2013

Diastereoselective intramolecular carbonyl hydrosilation for complex polyketide synthesis

Casey R. Medina
Western Washington University

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Diastereoselective Intramolecular Carbonyl Hydrosilation for Complex Polyketide Synthesis

By

Casey R. Medina

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

Kathleen L. Kitto, Dean of the Graduate School

Advisory Committee

Chair, Dr. Gregory W. O’Neil

Dr. Amanda Murphy

Dr. John D. Gilbertson
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Casey Medina
May 10th, 2013
Diastereoselective Intramolecular Carbonyl Hydrosilation for Complex Polyketide Synthesis

A Thesis
Presented to
The Faculty of
Western Washington University

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

By
Casey R. Medina
May 2013
Abstract

It has been found that β-hydroxyketone compounds can be reduced to the corresponding 1,3-diol through an intramolecular carbonyl hydrosilation. Furthermore, because this hydrosilation proceeds through a cyclic 6-membered ring transition state, this reduction can be performed diastereoselectively by placing a stereocenter on the 6-membered ring transition state. Prior to further investigations into this diastereoselective intramolecular carbonyl hydrosilation, a streamlined synthesis of β-hydroxyketone compounds has been developed. This new synthesis features an enone diboration/oxidation sequence found to be successful on a broad scope of enones in high yields. Further studies have shown that placing a stereocenter outside of the transition state ring invokes moderate levels of diastereoselectivity based on the Felkin-Ahn model of carbonyl addition. However, when stereocenters are placed both inside and outside of the transition state ring, as in the case of the matched and mismatched hydrosilations, diastereoselectivity is based solely off of the stereocenter inside of the transition state ring. This stereocontrol allows for the synthesis of antipropionate subunits with both anti-syn and syn-syn stereochemistry. The synthetic utility of this hydrosilation is shown by using this reaction to synthesize the stereocenters present in the highly studied natural product discodermolide.
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Research Advisor: Dr. Gregory W. O’Neil

Thesis Committee Members: Dr. Amanda Murphy
Dr. John D. Gilbertson

Project Contributors: Kyle Carter, Michael Miller, Josh Sears

Research Group Members: Elle Britton, Noah Burlow, Josh Corliss, Aaron Culler, Nathan Drake, Monika Grasso, Brianne King, Iris Phan, Sara Schaefer, Steven Swick, John Williams

Instrument Technicians: Charles Wandler
Dr. Hla Win-Piazza

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Western Washington University Department of Chemistry
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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>Deuterated chloroform</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic Acid</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>er</td>
<td>Enantiomeric ratio</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Et₂O</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>'Pr</td>
<td>iso-Propyl</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium Diisopropylamide</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>mL</td>
<td>Millileter(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole(s)</td>
</tr>
<tr>
<td>MP</td>
<td>Melting point</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>MTBE</td>
<td>Methyl tert-butyl ether</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>NHC</td>
<td>N-Heterocyclic Carbene</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>PG</td>
<td>Protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>Ph₂SiHCl</td>
<td>Chlorodiphenylsilane</td>
</tr>
<tr>
<td>PMB</td>
<td>p-Methoxybenzyl</td>
</tr>
<tr>
<td>PPh₃</td>
<td>Triphenylphosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Sat.</td>
<td>Saturated</td>
</tr>
<tr>
<td>SM</td>
<td>Starting material</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer chromatography</td>
</tr>
<tr>
<td>B₂cat₂</td>
<td>Bis(catecholato)diboron</td>
</tr>
</tbody>
</table>

![B₂cat₂ Image]

![Bcat Image]
$\text{B}_2\text{pin}_2$  Bis(pinacolato)diboron

$\text{Bpin}$

$\text{ICy}$  1,3-Dicyclohexylimidazol
1. Carbonyl Reduction

The reduction of a carbonyl to a primary or secondary alcohol is a commonly used reactions in organic synthesis. Many molecules, from simple precursor molecules to complex natural products and drugs contain alcohol functional groups. Reducing a carbonyl is a very common technique to install this alcohol functionality. A carbonyl reduction can be seen as adding a molecule of H\_2 across the carbon oxygen double bond (Scheme 1-1). This type of reduction is called a hydrogenation and is usually performed in the presence of a catalyst such as palladium or nickel with a carbon support.\(^1\) A reduction is usually signified by placing ‘[H]’ above the reaction arrow (Scheme 1-1).

Scheme 1-1. Carbonyl hydrogenation with a palladium or nickel catalyst on a carbon support

\[
\text{O} \quad \text{R}^1 \quad \text{R}^2 \quad + \quad \text{H}_2 \quad \rightarrow \quad \text{O}^\text{H} \quad \text{R}^1 \quad \text{R}^2
\]

1.1 Metal Hydride Reduction of Carbonyls

A more commonly used technique for the reduction of a carbonyl is the addition of a hydride to the carbonyl followed by protonation of the oxygen (Scheme 1-2).\(^1\) A hydride is a hydrogen atom with two electrons and a formal negative charge. Many hydride sources have been developed for this purpose. Examples of commonly used hydride sources are lithium aluminum hydride (LiAlH\_4), sodium borohydride (NaBH\_4), and lithium borohydride (LiBH\_4).\(^2\) The mechanism for this type of reduction starts with the hydride adding into the carbonyl carbon. This pushes the electrons from the pi bond of the carbonyl onto the oxygen
creating an oxygen anion. The next step is the protonation of the oxygen anion through an aqueous workup to create the desired alcohol (Scheme 1-2).^1

**Scheme 1-2.** Hydride reduction of a carbonyl with mechanism

The hydride species used in these reductions are often very reactive, containing a formal negative charge on the metal delivering the hydride.\(^2\) These reactive hydride species can often cause difficulty when trying to reduce a carbonyl on a molecule with other functional groups present. It is important to take into consideration whether the other functional group will be reduced as well. An example of this is the attempted reduction of cyclopent-2-enone 1 to cyclopent-2-en-1-ol 3 using NaBH\(_4\) as the reducing agent. Rather than only reducing the carbonyl, NaBH\(_4\) is capable of reducing alkenes as well, so the substrate is reduced at both the carbonyl and the alkene yielding cyclopentanol 2 as the product (Scheme 1-3).\(^3\)

**Scheme 1-3.** Unselective reduction of cyclopent-2-enone

\(^1\) Trends in Chemistry (2023).
It is important to know which reducing agent to use with complex molecules containing multiple functional groups. Table 1-1 shows a few common reducing agents along with the functional groups that they are capable of reducing. Lithium aluminum hydride (LiAlH$_4$) is the strongest reducing agent of the reagents shown. It is able to reduce all carbonyl groups as well as other function groups. Sodium borohydride (NaBH$_4$) and lithium borohydride (LiBH$_4$) are structurally very similar, but switching cations from sodium to lithium increases the reducing ability of LiBH$_4$ in certain polar solvents such as tetrahydrofuran (THF) and diethylether (Et$_2$O). Borane (BH$_3$) is commonly used as its THF- or Me$_2$S- derivative and is often used to reduce carboxylic acids and amides. Borane itself is unable to reduce amides, but when the borane complexes with another reagent such as tetrahydropyran it is then capable of the reduction. Borane is also commonly used for alkene reductions. DIBAL-H is a useful reagent for reducing carbonyls because of its slightly milder conditions and ability to reduce an ester to its corresponding aldehyde without further reduction.$^2$

Table 1-1. Common reducing agents and their reactivity towards various function groups

<table>
<thead>
<tr>
<th></th>
<th>NaBH$_4$</th>
<th>LiBH$_4$</th>
<th>LiAlH$_4$</th>
<th>BH$_3$</th>
<th>DIBAL-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehyde</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ketone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ester</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Carboxylic acid</td>
<td>✓/−</td>
<td>✓/−</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Cyanide</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkene</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
Some examples of reductions using these reagents are shown below (Scheme 1-4).

The first example demonstrates a sodium borohydride reduction chemoselectively reducing a ketone in the presence of an alkene and two esters. The second example shows an amide being reduced with a borane complex. In this case the borane (BH$_3$) complexes with the reagent, tetrahydropyran, to make the active reducing species. The third example shows the ability of DIBAL-H to reduce esters to aldehydes and stop at the aldehyde without further reduction to the alcohol.

**Scheme 1-4.** Reduction examples with NaBH$_4$, BH$_3$, and DIBAL-H

In the case of both borane and DIBAL-H, the hydride bearing metal is neutrally charged. In order for the hydride to become reactive, the reducing agent must be activated. This activation can be from another reagent in the reaction mixture such as a solvent or from the substrate itself. In the example above (Scheme 1-4), borane is activated by the reagent tetrahydropyran (THP). The oxygen on tetrahydropyran adds into borane giving the boron a
formal negative charge and allowing for transfer of the hydride.\(^5\) DIBAL-H is activated by the substrate (Scheme 1-5). The carbonyl oxygen of the ester adds into the aluminum of DIBAL-H giving it a formal negative charge. The hydride transfers to the carbonyl carbon reducing the carbonyl.\(^2\)

**Scheme 1-5.** Activation of DIBAL-H for reduction

1.2 Biological Hydride Source, NAD(P)H

Carbonyl reductions are also common to a number of important biosynthetic pathways. Nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) or nicotinamide adenine dinucleotide hydrogen (NADH) (Figure 1-1) are coenzymes that provide hydrides for use by the body and other living organisms for biological functions. A coenzyme is a moiety that is used by another enzyme for a certain function, in this case redox reactions. The nicotinamide ring of NAD(P)H is the portion of the molecule that is involved in accepting and releasing the hydride. These coenzymes can be seen in both the reduced form, NAD(P)H, and the oxidized from, NAD(P)\(^+\). These coenzymes are involved in numerous functions throughout metabolism, anabolism, and cell protection. Essentially all of the controlled redox reactions that take place in the body use NAD(P)H as the hydride acceptor or donor. An example of the function of NADPH in fatty acid synthesis is shown below (Scheme 1-6).\(^7\)
Figure 1-1. Structure of NADPH and NADH in both their reduced and oxidized form

Scheme 1-6. The role of NADPH in fatty acid synthesis

β-Ketothioester 4 is an intermediate in fatty acid biosynthesis. In the next step of this pathway, the reduced NADPH donates a hydride from the nicotinamide ring by pushing the lone pair of electrons on nitrogen up around the ring and forcing off the hydride which adds to the ketone of 4 to create β-hydroxythioester 5 and the oxidized NADP⁺.
1.3 Stereoselective Reduction of Carbonyls

It is also possible to reduce a carbonyl stereoselectively. Stereoselective reductions result in either a single enantiomer or diastereomer product. One example of a diastereoselective reduction with L-selectride is shown below (Scheme 1-5). L-Selectride, or lithium tri(sec-butyl)borohydride (Li(s-Bu)_3BH), is a bulky hydride source, it contains three large sec-butyl groups attached to the boron, creating a very hindered hydride. This steric bulk allows the hydride to be selectively delivered to the least sterically hindered side of the molecule. In the archazolid western hemisphere synthesis, five different reducing agents were tested to determine which gave the highest selectivity and yield (Table 1-2). It was found that L-selectride would selectively add its hydride to one side of the ketone on 6 over the other giving the proper western hemisphere 7 in a 10:1 ratio (Scheme 1-7). A method for predicting this stereo control will be described in the next section.

Scheme 1-7. Example of L-selectride reduction
Table 1-2. Diastereoselectivity and yields of various reducing agents

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diastereoselectivity</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaBH₄</td>
<td>3.1:1</td>
<td>78%</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>3.3:1</td>
<td>72%</td>
</tr>
<tr>
<td>LiAlH₄</td>
<td>3.1:1</td>
<td>64%</td>
</tr>
<tr>
<td>LiB(Et)₃H</td>
<td>20:1</td>
<td>46%</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>10:1</td>
<td>73%</td>
</tr>
</tbody>
</table>

DIP-Cl is a chiral reducing agent that can be obtained as both the (+) and (-) enantiomer. When used to reduce a carbonyl, the stereochemistry of the alcohol product obtained depends on which enantiomer of DIP-Cl is used. The isopinocampheyl group on the boron is derived from the natural product α-pinene (Scheme 1-8). α-Pinene can be isolated from pine resin as well as resin’s from other coniferous plants and even a few non-coniferous plants. It occurs naturally in both the (+) and (-) enantiomers. Either (+) or (-) DIP-Cl is synthesized depending on which α-pinene enantiomer is used. In this example (Scheme 1-8), the ketone of 8 is reduced using the (-) enantiomer of DIP-Cl to give the proper enantiomer of Singulair 9.
These are just a few examples of the methods used to reduce carbonyls. There are many different techniques to reduce carbonyls enantioselectively, diastereoselectively, chemoselectively, under both mild and harsh conditions. The method chosen to reduce a carbonyl is very substrate dependent. A reagent that is successful on one substrate may not work as well on another if it has different functional groups or is less stable. It is important to note that the majority of metal hydride carbonyl reductions proceed under harsh conditions that could be detrimental to less stable substrates. This is especially a concern when it comes to natural product synthesis, where fragments may become less stable and more reactive as more functional groups are added.

1.4 Predicting Stereochemistry for Diastereoselective Reductions

A widely used model to predict the diastereoselectivity of nucleophilic attack to a carbonyl is the Felkin-Ahn model. The Felkin-Ahn model has been refined over the years including computational analyses by Ahn and Einstein. An important addition to this model is the inclusion of the Burgi-Dunitz trajectory of attack where the nucleophile adds to
the carbonyl carbon at an angle of 107° from the oxygen.\textsuperscript{13} The Felkin-Ahn model predicts that a nucleophile, or the hydride in the case of reduction, will add to the carbonyl opposite of the large group and across the small group (Scheme 1-9). Very high diastereoselectivity can be obtained depending on the relative size of the three groups (where $R_L = R_{\text{Large}}$, $R_M = R_{\text{Medium}}$, and $R_S = R_{\text{Small}}$). In this example (Scheme 1-9), $R_L$ is a phenyl group (10) compared to $R_M$ being a methyl group and $R_S$ being a hydrogen and the reduction occurs in a 98:2 ratio of diastereomers favoring the Felkin predicted anti-product 11.\textsuperscript{14}

**Scheme 1-9.** Felkin-Ahn model with example\textsuperscript{14}

The Felkin-Ahn model is not accurate at predicting all nucleophilic additions to carbonyls. In the case of $\alpha$-amino and $\alpha$-hydroxy compounds, the Felkin-Ahn will not always give the correct stereochemistry for the product.\textsuperscript{15} In these compounds, the metal will chelate to the carbonyl and the $\alpha$-amino or $\alpha$-hydroxy group of the molecule creating a five membered ring transition state keeping the carbonyl and the $\alpha$-amino or $\alpha$-hydroxy group eclipsed. The nucleophile will then add to the carbonyl from the side of the smaller group (Scheme 1-10). In the example below, there is an alcohol alpha to the aldehyde in 12. When the nucleophile adds into the aldehyde, the metal chelates to the aldehyde and hydroxyl group in transition state 14 forming a five membered ring. This complex allows the
nucleophile to add into the less hindered side giving the syn-product 13. This model was proposed by Cram in 1959 and is called the Cram Chelate model.\textsuperscript{15}

**Scheme 1-10.** Cram Chelate model with example.
2. Carbonyl Hydrosilation

2.1 Hydrosilation as an alternative to Main Group Metal Hydrides

Hydrosilation is a reduction method using silicon-based hydrides called hydridosilanes, or hydrosilanes. It is a powerful reduction method and can be used to reduce alcohols, aldehydes, ketones, amides, esters, etc. One advantage of using a hydrosilation reduction over other metal mediated reduction methods is that it typically proceeds under much milder conditions. This becomes more important when working with less stable substrates such as in natural product synthesis. Another major benefit of the mild conditions of hydrosilations is that it can selectively reduce a certain functional group in the presence of other sensitive functional groups, such as epoxides, ketals, etc.

Hydridosilanes are organosilicon compounds with at least one silicon-hydrogen bond. They can be called hydridosilanes, hydrosilanes, or simply just silanes. These silanes have properties similar to their hydrocarbon analogs and are generally not as reactive as other metal hydride sources, allowing them to serve as mild air and often water stable hydride sources. The bond strength of the silicon hydrogen bond is slightly weaker than its corresponding carbon hydrogen bond, but essentially the same (Figure 2-1). Trimethylsilane or triethylsilane having bond dissociation energies of 90.3 kcal/mol and 90.1 kcal/mol respectively, compared to the corresponding carbon-hydrogen bond with dissociation energy of about 92 kcal/mol. The most important factor that allows silanes to serve as a hydride source is the difference in electronegativity of silicon and hydrogen vs. carbon and hydrogen. The electronegativity of carbon is 2.5, hydrogen is 2.2 and silicon is 1.9. In
the carbon-hydrogen bond, the bond is polarized towards carbon giving the hydrogen a slight positive charge and causing it to act more as a proton. In the silicon hydrogen bond, the bond is polarized towards hydrogen, giving the hydrogen a slight negative charge and allowing it to act as a hydride source (Figure 2-1).

**Figure 2-1.** Bond dissociation energy and polarity differences between Si-H and C-H

<table>
<thead>
<tr>
<th>Bond Dissociation Energy</th>
<th>Polarity Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si-H</td>
<td>C^5-—H^6+</td>
</tr>
<tr>
<td>90.3 kcal/mol</td>
<td>Si^8+—H^8-</td>
</tr>
<tr>
<td>Si-H</td>
<td>90.1 kcal/mol</td>
</tr>
<tr>
<td>C-H</td>
<td>92 kcal/mol</td>
</tr>
</tbody>
</table>

2.2 General Mechanism

Tetravalent silane reagents are neutral and lack the nucleophilicity that the majority of metal-based reducing agents possess. Therefore, the atomic center being reduced must be sufficiently electron deficient in order for hydride transfer to occur. This also allows for the possibility of highly selective reductions using organosilicon hydrides. There are two general routes for the reduction mechanism, the σ-route and the π-route. In both cases, the atomic center being reduced is electron deficient. The σ-route is denoted as that because of its stepwise cleavage of a σ-bond to the corresponding carbocation followed by hydride addition to that carbocation to produce the reduced product (Scheme 2-1). In the σ-route, the σ-bond being cleaved is generally from a carbon to a good leaving group (X) and the leaving group leaves before the hydride is added.
Scheme 2-1. $\sigma$-Route mechanism

In the $\pi$-route, the hydride is added to a $\pi$-bond. The double bond being reduced can be either an alkene, carbonyl, imine, or thioketone. Again, the atomic center being reduced must be electron deficient, so in this mechanism a Lewis acid interacts with one side of the double bond allowing for a resonance structure with the other side bearing a carbocation. The hydride will then add into the carbocation to give the reduced product (Scheme 2-2). Further, it is possible for a molecule to go through the $\pi$-route of reduction and sequentially through the $\sigma$-route to give the double reduced product, generally a methylene group.

