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Preparation of Z-substituted styrenes using hiyama and suzuki cross couplings: a synthesis of glandulone B

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Preparation of *Z*-substituted styrenes using Hiyama and Suzuki Cross Couplings: A synthesis of glandulone B

By

Courtney A. Engles

Accepted in Partial Completion
Of the Requirements of the Degree
Master of Science

Moheb A. Ghali, Dean of the Graduate School

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MASTER'S THESIS

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May 18, 2011

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Preparation of *Z*-substituted styrenes using Hiyama and Suzuki Cross Couplings: A synthesis of glandulone B

A Thesis
Presented to
The Faculty of
Western Washington University

In Partial Fulfillment
Of the Requirements for the Degree
Master of Science

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May 2011

Abstract

The heliannuols are a family of allelochemicals that have been isolated from the common sunflower (*Helianthus annuus*). The 8-membered cyclic ether moiety found in many of the heliannuols is a rare motif in nature and provides a challenging synthetic target. It has been found that conformational constraint in the form of a *Z* olefin helps promote the cyclization of aryl epoxides to the 8-membered cyclic ether. Hiyama couplings of aryl iodides and cyclic vinyl siloxanes produce *Z*-styrenes in good to excellent yields. Due to the expense of the catalyst used for the synthesis of the siloxanes, an alternate pathway to the *Z* olefins utilizing vinyl cyclic boronic half acids was also pursued, but was ultimately unsuccessful. Due to the success of Hiyama couplings, the synthesis of glandulone B was pursued. The dimethoxyhydroquinone derivative of glandulone B was synthesized from an aryl iodide and cyclic vinyl siloxane in a 23% yield over 4 steps. Oxidation of the dimethoxyhydroquinone to glandulone B was explored.

Acknowledgements

I would like to thank the National Science Foundation for funding this research. I would also like to thank Dr. Greg O'Neil and Dr. Betsy Raymond for their advice and time. A special thanks to my family and friends for their love and support throughout my academic career. Most of all, I would like to thank Dr. Vyvyan for giving me the opportunity to be a part this research and for his time and patience helping me develop my skills and knowledge as an organic chemist.

Table of Contents

Tables and Figures

List of Abbreviations

anal	Analysis
Bn	Benzyl
Bu	Butyl
Bz	Benzoate
cat.	catalytic amount
Comb.	Combustion
m-CPBA	*meta*-chloroperbenzoic acid
Conc.	Concentrated
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl Acetate
FT-IR	Fourier-Transform Infrared Spectometry
GC/MS	Gas-Chromatography Mass Spctrometry
Hz	Hertz
HRMS	High Resolution Mass Spectrometry
IR	Infrared Spectrometry
Me	Methyl
MHz	Megahertz
MOM	Methoxymethyl
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
ppm	Parts per million
^{i}Pr	isopropyl
Pv	Pivaloate
sat. aq.	Saturated Aqueous

TBAF	Tetra *n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl ether
THF	Tetrahydrofuran
Tf	Triflate
TLC	Thin Layer Chromatrgraphy

1. Introduction.

1.1 Weeds.

With the world's population rapidly increasing, fewer farmers are feeding more people than ever before. To optimize growing conditions and crop yields, pesticides and fertilizers are widely used. This is a major problem; chemicals from both pollute groundwater, and pesticide residue can be detected in certain foods.[1] With 30% of the world's food supply destroyed by weeds, rodents, insects, and disease, it is becoming vital to find ways to reduce their impact on the world's food supply. This research focuses specifically on weed control.

There are nearly 7,000 different species of weeds; 200 to 300 of which are particularly troubling to farmers.[2] Weeds such as these compete with crops for resources, thereby lowering crop yields. In addition to affecting crop yields, weeds contaminate the soil with their seeds, so that the same weeds will grow in subsequent growing seasons. In order to combat weeds, synthetic herbicides were developed in the late 1940s. The first selective herbicides were 2,4-dichlorophenoxy acetic acid (2,4-D) (**1**) and 2-methyl-4-chlorophenoxyacetic acid (MCPA) (**2**) (Figure 1-1). These herbicides were modeled after the plant hormone auxin, which is responsible for cell growth and division.[3]

[1] Macías, F. A.; Galindo, J. C.; Molinillo, J. M.; Cutler, H. G. *Allelopathy: Chemistry and Mode of Action of Allelochemicals*; CRC Press: New York, 2004.

[2] Vyvyan, J. R. *Tetrahedron* **2002**, *58*, 1631-1646.

[3] Hall, Nina. *The New Chemistry;* Cambridge University Press; New York, **2000**.
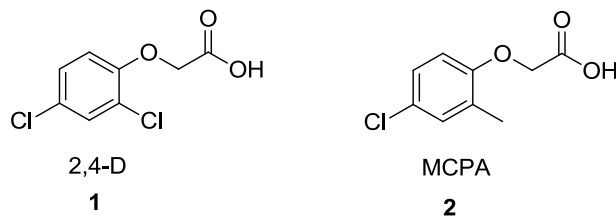
Figure 1-1: The first selective herbicides.

In the 1950s these were the most effective and widely used herbicides in the United States. It was not until the mid-1970s that weeds started to grow resistant to herbicides. Since then, a nearly exponential increase in the number of weeds resistant to herbicides has been observed (Figure 1-2).[4]
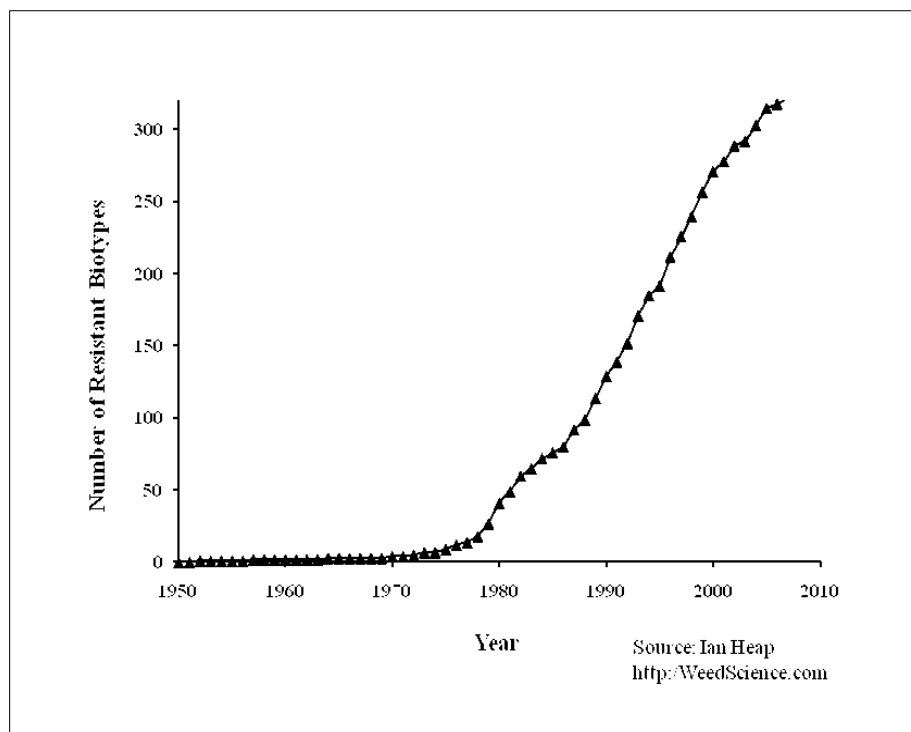
Figure 1-2: Weed resistance to herbicides.[4]

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[4] Weed Research. http://www.weedresearch.com (accessed Feb 17, 2010).

Due to this increase, there is a constant demand for the development of new, more potent, herbicides. In 2005, roughly $7 billion was spent on herbicides in the United States.[5] Cornell University did a study in 2008 in which they estimated the annual impact of invasive plants on US agriculture, wildlife, and recreation to be $34.7 billion.[6]

For the development of new herbicides, scientists are turning to allelopathy. Allelopathy is defined as "any direct or indirect effect by one plant, including microorganisms, on another through the production of chemicals released into the environment."[2] This includes both stimulatory and inhibitory effects. The modes by which these allelochemicals are released into the environment include volitilization from the leaves, leeching from decomposing plant matter, and exuding from the roots. These chemicals are then absorbed by the affected plant.[2]

1.2 Heliannuols and helianane.

1.2.1 Discovery and structure.

The helianane family of sesquiterpenes, including heliannuols A-L (**3-14**), were isolated from the sunflower, *Helianthus annuus,*[7,8,9,10,11,12] and exhibit potential as selective natural herbicides. The heliananes (**15a-c**) isolated from the marine sea sponges *Haliclona*

[5] Gianessi, L.; Reigner, N. The Value of Herbicids in U.S. Crop Production 2005 Update, 2006. Crop Life Foundation. http://www.croplifefoundation.org/Documents/Pesticide Benefits/Herbicides/2005 Update/2005UpdateReportand Data.pdf (accessed April 20, 2011).

[6] Weed Science Society of America Newsletter. http://www.wssa.net (accessed Feb 17, 2010).

[7] Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G.; Fronczek, F. R. *Tetrahedron. Lett.* **1993**, *34*, 1999.

[8] Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G.; Fronczek, F. R. *J. Org. Chem.* **1994**, *59*, 8261.

[9] Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Tetraderon Lett.* **1999**, *40*, 4725.

[10] Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *J. Nat. Prod.* **1999**, *62*, 1636.

[11] Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *J. Chem. Ecol.* **2000**, *26*, 2173

[12] Macías, F. A.; Torres, A.; Galindo, J. L. G.; Varela, R. M.; Álvarez, J. A.; Molinillo, J. M. G. *Phytochem.* **2002**, *61*, 687.

fasigera and *Spirastrella hartmani*, share the same unique core structure (Figure 1-3).[13,14]

The heliananes have been shown to be cytotoxic against three human tumor cell lines: breast,

colon, and lung.[14]   This cytotoxicity would make their synthesis potentially useful.

Heliannuol A
3

Heliannuol B
4

Heliannuol C
5

Heliannuol D
6

Heliannuol E
7

Heliannuol F
8

Heliannuol G
9

Heilannuol H
10

Heliannuol I
11

Heliannuol J
12

Heliannuol K
13

Heliannuol L
14

Heliananes
15a R = H
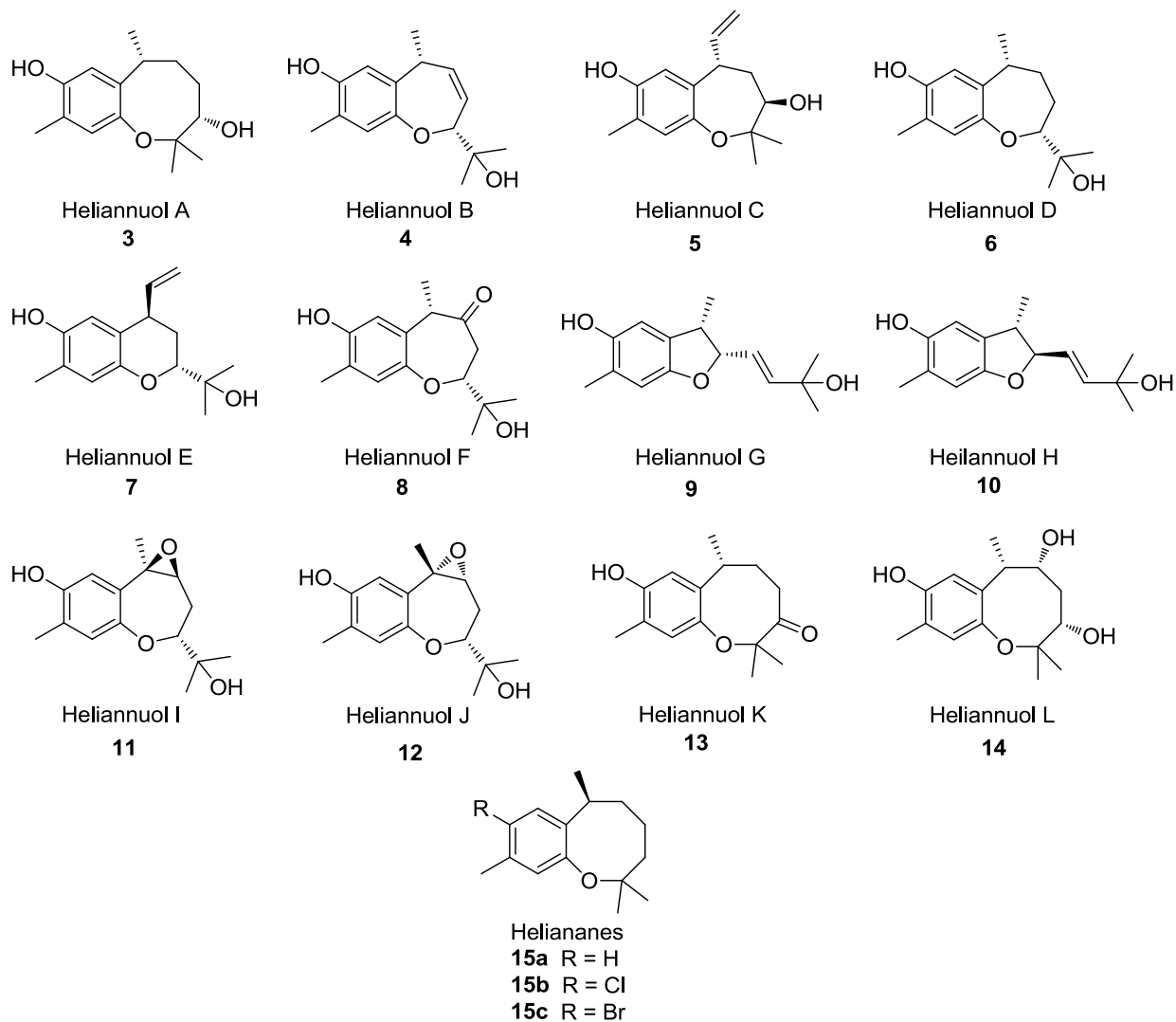**15b** R = Cl
15c R = Br

Figure 1-3: Heliannuols A-L and helianane.

[13] Harrison, B.; Crews, P. *J. Org. Chem.* **1997**, *62*, 2646.
[14] Martín, M. J.; Berrué, F.; Amade, P.; Fernández, R.; Francesch, A.; Reyes, F.; Cuevas, C. *J. Nat. Prod.* **2005**, *68*, 1554.

The heliannuols and heliananes have a novel sesquiterpenoid structure. Their core contains a benzene ring fused to a 5-, 6-, 7-, or 8-membered cyclic ether. Common to all family members is either a methyl or a vinyl group in the benzylic position and a methyl group on the aromatic core *meta* to the cyclic ether oxygen. All heliannuols have a hydroxyl *para* to the ethereal oxygen, and the cyclic ether has varying degrees of oxidation. Medium ring cyclic ethers fused to an aromatic core are a rare motif in nature and their challenging structures make them interesting synthetic targets,[15,16,17,18,19,20,21] especially heliannuols A, K, L and the heliananes.

The effects of Heliannuols A, B, C, and D on seed germination and root growth of monocotyledon and dicotyledon species were tested by Macías.[9] It was found that both root growth and seed germination were inhibited for dicotyledon species, but stimulated for monocotyledon plant species. Heliannuols A and D were found to be the most potent, showing activity at 10^{-9} M concentration. Unfortunately, the heliannuols exist in nature in such small quantities that isolation from the natural source for use as herbicides would be impractical.

1.2.2 Proposed biosynthetic pathway.

Scientists have been able to isolate several compounds from both the sunflower and the Indonesian sea sponge that are believed to be precursors to the heliannuols and helianane (Figure 1-4).[1]

---

[15]Grimm, E. L.; Levac, S.; Timble, L. A. *Tetrahedron Lett.* **1994**, *35*, 6847.
[16] Vyvyan, J. R.; Looper, R. E. *Tetrahedron Lett.* **2000**, *41*, 1151.
[17] Shishido, K. J.; Takabatake, K. *J. Chem. Soc., Perkin Trans 1*. **2000**, 1807-1808.
[18] Venkateswaran, R.V.; Tuhina, K.; Bhowmik, D. R. *Chem. Commun.* **2002**, 634.
[19] Ollivier, J.; Lecornue, F. *Synlett*, **2004**, 1613.
[20] Snieckus, V.; Stefinovic, M. *J. Org. Chem.* **1998**, *63*, 2808-2809.
[21] Shishido, K.; Kishuku, H.; Shindo, M. *Chem. Commun.* **2003**, 350-351.
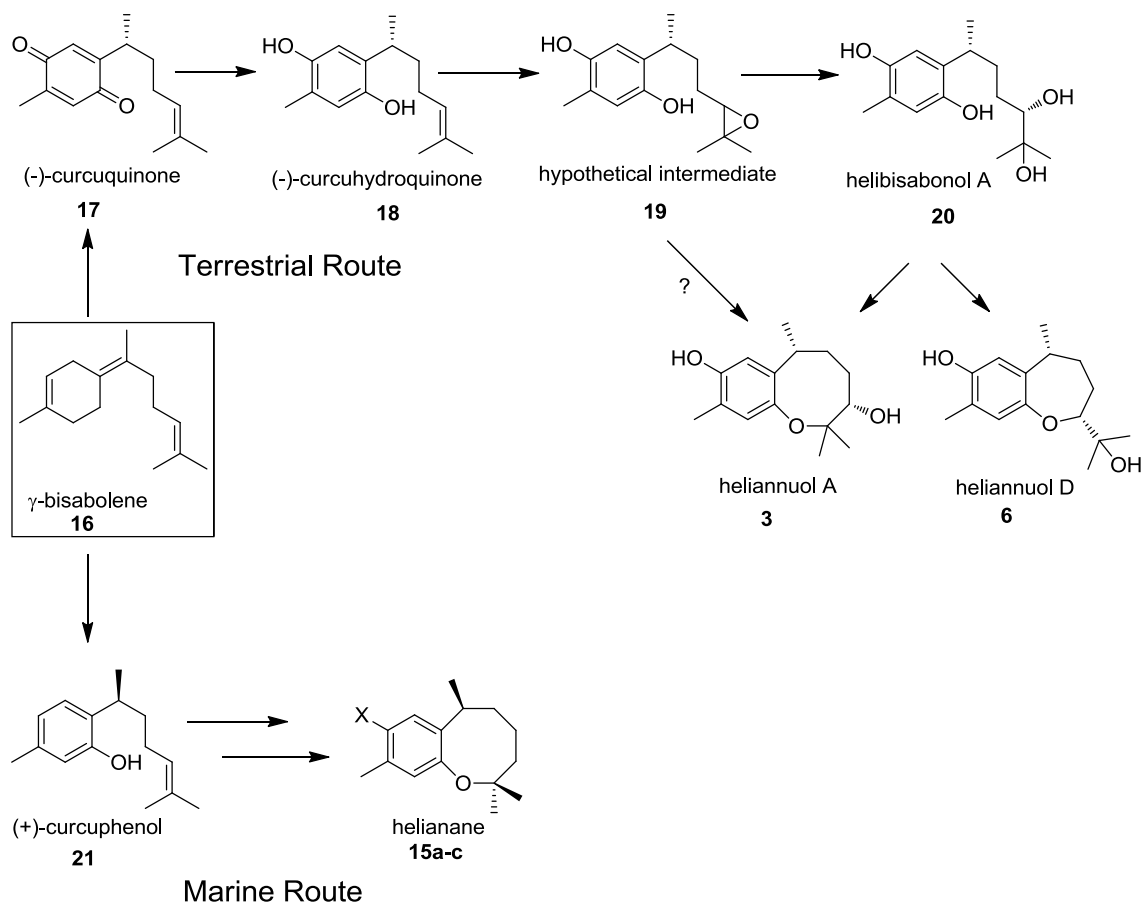
Figure 1-4: Proposed biosynthetic pathway.[1]

It is believed the biosynthetic path starts with γ-bisabolene (**16**). In the terrestrial route, **16** is oxidized to (-)-curcuquinone (**17**). This is then reduced to (-)-curcuhydroquinone (**18**). It is hypothesized that intermediate epoxide **19** is formed during the biosynthesis of **18** to helibisabonol A (**20**). Subsequent cyclization can give either the 7-membered cyclic ether **6** or 8-membered cyclic ether **3**. In the marine route, γ-bisabolene (**16**) is oxidized to (+)-curcuphenol (**21**), which is further oxidized and cyclized through unknown intermediates to form **15**.

1.3 Glandulones.

Isolated from the non-capitate glandular trichomes of *Helianthus annuus* are the benzoquinones glandulone A, B, and C (Figure 1-5).[22] These bisabolene sesquiterpenes are similar to those involved in the biosynthetic pathway for the heliannuols. Glandulone A (**22**) and (-)-curcuquinone (**17**) have the same structure except **22** contains an α,β-unsaturated aldehyde. In addition to the aldehyde, glandulone B (**23**) possesses a *Z* olefin. Glandulone C (**24**) contains a partially reduced quinone. These natural products possess anti-microbial properties, and have exhibited cytostatic effects against the bacterium *Bacillus brevis*.[22] This is an aerobic, spore-forming bacterium involved in the degradation of most substrates, such as proteins, starch, pectin, etc., derived from plant and animal sources.[23]

Glandulone A
22

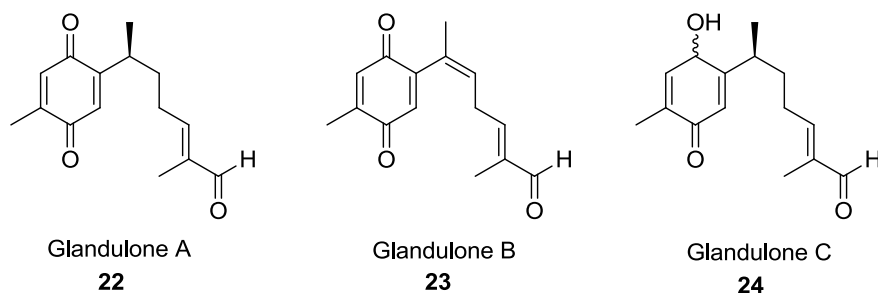Glandulone B
23

Glandulone C
24

Figure 1-5: Glandulones A, B, and C.

[22] Spring, O.; Rodon, U.; Macías, F. A. *Phytochem.* **1992**, *31*, 1541-1544.
[23] Online Textbook of Bacteriology. htttp://www.textbookofbacteriology.net/Bacillus.html (accessed April 2, 2011).

1.4 Challenges of medium sized ring synthesis.

1.4.1 Baldwin's rules.

J. E. Baldwin developed a set of principles and descriptions for the feasibility of ring-formation through nucleophilic attack.[24]   Baldwin used four parameters to describe these cyclization reactions. The first parameter assumes that the attacking nucleophile is a first-row element. The other three principles describe the structure of the cyclization product. The prefix is the size of the ring formed. In our case, the formation of the seven-membered ring would be denoted with a prefix of '7', or the eight-membered ring with an '8'. Following the prefix is a description of the site where nuclephilic attack occurs. This illustrated below for a phenol nucleophile on an epoxide (Figure 1-6). If the phenol attacks the less-substituted position of the epoxide, the resulting hydroxyl group will be on the outside of the ring, not directly attached to the ring formed. This is indicated with the term *exo*. However, if the phenol attacks the *more* substituted carbon, the resulting hydroxyl group will be attached to ring formed. This is denoted as an *endo* attack. Finally, the suffix describes the hybridization of the carbon atom to which the new bond is formed. A sp^3 hybridized carbon is denoted by *tet*, sp^2 is trig, and *sp* is *dig*.
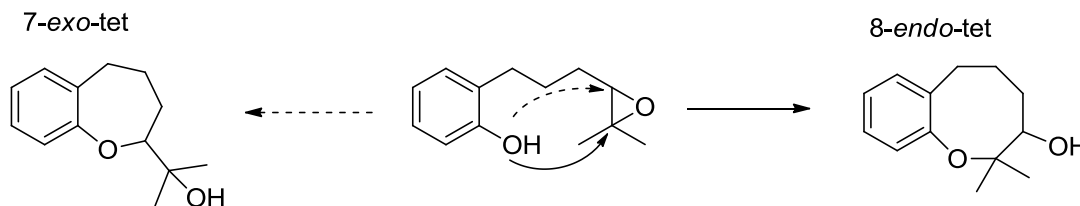

Figure 1-6: Example of Baldwin's classification system.

[24] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

Baldwin used this classification system along with literature data to predict the favorability of ring closure reactions (Table 1-1).

Table 1-1: Summary of Baldwin's rules.[25]

	Exocyclic			Endocyclic	
Ring Size	sp *(dig)*	sp^2 *(trig)*	sp^3 *(tet)*	sp *(dig)*	sp^2 *(trig)*
3	Unfavorable	Favorable	Favorable	Favorable	Unfavorable
4	Favorable	Favorable	Favorable	Favorable	Unfavorable
5	Favorable	Favorable	Favorable	Favorable	Unfavorable
6	Favorable	Favorable	Favorable	Favorable	Favorable
7	Favorable	Favorable	Favorable	Favorable	Favorable

For the heliannuols, the epoxide-opening ring-closure shown in Figure 1-6 has two possible outcomes; 7-*exo*-tet and 8-*endo*-tet. Inspection of Table 1-1 makes it immediately obvious that there are no predictions for the formation of medium (8-12) or large (>13) sized rings. Also, Baldwin's rules do not address endo-*tet* cyclizations.

1.4.2 Ring formation studies.

In addition to Baldwin's rules, it is important to look at studies measuring the rate of ring closure by ring size to gain insight into the challenge of synthesizing medium sized rings. One such study is of the relative rate of cyclization of diethyl (ω-bromoalkyl)-malonate ester anions as a function of ring size (Table 1-2).[26]

---

[25] Adapted from: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd Ed. Part A. *Structure and Mechanisms*; Plenum Press: New York, 1990.
[26] Casadei, M. A.; Galli, G.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051.

**Table 1-2. Rate of cyclization of diethyl (ω-bromoalkyl)-
malonate ester anions as a function of ring size.[26]**
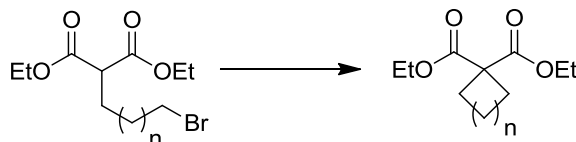
n	Ring Size	Relative Rate (sec^{-1})
1	4	0.58
2	5	833
3	6	1.0
4	7	8.7×10^{-3}
5	8	1.5×10^{-4}
6	9	1.7×10^{-5}
7	10	1.4×10^{-6}
8	11	2.9×10^{-6}
9	12	4.0×10^{-4}
10	13	7.4×10^{-4}
14	17	2.9×10^{-3}
17	21	4.3×10^{-3}

The fastest cyclization occurred at 833 sec^{-1} for the five-membered ring. The slowest cyclization rate of 1.4×10^{-6} sec^{-1} was achieved with the ten-membered ring. The formation of medium sized rings (7-10) are slower than both the smaller and the larger rings.

In addition to rate of cyclization of diethyl (ω-bromoalkyl)-malonate ester anions, Illuminati and Mandolini conducted kinetic studies focused on the cyclization rate of ω-bromoalkanecarboxylates.[27]

---

[27] Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, 95.
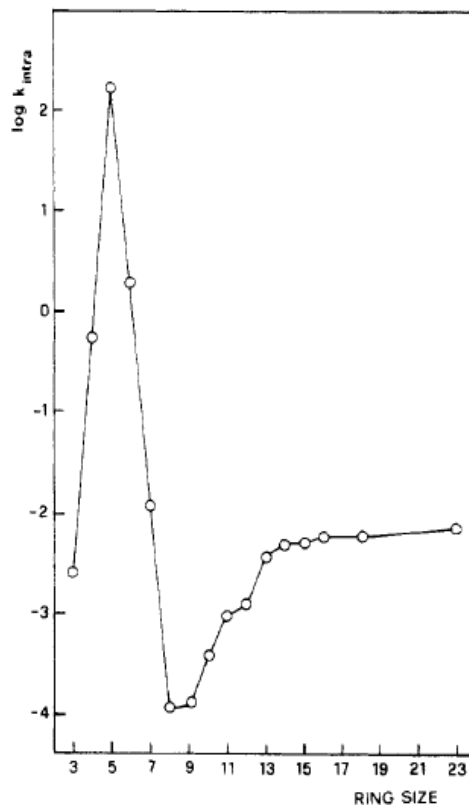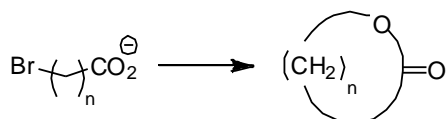
Figure 1-7: Cyclization rates of ω-bromoalkanecarboxylates vs. ring size.[27]

Figure 1-7 shows the rate of cyclization of a bromoester to the lactone by ring size formed. As in the previous example, the cyclization rate for 8-, and 9-membered rings are significantly slower than other rings sizes. The 8-membered ring forms slightly slower than the 9-membered ring. These reduced rates have to do with a combination of entropic and enthalpic factors.

The probability of achieving the required molecular orientation for ring formation is dependent on the length of the chain. When a chain of carbon-carbon bonds rotate freely in

solution, the two reactive ends meet randomly. As the chain gets longer, the likelihood that the two ends will meet decreases because they are separated further in space.[28] Upon ring formation, the previously freely-rotating carbon chain looses much of its freedom to rotate. This results in an unfavorable loss of entropy, but only to a certain point. Large rings are not as rigid and have significantly more rotation around their bonds.[28] This results in a smaller decrease in entropy upon ring formation compared to the medium-sized rings. This explains in part why medium sized rings are more difficult to form than either small or large rings.

Ring strain also contributes to the difficulty of forming medium-sized rings. Upon ring formation, bond angles become distorted from the ideal 109.5° for sp^3 hybridized carbon. The magnitude of distortion depends on ring size. In order to minimize these distortions, the hydrogens on the chain may be forced out of their preferred staggered conformations, thereby increasing the strain of the cyclized product.[28] These factors contribute to the difficulty of forming medium-sized rings. Despite the difficulty of forming a medium-sized ring, several groups have been able to achieve cyclization to form both the 7- and 8-membered cyclic ethers present on the heliannuols and helianane.

