# Development of Tandem Reaction for Synthesis of Highly Functionalized Carbocycles

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# Development of Tandem Reaction for Synthesis of Highly Functionalized Carbocycles

A Thesis

By

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# Abstract

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Development of Tandem Reaction for Synthesis

of Highly Functionalized Carbocycles

(Under the direction of James P. Morken)

The Suzuki-Miyaura cross-coupling reaction is a common strategy for the formation of a new carbon-carbon bond in organic synthesis. However, intramolecular coupling of allylboron ester and aryl electrophiles has never been reported. Herein, Pd-catalyzed intramolecular cross-coupling of allylboronic pinacol ester and vinyl or aryl bromides is presented. Pt-catalyzed 1,2-diboration of 1,3-dienes give α-chiral bis-allylboronic esters, which can undergo diastereoselective additions to carbonyl electrophiles tethered to vinyl or aryl halides to generate a new allylboronic ester moiety. Under Suzuki coupling conditions, the allylboronic esters moiety and the vinyl bromides in the allylation products can cross-couple in an intramolecular fashion to afford highly substituted four-, five-, and six-membered rings with excellent yields and moderate diastereoselectivity.

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**List of Abbreviations**

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

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

9-BBN: 9-borabicyclo[3.3.1]nonane

Bn: benzyl

Cy: cyclohexyl

dba: dibenzylidene acetone

DCM: dichloromethane

DMAP: 4-dimethylaminopyridine

DMF: dimethylformamide

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

DPEPhos: (oxydi-2,1-phenylene)bis(diphenylphosphine)

dppe: ethylenebis(diphenylphosphine

dppm: diphenylphosphinomethane

dppp: 1,3-bis(diphenylphosphino)propane

*di-t*Buf: 1,1'-bis(di-*tert*-phosphino)ferrocene

dr: diastereomer ratio

EtOAc: ethyl acetate

ee: enantiomeric excess

equiv: equivalent(s)

er: enantiomer ratio

h: hour

HRMS: high resolution mass spectroscopy

IR: infrared spectroscopy

JohnPhos: (2-biphenyl)di-*tert*-butylphosphine

L: ligand

M: molar

mol: mole

NMR: nuclear magnetic resonance

NOESY: nuclear overhauser effect spectroscopy

Nuc: nucleophile

$PCy_3$: tricyclohexyl phosphine

$PPh_3$: triphenylphosphine

Ph: phenyl

pin: pinacol

PMA: phosphomolybdic acid

PEPPSI-IPent: [1,3-Bis(2,6-Di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)

*p*-TsOH: *para*-toluene sulfonic acid

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

RuPhos: 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

SFC: supercritical fluid chromatography

SiO2: silica gel

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

TBAF: tetra-*n*-butylammonium fluoride

TBDPS: *tert*-butyldiphenylsilyl

THF: tetrahydrofuran

XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

## I. Introduction and Background

New strategies to synthesize compounds of different ring sizes are of great interest to synthetic chemists because many natural products and medicinally relevant molecules contain cyclic structures. An intramolecular cross-coupling reaction represents one such methodology for building complex carbocycles efficiently. In the first chapter, previous work on Pd-catalyzed four-membered ring formation and allyl-aryl couplings will be reviewed. In the following chapter our contribution and related chemistry to this area will be discussed.

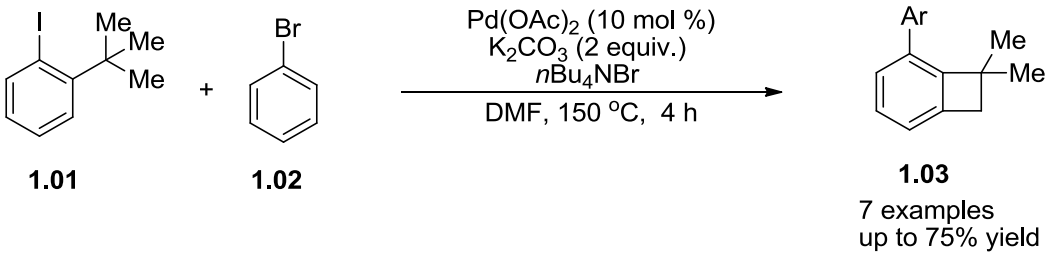
### A. Selective Examples of Pd-Catalyzed Intramolecular Cross-Coupling for the Synthesis of Four-Membered Rings

Cyclobutanes are both important structural elements in active pharmaceuticals and valuable intermediates for organic synthesis[1]. Yet, there are not many reported examples to synthesize these intermediates and most common way to synthesize cyclobutane are [2+2] cycloaddition.[2,3] One of the examples was reported by Dyker[4] and showed that compound **1.01** with bromobenzene **1.02** can undergo tandem intramolecular ring formation to afford benzocyclobutane **1.03** with 10 mol% $Pd(OAc)_2$ (Scheme 1). This is the one of the few examples of a Pd-catalyzed reaction that can generate four-membered ring. However, only a couple substrates are reported and the need to expand the scope of the reaction for synthetic utility has gained attention since it was first reported. After

[1] Sadana, A.K.; Saini, R. K.; Buillups, W. E. *Chem. Rev.* **2003**, *103*, 1539
[2] Eaton, P. E.; Cole, T. W., Jr. *J. Am. Chem. Soc.* **1964**, *86* , 3157
[3] Namyslo, J. C. ; Kaufmann, D. E., *Chem. Rev.* **2003**, *103,* 1485
[4] Dyker, G. *Angew. Chem*., *Int. Ed. Engl.* **1994**, *33*, 103.

extensive research in this area, Baudoin[5] and co-workers introduced an efficient system for the synthesis of benzocyclobutanes (BCB). C-H activation of methyl groups **1.04** with $Pd(OAc)_2$ and P(*t*-Bu)$_3$ leads to a variety of substituted BCB **1.05** which were obtained in moderate to excellent yield (Scheme 2). The limitation of this method is that if only applied to aromatic compounds and vinyl and aliphatic substrates have not been reported.

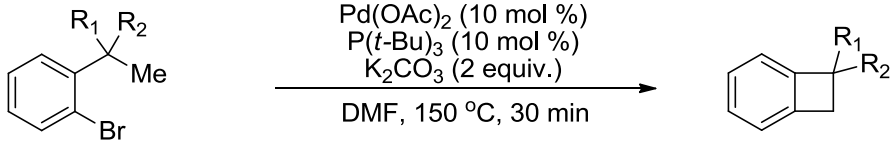
**Scheme 1:** Pd-Catalyzed C-H Activation of Benzylic Alkyl Substrates




**1.01** **1.02** **1.03**

7 examples
up to 75% yield

**Scheme 2:** Pd-Catalyzed C-H Activation of Methyl Groups: Synthesis of Benzocyclobutenes




**1.04** **1.05**

$R_1$ =Me, Et, $CO_2$Me, Propyl, Vinyl,

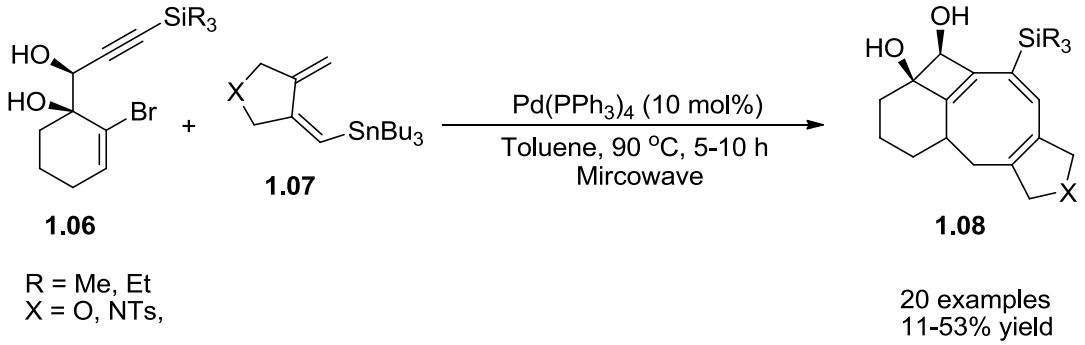
$R_2$ =Me, $CO_2$*t*-Bu, $CO_2$Me, CN,

28 examples
44-92% yield

[5] a) Baudoin, O.; Herrbach, A.; Guerritte, F. *Angew. Chem*., *Int. Ed*. **2003**, *42*, 5736.
b) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, L. J.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157.

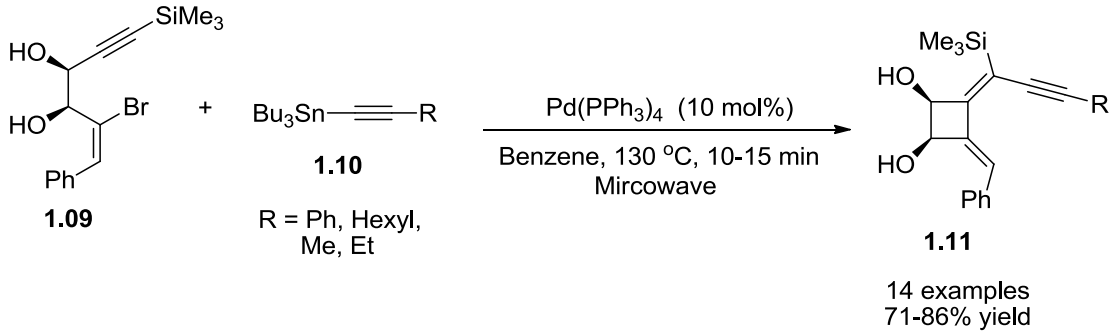
Another strategy to form strained ring systems was presented by Suffert group[6] in 2004. They reported that propargylic diols **1.06** can undergo 4-*exo*-dig cylcocarbopalladation. The intermediate of this reaction can further react with vinyl-stannane **1.07** followed by a conrotatory 8π-electrocyclization to form highly functionalized tetracyclic trienes **1.08** in a cascade sequence (Scheme 3). This is the first reported example of formation for cyclobutanes with vinyl metal reagents. The substrate scope was later expanded[7], reporting that with a palladium catalysis treatment simple γ-bromopropargylic diols **1.09** with tributylstannylated alkynes **1.10** under microwave irradiation afforded desired cyclobutanediol product **1.11** shown in Scheme 4.

**Scheme 3:** Four-*Exo*-Dig Cyclocarbopalladation/8π Electrocyclization: Synthesis of Tricylic Trienes




[6] Salem, B.; Suffert, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2826.
[7] Bour, C.; Suffert, J. *Eur. J. Org. Chem.* **2006**, 1390.

**Scheme 4:** Four-*Exo*-Dig Cyclocarbopalladation of Acyclic Propargylic Diols with Alkynylstannes

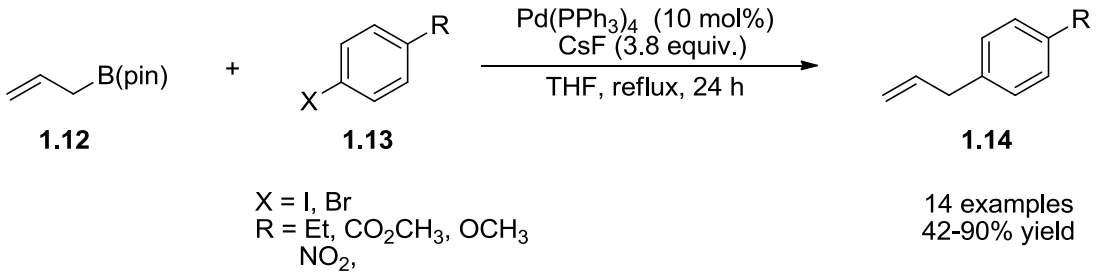



**B. Intermolecular Cross-Coupling Reaction of Allylboronic Acid Derivatives with Aryl Electrophiles**

Cross-coupling reaction of allylic boronic ester with aryl, alkenyl, and allyl group is a synthetically important transformation in organic synthesis because the newly formed carbon-carbon bond is a powerful tool to bring complex fragments together in synthesis. Due to the synthetic utility of this type of reaction, several groups have developed methods to cross-couple allylboronic acid derivatives. One of examples was shown by Kalinin[8] in 1996 and the related example was reported by Behera and Shah[9] in 2005. They used allylboronic acid ester **1.12** with bromo- and iodo-benzene **1.13** as the cross-couple partner to successfully form allylated product **1.14** (Scheme 5). However, this method only works well with simple allylboronic acid pinacol ester (allyl Bpin) and regioselectivity is poor when unsymmetric allylboron derivatives were employed in this reaction.

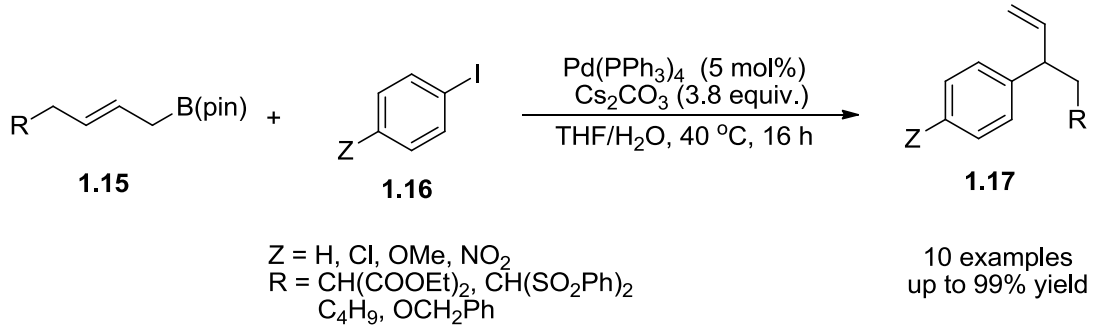
[8] Kalinin, V. N.; Denisov, F. S.; Bubnov, Y. N. *Mendeleev Commun*. **1996**, *6*, 206.
[9] Kotha, S.; Behera, M.; Shah, V. R. *Syn. Lett.* **2005**, *12*, 1877.

**Scheme 5:** Suzuki-Miyaura Cross-Coupling of Allyl Bpin and Aryl Halides




In 2006, Szabó[10] and his co-workers reported that Pd-catalyzed arylation with functionalized allylboronic acids **1.15** can regioselectivly form branched allylic isomer **1.17** (Scheme 6). This is the first example of branched selective allylation without any directing groups or specially designed ligands needed for the reaction. In addition, the new stereogenic carbon that is generated from the branched allylic product creates opportunities for potential asymmetric development of this reaction.

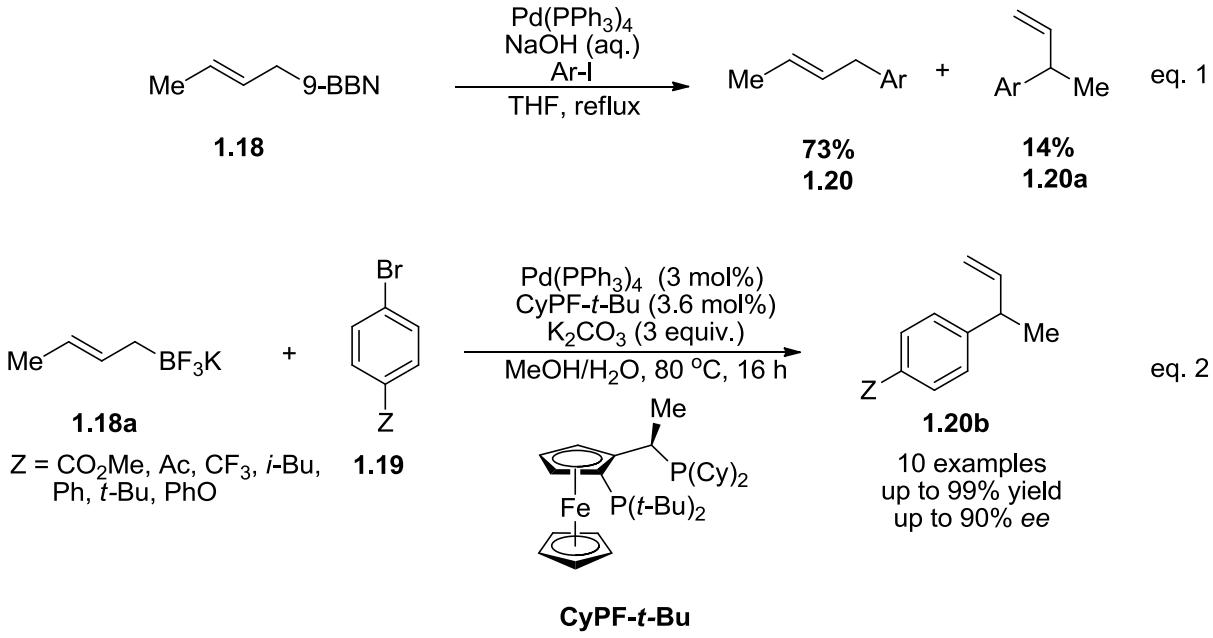
**Scheme 6:** Pd-Catalyzed Regioselective Coupling of Allylboronic Acid with Aryl Iodides




[10] Sebeluis, S.; Olsson, J. V.; Wallner, A.O.; Szabó, J. K. *J. Am. Chem. Soc.* **2006**, *128*, 8150.

Before initial findings of the Szabó group, Miyaura[11] showed that compound **1.18** can cross-couple with iodobenzene in presence $Pd(Ph_3)_4$ and generated a mixture of products **1.20** and **1.20a** (Scheme 7, eq. 1). After extensive ligand screening for this reaction, Miyaura[12] and his co-workers found that CyPF-*t*-Bu (a chiral Josiphos) ligand could be used for asymmetric cross-coupling with allyltrifluoroborates **1.18a** and aryl or 1-alkenyl bromides **1.19** with high selectivity for the branched product **1.20b** (Scheme 7, eq. 2). This is the first example of asymmetric coupling of an allylic boron reagent via the γ-selective cross-coupling with **1.18a** and **1.19b**. Different phosphine ligands have significant impact on regioselectivities of the coupling position and enantioselectivities of the reaction. Thus, first asymmetric coupling of allylic boron reagent with aryl bromides is reported with excellent enantioselectivity.

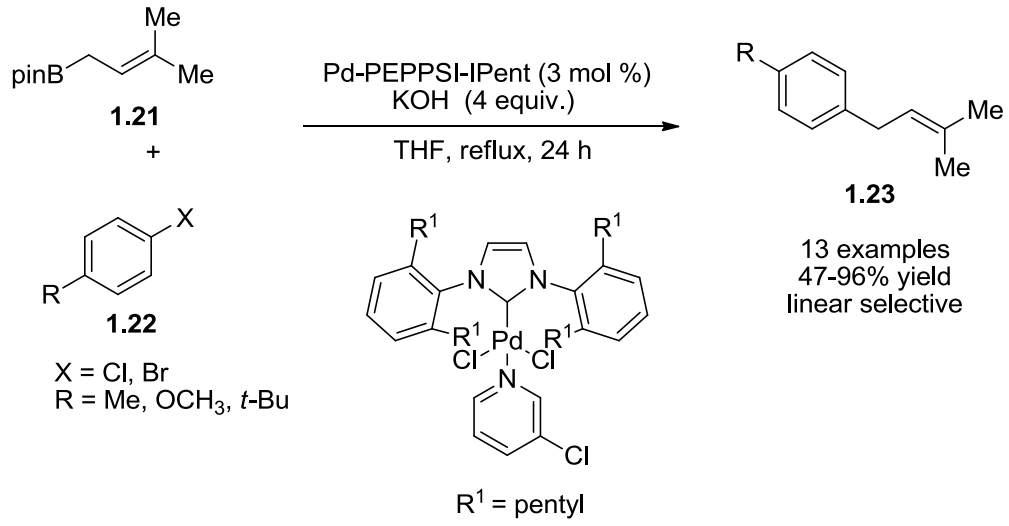
**Scheme 7:** Coupling Reactions of Allylboron compound with Aryl Bromid




[11] Miyaura, N. *Top. Curr. Chem.* **2002**, *218*, 11.
[12]Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett*. **2006**, *35*, 704.

Recently, Organ[13] showed that the sterically bulky Pd-PEPPSI-IPent is an efficient complex in the Pd-catalyzed allylation of allylboronate derivatives **1.21** (Scheme 8). This ligand showed superior α-selectivity to afford product **1.23** in comparison to all other Pd catalysts studied in the cross-coupling of allylboronic acid pinacol ester with a variety of aryl halides. In addition, this is the first example to demonstrate that N-heterocyclic carbenes (NHC) can be used as a ligand in this type of coupling reaction. This method can serve as a complementary method to Miyaura and Szabó's branched selective allylboronate coupling shown above.

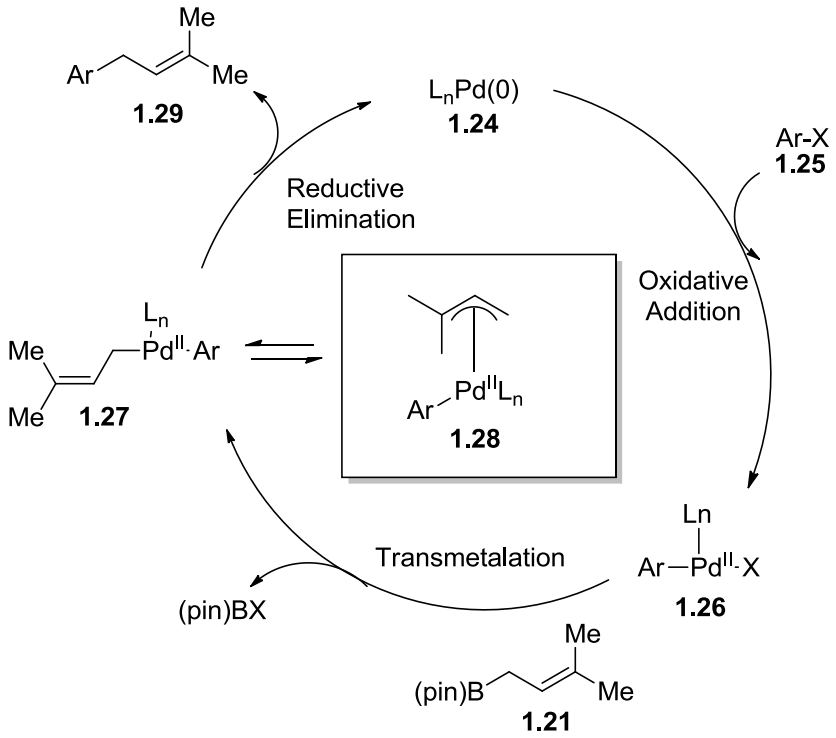
**Scheme 8:** α-Selective Cross-Coupling of Allylboronic Acid Pinacol Ester and Aryl Halides with Pd-PEPPSI-IPent




[13] Farmer, L. J.; Hunter N. H.; Organ, G. M. *J. Am. Chem. Soc.* **2012**, *134*, 17470.

The studies described above on the cross-coupling of allylboron reagents with aryl halide to form carbon-carbon bonds have proposed that this transformation proceeds via a Pd π-allyl complex **1.28** (Scheme 9). After oxidative addition of aryl halide to form Pd(II) species **1.26**, base assisted transmetalation of allyl boron will form $\eta^3-\pi$ allyl **1.28**. Several computational and mechanistic support the proposed mechanism.[14,15]

**Scheme 9:** Proposed Mechanism for Formation of Pd π-Allylic Intermediate



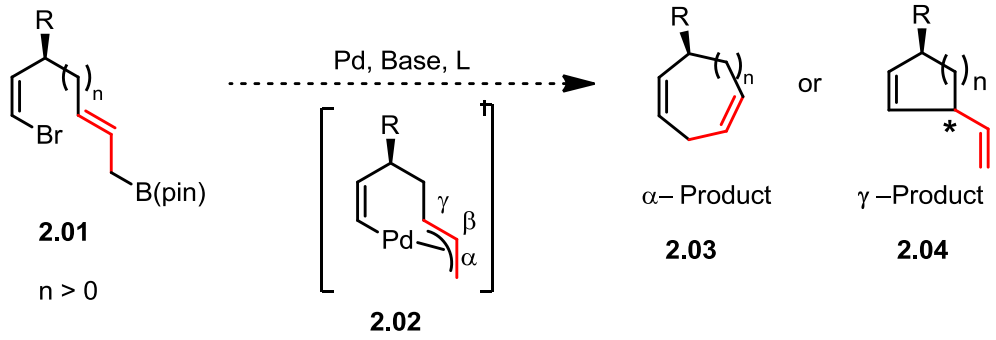

[14] Yasunori, Y.;Takada, S.; Miyaura, N. *Organometallic.* **2009**, *28*, 152.
[15] M. J. Larsson; Szabó, J. K. *J. Am. Chem. Soc*, **2013**. *135*, 443.

## II. Development of Enantioselective 1,2-Diboration of Cis 1,1-Disubsituted-1,3-Dienes and Sequential Allylation and Cross-Coupling

### A. Introduction

Coupling of allylboronic ester derivatives with aryl and vinyl halides is a useful method for the construction of carbon-carbon bonds in organic chemistry. While there are a only few reports of using these coupling partners to form C-C bonds in an intermolecular fashion, no reported examples are known for intramolecular variants. One possible reason for the lack of reports of this type of transformation is the challenge of synthesizing substrates with a vinyl bromide tethered to an allylboronic ester such as **2.01** in an enantioselective fashion (Scheme 10). Another foreseeable challenge is the possible formation of regioisomeric products; during the reaction, the Pd π-allyl intermediate **2.02** can reductively eliminate at either the α- or γ-position, which would afford a larger ring size product **2.03** or a smaller ring size product **2.04** respectively. Recently, our group has developed a method to synthesize intermediates **2.01** efficiently, which could enable us to examine whether **2.01** can undergo intramolecular cross-coupling to form different ring sizes product **2.03** or **2.04** selectively. In the next chapter, methods to synthesize **2.01** and related chemistry will be discussed.

**Scheme 10: Intramolecular Allylboronic Ester Cross-Coupling**



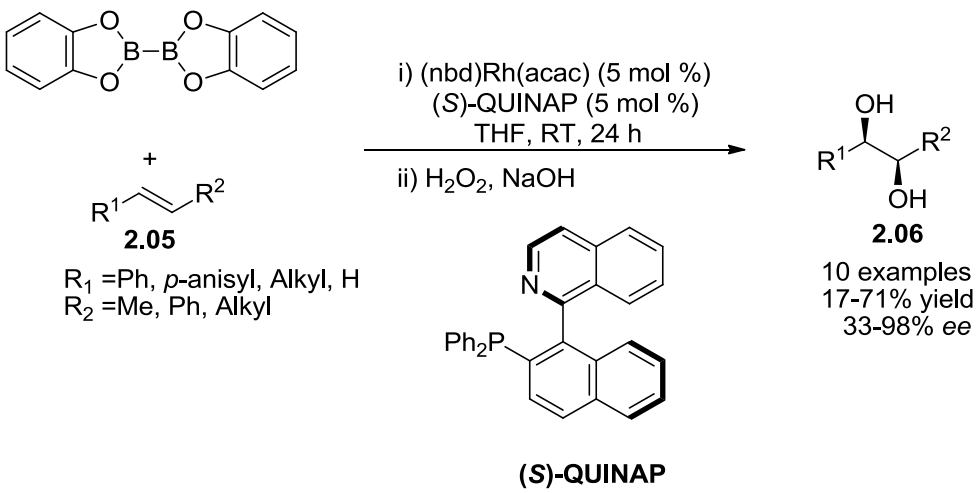

## B. Background

### i) Previous Research on Enantioselective Alkene/Alkyne Diboration

In 2003, our group[16] reported the first enantioselective diboration of alkenes with $B_2(cat)_2$ under the influence of chiral Rh(I)-QUINAP complex. Several terminal and internal alkenes **2.05** were shown to undergo diboration to give the desired optically active 1,2-diols **2.06** after oxidation (Scheme 11). Although this reaction accomplished the desired transformation, the process is impractical for large-scale implementation due to the cost of the QUINAP ligand and $B_2(cat)_2$. In addition, terminal alkenes suffer from low yields and poor enantioselectivities.

[16] Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702.

