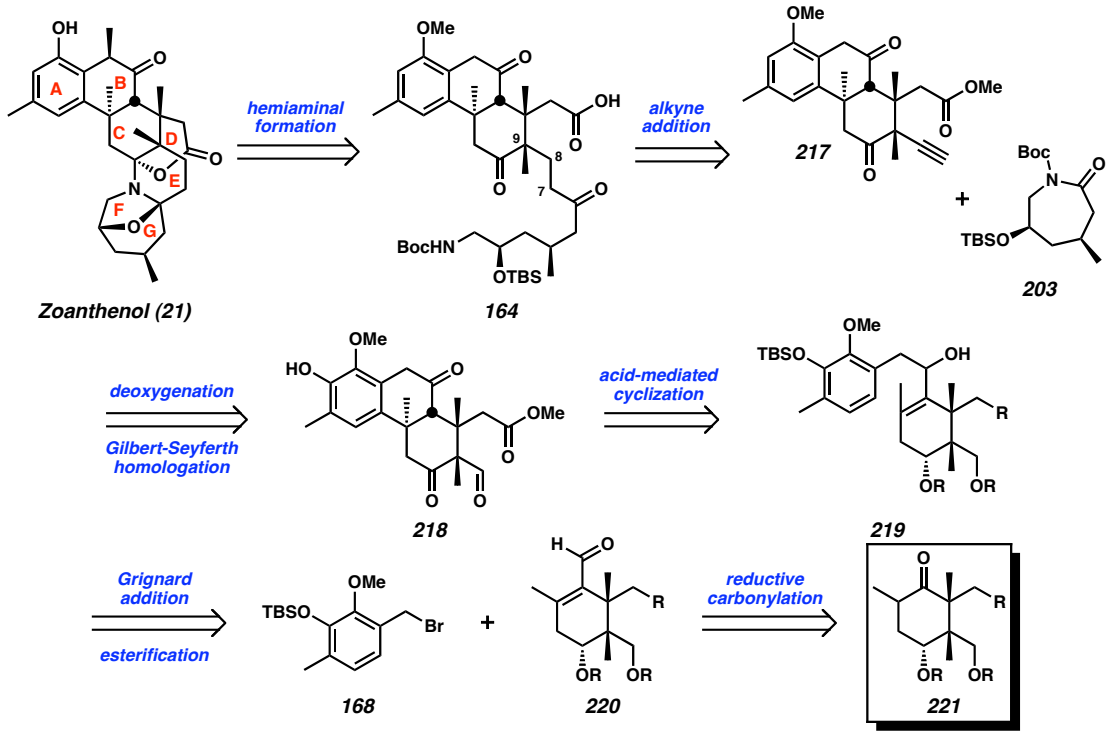
CHAPTER THREE

Acid-Mediated Cyclization Approaches to the Densely Substituted Carbocyclic Core of Zoanthenol[†]

3.1.1 Revised Retrosynthetic Analysis

Chapter 2 described an interesting acid-mediated S_N'-type cyclization to construct the carbocyclic core of zoanthenol. Efforts to elaborate the product of this route were unsuccessful, thus the retrosynthetic analysis was altered to include the all-carbon quaternary stereocenter at C(9) prior to our key cyclization step. Disconnection of side-chain-appended intermediate **164** at the C(8)–C(9) bond, revealed tricyclic alkyne **217** and lactam **203** (Scheme 3.1.1). The alkyne was envisioned to arise from aldehyde **218**, which would be accessed via an acid-mediated cyclization of an allylic alcohol such as **218**. This tethered A–C ring system would in turn be derived from aryl bromide **168** and enal **220**. Enal **220** would be available from a ketone such as **221** by means of a reductive carbonylation as described in Chapter 2.

[†] This work was conducted in close collaboration with Dr. Douglas C. Behenna, a former graduate student in the Stoltz Group.



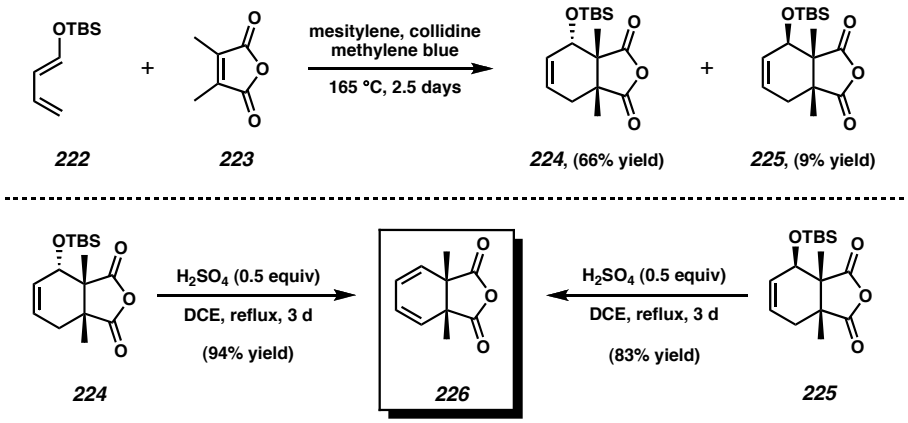
Scheme 3.1.1 Revised retrosynthesis of zoanthenol.

3.2 Toward a Vicinal Quaternary Center-Containing C Ring Synthon

3.2.1 Synthesis and Desymmetrization of a meso*-Anhydride*

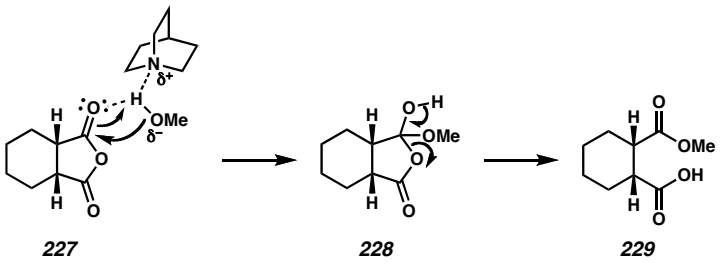
Given our previous difficulties installing the all-carbon quaternary stereocenter at C(9), we chose to tackle the synthesis of the vicinal quaternary centers first. Fortunately, an effective approach to a similar problem had recently been published.[1] In their total synthesis of merrilactone A, Danishefsky and coworkers treated electron-rich diene **222** and dimethyl maleic anhydride (**223**) with mesitylene, collidine, and methylene blue at 165 °C for 3 days to form cycloadduct **224** in 74% yield (Scheme 3.2.1).[1] The scalable nature of this reaction allowed access to quantities as large as 75.7 g (66% yield) of endo adduct **224** and 10.5 g of exo adduct **225** (9% yield) from a single large-scale reaction. It was envisioned that this Diels-Alder adduct could be advanced to a *meso*-symmetric compound, which could be treated with a chiral reagent to allow entry into an

enantioselective synthesis. We anticipated that employing a strong acid would induce desilylation followed by in situ dehydration. Gratifyingly, treatment of either the *endo* (**224**) or *exo* (**225**) Diels-Alder adduct with 0.5 equivalents of sulfuric acid in 0.1 M 1,2-dichloroethane produced anhydride **226** in excellent yield.[2]



Scheme 3.2.1 Synthesis of vicinal all-carbon quaternary centers.

Several reports indicated the feasibility of a *meso*-anhydride desymmetrization as a viable entry into an enantioselective synthesis.[3] These reactions involve alcoholysis of an anhydride, catalyzed or mediated by a cinchona alkaloid or derivative. The alkaloid activates the alcohol by a hydrogen bond, forming a noncovalent adduct such as **227** (Scheme 3.2.2).[3a] This adduct preferentially activates one of the anhydride carbonyls, serving as both a Brønsted acid catalyst and a nucleophile. Thus, the carbonyl is activated via a developing hydrogen bond, while methoxide is delivered selectively to the same carbonyl. Collapse of tetrahedral intermediate **228** leads to half ester **229**.



Scheme 3.2.2 Mechanism of *meso*-anhydride desymmetrization by cinchona alkaloids.

The desymmetrization of *meso*-anhydrides is known for a number of bicyclic and tricyclic systems (**232**–**238**, Figure 3.2.1).[4] Interestingly, Bolm and coworkers found that compounds **239**–**241** were completely unreactive. The authors hypothesize that steric interactions prevent reactivity, though these effects appear to be quite subtle.[4] This presumed steric constraint cast doubt on the likelihood of success in our own system because both of the carbonyls in anhydride **226** are neopentyl in nature. Nevertheless, we proceeded with our efforts to desymmetrize *meso* anhydride **226**.

