CHAPTER TWO

Early Efforts Toward the Synthesis of Zoanthenol

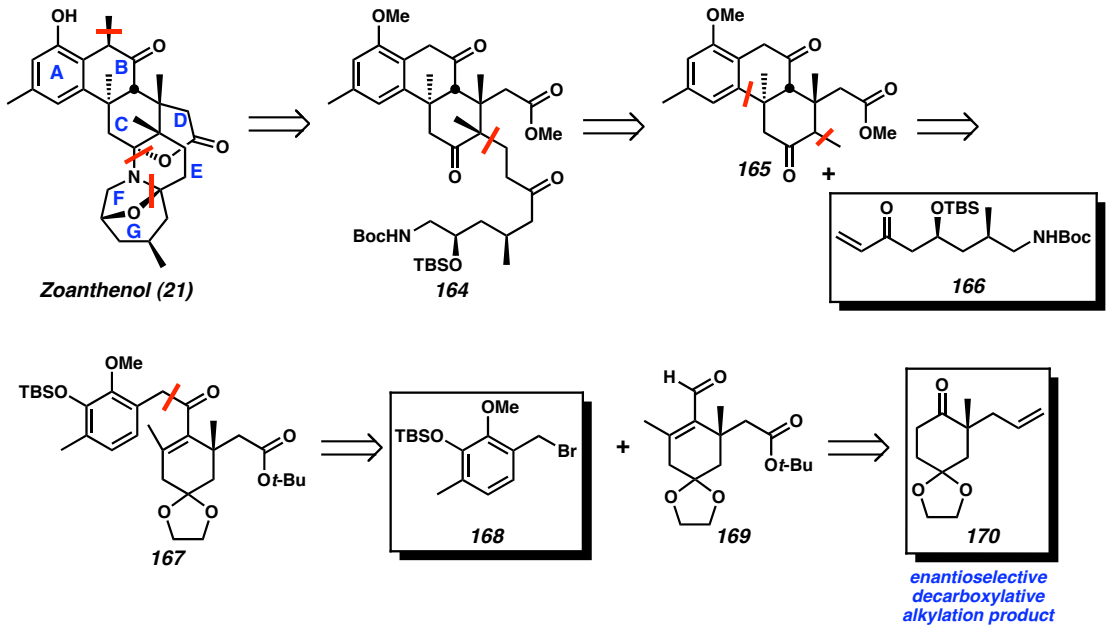
Discovery of an Unusual Acid-Catalyzed Cyclization and Development of an Enantioselective Route to a Synthon for the DEFG Rings[†]

2.1.1 Introduction and Retrosynthetic Analysis[1]

In Chapter 1, we highlighted the range of biological activities and structural features presented by the zoanthamine family of alkaloids. When we began our efforts toward the synthesis of this intriguing family of natural products, we were drawn to zoanthenol (**21**) as an initial synthetic target because it retains the major stereochemical challenges of the zoanthamines, while its aromatic A ring offers the opportunity to explore unique retrosynthetic possibilities.[2] It was our hope that the challenges encountered during the synthesis of zoanthenol would guide our future synthetic efforts toward the remaining family members. With seven rings and nine stereocenters confined to a 30-carbon framework, zoanthenol is a densely functionalized, topographically complex target molecule. The C ring poses the greatest stereochemical challenge with five contiguous stereocenters, three of which are all-carbon quaternary centers. Our overarching strategy was to generate one quaternary center in an enantioselective fashion and then derive the remaining stereocenters diastereoselectively. A convergent union of the A and C rings by a 2-carbon tether and subsequent closure of the B ring was another design feature. We planned to introduce all the functionality of the heterocyclic C(1) to C(8) fragment in a single operation (i.e., **164** ⇒ **165** + **166**). Previous work by the Kobayashi and Williams groups demonstrated that the complicated hemiaminals forming the DEFG

[†] The work described in this chapter was performed primarily by former graduate students in the Stoltz group, Dr. Douglas C. Behenna (Carbocyclic Core) and Dr. Jeffrey T. Bagdanoff (DEFG Synthon), prior to my arrival at Caltech.

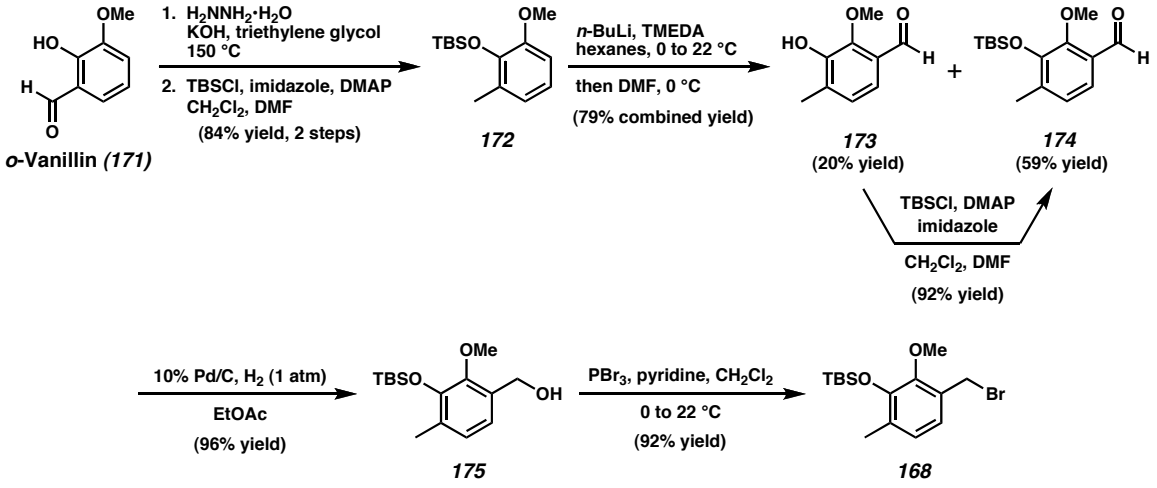
rings were thermodynamically favored.[3] Thus, the DEFG heterocycles could be retrosynthetically unraveled to give triketone **164** (Scheme 2.1.1). Disconnection of the C(8)-C(9) bond and removal of the C(9) and C(19) methyl groups could afford ketone **165** and enone **166**. We envisioned the cleavage of the tricyclic core structure **165** by scission of the C(12)-C(13) bond employing an intramolecular conjugate addition of the A ring into a C ring enone (i.e., **166**).[4] We reasoned that this type of intramolecular Friedel-Crafts reaction would require a highly electron-rich arene for effective cyclization; therefore, oxygenation was incorporated at C(16) of enone **167** to increase the nucleophilicity of the A ring. Enone **167** could arise from 1,2-addition of a Grignard reagent derived from bromide **168** into enal **169**, which in turn could be derived from α-quaternary allyl ketone **170**, which was accessible in enantioenriched form as the product of an enantioselective decarboxylative alkylation reaction.[5]



Scheme 2.1.1 Retrosynthetic analysis of zoanthenol.

2.2.1 Synthesis of the A Ring Synthon

The A ring synthon could be readily accessed in five steps from *o*-vanillin (**171**, Scheme 2.2.1). Wolff-Kishner reduction of **171** followed by silylation provided arene **172** in 84% yield over two steps. *Ortho*-lithiation was directed by the C(17) methoxy group, and quenching with *N*,*N*-dimethylformamide provided a mixture of aldehyde **174** and the corresponding desilylated aldehyde **173**. Resilylation of **173** proceeded smoothly under standard conditions to provide **174**. Aldehyde reduction was accomplished by treatment with 10% Pd/C under a balloon of hydrogen to afford benzylic alcohol **175** in 96% yield.[6] Treatment of this benzylic alcohol (**175**) with phosphorus tribromide and pyridine led to benzyl bromide **168** in 92% yield after distillation. This approach to the A ring synthon was efficient and highly scaleable, allowing production of 20–25 g of benzyl bromide **168** per batch.

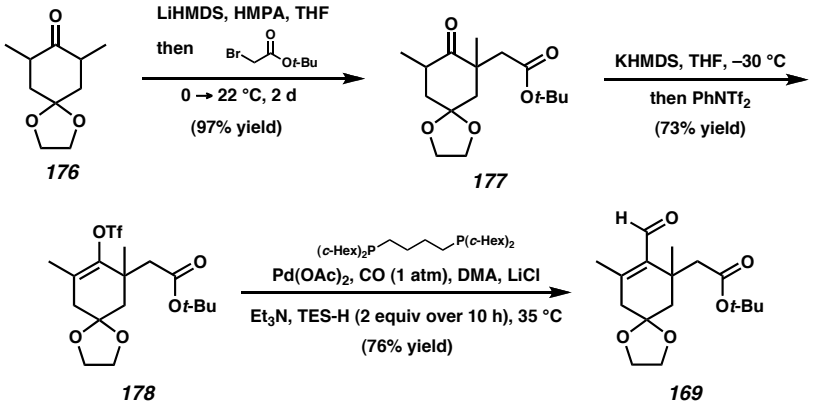


Scheme 2.2.1 Synthesis of the A ring synthon.

2.2.2 Synthesis of the C Ring Synthon

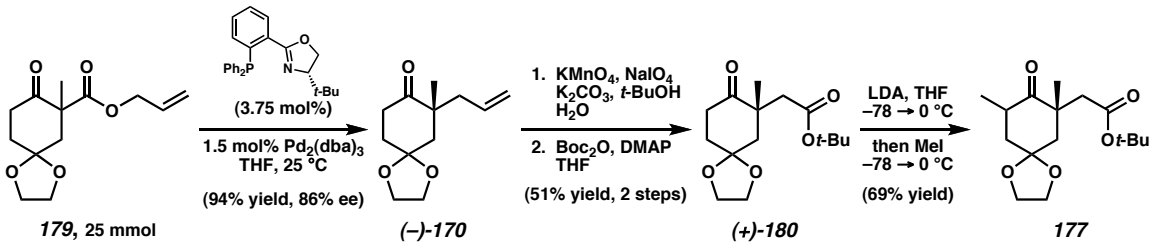
In order to determine the feasibility of the 6-*exo* conjugate addition, the target enal was synthesized as a racemate (Scheme 2.2.2). Known 1,6-dimethyl ketone **176**[7] was deprotonated and alkylated to give ketoester **177** in excellent yield as a mixture of

diastereomers. Deprotonation of methyl ketone **177** and quenching with $PhNTf_2$ afforded enol triflate **178**. After significant optimization to accommodate the steric challenges of the substrate, an efficient one-step reductive carbonylation of triflate **178** was developed. Treatment of triflate **178** under an atmosphere of CO with $Pd(OAc)_2$, 1,4-bis-(dicyclohexylphosphino)butane as a ligand, and TES-H as a reducing agent afforded the desired enal **169** in good yield. To our knowledge, this is the first time that such a hindered vinyl triflate has been carbonylated directly to the enal oxidation state.[8]



Scheme 2.2.2 Racemic synthesis of the C ring synthon.

