2.1 Introduction and Biosynthesis

In 2003, several novel natural products were isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos*. The structure of one of these compounds, bielschowskysin (36), eluded characterization until an X-ray crystal structure was obtained approximately one year later.\(^1\) Bielschowskysin belongs to a sub-class of molecules called *pseudopteranes*, and is one of several structurally and biosynthetically related diterpenes (Figure 2.1.1).\(^2\) Furthermore, bielschowskysin has been identified as a potent inhibitor of EKVX lung cancer cells (GI\(_{50}\) = 10 nM).
Figure 2.1.1 Bielschowskysin and Related Natural Products.

A characteristic feature of these molecules is a cis-fused [5,5] oxa-bicycle, as well as a dihydrofuran unit that is sometimes disguised as a 1,4 diketone moiety. Bielschowskysin is arguably the most structurally complex member of this group due to its polycyclic ring system bearing eleven stereocenters, one of which is a quaternary stereocenter contained in a tetrasubstituted cyclobutane ring that is also fused to a substituted oxocane ring, resulting in a highly strained cage-like structure.

Although the biosynthetic pathway of bielschowskysin has not been confirmed, Trauner has hypothesized that bielschowskysin is obtained from bipinnatin J (110) via a stereo- and chemoselective epoxidation of the $\Delta^7$8 olefin (110), followed by the addition of water furan 111, and subsequent [2+2] cycloaddition of intermediate 112 provides the cyclobutane core (113) (Scheme 2.1.1).

Scheme 2.1.1

Along with all of the molecules in Figure 2.1.1, bipinnatin J is also a member of the larger cembranoid class of natural products, which are biosynthesized by intramolecular $S_N$1 attack of geranylgeranyldiphosphate (114) and quenching of the
resultant tertiary carbocation to form the cembrane core (115) (Scheme 2.1.2). The cembrane core can undergo various enzymatic oxidations and transformations to provide an array of natural products.\(^6\)

*Scheme 2.1.2*

\[
\text{geranyl/geranyl diphosphate (114)} \xrightarrow{-\text{OPP}} \text{cembrane core core (115)}
\]

### 2.2 Outside Efforts Toward the Total Synthesis of Bielschowskysin

Although there are no reported total syntheses of bielschowskysin, there are two reported partial syntheses of the cyclobutane core found in the natural product. First, Doroh and Sulikowski subject alcohol 116 to a [2+2] photocycloaddition providing cyclobutane 117 in 50\% yield with a 3.6:1 diastereomeric ratio (Scheme 2.2.1).\(^7\) It is thought that this reaction occurs through an unobserved diradical intermediate 118, which then proceeds to form cyclobutane 117. The diastereoselectivity of this reaction is notable in consideration of the observed isomerization of alcohol 116 to isomer 119 under the reaction conditions. Additionally, possible \(\sigma\)-bond rotation of diradical intermediate 118 to its diasterotopic isomer 120, which could also be formed from allylic alcohol 119, could lead to the undesired diastereomer 121.\(^8\)
Scheme 2.2.1

A second approach, reported by Lear and coworkers, uses a similar method to form the core cyclobutane via photocycloaddition of allene 123 (Scheme 2.2.2). The synthesis of allene 123 is accomplished in twelve steps beginning with commercially available L-malic acid (122). Treatment of allene 123 with UV light in a nonpolar cosolvent provides the desired exo-cyclobutene 124 in 70% yield.

Scheme 2.2.2

Although these partial syntheses provide access to the strained cyclobutane found in bielschowskysin, they do not address the formation of either the critical C(6)
quaternary stereocenter or the pendant oxocane ring. As such, a [2+2] cycloaddition to form the quaternary stereocenter on a larger system bearing these components would not be without significant challenges. While a well-organized transition state might be feasible via an enzymatic pathway, practical synthetic limitations encouraged us to envision forming bielschowskysin by other methods such as an aldol condensation or Michael addition.

2.3 Retrosynthesis: Use of a Cyclopropane to Access the Cyclobutane Core

While planning an initial synthetic route to bielschowskysin (36), a suitable model system was designed to investigate the key formation of the cyclobutane core and the quaternary stereocenter. Hence, our first synthetic target was cyclobutane 125 (Figure 2.3.1). Unlike the previous partial syntheses, this model system includes the quaternary stereocenter found in the natural product.

*Figure 2.3.1 Model System for Studies Toward Bielshowskysin’s Cyclobutane Core.*

Thus, we predicated our synthetic strategy upon the formation of cyclobutane 125 via a Lewis acid–mediated cyclopropane fragmentation of ketone 126, followed by a 1,4 Michael addition (Scheme 2.3.1). We envisioned cyclopropane 126 arising from α-diazo-β-ketoester 127 by a cyclopropanation reaction using either a copper or rhodium
catalyst. In turn, \(\alpha\)-diazo-\(\beta\)-ketoester 127 can be obtained from allylic alcohol 128 via esterification and diazotization. The latter compound, alcohol 128, can be prepared via Suzuki coupling between iodide 129 and boronic acid 130. Moreover, we postulated that allylic alcohol 128 could lead to a suitable substrate for a palladium(II)-catalyzed oxidative kinetic resolution to provide a secondary alcohol in high enantioselectivity, thus, providing access to an enantioselective synthesis of bielschowskysin.

Scheme 2.3.1

The proposed key step in our synthesis of cyclobutane 125 is a Lewis acid–mediated cyclopropane fragmentation resulting in an enolate and an enone. We envision that these species will react via a Michael addition to provide the cyclobutane moiety (Figure 2.3.2). Complexation of the Lewis acid to the \(\beta\)-ketoester in compound 126 will lead to weakening of the bridging \(\sigma\)-bond of the cyclopropane ring shown in intermediate 131. Lone pair donation by the furan will result in fragmentation to form a stabilized enolate 132. The latter bond cleavage is preferred for two reasons: first, fragmentation of the most strained bond will relieve ring strain and lower the overall energy of the molecule; second, the \(\pi^*\) orbitals of the \(\beta\)-ketoester moiety have good overlap with the breaking C–C \(\sigma\)-bond, leading to favorable enolate generation. Following fragmentation, 1,4-addition produces cyclobutane 133, which can undergo
rapid tautomerization to provide charged species 134, followed by the addition of water to furnish dihydrofuran 125\(^\text{10}\).

**Figure 2.3.2 Proposed Mechanism for the Formation of Cyclobutane 125.**

![Proposed Mechanism for the Formation of Cyclobutane 125.](image)

### 2.4 Initial Synthetic Efforts

The synthesis began with furan 135\(^\text{11}\), which underwent magnesium-halogen exchange using conditions developed by Knochel\(^\text{12}\) followed by a sequential quench of trimethyl borate and 1 M HCl to furnish boronic acid 130 in 85% yield (Scheme 2.4.1). Coupling of enone 129 with boronic acid 130 under similar conditions reported by Johnson provided compound 136 in excellent yield\(^\text{13,14}\). At this stage, cleavage of the TBS group under acidic conditions provided allylic alcohol 128 in 98% yield. Exposure of allylic alcohol 118 to diketene and a catalytic amount of 4-(N,N-dimethylamino)pyridine (DMAP) afforded unstable β-ketoester 137. Unfortunately, immediate treatment of β-ketoester 137 with p-ABSA and Et\(_3\)N did not yield the desired diazo product; instead, a complex mixture of byproducts was obtained. This mixture of byproducts is the likely result of a Michael addition by the β-ketoester moiety, as well as
subsequent deprotonation at C(α) followed by β-elimination of the carboxylate functionality.

Scheme 2.4.1

To circumvent this problem, we postulated that the diazotization of β-ketoester 137 should be examined under neutral conditions. Moreover, we realized that the previous step, the synthesis of β-ketoester 137, is accomplished in a neutral environment. These observations led us to consider 2-diazoacetoacetic acid as an amenable partner in a DCC coupling reaction with allylic alcohol 128.15

The synthesis of 2-diazoacetoacetic acid (139) was carried out from α-diazobenzylacetoacetate (138)16 by facile hydrogenolysis of the benzyl group, which provided the desired product along with a minor amount of acetoacetic acid in >95% conversion and purity.17 To our delight, the planned DCC coupling reaction between 2-diazoacetoacetic acid (139) and alcohol 128 occurred in a straightforward manner to furnish targeted enone 127 in 75% yield (Scheme 2.4.2).
The generation and coupling of 2-diazoacetoacetic acid (139) with allylic alcohol 128 was crucial for the synthesis of enone 127, as these conditions minimized the risk of side reactions, and simplified the standard two-step procedure. With this more efficient route to enone 127, we next investigated the esterification of 2-diazoacetoacetic acid (139) with a number of heteroatom nucleophiles to test the generality of this reaction and compare it with the two-step standard method.

