CHAPTER THREE

Current Approaches to the Synthesis of Zoanthenol: Synthesis of the ABC Ring System Containing All of the Quaternary Stereocenters[†]

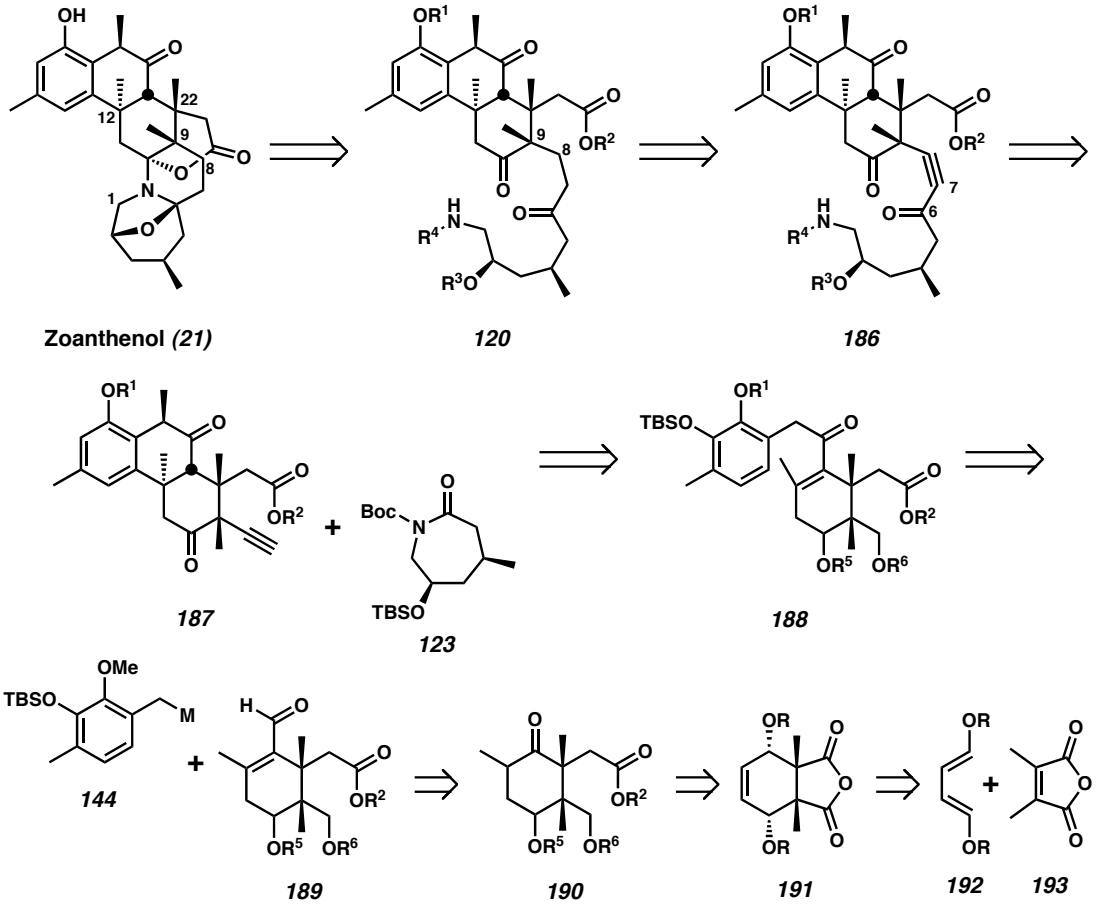
3.1 Revised Retrosynthetic Plan

Our early efforts outlined an expeditious synthesis of the ABC rings of zoanthenol. However, selective late-stage alkylation to form the final quaternary stereocenter proved difficult by a number of strategies. As a result, we decided to alter our retrosynthetic analysis to incorporate the formation of the C(9) quaternary stereocenter early in the synthesis (Scheme 3.1). We envisioned that with the vicinal C(9) and C(22) stereocenters established, we would be able to apply our previously developed methods for cyclization, either S_N' cyclization or Friedel-Crafts type conjugate addition, to directly generate a zoanthenol ABC ring system with all three quaternary centers. In accordance with this plan, we targeted alkyne **186** as an intermediate. Retrosynthetic disconnection of the C(1)-C(6) fragment of alkyne **186** was envisioned to occur by addition of the anion of alkyne **187** into caprolactam **123**. Caprolactam **123** was a previously projected intermediate and had been already synthesized in our laboratories.[1] ABC ring fragment **187** would be simplified to enone **188** via one of our cyclization methods. Using methods analogous to those demonstrated in Chapter Two, enone **188** would be reduced in complexity to ketone **190**. Oxidation state adjustment and a one-carbon homologation of *meso*-anhydride **191** could afford ketone **190**. We targeted *meso*-anhydride **191** as an opportunity to generate enantioenriched intermediates by desymmetrization. Finally, *meso*-anhydride **191** could arise via a Diels-Alder reaction of

[†] This work was performed in collaboration with Ms. Jennifer Stockdill, a graduate student in the Stoltz group.

1,4-oxygenated diene **192** and 2,3-dimethylmaleic anhydride (DMMA, **193**). Although challenging, such a Diels-Alder reaction would generate both the C(9) and C(22) quaternary stereocenters in a single step with reliable relative stereochemistry.

Scheme 3.1 Revised Retrosynthetic Plan for Zoanthenol



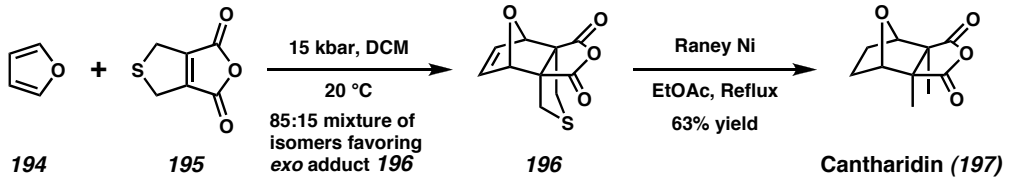
3.2 Synthesis of a C Ring Synthon Containing Vicinal Quaternary Stereocenters

3.2.1 *Diels-Alder Reactions of DMMA*

The preceding plan relies on a Diels-Alder reaction of DMMA. Such reactions are rare and difficult to accomplish.[2] However, the difficulty of generating compounds containing vicinal quaternary stereocenters with predictable relative stereochemistry has

stimulated significant work on the problem of DMMA Diels-Alder reactions. In particular, sulfur heterocycle **195** has been developed as a surrogate for DMMA (Scheme 3.2).[3] The sulfur atom is believed to constrain what would be the methyl groups in DMMA, making them both sterically smaller and less electron donating to the olefin. Dihydrothiophene **195** has been successfully applied in an elegant Diels-Alder strategy to synthesize cantharidin, where DMMA failed to react.[4] It's noteworthy that diydrothiophene **195** still required extremely high pressure (15 kbar) to successfully react with furan.

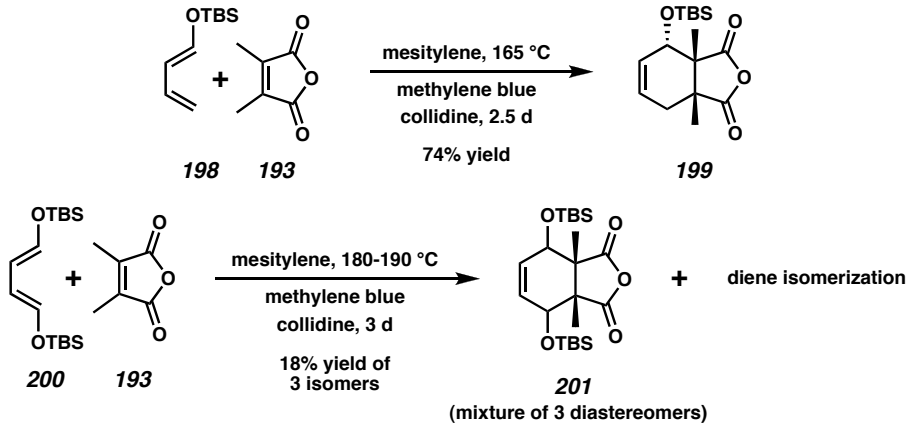
Scheme 3.2 Dauben's Synthesis of Cantharidin



Despite these difficulties, we were encouraged by Danishefsky and Birman's use of a DMMA Diels-Alder reaction in their recent synthesis of merrilactone A (Scheme 3.3).[5] The first step of their synthesis combines oxygenated diene **198** and DMMA in good yield. We hoped to react an even more electron rich 1,4-dioxygenated diene **200**[6] in a similar manner to give the *meso*-Diels-Alder adduct **201**. However, despite the similarity of the reactions, less than 20% yield of Diels-Alder adducts were produced under thermal conditions. This yield of Diels-Alder adducts consisted of similar amounts of three diastereomers. Furthermore, NMR studies with 1,4-dioxygenated diene **200**

showed that isomerization of olefin geometry was favorable and occurred faster than the Diels-Alder reaction. As a result, the use of diene **200** seemed impractical.

Scheme 3.3 Diels-Alder Reactions of DMMA

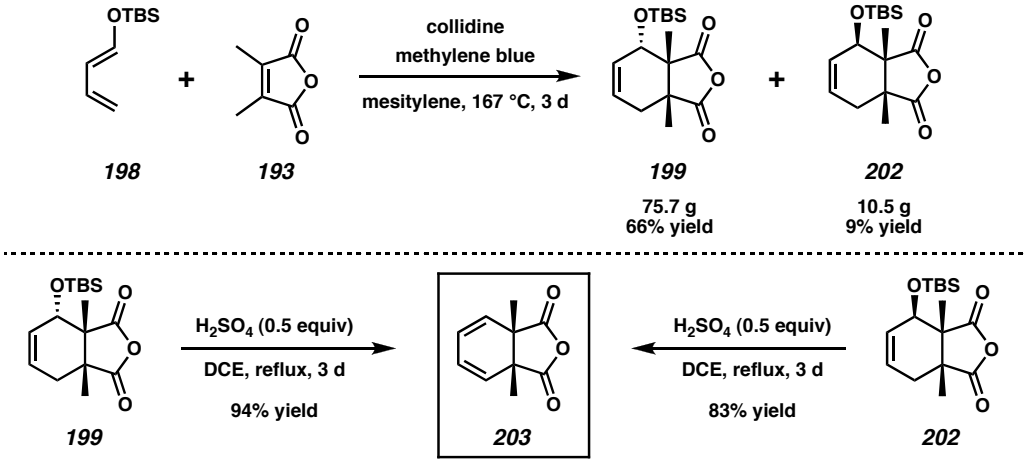


3.2.2 *Advancing Danishefsky's DMMA Diels-Alder Adduct*

Alternatively, we decided to advance Danishefsky's Diels-Alder adduct **199**. Rather than desymmetrize a bisoxygenated Diels-Alder adduct (i.e., **201**), our strategy was to deprotect silyl ether **199** and eliminate it to a *meso*-diene (i.e., **203**) anhydride suitable for desymmetrization. We were encouraged to find the reaction that Danishefsky reported between silyloxy diene **198**[7] and DMMA[8] to be highly reproducible and amenable to scale (Scheme 3.4). Typically, we carried out the reaction on a 0.350 mol scale to give an isolated yield of more than 70 g of *endo*-Diels-Alder product **199**. Treatment of the Diels-Alder adduct with sulfuric acid in refluxing dichloroethane caused TBS deprotection and elimination to *meso*-diene **203** in excellent yield. Additionally, significant amounts of *exo*-Diels-Alder adduct **202** were isolated in the Diels-Alder reaction and underwent elimination to *meso*-diene **203** under identical conditions. Unlike

Danishefsky's synthesis, our route eliminates the allylic stereocenter, thus the *exo*-Diels-Alder adduct **202** improved the overall throughput of the route. With diene **203** in hand, our next goal was to effectively desymmetrize it.

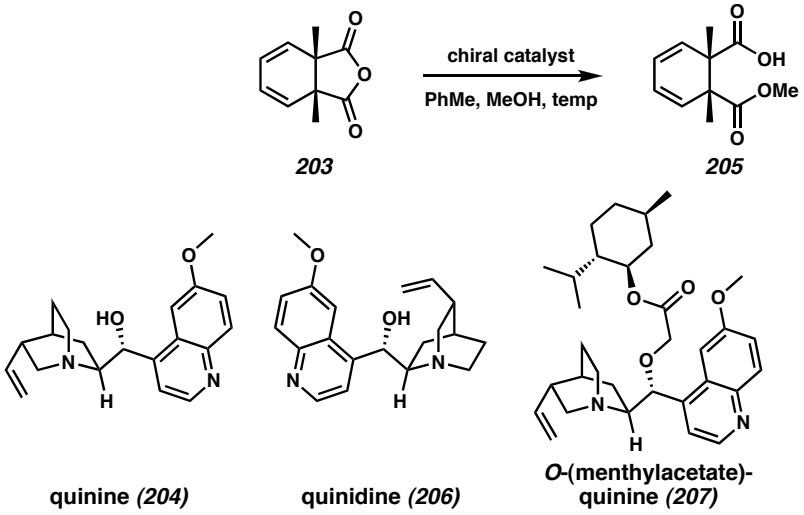
Scheme 3.4 Diels-Alder Route to *meso*-Diene **203**



The desymmetrization of cyclic *meso*-anhydrides to chiral monoesters has been studied by Fujisawa,[9] Bolm,[10] and Deng.[11] Such asymmetric alcoholysis of cyclic anhydrides with cinchona alkaloids has been reviewed.[12] However, prior to our work this strategy had never been applied to set multiple quaternary stereocenters. To our delight, we found that with slight modifications to Bolm's conditions excellent chemical yields and good enantioselectivities could be achieved (Scheme 3.5). Typically, for material throughput purposes, we performed the reaction with catalytic quinine (**204**) and stoichiometric DBU, which gave quick conversion but racemic product. However, with judicious choice of the stoichiometric achiral base, pempidine, the reaction could be completed catalytically with good enantioselectivity (Entry 2). In general, lowering the reaction temperature did cause a significant increase in ee, but also drastically increased

reaction time. Because some of the potential routes we considered to complete zoanthenol reorient monoester **205**, it is noteworthy that the use of quinidine (**206**) provides access to the opposite enantiomer obtained from quinine with similar ee (Entry 3). Additionally, we have found that menthol derivatives **207** and **208** give superior chiral induction.[13] To date, our best results are from quinine derivative **208**, which gave monoester **205** in 85% ee (Entry 5). Likely we will be able to increase the ee of this material by recrystallization. To our knowledge, this is the first desymmetrization of an anhydride to set the absolute configuration of vicinal quaternary stereocenters and is one of only a handful methods available to do so.

Scheme 3.5 Desymmetrization of *meso*-Anhydride **203**

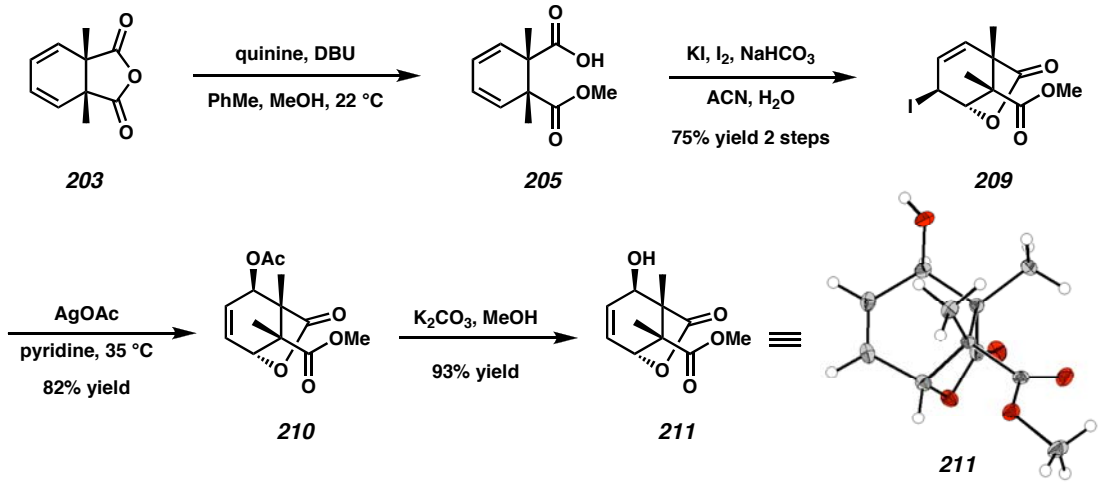


Entry	Chiral Controller (mol%)	Other Conditions	Temperature (°C)	Time (d)	Sign of Rotation	%ee (% yield)
1	*204* (105)	MeOH (5 equiv)	22	0.3	–	50
2	*204* (10)	MeOH (3 equiv) pempidine (1 equiv) 50% CCl_4 v/v	-50	18	–	70 (88)
3	*206* (100)	MeOH (3 equiv)	-50	6	+	70
4	*207* (105)	MeOH (10 equiv)	-25	3	–	72
5	*208* (101)	MeOH (3 equiv)	-50	10	+	85

3.2.3 *C Ring Synthon Reoxygenation*

Due to the difficulty of performing the DMMA Diels-Alder reaction with a 1,4-dioxygenated diene and our desire to desymmetrize a *meso*-diene, we were faced with the problem of reoxygenating the C ring (Scheme 3.6). Selenolactonization and halolactonization were both explored. Classical iodolactonization conditions proved most advantageous, giving predominantly a single iodolactone isomer by the end of the reaction.[14] Typically, the reaction was performed as a two-step sequence without purification of the intermediate monoester **205**. The bridged bicyclic nature of iodolactone **209** hinders S_N2 displacement of the iodide from the concave face, but is well disposed for S_N2' displacement. Treatment of iodolactone **209** with silver (I) acetate in pyridine at 35 °C afforded selectively S_N2' displacement to give allylic acetate **210** with the desired 1,4 oxygenation pattern. Selective acetate cleavage from bicyclic lactone **211** was accomplished by brief treatment with potassium carbonate in methanol. The stereochemical course of this sequence was confirmed by X-ray structure determination of allylic alcohol **211**. This efficient three-step sequence achieves stereospecific 1,4-reoxygenation of the C ring synthon and has proved robust and amenable to scale. Allylic alcohol **211** represents an important branch point in our synthetic efforts. Several increasingly functionalized C ring equivalents were derived from allylic alcohol **211**.

Scheme 3.6 Installation of 1,4-Oxygenation on Diene **203**



203 ***205*** ***209*** ***210*** ***211*** ***211***

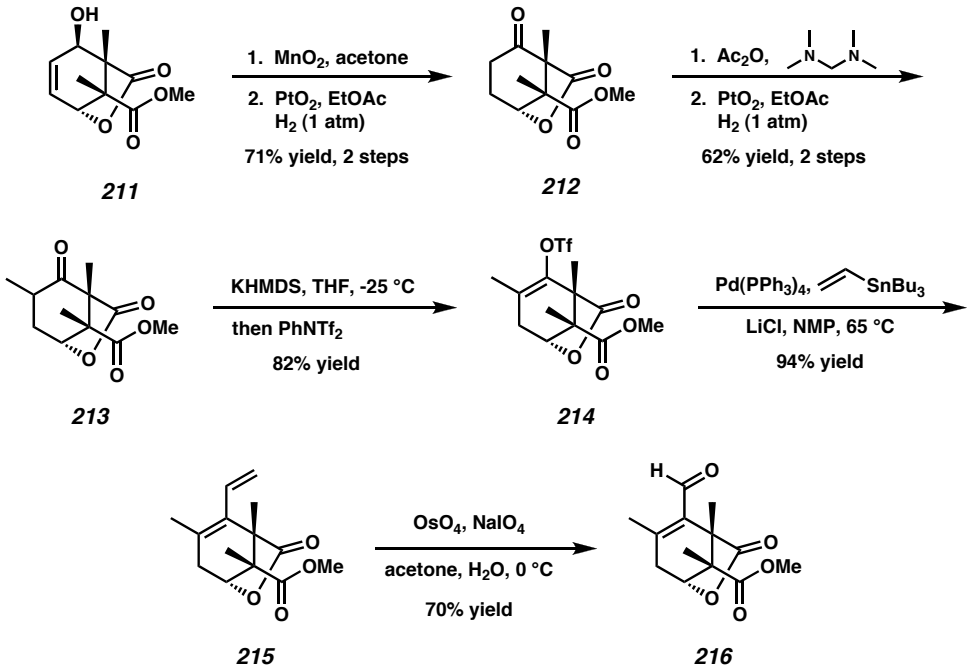
3.3 The Lactone C Ring Synthon Approach

3.3.1 *Completion of the Lactone C Ring Synthon*

The most straightforward elaboration of allylic alcohol **211**, namely leaving its ester and lactone functionality unmodified, gave us speedy access to molecules containing coupled A and C ring synthons. In turn, we could quickly begin experimentation with key B ring cyclization reactions. The sequence began with the conversion of allylic alcohol **211** to ketone **212** (Scheme 3.7). In theory, this transformation could be achieved by transition metal-catalyzed olefin isomerization. Isomerizations were attempted with a large number of catalysts, but all showed insufficient reactivity.[15] In practice, a two-step procedure consisting of manganese (IV) oxide oxidation and olefin reduction to give ketone **212** was superior. Direct methylation of ketone **212** with LDA and methyl iodide in THF consistently gave a surprising mixture of bismethylation and the starting ketone **212**. As a result, a two-step protocol of methylene installation with *N*,*N*,*N*',*N*'-tetramethyldiaminomethane and hydrogenation

with Adams catalyst gave good yields of separable methyl ketones **213**. Triflate formation from both methyl ketone diastereomers occurred under standard conditions. Unfortunately, enol triflate **214** failed to undergo carbonylation when submitted to the one-step palladium-catalyzed carbonylation conditions we developed for hindered enol triflates.[16] However, Stille coupling of enol triflate **214** with vinyl tributyltin followed by oxidative cleavage by osmium (VIII) tetroxide and sodium periodate did afford acceptable yields of enal **216**.

Scheme 3.7 Elaboration to the Complete Lactone C Ring Synthon.