Scheme 2-2. $\pi$-Route mechanism

2.3 Ketone Hydrosilation

The silane-mediated reduction of ketones to their corresponding secondary alcohol can be performed under a variety of conditions including acid and base catalyzed condition and transition metal catalyzed conditions. It is also possible to reduce ketones diastereoselectively and chemoselectively depending on the reagents used. Below are examples of organosilicon hydride reductions of ketones under various conditions.
An example of a Lewis-acid mediated ketone hydrosilation is the reduction of cyclohexanone 15 to cyclohexanol 16. This hydrosilation can be performed in 74% yield using 3.0 equivalents of both triethylsilane (Et₃SiH) and trifluoroacetic acid (TFA) for 24 hours at 55°C followed by an aqueous potassium carbonate (K₂CO₃) workup (Scheme 2-3). This reaction follows the π-route mechanism by having TFA act as the Lewis acid, interacting with the carbonyl of 15, followed by addition of the hydride.²¹

**Scheme 2-3.** Ketone reduction by triethylsilane and trifluoroacetic acid²¹

It is also possible to do the double reduction of a carbonyl down to the methylene subunit (Scheme 2-4). The following example is also a Lewis-acid mediated reduction. In this example, adamantanone 17 is reduced by 2.2 equivalents of triethylsilane and boron trifluoride (BF₃) all the way down to adamantane 18. In the first step of the reaction, the Lewis-acidic boron trifluoride interacts with the carbonyl oxygen of 17 to increase the electron deficiency of the carbonyl carbon. The first equivalent of triethylsilane reduces the carbonyl to the intermediate 19 and the byproduct triethylsilyl fluoride. It is then unknown whether or not a second equivalent of BF₃ adds to the oxygen followed by hydride addition, or whether the OBF₂⁻ leaves, leaving a carbocation before the second equivalent of hydride is added. In either situation, the carbon is reduced for a second time leaving the fully reduced product 18 in quantitative (100%) yield (Scheme 2-4).²²
When going through a Lewis-base mediated mechanism, it is common for a pentavalent silicon intermediate with a formal negative charge on silicon to be formed. This pentavalent silicon species is allowed because silicon is in the third row of the periodic table and has access to its d-orbitals to form expanded octets. These pentavalent organosilicon hydride species have increased nucleophilicity and can react with ketones that have not been previously activated by a Lewis acid. Similar to how borane and DIBAL-H are activated before their hydride is transferred; hydridosilanes can also be activated prior to reduction. In this example, 2 equivalents of dilithiated catechol react with trichlorosilane to form the pentavalent silane intermediate. The pentavalent silane intermediate then reduces benzaldehyde at 0°C to give benzyl alcohol in 95% yield (Scheme 2-5).
In the transition metal catalyzed hydrosilation, the nucleophilicity of the hydride is increased by the metal inserting itself into the silicon hydrogen bond to give a metal hydride source. In this example, cyclohexanone 23 is reduced to triethylsilyl (TES) protected cyclohexanol 24. This reaction can be useful in synthesis because it reduces the carbonyl and TES protects it all in one step, whereas this would normally be a two-step process to reduce the carbonyl in the first step and TES protect it in the second. In this case, copper(I) chloride is used with an N-heterocyclic carbene ligand 25 (Scheme 2-6). The catalytic cycle for this reaction is shown (Scheme 2-7). The metal catalyst 26 inserts itself into the silicon hydrogen bond via oxidative addition to give the metal hydride source 27. The ketone then comes in and goes through a σ-bond metathesis with the metal hydride 27 to form the metal alkoxide 28. The metal alkoxide goes through a reductive elimination to form the TES protected alcohol product 29 and reform the active catalyst 26.24

Scheme 2-6. Transition metal catalyzed hydrosilation of cyclohexanone24
Scheme 2-7. Mechanism for the transition metal catalyzed hydrosilation

Hydrosilations can be performed with high diastereoselectivity in certain situations. In the case of 4-tert-butylcyclohexanone 30, the ketone can be reduced using a large silane reagent, tristrimethylsiloxy-silicon hydride 33 ((Me₃SiO)₃SiH), in a ratio of 99:1 trans 31 to cis 32 (Scheme 2-8). The selectivity for this reaction is provided by the large size of the (TMSO)₃SiH group. The t-butyl substituent on cyclohexanone is large enough to essentially be locked in the equatorial position. The size of the silane reagent forces it to add its hydride axially to the carbonyl, pushing the alcohol into the equatorial position 34 (Scheme 2-8). In this case, the diastereoselectivity is based solely on steric hindrance of the silane reagent 33 and the large t-butyl substituent being locked in the equatorial position. If either the substituent or the silane reagent were not as bulky, the diastereoselectivity would be affected.²⁵
**Scheme 2-8.** Diastereoselective hydrosilation of 4-tert-butylcyclohexanone\textsuperscript{25}

It is also possible to perform diastereoselective hydrosilations via a proton bridged Cram-cyclic model, a variation of the Cram-chelate model.\textsuperscript{15} Hiyami and coworkers have shown that it is possible to synthesize the cis isomer of various 2-amino alcohols, 1,2-diols, and 3-hydroxyalkanoic acid derivatives\textsuperscript{26-28} using this Cram-cyclic model. The amino or alcohol group forms a proton-bridge to the carbonyl and the methyl group alpha to the carbonyl directs the hydride addition (Scheme 2-9). This often gives selectivities of >99:1 in high yields (Scheme 2-9).\textsuperscript{28}
Scheme 2-9. Diastereoselective hydrosilation via Cram-cyclic model to form cis products

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \quad \text{CO} \quad \text{O} \quad \text{Et} & \quad \text{PhMe}_2\text{SiH, TFA} \quad 0^\circ \text{C, 2.5 h} \\
\rightarrow & \quad \text{Ph} \quad \text{OH} \quad \text{NH} \quad \text{CO} \quad \text{O} \quad \text{Et} \\
& \quad 87\% >99:1 \text{ dr}
\end{align*}
\]

It is also possible to form the trans selectivity using F\text{–} as a reagent for the hydrosilation instead of an acid with the same PhMe\textsubscript{2}SiH silane reagent. The mechanism for this reaction follows the Felkin-Ahn model to determine selectivity (Scheme 2-10). Again, these compounds are reduced in high yields and excellent diastereoselectivities (Scheme 2-10).

Scheme 2-10. Diastereoselective hydrosilation via Felkin-Ahn model to form trans products

\[
\begin{align*}
\text{Ph} \quad \text{CO} \quad \text{CO} \quad \text{NEt}_2 & \quad \text{PhMe}_2\text{SiH, TASF} \quad \text{DMPU, 0\degree C, 12 h} \\
\rightarrow & \quad \text{Ph} \quad \text{OH} \quad \text{CO} \quad \text{CO} \quad \text{NEt}_2 \\
& \quad 98\% >99:1
\end{align*}
\]

\[
\begin{align*}
\text{Ph} \quad \text{CO} \quad \text{CO} \quad \text{N} & \quad \text{Ph} \\
\rightarrow & \quad \text{Ph} \quad \text{OH} \quad \text{CO} \quad \text{CO} \quad \text{N} \\
& \quad 91\% 98:2
\end{align*}
\]

20
Chemoselective hydrosilations are also possible depending on the reagents used. A chemoselective reaction affects only one functional group in the presence of others. Plietker and coworkers found an iron catalyst that can chemoselectively reduce an aldehyde in the presence of other functional groups using polymethylhydrosiloxane (PHMS) as the silane reagent. This catalytic system is capable of selectively reducing aldehydes in the presence of alkenes (Scheme 2-11). In the first example, the aldehyde 35 is reduced chemoselectively using PHMS, Bu$_3$N[Fe(CO)$_3$(NO)] (TBAFe) as the iron catalyst and PC$_y_3$ as the additive in 1,4-dioxane followed by a basic workup to give the corresponding primary alcohol 36 in 96% yield without touching either of the alkenes. The second example is from Beller and coworkers who found a method to chemoselectively reduce the ketone 37 in the presence of alkenes using PMHS as the silane reagent, Fe(OAc)$_2$ as the catalyst and PC$_y_3$ as the additive to give the corresponding secondary alcohol 38.

Scheme 2-11. Chemoselective aldehyde reduction using an iron catalyst and PHMS

It is important to pay attention to the conditions being used when attempting a chemoselective hydrosilation because not all silane reagents are chemoselective. In the example below, the ketone is reduced, but 2 other alkenes are also reduced in the reduction of
$1\alpha,11$-(2-oxethano) thioketal steroid 40 with excess triethylsilane and TFA giving the triple reduced product 41 (Scheme 2-12).$^{31}$

**Scheme 2-12.** Hydrosilation of $1\alpha,11$-(2-oxethano) thioketal steroid with excess Et$_3$SiH$^{31}$
3. Previous Hydrosilation Results

3.1 Original Project Goals

The previous work on this project was performed by Kyle Carter and Michael Miller under the direction of Dr. Gregory W. O’Neil. Their work was published in Organic Letters in 2010 titled Direct Conversion of β-Hydroxyketones to Cyclic Disiloxanes. The original goal of this project was to first synthesize β-hydridosiloxyketone compounds from their corresponding β-hydroxyketones and then develop conditions for an enantioselective intramolecular carbonyl hydrosilation to generate the corresponding enantioenriched cyclic disiloxane (Scheme 3-1). An intramolecular carbonyl hydrosilation is a reduction of a ketone where the hydride on silicon is tethered to the substrate. Once the ketone is reduced, the negatively charged oxygen adds back to silicon forming the cyclic disiloxane product. From there, it would be possible to remove silicon to access various propionate subunits. A propionate subunit is defined as a molecule with alternating methyl and hydroxyl groups on adjacent carbons of the backbone. These propionate subunits are common to a large number of important natural products. Highlighted below are just a few examples of natural products in which these propionate subunits can be found including scytophycin C, bourgeanic acid, zincophorin, and discodermolide (Scheme 3-2).
Scheme 3-1. Intramolecular carbonyl hydrosilation of β-hydroxyketones
3.2 Substrate Synthesis and Scope of Reaction

The first step in this project was to create the β-hydroxyketone compounds required for further studies. 3-Hydroxy-1-phenylpropan-1-one 46 was the first β-hydroxyketone synthesized because it could be made in a single step by free radical oxidation of 3-phenylpropan-1-ol 45 (Scheme 3-3) which was accomplished in 50-70% yield. From there, the hydroxyl group was silylated with either i-PrSiHCl or t-BuSiHCl in the presence of imidazole at 0° C to create the corresponding β-hydridosiloxyketones 47 and 48. This reaction was straight forward and accomplished in 70-80% yield (Scheme 3-3).
Scheme 3-3. Synthesis of β-hydridosiloxyketone compounds from 3-phenylpropan-1-ol

However, when Ph₂SiHCl was used to create the β-hydridosiloxyketone 49, a small amount (<10%) of the corresponding cyclic disiloxane 50 was formed (Scheme 3-4). It was assumed that a small amount of the β-hydridosiloxyketone 49 had gone through an intramolecular carbonyl hydrosilation under these conditions to reduce the ketone and form the 6-membered disiloxane ring. This was unexpected as it did not happen with the synthesis of the two previous β-hydridosiloxyketones 47 and 48 and it usually requires additional conditions to promote hydrosilation. With this result, the cause of the hydrosilation was investigated. Knowing that hydrosilation reactions could be acid promoted, the first thought was that the small amount of HCl produced from the alcohol adding into the silane was catalyzing the hydrosilation.

Scheme 3-4. Small amount of cyclic disiloxane formation upon addition of silane

Anwar and Davis have shown that a similar intramolecular carbonyl hydrosilation can be catalyzed by the addition of a Lewis acid. They attempted various Lewis-acid catalysts
such as tin chloride ($\text{SnCl}_4$), magnesium bromide etherate ($\text{MgBr}_2\cdot\text{Et}_2\text{O}$), titanium chloride ($\text{TiCl}_4$) and boron trifluoride etherate ($\text{BF}_3\cdot\text{Et}_2\text{O}$). All of the catalysts were successful in the intramolecular carbonyl hydrosilation to form the cyclic disiloxane, but some attained better diastereoselectivity than others (Scheme 3-5). Using 10 mol-% of $\text{SnCl}_4$ attained a diastereomeric ratio of 120:1 anti: syn with a 67% yield.\(^{37}\)

**Scheme 3-5.** Intramolecular carbonyl hydrosilation with various Lewis-acid catalysts\(^{37}\)

<table>
<thead>
<tr>
<th>Catalyst (mol. eq.)</th>
<th>Ratio anti : syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{SnCl}_4$ (0.1)</td>
<td>120 : 1</td>
</tr>
<tr>
<td>$\text{MgBr}_2\cdot\text{Et}_2\text{O}$ (0.1)</td>
<td>60 : 1</td>
</tr>
<tr>
<td>$\text{TiCl}_4$ (0.5)</td>
<td>30 : 1</td>
</tr>
<tr>
<td>$\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.5)</td>
<td>320 : 1</td>
</tr>
</tbody>
</table>

Additional acid catalysts were therefore screened in an attempt to increase the conversion of 49 to cyclic disiloxane 50. The proposed mechanism for this intramolecular carbonyl hydrosilation would be similar to that proposed by Anwar and Davis. It was thought to proceed through a cyclic 6-membered transition state 51 with a Lewis acid activating the carbonyl for hydride transfer. Once the hydride is transferred, the anionic oxygen adds into the silicon group creating the cyclic disiloxane product 50 (Scheme 3-6). When these acid-mediated hydrosilation conditions were attempted with the mixture of β-hydridosiloxketone 49 and <10% cyclic disiloxane 50, the major product obtained was only
reformation of the β-hydroxyketone starting material 46 (Scheme 3-7). Various Lewis acids were screened including BF$_3$•Et$_2$O, MgBr$_2$•Et$_2$O, pyridinium paratoluene sulfonate (PPTS), camphorsulfonic acid (CSA), (PhO)$_2$P(O)OH, and imidazole•HCl.

**Scheme 3-6.** Proposed transition state

![Scheme 3-6](image)

**Scheme 3-7.** Lewis acid screening

![Scheme 3-7](image)

Addition of a Lewis acid did not increase the conversion to cyclic disiloxane F. Addition of amine bases to the reaction mixture were screened next. It turned out the addition of either triethylamine (Et$_3$N) or Hünig's base ($N,N$-diisopropylethylamine, $i$-Pr$_2$NEt) greatly increased the conversion to the cyclic disiloxane. Conveniently, it turns out that the silyl addition and intramolecular carbonyl hydrosilation to form the cyclic disiloxane can be done in one step rather than two. Attempted isolation of the cyclic disiloxane product by column chromatography on silica gel proved troublesome, as they are prone to decomposition on silica. However, isolation by column chromatography using Florasil yielded better success, providing cyclic disiloxanes 50 and 53 in 47% and 42% yields respectively (Scheme 3-8).
Desilylation with tetrabutylammonium fluoride (TBAF) in THF provided the 1,3-diol product. Furthermore, desilylation is possible without isolation of the cyclic disiloxane. To prove that the cyclic disiloxane product isolated from the β-hydroxyketone was the correct product, silylation of the 1,3-diols 54 and 55 with diphenylchlorosilane (Ph₂SiCl₂) and imidazole provided the cyclic disiloxane product and the characterization data were compared and found to match. Overall, it is more successful to perform the intramolecular carbonyl hydrosilation and promptly desilate without isolation of the cyclic disiloxane to form the 1,3-diol product.

**Scheme 3-8.** Amine additives for hydrosilation promotion

Now that successful hydrosilation conditions had been discovered, the substrate scope of this reaction was tested. The synthesis of the β-hydroxyketone starting material involved a multistep sequence consisting of 5 steps and resulted in overall yields of 30-50% (Scheme 3-9). This multistep synthesis starts with an aldol reaction between an aldehyde 56 and ethyl acetate in the presence of lithium diisopropylamide (LDA) to form the β-hydroxyester 57. Next, the alcohol is oxidized using sulfuric acid and chromium trioxide (Jones’ reagent) to give the β-ketoester 58. In order to selectively reduce the ester to the alcohol without reduction of the ketone, the ketone must be protected as the acetal using ethylene glycol giving the acetal protected ketone 59. Lithium aluminum hydride can then be used to
selectively reduce the ester to the alcohol 60, followed by deprotection of the acetal under acidic conditions to produce the corresponding β-hydroxyketone 61.

**Scheme 3-9.** Synthesis of β-hydroxyketone compounds

The substrate scope of the hydrosilation/desilylation to synthesize 1,3-diols was tested on various β-hydroxyketones (Scheme 3-10). It was found that the majority of substrates were successfully hydrosilylated to provide the corresponding 1,3-diol in good yields from the low 60’s up to 76% 54, 55, 62-65. This hydrosilation is tolerant to aryl groups 54 and 65, alkyl chains 55 and 62, α,β-unsaturated ketones 63 and 64, and even electrons withdrawing substrates 65. There were a few substrates that proved troublesome in this reaction, however. The t-butyl derived β-hydroxyketone 67 was isolated in only 32% yield, but 75% based on recovered starting material (brsm). It seems that this reaction is affected by the steric bulk of large R groups such as t-butyl groups, and this hinders the ability of the hydride to transfer. Also, the p-methoxyphenyl derived β-hydroxyketone 68 proceeded in 42% yield (78% brsm) showing that the electron donating properties of the methoxy substituent decrease the electron deficiency of the carbonyl carbon making it less likely to get reduced. Other interesting results include the hydrosilation of two α,β-
unsaturated β-hydroxyketone to give products 63 and 64 which were reduced in 65% and 70% yield respectively. These results show that this hydrosilation has high levels of chemoselectivity for ketones over alkenes. In both cases, the alkene was not touched by the hydrosilation. Lastly, the attempted hydrosilation of 4-hydroxybutan-2-one 66 provided no success whatsoever. Likely the substrate is too unstable for the hydrosilation conditions.

**Scheme 3-10.** Substrate scope of hydrosilation/desilylation 1,3-diol synthesis

3.3 Mechanistic Studies

Mechanistic studies were performed to predict a mechanism for this hydrosilation. Based on two studies, it was found that imidazole is essential for the hydrosilation to occur (Scheme 3-11). The first study tested the hydrosilation on two substrates in the presence of
Ph$_2$SiHCl and Et$_3$N with no imidazole and found that the only product formed was the $\beta$-hydridosiloxynketones 49 and 69. Absolutely no hydrosilation had occurred. The second test used $N$-methylimidazole in the place of imidazole and found that again, $\beta$-hydridosiloxynketones 49 and 69 were the exclusive products of this reaction. Not only is imidazole required for this reaction, but the hydrogen on the amine is also required.

**Scheme 3-11.** Hydrosilation in the absence of imidazole

The requirement for the $\beta$-hydroxy functionality was tested next. The first test simply used ethyl ketone 70 under the usual hydrosilation conditions and achieved no reaction (Scheme 3-12). The carbonyl had not reacted under the hydrosilation conditions when the $\beta$-hydroxy functionality was not present. The second test looked at an $\alpha$-hydroxy ketone 80 as a possible hydrosilation substrate. It turned out that this reaction was slightly successful, yielding the corresponding 1,2-diol 81 in 14% yield after desilylation (Scheme 3-12. But the 5-members transition state seems to be too small for high yielding hydrosilations to occur.
Scheme 3-12. Hydrosilation in the absence of the β-hydroxy functionality

The proposed mechanism for this hydrosilation occurs via nucleophilic activation (Scheme 3-13). The first step is formation of the β-hydridosilox酮 83 by the addition of the alcohol of 82 to Ph₂SiHCl in the presence of imidazole. In the next step the imidazole·HCl is deprotonated by the triethylamine to reform imidazole and form Et₃N·HCl. For the hydrosilation, there are two proposed transition states that could be possible, 84 and 85. In both proposed transition states, the silicon is activated by imidazole to create a pentacoordinate silane with a more reactive hydride. Silicon activation by imidazole is well known and has been studied through $^{29}$Si NMR by Stout and coworkers. The hydride then adds to the carbonyl in a 6-membered chair-like transition state, 84 or 85, to form the cyclic disiloxane product 86. In proposed transition state 84, imidazole activates silicon from the bottom and the triethylamine interacts with the hydrogen on the other nitrogen of the imidazole ring. In proposed transition state 85, imidazole activates silicon from the top, and the hydrogen on the opposite side of the imidazole ring hydrogen bonds with the carbonyl activating it even further. It is thought that the hydrosilation proceeds through proposed transition state 84 because previous studies have shown triethylamine is required for hydrosilation to occur, and triethylamine is not involved in 85.
3.4 Diastereoselective Hydrosilation

Having the hydrosilation occurrs through a 6-membered ring chair-like transition state opens up the possibility for a diastereoselectively hydrosilation. A six membered ring in the chair conformation prefers to have any substituents in the equatorial position because it is the lower energy conformation and avoids steric strain from other groups on the ring.\(^1\) Adding a substituent to one of the carbons that are in the chair-like transition state ring 87 would cause that substituent to be preferentially in the equatorial position 89 which would promote formation of a single diastereomer product 88 (Scheme 3-14).
Scheme 3-14. Diastereoselective hydrosilation

Based on the transition state shown, the stereocenter would promote syn stereochemistry in the product. Substrates with a methyl group on the carbon alpha to the carbonyl 90-92 were synthesized to test this prediction and it was found that this methyl group did in fact promote syn stereochemistry in the propionate product. These hydrosilations proceeded in great yields, 76% to 91% and varied from 6:1 syn to anti stereoselectivity all the way up to >10:1 (Scheme 3-15). Using this hydrosilation is a new synthetic route to syn-propionate subunits.

Scheme 3-15. Proposed diastereoselective hydrosilation
Now that diastereoselectivity had been achieved by adding a stereocenter on the alpha carbon inside of the transition state ring, we were curious whether or not diastereoselectivity could be achieved from placing a stereocenter on the other side of the carbonyl 96. This hydrosilation would most likely proceed through Felkin control 98. The hydride would add in from the opposite side of the large ‘R’ group and past the hydrogen on this stereocenter to give the cyclic disiloxane product 97 (Scheme 3-16). But before this hydrosilation was to be tested, a quicker method for synthesis of the β-hydroxyketone starting material was sought after.