1.5 Previous syntheses of the heliannuols.

Grimm

The first article describing the synthesis of a heliannuol after their discovery by Macías was published by Grimm and coworkers (Scheme 1-1).[15] The key step in this synthesis is the intramolecular Julia-type coupling in which LiHMDS deprotonates the methyene adjacent to the sulfone on **25**. The sulfone anion then attacks the carbonyl group

[28] Werner, E. W. M. S. Thesis. Western Washington University. Bellingham WA, July 2007.

of the ester to give a tetrahedral intermediate, which collapses to give the cyclic ketone **26** in an 87% yield. The ketone in **26** was reduced to alcohol **28** in an 83% yield, followed by reductive desulfonation and deprotection of the methyl ether to form (±)-**3** in a 23% overall yield from **25**. Alternatively, Grimm was also to do the Julia coupling on the aldehyde sulfone **27**. The secondary alcohol in **28** is thus formed directly in a 59% yield, eliminating a step in the total synthesis of (±)-**3**. However, because the yield from **27** to **28** is smaller than the combined yield of **25** to **28**, only an 18% overall yield of (±)-**3** was achieved from the aldehyde sulfone **27.**

Scheme 1-1: Grimm's synthesis of (±)-heliannuol A.
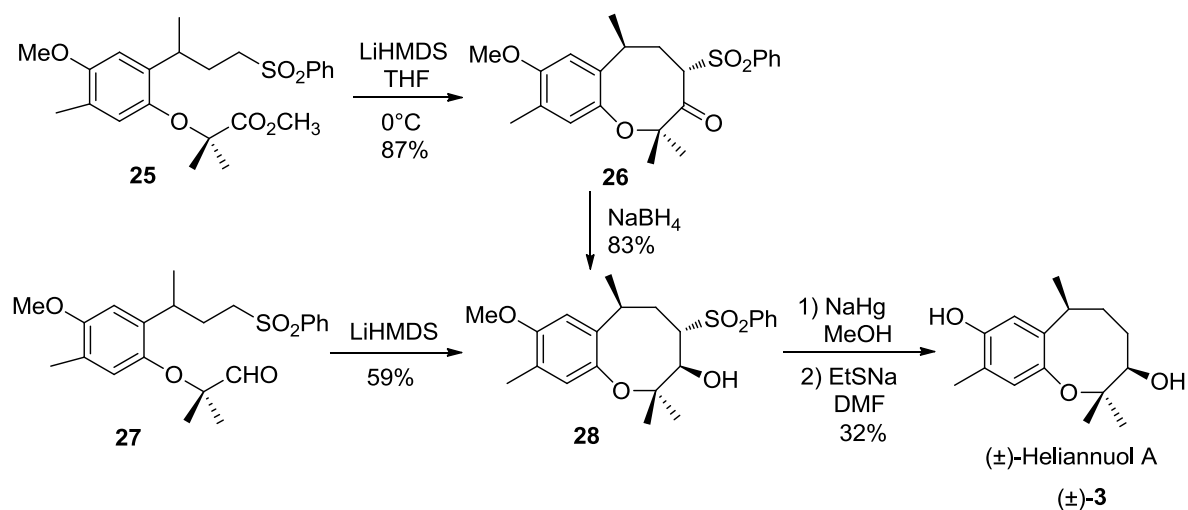
Vyvyan

There are two groups which used a base mediated intramolecular cyclization of an epoxide to synthesize some of the heliannuols. The first synthesis of (±)-heliannuol D and (±)-*epi*-heliannuol D was published by Vyvyan and Looper.[16] Their synthetic strategy was based on the proposed biosynthetic pathway involving an epoxide cyclization. An aryl-zinc species was coupled using a palladium catalyst to make **29**. This derivative was converted to

diastereometric epoxides **30** and **31** in an 87% yield. After separation, the epoxides were

treated with base to give the 7-membered cyclized products **32** and **33** in an 86% and 84%

yield, respectively (Scheme 1-2). Deprotection of the methoxy ether in each product with

sodium ethanethiolate afforded (±)-heliannuol D (±-**6**) and (±)-*epi*-heliannuol D (±-*epi*-**6**) in

90% and 93% yield. The total synthesis of (±)-heliannuol D included 9 steps to give a 12%

overall yield. Subsequent improvement by Vyvyan and Loitz in the synthesis of the phenol

29 raised the overall yield to 25%.[29]

Scheme 1-2: Vyvyan and Looper's synthesis of (±)-heliannuol D.
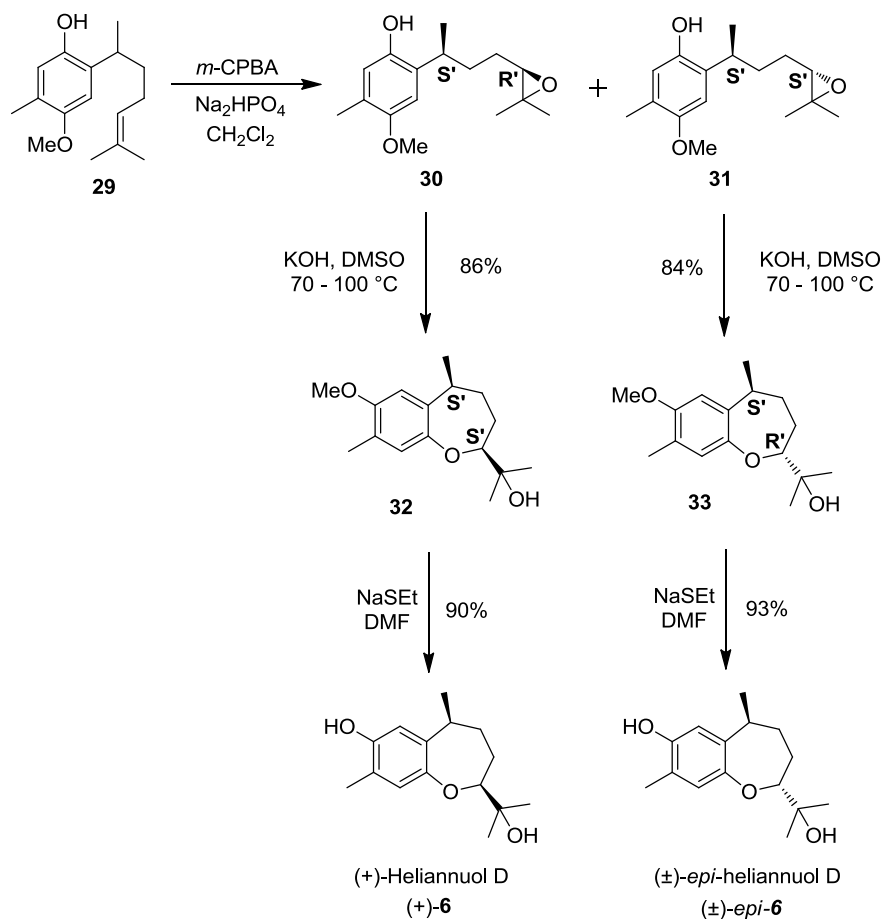
[29] Vyvyan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S.; Peterson, E. A.; Staben, S. T. *J. Org. Chem.* **2004**, *69*, 2461.

Shishido

Shishido's group also employed cyclization of an epoxide in their synthesis of the heliannuols. This strategy was used to synthesize both (-)-heliannuol D, and (+)-heliannuol A.[17] The epoxide used to form cyclic ether (-)-**6** and (+)-**3** was prepared via asymmetric dihydroxylation of **34** with AD-mix α, followed by conversion of the diol to epoxide **35**. The absolute stereochemistry at the benzylic carbon was set using *Candida antarctica* lipase (CAL)-catalyzed transesterification of the prochiral diol substrate. Epoxide **35** was treated with a weak base and deprotected to give the 7-*exo*-tet product (-)-**6**, and the 8-*endo*-tet product (+)-**3** in a 54% and 4% yield, respectively (Scheme 1-3).

Scheme 1-3: Shishido's synthesis of (-)-heliannuol D and (+)-heliannuol A.
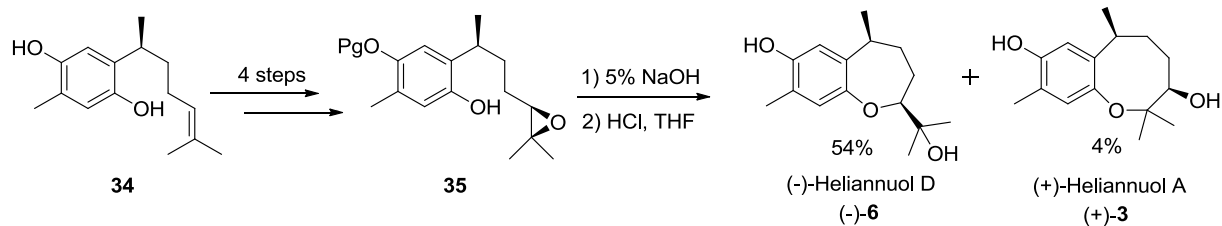
Venkateswaran

An approach different from that of Shishido, Vyvyan, or Grimm, was taken by Venkateswaran and coworkers.[18] Their key step was the hydrogenation of the cyclopropane in tricyclic substrate **36** to form the 8-membered cyclic ether. This was followed by a reduction of the ketone to the alcohol using sodium borohydride to establish relative stereochemistry and afford **37** in a combined 81% yield (Scheme 1-4). Venkateswaran and coworkers also used this method, followed by reduction of the alcohol to obtain *O*-methyl-helianane (**39**).

Scheme 1-4: Venkateswaran's synthesis of (±)-*O*-methyl heliannuol A.
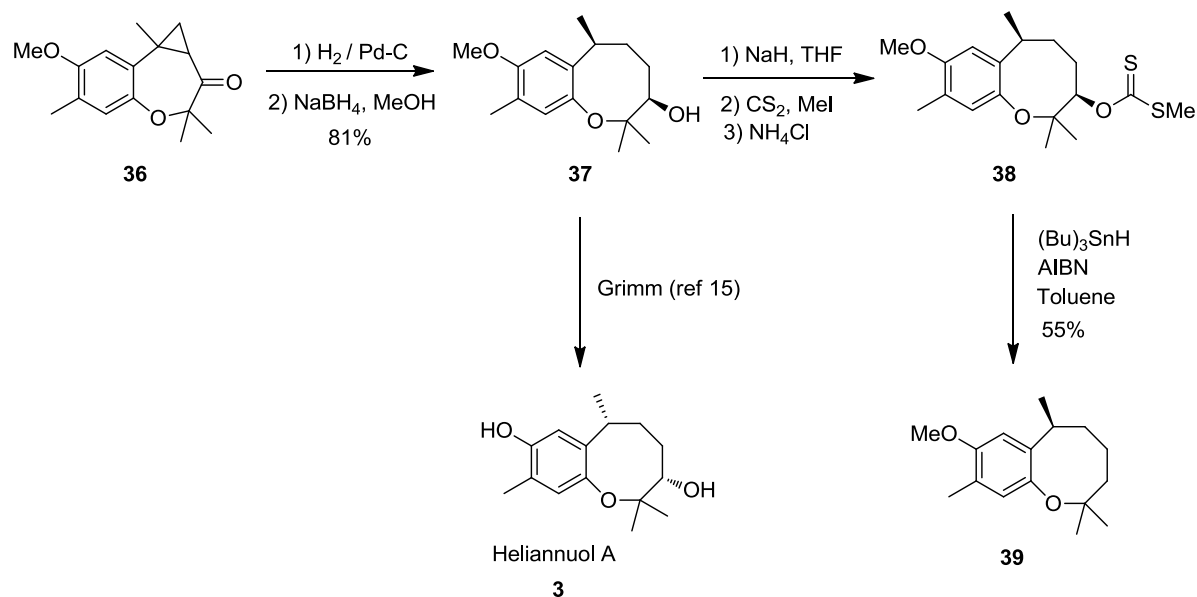
Ollivier

Olliver and coworkers employed a strategy similar to that of Venkateswaran.[19] From the cyclopropane-fused cyclic ether **40**, Olliver's group was able to synthesize heliannuols A, K, and L (Scheme 1-5). Ring expansion of **40** using iron(III) chloride as a Lewis acid yielded the 8-membered β-chloroketone **41**. This was followed by dehydrohalogenation to give the cyclic ketone **42**, which was then be converted to heliannuol A (**3**), K (**13**), or L (**14**) by simple reactions.

Scheme 1-5: Ollivier's synthesis of heliannuols A, K, and L.
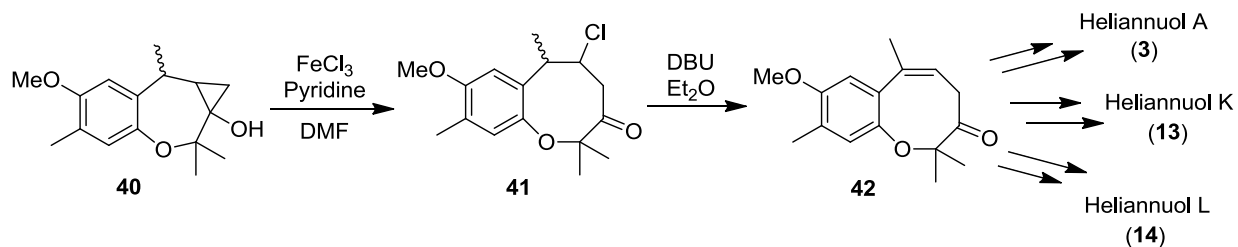
Snieckus

Snieckus and coworkers were the first to employ a ring-closing metathesis strategy in the synthesis of the heliannuols.[20] The ring closing metathesis precursor **44** was formed in seven steps from *m*-cresol O-carbamate (**43**) in an overall 19% yield (Scheme 1-6). This was then subjected to ring closing metathesis conditions using Grubbs' 1st generation catalyst, followed by hydrogenation of the intermediate alkene to give (±)-**15a** in 30% yield.

Scheme 1-6: Snieckus's synthesis of (±)-helianane.
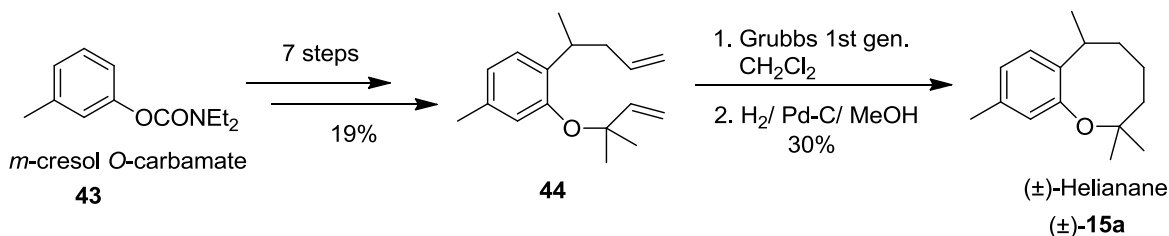
Shishido synthesis #2

To date, the most effective synthesis of (-)-heliannol A has been achieved by Shishido's group.[21] Similar to Snieckus, Shishido and coworkers employed a ring closing metathesis strategy (Scheme 1-7). Diene **45** was subjected to ring closing metathesis conditions to afford an 88% yield of the 8-membered cyclic ether **46**. To evaluate the substrate-controlled epoxidation, the minimum energy conformation of **46** was calculated

(Figure 1-8).   From this, it was determined that the diastereoselective epoxidation would proceed from the bottom face of the double bond giving the desired α-epoxide.   A n.O.e correlation between the H_a and H_b protons on **47** was observed, confirming the relative stereochemistry.   Regioselective reduction of the epoxide by lithium aluminum hydride resulted in alcohol **48** in 83% yield. Deprotection of the MOM protecting group produced (-)-**3**.

Scheme 1-7: Shishido's synthesis of (-)-heliannuol A.

Figure 1-8: Most stable conformation calculated for 46.[21]

18
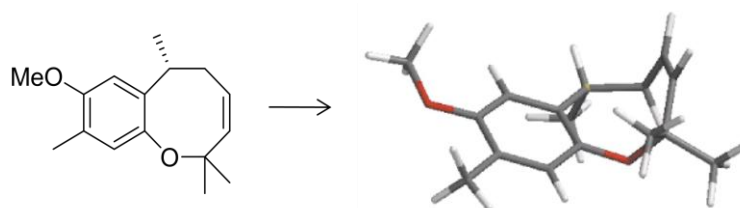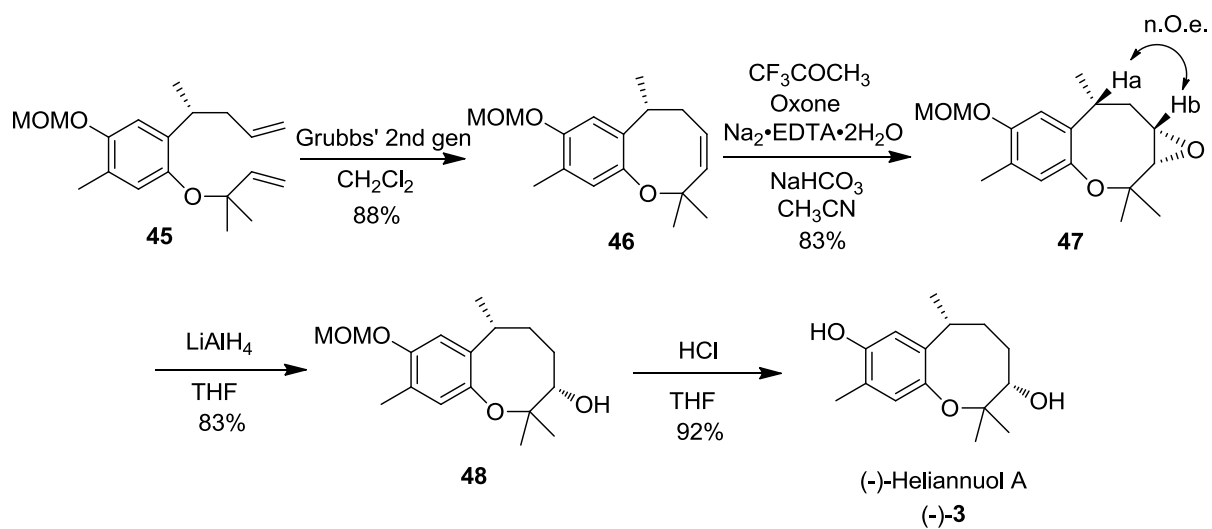
1.6 Unpublished work on the heliannuols and glandulones by the Vyvyan group.

Aromatic bisabolene natural products have been an area of interest for synthetic chemists for many years.[29] Many aromatic bisabolenes are components of plant essential oils. Other aromatic bisabolenes show antibiotic, antifungal, antimicrobial, and antitumor properties.[29] It is believed that these aromatic bisabolenes are involved in the biosynthetic pathway to the heliannuols. As part of the continued investigation into the total synthesis of the heliannuols, the Vyvyan group became interested in the preparation of various functionalized aromatic bisabolenes, such as the glandulones.

Glandulones

To date, there has only been one synthesis of a glandulone. Vyvyan, Looper, and Loitz reported the total synthesis of (±)-glandulone A (Scheme 1-8) along with (±)-curcuhydroquinone and (±)-curcuquinone in 2004.[29] The alkenylzinc reagent **49** employed for the synthesis of (±)-**22** was prepared via a reaction of Rieke zinc with the corresponding alkyl halide. A Negishi coupling with aryl bromide **50** produced aromatic bisabolene **51**. This was then oxidized to quinone **52** using ceric ammonium nitrate in acetonitrile and water in an 83% yield. An allylic oxidation to install the α,β-unsaturated aldehyde produced (±)-glandulone A (**22**).

The oxidation to the aldehyde, however, was problematic. The use of selenium oxide with *t*-butylhydroperoxide produced a low yield and gave a mixture of the desired product **22** with the corresponding allylic alcohol. To improve the yield, the α,β-unsaturated aldehyde was installed first to give **53** in a 55% yield using selenium oxide and ethanol. Finally,

oxidative deprotection using ceric ammonium nitrate afforded a 91% conversion to (±)-glandulone A (±-**22**).

Scheme 1-8: Synthesis of (±)-glandulone A.
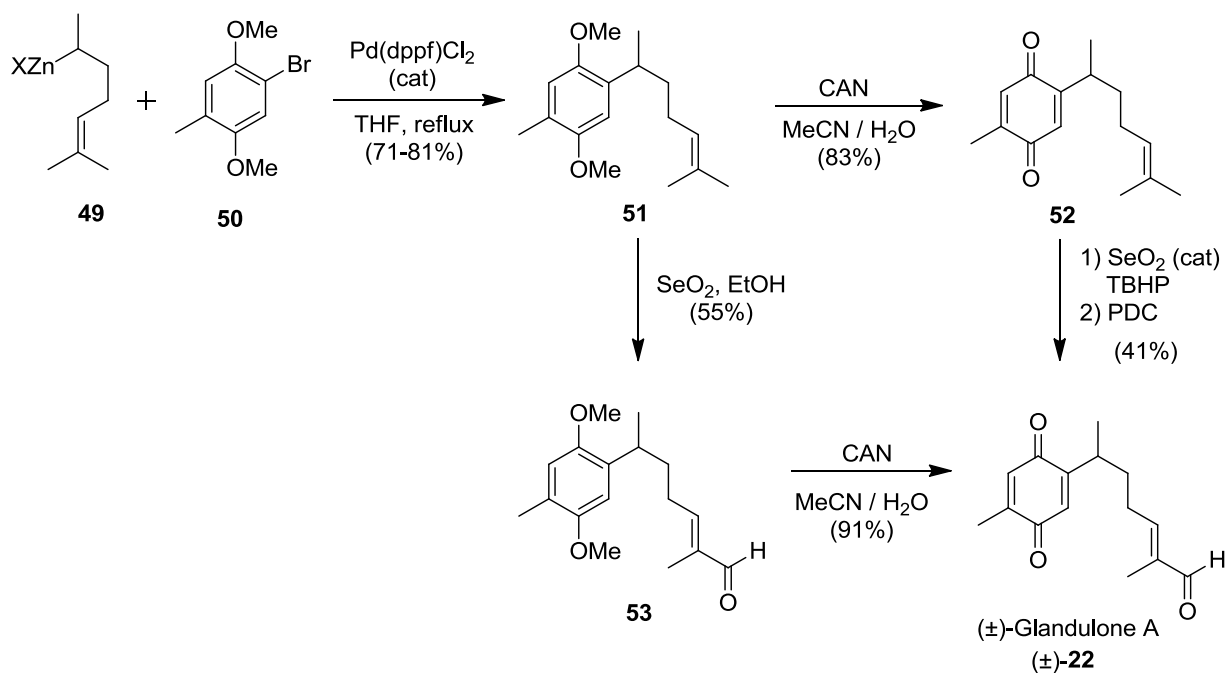
An olefin cross-metathesis of the aromatic bisabolene **51** with methacrolein (**54**) was examined as another route to the α,β-unsaturated aldehyde (Scheme 1-9). Following conditions reported in literature, Grubbs' 2nd generation catalyst was used. It was found that the *E* and *Z* isomers were formed in a 2:1 ratio with a 52% conversion to the desired E-isomer **53**.

Scheme 1-9: Olefin cross-metathesis with methacrolein to form aldehyde 53.
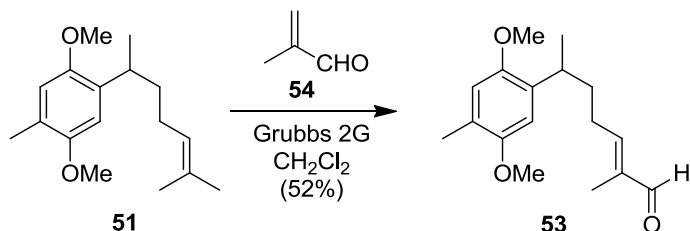
Loitz

Celeste Loitz of the Vyvyan group applied an epoxide attack strategy similar to that of Shishido for the formation of heliannuol A.[30] Epoxide **55** was first synthesized in an 16% overall yield from MOM-protected *m*-cresol. It was thought that by using Lewis acidic conditions, attack of the epoxide by the nucleophile at the more substituted carbon would be favored, and thus, the formation of the 8-membered cyclic ether would predominate over the formation of the 7-membered cyclic ether moiety. The Lewis acid would coordinate to the epoxide oxygen, creating a partial positive charge on the more substituted carbon, which would then lead to the nucleophilic attack of the phenol at this position. It was found that under Lewis acidic conditions, however, the epoxide is susceptible to rearrangement (Scheme 1-10). Rearrangement led to the formation of both ketone **57** and the aldehyde **58**. Attack by the nucleophilic chloride from the Lewis acid produced the chlorohydrin **56**. Unfortunately, no cyclized product was observed.

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[30] Loitz, C. M.S. Thesis. Western Washington University. Bellingham WA, May 2004.

Scheme 1-10: Loitz cyclization strategy.
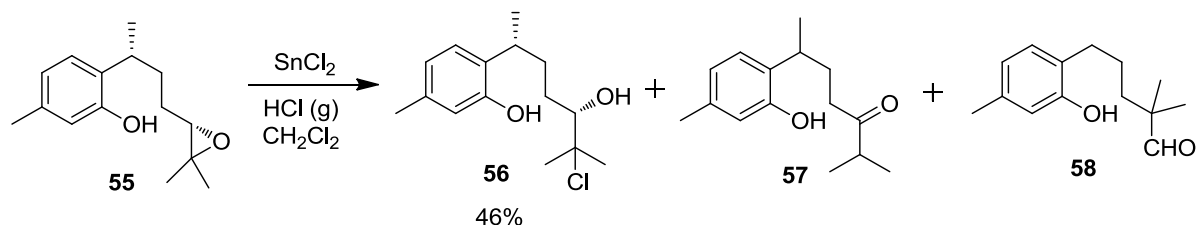
Werner

As discussed previously, the difficulty of medium ring size formation stems from both entropic and enthalpic factors. The long alkyl chain must be in a conformation in which the reactive ends are close enough to react, forming the desired cyclized product. Due to the length and free rotation of the alkyl chain, the probability of the two ends being in the desired proximity to react is very small. To reduce the amount of free rotation, Werner proposed the insertion of a conformational constraint in the form of a benzylic olefin.[28] Through 3D modeling, it was found that this also reduced the distance between the phenolic oxygen and more substituted carbon on the epoxide by 0.88 Å (Figure 1-9).
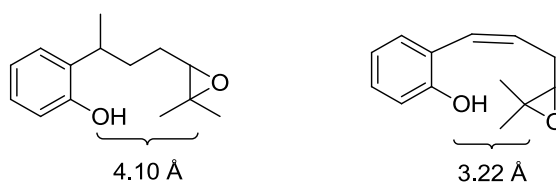
Figure 1-9: Comparison of epoxides with and without conformational constraint.

Conformational constraint was achieved by the selective reduction of the alkyne **59** with P-2 nickel to diene **60**. Subsequent epoxidation with *meta*-chloroperbenzoic acid and dibasic sodium phosphate resulted in a 58% yield of the conformationally constrained phenolic epoxide **61** (Scheme 1-11).

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Use of triphenylphosphine gold (I) triflamide, which is a softer Lewis acid with a non-nucleophilic counter ion, allowed the cyclization to compete with the side reactions that Loitz had observed. Using 25 mol % of this catalyst, a 45% conversion to the desired 8-membered cyclic ether **62** was achieved along with a 45% combined conversion of the rearrangement products. Attempts to synthesize conformationally constrained epoxides analogous to those required for the synthesis of the heliannuols were not successful, however, due in large part to the instability of dienes like **60**.

Scheme 1-11: Synthesis of epoxide with conformational constraint and subsequent cyclization.
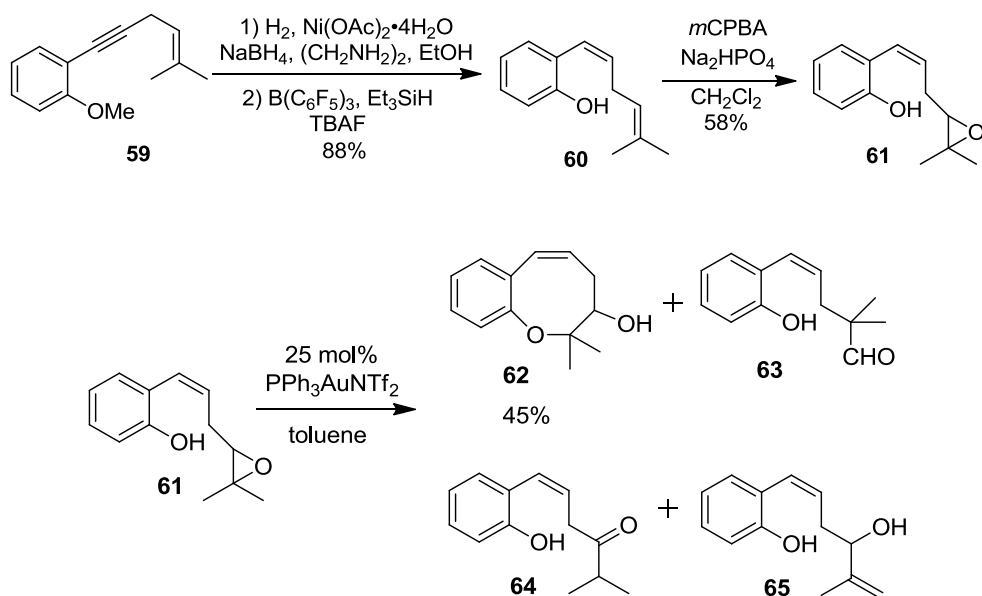
Bray/Wold/Porter

In order to explore the role of the conformational constraint in the epoxide cyclization strategy further, an easier, more efficient method was sought for the formation of the conjugated olefin. Ideally, a *Z* olefin would be installed so that after cyclization, simple

reduction would result in the benzylic methyl substituent found on the cyclic ethers in the heliannuols and helianones.

Trost and coworkers reported the formation of *Z*-olefins in a Hiyama-type cross-coupling of aryl iodides with cyclic vinyl siloxanes.[31] Cyclic vinyl siloxanes with a variety of substituents and ring sizes can be prepared via a ruthenium-catalyzed alkyne hydrosilylation. Using this strategy, our 7-membered cyclic vinyl siloxane **69** would be prepared via hydrosilylation of propargylic alcohol **70**. Then, the desired *Z* olefin and epoxide precursor **67** can be achieved from a coupling of an aryl iodide **68** with vinyl siloxane **69** (Scheme 1-12).

Scheme 1-12: Retrosynthesis of epoxide using vinyl siloxane.
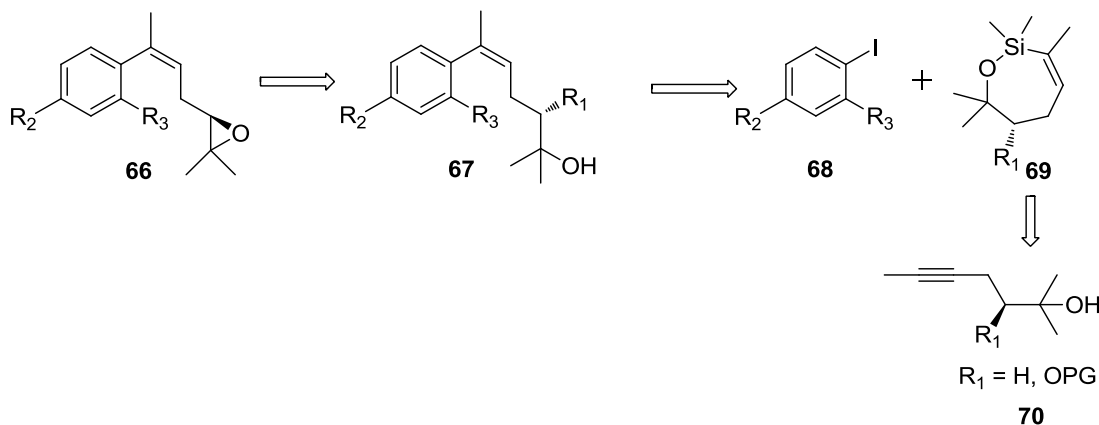
Erik Wold and Chris Porter of the Vyvyan group worked to synthesize siloxane **69** from simple starting materials (Scheme 1-13).[32] Treatment of 2-methyl-2-hepten-5-yne (**71**) with AD-mix α in a biphasic solution of *tert*-butanol and water gave diol **72** in 45-66% yields with a 91% ee. The secondary hydroxyl group was protected as benzyl ether **70a**, benzoate ester **70b**, *tert*-butyldimethylsilyl ether **70c**, or pivaloate **70d** in 61%, 97%, 62%, and 30%

[31] Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 30-31.
[32] Porter, C.; Wold, E. Unpublished Results. Western Washington University. Bellingham, WA.

yields, respectively. The protection of the secondary alcohol prevents hydrosilylation from occurring at this site versus at the tertiary hydroxyl group. Reaction of **70** with tetramethyldisilizane for two hours, followed by treatment with ruthenium catalyst [Cp*Ru(NCMe)$_3$]PF$_6$ (**73**) (Figure 1-10) resulted in the formation of protected cyclic vinyl siloxanes **69a-69d** in good to excellent yields.

Scheme 1-13: Synthesis of protected vinyl siloxane.
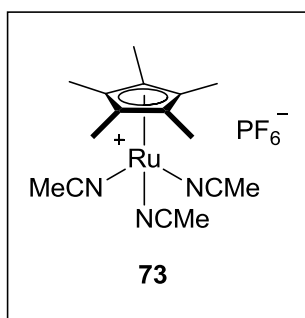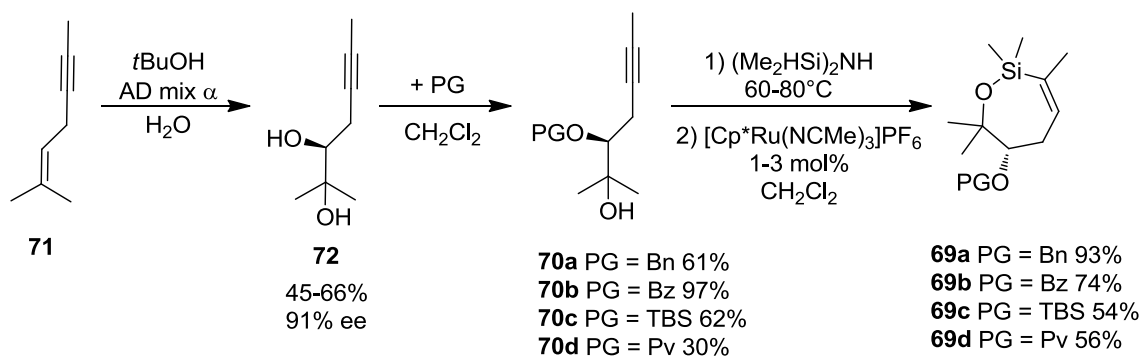
Figure 1-10: [Cp*Ru(NCMe)$_3$]PF$_6$ catalyst.