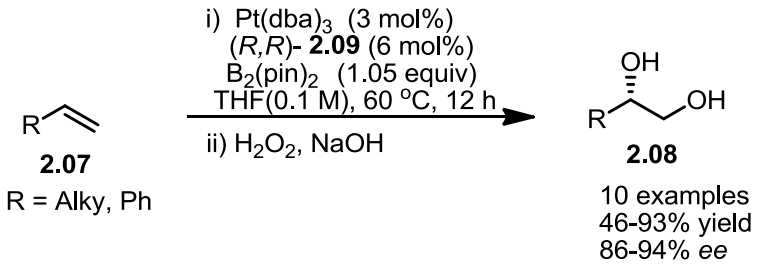
**Scheme 11:** Rh-Catalyzed 1,2-Diboration of Alkenes and $B_2(cat)_2$.

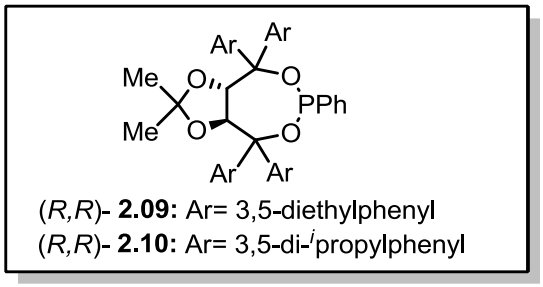



In 2010, we[17] reported that Pt-catalyzed diboration can overcome this limitation and can enhance the reactivity toward terminal alkenes. In the presence of a catalytic amount of $Pt(dba)_3$ and TADDOL-phosphonite ligand **2.09**, alkenes smoothly reacted with $B_2(pin)_2$ and, followed by oxidation, afforded diol **2.08** in up to 93% yield and 94% *ee* (Scheme 12). Notably, this catalyst system was a significant improvement over the Rh-cataylzed alkene diboration due to shorter reaction time, cheaper catalyst and reagents.

[17] Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *131,* 13210.

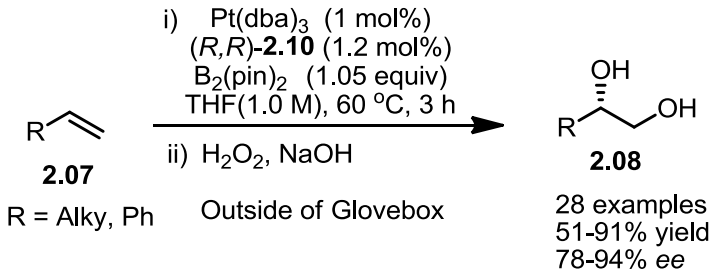
**Scheme 12:** Pt-Catalyzed 1,2-Diboration of Alkenes and $B_2(pin)_2$




Recently, after extensive investigation of catalyst systems and reaction condition, it was found that alkene diboration can be accomplished in three hours with only 1 mol% $Pt(dba)_3$ and 1.2 mol% (*R,R*)-**2.10** (Scheme 13). [18] The substrate scope and enantioselectivity of this reaction were also expanded and improved. In addition, alkene diboration can be performed outside the glovebox, which makes this method more applicable and suitable in both academic and industrial settings.

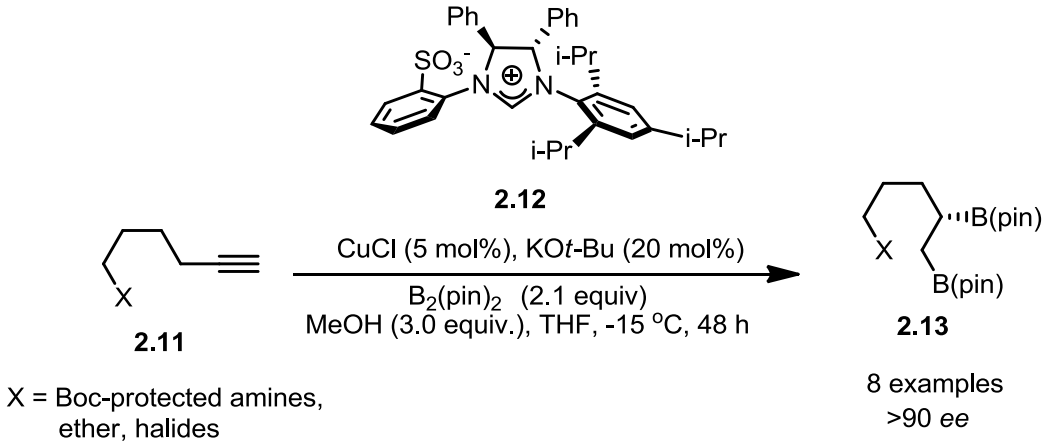
**Scheme 13:** Improved Pt-Catalyzed 1,2-Diboration of Terminal Alkenes with $B_2(pin)_2$




[18] Coombs, R. J.; Haeffner, L. T.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc*. **2013**, *135,* 11222.

An alternative route to access those 1,2 bis(boronate) esters has been reported by Hoveyda.[19] Terminal alkynes were shown to undergo Cu-catalyzed double-hydroboration with $B_2(pin)_2$ and chiral N-heterocylic carbene (NHC) ligand **2.12** to afford enantioenriched 1,2-bisboronates (Scheme 14).[20] The reaction is tolerated with Boc-protected amines, ether, halides and propargylic heteroatoms with excellent enantioselectivities.

**Scheme 14:** NHC-Copper-Catalyzed Bis(hydroboration) of Terminal Alkynes

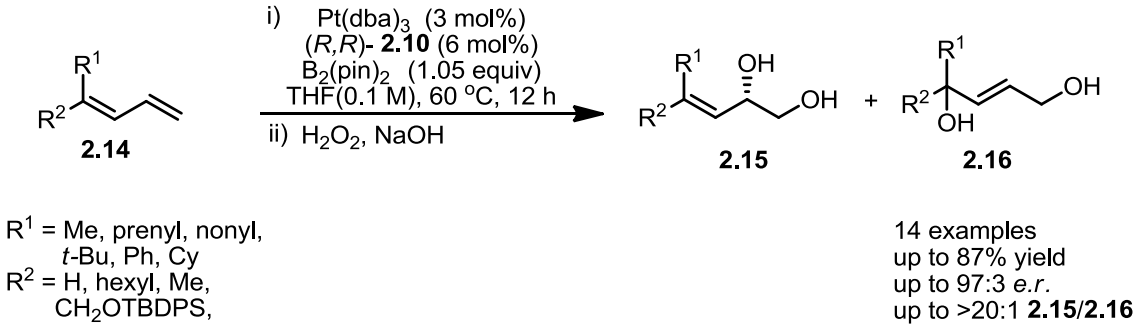



[19] Jang, W.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859.
[20] (a) Hoveyda, A. H.; Lee, Y.; Jang, H., *J. Am. Chem. Soc*. **2009**, *131*, 18234. (b) Hoveyda, A. H.; Lee, Y., *J. Am. Chem. Soc*., **2009**, *131*, 3160.

**ii) Development of Enantioselective 1,2-Diboration of *Cis*-1,1-Disubsituted 1,3 Dienes**

In 2011, our group[21] developed a catalytic enantioselective method for the 1,2-diboration of *cis*-1,1-disubsituted-1,3-dienes **2.14** using $Pt(dba)_3$ and (*R,R*)-**2.10** (Scheme 15). The 1,2-diboration product was formed preferentially over the 1,4-diboration product. The reaction tolerated a variety of functional groups with excellent enantioselectivity.

**Scheme 15:** Pt-Catalyzed 1,2-Diboration of *Cis*-1,1-Disubsituted-1,3-Dienes and $B_2(pin)_2$

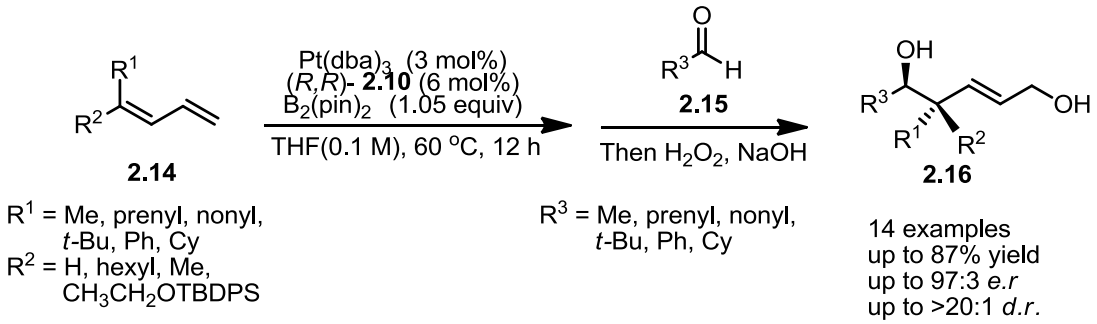



One special feature of the 1,2-bis(boronate) resulting from 1,2-diboration of *cis*-1,3-dienes **2.14** is that it reacts as a chiral allylboronate. According to studies by Hoffmann[22], the chiral allyboronate can undergo allylation reaction with aldehydes **2.15** in a diastereoselective fashion. After the diboration of *cis*-1,3-dienes, addition of

[21] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem., Int. Ed*. **2011**, *51*, 521.
[22] Hoffmann, R. W. *Pure Appl. Chem*. **1988**, *60*, 123.

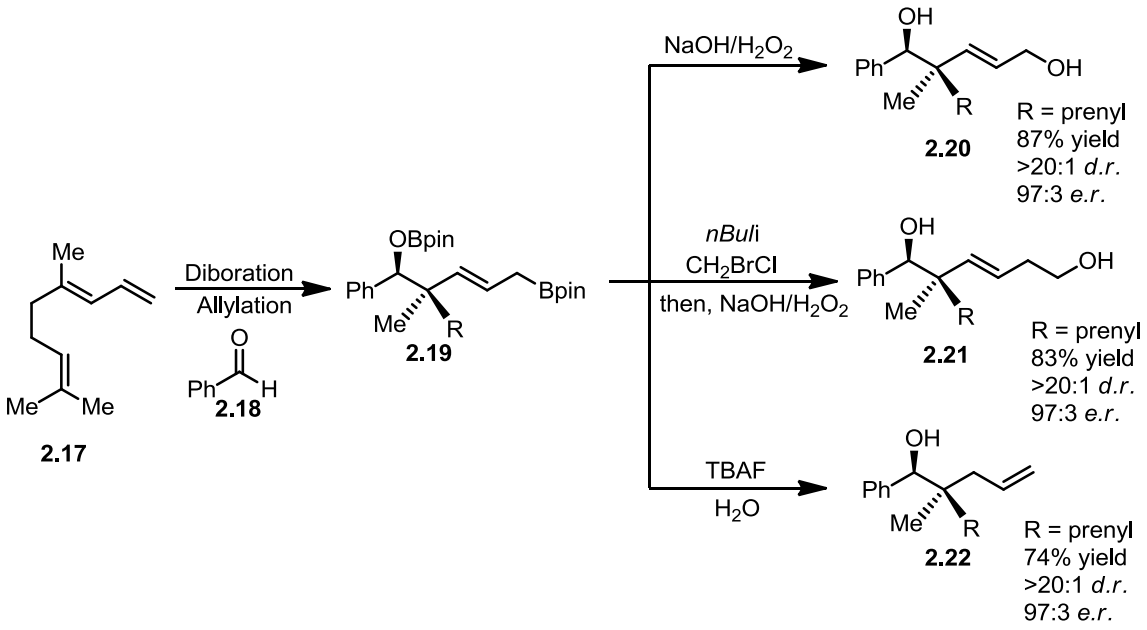
aldehyde followed by oxidative work-up yielded allylation product **2.16** in moderate to excellent yields with greater than 20:1 diastereoselectivity (Scheme 16).

**Scheme 16:** Asymmetric Allylboration of Aldehydes




This method is appealing because there are several ways to functionalize this allylboronate product *in situ*. As shown in Scheme 17, the diene **2.17** was subjected to diboration and treated with benzaldehyde **2.18** for allylation. After oxidative workup, it afforded allylic alcohol **2.20**. An alternative way to manipulate the intermediate allylboronate is to subject it to homologation conditions with bromochloromethane and *n*-BuLi to deliver the homoallylic alcohol product **2.21**. Finally, the allylboronation product can undergo protodeboronation with TBAF and water to obtain product **2.22**.

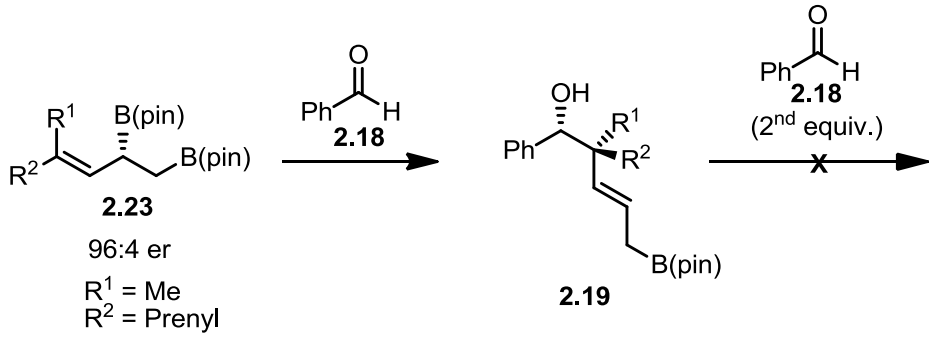
**Scheme 17:** Diboration/Allylation/Functionalization of 1,3-Diene



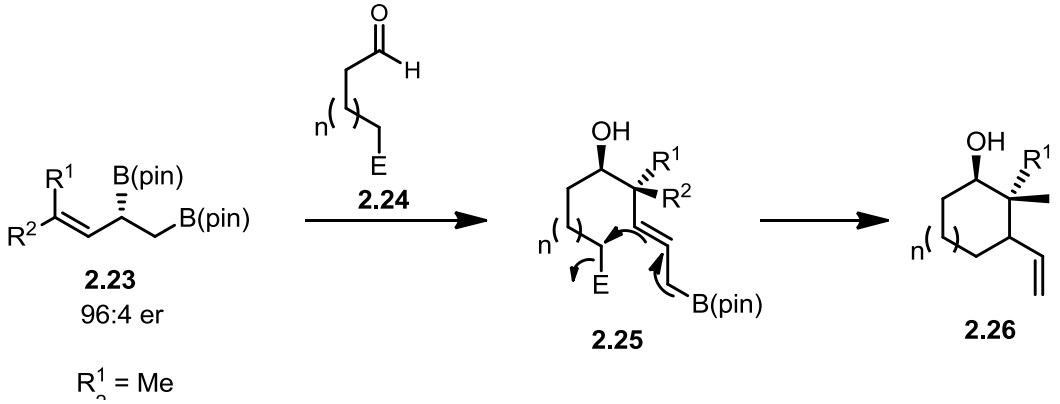

### iii) Development of Enantioselective Cascade Reaction for Diboration/Double Allylation with 1,4-Dicarbonyl Compounds

The first allylboron reagents **2.23** that were generated from diboration reacted smoothly with aldehyde **2.18** to generate a new allylboronic ester **2.19**. Over-allylation was never observed with 1,1-disubsituted dienes because of the steric hindrance imposed from the adjacent carbon quaternary center (Scheme 18). One could envision that the allylboron moiety **2.25** (Scheme 19) could overcome this steric barrier through an intramolecular cyclization to give a complex carbocyclic structure **2.26**. One way to utilize the allylboronate to achieve a ring-closing reaction is to use bis-functional electrophiles **2.24**.

**Scheme 18**: Diboration/Allylation of *Cis*-1,1-Disubsituted-1,3-Dienes




**Scheme 19:** Diboration of *Cis*-1,1-Disubsituted-1,3-Dienes and Double Allylation with Bis-Electrophiles

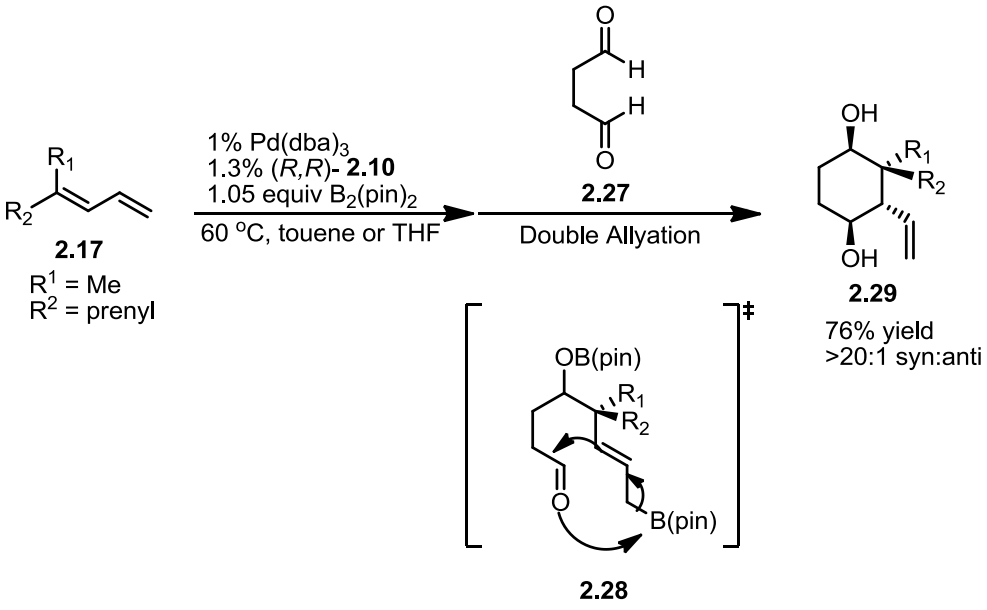



In 2013, our group[23] found that diboration of **2.17** followed by allylation with dicarbonyls **2.27** provides a strategy to build complex carbocycles rapidly. After the allylboronate reacted with one of the carbonyl groups in the electrophile, a second allylboron **2.28** is generated that can further react intramolecularly to afford highly

[23] Ferris, G. E.; Hong, K.; Roundtree. I. A.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 2501.

complex 1,4-cyclic diols **2.29** (Scheme 20). This methodology is limited to dialdehydes which formed six-membered rings. By replacing the dicarbonyl with more stable bis-electrophiles such as bromoaldehydes, we hoped to overcome this limitation and to expand the substrate scope including four-, five-, and seven-membered ring systems.

**Scheme 20:** Diene Diboration/Double Allylation of 1,4 Dicarbonyls



## C. Research Goal

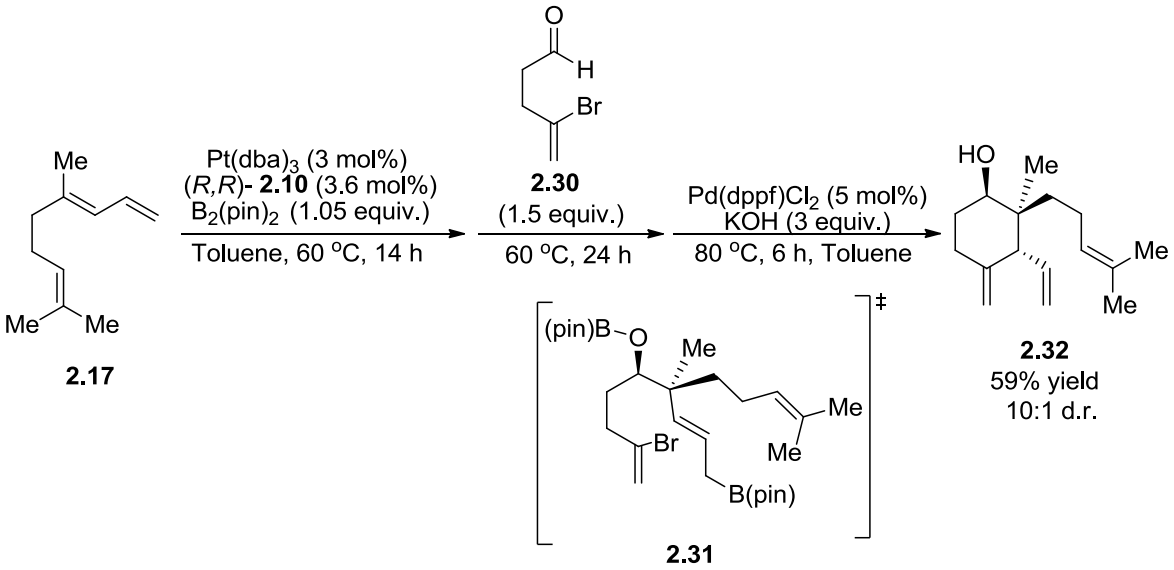
Coupling of allylboronic ester with aryl and vinyl halides is a very powerful method for the formation of carbon-carbon bonds in organic synthesis. While there are some notable examples of using these coupling partners to form new carbon-carbon bonds in an intermolecular fashion, no reported examples are known for intramolecular variants. Developing a method for this type of cross-coupling in an intramolecular fashion could provide a new way for preparing cyclic structure of varying ring sizes.

Inspired by our success in double allylation using dicarbonyls together with diboron reagents derived from dienes to form highly complex 1,4-cyclic diols **2.29**, we decided to investigate the use of different bi-functional electrophiles, such as bromoaldehydes to see if they will react in an intramolecular fashion under Suzuki cross-coupling reaction conditions.

## D. Preliminary Result with Intramolecular Allylboronic Ester Cross-Coupling

In the course of this investigation, it was discovered that allylboronic esters **2.31** generated from diboration/allylation can efficiently undergo ring closure under Pd-catalysis. In the presence of $Pd(dppf)Cl_2$ and KOH, allylboron intermediate **2.31** cross-couples in an intramolecular fashion to afford complex carbocycle **2.32** in a highly selective manner (Scheme 21). In rest of the thesis, diastereoselectivity refers to selectivity of the vinyl group **2.32** because the configuration of the hydroxyl group and quaternary center is already set through diboration/allylation step and generally occurs in >20:1 selectivity.

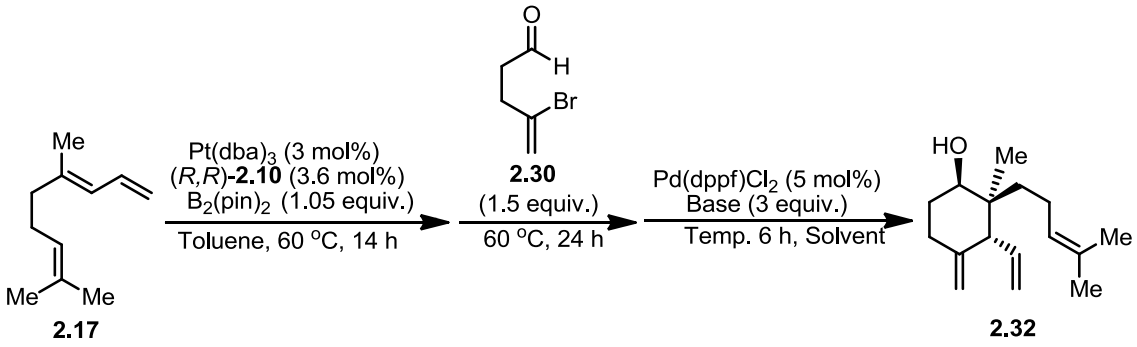
**Scheme 21**: One Pot Diboration/Allylation/Pd-Catalyzed Intramolecular Cross-Coupling



**(i) Development of Pd-Catalyzed Intramolecular Coupling Reaction**

In order to optimize the intramolecular coupling reaction, diene **2.17** and bromoaldehyde **2.30** were chosen as model substrates to study while screening a variety of reaction conditions (Table 1). Interestingly, our initial result with typical Suzuki cross-coupling conditions affords compound **2.32** as the major product with 10:1 d.r. (entry 1) and the selectivity was not sensitive to reaction conditions. Preliminary base screening revealed that hydroxide bases are most efficient in the allylboron cross-coupling (entries 1, 2). When weaker bases were employed, only a trace amount of product was isolated (entries 3, 4). A variety of solvents were also investigated to probe impact on both the yield and diastereoselectivity. With the use of more polar solvents such as 1,4-dioxane and acetonitrile (entries 5, 6), the reaction did not occur. When switching to toluene (entry 7), the product was obtained in 40% yield with 10:1 d.r.. With toluene affording the most promising result, several more experiments were carried out at different temperatures. At lower reaction temperatures (entry 8), lower conversion was observed without any change in diastereoselectivity. The best result was achieved at 80 $^{o}$C with toluene, giving 59% yield of the desired product. The screening results suggested that bases, temperatures and solvents have little effect on the diastereoselectivity of this reaction. One attractive feature for this type of tandem reaction is that one purification is needed through a three-step sequence.

**Table 1:** Optimization of Suzuki-Miyaura Reaction Conditions

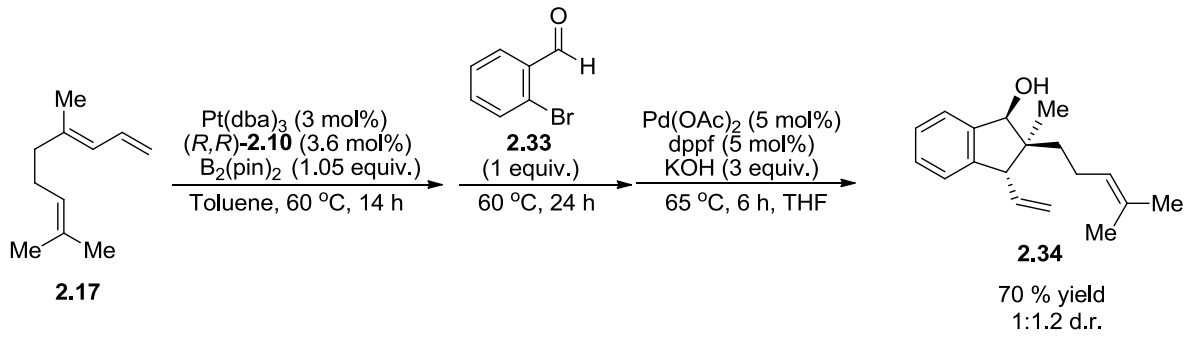



| Entry | Base | Solvent | Temp. | Isolated Yield |
|---|---|---|---|---|
| 1 | NaOH | THF | 60 °C | 51% |
| 2 | KOH | THF | 60 °C | 53% |
| 3 | CsF | THF | 60 °C | Trace |
| 4 | $Cs_2CO_3$ | THF | 60 °C | Trace |
| 5 | KOH | 1, 4-dioxane | 60 °C | Trace |
| 6 | KOH | acetonitrile | 60 °C | Trace |
| 7 | KOH | Toluene | 60 °C | 40% |
| 8 | KOH | Toluene | 40 °C | 30% |
| 9 | KOH | Toluene | 80 °C | 59% |

## E. Development of Pd-Catalyzed Intramolecular Coupling for Five-Memebered Products

When the optimized conditions were applied to 2-bromobenzaldehyde **2.33**, an unknown byproduct (suspected to be protodeboronation) was formed in significant quantities. To eliminate the byproduct formation, the solvent was switched to THF and temperature lowered to 65°C. The reaction proceeded smoothly to give product **2.34** in 70% yield and 1.2:1 d.r. (Scheme 22).