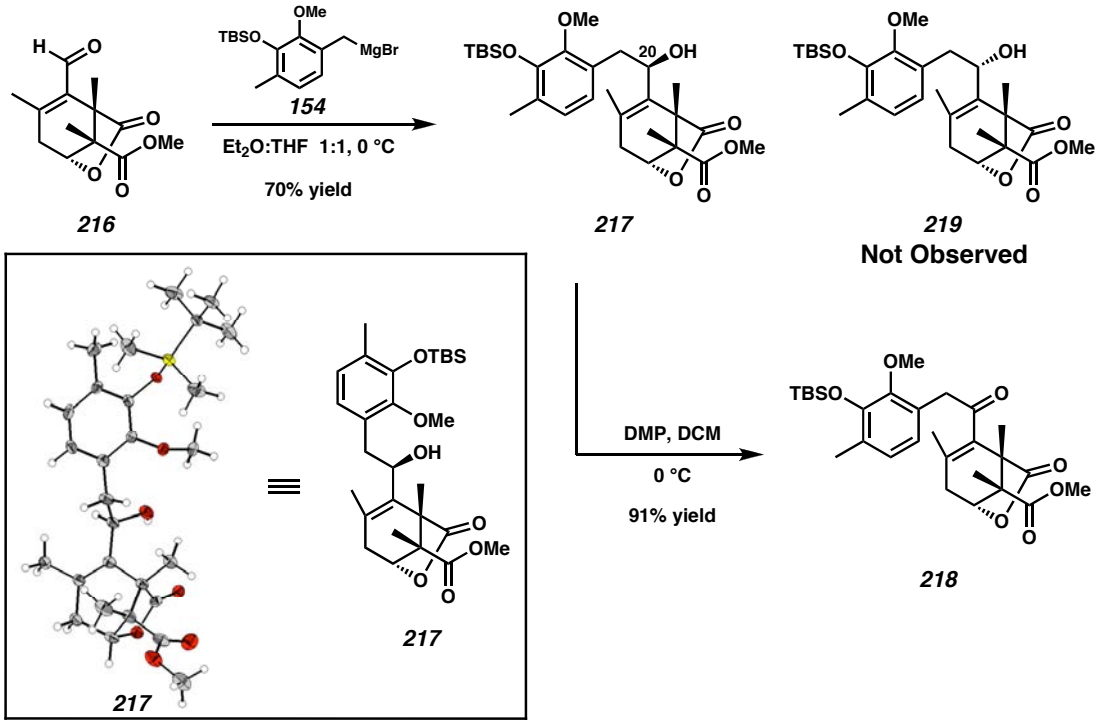


3.3.2 *A and C Ring Fragment Coupling*

Coupling of enal **216** with the A ring Grignard reagent **154** proved more difficult than anticipated (Scheme 3.8). Enal **216** was insoluble in the methylene chloride/ethyl ether mixtures that were found to give good diastereoselectivity for allylic alcohol **155** in

Chapter Two. Enal **216** did not undergo 1,2-addition when not dissolved. A large amount of tetrahydrofuran was required to dissolve enal **216** and, under those conditions, addition strongly favored the formation of allylic alcohol **217**, corresponding to the diastereomeric series at C(20), which did not undergo S_N' cyclization when exposed to TFA.[16] The assignment of allylic alcohol **217**'s C(20) stereocenter was made initially by comparison to ^{1}H NMR splitting patterns in allylic alcohol **155** and later confirmed by X-ray structure determination. Allylic alcohol **217** underwent smooth oxidation with Dess-Martin periodinane to give enone **218**. Attempts to generate allylic alcohol **219** for S_N' cyclization by either Mitsunobu inversion or reduction of enone **218** were unsuccessful.[17] As a result, S_N' cyclization strategy was not accessible with the lactone C ring synthon.

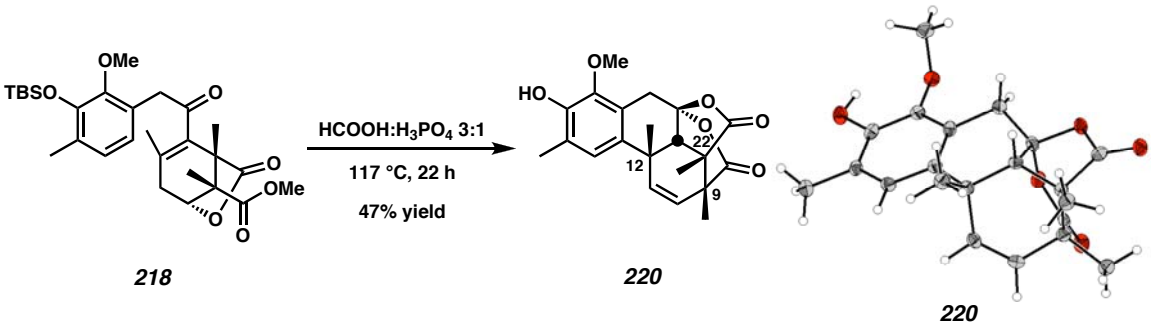
Scheme 3.8 Grignard Addition



3.3.3 *Cyclization By Friedel-Crafts Conjugate Addition*

A number of Lewis and Brønsted acidic conditions are known to promote intramolecular conjugate addition of electron rich arenes into enones.[18] Enone **218** underwent only loss of the TBS group and decomposition when treated with TFA at 110 °C, $AlCl_3$ in toluene at 100 °C, or polyphosphoric acid at 100 °C. However, when treated with a mixture of formic acid and 85% phosphoric acid, enone **218** underwent an interesting cyclization reaction to afford the unusual caged bisacetoxyacetal **220** in 47% yield. Unfortunately, bisacetoxyacetal **220** exhibited the undesired relative stereochemistry between the newly formed C(12) stereocenter and the other quaternary stereocenters (C(9) and C(22)) as determined by X-ray structure analysis.

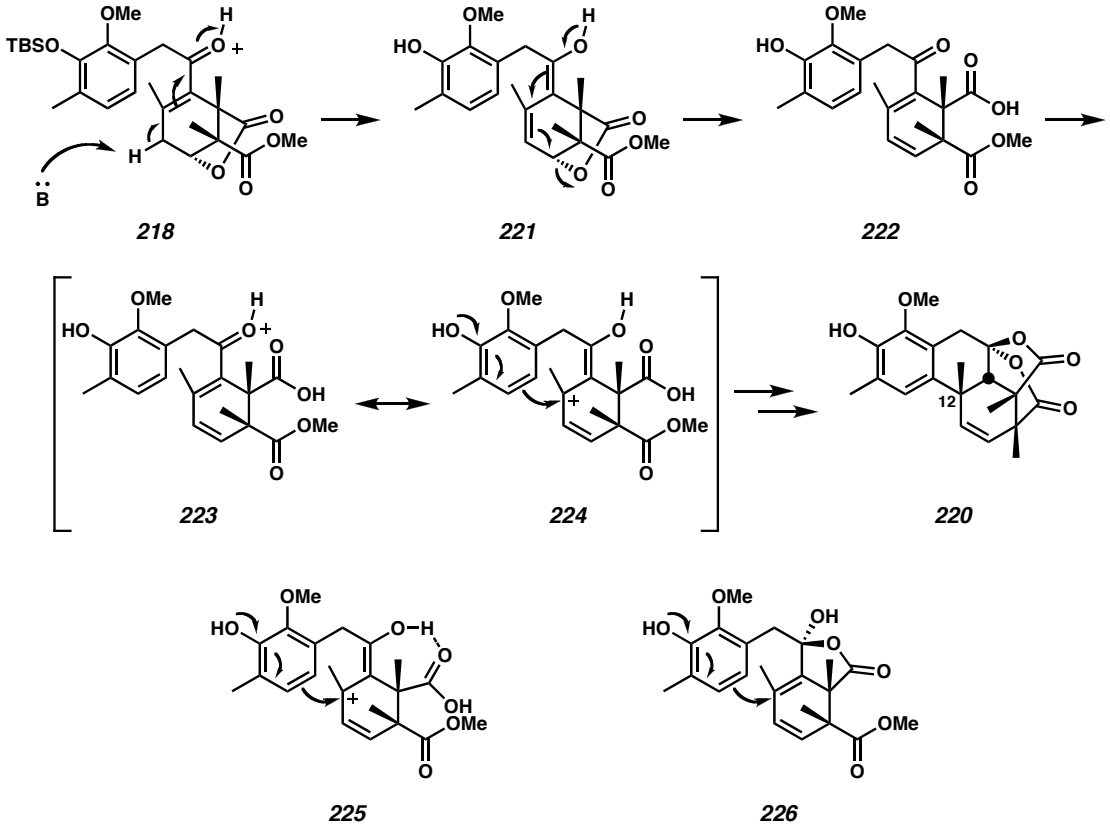
Scheme 3.9 Acid-Mediated Cyclization



Unique to the formic acid/phosphoric acid conditions was an elimination to give the C(11)-C(12) olefin. This was likely crucial to the mechanism of the successful conjugate addition (Scheme 3.10). The formation of extended enol **221** may trigger the elimination of the carboxylic acid to give extended enone **222**. Protonation of enone **222** leads to resonance form **224**, which stabilizes the positive charge as a tertiary allylic

carbocation. The increased contribution of this resonance form encourages conjugate addition and explains the lack of cyclization in cases where no elimination took place. The complete selectivity for bisacetoxyacetal **220**, with the undesired C(12) stereochemistry, suggests that some preorganization involving the ketone moiety guides the outcome of the cyclization. Possibilities for preorganization include intramolecular hydrogen bonding (structure **225**) or hemiacetal formation (structure **226**). Encouraged by the bond-forming reactivity, we hoped to design a substrate that was disposed to generate the desired C(12) stereochemistry.

Scheme 3.10 Possible Mechanism for Enone Cyclization

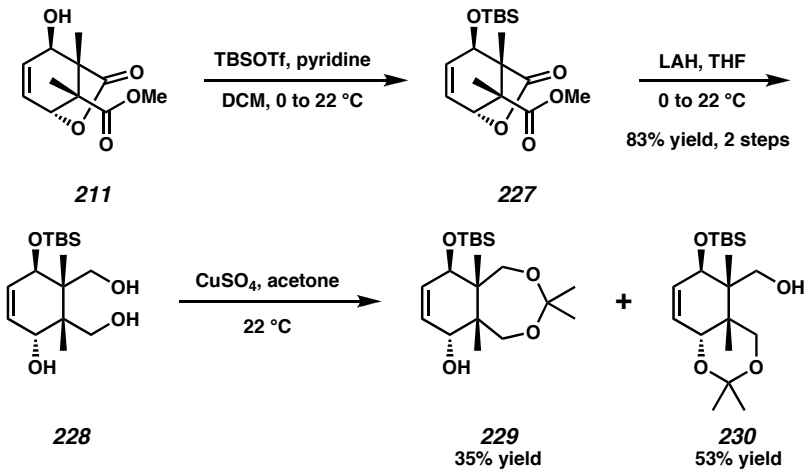


3.4 Studies Toward Elaborated C Ring Synthons

3.4.1 *Elaboration of Intermediate Allylic Alcohol **211***

Our attempts to synthesize more advanced substrates for cyclization had two goals: first, to better differentiate the lactone and methyl ester functionality in allylic alcohol **211** before cyclization, and second, to bias the cyclization toward the desired stereochemistry of the benzylic quaternary center. We began with intermediate allylic alcohol **211**, which was readily protected with TBSOTf to give silyl ether **227** (Scheme 3.11). Less reactive silylating agents (e.g., TBSCl) failed to give complete conversion to silyl ether **227** and demonstrated the challenges of performing even simple manipulations at neopentyl sites. Reduction of silyl ether **227** with LAH in THF afforded triol **228** in 83% yield over two steps. Differential protection of the triol presented a number of challenges. Strongly acidic conditions for acetonide formation removed the silyl protecting group. Anhydrous copper (II) sulfate in acetone showed good reactivity but gave a surprising mixture of 1,3-dioxepane **229** and acetonide **230**.[19,20] Although 1,3-dioxolane **230** is shown as the major product of the reaction, the ratio of the two products varied significantly.[21] While this mixture of products might seem undesirable on first consideration, both modes of protection proved useful in further elaboration.

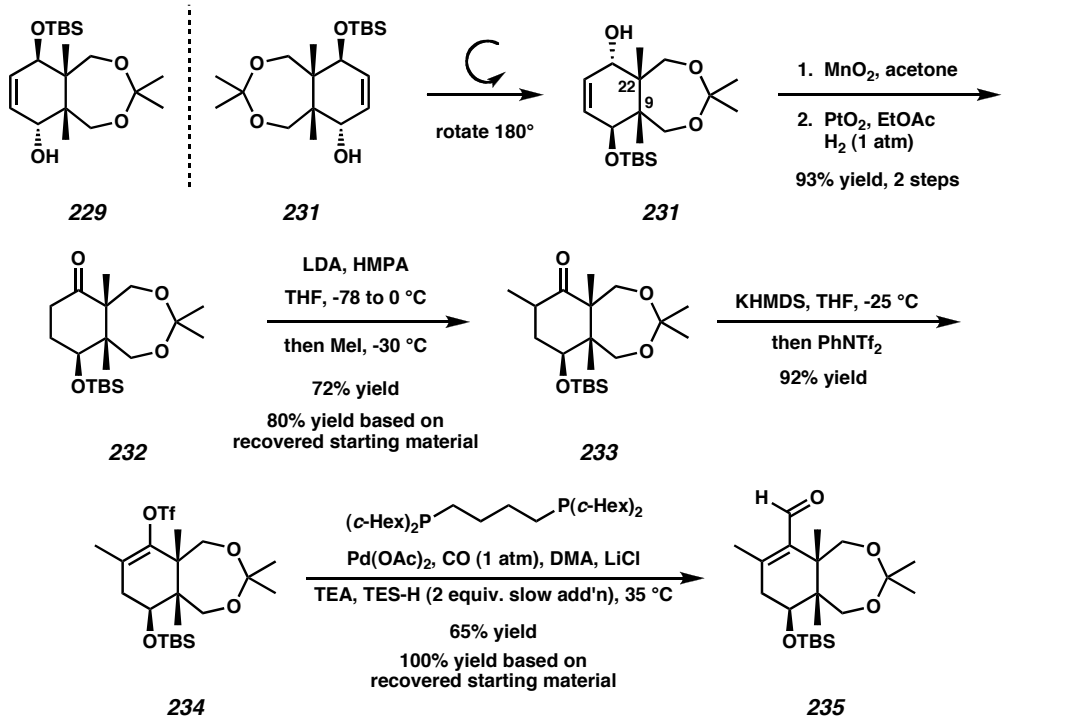
Scheme 3.11 C Ring Elaboration



3.4.2 *Development of the 1,3-Dioxepane Containing C Ring Synthon*

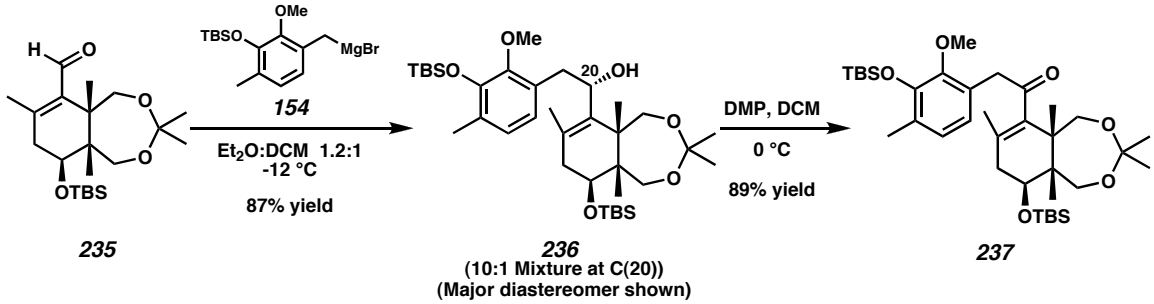
1,3-Dioxepane **229** offered a serendipitous opportunity to construct a C ring fragment capable of elaboration to zoanthenol. Although we typically depict 1,3-dioxepane as enantiomer **229**, we have equally ready access to enantiomer **231** from our desymmetrization process (Scheme 3.12). When rotated by 180°, enantiomer **231** suggests the orientation of the C(9) and C(22) quaternary stereocenters shown. This perspective allowed us to construct a 1,3-dioxepane-containing C ring synthon in a manner analogous to our previous efforts with enal **145** and enal **216**. Conversion of allylic alcohol **231** to ketone **232** was accomplished in excellent yield by a two-step oxidation and hydrogenation sequence. Conventional methylation with LDA and methyl iodide afforded a combined 72% yield of separable methyl ketones **233**. Both ketone diastereomers were readily converted to triflate **234**. Pleasantly, triflate **234** was a good substrate for our palladium-catalyzed carbonylation and afforded a 65% yield of enal **235**, with the remaining material recovered as unreacted triflate.

Scheme 3.12 Completion of the 1,3-Dioxepane-Based C Ring Synthon



Addition of our A ring Grignard synthon gave a good yield of allylic alcohol **236** as a 10:1 mixture of diastereomers. The relative stereochemistry at C(20) of the major diastereomer was assigned by comparison of ^{1}H NMR splitting patterns. Oxidation of allylic alcohol **236** occurred without incident to give enone **237**.

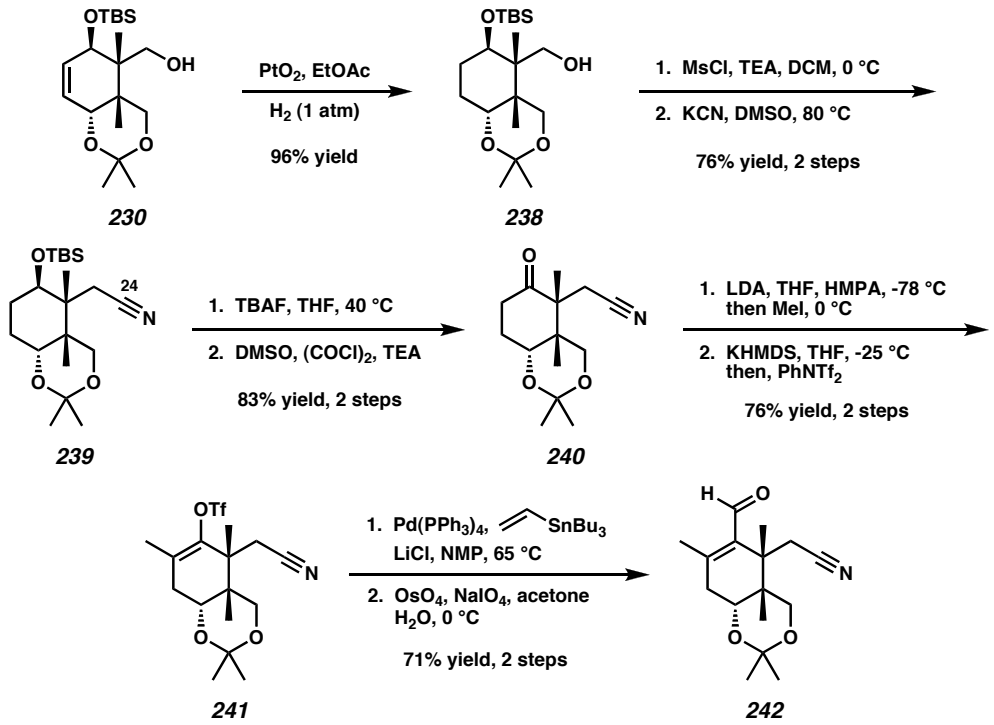
Scheme 3.13 Completion of the 1,3-Dioxepane-Containing Cyclization Substrate



3.4.3 *Development of the 1,3-Dioxane-Containing C Ring Synthon*

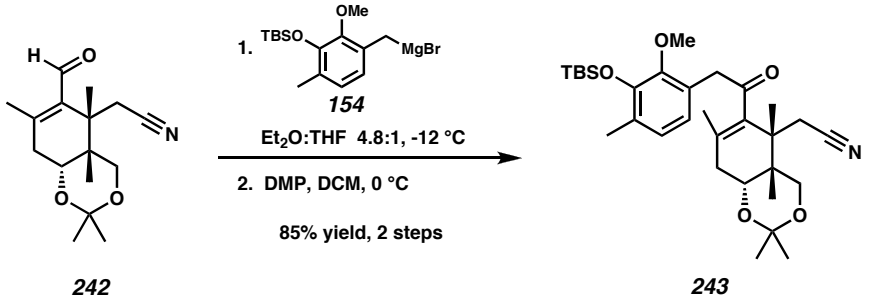
Acetonide **230** was used as a starting material to develop an alternative C ring synthon (Scheme 3.14). The major advantage of this strategy was that it allowed us to consider several methods of homologation to install C(24). Hydrogenation of acetonide **230** with Adams catalyst gave clean conversion to primary alcohol **238**. This molecule had appropriately protected functionality to investigate strategies for homologation. One strategy involved oxidation of alcohol **238** to the corresponding aldehyde and reaction with various Wittig reagents. However, these reactions proved sluggish, and even with a large excess of reagents poor conversion occurred.[22] Another strategy for homologation was cyanide displacement of a leaving group. Although S_N2 displacements at neopentyl positions are difficult to achieve,[23] the opportunity to introduce C(24) in the correct oxidation state as a nitrile encouraged us to pursue the strategy. In the event, mesylation of alcohol **238** with mesyl chloride and TEA, followed immediately by treatment of the crude mesylate with potassium cyanide in DMSO at 80 °C, afforded a 76% yield of nitrile **239**.[24] This material was converted to ketone **240** by silyl ether cleavage and Swern oxidation. Intermediate ketone **240** was converted by standard means to enol triflate **241**. Unfortunately, enol triflate **241** failed to undergo palladium-catalyzed carbonylation, but was instead converted to enal **242** by Stille coupling with tributylvinyltin followed by oxidative cleavage.

Scheme 3.14 Completion of the Nitrile Homologated C Ring Synthon



Fragment coupling with the A ring synthon and completion of enone **243** occurred as anticipated (Scheme 3.15). 1,2-Addition of Grignard reagent **154** afforded a good yield of a 3:1 mixture of diastereomeric allylic alcohols. This mixture was readily oxidized with Dess-Martin periodinane to give enone **243** in 85% yield for two steps.

Scheme 3.15 Completion of the Nitrile-Containing Cyclization Substrate

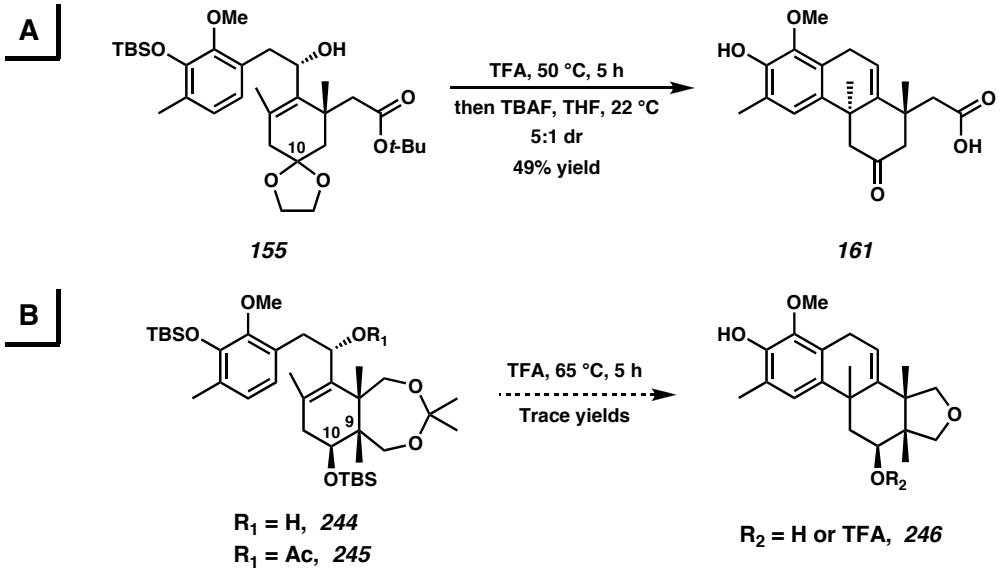


3.5 B Ring Formation Strategies for Advanced C Ring Synthons

3.5.1 *Cyclization Strategies for Substrates in the Alcohol Oxidation State at C(20)*

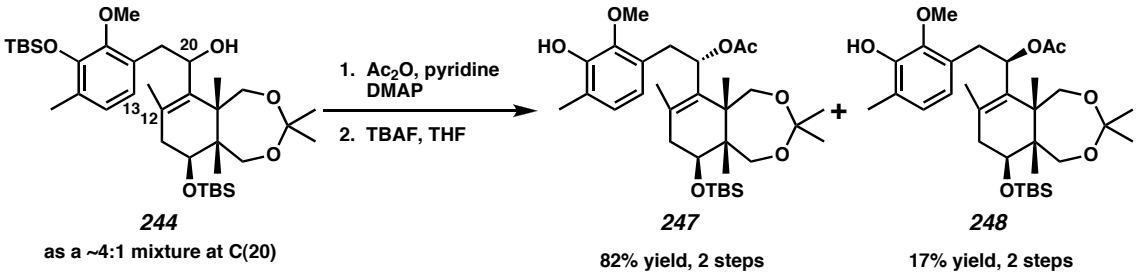
With ready access to several iterations of AC ring adducts, we turned our attention to finding reactions that would efficiently complete the B ring by forming the C(12)-C(13) bond. Directly inspired by our TFA-mediated cyclization of allylic alcohol **155**,[16] we attempted the same transformation with our advanced AC ring adducts (Scheme 3.16). We anticipated that the addition of the remote quaternary stereocenter at C(9) would have little impact on the reaction and that the additional alcohols deprotected during the reaction would be no more burdensome than the phenol present in the original reaction. We were disappointed to find that when either allylic alcohol **244** or acetate **245** were treated with trifluoroacetic acid at 65 °C, only a very small portion of the material exhibited an ^{1}H NMR spectra consistent with cyclization. The cyclized material represented only one of seven isolated products from the reaction, and was tentatively assigned as tetrahydrofuran **246** of the structures shown in Scheme 3.16. The low yield and likely formation of a tetrahydrofuran in structure **246** precluded the use of this strategy with 1,3-dioxepane substrates. Cyclizations of the analogous nitrile-containing AC ring adduct also failed.[25] We hypothesized that the difference in reactivity between allylic alcohols **155** and **244** might be caused by the different C(10) oxidation states. However, the C(10) ketone derived from allylic acetate **245** also failed to undergo significant S_N' cyclization.[26]

Scheme 3.16 Trifluoroacetic Acid-Mediated Cyclization



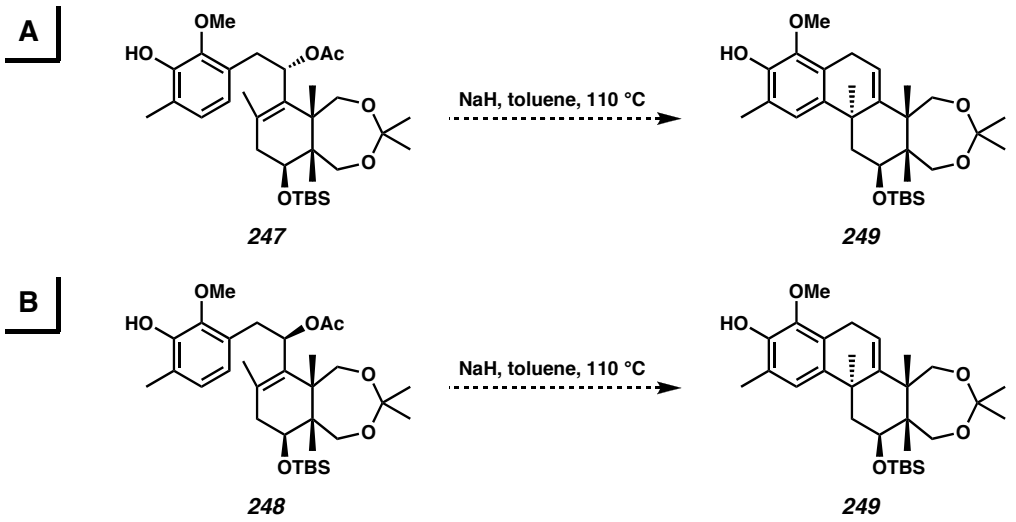
As an alternative, we explored reactions utilizing allylic leaving groups. Allylic alcohol **244** was converted to phenol acetates **247** and **248** by acylation and deprotection of the phenolic silyl group (Scheme 3.17). Fortuitously, the diastereomeric phenols were separable by column chromatography, and their relative stereochemistry was assigned by comparison to ^{1}H NMR spectra of analogous compounds.