The simple cyclic vinyl siloxane **69e** was also synthesized (Scheme 1-14). Treatment of 1-chloro-2-butyne (**74**) with acetyl acetone and potassium carbonate gave a 55-70% yield of **75**. Ketone **75** was refluxed with methylmagnesium bromide in ether. Subsequent distillation afforded a 70-78% yield of **70e**. Alcohol was then subjected to hydrosilylation

conditions previously described. Addition of ruthenium catalyst resulted in the formation of

simple vinyl siloxane **69e** in a 22-30% yield.

Scheme 1-14: Synthesis of simple vinyl siloxane.
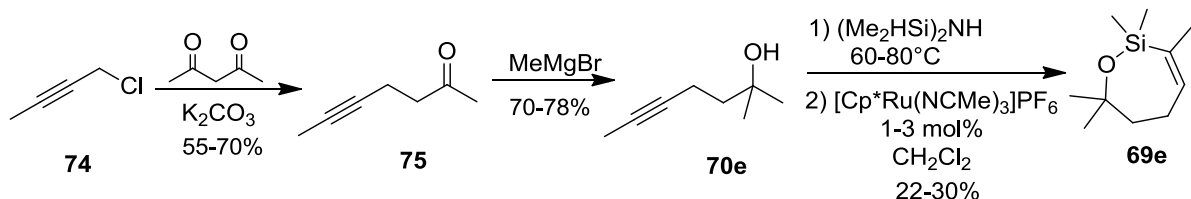
Using Hiyama coupling conditions described by Trost,[31] aryl iodide **76a-c** and

protected vinyl siloxanes **69b** and **69d** were treated with tetra-*n*-butylammonium fluoride and

tris(dibenzylideneacetone)dipalladium (0) at 55 °C for 16-24 hours (Table 1-3). This gave

the desired *Z* olefins **77a-d** in yields ranging from 47-74%.

Table 1-3: Hiyama couplings.
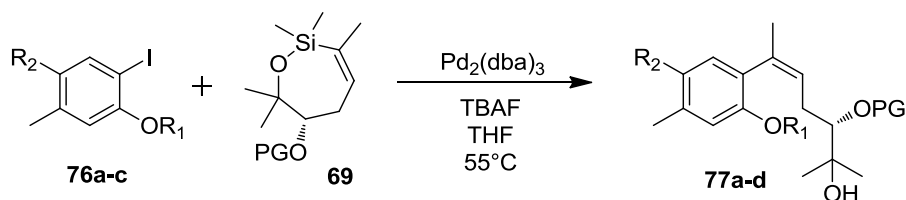
Ar-I	R$_1$	R$_2$	PG	Product	% Yield
76a	MOM	H	Pv	**77a**	74
76a	MOM	H	Bz	**77b**	56
76b	Bz	H	Bz	**77c**	47
76c	MOM	OMe	Bz	**77d**	58

Another reason for the development of the *Z* olefin from cyclic vinyl siloxanes was a

planned cyclization via Buchwald-Hartwig etherification. Buchwald reported the use of

palladium-catalyzed intramolecular C-O bond formation to form 5-, 6- and 7-membered

cyclic ethers in good yields.[33] A Buchwald-Hartwig etherification requires a bromine instead of a hydroxyl group on the benzene ring (Scheme 1-15). To form the cyclized product **E**, palladium oxidatively inserts into the aryl-bromine bond on **A** to afford **B**. The base required for this reaction deprotonates the tertiary alcohol and the oxygen is then able to coordinate to the palladium as shown in **C**. Reductive elimination of **D** results in the desired intramolecular C-O bond formation to give the cyclic ether **E**.

Scheme 1-15: Palladium catalyzed C-O bond formation catalytic cycle.[34]
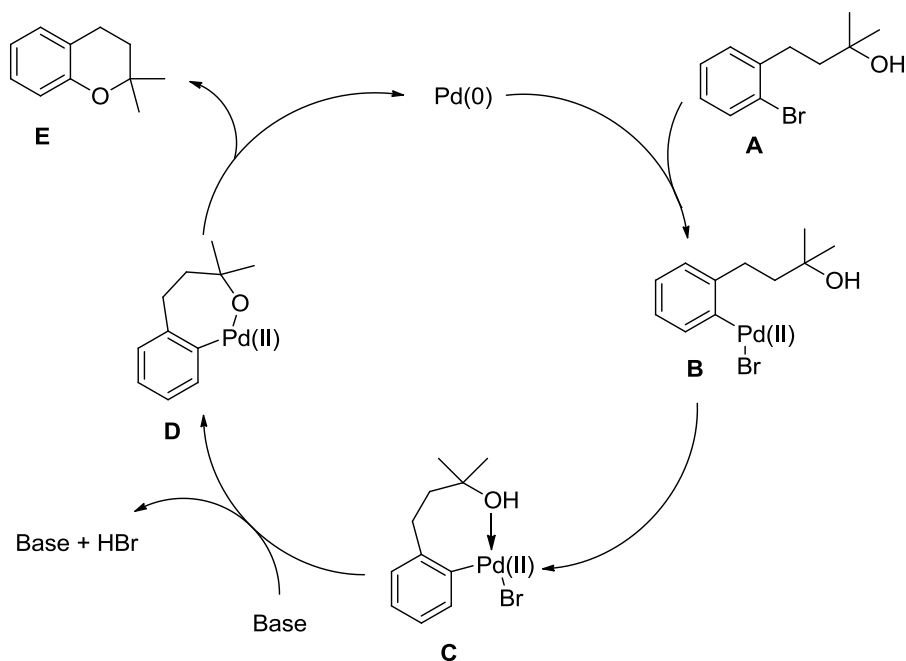
By combining Hiyama couplings with these Buchwald-Hartwig etherifications, we may be able to synthesize our benzene-fused 8-membered cyclic ether. A coupling of the vinyl siloxane **82** with 3-bromo-4-iodotoluene (**81**) would result in **80**: an aryl-bromide possessing a conformationally constrained tether with a tertiary alcohol (Scheme 1-16). This

[33] Buchwald, S. L.; Kuwabe, S.; Torraca, K. E. *J. Am. Chem. Soc.* **2001**, *123*, 12202-12206.
[34] Buchwald, S. L.; Wolfe, J. P.; Palucki, M. *J. Am. Chem. Soc.* **1996**, *118*, 10333-10334.

would be subjected to Buchwald-Hartwig etherification conditions, which would form the C-O bond to make the cyclic ether in **79**. Reduction of the alkene would then give the desired product **78**.

Scheme 1-16: Retrosynthesis using Buchwald-Hartwig etherification.
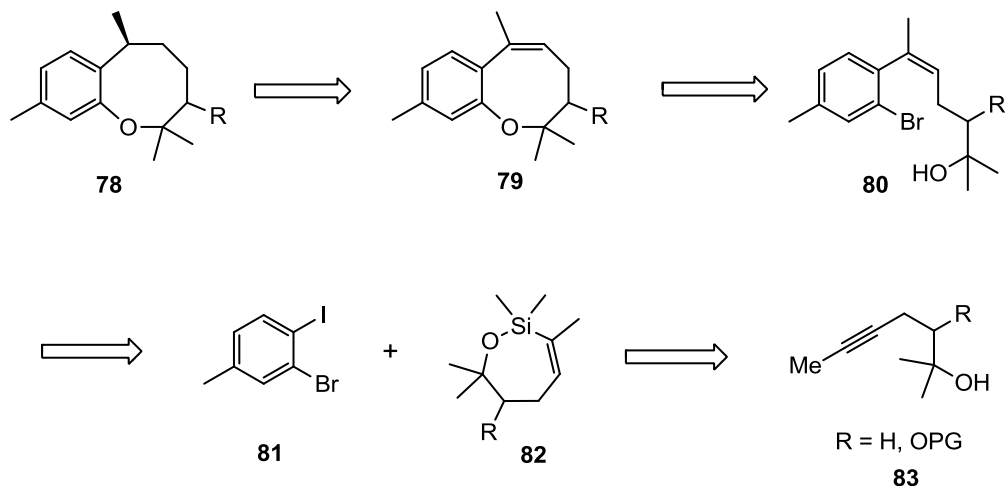
Using Buchwald-Hartwig conditions optimized by Bray, cyclizations were attempted on the respective aryl bromides **84** (Table 1-4).[35] Hiyama couplings consistently gave good to excellent yields of **86**. When treated with bis(dibenzylideneacetone)palladium(0), CTC-Q-PHOS, and sodium *tert*-butoxide, cyclized product **87** was only observed when R^1 and X are hydrogen and R^2 is a methyl group. In most cases, debrominated product **88** was observed instead of the desired cyclized product.

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[35] Bray, Scott. Unpublished results. Western Washington University. Bellingham WA.

Table 1-4: Hiyama coupling and Buchwald etherification of aryl bromides.
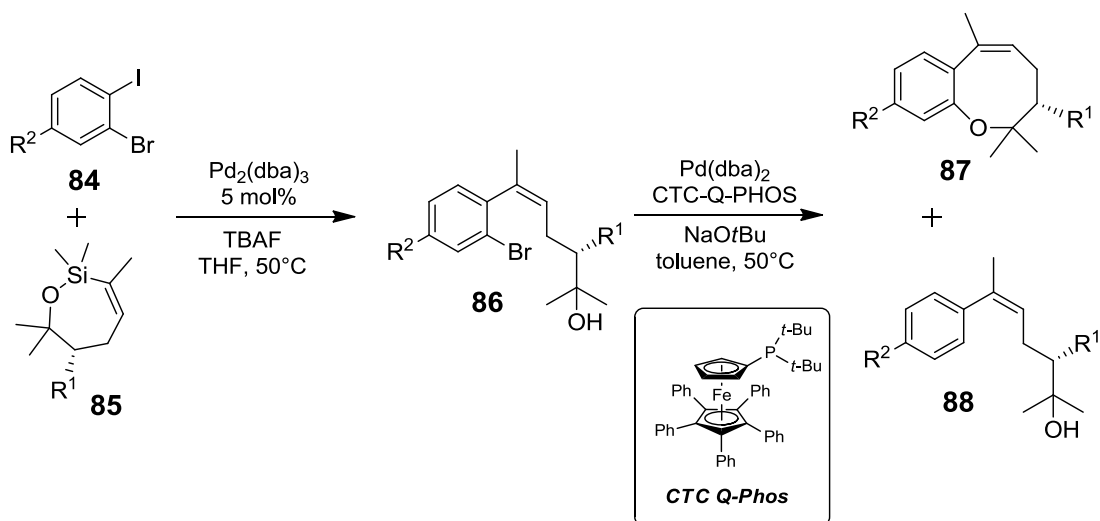
R^1	R^2	% Yield 86	% Yield 87	% Yield 88
H	H	87	0	26
H	Me	99	10	6
OBn	Me	61	0	3
OTBS	Me	35	0	0

2. Exploration of electronics to promote Buchwald-Hartwig etherification.

With the preliminary results for Buchwald cyclizations complete, the next step was to explore how the electronic properties of the substrate would affect the cyclization. In a Buchwald-Hartwig etherification, after palladium inserts into the carbon-bromine bond, the nucleophilic oxygen attacks the palladium, and reductive elimination results in the formation of cyclized product[34] (see Scheme 1-14). However, if the compound undergoes reductive elimination before the oxygen attacks palladium, debrominated product is observed (Scheme 2-1).

Scheme 2-1: Formation of debrominated product 88
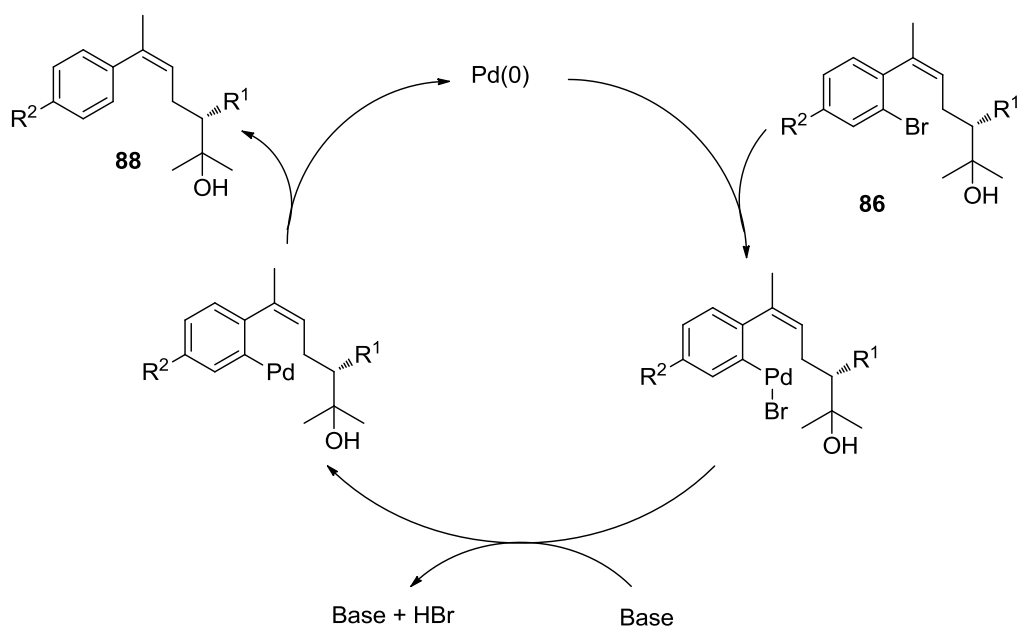
2.1 Electron withdrawing substituents.

Since we had observed the formation of debrominated product **88**, we concluded that the problematic step in the reaction was the nucleophilic attack of the oxygen. We hypothesized that installation of an electron withdrawing group would pull electron density

out of the aryl ring, making the palladium more electrophilic and thus, more susceptible to nucleophilic attack by the oxygen.

The addition of the slightly electron-withdrawing chlorine was first explored (Scheme 2-2). Commercially available 2-chloro-3-methylaniline (**89**) was protected with an acetate group by stirring it with pyridine and acetic anhydride in ethyl acetate overnight[36] to give **90** in a 75% yield. Treatment of **90** with bromine in acetic acid[36] formed **91** in a 66% yield, and cleavage of the amide under acidic conditions[36] gave a 96% yield of **92**. Analysis of the NMR spectrum of the trisubstituted aniline showed purification was not necessary. Iodination to install the iodine *ortho* to the bromine[37] resulted in yields of 41-51% of 3-bromo-6-chloro-4-iodotoluene (**93**).

Scheme 2-2: Synthesis of 3-bromo-6-chloro-4-iodotoluene (93).
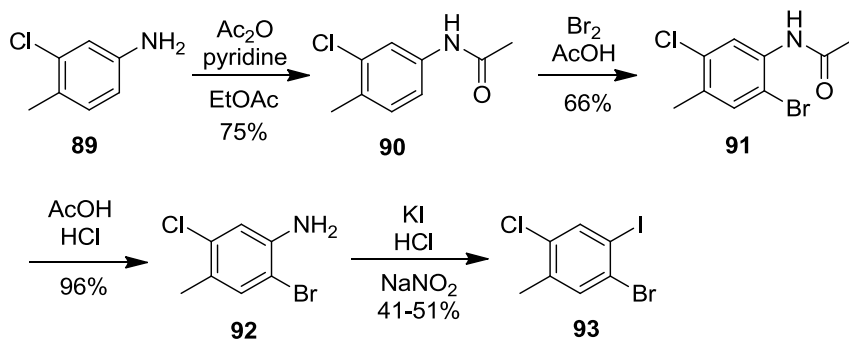
A Hiyama coupling of **93** with the simple 7-membered vinyl siloxane **69e** using the typical Hiyama coupling conditions (tris(dibenzylideneacetone)dipalladium (0), tetra *n*-butylammonium fluoride, in THF at 55 °C for 17-24 hours)[31] produced an 80% purified yield of **94** (Scheme 2-3). Attempted intramolecular C-O bond formation using conditions

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[36] Bavetsias, V; Skelton, L.A; Yafai, F. *J. Med. Chem.*, **2002**, *45 (17),* 3692-3702.
[37] Jensen, T.; Pedersen, H.; Bang-Anderson, B. *Angew. Chem.* **2007**, 47 (5), 888-890.

optimized by Scott Bray did not produce the desired 8-membered cyclic ether, but rather a 27% yield of the debrominated product **95** was isolated and confirmed by gas-chromatography mass-spectrometry (GC-MS) analysis.

Scheme 2-3: Hiyama and Buchwald cyclization of 93.
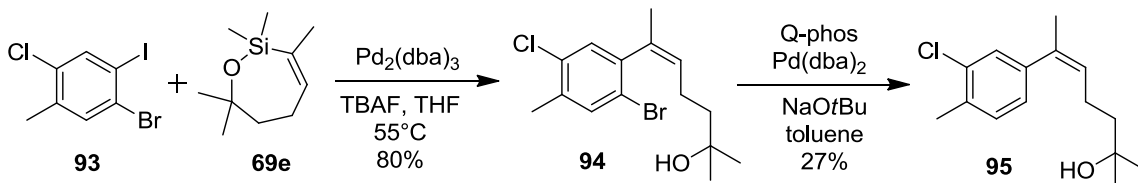
The stronger electron withdrawing acetyl group was tested next. Protection of *m*-methylaniline (**96**) with an acetate[36] to provide **97** was accomplished in a quantitative yield (Scheme 2-4). Acetylation of **97** with acetyl chloride and aluminum chloride was followed by deprotection of the amine.[38] Since the amine is an *ortho/para* director in electrophilic aromatic substitutions, both positions of **97** were acetylated and isomers **98a** and **98b** were observed. In the literature procedure, the isomers were separated via distillation, but we were unable to do so. Isolation of **98a** was achieved via column chromatography of the distilled isomers in a mixture of ethyl acetate and hexanes to give a 15% yield of **98a** and a 7.5% yield of isomer **98b**, compared to a literature value of 5% for **98a**.[38] Iodination of the *ortho* position using iodine monochloride and calcium carbonate[39] afforded a 57% yield of trisubstituted aniline **99**. Treatment with hydrogen bromide, sodium nitrite, and copper (I) bromide gave solid **100** in a 28% yield.

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[38] Royer, R.; Eckert, B. *J. Org. Chem.* **1952**, *17*, 1463-1465.
[39] Fujita, K.; Takahashi, Y.; Owaki, M. *Org. Lett*. **2004**, *6*, 2785-2788.

Scheme 2-4: Synthesis of 1-(4-bromo-5-iodo-2-methylphenyl)ethanone (100).
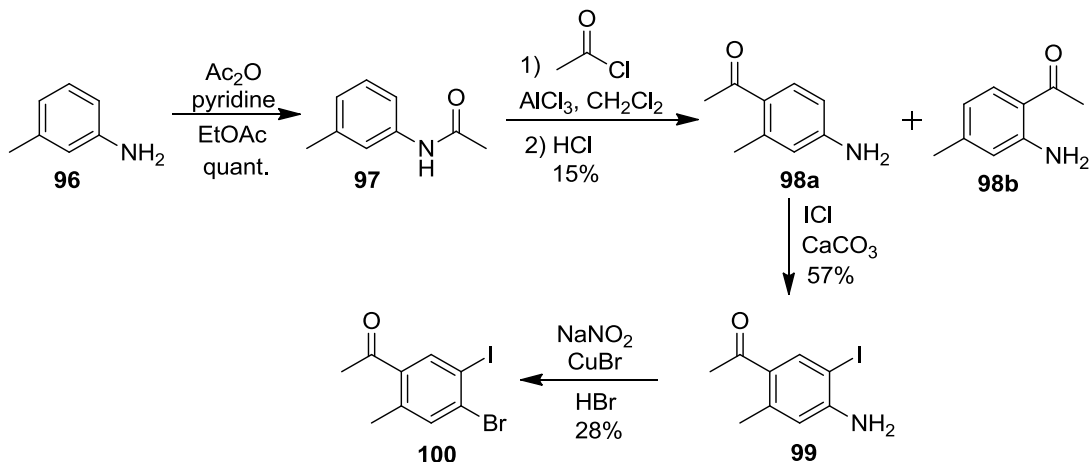
Hiyama coupling of **100** with the simple 7-membered cyclic vinyl siloxane **69e** resulted in a 60% yield of coupled product **101** (Scheme 2-5). This was then subjected to intramolecular C-O bond-forming conditions[33] which yielded a mixture of products. Purification and ^{1}H NMR analysis showed that the desired cyclized product **102** was formed in a 17% yield. However, the material contained impurities and attempts to purify the material further were unsuccessful. We concluded that the use of a strongly electron withdrawing group *para* to the bromine does assist in the formation of the 8-membered cyclic ether, however, the conversion is not as clean as the cyclization of **86**.

Scheme 2-5: Hiyama and Buchwald cyclization of 100.

33
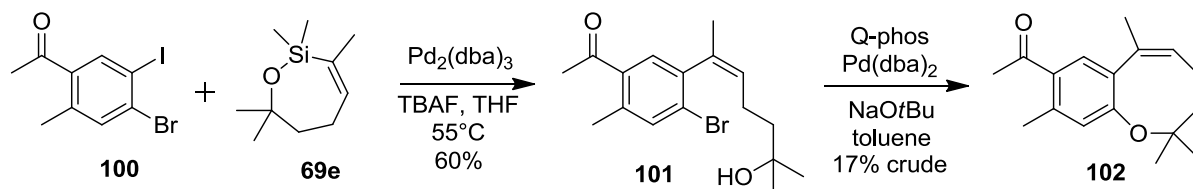
2.2 Electron donating substituent

To complete our analysis of aromatic substitution on the rate of cyclization, it would be beneficial to test the Buchwald-Hartwig etherification on a substrate containing electron donating group. Our hypothesis was that an electron-donating group will not promote cyclization because it will push electron density into the ring, making the palladium less electrophilic. Installation of an ester *para* to the bromine from aromatic ketone **100** would give the desired coupling partner **103** (Table 2-1). An ester would also easily be cleaved in subsequent steps to give the phenol found in both the heliannuols and the aromatic bisabolenes involved in the biosynthetic pathway. Previously synthesized 1-(4-bromo-5-iodo-2-methylphenyl)ethanone (**100**) was refluxed overnight with *m*CPBA in dichloromethane.[40] Additional dichloromethane was added the next day due to evaporation of solvent and solution was allowed to reflux for an additional 72 hours. Workup and analysis of crude material indicated mixture was almost completely starting material. The aromatic ring is not very electron rich with the acetate group, so it was theorized that desired product may be formed if solution was refluxed at a higher temperature. Use of 1,2-dichloroethane allowed for reflux at 84 °C versus 40 °C with dichloromethane. Workup, purification, and NMR of the fractions showed decomposition of starting material and no conversion to desired product.

In a final attempt to form the ester from the aromatic ketone, a different reaction was tried. Sublimed iodine, hydrogen peroxide, and acetic acid were stirred for 30 minutes before the addition of **100** dissolved in additional acetic acid.[41] Addition of the ketone

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[40] Houser, F. M. *J. Org. Chem.* **2000**, *65*, 1842-1849.
[41] Gaikwad, D. D. *Synth. Commun.* **2007**, *37*, 4093-4097.

resulted in the precipitation of the starting material. DMSO was added to re-dissolve the solid, and the mixture was stirred for 1 hour. Workup and NMR showed that **100** did not react to form the desired ester **103**.

Table 2-1: Attempted synthesis of ester 103.
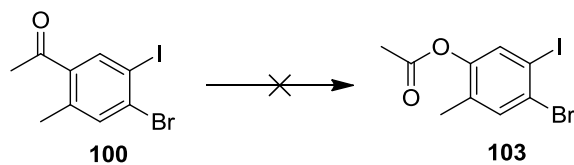
Conditions	Result
*m*CPBA, CH$_2$Cl$_2$, reflux	NR
*m*CPBA, 1,2-DCE, reflux	NR
I$_2$, H$_2$O$_2$, AcOH	NR

3: Synthesis of cyclic boronic half-acids for Suzuki-Miyaura couplings.

While the Hiyama couplings have consistently given good to excellent yields with aryl iodides and the cyclic vinyl siloxane, the price of the catalyst used to make the vinyl siloxane is very high.[42] Thus, the continued investigation into both the Buchwald-Hartwig etherification and epoxide cyclization strategies was explored using an alternate method to the *Z* olefin tether.

3.1 Synthetic strategy.

At the National American Chemical Society meeting in March of 2009, McNulty and coworkers presented the synthesis of 6-membered cyclic alkenyl boronic half acids (Scheme 3-1).[43] This required a coupling of a homoallylic alcohol **104** with acyclic allyl boronate ester **105** or **106**. Interestingly, Grubbs' first generation catalyst was used to perform this cross-metathesis, because it was found that yields with Grubbs' second generation catalyst were only half that of what was obtained with the first generation catalyst.[43] Treatment of the 6-membered cyclic boronic half acid **107** and a halogenated coupling partner with Suzuki coupling conditions resulted in the formation of the desired (*Z*)-olefin **108** in good yields.[43]

Scheme 3-1: McNulty's synthesis of cyclic alkenyl boronic half acids.
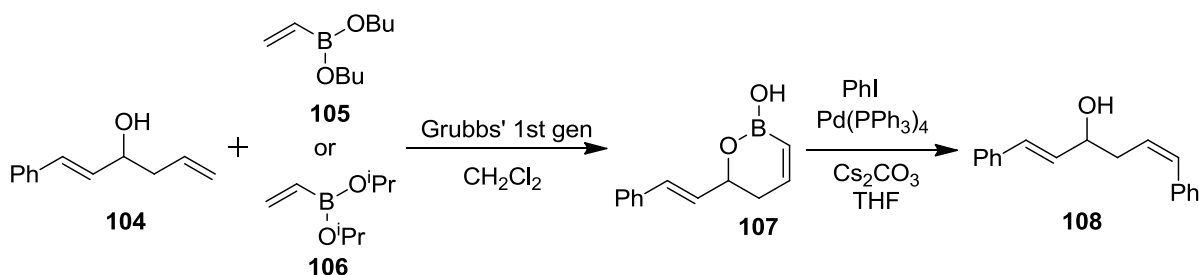
[42] CAS #99604-67-8, Strem catalogue #44-7880. 1g for $333, Strem Catalogue No 22. 2008-2010.
[43] McNulty, L.; Bishop, J. *Abstracts of Papers*, 237th National Meeting of the American Chemical Society, Salt Lake City, UT, March 22-26, 2009.

For our project, a cyclic boronic half acid with a structure similar to the cyclic vinyl siloxane **69** was desired. For this, a new retrosynthetic strategy was derived (Scheme 3-2). Boronate ester **114** and homoallylic alcohol **115** would cyclize to form boronic half acid **112**. A coupling to form the *Z*-olefin tether on **111a** or **111b** could be accomplished using Suzuki-Miyaura conditions. From there, either the epoxide **109** could be formed and cyclization attempted (R_1 = OH) or a Buchwald-Hartwig etherification to **110** (R_1 = Br) could be tried to get to the product **3**.

Scheme 3-2: Retrosynthesis using cyclic boronic half acid.
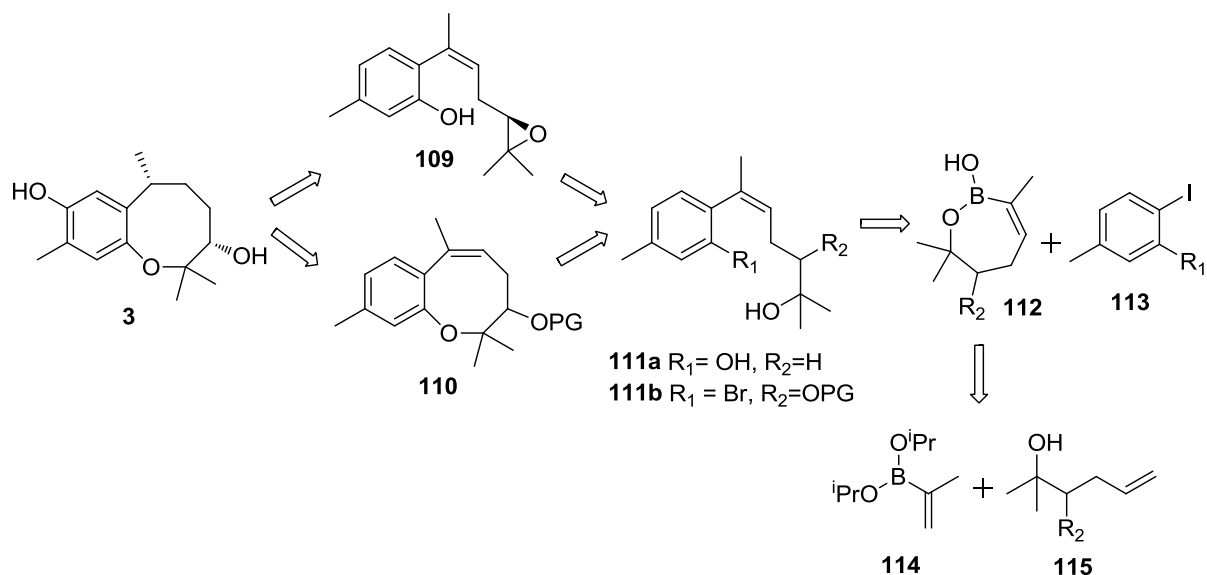
3.2 Synthsis of the alkenyl boronate esters.

The first step to the strategy was to synthesize the alkenyl boronate ester **114**. Using a procedure from the literature,[44] trimethyl borate (**116**) was reacted with isopropenylmagnesium bromide in THF to form **117** in a 45% yield (Scheme 3-3). Since

[44] Molander, G. A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148-11149.

water is the biproduct of the conversion of the boronic acid **117** to the diisopropylboronate ester **114**, a Dean-Stark trap was used. Boronic acid **117** was refluxed in benzene with excess isopropyl alcohol. When the calculated amount of water was collected in the trap, the reflux was stopped, the reaction was worked up, and **114** was obtained in a 44% yield. The product was determined by NMR analysis to be pure enough for subsequent reaction.

Scheme 3-3: Synthesis of 114.
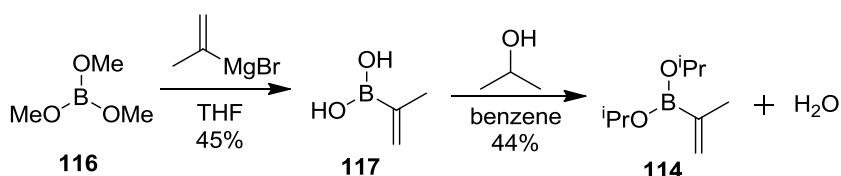
McNulty described being able to use both the diisopropylboronate ester **106** as well as the dibutylboronate ester **105**. With this in mind, the dibutylboronate ester **118** was also synthesized (Scheme 3-4). Trimethyl borate (**116**) was reacted with isopropenyl magnesium bromide. This time, after the Grignard was added and solution was stirred for 20 min, a small amount of water was added to the mixture along with the antioxidant phenothiazine.[45] Quenching was accomplished with a slow addition of hydrochloric and phosphoric acids. Extraction with 1-butanol resulted in the formation of desired product **118** in 68% yield after distillation.

Scheme 3-4: Synthesis of 118.
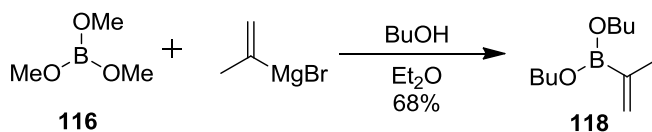
[45] Matteson, D. *J. Am. Chem. Soc*. **1960**, *82*, 4228-33.

A cyclization of simple homoallylic alcohol **119** was attempted with boronate ester **118** using conditions described by McNulty in a personal communication received after the ACS meeting (Scheme 3-5).[46] Workup and purification afforded a 67% yield of cyclized product **120**. NMR analysis of the material showed trace impurities, but it was deemed pure enough to attempt a Suzuki-Miyaura coupling.[47] Iodobenzene (**121**) and cyclized boronic half acid **120** were heated overnight at 90 °C with tetrakis(triphenylphosphine)palladium (0) and potassium phosphate in dioxane. Purification yielded the coupled product **122** in a 23% yield.

