CHAPTER TWO

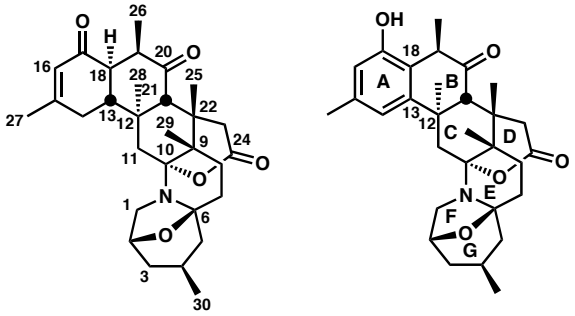
Early Approaches to the Synthesis of Zoanthenol

2.1 Synthetic Planning

2.1.1 *Introduction*

In late 2000, our laboratory became interested in the total synthesis of the zoanthamine alkaloids. At that time, Tanner[1] and Williams[2] had published the most comprehensive strategies toward the total synthesis of these natural products. In 1998, Kobayashi[3] and Williams[4] had described routes for the construction of the heterocyclic portion of these molecules. No work had yet been published toward the total synthesis of zoanthenol. Our interest in zoanthenol was piqued by its unique aromatic A ring. Aromatization of the A ring removes the C(13) and C(18) stereocenters from the zoanthamine skeleton (Figure 2.1). Despite this simplification, we felt that zoanthenol still embodied the core challenges of the zoanthamines. Additionally, the aromatic A ring allowed us to consider a number of disconnections of the C(12)-C(13) bond that were not readily applicable to the non-aromatic zoanthamines.

Figure 2.1 Zoanthamine and Zoanthenol



Zoanthamine *(5)* **Zoanthenol *(21)***

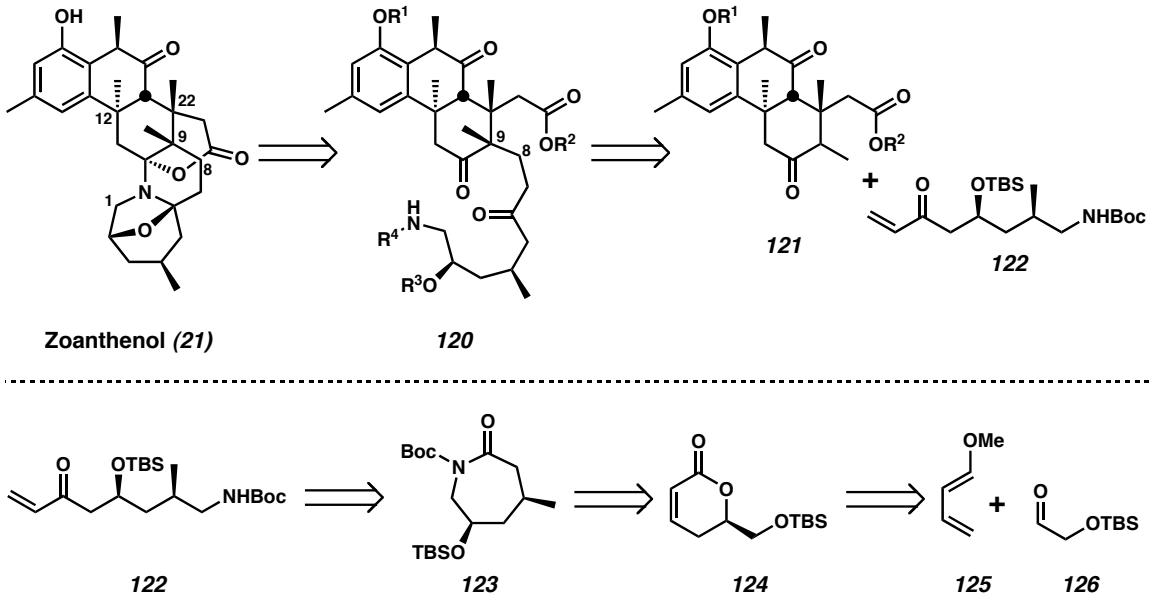
2.1.2 *Retrosynthesis*

Zoanthenol is a densely functionalized, topographically complex target molecule. Though only a C_{30} molecule, it is comprised of seven rings and nine stereocenters. The C ring poses the single greatest stereochemical challenge with three quaternary centers and five contiguous stereocenters (Scheme 2.1). The quaternary stereocenters are disposed in vicinal (C(9) and C(22)) and remote (C(12) and C(22)) relationships. Our overarching strategy in assembling the C ring was to generate one of these quaternary centers in enantioenriched fashion, and then derive the rest of the stereocenters in a highly diastereoselective manner. Another design feature common to all our strategies was to unite A and C ring synthons in a convergent manner by forging the B ring. With respect to the heterocyclic portion of the molecule, our goal was to introduce all the functionality of the C(1) to C(8) fragment in a single operation.

Our disconnections began with the heterocyclic portion of the molecule. Previous work had demonstrated that the complicated hemiaminals forming the DEFG rings were thermodynamically favored.[3,4] Thus, retrosynthetically, the heterocycles could be unraveled to give triketone **120** with a linear C(1) to C(8) side chain (Scheme 2.1). Disconnection of the C(8)-C(9) bond in the sense of a conjugate addition of an enamine affords methyl ketone **121** and enone **122**. Enone **122** may be derived from a vinyl anion addition to the amide carbonyl of caprolactam **123**. Caprolactam **123** may be simplified to lactone **124** by conjugate methyl addition and amination. Ultimately, lactone **124** may arise in enantioenriched form via an asymmetric hetero Diels-Alder reaction pioneered by Jacobsen and coworkers.[5] The synthesis of optically active caprolactam **123** was carried

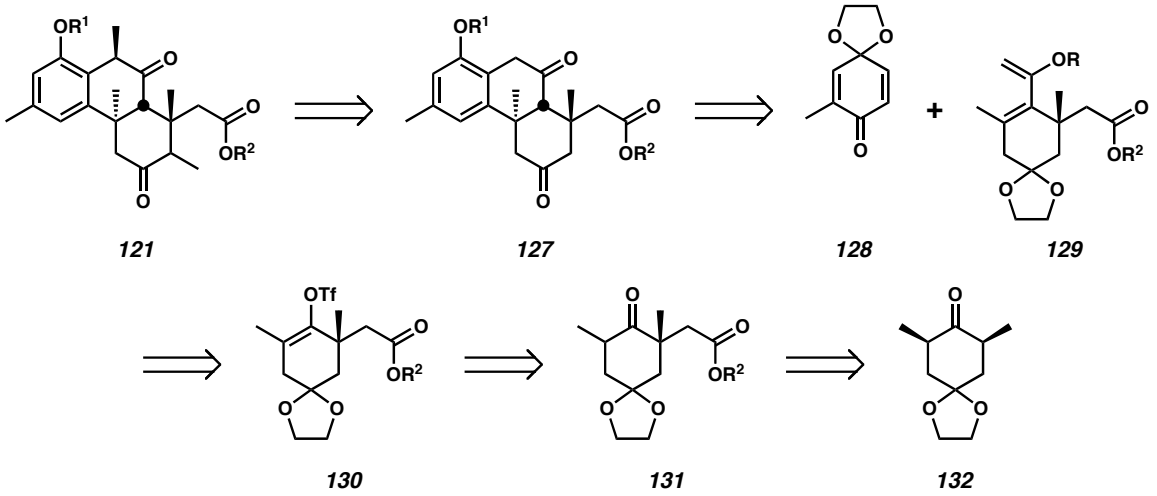
out by Dr. Jeffrey Bagdanoff, a former graduate student in the lab, and has been detailed elsewhere.[6]

Scheme 2.1 Retrosynthetic Analysis of Zoanthenol



Further simplification of methyl ketone **121** commences by removing the methyl group at C(9) to afford tricyclic diketone **127** (Scheme 2.2). Oxidation state adjustment and Diels-Alder disconnection across the B ring of diketone **127** yields the known mono-protected quinone **128**[7] and diene **129** as target fragments. Diene **129** could be assembled by Stille coupling involving enol triflate **130**, which could in turn be derived from ketoester **131**. Finally, asymmetric deprotonation of meso ketone **132** and reaction with an appropriate electrophile could afford ketoester **131** in enantioenriched form.

Scheme 2.2 Retrosynthetic Analysis of Zoanthenol's ABC Ring System

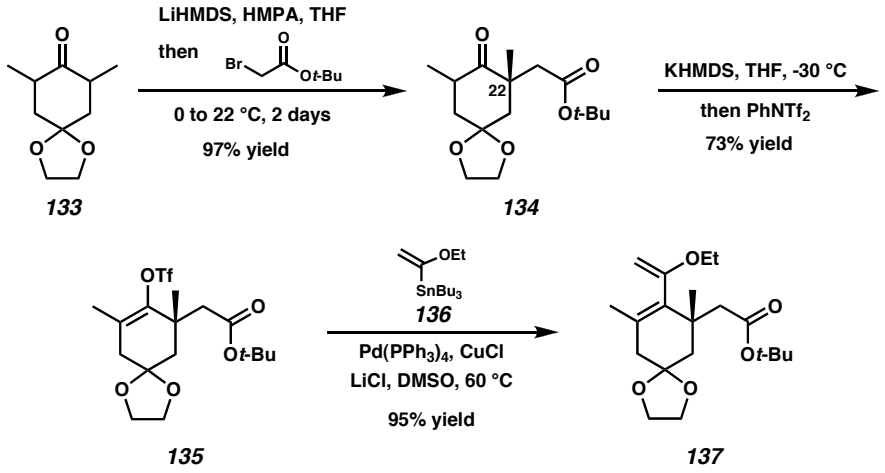


2.2 A Diels-Alder Approach to the Zoanthenol ABC Ring System

2.2.1 *Racemic Synthesis of the Substrate Diene*

In order to determine the feasibility of the quinone Diels-Alder strategy, the target diene was synthesized racemically (Scheme 2.3). Known dimethyl ketone **133**[8,9] was deprotonated with LiHMDS and alkylated with *t*-butyl bromoacetate in the presence of HMPA to give ketoester **134** in excellent yield as a mixture of diastereomers. Low temperature deprotonation of ketoester **134** with KHMDS and quenching with $PhNTf_2$ afforded enol triflate **135**, which underwent Stille coupling with vinyl stannane **136** to produce a diene **137** in excellent yield. The use of copper (I) chloride promoted Stille coupling conditions, reported by Corey, was essential.[10] Numerous other conditions failed to give significant amounts of diene **137**.

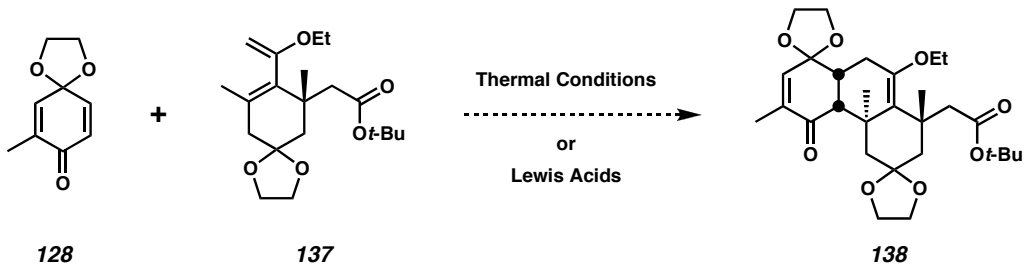
Scheme 2.3 Diene Synthesis



2.2.2 *Diels-Alder Reactions for B Ring Synthesis*

With quantities of both quinone **128** and diene **137** in hand, numerous trials to effect Diels-Alder reaction were performed. Thermal reaction of the two reactants up to 180 °C failed to give any Diels-Alder adducts. Treatment with Lewis acids including tin (IV) chloride, titanium (IV) chloride, ethyl aluminum dichloride, TBSOTf, methyl aluminum dichloride, and $TiCl_2(O\textit{i}\text{-}Pr)_2$ also failed to give a productive reaction.[11] More asynchronous or stepwise versions of the reaction that replaced ethyl enol ether **137** with its enolate equivalent did not produce any of the desired C-C bonds.

Scheme 2.4 Attempted Diels-Alder Reactions

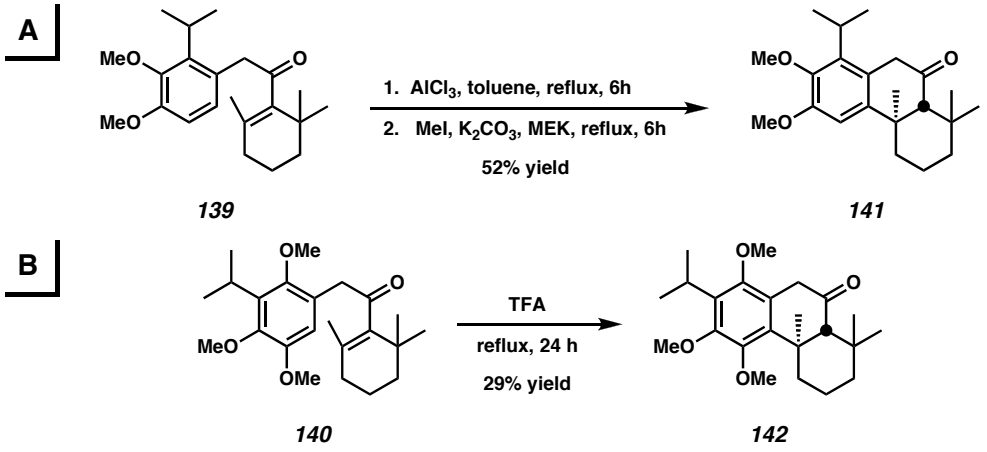


2.3 An Intramolecular Conjugate Addition Approach to the Zoanthenol ABC Rings

2.3.1 *Revised Retrosynthetic Analysis*

As a result of our inability to construct the B ring in a single Diels-Alder reaction, we considered strategies that would construct the B ring in a stepwise manner. One such strategy with good historical precedent was the intramolecular conjugate addition of electron-rich arenes into enones. This reaction has been demonstrated with steric environments as demanding as zoanthenol, as shown with enones **139** and **140** (Scheme 2.5).[12] These cyclizations were commonly employed in syntheses of Abietane natural products.[13] This Friedel-Crafts cyclization has been shown to proceed under either strongly Lewis acidic or Brønsted acidic conditions, but the reaction does require an extremely electron-rich arene for effective cyclization.[14]

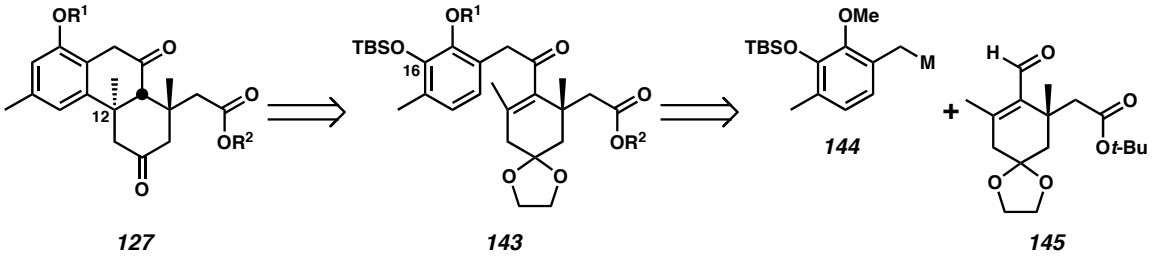
Scheme 2.5 Intramolecular Conjugate Additions in the Synthesis of Abietane Skeleton



Encouraged by the ability of such intramolecular 6-*endo* conjugate additions to form difficult benzylic quaternary centers, analogous to zoanthenol's C(12) stereocenter, we altered our retrosynthesis of diketone **127** to incorporate this disconnection (Scheme

2.6). In order to increase the nucleophilicity of the aromatic ring and facilitate conjugate addition, oxygenation was incorporated at C(16) of enone **143**. In turn, we envisioned enone **143** could arise by 1,2-addition of organometallic reagent **144** into enal **145**.

Scheme 2.6 Intramolecular Conjugate Addition Approach

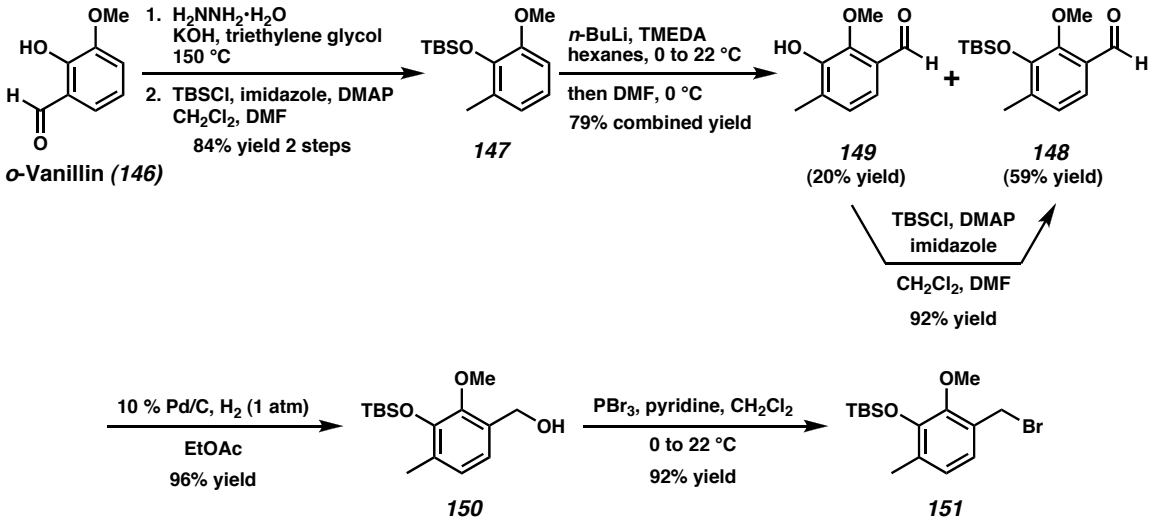


2.3.2 *Synthesis of A Ring Fragment*

The synthesis of the A ring synthon commenced with Wolff-Kishner reduction[15] of *o*-vanillin (**146**) and silyl protection to afford arene **147** in 84% yield over two steps after distillation (Scheme 2.7). Methoxy-directed *ortho*-lithiation of arene **147** and quenching with N,N′-dimethylformamide (DMF) afforded a mixture of the desired benzaldehyde **148** and desilylated benzaldehyde **149**. After chromatographic separation, phenol **149** was readily resilylated under standard conditions to provide additional benzaldehyde **148**. Carefully monitored reduction of benzaldehyde **148** with 10% Pd/C under a balloon of hydrogen afforded an excellent yield of benzylic alcohol **150**. If alcohol **150** was allowed to persist under the reaction conditions for several additional hours after the consumption of benzaldehyde **148**, significant over-reduction was observed. Benzylic alcohol **150** was converted with phosphorus tribromide and pyridine to benzyl bromide **151** in 92% yield after distillation. Benzyl bromide **151** was

anticipated to allow for the synthesis of several potential organometallic nucleophiles. Overall, the synthesis of the A ring synthon was efficient and scalable. We routinely produced 20-25 g of benzyl bromide **151** per batch.