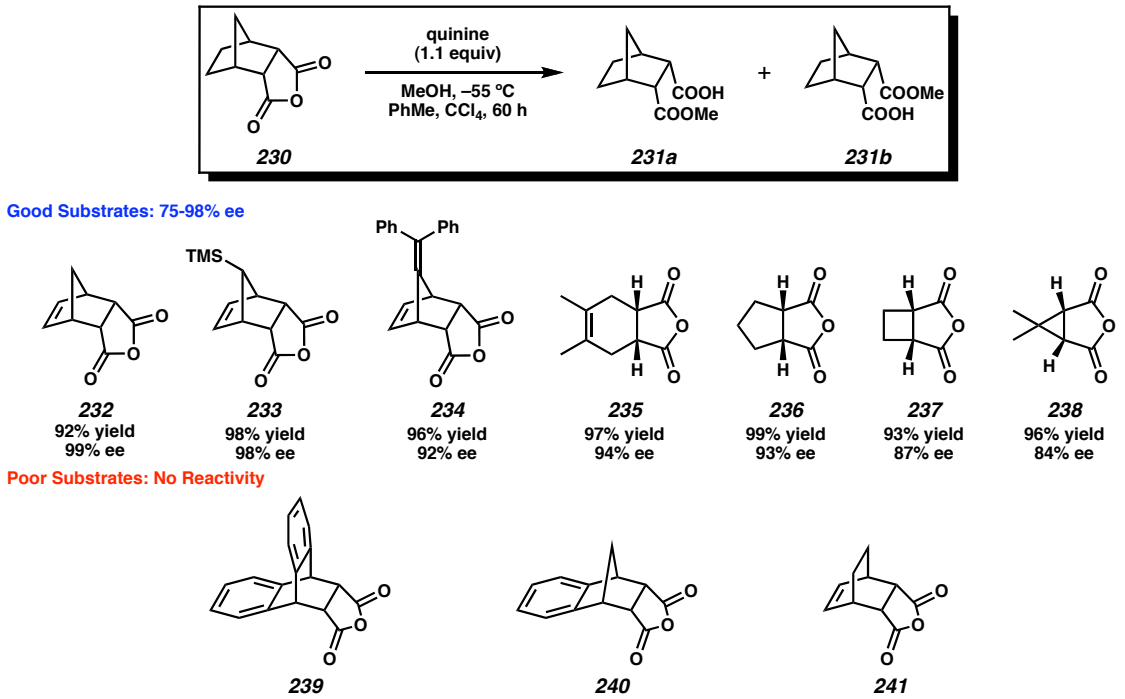
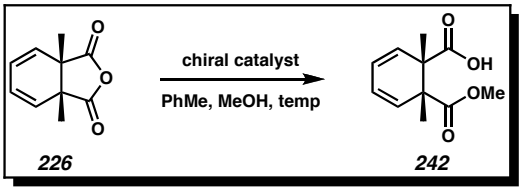
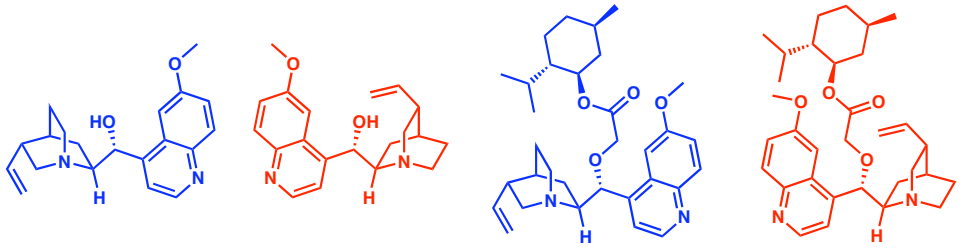


Figure 3.2.1 Known *meso*-anhydride desymmetrization substrates.

At this point, we were poised to attempt the key desymmetrization step. To our delight, desymmetrization of anhydride **226** was accomplished at ambient temperature upon treatment with quinine and methanol in toluene to form half-ester **242** in > 99% yield and 50% ee (Entry 1, Table 3.2.1). Cooling the reaction to –50 °C increased the ee to 74% (Entry 2), and treatment of **226** with catalytic quinine (**243**), 1 equiv pentamethylpiperidine (pempidine) and methanol for 18 days at –50 °C provided half-ester **242** in 88% yield and 70% ee (Entry 3). The use of quinidine (**244**) resulted in the

formation of the opposite enantiomer of the half-ester in 70% ee (Entry 4). Quinine derivative **245** allowed access to the desymmetrized product in 72% ee at –25 °C (Entry 5). The best enantioselectivities were observed upon treatment with menthyl-acetate-substituted quinidine derivative **246**.[5] In this case, subjecting anhydride **226** to **246**, MeOH, and PhMe at –50 °C provided half-ester **242** in 85% ee (Entry 6). A number of alternative alcohols were also screened, but they did not show improved enantioselectivity in the reaction.[6] Interestingly, significant rate acceleration was observed for the menthyl acetate derivatives **245** and **246**. Although this effect has not been studied in detail, it is feasible that the alcohol moiety in the parent structures could intramolecularly hydrogen bond to the tertiary amine and compete with hydrogen bonding to methanol. Such competition would be prevented by use of menthyl acetate derivatives **245** and **246**. Importantly, this work represents the first example of a desymmetrization of a *meso* anhydride that simultaneously sets the absolute stereochemistry of vicinal all-carbon quaternary centers. Additionally, the ability to access either enantiomer of half-ester **242** has enabled important flexibility in our synthetic efforts.





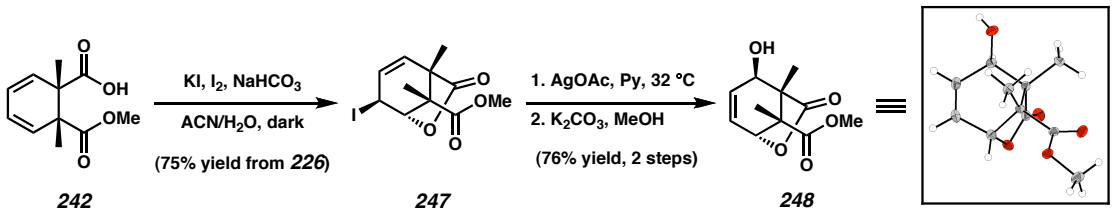
quinine *(243)* | quinidine *(244)* | *O*-(menthylacetate)-quinine *(245)* | *O*-((–)-menthylacetate)-quinidine *(246)*

Entry	Chiral Controller (mol%)	Other Conditions	Temperature (°C)	Time (d)	Sign of Rotation	%ee (% yield)
1	*243* (105)	MeOH (5 equiv)	22	0.3	–	50 (>99)
2	*243* (105)	MeOH (5 equiv)	–50	0.3	–	74
3	*243* (10)	MeOH (3 equiv) pempidine (1 equiv) 50% CCl_4 v/v	–50	18	–	70 (88)
4	*244* (100)	MeOH (3 equiv)	–50	6	+	70
5	*245* (105)	MeOH (10 equiv)	–25	3	–	72
6	*246* (101)	MeOH (3 equiv)	–50	10	+	85

Table 3.2.1 Optimized synthesis and desymmetrization of a C ring *meso*-anhydride.

3.2.2 Elaboration of the Half-Ester

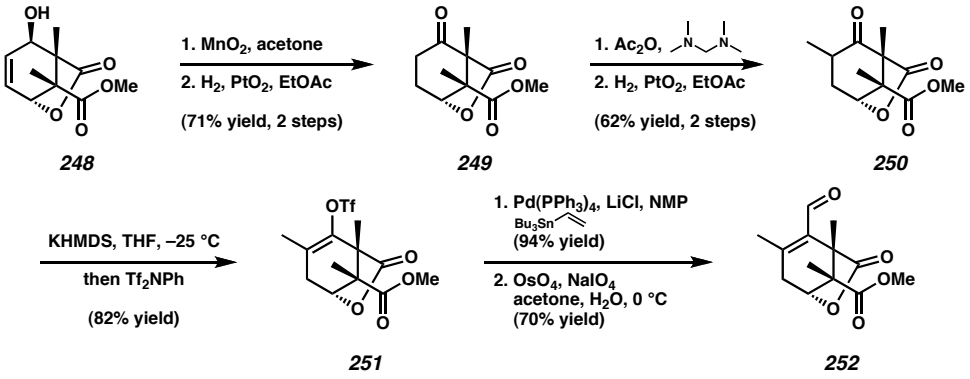
With our desymmetrized diene in hand, we sought to relay the stereochemical information into the C ring. We investigated several approaches toward this goal, including an Arndt-Eistert homologation,[7] a homologation/π-allyl sequence,[8] and a selenolactonization/oxidative rearrangement sequence.[9] Ultimately, we found that iodolactonization could be affected with good positional selectivity and yield (Scheme 3.2.3). Treatment of the iodolactone with silver acetate led to *syn*-periplanar attack of the incoming acetate nucleophile to provide, after methanolysis, allylic alcohol **248**. The connectivity and relative stereochemistry were proven by X-ray analysis of a single crystal.



