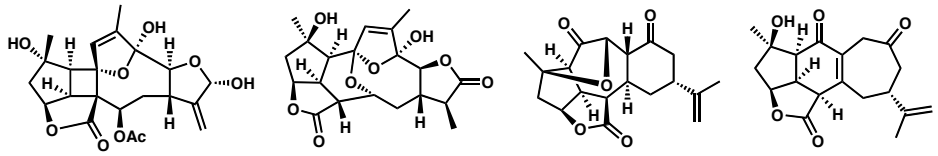
CHAPTER 2

Synthetic Efforts Toward Bielschowskysin Using a Palladium(II)-catalyzed Oxidative Kinetic Resolution

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.



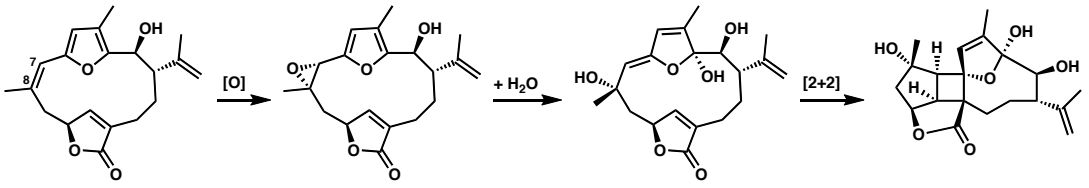
bielschowskysin ***verrillin*** ***ineleganolide*** ***scabrolide A***

36 ***107*** ***108*** ***109***

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.[3] 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.[4]

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).[5]

Scheme 2.1.1

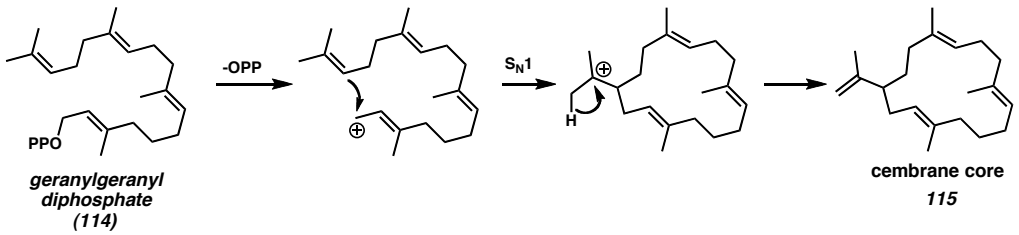


bipinnatin J (110) ***111*** ***112*** ***113***

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_N1 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]

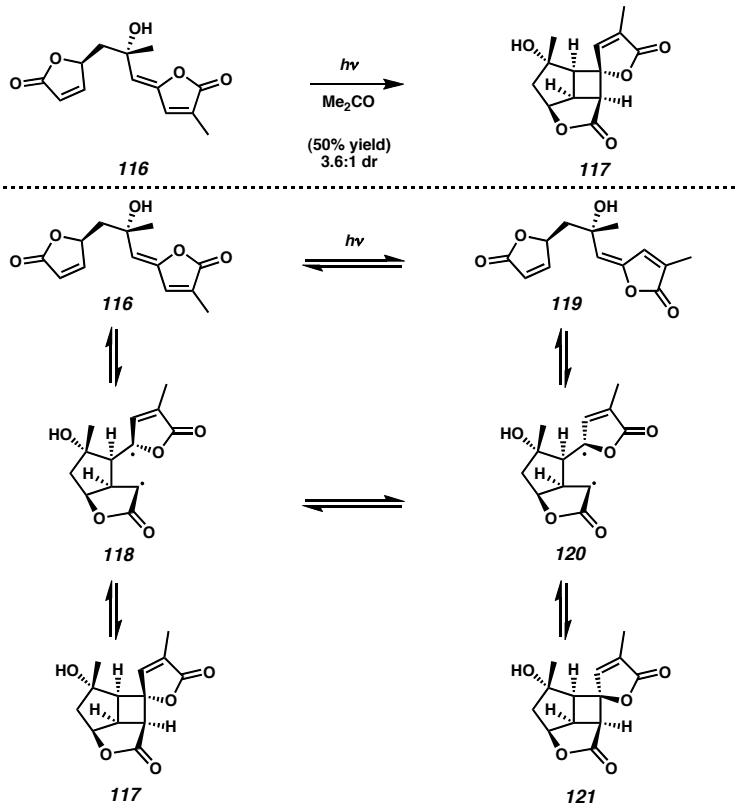
Scheme 2.1.2



2.2 Outside Efforts Toward the Total Synthesis of Bielschowskysin

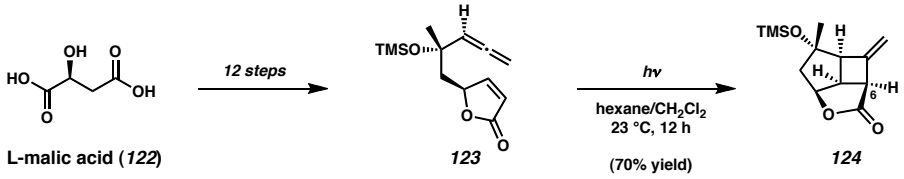
Although there are no reported total syntheses of bielschowskysin, there are two reported partial syntheses of the cyclobutane core found in the natural product. First, Doroh and Sulikowski subject alcohol **116** to a [2+2] photocycloaddition providing cyclobutane **117** in 50% yield with a 3.6:1 diastereomeric 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 σ-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 photocylcoaddition of allene **123** (Scheme 2.2.2).[9] 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 co-solvent provides the desired *exo*-cyclobutene **124** in 70% yield.

Scheme 2.2.2



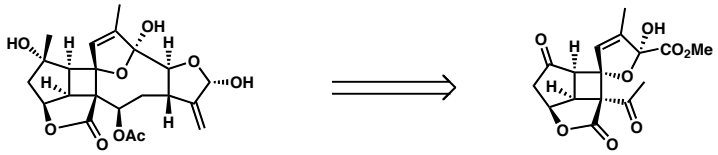
Although these partial syntheses provide access to the strained cyclobutane found in bielschowskysin, they do not address the formation of either the critical C(6)

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.

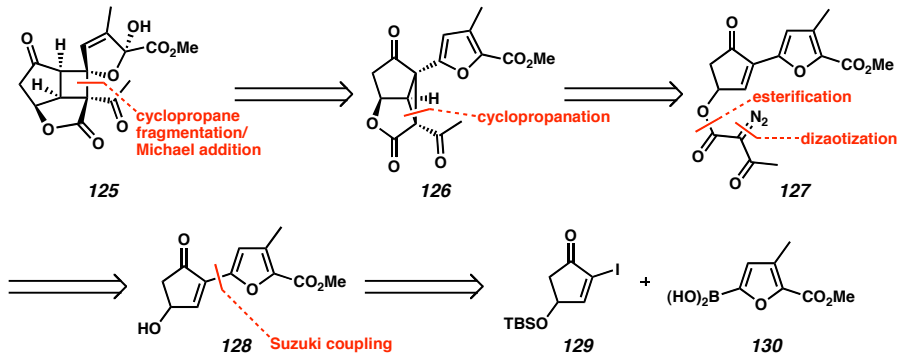


bielschowskysin (36) ***125***

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, α-diazo-β-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.