Gratifyingly, esterification of 2-diazoacetoacetic acid occurs efficiently for a variety of alcohols (Table 2.4.1). Primary and secondary alcohols couple with acid 139 in good to excellent yields (entries 1-6). Allylic alcohols are also competent substrates, and lead to their respective α-diazo-β-ketoesters in good yields (entries 7-10). As shown in entry 11, phenols are also viable substrates in the coupling reaction. Furthermore, the coupling of acid 139 with phenethylamine (162) to produce the α-diazo-β-ketoamide 163 in 95% yield illustrates that amines are also tolerated under these conditions (entry 12).
Table 2.4.1 Esterification of 2-diazoacetoacetic acid (139) with Heteroatom Nucleophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{O}_2\text{N} - \text{C}_2\text{H}_2\text{OH})</td>
<td>(\text{O}_2\text{N} - \text{C}_2\text{H}_2\text{CO}_2\text{H})</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>(\text{C}_6\text{H}_5\text{CH}_2\text{OH})</td>
<td>(\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{H})</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>(\text{MeC}_6\text{H}_4\text{CH}_2\text{OH})</td>
<td>(\text{MeC}_6\text{H}_4\text{CH}_2\text{CO}_2\text{H})</td>
<td>80</td>
</tr>
<tr>
<td>4(d)</td>
<td>(\text{C}<em>6\text{H}</em>{11}\text{OH})</td>
<td>(\text{C}<em>6\text{H}</em>{11}\text{CO}_2\text{H})</td>
<td>77</td>
</tr>
<tr>
<td>5(d)</td>
<td>(\text{C}<em>6\text{H}</em>{11}\text{C}_6\text{H}_5\text{OH})</td>
<td>(\text{C}<em>6\text{H}</em>{11}\text{C}_6\text{H}_5\text{CO}_2\text{H})</td>
<td>81</td>
</tr>
<tr>
<td>6(d)</td>
<td></td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>(\text{C}_6\text{H}_5\text{CH} = \text{CHCH}_2\text{OH})</td>
<td>(\text{C}_6\text{H}_5\text{CH} = \text{CHCH}_2\text{CO}_2\text{H})</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>(\text{C}_6\text{H}_5\text{CH} = \text{CHCH}_2\text{OH})</td>
<td>(\text{C}_6\text{H}_5\text{CH} = \text{CHCH}_2\text{CO}_2\text{H})</td>
<td>77</td>
</tr>
<tr>
<td>9(c)</td>
<td>(\text{C}_6\text{H}_5\text{CO}_2\text{O})</td>
<td>(\text{C}_6\text{H}_5\text{CO}_2\text{O}_2\text{N})</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>(\text{C}_6\text{H}_5\text{CO}_2\text{O})</td>
<td>(\text{C}_6\text{H}_5\text{CO}_2\text{N}_2\text{O})</td>
<td>77</td>
</tr>
<tr>
<td>11(d)</td>
<td>(\text{C}_6\text{H}_5\text{CH} = \text{CHCO}_2\text{H})</td>
<td>(\text{C}_6\text{H}_5\text{CH} = \text{CHCO}_2\text{N}_2\text{O})</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>(\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2)</td>
<td>(\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2\text{CO}_2\text{H})</td>
<td>95</td>
</tr>
</tbody>
</table>

a Standard conditions: 0.50 mmol substrate, 2-diazoacetic acid (139), 2.2 equiv), DCC (2.0 equiv), DMAP (0.10 equiv), 3.30 mL CH\(_2\)Cl\(_2\), 23 °C, 60–90 min.  
b Isolated yield.  
c 0.30 mmol substrate.  
d Reaction at 40 °C, 60–90 min.

With our study of 2-diazoacetoacetic acid couplings complete, our attention returned to enone 127, and we began to investigate its ability to undergo
cyclopropanation. We initiated our studies with Cu(TBSal)$_2$ as the catalyst because it has proven to be a robust catalyst system for cyclopropanation in similar systems.$^{20}$ Unfortunately, when enone 127 was treated with a variety of rhodium and copper catalysts, including Cu(TBSal)$_2$, cyclopropane 126 was never observed (Scheme 2.4.3).$^{21}$ In searching the literature, no examples of an α-diazo-β-ketoester undergoing cyclopropanation with an enone were found. Therefore, we hypothesized that the enone functionality contributed to a withdrawal of electron density from the olefin, and thus inhibited cyclopropanation.

Scheme 2.4.3

Following these initial cyclopropanation studies, we elected to modify the synthesis by reducing the ketone functionality in compound 136 (Scheme 2.4.1). We hypothesized that this would increase the electron density and the corresponding nucleophilicity of the olefin to facilitate cyclopropanation. Furthermore, 1,2-reduction of the enone functionality in compound 136 would provide the necessary substrate (37) with which to explore the palladium(II)-catalyzed oxidative kinetic resolution.

The synthesis of alcohol 37 is accomplished from enone 136 via a Luche reduction in high yield and excellent diastereoselectivity (Scheme 2.4.4).$^{22}$ The observed diastereoselectivity in this reduction is attributed to the bulky siloxy moiety at C(4), that likely prevents the approach of the hydride species from the β-face.$^{23}$
2.5 The Palladium(II)-catalyzed Oxidative Kinetic Resolution

As stated previously, we envisioned using the palladium(II)-catalyzed oxidative kinetic resolution as a method to establish the absolute stereochemistry of the C(4) stereocenter that is present in alcohol 37. Thus, with allylic alcohol 37 in hand, we examined the palladium(II)-catalyzed oxidative kinetic resolution. To our delight, treatment of racemic alcohol 37 under the original conditions developed for the palladium(II)-catalyzed oxidative kinetic resolution furnished ketone 136 in 57% conversion, and more importantly, afforded enantioenriched alcohol 37 in ≥ 95% ee and high selectivity for the overall process (s = 23, Scheme 2.5.1).24

Furthermore, the opposite enantiomer of alcohol can be obtained by treating (4S)-enone 136 under the previously optimized Luche conditions to provide (1S, 4S)-alcohol 37 (Scheme 2.5.1).25 Since the absolute configuration of bielschowskysin is unknown, accessing both enantiomers of alcohol 37 in this fashion is important as it provides a route to potentially synthesize either enantiomer of the natural product.
2.6 Further Investigations into the Model System

Given the success of the critical palladium(II)-catalyzed oxidative kinetic resolution, our efforts were now solely focused on the synthesis of intermediate 126 and subsequent investigation into the formation of cyclobutane 127 (Scheme 2.6.1).

Scheme 2.6.1

Beginning with furan 37, acetate protection of the alcohol and subsequent cleavage of the silyl ether unveiled allylic alcohol 164 in 85% overall yield (Scheme 2.6.2). The latter compound underwent esterification with diketene and subsequent diazotization to furnish α-diazo-β-ketoester 165 in good overall yield. Although the synthesis of compound 165 could be accomplished by coupling of alcohol 37 with 2-diazoacetoacetic acid (139), the traditional two-step procedure ultimately proceeded in overall higher yield in this case. Initially, attempts to form the cyclopropane ring using rhodium catalysts, such as Rh₂(oct)₆, did not provide any of the desired product. Furthermore, the use of various copper sources, such as copper bronze or Cu(acac)₂, led only to trace amounts of the desired product. Gratifyingly, formation of the cyclopropane was accomplished using 2 mol% Cu(TBSal)₂ in either refluxing toluene or heating in a microwave using 1,2-dichloroethane as solvent to provide cyclopropane 166 in 55% yield. In general, the microwave conditions furnished cleaner reactions and more consistent yields during the scale-up process. In obtaining cyclopropane 166, we verified
our hypothesis that the olefin in enone 136 was simply too electron deficient to undergo cyclopropanation.

Scheme 2.6.2

Although the synthesis of cyclopropane 166 was a significant accomplishment, this intermediate still needed to be elaborated to ketone 126. Initially, it was thought that cyclopropane 166 would undergo acetate cleavage to provide alcohol 167, followed by Dess-Martin periodinane oxidation to arrive at ketone 126 (Scheme 2.6.3). Gratifyingly, when cyclopropane 166 was subjected to these conditions, the desired ketone (126) appeared to be obtained in high overall yield. We next investigated the Lewis acid–mediated cyclopropane fragmentation and subsequent Michael addition en route to cyclobutane 125. Initial screening with several lanthanide Lewis acids found that treatment of ketone 126 with La(OTf)₃ in methanol at 55 °C provided one product (168) as a single diastereomer in a 55% yield (unoptimized). Unfortunately, we were unable to confirm the structure of compound 168 by NMR; thus, we chose to esterify compound 168 to yield compound 169 in 79% yield. This enabled us to grow crystals of compound 169 suitable for analysis by X-ray crystallography. To our dismay, the X-ray data showed the structure of an unexpected product, β-ketoester 168.
Upon examination of the connectivity of β-ketoester 169, we noticed that the oxidation states of C(1) and C(4) were opposite to those of desired ketone 126. This is the likely result of an undesired trans-esterification reaction that occurs when cyclopropane 166 undergoes acetate cleavage (Scheme 2.6.4). Treatment of cyclopropane 166 with K$_2$CO$_3$ in methanol presumably provided alkoxide 170. This alkoxide could potentially undergo a trans-esterification reaction and protonation to form alcohol 171. Finally, treatment of alcohol 171 with Dess-Martin periodinane provided α-cyclopropyl ketone 172, which was originally misassigned as ketone 126.
To confirm this undesired rearrangement, we partially incorporated deuterium at C(1), allowing us to follow the chemical shifts of the protons on both C(1) and C(4) during the course of acetate removal (Scheme 2.6.5). As hypothesized, the C(1) proton of intermediate 166 underwent a downfield shift in the $^1\text{H}$ NMR, while the C(4) proton exhibited a slight upfield shift. Furthermore, cyclopropyl proton $H_A$ exhibits a 0.50 ppm shift that we have attributed to conformational changes that result from trans-esterification.$^{27}$ These results confirmed that the trans-lactonization reaction did in fact occur during acetate removal.

Scheme 2.6.5

In an effort to circumvent the trans-lactonization reaction, we synthesized a variety of compounds similar to cyclopropane 166 that differed only in the hydroxyl protecting group at C(1) (Figure 2.6.2).$^{28}$ We postulated that these protecting groups may be removed under conditions that suppress the formation of alcohol 171. Unfortunately,
all attempts to deprotect compounds 173–177 in Figure 2.7.2 led solely to undesired alcohol 171. This result led us to conclude that the undesired lactone (171) is likely the thermodynamic product.