Scheme 3.2.3 C ring functionalization: iodolactonization and displacement.

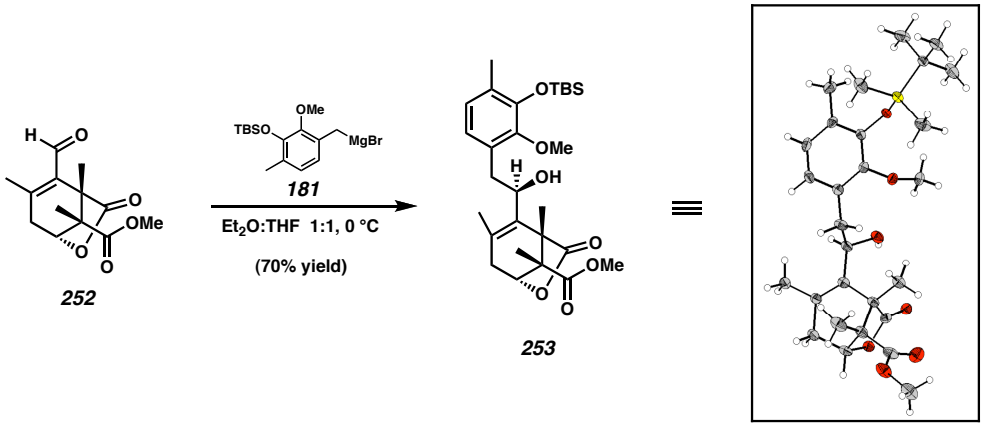
3.3.1 Toward a Lactone-Derived C Ring Synthon

Allylic alcohol **248** served as an ideal branch point for our synthetic investigations, ultimately allowing access to a variety of C ring synthons. Initially, it was advanced to a lactone-derived synthon, enabling quick access to cyclization substrates. Along these lines, a simple two-step protocol involving allylic oxidation with MnO_2[10] followed by hydrogenation with Adams' catalyst[11] was employed to provide ketone **249** (Scheme 3.3.1). Methylation of this substrate using simple LDA/MeI conditions afforded almost exclusively bis-alkylated products as a mixture with starting ketone. Thus, we chose to employ a 2-step protocol for the installation of the methyl group. Methylenation was accomplished with *N*,*N*-tetramethylmethylenediamine and acetic anhydride.[12] Hydrogenation once again occurred cleanly upon treatment with Adams' catalyst under a balloon of H_2, providing methyl ketone **250** as a mixture of diastereomers. Enolization and trapping with *N*-phenyl bis(trifluoromethanesulfonamide) provided enol triflate **251**. Stille coupling proceeded smoothly to provide a diene, which was oxidatively cleaved to provide enal **252**.



Scheme 3.3.1 Synthesis of a lactone-derived C ring synthon.

In previous C ring synthons, we were able to increase the selectivity during our fragment coupling step by conducting the Grignard addition in a mixture of CH_2Cl_2 and Et_2O. Unfortunately, enal **252** was insoluble in this mixture of solvents (Scheme 3.3.2). Thus, we turned to use of a combination of THF and Et_2O. Under these conditions, the reaction proceeded smoothly to provide allylic alcohol **253**. However, we observed complete selectivity for addition in the opposite sense from that of our previous substrate.[13,14,15]



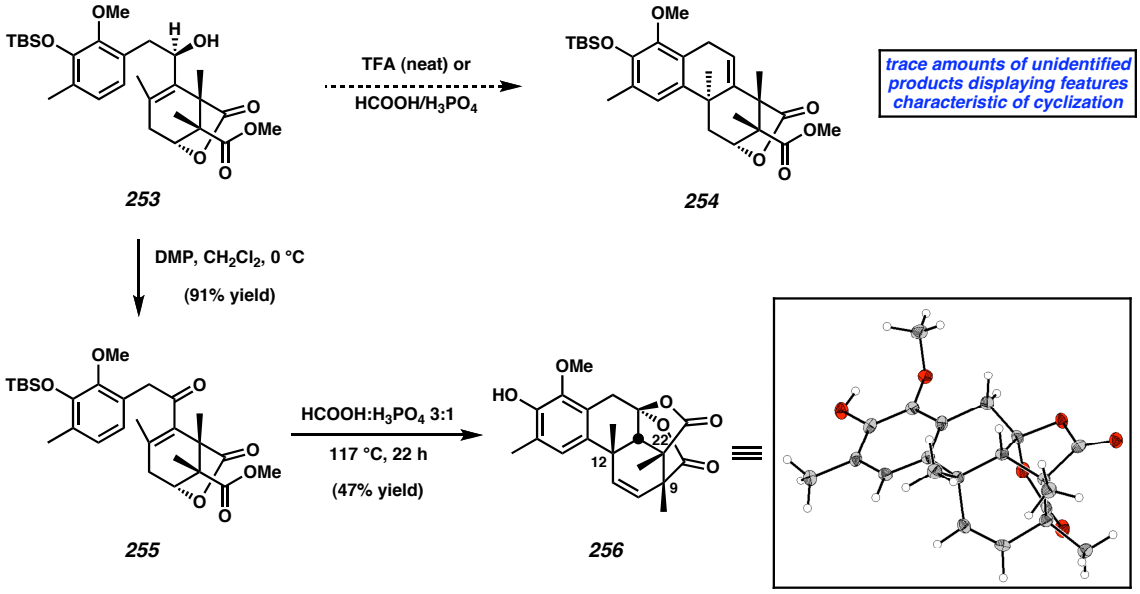
Scheme 3.3.2 Grignard addition to synthon **252**.

3.3.2 Acid-Mediated Cyclizations of Lactone-Derived A–C Ring Systems

Owing to our success with allylic alcohol substrates in our early work, we subjected allylic alcohol **253** to neat trifluoroacetic acid at 65 °C (Scheme 3.3.3). From these

conditions, we observed almost exclusive desilylation of the A ring, and only a trace amount of a cyclized product was observed. Treatment with a mixture of formic acid and 85% phosphoric acid led to substantial decomposition as well as a trace amount of a compound that appeared to be cyclized. Overall, we found that this system could not be efficiently cyclized.

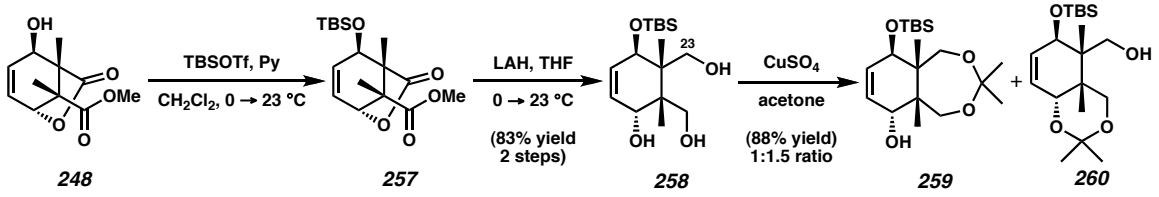
With the goal of increasing the reactivity of the system, we oxidized allylic alcohol **253** to the corresponding enone using Dess-Martin periodinane. Upon treatment with TFA at temperatures as high as 110 °C, with $AlCl_3$ in toluene at 100 °C, or with polyphosphoric acid at 100 °C, we only observed A-ring desilylation or decomposition. Interestingly, treatment with a 3:1 (v/v) ratio of formic acid and 85% phosphoric acid induced cyclization of enone **255** to afford the unusual caged bisacetoxyacetal **256** in 47% yield. Unfortunately, X-ray crystallographic analysis of a single crystal revealed that pentacycle **256** did not possess the desired relative stereochemistry between the newly formed C(12) stereocenter and the C(9) and C(22) centers.



Scheme 3.3.3 Lactone-derived A–C ring system cyclizations.