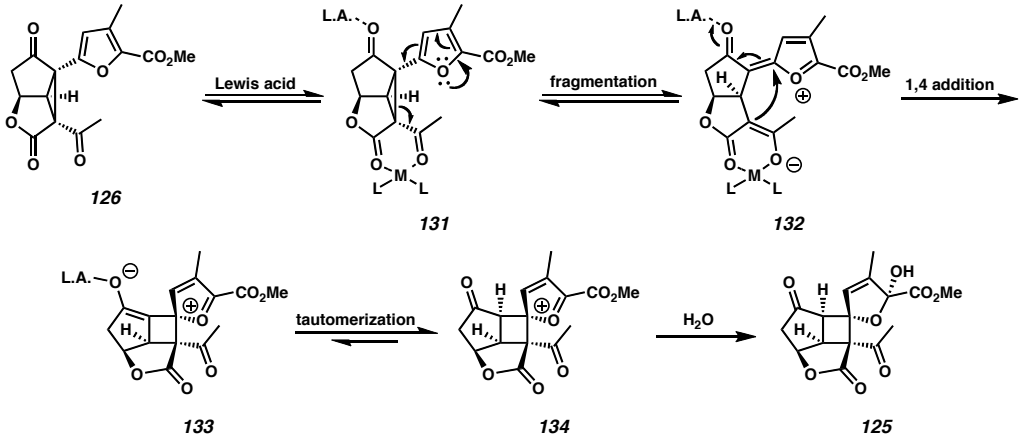
Scheme 2.3.1



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 β-ketoester in compound **126** will lead to weakening of the bridging σ-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 π^* orbitals of the β-ketoester moiety have good overlap with the breaking C–C σ-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**.[10]

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

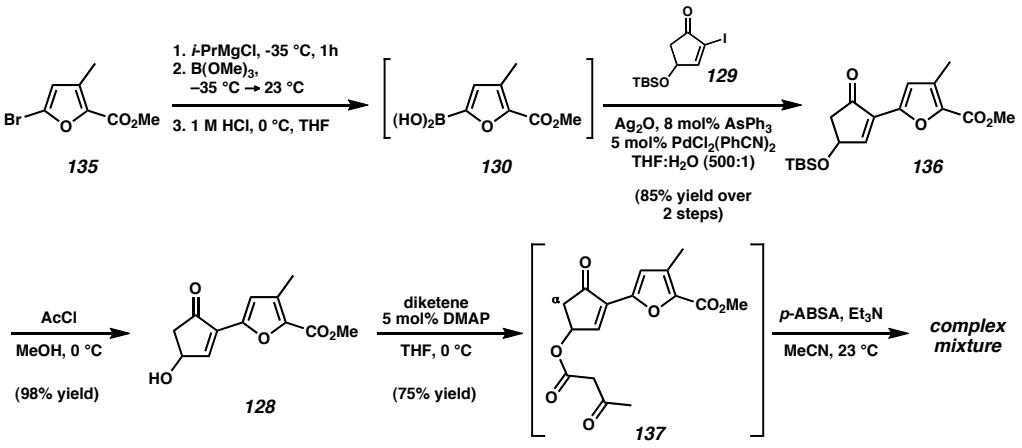


2.4 Initial Synthetic Efforts

The synthesis began with furan **135**,[11] which underwent magnesium-halogen exchange using conditions developed by Knochel,[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.[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_3N 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.

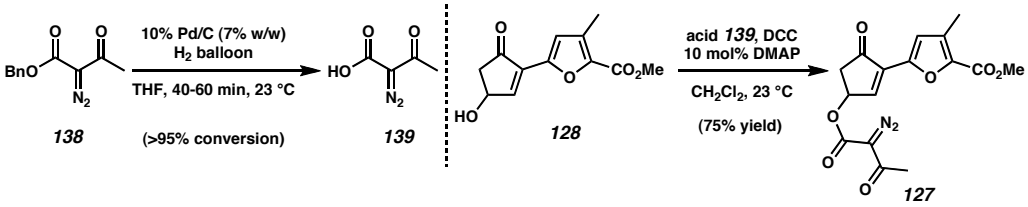
Scheme 2.4.1



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).

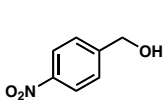
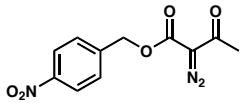
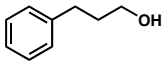
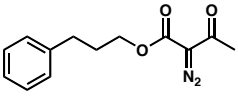
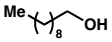
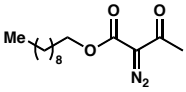
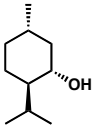
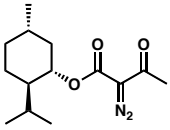
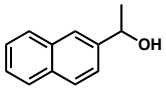
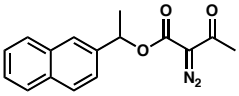
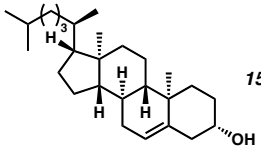
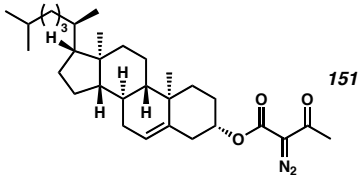
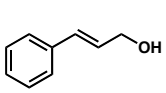
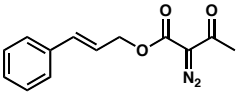
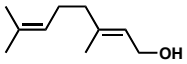
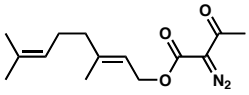
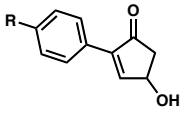
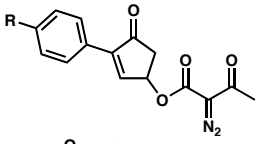
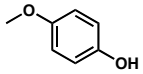
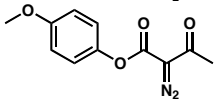
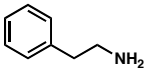
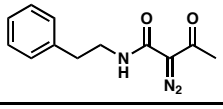
Scheme 2.4.2



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).[18] 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).[19]

*Table 2.4.1 Esterification of 2-diazoacetoacetic acid (**139**) with Heteroatom Nucleophiles.*

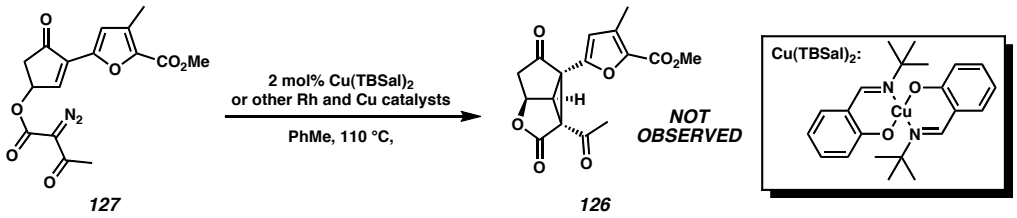
Entry	Substrate[a]		Product		Yield[b]
1		*140*		*141*	92
2		*142*		*143*	85
3		*144*		*145*	80
4[d]		*146*		*147*	77
5[d]		*148*		*149*	81
6[d]		*150*		*151*	87
7		*152*		*153*	82
8		*154*		*155*	77
9[c,d]		*R = H* *156*		*R = H* *157*	95
10		*R = NO₂* *158*		*R = NO₂* *159*	77
11[d]		*160*		*161*	75
12		*162*		*163*	95

[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_2Cl_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

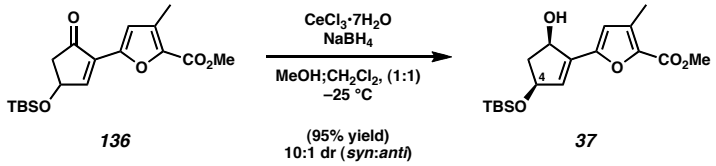


127 *126*

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]

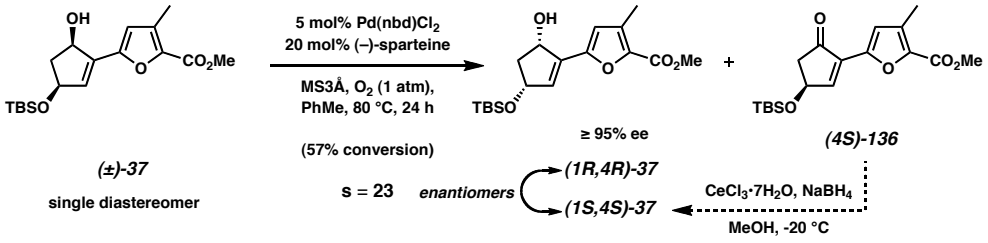
Scheme 2.4.4



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]

