2011

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

Courtney A. Engles
Western Washington University

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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

ADVISORY COMMITTEE

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Dr. Gregory W. O'Neil

Dr. Elizabeth A. Raymond
MASTER'S THESIS

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Courtney Engles
May 18, 2011
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

By
Courtney A. Engles
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.
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<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>anal</td>
<td>Analysis</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoate</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic amount</td>
</tr>
<tr>
<td>Comb.</td>
<td>Combustion</td>
</tr>
<tr>
<td>m-CPBA</td>
<td><em>meta</em>-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl Acetate</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier-Transform Infrared Spectrometry</td>
</tr>
<tr>
<td>GC/MS</td>
<td>Gas-Chromatography Mass Spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
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<tr>
<td>IR</td>
<td>Infrared Spectrometry</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>Pv</td>
<td>Pivaloate</td>
</tr>
<tr>
<td>sat. aq.</td>
<td>Saturated Aqueous</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra (n)-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butylidemethylsilyl ether</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
</tbody>
</table>
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.\(^3\)

---

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).  

![Figure 1-2: Weed resistance to herbicides.](http://www.weedresearch.com)
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 volatilization from the leaves, leaching 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*


*fasi*gera* and *Spirastrella* *hartmani*, share the same unique core structure (Figure 1-3).\textsuperscript{13,14}

The heliananes have been shown to be cytotoxic against three human tumor cell lines: breast, colon, and lung.\textsuperscript{14} This cytotoxicity would make their synthesis potentially useful.

\textbf{Figure 1-3: Heliannuols A-L and helianane.}


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, 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. 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).\textsuperscript{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.

Figure 1-4: Proposed biosynthetic pathway.¹
1.3 Glandulones.

Isolated from the non-capitate glandular trichomes of *Helianthus annuus* are the benzoquinones glandulone A, B, and C (Figure 1-5). 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*. 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.

![Structural formulas of Glandulones A, B, and C](image)

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

---

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. 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 the 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.](image)

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.**

<table>
<thead>
<tr>
<th>Ring Size</th>
<th>Exocyclic</th>
<th>Endocyclic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sp (dig)</td>
<td>sp² (trig)</td>
</tr>
<tr>
<td>3</td>
<td>Unfavorable</td>
<td>Favorable</td>
</tr>
<tr>
<td>4</td>
<td>Favorable</td>
<td>Favorable</td>
</tr>
<tr>
<td>5</td>
<td>Favorable</td>
<td>Favorable</td>
</tr>
<tr>
<td>6</td>
<td>Favorable</td>
<td>Favorable</td>
</tr>
<tr>
<td>7</td>
<td>Favorable</td>
<td>Favorable</td>
</tr>
</tbody>
</table>

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).

---


Table 1-2. Rate of cyclization of diethyl (ω-bromoalkyl)-malonate ester anions as a function of ring size.²⁶

![Cyclization Reaction](image)

<table>
<thead>
<tr>
<th>n</th>
<th>Ring Size</th>
<th>Relative Rate (sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0.58</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>833</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>8.7 x 10⁻⁵</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>1.5 x 10⁻⁴</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>1.7 x 10⁻⁵</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>1.4 x 10⁻⁶</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>2.9 x 10⁻⁶</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>4.0 x 10⁻⁴</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>7.4 x 10⁻⁴</td>
</tr>
<tr>
<td>14</td>
<td>17</td>
<td>2.9 x 10⁻³</td>
</tr>
<tr>
<td>17</td>
<td>21</td>
<td>4.3 x 10⁻⁵</td>
</tr>
</tbody>
</table>

The fastest cyclization occurred at 833 sec⁻¹ for the five-membered ring. The slowest cyclization rate of 1.4 x 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

---

Figure 1-7: Cyclization rates of ω-bromoalkanecarboxylates vs. ring size.  

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. 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. 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. 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). The key step in this synthesis is the intramolecular Julia-type coupling in which LiHMDS deprotonates the methylene adjacent to the sulfone on 25. The sulfone anion then attacks the carbonyl group

---

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. 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.


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.\(^\text{17}\) 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.\(^\text{18}\) 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. 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.\textsuperscript{20} The ring closing metathesis precursor 44 was formed in seven steps from \textit{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 (-)-heliananol A has been achieved by Shishido's group.\textsuperscript{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.**

![Diagram of the synthesis of (-)-heliannuol A.](image)

**Figure 1-8: Most stable conformation calculated for 46.**

\(^{21}\)
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.\textsuperscript{29} Many aromatic bisabolenes are components of plant essential oils. Other aromatic bisabolenes show antibiotic, antifungal, antimicrobial, and antitumor properties.\textsuperscript{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.\textsuperscript{29} The alkenylzinc reagent \textsuperscript{49} employed for the synthesis of (±)-\textsuperscript{22} was prepared via a reaction of Rieke zinc with the corresponding alkyl halide. A Negishi coupling with aryl bromide \textsuperscript{50} produced aromatic bisabolene \textsuperscript{51}. This was then oxidized to quinone \textsuperscript{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 (\textsuperscript{22}).

The oxidation to the aldehyde, however, was problematic. The use of selenium oxide with \textit{t}-butylhydroperoxide produced a low yield and gave a mixture of the desired product \textsuperscript{22} with the corresponding allylic alcohol. To improve the yield, the α,β-unsaturated aldehyde was installed first to give \textsuperscript{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.
Loitz

Celeste Loitz of the Vyvyan group applied an epoxide attack strategy similar to that of Shishido for the formation of heliannuol A. 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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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. 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).
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.

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 heliananes.

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-butylimethylsilyl ether 70c, or pivaloate 70d in 61%, 97%, 62%, and 30% yields respectively.


\(^{32}\) 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.**

![Scheme 1-13: Synthesis of protected vinyl siloxane.](image)

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, 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.

