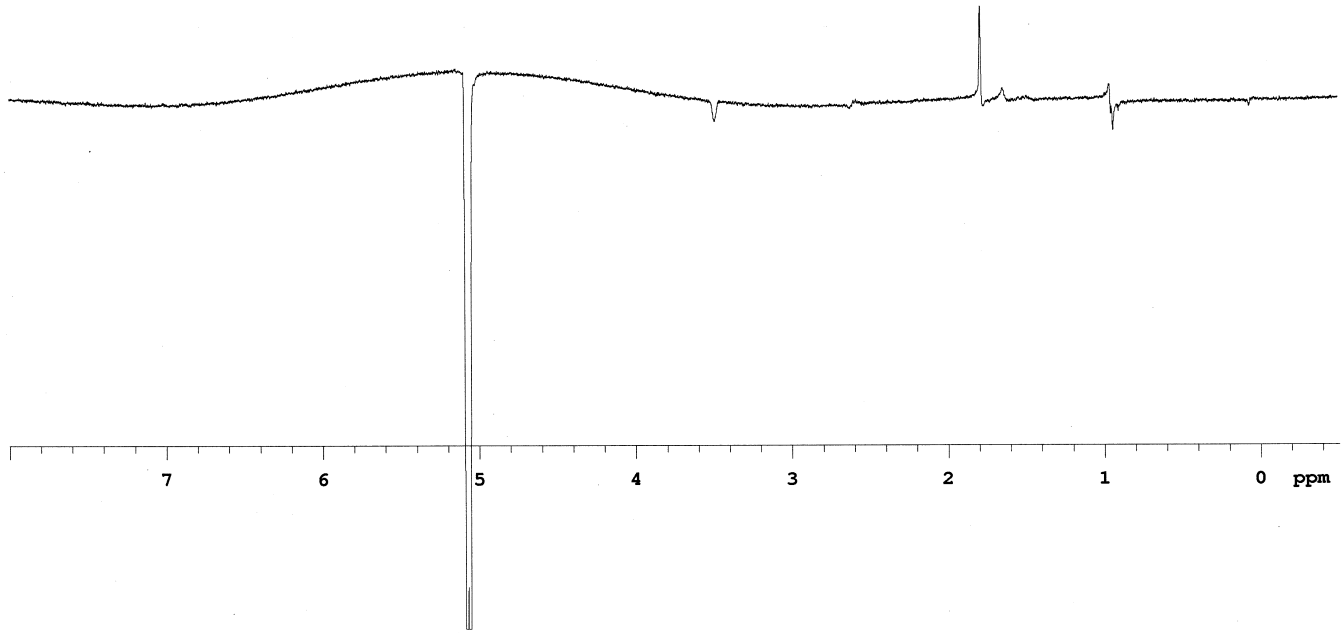


Table 3.2, entry 4



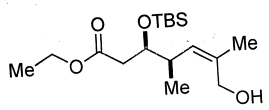
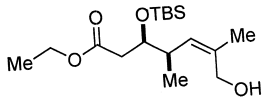


Table 3.2, entry 5



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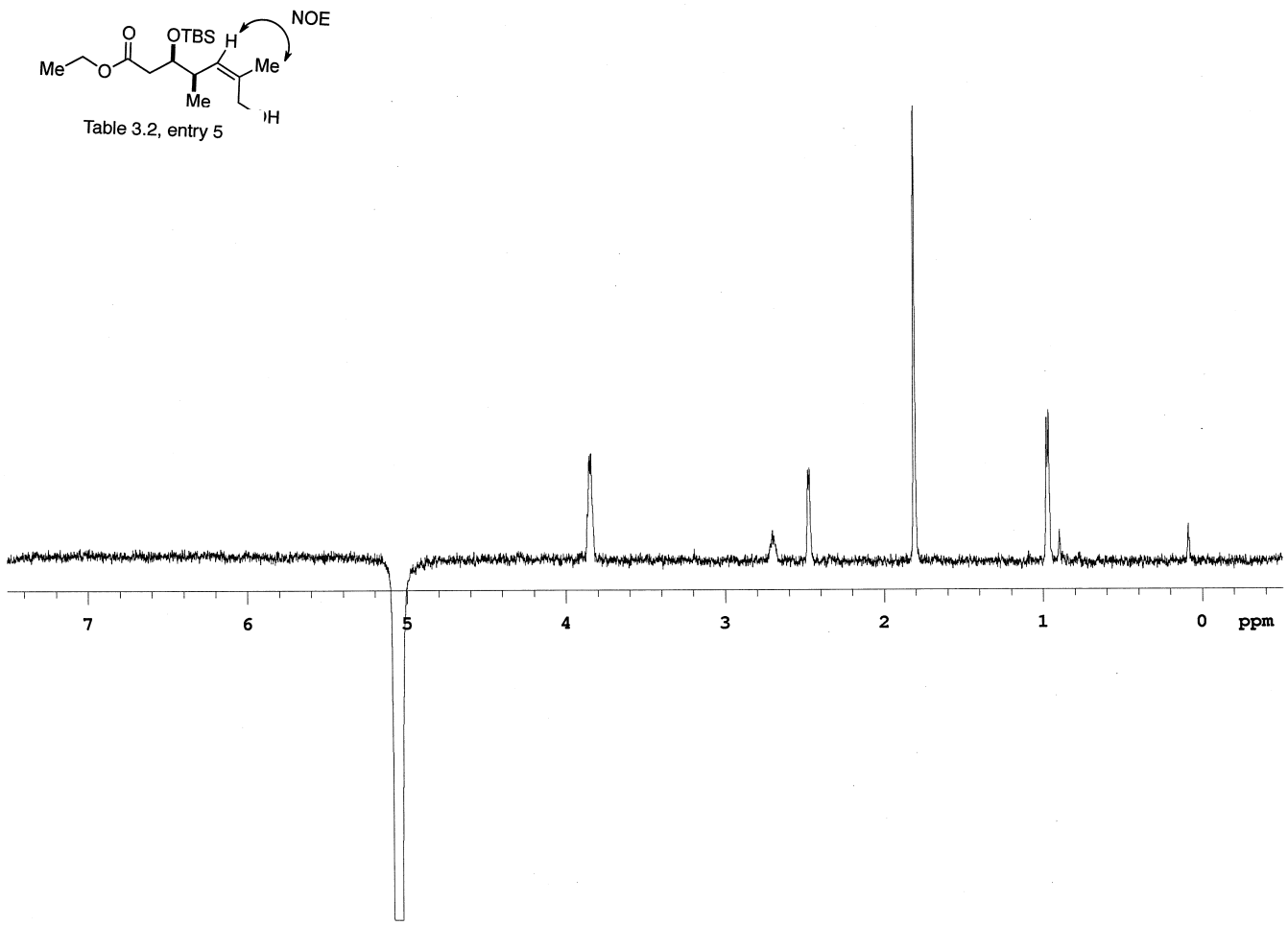
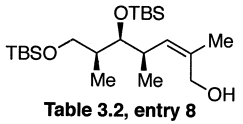

NOE
O
OTBS
H
Me
O
Me
Me
Table 3.2, entry 5
7
6
5
4
3
2
1
0
ppm



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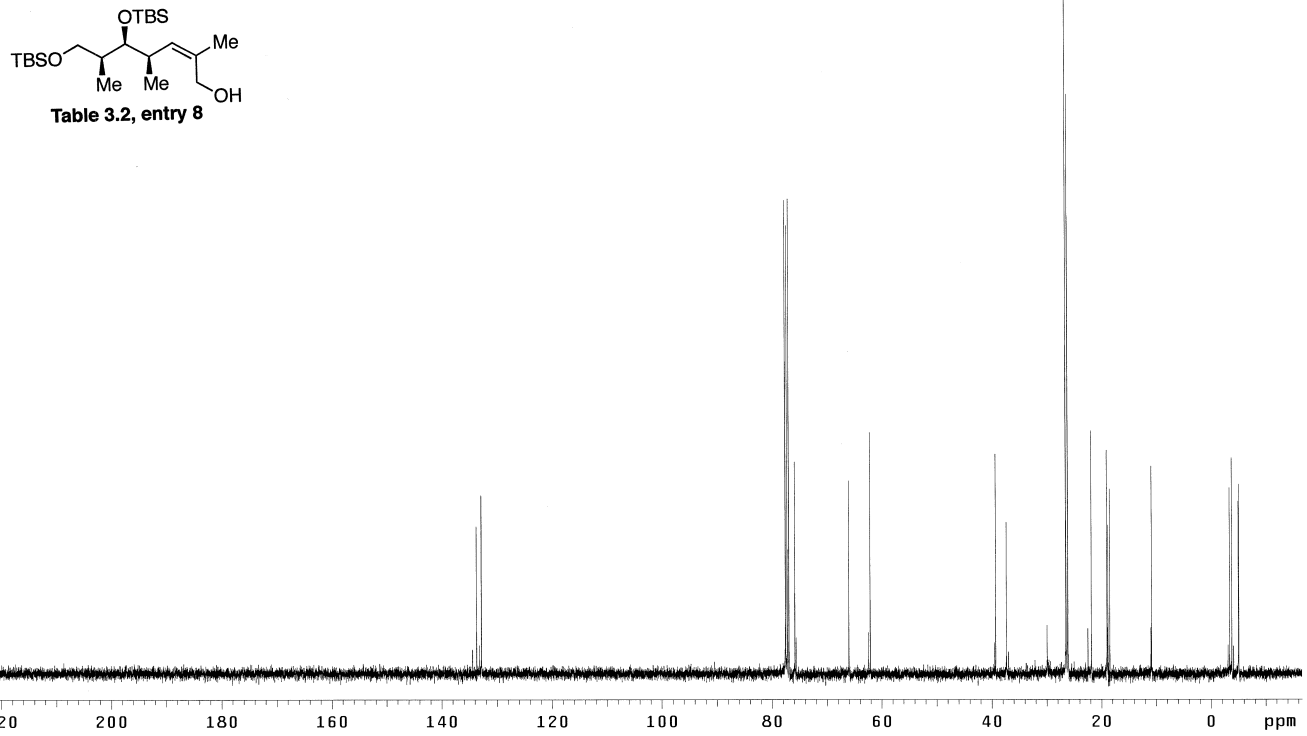

Table 3.2, entry 8

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Sample: RJE-V-071-column-NOE
Sample Name: 110422_001
File: /home/Morken/elyro/RJE-V-071-column-NOE_V_071_01.fid
    ACQUISITION                DECOUPLER
Pulse Sequence: 2D NOESY 1D    dn              C13
 at              1.998         dm              nnn
 np             32018               SAMPLE
 fb              2600         date   Apr 22 2011
 bs                 4         solvent      cdcl3
 ss                -2         file /home/Morken/~