Scheme 2.7 Synthesis of A Ring Benzyl Bromide



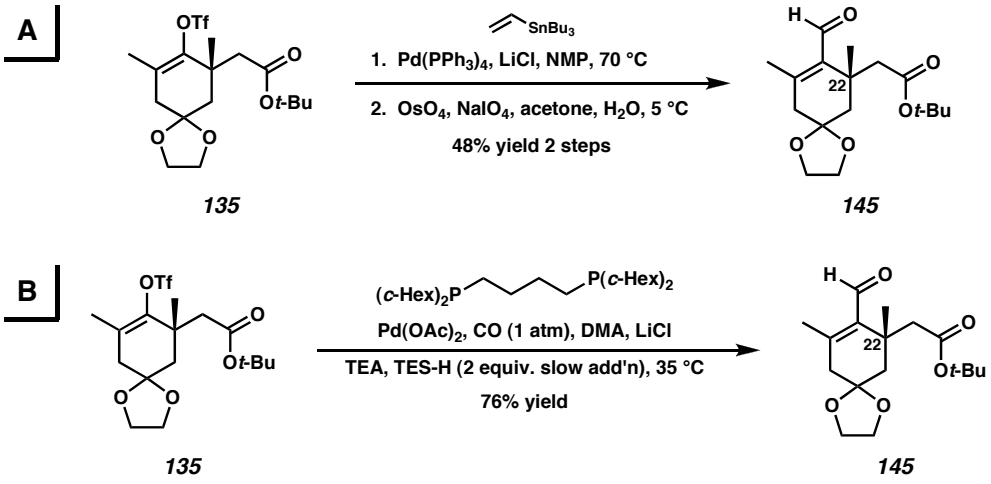
2.3.3 *Synthesis of the C Ring Synthon*

Two syntheses of the desired enal **145** were developed starting from intermediate triflate **135** (Scheme 2.8). A two-step approach involved Stille coupling with vinyl tributyltin to produce an intermediate diene. Oxidative cleavage with osmium (VIII) tetraoxide (OsO_4) and sodium periodate gave enal **145** (Reaction A). This route had several disadvantages. The oxidative cleavage required a minimum of 5 mol% of the expensive and toxic OsO_4 to consume all the hindered diene. In addition, modest yields in the oxidative cleavage resulted from poor olefin selectivity during the dihydroxylation.

As a result of these difficulties, a one-step palladium-catalyzed carbonylation method was developed for the synthesis of enal **145** (Reaction B). Treatment of triflate

135 under an atmosphere of carbon monoxide with palladium (II) acetate, 1,4-bis-(dicyclohexylphosphino)butane as a ligand, and TES-H as a reducing agent afforded the desired enal **145** in good yield. The use of this bulky, electron-rich bisphosphine ligand was essential. For example, the use of 1,4-bis(diphenylphosphino)butane (DPPB) afforded significant amounts of the corresponding reduced olefin. Additionally, the slow addition of the hydride source, TES-H, was necessary to minimize direct reduction of triflate **135**. While operationally demanding, this reaction greatly improved the efficiency and throughput in making enal **145**.[16]

Scheme 2.8 Syntheses of C Ring Enal



2.3.4 *Asymmetric Tsuji Allylation for the Synthesis of C Ring Enal **145***

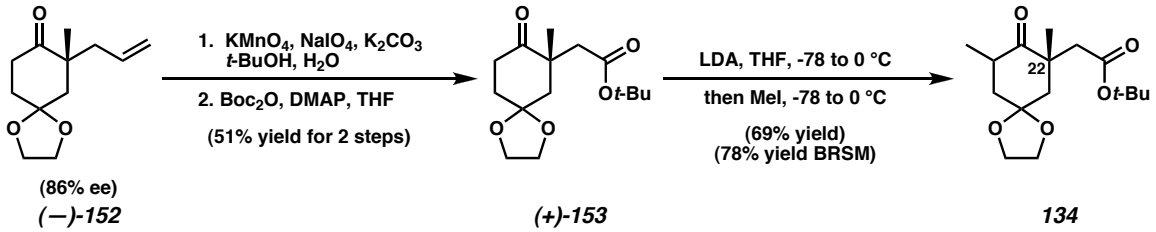
Although racemic material was adequate for exploratory studies, our goal from the outset was the catalytic asymmetric total synthesis of zoanthenol. In accord with our strategy to set a single enantiopure stereocenter and relay that stereochemistry

diastereoselectively throughout the structure, we considered several approaches to set the C(22) quaternary stereocenter in ketoester **134** enantioselectively (Scheme 2.3).

Our first strategy was based on the enantioselective deprotonation of *meso*-ketones. The use of chiral lithium amides for asymmetric deprotonation of ketones was pioneered by Koga[17] and refined by Simpkins.[18] While we had some success in the desymmetrization of *meso*-ketone **132**, the use of stoichiometric amounts of chiral lithium amides seemed impractical on scale.[19]

Ultimately, we found that the asymmetric Tsuji allylation methodology developed in our laboratory was a reliable and efficient method to produce enantioenriched ketoester **134** (Scheme 2.9). Quaternary (*S*)-(–)-ketone **152** could be produced in good ee from several enolate precursors by a palladium (0) phosphinooxazoline catalyst.[20] Oxidative olefin cleavage and esterification gave (+)-*t*-butyl ester **153** in 51% yield over two steps. Methylation of (+)-*t*-butyl ester **153** under standard conditions gave a separable mixture of diastereomeric methyl ketoesters **134**, an intermediate in our racemic C ring synthesis.

Scheme 2.9 Asymmetric Synthesis of Ketoester **134**

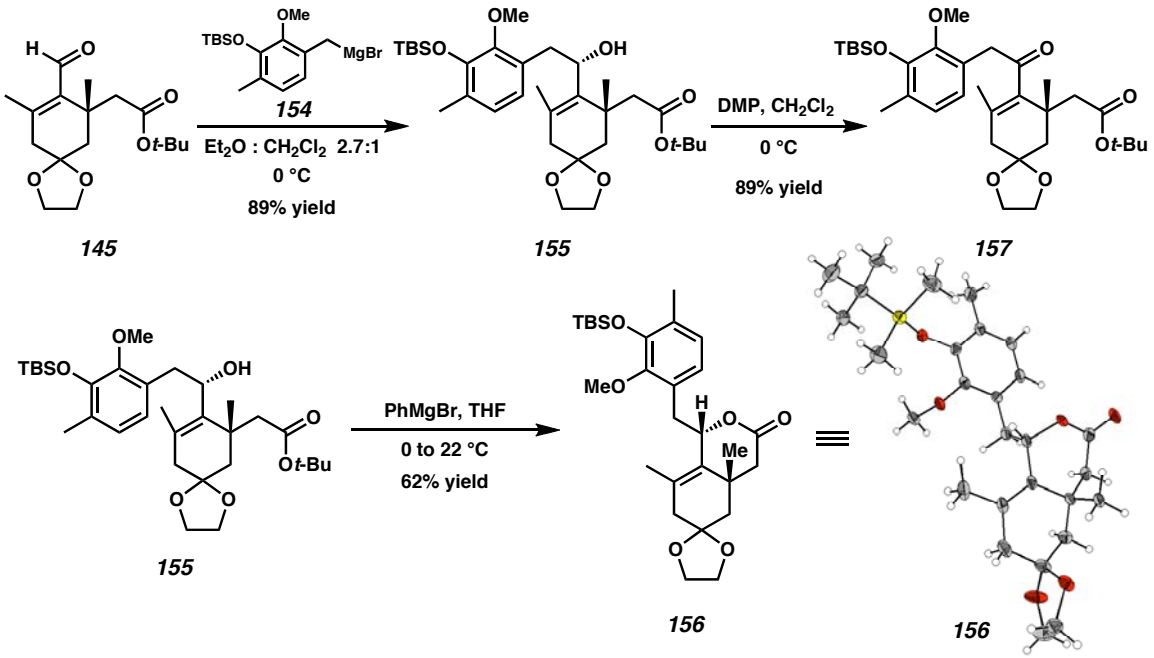


2.3.5 *Fragment Coupling and Cyclization Attempts*

With the new A and C ring fragments available, work to complete an intramolecular conjugate addition substrate began (Scheme 2.10). Treatment of benzyl

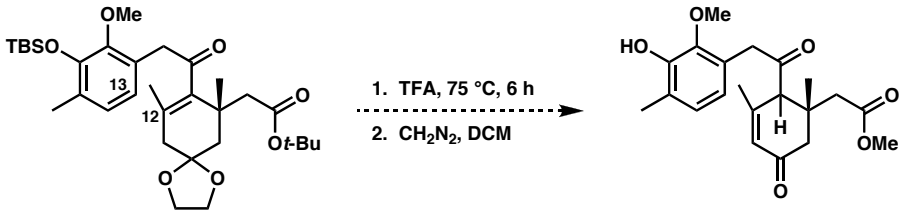
bromide **151** with magnesium turnings in refluxing ethyl ether afforded good conversion to Grignard reagent **154**. While the generation of Grignard reagent **154** was highly reproducible, it should be noted that analogous benzyl bromides with different protecting groups (e.g., methoxy replaced with BOM) afforded very poor yields of organomagnesium and organozinc reagents. Grignard reagent **154** was added immediately upon generation to enal **145** to produce allylic alcohol **155**. We found that the use of methylene chloride as a cosolvent improved the diastereoselectivity of the 1,2-addition and minimized the formation of lactone **156** in situ. Fortuitously, lactone **156**, which could be intentionally formed by deprotonation in ethereal solvents, was amenable to X-ray structure determination and established the relative configuration of the newly formed alcohol stereocenter. Simple Dess-Martin oxidation of allylic alcohol **155** provided the desired enone **157**.

Scheme 2.10 Grignard Addition



Enone **157** was subjected to numerous acidic conditions that were precedented to affect intramolecular cyclization (Scheme 2.11). However, none produced the desired C(12)-C(13) bond.[21] Treatment with trifluoroacetic acid (TFA) followed by methylation afforded a mixture of products resembling enone **158**. This tentative structural assignment piqued our interest in the possibility of a 6-*exo* acid-mediated cyclization.

Scheme 2.11 Attempted Cyclization



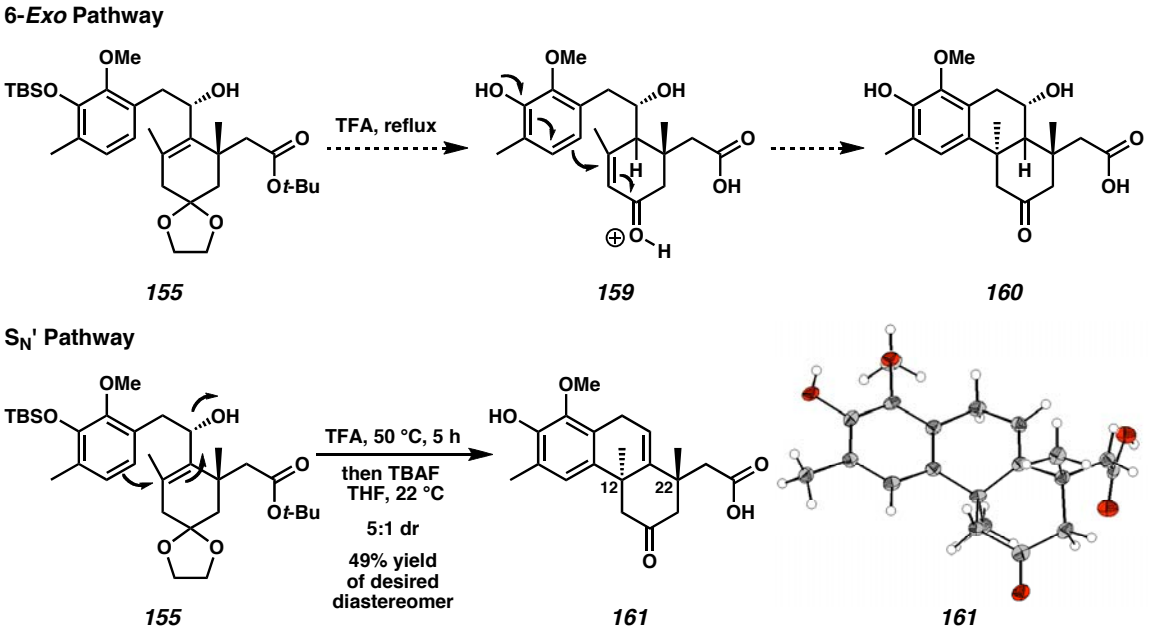
157 *158*

2.4 Development of an S_N' Strategy for the Zoanthenol ABC Ring System

In order to examine the possibility of 6-*exo* cyclization, allylic alcohol **155** was exposed to refluxing TFA (Scheme 2.12). We anticipated the loss of protecting groups and olefin migration would afford enone **159**. Enone **159** could then undergo 6-*exo* conjugate addition giving keto alcohol **160**. The major product isolated from the reaction contained a single aromatic C-H by ^{1}H NMR, suggesting that cyclization had occurred. However, the presence of another olefinic proton in the NMR suggested an elimination had occurred. Proton NMR also showed a roughly 5:1 mixture of diastereomeric acids, which were chromatographically separable. To our delight, upon standing in $CDCl_3$, the major product formed crystals suitable for X-ray diffraction. Cyclization of allylic alcohol **155** had indeed occurred, but not by the anticipated 6-*exo* mechanism. Instead,

an S_N' cyclization had produced acid **161**.[22] The solid state structure confirmed the desired *trans* disposition of the methyl groups at C(12) and C(22). Optimized conditions, including lowering the temperature to 50 °C and desilylation of the crude reaction mixture with TBAF afforded a 49% yield of diastereomerically pure acid **161**.[23]

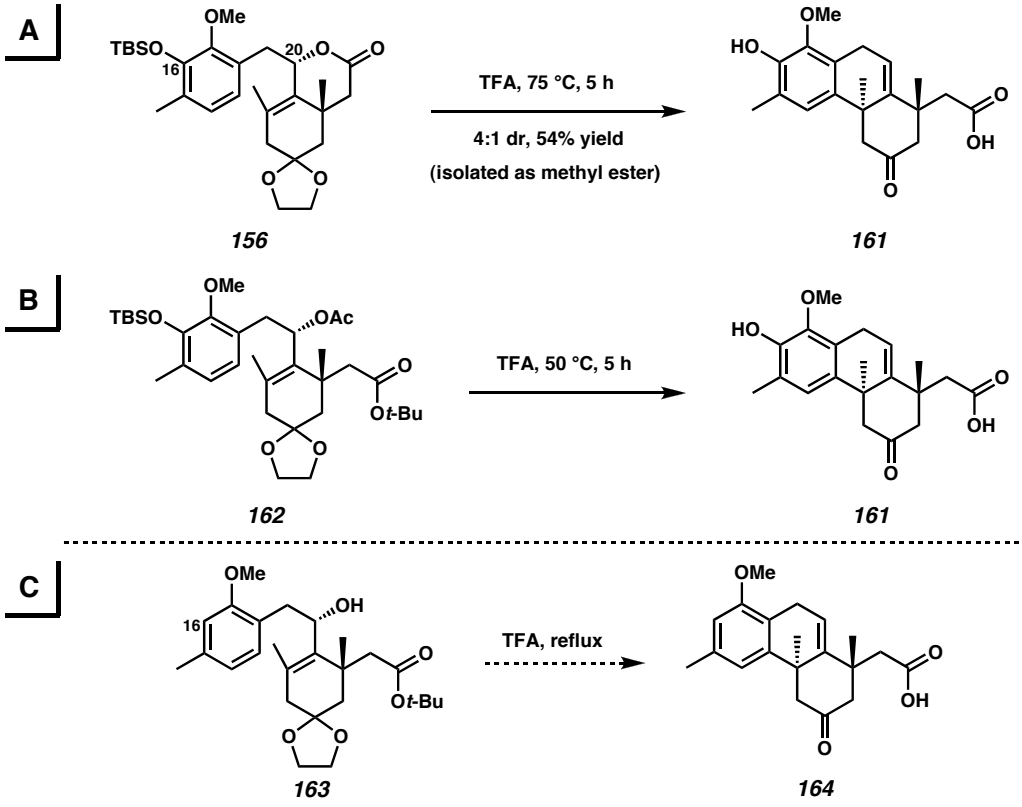
Scheme 2.12 Trifluoroacetic Acid-Mediated Cyclization



The S_N' Friedel-Crafts reaction to produce carboxylic acid **161** achieved the important goal of generating the C(12) quaternary stereocenter with the desired relative configuration. In order to improve the yield and better understand the reaction pathway, a number of modifications were evaluated. The choice of acid in the reaction is crucial. Trifluoroacetic acid was unique in promoting S_N' cyclization. Both stronger acids (e.g., triflic acid) and weaker acids (e.g., acetic acid) failed to produce carboxylic acid **161**. Even the dilution of neat TFA with methylene chloride, benzene, or acetic acid caused

nearly complete inhibition of cyclization. Interestingly, both lactone **156** and allylic acetate **162**[24] underwent cyclization in TFA to give acid **161** with similar yields and diastereoselectivities as allylic alcohol **155** (Scheme 2.13).[25] The des-oxy arene **163** failed to generate any cyclized products, even under forcing conditions. This confirmed the importance of the arene nucleophilicity imparted by C(16) oxygenation. Additionally, compounds analogous to lactone **156** and allylic alcohol **155**, but epimeric at C(20), failed to cyclize when treated under the same conditions.