<table>
<thead>
<tr>
<th>Ar-I</th>
<th>R₁</th>
<th>R₂</th>
<th>PG</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>76a</td>
<td>MOM</td>
<td>H</td>
<td>Pv</td>
<td>77a</td>
<td>74</td>
</tr>
<tr>
<td>76a</td>
<td>MOM</td>
<td>H</td>
<td>Bz</td>
<td>77b</td>
<td>56</td>
</tr>
<tr>
<td>76b</td>
<td>Bz</td>
<td>H</td>
<td>Bz</td>
<td>77c</td>
<td>47</td>
</tr>
<tr>
<td>76c</td>
<td>MOM</td>
<td>OMe</td>
<td>Bz</td>
<td>77d</td>
<td>58</td>
</tr>
</tbody>
</table>

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. 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.

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

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 \textit{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.

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>% Yield 86</th>
<th>% Yield 87</th>
<th>% Yield 88</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>87</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>99</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>OBn</td>
<td>Me</td>
<td>61</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>OTBS</td>
<td>Me</td>
<td>35</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
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**

![Scheme 2-1: Formation of debrominated product 88](image)

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).**

\[ \text{Cl-} \text{NH}_2 \xrightarrow{\text{Ac}_2\text{O, pyridine, EtOAc}} \text{Cl-} \text{N} \xrightarrow{\text{Br}_2, \text{AcOH}} \text{Cl-} \text{Br} \]

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


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

\textbf{Scheme 2-3: Hiyama and Buchwald cyclization of \textit{93}.}

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

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\textsuperscript{33} which yielded a mixture of products. Purification and \textsuperscript{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 \textit{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.**
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 mCPBA in dichloromethane. 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. Addition of the ketone

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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.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCPBA, CH₂Cl₂, reflux</td>
<td>NR</td>
</tr>
<tr>
<td>mCPBA, 1,2-DCE, reflux</td>
<td>NR</td>
</tr>
<tr>
<td>I₂, H₂O₂, AcOH</td>
<td>NR</td>
</tr>
</tbody>
</table>

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. 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). 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. 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.

Scheme 3-1: McNulty's synthesis of cyclic alkenyl boronic half acids.

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42 CAS #99604-67-8, Strem catalogue #44-7880. 1g for $333, Strem Catalogue No 22. 2008-2010.
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 (R₁ = OH) or a Buchwald-Hartwig etherification to 110 (R₁ = Br) could be tried to get to the product 3.

Scheme 3-2: Retrosynthesis using cyclic boronic half acid.

3.2 Synthesis 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

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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. 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.

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). 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. 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. 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

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46 McNulty, L. Butler University, Indianapolis, IN. Personal communication, 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.
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 isopropenylmagnesium bromide to be quenched with 1M HCl was used (Scheme 3-8). The \(^1\text{H}\) 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 \(^1\text{H}\) NMR spectrum of the product showed a mixture of boronic acid 117 with its dimer 125.
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

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.

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
127 & \quad \text{\Rightarrow} \\
\text{128} & 
\end{align*}
\]

To synthesize 5-methylhex-1,4-diene (128), isobutyraldehyde (129) was treated with sulfuryl
carbide (Scheme 3-10). Distillation afforded α-chloroisobutyraldehyde (130) in a 74%
yield. This was reacted with allylmagnesium bromide and lithium powder. 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 separate steps, we decided isolate the intermediate 131. Allylmagnesium

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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. 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

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).

Hydrolysis with water and Amberlyst®-15 ion exchange resin to form 135 was performed according to a procedure found in literature. 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 CH₂Cl₂ 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 as well as with copper (II) sulfate and sodium iodide in HPLC grade acetone. 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.

54 Mohan, R. S.; Bailey, A. D. Synlett 2006, 2, 215-218.
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). 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 resulted in a 19% yield of 138. When this procedure was repeated, a yield of 36% was achieved.

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. The only compounds that were varied for

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. 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. 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 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 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.

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.
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$_2$Cl$_2$ (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, 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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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.

<table>
<thead>
<tr>
<th>Alcohol 141 (equiv)</th>
<th>Boronate Ester 118 (equiv)</th>
<th>Grubbs (mol %)</th>
<th>CH$_2$Cl$_2$ (M)</th>
<th>Yield of 142 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>0.5</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>0.5</td>
<td>32</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
<td>0.25</td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
<td>0.5</td>
<td>90$^a$</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
<td>1.0</td>
<td>45</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
<td>0.5</td>
<td>47</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>12</td>
<td>0.5</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>14</td>
<td>0.5</td>
<td>64</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>5</td>
<td>0.5</td>
<td>79</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>7</td>
<td>0.5</td>
<td>73</td>
</tr>
</tbody>
</table>

$^a$ This reaction was performed on double the scale.
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

↓

OMe

143

↓

OMe

OMe

144

path A

OMe

145

↓

MeO

146 + OMe

147

path B

OMe

148

↓

OMe

149

OMe

146 + OMe

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).\textsuperscript{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.\textsuperscript{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.](image)

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).\textsuperscript{32} Freshly distilled dihydropyran was used to protect 4-pentyn-1-ol (152) under mildly acidic conditions.

\textsuperscript{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\(^\text{60}\) (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.

\[ \text{Primary aryl alcohol 145 was treated with dipyridyl diselenide and trimethylphosphine to afford a quantitative yield of an intermediate presumed to be 157 (Scheme 4-5). Subsequent treatment with Dess-Martin periodinane, workup, and purification gave the dehydrated product 144 in a 29% yield as well as a 10% yield of unreacted intermediate 157. This step was repeated using 1.0 M trimethylphosphine with similar yields. Due to the low yield of this step, path B from the 6-membered cyclic vinyl siloxane 150 was attempted.} \]


4.4 Synthesis from 6-membered cyclic vinyl siloxane 150.

With a model aryl alcohol 158 having been previously synthesized, 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). 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.