Scheme 2.5.1

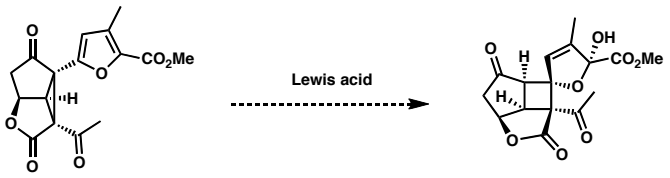


Furthermore, the opposite enantiomer of alcohol can be obtained by treating (4*S*)-enone **136** under the previously optimized Luche conditions to provide (1*S*, 4*S*)-alcohol **37** (Scheme 2.5.1).[25] Since the absolute configuration of bielschowskysin is unknown, accessing both enantiomers of alcohol **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

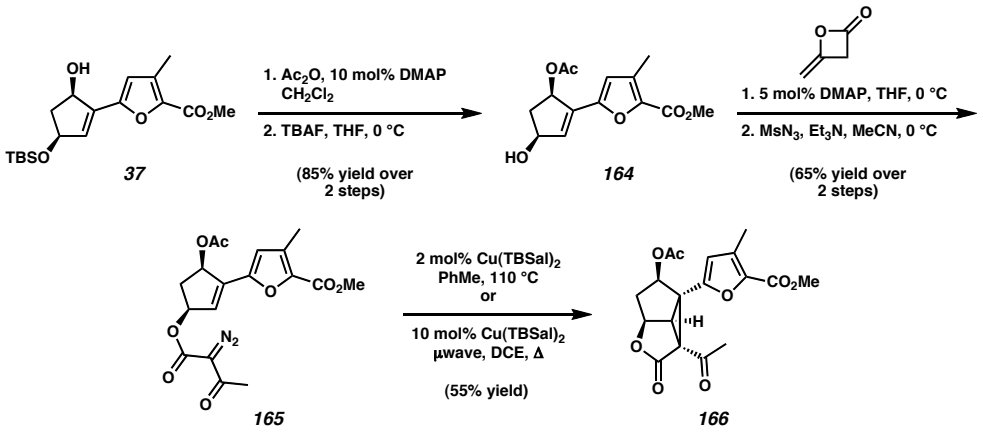


126 ***125***

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 $Rh_2(oct)_4$, 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

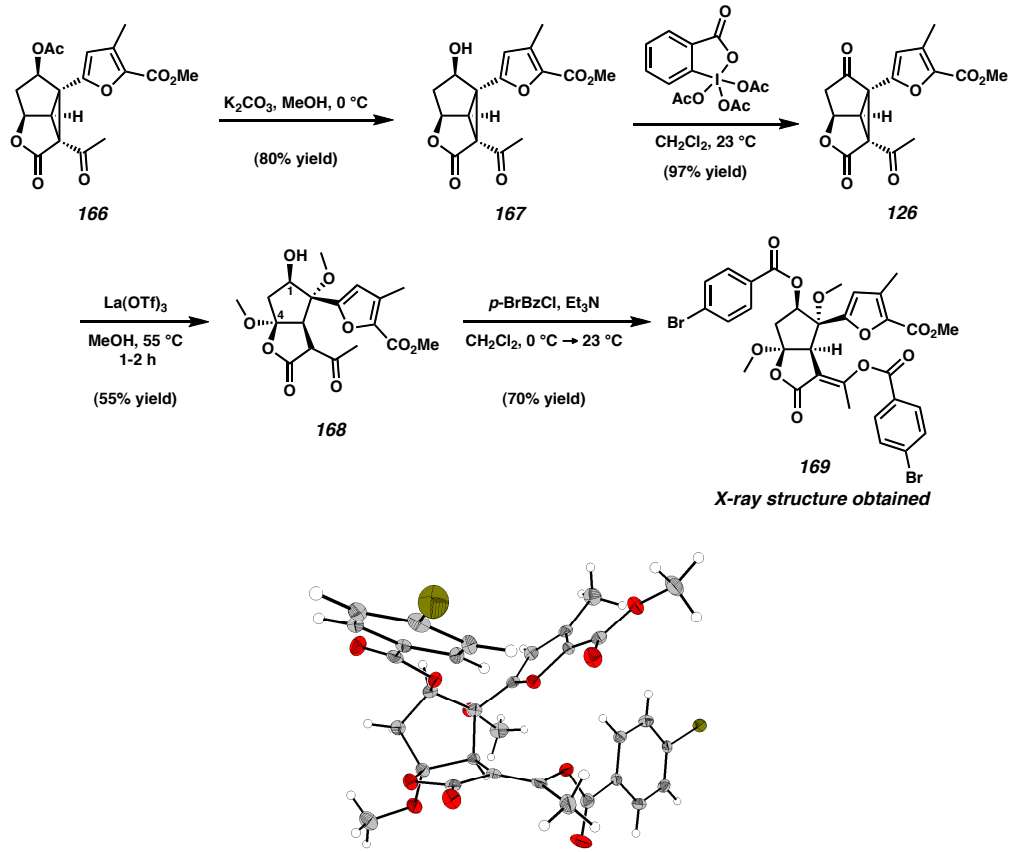
our hypothesis that the olefin in enone **136** was simply too electron deficient to undergo cyclopropanation.

Scheme 2.6.2



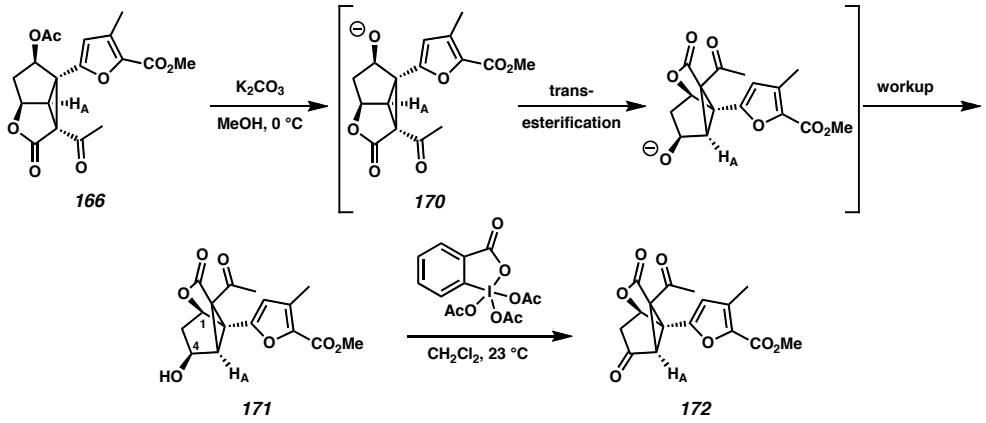
Although the synthesis of cyclopropane **166** was a significant accomplishment, this intermediate still needed to be elaborated to ketone **126**. Initially, it was thought that cyclopropane **166** would undergo acetate cleavage to provide alcohol **167**, followed by Dess-Martin periodinane oxidation to arrive at ketone **126** (Scheme 2.6.3).[26] 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**.

Scheme 2.6.3



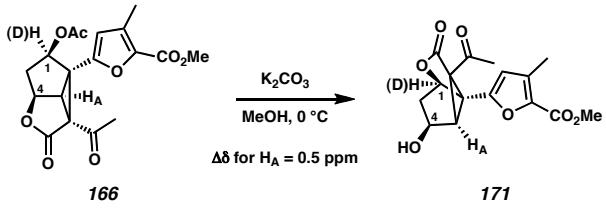
Upon examination of the connectivity of β-ketoester **169**, we noticed that the oxidation states of C(1) and C(4) were opposite to those of desired ketone **126**. This is the likely result of an undesired trans-esterification reaction that occurs when cyclopropane **166** undergoes acetate cleavage (Scheme 2.6.4). Treatment of cyclopropane **166** with K_2CO_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**.

Scheme 2.6.4



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}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.

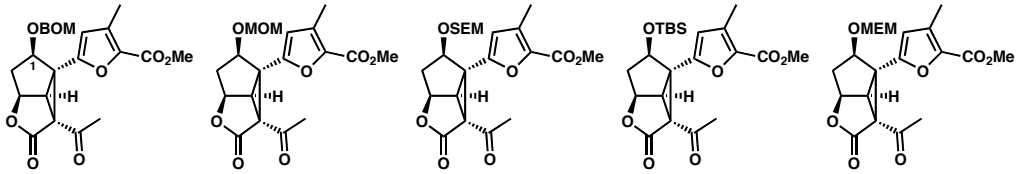
Scheme 2.6.5



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.[29]

Figure 2.6.2 Various Cyclopropane Derivatives.

