Model Studies, Methodologies, and Progress Toward A Synthesis of Lyngbyaloside B.

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
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Thomas R. Hoye, Adviser

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I thank former Hoye group labmates JunHa Jeon and Lucas Kopel, the people who had to put up with me the most during my time at the University of Minnesota. I would also like to thank Heidi Dahlmann, Patrick Willoughby, and Nathan Connell, who worked with me as LANDO students over the summers of ’06, ’07, and ‘09 respectively. Obviously I thank Tom Hoye for too many reasons to mention, and the same can be said for Wayland Noland. I’d like to specifically thank Tom Hoye, Chris Cramer, Wayland Noland, Bill Tolman, Andy Taton, and Kris McNeill for being outstanding teachers during my first year graduate coursework. I thank Shana Sturla and Robert Fecik for discussions in helping me decide where to postdoc. I would like to thank my friends Alexander David Stupica and Morgan Janae Kirkendall. Lastly I would like to thank the reader of this thesis. I sincerely hope that you can learn something from what I have done during my time in the Hoye lab.
Abstract:

The bulk of the work done in this thesis falls into the categories of studying acylketene intermediates and developing strategies toward the synthesis of lyngbyaloside B. In the first chapter, a model system of lyngbyaloside B and lyngbouilloside was created to study the dual macrolactonization/pyran-hemiketal formation reaction. In the second chapter, methods for the efficient creation of acylketene intermediates at room temperature were advanced. In the third chapter, the selectivity of additions to acylketene was explored. In the fourth chapter, an aldol method useful to the synthesis of lyngbyaloside B was explored, leading to the discovery of a novel decarboxylative isomerization, which was also explored. In the fifth chapter, progress toward the total synthesis of lyngbyaloside B is presented. Lastly, the sixth chapter involves studies that do not cleanly fit into the previous 5 chapters.
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<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>ACP</td>
<td>Acyl Carrier Protein</td>
</tr>
<tr>
<td>Anal.</td>
<td>Analysis</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal-Butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary-Butyl</td>
</tr>
<tr>
<td>ca.</td>
<td>approximately</td>
</tr>
<tr>
<td>Calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionization</td>
</tr>
<tr>
<td>CM</td>
<td>Cross Metathesis</td>
</tr>
<tr>
<td>COSY</td>
<td>2-dimensional Correlated Spectroscopy</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical Shift in parts per million</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethyl-4-aminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N-dimethylpropyleneurea</td>
</tr>
<tr>
<td>DMS</td>
<td>Dimethylsulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>E</td>
<td>Entgegen (opposite)</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionization</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl Acetate</td>
</tr>
<tr>
<td>equiv</td>
<td>Equivalents</td>
</tr>
</tbody>
</table>
ee  Enantiomeric excess

Gram(s)

G1  First Generation Grubbs initiator

G2  Second Generation Grubbs initiator

GC-MS  Gas Chromatography – Mass Spectrometry

HG1  First Generation Hoveyda/Grubbs Initiator

HG2  Second Generation Hoveyda/Grubbs Initiator

HMPA  Hexamethylphosphoric triamide

HRMS  High Resolution Mass Spectrometry

Hz  Hertz (cycles per second)

IR  Infrared

J  Coupling Constant

LAH  Lithium aluminum hydride

LDA  Lithium diisopropylamide

m  multiplet

Me  Methyl

MHz  Megahertz

mol  Mole(s)

mmol  milliMole(s)

MOM  Methoxymethyl

mp  melting point

MPLC  Medium Pressure Liquid Chromatography

4Å MS  4-Angstrom molecular sieves

NBS  N-bromosuccinimide

ND  Not determined

NMO  4-Methylmorpholine-N-oxide

NMR  Nuclear magnetic resonance

NOE  Nuclear Overhauser Effect/Enhancement

NR  No reaction

pentet
PCP  Peptidyl Carrier Protein
PDC  Pyridinium Dichromate
Ph   Phenyl
ppm  Parts per million
PPTS Pyridinium \( p \)-toluenesulfonic acid
\( i \)-Pr Isopropyl
q     quartet
R     Rectus (configurational)
RCM   Ring-closing metathesis
\( R_f \) Ratio to front
rt    Room temperature
S     Sinester (configurational)
s     singlet
t     triplet
TBAF  Tetrabutylammonium fluoride
TBS   \textit{tertiary}-Butyldimethylsilyl
TES   Triethylsilyl
TFA   Trifluoroacetic acid
THF   Tetrahydrofuran
TLC   Thin layer chromatography
TMS   Trimethylsilyl
TOF   Time of flight
\( t_R \) Retention time
Ts    \textit{para}-Toluene sulfonyl
Rf    Ratio to front
Z     \textit{Zusammen} (together)
Compound and Scheme Numbering Ranges:

Compound Numbering Ranges by Chapter:
Chapter I: 101-1102
Chapter II: 201-292
Chapter III: 301-333
Chapter IV: 401-498
Chapter V: 501-5107
Chapter VI: 601-631

Scheme Numbering Ranges by Chapter:
Chapter I: 101-128
Chapter II: 201-219
Chapter III: 301-315
Chapter IV: 401-447
Chapter V: 501-535
Chapter VI: 601-608
Chapter I

A Lyngbyaloside B and Lyngbouilloside Model System for Acylketene Macrolactonization.
1.1 Introduction

The goal of the research in the studies described in this thesis chapter is to expand our knowledge of the acylketene dual macrolactonization/pyran hemiketal formation reaction and determine its viability for future synthetic efforts. The reaction was first demonstrated in our laboratory by Mike Danielson en route to a synthesis of callipeltoside A.\textsuperscript{1,2} In the event, 1,3-dioxin-4-one \textbf{101} is heated in a hydrocarbon solvent, inducing a retro-hetero Diels-Alder reaction that extrudes acetone, generating the highly reactive acylketene intermediate \textbf{102} (Scheme 101).\textsuperscript{3} Our belief was that lactonization onto acylketene occurred, giving \textbf{103}, followed by hemiketal formation to \textbf{104}.\textsuperscript{4} Regardless of the order of events, this transformation has considerable synthetic utility, converting a linear precursor into a bridged bicyclic system.\textsuperscript{5,6}

\textbf{Scheme 101}

\begin{center}
\includegraphics[width=\textwidth]{Scheme101.png}
\end{center}

1.2 The Use of Acylketenes as Macrocyclization Precursors

The use of acylketenes as intermediates for macrocyclization was first demonstrated in 1989 by Boeckman (\textbf{105} to \textbf{106}) and Paquette (\textbf{107} to \textbf{108}) for their total syntheses of (+)-ikarugamycin (Scheme 102).\textsuperscript{7,8} These simultaneously reported results were the first to show that that lactamization reactions using acylketenes were not only possi-
ble, but could be high yielding, even in complex molecular settings. An attractive feature of these lactamization reactions is the ease of use, as only heating is required. This method was a huge leap forward from the typical acid activation strategies previously employed for lactamizations.

**Scheme 102**

![Scheme 102](image)

The next significant advance in the area of acylketene macrocyclizations came later in 1989 from the Boeckman lab (Scheme 103). They showed that macrolactonizations to make 10-membered (109 to 110) and 15-membered (111 to 112) rings were possible and showcased the methodology in a total synthesis of kromycin (113 to 114). In this remarkable lactonization, two hydroxyl groups could have engaged the acylketene
intermediate, but only one isomer is isolated. This macrocyclization also showed that methyl groups could be tolerated in the 2-position of the dioxinone starting material.

As powerful as the Boeckman cyclization is for the creation of medium to large ring systems, the reaction can be sensitive to issues related to ring strain. In their 1993 paper in the Journal of Organic Chemistry, Kurth and co-workers showed that a fully saturated 10-membered ring could not be formed (115e to 116e, Scheme 104), and 11-membered rings derived from 115a-c could not be accessed.\textsuperscript{10} In both cases the major product was dimer, with the next major product being trimer. The 10-membered ring failure is especially interesting because Boeckman had showed a 10-membered ring containing an alkene as one of his examples.\textsuperscript{9} In the case of 12-membered ring formation (115d to 116d), monomer was obtained, but dimer was still the major product. Collectively, these results showed that certain ring sizes were problematic and that one couldn’t be sure this methodology would work without actually trying it on the system of interest.

**Scheme 104**

<table>
<thead>
<tr>
<th>entry</th>
<th>[X]</th>
<th>Ring Size</th>
<th>monomer</th>
<th>dimer</th>
<th>trimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>cis-CH=CH-</td>
<td>11</td>
<td>0</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>b</td>
<td>trans-CH=CH-</td>
<td>11</td>
<td>0</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>c</td>
<td>-CH_2CH_2</td>
<td>11</td>
<td>0</td>
<td>49</td>
<td>13</td>
</tr>
<tr>
<td>d</td>
<td>-CH_2CH_2</td>
<td>12</td>
<td>28</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>e</td>
<td>-CH_2</td>
<td>10</td>
<td>0</td>
<td>60</td>
<td>26</td>
</tr>
</tbody>
</table>

In the following years, several groups used the Boeckman cyclization in the pursuit of syntheses of natural products. The reader is directed to a review by Sorensen for further information regarding these endeavors.\textsuperscript{11} Our group was pursuing a total synthesis of (–)–callipeltoside A, and identified the Boeckman protocol as potentially being advantageous for making the core ring system.\textsuperscript{12} Dioxinone 117 was synthesized by Hongyu Zhao, the graduate student who was then working on the project (Scheme 105).\textsuperscript{13} Hongyu refluxed this substrate in toluene, giving acylketene 118. Alcohol addition to acylketene gave β-keto ester 120 (via 119) as the product in 65% yield. A byproduct from this reac-
tion was methyl ketone 121 (15% yield), which undoubtedly arrives from a competitive trapping of water by acylketene 118, followed by decarboxylation. It was found that the relative amounts of methyl ketone increased over time, suggesting that reversibility from 120 back to acylketene 118 was a problem.

Scheme 105

After Hongyu graduated, the callipeltoside project was given to Mike Danielson, who had trouble reproducing Hongyu’s lactonization yields, as methyl ketone formation during lactonization was consistently a problem, even with scrupulously dried toluene. Since the problem of water addition to acylketene was at least partially a problem of reversion of the β-keto ester product back to acylketene, Mike’s idea was to trap the β-keto ester as its corresponding pyran-hemiketal. Since the hemiketal will be closed nearly all of the time, acylketene formation should thus be slowed down or eliminated. This idea was validated by the synthesis of substrates 101/122-123, and by their lactonizations to 104/124-125 (Scheme 106). Noteworthy are substrates 123, containing four free hydroxyl groups. Mike found these lactonizations to be reproducible, and methyl ketone formation was no longer a problem. Substrate 101β was taken forward to complete the total synthesis of (-)-callipeltoside A.
1.3 Lyngbyaloside B and Lyngbouilloside

Potential targets on which to apply the dual macrolactonization/pyran-hemiketal formation method were chosen. In 2002, the structures of macrolides lyngbyaloside B (126)\textsuperscript{14} and lyngbouilloside (127)\textsuperscript{15} were published by the Moore and Gerwick labs, respectively (Figure 1). These natural products piqued our interest for several reasons. Both

\textbf{Figure 1 – Lyngbyaloside B (126) and Lyngbouilloside (127)
of them are rare (0.6 mg of 126 and 4.5 mg of 127 have been isolated), cytotoxic (126 has IC$_{50}$ = 4.3 µM against KB cells, 127 has IC$_{50}$ = 17 µM against neuroblastoma cells), and have unproven structures, as no crystal structural was obtainable for either compound. Additionally, the relative configuration of the sugar and aglycon fragments is unknown for both natural products, as well as the absolute configurations.

In addition to being structurally interesting, at least one of the natural products appears to have been assigned incorrectly. $^1$H and $^{13}$C NMR data for atoms within the macrolide rings are virtually identical even though they are assigned as hydroxyl epimers at C11 (Figure 2). The methine peaks of the secondary alcohol are broad multiplets, making J based assignment difficult. Additionally, no meaningful differences can be distinguished from their 2D spectra.

**Figure 2 – $^1$H Chemical Shifts of Lyngbyaloside B (126) and Lyngbouilloside (127)**

The likelihood for success of a dual macrolactonization/pyran formation reaction in a synthesis of lyngbyaloside B or lyngbouilloside can be called into question for several reasons. Macrolactonizations of tertiary alcohols are quite rare, and perhaps more importantly, low yielding. Only 3 are abstracted in the Beilstein and Scifinder databases, and are shown below (Scheme 107). Masamune used electrophilic mercury(II) to activate thioester 128 towards nucleophilic attack, giving desired product 129 in 36% yield. Ley used electrophilic Cu(I) activation of thioester 130 to achieve macrolactonization of model system 131 in 40% yield. Finally, Weiler used the Yamaguchi conditions to
achieve macrolactonization in the simple unbutressed system 132 to yield 133 in 54% yield.\(^\text{18}\)

**Scheme 107 – Tertiary Alcohol Macrolactonizations**

None of the lactonization substrates in Scheme 107 are similar enough to ours to ensure that our desired ring closures will work. Another cause for concern is that if macrolactonization of a tertiary alcohol is sufficiently slow, competing 8-membered ring formation could potentially occur in our system since it contains more than one hydroxyl group. While this was not observed in Mike Danielson’s lactonizations with a secondary alcohol (102 to 134, Scheme 108), this concern becomes pronounced when a literature search reveals that acylketenes can be used to make 8-membered rings in good yield.

Petasis produced a variety of 8-membered rings such as 136 by using 1,3-dioxin-4-ones such as 135 as acylketene precursors.\(^\text{19}\) Concern becomes alarm when one considers that the reaction works well with primary and secondary alcohols, but fails entirely with tertiary alcohols.\(^\text{19}\)
Finally, the question can be raised of whether the desired tertiary macrolactone product would be stable over the course of the reaction, since tertiary β-ketoesters form acylketene over an order of magnitude faster than do primary or secondary ones. In fact, the rate of reversion of tertiary β-ketoesters to acylketene is approximately the same as the rate of formation of acylketene from 2,2,6-trimethyl-4H-1,3-dioxin-4-one (Scheme 109). If acylketene is formed reversibly during the reaction, the likelihood of dimerization and oligomerization (and thus, lower yields) increases.

1.4 A Lyngbyaloside B/Lyngbouilloside Model System

It seemed a wise decision to make a model system of lyngbyaloside B/lyngbouilloside to address the issues raised in the previous section. First and foremost, the model system had to be realistic enough so that the result should translate to the real system. Additionally, it should be finishable in significantly less time than would the real system. For these reasons the model target shown below was chosen (Figure 3). The model system is racemic, lacks the alkenyl side chains, is epimeric at the C11 hydroxyl, and lacks the C10 methyl group. These decisions balance the need for realism and synthetic pract-
cality. An added bonus of using an epimeric mixture at C11 is that it will allow us to determine if one diastereomer is closing more efficiently than the other (as measured by desired products and/or byproducts formed). The epimers can also be compared to the literature data for the natural products to perhaps gain insight into what the actual configuration is at C11 in the natural products.

**Figure 3 – A Model System of Lyngbyaloside B (105) and Lyngbouilloside (106)**

The initial retrosynthetic plan is outlined below (Scheme 110). It was reasoned that dimethylacetonedicarboxylate (141) and diacetone alcohol (142) could be converted to precursors 143 and 144, respectively. A recently disclosed ruthenium catalyzed regioselective α-alkylation could then potentially be performed on these reactants to form

**Scheme 110**
ketone \(145^{23,24}\). From there, reduction and protection would give \(146\), which could have its acetal opened regioselectively and be oxidized to \(147\). A vinylogous Mukaiyama aldol reaction and protection could then give \(148\).

The mechanism for the desired key ruthenium catalyzed regioselective \(\alpha\)-alkylation is shown below (Scheme 111). A methyl ketone \(149\) and primary alcohol \(150\) are combined with catalytic \(\text{RuCl}_2(\text{PPh}_3)_3\), \(\text{KOH}\), dioxane, and 1-dodecene. The primary alcohol is oxidized to aldehyde \(151\) by ruthenium, generating a ruthenium dihydride species. The base deprotonates the methyl ketone and condensation occurs with the newly formed aldehyde, giving enone \(152\). The ruthenium dihydride then promotes hydrogenation of the enone, giving the desired product \(153\) and regenerating the ruthenium catalyst. The protocol calls for 1-dodecene to be added, otherwise the methyl ketone starting material and the ketone-containing product can be over-reduced to the carbinol by the intermediate ruthenium dihydride. Because we ultimately want to reduce the ketone to an alcohol anyway, this was not viewed as a potential limitation.

**Scheme 111**

![Scheme 111](image)

The reactants for the reaction were made as outlined Scheme 112: Diacetone alcohol \((142)\) was protected with TBS, \(^{25}\) MTM, \(^{26}\) and BOM protecting groups \((144a-c)\). Notable was when benzylolation was attempted by first deprotonating with sodium hydride, followed by addition of benzyl bromide, that none of the desired product was formed, instead benzylacetone \((154)\) and 1,1-dibenzylacetone \((155)\) were formed (Scheme 112).
The primary alcohol 143 for the coupling reaction was made by sodium borohydride reduction of 141 to 156, then LAH reduction to triol 157. The two-step procedure worked much better than direct reduction to the triol with sodium borohydride, mostly due to solubility issues. Direct LAH reduction of 141 was tried with poor results, potentially due to the acidity of the α-protons. The triol was then protected with anisaldehyde dimethylacetal under acid catalysis.

Scheme 112

With the materials in hand we set out to do the coupling reaction. First it was tested on a simple system (Scheme 113). Acetophenone 158 and isobutanol 159 were subjected to the conditions described by Cho. Indeed, the desired product 160 was formed, along with its byproduct carbinol 161 formed by over-reduction. Some starting acetophenone also remained, along with its byproduct carbinol 162. An additional byproduct of acetophenone condensation and reduction, namely 163, was also detected. These results gave us confidence going forward, however, when the ruthenium-catalyzed α-alkylation was tried using the reactants for the model system only decomposition occurred. By ESI analysis there was no desired product (or its reduced form) formed during the reaction. The most obvious problem with this system is that when oxidized the aldehyde has a β-leaving group. This causes loss of anisaldehyde (which was observed) from the aldehyde. Moreover, the starting ketone also has a β-leaving group, and can simply eliminate. This resulted in a very complex product mixture.
After the failure of direct coupling, we sought out a more conventional alkylation method. Conversion of 143 to its iodide 164 (I₂, PPh₃, imidazole) was performed, and ketone and hydrazone nucleophiles 144a and 165 were used after deprotonation with LDA (Scheme 114). In both cases the desired products 145a and 166 were formed, but both methods could not be optimized to efficiently give good yields, so this approach was also abandoned.
Success was finally achieved by using the dianion of tert-butyl acetoacetate (167) as a nucleophile, giving desired product 168 upon reaction with iodide 164 (Scheme 115). This approach gave consistently good yields and was reproducible, although elimination product 169 often occurred to various extents. Sodium borohydride reduction of the resulting product to give 170 was straightforward, as was BOM protection to give 171. This route also was amicable to scaleup without chromatography, because the crude products could be carried forward into the next reaction without negative consequences.

Scheme 115

The tertiary alcohol was installed by refluxing MeMgBr with ester 171, giving 172 (Scheme 116). DIBAL-H reduction opened the acetal regioselectively to 173, but with formation of an alkene-containing impurity. This impurity was removed by oxidizing with OsO₄/NMO, then purification by column chromatography. TPAP oxidation gave aldehyde 174. Other oxidation conditions (PDC, Moffat, TEMPO, Swern) gave significantly worse yields.
The next step in the sequence was a vinylogous Mukaiyama aldol reaction. It was anticipated that reaction would be highly anti selective based on model work done by Evans (Scheme 117). Evans showed that regardless of the Lewis acid used, traditional silyl enol ethers add in anti fashion to protected β-hydroxy aldehydes such as 175, giving primarily adducts such as 176.

**Scheme 116**

![Scheme 116 Diagram]

In our case, we are using a silyl dienol ether as the nucleophile, and it gave essentially no selectivity in the reaction (174 to 177, Scheme 118). Other Lewis acids were tried, but gave significantly worse yields with no benefit to selectivity. Additionally, anionic versions of the reaction were attempted with no success. At the time the reaction was applied, there existed no examples of addition of the silyl dienol ether of 2,2,6-trimethyl-1,3-dioxin-4-one to aldehydes with a β-hydroxyl group and no substituent in the α-position. After the reaction was scaled up however, Crimmins reported results similar to ours, that there is little selectivity in the reaction.
Scheme 118

The product, which was an ca. 1:1:1:1 mixture of diastereomers, was TES protected (TESCl, imidazole, DCM), giving 178, which was suitable for testing the lactonization of a tertiary alcohol. When refluxed in benzene (12 hours) or toluene (1.5 hours), lactonization to 179 occurred (Scheme 119). The product was purified by MPLC, and ESI clearly showed monomeric product. Unfortunately, the diastereomers could not be separated, thus structural assignment was difficult. While clearly being a good result, we hoped for more success in the future at purifying and characterizing the diastereomers.

Scheme 119

After successfully lactonizing the model system, the focus turned to the dual macro lactonization/pyran hemiketal formation reaction. The alcohol at C7 in 178 was deprotected using DDQ and pH = 7 phosphate buffer (Scheme 120). To our delight, the 1,3-syn (180) and 1,3-anti (181) diastereomers could be separated by MPLC. This was especially satisfying because now not only could we assign each, but subject each separately to the reaction to help test its scope, something we didn’t plan on from the outset of the project, as we had anticipated the vinylogous Mukaiyama aldol reaction would give only the 1,3-anti product.
Scheme 120

The 1,3-anti product 181 was refluxed in benzene for 12 hours. We were pleased to see the desired products 182 and 183 form (Scheme 121). No 8-membered ring could be detected in the reaction mixture. The most satisfying aspect of the reaction perhaps was the purification. The epimers at C11 were readily separable! The final products were isolated as single diastereomers despite being a 1:1:1:1 mixture just 2 steps earlier. The isolated yield of 67% represents the highest yielding macro lactonization of a tertiary alcohol. At this point the model system could be considered a success. Each C11 epimer closed efficiently, monomeric product is obtained, and no 8-membered ring was formed.

Scheme 121

Although the lactonization was successful, one can question what the mechanism is. Is macro lactonization preceding hemiketal formation, or vice versa? One can consider $K_{eq}$ between acylketene 184 and hemiketal ketene 185 (Scheme 122). While we don’t know what $K_{eq}$ is, we can be confident that the value will be less for its C5 epimer. If the efficiencies of the reaction remain the same for both epimers, one could interpret that as the pyran hemiketal not being involved, since, as diastereomers, we would expect they could or would have quite different cyclization efficiencies.
The lactonization with the 1,3-syn epimer 180 was performed (Scheme 123).

Once again, the reaction was successful, although the isolated yield was slightly lower (186, 51%). No 8-membered ring was formed. The C11 epimers could not be separated after this reaction. It is difficult to use this result to argue for or against macrolactonization preceding hemiketal formation, and we cannot prove which is occurring first. It is important to point out however that conversion of 184 to 185 likely requires catalysis, whereas the macrocyclization does not.

At the outset of the project we were concerned about the thermal stability of the tertiary macrolactone/pyran. Although we know that tertiary β-keto esters are relatively unstable relative to their primary and secondary counterparts, our final product is not a β-keto ester, but the hemiketal of one. We sought to test whether or not acylketene could be formed reversibly under the reaction conditions, and if the hemiketal indeed protected the product against reversion back to acylketene. This was done by heating the isolated product 182 with a large excess of water. If acylketene is being formed reversibly, we can reasonably expect water to add to it, generating a β-keto acid, which would decarboxylate to a methyl ketone. When this was done (toluene reflux, 40 minutes) no change in the start-
ing material was observed. The 40-minute reaction time corresponds to approximately 
two half-lives of tert-butyl acetoacetate.\textsuperscript{20} Thus, we can be confident that the hemiketal is 
indeed protecting the ester from reversion back to acylketene.

1.5 An Alternative Model System for Studying Acylketene Macrolactonization/Pyran-Hemiketal Formation

Although the model system was complete, we still remained interested in studying 
the dual macrocyclization/pyran hemiketal formation reaction, particularly issues of ki-
netics and reversibility. A simpler model system, the dioxinone 187, was designed 
(Scheme 124). The model system was as ‘bare bones’ as could be, a linear chain contain-
ing only two hydroxyl groups. To start, 1,7-heptanediol 188 was BOM protected under 
standard conditions, and the resulting mono-ol 189 was oxidized with TPAP/NMO. 
VinylMgBr addition gave 190 followed by another TPAP/NMO oxidation to give enone 191. Conjugate addition of the copper enolate of the anion of 2,2,6-trimethyl-1,3-dioxin-
4-one,\textsuperscript{19} followed by sodium borohydride reduction and BOM deprotection gave model 
substrate 187. This approach was satisfactory, but the final step surprisingly worked very 
poorly. Many hydrogenation conditions (and pressures) were tried with little success. 
Turning to BF\textsubscript{3}·OEt\textsubscript{2}/DMS mixture caused deprotection, but in poor yield of ~20%.

Scheme 124

```
O
OH

188

BOMCI

Hunig's base

DCM

47%

OH

O

OBOM

189

1) TPAP/NMO

2) vinylMgBr

35%

OH

OBOM

190

O

Me

Me

O

Me

Me

O

Me

Me

OH

OH

187

1) Li

2) NaBH\textsubscript{4}/EtOH

3) BF\textsubscript{3}·OEt\textsubscript{2}/DMS

53%

O

OBOM

191

A shorter more successful route was devised and executed (Scheme 125). Starting 
with diol 192, sodium periodate oxidation gave aldehyde 193, which could be used with-
```
out chromatography in the next reaction with vinylMgBr to give allylic alcohol 194. Parikh-Doering oxidation of the resulting allylic alcohol gave enone 195.\textsuperscript{37} Conjugate addition of the copper enolate of the anion of 2,2,6-trimethyl-1,3-dioxin-4-one, followed by dual borane-THF hydroboration/oxidation and ketone reduction gave model substrate 187 in only 5 steps.

**Scheme 125**

As hoped, the model substrate also successfully underwent the dual macrocyclization/pyran hemiketal formation reaction (Scheme 126). Additionally, it was discovered that the benzene solvent did not require pre-drying to achieve success, giving 196 in 80% yield and \(~96:4\) diastereomeric ratio. This is important because it suggests that the concerted addition of the hydroxyl to acylketene can outcompete the addition of water.\textsuperscript{38} In fact, when the system is saturated with water (a pool of water sits in the reaction flask with the benzene), the desired product is still formed in \textit{ca. 2:1} preference over its methyl ketone 197 arising from water addition and decarboxylation. When isolated 196 is subjected to the same conditions, no further conversion to 197 is observed, showing that acylketene is not being formed under the reaction conditions once the initial ring closures occur.
Additional insight was gained by the use of labeled water. When heated in benzene with D₂O, partial deuteration (both mono and bis) of the α (C2) protons in 196 occurred. This suggests that 196 is in equilibrium with keto form 198 (Scheme 22), which tautomerizes to its enol 199, which can exchange with D₂O. Acylketene 1100 is not formed under the reaction conditions however, since no methyl ketone 197 is formed. Also, heating in the presence of 18O labeled water did not lead to incorporation of labeled oxygen into the starting material (based on ESI measurements). This result suggests that carbocation 1101 is not formed during the reaction by protonation and loss of water.
Since deuterium could be incorporated into the α protons in 196, the rates were measured. This gave us a chance to compare our substrate to that of a simple β-ketoester, ethyl acetoacetate (1102). The difference between the rates of incorporation between these two substrates should give us an idea of how well the hemiketal protects the ester against enolization, and thus, acylketene formation. In the first set of experiments, 1102 was heated in benzene to 80 °C with an excess of D₂O present (Figure 4). ESI measurements taken at 0.25 and 0.5 hours showed ~33%, and ~78% incorporation respectively based on the growth of the parent +1 and +2 isotopic peak ion counts. These numbers give an approximate half-life of enolization of 0.3 hours. In contrast, the same conditions using substrate 196 led to only ~10% deuterium incorporation at 12 hours, which corresponds to a half-life of ~2-3 days. Thus, hemiketal formation within 196 slows down the rate of enolization by a factor of ~180. Although the error bar for this style of comparison is likely very large, we can still be confident in the magnitude of the difference, which is ~2 orders of magnitude.

Figure 4 – Deuterium Incorporation into substrates 1102 and 196 using D₂O

Conditions: excess D₂O in benzene - 80 °C

We then sought out a more well behaved system: one in which solubility of water was not a concern. We used neat d₄-MeOH as a deuterium source in the enolization tests instead of D₂O. It was found that the apparent rate of enolization was much higher in this medium, and heating was not required. Compound 1102 was found to be deuterated ~44% over the course of 1 hour, giving a half-life of just over an hour (Figure 5). Substrate 196 incorporated ~37% deuterium at 5 days, giving a half-life of ca. 7 days. Com-
parison of these numbers suggests that hemiketal formation within 196 slows down enolization by a factor of ~170. Once again, there is probably a significant error bar in a comparison like this, however it is satisfying to see that the relative values for the D₂O and d₄-MeOH rates are approximately the same even though the experiments were run at different temperatures and had different solubility.

**Figure 5 - Deuterium Incorporation into substrates 1102 and 196 using d₄-MeOH**

Conditions: excess d₄-MeOH at room temperature.

Finally, it was found that in the case of d₄-MeOH at room temperature, a preponderance of the bis-deuterium incorporated product was made over the mono-deutero compound, even at less than 50% conversion! Approx. 58% of starting material was undeuterated, followed by ~9% mono-deuteration, and ~33% bis-deuteration.

**Scheme 128**

This suggests that enolization between 198 and 199 is faster than reclosure of 198 back to 196 (Scheme 128). This result was not expected and is not observed in the case where 196 is heated in D₂O/benzene, where the deuteration is roughly statistical. This result seemed a nice way to close the book on the work of the subject.

In conclusion, the results described in this chapter illustrate the viability of the dual macrolactonization/pyran hemiketal formation reaction on a realistic model system.
of lyngbyaloside B and lyngbouilloside. These results, along with lactonizations related to the callipeltoside A synthesis, were published as the Hoye group’s first and currently only *Angewandte Chemie* paper, and the total synthesis of lyngbyaloside B is being pursued.\(^{39}\)

### 1.6 Experimental Section

**Dimethyl 3-hydroxypentanedioate (156).**

In a round bottomed flask equipped with a stirbar, 1,3-dimethylacetonedicarboxylate (141, 25.3 g, 145 mmol) was added to 25 mL of methanol. The flask was cooled using a dry ice/acetone bath, and NaBH\(_4\) (1.57 g, 41.3 mmol) was added slowly in portions. After addition the solution was allowed to come to room temperature and stirred for one hour. The reaction was quenched with 10 mL of H\(_2\)O and neutralized with 15% HCl solution. The product was extracted with ether (4 x 50 mL), dried over MgSO\(_4\), filtered, and concentrated in vacuo to yield 19.6 g (77%) of 156.

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta 4.47\) (pentet, \(J = 6\) Hz, 1H, \(\text{CHOH}\)), 3.72 (s, 6H, O\(\text{CH}_3\)), 3.50 (s, 1H, OH), 2.56 (d, \(J = 6\) Hz, 4H, -CH\(_2\)-).

**\(^13\)C NMR** (125 MHz, CDCl\(_3\)) \(\delta 172.3, 64.8, 52.0, 40.64\).

**HRMS** (ESI) Calcd. for (C\(_7\)H\(_{12}\)O\(_5\) + Na\(^+\)): 199.0583, found: 199.0573.

**GC-MS** \(T_r = 7.18\) min; m/z: 177, 143, 127, 116, 103, 74, 71, 61, and 59.

**IR** (neat) 3520, 3006, 2964, 2854, 1747, 1728, 1447, 1280, 1051, 990, and 850 cm\(^{-1}\).

**TLC** \(R_f = 0.35\) in 50% EtOAc in hexanes.
2-(2-(4-methoxyphenyl)-1,3-dioxan-4-yl)ethanol (143).\textsuperscript{40}

To a 500 mL round bottomed flask, 300 mL THF, a magnetic stirbar, and Lithium Aluminum Hydride powder (8.77 g, 230 mmol) were added. While stirring in an ice bath under N\textsubscript{2} atmosphere, diester 156 (8.95 g, 50.8 mmol) in 9 mL THF was added dropwise over 40 minutes via syringe pump. The reaction mixture was then allowed to warm to room temperature and was stirred an additional 1.5 hours. The reaction was quenched by adding the following via syringe pump while stirring vigorously: 9 mL H\textsubscript{2}O, followed by 18 mL 10\% NaOH solution, then 27 mL H\textsubscript{2}O. The reaction mixture was then filtered through a pad of celite in a sintered glass funnel using 1 liter of THF. The solution was then dried with MgSO\textsubscript{4}, filtered, and rotovapped before being used directly in the next step. The triol was added to a 250 mL round bottomed flask equipped with a magnetic stirbar, 125 mL of THF, 5.4 g 3 Angstrom molecular sieves, 5.8 g 4 Angstrom molecular sieves, and p-TsOH (0.80 g, 4.2 mmol). While stirring under N\textsubscript{2} atmosphere, anisaldehyde dimethylacetal (7.0 mL, 41 mmol) was added. After 20 hours, the reaction was quenched with 20 mL aqueous NaHCO\textsubscript{3}, extracted with EtOAc, dried (MgSO\textsubscript{4}), filtered, and concentrated in vacuo. Separation by MPLC (3 separate runs) gave 6.95 g (57\%) of 143.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.39 (d, J = 9.0 Hz, 2H, ArH), 6.88 (d, J = 9 Hz, 2H ArH), 5.49 (s, 1H, OCHO), 4.26 (ddd, J = 1.0, 5.0, and 11.0 Hz, 1H), 4.10 (dddd, J = 3.5, 3.5, 8.0, and 11.0 Hz, 1H), 3.96 (ddd, J = 2.5, 12.0, and 12.0 Hz, 1H), 3.84 (dd, J = 4.5 and 6.5 Hz, 1H), 3.82 (dd, J = 4.5 and 6.5 Hz, 1H), 3.80 (s, 3H, OMe), 2.18 (s, 1H, OH), 1.95-1.87 (m, 2H), 1.81 (dddd, J = 4.5, 4.5, 8.5, and 11.0 Hz, 1H), 1.51 (dddd, J = 2.5, 2.5, 2.5 and 13.0 Hz, 1H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 160.2, 131.3, 127.5, 113.8, 101.4, 76.7, 67.2, 60.5, 55.5, 38.3, 31.4.

HRMS (ESI) Calcd. for (C\textsubscript{13}H\textsubscript{18}O\textsubscript{4} + Na\textsuperscript{+}): 261.1097. Found: 261.1112.

GC-MS T\textsubscript{r} = 11.8 min; m/z: 238, 237, 207, 193, 153, 135, 121, 108, 92, and 77.

IR (thin film) 3425, 2956, 2841, 2709, 2033, 1652, 1648, 1635, 1519, 1462, and 830 cm\textsuperscript{-1}.

TLC R\textsubscript{f} = 0.45 in 70\% EtOAc in hexanes.
4-(tert-butyldimethylsilyloxy)-4-methylpentan-2-one (144a).

In a round bottomed flask equipped with a stirbar, diacetone alcohol 142 (40.0 mL, 324 mmol), DMAP (3.11 g, 25 mmol), imidazole (14.7 g, 216 mmol), and TBSCl (10.6 g, 70.2 mmol). The solution was placed under nitrogen, stirred, and heated to 70 °C for 42 hours. The mixture was then transferred to a separatory funnel and quenched with water. The aqueous layer was extracted with ether, washed with brine, dried (MgSO₄), filtered, and concentrated in vacuo. The crude material was purified by MPLC (2 separate runs), yielding 6.0 g (37%) of 144a.

**1H NMR** (500 MHz, CDCl₃) δ 2.55 (s, 2H, -CH₂CO), 2.20 (s, 3H, COCH₃), 1.33 (s, 6H, C(CH₃)₂), 0.87 (s, 9H, C(CH₃)₃), and 0.10 (s, 6H, Si(CH₃)₂).

**13C NMR** (125 MHz, CDCl₃) δ 208.6, 73.4, 58.0, 32.8, 30.3, 26.0, 18.2, −0.86.


**GC-MS** Tᵣ = 7.35 min; m/z: 215, 199, 185, 173, 115, and 75.

**IR** (neat) 2957, 2934, 2896, 2865, 1713, 1466, 1363, 1245, 1048, 835, and 770 cm⁻¹.

**TLC** Rₚ = 0.50 in 5% EtOAc in hexanes.

4-(2-iodoethyl)-2-(4-methoxyphenyl)-1,3-dioxane (164).

In a 100 mL round bottomed flask equipped with a stirbar, alcohol 143 (2.07 g, 8.70 mmol), triphenylphosphine (2.85 g, 10.9 mmol), I₂ (2.85 g, 11.2 mmol), and imidazole (2.36 g, 34.7 mmol) were added. After placing the flask under nitrogen and cooling in an ice bath, 24 mL of diethyl ether and 12 mL of benzene were added. After 5 hours the re-
action mixture was quenched with 40 mL of aqueous NaHCO₃, extracted with ether (2 x 75 mL), washed with brine, dried with MgSO₄, and filtered. The mixture was then separated by flash chromatography (15% EtOAc in Hexanes) to give 2.40 grams (80%) of 164.

**1H NMR** (500 MHz, CDCl₃) δ 7.41 (d, J = 9.0 Hz, 2H, ArH), 6.89 (d, J = 9.0 Hz, 2H, ArH), 5.49 (s, 1H, OCHO), 4.26 (ddd, J = 1.0, 5.0, and 12.0 Hz, 1H), 3.99 (ddd, J = 2.5, 2.5, and 9.0 Hz, 1H), 3.96 (ddd, J = 2.5, 2.5, and 9.0 Hz, 1H), 3.80 (s, 3H, OMe), 3.38-3.29 (m, 2H), 2.15 (dddd, J = 3.5, 6.0, 6.0, and 14.5 Hz, 1H), 2.02 (ddddd, J = 3.5, 7.0, 8.5, and 15.5 Hz, 1H), 1.85 (ddddd, J = 5.0, 12.5, 12.5, and 12.5 Hz, 1H), 1.52 (ddddd, J = 2.5, 2.5, 2.5, and 13.0 Hz, 1H).

**13C NMR** (125 MHz, CDCl₃) δ 160.1, 131.3, 127.4, 113.7, 101.2, 76.6, 66.9, 55.5, 39.6, 30.8, and 2.16.


**GC-MS** Tₚ = 12.7 min; m/z: 348, 347, 317, 193, 153, 135, 121, 108, and 77.

**IR** (neat) 2961, 2854, 2721, 1614, 1518, 1362, 1250, 1172, 1120, 1032, and 828 cm⁻¹.

**TLC** Rᵢ = 0.50 in 20% EtOAc in hexanes.

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6-(tert-butyldimethylsilyloxy)-1-(2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-6-methylheptan-4-one (145a).

In a round bottomed flask equipped with a stir bar and 2.5 mL THF under nitrogen at 0 °C, diisopropylamine (0.080 mL, 0.57 mmol) and n-butyl lithium (2.2 M, 0.25 mL, 0.55 mmol) were added. After stirring for 20 minutes, the solution was cooled to -78 °C, and ketone 144a (0.123 g, 0.535 mmol) was added. After 20 minutes, iodide 164 (0.200 g, 0.575 mmol) in 1.0 mL of THF was added. After stirring for 1 hour, DMPU (0.070 mL, 0.58 mmol) was added. The solution was held at -78 °C for 3 hours, then allowed to
warm to room temperature. After 15 hours, the reaction was quenched with 50 mL pH = 7 phosphate buffer, extracted with EtOAc (2 x 25 mL), washed with brine, dried with MgSO₄, filtered, and concentrated in vacuo. The crude reaction mixture was purified by MPLC (4% EtOAc in Hexanes), giving 18.0 mg (7.5%) of 145a.

**1H NMR** (500 MHz, CDCl₃) δ 7.41 (d, J = 9.0 Hz, 2H, ArH), 6.87 (d, J = 9.0 Hz, 2H, ArH), 5.45 (s, 1H, OCHO), 4.24 (dd, J = 5.0 and 11.5 Hz, 1H), 3.93 (ddd, J = 2.5, 12.0, and 12.0 Hz, 1H), 3.83-3.77 (m, 1H), 3.79 (s, 3H, OMe), 2.54 (dd, J = 7.0 and 7.0 Hz, 2H, COCH₂), 2.50 (s, 2H, COCH₂), 1.82-1.50 (m, 6H), 1.31 (s, 6H, C(Me)₂), 0.85 (s, 9H, C(Me)₃), 0.08 (s, 6H, Si(Me)₂).

**13C NMR** (125 MHz, CDCl₃) δ 210.3, 160.0, 131.6, 127.5, 113.7, 101.3, 73.5, 67.2, 57.0, 55.5, 45.2, 35.6, 31.4, 30.40, 30.38, 25.1, 19.2, 18.22, and -1.83.


**IR** (neat) 2964, 2934, 2854, 1713, 1614, 1515, 1462, 1367, 1251, 1171, 1111, 1037, 834, and 775 cm⁻¹.

**TLC** Rᵓ = 0.66 in 30% EtOAc in hexanes.

(165).

In a 25 mL round bottomed flask equipped with a stirbar, N,N-dimethylhydrazine (1.17 g, 19.5 mmol) and silyl ether 144a (1.09 g, 4.74 mmol) were added. Ethanol (10 mL) was added, and the solution was equipped with a reflux condenser and refluxed at 60 °C for 16 hours, when the TLC showed no starting silyl ether remaining. The excess dimethylhydrazone was removed via distillation, and the crude material was purified by flash chromatography (15% EtOAc in Hexanes) to give 0.994 g (76%) of 165.

**1H NMR** (500 MHz, CDCl₃) δ 2.46 (s, 6H, N(Me)₂), 2.36 (s, 2H, -CH₂-), 2.05 (s, 3H, NCCH₃), 1.26 (s, 6H C(Me)₂), 0.87 (s, 9H, C(Me)₃), 0.10 (s, 6H, Si(Me)₂).

**13C NMR** (125 MHz, CDCl₃) δ 166.9, 74.1, 53.8, 47.2, 30.3, 26.1, 19.4, 18.2, and -1.79.

GC-MS $T_r = 8.65$ min; m/z: 272, 257, 215, 173, 115, 100, and 73.

IR (neat) 2953, 2930, 2892, 2858, 2812, 1461, 1356, 1253, 1211, 1048, 838, 766 cm$^{-1}$.

TLC $R_f = 0.40$ in 20% EtOAc in hexanes.

6-(tert-butyldimethylsilyloxy)-1-(2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-6 methylheptan-4-ol (166).

In a round bottomed flask equipped with a stir bar and 3.0 mL THF under nitrogen at 0 °C, diisopropylamine (0.130 mL, 0.929 mmol) and n-butyl lithium (2.2 M, 0.335 mL, 0.737 mmol) were added. After stirring for 20 minutes, the solution was cooled to -78 °C, and hydrazone 165 (0.184 g, 0.676 mmol) was added. After 40 minutes, iodide 164 (0.251 g, 0.721 mmol) in 1.0 mL of THF was added. After 16 hours, the reaction mixture was quenched with pH = 7 phosphate buffer, extracted with CH$_2$Cl$_2$ (2 x 25 mL). The solvent was then concentrated in vacuo to approximately 10 mL, then the flask was cooled to -78 °C, and m-CPBA (0.221 g, 1.28 mmol) was added. After one hour, the reaction was allowed to warm to room temperature for 30 minutes. The reaction was quenched with aqueous Na$_2$S$_2$O$_3$, and aqueous NaHCO$_3$. The aqueous layer was then extracted with CH$_2$Cl$_2$ (2 x 25 mL), washed with brine, and dried with magnesium sulfate. After purification by MPLC (15% EtOAc in Hexanes), the solvent was removed in vacuo and 25 mL EtOH was added, followed by NaBH$_4$ (0.222 g, 6.6 mmol) in portions. After reacting for 45 minutes, the reaction mixture was quenched with water, extracted with CH$_2$Cl$_2$, washed with brine, dried with magnesium sulfate, and purified by MPLC (15% EtOAc in Hexanes) to give 62 mg (19%) of 166.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41 (d, $J = 9.0$ Hz, 2H, ArH), 6.87 (d, $J = 8.5$ Hz, 2H, ArH), 5.446 and 5.442 (~1:1) (s, 1H, OCH$_2$ArO), 4.23 (dd, $J = 11.5, 5.0$ Hz, 1H), 4.19 (d, $J = 9.0$ Hz, 1H), 4.00-3.95 (m, 1H), 3.92 (ddd, $J = 11.5, 11.5, 2.5$ Hz, 1H), 3.84-3.79 (m, 1H), 3.79 (s, 3H), 1.82-1.73 (m, 1H), 1.72-1.61 (m, 2H), 1.65 (dd, $J = 14.5, 10.5$ Hz,
$^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 (d, $J = 7.5$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 5.44 (s, 1H), 4.23 (dd, $J = 11.0$, 4.5 Hz, 1H), 3.93 (ddd, $J = 12.0$, 12.0, 2.5 Hz, 1H), 3.83-3.79 (m, 1H), 3.79 (s, 3H), 3.32 (s, 2H), 2.57 (t, $J = 7.5$ Hz, 2H), 1.84-1.77 (m, 2H), 1.76-1.51 (m, 4H), and 1.45 (s, 9H).

tert-butyl 6-(2-(4-methoxylphenyl)-1,3-dioxan-4-yl)-3-oxohexanoate (168).

To a 25 mL flask equipped with a stirbar, diisopropylamine (0.70 mL, 5.0 mmol), and THF (5 mL) were added. The flask was cooled to 0 °C, and n-BuLi (2.15 mL, 4.73 mmol) was added. After 15 minutes tert-buty lacetoacetate 167 (0.366 g, 2.31 mmol) dissolved in 1 mL THF was added. After 30 minutes the flask was cooled to -78 °C, and iodide (164) (0.40 g, 1.15 mmol) was added in 1 mL THF. After 40 minutes the reaction was allowed to warm to room temperature and neutralized with 10% HCl solution. The crude product was extracted with ethyl acetate, washed with brine, dried with magnesium sulfate, and concentrated in vacuo. Separation by MPLC (25% EtOAc/hexanes) gave 0.279 g (66%) of 168 as an oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 (d, $J = 7.5$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 5.44 (s, 1H), 4.23 (dd, $J = 11.0$, 4.5 Hz, 1H), 3.93 (ddd, $J = 12.0$, 12.0, 2.5 Hz, 1H), 3.83-3.79 (m, 1H), 3.79 (s, 3H), 3.32 (s, 2H), 2.57 (t, $J = 7.5$ Hz, 2H), 1.84-1.77 (m, 2H), 1.76-1.51 (m, 4H), and 1.45 (s, 9H).
\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl$_3$) $\delta$ 203.3, 166.6, 160.0, 131.6, 127.5, 113.7, 101.2, 82.1, 76.9, 67.1, 55.4, 50.8, 42.9, 35.4, 31.4, 28.5, 28.2, and 19.3.


\textbf{IR} (neat) 2964, 2925, 2852, 1734, 1715, 1615, 1518, 1457, 1368, 1310, 1248, 1170, 1147, 1104, 1033, and 829 cm$^{-1}$.

\textbf{TLC} $R_f$ = 0.45 in 30% EtOAc in hexanes.

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\textit{tert}-Butyl 3-hydroxy-6-((4)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)hexanoate (170)

To a 25 mL screw cap vial equipped with a stirrer, ketone \textbf{168} (0.170 g, 0.45 mmol), \textit{tert}-butyl alcohol (1 mL), and ethyl alcohol (1 mL) were added. To this stirred mixture, sodium borohydride (84.3 mg, 2.2 mmol) was slowly added in portions. After 4 hours the reaction mixture was concentrated in vacuo, and 10 mL satd. aq. NH$_4$Cl was added. The product was extracted with ethyl acetate, washed with brine, dried with sodium sulfate, and concentrated in vacuo to give \textbf{170} (0.172 g) as a clear oil in quantitative yield.

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl$_3$) $\delta$ 7.41 (d, $J$ = 9.0 Hz, 2H), 6.88 (d, $J$ = 9.0 Hz, 2H), 5.45 (s, 1H), 4.24 (ddd, $J$ = 11.0, 4.5 Hz, 1H), 3.97-3.95 (m, 1H), 3.93 (ddd, 12.5, 12.5, 2.5 Hz, 1H), 3.84-3.79 (m, 1H), 3.79 (s, 3H), 3.14 (dd, $J$ = 4.0, 3.0 Hz, 1H), 2.42 (dd, $J$ = 16.0, 3.0 Hz, 1H), 2.32 (dd, $J$ = 16.5, 9.0 Hz, 1H), 1.79 (ddddd, $J$ = 13.0, 13.0, 13.0, 5.5 Hz, 1H), 1.72-1.42 (m, 7H), and 1.46 (s, 9H).

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl$_3$) $\delta$ 172.8, 160.0, 131.7, 127.5, 113.7, 101.3, 81.5, 77.3, 68.2, 68.1, 67.2, 55.5, 42.45, 42.39, 36.5, 36.4, 36.1, 36.0, 31.51, 31.46, 28.3, 21.3, and 21.1.

\textbf{HRMS} (ESI) Calcd. for (C$_{21}$H$_{32}$O$_6$ + Na$^+$): 403.2091. Found: 403.2099.

\textbf{IR} (neat) 3456, 2958, 2857, 1730, 1715, 1606, 1527, 1464, 1396, 1362, 1246, 1171, 1149, 1033, and 827 cm$^{-1}$.

\textbf{TLC} $R_f$ = 0.28 in 30% EtOAc in hexanes.
**tert-butyl 3-(benzyloxymethoxy)-6-((4)-2-(methoxyphenyl)-1,3-dioxan-4-yl)hexanoate (171)**

To a 50 ml round bottom flask equipped with a stirbar, alcohol 170 (0.352 g, 0.926 mmol), THF (4 mL), and diisopropylethylamine (0.50 mL, 0.29 mmol), and benzyl chloromethyl ether (0.231 g, 1.47 mmol) was added. After stirring for 1 day, additional benzyl chloromethyl ether (0.26 g, 1.6 mmol) was added. After 3 days the reaction was quenched with 30 mL satd. aq. NaHCO₃, and extracted with ether (3 x 20 mL), washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by MPLC gave 171 (0.413 g, 89%), as a clear oil.

**¹H NMR** (500 MHz, CDCl₃) δ 7.39 (d, J = 8.5 Hz, 2H), 7.33-7.27 (m, 5H), 6.86 (d, J = 9.0 Hz), 5.42 and 5.41 (s, 1H), 4.82 (d, J = 7.0 Hz, 1H), 4.78 (d, J = 7.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.22 (app td, J = 11.0, 3.0, 3.0 Hz, 1H), 4.07-4.02 (m, 1H), 3.90 (ddd, J = 12.5, 2.5, 2.5 Hz, 1H), 3.78 (s, 3H), 3.78-3.72 (m, 1H), 2.52 (dd, J = 15.5, 7.5 Hz, 1H), 2.40 (dd, J = 15.0, 5.0 Hz, 1H), 1.81-1.72 (m, 1H), 1.70-1.45 (m, 7H), and 1.43 (s, 9H).

**¹³C NMR** (125 MHz, CDCl₃) δ 170.9, 160.0, 138.1, 131.7, 128.6, 128.07, 128.01, 127.8, 127.5, 113.7, 101.3, 94.2, 94.1, 80.7, 77.18, 75.1, 75.0, 69.8, 69.7, 67.2, 55.5, 41.62, 41.59, 36.22, 36.16, 35.0, 34.9, 31.50, 31.47, 28.3, 20.98, and 20.91.


**IR** (neat) 2938, 2862, 1728, 1618, 1588, 1519, 1454, 1390, 1363, 1302, 1249, 1169, 1146, 1105, 1029, 983, 956, 831, 739, and 690 cm⁻¹.