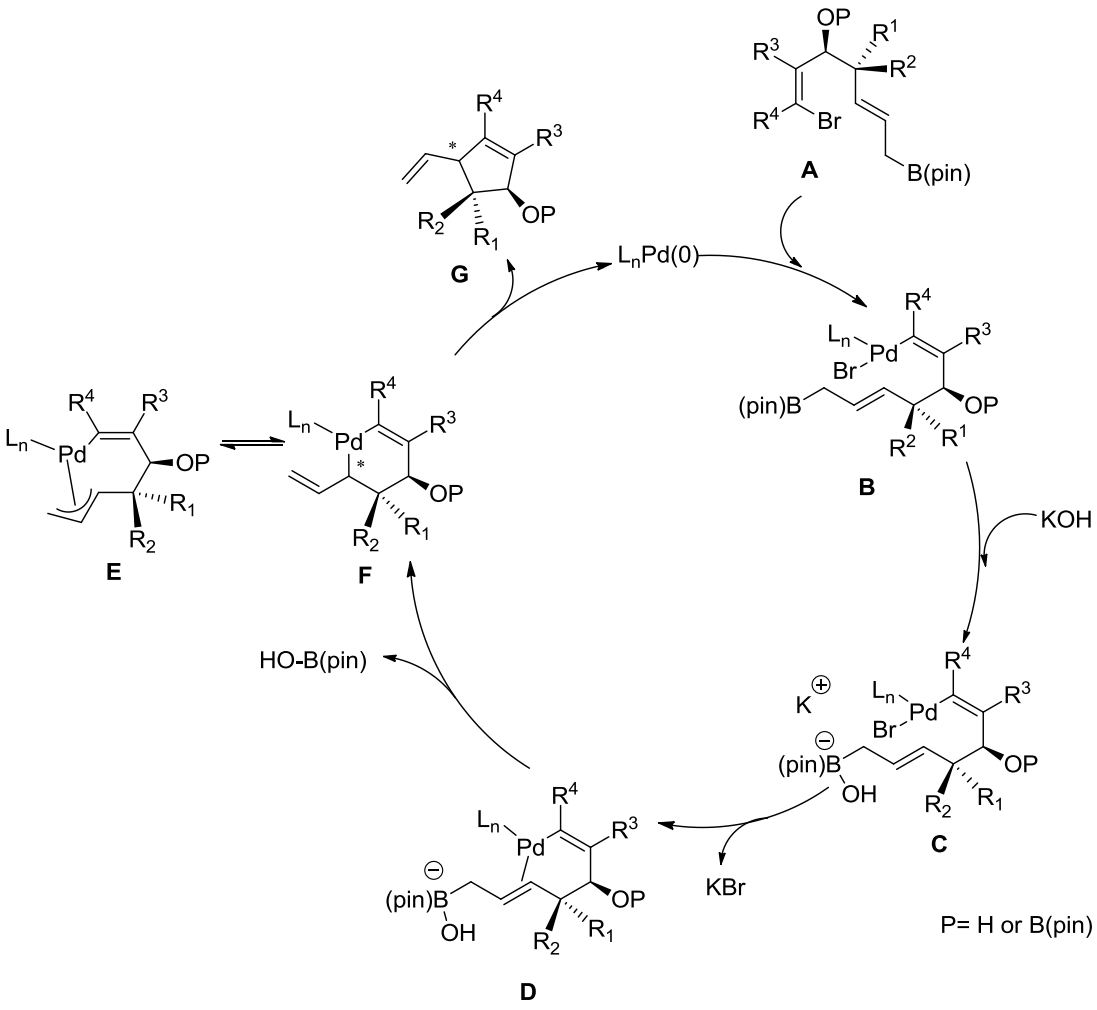
**Scheme 22:** Initial Result for Five-member Ring




The proposed catalytic cycle for the cross-coupling reaction is shown in Scheme 23. The cycle begins with oxidative addition of vinyl bromide intermediate **A** with Pd(0) to form complex **B**. After KOH activates allylboron intermediate **C** and Pd coordinates to the alkene in **D**, transmetalation occurs generating π-allyl complex **E** or **F**. Reductive elimination gives the product **G** and regenerates Pd(0). It is possible that the stereo-determining step for this reaction is reductive elimination. We suspected different ligands should have an impact on the diastereoselectivity for this type of cross-coupling reaction. Slowing the reductive elimination could allow for complete isomerization of the Pd-

bound allyl group and it can lead to more stable diastereomer, thus resulting in high diastereoselectivty.

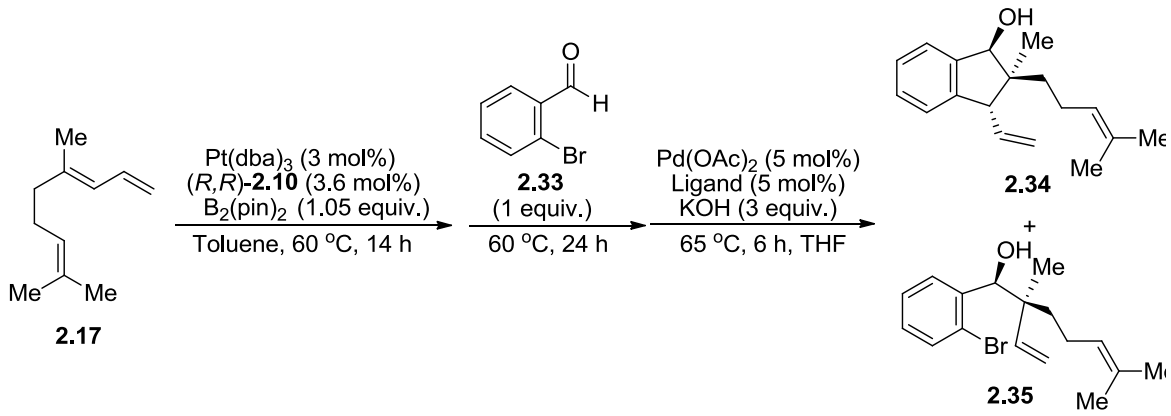
**Scheme 23:** Proposed Catalytic Cycle of Pd-Catalyzed Cross-Coupling



**(i) Ligand Screen for Five-Membered Ring Products**

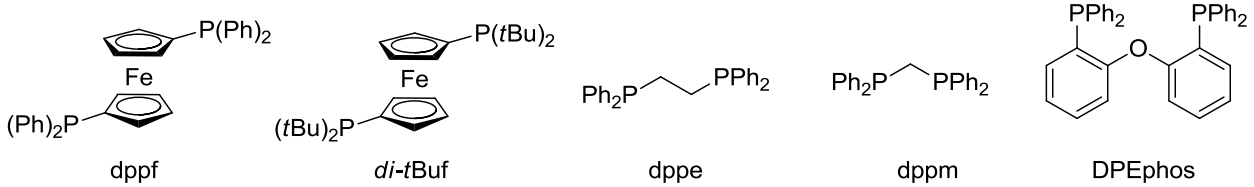
According to the strategy described above, we investigated if the diastereoselectivity could be improved by modifying the ligand structure. Switching to a bulkier ligand such as 1,1'-bis(di-*tert*-phosphino)ferrocene (*di*-*t*Buf) improved the d.r. to 3:1 (entry 2); however, using dppe, dppp and dppm only afforded protodeboronation byproduct **2.35** (entries 3-5). DPEPhos (entry 6) slightly improved the diastereoselectivity of the reaction. $PPh_3$ was used as a ligand (entry 7) and gave 1.5:1 d.r.. More electron rich ligand such as P(*p*-tolyl)$_3$ only led to an increased amount of protodeboronation product (entries 8). Increasing the electron density and the size of ligand by employing RuPhos (entry 9) increased the d.r. to 2.7:1, but unfortunately incomplete conversion and substantial protodeboronation was observed.

**Table 2.** Ligand Screen for Five-Membered Ring Product Formation




| entry | ligand | conv. | **2.34**:**2.35**[a] | d.r.[a] |
|---|---|---|---|---|
| 1 | dppf | 100% | >98:2 | 1.2:1 |
| 2 | *di*-*t*Buf | 100% | >98:2 | 3:1 |
| 3 | dppe | 100% | >2:98 | N/A |
| 4 | dppp | 100% | >2:98 | N/A |
| 5 | dppm | 100% | >2:98 | 1.8:1 |
| 6 | DPEphos | 68% | >98:2 | 1.5:1 |
| 7 | $PPh_3$ | 100% | >98:2 | 1.5:1 |
| 8 | P(*p*-tolyl)$_3$ | 100% | >2:98 | N/A |
| 9 | RuPhos | 48% | 70:30 | 2.7:1 |

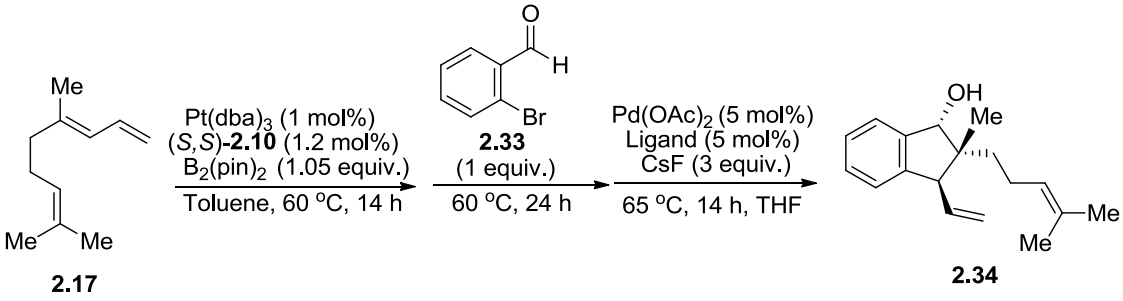
a. The d.r. and the ratio of **2.32** and **2.33** were determined by NMR



## F. Further Improvement of Reaction Conditions for Five-Membered Ring Formation

We later found that when using KOH as a base a significant amount of protodeboronation was observed in the cross-coupling reaction. We suspected that the proton source could be the water in KOH. After changing to CsF as the base, the protodeboronation product was not observed. With the new conditions, more ligands were screened in order to improve the diastereoselectivity of this reaction (Table 3). To deduce if the ligand (*S,S*)-**2.10** from the diboration is participating in the cross-coupling step, a background reaction without any new added ligand was performed and less than 5% product was observed (entry 1). Dppf and di-*t*Buf were used as ligands and afforded 1:1 and 1.7:1 d.r., respectively (entries 2, 3). When switching to monodentate ligands such as $PCy_3$ and $PPh_3$, diastereoselectivity improved slightly (entries 4, 5). A more electron-rich ligand such as RuPhos improved the d.r. to 3:1 (entry 8). Increasing the steric bulk of the ligand to JohnPhos and XPhos (entries 6, 7) led to the best diastereoselectivity most likely due to a slower reductive elimination which could favor equilibration of Pd-bound allyl intermediates. This would allow for complete isomerization prior to reductive elimination step, thus resulting in higher diastereoselectivity.

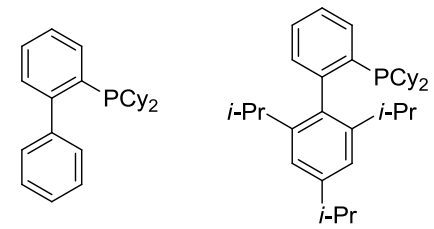
**Table 3. Ligands Survey with CsF in Pd-Catalyzed Cross-Coupling Reaction**




| entry | ligand | isolated Yield | d.r.[a] | e.r.[b] |
|---|---|---|---|---|
| 1 | none | <5 % | N/A | N/A |
| 2 | dppf | 52 % | 1:1 | 96:4 |
| 3 | *di*-*t*Buf | 54% | 1.7:1 | 96:4 |
| 4 | $P(Cy)_3$ | 54% | 1.7:1 | 96:4 |
| 5 | $PPh_3$ | 62% | 2:1 | 96:4 |
| 6 | JohnPhos | 48% | 4.5:1 | 96:4 |
| 7 | XPhos | 69% | 7:1 | 96:4 |
| 8 | RuPhos | 74% | 3:1 | 96:4 |

a) The diastereomer ratios were determined by $^1$HNMR.

b) Enatiomer ratios were determined by SFC analysis.

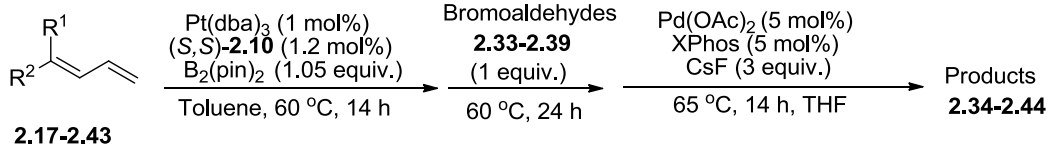



**JohnPhos** **XPhos** **RuPhos**

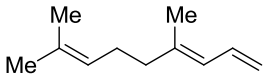
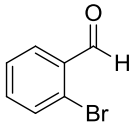
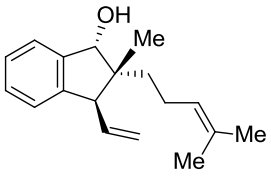
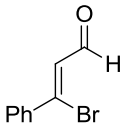
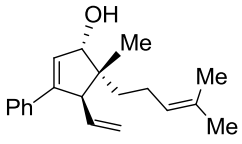
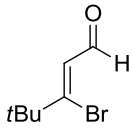
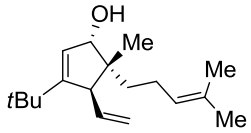
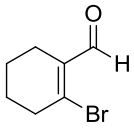
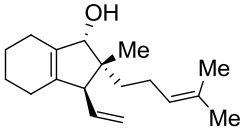
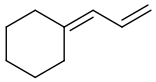
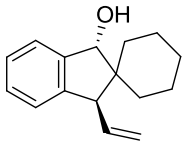
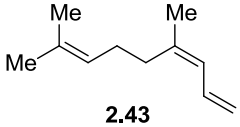
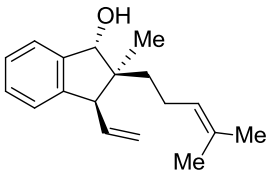
## G. Expanding the Substrate Scope of Tandem Diboration/Allylation/Cross-Coupling for Five-Membered Ring Synthesis

After an extensive ligands screen, several other substrates were applied to the tandem diboration/allylation/cross-coupling sequence under the optimized condition (Table 4). When 2-bromobenzaldehyde **2.33** was subjected to the reaction with diene **2.17**, the d.r. improved to 7:1 (entry 1). 3-Bromoacrylaldehyde derivatives such as phenyl **2.37** and *t*-butyl **2.38** also participated smoothly in the cross-coupling with 5.5:1 and 5.6:1 d.r. respectively (entries 2, 3). Sterically hindered aldehyde **2.39** (entry 4) also proceeded with moderate yield and excellent diastereoselectivity. Different dienes **2.36** and **2.43** can also be used in this sequence to give the desired products with moderate diastereoselectivity (entries 5, 6). Overall, this reaction is general and regio- and enatio-selective for cross-coupling of dienes and bromoaldehydes to form complex cyclopentanols from simple starting materials. The relative stereochemistry of the products in this reaction was determined by NOESY analysis. The major stereoisomer for the product is that where the vinyl group is anti to hydroxyl group. Further studies to understand the preferred stereochemical outcome are underway.

**Table 4.** Substrates Scope with Optimized Conditions




**2.17-2.43**

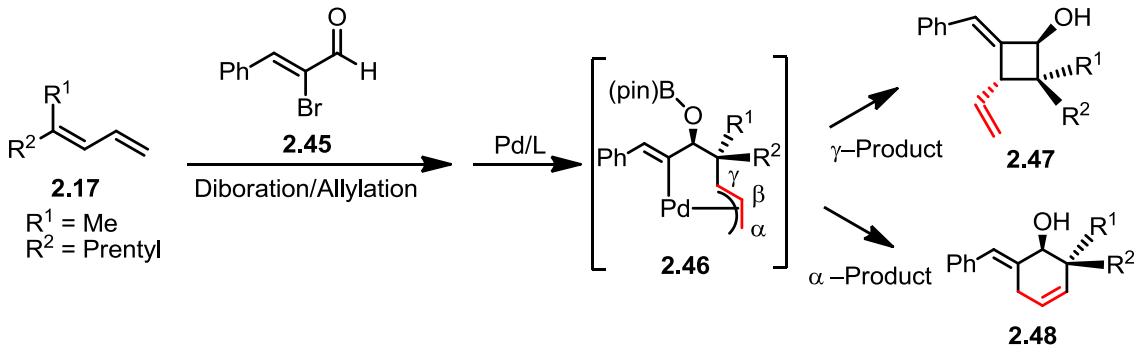
| entry | diene | bromoaldehyde | product | yield (%) | d.r. |
|---|---|---|---|---|---|
| 1 |  **2.17** |  **2.33** |  **2.34** | 69 | 7:1 |
| 2[a] | **2.17** |  **2.37** |  **2.39** | 64 | 5.7:1 |
| 3[a] | **2.17** |  **2.38** |  **2.40** | 73 | 5.5:1 |
| 4[b] | **2.17** |  **2.39** |  **2.41** | 30 | >20:1 |
| 5 |  **2.36** | **2.33** |  **2.42** | 60 | 5:1 |
| 6 |  **2.43** | **2.33** |  **2.44** | 65 | 2.7:1 |

a) 10 mol % $Pd(OAc)_2$/di-*t*Buf, 3 equiv. KOH for 5 h. b) Allylation performed at 80 °C for 48 h.

## H. Synthesis of Highly Functionalized Cyclobutanes from α-Bromoaldehydes

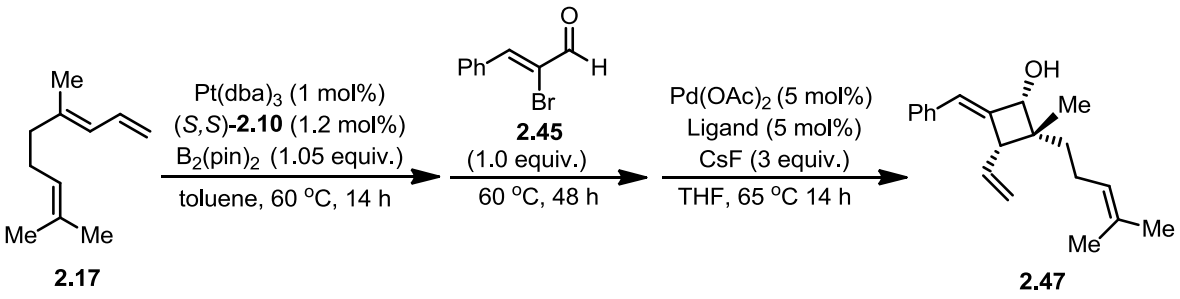
In order to further probe the scope of the tandem sequence, α-bromocinnamaldehydes such as **2.45** were used to attempt the formation of more challenging cyclobutanes. These electrophiles contain an inherent challenge due to the possible formation of regioisomeric products. During the course of the reaction, Pd π-allyl intermediate **2.46** is generated, allowing for reductive elimination at either the α- or γ-position, which would afford a six-membered ring **2.47** or a four-membered ring product **2.48** respectively (Scheme 24).

**Scheme 24**: Potential Regioisomeric Products with α-Bromocinnamaldehyde




We predicted that different ligands might influence where Pd preferred to sit in π-allyl intermediate **2.46**. With proper tuning of the ligands, one might selectively form one product over the other one. After an extensive ligand screen, the four-membered ring product is generated over the six-membered ring exclusively by $^{1}$H NMR (Table 5). Similar trends were observed as in the previous ligand screen with five-member ring formation; the reaction with XPhos and CsF in THF at 65 $^{o}$C gave the best diastereoselectivity compared to other phosphine ligands (entry 7).

## Table 5. Ligand Survey for Formation of Cyclobutanes




| entry | ligand | isolated Yield | d.r.[a] | e.r.[b] |
|---|---|---|---|---|
| 1 | none | <5 % | N/A | N/A |
| 2 | dppf | 52 % | 1.3:1 | 96:4 |
| 3 | *di-t*Buf | 54% | 1.7:1 | 96:4 |
| 4 | $PCy_3$ | 64% | 2:1 | 96:4 |
| 5 | $PPh_3$ | 54% | 1.7:1 | 96:4 |
| 6 | JohnPhos | <5% | N/A | N/A |
| 7 | XPhos | 65% | 4.7:1 | 96:4 |
| 8 | RuPhos | 70% | 2:1 | 96:4 |

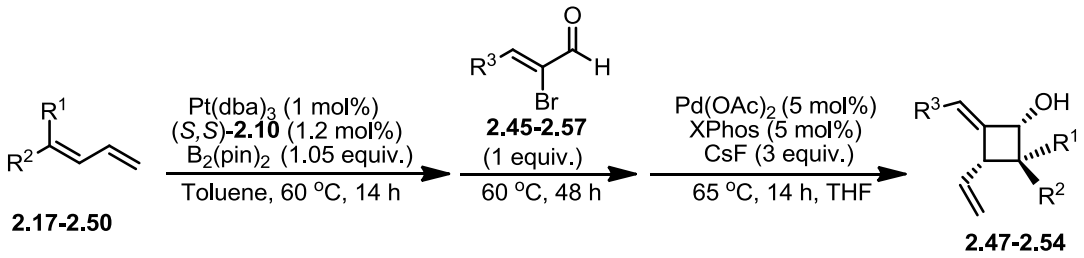
a) The diastereomer ratios were determined by $^1$H NMR.

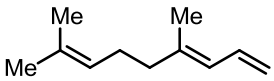
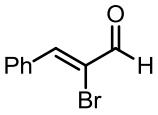
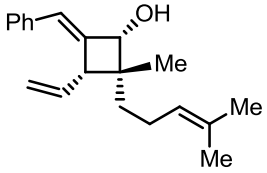
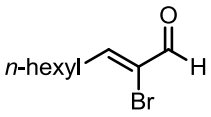
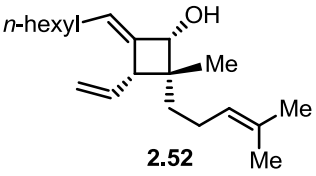
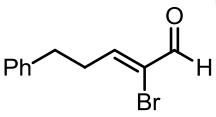
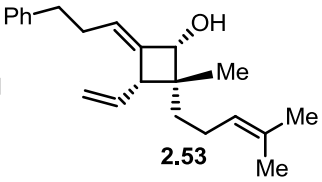
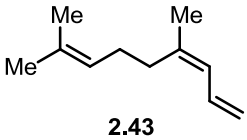
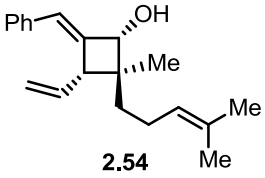
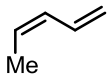
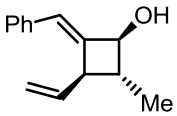
b) Enatiomer ratios were determined by SFC analysis.

**i) Application of Pd-Catalyzed Intramolecular Coupling to form Cyclobutanes**

A variety of dienes and α-bromoaldehydes were utilized as the substrates in the tandem process, giving a range of cyclobutane products in a regioselective fashion (Table 6). The reaction proceeds with both aromatic (**2.45**) and unsaturated α-bromoaldehydes (**2.49-2.50**) with diene **2.17** (entries 1-3). The use of different substituted dienes has a significant impact on the diastereoselectivity of this reaction (entries 4, 5) and gives 8.5:1 and 10:1 dr respectively. Cross-coupling with a monosubstituted *cis*-diene such as **2.51** gives a somewhat lower yield but excellent diastereoselectivity (entry 5). The decrease in yield can be attributed to lower 1,2:1,4 selectivity in the diene diboration step, which affords less of the desired allylboron reagent. Overall, substrates in this reaction can yield around 51-65% yield with moderate diastereomer ratio. The relative stereochemistry of the products in this reaction was also determined by NOESY. Interestingly, the major diastereomer of product is that where the vinyl group is syn to hydroxyl group, which is the opposite seen in the five-membered ring case. The reasoning for the flip in stereoselectivity is the focus of current laboratory efforts. Compared with previous methods to synthesize cyclobutanes,[6,7] our methodology offers the advantage of milder reaction conditions and avoids the need for toxic reagents

**Table 6.** Pd- Catalyzed Intramolecular Coupling to Form Four-Membered Substrates




| Entry | Diene | Bromoaldehyde | Product | Yield (%) | d.r. |
|---|---|---|---|---|---|
| 1 |  **2.17** |  **2.45** |  **2.47** | 65 | 4.7:1 |
| 2[a] | **2.17** |  **2.49** |  **2.52** | 54 | 3.5:1 |
| 3[a] | **2.17** |  **2.50** |  **2.53** | 53 | 3:1 |
| 4 |  **2.43** | **2.45** |  **2.54** | 63 | 8.5:1 |
| 5[b,c] |  **2.51** | **2.45** |  **2.55** | 52 | 10:1 |

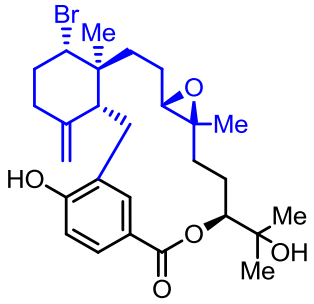
a) 10 mol % $Pd(OAc)_2$/di-*t*-Buf, 3 equiv. KOH for 5 h.

b) 2 equiv. of diene and 1 equiv. aldehyde were used in diboration and DCM was used for allylation at RT.

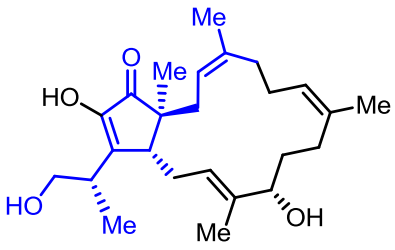
## I. Conclusion

A novel method for the Pd-catalyzed intramolecular cross-coupling reaction with allylboronic ester derivatives and aryl and vinyl halides has been developed. Tandem Pt-catalyzed enantioselective diboration of *cis*-disubstituted-1,3-dienes followed by subsequent allylation with a bromoaldehyde followed by cross-coupling can rapidly build up complex four-, five-, and six-membered carbocycles in a diastereoselective fashion. The desired structures were synthesized in an overall yield up to 73% and with up to 20:1 d.r. in a three step one-pot sequence. Future mechanistic studies are needed to determine the stereodefining step in the intramolecular cross-coupling. Such study could reveal features that are responsible for the selectivity observed in these reactions. Finally, we would like to apply this tandem reaction in the total synthesis sequiterpenoid natural products such as those shown in Scheme 25.

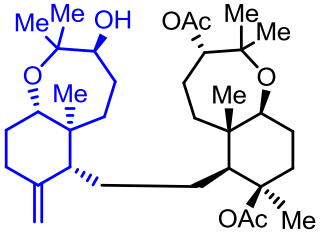
**Scheme 25**: Possible Natural Product Targets for Tandem Process




Bromophycolide




Terpestacin




Raspacionin

## III. Experimental Section:

### General Information

$^{1}H$ NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). $^{13}C$ NMR spectra were recorded on either a Varian Gemini-500 (125 MHz), or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha-P Spectrometer. Frequencies are reported in wavenumbers ($cm^{-1}$) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (ESI+) was performed at the Mass Spectrometry Facility, Boston College, Chestnut Hill, MA. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel ($SiO_2$, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography (TLC) was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm) and phosphomolybdic acid (PMA) in ethanol. Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector. Optical rotations were measured on a ATAGO AP-300 Polarimeter. All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), diethyl ether, dichloromethane and toluene were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated

alumina columns after being purged with argon. 2-bromobenzaldehyde was purchased from Alfa-Aesar and distilled over calcium hydride prior to use. All other reagents were purchased from Aldrich, Alfa Aesar or Acros and used without further purification.

## Experimental Procedures

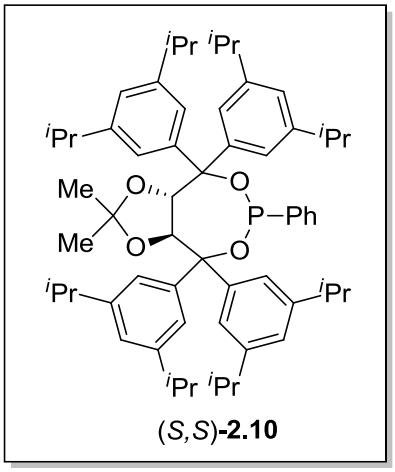
### I. Preparation of $Pt(dba)_3$

Tris(dibenzylideneacetone)platinum was prepared using the literature procedure[24] with slight modification. To a three-neck 500 mL round-bottomed flask equipped with a magnetic stir bar and reflux condenser was added dibenzylideneacetone (3.95 g, 16.9 mmol), tetrabutylammonium chloride (2.01 g, 7.23 mmol), and sodium acetate (3.56 g, 43.4 mmol). Methanol (210 mL) was added and the solution was heated to 70 °C in an oil bath until the solids dissolved (about 5 minutes). To a 50 mL pear-shaped flask was added potassium tetrachloroplatinate (1.00 g, 2.41 mmol). The salt was dissolved in water (8.0 mL) with mild heating. The potassium tetrachloroplatinate solution was transferred to the three-neck flask and the reaction was allowed to stir at 70 °C for 3 h. After 3 h, the reaction was cooled to ambient temperature, transferred to a 500 mL round-bottomed flask and concentrated under reduced pressure to half the volume. The reaction mixture was filtered on a Büchner funnel; solids were washed with copious amounts of water and methanol until all yellow dibenzylideneacetone crystals were removed. The platinum catalyst was placed under high vacuum for 24 h to remove residual methanol and water. Tris(dibenzylideneacetone)platinum was obtained as a dark brown solid (1.13 g, 52% yield).