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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. 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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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. 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.\textsuperscript{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.
A procedure for the oxidation to quinones using hypervalent iodine complexes was found in a literature search.\textsuperscript{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.\textsuperscript{66} Silver (II) oxide, aldehyde 143, dioxane, and 6 M HNO\textsubscript{3} were sonicated and stirred until silver (II) oxide was consumed. According to the literature, this was within 2-3 minutes.\textsuperscript{66} Since I was


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.**

![Dimethoxybenzenes](image)

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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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. 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).**

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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$_2$Cl$_2$ 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 $^{\text{UNITY}}$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 spectrometer 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 spectrometry 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 \( \text{N-}(3\text{-chloro-4-methylphenyl})\text{acetamide (90)} \)\(^{36} \)

![Diagram of the reaction](image)

Notebook Reference: CAEA011, CAEA035

A solution of \( \text{89} \) (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 \( \text{P}_2\text{O}_5 \) to afford \( \text{90} \) as a white solid (13.667 g, 0.075 mol, 75%). This procedure was repeated using 0.250 mol \( \text{89} \) with a 62% yield of \( \text{90} \).

**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\(^{-1}\).

**\(^1\text{HNMR}\)** (300 MHz, CDCl\(_3\)): \( \delta \) 7.56 (d, \( J = 2.3 \), 1H, ArH), 7.53 (s, 1H, NH), 7.25 (dd, \( J = 8.1 \) and 2.3, 1H, ArH), 7.13 (d, \( J = 8.1 \), 1H, ArH), 2.32 (s, 3H, OC\(_2\)H\(_3\)), and 2.17 (s, 3H, CH\(_3\)).

**\(^{13}\text{CNMR}\)** (75 MHz, CDCl\(_3\)): \( \delta \) 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)\textsuperscript{36}

![Chemical Structure](attachment:image.png)

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 °C 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\textsubscript{2}O\textsubscript{5}. The crude material was recrystallized using CH\textsubscript{3}CN 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.

\textbf{mp}: 154-155 °C

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

\textsuperscript{1}\textbf{HNMR} (500 MHz, CDCl\textsubscript{3}): $\delta$ 8.38 (s, 1H, NH), 7.51 (s, 1H, ArH), 7.38 (s, 1H, ArH), 2.31 (s, 3H, CH\textsubscript{3}), and 2.23 (s, 3H, CH\textsubscript{3}).

\textsuperscript{13}\textbf{CNMR} (75 MHz, CDCl\textsubscript{3}): $\delta$ 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)\textsuperscript{36}

![Chemical Structure](image)

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 °C 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.

\textbf{mp:} 86.4-86.8 °C at 760 mm Hg.

\textbf{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\textsuperscript{-1}.

\textbf{\textsuperscript{1}HNMR} (500 MHz, CDCl\textsubscript{3}): δ 7.25 (s, 1H, ArH), 6.78 (s, 1H, ArH), 6.59 (s, 2H, NH\textsubscript{2}), and 2.24 (s, 3H, CH\textsubscript{3}).

\textbf{\textsuperscript{13}CNMR} (75 MHz, CDCl\textsubscript{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)

\[
\begin{align*}
\text{Cl-} & \quad \text{NH}_2 \\
\text{Br} & \quad \rightarrow \\
\text{Cl-} & \quad \text{I} \\
\text{Br} & \\
92 & \quad \rightarrow \\
93 &
\end{align*}
\]

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 °C. The solution was stirred for 30 min then cooled to 0 °C. 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 °C using an ice bath. The reaction mixture was stirred for an additional 30 min at 0 °C. 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$_2$Cl$_2$ (150 mL) and the organic layer was washed successively with 10% NaOH (150 mL), 1.0 M Na$_2$S$_2$O$_3$ (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 °C

**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, ArH), 4.48 (s, 1H, ArH), and 2.30 (s, 3H, CH$_3$).

**$^{13}$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)\textsuperscript{32}

\[
\begin{align*}
\text{HO} & \quad \xrightarrow{\text{SOCl}_2} \quad \text{Cl} \\
\text{Pyridine} & \quad \xrightarrow{} \quad 74
\end{align*}
\]

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 °C at 760 mm Hg) afforded product 74 (9.801 g, 0.1108 mol, 78%).

\textsuperscript{1}HNMR (500 MHz, CDCl\textsubscript{3}): \( \delta 4.13 \) (s, 2H, CH\textsubscript{2}Cl), and \( \delta 1.87 \) (s, 3H, CCH\textsubscript{3}).
Preparation of hept-5-yn-2-one (75)\textsuperscript{32}

\[
\begin{align*}
\text{Cl} & + & \text{K}_2\text{CO}_3 \\
\text{74} & & \text{75}
\end{align*}
\]

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\textsubscript{2}CO\textsubscript{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\textsubscript{2}O (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\textsubscript{2}CO\textsubscript{3}. The solution was filtered and concentrated \textit{in vacuo} to give 75 (10.575 g, 96.047 mmol, 100%).

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

\textbf{\textsuperscript{1}HNMR} (500 MHz, CDCl\textsubscript{3}): \(\delta\) 2.64 (t, \(J = 6.5\), 2H, O=CH\textsubscript{2}), 2.39 (tq, \(J = 6.5\) and 2.4, 2H, H\textsubscript{3}CC≡CH\textsubscript{2}), 2.18 (s, 3H, O=CH\textsubscript{3}), and 1.11 (t, \(J = 2.4\), 3H, C≡CH\textsubscript{3}).

\textbf{\textsuperscript{13}CNMR} (75 MHz, CDCl\textsubscript{3}): \(\delta\) 203.8, 72.6, 72.2, 47.5, 26.4, 16.6, and 9.9.
Preparation of 2-methylhept-5-yn-2-ol (70e)

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. NH₄Cl (20 mL) was slowly added to the flask and solution was stirred for 15 min. Additional NH₄Cl 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 Na₂SO₄, 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%).

¹HNMR (500 MHz, CDCl₃): δ 2.25 (tq, J = 8.0 and 2.5, 2H, C≡CCH₂), 2.18 (s, 1H, OH), 1.77 (t, J = 2.5, 3H, C≡CCH₃), 1.69 (t, J = 8.0, 2H, HOCH₂H₂), 1.23 (s, 3H, CH₃), and 1.22 (s, 3H, CH₃).

¹³CNMR (CDCl₃, 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 CH₂Cl₂ (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]PF₆ (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.