**TLC** Rₜ = 0.7 in 30% EtOAc in hexanes.
4-(Benzylxymethoxy)-7-((4)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-2-methylheptan-2-ol (172)

To a 100 mL round bottom flask equipped with a stir bar, ester 171 (1.70 g, 3.40 mmol), THF (40 mL), and MeMgBr (3.4 mL, 3M in ether, 10.2 mmol) was added. The solution was refluxed for 12 hours, then allowed to cool to room temperature. The reaction was transferred to separatory funnel and quenched with 120 mL satd. aq. NH₄Cl. The product was extracted with ether (2 x 75 mL), washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by MPLC (40% EtOAc/hexanes) gave 172 (1.20 g, 77%) as a clear oil.

**¹H NMR** (500 MHz, CDCl₃) δ 7.40 (d, J = 8.5 Hz, 2H), 7.34-7.27 (m, 5H), 6.872 and 6.867 (dd, 9.0 Hz, 2H), 5.42 (s, 1H), 4.87 (d, 7.0 Hz, 1H), 4.78 (d, J = 6.5 Hz, 1H), 4.680 and 4.675 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.22 (dd, J = 11.0, 4.0 Hz, 1H), 4.06-4.01 (m, 1H), 3.90 (ddd, J = 12.0, 12.0, 2.5 Hz, 1H), 3.782 and 3.779 (s, 3H), 3.78-3.74 (m, 1H), 3.59 and 3.57 (s, 1H), 1.84-1.72 (m, 2H), 1.69-1.35 (m, 8H), 1.27 (s, 3H), and 1.23 (s, 3H).

**¹³C NMR** (125 MHz, CDCl₃) δ 160.0, 137.6, 131.6, 128.6, 127.96, 127.92, 127.5, 113.7, 101.2, 93.4, 93.3, 77.15, 77.12, 76.4, 76.3, 70.46, 70.45, 67.1, 55.4, 46.3, 46.2, 36.29, 36.25, 34.9, 34.8, 31.44, 31.42, 31.3, 28.59, 28.57, 20.43, and 20.42.


**IR** (neat) 3516, 2972, 2938, 2865, 1614, 1518, 1458, 1396, 1364, 1302, 1249, 1171, 1104, 1036, 828, and 739 cm⁻¹.

**TLC** Rᵣ = 0.20 in 30% EtOAc in hexanes.
**tert-butyl 3-(benzoxymethoxy)-6-((4)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)hexanoate (171)**

To a 250 mL flask equipped with a stirbar, diisopropylamine (6.6 mL, 47 mmol), and THF (65 mL) were added. The flask was cooled to 0 °C, and n-BuLi (19.5 mL, 42.9 mmol) was added. After 15 minutes tert-butylacetoacetate 167 (3.22 mL, 19.4 mmol) was added. After 30 minutes, the flask was cooled to -78 °C and iodide (164) (5.45 g, 1.15 mmol) was added in 20 mL THF. After 40 minutes the reaction was allowed to warm to room temperature and quenched with satd. aq. NH₄Cl. The crude product was extracted with ether (3 x 50 mL), washed with brine, dried with magnesium sulfate, and concentrated in vacuo. This crude product was dissolved in 100 mL ethyl alcohol, and sodium borohydride (1.0 g, 26 mmol) was added over 15 minutes. After 1 hour, the reaction was concentrated in vacuo, quenched with 100 mL satd. aq. NH₄Cl, and extracted with ethyl acetate, washed with brine, dried with sodium sulfate, and concentrated in vacuo. To the crude product was added Hunig’s base (12 g), THF (10 mL), and benzylchloromethyl ether (11.5 g, 73.4 mmol). After 1 day the reaction was quenched with 150 mL satd. aq. NaHCO₃, and extracted with ether (3 x 70 mL), washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by flash chromatography gave 171 (6.2 g, 79%) as a clear oil.

**¹H NMR (500 MHz, CDCl₃)** δ 7.40 (d, J = 8.5 Hz, 2H), 7.34-7.27 (m, 5H), 6.872 and 6.867 (dd, 9.0 Hz, 2H), 5.42 (s, 1H), 4.87 (d, 7.0 Hz, 1H), 4.78 (d, J = 6.5 Hz, 1H), 4.680 and 4.675 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.22 (dd, J = 11.0, 4.0 Hz, 1H), 4.06-4.01 (m, 1H), 3.90 (ddd, J = 12.0, 12.0, 2.5 Hz, 1H), 3.782 and 3.779 (s, 3H), 3.78-3.74 (m, 1H), 3.59 and 3.57 (s, 1H), 1.84-1.72 (m, 2H), 1.69-1.35 (m, 8H), 1.27 (s, 3H), and 1.23 (s, 3H).
\[ \text{HRMS (ESI) Calcd. for (C}_{27}\text{H}_{38}\text{O}_{6} + \text{Na}^+): 481.2561. Found: 481.2613.} \]

\[ \text{IR (neat) 3516, 2972, 2938, 2865, 1614, 1518, 1458, 1396, 1364, 1302, 1249, 1171, 1104, 1036, 828, and 739 cm}^{-1}. \]

\[ \text{TLC R}_f = 0.20 \text{ in 30\% EtOAc in hexanes}. \]

7-(Benzylcarboxymethoxy)-3-(4-methoxybenzylmethoxy)-9-methyldecane-1,9-diol (173)

To a 40 mL culture tube, acetal 172 (1.56 g, 3.40 mmol), and CH\(_2\)Cl\(_2\) (10 mL) were added. The tube was cooled to -78 °C, and DIBAL in toluene (16 mL, 24 mmol) were added. After being kept at this temperature for 48 hours, the reaction was transferred to a separatory funnel and quenched with satd. aq. Rochelle’s salt. The mixture was extracted with CH\(_2\)Cl\(_2\) (10 x 20 mL), and the combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. Purification by MPLC (80\% EtOAc in hexanes) gave 0.954 g of product contaminated by an inseparable olefinic impurity. The mixture was diluted with CDCl\(_3\) (3 mL), and NMO (0.251 g, 2.14 mmol), OsO\(_4\) (5.5 mg), and water (0.2 mL) were added. After 1 day, the mixture was concentrated in vacuo, filtered through a plug of silica gel (100\% EtOAc), and concentrated in vacuo again before purification by MPLC (85\% EtOAc/hexanes) to afford 173 (0.822 g, 53\% over two steps) as an oil.

\[ \text{HRMS (ESI) Calcd. for (C}_{27}\text{H}_{38}\text{O}_{6} + \text{Na}^+): 481.2561. Found: 481.2613.} \]

\[ \text{IR (neat) 3516, 2972, 2938, 2865, 1614, 1518, 1458, 1396, 1364, 1302, 1249, 1171, 1104, 1036, 828, and 739 cm}^{-1}. \]

\[ \text{TLC R}_f = 0.20 \text{ in 30\% EtOAc in hexanes}. \]

\[ \text{IR (neat) 3516, 2972, 2938, 2865, 1614, 1518, 1458, 1396, 1364, 1302, 1249, 1171, 1104, 1036, 828, and 739 cm}^{-1}. \]

\[ \text{TLC R}_f = 0.20 \text{ in 30\% EtOAc in hexanes}. \]

\[ \text{IR (neat) 3516, 2972, 2938, 2865, 1614, 1518, 1458, 1396, 1364, 1302, 1249, 1171, 1104, 1036, 828, and 739 cm}^{-1}. \]

\[ \text{TLC R}_f = 0.20 \text{ in 30\% EtOAc in hexanes}. \]
3.63-3.58 (m, 1H), 3.54 (s, 1H), 2.30 (app q, J = 5.0 Hz, 1H), 1.85-1.67 (m, 3H), 1.67-1.48 (m, 5H), 1.42-1.30 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 159.4, 137.6, 130.5, 129.6, 128.7, 128.0, 127.9, 114.1, 93.5, 93.4, 78.04, 78.00, 76.48, 76.45, 70.8, 70.5, 70.48, 60.9, 55.5, 5, 46.4, 36.0, 35.14, 35.12, 33.87, 33.84, 31.37, 28.7, 20.58, and 20.53.

\(\text{HRMS (ESI)}\) Calcd. for (C\(_{27}\)H\(_{40}\)O\(_6\) + Na\(^{+}\)): 483.2717. Found: 483.2762.

\(\text{IR (neat)}\) 3440, 2945, 2877, 1618, 1512, 1462, 1245, 1174, 1036, 822, 745, and 699 cm\(^{-1}\).

\(\text{TLC}\) \(R_f = 0.20\) in 50\% EtOAc in hexanes.

\[
\begin{align*}
\text{173} & \quad \text{TPAP, NMO} \\
\text{4 Angstrom M.S.} & \\
\text{174}
\end{align*}
\]

7-(Benzylmethoxy)-9-hydroxy-3-(4-methoxybenzyl)-9-methyldecanal (174)

To a 25 mL round bottom flask, diol 173 (0.212 g, 0.460 mmol), NMO (0.123 g, 1.05 mmol), CH\(_2\)Cl\(_2\) (9 mL), 4 Angstrom molecular sieves (0.361 g), and TPAP (10.2 mg, 6.3 mol\%) were added. After 50 minutes the reaction mixture was filtered through cotton and concentrated in vacuo. Purification by MPLC (60\% EtOAc/hexanes) gave 174 (0.154 g, 73\%) as an oil.

\(^{1}\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 9.76 (s, 1H), 7.31-7.28 (m, 5H), 7.22 (d, \(J = 8.0\) Hz, 2H), 6.86 and 6.85 (d, \(J = 8.5\) Hz, 2H), 4.86 (d, \(J = 6.5\) Hz, 1H), 4.78 (d, \(J = 6.5\) Hz, 1H), 4.682 and 4.679 (d, \(J = 12.0\) Hz, 1H), 4.61 (d, \(J = 11.5\) Hz, 1H), 4.44 (s, 2H), 4.04-3.98 (m, 1H), 3.89 (app p, \(J = 5.5\) Hz, 1H), 3.787 and 3.783 (s, 3H), 3.53 (s, 1H, -OH), 2.64 (dd, \(J = 7.0\), 16.5 Hz, 1H), 2.51 (ddd, \(J = 1.0\), 5.0, 16.0 Hz, 1H), 1.80 (ddd, \(J = 3.0\), 9.5, 14.0 Hz, 1H), 1.68-1.49 (m, 5H), 1.46-1.31 (m, 2H), 1.27 (s, 3H), 1.24 (s, 3H).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 201.6, 159.4, 137.6, 130.3, 129.6, 128.6, 128.0, 127.95, 127.92, 114.0, 111.9, 93.5, 93.4, 76.3, 73.8, 71.1, 70.47, 70.44, 55.4, 48.43, 48.42, 46.3, 34.94, 34.90, 34.67, 34.63, 31.3, 28.66, 28.64, 20.5, and 20.4.

\(\text{HRMS (ESI)}\) Calcd. for (C\(_{27}\)H\(_{38}\)O\(_6\) + Na\(^{+}\)): 481.2560. Found: 481.2614.
IR (neat) 3459, 2979, 2954, 2873, 1733, 1615, 1515, 1456, 1035, 822, 743, and 700 cm⁻¹.

TLC Rₜ = 0.45 in 50% EtOAc in hexanes.

6-(8-(Benzyloxymethoxy)-2,10-dihydroxy-4-(4, methoxybenzyloxy)-10-methylundecyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (177)

To a 25 mL round bottom flask equipped with a stirbar, aldehyde 174 (0.217 g, 0.452 mmol) and THF (8 mL) were added. The flask was cooled to -78 °C, and BF₃·OEt₂ (0.13 mL, 1.0 mmol) was added. After 1.5 minutes, diene (1.0 mL, ~4 mmol) was added dropwise. After 15 minutes the reaction was quenched with a 1:1 mixture of isopropanol/chloroform (10 mL) and 3 mL of pH=10 phosphate buffer. After being allowed to warm to room temperature, the reaction was transferred to a separatory funnel and extracted with ether, dried with sodium sulfate, filtered, and concentrated in vacuo. Purification by MPLC (75% EtOAc/hexanes) gave 177 (0.173 g, 64%).

¹H NMR (500 MHz, CDCl₃) δ 7.37-7.28 (m, 5H), 7.23 and 7.22 (d, J = 8.0 Hz, 2H), 6.89-6.86 (m, 2H), 5.31 and 5.28 (s, 1H), 4.90-4.87 (m, 1H), 4.82-4.87 (m, 1H), 4.71-4.67 (m, 1H), 4.65-4.61 (m, 1H), 4.55 and 4.49 (d, J = 11.0 Hz, 1H), 4.40 and 4.33 (dd, J = 11.5, 4.0 Hz, and J = 11.0, 5.0 Hz, 1H), 4.15-4.10 and 4.05-3.96 (m, 1H), 4.05-3.96 (m, 1H), 3.82-3.72 (m, 3H), 3.69-3.63 (m, 1H), 3.47 (s, 1H), 2.89 (s, 1H), 2.36-2.30 (m, 1H), 2.25 (dd, J = 15.0 Hz, 5.0 Hz, 1H), 1.82 and 1.80 (ddd, J = 14.5, 6.0, 3.0 Hz, and ddd, J = 9.5, 6.0, 3.0 Hz, 1H), 1.73-1.63 (m, 2H), 1.68 and 1.67 (s, 6H), 1.63-1.45 (m, 5H), 1.40-1.30 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 169.25, 169.18, 161.3, 161.2, 159.6, 137.6, 130.1, 129.8, 129.7, 128.7, 128.0, 127.9, 114.2, 114.15, 106.7, 106.67, 95.3, 95.2, 93.57, 93.52, 79.17,
79.09, 76.4, 76.0, 71.1, 70.5, 70.4, 68.77, 68.76, 65.9, 55.4, 47.2, 46.4, 41.96, 41.92, 40.7, 39.73, 39.71, 35.21, 35.19, 35.09, 33.70, 33.66, 33.59, 31.3, 29.7, 29.3, 28.77, 28.73, 25.5, 25.30, 25.25, 24.9, 20.79, 20.75, 19.92, 19.88.

**HRMS** (ESI) Calcd. for (C$_{34}$H$_{48}$O$_9$ + Na$^+$): 623.3191. Found: 623.3212.

**IR** (neat) 3413, 2949, 2881, 1732, 1698, 1641, 1515, 1458, 1394, 1029, 903, 812, and 747 cm$^{-1}$.

**TLC** $R_f$ = 0.25 in EtOAc.

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6-(8-(Benzyloxymethoxy)-10-hydroxy-4-(4-methoxybenzylxy)-10-methyl-2-(triethylsilyloxy)undecyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (178)

To a 5 mL screw cap vial, diol 177 (84 mg, 0.14 mmol), imidazole (0.143 g, 2.09 mmol), CH$_2$Cl$_2$ (1 mL), and triethylchlorosilane (84 µL, 0.50 mmol) were added. After 50 minutes, the reaction was quenched with satd. aq. NaHCO$_3$ and extracted with CH$_2$Cl$_2$, washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by MPLC (35% EtOAc/hexanes) afforded 178 (45 mg, 45%) as an oil.

**$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.36-7.27 (m, 5H), 7.22 and 7.21 (d, $J$ = 8.0 Hz, 2H), 6.87-6.84 (m, 2H), 5.26 and 5.23 (s, 1H), 4.89-4.86 (m, 1H), 4.80-4.77 (m, 1H), 4.69 (d, $J$ = 11.5 Hz, 1H), 4.63-4.59 (m, 1H), 4.46 and 4.43 (d, $J$ = 10.5 Hz, 1H), 4.35 and 4.30 (dd, $J$ = 11.5, 4.0 Hz, and dd, $J$ = 10.5 and 3.0 Hz, 1H), 4.16-4.07 (m, 1H), 4.05-3.99 (m, 1H), 3.796 and 3.792 (s, 3H), 3.57-3.54 (m, 1H), 3.54-3.50 and 3.48-3.42 (m, 1H), 2.39 and 2.26 (dd, $J$ = 14.5, 6.0 Hz, and dd, $J$ = 14.0, 6.5 Hz, 1H), 2.38-2.33 (m, 1H), 1.84-1.77 (m, 2H), 1.71-1.48 (m, 6H), 1.67 (s, 3H), 1.65 (app s, 6H), 1.61 (s, 3H), 1.41-1.29 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H).
13C NMR (125 MHz, CDCl3) δ 169.4, 169.1, 161.3, 161.2, 159.4, 137.6, 131.0, 130.8, 129.5, 129.2, 128.7, 128.0, 127.9, 113.98, 113.95, 106.5, 106.6, 95.56, 95.50, 93.4, 76.4, 75.7, 75.2, 70.54, 70.48, 70.2, 67.2, 66.9, 55.5, 46.3, 43.1, 42.2, 41.9, 35.1, 34.3, 34.0, 31.4, 29.8, 28.6, 25.9, 25.8, 24.8, 24.6, 20.5, 20.2, 7.13, 7.09, 5.29, 5.19.

HRMS (ESI) Calcd. for (C40H62O9Si + Na+) : 737.4055. Found: 737.4098.

TLC Rf = 0.30 in 40% EtOAc in hexanes.

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Synthesis of 179

A Dean Stark apparatus was attached to a 250 mL round bottom flask containing 180 mL freshly distilled benzene (from CaH2). The flask was heated until approx. 15 mL of benzene was collected in the trap. The trap was then removed, and dioxinone 178 (13 mg, 18 µmol) was added to the flask, which was then attached to a reflux condenser and refluxed. After 12 hours the mixture was allowed to cool to room temp and concentrated in vacuo. Purification by MPLC (25% EtOAc/hex) gave 179 (6.1 mg, 50%) of the desired product as a mixture of diastereomers.

1H NMR (500 MHz, CDCl3) δ 7.36-7.32 (m, 4H), 7.32-7.19 (m, 3H), 6.9-6.85 (m, 2H), 4.93-4.75 (m, 2H), 4.70-4.54 (m, 2H), 4.52-4.26 (m, 3H), 4.22-4.02 (m, 1H), 3.80-3.79 (m, 3H), 3.59-3.32 (m, 2H), 3.28-3.08 (m, 1H), 2.84-2.36 (m, 2H), 2.12-1.95 (m, 1H), 1.92-1.67 (m, 3H), 1.63-1.51 (m, 6H), 1.47-1.34 (m, 3H), 1.28-1.24 (m, 3H), 0.96-0.93 (m, 9H), 0.62-0.57 (m, 6H).

6-(8-(Benzyloxymethoxy)-4,10-dihydroxy-10-methyl-2-(triethylsilyloxy)undecyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (181/180)

To a 5 mL screw cap vial, dioxinone 178 (35 mg, 49 µmol), CH₂Cl₂ (1.5 mL), pH=7 buffer (100 µL), and DDQ (0.115 g, 0.507 mmol) were added. After stirring for 40 minutes, the reaction was quenched with satd. aq. NaHCO₃ and extracted with CH₂Cl₂, washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by MPLC afforded 1,3-anti diastereomer 181 (7.1 mg, 24%) and 1,3-syn diastereomer 180 (8.2 mg, 28%) as clear oils.

Characterization for β isomer.

\[^{1}H\text{ NMR}\ (500\text{ MHz, }\text{CDCl}_3)\ \delta\ 7.36-7.27\ (m, 5H),\ 5.27\ (s, 1H),\ 4.88\ (d, J = 7.0\ Hz, 1H),\ 4.79\ (d, J = 7.0\ Hz, 1H),\ 4.69\ (d, J = 12.0\ Hz, 1H),\ 4.62\ (d, J = 11.5\ Hz, 1H),\ 4.28\ (app, J = 6.0\ Hz, 1H),\ 4.07-4.01\ (m, 1H),\ 3.91-3.85\ (m, 1H),\ 3.56\ (s, 1H),\ 2.87\ (s, 1H),\ 2.51\ (dd, J = 14.0, 6.0\ Hz, 1H),\ 2.45\ and\ 2.44\ (dd, J = 14.0, 3.0\ Hz, 1H),\ 1.82\ (ddd, J = 14.5, 10.0, 3.5\ Hz, 1H),\ 1.69\ (s, 3H),\ 1.67\ (s, 3H),\ 1.66-1.52\ (m, 5H),\ 1.51-1.42\ (m, 2H),\ 1.40-1.30\ (m, 2H),\ 1.28\ (s, 3H),\ 1.23\ (s, 3H),\ 0.97\ (t, J = 8.0\ Hz, 9H),\ 0.63\ (q, J = 8.0\ Hz, 6H).

\[^{13}C\text{ NMR}\ (125\text{ MHz, }\text{CDCl}_3)\ \delta\ 168.29,\ 160.7,\ 137.4,\ 128.4,\ 127.7,\ 95.2,\ 93.1,\ 76.1,\ 70.1,\ 68.0,\ 67.77,\ 67.72,\ 45.93,\ 45.89,\ 42.21,\ 42.16,\ 41.28,\ 38.06,\ 37.99,\ 34.5,\ 34.4,\ 30.9,\ 28.27,\ 28.2,\ 25.5,\ 24.3,\ 20.6,\ 20.5,\ 6.5,\ \text{and}\ 4.5.

\text{HRMS (ESI) Calcd. for}\ (\text{C}_{32}\text{H}_{54}\text{O}_{8}\text{Si} + \text{Na}^{+}):\ 617.3480.\ \text{Found:}\ 617.3461.

\text{TLC } R_f = 0.31\ \text{in} 70\%\ \text{EtOAc in hexanes}.

Characterization for α isomer.
\[^{1}\text{H NMR}\] (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.35-7.27 (m, 5H), 5.28 (s, 1H), 4.886 and 4.884 (d, \(J = 7.0\) Hz, 1H), 4.792 and 4.789 (d, \(J = 7.0\) Hz, 1H), 4.69 (d, \(J = 12.0\) Hz, 1H), 4.62 (d, \(J = 12.0\) Hz, 1H), 4.18 (app p, \(J = 6.0\) Hz, 1H), 4.07-4.00 (m, 1H), 3.76-3.69 (m, 1H), 3.56 (s, 1H), 2.76 (s, 1H), 2.45 (dd, \(J = 14.0, 5.0\) Hz, 1H), 2.39 (dd, \(J = 14.5, 7.0\) Hz, 1H), 1.82 (ddd, \(J = 14.0, 10.0, 6.0\) Hz, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.65-1.53 (m, 5H), 1.50-1.30 (m, 4H), 1.28 (s, 3H), 1.23 (s, 3H), 0.97 (t, \(J = 8.0\) Hz, 9H), 0.64 (q, \(J = 8.0\) Hz, 6H).

\[^{13}\text{C NMR}\] (125 MHz, CDCl\textsubscript{3}) \(\delta\) 168.5, 161.0, 137.6, 132.0, 128.7, 128.0, 127.9, 106.7, 95.7, 93.4, 76.4, 70.5, 70.4, 69.9, 69.8, 46.3, 46.2, 43.8, 42.6, 38.2, 38.1, 34.9, 34.8, 31.3, 28.63, 28.58, 25.7, 24.9, 20.85, 20.77, 6.9, and 5.1.

\[^{\text{HRMS}}\] (ESI) Calcd. for \((\text{C}_{32}\text{H}_{54}\text{O}_{8}\text{Si} + \text{Na}^+): 617.3480.\) Found: 617.3485.

\[^{\text{TLC}}\] \(R_f = 0.29\) in 70\% EtOAc in hexanes.

To 125 mL of freshly distilled benzene (from CaH\textsubscript{2}), an additional 25 mL was distilled away. To the remaining benzene, dioxinone 181 (7.1 mg, 12 \(\mu\)mol) was added. The solution was refluxed for 12 hours before being allowed to cool to room temperature. The reaction mixture was concentrated in vacuo, and purified by MPLC to afford 182 (2.2 mg, 34\%) and 183 (2.1 mg, 33\%) as clear oils.

Less Polar Isomer:
$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36-7.29 (m, 5H), 4.85 (d, $J = 7.2$ Hz, 1H), 4.81 (d, $J = 6.9$ Hz, 1H), 4.68 (d, $J = 2.4$ Hz, 1H), 4.66 (d, $J = 11.4$ Hz, 1H), 4.60 (d, $J = 11.7$ Hz, 1H), 4.10 (dddd, $J = 11.1$, 11.1, 4.8, 4.8 Hz, 1H), 4.03 (dddd, $J = 8.1$, 7.2, 5.4, 3.0 Hz, 1H), 3.74 (dddd, $J = 11.1$, 8.1, 2.4, 2.4 Hz, 1H), 2.68 (dd, $J = 15.9$, 3.0 Hz, 1H), 2.52 (d, $J = 12.6$ Hz, 1H), 2.42 (d, $J = 12.6$ Hz, 1H), 2.02 (dd, $J = 12.3$, 4.8, 1.2 Hz, 1H), 1.78-1.58 (m, 4H), 1.57 (s, 3H), 1.54-1.45 (m, 2H), 1.42 (s, 3H), 1.37-1.16 (m, 4H), 0.95 (t, $J = 7.8$ Hz, 9H), 0.59 (q, $J = 7.8$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.8, 138.2, 128.6, 127.9, 127.8, 96.9, 93.7, 83.8, 72.6, 70.0, 69.98, 65.2, 47.3, 44.3, 44.2, 42.1, 35.7, 32.3, 28.5, 27.9, 22.8, 7.0, and 5.0.

HRMS (ESI) Calcd. for (C$_{29}$H$_{48}$O$_7$Si + Na$^+$): 559.3062. Found: 559.3057.

TLC $R_f = 0.30$ in 10% EtOAc in hexanes.

More Polar Isomer:

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.37-7.28 (m, 5H), 4.82 (s, 2H), 4.69 (d, $J = 11.7$ Hz, 1H), 4.57 (d, $J = 11.7$ Hz, 1H), 4.27 (d, $J = 2.4$ Hz, 1H), 4.13 (dddd, $J = 11.1$, 11.1, 4.8, 4.8 Hz, 1H), 3.93 (dddd, $J = 12.9$, 11.4, 3.9, 2.7 Hz, 1H), 3.89 (app p, $J = 5.4$ Hz, 1H), 2.63 (d, $J = 13.2$ Hz, 1H), 2.62 (dd, $J = 15.6$, 4.5 Hz, 1H), 2.53 (d, $J = 12.9$ Hz, 1H), 2.01 (dd, $J = 12.0$, 4.5, 1.5 Hz, 1H), 1.79 (d of app p, $J = 12.6$, 2.1 Hz, 1H), 1.73-1.57 (m, 3H), 1.60 (s, 3H), 1.57-1.44 (m, 2H), 1.42 (s, 3H), 1.39-1.13 (m, 4H), 0.95 (t, $J = 7.5$ Hz, 9H), 0.59 (q, $J = 7.5$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.9, 138.1, 128.6, 127.9, 127.8, 96.5, 93.8, 84.2, 75.6, 70.0, 67.5, 65.0, 49.2, 44.4, 42.2, 42.0, 35.5, 34.3, 28.9, 28.5, 20.1, 7.0, and 5.0.

HRMS (ESI) Calcd. for (C$_{29}$H$_{48}$O$_7$Si + Na$^+$): 559.3062. Found: 559.3044.

TLC $R_f = 0.24$ in 10% EtOAc in hexanes.
Rac-(1S,11S,13S)-7-(benzyloxymethoxy)-1-hydroxy-5,5-dimethyl-13-(triethylsilyloxy)-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (186)

To 125 mL of freshly distilled benzene (from CaH₂), an additional 25 mL was distilled away. To the remaining benzene, dioxinone 180 (8.2 mg, 14 µmol) was added. The solution was refluxed for 12 hours before being allowed to cool to room temperature. The reaction mixture was concentrated in vacuo, and purified by MPLC to afford 3.8 mg (51%) of 186 as a mixture of diastereomers.

¹H NMR (300 MHz, CDCl₃) δ 7.36-7.27 (m, 5H), 6.04 and 5.88 (s, and d, J = 0.9 Hz, 1H), 4.668 and 4.683 (d, J = 12.0 and 11.7 Hz, 1H), 4.594 and 4.572 (d, J = 12.0 Hz, 1H), 4.37 (app p, J = 3.0 Hz), 4.35-4.24 (m, 1H), 4.21-4.12 (m, 1H), 4.11-4.01 (m, 1H), 2.61-2.51 (m, 1H), 2.62 and 2.54 (d, J = 12.6 and 12.0 Hz, 1H), 2.43 and 2.41 (d, J = 12.6 and 13.0 Hz, 1H), 2.34 (d, J = 9.0 Hz, 1H), 2.14 (dd, J = 13.8, 2.7 Hz, 1H), 2.09-1.98 (m, 1H), 1.84 (dd, J = 13.8, 3.0 Hz, 1H), 1.77-1.57 (m, 5H), 1.56 and 1.53 (s, 3H), 1.53-1.47 (m, 3H), 1.46 and 1.43 (s, 3H), 0.96 (t, J = 7.8 Hz, 9H), 0.62 and 0.61 (q, J = 7.5 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 169.7, 169.4, 138.36, 138.31, 128.66, 128.57, 127.95, 127.88, 127.77, 127.71, 96.5, 96.3, 93.9, 93.3, 82.2, 81.6, 73.9, 73.1, 69.83, 69.80, 67.4, 67.2, 65.9, 63.2, 48.9, 48.7, 45.6, 44.2, 40.2, 39.0, 38.4, 35.6, 35.0, 34.5, 31.98, 31.93, 28.0, 27.4, 23.0, 18.4, 6.9, 4.7.


TLC Rᵣ = 0.30 in 15% EtOAc in hexanes.

δ-Alkylation of acetophenone (158) by isobutanol (159)
To a 7 mL screw cap vial, acetophenone 158 (285 mg, 2.37 mmol), isobutanol 159 (182 mg, 2.45 mmol), KOH (127 mg, 2.27 mmol), 1-dodecene (401 mg, 2.38 mmol), and dioxane (4.5 mL) were added. RuCl$_2$(PPh$_3$)$_3$ (42 mg, 2 mol%) was then added, and the vial was sealed and heated in an oil bath at 80 °C for 3 days. The reaction mixture was allowed to cool to room temperature, and an aliquot was removed and filtered through silica gel before GCMS analysis. Integration of the peak areas shows desired product 160 at 30%, reduced desired product 161 at 39%, reduced acetophenone 162 at 17%, acetophenone at 12%, and reduced acetophenone condensation product 163 at 1% of the total area of products. Several peaks corresponding to dodecene isomers are also observed.

![Chemical Structure](image)

7-(Benzyloxymethoxy)heptan-1-ol (189)

To a 100 mL flask, heptane-1,7-diol 188 (1.80 g, 13.6 mmol), CH$_2$Cl$_2$ (50 mL), and Hunig’s base (5 mL, 28.7 mmol) were added. The flask was cooled to 0 °C, and BOMCl (60% solution, 3.0 mL, 12.7 mmol) was added over 20 minutes. After 3 hours the reaction was quenched with 30 mL 10% aq. NaOH solution. The reaction mixture was stirred for 12 hours before being concentrated in vacuo. The crude product was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were concentrated in vacuo and purified by flash chromatography (30% EtOAc/hexanes) to give 189 (1.50 g, 47%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36-7.26 (m, 5H), 4.75 (s, 2H), 4.60 (s, 2H), 3.63 (t, $J$ = 6.0 Hz, 2H), 3.58 (t, $J$ = 6.5 Hz, 2H), 1.63-1.53 (m, 4H), 1.42-1.32 (m, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.2, 128.6, 128.0, 127.8, 94.8, 94.9, 32.9, 29.8, 29.4, 26.4, 25.9.

HRMS (ESI) Calcd for (C$_{15}$H$_{24}$O$_3$ + Na$^+$): 275.1618. Found: 275.1623.

GC-MS $t_r$ = 12.2 min; m/z: 253, 188, 175, 157, 128, 120, 119, 107, 97, 92, 91, 65, and 55.

IR (neat) 3421, 3063, 3034, 2934, 2857, 1491, 1455, 1377, 1204, 1159, 1111, 1045, 952, 938, 738, 698 cm$^{-1}$.

TLC $R_f$ = 0.50 in 40% EtOAc in hexanes.
9-(Benzyloxymethoxy)non-1-en-3-ol (190)
To a 100 mL flask, alcohol 189 (1.44 g, 5.71 mmol), NMO (0.722 g, 6.17 mmol), CH₂Cl₂ (30 mL), and 4 Angstrom molecular sieves were added. The flask was cooled to 0 °C, and TPAP (0.160 g, 0.45 mmol, 8 mol %) was added. After 6 hours the reaction mixture was filtered through silica gel and concentrated in vacuo. To this crude aldehyde was added 50 mL of THF. The flask was cooled to -78 °C, and 7.0 mL vinylMgBr solution (~1.05 M, 7.35 mmol) was added. After 30 minutes the mixture was allowed to warm to room temperature and quenched with satd. aq. NH₄Cl. The reaction mixture was extracted with ether (3 x 50 mL), washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by MPLC afforded 190 (0.561 g, 35%) as an oil.

¹H NMR (500 MHz, CDCl₃) δ 7.36-7.27 (m, 5H), 5.86 (ddd, J = 17.5, 10.5, 6.5 Hz, 1H), 5.21 (dt, J = 17.0, 1.5, 1.5 Hz, 1H), 5.10 (dt, J = 10.5, 1.5, 1.5 Hz, 1H), 4.76 (s, 2H), 4.60 (s, 2H), 4.09 (dddd, J = 6.5, 6.5, 6.5, 1.5, 1.5 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 1.64-1.56 (m, 2H), 1.56-1.47 (m, 2H), 1.43-1.30 (m, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 141.4, 138.2, 128.6, 128.0, 127.8, 114.8, 94.8, 73.4, 69.4, 68.2, 37.1, 29.8, 29.5, 26.3, and 25.4.


GC-MS tᵣ = 12.1 min; m/z: 207, 172, 170, 154, 140, 128, 119, 107, 97, 92, 91, 79, 65, and 57.

IR (neat) 3440, 3088, 3067, 3033, 2935, 2859, 1498, 1455, 1380, 1162, 1114, 1047, 1028, 921, 736, 697 cm⁻¹.

TLC Rₚ = 0.30 in 20% EtOAc in hexanes.
9-(Benzyloxymethoxy)non-1-en-3-one (191)

To a 100 mL flask, alcohol 190 (0.561 g, 2.02 mmol), NMO (0.285 g, 2.43 mmol), CH₂Cl₂ (25 mL), and 4 Angstrom molecular, and TPAP (76 mg, 0.21 mmol, 10 mol%) were added. After 24 hours the mixture was filtered through silica gel and concentrated in vacuo. The crude product mixture was purified by MPLC (20% EtOAc/hex) to afford 191 (0.295 g, 53%), along with 100 mg 18% of recovered starting material.

^1H NMR (500 MHz, CDCl₃) δ 7.36-7.26 (m, 5H), 6.34 (dd, J = 17.5, 10.5 Hz, 1H), 6.21 (dd, J = 17.5, 1.0 Hz, 1H), 5.81 (dd, J = 10.5, 1.0 Hz, 1H), 4.75 (s, 2H), 4.60 (s, 2H), 3.57 (t, J = 6.5 Hz, 1H), 2.58 (t, J = 7.5 Hz, 1H), 1.67-1.56 (m, 4H), 1.43-1.30 (m, 4H).

^13C NMR (125 MHz, CDCl₃) δ 201.1, 138.1, 136.7, 128.6, 128.10, 128.05, 127.8, 94.8, 69.4, 68.1, 39.7, 29.7, 29.2, 26.2, and 24.0.

HRMS (ESI) Calcd for (C_{17}H_{24}O_{3} + Na^+): 299.1618. Found: 299.1630.

GC-MS t_r = 12.1 min; m/z: 170, 139, 128, 119, 110, 98, 92, 91, 83, 65, and 55.

IR (neat) 3031, 2936, 2863, 1699, 1683, 1616, 1497, 1455, 1401, 1380, 1206, 1156, 1114, 1048, 1028, 989, 962, 737, 698 cm⁻¹.

TLC R_f = 0.60 in 20% EtOAc in hexanes.

6-(10-(Benzyloxymethoxy)-4-hydroxydecyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (S101)

To a 25 mL flask, diisopropylamine (0.34 mL, 2.4 mmol) and THF (4 mL) were added and cooled to 0 °C before addition of n-BuLi (1.0 mL, 2.5 mmol). After 15 minutes the
flask was cooled to -78 °C, and dioxinone 137 (0.32 mL, 2.4 mmol) was added. After 45 minutes CuI (0.76 g, 4.0 mmol) was added. After 15 minutes, enone 191 (0.295 g, 1.07 mmol) was added. After 20 minutes the reaction was allowed to warm to room temperature and quenched with satd. aq. NH₄Cl. The reaction mixture was concentrated in vacuo, and extracted with ether, washed with brine, and concentrated in vacuo. The crude product was dissolved in 3 mL of ethanol and NaBH₄ was added (75 mg, 1.9 mmol). After 2 hours the reaction mixture was concentrated in vacuo and extracted with ether, washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by MPLC (40% EtOAc/hex) afforded S101 (23 mg, 5.1% over two steps) as an oil.

\(^1\)H NMR (500 MHz, CDCl₃) δ 7.37-7.27 (m, 5H), 5.24 (s, 1H), 4.76 (s, 2H), 4.60 (s, 2H), 3.62-3.59 (m, 1H), 3.58 (t, J = 6.5 Hz, 2H), 2.24 (ddd, J = 8.5, 7.0, 3.0 Hz, 2H), 1.77-1.65 (m, 2H), 1.68 (s, 6H), 1.64-1.56 (m, 3H), 1.55-1.47 (m, 1H), 1.47-1.29 (m, 8H).

\(^{13}\)C NMR (125 MHz, CDCl₃) δ 171.9, 161.5, 138.1, 128.6, 128.0, 127.8, 106.5, 94.8, 93.4, 71.6, 69.4, 68.2, 37.8, 36.7, 33.8, 29.8, 29.6, 26.4, 25.7, 25.24, 25.22, and 22.1.


TLC \(R_f=0.30\) in 40% EtOAc in hexanes.

6-(4,10-Dihydroxydecyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (187)
To a 5 mL screw cap vial, dioxinone S101 (21 mg, 50 µmol), CH₂Cl₂ (0.5 mL), and dimethyl sulfide (40 µL, 0.54 mmol) were added. The vial was cooled to -78 °C, and BF₃·OEt₂ (0.15 mmol) was added. After 4 hours the reaction was filtered through a plug of silica gel and purified by MPLC (100% EtOAc) to afford 2.0 mg (13%) of the desired product as a clear oil.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.25 (s, 1H), 3.65 (t, \(J = 6.5\) Hz, 2H), 3.63-3.58 (m, 1H), 2.25 (ddd, \(J = 9.0, 7.0, 3.0\) Hz, 2H), 1.77-1.71 (m, 1H), 1.70-1.63 (m, 1H), 1.68 (s, 6H), 1.62-1.53 (m, 3H), 1.53-1.48 (m, 1H), 1.48-1.41 (m, 3H), 1.42-1.26 (m, 5H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.9, 161.6, 106.5, 93.5, 71.6, 63.1, 37.7, 36.7, 33.8, 32.8, 29.5, 25.9, 25.7, 25.26, 25.23, and 22.1.

HRMS (ESI) Calcd for (C\(_{16}\)H\(_{28}\)O\(_5\) + Na\(^+\)): 323.1829. Found: 323.1828.

TLC \(R_f = 0.33\) in 100% EtOAc.

6-(4,10-Dihydroxydecyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (187)

To a 100 mL flask, alcohol 194 (5.0 g, 35.7 mmol), triethylamine (15 mL), and DMSO (5.0 mL) were added. The flask was cooled to 0 °C, and sulfur trioxide-pyridine complex (8.0 g, 50.3 mmol) was added. After 40 minutes the reaction was filtered through a column of silica gel to yield crude enone. In a separate 250 mL flask, disopropylamine (7.0 mL, 50 mmol) and THF (150 mL) were added and cooled to 0 °C before addition of n-BuLi (20 mL, 50 mmol). After 15 minutes the flask was cooled to -78 °C, and dioxinone 137 (7.0 g, 49 mmol) was added. After 45 minutes Cul (17.8 g, 93.6 mmol) was added. After 15 minutes, crude enone 195 (~5.0 g, 35 mmol) was added. After 20 minutes the reaction was allowed to warm to room temperature and quenched with satd. aq. NH\(_4\)Cl. The reaction mixture was concentrated in vacuo, and extracted with ether, washed with brine, and concentrated in vacuo. This crude product was chromatographed in 40% Ethyl Acetate/hexanes to remove less polar byproducts of enone dimer and oligomerization,
giving 7.0 g of an inseparable mixture of the desired 1,4-addition compound and recovered dioxinone 137. From this mixture, 3.6 g was placed in a 250 mL flask and dissolved in 100 mL diethyl ether and cooled to 0 °C. To this mixture was added BH₃·DMS (6 mL) over a 15 minute period. After 1 hour, the reaction was quenched with water (30 mL) added via syringe pump over a 3 hour period. At this time, satd. aq. sodium bicarbonate was added (40 mL) and hydrogen peroxide (20 mL, 30% aq. solution) was added. After being allowed to stir for 12 hours, the reaction was then quenched with satd. aq. sodium thiosulfate until the solution gave a negative peroxide test by starch iodide paper. The reaction mixture was then extracted with ether and washed with brine. Purification by flash chromatography (70% EtOAc/hex to 100% EtOAc gradient) was performed to remove unreacted dioxinone 137, and the remaining more polar products were collected and purified by MPLC (100% EtOAc) to afford 187 (39 mg, ~1%) as a clear oil.

**Rac-(1S, 11S)-1-hydroxy-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (196)**

To a 500 mL flask containing 250 mL of benzene, dioxinone 187 (8.0 mg, 27 µmol) was added. The mixture was refluxed for 12 hours before being allowed to cool to room temperature. Purification by pipette column (5% EtOAc/hex) afforded 196 (5.0 mg, 80%) as a clear oil, having an ~9:1 d.r.

\(^1\text{H NMR}\) (500 MHz, CDCl₃) δ 4.78 (ddd, \(J = 11.0, 9.0, 4.0\) Hz, 1H), 4.34 (d, \(J = 2.5\) Hz, 1H), 3.83 (ddd, \(J = 11.0, 5.5, 4.5\) Hz, 1H), 3.83-3.78 (m, 1H), 2.62 (d, \(J = 12.0\) Hz, 1H), 2.50 (d, \(J = 12.0\) Hz, 1H), 1.92 (dddd, \(J = 13.5, 13.5, 13.5, 4.0, 4.0\) Hz, 1H), 1.78 (dddd, \(J = 12.0, 8.5, 6.5, 2.5\) Hz, 1H), 1.77-1.64 (m, 2H), 1.60 (dddd, \(J = 14.0, 7.0, 4.0, 3.0\) Hz, 1H), 1.52-1.36 (m, 6H), 1.27-1.14 (m, 3H).
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.1, 95.5, 72.0, 64.1, 47.4, 34.5, 33.1, 31.7, 26.6, 26.2, 25.7, 22.6, 19.0.

HRMS (ESI) Calcd for (C$_{13}$H$_{22}$O$_4$ + Na$^+$): 265.1410. Found: 265.1412.

GC-MS $t_r = 10.27$ and 10.33 min (both −H$_2$O); m/z: 224, 209, 196, 182, 169, 157, 138, 121, 107, 95, 81, 67, 55 and 224, 207, 196, 182, 164, 143, 122, 110, 95, 81, 67, and 55.

TLC $R_f = 0.25$ in 5% EtOAc in hexanes.

The 6-enal (193)$^{41}$

To a 250 mL flask, diol 192 (7.08 g, 49.2 mmol), Et$_2$O (70 mL), THF (40 mL), MeOH (30 mL), H$_2$O (50 mL), and sodium periodate (14.0 g, 65.4 mmol) were added. After stirring for 2 hours, the reaction mixture was transferred to a larger flask and concentrated in vacuo before being extracted with ether, washed with brine, and dried with sodium sulfate to afford 193 (5.48 g, 99%) as an oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.77 (t, $J = 1.5$ Hz, 1H), 5.79 (dddd, $J = 17.0$, 10.0, 6.5, 6.5 Hz, 1H), 5.01 (ddddd, $J = 17.0$, 1.5, 1.5, 1.5 Hz, 1H), 4.96 (dddd, $J = 10.5$ Hz, 1.5, 1.5, 1.5 Hz, 1H), 2.44 (td, $J = 7.0$, 1.5 Hz, 2H), 2.08 (ddddd, $J = 7.0$, 7.0, 7.0, 1.5 Hz, 2H), 1.65 (app p, $J = 7.5$ Hz, 2H), 1.43 (app p, $J = 7.5$ Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 202.8, 138.4, 115.0, 43.9, 33.6, 28.5, 21.7.

GC-MS $t_r = 4.0$ min; m/z: 111, 94, 84, 83, 79, 68, and 55.

IR (neat) 3078, 2978, 2936, 2864, 1713, 1641, 1461, 1414, 1288, 1237, 994, 914, and 835 cm$^{-1}$.

TLC $R_f = 0.50$ in 10% EtOAc/hexanes.
Nona-1,8-dien-3-ol (194)\textsuperscript{42}

To a 250 mL flask, aldehyde 193 (5.48 g, 48.9 mmol) and THF (85 mL) were added. The flask was cooled to 0 °C and vinylMgBr (1.05 M, 48.0 mL, 50.4 mmol) was added over 10 minutes. After 30 minutes the reaction mixture was allowed to warm to room temperature before being quenched with satd. aq. NH\textsubscript{4}Cl and concentrated in vacuo before being extracted with ether, washed with brine, and concentrated in vacuo again. Purification by flash chromatography (20% EtOAc/hex) afforded 194 (6.18 g, 90%) as an oil.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.87 (ddd, \(J = 17.0, 10.0, 6.0\) Hz, 1H), 5.80 (ddddd, \(J = 17.0, 10.0, 3.5, 3.5\) Hz, 1H), 5.22 (dd, \(J = 17.0, 1.5, 1.5\) Hz, 1H), 5.10 (dd, \(J = 10.5, 1.5, 1.5\) Hz, 1H), 4.99 (ddddd, \(J = 17.0, 1.5, 1.5, 1.5, 1.5\) Hz, 1H), 4.94 (ddddd, \(J = 10.5, 2.5, 1.5, 1.5\) Hz), 4.10 (app p, 6.5 Hz, 1H), 2.06 (ddddd, \(J = 6.5, 6.5, 6.5, 1.5, 1.5\) Hz, 2H), 1.66-1.23 (m, 6H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 141.4, 139.0, 114.8, 114.6, 73.4, 37.0, 33.8, 28.9, 25.0.

GC-MS \(t_r = 5.6\) min; m/z: 139, 125, 107, 93, 83, 67, 57.

IR (neat) 3365, 3078, 2978, 2933, 2859, 1641, 1463, 1436, 1311, 1051, 991, 911 cm\textsuperscript{-1}.

TLC \(R_f = 0.20\) in 10% EtOAc in hexanes.

\[ \begin{array}{c}
\text{O} \\
\text{vinylMgBr} \\
\text{THF -78 °C} \\
\text{90%}
\end{array} \]

Nona-1,8-dien-3-one (195)

To a 100 mL flask, alcohol 194 (5.0 g, 35.7 mmol), triethylamine (15 mL), and DMSO (5.0 mL) were added. The flask was cooled to 0 °C, and sulfur trioxide-pyridine complex (8.0 g, 50.3 mmol) was added. After 40 minutes the reaction was filtered through a col-
umn of silica gel to yield crude aldehyde. A small amount of this unstable enone 195 was purified by MPLC (7% EtOAc/hexanes) for characterization purposes.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.35 (dd, $J = 17.5$, 10.5 Hz, 1H), 6.22 (dd, $J = 17.5$, 1.0 Hz, 1H), 5.82 (dd, $J = 10.5$, 1.0 Hz, 1H), 5.80 (dddd, $J = 17.0$, 10.0, 6.5, 6.5 Hz, 1H), 5.01 (dddd, $J = 17.5$, 1.5, 1.5, 1.5 Hz, 1H), 4.95 (dddd, $J = 10.5$, 1.0, 1.0, 2.5 Hz), 2.59 (t, $J = 7.5$ Hz, 2H), 2.07 (dddd, $J = 7.0$, 7.0, 7.0, 1.5, 1.5 Hz, 2H), 1.64 (app p, $J = 7.5$ Hz, 2H), 1.42 (app p, $J = 7.5$ Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 201.0, 138.6, 136.7, 128, 1, 114.8, 39.6, 33.7, 28.6, 23.6.

GC-MS $t_r = 5.6$ min; m/z: 137, 123, 109, 96, 83, 70, 55.

IR (neat) 2934, 2859, 1700, 1684, 1641, 1617, 1457, 1438, 1402, 1372, 1209, 1189, 1079, 992, 966, 911 cm$^{-1}$.

TLC $R_f = 0.60$ in 10% EtOAc in hexanes.

\[ \text{Lactonization vs. water addition competition test.} \]

To a culture tube, dioxinone 187 (1.0 mg) was added, along with 100 µL of water and 100 mL of benzene. The culture tube was sealed and heated at 80 °C for 16 hours. The solvent was removed in vacuo and a $^1$H NMR was taken. Integration of the methyl ketone of 197 (2.15 ppm) vs. a proton on the macrolide 196 (4.78 ppm) gave ca. 2:1 ratio.

HRMS (ESI) Calcd for (C$_{12}$H$_{24}$O$_3$ + Na$^+$): 239.1617. Found: 239.1616.
Chapter II

2.1 Introduction

Chemists have long speculated as to how nature makes natural products. One of these chemists, J. Norman Collie, went so far as to boldly hypothesize that polyketides (a term which he coined) were formed by the condensation of ketene units. While this has been discredited, we believe that Collie could partially be right. We believe that the formation of acylketene could be happening in nature from thioacetoacetates. Additional motivation for research in this area is the fact that the methods of formation of acylketenes are limited. The most common methods are outlined below.

**Scheme 201**

As shown in Scheme 201, 1,3-dioxin-4-ones **201** can be forced to undergo a retro-hetero Diels-Alder reaction, forming acylketenes **202**. 2-Diazo-1,3-dicarbonyl compounds **203** can be either heated or activated photochemically to extrude nitrogen, generating a carbene, which can insert into a neighboring carbonyl. β-Keto esters **204** (via their enol) thermally lose alcohol to form acylketene. Furan-2,3-diones **205** undergo chelotropic extrusion of carbon monoxide to form acylketene. Acylated ethoxy alkynes **206** undergo a retro-ene reaction to extrude ethylene to form acylketene. Also, β-keto acid chlorides **207** eliminate HCl to form acylketenes. Each of these methods requires either significant heating and/or uncommon starting materials. We would like to develop a reliable way of forming acylketenes at room temperature. Enter β-keto thioesters.
2.2 Acylketenes From Thioacetoacetates – Electrophilic Activation

We are not the first to propose that acylketenes could come from β-keto thioesters. Douglas studied the alkaline hydrolysis of S-acetoacetyl-CoA and found results consistent with an E1cb mechanism, suggesting a rate limiting elimination step to acylketene.\(^\text{49,50}\) While this method is interesting from an academic standpoint, the basic conditions required are a limitation for its synthetic practicality (since hydroxide adds to acylketene), and this method is not commonly used.

How else might acylketenes be generated from β-keto thioesters? One such way could be electrophilic activation of the thioester 208 to form an activated species 209 (Scheme 202). This activated species could undergo direct attack from a nucleophile at the thioester carbonyl, forming a tetrahedral intermediate, which would break down to cleave the carbon sulfur bond, giving ester 210 directly. Another scenario could be an E1cb mechanism, where the enolate 211/212 (or its enol) extrudes the activated thiol directly, giving acylketene 213 as an intermediate. Then end result would be the same regardless of the mechanism.