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

## II. Preparation *of* (*S*,*S*)-*i*Pr$_2$TADDOL-PPh

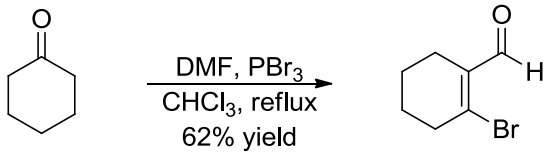
(*S*,*S*)-*i*Pr$_2$TADDOL-PPh was prepared according to the literature procedure. The $^1$H and $^{31}$P, NMR spectra were in accord with previously reported data.[25]



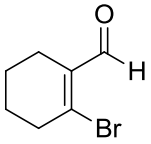

(*S*,*S*)-**2.10**

## II. Preparation of (*Z*)-Bromoaldehyde

### A. Representative Procedure for (*Z*)-Bromoaldeyde




**2.39**

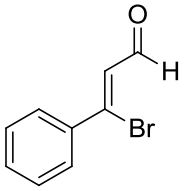



**(*Z*)-2-bromocyclohex-1-enecarbaldehyde (2.39).** The title compound was prepared according to the literature procedure.[26] To a solution of DMF (2.4 ml, 30.6 mmol) in $CHCl_3$ (20 mL) was added $PBr_3$ (2.6 ml, 27.5 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 1 h to give a yellow suspension. A

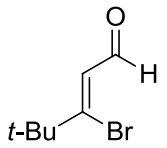
[25] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem*., *Int. Ed*. **2011**, *51*, 521

[26] Harrowven, C. D.; Pascoe, D. D.; Guy, I. L. *Angew. Chem., Int. Ed*. **2007**, *46*, 425 –428

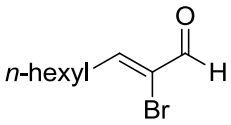
solution of cyclohexanone (1.0 g, 10.2 mmol) in $CHCl_3$ (10 mL) was added and the mixture was allowed to reflux for 3 h. The reaction was cooled to 0°C and saturated aq. $NaHCO_3$ was added slowly to quench the reaction. The mixture was then extracted with ether (3 × 50 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated under vacuum and purified by silica gel chromatography (10:1 hexane/ethyl acetate) to afford (*Z*)-2-bromocyclohex-1-enecarbaldehyde as a yellow oil (1.20 g, 63%). The $^1H$ NMR spectra were in accord with previously reported data.[29]




**(*Z*)-3-bromo-3-phenylacrylaldehyde (2.37).** The title compound was prepared according to the literature procedure.[29] The $^1H$ NMR spectra was in accord with previously reported data.[27]

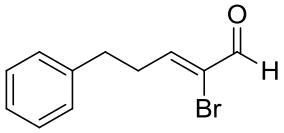



**(*Z*)-3-bromo-4,4-dimethylpent-2-enal (2.38).** The title compound was prepared according to the literature procedure.[29] The $^1H$ NMR spectra matched with previously reported data.[30]



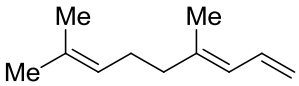

**(*Z*)-2-bromonon-2-enal (2.49).** The title compound was prepared according to literature procedure.[28] The $^1H$ NMR spectra was in accord with previously reported data.[29]

[27] Zhang, Y.; Herndon, W. J. *Org. Lett.* **2003**, *5*, 2043 –2045
[28] Gilley, B. C.; Buller, J. M.; Kobayashi, Y. *Org. Lett,* **2007**, *9*, 3631
[29] Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1987**, *52*, 4369

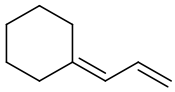



**(*Z*)-2-bromo-4-phenylbut-2-enal (2.50).** The title compound was also prepared according to the literature procedure.[31] $R_f$ = 0.46 in 5:1 hexane/ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$): δ 9.16 (1H, s), 7.35-7.31 (2H, m), 7.26-7.22 (3H, m), 7.15-7.14 (1H, m), 2.90-3.84 (4H, m) ; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 186.0, 154.3, 140.0, 129.3, 128.7, 128.4, 126.6, 33.5, 33.4; IR (neat): 3026.4 (w), 2926.0 (w), 2739.6 (w), 1695.2 (s), 1615.2 (m), 1453.5 (m), 1116.3 (m), 1076.6 (m), 979.0 (w), 746.4 (m), 697.5 (s) cm$^{-1}$; HRMS-(ESI+) for $C_{11}H_{12}BrO$ [M+H]: calculated: 239.0072, found: 239.0081.

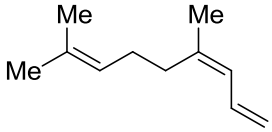
## IV. Preparation of 1,1-Disubstitued Dienes




**(*E*)-4,8-dimethylnona-1,3,7-triene (2.17).** The title compound was prepared according to the literature procedure.[27] The $^1$H NMR spectra matched with previously reported data.[27]



**Allylidenecyclohexane (2.36).** The title compound was prepared according to the literature procedure.[27] The $^1$H NMR spectra matched with previously reported data.[27]




**(*Z*)-4,8-dimethylnona-1,3,7-triene (2.43).** The title compound was prepared according to the literature procedure.[27] The $^1$H spectra matched with previously reported data.[27]

## V. Representative Procedure for Diboration/Allylation/Cross-Coupling with X-Phos and CsF (Method A)

To an oven-dried 2-dram vial equipped with a magnetic stir bar in the glove box was added $Pt(dba)_3$ (1 mol%), (*S,S*)-*i*$Pr_2$TADDOL-PPh (1.2 mol%), $B_2(pin)_2$ (1.05 equiv), and toluene ([substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, brought back to the glove box and charged with diene (1.0 equiv.). The vial was resealed, removed from the glove box, and stirred at 60 °C for 14 h. After cooling to room temperature, the reaction mixture was again brought into the box and aldehyde (1.0 equiv.) was added. The vial was resealed with a polypropylene cap, removed from the glove box and heated to 60 °C in an oil bath for 24 h. The reaction mixture was then cooled to room temperature, transferred to a 6-dram scintillation vial using ethyl acetate (2 mL), and concentrated by rotary evaporation and dried under high vacuum for 6 h prior to the cross coupling. In the glove box, $Pd(OAc)_2$ (5 mol%), XPhos (5 mol%), CsF (3 equiv.) and THF ([substrate] = 0.2 M) were added to the crude reaction mixture. The vial was removed from the box and heated to 65 °C in an oil bath for 14 h. The crude reaction mixture was filtered through a short pad of silica gel and washed with 1:1 ethyl acetate and hexane. The crude product was purified by silica gel chromatography.

**VI. Representative Procedure for Cross-Coupling using *Di-t*BuF and KOH (Method B)**

The diboration and allylation were performed according to Method A. $Pd(OAc)_2$ (10 mol%), 1,1'-Bis(di-t-butylphosphino)ferrocene (*di-t*BuF) (10 mol%), KOH (3 equiv.) and THF ([substrate] = 0.2 M) were added to reaction mixture in 6-dram scintillation vial in the glove box. The vial was removed from the box and was heated to 65 °C in an oil bath for 5 h. The crude reaction mixture was filtered through a short pad of silica gel and washed with 1:1 ethyl acetate and hexanes. The crude reaction mixture was purified by silica gel chromatography.

**VII. Representative Procedure for Cross-Coupling using $PdCl_2(dppf)_2$ and KOH (Method C)**

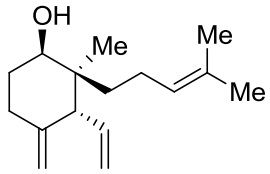
The diboration and allylation were performed according to Method A. $PdCl_2(dppf)_2$ (5 mol %), KOH (3 equiv.) and toluene ([substrate] = 0.2 M) and were added to the reaction the mixture in 6-dram scintillation vial in the glove box. The vial was removed from the box and heated to 80 °C in an oil bath for 6 h. The crude reaction mixture was filtered through a short pad of silica gel and washed with ethyl acetate and hexanes. The crude reaction mixture was purified by silica gel chromatography.

**VII. Representative Procedure for Cross-Coupling using XPhos and CsF (Method D)**

After the diboration, the reaction mixture was then cooled to ambient temperature and the solvent was removed *in vacuo*. The vial was purged with $N_2$ sealed and then brought back to the glove box and charged with dichloromethane ([substrate] = 1.0 M) and 2-bromoaldehyde (0.5 equiv). The reaction was removed from the box and allowed to stir at room temperature for 12 h. The reaction mixture was transferred to a 6-dram

scintillation vial with ethyl acetate (2 mL), and concentrated by rotary evaporation and placed under high vacuum for 6 h prior to cross-coupling. In the glove box, $Pd(OAc)_2$ (5 mol%), XPhos (5 mol%), CsF (6 equiv) and THF ([substrate] = 0.2 M) were added to the crude reaction mixture. The vial was removed from the box and heated to 65 °C in an oil bath for 14 h. The crude reaction mixture was filtered through a short pad of silica gel and washed with ethyl acetate and hexanes. The crude was reaction mixture purified by silica gel chromatography.

## IX. Product Characterization and Proof of Stereochemistry

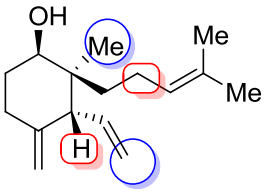


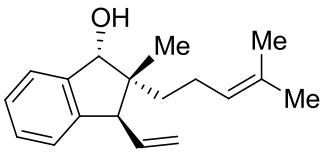

**(*1R,2S,3R*)-2-methyl-4-methylene-2-(4-methylpent-3-en-1-yl)-3-vinylcyclohexanol (2.32).** The reaction was performed according to representative diboration/allylation/cross-coupling procedure (method C). The resulting crude reaction mixture was purified by silica gel chromatography (0-10% ethyl acetate in hexanes, stain in PMA) to afford a light yellow oil (27.1 mg, 58%). $R_f$ = 0.76 in 4:1 hexanes/ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$): δ 5.87 (1H, ddd, *J* = 17.1 Hz, 9.8 Hz, 9.8 Hz), 5.14-5.00 (2H, m), 5.05 (1H, dd, *J* = 1.5 Hz, 2.9 Hz) 4.80 (1H, s), 4.61 (1H, s), 3.74 (1H, t, *J* = 2.9 Hz), 2.90 (1H, d, *J* = 9.5 Hz), 2.42-2.36 (1H, m), 2.23-2.18 (1H, m), 2.02-1.88 (2H, m), 1.82-1.73 (1H, m), 1.68 (3H, s), 1.61 (3H, s), 1.48-1.42 (2H, m), 1.33-1.22 (2H, m), 0.86 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.0, 136.6, 131.4, 125.0, 117.4, 109.1, 72.2, 53.6, 41.2, 36.1, 30.0, 29.9, 25.7, 21.8, 19.1 17.6; IR (neat): 3429.21 (br), 3074.7 (w), 2965.1 (w), 2931.0 (m), 2875.33 (m), 1444.0 (m), 1376.8 (m), 1123.0 (s), 838.0 (s), 1028.0 (w), 971 (s), 447.4 (w) $cm^{-1}$;

HRMS-(ESI+) for $C_{16}H_{25}$ [M+H–$H_2O$]: calculated: 217.1956, found: 217.1955; $[\alpha]^{20}_D$: –19.98 (c = 1.00, $CHCl_3$, *l* = 10 mm)

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to products **2.34** derived from (*R,R*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:



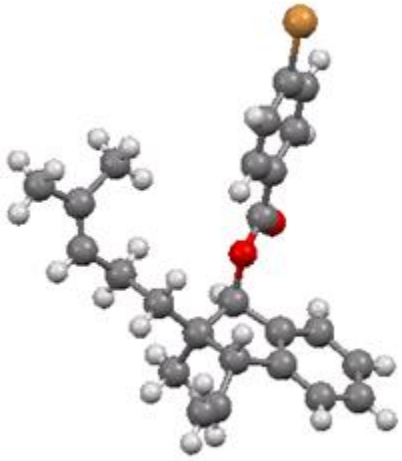




**(1*R*,2*R*,3*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinyl-2,3-dihydro-1H-inden-1-ol (2.34).** The reaction was performed according to representative diboration/allylation/cross-coupling procedure (method A) with (*E*)-4,8-dimethylnona-1,3,7-triene (30.0 mg, 0.20 mmol), $Pt(dba)_3$ (1.8 mg, 2.0 µmol), (*S,S*)-*i*$Pr_2$TADDOL-PPh (2.2 mg, 2.4 µmol), $B_2(pin)_2$ (52.3 mg, 0.21 mmol), toluene (0.2 mL, 1.0 M), 2-bromobenzaldehyde (39.0 mg, 0.20 mmol) and $Pd(OAc)_2$ (2.3 mg, 10.0 µmol), XPhos (4.8 mg, 10.0 µmol), CsF (91.0 mg, 0.60 mmol) and THF (2 ml, 1.0M). The crude was purified by silica gel chromatography (0-5% ethyl acetate in hexanes, stain in PMA) to afford a light yellow oil (36.7 mg, 69%). $R_f$= 0.54 in 5:1 hexanes/ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.39-7.37 (1H, d, *J* = 7.5 Hz), 7.28-7.21 (2H, m), 7.11-7.09 (1H, d, *J* = 7.5 Hz), 5.75 (1H, ddd, *J* = 17.0 Hz, 10.0 Hz. 10.0 Hz), 5.26-5.20 (3H, m), 4.63 (1H,

s), 3.60 (1H, d, $J$ = 10.0 Hz), 2.10 (2H, dd, $J$ = 7.8 Hz, 7.8 Hz ), 1.79-1.73 (1H, m), 1.70 (3H, s), 1.64 (3H, s), 1.54-1.48 (1H, m), 0.83 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 145.3, 143.8, 140.3, 136.5, 131.7, 128.5, 127.1, 125.1, 125.0, 118.5, 81.9, 57.3, 50.6, 34.5, 25.7, 23.3, 19.2, 17.6; IR (neat): 3360.5 (br), 3072.8 (w), 2962.8 (m), 2923.0 (m), 2855.1 (m), 1458.1 (m), 1375.5(m), 1017.4 (m), 914.2 (m), 756.4 (s) $cm^{-1}$; HRMS–(ESI+) for $C_{18}H_{23}$ [M+H–$H_2O$]: calculated: 239.1799, found: 239.1809; $[\alpha]^{20}_D$: +29.97 (c = 1.00, $CHCl_3$, $l$ = 10 mm).

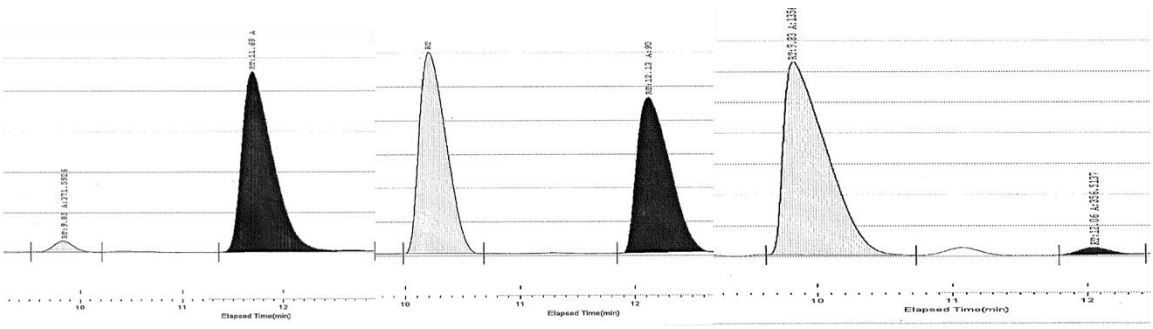
***Proof of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the reaction product. A mixture of the products resulting from use of (*R,R*)-*i*Pr$_2$TADDOL-PPh and (*S,S*)-*i*Pr$_2$TADDOL-PPh as the ligands in the diboration reaction were used to determine separation conditions. The absolute stereochemistry was assigned by X-ray crystallography of the bis(benzoate) of the reaction product (prepared using benzoic anhydride, triethylamine, and catalytic DMAP) using anomalous dispersion . Flack parameter = -0.004



X-ray crystal structure was obtained using (*S,S*)-*i*Pr$_2$TADDOL-PPh

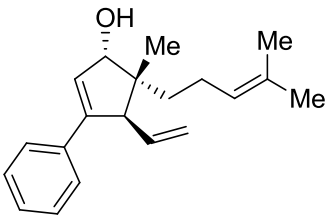
*Chiral SFC (AS-H, Chiraldex, 1.5 mL/min, 2% MeOH, 100 bar, 35 $^{o}$C)-analysis of the reaction product.*



Reaction Product | Racemic | Reaction Product from opposite enantiomer

Peak Info

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 50.9286 | 9439.4577 | 10.2 | 594.551 | 0.0106 |
| 2 | 49.0714 | 9095.2253 | 12.13 | 459.252 | 0.0125 |
| Total: | 100 | 18534.683 | | | |

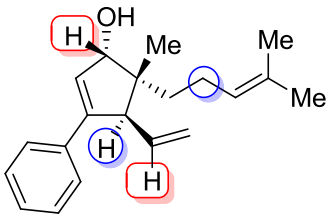


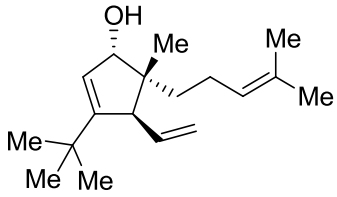

**(1*S*,4*S*,5*R*)-5-methyl-5-(4-methylpent-3-en-1-yl)-3-phenyl-4-vinylcyclopent-2-enol (2.39).** The reaction was performed according to representative procedure (method B) with *di-t*BuF and KOH. The crude was purified by silica gel chromatography (0-5% ethyl acetate in hexanes, stain in PMA) to afford a clear oil (36.7 mg, 65%). $R_f$ = 0.25 in 5:1 hexanes/ethyl acetate on. $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.52-7.50 (2H, m), 7.32-7.29 (2H, m), 7.26-7.23 (1H, m), 6.38 (1H, d, *J* = 2.9 Hz), 5.88 (1H, ddd, *J* = 17.6 Hz, 10.3 Hz, 8.8 Hz), 5.20 (1H, t, *J* = 7.3 Hz), 5.10-5.05 (2H, m), 4.19 (1H, d, *J* = 2.9Hz), 3.20 (1H, d, *J* = 8.3 Hz), 2.11 (2H, *J* = 16.1 Hz, 7.8 Hz), 1.70 (3H, s), 1.64 (3H, s), 1.63-1.57 (1H, m), 1.52-1.43 (1H, m) 1.07 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 148.9,

140.7, 135.5, 131.4, 128.3, 128.0, 126.7, 126.6, 125.2, 116.9, 83.1, 59.6, 48.0, 33.1, 26.1, 25.7, 22.9, 17.7; IR: (neat)3378.0 (br), 3056.2 (w), 2961.1 (m), 2923.2 (m), 2854.4 (m), 1445.9 (m), 1375.2 (m), 1035.3 (m), 911.4 (m), 759.0 (s), 691.6 (s) $cm^{-1}$; HRMS-(ESI+) for $C_{20}H_{25}$ [M+H–$H_2O$]: calculated: 265.1954, found: 265.1956; $[\alpha]^{20}_D$:–219.8 (c = 1.00, $CHCl_3$, *l* = 10 mm).

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to products **2.34** derived from (*S,S*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:



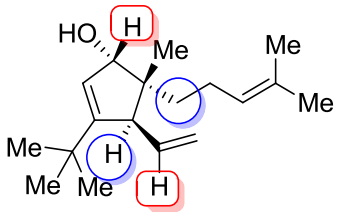



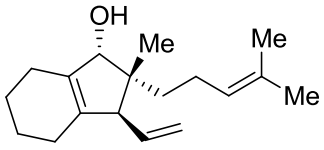

**(1*S*, 4*S*, 5*R*)-3-(tert-butyl)-5-methyl-5-(4-methylpent-3-en-1-yl)-4-vinylcyclopent-2-enol (2.40).** The reaction was performed according to representative procedure (method B) with *di-t*BuF and KOH. The crude was purified by silica gel chromatography (0-5% ethyl acetate in hexanes, stain in PMA) to afford a clear oil (38.3 mg, 73%). $R_f$ = 0.53 in 5:1 hexanes/ethyl acetate. 1H NMR (500 MHz, $CDCl_3$): δ 5.62 (1H, ddd, *J* = 16.6 Hz, 10.8 Hz, 10.8 Hz), 5.41 (1H, s), 5.08 (1H, m), 5.00-4.96 (2H, m), 4.29 (1H, br s), 3.05 (1H, d,

*J* = 9.8 Hz), 1.93 (2H, dd, *J* = 7.8 Hz, 16.1 Hz), 1.62 (3H, s), 1.56 (3H, s), 1.44-1.38 (1H, m), 1.30-1.27 (1H, m), 1.00 (9H, s), 0.86 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 157.9, 139.8, 131.3, 125.2, 124.9, 116.1, 83.3, 58.6, 49.5, 34.3, 33.8, 29.5, 25.7, 23.4, 20.8, 17.6; IR (neat): 3349.6 (br), 2962.1 (s), 2925.3 (s), 2866.9 (m), 1458.2 (m), 1362.2 (m), 1254.6 (m), 1084.4 (m), 1009.2 (s), 908.3 (s) cm$^{-1}$; HRMS-(ESI+) for $C_{18}H_{29}$ [M+H–$H_2O$]: calculated: 245.2264, found: 245.2269; $[\alpha]^{20}_D$: +129.9 (c = 1.00, $CHCl_3$, *l* = 10 mm).

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to product **2.34** derived from (*S,S*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:



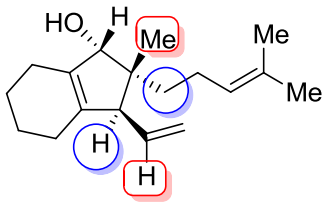



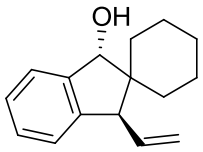

**(1*R*,2*R*,3*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinyl-2,3,4,5,6,7-hexahydro-1H-inden-1-ol -2-enol (2.41)**. The reaction was performed according to representative diboration/allylation/cross-coupling procedure (method A) with the allylation step was carried out 60 °C for 48 h. The crude was purified by silica gel chromatography (0-5% ethyl acetate in hexanes, stain in PMA) to afford a clear oil (15.6 mg, 30%). $R_f$ = 0.63 in 5:1 hexanes/ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$): δ 5.58 (1H, ddd, *J* = 16.9 Hz, 9.8

Hz, 9.8 Hz), 5.17 (1H, t, $J$ = 6.8 Hz), 5.07-5.02 (2H, m), 3.99 (1H, s), 2.85 (1H, br, d, $J$ = 9.7 Hz), 2.18-2.12 (1H, m), 2.02-1.95 (3H, m), 1.90-1.71 (3H, m), 1.69 (3H, s), 1.66-1.58 (6H, s), 1.59-1.51 (1H, m), 1.44-1.38 (1H, m), 0.88 (2H, m); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 139.9, 137.8, 136.4, 131.5, 125.3, 117.0, 86.0, 60.5, 47.6, 35.6, 25.7, 24.3, 23.6, 23.4, 22.9, 22.8, 21.0, 17.6; IR (neat): 3407.5 (br), 2963.5 (m), 2926.2 (s), 2856.2 (m), 1445.6 (m), 1376.8 (m), 1320.1 (m), 1146.2 (m), 913.1 (w), 850.6 (w), 617.8 (w) cm$^{-1}$; HRMS-(ESI+) for $C_{18}H_{27}$ [M+H–$H_2O$]: calculated: 243.2113, found: 243.2125; $[\alpha]^{20}_D$: +29.97 (c = 1.00, $CHCl_3$, $l$ = 10 mm).

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to product **2.34** derived from (*S,S*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:

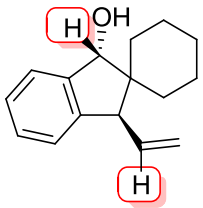


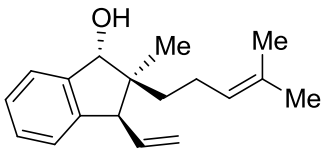



**(1'*R*,3'*S*)-3'-vinyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden-1'-ol (2.42).** The reaction was performed according to representative diboration/allylation/cross-coupling procedure (method A) with allylidenecyclohexane (24.0 mg, 0.20 mmol) and 2-bromobenzaldehyde (39.0 mg, 0.20 mmol). The crude was purified by silica gel chromatography (0-5% ethyl acetate in hexanes) to afford a light yellow oil (27.4 mg, 60.0%). $R_f$ = 0.40 in 5:1 hexanes/ethyl acetate, stain in PMA. δ 7.40-7.38 (1H, m), 7.26-7.25 (2H, m), 7.13-7.11 (1H, m), 5.77 (1H, ddd, *J* = 17.1 Hz, 9.8 Hz, 9.8 Hz), 5.20-5.13 (2H, m), 4.93 (1H, s), 3.61 (1H, d, *J* = 9.3 Hz), 1.66-1.44 (3H, m), 1.35-1.22 (6H, m), 0.94-0.88 (1H, m); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.4, 143.5, 136.5, 128.4, 127.1, 125.2, 124.7, 117.4, 79.5, 56.1, 51.1, 29.8, 29.1, 26.1, 23.1, 22.6; IR (neat): 3369.5 (br), 2923.0 (s), 2853.1 (m), 1507.9 (m), 1451.0 (m), 1203.3 (m), 1015.7 (m), 975.7 (m), 750.7 (s) $cm^{-1}$; HRMS-(ESI+) for $C_{16}H_{19}$ [M+H–$H_2O$]: calculated: 211.1487, found: 211.1497; $[\alpha]^{20}_D$: +59.94 (c = 1.00, $CHCl_3$, *l* = 10 mm).

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to product **2.34** derived from (*S,S*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:

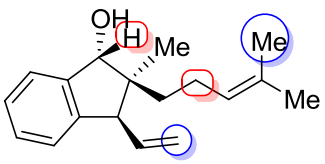


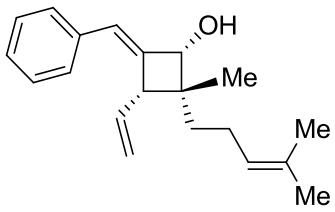



**(1*R*,2*S*,3*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinyl-2,3-dihydro-1H-inden-1-ol (2.44).** The reaction was performed according to representative diboration/allylation/cross-coupling procedure (method A) with (*Z*)-4,8-dimethylnona-1,3,7-triene (30.0 mg, 0.20 mmol) and 2-bromobenzaldehyde (39.0 mg, 0.20 mmol). The crude was purified by silica gel chromatography (0-5% ethyl acetate in hexanes) to afford a light yellow oil (31.1 mg, 65%). $R_f$ = 0.50 in 5:1 hexanes/ethyl acetate, stain in PMA. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.40-7.36 (1H, m), 7.30-7.22 (2H, m), 7.16-7.10 (1H, m), 5.78 (1H, ddd, *J* = 16.6 Hz, 9.3 Hz, 9.3 Hz), 5.14-5.04 (3H, m), 4.89 (1H, s), 3.50 (1H, d, *J* = 9.3 Hz), 2.10-1.96 (2H, m), 1.68 (3H, s), 1.60 (3H, s), 1.49 (1H, t, *J* = 8.8 Hz), 1.20-1.12 (1H, m), 1.04 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.2, 143.6, 137.5, 131.4, 128.2, 127.2, 125.2, 124.9, 124.3, 116.4, 81.4, 58.5, 50.9, 36.0, 25.7, 23.3, 18.9, 17.6; IR (neat): 3379.7 (br), 2957.1 (m), 2922.3 (s), 2853.0 (m), 1459.3 (m), 1376.9 (m), 1266.0 (w), 1023.3 (m), 914.8 (w), 753.9 (m), 699.0 (m) cm$^{-1}$; HRMS-(ESI+) for $C_{18}H_{23}$ [M+H–$H_2O$]: calculated: 239.1800 found: 239.1810; $[\alpha]^{23}_D$: +39.96 (c = 1.00, $CHCl_3$, *l* = 10 mm).