¹HNMR (500 MHz, CDCl₃): δ 6.24 (m, 1H, C=CH), 2.32 (m, 2H, C=CHCH₂), 1.87 (m, J = 2.9 and 2.4, 2H, (CH₃)₂CCH₂), 1.70 (q, J = 1.8, 3H, H₃CC=CH), 1.25 (s, 6H, (CH₃)₂C), and 0.18 (s, 6H, (CH₃)₂Si).

¹³CNMR (75 MHz, CDCl₃): 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, ArH), 7.07 (s, 1H, ArH), 5.52 (tq, J = 7.3 and 2.5, 1H, C=CH), 2.37 (s, 3H, Ar-CH$_3$), 1.93 (d, J = 2.5, 3H, HC=CH$_3$), 1.82 (m, 2H, C=CHCH$_2$), 1.26 (t, J = 7.3, 2H, HOCCCH$_2$), and 1.12 (s, 6H, HO(C(CH$_3$)$_2$).

**$^{13}$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-2H-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.

**¹H NMR** (500 MHz, CDCl₃): δ 7.11 (d, J = 7.8, 1H, ClCCC₃H), 6.84 (d, J = 1.7, 1H, ClCCH), 6.78 (dd, J = 7.8 and 1.7, 1H, Ar), 5.42 (td, J = 5.9 and 1.5, 1H, H₃CC=CH), 2.23 (s, 3H, Ar-CH₃), 1.99 (d, J = 1.5, 3H, HC=CCH₃), 1.75 (m, 2H, C=CHCH₂), 1.52 (m, 2H, HOCCH₂), and 1.39 (s, 6H, HOC(CH₃)₂).

**¹³C NMR** (75 MHz, CDCl₃): 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)\textsuperscript{36}

![Chemical Reaction]

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, 250.3 mmol, 100%).

\textsuperscript{1}HNMR (500 MHz, CDCl\textsubscript{3}): $\delta$ 7.35 (s, 1H, ArH), 7.27 (d, $J = 7.0$, 1H, ArH), 7.19 (t, $J = 7.0$, 1H, ArH), 6.92 (d, $J = 7.0$, 1H ArH), 2.33 (s, 3H, Ar-CH\textsubscript{3}), and 2.17 (s, 3H, OCCH\textsubscript{3}).
Preparation of 1-(4-amino-2-methylphenyl)ethanone (98a)\textsuperscript{38}

![Chemical Structure](image)

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\textsubscript{2}Cl\textsubscript{2} (206.5 mL) were added. Stirring was initiated and AlCl\textsubscript{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\textsubscript{2}Cl\textsubscript{2}, washed with water and 10\% NaOH until the pH of the aqueous layer was approximately 8. The organic layer was dried over Na\textsubscript{2}SO\textsubscript{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\textsubscript{2}SO\textsubscript{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.

**¹HNMR** (500 MHz, CDCl₃): δ 7.66 (d, J = 8.0, 1H, OCCC'), 6.50 (d, J = 8.0, 1H, H₂NCC'), 6.48 (s, 1H, CH₃CC'), 4.00 (s, 2H, NH₂), 2.53 (s, 3H, H₃CCO), and 2.51 (s, 3H, H₃C-Ar).

**¹³CNMR**: (125 MHz, CDCl₃): 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 Na₂SO₄. 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.

**¹H NMR** (500 MHz, CDCl₃): δ 8.07 (s, 1H, ICC₃H), 6.54 (s, 1H, H₂NCC₃H), 4.46 (s, 2H, NH₂), 2.50 (s, 3H, OCCH₃), and 2.47 (s, 3H, Ar-C H₃).

**¹³C NMR** (75 MHz, CDCl₃): 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\textsubscript{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\textsubscript{3} (100 mL), and aq. half sat. brine (125 mL). The combined organic layers were dried over MgSO\textsubscript{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%).

\textbf{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\textsuperscript{-1}.

\textbf{\textsuperscript{1}HNMR} (500 MHz, CDCl\textsubscript{3}): δ 8.09 (s, 1H, ICC\textsubscript{H}), 7.53 (s, 1H, BrCC\textsubscript{H}), 2.55 (s, 3H, O=CC\textsubscript{H}), and 2.44 (s, 3H, BrCCHCC\textsubscript{H}).

\textbf{\textsuperscript{13}CNMR} (75 MHz, CDCl\textsubscript{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 Pd₂(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.

**¹H NMR** (500 MHz, CDCl₃): δ 7.48 (s, 1H, BrCCH), 7.40 (s, 1H, ClCCH), 5.52 (tq, J = 6.5 and 1.5, 1H, C=CH), 2.56 (s, 3H, OCH₃), 2.47 (s, 3H, Ar-CH₃), 1.93 (d, J = 1.5, 3H, HC=CH₃), 1.82 (m, 2H, C=CHCH₂), 1.26 (t, J = 6.5, 2H, HOCH₂), and 1.12 (s, 6H, HOC(CH₃)₂).

**¹³C NMR** (75 MHz, CDCl₃): 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-2H-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** (Cl, 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\(^{-1}\).

\(^1\)H\(\text{NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 7.50 (s, 1H, OCC\(_2\)H), 7.21 (s, 1H, ClCC\(_2\)H), 5.52 (tq, \(J = 1.5\) and 7.0, 1H, C=C\(_2\)H), 2.58 (s, 3H, Ar-CH\(_3\)), 2.51 (d, \(J = 1.5\), 3H, HC=C\(_3\)H), 2.03 (m, 2H, C=CH\(_2\)), 1.54 (t, \(J = 7.0\), 2H, HOCH\(_2\)), and 1.14 (s, 6H, OC(CH\(_3\))\(_2\)).

\(^{13}\)C\(\text{NMR}\) (75 MHz, CDCl\(_3\)): \(\delta\) 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)\textsuperscript{44}

![chemical structure of prop-1-en-2-ylboronic acid (117)](image)

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 °C, 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\textsubscript{4}, filtered, and concentrated \textit{in vacuo} to give 117 (2.385 g, 27.00 mmol, 45%).

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

\textbf{\textsuperscript{1}HNMR} (300 MHz, CDCl\textsubscript{3}): \(\delta\) 6.14 (s, 1H, C=CH\textsubscript{2}), 5.85 (s, 1H, C=CH\textsubscript{2}), 1.90 (s, 3H, CCH\textsubscript{3}), and 1.85 (s, 2H, OH).