 d1             1.000         elyro/RJE-V-071-co~
 nt               128         lumn-NOE_V_071_01.~
 ct                 4                      fid
   TRANSMITTER                      SPECIAL
 tn                H1         temp       not used
 sfrq         499.884          gain              20
 tof            499.8          spin               0
 tpwr              62          pw90           6.900
 pw             6.900               FLAGS
       NOESY                    sspul              y
 mix            0.500          il                 n
 sweeppwr          44          in                 n
 sweeppw    1500.000           dp                 y
 sweepshp    sech180           hs                nn
     SEL PULSE                      PROCESSING
 selfrq         499.8          lb              0.50
 selshape NOESY1D_5~           fn         not used
                  _07p              DISPLAY
 selpwr            3           sp           -1029.1
 selpw       77092.1           wp            8012.3
     GRADIENT                  vs            164692
 gzlvl1         5128           sc                 0
 gt1        0.000500           wc               250
 gzlvl2         4102           hzmm           18.75
 gt2        0.005000           is             500.00
 gstab      0.000500           rfl            3554.0
 hsglvl         5128           rfp            2524.4
 hsgt       0.002000           th                54
   PRESATURATION               ins           100.000
 satfrq         499.8          ai  cdc  ph
 satpwr           -13
 satdly             0
 satmode          nnn
```

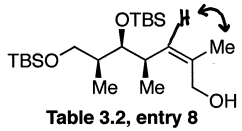
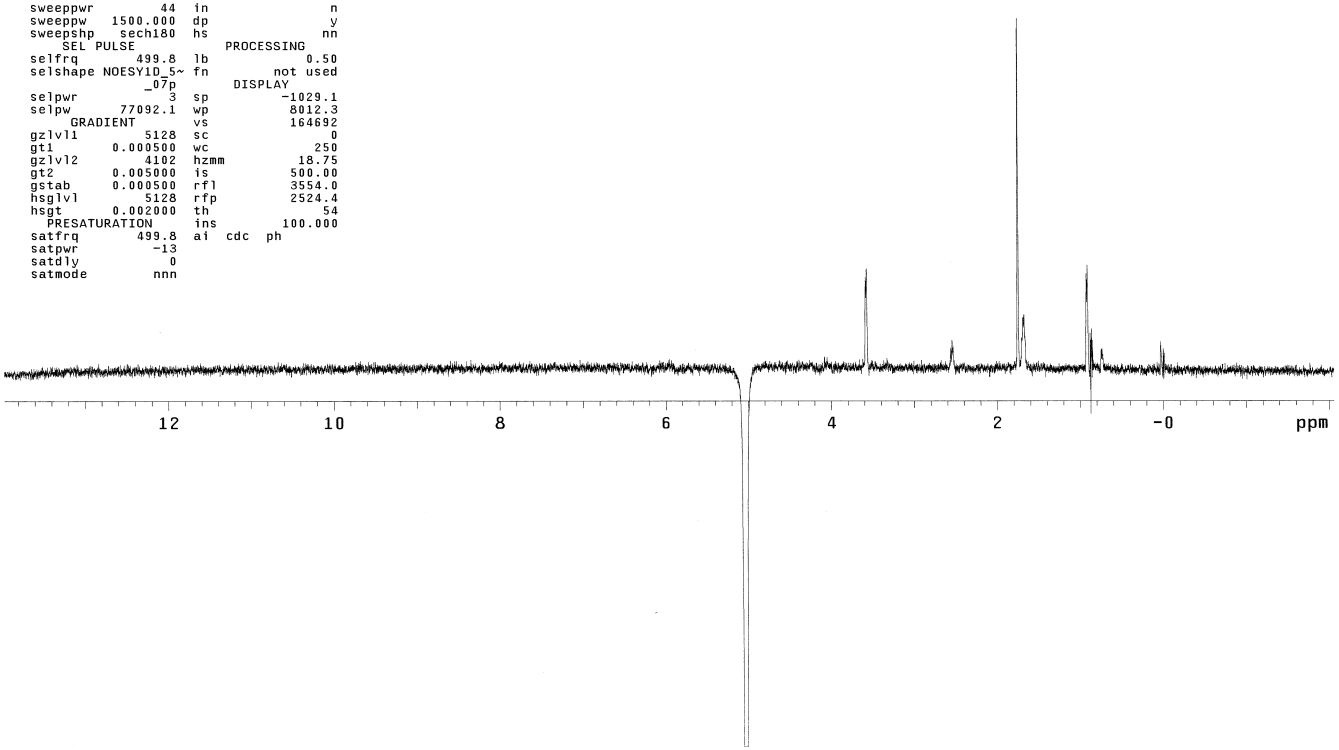
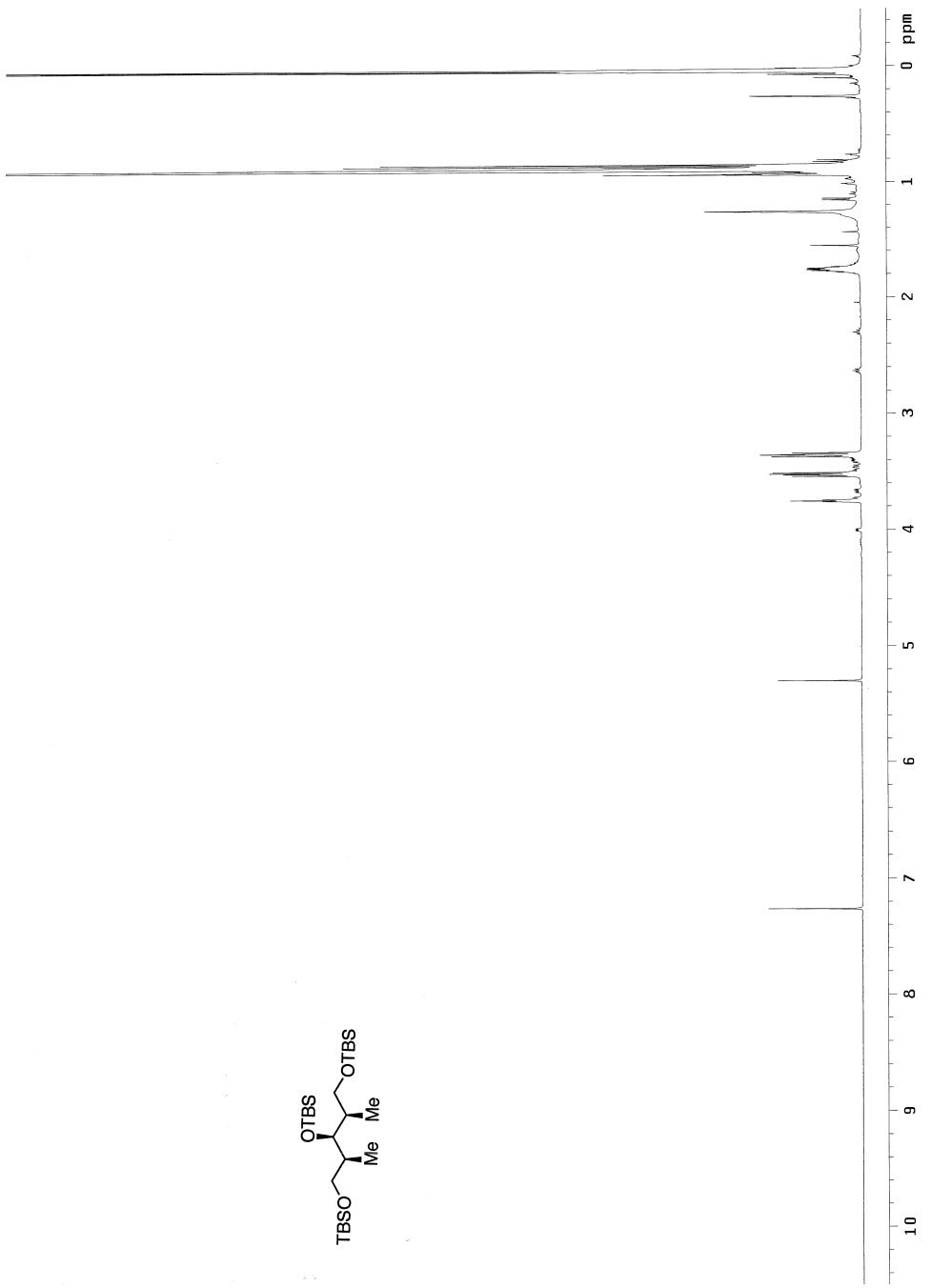
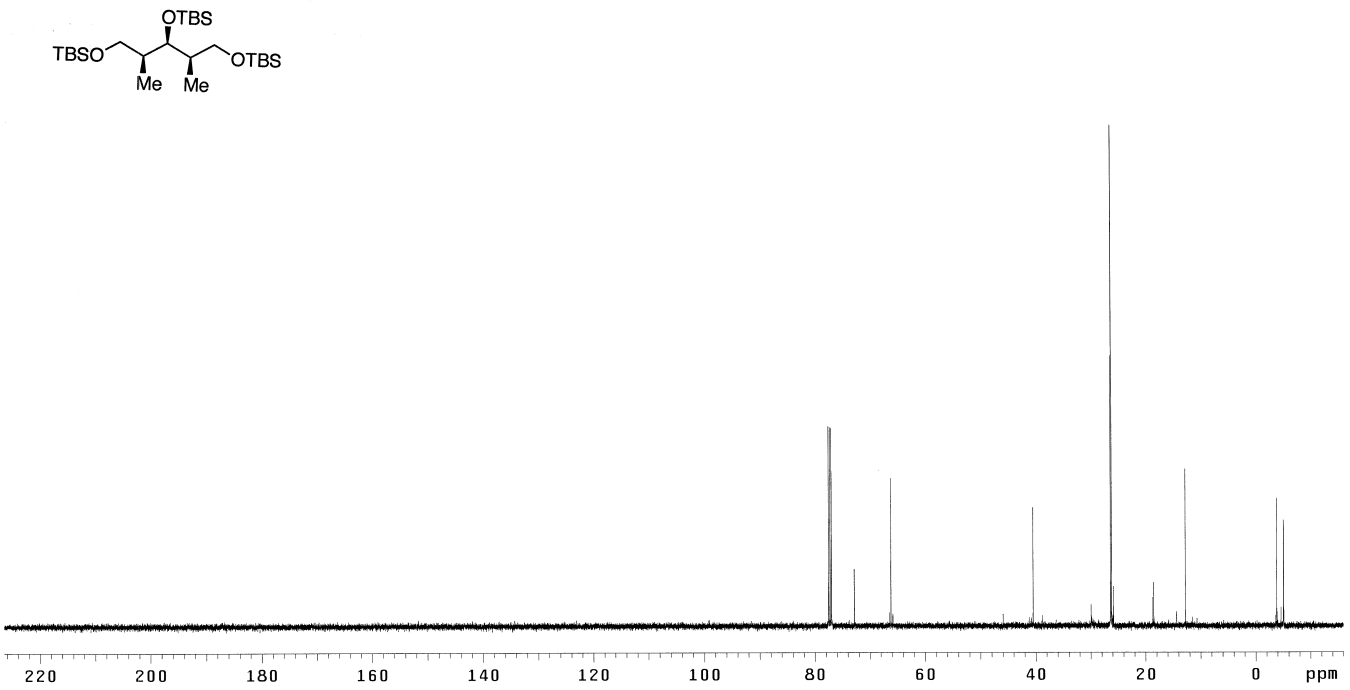


Table 3.2, entry 8




OTBS
OTBS
Me
Me
TBSO
10
9
8
7
6
5
4
3
2
1
0 ppm


OTBS
TBSO
OTBS
Me
Me
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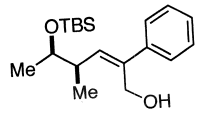
200
180
160
140
120
100
80
60
40
20
0
ppm



