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.† 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. 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). 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. It’s noteworthy that dihydrothiophene 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). 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 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 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.

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. 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

<table>
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<th>Entry</th>
<th>Chiral Controller (mol%)</th>
<th>Other Conditions</th>
<th>Temperature (°C)</th>
<th>Time (d)</th>
<th>Sign of Rotation</th>
<th>%ee (% yield)</th>
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<td>1</td>
<td>204 (105)</td>
<td>MeOH (5 equiv)</td>
<td>22</td>
<td>0.3</td>
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<td></td>
<td>pempidine (1 equiv)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>50% CCl₄ v/v</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
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<td>MeOH (3 equiv)</td>
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<td>6</td>
<td>+</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
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<td>MeOH (10 equiv)</td>
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<td>3</td>
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<td>72</td>
</tr>
<tr>
<td>5</td>
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<td>-50</td>
<td>10</td>
<td>+</td>
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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 SN2 displacement of the iodide from the concave face, but is well disposed for SN2’ displacement. Treatment of iodolactone 209 with silver (I) acetate in pyridine at 35 °C afforded selectively SN2’ 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

![Chemical Structures](image)

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. 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. 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.\textsuperscript{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.\textsuperscript{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, AlCl₃ 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.
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. Another strategy for homologation was cyanide displacement of a leaving group. Although S$_2$N$_2$ displacements at neopentyl positions are difficult to achieve, 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 ºC, afforded a 76% yield of nitrile 239. 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.
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 trifluoracetic acid at 65 °C, only a very small portion of the material exhibited an 1H 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, 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 $\pi$-allyl complexes generated from the phenol acetates 247 and 248 as electrophiles (Scheme 3.19). In keeping with the double inversion mechanism of classical $\pi$-allyl chemistry, we anticipated isomer 248 would produce the desired stereochemistry at C(12). 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 1H 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. Finally, cyclization of enone 243 with AlCl₃ 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. 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. 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

A

1. TBAF, THF
2. NBS, ACN
3. TBSCl, imidazole
   DMAP, DMF, 40 °C
   29% yield, 3 steps

B

NBS, ACN, DCM, 22 °C
80% yield of a 4:1 mixture of positional isomers favoring bromide 251

C

1. TBAF, THF
2. NBS, ACN, 0 to 22 °C
3. TBSCI, imidazole
   DMAP, DMF, DCM, 40 °C
   40% yield, 3 steps

D

NBS, ACN, DCM, 22 °C
88% yield of a 3.3:1 mixture of positional isomers favoring bromide 252
The synthesis of aryl bromides allowed us to investigate several metal-based strategies for the formation the B ring. Palladium-catalyzed 6-\textit{exo} Heck cyclizations have been demonstrated to be efficient in forming the final bond (C(12)-C(13)) of the zoanthenol B ring.\textsuperscript{31} In general, \textit{exo}-Heck reactions are more favorable and much more common, but in certain cases 6-\textit{endo} Heck cyclizations have been accomplished.\textsuperscript{32} The intramolecular Heck reaction has been extensively reviewed.\textsuperscript{33} We attempted 6-\textit{endo} Heck cyclizations of bromoarene \textit{251}, but recovered only debrominated material (Scheme 3.22).\textsuperscript{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 \textit{237}.

Another strategy that we investigated based on our bromoarenes was radical conjugate addition. As with Heck reactions, \textit{endo} radical conjugate addition cyclization reactions are much less common than \textit{exo} reactions.\textsuperscript{35} However, a good precedent for
arene radical conjugate addition to make a quaternary center and a six-membered ring had been demonstrated.\textsuperscript{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\textsubscript{3}SnH), 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\textsubscript{3}SnH 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\textsubscript{1/2} = \sim10 h at 30 °C) than AIBN (t\textsubscript{1/2} = \sim10 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.\textsuperscript{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.\textsuperscript{38}
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. 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. 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. TBSCI was purchased from Gelest. TBSOTf was freshly prepared by the method of Corey. 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, KMnO₄, or CAM staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me₄Si (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