Scheme 3.17 Derivatization and Separation of Allylic Alcohol **244**



A straightforward strategy for cyclization relied on treatment of phenol acetates **247** and **248** with sodium hydride to generate phenoxides in situ (Scheme 3.18). We anticipated that these phenoxides might act as carbon nucleophiles in an S_N' process. In the event, treatment with sodium hydride in most solvents simply led to acetate cleavage near ambient temperature. However, in toluene the phenoxides did not show significant deacetylation until much higher temperatures. In the case of phenol **247**, which we anticipated would be more likely to undergo S_N' cyclization,[16] an interesting oxidative cleavage occurred to give enal **235**. No cyclization was observed for either phenoxide.

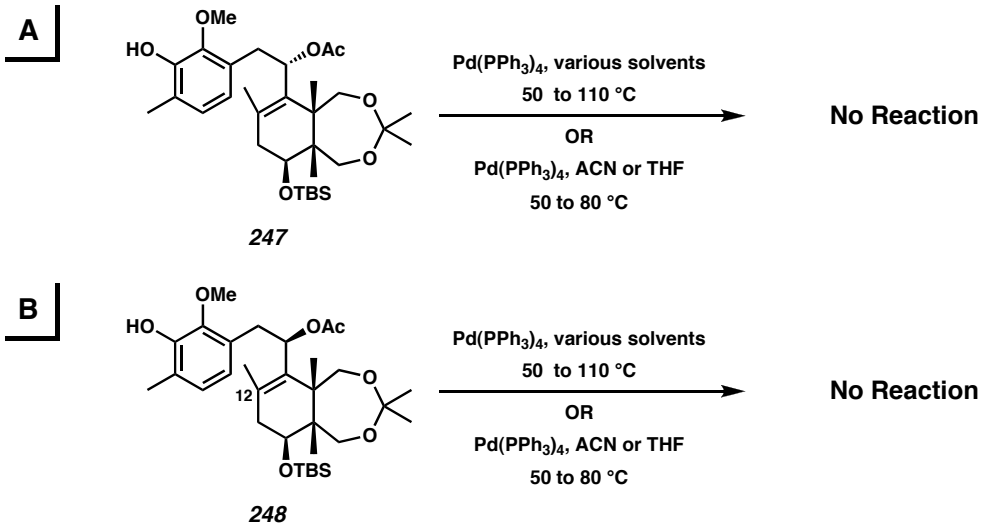
Scheme 3.18 Base-Promoted Cyclization Strategy



Another approach involved the use of palladium π-allyl complexes generated from the phenol acetates **247** and **248** as electrophiles (Scheme 3.19). In keeping with the double inversion mechanism of classical π-allyl chemistry, we anticipated isomer **248** would produce the desired stereochemistry at C(12).[27] Unfortunately, no evidence of oxidative addition into the allylic acetate was ever observed under any conditions. This

lack of reactivity was likely due to the number of sterically demanding substituents on the allyl portion of the molecule.

Scheme 3.19 Palladium π-Allyl Cyclization Strategy

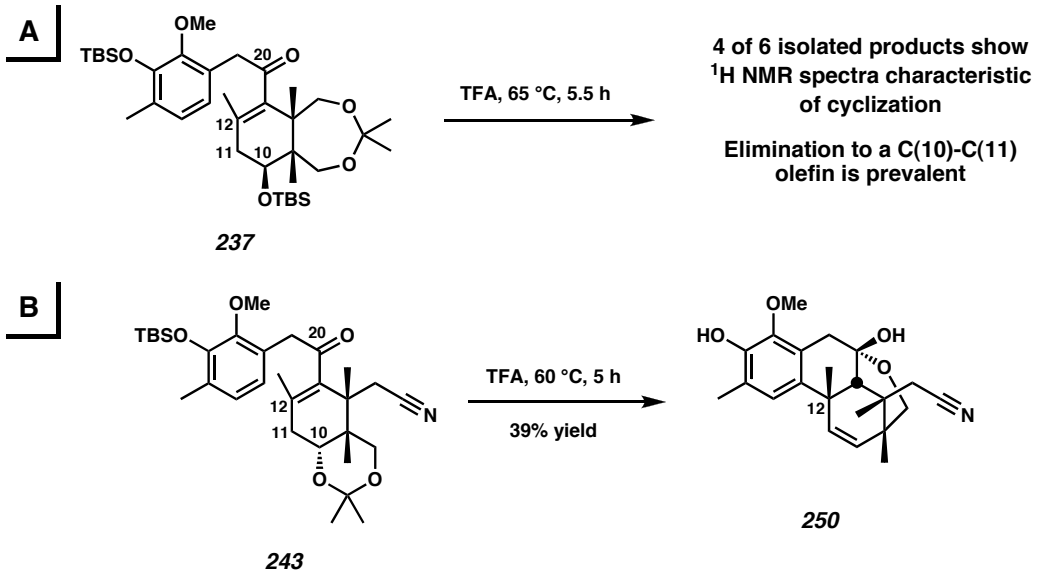


3.5.2 *Cyclization Strategies for Enone Substrates*

Another group of strategies for B ring formation used the AC ring adducts in the ketone oxidation state at C(20) as starting materials (Scheme 3.20). Upon exposure of enones **237** and **243** to trifluoroacetic acid, we anticipated elimination to form a C(10)-C(11) olefin in a manner similar to the formation of bisacetoxy acetal **220**. However, we anticipated that the different functionality of enones **237** and **243** would disrupt the preorganization of the substrate that led to the undesired stereochemistry at C(12) in bisacetoxy acetal **220**. Attempted trifluoroacetic acid cyclization of enone **237** led to a complex mixture of products. Although the majority of isolated products had ^{1}H NMR spectra consistent with cyclization, diastereoselectivity at C(12) appeared low and tetrahydrofuran formation seemed likely. Treatment of enone **243** with trifluoroacetic

acid at 60 °C led predominantly to a cyclized product, which was assigned as hemiacetal **250** by comparison to bisacetoxy acetal **220**. Unfortunately, selectivity was again obtained for the undesired C(12) stereochemistry.[28] Finally, cyclization of enone **243** with $AlCl_3$ in various solvents did not produce any cyclized products.

Scheme 3.20 Trifluoroacetic Acid-Mediated Enone Cyclizations

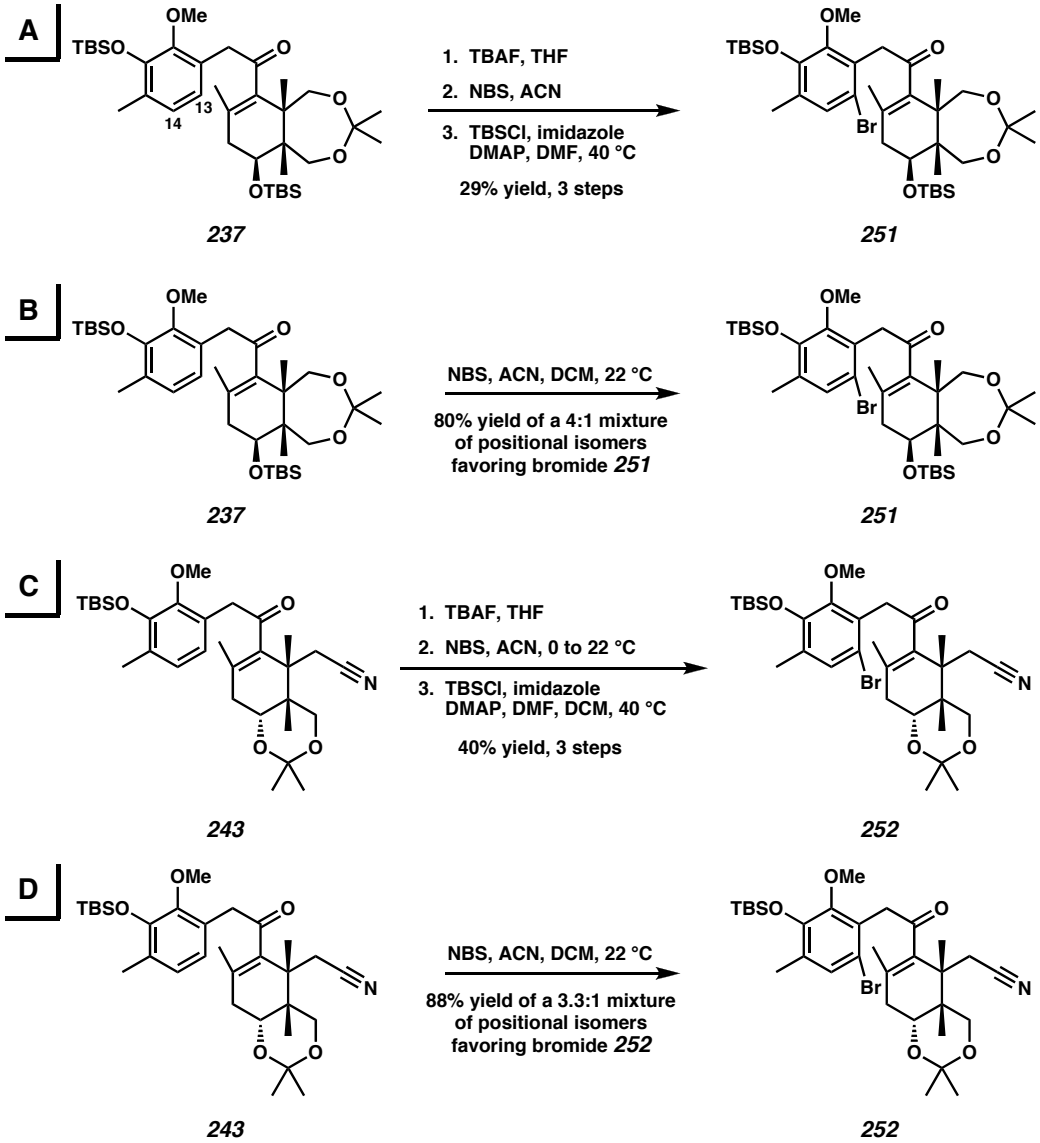


3.5.3 *Cyclization Strategies for Aryl Bromides*

In addition to cyclization strategies of our AC ring enones discussed above, we also considered cyclization strategies based on bromination of the arene nucleus at C(13) (Scheme 3.21). *N*-Bromosuccinimide (NBS) was well known to brominate *para* to electron releasing groups.[29] While there was little precedent for the superiority of silyl ethers over methoxy ethers as the directing group in this reaction, there was significant evidence that phenols were superior to methoxy ethers.[30] As a result, we carried out a three-step protocol to regioselectively produce aryl bromide **251**. Subsequently, we

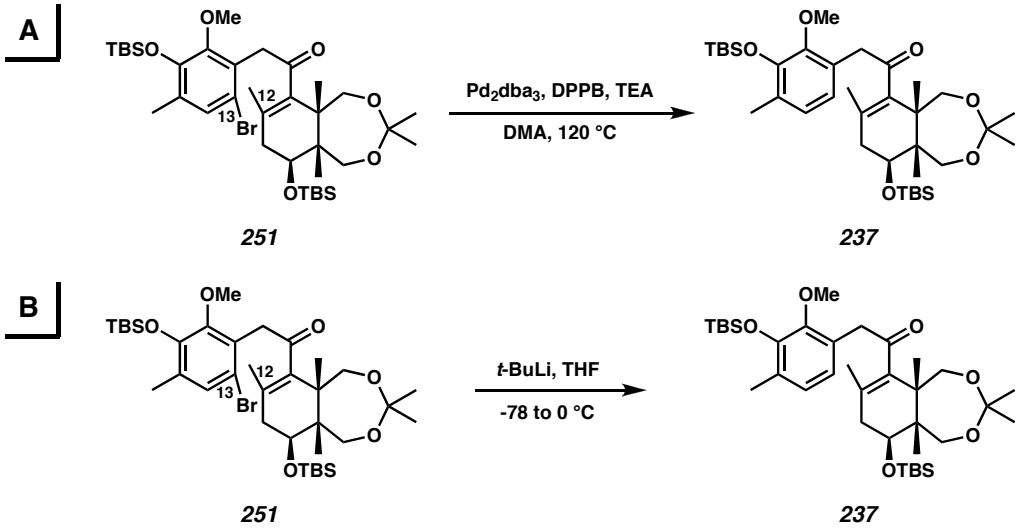
found that direct bromination of enone **237** gave a favorable 4:1 mixture of bromide positional isomers in high yield. This mixture of bromide isomers was adequate for our investigations of cyclization reactions. Homologated enone **243** underwent both the regioselective three-step bromination and direct bromination with similar results to enone **237**.

Scheme 3.21 Bromination Methods for Enone **237** and **243**



The synthesis of aryl bromides allowed us to investigate several metal-based strategies for the formation the B ring. Palladium-catalyzed 6-*exo* Heck cyclizations have been demonstrated to be efficient in forming the final bond (C(12)-C(13)) of the zoanthenol B ring.[31] In general, *exo*-Heck reactions are more favorable and much more common, but in certain cases 6-*endo* Heck cyclizations have been accomplished.[32] The intramolecular Heck reaction has been extensively reviewed.[33] We attempted 6-*endo* Heck cyclizations of bromoarene **251**, but recovered only debrominated material (Scheme 3.22).[34] Analogously, metal-halogen exchange with *tert*-butyl lithium at -78 °C was successful as judged by debromination, but the resulting anion failed to undergo conjugate addition, and led to the isolation of enone **237**.

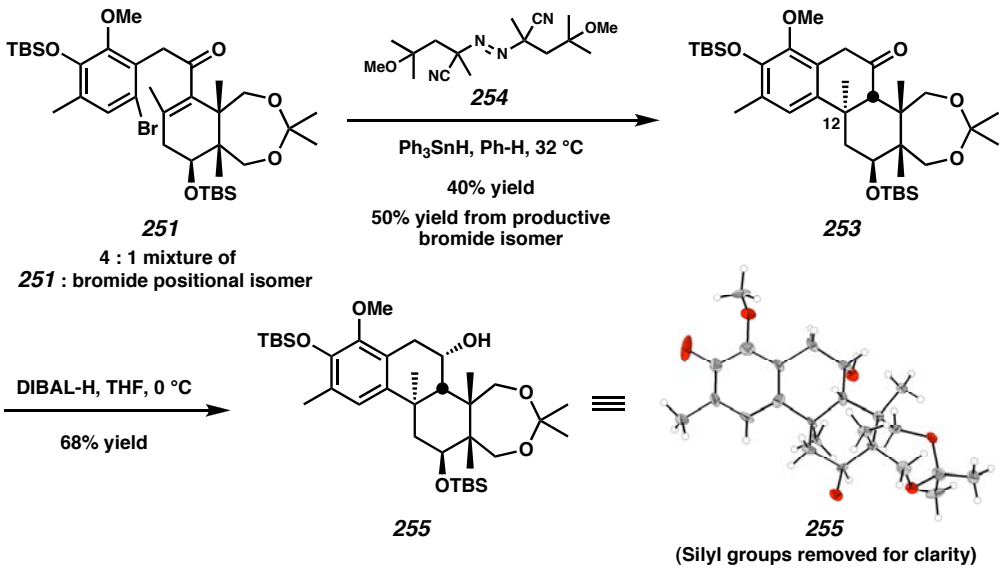
Scheme 3.22 Heck and Metal-Halogen Exchange Strategies for Cyclization



Another strategy that we investigated based on our bromoarenes was radical conjugate addition. As with Heck reactions, *endo* radical conjugate addition cyclization reactions are much less common than *exo* reactions.[35] However, a good precedent for

arene radical conjugate addition to make a quaternary center and a six-membered ring had been demonstrated.[36] To our delight, we found that in the presence of an azo radical initiator (e.g., AIBN) and a hydrogen atom donor (e.g., Bu_3SnH), aryl bromide **251** did form significant amounts of ketone **253** (Scheme 3.23). To date, our best conditions involve azo compound **254** (V-70) and slow addition of Ph_3SnH at 32 °C. In addition to the desired product, significant amounts of the debrominated enone **237** are obtained. The use of V-70 (**254**), which decomposes more readily ($t_{1/2}$ = ~10 h at 30 °C) than AIBN ($t_{1/2}$ = ~10 h at 80 °C), allows us to initiate the radical reaction at lower temperatures and reduces the amount of debrominated enone recovered. The stereochemical outcome of the radical-based cyclization was unambiguously confirmed by X-ray structure analysis of alcohol **255**, which was obtained from DIBAL-H reduction of ketone **255**.[37] While the yield of ketone **253** is still modest, our initial experiments in switching from AIBN to V-70 suggest that many reaction parameters will need to be further optimized (e.g., amounts of reagents, temperature, and rate of addition). We also plan to explore other avenues of optimization, such as the use of Lewis acids.[38]

Scheme 3.23 Radical Cyclization Methods for B Ring Formation



Currently, our efforts are directed at the optimization of the radical conjugate addition reaction conditions and employing the C(24) homologated series of compounds (e.g., aryl bromide **252**) as substrates for radical cyclization.[39] We believe that this radical cyclization strategy provides a novel, efficient, and functional group tolerant method to form the key C(12) quaternary stereocenter and close the B ring. The synthesis of the ABC ring fragments containing all three of zoanthenol's quaternary stereocenters represents an important milestone toward the total synthesis of this interesting alkaloid.

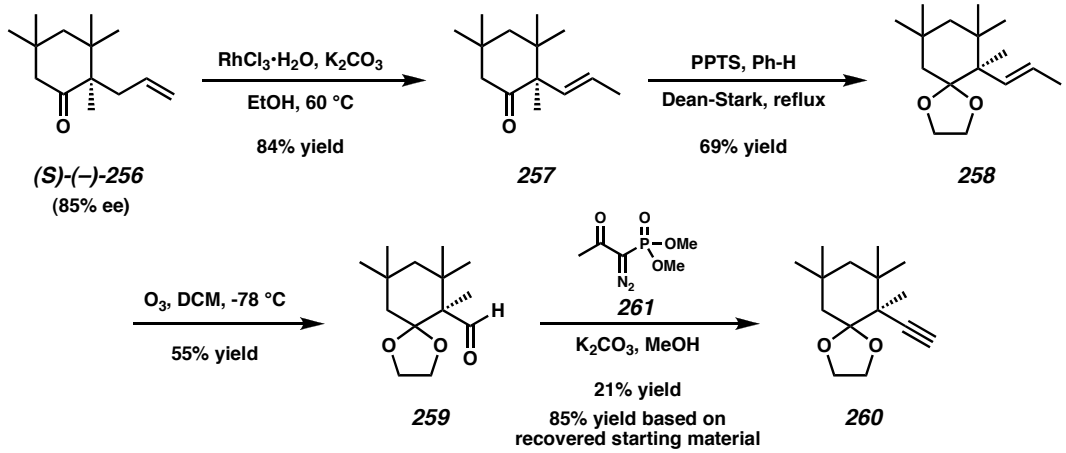
3.6 Model Studies for the Incorporation of the C(1)-C(6) Fragment

A final goal in validating our revised retrosynthetic plan was to model the fragment coupling between caprolactam **123** and the ABC ring fragment containing an alkyne. While alkynes are generally excellent nucleophiles, we judged it prudent to

model this reaction due the extremely crowded steric environment around the C ring and multiple sites of possible addition into caprolactam **123**. A similar alkyne addition strategy was employed in Miyashita's recent synthesis of norzoanthamine.[40]

The model alkyne we designed was intended to represent the worst case steric environment about the C ring (Scheme 3.24). Allyl ketone **256** was prepared in enantioenriched form by our asymmetric Tsuji allylation.[41] Isomerization of the allyl group was achieved with rhodium (III) chloride hydrate to give a 10:1 mixture favoring vinyl ketone **257**. Ketalization of vinyl ketone **258** under standard conditions followed by ozonolysis afforded aldehyde **259**. Conversion to the target alkyne **260** was accomplished using diazo compound **261** according to the Ohira-Bestmann modification of the Gilbert-Seyferth protocol.[42,43]

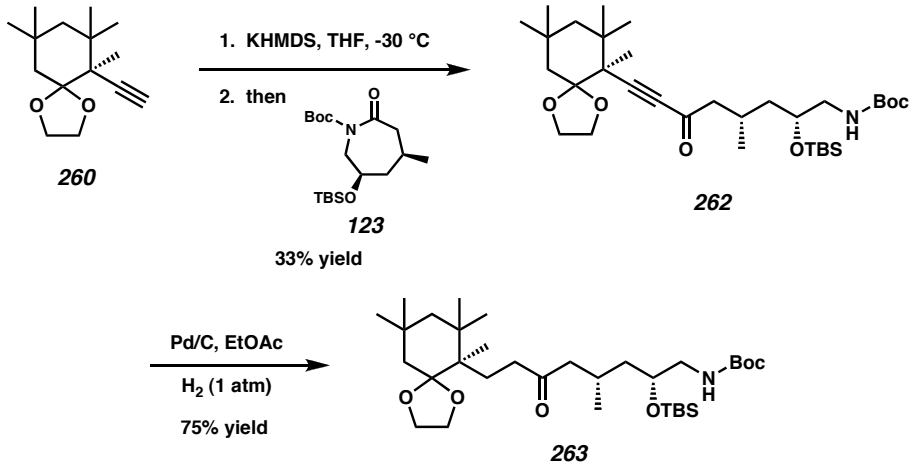
Scheme 3.24 Synthesis of C Ring Model Alkyne



With alkyne **260** in hand we began coupling studies with caprolactam **123** (Scheme 3.25). KHMDS proved to be optimal as the base for the deprotonation of alkyne **260**.[44] While achieving high conversion to ynone **262** proved difficult, the alkyne

anion did cleanly add to the lactam carbonyl of caprolactam **123**.[45] This consistently low conversion is puzzling, as deuterium quenching experiments with the lithium salt of alkyne **260** showed >90% deuterium incorporation. However, the exclusive formation of ynone **262** validates the retrosynthetic disconnection as feasible. Hydrogenation of ynone **262** with Pd/C afforded ketone **263** as expected.