\textbf{\textsuperscript{13}CNMR} (75 MHz, CDCl\textsubscript{3}): \(\delta\) 129.1, 110.0, and 20.7.
Preparation of diisopropyl prop-1-en-2-ylboronate (114)

\[
\begin{array}{c}
\text{OH} \quad \text{B} \quad \text{O} \quad \text{Pr} \\
\text{HO} \quad \text{C}_6\text{H}_6 \quad \text{O} \quad \text{Pr}
\end{array}
\]

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\(^{-1}\).

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

\(^{13}\)\text{CNMR} (75 MHz, CDCl\(_3\)): \(\delta\) 133.0, 122.9, 64.7, 24.3, and 21.2.
Preparation of dibutyl prop-1-en-2-ylboronate (118)\textsuperscript{45}

\[
\begin{array}{c}
\text{O} & \text{Me} & \text{B} & \text{MeO} \\
\text{OMe} & 116 & \rightarrow & \text{BuOH} & \text{BuO} & \text{B} & \text{OBu} \\
\text{MgBr} & \text{Ether} & & & & & 118
\end{array}
\]

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. H₂O (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. H₃PO₄ (1.4 mL) in H₂O (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. NaHCO₃ 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\textsuperscript{-1}. 

88
$^1$HNMR (300 MHz, CDCl$_3$): 5.48 (s, 1H, C=CH$_2$), 5.26 (s, 1H, C=CH$_2$), 3.89 (t, $J$ = 6.5, 2H, OCH$_2$), 1.56 (m, 4H, (OCH$_2$CH$_2$)$_2$), 1.37 (m, 4H, (OCH$_2$CH$_2$CH$_2$)$_2$), and 0.95 (td, $J$ = 7.0 and 1.2, 6H, (CH$_2$CH$_3$)$_2$).

$^{13}$CNMR (75 MHz, CDCl$_3$): 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-2H-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 CH₂Cl₂ (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.

**¹H NMR** (300 MHz, CDCl₃): 6.52 (s, 1H, C=CH), 4.03 (t, J = 6.5, 2H, BOCH₂), 2.27 (m, 2H, OCH₂CH₂), and 1.78 (s, 3H, CH₃).
Preparation of (Z)-4-phenylpent-3-en-1-ol (122)

![Reaction Diagram]

Notebook Entry: CAEA197.

A 10 mL screwcap vial was charged with tetrakis(triphenylphosphine) palladium (0) (81 mg, 0.070 mmol, 10 mol%) and K₃PO₄ (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 °C 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 Na₂SO₄, 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%).

**Rₛ:** 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.

**¹H NMR** (300 MHz, CDCl₃) δ: 7.32 (m, 2H, ArH), 7.25 (m, 1H, Ar-H), 7.20 (m, 2H, ArH), 5.47 (tq, J = 8.0 and 1.5, 1H, C=CH), 3.61 (t, J = 7.3, 2H, HO-CH₂), 2.25 (dt, J = 8.0, 7.3, 2H, CHCH₂), 2.06 (d, J = 1.5, 3H, -CH₃), and 1.53 (s, 1H, -OH).
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 MgSO₄. 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.

**¹HNMR** (500 MHz, CDCl₃): δ 5.42 (s, 1H, C=CH₂), 5.19 (s, 1H, C=CH₂), 4.33 (sept, J = 6.0, 2H, OCH), 1.83 (s, 3H, CCH₃), and 1.12 (d, J = 6.0, 12H, (CH(CH₃)₂)_2).

**¹³CNMR** (CDCl₃, 75 MHz): δ 133.0, 122.9, 64.7, 24.3, and 21.2.
Preparation of 2-chloro-2-methylpropanal (130)\textsuperscript{49}

\[
\begin{align*}
\text{129} & \xrightarrow{\text{SO}_2\text{Cl}_2} \text{130}
\end{align*}
\]

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 \textbf{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 °C and 40 °C. The drying tube was connected to an acid trap, and the solution was refluxed for 2 h. Distillation (b.p. 86 °C at 760 mm Hg) resulted in \textbf{130} (39.188 g, 370.05 mmol, 74%).

\textsuperscript{1}HNMR (300 MHz, CDCl\textsubscript{3}): \delta 9.35 (s, 1H, OCH), and 1.55 (s, 6H, C(CH\textsubscript{3})\textsubscript{2}).
Preparation of 2-chloro-2-methylhex-5-en-3-ol (131)\textsuperscript{50}

\[
\begin{align*}
\text{H} & \quad \text{Cl} \\
\begin{array}{c}
\text{O} \\
130
\end{array} & \quad \text{THF} & \quad \begin{array}{c}
\text{OH} \\
131
\end{array}
\end{align*}
\]

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 °C 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 °C for another hour. The reaction was quenched with 10% H\textsubscript{2}SO\textsubscript{4}, and a white gel was formed. To dissolve the white gel, 6 M H\textsubscript{2}SO\textsubscript{4} (25 mL) was added with vigorous stirring. The aqueous layer was extracted with ether (2 \times 100 mL). The combined organic layers were washed sat. aq. NaCl (2 \times 50 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. The drying agent was filtered off, and the solution was concentrated \textit{in vacuo}. Distillation (b.p. 80 °C at 15 mm Hg) gave 131 (1.985 g, 13.50 mmol, 18%).

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

\textbf{\textsuperscript{1}HNMR} (300 MHz, CDCl\textsubscript{3}): δ 5.91 (dddd, \textit{J} = 17.0, 10.6, 7.6 and 6.5, 1H, H\textsubscript{2}C=CH), 5.15 (m, 2H, HC=CH\textsubscript{2}), 3.60 (dd, \textit{J} = 9.9 and 2.4, 1H, HOCH), 2.51 (m, 1H, CHCH\textsubscript{2}), 2.18 (m, 1H, CHCH\textsubscript{2}), 1.61 (s, 3H, CH\textsubscript{3}), and 1.58 (s, 3H, CH\textsubscript{3}).