**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\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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, 1750, 1320, 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 \( \text{H}_2\text{SO}_4 \) (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. \( \text{NaHCO}_3 \) (2 x 300 mL) \([\text{Caution: gas evolution!}]\) and extracted with \( \text{CH}_2\text{Cl}_2 \) (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); \(^1\text{H NMR (500 MHz, CDCl}_3 \)) \( \delta \) 6.18-6.13 (m, 2H), 5.66-5.61 (m, 2H), 1.37 (s, 6H); \(^{13}\text{C NMR (125 MHz, CDCl}_3 \)) \( \delta \) 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) \([\text{M+H}]^+\) calc'd for \([\text{C}_{16}\text{H}_{26}\text{SiO}_4+\text{H}]^+\): \( m/z \) 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\(_3\)) \( \delta \) 5.80-5.45 (m, 4H), 3.66 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 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, \( \lambda = 254 \) nm) of the asymmetric reaction performed with a catalytic amount of menthol derivative 208 showed carboxylic acid 205 to be of 85% ee (\( t_{\text{fast}} = 10.11 \) min, major; \( t_{\text{slow}} = 12.13 \) 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\(_2\)O (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\(_2\)S\(_2\)O\(_3\) 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\(_6\)D\(_6\)) \( \delta \) 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\(_6\)D\(_6\)) \( \delta \) 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 [C₁₁H₁₄O₄I]⁺: m/z 336.9937, found 336.9930.

**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 H₂O (500 mL) and CH₂Cl₂ (300 mL), and extracted with CH₂Cl₂ (7 x 150 mL). The combined organics were dried (MgSO₄), 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: Rₜ 0.57 (50% EtOAc in hexanes); ᵃ¹H NMR (500 MHz, CDCl₃) 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); ᵃ¹³C NMR (125 MHz, CDCl₃) 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 [C₁₃H₁₆O₆+H]⁺: m/z 269.1025, found 269.1014.
**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$_2$CO$_3$ (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$_2$O (200 mL), brine (300 mL), and CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$O/heptanes at ambient temperature: mp 94.5-95.5 °C (Et$_2$O/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.
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 MnO₂ (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 PtO₂ (67.1 mg, 0.296 mmol, 0.03 equiv), and the reaction mixture was sparged with H₂ (5 min) and stirred vigorously under an atmosphere of H₂ (balloon) for 1.5 h. The reaction mixture was flushed with N₂ 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, CDCl₃) $\delta$ 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, CDCl₃) $\delta$ 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 [C₁₁H₁₄O₅]$^+$: m/z 226.0841, found 226.0847.
Methyl ketone 213. To a cooled (15 °C) solution of ketone 212 (1.31 g, 5.77 mmol, 1.00 equiv) and Ac₂O (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 Ac₂O (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. NaHCO₃ (20 mL), and ice (40 g), and extracted with CH₂Cl₂ (4 x 40 mL). The combined organics were dried (Na₂SO₄) 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 PtO₂ (131 mg, 0.577 mmol, 0.10 equiv), and the reaction mixture was sparged with H₂ (5 min) and stirred vigorously under an atmosphere of H₂ (balloon) for 5.5 h. The reaction mixture was flushed with N₂ 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: Rf 0.57, 0.29 (50% EtOAc in hexanes, 50% Et₂O in hexanes developed twice); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 202.3, 174.1,
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, PhNTf₂ (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 (MgSO₄), 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% Et₂O in hexanes developed twice); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta 4.59 \) (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, CDCl₃) \( \delta 174.1, 172.1, 138.2, 128.2, 118.4 \) (app. d, \( J_{C,F} = 319 \) 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.
**Diene 215.** To a solution of triflate 214 (865 mg, 2.32 mmol, 1.00 equiv), Pd(PPh₃)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 H₂O (50 mL) and Et₂O (50 mL), and extracted with Et₂O (5 x 30 mL). The combined organics were washed with brine (2 x 20 mL), dried (MgSO₄), 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:  