Scheme 3.25 Alkyne Fragment Coupling



3.7 Concluding Remarks

We have demonstrated effective methods for the synthesis of a number of C ring synthons containing vicinal quaternary stereocenters. Our desymmetrization of *meso*-anhydride **203** affords access to either enantiomeric series of these synthons. Oxidation of our C ring intermediates was efficiently achieved by iodolactonization and S_N2' displacement. The resulting allylic alcohol **211** served as a branch point for the synthesis of three progressively more functionalized C ring synthons, the most elaborate of which includes homologation by cyanide displacement to install C(24).

Methods developed in Chapter Two allowed us to append each of these C ring synthons with an appropriately functionalized arene and explore methods to construct the challenging C(12) quaternary center by forming the C(12)-C(13) bond. Unfortunately, our previous S_N' and acid-mediated conjugate addition strategies proved unworkable when the cyclization substrates contained the additional quaternary center. The S_N' reactions gave only trace amounts of cyclized products, while the cyclized products generated by conjugate addition consistently had the undesired configuration at the formed quaternary stereocenter. However, a radical conjugate addition strategy was developed and demonstrated to form the benzylic C(12) quaternary stereocenter with high selectivity for the desired configuration. This radical cyclization approach has the significant advantage of using mild reaction conditions and being highly functional group tolerant. Products from the radical cyclization reactions are well poised to complete the synthesis. Finally, we showed our alkyne addition strategy for fragment coupling of the C(1)-C(6) portion of zoanthenol to be feasible even with extremely hindered alkynes.

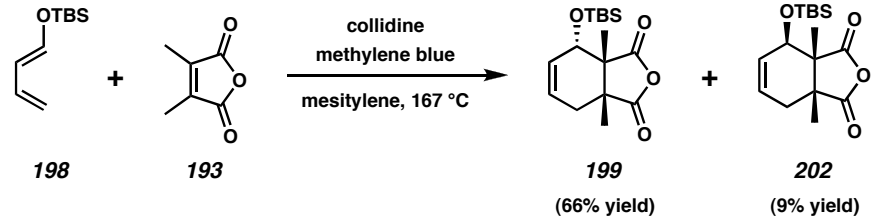
3.8 Experimental Procedures

3.8.1 *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. 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. LiCl was flame-dried

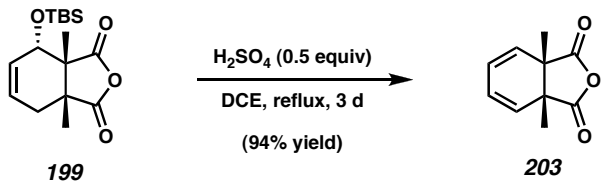
under vacuum prior to use. Magnesium turnings were of 99.98% purity and purchased from Aldrich. TBSCl was purchased from Gelest. TBSOTf was freshly prepared by the method of Corey.[46] V-70 was purchased from Waco Chemicals. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, 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 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 individual structures for deposition numbers).

3.8.2 *Preparation of Compounds*

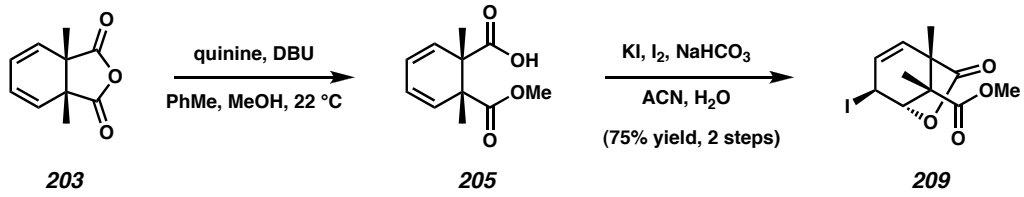


198 *193* *199* (66% yield) *202* (9% yield)

***Endo*-Diels-Alder adduct 199 and *Exo*-Diels-Alder adduct 202.** A mixture of diene **198** (67.3 g, 367.2 mmol, 1.00 equiv), 2,3-dimethylmaleic anhydride (46.3 g, 367.2 mmol, 1.00 equiv), collidine (2.91 mL, 22.0 mmol, 0.06 equiv), methylene blue (68.0 mg, 0.213 mmol, 0.000579 equiv), and mesitylene (80 mL) in a flamed-dried Ar filled Schlenk was sparged with Ar for 10 min, sealed, and heated to 167 °C for 3 d. Upon cooling, the reaction mixture was concentrated at 80 °C to give an oil, which was purified by flash chromatography on silica gel (1 to 10% EtOAc in hexanes) to give known *endo*-Diels-Alder adduct **199** (75.7 g, 66% yield), which solidified on standing: R_f 0.42 (15% EtOAc in hexanes) and *exo*-Diels-Alder adduct **202** (10.5 g, 9.2% yield) as an amorphous solid: : R_f 0.58 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (m, 1H), 5.99 (m, 1H), 4.35 (d, J = 5.5 Hz, 1H), 2.61 (dd, J = 6.3, 16.3 Hz, 1H), 2.42 (app. dt, J = 3.3, 16.5 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.4, 175.1, 132.2, 129.8, 69.1, 53.8, 46.5, 34.2, 25.6, 21.6, 18.0, 17.6, -4.4, -5.2; IR (Neat film NaCl) 2952, 2930, 1774, 1250, 986, 1091, 986, 958, 914, 838, 778 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{16}H_{26}SiO_4+H]^+$: m/z 311.1679, found 311.1671.



Diene 203. To a solution of *endo*-Diels-Alder adduct **199** (19.0 g, 61.4 mmol, 1.0 equiv) in DCE (614 mL) was added H_2SO_4 (1.71 mL, 30.7 mmol, 0.50 equiv), and the resulting solution was refluxed for 3 d. Upon cooling the reaction mixture was washed with sat. aq. $NaHCO_3$ (2 x 300 mL) [*Caution: gas evolution!*] and extracted with CH_2Cl_2 (2 x 120 mL). The combined organics from two such reactions were concentrated to give an oil and purified by flash chromatography on silica gel (1 to 10% EtOAc in hexanes) to give diene **203** (20.7 g, 94% yield) as a white solid: mp 61.5-62.5 °C; R_f 0.33 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18-6.13 (m, 2H), 5.66-5.61 (m, 2H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.1, 126.3, 124.5, 49.9, 18.6; IR (Neat film NaCl) 2984, 2940, 2848, 1856, 1785, 1233, 1196, 962, 912 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{16}H_{26}SiO_4+H]^+$: *m/z* 311.1679, found 311.1671.

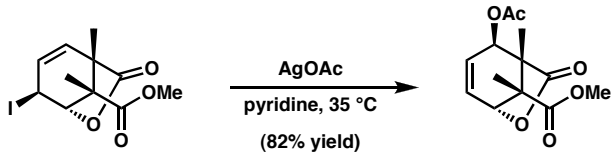


Iodolactone 209. To a solution of diene **203** (17.2 g, 96.6 mmol, 1.00 equiv), quinine (3.48 g, 9.66 mmol, 0.10 equiv), and DBU (15.9 mL, 106 mmol, 1.1 equiv) in toluene (483 mL) was added MeOH (39.1 mL, 966 mmol, 10.0 equiv). After 5 h, the reaction mixture was concentrated and the residue was diluted with EtOAc (1.00 L), washed with 2 M HCl (3 x 200 mL) and brine (1 x 200 mL), dried ($MgSO_4$), and

concentrated. Upon standing under vacuum, carboxylic acid **205** solidified and was typically used immediately in the next step without purification: R_f 0.19 (30% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80-5.45 (m, 4H), 3.66 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.5, 175.1, 131.6, 131.5, 121.9, 121.8, 52.1, 48.4, 48.1, 20.2 (2C); IR (Neat film NaCl) 2985, 2954, 1731, 1700, 1258, 1240, 1132, 1102, 702 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{11}H_{14}O_4]^+$: *m/z* 210.0892, found 210.0898; $[\alpha]_D^{26}$ –10.94 (c 1.03, $CHCl_3$, 50% ee) from reaction with stoichiometric quinine. HPLC analysis (Chirapak AD 4.6 x 25 mm, 5.0% IPA in 95% hexane with 0.1% TFA, 1.0 mL/min, λ = 254 nm) of the asymmetric reaction performed with a catalytic amount of menthol derivative **208** showed carboxylic acid **205** to be of 85% ee (t_{fast} = 10.11 min, major; t_{slow} = 12.13 min, minor).

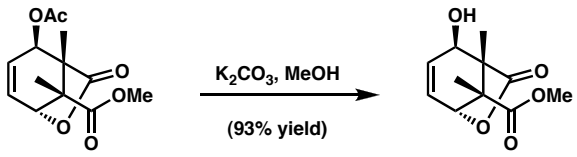
The above residue containing carboxylic acid **205** (theoretical yield: 96.6 mmol, 1.00 equiv) was dissolved in ACN (380 mL) and H_2O (380 mL) and treated with $NaHCO_3$ (24.3 g, 290 mmol, 3.00 equiv), KI (43.3 g, 261 mmol, 2.70 equiv), and I_2 (66.2 g, 261 mmol, 2.70 equiv) and the flask was wrapped in foil to exclude light. After 10 h, the reaction mixture was quenched in the dark with sat. aq. $Na_2S_2O_3$ until colorless, diluted with EtOAc (650 mL), extracted with EtOAc (2 x 300 mL), washed with brine (200 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to provide iodolactone **209** (24.4 g, 75% yield, 2 steps) as an unstable solid (typically used immediately in the next step): R_f 0.35 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.33 (ddd, *J* = 1.5, 3.0, 9.3 Hz, 1H), 4.86 (dd, *J* = 1.5, 9.3 Hz, 1H), 4.63 (app. t, *J* = 2.1 Hz, 1H), 4.29 (m, 1H), 3.13 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 175.3, 173.0,

133.0, 130.1, 80.4, 53.6, 52.5, 47.0, 16.9, 16.0, 15.0; IR (Neat film NaCl) 2953, 1795, 1732, 1450, 1293, 1247, 1141, 1107, 1062, 969 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{11}H_{14}O_4I]^+$: m/z 336.9937, found 336.9930.



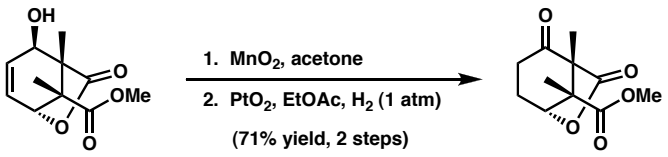
209 *210*

Allylic acetate 210. To a solution of iodolactone **209** (23.0 g, 68.5 mmol, 1.00 equiv) in pyridine (140 mL) was added AgOAc (34.3 g, 206 mmol, 3.00 equiv). The reaction mixture was wrapped in foil to exclude light and heated to 35 °C. After 3.5 d, the reaction mixture was concentrated (~5 torr at 50 °C), diluted with H_2O (500 mL) and CH_2Cl_2 (300 mL), and extracted with CH_2Cl_2 (7 x 150 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography on silica gel (15 to 35% EtOAc in hexanes) to provide allylic acetate **210** (15.2 g, 82% yield) as an oil: R_f 0.57 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddd, J = 1.0, 5.6, 9.1 Hz, 1H), 5.98 (ddd, J = 1.0, 3.5, 9.0 Hz, 1H), 5.35 (dd, J = 1.5, 3.5 Hz, 1H), 4.85 (dd, J = 1.0, 6.0 Hz, 1H), 3.75 (s, 3H), 2.11 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 173.0, 169.6, 131.1, 129.5, 76.8, 69.9, 54.7, 52.7, 50.0, 20.7, 15.6, 13.6; IR (Neat film NaCl) 2986, 2953, 1788, 1735, 1373, 1257, 1219, 1024, 962 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{13}H_{16}O_6+H]^+$: m/z 269.1025, found 269.1014.



210 ***211***

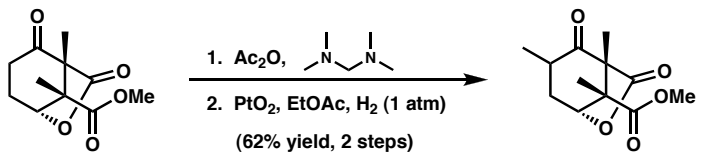
Allylic alcohol 211. To a solution of allylic acetate **210** (15.2 g, 56.2, 1.00 equiv) in MeOH (275 mL) was added K_2CO_3 (1.55 g, 11.3 mmol, 0.20 equiv) and the reaction was vigorously stirred. After 10 min, TLC analysis indicated consumption of the starting material, and the reaction mixture was quenched with H_2O (200 mL), brine (300 mL), and CH_2Cl_2 (200 mL). The pH of the aqueous layer was adjusted to pH 7 with 3 M HCl (~8 mL) [*Caution: gas evolution!*] and extracted with CH_2Cl_2 (10 x 50 mL). The combined organics were washed with brine (100 mL), concentrated, and purified by flash chromatography on silica gel (25 to 35% EtOAc in hexanes) to provide allylic alcohol **211** (11.9 g, 93% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from Et_2O/heptanes at ambient temperature: mp 94.5-95.5 °C (Et_2O/heptane); R_f 0.38 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (ddd, J = 1.5, 5.8, 9.3 Hz, 1H), 6.04 (ddd, J = 1.0, 3.3, 9.3 Hz, 1H), 4.79 (dd, J = 1.0, 5.5 Hz, 1H), 4.15 (dd, J = 1.0, 3.5 Hz, 1H), 3.72 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 173.6, 134.8, 127.3, 77.4, 69.8, 54.7, 52.6, 50.8, 15.5, 13.7; IR (Neat film NaCl) 3484, 2954, 1773, 1731, 1454, 1259, 1137, 1110, 1049, 1031, 983, 955 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{11}H_{14}O_5+H]^+$: m/z 227.0919, found 227.0924.



211 *212*

Ketone 212. To a solution of allylic alcohol **211** (2.23 g, 9.86 mmol, 1.00 equiv) in acetone (100 mL) was added activated MnO_2 (17.1 g, 197 mmol, 20.0 equiv) and the reaction mixture was stirred at ambient temperature for 1.25 h. The reaction mixture was filtered, washed with acetone, and concentrated to an oil.

To a solution of this crude material in EtOAc (60 mL) was added PtO_2 (67.1 mg, 0.296 mmol, 0.03 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 1.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (30 to 50% EtOAc in hexanes) to provide ketone **212** (1.59 g, 71% yield) as an amorphous solid: R_f 0.38 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (dd, J = 1.2, 3.9 Hz, 1H), 3.75 (s, 3H), 2.62-2.56 (m, 2H), 2.47-2.37 (m, 1H), 2.15-2.01 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 173.4, 171.3, 79.4, 62.4, 56.5, 53.0, 33.9, 24.9, 14.3, 9.3; IR (Neat film NaCl) 2989, 2955, 1790, 1732, 1343, 1267, 1227, 1152, 1089, 1018, 966 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{11}H_{14}O_5]^+$: m/z 226.0841, found 226.0847.

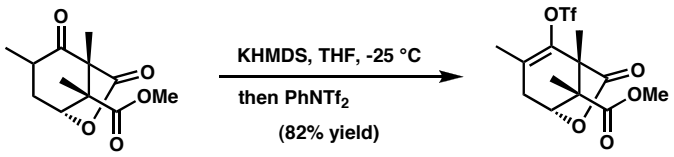


212 *213*

Methyl ketone 213. To a cooled (15 °C) solution of ketone **212** (1.31 g, 5.77 mmol, 1.00 equiv) and Ac_2O (6.55 mL, 69.3 mmol, 12.0 equiv) was added *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (4.73 mL, 34.6 mmol, 6.00 equiv) in a dropwise manner over 30 min. At the end of the addition, the reaction was allowed to come to ambient temperature. After 4 h, additional Ac_2O (6.00 mL, 63.5 mmol, 11.0 equiv) and *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (7.00 mL, 51.3 mmol, 8.89 equiv) were added and the reaction was warmed to 32 °C for 12 h. The reaction mixture was then cooled, concentrated in vacuo, quenched into water (40 mL), sat. aq. $NaHCO_3$ (20 mL), and ice (40 g), and extracted with CH_2Cl_2 (4 x 40 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude solid that was used immediately in the next step.

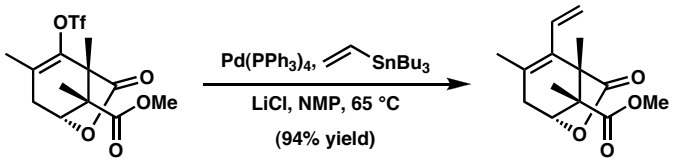
To a solution of the crude material in EtOAc (100 mL) was added PtO_2 (131 mg, 0.577 mmol, 0.10 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 5.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (20 to 40% EtOAc in hexanes) to provide a single diastereomer of methyl ketone **213** (854 mg, 62% yield) as an amorphous solid: R_f 0.57, 0.29 (50% EtOAc in hexanes, 50% Et_2O in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (m, 1H), 3.75 (s, 3H), 2.75-2.56 (m, 2H), 1.82-1.66 (m, 1H), 1.27 (s, 3H), 1.14 (d, J = 6.3 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 174.1,

171.3, 79.4, 62.0, 57.3, 53.0, 38.9, 34.0, 14.7, 13.9, 9.6; IR (Neat film NaCl) 2987, 2954, 1788, 1726, 1259, 1154, 1077, 1038 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{12}H_{16}O_5]^+$: m/z 240.0998, found 240.0996.



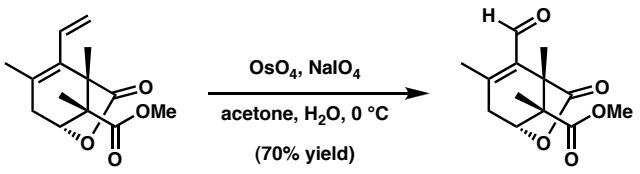
213 ***214***

Triflate 214. To a cooled (-25 °C) solution of KHMDS (339 mg, 1.70 mmol, 1.20 equiv) in THF (12 mL) was added methyl ketone **213** (340 mg, 1.42 mmol, 1.00 equiv) in THF (10 mL) in a dropwise manner over 10 min. After 1.5 h at -25 °C, $PhNTf_2$ (708 mg, 1.98 mmol, 1.40 equiv) in THF (5 mL) was added, and the reaction was maintained for an additional 30 min at -25°C. The reaction mixture was quenched into half-saturated brine (40 mL) and EtOAc (40 mL), and extracted with EtOAc (4 x 15 mL). The combined organics were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 40% EtOAc in hexanes) to provide triflate **214** (435 mg, 82% yield) as an oil: R_f 0.20 (50% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (app. t, J = 2.7 Hz, 1H), 3.75 (s, 3H), 2.63-2.47 (m, 2H), 1.86 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 172.1, 138.2, 128.2, 118.4 (app. d, $J_{C\text{-}F}$ = 319 Hz), 77.2, 54.6, 53.0, 50.4, 35.0, 17.2, 12.6, 10.0; IR (Neat film NaCl) 2956, 1790, 1727, 1408, 1208, 1138, 824 cm^{-1}; HRMS (EI) $[M+H]^+$ calc'd for $[C_{13}H_{15}O_7F_3S+H]^+$: m/z 373.0569, found 373.0550.



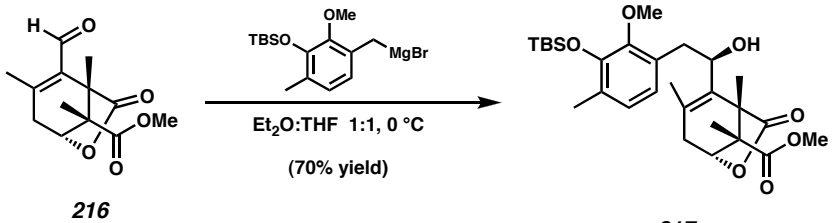
214 *215*

Diene 215. To a solution of triflate **214** (865 mg, 2.32 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (134.2 mg, 0.116 mmol, 0.05 equiv), and LiCl (295 mg, 6.97 mmol, 3.00 equiv) in NMP (18 mL) was added tributyl(vinyl)tin (1.02 mL, 3.48 equiv, 1.50 equiv), and the mixture was heated to 65 °C for 9.5 h. The reaction mixture was cooled to ambient temperature, quenched with H_2O (50 mL) and Et_2O (50 mL), and extracted with Et_2O (5 x 30 mL). The combined organics were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (5 to 25% EtOAc in hexanes) to provide diene **215** (545 mg, 94% yield) as an oil: R_f 0.63, 0.80 (50% Et_2O in hexanes developed thrice, 50% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (ddd, J = 1.2, 11.3, 17.6 Hz, 1H), 5.34 (dd, J = 2.0, 11.3 Hz, 1H), 5.02 (dd, J = 2.3, 17.6 Hz, 1H), 4.53 (app. t, J = 2.7 Hz, 1H), 3.70 (s, 3H), 2.37 (s, 2H), 1.72 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 173.7, 132.3, 131.5, 130.2, 120.6, 77.7, 53.6, 52.5, 49.3, 35.3, 20.0, 12.9, 12.5; IR (Neat film NaCl) 2985, 2951, 2911, 1782, 1730, 1267, 1198, 1144, 1089, 1035, 972 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{18}O_4]^+$: m/z 250.1205, found 250.1204.



215 *216*

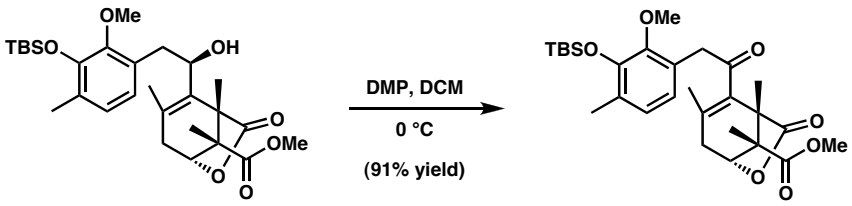
Enal 216. To a cooled (0 °C) solution of diene **215** (271 mg, 1.08 mmol, 1.00 equiv) in acetone (8.00 mL) and H_2O (8.00 mL) was added OsO_4 (27.5 mg, 0.108 mmol, 0.10 equiv) and $NaIO_4$ (511 mg, 2.38 mmol, 2.20 equiv). After 8.5 h at 0 °C, the reaction mixture was quenched with brine (30 mL) and EtOAc (30 mL), and extracted with EtOAc (5 x 30 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (25 to 50% EtOAc in hexanes) to provide enal **216** (191 mg, 70% yield) as a solid: R_f 0.48 (50% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 4.54 (app. t, J = 2.4 Hz, 1H), 3.72 (s, 3H), 2.57 (d, J = 1.8 Hz, 2H), 2.07 (s, 3H), 1.49 (s, 2H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 176.0, 172.8, 151.0, 131.6, 76.7, 53.9, 52.7, 48.2, 37.5, 19.2, 12.5, 12.3; IR (Neat film NaCl) 2952, 1786, 1729, 1681, 1333, 1273, 1250, 1201, 1136, 1082, 1034, 969 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{13}H_{16}O_5]^+$: m/z 252.0998, found 252.0984.