*Figure 2.6.2 Various Cyclopropane Derivatives.*

![Cyclopropane Derivatives](image)

Other interesting observations can be made from the Lewis acid–mediated fragmentation reaction of cyclopropyl ketone 172 to provide unexpected alcohol 168 (Scheme 2.6.3). Beginning with ketone 172 in Scheme 2.6.6, we believe that Lewis acidic activation weakens the cyclopropane ring to allow the furan ring to assist in fragmentation to form an enolate and extended oxocarbenium ion in intermediate 178, both of which are quenched respectively by the overall addition of methanol to provide ketone 179. Thus, fragmentation of the cyclopropane ring occurred as anticipated; however, the addition of methanol preserved the aromaticity in the furan ring rather than undergoing a 1,2-addition into the oxocarbenium ion. We hypothesized that the driving force for the observed chemoselectivity in the methanol addition is due to rearomatization. Furthermore, under these conditions, an additional molecule of methanol can add into ketone 179 from the less-hindered α-face to form a hemiketal at C(4), which in turn, can undergo trans-esterification to produce alcohol 168. Notably, formation of the hemiketal at C(4) can occur at any point in the reaction; however, *trans-esterification to generate the fused lactone is not favorable until the cyclopropane ring undergoes fragmentation.* Another possible reason for the trans-esterification in Scheme
2.6.6 is the increased steric interaction that the bridged lactone in compound 179 would sustain with the furan moiety, compared to the fused lactone in alcohol 168.

Scheme 2.6.6

To examine our hypothesis of trans-esterification, we subjected compound 171 to identical Lewis acidic conditions that resulted in the formation of alcohol 181 in 65% yield as a single diastereomer (Scheme 2.6.7). Alcohol 181 can undergo subsequent functionalization to provide compound 182, allowing for suitable X-ray analysis (Figure 2.6.3). We initially believed that the hemiketal in intermediate 180 might force the alcohol into a pseudo-axial position and promote trans-esterification. However, by forming alcohol 181 without the ability for ketalization, we have shown that trans-esterification is facile once the cyclopropane ring has fragmented, regardless of the C(4) oxidation state.
Scheme 2.6.7

2.7 Future Directions

Since the formation of alcohol 171 could not be averted, we decided to evaluate an alternative synthetic strategy focusing on initial construction of a macrocyclic intermediate.\textsuperscript{31} By beginning with macrocycle 188 (Scheme 2.8.1), we can reinforce chemo- and diastereoselectivity later in the synthesis. We believe there are at least two possible routes that could provide the cyclobutane core and the substituted oxocane ring found in bielschowskysin. The first route relies on a Michael addition and subsequent aldol reaction to provide the cyclobutane core, while the second route employs a reduction of an intermediate cyclopropane ring followed by a similar aldol addition to arrive at the highly strained core.\textsuperscript{32}

We believe that ester 183 in Scheme 2.7.1 would serve as an excellent starting point since the enantio- and diastereoselective syntheses of similar compounds has been disclosed previously. Conversion of ester 183 to furan 185 could be accomplished in
three transformations: LiAlH$_4$ reduction of the ester to the primary alcohol, Dess-Martin periodinane oxidation, followed by Grignard addition of reagent 184 into the newly formed aldehyde. With furan 185 in hand, deoxygenation of the secondary alcohol followed by acidic hydrolysis of the ketal will provide aldehyde 186. At this stage, removal of the MEM protecting group, followed by formation of the α-diazoacetate moiety would provide intermediate 187. It is thought that exposure of compound 187 to SnCl$_2$ would effect the key intramolecular Roskamp reaction to provide macrocycle 188.\textsuperscript{33} Once formed, treating macrocycle 188 with monomagnesium peroxypthalate (MMPP),\textsuperscript{34} a mild oxidizing agent, would oxidize the furan to provide enedione 189. This compound is now ready to undergo critical, sequential enolate additions to furnish the cyclobutane core. Hence, treatment of enedione 189 with DBU would first deprotonate the β-ketoester moiety resulting in a 1,4 Michael addition to form lactone 190. It is thought that protonation of the resulting enolate from the Michael addition will occur from the less-hindered α-face to provide the desired diastereomer needed for the Aldol addition. Once lactone 190 has formed, another equivalent of DBU could again deprotonate the β-ketoester moiety to promote an aldol addition and subsequent hemiketalization to afford cyclobutane 191.
A second approach, although not as rapid as above, utilizes our knowledge of the cyclopropane system to build the γ-lactone moiety and subsequently set the relative stereochemistry at C(2) by reduction of the cyclopropane ring. Starting with macrocycle 192 (Scheme 2.7.1), standard diazotization of the β-ketoester moiety followed by copper catalyzed cyclopropanation would afford cyclopropane 193. At this stage, removal of the TBS group followed by a Dess-Martin periodinane oxidation would provide ketone 194. Treating this product with La(OTf), and NaBH₄ is expected to reduce the cyclopropane ring at C(2) as well as the C(7) ketone to provide alcohol 195 in high diastereoselectivity. We believe that the desired diastereoselectivity in the cyclopropane reduction is favored as a result of the observed selectivity that methanol showed in the model system in Scheme 2.6.6. Furthermore, with the macrocycle in place, hydride addition into the C(7) ketone should occur from the accessible α-face to provide the correct diastereomer. Protection of the alcohol in compound 195 as a MEM ether preserves the C(7)-oxygen’s
ability to direct. Hence, treating this compound with mCPBA should result in a regio- and diastereoselective epoxidation of the furan to produce epoxide 196. At this stage, electron donation by the furan should be facile and lead to epoxide opening and the formation of oxocarbenium ion 197. This intermediate is in equilibrium with enol 198, which could undergo an aldol addition into the oxocarbenium ion followed by epimerization of the hemiketal to provide cyclobutane 199.

Scheme 2.7.2

Both routes discussed above use similar macrocycles as key intermediates in the synthesis of compounds 191 and 199 respectively. The macrocycle is vital in both of these routes as it controls the diastereoselectivity at several stereocenters. Thus, future studies toward bielschowskysin should focus on the formation of either macrocycle 188 or macrocycle 192 prior to any investigations into the cyclobutane core.
2.8 Concluding Remarks

Although the cyclopropane route did not achieve its ultimate goal in synthesizing the cyclobutane ring, several successful aspects of our research can be extracted. Foremost, we have successfully implemented the palladium(II)-catalyzed oxidative kinetic resolution early in the synthesis to provide alcohol 37 in $\geq 95\%$ ee and 43\% yield. Moreover, this methodology could allow for rapid access to either enantiomer of allylic alcohol 37, an important intermediate in synthesizing advanced compounds within our synthetic efforts. Secondly, we have effectively developed a general method for obtaining $\alpha$-diazo-$\beta$-ketoesters using 2-diazoacetoacetic acid (139). The latter reagent is readily generated, and has been synthesized on reasonable scale (ca. 5.0 mmol) in a straightforward manner from commercially available starting materials. The coupling of 2-diazoacetoacetic acid (139) using DCC under neutral conditions provided the desired products in high yields and tolerated a variety of alcohols. In addition, amines can be used as substrates for the amidation with 2-diazoacetoacetic acid, thus providing access to $\alpha$-diazo-$\beta$-ketamides. Although our synthetic endeavors did not yield the cyclobutane core found in bielschowskysin, we did discover an important trans-esterification process that was later observed during synthetic efforts toward ineleganolide (108, Figure 2.1.1). Finally, an understanding of the reactivity of these molecules has been gained, thus allowing for efficient synthetic revisions and paving the way for further research.
2.9 Experimental Procedures

2.9.1 Materials and Methods

Unless otherwise stated, reactions were performed at ambient temperature (typically 20–22 °C) in flame-dried glassware under an argon or nitrogen atmosphere using dry solvents. Solvents were dried by passage through an activated alumina column under argon. Et₃N, iPr₂NH, iPr₂NEt, and pyridine were freshly distilled from CaH₂. Trifluoroacetic acid (99%) was purchased from Aldrich. Tf₂O was freshly distilled from P₂O₅. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, KMnO₄, or CAM staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz respectively) and are reported relative to solvent for ¹H NMR (CHCl₃ = 7.27 ppm, C₆H₆ = 7.16 ppm, CH₂Cl₂ = 5.30 ppm, DMSO = 2.51 ppm) and ¹³C NMR (CDCl₃ = 77.0 ppm, C₆D₆ = 128.4 ppm). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, td = triplet of doublets, dd = doublet of doublets, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer BX-11 FT-IR spectrometer and are reported in frequency of absorption (cm⁻¹). High resolution mass
spectra were obtained from the California Institute of Technology Mass Spectral Facility. Crystallographic analyses were performed at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, from the CCDC by quoting the publication citation and the deposition number (see Appendix 3 for deposition numbers).

2.9.2 Preparation of Compounds

Enone 136. To a solution of furan 135 (609 mg, 2.78 mmol, 1.00 equiv) in THF (15 mL) at −35 °C, was added a 1.84 M solution (THF) of iPrMgCl (1.96 mL, 3.61 mmol, 1.30 equiv) to the reaction. The reaction stirred for 45 minutes and the temperature was maintained between -40 and -30 °C. At this stage, trimethylborate (1.24 mL, 11.1 mmol, 4.00 equiv) was added rapidly at -30 °C, and the reaction was allowed to warm to ambient temperature and stir overnight. The reaction was cooled to 0 °C, 1 M HCl was added, and the mixture stirred for 30 minutes. The reaction was diluted with EtOAc and H₂O, and the layers were separated. The aqueous layer was then washed 2x with EtOAc. The organic layers were combined, and washed with saturated K₂CO₃ (aq.) until the aqueous layer was basic. The basic aqueous layer was then acidified using 1 M HCl, and then washed 5x with EtOAc. The latter batch of EtOAc was washed with brine, dried with Na₂SO₄, filtered, and concentrated in vacuo to afford boronic acid 130 (375 mg,
73%) as a light-brown solid. This compound was used directly in the following Suzuki coupling reaction.