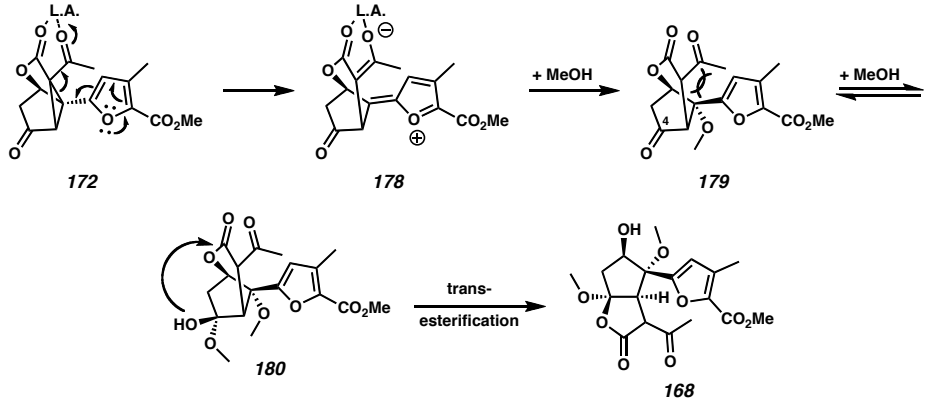


173 ***174*** ***175*** ***176*** ***177***

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**.[30] 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

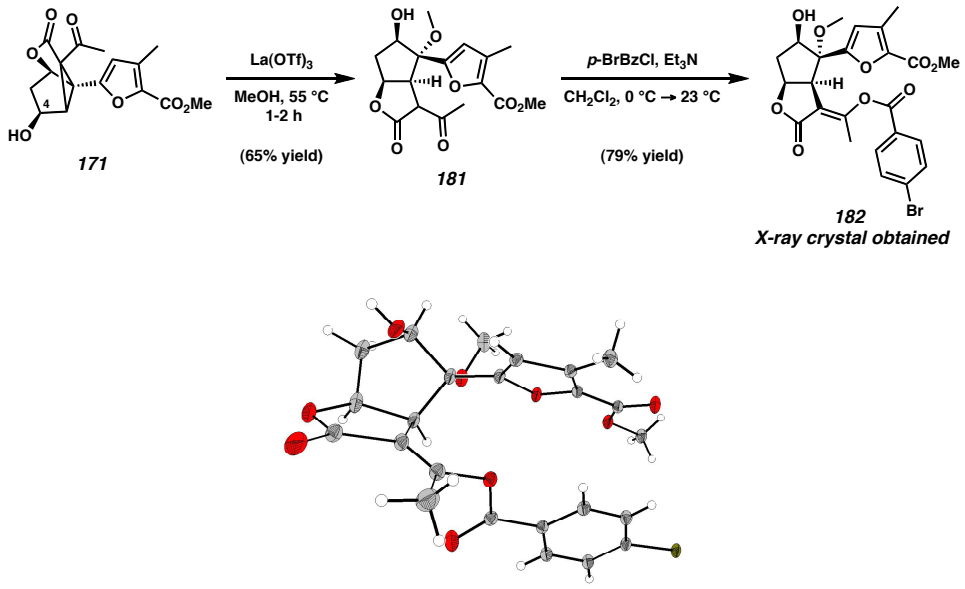
2.6.6 is the increased steric interaction that the bridged lactone in compound **179** would sustain with the furan moiety, compared to the fused lactone in alcohol **168**.

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



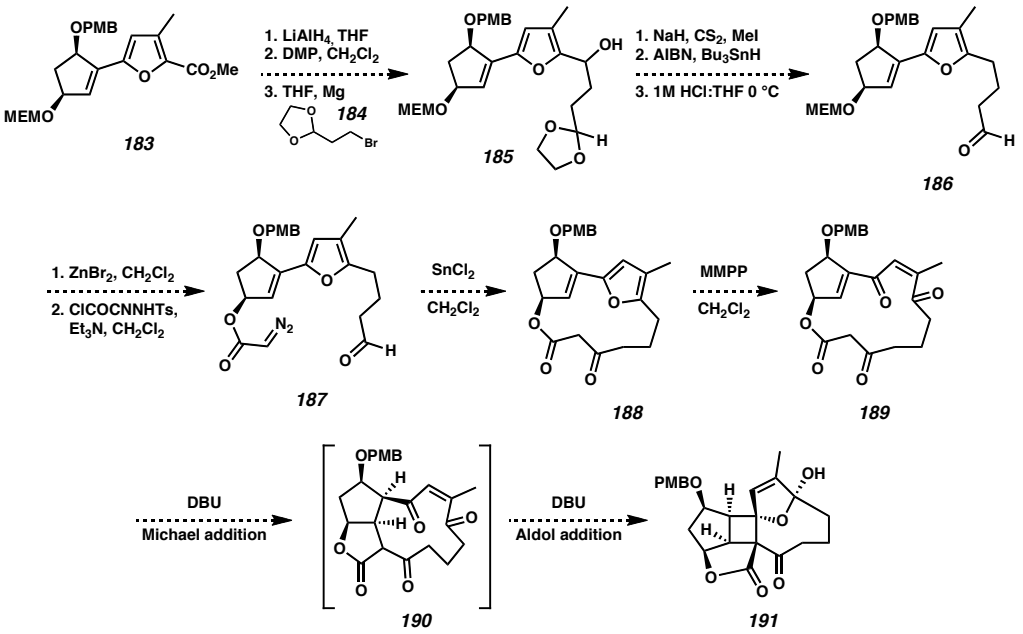
2.7 Future Directions

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.[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.[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**.[33] Once formed, treating macrocycle **188** with monomagnesium peroxyphthalate (MMPP),[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**.

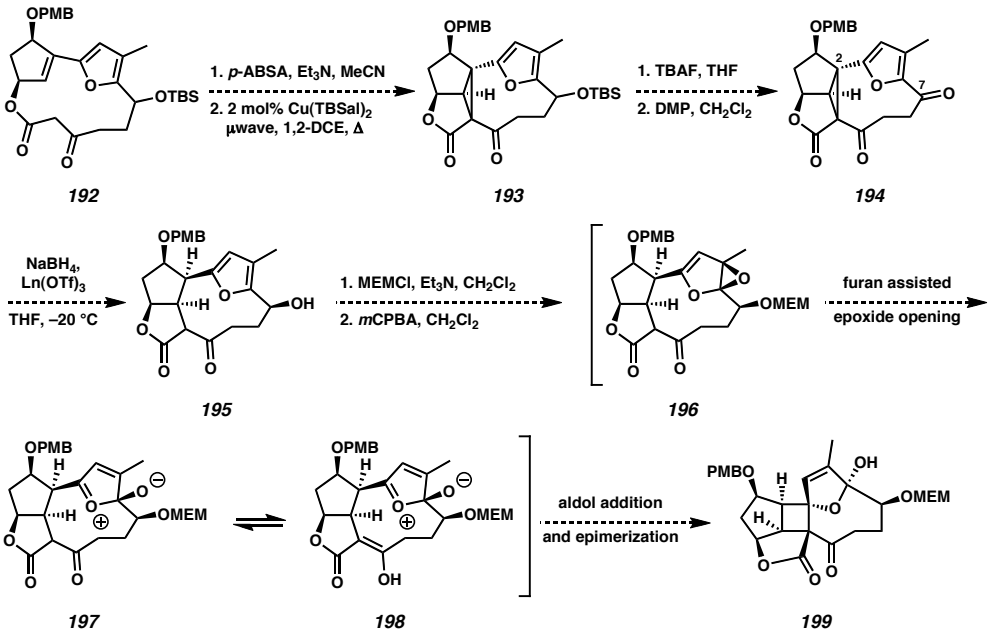
Scheme 2.7.1



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 $La(OTf)_3$ and $NaBH_4$ 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 *m*CPBA 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 ≥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 α-diazo-β-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 α-diazo-β-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).[35] 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.