216 *217*

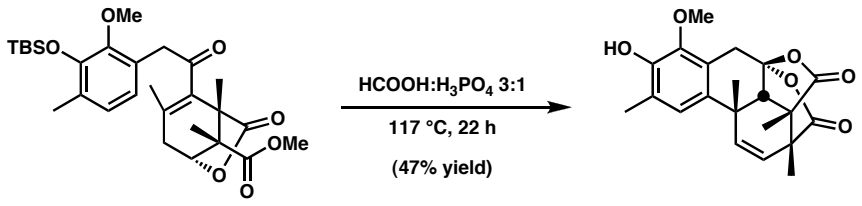
Allylic alcohol 217. A flame-dried two-neck round-bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (1.03 g, 42.4 mmol,

32.4 equiv) and Et_2O (12 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (150 μL, 1.74 mmol, 1.33 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (677 mg, 1.96 mmol, 1.50 equiv) in Et_2O (7.0 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 **216** (330 mg, 1.31 mmol, 1.00 equiv) in Et_2O (10 mL) and THF (30 mL). After 1 h at 0 °C, the reaction mixture was allowed to come to ambient temperature, and after an additional 30 min, the reaction was quenched with ice cold H_2O (50 mL), 2 M HCl (2.0 mL), and Et_2O (20 mL), and extracted with Et_2O (4 x 40 mL). The combined organics were washed with brine (2 x 30 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 50% EtOAc in hexanes) to give allylic alcohol **217** (477 mg, 70% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from EtOAc/heptanes at ambient temperature: mp 154-155 °C (EtOAc/heptane); R_f 0.50 (35% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 7.7 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 4.75 (bs, 1H), 4.52 (app. t, J = 2.6 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.00-2.80 (m, 2H), 2.76-2.54 (bs, 1H), 2.36 (m, 2H), 2.20 (s, 3H), 1.78 (s, 3H), 1.50 (s, 3H), 1.29 (s, 3H), 1.02 (s, 9H), 0.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.7, 173.8, 149.4, 147.1, 132.5, 131.8, 129.8, 129.6, 126.3, 123.5, 123.3, 72.0, 60.1, 54.4, 52.6, 50.0, 37.4, 37.0, 26.0, 19.4, 18.6, 17.1, 13.1, 12.9, -4.1; IR (Neat film NaCl) 3519, 2953, 2930, 2858, 1777, 1731, 1462, 1419, 1259, 1073, 840 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calc'd for $[C_{28}H_{42}SiO_7+Na]^+$: m/z 541.2598, found 541.2571.



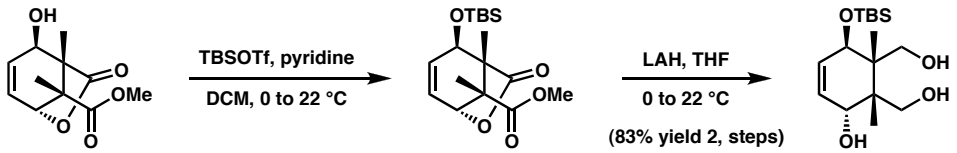
217 *218*

Enone 218. To a cooled (0 °C) solution of allylic alcohol **217** (129 mg, 0.248 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (210 mg, 0.496 mmol, 2.00 equiv) and the resulting mixture was stirred for 1 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 (15 to 40% EtOAc in hexanes) to give enone **218** (117 mg, 91% yield) as a foam: R_f 0.57 (35% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 4.61 (app. t, J = 2.4 Hz, 1H), 3.94 (d, J = 17.7 Hz, 1H), 3.76 (d, J = 17.7 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.46 (dd, J = 2.7, 18.9 Hz, 1H), 2.35 (dd, J = 1.5, 18.9 Hz, 1H), 2.20 (s, 3H), 1.66 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.02 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 176.2, 173.1, 150.0, 146.9, 135.4, 130.6, 130.0, 125.7, 124.4, 123.3, 77.8, 59.8, 53.5, 52.7, 47.8, 46.2, 34.3, 26.0, 18.8, 18.4, 17.0, 12.5, 11.7, -4.3; IR (Neat film NaCl) 2953, 2930, 2858, 1785, 1732, 1463, 1421, 1286, 1252, 1236, 840 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{28}H_{40}SiO_7+H]^+$: m/z 517.2622, found 517.2631.



218 *220*

Bisacetoxyacetal 220. A solution of enone 218 (58.5 mg, 0.113 mmol, 1.00 equiv) in formic acid (2.40 mL) and 85% H_3PO_4 (800 μL) was fitted with a reflux condenser and heated at 117 °C for 22 h. The reaction mixture was cooled to ambient temperature, diluted with ice cold H_2O (60 mL) and extracted with Et_2O (5 x 15 mL). The combined organics were dried ($MgSO_4$) and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 40% EtOAc in hexanes) to give bisacetoxyacetal **220** (19.6 mg, 47% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from Et_2O/hexanes at ambient temperature: mp 185-190 °C decomp. (Et_2O/hexanes); R_f 0.32 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.14 (dd, J = 0.9, 9.3 Hz, 1H), 5.62 (bs, 1H), 5.42 (d, J = 9.3 Hz, 1H), 3.77 (s, 3H), 3.61 (d, J = 15.9 Hz, 1H), 3.02 (dd, J = 0.9, 15.9 Hz, 1H), 2.48 (s, 1H), 2.52 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 169.5, 145.9, 144.4, 137.4, 130.8, 126.0, 124.9, 124.7, 121.8, 105.7, 60.9, 53.0, 45.9, 38.0, 32.2, 31.5, 16.3, 16.2, 15.8; IR (Neat film NaCl) 3468, 2978, 2942, 1801, 1757, 1360, 1213, 1057, 937, 914, 732 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{21}H_{22}O_6]^+$: *m/z* 370.1416, found 370.1410.

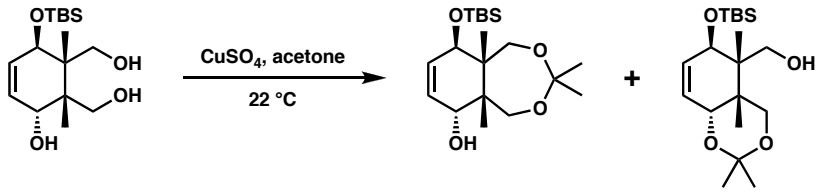


211 ***227*** ***228***

Triol 228. To cooled (0 °C) solution of allylic alcohol **211** (4.37 g, 19.3 mmol, 1.00 equiv) and pyridine (3.12 mL, 38.7 mmol, 2.00 equiv) in CH_2Cl_2 (19 mL) was added TBSOTf (6.66 mL, 29.0 mmol, 1.50 equiv) in a dropwise manner. At the end of the addition, the reaction was allowed to warm to ambient temperature and stirred for 15 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), quenched with sat. aq. NH_4Cl (75 mL), and extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to give crude silyl ether **227**, which was typically used without purification in the next step: R_f 0.69 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (ddd, J = 1.0, 6.0, 9.0 Hz, 1H), 5.89 (ddd, J = 1.0, 3.5, 9.0 Hz, 1H), 4.78 (d, J = 5.5 Hz, 1H), 4.08 (dd, J = 1.0, 3.5 Hz, 1H), 3.72 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 173.7, 134.8, 126.9, 77.3, 70.5, 54.9, 52.5, 51.3, 25.6, 17.9, 15.7, 14.7, -4.5, -5.1; IR (Neat film NaCl) 2952, 2933, 2857, 1779, 1737, 1725, 1454, 1374, 1254, 1095, 1065, 957, 841, 780 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{17}H_{28}SiO_5+H]^+$: m/z 341.1784, found 341.1781.

The above residue containing silyl ether **227** (theoretical yield: 19.3 mmol, 1.00 equiv) was dissolved in THF (193 mL), cooled (0 °C), and treated with LAH (2.20 g, 58.0 mmol, 3.00 equiv) in portions. At the end of the addition, the reaction was allowed to come to ambient temperature and stirred for 18 h. The cooled (0 °C) reaction mixture was quenched by the careful dropwise addition of EtOAc (66 mL) until out gassing

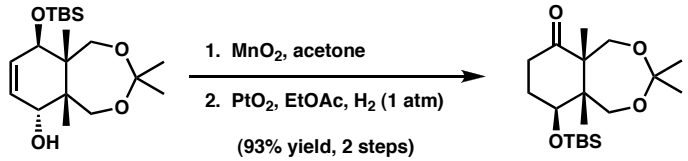
ceased, addition of Celite (7.0 g), and, finally, careful addition of sat. aq. Na_2SO_4 (33 mL). The resulting slurry was filtered, dried (Na_2SO_4), and concentrated to give triol **228** (5.05 g, 83% yield, 2 steps) as a white solid of ~95% purity. Analytically pure material could be obtained by recrystallization from 1% EtOAc in benzene: mp 130.5-132.0 °C (EtOAc/benzene); R_f 0.22 (30% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68-5.62 (m, 2H), 4.45 (s, 1H), 4.20 (s, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.69 (d, *J* = 11.5 Hz, 1H), 3.50 (d, *J* = 12.0 Hz, 1H), 1.15 (s, 3H), 0.89 (s, 9H), 0.84 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 129.1, 73.6, 69.3, 65.6, 63.7, 46.1, 45.2, 25.8, 18.0, 16.2, 13.6, -4.0, -5.0; IR (Neat film NaCl) 3255, 2955, 2929, 2886, 2857, 1472, 1253, 1076, 1049, 1026, 880, 835 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{16}H_{32}SiO_4+H]^+$: *m/z* 317.2148, found 317.2162.



228 ***229*** (35% yield) ***230*** (53% yield)

1,3-Dioxepane 229 and Acetonide 230. To a solution of triol **228** (3.75 g, 11.9 mmol, 1.00 equiv) in acetone (120 mL) was added anhydrous $CuSO_4$ (9.46 g, 59.3 mmol, 5.00 equiv), and the reaction mixture was stirred for 40 min. An additional portion of $CuSO_4$ (1.89 g, 11.9 mmol, 1.00 equiv) was added to the reaction mixture, and after an additional 3 h of stirring, a final portion of $CuSO_4$ (1.00 g, 6.27 mmol, 0.53 equiv) was added. After 30 min, the reaction mixture was filtered, concentrated, and purified by flash chromatography on silica gel (5 to 15% EtOAc in hexanes) to give 1,3-dioxepane

229 (1.48 g, 35% yield) as a waxy solid: R_f 0.66 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (dt, *J* = 2.1, 10.2 Hz, 1H), 5.49 (dt, *J* = 2.1, 10.2 Hz, 1H), 4.99 (s, 1H), 4.23 (app. q, *J* = 2.4 Hz, 1H), 3.73 (d, *J* = 12.3 Hz, 1H), 3.58 (d, *J* = 12.6 Hz, 1H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.19 (d, *J* = 12.6 Hz, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.71 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 131.7, 129.2, 101.8, 73.5, 68.1, 63.8, 63.0, 46.9, 46.3, 26.5, 25.7, 25.4, 18.8, 18.7, 11.7, -3.7, -4.5; IR (Neat film NaCl) 3446, 2983, 2954, 2858, 1472, 1372, 1253, 1221, 1085, 1070, 1044, 835, 775 cm^{-1}; HRMS (FAB) [M-H_2+H]$^+$ calc'd for [$C_{19}H_{35}SiO_4$]$^+$: *m/z* 355.2305, found 355.2317 and acetonide **230** (2.25 g, 53% yield) as an oil: R_f 0.76 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 4.4, 9.6 Hz, 1H), 5.69 (dd, *J* = 4.8, 9.9 Hz, 1H), 4.12 (d, *J* = 4.5 Hz, 1H), 4.01 (d, *J* = 12.9 Hz, 1H), 3.91 (s, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.64 (d, *J* = 10.2 Hz, 1H), 3.56 (d, *J* = 12.9 Hz, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 124.4, 98.6, 71.7, 70.9, 68.9, 65.2, 43.8, 35.1, 28.4, 25.7, 20.9, 20.0 (bs), 17.9, 15.3, -4.1, -5.1; IR (Neat film NaCl) 3451, 2955, 2931, 2886, 2858, 1379, 1256, 1104, 1056, 836, 775 cm^{-1}; HRMS (FAB) [M+H]$^+$ calc'd for [$C_{19}H_{36}SiO_4$+H]$^+$: *m/z* 357.2461, found 357.2478.

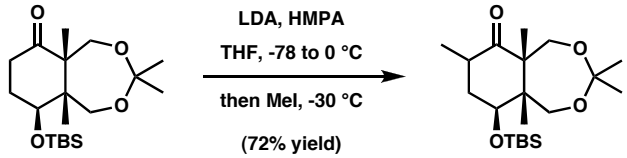


229 ***232***

Ketone 232. To a solution of 1,3-dioxepane **229** (798 mg, 2.24 mmol, 1.00 equiv) in acetone (23 mL) was added activated MnO_2 (3.89 g, 44.7 mmol, 20.0 equiv),

and the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was filtered, washed with acetone, and concentrated to an oil.

To a solution of this crude material in EtOAc (28 mL) was added PtO_2 (16.0 mg, 67.2 μmol, 0.03 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 1.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide ketone **232** (744 mg, 93% yield, 2 steps) as an amorphous solid: R_f 0.52 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (bs, 1H), 4.15 (bs, 1H), 3.40 (bs, 2H), 2.99 (bs, 1H), 2.31 (m, 2H), 2.10-1.70 (m, 2H), 1.33 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H), 0.89 (s, 9H), 0.64 (bs, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 101.8, 67.3, 65.1, 64.0, 57.1, 47.2, 37.9, 29.4, 25.8, 24.8, 24.4, 18.0, 15.8, 11.5, -4.4, -5.1; IR (Neat film NaCl) 2954, 2857, 1709, 1220, 1096, 1073, 884, 836 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{19}H_{36}O_4Si+H]^+$: m/z 357.2461, found 357.2473.

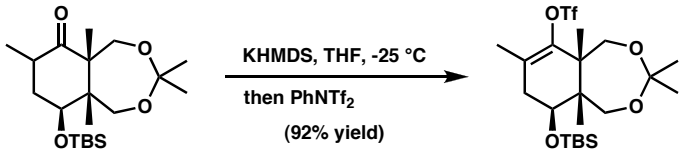


232 *233*

Methyl Ketones 233. A solution of LDA in THF was prepared by dropwise addition of 2.45 M *n*-BuLi solution in hexanes (1.21 mL, 2.96 mmol, 1.20 equiv) to diisopropylamine (519 μL, 3.70 mmol, 1.50 equiv) in THF (30.0 mL) at 0 °C, followed by stirring for 1 h. Upon cooling the solution to -78 °C, a solution of ketone **232** (879 mg, 2.47 mmol, 1.00 equiv) in THF (30.0 mL) was added in a dropwise manner, and the

reaction mixture was stirred at -78 °C for 30 min. HMPA (1.07 mL, 6.17 mmol, 2.50 equiv) was added and the reaction mixture brought to 0 °C for 1 h. After cooling again to -78 °C, the reaction mixture was treated with MeI (200 μL, 3.21 mmol, 1.30 equiv), and after 15 min allowed to warm to -30 °C. The reaction was allowed to warm to 0 °C slowly over 10 h, quenched with H_2O (150 mL) and EtOAc (75 mL), and extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to give recovered ketone **232** (90.9 mg, 10% yield), the high R_f diastereomer methyl ketone **233a** (219 mg, 24% yield) as an oil: R_f 0.65 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (dd, J = 4.7, 12.2 Hz, 1H), 4.22 (d, J = 12.0 Hz, 1H), 3.49 (d, J = 12.6 Hz, 1H), 3.34 (d, J = 12.3 Hz, 1H), 2.93 (d, J = 11.7 Hz, 1H), 2.41 (dq, J = 6.3, 19.8 Hz, 1H), 1.98 (dt, J = 5.1, 12.9 Hz, 1H), 1.53 (d, J = 13.2 Hz, 1H), 1.34 (s, 3H), 1.10 (s, 3H), 1.01 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.55 (s, 3H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 101.9, 67.0, 65.5, 63.9, 56.8, 48.1, 41.0, 38.6, 25.8, 24.8, 24.5, 18.0, 15.7, 14.7, 11.3, -4.3, -5.1; IR (Neat film NaCl) 2984, 2955, 2935, 2858, 1709, 1220, 1095, 1072, 1044, 868, 837, 776 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{20}H_{38}O_4Si+H]^+$: m/z 371.2618, found 371.2607, and the low R_f diastereomer methyl ketone **233b** (436 mg, 48% yield) as an oil: R_f 0.36 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (d, J = 12.6 Hz, 1H), 3.60 (d, J = 12.0 Hz, 1H), 3.58 (bs, 1H), 3.41 (d, J = 12.6 Hz, 1H), 3.02-2.80 (m, 2H), 1.91 (ddd, J = 4.2, 5.6, 14.0 Hz, 1H), 1.58 (m, 1H), 1.30 (s, 3H), 1.24 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 101.2, 73.0, 67.8, 64.3, 54.4, 47.0, 37.7, 35.3,

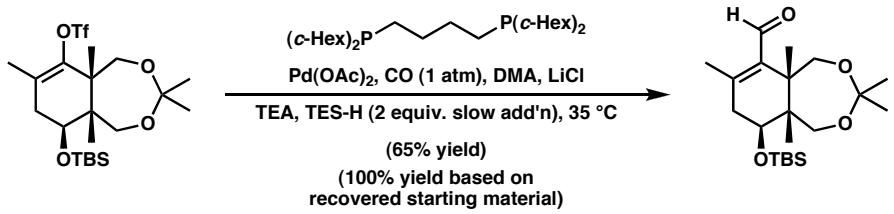
25.8, 25.0, 23.9, 19.4, 18.1, 16.9, 14.7, -4.6, -5.0; IR (Neat film NaCl) 2933, 2858, 1709, 1255, 1222, 1078, 1046, 838, 775 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{20}H_{38}O_4Si+H]^+$: *m/z* 371.2618, found 371.2625.



233 ***234***

Triflate 234. To a cooled (-25 °C) solution of KHMDS (668 mg, 3.35 mmol, 1.20 equiv) in THF (40 mL) was added the low R_f diastereomer methyl ketone **233b** (1.04 g, 2.79 mmol, 1.00 equiv) in THF (20 mL) in a dropwise manner over 10 min. After 2.0 h at -25 °C, $PhNTf_2$ (1.30 g, 3.63 mmol, 1.30 equiv) in THF (20 mL) was added, and the reaction was maintained for an additional 30 min at -25°C. The reaction mixture was quenched into half-saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL), and extracted with EtOAc (5 x 50 mL). The combined organics were washed with brine (1 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (0 to 10% EtOAc in hexanes) to provide triflate **234** (1.30 g, 92% yield) as an oil: R_f 0.69 (10% Et_2O in hexanes); ^1H NMR (300 MHz, C_6D_6) δ 4.18 (dd, *J* = 6.3, 9.9 Hz, 1H), 3.79 (d, *J* = 12.3 Hz, 1H), 3.65 (d, *J* = 12.9 Hz, 1H), 3.41 (d, *J* = 12.3 Hz, 1H), 3.33 (d, *J* = 12.6 Hz, 1H), 2.08 (dd, *J* = 6.5, 17.6 Hz, 1H), 1.91 (ddd, *J* = 1.1, 9.9, 17.6 Hz, 1H), 1.61 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 0.98 (s, 9H), 0.49 (s, 3H), 0.15 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.9, 127.1, 119.7 (q, $J_{C\text{-}F}$ = 318 Hz), 102.0, 65.4, 65.2, 62.7, 47.4, 45.9, 38.2, 26.5, 25.0, 24.9, 18.6, 18.3, 17.0, 11.0, -3.8,

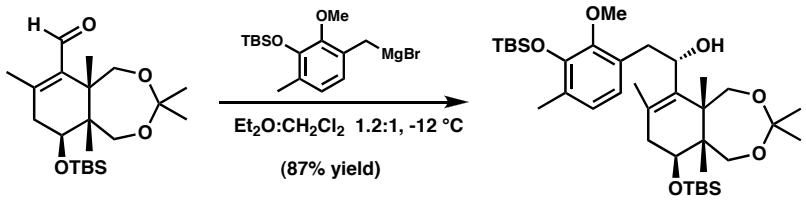
-4.6; IR (Neat film NaCl) 2988, 2954, 2858, 1405, 1213, 1141, 1078, 879 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{21}H_{37}SSiO_6F_3+H]^+$: m/z 503.2110, found 503.2094.



234 ***235***

Enal 235. A solution of flame-dried LiCl (433 mg, 10.2 mmol, 3.0 equiv), $Pd(OAc)_2$ (153 mg, 0.680 mmol, 0.20 equiv), and 1,4-bis-(dicyclohexylphosphino)butane (306 mg, 0.680 mmol, 0.20 equiv) in DMA (16 mL) was sparged with CO and warmed to 85 °C until a color change from red/orange to pale yellow was observed, at which point the reaction mixture was cooled to 40 °C. To the homogenous reaction mixture was added TEA (1.89 mL, 13.6 mmol, 4.00 equiv) and enol triflate **234** (1.71 g, 3.40 mmol, 1.00 equiv) in DMA (20 mL). A solution of Et_3SiH (1.09 mL, 6.80 mmol, 2.0 equiv) in DMA (10.0 mL) was added by syringe pump to the reaction over 10 h. After an additional 14 h at 40 °C, the reaction mixture was cooled to ambient temperature, poured into H_2O (100 mL) and Et_2O (100 mL), and extracted with Et_2O (5 x 50 mL). The combined organic layers were washed with H_2O (20 mL), brine (2 x 20 mL), dried (Na_2SO_4), and concentrated to give an oil, which was purified by flash chromatography on silica gel (2 to 10% EtOAc in hexanes) to give recovered triflate **234** (606 mg, 35% yield) and enal **235** (841 mg, 65% yield) as a pale yellow oil: R_f 0.50, 0.55 (10% EtOAc in hexanes developed twice, 25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 4.19 (dd, *J* = 7.1, 9.2 Hz, 1H), 3.73 (d, *J* = 12.3 Hz, 1H), 3.60 (d, *J* = 12.0 Hz, 1H), 3.57 (d, *J* = 12.3 Hz, 1H), 3.34 (d, *J* = 12.3 Hz, 1H), 2.32-2.22 (m, 2H), 2.09 (s, 3H),

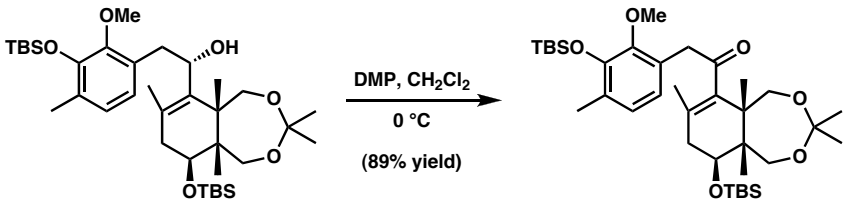
1.31 (s, 3H), 1.24 (s, 6H), 0.89 (s, 9H), 0.53 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 92.7, 154.2, 135.2, 101.0, 65.2, 65.0, 61.4, 45.2, 43.7, 41.3, 25.8, 24.6, 19.6, 18.0, 17.5, 10.7, -4.4, -5.1; IR (Neat film NaCl) 2986, 2953, 2888, 2857, 1677, 1371, 1221, 1101, 1073, 870, 837, 780 cm^{-1}; HRMS (FAB) $[M-H_2+H]^+$ calc'd for $[C_{20}H_{37}O_5]^+$: *m/z* 385.2410, found 385.2412.