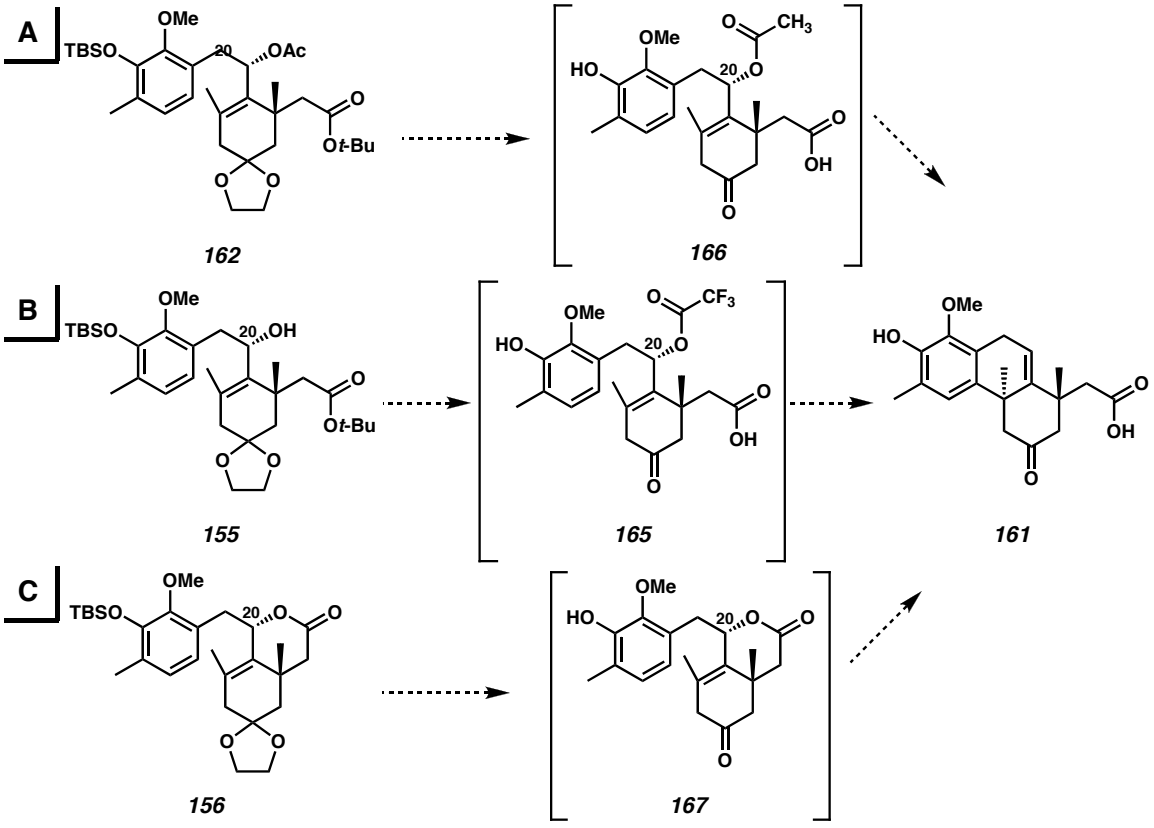
Scheme 2.13 Further Substrates for TFA-Mediated S_N' Cyclization



Taken together, these experiments give some insight into the likely pathways for the S_N' reaction (Scheme 2.14). The unique ability of TFA, among numerous other Lewis and Brønsted acids, to mediate the reaction suggests that its properties as a strong acid, a

dehydrating agent, and a good leaving group (as a trifluoroacetate) are important to the reaction mechanism. It seems likely that all three substrates proceed through an intermediate with a leaving group at C(20). Allylic alcohol **155** may be converted to intermediate trifluoroacetate **165** in situ,[26] while the other substrates already contain good leaving groups. Because the C(20) epimers of the substrates do not readily undergo cyclization, it seems likely that the reactions proceed via a concerted displacement that relies on the trajectory of the leaving group, rather than through a full allyl cation.

Scheme 2.14 Possible Pathways in the S_N' Reaction



2.5 Elaboration Toward the Zoanthenol ABC Ring System

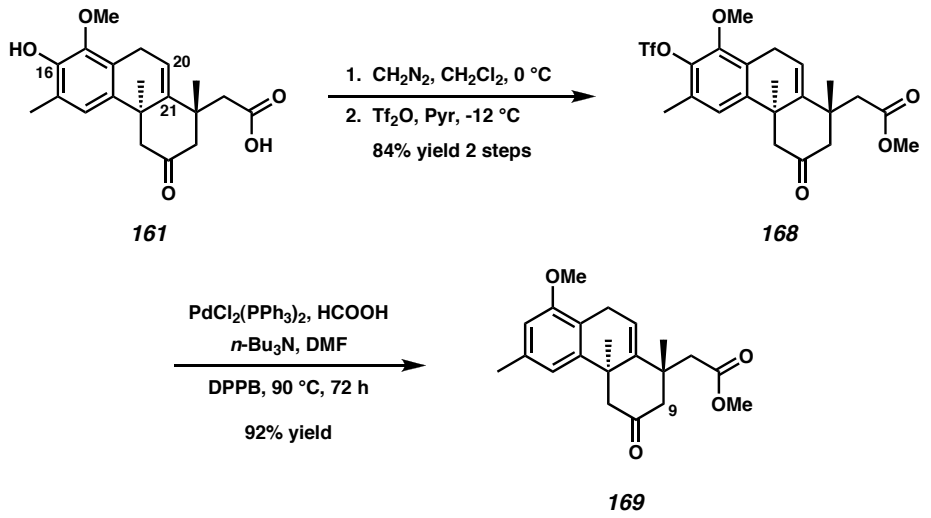
2.5.1 *General Remarks*

With an efficient route in hand to construct the zoanthenol ABC ring system with two of the three quaternary stereocenters, we turned our attention to adjusting the functionality on the rings to complete the synthesis. Our objectives were the removal of the now superfluous phenol and the reoxygenation of the olefin in carboxylic acid **161**.

2.5.2 *Reduction of the Phenol*

The C(16) phenol moiety had served only to increase the nucleophilicity of the arene in the cyclization. With that complete, our next task was its deoxygenation (Scheme 2.15). Esterification of carboxylic acid **161** with diazomethane followed by treatment with triflic anhydride and pyridine afforded aryl triflate **168** in good yield for the two steps. The reduction of congested bis-*ortho* substituted aryl triflates are typically difficult. However, conditions specifically designed for such substrates,[27] involving a number of potential hydride sources, proved highly effective in producing deoxygenated ketoester **169**. Ketoester **169** was an important branch point. It provided a suitable substrate to investigate both the installation of the C(9) substituents and the olefin oxygenation.

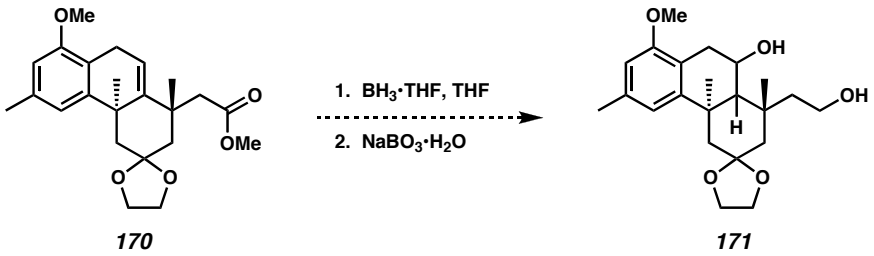
Scheme 2.15 A Ring Deoxygenation



2.5.3 *Olefin Refunctionalization*

Due to our serendipitous discovery of the S_N' reaction, we had not anticipated the reoxygenation of the olefin in our retrosynthetic planning. Significant experimentation was required to find a synthetic strategy to reoxygenate the olefin of ketoester **169**. A number of atom-transfer oxidations were considered. Epoxidation conditions based on *m*CPBA, DMDO, UHP,[28] iron (III) acetylacetate and hydrogen peroxide,[29] hexafluoroacetone and hydrogen peroxide,[30] potassium permanganate and copper (II) sulfate,[31] and methyltrioxorhenium and hydrogen peroxide[32] all failed to give the desired oxidation.[33] Hydroboration of ester **170** with BH_3•THF did appear to affect hydroboration from both faces of the olefin. However, the products also seemed to have undergone reduction of the ester functionality and were inseparable (Scheme 2.16). Milder and more sterically demanding hydroborating reagents either caused ester reduction or failed to react at all.

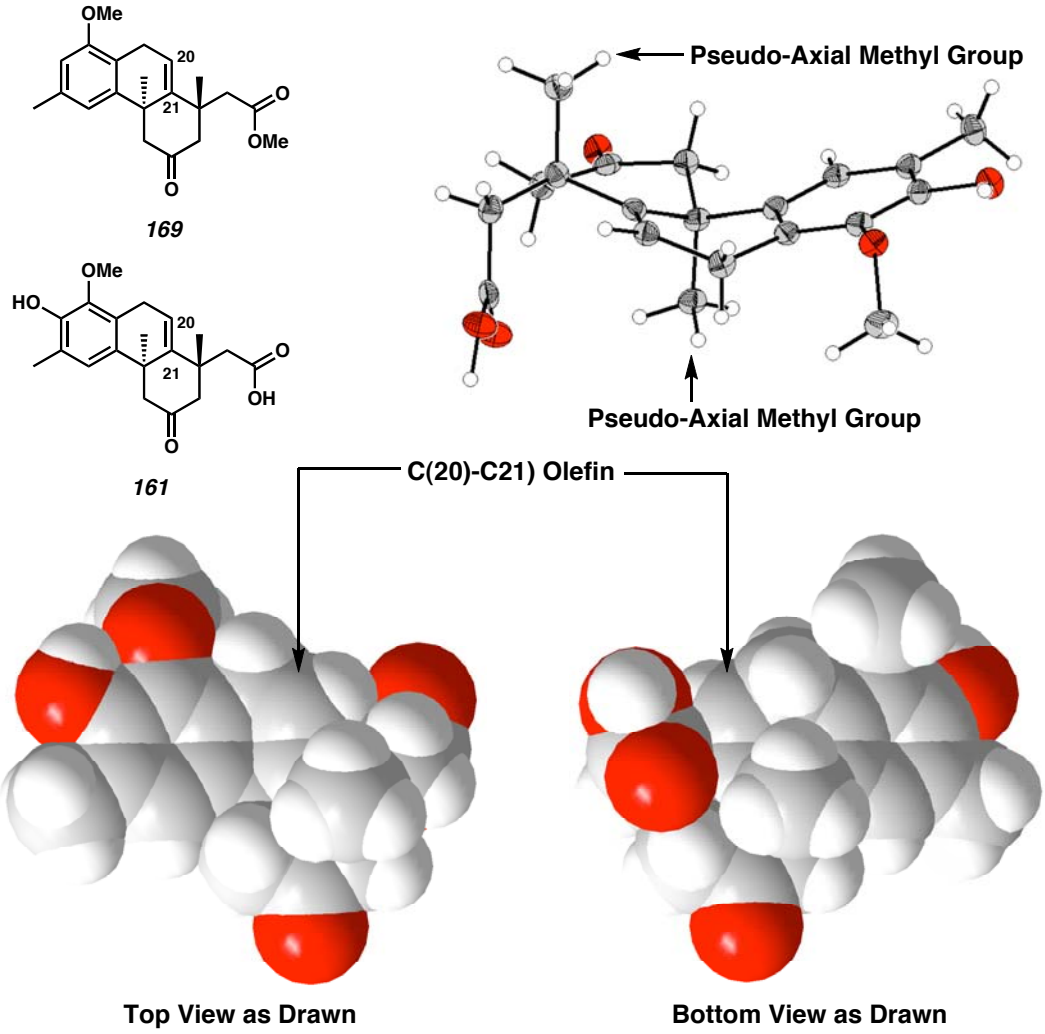
Scheme 2.16 Hydroboration of Ester **170**



170 *171*

These difficulties were largely attributed to steric encumbrance around the C(20)-C(21) olefin. Figure 2.2 shows representations of the solid state structure of carboxylic acid **161**. While it is often problematic to infer solution conformations from solid state structures, the rigid nature of the carbocyclic system found in carboxylic acid **161** and ketoester **169** make it reasonable to assume that they will have conformations similar to one another in solution and in the solid state. The ball and stick model demonstrates that the C ring methyl groups are disposed in a nearly axial manner on either face of the olefin. The space-filling model demonstrates that a significant portion of the olefin is obstructed. In light of this, we chose to pursue a more classical, and importantly intramolecular, method of olefin oxygenation.

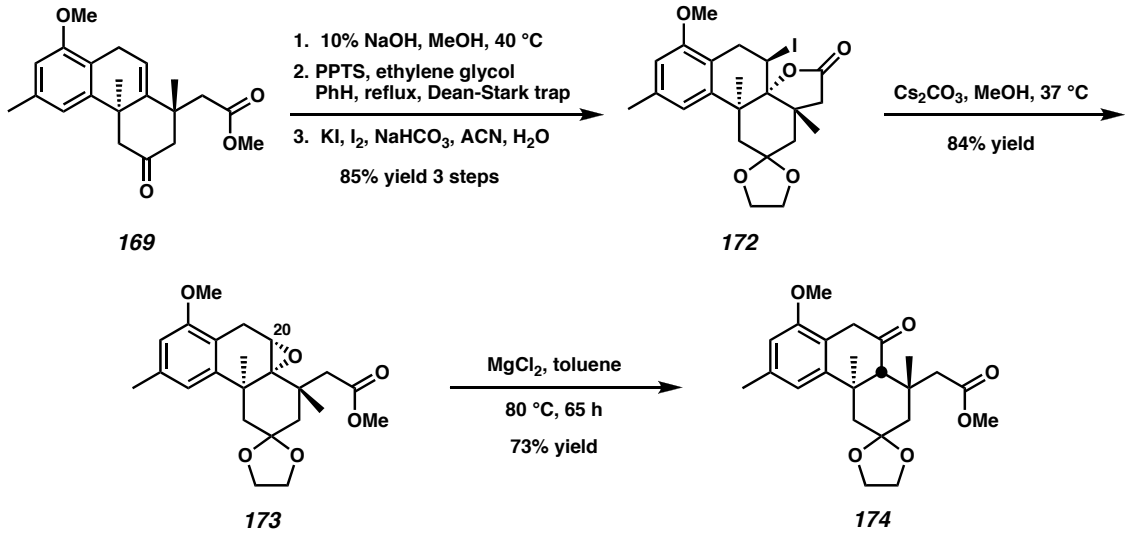
Figure 2.2 Ball and Stick and Space-Filling Representations of Carboxylic Acid **161**'s Solid State Structure



Our intramolecular functionalization began with saponification of ketoester **169** followed by ketalization under Dean-Stark conditions (Scheme 1.17). Although the two operations could be performed in either order, the rate of ketalization was greatly improved when the carboxylic acid was present in the molecule. Treatment of the crude ketalized acid with potassium iodide and iodine under mildly basic conditions gave iodolactone **172** in 85% yield for three steps after recrystallization. Treatment with

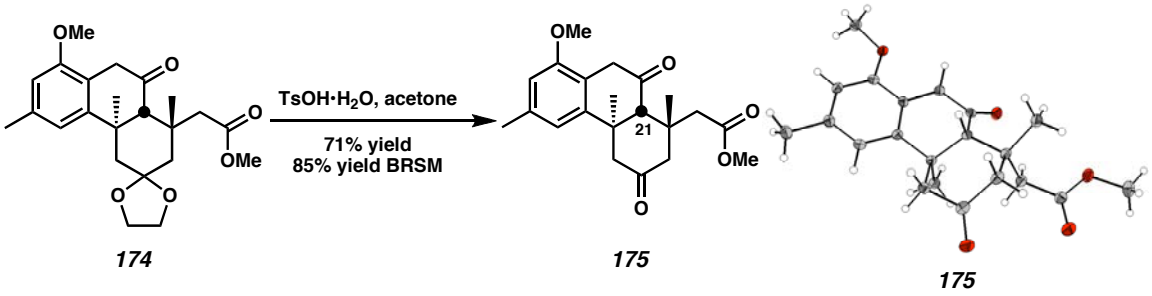
cesium carbonate in methanol afforded smooth conversion to epoxide **173**. Hydride migration from C(20) was affected by heating epoxide **173** in nonpolar solvents with magnesium chloride.[34,35] Though the reaction was somewhat sluggish, it gave clean conversion to rearranged ketoester **174** in 73% yield.