\textbf{\textsuperscript{13}CNMR} (75 MHz, CDCl\textsubscript{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. NH₄Cl (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 Na₂SO₄, 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%).

Rᶠ = 0.45 in 6:1 hexanes : EtOAc

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

**¹H NMR** (300 MHz, CDCl₃): δ 5.70 (dddd, J = 16.2, 9.9, 8.1, and 5.7, 1H, H₂C=CH), 5.09 (m, 2H, HC=CH₂), 2.58 (m, 1H, CH₂), 2.36 (m, 1H, CH₂), 2.08 (s, 3H, O=CC₃H₃), 1.97 (s, 1H, HOCH), 1.57 (s, 3H, CH₃), and 1.55 (s, 3H, CH₃).

**¹³C NMR** (125 MHz, CDCl₃): 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)\textsuperscript{51}

![Chemical Reaction Diagram]

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\(_3\)) \(\delta\): 3.99 (s, 1H, CH), 3.56 (s, 6H, (OCH\(_3\))\(_2\)), 2.22 (s, 1H, OH), and 1.18 (s, 6H, (CH\(_3\))\(_2\)).

**\(^{13}\)CNMR** (125 MHz, CDCl\(_3\)) \(\delta\): 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. NH₄Cl. Water was added to dissolve the precipitate that had formed during quenching. The solution was poured into a separatory funnel with sat. aq. NH₄Cl (250 mL), and extracted with pentane (3 × 125 mL). The combined organic layers were dried over MgSO₄, 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.

**¹H NMR** (500 MHz, CDCl₃): δ 5.17 (t of septets, J= 6.5 and 1.5, 1H, C=CH), 2.93 (d, J= 6.5, 2H, CH₂), 1.71 (s, 3H, C-CH₃), 1.62 (s, 3H, C-CH₃), and 0.15 (s, 9H, Si(CH₃)₃).

**¹³C NMR** (125 MHz, CDCl₃): 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-yn-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 (1.00 g, 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 Na₂S₂O₅. 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 Na₂SO₄. 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.

**¹HNMR** (500 MHz, CDCl₃): 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, CH₂), 2.45 (dd, J= 16.5 and 8.5, 1H, CH₂), 2.37 (s, 1H, OH), 1.25 (s, 3H, CCH₃), 1.19 (s, 3H, CCH₃), and 0.17 (s, 9H, Si(CH₃)₃).

**¹³CNMR** (125 MHz, CDCl₃): δ 103.7, 88.1, 75.4, 72.4, 26.4, 24.4, 23.8, and 0.00.

**Combustion**: Calculated for C₁₀H₂₀O₂Si: C, 59.95; and H, 10.06. Found: C, 60.04; and H, 10.13.
**Preparation of 2-methyl-6-(trimethylsilyl)hex-5-yn-2,3-diol with “homemade” AD-mix β (138)**

![Chemical Structures](image)

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)

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$_2$CO$_3$ (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$_2$O 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$_2$SO$_4$, 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, CH), 2.63 (d, $J$=4.2, 1H, OH), 2.45 (dd, $J$= 3.6 and 2.5, CH$_2$), 2.41 (dd, $J$= 8.7 and 2.5, 1H, CH$_2$), 2.22 (s, 1H, OH), 2.09 (t, $J$= 3.0, 1H, HC≡C), 1.26 (s, 3H, CH$_3$), and 1.19 (s, 3H, CH$_3$).

$^{13}$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)

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=CH), 5.16 (m, 2H, CH$_2$), 3.43 (dd, $J$= 10.8 and 3.0, 1H, HOCH), 2.38 (m, 1H, CH$_2$), 2.12 (m, 1H, CH$_2$), 1.23 (s, 3H, CH$_3$), and 1.18 (s, 3H, CH$_3$).

$^{13}$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)

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 CH₂Cl₂ (1.4 mL) yielded 142 (22 mg, 0.35 mmol, 70%) as a brown oil.

\[
\text{BuO}^-\text{B} \quad \text{118} \quad \text{OH} \quad \text{141} \quad \text{Grubbs G1} \quad \text{CH}_2\text{Cl}_2 \quad \text{142}
\]

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, CDCl₃): δ 7.31 (m, 5H, ArH), 6.52 (s, 1H, C=CH), 5.09 (t, J= 1.0, 1H, OCH), 4.39 (s, 1H, OH), 2.41 (m, 2H, C=CHCH₂), and 1.82 (d, J = 1.5, 3H, CC₃H₃).

\(^{13}\)CNMR (125 MHz, CDCl₃): δ 143.9, 128.4, 127.5, 125.7, 76.0, 36.6, and 18.6.

Combustion: Calculated for C₁₁H₁₃BO₂: 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)\textsuperscript{59}

![Reaction Scheme]

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)\textsubscript{3}]PF\textsubscript{6} (757 mg, 1.50 mmol, 2 mol\%) and CH\textsubscript{2}Cl\textsubscript{2} (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\textsuperscript{-1}.

\textsuperscript{1}HNMR (500 MHz, CDCl\textsubscript{3}): δ 6.37 (tq, J = 4.5 and 1.5, 1H, C=CH), 3.91 (t, J=5.5, 2H, OCH\textsubscript{2}), 2.22 (tdq, J = 5.5, 4.5, and 1.5, 2H, CHCH\textsubscript{2}), 1.71 (dt, J= 5.5and 1.5, 3H, CCH\textsubscript{3}), and 0.18 (s, 6H, Si(CH\textsubscript{3})\textsubscript{2}).

\textsuperscript{13}CNMR (125 MHz, CDCl\textsubscript{3}): δ 140.3, 135.1, 62.2, 30.9, 20.6, and -1.8.

HRMS (CI, NH\textsubscript{3}) Calculated for C\textsubscript{7}H\textsubscript{18}NOSi (M + NH\textsubscript{4}): 160.1158. Found: 160.1161.

Combustion: Calculated for C\textsubscript{7}H\textsubscript{14}OSi: C, 59.09; and H, 9.92. Found: C, 58.84; and H, 9.73.
Preparation of 2-(pent-4-yn-1-yloxy)tetrahydro-2H-pyran (153)$^{59}$

\[
\begin{align*}
\text{DHP} & \quad \text{HCl} \\
\text{152} & \quad \text{153}
\end{align*}
\]

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$^{-1}$.