\[ R_f \ 0.63, \ 0.80 \ (50\% \ \text{EtOAc in hexanes} \ \text{developed thrice}, \ 50\% \ \text{EtOAc in hexanes} \ \text{developed twice}); \ \text{¹H NMR (300 MHz, CDCl₃)} \ \delta \ 6.01 \ (\text{ddd}, \ J = 1.2, \ 11.3, \ 17.6 \ \text{Hz}, \ 1\text{H}), \ 5.34 \ (\text{dd}, \ J = 2.0, \ 11.3 \ \text{Hz}, \ 1\text{H}), \ 5.02 \ (\text{dd}, \ J = 2.3, \ 17.6 \ \text{Hz}, \ 1\text{H}), \ 4.53 \ (\text{app. t}, \ J = 2.7 \ \text{Hz}, \ 1\text{H}), \ 3.70 \ (\text{s}, \ 3\text{H}), \ 2.37 \ (\text{s}, \ 2\text{H}), \ 1.72 \ (\text{s}, \ 3\text{H}), \ 1.23 \ (\text{s}, \ 3\text{H}), \ 1.20 \ (\text{s}, \ 3\text{H}); \ \text{¹³C NMR (75 MHz, CDCl₃)} \ \delta \ 176.7, \ 173.7, \ 132.3, \ 131.5, \ 130.2, \ 120.6, \ 77.7, \ 53.6, \ 52.5, \ 49.3, \ 35.3, \ 20.0, \ 12.9, \ 12.5; \ \text{IR (Neat film NaCl)} \ 2985, \ 2951, \ 2911, \ 1782, \ 1730, \ 1267, \ 1198, \ 1144, \ 1089, \ 1035, \ 972 \ \text{cm}^{-1}; \ \text{HRMS (EI)} \ [\text{M}]^+ \ \text{calc'd for [C}_{14}H_{18}O_4]^+: \ m/z \ 250.1205, \ \text{found} \ 250.1204. \]
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 H₂O (8.00 mL) was added OsO₄ (27.5 mg, 0.108 mmol, 0.10 equiv) and NaIO₄ (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 (Na₂SO₄) 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: Rᶠ 0.48 (50% EtOAc in hexanes developed twice); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 [C₁₃H₁₆O₅]⁺: m/z 252.0998, found 252.0984.

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 Et₂O (12 mL) under an N₂ 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 Et₂O (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 Et₂O (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 H₂O (50 mL), 2 M HCl (2.0 mL), and Et₂O (20 mL), and extracted with Et₂O (4 x 40 mL). The combined organics were washed with brine (2 x 30 mL), dried (MgSO₄), 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); Rₜ 0.50 (35% EtOAc in hexanes developed twice); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 [C₂₈H₄₂SiO₇+Na]^+: m/z 541.2598, found 541.2571.
**Enone 218.** To a cooled (0 °C) solution of allylic alcohol 217 (129 mg, 0.248 mmol, 1.00 equiv) in CH₂Cl₂ (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 Et₂O (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, CDCl₃) 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, CDCl₃) 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 [C₂₈H₄₀SiO₇+H]⁺: $m/z$ 517.2622, found 517.2631.
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$_3$PO$_4$ (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$_2$O (60 mL) and extracted with Et$_2$O (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$_2$O/hexanes at ambient temperature: mp 185-190 °C decomp. (Et$_2$O/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.
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 CH₂Cl₂ (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 CH₂Cl₂ (200 mL), quenched with sat. aq. NH₄Cl (75 mL), and extracted with CH₂Cl₂ (4 x 50 mL). The combined organics were dried (MgSO₄) 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, CDCl₃) \( \delta \) 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, CDCl₃) \( \delta \) 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 [C₁₅H₂₈SiO₅+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. \( \text{Na}_2\text{SO}_4 \) (33 mL). The resulting slurry was filtered, dried (\( \text{Na}_2\text{SO}_4 \)), 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); \( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 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); \( ^{13}\text{C} \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 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.

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\(_3\)) \( \delta \) 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\(_6\)D\(_6\)) \( \delta \) 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, 1253, 1221, 1085, 1070, 1044, 835, 775 cm\(^{-1}\); HRMS (FAB) \([\text{M-H}_2+\text{H}]^+\) calc’d for \([\text{C}_{19}\text{H}_{35}\text{SiO}_4]\)^+: \( m/z \) 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\(_3\)) \( \delta \) 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, 9H), 0.88 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 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) \([\text{M+H}]^+\) calc’d for \([\text{C}_{19}\text{H}_{36}\text{SiO}_4+\text{H}]^+\): \( m/z \) 357.2461, found 357.2478.