3.4.1 Functionalization of Allylic Alcohol ***248***

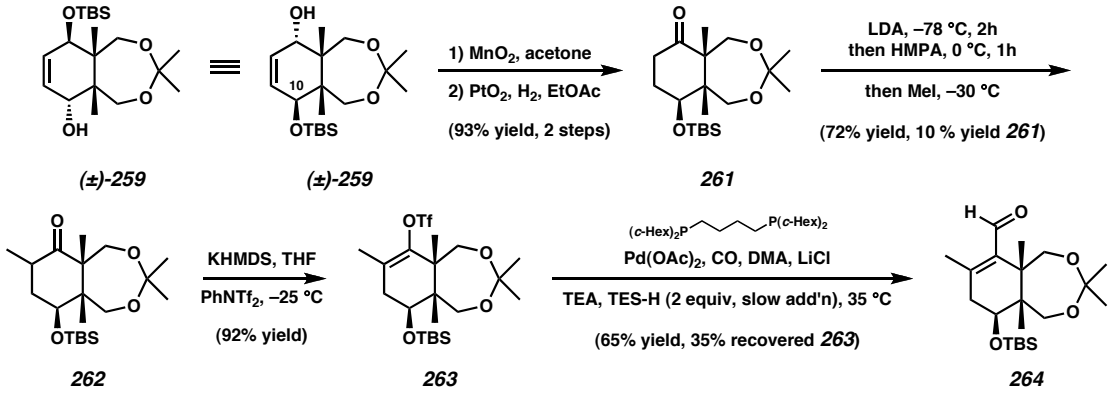
During the above investigations, we were also working to functionalize allylic alcohol **248** toward alternative C ring precursors. Accordingly, allylic alcohol **248** was smoothly silylated upon treatment with TBSOTf and pyridine to provide silyl ether **257** (Scheme 3.4.1).[16] At this point, we sought to differentiate the oxidation states of the lactone and methyl ester carbonyl carbons and selectively homologate C(23). Though several options were pursued, the most facile manner to accomplish this goal was to conduct a global reduction with lithium aluminum hydride, and then selectively constrain the 1,3-diol as a cyclic acetal. In the event, LAH reduction proceeded in good yield to provide triol **258**. Subsequent treatment of the triol with anhydrous copper(II) sulfate in acetone[17] afforded a mixture of acetal products **259** and **260**. Although we targeted selectivity for the 6-membered ring, we were aware of the competition that could exist between the 6 and 7-membered ring products.[18] The energy gained by formation of the more stable 6-membered ring is partially counteracted by the 1,3-diaxial interactions (H_{axial}/CH_{3axial}) developed in the process. The greater conformational flexibility of the 7-membered ring avoids the diaxial interaction, but such a ring system is inherently less stable.[18] Although this mixture of products seemed like an obstacle at first, we were able to utilize it as another branching point for our synthetic efforts. Thus, we simply split our material to generate two different C ring synthons.[19]



Scheme 3.4.1 Lactone reduction and triol differentiation.

3.5.1 Toward a 7-Membered Acetal-Derived C Ring

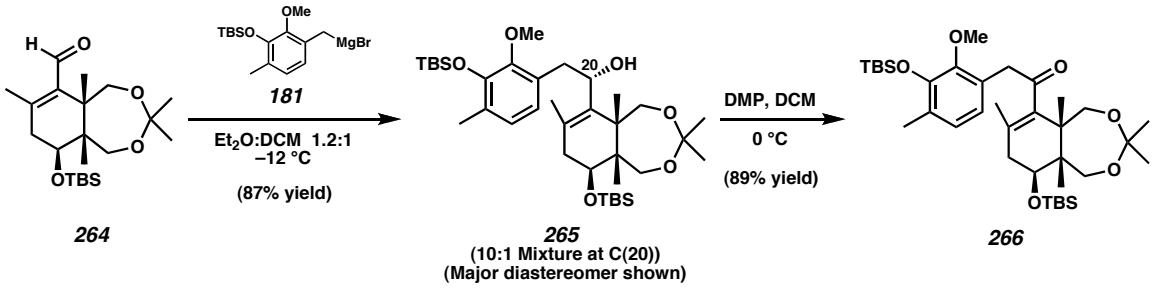
Because our desymmetrization strategy provided access to either enantiomer of all of our intermediates (see Section 3.1.1), we were able to utilize the 7-membered ring acetal product to access a C ring synthon with inverted stereochemistry at C(10) (Scheme 3.5.1). C ring synthons **252** (Scheme 3.3.1), **278** (Scheme 3.6.1), and **280** (Scheme 3.7.1) all feature an α-disposed secondary alcohol at C(10). Access to a C ring synthon with a β-disposed alcohol derivative was of interest because we were uncertain about the role this stereocenter might play in both the acid-mediated cyclizations and radical conjugate addition reactions (see Chapter 4). Thus, oxidation of allylic alcohol **259** followed by hydrogenation with Adams' catalyst afforded ketone **261** in excellent yield over the two steps. The ketone was then methylated under standard conditions to provide methyl ketone **262** as a mixture of diastereomers. Enolization with KHMDS and trapping with *N*-phenyl bis(trifluoromethanesulfonamide) afforded enol triflate **263** in 92% yield. Treatment of enol triflate **263** under the reductive carbonylation conditions developed during our early work[13] led to formation of enal **264** in 65% yield with quantitative recovery of enol triflate **263**.



Scheme 3.5.1 Synthesis of a 7-membered acetal-derived C ring.

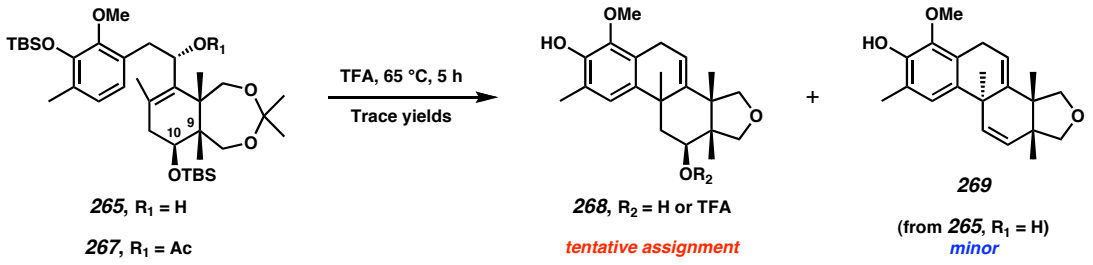
3.5.2 Acid-Mediated Cyclization of the 7-Membered Acetal Substrate

With enal **264** in hand, we employed our mixed-solvent Grignard conditions for fragment coupling, which gratifyingly afforded the desired stereochemistry of the C(20) alcohol in 87% yield with a 10:1 diastereomeric ratio (**265**, Scheme 3.5.2). Subsequent oxidation of this alcohol with Dess-Martin periodinane[20] provided the corresponding enone (**266**) in 89% yield.



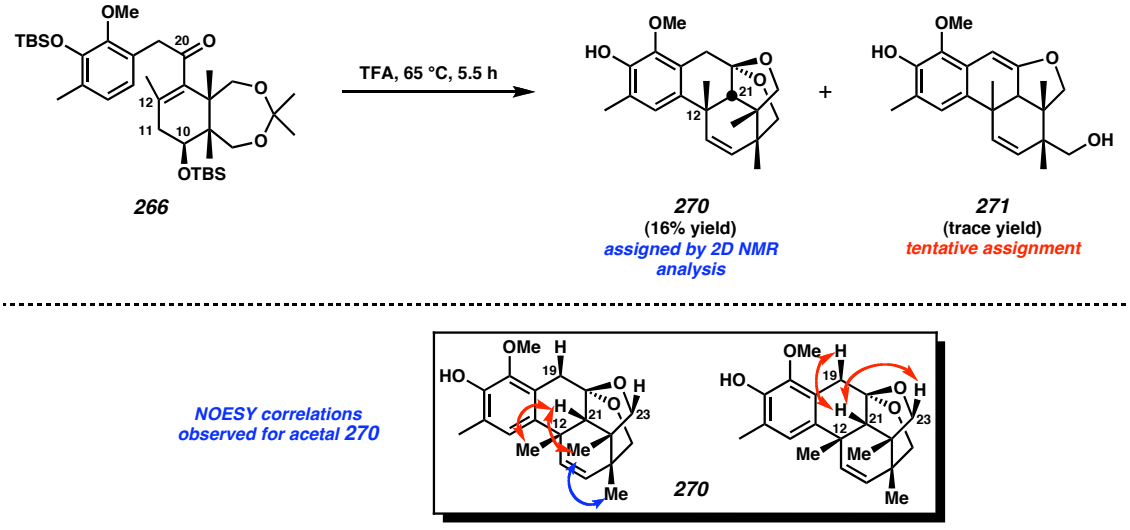
Scheme 3.5.2 Grignard addition and oxidation to access cyclization substrates.