Scheme 3-16. Diastereoselectivity hydrosilation via Felkin control$^{12}$
4. Diboration/Oxidation for Synthesis of β-Hydroxyketones

4.1 Proposed Synthesis

The proposed synthetic route for β-hydroxyketone starting material involves a diboration and oxidation of a terminal enone to obtain the β-hydroxyketone product in two steps from the enone, essentially saving three steps from the previous method (Scheme 3-9). The new method will start with a 1,4-diboration of a terminal enone 99 to provide the β-ketoborinate ester 100 followed by oxidation of the carbon boron bond to provide the corresponding β-hydroxyketone 101 (Scheme 4-1). The boron reagent used in this would be bis(pinacolato)diboron 102 (B2pin2). The hydrosilation focuses on primary alcohol substrates, so it is required that terminal enones are used in order to obtain the primary alcohol required.

Scheme 4-1. Synthetic scheme for new β-hydroxyketone synthesis

The idea for using this diboration oxidation sequence came from the previous research I had done in Dr. Timothy Clark’s lab. Dr. Clark’s lab has moved from Western Washington University to University of San Diego. His research focuses on the addition of
boron into organic substrates to produce organoboranes. My project involved a copper catalyzed diboration of aldehydes and ketones. The (ICy)CuCl precatalyst used in this diboration contained an N-heterocyclic carbene (NHC) ligand. The active (ICy)CuOt-Bu catalyst was formed in situ from the addition of NaOt-Bu to the precatalyst. This catalyst would add B₂pin₂ across the double bond of the carbonyl to give the 1,2-diboration product. The oxygen boron bond was hydrolyzed by filtration through a plug of silica gel to yield the corresponding α-hydroxyboronate ester product.

Scheme 4-2. Copper-catalyzed diboration of aldehydes and ketones followed by hydrolysis

Cameron Moore, another member of Dr. Clark’s group, had worked on a similar project, the 1,4-diboration of α,β-unsaturated carbonyls. Diboration of cyclohex-2-enone under the same catalytic conditions gave the 1,4-diboration product. After hydrolysis of the 1,4-diboration product, β-ketoboronate ester was obtained (Scheme 4-3). This product is now one step away from β-hydroxyketone which is similar to the desired β-hydroxyketone for hydrosilation. Seeing these results gave me the idea of using a similar 1,4-diboration with terminal enones, followed by an oxidation to give the
corresponding primary β-hydroxyketone. It was not practical to use the same (ICy)CuCl catalyst from Dr. Clark’s research to synthesize the primary β-hydroxyketone compounds because this catalyst is extremely air and water sensitive and requires the use of a glovebox. Screening other 1,4-diboration catalysts would be required.

Scheme 4-3. 1,4-diboration of cyclohex-2-enone followed by hydrolysis

4.2 1,4-Conjugate Diboration Catalysts

1,4-Diboration of enones is relatively new with the first 1,4-diboration published in 1997. Since then, several other methods for this diboration have been published with the general trend of milder reaction conditions and cheaper catalysts being used as the reaction is further studied. The first 1,4-diboration proposed by Rice and coworkers in 1997 uses 5 mol-% of a platinum catalyst, [Pt(C_2H_2)(PPh_3)_2], heated to 80°C for 12 hours using either B_2pin_2 102 or bis(catacholato)diboron 113 (B_2cat_2). The boron enolate product 111 is then quenched with water to provide the β-ketoboronate ester 112 in 90% yield (Scheme 4-4).
Scheme 4-4. Platinum catalyzed diboration by Rice and coworkers\textsuperscript{40}

The catalytic cycle for this reaction starts with the platinum catalyst 114 going through an oxidative addition with the diboron reagent 102 or 113 (102 shown) to provide platinum with two Bpin ligands on it 115. The platinum catalyst 115 then adds to the enone to give the platinum enolate 116 containing the carbon boron bond desired. Reductive elimination gives the 1,4-diboration product 111 and reforms the platinum catalyst 114 (Scheme 4-5).\textsuperscript{40}

Scheme 4-5. Platinum catalyzed diboration catalytic cycle\textsuperscript{40}
Yun and coworkers discovered a copper (I) catalyzed diboration of enones using a CuCl catalyst and NaOtt-Bu additive. This catalytic system contains a proton source, methanol, in the reaction mixture, so instead of producing the boron enolate, the enolate gets protonated by methanol and the β-boration product 117 is produced (Scheme 4-6). This diboration can be achieved asymmetrically by the addition of a chiral ligand. Using the (R)-(S)-josiphos ligand 118, the product is formed in 97% yield and 97% ee (Scheme 4-6).41

Scheme 4-6. Copper (I) chloride catalyzed diboration and asymmetric diboration41

The catalytic cycle for this diboration was proposed by Oestreich and coworkers (Scheme 4-7), and starts by combining CuCl and NaOtt-Bu to form the CuOtt-Bu precatalyst 119 which goes through a sigma bond metathesis with B2pin2 102 to form the copper-Bpin active catalyst 120. Next, 120 adds into the alkene of the enone to form the carbon boron bond on the beta carbon 121. Migration of copper occurs to form the copper enolate 122 which is subsequently protonated by methanol followed by a tautomerization to form the desired β-ketoborionate ester product 124 along with copper methoxide 123. To reform the active catalyst 120, 123 goes through a sigma bond metathesis with another equivalent of B2pin2 102. The final sigma bond metathesis to reform the active catalyst 120 is proposed to be the slow step and thus the rate determining step in this catalytic cycle.42
Hoveyda and coworkers have discovered metal free conditions for enone diboration. In this example they start with a disubstituted enone 125, which, because of sterics, is the most unreactive enone to 1,4-diboration, and are able to diborate in 96% yield to produce a quaternary carbon containing boron product 126 (Scheme 4-8). This reaction requires 2.5 mol-% of the NHC catalyst 127 and 2.5 mol-% of NaOt-Bu with 1.1 eq. of B2pin2 and goes to >98% conversion in 6 hours. Under the same conditions, monosubstituted enones were able to go to completion within one hour. The mechanism for this reaction starts with the activation of the diboron reagent 102 by nucleophilic addition of 127 to one of the borons. This forms an activated sp²-sp³ hybridized diboron reagent 128. The activated diboron reagent then adds to the alkene of cyclic enone 129 to form diboron species 130. The
nucleophile leaves the boron reagent and the boron migrates to the oxygen to form the boron enolate 131. After an aqueous workup, the enolate is quenched to provide the β-boration product (Scheme 4-8).\(^43\)

**Scheme 4-8.** Metal-free 1,4-diboration and mechanism\(^43\)

Knowing that the sp\(^2\)-sp\(^3\) hybridized diboron reagent is more active than the sp\(^2\)-sp\(^2\) hybridized diboron, Santos and coworkers created a novel diboron reagent called pinacolato diisopropanolaminato diboron 132 (PDIPA) that contains an sp\(^2\) hybridized Bpin group and an activated sp\(^3\) hybridized amino boron group (Scheme 4-9). Having this preactivated diboron species helps speed up both rate determining sigma bond metathesis steps in the mechanism, allowing faster formation of the active catalyst 120. (Scheme 4-7). This catalytic system is capable of diborating the less reactive α,β-unsaturated ester 133 to give product 134 in 96% yield (Scheme 4-9).\(^44\) This reaction follows a very similar catalytic cycle
to that proposed by Oestreich and coworkers,\textsuperscript{42} the only difference being PDIPA is used in place of B$_2$pin$_2$ and trifluoroethanol is used in place of methanol (Scheme 4-9).\textsuperscript{44,45}

**Scheme 4-9.** PDIBA diboration of $\alpha,\beta$-unsaturated ester and catalytic cycle\textsuperscript{44}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{133} & \quad \text{PDIPA} \\
& \quad \text{CuCl, CF$_3$CH$_2$OH, CH$_2$Cl$_2$, 0$^\circ$C-rt} \\
& \quad \text{Bnip} \quad \text{134} \ 96\% \\
& \quad \text{PDIPA} \quad \text{H} \\
& \quad \text{B-B} \\
& \quad \text{132}
\end{align*}
\]

Recently, Yun and coworkers described a diboration that proceeds in an aqueous environment under an N$_2$ atmosphere. This diboration uses CuCl as the catalyst and NaOt-Bu as the additive in a 2:1 mixture of THF to H$_2$O (Scheme 4-10). For the majority of substrates tested, the reaction goes to completion in 1-3 hours for a variety of different enones, including terminal enones, substituted enones, and $\alpha,\beta$-unsaturated esters and amides. Larger substituents on the enone decreased the conversion rate and stopped the reaction from going to completion in less than 6 hours for some substrates.\textsuperscript{46}

**Scheme 4-10.** Aqueous diboration under an N$_2$ atmosphere\textsuperscript{46}

\[
\begin{align*}
\text{R} \quad \text{O} & \quad \text{R} \\
\text{135} & \quad \text{B$_2$pin$_2$} \\
& \quad \text{CuCl/NaOt-Bu, THF:H$_2$O = 2:1, rt} \\
& \quad \text{Bpin} \quad \text{136} \\
& \quad \text{R} \quad \text{O} \\
& \quad \text{R}
\end{align*}
\]
Santos and coworkers also described an aqueous diboration in an open air atmosphere using a Cu(II) catalyst. In this mechanism, water activates the diboron reagent 102 and the additive picoline 135 deprotonates the water (Scheme 4-11). The activated diboron then goes through a transmetalation with copper to enter a similar catalytic cycle as above (Scheme 4-7) to yield the diboration product 136.  

**Scheme 4-11.** Aqueous Cu(II)-picoline diboration
5. β-Hydroxyketone Synthesis

5.1 Initial Diboration Results

The new proposed synthesis of β-hydroxyketone compounds C starts with a terminal enone A that will go through a 1,4-diboration most likely with B$_2$pin$_2$ D to produce the β-ketoboronate ester B. The carbon boron bond of B will then be oxidized to provide the corresponding β-hydroxyketone C in two steps from the terminal enone (Scheme 5-1) rather than the five steps that it previously required from the corresponding aldehyde (Scheme 3-9).

**Scheme 5-1.** New synthesis of β-hydroxyketone compounds

The first step was to find conditions for enone diboration. Looking at all the examples, this seemed to be a fairly straight-forward task. However, initial diboration attempts were not successful (Scheme 5-2). The first attempted diboration followed metal free conditions set forward by Fernandez and coworkers.\textsuperscript{48} Triphenylphosphine (PPh$_3$) was used as the catalyst and cesium carbonate (Cs$_2$CO$_3$), a strong base, was required for the reaction. The PPh$_3$ worked to activate B$_2$pin$_2$ for 1,4-addition to the enone and MeOH was used as a proton source to protonate the enolate. Little to no diboration product was present by $^1$H NMR analysis, and all starting material had been used up or decomposed. These reaction conditions seem to be too harsh for the terminal enone substrates. Terminal enones are not as stable as their substituted counterparts, and Cs$_2$CO$_3$ is a very strong base that could
be causing decomposition. For the second attempt, these conditions were modified by replacing Cs₂CO₃ with the milder amine base 1,8-diazabicycloundec-7-ene 137 (DBU). However, these modified conditions turned out to be unsuccessful as well. Our final attempt with these conditions used only DBU 137 as the catalyst in the hopes that it would be enough to activate the diboron for 1,4-addition to the enone. This turned out to be unsuccessful as well, sending us back to the literature to find a new procedure.

**Scheme 5-2. Initial enone diboration attempts**

After looking through various enone diboration protocols, it became clear that terminal enone diboration has not been highly studied. Only two papers were found, each with only a single example of a terminal α,β-unsaturated ketone being diborated. The first example is from Yun and coworkers and used a CuCl and NaOt-Bu catalyst in THF and NaOT-Bu.
water$^{46}$ (Scheme 5-3) and the second is by Santos and coworkers and performed in a completely aqueous system with a Cu(II)SO$_4$ catalyst and picoline base$^{47}$ (Scheme 4-11). The protocol Yun and coworkers was attempted first because of the ease of the catalytic system. Using a benzaldehyde derived enone 138, Yun’s catalytic system was followed, and at first looked to be very successful (Scheme 5-4). The $^1$H NMR of the product 139 was very clean and all the proper peaks were present. A COSY spectra was taken to prove to ourselves that this was indeed the product that we were looking for. By mass, it was a 97% yield, but upon further inspection of the $^1$H NMR integrations, the singlet at $\sim$1.2 that represents the 12 hydrogens of the Bpin group was integrating to about 24 hydrogens, approximately twice what it was supposed to. This over integration was most likely due to unreacted B$_2$pin$_2$ still present in the final product. Purification by column chromatography on silica gel was unsuccessful at removing this extra B$_2$pin$_2$ so the next step was to optimize these reaction conditions.

**Scheme 5-3.** Example of terminal enone diboration$^{46}$

![Scheme 5-3](image)

**Scheme 5-4.** Successful diboration

![Scheme 5-4](image)

97% yield, $\sim$half B$_2$pin$_2$
Before attempting to optimize the reaction conditions, it is important to understand the reaction mechanism. This reaction proceeds through a copper catalyzed mechanism with Cu-bpin as the active catalyst (Scheme 5-5). The first step is creation of the CuOr-Bu precatalyst 119 from CuCl and NaOr-Bu. The precatalyst 119 goes through a sigma bond metathesis with B₂pin₂ 102 to form the active CuBpin catalyst 120. The active catalyst adds to the alkene of the enone 99 to form the β-boration product 140, which is in resonance with the copper enolate 141. Water protonates the enolate followed by tautomerization to from the β-ketoboronate ester product 100 along with copper hydroxide 142. In the proposed rate-determining step of the catalytic cycle, copper hydroxide goes through a sigma bond metathesis with B₂pin₂ to reform the active catalyst 120. 42, 46
**Scheme 5-5.** Proposed catalytic cycle for the diboration of terminal enones\(^{42,46}\)

5.2 Optimization and Scope of Reaction

Enone 138 was used as the model substrate for optimization studies because it was easy to synthesize and seemed to be stable and nonvolatile. Knowing that triphenylphosphine helped to activate diboron reagents for addition,\(^ {42,48}\) the first optimization attempt involved the addition of 20 mol-% of triphenylphosphine to the catalytic system (Scheme 5-6). This did not lead to any improvement on the yield, but it did allow for isolation of the β-ketoboronate 139 ester with no \(\text{B}_2\text{pin}_2\) contaminant, albeit in only a 35% yield. Knowing that
terminal enones are not the most stable substrates, and could potentially be decomposing in
the reaction mixture, the starting enone was used in excess to the B$_2$pin$_2$. Using 1.2 to 2.0
equivalents of the enone starting material, the β-ketoboronic ester products 139 were
isolated in 62-82% yield with no B$_2$pin$_2$ contaminant. Finally, doubling the equivalents of
B$_2$pin$_2$ or NaOt-Bu were attempted and led to no improvements (Scheme 5-6).

**Scheme 5-6.** Diboration optimization

With successful diboration conditions in hand, the substrate scope was tested.
Terminal enone substrates were synthesized by 3 different methods depending on what our
starting material was (Scheme 5-7). The first method starts with a vinyl Grignard addition to
an aldehyde 143 to yield the allylic alcohol 144 followed by a Jones’ oxidation to give the
desired enone 99. The second method starts by creating a Weinreb amide 146 from an ester
145,$^{49}$ followed by vinyl Grignard addition to the Weinreb amide 146 to give the
corresponding enone 99. This technique was used on the more precious enones derived from the more expensive Roche ester starting material. The final technique was used to create dienones 149. It began with the addition of a vinyl Grignard to the vinyl aldehyde 147 to synthesize the diallyl alcohol 148. A tetrapropylammonium perruthenate (TPAP) oxidation was required to oxidize the alcohol into the final dienone product 149.

**Scheme 5-7. Terminal enone synthesis**

The enone products synthesized above were then subjected to the diboration conditions in an attempt to understand the scope of this reaction (Scheme 5-8). In the top row of products 139, 150-152, 1.2 equivalents of the enone was used in each case because these enone substrates were less stable and prone to decomposition in the reaction mixture. These substrates 139, 150-152 took 3 hours for the diboration to go to completion. The substrates in the second row 153-156 were derived from more expensive starting material and required more steps to arrive at the enone making them more precious than the top row. Luckily, enones 153-156 were much more stable than 139, 150-152 and were able to undergo the diboration using 1.0 equivalents of the enone and 1.1 of B₂pin₂. It was even found that
these substrates could be resubjected to the reaction conditions if they did not go to completion in the first attempt. These substrates took 6 hours for the diboration to go to completion, but were stable enough that they could be left overnight with no effect on the yield. The last two substrates, 157 and 158, were dienone compounds that contain alkenes on either side of the ketone, one being terminal and the other disubstituted 157 or trisubstituted 158. In the case of 157, the diboration proceeded in only 42% yield, but maintained ~90% chemoselectivity for the terminal alkene over the disubstituted alkene. When the trisubstituted substrate 158 was tested, 79% yield was obtained with 100% chemoselectivity for the terminal enone.

**Scheme 5-8.** Testing the scope of enone diboration

![Scheme 5-8](image-url)
5.3 Oxidation of Carbon Boron Bond

Now that the β-ketoboronate esters were successfully synthesized in high yields, oxidation procedures to obtain the desired β-hydroxyketone were screened. The common oxidation conditions of H₂O₂ and NaOH stirring for an hour in THF led to little success for the substrates tested (Scheme 5-9). These conditions were likely too harsh for the substrates because little to no product was obtained and all of the starting material was gone.

**Scheme 5-9. Initial oxidation attempts**

After a quick literature search, an alternative and much milder oxidation using sodium perborate tetrahydrate in a 1:1 mixture of THF and H₂O was found. The first attempt with this oxidation was with β-ketoboronate ester 139, which was oxidized to 159 in 71% yield in 3 hours. However, purification proved difficult for this substrate and the product was isolated with a slight pinacol contaminant in the product (Scheme 5-10). Pinacol is the byproduct from oxidizing a Bpin group.

**Scheme 5-10. Successful oxidation**

71% yield, pinacol contaminant
The scope of this oxidation was tested with the β-ketoboronate esters that were previously synthesized. In most cases, excellent yields were obtained with this oxidation. With the exception of 2 substrates that proved to be more difficult to work with than the rest, all of the yields were 89% or higher (Scheme 5-11). Most products were isolated with no trouble by column chromatography, however, a few had pinacol contaminants that could not be removed by chromatography. However it was later found that the pinacol could be removed by leaving the substrate on high vacuum at 45° C over-night.

**Scheme 5-11. Oxidation results using NaBO$_3$·4H$_2$O**

![Scheme 5-11](image)

In an attempt to increase the yield of this sequence, the isolation of the β-ketoboronate ester was skipped and the crude product was taken directly through the oxidation (Scheme 5-12). Boronate esters are known to decompose when in contact with silica gel. The hydroxyl groups on the silica gel can interact with the empty p orbital of boron and cause loss of the Bpin group. This was attempted on two substrates, and in both
cases it resulted in a higher yield over the two steps. Compound 160 obtained an 81% yield without isolation of the β-ketoboronate ester intermediate, while with isolation of the intermediate a combined yield of 61% was obtained. The 81% yield was calculated by mass % from the 1H NMR since some pinacol contaminant was present, however we now know that this pinacol contaminant can be removed via high vacuum. The hexanal derived substrate 162 was also isolated in a higher 76% yield without isolation of the intermediate, compared to a 58% yield with intermediate isolation.

**Scheme 5-12.** Direct diboration and oxidation

\[
\text{R} = \text{CuCl, NaOt-Bu} \quad 2:1 \text{THF:H}_{2}\text{O} \quad \text{R} \quad \text{Bpin} \quad \text{NaBO}_{3} \cdot 4\text{H}_{2}\text{O} \quad 1:1 \text{THF:H}_{2}\text{O} \quad \text{R} \quad \text{OH}
\]

\[
\text{Ph} \quad \text{OH} \quad 160 \quad 81\% \quad \text{H}_{3}\text{C} \quad \text{OH} \quad 162 \quad 76\%
\]

*pinacol contaminant, yield calculated my mass%
6. Felkin Controlled Diastereoselective Hydrosilation

6.1 Diastereoselectivity of Hydrosilation

With a successful synthetic route for β-hydroxyketones, the next step was hydrosilation of these new compounds. The idea behind this hydrosilation is that the methyl group and the large group on the carbon alpha to the carbonyl 96 that is not on the transition state ring will be able to control the diastereoselectivity of the propionate product. The diastereoselectivity of this reaction is expected to proceed through the Felkin-Ahn model 98 (Scheme 6-1). The Felkin-Ahn model is a well-known and widely accepted model for addition to carbonyls. In the Felkin-Ahn model, the large R group on the alpha carbon is to be perpendicular to the carbonyl and the medium methyl group is 120 degrees counterclockwise from the large group 98. From the Felkin-Ahn model it is expected that the anti-propionate product 97 will be synthesized (Scheme 6-1).