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 PtO₂ (16.0 mg, 67.2 μmol, 0.03 equiv), and the reaction mixture was sparged with H₂ (5 min) and stirred vigorously under an atmosphere of H₂ (balloon) for 1.5 h. The reaction mixture was flushed with N₂ 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$_4$Si+H]$^+$: m/z 357.2461, found 357.2473.

![Methyl Ketones 233](image)

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 H₂O (150 mL) and EtOAc (75 mL), and extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine (50 mL), dried (Na₂SO₄), 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 Rₜ diastereomer methyl ketone 233a (219 mg, 24% yield) as an oil: Rₜ 0.65 (10% EtOAc in hexanes developed 2 times); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 [C₂₅H₃₈O₄Si+H]⁺: m/z 371.2618, found 371.2607, and the low Rₜ diastereomer methyl ketone 233b (436 mg, 48% yield) as an oil: Rₜ 0.36 (10% EtOAc in hexanes developed 2 times); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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.

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\(_2\)SO\(_4\)), 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\(_2\)O in hexanes); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\) 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); \(^1^3\)C NMR (75 MHz, C\(_6\)D\(_6\)) \(\delta\) 145.9, 127.1, 119.7 (q, \(J_{C,F} = 318\) 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,
IR (Neat film NaCl) 2988, 2954, 2858, 1405, 1213, 1141, 1078, 879 cm⁻¹; HRMS (FAB) [M+H]^+ calc'd for [C₂₁H₃₇SSiO₆F₃+H]^+: m/z 503.2110, found 503.2094.

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 Et₃SiH (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 H₂O (100 mL) and Et₂O (100 mL), and extracted with Et₂O (5 x 50 mL). The combined organic layers were washed with H₂O (20 mL), brine (2 x 20 mL), dried (Na₂SO₄), 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: R⃗f 0.50, 0.55 (10% EtOAc in hexanes developed twice, 25% Et₂O in hexanes); ¹H NMR (300 MHz, CDCl₃) 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$_3$) $\delta$ 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.

**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$_2$O (45 mL) under an N$_2$ atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (75.0 $\mu$L, 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$_2$O (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$_2$O (45 mL) and CH$_2$Cl$_2$ (90 mL). After 1 h at -12 °C, the reaction was quenched with H$_2$O (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$_2$SO$_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 12.5% Et$_2$O 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$_2$O in hexanes, 10% EtOAc in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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-H$_2$+H]$^+$ calc'd for [C$_{36}$H$_{63}$Si$_2$O$_6$]+: $m/z$ 647.4163, found 647.4156.

**Enone 237.** To a cooled (0 °C) solution of allylic alcohol 236 (1.24 g, 1.91 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (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$_2$O (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$_2$O in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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); 13C NMR (75 MHz, CDCl₃) 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, 1099, 1073, 864, 836, 780 cm⁻¹; HRMS (FAB) [M+H]+ calc'd for [C₃₆H₆₃Si₂O₆+H]+: m/z 647.4163, found 647.4140.

Alcohol 238. To a solution of acetonide 230 (5.64 g, 15.8 mmol, 1.00 equiv) in EtOAc (198 mL) was added PtO₂ (108 mg, 0.475 mmol, 0.03 equiv), and the reaction mixture was sparged with a stream of H₂ 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: Rᶠ 0.76 (35% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz,
CDCl₃) 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 [C₁₉H₃₈SiO₄+H]⁺: m/z 359.2618, found 359.2632.

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 CH₂Cl₂ (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 CH₂Cl₂ (40 mL), ice cold H₂O (50 mL), and brine (25 mL), and extracted with CH₂Cl₂ (3 x 35 mL). The combined organics were washed with brine (30 mL), dried (Na₂SO₄), 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 H₂O (150 mL), and extracted with EtOAc (7 x 40 mL). The combined organics were washed with brine (30 mL), dried (Na₂SO₄), 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: Rf 0.42 (20% EtOAc in hexanes); ¹H NMR (300 MHz, CDCl₃) 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-$\text{H}_2$$+\text{H}]^+$ calc'd for [C$_{20}$H$_{36}$NO$_3$Si]$^+$: m/z 366.2464, found 366.2459.