Scheme 3-5: Attempted cyclization and cross metathesis of boronate ester.
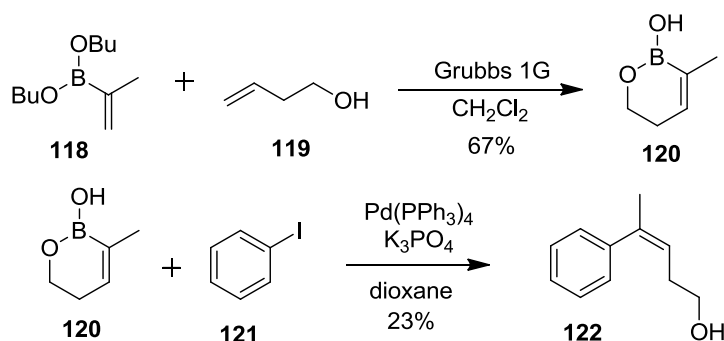
Later, when the coupling of **118** with **119** to form the cyclic boronic half acid **120** was repeated, close inspection of the NMR spectrum revealed that isomers may have been formed because duplicate peaks were present (Scheme 3-6). This reaction is believed to proceed via transesterification to form intermediate **120a**, followed by ring-closing metathesis to give the desired product.[43] If this occurs in the desired order the cyclic product **120** will be formed. However, if transesterification does not occur prior to cross-metathesis, the isomer **123a** or **123b** will be formed. Since the hydroxyl proton on either the alcohol or

[46] McNulty, L. Butler University, Indianapolis, IN. Personal communication, 2009.
[47] Ligon, T. M.S. Thesis. Western Washington University. Bellingham WA, August 2009.

the boronic acid does not appear in the NMR spectrum, we were unable to distinguish between **123a** and **123b** by NMR spectroscopy. Distinction via linear IR spectroscopy may have been possible if **120** could be isolated. Linear IR spectroscopy would give a spectrum with absorbance intensities relative to concentration. Since isomers **123a** and **123b** have three times the number of hydroxyl groups as **120**, they should give an -OH absorbance three times larger. However, because I could not separate the possible isomers, an IR of the mixture would not allow for distinction.

Scheme 3-6: Possible isomers of cyclization
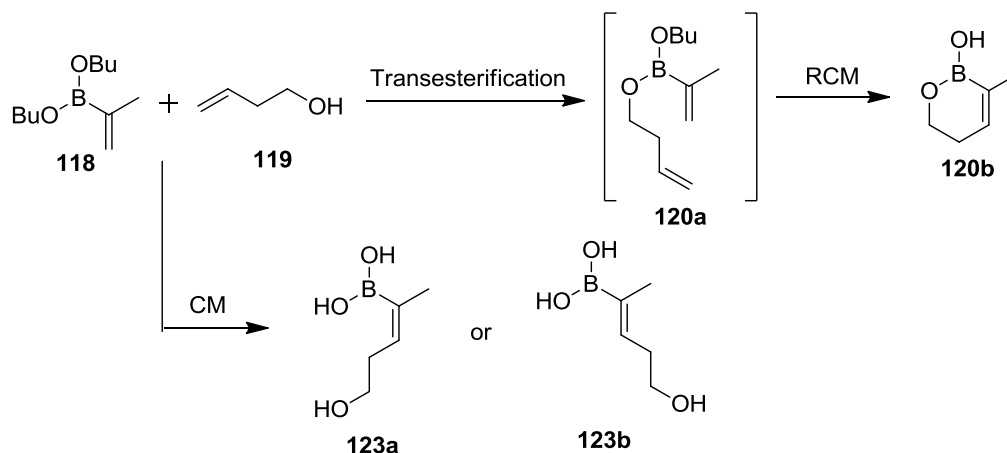
To try to obtain the cyclic boronic half acid **120** without the possibility of forming the side product **123a** or **123b**, a dibutenylboronate ester like **124** would be needed. An intramolecular ring closing metathesis with Grubbs' catalyst would give the desired cyclic boronic acid after workup and a comparison could be done with previous NMR spectra of **120** (Scheme 3-7). To do this, previously made alkenyl boronic acid **117** was reacted with excess 3-buten-1-ol (**119**) in benzene using a Dean-Stark trap. Workup and NMR analysis of this reaction showed mostly alcohol **119**, with trace amounts of **117**.

Scheme 3-7: Synthetic plan for formation of 120.
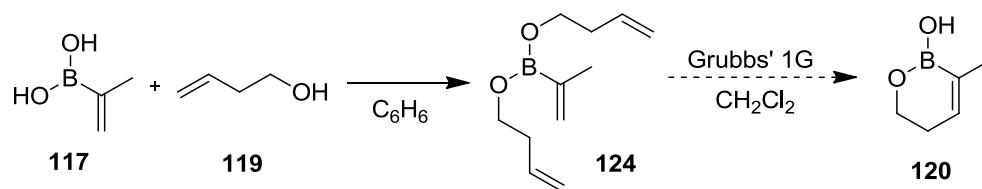
The original path to diisopropyl alkenyl boronate ester **116** gave an overall 20% yield, which is low for a two-step synthesis. Therefore we sought a new, higher yielding route. An adapted literature procedure[44] which called for the reaction of **116** with ispropenylmagnesium bromide to be quenched with 1M HCl was used (Scheme 3-8). The ^{1}H NMR spectrum of the crude material showed a combination of desired boronic acid **117** along with its dimer **125** in a combined 66% yield. These were not able to be separated.

Scheme 3-8: Formation of boronic acid 117.
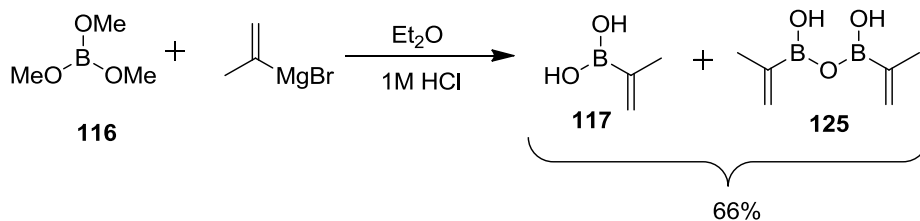
In another attempt to synthesize the diisopropylboronate ester **114**, trimethyl borate was reacted with isopropenyl magnesium bromide in THF. After the drying agent was filtered off, excess isopropyl alcohol was added to the flask and the mixture was concentrated. Boronic acids have a tendency to trimerize or oligomerize. We hoped that by adding excess isopropyl alcohol to the solution before concentration, that the boronic acid would react with the isopropyl alcohol, instead of itself, to form **114**. The ^{1}H NMR spectrum of the product showed a mixture of boronic acid **117** with its dimer **125**.

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Another way to form the diisopropylboronate ester **114** could be by starting with *triisopropyl* borate (**126**) instead of trimethyl borate (Scheme 3-9). Triisopropyl borate was reacted with isopropenylmagnesium bromide under the same conditions as previously described. Workup and NMR analysis revealed that boronate ester **114** was formed along with boronic acid **117**. Since the acid was present, treatment of the mixture with isopropyl alcohol in benzene using a Dean-Stark trap could convert the acid to the isopropoxy group. When this experiment was performed, NMR analysis revealed the disappearance of the vinyl peaks, indicating the decomposition of starting material.

Scheme 3-9: Attempted synthesis of 114.
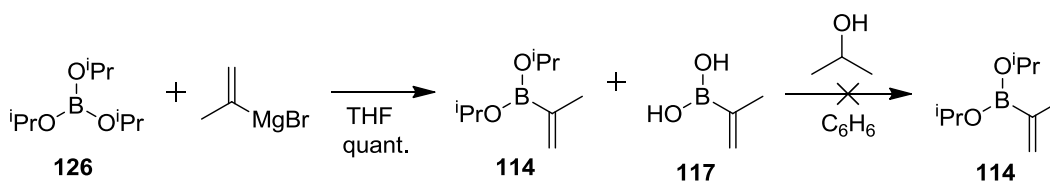
When the reaction of **126** with isopropenylmagnesium bromide was repeated with a non-aqueous workup, the NMR spectrum showed lots of starting material, and some **114** may have been present. The remaining ether and triisopropyl borate were distilled off to give a 15% yield of **114**.

In August of 2010, McNulty published the paper on the synthesis of cyclic boronic half acids.[48] This paper contained the procedure for the synthesis of allylic diisopropylboronate ester **106**. An adaption of this procedure was used for the synthesis of our desired substrate. Trimethyl borate was reacted with isopropenylmagnesium bromide in ether and quenched with 30% HCL. During concentration, a precipitate began to form. It

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[48] McNulty, L.; Kohlbacher, K.; Borin, K. *J. Org. Chem.* **2010**, *75*, 6001-6004.

was at this point excess isopropyl alcohol and hexanes were added to the flask and the solution was refluxed. This procedure afforded a 58% crude yield of **114**. Attempted purification by distillation resulted in decomposition of material, therefore crude diisopropylboronate ester **114** was used in future experiments.

3.3 Synthesis of homoallylic alcohol 127.

The original plan for the synthesis of 2-methylhex-5-ene-2,3-diol (**127**) was relatively straightforward: synthesize 5-methylhex-1,4-diene (**128**), and perform a Sharpless dihydroxylation to form the homoallylic alcohol **127** (Figure 3-1).

Figure 3-1: Planned synthesis of homoallylic alcohol 127 using dihydroxylation.
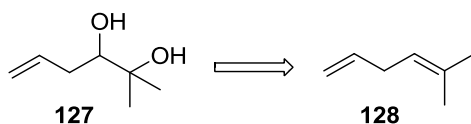
To synthesize 5-methylhex-1,4-diene (**128**), isobutyraldehyde (**129**) was treated with sulfuryl chloride (Scheme 3-10).[49] Distillation afforded α-chloroisobutyraldehyde (**130**) in a 74% yield. This was reacted with allylmagnesium bromide and lithium powder.[50] The crude material was analyzed by NMR. The ^{1}H NMR spectrum showed a vinyl resonance, indicating that some product may have been formed. Due to the broad overlapping signals present between 0.9 ppm and 5.2 ppm in the spectrum, it was difficult to tell if the desired product **128** had formed.

Since the reaction with allylmagnesium bromide and lithium powder can be performed as two seperate steps, we decided isolate the intermediate **131**. Allylmagnesium

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[49] Stevens, C.; Gillis, B. *J. Am. Chem. Soc.* **1957**, *79*, 3448-3451.
[50] Barluenga, J. *J. Chem. Res. (M)*. **1980**, 677-692.

bromide was added to **130** in THF at -78 °C. Distillation afforded only an 18% yield of the coupled product **131**. The low yield may be due to decomposition of the Grignard reagent during storage. Also, during quenching, the solution turned into a gel. Addition of 6M sulfuric acid along with vigorous stirring was required to dissolve the gel. The strong acid conditions may have promoted decomposition of the product. A reductive elimination of **131** to form diene **128** should be possible by treatment with lithium powder.[51] However, when this experiment was performed, it appeared that only reduction of the chlorine had occurred to form **132** in a 45% yield. Alcohol **131** was protected with an acetate group in a 16% yield. Attempts at reductive elimination of the acetate with lithium, zinc and magnesium were all unsuccessful.

Scheme 3-10: Attempted synthesis of 128.
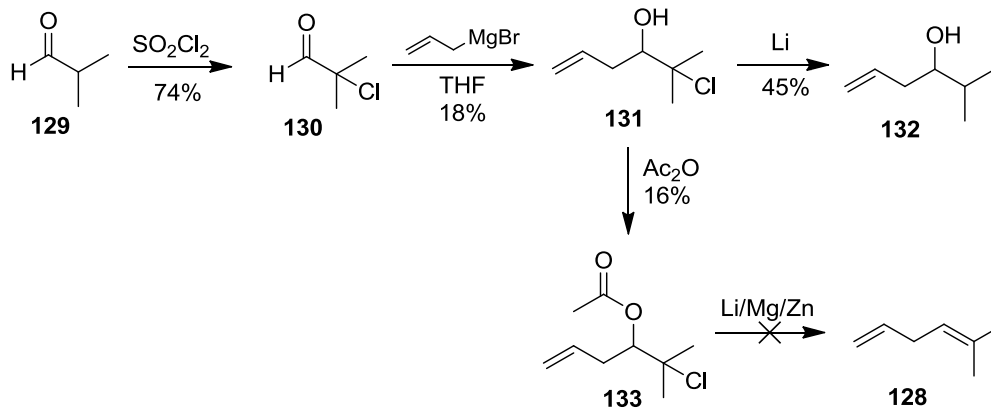
Since this route was not successful, another route was developed. In this strategy, 2-hydroxy-2-methylpropanal (**135**) would be reacted with allylmagnesium bromide to create the homoallylic alcohol **127**. The α-chloroisobutyraldehyde synthesized for the previous route to the homoallylic alcohol was used. Aldehyde **130** was treated with sodium in

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[51] Stevens, C. L.; Gillis, B. *J. Am. Chem. Soc.*, **1954**, *76*, 2694-2698.

methanol and white salts precipitated. When the pH of the solution was between 7 and 9, the mixture was centrifuged and the supernatant oil was distilled to afford acetal **134** in a 42% yield (Scheme 3-11).[51]

Hydrolysis with water and Amberlyst®-15 ion exchange resin to form **135** was performed according to a procedure found in literature.[52] NMR analysis of crude material indicated the absence of the methoxy protons. The aldehyde proton was also absent but some resonances in the aromatic region were present. Thinking that there might be some cross-contamination, this reaction was retried in water and CH_2Cl_2 so that any organic impurities would stay in the organic layer. In this second attempt, Amberlyst®-15 ion exchange resin was reacted with **134** in the biphasic solution. Workup and analysis of the crude product indicated no reaction had occurred, and starting material was recovered. Treatment with Amberlyst®-15, ion exchange resin in water overnight resulted in a 2% yield by NMR analysis of the desired product **135**. With such a small yield, pure product was not isolated. Hydrolysis of the dimethyl acetal **134** was also tried using *p*-toluenesulfonic acid (TsOH) in water and THF[53] as well as with copper (II) sulfate and sodium iodide in HPLC grade acetone.[54] In both cases the NMR spectrum of the crude product showed significant impurities. With the copper (II) sulfate and sodium iodide reaction, a minute aldehyde peak was observed in the NMR spectrum.

[52] Fessner, W. D. *Euro. J. Org. Chem.* **2000**, 125-132
[53] Seebach, D.; Beck, A. *Org. Synth.* **1971**, *51*, 39-42.
[54] Mohan, R. S.; Bailey, A. D. *Synlett* **2006**, *2*, 215-218.

Scheme 3-11: Second attempted synthesis of 127.
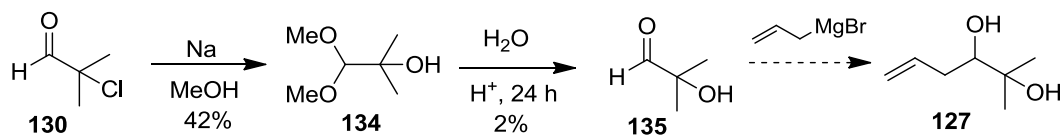
The final method for the synthesis of homoallylic alcohol **127** involved introduction of the diol first. Trimethylsilyl acetylene (**136**) was coupled with 1-bromo-3-methyl-2-butene to make enyne **137** (Scheme 3-12).[28] Distillation of afforded **137** in a 44% yield. This reaction was repeated with new *n*-butyllithium in 79% yield. Sharpless' dihydroxylation AD-mix β in a biphasic solution of *tert*-butanol and water at 0 °C[55] resulted in a 19% yield of **138**. When this procedure was repeated, a yield of 36% was achieved.

Scheme 3-12: Synthesis of diol 138.
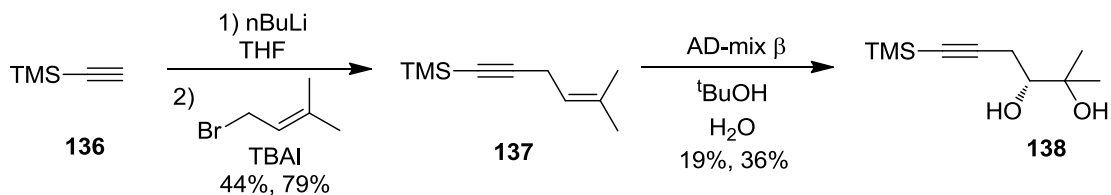
Previous Sharpless dihydroxylations by the Vyvyan group have given yields in the range of 44-64%. For the dihydroxylation of the protected enyne **137**, a lower yield of 19% and 36% was achieved. Because of this, Sharpless' asymmetric dihydroxylation reaction was optimized.

AD-mix α and β are composed of potassium carbonate, potassium osmate (IV) dihydrate, potassium ferricyanide, and either (DHQ)₂PHAL as the chiral ligand for α, or (DHQD)₂PHAL as the chiral ligand for β.[55] The only compounds that were varied for

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[55] Sharpless, B. K.; Kolb, H. C.; Van Nieuwenhze, M. S. *Chem. Rev.* **1994**, *94*, 2483-2547.

optimization were the oxidant, potassium osmate (IV) dihydrate, and the chiral ligand (DHQD)$_2$PHAL. This is because potassium osmate (IV) dihydrate is the oxidant for this reaction and is also responsible for binding with the olefin to induce dihydroxylation. Sharpless describes being able to adjust the amount of osmium to improve yields with difficult compounds.[55] The amount of chiral ligand was varied in order to see if it had any impact on the conversion to the diol. Commercial, AD-mixes are made up of three equivalents of potassium carbonate, 0.4 mol % potassium osmate (IV) dihydrate, three equivalents of potassium ferricyanide, and 1 mol % chiral ligand. During optimization, one equivalent of methane sulfonamide and equal volumes of *tert*-butanol and water were used, and the mixture was allowed to react for three hours.[55] The highest yield of 56% was achieved with three equivalents of potassium carbonate and potassium ferricyanide, 0.5 mol % potassium osmate (IV) dihydrate, and 1.5 mol % (DHQD)$_2$PHAL.

A Lindlar hydrogenation was attempted on **138** to reduce the alkyne to its respective alkene. Treatment of **138** with palladium on barium sulfate, and quinoline in pentane under a hydrogen atmosphere[56] gave unreacted starting material. Another Lindlar reduction was attempted using palladium on calcium carbonate with the same result. Instead of reducing to the alkene first, a deprotection of the TMS group was tried (Scheme 3-13). TMS-diol **138** was successfully deprotected potassium carbonate and methanol[57] to form **139** in a 61-84% yield. The final step to form **127** is the reduction of the alkyne to alkene. Terminal alkyne **139** was treated with palladium on barium sulfate and quinoline, in ethyl acetate under hydrogen to give an average yield of 64% for the homoallylic alcohol **127**.

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[56] Tallman, K. A.; Porter, N. A. *J. Am. Chem. Soc.* **2009**, *131*, 5635-5641.
[57] Vyvyan, J. R. PhD. Thesis. University of Minnesota. Minneapolis MN, August 1995.

Scheme 3-13: Formation of the homoallylic alcohol.
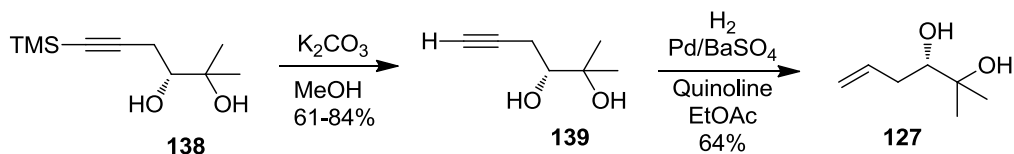
The Lindlar reduction to homoallylic alcohol **127** proved to be a problematic step. One would expect the reduction from the alkyne to the alkene to be fast, and the subsequent reduction of the alkene to the alkane to be non-existant. This is because a linear conformation is required for a compound to be able to abstract a hydrogen off the surface of the palladium. Since alkynes are linear this is not a problem, but alkenes are planar, so they should not be able to come close to the palladium to pick up hyrdrogens. Experimentally, it was found that conversion of the alkyne to the alkene was slow, but upon complete consumption of the alkyne, reduction to the alkane proceeded very fast. Periodic NMR analysis was required to check the progress of the reaction. In two cases, almost complete conversion to the alkene was observed when checking the progress of the reaction. However, when the reaction was subsequently worked up and purified, NMR analysis indicated complete reduction to the alkane. The reactions in which the alkene was not over-reduced had to be stopped when some alkyne was still remaining. This reaction was also problematic because of the presence of quinoline. While quinoline is added to poison the catalyst, it remains present in the crude material. To try to remove this, a new workup including washing the organic layer with sat. aq. ammonium chloride was tried. Quinoline was still present, so a 5% HCl wash was also included. This did help reduce the amount of quinoline present, but not significantly.

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3.4 Formation of cyclic boronic half acid 140.

At this point, some crude homoallylic alcohol **127** had been synthesized, along with purified dibutylboronate ester **118**. A cyclization with the dibutylboronate ester was attempted (Scheme 3-14). Homoallylic alcohol **127** (1 equiv), boronate ester **118** (3 equiv), Grubbs' 1st generation catalyst (5 mol%), and CH_2Cl_2 (0.5 M) were refluxed for 24. By ^{1}H NMR analysis, the crude mixture contained mostly unreacted starting material. However, some additional peaks were present that may indicate that some **140** formed. In an attempt to isolate **140**, flash chromatography was performed. From the spectrum of the purified material, it is unclear exactly what formed. The vinyl peaks had shifted downfield slightly, which may indicate that the cross-metathesis did occur to form the cyclized product. Two resonances indicating a proton adjacent to an oxygen are present, and have shifted slightly from the homoallylic alcohol, which also may indicate cyclization. Unfortunately, multiple peaks in the aliphatic region (1-2 ppm) were present in the spectrum. It is possible these are from the impurities mixed with alcohol **127**, or that they are from the butanol group that was cleaved off of boronate ester **118** during workup. These additional peaks may have masked some important peaks that would confirm cyclization product. This ambiguity in the ^{1}H NMR leads to another question: if the cyclization worked, did transesterification occur at the secondary or tertiary site and can we differentiate between the products? Using ChemDraw software,[58] the resonances for both ^{1}H NMR and ^{13}C NMR were calculated for the 6-membered cyclic boronic half acid **140a**, and the 7-membered cyclic boronic half acid **140b**. For both ^{1}H and ^{13}C NMR, these compounds have almost identical calculated chemical shifts.

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[58] *ChemBioDraw*, version 12.0; CabridgeSoft: Cambridge, MA; 2009.

Scheme 3-14: Attempted cyclization with homoallylic alcohol 127.
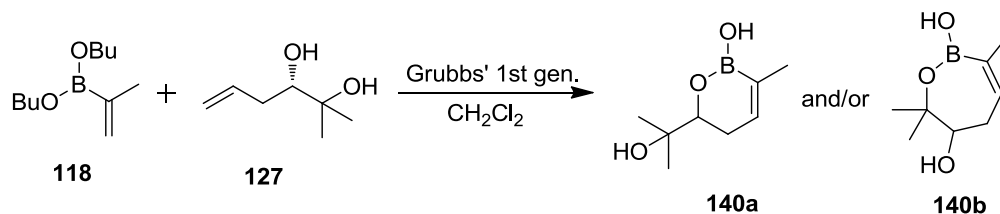
In the hope that optimization of this reaction would result more pure material, the cyclization reaction was optimized using a commercial 1-phenyl-3-butenol (**141**) (Table 3-1). The highest yield of 90% was obtained with 2 equivalents of **118**, 5 mol% Grubbs' 1st generation catalyst, and 0.5 M CH$_2$Cl$_2$.

Table 3-1: Optimization of boronic half-acid cyclization.
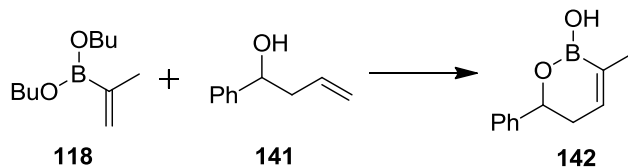
Alcohol **141** (equiv)	Boronate Ester **118** (equiv)	Grubbs (mol %)	CH$_2$Cl$_2$ (M)	Yield of **142** (%)
1	1	5	0.5	50
1	2	4	0.5	32
1	2	5	0.25	30
1	2	5	0.5	90[a]
1	2	5	1.0	45
1	2	8	0.5	47
1	2	12	0.5	60
1	2	14	0.5	64
1	3	5	0.5	79
1	3	7	0.5	73

[a] This reaction was performed on double the scale.

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Using the optimized conditions, a cyclization with diisopropyl propen-2-ylboronate (**114**) to form the cyclic boronic half acid **142** was accomplished in a 73% yield. This is comparable to yield achieved with the dibutylboronate ester **118**.

A Suzuki-Miyaura coupling was attempted with cyclic boronic half acid **140** and iodobenzene. Purification and NMR analysis indicated none of the desired product was formed. This was evident by the absence of vinyl proton peaks in the NMR spectrum, and could be due to the impurity of cyclic boronic half acid **140**.

4: Synthesis of glandulone B.

Given the success of Hiyama couplings of cyclic alkenyl siloxanes like **69** with aryl halides for the formation of *Z*-styrenes, this strategy was applied to the synthesis of glandulone B (**23**).

4.1 Synthetic strategy.

Glandulone B contains an aromatic bisabolene skeleton with a *Z* olefin. Two paths were envisioned for the synthesis of this compound (Scheme 4-1). In path A, a 7-membered cyclic vinyl siloxane **147** would be coupled to 1-iodo-2,5-dimethoxy-4-methylbenzene (**146**) using Hiyama coupling conditions. This would form the *Z*-olefin tether containing a primary alcohol in **145**. A dehydration performed on the coupled compound **145** should form the aryl diene **144**. This is where retrosynthetic path A and B converge.

The second pathway (B) to the synthesis of glandulone B is similar to path A, but involves a 6-membered cyclic vinyl siloxane. This 6-membered cyclic vinyl siloxane **150** could be coupled with 1-iodo-2,5-dimethoxy-4-methylbenzene (**146**) under the same Hiyama coupling conditions to produce **149**, which contains a *Z*-olefin 1 carbon shorter than **145** (from path A). Oxidation of the primary alcohol would result in the formation of aldehyde **148**. Subsequent Wittig olefination would form aryl diene **144**, which is where paths A and B converge.

From the diene **144**, a cross-metathesis with methacrolein forms the side chain present in glandulone B. Final oxidation of **143** to the quinone **23** would give the target compound glandulone B (**23**).

Scheme 4-1: Retrosynthetic strategy for glandulone B.

Glandulone B
23

143

144

path A

path B

145

148

146   **147**

149

146   **150**
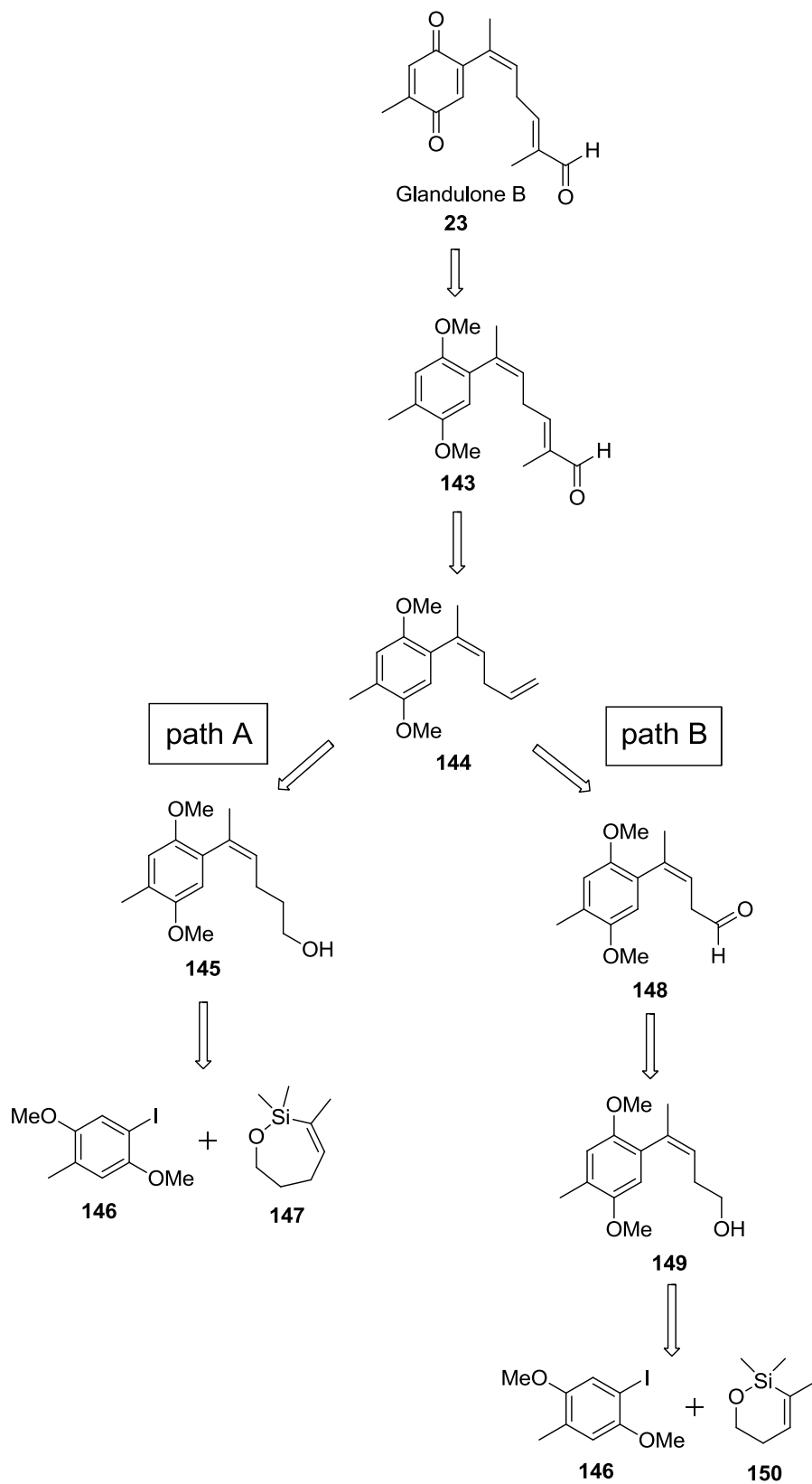
The benefit of path A over path B is the number of steps involved. Path A is one step shorter than B. From previous experience, it is believed that both Hiyama couplings should give similar yields. Therefore, if the yield of the dehydration of **145** to form the aryl diene **144** is good to excellent, the combined yield to the diene may be greater than the oxidation/ Wittig of **149**, such that the overall yield to glandulone B would be greater.

4.2 Synthesis of cyclic vinyl siloxanes 147 and 150.

The 6-membered cyclic vinyl siloxane was synthesized from commercially available 3-pentyn-1-ol (**151**) (Scheme 4-2).[31,59] Pentynol **151** was reacted with tetramethyldisilizane to form the hydrosilylation intermediate. It is important to distill off all excess tetramethyldisilizane at this stage because it will poison the catalyst used in the cyclization step, which would result in lower yields.[31] Subsequent reaction with ruthenium catalyst **73** and distillation of the crude product afforded a 30% yield of cyclic silane **150**. When this procedure was repeated, a 45% yield of **150** was achieved.

Scheme 4-2: Synthesis of 6-membered cyclic vinyl siloxane.
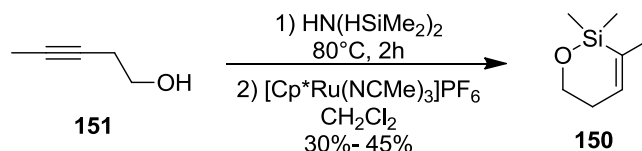
The synthesis of the 7-membered vinyl siloxane **147** required more steps than the 6-membered vinyl siloxane **150**. To synthesize the desired 7-membered ring, 4-hexyn-1-ol (**155**) was synthesized since it is not commercially available (Scheme 4-3).[32] Freshly distilled dihydropyran was used to protect 4-pentyn-1-ol (**152**) under mildly acidic conditions

[59]Porter, C. Unpublished Results. Western Washington University. Bellingham, WA.

for a 46% yield of **153**. Use of *n*-butyllithium and methyl iodide at -78 °C forms

intermediate **154**. Deprotection of intermediate **154** was accomplished using *p*–

toluenesulfonic acid and methanol. To purify crude hexynol **155**, the methanol was distilled

off for a 17% yield of 4-hexyn-1-ol (**155**). It was found that hexynol **155** was heat-sensitive,

which was evident by the production of smoke while **155** was being distilled off.   I

concluded that it was likely that some product decomposed during distillation, thereby

lowering the yield.