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to products **2.34** derived from (*S,S*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:

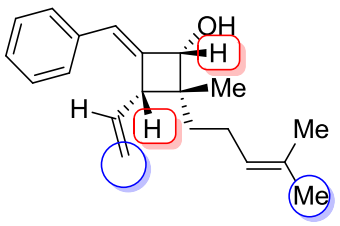




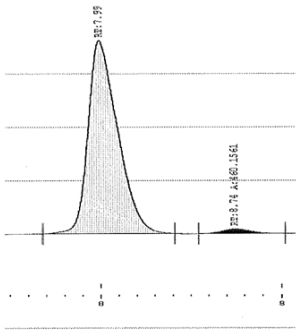

**(1*R*,2*S*,3*R*,*E*)-4-benzylidene-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclobutanol (2.47).** The reaction was performed according to representative diboration/allylation/cross-coupling procedure (method A) with the allylation step was carried out 60 °C for 48 h. The crude was purified by silica gel chromatography (0-10% ethyl acetate in hexanes, stain in PMA) to afford a colorless oil (36.7 mg, 65%). $R_f$ = 0.34 in 5:1 hexanes/ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.24-7.22 (4H, m), 7.20-7.12 (1H, m), 6.56 (1H, br,s), 5.63 (1H, ddd, *J* = 17.6 Hz, 9.2 Hz, 9.2 Hz), 5.13-5.05 (3H, m), 4.30 (1H, br, s), 3.23 (1H, d, *J* = 8.4 Hz), 2.03-1.97 (2H, m), 1.65 (3H, s), 1.58 (3H, s), 1.52-1.45 (1H, m), 1.37-1.31 (1H, m), 1.24 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 145.4, 135.7, 135.5, 131.4, 129.0, 127.9, 126.9, 124.9, 124.2, 117.5, 79.1, 54.4, 46.6, 30.5, 25.7, 24.7, 23.4, 17.6; IR (neat): 3358.9 (br), 2958.0 (m), 2921.9 (s), 2857.7 (m), 1449.6 (m), 1375.7 (m), 1292.6 (m), 912.1 (m), 753.9 (m) 695.2 (s) cm$^{-1}$; HRMS-(ESI+) for $C_{20}H_{25}$ [M+H–$H_2O$]: calculated: 265.1950, found: 265.1956; $[\alpha]^{20}_D$: –39.96 (c = 1.00, $CHCl_3$, *l* = 10 mm).

***Proof of Stereochemistry:***

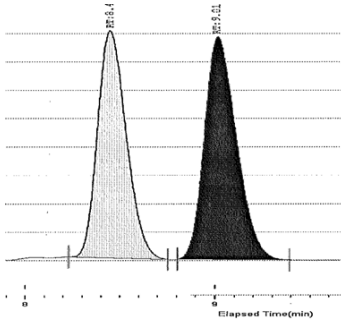
The absolute stereochemistry was assigned by analogy to other products derived from (*S,S*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:



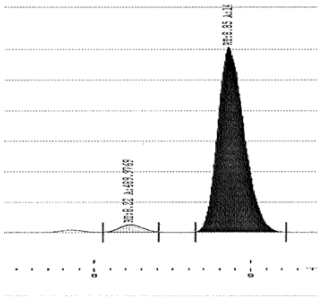
*Chiral SFC (OD-H, Chiraldex, 3 mL/min, 5% MeOH, 100 bar, 35 °C)-analysis of the reaction product.*



Reaction Product



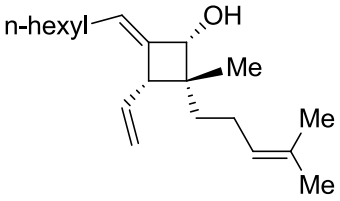

Racemic



Reaction Product from opposite enantiomer

Peak Info

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 97.7946 | 20404.7492 | 7.99 | 1803.1186 | 0.0116 |
| 2 | 2.2054 | 460.1561 | 8.74 | 43.1709 | 0.0127 |
| Total: | 100 | 20864.9053 | | | |

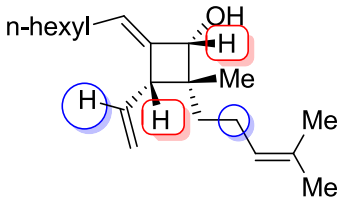


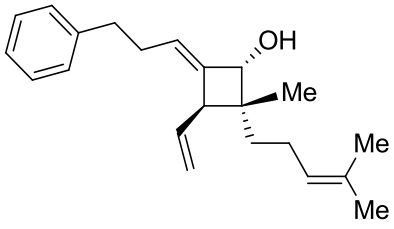

**(1*R*,2*R*,3*R*,*E*)-4-heptylidene-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclobutanol (2.52).** The reaction was performed according to Representative diboration/allylation/cross-Coupling procedure (method B) with the allylation step was carried out 60 °C for 48 h. The crude was purified by silica gel chromatography (0-10% ethyl acetate in hexanes, stain in PMA) to afford a light yellow oil (31.4 mg, 54%). $R_f$ = 0.74 in 5:1 hexanes/ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$): δ 5.81 (1H, ddd, *J* = 17.1 Hz, 9.8 Hz, 9.8Hz), 5.53 (1H, t, *J* = 9.7 Hz), 5.13-5.03 (3H, m), 4.11 (1H, br, s), 2.87 (1H, d, *J* = 9.8 Hz), 2.08-1.90 (4H, m), 1.68 (3H, s), 1.60 (3H, s), 1.48-1.40 (1H, m), 1.37-1.20 (9H, m) 1.17 (3H, s), 0.88 (3H, t, *J* = 7.1 Hz) ; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 143.1,

137.0, 131.2, 125.1, 124.2, 116.3, 78.2, 52.9, 45.9, 31.7, 30.2, 29.9, 28.8, 27.2, 25.7, 24.4, 23.5, 22.6, 17.6, 14.1; IR (neat): 3428.5 (m), 2963.0 (m), 2922.3 (m), 2852.9 (m), 1458.1 (m), 1375.6 (m), 1049.5 (m), 998.4 (m), 940.3 (m), 738.5 (s); HRMS-(ESI+) for $C_{20}H_{33}$ [M+H–$H_2O$]: calculated: 273.2582, found: 273.2584; $[\alpha]^{20}_D$: –9.99 (c = 1.00, $CHCl_3$, *l* = 10 mm).

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*S,S*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:



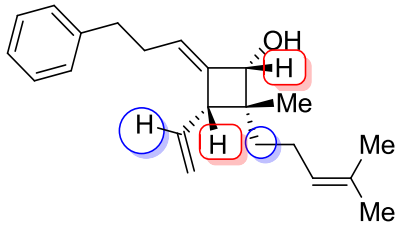



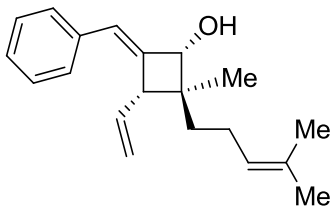

**(1*R*,2*R*,3*R*,*E*)-2-methyl-2-(4-methylpent-3-en-1-yl)-4-(3-phenylpropylidene)-3-vinylcyclobutanol (2.53).** The reaction was performed according to representative diboration/allylation/cross-coupling procedure (method B) with the allylation step was carried out 60 °C for 48 h. The crude was purified by silica gel chromatography (0-10% ethyl acetate in hexanes, stain in PMA) to afford a light yellow oil (32.9 mg, 54%). $R_f$ = 0.34 in 5:1 hexanes/ethyl acetate. $^1$H NMR (500 MHz,

$CDCl_3$): δ 7.29-7.23 (2H, m), 7.20-7.10 (3H, m), 5.65 (1H, ddd, $J$ = 17.1 Hz, 9.8 Hz, 9.8 Hz), 5.56 (1H, t, $J$ = 7.8 Hz), 5.11 (1H, t, m), 5.07-5.02 (2H, m), 4.10 (1H, br, s), 2.78 (1H, d, $J$ = 9.3), 2.70-2.58 (2H, m), 2.40-2.24 (2H, m), 2.06-1.90 (2H, m), 1.70 (3H, s), 1.60 (3H, s), 1.43-1.32 (1H, m), 1.30-1.18 (1H, m), 1.14 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.2, 141.8, 136.8, 131.2, 128.6, 128.2, 125.8, 125.1, 122.8, 116.5, 78.1, 52.7, 45.9, 36.2, 30.1, 29.0, 25.7, 24.4, 23.4, 17.6; IR (neat): 3351.7 (br), 3026.3 (w), 2959.2 (m), 2921.5 (m), 2855.2 (m), 1495.6 (m), 1375.6 (m), 1086.6 (m), 910.8 (m), 745.3 (s), 697.3 (w) cm$^{-1}$; HRMS-(ESI+) for $C_{22}H_{29}$ [M+H–$H_2O$]: calculated: 293.2269, found: 293.2284; $[\alpha]^{20}_D$: –19.98 (c = 1.00, $CHCl_3$, $l$ = 10 mm).

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*S,S*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:

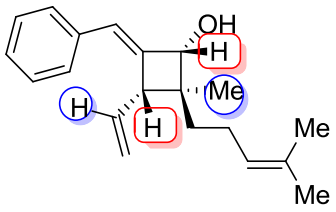


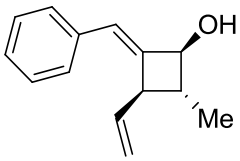



**(1*R*,2*S*,3*R*,*E*)-4-benzylidene-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclobutanol (2.54).** The reaction was performed according to representative diboration/allylation/cross-coupling procedure (method A) with the allylation step was carried out 60 °C for 48 h. The crude was purified by silica gel chromatography (0-10% ethyl acetate in hexanes, stain in PMA) to afford a light yellow oil (35.6 mg, 63%). $R_f$ = 0.34 in 5:1 hexanes/ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.35-7.30 (1H, m), 7.26-7.23 (1H, m), 7.22-7.15 (2H, m), 6.55 (1H, t, *J* = 2.5 Hz), 5.49 (1H, ddd, *J* = 17.1 Hz, 9.3 Hz, 9.3 Hz), 5.17-5.05 (3H, m), 4.40 (1H, br, s), 3.29 (1H, dd, *J* = 9.3 Hz, 2.5 Hz), 2.10-2.00 (2H, m), 1.72 (3H, s), 1.64 (3H, s) 1.62-1.58 (2H, m), 0.92 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 146.3, 135.4, 135.3, 131.6, 129.2, 127.8, 126.7, 124.6, 122.4, 117.8, 76.9, 51.9, 47.5, 41.6, 25.7, 23.1, 17.6, 13.5; IR (neat): 3377.4 (br), 3057.7 (w), 2963.9 (m), 2923.5.6 (m), 1492.8 (m), 1376.9 (m), 1108.2 (m), 911.4 (m), 792.2 (s); HRMS-(ESI+) for $C_{20}H_{25}$ [M+H–$H_2O$]: calculated: 265.1956, found: 265.1954; $[\alpha]^{23}_D$: –209.8 (c = 1.00, $CHCl_3$, *l* = 10 mm).

***Proof of Stereochemistry:***

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

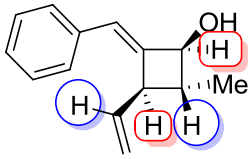


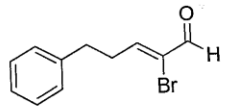


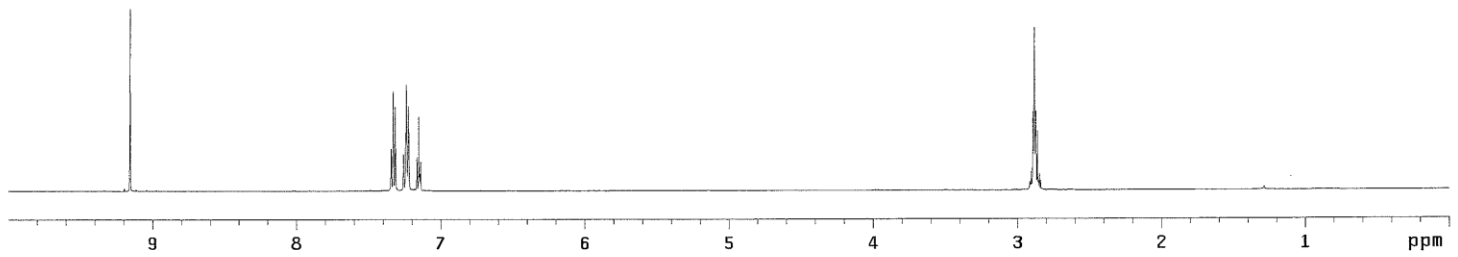

**(1*S*,3*R*,4*R*,*E*)-2-benzylidene-4-methyl-3-vinylcyclobutanol (2.55).** The reaction was performed according to representative procedure (method D). The crude was purified by silica gel chromatography (0-10% ethyl acetate in hexanes, stain in PMA) to afford a light yellow oil (20.4 mg, 51%). $R_f$ = 0.14 in 5:1 hexanes/ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.32-7.28 (1H, m), 7.27-7.25 (3H, m), 7.20-7.17 (1H, m), 6.52 (1H, t, *J* = 2.4 Hz), 5.64 (1H, ddd, *J* = 17.1 Hz, 8.5 Hz, 8.5 Hz), 5.10 (1H, d, *J* = 17.1 Hz), 4.96 (1H, d, *J* = 11.6 Hz), 4.25 (1H, d, *J* = 8.5 Hz), 3.08 (1H, td, *J* = 7.9, 2.4 Hz), 2.03-1.96 (1H, m), 1.26 (3H, d, *J* = 6.7 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 142.9, 134.1, 131.7, 125.4, 124.2, 123.2, 118.1, 111.90, 72.7, 45.3, 43.6, 13.6; IR (neat): 3341.6 (br), 2953.2 (m), 2933.3 (m), 1492.7 (m), 1374.6 (w), 1116.5 (m), 1028.6 (w), 755.0 (s), 695.8 (s)cm$^{-1}$; HRMS-(ESI+) for $C_{14}H_{15}$ [M+H–$H_2O$]: calculated: 183.1173, found: 183.11730; $[\alpha]^{23}_D$: +88.2 (c = 1.00, $CHCl_3$, *l* = 10 mm).

***Proof of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry was determined by NOESY analysis and the following NOEs were observed:




O
H
Br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ppm

O
H
Br
ppm
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100
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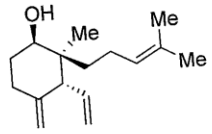
160
180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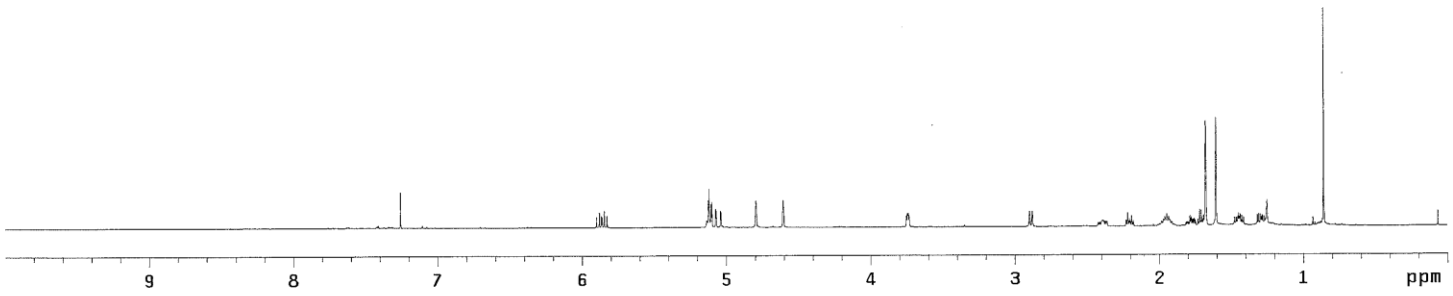
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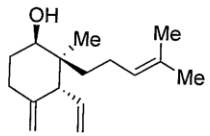
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Me
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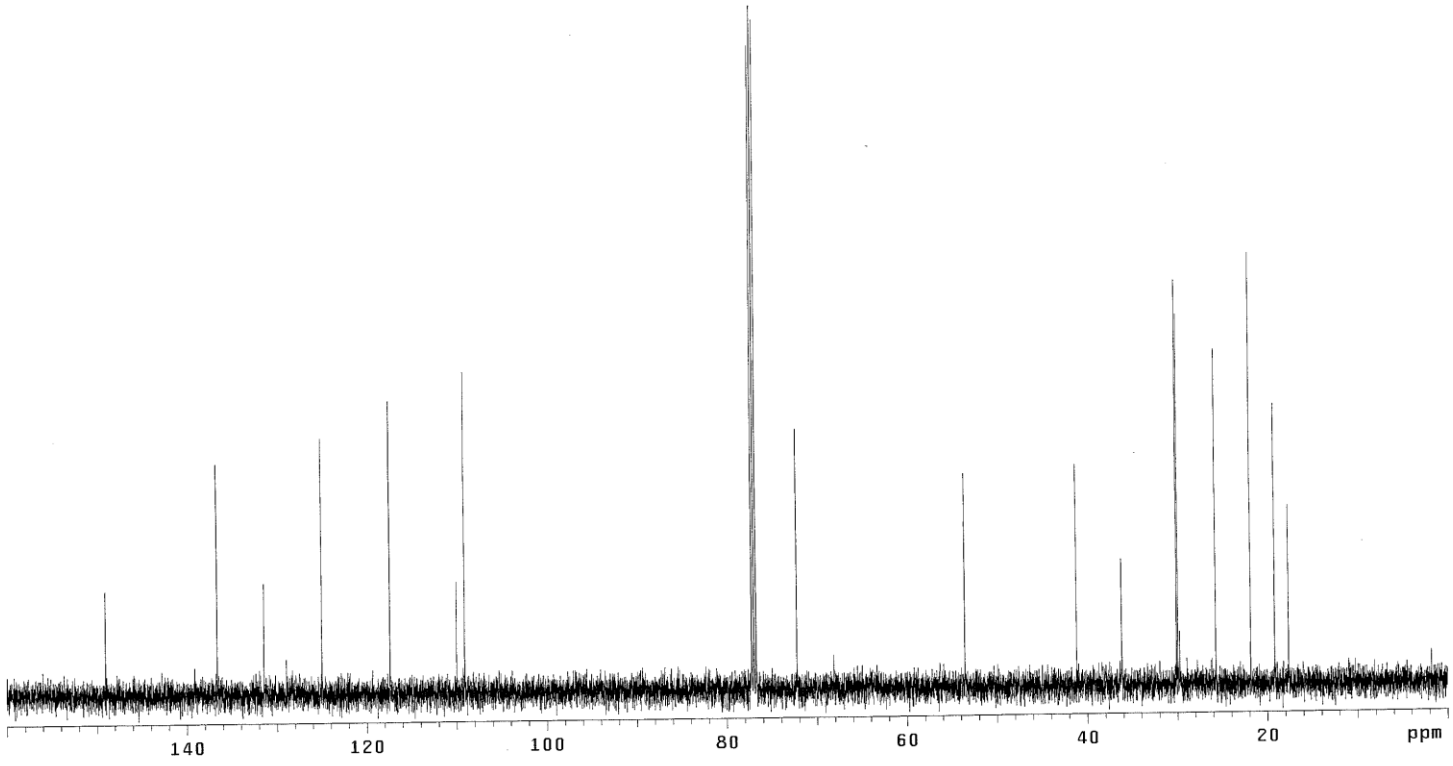
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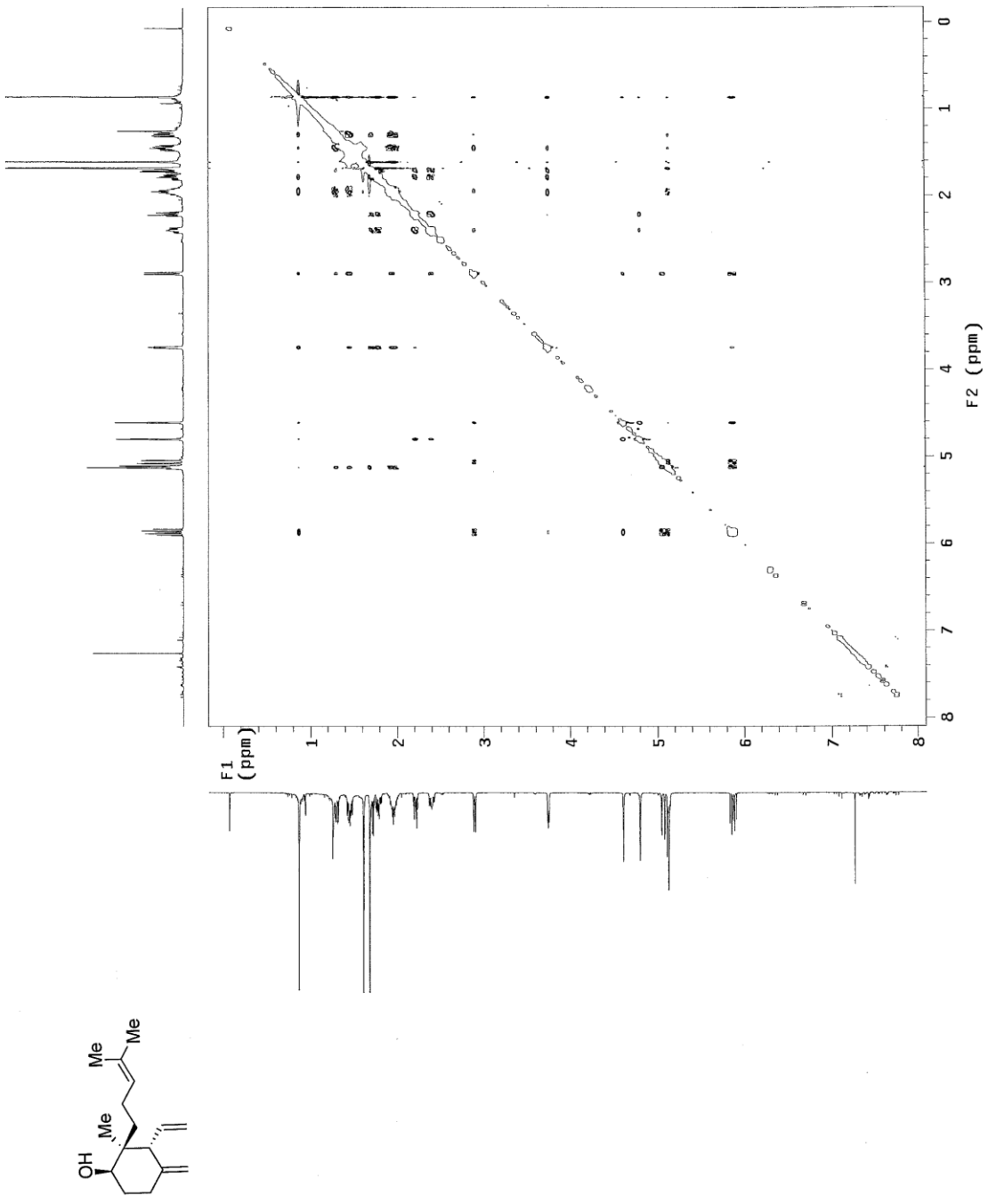
ppm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F2 (ppm)
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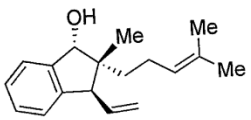
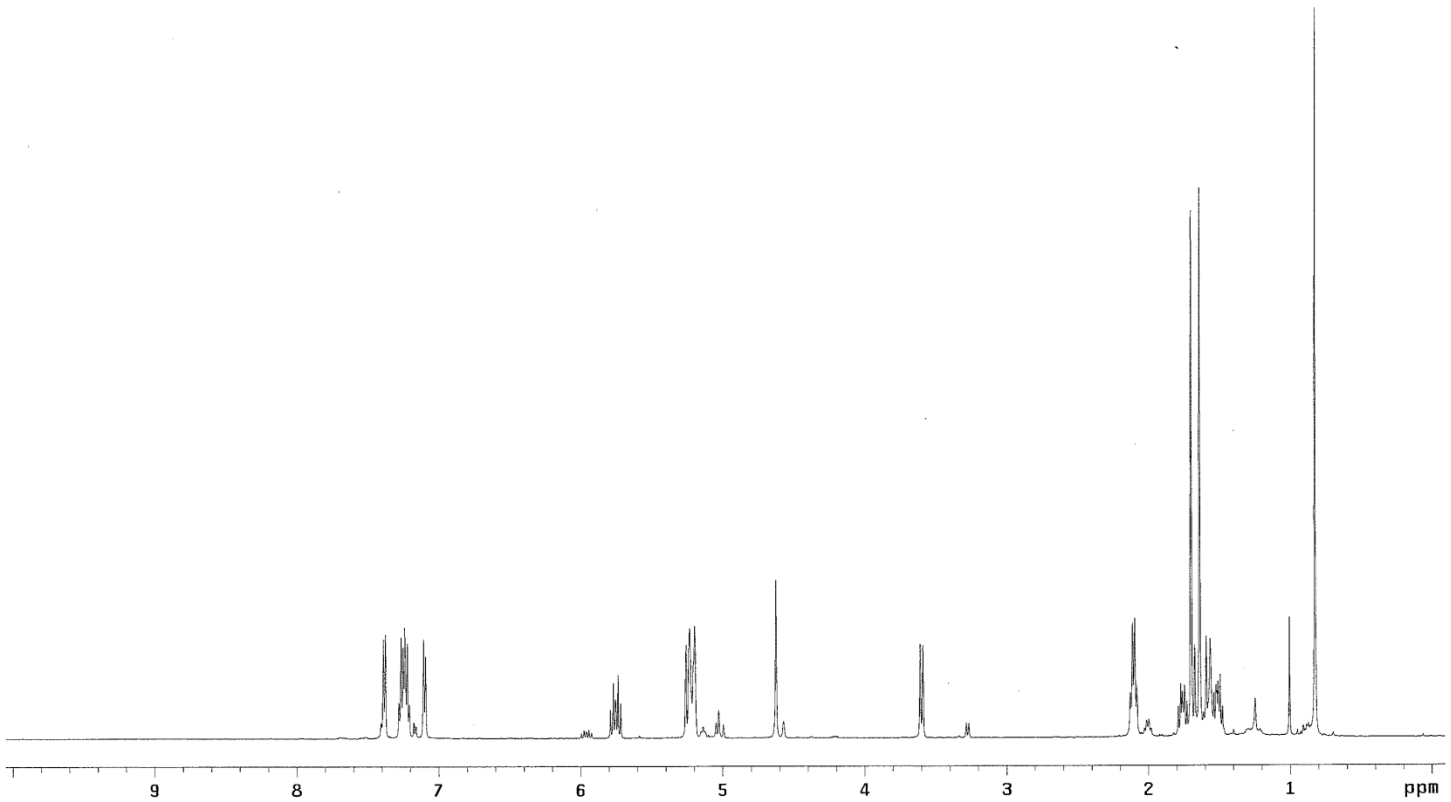
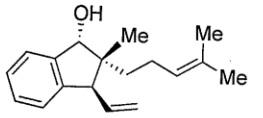
Me
Me
Me