To a solution of vinyl iodide 129 (87.0 mg, 0.260 mmol, 1.00 equiv), boronic acid 130 (71.0 mg, 0.390 mmol, 1.50 equiv), Ag₂O (180 mg, 0.770 mmol, 3.00 equiv), and Ph₃As (8.00 mg, 0.0260 mmol, 0.100 equiv) in THF (1.30 mL) was added PdCl₂(PhCN)₂ (5.00 mg, 0.0130 mmol, 0.0500 equiv) and H₂O (50.0 μL). The reaction was stirred until consumption of vinyl iodide 129 as indicated by TLC (ca. 1.5 h) and filtered through a pad of celite. The solvent was concentrated in vacuo, and the residue was purified by flash chromatography using 3:97 → 5:95 EtOAc:hexanes to afford furan 136 as a white solid (74 mg, 80%).

**Furan 136**

**IR (film) 3133, 2949, 2928, 2891, 2857, 1721, 1703, 1594, 1509, 1448 cm⁻¹; HRMS (FAB⁺) calc’d for [C₁₈H₂₆SiO₅]⁺: m/z 350.1550, found 350.1542.**

![Reaction equation](image)

**Alcohol 128.** To a solution of acetyl chloride (50.5 μL, 0.710 mmol, 5.00 equiv) in MeOH (570 μL) at 0 °C, was added enone 136 (52.5 mg, 0.150 mmol, 1.00 equiv) in one portion. Enone 136 dissolved slowly over 20–30 minutes at 0 °C, and once completely in solution, the reaction stirred for 45 minutes at 0 °C. The reaction was then diluted with
brine and EtOAc. These layers were separated, and the aqueous layer was washed 2x with EtOAc. The organic layers were combined, washed with brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. This semi-solid was diluted with toluene, and then reconcentrated under vacuum (repeated 3x). Upon final concentration in vacuo, alcohol 128 was obtained as a white solid (35.3 mg, 99%). ¹H NMR (500 MHz, CDCl₃) δ 7.86 (d, J = 2.9 Hz, 1H), 7.02 (s, 1H), 5.21 (br, 1H), 3.90 (s, 3H), 2.96 (dd, J = 6.1, 18.8 Hz, 1H), 2.71 (d, J = 5.40 Hz, 1H), 2.49 (dd, J = 2.2, 18.8 Hz, 1H), 2.34 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 201.8, 160.0, 154.9, 147.1, 139.9, 134.1, 132.4, 116.1, 68.3, 51.7, 45.2, 11.6; IR (film) 3447, 2920, 2850, 1716, 1506, 1440, 1405, 1295, 1167, 1102 cm⁻¹; HRMS (FAB⁺) calc’d for [C₁₂H₁₃O₅]⁺: m/z 237.0763, found 237.0763.

Acid 139. 10% Pd/C (17.5 mg, 7% w/w) was added to a solution of benzyl ester 138 (250 mg, 1.15 mmol, 1.00 equiv) in THF (11.5 mL) at 23 °C. The N₂ atmosphere was evacuated and backfilled with H₂ (balloon), this was repeated three additional times. The reaction was complete within 40–60 minutes as monitored by TLC (4:6 EtOAc:Hexanes). Once finished, the reaction mixture was passed through a short pad of celite (Et₂O eluent), and the solvent was concentrated in vacuo to obtain 2-diazoacetoacetic acid (139) as a pale-yellow solid that was used directly in the esterification step. Compound 139 was ca. 95% pure by ¹H NMR. Note: A pure (98%) sample of acid 139 was obtained by crystallization using Et₂O/Heptane and cooling at -20 °C. ¹H NMR (300 MHz, CDCl₃) δ
2.46 (s, 3H); IR (film) 2932, 2150, 1722, 1601, 1302 cm⁻¹; HRMS (EI⁺) calc’d for [C₆H₄N₂O₃⁺]: m/z 128.0222; found, 128.0227.

**Enone 127.** To a solution of alcohol 128 (71.0 mg, 0.300 mmol, 1.00 equiv), acid 139 (92.1 mg, 0.720 mmol, 2.40 equiv), and DMAP (3.67 mg, 0.0300 mmol, 0.100 equiv) in CH₂Cl₂ (2.00 mL) at 23 °C, was added DCC (206 mg, 1.00 mmol, 2.0 equiv) in one portion. After the addition of DCC, the reaction was heated to 40 °C for 90 minutes. The reaction was allowed to cool to ambient temperature, filtered through a plug of celite (Et₂O eluent), and the resulting filtrate was partitioned between H₂O and Et₂O. The aqueous layer was extracted 2x with Et₂O. The organic extracts were combined, washed once with H₂O, and then once with brine. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The product was purified by flash chromatography using 25:75 EtOAc:Hexanes to afford compound 127 as a light-yellow solid (78 mg, 75% yield). ¹H NMR (500 MHz, C₆D₆) δ 7.30 (s, 1H), 7.23 (s, 1H), 5.24 (m, 1H), 3.46 (s, 3H), 2.33 (dd, J = 6.6, 18.6 Hz, 1H), 2.24 (s, 3H), 2.18 (s, 3H), 1.90 (d, J = 18.6 Hz, 1H); ¹³C NMR (125 MHz, C₆D₆) δ 199.3, 188.6, 160.8, 159.9, 149.1, 147.3, 141.4, 136.4, 132.7, 117.5, 71.2, 51.5, 42.0, 28.4, 11.8; IR (film) 2954, 2145, 1715, 1660, 1366, 1312, 1155, 1062; HRMS (FAB⁺) calc’d for [C₁₆H₁₄N₂O₇⁺]: m/z 346.0801; found, 346.0817.
General Procedure for the Esterification of Acid 139 (Table 2.4.1). To a solution of substrate (0.500 mmol, 1 equiv), acid 139 (1.20 mmol, 2.4 equiv), and DMAP (0.0500 mmol, 0.10 equiv) in CH₂Cl₂ (3.30 mL) at 23 °C, was added DCC (1.00 mmol, 2.0 equiv) in one portion. Note: For 1° alcohols, the reaction remained at 23 °C. However, for 2° alcohols, the reaction was heated to 40 °C after the addition of DCC. The reaction was monitored by TLC, and the reaction was complete in 60–90 minutes. The reaction was filtered through a plug of celite (Et₂O eluent), and the resulting filtrate was partitioned between H₂O and Et₂O. The aqueous layer was extracted 2x with Et₂O. The organic extracts were combined, washed with NaHCO₃ (saturated), and then with brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The products were purified by flash chromatography.

Substrate 141. See General Procedure for the Esterification of Acid 139 (92% yield). Product was purified by flash chromatography (20:80 EtOAc:Hexanes). Rₛ = 0.40 (30:70 EtOAc:Hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.23 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 5.35 (s, 2H), 2.47 (s, 2H); IR (film) 2148, 1711, 1344 cm⁻¹.
Substrate 143. See General Procedure for the Esterification of Acid 139 (85% yield). Product was purified by flash chromatography (17:83 EtOAc:Hexanes). R_f = 0.45 (30:70 EtOAc:Hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.27 (m, 2H), 7.23-7.16 (m, 2H), 4.27 (t, J = 6.3 Hz, 2H), 2.71 (t, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.08-2.01 (m, 2H); ^13C NMR (75 MHz, CDCl_3) δ 190.0, 161.2, 140.6, 128.4, 128.2, 126.1, 64.6, 32.0, 30.0, 28.1; IR (film) 2141, 1716, 1660, 1314 cm\(^{-1}\); HRMS (EI\(^{+}\)) calc'd for [C\(_{13}\)H\(_{15}\)N\(_2\)O\(_3\)]\(^{+}\): m/z 247.1083; found, 247.1089.

Substrate 145. See General Procedure for the Esterification of Acid 139 (80% yield). Product was purified by flash chromatography (5:95 EtOAc:Hexanes). R_f = 0.50 (20:80 EtOAc:Hexanes); ^1H NMR (300 MHz, CDCl_3) δ 4.24 (t, J = 6.6 Hz, 2H), 2.49 (s, 3H), 1.71-1.66 (m, 2H), 1.33-1.27 (m, 14H), 0.89 (t, J = 6.9 Hz, 3H); ^13C NMR (75 MHz, CDCl_3) δ 190.2, 161.5, 65.5, 31.8, 29.4, 29.4, 29.2, 29.1, 28.6, 28.2, 25.7, 22.6, 14.1; IR (film) 2927, 2856, 2138, 1721, 1663, 1313 cm\(^{-1}\); HRMS (EI\(^{+}\)) calc'd for [C\(_{14}\)H\(_{25}\)N\(_2\)O\(_3\)]\(^{+}\): m/z 269.1865; found, 269.1864.
**Substrate 147.** See General Procedure for the Esterification of Acid 139 (77% yield). Product was purified by flash chromatography (10:90 EtOAc:Hexanes). All spectroscopic data is identical to that reported by Doyle.\(^{37}\)

**Substrate 149.** See General Procedure for the Esterification of Acid 139 (81% yield). Product was purified by flash chromatography (10:90 EtOAc:Hexanes). \(R_f = 0.20\) (10:90 EtOAc:Hexanes); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.90-7.83 (m, 4H), 7.55-7.50 (m, 3H), 6.21 (q, \(J = 6.6\) Hz, 1H), 2.49 (s, 3H), 1.72 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 190.0, 160.7, 138.0, 133.1, 133.0, 128.6, 128.0, 127.6, 126.4, 126.3, 125.2, 123.6, 73.8, 28.2, 22.1; IR (film) 2140, 1715, 1658, 1305 cm\(^{-1}\); HRMS (FAB\(^+\)) calc'd for [C\(_{16}\)H\(_{15}\)N\(_2\)O\(_3\)]\(^+\): \(m/z\) 283.1083; found, 283.1079.