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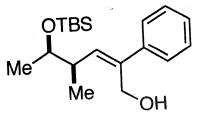
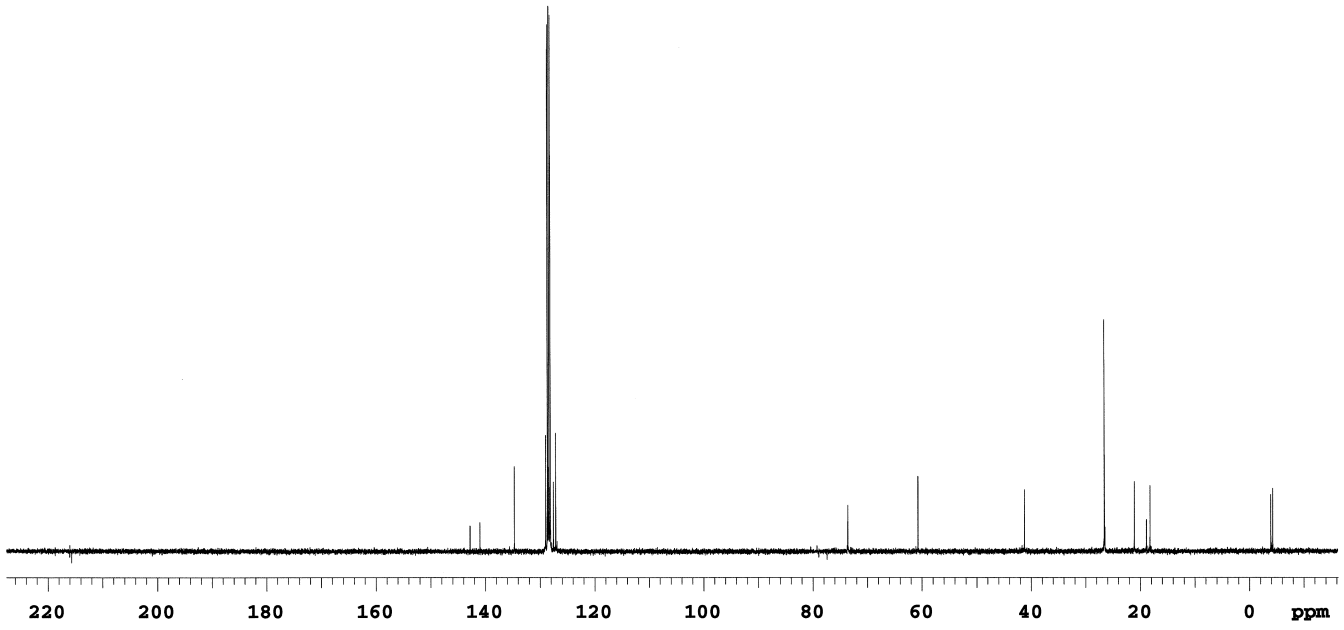


Table 3.3, entry 3



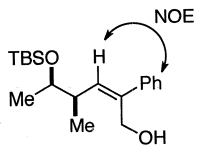
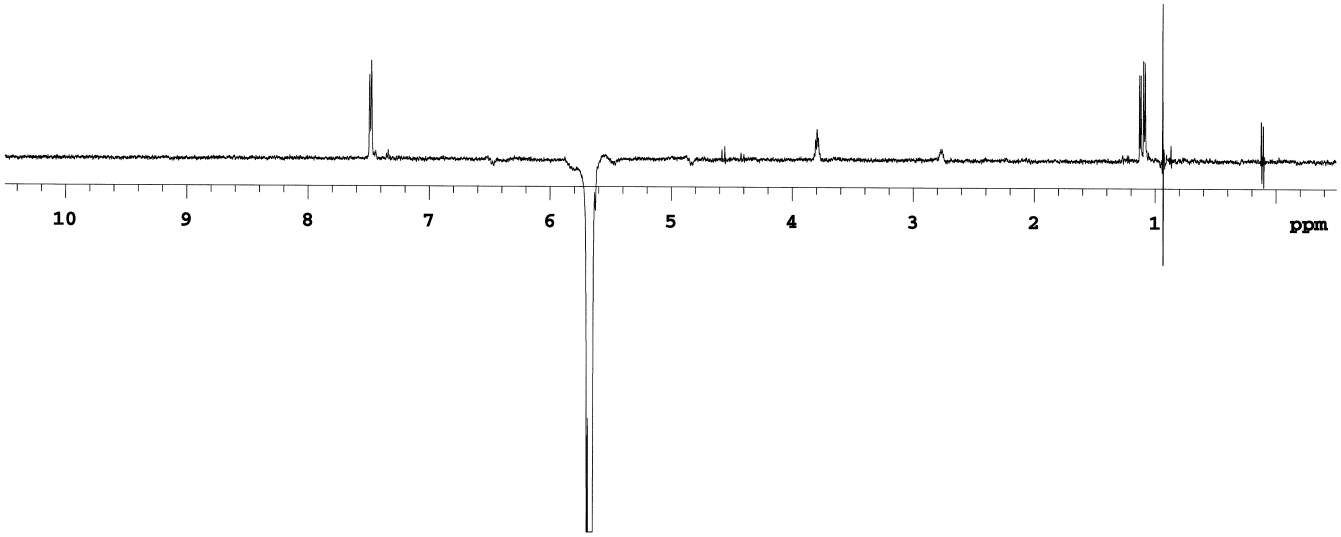
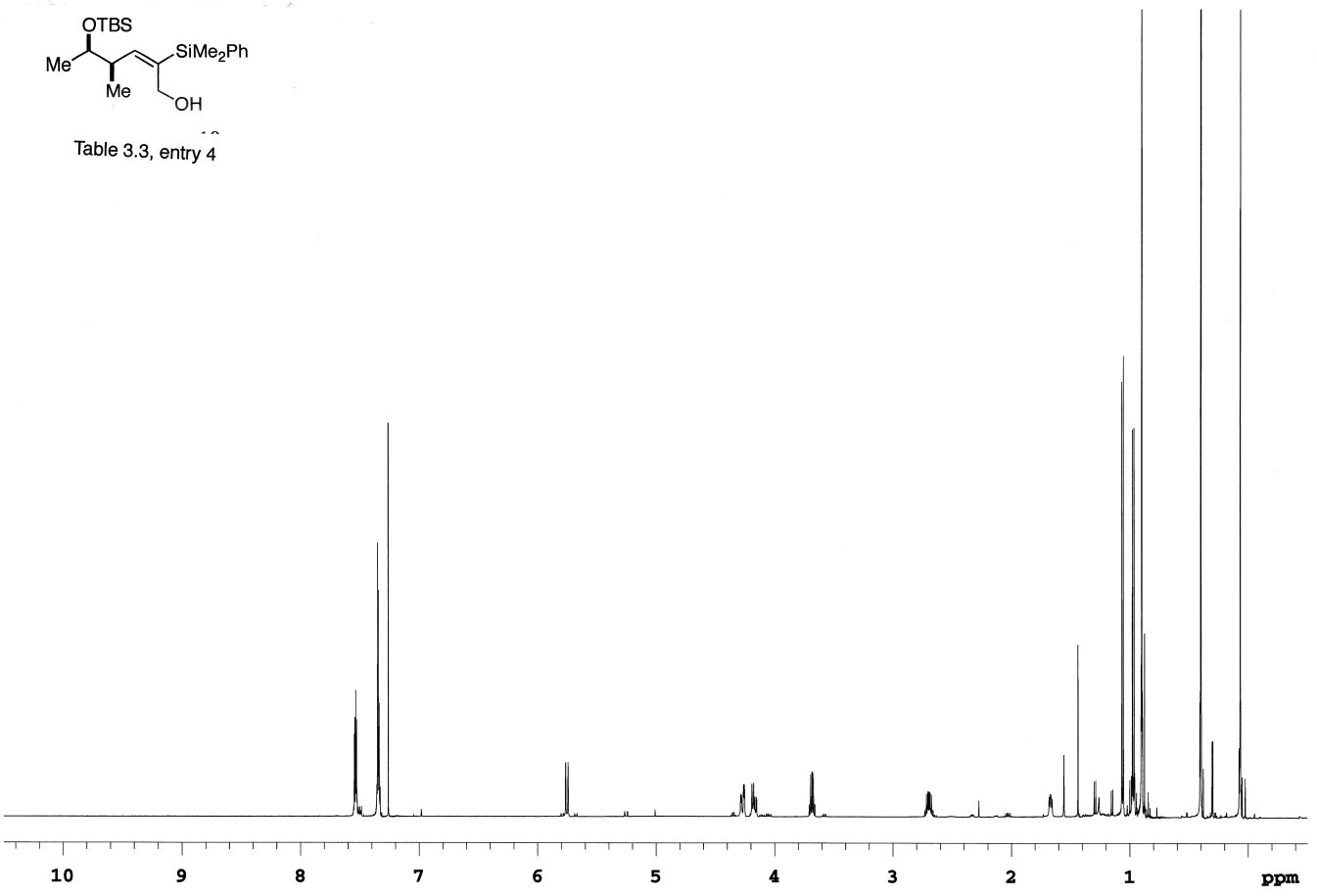


Table 3.3, entry 3

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Me
SiMe2Ph
OH
Table 3.3, entry 4
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8
7
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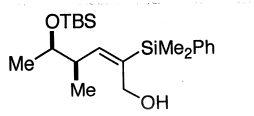
3
2
1
ppm



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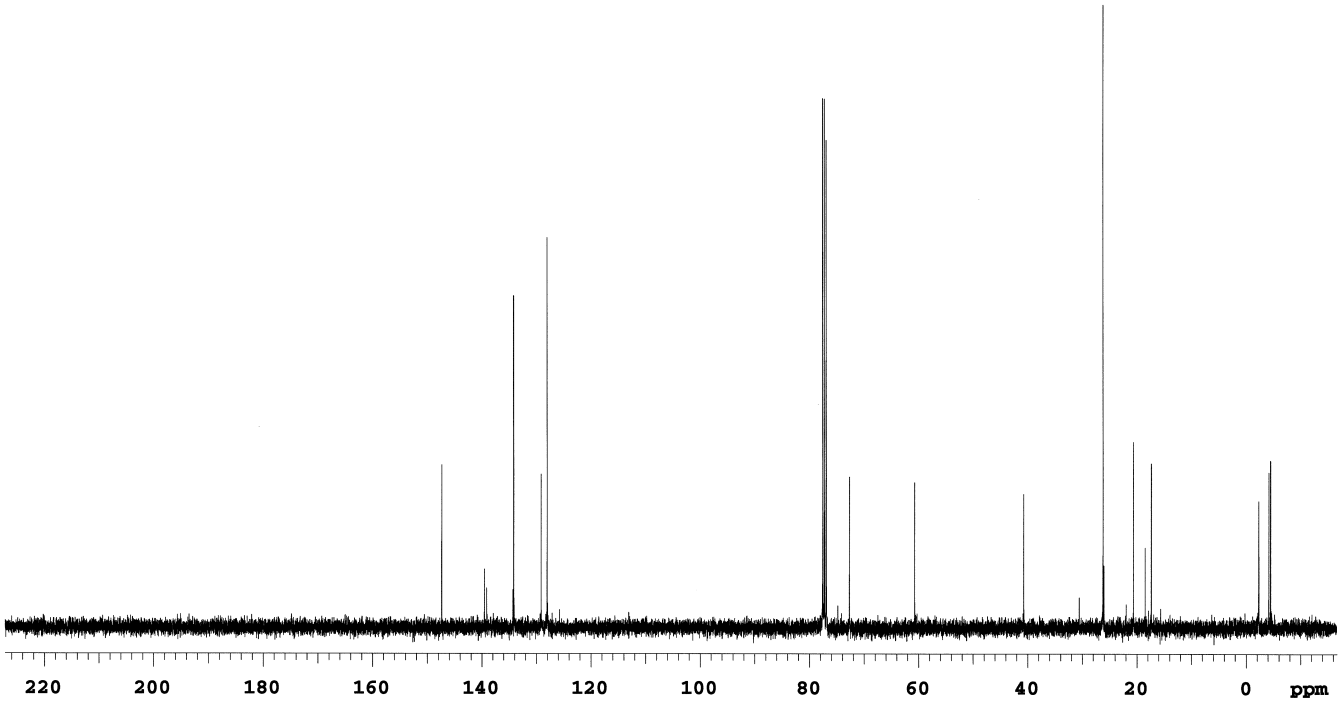

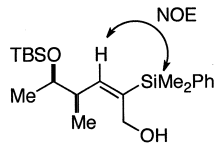

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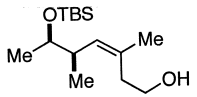

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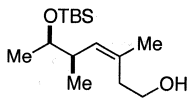

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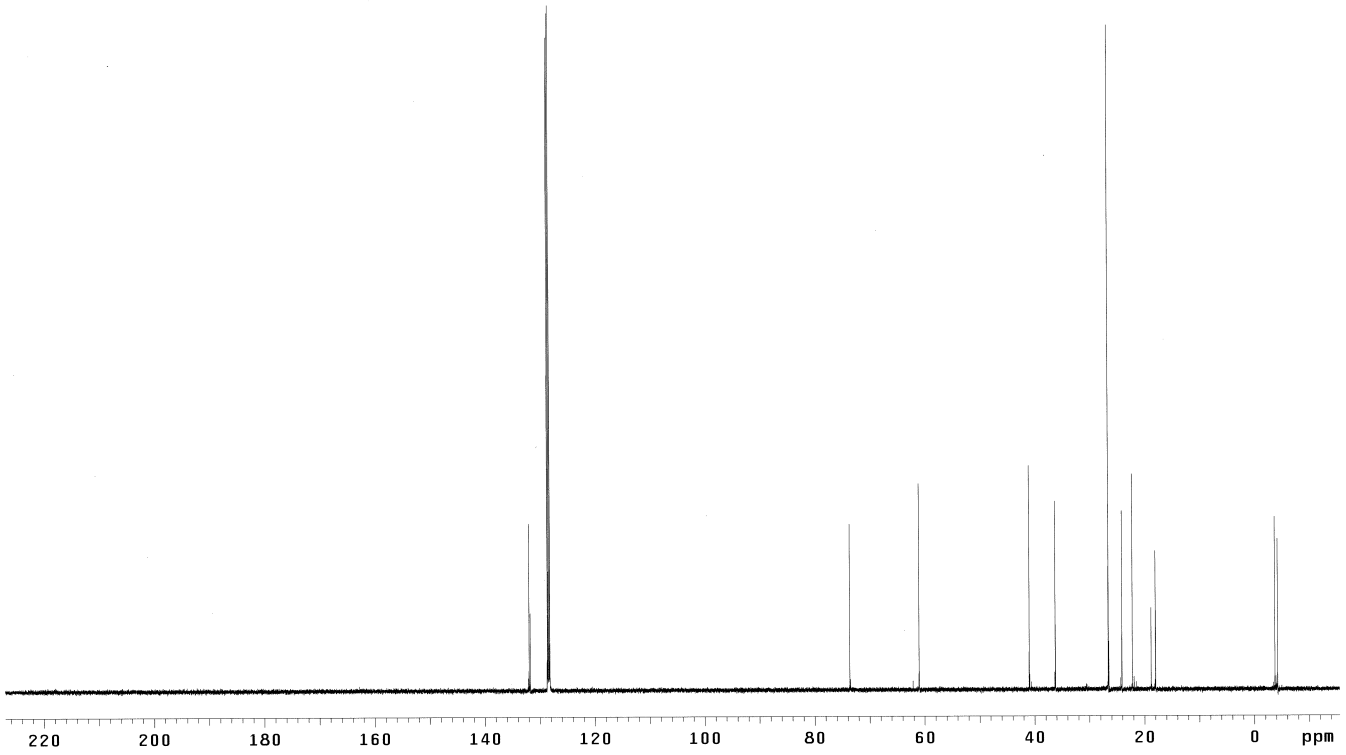

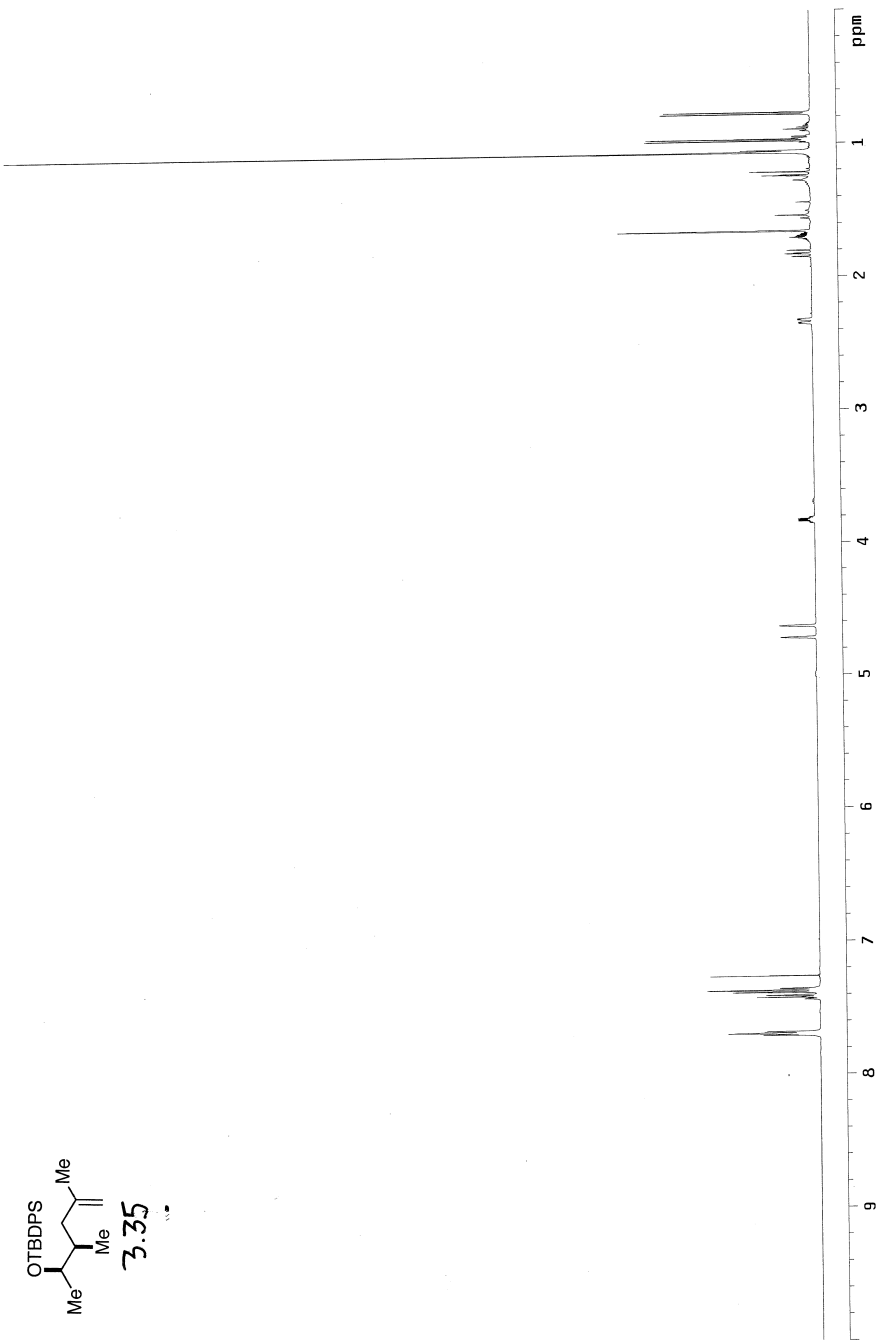