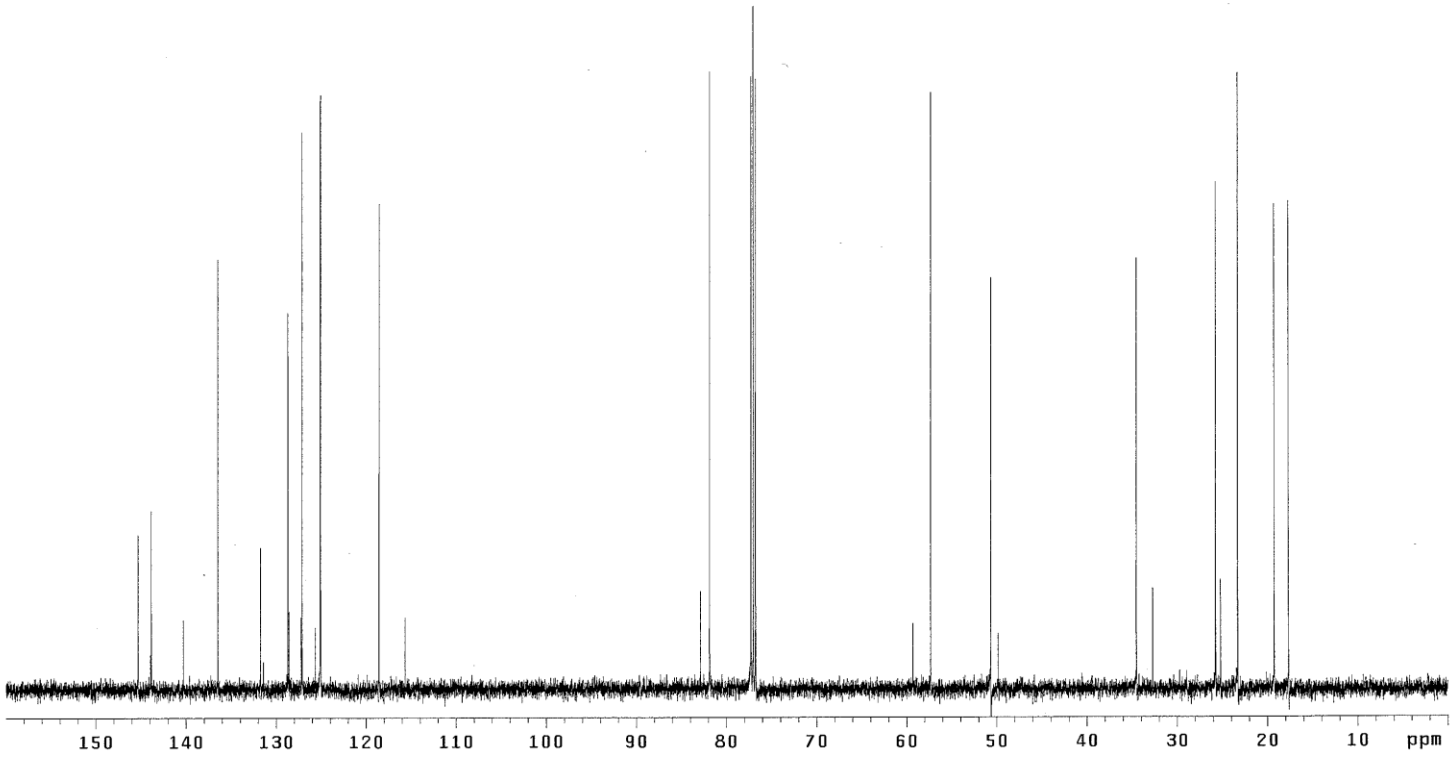


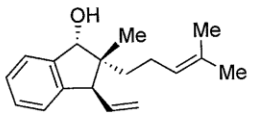

with minor diastereomer



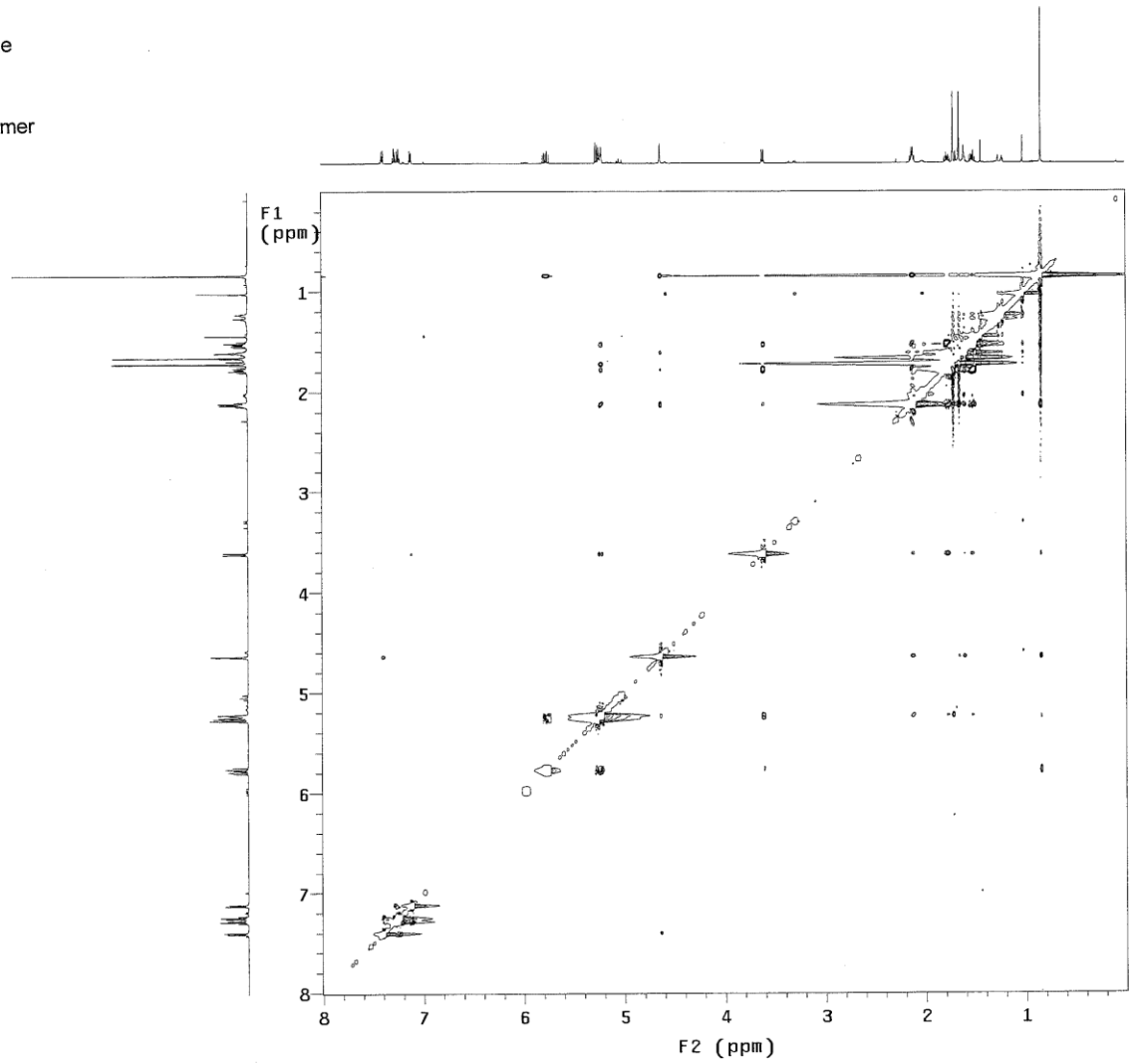


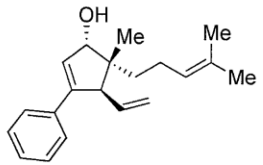

with minor diastereomer



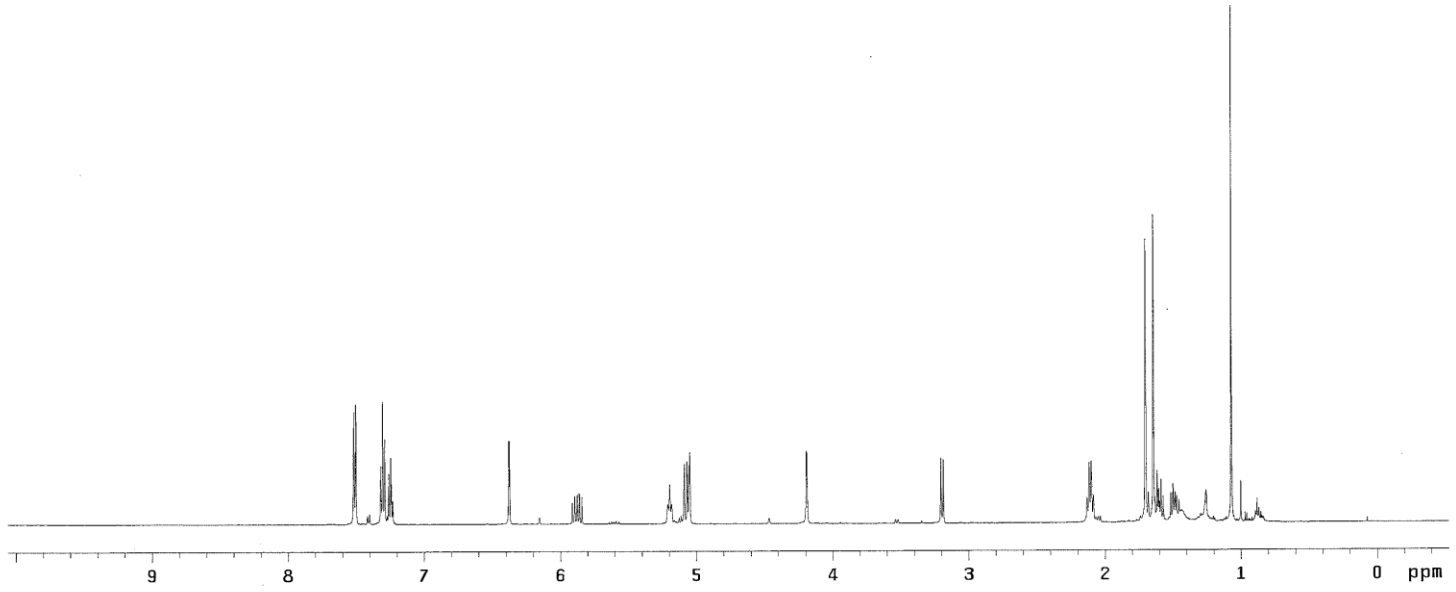


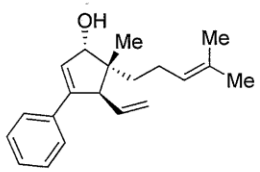

with minor diastereomer



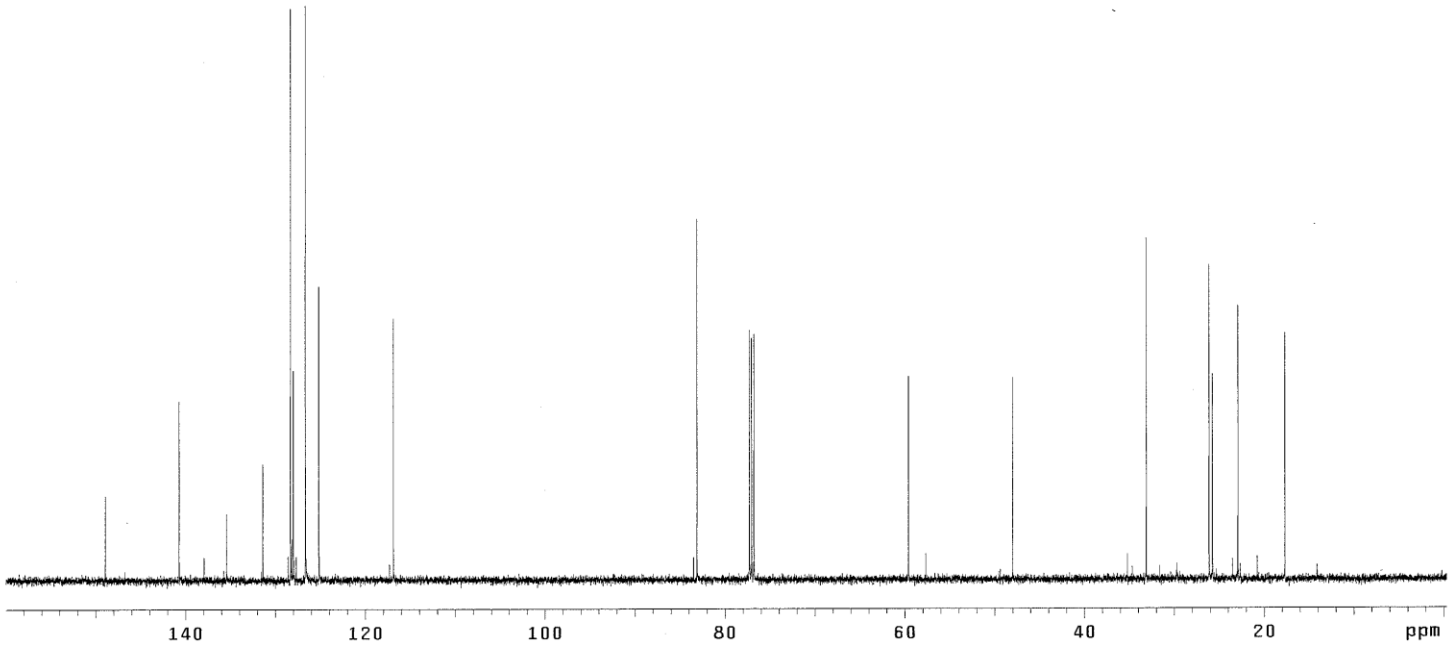


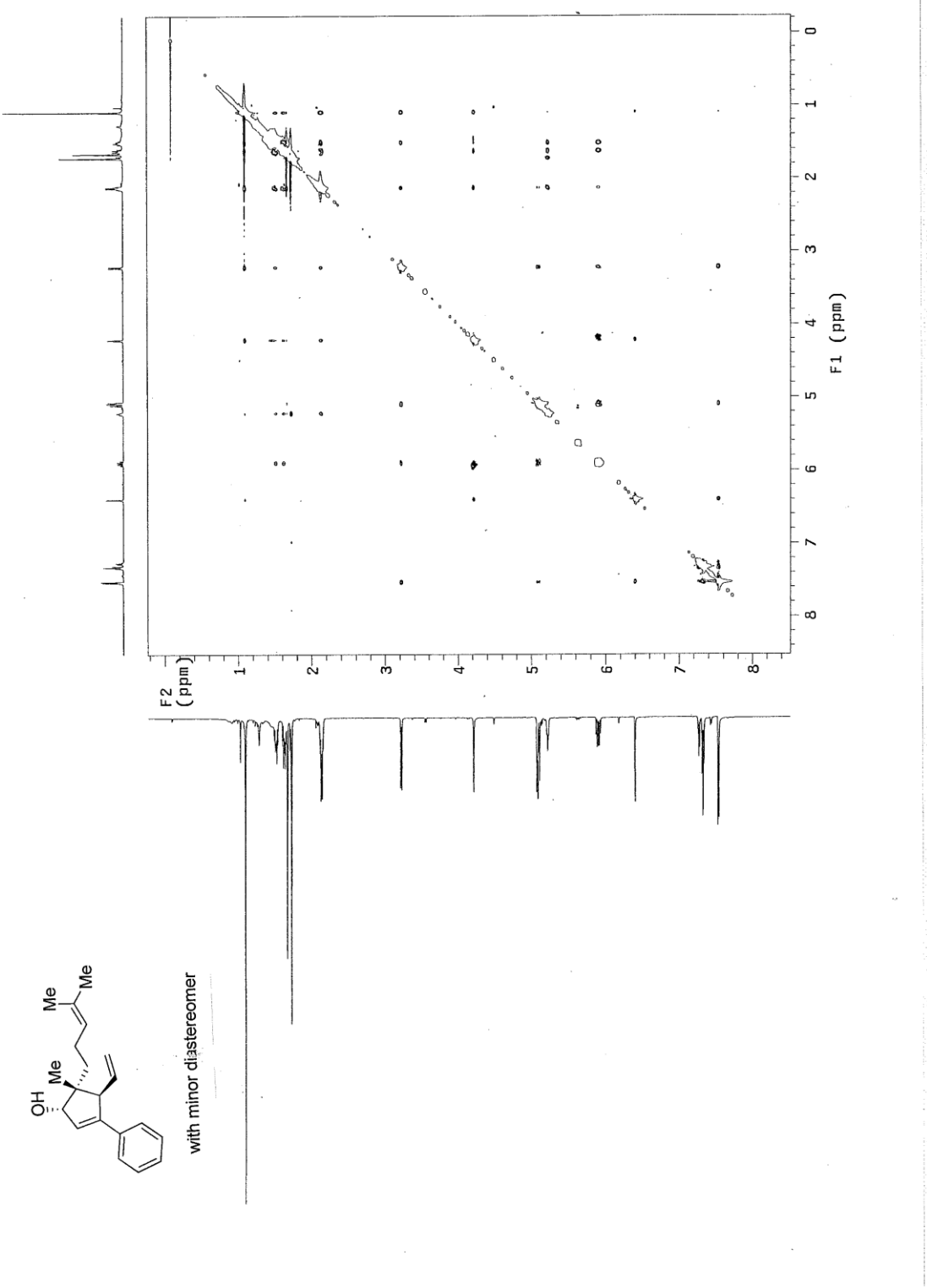

with minor diastereomer






with minor diastereomer

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F1 (ppm)
with minor diastereomer
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Me

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ppm
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8
7
6
5
4
3
2
1

Me
Me
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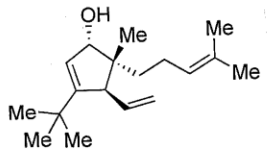
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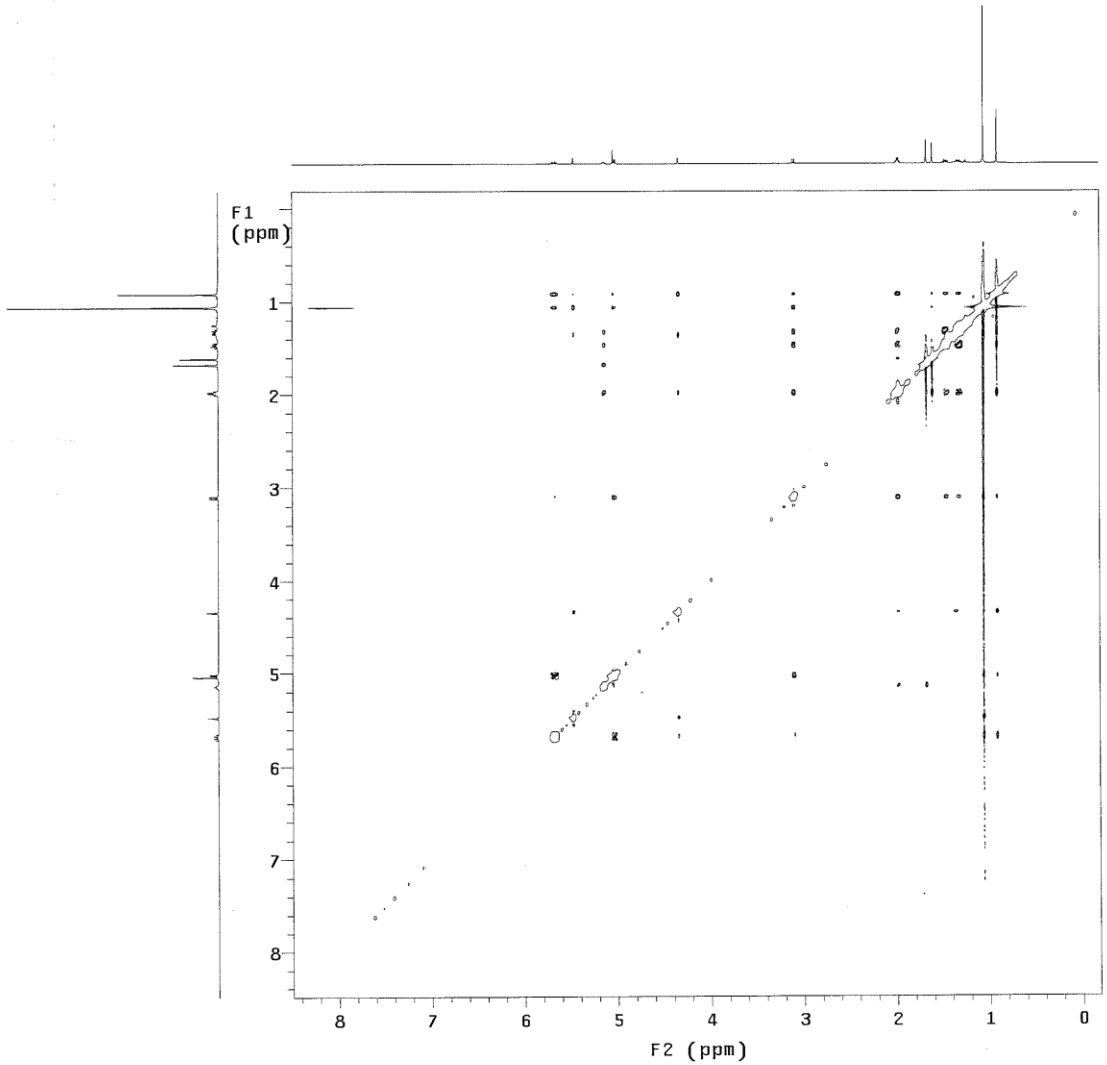
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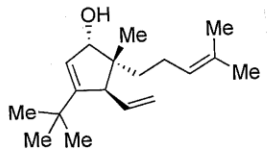
F2 (ppm)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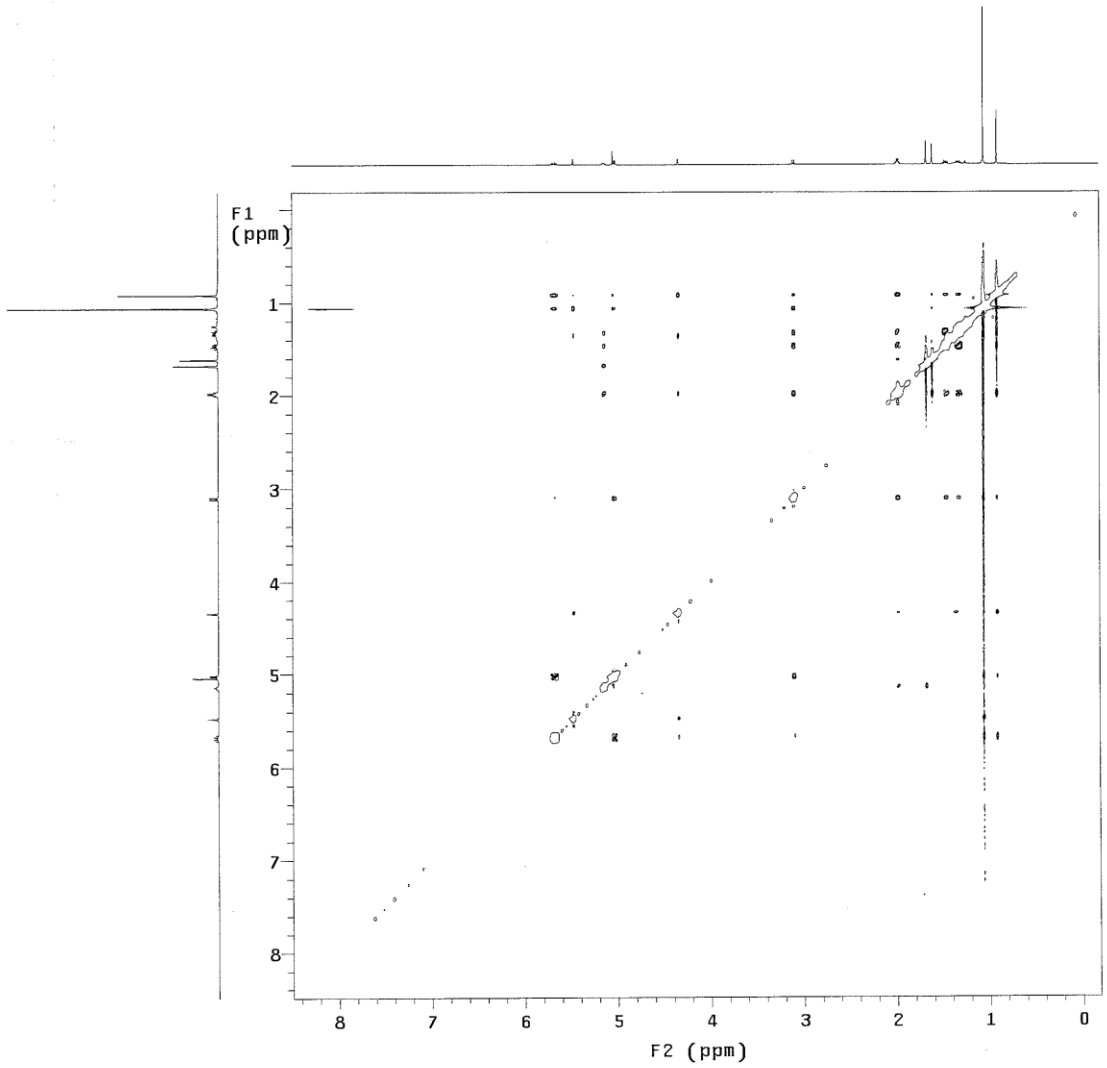
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ppm
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6
7
8
9