At this point, we were well poised to begin testing cyclization conditions for this system. Accordingly, allylic alcohol **265** was treated with neat trifluoroacetic acid, but provided only trace amounts of products that appeared to be cyclized (Scheme 3.5.3). The methylene coupling constants in the ^{1}H NMR for **268** indicated the presence of a tetrahydrofuran-type ring, and a methine signal in the ^{1}H NMR spectra indicated the presence of the C(10) alcohol functionality. Analysis of the ^{19}F NMR spectra for **268** indicated that in one case, the alcohol was substituted by a trifluoroacetate group. Tetracycle **269** was only isolated in trace amounts, but it was successfully assigned after it was isolated unexpectedly in a later reaction (see Section 3.7.2).



Scheme 3.5.3 Cyclization of allylic alcohol **265**.

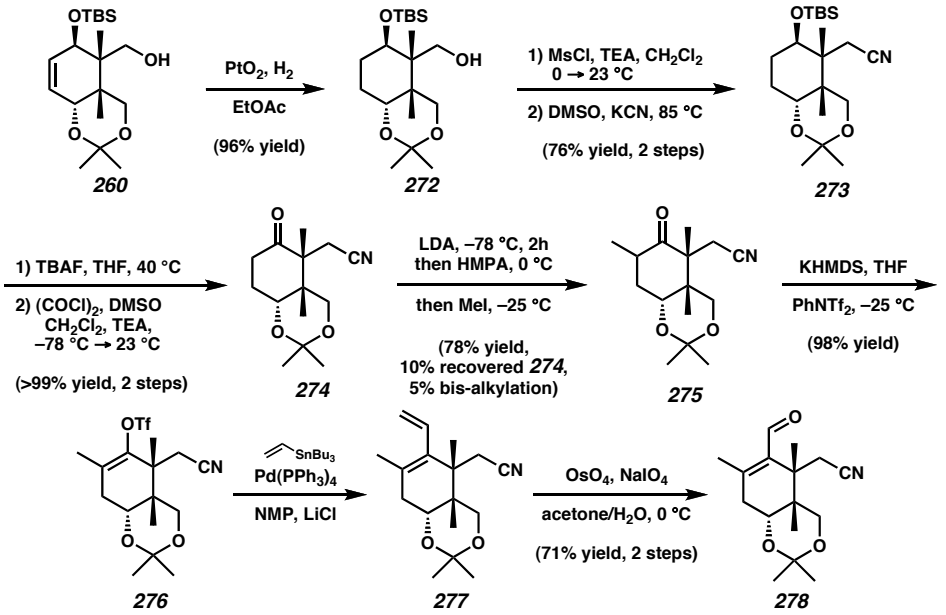
When enone **266** was subjected to TFA at 60 °C (Scheme 3.5.4), we were able to isolate 4 compounds that showed evidence of cyclization, with the major cyclized product having an intriguing set of spectral properties. We found that this compound possessed two olefinic resonances in its ^{1}H NMR spectrum, and it did not display a carbonyl stretching frequency in the IR spectrum, nor could a carbonyl carbon be seen in its ^{13}C NMR spectrum. Ultimately, by comparing the spectra with those observed for cyclization product **256**, we were able to determine that the product observed in this case must be **270**. The methylene coupling constants are also consistent with this assignment, and the C(12) and C(21) stereochemistry was initially assigned by analogy to **256** as well as by geometrical constraints. Ultimately, we were able to confirm this assignment by 2D NMR spectroscopy. Strong NOESY correlations were observed between the methine H at C(21) and the methyl groups at the C(12) and C(22) quaternary centers as well as the psuedoaxial Hs at C(19) and C(23). Furthermore, a substantial 3-bond coupling was observed between the equatorial H at C(19) and C(21).



Scheme 3.5.4 Cyclization of 7-membered acetal-derived enone substrate.

3.6.1 Synthesis of a Homologated C Ring Synthon

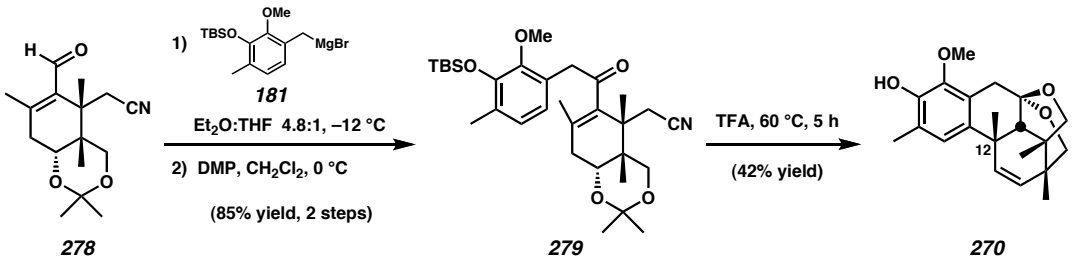
Concomitant with our investigations of the 7-membered acetal C ring, we were also exploring further functionalization of the 6-membered acetonide substrate. Our first goal in this system was to homologate the primary alcohol by one carbon. Although alcohol **260** could be readily oxidized to the corresponding aldehyde, we were unable to homologate this position using the methoxy methylene Wittig reagent.[21] Thus, we chose to hydrogenate the double bond (**272**), activate the primary alcohol by mesylation, and conduct a KCN displacement to form nitrile **273** (Scheme 3.6.1). Given the challenging nature of S_N2 chemistry at neopentyl centers,[22] we were delighted to observe good yields over the homologation sequence. Desilylation was accomplished upon treatment with TBAF in THF at 40 °C to reveal a secondary alcohol, which was quantitatively converted to ketone **273** under Swern oxidation conditions. Ketone α-methylation again resulted in formation of significant amounts of bis-methylation products. Presumably, the first methylation occurs with good selectivity for the equatorial product, owing to the bicyclic nature and conformational rigidity of the system. Thus, the remaining proton is likely the more acidic axial proton. We found it highly challenging to overcome the preference for the double methylation product. Ultimately, we found that reverse dropwise addition of the enolate solution into methyl iodide at –35 °C allowed formation of the mono-methyl product as the major product. In order to obtain this selectivity, the reaction was quenched before it reached complete conversion, and starting material was readily re-isolated. In the event, the desired methyl ketone **275** was obtained in 78% yield with 10% yield of recovered ketone **274** and only 5% over-alkylation. Methyl ketone **275** was then enolized and trapped with Tf_2NPh to give enol triflate **276** in 97% yield. Stille coupling with vinyl tributylstannane proceeded smoothly and was followed by oxidative cleavage of the terminal olefin to provide enal **278** in good yield for the two steps.



Scheme 3.6.1 Synthesis of a homologated C ring synthon.

3.6.2 Acid-Mediated Cyclizations of the Homologated A–C Ring System

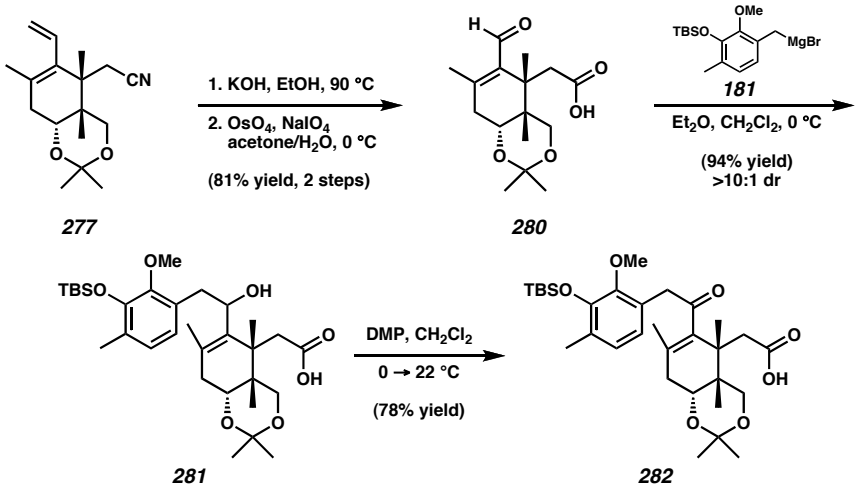
With our homologated C ring synthon in hand, we were excited to investigate the cyclization of the corresponding fragment-coupled product. We anticipated that the nitrile functionality in this substrate would prevent acetal formation in our enone cyclization. Addition of Grignard **181** occurred smoothly in a mixture of Et_2O and THF to afford a 4.8:1 ratio of diastereomers (Scheme 3.6.2). This mixture was oxidized to enone **279** in 85% yield over the two steps. Much to our surprise, treatment of **279** with neat TFA again led to acetal **270** in 42% yield. The loss of the nitrile functionality was unexpected,[23] and a mechanism for this transformation will be discussed in Section 3.8.1.