Scheme 202

What would be a good electrophile to initiate the desired transformation? Kishi\(^\text{51}\) and Ley\(^\text{17}\) used silver(I) and copper(I) salts to initiate attack of nucleophiles at thioacetoacetates in the context of macrocyclizations (214 to 215 and 216 to 217) (Scheme 203). Silver(I) salts were determined to be a good place to begin our investigation due to
their ready availability in our laboratory. First, controls were run (Scheme 204). Thiophenylacetoacetate (218) has ca. 40% enol content (219) in CDCl₃. When 218 is placed in CDCl₃ with isopropanol overnight, no reaction occurs. In a mixture of isopropanol and acetonei-PrOH, no reaction was observed. In a mixture of acetone and IPA/acetone, a trace amount of the reaction was observed after 24 hours.
acetone, 218 undergoes a small amount of esterification to isopropylacetoacetate (220), detectable by $^1$H NMR analysis. In the presence of acetone alone, no reaction occurs. Additional control experiments showed that 218 would not form 220 under acid catalysis by trifluoroacetic acid, instead isopropyl trifluoroacetate (222) is formed. When dioxinone 221 is incubated with IPA and TFA, no 220 is formed, only 222. Incubating 218 with acetone and TFA resulted in no reaction, and incubating 221 with IPA and silver trifluoroacetate also led to no reaction. Collectively, these controls tell us that dioxinone 221 is stable to the reaction conditions, and that 218 is also stable to neutral and acidic conditions.

When silver trifluoroacetate or silver phosphate is added to 218 with IPA or an IPA/acetone mixture, with or without a sodium phosphate buffer, 220 is formed (Scheme 205). A ‘silver mirror’ is not formed during the reaction, suggesting that silver(0) is not produced. Thiophenol is not observed in the reaction mixture either, suggesting that it has been captured by silver, forming insoluble AgSPh (223). Interesting to note is that the product is formed even in the presence of acetone, which is known to be able to trap acylketene. However, competitions between alcohol addition and [4+2] cycloaddition lead to a vast preponderance of the alcohol addition product (~300:1 ratio even with a 20-fold excess of ketone). The observed product is consistent with what would be seen if acylketene is involved, if we did see 221 formed in the reaction under these conditions, it would be evidence of another (i.e. stepwise) mechanism.

Scheme 205

When silver activation was performed and the only trapping agent used was acetone, 221 was formed as the sole product based on $^1$H NMR (Scheme 206). Complete consumption of 218 had occurred. This transformation is unprecedented according to the
Beilstein and Scifinder databases. Potential mechanisms for this process are also outlined in Scheme 206. When 218 or its enol is activated by silver, the keto/enol pair 224/225 is made. Since these species are cationic, proton loss is likely fast, giving the zwitterionic intermediate 226. Alternatively, the cationic pair of 224/225 could lose PhSAg directly, giving acylium intermediates 227 or 228. While acylium ions are typically considered high energy intermediates, they have been observed in cases where they are in conjugation with an aromatic ring. Simple proton loss from either intermediate would give acetylketene 213 directly. The most likely mechanism of dioxinone formation would be the [4+2] cycloaddition 229, as this is a precededent mode of reactivity for acylketenes. Nevertheless, alternative mechanisms such as ketone addition to acylium species to form 230 or 231 cannot be readily dismissed, nor can the stepwise formation and cyclization of the enol hemiketal 232. However, this pathway would require a cationic species to have a long enough lifetime to react in a bimolecular fashion and would likely be much slower than simple proton loss to enter the acylketene/acylium reaction pathway.

Scheme 206
Dioxinone formation was also successful using other ketones, such as cyclopropyl methyl ketone, diethyl ketone, and acetophenone, giving dioxinones 233-235, respectively (Scheme 207). The reaction failed when using the exceptionally hindered diisopropyl ketone and dibenzyl ketone. Substitution at the γ-position of the thioacetoacetate is tolerated by the reaction, as allyl-containing compound 236 gave dioxinone 237 in 75% isolated yield when trapped with diethyl ketone. Internal competition with a tertiary alcohol vs. a methyl ketone (diacetone alcohol 238) resulted in exclusive trap of the tertiary alcohol to give acetoacetate 239, reinforcing the significant rate difference between capture of a hydroxyl group vs a ketone.

Scheme 207

Since the silver activation can be used to successfully make dioxinones, one can ask the question of whether or not this chemistry is useful. The Barrett group has shown that various R substituents on dioxinone 240 can lead to dramatic rate differences in thermolysis rates to form acylketene (Scheme 208). When heated in toluene with alcohol 241, the acetoacetylated adduct 242 was formed. Cyclohexyl-containing dioxinone 243 gave only a 5% yield of product, reflective of its slow rate of acylketene formation.
Commonly used dioxinone 221 gave a 15% yield. Interestingly, when an aromatic ring was present in the 2-position as in dioxinones 235 and 244, the rate of thermolysis increased by a sizable margin. The rate of thermolysis of 235 is especially useful, and Barrett went on to use this dioxinone as an acylketene precursor. The fact that we can make this specific dioxinone using the silver activation methodology is noteworthy because this particular dioxinone does not appear to be accessible thermally, because Birney has shown that microwave heating of dioxinone 221 in the presence of acetophenone does not lead to the desired dioxinone 235, but instead leads to formation of dehydroacetic acid 245. This product is formed by the [4+2] dimerization of acetylketene.

Mechanistic considerations led us to explore competitive thioester activations (Scheme 209). When 218 was mixed with phenyl thioacetate 246 and activated with limiting AgO_{2}CCF_{3} in the presence of isopropanol, it was found that 218 was preferentially activated (14:1 ratio of 220:247 at ~80% conversion). The result implies one of two things: first, the initial activation on sulfur could be directed by the carbonyl or enol of the thioacetoacetate, leading to the observed rate difference. Alternatively, the activation of the thioester by silver could be reversible. As the thioacetoacetate can shed a proton to lose its positive charge, its activated species could have a significantly longer lifetime than the simple thioacetate. This result seems to argue against acylium formation, be-
cause one might expect similar ratios of activation of 218 and 246 if this was a dominant pathway. Additionally, when the competition was performed using silver phosphate instead of silver trifluoroacetate, only 220 was formed, not 247. Reasons for this exclusive activation of 218 in this case are not clear.

Scheme 209

We also performed the competitive activation of 218 with thioacetoacetate 248 (Scheme 210). When activated with silver trifluoroacetate in the presence of isopropanol, 220 is formed in preference to 249 (5:1 ratio). Additionally, when silver phosphate is used as the activating agent, 220 is formed exclusively.

Scheme 210

The silver activation was also attempted using other trapping agents. It is known that enol ethers will engage acylketene in [4+2] cycloadditions at elevated temperatures. As a control, dioxinone 223 was heated with butyl vinyl ether, and the desired [4+2] adduct 232 was formed (Scheme 211). When butyl vinyl ether was used along with silver activation of 218, no desired product formed. Instead acetal 233 was cleanly formed.
along with acetaldehyde. This byproduct comes from silver activating the vinyl ether instead of the thioester. The activated vinyl ether is trapped by trace water, generating acetaldehyde and \( n \)-butanol. The \( n \)-butanol can then trap another activated vinyl ether, giving ketal 251. The silver activation was also attempted in the presence of dicyclopentadiene 252 in hopes of attaining a \([2+2]\) adduct, which was not successful. \([4+2]\) Trapping with alkyne 253, nitrile 254, and ethoxyacetylene 255 also were not successful, but there is no precedence for these substrates being trapped by acylketene an at room temperature. The biggest limitation in getting other functionality to react using the silver activation method is that there is a ketone in the starting thioacetoacetate. If the trapping agent is not trapped faster than this ketone, the starting material will dimerize and oligomerize, leading to complicated reaction mixtures.

Additional studies related to silver activation are shown in Scheme 212. It was hoped that exposure of diketothioester 256 to silver trifluoroacetate would lead to formation of ketene 257, followed by a 6-pi electrocyclization to give pyrone 258, which is a natural product isolated from *Cyathus stercoreus*.\(^{57}\) Dianion formation from 218, followed by addition of crotonaldehyde, led to formation of 259, but this substrate was unstable and spontaneously cyclizes to 260, also a known compound, and this idea was abandoned.\(^{58}\) The synthesis of thioester 261 was also attempted to test the tolerance of the silver activation chemistry to substitution on the \( \gamma \)-position. Attempted transesterification of ester 262 with thiophenol under catalysis by Amberlyst-15 interestingly gave thioeno-
lather 263 in high conversion, with the alkene out of conjugation with the ester, something that was not expected.

Scheme 212

\[
\begin{align*}
\text{Me} & & \text{O} & & \text{O} & & \text{O} & & \text{SO} & & \text{Me} \\
\text{Me} & & \text{O} & & \text{O} & & \text{O} & & \text{H} & & \text{Me}
\end{align*}
\]

Finally, additional metals were examined in attempts to induce activation of 218, but none were successful. These were silver(I) nitrate, silver(I) bromide, silver(I) chloride, copper(II) sulfate, copper(I) bromide, copper(I) chloride, copper(I) iodide, copper(II) oxide, cesium(I) chloride, cesium(I) iodide, Pd(Cl)\(_2\)(PPh\(_3\))\(_2\), and Ru(Cl)\(_2\)(PPh\(_3\))\(_3\). The failure of the aforementioned silver reagents was likely due to solubility issues.

2.3 Alternative Thioester Activation Strategies

Another potential mechanism of activation of a thioacetooacetate is via oxidation. A reasonable mechanistic landscape is outlined in Scheme 213. Oxidation of 208 would give S-acyl sulfoxide 264. This activated species could be attacked by a hydroxylic nucleophile to give ester 210. Alternatively, the enol of 264 (265) could undergo a [3.2] sigmatropic rearrangement, giving ketene 266, which could eliminate sulfenic acid to give 213, or be attacked by a nucleophile before loss of sulfenic acid. The S-acyl sulfoxide could also lose a proton (267/268) and undergo an E1cb elimination of sulfenic acid to give 213. Additionally, structures 269 and 270 should also be considered. Thioester 270 could arise from rearrangement of 264 via 269, coming from intramolecular attack of the sulfoxide oxygen on the acyl group, or, alternatively, it could arise by sulfenic acid being trapped by acylketene.
The oxidative activation of simple thioacetates is known; oxidative activation of thioacetoacetates is not. Bunton used OXONE and aqueous acetonitrile to activate a variety of phenyl thiobenzoates \[214\]. The products of the activation were carboxylic acids \[215\] and sulfonic acids \[216\]. It was believed that formation of an S-acyl sulfoxide occurred, which activated the carbonyl towards addition of water. Further oxidation of the sulfenic acid occurred, giving the final sulfonic acid. Bunton found that the reaction was first order in peroxymonosulfate ion, that electron-donating groups on the aryl rings sped up the reaction, and that there was no buildup of reactive intermediate. This is consistent with a rate limiting oxidation step.

Would the oxidative activation work with a thioacetoacetate? To answer this question, \((n\text{Bu})_4\text{N-oxone was made.}\) This was necessary because OXONE is not soluble.
in organic solvents. In the presence of isopropanol, oxidative activation of 218 was successful, giving 220 as the major product (Scheme 215). However, in the presence of acetone, no \([4+2]\) trapping is observed. This suggests that while the thioester is indeed being activated, it does not generate acylketene, or if it does it is trapped by another nucleophile (e.g. sulfenic acid) faster than the \([4+2]\) cycloaddition with acetone occurs. Additional oxidants were tried. Neither peroxycetic acid or DMDO gave reaction. PhIO gave a messy collection of products when using IPA as the trapping agent. When acetone was used as the trapping agent, no \([4+2]\) addition product was detected, again suggesting that acylketene is not involved in the process.

**Scheme 215**

Another oxidative method of activation known in the literature is Mukaiyama’s activation of thioesters by NBS in the presence of an alcohol. The process is shown in Scheme 216. Thioester 274 is added to NBS in the presence of ethanol, giving 275 as the final product. The presumed bromonium intermediate 276 is attacked at sulfur by the alcohol nucleophile, generating 277. Bromide cleaves the alkyl group from the activated sulfur species, generating S-acyl sulfoxide 278, which is then attacked by remaining alcohol in the reaction pot.

**Scheme 216**
Unfortunately for our cause, the method fails for thiophenylacetoacetate 218 (Scheme 217). The enol is more nucleophilic towards the electrophilic bromine than the sulfur is, thus the product is simply 279.

Scheme 217

Another method of activation of thioacetoacetates that was considered was acylation. This idea came from considering how nature might activate a PKS-bound polyketide for chain release by a mechanism other than activation by a thioesterase. The general idea is outlined in Scheme 218. If the enol of an acyl carrier protein (ACP) bound thioester such as 280 was acylated on oxygen, substrate 281 would be formed. A 1,5-acyl shift from this intermediate would transfer the acyl group to the ACP while cleaving the original sulfur-acyl bond, giving acylketene 282 and acyl-ACP 283.

Scheme 218

Partial validation of this idea came upon a literature search that showed that O-acylated thioester 284 gave pyrone 285 upon heating with ZnCl₂ (Scheme 219). Although the authors do not present a mechanism, or implicate acylketene, we can propose that a 1,5-acyl shift has occurred, giving 286, which can undergo a Diels-Alder reaction.

Scheme 219
with additional 284 in the reaction pot to give substrate 287, which should be highly prone to elimination to give 285.

Unfortunately, efforts to promote dioxinone formation by acylative activation of substrate 218 in the presence of acetic anhydride/acetone or trifluoroacetic anhydride/acetone failed. It seems that a better way to study this transformation would be to attempt to reproduce the results Babu and Pozzo under milder conditions,\textsuperscript{64} and by studying the effects having alternative acyl groups on substrate 284 (e.g. benzoyl, \textit{p}-nitrobenzoyl). As it stands, acylative activation is an intriguing idea, but was not validated at room temperature like the oxidative and silver activated methods were.

2.4 Conclusion/Future Directions

In conclusion, we were able to successfully use silver(I) salts to activate phenyl thioacetoacetate, trapping with alcohols and ketones. The conversion of a thioacetoacetate to a 1,3-dioxin-4-one was unprecedented before our discovery. The oxidative activation has shown more limited scope, working with alcohols but not ketones, and we cannot implicate acylketene in the activation. Potential future direction in this area could be the application of the dioxinone formation methodology on a natural product. When the 1,3-dioxin-4-one subunit (288) is submitted into the Beilstein database in an Isolation from Natural Product (INP) search, four targets are found (289-292) (Figure 6). These targets could potentially be made by the silver activation methodology, and would help define its scope in a more complex molecular environment.

Figure 6 – Dioxin-4-one Natural Products
2.5 Experimental Section

\[
\begin{array}{c}
\text{Me} \quad \text{O} \quad \text{O} \\
\text{Me} \quad \text{O} \quad \text{O} \\
\end{array}
\quad \text{PhSH} \\
\text{toluene reflux} \\
89\%
\rightarrow
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{SPh} \\
\end{array}
\]

**S-phenyl 3-oxobutanethioate (218)**

In a 125 mL round bottomed flask, dioxinone 221 (5.25 g, 37.7 mmol), thiophenol (3.3 mL, 32.1 mmol), and toluene (70 mL) were added. The flask was equipped with a reflux condenser, and refluxed for 2 hours. After being allowed to cool to room temperature, the solvent was removed in vacuo. Flash chromatography (10% EtOAc/Hexanes) gave 218 (5.5 g, 89%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 12.6 (s, 1H, enolic –OH), 7.48-7.42 (m, 5H), 5.48 (s, 1H, vinylic enol), 3.74 (s, 2H), 2.26 (s, 3H), 1.94 (s, 3H, enol –CH\(_3\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 199.6, 193.3, 190.6, 174.8, 135.1, 134.5, 129.9, 129.7, 129.5, 129.3, 127.2, 127.0, 98.9, 57.8, 30.4, 21.3.

HRMS (ESI) Calcd for (C\(_{10}\)H\(_{10}\)O\(_2\)S + Na\(^+\)): 217.0294. Found: 217.0327.

IR (neat) 3059, 3010, 2964, 2922, 1726, 1698, 1621, 1478, 1441, 1401, 1359, 1295, 1192, 1157, 1078, 1024, 970, 825, 748, and 689 cm\(^{-1}\).

TLC R\(_f\) = 0.60 in 15% EtOAc/hexanes.

\[
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{N}_2 \\
\end{array}
\quad \text{PhSH} \\
\text{toluene reflux} \\
\rightarrow
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{SPh} \\
\end{array}
\]

**S-phenyl-2-methyl-3-oxobutanethioate (248)**

In a 100 mL round bottomed flask, diazo compound S201 (0.87 g, 6.9 mmol), thiophenol (0.85 mL, 7.8 mmol), and toluene (30 mL) were added. The flask was equipped with a reflux condenser, and the solution was refluxed for 2 hours. After being allowed to cool to room temperature, the solvent was removed in vacuo, and the residue was purified by flash chromatography (15% EtOAc/Hexanes) to give 248 (0.78 g, 48%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.47-7.40 (m, 5H), 3.83 (q, \(J = 7.0\) Hz, 1H), 2.28 (s, 3H), 2.03 (s, 3H, enol –CH\(_3\)), 1.97 (s, 3H, enol –CH\(_3\)), 1.45 (d, \(J = 7.0\) Hz, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 202.5, 195.2, 171.9, 135.5, 134.6, 129.9, 129.7, 129.5, 129.3, 126.9, 104.0, 61.9, 28.6, 19.8, 13.8, and 12.2.

HRMS (ESI) Calcd for (C$_{11}$H$_{12}$O$_2$S + Na$^+$): 231.0450. Found: 231.0457.

IR (neat) 3062, 2989, 2938, 2876, 1728, 1693, 1610, 1583, 1478, 1441, 1422, 1358, 1330, 1308, 1271, 1211, 1170, 1106, 1076, 1025, 978, 933, 813, 750, 706, and 690 cm$^{-1}$.

TLC R$_f$ = 0.45 in 15% EtOAc/hexanes.

2-cyclopropyl-2,6-dimethyl-4H-1,3-dioxin-4-one (233)

In a 25 mL flask, thioester 218 (0.064 g, 0.33 mmol), cyclopropyl methyl ketone (92 µL, 0.98 mmol), and CDCl$_3$ (1.05 mL) were added. While stirring, silver trifluoroacetate (0.080 g, 0.36 mmol) was added. After 1.5 hours, the reaction was filtered through silica gel using ethyl acetate as the eluent. After concentration in vacuo, the residue was purified by MPLC (20% EtOAc/Hex) to give 233 (0.051 g, 78%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.20 (q, J = 0.5 Hz, 1H), 1.98 (d, J = 1.0 Hz, 3H), 1.66 (s, 3H), 1.39 (dddd, J = 8.5, 8.5, 5.5, 5.5 Hz, 1H), 0.68-0.55 (m, 4H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.9, 161.4, 107.5, 94.0, 22.8, 20.1, 19.0, 2.0, 1.89.


IR (neat) 3096, 3016, 1738, 1729, 1644, 1438, 1395, 1353, 1271, 1231, 1140, 1089, 1049, 991, 967, 927, 884, 846, and 804 cm$^{-1}$.

TLC R$_f$ = 0.41 in 20% EtOAc/hexanes.

2,2-diethyl-6-methyl-4H-1,3-dioxin-4-one (234)
In a 25 mL flask, thioester 218 (0.112 g, 0.577 mmol), 3-pentanone (0.153 g, 1.78 mmol), and CDCl₃ (2.0 mL) were added. While stirring, silver trifluoroacetoacetate (0.140 g, 0.639 mmol) was added. After 1.5 hours, the reaction was filtered through silica gel using ethyl acetate as the eluent. After concentration in vacuo, the residue was purified by flash chromatography (20% EtOAc/Hex) to give 234 (0.0701 g, 72%).

**¹H NMR** (500 MHz, CDCl₃) δ 5.19 (q, J = 1.0 Hz, 1H), 1.99 (d, J = 1.0 Hz, 3H), 2.0-1.91 (m, 4H), 0.98 (t, J = 7.5 Hz, 6H).

**¹³C NMR** (125 MHz, CDCl₃) δ 169.2, 162.0, 110.8, 93.7, 28.2, 20.1, and 7.6.


**IR** (neat) 2979, 2945, 2886, 1736, 1722, 1642, 1459, 1393, 1348, 1313, 1320, 1209, 1185, 1161, 1060, 1053, 998, 952, 905, 806 cm⁻¹.

**TLC** Rᵢ = 0.45 in 20% EtOAc/hexanes.

---

2,6-dimethyl-2-phenyl-4H-1,3-dioxin-4-one (235)

In a 25 mL flask, thioester 218 (0.062 g, 0.32 mmol), acetophenone (0.117 g, 0.97 mmol), and CDCl₃ (1.1 mL) were added. While stirring, silver trifluoroacetoacetate (0.077 g, 0.35 mmol) was added. After 1.5 hours, the reaction was filtered through silica gel using ethyl acetate as the eluent. After concentration in vacuo, the residue was purified by MPLC (15% EtOAc/Hex) to give 235 (0.051 g, 78%).

**¹H NMR** (500 MHz, CDCl₃) δ 7.47 (m, 2H), 7.39-7.36 (m, 3H), 5.16 (s, 5.16), 2.00 (s, 3H), 1.88 (s, 3H).

**¹³C NMR** (125 MHz, CDCl₃) δ 169.3, 161.5, 140.7, 128.2, 128.8, 125.1, 106.7, 96.8, 29.7, and 20.3.


**IR** (neat) 3097, 3057, 3006, 2925, 1711, 1693, 1433, 1393, 1383, 1356, 1268, 1241, 1197, 1177, 1089, 1018, 974, 869, 829, 765, 702, and 660 cm⁻¹.
**TLC** \( R_f = 0.21 \) in 10% EtOAc/hexanes.

![Reaction Scheme]

**S-phenyl 3-oxohept-6-enethioate (236)**

In a 25 mL flask THF (4 mL) and diisopropylamine (0.47 mL, 3.35 mmol) were added and cooled to -78 °C. \( n \)-BuLi (1.3 mL, 3.25 mmol) was then added. After 10 minutes, ester 218 (0.297 g, 1.53 mmol) was added. After 10 minutes, allyl iodide (0.14 mL, 1.5 mmol) was added. After 30 minutes the reaction was quenched with pH = 7 buffer and neutralized with aqueous HCl. The crude product was extracted with DCM, washed with brine, and purified by flash chromatography (15% EtOAc/Hex) to give 0.112 g (48%) of 236.

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \( \delta 12.6 \) (s, 1H, enol –OH), 7.49-7.43 (m, 5H), 5.80 (dddd, \( J = 17.0, \ 10.5, \ 6.5, \ 6.5 \) Hz, 1H), 5.49 (s, 1H, vinylic enol proton), 5.08-4.98 (m, 2H), 3.75 (s, 2H), 2.68 (t, \( J = 7.0 \) Hz, 2H), 2.37-2.26 (m, 2H).

**\(^13\)C NMR** (125 MHz, CDCl\(_3\)) \( \delta 201.1, \ 193.5, \ 190.7, \ 177.2, \ 136.64, \ 136.63, \ 135.2, \ 134.6, \ 130.0, \ 129.8, \ 129.5, \ 129.4, \ 127.2, \ 127.1, \ 116.0, \ 115.9, \ 98.5, \ 76.9, \ 57.2, \ 42.5, \ 34.6, \ 30.3, \) and 27.5.

**HRMS (ESI)** Calcd for (C\(_{13}\)H\(_{14}\)O\(_2\)S + Na\(^+\)): 257.0607. Found: 257.0628.

**IR** (neat) 3077, 3066, 3003, 2978, 2920, 2855, 1727, 1690, 1640, 1616, 1584, 1478, 1441, 1404, 1360, 1335, 1295, 1180, 1078, 1024, 999, 916, 842, 794, 748, 706, and 690 cm\(^{-1}\).

**TLC** \( R_f = 0.50 \) in 15% EtOAc/hexanes.

![Reaction Scheme]

**6-(but-3-en-1-yl)-2,2-diethyl-4H-1,3-dioxin-4-one (237)**
In a 25 mL flask, thioester 236 (0.0578 g, 0.247 mmol), 3-pentanone (0.0624 g, 0.726 mmol), and CHCl₃ (0.8 mL) were added. While stirring, silver trifluoroacetoacetate (0.0610 g, 0.278 mmol) was added. After 1.5 hours, the reaction was filtered through silica gel using ethyl acetate as the eluent. After concentration in vacuo, the residue was purified by MPLC (15% EtOAc/Hex) to give 237 (0.038 g, 75%).

$^{1}H$ NMR (500 MHz, CDCl₃) $\delta$ 5.78 (dddd, $J = 16.5, 10.5, 6.0, 6.0$ Hz, 1H), 5.20 (s, 1H), 5.08 (ddt, $J = 16.5, 1.0, 1.0$ Hz, 1H), 5.05 (ddt, $J = 10.5, 1.0, 1.0$ Hz, 1H), 2.36-2.29 (m, 4H), 2.02-1.92 (m, 4H), 0.98 (t, $J = 7.5$ Hz, 6H).

$^{13}C$ NMR (125 MHz, CDCl₃) $\delta$ 171.3, 161.7, 136.2, 116.4, 110.7, 93.4, 33.2, 30.0, 28.3, and 7.6.


IR (neat) 3082, 2982, 2945, 2887, 1738, 1732, 1464, 1387, 1345, 1314, 1281, 1234, 1210, 1163, 1107, 1061, 1048, 1003, 955, 913, and 809 cm⁻¹.

TLC $R_f = 0.4$ in 15% EtOAc/hexanes.

2-methyl-4-oxopentan-2-yl 3-oxobutanoate (239)

In a 25 mL flask, thioester 218 (0.104 g, 0.536 mmol), diacetone alcohol 238 (0.185 g, 1.59 mmol), and CHCl₃ (1.8 mL) were added. While stirring, silver trifluoroacetoacetate (0.130 g, 0.594 mmol) was added. After 1.5 hours, the reaction was filtered through silica gel using ethyl acetate as the eluent. After concentration in vacuo, the residue was purified by flash chromatography (30% EtOAc/Hex) to give 239 (0.086 g, 80%).

$^{1}H$ NMR (500 MHz, CDCl₃) $\delta$ 12.1 (s, 1H, enol –OH), 4.92 (s, 1H, vinylic enol –CH), 3.38 (s, 2H), 3.05 (s, 2H), 2.26 (s, 3H), 2.16 (s, 3H), 1.93 (s, enolic –CH₃), 1.55 (s, 6H).

$^{13}C$ NMR (125 MHz, CDCl₃) $\delta$ 205.7, 201.0, 166.6, 81.9, 52.1, 51.4, 31.9, 30.3, and 26.5.

IR (neat) 2983, 2942, 1740, 1722, 1650, 1421, 1369, 1322, 1278, 1155, 1120, 1030, 951, 850, 806, and 773 cm$^{-1}$.

**TLC** $R_f = 0.4$ in 30% EtOAc/hexanes.

(\textit{E})-\textit{S}-phenyl-5-hydroxy-3-oxooct-6-enethioate (259)  
(\textit{E})-6-(prop-1-en-1-yl)dihydro-2\textit{H}-pyran-2,4(3\textit{H})-dione (260)

In a 25 mL flask THF (3 mL) and diisopropylamine (0.5 mL, 3.6 mmol) were added and cooled to -78 °C. $n$-BuLi (1.4 mL, 3.5 mmol) was then added. After 10 minutes, ester 218 (0.308 g, 1.59 mmol) was added. After 10 minutes, crotonaldehyde (0.14 mL, 1.69 mmol) dissolved in 0.5 mL THF was added. After 5 minutes the reaction was quenched with satd. aqueous ammonium chloride solution, and the solvent was removed in vacuo. The product was then extracted with ether, filtered through silica gel, and purified by flash chromatography (40% EtOAc/hexanes) to yield 259 (0.072 g, 17%), which partially converted to 260 upon standing.

Data for 259

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.49-7.42 (m, 5H), 5.78-5.68 (m, 1H), 5.56 (s, vinylic enol –CH), 5.53-5.46 (m, 1H), 4.54 (ddd, $J = 6.5$, $6.5$, $6.5$ Hz, methine –CH), 4.44 (ddd, $J = 6.5$, $6.5$, $6.5$ Hz, enolic methine –CH), 3.80 (s, 2H), 2.78-2.77 (m, 1H), 2.55 (s, 1H, -OH), 2.43-2.35 (m, 1H), 1.72-1.68 (m, 3H).

**TLC** $R_f = 0.45$ in 30% EtOAc/hex.

Data for 260

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.91 (ddq, $J = 15.5$, $6.5$, 1.0 Hz, 1H), 5.59 (ddq, $J = 15.5$, $6.5$, 1.5 Hz, 1H), 5.11 (m, 1H), 3.54 (d, $J = 19.0$ Hz, 1H), 3.47 (d, $J = 19.0$ Hz, 1H), 2.77 (dd, $J = 17.5$, 3.5 Hz, 1H), 2.63 (dd, $J = 17.5$, 9.5 Hz, 1H), 1.78 (dd, $J = 7.0$, 1.0 Hz, 3H).
Chapter III

Selectivity in Additions of Hydroxylic Nucleophiles to Acetyketene.
3.1 Introduction

The motivation behind the work described in this chapter has stemmed from interesting selectivity that has been seen in both the literature and our laboratory in the context of trapping of acylketene intermediates. During Boeckman’s synthesis of (-)-kromycin, substrate 301 was heated to form an acylketene intermediate in the presence of two alcohols (Scheme 301). Boeckman reports isolating macrolide 302 in 70 percent yield with no isolable amount of the isomeric 13-membered ring lactone formed.\(^9\)

**Scheme 301**

![Scheme 301](image)

In our laboratory during the synthesis of callipeltoside A, Mike Danielson heated tetrol 303 to create acylketene, and found that there was a large preference for 12-membered ring formation over the 13-membered ring, forming compound 304 in 73% yield\(^1\) (Scheme 302). The goal of this project has been to learn more about the creation of acylketenes from 1,3-dioxin-4-ones and β-keto esters, as well as study the factors that govern selectivity upon addition of nucleophiles to acylketenes.

**Scheme 302**

![Scheme 302](image)

3.2 Kinetics and Mechanism of Acylketene Formation From 1,3-Dioxin-4-ones and β-Ketoesters

The formation of acylketene from 1,3-dioxin-4-ones is a retro [4+2] cycloaddition. Kinetic studies have shown the reversion rate to be largely insensitive to solvent po-
larity and added catalysts, suggesting a concerted reversion. Trapping with an alcohol forms a \( \beta \)-keto ester (Scheme 303). Literature values for the reversion rates of 2,2,6-trimethyl-1,3-dioxin-4-one 305 to form acetyketene 306 are given in Table 1. Experimental values determined by us in our laboratory are given in Table 2. The reaction is driven to the \( \beta \)-keto ester by removal of acetone.

**Scheme 303**

![Scheme 303](image)

**Table 1** – Literature Values for Rate of Decomposition of 305.\(^{65}\)

<table>
<thead>
<tr>
<th>temperature (°Celsius)</th>
<th>half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>81.7</td>
<td>5.8 hours</td>
</tr>
<tr>
<td>91.7</td>
<td>1.73 hours</td>
</tr>
<tr>
<td>98.5</td>
<td>0.63 hours</td>
</tr>
<tr>
<td>106.7</td>
<td>0.35 hours</td>
</tr>
</tbody>
</table>

**Table 2** – Our Experimental Values for Rate of Decomposition of 305.

<table>
<thead>
<tr>
<th>temperature (°Celsius)</th>
<th>solvent</th>
<th>half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room Temp.</td>
<td>(d_6)-acetone</td>
<td>&gt;4 months</td>
</tr>
<tr>
<td>80</td>
<td>benzene</td>
<td>4 hours</td>
</tr>
<tr>
<td>110</td>
<td>toluene</td>
<td>0.3 hours</td>
</tr>
</tbody>
</table>

Our experimentally determined values are within reasonable agreement of those in the literature. Additionally, we have found that refluxing 305 in \(m\)-xylene at 139 °C for 2 minutes provides \( \beta \)-keto esters in over 95 percent conversion. Conversion was monitored by NMR analysis of aliquots taken during the course of a reaction with an alcohol. The room temperature reversion rate was taken by monitoring the incorporation of \(d_6\)-acetone into compound 305 in a sealed NMR tube.

\( \beta \)-Keto esters form acylketenes under pyrolytic conditions. This has been proven directly by trapping of acylketene at liquid Argon temperature via flash vacuum pyrolysis.\(^{46}\) The fragmentation has been shown by IR analysis to proceed through the enol (308) of the \( \beta \)-keto ester (Scheme 304). The diene unit of the \( \beta \)-keto ester (309) must also con-
form to the s-trans conformation to become reactive. The addition of alcohol to acylketene also has been shown to generate the enol of the β-keto ester, suggesting concerted addition via a six atom transition state. Computational studies also back this theory.\textsuperscript{38,66}

**Scheme 304**

![Scheme 304](image)

Additional evidence for a six atom transition state is that acylketenes that cannot access the s-Z conformation react slowly with alcohols. Specific examples of this are acylketene \textsuperscript{310}, for which there is a crystal structure, and \textsuperscript{311}, which persists in methanol at room temperature (Figure 7).\textsuperscript{67,68} This is in stark contrast to acylketene \textsuperscript{306}, which has a half life of less than 1 µs in water.\textsuperscript{69}

**Figure 7 – Stable Acylketenes \textsuperscript{310} and \textsuperscript{311}**

![Figure 7](image)

Literature data for the rates of reversion of β-keto esters to acylketenes are provided in Table 3.\textsuperscript{70} It should be noted that tert-butyl acetoacetates fragment much faster than do primary or secondary acetoacetates, presumably due to relief of steric strain in the enol form of the β-keto ester. This transesterification reaction is driven by a large excess of alcohol, and/or removal of the more volatile alcohol (Scheme 305).

**Scheme 305**

![Scheme 305](image)
Table 3 – Rates of β-Keto Ester Reversion to Acylketene.\textsuperscript{70}

<table>
<thead>
<tr>
<th>R1</th>
<th>temperature (°Celsius)</th>
<th>half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>91.9</td>
<td>19.8 hours</td>
</tr>
<tr>
<td>Et</td>
<td>91.9</td>
<td>18.9 hours</td>
</tr>
<tr>
<td>Et</td>
<td>98.7</td>
<td>10.1 hours</td>
</tr>
<tr>
<td>Et</td>
<td>106</td>
<td>5.2 hours</td>
</tr>
<tr>
<td>iPr</td>
<td>91.9</td>
<td>13.8 hours</td>
</tr>
<tr>
<td>tBu</td>
<td>91.9</td>
<td>1.2 hours</td>
</tr>
<tr>
<td>tBu</td>
<td>98.7</td>
<td>0.77 hours</td>
</tr>
<tr>
<td>tBu</td>
<td>106</td>
<td>0.37 hours</td>
</tr>
</tbody>
</table>

It is important to stress that this is a first order reaction. The rate limiting step is the formation of acylketene, and the reaction shows zero order dependence on the alcohol used for trapping the intermediate. We have shown this in a transesterification of methyl acetoacetate \textsuperscript{312} by dodecanol to form dodecyl acetoacetate \textsuperscript{313} at varying amounts of alcohol (Scheme 306). The results of these competitions are summarized in Table 4. These data were acquired by NMR analysis of aliquots taken during the course of the reactions.\textsuperscript{71}

Scheme 306

Table 4 – Conversion of Methyl Acetoacetate (\textsuperscript{312}) to Dodecyl Acetoacetate (\textsuperscript{313}).

<table>
<thead>
<tr>
<th>[M] dodecanol</th>
<th>30 minutes</th>
<th>60 minutes</th>
<th>120 minutes</th>
<th>240 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 M</td>
<td>34%</td>
<td>60%</td>
<td>86%</td>
<td>98%</td>
</tr>
<tr>
<td>0.07 M</td>
<td>32%</td>
<td>56%</td>
<td>82%</td>
<td>94%</td>
</tr>
</tbody>
</table>

3.3 Competition Between Hydroxylic Nucleophiles for Acylketene Trapping

Since the addition of a heteroatom-H bond to acylketene is proposed to be concerted, we expect that the strength of the bond being broken will play a large role in its selectivity. A list of bond strengths is provided in Table 5.\textsuperscript{72,73} We decided to study this phenomenon, but also take it a step further. If bond strengths, rather than nucleophilicities, are more important in the rates of addition to acylketene, then we believe there
should be a preference for addition of a hydroxyl that is a better H-bond acceptor in diol systems.

Table 5 – Heteroatom-H bond strengths

<table>
<thead>
<tr>
<th>X-H bond</th>
<th>bond strength</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO-H</td>
<td>104 kcal/mol</td>
<td>72</td>
</tr>
<tr>
<td>RNH-H</td>
<td>92 kcal/mol</td>
<td>73</td>
</tr>
<tr>
<td>R₂N-H</td>
<td>86 kcal/mol</td>
<td>73</td>
</tr>
<tr>
<td>RS-H</td>
<td>87 kcal/mol</td>
<td>72</td>
</tr>
</tbody>
</table>

A variety of competition experiments were performed. The competitions were run under pseudo-first order conditions, flooded in the species being competed. Thus, the product ratio is equal to the ratio of the rate constants for the addition of the reacting species to acylketene (equations 1 and 2), assuming that the reactions are essentially irreversible over the times measured.

\[
\frac{k_1[\text{Acylketene}]x[\text{Reactant 1}]}{k_2[\text{Acylketene}]x[\text{Reactant 2}]} = \frac{[\text{Product 1}]}{[\text{Product 2}]} \quad \text{eq. 1}
\]

If \(\frac{[\text{Reactant 1}]}{[\text{Reactant 2}]}\) remains ~ constant, then \(\frac{k_1}{k_2} = \frac{[\text{Product 1}]}{[\text{Product 2}]}\) \(\text{eq. 2}\)

Product ratios were assigned by NMR analysis of aliquots taken at 1.5 and 3 half lives of dioxinone 305. Although we have not fully quantified the reversion rates to acylketene from \(\beta\)-keto amides and thioesters, observing the product ratios over time allows us to see if competing reactions or the reversibility of the reaction is a problem.

Our first competition was between octylamine and dodecanol (Scheme 307). We found that the products of this reaction are enamines 314 and 315, and octylamine is more reactive. At 30 minutes the ratio of octylamine trapped product 315 to dodecanol trapped product 314 is 3.8 to 1. At 60 minutes the ratio had increased to 4.1 to 1. Since the octylamine N-H bond is more than 10 kcal/mol weaker than the dodecanol O-H bond, its preferential trapping was not unexpected.74
We then decided to try a more hindered amine. This was accomplished by a competition of dipentylamine and dodecanol (Scheme 308). We found that the more sterically hindered amine was still more reactive than the alcohol. At 30 minutes, dipentylamine trapped product 316 favored dodecanol trapped adduct 313 by a factor of 1.8 to 1. At 60 minutes 316 favored 313 by a factor of 2.2 to 1. The increase in the amount of 316 is reflective of the reversible nature of acylketene formation from 313.

**Scheme 308**

```
\[
\text{Scheme 308}
\]

```

```
\[
\begin{align*}
\text{305} & \quad 7 \text{ eq. } (R^1)\text{SH and } R^2\text{OH} \\
\text{R}^1 = \text{n-pentyl, } R^2 = \text{dodecyl} \\
\text{toluene reflux} \\
\text{313} & \quad + \text{R}^1\text{NH}_2 \quad R^1\text{NH} \text{R}^1 \\
\text{ratio 313 : 316} & \quad 1 : 1.8 \text{ at } 30 \text{ min} \\
& \quad 1 : 2.2 \text{ at } 60 \text{ min}
\end{align*}
\]

```

Attempting to test the relative rates of addition of octanethiol and dodecanol yielded a surprise (Scheme 309). Although thiols will readily add to acylketene, we found that this competition yielded β-keto ester 313 exclusively. It would seem that one of two (or a combination of the two) events is occurring. One explanation is that the thioester is sufficiently electrophilic to engage in nucleophilic substitution with the extra alcohol present. The other is that β-keto thioesters are not thermally stable and generate acylketenes much faster than β-keto esters. Thus, under these conditions, compound 317 is not observed even after only 1.5 half lives of 305. It should be stressed that compound 317 can be made by addition to acylketene, just not in the presence of another nucleophile.

**Scheme 309**

```
\[
\text{Scheme 309}
\]

```

```
\[
\begin{align*}
\text{305} & \quad 7 \text{ eq. } R^1\text{SH and } R^2\text{OH} \\
\text{R}^1 = \text{octyl, } R^2 = \text{dodecyl} \\
\text{toluene reflux} \\
\text{317} & \quad + \text{R}^2\text{OH} \\
\text{313} & \quad \text{R}^2\text{OH} \\
\text{ratio 317 : 313} & \quad \\
\end{align*}
\]

```

80
The next phase of the competition experiments involved the selectivity of primary and secondary alcohol trapping, and the reactivity of diols. First, the relative rates of primary and secondary β-keto ester formation were found by competition with 1-pentanol and 2-hexanol under a variety of conditions to obtain β-keto esters 318 and 319 (Scheme 310). The results are summarized in Table 6.

**Scheme 310**

![Scheme 310](image)

**Table 6 – Kinetic Trapping of 1-Pentanol and 2-Hexanol by Acylketene**

<table>
<thead>
<tr>
<th>1° to 2° ratio</th>
<th>conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 to 1</td>
<td>110 °C, toluene, ~0.1 M alcohols</td>
</tr>
<tr>
<td>2.0 to 1</td>
<td>110 °C, toluene, ~0.01 M alcohols</td>
</tr>
<tr>
<td>2.0 to 1</td>
<td>80 °C, benzene, ~0.01 M alcohols</td>
</tr>
</tbody>
</table>

We then moved on to competitions using diols. Our first competition was with 1,2-butandiol 320. We wanted to see how the selectivity changes when the primary and secondary alcohol are part of the same molecule. We performed this competition under various conditions, giving β-keto esters 321 and 322 as products (Scheme 311). The results are summarized in Table 7.

**Scheme 311**

![Scheme 311](image)

**Table 7 – Kinetic Trapping of 1,2-Butanediol by Acylketene**

<table>
<thead>
<tr>
<th>1° to 2° ratio</th>
<th>conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9 to 1</td>
<td>110 °C, toluene, ~0.1 M alcohol</td>
</tr>
<tr>
<td>2.9 to 1</td>
<td>110 °C, toluene, ~0.005 M alcohol</td>
</tr>
<tr>
<td>2.9 to 1</td>
<td>80 °C, benzene, ~0.005 M alcohol</td>
</tr>
</tbody>
</table>

Our next diol tested was 1,3-butandiol 323. We believed that the primary alcohol in the 1,3-diol would react significantly faster than that of the 1,2-system. Our reasoning
was the following: the secondary alcohol is a better H-bond donor than the primary alcohol, and by accepting the H-bond the primary alcohol bears a partial positive charge. Thus its own O-H bond will be weakened accordingly. Since the 1,2-diol is only weakly H-bound, this effect will be minimized. Energy minimizations at the HF 6-31G level of theory indicate the energy minimum for 1,2-butanediol has the hydroxyls antiperiplanar, while 1,3-butanediol is H-bound, as expected (Figure 8).

**Figure 8 – Energy Minima of 1,2-Butanediol and 1,3-Butanediol**

The products of the competition of 323 with acylketene were β-keto esters 324 and 325 (Scheme 312). The results of these competitions are summarized in Table 8.

**Scheme 312**

<table>
<thead>
<tr>
<th>1° to 2° ratio</th>
<th>conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 to 1</td>
<td>110 °C, toluene, ~0.1 M alcohol</td>
</tr>
<tr>
<td>2.8 to 1</td>
<td>110 °C, toluene, ~0.005 M alcohol</td>
</tr>
<tr>
<td>2.8 to 1</td>
<td>80 °C, benzene, ~0.1 M alcohol</td>
</tr>
<tr>
<td>2.9 to 1</td>
<td>80 °C, benzene, ~0.005 M alcohol</td>
</tr>
</tbody>
</table>

*Table 8 – Kinetic Trapping of 1,3-Butanediol by Acylketene*

We found that the reactivity of the primary and secondary alcohols were almost identical in the 1,2-diol and 1,3-diol case, suggesting that either our H-bond activation hypothesis is incorrect, or that H-bonding at these elevated temperatures is negligible.
The first promising results of H-bond activation of an alcohol came during a competition of syn and anti 2,4-pentanediol, 326 and 327 respectively (Scheme 313). We found a preference for the addition of the more strongly H-bound syn diol. The syn diol is more strongly H-bound than the anti diol, since both of its methyl groups are equatorial in its H-bound chair formation. The anti diol has a destabilizing axial methyl group in its H-bonded chair. The differential H-bonding of these diols shows up in their NMR spectra. In CDCl₃ the O-H protons of the syn diol 326 have a chemical shift of 3.4 ppm, as opposed to 2.9 ppm for the anti diol 327. The products of this competition were β-keto esters 328 and 329. Results are summarized in Table 9.

### Scheme 313

![Scheme 313](image)

<table>
<thead>
<tr>
<th>syn to anti ratio</th>
<th>conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 to 1</td>
<td>110 °C, toluene, ~0.1 M alcohols</td>
</tr>
<tr>
<td>1.8 to 1</td>
<td>80 °C, benzene, ~0.1 M alcohols</td>
</tr>
</tbody>
</table>

To probe the issue of acylketene formation from β-keto thioester 317, it was used in place of 305 in the toluene experiment from Scheme 313. It was found that the ratio of 328/329 in toluene was the same, suggesting a common intermediate (acylketene). After 20 minutes of heating at 110 °C, ca. 33% conversion from 317 to 328/329 had occurred, meaning the half-life of 317 is comparable (but slower) than dioxinone 305.

Since the selectivity of addition in the diol systems was not what we had initially hoped for, we looked for other methods of generating acylketene from 1,3-dioxin-4-ones. Acylketenes can be generated from 1,3-dioxin-4-ones by UV irradiation. The primary use in the literature has been photolysis to form and trap acylketene in kinetic studies.³⁹ Photochemical generation intrigued us for several reasons. The first is that it could provide a non-thermal method of acylketene formation, which should provide greater selectivity.
due to the lower temperatures that could be used. The second is that the reversibility of \( \beta \)-keto esters to acyketenes should be eliminated, and lastly a wider range of low boiling solvents could be used.

Synthetic applications of this process are rare, an example being irradiation of 305 at 254 nm in ethanol to produce ethyl acetoacetate in 40% yield.\(^{75}\) The more well known and well explored photochemistry of 1,3-dioxin-4-ones is [2+2] cycloadditions with alkenes, which occurs at 300 nm, giving substituted dioxinones 330 (Scheme 314).\(^{76}\)

**Scheme 314**

![Scheme 314](image)

We began our investigation into this process by irradiating 305 at 300 nm in varying types of glassware. Kimax, pyrex, borosilicate glass, and quartz showed no formation of \( \beta \)-keto ester when irradiated in the presence of alcohols. Irradiation at 254 nm in acetonitrile or \( n \)-pentane gave \( \beta \)-keto esters, but also other unidentified products. Competitions using 1,2-butanediol and 1,3-butanediol gave primary to secondary ratios of 3.3 and 2.8 to 1, respectively, yet with other unidentified products present.

The usefulness of this esterification reaction is limited by competing [2+2] cycloadditions when alkenes are present. We performed a photolysis of 305 with 3-buten-1-ol at 254 nm in acetonitrile (Scheme 315). The reaction gave desired \( \beta \)-keto ester 331, but also 332 and 333 as major products. The regio and stereochemistry of the unwanted cycloaddition products was not assigned.

**Scheme 315**

![Scheme 315](image)

In summary, the competition studies described here seem to reinforce the concerted nature of the addition of hydroxylic nucleophiles to acyketene. While we were
successful in our studies, we did not hit upon a result that breaks significant new ground in the area, and as a consequence these studies remain unpublished.

3.4 Experimental Section

\[
\begin{align*}
\text{Me} & \quad \text{dodecanol (10 equiv, 0.15 M)} \\
312 & \quad \text{or 5 equiv, 0.07 M} \\
\text{toluene 110 °C} & \quad \text{313}
\end{align*}
\]

**Thermal transesterification of methyl acetoacetate (312) to dodecylacetoacetate (313)**

At 0.15 M

In a 100 mL flask, toluene (50 mL), 312 (0.088 g, 0.76 mmol), and dodecanol (1.40 g, 7.53 mmol, 10 equivalents) were added. The flask was fitted with a reflux condenser, refluxed, and aliquots were taken from the reaction mixture at 30, 60, 120, and 180 minutes. Conversions were determined by \(^1\)H NMR by comparison of the peak at 4.14 ppm of 313 vs. remaining dodecanol (3.64 ppm). Relative integrations of 313 to dodecanol for each time point were 1:28.2 (34%), 1:15.6 (60%), 1:10.6 (86%), and 1:9.2 (98%).

At 0.07 M

In a 100 mL flask, toluene (53 mL), 312 (0.087 g, 0.75 mmol), and dodecanol (0.700 g, 3.76 mmol mmol, 5 equivalents) were added. The flask was fitted with a reflux condenser, refluxed, and aliquots were taken from the reaction mixture at 30, 60, 120, and 180 minutes. Conversions were determined by \(^1\)H NMR by comparison of the peak at 4.14 ppm of 313 vs. remaining dodecanol (3.64 ppm). Relative integrations of 313 to dodecanol for each time point were 1:14.6 (32%), 1:7.87 (56%), 1:5.11 (82%), and 1:4.3 (94%).

---

\[
\begin{align*}
\text{O} & \quad \text{O} \\
305 & \quad \text{R}^1\text{NH}_2 \text{ and } \text{R}^2\text{OH} \\
\text{toluene reflux} & \quad \text{314} \\
\text{314 : 315} & \quad \text{ratio 314 : 315} \\
& \quad 1 : 3.8 \text{ at 30 min} \\
& \quad 1 : 4.1 \text{ at 60 min}
\end{align*}
\]

**Competitive Formation of 314 and 315**
In a 100 mL flask, toluene (50 mL), 305 (0.0541 g, 0.381 mmol), dodecanol (0.527 g, 2.83 mmol), and octylamine (0.374, 2.90 mmol) were added. The flask was fitted with a reflux condenser, refluxed, and aliquots were taken from the reaction mixture at 30 and 60 minutes. Conversions were determined by $^1$H NMR by comparison of the peak at 3.13 ppm for substrate 315 and 4.01 ppm for substrate 314. Relative integrations of 314 to 315 were 1 : 3.8, and 1 : 4.1 for each time point.

Competitive Formation of 313 and 316

In a 100 mL flask, toluene (50 mL), 305 (0.0512 g, 0.360 mmol), dodecanol (0.514 g, 2.76 mmol), and dipentylamine (0.447 g, 2.85 mmol) were added. The flask was fitted with a reflux condenser, refluxed, and aliquots were taken from the reaction mixture at 30 and 60 minutes. Conversions were determined by $^1$H NMR by comparison of the peak at 4.14 ppm for substrate 313 and 3.18 ppm for substrate 316. Relative integrations of 313 to 316 were 1 : 1.8, and 1 : 2.2 for each time point.

S-octyl 3-oxobutanethioate (317)

In a 5 mL vial 305 (1.05 g, 7.39 mmol) and octanethiol (1.09 g, 7.46 mmol) were added. The vial was microwaved in a 600W Emerson commercial microwave for 5 minutes. After allowing the reaction mixture to cool, $^1$H NMR analysis showed complete conversion to 317.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 12.7 (q, $J = 0.6$ Hz, 1H, enol –OH), 5.43 (q, $J = 0.6$ Hz, 1H, vinylic enol –CH), 3.66 (s, 2H), 2.92 (t, $J = 7.2$ Hz, 2H), 2.91 (t, $J = 7.2$ Hz, 2H,
enol form), 2.27 (s, 3H), 1.93 (dd, \(J = 0.6, 0.6\) Hz, 3H, enol –CH\(_3\)), 1.64-1.54 (m, 2H), 1.38-1.27 (m, 10H), 0.88 (t, \(J = 6.9\) Hz, 3H).

**Competitive Formation of 318 and 319**

In a 500 mL flask, toluene (200 mL), 305 (0.110 g, 0.775 mmol), 1-pentanol (0.686 g, 7.97 mmol), and 2-hexanol (0.793, 7.77 mmol) were added. The flask was fitted with a reflux condenser, and refluxed for 40 minutes. Conversions were determined by \(^1\)H NMR by comparison of the peak at 4.14 ppm for substrate 318 and 4.96 ppm for substrate 319, giving a ratio of 2.1 to 1 for 318 : 319.