Scheme 2.17 Reoxygenation of the C(20)-C(21) Olefin



Typically, rearrangements of epoxides to carbonyl compounds give products of *syn*-hydride migration due to a concerted hydride shift, but anomalous products are known.[36] As a result, we wished to confirm the stereochemical outcome of the hydride migration (Scheme 2.18). Exposure of ketoester **174** to tosic acid in acetone produced diketone **175**, which gave crystals from acetone/heptane suitable for X-ray structure determination. The structure confirmed the desired C(21) stereochemistry from the hydride shift. With a successful strategy in hand for olefin refunctionalization, our next major objective was the synthesis of the final quaternary stereocenter.

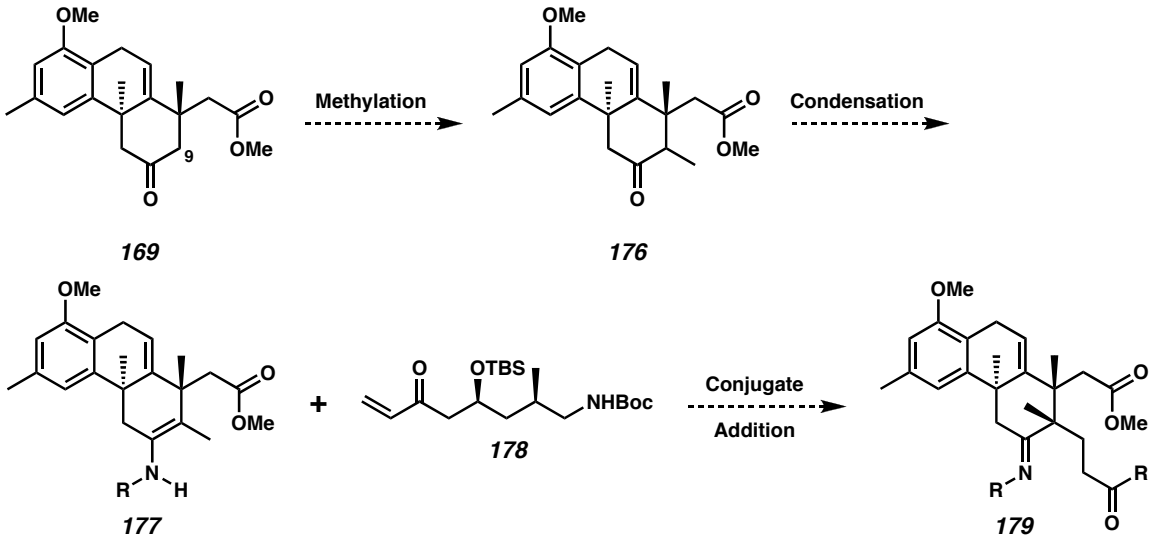
Scheme 2.18 Confirmation of the Hydride Migration Stereochemistry



2.6 Introduction of the C(9) Quaternary Stereocenter

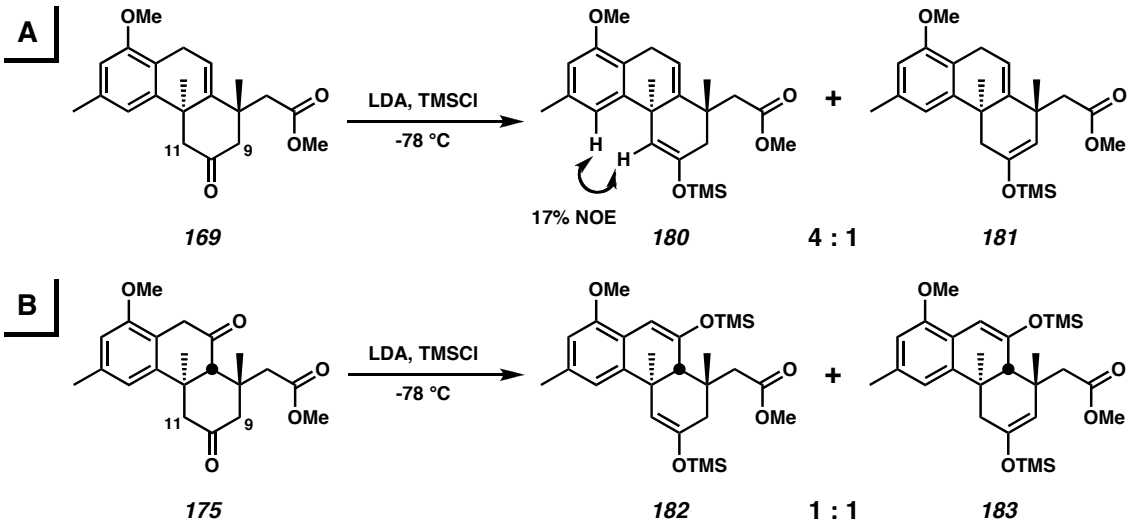
As shown in Scheme 2.19, our initial strategy for constructing the C(9) quaternary center involved three steps: (1) position-selective methylation at C(9), (2) condensation with an amine to give an enamine, and (3) conjugate addition of the enamine **177** or deprotonated metalloenamine into enone **178**. This strategy was closely modeled on the work of Williams.[37]

Scheme 2.19 Initial Strategy for Functionalization at C(9)



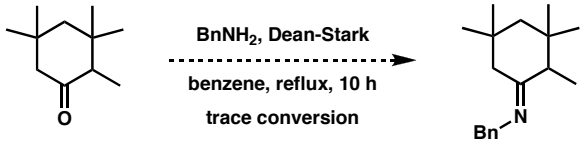
Selective enolization of C(9) over C(11) proved difficult (Scheme 2.20). When treated under kinetic conditions, ketoester **169** showed an unfavorable 4:1 ratio of silyl enol ethers. Though the silyl enol ethers were not separable, the major product was identified as silyl enol ether **180** due to a strong NOE interaction between vinylic enol proton and the arene proton. Analogous silylation with diketone **175** afforded an improved 1:1 mixture of silyl enol ethers **182** and **183**.[38] The bis silyl enol ethers were again inseparable and significant experimentation failed to improve the ratio. Under thermodynamic enolization conditions, nearly exclusive enolization was obtained at C(11) with ketoester **169**.[39]

Scheme 2.20 Positional Selectivity in Kinetic Silyl Enol Ether Formation



Further difficulties were encountered when trying to model the condensation to form the required imine (Scheme 2.21). Known ketone **184**[40] was treated with Dean-Stark dehydration conditions in the presence of benzyl amine, but afforded only trace amounts of what appeared to be the desired imine **185**.

Scheme 2.21 Amine Condensation with a Sterically Demanding Ketone



184 *185*

Our difficulty in modeling the conjugate addition strategy led us to consider other strategies to generate the C(9) quaternary stereocenter. Specifically, we examined a cyclopropanation approach,[41] similar to Hirama's strategy,[42] and a Tsuji allylation-based approach.[43] Ultimately, due to the lack of success with these additional strategies, we made the strategic decision to install the difficult vicinal quaternary stereocenters (i.e., C(9) and C(22)) early in the synthesis.

2.7 Concluding Remarks

A concise method for the construction of the zoanthenol ABC ring system was developed. Common to all our routes was the underlying strategy of combining A and C ring synthons and in the process generating the B ring. The final convergent strategy generated a fully functionalized A ring synthon from *o*-vanillin in six steps. Racemic synthesis of the C ring synthon was completed in just three steps from known materials. Of note is the carbonylation of hindered triflate **135** to enal **145**. Addition of the A ring Grignard **154** to enal **145** proceeded in a highly diastereoselective manner to combine the A and C ring fragments.

In the key step of the synthesis, allylic alcohol **155** underwent a S_N' Friedel-Crafts reaction in TFA. This diastereoselective transformation forms the B ring, sets the

difficult benzylic quaternary stereocenter, and removes three protecting groups in a single step. Only eight linear steps were required to establish the ABC ring system of zoanthenol. To our knowledge, this represents the first use of such an S_N' cyclization in total synthesis. Significant progress was made in advancing the ABC ring system to include all the functionality needed to complete the synthesis. Ultimately, difficulties in forming the final quaternary stereocenter at a late stage forced us to re-evaluate our retrosynthetic path. The route did not allow us to complete the total synthesis, but experience with the advanced ABC carbocycles taught us invaluable lessons about the difficulty of generating quaternary stereocenters and the increased challenge of performing otherwise standard chemistries adjacent to them.

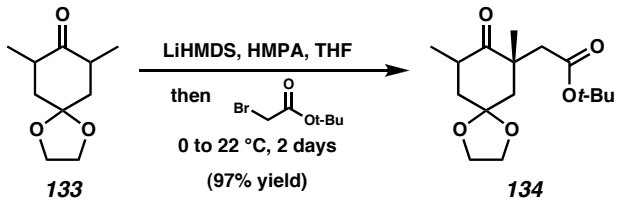
2.8 Experimental Procedures

2.8.1 *Materials and Methods*

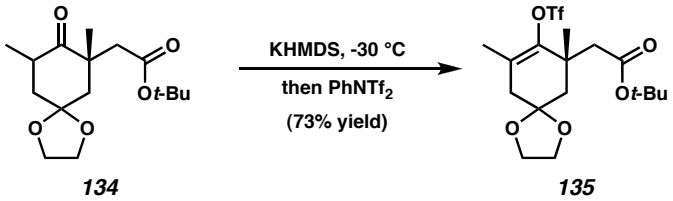
Unless otherwise stated, reactions were performed at ambient temperature (typically 19-24 °C) in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. TMEDA, HMPA, TEA, DIPA and pyridine were freshly distilled from CaH. KHMDS (95%) was purchased from Aldrich and stored in a glovebox until use. Trifluoroacetic acid (99%) was purchased from Aldrich. Tf_2O was freshly distilled from P_2O_5. Magnesium chloride (~325 mesh, <1.5% H_2O) was purchased from Aldrich. 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. ^{1}H 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 Me_4Si (δ 0.0). Data for ^{1}H 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, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer Paragon 1000 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 Three for deposition numbers).

2.8.2 *Preparation of Compounds*

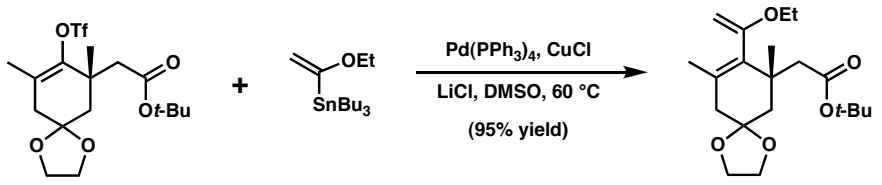


Ketoester 134. To a cooled (0 °C) 1.00 M LiHMDS (52.2 mL, 52.2 mmol, 1.20 equiv) solution in THF was added ketone **133** (8.00 g, 43.5 mmol, 1.00 equiv) in THF (50 mL) in a dropwise manner over 30 min. After an additional 30 min at 0 °C, HMPA (8.31 mL, 47.8 mmol, 1.10 equiv) was added and maintained at 0 °C for 1 h. *t*-butyl bromoacetate (10.6 mL, 69.5 mmol, 1.60 equiv) was added in portions over 1 h and, after a further 2 h at 0 °C, allowed to warm to ambient temperature. After 48 h, the reaction mixture was poured into H_2O (300 mL), extracted with Et_2O (6 x 150 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (7 to 10% EtOAc in hexanes) to provide ketoester **134** (12.5 g, 97% yield) as a pale yellow oil (as a ~3:1 mixture of diastereomers). See below for full characterization of both methyl diastereomers, synthesized in enantioenriched form via asymmetric allylation.



Triflate 135. To a cooled (-30 °C) solution of KHMDS (4.41 g, 22.1 mmol, 1.20 equiv) in THF (35 mL) was added ketoester **134** (5.50 g, 18.5 mmol, 1.00 equiv) in THF (30 mL) in a dropwise manner over 10 min. After 5 h at -30 °C, $PhNTf_2$ (7.20 g, 20.2

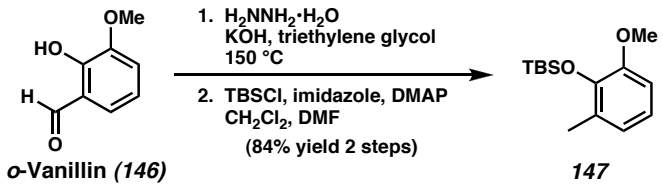
mmol, 1.09 equiv) in THF (30 mL) was added, maintained for an additional 30 min at -30 °C, and warmed to 0 °C for 2 h. The reaction mixture was diluted with Et_2O (200 mL), poured into a mixture of brine (150 mL), H_2O (150 mL), and 1 M NaOH (50 mL), and extracted with Et_2O (3 x 50 mL). The organic layers were washed with 1 M NaOH (6 x 50 mL), H_2O (50 mL), and brine (3 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (7 to 10% EtOAc in hexanes and 0.5 % TEA) to provide triflate **135** (5.74 g, 73% yield) as a pale yellow oil: R_f 0.63 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02-3.92 (comp. m, 4H), 2.71 (d, J = 14.5 Hz, 1H), 2.45 (s, 2H), 2.42 (d, J = 13.5 Hz, 1H), 2.30 (d, J = 14.7 Hz, 1H), 1.78 (s, 3H), 1.70 (d, J = 13.8 Hz, 1H), 1.42 (s, 9H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.2, 146.9, 124.5, 118.7 (q, $J_{C\text{-}F}$ = 319 Hz), 106.2, 80.5, 64.4, 64.3, 43.1, 42.0, 41.9, 39.2, 28.0, 25.0, 17.8; IR (Neat film NaCl) 2980, 2935, 2888, 1726, 1403, 1212, 1142, 1007, 862 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{17}H_{25}SF_3O_7+H]^+$: m/z 431.1351, found 431.1365.



135 *136* *137*

Diene 137. A solution of triflate **135** (azeotroped from PhH, 717 mg, 1.67 mmol, 1.0 equiv) in DMSO (17 mL) was added to an argon-filled, flame-dried Schlenk flask (50 mL) charged with LiCl (flamed-dried under vacuum, 422 mg, 10.0 mmol, 6.0 equiv), $Pd(PPh_3)_4$ (193 mg, 0.167 mmol, 0.10 equiv), and CuCl (825 mg, 8.33 mmol, 5.0 equiv). The flask was purged (5 x) with argon, and vinyl stannane **136** (1.02 g, 2.83 mmol, 1.70

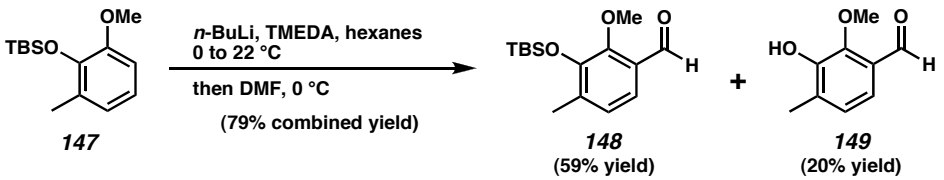
equiv) was added as a neat liquid. The resulting mixture was degassed (3 x) by the freeze/pump-thaw process (-78 to 25 °C, Ar), and stirred at ambient temperature for 1 h, then for a further 12 h at 60 °C. The reaction mixture was quenched with Et_2O (30 mL), brine (120 mL), and 5% aq. NH_4OH (30 mL), and the aqueous layer was further extracted with Et_2O (4 x 30 mL). The combined organic layers were washed with H_2O (4 x 30 mL), then brine (2 x30 mL), dried ($MgSO_4$), and concentrated to give an oil, which was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give diene **137** (557 mg, 95% yield) as a pale yellow oil: R_f 0.59 (20% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (d, *J* = 1.8 Hz, 1H), 4.08-3.90 (comp. m, 4H), 3.84 (d, *J* = 1.8 Hz, 1H), 3.72 (dq, *J* = 1.5, 6.9 Hz, 2H), 2.62 (d, *J* = 14.4 Hz, 1H), 2.39 (d, *J* = 13.8 Hz, 1H), 2.35 (d, *J* = 17.7 Hz, 1H), 2.28 (dd, *J* = 1.0, 13.7 Hz, 1H), 2.25 (d, *J* = 18.0 Hz, 1H), 1.67 (s, 3H), 1.56 (d, *J* = 13.8 Hz, 1H), 1.43 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 158.9, 135.7, 130.3, 107.6, 86.3, 79.7, 64.2, 64.0, 62.5, 44.5, 41.6, 40.3, 38.4, 28.2, 26.6, 21.1, 14.5; IR (Neat film NaCl) 2978, 2930, 2879, 1722, 1606, 1368, 1268, 1142, 1093, 977, 806 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{20}H_{32}O_5+H]^+$: *m/z* 353.2328, found 353.2334.



Arene 147. To a warmed solution (110 °C for 45 min) of *o*-vanillin (60.0 g, 0.394 mol, 1.00 equiv) and NH_2NH_2•H_2O (53.6 mL, 1.10 mol, 2.79 equiv) in triethylene glycol (320 mL) in a 1 L round bottom flask was added KOH (132 g, 2.37 mol, 6.02

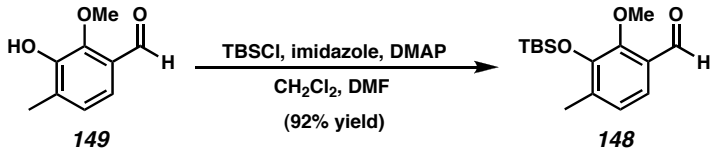
equiv) [*Caution: gas evolution and exotherm*] in portions over 20 min. The reaction mixture was maintained at 150 °C under a reflux condenser for 5 h, cooled to ambient temperature, and poured into H_2O (750 mL), ice (200 g), and 6 M HCl (500 mL). The mixture was further acidified to pH 2 with 6 M HCl, then extracted with $CHCl_3$ (7 x 200 mL), dried ($MgSO_4$), and evaporated to give a green solid (~60 g) that was immediately used in the next step without further purification.