235 ***236***

Allylic alcohol 236. A flame-dried two-neck round-bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (3.00 g, 123 mmol, 56.1 equiv) and Et_2O (45 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (75.0 μL, 0.870 mmol, 0.40 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (1.37 g, 3.96 mmol, 1.80 equiv) in Et_2O (18.0 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 (-12 °C) solution of enal **235** (841 mg, 2.20 mmol, 1.00 equiv) in Et_2O (45 mL) and CH_2Cl_2 (90 mL). After 1 h at -12 °C, the reaction was quenched with H_2O (150 mL), 2 M citric acid (20 mL), brine (20 mL), and EtOAc (50 mL), and extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 12.5% Et_2O in hexanes) to give allylic alcohol **236** (1.24 g, 87% yield) as a foam consisting of a 10:1 mixture of

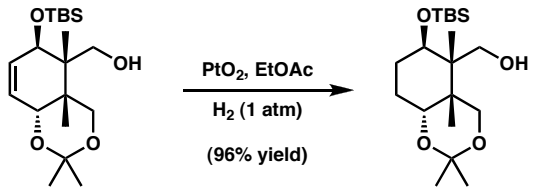
diastereomers. Only the major component (stereochemistry shown above) could be isolated in pure form: R_f 0.41, 0.29 (25% Et_2O in hexanes, 10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 7.5 Hz, 1H), 4.46 (d, *J* = 10.2 Hz, 1H), 4.16 (dd, *J* = 7.1, 9.5 Hz, 1H), 3.71 (s, 3H), 3.62 (d, *J* = 12.6 Hz, 1H), 3.53 (d, *J* = 12.3 Hz, 1H), 3.39 (d, *J* = 12.3 Hz, 1H), 3.32 (bs, 1H), 3.27 (dd, *J* = 10.7, 14.0 Hz, 1H), 2.59 (dd, *J* = 3.0, 14.1 Hz, 1H), 2.46 (s, 1H), 2.20 (s, 3H), 2.10-2.00 (m, 2H), 1.98 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.03 (s, 9H), 0.90 (s, 9H), 0.56 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.5, 147.2, 134.6, 132.2, 130.8, 129.4, 126.4, 123.1, 100.8, 72.6, 66.1, 65.7, 62.2, 60.0, 47.1, 43.6, 40.0, 38.4, 26.0, 25.9, 24.7(2C), 20.9, 18.6, 18.1, 17.8, 17.0, 10.9, -4.0, -4.2, -4.3, -5.1; IR (Neat film NaCl) 3479, 2955, 2931, 2858, 1463, 1253, 1221, 1074, 838, 780 cm^{-1}; HRMS (FAB) $[M\text{-}H_2+H]^+$ calc'd for $[C_{36}H_{63}Si_2O_6]^+$: *m/z* 647.4163, found 647.4156.



236 ***237***

Enone 237. To a cooled (0 °C) solution of allylic alcohol **236** (1.24 g, 1.91 mmol, 1.00 equiv) in CH_2Cl_2 (120 mL) was added Dess-Martin periodinane (1.21 g, 2.86 mmol, 1.50 equiv) and the resulting mixture was stirred for 2 h. The reaction mixture was concentrated to ~40 mL, diluted with Et_2O (250 mL), filtered, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (2.5 to 5% EtOAc in hexanes) to give enone **237** (1.10 g, 89% yield) as a foam: R_f 0.43, 0.69 (10% EtOAc in hexanes, 10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, *J* = 7.5 Hz, 1H),

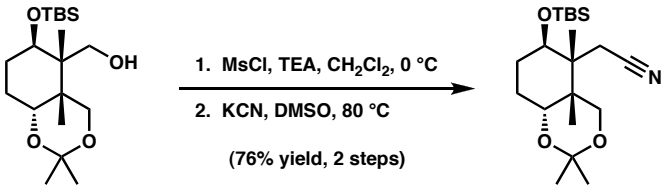
6.63 (d, *J* = 7.8 Hz, 1H), 4.28 (dd, *J* = 7.1, 9.5 Hz, 1H), 3.92 (d, *J* = 18.3 Hz, 1H), 3.80 (d, *J* = 18.0 Hz, 1H), 3.75 (d, *J* = 11.4 Hz, 1H), 3.64 (s, 3H), 3.52 (d, *J* = 12.6 Hz, 1H), 3.39 (d, *J* = 12.3 Hz, 1H), 2.20 (s, 3H), 2.12-1.98 (m, 2H), 1.72 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.13 (s, 3H), 1.02 (s, 9H), 0.90 (s, 9H), 0.66 (s, 3H), 0.15 (s, 6H), 0.09 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 150.1, 147.0, 138.2, 129.9 (2C), 125.8, 125.3, 123.2, 101.1, 65.9, 65.5, 61.5, 60.0, 47.1, 45.3, 42.9, 37.9, 26.1, 25.9, 24.7 (2C), 20.7, 18.6, 18.1, 17.1, 11.1, -4.2 (2C), -4.4, -5.1; IR (Neat film NaCl) 2954, 2930, 2858, 1699, 1463, 1252, 1221, 1099, 1073, 864, 836, 780 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{36}H_{63}Si_2O_6+H]^+$: *m/z* 647.4163, found 647.4140.



230 ***238***

Alcohol 238. To a solution of acetonide **230** (5.64 g, 15.8 mmol, 1.00 equiv) in EtOAc (198 mL) was added PtO_2 (108 mg, 0.475 mmol, 0.03 equiv), and the reaction mixture was sparged with a stream of H_2 gas for 4 h. The reaction mixture was concentrated (~10 mL), filtered through a plug of silica gel, and concentrated to give hydrogenated alcohol **238** (5.47 g, 96% yield) as an oil: R_f 0.76 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (dd, *J* = 5.5, 12.0 Hz, 1H), 3.98 (dd, *J* = 5.0, 10.3 Hz, 1H), 3.88 (d, *J* = 13.0 Hz, 1H), 3.79 (app. t, *J* = 3.0 Hz, 1H), 3.45 (s, 1H), 3.32 (d, *J* = 12.0 Hz, 1H), 3.04 (app. t, *J* = 11.0 Hz, 1H), 2.12 (app. tt, *J* = 3.8, 14.3 Hz, 1H), 1.86 (app. tt, *J* = 3.0, 14.0 Hz, 1H), 1.48 (s, 3H), 1.47-1.37 (m, 1H), 1.42 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 98.5, 75.0, 74.4, 69.5, 66.8, 43.5, 35.0, 29.5, 25.9, 25.1, 21.9, 20.2, 18.8, 18.0, 17.2, -4.6, -5.0; IR (Neat film NaCl) 3497, 2953, 2936, 2883, 2858, 1472, 1379, 1257, 1196, 1083, 1060, 1034, 1005, 866, 834, 774 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{19}H_{38}SiO_4+H]^+$: *m/z* 359.2618, found 359.2632.

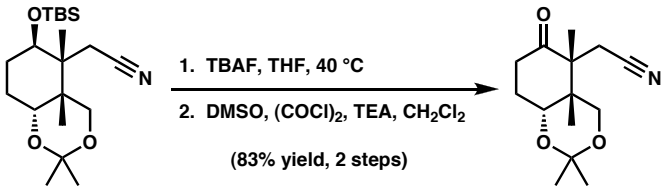


238 ***239***

Nitrile 239. To a cooled (0 °C) solution of alcohol **238** (880 mg, 2.45 mmol, 1.00) and TEA (1.02 mL, 7.36 mmol, 3.00 equiv) in CH_2Cl_2 (25 mL) was added methanesulfonyl chloride (228 μL, 2.95 mmol, 1.20 equiv) in a dropwise manner. After 30 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (40 mL), ice cold H_2O (50 mL), and brine (25 mL), and extracted with CH_2Cl_2 (3 x 35 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), and concentrated to a waxy solid that was used in the next step immediately.

The above residue was dissolved in DMSO (25 mL) and treated with KCN (400 mg, 6.14 mmol, 2.50 equiv) at 80 °C for 4 h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc (50 mL) and H_2O (150 mL), and extracted with EtOAc (7 x 40 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide nitrile **239** (682 mg, 76% yield) as a solid : R_f 0.42 (20% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (d, *J* = 8.7 Hz, 1H), 3.83 (d, *J* = 8.4 Hz, 1H), 3.70-3.60 (m, 2H), 3.49 (d, *J* = 8.1 Hz, 1H), 3.46 (d, *J* = 8.7 Hz, 1H), 2.18-2.04 (m,

1H), 1.74-1.45 (m, 3H), 1.55 (s, 6H), 1.14 (s, 3H), 0.90 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.7, 78.8, 76.1, 74.8, 71.0, 70.1, 50.8, 48.8, 28.8 (2C), 27.6 (2C), 25.8, 22.6, 18.0, 9.5, -3.9, -5.0; IR (Neat film NaCl) 2956, 2934, 2882, 2860, 1460, 1254, 1183, 1080, 1047, 916, 868, 835, 772 cm^{-1}; HRMS (FAB) [M-H_2+H]$^+$ calc'd for $[C_{20}H_{36}NO_3Si]^+$: *m/z* 366.2464, found 366.2459.

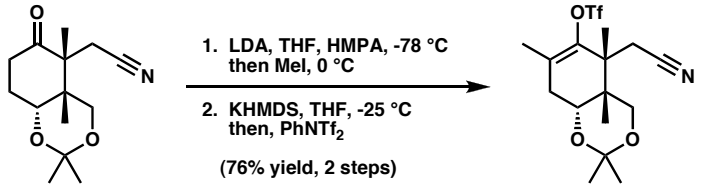


239 ***240***

Ketone 240. To a solution of nitrile **239** (1.13 g, 3.08 mmol, 1.00 equiv) in THF (18.5 mL) was added a 1.0 M solution of TBAF (9.23 mL, 9.23 mmol, 3.00 equiv) in THF, and the reaction mixture was heated to 40 °C for 7.5 h. An additional portion of a 1.0 M solution of TBAF (2.00 mL, 2.00 mmol, 0.65 equiv) in THF was added. After a further 1 h, the reaction mixture was cooled to ambient temperature, diluted with EtOAc (100 mL) and brine (75 mL), and extracted with EtOAc (5 x 75 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), and concentrated to an oil, which was used without further purification.

A solution of DMSO (1.75 mL, 24.6 mmol, 8.0 equiv) in CH_2Cl_2 (100 mL) was cooled (-78 °C) and oxalyl chloride (1.88 mL, 21.5 mmol, 7.00 equiv) was added in a dropwise manner. After 40 min at -78 °C, a solution of the crude alcohol generated above in CH_2Cl_2 (20 mL) was added in a dropwise manner down the wall of the flask over 13 min. After an additional 2.5 h at -78 °C, TEA (8.58 mL, 61.6 mmol, 20.0 equiv) was added and the reaction mixture was allowed to warm to ambient temperature over 3

h, diluted with half-saturated NH_4Cl (75 mL), and extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were washed with saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$), concentrated to an oil, and purified by flash chromatography on silica gel (2.5 to 35% EtOAc in hexanes) to provide ketone **240** (683 mg, 83% yield) as an oil: R_f 0.49 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (d, J = 8.7 Hz, 1H), 4.01 (dd, J = 4.4, 10.7 Hz, 1H), 3.95 (d, J = 9.3 Hz, 1H), 3.50 (d, J = 9.3 Hz, 1H), 3.41 (d, J = 8.1 Hz, 1H), 2.68-2.41 (m, 2H), 2.41-2.24 (m, 1H), 2.10-1.90 (m, 1H), 1.61 (s, 6H), 1.23 (s, 3H), 1.14 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 121.3, 77.5, 75.0, 74.1, 70.7, 58.0, 50.4, 35.6, 28.6, 27.7, 27.5, 21.4, 16.7; IR (Neat film NaCl) 2983, 2881, 2254, 1714, 1387, 1373, 1171, 1052, 907, 729, 651 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{21}NO_3]^+$: m/z 251.1521, found 251.1518.

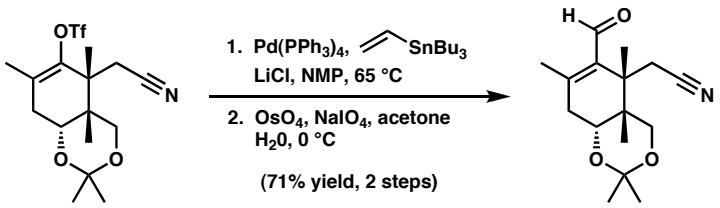


240 *241*

Triflate 241. A solution of LDA in THF was prepared by dropwise addition of 2.50 M *n*-BuLi solution in hexanes (580 μL, 1.45 mmol, 1.05 equiv) to diisopropylamine (252 μL, 1.79 mmol, 1.30 equiv) in THF (15.0 mL) at 0 °C, followed by stirring for 30 min. Upon cooling the solution to -78 °C, a solution of ketone **240** (347 mg, 1.38 mmol, 1.00 equiv) in THF (15.0 mL) was added in a dropwise manner, and the reaction mixture was stirred at -78 °C for 2 h. HMPA (552 μL, 3.18 mmol, 2.30 equiv) was added and the reaction mixture was brought to 0 °C for 1 h. After cooling again to -78 °C, the solution containing the enolate was added to a solution of MeI (258 μL, 4.14 mmol, 3.00 equiv) in

THF (4.00 mL) at -30 °C in a dropwise manner over 25 min. After 6 h at -25 °C, the reaction mixture was quenched with H_2O (30 mL) and CH_2Cl_2 (30 mL), and extracted with CH_2Cl_2 (5 x 30 mL). The combined organics were washed, dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give to an inseparable mixture of diastereomeric methyl ketones (286 mg, 78% yield).

To a cooled (-25 °C) solution of KHMDS (300 mg, 1.50 mmol, 1.40 equiv) in THF (17 mL) was added the above mixture of methyl ketones (286 mg, 1.07 mmol, 1.00 equiv) in THF (15 mL) in a dropwise manner over 10 min. After 2.5 h at -25 °C, $PhNTf_2$ (614 mg, 1.72 mmol, 1.60 equiv) in THF (10.7 mL) was added, and the reaction maintained for an additional 30 min at -25°C. The reaction mixture was quenched into half-saturated $NaHCO_3$ (100 mL) and extracted with EtOAc (4 x 70 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 25% Et_2O in hexanes) to provide triflate **241** (420 mg, 98% yield, 76% yield for 2 steps) as an oil: R_f 0.41 (50% Et_2O in hexanes); ^1H NMR (300 MHz, C_6D_6) δ 4.16 (d, J = 8.7 Hz, 1H), 3.95 (d, J = 9.3 Hz, 1H), 3.52 (dd, J = 6.2, 8.6 Hz, 1H), 3.46 (d, J = 9.0 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 2.17 (dd, J = 6.0, 18.0 Hz, 1H), 1.95 (dd, J = 8.1, 18.0 Hz, 1H), 1.50 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.7, 125.1, 121.5, 119.5 (app. d, $J_{C\text{-}F}$ = 296 Hz), 75.2, 74.7, 74.3, 71.0, 51.2, 50.4, 36.1, 28.2, 27.4, 21.6, 18.1, 16.4; IR (Neat film NaCl) 2988, 2942, 2884, 1403, 1211, 1141, 1053, 990, 874 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{22}NO_5F_3S]^+$: m/z 397.1171, found 397.1179.

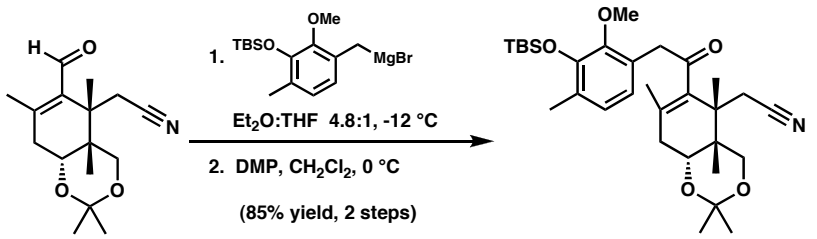


241 *242*

Enal 242. To a solution of triflate **241** (1.41 g, 3.54 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (307 mg, 0.266 mmol, 0.075 equiv), and LiCl (450 mg, 10.6 mmol, 3.00 equiv) in NMP (59 mL) was added tributyl(vinyl)tin (1.55 mL, 5.31 equiv, 1.50 equiv), and the mixture was heated to 65 °C for 0.5 h. The reaction mixture was cooled to ambient temperature, quenched with H_2O (300 mL) and Et_2O (200 mL), and extracted with Et_2O (4 x 125 mL). The combined organics were washed with brine (170 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide the intermediate diene (1.04 g, quantitative yield) as a viscous oil containing a small amount of solvent.

To a cooled (0 °C) solution of the intermediate diene (116.7 mg, 0.42 mmol, 1.00 equiv) in acetone (5.30 mL) and H_2O (5.30 mL) was added OsO_4 (10.8 mg, 42.3 μmol, 0.10 equiv) and $NaIO_4$ (227 mg, 1.06 mmol, 2.50 equiv). After 3.5 h at 0 °C, the reaction mixture was diluted with H_2O (35 mL) and EtOAc (35 mL), and extracted with EtOAc (5 x 15 mL). The combined organics from four such reactions were washed with brine (200 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (20 to 35% EtOAc in hexanes) to provide enal **242** (332 mg, 71% yield, 2 steps) as an oil: R_f 0.28 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 4.21 (d, J = 9.0 Hz, 1H), 3.87 (d, J = 9.3 Hz, 1H), 3.85 (d, J = 8.4 Hz, 1H), 3.70 (d, J = 9.0 Hz, 1H), 3.51 (d, J = 8.7 Hz, 1H), 2.78 (dd, J = 6.0, 19.8 Hz, 1H), 2.49 (dd, J = 9.0, 19.8 Hz, 1H), 2.16 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.20 (s, 3H),

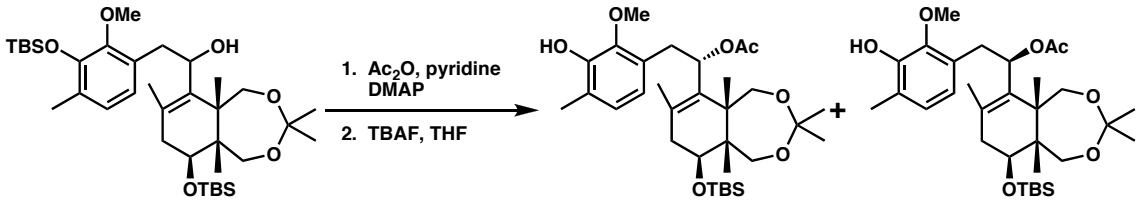
1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 153.2, 136.8, 121.5, 76.0, 74.2, 74.1, 70.4, 48.7, 48.0, 38.7, 28.7, 27.3, 20.7, 19.0, 18.0; IR (Neat film NaCl) 2982, 2938, 2880, 1671, 1628, 1386, 1177, 1050 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{23}NO_3]^+$: m/z 277.1678, found 277.1677.



242 ***243***

Enone 243. A flame-dried two-neck round-bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (1.66 g, 68.4 mmol, 57.0 equiv) and Et_2O (27 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (120 μL, 1.39 mmol, 1.16 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (1.24 g, 3.60 mmol, 3.00 equiv) in Et_2O (8.0 mL) was added in a dropwise manner over 30 min, and heating was continued for an additional 20 min. The Grignard reagent was then cooled (0 °C) and added to a cooled (0 °C) solution of enal **242** (332 mg, 1.20 mmol, 1.00 equiv) in THF (12 mL). After 1 h at 0 °C, the reaction was quenched with 0.5 M citric acid (40 mL) and EtOAc (40 mL), and extracted with EtOAc (5 x 25 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give a separable 3:1 mixture of diastereomeric allylic alcohols (533.3 mg, 85% yield).

To a cooled (0 °C) solution of the above allylic alcohol (76.0 mg, 0.140 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL) was added Dess-Martin periodinane (89.1 mg, 0.211 mmol, 1.50 equiv) and the resulting mixture was stirred for 2 h. The reaction mixture was diluted with Et_2O (35 mL), filtered, concentrated to an oil, and purified by flash chromatography on silica gel (5 to 20% EtOAc in hexanes) to give enone **243** (75.7 mg, 100% yield, 85% yield 2 steps) as an oil: R_f 0.47 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 4.16 (d, *J* = 8.7 Hz, 1H), 4.08 (d, *J* = 9.0 Hz, 1H), 3.87 (dd, *J* = 6.0, 8.4 Hz, 1H), 3.86 (s, 2H), 3.64 (s, 3H), 3.53 (d, *J* = 8.7 Hz, 1H), 3.52 (d, *J* = 9.0 Hz, 1H), 2.54 (dd, *J* = 6.0, 17.7 Hz, 1H), 2.30 (dd, *J* = 8.3, 18.2 Hz, 1H), 2.21 (s, 3H), 1.79 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.02 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 150.0, 147.0, 138.7, 130.0, 128.2, 125.8, 125.2, 123.3, 121.6, 75.5 (2C), 75.2, 70.5, 59.9, 49.7, 47.2, 47.1, 35.5, 28.7, 27.6, 26.0, 21.1, 20.8, 18.5, 18.2, 17.1, -4.2; IR (Neat film NaCl) 2932, 2859, 1699, 1464, 1422, 1286, 1073, 1047, 856, 841 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{31}H_{47}NSiO_5+H]^+$: *m/z* 542.3302, found 542.3296.



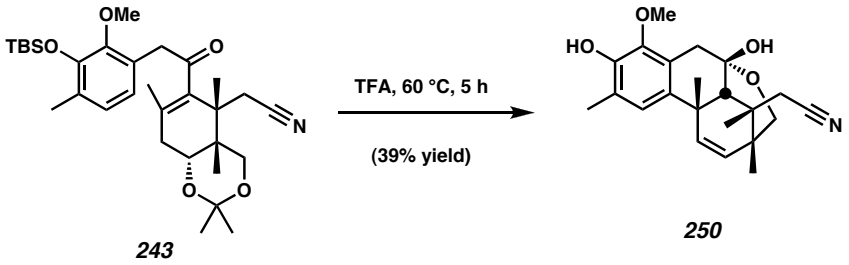
244 **as a ~4:1 mixture at C(20)** ***247*** **(82% yield 2 steps)** ***248*** **(17% yield 2 steps)**

Allylic acetates 247 and 248. To a solution of allylic alcohol **244** (120 mg, 0.185 mmol, 1.00 equiv) in Ac_2O (4.00 mL) and pyridine (1.00 mL) was added DMAP (11.3 mg, 92.4 μmol, 0.50 equiv). After 3 h, the reaction mixture was concentrated and

purified by flash chromatography on silica gel (2.5 to 10% Et_2O in hexanes) to give an inseparable mixture of intermediate acetates (122.1 mg).