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Me
Me
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ppm
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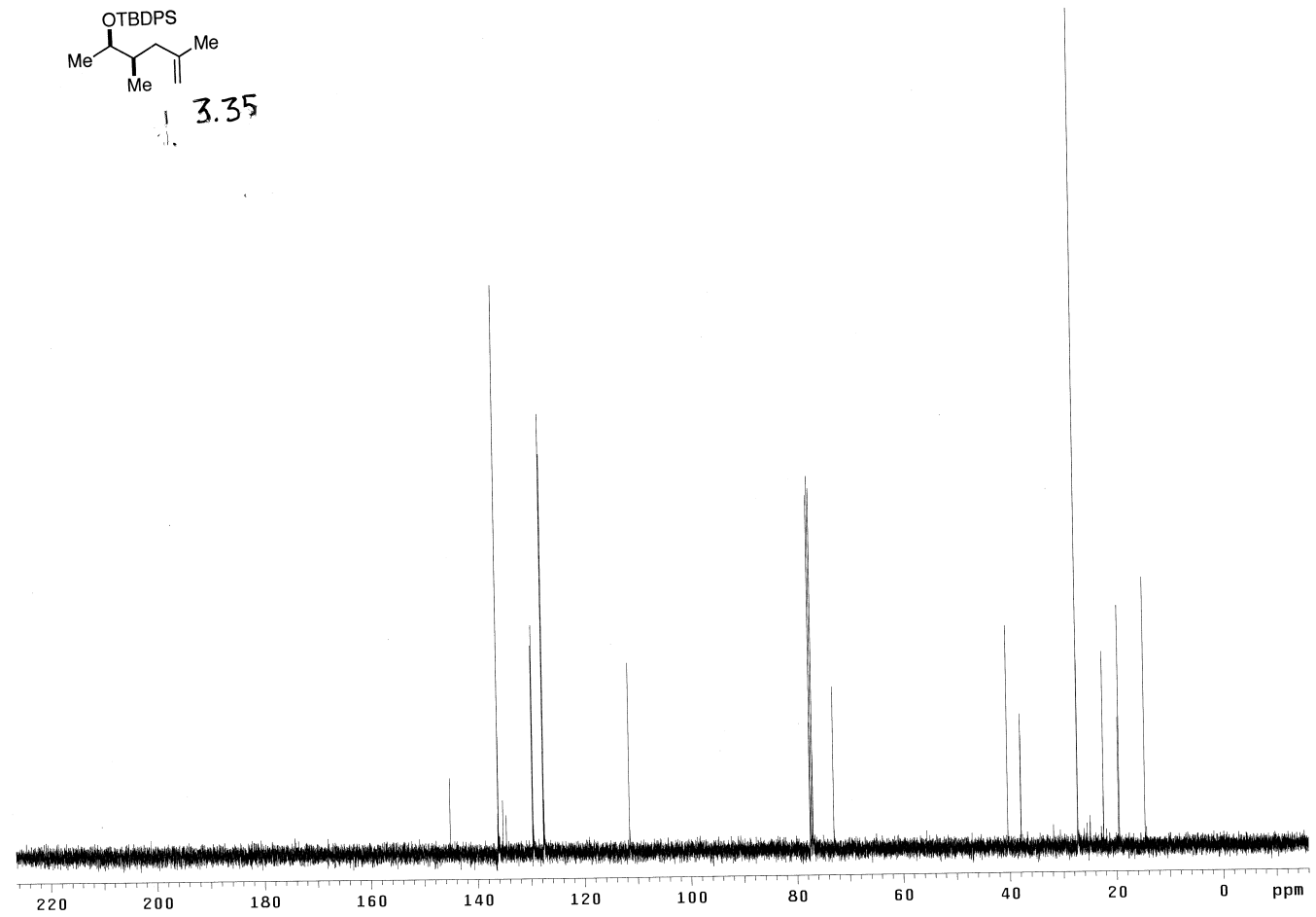
3
4
5
6
7
8
9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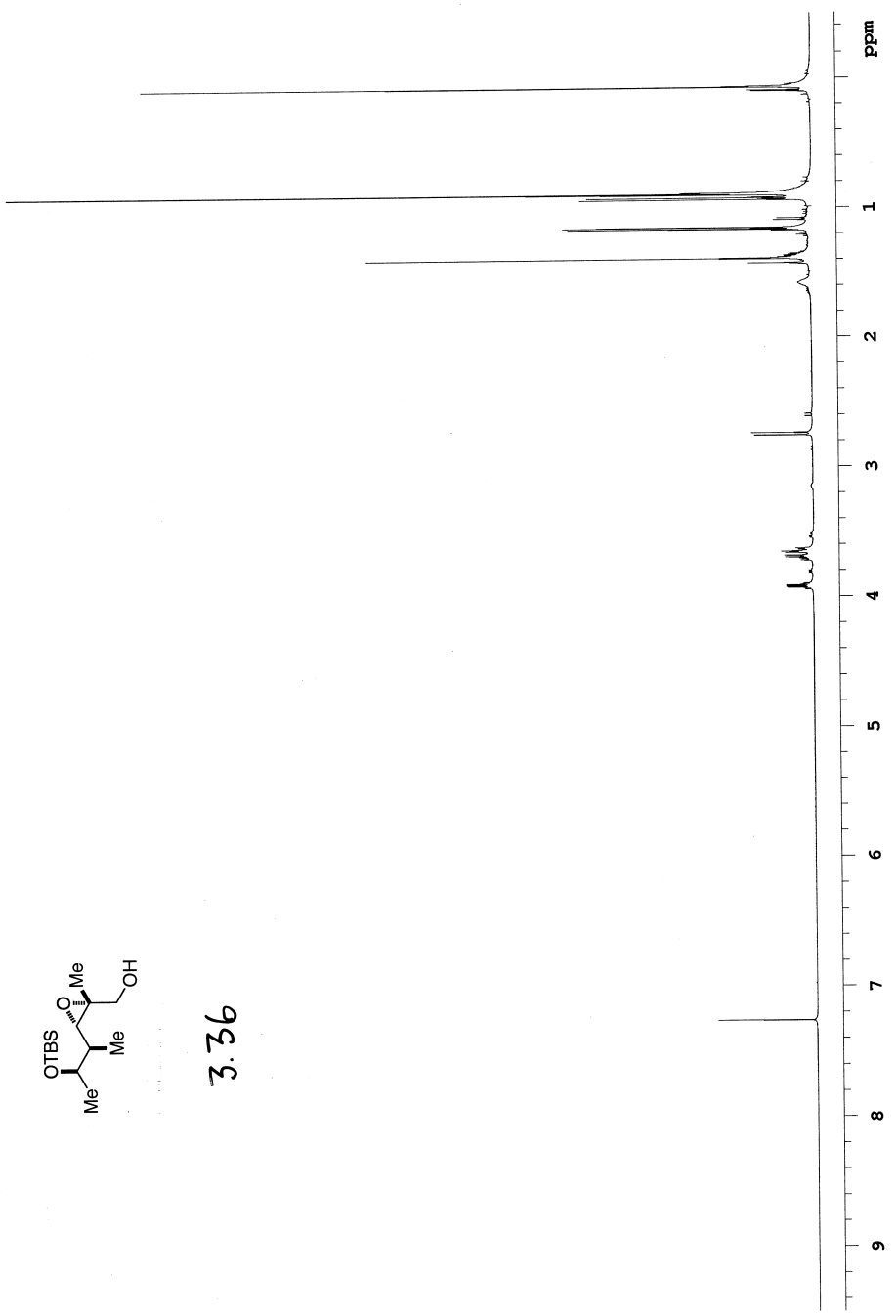
ppm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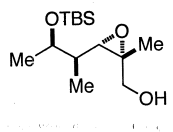

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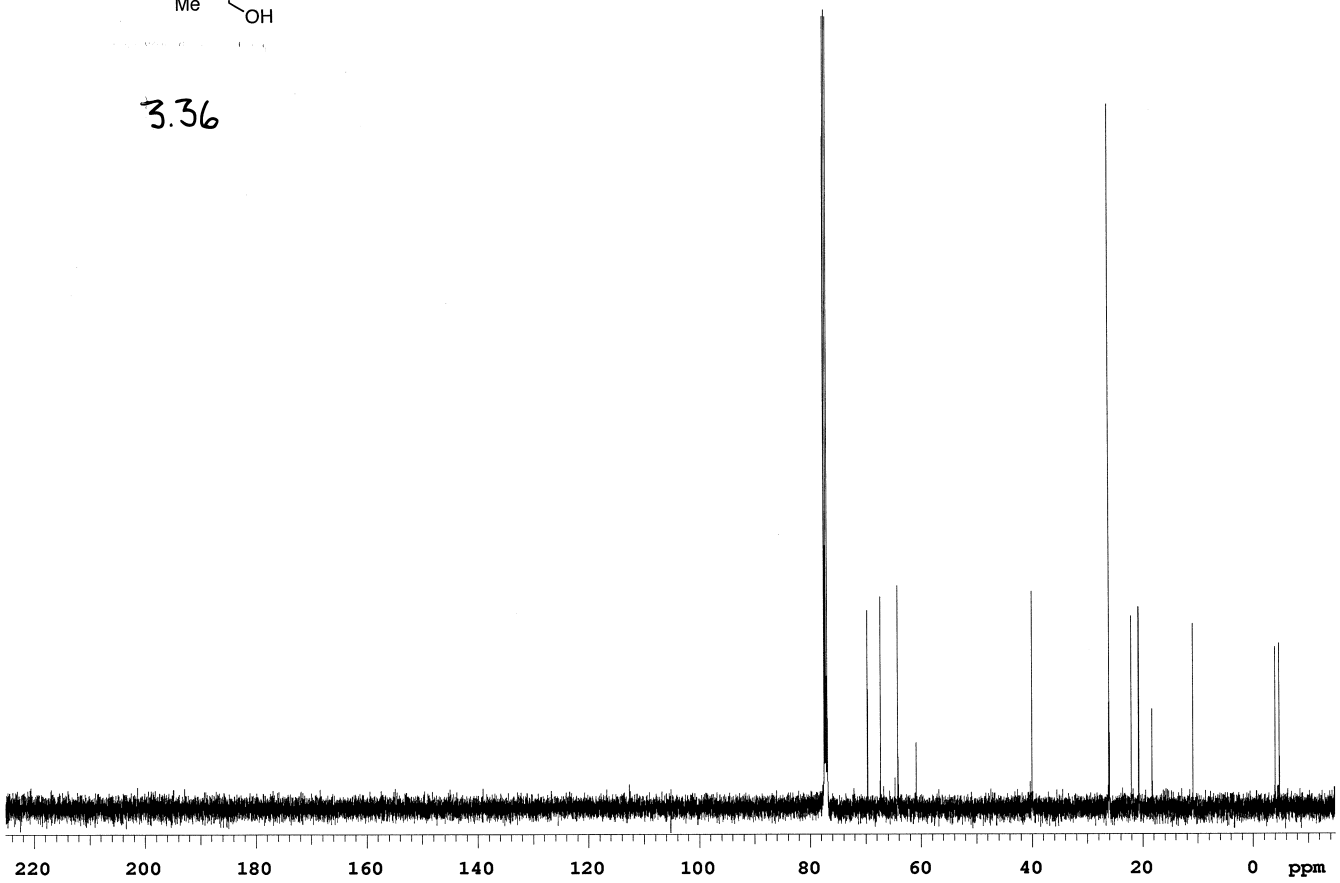
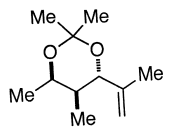
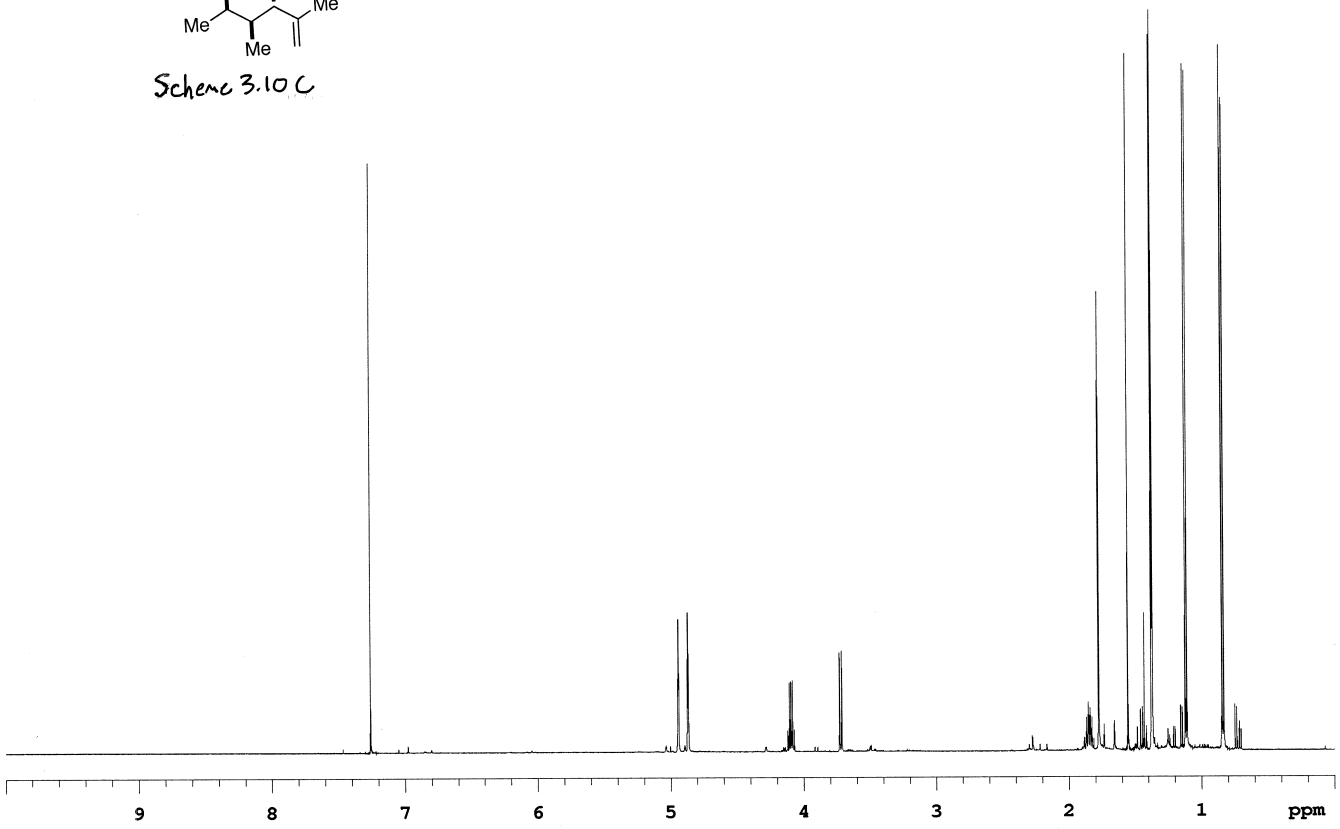
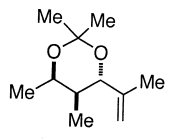


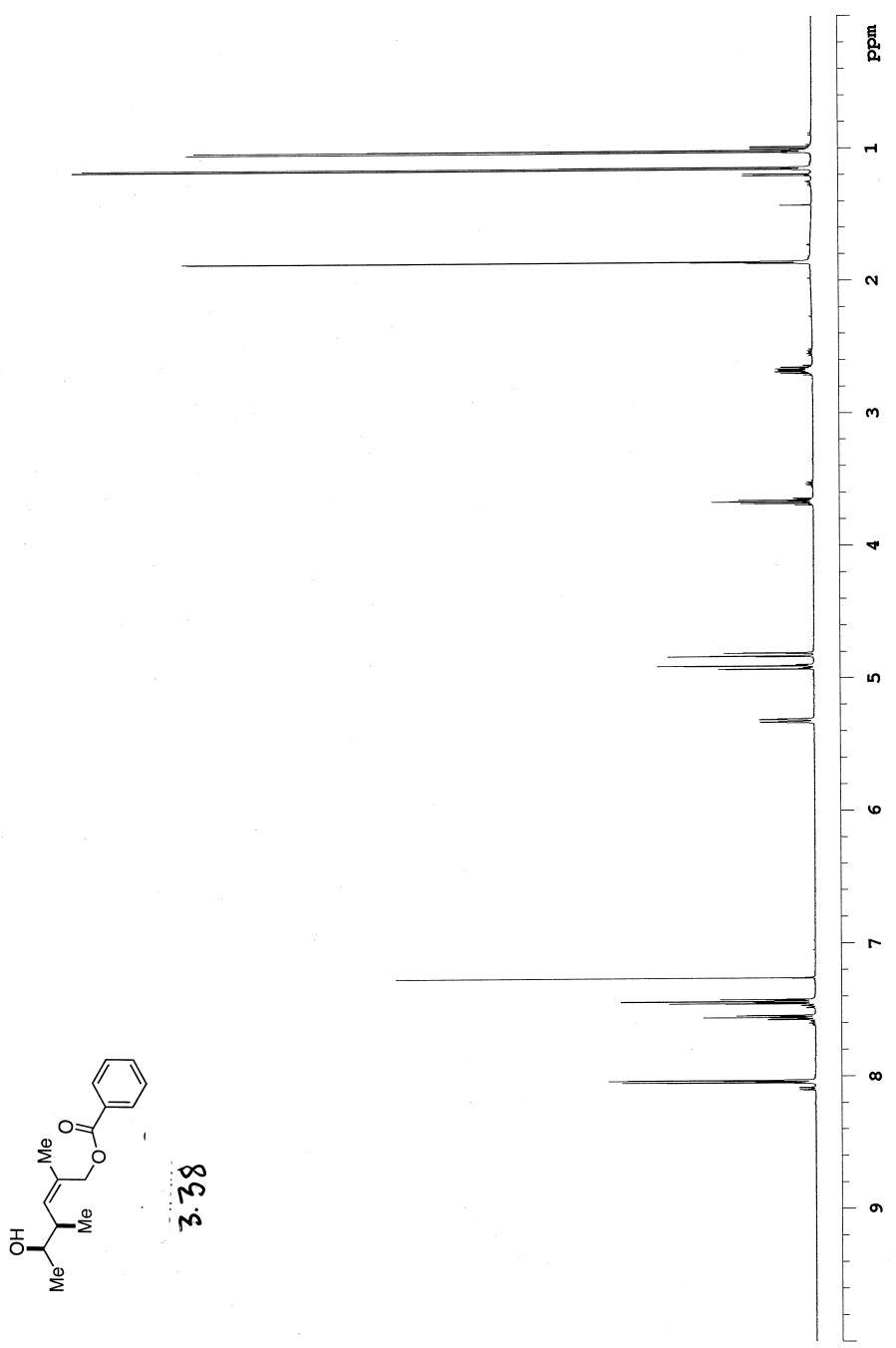


Scheme 3.10 C





Scheme 3.10C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Me
O
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ppm
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5
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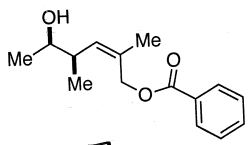
7
8
9