To a solution of this crude solid in DMF (300 mL) and CH_2Cl_2 (300 mL) were added imidazole (53.6 g, 0.788 mol, 2.00 equiv), DMAP (62.5 g, 0.512 mol, 1.30 equiv), and TBSCl (62.1 g, 0.414 mol, 1.05 equiv). After 4 h at ambient temperature, the reaction mixture was poured into H_2O (1.3 L), extracted with CH_2Cl_2 (3 x 150 mL), and the combined organic layers were washed with cold 0.25 M HCl (2 x 250 mL), 1 M NaOH (250 mL), and brine (2 x 200 mL). Evaporation of the organics gave an oil, which was purified by distillation at reduced pressure (~2 mmHg) to give arene **147** (83.6 g, bp 120-127 °C at 2 mmHg, 84% yield over 2 steps) as a colorless oil: R_f 0.74 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83-6.69 (comp. m, 3H), 3.78 (s, 3H), 2.24 (s, 3H), 1.01 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 143.1, 129.6, 122.8, 120.5, 109.1, 54.8, 26.1, 18.9, 17.1, -3.9; IR (Neat film NaCl) 2955, 2930, 1488, 1280, 1251, 1233, 1086, 920, 781 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{14}H_{24}SiO_2+H]^+$: *m/z* 253.1624, found 253.1633.



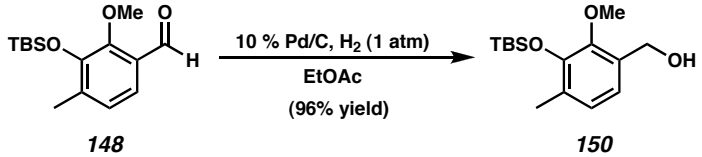
Benzaldehyde 148 from arene **147**. To a cooled (0 °C) solution of arene **147** (30.0 g, 119 mmol, 1.00 equiv), and TMEDA (25.1 mL, 166 mmol, 1.40 equiv) in hexanes (200 mL) was added *n*-BuLi (2.25 M in hexanes, 63.4 mL, 142 mmol, 1.20 equiv) in a dropwise manner over 15 min. After 1 h at 0 °C, the reaction mixture was allowed to warm to ambient temperature for 6 h. The reaction mixture was cooled (0 °C) again and DMF (15.6 mL, 202 mmol, 1.70 equiv) was added dropwise over 10 min. After an additional 1 h at 0 °C, saturated aqueous NH_4Cl (100 mL) was added, and the mixture was allowed to warm to ambient temperature overnight. The mixture was poured into H_2O (200 mL) and Et_2O (200 mL), then extracted with Et_2O (2 x 100 mL). The aqueous layers were then acidified with 2 M HCl to pH 1, and further extracted with Et_2O (5 x 150 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and evaporated to give an oil that was purified by gradient flash chromatography on silica gel (2 to 20% EtOAc in hexanes) to give benzaldehyde **148** (19.7 g, 59% yield) as a colorless oil: R_f 0.67 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.36 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 3.81 (s, 3H), 2.28 (s, 3H), 1.03 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 154.2, 147.2, 138.4, 128.1, 126.4, 120.7, 62.5, 26.0, 18.6, 17.9, -4.1; IR (Neat film NaCl) 2957, 2932, 2859, 1691, 1464, 1273, 1255, 838 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{15}H_{24}SiO_3+H]^+$: m/z 281.1573, found 281.1572 and phenol **149** (3.9 g, 20% yield) as a white solid: mp 90.0-91.0 °C; R_f 0.25 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 10.18 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.02 (bs, 1H), 3.95 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 148.4, 147.5, 132.8, 126.7, 126.5, 121.3, 63.8, 16.3; IR (Neat film NaCl) 3410, 2938, 2857, 1686, 1466, 1261, 1061, 782 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_9H_{10}O_3+H]^+$: *m/z* 167.0708, found 167.0708.



149 ***148***

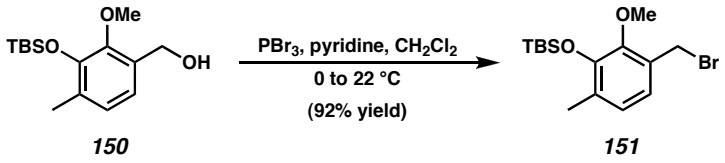
Benzaldehyde 148 from phenol **149**. To a solution of phenol **149** (10.0 g, 60.2 mmol, 1.00 equiv) in DMF (60 mL) and CH_2Cl_2 (60 mL) were added imidazole (8.20 g, 120 mmol, 2.00 equiv), DMAP (9.55 g, 78.3 mmol, 1.30 equiv), and TBSCl (11.7 g, 78.3 mmol, 1.30 equiv). After 36 h, the reaction mixture was quenched with H_2O (200 mL) and CH_2Cl_2 (200 mL), and extracted with CH_2Cl_2 (3 x 50 mL) The combined organics were washed with H_2O (200 mL) and then brine (100 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to provide benzaldehyde **148** (15.5 g, 92% yield).



148 ***150***

Benzyl alcohol 150. A flame-dried 100 mL round-bottom flask was charged with 10% Pd/C (270 mg), EtOAc (55 mL), and benzaldehyde **148** (2.0 g, 7.13 mmol, 1.00 equiv) under an N_2 atmosphere. The reaction mixture and head space were sparged with

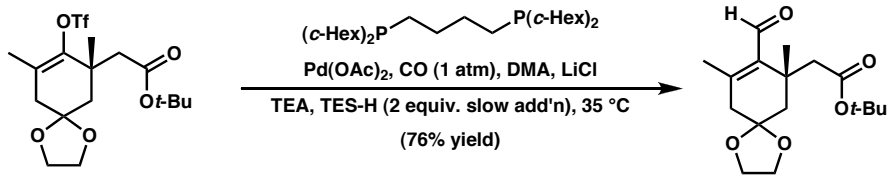
H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 3 h. Immediately following the completion of the reaction, as indicated by TLC, the reaction mixture was sparged with N_2 for 15 min then concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 15% EtOAc in hexanes) to provide benzyl alcohol **150** (1.93 g, 96% yield) as a colorless oil: R_f 0.33 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.65 (d, *J* = 6.3 Hz, 2H), 3.75 (s, 3H), 2.25 (t, *J* = 6.3 Hz, 1H), 2.21 (s, 3H), 1.03 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.4, 147.0, 132.4, 130.6, 126.1, 121.1, 61.7, 60.5, 26.0, 18.6, 17.2, -4.2; IR (Neat film NaCl) 3340, 2956, 2931, 2859, 1464, 1420, 1285, 839, 782 cm^{-1}; HRMS (FAB) $[M+H-H_2]^+$ calc'd for $[C_{15}H_{25}SiO_3]^+$: m/z 281.1573, found 281.1564.



150 ***151***

Benzyl bromide 151. To a cooled (0 °C) solution of benzyl alcohol **150** (16.0 g, 56.7 mmol, 1.00 equiv) and pyridine (4.36 mL, 53.9 mmol, 0.95 equiv) in CH_2Cl_2 (200 mL) was added PBr_3 (4.84 mL, 51.0 mmol, 0.90 equiv) in CH_2Cl_2 (50 mL) over 30 min. After stirring an additional 30 min at 0 °C, the reaction mixture was allowed to come to ambient temperature and stirred for a further 2.5 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL), brine (500 mL), and H_2O (250 mL), then extracted with Et_2O (2 x 150 mL), dried over Na_2SO_4, and concentrated. The resulting oil was passed through a plug of silica gel (10 cm h x 5.5 cm d) (1:1 hexanes:CH_2Cl_2), concentrated, and the resultant oil was purified by distillation at reduced pressure (~2 mmHg) to provide benzyl bromide **151** (27.4 g, bp 146-147 °C at ~2 mmHg, 92% yield) as a colorless oil: R_f 0.50

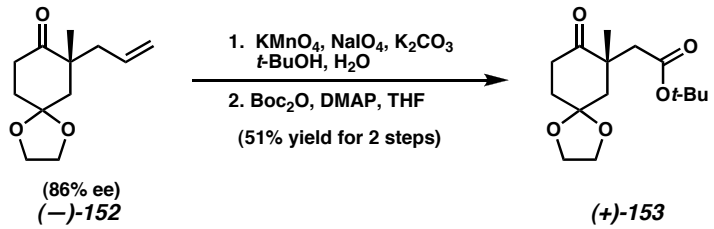
(2.5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 4.56 (s, 2H), 3.83 (s, 3H), 2.23 (s, 3H), 1.04 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7, 147.2, 131.9, 129.6, 126.2, 123.2, 60.4, 28.8, 26.0, 18.6, 17.3, -4.2; IR (Neat film NaCl) 2957, 2931, 2859, 1464, 1421, 1289, 1259, 1239, 1072, 840, 782 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{15}H_{25}SiBrO_2+H]^+$: *m/z* 345.0885, found 345.0885.



135 ***145***

Enal 145. A solution of flame-dried LiCl (600 mg, 14.2 mmol, 2.69 equiv), $Pd(OAc)_2$ (156 mg, 0.695 mmol, 0.132 equiv), and 1,4-bis-(dicyclohexylphosphino)butane (314 mg, 0.695 mmol, 0.132 equiv) in DMA (16 mL) was sparged with CO and warmed to 90 °C until a color change from red/orange to pale yellow was observed, at which point the reaction mixture was cooled to 35 °C. To the homogenous reaction mixture was added TEA (2.60 mL, 18.6 mmol, 3.53 equiv) and enol triflate **135** (2.27 g, 5.27 mmol, 1.00 equiv) in DMA (16 mL). A solution of Et_3SiH (1.47 mL, 9.28 mmol, 1.76 equiv) in DMA (8.5 mL) was added by syringe pump to the reaction over 10 h. After an additional 14 h at 35 °C, the reaction mixture was cooled to ambient temperature, $KF•2H_2O$ (2.00 g) was added, the mixture was stirred for 45 min, and then poured into ice water (200 mL). This mixture was extracted with 1:1 Et_2O:hexanes (5 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried (Na_2SO_4), and concentrated to give an oil, which was purified by gradient

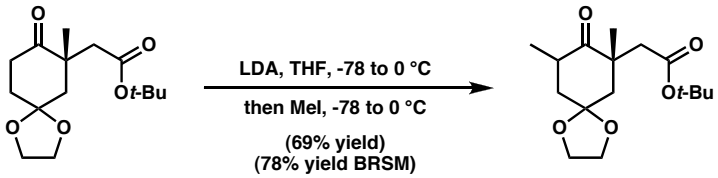
flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to give enal **145** (1.24 g, 76% yield) as a pale yellow oil: R_f 0.42, 0.41 (35% EtOAc in hexanes, 20% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1H), 4.00-3.90 (comp. m, 4H), 3.04 (d, *J* = 14.4 Hz, 1H), 2.54 (app. dt, *J* = 1.0, 19.2 Hz, 1H), 2.37 (dd, *J* = 1.8, 18.9 Hz, 1H), 2.34 (d, *J* = 14.7 Hz, 1H), 2.15 (d, *J* = 13.6 Hz, 1H), 2.12 (s, 3H), 1.53 (dd, *J* = 2, 13.6 Hz, 1H), 1.35 (s, 9H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.0, 171.3, 152.8, 137.4, 106.5, 79.8, 64.3, 64.0, 44.7 (2C), 42.4, 38.3, 28.0, 26.5, 19.3; IR (Neat film NaCl) 2977, 2932, 2884, 1721, 1673, 1368, 1161, 1141, 1079 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{17}H_{26}O_5+H]^+$: *m/z* 311.1858, found 311.1849.



(+)-*t*-Butyl ester 153. A solution of ketone (–)-**152** (1.00 g, 4.76 mmol, 1.00 equiv) and K_2CO_3 (987 mg, 7.14 mmol, 1.5 equiv) in *t*-BuOH (60 mL) was treated (slight exotherm) with a premixed (30 min) solution of $NaIO_4$ (8.14 g, 38.1 mmol, 8.00 equiv) and $KMnO_4$ (113 mg, 0.714 mmol, 0.15 equiv) in H_2O (100 mL) and stirred in a room temperature bath for 3 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL), extracted with CH_2Cl_2 (6 x 50 mL), dried ($MgSO_4$), and concentrated to an oil, which was used immediately in the next step.

A solution of the above crude carboxylic acid in THF (40 mL) was treated with Boc_2O (3.40 g, 15.6 mmol, 3.27 equiv) and DMAP (200 mg, 1.64 mmol, 0.344 equiv). After 12 h, additional Boc_2O (2.00 g, 9.16 mmol, 1.93 equiv) and DMAP (175 mg, 1.43 mmol,

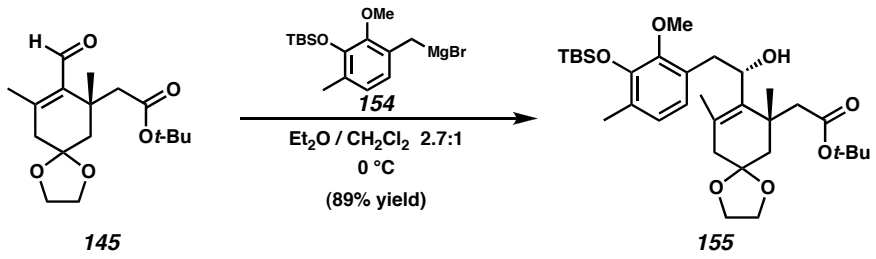
0.30 equiv) were added, and the reaction was stirred for a further 3 h. The reaction mixture was concentrated and purified by gradient flash chromatography on silica gel (5 to 25% Et_2O in hexanes) to give (+)-*t*-butyl ester **153** (688 mg, 51% yield) as a colorless oil: R_f 0.27 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03-3.94 (comp. m, 4H), 2.70 (d, *J* = 15.9 Hz, 1H), 2.63 (d, *J* = 6.6 Hz, 1H), 2.60 (d, *J* = 6.0 Hz, 1H), 2.49 (d, *J* = 15.9 Hz, 1H), 2.22 (dd, *J* = 1.4, 14.0 Hz, 1H), 2.20-2.08 (m, 1H), 2.04-1.92 (m, 1H), 1.78 (dd, *J* = 2.4, 14.1 Hz, 1H), 1.40 (s, 9H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 170.7, 107.6, 80.7, 64.4, 64.2, 46.0, 44.7, 44.5, 35.6, 33.9, 28.0, 25.1; IR (Neat film NaCl) 2976, 2935, 2885, 1725, 1714, 1368, 1157, 1120, 1074 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{15}H_{24}O_5]^+$: *m/z* 284.1624, found 284.1633; $[\alpha]_D^{26}$ +45.63 (c 1.89, CH_2Cl_2, 86% ee).



(+)-153 *134*

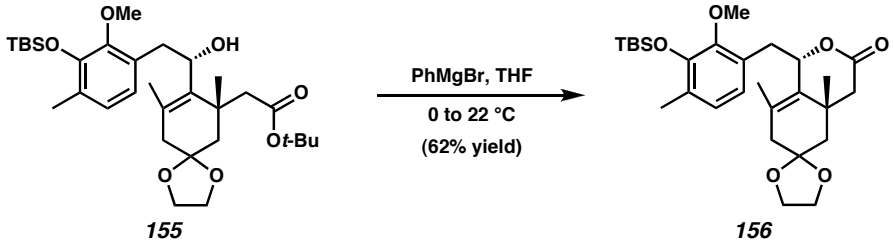
Methyl ketones 134a and 134b. A solution of LDA in THF was prepared by dropwise addition of 2.45 M *n*-BuLi solution in hexanes (787 μL, 1.93 mmol, 1.4 equiv) to diisopropylamine (290 μL, 2.07 mmol, 1.5 equiv) in THF (20.7 mL) at 0 °C, followed by stirring for 1 h. Upon cooling the solution to -78 °C, a solution of (+)-*t*-butyl ester **153** (392 mg, 1.38 mmol, 1.00 equiv) in THF (2.00 mL) was added in a dropwise manner, and the reaction mixture was stirred at -78 °C for 1 h, then 0 °C for 1 h. After cooling again to -78 °C, the reaction mixture was treated with MeI (258 μL, 4.13 mmol, 3.00 equiv), allowed to warm to ambient temperature slowly over 5 h, and stirred for an

additional 12 h at ambient temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (6 x 30 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (3 to 10% EtOAc in hexanes) to give diastereomeric methyl ketones **134a** and **134b** (284 mg, 69% combined yield) as colorless oils and recovered *t*-butyl ester **153** (43.2 mg, 11% yield). High R_f diastereomer **134a**: R_f 0.43 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-3.90 (comp. m, 4H), 2.89 (app. d of sept., J = 1.2, 6.6 Hz, 1H), 2.73 (d, J = 16.5 Hz, 1H), 2.36 (d, J = 13.8 Hz, 1H), 2.16 (d, J = 16.2 Hz, 1H), 2.06-1.96 (comp. m, 1H), 1.93 (d, J = 13.5 Hz, 1H), 1.85 (dd, J = 3.3, 13.8 Hz, 1H), 1.42 (s, 9H), 1.29 (s, 3H), 1.07 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 170.9, 107.5, 80.4, 64.6, 64.0, 46.0, 44.5, 44.3, 41.9, 38.0, 28.1, 26.4, 14.7; IR (Neat film NaCl) 2976, 2932, 2880, 1726, 1710, 1367, 1146, 1080 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{26}O_5]^+$: m/z 298.1780, found 298.1791; $[\alpha]_D^{26}$ +45.13 (c 1.06, CH_2Cl_2, 86% ee). Low R_f diastereomer **134b**: R_f 0.32 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-3.85 (comp. m, 4H), 3.21 (d, J = 14.7 Hz, 1H), 3.09 (app. d of sept., J = 1.5, 6.6 Hz, 1H), 2.32 (d, J = 14.4 Hz, 1H), 2.14-2.00 (comp. m, 2H), 1.76 (d, J = 14.7 Hz, 1H), 1.68 (app. t, J = 14.0 Hz, 1H), 1.36 (s, 9H), 1.08 (s, 3H), 1.03 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 170.4, 107.2, 80.8, 64.6, 64.0, 46.8, 46.1, 45.2, 43.9, 37.7, 27.9, 23.0, 14.4; IR (Neat film NaCl) 2976, 2933, 2884, 1726, 1717, 1457, 1367, 1232, 1160, 1141, 1084, 979 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{26}O_5]^+$: m/z 298.1780, found 298.1775; $[\alpha]_D^{26}$ –25.44 (c 1.17, CH_2Cl_2, 86% ee).