**Competitive Formation of 321 and 322**

In a 250 mL flask, toluene (70 mL), 305 (0.005 g, 0.04 mmol), and 320 (0.031 g, 0.34 mmol) were added. The flask was fitted with a reflux condenser, and refluxed for 75 minutes. Conversions were determined by \(^1\)H NMR by comparison of the peak at 4.97 ppm for substrate 321 and 4.24 ppm for substrate 322, giving a ratio of 1 to 2.9 for 321 : 322.

**Competitive Formation of 324 and 325**

In a 250 mL flask, toluene (70 mL), 305 (0.005 g, 0.04 mmol), and 320 (0.031 g, 0.34 mmol) were added. The flask was fitted with a reflux condenser, and refluxed for 75 minutes. Conversions were determined by \(^1\)H NMR by comparison of the peak at 5.17
ppm for substrate 324 and 4.4 ppm for substrate 325, giving a ratio of 1 to 2.8 for 324 : 325.

Competitive Formation of 324 and 325

In a 250 mL flask, toluene (70 mL), 305 (0.102 g, 0.718 mmol), and 326/327 (0.763 g, 7.33 mmol) were added. The flask was fitted with a reflux condenser, and refluxed for 40 minutes. Conversions were determined by $^1$H NMR by comparison of the peak at 5.16 ppm for substrate 328 and 5.07 ppm (as judged by an authentic sample) for substrate 329, giving a ratio of 1.5 to 1 for 328 : 329.

Competitive Formation of 324 and 325

In a 25 mL flask, toluene (5 mL), 317 (0.0842 g, 0.366 mmol), and 326/327 (0.405 g, 3.89 mmol) were added. The flask was fitted with a reflux condenser, and refluxed for 20 minutes. Conversions were determined by $^1$H NMR by comparison of the peak at 5.16 ppm for substrate 328 and 5.07 ppm (as judged by an authentic sample) for substrate 329, giving a ratio of 1.5 to 1 for 328 : 329. At 20 minutes, ca. 33% conversion from 317 to 328/329 had occurred.
Chapter IV

Optimizing the Magnesium Halide Catalyzed anti-Aldol Reaction Leads to the Discovery and Development of a Novel Decarboxylative Isomerization.
4.1 Methods of anti-Aldol Formation

The stereoselective aldol reaction is one of the most important reactions for C-C bond formation. Our initial interest in the aldol reaction stemmed from the fact that we could potentially use it to make the northern fragment of the lyngbyaloside B aglycon. The vast majority of aldol reactions in the literature are syn selective, however, we required anti. Each method of synthesis of anti aldols has its virtues and deterrents.

Ghosh has developed the auxiliary 401. Its titanium enolate gives good anti selectivity (402) for both enolizable and non-enolizable aldehydes (Scheme 401). The deterrent to its use is the low yields obtained (crotonaldehyde gives a 41% yield) and the fact that the auxiliary takes 10 steps to make, including an enzymatic resolution step.

Scheme 401

Masamune has developed the norephedrine-based auxiliary 403 (Scheme 402). While the scope of aldehydes that can be used is good, the auxiliary requires commercially unavailable mesitylene sulfonyl chloride to make. Additionally, commercially unavailable dicyclohexyl boryl triflate is required to make the enolate. While anti-selective when dicyclohexyl boryl triflate is used (cf. 404), other dialkyl boryl triflates give significantly worse yields and often give syn adducts as the major products (dibutylboryl triflate gives a 87:13 syn:anti ratio with isobutyraldehyde).

Scheme 402

Kurosu has developed the norephedrine-based auxiliary 405 (Scheme 403). Results with this auxiliary (406) are inconsistent due to its high moisture sensitivity, and the
wide range of selectivities that are observed over a relatively small range of catalyst loadings. Because the selectivities were not what we desired, and the required reagents are expensive, this auxiliary was given little consideration.

**Scheme 403**

Oppolzer developed the sultam-based auxiliary 407 (Scheme 404). During this method a boron enolate is made, then reacted with a titanium tetrachloride/aldehyde mixture. This method gives good selectivities, but requires an auxiliary that is not readily available, the extremely moisture sensitive diethylboron triflate, and the use of 2 equivalents of aldehyde. Crotonaldehyde has been used with this auxiliary to give a 60% isolated yield of product 408.

**Scheme 404**

Wessjohan developed a chromium-Reformatsky method based on compound 409 (Scheme 405). This reaction gives decent anti selectivity (77-95%), and good yields (88-96%) of 410. Only two aldehydes were tested, benzaldehyde and isobutyraldehyde. Their explanation about how their previous assignments were incorrect did not fill us with confidence, otherwise this seems to be an attractive method.

**Scheme 405**
Heathcock developed methods using boron enolates of oxazolidinones 411 and 412, giving anti aldol adducts 413 and 414, respectively (Scheme 406). The boron enolate of the oxazolidinone is used in conjunction with Lewis acid complexed aldehydes. This method works well with the valine and t-leucine based auxiliaries but is reported to not work as well with the phenylalanine-based auxiliary that we had in our lab.

**Scheme 406**

\[
\begin{align*}
\text{Bu}_2\text{BOTf, } & \text{i-PrEtN;} \\
\text{Et}_2\text{AlCl/R}_2\text{CHO complex} & \rightarrow \\
\text{R}^1 = \text{i-Pr} & \text{ 411} \\
\text{R}^1 = \text{t-Bu} & \text{ 412} \\
\text{R}^1 = \text{i-Pr} & \text{ 413} \\
\text{R}^1 = \text{t-Bu} & \text{ 414}
\end{align*}
\]

Evans used the 2-benzyloxazolidinone auxiliary 415 to perform a magnesium halide-catalyzed anti aldol reaction, giving 410 (Scheme 407). This method has many advantages over the other aldol methods. The auxiliary can be made by a trivial acylation step on the commercially available oxazolidinone. The other reagents required are readily available and inexpensive, and the reaction can be performed at room temperature. An added bonus is that silylated aldol adducts are formed, allowing easy determination of diastereomeric ratios by gas chromatography. Unprotected aldol adducts undergo retro aldol reaction upon attempted GC analysis.

**Scheme 407**

\[
\begin{align*}
\text{Bn} & \text{Me} \\
\text{RCHO, } & \text{MgCl}_2, \text{Et}_3\text{N} \\
\text{TMSCl, EtOAc} & \rightarrow \\
\text{TFA, MeOH} & \rightarrow \\
\text{R} & \text{ 410}
\end{align*}
\]

The disadvantage to this method is the substrate scope, as shown in Scheme 408. Only non-enolizable aldehydes are suitable using the conditions Evans discloses. The reason is that enolizable aldehydes are not stable to the reaction conditions. While this was initially discouraging, it was looked upon as an opportunity. Our goal became to expand the scope of the reaction to allow for synthetically useful yields of anti aldols of enolizable aldehydes.
Scheme 408

![Scheme 408](image)

The aldolate 410, which can reversibly add to an aldehyde. The aldolate 418 is trapped by trimethylchlorosilane, giving adduct 419. Decomplexation of magnesium chloride gives anti aldol adduct 420 and regenerates the catalyst.

Scheme 409

![Scheme 409](image)

Evans discloses several details about the reaction. Among them: TMSCl is necessary to turn over the reaction to regenerate the catalyst. Other silylating agents were reported to give lower yields or diastereoselectivity. MgCl₂ and MgBr₂ gave better con-
versions and/or selectivity than Mg(TfO)$_2$, Mg(NTf$_2$)$_2$, and Mg(ClO$_4$)$_2$. Ethyl acetate was found to be the best solvent for the reaction, but THF is also satisfactory. Other amine bases are reported to not work as well as triethylamine. The % conversion of less reactive aldehydes can be increased by using the additive NaSbF$_6$. The reaction does not appear to be a Mukaiyama aldol reaction, since the silyl enol ether of 415 is never observed, and an independently made sample was inert under the reaction conditions. The stereoselectivity of the reaction comes from a boat transition state being favored over the chair.

4.2 Exploring and Optimizing the Evans Magnesium-Halide Catalyzed anti-Aldol Reaction for Enolizable Aldehydes

Our initial experiment using the Evans conditions was one of crossover. Using the conditions Evans describes and MgBr$_2$ as the catalyst, oxazolidinone 421 was reacted with both benzaldehyde and trans-cinnamaldehyde giving aldol adducts 422 and 423 respectively (Scheme 410). High conversions were observed by GC-MS analysis. Addition of cinnamaldehyde to the reaction containing 422 did not result in formation of adduct 423. This was good for our cause, since it showed that the silylation was irreversible under the reaction conditions. If silylation was reversible, then the reaction with enolizable aldehydes would likely be impossible, since upon desilylation and retro aldol, the aldehydes would be consumed under the reaction conditions.

Scheme 410

Our initial attempt using an enolizable aldehyde, crotonaldehyde, was of limited success (Scheme 411). Some desired adduct 424 could be isolated, but primarily starting material 421 remained. The aldehyde was consumed in the reaction, with $^1$H NMR analy-
sis giving evidence for formation of silyl enol ether, presumably through coordination with MgBr$_2$, deprotonation of the gamma proton, and silylation by TMSCl. Although this was disappointing, it was still an exciting result because it showed that the desired transformation was not impossible.

**Scheme 411**

In order to help us understand why the aldehydes were being consumed, a series of control experiments were run to judge their stability to various conditions. When crotonaldehyde was placed with MgBr$_2$ in ethyl acetate, no reaction occurred. When crotonaldehyde was placed with both triethylamine and TMSCl in ethyl acetate, ~80% of the starting material remained after 12 hours. It wasn’t until crotonaldehyde was incubated with MgBr$_2$, TMSCl, and triethylamine in ethyl acetate that the aldehyde was rapidly consumed. One thing became clear from these results: in order to obtain a good yield, the aldehyde must be subjected to the reaction conditions in a controlled fashion.

Evans disclosed that the addition of NaSbF$_6$ gave increased % conversion in the cases of slow reacting aldehydes.$^{85}$ We considered that this additive could be advantageous to reactions with enolizable aldehydes as well, and this was indeed the case (Scheme 412). When 421 was subjected to the magnesium chloride catalyzed conditions below, the addition of NaSbF$_6$ increased % conversion to 424 from 25% to 45% with no other changes to the reaction conditions. The additive is likely precipitating chloride ion that is being generated in the reaction, although we cannot rule out that it has another role as well.
Since the aldehyde is not stable to the reaction conditions, it was reasoned that we should attempt to speed up the reaction as much as possible. To do that, we used more magnesium chloride - a full equivalent (Scheme 413). This would hopefully ensure that there was always a reasonable amount of magnesium enolate present. Additionally, the role of TMSCl was further probed. We set up three reactions using 421, all the same except for the time at which TMSCl was added. In the first, TMSCl was present from the outset. In the second, TMSCl was added 10 minutes after the addition of aldehyde. In the third, it was added 30 minutes later. We found that the longer the addition of TMSCl was delayed, the lower the % conversion to 424. This is understandable, since without TMSCl, aldolate formation is reversible, and the aldehyde is not stable to the reaction conditions. Additionally, it was found that the diastereomeric ratio was lower upon waiting to add the TMSCl. This would be the case if silylation were the rate limiting step, and if the desired anti adduct was silylated the fastest of the four possible diastereomers, yet was not the most stable.
Because some of the aldehyde was inevitably going to be consumed via silylation and because silylation is critical to turn the reaction over, it was reasoned that increasing the amounts of aldehyde and TMSCl in the reaction mixture would lead to a more efficient reaction. Additionally, it was reasoned that adding the aldehyde slowly would be advantageous, since there is only a limited amount of magnesium enolate present any moment in time. This ensures that the enolate to aldehyde ratio will remain high during the reaction. Indeed, syringe pump addition of the aldehyde to 421 led to the highest % conversions observed up to that point (Scheme 414). Diastereomeric purity of 424 was also increased, likely because we are speeding up the rate-limiting step by having more TMSCl present, and that the kinetic aldolate is the desired one. When the same reaction was performed at 0 °C, the results were much worse. Conversions were lower, and diastereomeric purity suffered. This is consistent with the lower temperature slowing down the rate limiting step, allowing for reversible aldolate formation, leading to more of the undesired thermodynamic isomers. Since THF was reported by Evans to work for the reaction, it was tried as well. Conversions and selectivities were not as high.

**Scheme 414**

Now that we had our first reasonably good result, we went back to look at the NaSbF₆ additive again, the hope being that it wouldn’t be necessary using our new conditions (421 to 424, Scheme 415). It was found that removal of NaSbF₆ led to significantly worse conversions. We found there was no added benefit to using more than 0.5 equivalents of the additive, as 1.0 and 1.5 equivalents gave essentially the same results.
was not particularly moisture sensitive. Water that was present was probably consumed

![Scheme 416](image)

Although we knew we could get decent results with 1 equivalent of magnesium chloride, we sought to lower the catalyst loadings. As shown in Scheme 416, this task proved a difficult one. Lowering the catalyst loading to 60% resulted in significantly worse conversion of 421 to 424. A full equivalent of magnesium bromide was found to be inferior as well, giving only 41% conversion. An attempt with calcium chloride as the Lewis acid gave no product.

![Scheme 416](image)

An advantage to the conditions we had developed thus far was that the reaction was not particularly moisture sensitive. Water that was present was probably consumed
by the excess TMSCl, which is a nice feature of the chemistry. We performed the reaction several times, adding water on purpose to observe if and how moisture-sensitive the reaction was (Scheme 417). We found that we could achieve good conversions of 415 to 425 after adding up to 0.5 equivalents of water to the reaction mixture. Since this is far more water than would be available from a non-predried solvent, we can comfortably say that the reaction is not moisture sensitive.

**Scheme 417**

<table>
<thead>
<tr>
<th>equiv. water added</th>
<th>conversion</th>
<th>diastereomeric purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>none</td>
<td>96%</td>
<td>90%</td>
</tr>
<tr>
<td>0.25 equiv.</td>
<td>89%</td>
<td>91%</td>
</tr>
<tr>
<td>0.5 equiv.</td>
<td>87%</td>
<td>90%</td>
</tr>
<tr>
<td>0.5 equiv.</td>
<td>87%</td>
<td>90%</td>
</tr>
<tr>
<td>0.5 equiv.</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>1.0 equiv.</td>
<td>53%</td>
<td>88%</td>
</tr>
<tr>
<td>1.5 equiv.</td>
<td>37%</td>
<td>87%</td>
</tr>
</tbody>
</table>

The impact of our modification to the Evans conditions is shown below using hexanal as the aldehyde (Scheme 418). Under the Evans conditions, only 5% conversion

**Scheme 418**

**421**

**426** 5% conversion

80% conversion 90% desired diastereomer
is obtained from 421 to 426 even after extended reaction time. Our modifications give 80% conversion.

While our modifications to the Evans procedure (increased MgCl₂, increased TMSCl, increased amount of aldehyde, syringe pump addition of aldehyde, 0.5 equiv NaSbF₆) were successful for crotonaldehyde, there was still a significant barrier towards getting other non-enolizable aldehydes to work in the reaction, the biggest problem being aldehydes that were α-branched. As shown below, isobutyraldehyde gave only 25% conversion of 415 to 427 when using our conditions (Scheme 419). In an attempt to increase the conversions, different solvents and solvent mixtures were used. Triethylamine, DMSO, DCM, DMF, ACN, DMPU, acetone, and diglyme were used, all with no success. Mixed solvent systems using 3:1 EtOAc/DMSO, 3:1 EtOAc/DMF, and 3:1 EtOAc/DMPU also gave no conversion. It should be noted that the reasons for the failure of the reaction are not necessarily the same for each solvent tried. If any step along the reaction pathway is shut down, then no conversion will be observed.

**Scheme 419**

<table>
<thead>
<tr>
<th>solvent (0.5 M)</th>
<th>conversion</th>
<th>diastereomeric purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOAc</td>
<td>25%</td>
<td>85%</td>
</tr>
<tr>
<td>NEt₃</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>DMSO</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>&lt;1%</td>
<td>--%</td>
</tr>
<tr>
<td>DMF</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>DMPU</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>Acetone</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>diglyme</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>EtOAc/DMSO (3:1)</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>EtOAc/DMF (3:1)</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>EtOAc/DMPU (3:1)</td>
<td>0%</td>
<td>--%</td>
</tr>
</tbody>
</table>

Since the only solvent that worked in the reaction was an ester, other ester containing solvents were tried (Scheme 420). Ethyl trifluoroacetate, methyl methacrylate,
methyl 2-methoxyethanoate, butyrolactone, and diethyl furan-3,4-dicarboxylate gave no conversion of 415 to 427. In the case of methyl methacrylate, extensive polymerization occurred.

**Scheme 420**

![Scheme Diagram]

Other additives were used (Scheme 421). In place of NaSbF$_6$ we examined AgSbF$_6$, LiPF$_6$, LiAsF$_6$, NaBF$_4$, and K$_2$SO$_4$. All the additives tried were inferior to NaSbF$_6$ in converting 415 to 427.

**Scheme 421**

<table>
<thead>
<tr>
<th>Additive</th>
<th>conversion</th>
<th>diastereomeric purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaSbF$_6$ (0.5 equiv.)</td>
<td>25%</td>
<td>85%</td>
</tr>
<tr>
<td>AgSbF$_6$ (1.1 equiv.)</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>LiPF$_6$ (1.0 equiv.)</td>
<td>3%</td>
<td>86%</td>
</tr>
<tr>
<td>LiAsF$_6$ (1.0 equiv.)</td>
<td>9%</td>
<td>83%</td>
</tr>
<tr>
<td>NaBF$_4$ (1.1 equiv.)</td>
<td>0%</td>
<td>--%</td>
</tr>
<tr>
<td>K$_2$SO$_4$ (1.1 equiv.)</td>
<td>5%</td>
<td>85%</td>
</tr>
</tbody>
</table>
Since we believed that silylation was the rate determining step in the reaction, we sought to enhance the reactivity of the silylating agent. This was accomplished by adding various additives. LiBr, NaBr, LiI, NaI, AgSO$_3$CF$_3$, and NaSO$_3$CF$_3$ were used (Scheme 422). Another consequence of these additives is that the nature of the MgCl$_2$ will change. For example, addition of iodide should generate in situ some MgClI and MgI$_2$. This could potentially have been of benefit to the reaction. Of the additives, only LiI resulted in a conversion of 415 to 427 higher than 10%. LiI was also promising because the observed diastereomeric purity was increased vs. when it was omitted from the reaction mixture.

**Scheme 422**

![Scheme 422 Diagram]

Since lithium iodide was the most promising additive used, it was decided to use more of it (Scheme 423). As the loadings were increased, conversion from 415 to 427 also **Scheme 423**

![Scheme 423 Diagram]
increased, but with formation of a new byproduct.

To probe the origin of this byproduct, control experiments were run. Using the same conditions as in Scheme 424 but omitting the aldehyde resulted in no reaction. When pure aldol adduct 424 was subjected to the reaction conditions, the oxazoline 428 was formed (Scheme 78). While the formation of this byproduct is interesting, we sought to minimize it to give the best possible yields of aldol adduct.

**Scheme 424**

![Scheme 424](image)

Since we knew that oxazolines were being formed from their corresponding aldol adducts, we decided to limit the reaction time. The best result is shown in Scheme 425. We found that an increased concentration and shorter reaction time led to the highest conversion of desired product while minimizing the undesired oxazoline byproduct 429 based on GC measurements of conversion of 415 to 427 and 429.

**Scheme 425**

![Scheme 425](image)

This first pass of conditions optimization was successful, but limitations still were present. Notably, it was still necessary to use 3 equivalents of aldehyde and sluggish reac-
tivity was still a problem with other enolizable aldehydes. Our efforts to further understand and optimize the conditions to be practical led us to measure product formation over time using an internal standard. For this study we used crotonaldehyde as the electrophile and tetradecane as the internal standard. Conversion was measured (peak integration) vs. both the starting material and the internal standard by GC analysis. Comparisons over time (2 hour addition time) showed that the ratio of product 425 to standard maximized at 2 hours, decreased afterwards, suggesting that the product is not stable to the reaction conditions over extended periods of time (Scheme 426). The ratio of starting material 415 to standard also decreased over time, as expected, however since the ratio of product to standard decreases over time, the rate of loss of product (bad) wins out over the rate of formation of product from the starting material (good). Without an internal standard, one could be tricked into thinking yields are improving over time, since the product to starting material ratio keeps getting larger over time. The ultimate moral of the story is that the reactions shouldn’t go any longer than the addition time of the aldehyde, provided it is added slowly enough to react efficiently. This knowledge already made the previous conditions obsolete.

**Scheme 426**

![Scheme 426](image)

Used internal standard to measure conversion vs addition time (2 hour addn)

<table>
<thead>
<tr>
<th>time (h)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4.5</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>standard</td>
<td>31%</td>
<td>29%</td>
<td>31%</td>
<td>34%</td>
<td>42%</td>
</tr>
<tr>
<td>S.M.</td>
<td>25%</td>
<td>17%</td>
<td>16%</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Products</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>S.M./std</td>
<td>0.81</td>
<td>0.59</td>
<td>0.52</td>
<td>0.41</td>
<td>0.26</td>
</tr>
<tr>
<td>Prod/std</td>
<td>1.39</td>
<td>1.48</td>
<td>1.39</td>
<td>1.23</td>
<td>1.00</td>
</tr>
<tr>
<td>Prod/S.M.</td>
<td>1.72</td>
<td>2.53</td>
<td>2.68</td>
<td>3.0</td>
<td>3.8</td>
</tr>
</tbody>
</table>

We also became interested in exploring whether alternative bases could lead to improved yields and/or selectivities (Scheme 427). The bases DABCO, Hunig’s base, TMEDA, 1-methylimidazole, DMAP, hexamethylenetetramine, DBN, DBU, proton
sponge, 4-methylmorpholine, tetramethylguanidine, and pyridine were used in the conversion of 415 to 425. None of the bases used improved upon the conversions or selectivities of triethylamine.

**Scheme 427**

We also were intrigued by the possibility that an alternative trapping agent could be more efficient than TMSCl. Screening commenced of the reagents dimethylchlorosilane, trimethylsilyl cyanide, trimethylsilyl azide, hexamethyldisilazane, trimethylsilylthiocyanate, trimethylsilylimidazole, N,N'-bis trimethylsilyl urea, bis trimethylsilyl trifluoroacetamide, trimethylsilyl urea, phenylselenyl chloride, tosyl chloride, trifluoromethanesulfonyl anhydride, trifluoroacetic anhydride, methanesulfonyl chloride, bisdimethylaminophosphorochloridate, diethylchlorophosphonate, and 2,4-dinitrobenzenesulfonyl chloride (Scheme 428). Only dimethylchlorosilane gave reasonable conversion of 415 to 425, but still a lower diastereomeric ratio than when TMSCl is used.
Also intriguing was the thought of an alternative metal providing a more efficient or selective reaction. Using benzaldehyde as the trapping reagent, we screened the metals readily available in the Hoye lab using oxazolidinone 415 and benzaldehyde as the electrophile (Scheme 429). Many of the metals were only available as their hydrates, but they were tested anyway since TMSCl can act as a drying agent. Conversion to adduct 430 was measured by GC-MS.
Scheme 430

The results of the most successful of the metals studied are shown in Scheme 430 for the conversion of 415 to 430. The selectivities were not as high as the magnesium-catalyzed reactions, nevertheless these alternative metal catalyzed reactions were previously without precedent.

Scheme 430
During the metal screening it was found that several metals catalyzed the formation of a direct ethyl acetate/benzaldehyde coupling reaction, giving 431 in poor yield (Scheme 431). It was noted that this transformation could become valuable if optimized.

**Scheme 431**

Using magnesium bromide etherate in the absence of oxazolidinone gave the ester coupled product 431 as the major one by GC, but this reaction was not optimized further (Scheme 432). Noteworthy is the formation of trimethylsilylbenzyl alcohol 432 and trimethylsilylbenzoate 433 as byproducts. This process is magnesium bromide catalyzed, and is known.\textsuperscript{87}

**Scheme 432**

After the screening methods commenced, isolated yields were obtained for the conversion of 415 to its corresponding aldol adducts 434, 435, 436, and 437 (Scheme
We feel that these results could be important in other catalytic contexts, as soft enolization with these metals is likely to be facile with ketones, aldehydes, and thioesters.

Scheme 433

Ultimately, two sets of conditions were settled upon for the magnesium halide catalyzed conditions (Scheme 434). The first (conditions A) use N-acyloxazolidinone 415

Scheme 434
as a limiting reagent, and syringe pump addition of 3 equivalents of aldehyde, giving aldol adducts 410a-f. Alternatively, conditions B use limiting aldehyde and 2 equivalents of 415. Synthetically useful amounts of products can be attained by these methods, and yields are competitive with other anti-aldol methods. 77,78,80,81,83,84,85,86

4.3 Development of the Iodide-Catalyzed Decarboxylative Isomerization Reaction

We were able to modify the Evans anti aldol conditions to give synthetically useful amounts of product from enolizable aldehydes. Our attention then turned towards studying the formation of the oxazoline byproduct that was unexpectedly formed when lithium iodide was used as an additive. Our initial mechanistic proposal is outlined in Scheme 435. We thought that the addition of lithium iodide to magnesium chloride generated in situ the highly reactive magnesium iodide. Coordination between the carbonyls of oxazolidinone 410 would lead to intermediate 438 that was activated towards nucleophilic attack at the 5 position of the oxazolidinone by iodide, generating intermediate 439. We expected that this would decarboxylate, leading to intermediates 440 and 441. From there, N- or O- alkylation could occur, leading to acylaziridine 442 and oxazoline 443 respectively. Although we did not observe formation of aziridine 442, they are known to undergo isomerization in the presence of iodide salts to oxazolines 443 (the Heine rearrangement). 88
Before a detailed study was done on this reaction, we looked to the literature to see what was known in this area. We found three examples of cases where \( N \)-acyl oxazolidinones were converted to oxazolines. When oxazolidinone 444a (\( R = \) phenyl) was heated with a Bunsen burner in the presence of CaO, oxazoline 445a was obtained in 65% yield (Scheme 436).\(^8^9\) This method appears to have a limited substrate scope, since under the same conditions oxazolidinone 444b, having an ethyl instead of a phenyl group, gave a 66% yield of product 445b, and in only 25% purity. In another method, trifluoromethyl oxazolidinone 446 was rearranged to oxazoline 447 in 76% yield.\(^9^0\) This method was only applied to this particular compound. In another method, Cook performed a decarboxylative cyclization of 5-vinyl substituted oxazolidinones 448.\(^9^1\) This reaction proceeds via \( \pi \) allyl palladium intermediate 449 to give oxazolines 450. Yields and diastereoselectivity for this process are high, but this method requires a vinyl substituent at the 5-position to be successful. After looking at these examples, it seemed that the iodide induced decarboxylative cyclization could have advantages over them. We knew that we didn’t need to heat to high temperatures, and additionally, we weren’t limited by needing a particular substituent in the 5-position.
In initial optimization, we looked at various solvents and additives. Solvents that were screened were EtOAc, DCM, chloroform, 1,2-dichloroethylene, carbon tetrachloride, DMSO, DMF, THF, dioxane, DME, tBuOH, ACN, acetone, and toluene. Co-catalyst metals used were magnesium chloride, calcium chloride, and barium chloride. Additional co-catalysts used were TMSCl, tetra n-butyl ammonium iodide, and sodium hexafluoroantimonate. After screening these conditions, it was found that DCM was the best solvent (as measured by conversion by GC-MS), and that other co-catalysts were not necessary, only lithium iodide was required.

Problems with these conditions were observed when the product was attempted to be isolated (Scheme 437). Using oxazolidinone 451 as the starting material, instead of isolating oxazoline 452 (which is observed by GC), we isolated the iodide-attached amide 453. This iodo compound was unstable and closed to oxazoline 452 upon GC-MS, ESI analysis, and LCMS. We found that addition of bases (e.g. potassium tert-butoxide) to this iodo compound caused cyclization to the desired product.
Having the base present from the outset was met with limited success (Scheme 438). Although potassium tert-butoxide closed the iodo-attached amide 453, it also reacted with 451, generating deacylated starting material 454 and ester 455. Additionally, it was found that when the base (e.g. DBU, imidazole) was present from the outset, we did not obtain our desired product, instead the iodo-attached amide 453. When the order of events was changed, and base was not added until filtration through silica gel occurred, the desired oxazoline 452 was formed. These results strongly suggested that our initial mechanistic proposal was wrong.
The picture became clearer when we took oxazolidinone 451 and added LiI to a solution in chloroform (Scheme 439). $^1$HNMR analysis of the reaction mixture shows consumption of the starting material, but with no iodoamide 453 formed! This strongly suggests that the intermediate 456 is not decarboxylating under the reaction conditions, as 457 is not formed. Indeed, when a proton source is added to the reaction mixture (e.g. ammonium chloride), the iodo-attached amide 453 is formed. Thus, decarboxylation is not occurring until intermediate 456 becomes protonated. Addition of a base then caused closure to oxazoline 452.

**Scheme 439**

Ultimately it was decided upon that ammonium chloride would be used as the proton source to induce decarboxylation, and that DBU would be added to afford the ring closure. This was done over two steps, because reaction times took longer if DBU was present from the outset, presumably due to the lower Lewis acidity of lithium when DBU was present. Results for aroyl substituents are recorded in Scheme 440. Substrates 451 and 458-460 were converted to oxazolines 452 and 461-463. Although the substrates were allowed to react for the same amount of time, substrate 459, having an electron-withdrawing nitro group reacted the fastest, and substrate 438, having an electron donat-
ing methoxy group reacted the slowest. These results were counterintuitive, since one may think that an electron donating substituent would allow the substrate to bind lithium better. While this may be true, the rate-limiting step for the ring-opening is iodide attack at the 5-position, not lithium binding, and substrate 438 is attacked more slowly than lithium-bound 459.

**Scheme 440**

![Scheme 440](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Compound #</th>
<th>yield (%)</th>
<th>Compound #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>451</td>
<td>76%</td>
<td>452</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>458</td>
<td>73%ᵇ</td>
<td>461</td>
</tr>
<tr>
<td>4-NO₂C₆H₄</td>
<td>459</td>
<td>45%</td>
<td>462</td>
</tr>
<tr>
<td>2-naphthyl</td>
<td>460</td>
<td>80%</td>
<td>463</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield after chromatography. ᵇ 8% recovered starting material.

Reaction rate:

4-NO₂C₆H₄ > Ph ~ 2-naphthyl > 4-MeOC₆H₄

We found that alkanoyl substituents also were successful in the cyclization, but required mild heating (50 °C) to occur at a useful rate (Scheme 441). Compounds 464-466 were converted to oxazolines 467-469. Noteworthy is that for the case of 464 ~10% recovered deacylation product was obtained. Apparently a very small R group allows iodide to attack the amide position directly. Deacylation was not observed with any other.

**Scheme 441**

![Scheme 441](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Compound #</th>
<th>yield (%)</th>
<th>Compound #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>464</td>
<td>62%ᵇ</td>
<td>467</td>
</tr>
<tr>
<td>Et</td>
<td>465</td>
<td>71%</td>
<td>468</td>
</tr>
<tr>
<td>ⁿPr</td>
<td>466</td>
<td>82%</td>
<td>469</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield after chromatography. ᵇ 10% recovered deacylation product.
substrates. Additionally, the example of the structurally more complex oxazolidinone 470 to oxazoline 471 was performed, affording a 69% yield. Noteworthy is that no epimerization of the α-proton occurred during either the decarboxylation or cyclization steps.

4.4 Extension of Decarboxylative Isomerization to Alternative Ring Systems

We sought to determine the scope of the lithium iodide initiated decarboxylation by using it to make other ring systems. Ring systems that were considered are shown in Scheme 442. We considered the following transformations: A) Could oxazolidinones lacking an acyl group, such as 454 and 472-473, be converted to an aziridines 474-476 after decarboxylation? B) Could a thioamide such as 477 be converted to thiazoline 478? C) Could carbamate and urea compounds 479 and 480 be converted to their corresponding 2-alkoxy or 2-amino oxazolines 481 and 482? D) Could the decarboxylative isomerization still be successful with a substituent in the 5-position, such as compound 483, giving rise to 5-substituted oxazoline 484? E) Could this methodology work to make 6-membered rings, such as carbamate 485 giving rise to oxazine 486?

Scheme 442

The attempts to obtain an aziridine were unsuccessful (Scheme 443). In the case of oxazolidinone 454, no reaction occurred under our conditions. The benzyl-attached oxazolidinone 472 gave only decomposition products under our conditions, no evidence for aziridine formation could be found. We were pleased to see that the tosyl-protected...
oxazolidinone 473 underwent ring opening to give 487 in 66% yield. Attempts to close this to an aziridine in the presence of DBU were unsuccessful however. We suspect that the intermediate aziridine is formed but that it is unstable and is ring opened by the base that is present.

Scheme 443

The synthesis of a thiazoline by decarboxylative isomerization was unsuccessful (Scheme 444). Oxazolidinone 451 was converted to its thioacyl derivative 488 by heating with P₂S₅. Unfortunately, we could not acquire the desired thiazoline upon application of our conditions. Starting material was very slowly consumed, but we could not find evidence for formation of the desired product. No isolable intermediates were formed, and the desired mass of thiazoline was not observed by GC-MS or ESI measurements.

Scheme 444

Attempts to make a 2-alkoxyoxazoline were not successful (Scheme 445). We were surprised to see that oxazolidinone 489 did not give desired product, but instead gave deacylated and decarboxylated starting material 454. The formation of methyl iodide was also observed in the ¹H NMR spectrum. The same behavior was observed for oxazolidinone 490, except that the reaction was much slower, requiring heating. No de-
desired product was detected by any spectroscopic or spectrometric method. The oxazolidinone 491 gave bizarre results. Upon addition of iodide, phenol was eliminated from the starting material (as compared to an authentic TLC standard), and ESI gave evidence of dimeric material. No evidence could be obtained that the reaction gave desired product.

**Scheme 445**

\[
\begin{align*}
\text{Scheme 445} \\
\text{Oxazolidinone 491} & \xrightarrow{\text{LiI, NH}_4\text{Cl; DBU, CDCl}_3, 75 \, ^\circ \text{C}, 2 \text{ days}} \text{Decomposition}
\end{align*}
\]

The formation of a 2-amino oxazoline was also troublesome (Scheme 446). Oxazolidinone 492 appeared to ring open to 493 as judged by \(^1\)H NMR spectroscopy, but no product could be isolated after addition of base. In the case of oxazolidinone 494, no evidence for the desired transformation could be obtained, even though starting material was consumed.

**Scheme 446**

\[
\begin{align*}
\text{Scheme 446} \\
\text{Oxazolidinone 492} & \xrightarrow{\text{LiI, NH}_4\text{Cl, CDCl}_3, 75 \, ^\circ \text{C}, 2 \text{ days}} \text{Decomposition}
\end{align*}
\]

It was found that substitution in the 5-position of the oxazolidinone effectively shut down the iodide initiated decarboxylation reaction (Scheme 447). Oxazolidinone
methyl substituted in the 5-position, gave no reaction in the presence of LiI at room
temperature. Upon heating the starting material slowly converted to baseline material by
TLC. The oxazinone substrate 496 was opened by LiI at r.t. to give 497 after addition of
DBU. Interestingly, some 498 was also formed during the reaction, coming from attack
of iodide at the 4-position instead of the 6-position of the oxazinone.

Scheme 447

A hierarchy of reactivity towards lithium iodide was assembled (Figure 9). The
fastest reacting substrates were those with N-aroyl substituents. Electron withdrawing
groups speed up attack by iodide, as para-nitro compound 459 reacted faster than phenyl
or naphthyl substituted compounds 451 and 460, which reacted at approximately the same
rate as oxazinone 496. para-Methoxy compound 458 reacted the slowest amongst the
aroyl substituted oxazolidinones. N-Tosyl oxazolidinone 473 reacted slower than the N-
aryl substituted compounds but faster than the N-alkyl compounds 464-466. Ring open-
ing of 492 was slower yet, and thiooxazolidinone 488 and 5-substituted 495 were essen-
tially inert to the reaction.
In summary, we developed a novel lithium iodide initiated decarboxylative isomerization of N-acyl oxazolidinones to 2-oxazolines. The method works well for both enolizable and non-enolizable N-acyl substituents and works as long as the 5-position is unsubstituted. These results complement the previous methods for this transformation by allowing significantly lower temperatures and improved substrate scope. Although other ring systems were not efficiently formed under these conditions, it still remains possible that conditions could be found in which they may.

4.5 Experimental Section

\[
\begin{align*}
\text{415} & \quad \xrightarrow{1)} \text{MgCl}_2, \text{LiI}, \text{Et}_3\text{N}, \text{TMSCl}, \text{EtOAc, syringe pump addition of enolizable aldehyde} \\
\text{410a} & \quad \xrightarrow{2)} \text{p-TsOH; MeOH}
\end{align*}
\]

\((S)-4\text{-benzyl-3-((2R,3R,E)-3-hydroxy-2-methylhex-4-enoyl)oxazolidin-2-one (410a)}^{95}\)

**Method A:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.100 g, 0.429 mmol), MgCl\(_2\) (0.042 g, 0.44 mmol), and LiI (0.116 g, 0.866 mmol) were
added. Ethyl acetate (0.85 mL), triethylamine (0.30 mL, 2.2 mmol) and TMSCl (0.22 mL, 1.7 mmol) were then added sequentially. After 10 minutes, crotonaldehyde (107 μL, 1.28 mmol) was diluted to 0.75 mL with ethyl acetate and added via syringe pump over three hours. The reaction mixture was analyzed by GC (~90% diastereomeric purity) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of p-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 0.086 g (66%) of 410a.

**Method B:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.200 g, 0.858 mmol), MgCl₂ (0.084 g, 0.88 mmol), and LiI (0.228 g, 1.70 mmol) were added. Ethyl acetate (1.7 mL), triethylamine (0.60 mL, 4.3 mmol) and TMSCl (0.44 mL, 3.4 mmol) were then added sequentially. After 10 minutes, a solution of crotonaldehyde (36 μL, 0.42 mmol, 0.49 equivalents) in 0.21 mL of ethyl acetate was added via syringe pump over one hour. The reaction mixture was analyzed by GC (~90% diastereomeric purity) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of p-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 0.086 g (66%) of 410a.

**1H NMR** (500 MHz, CDCl₃) δ 7.35-7.32 (m, 2H, ArH), 7.29-7.23 (m, 3H, ArH), 5.78 (ddq, J = 15.5, 6.5 × 3, 1.0 Hz, 1H), 5.54 (ddq, J = 15.0, 7.0, 1.5 Hz, 1H), 4.69 (dddd, J = 10.0, 7.5, 3.0, 3.0 Hz, 1H), 4.21 (dd, J = 9.0, 7.0 Hz, 1H), 4.16 (dd, J = 9.0, 3.0 Hz, 1H), 3.94 (app p, J = 7.0 Hz, 1H), 3.29 (dd, J = 13.5, 3.5 Hz, 1H), 2.78 (dd, J = 13.5, 9.5 Hz, 1H), 2.54 (s, 1H, -OH), 1.73 (dd, J = 6.5, 1.0 Hz, 3H), and 1.17 (d, J = 6.5 Hz, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 176.6, 153.7, 135.4, 131.7, 129.7, 129.3, 129.1, 127.5, 75.9, 66.2, 55.7, 43.5, 38.0, 17.9, 14.7.


**GC-MS** (silylated) tᵣ = 12.9 min; m/z: 375, 360, 305, 290, 285, 198, 183, 170, 155, 143, 117, 109, 91, 75, and 73.
IR (neat) 3518, 3029, 2976, 2920, 2883, 1782, 1695, 1502, 1455, 1392, 1349, 1257, 1211, 1103, 1014, 968, 923, 800, 762, and 702 cm$^{-1}$.

TLC $R_f = 0.47$ in 30% EtOAc in hexanes.

Mp = 110-114 °C.

$[\alpha]^{\text{rt}} = 38.5^\circ$ (c = 0.785, CHCl$_3$).

\[\begin{align*}
415 & \xrightarrow{1)} \text{MgCl}_2, \text{LiI, Et}_3\text{N, TMSCl, EtOAc, syringe pump addition of enolizable aldehyde} \\
& \xrightarrow{2)} \text{p-TsOH, MeOH} \\
410b
\end{align*}\]

(S)-4-benzyl-3-((2R,3R,E)-3-hydroxy-2,6-dimethylhept-4-enoyl)oxazolidin-2-one (410b)

**Method A:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.100 g, 0.429 mmol), MgCl$_2$ (0.042 g, 0.44 mmol), and LiI (0.116 g, 0.866 mmol) were added. Ethyl acetate (0.85 mL), triethylamine (0.30 mL, 2.2 mmol) and TMSCl (0.22 mL, 1.7 mmol) were then added sequentially. After 10 minutes, 4-methyl-2-pentenal (150 µL, 1.28 mmol) was diluted to 0.75 mL with ethyl acetate and added via syringe pump over three hours. The reaction mixture was analyzed by GC (~71% diastereomeric purity) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of p-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 0.080 g (56%) of 410b.

**Method B:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.199 g, 0.854 mmol), MgCl$_2$ (0.083 g, 0.87 mmol), and LiI (0.233 g, 1.74 mmol) were added. Ethyl acetate (1.7 mL), triethylamine (0.60 mL, 4.3 mmol) and TMSCl (0.44 mL, 3.4 mmol) were then added sequentially. After 10 minutes, a solution of 4-methyl-2-pentenal (50 µL, 0.43 mmol, 0.50 equivalents) in 0.21 mL of ethyl acetate was added via syringe pump over one hour. The reaction mixture was analyzed by GC (~71% diastereomeric purity) and passed through a plug of silica gel using ethyl acetate as the elu-
ent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of p-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 0.070 g (49%) of **410b**.

**1H NMR** (500 MHz, CDCl₃) δ 7.35-7.24 (m, 5H, ArH), 5.74 (dd, J = 15.5, 6.5 Hz, 1H), 5.46 (ddd, J = 15.5, 7.5, 1.0 Hz, 1H), 4.70 (dddd, J = 10.5, 7.0, 3.0, 3.0 Hz, 1H), 4.23-4.15 (m, 3H), 3.94 (app p, J = 7.0 Hz, 1H), 3.31 (dd, J = 13.5, 3.5 Hz, 1H), 2.77 (dd, J = 13.5, 9.5 Hz, 1H), 2.52 (s, 1H, -OH), 2.32 (app octet, J = 6.5 Hz, 1H), 1.16 (d, J = 7.0 Hz, 3H), and 1.01 (d, J = 6.5 Hz, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 176.6, 153.7, 141.5, 135.4, 129.7, 129.2, 127.5, 127.4, 76.1, 66.2, 55.7, 43.6, 38.0, 30.9, 22.44, 22.42, 14.8.


**GC-MS** (silylated) tᵣ = 13.4 min; m/z: 403, 388, 360, 347, 305, 290, 270, 250, 226, 211, 183, 171, 117, 91, 81, and 73.

**IR** (neat) 3490, 3063, 3033, 2967, 2937, 2875, 1779, 1698, 1455, 1389, 1352, 1291, 1211, 1112, 1078, 1054, 1030, 1013, 971, 915, 841, and 811 cm⁻¹.

**TLC** Rᵣ = 0.53 in 30% EtOAc in hexanes.

\[ \left[ \alpha \right] _{D}^\text{o} = 25.5^\circ \ (c = 0.815, \text{CHCl}_3). \]

---

(S)-4-benzyl-3-((2R,3R)-3-hydroxy-2,4-dimethylpentanoyl)oxazolidin-2-one (410c)

**Method A:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.100 g, 0.429 mmol), MgCl₂ (0.042 g, 0.44 mmol), and LiI (0.117 g, 0.873 mmol) were added. Ethyl acetate (0.85 mL), triethylamine (0.30 mL, 2.2 mmol) and TMSCl (0.22 mL, 1.7 mmol) were then added sequentially. After 10 minutes, isobutyraldehyde (150 µL, 1.28 mmol) was diluted to 0.75 mL with ethyl acetate and added via syringe pump over three hours. The reaction mixture was analyzed by GC (~70% diastereomeric purity)
and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of p-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 0.058 g (44%) of 410c.

**Method B:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.202 g, 0.867 mmol), MgCl$_2$ (0.083 g, 0.87 mmol), and LiI (0.230 g, 1.72 mmol) were added. Ethyl acetate (1.7 mL), triethylamine (0.60 mL, 4.3 mmol) and TMSCl (0.44 mL, 3.4 mmol) were then added sequentially. After 10 minutes, a solution of isobutyraldehyde (39 µL, 0.43 mmol, 0.50 equivalents) in 0.21 mL of ethyl acetate was added via syringe pump over one hour. The reaction mixture was analyzed by GC (~73% diastereomeric purity) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of p-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 0.057 g (43%) of 410c.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.53-7.32 (m, 2H, ArH), 7.29-7.24 (m, 3H, ArH), 4.68 (dddd, J = 10.0, 6.5, 3.0, 3.0 Hz, 1H), 4.19 (dd, J = 9.0, 7.0 Hz, 1H), 4.17 (dd, J = 9.0, 3.0 Hz, 1H), 4.05 (app p, 7.0 Hz, 1H), 3.51 (dd, J = 7.5, 4.5 Hz, 1H), 3.34 (dd, J = 13.5, 3.5 Hz, 1H), 2.76 (dd, J = 13.5, 4.5 Hz, 1H), 2.67 (s, 1H, -OH), 1.84 (doublet of septets, 4.5, 7.0 Hz, 1H), 1.21 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), and 0.97 (d, J = 7.0 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 177.6, 153.9, 135.4, 129.6, 129.2, 127.5, 79.8, 66.2, 55.8, 40.6, 38.0, 30.8, 20.1, 15.9, 15.2.

HRMS (ESI) Calcd. for (C$_{17}$H$_{23}$O$_4$N + Na$^+$): 328.1519. Found: 328.1526.

GC-MS (silylated) t$_r$ = 12.9 min; m/z: 377, 362, 334, 305, 290, 250, 234, 201, 185, 157, 145, 117, 91, and 73.

IR (neat) 3535, 3026, 2963, 2939, 2877, 1778, 1688, 1598, 1449, 1381, 1351, 1291, 1205, 1100, 995, 962, 831, 752, 729, and 696 cm$^{-1}$.

TLC R$_f$ = 0.50 in 30% EtOAc in hexanes.
Mp = 70-73 °C.

$[\alpha]^{\text{II}}_D = 37.6^\circ$ (c = 1.04, CHCl$_3$).

(S)-4-benzyl-3-((2R,3R)-3-cyclohexyl-3-hydroxy-2-methylpropanoyl)oxazolidin-2-one (410d)

**Method A:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.100 g, 0.429 mmol), MgCl$_2$ (0.041 g, 0.43 mmol), and LiI (0.116 g, 0.866 mmol) were added. Ethyl acetate (0.85 mL), triethylamine (0.30 mL, 2.2 mmol) and TMSCl (0.22 mL, 1.7 mmol) were then added sequentially. After 10 minutes, cyclohexanecarboxaldehyde (150 µL, 1.28 mmol) was diluted to 0.75 mL with ethyl acetate and added via syringe pump over three hours. The reaction mixture was analyzed by GC (~88% diastereomeric purity) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of p-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 0.090 g (61%) of 410d.

**Method B:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.200 g, 0.858 mmol), MgCl$_2$ (0.083 g, 0.87 mmol), and LiI (0.233 g, 1.74 mmol) were added. Ethyl acetate (1.7 mL), triethylamine (0.60 mL, 4.3 mmol) and TMSCl (0.44 mL, 3.4 mmol) were then added sequentially. After 10 minutes, a solution of cyclohexanecarboxaldehyde (52 µL, 0.43 mmol, 0.50 equivalents) in 0.21 mL of ethyl acetate was added via syringe pump over one hour. The reaction mixture was analyzed by GC (~88% diastereomeric purity) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of p-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After
concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 0.079 g (53%) of 410d.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35-7.32 (m, 2H, ArH), 7.29-7.23 (m, 3H, ArH), 4.68 (dddd, $J = 10.0, 6.5, 3.0, 3.0$ Hz, 1H), 4.19 (dd, $J = 9.0, 7.0$ Hz, 1H), 4.16 (dd, $J = 9.0, 3.0$ Hz, 1H), 4.09 (app p, $J = 7.0$ Hz, 1H), 4.19 (dd, $J = 9.0, 7.0$ Hz, 1H), 4.16 (dd, $J = 9.0, 3.0$ Hz, 1H), 2.76 (dd, $J = 13.0, 9.5$ Hz, 1H), 2.70 (s, 1H, -OH), 1.91-1.88 (m, 1H), 1.84-1.77 (m, 2H), 1.68-1.66 (m, 1H), 1.62-1.61 (m, 1H), 1.50-1.46 (m, 1H), 1.31-1.22 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.8, 153.8, 135.4, 129.6, 129.2, 127.5, 79.4, 66.2, 55.7, 41.1, 39.9, 38.0, 30.4, 26.7, 26.6, 26.3, 15.3.

HRMS (ESI) Calcd. for (C$_{20}$H$_{27}$O$_4$N + Na$^+$): 368.1832. Found: 368.1810.

GC-MS (silylated) $t_r = 14.4$ min; m/z: 417, 402, 334, 305, 290, 250, 225, 207, 185, 157, 117, 981, 760, 748, and 700 cm$^{-1}$.

IR (neat) 3478, 2922, 2852, 1780, 1693, 1596, 1577, 1450, 1386, 1348, 1209, 1108, 1015, 981, 760, 748, and 700 cm$^{-1}$.

TLC $R_f = 0.53$ in 30% EtOAc in hexanes.

Mp = 61-64 °C.

[$\alpha$]$^D = 30.0^\circ$ (c = 0.870, CHCl$_3$).

(S)-4-benzyl-3-((2R,3R)-3-hydroxy-2-methylhexanoyl)oxazolidin-2-one (410e)

**Method A:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.100 g, 0.429 mmol), MgCl$_2$ (0.041 g, 0.43 mmol), and LiI (0.113 g, 0.843 mmol) were added. Ethyl acetate (0.85 mL), triethylamine (0.30 mL, 2.2 mmol) and TMSCl (0.22 mL, 1.7 mmol) were then added sequentially. After 10 minutes, butyraldehyde (116 $\mu$L, 1.28 mmol) was diluted to 0.75 mL with ethyl acetate and added via syringe pump over
three hours. The reaction mixture was analyzed by GC diastereomers overlap) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of \textit{p}-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was observed by NMR (~56% diastereomeric purity) and purified by MPLC (30% EtOAc/70% Hexanes) to give 0.037 g (28%) of 410e.

**Method B:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.199 g, 0.854 mmol), MgCl$_2$ (0.081 g, 0.85 mmol), and LiI (0.229 g, 1.71 mmol) were added. Ethyl acetate (1.7 mL), triethylamine (0.60 mL, 4.3 mmol) and TMSCl (0.44 mL, 3.4 mmol) were then added sequentially. After 10 minutes, a solution of butyraldehyde (38 \textmu L, 0.43 mmol, 0.50 equivalents) in 0.21 mL of ethyl acetate was added via syringe pump over one hour. The reaction mixture was analyzed by GC (diastereomers overlap) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of \textit{p}-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was observed by NMR (~56% diastereomeric purity) and purified by MPLC (30% EtOAc/70% Hexanes) to give 0.039 g (30%) of 410e.

$^1$H NMR (500 MHz, CDCl$_3$) \(\delta\) 7.35-7.32 (m, 2H, ArH), 7.29-7.23 (m, 3H, ArH), 4.68 (dd, \(J = 10.0, 7.0, 3.0, 3.0 \text{ Hz}, 1\text{H})\), 4.20 (dd, \(J = 9.0, 7.0 \text{ Hz}, 1\text{H})\), 4.17 (dd, \(J = 9.0, 3.0 \text{ Hz}, 1\text{H})\), 3.89 (app p, \(J = 7.0 \text{ Hz}, 1\text{H})\), 3.74 (app q, \(J = 6.0 \text{ Hz}, 1\text{H})\), 3.32 (dd, \(J = 13.5, 3.5 \text{ Hz}, 1\text{H})\), 2.78 (dd, \(J = 13.5, 10.0 \text{ Hz}, 1\text{H})\), 2.55 (d, \(J = 7.0\text{Hz}, 1\text{H}, -\text{OH})\), 1.63-1.55 (m, 2H), 1.51-1.39 (m, 2H), 1.22 (d, \(J = 6.5 \text{ Hz}, 3\text{H})\), and 0.96 (t, \(7.0 \text{ Hz}, 3\text{H})\).