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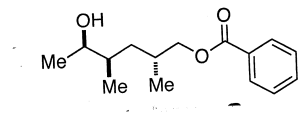

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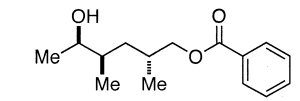

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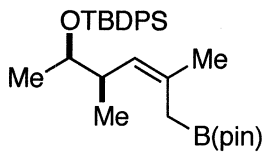

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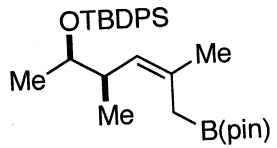

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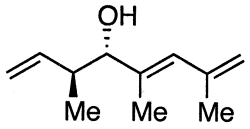

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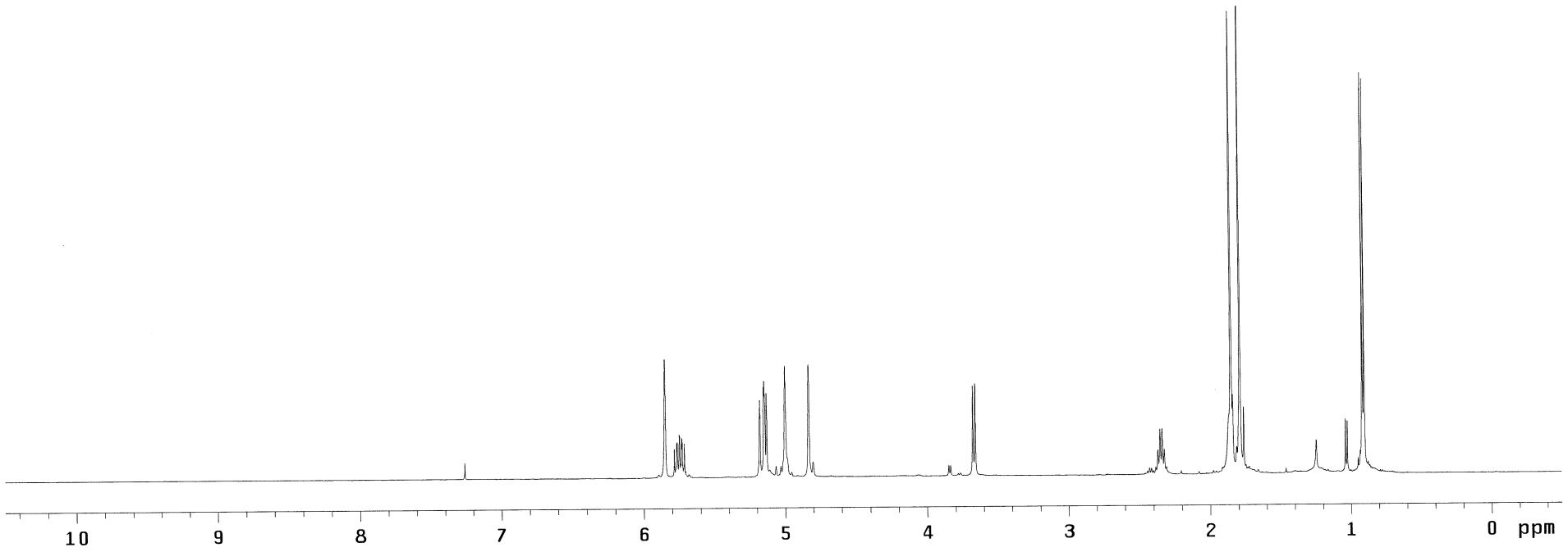

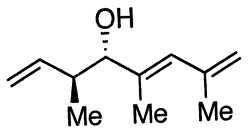

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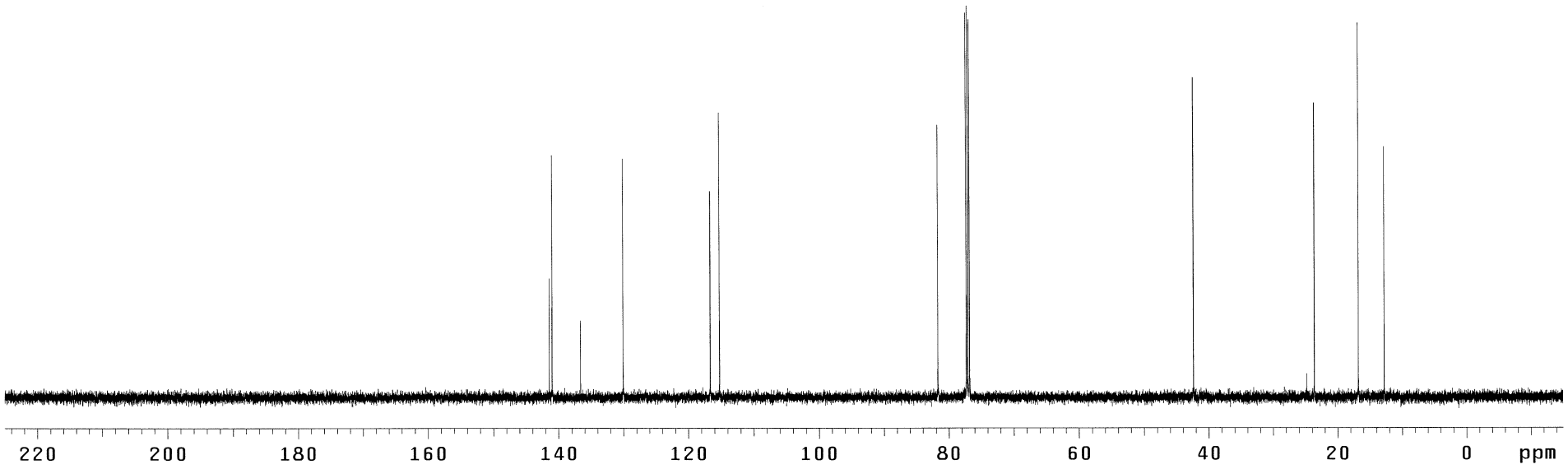

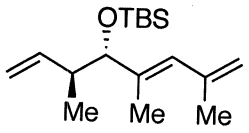

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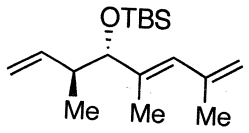

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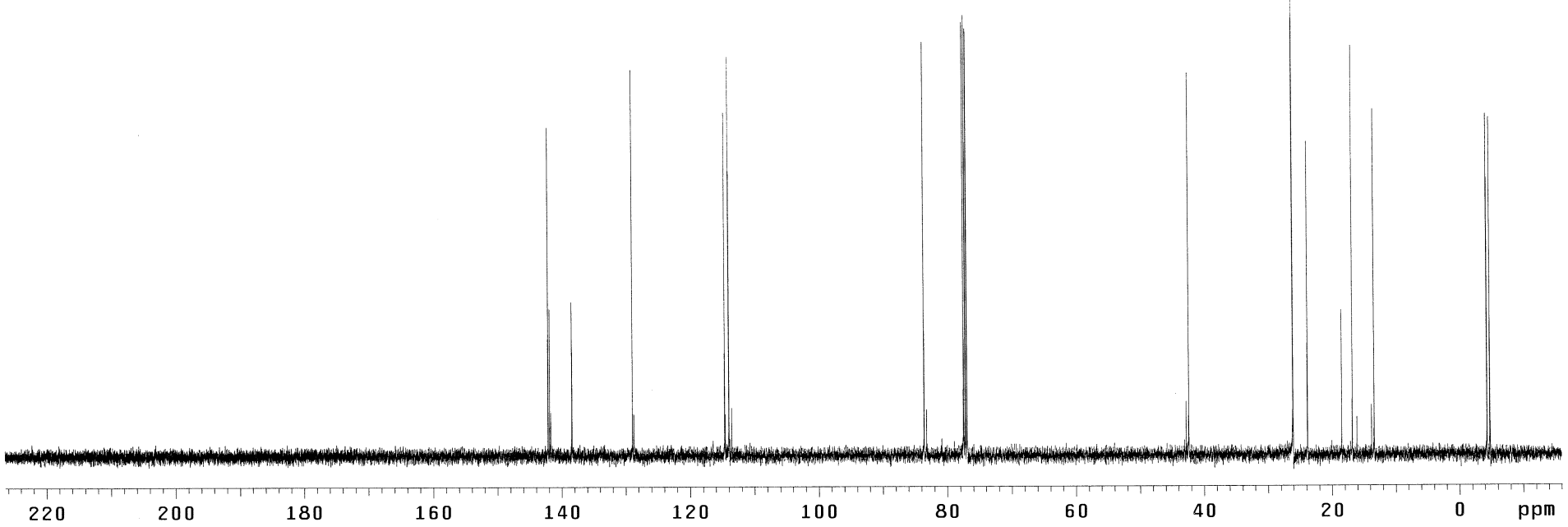

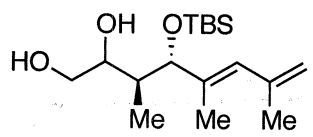

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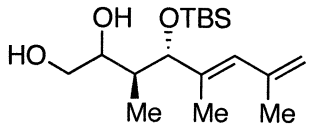