$^1$**HNMR** (300 MHz, CDCl$_3$): \( \delta 4.61 \) (t, \( J = 4.2 \), 1H, OCHO), 3.87 (m, 2H, OCH$_2$), 3.50 (m, 2H, OCH$_2$), 2.34 (td, \( J = 6.3 \) and 3.6, CCH$_2$), 1.95 (t, \( J = 3.0 \), 1H, C=CH), 1.84 (m, 4H, H$_2$CCH$_2$ and OCHCH$_2$), and 1.54 (m, 4H, OCH$_2$CH$_2$ and OCH$_2$CH$_2$CH$_2$).

$^{13}$**C 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)**

![Chemical reaction](image)

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$_2$Cl$_2$ (50 mL), washed with brine (2 × 45 mL), dried over Na$_2$SO$_4$, 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$_2$CO$_3$ (2 × 25 mL), brine (2 × 25 mL), dried over Na$_2$SO$_4$, 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$_3$): $\delta$ 3.74 (t, $J$ = 6.0, 2H, HOCH$_2$), 2.25 (m, 2H, CCH$_2$), 2.10 (s, 1H, OH), 1.77 (t, $J$ = 2.4, 3H, CCH$_3$), and 1.73 (quintet, $J$ = 6.6, 2H, H$_2$CCH$_2$).

$^{13}$CNMR (75 MHz, CDCl$_3$): $\delta$ 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)\(^{59}\)

\[
\text{155} \xrightarrow{1) \text{HN(HSiMe}_2\text{)}_2, 80^\circ\text{C, 2h}} \text{147}
\]

Notebook Entry: CAEB191

General procedure B for the cyclization to form vinyl siloxanes was followed. Alcohol 155 (2.454 g, 25.00 mmol), tetramethyldisilane (8.86 mL, 50.0 mmol), [Cp*Ru(NCMe)_3]PF_6 (0.315 g, 0.625 mmol, 2.5 mol%) and CH_2Cl_2 (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): \(\delta\) 6.28 (t, \(J = 5.7\), 1H, C=CH), 3.89 (t, \(J = 5.4\), 2H, OCH\(_2\)), 2.31 (q, \(J = 5.4\), 2H, CHCH\(_2\)), 1.82 (quintet, \(J = 6.0\), 2H, OCH\(_2\)CH\(_2\)), 1.72 (t, \(J = 1.8\), 3H, CCH\(_3\)), and 0.20 (s, 6H, Si(CH\(_3\))\(_2\)).

**\(^13\)CNMR** (125 MHz, CDCl\(_3\)): \(\delta\) 141.9, 137.5, 64.5, 30.9, 28.7, 22.6, and -1.1.

**HRMS** (Cl, 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)\textsuperscript{60}

\[
\begin{array}{c}
\text{MeO} \quad \text{I} \\
\text{156} \quad \text{ICl} \\
\text{Et}_2\text{O} \quad \text{CH}_2\text{Cl}_2 \\
\text{MeO} \quad \text{OMe} \\
\text{146}
\end{array}
\]

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\textsubscript{2}Cl\textsubscript{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\textsubscript{3} (7.4 g), and sat. aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{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\textsubscript{3} (2.223 g) and Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (2 × 75 mL), and dried over Na\textsubscript{2}SO\textsubscript{4}. The mixture was filtered and concentrated\textit{ 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.

\textsuperscript{1}HNMR (500 MHz, CDCl\textsubscript{3}): δ 7.17 (s, 1H, ArH), 6.70 (s, 1H, ArH), 3.81 (s, 3H, OCH\textsubscript{3}), 3.77 (s, 3H, OCH\textsubscript{3}), and 2.19 (s, 3H, ArCH\textsubscript{3}).

\textsuperscript{13}CNMR (125 MHz, CDCl\textsubscript{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, 0.025 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.

**¹HNMR** (500 MHz, CDCl₃): δ 6.74 (s, 1H, ArH), 6.52 (s, 1H, ArH), 5.50 (tq, J = 7.3 and 1.5, 1H, C=CH), 3.78 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 3.57 (t, J = 6.4, 2H, OCH₂), 2.23 (s, 3H, ArCH₃), 1.98 (d, J = 1.5, 3H, CCH₃), 1.93 (tdq, J = 7.3, 6.5, and 1.0, 2H, CHCH₂), 1.84 (s, 1H, OH), and 1.59 (quintet, J = 6.5, 2H, CH₂CH₂).

**¹³CNMR** (125 MHz, CDCl₃): 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.


**Combustion** : Calculated for C₁₅H₂₂O₃: C, 71.97; and H, 8.86. Found: C, 72.23; and H, 8.64.
Preparation of 1,2-di(pyridin-2-yl)diselenide$^{69}$

\[
\begin{align*}
\text{MgCl} & \quad \text{Se} \\
\text{THF} & \\
\end{align*}
\]

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$_2$SO$_4$, 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%).

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, NCH), 7.77 (d, \(J = 7.9\), 1H, CCH), 7.54 (td, \(J = 7.9\), and 1.8, 1H, NCHCH), and 7.08 (td, \(J = 4.3\), and 1.2, 1H, CCHCH).

\(^{13}\)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)

![Chemical Structure](image)

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 CH₂Cl₂ (50 mL). The filtrate was concentrated in vacuo to give crude intermediate. The intermediate was taken up in dry CH₂Cl₂ (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 ¹H NMR. When the reaction was complete, the mixture was stirred with sat. aq. NaHCO₃ (2 mL) for 1 hour. The aqueous layer was extracted with CH₂Cl₂ 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%).
$^1\text{HNMR}$ (500 MHz, CDCl$_3$): δ 6.73 (s, 1H, ArH), 6.54 (s, 1H, ArH), 5.72 (ddt, $J = 16.5, 10.0,$ and 6.5, 1H, H$_2$C=CH), 5.46 (td, $J = 7.6,$ and 1.8, 1H, C=CH), 4.97 (m, 2H, HC=CH$_2$), 3.76 (s, 3H, OCH$_3$), 3.75 (s, 3H, OCH$_3$), 2.61 (t, $J = 6.5,$ 2H, CH$_2$), 2.22 (s, 3H, ArCH$_3$), and 2.01 (s, 3H, CCH$_3$).