$^{13}$C NMR (125 MHz, CDCl$_3$) \(\delta\) 177.1, 153.8, 135.4, 129.7, 129.2, 127.6, 74.6, 66.3, 55.7, 43.5, 38.1, 37.4, 18.9, 14.9, 14.2.

HRMS (ESI) Calcd. for (C$_{17}$H$_{23}$O$_4$N + Na$^+$): 328.1519. Found: 328.1537.

GC-MS (silylated) \(t_f = 12.9\) min; m/z: 377, 362, 334, 305, 290, 250, 244, 185, 172, 157, 145, 117, 91, and 73.

IR (neat) 3513, 3067, 3037, 2967, 2940, 2879, 1779, 1698, 1495, 1456, 1387, 1352, 1290, 1210, 1113, 1077, 1052, 1013, 974, 916, and 849 cm$^{-1}$.

TLC \(R_f = 0.47\) in 30% EtOAc in hexanes.
Mp = 61-64 °C.
$[\alpha]^{D}_{D} = 51.3^\circ$ (c = 0.870, CHCl$_3$).

- **(S)-4-benzyl-3-((2R,3R)-3-hydroxy-2,5-dimethylhexanoyl)oxazolidin-2-one (410f)**

**Method A:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.100 g, 0.429 mmol), MgCl$_2$ (0.041 g, 0.43 mmol), and LiI (0.115 g, 0.858 mmol) were added. Ethyl acetate (0.85 mL), triethylamine (0.30 mL, 2.2 mmol) and TMSCl (0.22 mL, 1.7 mmol) were then added sequentially. After 10 minutes, 3-methyl-2-butanal (138 µL, 1.29 mmol) was diluted to 0.75 mL with ethyl acetate and added via syringe pump over three hours. The reaction mixture was analyzed by GC (diastereomers overlap) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of $p$-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was observed by NMR (~63% diastereomeric purity) and purified by MPLC (30% EtOAc/70% Hexanes) to give 0.080 g (59%) of 410f.

**Method B:** To an oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (0.201 g, 0.862 mmol), MgCl$_2$ (0.082 g, 0.86 mmol), and LiI (0.232 g, 1.73 mmol) were added. Ethyl acetate (1.7 mL), triethylamine (0.60 mL, 4.3 mmol) and TMSCl (0.44 mL, 3.4 mmol) were then added sequentially. After 10 minutes, a solution of 3-methyl-2-butanal (46 µL, 0.43 mmol, 0.50 equivalents) in 0.21 mL of ethyl acetate was added via syringe pump over one hour. The reaction mixture was analyzed by GC (diastereomers overlap) and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL of methanol was added, along with 25 mg of $p$-TsOH. After 15 minutes, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was observed by NMR (~63% diastereomeric purity) and purified by MPLC (30% EtOAc/70% Hexanes) to give 0.080 g (59%) of 410f.
purity) and purified by MPLC (30% EtOAc/70% Hexanes) to give 0.066 g (49%) of 410f.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta \) 7.35-7.23 (m, 5H, ArH), 4.69 (dddd, \(J = 10.5, 6.5, 3.0, 3.0\) Hz, 1H), 4.19 (dd, \(J = 9.5, 7.0\) Hz, 1H), 4.17 (dd, \(J = 9.0, 2.5\) Hz, 1H), 3.86 (app p, 7.0 Hz, 1H), 2.76 (dd, \(J = 13.5, 9.5\) Hz, 1H), 2.47 (d, \(J = 8.5\) Hz, 1H), 1.91 (m, 1H), 1.47 (ddd, \(J = 14.0, 10.0, 4.5\) Hz, 1H), 1.35 (ddd, \(J = 12.5, 9.5, 2.5\) Hz, 1H), 1.22 (d, \(J = 7.0\) Hz, 3H), 0.96 (d, \(J = 6.5\) Hz, 3H), and 0.93 (d, \(J = 6.5\) Hz, 3H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta \) 177.1, 153.7, 135.4, 129.6, 129.2, 127.6, 73.1, 66.2, 55.8, 44.6, 43.9, 38.1, 24.7, 24.0, 21.8, 14.9.

HRMS (ESI) Calcd. for (C\(_{18}\)H\(_{25}\)O\(_4\)N + Na\(^+\)): 342.1676. Found: 342.1671.

GC-MS (silylated) \(t_r = 13.1\) min; m/z: 391, 376, 334, 305, 290, 250, 244, 234, 199, 159, 157, 144, 117, 103, 91, and 73.

IR (neat) 3517, 3063, 3037, 2960, 2940, 2871, 1779, 1702, 1498, 1456, 1388, 1351, 1289, 1210, 1076, 1053, 920, 849, and 817 cm\(^{-1}\).

TLC \(R_f = 0.53\) in 30% EtOAc in hexanes.

\([\alpha]^{\text{rt}} = 39.8^\circ\) (c = 0.720, CHCl\(_3\)).

\((S)-4\)-Benzyl-3-propanoyloxazolidin-2-one (415)\(^{96}\)

To a 2 L round bottom flask equipped with a stirbar, \((S)-4\)-benzyl-2-oxazolidinone 454 (47.5 g, 268 mmol) and 1.0 L of THF was added and placed under N\(_2\) atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 113 mL, 282 mmol) was added. After 20 minutes propanoyl chloride (25.6 mL, 295 mmol) was added dropwise. After 2.5 hours the reaction mixture was allowed to warm to room temperature and was quenched with 150 mL of satd. aq. NH\(_4\)Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH\(_2\)Cl\(_2\) (2 x 300 mL). The
combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield **415** (62.5 g, 99%) of the desired product as a white solid.

**1H NMR** (500 MHz, CDCl$_3$) δ 7.35-7.32 (m, 2H, ArH), 7.29-7.26 (m, 1H, ArH), 7.22-7.21 (m, 2H, ArH), 4.68 (dddd, J = 10.5, 7.5, 3.0, 3.0 Hz, 1H, NCH), 4.21 (dd, J = 9.0, 7.5 Hz, 1H, -CHaHbO), 4.17 (dd, J = 9.0, 3.0 Hz, 1H, -CHaHbO), 3.17 (dd, J = 9.0, 3.0 Hz, 1H, -CHaHbO), 3.04-2.89 (m, 2H, COCH$_2$Me), 2.76 (dd, J = 13.5, 3.5 Hz, 1H, -CHaHbAr), and 1.21 (t, J = 7.5 Hz, 3H, -CH$_3$).

**13C NMR** (125 MHz, CDCl$_3$) δ 174.3, 153.7, 135.5, 129.6, 129.1, 127.5, 66.4, 55.3, 38.1, 29.4, and 8.5.

**HRMS** (ESI) Calcd for (C$_{13}$H$_{15}$NO$_3$ + Na$^+$): 256.0944. Found: 256.0957.

**GC-MS** t$_r$ = 11.2 min; m/z: 233, 204, 148, 142, 133, 117, 91, 77, 65, and 57.

**IR** (neat) 3063, 3029, 2981, 2941, 2882, 1961, 1779, 1699, 1607, 1497, 1481, 1455, 1391, 1374, 1352, 1291, 1248, 1212, 1119, 1079, 1052, 1009, 957, 920, 841, 805, 761, 743, 703, and 627 cm$^{-1}$.

**TLC** R$_f$ = 0.56 in 30% EtOAc in hexanes.

$[\alpha]_{RT}^{D}$ = +55.6 (c = 1.27, CHCl$_3$).

mp = 43-46 °C.

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(R)-4-benzyl-3-((2S,3S,E)-2-methyl-3-(trimethylsilyloxy)hex-4-enoyl)oxazolidin-2-one (ent-425)

To a flame dried reaction vessel equipped with a stirbar, oxazolidinone **ent-415** (14.1 g, 60.5 mmol), MgCl$_2$ (5.77 g, 60.6 mmol), and NaSbF$_6$ (8.05 g, 31.1 mmol) were added and placed under nitrogen. While stirring, 90 mL ethyl acetate was added, then triethylamine (42.0 mL, 303 mmol) and TMSCl (29.0 mL, 227 mmol) were also added. After stirring for 30 minutes, crotonaldehyde (16.0 mL, 180 mmol) was diluted with 4.0 mL ethyl acetate and added via syringe pump over three hours. After 6 hours from the start of
addition, the reaction mixture was passed through a silica gel column using diethyl ether as the eluent. The solvent was removed in vacuo, then 45 mL of pentane was added, and the filtered reaction mixture was placed in a refrigerator (-20 °C). After two days the crystals were vacuum filtered giving 16.2 g (71.4%) of ent-425. GC of the crystals showed a 97:3 diastereomeric ratio.

\[ ^1H \text{ NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta 7.35-7.24 \text{ (m, 5H, ArH)}, 5.65 \text{ (dq, } J = 6.5, 6.5, 6.5, \text{ and } 15.0 \text{ Hz, 1H, } -\text{CH} = \text{CHMe}), 5.42 \text{ (dd, } J = 1.5, 1.5, 1.5, 8.0, \text{ and } 15.0 \text{ Hz, 1H, } -\text{CH} = \text{CHMe}), 4.71 \text{ (ddddd, } J = 3.0, 3.0, 8.0, \text{ and } 9.5 \text{ Hz, 1H, NCH}), 4.36 \text{ (dd, } J = 8.5 \text{ and } 8.5 \text{ Hz, 1H, CHOTMS}), 4.17 \text{ (dd, } J = 8.0 \text{ and } 8.5 \text{ Hz, 1H, } -\text{CHaHbPh}), 4.11 \text{ (dd, } J = 3.0 \text{ and } 9.0 \text{ Hz, 1H, } -\text{CHaHbPh}), 3.95 \text{ (dq, } J = 7.0, 7.0, 7.0, \text{ and } 8.5 \text{ Hz, 1H, COCHMe}), 3.30 \text{ (dd, } J = 3.0 \text{ and } 13.5 \text{ Hz, 1H, CO}_2\text{CHaHbC}-), 2.71 \text{ (dd, } J = 9.5 \text{ and } 13.0 \text{ Hz, 1H, CO}_2\text{CHaHbC}-), 1.71 \text{ (dd, } J = 1.5 \text{ and } 6.5 \text{ Hz, 3H, CH=CHMe}), 1.04 \text{ (d, } J = 7.0 \text{ Hz, 3H, CHMe}), 0.08 \text{ (s, 9H, SiMe}_3).\]

\[ ^13C \text{ NMR} (125 \text{ MHz}, \text{CDCl}_3) \delta 176.1, 153.3, 135.7, 132.2, 129.7, 129.1, 129.0, 127.5, 76.8, 65.9, 55.3, 44.5, 38.3, 17.8, 14.0, 0.7.\]

\[ \text{HRMS (ESI) Calcd. for } (\text{C}_{20}\text{H}_{29}\text{O}_4\text{NSi + Na}^+) \text{: 398.1758. Found: 398.1807.}\]

\[ \text{GC-MS } T_r = 13.34 \text{ min; m/z: 375, 360, 305, 290, 198, 183, 143, 117, 91, and 73.}\]

\[ \text{IR (neat) 2984, 2918, 1782, 1701, 1454, 1387, 1249, 1211, 1102, 1188, 1048, 1037, 970, 878, 842, and 760 cm}^{-1}.\]

\[ \text{TLC } R_f = 0.25 \text{ in 15% EtOAc in hexanes.}\]

\[ [\alpha]_{RT}^\text{D} = -16.6 \text{ (c = 1.10, CHCl}_3).\]
To a oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (74.9 mg, 0.32 mmol), and Eu(OTf)₃ (61.1 mg, 0.102 mmol, 32 mol %) were added. Ethyl acetate (0.75 µL), triethylamine (0.22 mL, 1.6 mmol), TMSCl (0.165 mL, 1.28 mmol), and benzaldehyde (36 µL, 0.35 mmol) were then added sequentially. After stirring for 8 hours, the reaction mixture was analyzed by GC and passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL ethanol was added, along with 25 mg of p-TsOH. After stirring for 1.5 hours, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (20% EtOAc/80% Hexanes) to give 47.2 mg (43%) of 434, along with 34.8 mg (32%) of 435. The column was then flushed with ethyl acetate, collecting the combined polar products 436 and 437. Purification by MPLC (60% EtOAC/40% Hexanes) gave 10.1 mg (9%) of 436 and 5.2 mg (5%) of 437.

**Data for 434**

**¹H NMR** (500 MHz, CDCl₃) δ 7.44-7.42 (m, 2H), 7.39-7.36 (m, 2H), 7.33-7.25 (m, 4H), 7.16-7.14 (m, 2H), 4.82 (d, J = 8.0 Hz, 1H), 4.68 (dddd, J = 3.0, 3.0, 7.5, 9.5 Hz, 1H), 4.34 (app p, J = 7.0 Hz, 1H), 4.18 (dd, J = 9.0, 7.0 Hz, 1H), 4.12 (dd, J = 9.0, 3.0 Hz, 1H), 3.19 (dd, J = 13.5, 3.5 Hz, 1H), 3.09 (br s, 1H, -OH), 2.66 (dd, J = 13.5, 9.5 Hz, 1H), 1.10 (d, J = 7.0 Hz, 3H).

**¹³C NMR** (125 MHz, CDCl₃) δ 176.8, 153.7, 142.2, 135.4, 129.7, 129.1, 128.8, 128.2, 127.5, 126.8, 77.6, 66.1, 55.6, 44.5, 37.7, 15.1.


IR (neat) 3493, 3090, 3063, 3037, 2979, 2935, 2886, 1783, 1698, 1491, 1452, 1391, 1356, 1295, 1252, 1214, 1110, 1091, 1056, 1015, 968, 913, and 841 cm⁻¹.

**TLC** \( R_f = 0.42 \) in 30% EtOAc in hexanes.

\( \text{Mp} = 58-62 \degree C. \)

\([\alpha]^{ir} = -7.9^\circ (c = 0.44, \text{CDCl}_3).\)

Data for **435**

\(^1\text{H NMR}\) (500 MHz, CDCl₃) \( \delta \) 7.47-7.45 (m, 2H), 7.38-7.26 (m, 6H), 7.16-7.14 (m, 2H), 5.17 (d, \( J = 4.5 \) Hz, 1H), 4.68 (dddd, \( J = 9.5, 8.0, 3.0, 3.0 \) Hz, 1H), 4.19 (app p, \( J = 7.0 \) Hz, 1H), 4.20 (dd, \( J = 9.0, 7.5 \) Hz, 1H), 4.15 (dd, \( J = 9.0, 3.0 \) Hz, 1H), 3.13 (dd, \( J = 13.5, 3.5 \) Hz, 1H), 2.81 (br s, 1H, -OH), 2.60 (dd, \( J = 13.0, 9.5 \) Hz, 1H), 1.18 (d, \( J = 7.0 \) Hz, 3H).

\(^{13}\text{C NMR}\) (125 MHz, CDCl₃) \( \delta \) 176.4, 153.3, 141.5, 135.3, 129.6, 129.2, 128.5, 127.8, 127.6, 126.5, 74.1, 66.3, 55.3, 44.7, 37.9, 11.1.

**HRMS** (ESI) Calcd. for (C_{20}H_{21}O_{4}N + Na⁺): 362.1363. Found: 362.1363.

**GC-MS** (silylated) \( t_r = 13.3 \) min; m/z: 411, 396, 321, 305, 290, 250, 234, 219, 206, 191, 179, 163, 145, 117, 91, and 73.

**IR** (neat) 3502, 3090, 3063, 3027, 3079, 2925, 1779, 1698, 1498, 1452, 1387, 1360, 1218, 1108, 1074, 1048, 1030, 913, and 842 cm⁻¹.

**TLC** \( R_f = 0.35 \) in 30% EtOAc in hexanes.

\([\alpha]^{ir} = +24^\circ (c = 0.50, \text{CDCl}_3).\)

Data for **436**

\(^1\text{H NMR}\) (500 MHz, CDCl₃) \( \delta \) 7.39-7.27 (m, 8H), 7.21-7.20 (m, 2H), 4.84 (d, \( J = 8.5 \) Hz, 1H), 4.68 (dddd, \( J = 10, 7.5, 3.0, 3.0 \) Hz, 1H), 4.25 (dq, \( J = 8.0, 7.0 \) Hz, 1H), 4.15 (dd, \( J = 8.5, 3.5 \) Hz, 1H), 4.13 (dd, \( J = 9.0, 8.5 \) Hz, 1H), 3.26 (dd, \( J = 13.5, 3.5 \) Hz, 1H), 2.79 (dd, \( J = 13.5, 9.5 \) Hz, 1H), 2.72 (br s, 1H), 1.12 (d, \( J = 7.0 \) Hz, 3H).

\(^{13}\text{C NMR}\) (125 MHz, CDCl₃) \( \delta \) 176.5, 153.5, 141.9, 135.3, 129.6, 129.2, 128.8, 128.3, 127.6, 126.7, 77.13, 66.4, 55.5, 44.8, 38.1, 15.1.

**HRMS** (ESI) Calcd. for (C_{20}H_{21}O_{4}N + Na⁺): 362.1363. Found: 362.1375.
GC-MS (silylated) $t_r = 13.2$ min; m/z: 411, 396, 321, 305, 290, 250, 234, 219, 206, 191, 179, 163, 145, 117, 91, and 73.

IR (neat) 3444, 3087, 3063, 3033, 2986, 2937, 2890, 1783, 1695, 1491, 1455, 1386, 1351, 1289, 1253, 1211, 1108, 1073, 1032, 1010, 969, 920, 843, and 816 cm$^{-1}$.

TLC $R_f = 0.65$ in 50% EtOAc in hexanes.

Mp = 143-147 °C.

$[\alpha]^{rt} = +117^\circ$ (c = 0.25, CDCl$_3$).

Data for 437

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.4-7.25 (m, 8H), 7.21-7.19 (m, 2H), 5.10 (d, $J = 4.0$ Hz, 1H), 4.60 (dddd, $J = 10.0$, 8.0, 3.0, 3.0 Hz, 1H), 4.15 (dd, $J = 9.0$, 2.5 Hz, 1H), 4.10 (dd, $J = 4.0$, 7.0 Hz, 1H), 4.08 (dd, $J = 9.0$, 8.5 Hz, 1H), 3.88 (br s, 1H), 3.24 (dd, $J = 13.5$, 3.5 Hz, 1H), 2.78 (dd, $J = 13.5$, 9.5 Hz, 1H), 1.22 (d, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.0, 153.1, 141.4, 135.2, 129.6, 129.2, 128.5, 127.7, 127.6, 126.3, 74.0, 66.4, 55.4, 44.7, 38.0, 11.1.


GC-MS (silylated) $t_r = 13.2$ min; m/z: 411, 396, 321, 305, 290, 250, 234, 219, 206, 191, 179, 163, 145, 117, 91, and 73.

IR (neat) 3510, 3086, 3062, 3029, 2977, 2937, 2879, 1778, 1698, 1694, 1604, 1495, 1480, 1454, 1385, 1365, 1290, 1211, 1109, 1076, 1050, 1030, 1014, 990, 968, 918, 841, and 813 cm$^{-1}$.

TLC $R_f = 0.55$ in 50% EtOAc in hexanes.

$[\alpha]^{rt} = +49^\circ$ (c = 0.26, CDCl$_3$).
(S)-4-benzyl-3-((2R,3S)-3-hydroxy-2-methyl-3-phenylpropanoyl)oxazolidin-2-one (434) and (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-phenylpropanoyl)oxazolidin-2-one (436)

To a oven dried reaction vessel equipped with a stirbar, oxazolidinone 415 (74.8 mg, 0.32 mmol), and SmI₂ (0.1 M in THF, 0.6 mL, 20 mol%) were added. Ethyl acetate (0.75 µL), triethylamine (0.22 mL, 1.6 mmol), TMSCl (0.165 mL, 1.28 mmol), and benzaldehyde (36 µL, 0.35 mmol) were then added sequentially. After stirring for 6 days, the reaction showed nearly complete conversion by GC. The mixture was passed through a plug of silica gel using ethyl acetate as the eluent. After removing the solvent in vacuo, 4 mL ethanol was added, along with 24 mg of p-TsOH. After stirring for 1.5 hours, the desilylation was complete as judged by TLC. After concentration in vacuo, the desilylated mixture was purified by MPLC (30% EtOAc/70% Hexanes) to give 59.2 mg (54%) of 434, along with 25.2 mg (23%) of 436.

\[
\begin{align*}
\text{Oxazolidinone} & \xrightarrow{1. \text{n-BuLi}} 1. \text{b. benzoyl chloride} \\
\text{Silyl ethers} & \xrightarrow{2. \text{b. benzoyl chloride}} \text{Desilylated products}
\end{align*}
\]

(S)-4-Benzyl-3-(phenylcarbonyl)oxazolidin-2-one (451)

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxazolidinone 454 (0.951 g, 5.37 mmol) and 16 mL of THF was added and placed under N₂ atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 2.21 mL, 5.52 mmol) was added. After 20 minutes benzoyl chloride (0.69 mL, 5.9 mmol) was added dropwise. After 2.5 hours the reaction mixture was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH₄Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield 451 (1.49 g, 98.6%) of the desired product as a white solid.

H NMR (300 MHz, CDCl₃) δ 7.67-7.64 (m, 2H, ArH), 7.61-7.54 (m, 1H, ArH), 7.47-7.42 (m, 2H, ArH), 7.38-7.29 (m, 3H, ArH), 7.26-7.23 (m, 2H, ArH), 4.89 (dd, J = 9.0, 135
9.0, 5.4, 3.3 Hz, 1H, NCH), 4.34 (dd, \(J = 9.0, 9.0\) Hz, 1H, \(-CHCH_aH_bO\)), 3.45 (dd, \(J = 9.0, 9.7\) Hz, 1H, \(-CHHaHbAr\)), and 2.96 (dd, \(J = 13.2, 9.0\) Hz, 1H, \(-CHaHbAr\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.9, 153.3, 134.9, 133.0, 132.4, 129.5, 129.0, 128.9, 127.9, 127.4, 66.3, 55.8, and 37.4.

HRMS (ESI) Calcd for \((C_{17}H_{15}NO_5 + Na^+): 304.0944.\) Found: 304.0943.

GC-MS \(t_r = 13.7\) min; \(m/z: 281, 190, 133, 117, 105, 91, 77, 65,\) and 51.

IR (neat) 3088, 3063, 3031, 2985, 1788, 1687, 1681, 1676, 1447, 1390, 1355, 1307, 1201, 1175, 1167, 1111, 1045, 1028, 933, 792, 739, 716, 702, 669, and 642 cm\(^{-1}\).

TLC \(R_f = 0.36\) in 30% EtOAc in hexanes.

\([\alpha]^{RT}_D = +124 (c = 0.545, CHCl_3).\)

mp = 142-145 °C.

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\((S)-4\)-Benzyl-2-phenyl-4,5-dihydrooxazole (452)\(^{98}\)

To a 6 mL screw cap vial equipped with a stirbar, \((S)-4\)-benzyl-3-(phenylcarbonyl)-oxazolidin-2-one 451 (0.0596 g, 0.212 mmol), lithium iodide (0.0590 g, 0.440 mmol), ammonium chloride (0.0233 g, 0.440 mmol), and 1.1 mL of methylene chloride were added. The vial was then capped and the mixture was stirred at room temperature for 12 hours. DBU (0.095 mL, 0.637 mmol) was added. After 6 hours the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (40% EtOAc in hexanes) to afford 452 (0.0381 g, 76%) as a clear oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.59-7.94 (m, 2H, ArH), 7.50-7.47 (m, 1H, ArH), 7.43-7.40 (m, 2H, ArH), 7.33-7.29 (m, 2H, ArH), 7.26-7.23 (m, 3H, ArH), 4.58 (dddd, \(J = 9.0, 9.0, 9.0,\) and 5.0 Hz, 1H, NCH), 4.35 (dd, \(J = 9.0, 9.0\) Hz, 1H, \(-CHaHbO\)), 4.15 (dd, \(J = 9.0, 9.0\) Hz, 1H, -CHbAr), 3.40 (dd, \(J = 9.0, 9.0\) Hz, 1H, -CHaHbAr), 2.96 (dd, \(J = 13.2, 9.0\) Hz, 1H, -CHaHbAr).
8.0, 8.0 Hz, 1H, -CHaHbO), 3.25 (dd, J = 14.0, 5.5 Hz, 1H, -CHaHbAr), and 2.73 (dd, J = 14.0, 9.0 Hz, 1H, -CHaHbAr).

13C NMR (125 MHz, CDCl3) δ 164.0, 137.9, 131.3, 129.6, 128.5, 128.3, 128.2, 126.5, 71.8, 67.9, and 41.8.


GC-MS tR = 12.0 min; m/z: 237, 218, 206, 146, 118, 105, 91, 77, 65, and 51.

IR (neat) 3061, 3027, 2960, 2929, 2899, 1651, 1603, 1579, 1495, 1455, 1450, 1358, 1085, 1060, 1025, 967, 780, and 695 cm⁻¹.

TLC Rf = 0.50 in 30% EtOAc in hexanes.

[α]RT = +8.0 (c = 0.670, CHCl3).

(S)-N-(1-Iodo-3-phenylpropan-2-yl)benzamide (453)

To a 6 mL screw cap vial equipped with a stirbar, (S)-4-benzyl-3-(phenylcarbonyl)-oxazolidin-2-one 451 (0.0314 g, 0.112 mmol), lithium iodide (0.0667 g, 0.497 mmol), methyl iodide (0.021 mL, 0.337 mmol), and 0.5 mL of methylene chloride were added. The vial was then capped and the mixture was stirred at room temperature for 16 hours. The mixture was then filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (25% EtOAc in hexanes) to afford 0.0227 g (55%) of the desired product as a brown oil.

1H NMR (500 MHz, CDCl3) δ 7.75-7.74 (m, 2H, ArH), 7.54-7.43 (m, 3H, ArH), 7.35-7.25 (m, 5H, ArH), 6.23 (d, J = 7.5 Hz, 1H, CNH), 4.12 (ddddd, J = 8.0, 8.0, 5.5, 4.5, 4.0 Hz, 1H, NCH), 3.54 (dd, J = 4.0, 10.0 Hz, 1H, CHaHbI), 3.28 (dd, J = 3.5, 10.0 Hz, 1H, CHaHbI), 3.05 (dd, J = 13.5, 6.0 Hz, 1H, -CHaHbAr), and 2.90 (dd, J = 13.5, 8.5 Hz).

13C NMR (125 MHz, CDCl3) δ 166.9, 136.9, 134.4, 131.9, 129.4, 129.0, 128.9, 127.3, 127.1, 50.0, 40.6, and 14.1.

IR (neat) 3355, 3062, 3036, 2955, 2922, 1725, 1627, 1600, 1540, 1530, 1493, 1452, 1378, 1318, 1274, 1180, 1113, 1025, 911, 733, and 706 cm⁻¹.
(S)-4-Benzyl-3-(4-methoxyphenylcarbonyl)oxazolidin-2-one (458)

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxazolidinone 454 (1.23 g, 6.93 mmol) and 21 mL of THF was added and placed under N₂ atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 2.86 mL, 7.15 mmol) was added. After 20 minutes para-methoxy benzoyl chloride (1.03 mL, 7.61 mmol) was added dropwise. After 2.5 hours the reaction was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH₄Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield 458 (2.06 g, 95.5%) of the desired product as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.71-7.68 (m, 2H, ArH), 7.35-7.27 (m, 3H, ArH), 7.23-7.21 (m, 2H, ArH), 6.94-6.91 (m, 2H, ArH), 4.88 (dddd, J = 9.5, 9.5, 6.5, 3.5 Hz, 1H, NCH), 4.32 (dd, J = 9.0, 8.0 Hz, 1H, -CHCH₃), 4.21 (dd, J = 8.5, 6.0 Hz, 1H, -CHCH₂H₂O), 3.87 (s, 3H, ArCH₃), 3.41 (dd, J = 14.0, 3.5 Hz, 1H, -CH₃), and 2.94 (dd, J = 13.5, 9.0 Hz, 1H, -CH₂H₂Ar).

¹³C NMR (125 MHz, CDCl₃) δ 169.3, 163.5, 153.9, 135.3, 132.1, 129.7, 129.1, 127.6, 125.2, 113.5, 66.5, 56.1, 55.6, and 37.6.


GC-MS tᵣ = 14.6 min; m/z: 311, 220, 178, 135, 107, 91, 77, and 65.

IR (neat) 3029, 2974, 2939, 2838, 1781, 1676, 1605, 1513, 1456, 1386, 1351, 1302, 1256, 1211, 1177, 1110, 1096, 1026, 840, 770, 756, 727, and 702 cm⁻¹.

**TLC** Rᵣ = 0.33 in 30% EtOAc in hexanes.

[α]ᵣ = +120 (c = 0.375, CHCl₃).
mp = 152-154 °C.

(S)-4-Benzyl-3-(4-nitrophenylcarbonyl)oxazolidin-2-one (459)

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxazolidinone 454 (1.10 g, 6.23 mmol) and 14 mL of THF was added and placed under N₂ atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 2.57 mL, 6.43 mmol) was added. After 20 minutes para-nitro benzoil chloride (1.40 mL, 7.55 mmol) was added dropwise. After 2.5 hours the reaction mixture was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH₄Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield 459 (1.92 g, 94.6%) of the desired product as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 8.28 (d, J = 9.0 Hz, 2H, ArH), 7.74 (d, J = 8.5 Hz, 2H, ArH), 7.38-7.30 (m, 3H, ArH), 7.24 (d, J = 6.5 Hz, 2H, ArH), 4.91 (dddd, J = 8.5, 8.5, 5.0, 3.5 Hz, 1H, NCH), 4.39 (ddd, J = 8.5, 8.5 Hz, 1H, -CH(CH₃)₂H₃O), 4.30 (ddd, J = 9.0, 5.0 Hz, 1H, -CH(CH₃)₂H₃O), 3.43 (dd, J = 13.5, 3.0 Hz, 1H, -CH₂H₂Ar), and 3.00 (dd, J = 13.5, 9.0 Hz, 1H, -CH₂H₂Ar).

¹³C NMR (125 MHz, CDCl₃) δ 168.1, 153.1, 149.8, 139.1, 134.7, 129.9, 129.6, 129.3, 127.9, 123.4, 66.9, 55.7, and 37.5.


GC-MS tᵣ = 15.2 min; m/z: 326, 281, 241, 207, 177, 150, 104, 91, 76, and 50.

IR (neat) 3109, 3086, 3028, 1790, 1694, 1685, 1604, 1519, 1452, 1391, 1351, 1316, 1214, 1106, 1033, 1013, 911, 861, 848, 836, and 704 cm⁻¹.

TLC Rᵣ = 0.28 in 30% EtOAc in hexanes.

[α]ᵣ = +113 (c = 0.420, CHCl₃).

mp = 120-125 °C.
(S)-4-Benzyl-3-(naphthalene-2-carbonyl)oxazolidin-2-one (460)

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxazolidinone 454 (0.953 g, 5.38 mmol) and 11 mL of THF was added and placed under N₂ atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 2.22 mL, 5.55 mmol) was added. After 20 minutes 2-naphthoyl chloride (1.13 mL, 5.95 mmol) was added dropwise. After 2.5 hours the reaction was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH₄Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield 460 (1.65 g, 92.5%) of the desired product as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 8.21 (app s, 1H, ArH), 7.91 (d, J = 8.0 Hz, 1H, ArH), 7.87 (d, J = 8.0 Hz, 2H, ArH), 7.69 (dd, J = 8.5, 1.5 Hz, 1H, ArH), 7.58 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H, ArH), 7.53 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H, ArH), 7.37-7.34 (m, 2H, ArH), 7.32-7.29 (m, 1H, ArH), 7.26-7.25 (m, 2H, ArH), 4.9 (ddd, J = 9.0, 9.0, 5.5, and 3.5 Hz, 1H, NCH), 4.3 (dd, J = 9.0, 8.0 Hz, 1H, -CHCH₃HbO), 4.2 (dd, J = 9.0, 6.0 Hz, 1H, -CHCH₃HbO), 3.4 (dd, J = 13.5, 3.0 Hz, 1H, -CH₂HbAr), and 3.0 (dd, J = 13.5, 9.0 Hz, 1H, -CH₂HbAr).

¹³C NMR (125 MHz, CDCl₃) δ 170.1, 153.6, 135.4, 135.2, 132.3, 130.8, 130.5, 129.7, 129.4, 129.2, 128.4, 128.0, 127.7, 127.6, 126.9, 125.3, 66.6, 56.1, and 37.6.


GC-MS tᵣ = 16.25 min; m/z: 331, 207, 155, 127, 117, and 91.

IR (neat) 3082, 3062, 3030, 2987, 1794, 1791, 1683, 1386, 1358, 1307, 1241, 1211, 1202, 1108, 1047, 1023, 812, 780, 763, 756, 739, and 728 cm⁻¹.

TLC Rᵣ = 0.40 in 30% EtOAc in hexanes.

[α]ᵣ⁰ = +119 (c = 0.365, CHCl₃).
mp = 173-175 °C.

(S)-4-Benzyl-2-(4-methoxyphenyl)-4,5-dihydrooxazole (461)<sup>99</sup>

To a 6 mL screw cap vial equipped with a stirbar, (S)-4-benzyl-3-(4-methoxyphenyl-carbonyl)oxazolidin-2-one 458 (0.0597 g, 0.192 mmol), lithium iodide (0.0528 g, 0.394 mmol), ammonium chloride (0.0202 g, 0.381 mmol), and 1.0 mL of methylene chloride were added. The vial was then capped and the mixture was stirred at room temperature for 12 hours. DBU was added (0.085 mL, 0.570 mmol). After 6 hours the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (40% EtOAc in hexanes) to afford 461 (0.0374 g, 73%) of the desired product as a white solid, along with 0.0051 g (8%) of recovered starting material.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.90-7.87 (m, 2H, ArH), 7.31-7.20 (m, 5H, ArH), 6.92-6.89 (m, 2H, ArH), 4.54 (dddd, J = 9.0, 9.0, 7.5, 5.0 Hz, 1H, NCH), 4.31 (dd, J = 9.0, 9.0 Hz, 1H, -CHaHbO), 4.11 (dd, J = 7.5, 8.5 Hz, 1H, -CHaHbO), 3.83 (s, 3H, ArCH<sub>3</sub>), 3.23 (dd, J = 13.5, 9.0 Hz, 1H, -CHaHbO), and 2.71 (dd, J = 13.5, 5.0 Hz, 1H, -CHaHbO).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 163.8, 162.1, 138.1, 138.0, 129.3, 128.5, 126.5, 120.3, 113.7, 71.8, 67.8, 55.4, and 41.9.

HRMS (ESI) Calcd for (C<sub>17</sub>H<sub>18</sub>NO<sub>2</sub>)<sup>+</sup>: 268.1332. Found: 268.1353.

GC-MS t<sub>r</sub> = 13.07 min; m/z: 265, 222, 176, 149, 135, 121, 91, 77, and 65.

IR (neat) 3026, 3002, 2959, 2933, 2900, 2838, 1652, 1607, 1578, 1512, 1494, 1453, 1444, 1417, 1358, 1310, 1254, 1168, 1078, 1028, 1010, 968, 844, 740, 701, and 677 cm<sup>-1</sup>.

TLC R<sub>f</sub> = 0.40 in 30% EtOAc in hexanes.

[α]<sup>RT</sup> = +12.3 (c = 0.925, CHCl<sub>3</sub>).

mp = 155-158 °C.
(S)-4-Benzyl-2-(4-nitrophenyl)-4,5-dihydrooxazole (462)

To a 6 mL screw cap vial equipped with a stirbar, (S)-4-benzyl-3-(4-nitrophenyl-
carbonyl)oxazolidin-2-one 459 (0.0692 g, 0.212 mmol), lithium iodide (0.0591 g, 0.441
mmol), ammonium chloride (0.0227 g, 0.428 mmol), and 1.1 mL of methylene chloride
were added. The vial was then capped and the mixture was stirred at room temperature
for 12 hours. DBU was added (0.095 mL, 0.637 mmol). After 6 hours the mixture was
filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pre-
sure liquid chromatography (40% EtOAc in hexanes) to afford 462 (0.0270 g, 45%) as a
white solid.

\( ^1\text{H} \text{NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 8.28-8.25 (m, 2H, ArH), 8.12-8.10 (m, 2H, ArH), 7.33-
7.30 (m, 3H, ArH), 7.24-7.23 (m, 2H, ArH), 8.13-8.10 (m, 2H, ArH), 7.33-7.30 (m, 3H,
ArH), 7.26-7.23 (m, 2H, ArH), 4.65 (dddd, \( J = 9.0, 8.5, 7.5, 5.0 \) Hz, 1H, NCH), 4.42 (dd,
\( J = 8.5, 8.5 \) Hz, 1H, \(-\text{CH}_2\text{HbO})\), 4.21 (dd, \( J = 8.5, 7.5 \) Hz, 1H, \(-\text{CH}_2\text{HbO})\), 3.23 (dd, \( J =
14.0, 5.0 \) Hz, 1H, \(-\text{CH}_2\text{HbAr})\), and 2.78 (dd, \( J = 14.0, 8.5 \) Hz, 1H, \(-\text{CH}_2\text{HbAr})\).

\( ^{13}\text{C} \text{NMR} \) (125 MHz, CDCl\(_3\)) \( \delta \) 162.4, 149.7, 137.7, 133.8, 129.5, 129.4, 128.8, 126.9,
123.7, 72.5, 68.3, and 41.8.

HRMS (ESI) Calcd for (C\(_{16}\)H\(_{15}\)N\(_2\)O\(_3\))^+: 283.1077. Found: 283.1159.

GC-MS \( t_r \) = 13.6 min; m/z: 282, 236, 191, 163, 117, 91, and 65.

IR (neat) 3035, 2951, 2933, 2909, 2869, 1652, 1646, 1598, 1538, 1523, 1490, 1354,
1340, 1318, 1279, 1107, 1086, 1065, 953, 860, 847, 757, and 702 cm\(^{-1}\).

TLC \( R_f \) = 0.50 in 30% EtOAc in hexanes.

\([\alpha]^{\text{RT}}_D = +7.8 \) (c = 0.410, CHCl\(_3\)).

mp = 154-157°C.
(S)-4-Benzyl-2-(naphthyl-2-yl)-4,5-dihydrooxazole (463)

To a 6 mL screw cap vial equipped with a stirbar, (S)-4-benzyl-3-(naphthalene-2-carbonyl)oxazolidin-2-one 460 (0.0636 g, 0.192 mmol), lithium iodide (0.0523 g, 0.390 mmol), ammonium chloride (0.0205 g, 0.387 mmol), and 1.0 mL of methylene chloride were added. The vial was then capped and the mixture was stirred at room temperature for 12 hours. DBU was added (0.086 mL, 0.577 mmol). After 6 hours the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (40% EtOAc in hexanes) to afford 463 (0.0441 g, 80%) as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.46 (app s, 1H, ArH), 8.07 (dd, $J = 8.5, 1.5$ Hz, 1H, ArH), 7.93-7.87 (m, 3H, ArH), 7.58-7.52 (m, 2H, ArH), 7.35-7.24 (m, 5H, ArH), 4.66 (ddd, $J = 9.0, 9.0, 7.0, 5.0$ Hz, 1H, NCH), 4.42 (dd, $J = 9.0, 8.5$ Hz, 1H, -CH$_2$HbO), 4.22 (dd, $J = 8.0, 7.5$ Hz, 1H, -CH$_2$HbO), 3.31 (dd, $J = 13.5, 5.0$ Hz, 1H, -CH$_2$HbAr), and 2.80 (dd, $J = 13.5, 8.5$ Hz, 1H, -CH$_2$HbAr).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.1, 138.0, 134.7, 132.7, 129.3, 128.9, 128.8, 128.6, 128.1, 127.8, 127.5, 126.5, 125.1, 124.9, 71.9, 68.0, and 41.9.

HRMS (ESI) Calcd for (C$_{20}$H$_{18}$NO$^+$): 288.1383. Found: 288.1373.

GC-MS $t_r = 14.47$ min; m/z: 287, 285, 196, 158, 155, 141, 127, and 91.

IR (neat) 3058, 3026, 2924, 2891, 1651, 1597, 1575, 1495, 1475, 1453, 1390, 1361, 1229, 1194, 1129, 1061, 971, 968, 906, 868, 833, 751, 718, and 699 cm$^{-1}$.

TLC $R_f = 0.60$ in 30% EtOAc in hexanes.

$[\alpha]^{R \circ}$ = +13.2 (c = 0.560, CHCl$_3$).

mp = 178-180 °C.
(S)-4-Benzyl-3-ethanoyloxazolidin-2-one (464)

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxazolidinone 454 (3.28 g, 18.5 mmol) and 30 mL of THF was added and placed under N₂ atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 7.50 mL, 18.7 mmol) was added. After 20 minutes acetyl chloride (1.45 mL, 20.3 mmol) was added dropwise. After 2.5 hours the reaction mixture was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH₄Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield 464 (3.83 g, 94.5%) of the desired product as a white solid.

**¹H NMR** (500 MHz, CDCl₃) δ 7.35-7.32 (m, 2H, ArH), 7.29 (d, J = 7.0 Hz, 1H, ArH), 7.21 (d, J = 7.0 Hz, 2H, ArH), 4.67 (dddd, J = 10.5, 7.5, 3.0, and 3.0 Hz, 1H, NCH), 4.20 (dd, J = 9.0, 7.5 Hz, 1H, -CHaHbO), 4.16 (dd, J = 9.0, 3.0 Hz, 1H, -CHaHbO), 3.31 (dd, J = 13.5, 3.0 Hz, 1H, -CHaHbAr), 2.78 (dd, J = 13.5, 9.5 Hz, 1H, -CHaHbAr), and 2.56 (s, 3H, -CH₃).

**¹³C NMR** (125 MHz, CDCl₃) δ 170.4, 153.8, 135.4, 129.6, 129.2, 127.5, 66.3, 55.2, 38.0, and 24.0.


**GC-MS** τᵣ = 10.7 min; m/z: 219, 204, 190, 177, 160, 134, 128, 115, 91, 86, 77, 65, and 51.

**IR** (neat) 3071, 3040, 3028, 2991, 2957, 2926, 1775, 1698, 1490, 1476, 1455, 1388, 1368, 1356, 1322, 1217, 1206, 1137, 1098, 1078, 1051, 1009, 973, 785, 762, 741, 719, 700, 643, and 613 cm⁻¹.

**TLC** Rᵣ = 0.44 in 30% EtOAc in hexanes.

[α]ᵣᵣ = +63.0 (c = 1.20, CHCl₃).

mp = 107-110 °C.
(S)-4-Benzyl-3-(2-methylpropanoyl)oxazolidin-2-one (466)<sup>101</sup>

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxazolidinone 454 (1.20 g, 6.77 mmol) and 20 mL of THF was added and placed under N<sub>2</sub> atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 2.85 mL, 7.12 mmol) was added. After 20 minutes 2-methylpropanoyl chloride (0.75 mL, 7.11 mmol) was added dropwise. After 2.5 hours the reaction mixture was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH<sub>4</sub>Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield 466 (1.52 g, 91%) of the desired product as a white solid.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.33 (dd, J = 7.5, 7.0 Hz, 1H, ArH), 7.28 (d, J = 7.5 Hz, 1H, ArH), 7.21 (d, J = 7.0 Hz, 2H, ArH), 4.67 (dddd, J = 10.5, 7.5, 3.0, 3.0 Hz, 1H, NCH), 4.20 (dd, J = 9.0, 7.5 Hz, 1H, -CHaHbO), 4.16 (dd, J = 9.0, 3.0 Hz, 1H, -CHaHbO), 3.76 (septet, 7.0 Hz, 1H, -CHMe<sub>2</sub>), 3.26 (dd, J = 13.5, 3.5 Hz, 1H, -CHaHbAr), 2.77 (dd, J = 13.0, 9.5 Hz, 1H, -CHaHbAr), 1.24 (d, J = 7.0 Hz, 3H, -CH<sub>3</sub>), and 1.19 (d, J = 7.0 Hz, 3H, -CH<sub>3</sub>).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 177.8, 153.2, 135.5, 129.6, 129.1, 127.5, 66.2, 55.5, 38.1, 32.8, 19.4, and 18.9.

HRMS (ESI) Calcd for (C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub> + Na<sup>+</sup>): 270.1101. Found: 270.1091.

GC-MS t<sub>r</sub> = 11.2 min; m/z: 247, 178, 162, 156, 133, 117, 91, 86, 77, 71, and 65.

IR (neat) 3087, 3067, 3031, 2993, 2969, 2945, 2877, 1784, 1698, 1483, 1453, 1385, 1356, 1295, 1236, 1205, 1113, 1092, 1049, 1022, 974, 841, 773, 758, 737, 699, and 687 cm<sup>-1</sup>.

TLC R<sub>f</sub> = 0.55 in 30% EtOAc in hexanes.

[α]<sup>RT</sup> = +61.7 (c = 1.12, CHCl<sub>3</sub>).
mp = 65-66 °C.

(\textit{S}-4-Benzyl-2-methyl-4,5-dihydrooxazole (467)\textsuperscript{102}

To a 6 mL screw cap vial equipped with a stirbar, (\textit{S})-4-benzyl-3-ethanoyloxazolidin-2-one 464 (0.112 g, 0.511 mmol), lithium iodide (0.280 g, 2.09 mmol), ammonium chloride (0.0545 g, 1.03 mmol), and 2.5 mL of chloroform were added. The vial was then capped and the mixture was stirred at 50 °C in an oil bath for 16 hours. After being allowed to cool to room temperature, DBU (0.230 mL, 1.54 mmol) was added. After 6 hours at room temperature, the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (30% EtOAc in hexanes) to afford 230 (0.0554 g, 62\%) as a clear oil, along with 0.0089 g (10\%) of the deacylation product (\textit{S})-4-benzyl-2-oxazolidinone (467).

\textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}) δ 7.31-7.28 (m, 2H, ArH), 7.23-7.19 (m, 3H, ArH), 4.38-4.32 (m, 1H, NCH), 4.17 (dd, J = 9.5, 8.5 Hz, 1H, -\textit{CH}\textsubscript{2}H\textsubscript{B}O), 3.93 (dd, J = 8.5, 7.5 Hz, 1H, -\textit{CH}\textsubscript{2}H\textsubscript{B}O), 3.08 (dd, J = 14.0, 5.5 Hz, 1H, -\textit{CH}\textsubscript{2}H\textsubscript{B}Ar), 2.64 (dd, J = 13.5, 8.5 Hz, 1H, -\textit{CH}\textsubscript{2}H\textsubscript{B}Ar), and 1.96 (d, J = 1.0 Hz, 3H, -\textit{CH}\textsubscript{3}).

\textbf{13C NMR} (125 MHz, CDCl\textsubscript{3}) δ 165.2, 138.2, 129.3, 128.7, 126.6, 71.9, 67.6, 41.9, and 14.1.

\textbf{HRMS} (ESI) Calcd for (C\textsubscript{11}H\textsubscript{13}NO + Na\textsuperscript{+}): 198.0889. Found: 198.0913.

\textbf{GC-MS} \textit{t}\textsubscript{r} = 8.17 min; m/z: 175, 145, 130, 115, 103, 91, 84, and 56.

\textbf{IR} (neat) 3061, 3028, 2970, 2931, 2906, 2859, 1674, 1603, 1497, 1475, 1454, 1439, 1387, 1345, 1231, 1031, 984, 914, 855, 754, 702, 667, and 614 cm\textsuperscript{-1}.

\textbf{TLC} \textit{R}\textsubscript{f} = 0.50 in 70\% EtOAc in hexanes.

\textit{[\alpha]}\textsuperscript{RT} = -47.6 (c = 0.235, CHCl\textsubscript{3}).
(S)-4-Benzyl-2-ethyl-4,5-dihydrooxazole (468)\(^{102}\)

To a 6 mL screw cap vial equipped with a stirbar, (S)-4-benzyl-3-propanoyloxazolidin-2-one 415 (0.0936 g, 0.402 mmol), lithium iodide (0.218 g, 1.63 mmol), ammonium chloride (0.0480 g, 0.906 mmol), and 2.0 mL of chloroform were added. The vial was then capped and the mixture was stirred at 50 °C in an oil bath for 16 hours. After being allowed to cool to room temperature, 0.185 mL (1.24 mmol) of DBU was added. After 6 hours at room temperature, the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (30% EtOAc in hexanes) to afford 468 (0.0541 g, 71%) as a clear oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.31-7.28 (m, 2H, ArH), 7.23-7.19 (m, 3H, ArH), 4.39-4.33 (m, 1H, NCH), 4.14 (dd, \(J = 9.0, 9.0\) Hz, 1H, -CHaHbO), 3.94 (dd, \(J = 8.0, 7.5\) Hz, 1H, -CHaHbO), 3.11 (dd, \(J = 13.5, 4.5\) Hz, 1H, -CHaHbAr), 2.63 (dd, \(J = 13.5, 9.0\) Hz, 1H, -CHaHbAr), 2.27 (q, \(J = 7.5\) Hz, 2H, -CHaHbCH\(_3\)), and 1.18 (t, \(J = 7.5\) Hz, 3H, -CH\(_2\)CH\(_3\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 169.3, 138.1, 129.4, 128.6, 126.6, 71.7, 67.3, 41.9, 21.6, and 10.5.

HRMS (ESI) Calcd for (C\(_{12}\)H\(_{16}\)NO\(_5\))\(^+\): 190.1226. Found: 190.1247.

GC-MS \(t_r = 8.7\) min; m/z: 189, 159, 130, 115, 98, 91, 70, and 51.

IR (neat) 3064, 3027, 2979, 2946, 2921, 2900, 1683, 1667, 1654, 1603, 1497, 1454, 1377, 1358, 1270, 1214, 1185, 1016, 993, 962, 921, 754, and 701 cm\(^{-1}\).

TLC \(R_f = 0.33\) in 30% EtOAc in hexanes.

\([\alpha]^{RT}_{D} = -26.5\) (c = 0.200, CHCl\(_3\)).
(**S**)-4-Benzyl-2-isopropyl-4,5-dihydrooxazole (469)\(^{102}\)

To a 6 mL screw cap vial equipped with a stirbar, (**S**)-4-benzyl-3-(2-methylpropanoyl)-oxazolidin-2-one 466 (0.126 g, 0.510 mmol), lithium iodide (0.268 g, 2.00 mmol), ammonium chloride (0.0540 g, 1.02 mmol), and 2.5 mL of chloroform were added. The vial was then capped and the mixture was stirred at 50 °C in an oil bath for 16 hours. After being allowed to cool to room temperature, DBU (0.230 mL, 1.54 mmol) was added. After 6 hours at room temperature the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (40% EtOAc in hexanes) to afford 469 (0.0850 g, 82%) as a clear oil.

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.28 (m, 2H, ArH), 7.23-7.19 (m, 3H, ArH), 4.35 (ddddd, \(J = 9.5, 8.0, 7.0, 5.0, 1.0\) Hz, 1H, NCH), 4.12 (dd, \(J = 9.0, 8.5\) Hz, 1H, -CHaHbO), 3.95 (dd, \(J = 8.5, 7.0\) Hz, 1H, -CHaHbO), 3.10 (dd, \(J = 14.0, 5.0\) Hz, 1H, -CHaHbAr), 2.63 (dd, \(J = 13.5, 8.5\) Hz, 1H, -CHaHbAr), 2.54 (d of septets, \(J = 0.5, 7.0\) Hz, 1H, -CHMe\(_2\)), 1.181 (d, \(J = 7.0\) Hz, 3H, -CH\(_3\)), and 1.17 (d, \(J = 7.0\) Hz, 3H, -CH\(_3\))

**\(^13\)C NMR** (125 MHz, CDCl\(_3\)) \(\delta\) 172.4, 138.1, 129.5, 128.6, 126.6, 71.5, 67.2, 41.8, 28.3, 19.92, and 19.88.