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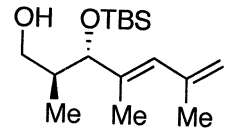

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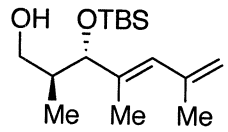

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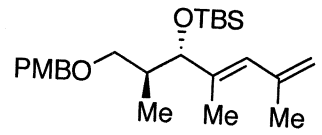

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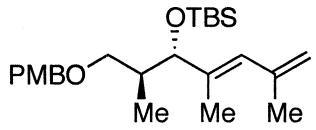

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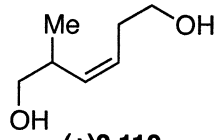

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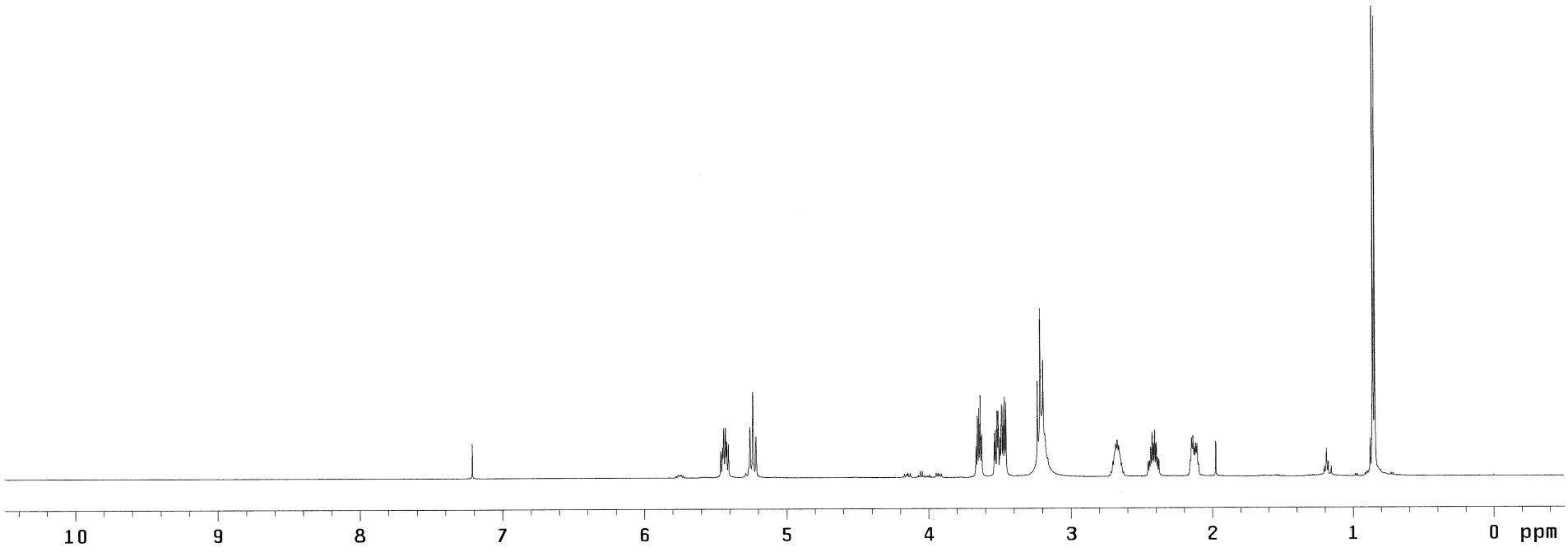

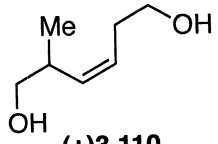

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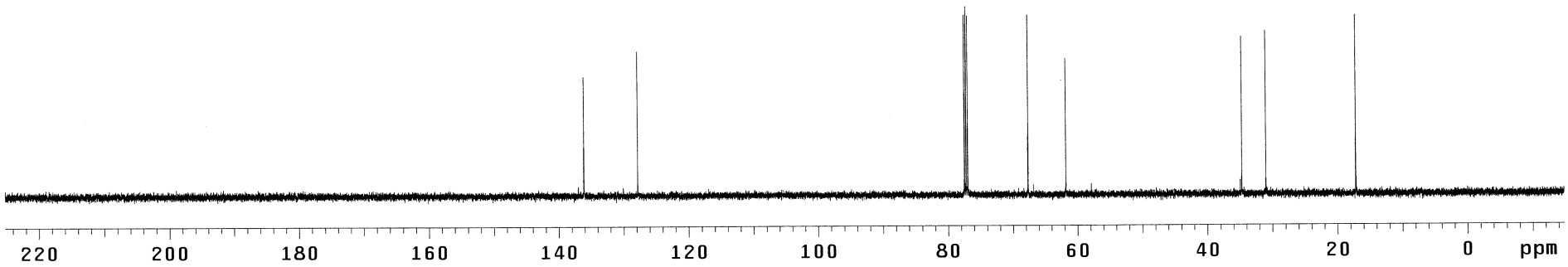

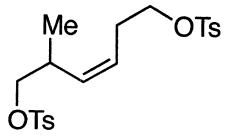

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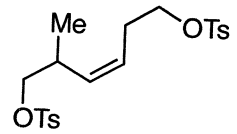

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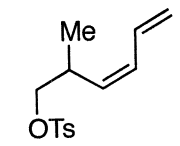