To a solution of the above acetates in THF (4.00 mL) was added a 1.0 M solution of TBAF (1.06 mL, 1.06 mmol, 6.00 equiv). After a further 30 min, the reaction mixture was diluted with H_2O (30 mL) and CH_2Cl_2 (30 mL), and extracted with CH_2Cl_2 (6 x 30 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (5 to 20% EtOAc in hexanes) to give isomerically pure allylic acetate **248** (17.5 mg, 17% yield, two steps) as a white foam: R_f 0.34 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 5.64 (dd, *J* = 3.6, 10.8 Hz, 1H), 5.53 (s, 1H), 4.17 (dd, *J* = 7.1, 9.5 Hz, 1H), 3.79 (s, 3H), 3.55 (s, 2H), 3.52 (d, *J* = 12.6 Hz, 1H), 3.37 (d, *J* = 12.3 Hz, 1H), 3.13 (dd, *J* = 10.8, 14.4 Hz, 1H), 2.93 (dd, *J* = 3.6, 14.4 Hz, 1H), 2.21 (s, 3H), 2.12-2.00 (m, 2H), 1.96 (s, 3H), 1.82 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 0.89 (s, 9H), 0.55 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.5, 147.0, 145.4, 133.8, 131.5, 128.0, 126.0, 123.4, 121.4, 101.0, 72.1, 65.5, 65.3, 61.9, 61.1, 46.7, 43.1, 40.0, 35.1, 25.9, 24.8, 24.6, 21.5, 20.9, 18.1, 16.9, 15.5, 11.1, -4.3, -5.1; IR (Neat film NaCl) 3448, 2950, 2856, 1739, 1463, 1373, 1248, 1220, 1067, 1039, 836 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{32}H_{52}SiO_7+H]^+$: *m/z* 577.3561, found 577.3547, and allylic acetate **247** (83 mg, 82% yield, two steps) as a white foam: R_f 0.33 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 5.77 (bs, 1H), 5.59 (s, 3H), 4.09 (m, 1H), 3.81 (s, 3H), 3.50 (d, *J* = 12.3 Hz, 1H), 3.44-3.30 (m, 2H), 3.14 (dd, *J* = 9.6, 13.8 Hz, 1H), 2.99 (d, *J* = 12.0 Hz, 1H), 2.84 (dd, *J* = 5.1, 13.8 Hz, 1H), 2.20 (s, 3H), 2.12-2.00 (m, 2H), 1.98 (s, 3H), 1.89 (s, 3H), 1.28 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 0.89

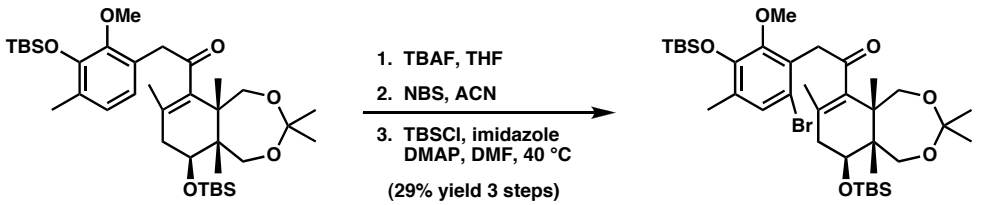
(s, 9H), 0.51 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.6, 147.1, 145.5, 134.8, 131.2, 128.0, 126.0, 123.6, 121.7, 100.8, 72.4, 65.8, 65.6, 62.0, 61.1, 47.0, 43.6, 40.0, 36.6, 35.4, 25.9, 24.6, 24.4, 21.3, 21.2, 18.1, 15.4, 10.9, -4.4, -5.1; IR (Neat film NaCl) 3418, 2985, 2952, 2857, 1741, 1464, 1371, 1248, 1221, 1067, 1040, 836, 777 cm^{-1}; HRMS (FAB) $[M\text{-}H_2\text{+}H]^+$ calc'd for $[C_{32}H_{51}SiO_7]^+$: *m/z* 575.3404, found 575.3405.



243 ***250***

Hemiacetal 250. A solution of enone **243** (29.9 mg, 55.2 μmol, 1.00 equiv) in trifluoroacetic acid (4.00 mL) was heated to 60 °C for 5 h. The reaction mixture was then cooled to ambient temperature, concentrated to an oil, and purified by flash chromatography on silica gel (5 to 50% EtOAc in hexanes) to give hemiacetal **250** (7.9 mg, 39% yield) as an off-white solid: R_f 0.30 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 5.97 (dd, *J* = 1.0, 9.5 Hz, 1H), 5.55 (s, 1H), 5.33 (d, *J* = 9.5 Hz, 1H), 4.18 (d, *J* = 8.5, 1H), 3.74 (s, 3H), 3.60 (d, *J* = 8.5 Hz, 1H), 3.55 (d, *J* = 11.5 Hz, 1H), 3.25 (d, *J* = 16.0, 1H), 3.09 (d, *J* = 11.5, 1H), 2.76 (d, *J* = 15.5, 1H), 2.23 (s, 3H), 1.76 (s, 1H), 1.42 (s, 3H), 1.15 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 144.1, 135.4, 135.1, 130.0, 124.7 (2C), 124.2, 123.1, 105.1, 75.1, 70.1, 60.5, 53.9, 41.7, 39.2, 35.3, 33.8, 31.6, 18.8, 17.7, 15.7; IR (Neat film NaCl) 3402, 2969, 2931, 2876, 2242, 1485, 1419, 1358, 1209, 1102, 1063, 981, 912, 732 cm^{-1}; MS (FAB) [M-

HCN]$^+$ calc'd for $[C_{21}H_{26}O_4]^+$: *m/z* 342.1831, found 342.2 (Hi-Res data not possible due to substrate fragmentation).



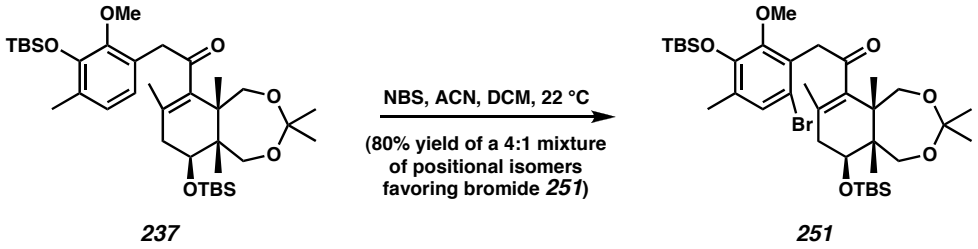
237 ***251***

Aryl bromide 251. To a solution of enone **237** (114 mg, 0.176 mmol, 1.00 equiv) in THF (8.0 mL) was added a 1.0 M solution of TBAF (176 μL, 0.176 mmol, 1.00 equiv) in THF. After 5 min, the reaction mixture was diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL), and extracted with CH_2Cl_2 (4 x 25 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (5 to 25% EtOAc in hexanes) to give the intermediate phenol (91 mg, 97% yield).

To a solution of intermediate phenol (36.0 mg, 67.6 μmol, 1.00 equiv) in ACN (2.0 mL) was added NBS (18.0 mg, 101 μmol, 1.50 equiv). After 2.5 h, the reaction was diluted with H_2O (8 mL) and EtOAc (8 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (2.5 to 15% EtOAc in hexanes) to give the intermediate bromide (14.4 mg, 35% yield).

To a solution of intermediate bromide (14.4 mg, 23.5 μmol, 1.00 equiv), imidazole (36.0 mg, 0.530 mmol, 22.5 equiv), and TBSCl (26.6 mg, 0.177 mmol, 7.50 equiv) in DMF (2.5 mL) was added DMAP (21.5 mg, 0.176 mmol, 7.50 equiv) and the reaction was warmed to 40 °C. After 36 h, the reaction was diluted with H_2O (8 mL) and EtOAc (8 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried

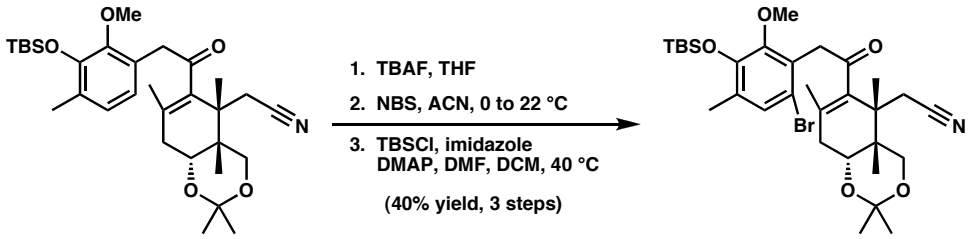
(Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (1 to 5% Et_2O in hexanes) to give isomerically pure bromide **251** (14.5 mg, 85% yield, 29% yield for three steps) as a white foam: R_f 0.76, 0.79 (10% Et_2O in hexanes, 25% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 1H), 4.29 (dd, *J* = 7.1, 9.5 Hz, 1H), 4.11 (d, *J* = 18.6 Hz, 1H), 4.00 (d, *J* = 18.6 Hz, 1H), 3.77 (d, *J* = 12.3 Hz, 1H), 3.62 (s, 3H), 3.55 (d, *J* = 12.9 Hz, 1H), 3.54 (d, *J* = 12.6 Hz, 1H), 3.39 (d, *J* = 12.3 Hz, 1H), 2.19 (s, 3H), 2.14-2.04 (m, 2H), 1.82 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.01 (s, 9H), 0.90 (s, 9H), 0.67 (s, 3H), 0.15 (s, 6H), 0.14 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 151.0, 146.4, 137.8, 131.4, 130.9, 129.4, 126.0, 116.4, 101.1, 66.0, 65.5, 61.5, 60.0, 48.0, 45.5, 43.0, 38.1, 26.0, 25.9, 24.7 (2C), 20.7, 18.5, 18.2, 18.1, 16.9, 11.1, -4.2, -4.3, -4.4, -5.1; IR (Neat film NaCl) 2954, 2930, 2858, 1700, 1471, 1404, 1233, 1220, 1099, 1075, 855, 837, 779 cm^{-1}; HRMS (FAB) $[M\text{-}H_2+H]^+$ calc'd for $[C_{36}H_{60}Si_2O_6Br]^+$: *m/z* 723.3112, found 723.3128.



237 *251*

Aryl bromide 251 directly from enone **237**. To a solution of enone **237** (200 mg, 0.309 mmol, 1.00 equiv) in ACN (8.0 mL) and CH_2Cl_2 (1.2 mL) was added NBS (66.0 mg, 0.371 mmol, 1.20 equiv). After 2.5 h, the reaction was diluted with H_2O (30 mL) and EtOAc (15 mL), and extracted with EtOAc (5 x 15 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (1 to 5% Et_2O in hexanes) to give aryl bromide **241** (179

mg, 80% yield) as a 4:1 mixture of bromide isomers favoring the desired aryl bromide **251**.



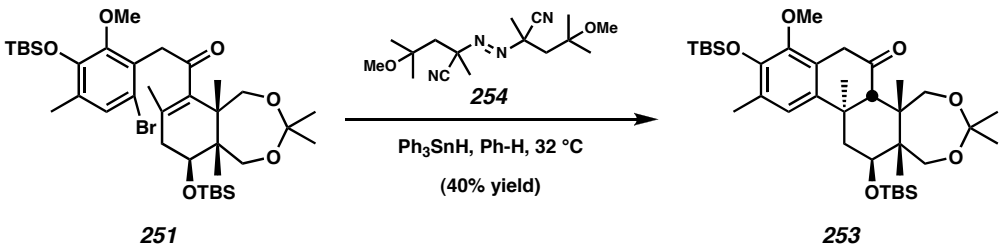
243 ***252***

Aryl bromide 252. To a solution of enone **243** (60.0 mg, 0.111 mmol, 1.00 equiv) in THF (3.7 mL) was added a 1.0 M solution of TBAF (166 μL, 0.166 mmol, 1.50 equiv) in THF. After 15 min, the reaction mixture was diluted with EtOAc (15 mL), H_2O (5 mL), and saturated aqueous NH_4Cl (5 mL), and extracted with EtOAc (5 x 20 mL). The combined organics were dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (20 to 30% EtOAc in hexanes) to give the intermediate phenol (40.0 mg, 85% yield).

To a cooled (0 °C) solution of intermediate phenol (33.7 mg, 78.8 μmol, 1.00 equiv) in ACN (1.6 mL) was added NBS (15.4 mg, 86.7 μmol, 1.10 equiv), and the reaction mixture was allowed to come to ambient temperature. After 5 h, the reaction was diluted with H_2O (10 mL) and EtOAc (20 mL), and extracted with EtOAc (5 x 10 mL). The combined organics were dried ($MgSO_4$), concentrated, and used without further purification in the next step.

To a solution of the above crude material (theory: 78.8 μmol, 1.00 equiv), imidazole (16.1 mg, 0.236 mmol, 3.00 equiv), TBSCl (17.8 mg, 0.118 mmol, 1.50 equiv) in DMF (200 μL) and CH_2Cl_2 (200 μL) was added DMAP (9.6 mg, 78.8 μmol, 1.00

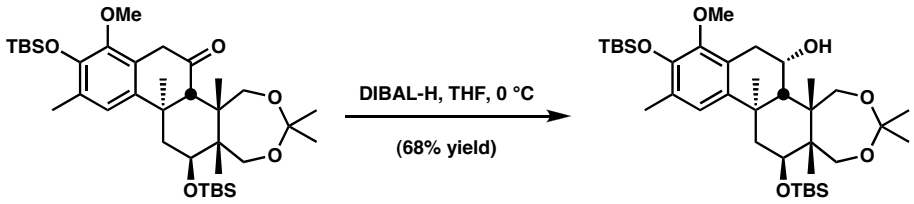
equiv) and the reaction was stirred at ambient temperature for 24 h and then at 30 °C for 18 h. An additional portion of DMAP (10.0 mg, 81.9 μmol, 1.04 equiv) and TBSCl (20.0 mg, 132.7 μmol, 1.69 equiv) were added and the reaction mixture was heated at 40 °C for 4 h. The reaction was diluted with EtOAc (10 mL), washed with saturated aqueous NH_4Cl (3 x 5 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were concentrated and purified by flash chromatography on silica gel (5 to 15% Et_2O in hexanes) to give isomerically pure bromide **252** (23.0 mg, 47% yield, 40% yield for three steps) as an amorphous white solid: R_f 043 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 4.29 (d, *J* = 8.5 Hz, 1H), 4.10 (d, *J* = 7.0 Hz, 1H), 4.07 (d, *J* = 7.0 Hz, 1H), 4.06 (d, *J* = 4.0 Hz, 1H), 3.88 (dd, *J* = 6.3, 8.8 Hz, 1H), 3.62 (s, 3H), 3.54 (app. t, *J* = 9.3 Hz, 1H), 2.55 (dd, *J* = 6.3, 17.8 Hz, 1H), 2.32 (dd, *J* = 8.5, 18.0 Hz, 1H), 2.18 (s, 3H), 1.87 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.01 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 150.9, 146.4, 138.3, 131.4, 129.3, 128.7, 126.0, 121.5, 116.3, 75.5, 75.3, 75.2, 70.5, 60.0, 49.7, 47.7, 47.2, 35.7, 28.7, 27.6, 26.0, 21.0, 20.8, 18.1, 16.8, -4.3; IR (Neat film NaCl) 2932, 2860, 2252, 1699, 1470, 1404, 1234, 1171, 1083, 1047, 853, 842, 734 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{31}H_{46}NSiBrO_5+H]^+$: *m/z* 620.2407, found 620.2394.



251 *253*

Cyclized ketone 253. To a solution of aryl bromide **251** (25.0 mg, 34.4 μmol, 1.00 equiv of a 4:1 mixture of isomers) and initiator V-70 (**254**) (15.9 mg, 51.7 μmol,

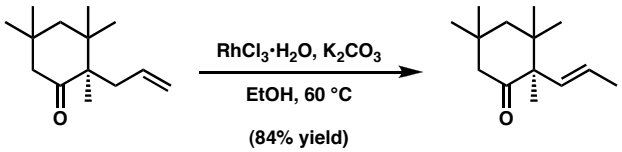
1.50 equiv) in benzene (2.0 mL) at 32 °C was added a solution of Ph_3SnH (24.2 mg, 68.8 μmol, 2.00 equiv) in benzene (0.5 mL) by syringe pump over 5 h. At the end of the addition, the reaction was cooled to ambient temperature, concentrated, and purified by flash chromatography on silica gel (2 to 7.5% Et_2O in hexanes) to give ketone **253** (8.9 mg, 40% yield, 50% yield based on the correct isomer of the starting material) as an oil: R_f 0.52 (25% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.43 (dd, J = 4.5, 12.5 Hz, 1H), 3.97 (d, J = 12.5 Hz, 1H), 3.66 (d, J = 22.0 Hz, 1H), 3.64 (s, 3H), 3.55 (d, J = 12.5 Hz, 1H), 3.39 (d, J = 22.0 Hz, 1H), 3.33 (d, J = 12.5 Hz, 1H), 2.84 (s, 1H), 2.22 (s, 3H), 2.18 (dd, J = 4.5, 12.5 Hz, 1H), 1.92 (app. t, J = 12.5 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.03 (s, 9H), 0.94 (s, 9H), 0.57 (s, 3H), 0.19 (s, 6H), 0.18 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 147.8, 145.1, 141.5, 129.0, 123.8, 120.8, 100.9, 65.8, 62.2, 62.1, 59.3, 58.8, 44.7, 43.5, 42.5, 41.2, 41.0, 27.4, 26.0 (2C), 24.8, 24.6, 20.0, 18.6, 18.2, 17.6, 10.1, -4.0, -4.2 (2C), -4.9; IR (Neat film NaCl) 2954, 2929, 2857, 1715, 1472, 1462, 1254, 1221, 1088, 1071, 838 cm^{-1}; HRMS (FAB) $[M-H_2+H]^+$ calc'd for $[C_{36}H_{61}Si_2O_6]^+$: m/z 645.4007, found 645.4007.



253 *255*

Alcohol 255. To a cooled (0 °C) solution of ketone **253** (19.9 mg, 30.8 μmol, 1.00 equiv) in THF (5.0 mL) was added a 1.0 M solution of DIBAL-H (250 μL, 0.250 mmol, 8.12 equiv) in toluene. After 4 h, an additional portion of DIBAL-H (100 μL,

0.100 mmol, 3.25 equiv) in toluene was added. After an additional 1 h at 0 °C, the reaction mixture was quenched with Na_2SO_4•$10H_2O$ (300 mg) in a portionwise manner, filtered, washed (CH_2Cl_2), concentrated, and purified by flash chromatography on silica gel (10 to 40% Et_2O in hexanes) to give alcohol **255** (13.6 mg, 68% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from CH_2Cl_2 at ambient temperature: mp 185-190 °C decomp. (CH_2Cl_2); R_f 0.21 (25% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.68 (s, 1H), 4.47 (dd, *J* = 3.8, 12.3 Hz, 1H), 4.28 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 13.0 Hz, 1H), 3.65 (s, 3H), 3.53 (d, *J* = 12.0 Hz, 1H), 3.37 (d, *J* = 12.5 Hz, 1H), 2.95 (s, 1H), 2.94 (s, 1H), 2.20 (s, 3H), 2.07 (dd, *J* = 4.0, 12.5 Hz, 1H), 1.66 (s, 1H), 1.62 (d, *J* = 12.0 Hz, 1H), 1.58 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.20 (bs, 1H), 1.11 (s, 3H), 1.03 (s, 9H), 0.92 (s, 9H), 0.57 (s, 3H), 0.19 (s, 3H), 0.17 (s, 6H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 144.4, 141.8, 128.3, 122.8, 122.1, 100.9, 66.4, 65.4, 65.3, 63.0, 59.2, 48.6, 45.7, 45.4, 44.6, 37.5, 36.7, 29.6, 26.1, 26.0, 25.0, 24.6, 22.2, 18.6, 18.1, 17.5, 10.4, -4.0 (2C), -4.1, -4.9; IR (Neat film NaCl) 3454, 2954, 2930, 2858, 1473, 1252, 1220, 1089, 1061, 836 cm^{-1}; HRMS (FAB) [M-H_2+H]$^+$ calc'd for $[C_{36}H_{63}Si_2O_6]^+$: *m/z* 647.4163, found 647.4162.

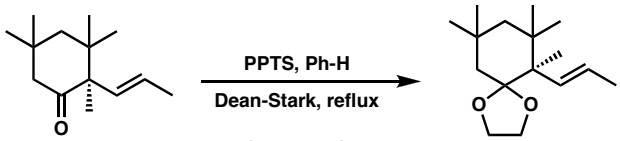


256
(85% ee)

257

Vinyl ketone 257. To a solution of allyl ketone **256** (905 mg, 4.35 mmol, 1.00 equiv) in EtOH (45 mL) in a sealable Schlenk flask (100 mL) was added K_2CO_3 (601 mg, 4.35 mmol, 1.00 equiv) and $RhCl_3$•H_2O (49.4 mg, 0.218 mmol, 0.05 equiv). The reaction

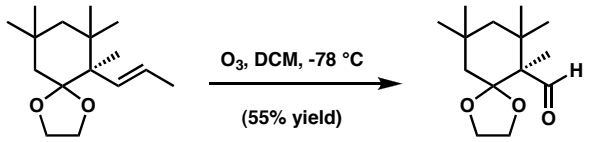
mixture was sparged with Ar for 10 min, sealed and heated to 60 °C for 12 h. After cooling to ambient temperature, the reaction mixture was filtered, washed with EtOH, concentrated, and purified by flash chromatography on silica gel (7.5 to 10% Et_2O in pentane) to give vinyl ketone **257** (759 mg, 84% yield of a 10:1 mixture containing allyl ketone **256** as the minor component) as an amorphous solid: R_f 0.67, 0.46 (25% Et_2O in hexanes, 5% Et_2O in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dq, J = 1.8, 15.5 Hz, 1H), 5.42 (dq, J = 6.3, 15.3 Hz, 1H), 2.53 (d, J = 13.2 Hz, 1H), 2.11 (dd, J = 1.8, 13.5 Hz, 1H), 1.85 (d, J = 14.4 Hz, 1H), 1.71 (dd, J = 1.7, 6.5 Hz, 3H), 1.42 (dd, J = 1.8, 14.4 Hz, 1H), 1.09 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.90 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 132.5, 126.2, 56.4, 50.7, 49.6, 40.6, 35.4, 33.7, 30.2, 26.9, 26.8, 18.6, 15.6; IR (Neat film NaCl) 2957, 1707, 1458, 1391, 1370, 1283, 977 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{24}O]^+$: m/z 208.1827, found 208.1820; $[\alpha]_D^{25}$ –59.07 (c 1.04, $CHCl_3$, 85% ee).



257 ***258***

Ketal 258. A solution of the vinyl ketone **257** (700 mg, 3.36 mmol, 1.00 equiv), ethylene glycol (1.30 mL, 23.5 mmol, 7.00 equiv), and pyridinium *p*-toluenesulfonate (211 mg, 0.84 mmol, 0.25 equiv) in benzene (70 mL) was fitted with a Dean-Stark apparatus and refluxed at 100 °C for 30 h. The reaction mixture was cooled to ambient temperature, diluted with saturated aqueous $NaHCO_3$ (40 mL), and extracted with Ph-H (3 x 30 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4),

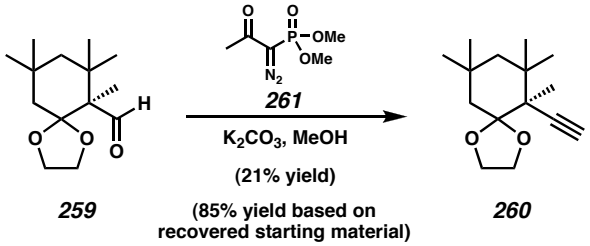
concentrated, and purified by flash chromatography on silica gel (1 to 2% Et_2O in hexane) to give acetal **258** (585 mg, 70% yield) as an oil: R_f 0.61, 0.67 (5% Et_2O in hexanes developed twice, 25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (dq, *J* = 1.5, 15.8 Hz, 1H), 5.44 (dq, *J* = 6.3, 15.8 Hz, 1H), 3.92-3.78 (m, 4H), 1.72 (dd, *J* = 1.7, 6.5 Hz, 3H), 1.52 (s, 2H), 1.37 (d, *J* = 14.1 Hz, 1H), 1.30 (d, *J* = 14.1 Hz, 1H), 1.03 (s, 6H), 1.02 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 124.3, 113.8, 64.6, 64.4, 49.8, 48.6, 42.2, 38.0, 32.3, 32.0, 31.5, 28.3, 27.7, 18.7, 14.2; IR (Neat film NaCl) 2952, 1455, 1388, 1225, 1146, 1124, 1078, 981 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{28}O]^+$: m/z 252.2089, found 252.2090; $[\alpha]_D^{24}$ +1.51 (c 1.11, $CHCl_3$, 85% ee).