**HRMS** (ESI) Calcd for (C\(_{13}\)H\(_{17}\)NO\(_5\) + H\(^+\)): 204.1383. Found: 204.1377.

**GC-MS** \(t_r = 8.9\) min; m/z: 203, 188, 173, 130, 91, 84, 65, and 51.

**IR** (neat) 3064, 3027, 2973, 2934, 2900, 1667, 1654, 1603, 1497, 1471, 1454, 1386, 1361, 1199, 1147, 1095, 979, 929, 753, and 702 cm\(^{-1}\).

**TLC** \(R_f = 0.50\) in 40% EtOAc in hexanes.

[\(\alpha\)]\(^{RT}\) = -29.8 (c = 0.255, CHCl\(_3\)).

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**\((R)\)-4-Benzyl-3-((2S,3S,E)-3-(benzyloxymethoxy)-2-methylhex-4-enoyl)oxazolidin-2-one (470)**

In a 25 mL round bottom flask equipped with a stirbar, **\((R)\)-4-benzyl-3-((2S,3S,E)-3-hydroxy-2-methylhex-4-enoyl)oxazolidin-2-one** **\(\textit{ent-410a}\)** (0.484 g, 1.59 mmol), benzyl
chloromethyl ether (0.60 mL, 2.53 mmol), diisopropylethylamine (0.60 mL, 3.44 mmol), and 3 mL of DCM were added. After 12 hours the mixture was quenched with 15 mL pH = 10 buffer, and extracted with diethyl ether (2 x 25 mL). The combined organic layers were concentrated in vacuo and purified by flash chromatography giving 470 (0.657 g, 97%) as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.36-7.24 (m, 10H, ArH), 5.81 (dq, $J = 15.0, 6.5$ Hz, 1H, C=CHMe), 5.33 (ddq, $J = 15.5, 9.5, 1.5$ Hz, 1H, -CH=CHMe), 4.83 (d, $J = 7.0$ Hz, 1H, BnOC=HbO), 4.78-4.72 (m, 1H, NCH), 4.72 (d, $J = 11.5$ Hz, 1H, PhCHAhbO), 4.43 (dd, $J = 9.5, 9.0$ Hz, 1H, -CHAhbO), 4.42 (d, $J = 11.5$ Hz, 1H, PhCHAhbO), 4.19 (dd, $J = 9.0, 8.0$ Hz, 1H, -CHAhbO), 4.15-4.08 (m, 2H), 3.28 (dd, $J = 13.5, 3.0$ Hz, 1H, -CHAhbAr), 2.81 (dd, $J = 13.5, 9.5$ Hz, 1H, -CHAhbAr), 1.75 (dd, $J = 6.0, 1.0$ Hz, 3H, -CHCH$_3$), and 1.12 (d, $J = 7.0$ Hz, 3H, -CH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.9, 153.4, 138.2, 135.5, 133.1, 129.7, 129.2, 128.6, 128.4, 128.3, 127.8, 127.5, 91.4, 79.4, 69.6, 65.9, 55.3, 42.3, 38.1, 18.0, 14.4.

HRMS (ESI) Calcd for (C$_{25}$H$_{29}$NO$_5$ + Na$^+$): 446.1938. Found: 446.1944.

IR (neat) 3030, 2970, 2937, 2919, 2884, 1782, 1699, 1497, 1454, 1389, 1351, 1250, 1212, 1146, 1102, 1035, 1027, 973, 924, 728, and 700 cm$^{-1}$.

TLC $R_f$ = 0.70 in 40% EtOAc in hexanes.

(R)-4-Benzyl-2-((2S,3S,E)-3-(benzyloxymethoxy)hex-4-en-2-yl)-4,5-dihydrooxazole (471)

To a 6 mL screw cap vial equipped with a stirbar, (R)-4-Benzyl-3-((2S,3S,E)-3-(benzyloxymethoxy)-2-methylhex-4-enoyl)oxazolidin-2-one 470 (0.0374 g, 0.0884 mmol), lithium iodide (0.575 g, 0.429 mmol), ammonium chloride (0.0105 g, 0.198 mmol), and 0.33 mL of chloroform was added. The vial was then capped and the mixture was stirred at 50 °C in an oil bath for 12 hours. After allowing the reaction mixture to cool to room temperature, DBU (0.049 mL, 0.329 mmol) was added. After 6 hours at
room temperature the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (30% EtOAc in hexanes) to afford 471 (0.0231 g, 69%) as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.33-7.25 (m, 7H, ArH), 7.22-7.17 (m, 3H, ArH), 5.75 (dq, J = 15.0, 6.5 Hz, 1H, -CH=CHMe), 5.26 (ddq, J = 15.5, 9.0, 2.0 Hz, 1H, -CH=CHMe), 4.81 (d, 7.0 Hz, 1H, BnOCH$_2$HbO), 4.675 (d, J = 7.5 Hz, 1H, BnOCH$_2$HbO), 4.674 (d, J = 11.5 Hz, 1H, ArCH$_2$HbO), 4.45 (ArCH$_2$HbO), 4.09 (dd, J = 9.5, 8.5 Hz, 1H, -CH$_2$HbO), 3.94 (dd, J = 8.5, 7.5 Hz, 1H, BOMOC$_2$H), 3.14 (dd, J = 13.5, 4.5 Hz, 1H, -CH$_2$HbAr), 2.72 (dq, J = 7.0, 7.5 Hz, 1H, CH$_3$CH), 1.73 (dd, J = 6.5, 2.0 Hz, 3H, CH=CHCH$_3$), and 1.11 (d, J = 7.5 Hz, 3H, CH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.5, 138.2, 132.3, 129.4, 128.7, 128.6, 128.5, 128.1, 127.8, 126.6, 115.1, 91.4, 78.7, 71.7, 69.3, 67.3, 42.0, 39.1, 18.0, and 14.3.


GC-MS $t_r = 14.7$ min; m/z: 379, 355, 341, 327, 288, 258, 243, 242, 228, 218, 207, 188, 161, 150, 117, 91, and 65.

IR (neat) 3030, 2939, 2885, 1667, 1654, 1505, 1455, 1383, 1174, 1100, 1036, 1027, 971, 924, 733, and 698 cm$^{-1}$.

TLC $R_f = 0.50$ in 40% EtOAc in hexanes.

[$\alpha$]$_{D}$ = +70.5 (c = 0.210, CHCl$_3$).

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(S)-3,4-Dibenzyloxazolidin-2-one (472)$^{103}$

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxazolidinone 454 (1.09 g, 6.16 mmol) and 20 mL of THF was added and placed under N$_2$ atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 2.5 mL, 6.25 mmol) was added. After 15 minutes benzyl bromide (0.75 mL, 6.31 mmol) was added dropwise. After 3 hours the reaction was allowed to warm to room temperature. After 20 hours the
solvent was then removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq NaOH. This aqueous layer was extracted again with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. Medium Pressure Liquid Chromatography was performed (30% EtOAc in hexanes) to yield 472 (1.20 g, 73%), of the desired product as a clear oil.

\(^1\)H NMR (500 MHz, CDCl₃) δ 7.37-7.24 (m, 8H, ArH), 7.04 (d, J = 7.0 Hz, 2H, ArH), 4.87 (d, J = 15.0 Hz, 1H, ArCHaHbN), 4.13 (dd, J = 9.0, 8.5 Hz, 1H, -CHaHbO), 4.12 (d, J = 15.0 Hz, 1H, ArCHaHbN), 4.01 (dd, J = 9.0, 6.0 Hz, 1H, -CHaHbO), 3.80 (dddd, J = 8.5, 8.5, 5.5, 5.5 Hz, 1H, Ar), and 2.63 (dd, J = 13.5, 9.0 Hz, 1H, -CHaHbAr).

\(^1^3\)C NMR (125 MHz, CDCl₃) δ 158.5, 136.0, 135.7, 129.2, 129.1, 129.0, 128.4, 128.2, 127.3, 67.1, 55.5, 46.5, and 38.6.

HRMS (ESI) Calcd for (C\(_{17}\)H\(_{17}\)NO\(_2\) + Na\(^+\)): 290.1152. Found: 290.1179.

GC-MS \(t_r = 13.6\) min; m/z: 267, 176, 130, 117, 104, 91, 77, 65, and 51.

IR (neat) 3062, 3029, 2969, 2924, 1966, 1754, 1747, 1605, 1495, 1359, 1258, 1174, 1091, 1065, 1028, 801, 762, 740, and 703 cm\(^{-1}\).

TLC \(R_f = 0.23\) in 30% EtOAc in hexanes.

\([\alpha]^{\text{RT}} = -9.0\) (c = 1.0, CHCl₃).

\[(S)-4\text{-Benzyl-3-tosyloxazolidin-2-one (473)}\] \(^{104}\)

To a 100 mL round bottom flask equipped with a stirbar, \((S)-4\text{-benzyl-2-oxazolidinone 454 (1.01 g, 5.70 mmol)}\) and 20 mL of THF was added and placed under N\(_2\) atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 2.4 mL, 6.0 mmol) was added. After 20 minutes paratoluenesulfonyl chloride (1.15 g, 6.03 mmol) was added dropwise. After 2.5 hours the reaction was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH₄Cl. The majority of the THF
was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. Medium Pressure Liquid Chromatography was performed (30% EtOAc in hexanes) to yield 473 (1.48 g, 78%), of the desired product as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.01 (d, J = 8.5 Hz, 2H, ArH), 7.38-7.26 (m, 5H, ArH), 7.21 (d, J = 7.0 Hz, 2H, ArH), 4.46 (dddd, J = 11.0, 7.5, 3.0, 3.0 Hz, 1H, CHN), 4.15 (dd, J = 9.0, 9.0 Hz, 1H, -CH$_2$HbO), 4.09 (dd, J = 8.5, 3.5 Hz, 1H, -CHaHbO), 4.09 (dd, J = 3.5, 3.5 Hz, 1H, -CHbHbO), 3.53 (dd, J = 13.0, 3.0 Hz, 1H, -CHbHbAr), 2.83 (dd, J = 13.5, 10.0 Hz, 1H, -CHaHbAr), and 2.4 (s, 3H, ArCH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 152.2, 145.9, 135.3, 134.8, 130.0, 129.6, 129.3, 128.7, 127.7, 66.8, 58.2, 39.9, and 21.9.

HRMS (ESI) Calcd for (C$_{17}$H$_{17}$NO$_4$S$^+$ Na$^-$): 354.0770. Found: 354.0778.

GC-MS $t_r$ = 15.0 min; m/z: 331, 240, 207, 155, 117, 91, 77, and 65.

IR (thin film) 3063, 3028, 2929, 1781, 1599, 1495, 1450, 1367, 1169, 1127, 1093, 1063, 1040, 1002, 812, 758, 736, 703, 666, and 619 cm$^{-1}$.

TLC $R_f$ = 0.35 in 30% EtOAc in hexanes.

$[\alpha]^{25}_{D}$ = +15.9 (c = 0.520, CHCl$_3$).

mp = 134-136 °C.

\[ \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Bn} \\
\text{O} \\
\text{N} \\
\text{Bn} \\
\end{array} \xrightarrow{\text{P$_2$S$_5$}} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Bn} \\
\text{O} \\
\text{S} \\
\end{array} \]

(s)-4-Benzyl-3-(phenylcarbonothioyl)oxazolidin-2-one (477)

In a 25 mL round bottom flask, (s)-4-benzyl-3-(phenylcarbonyl)oxazolidin-2-one 451 (0.218 g, 0.776 mmol), P$_2$S$_5$ (0.338 g, 1.52 mmol), and toluene (7.0 mL) were added. The mixture was refluxed at 110 °C under nitrogen for 24 hours before being allowed to cool to room temperature. The mixture was then separated by flash chromatography (12% EtOAc in hexanes) to afford 477 (0.173 g, 75%) as a yellow solid.
\(^{1}H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.48-7.45 (m, 3H, ArH), 7.38-7.25 (m, 7H, ArH), 5.27 (dddd, \(J = 10.5, 7.0, 3.0, 3.0\) Hz, 1H, NCH), 4.37 (dd, \(J = 9.0, 7.5\) Hz, 1H, -CH\(_a\)HbO), 4.31 (dd, \(J = 9.0, 3.5\) Hz, 1H, -CH\(_a\)HbO). 3.73 (dd, \(J = 13.5, 3.0\) Hz, 1H, -CH\(_a\)HbAr), and 2.94 (dd, \(J = 13.5, 10.0\) Hz, 1H, -CH\(_a\)HbAr).

\(^{13}C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 206.0, 151.1, 142.8, 135.3, 131.3, 129.6, 129.3, 127.9, 127.7, 127.5, 66.2, 60.7, and 36.3.

HRMS (ESI) Calcd for (C\(_{17}\)H\(_{15}\)NO\(_2\)S + Na\(^{+}\)): 320.0716. Found: 320.0774.


IR (neat) 3062, 3026, 1798, 1794, 1791, 1455, 1445, 1390, 1344, 1321, 1290, 1246, 1169, 1002, 990, 753, 728, and 693 cm\(^{-1}\).

TLC \(R_f = 0.60\) in 30% EtOAc in hexanes.

\(\alpha\)^RT = +296 (c = 0.225, CHCl\(_3\)).

mp = 157-160 °C.

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\((S)\)-4-Benzyl-3-(2,2-dimethylpropanoyl)oxazolidin-2-one (S401)

To a 100 mL round bottom flask equipped with a stirbar, \((S)\)-4-benzyl-2-oxazolidinone 454 (1.04 g, 5.87 mmol) and 20 mL of THF was added and placed under N\(_2\) atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 2.50 mL, 6.25 mmol) was added. After 20 minutes 2,2-dimethylpropanoyl chloride (0.79 mL, 6.5 mmol) was added dropwise. After 2.5 hours the reaction mixture was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH\(_4\)Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq. NaOH. This aqueous layer was extracted again with CH\(_2\)Cl\(_2\) (2 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield S401 (1.41 g, 92%) of the desired product as a white solid.
\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \(\delta 7.34-7.31\) (m, 2H, ArH), 7.28-7.25 (m, 1H, ArH), 7.22 (d, \(J = 7.0\) Hz, 2H, ArH), 4.70 (dddd, \(J = 10.0, 7.5, 3.0, 3.0\) Hz, 1H, NCH), 4.20 (dd, \(J = 8.5, 8.0\) Hz, 1H, -CH\textsubscript{2}H\textsubscript{2}O), 4.14 (dd, \(J = 9.0, 3.0\) Hz, 1H, -CH\textsubscript{2}H\textsubscript{2}O), 3.23 (dd, \(J = 13.5, 3.0\) Hz, 1H, -CH\textsubscript{2}H\textsubscript{2}Ar), 2.76 (dd, \(J = 13.5, 10.0\) Hz, 1H, -CH\textsubscript{2}H\textsubscript{2}Ar), and 1.40 (s, 9H, tBu).

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}) \(\delta 178.7, 152.5, 135.7, 129.6, 129.1, 127.5, 66.3, 57.6, 41.9, 38.0,\) and 26.5.

\textbf{HRMS} (ESI) Calcd for (C\textsubscript{15}H\textsubscript{19}NO\textsubscript{3} + Na\textsuperscript{+}): 284.1257. Found: 284.1297.

\textbf{GC-MS} \(t_r = 11.4\) min; m/z: 261, 246, 204, 190, 177, 170, 160, 142, 133, 117, 91, 86, 77, 65, and 57.

\textbf{IR} (neat) 3086, 3024, 2974, 2920, 2874, 1789, 1781, 1688, 1497, 1483, 1463, 1454, 1388, 1349, 1289, 1273, 1242, 1199, 1191, 1114, 1054, 1038, 1019, 846, 769, 732, 699, and 653 cm\textsuperscript{-1}.

\textbf{TLC} \(R_f = 0.72\) in 30\% EtOAc in hexanes.

\([\alpha]\text{RT} = +40.2\) (c = 1.12, CHCl\textsubscript{3}).

\(\text{mp} = 90-92\) °C.

\(\text{O} \quad \text{O} \quad \text{B} \quad \text{S} \quad \text{O} \quad \text{O} \quad \text{Me} \quad \text{LiI}, \text{CH}_2\text{Cl}_2 \quad \text{HNI} \quad \text{Bn} \quad \text{S} \quad \text{O} \quad \text{O} \quad \text{Me} \quad 473 \quad 487\)

\((S)-N-(1-Iodo-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (487)\textsuperscript{105}\)

To a 6 mL screw cap vial equipped with a stirbar, \((S)-4-benzyl-3-tosyloxazolidin-2-one 473\) (0.0417 g, 0.126 mmol), lithium iodide (0.0340 g, 0.254 mmol), ammonium chloride (0.0135 g, 0.255 mmol), and 0.60 mL of chloroform were added. The vial was then capped and the mixture was placed in an oil bath at 50 °C while stirring for 12 hours. The mixture was allowed to come to room temperature and was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (30\% EtOAc in hexanes) to afford 487 (0.0240 g, 66\%) as a drab yellow solid.
$^1\text{H NMR}$ (500 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J = 8.5$ Hz, 2H, ArH), 7.25-7.21 (m, 5H, ArH), 7.07-7.05 (m, 2H, ArH), 4.65 (d, $J = 8.0$ Hz, 1H, CNH), 3.25-3.18 (m, 1H, CNH), 3.17 (d, $J = 4.5$ Hz, 2H, CH$_2$I), 2.80 (dd, $J = 13.5$, 7.0 Hz, 1H, -CHaHbAr), 2.75 (dd, $J = 14.0$, 6.5 Hz, 1H, -CHaHbAr), and 2.42 (s, 3H, ArCH$_3$).

$^{13}\text{C NMR}$ (125 MHz, CDCl$_3$) $\delta$ 143.6, 137.2, 136.0, 129.7, 129.1, 128.8, 127.1, 127.0, 54.0, 41.1, 21.5, and 13.4.

$\text{HRMS}$ (ESI) Calcd for (C$_{16}$H$_{18}$INO$_2$S + Na$^+$): 437.9995. Found: 438.0036.

$\text{GC-MS}$ $t_r = 13.5$ min; m/z: 287, 207, 172, 155, 132, 117, 105, 91, 77, 65, and 51.

$\text{IR}$ (neat) 3265, 3043, 3027, 1593, 1492, 1455, 1422, 1348, 1317, 1304, 1217, 1160, 1089, 1059, 1032, 958, 941, 908, 844, 809, 743, and 698 cm$^{-1}$.

$\text{TLC}$ $R_f = 0.50$ in 30% EtOAc in hexanes.

$[\alpha]^{RT}$ = $-8.2$ (c = 0.195, CHCl$_3$).

$\text{mp} = 95$-$99$ °C.

(S)-1-(4-Benzyl-2-oxooxazolidin-3-yl)butane-1,3-dione (S402)

In a 25 mL round bottom flask, (S)-4-benzyl-2-oxazolidinone 454 (0.370 g, 2.09 mmol), dioxinone S403 (0.309 mL, 2.33 mmol), and 10 mL of toluene were added. The mixture was heated at reflux at 110 °C in an oil bath for 2 hours before being allowed to cool to room temperature. The solvent was then removed in vacuo, and the mixture purified by medium pressure liquid chromatography (30% EtOAc in hexanes) to afford S402 (0.498 g, 91%) as a slightly cloudy oil.

$^1\text{H NMR}$ (500 MHz, CDCl$_3$) $\delta$ 7.35-7.33 (m, 2H, ArH), 7.29-7.21 (m, 3H, ArH), 4.72 (dddd, $J = 10.5$, 7.5, 3.0, 3.0 Hz, 1H, NCH), 4.23 (dd, $J = 9.0$, 7.5 Hz, 1H, -CHaHbO), 4.17 (dd, $J = 9.0$, 2.5 Hz, 1H, -CHaHbO), 4.07 (d, $J = 16.5$ Hz, 1H, NCOCHaHbCOMe), 4.06 (d, $J = 16.5$ Hz, 1H, NCOCHaHbCOMe), 3.38 (dd, $J = 13.5$, 3.5 Hz, 1H, -CHaHbAr), 2.80 (dd, $J = 13.5$, 9.5 Hz, 1H, -CHaHbAr), and 2.29 (s, 3H, COCH$_3$).
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.1, 166.6, 153.9, 135.3, 129.6, 129.2, 127.5, 66.6, 55.2, 51.6, 37.8, and 30.3.

HRMS (ESI) Calcd for (C$_{14}$H$_{15}$NO$_4$ + Na$^+$): 284.0893. Found: 284.0900.

GC-MS product unstable to GC (acylketene).

IR (neat) 3032, 3004, 2983, 2922, 1779, 1773, 1724, 1698, 1450, 1390, 1359, 1329, 1298, 1219, 1158, 1116, 1074, 1055, 758, 739, and 705 cm$^{-1}$.

TLC $R_f = 0.25$ in 30% EtOAc in hexanes. 

$[\alpha]^{\text{RT}}_D = +62.2. \ (c = 0.360, \ \text{CHCl}_3)$.

(S)-4-Benzyl-3-(2-bromoethanoyl)oxazolidin-2-one (S404)

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxazolidinone 454 (0.854 g, 4.82 mmol) and 40 mL of THF was added and placed under N$_2$ atmosphere. The flask was then cooled to -78 °C, and n-BuLi (2.5M in hexanes, 1.95 mL, 4.87 mmol) was added. After 15 minutes bromoacetyl bromide (0.46 mL, 5.28 mmol) was added dropwise. After 2.5 hours the reaction was allowed to warm to room temperature and was quenched with 15 mL of satd. aq. NH$_4$Cl. The majority of the THF was removed in vacuo. Methylene chloride was added and this solution was washed with 10% aq NaOH. This aqueous layer was extracted again with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic layers were washed two more times with 10% sodium hydroxide (30 mL), washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo to yield S404 (1.25 g, 87%) as a light brown oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.36-7.29 (m, 3H, ArH), 7.22-7.17 (m, 2H, ArH), 4.70 (dddd, $J = 9.0, 7.5, 3.5, 3.5$ Hz, 1H, NCH), 4.56 (d, $J = 12.5$ Hz, 1H, CHaHbBr), 4.54 (d, $J = 13.0$ Hz, 1H, CHaHbBr), 4.28 (dd, $J = 9.0, 8.0$ Hz, 1H, -CHaHbO), 4.23 (dd, $J = 9.0, 3.0$ Hz, 1H, -CHaHbO), 4.33 (dd, $J = 13.5, 3.0$ Hz, 1H, -CHaHbAr), and 2.81 (dd, $J = 13.5, 9.5$ Hz, 1H, -CHaHbAr).
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.1, 153.1, 134.9, 129.6, 129.3, 129.1, 127.7, 127.5, 66.8, 55.6, 37.7, and 28.4.

HRMS (ESI) Calcd for (C$_{12}$H$_{12}$BrNO$_3$ + Na$^+$): 319.9893. Found: 319.9885.

GC-MS $t_r$ = 11.7 min; m/z: 253, 224, 207, 174, 160, 134, 116, 91, 86, 77, 65, and 51.

IR (neat) 3062, 3028, 2973, 2922, 1783, 1716, 1685, 1497, 1478, 1455, 1418, 1393, 1360, 1325, 1207, 1156, 1100, 1052, 1018, 997, 760, 739, 703, and 666 cm$^{-1}$.

TLC $R_f$ = 0.45 in 30% EtOAc in hexanes.

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$(S)$-Ethyl 4-benzyl-2-oxooxazolidine-3-carboxylate (489)

To a 100 mL round bottom flask equipped with a stirbar, $(S)$-4-benzyl-2-oxazolidinone 217 (0.903 g, 5.10 mmol) and 30 mL of THF was added and placed under $N_2$ atmosphere. The flask was then cooled to 0 °C, and n-BuLi (2.5M in hexanes, 2.0 mL, 5.0 mmol) was added. After 20 minutes methyl chloroformate (0.40 mL, 5.2 mmol) was added dropwise and allowed to warm to room temperature. After 12 hours the reaction mixture was quenched with 15 mL of water. The majority of the THF was removed in vacuo. Methylene chloride was added and extracted with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic layers were concentrated in vacuo and purified by flash chromatography (40% EtOAc/hexanes) to afford 489 (1.01 g, 85%) as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36-7.33 (m, 2H, ArH), 7.30-7.27 (m, 1H, ArH), 7.22-7.20 (m, 2H, ArH), 4.54 (dddd, $J$ = 9.5, 7.5, 3.5, 3.0 Hz, 1H, NCH), 4.21 (ddd, $J$ = 9.0, 8.0, 0.5 Hz, 1H, -CH$_2$HbO), 4.14 (dd, $J$ = 9.0, 3.0 Hz, 1H, -CH$_2$HbO), 3.94 (s, 3H, OMe), 3.33 (dd, $J$ = 13.0, 3.5 Hz, 1H, -CH$_2$HbAr), and 2.82 (dd, $J$ = 13.5, 9.5 Hz, 1H, -CH$_2$HbAr).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 151.9, 135.2, 129.6, 129.2, 127.6, 66.0, 56.3, 54.4, and 38.6.

HRMS (ESI) Calcd for (C$_{12}$H$_{13}$NO$_4$ + Na$^+$): 258.0737. Found: 258.0764.

GC-MS $t_r$ = 11.3 min; m/z: 235, 191, 176, 160, 144, 134, 116, 100, 91, 72, 65, and 56.
IR (neat) 3084, 3064, 3028, 2990, 2961, 2932, 1780, 1721, 1496, 1478, 1445, 1439, 1400, 1372, 1329, 1229, 1190, 1094, 1070, 1014, 981, 777, 756, and 705 cm⁻¹.

**TLC** R<sub>f</sub> = 0.70 in 40% EtOAc in hexanes.

[α]<sub>RT</sub> = 47.4 (c = 0.405, CHCl₃).

mp = 112-114 °C.

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**S-Isobutyl 4-benzyl-2-oxooxazolidine-3-carboxylate (490)**

To a 100 mL round bottom flask equipped with a stirbar, (S)-4-benzyl-2-oxooxazolidinone 454 (0.995 g, 5.63 mmol) and 30 mL of THF was added and placed under N₂ atmosphere. The flask was then cooled to 0 °C, and n-BuLi (2.5M in hexanes, 2.25 mL, 5.62 mmol) was added. After 20 minutes isobutyl chloroformate (0.73 mL, 5.6 mmol) was added dropwise and allowed to warm to room temperature. After 12 hours the reaction mixture was quenched with 15 mL of satd. aq. NaHCO₃. The majority of the THF was removed in vacuo. Methylene chloride was added and extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were concentrated in vacuo and purified by flash chromatography (25% EtOAc/hexanes) to afford 490 (1.33 g, 86%) as a white solid.

**¹H NMR** (500 MHz, CDCl₃) δ 7.36-7.33 (m, 2H, ArH), 7.30-7.27 (m, 1H, ArH), 7.21-7.19 (m, 2H, ArH), 4.52 (ddd, J = 10.0, 8.0, 3.0, 3.0 Hz, 1H, NCH), 4.19 (dd, J = 8.5, 8.0 Hz, 1H, -CH₂HBO), 4.12 (dd, J = 9.5, 3.0 Hz, 1H, -CH₂HBO), 4.11 (d, J = 6.5 Hz, 2H, -CO₂CH₂-), 3.34 (dd, J = 13.0, 3.5 Hz, 1H, -CH₂HBO), 2.82 (dd, J = 13.5, 10.0 Hz, 1H, -CH₂HBO), 2.08 (septet, J = 7.0 Hz, 1H, CHMe₂), and 1.02 (d, J = 6.5 Hz, 6H, -CH₃₂).

**¹³C NMR** (125 MHz, CDCl₃) δ 151.8, 151.2, 135.2, 129.5, 129.2, 127.6, 73.5, 65.9, 56.2, 38.7, 28.0, and 19.2.

**HRMS** (ESI) Calcd for (C₁₅H₁₉NO₄ + Na⁺): 300.1206. Found: 300.1220.

**GC-MS** t<sub>r</sub> = 12.2 min; m/z: 277, 237, 221, 204, 177, 160, 134, 116, 91, 86, 65, and 57.
IR (neat) 3030, 2963, 2934, 2878, 1821, 1724, 1471, 1455, 1397, 1381, 1358, 1316, 1294, 1273, 1212, 1195, 1083, 1062, 1014, 983, 773, 752, 736, and 701 cm\(^{-1}\).

**TLC** \(R_f = 0.45\) in 30% EtOAc in hexanes.

\([\alpha]^\text{RT}\) = +30.8 (c = 0.480, CHCl\(_3\)).

mp = 50-52 °C.

(\(S\))-Phenyl 4-benzyl-2-oxooxazolidine-3-carboxylate (491)

To a 100 mL round bottom flask equipped with a stirbar, (\(S\))-4-benzyl-2-oxazolidinone 454 (0.845 g, 4.77 mmol) and 30 mL of THF was added and placed under N\(_2\) atmosphere. The flask was then cooled to 0 °C, and n-BuLi (2.5M in hexanes, 1.9 mL, 4.8 mmol) was added. After 20 minutes phenyl chloroformate (0.60 mL, 4.8 mmol) was added dropwise and allowed to warm to room temperature. After 12 hours the reaction mixture was quenched with 15 mL of satd. aq. NaHCO\(_3\). The majority of the THF was removed in vacuo. Methylene chloride was added and extracted with CH\(_2\)Cl\(_2\) (3 x 25 mL). The combined organic layers were concentrated in vacuo and purified by flash chromatography (30% EtOAc/hexanes) to afford 491 (1.25 g, 89%) as a white solid.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.41 (m, 2H, ArH), 7.37-7.34 (m, 2H, ArH), 7.31-7.28 (m, 2H, ArH), 7.26-7.22 (m, 4H, ArH), 4.66 (dddd, \(J = 3.0, 3.0, 7.5, 8.0, 11.0 \text{ Hz}, 1H, \text{NCH}\)), 4.29 (dd, \(J = 8.5, 8.5 \text{ Hz}, 1H, -\text{CHaHbO}\)), 4.22 (dd, \(J = 9.0, 2.5 \text{ Hz}, 1H, -\text{CHaHbO}\)), 3.42 (dd, \(J = 13.5, 3.0 \text{ Hz}, 1H, -\text{CHaHbAr}\)), and 2.93 (dd, \(J = 13.0, 9.5 \text{ Hz}, 1H, -\text{CHaHbAr}\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 151.5, 150.3, 149.7, 135.0, 129.8, 129.6, 129.3, 127.7, 126.7, 121.5, 66.1, 56.5, and 38.7.

**HRMS** (ESI) Calcd for (C\(_{17}\)H\(_{15}\)NO\(_4\) + Na\(^+\)): 320.0893. Found: 320.0901.

**GC-MS** \(t_r = 13.9\text{ min}; m/z: 297, 253, 204, 160, 142, 117, 94, 91, 77, \text{ and } 65.\)

IR (neat) 3070, 3028, 2925, 1825, 1798, 1736, 1591, 1494, 1455, 1392, 1364, 1317, 1273, 1202, 1180, 1161, 1079, 1068, 1032, 998, 914, 764, 746, 702, and 689 cm\(^{-1}\).
TLC R_f = 0.45 in 30% EtOAc in hexanes.

[α]^{RT} = +40.7 (c = 0.395, CHCl_3).

mp = 130-132 °C.

(5)-4-Benzyl-2-oxo-N-phenyloxazolidine-3-carboxamide (492)

In a 15 mL culture tube with a Teflon lined cap, (5)-4-benzyl-2-oxazolidinone 454 (0.518 g, 2.93 mmol), phenyl isocyanate (0.320 mL, 2.94 mmol), and 1 mL of toluene was added. The tube was capped and placed in an oil bath at 125 °C. After 20 hours, the mixture was allowed to cool to room temperature and separated by flash chromatography (30% EtOAc in hexanes) to afford 492 (0.680 g, 78%) as a drab white solid.

1^H NMR (500 MHz, CDCl_3) δ 9.92 (s, 1H, -NH), 7.54 (m, 2H, ArH), 7.37-7.33 (m, 4H, ArH), 7.30-7.27 (m, 1H, ArH), 7.25-7.23 (m, 2H, ArH), 7.16-7.12 (m, 1H, ArH), 4.76 (dddd, J = 9.0, 8.0, 3.0, 3.0, 1.0 Hz, 1H, NCH), 4.29 (dd, J = 9.5, 8.0 Hz, 1H, -CHaHbO), 4.24 (dd, J = 9.0, 3.0, 1.0 Hz, 1H, -CHaHbO), 3.42 (dd, J = 13.5, 3.5 Hz, 1H, -CHaHbAr), and 2.91 (dd, J = 13.5, 9.0 Hz, 1H, -CHaHbAr).

13^C NMR (125 MHz, CDCl_3) δ 155.8, 148.9, 137.2, 135.2, 129.7, 129.3, 129.2, 127.6, 124.6, 120.2, 66.7, 55.3, and 38.6.

HRMS (ESI) Calcd for (C_{17}H_{16}N_{2}O_{3} + Na^+): 319.1053. Found: 319.1059.

GC-MS t_r = 12.5 min; m/z: 253, 212, 207, 191, 177, 163, 147, 133, 119, 93, 77, 65, and 51.

IR (neat) 3313, 3275, 3062, 3029, 1755, 1707, 1601, 1556, 1500, 1448, 1400, 1356, 1312, 1272, 1222, 1100, 1076, 1008, 755, 693 cm^{-1}.

TLC R_f = 0.55 in 30% EtOAc in hexanes.

[α]^{RT} = 81.5 (c = 0.265, CHCl_3).

mp = 103-105 °C.
(S)-4-Benzyl-N-ethyl-2-oxazolidine-3-carboxamide (494)

In a 15 mL culture tube with a Teflon lined cap, (S)-4-benzyl-2-oxazolidinone 454 (0.962 g, 5.43 mmol), ethyl isocyanate (0.381 mL, 5.36 mmol), toluene (6 mL), and DMF (5 mL) of were added. The tube was capped and placed in an oil bath at 110 °C. After 5 days the mixture was allowed to cool to room temperature and separated by flash chromatography (30% EtOAc in hexanes), and then medium pressure liquid chromatography (20% EtOAc in hexanes) to afford 494 (0.118 g, 9%) as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.82 (s, 1H, N-H), 7.34-7.31 (m, 2H, ArH), 7.29-7.26 (m, 1H, ArH), 7.22-7.21 (m, 2H, ArH), 4.67 (dddd, $J = 9.0, 8.0, 3.0, 3.0$ Hz, 1H, NCH), 4.23 (ddd, $J = 8.5, 8.5, 0.5$ Hz, 1H, -CHaHbO), 4.17 (dd, $J = 9.0, 3.5$ Hz, 1H, -CHaHbAr), 3.36 (dd, $J = 13.5, 3.0$ Hz, 1H, -CHaHbAr), 2.85 (dd, $J = 13.5, 9.5$ Hz, 1H, -CHaHbAr), and 1.23 (t, $J = 7.0$ Hz, 3H, -CH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.8, 151.4, 135.5, 129.6, 129.1, 127.4, 66.6, 55.3, 38.8, 35.2, and 15.1.

HRMS (ESI) Calcd for (C$_{13}$H$_{16}$N$_2$O$_3$ + Na$^+$): 271.1053. Found: 271.1057.

GC-MS $t_r = 11.6$ min; m/z: 248, 233, 219, 204, 177, 157, 134, 115, 92, 91, 86, 77, 65, and 58.

IR (neat) 3351, 3028, 2975, 2932, 1756, 1697, 1540, 1454, 1401, 1358, 1270, 1229, 1177, 1105, 1006, 833, 765, and 702 cm$^{-1}$.

TLC $R_f$ = 0.23 in 20% EtOAc in hexanes.

$\left[\alpha\right]^{RT} = +109$ (c = 0.170, CHCl$_3$).

5-Methyl-3-(phenylcarbonyl)oxazolidin-2-one (495)$^{106}$
In a 25 mL flask, 1-amino-2-propanol S405 (1.04 g, 13.8 mmol), and ethylene carbonate (1.22 g, 13.8 mmol) were combined without solvent. After allowing to stand for 12 hours, NMR showed complete conversion to the acyclic carbamate. Potassium carbonate was added (1.0 g, 7.24 mmol) and the mixture heated to 150 °C for 1 hour. After allowing the mixture to cool at room temperature, NMR showed complete conversion to the desired oxazolidinone. The mixture was transferred to a 50 mL flask, then triethylamine (6.0 mL), benzoyl chloride (4.5 mL, 38.4 mmol), and 20 mL of methylene chloride was added along with a stirbar, and the solution was allowed to stir at room temperature for 2 days. The solution was then washed with 20 mL 10% aq. NaOH, and extracted with methylene chloride (3 x 20 mL). The combined organic layers were then concentrated in vacuo and purified by flash chromatography (25% EtOAc in hexanes). The product was then dissolved in a hot solution of EtOAc/pentane (1:2), and allowed to sit in a -20 °C freezer for 1 day. Vacuum filtration gave 495 (0.61 g, 21%) as white crystals.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.65 (d, $J = 8.0$ Hz, 2H, o-ArH), 7.54 (ddd, $J = 7.5$, 7.5, 1.0 Hz, 1H, p-ArH), 7.43 (ddd, $J = 8.0$, 7.5 Hz, 2H, m-ArH), 4.85-4.78 (m, 1H, CH$_3$CH), 4.23 (ddd, $J = 11.0$, 8.0, 2.0 Hz, 1H, NCH$_a$H$_b$), 3.75 (ddd, $J = 10.5$, 7.5, 2.0 Hz, 1H, NCH$_a$H$_b$), and 1.55 (dq, $J = 6.5$, 6.5, 2.0 Hz, 3H, CHCH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.0, 153.0, 132.9, 132.5, 129.2, 128.0, 71.1, 50.4, and 20.3.

HRMS (ESI) Calcd for (C$_{11}$H$_{11}$NO$_3$ + Na$^+$): 228.0631. Found: 228.0635.

GC-MS $t_r = 10.4$ min; m/z: 205, 177, 161, 123, 105, 77, and 51.

IR (neat) 3058, 3036, 3005, 2988, 1788, 1769, 1682, 1674, 1654, 1478, 1464, 1447, 1383, 1355, 1338, 1229, 1201, 1114, 1075, 941, 927, 865, 851, 793, 762, 745, 714, 695, 666, and 647 cm$^{-1}$.

TLC $R_f = 0.30$ in 30% EtOAc in hexanes.

mp = 110-112 °C.
3-(Phenylcarbonyl)-1,3-oxazinan-2-one (496)

In a 50 mL round bottom flask, 3-amino-1-propanol S406 (9.91 g, 132 mmol) and ethylene carbonate (11.7 g, 133 mmol) were added and heated to 160 °C in an oil bath and vacuum distilled at 3 mm Hg over 3 hours. A ~1:1 mixture of the desired product and ethylene glycol were collected (20.1 g, ~97% yield by mass). From this mixture 3.54 g (~21.7 mmol) was taken and added to a 100 mL flask. To this flask triethylamine (18 mL), benzoyl chloride (8.0 mL, 68 mmol), and 50 mL of CH₂Cl₂ were added and stirred. After 12 hours the mixture was quenched with 10 mL 10% NaOH, and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine and dried with sodium sulfate in an attempt to induce selective crystallization. The mixture was then separated by flash chromatography using 40% EtOAc in hexanes to obtain 496 (2.76 g, 62% yield). The material could be further purified by recrystallization from 1:1 pentane:EtOAc.

$^1$H NMR (500 MHz, CDCl₃) δ 7.59-7.56 (m, 2H, ArH), 7.51-7.47 (m, 1H, ArH), 7.41-7.38 (m, 2H, ArH), 4.42 (t, $J = 5.5$ Hz, 2H, -OCH₂-), 3.90 (t, $J = 6.5$ Hz, 2H, -NCH₂-), and 2.21 (app p, $J = 6.5$ Hz, 2H, -CH₂-).

$^{13}$C NMR (125 MHz, CDCl₃) δ 173.1, 152.2, 135.3, 131.7, 128.1, 127.8, 67.2, 42.9, 22.1.


GC-MS $t_r = 11.2$ min; m/z: 205, 177, 132, 121, 105, 91, 77, 56, and 51.

IR (neat) 3061, 3030, 2978, 2909, 1738, 1733, 1683, 1601, 1582, 1476, 1448, 1402, 1304, 1294, 1271, 1193, 1168, 1117, 1070, 986, 957, 861, 795, 760, 729, 701, and 664 cm⁻¹.

TLC $R_f = 0.50$ in 50% EtOAc in hexanes.

mp = 98-100 °C.

![Chemical structure](image)

2-Phenyl-5,6-dihydro-4H-1,3-oxazine (487)
In a 3 mL screw cap vial equipped with a stirbar, oxazinone 496 (107 mg, 0.522 mmol), lithium iodide (142 mg, 1.06 mmol), ammonium chloride (57.6 mg, 1.09 mmol), and methylene chloride were added. After stirring for 12 hours at room temperature, DBU (0.23 mL, 1.54 mmol) was added. After stirring for 6 hours, the reaction was filtered through silica gel. After concentration in vacuo, the residue was purified by MPLC (50% EtOAc/Hex) to give 487 (16.5 mg, 20%).

1H NMR (500 MHz, CDCl3) δ 7.88-7.87 (m, 2H, ArH), 7.42-7.34 (m, 3H, ArH), 4.36 (t, J = 5.0 Hz, 2H, -OCH2-), 3.61 (t, J = 6.0 Hz, 2H, -NCH2-), and 1.98 (app p, J = 6.0 Hz, 2H, -CH2-).

13C NMR (125 MHz, CDCl3) δ 155.7, 134.3, 130.4, 128.2, 127.0, 65.3, 42.9, 22.1.


GC-MS t_r = 8.6 min; m/z: 161, 160, 131, 105, 77, and 51.

IR (neat) 2935, 2886, 2857, 1653, 1580, 1449, 1348, 1270, 1132, 1104, 1071, 1023, 930, 780, and 696 cm⁻¹.

TLC R_f = 0.3 in 50% EtOAc in hexanes.

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**N-(3-iodopropyl)benzamide (498)**

In a 3 mL screw cap vial equipped with a stirbar, oxazinone 496 (39.7 mg, 0.194 mmol), lithium iodide (105 mg, 0.784 mmol), ammonium chloride (21.1 mg, 0.398 mmol), and methylene chloride (1.1 mL) were added. After stirring for 12 hours at room temperature, the reaction was filtered through silica gel. After concentration in vacuo, the residue was purified by MPLC (30% EtOAc/Hex) to give 498 (22.1 mg, 71%).

1H NMR (500 MHz, CDCl3) δ 7.78-7.76 (m, 2H, ArH), 7.52-7.48 (m, 1H, ArH), 7.44-7.41 (m, 2H, ArH), 6.55 (br s, 1H, NH), 3.64 (t, J = 6.5 Hz, 2H, ICH2-), 3.62 (q, J = 7.0 Hz, 2H, -NCH2-), and 2.11 (p, J = 6.5 Hz, 2H, -CH2-).

13C NMR (125 MHz, CDCl3) δ 167.9, 134.5, 131.7, 128.8, 127.0, 113.2, 110.4, 107.1, 102.3, 93.0, 78.0, and 696 cm⁻¹.

GC-MS $t_r = 8.6$ min (cyclized); m/z: 161, 131, 105, 77, and 51.

IR (neat) 3317, 3065, 3030, 2961, 2938, 2869, 1650, 1644, 1603, 1577, 1543, 1490, 1445, 1291, 1217, 1179, 1084, 1076, 802, 696, and 665 cm$^{-1}$.

TLC $R_f = 0.60$ in 50% EtOAc in hexanes.

(S)-4-Benzyl-2-oxazolidinone (454)

To a 6 mL screw cap vial equipped with a stirbar, (S)-methyl-4-benzyl-2-oxooxazolidine-3-carboxylate 489 (0.0738 g, 0.314 mmol), lithium iodide (0.171 g, 1.27 mmol), ammonium chloride (0.0329 g, 0.621 mmol), and 1.6 mL of chloroform were added. The vial was then capped and the mixture was stirred at 50 °C in an oil bath for 6 hours. After being allowed to cool to room temperature, DBU (0.140 mL, 0.939 mmol) was added. After 6 hours at room temperature the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (80% EtOAc in hexanes) to afford 454 (0.0346 g, 62%) as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34 (dd, $J = 7.5$, 7.0 Hz, 2H, ArH), 7.29 (d, $J = 7.0$ Hz, 1H, ArH), 7.18 (d, $J = 7.0$ Hz, 2H, ArH), 5.51 (s, 1H, -NH), 4.46 (dd, $J = 8.5$, 8.5 Hz, 1H, -CH$_2$HBO), 4.15 (dd, $J = 8.5$, 5.5 Hz, 1H, -CH$_2$HBO), 4.09 (app p, $J = 7.0$ Hz, NCH), and 2.88 (d, $J = 7.0$ Hz, 2H, -CH$_2$Ph).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.4, 136.1, 129.24, 129.18, 127.5, 69.8, 54.0, and 41.7.

HRMS (ESI) Calcd for (C$_{10}$H$_{11}$NO$_2$ + Na$^+$): 200.0682. Found: 200.0697.

GC-MS $t_r = 10.79$ min; m/z: 177, 130, 117, 103, 92, 91, 86, 77, 65, 58, and 51.

IR (neat) 3286, 3030, 2970, 2946, 2924, 2851, 1959, 1741, 1709, 1603, 1548, 1496, 1476, 1455, 1406, 1366, 1324, 1300, 1250, 1096, 1063, 1021, 938, 900, 806, 773, 757, and 706 cm$^{-1}$.

TLC $R_f = 0.30$ in 40% EtOAc in hexanes.

$[^{[\alpha]}]_{D}^{RT} = -77.3$ (c = 0.295, CHCl$_3$).

mp = 87-89 °C.
Chapter V

Progress Toward the Total Synthesis of Lyngbyaloside B.
5.1 Introduction/Retrosynthesis

The natural product lyngbyaloside B (501) is a current target of our research program. We are interested in this target for a combination of reasons. First, we would like to apply the acylketene dual macrolactonization/pyran hemiketal formation to a complex target. Second, because there are no total syntheses of this target, we would like to prove its structure. Lastly, bioactivity of this target is intriguing. Our retrosynthetic plan is outlined in Scheme 501. The centerpiece of our strategy is a dual macrolactonization/pyran hemiketal formation reaction from a substrate such as 502, generating a bridged bicyclic system from a linear precursor in a single step. Glycosidation and protecting group manipulation would give lyngbyaloside B (501). We reasoned that this precursor could be made by a cross metathesis reaction from substrates such as 503 and 504. Substrate 503 could be made from 505, which is the product of the diastereoselective magnesium chloride catalyzed anti aldol reaction, which is covered in Chapter IV of this document.
The other metathesis partner would be 504, which we reasoned could be derived from geraniol acetate (506).

The retrosynthetic plan for 504 is outlined in Scheme 502. While the ideal substrate to use would be 507, we had doubts about its stability throughout the course of a metathesis reaction. For that reason, 508 was seen as a more realistic choice, and the diene side chain can be installed later in the synthesis. The diol 508 we believed could be made by a regioselective epoxidation and directed hydride delivery from substrate 509, which can be made from crotylation of enal 510, which is made from geraniol acetate (506).

Scheme 502

5.2 Synthesis Progress

The synthesis started with ozonolysis of geraniol acetate to the aldehyde 511 (Scheme 503). The reaction is selective towards the distal alkene and proceeds directly to the aldehyde in the presence of pyridine. Reduction of the aldehyde, BOM protection,
and acetate removal gave allylic alcohol 512. Allylic oxidation using manganese dioxide gave enal 510 in 79% yield.

The key step to install the desired syn stereochemistry in 509 was the Kobayashi crotylation reaction (Scheme 504).\textsuperscript{109} Z-Crotyltribromosilane (513), made by hydrosilylation of 1,3-butadiene,\textsuperscript{110} is mixed with aldehyde, and catalytic DMF is added. Based on reported silicon NMR chemical shifts, DMF coordinates to the silicon to activate it, leading to transition states 514 and 515.\textsuperscript{109} These transition states lead to alcohols 516 and 517 respectively. Another important aspect of this chemistry is that it can be modified to be asymmetric by the use of chiral Lewis bases to activate the silicon.\textsuperscript{111}

Scheme 504

When aldehyde 510 was reacted with trichlorosilane in DMF at 0 °C, the desired product 509a was formed (Scheme 505). This product was accompanied by ~20% of a minor diasteromer. Lowering the temperature to -20 °C with ether as a co-solvent led to a worse diastereomeric ratio. While the initial expectation was that the minor diastereomer was the anti-crotylation product, it in fact turned out to be the Z-alkene isomer 509b! Isomerization of starting material between \textit{E} and \textit{Z} forms 510 and 518 could be monitored by \textsuperscript{1}H NMR, and favored the \textit{E}-isomer by 2:1 at equilibrium.
The next step in minimizing this isomerization was to find the exact conditions in which it was occurring, and finding conditions in which it could be minimized. Since the $E$-alkene product likely occurs through an isomerization if 510, it was reasoned that speeding up the reaction would lead to less isomerization. Additionally, it was hypothesized that trace HCl could be responsible for the isomerization. It was found that running the reaction at room temperature indeed led to less isomerization, giving a 5.5 to 1 $E:Z$ ratio in product 509 (Scheme 506). Additionally, it was found that the reaction gave the same diastereomeric ratio in the presence and absence of sodium carbonate as a base. Since sodium carbonate should neutralize any trace HCl present, this result suggests that the isomerization is not HCl catalyzed.

**Scheme 506**

![Scheme 506 Diagram]

The solvent was DMF and the temperature was room temperature (r.t.) for the reaction. No additive was used. The product ratio was 5.5:1.

The solvent was CDCl3 and the additive was 1.2 equiv. Na2CO3. The ratio of 510/518 was 2:1.

The solvent was DMF and the additive was 1.2 equiv. Na2CO3. The ratio of 510a:510b was 4:1. The ratio of 510a:510b was 3:1.

The temperature was 0 °C and -20 °C. The ratio of 509a:509b was 4:1. The ratio of 509a:509b was 3:1.
When aldehyde 510 was added to Z-crotyltrichlorosilane in CDCl₃ with sodium carbonate, the aldehyde isomerizes to a 2:1 ratio of E:Z isomers; the same ratio that is observed before completion of the reaction when DMF is present. This result suggests that the silane reagent itself is responsible for the isomerization. This is bad in a sense that the problem is likely to persist in the presence of chiral Lewis bases that would be required for asymmetric crotylation. When aldehyde 510 was placed in the presence of the Leighton reagent (519), isomerization of the aldehyde still occurred (Scheme 507). This particular reaction was also plagued by poor conversion, as it is known that α,β-un-saturated enals are poor substrates for crotylation with this reagent.

**Scheme 507**

![Scheme 507](image)

Since the problems associated with the enal isomerization seemed due to the Lewis acidity of the silicon atom of the trichlorosilane, it was reasoned that a less Lewis acidic silicon atom would slow down the rate of isomerization. Sakurai crotylation, using a crotyltrifluorosilane, seemed to fit the bill. Z-Crotyltrifluorosilane 520 was made by heating a mixture of 513, SbF₃, and dibutyl ether and distilling 520 (b.p. = 54 °C) directly from the reaction flask (Scheme 508). When this reagent was added to enal 510 in the presence of CsF in THF at r.t., desired 509 was formed in a 9:1 E:Z ratio. At low conversions the E:Z ratio was higher, but when pushed to completion (1.7 equiv silane, 6 equiv

**Scheme 508**

![Scheme 508](image)
CsF) some isomerization of the starting material did occur. The syn/anti ratio for this reaction was found to be ~95:5 by NMR. The workup of the reaction was found to be much less tedious than that of the Kobayashi crotylation, which tended to form gels upon workup.

The next challenge in the synthetic sequence is that of regioselective and stereoselective epoxidation of 509. There are four possible diastereomers that can arise from mono-epoxidation of this substrate, compounds 521-524 (Scheme 509). It was reasoned that the regioselectivity of the epoxidation would be governed by a combination of two factors; the electronic differences in the alkenes, and the rate acceleration due to the neighboring hydroxyl group. The stereoselectivity of the epoxidation should come as a consequence of A(1,3) strain.