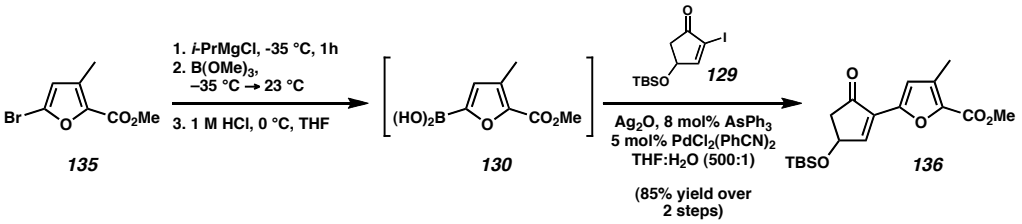
2.9 Experimental Procedures

2.9.1 *Materials and Methods*

Unless otherwise stated, reactions were performed at ambient temperature (typically 20–22 ºC) 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. Et_3N, $i Pr_2NH$, $i Pr_2NEt$, and pyridine were freshly distilled from CaH_2. Trifluoroacetic acid (99%) was purchased from Aldrich. Tf_2O was freshly distilled from P_2O_5. 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, $KMnO_4$, 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 ^{13}C 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 ($CHCl_3$ = 7.27 ppm, C_6H_6 = 7.16 ppm, CH_2Cl_2 = 5.30 ppm, DMSO = 2.51 ppm) and ^{13}C NMR ($CDCl_3$ = 77.0 ppm, C_6D_6 = 128.4 ppm). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicitiy, 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).

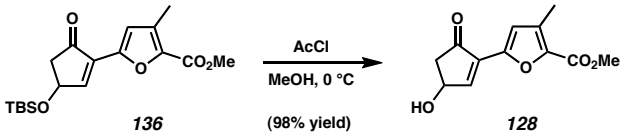
2.9.2 *Preparation of Compounds*



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 *i*PrMgCl (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 H_2O, and the layers were separated. The aqueous layer was then washed 2x with EtOAc. The organic layers were combined, and washed with saturated K_2CO_3 (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 Na_2SO_4, filtered, and concentrated in vacuo to afford boronic acid **130** (375 mg,

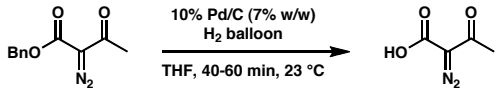
73%) as a light-brown solid. This compound was used directly in the following Suzuki coupling reaction.

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), Ag_2O (180 mg, 0.770 mmol, 3.00 equiv), and Ph_3As (8.00 mg, 0.0260 mmol, 0.100 equiv) in THF (1.30 mL) was added $PdCl_2(PhCN)_2$ (5.00 mg, 0.0130 mmol, 0.0500 equiv) and H_2O (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%). R_F 0.15 (90:10 hexanes:EtOAc, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.7 Hz, 1H), 7.03 (s, 1H), 5.03 (m, 1H), 3.90 (s, 3H), 2.88 (dd, *J* = 5.9, 18.3 Hz, 1H), 2.42 (dd, *J* = 2.2, 18.6 Hz, 1H), 2.34 (s, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 160.1, 156.0, 147.4, 140.0, 133.7, 132.6, 116.1, 68.9, 51.8, 45.9, 25.8, 18.3, 11.5, -4.8; IR (film) 3133, 2949, 2928, 2891, 2857, 1721, 1703, 1594, 1509, 1448 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{18}H_{26}SiO_5]^+$: *m/z* 350.1550, found 350.1542.



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

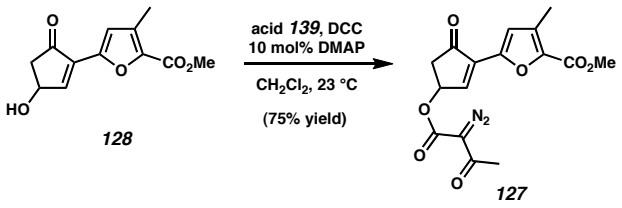
brine and EtOAc. These layers were separated, and the aqueous layer was washed 2x with EtOAc. The organic layers were combined, washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. This semi-solid was diluted with toluene, and then reconcentrated under vacuum (repeated 3x). Upon final concentration in vacuo, alcohol **128** was obtained as a white solid (35.3 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[C_{12}H_{13}O_5]^+$: *m/z* 237.0763, found 237.0763.



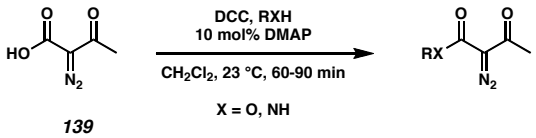
138 *139*

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 N_2 atmosphere was evacuated and backfilled with H_2 (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 (Et_2O 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 ^{1}H NMR. *Note:* A pure (98%) sample of acid **139** was obtained by crystallization using Et_2O/Heptane and cooling at -20 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ

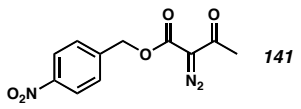
2.46 (s, 3H); IR (film) 2932, 2150, 1722, 1601, 1302 cm^{-1}; HRMS (EI^+) calc'd for $[C_4H_4N_2O_3]^+$: *m/z* 128.0222; found, 128.0227.



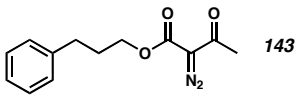
Enone 127. To a solution of alcohol **128** (71.0 mg, 0.300 mmol, 1.00 equiv), acid **139** (92.1 mg, 0.720 mmol, 2.40 equiv), and DMAP (3.67 mg, 0.0300 mmol, 0.100 equiv) in CH_2Cl_2 (2.00 mL) at 23 °C, was added DCC (206 mg, 1.00 mmol, 2.0 equiv) in one portion. After the addition of DCC, the reaction was heated to 40 °C for 90 minutes. The reaction was allowed to cool to ambient temperature, filtered through a plug of celite (Et_2O eluent), and the resulting filtrate was partitioned between H_2O and Et_2O. The aqueous layer was extracted 2x with Et_2O. The organic extracts were combined, washed once with H_2O, and then once with brine. The organic layer was dried over $MgSO_4$, 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, C_6D_6) 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); ^{13}C NMR (125 MHz, C_6D_6) 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 $[C_{16}H_{14}N_2O_7]^+$: *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 CH_2Cl_2 (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 (Et_2O eluent), and the resulting filtrate was partitioned between H_2O and Et_2O. The aqueous layer was extracted 2x with Et_2O. The organic extracts were combined, washed with $NaHCO_3$ (saturated), and then with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The products were purified by flash chromatography.

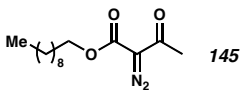


Substrate 141.[36] See General Procedure for the Esterification of Acid **139** (92% yield). Product was purified by flash chromatography (20:80 EtOAc:Hexanes). R_F = 0.40 (30:70 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 5.35 (s, 2H), 2.47 (s, 2H); IR (film) 2148, 1711, 1344 cm^{-1}.



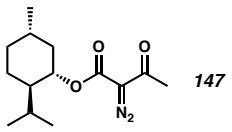
143

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); ^{1}H 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); ^{13}C 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 $[C_{13}H_{15}N_2O_3]^+$: *m/z* 247.1083; found, 247.1089.



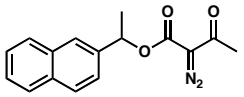
145

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); ^{1}H 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); ^{13}C 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 $[C_{14}H_{25}N_2O_3]^+$: *m/z* 269.1865; found, 269.1864.



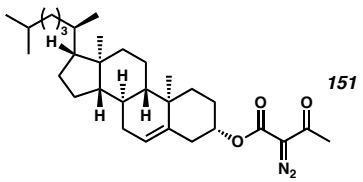
147

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]



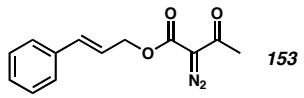
149

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $[C_{16}H_{15}N_2O_3]^+$: *m/z* 283.1083; found, 283.1079.