Scheme 6-1. Possible diastereoselective hydrosilation based on the Felkin-Ahn model

This hydrosilation produced varying results depending on the substrate used (Scheme 6-2). It was found that the R group had to be very large in order to give high
diastereoselectivity, but too large of a group would shut down the reaction. When R = Ph (167), the large group promoted high diastereoselectivity in the product, >9:1. However, with 168, R = OTBS, the sterics interference is too large and hydrosilation prevented, providing only starting material after desilylation. However, when a smaller alcohol protecting group such as PMB 169 is used, no diastereoselectivity is obtained. Same as in the case of 170, little diastereoselectivity is obtained with the PMB protection. Slightly higher diastereoselectivity is obtained when the PMB protection is swapped for the larger TBS as in 171, but diastereoselectivity is still minimal. Synthesis of anti-propionate subunits via this Felkin-controlled hydrosilation did not prove to be very successful.

Scheme 6-2. Hydrosilation of various β-hydroxyketone substrates
6.2 Matched and Mismatched Hydrosilation and Substrate Synthesis

With multiple results of both syn-propionate synthesis via the methyl group inside TS ring and anti-propionate synthesis via the Felkin controlled model, we were interested in determining which methyl group had the stronger effect on selectivity. It was assumed that the methyl group inside the transition state ring would have the higher selectivity based on previous hydrosilation results (Scheme 3-15). To test this, the following two compounds were synthesized and termed matched I and mismatched J (Figure 6-1).

![Chemical Structures]

**Figure 6-1.** Matched and mismatched substrates

The reasoning behind the names matched and mismatched is based off of the stereocontrol that both of the methyl groups incorporate after the hydrosilation (Scheme 6-3). The methyl group on the C₁ carbon promotes anti-propionate synthesis while the methyl group on the C₂ carbon promotes syn-propionate synthesis. When the C₁ and C₂ methyl groups are anti to each other in the β-hydroxyketone 172, this is termed the matched compound because both methyl groups promote the same stereochemistry for the hydroxyl group being formed (dashed in the case of 172). This will create the anti-syn stereotriad (Scheme 6-3). When the two methyl groups are syn to each other, as in 173, the molecule is termed mismatched, because one methyl groups promotes one diastereomer of product, while the other methyl group promotes a different diastereomer (Figure 6-3).
The synthesis of the matched and mismatched substrates proved to be challenging, the mismatched in particular. Both substrates were derived from the (R)-Roche Ester 174, a commercially available chiral starting material, because it already contains the methyl group on the C1 carbon in a single enantiomer (Scheme 6-4). Obtaining the methyl group on the C2 carbon in a single enantiomer was the challenging part of this synthesis. After some time, we settled on doing asymmetric aldol reactions on a protected ethyl ketone 177 derived from the (R)-Roche Ester 174. Using different catalysts and bases, it is possible to have the enolate of ethyl ketone 177 add into formaldehyde asymmetrically to give either the matched 175 or mismatched 176 substrate (Scheme 6-4).
Scheme 6-4. (R)-Roche Ester derived synthetic route for matched and mismatched substrates

The first step in the ethyl ketone 177 synthesis was protecting the alcohol of (R) Roche ester 174. A PMB protecting group was decided on based on the results from the paper by Urpi and coworkers on asymmetric aldol reactions using this ethyl ketone.\(^5^4\) The PMB protected ester 178 was synthesized in 94% yield by the addition of PMB acetimidate to the Roche ester in DCM with a catalytic amount of CSA (Scheme 6-5).\(^5^5\) Next, the Weinreb amide 179 was synthesized from the protected ester 178 by the addition of i-PrMgCl to 178 and N,O-dimethylhydroxylamine in THF.\(^4^9\) The Weinreb amide is useful for ketone synthesis because it allows for the addition of Grignard reagents directly to the Weinreb amide to synthesize ketones.\(^5^6\) If the Grignard reagent was added directly to the ester, it would add once, push off the ester group to create the ketone, then a second equivalent of Grignard would add into the ketone giving an undesired product.\(^1^1\) When a Grignard is added to the Weinreb amide, the intermediate 180 is produced, and this intermediate is stable in the reaction mixture preventing a second Grignard addition.
aqueous workup, this intermediate collapses with loss of the amine group to give the desired ketone 177 in 80% yield, 75% from 174 (Scheme 6-5).

**Scheme 6-5.** Ethyl ketone synthesis (references on slides)

The last step in synthesizing the matched and mismatched substrates involved asymmetric aldol reactions with the enolate adding into formaldehyde (Scheme 6-6).

Formaldehyde is a gas that is particularly difficult to work with because in order to obtain pure formaldehyde, it requires the pyrolysis of paraformaldehyde, the polymer of formaldehyde. Once paraformaldehyde is pyrolyzed, the resulting formaldehyde is very sensitive to moisture and when in contact with even the smallest amount of moisture it will polymerize again. Extreme caution is required when working with formaldehyde to minimize the moisture as much as possible.
In the synthesis of the matched substrate 175, dicyclohexylboron chloride (Cy₂BCl), a very large reagent, is used with triethylamine, a small base, for preferential formation of the E-enolate. Paraformaldehyde undergoes pyrolysis to yield pure formaldehyde gas which is transferred via cannula to a solution of ether at -78°C. This formaldehyde solution is then added to the enolate, which adds into formaldehyde via a chair like transition state 181. This transition state allows for the methyl group to adopt the anti-position to the other methyl group giving the matched substrate 175. The mismatched substrate is synthesized in a similar manner, using (i-PrO)TiCl₃ as the Lewis acid, a smaller Lewis acid, and a large base, Hünig's base (i-Pr₂EtN), promoting formation of the Z-enolate. The Z-enolate adds into formaldehyde by the transition state 182. The difficulty with this reaction came from the solubility of formaldehyde. At first, the reaction was attempted by pyrolyzing paraformaldehyde into DCM then adding the DCM formaldehyde solution to the enolate, but this was unsuccessful. The problem arose with solubility of formaldehyde in DCM, where it tended to polymerize rather than dissolve in the DCM. However, when this was attempted again with the enolate in DCM and formaldehyde in ether, decent success was obtained with this reaction.
Scheme 6-6. Asymmetric aldol reactions to synthesize the matched and mismatched substrates

Now that both the matched 175 and mismatched 176 substrates had been synthesized, the hydrosilation was attempted on these substrates. Both substrates resulted in good yields, 68% from the matched substrate and 72% from the mismatched (Scheme 6-7). As expected, the C₂ methyl group has greater control of the product stereochemistry. In both cases, the syn-propionates were synthesized. The C₁ methyl in the mismatched substrate did not have any effect on the stereochemistry of the product. Both cases resulted in >10:1 diastereoselectivity of the syn-propionate by ¹H NMR analysis. This is useful because it allows synthesis of both the syn-syn-propionate subunit 184 along with the anti-syn-propionate subunit 183 depending on whether matched or mismatched substrate is used.
6.3 Reagent Purity and Silane Disproportionation

The leading cause of low yields or no reaction occurring from this hydrosilation is due to impure reagents. Imidazole must be recrystallized from DCM prior to use and triethylamine and DCM must be either distilled over calcium hydride to remove water or obtained from a solvent system. It is often difficult to control the purity of the silane reagent itself. It is required to distill the silane directly out of the bottle before use, but even after distillation, it decomposes after a set amount of time, generally two to three weeks. At this point, more silane must be distilled prior to use. After 4-5 months the bottle itself will go bad and cause complete loss of activity even after distillation. Our prediction for the decomposition is a disproportionation or redistribution of the groups on silicon.

Evidence for the rearrangement of silicon compounds has been shown by Forbes and Anderson. They looked at the disproportionation of silicon trichlorothiocyanate 185 and its
ability to form silicon tetrachloride \textbf{186} and silicon tetrathiocyanate \textbf{187} without the addition of any catalyst (Scheme 6-8). It was found that after five months in a sealed tube at room temperature, silicon trichlorothiocyanate \textbf{185} rearranged to the extent of 35\%, meaning that 35\% of \textbf{185} had transformed into a combination of \textbf{186} and \textbf{187} in a ratio of 3:1. After 19 months in a sealed tube at room temperature, \textbf{185} had been found to rearrange to the extent of 63\%, leaving only 37\% of \textbf{185} and the rest as a mixture of \textbf{186} and \textbf{187}.\textsuperscript{57}

\textbf{Scheme 6-8.} Disproportionation of silicon trichlorothiocyanate\textsuperscript{57}

It is predicted that after a certain amount of time, our silane reagent, diphenylchlorosilane \textbf{188}, rearranges in a similar way. It is also thought that the electron rich phenyl groups on silicon speed on this rearrangement by stabilizing the formation of a cation or an anion on the silicon center. One of the proposed disproportionations is shown (Scheme 6-9), where a hydride from silane \textbf{188} adds into the silicon center of another molecule of \textbf{188} to give a positively charged tricoordinate silicon species \textbf{189} that is stabilized by electron donation from the phenyl groups along with a negatively charged pentacoordinate silicon \textbf{190}, also stabilized by the phenyl groups. From there, a phenyl group from \textbf{190} will migrate to \textbf{189} to neutralize both silicon species and give the rearrangement products \textbf{191} and \textbf{192}. This is not the only way for silane \textbf{188} to rearrange; there are a variety of products that could be produced from similar rearrangement (Scheme 6-10). It was attempted to monitor this
rearrangement by $^1$H NMR, however this proved to be unsuccessful. Even after three weeks, the spectra looked almost identical to directly after distillation however the silane did not work in the hydrosilation reaction.

**Scheme 6-9.** Proposed disproportionation of Ph$_2$SiHCl

![Scheme 6-9](image)

**Scheme 6-10.** Possible rearrangement products

![Scheme 6-10](image)
7. Discodermolide

7.1 Isolation and Biological Properties

To show the synthetic utility of our hydrosilation reaction, we decided to continue on from our matched hydrosilation product 183 to synthesize the stereocenters present in the different fragments of (-)-discodermolide (Figure 7-1). Discodermolide is a highly studied natural product because of its possible anti-cancer properties. Discodermolide was first isolated in 1990 by Longley and coworkers from the marine sponge Discodermia dissolute. This sponge was collected by scuba at Lucay in the Grand Bahama Island at a depth of 33 meters. After extracting the sponge with methanol and toluene, purifying the extract on silica gel and reverse-phase chromatography, discodermolide was found in the ethyl acetate layer in 0.002% yield (w/w from frozen sponge). They found that discodermolide itself was unstable at room temperature on high vacuum, so it was required to synthesize the acetylated version in order to characterize it and determine its structure.

![Figure 7-1. (+)-Discodermolide](image)
The main biological function of discodermolide is as a microtubule stabilizing agent. Computer analysis of (+)-discodermolide has shown its potential as an antimitotic compound and Day and coworkers have confirmed this prediction. Discodermolide is often compared to Epothilone A and paclitaxel for its antimitotic activity. Unlike Epothilone A, which inhibits microtubule formation Discodermolide works through the same mechanism as paclitaxel by hyper-stabilizing microtubules. Specifically, discodermolide will cause hyperstabilization of the mitotic spindle during mitosis causing cell cycle arrest and cell death. Even with concentrations of discodermolide as low as 10 nM it could be seen that filamentous and bundled microtubules were beginning to form and concentrating around the nucleus. As the concentration of discodermolide was increased to 1 µM, the microtubule bundles became increasingly prominent and elongated. Similarly, paclitaxel at 10 nM concentration had essentially no effect on the microtubule network. Paclitaxel at 10 µM concentration showed high levels of microtubule bundles, but they were still not as extensive as 1 µM discodemolide, showing that discodermolide is a much more potent microtubule stabilizing agent than paclitaxel.

CA46 cells were used to further test the effect of discodermolide because these cells arrest in the classic “C-mitosis” which is easy to see and quantify. The effects of increasing discodermolide on the growth of these cells was tested and an IC$_{50}$ value of 30 nM discodermolide was obtained compared to 40 nM paclitaxel. At a 1 µM discodermolide concentration, 68% of the cells were in mitotic arrest.

The mechanism for the increased potency over paclitaxel was determined by Schreiber and coworkers. It was found that both paclitaxel and discodermolide compete for
the same binding location on β-tubulin, but not the same binding site, and discodermolide binds this location much more strongly than paclitaxel. However, discodermolide and paclitaxel bind β-tubulin at different binding sites. Paclitaxel binds the M-loop\textsuperscript{62} while discodermolide interacts with the N-terminal H1-S2 loop.\textsuperscript{63} Knowing that they both bind in different locations allows for discodermolide and paclitaxel to work together complementary, which has been observed previously both in vitro and in vivo.\textsuperscript{63}

The ability to hyper-stabilize cancer cell microtubules causing mitotic arrest is easy to visualize as a possible cancer treatment and has been shown to destroy cancer cells.\textsuperscript{58} But it has also been discovered that microtubule stabilizing molecules, such as discodermolide, are possible cures for Alzheimer’s disease and other neurodegenerative diseases as well. Microtubules form linear arrays in the axons of neurons. The positive end is directed towards the synapses of the neuron while the negative end is pointed towards the cell body. The directionality and organization of these microtubules is important for proper function of the nerve cell. This system, along with many other structures, is a part of the axonal transport machinery. Taupathies are a group of neurodegenerative diseases, that include Alzheimer’s disease, that are believed to involve lack of axonal transportation, specifically involving the misfolding and aggregation of the microtubule associated protein tau.\textsuperscript{64} Aggregations of tau proteins cause buildup of amyloid plaques that are characteristic of Alzheimer’s disease. With these finding, the idea of a microtubule stabilizing drug as a potential cure for Alzheimer’s disease and other neurodegenerative diseases is a distinct possibility.\textsuperscript{65}
7.2 Previous Synthesis

With all the possible biological applications of discodermolide, it has become a popular target for natural product synthesis. Both (+) and (-)-discodermolide have been synthesized in multiple laboratories. The first laboratory to report the synthesis of (+)-discodermolide, the naturally occurring enantiomer, was Schreiber’s.\textsuperscript{66} Prior to his synthesis of (+)-discodermolide, he had reported the synthesis of its enantiomer, the unnatural (-)-discodermolide.\textsuperscript{67} Since then, several other syntheses’ have been reported.\textsuperscript{68} The most notable synthesis is the gram-scale synthesis by Smith and co-workers.\textsuperscript{69} This, along with Patterson’s first generation synthesis\textsuperscript{70} permitted Novartis to synthesize 60 g of (+)-discodermolide\textsuperscript{71} for phase I clinical trials.\textsuperscript{72} We will look at Smith’s synthesis of (-)-discodermolide in more detail since our chemistry is on its way to synthesizing the (-)-enantiomer of discodermolide.\textsuperscript{73}

The retrosynthesis reported by Smith for (-)-discodermolide starts by breaking the molecule into three different fragments, A, B and C (Scheme 7-1). These three fragments can be further broken down into a single common precursor (CP).\textsuperscript{73} This common precursor was of particular interest to us and our hydrosilation research. The common precursor
contains a stereotriad with anti-syn stereochemistry, the exact same stereochemistry as the anti-syn stereotriad that results from the hydrosilation of the matched substrate I. In our case we happened to start with the \((R)\)-roche ester for our matched and mismatched research, so we will continue on with this enantiomer to create the stereocenters from \((-\)discodermolide. The enantiomer can be synthesized simply by starting with the \((S)\)-roche ester instead of the \((R)\).

**Scheme 7-1.** Smith’s retrosynthesis of \((-\)discodermolide\)**

Smith and coworkers synthesize the common precursor by starting with the \((R)\)-roche ester 174 and PMB protecting it followed by LiAlH\(_4\) reduction of the ester to an alcohol 193. Next, an aldol was required to create the stereotriad so the alcohol was oxidized up to the aldehyde 194 by a swern oxidation and an Evan’s aldol was performed to give the desired
stereotriad 195. The oxazolidinone auxiliary was removed by formation of the Weinreb amide and completion of CP (Scheme 7-2). Similarly, in our synthesis five steps are also required to synthesize the stereotriad using a hydrosilation to set the hydroxyl stereocenter (Scheme 7-3).

**Scheme 7-2.** Smith and coworkers CP synthesis

![Scheme 7-2](image)

**Scheme 7-3.** Hydrosilation to synthesize the stereotriad

![Scheme 7-3](image)

**7.3 Fragment Synthesis**

To show the synthetic utility of our hydrosilation reaction, we decided to continue on from our common precursor 183 to synthesize the stereocenters present in the 3 fragments of (-)-discodermolide. The stereocenters of A were synthesized by selectively oxidizing the
primary alcohol into the aldehyde 186 via a TEMPO oxidation (Scheme 7-4). This was achieved in 91% yield. Next, an Evan’s aldol was performed to give 197 in 85% yield with the same stereopentad as fragment A. For fragment B, the stereotriad of our common precursor 183 was the same, so no further reaction were needed. For fragment C, the four stereocenters in the lactone ring were obtained after four reactions (Scheme 7-5). The first reaction was an acetal protection of the 1,3-diol to form 198 in 97% yield. Next, the PMB group was removed by addition of DDQ to give the alcohol 199 in 84% yield. Oxidation of the primary alcohol via TEMPO provided aldehyde 200 in 82%. And finally, an asymmetric allylation of the aldehyde using Leighton’s allylation reagent\textsuperscript{74} 201 provided 202, which contains the 4 stereocenters present in the lactone ring of fragment C.

**Scheme 7-5.** Synthesis of the stereopentad present in fragment A
Scheme 7-6. Synthesis of the stereopentad present in fragment C
8. Conclusion

The hydrosilation research was continued after a new synthetic route to obtain β-hydroxyketones was discovered. This new route consisted of the diboration of terminal enone compounds to the corresponding β-ketoborurate ester. Next, the carbon boron bond was oxidized to provide the β-hydroxyketone in two steps from the enone. The diboration proceeded in high yields, varying from 64% for the difficult substrates, up to the 80-95% range where most substrates consisted. The oxidation proceeded in high 89-100% yields in the majority of substrates, only a few outliers in the 70% range.

The hydrosilation to create anti-propionate subunits was tested and gave varying results depending on the substrate. The diastereoselectivity was found to be much lower than desired for most substrates. However, the matched and mismatched hydrosilation provided great success, allowing synthesis of the anti-syn propionate from the matched substrate in >10:1 diastereoselectivity along with the syn-syn propionate from the mismatched substrate in >10:1 diastereoselectivity. This results shows that the methyl substituent inside the transition state ring has complete control of the diastereoselectivity of the product.

The stereotriad from the matched substrate 183 matched the common precursor CP used by Smith and coworkers to synthesize (-)-discodermolide. We were able to take our stereotriad and use it as a common precursor to synthesize all the stereocenters present in the three fragments of (-)-discodermolide.
9. Future Work

The next step in our research involves different ways of opening the cyclic disiloxane ring rather than just completely removing it using TBAF. The current idea is to use t-BuLi in place of TBAF and have the t-Bu group add to the silicon and break one of the oxygen silicon bonds, essentially putting a diphenyl t-butyl silicon protection on one of the hydroxyl groups (Scheme 9-1). This will allow for selective protection of one of the alcohol groups in the propionate subunit without the additional step. It will be particularly useful to protect the secondary alcohol in this manner because it is not currently possible to protect a secondary alcohol in the presence of a primary alcohol.

**Scheme 9-1.** t-BuLi opening of the cyclic disiloxane

![Chemical structure](image)

Additional future work involves the synthesis of the natural product Nhatrangin A (Figure 9-1). Nhatrangin A has been shown to have anticancer activity against lymphocytic murine leukemia (P-388). In vivo tests on mice revealed that microgam dosages were enough to show increased survival time in mice injected with the P-388 leukemia cell line. In the main chain of Nhatrangin A, the anti-syn stereotriad that is produced from the matched hydrosilation is present (Figure 9-1).
Figure 9-1. Structure of Nhatrangin A with stereotriad highlighted
10. Experimental

Enone synthesis:

**Enone synthesis from aldehydes:**

Under an N\textsubscript{2} atmosphere, the aldehyde (5.0 mmol) was dissolved in THF (12 mL) in a 50 mL flame dried Schlenk tube and cooled to 0° C in an ice/water bath. A freshly made solution of vinylmagnesium bromide (1.0 M, 6.0 mmol, 1.2 eq.) was added slowly and the reaction was allowed to stir for 30 minutes. The reaction was quenched with a saturated ammonium chloride solution. The aqueous layer was extracted with methyl tert-butyl ether (3 x 25 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude product was then dissolved in acetone (25 ml) and cooled to 0° C. Jones reagent (4.0 M, 5.0 mmol, 1.0 eq.) was added dropwise and the reaction was allowed to stir for 10 minutes before the addition of isopropanol (1 mL). Water (10 mL) was added and the reaction mixture was extracted with methyl tert-butyl ether (3 x 25 mL) and the combined organic layers were washed with a brine solution (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo.