Scheme 3.6.2 Fragment coupling and cyclization of the nitrile-derived A–C system.

3.7.1 Modification of the Homologated A–C Ring System.

In order to access a system more similar to **183** (Scheme 2.2.4), nitrile **277** was hydrolyzed to the corresponding acid and oxidatively cleaved the terminal olefin to provide enal **280** (Scheme 3.7.1). Addition of Grignard **181** to a solution of enal **280** in Et_2O and CH_2Cl_2 provided allylic alcohol **281** in 94% yield and > 10:1 diastereomeric ratio.[24] The allylic alcohol could then be oxidized readily to provide enone **282**.

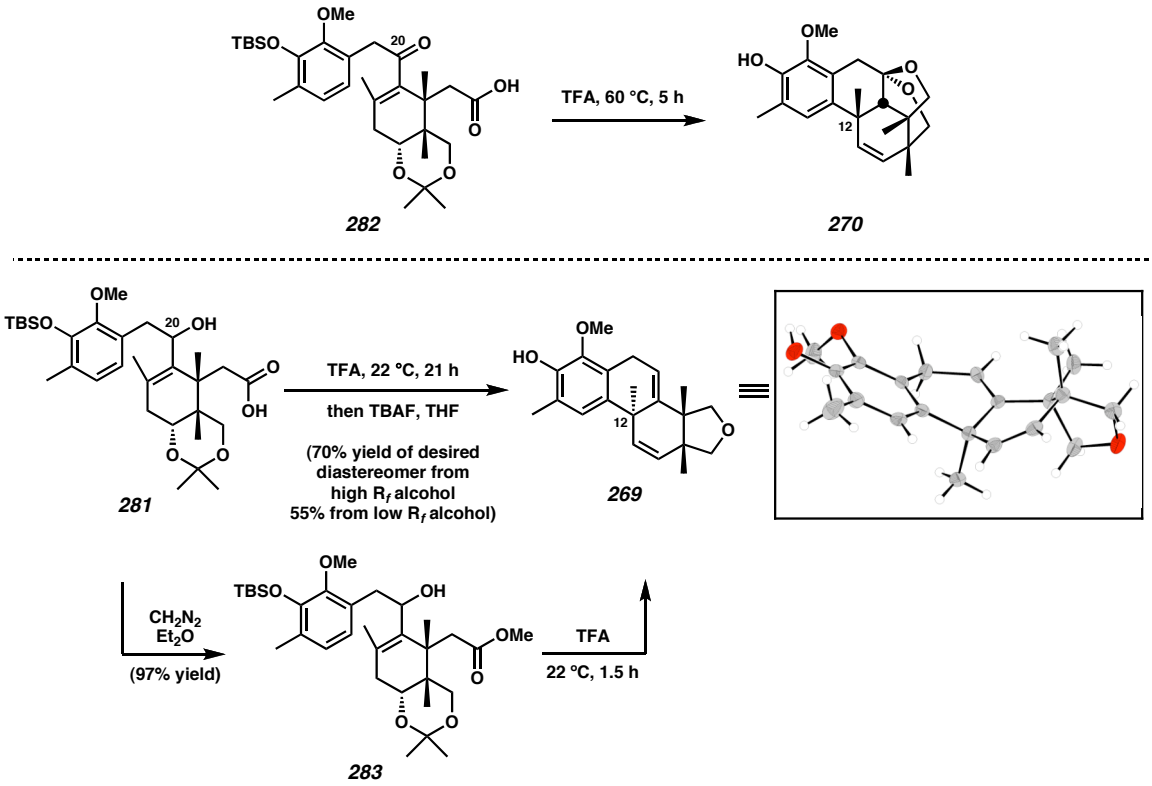


Scheme 3.7.1 Synthesis of an acid-derived A–C ring system.

3.7.2 Acid-Mediated Cyclizations of Carboxylic Acid-Derived A–C Ring Systems

Cyclization precursors **281** and **282** held great promise for the acid-mediated cyclization because they represented the most similar substrates prepared to date when compared with our successful acid-cyclization system. Specifically, they possessed a homologated acid functionality on the C ring, as was present in allylic alcohol **183**.[13] Upon subjecting enone **282** to neat TFA, we were astounded to find that we had again formed acetal (**270**, Scheme 3.7.2). The repeated formation of this compound from significantly different substrates was perplexing. We were excited, however, about the prospects for allylic alcohol **281**, which was not expected to form such an acetal given the lower oxidation state at C(20). Indeed, upon treatment with neat TFA, now at ambient

temperature instead of 55–65 °C we observed the formation of a new compound displaying the desired relative stereochemistry at C(12). Unfortunately, upon examination of the ^{13}C NMR and IR spectra, we found that there were no signals corresponding to the carboxylic acid or lactone functionalities that we would have anticipated. Thus, we assigned the observed product as **269**. X-Ray diffraction data obtained from a single crystal confirmed both the desired relative stereochemistry and our assignment of the fourth ring as a tetrahydrofuran-type ring.

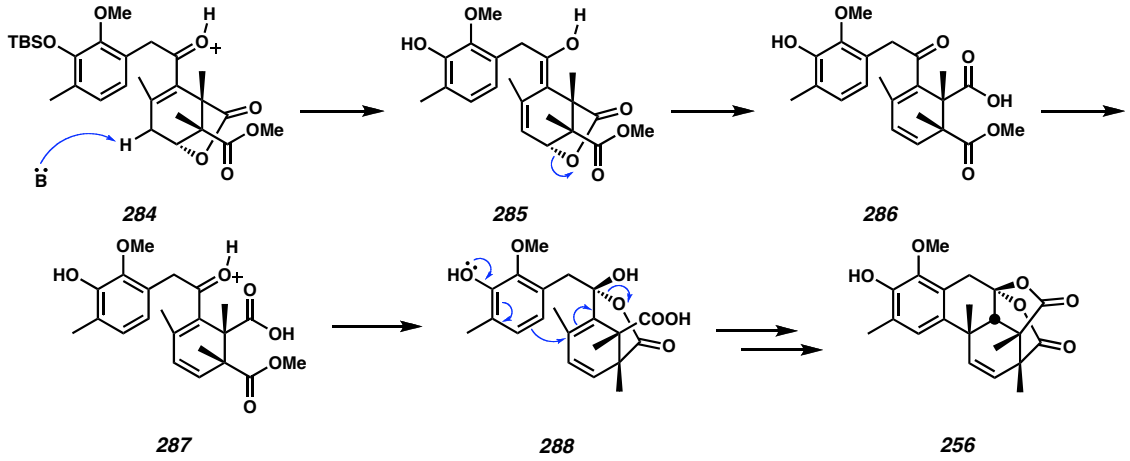


Scheme 3.7.2 Cyclization of carboxylic acid-derived tethered A–C ring systems.

3.8.1 Mechanistic Hypotheses

Before discussing general mechanistic insights, we outline the proposed mechanism and potential interactions governing the stereoselectivity for each substrate type employed in the acid-mediated cyclization. In the lactone-derived C ring system, enone **255** (Scheme 3.3.3) may be activated by protonation, providing extended enol **285**