Scheme 509

The relative energies of conformers of a model substrate, (Z)-2-hydroxy-3-pentene, at the MM2 level are shown in Scheme 510. The lowest energy conformer (A) has the hydroxyl group perpendicular to the methyl group on the alkene, and has the methyl group of the carbinol pointed away from the methyl group of the alkene. This minimizes A(1,3) strain in the system. Rotating the carbinol counterclockwise (B) aligns the hydroxyl with the allylic methyl group, which causes a penalty of 2.7 kcal/mol. Further rotation (C) lowers the energy back to 0.34 kcal/mol. The worst interaction (D) comes when the hydroxyl is perpendicular to the alkene, and the two methyl groups align. Other rotamers E and F are 0.4 and 0.66 kcal/mol less stable than A. Since epoxidations with m-CPBA are directed by hydroxyl groups, rotamer A should be the most relevant to the selectivity.
When 509 was reacted with \textit{m}-CPBA, the desired epoxide 521 was formed (Scheme 511). The reaction was run in the presence of sodium carbonate to eliminate the potential acid catalyzed opening of the trisubstituted alkene. When stopped before 100% conversion the reaction shows complete regioselectivity for the trisubstituted alkene. The observed diastereomeric ratio was 96:4 by NMR, and the undesired diastereomer was likely derived from the \textit{anti}-crotylation byproduct from the previous step, not an epoxide diastereomer. The yield of the reaction was very good, 85% after chromatography, although simple filtration through silica gel was enough to purify the compound.

The next step in the pathway was a regioselective hydride opening of the epoxide to form a 1,3-diol. Red-Al is the most common reagent for this purpose, and it was the first hydride reducing agent attempted for the reduction of 521 (Scheme 512). Unfortunately, the reaction failed to give any hint of desired product 508. At room temperature no reaction occurred, other than hydrogen gas evolution, even in the presence of 4 equiv of Red-Al. When heated (60 °C), still no desired product is formed, instead the benzyloxymethyl group is cleaved. Higher temperatures yet (110 °C) gave complete BOM removal and consumption of the terminal alkene. Upon further analysis, there was a flaw in
the concept of this directed reduction – that of conformation. As illustrated by the previous epoxidation, the hydroxyl group likes to be perpendicular to the alkene and/or epoxide, as in 525. To access a conformation in which the hydroxyl could deliver the hydride intramolecularly would cause the crotyl group and methyl of the trisubstituted alkene to be in the same location in space and is very unlikely.

Scheme 512

The best chance of success to give the desired product seemed to be an undirected attack of the epoxide by a hydride reagent. Lithium aluminum hydride, when reacted with epoxide 521, gave desired compound 508, but also a significant amount of the 1,2-diol 526 (Scheme 513). These results illustrate the reducing power of LAH, as it is unlikely that either product arises from a directed reduction (LAH will reduce simple epoxides to alcohols in the absence of a directing hydroxyl group). Since the regioselectivity of this transformation was less than ideal, significant attempts were made to improve the reaction by opening the epoxide with other strong reducing agents. Hydride sources used were LiEt3BH (super hydride), LiBH4, and NaAlH4. LiEt3BH at room temperature gave no reaction, and starting material could be recovered. At higher temperatures consumption of the epoxide occurred, but desired products were not formed. Although we were initially excited about the idea of NaAlH4 as a reducing agent, it turns out to be remarkably weak. In fact, NaAlH4 can be added to neat isobutyraldehyde and no reaction occurs (the same test with LAH causes spontaneous ignition). LiBH4 gave no reaction at room temperature. At elevated temperature some 508 and 526 could be detected, but purification of these diols was problematic, as borate esters are formed during workup.
Alternative methods of installing the desired tertiary alcohol were considered and explored. As shown in Scheme 514, it was anticipated that directed hydration methods would work for substrate 527, but would give the incorrect relative configuration between the two carbinols (due to backside attack on the activated alkene). This problem could be solved by using the alternative alkene geometry (Z vs. E). Another method that was considered was intramolecular hydrosilylation of the alkene, followed by oxidative cleavage of the carbon-silicon bond. The potential advantage to this method is that the newly formed hydroxyl group is on the same face as the directing hydroxyl (opposite stereochemistry of directed hydration). An example of this chemistry is the conversion of homoallylic alcohol 528 to silane 529 by catalysis with chloroplatinic acid. This or-
ganosilane undergoes oxidation with retention of configuration, giving 1,3-diol 530. The chemistry also works with allylic alcohols, as substrate 531 is converted to 532 and 533 after chloroplatinic acid catalysis and silane oxidation, respectively.\textsuperscript{117}

While the directed hydrosilylation of alkenes seemed promising, we were unable to find examples in which a tertiary alcohol was made using the method. Nevertheless, we attempted the directed hydrosilylation of geraniol (534) by incubating with excess tetramethylsilazane 535 (Scheme 515). After complete conversion to 536 (GC and NMR), excess 535 was removed in vacuo (boiling point 80 °C). Substrate 536 reacted with catalytic chloroplatinic acid, but the results were not promising. Hydrolysis of 536 back to 534 was a major competing event. Additionally, 15 peaks were observed by GC when the reaction was taken to 60 °C. Knowing that hydrolysis of the primary alcohol was a problem, and that the distal alkene potentially was also causing problems, substrate 537 was synthesized by addition of methylmagnesium bromide to substrate 510, and reaction with 535. This substrate was much less susceptible to hydrolysis, and gave a more tractable outcome when reacted with chloroplatinic acid. Complete consumption of starting material was observed, but product could not be isolated after the second step. No evidence could be found for formation of the desired 1,3-diol by mass spec methods (GC-MS and ESI-MS). It is unclear why this reaction apparently failed, and further control experiments are probably necessary to determine whether or not the chemistry could work.

\textbf{Scheme 515}

\begin{center}
\includegraphics{scheme515.png}
\end{center}

Directed oxymercuration to install the tertiary alcohol was also explored.\textsuperscript{118} Using substrate 538, reaction with mercuric acetate and water lead to consumption of starting
material (Scheme 516). Subsequent addition of sodium borohydride led to rapid forma-
tion of mercury, giving desired diol 539 and borate adduct 540.

Scheme 516

Given the success of the previous oxymercuration, a more realistic substrate was
made and used (Scheme 517). Compound 541 was made by addition of isopropyl-
magnesium chloride to substrate 510 (E/Z ratio 92:8). This substrate underwent clean conver-
sion to 542, which proved to be stable, observable by NMR and ESI. The success of this
oxymercuration led to attempts to perform this reaction on the crotylated substrate 509,
but the terminal alkene reacted competitively with the desired internal oxymercuration.
When followed by NMR, the terminal alkene resonances of 509 were lost at the same rate
the internal alkene proton was consumed. Brown has shown that terminal alkenes react
faster than internal alkenes, so the approximately equal rate of consumption speaks to the
rate enhancement of the directing hydroxyl group.119

Scheme 517

Demercuration methods from substrate 542 were explored (Scheme 518). It was
found that reacting sodium sulfide120 with 542 led to elimination of the neighboring hy-
droxyl groups, giving both 541 and the new allylic alcohol 543. Substrate 543 has a char-
acteristic coupling constant of 16 Hz at the newly formed alkene, consistent with the E
configuration. Interestingly, this compound must arise from syn elimination of the second-
dary hydroxyl group. The Z-alkene that would arise from the typically more preferred
anti elimination was not observed, probably due to a high steric penalty of formation, as
multiple 1,7 interactions would be formed. Reaction of mercuric acetates with 1,3-
propanedithiol had been reported to cause demercuration, but reaction with 542 only led
to ligation at mercury (544).121 Interestingly, this compound was stable to ESI analysis.

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Ultimately the best conditions were found to be the most common, as aqueous sodium hydroxide and sodium borohydride produced the 1,3-diol 545 in a 85:15 diastereomeric ratio. Borate ester formation was not a problem with these conditions as was previously, since excess sodium hydroxide was used.

**Scheme 518**

Stereochemical assignment of 545 and its diastereomer 546 was initially carried out by coupling constant analysis (Scheme 519). The major product, assigned as 545, had methine $J$ values of 8.4, 4.8, and 4.8 Hz. The minor product 546 had methine $J$ values of 10.5, 5.4, and 1.8 Hz. The second set of $J$ values is consistent with a more strongly hydrogen bound 1,3-diol, which 546 would be, due to having its bulky substituent equatorial-like on its 6-membered hydrogen bound form. By contrast, 545 spends less time in its chair conformation due to having a large axial like substituent. This thinking and initial stereochemical assignment was validated by conversion of each diastereomer to its PMP acetal (547 and 548 respectively) under acid catalysis, and observation of NOEs by NMR.
At this stage it was recognized that it could be advantageous to perform an alkoxymercuration instead of an oxymercuration. An alkoxymercuration with a suitable alcohol could also serve as a protecting group, giving protected 1,3-diol 549 (Scheme 520). Since tertiary alcohols are typically not easy to protect, this strategy could conceivably be less burdensome. Unfortunately, lack of reactivity proved to be a problem, as 541 was inert to mercuric acetate and benzyl alcohol. Using the more reactive mercuric trifluoroacetate caused no reaction at room temperature and decomposition of the substrate at elevated temperatures. Attempts to buffer the reaction did not lead to formation of desired product. Although further attempts were not tried, other interesting trapping agents can be conceived of, e.g. trichloroethanol. This alcohol is much smaller than benzyl alcohol, making it more likely to react, and could be removed by reductive methods (e.g. zinc powder).

Given the success of the oxymercuration/demercuration sequence, our attention turned to the issue of the E/Z double bond being oxymercurated. Since the oxygen is installed by backside attack of the activated alkene, the geometry at the 1,3-diol is opposite

\[ \text{Scheme 519} \]

\[ \text{Scheme 520} \]
1.22 Crotylation also is not a viable route before oxymercuration, as the terminal alkene oxymercuration competes. We needed a method to install a Z-alkene and control the absolute configuration. Both these requirements would be satisfied by use of the Crimmins aldol reaction on a Z-α,β unsaturated aldehyde. 123 Since we didn’t have such an aldehyde, we used geranial (550) instead (made by MnO2 oxidation of geraniol). This substrate (E:Z ratio 9:1) was reacted with the titanium enolate of 551 in the presence of (-)-sparteine, and gave desired adduct 552, also in a 9:1 E:Z ratio (Scheme 521). This is important because it shows that 550 does not rapidly isomerize under the reaction conditions as had been a problem with the previous crotylation conditions. Thus, simply using the Z-alkene isomer should be successful. Given the successes of this reaction and the oxymercuration, studies regarding 1,3-induction were ceased at this point, as there were more pressing issues related to the synthesis that required attention.

Scheme 521

5.3 Fragment Coupling Strategy

The next most important issue for the synthesis was the development of a coupling strategy to combine the northern and southern hemispheres of the natural product. Our group has a long-standing interest in alkene metathesis chemistry, so this was one such strategy considered. We wondered if a substrate such as 553 could be productive in a cross metathesis with an alkene such as 554, which would give rise to product 555 (Scheme 522). Another coupling strategy considered for formation of 555 was a modified Julia olefination, where an aldehyde such as 556 would be reacted with a sulfone such as 557.
An example of why it was thought that the desired cross metathesis reaction could work is shown in Scheme 523. In this example, McGarvey attempted a cross metathesis between terminal alkenes 558 and 559. In this case, both alkenes are of the same general “Type”, leading to a statistical mixture of products arising from homodimerization of 558 and 559, along with the desired cross metathesis. When McGarvey instead used the internal alkene 560, the desired product 561 was isolated in 82% yield. In this case, dimerization of 559 is rapid and reversible, but 560 does not homodimerize. When 560 is an acceptor of the alkylidene derived from 559, the desired product forms. This product does not further participate in metathesis.

Similar to the successful example of McGarvey, we attempted the selective cross metathesis of substrates 553 and 562 using Grubbs’ second generation initiator (Scheme 524). It was found under these conditions that the only product formed was the dimer of 562; substrate 553 had not been altered. Using the unprotected substrate 563, along with
protecting the alcohol of the terminal alkene of the coupling partner as an acetate (564) led to formation of product 565 in 33% isolated yield. Since no homodimerization of 563 was observed, it was thought that increasing the amount of 563 relative to the amount of 564 could lead to a higher yield. Unfortunately this wasn’t the case. When 3 equivalents of 563 were used, the isolated yield of 565 remained at 30%, and mass recovery for the reaction was less than 50%. It is unclear why this reaction did not work better, but we suspect that alkene isomerization was a problem, since 563 was not recovered. It was found that substrate 563 would not homodimerize, nor would it with the hydroxyl BOM or TMS protected. Since the success of the metathesis depends on the ability of the internal alkene to accept an alkylidene, we sought to change the substrate.

**Scheme 524**

We hypothesized that outer-sphere steric effects may be leading to the lack of reactivity in the oxazolidinone substrates, so the oxazolidinone in 553 was cleaved to the primary alcohol by lithium borohydride, giving substrate 566 (Scheme 525). This substrate also was unreactive in the presence of G2. Taking the reaction to 100 °C in toluene led to decomposition of the substrate with no evidence of dimerization. It was likely that the unprotected primary alcohol was the cause of problems, so it was benzoyl protected, giving substrate 567. When heated in benzene with G2, no dimerization occurred, but clean benzylidene attachment was observed by ESI. This is an important result, because it showed that the internal alkene could be attacked by an alkylidene. Despite this, reaction of 567 with 564 under the same conditions only led to dimerization of 564. Since the desired cross metathesis is a bimolecular reaction, it was hypothesized that we could speed up the formation of the desired product by running the reaction more concentrated. The most concentrated we could run the reaction was with no solvent, so this was tried. Sub-
substrates 567 and 564 were mixed with G2 in CH₂Cl₂. Then while heating, a nitrogen stream was passed over the reaction until the solvent evaporated. These conditions led to the formation of the desired product 569, exclusively as the E-alkene isomer. The yield for this process was only 10% however. It was hypothesized that the terminal alkene was being lost during the reaction due to its volatility at the reaction temperature.

**Scheme 525**

When cross metathesis was performed between substrates 567 and benzoyl protected substrate 570 under various conditions, product 571 was formed (Scheme 526). Using G2, yields topped out at ~60% when performed at 70 °C. Using the Hoveyda-Grubbs second generation initiator, approximately the same yield was obtained. When
the temperature was lowered, however, yields increased. The higher yields under milder temperature are likely due to increased catalyst lifetime vs. the higher temperature.

The next logical step in the metathesis optimization was using a more realistic terminal alkene coupling partner. To this end, 3-methylbutanal 572 was syn-crotylated with trichlorosilane 513, and benzoyl protected to give compound 573 (Scheme 527). When this alkene was mixed with 567 and reacted with HG2 under solvent free conditions, a 29% yield of 574 (and its corresponding diastereomer) was obtained. Performing the reaction in a sealed tube after solvent removal didn’t lead to an increase in yield. The problem with the reaction is that the homodimer of 573 is very slow to open back up; it is not rapidly reversible like the previous examples. We believed we could get around this problem by doing syringe pump addition of 573 to the reaction vessel, since homodimerization should be significantly slower if its concentration is minimized. While in theory this should work, yields were unable to be improved by syringe pump addition. The homodimer of 573 dominated the product distribution even at very long addition times.

Scheme 527

At this point we wondered if a relay metathesis method could be successful. The Hoye lab had shown that addition of a relay can activate otherwise inert alkenes toward metathesis chemistry. An example of this is shown in Scheme 528, where malonate substrate 575, when reacted with Grubbs first generation initiator, is inert, and the desired ring-closed product 576 is not formed. When armed with a relay (577), the desired product forms. Likewise, in our case we knew that substrate 567 does not form the ruthenium-
loaded 578. Substrate 567 is capable of accepting an alkylidene however. Perhaps an in situ relay activation, using a diallyl malonate substrate, would lead to cross metathesis of the relay (579), then the ruthenium can load onto the terminal alkene (580) and be transferred to the internal alkene in an intramolecular fashion. Doing so would fundamentally change the reactivity of 567.

**Scheme 528**

While the idea of in situ relay activation is promising and deserves to be studied in a simpler system, application in this system was disappointing. Reaction of 567 and 573 along with 581 failed to form the desired product (Scheme 529). ESI gave evidence of a variety of byproducts, such as the expected ring-closed malonate 582, truncated starting material 583, and unreacted 567. Also detected were relay-activated compounds 584 and 585. Interestingly compound 586, having its alkene capped with an ethylidene, was detected, along with bis-cross metathesis product 587. Other activating agents that were tried were allyl ether and allyl phosphonate, but neither led to the formation of desired product. It is clear that in this case, a relay would have to be built into one of the starting materials for this chemistry to have a shot at working.
It was also decided that it was worth attempting the cross metathesis with the most realistic substrate possible - the real substrate 508 (Scheme 530). Unfortunately, when 567 was reacted with 508, no desired product 588 was formed, only the homodimer of 508. Attention then shifted to other methods of coupling the desired fragments.

Scheme 530

An alternative powerful coupling method is the modified Julia olefination reaction. Using phenyltetrazole or benzothiazole sulfones, the method typically gives good yields when the sulfone anion is reacted with aldehydes. To explore whether or not this reaction could help us, α-branched phenyltetrazole (PT) 589 and benzothiazole (BT) sulfone 590 were made (Scheme 531). Each sulfone was made by the Mitunobu reaction of thiols 591 and 592 with 2-methylpropanol, followed by m-CPBA oxidation.
Scheme 531

For practice, each sulfone was reacted with anisaldehyde and cyclohexanecarboxaldehyde (1 equiv each), giving alkenes 593 and 594 (Scheme 532). It was found that the BT sulfone 590 led to higher conversions, but gave a mixture of E and Z alkenes when reacted with the α-branched cyclohexanecarboxaldehyde. Reactions with PT sulfone 589 led to lower conversion but complete E alkene selectivity.

Scheme 532

<table>
<thead>
<tr>
<th>entry</th>
<th>sulfone</th>
<th>aldehyde</th>
<th>product</th>
<th>yield</th>
<th>E:Z ratio</th>
</tr>
</thead>
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<td>anisaldehyde</td>
<td>72% conv. to 593, E exclusive</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>589</td>
<td>cyclohexanecarboxaldehyde</td>
<td>97% conv. to 594, E exclusive</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>590</td>
<td>anisaldehyde</td>
<td>~100% conv. to 593, E exclusive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>590</td>
<td>cyclohexanecarboxaldehyde</td>
<td>~100% conv. to 594, E:Z ratio 1:1.8</td>
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<td></td>
</tr>
</tbody>
</table>

Reaction of these sulfones with the real substrates, protected as either BOM (595) or TBS (596) ethers, gave poor isolated yields (Scheme 533). This is as far as the olefination method was explored. A considerable amount of work can still be done to optimize these conditions by whoever continues working toward the total synthesis.

Scheme 533

<table>
<thead>
<tr>
<th>entry</th>
<th>sulfone</th>
<th>aldehyde</th>
<th>product</th>
<th>yield</th>
<th>E:Z ratio</th>
</tr>
</thead>
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<td>597</td>
<td>17%</td>
<td>7.3 to 1</td>
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<td>590</td>
<td>596</td>
<td>598</td>
<td>26%</td>
<td>48 to 1</td>
</tr>
</tbody>
</table>
5.4 Summary/Future Directions

In summary, fragments 567 and 508 were made to study issues related to the synthesis of lyngbyaloside B (501) (Scheme 534). When a coupling strategy is decided upon and optimized, conversion to a substrate such as 502 should be possible. We have shown in a model system of 502 (cf. Chapter I of this document) that dual macrolactonization/pyran hemiketal formation should be an efficient process. The remaining steps to the total synthesis are protecting group manipulations, installation of the diene side chain, and glycosidation. On complex substrates, no chemistry is trivial however. While metathesis between 567 and 508 proved problematic, there exist other interesting experiments that have yet to be tried, such as installation of a relay onto 567, or silicon tethering 567 with 508 together to increase their proximity and reactivity towards each other. Additional tuning of the sterics around each alkene could also be a promising endeavor (e.g. substrate 5100 successfully engaged in cross metathesis with alkene 570). Additionally, protection of 508 to increase steric bulk around the alkene should slow down the rate of dimerization, making syringe pump addition to the acceptor diene more likely to work. An efficient olefination method also cannot be ruled out.

Scheme 534
While there was no progress toward the total synthesis of lyngbyaloside B at the outset of this project, progress toward the structurally similar lyngbouilloside has been recently reported by the Cossy and Ley labs (Scheme 535).\(^{130,131}\) In Cossy’s synthesis of an uncyclized compound 5101, dioxinone 5102 and crotyl compound 5103 are combined by cross metathesis, followed by hydrogenation and directed reduction. In Ley’s synthesis of the macrolactone core (5104), the ester enolate of 5105 is added to the lactone 5106, followed by methyl ketal formation (5107). Ring-closing metathesis, followed by deprotections and hydrogenation give the intact core 5104.

Scheme 535

Although Cossy’s report did not take intermediate 5101 forward, it seems obvious that she is planning an acylketene lactonization to make the core ring system. The similarities to our route and hers are such that it may be worth evaluating an entirely new retrosynthetic plan. Regardless, the complexity of lyngbyaloside B, along with uncertainty of its configuration, should mean that this remains an interesting project for years to come.
5.5 Experimental Section

(R)-4-benzyl-3-((2S,3S,E)-2-methyl-3-(trimethylsilyloxy)hex-4-enoyl)oxazolidin-2-one (505) To a flame dried reaction vessel equipped with a stir bar, oxazolidinone ent-551 (14.1 g, 60.5 mmol), MgCl$_2$ (5.77 g, 60.6 mmol), and NaSbF$_6$ (8.05 g, 31.1 mmol) were added and placed under nitrogen. While stirring, 90 mL ethyl acetate was added, then triethylamine (42.0 mL, 303 mmol) and TMSCl (29.0 mL, 227 mmol) were also added. After stirring for 30 minutes, crotonaldehyde (16.0 mL, 180 mmol) was diluted with 4.0 mL ethyl acetate and added via syringe pump over three hours. After 6 hours from the start of addition, the reaction mixture was passed through a silica gel column using diethyl ether as the eluent. The solvent was removed in vacuo, then 45 mL of pentane was added, and the filtered reaction mixture was placed in a refrigerator (-20 °C). After two days the crystals were vacuum filtered giving 16.2 g (71.4%) of the desired product. GC of the crystals shows a 97:3 diastereomeric ratio.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35-7.24 (m, 5H, ArH), 5.65 (dq, $J = 6.5, 6.5, 6.5, 15.0$ Hz, 1H, -CH=CHMe), 5.42 (ddq, $J = 1.5, 1.5, 1.5, 8.0, 15.0$ Hz, 1H, -CH=CHMe), 4.71 (dddd, $J = 3.0, 3.0, 8.0, 9.5$ Hz, 1H, NCH), 4.36 (dd, $J = 8.5$ and 8.5 Hz, 1H, CHOTMS), 4.17 (dd, $J = 8.0$ and 8.5 Hz, 1H, -CHaHbPh), 4.11 (dd, $J = 3.0$ and 9.0 Hz, 1H, -CHaHbPh), 3.95 (dq, $J = 7.0, 7.0, 7.0, 8.5$ Hz, 1H, COCMe), 3.30 (dd, $J = 3.0$ and 13.5 Hz, 1H, CO$_2$CHaHbC-), 2.71 (dd, $J = 9.5$ and 13.0 Hz, 1H, CO$_2$CHaHbC-), 1.71 (dd, $J = 1.5$ and 6.5 Hz, 3H, CH=CHMe), 1.04 (d, $J = 7.0$ Hz, 3H, CHMe), 0.08 (s, 9H, SiMe$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 176.1, 153.3, 135.7, 132.2, 129.7, 129.1, 129.0, 127.5, 76.8, 65.9, 55.3, 44.5, 38.3, 17.8, 14.0, 0.7.

HRMS (ESI) Calcd for (C$_{20}$H$_{29}$O$_4$NSi + Na$^+$): 398.1758. Found: 398.1807.

GC-MS $T_r = 13.34$ min; m/z: 375, 360, 305, 290, 198, 183, 143, 117, 91, and 73.
IR (neat) 2984, 2918, 1782, 1701, 1454, 1387, 1249, 1211, 1102, 1188, 1048, 1037, 970, 878, 842, and 760 cm$^{-1}$.

TLC $R_f = 0.25$ in 15% EtOAc in hexanes.

[$\alpha$]$^\text{RT}$ -16.6 (c = 1.10, CHCl$_3$).

(S)-4-benzyl-3-((2R,3R,E)-3-hydroxy-2-methylhex-4-enoyl)oxazolidin-2-one (563)

Silylated aldol adduct 505 (4.79 g, 12.8 mmol) was added to a flask containing methanol (55 mL) and p-TsOH (120 mg, 5 mol%). After 80 minutes of stirring at rt, the solvent was removed in vacuo, extracted with ether (2 x 60 mL) from pH = 10 buffer (30 mL), washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo to give the desired product (3.87 g) in quantitative yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35-7.32 (m, 2H, ArH), 7.29-7.23 (m, 3H, ArH), 5.78 (ddq, $J = 15.5$, 6.5 x 3, 1.0 Hz, 1H), 5.54 (ddq, $J = 15.0$, 7.0, 1.5 x 3 Hz, 1H), 4.69 (dddd, $J = 10.0$, 7.5, 3.0, 3.0 Hz, 1H), 4.21 (dd, $J = 8.5$, 7.0 Hz, 1H), 4.16 (dd, $J = 9.0$, 3.0 Hz, 1H), 3.94 (app p, $J = 7.0$ Hz, 1H), 3.29 (dd, $J = 13.5$, 3.5 Hz, 1H), 2.78 (dd, $J = 13.5$, 9.5 Hz, 1H), 2.54 (s, 1H, -OH), 1.73 (dd, $J = 6.5$, 1.0 Hz, 3H), and 1.17 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 176.6, 153.7, 135.4, 131.7, 129.7, 129.3, 129.3, 127.5, 75.9, 66.2, 55.7, 43.5, 38.0, 17.9, and 14.7.

HRMS (ESI) Calcd for (C$_{17}$H$_{21}$O$_4$N + Na$^+$): 326.1363. Found: 326.1381.

IR (neat) 3489, 3037, 2987, 2941, 2922, 1778, 1698, 1458, 1390, 1348, 1211, 1101, 1010, 968, 759, and 706 cm$^{-1}$.

TLC $R_f = 0.18$ in 20% EtOAc in hexanes.

[$\alpha$]$^\text{RT}$ -40.7$^\circ$ (c = 1.05, CHCl$_3$).
(R)-4-Benzyl-3-((2S,3S,E)-2-methyl-3-(triethylsilyloxy)hex-4-enoyl)oxazolidin-2-one (S501) Oxazolidinone 563 (94.5 mg, 0.31 mmol) was added to a flask containing DCM (0.2 ml), imidazole (117 mg, 1.72 mmol), DMAP (14.2 mg, 0.12 mmol), and TESCl (130 µL, 0.77 mmol). After the reaction was complete by TLC (~6 hrs), satd. aq. sodium bicarbonate was added and the mixture extracted with DCM, washed with brine, dried with Na₂SO₄, and concentrated in vacuo. Purification by MPLC (20% EtOAc/hexanes) afforded 0.107 g (83%) of the desired product.

**¹H NMR** (500 MHz, CDCl₃) δ 7.36-7.23 (m, 5H), 5.65 (dq, J = 15.0, 6.5 Hz, 1H), 5.42 (ddq, J = 15.5, 8.5, 1.0 Hz, 1H), 4.69 (dddd, J = 11.0, 7.5, 3.0, 3.0 Hz, 1H), 4.29 (dd, J = 8.5, 8.5 Hz, 1H), 4.16 (dd, J = 9.0, 8.0 Hz, 1H), 4.12 (dd, J = 9.0, 3.0 Hz, 1H), 3.95 (dq, J = 8.5, 7.0 Hz, 1H), 3.34 (dd, J = 13.5, 8.5 Hz, 1H), 2.67 (dd, J = 13.5, 10.0 Hz, 1H), 1.71 (dd, J = 6.5, 1.5 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.92 (t, J = 8.0 Hz, 9H), and 0.56 (q, J = 7.5 Hz, 6H).

**¹³C NMR** (125 MHz, CDCl₃) δ 175.9, 153.3, 135.8, 132.3, 129.6, 129.1, 128.9, 127.4, 76.5, 65.9, 55.4, 44.6, 38.3, 17.8, 13.9, 7.0, and 5.3.


**GC-MS** Tᵣ = 14.6 min; m/z: 417, 388, 347, 318, 262, 211, 185, 115, and 91.

**IR** (neat) 2957, 2913, 2876, 1787, 1703, 1454, 1386, 1349, 1246, 1210, 1150, 1089, 1060, 1050, 833, and 745 cm⁻¹.

**TLC** Rᵣ = 0.40 in 20% EtOAc in hexanes.

\[ [\alpha]^{RT} = -5.30^\circ \] (c = 0.755, CHCl₃).

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**Geraniol acetate (S502)**. Geraniol acetate (506) (3.2 mL, 14.9 mmol) was added to a 250 mL round bottom flask containing DCM (115 mL) and
pyridine (3.75 mL). After ozonolysis for 110 minutes, TLC showed complete consumption of starting material. Oxygen was bubbled through the system for 30 minutes, then 3 mL dimethyl sulfide was added, and the mixture stirred at rt for 12 hours. Extraction (DCM from water), washing (brine), and drying (sodium sulfate), and concentration in vacuo gave crude aldehyde. To this aldehyde was added ethanol (10 mL) and NaBH₄ (300 mg) in portions over 10 minutes. After 20 minutes TLC showed complete consumption of starting material. The reaction was quenched with 10 mL pH = 7 buffer, then 10 mL pH = 4 buffer. The ethanol was removed under vacuum, and the product mixture extracted with DCM, washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by flash chromatography gave 1.7 g (66%) of the desired product as an oil.

**¹H NMR** (500 MHz, CDCl₃) δ 5.38 (tq, J = 7.0, 1.0 Hz, 1H), 4.58 (d, J = 7.0 Hz, 2H), 3.64 (t, J = 6.5 Hz, 2H), 2.13 (t, J = 7.5 Hz, 2H), 2.05 (s, 3H), 1.72 (s, 3H), 1.73-1.68 (m, 2H), and 1.59 (br s, 1H).

**¹³C NMR** (125 MHz, CDCl₃) δ 171.3, 142.0, 118.8, 62.7, 61.5, 35.9, 30.6, 21.2, and 16.5.


**GC-MS** T_r = 8.01 min; m/z: 129, 112, 84, 79, 67, and 55.

**IR** (neat) 3437, 2941, 2879, 1738, 1675, 1446, 1381, 1367, 1235, 1055, 1025, 953, and 921 cm⁻¹.

**TLC** R_f = 0.20 in 30% EtOAc in hexanes.

(E)-6-(benzyloxymethoxy)-3-methylhex-2-en-1-ol (512) Acetate S502 (1.7 g, 9.9 mmol) was added to a flask with DCM (5 mL), benzyl chloromethyl ether (3.1 mL, 60% solution, 13.1 mmol), and Hunig’s base (3.4 mL). After two hours the reaction showed complete consumption of starting material by TLC. Potassium carbonate (5 g), methanol (10 mL), and KOH (3.1 g) were then added. After two hours the mixture was concen-
trated in vacuo, and satd. aq. NH₄Cl was added. Extraction (DCM), washing (brine), drying (sodium sulfate), and concentration gave a mixture that was purified by flash chromatography (40% EtOAc/hex) to afford 2.1 g (81%) of the desired product as an oil.

**1H NMR** (500 MHz, CDCl₃) δ 7.36-7.26 (m, 5H), 5.42 (tq, \(J = 7.0, 1.5\) Hz, 1H), 4.75 (s, 2H), 4.60 (s, 2H), 4.13 (d, \(J = 7.0\) Hz, 2H), 3.58 (t, \(J = 6.5\) Hz, 2H), 2.1 (d, \(J = 7.0\) Hz, 2H), 1.76-1.70 (m, 2H), 1.68 (s, 3H), and 1.42 (br s, 1H).

**13C NMR** (125 MHz, CDCl₃) δ 139.2, 138.0, 128.6, 128.0, 127.8, 123.9, 94.8, 69.4, 67.7, 59.4, 36.2, 27.9, and 16.3.

**HRMS** (ESI) Calcd for \((C_{15}H_{22}O₃ + Na⁺)\): 273.1461. Found: 273.1461.

**IR** (neat) 3415, 2946, 2879, 1750, 1668, 1451, 1384, 1163, 1114, 1042, 1027, 738, and 698 cm⁻¹.

**TLC** \(R_f = 0.25\) in 30% EtOAc in hexanes.

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(E)-6-benzyloxymethoxy)-3-methylhex-2-enal (510) Alcohol 512 (0.99 mmol) was added to a flask containing hexanes (2.5 mL) and manganese dioxide (947 mg, 10.9 mmol). After stirring for 12 hours at rt, the mixture was filtered through celite to afford 200 mg (82%) of the desired product, which was of sufficient purity to use in the next reaction.

**1H NMR** (500 MHz, CDCl₃) δ 10.0 (d, \(J = 8.0\) Hz, 1H), 7.37-7.27 (m, 5H), 5.90 (d, \(J = 8.0\) Hz, 1H), 4.75 (s, 2H), 4.60 (s, 2H), 3.59 (t, \(J = 6.0\) Hz, 2H), 2.30 (t, \(J = 8.0\) Hz, 2H), 2.17 (s, 3H), and 1.84-1.77 (m, 2H).

**13C NMR** (125 MHz, CDCl₃) δ 191.4, 163.5, 138.0, 128.6, 128.0, 127.9, 127.6, 94.9, 69.7, 67.3, 37.4, 27.4, and 17.8.

**HRMS** (ESI) Calcd for \((C_{15}H_{20}O₃ + Na⁺)\): 271.1305. Found: 271.1305.

**GC-MS** \(T_r = 11.9\) min; m/z: 233, 218, 185, 174, 157, 142, 111, 97, 91, 84, 65, and 55.

**IR** (neat) 2937, 2887, 1676, 1611, 1590, 1388, 1190, 1155, 1109, 1089, 1049, 735, and 704 cm⁻¹.

**TLC** \(R_f = 0.45\) in 30% EtOAc in hexanes.
(Z)-but-2-enyltrichlorosilane (513) Butadiene (S503) (12.0 mL, 142 mmol) was added to a sealable tube with a Teflon cap. To the tube trichlorosilane (15.1 mL, 149 mmol) was added, then palladium tris(triphenylphosphine) (0.417 g, 0.25 mol %) was added, and the mixture stirred for 24 hours at rt. The product was then distilled at atmospheric pressure to collect the desired product (19.8 g, 74%) at a boiling point range of 144-147 °C. No loss of configurational stability (NMR) was found after several months of storage at -20 °C.

\[ ^1H \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 5.76-5.68 (m, 1H), 5.42 (dtq, J = 8.5, 8.5, 1.5 \text{ Hz, 1H}), 2.35 (d, J = 8.0 \text{ Hz, 2H}), \text{and} 1.66 (dd, J = 7.0, 1.0 \text{ Hz, 3H}). \]

\[ ^{13}C \text{NMR} (125 \text{ MHz, CDCl}_3) \delta 128.5, 118.8, 24.9, \text{and} 13.2. \]

(Z)-but-2-enytrifluorosilane (520) Chlorosilane 513 (2.0 mL, 12.7 mmol) was added to dibutyl ether (15 mL) and antimony trifluoride (2.4 g, 64.3 mmol). The mixture was equipped with a distillation apparatus and heated in an oil bath at ~120 °C for 8 hours. The desired product (0.87 g, 49%) was obtained.

\[ ^1H \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 5.6 (dddddd, J = 10, 8.5, 7.0, 7.0, 1.5, 1.5 \text{ Hz, 1H}), 5.37 (dddddd, J = 10.0, 8.0, 8.0, 2.0, 2.0, 2.0 \text{ Hz, 1H}), 1.96-1.92 (m, 2H), 1.647-1.627 (m, large \text{ J} = 6.5 \text{ Hz, 3H}). \]

(+/-)-(3S,4R,E)-9-(Benzyloxymethoxy)-3,6-dimethylnona-1,5-dien-4-ol (509a) and (+/-)-(3S,4R,Z)-9-(Benzyloxymethoxy)-3,6-dimethylnona-1,5-dien-4-ol (509b)
Aldehyde 510 (43 mg, 0.17 mmol) was added to DMF (0.9 mL) and Z-crotyltrichlorosilane at 0 °C. After 2.5 hrs the reaction was quenched with pH = 7 buffer and pH = 10 buffer (10 mL each). Extraction (DCM), washing (brine), drying (sodium sulfate), concentration, and purification by MPLC gave 509a (22.4 mg) and 509b (5.6 mg) in ~4:1 ratio (53% yield).

_E-syn diastereomer 509a_

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.27 (m, 5H), 5.79 (ddd, \(J = 18.0, 10.5, 7.0\) Hz, 1H), 5.20 (dq, \(J = 9.0, 1.5\) Hz, 1H), 5.08 (ddd, \(J = 10.0, 1.5, 1.5\) Hz, 1H), 5.06 (m, 1H), 4.75 (s, 2H), 4.61 (s, 2H), 4.24 (dd, \(J = 8.0, 6.5\) Hz, 1H), 3.61-3.55 (m, 2H), 2.34 (app sextet, \(J = 7.0\) Hz, 1H), 2.15-2.05 (m, 2H), 1.77-1.69 (m, 2H), 1.69 (d, \(J = 1.5\) Hz, 3H), 1.41 (br s, 1H), and 1.02 (d, \(J = 6.5\) Hz, 3H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 140.2, 139.1, 138.1, 128.6, 128.0, 127.9, 125.7, 115.7, 94.8, 71.8, 69.5, 67.8, 44.2, 36.4, 28.1, 16.9, and 15.2.

HRMS (ESI) Calcd for (C\(_{19}\)H\(_{28}\)O\(_3\) + Na\(^+\)): 327.1931. Found: 327.1975.

IR (neat) 3440, 2931, 2882, 1450, 1385, 1161, 1047, 1027, 908, 745, and 696 cm\(^{-1}\).

TLC \(R_f = 0.50\) in 30% EtOAc in hexanes.

_Z-syn diastereomer 509b_

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.27 (m, 5H), 5.81 (ddd, \(J = 17.5, 10.5, 7.5\) Hz, 1H), 5.25 (d, \(J = 9.0\) Hz, 1H), 5.08 (ddd, \(J = 10.0, 1.5, 1.5\) Hz, 1H), 5.07-5.05 (m, 1H), 4.76 (s, 2H), 4.61 (s, 2H), 4.23 (app t, \(J = 7.5\) Hz, 1H), 3.61-3.57 (m, 2H), 2.34 (app sextet, \(J = 7.0\) Hz, 1H), 2.27 (ddd, \(J = 13.5, 8.0, 8.0\) Hz, 1H), 2.12 (ddd, \(J = 13.5, 7.0, 7.0\) Hz, 1H), 1.81 (br s, 1H), 1.75-1.68 (m, 2H), 1.73 (d, \(J = 1.0\) Hz, 3H), and 1.03 (d, \(J = 7.0\) Hz, 3H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 140.4, 139.3, 128.6, 128.0, 127.9, 127.0, 115.5, 94.7, 71.1, 69.6, 67.4, 43.9, 28.8, 27.9, 23.5, and 15.2.

HRMS (ESI) Calcd for (C\(_{19}\)H\(_{28}\)O\(_3\) + Na\(^+\)): 327.1931. Found: 327.1927.
(+/-)-(3S,4R,E)-9-(Benzyloxymethoxy)-3,6-dimethylnona-1,5-dien-4-ol (509) Aldo-
hyde 510 (170 mg, 0.68 mmol) was added to THF (1.7 mL), CsF (627 mg, 4.1 mmol) and
Z-crotyltrifluorosilane (150 µL, ~1.7 equiv). After stirring for 12 hours at rt, satd. aq. so-
dium bicarbonate was added. Extraction (ether), washing (brine), drying (sodium sulfate),
and concentration in vacuo was performed, then MPLC (20% EtOAc/hex) to afford the
desired product (104 mg, 50%).

(+/-)-(1R,2S)-1-((2S,3S)-3-(3-(Benzyloxymethoxy)propyl)-3-methyloxiran-2-yl)-2-
 methylbut-3-en-1-ol (521) Alcohol 509 (56 mg, 0.18 mmol) was to added to a flask with
DCM (1 mL), sodium carbonate (25.8 mg, 0.24 mmol), and m-CPBA (52 mg, 0.30
mmol). The mixture was immediately placed in a refrigerator (-20 °C) and remained for
12 hours. The mixture was then filtered through silica gel and purified by MPLC (40%
EtOAc/hex) to afford 50 mg (85%) of the desired compound.

\[ \text{H NMR (500 MHz, CDCl}_3\text{)} \delta 7.36-7.28 (m, 5H), 7.75 (ddd, J = 17.5, 10.5, 8.0 Hz, 1H),
5.12 (ddd, J = 17.5, 1.5, 1.5 Hz, 1H), 5.08 (ddd, J = 10.5, 1.5, 1.0 Hz, 1H), 4.75 (s, 2H),
4.59 (s, 2H), 3.61-3.54 (m, 2H), 3.33 (dd, J = 7.5, 7.5 Hz, 1H), 2.76 (d, J = 8.0 Hz, 1H),
2.40 (app sextet, J = 7.5 Hz, 1H), 2.00 (s, 1H), 1.71-1.60 (m, 3H), 1.55 (ddd, J = 13.0,
6.5, 6.5 Hz, 1H), 1.30 (s, 3H), and 1.13 (d, 7.0 Hz, 3H).

\[ \text{C NMR (125 MHz, CDCl}_3\text{)} \delta 139.5, 138.1, 128.6, 128.0, 127.9, 115.9, 94.8, 72.8, 69.6,
67.9, 65.6, 62.7, 42.5, 35.5, 25.3, 17.8, and 15.7.

HRMS (ESI) Calcd for (C_{19}H_{28}O_4 + Na^+): 343.1880. Found: 343.1941.

IR (neat) 3459, 2966, 2938, 2886, 1595, 1387, 1290, 1250, 1162, 1110, 1042, 1002, 918,
836, 733, and 699 cm\(^{-1}\).

TLC \text{R}_f = 0.28 in 30% EtOAc in hexanes.
(+/-)-(3S,4S,6S)-9-(Benzyloxymethoxy)-3,6-dimethyl-1-ene-4,6-diol (508) and (+/-)-(3S,4R,5R,6S)-9-(Benzyloxymethoxy)-3,6-dimethyl-1-ene-4,5-diol (526) Epoxide 521 (25 mg, 0.078 mmol) was added to a flask containing THF (1 mL). LAH powder (29 mg, 0.76 mmol) was added, and the mixture heated to 60 °C for 16 hours. Water was then added, and the mixture filtered through Celite. The solvent was removed in vacuo, and purification by MPLC (40% EtOAc/hex) gave 1,2-diol 526 (10 mg, 40%) and 1,3-diol 508 (8.0 mg, 32%).

1,3-diol 508

1H NMR (500 MHz, CDCl3) δ 7.37-7.27 (m, 5H), 5.78 (ddd, J = 18.0, 9.5, 7.5 Hz, 1H), 5.08 (ddd, J = 7.0, 1.5, 1.5 Hz, 1H), 5.07-5.05 (m, 1H), 4.76 (s, 2H), 4.60 (s, 2H), 3.90 (ddd, J = 11.0, 6.0, 2.0 Hz, 1H), 3.65-3.58 (m, 2H), 3.36 (br s, 2H), 2.25 (app sextet, J = 6.5 Hz, 1H), 1.74-1.65 (m, 2H), 1.65-1.55 (m, 3H), 1.49 (dd, J = 14.0, 1.5 Hz, 1H), 1.27 (s, 3H), and 1.05 (d, J = 7.0 Hz, 3H).

13C NMR (125 MHz, CDCl3) δ 140.9, 138.0, 128.6, 128.0, 127.9, 115.6, 94.8, 73.2, 72.5, 69.7, 68.7, 44.5, 43.2, 41.7, 25.9, 24.1, and 15.1.


IR (neat) 3404, 3090, 3037, 2951, 2873, 1724, 1642, 1495, 1454, 1409, 1381, 1255, 1165, 1116, 1047, 920, 851, 737, and 698 cm⁻¹.

TLC Rf = 0.22 in 40% EtOAc in hexanes.

1,2-diol 526

1H NMR (500 MHz, CDCl3) δ 7.37-7.27 (m, 5H), 5.81 (ddd, J = 18.0, 10.5, 7.5 Hz, 1H), 5.11 (ddd, J = 17.0, 1.5, 1.5 Hz, 1H), 5.08 (d, J = 10.0 Hz, 1H), 4.76 (s, 2H), 4.61 (s, 2H), 3.59 (app t, J = 6.5 Hz, 2H), 3.50-3.47 (m, 2H), 2.39 (app sextet, J = 6.5 Hz, 1H), 2.08 (br s, 2H), 1.72-1.58 (m, 3H), 1.58-1.49 (m, 1H), 1.31-1.22 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H), and 0.94 (d, J = 6.5 Hz, 3H).
\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \delta \ 141.3, 138.1, 128.6, 128.0, 127.9, 115.5, 94.9, 74.7, 74.3, 69.5, 68.5, 40.9, 35.5, 30.3, 27.5, 14.4, \text{ and } 14.44. \]

\[ \text{HRMS (ESI) Calcd for (C}_{19}\text{H}_{30}\text{O}_4 + \text{Na}^+): 320.2036. \text{ Found: 345.2034.} \]

\[ \text{IR (neat) 3448, 2959, 2935, 2879, 1724, 1642, 1454, 1418, 1380, 1291, 1246, 1206, 1173, 1113, 1048, 1027, 998, 916, 737, and 698 \text{ cm}^{-1}.} \]

\[ \text{TLC } R_f = 0.33 \text{ in 40\% EtOAc in hexanes.} \]

(E)-(3,7-dimethylocta-2,6-dien-1-yl)oxydimethylsilane (536) In a 3 mL screw cap vial, geraniol (534) (323 mg, 2.10 mmol) and tetramethyldisilazane (535) (0.617 g, 4.64 mmol) were added. After 5 hours, the solvent was removed in vacuo, giving 536 (0.438 g, 99\%).

\[ ^{1}\text{H NMR} \ (300 \text{ MHz, CDCl}_3) \delta \ 5.35 \ (dddd, J = 13.5, 9.0, 2.0, 2.0, 2.0 \text{ Hz, 1H}), \ 5.09 \ (ddddd, J = 11.5, 11.5, 2.5, 2.5, 2.5, 2.5 \text{ Hz, 1H}), \ 4.63 \ (septet, J = 4.5 \text{ Hz, 1H}), \ 4.19 \ (dddd, J = 11.0, 1.5, 1.5, 1.5 \text{ Hz, 2H}), \ 2.12-1.98 \ (m, 4H), \ 1.68 \ (q, J = 2.0 \text{ Hz, 3H}), \ 1.65 \ (d, J = 2.0 \text{ Hz, 3H}), \ 1.60 \ (d, J = 2.0 \text{ Hz, 3H}), \ 0.22 \ (d, J = 5.0 \text{ Hz, 6Hz}). \]

\[ ^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3) \delta \ 138.7, 131.8, 124.2, 123.3, 61.1, 39.8, 26.5, 25.9, 17.9, 16.5, \text{ and } -1.2 \text{ ppm.} \]

\[ \text{GC-MS } T_r = 7.6 \text{ min; m/z: 212, 197, 169, 155, 143, 136, 127, 121, 113, 101, 93, 75, 69, 59, \text{ and } 53.} \]

\[ \text{IR (neat) 2961, 2911, 2852, 2108, 1450, 1385, 1251, 1106, 1062, 902, 834, \text{ and } 765 \text{ cm}^{-1}.} \]

\[ \text{TLC } R_f = 0.5 \text{ in 10\% EtOAc in hexanes.} \]
(R)-4-Benzyl-3-((2S,3S,E)-3-(benzyloxymethoxy)-2-methylhex-4-enoyl)oxazolidin-2-one (553)
Alcohol 563 (0.484 g, 1.59 mmol) was added to a flask containing DCM (3 mL), Hunig’s base (0.6 mL), and BOMCl (0.60 mL, 60% solution, 2.5 mmol). The mixture was stirred at rt for 12 h, then quenched with pH = 10 buffer. Extraction (ether), washing (brine), and concentration in vacuo gave crude product that was purified by flash chromatography (20% EtOAc/hex) to afford 0.657 g (97%) of the desired product as an oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.36-7.24 (m, 10H, ArH), 5.81 (dq, $J = 15.0, 6.5$ Hz, 1H, C=CHMe), 5.33 (ddq, $J = 15.5, 9.5, 1.5$ Hz, 1H, -CH=CHMe), 4.83 (d, $J = 7.0$ Hz, 1H, BnOCH$_3$), 4.78-4.72 (m, 1H, NCH), 4.72 (d, $J = 11.5$ Hz, 1H, PhCH$_2$HbO), 4.66 (d, $J = 7.0$ Hz, 1H, BnOCH$_2$HbO), 4.43 (dd, $J = 9.5, 9.0$ Hz, 1H, -CH$_2$HbO), 4.42 (d, $J = 11.5$ Hz, 1H, PhCH$_2$HbO), 4.19 (dd, $J = 9.0, 8.0$ Hz, 1H, -CH$_2$HbO), 4.15-4.08 (m, 2H), 3.28 (dd, $J = 13.5, 3.0$ Hz, 1H, -CH$_2$HbAr), 2.81 (dd, $J = 13.5, 9.5$ Hz, 1H, -CH$_2$HbAr), 1.75 (dd, $J = 6.0, 1.0$ Hz, 3H, =CHCH$_3$), and 1.12 (d, $J = 7.0$ Hz, 3H, -CH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.9, 153.4, 138.2, 135.5, 133.1, 129.7, 129.2, 128.6, 128.4, 128.3, 127.8, 127.5, 91.4, 79.4, 69.6, 65.9, 55.3, 42.3, 38.1, 18.0, and 14.4.

HRMS (ESI) Calcd for (C$_{25}$H$_{29}$NO$_5$ + Na$^+$): 446.1938. Found: 446.1944.

IR (neat) 3030, 2970, 2937, 2919, 2884, 1782, 1699, 1497, 1454, 1389, 1351, 1250, 1212, 1146, 1102, 1035, 1027, 973, 924, 748, and 700 cm$^{-1}$.

TLC R$_f$ = 0.5 in 30% EtOAc in hexanes.

(E)-7-((benzyloxy)methoxy)-4-methylhept-3-en-2-ol (538)
In a 25 mL round bottomed flask, alcohol 512 (0.662 g, 2.65 mmol), manganese dioxide (3.6 g), and hexanes (7 mL) were added. After incubation for 12 hours, the reaction was filtered through Celite and concentrated in vacuo. To this residue was added 8 mL of THF, then 5 mL of a 3M solution (15 mmol) of methylmagnesium bromide solution in THF. After 2 hours the reaction was quenched by excess water, and neutralized with 10%
aqueous HCl. The organic layer was extracted with ether, washed with brine, and dried with magnesium sulfate before concentration in vacuo and purification my MPLC (30% EtOAc/Hex) to give 538 (64 mg, 24%).

1H NMR (500 MHz, CDCl3) δ 7.36-7.27 (m, 5H), 5.24 (d, J = 8.5 Hz, 1H), 4.76 (s, 2H), 4.61 (s, 2H), 4.61-4.55 (m, 1H), 3.57 (t, J = 6.5 Hz, 2H), 2.07 (t, J = 7.5 Hz, 2H), 1.75-1.65 (m, 2H), 1.69 (s, 3H), 1.23 (d, J = 6.5 Hz, 3H).

13C NMR (125 MHz, CDCl3) δ 4235Carbon 138.1, 137.3, 129.6, 128.6, 128.0, 127.9, 94.8, 69.5, 67.7, 64.9, 36.1, 27.9, 23.9, and 16.6.