With the desired hexynol **155** synthesized, hydrosilylation was performed by

treatment with tetramethyldisilizane as previously described. Subsequent reaction with

ruthenium catalyst in dichloromethane resulted in the formation of the desired 7-membered

cyclic vinyl siloxane **147**. The low yield on the final step was a result of unknowingly using

impure **155** that had been previously synthesized by another group member. When the

hydrosilylation was performed with pure alcohol by Porter, a 98% purified yield of **147** was

achieved.

Scheme 4-3: Synthesis of 7-membered cyclic vinyl siloxane.
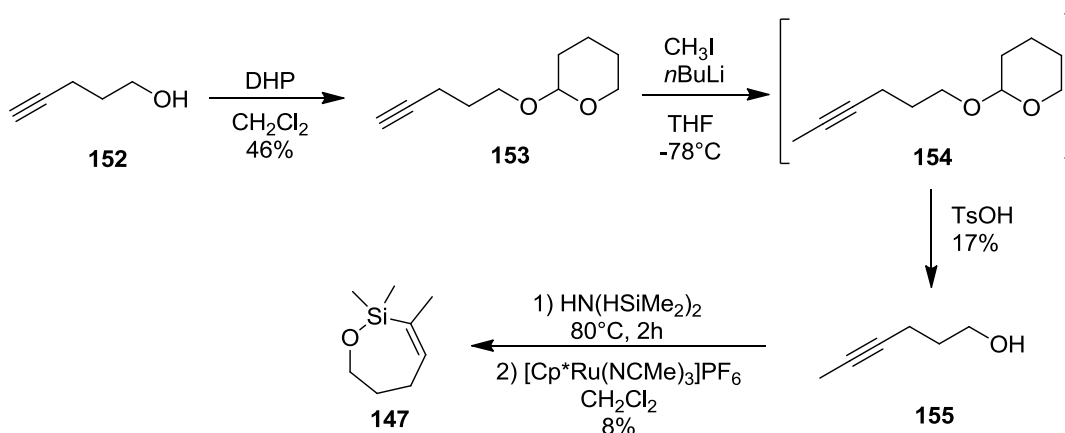
4.3: Synthesis from 7-membered cyclic vinyl siloxane 147.

The Hiyama coupling partner needed for the synthesis of glandulone B is 1-iodo-2,5-dimethoxy-4-methylbenzene (**146**). Iodination of 2,5-dimethoxytoluene (**156**) resulted in a 63% yield of product **146** as fine white crystals[60] (Scheme 4-4). A Hiyama coupling of **146** with vinyl siloxane **147** resulted in a 48-58% yield of **145**.

Scheme 4-4: Synthesis of 145.
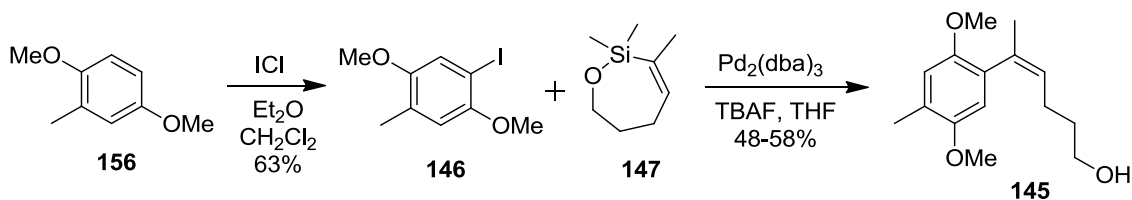
In order to form the diene **144** from the aryl alcohol **145**, a dehydration needed occur. From a literature search, an article which described the use of dipyridyl diselenides and Dess-Martin periodinane to dehydrate primary alcohols under mild conditions and in excellent yields was found.[61] Synthesis of 2,2'-dipyridyldiselenide was accomplished with the treatment of bromopyridine with isopropylmagnesium chloride and elemental selenium. Primary aryl alcohol **145** was treated with dipyridyl diselenide and trimethylphosphine to afford a quantitative yield of an intermediate presumed to be **157** (Scheme 4-5). Subsequent treatment with Dess-Martin periodinane, workup, and purification gave the dehydrated product **144** in a 29% yield as well as a 10% yield of unreacted intermediate **157**. This step was repeated using 1.0 M trimethylphosphine with similar yields. Due to the low yield of this step, path B from the 6-membered cyclic vinyl siloxane **150** was attempted.

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[60] Reed, M. W.; Wald, A.; Meyer, R. B. *J. Am. Chem. Soc.* **1998**, *120*, 9729-9734.
[61] Vilarrasa, J.; Burés, J.; Andreou, T. *Tetrahedron Lett*. **2010**, *51*, 1863-1866.

Scheme 4-5: Synthesis to diene 144.
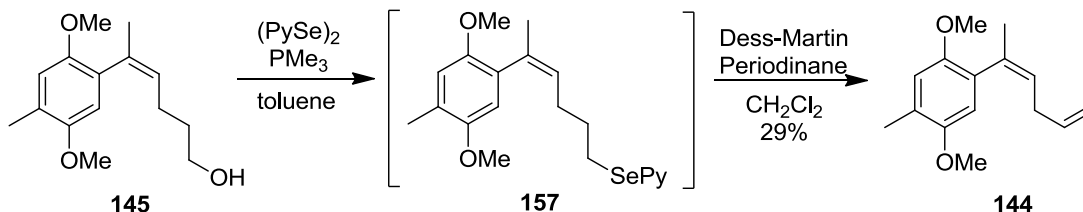
4.4 Synthesis from 6-membered cyclic vinyl siloxane 150.

With a model aryl alcohol **158** having been previously synthesized,[62] different oxidation procedures to corresponding aldehyde **159** were tested (Scheme 4-6). A literature procedure for the oxidation of primary alcohols to an aldehyde involved treatment of aryl alcohol **158** with [bis(trifluoroacetoxy)iodo]benzene and 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO).[63] Experimentally, the progress of the reaction was difficult to monitor by TLC. In addition, analysis of crude material by NMR indicated decomposition of material.

In a second attempt to make the aldehyde, excess Dess-Martin periodinane was used in excess with the aryl alcohol **158**. A 26% yield of crude **159** was obtained. Attempts to purify **159** resulted in decomposition. A Wittig reaction was tried on crude aldehyde **159** using methyl tripheylphosphonium bromide and *n*-butyllithium. Absence of vinyl peaks in the ^{1}H NMR spectrum indicated that product **160** was not formed. This is most likely due to the unstable nature of the aldehyde as well as the harsh reaction conditions.

[62] Denmark, Scott E.; Sweis, Ramzi E. *Org. Lett.* **2002,** *4,* 3771-3774
[63] Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974-6977

Scheme 4-6: Attempted oxidation and reduction of 159.
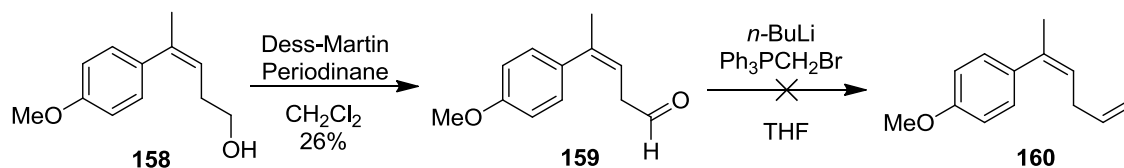
Using aryl iodide **146**, a Hiyama coupling was performed with the 6-membered cyclic vinyl siloxane **150** to give the aryl alcohol **149** in a 57% yield (Scheme 4-7).

Scheme 4-7: Hiyama coupling with 6-membered cyclic vinyl siloxane 150.
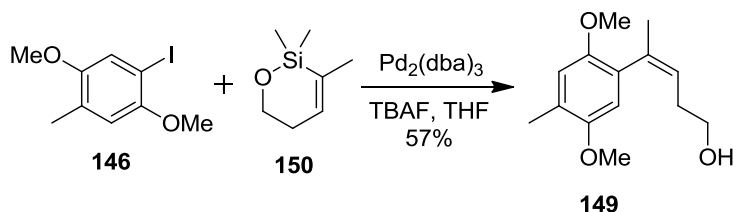
When repeating this experiment it was noticed that the starting cyclic siloxane decomposed. Since both the aryl iodide and cyclic silane had just been remade, we believed that the new starting materials may be the reason why the reaction did not work, both were re-purified. The coupling was tried again with the re-purified material and new tetra *n*-butylammonium fluoride, without success. Another Pd(0) catalyst, bis(dibenzylideneacetone)palladium (0) was also tried, without success. Eventually, it was determined that the palladium catalyst's activity had decreased. To confirm this was the cause, a small scale Hiyama coupling was performed with 10 mol% catalyst instead of the usual 2.5 mol%. The result was a 92% purified yield of product. Repetition of this experiment with the larger catalyst loading has consistently given purified product in a 90% yield.

Next, a small scale Swern oxidation was attempted to obtain **148**. Aryl alcohol **149** was treated with oxalyl chloride, DMSO, and triethylamine. Workup and NMR analysis indicated minimal conversion to aldehyde. In addition, two aldehyde peaks were present in the NMR spectrum, possibly indicating the formation of isomers. A second Swern oxidation was attempted with a newer bottle of oxalyl chloride as well as freshly distilled triethylamine. After three hours NMR analysis indicated mostly starting material, along with minute traces of the two aldehydes.

It was decided to try a Dess-Martin oxidation on our aryl alcohol **149** (Scheme 4-8). In one hour, a quantitative crude yield of **148** was achieved. Analysis indicated complete consumption of starting material, and the crude material was fairly pure. Small-scale purification by flash chromatography resulted in a less pure material as it did with aldehyde **159**. Larger scale Dess-Martin oxidations have been repeated, with reaction times averaging around 4-6 hours, and yields ranging from 88% to 93% of nearly-pure product. To form **144**, a Wittig reaction was employed.[64] The crucial part of this reaction is the formation of the ylide. For this particular reaction, *n*-butyllithium was added dropwise to a stirred solution of methyltriphenylphosphonium bromine in THF at -78 °C. Prior to this reaction, methyltriphenylphosphonium bromide was flame dried under vacuum. This resulted in a bright yellow solution, typically with some precipitated salts. Since the ylide is indicated by a deep red solution, the flask was removed from the dry ice bath and allowed to warm up to room temperature while being stirred. As the solution warmed, the yellow color slowly turned to a bright orange-red and the salts dissolved. Once the neon orange-red solution was present, the solution was cooled again to -78 °C before aldehyde **148** was added. Typically,

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[64] Duffy, T. B.S. Honors Thesis. Western Washington University. Bellingham WA, June 2005.

after stirring for 48 hours, TLC indicated consumption of the aldehyde. Workup and purification results in typical yields of **144** in the mid-50% range.

An olefin cross-metathesis between **144** and methacrolein (**54**) would give the dimethoxyhydroquinone analogue of glandulone B. A solution of freshly distilled methacrolein (**54**), Grubbs' 2nd generation catalyst, and diene **144** in dichloromethane was refluxed overnight.[29] Due to evaporation of the solvent, only starting material was recovered. To prevent the solvent from evaporating, this procedure was repeated in a screwcap vial with toluene as the solvent at 50 °C. Progress of the reaction was monitored by TLC. After 1 day, there was a small conversion to the aldehyde. Additional Grubbs' catalyst and methacrolein were added to the reaction, and after 3 more days the reaction was worked up and purified to give a 48-53% yield of the desired aldehyde **143**. The olefin cross-metathesis was also performed with methyl *tert*-butyl ether as a solvent in a screwcap vial under the same conditions with a similar yield.

Scheme 4-8: Synthesis of aldehyde 143 from 149.
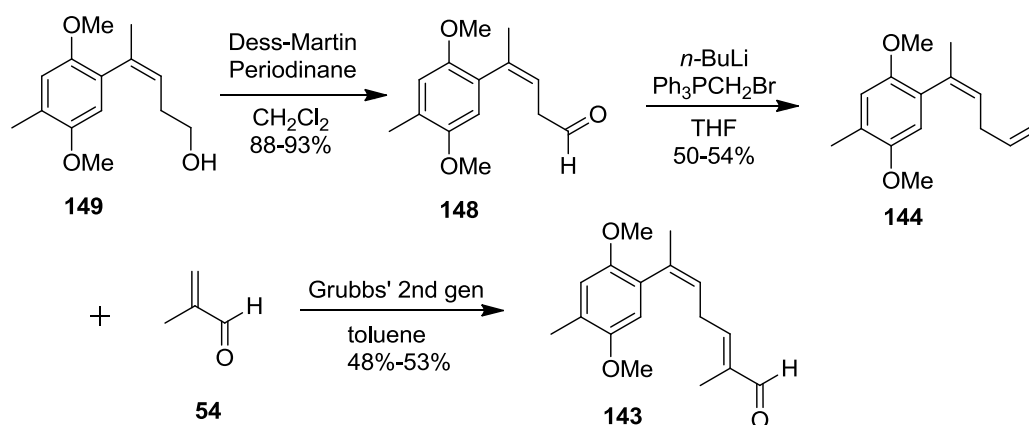
The final step in the synthesis of glandulone B is the oxidation of **143** to the quinone **23**. For the synthesis of glandulone A (**22**), a ceric ammonium nitrate (CAN) oxidation resulted in spectroscopically pure quinone.[29] This method seemed likely to work on our substrate due to the similarity in structures. Ceric ammonium nitrate dissolved in water was added dropwise to aldehyde **143** in acetonitrile (Scheme 4-9). Analysis of crude material indicated that desired quinone **23** was not formed. The CAN oxidation was tried again, this time adding aldehyde **143** with acetonitrile to the aqueous solution of CAN. NMR analysis showed a mixture of many products. Purification by flash chromatography did not yield **23**.

Since the cross-metathesis to form **143** should not be affected by the presence of a quinone versus the hydroquinone dimethyl ether, a CAN oxidation was tried on the aryl diene **144**. Analysis of the crude product indicated that diene **144** oxidizes to the quinone **161** easily. Repetition of this experiment gave material that was not as pure, and purification resulted in a 38% yield. A cross-metathesis of quinone **161** with methacrolein (**54**) did not result in the formation of glandulone B (**23**), however.

Scheme 4-9: Attempted oxidation of glandulone B.
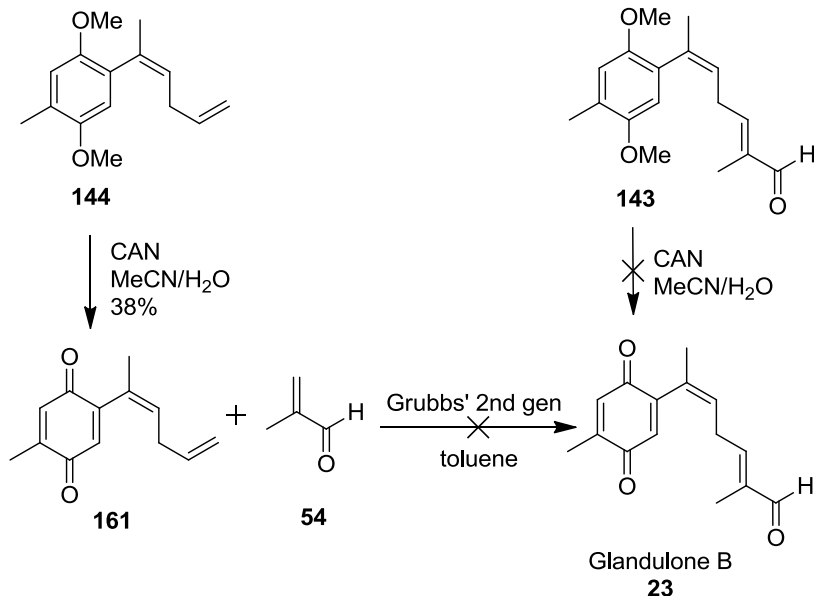
A procedure for the oxidation to quinones using hypervalent iodine complexes was found in a literature search.[65] Reaction of diene **144** in aqueous methanol, with 4 equivalents of [bis(trifluoroacetoxy)iodo] benzene (PIFA) resulted in decomposition of the starting material. This was tried again with 1.5 equivalents of PIFA, and the reaction was monitored more closely, but with the same result. A PIFA oxidation was also tried on aldehyde **143**. Within 5 minutes, starting material was consumed. Workup and NMR analysis showed the absence of an aldehyde and vinyl resonances, however, indicating none of the desired product was produced.

Another way to oxidize dimethoxy benzenes is with silver (II) oxide.[66] Silver (II) oxide, aldehyde **143**, dioxane, and 6 M HNO_3 were sonicated and stirred until silver (II) oxide was consumed. According to the literature, this was within 2-3 minutes.[66] Since I was

[65] Kita, Y.; Tohma, H.; Morioka, H. *Tetrahedron Lett.* **2001**, *42*, 6899-6902.
[66] Rapoport, H.; Snyder, C. D. *J. Am. Chem. Soc.* **1972**, *94*, 227-231.

unable to observe the consumption of silver (II) oxide, the literature procedure was followed and the reaction was worked up after 3 minutes. NMR analysis showed no oxidation to the quinone. This was repeated, and progress of the reaction was monitored by TLC. After 24 hours, no reaction to was observed. Workup and ^{1}H NMR analysis confirmed only the presence of starting material **143**.

To test if the conjugation of the system was interfering with the oxidation to the quinone, these oxidations were carried out on dimethoxybenzenes **162** and **163** (Figure 4-1). Under CAN conditions, both formed their respective quinones within 10-15 minutes of addition of aqueous CAN to the substrate. The oxidation using a hypervalent iodine (III) reagent showed no starting material remaining after 5 minutes. NMR analysis indicated decomposition of starting material. Silver (II) oxide oxidation produced no reaction. Since the CAN oxidation proceeded smoothly to the quinone, most likely the conjugation of the dimethoxy aryl ether moiety with the *Z* olefin on **143** is interfering with the oxidation to the respective quinone.

Figure 4-1: Dimethoxybenzenes used for test oxidations.

162	**163**
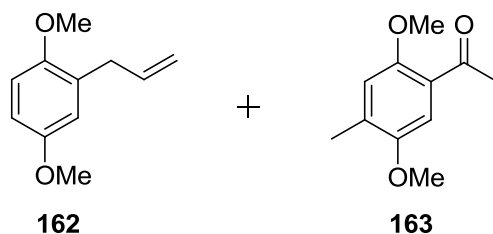
Typically, oxidations to quinones are easier from their hydroquinone derivative versus the dimethoxyhydroquinone.[67,68] For the dimethoxyhydroquinone such as **143**

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[67] Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627-3629.

oxidative demethylation is required to produce the corresponding quinone, whereas an oxidation of the hydroquinone will produce the quinone. Oftentimes, the result of oxidative demethylation is dimerization of the dimethoxyhydroquinone.[67] Since we had troubles with the oxidation of **143** to glandulone B (**23**), we propose that synthesis to the hydroquinone **167**, and subsequent oxidation should produce glandulone B (**23**) (Scheme 4-10). To do this, our aryl iodide coupling partner would be protected with a methoxy methyl (MOM) group to give **164**. Hiyama coupling of **164** with the cyclic vinyl siloxane **150** would give the *Z*-styrene. Subsequent oxidation, olefination, and cross metathesis with methacrolein would result in the formation of **166**. Deprotection of the MOM group should be relatively easy, and would give hydroquinone **167**. A final oxidation should yield our target compound, glandulone B (**23**).

Scheme 4-10: Proposed synthesis to glandulone B (23).
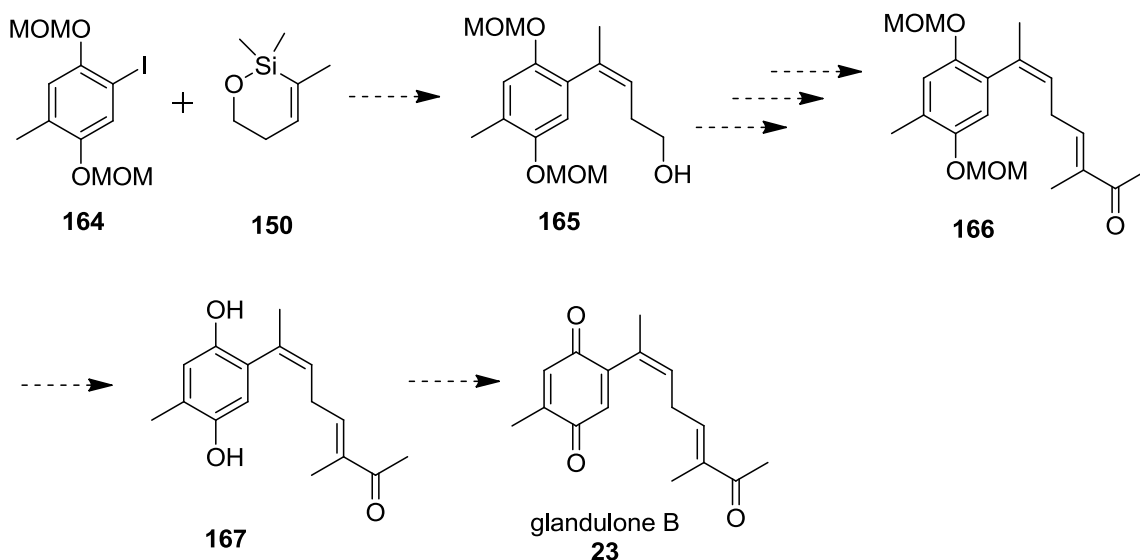
[68] Menisci, F.; Citterio, E. V.; Fontana, F.; De Betnardinis, S. *J. Org. Chem.* **1989**, *54*, 728-731.

5. Conclusion

In conclusion, I have shown that insertion of a strongly electron withdrawing group such as an acetyl group onto the aromatic ring improves Buchwald-Hartwig etherifications of substrates like **101**, although the yield of cyclized product is still quite low.
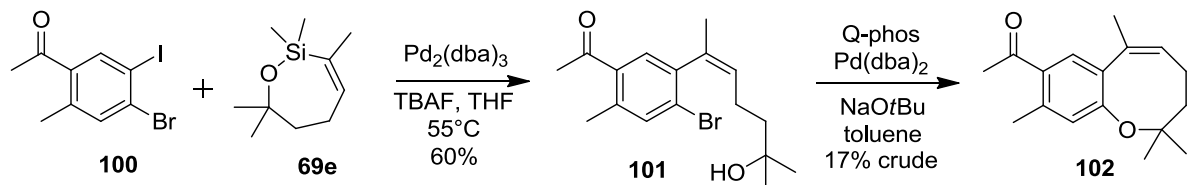
For the synthesis of cyclic boronic half acids, I was able to synthesize both the dibutylboronate ester and diisopropylboronate ester **114** and **118** from trimethyl borate in good yields. I was also able to synthesize homoallylic alcohol coupling partner **127**.
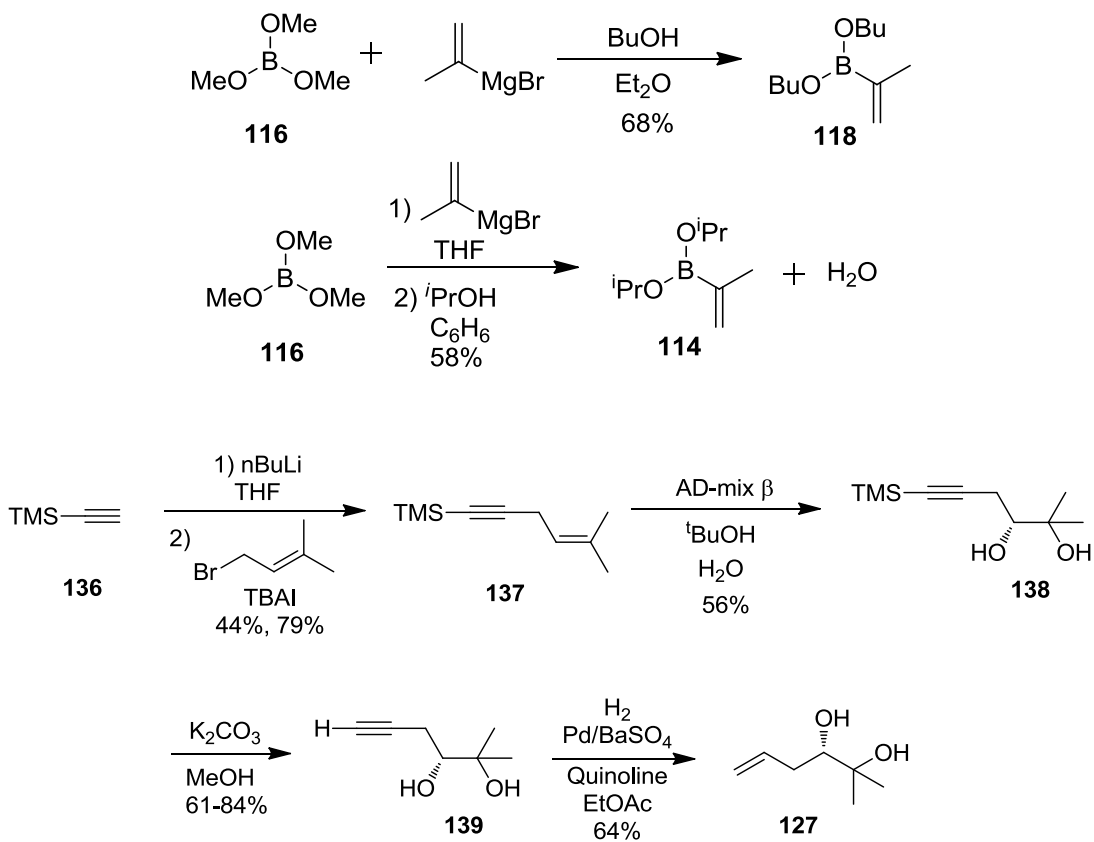
Unfortunately, I was unable to form the cyclic vinyl boronic half acids using an olefin cross metathesis of **127** and **114/118**.

Finally, I was able to use a Hiyama coupling of the 6-membered cyclic vinyl siloxane **150** to form *Z*-styrene **149** required for the synthesis of the dimethoxyhydroquinone analogue of glandulone B (**143**).
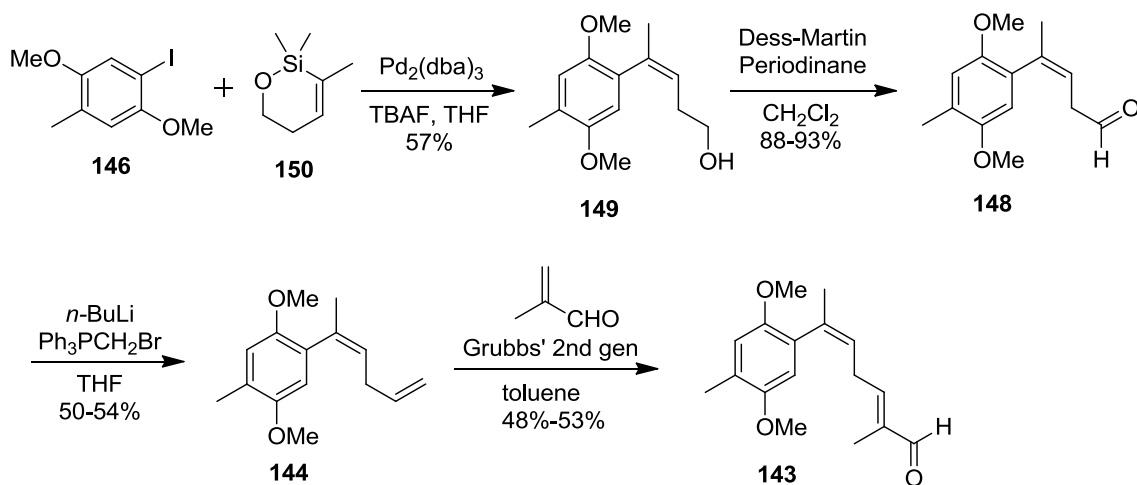
Experimental Section

General Experimental Procedures

All procedure involving air- or moisture-sensitive reagents were performed in oven-dried glassware under a nitrogen or argon atmosphere. Ether, THF, CH_2Cl_2 and toluene were dried by passing through a column of activated alumina using an Innovative Technology Pure Solv™ 400 Solvent Purification System. All reactions were stirred at room temperature unless otherwise noted. In all procedures, unless otherwise noted, concentration was performed by rotary evaporation. Drying agents were removed using gravity filtration and fluted filter paper (P2 Fischer Qualitative Circles).

All chromatography was done with mixtures of hexanes and ethyl acetate unless otherwise noted. Thin layer chromatography was done using Sorbent Technologies 200μm silica layer fluorescence UV_{254} TLC plates. For purifications, column reservoir volumes, column diameters, and solvent mixtures are given (for example "500 mL, 1" column, 6:1 hexanes: EtOAc"). Flash chromatography was carried out with hand packed columns of silica gel (Silicycle, Chemical Division, 230-400 mesh).

^{1}H and ^{13}CNMR spectra were acquired on either Varian Mercury (300 MHz) or ^{UNITY}INOVA (500 MHz) spectrometers. All chemical shits are reported in ppm, and all coupling constants are reported in Hertz. ^{1}H chemical shifts are referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{1}H NMR data are reported in the following format: chemical shift [integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (*J*), number of protons, and proton assignment]. ^{13}C NMR spectra are referenced to $CDCl_3$ at 77.0 ppm.

IR spectra were obtained on a Thermo Scientific Nicolet iS10 FT-IR spectometer with a Smart iTR attachment. All absorptions are reported in cm^{-1}. Absorbances in the IR spectrum are referred to as: w = weak, m = medium, s = strong, and br = broad.

Combustion analysis was performed by Chemisar Laboratories, Guelph, ONT, Canada. Results are reported using the following format: empirical formula; calculated percent carbon, calculated percent hydrogen; observed percent carbon, observed percent hydrogen. High resolution mass spectometry was performed by the Mass Spectrometry Facility at the University of California, Irvine.

General Procedure A: Protection of an aniline with an acetate.
Preparation of *N*-(3-chloro-4-methylphenyl)acetamide (90)[36]
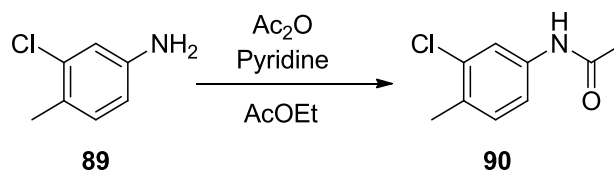
Notebook Reference: CAEA011, CAEA035

A solution of **89** (12.0 mL, 14.0 g, 0.100 mol), in ethyl acetate (75 mL) and pyridine (7.00 mL, 6.87 g, 0.110 mol) was charged to a 250 mL round bottomed flask under argon. This solution was cooled to 0 °C and acetic anhydride (10.4 mL, 11.3 g, 0.110 mol) was added dropwise. The mixture was stirred and allowed to warm to room temperature overnight. The solvents were removed *in vacuo* and the solid residue was triturated with diethyl ether (50 mL). The solid was collected by filtration, washed with cold diethyl ether (100 mL), and hexanes (100 mL). The product was dried over P_2O_5 to afford **90** as a white solid (13.667 g, 0.075 mol, 75%). This procedure was repeated using 0.250 mol **89** with a 62% yield of **90**.

mp: 105-106 °C

FT-IR (Neat): 3291 (m), 3175 (s), 2957 (s), 1663 (m), 1538 (m), 1376 (m), 1314 (m), 868 (s), 821 (s), and 726 (s) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$): δ 7.56 (d, *J* = 2.3, 1H, Ar**H**), 7.53 (s, 1H, N**H**), 7.25 (dd, *J* = 8.1 and 2.3, 1H, Ar**H**), 7.13 (d, *J* = 8.1, 1H, Ar**H**), 2.32 (s, 3H, OCC**H₃**), and 2.17 (s, 3H, C**H₃**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 168.5, 136.6, 134.4, 131.5, 130.9, 120.5, 118.2, 24.5, and 19.4.