**Substrate 151.** See General Procedure for the Esterification of Acid 139 (87% yield). Product was purified by flash chromatography (5:95 EtOAc:Hexanes). \(^1\)H NMR (CDCl\(_3\)) is identical to that reported by Doyle.\(^{38}\)
**Substrate 153.** See General Procedure for the Esterification of Acid 139 (82% yield). Product was purified by flash chromatography (15:85 EtOAc:Hexanes). $R_f = 0.50$ (20:80 EtOAc:Hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.44-7.28 (m, 5H), 6.70 (d, $J = 15.6$ Hz, 1H), 6.31 (dt, $J = 6.6$, 15.6 Hz, 1H), 4.90 (dd, $J = 1.5$, 6.6 Hz, 2H), 2.51 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 190.0, 161.1, 135.7, 135.3, 128.6, 128.3, 126.3, 126.6, 122.2, 65.8, 28.2; IR (film) 2140, 1716, 1659, 1316 cm$^{-1}$; HRMS (El$^+$) calcd for [C$_{13}$H$_{12}$N$_2$O$_3$]$^+$: m/z 244.0848; found, 244.0839.

**Substrate 155.** See General Procedure for the Esterification of Acid 139 (77% yield). Product was purified by flash chromatography (10:90 EtOAc:Hexanes). $R_f = 0.50$ (20:80 EtOAc:Hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.37 (dt, $J = 1.2$, 3.6 Hz, 1H), 5.10-5.04 (m, 1H), 4.75 (d, $J = 7.2$ Hz, 2H), 2.49 (s, 3H), 2.13-2.05 (m, 4H), 1.74 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 190.1, 161.4, 143.4, 131.9, 123.5, 117.6, 62.1, 39.4, 28.1, 26.1, 25.6, 17.6, 16.4; IR (film) 2138, 1717, 1662, 1309 cm$^{-1}$; HRMS (FAB$^+$) calcd for [C$_{14}$H$_{21}$N$_2$O$_3$]$^+$, m/z 265.1552; found, 265.1548.

**Substrate 157.** See General Procedure for the Esterification of Acid 139 (95% yield). Product was purified by flash chromatography (15:85 EtOAc:Hexanes). $R_f = 0.40$ (30:70
EtOAc:Hexanes); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.76-7.73 (m, 2H), 7.68 (d, \(J = 2.7\) Hz, 1H), 7.42-7.40 (m, 2H), 6.05 (dt, \(J = 2.4, 6.6\) Hz, 1H), 3.10 (dd, \(J = 6.6, 18.6\) Hz, 1H), 2.66 (dd, \(J = 1.8, 18.6\) Hz, 1H), 2.50 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 202.0, 189.6, 160.9, 150.8, 146.3, 129.7, 129.6, 128.5, 127.6, 70.7, 42.4, 28.3; IR (film) 2144, 1716, 1654, 1313 cm\(^{-1}\); HRMS (FAB\(^+\)) calc'd for \([C_{15}H_{13}N_2O_4]^+\): \(m/z\) 285.0875; found, 285.0869.

Hydroxy Enone 158. A flask containing 4-(tert-butyldimethylsilyloxy)-2-iodocyclopent-2-enone\(^{40}\) (400 mg, 1.60 mmol, 1.40 equiv) was charged with p-nitrophenyl pinacolato borate (388 mg, 1.15 mmol, 1.00 equiv),\(^{41}\) silver(I) oxide (800 mg, 3.45 mmol, 3.00 equiv), and Ph\(_3\)As (35.2 mg, 0.120 mmol, 0.100 equiv) at 23 °C. THF (5.5 mL) and H\(_2\)O (290 \(\mu\)L) were added, followed by addition of PdCl\(_2\)(PhCN)\(_2\) (22.1 mg, 0.0580 mmol). The reaction mixture was stirred for 15 minutes at 23 °C, at which point TLC (5:95 EtOAc:Hexanes) indicated the reaction was complete. The reaction was passed through a pad of celite (EtOAc eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (7:93 EtOAc:Hexanes) to afford the Suzuki product as an oil (405 mg, 95% yield).

This product (125 mg, 0.370 mmol, 1.00 equiv) was then added to a solution of AcCl (130 \(\mu\)L, 1.90 mmol, 5.10 equiv) in MeOH (7.5 mL) at 0 °C. The reaction was allowed to stir for 20 minutes, upon which TLC (40:60 EtOAc:Hexanes) showed consumption of the Suzuki product. The reaction was diluted with brine and EtOAc.
The layers were separated, and the aqueous layer was washed 2x with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. TBSOH was removed azeotropically with toluene to afford alcohol 158 (80 mg, 99% yield). Rₚ = 0.20 (50:50 EtOAc:Hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.25-8.20 (m, 2H), 7.91-7.87 (m, 2H), 7.82 (d, J = 2.4 Hz, 1H), 5.15 (m, 1H), 3.05 (dd, J = 6.6, 18.9 Hz, 1H), 2.60 (dd, J = 2.1, 18.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 203.2, 159.3, 147.8, 142.1, 136.7, 128.4, 123.7, 67.7, 45.7; IR (film) 3415, 1711, 1516, 1348 cm⁻¹; HRMS (EI⁺) calc’d for [C₁₁H₉NO₄]⁺: m/z 219.0532; found, 219.0506.

Substrate 159. See General Procedure for the Esterification of Acid 139 (77% yield). Product was purified by flash chromatography (50:50 EtOAc:Hexanes). Rₚ = 0.30 (30:70 EtOAc:Hexanes); ¹H NMR (300 MHz, CDCl₃): δ 8.28 (m, 2H), 7.97-7.93 (m, 2H), 7.87 (d, J = 2.7 Hz, 1H), 6.09 (dt, J = 2.7, 6.6 Hz, 1H), 3.18 (dd, J = 6.6, 18.9 Hz, 1H), 2.70 (dd, J = 2.1, 18.9 Hz, 1H), 2.51 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 201.0, 189.4, 160.9, 153.8, 148.3, 144.4, 135.9, 128.6, 124.0, 70.4, 42.3, 28.3; IR (film) 2145, 1717, 1519, 1350, 1317 cm⁻¹; HRMS (EI⁺) calc’d for [C₁₅H₁₁N₃O₆]⁺: m/z 329.0648; found, 329.0647.
Substrate 161. See General Procedure for the Esterification of Acid 139 (75% yield). Product was purified by flash chromatography (15:85 EtOAc:Hexanes). R_f = 0.20 (20:80 EtOAc:Hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.28-7.23 (m, 2H), 7.13-7.08 (m, 2H), 4.00 (s, 3H), 2.71 (s, 3H); ^13C NMR (75 MHz, CDCl_3) δ 189.9, 160.4, 157.6, 143.0, 122.3, 114.5, 55.6, 28.3; IR (film) 2142, 1732, 1507, 1324, 1191 cm\(^{-1}\); HRMS (FAB\(^+\)) calc'd for [C\(_{11}\)H\(_{11}\)N\(_2\)O\(_4\)]\(^+\): m/z 235.0179; found, 235.0174.

Substrate 163. See General Procedure for the Esterification of Acid 139 (95% yield). Product was purified by flash chromatography (40:60 EtOAc:Hexanes). R_f = 0.25 (40:60 EtOAc:Hexanes); ^1H NMR (300 MHz, CDCl_3) δ 8.21 (br, 1H), 7.32-7.19 (m, 5H), 3.60 (q, J = 6.9 Hz, 2H), 2.84 (t, J = 7.4 Hz, 2H), 2.29 (s, 3H); ^13C NMR (75 MHz, CDCl_3) δ 189.8, 160.5, 138.9, 129.0, 128.8, 126.8, 41.4, 36.1, 26.9; IR (film) 3309, 2124, 1667, 1538, 1312 cm\(^{-1}\); HRMS (El\(^+\)) calc'd for [C\(_{12}\)H\(_{13}\)N\(_3\)O\(_2\)]\(^+\): m/z 231.1008; found, 231.1007.

Alcohol 37. To a solution of furan 136 (100 mg, 0.290 mmol, 1.00 equiv) and CeCl\(_3\)•7H\(_2\)O (430 mg, 1.10 mmol, 4.00 equiv) in MeOH:CH\(_2\)Cl\(_2\) (4.90 mL, 1:1) at -25 °C, was added sodium borohydride (43.0 mg, 1.10 mmol, 4.00 equiv) portionwise while
maintaining the reaction between -25 and -20 °C. Upon consumption of the ketone as visualized by TLC (ca. 30 min.), the reaction was diluted with EtOAc and H₂O. The solution was allowed to warm to ambient temperature and the layers were separated. The aqueous layer was extracted 3x with EtOAc, and the organic layers were combined and washed with brine. The EtOAc layer was dried with Na₂SO₄, filtered, and concentrated in vacuo to provide allylic alcohol 137 as a yellow oil (96 mg, 95%). R_f = 0.20 (20:80 EtOAc:hexanes, UV); ¹H NMR (500 MHz, CDCl₃) δ 6.58 (s, 1H), 6.39 (s, 1H), 4.84 (m, 1H), 4.79 (m, 1H), 3.91 (s, 3H), 2.76 (dt, J = 6.9, 14.2 Hz, 1H), 2.36 (s, 3H), 1.98 (d, J = 9.3 Hz, 1H), 1.77 (d, J = 14.2 Hz, 1H), 0.92 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 160.0, 151.7, 139.5, 136.2, 133.0, 132.6, 113.7, 74.8, 74.2, 51.5, 44.7, 25.8, 18.1, 11.6, -4.6, -4.7; IR (film) 3420, 2954, 2930, 2857, 1711, 1440, 1298, 1101 cm⁻¹; HRMS (FAB⁺) calc'd for [C₁₈H₂₇O₅Si]⁺: m/z 351.1628; found 351.1632.