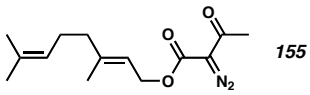
151

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]



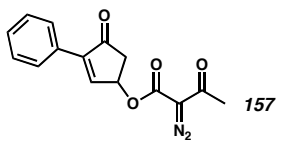
153

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, $CDCl_3$) δ 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, $CDCl_3$) δ 190.0, 161.1, 135.7, 135.3, 128.6, 128.3, 126.6, 122.2, 65.8, 28.2; IR (film) 2140, 1716, 1659, 1316 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{12}N_2O_3]^+$: *m/z* 244.0848; found, 244.0839.



155

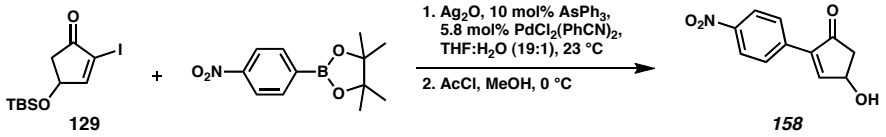
Substrate 155. See General Procedure for the Esterification of Acid **139** (77% yield). Product was purified by flash chromatography (10:90 EtOAc:Hexanes). R_F = 0.50 (20:80 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (dt, *J* = 1.2, 3.6 Hz, 1H), 5.10-5.04 (m, 1H), 4.75 (d, *J* = 7.2 Hz, 2H), 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, $CDCl_3$) δ 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$^+$) calc'd for $[C_{14}H_{21}N_2O_3]^+$, *m/z* 265.1552; found, 265.1548.



157

Substrate 157.[39] 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

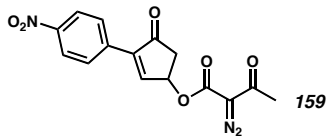
EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 7.68 (d, *J* = 2.7 Hz, 1H), 7.42-7.40 (m, 2H), 6.05 (dt, *J* = 2.4, 6.6 Hz, 1H), 3.10 (dd, *J* = 6.6, 18.6 Hz, 1H), 2.66 (dd, *J* = 1.8, 18.6 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 189.6, 160.9, 150.8, 146.3, 129.7, 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_3As (35.2 mg, 0.120 mmol, 0.100 equiv) at 23 °C. THF (5.5 mL) and H_2O (290 μL) 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).

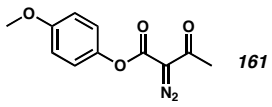
This product (125 mg, 0.370 mmol, 1.00 equiv) was then added to a solution of AcCl (130 μL, 1.90 mmol, 5.10 equiv) in MeOH (7.5 mL) at 0 °C. The reaction was allowed to stir for 20 minutes, upon which TLC (40:60 EtOAc:Hexanes) showed consumption of the Suzuki product. The reaction was diluted with brine 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 Na_2SO_4, filtered, and concentrated in vacuo. TBSOH was removed azeotropically with toluene to afford alcohol **158** (80 mg, 99% yield). R_F = 0.20 (50:50 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[C_{11}H_9NO_4]^+$: *m/z* 219.0532; found, 219.0506.



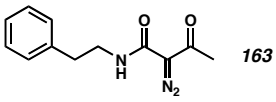
159

Substrate 159. See General Procedure for the Esterification of Acid **139** (77% yield). Product was purified by flash chromatography (50:50 EtOAc:Hexanes). R_F = 0.30 (30:70 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[C_{15}H_{11}N_3O_6]^+$: *m/z* 329.0648; found, 329.0647.



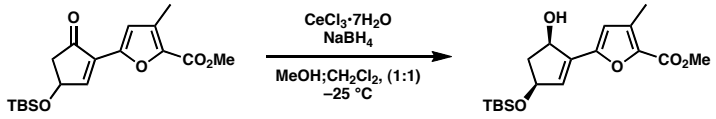
161

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); ^{1}H 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); ^{13}C 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 $[C_{11}H_{11}N_2O_4]^+$: *m/z* 235.0179; found, 235.0174.



163

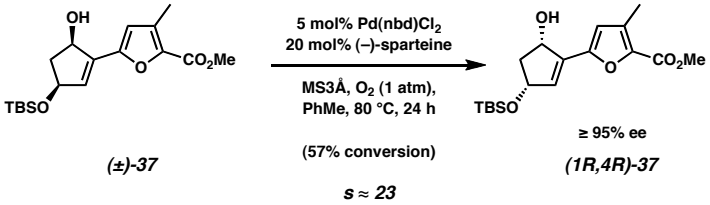
Substrate 163. See General Procedure for the Esterification of Acid **139** (95% yield). Product was purified by flash chromatography (40:60 EtOAc:Hexanes). R_F = 0.25 (40:60 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.32-7.19 (m, 5H), 3.60 (q, *J* = 6.9 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.29 (s, 3H); ^{13}C 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 (EI$^+$) calc'd for $[C_{12}H_{13}N_3O_2]^+$: *m/z* 231.1008; found, 231.1007.



136 (95% yield) 10:1 dr (*syn*:*anti*) ***37***

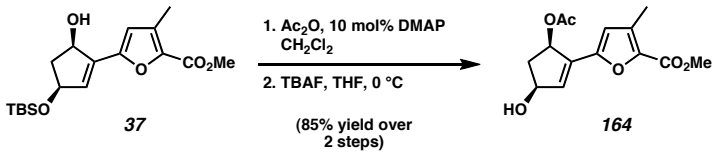
Alcohol 37. To a solution of furan **136** (100 mg, 0.290 mmol, 1.00 equiv) and $CeCl_3$•$7H_2O$ (430 mg, 1.10 mmol, 4.00 equiv) in MeOH:CH_2Cl_2 (4.90 mL, 1:1) at -25 °C, was added sodium borohydride (43.0 mg, 1.10 mmol, 4.00 equiv) portionwise while

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 H_2O. 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 Na_2SO_4, 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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[C_{18}H_{27}O_5Si]^+$: *m/z* 351.1628; found 351.1632.



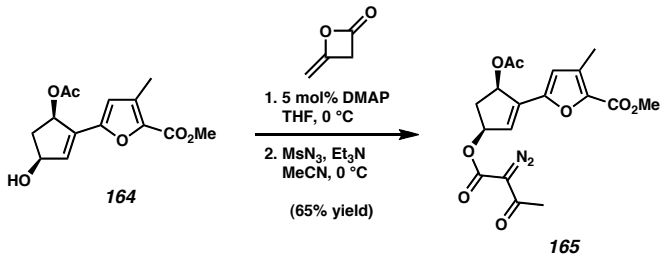
(*1R,4R*)-Alcohol 37. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with powdered molecular sieves (3ÅMS, 150 mg) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (0.380 mg, 1.42 μmol, 0.0500 equiv) was added, followed by toluene (285 μL). To this yellow suspension was added (–)-sparteine (1.33 mg, 5.67 μmol, 0.200 equiv), and the top of the Schlenk tube was then fitted with an O_2 balloon. The reaction was purged under vacuum and replaced with O_2, 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, EtOAc).[42]



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_2O, sat. $NaHCO_3$ (aq.), and brine. The organic layer was then dried with Na_2SO_4, filtered, and concentrated in vacuo to yield an allylic acetate (101 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, *J* = 0.9, 2.1 Hz, 1H), 6.26 (s, 1H), 5.85 (dd, *J* = 4.2, 7.5 Hz, 1H), 4.84 (m, 1H), 3.90 (s, 3H), 2.96 (dt, *J* = 7.5, 14.4 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).