$^{13}\text{CNMR}$ (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)

![Chemical Structure]

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•3H2O (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 PdBr2 (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 H2O. The aqueous layer was extracted with CH2Cl2 (3 × 15 mL), and the combined organic layers were dried over Na2SO4, 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.

**¹HNMR** (300 MHz, CDCl3): δ 7.13 (d, J= 8.8, 2H, Ar-H), 6.87 (d, J= 8.8, 2H, Ar-H), 5.44 (m, 1H, C=CH), 3.81 (s, 3H, OCH₃), 3.61 (t, J = 6.5, 2H, HOCH₂), 2.26 (q, J= 6.5, 2H, HCCCH₂), and 2.04 (d, J= 1.2, 3H, CCH₃).

**¹³CNMR** (75 MHz, CDCl3): 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 C₁₂H₁₆O₂: 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 CH₂Cl₂ (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, Na₂S₂O₃ (0.250 g) was dissolved in sat. aq. NaHCO₃ (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 MgSO₄. 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.

¹HNMR (500 MHz, CDCl₃): δ 9.64 (t, J = 1.5, 1H, O=CH), 7.08 (d, J = 8.8, 2H, ArH), 6.89 (d, J = 8.8, 2H, ArH), 5.56 (tq, J = 7.3, and 1.3, 1H, C=CH), 3.81 (s, 6H, OCH₃), 3.14 (d, J = 7.3, 2H, OCCH₂), and 2.09 (d, J = 1.3, 3H, CCH₃).
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$_3$): $\delta$ 6.73 (s, 1H, ArH), 6.53 (s, 1H, ArH), 5.51 (t, $J = 7.5$, 1H, C=CH), 3.78 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 3.56 (t, $J = 6.0$, 2H, HOCH$_2$), 2.23 (s, 3H, ArCH$_3$), 2.10 (q, $J = 6.0$, 2H, CHCH$_2$), and 2.00 (s, 3H, CCH$_3$).

$^{13}$**CNMR** (75 MHz, CDCl$_3$): $\delta$ 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)

![Chemical structure of 149 and 148 with reagents](image)

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 CH2Cl2 (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\(^{-1}\).

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)):\(\delta\) 9.61 (t, \(J = 1.5\) Hz, 1H, CHO), 6.73 (s, 1H, ArH), 6.50 (s, 1H, ArH), 5.68 (tq, 7.3 and 1.5, 1H, C=CH), 3.77 (s, 3H, OCH\(_3\)), 3.74 (s, 3H, OCH\(_3\)), 2.98 (dd, \(J = 7.5\) and 1.5, 2H, O=CH\(_2\)), 2.23 (s, 3H, Ar-CH\(_3\)), and 2.08 (d, \(J = 1.5\) Hz, 3H, CCH\(_3\)).

**\(^{13}\)C NMR** (125 MHz, CDCl\(_3\)):\(\delta\) 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.

Preparation of \((Z)-1-(\text{hexa-2,5-dien-2-yl})-2,5\text{-dimethoxy-4-methylbenzene (144)}\)

![Reaction Scheme]

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 \(-78^\circ\text{C}\). 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 \(-78^\circ\text{C}\). 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 \(\text{H}_2\text{O}\), and the aqueous layer was extracted with ether (3 \(\times\) 15 mL). The organic layers were washed with brine (3 \(\times\) 15 mL), dried over \(\text{MgSO}_4\), filtered and concentrated \textit{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.

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

\textbf{\(^1\text{H}NMR\) (500 MHz, CDCl\(_3\))}: \(\delta\) 6.73 (s, 1H, ArH), 6.54 (s, 1H, ArH), 5.72 (ddt, \(J = 16.5, 10.0, \text{and 6.5, 1H, H}_2\text{C}=\text{CH}\)), 5.46 (td, \(J = 7.6, \text{and 1.8, 1H, C}=\text{CH}\)), 4.97 (m, 2H, HC=CH\(_2\)), 3.76 (s, 3H, OCH\(_3\)), 3.75 (s, 3H, OCH\(_3\)), 2.61 (t, \(J = 6.5, 2\text{H, CH}_2\)), 2.22 (s, 3H, ArCH\(_3\)), and 2.01 (s, 3H, CCH\(_3\)).
$^{13}$CNMR (75 MHz, CDCl$_3$): $\delta$ 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 (Cl+) 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\textit{E}, 5\textit{Z})-6-(2,5-dimethoxy-4-methylphenyl)-2-methylhepta-2,5-dienal (143)

![Chemical structure diagram]

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$_2$Cl$_2$ (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 \textit{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.

\textbf{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$_3$): $\delta$ 9.36 (s, 1H, CHO), 6.74 (s, 1H, ArH), 6.51 (s, 1H, ArH), 6.43 (tq, $J$ = 7.3 and 1.5, 1H, C=CH), 5.53 (tq, $J$ = 7.3 and 1.5, 1H, C=CH), 3.77 (s, 3H, OCH$_3$), 3.76 (s, 3H, OCH$_3$), 2.89 (t, $J$ = 7.3, 2H, CH$_2$), 2.24 (s, 3H, ArCH$_3$), 2.02 (d, $J$ = 1.0, 3H, CCH$_3$), and 1.59 (d, $J$ = 1.0, 3H, CCH$_3$).

$^{13}$CNMR (125 MHz, CDCl$_3$): $\delta$ 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.


\textbf{Combustion}: Calculated for C$_{16}$H$_{20}$O$_3$: C, 73.82; and H, 7.74. Found: C, 74.09; and H, 7.53.


42. CAS #99604-67-8, Strem catalogue #44-7880. 1g for $333, Strem Catalogue No 22. 2008-2010.
46. McNulty, L. Butler University, Indianapolis, IN. Personal communication, 2009.