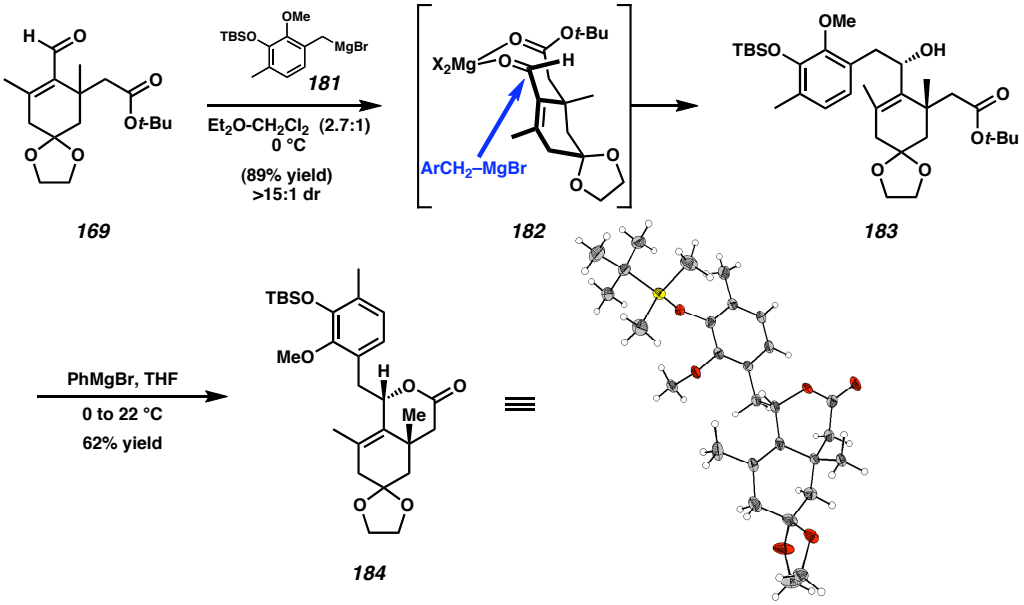
Although racemic material was useful for exploratory studies, our goal from the outset was an asymmetric synthesis of zoanthenol. Toward this end, we were delighted to find that our recently developed asymmetric decarboxylative alkylation methodology[5] was a reliable and efficient method to convert allyl β-ketoester **179** to α-quaternary ketone (–)-**170** in excellent yield and high ee on 25 mmol scale (Scheme 2.2.3). Oxidative olefin cleavage and esterification gave *t*-butyl ester (+)-**180** in 51% yield over two steps. Subsequent methylation provided a good yield of methyl ketoester **177**, an intermediate in our C ring synthesis, allowing entry into a catalytic enantioselective synthesis of zoanthenol.



Scheme 2.2.3 Decarboxylative alkylation enables enantioselective synthesis.

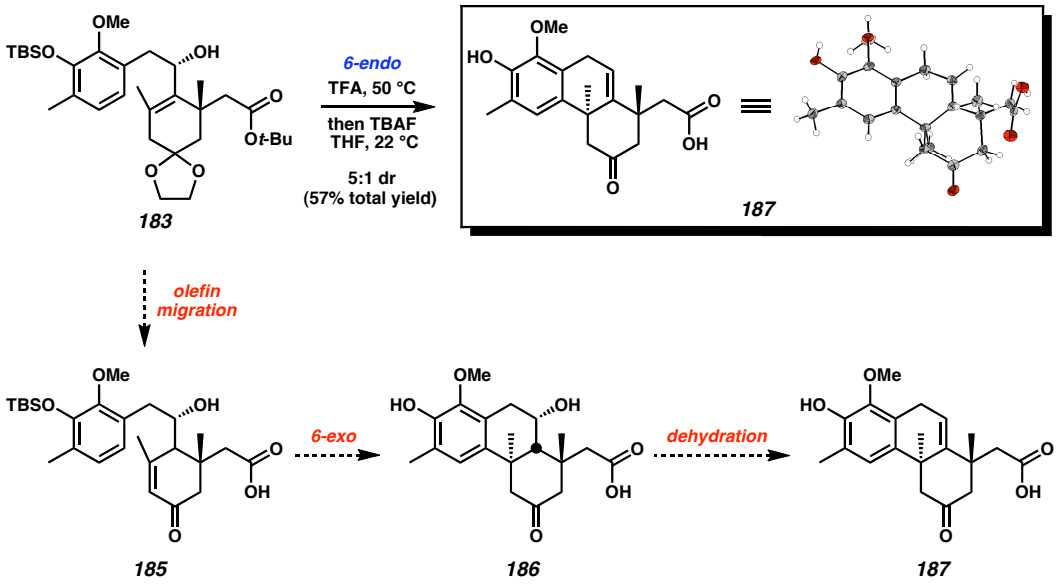
2.2.3 Synthesis of the Tricyclic Core of Zoanthenol

Addition of Grignard reagent **181**, derived from A-ring synthon **168**, to enal **169** produced allylic alcohol **183** in high yield and diastereoselectivity (Scheme 2.2.4). Use of methylene chloride as a co-solvent for the addition reaction was critical. We hypothesize that the addition of this noncoordinating solvent encourages the chelation of Mg between the aldehyde and the *t*-butyl ester, resulting in selective attack of the *Re* face of the aldehyde by the incoming Grignard reagent (**182**). This stereochemistry was confirmed by formation of lactone **184** and examination of a single crystal by X-ray structure analysis.



Scheme 2.2.4 Diastereoselective Grignard addition.

With the A and C rings joined, we could begin to investigate the 6-*exo* cyclization by exposing allylic alcohol **183** to TFA at reflux (Scheme 2.2.5). We anticipated that loss of protecting groups and olefin migration would afford enone **185**, which would undergo 6-*exo* conjugate addition to form keto-alcohol **186**. To our delight, the major product contained a single aromatic C-H peak by ^{1}H NMR, as well as two isolated aliphatic CH_3 groups, signaling that the reaction generated a product containing the two desired quaternary centers. However, the spectrum also possessed an olefinic resonance. Upon standing in $CDCl_3$, the major product formed crystals suitable for X-ray diffraction. Interestingly, cyclization of allylic alcohol **183** had occurred, but via 6-*endo* S_N' cyclization to give acid **187**.[9,10] Additionally, the solid-state structure confirmed the anti disposition of the methyl groups at C(12) and C(22) in **187**.

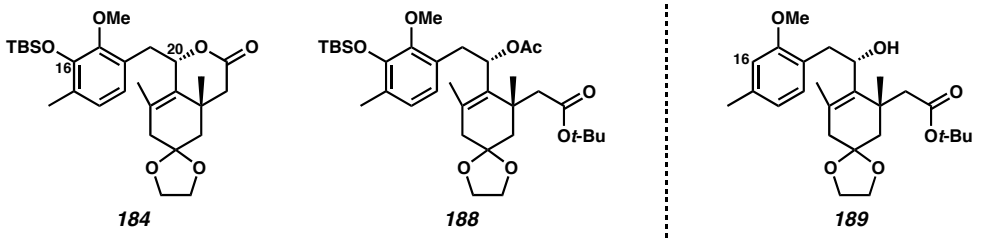


Scheme 2.2.5 Discovery of an unusual acid-mediated cyclization.

The S_N' Friedel-Crafts reaction to produce carboxylic acid **187** achieved the important goal of generating the C(12) quaternary stereocenter with the desired relative configuration. In order to better understand the reaction pathway, a number of parameters were evaluated. The choice of acid in the reaction is crucial, as trifluoroacetic acid was unique in promoting S_N' cyclization. Both stronger acids (e.g.,

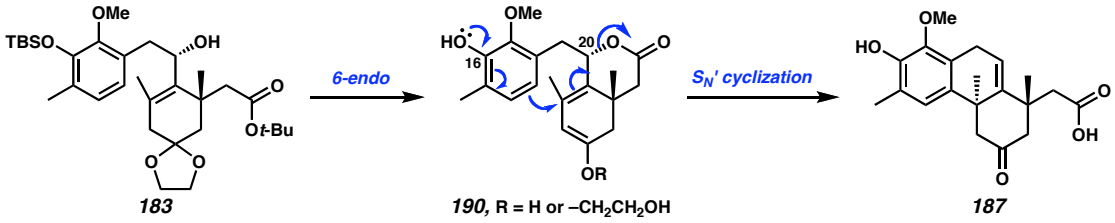
triflic acid) and weaker acids (e.g., acetic acid) failed to produce tricycle **187**. Even the dilution of neat TFA with methylene chloride, benzene, or acetic acid caused the cyclization to fail.

Interestingly, both lactone **184** and allylic acetate **188** underwent cyclization in TFA to give acid **187** with similar yields and diastereoselectivities (Scheme 2.2.6).[11] Furthermore, C(16) des-oxy arene **189** failed to generate any cyclized products, confirming the importance of the nucleophilicity imparted by C(16) oxygenation. Finally, the allylic alcohol substrate epimeric at C(20) does not undergo cyclization.[12]



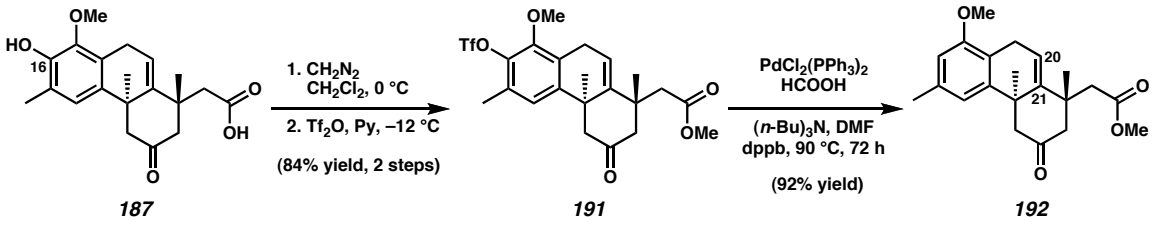
Scheme 2.2.6 Other substrates for cyclization.

The unique ability of TFA to mediate the reaction suggests that its properties as a strong acid and a dehydrating agent are important to the reaction mechanism. The selectivity of the system indicates that all three substrates (**183**, **184**, and **185**) may proceed through intermediate lactone **190** (i.e., allylic alcohol **183** and acetate **188** may be converted to the lactone in situ), and that the reactions proceed via a partially concerted displacement relying on the directing ability of a carboxylate leaving group and not via a full allylic cation (Scheme 2.2.7).



Scheme 2.2.7 A proposed mechanism for the S_N' cyclization.