(1R,4R)-Alcohol 37. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with powdered molecular sieves (3ÅMS, 150 mg) and flame-dried under vacuum. After cooling under dry N₂, Pd(nbd)Cl₂ (0.380 mg, 1.42 µmol, 0.0500 equiv) was added, followed by toluene (285 µL). To this yellow suspension was added (-)-sparteine (1.33 mg, 5.67 µmol, 0.200 equiv), and the top of the Schlenk tube was then fitted with an O₂ balloon. The reaction was purged under vacuum and replaced with O₂, and this process was repeated 4x's. The light yellow suspension was stirred at ambient
temperature for 10 minutes, then heated to 80 °C for an additional 10 minutes. The reaction mixture darkened to an orange suspension. Upon completion of the 10 minutes, racemic alcohol 37 (10.0 mg, 28.4 µmol, 1.00 equiv, in 100µL of PhMe) was added to the reaction mixture. The suspension was then heated to 80 °C for 24 hours. The reaction was allowed to cool to ambient temperature, and was then filtered through a small pad of celite using toluene as eluent. The filtrate was concentrated in vacuo, and the \(^1\)H NMR of this material indicated a 43% yield of (\(1R,4R\))-alcohol 37 (4.3 mg, 43% yield, 95% ee). \([\alpha]_D^{24.98} +26.4 \ (c = 0.15, \text{EtOAc})\).  

**Allylic Alcohol 164.** To a solution of alcohol 37 (96.0 mg, 0.270 mmol, 1.00 equiv) in pyridine (2.70 mL, 0.100 M) was added acetic anhydride (0.270 mL, 2.50 mmol, 9.00 equiv) and DMAP (3.30 mg, 0.0270, 0.100 equiv) at ambient temperature. The reaction was stirred until consumption of allylic alcohol 37 as monitored by TLC (ca. 30 min). The solution was cooled to 0 °C and diluted with EtOAc:brine (1:1). The aqueous solution was extracted 2x with EtOAc. The combined organic layer was successively washed with sat. CuSO\(_4\) (aq.), H\(_2\)O, sat. NaHCO\(_3\) (aq.), and brine. The organic layer was then dried with Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo to yield an allylic acetate (101 mg, 95%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.49 (dd, \(J = 0.9, 2.1 \text{ Hz, 1H}\), 6.26 (s, 1H), 5.85 (dd, \(J = 4.2, 7.5 \text{ Hz, 1H}\), 4.84 (m, 1H), 3.90 (s, 3H), 2.96 (dt, \(J = 7.5, 14.4 \text{ Hz, 1H}\), 2.33 (s, 3H), 2.10 (s, 3H), 1.73 (m, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H).
A solution of TBAF (0.290 mL of 1M solution in THF, 0.289 mmol, 1.20 equiv) was added to the crude silyl ether (95 mg, 0.241 mmol, 1.00 equiv) in THF (4.8 mL) at 0 °C and under N₂. The reaction was allowed to warm to ambient temperature and monitored by TLC. Once complete, the reaction was diluted with H₂O, and the reaction was extracted 3x with EtOAc. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. The crude solid was purified by flash chromatography (50:50, EtOAc:hexanes) to provide allylic alcohol 164 as a white solid (64 mg, 85% from alcohol 37).: R_f 0.2 (40:60, EtOAc:hexanes, UV); ¹H NMR (500 MHz, CDCl₃) δ 6.60 (d, J = 2.4 Hz, 1H), 6.29 (s, 1H), 5.88 (dd, J = 2.9, 7.3 Hz, 1H), 4.83 (m, 1H), 3.88 (s, 3H), 2.88 (app dt, J = 14.7, 7.1, 1H), 2.32 (s, 3H), 2.07 (s, 3H), 1.81 (app dt, J = 12.2, 2.9 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 160.0, 150.6, 140.1, 134.6, 133.6, 132.6, 113.8, 75.7, 74.4, 51.7, 41.5, 21.3, 11.7; IR (film) 3424, 2953, 1712, 1598, 1511, 1440, 1374, 1297, 1240, 1197, 1104, 1035 cm⁻¹; HRMS (EI⁺) calc’d for [C₁₄H₁₆O₆]^+: m/z 280.2804, found 280.2800.

**Ester 165.** A solution of allylic alcohol 164 (15.0 mg, 0.0540 mmol, 1.00 equiv) and diketene (8.00 µL, 0.110 mmol, 2.00 equiv) in THF (1.10 mL) was cooled to 0 °C, and DMAP (0.350 mg, 0.00270 mmol, 0.0500 equiv) was added. The reaction was stirred at 0 °C for 10 minutes, and was then allowed to warm to ambient temperature. Once
complete by TLC (ca. 30 min), the reaction was concentrated in vacuo and carried on directly. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.59 (d, \(J = 1.8\) Hz, 1H), 6.34 (s, 1H), 5.99 (dd, \(J = 2.7, 7.2\) Hz, 1H), 5.73 (m, 1H), 3.90 (s, 3H), 3.48 (s, 2H), 3.00 (dt, \(J = 7.8, 15.6\) Hz, 1H), 2.34 (s, 3H), 2.10 (s, 3H), 1.94 (dt, \(J = 7.8, 15.6\) Hz, 1H).

The crude \(\beta\)-ketoester (380 mg, 1.0 mmol, 1.0 equiv) was dissolved in MeCN (10.4 mL), and MsN\(_3\) (630 mg, 5.20 mmol, 5.00 equiv) followed by Et\(_3\)N (0.870 mL, 6.20 mmol, 6.00 equiv) was added to the reaction. The resulting solution was stirred at ambient temperature until complete by TLC (ca. 6 h). The reaction was concentrated in vacuo, and the resulting crude oil was purified by silica gel chromatography (80:20 → 75:25, hexanes:EtOAc) to yield ester 165 as a light-yellow solid (338 mg, 65% average). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.60 (d, \(J = 2.2\) Hz, 1H), 6.30 (s, 1H), 6.19 (m, 1H), 6.07 (m, 1H), 3.88 (s, 3H), 2.47 (s, 3H), 2.44 (m, 2H), 2.33 (s, 3H), 2.08 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 190.0, 170.8, 161.2, 159.8, 149.9, 140.5, 136.2, 132.5, 130.5, 114.7, 79.0, 76.2, 51.8, 39.1, 28.4, 21.2, 11.7; IR (film) 2142, 1713, 1657, 1295, 1237 cm\(^{-1}\); HRMS (EI\(^+\)) calc’d for [C\(_{18}\)H\(_{18}\)N\(_2\)O\(_8\)]\(^+\): m/z 390.1063, found 390.1061.

Cyclopropane 166. \(\mu\)wave conditions: The microwave is pre-warmed by undergoing an actual run with just DCE in the reaction tube. A solution of compound 165 (45.0 mg, 0.120 mmol, 1.00 equiv) and Cu(TBSal)\(_2\) (5.00 mg, 0.0120 mmol, 0.100 equiv) in DCE (3.00 mL) was heated for 20 min at 105 °C in the microwave. The following parameters
for the µwave are as follows: Power = 150 W, Temperature = 105 °C, Pressure = 200 atm, Ramp = 1 minute, Run Time = 20 minutes. The reaction was concentrated in vacuo, and the resulting crude oil was purified by silica gel chromatography (40:60 EtOAc:hexanes) to yield cyclopropane 166 as a white solid (21 mg, 55%). $^1$H NMR (500 MHz, C$_6$D$_6$) δ 6.20 (s, 1H), 5.47 (dd, $J = 1.7, 7.3$ Hz, 1H), 4.01 (m, 1H), 3.53 (d, $J = 4.6$ Hz, 1H), 3.39 (s, 3H), 2.39 (s, 3H), 2.13 (s, 3H), 1.73 (d, $J = 14.4$ Hz, 1H), 1.71 (s, 3H), 1.29 (ddd, $J = 3.4, 7.6, 14.6$ Hz, 1H); $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 195.7, 170.8, 170.5, 160.0, 150.8, 141.5, 132.8, 116.2, 81.6, 78.4, 52.8, 51.9, 50.4, 46.0, 45.8, 29.7, 20.8, 12.0; IR (film) 2954, 1770, 1747, 1714, 1230 cm$^{-1}$; HRMS (EI$^+$) calcd for [C$_{18}$H$_{19}$O$_8$]$^+$: m/z 363.1080, found 363.1085.