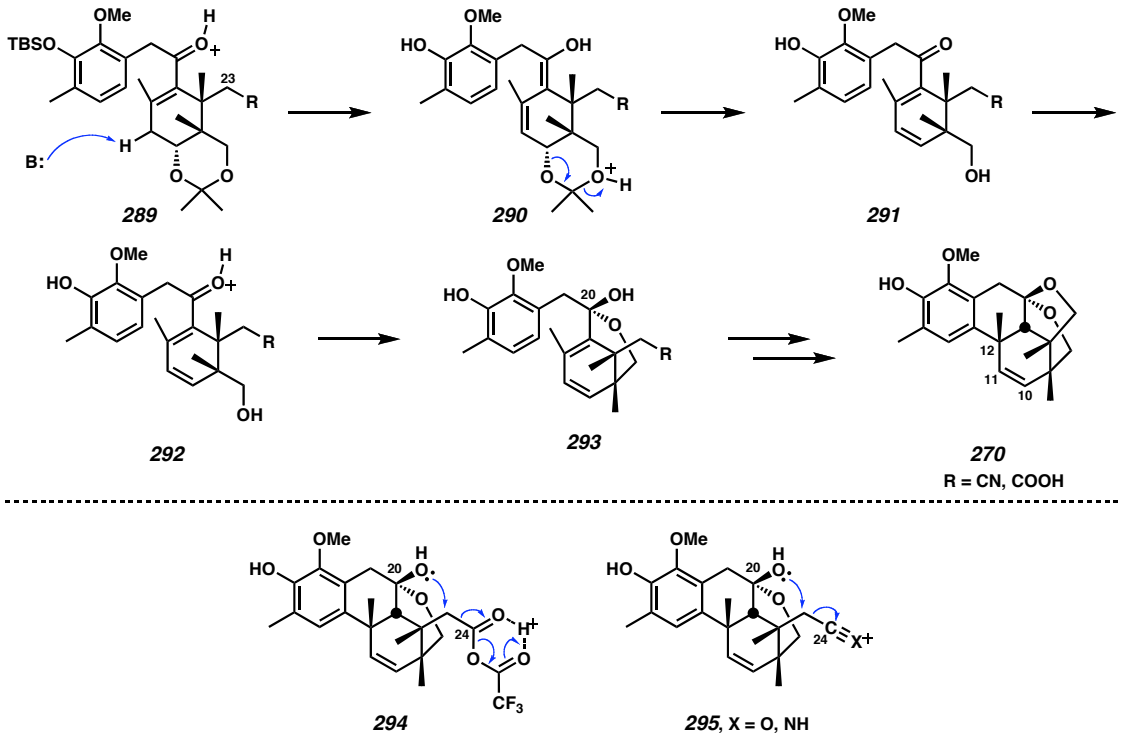
(Scheme 3.8.1). Regeneration of the enone and elimination of the lactone moiety would give carboxylic acid **286**. Subsequent enone protonation leads to resonance-stabilized cation **287**. Formation of hemi-acetal **288** leaves only the concave face of the olefin available for nucleophilic attack by the electron-rich A ring, thus yielding bis-lactone **256** after tautomerization and condensation.



Scheme 3.8.1 Proposed mechanism for formation of bis-lactone **256**.

Cyclization of the enone versions of the 7-membered ring acetal (**266**), nitrile (**279**), and carboxylic acid (**282**) substrates led to the formation of acetal **270** (Scheme 3.8.2). In the latter two cases, we were surprised to observe loss of C(24). We propose that these substrates begin with a mechanism similar to that described above, wherein enone activation leads to deprotonation of **289** to form **290**. Subsequent reformation of the ketone again leads to elimination of the alcohol functionality at C(10) and formation of a C(10)–C(11) olefin. Protonation leads to a similar resonance stabilized cation **292**, which proceeds through hemiacetal **293**, ultimately providing acetal **270**. Attack by the A ring will occur from the concave face of hemiacetal **293** because the convex face is inaccessible. Intermediates **294** and **295** represent two potential mechanisms by which C(24) could be lost. In the case of the acid-derived substrate (**282**), a bifurcated hydrogen bond could be formed (**294**), which would activate C(23) for attack by the

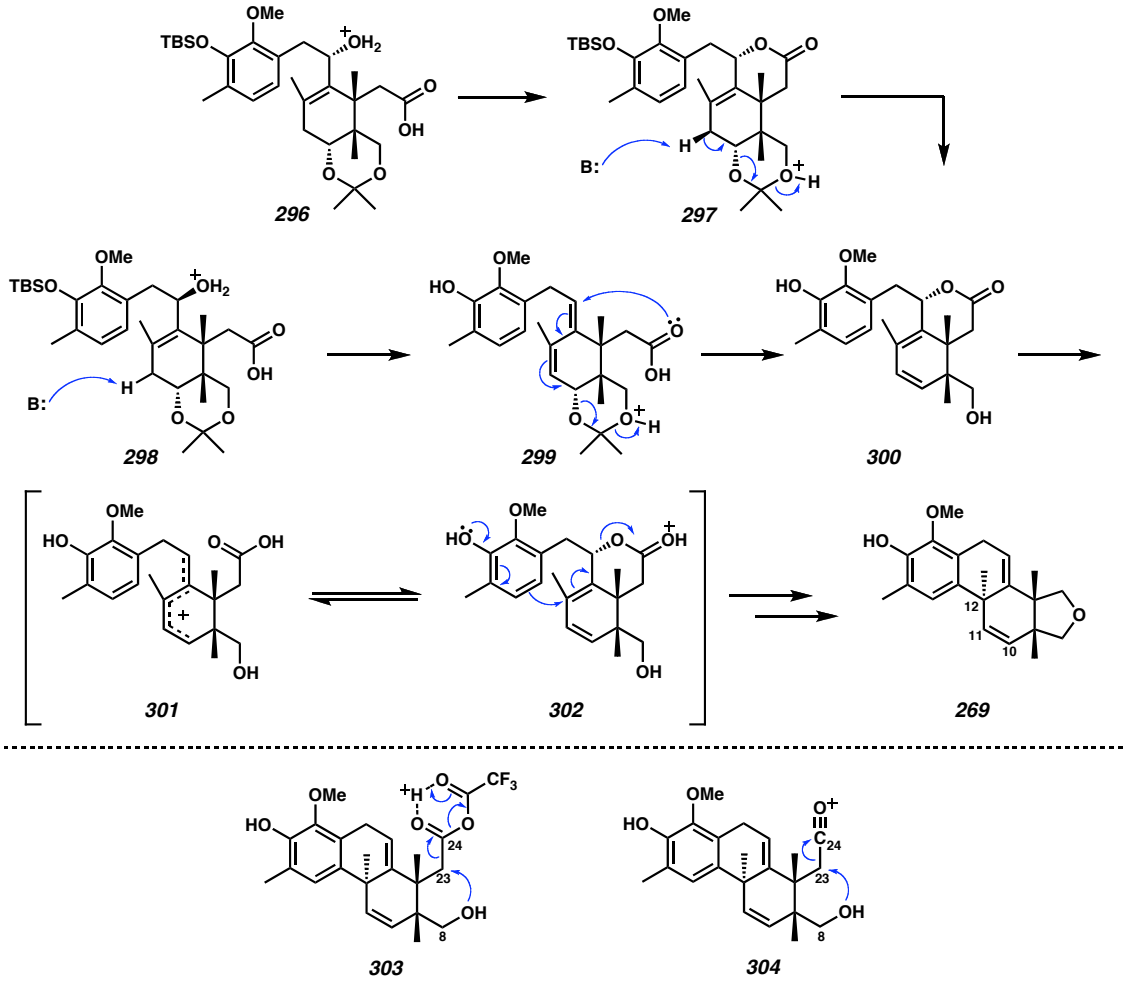
C(20) hemi-acetal. Concomitant liberation of CO and loss of TFA would provide the observed acetal. Alternatively, intermediate **294** could eliminate TFA directly to form acylium **295**. Attack by the C(20) hemi-acetal would then afford acetal **270**. Either of these intermediates could be accessed upon hydrolysis of the nitrile to form a carboxylic acid. Alternatively, protonation of the nitrile on N would form a nitrilium, resulting in elimination to form HCN and the acetal product.



Scheme 3.8.2 Proposed mechanism for formation of acetal **270**.

For allylic alcohol substrate **281**, the α-diastereomer likely forms lactone **297** very quickly (Scheme 3.8.3). Subsequent elimination of the C(10) acetal would then result in intermediate **300**. The β-diastereomer could undergo dehydration, forming diene **299**. Carboxylic acid attack would then lead to lactone **300**. Protonation of the lactone carbonyl would induce an equilibrium between highly stabilized carbocation **301** and **302**. We anticipate that protonated lactone **300** is the intermediate that actually undergoes cyclization, given the extraordinary selectivity observed for this system.

Furthermore, the stability of this intermediate likely aids in the formation of the product in the relatively high yields observed. Once again, we were surprised to observe loss of the C(24) carbonyl during the cyclization. We believe that the cyclization occurs much more quickly than the C(23)–C(24) bond cleavage. Thus, we propose similar intermediates to those described above, with the exception that it is the C(8) alcohol that attacks activated anhydride **303** or acylium **304** to release CO and form tetrahydrofuran-type product **269**.



Scheme 3.8.3 Proposed mechanism for formation of tetracycle **269**.