With an efficient route in hand to construct a zoanthenol carbocyclic ring system containing two of the three quaternary stereocenters, we turned our attention to the completion of our proposed intermediate **165**. Following diazomethane-mediated esterification, deoxygenation of the C(16) phenol was accomplished by formation of aryl triflate **191** and subsequent treatment with $PdCl_2(PPh_3)_2$ and formic acid to form **192** in 92% yield (Scheme 2.2.8).[13]

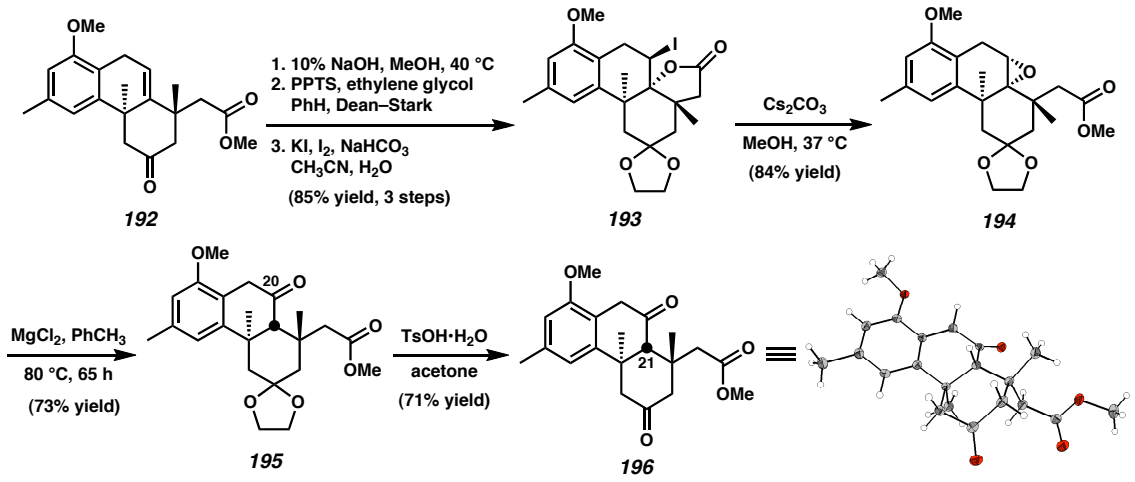


Scheme 2.2.8 Deoxygenation of the A ring.

Due to our serendipitous discovery of the S_N' reaction, we had not anticipated the reoxygenation of the olefin in our retrosynthetic planning. As such, significant experimentation was required to find a synthetic strategy to convert the C(20)–C(21) olefin of ketoester **192** into the desired C(20) ketone.[14] The X-ray structure in Scheme 2.2.5 illustrates the pseudo-axial nature of the methyl groups surrounding the olefin, which partially block the π bond and hinder the approach of typical oxidants.

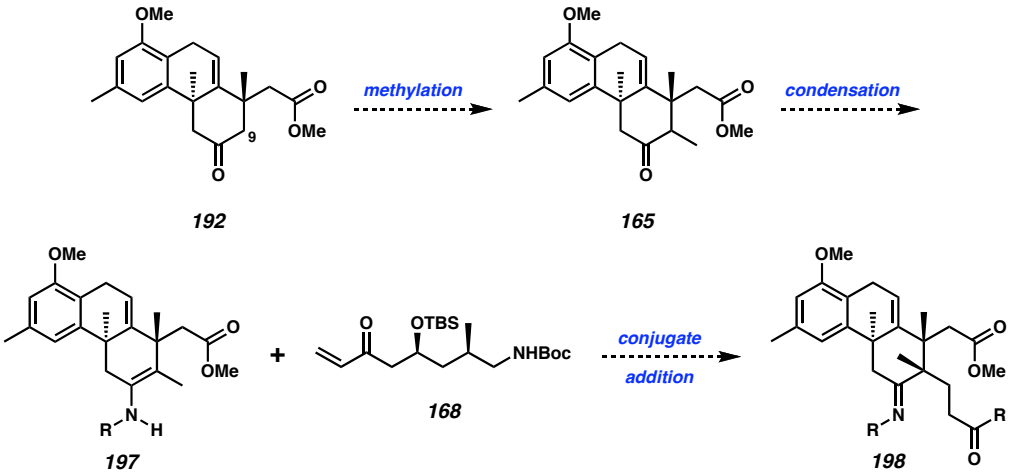
Thus, we chose to pursue an alternative, intramolecular method of olefin oxygenation. Our approach began with saponification of ketoester **192** followed by ketalization (Scheme 2.2.9). Treatment of the crude product with KI, I_2, and base gave iodolactone **193** in 85% yield over three steps after recrystallization. Lactone methanolysis under basic conditions afforded smooth conversion to epoxide **194**. Hydride migration from C(20) was accomplished by heating epoxide **194** in toluene with $MgCl_2$,[15] resulting in smooth conversion to rearranged ketoester **195** in 73% yield. Treatment of ketoester **195** with *p*-toluenesulfonic acid produced diketone **196**, which

was characterized by X-ray crystallography. The solid-state structure confirmed that the desired C(21) stereochemistry was obtained from the hydride shift.



Scheme 2.2.9 Refunctionalization of the C(20)-C(21) olefin.

Having completed the synthesis of the carbocyclic core, we turned our attention to the installation of the C(9) methyl group and side chain attachment. As illustrated in Scheme 2.2.10, methylation of tricycle **192** would be followed by condensation with a primary amine to form enamine **197**. Conjugate addition of this enamine into enone **168** would then provide readily hydrolyzable imine **198**.

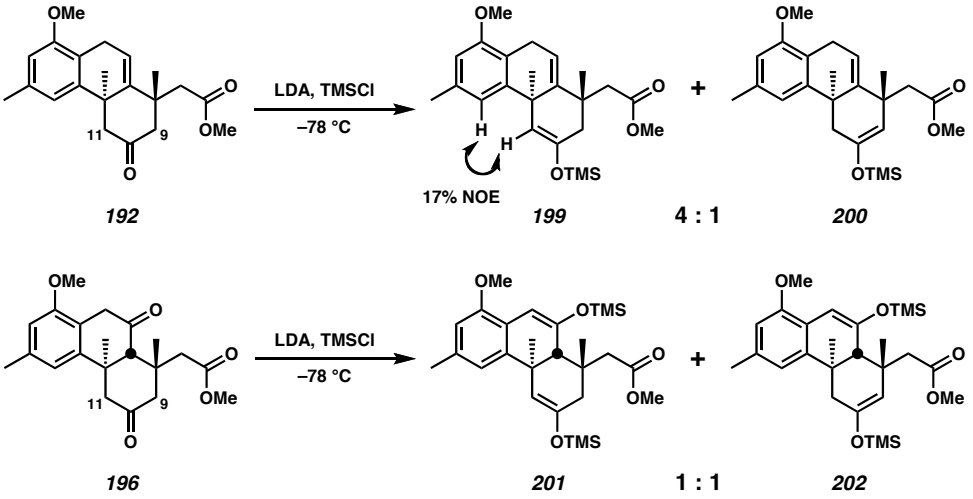


Scheme 2.2.10 Plan for elaboration of the tricyclic core.

Initial conditions tested seemed to favor enolization at C(11) rather than C(9). In order to solidify the nature of the system's behavior without the complication of

diastereomers, silyl enol ethers were generated under kinetic and thermodynamic conditions (Scheme 2.2.11). Interestingly, when tricycle **192** was treated with kinetic enolization conditions, a 4:1 ratio of silyl enol ethers (**199**:**200**) was observed. The major product of the inseparable mixture of enol ethers was identified as **199** via 1D nOe experiments. Given our uncertainty about the cause of the selectivity in this system, we also tested tricycle **196**. In this case, a 1:1 ratio of silyl enol ethers was observed. This improvement was promising, though certainly not viable at this stage of the synthesis.[16] Despite efforts to improve the selectivity of these alkylations, we were unable to improve the ratio beyond a 1:1 mixture. Ketoester **196** was treated under thermodynamic enolization conditions and nearly exclusive enolization was observed at C(11).[17]

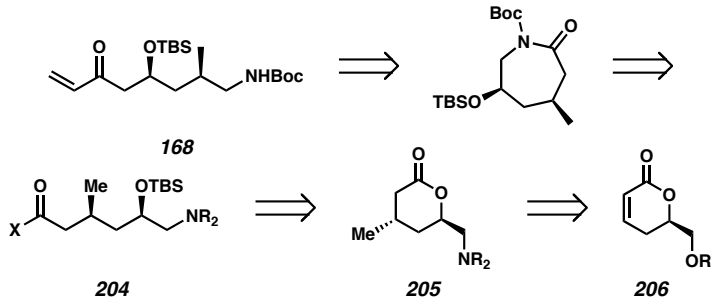
In addition to the challenges faced in the methylation step, we found that a very simple system modeling the conjugate addition step was unreactive.[18] Thus, we considered other options for the installation of this quaternary center. We examined a cyclopropanation approach similar to Hirama's strategy (see Chapter 1)[19] and a Tsuji alkylation-based approach.[20] Ultimately, we chose to alter our synthetic strategy to include the vicinal all-carbon quaternary centers from an early stage, as will be discussed in Chapter 3.



Scheme 2.2.11 Attempts to enolize at C(9).

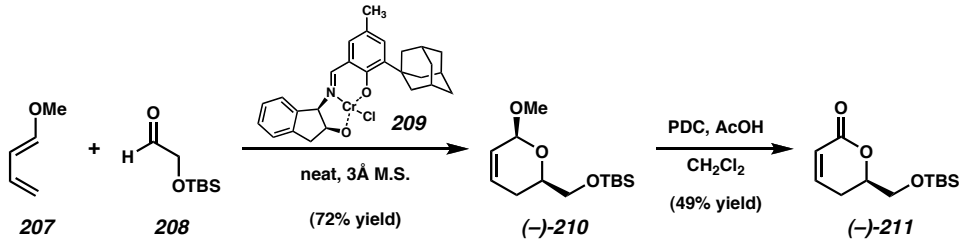
2.3.1 Enantioselective Synthesis of the DEFG Synthon

Once we access a suitable carbocyclic core structure, we will need to couple it to an appropriately functionalized side chain in order to form the heterocyclic DEFG ring system of zoanthenol. Our initial target for such a synthon was α,β-unsaturated ketone **166** (Scheme 2.3.1). We envisioned that enone **166** could be accessed from caprolactam **203**, which we disconnected across the amide C—N bond to reveal amine **204**. This amine, in turn, could be derived from δ-lactone **205**, accessible from α,β-unsaturated lactone **206**.