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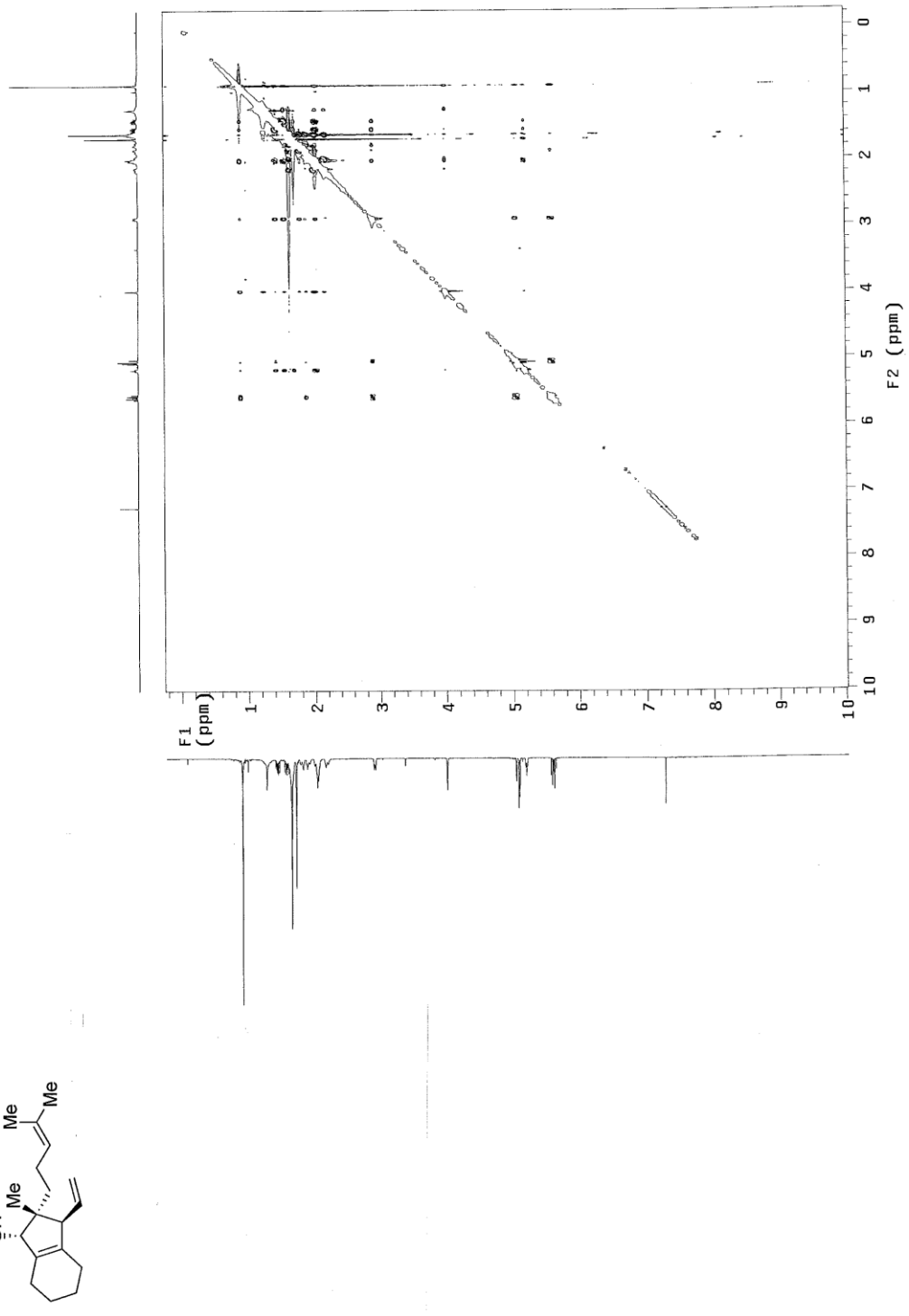
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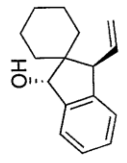
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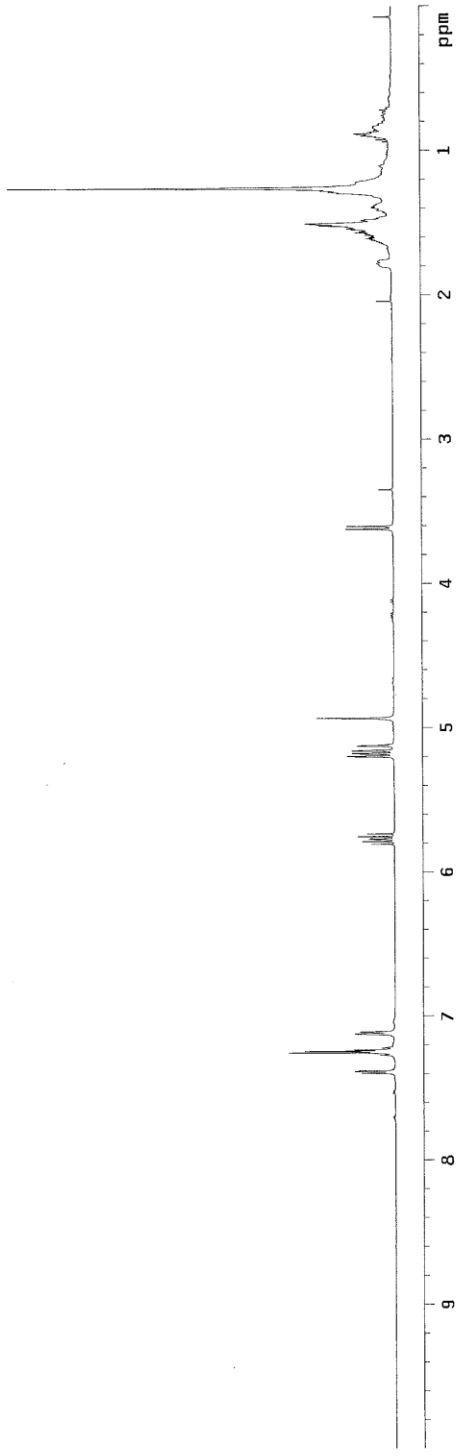
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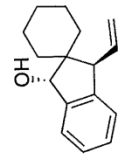
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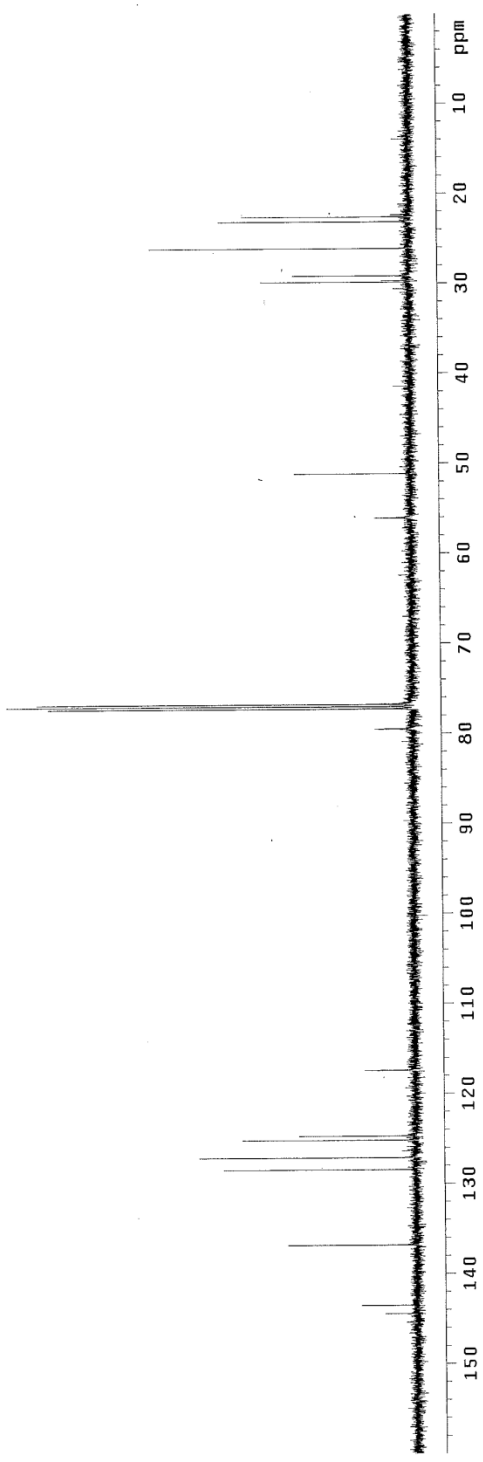
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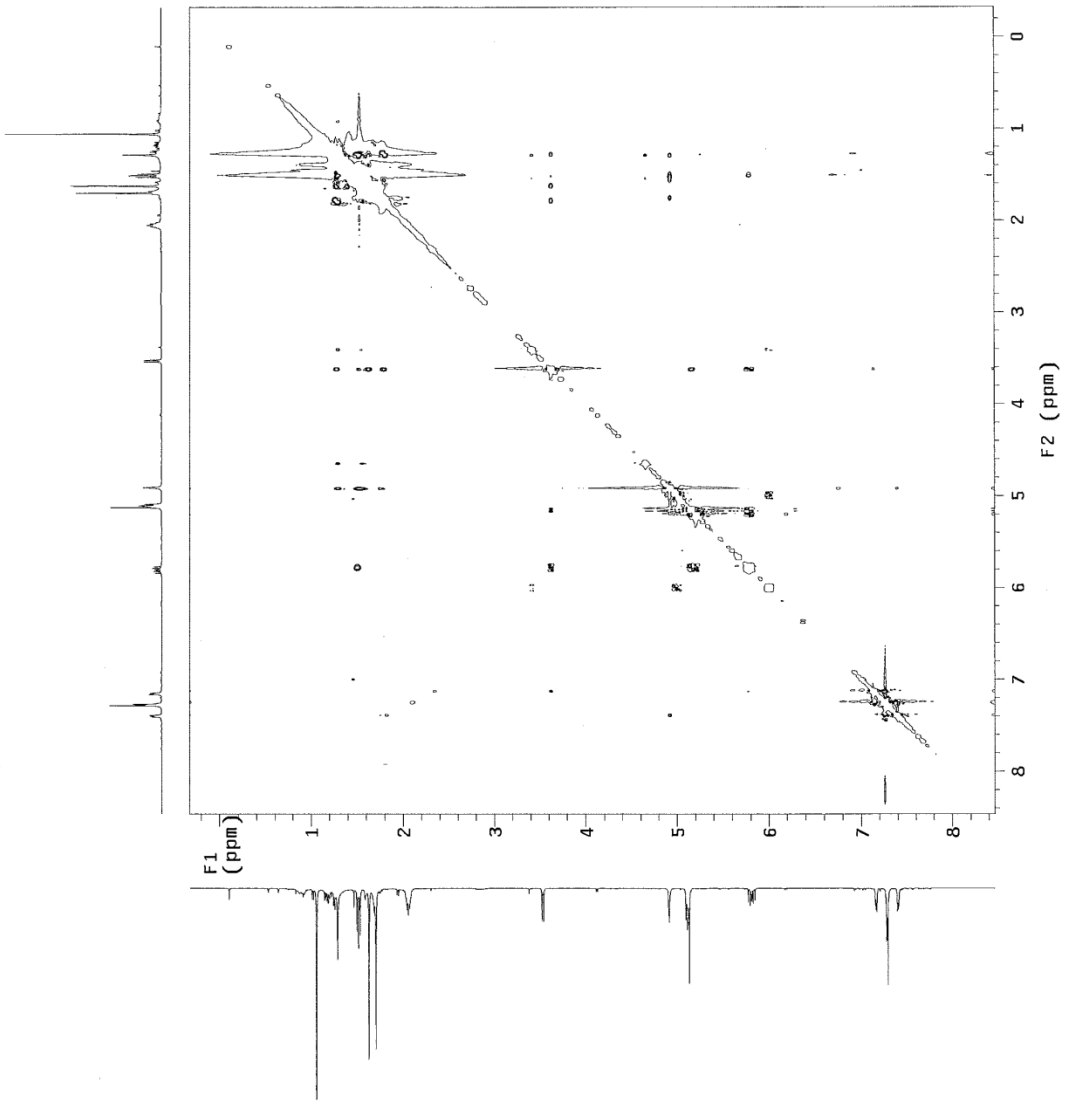
F1 (ppm)
F2 (ppm)
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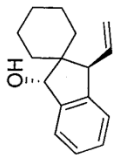
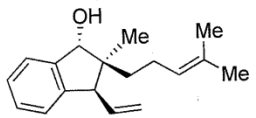
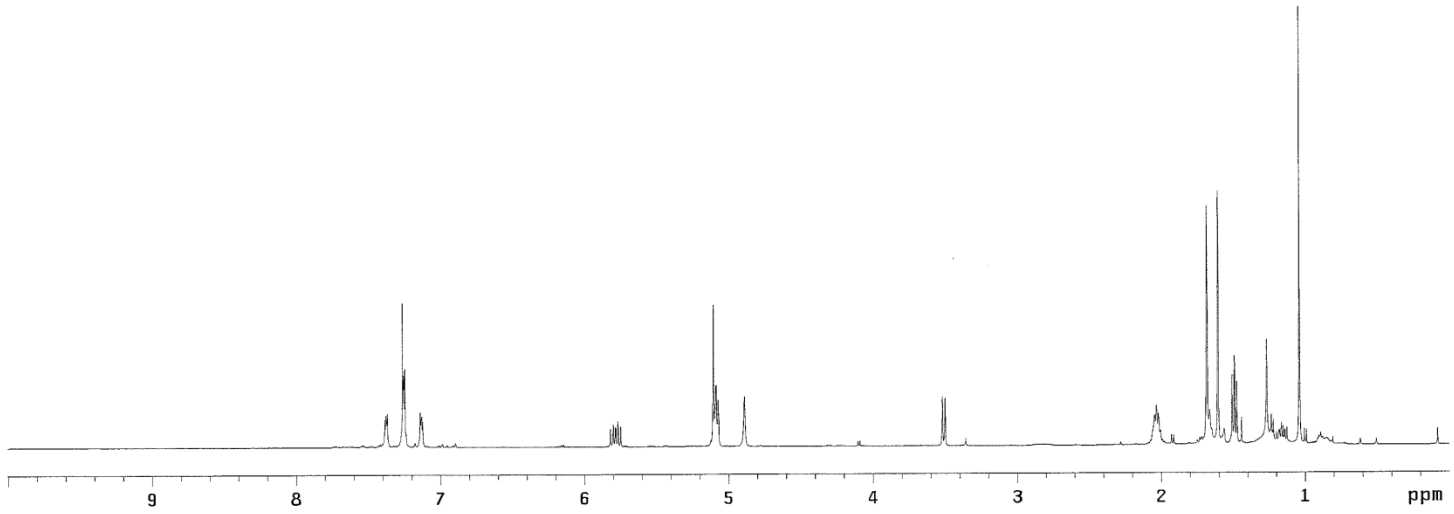
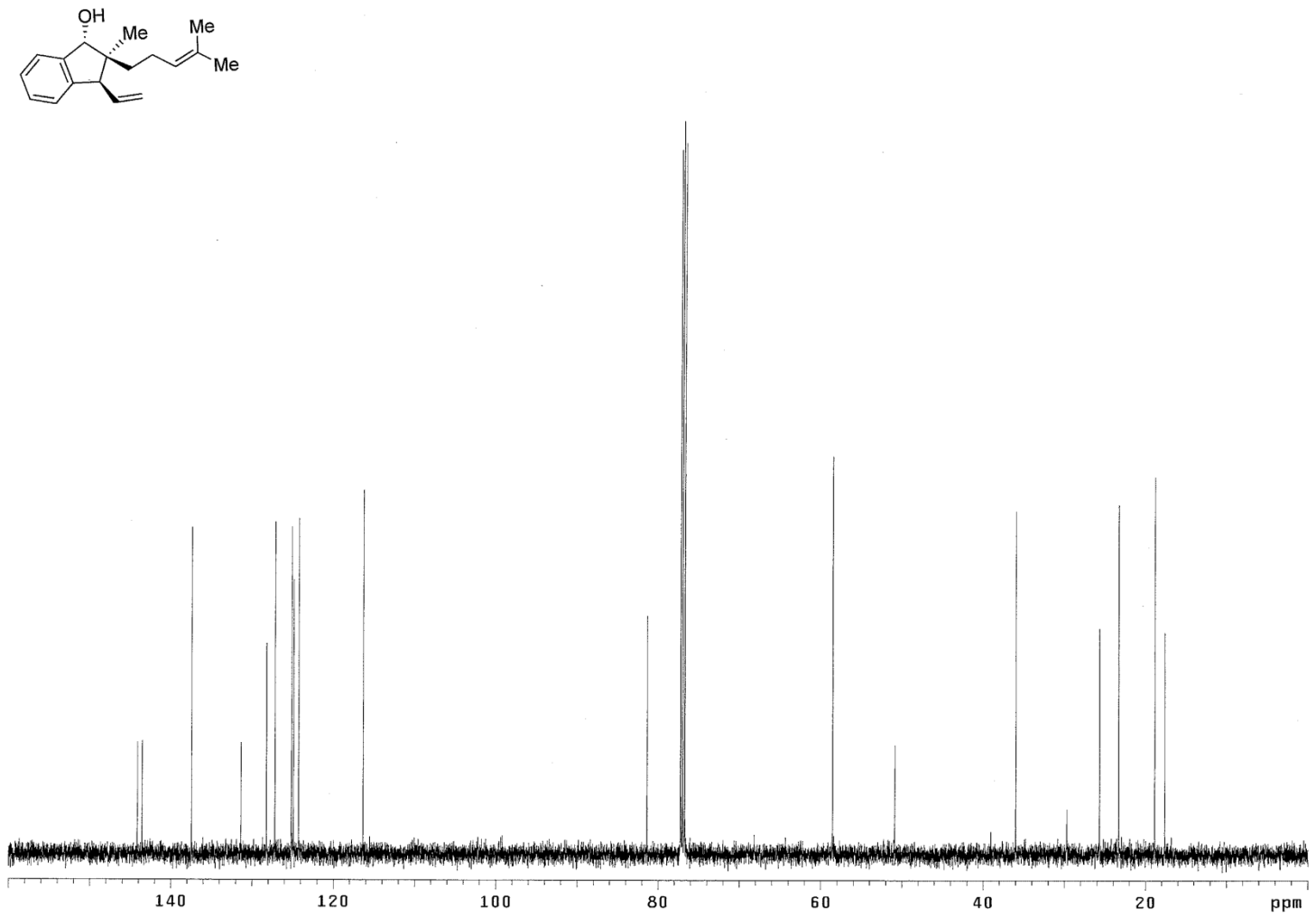
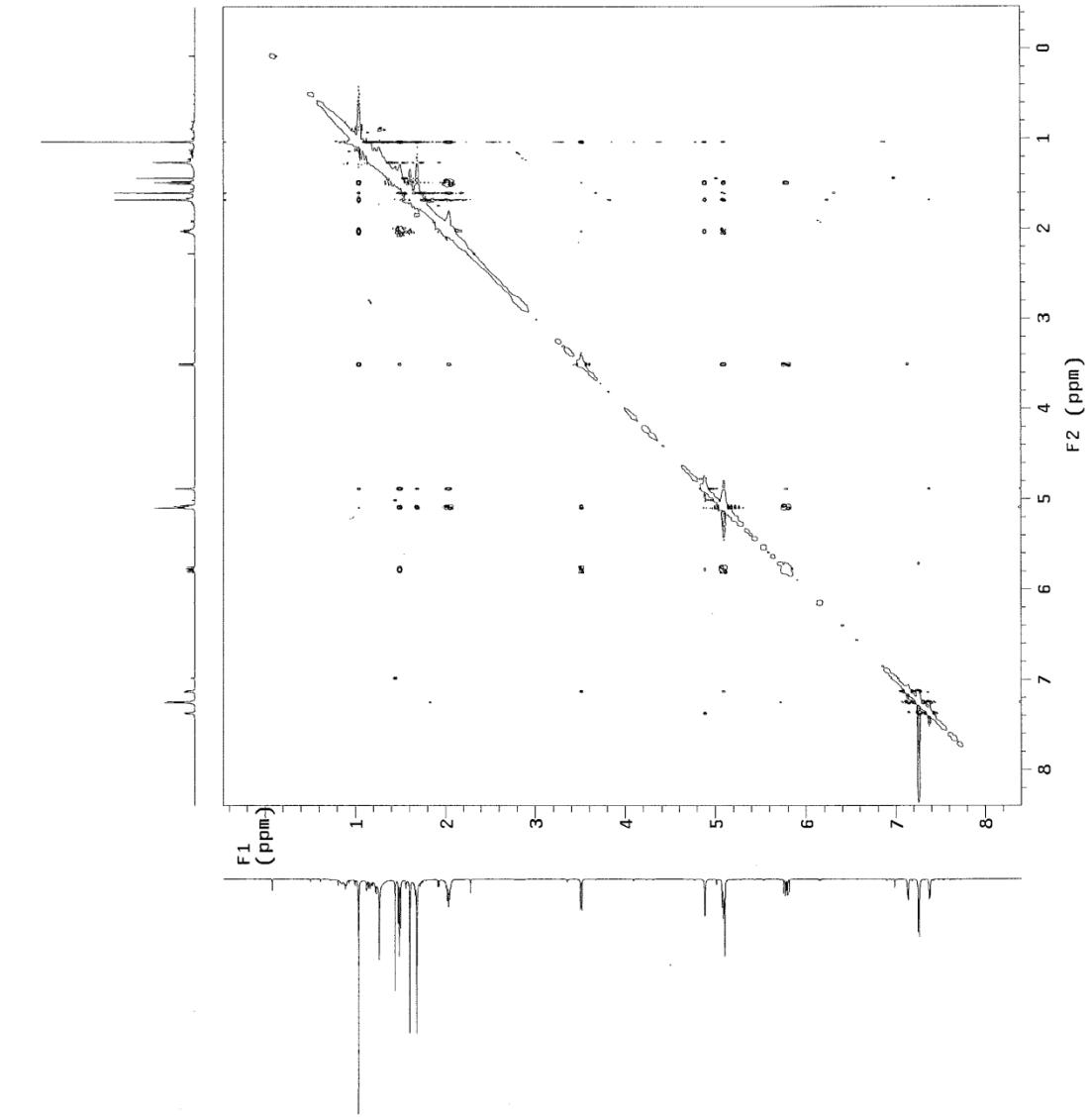
3
4
5
6
7
8
0

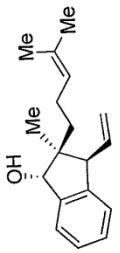

OH

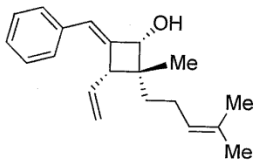

OH
Me
Me
Me

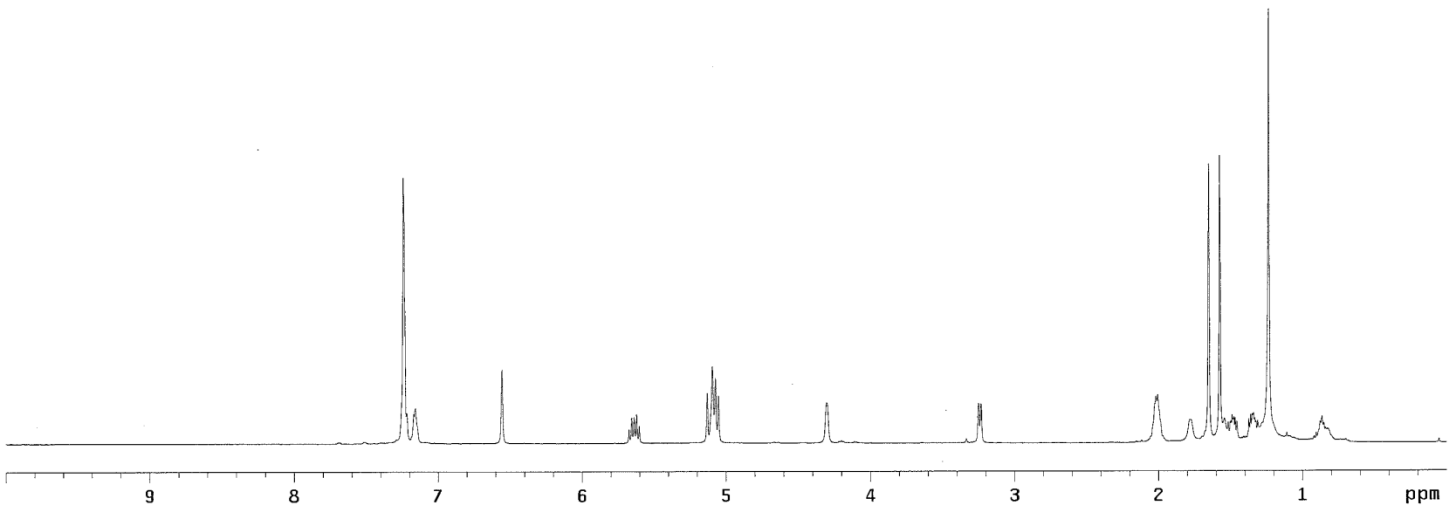

9
8
7
6
5
4
3
2
1
ppm


OH
Me
Me
Me
140
120
100
80
60
40
20
ppm


F1 (ppm)
F2 (ppm)


Me
Me
Me
OH


OH
Me
Me
Me


9
8
7
6
5
4
3
2
1
ppm

OH
Me
Me
Me
ppm
10
20
30
40
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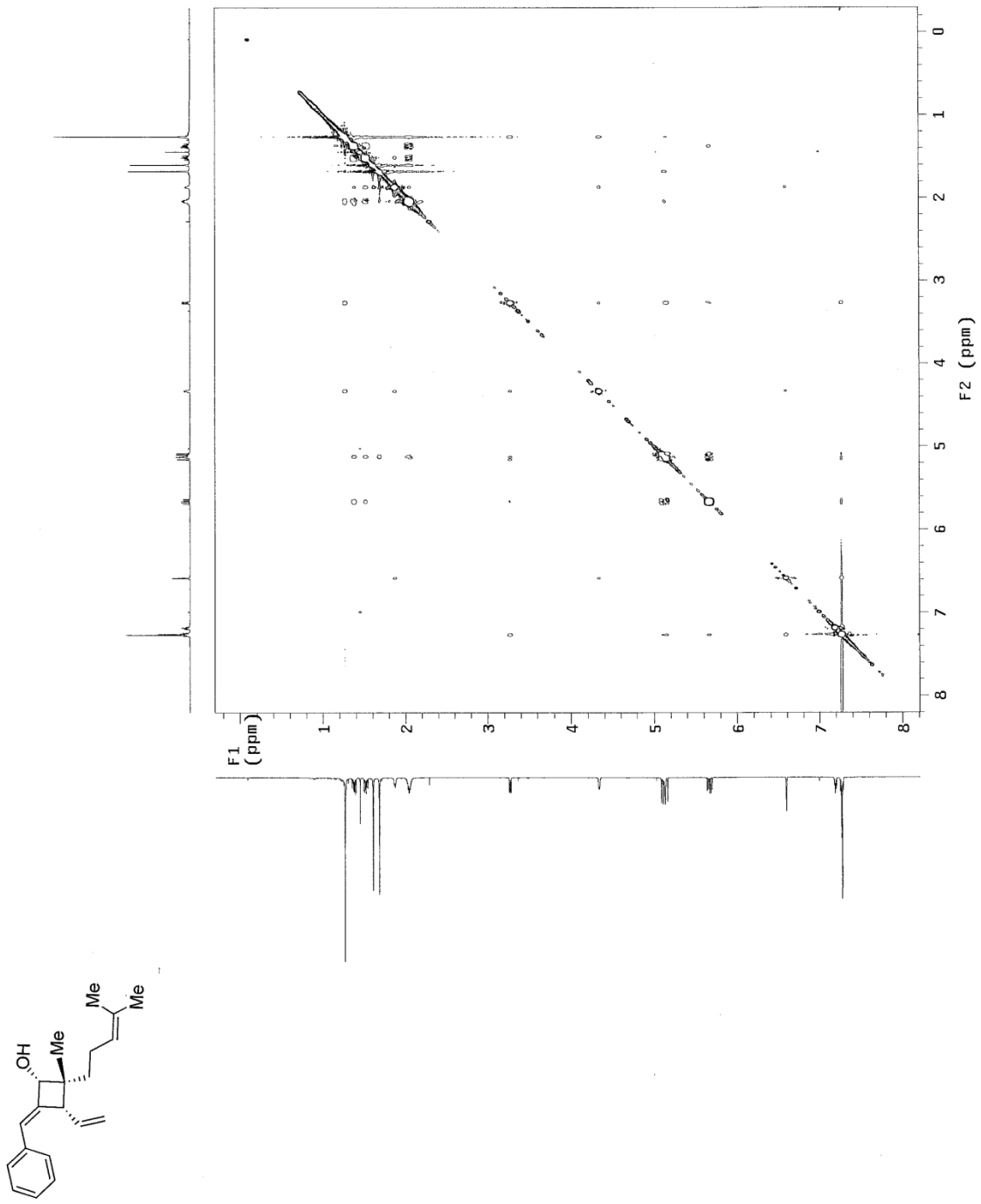
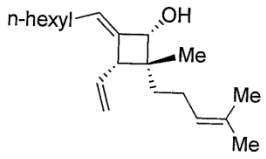
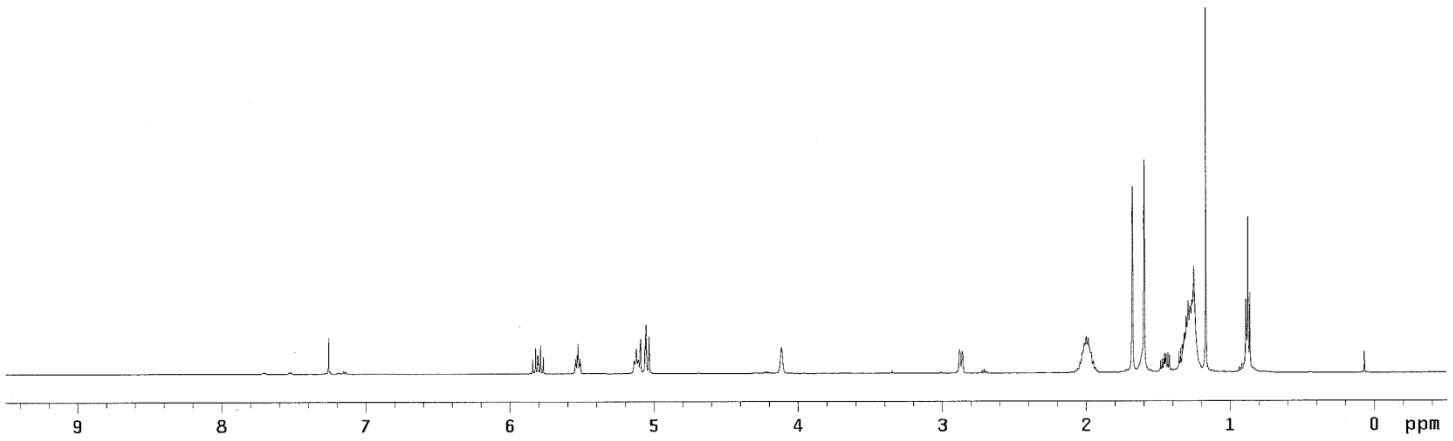
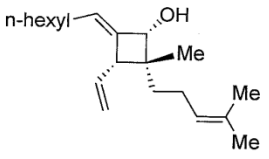
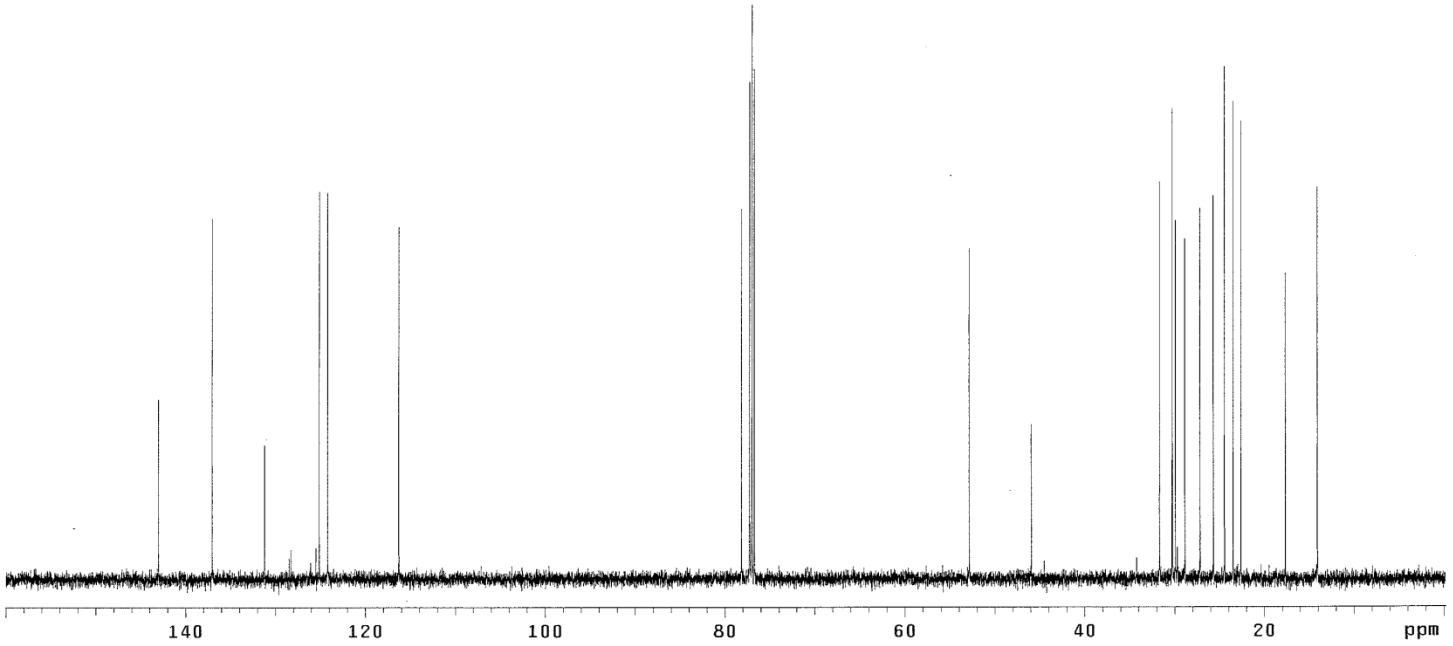
60
70
80
90
100
110
120
130
140
150