**Enone synthesis from weinreb amide:**

\[
\begin{align*}
\text{(R)-5-((4-methoxybenzyl)oxy)-4-methylpent-1-en-3-one.}
\end{align*}
\]

Under an N\textsubscript{2} atmosphere, (R)-N-methoxy-3-((4-methoxybenzyl)oxy)-N,2-dimethylpropanamide (0.649 g, 2.43 mmol, 1 eq.) dissolved in THF (13 mL), was added to a
50 mL flame dried Schlenk tube equipped with a stir bar and cooled to -15° C in an acetone/ice bath. A freshly made solution of vinylmagnesium bromide (8.2 mL, 1.0 M, 8.21 mmol, 3.2 eq) was added dropwise. The reaction mixture was stirred and allowed to warm to room temperature over 5 hours. The reaction was quenched with a saturated ammonium chloride solution. The aqueous layer was extracted with methyl tert-butyl ether (3 x 25 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 hexanes:EtOAc) provided (R)-5-((4-methoxybenzyl)oxy)-4-methylpent-1-en-3-one as a clear colorless oil (0.350 g, 1.50 mmol, 62%).

\[ \text{H NMR (500 MHz, chloroform-}d\text{):} \delta = 7.22 \text{ (d,} J = 9.0, 2H), 6.87 \text{ (d,} J = 9.0, 2H), 6.44 \text{ (dd,} J = 11.0, 18.0, 1H), 6.28 \text{ (dd,} J = 1.5, 18.0, 1H), 5.80 \text{ (dd,} J = 1.5, 10.5, 1H), 4.4d \text{ (d,} J = 11.0, 1H), 4.40 \text{ (d,} J = 11.5, 1H), 3.80 \text{ (s,} 3H), 3.67 \text{ (dd,} J = 9.5, 2.0, 1H), 3.44 \text{ (dd,} J = 8.5, 3.0, 1H), 3.17 \text{ (sextet,} J = 6.0, 1H), 1.11 \text{ (d,} J = 6.5, 3H). \]

\[ \text{C NMR (125 MHz, chloroform-d):} \delta = 202.7, 159.4, 135.7, 130.4, 129.4, 128.6, 113.9, 73.1, 71.9, 55.5, 43.9, 14.1. \]

\[ \text{IR (neat):} 2935, 2857, 1697, 1676, 1611, 1512, 1245, 1093, 1033, 972, 818 \text{ cm}^{-1}. \]

\[ \text{HRMS (ESI)} \text{ calcd for (C}_{14}\text{H}_{18}\text{O}_{3} + \text{Na})^{+} 257.1154, \text{ found 257.1152.} \ ]

\[ \alpha = -9.25 \text{ (c = 9.8, CH}_{2}\text{Cl}_{2}) \]

(R)-5-((tert-butyldimethylsilyl)oxy)-4-methylpent-1-en-3-one.

Under an N₂ atmosphere, (R)-3-((tert-butyldimethylsilyl)oxy)-N-methoxy-N,2-dimethylpropanamide (0.965 g, 3.74 mmol, 1 eq.) dissolved in THF (19 mL), was added to a
50 mL flame dried Schlenk tube equipped with a stir bar and cooled to -15° C in an acetone/ice bath. A freshly made solution of vinylmagnesium bromide (12.0 mL, 1.0 M, 12.0 mmol, 3.2 eq) was added dropwise. The reaction mixture was stirred and allowed to warm to room temperature over 5 hours. The reaction was quenched with a saturated ammonium chloride solution. The aqueous layer was extracted with methyl tert-butyl ether (3 x 25 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:EtOAc) provided (R)-5-((tert-butylidimethylsilyloxy)-4-methylpent-1-en-3-one as a clear colorless oil (0.455 g, 2.00 mmol, 53%).

**¹H NMR** (500 MHz, chloroform-­d): δ = 6.45 (dd, J = 10.0, 17.5, 1H), 6.26 (dd, 1.5, 17.5, 1H), 5.79 (dd, J = 1.5, 10.5, 1H), 3.80 (dd, J = 7.5, 10.0, 1H), 3.62 (dd, J = 6.0, 9.5, 1H), 3.09 (sextet, J = 6.5, 1H), 1.07 (d, J = 7.0, 3H), 0.85 (s, 9H), 0.3 (s, 3H), 0.1 (s, 3H). **¹³C NMR** (125 MHz, chloroform-­d): δ = 203.5, 136.3, 128.3, 65.6, 46.0, 26.0, 18.4, 13.6, -5.3. **IR** (neat): 2956, 2929, 2857, 1700, 1680, 1463, 1252, 1099, 834, 775 cm⁻¹. **HRMS** (ESI) calcd for (C₁₂H₂₄O₂Si + Na)⁺ 251.1443, found 251.1443. [α] = -36.2 (c = 10.5, CH₂Cl₂)

![Structure of (S)-4-((tert-butylidimethylsilyloxy)pent-1-en-3-one](attachment:image)

**Under an N₂ atmosphere,** (S)-2-((tert-butylidimethylsilyloxy)-N-methoxy-N-methylpropanamide (1.388 g, 5.62 mmol, 1 eq.) dissolved in THF (28 mL), was added to a
100 mL flame dried Schlenk tube equipped with a stir bar and cooled to -15° C in an acetone/ice bath. A freshly made solution of vinylmagnesium bromide (18.0 mL, 1.0 M, 18.0 mmol, 3.2 eq) was added dropwise. The reaction mixture was stirred and allowed to warm to room temperature over 5 hours. The reaction was quenched with a saturated ammonium chloride solution. The aqueous layer was extracted with methyl tert-butyl ether (3 x 25 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 hexanes:EtOAc) provided (S)-4-((tert-butyldimethylsilyl)oxy)pent-1-en-3-one as a clear colorless oil (0.679 g, 3.17 mmol, 57%).

\[ \text{1H NMR (500 MHz, chloroform-d): } \delta = 6.87 (dd, J = 11.0, 18.0, 1H), 6.40 (dd, J = 2.0, 17.5, 1H), 5.77 (dd, J = 2.0, 11.0, 1H), 4.29 (q, 6.5, 1H), 1.31 (d, J = 7.0, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). \]

(S)-4-((4-methoxybenzyl)oxy)pent-1-en-3-one.

Under an N\(_2\) atmosphere, (S)-N-methoxy-2-((4-methoxybenzyl)oxy)-N-methylpropanamide (0.585 g, 2.31 mmol, 1 eq.) dissolved in THF (50 mL), was added to a 100 mL flame dried Schlenk tube equipped with a stir bar and cooled to -15° C in an acetone/ice bath. A freshly made solution of vinylmagnesium bromide (2.88 mL, 2.0 M, 5.75 mmol, 2.5 eq) was added dropwise. The reaction mixture was stirred for 1 hour. The reaction was quenched with a
saturated ammonium chloride solution. The aqueous layer was extracted with methyl tert-
butyl ether (3 x 25 mL) and the combined organic layers were dried over anhydrous
magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column
chromatography on silica gel (4:1 hexanes:EtOAc) provided (S)-4-((4-
methoxybenzyl)oxy)pent-1-en-3-one as a clear colorless oil (0.329 g, 1.50 mmol, 65%).

\[ ^1H \text{ NMR (500 MHz, chloroform-}d \text{): } \delta = 7.26 \text{ (d, } J = 9.0, 2H), 6.88 \text{ (d, } J = 9.0, 2H), 6.79 \text{ (dd, } J = 10.0, 17.0, 1H), 6.43 \text{ (dd, } J = 2.0, 17.5, 1H), 5.80 \text{ (dd, } J = 2.0, 11.0, 1H), 4.49 \text{ (d, } J = 11.0, 1H), 4.38 \text{ (d, } J = 11.0, 1H), 4.09 \text{ (q, } J = 7.0, 1H), 3.81 \text{ (s, 3H), 1.36 \text{ (d, } J = 7.5, 3H).} \]

\[ ^13C \text{ NMR (125 MHz, chloroform-}d \text{): } \delta = 201.6, 159.4, 130.9, 129.8, 129.6, 129.5, 113.9, 79.5, 71.5, 55.3, 17.8. \] [\alpha]

\[ \]

**Neral.**

Under an open air atmosphere, PhI(OAc)_2 (2.30 g, 7.13 mmol, 1.1 eq.) and TEMPO (0.101 g,
0.65 mmol, 0.1 eq.) were dissolved in acetonitrile (6.5 mL) and pH 7.0 buffer (1.6 mL) in a
50 ml round bottom flash equipped with a stir bar and cooled to 0° C in an ice/water bath.
Nerol (1.135 mL, 6.48 mmol, 1.0 eq.) was added and the reaction was stirred for three hours
and allowed to warm to room temperature. The reaction was quenched with saturated
aqueous sodium thiosulfate (5 mL) and the layers were separated. The aqueous layer was
extracted with DCM (3 x 15 mL) and the combined organic layers were dried over anhydrous
magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:EtOAc) provided Neral as a clear slightly red oil (1.200 g, 6.48 mmol, >100% yield) with a small amount of PhI(OAc)$_2$ contaminant. Was used in next reaction without further purification.

$^1$H NMR (500 MHz, chloroform-$d$): $\delta = 9.89$ (d, $J = 8.5$, 1H), 5.88 (d, $J = 8.0$, 1H), 5.13-5.07 (m, 1H), 2.58 (t, $J = 7.5$, 2H), 2.23 (q, $J = 7.5$, 2H), 1.98 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H).

$\text{(Z)-5,9-dimethyldeca-1,4,8-trien-3-ol.}$

Under an N$_2$ atmosphere, semi-crude Neral (6.48 mmol, 1.0 eq.) was dissolved in THF (18 mL) in a flame dried 50 mL Schlenk tube and cooled to 0° C in an ice/water bath. Freshly prepared vinylmagnesium bromide (8.5 mL, 1.5 M, 13.0 mmol, 2.0 eq.) was added slowly to the reaction mixture and the reaction was allowed to stir for 30 minutes at 0° C. The reaction was quenched with saturated aqueous ammonium chloride (25 mL) and the layers were separated. The aqueous layer was extracted with MTBE (3 x 25 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (20:1 to 10:1 hexanes:EtOAc) provided (Z)-5,9-dimethyldeca-1,4,8-trien-3-ol as a clear colorless oil (1.10 g, 6.11 mmol, 94%).
\(^1\)H NMR (500 MHz, chloroform-\(d\)): \(\delta = 5.88\) (ddd, \(J = 5.5, 10.5, 17.5, 1\)H), 5.26-5.20 (m, 2H), 5.14-5.08 (m, 2H), 4.85 (t, \(J = 7.0, 1\)H), 2.18-2.08 (m, 4H), 1.75 (d, \(J = 1.5, 3\)H), 1.69 (s, 3H), 1.61 (s, 3H). \(^1\)C NMR (125 MHz, chloroform-\(d\)): \(\delta = 140.3, 139.6, 132.7, 126.9, 124.0, 114.5, 69.6, 32.6, 26.6, 25.9, 23.7, 17.9\).

(E)-1-phenylpenta-1,4-dien-3-one.

Under an N\(_2\) atmosphere, 4Å molecular sieves were activated by flame drying three times in a 50 mL Schlenk tube equipped with a stir bar. (E)-1-phenylpenta-1,4-dien-3-ol (0.800 g, 5.0 mmol, 1.0 eq.), DCM (32 mL), and acetonitrile (3.2 mL) were added to the molecular sieves. N-methylmorpholine-N-oxide (0.880 g, 7.5 mmol, 1.5 eq.) was added and the reaction was stirred for 5 minutes. Tetrapropylammonium perruthenate (0.176 g, 0.5 mmol, 0.1 eq.) was added and the reaction was allowed to stir overnight. The reaction mixture was filtered through a plug of silica with EtOAc and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel provided (E)-1-phenylpenta-1,4-dien-3-one as a clear slightly yellow oil (0.408 g, 2.6 mmol, 52%).

\(^1\)H NMR (500 MHz, chloroform-\(d\)): \(\delta = 7.69\) (d, \(J = 16.0, 1\)H), 7.60-7.52 (m, 2H), 7.45-7.40 (m, 2H), 7.03 (d, \(J = 16.5, 1\)H), 6.78-6.70 (m, 1H), 6.40 (d, \(J = 17.5, 1\)H), 5.91 (d, \(J = 10.5, 1\)H).
(Z)-5,9-dimethyldeca-1,4,8-trien-3-one.

Under an N\textsubscript{2} atmosphere, 4Å molecular sieves were activated by flame drying three times in a 50 mL Schlenk tube equipped with a stir bar. (Z)-5,9-dimethyldeca-1,4,8-trien-3-ol (0.360 g, 2.0 mmol, 1.0 eq.), DCM (13 mL), and acetonitrile (1.3 mL) were added to the molecular sieves. N-methylmorpholine-N-oxide (0.352 g, 3.0 mmol, 1.5 eq.) was added and the reaction was stirred for 5 minutes. Tetrapropylammonium perruthenate (0.070 g, 0.20 mmol, 0.1 eq.) was added and the reaction was allowed to stir overnight. The reaction mixture was filtered through a plug of silica with EtOAc and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel provided (Z)-5,9-dimethyldeca-1,4,8-trien-3-one as a clear slightly yellow oil (0.118 g, 0.66 mmol, 33%) along with (Z)-5,9-dimethyldeca-1,4,8-trien-3-ol (0.198 g, 1.10 mmol, 55% of starting material recovered) providing a yield based on recovered starting material of 74%.

\textbf{\textsuperscript{1}H NMR} (500 MHz, chloroform-\textit{d}): \(\delta = 6.40\) (dd, \(J = 9.5, 18.0, 1\text{H}\)), 6.25 (d, \(J = 1.5, 1\text{H}\)), 6.21 (dd, \(J = 1.0, 17.0, 1\text{H}\)), 5.73 (dd, \(J = 1.5, 11.0, 1\text{H}\)), 5.15 (tq, \(J = 1.5, 9.0, 1\text{H}\)), 2.61 (t, 7.5, 2H), 2.16 (q, \(J = 7.0, 2\text{H}\)), 1.93 (d, \(J = 1.5, 3\text{H}\)), 1.67 (d, \(J = 1.0, 3\text{H}\)), 1.63 (s, 3H). \textbf{\textsuperscript{13}C NMR} (125 MHz, chloroform-\textit{d}): \(\delta = 190.1, 161.0, 138.3, 132.2, 127, 123.7, 122.3, 34.2, 26.8, 25.9, 25.7, 17.6\). \textbf{IR} (neat): 2968, 2915, 2856, 1724, 1661, 1674, 1622, 1601, 1447, 1400, 1376, 1243, 1117, 983, 959, 853, 713 cm\textsupersubscript{-1}. 86
Enone diboration:

![Enone diboration](image)

1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (139).

Under an N₂ atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.020 g, 0.20 mmol, 0.20 eq.) and NaOt-Bu (0.020 g, 0.20 mmol, 0.20 eq), dissolved in THF (2.0 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.254 g, 1.0 mmol, 1.0 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before 1-phenylprop-2-en-1-one (0.158 g, 1.2 mmol, 1.2 eq.) and water (1.0 mL) were added and the reaction was allowed to stir for 3 hours. The reaction mixture was quenched with a saturated Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:Ethyl Acetate) provided 1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one as a clear colorless oil (0.166 g, 0.64 mmol, 64%).

\(^1\)H NMR (500 MHz, chloroform-\(d\)): \(\delta = 7.97 (d, J = 7.0, 2H), 7.54 (t, J = 7.5, 1H), 7.44 (t, J = 7.5, 2H), 3.16 (t, J = 7.0, 2H), 1.25 (s, 12H), 1.07 (t, J = 7.0, 2H).\n
\(^13\)C NMR (125 MHz, chloroform-\(d\)): \(\delta = 200.8, 137.1, 133.0, 128.7, 128.2, 83.3, 33.9, 25.0.\n
\(^13\)B NMR (160 MHz,
chloroform-$d$): $\delta = 33.6$. **IR** (neat): 2977, 2933, 1685, 1379, 1371, 1316, 1221, 1144, 690 cm$^{-1}$. **HRMS** (ESI) calcd for ($C_{15}H_{21}BO_3 + Na)^+ 283.1484$, found 283.1490.

\[
\begin{align*}
\text{4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (150).}
\end{align*}
\]
Under an N$_2$ atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.020 g, 0.20 mmol, 0.20 eq.) and NaOt-Bu (0.020 g, 0.20 mmol, 0.20 eq), dissolved in THF (2.0 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.254 g, 1.0 mmol, 1.0 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before 4-phenylpent-1-en-3-one (0.192 g, 1.2 mmol, 1.2 eq.) and water (1.0 mL) were added and the reaction was allowed to stir for 3 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:Ethyl Acetate) provided 4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one as a clear colorless oil (0.197 g, 0.68 mmol, 68%).

**$^1$H NMR** (500 MHz, chloroform-$d$): $\delta = 7.31$ (t, $J = 7.5$, 2H), 7.25-7.2 (m, 3H), 3.77 (q, $J = 7.0$, 1H), 2.59-2.45 (m, 2H), 1.38 (d, $J = 7.0$, 3H), 1.21 (s, 12H), 0.90-0.78 (m, 2H). **$^{13}$C**
NMR (125 MHz, chloroform-d): $\delta = 211.6, 141.2, 129.0, 128.1, 127.1, 83.2, 52.5, 36.3, 25.0, 24.9, 17.9$.  
$^{11}$B NMR (160 MHz, chloroform-d): $\delta = 34.3$. IR (neat): 2976, 2930, 1712, 1371, 1315, 1144, 699 cm$^{-1}$. HRMS (ESI) calcd for (C$_{17}$H$_{25}$BO$_3$ + Na)$^+$ 311.1798, found 311.1799.

5-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one (151).

Under an N$_2$ atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.030 g, 0.30 mmol, 0.20 eq.) and NaOr-Bu (0.030 g, 0.30 mmol, 0.20 eq.), dissolved in THF (3.0 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.381 g, 1.5 mmol, 1.0 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before 5-methylhex-1-en-3-one (0.202 g, 1.8 mmol, 1.2 eq.) and water (1.5 mL) were added and the reaction was allowed to stir for 3 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:Ethyl Acetate) provided 5-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one as a clear colorless oil (0.284 g, 0.79 mmol, 79%).
**1H NMR** (500 MHz, chloroform-\textit{d}): $\delta = 2.54$ (t, $J = 7.0$, 2H), 2.26 (d, $J = 6.5$, 2H), 2.12 (sept, $J = 6.5$, 1H), 1.23 (s, 12H), 0.90 (d, $J = 6.5$, 6H), 0.88 (t, $J = 6.5$, 2H). **13C NMR** (125 MHz, chloroform-\textit{d}): $\delta = 211.5$, 83.2, 51.5, 38.4, 25.2, 25.0, 24.8, 22.8. **11B NMR** (160 MHz, chloroform-\textit{d}): $\delta = 34.4$. IR (neat): 2957, 1711, 1414, 1379, 1370, 1313, 1144, 968, 872, 844 cm$^{-1}$. HRMS (ESI) calcd for (C$_{13}$H$_{25}$BO$_3$ + Na)$^+$ 263.1797, found 263.1791.

![Chemical Structure](image)

**1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octan-3-one** (152).

Under an N$_2$ atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.020 g, 0.20 mmol, 0.20 eq.) and NaOt-Bu (0.020 g, 0.20 mmol, 0.20 eq), dissolved in THF (2.0 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.254 g, 1.0 mmol, 1.0 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before oct-1-en-3-one (0.151 g, 1.2 mmol, 1.2 eq.) and water (1.0 mL) were added and the reaction was allowed to stir for 3 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:Ethyl Acetate) provided 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octan-3-one as a clear colorless oil (0.163 g, 0.64 mmol, 64%).
\(^{1}\text{H NMR}\) (500 MHz, chloroform-\(d\)): \(\delta = 2.55\) (t, \(J = 7.0\), 2H), 2.37 (t, \(J = 7.5\), 2H), 1.56 (quintet, \(J = 7.5\), 2H), 1.33-1.23 (m, 4H), 1.23 (s, 12H), 0.90 (t, \(J = 7.0\), 2H), 0.87 (t, \(J = 7.5\), 3H). \(^{13}\text{C NMR}\) (125 MHz, chloroform-\(d\)): \(\delta = 212.0\), 83.3, 42.4, 37.7, 31.6, 25.0, 24.0, 22.7, 14.1. \(^{11}\text{B NMR}\) (160 MHz, chloroform-\(d\)): \(\delta = 34.4\). \(\text{IR}\) (neat): 2931, 1712, 1378, 1313, 1145, 968, 841 cm\(^{-1}\). \(\text{HRMS}\) (ESI) calcd for (\(\text{C}_{14}\text{H}_{27}\text{BO}_{3} + \text{Na}\))\(^{+}\) 277.1954, found 277.1943.