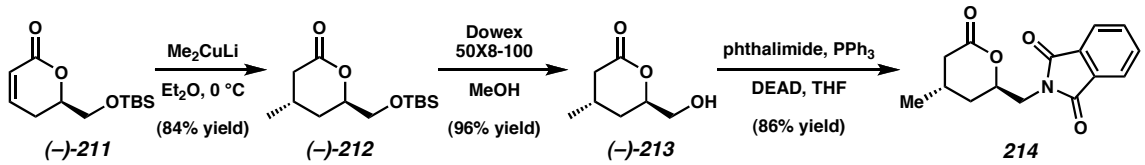
Scheme 2.3.1 Retrosynthetic analysis of the DEFG synthon.

To access **206** in enantioenriched form, we initially investigated an approach beginning with a glycal, which required oxidation to a lactone as well as the removal of superfluous oxygenation.[21] Additionally, we could access either racemic or enantioenriched material from (±)-glycidol or (*S*)-glycidol.[22] Ultimately, we employed an efficient and enantioselective method developed by Jacobsen and coworkers for the synthesis of α,β-unsaturated lactone **211**.[23] In their work, diene **207** and aldehyde **208** were treated with hetero-Diels-Alder catalyst **209** (Scheme 2.3.2), which facilitates cycloaddition reactions between electron-rich dienes and aldehydes. The desired dihydropyran was isolated in 72% yield and could be converted to the necessary lactone using acidic pyridinium dichromate conditions.



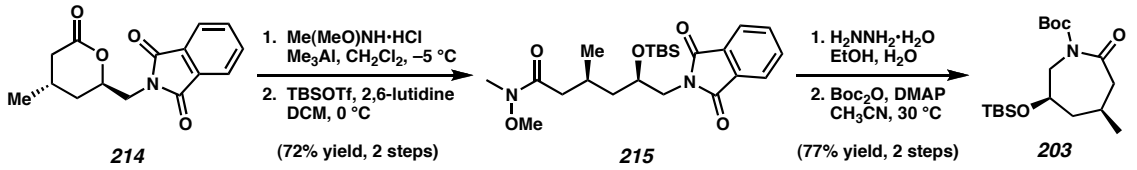
Scheme 2.3.2 Jacobsen hetero-Diels-Alder cycloaddition.

At this point, a selective 1,4-addition was accomplished by treatment of **211** with Gilman's reagent to afford **212** as a single diastereomer (Scheme 2.3.3). Treatment with an acidic resin induced desilylation to provide alcohol **213**, and subsequent Mitsunobu reaction provided phthalamide derivative **214**.



Scheme 2.3.3 Conjugate addition and Mitsunobu reaction provide key intermediate.

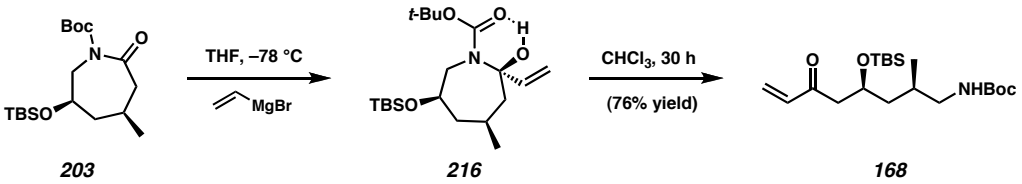
The chiral lactone was then treated under standard Weinreb amide formation conditions, and the intermediate alcohol was immediately trapped by addition of TBSOTf and 2,6–lutidine to yield Weinreb amide **215** (Scheme 2.3.4). Treatment of **215** with hydrazine hydrate in refluxing ethanol revealed the free primary amine, which spontaneously cyclized with the Weinreb amide to form a caprolactam. Carbamate formation with Boc anhydride provided key caprolactam **203**.



Scheme 2.3.4 Conversion of the δ-lactone to the ε-lactam synthon.

The final step in accessing synthon **166** was to add a single vinyl equivalent to the Boc-protected caprolactamate. Thus, treatment of **203** with vinyl magnesium bromide provided the isolable Grignard adduct **216** (Scheme 2.3.5). The chelation of Mg between

the Boc carbonyl and the amide carbonyl encourages addition of a single equivalent of the nucleophile, and we anticipate that a similar hydrogen-bonding event slows the collapse of hemiaminal **216**. Upon standing in $CHCl_3$, desired enone **166** is produced. Additionally, because we had observed this exquisite selectivity for a single addition, we were ultimately able to employ caprolactam **203** as our DEFG synthon in an alternative route.



Scheme 2.3.5 Vinylation of the ε-lactam to access the enone synthon.

2.4.1 Summary of Early Synthetic Work

In conclusion, a concise method for the construction of the zoanthenol carbocyclic skeleton was developed. This approach is highlighted by an unusual diastereoselective S_N' cyclization of allylic alcohol **183** producing tricycle **187** bearing all-carbon quaternary centers at C(12) and C(22) in the desired anti configuration. This key step in our route is flanked by a number of novel transformations. Most notably, we demonstrate an unusual palladium-catalyzed formylation of a hindered vinyl triflate, a highly diastereoselective Grignard addition to a congested enal, and an iodolactonization and subsequent epoxide rearrangement utilizing the pendant C(24) carboxylate to incorporate the C(20) ketone. Gratifyingly, application of our catalytic asymmetric decarboxylative alkylation methodology allows ready access into an enantioselective synthesis of zoanthenol. Our studies have also encompassed the synthesis of a fully functionalized, enantiopure DEFG synthon for late-stage coupling with our carbocyclic core structures. The synthesis of this synthon features a Jacobsen enantioselective hetero-Diels-Alder followed by a selective conjugate addition. Additionally, selective

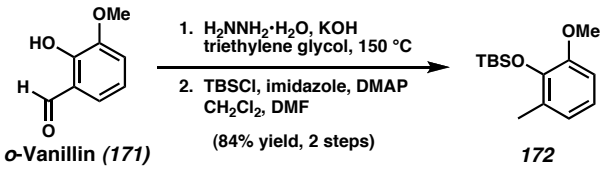
ring opening and ring closing events allow for an elegant elaboration of the key α,β-unsaturated lactone. Namely, Weinreb amide formation with immediate trapping enables the conversion of a δ-lactone to a linear intermediate, which upon phthalamide decomposition immediately closes again to a caprolactam. The carbamate produced upon Boc protection is then critical in allowing selective mono-addition of organometallic species into the caprolactam.

2.5.1 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

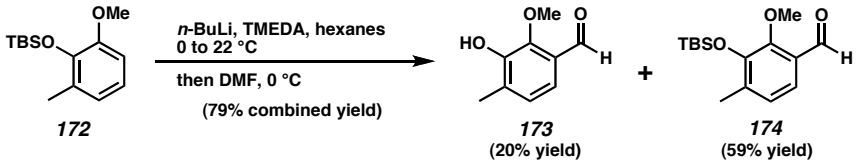
follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet, bm = broad multiplet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech 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 B for deposition numbers).

2.5.2 Preparation of Compounds



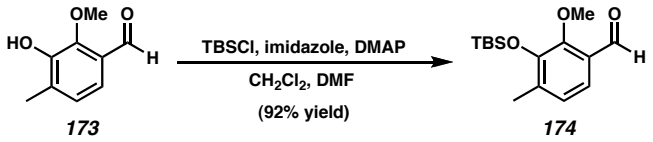
Arene 172. To a warmed solution (110 °C for 45 min) of *o*-vanillin (**171**, 60.0 g, 0.394 mol, 1.00 equiv) and $NH_2NH_2•H_2O$ (53.6 mL, 1.10 mol, 2.79 equiv) in triethylene glycol (320 mL) in a 1 L round bottom flask was added KOH (132 g, 2.37 mol, 6.02 equiv) (*Caution: gas evolution and exotherm*) 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 **172** (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.

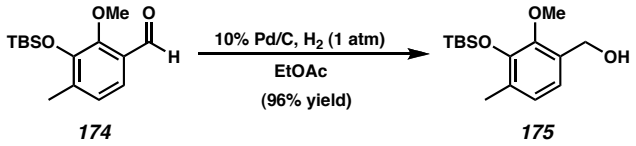


Benzaldehyde 174 from arene 172. To a cooled (0 °C) solution of arene **172** (30.0 g, 119 mmol, 1.00 equiv), and TMEDA (25.1 mL, 166 mmol, 1.40 equiv) in hexanes (200 mL) was added *n*-BuLi (2.25 M in hexanes, 63.4 mL, 142 mmol, 1.20 equiv) in a dropwise manner over 15 min. After 1 h at 0 °C, the reaction 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 **174** (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.

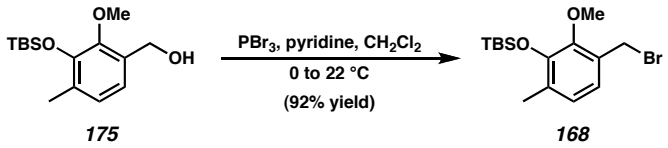


Benzaldehyde 174 from phenol 173. To a solution of phenol **173** (10.0 g, 60.2 mmol, 1.00 equiv) in DMF (60 mL) and CH_2Cl_2 (60 mL) were added imidazole (8.20 g, 120 mmol, 2.00 equiv), DMAP (9.55 g, 78.3 mmol, 1.30 equiv), and TBSCl (11.7 g, 78.3 mmol, 1.30 equiv). After 36 h, the reaction mixture 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 **174** (15.5 g, 92% yield).



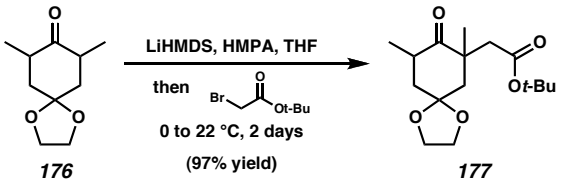
Benzyl alcohol 175. A flame-dried 100 mL round bottom flask was charged with 10% Pd/C (270 mg), EtOAc (55 mL), and benzaldehyde **174** (2.0 g, 7.13 mmol, 1.00 equiv) under an N_2 atmosphere. The reaction mixture and headspace were sparged with H_2 (5 min) and stirred vigorously under an atmosphere of 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 **175** (1.93 g, 96% yield) as a colorless oil: R_f 0.33 (20% EtOAc in hexanes); ^1H 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 149.4, 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+) $[M+H-H_2]^+$ *m/z* calc'd for $[C_{15}H_{25}SiO_3]^+$: 281.1573, found 281.1564.

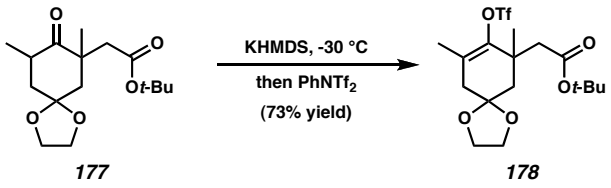


175 *168*

Benzyl bromide 168. To a cooled (0 °C) solution of benzyl alcohol **175** (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 **168** (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); ^1H 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 149.7, 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+) $[M+H]^+$ *m/z* calc'd for $[C_{15}H_{25}SiBrO_2+H]^+$: 345.0885, found 345.0885.