Preparation of *N*-(2-bromo-5-chloro-4-methylphenyl)acetamide (91)[36]
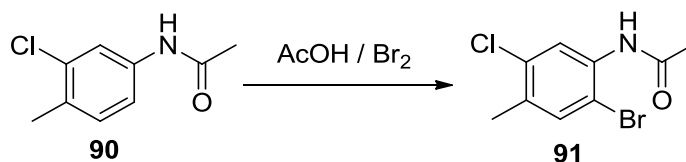
Notebook Reference: CAEA015, CAEA039

A 3-necked 500 mL round bottomed flask, equipped with a mechanical stirrer, addition funnel, gas inlet, thermometer, and stir bar was put under argon. A solution of **90** (12.002 g, 65.40 mmol) in glacial acetic acid (65 mL), was charged to the flask. The mixture was stirred and bromine (4.00 mL, 12.4 g, 77.6 mmol) was added dropwise over a period of 20 min while the temperature of the reaction mixture was kept below 15 ºC with an ice bath. The solution was stirred for a further 1.5 h after the addition of bromine was complete. The thick, semi-solid mixture was then poured into ice-water (250 mL) with the aid of additional water (800 mL). The mixture was vacuum filtered and the solid dried over P_2O_5. The crude material was recrystallized using CH_3CN to give product as a colorless solid. The filtrate was concentrated and recrystallized to give additional **91** (11.085 g, 44.3 mmol, 65%). The procedure was repeated using 0.150 mmol of **90** producing a 67% yield of **91**.

mp: 154-155 ºC

FT-IR (neat): 3274 (m), 3067 (s), 2987 (s), 1663 (w), 1568 (m), 1375 (m), 1287 (s), 874 (m), 709 (s), and 659 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 8.38 (s, 1H, N**H**), 7.51 (s, 1H, Ar**H**), 7.38 (s, 1H, Ar**H**), 2.31 (s, 3H, C**H$_3$**), and 2.23 (s, 3H, C**H$_3$**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 168.2, 134.2, 134.0, 133.4, 133.1, 122.2, 110.9, 24.8, and 19.4.

Preparation of 2-bromo-5-chloro-4-methylaniline (92)[36]
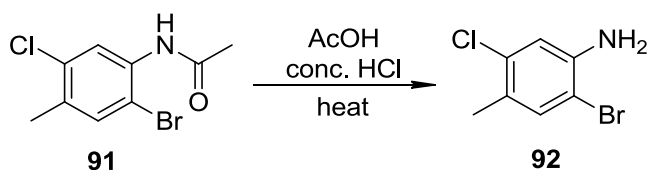
Notebook Reference: CAEA019, CAEA043

A solution of **91** (10.00 g, 38.0 mmol) in glacial acetic acid (7.50 mL, 130. mmol) and concentrated HCl (14.9 mL, 0.489 mol) was refluxed at 115 ℃ for 16 h. The reddish-brown mixture was allowed to cool to room temperature before water (31 mL) was added. The mixture was cooled in an ice bath while 50% w/v NaOH was added to adjusted to pH = 5. A precipitate formed. The mixture was vacuum filtered and the solid was washed with water. This resulted in a quantitative yield of **92** as a tan solid (8.609 g, 38.0 mmol). The procedure was repeated with 0.100 mol **91** to give a 96% yield of **92**.

mp: 86.4-86.8 ℃ at 760 mm Hg.

FT-IR (neat): 3475 (m), 3050 (s), 2952 (s), 1620 (m), 1493 (m), 1387 (s), 1275 (m), 877 (s), 846 (s), 738 (s), and 705 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 7.25 (s, 1H, Ar**H**), 6.78 (s, 1H, Ar**H**), 6.59 (s, 2H, N**H$_2$**), and 2.24 (s, 3H, C**H$_3$**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 144.4, 139.6, 135.5, 128.4, 117.4, 108.7, and 20.4.

Preparation of 1-bromo-4-chloro-2-iodo-5-methylbenzene (93)
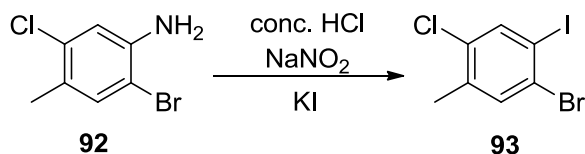
Notebook Reference: CAEA023, CAEA047

A mixture of **92** (7.70 g, 35.0 mol), water (145 mL), and conc. HCl (143 mL) was stirred and heated to 80 ºC. The solution was stirred for 30 min then cooled to 0 ºC. Sodium nitrite (2.673 g, 38.7 mmol) was dissolved in water (5 mL) and added to the solution while keeping the internal temperature below 10 ºC using an ice bath. The reaction mixture was stirred for an additional 30 min at 0 ºC. Potassium iodide (6.414 g, 38.7 mmol) was dissolved in water (5 mL) and added to the reaction. The solution turned dark brown and was stirred overnight. The suspension was extracted with CH_2Cl_2 (150 mL) and the organic layer was washed successively with 10% NaOH (150 mL), 1.0 M $Na_2S_2O_3$ (150 mL), 10% HCl (150 mL), sat. aq. $NaHCO_3$ (150 mL), and brine (150 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Filtration through a plug of silica gel with hexanes, and concentration afforded crude product. Recrystallization using ethanol gave **93** as an orange solid (5.981 g, 18.1 mmol, 51%). This procedure was repeated with 90 mmol of **92** to give a 41% yield of **93**.

mp: 80.0-80.5 ºC

FT-IR (Diamond ATR): 3073 (s), 2919 (s), 1571 (m), 874 (w), 860 (w), 759 (s), and 703 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 7.79 (s, 1H, Ar**H**), 4.48 (s, 1H, Ar**H**), and 2.30 (s, 3H, C**H$_3$**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 139.5, 137.9, 134.1, 127.6, 97.4, and 19.6.

Preparation of 1-chlorobut-2-yne (74)[32]
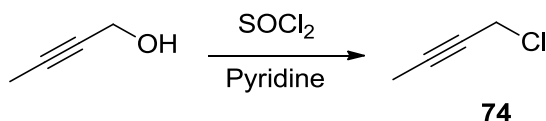
Notebook Reference: CAEA091

A 250 mL round bottomed flask equipped with a water condenser and addition funnel was put under argon. The flask was charged with thionyl chloride (11.0 mL, 18.0 g, 0.151 mol), dry ether (50 mL), and pyridine (10 drops). The mixture was stirred and brought to a boil. Over the period of 1 h, 2-butynol (10.7 mL, 10.0 g, 0.142 mol) was added dropwise. During the addition of the alcohol, the solution turned opaque white, then a clear dark orange. The reaction mixture was refluxed for an additional 5 hours before it was cooled to room temperature. Distillation (b.p. 100 ℃ at 760 mm Hg) afforded product 74 (9.801 g, 0.1108 mol, 78%).

^{1}HNMR (500 MHz, CDCl$_3$): δ 4.13 (s, 2H, **CH$_2$**Cl), and 1.87 (s, 3H, CC**H$_3$**).

Preparation of hept-5-yn-2-one (75)[32]
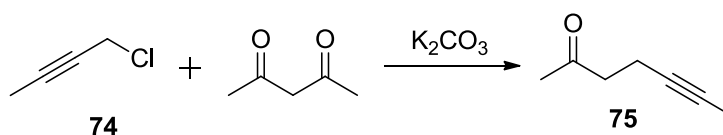
Notebook Reference: CAEA093

A 250 mL round bottomed flask was charged with **74** (8.503 g, 96.05 mmol) along with 2,4-pentandione (11.20 mL, 10.98 g, 105.6 mmol), anhydrous ethanol (55 mL), and K_2CO_3 (14.575 g, 105.6 mmol). The solution was refluxed for 24 hours. Excess ethyl acetate and ethanol were distilled off, leaving behind a solid residue. The solid was dissolved in H_2O (100 mL), and the solution was extracted with ether (4 × 20 mL). The combined organic layers were washed with aq. sat. NaCl (2 × 40 mL) and dried over K_2CO_3. The solution was filtered and concentrated *in vacuo* to give **75** (10.575 g, 96.047 mmol, 100%).

FT-IR (Diamond ATR): 2921 (w), 2860 (w), 1715 (s), 1434 (w), 1365 (s), 1228 (m), 1163 (s), and 953 (w) cm^{-1}.

¹HNMR (500 MHz, CDCl$_3$): δ 2.64 (t, J = 6.5, 2H, O=CC**H₂**), 2.39 (tq, J= 6.5 and 2.4, 2H, H₃CC≡CC**H₂**), 2.18 (s, 3H, O=CC**H₃**), and 1.11 (t, J = 2.4, 3H, C≡C**H₃**).

¹³CNMR (75 MHz, CDCl$_3$): δ 203.8, 72.6, 72.2, 47.5, 26.4, 16.6, and 9.9.

Preparation of 2-methylhept-5-yn-2-ol (70e)[32]

75   **70e**
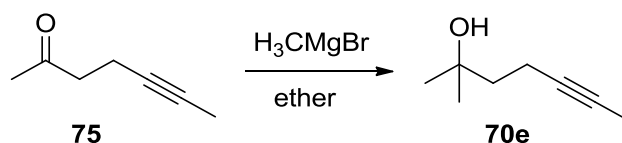
Notebook Reference: CAEA095

Methylmagnesium bromide (35.0 mL of a 3.0 M solution in ether, 106 mmol) and dry ether (35 mL) were charged to a 2-necked 250 mL round bottomed flask under argon. The flask was fitted with a heating mantle and the solution heated to reflux. Additional dry ether (11 mL) and **75** (11.0 mL, 96.4 mmol) were added dropwise to the solution. After the addition of **75** was complete, the reaction was refluxed for an additional 60 min. To quench the reaction, aq. sat. NH_4Cl (20 mL) was slowly added to the flask and solution was stirred for 15 min. Additional NH_4Cl solution was added until the pH of the mixture was 8. Salts precipitated and were filtered off. The filtrate was collected and extracted with ether (3 × 50 mL). The combined organic layers were washed with aq. sat. NaCl (2 × 35 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give crude product. Vacuum distillation of the crude material (b.p. 78 ºC at 15 mm Hg) afforded pure **70e** (4.011 g, 31.8 mmol, 33%).

^{1}HNMR (500 MHz, CDCl$_3$): δ 2.25 (tq, J = 8.0 and 2.5, 2H, C≡CC**H₂**), 2.18 (s, 1H, **OH**), 1.77 (t, J = 2.5, 3H, C≡CC**H₃**), 1.69 (t, J = 8.0, 2H, HOCC**H₂**), 1.23 (s, 3H, **CH₃**), and 1.22 (s, 3H, **CH₃**).

^{13}CNMR (CDCl$_3$, 75 MHz): δ 76.0, 72.6, 67.3, 38.8, 25.5, 10.5, and 0.0.

General Procedure B: Cyclization to form vinyl siloxanes
Preparation of 2,2,3,7,7-pentamethyl-2,5,6,7-tetrahydro-1,2-oxasilepine (69e)[32]
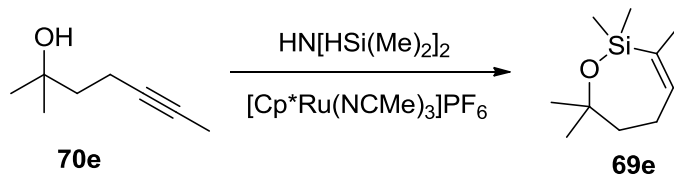
Notebook Reference: CAEA029, CAEA101

A 2-necked 100 mL round bottomed flask equipped with a water condenser, stir bar, and septa was put under argon. The flask was charged with **70e** (2.776 g, 22.01 mmol) and tetramethyldisilazane (11.4 mL, 8.57 g, 66.0 mmol). The solution was stirred and the flask was lowered into an 80 °C oil bath for 2.5 hours. The flask was removed from the oil bath and the excess disilazane was distilled off. The residue was taken up in dry CH_2Cl_2 (40 mL) and charged to a 250 mL round bottomed flask under argon. Stirring was initiated and the solution was cooled to 0 °C. The flask was charged with $[Cp*Ru(NCMe)_3]PF_6$ (0.279 g, 0.55 mmol), and the mixture was stirred overnight at room temperature. The mixture was diluted with ether and filtered through a plug of Florisil with additional ether (300 mL). The filtrate was concentrated *in vacuo* and purified by Kugelrohr distillation (b.p. 111°C at 30 mm Hg) to give **69e** as a clear colorless oil (1.627 g, 8.144 mmol, 37%). This procedure was repeated with 30 mmol of **70e** for a 69% yield of **69e**.

^{1}HNMR (500 MHz, CDCl$_3$): δ 6.24 (m, 1H, C=C**H**), 2.32 (m, 2H, C=CHC**H$_2$**), 1.87 (m, J = 2.9 and 2.4, 2H, (CH$_3$)$_2$CC**H$_2$**), 1.70 (q, J =1.8, 3H, **H$_3$**CC=CH), 1.25 (s, 6H, (C**H$_3$**)$_2$C), and 0.18 (s, 6H, (C**H$_3$**)$_2$Si).

^{13}CNMR (75 MHz, CDCl$_3$): δ 142.6, 135.9, 73.8, 42.4, 30.4, 26.7, 22.4, and 0.8.

General Procedure C: Hiyama coupling with vinyl siloxane
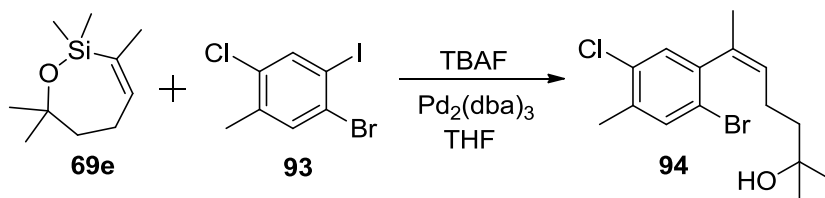# Preparation of (Z)-6-(2-bromo-5-chloro-4-methylphenyl)-2-methylhept-5-en-2-ol (94)

Notebook Reference: CAEA057

A 3-necked 50 mL round bottomed flask equipped with a stir bar, water condenser, and septa was put under argon. The flask was charged with **69e** (0.336 g, 2.00 mmol) and dry THF (4 mL). This was followed by the addition of aryl iodide **93** (0.994 g, 3.00 mmol) and TBAF (4.0 mL, 1.0 M in THF, 4.0 mmol). The solution was stirred for 5 minutes before Pd$_2$(dba)$_3$ (0.046 g, 0.050 mmol, 2.5 mol%) was added to the flask. The flask was lowered into a 55 °C oil bath and the reaction mixture was stirred for 16 h. Progress of the reaction was monitored by TLC. The flask was removed from the oil bath and allowed to cool to room temperature after **69e** was consumed. The mixture was filtered through a plug of silica gel with excess ether (200 mL) to remove the catalyst. The filtrate was concentrated *in vacuo* to give crude material as a thick oil. Purification by flash chromatography (250 mL, 1" column, 6:1 hexanes : EtOAc) gave **94** as a yellow oil (0.0532 g, 1.60 mmol, 80%).

FT-IR (Diamond ATR): 3377 (br s), 2968 (s), 2926 (m), 1475 (s), 1443 (w), 1146 (w), 1062 (s), and 885 (w) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 7.44 (s, 1H, Ar**H**), 7.07 (s, 1H, Ar**H**), 5.52 (tq, *J* =7.3 and 2.5, 1H, C=C**H**), 2.37 (s, 3H, Ar-C**H$_3$**), 1.93 (d, *J* =2.5, 3H, HC=CC**H$_3$**), 1.82 (m, 2H, C=CHC**H$_2$**), 1.26 (t, *J* = 7.3, 2H, HOCC**H$_2$**), and 1.12 (s, 6H, HOC(C**H$_3$**)$_2$).

^{13}CNMR (75 MHz, CDCl$_3$): δ 143.4, 137.7, 136.1, 131.5, 130.9, 121.7, 111.6, 105.3, 72.5, 44.7, 30.6, 26.0, 25.9, and 21.1.

General Procedure D: Buchwald-Hartwig etherification
Preparation of (Z)-8-Chloro-2,2,6,9-tetramethyl-3,4-dihydro-2*H*-benzo[*b*]oxocine (95)
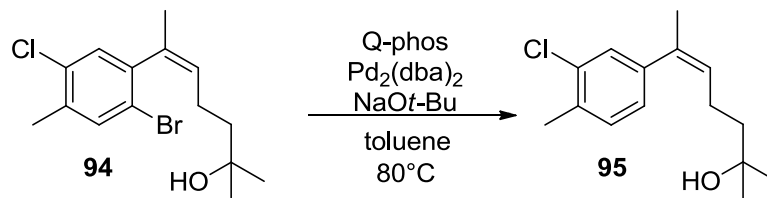
Notebook Reference: CAEA067

In a glove box, a 4 mL screw cap vial was charged with Q-Phos (0.0227 g, 0.0320 mmol, 10 mol%), bis(dibenzylideneacetone)dipalladium (0) (0.0184 g, 0.0320 mmol, 10 mol%), sodium *tert*-butoxide (0.0462 g, 0.480 mmol) and a stir bar. The vial was capped with a septum and removed from the glove box. A solution of **94** (0.1057 g, 0.3202 mmol) in toluene (0.5 mL) was added to the vial. Another aliquot of toluene (1.5 mL) was added to the vial. The solution was stirred at 80 °C for 15.5 h. The reaction progress was monitored by TLC. The solution was eluted through a silica gel plug with 6:1 hexanes : EtOAc. Purification was accomplished using a Monstrpet® for flash chromatography in 3:1 hexanes : EtOAc. Debrominated product **95** was isolated (0.023 g, 0.086 mmol, 27%).

FT-IR (Diamond ATR): 3419 (br s), 2971 (s), 2924 (s), 2854 (m), 1684 (m), 1606 (m), 1567 (w), 1499 (m), 1450 (w), 1365 (s), 1167 (s), and 904 (m) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 7.11 (d, *J* =7.8, 1H, ClCCC**H**), 6.84 (d, *J* =1.7, 1H, ClCC**H**), 6.78 (dd, *J* =7.8 and 1.7, 1H, Ar), 5.42 (td, *J* =5.9 and 1.5, 1H, H$_3$CC=C**H**), 2.23 (s, 3H, Ar-C**H$_3$**), 1.99 (d, *J* = 1.5, 3H, HC=CC**H$_3$**), 1.75 (m, 2H, C=CHC**H$_2$**), 1.52 (m, 2H, HOCC**H$_2$**), and 1.39 (s, 6H, HOC(C**H$_3$**)$_2$).

^{13}CNMR (75 MHz, CDCl$_3$): δ 139.9, 136.4, 130.5, 130.3, 128.7, 127.1, 122.2, 121.9, 71.0, 43.9, 29.2, 25.6, 24.3, and 17.0.

Preparation of N-*m*-tolylacetamide (97)[36]

96 → **97** (Ac$_2$O, Pyridine, AcOEt)
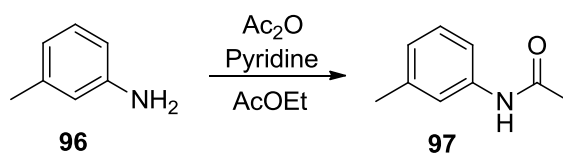
Notebook Reference: CAEA053

General Procedure A for the protection of an aniline with an acetate was followed. **96** (26.8 mL, 26.3 g, 250 mmol), acetic anhydride (26.3 mL, 28.5 g, 275 mmol), pyridine (22.3 mL, 21.9 g, 275 mmol), and EtOAc (310 mL) yielded **97** (37.289 g, 250.30 mmol, 100%).

^{1}HNMR (500 MHz, CDCl$_3$): δ 7.35 (s, 1H, Ar**H**), 7.27 (d, J = 7.0, 1H, Ar**H**), 7.19 (t, *J* = 7.0, 1H, Ar**H**), 6.92 (d, *J* = 7.0, 1H Ar**H**), 2.33 (s, 3H, Ar-C**H$_3$**), and 2.17 (s, 3H, OCC**H$_3$**).

Preparation of 1-(4-amino-2-methylphenyl)ethanone (98a)[38]
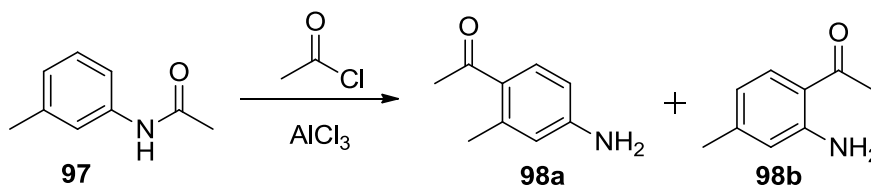
Notebook Reference: CAEA061

To a 2-necked 500 mL flask equipped with a condenser and acid trap, **97** (37.276 g, 250 mmol), and acetyl chloride (30.2 mL, 427 mmol) in CH_2Cl_2 (206.5 mL) were added. Stirring was initiated and $AlCl_3$ (103.107 g, 427 mmol) was added in small portions over 1 hour. After the addition was complete, the mixture was refluxed for 1 hour. The dark red solution was cooled to room temperature and slowly poured onto ice. The aqueous layer was extracted with CH_2Cl_2, washed with water and 10% NaOH until the pH of the aqueous layer was approximately 8. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give an orange solid. The solid was hydrolyzed by refluxing with conc. HCl (30 mL) for 1 h. Using 15% NaOH (200 mL), the pH of the solution was adjusted to 10. The product formed as a precipitate, and ether (500 mL) was used to dissolve the solid. The organic layer was collected and washed with water and brine and dried over Na_2SO_4. The drying agent was removed and the solution was concentrated to give isomers **98a** and **98b**. Flash chromatography (2000 mL, 3 ¾" column, 3:1 hexanes : EtOAc) was used to separate isomers. Desired isomer **98a** was collected as a tan solid (5.649 g, 37.50 mmol, 15%). Isomer **98b** (2.874 g, 20.00 mmol, 8%) was also isolated.

Data for **98a**:

R$_f$ = 0.2 in 3:1 hexanes : EtOAc.

mp: 91.4-92.4 °C

FT-IR (Diamond ATR): 3448 (s), 3342 (s), 2995 (m), 2933 (w), 1652 (s), 1632 (m), 1596 (s), 1552 (s), 1459 (m), 1251 (s), 1140 (m), and 817 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 7.66 (d, J =8.0, 1H, OCCC**H**), 6.50 (d, J =8.0, 1H, H$_2$NCC**H**), 6.48 (s, 1H, CH$_3$CC**H**), 4.00 (s, 2H, N**H$_2$**), 2.53 (s, 3H, **H$_3$**CCO), and 2.51 (s, 3H, **H$_3$**C-Ar).

^{13}CNMR: (125 MHz, CDCl$_3$): δ 200.5, 151.7, 144.1, 134.9, 128.6, 119.2, 112.6, 30.4, and 24.5.

Preparation of 1-(4-amino-5-iodo-2-methylphenyl)ethanone (99)
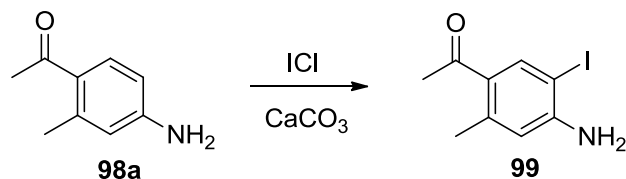
Notebook Reference: CAEA073

A solution of calcium carbonate (4.688 g, 4.700 mmol) in water (12 mL) was added to a solution of **98a** (4.044 g, 30.03 mmol) in methanol (20 mL). This was followed by a dropwise addition of a solution of iodine monochloride (5.022 g, 31.8 mmol) in methanol (20 mL). The mixture was stirred at room temperature for 18 hours, then diluted with ether (50 mL) and quenched with water (50 mL). The aqueous layer was extracted with ether (100 mL) and the combined organic phases were dried over Na_2SO_4. The drying agent was filtered off and solution was concentrated *in vacuo*. Purification via recrystallization with ethanol afforded **99** (4.917 g, 17.10 mmol, 57%).

mp: 118.3-120.2 °C

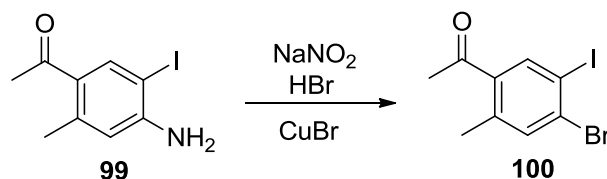**FT-IR** (Diamond ATR): 3456 (m), 3342 (s), 3196 (m), 2966 (w), 1650 (s), 1625 (s), 1588 (s), 1445 (m), and 1253 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 8.07 (s, 1H, ICC**H**), 6.54 (s, 1H, H$_2$NCC**H**), 4.46 (s, 2H, N**H$_2$**), 2.50 (s, 3H, OCC**H$_3$**), and 2.47 (s, 3H,Ar-C **H$_3$**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 197.5, 149.8, 142.3, 138.7, 129.0, 116.9, 78.2, 28.7, and 22.4.

Preparation of 1-(4-bromo-5-iodo-2-methylphenyl)ethanone (100)

Notebook Reference: CAEA077

A solution of NaNO$_2$ (1.239 g, 18.03 mmol) in water (16.3 mL) was added dropwise to a mixture of **99** (4.133 g, 15.01 mmol) and HBr (47%, 36.2 mL) at -10 °C over a 15 min period. The solution was stirred for a further 10 min before the temperature was increased to 0°C and stirred for 2 h. This solution was then added dropwise to a vigorously stirred mixture of CuBr (2.601 g, 18.02 mmol) and HBr (27%, 20.0 mL) at 60 °C over a period of 30 min. The mixture was stirred for a further 30 min at 80 °C. The solution was cooled to room temperature before extracting with water (200 mL) and EtOAc (200 mL). The combined organic layers were washed with 1M HCl (150 mL), sat. aq. NaHCO$_3$ (100 mL), and aq. half sat. brine (125 mL). The combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo*. Crude material was purified via column chromatography (500 mL, 1" column, 3:1 hexanes : EtOAc) to afford product **100** (1.443 g, 4.230 mmol, 28%).

FT-IR (Diamond ATR): 2974 (w), 2923 (w), 1674 (s), 1570 (m), 1526 (m), 1235 (s), 1125 (m), 955 (s), 884 (s), and 863 (w) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 8.09 (s, 1H, ICC**H**), 7.53 (s, 1H, BrCC**H**), 2.55 (s, 3H, O=CC**H$_3$**), and 2.44 (s, 3H, BrCCHCC**H$_3$**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 199.1, 140.6, 140.1, 137.7, 135.9, 133.4, 97.0, 29.4, and 21.0.

Preparation of (Z)-1-(4-bromo-5-(6-hydroxy-6-methylhept-2-en-2-yl)-2-methylphenyl)ethanone (101)
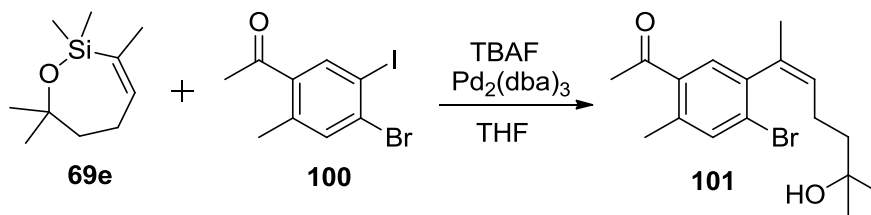
Notebook Reference: CAEA105

General procedure C for Hiyama couplings with vinyl siloxanes was followed. **69e** (226 mg, 1.33 mmol, 2.5 mol%), TBAF (2.6 mL, 1.0 M in THF, 2.6 mmol), **100** (646 mg, 2.00 mmol), and Pd$_2$(dba)$_3$ (33 mg, 0.033 mmol) in THF (2.6 mL) yielded **101** (260 mg, 79.8 mmol, 60%).

FT-IR (Diamond ATR): 3331 (br s), 2964 (s), 2927 (s), 2874 (w), 1684 (s), 1594 (w), 1533 (m), and 1245 (m) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 7.48 (s, 1H, BrCC**H**), 7.40 (s, 1H, ClCC**H**), 5.52 (tq, J =6.5 and 1.5, 1H, C=C**H**), 2.56 (s, 3H, OCC**H$_3$**), 2.47 (s, 3H, Ar-C**H$_3$**), 1.93 (d, J =1.5, 3H, HC=CC**H$_3$**), 1.82 (m, 2H, C=CHC**H$_2$**), 1.26 (t, J = 6.5, 2H, HOCC**H$_2$**), and 1.12 (s, 6H, HOC(C**H$_3$**)$_2$).

^{13}CNMR (75 MHz, CDCl$_3$): δ 200.6, 140.6, 138.6, 136.7, 136.0, 135.3, 130.6, 129.6, 126.1, 70.8, 43.1, 29.5, 24.2, 21.1, 19.8, and 13.7.

Preparation of (Z)-1-(2,2,6,9-tetramethyl-3,4-dihydro-2*H*-benzo[b]oxocin-8-yl)ethanone (102)
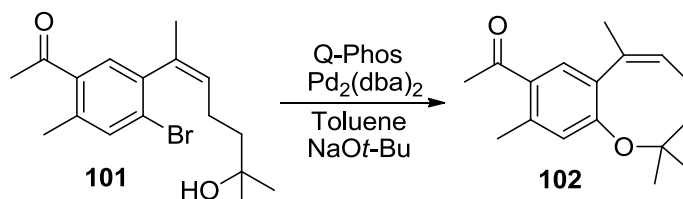
Notebook Reference: CAEA109

General procedure D for Buchwald cyclizations was followed. Bis(dibenzylideneacetone) dipalladium (0) (18.4 mg, 0.0320 mmol), sodium *tert*-butoxide (46.2 mg, 0.480 mmol), Q-phos (22.7 mg, 0.0320 mmol), and **101** (105 mg, 0.320 mmol) in toluene (2 mL) gave **102** (14 mg, 0.054 mmol, 17%). Attempts to purify the product further were unsuccessful.

GC/MS (CI, MeOH) $^m/_z$ 243 (40, M$^+$), 187 (100).

FT-IR (Diamond ATR): 3418 (br s), 2966 (m), 2923 (s), 2853 (w), 1680 (s), 1603 (w), 1556 (w), 1356 (m), 1252 (m), and 1150 (m) cm^{-1}.

¹HNMR (500 MHz, CDCl$_3$): δ 7.50 (s, 1H, OCC**H**), 7.21 (s, 1H, ClCC**H**), 5.52 (tq, *J* =1.5 and 7.0, 1H, C=C**H**), 2.58 (s, 3H, Ar-C**H$_3$**), 2.51 (d, *J* =1.5, 3H, HC=CC**H$_3$**), 2.03 (m, 2H, C=CHC**H$_2$**), 1.54 (t, *J* = 7.0, 2H, HOCC**H$_2$**), and 1.14 (s, 6H, OC(C**H$_3$**)$_2$).

¹³CNMR (75 MHz, CDCl$_3$): δ 196.9, 167.0, 154.0, 136.5, 136.0, 131.9, 131.0, 128.8, 128.1, 43.9, 29.7, 29.2, 25.4, 24.2, and 21.3.

Preparation of prop-1-en-2-ylboronic acid (117)[44]

116 → **117**
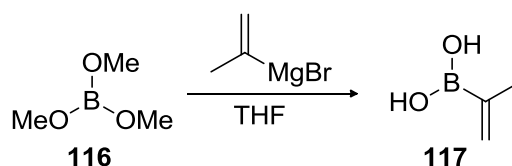
Notebook Reference: CAEA133

Trimethyl borate (6.8 mL, 60 mmol) in THF (25 mL) was charged to a 2-necked 500 mL round bottomed flask under argon.   Isopropenylmagnesium bromide (40 mL, 0.5 M in THF, 20 mmol) was added dropwise while the solution was stirred. When the addition was complete, the solution was stirred at room temperature for 2 hours. To quench, the solution was cooled to 0 ºC, and 1M HCl (50 mL) was added slowly. The aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo* to give **117 (**2.385 g, 27.00 mmol, 45%).

FT-IR (Diamond ATR): 3398 (br s), 2964 (s), 1619 (m), 1340 (s), and 1200 (m) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$): δ 6.14 (s, 1H, C=C**H$_2$**), 5.85 (s, 1H, C=C**H$_2$**), 1.90 (s, 3H, CC**H$_3$**), and 1.85 (s, 2H, O**H**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 129.1, 110.0, and 20.7.