\(\text{(R)}\)-1-((4-methoxybenzyl)oxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (153).

Under an \(N_2\) atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.010 g, 0.10 mmol, 0.20 eq.) and NaOt-Bu (0.010 g, 0.10 mmol, 0.20 eq), dissolved in THF (1.0 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.127 g, 0.5 mmol, 1.0 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before \(\text{(R)}\)-5-((4-methoxybenzyl)oxy)-4-methylpent-1-en-3-one (0.137 g, 0.6 mmol, 1.2 eq.) and water (0.5 mL) were added and the reaction was allowed to stir for 3 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated \textit{in vacuo}. After three hours, the reaction had not gone to completion, the enone was still present in the crude \(^{1}\text{H NMR}\)
spectra. The crude product was resubjected to the same reaction conditions and the yield was based off of the amount of enone used. Purification by flash column chromatography on silica gel (10:1 to 4:1 hexanes:Ethyl Acetate) provided (R)-1-((4-methoxybenzyl)oxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one as a clear colorless oil (0.197 g, 0.54 mmol, 91%).

\[ \text{IR (neat): 2976, 2933, 1711, 1612, 1513, 1371, 1245, 1144, 819 cm}^{-1} \]

\[ \text{HRMS (ESI) calcd for } (C_{20}H_{31}BO_5^+ + Na)^+ 385.2166, \text{ found } 385.2156. \]  
\[ [\alpha] = -20.3 \text{ (c = 10.8, CH}_2\text{Cl}_2) \]

\[ \text{(R)-1-((tert-butyldimethylsilyl)oxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (154).} \]

Under an N\textsubscript{2} atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.020 g, 0.20 mmol, 0.18 eq.) and NaOt-Bu (0.020 g, 0.20
mmol, 0.18 eq.), dissolved in THF (4.0 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.334 g, 1.32 mmol, 1.1 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before (R)-5-((tert-butyldimethylsilyl)oxy)-4-methylpent-1-en-3-one (0.250 g, 1.10 mmol, 1.0 eq.) and water (2.0 mL) were added and the reaction was allowed to stir for 8 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:Ethyl Acetate) provided (R)-1-((tert-butyldimethylsilyl)oxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one as a clear colorless oil (0.367 g, 1.03 mmol, 94%).

$^1$H NMR (500 MHz, chloroform-d): δ = 3.72 (dd, J = 10.0, 2.0, 1H), 3.56 (dd, J = 10.0, 4.0, 1H), 2.75 (sextet, J = 6.0, 1H), 2.64 (t, J = 7.0, 2H), 1.23 (s, 6H), 1.22 (s, 6H), 1.02 (d, J = 6.5, 3H), 0.92-0.86 (m, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). $^{13}$C NMR (125 MHz, chloroform-d): δ = 214.3, 83.2, 65.7, 48.5, 37.8, 26.0, 25.0, 24.9, 18.4, 13.4, -5.3. $^{11}$B NMR (160 MHz, chloroform-d): δ = 33.7. IR (neat): 2929, 2858, 1714, 1379, 1371, 1313, 1145, 1097, 835, 775 cm$^{-1}$. HRMS (ESI) calcd for (C$_{18}$H$_{37}$BO$_4$Si + Na)$^+$ 379.2456, found 379.2461. [α] = -21.1 (c = 10.3, CH$_2$Cl$_2$)
(S)-4-((tert-butyldimethylsilyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (155).

Under an N₂ atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.020 g, 0.20 mmol, 0.20 eq.) and NaOt-Bu (0.020 g, 0.20 mmol, 0.20 eq), dissolved in THF (2.0 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.280 g, 1.1 mmol, 1.1 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before (S)-4-((tert-butyldimethylsilyl)oxy)pent-1-en-3-one (0.214 g, 1.00 mmol, 1.0 eq.) and water (1.0 mL) were added and the reaction was allowed to stir for 8 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:Ethyl Acetate) provided (S)-4-((tert-butyldimethylsilyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one as a clear colorless oil (0.270 g, 0.79 mmol, 79%).

¹H NMR (500 MHz, chloroform-d): δ = 4.15 (q, J = 6.5, 1H), 2.73 (dddd, J = 6.5, 6.5, 19.5, 44.0, 2H), 1.27 (d, J = 7.0, 3H), 1.22 (s, 6H), 1.22 (s, 6H), 0.91 (s, 9H), 0.90-0.86 (m, 2H), 0.7 (s, 3H), 0.6 (s, 3H). ¹³C NMR (125 MHz, chloroform-d): δ = 215.1, 83.2, 74.9, 32.3,
26.0, 25.0, 25.0, 21.3, 18.3, -4.5, -4.9. \(^{11}\)B NMR (160 MHz, chloroform-\(d\)): \(\delta = 33.4\). IR (neat): 2955, 2931, 2858, 1716, 1379, 1371, 1251, 1145, 834, 776 cm\(^{-1}\). HRMS (ESI) calcd for (C\(_{17}\)H\(_{35}\)BO\(_4\)Si + Na\(^+\) 365.2299, found 365.2307. \([\alpha] = -6.8\ (c = 10.7, \text{CH}_2\text{Cl}_2)\)

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{O} \\
\text{OPMB} \\
\text{B-O} \\
\text{CH}_3 \\
\text{O} \\
\text{CH}_3 \\
\text{H}_3\text{C} \\
\end{array}
\]

(S)-4-((4-methoxybenzyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (156).

Under an N\(_2\) atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.020 g, 0.20 mmol, 0.14 eq.) and NaOt-Bu (0.020 g, 0.14 mmol, 0.20 eq), dissolved in THF (3.5 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.406 g, 1.6 mmol, 1.1 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before (S)-4-((4-methoxybenzyl)oxy)pent-1-en-3-one (0.320 g, 1.45 mmol, 1.0 eq.) and water (1.7 mL) were added and the reaction was allowed to stir for 8 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel (4:1 hexanes:Ethyl Acetate) provided (S)-4-((4-methoxybenzyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one as a clear colorless oil (0.447 g, 1.29 mmol, 89%).

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$^1$H NMR (500 MHz, chloroform-$d$): $\delta = 7.28$ (d, $J = 8.5$, 2H), 6.88 (d, $J = 9.0$, 2H), 4.51 (d, $J = 11.0$, 1H), 4.38 (d, $J = 11.5$, 2H), 3.93 (q, $J = 7.0$, 1H), 3.81 (s, 3H), 2.72 (t, $J = 6.5$, 2H), 1.32 (d, $J = 7.0$, 3H), 1.23 (s, 12H), 0.93 (t, $J = 6.5$, 2H).  $^{13}$C NMR (125 MHz, chloroform-$d$): $\delta = 213.7$, 159.2, 129.8, 129.5, 113.9, 83.1, 80.0, 71.4, 55.3, 32.4, 24.8, 24.8, 17.9.  IR (neat): 2977, 2934, 1714, 1612, 1513, 1379, 1370, 1314, 1244, 1144, 1034, 822 cm$^{-1}$.

(E)-1-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-one (157).

Under an N$_2$ atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.010 g, 0.10 mmol, 0.20 eq.) and NaOt-Bu (0.010 g, 0.10 mmol, 0.20 eq.), dissolved in THF (2 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.140 g, 0.55 mmol, 1.1 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before (E)-1-phenylpenta-1,4-dien-3-one (0.079 g, 0.50 mmol, 1.0 eq.) and water (1 mL) were added and the reaction was allowed to stir for 8 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:Ethyl Acetate) provided (S)-4-((4-methoxybenzyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one as a clear colorless oil (0.060 g, 0.21 mmol, 42%).
$^1$H NMR (500 MHz, chloroform-$d$): $\delta = 7.54$ (m, 2H), 7.39 (m, 2H), 7.22 (m, 2H), 7.14 (m, 1H), 6.74 (d, $J = 16.5$, 1H), 2.86 (t, $J = 7.5$, 2H), 1.26-1.20 (m, 12H), 1.02 (t, $J = 7.0$, 2H), 0.90 (m, 2H).

(Z)-5,9-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)deca-4,8-dien-3-one (158).

Under an N$_2$ atmosphere, a 10 mL flame dried Schlenk tube equipped with a stir bar was charged with Copper(I) Chloride (0.004 g, 0.04 mmol, 0.20 eq.) and NaOt-Bu (0.004 g, 0.04 mmol, 0.20 eq), dissolved in THF (1.0 mL), and allowed to stir at room temperature for 10 minutes. Bis(pinacolato)diboron (0.056 g, 0.22 mmol, 1.1 eq.) was added, causing the reaction mixture to turn black. The reaction was stirred at room temperature for 10 minutes before (Z)-5,9-dimethyldeca-1,4,8-trien-3-one (0.036 g, 0.20 mmol, 1.0 eq.) dissolved in THF (1.0 mL) and water (1.0 mL) were added and the reaction was allowed to stir for 8 hours. The reaction mixture was quenched with a saturate Brine solution (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:Ethyl Acetate) provided (Z)-5,9-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)deca-4,8-dien-3-one as a clear colorless oil (0.048 g, 0.16 mmol, 79%).
\textbf{H NMR} (500 MHz, chloroform-\textit{d}): $\delta = 6.03$ (d, $J = 1.5$, 1H), 5.13 (tq, $J = 1.5$, 7.5, 1H), 2.57 (q, $J = 7.0$, 4H), 2.12 (q, $J = 8.5$, 2H), 1.85 (d, $J = 1.5$, 3H), 1.67 (d, $J = 1.0$, 3H), 1.61 (s, 3H), 1.24 (s, 12H), 0.90 (t, $J = 7.5$, 2H). \textbf{C NMR} (125 MHz, chloroform-\textit{d}): $\delta = 200.6$, 157.9, 131.9, 123.9, 123.6, 83.0, 39.0, 33.8, 26.8, 25.7, 25.6, 24.8, 17.7. \textbf{IR} (neat): 2975, 2927, 1687, 1620, 1443, 1414, 1371, 1310, 1243, 1145, 1093, 968, 842 cm$^{-1}$.

**Boronate ester oxidation:**

\[
\begin{align*}
&\text{Boronate ester oxidation:} \\
&3\text{-hydroxy-1-phenylpropan-1-one (159).}
\end{align*}
\]

In an open air atmosphere 1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (0.061 g, 0.24 mmol, 1.0 eq.) was dissolved in THF (1.3 mL) and H$_2$O (1.3 mL) in a scintillation vial. NaBO$_3$·4H$_2$O (0.100 g, 1.25 mmol, 5.0 eq.) was added and the reaction was stirred vigorously for 3 hours at room temperature. H$_2$O (10 mL) was added to increase the size of the aqueous layer and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel (1:1 hexanes:Ethyl Acetate) provided 3-hydroxy-1-phenylpropan-1-one (0.025 g, 0.17 mmol, 71%, ~90% pure).
$^1$H NMR (500 MHz, chloroform-$d$): $\delta = 7.97 \ (d, \ J = 6.0, \ 2H), \ 7.59 \ (t, \ J = 6.0, \ 1H), \ 7.48 \ (t, \ J = 7.0, \ 2H), \ 4.04 \ (t, \ J = 5.5, \ 2H), \ 3.24 \ (t, \ J = 5.0, \ 2H)$.

\[
\text{Ph} \quad \text{O} \quad \text{OH} \\
\text{CH}_3
\]

1-hydroxy-4-phenylpentan-3-one (160).

In an open air atmosphere 4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (0.176 g, 0.61 mmol, 1.0 eq.) was dissolved in THF (3.0 mL) and H$_2$O (3.0 mL) in a scintillation vial. NaBO$_3$·4H$_2$O (0.244 g, 3.05 mmol, 5.0 eq.) was added and the reaction was stirred vigorously for 3 hours at room temperature. H$_2$O (10 mL) was added to increase the size of the aqueous layer and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated $\textit{in vacuo}$. Purification by flash column chromatography on silica gel (1:1 hexanes:Ethyl Acetate) provided 1-hydroxy-4-phenylpentan-3-one (0.097 g, 0.54 mmol, 89%).

$^1$H NMR (500 MHz, chloroform-$d$): $\delta = 7.34 \ (t, \ J = 7.0, \ 2H), \ 7.28 \ (d, \ J = 7.0, \ 1H), \ 7.21 \ (d, \ J = 7/0, \ 2H), \ 3.79-3.73 \ (m, \ 3H), \ 2.61 \ (t, \ J = 5.0, \ 2H), \ 1.41 \ (d, \ J = 6.5, \ 3H)$. $^{13}$C NMR (125 MHz, chloroform-$d$): $\delta = 211.8, \ 140.1, \ 129.1, \ 127.9, \ 127.4, \ 58.1, \ 53.4, \ 42.7, \ 17.1$. 

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**1-hydroxy-5-methylhexan-3-one (161).**

In an open air atmosphere 5-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one (0.276 g, 1.15 mmol, 1.0 eq.) was dissolved in THF (6.0 mL) and H₂O (6.0 mL) in a scintillation vial. NaBO₃·4H₂O (0.460 g, 5.75 mmol, 5.0 eq.) was added and the reaction was stirred vigorously for 3 hours at room temperature. H₂O (10 mL) was added to increase the size of the aqueous layer and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (1:1 hexanes:Ethyl Acetate) provided 1-hydroxy-5-methylhexan-3-one (0.110 g, 0.85 mmol, 74%).

**¹H NMR** (500 MHz, chloroform-*)

δ = 3.84 (t, *J* = 5.5, 2H), 2.65 (t, *J* = 5.5, 2H), 2.53 (broad s, 1H), 2.31 (d, *J* = 7.0, 2H), 2.15 (sep, *J* = 7.0, 1H), 0.92 (d, *J* = 6.5, 6H).

**1-hydroxyoctan-3-one (162).**

In an open air atmosphere 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octan-3-one (0.127 g, 0.5 mmol, 1.0 eq.) was dissolved in THF (2.5 mL) and H₂O (2.5 mL) in a scintillation vial. NaBO₃·4H₂O (0.200 g, 2.5 mmol, 5.0 eq.) was added and the reaction was stirred vigorously for 3 hours at room temperature. H₂O (10 mL) was added to increase the size of the aqueous
layer and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (1:1 hexanes:Ethyl Acetate) provided 1-hydroxy-4-phenylpentan-3-one (0.065 g, 0.45 mmol, 90%).

\[ \text{H NMR} \ (500 \text{ MHz, chloroform-}d) : \delta = 3.84 \ (t, \ J = 5.5, \ 2H), \ 2.67 \ (t, \ J = 5.5, \ 2H), \ 2.43 \ (t, \ J = 7.5, \ 2H), \ 1.58 \ (q, \ J = 7.5, \ 2H), \ 1.35-1.25 \ (m, \ 4H), \ 0.88 \ (t, \ J = 6.5, \ 3H). \ \text{C NMR} \ (125 \text{ MHz, chloroform-}d) : \delta = 212.2, \ 57.9, \ 44.2, \ 43.4, \ 31.3, \ 23.3, \ 22.4, \ 13.9. \]

(R)-5-hydroxy-1-((4-methoxybenzyl)oxy)-2-methylpentan-3-one (163).

In an open air atmosphere, (R)-1-((4-methoxybenzyl)oxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (0.156 g, 0.43 mmol, 1.0 eq.) was dissolved in THF (2.5 mL) and H$_2$O (2.5 mL) in a scintillation vial. NaBO$_3$·4H$_2$O (0.160 g, 2.00 mmol, 5.0 eq.) was added and the reaction was stirred vigorously for 3 hours at room temperature. H$_2$O (10 mL) was added to increase the size of the aqueous layer and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The reaction had not gone to completion by H NMR analysis. The crude product was resubjected to the same reaction condition with 0.100 g of NaBO$_3$·4H$_2$O
until completion by TLC analysis. Purification by flash column chromatography on silica gel (1:1 hexanes:Ethyl Acetate) provided (R)-5-hydroxy-1-((4-methoxybenzyl)oxy)-2-methylpentan-3-one as a clear colorless oil (0.098 g, 0.39 mmol, 91%).

$^1$H NMR (500 MHz, chloroform-$d$): $\delta$ = 7.21 (d, $J$ = 9.0, 2H), 6.87 (d, $J$ = 9.0, 2H), 4.43 (d, $J$ = 11.5, 1H), 4.40 (d, $J$ = 11.5, 2H), 3.90-3.80 (m, 2H), 3.59 (dd, $J$ = 8.5, 9.5, 1H), 3.47 (dd, $J$ = 7.0, 9.0, 1H), 2.89 (sex., $J$ = 6.5, 1H), 2.76 (ddd, $J$ = 4.0, 6.5, 17.5, 1H) 2.71 (ddd, $J$ = 2.5, 4.5, 16.0, 1H), 2.56 (t, $J$ = 6.5, 1H), 1.07 (d, $J$ = 7.0, 3H). $^{13}$C NMR (125 MHz, chloroform-$d$): $\delta$ = 214.4, 159.3, 129.8, 129.3, 113.8, 73.0, 71.9, 58.1, 55.3, 46.7, 44.0, 24.9, 13.2. IR (neat): 3430, 2937, 1707, 1612, 1459, 1364, 1302, 1245, 1173, 1076, 1032, 818 cm$^{-1}$. HRMS (ESI) calcd for (C$_{14}$H$_{20}$O$_4$ + Na)$^+$ 275.1259, found 275.1251.

(R)-1-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methylpentan-3-one (164).

In an open air atmosphere (R)-1-((tert-butyldimethylsilyl)oxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (0.139 g, 0.39 mmol, 1.0 eq.) was dissolved in THF (2.0 mL) and H$_2$O (2.0 mL) in a scintillation vial. NaBO$_3$·4H$_2$O (0.160 g, 2.0 mmol, 5.0 eq.) was added and the reaction was stirred vigorously for 7 hours at room temperature. H$_2$O (10 mL) was added to increase the size of the aqueous layer and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on
silica gel (4:1 to 1:1 hexanes:Ethyl Acetate) provided (R)-1-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methylpentan-3-one as a clear colorless oil (0.099 g, 0.39 mmol, 100%).

\[ ^1\text{H NMR} \text{ (500 MHz, chloroform-}d\text{):} \delta = 3.90\text{-}3.78 \text{ (m, 2H), 3.74 (dd, } J = 7.5, 9.5, 1\text{H), 3.66 (dd, } J = 5.0, 9.5, 1\text{H), 2.83}\text{-}2.68 \text{ (m, 3H), 2.57 (t, } J = 6.5, 1\text{H), 1.04 (d, } J = 6.5, 3\text{H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).} \]

\[ ^{13}\text{C NMR} \text{ (125 MHz, chloroform-}d\text{):} \delta = 215.2, 65.8, 58.3, 49.1, 44.6, 26.0, 18.4, 13.0, -5.4, -5.4. \]

\[ \text{IR (neat): 3399, 2955, 2929, 2857, 1707, 1472, 1388, 1253, 1078, 834, 775 cm}^{-1}. \]

\[ \text{HRMS (ESI) calcd for } (\text{C}_{12}\text{H}_{26}\text{O}_3\text{Si + Na})^+ 269.1549, \text{ found 269.1549}. \]

\[ [\alpha] = -34.5 \text{ (c = 8.4, CH}_2\text{Cl}_2) \]

(S)-4-((tert-butyldimethylsilyl)oxy)-1-hydroxypentan-3-one (165).

In an open air atmosphere (S)-4-((tert-butyldimethylsilyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (0.260 g, 0.76 mmol, 1.0 eq.) was dissolved in THF (3.8 mL) and H\textsubscript{2}O (3.8 mL) in a scintillation vial. NaBO\textsubscript{3}\cdot4H\textsubscript{2}O (0.304 g, 2.38 mmol, 5.0 eq.) was added and the reaction was stirred vigorously for 5 hours at room temperature. H\textsubscript{2}O (10 mL) was added to increase the size of the aqueous layer and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 to 1:1
hexanes:Ethyl Acetate) provided (S)-4-((tert-butyldimethylsilyl)oxy)-1-hydroxypentan-3-one as a clear colorless oil (0.173 g, 0.74 mmol, 98%).

\[ ^1H\text{ NMR} (500\text{ MHz, chloroform-}d): \delta = 4.15\ (q, J = 7.0, 1\text{H}), 3.86\ (s, 2\text{H}), 2.85\ (dddd, J = 5.0, 6.0, 19.0, 57.0, 2\text{H}), 2.42\ (s, 1\text{H}), 1.29\ (d, J = 7.0, 3\text{H}), 0.92\ (s, 9\text{H}), 0.09\ (s, 6\text{H}). \]

\[ ^{13}\text{C NMR} (125\text{ MHz, chloroform-}d): \delta = 215.5, 75.0, 57.9, 39.4, 25.9, 20.9, 18.2, -4.5, -4.9. \]

\[ \text{IR (neat): 3429, 1256, 2930, 2886, 2858, 1715, 1473, 1362, 1252, 1118, 832, 776\ cm}^{-1}. \]

\[ \text{HRMS (ESI) calcd for (C}_{11}\text{H}_{24}\text{O}_{3}\text{Si + Na)}\,^+\ 255.1392, \text{ found 255.1386. } [\alpha] = -3.6\ (c = 10.1, \text{ CH}_2\text{Cl}_2) \]

(S)-1-hydroxy-4-((4-methoxybenzyl)oxy)pentan-3-one (166).