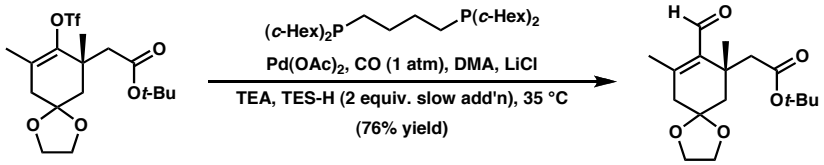


Ketoester 177. To a cooled (0 °C) 1.00 M LiHMDS (52.2 mL, 52.2 mmol, 1.20 equiv) solution in THF was added ketone **176** (8.00 g, 43.5 mmol, 1.00 equiv) in THF (50 mL) in a dropwise manner over 30 min. After an additional 30 min at 0 °C, HMPA (8.31 mL, 47.8 mmol, 1.10 equiv) was added and maintained 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 **177** (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 alkylation.



Triflate 178. To a cooled (–30 °C) solution of KHMDS (4.41 g, 22.1 mmol, 1.20 equiv) in THF (35 mL) was added ketoester **177** (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),

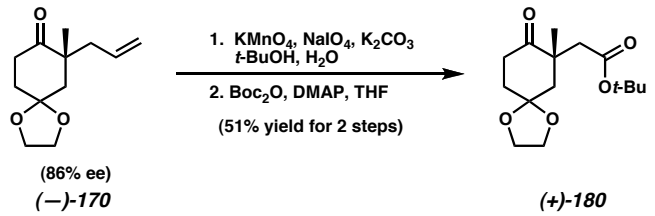
H_2O (50 mL), and brine (3 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (7 to 10% EtOAc in hexanes and 0.5 % TEA) to provide triflate **178** (5.74 g, 73% yield) as a pale yellow oil: R_f 0.63 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 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 170.2, 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+) $[M+H]^+$ m/z calc'd for $[C_{17}H_{25}SF_3O_7+H]^+$: 431.1351, found 431.1365.



178 *169*

Enal 169. 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 **178** (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

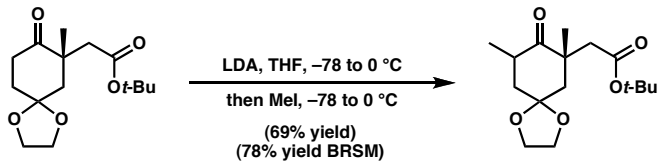
oil, which was purified by gradient flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to give enal **169** (1.24 g, 76% yield) as a pale yellow oil: R_f 0.42, 0.41 (35% EtOAc in hexanes, 20% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1H), 4.00–3.90 (comp. 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 191.0, 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+) $[M+H]^+$ m/z calc'd for $C_{17}H_{26}O_5$+H$^+$: 311.1858, found 311.1849.



(+)-*t*-Butyl ester 180. A solution of ketone (–)-**170** (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 **180** (688 mg, 51% yield) as a colorless oil: R_f 0.27 (10% EtOAc in hexanes developed twice); ^{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) $[M]^+$ *m/z* calc'd for $[C_{15}H_{24}O_5]^+$: 284.1624, found 284.1633; α_D^{26} +45.63 (c 1.89, CH_2Cl_2, 86% ee).



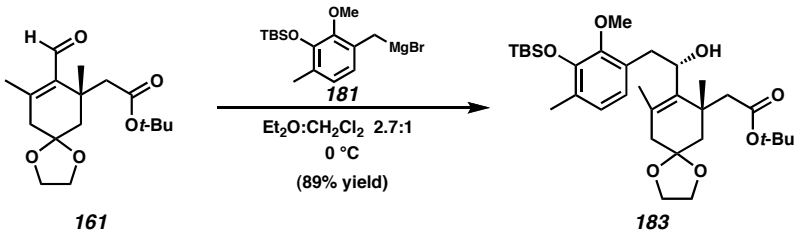
(+)-180 *177*

Methyl ketones 177a and 177b. 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 **180** (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 **177a** and **177b** (284 mg, 69% combined yield) as colorless oils and recovered (+)-*t*-butyl ester **180** (43.2 mg, 11% yield).

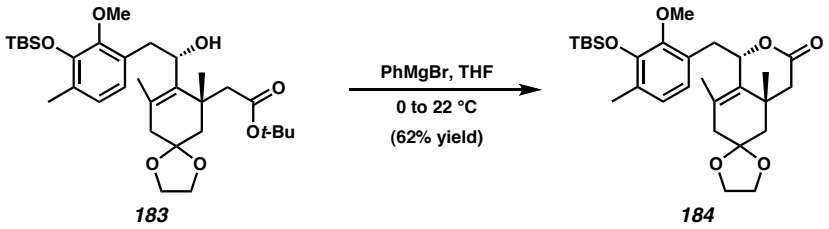
High R_f diastereomer 177a: R_f 0.43 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10–3.90 (comp. m, 4H), 2.89 (app. d of sept., J = 1.2, 6.6 Hz, 1H), 2.73 (d, J = 16.5 Hz, 1H), 2.36 (d, J = 13.8 Hz, 1H), 2.16 (d, J = 16.2 Hz, 1H), 2.06–1.96 (comp. m, 1H), 1.93 (d, J = 13.5 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) $[M]^+$ m/z calc'd for $[C_{16}H_{26}O_5]^+$: 298.1780, found 298.1791; α_D^{26} +45.13 (c 1.06, CH_2Cl_2, 86% ee).

Low R_f diastereomer 177b: 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) $[M]^+$ m/z calc'd for $[C_{16}H_{26}O_5]^+$: 298.1780, found 298.1775; α_D^{26} –25.44 (c 1.17, CH_2Cl_2, 86% ee).



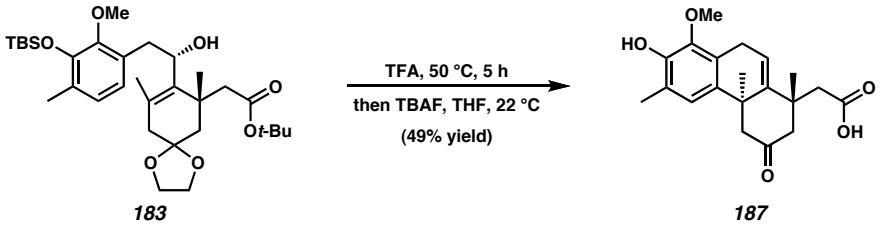
Allylic alcohol 183. A flame-dried two-neck round bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (9.00 g, 370 mmol,

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 **168** (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 **169** (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 **183** (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 172.1, 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+) $[M+H]^+$ *m/z* calc'd for $[C_{32}H_{52}SiO_7+H]^+$: 577.3561, found 577.3543.



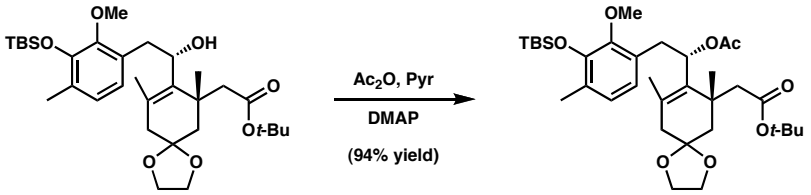
183 *184*

Lactone 184. To a cooled (0 °C) solution of allylic alcohol **183** (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 **184** (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 171.4, 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+) $[M+H]^+$ m/z calc'd for $[C_{28}H_{42}SiO_6+H]^+$: 503.2829, found 503.2809.



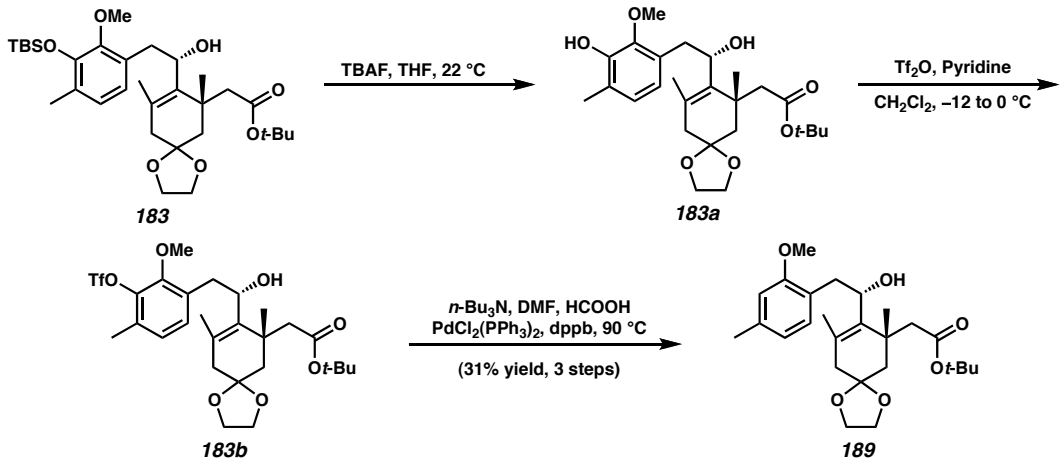
183 *187*

Acid 187. A solution of allylic alcohol **183** (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 **187** (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+) $[M+H]^+$ *m/z* calc'd for $[C_{20}H_{24}O_5+H]^+$: 345.1702, found 345.1709.



187 *188*

Allylic acetate 188. To a solution of allylic alcohol **187** (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 **188** (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]$^+$ m/z calc'd for [$C_{34}H_{53}O_8Si$]$^+$: 617.3510, found 617.3487.

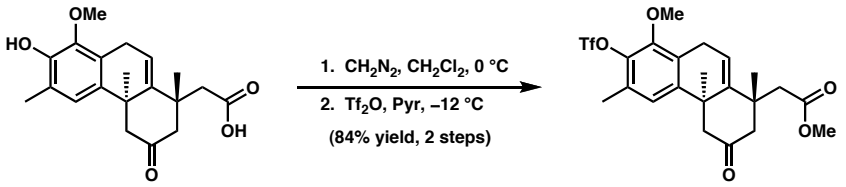


Arene 189. To a solution of allylic alcohol **183** (554 mg, 0.962 mmol, 1.0 equiv) in THF (10 mL) was added 1.00 M TBAF in THF (1.50 mL, 1.50 mmol, 1.56 equiv). After 5 min, the reaction mixture was concentrated to ~ 5 mL and was purified by gradient flash chromatography on silica gel (20 to 40% EtOAc in hexanes) to give phenol **183a** (223 mg, 52% yield).