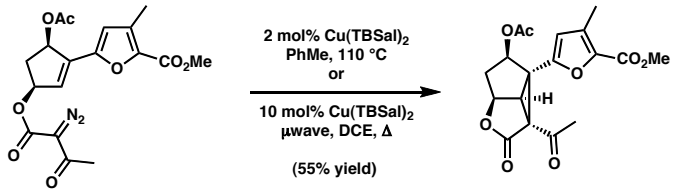
A solution of TBAF (0.290 mL of 1M solution in THF, 0.289 mmol, 1.20 equiv) was added to the crude silyl ether (95 mg, 0.241 mmol, 1.00 equiv) in THF (4.8 mL) at 0 °C and under N_2. The reaction was allowed to warm to ambient temperature and monitored by TLC. Once complete, the reaction was diluted with H_2O, and the reaction was extracted 3x with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, 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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[C_{14}H_{16}O_6]^+$: *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, $CDCl_3$) δ 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 β-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_3N (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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $[C_{18}H_{18}N_2O_8]^+$: *m/z* 390.1063, found 390.1061.

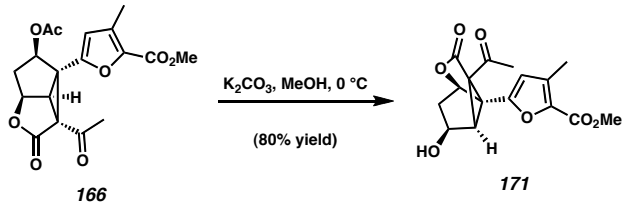


165 ***166***

Cyclopropane 166. ***µwave 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

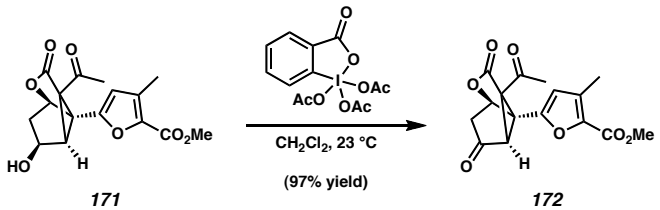
for the μwave are as follows: Power = 150 W, Temperature = 105 °C, Pressure = 200 atm, Ramp = 1 minute, Run Time = 20 minutes. The reaction was concentrated in vacuo, and the resulting crude oil was purified by silica gel chromatography (40:60 EtOAc:hexanes) to yield cyclopropane **166** as a white solid (21 mg, 55%). ^{1}H NMR (500 MHz, C_6D_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_6D_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^{+}) calc'd 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%).



166 *171*

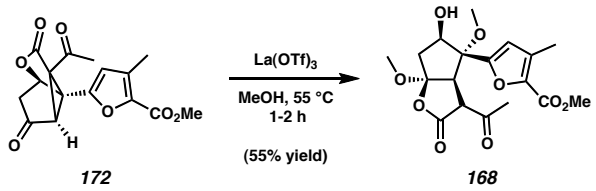
Alcohol 171. K_2CO_3 (32.0 mg, 0.240 mmol, 2.00 equiv) was added to a solution of cyclopropane **166** (43.0 mg, 0.120 mmol, 1.00 equiv) in MeOH (2.30 mL) at 0 °C. The reaction was stirred at 0 °C and monitored by TLC. Once complete, the reaction was diluted with saturated NH_4Cl (aq.) and EtOAc, the layers were then separated, and the aqueous layer was further extracted 2x with EtOAc. The organic layers were combined, washed with H_2O and brine, dried with Na_2SO_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_6D_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_6D_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 $[C_{16}H_{16}O_7Na]^+$: m/z 343.0794, found 343.0811.



171 *172*

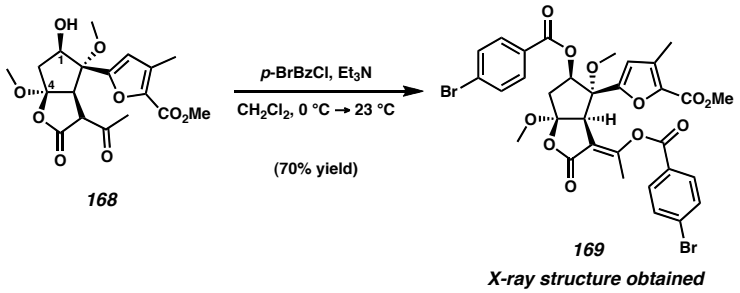
Ketone 172. To a solution of alcohol **171** (62.0 mg, 0.190 mmol, 1.00 equiv) in CH_2Cl_2 (3.90 mL) was added Dess-Martin periodinane (160 mg, 0.390 mmol, 2.00 equiv), and

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 $Na_2S_2O_4$ (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_2SO_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_6D_6) δ 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_6D_6) δ 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.



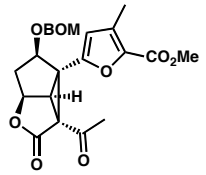
Alcohol 168. Crude ketone **172** (11.0 mg, 0.0340 mmol, 1.00 equiv) and $La(OTf)_3$ (20.0 mg, 0.0340 mmol, 1.00 equiv) were dissolved in MeOH (0.670 mL) at ambient temperature, then heated to 55 °C and stirred until the majority of starting material appeared consumed by TLC. The reaction was diluted with EtOAc and H_2O and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_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_6D_6) δ 5.90 (s, 1H), 4.26 (dd, *J* = 1.7, 5.6

Hz, 1H), 4.24 (m, 1H), 4.04 (d, J = 5.8 Hz, 1H), 3.38 (s, 3H), 3.20 (s, 3H), 2.80 (s, 3H), 2.56 (dd, J = 4.2, 14.2 Hz, 1H), 2.26 (s, 3H), 2.20 (d, J = 14.2 Hz, 1H), 2.15 (s, 3H), 1.84 (d, J = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 170.6, 159.8, 154.1, 140.9, 132.0, 119.4, 115.9, 87.4, 76.9, 60.5, 52.0, 51.5, 51.4, 48.0, 43.7, 29.5, 11.8; IR (film) 3465, 2955, 1771, 1722, 1441, 1297, 1197, 1102 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{18}H_{22}O_9]^+$: m/z 382.1264, found 382.1259.



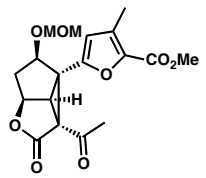
Furan 169. Triethylamine (19.0 mL, 0.140 mmol, 2.40 equiv) was added at ambient temperature to a solution of alcohol **168** (22.0 mg, 0.0580 mmol, 1.00 equiv) in CH_2Cl_2 (310 mL). DMAP (0.700 mg, 0.00580 mmol, 0.100 equiv) and *p*-bromobenzoyl bromide (28.0 mg, 0.130 mmol, 2.20 equiv) were then added, and the reaction stirred for 1 hour at ambient temperature. The reaction was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was washed once with EtOAc. The EtOAc layers were combined, washed with saturated $NaHCO_3$ (aq.), washed with brine, dried with Na_2SO_4, 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. ^{1}H NMR (500 MHz, C_6D_6) 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); ^{13}C NMR (125 MHz, C_6D_6) δ 168.1, 164.6, 161.9, 161.6, 159.2, 152.9,

141.0, 132.1, 132.0, 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 $[C_{32}H_{30}O_{11}Br^{81}Br]^+$: *m/z* 750.0135, found 750.0159. mp = 175-177 °C (heptane/EtOAc).



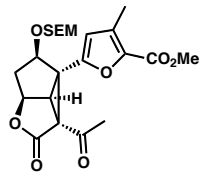
173

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, C_6D_6) 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); ^{13}C NMR (125 MHz, C_6D_6) 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 $[C_{24}H_{23}DO_8]^+$: *m/z* 441.1534, found 441.1523.



174

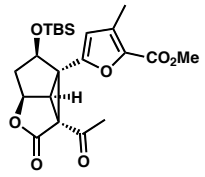
Cyclopropane 174. Cyclopropane **174** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane **174** was obtained as an oil (2.3 mg, 62%). ^{1}H NMR (500 MHz, C_6D_6) δ 5.95 (s, 1H), 4.78 (d, *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_6D_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.



175

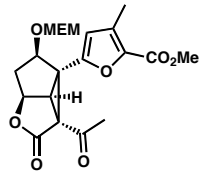
Cyclopropane 175. Cyclopropane **175** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane **175** was obtained as an oil (2.9 mg, 62%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.02 (s, 1H), 4.94 (d, *J* = 7.1Hz, 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* = 4.6Hz, 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_6D_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 $[C_{22}H_{29}DO_8SiNa]^+$: *m/z* 474.1773, found 474.1675.