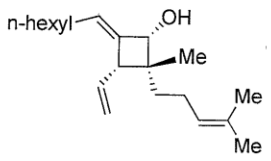

F1 (ppm)
F2 (ppm)
OH
Me
Me
Me

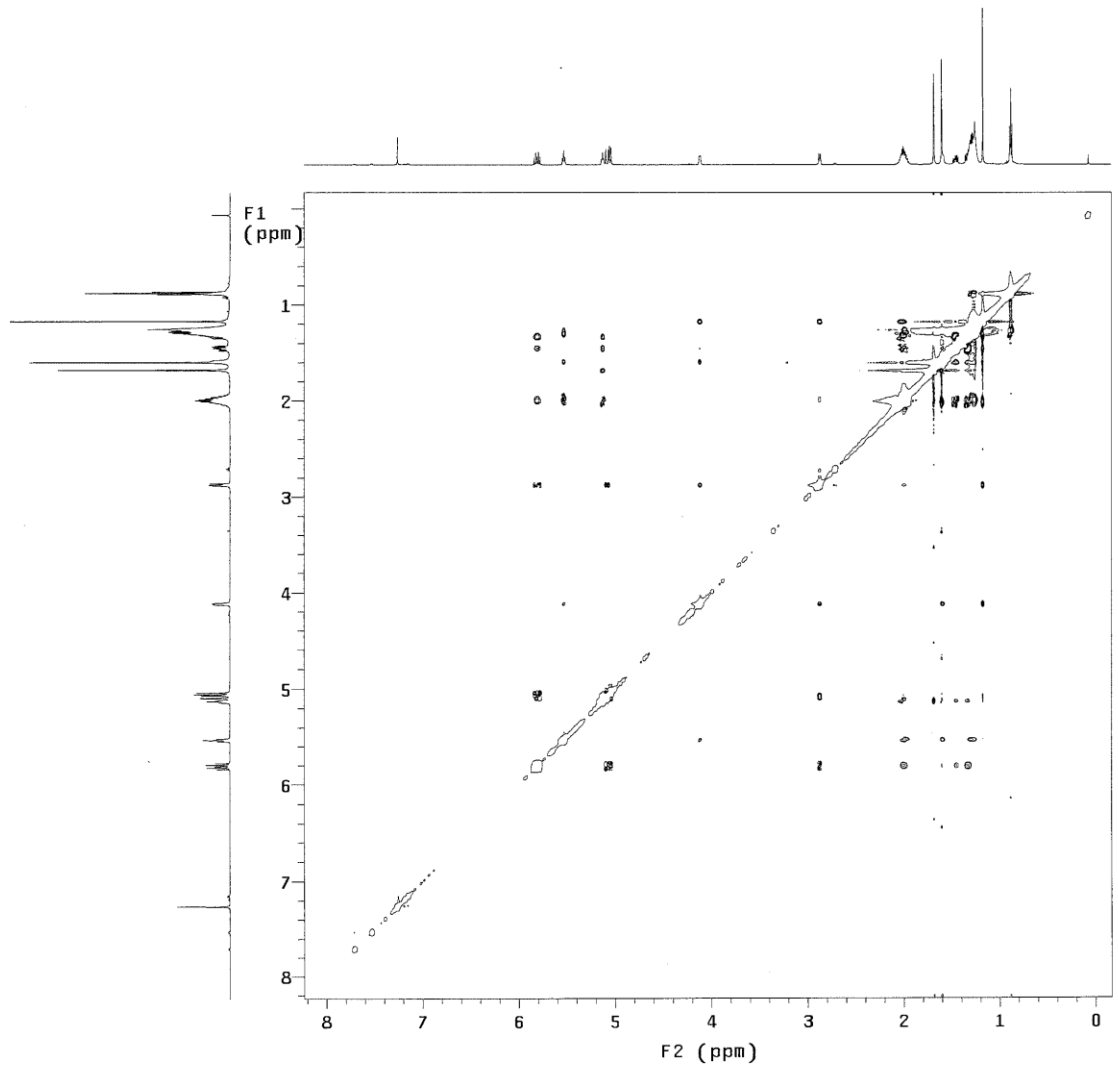

n-hexyl
OH
Me
Me
Me

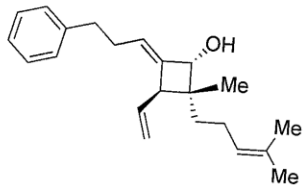

9
8
7
6
5
4
3
2
1
0
ppm


n-hexyl
OH
Me
Me
Me

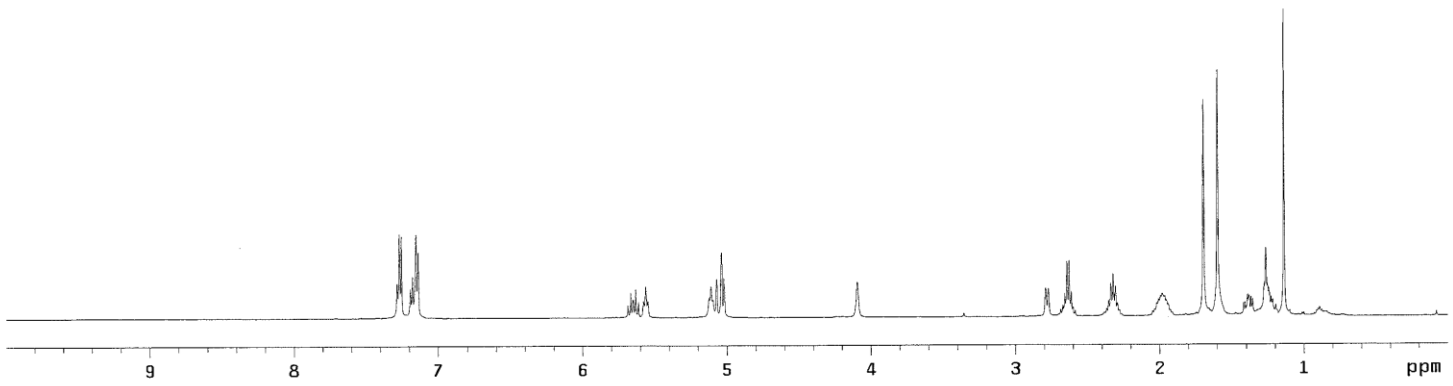

140
120
100
80
60
40
20
ppm


n-hexyl
OH
Me
Me
Me

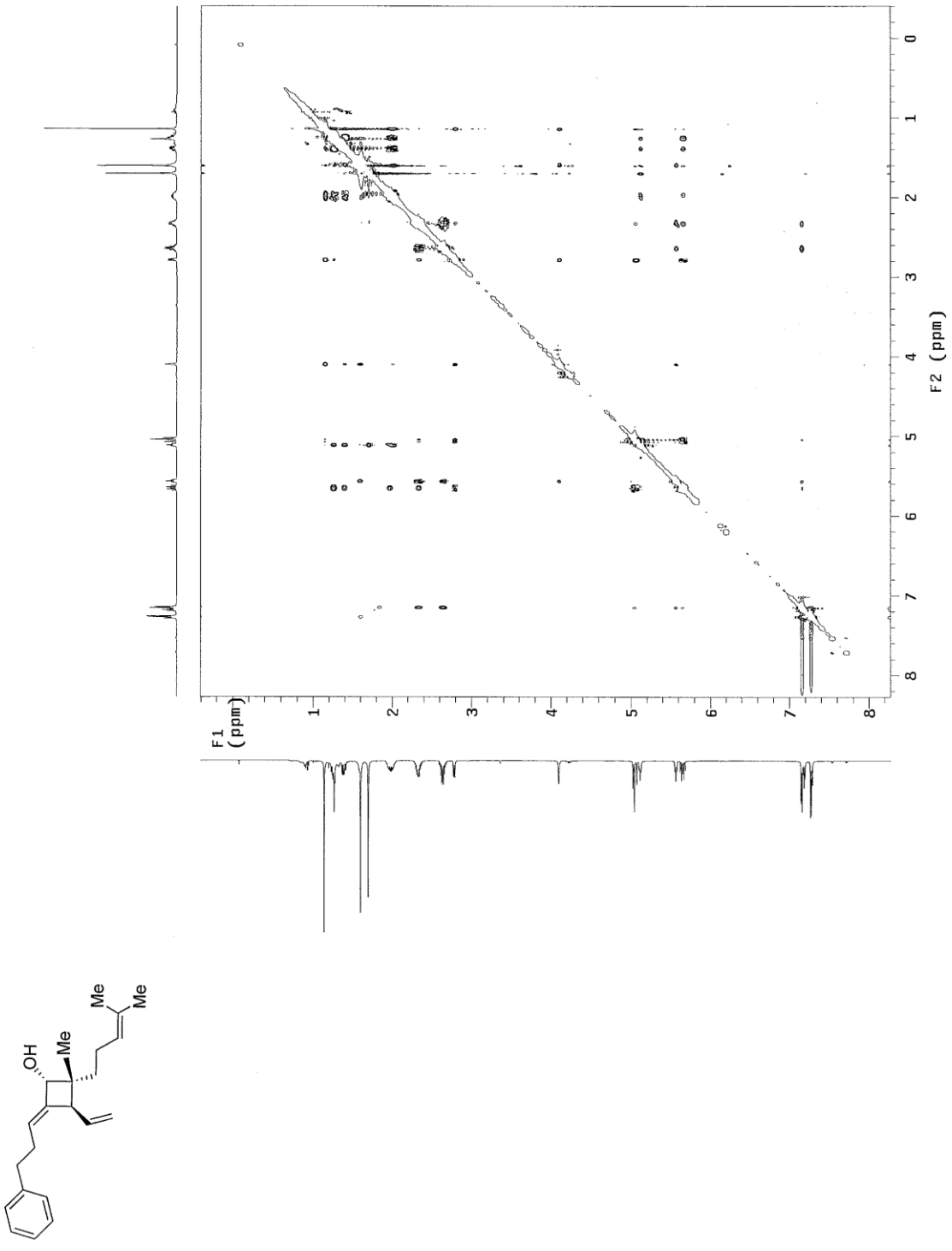

F1
(ppm)
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
F2 (ppm)

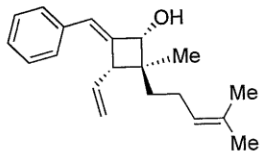

OH
Me
Me
Me



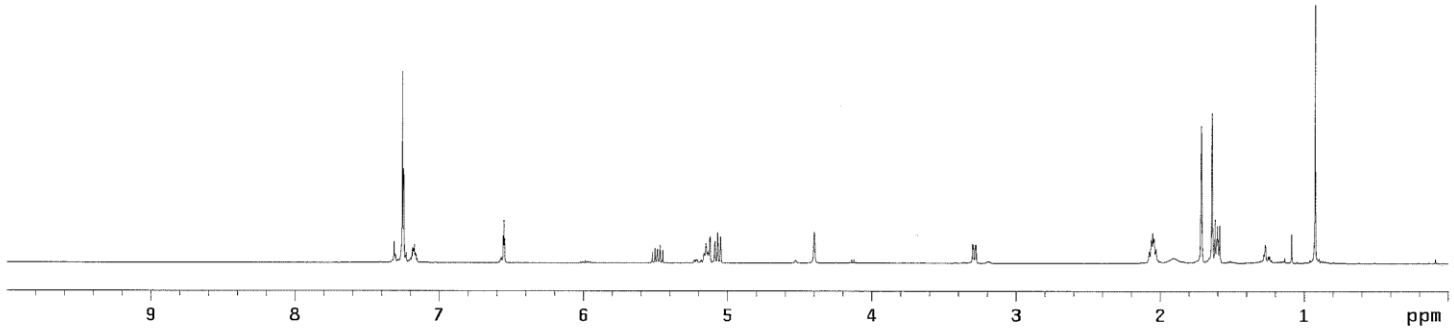

9
8
7
6
5
4
3
2
1
ppm

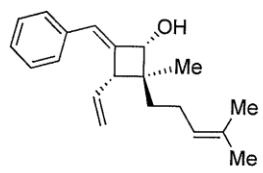
OH
Me
Me
Me
ppm
20
40
60
80
100
120
140


F1 (ppm)
F2 (ppm)
OH
Me
Me
Me

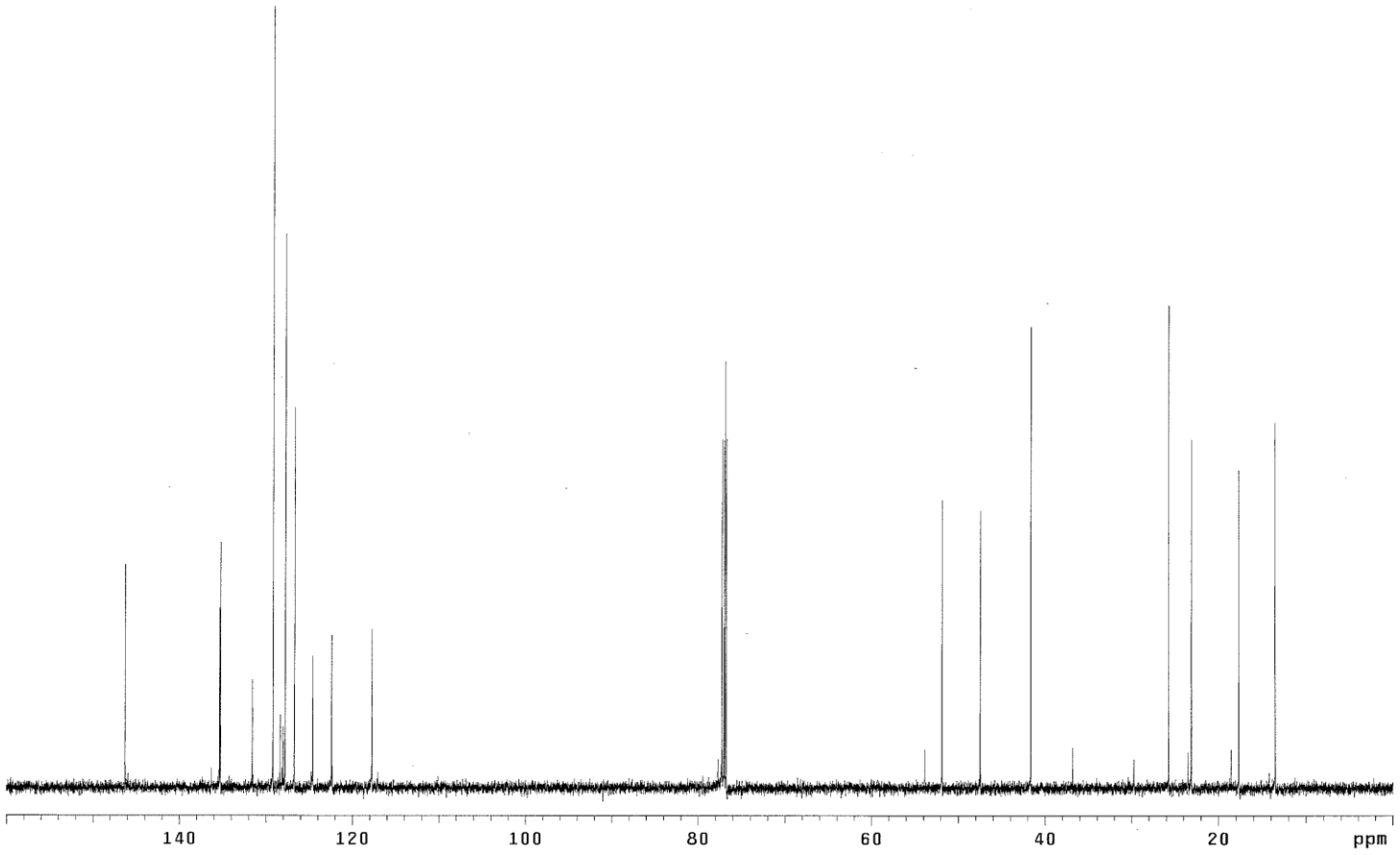


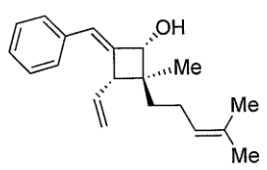

with minor diastereomer



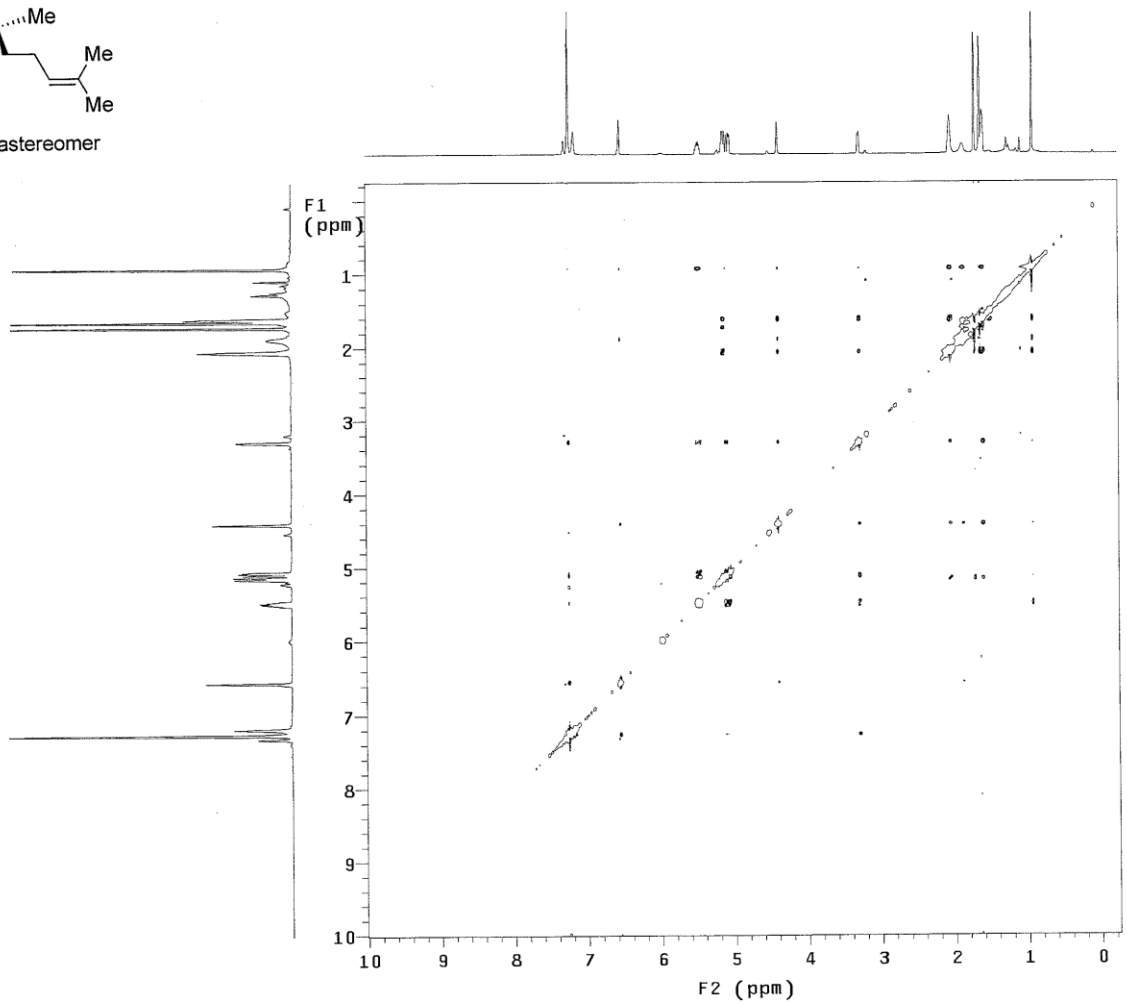


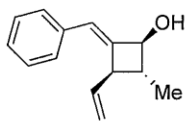

with minor diastereomer



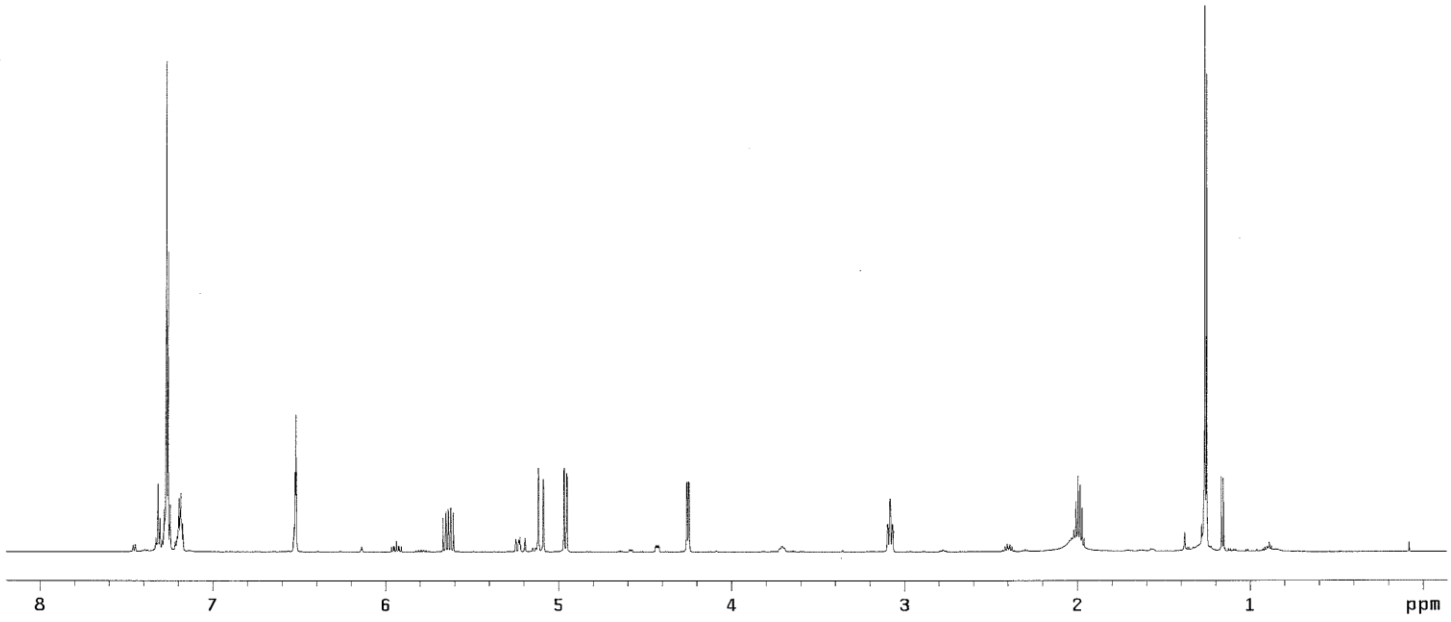


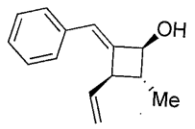

with minor diastereomer



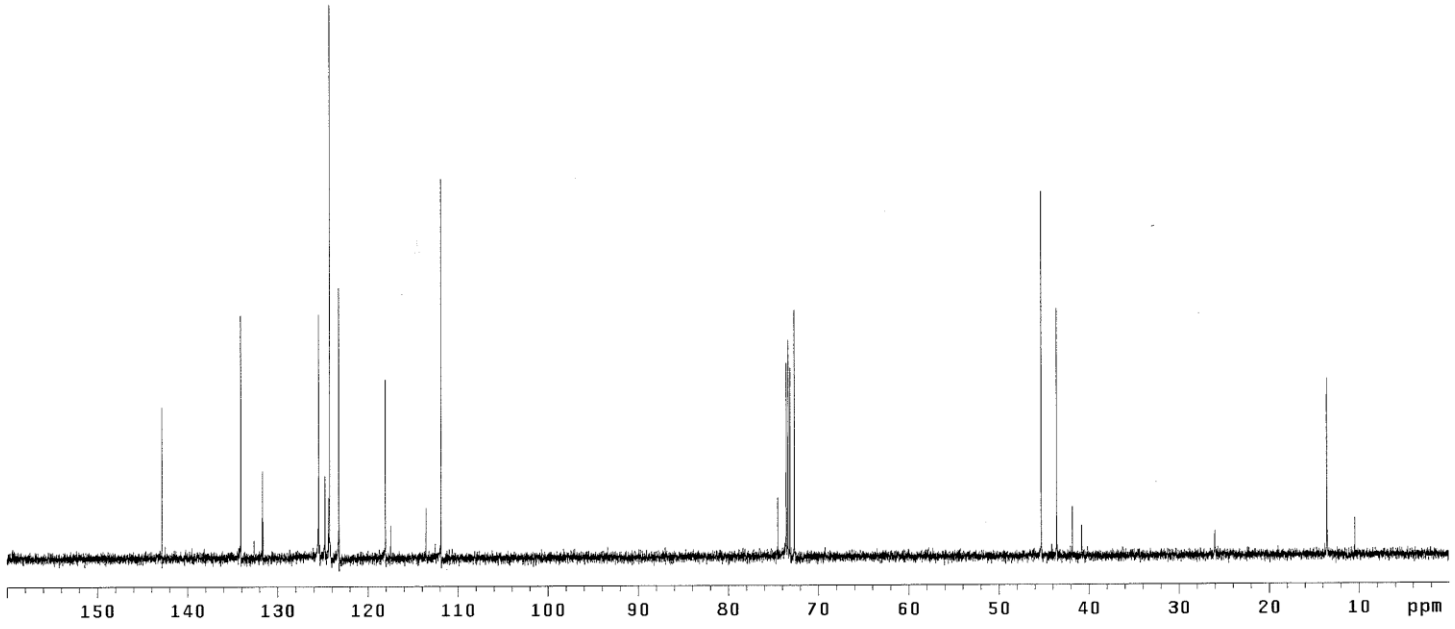


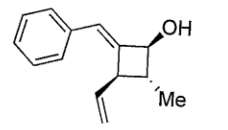

with minor diastereomer






with minor diastereomer






with minor diastereomer