258 ***259***

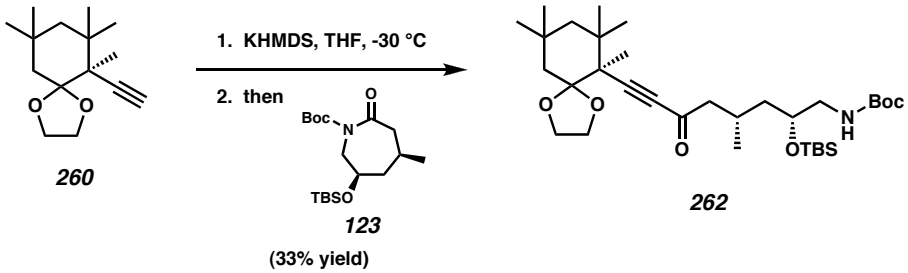
Aldehyde 259. Through a cooled (-78 °C) solution of acetal **258** (252 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (25 mL) was bubbled a stream of ozone until the reaction mixture turned blue. The reaction mixture was quenched with dimethyl sulfide (0.20 mL), allowed to warm to ambient temperature, concentrated to an oil, and purified by flash chromatography on silica gel (2.5 to 10% Et_2O in hexane) to give aldehyde **259** (132 mg, 55% yield) as an oil: R_f 0.41, 0.29 (25% Et_2O in hexanes, 5% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 3.98-3.85 (m, 4H), 1.69 (d, *J* = 14.4 Hz, 3H), 1.57 (dd, *J* = 1.2, 14.4 Hz, 1H), 1.50 (d, *J* = 14.4 Hz, 1H), 1.37 (dd, *J* = 1.2, 14.4 Hz, 1H), 1.08 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 206.2, 112.1, 64.5, 64.3, 58.0, 50.3, 43.0, 38.1, 32.9, 31.6, 30.6, 27.8, 27.7, 11.1; IR (Neat film NaCl) 2954, 2899, 1722, 1241, 1110, 1075, 964 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{24}O_3]^+$: m/z 240.1726, found 240.1720; $[\alpha]_D^{24}$ –39.53 (c 0.385, $CHCl_3$, 85% ee).



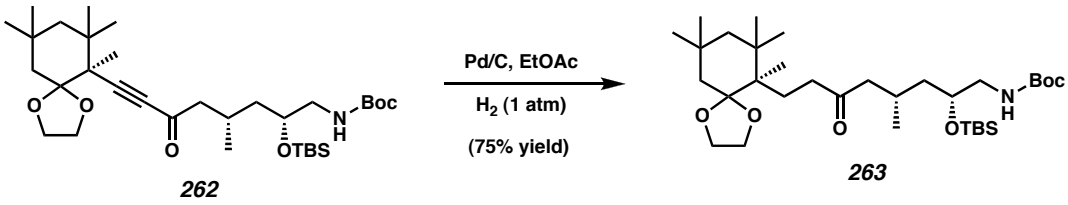
Alkyne 260. To a solution of aldehyde **259** (75.0 mg, 0.312 mmol, 1.00 equiv), and K_2CO_3 (108 mg, 0.780 mmol, 2.50 equiv) in MeOH (3.10 mL) was added diazoketone **261** (89.9 mg, 0.468 mmol, 1.5 equiv). After 1 h, an additional portion of K_2CO_3 (214 mg, 1.56 mmol, 5.00 equiv) and of diazoketone **261** (150 mg, 0.780 mmol, 2.5 equiv) were added. After a further 4 h, a final portion of K_2CO_3 (200 mg, 1.45 mmol, 4.65 equiv) and of diazoketone **261** (200 mg, 1.05 mmol, 3.37 equiv) were added. After stirring for 20 h, the reaction mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (8 x 5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (1 to 7% Et_2O in hexanes) to give recovered aldehyde **259** (55.6 mg, 74% yeld) and alkyne **260** (15.5 mg, 21% yield, 85% yield based on recovered aldehyde **259**) as an oil: R_f 0.40 (5% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, C_6D_6) δ 3.62-3.40 (m, 4H), 2.01 (d, J = 14.1 Hz, 1H), 1.93 (s, 1H), 1.72 (d, J = 14.1 Hz, 1H), 1.47 (dd, J = 1.8, 13.8 Hz, 1H), 1.36 (s, 3H), 1.34 (s, 3H), 1.22 (s, 3H), 1.17 (dd, J = 1.7, 14.3 Hz, 1H), 1.10 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.5, 89.1, 76.6, 70.7,

65.5, 64.2, 49.8, 47.3, 42.5, 38.0, 34.6, 31.4, 29.8, 28.8, 24.9, 16.2; IR (Neat film NaCl) 3309, 2954, 2911, 2111, 1454, 1390, 1367, 1235, 1148, 1088, 1073, 984 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{15}H_{24}O_2]^+$: m/z 236.1776, found 236.1786; $[\alpha]_D^{26}$ –20.35 (c 1.25, CH_2Cl_2, 85% ee).



Ynone 262. To a cooled (-30 °C) solution of KHMDS (24.1 mg, 0.121 mmol, 2.20 equiv) in THF (1.00 mL) was added alkyne **260** (13.0 mg, 0.055 mmol, 1.00 equiv) in THF (1.00 mL). The solution was maintained for 30 min each at -30 °C, 0 °C, and 22 °C. The alkyne anion was cooled to -78 °C, and caprolactam **123** (23.6 mg, 0.066 mmol, 1.2 equiv) in THF (1.00 mL) was added. After 1 h, additional KHMDS (12.0 mg, 0.061 mmol, 1.10 equiv) in THF (0.50 mL) was added. After a further 5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.50 mL), diluted with H_2O (2 mL), brine (4 mL), and Et_2O (4 mL), and extracted with Et_2O (6 x 4 mL) and CH_2Cl_2 (2 x 2 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 15% EtOAc in hexanes) to give ynone **262** (10.9 mg, 33% yield) as a oil: R_f 0.24, 0.50 (10% EtOAc in hexanes developed twice, 20% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.07-4.02 (m, 1H), 4.00-3.94 (m, 3H), 3.84 (bs, 1H), 3.38-3.30 (m, 1H), 2.97 (dt, J = 6.0, 14.5 Hz, 1H), 2.58 (dd, J = 5.5, 15.5 Hz, 1H), 2.38 (dd, J = 8.0, 15.5 Hz, 1H), 2.26-2.16

(m, 1H), 1.76 (d, J = 14.0 Hz, 1H), 1.62-1.44 (comp. m, 4H), 1.46 (s, 9H), 1.40-1.30 (m, 1H), 1.26 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 87.2, 155.9, 112.1, 98.7, 83.7, 79.1, 69.4, 65.5, 64.6, 53.2, 49.8, 48.1, 45.9, 43.0, 42.2, 38.7, 33.8, 31.4, 29.7, 29.6, 28.4, 28.0, 26.3, 25.9, 25.6, 20.2, 18.0, -4.5, -4.6; IR (Neat film NaCl) 3383, 2955, 2930, 2208, 1716, 1673, 1504, 1391, 1366, 1252, 1171, 1090, 836 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{33}H_{59}NO_6Si+H]^+$: m/z 594.4190, found 594.4208; $[\alpha]_D^{26}$ –36.12 (c 0.545, EtOAc).



Ketone 263. To a solution of ynone **262** (10.9 mg, 18.3 μmol, 1.00 equiv) in EtOAc (6 mL) was added 10% Pd/C (4.0 mg), and the reaction mixture was sparged with H_2 (5 min). After 18 h of vigorous stirring under an atmosphere of H_2 (balloon), the reaction mixture was concentrated and purified by flash chromatography on silica gel (5 to 10% EtOAc in hexanes). NMR analysis of the chromatographed product indicated the presence of some partially hydrogenated material. A solution of this material in EtOAc (5 mL) was treated again with 10% Pd/C (5.0 mg) under an atmosphere of H_2 (balloon) for 4 h. The reaction mixture was concentrated to an oil and purified by flash chromatography on silica gel (5 to 10% EtOAc in hexanes) to give ketone **263** (8.2 mg, 75% yield) as a oil: R_f 0.53 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 1H), 3.96 (app. t, J = 6.8 Hz, 1H), 3.83 (app. q, J = 7.0 Hz, 1H), 3.79 (bs, 1H),

3.74 (app. q, *J* = 7.0 Hz, 1H), 3.34-3.26 (m, 1H), 2.98 (dt, *J* = 6.5, 13.5 Hz, 1H), 2.60-2.50 (m, 1H), 2.48-2.36 (m 2H), 2.20 (dd, *J* = 7.8, 16.3 Hz, 1H), 2.12-2.02 (m, 1H), 2.00-1.92 (m, 1H), 1.56-1.24 (comp. m, 9H), 1.44 (s, 9H), 1.15 (d, *J* = 14.0 Hz, 1H), 1.11 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H), 0.92-0.89 (m, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.9, 156.2, 115.2, 79.3, 69.8, 64.9, 62.6, 50.6, 50.5, 46.2, 44.2, 42.7, 41.4, 40.9, 39.1, 34.7, 31.5, 30.0, 29.4, 28.7, 28.3, 26.8, 26.1, 26.0, 24.4, 20.6, 18.3, 16.8, -4.3; IR (Neat film NaCl) 3391, 2953, 2930, 1714, 1503, 1366, 1253, 1173, 1076, 836, 776 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{33}H_{63}NO_6Si+H]^+$: *m/z* 598.4503, found 598.4489; $[\alpha]_D^{26}$ 9.33 (c 0.105, CH_2Cl_2).

3.9 Notes and Citations

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(1) 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.

(2) For limitations of DMMA Diels-Alder reactions, see: (a) Rae, I. D.; Serelis, A. K. *Aust. J. Chem.* **1990**, *43*, 1941-1948. (b) Ziegler, K.; Flaig, W.; Velling, G. *Justus Liebig Ann. Chem.* **1950**, *567*, 204-214.

(3) For synthesis of dihydrothiophene **195**, see: (a) Baker, B. R.; Querry, M. V.; Kadish, A. F. *J. Am. Chem. Soc.* **1980**, *102*, 6893-6894. (b) Dauben, W. G.; Gerdes, J. M.; Smith, D. B. *J. Org. Chem.* **1985**, *50*, 2576-2578.

(4) (a) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6894-6896.

(5) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080-2081.

(6) For the synthesis of known diene **200,** see: Duke, R. K.; Rickards, R. W. *J. Org. Chem.* **1984**, *49*, 1898-1904.

(7) Diene **198** is readily available in one step from crotonaldehyde and TBSOTf, see: Trost, B. M.; Chupak, L. S.; Lübbers, T. *J. Org. Chem.* **1997**, *62*, 736-737.

(8) DMMA is commercially available, but on scale is readily and more economically made from maleic anhydride, see: Baumann, M. E.; Bosshard, H.; Breitenstein, W.; Rihs, G.; Winkler, T. *Helv. Chim. Acta* **1984**, *67*, 1897-1905.

(9) Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2128-2130.

(10) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984-6991.

(11) (a) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542-9543. (b) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302-11303.

(12) (a) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965-2983. (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621-631.

(13) We acknowledge Thomas C. Scotton for the synthesis and testing of **207**. Menthol derivative **208** was a generous gift from Prof. Deng.

(14) Analysis of samples taken early during the reaction suggest that iodolactone **209** is a thermodynamic sink as other isomers appear to be initially formed.

(15) The most isomerization to ketone **212** (~30%) was observed with $RhI_3 \bullet H_2O$ in EtOH at 80 °C.

(16) See Chapter Two for details.

(17) Standard Mitsunobu conditions do not give reactivity, likely due to steric difficulties caused by nearby quaternary centers. For Mitsunobu protocol, see: Majetich, G.; Defauw, J.; Ringold, C. *J. Org. Chem.* **1988**, *53*, 50-68.

Reduction of enone **218** with $NaBH_4$ gave selective reduction of the methyl ester. Reduction under Luche conditions afforded only the undesired diastereomer **217**.

(18) See Chapter Two for more examples and discussion.

(19) The purity of triol **228** drastically modulates the efficacy of $CuSO_4$ in the acetonide forming reaction. Chromatography or recrystallization is required to remove what

are likely hydrated aluminum salts. Without purification of triol **228**, the reaction often fails to progress to more than 20% conversion.

(20) For other examples of favorable 1,3-dioxepane formation in synthesis, see: (a) Ritter, T.; Zarotti, P.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4371-4374. (b) Brewster, A. G.; Leach, A. *Tetrahedron Lett.* **1986**, *27*, 2539-2542.

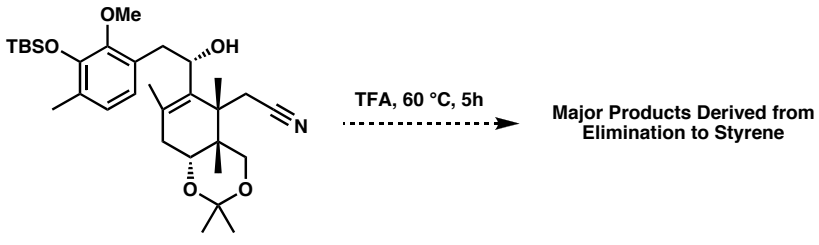
(21) The ratio of products seemed to depend most on the duration of the reaction, suggesting that some equilibration was possible between the products. On a number of occasions 1,3-dioxepane **229** was the major product (e.g., 44% yield of 1,3-dioxepane **229**, and 41% yield of 1,3-dioxolane **230**).

(22) Reaction with the methoxy methylene Wittig reagent gave ~25-40% yields.

(23) For recent examples, see: (a) Sano, S.; Kenji, M. *Eur. J. Org. Chem.* **1999**, *7*, 1679-1686. (b) Hamilton, J. G. C.; Hooper, A. M.; Mori, K.; Pickett, J. A.; Sano, S. *Chem. Commun.* **1999**, 355-356. (c) Hoffman, H. M. R.; Eggert, U.; Gibbels, U.; Giesel, K.; Koch, O.; Lies, R.; Rabe, J. *Tetrahedron* **1988**, *44*, 3899-3918.

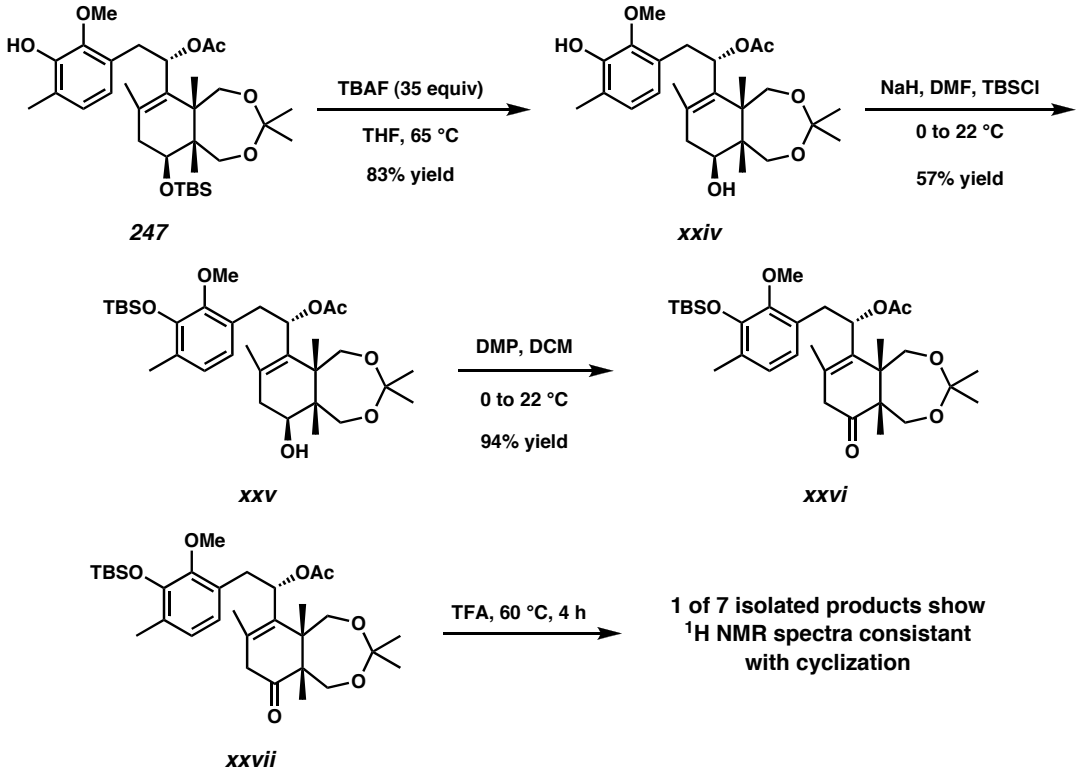
(24) DMSO was uniquely effective among polar solvents used in optimization trials of the KCN displacement reactions. ACN, DMF, NMP, and HMPA all proved to be grossly inferior. The addition of 18-C-6 did not improve the yield of the reaction.

(25) Attempts to carry out S_N' cyclization of allylic alcohol **xxiii** gave mostly styrene elimination products.



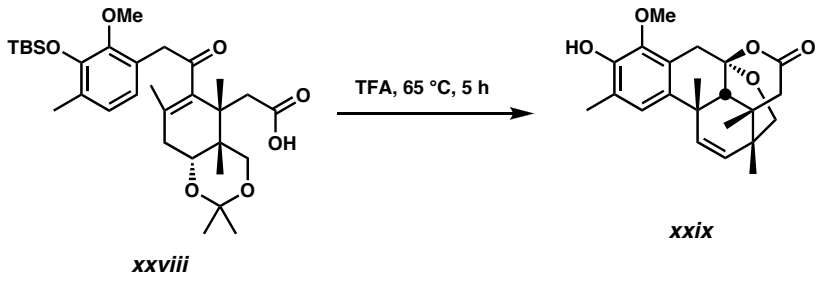
xxiii

(26) Synthesis of keto allylic acetate **247** was completed in several steps as shown below. The attempted S_N' cyclization of keto allylic acetate **xxvii** qualitatively gave less cyclized material and many more byproducts than either allylic alcohol **244** or allylic acetate **255**.



(27) Both C(20) stereoisomers were tried in parallel because the identity of each isomer had not been rigorously proven.

(28) Trifluoroacetic acid cyclization of the related enone **xxviii** afforded the related mixed acetal **xxix**.



(29) (a) Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328-5331. (b) Berthelot, J.; Guette, C.; Desbène, P.-J.; Basselier, J.-J. *Can. J. Chem.* **1989**, *67*, 2061-2066.

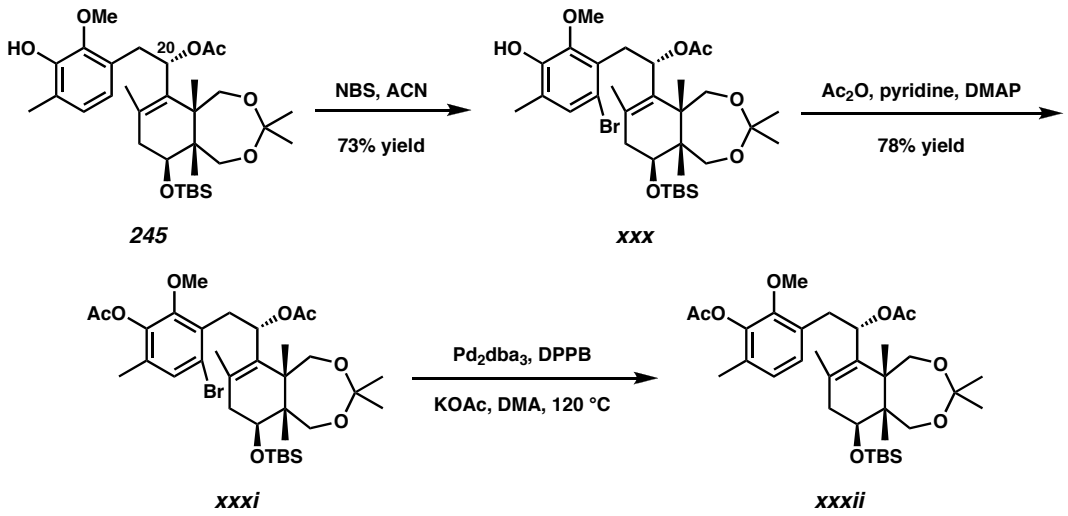
(30) Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *Synlett.* **1997**, 1241-1242.

(31) (a) Hirai, G.; Koizumi, Y.; Moharram, S. M.; Oguri, H.; Hirama, M. *Org. Lett.* **2002**, *4*, 1627-1630. (b) Hirai, G.; Oguri, H.; Moharram, S. M.; Koyama, K.; Hirama, M. *Tetrahedron Lett.* **2001**, *42*, 5783-5787.

(32) (a) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834-7835. (b) Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312-2313. (c) Gibson, S.E.; Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743-1744. (d) Gibson, S.E.; Guillo, N.; Tozer, M. J. *Chem. Commun.* **1997**, 637-638.

(33) (a) Link, J. T. The Intramolecular Heck Reaction. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons: New York, 2002, 60, pp 157-325. (b) Bräse, S.; De Meijee A. Intramolecular Heck Reaction. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002, pp 1223-1254.

(34) Attempted Heck reactions from substrates with the C(20) alcohol oxidation also resulted in debrominated material.



(35) For an excellent review of intramolecular radical conjugate addition, see: Zhang, W. *Tetrahedron* **2001**, *57*, 7237-7262.

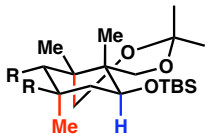
(36) Rajamannar, T.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1994**, 25-26.

(37) TBS groups removed from the figure for clarity.

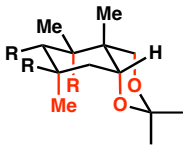
(38) Lewis acids have been used numerous times to promote radical conjugate additions, see: (a) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc*. **1999**, *121*, 7517-7526. (b) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417-2428. (c) Murakata, M.; Tsutsui, H.; Hoshino, O, *Org. Lett*. **2001**, *3*, 299-302. (d) Sibi, M. P.; Manyem, S. *Org. Lett*. **2002**, *4*, 2929-2932.

(39) Preliminary studies with aryl bromide **252** suggest that cyclized products with both C(12) relative stereochemistries are formed. Our conjecture at this time is that the C(10) stereocenter may play a crucial role in determining the stereochemical

outcome of the radical conjugate addition reaction due to the additional 1,3-diaxial interactions that occur formed in the products.



Cyclization product from aryl bromide *251* experiences only 1 new 1,3-diaxial interaction



Cyclization product from aryl bromide *252* experiences several new 1,3-diaxial interactions

(40) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495-499.

(41) See Chapter Four for details.

(42) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561-564. (b) Müller, S.; Liepold, B.; Ruth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522.

(43) Complete consumption of aldehyde **259** is observed by TLC during the reaction. However, it reappears again upon workup, suggesting that the collapse of the intermediate addition adduct to the olefin is slow. Attempts to drive the reaction to completion with heat or additional equivalents of phosphate **261** were unsuccessful. Reaction of aldehyde **259** with lithiated TMS diazomethane gave a slightly higher yield (~35%), but no aldehyde could be recovered.

(44) KHMDS caused significantly less degradation of caprolactam **123** than potassium *t*-butoxide, or LDA.

(45) It should be noted that ynone **262** is diastereomeric to an exact zoanthenol model. (*R*)-Alkyne **260** would be required to model the correct absolute stereochemistry of the natural product. Caprolactam **123** is of the correct enantiomeric series for completion of the natural product.

(46) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455-3458.