Allylic alcohol 155. A flame-dried two-neck round-bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (9.00 g, 370 mmol, 34.6 equiv) and Et_2O (120 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (1.53 mL, 17.8 mmol, 1.66 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (5.91 g, 17.1 mmol, 1.60 equiv) in Et_2O (50 mL) was added in a dropwise manner over 30 min and heating was continued for an additional 30 min. The Grignard reagent was then cooled (0 °C), and added to a cooled (0 °C) solution of enal **145** (3.32 g, 10.7 mmol, 1.00 equiv) in Et_2O (100 mL) and CH_2Cl_2 (100 mL). After 1 h, the reaction mixture was quenched with H_2O (200 mL) and saturated aqueous NH_4Cl (100 mL), extracted with Et_2O (3 x 200 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (7.5 to 20% EtOAc in hexanes) to give allylic alcohol **155** (5.51 g, 89% yield) as a thick syrup: R_f 0.59 (20% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 2H), 4.43 (dd, J = 2.1, 9.9 Hz, 1H), 4.04-3.90 (comp. m, 4H), 3.68 (s, 3H), 3.22 (bs, 1H), 3.17 (dd, J = 9.9, 13.8 Hz, 1H), 2.84 (dd, J = 3.3, 13.8 Hz, 1H), 2.64 (d, J = 13.5 Hz, 1H), 2.31 (d, J = 17.4 Hz, 1H), 2.24-2.04 (comp. m, 3H), 2.19 (s, 3H), 2.07 (s, 3H), 1.57 (dd, J = 2.3, 13.8 Hz, 1H), 1.40 (s, 9H), 1.12 (s, 3H), 1.02 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.1, 149.6, 147.0, 136.7, 131.3, 130.5, 128.7, 125.7, 123.5, 107.6, 80.9, 70.6,

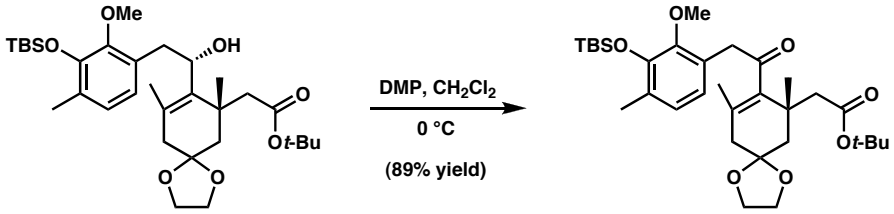
64.2, 63.9, 59.9, 46.4, 43.3, 42.0, 41.3, 36.6, 28.0, 26.8, 26.0, 21.1, 18.6, 17.0, -4.1 (2C); IR (Neat film NaCl) 3499, 2957, 2931, 2896, 2859, 1706, 1462, 1419, 1368, 1286, 1075, 840 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{32}H_{52}SiO_7+H]^+$: *m/z* 577.3561, found 577.3543.



155 *156*

Lactone 156. To a cooled (0 °C) solution of allylic alcohol **155** (108 mg, 0.187 mmol, 1.00 equiv) in THF (12 mL) was added 3.0 M PhMgBr in Et_2O (68.6 μL, 0.206 mmol, 1.10 equiv). Additional 3.0 M PhMgBr in Et_2O (85.0 μL, 0.255 mmol, 1.36 equiv) was added in portions over 4 h. The reaction mixture was quenched into H_2O (30 mL) and EtOAc (30 mL), acidified to pH 2 with 0.1 M HCl, extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to give lactone **156** (58.5 mg, 62% yield) as white solid. Crystals suitable for X-ray analysis were obtained by crystallization from hexanes at ambient temperature: mp 139-140 °C (hexanes); R_f 0.40 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 9.0 Hz, 1H), 4.08-3.95 (m, 2H), 3.95-3.86 (m, 2H), 3.67 (s, 3H), 3.07 (dd, *J* = 3.5, 14.3 Hz, 1H), 2.75 (dd, *J* = 10.2, 14.4 Hz, 1H), 2.48 (s, 2H), 2.43 (s, 2H), 2.19 (s, 3H), 1.82 (d, *J* = 13.2 Hz, 1H), 1.71 (d, *J* = 13.2 Hz, 1H), 1.71 (s, 3H), 1.22 (s, 3H), 1.03 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.4, 149.7, 147.0, 131.2, 129.8, 128.1, 126.0, 125.5, 123.5, 107.8, 80.0, 64.4, 63.6,

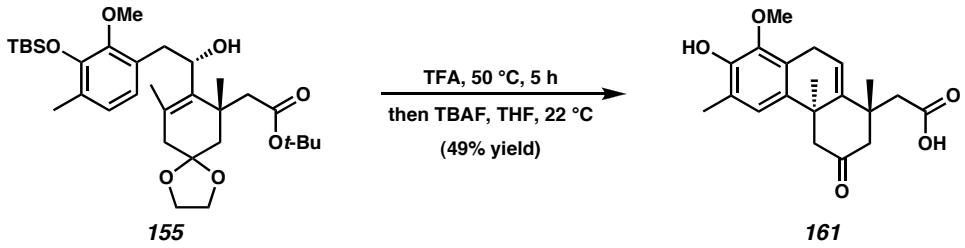
60.0, 45.7, 44.1, 43.4, 38.2, 35.9, 26.0, 25.9, 19.0, 18.5, 17.1, -4.2 (2C); IR (Neat film NaCl) 2957, 2931, 2886, 2859, 1751, 1463, 1419, 1251, 1237, 1078, 841 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{28}H_{42}SiO_6+H]^+$: *m/z* 503.2829, found 503.2809.



155 *157*

Enone 157. To a cooled (0 °C) solution of allylic alcohol **155** (200 mg, 0.347 mmol, 1.00 equiv) in CH_2Cl_2 (22 mL) was added Dess-Martin periodinane (221 mg, 0.521 mmol, 1.50 equiv) and the resulting mixture was stirred for 2 h. The reaction mixture was diluted with Et_2O (75 mL), filtered, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (7.5 to 20% Et_2O in hexanes) to give enone **157** (177 mg, 89% yield) as a pale yellow oil: R_f 0.37 (25% Et_2O in hexanes developed twice); ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 7.0 Hz, 1H), 4.08-4.02 (m, 1H), 4.02-3.92 (comp. m, 3H), 3.92 (d, *J* = 18.5 Hz, 1H), 3.84 (d, *J* = 18.0 Hz, 1H), 3.65 (s, 3H), 2.76 (d, *J* = 14.5 Hz, 1H), 2.46 (d, *J* = 14.5 Hz, 1H), 2.37 (d, *J* = 18.0 Hz, 1H), 2.35 (dd, *J* = 1.5, 13.5 Hz, 1H), 2.28 (d, *J* = 18.0 Hz, 1H), 2.21 (s, 3H), 1.75 (s, 3H), 1.57 (d, *J* = 13.5 Hz, 1H), 1.43 (s, 9H), 1.30 (s, 3H), 1.03 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 171.3, 150.0, 147.0, 140.9, 129.9, 128.1, 125.8, 125.5, 123.4, 107.4, 80.0, 64.3, 64.0, 59.9, 47.3, 44.1, 41.6, 40.5, 38.4, 28.2, 26.6, 26.1, 20.8, 18.6, 17.1, -4.2; IR (Neat film NaCl) 2959, 2931, 2886, 2860, 1724, 1699,

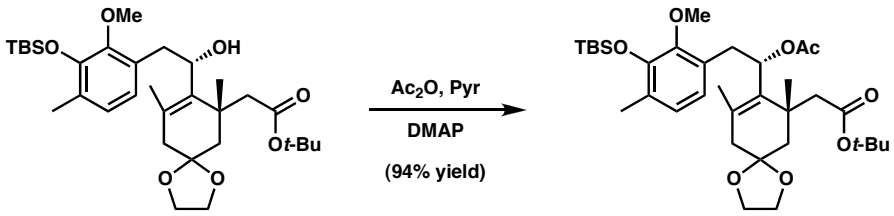
1463, 1421, 1368, 1286, 1253, 1234, 1145, 1075, 1014, 857, 839, 782 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{32}H_{50}SiO_7+H]^+$: *m/z* 575.3404, found 575.3394.



155 *161*

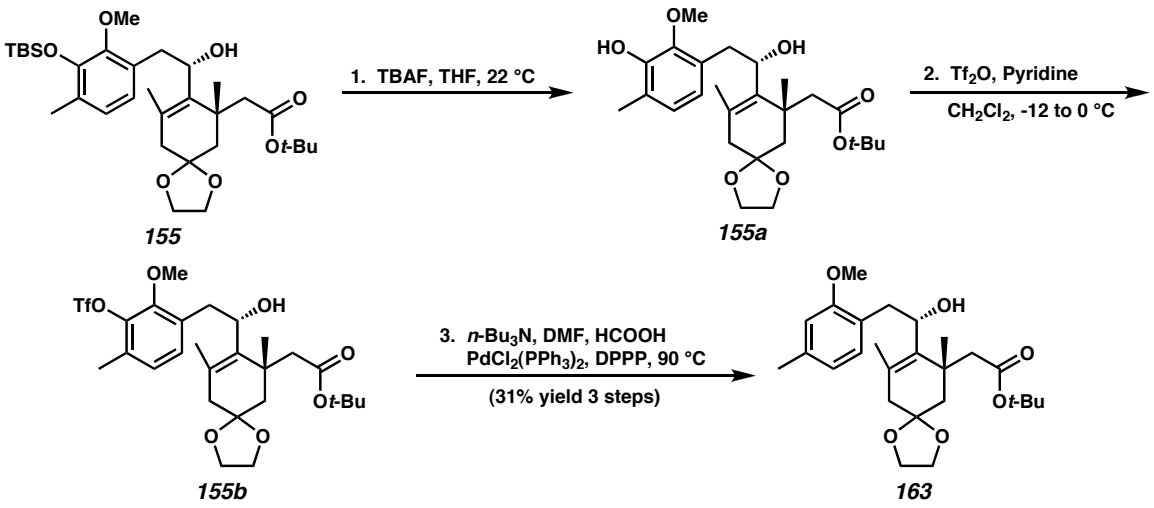
Acid 161. A solution of allylic alcohol **155** (5.50 g, 9.53 mmol, 1.00 equiv) in TFA (240 mL) was warmed to 50 °C for 5 h. The reaction mixture was concentrated and the resulting residue was dissolved in THF (100 mL) and 1.0 M TBAF (12.0 mL, 12.0 mmol, 1.26 equiv) in THF was added. After 1 h, the reaction mixture was concentrated to ~25 mL, quenched with H_2O (100 mL), brine (100 mL), and 3 M HCl (100 mL), and extracted with EtOAc (6 x 100 mL). The organic layers were concentrated to an oil, which was purified by flash chromatography on silica gel (1:1 CH_2Cl_2:$CHCl_3$ + 1% AcOH) to give acid **161** (1.62 g, 49% yield) as a white foam. Crystals suitable for X-ray analysis were obtained by crystallization from $CDCl_3$ at ambient temperature: mp 112-113 °C ($CDCl_3$); R_f 0.32 (1:1 CH_2Cl_2 : $CHCl_3$ + 3% MeOH developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.05 (dd, *J* = 1.8, 6.3 Hz, 1H), 5.63 (bs, 1H), 3.78 (s, 3H), 3.58 (dd, *J* = 6.6, 20.7 Hz, 1H), 3.47 (d, *J* = 17.7 Hz, 1H), 3.17 (d, *J* = 18.3 Hz, 1H), 3.11 (d, *J* = 17.4 Hz, 1H), 2.93 (d, *J* = 15.9 Hz, 1H), 2.76 (d, *J* = 17.4 Hz, 1H), 2.50 (d, *J* = 15.6 Hz, 1H), 2.34 (d, *J* = 17.1 Hz, 1H), 2.24 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 210.8, 176.8, 146.0, 145.4, 143.9, 137.6, 125.3, 123.1, 121.6, 120.6, 61.2, 50.1, 49.2, 46.2, 39.5, 39.0, 33.3, 30.7, 24.9, 16.0; IR (Neat film NaCl) 3500-

2500, 2963, 2926, 1707, 1489, 1461, 1422, 1360, 1295, 1228, 1071, 955, 711 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{20}H_{24}O_5+H]^+$: *m/z* 345.1702, found 345.1709.



155 *162*

Allylic acetate 162. To a solution of allylic alcohol **155** (88.0 mg, 0.153 mmol, 1.00 eq) in pyridine (250 μL) and acetic anhydride (3.00 mL) was added DMAP (28.0 mg, 0.229 mmol, 1.50 equiv). After 2 h, the reaction mixture was concentrated to an oil, which was purified by gradient flash chromatography on silica gel (5 to 10% EtOAc in hexanes) to give allylic acetate **162** (89.3 mg, 94% yield) as a colorless oil: R_f 0.68 (20% EtOAc in hexanes developed twice); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 5.73 (dd, *J* = 2.8, 10.8 Hz, 1H), 4.12-4.04 (m, 1H), 4.00-3.90 (comp. m, 3H), 3.70 (s, 3H), 3.07 (app. t, *J* = 12.5 Hz, 1H), 2.97 (dd, *J* = 3.3, 13.8 Hz, 1H), 2.66 (d, *J* = 15.0 Hz, 1H), 2.57 (d, *J* = 14.5 Hz, 1H), 2.38 (d, *J* = 17.5 Hz, 1H), 2.26 (d, *J* = 13.0 Hz, 1H), 2.24 (d, *J* = 17.5 Hz, 1H), 2.18 (s, 3H), 1.97 (s, 3H), 1.80 (s, 3H), 1.48 (d, *J* = 14.5 Hz, 1H), 1.42 (s, 9H), 1.28 (s, 3H), 1.03 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 169.3, 150.0, 146.9, 135.0, 131.1, 129.3, 129.2, 125.3, 123.4, 107.3, 79.7, 71.5, 64.3, 63.9, 59.9, 43.5, 40.7, 39.9, 35.9, 28.2, 26.2, 26.1, 21.3, 21.0, 18.5, 17.1, -4.2, -4.4; IR (Neat film NaCl) 2958, 2931, 2896, 2860, 1740, 1463, 1419, 1368, 1287, 1235, 1147, 1079, 1014, 854, 841, 783, 734 cm^{-1}; HRMS (FAB) $[M+H-H_2]^+$ calc'd for $[C_{34}H_{53}O_8Si]^+$: *m/z* 617.3510, found 617.3487.

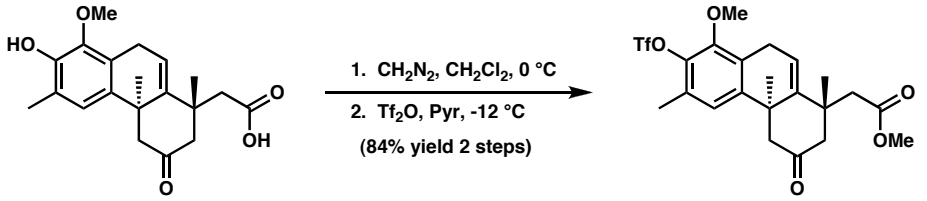


Arene 163. To a solution of allylic alcohol **155** (554 mg, 0.962 mmol, 1.0 equiv) in THF (10 mL) was added 1.00 M TBAF in THF (1.50 mL, 1.50 mmol, 1.56 equiv). After 5 min, the reaction mixture was concentrated to ~5 mL and was purified by gradient flash chromatography on silica gel (20 to 40% EtOAc in hexanes) to give phenol **155a** (223 mg, 52% yield).

To a cooled (-12 °C) solution of phenol **155a** (202 mg, 0.438 mmol, 1.00 equiv) and pyridine (142 μL, 1.75 mmol, 4.0 equiv) in CH_2Cl_2 (5 mL) was added Tf_2O (74.3 μL, 0.526 mmol, 1.2 equiv). After 2 h, additional Tf_2O (10.0 μL, 0.071 mmol, 0.16 equiv) was added. After a further 2 h, the reaction mixture was quenched into a mixture of H_2O (10 mL), brine (10 mL), and CH_2Cl_2 (10 mL), then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (15 to 25% EtOAc in hexanes + 1% TEA) to give triflate **155b** (193 mg, 75% yield).