**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$_2$SO$_4$), 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$_2$Cl$_2$ (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$_2$Cl$_2$ (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 NH₄Cl (75 mL), and extracted with CH₂Cl₂ (4 x 50 mL). The combined organics were washed with saturated NaHCO₃ (30 mL), dried (MgSO₄), 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, CDCl₃) \( \delta \) 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, CDCl₃) \( \delta \) 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.

**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 H₂O (30 mL) and CH₂Cl₂ (30 mL), and extracted with CH₂Cl₂ (5 x 30 mL). The combined organics were washed, dried (MgSO₄), and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give 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, PhNTf₂ (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 NaHCO₃ (100 mL) and extracted with EtOAc (4 x 70 mL). The combined organics were dried (Na₂SO₄) and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 25% Et₂O in hexanes) to provide triflate 241 (420 mg, 98% yield, 76% yield for 2 steps) as an oil:  

\[ R_f \ 0.41 \ (50\% \ Et_2O \ in \ hexanes); \ \text{^1H \ NMR} \ (300 \ MHz, \ C_6D_6) \ \delta \ 4.16 \ (d, \ J = 8.7 \ Hz, \ 1H), \ 3.95 \ (d, \ J = 9.3 \ Hz, \ 1H), \ 3.52 \ (dd, \ J = 6.2, \ 8.6 \ Hz, \ 1H), \ 3.46 \ (d, \ J = 9.0 \ Hz, \ 1H), \ 3.36 \ (d, \ J = 9.0 \ Hz, \ 1H), \ 2.17 \ (dd, \ J = 6.0, \ 18.0 \ Hz, \ 1H), \ 1.95 \ (dd, \ J = 8.1, \ 18.0 \ Hz, \ 1H), \ 1.50 \ (s, \ 3H), \ 1.01 \ (s, \ 3H), \ 0.97 \ (s, \ 3H), \ 0.90 \ (s, \ 3H), \ 0.88 \ (s, \ 3H); \^13C \ NMR \ (75 \ MHz, \ C_6D_6) \ \delta \ 145.7, \ 125.1, \ 121.5, \ 119.5 \ (app. \ d, \ J_{C-F} = 296 \ Hz), \ 75.2, \ 74.7, \ 74.3, \ 71.0, \ 51.2, \ 50.4, \ 36.1, \ 28.2, \ 27.4, \ 21.6, \ 18.1, \ 16.4; \ IR \ (Neat \ film \ NaCl) \ 2988, \ 2942, \ 2884, \ 1403, \ 1211, \ 1141, \ 1053, \ 990, \ 874 \ cm^{-1}; \ HRMS \ (EI) \ [M]^+ \ \text{calc'd for } [C_{16}H_{22}NO_3F_3S]^+: \ m/z \ 397.1171, \ found \ 397.1179.\]
Enal 242. To a solution of triflate 241 (1.41 g, 3.54 mmol, 1.00 equiv), Pd(PPh₃)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 H₂O (300 mL) and Et₂O (200 mL), and extracted with Et₂O (4 x 125 mL). The combined organics were washed with brine (170 mL), dried (MgSO₄), 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 H₂O (5.30 mL) was added OsO₄ (10.8 mg, 42.3 μmol, 0.10 equiv) and NaIO₄ (227 mg, 1.06 mmol, 2.50 equiv). After 3.5 h at 0 °C, the reaction mixture was diluted with H₂O (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 (MgSO₄), 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: Rf 0.28 (35% EtOAc in hexanes); ¹H NMR (300 MHz, CDCl₃) 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.

![Chemical structures](image)

**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$_2$O (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$_2$O (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$_2$SO$_4$) 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$_2$Cl$_2$ (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$_2$O (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$_3$) $\delta$ 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 (ddd, $J$ = 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 (ddd, $J$ = 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$_3$) $\delta$ 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.

**Allylic acetates 247 and 248.** To a solution of allylic alcohol 244 (120 mg, 0.185 mmol, 1.00 equiv) in Ac$_2$O (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% Et₂O 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 H₂O (30 mL) and CH₂Cl₂ (30 mL), and extracted with CH₂Cl₂ (6 x 30 mL). The combined organics were dried (Na₂SO₄), 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, CDCl₃) 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, CDCl₃) 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 [C₃₂H₅₂SiO₇+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, CDCl₃) 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$_3$) $\delta$ 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, 1248, 1221, 1067, 1040, 836, 777 cm$^{-1}$; HRMS (FAB) [M-H$_2$+H]$^+$ calc'd for [C$_{32}$H$_{51}$SiO$_7$]$^+$: m/z 575.3404, found 575.3405.