**Thermal conditions:** A solution of Cu(TBSal)$_2$ (1.30 mg, 0.00300 mmol, 0.0200 equiv) in toluene (2.40 mL) was heated, under Ar, to 108 °C. A warm solution of diazo 165 (62.0 mg, 0.150 mmol, 1.00 equiv) in toluene (0.400 mL) was added dropwise over 6 minutes. The reaction was heated to 112 °C, and monitored by TLC (40:60 EtOAc:hexanes). After 100 minutes, the reaction was complete, and allowed to cool to ambient temperature. The solvent was removed in vacuo, and the dark residue was purified by flash chromatography (40:60 EtOAc:hexanes) to provide cyclopropane 166 (35 mg, 56%).
**Alcohol 171.** K$_2$CO$_3$ (32.0 mg, 0.240 mmol, 2.00 equiv) was added to a solution of cyclopropane 166 (43.0 mg, 0.120 mmol, 1.00 equiv) in MeOH (2.30 mL) at 0 °C. The reaction was stirred at 0 °C and monitored by TLC. Once complete, the reaction was diluted with saturated NH$_4$Cl (aq.) and EtOAc, the layers were then separated, and the aqueous layer was further extracted 2x with EtOAc. The organic layers were combined, washed with H$_2$O and brine, dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo to afford a crude oil. The latter was purified by silica gel chromatography (50:50 EtOAc:Hexanes) to provide alcohol 171 as a glue (30 mg, 80%). $^1$H NMR (500 MHz, C$_6$D$_6$) δ 5.66 (s, 1H), 4.69 (m, 1H), 4.03 (app. q, J = 1.7, 5.6 Hz, 1H), 3.42 (s, 3H), 3.34 (d, J = 5.6 Hz, 1H), 2.28 (s, 3H), 2.12 (s, 3H), 1.53 (d, J = 14.4 Hz, 1H), 1.13 (ddd, J = 3.4, 7.3, 14.4 Hz, 1H); $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 209.4, 196.2, 171.1, 159.6, 148.7, 141.6, 132.3, 114.6, 84.0, 71.5, 58.4, 51.4, 46.8, 45.9, 29.8, 11.8; IR (film) 3469, 1770, 1706, 1299, 1081 cm$^{-1}$; HRMS (EI) calc’d for [C$_{16}$H$_{16}$O$_7$Na]$^+$: m/z 343.0794, found 343.0811.

**Ketone 172.** To a solution of alcohol 171 (62.0 mg, 0.190 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (3.90 mL) was added Dess-Martin periodinane (160 mg, 0.390 mmol, 2.00 equiv), and
the resulting slurry stirred until consumption of starting material (ca. 1 h). The reaction was diluted with EtOAc and a 1:1 ratio of saturated Na$_2$S$_2$O$_4$ (aq.) to saturated NaHCO$_3$(aq.), and stirred vigorously for 5 minutes. The layers were separated and the organic layer was washed with brine, dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo to yield crude ketone 172 as a colorless oil (60 mg, 97%). The ketone was carried on crude as attempts toward further purification resulted in decomposition. $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 5.53 (s, 1H), 4.59 (dd, $J$ = 1.2, 4.4 Hz, 1H), 3.49 (d, $J$ = 1.2 Hz, 1H), 3.43 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.90 (d, $J$ = 17.6 Hz, 1H), 1.66 (dd, $J$ = 4.6, 17.6 Hz, 1H); $^{13}$C NMR (125 MHz, C$_6$D$_6$) $\delta$ 202.0, 193.2, 168.7, 159.6, 146.2, 140.0, 142.4, 132.3, 115.9, 78.4, 54.4, 52.6, 51.6, 49.9, 45.3, 29.5, 11.8; IR (film) 2924, 2854, 1180, 1750, 1715, 1559, 1438, 1294, 1102 cm$^{-1}$; HRMS (EI$^+$) calc’d for [C$_{16}$H$_{14}$O$_7$]$^+$: $m/z$ 318.0740, found 318.0732.

Alcohol 168. Crude ketone 172 (11.0 mg, 0.0340 mmol, 1.00 equiv) and La(OTf)$_3$ (20.0 mg, 0.0340 mmol, 1.00 equiv) were dissolved in MeOH (0.670 mL) at ambient temperature, then heated to 55 °C and stirred until the majority of starting material appeared consumed by TLC. The reaction was diluted with EtOAc and H$_2$O and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using 66:34 EtOAc:Hexanes to afford alcohol 168 as an oil (8.0 mg, 55%); $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 5.90 (s, 1H), 4.26 (dd, $J$ = 1.7, 5.6
Furan 169. Triethylamine (19.0 mL, 0.140 mmol, 2.40 equiv) was added at ambient temperature to a solution of alcohol 168 (22.0 mg, 0.0580 mmol, 1.00 equiv) in CH₂Cl₂ (310 mL). DMAP (0.700 mg, 0.00580 mmol, 0.100 equiv) and p-bromobenzoyl bromide (28.0 mg, 0.130 mmol, 2.20 equiv) were then added, and the reaction stirred for 1 hour at ambient temperature. The reaction was diluted with EtOAc and H₂O, the layers were separated, and the aqueous layer was washed once with EtOAc. The EtOAc layers were combined, washed with saturated NaHCO₃ (aq.), washed with brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. Crystals suitable for X-ray analysis were obtained by crystallization of crude furan 169 (30 mg, yield 70%) from EtOAc:heptane. ¹H NMR (500 MHz, C₆D₆) δ 7.97 (m, 2H), 7.39 (m, 2H), 7.25 (m, 2H), 7.10 (m, 2H), 5.99 (s, 1H), 5.73 (m, 1H), 3.93 (s, 1H), 3.24 (s, 3H), 3.13 (s, 3H), 2.88 (s, 3H), 2.54 (s, 3H), 2.49 (m, 2H), 2.15 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 168.1, 164.6, 161.9, 161.6, 159.2, 152.9,
141.0, 132.1, 132.0, 131.8, 131.4, 129.3, 128.8, 128.6, 127.7, 114.9, 114.7, 114.2, 87.4, 78.1, 55.5, 52.3, 51.6, 50.1, 39.3, 17.4, 11.4; IR (film) 2948, 1762, 1725, 1589, 1227, 1101, 1070, 1010 cm⁻¹; HRMS (FAB⁺) calc’d for [C₃₂H₂₈O₁₁Br₈⁺]: m/z 750.0135, found 750.0159. mp = 175-177 °C (heptane/EtOAc).

Cyclopropane 173. Cyclopropane 173 was obtained from allylic alcohol 37 using the same route employed to obtain cyclopropane 166 (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane 173 was obtained as an oil (3.5 mg, 74%). ¹H NMR (500 MHz, C₆D₆) δ 7.30 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 7.6 Hz, 1H), 7.06 (t, J = 7.3 Hz, 2H), 5.93 (s, 1H), 4.93 (d, J = 7.1 Hz, 1H), 4.63 (d, J = 7.1 Hz, 1H), 4.60 (s, 2H), 4.11 (m, 1H), 3.42 (d, J = 4.6 Hz, 1H), 3.39 (s, 3H), 2.42 (s, 3H), 2.12 (s, 3H), 1.86 (d, J = 14.2 Hz, 1H), 1.20 (dd, J = 3.2, 14.2 Hz, 1H); ¹³C NMR (125 MHz, C₆D₆) δ 195.0, 169.4, 158.9, 150.4, 140.4, 138.0, 131.4, 128.2, 114.2, 93.3, 80.7, 69.7, 51.4, 50.6, 50.3, 44.8, 28.6, 11.1; IR (film) 2952, 1769, 1713, 1297, 1102, 1037 cm⁻¹; HRMS (EI⁺) calc’d for [C₂₄H₂₃DO₈⁺]: m/z 441.1534, found 441.1523.
Cyclopropane 174. Cyclopropane 174 was obtained from allylic alcohol 37 using the same route employed to obtain cyclopropane 166 (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane 174 was obtained as an oil (2.3 mg, 62%). $^1$H NMR (500 MHz, C$_6$D$_6$) δ 5.95 (s, 1H), 4.78 (d, $J = 7.1$ Hz, 1H), 4.48 (d, $J = 7.1$ Hz), 4.09 (m, 1H), 3.43 (d, $J = 4.9$, 1H), 3.39 (s, 3H), 3.23 (s, 3H), 2.43 (s, 3H), 2.13 (s, 3H), 1.82 (d, $J = 14.2$, 1H), 1.20 (dd, $J = 3.4$, 14.2 Hz, 1H); $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 196.0, 170.3, 159.8, 151.3, 141.2, 132.3, 115.0, 96.1, 81.5, 56.3, 52.3, 51.5, 51.1, 45.8, 45.7, 29.4, 12.0; IR (film) 2926, 1767, 1711, 1402, 1297, 1100 cm$^{-1}$; HRMS (EI) calc’d for [C$_{18}$H$_{19}$DO$_8$]$^+$: m/z 365.1221, found 365.1216.

Cyclopropane 175. Cyclopropane 175 was obtained from allylic alcohol 37 using the same route employed to obtain cyclopropane 166 (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane 175 was obtained as an oil (2.9 mg, 62%). $^1$H NMR (500 MHz, C$_6$D$_6$) δ 6.02 (s, 1H), 4.94 (d, $J = 7.1$Hz, 1H), 4.65 (d, $J = 7.1$ Hz, 1H), 4.13-4.11 (m, 1H), 3.78-3.73 (m, 1H), 3.46 (d, $J = 4.6$Hz, 1H), 3.42 (s, 3H), 2.44 (s, 3H), 2.15 (s, 3H), 1.93 (d, $J = 14.2$ Hz, 1H), 1.27 (dd, $J = 3.2$, 13.9 Hz, 1H), 0.94-0.90 (m), 0.01 (s, 9H); $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 196.0, 170.3, 159.8, 151.5, 141.2, 132.4,
115.2, 94.3, 81.6, 66.5, 56.2, 51.6, 51.1, 45.9, 46.0, 29.5, 18.6, 12.0, -0.80; IR (film) 2953, 1770, 1713, 1440, 1297 cm\(^{-1}\); HRMS (FAB\(^+\)) calc’d for [C\(_{22}\)H\(_{29}\)DO\(_8\)SiNa\(^+\): m/z 474.1773, found 474.1675.