A flame-dried 25 mL Schlenk flask was charged with triflate **155b** (193 mg, 0.325 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (27.3 mg, 0.0389 mmol, 0.12 equiv), 1,4-bis-(diphenylphosphino)butane (40.2 mg, 0.0974 mmol, 0.30 equiv), DMF (4 mL), *n*-Bu_3N

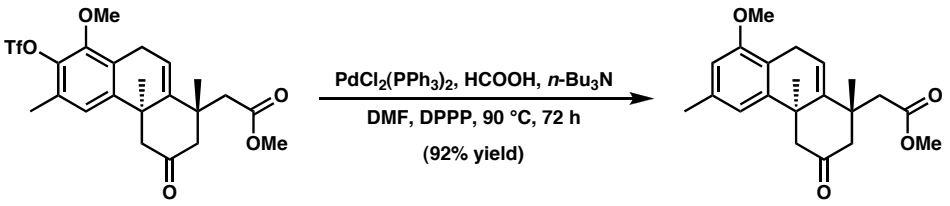
(650 μL, 2.73 mmol, 8.40 equiv), and HCOOH (61.3 μL, 1.62 mmol, 5.00 equiv) under an Ar atmosphere and heated to 90 °C. After 22 h, the reaction mixture was quenched with H_2O (40 mL), extracted with Et_2O (5 x 15 mL), dried ($MgSO_4$), and concentrated to a residue, which was purified by gradient flash chromatography on silica gel (10 to 15% acetone in hexanes) to give arene **163** (117 mg, 80% yield) as a white solid: mp 135-136 °C; R_f 0.50 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.68 (s, 1H), 4.46 (dd, *J* = 2.3, 10.1 Hz, 1H), 4.02-3.90 (comp. m, 4H), 3.80 (s, 3H), 3.08 (dd, *J* = 10.2, 13.8 Hz, 1H), 3.07 (s, 1H), 2.94 (dd, *J* = 3.0, 13.8 Hz, 1H), 2.65 (d, *J* = 13.5 Hz, 1H), 2.33 (s, 3H), 2.30-2.10 (comp. m, 3H), 2.07 (s, 3H), 1.58 (dd, *J* = 2.1, 13.8 Hz, 1H), 1.40 (s, 9H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.1, 157.3, 137.3, 136.8, 131.4, 130.3, 125.1, 121.0, 111.2, 107.6, 80.8, 69.5, 64.2, 63.9, 55.0, 46.4, 43.3, 42.0, 41.3, 36.7, 28.0, 26.7, 21.5, 21.1; IR (Neat film NaCl) 3501, 2974, 2934, 1705, 1368, 1259, 1155, 1126, 1080, 1042 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{26}H_{38}O_6+H]^+$: *m/z* 447.2747, found 447.2749.



161 *168*

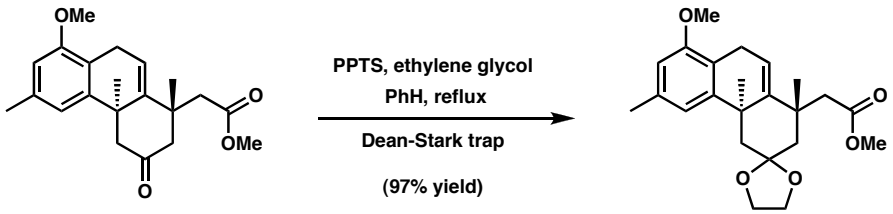
Triflate 168. To a cooled (0 °C) solution of acid **161** (994 mg, 2.88 mmol, 1.00 equiv) in CH_2Cl_2 (30 mL) was added a cooled (0 °C) solution of CH_2N_2 in Et_2O (~0.2 M, 18.7 mL, 1.30 equiv) in a dropwise manner over 10 min. After 20 min, TLC analysis indicated complete consumption of the starting material and the reaction mixture was concentrated *in vacuo*. To a cooled (-12 °C) solution of the crude reaction mixture and

pyridine (2.45 mL, 28.8 mmol, 10.0 equiv) in CH_2Cl_2 (50 mL) was added Tf_2O (1.01 mL, 7.20 mmol, 2.50 equiv) in a dropwise manner over 5 min. After 30 min, additional Tf_2O (1.01 mL, 7.20 mmol, 2.50 equiv) was added. After a further 1 h at -12 °C, the reaction mixture was allowed to warm to 0 °C, stirred for 1 h, and quenched with saturated aqueous $NaHCO_3$ (30 mL). The reaction mixture was poured into half saturated aqueous $NaHCO_3$ (60 mL), extracted with CH_2Cl_2 (5 x 30 mL), dried over K_2CO_3, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give triflate **168** (1.18 g, 84% yield) as an off-white solid: mp 123-125 °C (decomp.) (benzene); R_f 0.45 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.03 (dd, J = 2.0, 6.5 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.66 (dd, J = 6.3, 21.0 Hz, 1H), 3.50 (d, J = 17.7 Hz, 1H), 3.17 (app. d, J = 21.9 Hz, 1H), 3.09 (d, J = 17.4 Hz, 1H), 2.91 (d, J = 15.3 Hz, 1H), 2.76 (d, J = 17.4 Hz, 1H), 2.46 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 2.33 (d, J = 17.4 Hz, 1H), 1.29 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 171.5, 148.5, 146.0, 144.7, 140.0, 129.4, 127.6, 121.9, 119.7, 118.6 (q, $J_{C\text{-}F}$ = 318 Hz), 61.0, 51.5, 49.3, 48.8, 45.9, 39.4, 38.5, 33.1, 30.3, 24.3, 16.5; IR (Neat film NaCl) 2960, 1735, 1715, 1417, 1210, 1138, 1072, 903, 856 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{22}H_{25}SO_7F_3+H]^+$: m/z 491.1351, found 491.1363.



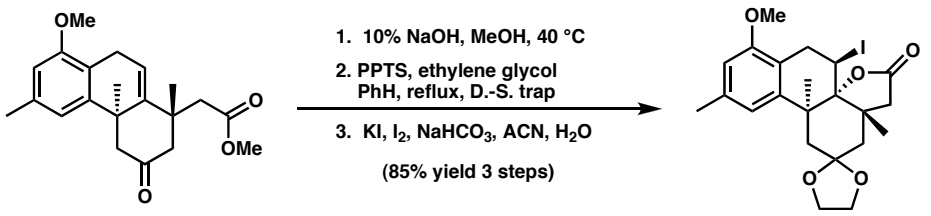
168 *169*

Ketoester 169. A flame-dried 250 mL Schlenk flask was charged with triflate **168** (azeotroped from PhH solution, 1.150 g, 2.34 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (198 mg, 0.282 mmol, 0.12 equiv), 1,4-bis-(diphenylphosphino)butane (290 mg, 0.704 mmol, 0.30 equiv), DMF (20 mL), *n*-Bu_3N (4.70 mL, 19.7 mmol, 8.40 equiv), and HCOOH (443 μL, 11.7 mmol, 5.00 equiv) under an N_2 atmosphere and heated to 90 °C. After 72 h, the reaction mixture was quenched with H_2O (150 mL) and Et_2O (40 mL), extracted with Et_2O (6 x 50 mL), dried ($MgSO_4$), and concentrated to a residue, which was purified by gradient flash chromatography on silica gel (5 to 10% acetone in hexanes) to give ketoester **169** (735 mg, 92% yield) as a colorless oil: R_f 0.53 (35% acetone in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.57 (s, 1H), 6.04 (dd, *J* = 1.8, 6.3 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 3.64 (dd, *J* = 6.3, 21.8 Hz, 1H), 3.47 (d, *J* = 17.4 Hz, 1H), 3.14 (d, *J* = 17.7 Hz, 1H), 3.02 (app. d, *J* = 21.6 Hz, 1H), 2.89 (d, *J* = 15.6 Hz, 1H), 2.77 (d, *J* = 17.4 Hz, 1H), 2.46 (d, *J* = 15.6 Hz, 1H), 2.35 (s, 3H), 2.32 (d, *J* = 17.4 Hz, 1H), 1.28 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2, 171.6, 156.1, 146.0, 144.0, 136.9, 120.8, 119.7, 116.3, 108.4, 55.3, 51.4, 49.6, 49.1, 46.2, 39.2, 38.5, 33.2, 30.9, 24.1, 21.9; IR (Neat film NaCl) 2956, 1735, 1711, 1584, 1462, 1314, 1198, 1134, 1064 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{21}H_{26}O_4+H]^+$: *m/z* 343.1909, found 343.1894.



169 ***170***

Ester 170. To a solution of ketoester **169** (200 mg, 0.581 mmol, 1.00 equiv), ethylene glycol (4.00 mL, 71.7 mmol, 124 equiv), and pyridinium *p*-toluenesulfonate (2.00 g, 7.96 mmol, 13.7 equiv) in benzene (70 mL) was fitted with a Dean-Stark apparatus and refluxed at 95 °C for 10 h. The reaction mixture was allowed to cool to ambient temperature, diluted with H_2O (50 mL), and CH_2Cl_2 (50 mL), and extracted with CH_2Cl_2 (5 x 30 mL). The combined organics were washed with a 1:1:1 solution of brine, H_2O, and sat. aq. $NaHCO_3$ (4 x 20 mL), dried (K_2CO_3), and concentrated to a oil, which was purified by gradient flash chromatography on silica gel (30% Et_2O in hexanes) to give ester **170** (217 mg, 97% yield) as a colorless oil: R_f 0.48 (50% Et_2O in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.54 (s, 1H), 6.00 (dd, *J* = 2.3, 6.2 Hz, 1H), 4.18-4.04 (m, 2H), 4.02-3.89 (m, 2H), 3.81 (s, 3H), 3.64 (s, 3H), 3.55 (dd, *J* = 6.2, 21.8 Hz, 1H), 2.96 (d, *J* = 21.8 Hz, 1H), 2.91 (d, *J* = 14.1 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 2.52 (dd, *J* = 2.0, 13.7 Hz, 1H), 2.34 (s, 3H), 2.32 (dd, *J* = 2.1, 14.1 Hz, 1H), 2.11 (d, *J* = 13.8 Hz, 1H), 1.56 (d, *J* = 14.1 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 155.9, 148.3, 144.8, 136.6, 121.2, 119.4, 116.6, 108.6, 107.9, 64.7, 63.2, 55.3, 51.1, 46.5, 45.4, 43.0, 39.3, 38.7, 30.8, 30.2, 24.0, 21.9; IR (Neat film NaCl) 2956, 2883, 1733, 1462, 1348, 1199, 1135, 1067, 1018 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{23}H_{30}O_5+H]^+$: *m/z* 387.2171, found 387.2179.



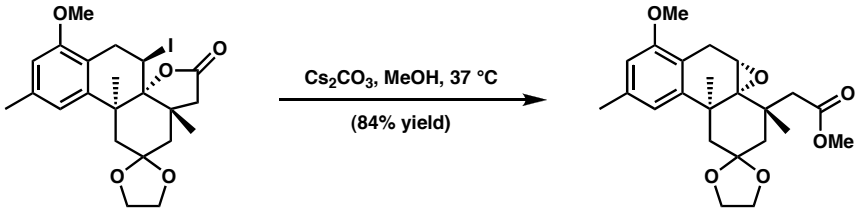
169 *172*

Iodolactone 172. A solution of ketoester **169** (200 mg, 0.581 mmol, 1.00 equiv) in MeOH (13 mL), and 10% w/v aqueous NaOH (13 mL) was heated at 40 °C for 10 h. The reaction mixture was cooled to ambient temperature, poured into brine (50 mL) and H_2O (10 mL), acidified with 3 M HCl to pH 0, extracted with EtOAc (6 x 20 mL), dried (Na_2SO_4), concentrated, and used in the next step without further purification.

A solution of the above crude carboxylic acid, ethylene glycol (500 μL, 8.97 mmol, 15.4 equiv), and pyridinium *p*-toluenesulfonate (500 mg, 1.99 mmol, 3.42 equiv) in benzene (50 mL) was fitted with a Dean-Stark apparatus and refluxed at 100 °C for 2 h. The cooled (0 °C) reaction mixture was diluted with H_2O (25 mL), brine (25 mL), and CH_2Cl_2 (50 mL), and extracted with CH_2Cl_2 (6 x 30 mL). The combined organics were dried (Na_2SO_4), concentrated, and used immediately in the next step without further purification.

To a solution of the crude ketal and $NaHCO_3$ (68.4 mg, 0.814 mmol, 1.4 equiv) in H_2O (5 mL) and acetonitrile (5 mL) was added KI (125 mg, 0.756 mmol, 1.3 equiv) and I_2 (192 mg, 0.756 mmol, 1.3 equiv). The reaction mixture was stirred in the dark for 30 h and quenched with saturated aqueous $Na_2S_2O_3$ (10 mL), H_2O (20 mL), and brine (20 mL). The reaction mixture was extracted with EtOAc (8 x 20 mL), dried (Na_2SO_4), concentrated, and recrystallized (15% acetone in hexanes, ~25 mL, from 80 to –20 °C) to give iodolactone **172** (247 mg, 85% yield) as a white solid: mp 155-160 °C (decomp.)

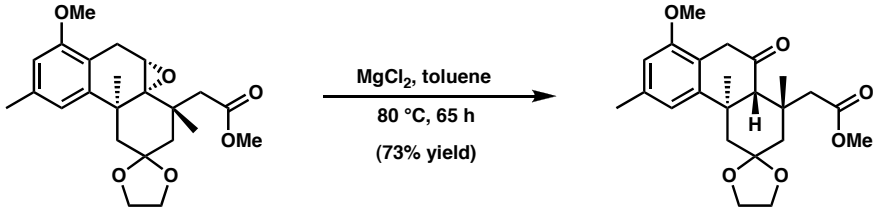
(acetone/hexanes); R_f 0.37 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 6.92 (s, 1H), 6.22 (s, 1H), 5.29 (app. t, *J* = 10.0 Hz, 1H), 3.75 (dd, *J* = 10.0, 19.3 Hz, 1H), 3.52-3.34 (comp. m, 3H), 3.34-3.26 (comp. m, 2H), 3.24 (s, 3H), 3.01 (d, *J* = 18.0 Hz, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 2.49 (d, *J* = 16.0 Hz, 1H), 2.45 (d, *J* = 18.0 Hz, 1H), 2.12 (s, 3H), 1.54 (d, *J* = 14.5 Hz, 1H), 1.13 (s, 3H), 0.98 (d, *J* = 14.5 Hz, 1H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.5, 156.9, 143.6, 138.1, 121.2, 117.6, 109.4, 107.2, 87.2, 64.5, 64.2, 55.1, 46.1, 45.8, 45.4, 43.2, 42.6, 36.5, 30.9, 30.8, 25.2, 22.2; IR (Neat film NaCl) 2964, 2881, 1790, 1461, 1229, 1203, 1071, 1023 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{22}H_{27}IO_5+H]^+$: *m/z* 499.0982, found 499.0986.



172 ***173***

Epoxide 173. To a solution of iodolactone **172** (75.0 mg, 0.151 mmol, 1.00 equiv) in MeOH (15 mL) was added Cs_2CO_3 (981 mg, 3.01 mmol, 20.0 equiv). The reaction mixture was warmed to 37 °C and vigorously stirred for 19 h. The reaction mixture was cooled to ambient temperature, diluted with H_2O (20 mL), brine (20 mL), and CH_2Cl_2 (20 mL), extracted with CH_2Cl_2 (5 x 20 mL) and EtOAc (5 x 25 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes + 1% TEA) to give epoxide **173** (51.0 mg, 84% yield) as a colorless oil: R_f 0.54, 0.28 (35% EtOAc in hexanes, 10% EtOAc in hexanes developed 3 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.45 (s, 1H), 4.12-4.08

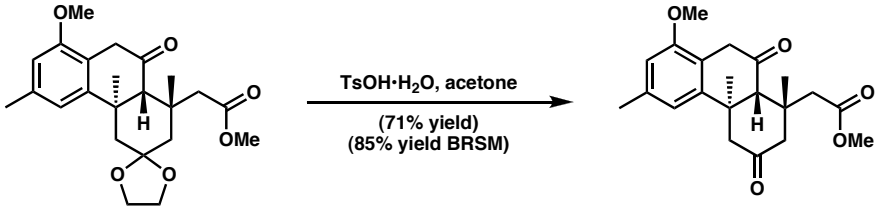
(m, 1H), 4.06-4.01 (m, 1H), 3.94-3.86 (comp. m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 3.58 (d, J = 2.5 Hz, 1H), 3.24 (d, J = 19.5 Hz, 1H), 2.90 (dd, J = 3.5, 20.0 Hz, 1H), 2.80 (dd, J = 1.0, 14.5 Hz, 1H), 2.79 (d, J = 14.5 Hz, 1H), 2.37 (d, J = 14.0 Hz, 1H), 2.31 (dd, J = 1.0, ~15 Hz, 1H), 2.30 (s, 3H), 2.03 (d, J = 15.0 Hz, 1H), 1.72 (d, J = 15.0 Hz, 1H), 1.63 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.8, 157.5, 144.9, 136.6, 120.4, 116.1, 108.9, 108.2, 65.7, 64.8, 63.7, 57.1, 55.2, 51.1, 48.8, 43.4, 41.7, 39.7, 38.3, 27.5, 26.7, 24.4, 22.2; IR (Neat film NaCl) 2950, 1734, 1590, 1462, 1360, 1196, 1135, 1075, 1017 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{23}H_{30}O_6+H]^+$: m/z 403.2121, found 403.2113.