GC-MS T_r = 16.4 min; m/z: 233, 207, 178, 147, 117, 91, and 65.

IR (neat) 3272, 2933, 2878, 1780, 1700, 1600, 1460, 1388, 1352, 1252, 1212, 1101, 1033, 970, 921, 749, and 701 cm⁻¹.

TLC R_f = 0.25 in 30% EtOAc in hexanes.

(E)-8-(Benzyloxymethoxy)-2,5-dimethyloct-4-en-3-ol (541) Aldehyde 512 (0.525 g, 2.11 mmol) was added to a flask with THF (7 mL). Isopropyl magnesium chloride (2.0 M in THF, 1 mL, 2.0 mmol) was added at 0 °C, and an additional 1.0 mL was added after 20 minutes. After 1.5 hours ESI analysis showed complete consumption of starting material. The reaction was quenched with water and brine, extracted (ether), washed (brine), dried (sodium sulfate), concentrated in vacuo, and purified by MPLC (30% EtOAc/hex) to afford 0.328 g (53%) of the desired product as an oil with E:Z ratio of 92:8.

1H NMR (500 MHz, CDCl3) δ 7.37-7.27 (m, 5H), 5.21 (dq, J = 9.0, 1.0 Hz, 1H), 4.76 (s, 2H), 4.61 (s, 2H), 4.06 (dd, J = 9.0, 7.0 Hz, 1H), 3.62-3.54 (m, 2H), 2.15-2.05 (m, 2H), 1.79-1.64 (m, 3H), 1.69 (d, J = 1.5 Hz, 3H), 1.28 (s, 1H), 0.94 (d, J = 6.5 Hz, 3H), and 0.84 (d, J = 6.5 Hz, 3H).

13C NMR (125 MHz, CDCl3) δ 138.8, 138.1, 128.6, 128.0, 127.9, 126.7, 94.9, 73.8, 69.5, 67.8, 36.4, 34.7, 28.1, 18.6, 18.3, and 16.9.

IR (neat) 3434, 2953, 2874, 1456, 1376, 1159, 11114, 1043, 1027, 950, 736, and 697 cm\textsuperscript{-1}.

TLC $R_f = 0.45$ in 30\% EtOAc in hexanes.

(3S,5R)-8-(benzyloxymethoxy)-2,5-dimethyloctane-3,5-diol (545) Alcohol 541 (44.1 mg, 0.15 mmol, $E:Z = 92:8$) was added to a flask with THF (0.08 mL), water (0.075 mL), and mercuric acetate (69 mg, 0.22 mmol). After 24 hrs, 1 mL of 10\% NaOH, then NaBH\textsubscript{4} (51 mg, 1.34 mmol) was added. After 3 hours the mixture was filtered through Celite, extracted (ether), washed (brine), dried (sodium sulfate), concentrated in vacuo, and purified by MPLC (40\% EtOAc/hex) to afford 36 mg (77\%) of the desired product as an 85:15 mixture of diastereomers.

$^1\text{H NMR}$ (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.36-7.26 (m, 5H), 4.76 (s, 2H), 4.61 (s, 2H), 3.76-3.71 (m, 1H), 3.63-3.59 (m, 2H), 3.45 (br s, 2H), 1.73-1.56 (m, 7H), 1.21 (s, 3H), 0.92 (d, $J = 3.6$ Hz, 3H), 0.90 (d, $J = 3.6$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl\textsubscript{3}) $\delta$ 138.0, 128.6, 128.0, 127.9, 94.7, 73.9, 73.2, 69.6, 68.6, 43.2, 37.2, 34.5, 29.0, 25.0, 18.4, and 17.8.

HRMS (ESI) Calcd for (C\textsubscript{18}H\textsubscript{30}O\textsubscript{4} + Na\textsuperscript{+}): 333.2036. Found: 333.2063.

IR (neat) 3424, 2962, 2880, 1468, 1454, 1381, 1254, 1115, 1042, 935, 852, 739, and 698 cm\textsuperscript{-1}.

TLC $R_f = 0.30$ in 40\% EtOAc/hexanes.

Diol 545 (18 mg, 0.06 mmol) was added to a flask with anisaldehyde dimethylacetal (10.7 mg, 0.06 mmol), THF (0.2 mL), 4 Angstrom molecular sieves (90 mg), and p-TsOH (4.8 mg). After 2 days the reaction was quenched with 10\% NaOH so-
olution, extracted (ether), washed (brine), dried (sodium sulfate), and purified by MPLC (15% EtOAc/hex) to obtain 18 mg (72%) of the desired compound and its epimer. The stereochemistry was confirmed by NOE.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.44-7.41 (m, 2H), 7.35-7.26 (m, 5H), 6.88-6.85 (m, 2H), 5.61 (s, 1H), 4.77 (s, 2H), 4.26 (s, 2H), 3.78 (s, 3H), 3.63 (dd, $J = 6.0$ Hz, 2H), 3.64-3.58 (m, 1H), 2.23 (ddd, $J = 14.0$, 10.0, 6.0 Hz, 1H), 1.81-1.61 (m, 3H), 1.57-1.38 (m, 3H), 1.27 (s, 3H), 1.00 (d, $J = 6.5$ Hz, 3H), and 0.92 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 159.8, 138.1, 132.3, 128.6, 128.0, 127.9, 127.6, 127.5, 94.9, 94.4, 77.7, 73.9, 69.6, 68.5, 55.5, 38.6, 33.3, 30.8, 28.8, 23.7, 18.7, and 18.2.

HRMS (ESI) Calcd for $(C_{26}H_{36}O_5 + Na^+)$: 451.2455. Found: 451.2463.

IR (neat) 2958, 2878, 1616, 1589, 1517, 1463, 1383, 1301, 1250, 1170, 1113, 1084, 1040, 912, 831, and 738 cm$^{-1}$.

TLC $R_f$ = 0.25 in 15% EtOAc/hexanes.

(2R,3S)-4-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-(benzylmethoxy)-3-methyl-4-oxobutanal (556) Aldol adduct 553 (105 mg, 0.25 mmol) was added to a flask with DCM (0.1 mL) and pyridine (22 mg, 0.28 mmol). A stream of ozone was bubbled through the flask at -78 °C for 12 minutes. The mixture was filtered through silica gel and concentrated in vacuo. The crude aldehyde (94 mg, 92%) was of sufficient purity to use in the next reaction.

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.73 (d, $J = 2.5$ Hz, 1H), 7.35-7.17 (m, 10H), 4.87 (d, $J = 7.0$ Hz, 1H), 4.85 (d, $J = 7.0$ Hz, 1H), 4.71 (d, $J = 11.5$ Hz, 1H), 4.72-4.68 (m, 1H), 4.64 (d, $J = 12.0$ Hz, 1H), 4.33 (ddddd, $J = 8.5$, 7.0, 7.0, 7.0 Hz, 1H), 4.27 (dd, $J = 8.5$, 3.0 Hz, 1H), 4.22-4.14 (m, 2H), 3.27 (dd, $J = 13.5$, 3.5 Hz, 1H), 2.77 (dd, $J = 13.5$, 9.5 Hz, 1H), and 1.24 (d, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.4, 173.3, 153.2, 137.2, 135.2, 129.6, 129.1, 128.6, 128.0, 127.9, 127.5, 95.5, 83.6, 70.4, 66.2, 55.4, 39.6, 37.8, and 12.8.
HRMS (ESI) Calcd for (C_{23}H_{25}O_6N + Na^+): 434.1574. Found: 434.1590.

IR (neat) 3035, 2987, 2947, 2923, 2895, 1790, 1774, 1738, 1706, 1502, 1454, 1394, 1290, 1218, 1114, 1042, 965, 745, and 705 cm^{-1}.

TLC R_f = 0.35 in 30% EtOAc in hexanes.

![Chemical Structure]

2,2-dimethylhex-5-en-3-yl acetate (564)

In a 25 mL flask, alcohol 562 (0.379 g, 2.96 mmol), acetic anhydride (0.967 g, 9.48 mmol), DMAP (0.0112 g, 0.09 mmol), pyridine (0.85 g), and DCM (10 mL) were added. After stirring at room temperature for 10 hours, the reaction mixture was quenched with 10 mL satd. aq. NaHCO_3. The product was extracted with DCM (3 x 15 mL), washed with brine, and dried with magnesium sulfate, and concentrated in vacuo. The product was of sufficient purity to use without chromatography.

^1H NMR (500 MHz, CDCl_3) δ 5.72 (dddd, J = 16.0, 10.5, 8.5, 6.0 Hz, 1H), 5.04 (dq, J = 17.0, 1.5, 1.5, 1.5 Hz, 1H), 5.00 (m, large J = 10.0 Hz, 1H), 4.78 (dd, J = 10.5, 2.5 Hz, 1H), 2.39-2.34 (m, 1H), 2.16 (ddddd, J = 13.5, 10.5, 8.5, 1.5, 1.5 Hz, 1H), 2.04 (s, 3H), and 0.91 (s, 9H).

^13C NMR (125 MHz, CDCl_3) δ 233.2, 171.1, 135.5, 117.1, 79.7, 34.8, 26.1, and 21.2.

GC-MS T_r = 5.23 min; m/z: 129, 113, 95, 87, 69, and 57.

IR (neat) 3090, 1745, 1711, 1487, 1369, 1243, 1018, 973 cm^{-1}.

![Chemical Structure]

(2R,3S,E)-3-(benzyloxymethoxy)-2-methylhex-4-en-1-ol (566) Oxazolidinone 553

(0.534 g, 1.26 mmol) was added to a flask with ether (12 mL). Lithium borohydride (54 mg, 2.45 mmol) was added. After 1.5 hours, methanol (3 mL) was added, and the solvent
removed in vacuo. Purification by flash chromatography (30% EtOAc/hex) afforded 0.253 g (80%) of the desired product.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37-7.27 (m, 5H), 5.67 (dq, $J = 15.5$, 6.5, 6.5, 6.5 Hz, 1H), 5.29 (ddq, $J = 15.5$, 8.5, 1.5, 1.5, 1.5 Hz, 1H), 4.81 (d, $J = 7.0$ Hz, 1H), 4.73 (d, $J = 11.5$ Hz, 1H), 4.67 (d, $J = 7.0$ Hz, 1H), 4.51 (d, $J = 11.5$ Hz, 1H), 3.95 (dd, $J = 8.5$, 8.5 Hz, 1H), 3.69 (ddd, $J = 10.5$, 6.5, 3.5 Hz, 1H), 3.62 (ddd, $J = 10.5$, 6.5, 4.0 Hz, 1H), 2.79 (br s, 1H), 1.84 (dddddd, $J = 8.0$, 7.0, 7.0, 7.0, 7.0, 3.5 Hz, 1H), 1.72 (dd, $J = 6.5$, 1.5 Hz, 3H), and 0.87 (d, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.8, 131.5, 129.5, 128.7, 128.1, 127.9, 91.2, 82.3, 69.9, 66.9, 40.0, 17.9, and 14.0.

HRMS (ESI) Calcd for (C$_{15}$H$_{22}$O$_3$ + Na$^+$): 273.1461. Found: 273.1449.

IR (neat) 3477, 2967, 2890, 1666, 1497, 1455, 1381, 1145, 1100, 1040, 972, 928, 739, and 698 cm$^{-1}$.

TLC $R_f = 0.5$ in 30% EtOAc in hexanes.

(2R,3S,E)-3-(benzyloxymethoxy)-2-methylhex-4-enyl benzoate (567) Oxazolidinone 566 (0.530 g, 1.25 mmol) was added to a flask with ether (5 mL). Lithium borohydride (85 mg, 3.86 mmol) was added. After 2 hours, 10% aq NaOH was added, and extracted with ether, washed (brine), dried (sodium sulfate), and concentrated in vacuo. DCM (7 mL), pyridine (0.6 mL), and benzoyl chloride (0.45 mL) were added. After two hours, pH = 10 buffer was added, and extraction (DCM), washing (brine), drying (sodium sulfate), and concentration in vacuo were performed. Purification by flash chromatography (7% EtOAc/hex) afforded the desired product as an oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.04-8.02 (m, 2H), 7.56-7.53 (m, 1H), 7.43-7.39 (m, 2H), 7.27-7.24 (m, 5H), 5.72 (dq, $J = 15.0$, 6.5, 6.5, 6.5 Hz, 1H), 5.33 (ddq, $J = 15.5$, 9.0, 1.5, 1.5, 1.5 Hz, 1H), 4.83 (d, $J = 7.0$ Hz, 1H), 4.68 (d, $J = 7.0$ Hz, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.48 (d, $J = 12.0$ Hz, 1H), 4.41 (dd, $J = 10.5$, 5.0 Hz, 1H), 4.34 (dd, $J = 10.5$, 5.5 Hz, 1H)
Hz, 1H), 4.11 (dd, J = 7.0, 7.0 Hz, 1H), 2.16 (dddd, J = 12.5, 7.0, 7.0, 5.5 Hz, 1H), 1.73 (dd, J = 6.5, 2.0 Hz, 3H), and 1.03 (d, J = 7.0 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 50.272 Carbon 166.8, 138.0, 133.0, 131.7, 130.6, 129.7, 128.7, 128.6, 128.5, 128.1, 127.8, 91.4, 78.1, 69.7, 66.7, 37.8, 18.0, and 13.6.


IR (neat) 2968, 2940, 2881, 1720, 1608, 1494, 1452, 1388, 1313, 1273, 1176, 1112, 1070, 1038, 1026, 971, 924, 738, 712, and 698 cm$^{-1}$.

TLC $R_f$ = 0.45 in 10% EtOAc in hexanes.

2,2-dimethylhex-5-en-3-yl benzoate (570)

In a 25 mL flask, alcohol 562 (1.31 g, 10.2 mmol), benzoyl chloride (1.2 mL, 10.2 mmol), pyridine (1.7 mL), and DCM (5 mL) were added. After stirring at room temperature for 1 hour, the reaction mixture was quenched with 30 mL of 10% NaOH solution, and extracted from DCM (2 x 30 mL). The product was washed with brine, dried with sodium sulfate, concentrated in vacuo, and purified by flash chromatography (10% EtOAc/hexanes) to give 570 (1.92g, 81%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.06-8.04 (m, 2H), 7.56-7.53 (m, 1H), 7.45-7.42 (m, 2H), 5.79 (dddd, J = 14.0, 10.5, 8.0, 6.5 Hz, 1H), 5.06-5.02 (m, 2H), 4.95 (dddd, J = 10.0, 2.0, 1.0, 1.0 Hz, 1H), 2.48 (ddddd, J = 14.5, 6.0, 3.0, 1.5, 1.5 Hz, 1H), 2.34 (ddddd, J = 14.0, 10.0, 7.5, 1.0, 1.0 Hz, 1H), 1.00 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 185.2, 166.4, 135.2, 132.9, 130.8, 129.7, 128.5, 117.4, 80.5, 34.9, and 26.3.

HRMS (ESI) Calcd for (C$_{15}$H$_{20}$O$_2$ + Na$^+$): 255.1355. Found: 255.1358.

GC-MS $T_r$ = 9.1 min; m/z: 232, 217, 191, 105, 95, 77, 67, and 55.

IR (neat) 2969, 2914, 2874, 1721, 1644, 1602, 1479, 1451, 1367, 1347, 1313, 1271, 1176, 1111, 1069, 1026, 981, 917, and 710 cm$^{-1}$. 

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TLC $R_f = 0.60$ in 10% EtOAc in hexanes.

(2R,3S,E)-3-(benzyloxymethoxy)-2,8,8-trimethylnon-4-ene-1,7-diyldibenzoate (571)

Alkenes 567 (25.4 mg, 0.072 mmol) and 570 (0.074 mmol) were added to a 5 mL screw cap vial. DCM (0.14 mL) and HG2 (4.3 mg, 0.0069 mmol) were added, and the vial equipped with a nitrogen line and heated at 40 °C. A needle was also added to the septum to allow for solvent evaporation and ethylene removal. At 14 hours, the heat was turned up to 55 °C, and allowed to react for 32 more hours. Purification by MPLC afforded 30.0 mg (77%) of the desired product, along with 7% of recovered internal alkene 567.

$^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 8.03-7.96 (m, 4H), 7.56-7.45 (m, 2H), 7.42-7.36 (m, 4H), 7.27-7.18 (m, 5H), 5.74-5.65 (m, 1H), 5.35 (m, 1H), 5.07 (dd, 2.5, 2.5 Hz, 1H), 5.05 (dd, $J = 2.5$, 2.5 Hz, 1H), 4.74 (d, $J = 7.0$ Hz, 1H), 4.60 (d, $J = 7.0$ Hz, 1H), 4.54 (d, $J = 12.0$ Hz, 1H), 4.50 (d, $J = 6.5$ Hz, 1H), 4.42 (d, $J = 12.0$ Hz, 1H), 4.34 (d, $J = 12.0$ Hz, 1H), 4.31 (d, $J = 11.0$ Hz, 1H), 4.30 (d, $J = 7.0$ Hz, 1H), 4.27 (dd, $J = 11.0$, 6.0 Hz, 1H), 4.21 (m, 1H), 4.01 (app q, $J = 8.5$ Hz, 1H), 2.55-2.47 (m, 1H), 2.41-2.32 (m, 1H), 5.05 (dddddd, $J = 7.0$, 7.0, 7.0, 7.0, 7.0, 7.0, 5.5 Hz, 1H), 1.93 (dddddd, $J = 7.0$, 7.0, 7.0, 7.0, 7.0, 5.5 Hz, 1H), 1.00 (s, 9H), 0.93 (d, $J = 7.0$ Hz, 3H), and 0.74 (d, $J = 7.0$ Hz, 3H).

$^{13}C$ NMR (125 MHz, CDCl$_3$) $\delta$ 166.73, 166.68, 166.24, 166.23, 138.11, 138.03, 132.9, 132.5, 130.67, 130.60, 130.57, 130.55, 129.76, 129.74, 128.52, 128.51, 128.48, 128.43, 127.94, 127.88, 127.68, 127.61, 91.47, 91.35, 81.0, 80.38, 80.24, 77.90, 77.82, 69.64, 69.58, 66.58, 66.40, 37.76, 37.69, 35.1, 33.63, 33.51, 26.2, 13.53, 13.44.

HRMS (ESI) Calcd for (C$_{34}$H$_{40}$O$_6$ + Na$^+$): 567.2717. Found: 567.2741.

IR (neat) 2969, 2907, 1722, 1715, 1602, 1584, 1452, 1367, 1314, 1275, 1176, 1113, 1070, 1038, 1026, 974, and 711 cm$^{-1}$.

TLC $R_f = 0.30$ in 10% EtOAc in hexanes.
(+/-)-(3R,4R)-3,6-dimethylhept-1-en-4-yl benzoate (573) Aldehyde 572 was added to DCM (10 mL) and Z-crotyltrichlorosilane (513) (0.65 mL). The flask was cooled to 0 °C and DMF (0.6 mL) was added dropwise. After 12 hours, 30 mL of 10% satd. aq. NaOH was added. Extraction (DCM), washing (brine), drying (sodium sulfate), and concentration in vacuo were performed. The crude alcohol was added to DCM (3 mL), pyridine (0.6 mL), and benzoyl chloride (0.5 mL) was added. After 8 hours, 10% satd aq NaOH (10 mL) was added. Extraction (DCM), washing (brine), drying (sodium sulfate), concentration in vacuo, and flash chromatography (10% EtOAc/hex) were performed to acquire 0.597 g (66%) of the desired product as an oil.

**1H NMR** (500 MHz, CDCl₃) δ 8.06-8.04 (m, 2H), 7.57-7.54 (m, 1H), 7.46-7.43 (m, 2H), 5.83 (ddd, J = 17.5, 10.5, 7.5 Hz, 1H), 5.20 (ddd, J = 8.5, 3.0, 3.0 Hz, 1H), 5.06 (ddd, J = 17.0, 1.5, 1.5 Hz, 1H), 5.06-5.03 (m, large J = 10.5 Hz, 1H), 2.53 (app sextet, J = 7.0 Hz, 1H), 1.68-1.59 (m, 2H), 1.43-1.38 (m, 1H), 1.07 (d, 7.0 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), and 0.91 (d, J = 7.0 Hz, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 166.5, 140.1, 132.9, 130.9, 129.8, 128.5, 115.5, 76.0, 42.2, 40.6, 24.9, 23.7, 22.1, and 15.4.

**HRMS** (ESI) Calcd for (C₁₆H₂₂O₂ + Na⁺): 269.1512. Found: 269.1523.

**GC-MS** Tᵣ = 9.5 min; m/z: 246, 231, 191, 160, 124, 105, 77, and 51.

**IR** (neat) 3090, 3070, 2961, 2937, 2869, 1720, 1447, 1314, 1274, 1177, 1113, 1068, 1028, 919, and 710 cm⁻¹.

**TLC** Rᵣ = 0.65 in 10% EtOAc in hexanes.
(2R,3S,6R,7R,E)-3-(benzyloxymethoxy)-2,6,9-trimethyldec-4-ene-1,7-diy1 dibenzoate (574a) and (2R,3S,6S,7S,E)-3-(benzyloxymethoxy)-2,6,9-trimethyldec-4-ene-1,7-diy1 dibenzoate (574b) Internal alkene 567 (28.1 mg, 0.079 mmol) and terminal alkene 573 (20.0 mg, 0.081 mmol) were added to a vial with DCM (0.13 mL). HG2 (4.9 mg) was added and a septum attached with a nitrogen line and another needle added to vent solvent and ethylene. The vial was heated to 55 °C for 2 days, then 70 °C for an additional day. Purification by MPLC (10% EtOAc/hex) afforded 12.6 mg of 574a and 574b as an inseparable mixture of diastereomers.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.04 (m, 4H), 7.56-7.51 (m, 2H), 7.43-7.39 (m, 4H), 7.26-7.24 (m, 5H), 5.75 (dd, $J$ = 15.5, 7.5 Hz, 1H), 5.71 (dd, $J$ = 15.5, 8.0 Hz, 1H), 5.36 (dd, $J$ = 15.5, 8.5 Hz, 1H), 5.22-5.16 (m, 1H), 4.81-4.75 (m, 1H), 4.67-4.61 (m, 2H), 4.48-4.44 (m, 1H), 4.41-4.31 (m, 2H), 4.12 (ddd, $J$ = 8.0, 3.0, 3.0 Hz, 1H), 2.61 (app septet, 7.0 Hz, 1H), 2.16-2.10 (m, 1H), 1.69-1.59 (m, 2H), 1.41-1.30 (m, 1H), 1.09 (d, $J$ = 7.0 Hz, 3H), 1.08 (d, $J$ = 7.0 Hz, 3H), 0.99 (d, $J$ = 7.0 Hz, 3H), 0.97 (d, $J$ = 7.0 Hz, 3H), and 0.92-0.89 (m, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.73, 166.34, 137.96, 137.95, 137.75, 137.69, 133.05, 133.03, 133.01, 130.68, 130.66, 130.52, 129.78, 129.73, 128.69, 128.67, 128.57, 128.53, 128.03, 127.99, 127.78, 91.45, 91.42, 80.99, 79.0, 77.97, 77.91, 75.96, 75.88, 69.78, 66.6, 66.56, 41.09, 40.8, 40.52, 40.49, 37.8, 24.92, 24.91, 23.7, 22.08, 22.06, 16.2, 15.7, 13.66, and 13.57.

HRMS (ESI) Calcd for (C$_{35}$H$_{42}$O$_6$ + Na$^+$): 581.2874. Found: 581.2875.

IR (neat) 2967, 2884, 1752, 1453, 1385, 1365, 1317, 1281, 1177, 1116, 1069, 1031, 1029, 977, and 713 cm$^{-1}$.

TLC $R_f$ = 0.4 in 10% EtOAc in hexanes.
(2R,3R)-3-(benzyloxymethoxy)-2-methyl-4-oxobutyl benzoate (595) Alkene 567 was added to DCM (1.5 mL) and pyridine (75 mg) in a vial. The vial was cooled to -78 °C and a stream of ozone was bubbled through for 17 minutes. Filtration through silica gel gave the desired product (0.196 g, 91%), which was of sufficient purity to use in the next step.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.74 (d, $J = 2.0$ Hz, 1H), 7.99-7.97 (m, 2H), 7.58-7.55 (m, 1H), 7.47 (m, 2H), 7.34-7.28 (m, 5H), 4.92 (d, $J = 7.5$ Hz, 1H), 4.83 (d, $J = 7.0$ Hz, 1H), 4.68 (d, $J = 12.0$ Hz, 1H), 4.64 (d, $J = 11.5$ Hz, 1H), 4.40-4.29 (m, 2H), 4.00 (dd, $J = 4.5$, 2.0 Hz, 1H), 2.57 (dddddd, $J = 7.0$, 7.0, 7.0, 7.0, 5.0, 5.0, Hz, 1H), and 1.16 (d, $J = 7.0$ Hz, 3H).


GC-MS $T_r = 13.98$ and 14.03 min (epimerizes during GC); m/z: 327, 281, 253, 207, 193, 161, 123, 105, 91, 77, and 65.

IR (neat) 2969, 2914, 2885, 1729, 1452, 1376, 1276, 1172, 1115, 1043, 1031, and 714 cm$^{-1}$.

TLC $R_f = 0.22$ in 10% EtOAc in hexanes.

(R)-4-benzyl-3-((2S,3S,E)-3-((tert-butyldimethylsilyl)oxy)-2-methylhex-4-enoyl)oxazolidin-2-one (S504) In a 25 mL round bottom flask equipped with a stirbar, oxazolidinone 563 (0.966 g, 3.18 mmol), TBSCI (0.533 g, 3.54 mmol), imidazole (0.56 g, 8.2 mmol), DMAP (98 mg, 0.80 mmol), and CH$_2$Cl$_2$ were added. After 36 hours, the reaction was complete as judged by TLC. The reaction was quenched with 10 mL satd. aq. NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 20 mL), and dried with sodium sulfate. Purification by MPLC (10% EtOAc/Hex) gave S504 (0.952 g, 72%).
\[^1H\ ]\text{NMR} \ (500\text{ MHz, CDCl}_3) \delta \ 7.35-7.32\ (m, 2H), \ 7.29-7.27\ (m, 1H), \ 7.25-7.23\ (m, 2H), \ 5.62\ (dq, J = 15.5, 6.5\ Hz, 1H), \ 5.40\ (ddq, J = 15.5, 8.5, 2.0\ Hz, 1H), \ 4.67\ (dddd, J = 10.5, 7.5, 3.0, 3.0\ Hz, 1H), \ 4.42\ (dd, J = 8.5, 8.5\ Hz, 1H), \ 4.17\ (dddd, J = 10.5, 7.5, 3.0, 3.0\ Hz, 1H), \ 4.12\ (dd, J = 9.0, 3.0\ Hz, 1H), \ 3.94\ (dq, J = 8.5, 7.0\ Hz, 1H), \ 3.37\ (dd, J = 13.5, 8.5\ Hz, 1H), \ 2.65\ (dd, J = 13.0, 10.0\ Hz, 1H), \ 1.71\ (dd, J = 6.5, 1.5\ Hz, 3H), \ 1.04\ (d, J = 7.0\ Hz, 3H), \ 0.85\ (s, 9H), \ 0.05\ (s, 3H), \text{and} \ 0.03\ (s, 3H).

\[^{13}\text{C NMR} \ (125\text{ MHz, CDCl}_3) \delta \ 175.8, \ 153.3, \ 135.8, \ 132.3, \ 129.6, \ 129.2, \ 128.7, \ 127.5, \ 76.1, \ 66.0, \ 55.6, \ 44.7, \ 38.6, \ 26.1, \ 18.3, \ 17.8, \ 14.0, -3.7, \text{and} \ -4.3.\n
\text{HRMS (ESI) Calcd for (C}_{23}\text{H}_{35}\text{O}_{4}\text{NSi} + \text{Na}^+: 440.2228. Found: 440.2320.}

\text{GC-MS} \ T_r = 14.09\text{ min; m/z: 360, 332, 290, 234, 185, 183, 117, 109, 91, and 73.}

\text{IR (neat) 2956, 2932, 2856, 1785, 1705, 1469, 1453, 1385, 1349, 1249, 1213, 1101, 1089, 1061, 1049, 969, 857, 837, 781, and 795 cm}^{-1}.

\text{TLC} \ R_f = 0.45\text{ in 15\% EtOAc in hexanes.}

\[
\begin{array}{c}
\text{HO} \quad \text{Me} \\
\text{S505} \\
\begin{array}{c}
\text{N} \\
\text{SH} \\
\text{Me} \\
\text{BT} \\
\text{592} \\
\text{590} \\
\end{array}
\end{array}
\]

\text{1. DIAD, PPh}_3 \ \text{THF 0 °C;}

\text{2. m-CPBA, CH}_2\text{Cl}_2 \ r.t.}

\text{2-(isobutylsulfonyl)benzo[d]thiazole (590)}

In a 100 mL round bottomed flask equipped with a stirbar, isobutanol (S505) (1.01 g, 13.6 mmol), THF (30 mL), and PPh\textsubscript{3} (3.84 g, 14.6 mmol) were added. To this stirred mixture, DIAD (3.04 mL, 15.3 mmol) was added dropwise at 0 °C. After 8 minutes, 2-mercaptobenzothiazole (592) (2.39 g, 14.3 mmol) was added with 9 mL of THF. After 12 hours the solvent was removed in vacuo, and the residue was dissolved in 30 mL of diethyl ether. Upon standing, triphenylphosphine oxide and reduced DIAD precipitates. Filtration gave crude thioether, which was dissolved in CH\textsubscript{2}Cl\textsubscript{2}. m-CPBA (7.4 g, 43 mmol) was then added. After 12 hours the reaction was quenched with sodium bisulfite and extracted with sodium bicarbonate, washed with brine, and concentrated in vacuo. Purification by flash chromatography (20% EtOAc/Hex) gave 590 (3.00 g, 91\%).
$^1$H NMR (500 MHz, CDCl$_3$) δ 8.21 (app d, $J = 8.0$ Hz, 1H), 8.02 (app d, $J = 8.0$ Hz, 1H), 7.64 (app dt, $J = 1.0$, 8.5 Hz, 1H), 7.59 (app dt, $J = 1.0$, 8.0 Hz, 1H), 3.44 (d, $J = 6.5$ Hz, 2H), 2.45 (app nonet, $J = 6.5$ Hz, 1H), and 1.13 (d, $J = 6.5$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.9, 152.9, 136.9, 128.2, 127.8, 125.6, 122.5, 62.3, 24.3, 22.8, and 22.1.

HRMS (ESI) Calcd for (C$_{11}$H$_{13}$O$_2$S$_2$N + Na$^+$): 278.0280. Found: 278.0266.

GC-MS $T_r = 11.93$ min; m/z: 255, 240, 199, 176, 149, 135, 108, 90, 82, 69, and 57.

TLC $R_f = 0.33$ in 15% EtOAc in hexanes.

(2$R$,3$S$,$E$)-3-(tert-butyldimethylsilyloxy)-2-methylhex-4-en-1-yl benzoate (S506)

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.05-8.02 (m, 2H), 7.59-7.53 (m, 1H), 7.47-7.41 (m, 2H), 5.58 (dq, $J = 15.3$, 6.0 Hz, 1H), 5.43 (ddq, $J = 15.3$, 7.5, 1.5 Hz, 1H), 4.36 (dd, $J = 10.8$, 5.1 Hz, 1H), 4.22 (dd, $J = 10.8$, 6.6 Hz, 1H), 4.07 (dd, $J = 6.9$, 6.9 Hz, 1H), 2.02 (app septet, $J = 6.6$ Hz, 1H), 1.69 (dd, $J = 6.3$, 1.2 Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.8, 132.9, 132.6, 130.7, 129.7, 128.5, 127.2, 75.5, 66.9, 39.8, 26.1, 18.4, 17.9, 13.5, -3.8, and -4.7.


GC-MS $T_r = 11.8$ min; m/z: 291, 221, 185, 179, 135, 105, 95, and 73.

IR (neat) 2957, 2930, 2895, 2857, 1724, 1469, 1465, 1450, 1389, 1313, 1275, 1252, 1112, 1089, 1070, 1051, 1028, 971, 834, 772, and 712 cm$^{-1}$.

TLC $R_f = 0.70$ in 20% EtOAc in hexanes.
5-(isobutylsulfonyl)-1-phenyl-1H-tetrazole (589)

In a 100 mL round bottomed flask equipped with a stirbar, isobutanol (S505) (1.00 g, 13.5 mmol), THF (30 mL), and PPh₃ (3.78 g, 14.4 mmol) were added. To this stirred mixture, DIAD (2.99 mL, 15.1 mL) was added dropwise at 0 °C. After 8 minutes, 1-phenyl-1H-tetrazole-5-thiol (591) (2.52 g, 14.1 mmol) was added with 9 mL of THF. After 12 hours the solvent was removed in vacuo, and the residue was dissolved in 30 mL of diethyl ether. Upon standing, triphenylphosphine oxide and reduced DIAD precipitates. Filtration gave crude thioether, which was dissolved in CH₂Cl₂. m-CPBA (7.4 g, 43 mmol) was then added. After 12 hours the reaction was quenched with sodium bisulfite and extracted with sodium bicarbonate, washed with brine, and concentrated in vacuo. Purification by flash chromatography (20% EtOAc/Hex) gave 589 (2.91 g, 81%).

¹H NMR (500 MHz, CDCl₃) δ 7.70-7.67 (m, 2H), 7.64-7.58 (m, 3H), 3.68 (d, J = 6.5 Hz, 2H), 2.48 (app nonet, J = 6.5 Hz, 1H), 1.16 (d, J = 6.5 Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 154.1, 131.6, 129.8, 125.3, 63.1, 24.1, 22.7.

TLC Rₓ = 0.45 in 20% EtOAc in hexanes.

(2R,3S,E)-3-((benzyloxy)methoxy)-2,6-dimethylhept-4-en-1-yl benzoate (597)

In a 3 mL screw cap vial equipped with a septa and stirbar, PT sulfone 589 (78.5 mg, 0.295 mmol), and DME (0.3 mL) were added. After cooling to -78 °C, KHMDS (0.62 mL, 0.5 M, 0.31 mmol) was added. The newly formed anion displayed a yellow color. After 10 minutes, aldehyde 595 (98 mg, 0.28 mmol) was added as a solution in DME (0.42 mL). After 8 hours, the mixture was allowed to warm to room temperature. GC/MS
analysis showed an 8.7:1 diastereomeric ratio. After extraction, purification by MPLC (8% EtOAc/Hex) gave 597 (26 mg, 24%).

**1H NMR** (500 MHz, CDCl₃) δ 8.05-8.03 (m, 2H), 7.56-7.53 (m, 1H), 7.43-7.40 (m, 2H), 7.28-7.23 (m, 5H), 5.69 (dd, J = 15.5, 7.0 Hz, 1H), 5.25 (ddd, J = 15.5, 8.5, 1.0 Hz, 1H), 4.83 (d, J = 6.5 Hz, 1H), 4.67 (d, J = 6.5 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.42 (dd, J = 10.5, 5.0 Hz, 1H), 4.36 (dd, J = 10.5, 6.0 Hz, 1H), 4.11 (dd, J = 8.0, 8.0 Hz, 1H), 2.33 (d of app octets, J = 7.0, 1.0 Hz, 1H), 2.16 (app septet, J = 7.0 Hz, 1H), 1.03 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.5 Hz, 6H).

**13C NMR** (125 MHz, CDCl₃) δ 166.8, 144.2, 138.0, 133.0, 130.6, 129.7, 128.6, 128.5, 128.1, 127.8, 124.3, 91.3, 78.1, 69.8, 66.7, 37.8, 31.2, 22.59, 22.55, 13.7.


**GC-MS** Tᵣ = 14.3 min; m/z: 219, 189, 124, 105, and 91.

**IR** (neat) 3069, 3029, 2957, 2877, 1723, 1603, 1492, 1452, 1384, 1312, 1276, 1180, 1112, 1036, 976, 741, 712, and 698 cm⁻¹.

**TLC** Rᵣ = 0.50 in 10% EtOAc in hexanes.

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(2R,3S,E)-3-(3-(benzyloxy)methoxy)-2,6-dimethylhept-4-en-1-yl benzoate (597)

In a 3 mL screw cap vial equipped with a septa and stirbar, BT sulfone 590 (78.9 mg, 0.309 mmol), and DME (0.3 mL) were added. After cooling to -78 °C, KHMDS (0.65 mL, 0.5 M, 0.32 mmol) was added. The newly formed anion displayed a dark orange color. After 10 minutes, aldehyde 595 (98 mg, 0.28 mmol) was added as a solution in DME (0.42 mL). After 8 hours, the mixture was allowed to warm to room temperature. GC/MS analysis showed an 7.3:1 diastereomeric ratio. After extraction, purification by MPLC (8% EtOAc/Hex) gave 597 (19 mg, 17%).
(2R,3S,E)-3-((tert-butyldimethylsilyl)oxy)-2,6-dimethyloct-4-en-1-yl benzoate (598)

In a 3 mL screw cap vial equipped with a septa and stirbar, BT sulfone 590 (60.8 mg, 0.238 mmol), aldehyde 596 (76 mg, 0.23 mmol), and DME (0.3 mL) were added. After cooling to -78 °C, KHMDS (0.5 mL, 0.5 M, 0.25 mmol) was added. After 6 hours, the mixture was allowed to warm to room temperature. GC/MS analysis showed a 48:1 diastereomeric ratio. After extraction (DCM from satd. aq. ammonium chloride), washing with brine, and drying with sodium sulfate, purification by MPLC (8% EtOAc/Hex) gave 598 (23 mg, 26%).

**1H NMR** (300 MHz, CDCl$_3$) δ 8.07-8.03 (m, 2H), 7.59-7.53 (m, 1H), 7.48-7.42 (m, 2H), 5.54 (dd, $J = 15.3, 6.6$ Hz, 1H), 5.35 (ddd, $J = 15.3, 7.5, 0.9$ Hz, 1H), 4.38 ($J = 10.8, 5.1$ Hz, 1H), 4.23 (ddd, $J = 10.8, 6.3$ Hz, 1H), 4.05 (dd, $J = 6.9$ Hz, 1H), 2.29 (d of app octets, $J = 6.6, 0.9$ Hz, 1H), 2.01 (dddt, $J = 6.6, 6.6, 6.6, 6.6, 5.1$ Hz, 1H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.008 (s, 3H).

**13C NMR** (75 MHz, CDCl$_3$) δ 166.8, 139.7, 132.9, 130.7, 129.7, 128.5, 128.4, 75.7, 66.9, 39.8, 31.0, 26.1, 22.6, 22.4, 18.4, 13.7, -3.6, -4.7.

**HRMS** (ESI) Calcd for (C$_{23}$H$_{36}$O$_3$Si + Na$^+$): 399.2326. Found: 399.2334.

**GC-MS** $T_r = 12.3$ min; m/z: 319, 213, 179, and 105.

**IR** (neat) 2954, 2928, 2884, 2854, 1721, 1463, 1448, 1379, 1356, 1268, 1250, 1172, 1110, 1069, 1025, 966, 929, 860, 830, 771, and 712 cm$^{-1}$.

**TLC** $R_f = 0.55$ in 10% EtOAc in hexanes.

(2R,4S,5R)-2-(4-methoxyphenyl)-5-methyl-4-((E)-prop-1-en-1-yl)-1,3-dioxane (5100)
In a 25 mL flask, oxazolidinone 563 (0.958 g, 3.16 mmol), diethyl ether (10 mL), THF (5 mL), and lithium borohydride (0.144 g, 6.54 mmol) were added. After 1 hour, 10 mL 10% NaOH solution was added, and the crude product was extracted from diethyl ether (4 x 20 mL) and concentrated in vacuo. To this crude diol were added 3 Angstrom molecular sieves (0.426 g), 4 Angstrom molecular sieves (0.560 g), THF (7 mL), anisaldehyde dimethylacetal (0.55 mL, 3.23 mmol), and p-TsOH (0.045 g, 0.24 mmol). After 24 hours the reaction was quenched with 10 mL satd. aq. sodium carbonate, filtered through celite, extracted with diethyl ether (3 x 25 mL), washed with brine, dried with sodium sulfate, and concentrated in vacuo. Purification by MPLC (5% EtOAc/hexanes) gave 5100.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.42 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 5.79 (ddq, $J = 15.0$, 6.5, 0.5 Hz, 1H), 5.51 (ddq, $J = 15.5$, 8.0, 1.5 Hz, 1H), 5.48 (s, 1H), 4.14 (dd, $J = 11.5$, 5.0 Hz, 1H), 3.83-3.79 (m, 2H), 3.78 (s, 3H), 3.51 (dd, $J = 11.5$, 11.0 Hz, 1H), 1.88 (dddt, $J = 11.5$, 7.0, 7.0, 7.0, 7.0, 5.0 Hz, 1H), 1.73 (dd, $J = 6.5$, 1.5 Hz, 3H), 0.75 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 160.1, 131.4, 130.4, 129.7, 127.7, 113.8, 101.3, 84.9, 73.3, 55.5, 34.2, 18.1, 12.7.


GC-MS $T_r = 11.1$ min; m/z: 248, 178, 135, and 81.

IR (neat) 2959, 2938, 2917, 2875, 2842, 1615, 1518, 1461, 1391, 1301, 1248, 1169, 1113, 1107, 1073, 1034, 967, 827, and 780 cm$^{-1}$.

TLC $R_f = 0.75$ in 30% EtOAc/hexanes.
Chapter VI:

Additional Studies
6.1 A Semipinacol Vinyl Shift onto a Benzylic Carbocation: Competition Between Homobenzyl and Homoallylic Carbocation Formation and Rearrangement

An early result from the Evans lab showed that the allylzinc reagent 601 could add to cyclohexanone to yield product 602 in good yield (Scheme 701). When this product was refluxed with formic acid, rearrangement to the quaternary aldehyde 603 occurred, likely through protonation of the tertiary alcohol in 602, and 1,2-vinyl shift with concomitant loss of water within 604 to give 605, followed by hydrolysis to aldehyde 603. This particular reaction is synthetically useful, as methods of formation of quaternary centers are limited.

Scheme 601

The vinyl shift from Scheme 601 is intriguing because of the potential intermediacy of a homoallyl cation from loss of water from intermediate 602. This intermediate, which is likely the highest energy intermediate along the reaction pathway, is stabilized by the vinyl group (606), similar to the stabilization of the homobenzyl cation by an aromatic system (607) (Figure 10).

Figure 10 – Homoallylic and Homobenzylic Cations
Our idea was to use this semipinacol reaction on a substrate capable of making both the homoallyl and homobenzyl cations. For example, in substrate 608, protonation of the tertiary alcohol (609) and loss of water would give a carbocation (610) that was simultaneously benzylic and homoallylic (Scheme 602). Likewise, protonation of the methyl ether (611), followed by loss of methanol would give a carbocation (612) that was simultaneously allylic and homobenzylic. Carbocation 610 would be expected to undergo a vinyl shift, leading to aldehyde 613, whereas carbocation 612 is expected to undergo a phenyl shift, leading to ketone 614.

Scheme 602

We decided to make substrate 608 and see which product was actually formed. To the best of our knowledge no competition of this type had been performed. The synthesis of the substrate 608 was accomplished by the deprotonation of allyl methyl ether (615), addition of anhydrous zinc chloride, and addition of acetophenone to the reaction pot (Scheme 603). When this isolated mixture was subjected to formic acid and refluxing toluene, the only isomer that was observed was 613. Thus, it would appear that the formation of the benzylic/homoallylic cation 610 is favored, although reversible formation of 612 cannot be ruled out without further control experiments. It would also be interesting to observe the effect of electron withdrawing groups on the aromatic ring, as destabilizing the benzylic cation could lead to a reversal of selectivity for which cation is formed.
6.2 An Unexpected SN2’ Reaction is Observed During an Attempted Deprotonation of Allyl Ethyl Ether.

During the synthesis of substrate 608 in the previous section, an allylzinc organometallic reagent was synthesized (Scheme 604). It was roughly during this time that the Hoye group had planned a group outing to the 8th International Symposium on Carbanion Chemistry, where we planned to show examples of the power of No-D NMR to observe organometallics. While the formation of an allylzinc reagent such as 617 is usually performed in THF solvent, we decided to try the reaction in pentane, as the No-D spectra would then be free of potentially interfering THF resonances. Conveniently, the tert-butyl lithium was packaged in pentane, so the potential for clean looking spectra was possible.

Scheme 604

When 616 was subjected to tert-butyl lithium, it was discovered that an entirely different process had occurred (Scheme 605). None of 618 could be observed, and very little 2-methylpropane 619 could be observed, which should be formed if deprotonation of 616 is occurring. The cleanly-formed product of this reaction was found to be the hydrocarbon 620 (Scheme 605). The reaction was followed by No-D NMR with varying amounts of tert-butyl lithium added, and SN2’ displacement is the major product. Also observed were EtOLi (621) and 2-methylpropene (622). This particular reaction is a case where the solvent choice is critical. In pentane exclusive addition of tert-butyl lithium to the substrate 616 occurs, but in THF the desired anion can be formed. This result was presented as part of the Hoye groups’ poster at the ISCC.
Scheme 605

\[
\text{Starting material in pentane} \rightarrow \text{Li} + \text{EtOLi} + \text{H} \rightarrow \text{618} + \text{619} + \text{620} + \text{621} + \text{622}
\]

- 1 equiv. \text{tBuLi} in pentane at 0 °C
- 2 equiv. \text{tBuLi}
- ~0.5 equiv. \text{tBuLi}

NMR spectra showing the reaction progress and products.
6.3 On The Biosynthesis of Hirsutellone A: A Formal 1,2-shift via Spontaneous Anionic Oxy-Cope/Enolate Isomerization?

The hirsutellones were isolated from the insect pathogenic fungus *Hirsutella nivea* BCC 2594, and show antituberculosis activity.136 Our group became interested in the hirsutellones due to their unknown biosynthesis and unique structural features, key of which are strained 12- or 13-membered rings embedded with a *para*-substituted phenyl ether. Of particular interest was the origin of hirsutellone A (623), in which an apparent 1,2-carbon shift from the putative biosynthetic precursor “prehirsutellone A” (624) had occurred (Scheme 606).

Scheme 606

The assumption that prehirsutellone A is the biogenic precursor to 623 is supported by experiments on the dimer hirsutellone F (625). When Isaka and co-workers subjected 625 to potassium carbonate in THF, full conversion to 623 occurred, with a 93% isolated yield after silica gel chromatography (Scheme 606).136b Since the base is likely causing a retro-hetero Michael addition from 625, this forms prehirsutellone A *in situ*, which undergoes the 1,2-carbon shift. What is striking about this transformation is its efficiency; no other byproducts could be observed during the reaction.

Scheme 606
During studies toward the synthesis of the hirsutellone A, Hoye group member Feng Shao made the model compound 626, and subjected it to a variety of conditions, including those reported by Isaka, and the 1,2-carbon shift to 627 did not occur (Scheme 607). Due to this result, it seemed to us that the unique reactivity of the prehirsutellone A could be traced to the strained nature of its 13-membered ring system.

**Scheme 607**

Together with Hoye group member Patrick Willoughby, the structure of prehirsutellone A was computationally modeled. A Macromodel conformational search revealed a structure suitable for further optimization at the DFT-based PBE1/6-311G(d,p) level, and this revealed several interesting features of 624 (Figure 13). First, the paracyclophane ring system is extraordinarily bent, having dihedral angles of 32° and 17° on each side of the aromatic ring. Also noteworthy is the close proximity of the carbons highlighted in Figure 11, being 3.1 Angstroms away in the energy-minimized conformer.

**Figure 11 – Conformation of 624**

While a simple 1,2-shift of 624 to 623 may not be unreasonable, we developed an alternative hypothesis (Scheme 608). Knowing that the pKa of hemiketal protons is significantly lower than simple alcohols, there should be a small, steady state amount of hemiketal alkoxide 628 present, even under biological conditions. The close proximity of the aromatic ring to the enone of the heterocyclic ring would mean that only a slight twist in the aromatic ring system would have to occur to satisfy the geometry of an anionic oxy-Cope rearrangement, which would give 629. The strained nature of the aromatic ring should significantly lessen the resonance energy penalty associated with breaking the sys-
tem of p-orbitals in 628. From 629, an enolate isomerization to the more stabilized β-ketoamide 630 could occur, which would give 623 upon protonation.

Scheme 608

As a test to determine the viability of this hypothesis, the energies of 624 and 631 were calculated (PBE1 6-311g(d,p)). These neutral species were chosen initially due to the belief that their energies would be easier to obtain than the anionic version of each. It was found that 631, the protonated oxy-Cope intermediate, was only ~19 kcal/mol higher in energy than 624 (Figure 12). This is an especially intriguing result when one considers that a typical aromatic resonance energy is ~36 kcal/mol. Thus, it appears that the significantly strained nature of the aromatic ring in 624 is a major factor in the transformation, and helps explain why Feng Shao’s acyclic model system was unreactive if this is indeed the correct mechanism.

Figure 12 – Relative Energies of 624 and 631

In conclusion, we have developed a unique oxy-Cope/enolate isomerization hypothesis to the 12-membered paracyclophane ring system of hirsutellone A, and preliminary computational data suggest it is reasonable. Keys to this transformation are the significantly bent nature of the aromatic ring, which lessens the resonance energy penalty.
upon dearomatization, and the close proximity of the aromatic ring to the enone of the heterocycle. Due to the high degree of strain of the hirsutellones, model systems may fail to capture the full nature of the distorted aromatic system and forced proximity of functionality. Future directions are clear – the anionic versions of 624 and 623 must be calculated, along with their corresponding transition state. These numbers should be compared to the activation energy of a direct 1,2-shift. Given that [3,3] sigmatropic rearrangements are typically rare in nature, these results could serve to expand our understanding of pericyclic reactions in complex environments.

6.4 Experimental Section

3-methoxy-2-phenylpent-4-en-2-ol (608)
Methyl allyl ether (615, 0.111 g, 1.54 mmol) and tBuLi (1.0 mL, 1.7 mmol) were added to a 15 mL flask at -78 °C under nitrogen. After 20 minutes, anhydrous ZnCl₂ (0.153 g, 1.12 mmol) in THF (1.5 mL) was added. After 5 minutes, acetophenone (0.132 g, 1.1 mmol) was added. After 30 minutes the reaction was allowed to warm to room temperature, and quenched with 10 mL satd. aq. ammonium chloride solution, extracted with ether (2 x 15 mL), washed with brine, and dried with sodium sulfate. Purification by MPLC (10% EtOAc/hexanes) gave the desired product (52 mg, 25%) as a 4:1 mixture of diastereomers.

\[ ^1\text{H} \text{NMR} \ (500 \text{ MHz}, \text{CDCl}_3) \delta \ 7.47-7.23 \ (m, 5H), 5.68 \ (\text{ddd}, \ J = 17.0, \ 10.5, \ 8.0 \text{ Hz}, \ 1H), 5.31-5.29 \ (m, \text{large} \ J = 8.5 \text{ Hz}, \ 1H), 5.18-5.13 \ (m, \text{large} \ J = 17.0 \text{ Hz}, \ 1H), 3.66 \ (d, \ J = 7.5 \text{ Hz}, \ 1H), 3.26 \ (s, \ 3H), 1.45 \ (s, \ 3H). \]

TLC \( R_f = 0.33 \) in 10% EtOAc in hexanes.
2-methyl-2-phenylbut-3-enal (613)

Alcohol 608 (3.5 mg) was placed in formic acid (50 µL) and toluene (1 mL) and refluxed for 40 minutes. GC showed complete conversion to a new compound, and NMR showed it to be substrate 613.

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.58 (s, 1H), 7.41-7.23 (m, 5H), 6.22 (dd, $J = 17.5, 9.5$ Hz, 1H), 5.41 (d, $J = 9.5$ Hz, 1H), 5.18 (d, $J = 17.5$ Hz, 1H), 1.54 (s, 3H).
Bibliography

It should also be considered that octylamine has twice as many heteroatom


GCMS monitoring of this reaction using either 142 or ethylacetocacetate gave erroneous results due to thermolysis of the compounds in the injector port of the instrument.


It should also be considered that octylamine has twice as many heteroatom-H bonds than dodecanol.