To a cooled (–12 °C) solution of phenol **183a** (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 **183b** (193 mg, 75% yield).

A flame-dried 25 mL Schlenk flask was charged with triflate **184b** (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

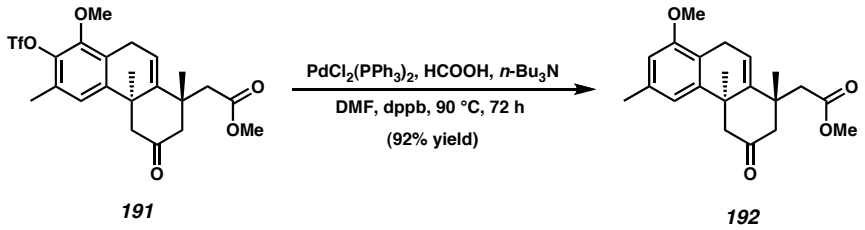
H_2O (40 mL), extracted with Et_2O (5 x 15 mL), dried ($MgSO_4$), and concentrated to a residue, which was purified by gradient flash chromatography on silica gel (10 to 15% acetone in hexanes) to give arene **189** (117 mg, 80% yield) as a white solid: mp 135–136 °C; R_f 0.50 (35% EtOAc in hexanes); ^{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 172.1, 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+) $[M+H]^+$ m/z calc'd for $[C_{26}H_{38}O_6+H]^+$: 447.2747, found 447.2749.



187 *191*

Triflate 191. To a cooled (0 °C) solution of acid **187** (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

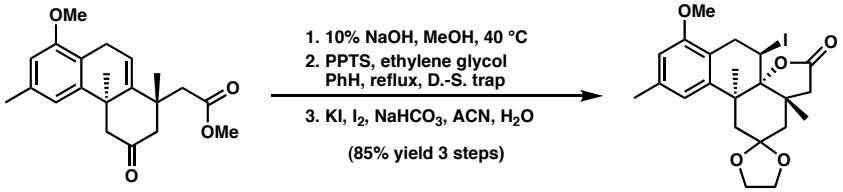
aqueous $NaHCO_3$ (30 mL). The reaction mixture was poured into half-saturated aqueous $NaHCO_3$ (60 mL), extracted with CH_2Cl_2 (5 x 30 mL), dried over K_2CO_3, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give triflate **191** (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+) $[M+H]^+$ *m/z* calc'd for $[C_{22}H_{25}SO_7F_3+H]^+$: 491.1351, found 491.1363.



191 ***192***

Ketoester 192. A flame-dried 250 mL Schlenk flask was charged with triflate **191** (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 **192** (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+) $[M+H]^+$ *m/z* calc'd for $[C_{21}H_{26}O_4+H]^+$: 343.1909, found 343.1894.

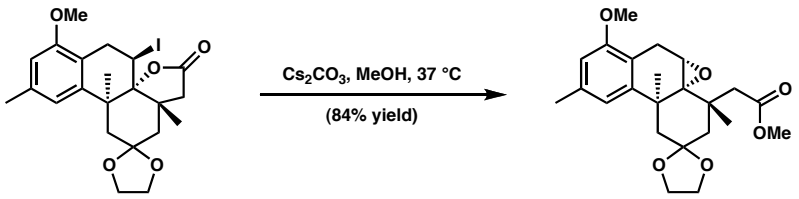


192 ***193***

Iodolactone 193. A solution of ketoester **192** (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.

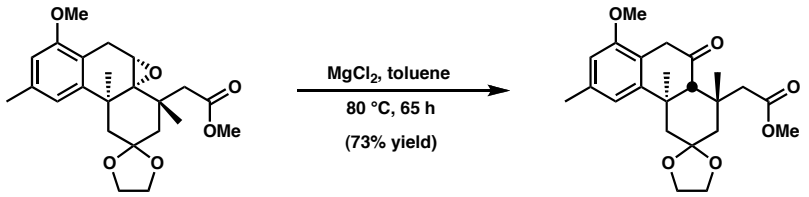
To a solution of the crude ketal and $NaHCO_3$ (68.4 mg, 0.814 mmol, 1.4 equiv) in H_2O (5 mL) and acetonitrile (5 mL) was added KI (125 mg, 0.756 mmol, 1.3 equiv) and I_2 (192 mg, 0.756 mmol, 1.3 equiv). The reaction mixture was stirred in the dark for 30 h and quenched with saturated aqueous $Na_2S_2O_3$ (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 **193** (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+) $[M+H]^+$ *m/z* calc'd for $[C_{22}H_{27}IO_5+H]^+$: 499.0982, found 499.0986.



193 *194*

Epoxide 194. To a solution of iodolactone **193** (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

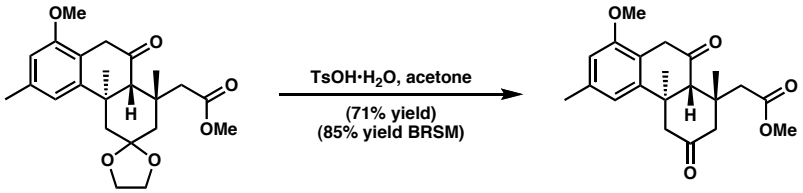
concentrated. The resulting residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes + 1% TEA) to give epoxide **194** (51.0 mg, 84% yield) as a colorless oil: R_f 0.54, 0.28 (35% EtOAc in hexanes, 10% EtOAc in hexanes developed 3 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 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+) $[M+H]^+$ *m/z* calc'd for $[C_{23}H_{30}O_6+H]^+$: 403.2121, found 403.2113.



194 *195*

Ketone 195. A solution of epoxide **194** (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 **195** (36.0 mg, 73% yield) as a colorless oil: R_f 0.55, 0.33 (35% EtOAc in hexanes,

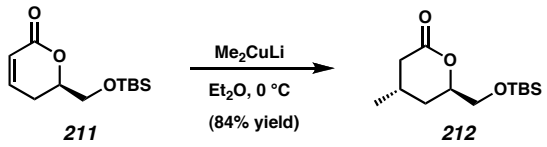
10% EtOAc in hexanes developed 3 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (s, 1H), 6.57 (s, 1H), 4.15–4.05 (m, 2H), 4.00–3.88 (m, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.64 (d, *J* = 22.5 Hz, 1H), 3.47 (dd, *J* = 1.5, 14.5 Hz, 1H), 3.34 (d, *J* = 22.0 Hz, 1H), 3.23 (d, *J* = 14.5 Hz, 1H), 2.58 (dd, *J* = 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) $[M]^+$ *m/z* calc'd for $[C_{23}H_{30}O_6]^+$: 402.2042, found 402.2027.



195 *196*

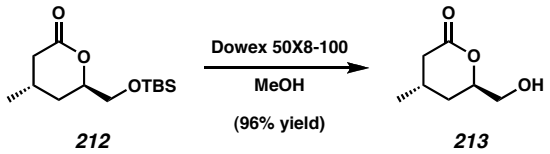
Diketone 196. A solution of ketone **195** (29.3 mg, 0.728 mmol, 1.00 equiv) in acetone (10 mL) was treated with TsOH•H_2O (100 mg, 0.526 mmol, 7.22 equiv) and stirred at ambient temperature for 4 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (25 mL), extracted with CH_2Cl_2 (6 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 **196** (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) $[M]^+$ m/z calc'd for $[C_{21}H_{26}O_5]^+$: 358.1780, found 358.1774.



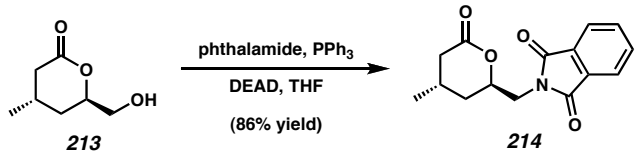
Lactone 212. MeLi (1.3 M in ether, 5.8 mL, 7.56 mmol) was added to a stirring slurry of CuI (714 mg, 3.89 mmol) in diethyl ether cooled to –78 °C. The vessel was warmed to 0 °C for 15 min, then cooled again to –78 °C. A solution of the α,β-unsaturated lactone **211** (471 mg, 1.95 mmol) in diethyl ether (4 mL) was then carefully added along the cooled inner walls of the reaction flask. After 1 h, the reaction mixture was quenched by the slow addition of saturated aqueous ammonium chloride (15 mL) at –78 °C. The reaction flask was gradually warmed to ambient temperature for 30 min, then diluted with ether (30 mL). The biphasic mixture was transferred to a separatory funnel and shaken vigorously to dissolve solids. The organic layer was washed with saturated aq ammonium chloride (2 x 20 mL), then brine (1 x 10 mL), dried over magnesium sulfate, and concentrated. The resulting material was purified by flash chromatography over silica gel (25% EtOAc:hexane eluent) to yield δ-lactone **212** (422 mg, 84% yield) as a clear oil: R_f 0.20 (25% EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47–4.40 (m, 1H), 3.70–3.73 (m, 2H), 2.55 (dd, J = 16.3, 5.1 Hz, 1H), 2.18–2.29 (m, 1H), 2.12 (dd, J = 16.4, 8.9 Hz, 1H), 1.90–1.99 (m, 1H), 1.52–1.60 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 77.8, 65.1, 38.1, 31.7, 26.2, 24.1,

21.4, 18.6, 5.00; IR (Neat film NaCl) 1743 cm^{-1}; HRMS (FAB+) $[M]^+$ *m/z* calc'd for $[C_{13}H_{26}O_3Si]^+$: 201.0947, found 201.0950; α_D^{20} –25.027° (c=1, $CDCl_3$).



212 *213*

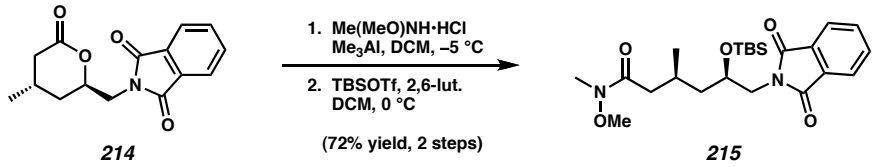
Alcohol 213. Lactone **212** (100 mg, 0.39 mmol) was dissolved in methanol (5.0 mL) and added to a reaction flask equipped with Dowex 50X8-100 cation exchange resin (1.0 g). The mixture was stirred at ambient temperature for 3 h, then filtered. The resin was washed with methanol (2 x 5 mL) and the combined organics were concentrated. The crude material was dried overnight under high vacuum to yield alcohol **213** (53 mg, 96% yield) as a clear oil: R_f 0.18 (80% EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47–4.52 (m, 1H), 3.75 (dd, *J* = 12.3, 3.6 Hz, 1H), 3.66 (dd, *J* = 12.1, 5.8 Hz, 1H), 2.69 (bs, 1H), 2.53–2.58 (m, 1H), 2.13–2.23 (m, 2H), 1.88–1.97 (m, 1H), 1.49–1.57 (m, 1H), 1.08 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 78.2, 65.1, 37.8, 31.1, 24.3, 21.4; IR (Neat film NaCl) 1722 cm^{-1}; HRMS (FAB+) $[M]^+$ *m/z* calc'd for $[C_7H_{12}O_3]^+$: 144.0786, found 144.0787; α_D^{20} –162.147° (c=1, $CDCl_3$).