In an open air atmosphere (S)-4-((4-methoxybenzyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (0.440 g, 1.26 mmol, 1.0 eq.) was dissolved in THF (7.0 mL) and H\textsubscript{2}O (7.0 mL) in a scintillation vial. NaBO\textsubscript{3}4H\textsubscript{2}O (0.500 g, 6.3 mmol, 5.0 eq.) was added and the reaction was stirred vigorously for 5 hours at room temperature. H\textsubscript{2}O (10 mL) was added to increase the size of the aqueous layer and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel (1:1 hexanes:Ethyl Acetate) followed by high vacuum at 45°C to remove excess pinacol provided (S)-1-
hydroxy-4-((4-methoxybenzyl)oxy)pentan-3-one as a clear colorless oil (0.271 g, 1.14 mmol, 90%).

\[^1\text{H} \text{NMR}\] (500 MHz, chloroform-\text{d}): \(\delta = 7.27\) (d, \(J = 8.5\), 2H), 6.89 (d, \(J = 9.0\), 2H), 4.48 (s, 2H), 3.92 (q, \(J = 7.0\), 1H), 3.86 (t, \(J = 5.5\), 2H), 3.81 (s, 3H), 2.82 (dddd, \(J = 5.5\), 11.0, 23.5, 33.0, 2H), 1.33 (d, \(J = 7.5\), 3H). \[^{13}\text{C} \text{NMR}\] (125 MHz, chloroform-\text{d}): \(\delta = 214.0, 159.5, 129.5, 129.4, 113.9, 80.2, 71.6, 57.7, 55.3, 39.5, 17.2\). \[^\text{IR}\] (neat): 3429, 2937, 1713, 1612, 1513, 1245, 1091, 1030, 818 cm\(^{-1}\). \([\alpha] = -30.7\) (c = 8.3, CH\(_2\)Cl\(_2\)).

**Carbonyl Hydrosilation, antipropionate synthesis:**

\[
\text{Ph} - \overset{\text{OH}}{\text{CH}_3} \overset{\text{OH}}{\text{CH}_3} + \text{Ph} - \overset{\text{OH}}{\text{CH}_3} \overset{\text{OH}}{\text{CH}_3}
\]

(3R,4S)-4-phenylpentane-1,3-diol/(3S,4R)-4-phenylpentane-1,3-diol (167).

Under an N\(_2\) atmosphere, 1-hydroxy-4-phenylpentan-3-one (0.088 g, 0.49 mmol, 1.0 eq.) was dissolved in DCM (5 mL) in an oven dried 10 mL Schlenk tube equipped with a stir bar. Triethylamine (0.410 mL, 2.94 mmol, 6.0 eq.), imidazole (0.266 g, 3.92 mmol, 8.0 eq.) and diphenylchloro silane (0.290 mL, 1.48 mmol, 3.0 eq.) were added in that order to the reaction. The reaction was allowed to stir overnight for at least 18 hours before it was transferred to a 100 mL round bottom flask with 30 mL of hexanes and placed in the freezer for 2 hours. The solution was filtered through a plug of celite to remove imidazole salts from the reaction mixture. Hexanes were removed \textit{in vacuo} and the crude product was used without isolation in the next step.
The crude product was dissolved in THF (3 mL) in a flame dried 10 mL Schlenk tube under an N₂ atmosphere. TBAF (4.5 mL, 1.0 M, 4.5 mmol, 9.0 eq.) was added dropwise and the reaction was stirred for 1 hour at room temperature. The reaction was quenched with a saturated NH₄Cl solution and the organic layer was extracted with EtOAc (3 x 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (1:1 hexanes:EtOAc) provided (3R,4S)-4-phenylpentane-1,3-diol/(3S,4R)-4-phenylpentane-1,3-diol as a clear colorless oil (0.060 g, 0.33 mmol, 68%) in >10:1 diastereoselectivity.

¹H NMR (500 MHz, chloroform- d): δ = 7.38-7.30 (m, 2H), 7.26-7.19 (m, 3H), 3.95-3.80 (m, 3H), 2.79 (quintet, J = 7.0, 1H), 2.58 (broad s, 1H), 2.02 (broad s, 1H), 1.91-1.85 (m, 1H), 1.70-1.62 (m, 1H), 1.28 (d, J = 7.0, 3H). ¹³C NMR (125 MHz, chloroform- d): δ = 143.2, 128.9, 128.8, 128.3, 128.0, 127.1, 62.0, 46.8, 35.8, 17.8 cm⁻¹.

(3R,4S)-4-(((4-methoxybenzyl)oxy)pentane-1,3-diol (169).

Under an N₂ atmosphere, (S)-1-hydroxy-4-(((4-methoxybenzyl)oxy)pentan-3-one (0.048 g, 0.20 mmol, 1.0 eq.) was dissolved in DCM (2 mL) in an oven dried 10 mL Schlenk tube equipped with a stir bar. Triethylamine (0.167 mL, 1.20 mmol, 6.0 eq.), imidazole (0.109 g, 1.60 mmol, 8.0 eq.) and diphenylchloro silane (0.117 mL, 0.60 mmol, 3.0 eq.) were added in that order to the reaction. The reaction was allowed to stir overnight for at least 18 hours.
before it was transferred to a 100 mL round bottom flask with 30 mL of hexanes and placed in the freezer for 2 hours. The solution was filtered through a plug of celite to remove imidazole salts from the reaction mixture. Hexanes were removed \textit{in vacuo} and the crude product was used without isolation in the next step.

The crude product was dissolved in THF (5 mL) in a flame dried 10 mL Schlenk tube under an N$_2$ atmosphere. TBAF (0.9 mL, 1.0 M, 0.9 mmol, 4.5 eq.) was added dropwise and the reaction was stirred for 1 hour at room temperature. The reaction was quenched with a saturated NH$_4$Cl solution and the organic layer was extracted with EtOAc (3 x 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel (4:1 to 1:2 hexanes:EtOAc) provided (3R,4S)-4-((4-methoxybenzyl)oxy)pentane-1,3-diol as a clear colorless oil (0.038g, 0.16 mmol, 83%) in approximately a 1:1 mixture of diastereomers.

$^1$H NMR (500 MHz, chloroform-$d$): $\delta$ = 7.25 (d, $J = 9.0$, 4H), 6.88 (d, $J = 9.0$, 4H), 4.60 (d, $J = 11.0$, 1H), 4.55 (d, $J = 11.0$, 1H), 4.42 (d, $J = 11.0$, 1H), 4.36 (d, $J = 11.5$, 1H), 3.92-3.87 (m, 1H), 3.80 (s, 6H), 3.69-3.64 (m, 1H), 3.52-3.46 (m, 1H), 3.40 (q, $J = 5.5$, 1H), 1.75-1.62 (m, 4H), 1.17 (d, $J = 6.5$, 6H).  $^{13}$C NMR (125 MHz, chloroform-$d$): $\delta$ = 159.3, 159.2, 130.4, 130.2, 129.5, 129.3, 78.1, 76.8, 75.0, 73.3, 70.7, 70.4, 61.4, 61.2, 55.3, 34.3, 33.7, 15.3, 14.0.  IR (neat): 3378, 2935, 1612, 1513, 1245, 1092, 1032, 821, 730 cm$^{-1}$.  

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(3S,4R)-5-((4-methoxybenzyl)oxy)-4-methylpentane-1,3-diol (170).

Under an N\textsubscript{2} atmosphere, (R)-5-hydroxy-1-((4-methoxybenzyl)oxy)-2-methylpentan-3-one (0.094 g, 0.37 mmol, 1.0 eq.) was dissolved in DCM (4 mL) in an oven dried 10 mL Schlenk tube equipped with a stir bar. Triethylamine (0.300 mL, 2.14 mmol, 6.0 eq.), imidazole (0.194 g, 2.90 mmol, 8.0 eq.) and diphenylchloro silane (0.210 mL, 1.07 mmol, 3.0 eq.) were added in that order to the reaction. The reaction was allowed to stir overnight for at least 18 hours before it was transferred to a 100 mL round bottom flask with 30 mL of hexanes and placed in the freezer for 2 hours. The solution was filtered through a plug of celite to remove imidazole salts from the reaction mixture. Hexanes were removed \textit{in vacuo} and the crude product was used without isolation in the next step.

The crude product was dissolved in THF (5 mL) in a flame dried 10 mL Schlenk tube under an N\textsubscript{2} atmosphere. TBAF (1.6 mL, 1.0 M, 1.6 mmol, 4.5 eq.) was added dropwise and the reaction was stirred for 1 hour at room temperature. The reaction was quenched with a saturated NH\textsubscript{4}Cl solution and the organic layer was extracted with EtOAc (3 x 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel (1:3 hexanes:EtOAc) provided (3S,4R)-5-((4-methoxybenzyl)oxy)-4-methylpentane-1,3-diol as a clear colorless oil (0.085g, 0.33 mmol, 90\%) in approximately a 1:1 mixture of diastereomers.
\[ ^1H \text{NMR} \ (500 \text{ MHz, chloroform-}d): \delta = 7.24 \ (d, J = 7.5, 4H), \ 6.88 \ (d, J = 8.0, 4H), \ 4.44 \ (s, 2H), \ 4.43 \ (s, 2H), \ 4.11 \ (s, 1H), \ 3.98 \ (d, J = 10.0, 1H), \ 3.85-3.80 \ (m, 4H), \ 3.80 \ (2, 6H), \ 3.78-3.74 \ (m, 1H), \ 3.60 \ (dd, J = 3.5, 9.0, 1H), \ 3.50 \ (q, J = 7.0, 2H), \ 3.43 \ (t, J = 8.0, 1H), \ 3.33 \ (\text{broad } s, 1H), \ 3.18 \ (\text{broad } s, 1H), \ 2.93 \ (\text{broad } s, 1H), \ 1.94-1.86 \ (m, 2H), \ 1.80-1.63 \ (m, 4H), \ 1.56-1.51 \ (m, 1H), \ 0.92 \ (d, J = 7.0, 3H), \ 0.85 \ (d, J = 7.5, 3H). \]^1C \text{NMR} \ (125 \text{ MHz, chloroform-}d): \delta = 159.6, \ 159.5, \ 130.1, \ 129.8, \ 129.6, \ 129.5, \ 114.1, \ 114.1, \ 77.6, \ 75.4, \ 75.2, \ 74.3, \ 73.4, \ 73.4, \ 62.4, \ 61.9, \ 55.5, \ 38.7, \ 38.5, \ 36.2, \ 35.2, \ 29.9, \ 13.8, \ 11.6.

![TBSO](image)

\text{(3S,4R)-(tert-butyldimethylsilyl)oxy)-4-methylpentane-1,3-diol (171).}

Under an N\_2 atmosphere, (R)-1-(tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methylpentan-3-one (0.049 g, 0.20 mmol, 1.0 eq.) was dissolved in DCM (2 mL) in an oven dried 10 mL Schlenk tube equipped with a stir bar. Triethylamine (0.167 mL, 1.20 mmol, 6.0 eq.), imidazole (0.109 g, 1.60 mmol, 8.0 eq.) and diphenylchloro silane (0.117 mL, 0.60 mmol, 3.0 eq.) were added in that order to the reaction. The reaction was allowed to stir overnight for at least 18 hours before it was transferred to a 100 mL round bottom flask with 30 mL of hexanes and placed in the freezer for 2 hours. The solution was filtered through a plug of celite to remove imidazole salts from the reaction mixture. Hexanes were removed \textit{in vacuo} and the crude product was used without isolation in the next step.

The crude product was dissolved in THF (5 mL) in a flame dried 10 mL Schlenk tube under an N\_2 atmosphere. TBAF (0.9 mL, 1.0 M, 0.9 mmol, 4.5 eq.) was added dropwise and the
reaction was stirred for 1 hour at room temperature. The reaction was quenched with a saturated NH₄Cl solution and the organic layer was extracted with EtOAc (3 x 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 to 1:1 hexanes:EtOAc) provided (3S,4R)-5-((tert-butyldimethylsilyl)oxy)-4-methylpentane-1,3-diol as a clear colorless oil (0.041g, 0.17 mmol, 83%) in approximately a 1.6:1 mixture of diastereomers.

¹H NMR (500 MHz, chloroform-d): δ = 4.49 (broad s, 2H), 4.03 (d, J = 11.0, 1H), 3.90-3.75 (m, 8H), 3.67 (dd, J = 6.0, 10.5, 2H), 3.57 (dd, J = 6.0, 9.5, 2H), 1.82-1.65 (m, 7H), 1.46-1.50 (m, 1H), 0.92 (d, J = 7.5, 3H), 0.89 (s, 18H), 0.82 (d, J = 6.5, 3H), 0.08 (s, 6H), 0.07 (s, 6H). ¹³C NMR (125 MHz, chloroform-d): δ = 78.2, 75.9, 69.1, 69.3, 62.4, 61.9, 39.8, 39.4, 36.4, 35.4, 26.0, 26.0, 18.3, 18.3, 13.5, 11.1, -5.4, -5.5, -5.5. IR (neat): 3334, 2954, 2928, 2884, 2857, 1472, 1463, 1525, 1053, 8333, 774 cm⁻¹. HRMS (ESI) calcd for (C₁₂H₂₈O₃Si + Na)⁺ 271.1705, found 271.1703.

Matched and Mismatched substrate synthesis:

(R)-methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate (178).

Under an N₂ atmosphere, (R)-methyl 3-hydroxy-2-methylpropanoate (2.22 mL, 20.0 mmol, 1.0 eq.) was dissolved in DCM (4 mL) in a flame dried 25 mL Schlenk tube. Camphorsulfonic acid (0.930 g, 4.0 mmol, 0.2 eq.) was added and the reaction was stirred.
Freshly synthesized 4-methoxybenzyl 2,2,2-trichloroacetimidate (15.0 mmol, 1.5 eq.) was added with DCM (6 mL) and the reaction was stirred overnight. The reaction mixture was diluted with MTBE (50 mL) and the organic layer was washed with saturated NaHCO₃ (2 x 30 mL), water (2 x 30 mL), and brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 hexanes:EtOAc) provided (R)-methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate as a clear slightly yellow oil (4.95 g, 20.0 mmol, quantitative yield).

\(^1\)H NMR (500 MHz, chloroform-\(d\)): \(\delta = 7.24\) (d, \(J = 8.5\), 2H), 6.87 (d, \(J = 9.0\), 2H), 4.46 (d, \(J = 11.0\), 1H), 4.44 (d, \(J = 11.0\), 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.62 (dd, \(J = 7.5, 9.0\), 1H), 3.45 (dd, \(J = 6.0, 9.0\), 1H), 2.77 (sex., \(J = 5.5\), 1H), 1.16 (d, \(J = 7.0\), 3H). \(^{13}\)C NMR (125 MHz, chloroform-\(d\)): \(\delta = 175.4, 159.2, 130.2, 129.2, 113.7, 72.8, 71.6, 55.3, 51.7, 40.2, 14.0\).

(R)-N-methoxy-3-((4-methoxybenzyl)oxy)-N,2-dimethylpropanamide (179).

Under an N\(_2\) atmosphere, provided (R)-methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate (20.0, 1.0 eq.) and N,O-dimethylhydroxylamine (4.1 g, 42.0 mmol, 2.1 eq.) were dissolved in THF (44 mL) in a 250 ml flame dried Schlenk tube and cooled to -20\(^\circ\) C in a monitored dry ice and acetone cold bath. Freshly prepared isopropylmagnesium chloride (28.0 mL, 3.0 M, 84.0 mmol, 4.2 eq.) was added over 20 minutes and the reaction was slowly warmed to 0\(^\circ\) C in an ice/water bath and allowed to stir for an additional hour.
The reaction mixture was quenched by the addition of saturated aqueous NH₄Cl (40 mL), extracted with MTBE (4 x 40 mL), DCM (4 x 40 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to provide (R)-N-methoxy-3-((4-methoxybenzyl)oxy)-N,2-dimethylpropanamide. The product was used crude in the next reaction.

\[ ^1H \text{ NMR} \ (500 \text{ MHz, chloroform-d): } \delta = 7.23 \ (d, J = 8.5, 2H), 6.86 \ (d, J = 8.0, 2H), 4.48 \ (d, J = 11.5, 1H), 4.40 \ (d, J = 12.0, 1H), 3.80 \ (s, 3H), 3.69 \ (s, 3H), 3.68 \ (t, J = 8.5, 1H), 3.39 \ (dd, J = 6.0, 9.0, 1H), 3.20 \ (s, 3H), 1.10 \ (d, J = 6.5, 3H). \]

(R)-1-((4-methoxybenzyl)oxy)-2-methylpentan-3-one (177).

Under an N₂ atmosphere, crude (R)-N-methoxy-3-((4-methoxybenzyl)oxy)-N,2-dimethylpropanamide (20.0 mmol, 1.0 eq.) was dissolved in THF (140 mL) in a flame dried 250 mL Schlenk tube and cooled to 0°C in an ice bath. Ethylmagnesium bromide (13.3 mL, 3.0M, 40.0 mmol, 2.0 eq.) was added slowly over 5 minutes and the reaction was allowed to stir until completion by TLC. After 45 minutes the reaction was completed by TLC. The reaction was quenched with saturated aqueous NH₄Cl (50 mL), extracted with MTBE (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo.

Purification by flash column chromatography on silica gel provided (R)-1-((4-
methoxybenzyl)oxy)-2-methylpentan-3-one as a clear slightly yellow oil (4.06 g, 17.2 mmol, 86%).

\[1H\text{ NMR} \ (500 \text{ MHz, chloroform}-d): \delta = 7.21 \ (d, \ J = 9.0, \ 2H), \ 6.87 \ (d, \ J = 9.0, \ 2H), \ 4.4 \ (d, \ J = 11.0, \ 1H), \ 4.39 \ (d, \ J = 11.5, \ 2H), \ 3.80 \ (s, \ 3H), \ 3.59 \ (dd, \ J = 8.0, \ 9.5, \ 1H), \ 3.42 \ (dd, \ J = 5.5, \ 9.5, \ 1H), \ 2.85 \ (sex., \ J = 7.5, \ 1H), \ 2.50 \ (q, \ J = 7.5, \ 2H), \ 1.06 \ (d, \ J = 7.5, \ 3H), \ 1.03 \ (t, \ J = 7.0, \ 3H). \ \[13C\text{ NMR} \ (125 \text{ MHz, chloroform}-d): \delta = 213.9, \ 159.2, \ 130.2, \ 129.2, \ 113.7, \ 72.9, \ 72.1, \ 55.3, \ 49.2, \ 46.2, \ 35.3, \ 13.7, \ 7.6.

(2R,4R)-1-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-3-one (175).