Hemiacetal 250. A solution of enone 243 (29.9 mg, 55.2 $\mu$mol, 1.00 equiv) in trifluoroacetic acid (4.00 mL) was heated to 60 $^\circ$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$_3$) $\delta$ 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$_3$) $\delta$ 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).

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$_2$O (50 mL) and CH$_2$Cl$_2$ (50 mL), and extracted with CH$_2$Cl$_2$ (4 x 25 mL). The combined organics were dried (Na$_2$SO$_4$), 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$_2$O (8 mL) and EtOAc (8 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried (Na$_2$SO$_4$), 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$_2$O (8 mL) and EtOAc (8 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried
(Na$_2$SO$_4$), concentrated, and purified by flash chromatography on silica gel (1 to 5% Et$_2$O 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$_2$O in hexanes, 25% Et$_2$O in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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-H$_2$+H]$^+$ calc'd for [C$_{36}$H$_{60}$Si$_2$O$_6$Br]+: m/z 723.3112, found 723.3128.

**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$_2$Cl$_2$ (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$_2$O (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$_2$SO$_4$), concentrated, and purified by flash chromatography on silica gel (1 to 5% Et$_2$O 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.

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), H₂O (5 mL), and saturated aqueous NH₄Cl (5 mL), and extracted with EtOAc (5 x 20 mL). The combined organics were dried (MgSO₄), 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 H₂O (10 mL) and EtOAc (20 mL), and extracted with EtOAc (5 x 10 mL). The combined organics were dried (MgSO₄), 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), TBSCI (17.8 mg, 0.118 mmol, 1.50 equiv) in DMF (200 μL) and CH₂Cl₂ (200 μL) was added DMAP (9.6 mg, 78.8 μmol, 1.00 equiv)
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 NH₄Cl (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% Et₂O in hexanes) to give isomerically pure bromide 252 (23.0 mg, 47% yield, 40% yield for three steps) as an amorphous white solid: \( R_f \) 0.43 (20% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl₃) 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, CDCl₃) 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 [C₃₁H₄₆NSiBrO₅+H]+: \( m/z \) 620.2407, found 620.2394.

**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 Ph₃SnH (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% Et₂O 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, CDCl₃) 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); ^13C NMR (125 MHz, CDCl₃) 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-H₂+H]+ calc'd for [C₃₆H₆₁Si₂O₆]: m/z 645.4007, found 645.4007.

**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, 0.250
0.100 mmol, 3.25 equiv) in toluene was added. After an additional 1 h at 0 °C, the reaction mixture was quenched with Na₂SO₄•10H₂O (300 mg) in a portionwise manner, filtered, washed (CH₂Cl₂), concentrated, and purified by flash chromatography on silica gel (10 to 40% Et₂O 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 CH₂Cl₂ at ambient temperature: mp 185-190 °C decom. (CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, 1089, 1061, 836 cm⁻¹; HRMS (FAB) [M-H₂+H⁺]⁺ calc'd for [C₃₆H₆₃Si₂O₆]+: m/z 647.4163, found 647.4162.

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 K₂CO₃ (601 mg, 4.35 mmol, 1.00 equiv) and RhCl₃•H₂O (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% Et₂O 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% Et₂O in hexanes, 5% Et₂O in hexanes developed twice); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 5.88 (dq, \( J = 1.8, 15.5 \text{ Hz}, 1 \text{H} \)), 5.42 (dq, \( J = 6.3, 15.3 \text{ Hz}, 1 \text{H} \)), 2.53 (d, \( J = 13.2 \text{ Hz}, 1 \text{H} \)), 2.11 (dd, \( J = 1.8, 13.5 \text{ Hz}, 1 \text{H} \)), 1.85 (d, \( J = 14.4 \text{ Hz}, 1 \text{H} \)), 1.71 (dd, \( J = 1.7, 6.5 \text{ Hz}, 3 \text{H} \)), 1.42 (dd, \( J = 1.8, 14.4 \text{ Hz}, 1 \text{H} \)), 1.09 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.90 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 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 \( [\text{C}_{14}\text{H}_{24}\text{O}]^{+} \): m/z 208.1827, found 208.1820; \([\alpha]_{D}^{25}\) –59.07 (c 1.04, CHCl₃, 85% ee).