213 *214*

Phthalimide 214. To a stirred solution of alcohol **213** (1.48 g, 10.28 mmol) in tetrahydrofuran (30 mL) was added triphenyl phosphine (2.83 g 10.79 mmol), then phthalimide (1.59 g, 10.76 mmol). Once all reagents had dissolved, the reaction mixture was cooled to 0 °C and DEAD (1.707 mL, 10.79 mmol) was added dropwise to the stirred solution. The reaction flask was then warmed to 30 °C for 12 h, then concentrated. The

concentrated reaction mixture was flashed over silica (4:1 hexanes:EtOAc). The resulting solid was recrystalized from dichloromethane to provide phthalimide **214** (2.42 g, 86% yield) as a white solid: m.p. 118–120 °C; R_f 0.16 (40% EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.88 (m, 2H), 7.71–7.76 (m, 2H), 4.74–4.83 (m, 1H), 4.04 (dd, *J* = 15.0, 8.3 Hz, 1H), 3.78 (dd, *J* = 15.0, 5.5 Hz, 1H), 2.63 (dd, *J* = 16.6, 5.4 Hz, 1H), 2.28 (m, 1H), 2.16 (dd, *J* = 16.5, 9.1 Hz, 1H), 1.86 (m, 1H), 1.66 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 168.1, 134.4, 132.0, 123.7, 74.1, 41.9, 37.9, 32.8, 24.0, 21.5; IR (Neat film NaCl) 1774, 1716 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{15}H_{15}NO_4+H]^+$: 274.1079, found 274.1076; α_D^{20} –68.6255° (c=1, $CDCl_3$).

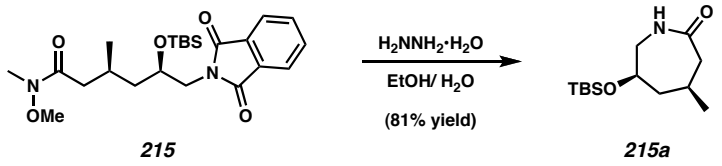


214 ***215***

Weinreb Amide 215. Trimethylaluminum (2.0 M in toluene, 10.32 mL, 20.64 mmol) was slowly added to a cooled (–10 °C) solution of *N,O*-dimethylhydroxylamine hydrochloride (2.01 g, 16.80 mmol) in dichloromethane (40 mL). The solution was stirred for 20 min before the dropwise addition of the Mitusunobu adduct **214** (2.26 g, 8.23 mmol) in dichloromethane (10 mL). The reaction was sturred at –10 °C for 30 min before the addition of sat. aq $NaHCO_3$ (20 mL). The reaction mixture was then allowed to warm to room temperature. The crude reaction mixture was diluted with dichloromethane (30 mL) and brine (20 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL). The combined organic layers were washed with brine (30 mL), then dried and concentrated to a volume of 10 mL over a rotovap bath temperature of 15 °C.

The crude amide was diluted with dichloromethane (20 mL) and cooled to 0 °C. To the cooled, stirred solution was added TBSOTf (3.79 mL, 16.51 mmol) followed by 2,6-

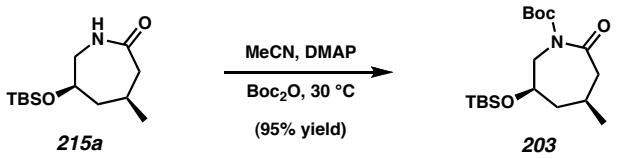
lutidine (1.442 mL, 12.38 mmol). The solution was maintained at 0 °C for 20 min, then quenched by addition of saturated ammonium chloride (20 mL). The biphasic mixture was allowed to warm to room temperature while stirring vigorously, then transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organics were washed with sat. aq $NaHCO_3$ solution (1 x 15 mL) and water (1 x 15 mL), then dried over $MgSO_4$ and concentrated. The crude product was flashed over silica gel (20% EtOAc:hexanes) to provide Weinreb amide **215** (2.58g, 72% yield) as an oil: R_f 0.30 (40% EtOAc:hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, J = 5.4, 3.1 Hz, 2H), 7.70 (dd, J = 5.6, 2.9 Hz, 2H), 4.05–4.14 (m, 1H), 3.68–3.78 (m, 2H), 3.65 (s, 3H), 3.14 (s, 3H), 2.38–2.45 (m, 1H), 2.18–2.29 (m, 1H), 1.51–1.60 (m, 1H), 1.38–1.47 (m, 1H), 1.03 (d, J = 6.3 Hz, 3H), 0.76 (s, 9H), –0.01 (s, 3H), –0.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 134.1, 132.3, 123.3, 68.3, 61.5, 44.0, 43.7, 39.7, 32.3, 26.9, 26.0, 20.8, 18.1, –4.3, –4.4; IR (Neat film NaCl) 3473.5, 2955.4, 2857.3, 1774.2, 1714.5, 1660.3 cm^{-1}; HRMS $[M+H]^+$ *m/z* calc'd for $[C_{23}H_{36}N_2O_5Si+H]^+$: 449.2472, found 449.2470; α_D^{20} –29.7° (c=1, $CDCl_3$).



215 *215a*

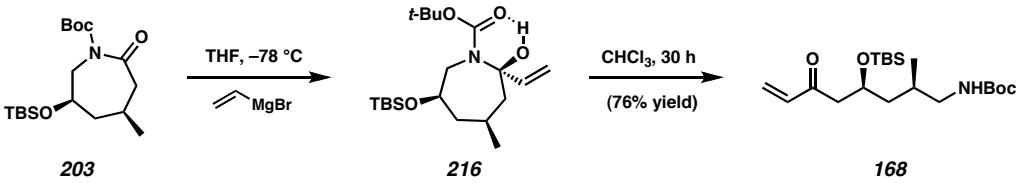
Caprolactam 215a. To a solution of **215** (2.848 g, 6.55 mmol) in absolute ethanol was added hydrazine monohydrate (1.75 mL, 32.77 mmol) and deionized water (0.39 mL). The solution was heated to 90 °C for 4 h. The reaction was then cooled in an ice bath and the thick cottony solids were filtered. The filtrate was then concentrated to a solid. The crude solid was taken up in EtOAc (50 mL), cooled in an ice bath, and filtered over a pad of Celite, rinsing with portions of EtOAc (2 x 20 mL). The organics were then dried

over sodium sulfate, and concentrated. The crude solid was subjected to chromatography over silica gel (30% EtOAc:hexane eluent) to yield the unprotected caprolactam **215a** (1.633g, 81% yield) as a white solid: m.p. 79–81 °C; R_f 0.22 (50% EtOAc:hexane) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (bs, 1H), 3.56–3.65 (m, 1H), 3.18–3.28 (m, 1H), 3.01–3.10 (m, 1H), 2.38 (dd, *J* = 13.7, 11.0 Hz, 1H), 2.25 (dd, *J* = 12.1, 1.7 Hz, 1H), 1.96–2.04 (m, 1H), 1.83–1.93 (m, 1H), 1.36 (q, *J* = 11.8 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 71.0, 49.7, 48.9, 44.2, 28.6, 26.1, 24.8, 18.4, –4.2, –4.4; IR (Neat film NaCl) 3239.9, 2929.8, 2857.6, 1673.1 cm^{-1}; HRMS (EI$^+$) [M+H]$^+$ *m/z* calc'd for [$C_{13}H_{27}NO_2Si$+H]$^+$: 242.1576, found 242.1576; α_D^{20} –15.0° (c=1, $CDCl_3$).



215a *203*

***N*-Boc-caprolactam 203.** To a solution of **215a** (853 mg, 3.313 mmol) in acetonitrile (40 ml) was added *t*-butyl carbonate anhydride (1.81 g, 8.28 mmol). After the *t*-butyl carbonate anhydride had completely dissolved, *N,N*-dimethylamino pyridine (1.01 g, 8.28 mmol) was added in several small portions. The resulting dark-brown solution was stirred for 10 min at ambient temperature, then warmed to 35 °C. After 5 hours, the reaction was quenched by addition of water (20 mL). The mixture was transferred to a separatory funnel and extracted with EtOAc (4 x 30 mL). The combined organics were washed with brine (1 x 30 mL), dried over sodium sulfate, and concentrated to give a brown waxy solid, which was purified by flash chromatography over silica (10% EtOAc:hexanes) to provide *N*-Boc-caprolactam **203** (1.314 g, 95% yield) as a waxy solid: m.p. 77–78°; R_f 0.22 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (dt, *J* = 14.8, 1.8 Hz, 1H), 3.63 (tdd, *J* = 22.0, 4.9, 2.2 Hz, 1H), 3.33 (dd, *J* = 15.0, 9.5 Hz, 1H), 2.56 (dd, *J* = 14.1, 10.9 Hz, 1H), 2.41 (d, *J* = 14.3 Hz, 1H), 1.96–2.03 (m, 1H), 1.87–1.94 (m, 1H), 1.51 (s, 9H), 1.27–1.39 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 152.5, 83.4, 70.4, 52.4, 47.7, 47.0, 28.4, 28.1, 26.1, 24.5, 18.4, 4.3, 4.4; IR (Neat film NaCl) 2932.4, 1710.2, 1645.1 cm^{-1}; HRMS $[M+H]^+$ *m/z* calc'd for $[C_{18}H_{35}NO_4Si+H]^+$: 358.2414, found 358.2426;
α_D^{20} –48.0° (c=1, $CDCl_3$).