Preparation of diisopropyl prop-1-en-2-ylboronate (114)
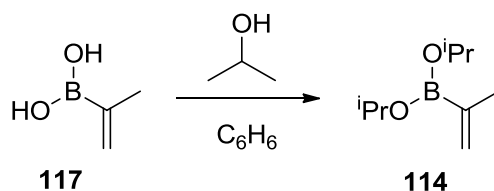
Notebook Reference: CAEA135

A solution of boronic acid **117** (1.721 g, 20.00 mmol) and isopropyl alcohol (3.8 mL, 50 mmol) was charged to a 50 mL round bottomed flask equipped a Dean-Stark trap, water condenser and drying tube. Benzene (10 mL) was added to the flask. The flask was fitted with a heating mantle and the solution was refluxed until water (0.85 mL) collected in the Dean-Stark trap. The aqueous layer was drained out of the trap and the solution was concentrated to give **114** (1.5025 g, 8.806 mmol, 44%).

FT-IR (Diamond ATR): 3186 (br s), 2965 (m), 1620 (w), 1357 (br s), and 1193 (s) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$): 5.42 (s, 1H, CC**H$_2$**), 5.19 (s, 1H, CC**H$_2$**), 4.33 (septet, J = 6.0, 1H, (H$_3$C)$_2$C**H**), 1.83 (s, 3H, CC**H$_3$**), 1.12 (d, J = 6.0, 12H, B(CH(C**H$_3$**)$_2$)$_2$).

^{13}CNMR (75 MHz, CDCl$_3$): δ 133.0, 122.9, 64.7, 24.3, and 21.2.

Preparation of dibutyl prop-1-en-2-ylboronate (118)[45]
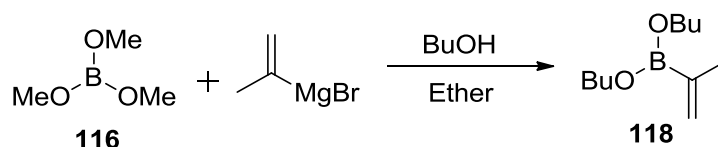
Notebook Reference: CAEA161, CAEA295

A 2 necked 250 mL round bottom flask equipped with an addition funnel and thermometer was put under argon. The flask was charged with **116** (2.5 mL, 22 mmol) and dry ether (10 mL). This solution was cooled below -50 °C before the addition of isopropenylmagnesium bromide (40.0 mL, 0.5 M in THF, 20.0 mmol) dropwise over 20 min. The mixture was gradually warmed to 20 °C to ensure completion of the reaction. The mixture was re-cooled to -60 °C to -78 °C before adding conc. H_2O (1 mL) and phenothiazine (6 mg). Mixture was gradually warmed from -70 °C to 0 °C during the addition of conc. HCl (0.8 mL) and conc. H_3PO_4 (1.4 mL) in H_2O (10 mL). The slow warming prevented congealing of mixture into an un-stirrable solid. A small amount of solid formed but dissolved at 5 °C with vigorous stirring. Solid NaCl was added to saturate the aqueous layer. The aqueous layer was extracted with 1-butanol (3 × 15 mL). The combined organic layers were washed with 10% NaCl (2 × 25 mL), and sat. aq. $NaHCO_3$ was added until the pH of the aqueous solution was 5. To dry the organic layers, they were transferred into an Erlenmeyer flask, frozen at -78 °C, the liquid was filtered off, and crystals were rinsed with cold ether. Distillation (b.p. 96 °C at 14 mm Hg) of filtrate gave **118** (2.686 g, 14.96 mmol, 68%).

FT-IR (Diamond ATR): 3422 (br s), 2959 (s), 2874 (w), 1620 (m), 1330 (br s), 1180 (s), and 1069 (w) cm^{-1}.

¹HNMR (300 MHz, CDCl₃): 5.48 (s, 1H, C=C**H₂**), 5.26 (s, 1H, C=C**H₂**), 3.89 (t, *J* =6.5, 2H, OC**H₂**), 1.56 (m, 4H,(OCH₂C**H₂)₂**), 1.37 (m, 4H, (OCH₂CH₂C**H₂)₂**), and 0.95 (td, *J* = 7.0 and 1.2, 6H, (CH₂C**H₃)₂**).

¹³CNMR (75 MHz, CDCl₃): δ 130.2, 135.7, 65.4, 35.4, 22.7, 20.6, and 15.4.

General Procedure E: Cyclization of boronate esters
Preparation of 3-methyl-5,6-dihydro-2*H*-1,2-oxaborinin-2-ol (120)
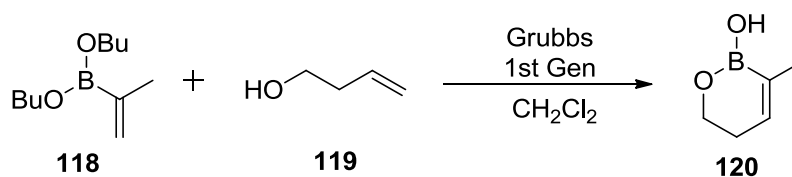
Notebook Reference: CAEA175

To a 2-necked 50 mL round bottom flask under argon, Grubbs' 1st generation catalyst was added (0.041 g, 0.050 mmol) along with CH_2Cl_2 (2 mL, 0.5 M). To the stirred solution, **119** (0.072 g, 1.0 mmol) and **118** (0.594 g, 3.00 mmol) were added. The mixture was refluxed for 24 h. The reaction was cooled to room temperature before the solution was concentrated *in vacuo*. Crude material was purified by flash chromatography (500 mL, 1" column, 3:1 hexanes : EtOAc) to afford **120** (0.075 g, 2.0 mmol, 67%).

FT-IR (Diamond ATR): 3486 (br s), 2920 (s), 2850 (m), 1419 (s), 1360 (s), 1221 (s), and 1092 (m) cm^{-1}.

¹HNMR (300 MHz, CDCl₃): 6.52 (s, 1H, C=C**H**), 4.03 (t, *J* =6.5, 2H, BOC**H₂**), 2.27 (m, 2H, OCH₂C**H₂**), and 1.78 (s, 3H, C**H₃**).

Preparation of (*Z*)-4-phenylpent-3-en-1-ol (122)
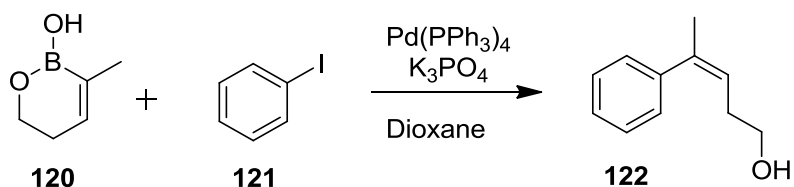
Notebook Entry: CAEA197.

A 10 mL screwcap vial was charged with tetrakis(triphenylphosphine) palladium (0) (81 mg, 0.070 mmol, 10 mol%) and K_3PO_4 (0.360 g, 1.70 mmol) before being brought under argon atmosphere. Dioxane (12.6 mL) was added, followed by the dropwise addition of **121** (0.114 g, 0.560 mmol) and **120** (0.075 g, 0.70 mmol). The vial was lowered into a 95 ºC oil bath, and the mixture was stirred overnight. Water (7 mL) was added and the aqueous layer was extracted with ether (7 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography was used for purification (100 mL, ½" column, 2:1 hexanes : EtOAc) and **122** was obtained as a colorless oil (21 mg, 0.13 mmol, 23%).

R$_f$: 0.47 in 2:1 hexanes : EtOAc

FT-IR (Diamond ATR): 3345 (br s), 3024 (w), 2425 (m), 1600 (m), 1435 (s), and 1025 (s) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$) δ: 7.32 (m, 2H, Ar**H**), 7.25 (m, 1H, Ar-H), 7.20 (m, 2H, Ar**H**), 5.47 (tq, *J* = 8.0 and 1.5, 1H, C=C**H**), 3.61 (t, *J* = 7.3, 2H, HO-C**H$_2$**), 2.25 (dt, *J* = 8.0, 7.3, 2H, CHC**H$_2$**), 2.06 (d, *J* = 1.5, 3H, -C**H$_3$**), and 1.53 (s, 1H, -O**H**).

Preparation of diisopropyl prop-1-en-2-ylboronate (114)
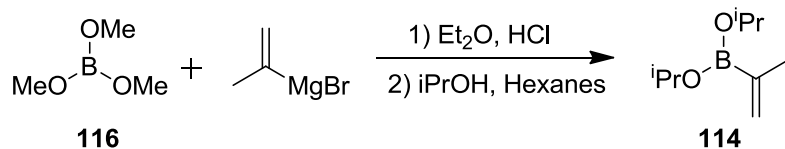
Notebook Reference: CAEB135

A 500 mL 2-necked round bottom flask equipped with a stir bar, addition funnel, and gas inlet was placed under argon. The flask was charged with **116** (4.5 mL, 40 mmol) and dry ether (50 mL). The solution was cooled to -5 °C, then isopropenylmagnesium bromide (0.5M in THF, 100 mL, 50 mmol) was added dropwise over 45 min. This solution was stirred for 1 hour before 30% HCl (70 mL) was used to quench the reaction. The aqueous layer was extracted with methyl *tert*-butyl ether (4 × 75 mL) and the combined organic layers were dried over MgSO$_4$. The mixture was filtered and concentrated *in vacuo* until a solid began to form. Isopropyl alcohol (6.1 mL, 80 mmol) and hexanes (100 mL) were added to the flask. A Dean-Stark trap was fitted to the flask, along with a heating mantle, and solution was refluxed until no more water was collected in the trap. The solution was concentrated to give **114** (3.987 g, 23.60 mmol, 59%). Attempts to purify the product further were unsuccessful.

FT-IR (Diamond ATR): 3186 (br s), 2965 (m), 1620 (w), 1357 (br s), and 1193 (s) cm^{-1}.
^{1}HNMR (500 MHz, CDCl$_3$): δ 5.42 (s, 1H, C=C**H$_2$**), 5.19 (s, 1H, C=C**H$_2$**), 4.33 (sept, *J*= 6.0, 2H, OC**H**), 1.83 (s, 3H, CC**H$_3$**), and 1.12 (d, *J*= 6.0, 12H, (CH(C**H$_3$**)$_2$)$_2$).
^{13}CNMR (CDCl$_3$, 75 MHz): δ 133.0, 122.9, 64.7, 24.3, and 21.2.

Preparation of 2-chloro-2-methylpropanal (130)[49]
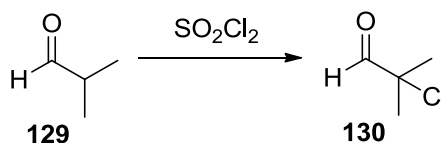
Notebook Reference: CAEA127

A 2-necked 250 mL round bottom flask was equipped with an addition funnel, water condenser, and drying tube. The flask was charged with **129** (45.6 mL, 36.0 g, 500 mmol), followed by the dropwise addition of sulfuryl chloride (39.6 mL, 66.0 g, 500 mmol). A cold water bath was used to keep the reaction temperature between 20 ℃ and 40 ℃. The drying tube was connected to an acid trap, and the solution was refluxed for 2 h. Distillation (b.p. 86 ℃ at 760 mm Hg) resulted in **130** (39.188 g, 370.05 mmol, 74%).

^{1}HNMR (300 MHz, CDCl$_3$): δ 9.35 (s, 1H, OC**H**), and 1.55 (s, 6H, C(C**H$_3$**)$_2$).

Preparation of 2-chloro-2-methylhex-5-en-3-ol (131)[50]

130   **131**

Notebook Reference: CAEA149

A solution of **130** (7.988 g, 75.00 mmol) in dry THF (40 mL) was charged to a 2-necked 250 mL round bottom flask under argon. The solution was stirred and cooled to -60 ºC before adding allylmagnesium bromide (1.0M in ether, 75.0 mL, 75.0 mmol) dropwise over the course of 1 h. After the addition was complete, the solution was stirred at -78 ºC for another hour. The reaction was quenched with 10% H_2SO_4, and a white gel was formed. To dissolve the white gel, 6 M H_2SO_4 (25 mL) was added with vigorous stirring. The aqueous layer was extracted with ether (2 × 100 mL). The combined organic layers were washed sat. aq. NaCl (2 × 50 mL) and dried over Na_2SO_4. The drying agent was filtered off, and the solution was concentrated *in vacuo*. Distillation (b.p. 80 °C at 15 mm Hg) gave **131** (1.985 g, 13.50 mmol, 18%).

FT-IR (Diamond ATR): 3436 (br s), 3978 (m), 2935 (m), 1641 (s), 1458 (m), 1067 (s), 991 (s), and 914 (s) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$): δ 5.91 (dddd, *J* = 17.0, 10.6, 7.6 and 6.5, 1H, H$_2$C=C**H**), 5.15 (m, 2H, HC=C**H$_2$**), 3.60 (dd, *J*= 9.9 and 2.4, 1H, HOC**H**), 2.51 (m, 1H, CHC**H$_2$**), 2.18 (m, 1H, CHC**H$_2$**), 1.61 (s, 3H, C**H$_3$**), and 1.58 (s, 3H, C**H$_3$**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 136.0, 118.3, 78.5, 75.1, 36.6, 28.9, and 28.0.

Preparation of 2-chloro-2-methylhex-5-en-3-yl acetate (133)

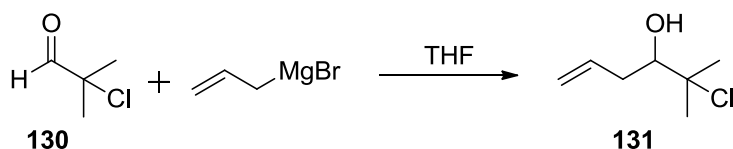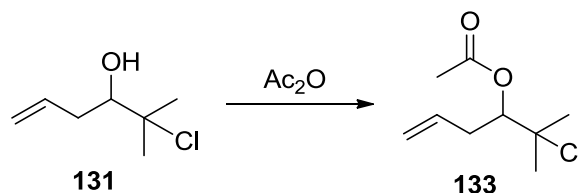

Notebook Reference: CAEA157

A 2-necked 250 mL round bottomed flask equipped with an addition funnel was placed under argon. The flask was charged with **131** (5.325 g, 50.00 mmol) in THF (35 mL). The solution was cooled to -78°C before adding acetic anhydride (5.16 mL, 5.58 g, 55.0 mmol) dropwise. Following the addition of acetic anhydride, the reaction was allowed to slowly warm to room temperature. As the reaction mixture warmed, a solid precipitated. Once at room temperature, sat. aq. NH$_4$Cl (40 mL) was used to quench the reaction as well as to dissolve the salt. The aqueous layer was extracted with ether (3 × 25 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. Crude material was purified using flash chromatography (1000 mL, 2 ¾" column, 6:1 hexanes : EtOAc) to give **133** (0.894 g, 8.08 mmol, 16%).

R$_f$ = 0.45 in 6:1 hexanes : EtOAc

FT-IR (Diamond ATR): 2981 (m), 2936 (w), 1733 (s), 1455 (s), and 1103 (s) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$): δ 5.70 (dddd, *J* = 16.2, 9.9, 8.1, and 5.7, 1H, H$_2$C=C**H**), 5.09 (m, 2H, HC=C**H$_2$**), 2.58 (m, 1H, C**H$_2$**), 2.36 (m, 1H, C**H$_2$**), 2.08 (s, 3H, O=CC**H$_3$**), 1.97 (s, 1H, HOC**H**), 1.57 (s, 3H, C**H$_3$**), and 1.55 (s, 3H, C**H$_3$**).

^{13}CNMR (125 MHz, CDCl$_3$): δ 170.3, 133.9, 117.8, 77.8, 69.9, 34.9, 29.2, 28.5, and 20.8.

Preparation of 1,1-dimethoxy-2-methylpropan-2-ol (134)[51]
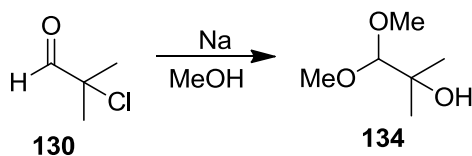
Notebook Entry: CAEA259, CAEA287

A 50 mL round bottomed flask under argon was charged with dry methanol (18.0 mL, 14.2 g, 445 mmol). Sodium metal (1.470 g, 64.05 mmol) was slowly as small pieces added until completely dissolved. While the solution was kept under 20 °C, **130** (6.848 g, 64.03 mmol) was added dropwise. The mixture was stirred at room temperature for 3 hours. The salts were then separated by centrifugation and the supernatant oil was collected. The methanol was removed by distillation. Further distillation of the residue (b.p. 59 °C at 20 mm Hg) gave **134** (3.687 g, 26.88 mmol, 42%) as a colorless oil.

FT-IR (Diamond ATR): 3466 (s, br), 2978 (m), 2936 (m), 1470 (w), and 1077 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$) δ: 3.99 (s, 1H, C**H**), 3.56 (s, 6H, (OC**H$_3$**)$_2$), 2.22 (s, 1H, O**H**), and 1.18 (s, 6H, (C**H$_3$**)$_2$).

^{13}CNMR (125 MHz, CDCl$_3$) δ: 111.3, 72.7, 58.1, and 23.8.

Preparation of trimethyl(5-methylhex-4-en-1-yn-1-yl)silane (137)[28]
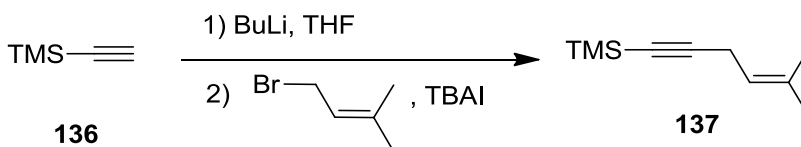
Notebook Reference: CAEB17, CAEB097

A dry 3-necked 500 mL round bottomed flask was placed under argon. The flask was charged with THF (325 mL), and cooled to -78 °C. This was followed by the addition of **136** (8.799 g, 12.70 mL, 89.70 mmol) and *n*-butyllithium (65.6 mL, 1.36 M in hexanes, 89.0 mmol). This solution was allowed to warm to room temperature before 4-bromo-2-methyl-2-butene (13.263 g, 89.60 mmol) and tetrabutylammonium iodide (2.63 g, 8.57 mmol) were added. The solution was heated to a gentle reflux and stirred overnight. The reaction mixture was then cooled to 0 °C and quenched with sat. aq. NH$_4$Cl. Water was added to dissolve the precipitate that had formed during quenching. The solution was poured into a separatory funnel with sat. aq. NH$_4$Cl (250 mL), and extracted with pentane (3 × 125 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. This material was vacuum distilled (b.p. 74-75 °C at 15 mm Hg) to give pure **137** (7.5877 g, 39.468 mmol, 44%) as a bright yellow oil. This procedure was repeated with a new bottle of *n*-butyllithium (1.6 M in hexanes) to give **136** in a yield of 79%.

FT-IR (Diamond ATR): 2962 (s), 2932 (m), 2175 (s), and 1450 (w) cm^{-1}.
^{1}HNMR (500 MHz, CDCl$_3$): δ 5.17 (t of septets, *J*= 6.5 and 1.5, 1H, C=C**H**), 2.93 (d, *J*= 6.5, 2H, C**H$_2$**), 1.71 (s, 3H, C-C**H$_3$**), 1.62 (s, 3H, C-C**H$_3$**), and 0.15 (s, 9H, Si(C**H$_3$**)$_3$).
^{13}CNMR (125 MHz, CDCl$_3$): δ 133.9, 118.5, 105.9, 93.7, 25.8, 19.1, 17.8, and 0.00.

Preparation of 2-methyl-6-(trimethylsilyl)hex-5-yne-2,3-diol with commercial AD-mix β (138)
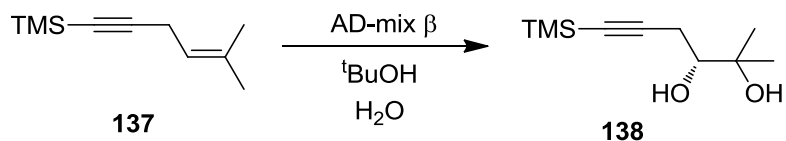
Notebook Reference: CAEB025, CAEB043

A 2-necked 250 mL round bottomed flask equipped with a thermometer and Teflon cap was charged with *tert*-butanol (30.0 mL) and water (30.0 mL). AD-mix β (8.402 g) was added to the flask along with methylsulfonamide (0.574 g, 6.00 mmol). The mixture was cooled to 0 °C before **137** (1.00g, 6.00 mmol) was added. The mixture was stirred at 0 °C until TLC indicated consumption of starting material. The reaction was quenched by slowly adding $Na_2S_2O_5$. The aqueous layer was extracted with ethyl acetate (5 × 30 mL). The combined organic layers were washed with 10% KOH (2 × 30 mL) and dried over Na_2SO_4. The solution was filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (500 mL, 1 $^3/_4$" column, 2:1 hexanes : EtOAc) to afford **138** (0.229 g, 1.14 mmol, 19%) as a yellow oil. This reaction was repeated using 100 mmol **137** with a 36% yield.

FT-IR (Diamond ATR): 3395 (br s), 2962 (m), 2899 (m), 2176 (s), 1466 (w), 1250 (s), and 1050 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 3.55 (dd, *J*=8.5 and 4.0, 1H, **CH**), 2.67 (s, 1H, **OH**), 2.51 (dd, *J*= 16.5 and 4.0, 1H, **CH$_2$**), 2.45 (dd, *J*= 16.5 and 8.5, 1H, **CH$_2$**), 2.37 (s, 1H, **OH**), 1.25 (s, 3H, CC**H$_3$**), 1.19 (s, 3H, CC**H$_3$**), and 0.17 (s, 9H, Si(C**H$_3$**)$_3$).

^{13}CNMR (125 MHz, CDCl$_3$): δ 103.7, 88.1, 75.4, 72.4, 26.4, 24.4, 23.8, and 0.00.

Combustion: Calculated for C$_{10}$H$_{20}$O$_2$Si: C, 59.95; and H, 10.06. Found: C, 60.04; and H, 10.13.

Preparation of 2-methyl-6-(trimethylsilyl)hex-5-yne-2,3-diol with "homemade" AD-mix β (138)
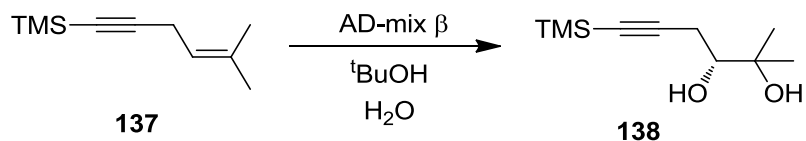
Notebook Reference: CAEB109, CAEB141, CAEB143, CAEB147, CAEB149, CAEB153, CAEB159, CAEB163

A 100 mL round bottomed flask was charged with *tert*-butanol (10 mL) and water (10 mL). Potassium carbonate (0.830 g, 6.00 mmol), potassium osmate (IV) dihydrate (6.7 mg, 0.020 mmol), potassium ferricyanide (1.976 g, 6.000 mmol), and DHQD$_2$(PHAL) (15.6 mg, 0.0200 mmol) were added to the flask. Once all the solids had dissolved, methanesulfonamide (0.190 g, 2.00 mmol) and enyne **137** (0.333 g, 2.00 mmol) were added to the solution. The reaction mixture was stirred for 3 hours at room temperature, before slowly adding Na$_2$S$_2$O$_5$ to quench the reaction. The aqueous layer was extracted with ethyl acetate (5 × 15 mL). The combined organic layers were washed with 10% KOH (2 × 15 mL), dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (500 mL, 1" column, 2:1 hexanes : EtOAc) to afford **138** (0.195 g, 0.980 mmol, 49%) as a yellow oil. This procedure was repeated with different loadings of potassium osmate (IV) dihydrate and DHQD$_2$(PHAL) to give between a 44% and 56 % yield of **138**. Characterization data matched that reported previously.

Preparation of 2-methylhex-5-yne-2,3-diol (139)
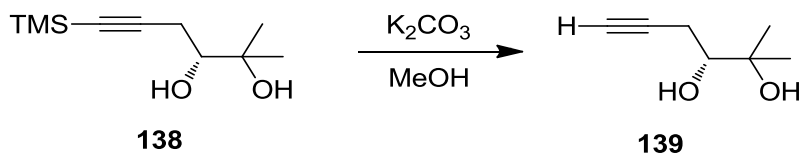
Notebook Reference: CAEB035, CAEB045, CAEB071, CAEB199

A 10 mL round bottomed flask under argon was charged with **138** (0.040 g, 0.20 mmol), dry methanol (0.63 mL), and K_2CO_3 (17.2 mg, 0.125 mmol). The solution was stirred and reaction progress was monitored by TLC. Upon consumption of **138**, the solution was concentrated *in vacuo*. The residue was partitioned between H_2O and ether. The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic layers were washed with brine (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (100 mL, ½ " column, 1:1 hexanes : EtOAc) gave pure **139** (23 mg, 0.14 mmol, 71%) as a light yellow oil. The reaction was repeated to give yields between 65% and 84%.

FT-IR (Diamond ATR): 3880 (s), 2976 (s), 2924 (m), 2119 (m), 1160 (s), 1066 (s) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$): δ 3.58 (m, 1H, C**H**), 2.63 (d, *J*=4.2, 1H, O**H**), 2.45 (dd, *J*= 3.6 and 2.5, C**H$_2$**), 2.41 (dd, *J*= 8.7 and 2.5, 1H, C**H$_2$**), 2.22 (s, 1H, O**H**), 2.09 (t, *J*= 3.0, 1H, **H**C≡C), 1.26 (s, 3H, C**H$_3$**), and 1.19 (s, 3H, C**H$_3$**).

^{13}CNMR (125 MHz, CDCl$_3$): δ 81.7, 76.8, 75.9, 72.4, 70.7, 26.3, 24.1, and 22.3.

HRMS (ESI) Calculated for C$_7$H$_{12}$O$_2$Na (M + Na): 151.0735. Found: 151.0739.

Combustion: Calculated for C$_7$H$_{12}$O$_2$: C, 65.60; and H, 9.44. Found: C, 65.40; and H, 9.23.

Preparation of 2-methylhex-5-ene-2,3-diol (127)
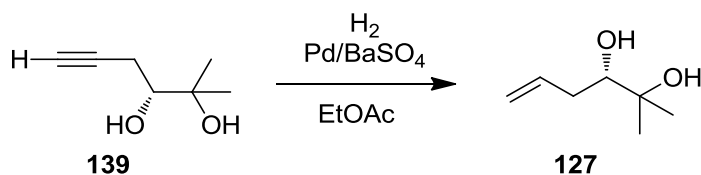
Notebook Reference: CAEB039, CAEB047, CAEB 081, CAEB207

A 2-necked 25 mL round bottomed flask under argon was charged with **139** (0.050 g, 0.57 mmol) and EtOAc (3 mL). This was followed by the addition of Pd/BaSO$_4$ (0.010 g, 20 wt %), and quinoline (4.6 µL, 10 wt%). The reaction mixture was put under hydrogen atmosphere and stirred. The reaction progress was monitored by NMR. When **139** was consumed, the flask was flushed with argon, the mixture was filtered through Celite with EtOAc, and the solution was concentrated *in vacuo*. The oil was taken up in ether (5 mL) and washed with 5% HCl. Concentration afforded crude diol **127** (0.025 g, 0.19 mmol, 34%). The crude material could not be purified. This procedure was repeated with three equivalents of 1-hexene in the reaction mixture, and an increased yield of 93% was achieved.

FT-IR (Diamond ATR): 3386 (br s), 2970 (s), 2873 (s), 1641 (m), 1380 (s), and 1020 (s) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$): δ 5.91 (m, 1H, C=C**H**), 5.16 (m, 2H, C**H$_2$**), 3.43 (dd, *J*= 10.8 and 3.0, 1H, HOC**H**), 2.38 (m, 1H, C**H$_2$**), 2.12 (m, 1H, C**H$_2$**), 1.23 (s, 3H, C**H$_3$**), and 1.18 (s, 3H, C**H$_3$**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 135.1, 118.0, 78.3, 72.7, 33.8, and 26.5.

Preparation of 3-methyl-6-phenyl-5,6-dihydro-2H-1,2-oxaborinin-2-ol (142)[48]
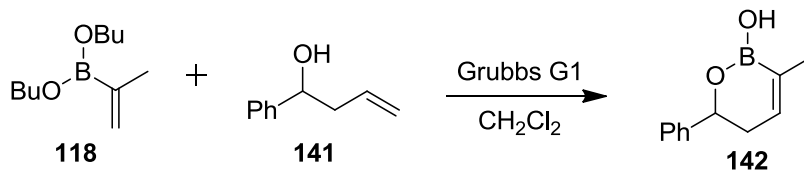
Notebook Reference: CAEB085

General procedure E for the cyclization of boronic esters was followed. Boronate ester **118** (99 mg, 0.50 mmol), alcohol **141** (24 μL, 0.17 mmol), Grubbs' 1st generation catalyst (20.5 mg, 0.0250 mmol), and dry CH_2Cl_2 (1.4 mL) yielded **142** (22 mg, 0.35 mmol, 70%) as a brown oil.

FT-IR (Diamond ATR): 3409 (br s), 3063 (w), 2933 (m), 2886 (m), 1626 (s), 1494 (m), 1452 (m), 1304 (s) 832 (m), 750 (s), and 697 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 7.31 (m, 5H, Ar**H**), 6.52 (s, 1H, C=C**H**), 5.09 (t, *J*= 1.0, 1H, OC**H**), 4.39 (s, 1H, O**H**), 2.41 (m, 2H, C=CHC**H₂**), and 1.82 (d, *J* = 1.5, 3H, CC**H₃**).

^{13}CNMR (125 MHz, CDCl$_3$): δ 143.9, 128.4, 127.5, 125.7, 76.0, 36.6, and 18.6.

Combustion: Calculated for $C_{11}H_{13}BO_2$: C, 70.26; and H, 6.97. Found: C, 70.57; and H, 7.00.

Preparation of 2,2,3-trimethyl-5,6-dihydro-*2H*-1,2-oxasiline (150)[59]

151 → **150**

1) HN(HSiMe₂)₂
80°C, 2h
2) [Cp*Ru(NCMe)₃]PF₆
DCM 0°C--rt
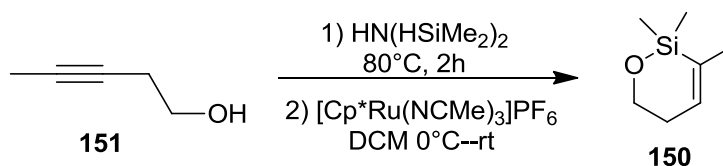
Notebook Entry: CAEB165, CAEB245

General procedure B was followed. Alcohol **151** (6.92 mL, 75.0 mmol), tetramethyldisilizane (26.6 mL, 150 mmol), [Cp*Ru(NCMe)₃]PF₆ (757 mg, 1.50 mmol, 2 mol%) and CH₂Cl₂ (75 mL) gave **150** (3.134 g, 21.75 mmol, 29%) as a colorless, clear oil.

This reaction was repeated on the same scale with a 45% yield.

bp: 155-165 °C at 760 mm Hg

FT-IR (Diamond ATR): 2956 (m), 2924 (m), 1613 (w), 1441 (w), 1251 (s), 1087 (s), and 821 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl₃): δ 6.37 (tq, *J* = 4.5 and 1.5, 1H, C=C**H**), 3.91 (t, *J*=5.5, 2H, OC**H₂**), 2.22 (tdq, *J* = 5.5, 4.5, and 1.5, 2H, CHC**H₂**), 1.71 (dt, *J*= 5.5and 1.5, 3H, CC**H₃**), and 0.18 (s, 6H, Si(C**H₃**)₂).

^{13}CNMR (125 MHz, CDCl₃): δ 140.3, 135.1, 62.2, 30.9, 20.6, and -1.8.

HRMS (CI, NH₃) Calculated for C₇H₁₈NOSi (M + NH₄): 160.1158. Found: 160.1161.

Combustion: Calculated for C₇H₁₄OSi: C, 59.09; and H, 9.92. Found: C, 58.84; and H, 9.73.