173 *174*

Ketone 174. A solution of epoxide **173** (49.0 mg, 0.122 mmol, 1.00 equiv) in toluene (30 mL) in a flame-dried Schlenk flask under an N_2 atmosphere was treated with magnesium chloride (2.00 g, 21.0 mmol, 172 equiv) and heated to 80 °C for 65 h. After cooling to ambient temperature, the reaction mixture was filtered and the filter cake was washed with toluene (2 x 25 mL). The filter cake was partitioned between EtOAc (20 mL) and ice cold water (20 mL), and further extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na_2SO_4), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to give ketone **174** (36.0 mg, 73% yield) as a colorless oil: R_f 0.55, 0.33 (35% EtOAc in hexanes, 10% EtOAc in hexanes developed 3 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73

(s, 1H), 6.57 (s, 1H), 4.15-4.05 (m, 2H), 4.00-3.88 (m, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.64 (d, *J* = 22.5 Hz, 1H), 3.47 (dd, *J* = 1.5, 14.5 Hz, 1H), 3.34 (d, *J* = 22.0 Hz, 1H), 3.23 (d, *J* = 14.5 Hz, 1H), 2.58 (dd, *J* = 2.5, 14.5 Hz, 1H), 2.56 (s, 1H), 2.45 (dd, *J* = 2.5, 13.5 Hz, 1H), 2.35 (s, 3H), 2.13 (d, *J* = 13.0 Hz, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 1.14 (dd, *J* = 1.5, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 173.9, 156.4, 149.4, 137.6, 117.3, 116.1, 108.7, 108.3, 65.2, 63.0, 62.8, 55.3, 50.9, 46.4, 42.5, 42.3, 40.0, 36.0, 35.6, 28.9, 25.6, 21.9; IR (Neat film NaCl) 2953, 2885, 1731, 1713, 1586, 1462, 1360, 1193, 1065 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{23}H_{30}O_6]^+$: *m/z* 402.2042, found 402.2027.



174 ***175***

Diketone 175. A solution of ketone **174** (29.3 mg, 0.728 mmol, 1.00 equiv) in acetone (10 mL) was treated with TsOH•H_2O (100 mg, 0.526 mmol, 7.22 equiv) and stirred at ambient temperature for 4 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (25 mL), extracted with CH_2Cl_2 (6 x 15 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (7.5 to 12.5% EtOAc in hexanes) to give starting ketone **164** (4.6 mg, 16% yield) and diketone **175** (18.6 mg, 71% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from acetone/heptanes at ambient temperature: mp 184-186 °C (acetone/heptanes); R_f 0.40 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.59 (s, 1H), 3.82 (s, 3H), 3.71 (d, *J* = 22.0 Hz, 1H), 3.69 (s, 3H),

3.46 (dd, *J* = 1.5, 14.5 Hz, 1H), 3.39 (d, *J* = 22.5 Hz, 1H), 3.08 (s, 1H), 2.99 (dd, *J* = 2.3, 12.8 Hz, 1H), 2.93 (dd, *J* = 2.3, 12.8 Hz, 1H), 2.89 (d, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.33 (d, *J* = 14.5 Hz, 1H), 2.21 (d, *J* = 12.5 Hz, 1H), 1.36 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 207.8, 171.9, 156.6, 147.6, 138.2, 117.1, 115.5, 109.3, 62.7, 55.4, 53.6, 52.2, 51.4, 45.7, 40.1, 39.5, 37.6, 28.0, 26.6, 21.9; IR (Neat film NaCl) 2953, 1732, 1713, 1586, 1462, 1331, 1194, 1063, 731 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{21}H_{26}O_5]^+$: *m/z* 358.1780, found 358.1774.

2.9 Notes and Citations

(1) (a) Tanner, D.; Anderson, P. G.; Tedenborg, L.; Somfai, P. *Tetrahedron* **1994**, *50*, 9135-9144. (b) Tanner, D.; Tedenborg, L.; Somfai, P. *Acta Chem. Scand.* **1997**, *51*, 1217-1223.

(2) Williams, D. R.; Brugel, T. A. *Org. Lett.* **2000**, *2*, 1023-1026.

(3) (a) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6237-6240. (b) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6241-6244.

(4) Williams, D. R.; Cortez, G. A. *Tetrahedron Lett.* **1998**, *39*, 2675-2678.

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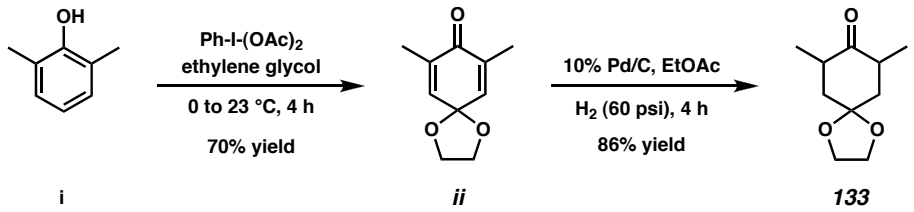
(6) Bagdanoff, J. T. Development of the Enantioselective Oxidation of Secondary Alcohols and Natural Products Total Synthesis. Ph.D., California Institute of Technology, Pasadena, CA, August 2005.

(7) (a) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559-1562. (b) Rose, P. A.; Lei, B.; Shaw, A. C.; Abrams, S. R.; Walker-Simmons, M. K.; Napper, S.; Quail, J. W. *Can. J. Chem.* **1996**, *74*, 1836-1843.

(8) Franck-Neumann, M.; Miesch, M.; Barth, F. *Tetrahedron* **1993**, *49*, 1409-1420.

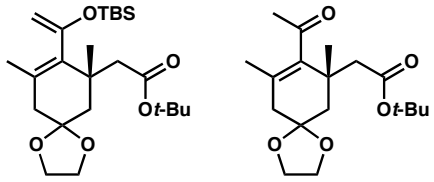
(9) In our experience, the dimethyl ketone **133** was best prepared by iodobenzene diacetate oxidation of 2,6 dimethylphenol **i** to give quinone **ii**. Quinone **ii** was readily reduced to ketone **133** with Pd/C under hydrogen (60 psi).



i *ii* ***133***

(10) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

(11) The use of TBS enol ether **iii** analogous to ethyl enol ether **137** in either thermal or Lewis acid-promoted reactions gave none of the desired reaction. Frequently enone **iv** was observed.

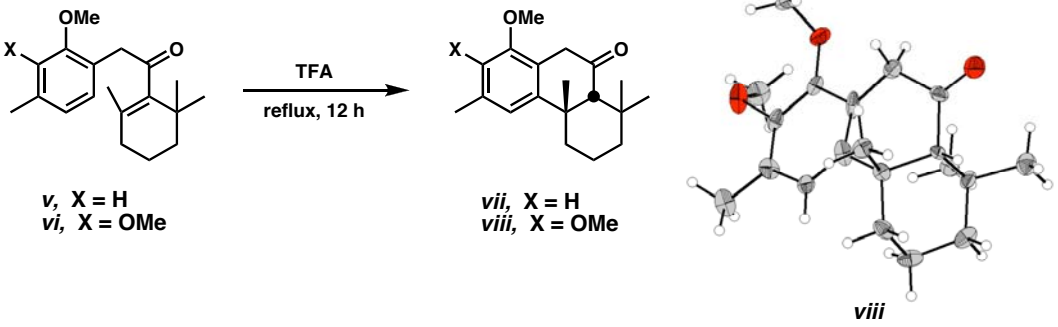


iii ***iv***

(12) (a) Matsumoto, T.; Ohmura, T. *Chem. Lett.* **1977**, 335-338. (b) Liebeskind, L. S.; Chidambaram, R.; Nimkar, S.; Liotta, D. *Tetrahedron Lett.* **1990**, *31*, 3723-3726.

(13) (a) Schmidt, C.; Thazhuthaveetil, J. *Can. J. Chem.* **1973**, *51*, 3620-3624. (b) Matsumoto, T.; Usui, S.; Morimoto, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1575-1579. (c) Matsumoto, T.; Usui, S. *Chem. Lett.* **1978**, 897-900. (d) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2396-2399.

(14) This was confirmed by cyclization of enones **v** and **vi**. Ketone **vii** was produced in only ~10% yield, while ketone **viii** was produced in ~40% yield. X-ray structure determination confirmed the relative configuration between the stereocenters in ketone **viii**.



v, X = H
vi, X = OMe

vii, X = H
viii, X = OMe

viii

(15) Stevens, R. V.; Angle, S. R.; Kloc, K.; Mak, K. F.; Trueblood, K. N.; Liu, Y.-X. *J. Org. Chem.* **1986**, *51*, 4347-4353.

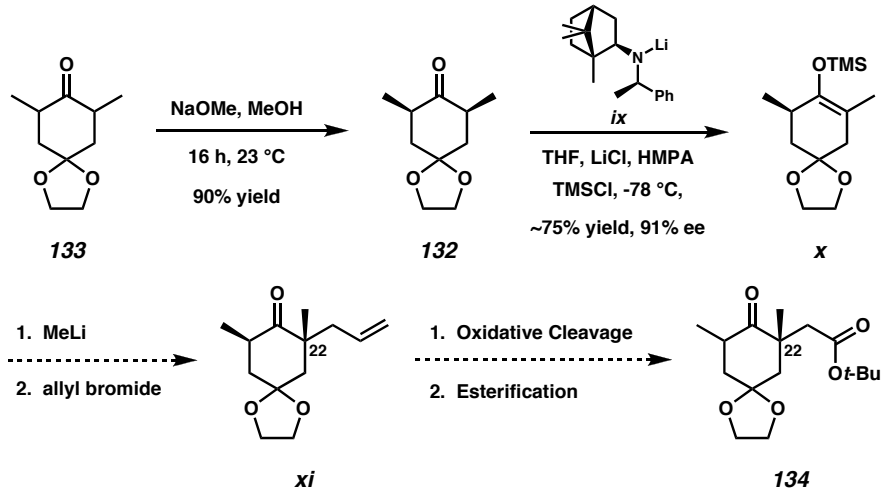
(16) To our knowledge this is the first time that such a hindered enol triflate was carbonylated directly to the enal oxidation state.

(17) (a) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543-545. (b) Sato, D.; Kawasaki, H.; Shimada, I,; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761-763. (c) Aoki, K.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 5105-5108.

(18) (a) Cox, P.; Simpkins, N. S. *Tetrahedron Asymmetry* **1991**, *2*, 1-26. (b) Cox, P.; Simpkins, N. S. *Synlett* **1991**, 321-323. (c) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533-534.

(19) Using chiral lithium amide **ix** we demonstrated that *meso*-ketone **132** could be desymmetrized in up to 91% ee by deprotonation and trapping with TMSCl. We planned to react the silyl enol ether **x** with an allyl electrophile to generate the quaternary center in ketone **xi**. Oxidative cleavage and esterification would complete the asymmetric synthesis of ketoester **134**. However, our experience in alkylating ketone **133** under non-enantioselective conditions suggested that

asymmetric allylation would be slow as well. This would provide ample time for racemization of the intermediate chiral enolate to occur.



(20) See Chapter 4 for details.

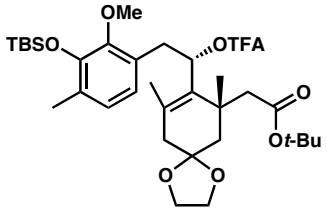
(21) Other acidic conditions included polyphosphoric acid, phosphoric acid/formic acid, and $AlCl_3$.

(22) For an excellent review of S_N' reactions, see: Paquette, L. A.; Stirling, C. J. M.; *Tetrahedron* **1992**, *48*, 7383-7423.

(23) Subsequent to, and independent of, our own studies of the S_N' cyclization of allylic alcohols and arenes under acid conditions, a similar report appeared in the literature, see: Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, *43*, 3435-3438.

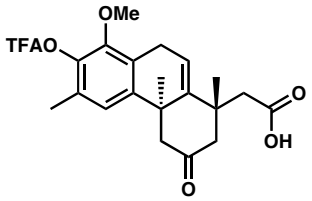
(24) Reaction of allylic acetate **162** in TFA produced more side products than the other substrates. This prevented quantification of dr and yield.

(25) Additionally, the analogous trifluoroacetate **xii** underwent cyclization in TFA to give comparable yields and diastereoselectivities as allylic alcohol **155**.



xii

(26) The formation of trifluoroacetates in situ is supported by the isolation of minor amounts of trifluoroacetylated product **xiii** from S_N' reactions in TFA.



xiii

(27) Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. G. *J. Org. Chem.* **1990**, *55*, 991-995.

(28) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett.* **1990**, 533-535.

(29) Tohma, M.; Tomita, T.; Kimura, M. *Tetrahedron Lett.* **1973**, *14*, 4359-4362.

(30) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett.* **2001**, 1305-1307.

(31) (a) Syamala, M. S.; Das, J.; Baskaran, S.; Chandrasekaran, S. *J. Org. Chem.* **1992**, *57*, 1928-1930. (b) Salvador, J. A. R.; Melo, M. L. S.; Neves, A. S. *Tetrahedron Lett.* **1996**, *37*, 687-690.

(32) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189-6190.

(33) A number of oxidation conditions gave oxidation at the benzylic C(19) position.

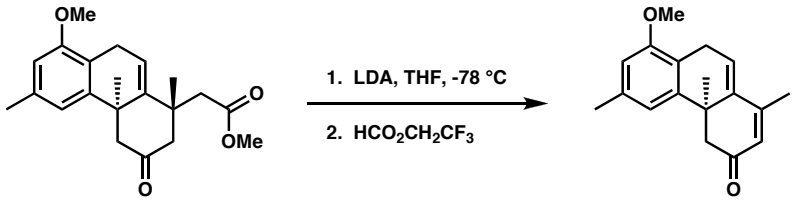
(34) The use of magnesium chloride was critical as use of magnesium bromide afforded the halogen exchange product. Treatment with BF_3•Et_2O gave the desired hydride shift with concomitant deketalization.

(35) Naqvi, S. M.; Horwitz, J. P.; Filler, R. *J. Am. Chem. Soc.* **1957**, *79*, 6283-6286.

(36) (a) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 5083-5089. (b) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070-3075.

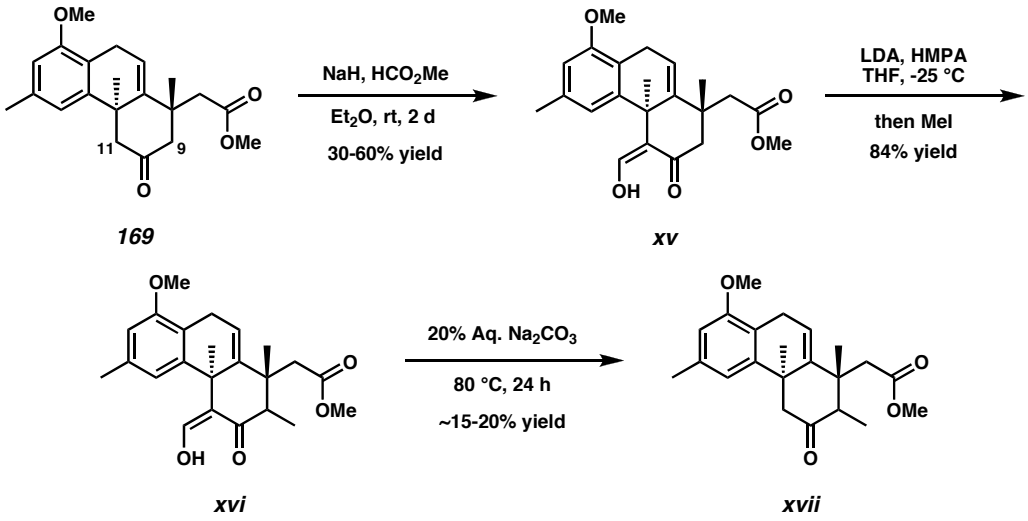
(37) Williams, D. R.; Cortez, G. A. *Tetrahedron Lett.* **1998**, *39*, 2675-2678.

(38) Under other kinetic enolate trapping conditions, fragmentation of ketoester **169** occurred to give the extended enone **xiv**.



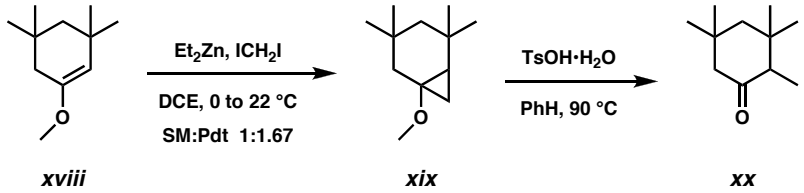
169 ***xiv***

(39) The ability to selectively deprotonate at C(11) led us to pursue a strategy to "protect" C(11). Ketoester **169** was condensed with methyl formate at C(11) and then successfully methylated at C(9). Unfortunately, despite extensive experimentation, no reagents could be found that were capable of removing the hydroxymethylene from methyl ketone **xvi** in greater than ~20% yield.



(40) Bofinger, K. R.; Hanack, M. *Chem. Ber.* **1985**, *118*, 2993-3003.

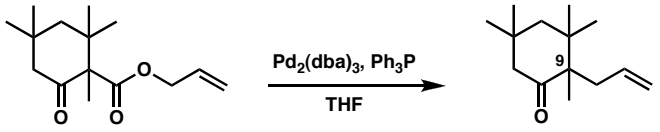
(41) Since selective enolization had proved difficult, we hoped to separate the isomers and cyclopropanate the C(9)-C(10) enol. To that end, cyclopropanation of steric model methyl enol ether **xviii** was attempted with diethyl zinc and methylene iodide. Treatment with tosic acid in benzene opened the cyclopropane **xix** to the desired methyl ketone **xx**. However, in our hands it was difficult to drive the reaction to more than ~60% conversion under optimized conditions.



(42) Hirai, G.; Oguri, H.; Hirama, M. *Chem. Lett.* **1999**, *28*, 141-142.

(43) We were delighted to find that pentamethyl β-ketoester **xxi** underwent allylation selectively at the more substituted α-site with Tsuji's conditions. We envisioned this method as a late-stage means to install the C(9) quaternary stereocenter in the presence of the other C ring quaternary stereocenters. In this case, chiral ligands

may have been used to override the inherent diastereoselectivity of the allylation. These allylation methods have the additional advantage of forming quaternary centers at room temperature in a few hours or less under neutral conditions.



xxi ***xxii***