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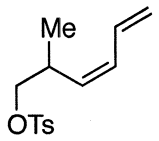

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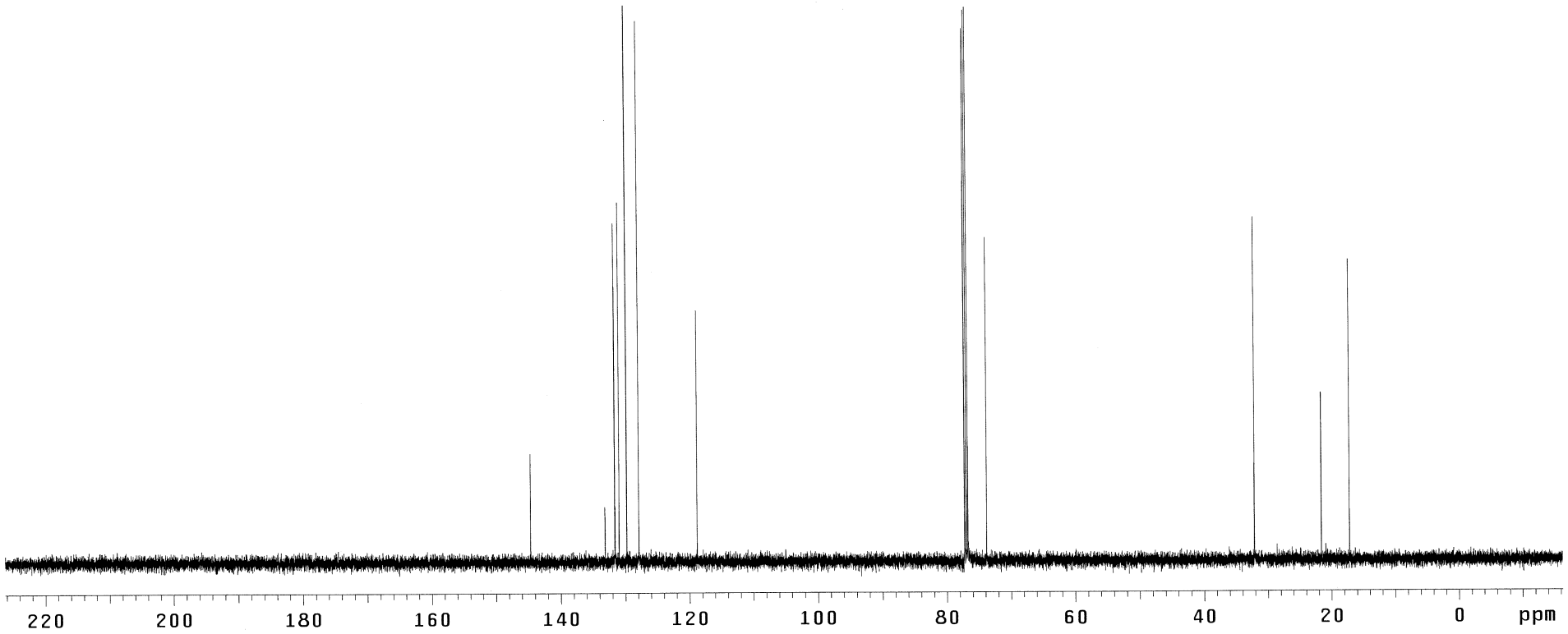

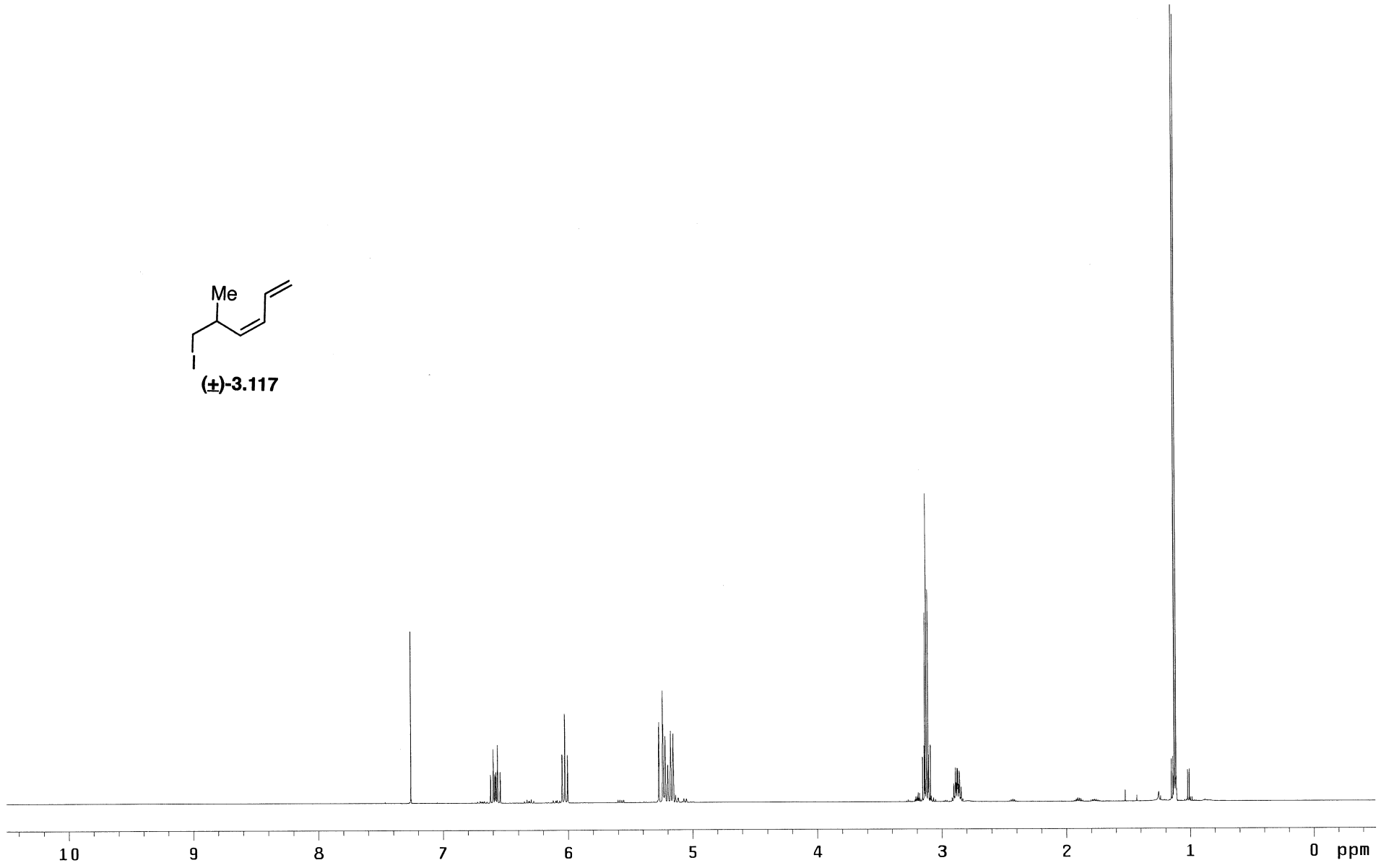
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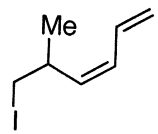
0
ppm



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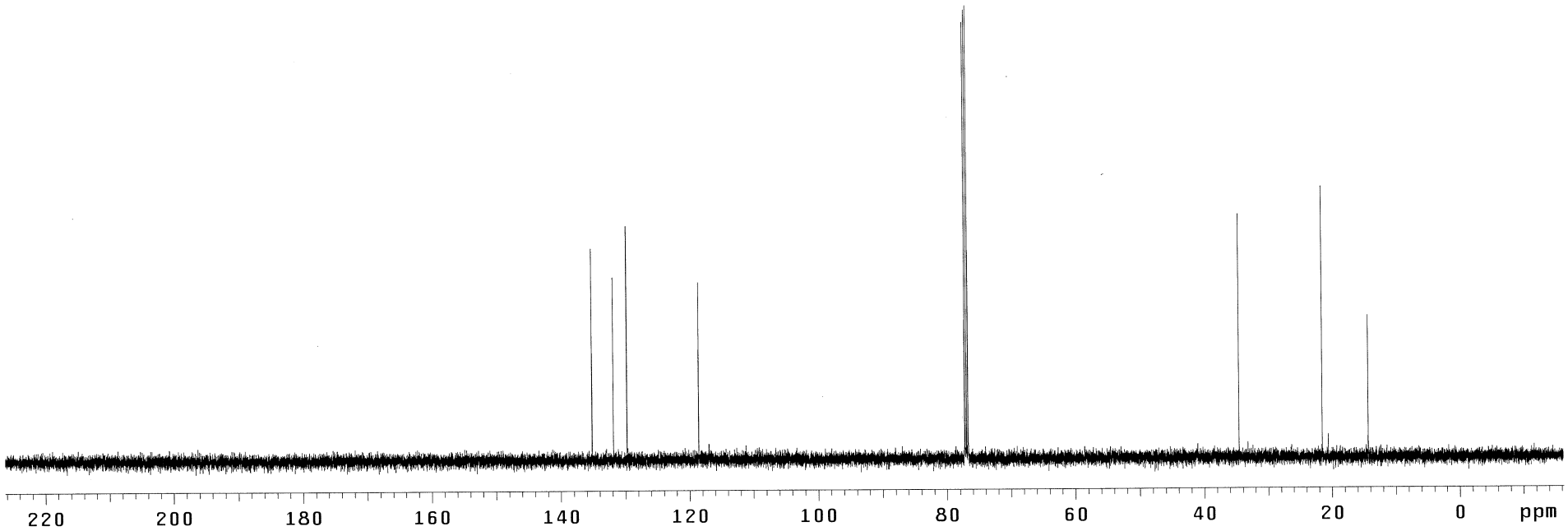
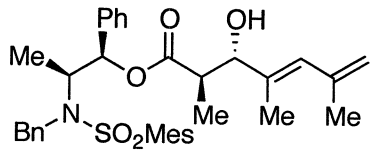
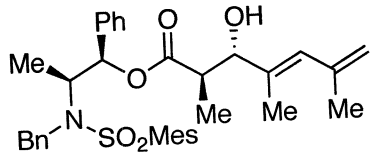


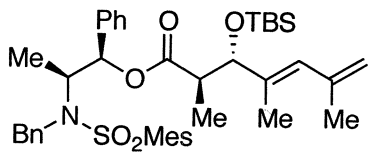


SI-13

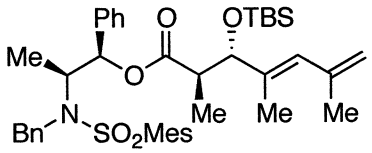

Ph
O
OH
Me
O
Me
Me
Me
Bn
N
SO2Mes

SI-13

220
200
180
160
140
120
100
80
60
40
20
0
ppm

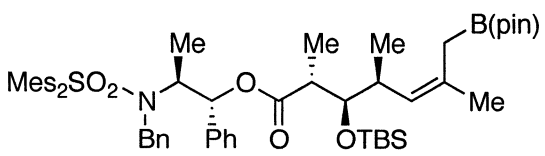


3-132

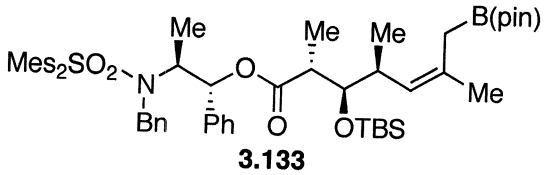

Ph
O
OTBS
Me
O
Me
Me
Me
Bn
N
SO2Mes

3-132

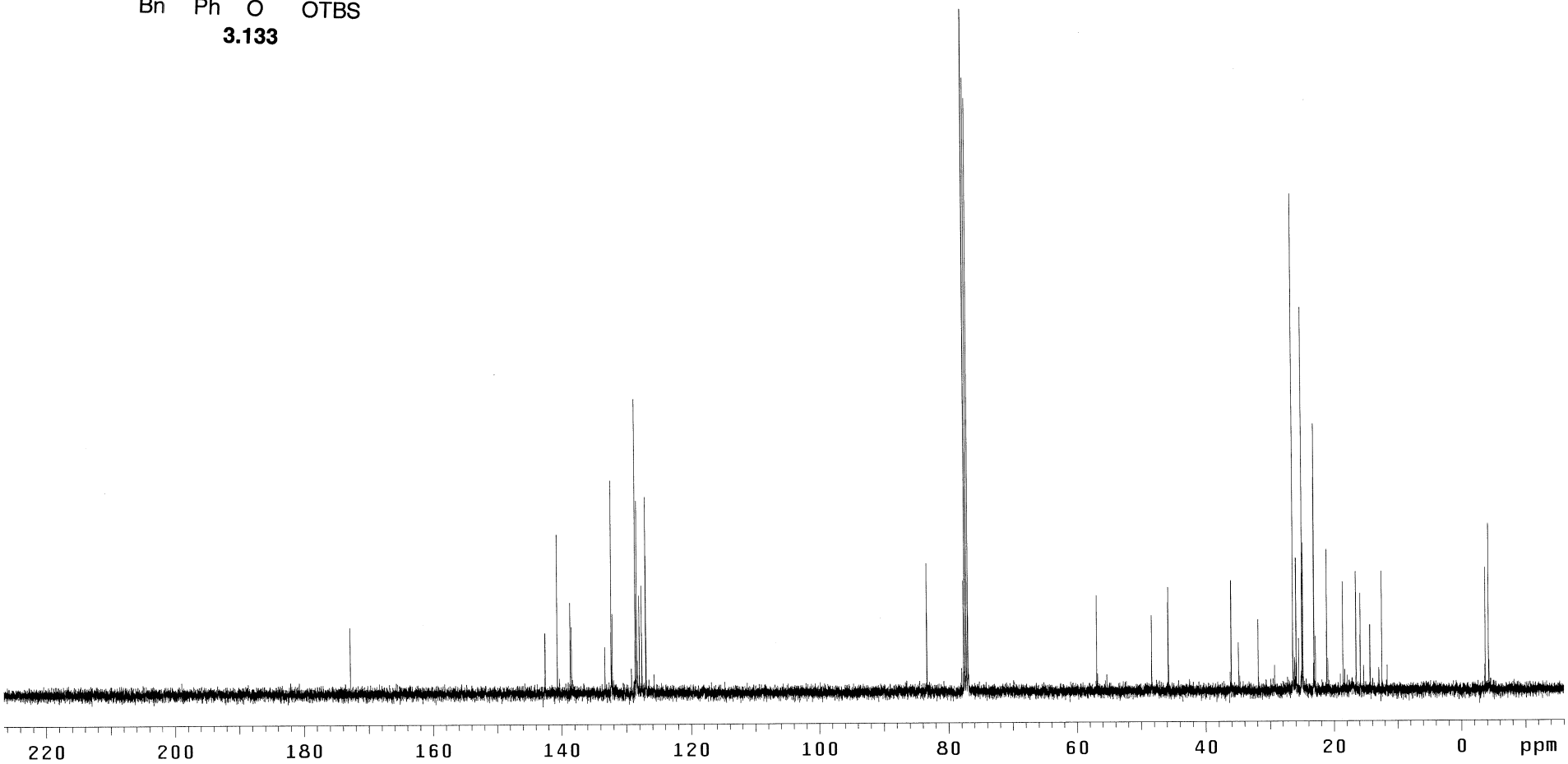
220
200
180
160
140
120
100
80
60
40
20
0
ppm



3.133


Me
Me
Me
B(pin)
Mes2SO2
N
O
Me
Bn
Ph
O
OTBS

3.133


220
200
180
160
140
120
100
80
60
40
20
0
ppm