Under an N\(_2\) atmosphere, dicyclohexylboron chloride (5.2 mL, 1.0 M, 5.2 mmol, 1.3 eq.) was dissolved in diethyl ether (16 mL) in a 100 mL flame dried Schlenk Tube and cooled to 0\(^\circ\) C in an ice/water bath. Triethylamine (0.892 mL, 6.4 mmol, 1.6 eq.) was added followed by (R)-1-((4-methoxybenzyl)oxy)-2-methylpentan-3-one (0.944 g, 4.0 mmol, 1.0 eq.) dissolved in diethyl ether (8 mL). The reaction mixture was stirred for two hours then cooled to -78\(^\circ\) C in a dry ice/acetone bath. While the reaction mixture was stirring, a solution of formaldehyde in diethyl ether was obtained by pyrolysis of dry paraformaldehyde (1.20 g, 40 mmol, 10.0 eq.), the resulting gas created being carried in a stream of N\(_2\) into a Schlenk tube containing diethyl ether (16 mL) cooled to -78\(^\circ\) C in a dry ice/acetone bath. The resulting formaldehyde solution was then added to the reaction mixture at -78\(^\circ\) C via cannula. After
stirring for one hour at -78º C, the solution was warmed to 0º C before the addition of methanol (16 mL) and pH 7.0 buffer (16 mL). Hydrogen peroxide (3.0 mL, 30% aqueous) was added dropwise at 0º C then removed from the ice/water bath and stirred for 1 hour at room temperature. The reaction mixture was extracted with DCM (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 to 1:1 hexanes:EtOAc) provided (2R,4R)-1-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-3-one as a clear colorless oil in quantitative yield (1.10 g, 4.0 mmol, 100%) in approximately 20:1 diastereoselectivity.

\[ \begin{align*} 
1^H \text{NMR} (500 \text{ MHz, chloroform-}d) &: \delta = 7.20 (d, J = 8.5, 2H), 6.87 (d, J = 9.0, 2H), 4.42 (d, J = 11.5, 1H), 4.38 (d, J = 11.0, 2H), 3.80 (s, 3H), 3.79-3.75 (m, 1H), 3.69-3.62 (m, 2H), 3.42 (dd, J = 5.0, 9.0, 1H), 3.15-3.08 (m, 1H), 2.92-2.84 (m, 1H), 2.52 (t, J = 6.5, 1H), 1.10 (d, J = 7.5, 3H), 1.04 (d, J = 7.5, 3H). \\
13^C \text{NMR} (125 \text{ MHz, chloroform-}d) &: \delta = 217.4, 159.3, 129.7, 129.3, 113.8, 73.1, 72.2, 64.6, 55.3, 48.5, 44.1, 13.9, 12.7. \\
\text{IR} \text{ (neat)} &: 3398, 2972, 2936, 2877, 1707, 1612, 1512, 1245, 1173, 1085, 1030, 818 \text{ cm}^{-1}. 
\end{align*} \]

(2S,4R)-1-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-3-one (176).

Under an N\textsubscript{2} atmosphere, TiCl\textsubscript{4} (3.36 mL, 1.0 M, 3.36 mmol, 0.84 eq.) was dissolved in DCM (4 mL) in a flame dried 25 mL Schlenk Tube and cooled to 0º C in an ice/water bath. Freshly distilled (i-PrO)\textsubscript{4}Ti (0.331 mL, 1.12 mmol, 0.28 eq.) was added dropwise and the
solution was stirred for 10 minutes at 0º C followed by 10 minutes at room temperature.
Meanwhile, in a second 50 mL flame dried Schlenk tube, by (R)-1-((4-methoxybenzyl)oxy)-2-methylpentan-3-one (0.944 g, 4.0 mmol, 1.0 eq.) was dissolved in DCM (8 mL) and cooled to -78º C in a dry ice/acetone bath. The (i-PrO)TiCl$_3$ solution in DCM was then transferred via cannula to the second Schlenk tube. The solution was stirred for 2 minutes before i-Pr$_2$NEt (0.766 mL, 4.4 mmol, 1.1 eq.) was added dropwise. The reaction was stirred for 30 minutes at -78º C. While the reaction mixture was stirring, a solution of formaldehyde in diethyl ether was obtained by pyrolysis of dry paraformaldehyde (1.20 g, 40 mmol, 10.0 eq.), the resulting gas created being carried in a stream of N$_2$ into a Schlenk tube containing diethyl ether (10 mL) cooled to -78º C in a dry ice/acetone bath. The resulting formaldehyde solution was then added to the reaction mixture at -78º C via cannula and the reaction mixture was allowed to stir for 1.5 hours at -78º C. The reaction was quenched with saturated aqueous NH$_4$Cl (20 mL) and stirred vigorously at room temperature for 5 minutes. MTBE (40 mL) was added to dilute the organic layer and the organic layer was washed with H$_2$O (20 mL), saturated NaHCO$_3$ (20 mL), and brine (20 mL). The aqueous layers were then extracted with MTBE (3 x 50 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (10:1 to 1:1 hexanes:EtOAc) provided (2S,4R)-1-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-3-one as a clear colorless oil (0.620 g, 2.34 mmol, 56%) in a 4:1 mixture of diastereomers.
$^1$H NMR (500 MHz, chloroform-d): $\delta = 7.20$ (d, $J = 8.5$, 2H), 6.87 (d, $J = 8.5$, 2H), 4.41 (d, $J = 11.5$, 1H), 4.37 (d, $J = 12.0$, 2H), 3.80 (s, 3H), 3.79-3.75 (m, 1H), 3.69-3.62 (m, 2H), 3.45 (dd, $J = 4.5$, 8.0, 1H), 3.21-3.16 (m, 1H), 2.94-2.86 (m, 1H), 2.71 (t, $J = 7.0$, 1H), 1.08 (d, $J = 7.5$, 3H), 1.00 (d, $J = 7.0$, 3H). $^{13}$C NMR (125 MHz, chloroform-d): $\delta = 217.6, 159.4, 129.5, 129.4, 113.9, 73.2, 73.0, 65.0, 55.2, 48.9, 45.1, 13.4, 12.7$. IR (neat): 3447, 2970, 2934, 2877, 1707, 1612, 1513, 1458, 1362, 1302, 1245, 1087, 1032, 818 cm$^{-1}$.

**Matched and Mismatched hydrosilation:**

\[
\begin{align*}
\text{PMBO} & \quad \text{OH} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{OH}
\end{align*}
\]

(2R,3S,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentane-1,3-diol (183).

Under an N$_2$ atmosphere, (2R,4R)-1-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-3-one (0.053 g, 0.20 mmol, 1.0 eq.) was dissolved in DCM (2 mL) in an oven dried 10 mL Schlenk tube equipped with a stir bar. Triethylamine (0.167 mL, 1.20 mmol, 6.0 eq.), imidazole (0.109 g, 1.60 mmol, 8.0 eq.) and diphenylchloro silane (0.117 mL, 0.60 mmol, 3.0 eq.) were added in that order to the reaction. The reaction was allowed to stir overnight for at least 18 hours before it was transferred to a 100 mL round bottom flask with 30 mL of hexanes and placed in the freezer for 2 hours. The solution was filtered through a plug of celite to remove imidazole salts from the reaction mixture. Hexanes were removed *in vacuo* and the crude product was used without isolation in the next step.

The crude product was dissolved in THF (5 mL) in a flame dried 10 mL Schlenk tube under an N$_2$ atmosphere. TBAF (0.9 mL, 1.0 M, 0.9 mmol, 4.5 eq.) was added dropwise and the
reaction was stirred for 1 hour at room temperature. The reaction was quenched with a saturated NH₄Cl solution and the organic layer was extracted with EtOAc (3 x 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (4:1 to 1:1 hexanes:EtOAc) provided (2R,3S,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentane-1,3-diol as a clear colorless oil (0.036g, 0.13 mmol, 68%) in approximately a 10:1 mixture of diastereomers.

**1H NMR** (500 MHz, chloroform-d): δ = 7.24 (d, J = 8.5, 2H), 6.88 (d, J = 9.0, 2H), 4.46 (s, 2H), 4.16 (s, 1H), 3.81 (s, 3h), 3.80-3.73 (m, 2H), 3.69-3.64 (m, 1H), 3.59 (dd, J = 4.0, 9.5, 1H), 3.45 (t, J = 9.0, 1H), 2.02-1.96 (m, 1H), 1.78-1.71 (m, 1H), 0.98 (d, J = 6.5, 3H), 0.76 (d, J = 6.5, 3H). **13C NMR** (125 MHz, chloroform-d): δ = 159.4, 129.4, 113.9, 76.5, 73.3, 55.3, 36.3, 35.8, 13.1, 8.7. **IR** (neat): 3264, 2969, 2935, 2890, 2870, 2839, 1612, 1514, 1299, 1247, 1058, 1039, 1025, 990, 817, 697 cm⁻¹.

![Structure](image)

(2S,3R,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentane-1,3-diol (184).

Under an N₂ atmosphere, (2S,4R)-1-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentane-3-one (0.053 g, 0.20 mmol, 1.0 eq.) was dissolved in DCM (2 mL) in an oven dried 10 mL Schlenk tube equipped with a stir bar. Triethylamine (0.167 mL, 1.20 mmol, 6.0 eq.), imidazole (0.109 g, 1.60 mmol, 8.0 eq.) and diphenylchloro silane (0.117 mL, 0.60 mmol, 3.0 eq.) were added in that order to the reaction. The reaction was allowed to stir overnight
for at least 18 hours before it was transferred to a 100 mL round bottom flask with 30 mL of hexanes and placed in the freezer for 2 hours. The solution was filtered through a plug of celite to remove imidazole salts from the reaction mixture. Hexanes were removed in vacuo and the crude product was used without isolation in the next step.

The crude product was dissolved in THF (5 mL) in a flame dried 10 mL Schlenk tube under an N$_2$ atmosphere. TBAF (0.9 mL, 1.0 M, 0.9 mmol, 4.5 eq.) was added dropwise and the reaction was stirred for 1 hour at room temperature. The reaction was quenched with a saturated NH$_4$Cl solution and the organic layer was extracted with EtOAc (3 x 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 to 1:1 hexanes:EtOAc) provided (2S,3S,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentane-1,3-diol as a clear colorless oil (0.038g, 0.14 mmol, 72%) in a greater than 10:1 mixture of diastereomers.

$^1$H NMR (500 MHz, chloroform-d): $\delta = 7.23$ (d, $J = 8.0$, 2H), 6.87 (d, $J = 9.0$, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.78-3.70 (m, 2H), 3.64 (d, $J = 5.0$, 2H), 3.44 (d, $J = 5.5$, 2H), 1.96-1.90 (m, 1H), 1.84-1.78 (m, 1H), 1.03 (d, $J = 7.0$, 3H), 1.01 (d, $J = 7.0$, 3H). $^{13}$C NMR (125 MHz, chloroform-d): $\delta = 159.2, 130.2, 129.4, 113.8, 74.4, 73.0, 67.2, 55.3, 37.7, 36.3, 12.3, 11.6$. IR (neat): 3384, 2963, 2932, 2876, 1612, 1513, 1459, 1245, 1078, 1032, 972, 819 cm$^{-1}$. 
Discodermolide stereopentad synthesis:

(2S,3R,4R)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanal (196).

In an open air atmosphere, (2R,3S,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentane-1,3-diol (0.054 g, 0.2 mmol, 1.0 eq.) was dissolved in DCM (2 mL) in a scintillation vial equipped with a stir bar and cooled to 0° C in an ice/water bath. Saturated aqueous NaHCO₃ (1.5 mL) was added and the reaction was stirred vigorously. Potassium bromide (0.0095 g, 0.08 mmol, 0.4 eq.), TEMPO (0.0031 g, 0.02 mmol, 0.1 eq.), and NaOCl (0.4 mL, 6% aq., 0.4 mmol, 2.0 eq.) were added in that order. The reaction was monitored by TLC and had gone to completion after 20 minutes. The reaction was quenched with water (10 mL), extracted with DCM (3 x 10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (1:1 hexanes:EtOAc) provided (2S,3R,4R)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanal as a clear colorless oil (0.048 g, 0.18 mmol, 91%).

¹H NMR (500 MHz, chloroform-d): δ = 9.74 (s, 1H), 7.24 (d, J = 8.5, 2H), 6.88 (d, J = 9.0, 2H), 4.46 (s, 2H), 4.09 (d, J = 9.0, 1H), 3.85 (s, 1H), 3.81 (s, 3H), 3.63 (dd, J = 4.0, 9.5, 1H), 3.50 (t, J = 9.5, 1H), 2.44 (qd, J = 2.5, 7.0, 1H), 2.10-1.96 (m, 1H), 1.14 (d, J = 7.0, 3H), 0.85 (d, J = 6.5, 3H). ¹³C NMR (125 MHz, chloroform-d): δ = 205.0, 159.4, 129.5, 113.9, 75.6, 75.5, 73.3, 55.3, 49.3, 35.5, 13.4, 6.2.
(S)-4-benzyl-3-((2S,3R,4S,5R,6R)-3,5-dihydroxy-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoyl)oxazolidin-2-one (197).

Under an N₂ atmosphere, (S)-4-benzyl-3-propionyloxazolidin-2-one (0.114 g, 0.5 mmol, 2.5 eq.) was dissolved in DCM (3 mL) in a flame dried 10 mL Schlenk tube and cooled to 0° C in an ice/water bath. TiCl₄ (0.55 mL, 0.55 mmol, 2.75 eq.) was added dropwise and the reaction was stirred for 5 minutes. i-Pr₂NEt (0.087 mL, 0.5 mmol, 2.5 eq.) was added dropwise and the reaction was stirred for 20 minutes. The reaction mixture was cooled to -78° C via a dry ice/acetone bath and N-Methyl-2-pyrrolidone (0.048 mL, 0.5 mmol, 2.5 eq.) was added and the reaction was stirred for 10 minutes. (2S,3R,4R)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanal (0.046 g, 0.017 mmol, 1.0 eq.) dissolved in DCM (3 mL) was added slowly and the reaction was stirred for 1 hour at -78° C before being warmed to 0° C and stirred for an addition 2 hours. The reaction was quenched with saturated aqueous NH₄Cl (10 mL). The aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 to 1:1 hexanes:EtOAc) provided (S)-4-benzyl-3-((2S,3R,4S,5R,6R)-3,5-dihydroxy-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoyl)oxazolidin-2-one as a clear colorless oil (0.072 g, 0.14 mmol, 85%) in a 4:1 mixture of diastereomers.
$^1$H NMR (500 MHz, chloroform-d): $\delta$ = 7.33 (t, $J$ = 7.5, 2H), 7.28 (d, $J$ = 7.0, 1H), 7.25 (d, $J$ = 9.0, 2H), 7.21 (d, $J$ = 8.5, 2H), 6.89 (d, $J$ = 8.5, 2H), 4.69-4.65 (m, 1H), 4.49 (d, $J$ = 12.0, 1H), 4.44 (d, $J$ = 11.5, 1H), 4.22-4.16 (m, 2H), 4.14 (d, $J$ = 3.0, 9.5, 1H), 4.09 (q, $J$ = 5.5, 1H), 4.02-3.95 (m, 2H), 3.80 (s, 3H), 3.62 (d, $J$ = 5.5, 1H), 3.59 (dd, $J$ = 4.0, 9.0, 1H), 3.48 (t, $J$ = 9.0, 1H), 3.31 (dd, $J$ = 3.5, 13.0, 1H), 2.63 (dd, $J$ = 10.0, 13.0, 1H), 2.06-1.98 (m, 1H), 1.76 (qd, $J$ = 2.0, 7.0, 1H), 1.29 (d, $J$ = 7.0, 3H), 1.01 (d, $J$ = 7.0, 3H), 0.73 (d, $J$ = 7.0, 3H).

$^{13}$C NMR (125 MHz, chloroform-d): $\delta$ = 177.2, 159.4, 153.0, 135.3, 129.5, 129.4, 129.0, 127.4, 113.9, 76.6, 74.9, 73.3, 66.0, 40.5, 38.2, 36.5, 35.7, 13.0, 12.2, 9.7. IR (neat): 3446, 2968, 1775, 1697, 1612, 1513, 1454, 1382, 1363, 1245, 1209, 1100, 1077, 1032, 970, 910, 824, 760, 729, 701 cm$^{-1}$.

**Discodermolide stereotetrad synthesis:**

(4R,5R)-4-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxane (198).

Under an N$_2$ atmosphere, (2R,3S,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentane-1,3-diol (0.107 g, 0.4 mmol, 1.0 eq.) was dissolved in DCM (4 mL) in a flame dried 10 mL Schlenk tube and cooled to 0$^\circ$ C in an ice/water bath. Dimethoxypropane (4.9 mL, 40.0 mmol, 10.0 eq.) then Camphorsulfonic acid (0.009 g, 0.04 mmol, 0.1 eq.) were added and the reaction was allowed to warm to room temperature as it stirred overnight. The reaction was quenched with saturated aqueous NaHCO$_3$ (10 mL). The aqueous layer was extracted with
DCM (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (20:1 to 10:1 hexanes:EtOAc) provided (4R,5R)-4-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxane as a clear colorless oil (0.119 g, 0.39 mmol, 97%).

$^1$H NMR (500 MHz, chloroform-d): $\delta = 7.25$ (d, $J = 8.5$, 2H), 6.87 (d, $J = 9.0$, 2H), 4.45 (d, $J = 11.5$, 1H), 4.38 (d, $J = 11.5$, 2H), 4.08 (dd, $J = 3.0$, 11.0, 1H), 3.80 (s, 3H), 3.75 (dd, $J = 2.5$, 10.0, 1H), 3.60 (dd, $J = 1.5$, 12.0, 1H), 3.50 (dd, $J = 3.0$, 9.0, 1H), 3.40 (dd, $J = 6.0$, 8.5, 1H), 1.81-1.75 (m, 1H), 1.55-1.49 (m, 1H), 1.38 (s, 3H), 1.37 (s, 3H), 1.05 (d, $J = 7.0$, 3H), 0.91 (d, $J = 7.0$, 3H). $^{13}$C NMR (125 MHz, chloroform-d): $\delta = 159.0$, 131.0, 129.1, 113.7, 98.6, 72.8, 72.2, 71.7, 67.3, 55.3, 35.4, 29.8, 29.6, 22.9, 19.1, 12.6, 10.2. IR (neat): 2964, 2934, 2856, 1613, 1513, 1459, 1378, 1364, 1245, 1098, 1008, 847, 821 cm$^{-1}$.

(R)-2-((4R,5R)-2,2,5-trimethyl-1,3-dioxan-4-yl)propan-1-ol (199).

Under an N$_2$ atmosphere, (4R,5R)-4-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxane (0.108 g, 0.35 mmol, 1.0 eq.) was dissolved in DCM (4 mL) and pH 7.0 buffer (4 mL) in a 25 ml Schlenk tube and cooled to 0$^\circ$ C in an ice/water bath. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.113 g, 0.5 mmol, 1.5 eq.) was added and the
reaction was monitored by TLC for completion. After 1 hour the reaction was complete and
diluted with DCM (10 mL) and pH 7.0 buffer (10 mL) and the layers were separated. The
aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic layers were
dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by
flash column chromatography on silica gel (10:1 to 4:1 hexanes:EtOAc) provided (R)-2-
((4R,5R)-2,2,5-trimethyl-1,3-dioxan-4-yl)propan-1-ol as a clear colorless oil (0.055g, 0.29
mmol, 84%).

**1H NMR** (500 MHz, chloroform-d): \(\delta = 4.12 \text{ (dd, } J = 3.0, 12.0, 1\text{H}), 3.82 \text{ (dd, } J = 2.5, 10.0,
1\text{H}), 3.61 \text{ (dd, } J = 1.5, 11.0, 1\text{H}), 3.60-3.52 \text{ (m, 2H), 3.10 \text{ (d, } J = 7.5, 1\text{H}), 1.92-1.84 \text{ (m, 1H),}
1.58-1.52 \text{ (m, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.10 \text{ (d, } J = 6.5, 3\text{H), 0.76 \text{ (d, } J = 7.0, 3\text{H).}} \)**

**13C NMR** (125 MHz, chloroform-d): \(\delta = 98.7, 78.4, 69.0, 67.0, 36.4, 30.0, 29.7, 19.1, 12.0, 10.5.\)

**IR** (neat): 3436, 2965, 2936, 2876, 1460, 1379, 1269, 1246, 1198, 1094, 1035, 1007, 957,
847, 749 cm\(^{-1}\).

(S)-2-((4S,5R)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanal (200).

In an open air atmosphere (R)-2-((4R,5R)-2,2,5-trimethyl-1,3-dioxan-4-yl)propan-1-ol
(0.062 g, 0.33 mmol, 1.0 eq.) was dissolved in DCM (3 mL) in a scintillation vial equipped
with a stir bar and cooled to 0°C in an ice/water bath. Saturated aqueous NaHCO\(_3\) (2.5 mL)
was added and the reaction was stirred vigorously. Potassium bromide (0.016 g, 0.13 mmol, 0.4 eq.), TEMPO (0.0052 g, 0.033 mmol, 0.1 eq.), and NaOCl (0.7 mL, 6% aq., 0.66 mmol, 2.0 eq.) were added in that order. The reaction was monitored by TLC and had gone to completion after 60 minutes. The reaction was quenched with water (10 mL), extracted with DCM (3 x 10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel (1:1 hexanes:EtOAc) provided (2S,3R,4R)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanal as a clear colorless oil (0.050 g, 0.27 mmol, 82%).

\textbf{\textsuperscript{1}H NMR} (500 MHz, chloroform-\textit{d}): $\delta = 9.73$ (d, $J = 2.5$, 1H), 4.17-4.90 (m, 3H), 3.65 (dd, $J = 1.0, 21.0$, 1H), 2.53-2.46 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.11 (d, $J = 6.5$, 3H), 0.95 (d, $J = 7.5$, 3H).
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11. References


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