**Cyclopropane 176.** Cyclopropane 176 was obtained from allylic alcohol 37 using the same route employed to obtain cyclopropane 166 (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane 176 was obtained as an oil (6.5 mg, 71%). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.71 (s, 1H), 4.15-4.13 (m, 1H), 3.42 (s, 3H), 3.33 (d, \(J = 4.6\) Hz, 1H), 2.45 (s, 3H), 2.13 (s, 3H), 1.63 (d, \(J = 13.7\) Hz, 1H), 1.21 (dd, \(J = 3.4, 13.7\) Hz, 1H), 1.09 (s, 9H), 0.29 (s, 3H), 0.10 (s, 3H); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)) \(\delta\) 196.3, 170.2, 159.7, 151.2, 141.4, 132.0, 114.4, 81.6, 53.6, 52.6, 51.4, 48.2, 45.3, 29.4, 26.3, 18.8, 11.9, -4.5, -4.6; IR (film) 2953, 2930, 2857, 1770, 1714, 1297, 1113 cm\(^{-1}\); HRMS (FAB\(^+\)) calc’d for [C\(_{22}\)H\(_{29}\)DO\(_8\)SiNa\(^+\): m/z 459.1800, found 458.1749.

**Cyclopropane 177.** Cyclopropane 177 was obtained from allylic alcohol 37 using the same route employed to obtain cyclopropane 166 (Scheme 2.6.2). For the cyclopropanation reaction, thermal conditions were used, and cyclopropane 177 was
obtained as an oil (9.1 mg, 42%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta 6.23\) (s, 1H), 5.11 (m, 1H), 5.02 (d, \(J = 7.1\) Hz, 1H), 4.92 (d, \(J = 7.1\) Hz, 1H), 3.99 (d, \(J = 4.9\) Hz, 1H), 3.86 (s, 3H), 3.83 (q, \(J = 4.4\) Hz, 2H), 3.58 (t, \(J = 4.4\) Hz, 2H), 3.39 (s, 3H), 2.46 (s, 3H), 2.34 (d, \(J = 14.2\) Hz, 1H), 2.29 (s, 3H), 2.20 (dd, \(J = 3.2, 14.2\) Hz, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta 196.2, 170.1, 159.4, 149.8, 140.2, 131.9, 114.7, 94.3, 81.5, 71.6, 67.4, 59.0, 51.6, 51.4, 50.9, 45.4, 45.2, 29.1, 11.6; IR (film) 2925, 1767, 1711, 1613, 1548, 1440, 1297, 1198, 1099, 1037 cm\textsuperscript{-1}; HRMS (EI\textsuperscript{+}) calc’d for [C\textsubscript{20}H\textsubscript{23}DNaO\textsubscript{9}]\textsuperscript{+}: \(m/z 432.1381\), found 432.1365.

**Alcohol 181.** Furan 171 (49.0 mg, 0.153 mmol, 1.00 equiv) and La(OTf\textsubscript{3}) (89.5 mg, 0.153 mmol, 1.00 equiv) were dissolved in MeOH (3.00 mL) at ambient temperature, and then heated to 55 °C and stirred for 1–2 hours. The reaction was diluted with EtOAc and H\textsubscript{2}O and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried with Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using 60:40 EtOAc:Hexanes to afford alcohol 181 as an oil (35 mg, 65%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta 6.34\) (s, 1H), 5.30 (br, 1H), 5.17 (t, \(J = 7.3\) Hz, 1H), 4.64 (d, \(J = 3.8\) Hz, 1H), 4.10 (t, \(J = 6.7\) Hz, 1H), 3.91 (d, \(J = 5.5\) Hz, 1H), 3.89 (s, 3H), 3.03 (s, 3H) 2.50 (ddd, \(J = 4.1, 7.1, 15.4\) Hz, 1H), 2.43 (s, 3H), 2.47 (s, 3H), 2.20 (d, \(J = 15.4\) Hz, 1H); \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta 200.0, 172.4, 159.9, 154.3, 140.9, 132.1, 116.2, 88.5, 83.5, 77.0, 58.6, 51.4, 51.4, 45.9, 40.0, 29.6,
11.8; IR (film) 3474, 2952, 1769, 1717, 1297, 1195, 1098 cm\(^{-1}\); HRMS (EI\(^+\)) calc'd for [C\(_{17}\)H\(_{21}\)O\(_8\)Na\(^+\)]: m/z 353.1236, found 353.1246.

**Furan 182.** Triethylamine (43.0 µL, 306 µmol, 4.00 equiv) was added at 0 °C and under N\(_2\), to a solution of alcohol 181 (27.0 mg, 76.6 µmol, 1.00 equiv) in CH\(_2\)Cl\(_2\) (955 µL). After 1 minute, p-bromobenzoyl bromide (42.0 mg, 192 µmol, 2.50 equiv) was added, and the reaction was stirred for 30 minutes at 0 °C. The reaction was allowed to warm to ambient temperature and stir for an additional 1 hour. The reaction was then diluted with Et\(_2\)O and H\(_2\)O, the layers were separated, and the aqueous layer was washed once with Et\(_2\)O. The Et\(_2\)O layers were combined, washed with saturated NaHCO\(_3\) (aq.), washed with brine, dried with MgSO\(_4\), filtered, and concentrated in vacuo. Crystals suitable for X-ray analysis were obtained by crystallization of crude furan 182 (54 mg, 98% yield) from EtOAc:heptane. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.78 (d, \(J = 8.5\) Hz, 2H), 7.62 (d, \(J = 8.5\) Hz, 2H), 6.38 (s, 1H)\(5.06\) (t, \(J = 6.4\) Hz, 1H), 4.46 (q, \(J = 7.2\), 3.5 Hz, 1H), 3.80 (m, 4H), 3.18 (s, 3H), 2.45 (s, 3H), 2.37 (m, 1H), 2.33 (s, 3H), 2.28 (d, \(J = 3.9\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 169.5, 162.0, 159.9, 153.5, 139.9, 132.0, 131.9, 131.6, 129.2, 129.0, 127.6, 115.8, 115.3, 88.7, 79.8, 52.6, 52.3, 51.5, 38.5, 17.1, 11.6; IR (film) 3445, 2950, 1749, 1705, 1589, 1439, 1399, 1300, 1231, 1070, 1010 cm\(^{-1}\); HRMS (EI\(^+\)) calc'd for [C\(_{24}\)H\(_{25}\)BrO\(_9\)]\(^+\): m/z 557.0423, found 557.0427. mp = 158-159 °C (EtOAc:Heptane).
2.10 Notes and References


3 The dihydrofuran unit actually disguises a 1,4 enedione moiety. However, as in ineleganolide (108) and scabrolide A (109), the olefin may further undergo various reactions such as 1,4-hetero-Michael addition or an olefin migration, respectively.

4 An oxocane is an 8-membered ethereal ring that is fully saturated.


8 Although this is possible, it is also feasible that the undesired diradical intermediate 120 is higher in energy and undergoes σ-bond rotation to the desired diradical intermediate 118. Since neither diradical intermediate 118 or 120 has been observed,
one can only speculate as to how prevalent $\sigma$-bond rotation is, as well as its impact on
the diastereoselectivity.


10 Although the addition of water into the oxocarbenium ion is shown as the last step of
the mechanism, it is possible that this may occur at any point after cyclopropane
fragmentation.


12 (a) Knochel, P.; Cahiez, G.; Rottlander, M.; Boymond, L. *Angew. Chem., Int. Ed.


15 For a related system that provides nonsymmetrical $\alpha$-diazomalonates, see: Kido, F.;

16 Prepared using standard diazotization conditions (see S.I.).

17 Although the crude product could be crystallized to higher purity using 95% EtOH at
–20 °C overnight, the crude solid was used in the coupling reaction and still provided
acceptable yields.


19 For examples of $\alpha$-diazo-$\beta$-ketoamides, see: (a) Jeganathan, A.; Richardson, S. K.;


21 The only isolated product from this reaction other than starting material was an α-hydroxy-β-ketoester that resulted from the overall addition of water to the "carbene".


25 In a separate run, ketone 136 was obtained in 40% yield and 93% ee after 18 hours.


27 Deuterium labeling may not be needed if the $^1$H NMR spectra of cyclopropane 166, alcohol 171, and ketone 172, are attained in C$_6$D$_6$, and each spectrum is analyzed and compared. The spectra, in C$_6$D$_6$, for these three compounds are in Appendix 2.2 (Spectra of Compounds Relevant to Chapter 2).

28 All compounds in Figure 2.6.2 had partial deuterium incorporation at C(1) similar to cyclopropane 166 in Scheme 2.6.5.
Chapter 2 – Synthetic efforts toward bielschowskysin using a palladium(II)-catalyzed OKR

29. Spartan calculations (semi-empirical, AM1) show that undesired alcohol 171 is 4.3 kcal lower in energy than desired alcohol 167.


31. See Appendix 2.1 for our attempts to form a macrocycle.


Furan 200 can be treated with MMPP to provide enedione 202 in an unoptimized 63% yield:

![Chemical structure](image)


This starting alcohol (156) was prepared in the same manner as compound 158, using phenyl boronic acid as the coupling partner. It was also made via a known route, see: D’Auria, M. Heterocycles 2000, 52, 185–194.


For a separate sample, alcohol 37 at 70% ee, gave an $\alpha_D^{24.9} +16.9.$