Enone 166. To a stirred solution of *N*-Boc-caprolactam **203** (1.0 g, 2.79 mmol, 1.00 equiv) in THF (10 mL) at –78 °C was added a 1.0 M solution of vinyl magnesium bromide (3.35 mL, 3.35 mmol, 1.2 equiv) dropwise. The solution was stirred at –78 °C for 1 h then

quenched with saturated NH_4Cl (5 mL) at –78 °C. The mixture was allowed to warm to ambient temperature then diluted with H_2O (10 mL) and Et_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water then brine and dried over Na_2SO_4 and concentrated to give a crude oil, which was purified by flash chromatography (10% EtOAc/Hexanes) to provide a mixture of **216** and **166**. A solution of the purified product in $CHCl_3$ (0.15 M) was prepared and allowed to stand at ambient temperature for 30 h before concentrating to afford enone **166** (818 mg, 2.121 mmol, 76% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (dd, J = 17.6, 10.2 Hz, 1H), 6.20 (dd, *J* = 17.6, 1.5 Hz, 1H), 5.80 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.78 (bm, 1H), 3.81 (m, 1H), 3.29 (bm, 1H), 3.01 (dt, *J* = 13.8, 6.1 Hz, 1H), 2.57 (dd, *J* = 15.8, 5.6 Hz, 1H), 2.39 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.13 (m, 1H), 1.52–1.28 (m, 2H), 1.44 (s, 9H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.06 (d, *J* = 3.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 156.0, 136.7, 128.0, 69.5, 47.3, 45.8, 42.3, 28.4, 26.0, 25.8, 20.3, 18.0, –4.6 Hz; IR (Neat film NaCl) 3379, 2957, 2930, 2858, 1714, 1705, 1505, 1366, 1253, 1173, 836, 776 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{20}H_{39}NO_4Si+H]^+$: 386.2727, found 286.2713.

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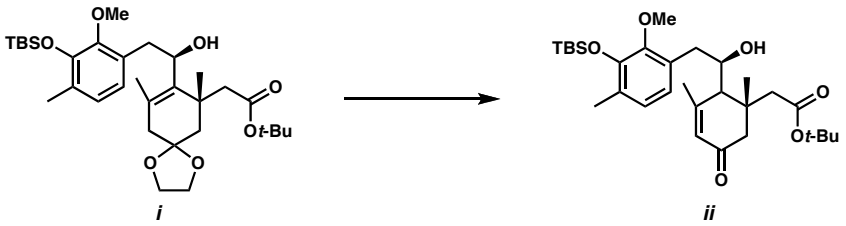
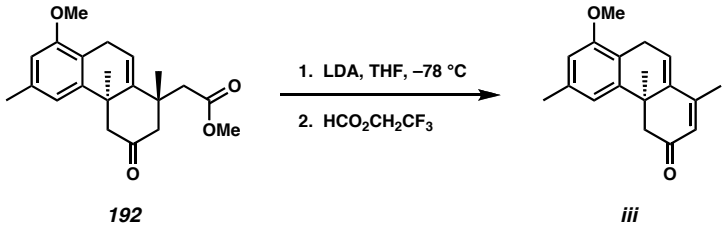
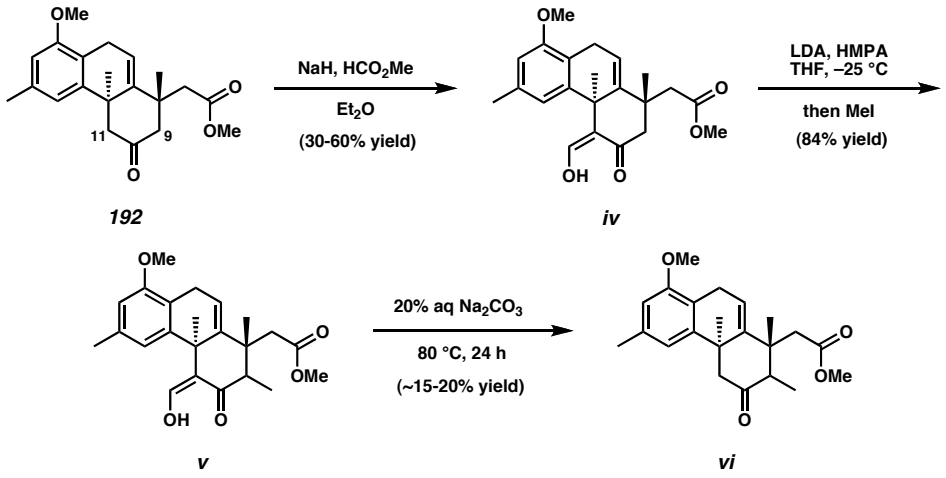
6. If alcohol **175** was allowed to persist under the reaction conditions for several additional hours after the consumption of benzaldehyde **174**, significant over-reduction was observed.
7. a) Franck-Neumann, M.; Miesch, M.; Barth, F. *Tetrahedron* **1993**, *49*, 1409–1420 b) In our experience, dimethyl ketone **176** was best prepared by iodobenzene diacetate oxidation of 2,6–dimethylphenol in ethylene glycol to give a quinone monoketal product, which was readily reduced to the ketone with Pd/C under hydrogen (60 psi).
8. Barnard, C. F. J. *Organometallics*, **2008**, *27*, 5402–5422 and references therein.
9. For related cyclizations, see: Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, *43*, 3435–3438.
10. We were uncertain at this point whether the observed product had resulted from dehydration of intermediate **186** or from a 6-*endo* S_N'-type cyclization to form **187** directly from **183**. Thus, **185** was synthesized independently and subjected to the reaction conditions. No cyclization products were observed, implying that the 6-*endo* S_N' cyclization pathway was operative.
11. The analogous trifluoroacetate also underwent cyclization in TFA to give yields and diastereoselectivities comparable to allylic alcohol **183**.
12. This alcohol diastereomer did not produce cyclized products. Rather, deketalization and olefin migration were observed.



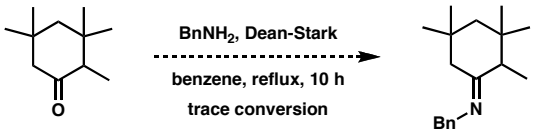
13. These conditions were specifically designed for highly congested aryl triflates, see: Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. G. *J. Org. Chem.* **1990**, *55*, 991–995.
14. Typical epoxidation conditions such as *m*CPBA, dimethyl dioxirane, urea hydroperoxide, iron(III) acetylacetate and hydrogen peroxide, hexafluoroacetone and hydrogen peroxide, potassium permanganate and copper(II) sulfate, and methyltrioxorhenium and hydrogen peroxide gave oxidation at the benzylic C(19) position or no reaction. Hydroboration was also unsuccessful.
15. a) Treatment with BF_3•Et_2O gave the desired hydride shift with concomitant deketalization; however, the yields were lower than the 2–step protocol. b) Naqvi, S. M.; Horwitz, J. P.; Filler, R. *J. Am. Chem. Soc.* **1957**, *79*, 6283–6286.
16. Under other kinetic enolate trapping conditions, fragmentation of ketoester **192** occurred to give the extended enone **iii**.



17. The ability to selectively deprotonate at C(11) led us to pursue a strategy to "protect" C(11). Ketoester **192** was condensed with methyl formate at C(11) to provide **iv** and then successfully methylated at C(9) to give **v**. Unfortunately, despite extensive experimentation, no reagents could be found that were capable of removing the hydroxymethylene from methyl ketone **vi** in greater than ~ 20% yield.

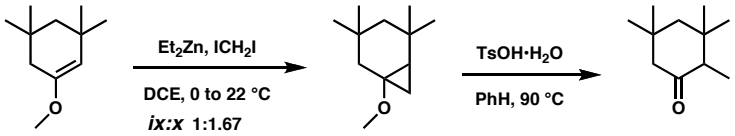


18. Known ketone **vii** was treated with Dean–Stark dehydration conditions in the presence of benzyl amine, but afforded only trace amounts of what appeared to be desired imine **viii**.



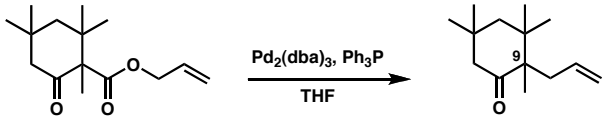
vii *viii*

19. a) Sugano, N.; Koizumi, Y.; Oguri, H.; Kobayashi, S.; Yamashita, S.; Hirama, M. *Chem. Asian J.* **2008**, *3*, 1549–1557.
b) Since selective enolization had proved difficult, we hoped to separate the isomers and cyclopropanate the C(9)–C(10) enol ether. To that end, cyclopropanation of steric model methyl enol ether **ix** was attempted with diethyl zinc and diiodomethane. Treatment with *p*–toluenesulfonic acid in benzene opened the cyclopropane **x** to the desired methyl ketone **xi**. However, in our hands it was difficult to drive the reaction to more than ~ 60% conversion under optimized conditions.



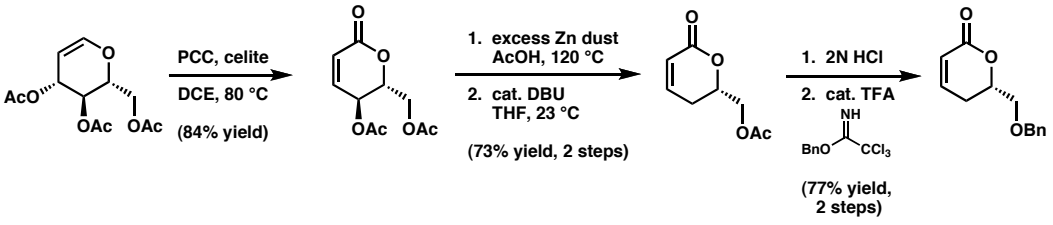
ix *x* *xi*

20. We were delighted to find that pentamethyl β-ketoester **xi** underwent alkylation selectively at the more substituted α-site with Tsuji's conditions to provide **xii**. 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 alkylation. These alkylation methods have the additional advantage of forming quaternary centers at room temperature in a few hours or less under neutral conditions.

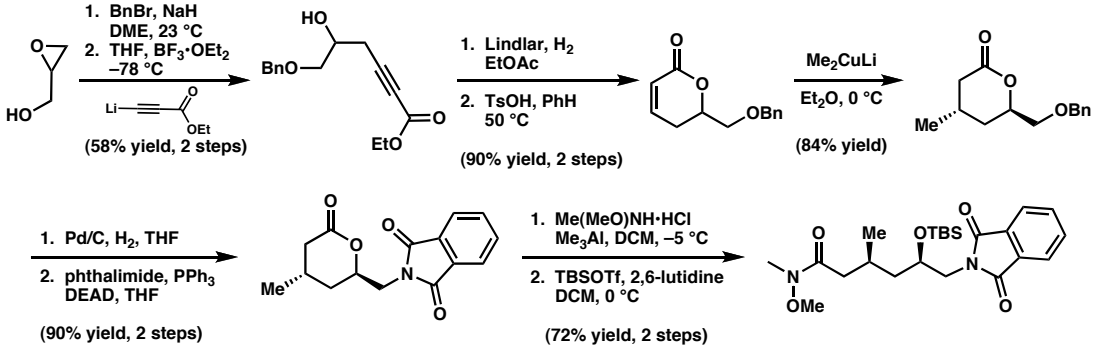


xi *xii*

21. To minimize cost, initial synthetic investigations were conducted using (*D*)-glucal.



22. Synthetic route from glycidol.



23. Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398–2400.