176

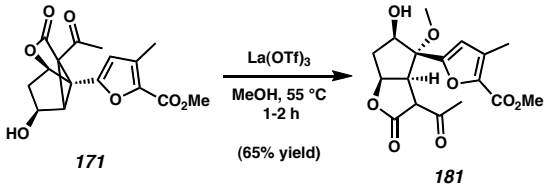
Cyclopropane 176. Cyclopropane **176** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane **176** was obtained as an oil (6.5 mg, 71%). ^1H NMR (500 MHz, C_6D_6) δ 5.71 (s, 1H), 4.15-4.13 (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_6D_6) δ 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 $[C_{22}H_{29}DO_7SiNa]^+$: *m/z* 459.1800, found 458.1749.



177

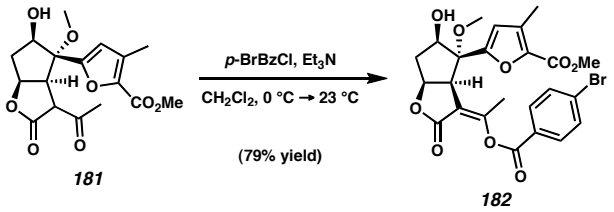
Cyclopropane 177. Cyclopropane **177** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, thermal conditions were used, and cyclopropane **177** was

obtained as an oil (9.1 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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^{-1}; HRMS (EI^{+}) calc'd for $[C_{20}H_{23}DNaO_9]^{+}$: *m*/*z* 432.1381, found 432.1365.



Alcohol 181. Furan **171** (49.0 mg, 0.153 mmol, 1.00 equiv) and La(OTf)$_3$ (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_2O and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_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%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, C_6D_6) δ 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 $[C_{17}H_{21}O_8Na]^+$: *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_2Cl_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_2O and H_2O, the layers were separated, and the aqueous layer was washed once with Et_2O. The Et_2O 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. ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $[C_{24}H_{23}BrO_9]^+$: *m/z* 557.0423, found 557.0427. mp = 158-159 °C (EtOAc:Heptane).

2.10 Notes and References

[1] Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sanchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661–1664.

[2] For verrillin, see: Rodriguez, A. D.; Shi, Y. P. *J. Org. Chem.* **2000**, *65*, 5839–5842.; For ineleganolide, see: Duh, C. Y.; Wang, S. K.; Chiang, M. Y. *Tetrahedron Lett.* **1999**, *40*, 6033–6035.; For scabrolide A, see; Sheu, J. H.; Ahmed, A. F.; Shiue, R. T.; Dai, C. F.; Kuo Y. H. *J. Nat. Prod.* **2002**, *65*, 1904–1908.

[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.

[5] (a) Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345–347. (b) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901–5904.

[6] For example, bipinnatin A can undergo two different cycloisomerization reactions to provide two known natural products. For examples, see: (a) Rodriguez, A. D.; Shi, J.-G. *J. Org. Chem.* **1998**, *63*, 420–421. (b) Rodriguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 4425–4432.

[7] Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903–906.

[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 σ-bond rotation is, as well as its impact on the diastereoselectivity.

[9] Miao, R.; Subramanian, G. G.; Lear, M. L. *Tetrahedron Lett.* **2009**, *50*, 1731–1733.

[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.

[11] Khatuya, J. *Tetrahedron Lett.* **2001**, *42*, 2643–2644.

[12] (a) Knochel, P.; Cahiez, G.; Rottlander, M.; Boymond, L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701–1703. (b) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 3333–3336.

[13] Myers, A.; Dragovich, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 7021–7022.

[14] Johnson, C. R.; Braun, M. P.; Ruel, F. S. *Org. Synth.* **1996**, *75*, 69–72.

[15] For a related system that provides nonsymmetrical α-diazomalonates, see: Kido, F.; Yamaji, K.; Abiko, T.; Kato, M. *J. Chem. Res.* **1993**, 18–19.

[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.

[18] Meyer, M. E.; Ferreira, E. M.; Stoltz, B. M. *Chem. Commun.* **2006**, 1316–1318.

[19] For examples of α-diazo-β-ketoamides, see: (a) Jeganathan, A.; Richardson, S. K.; Mani, R. S.; Haley, E. B.; Watt, D. S. *J. Org. Chem.* **1986**, *51*, 5362–5367. (b) Padwa,

A.; Zhi, L. *J. Am. Chem. Soc*. **1990**, *112*, 2037–2038. (c) Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L. *J. Org. Chem*. **1993**, *58*, 4646–4655.

[20] For examples of $Cu(TBSal)_2$ being used in total synthesis, see: (a) Corey, E. J.; Myers, A. G. *Tetrahedron Lett*. **1984**, *25*, 3559–3562. (b) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc*. **1987**, *109*, 4717–4718. (c) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc*. **1987**, *109*, 6187–6189. (d) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc*. **1994**, *116*, 3125–3126. (e) Fernandez, M. A.; Barba, L. *J. Org. Chem*. **1995**, *60*, 3580–3585.

[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".

[22] Germal, A. L.; Luche, J. L. *J. Am. Chem. Soc*. **1981**, *103*, 5454–5459.

[23] For a study of reduction conditions for a similar enone, see: Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983–2004.

[24] Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc*. **2001**, 123, 7725–7726.

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

[26] Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1991**, 113, 7277–7287.

[27] Deuterium labeling may not be needed if the ^1H NMR spectra of cyclopropane **166**, alcohol **171**, and ketone **172**, are attained in C_6D_6, and each spectrum is analyzed and compared. The spectra, in C_6D_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.

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

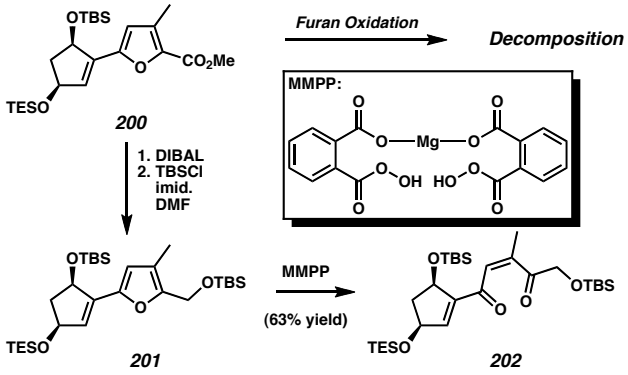
[30] For examples of nucleophilic addition into a cyclopropane ring, see: (a) Danishefsky, S.; Dynak, J. *J. Org. Chem.* **1974**, *39*, 1979–1980. (b) Isobe, M.; Lio, H.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1978**, *100*, 1940–1942. (c) Callant, P.; Wilde, H. D.; Vaderwalle, M. *Tetrahedron* **1981**, *37*, 2079–2084.

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

[32] For an example of a domino Michael addition followed by an aldol addition to provide a fused cyclobutane ring, see: (a) Ihara, M.; Toyota, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. I* **1986**, 2151–2161. (b) Ihara, M.; Ohnishi, M.; Takano, M. *J. Am. Chem. Soc.* **1992**, *114*, 4408–4410. (c) Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1993**, *115*, 8107–8115. (d) Takasu, K.; Misawa, K.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 8489–8491. (e) Stelmakh, A.; Stellfeld, T.; Kalesse, M. *Org. Lett.* **2006**, *8*, 3485–3488.

[33] (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260. (b) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131–1134. (c) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5055–5058.

[34] Furan **200** can be treated with MMPP to provide enedione **202** in an unoptomized 63% yield:



[35] Roizen, J. L.; Progress Toward an Enantioselective Total Synthesis of Ineleganolide. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 2009.

[36] Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936–2939.

[37] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958–964.

[38] Doyle, M. P.; Davies, S. B.; May, E. J. *J. Org. Chem.* **2001**, *66*, 8112–8119.

[39] 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.

[40] Reul, F. S.; Braun, M. P.; Johnson, C. R. *Org. Synth.* **1996**, *75*, 69–72.

[41] Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729–3732.

[42] For a separate sample, alcohol **37** at 70% ee, gave an $[\alpha]_D^{24.9}$ +16.9.