Preparation of 2-(pent-4-yn-1-yloxy)tetrahydro-2*H*-pyran (153)[59]

152   DHP / HCl   **153**
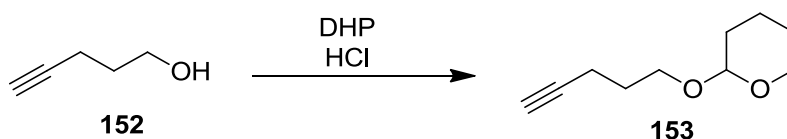
Notebook entry: CAEB233

Freshly distilled dihydropyran (30.0 mL, 29.8 g, 329 mmol) and **152** (8.0 mL, 86 mmol) were charged to a 100 mL round bottomed flask. The solution was stirred and the flask was cooled to 0 °C before conc. HCl (4 drops) was added. The flask was warmed to room temperature and stirred for an additional 3.5 h. Ether (40 mL) was used to quench the reaction. The mixture was washed with 10% NaOH (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Distillation (b.p. 104 °C at 20 mm Hg) gave pure **153** (6.599 g, 39.56 mmol, 46%) as a clear, colorless oil.

FT-IR (Diamond ATR): 2961 (s), 2660 (m), 2660 (w), 1639(w), 1589 (m), 1456 (s), 1261 (s), 1120 (s), 1033 (s), and 728 (s) cm^{-1}.

¹HNMR (300 MHz, $CDCl_3$): δ 4.61 (t, $J = 4.2$, 1H, OC**H**O), 3.87 (m, 2H, OC**H₂**), 3.50 (m, 2H, OC**H₂**), 2.34 (td, $J = 6.3$ and 3.6, CC**H₂**), 1.95 (t, $J = 3.0$, 1H, C≡C**H**), 1.84 (m, 4H, H₂CC**H₂** and OCHC**H₂**), and 1.54 (m, 4H, OCH₂C**H₂** and OCH₂CH₂C**H₂**).

¹³C NMR (75 MHz, $CDCl_3$): 99.0, 84.2, 68.6, 66.0, 62.4, 30.8, 28.9, 25.7, 19.7, and 15.5.

Preparation of hex-4-yn-1-ol (155)[59]
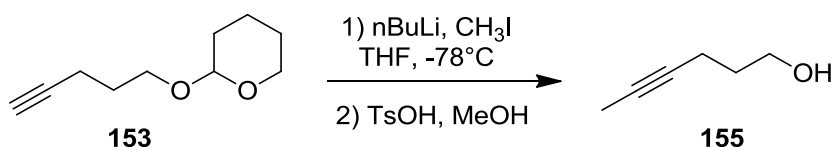
Notebook entry: CAEB219

A solution of **153** (6.599 g, 39.20 mmol) in THF (64 mL) was charged to an oven-dried three-necked 250 mL round bottom flask equipped with a thermometer, gas inlet, stir bar, and septa under argon. The solution was cooled to -78 °C before *n*-butyllithium (29.2 mL, 1.6 M in hexanes, 46.7 mmol) was added dropwise. The temperature was not allowed to warm above -55 °C during this addition. After the addition was complete, methyl iodide (3.20 mL, 7.30 g, 51.3 mmol) was added dropwise to the mixture. The solution was kept at -78 °C for one hour before it was slowly warmed to room temperature, and the solvent was removed *in vacuo*. The residue was diluted with CH_2Cl_2 (50 mL), washed with brine (2 × 45 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the intermediate. The flask containing the intermediate was charged with methanol (128 mL) and $p-$ toluenesulfonic acid (373 mg, 1.96 mmol). Progress of the reaction was monitored by TLC. The solvent was removed via distillation, and the residue was taken up in ether (100 mL), washed with 10% Na_2CO_3 (2 × 25 mL), brine (2 × 25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Distillation (b.p. 160-170 °C at 760 mm Hg) afforded **155** (639 mg, 6.66 mmol, 17%) as a clear, colorless oil.

^{1}HNMR (500 MHz, CDCl$_3$):δ 3.74 (t, *J*= 6.0, 2H, HOC**H$_2$**), 2.25 (m, 2H, CC**H$_2$**), 2.10 (s, 1H, **OH**), 1.77 (t, *J* = 2.4, 3H, CC**H$_3$**), and 1.73 (quintet, *J* = 6.6, 2H, H$_2$CC**H$_2$**).
^{13}CNMR (75 MHz, CDCl$_3$): δ 78.6, 76.3, 62.0, 31.7, 15.5, and 3.6.

Preparation of 2,2,3-trimethyl-2,5,6,7-tetrahydro-1,2-oxasilepine (147)[59]

155   **147**
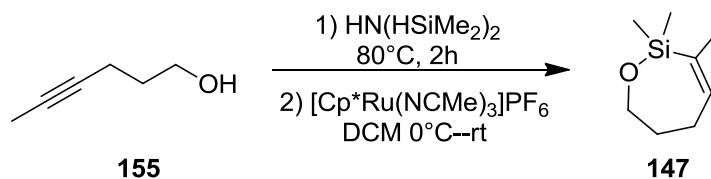
Notebook Entry: CAEB191

General procedure B for the cyclization to form vinyl siloxanes was followed. Alcohol **155** (2.454 g, 25.00 mmol), tetramethyldisilizane (8.86 mL, 50.0 mmol), [Cp*Ru(NCMe)₃]PF₆ (0.315 g, 0.625 mmol, 2.5 mol%) and CH₂Cl₂ (32 mL) yielded product **147** (0.283 g, 2.00 mmol, 8%).

FT-IR (Diamond ATR): 2949 (s), 2862 (m), 1619 (w), 1438 (m), 1250 (s), 1107 (s), and 818 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$):δ 6.28 (t, $J = 5.7$, 1H, C=C**H**), 3.89 (t, $J = 5.4$, 2H, OC**H$_2$**), 2.31 (q, $J = 5.4$, 2H, CHC**H$_2$**), 1.82 (quintet, $J = 6.0$, 2H, OCH$_2$C**H$_2$**), 1.72 (t, $J = 1.8$, 3H, CC**H$_3$**), and 0.20 (s, 6H, Si(C**H$_3$**)$_2$).

^{13}CNMR (125 MHz, CDCl$_3$):δ 141.9, 137.5, 64.5, 30.9, 28.7, 22.6, and -1.1.

HRMS (CI, NH$_3$) Calculated for C$_8$H$_{20}$NOSi (M + NH$_4$): 174.1314. Found: 174.1307.

Preparation of 1-iodo-2,5-dimethoxy-4-methylbenzene (146)[60]
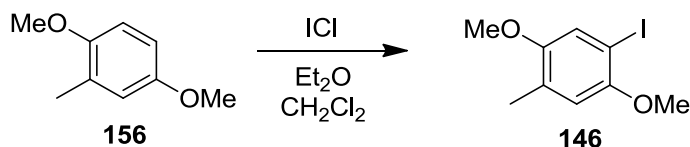
Notebook entry: CAEB243

Diethyl ether (75 mL) and **156** (10.00 g, 65.70 mmol) were charged to a 250 mL two-necked round bottomed flask equipped with an addition funnel, drying tube and magnetic stir bar. A solution of iodine monochloride (10.790 g, 66.500 mmol) in CH_2Cl_2 (30 mL) was added dropwise to the mixture. After addition was complete, the solution was allowed to stir for an additional 3 h. Slowly, the dark red/brown mixture was poured into a vigorously stirred solution of solid $NaHCO_3$ (7.4 g), and sat. aq. $Na_2S_2O_3$ (250 mL). The resulting light yellow solution was diluted with ether (75 mL). The aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with a solution of solid $NaHCO_3$ (2.223 g) and $Na_2S_2O_3$ (2 × 75 mL), and dried over Na_2SO_4. The mixture was filtered and concentrated *in vacuo* to give crude product as a solid. The crude material was recrystallized from methanol to give **146** (11.456 g, 41.196 mmol, 63%) as fine white crystals.

^{1}HNMR (500 MHz, CDCl$_3$):δ 7.17 (s, 1H, Ar**H**), 6.70 (s, 1H, Ar**H**), 3.81 (s, 3H, OC**H₃**), 3.77 (s, 3H, OC**H₃**), and 2.19 (s, 3H, ArC**H₃**).

^{13}CNMR (125 MHz, CDCl$_3$): δ 152.6, 152.3, 128.0, 121.1, 114.1, 81.4, 57.1, 56.1, and 16.5.

Preparation of (Z)-5-(2,5-dimethoxy-4-methylphenyl)hex-4-en-1-ol (145)
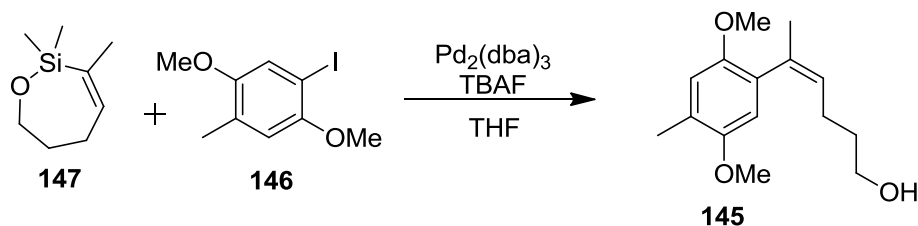
Notebook Entry: CAEB173, CAEB185

General procedure C for Hiyama couplings with vinyl siloxanes was followed. **147** (166.3 mg, 1.000 mmol), **146** (417 mg, 1.50 mmol), TBAF (2.0 mL, 1.0 M in THF, 2.0 mmol), and tris(dibenzylideneacetone) dipalladium (0) (22.9 mg, 0.0250 mmol) in THF (4 mL) gave **144** (0.129 g, 0.520 mmol, 52%) as a yellow oil. This procedure was repeated with 0.840 mmol of **145** for a 56% yield.

FT-IR (Diamond ATR): 3363 (br s), 2933 (s), 2850 (w), 1502 (s), 1464 (m), 1206 (s), 1041 (s), and 863(m) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$):δ 6.74 (s, 1H, Ar**H**), 6.52 (s, 1H, Ar**H**), 5.50 (tq, J = 7.3 and 1.5, 1H, C=C**H**), 3.78 (s, 3H, OC**H$_3$**), 3.77 (s, 3H, OC**H$_3$**), 3.57 (t, J = 6.4, 2H, HOC**H$_2$**), 2.23 (s, 3H, ArC**H$_3$**), 1.98 (d, J = 1.5, 3H, CC**H$_3$**), 1.93 (tdq, J = 7.3, 6.5, and 1.0, 2H, CHC**H$_2$**), 1.84 (s, 1H, O**H**), and 1.59 (quintet, J = 6.5, 2H, C**H$_2$**C**H$_2$**).

^{13}CNMR (125 MHz, CDCl$_3$):δ 151.7, 149.6, 134.6, 128.8, 127.7, 125.8, 114.6, 112.1, 62.4, 56.3, 56.0, 32.3, 25.8, 24.9, and 16.3.

HRMS (ESI) Calculated for C$_{15}$H$_{23}$NaO$_3$ (M + Na): 273.1467. Found: 273.1467.

Combustion: Calculated for C$_{15}$H$_{22}$O$_3$: C, 71.97; and H, 8.86. Found: C, 72.23; and H, 8.64.

Preparation of 1,2-di(pyridin-2-yl)diselenide[69]
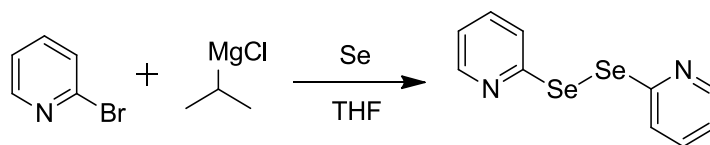
Notebook Entry: CAEB189

Magnesium turnings (0.608 g, 25.0 mmol) were gently crushed and added to a 50 mL round bottomed flask equipped with a water condenser, stir bar, and septa under argon. Enough dry THF was added to cover the magnesium turnings. Stirring was initiated and iodine (1 crystal) was added to the flask. The solution turned yellow/brown. Once the color faded, 2-chloropropane (2.28 mL, 25.0 mmol) in THF (0.5 mL) was added dropwise to the solution. A heat gun was used to initiate bubbling while 2-chloropropane was being added. When the addition was complete, solution was refluxed for 1 hour. Isopropyl magnesium chloride (2.57 g, 25.0 mmol) was transferred to a 50 mL round bottomed flask under argon. During the addition of 2-bromopyridine (2.4 mL, 25.0 mmol), the solution turned clear orange/red, then a red clay color. The solution stirred at room temperature for 2 hours before crushed elemental selenium (1.98 g, 25.0 mmol) was added. The mixture was stirred until all the selenium had dissolved, about 2 days. The solution was quenched with 10% HCl, and the aqueous layer was extracted with ether (4 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Crude material was purified by column chromatography (500 mL, 1" column, 3:1 hexanes : EtOAc) to give product (0.944 g, 3.00 mmol, 12%).

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[69] Bhasin, K. K.; Arora, V. *Applied Organometallic Chemistry* **2004**, *18*, 359-362.

mp: 48.6-50.1 °C

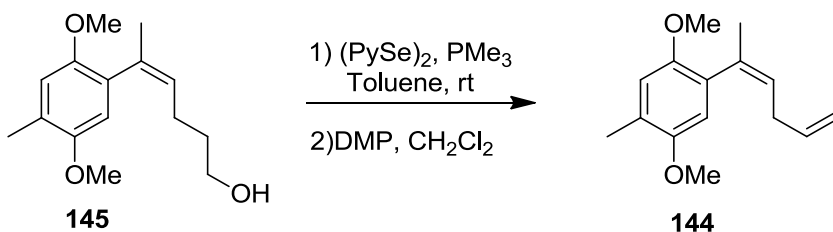**FT-IR** (Diamond ATR): 3060 (w), 1568 (s), 1556 (s), 1444 (m), 1104 (s), 1074 (s), and 746 (s) cm^{-1}.

^{1}HNMR(500 MHz, CDCl$_3$): δ 8.45 (dd, *J* = 4.3, and 1.2, 1H, NC**H**), 7.77 (d, *J* = 7.9, 1H, CC**H**), 7.54 (td, *J* = 7.9, and 1.8, 1H, NCHC**H**), and 7.08 (td, *J* = 4.3, and 1.2, 1H, CCHC**H**).

^{13}CNMR (125 MHz, CDCl$_3$): δ 154.4, 149.6, 137.5, 123.6, and 121.2.

Preparation of (Z)-1-(hexa-2,3-dien-2-yl)-2,5-dimethoxy-4-methylbenzene (144)

Notebook Entry: CAEB197

A 25 mL round bottom flask under argon was charged with **145** (37.6 mg, 0.150 mmol), dry toluene (1 mL), trimethylphosphine (97%, 51.8 mg, 0.165 mmol) and a solution of 1,2-di(pyridin-2-yl)diselane (18.6 µL, 0.180 mmol) in toluene (1 mL). The mixture was allowed to stir at room temperature until TLC indicated consumption of **145**. The solution was washed with water (2 mL), and aqueous layer was removed. The organic layer was filtered through a plug of silica gel with additional CH_2Cl_2 (50 mL). The filtrate was concentrated *in vacuo* to give crude intermediate. The intermediate was taken up in dry CH_2Cl_2 (1 mL) and charged to a 25 mL round bottomed flask under Ar. The solution was stirred and Dess-Martin periodinane (76.3 mg, 0.180 mmol) was added. Progress of the reaction was monitored by ^{1}HNMR. When the reaction was complete, the mixture was stirred with sat. aq. $NaHCO_3$ (2 mL) for 1 hour. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were concentrated *in vacuo*. Purification by flash chromatography (100 mL, ½" column, 6:1 hexanes : EtOAc) gave pure **144** as a yellow oil (10 mg, 29%), along with unreacted intermediate (6 mg, 0.02 mmol, 15%).

¹HNMR (500 MHz, CDCl$_3$): δ 6.73 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 5.72 (ddt, J = 16.5, 10.0, and 6.5, 1H, H$_2$C=C**H**), 5.46 (td, J = 7.6, and 1.8, 1H, C=C**H**), 4.97 (m, 2H, HC=C**H$_2$**), 3.76 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 2.61 (t , J = 6.5, 2H, C**H$_2$**), 2.22 (s, 3H, ArC**H$_3$**), and 2.01 (s, 3H, CC**H$_3$**).

¹³CNMR (75 MHz, CDCl$_3$): δ 150.4, 149.0, 136.7, 134.4, 127.3, 124.7, 124.5, 124.2, 113.5, 113.3, 111.1, 55.3, 54.9, 32.8, 23.6, and 15.2.

HRMS (ESI) Calculated for C$_{14}$H$_{20}$NaO$_3$ (M + Na): 259.1310. Found: 259.1311.

Preparation of (Z)-4-(4-methoxyphenyl)pent-3-en-1-ol (158)
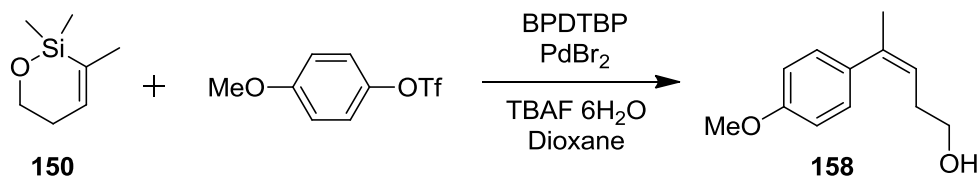
Notebook Reference: CAEB125, CAEB 127, CAEB 131, CAEB145, CAEB155

A 2-necked 25 mL round bottom flask equipped with a septa, stir bar, and gas inlet was put under argon. The flask was charged with TBAF•3H$_2$O (0.316 g, 1.00 mmol) dissolved in dry dioxane (1 mL). This was followed by water (54 µL, 3.0 mmol), di-*t*-butylbiphenylphosphine (14.9 mg, 0.0500 mmol), and PdBr$_2$ (6.7 mg, 0.025 mmol). The mixture was allowed to stir for 30 min before **150** (0.107 g, 0.750 mmol) and 4-methoxyphenyl trifluoromethanesulfonate (0.128 g, 0.500 mmol) were charged to the flask. Progress of the reaction was monitored by TLC. The reaction was quenched with H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 15 mL), and the combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. Flash chromatography (500 mL, 1", 3:1 hexanes: EtOAc) gave **158** (37 mg, 0.19 mmol, 39%) as a yellow/orange oil. This experiment was repeated and gave a range of 23-39% yields.

FT-IR (Diamond ATR): 3336 (br s), 2932 (m), 2835 (w), 1607 (s), 1573 (w), 1508 (s), 1373 (w), 1242 (s), 1028 (s), and 830 (s) cm^{-1}.

^{1}HNMR (300 MHz, CDCl$_3$): δ 7.13 (d, *J*= 8.8, 2H, Ar-**H**), 6.87 (d, *J*= 8.8, 2H, Ar-**H**), 5.44 (m, 1H, C=C**H**), 3.81 (s, 3H, OC**H$_3$**), 3.61 (t, *J* = 6.5, 2H, HOC**H$_2$**), 2.26 (q, *J*= 6.5, 2H, HCC**H$_2$**), and 2.04 (d, *J*= 1.2, 3H, CC**H$_3$**).

^{13}CNMR (75 MHz, CDCl$_3$): δ 158.3, 138.9, 133.9, 129.0, 122.7, 113.5, 62.7, 55.2, 32.6, and 25.9.

Combustion: Calculated for C$_{12}$H$_{16}$O$_2$: C, 74.97; and H, 8.39. Found: C, 75.14; and H, 8.20.

General Procedure F: Dess-Martin oxidation
Preparation of (*Z*)-4-(4-methoxyphenyl)pent-3-enal (159)
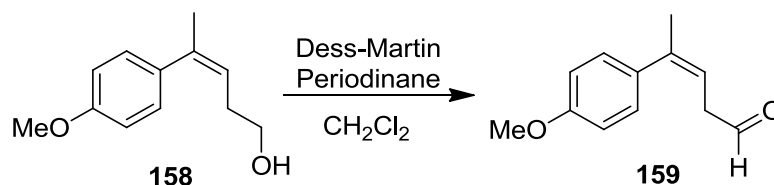
Notebook Entry: CAEB175

Dess-Martin periodinane (89.1 mg, 0.210 mmol) was added to a 10 mL round bottom flask under argon. The flask was charged with dry CH_2Cl_2 (1 mL) and **158** (25.0 mg, 0.140 mmol). Stirring was initiated and progress of the reaction was monitored by TLC. To work up the reaction, $Na_2S_2O_3$ (0.250 g) was dissolved in sat. aq. $NaHCO_3$ (2.5 mL) and ether (2.5 mL). This was added dropwise to the solution and the mixture was stirred overnight. The aqueous layer was extracted with ether (3 × 3 mL), washed with brine (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give **159** (7 mg, 0.04 mmol, 26%). Aldehyde **159** was prone to decomposition and therefore was not purified

^{1}HNMR (500 MHz, $CDCl_3$):δ 9.64 (t, *J* = 1.5, 1H, O=C**H**), 7.08 (d, *J* = 8.8, 2H, Ar**H**), 6.89 (d, *J* = 8.8, 2H, Ar**H**), 5.56 (tq, *J* = 7.3, and 1.3, 1H, C=C**H**), 3.81 (s, 6H, OC**H₃**), 3.14 (d, *J* = 7.3, 2H, OCC**H₂**), and 2.09 (d, *J* = 1.3, 3H, CC**H₃**).

Preparation of (Z)-4-(2,5-dimethoxy-4-methylphenyl)pent-3-en-1-ol (149)
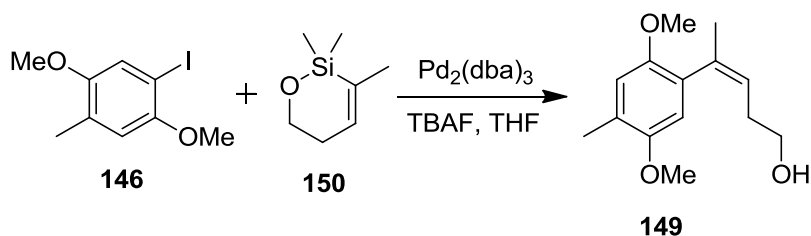
Notebook Entry: CAEB167, CAEB183, CAEB259, CAEB261, CAEB271.

General procedure C for Hiyama couplings with vinyl siloxanes was followed. Silane **150** (285 mg, 2.00 mmol), aryl iodide **146** (834 mg, 3.00 mmol), TBAF (4.0 mL, 1.0 M in THF, 4.0 mmol), and $Pd_2(dba)_3$ (45.8 mg, 0.0500 mmol, 2.5 mol%) in THF (8 mL) yielded **149** (100 mg, 0.420 mmol, 21%) as a yellow oil. This procedure was repeated multiple times with a 10 mol% catalyst loading and an average yield of 91% was achieved.

FT-IR (Diamond ATR): 3356 (br s), 2934 (m), 1502 (s), 1465 (m), 1208 (s), 1041 (s), and 865 (s) cm^{-1}.

^{1}HNMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H, Ar**H**), 6.53 (s, 1H, Ar**H**), 5.51 (t, $J = 7.5$, 1H, C=C**H**), 3.78 (s, 3H, OC**H₃**), 3.77 (s, 3H, OC**H₃**), 3.56 (t, $J = 6.0$, 2H, HOC**H₂**), 2.23 (s, 3H, ArC**H₃**), 2.10 (q, $J = 6.0$, 2H, CHC**H₂**), and 2.00 (s, 3H, CC**H₃**).

^{13}CNMR (75 MHz, $CDCl_3$): δ 151.8, 149.3, 137.6, 128.4, 125.9, 124.3, 114.4, 111.9, 62.0, 56.2, 56.0, 32.8, 25.2, and 16.3.

HRMS (ESI) Calculated for $C_{14}H_{20}NaO_3$ (M + Na): 259.1310. Found: 259.1311.

Combustion: Calculated for $C_{14}H_{20}O_3$: C, 71.16; and H, 8.53. Found: C, 71.44; and H, 8.72.

Preparation of (*Z*)-4-(2,5-dimethoxy-4-methylphenyl)pent-3-enal (148)

149 → **148**

(Dess-Martin Periodinane, CH₂Cl₂)
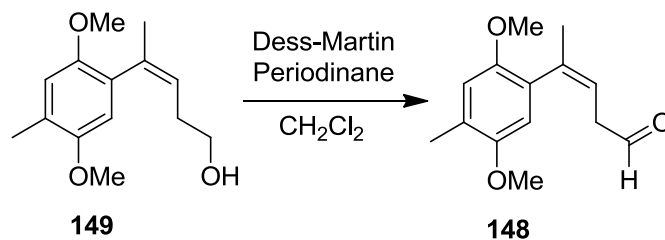
Notebook entry: CAEB211, CAEB223, CAEB249, CAEB263

General procedure F for a Dess-Martin oxidation was followed. Alcohol **149** (236 mg, 1.00 mmol), Dess-Martin periodinane (424 mg, 1.50 mmol) and CH_2Cl_2 (10 mL) yielded **148** (209 mg, 0.890 mmol, 89%) as a yellow oil. This procedure was repeated to give yields between 88% and 93%. Aldehyde **148** was prone to decomposition and therefore was not purified.

FT-IR (Diamond ATR): 2949 (s), 2830 (s), 1722 (s), 1503 (s), 1465 (m), 1210 (s), 1043 (s), and 866 (w) cm^{-1}.

^{1}HNMR (500 MHz, CDCl₃):δ 9.61 (t, *J* = 1.5 Hz, 1H, C**H**O), 6.73 (s, 1H, Ar**H**), 6.50 (s, 1H, Ar**H**), 5.68 (tq, 7.3 and 1.5, 1H, C=C**H**), 3.77 (s, 3H, OC**H₃**), 3.74 (s, 3H, OC**H₃**), 2.98 (dd, *J* = 7.5 and 1.5, 2H, O=CC**H₂**), 2.23 (s, 3H, Ar-C**H₃**), and 2.08 (d, *J* = 1.5 Hz, 3H, CC**H₃**).

^{13}CNMR (125 MHz, CDCl₃):δ 200.8, 151.7, 149.6, 139.6, 127.3, 126.5, 117.2, 114.6, 111.7, 56.1, 56.0, 44.7, 24.9 and 16.3.

HRMS (ESI) Calculated for $C_{14}H_{18}NaO_3$ (M + Na): 257.1154. Found: 257.1154.

Preparation of (Z)-1-(hexa-2,5-dien-2-yl)-2,5-dimethoxy-4-methylbenzene (144)
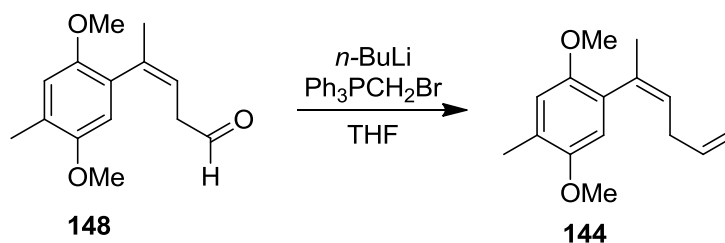
Notebook entry: CAEB225, CAEB251, CAEB265

A 50 mL round bottomed flask under argon was equipped with a thermometer and gas inlet.

n-Butyllithium (0.80 mL, 1.6 M in hexanes, 1.3 mmol) was added dropwise to a suspension

of methyltriphenylphosphonium bromide (447 mg, 1.25 mmol) in THF (10 mL) at -78 °C. A

bright yellow solution formed. This solution was allowed to warm up to room temperature.

Upon formation of a bright orange/red solution, the mixture was cooled back to -78 °C. A

solution of **148** (209 mg, 0.890 mmol) in THF (3 mL) was added to the flask. The color

immediately darkened. Progress of the reaction was monitored by TLC. The reaction was

quenched with H_2O, and the aqueous layer was extracted with ether (3 × 15 mL). The

organic layers were washed with brine (3 × 15 mL), dried over $MgSO_4$, filtered and

concentrated *in vacuo*. Purification by flash chromatography afforded pure **144** (180 mg,

0.774 mmol, 87%) as a yellow oil. This procedure was repeated twice with 0.92 mmol and

1.70 mmol of **148** to give 39% and 56% yields of **144**, respectively.

FT-IR (Diamond ATR): 2947 (m), 2828 (m), 1637 (w), 1502 (s), 1464 (m), 1209 (s), and 1044 (s) cm^{-1}.

^{1}HNMR (500 MHz, CDCl$_3$): δ 6.73 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 5.72 (ddt, J = 16.5, 10.0, and 6.5, 1H, H$_2$C=C**H**), 5.46 (td, J = 7.6, and 1.8, 1H, C=C**H**), 4.97 (m, 2H, HC=C**H$_2$**), 3.76 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 2.61 (t , J = 6.5, 2H, C**H$_2$**), 2.22 (s, 3H, ArC**H$_3$**), and 2.01 (s, 3H, CC**H$_3$**).

¹³CNMR (75 MHz, CDCl₃): δ 151.4, 150.1, 137.7, 135.4, 128.4, 125.7, 125.3, 114.5, 114.3, 112.1, 56.3, 55.9, 33.8, 24.6, and 16.3.

HRMS (CI+) Calculated for $C_{15}H_{21}O_2$: 233.1542. Found: 233.1542.

Combustion: Calculated for $C_{15}H_{20}O_2$: C, 77.55; and H, 8.68. Found: C, 77.46; and H, 8.42.

Preparation of (2*E*, 5*Z*)-6-(2,5-dimethoxy-4-methylphenyl)-2-methylhepta-2,5-dienal (143)
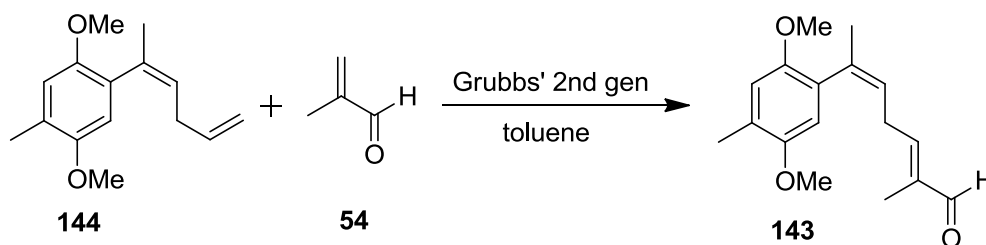
Notebook entry: CAEB237, CAEB269

Grubbs' 2nd generation catalyst (3.6 mg, 0.0040 mmol) was placed in a 10 mL screwcap vial under argon. Dry CH_2Cl_2 (2 mL) was added, along with **144** (50 mg, 0.22 mmol) and freshly distilled **54** (45 mg, 0.65 mmol). The vial was placed in a 50 °C oil bath and the mixture was stirred. Progress of the reaction was monitored by ^{1}HNMR. Additional Grubbs' catalyst (5 mg, 0.006 mmol) and **54** (45 mg, 0.65 mmol) were added after 24 hours. After 72 hours, the mixture was concentrated *in vacuo* and passed through a small silica plug (9:1 hexanes : EtOAc). The filtrate was concentrated and purified by flash chromatography to yield purified **143** (28 mg, 0.11 mmol, 48%) as a yellow oil. This procedure was repeated with 0.433 mmol of **144** to afford a 53% yield.

FT-IR (Diamond ATR): 2935 (m), 2829 (m), 1683 (s), 1502 (s), 1465 (m), 1206 (s), and 1041 (s) cm^{-1}.

[1]**HNMR** (500 MHz, $CDCl_3$):δ 9.36 (s, 1H, **CHO**), 6.74 (s, 1H, Ar**H**), 6.51 (s, 1H, Ar**H**), 6.43 (tq, *J* = 7.3 and 1.5, 1H, C=C**H**), 5.53 (tq, *J* = 7.3 and 1.5, 1H, C=C**H**), 3.77 (s, 3H, OC**H₃**), 3.76 (s, 3H, OC**H₃**), 2.89 (t, *J* = 7.3, 2H, C**H₂**), 2.24 (s, 3H, ArC**H₃**), 2.02 (d, *J* = 1.0, 3H, CC**H₃**), and 1.59 (d, *J* = 1.0, 3H, CC**H₃**).

[13]**CNMR** (125 MHz, $CDCl_3$): δ 195.3, 153.2, 151.6, 149.8, 138.8, 137.1, 127.7, 126.3, 122.7, 114.4, 111.9, 56.1, 56.0, 29.5, 24.9, 16.3, and 9.1.

HRMS: (CI+) Calculated for $C_{16}H_{21}O_3$: 261.1491. Found: 261.1485.\

Combustion: Calculated for $C_{16}H_{20}O_3$: C, 73.82; and H, 7.74. Found: C, 74.09; and H, 7.53.

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