**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 \( p \)-toluenesulphonate (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 NaHCO₃ (40 mL), and extracted with Ph-H (3 x 30 mL). The combined organics were washed with brine (20 mL), dried (Na₂SO₄),
concentrated, and purified by flash chromatography on silica gel (1 to 2% Et₂O in hexane) to give acetal 258 (585 mg, 70% yield) as an oil: $R_f$ 0.61, 0.67 (5% Et₂O in hexanes developed twice, 25% Et₂O in hexanes); $^1$H NMR (300 MHz, CDCl₃) $\delta$ 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, CDCl₃) $\delta$ 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 [C₁₆H₂₈O]⁺: m/z 252.2089, found 252.2090; $[\alpha]_D^{25} +1.51$ (c 1.11, CHCl₃, 85% ee).

Aldehyde 259. Through a cooled (-78 °C) solution of acetal 258 (252 mg, 1.00 mmol, 1.00 equiv) in CH₂Cl₂ (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% Et₂O in hexane) to give aldehyde 259 (132 mg, 55% yield) as an oil: $R_f$ 0.41, 0.29 (25% Et₂O in hexanes, 5% Et₂O in hexanes developed twice); $^1$H NMR (300 MHz, CDCl₃) $\delta$ 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, CDCl₃) 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 [C₁₄H₂₄O₃]⁺: m/z 240.1726, found 240.1720; [α]D²⁴ -39.53 (c 0.385, CHCl₃, 85% ee).

**Alkyne 260.** To a solution of aldehyde 259 (75.0 mg, 0.312 mmol, 1.00 equiv), and K₂CO₃ (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 K₂CO₃ (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 K₂CO₃ (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 H₂O (10 mL), extracted with CH₂Cl₂ (8 x 5 mL), dried (MgSO₄), concentrated, and purified by flash chromatography on silica gel (1 to 7% Et₂O in hexanes) to give recovered aldehyde 259 (55.6 mg, 74% yield) and alkyne 260 (15.5 mg, 21% yield, 85% yield based on recovered aldehyde 259) as an oil: Rf 0.40 (5% Et₂O in hexanes developed twice); ¹H NMR (300 MHz, C₆D₆) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (El) [M]+ calc’d for [C₁₅H₂₄O₂]⁺: m/z 236.1776, found 236.1786; [α]D₂⁶ –20.35 (c 1.25, CH₂Cl₂, 85% ee).

![Diagram](image)

**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 NaHCO₃ (0.50 mL), diluted with H₂O (2 mL), brine (4 mL), and Et₂O (4 mL), and extracted with Et₂O (6 x 4 mL) and CH₂Cl₂ (2 x 2 mL). The combined organics were dried (Na₂SO₄) 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: Rf 0.24, 0.50 (10% EtOAc in hexanes developed twice, 20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, 2208, 1716, 1673, 1504, 1391, 1366, 1252, 1171, 1090, 836 cm⁻¹; HRMS (FAB) [M+H]⁺ calc'd for [C₃₃H₅₉NO₆Si+H]⁺: m/z 594.4190, found 594.4208; [α]D²⁶ –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 H₂ (5 min). After 18 h of vigorous stirring under an atmosphere of H₂ (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 H₂ (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: Rf 0.53 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) 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$_3$) $\delta$ 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$_6$Si]+: m/z 598.4503, found 598.4489; [$\alpha$]$_D^{26}$ 9.33 (c 0.105, CH$_2$Cl$_2$).
3.9 Notes and Citations


(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.


(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 RhI₃•H₂O in EtOH at 80 °C.

(16) See Chapter Two for details.


Reduction of enone 218 with NaBH₄ 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 CuSO₄ 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.


(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.


(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.
(26) Synthesis of keto allylic acetate 247 was completed in several steps as shown below. The attempted SN_1 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.


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

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


TBS groups removed from the figure for clarity.


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.


(41) See Chapter Four for details.


(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 zoanthanol 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.