3.8.2 Mechanistic Summary and Substrate Requirements

Taken together, these results provide a general outline for the development of new substrates for future investigations. In all cases where cyclized products were observed from an enone precursor, elimination of the C(10) alcohol occurred. We hypothesize that the elimination to form the C(10)–C(11) olefin stabilized the developing carbocation and lowered the energy of the transition state sufficiently to allow cyclization. Additionally, these substrates led to the formation of an acetal at C(20). The equilibrium between the ketone and the acetal states may be sufficiently deactivating to slow cyclization until the C(10)–C(11) olefin is formed. The structural rigidity of the system is such that the equilibrium between the acetal and ketone intermediates likely predisposes these substrates toward formation of the undesired stereochemistry at C(12). In all of the enone substrates, protonation occurs from the β face, leading to *syn* stereochemistry at the newly formed stereocenters. In fact, the desired stereochemistry at C(12) has only been observed for substrates possessing an allylic alcohol as the electrophile. The highest selectivities and yields are observed for substrates where the alcohol is already in the α orientation (as depicted), allowing direct anti-periplanar attack via an S_N2'-type pathway. Additionally, the presence of a tethered carboxylic acid substantially improves both the selectivity and the yield of the cyclization. In the best case, the key directing lactone may be formed without initial loss of water, thus preventing decomposition pathways that may occur during intermediate steps.

Thus, any future substrates should display the following design elements. First, the electrophilic component of the substrate should be a secondary allylic alcohol, preferably with an α-disposed alcohol (Figure 3.8.1). The substrate should incorporate a carboxylic acid group pendant from the C(22) quaternary center. It may be necessary to have already installed C(23) before the cyclization, although it remains unclear at this point whether γ-lactone formation is required or whether a δ-lactone would direct the

cyclization equally well. If C(24) is present in the substrate, the R group at the C(9) quaternary center should not contain a nucleophilic moiety that can induce expulsion of CO from the carboxylic acid moiety. Furthermore, both C(8) and C(23) cannot be in the alcohol oxidation state, or a furan will be formed. Finally, in order to avoid excessive late-stage reinstallation of oxygenation, C(10) should be in the ketone oxidation state. In this way, the more activated intermediates with C(10)-C(11) olefination can be accessed (in the form of the enol tautomer) without loss of oxygenation.

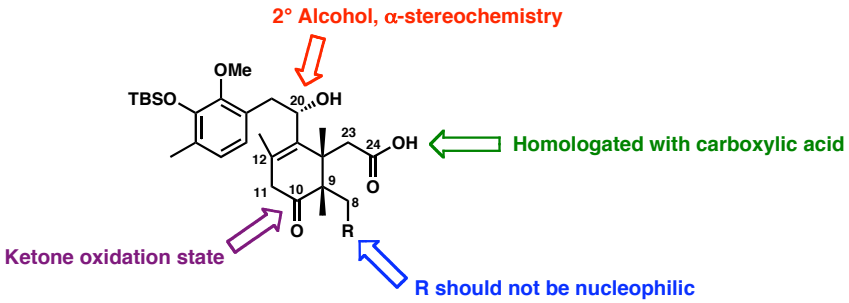


Figure 3.8.1 Requirements for future acid cyclization substrates.

3.9.1 Summary of Brønsted Acid Cyclization Efforts.

In summary, we have synthesized and tested a host of different cyclization precursors for the acid-mediated cyclization of tethered A–C ring systems to form the carbocyclic core of zoanthenol. Despite the harsh nature of this system, we have been able to access highly complex systems in very good yields when the multi-step nature of the reaction is considered. For example, in the case of allylic alcohol **281**, a desilylation, alcohol/lactone elimination, acetone elimination, and CO elimination all occur in addition to the cyclization. In total, 6 reactions occur in one reaction flask, with one reagent, to form the desired diastereomer of a tetracyclic compound possessing three all-carbon quaternary centers in 70% yield (corresponding to an average 94% yield per reaction). Clearly, this method has presented a number of challenges. However, the

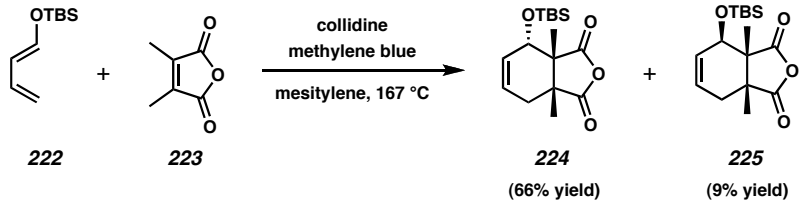
range of substrates that we have employed has helped us to develop a detailed grasp of the requirements of the system. Thus, we remain confident that this method is the most powerful of our current methods to form the C(12) quaternary center from a tethered A–C ring system.

3.10.1 Materials and Methods

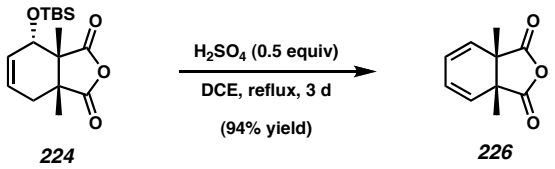
Unless otherwise stated, reactions were performed at ambient temperature (typically 19–24 °C) in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. HMPA, TEA, DIPA, and pyridine were freshly distilled from CaH_2. KHMDS (95%) was purchased from Aldrich and stored in a glovebox until use. Trifluoroacetic acid (99%) was purchased from Aldrich. LiCl was flame-dried under vacuum prior to use. Magnesium turnings were of 99.98% purity and purchased from Aldrich. TBSCl was purchased from Gelest. TBSOTf was freshly prepared as described by Corey.[25] All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad

singlet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Crystallographic analyses were performed at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, from the CCDC by quoting the publication citation and the deposition number (see Appendix B for deposition numbers).

3.10.2 Preparation of Compounds

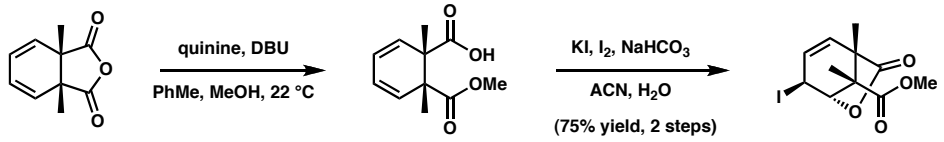


***Endo*-Diels-Alder Adduct 224 and *Exo*-Diels-Alder Adduct 225.** A mixture of diene **222** (67.3 g, 367.2 mmol, 1.00 equiv), 2,3-dimethylmaleic anhydride (**223**, 46.3 g, 367.2 mmol, 1.00 equiv), collidine (2.91 mL, 22.0 mmol, 0.06 equiv), methylene blue (68.0 mg, 0.213 mmol, 0.000579 equiv), and 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 **224** (75.7 g, 66% yield) which solidified on standing: R_f 0.42 (15% EtOAc in hexanes) and *exo*-Diels-Alder adduct **225** (10.5 g, 9% yield) as an amorphous solid: R_f 0.58 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (m, 1H), 5.99 (m, 1H), 4.35 (d, J = 5.5 Hz, 1H), 2.61 (dd, J = 6.3, 16.3 Hz, 1H), 2.42 (app. dt, J = 3.3, 16.5 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 175.1, 132.2, 129.8, 69.1, 53.8, 46.5, 34.2, 25.6, 21.6, 18.0, 17.6, −4.4, −5.2; IR (Neat film NaCl) 2952, 2930, 1774, 1250, 986, 1091, 986, 958, 914, 838, 778 cm^{-1}; HRMS (FAB+) $[M+H]^+$ m/z calc'd for $[C_{16}H_{26}SiO_4+H]^+$: 311.1679, found 311.1671.



224 *226*

Diene 226. To a solution of *endo*-Diels-Alder adduct **224** (19.0 g, 61.4 mmol, 1.0 equiv) in DCE (614 mL) was added H_2SO_4 (1.71 mL, 30.7 mmol, 0.50 equiv) and the resulting solution was refluxed for 3 d. Upon cooling the reaction mixture was washed with sat. aq. $NaHCO_3$ (2 x 300 mL) [*Caution: gas evolution!*] and extracted with CH_2Cl_2 (2 x 120 mL). The combined organics from two such reactions were concentrated to give an oil and purified by flash chromatography on silica gel (1 to 10% EtOAc in hexanes) to give diene **226** (20.7 g, 94% yield) as a white solid: mp 61.5–62.5 °C; R_f 0.33 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18–6.13 (m, 2H), 5.66–5.61 (m, 2H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 126.3, 124.5, 49.9, 18.6; IR (Neat film NaCl) 2984, 2940, 2848, 1856, 1785, 1233, 1196, 962, 912 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{16}H_{26}SiO_4+H]^+$: 311.1679, found 311.1671.

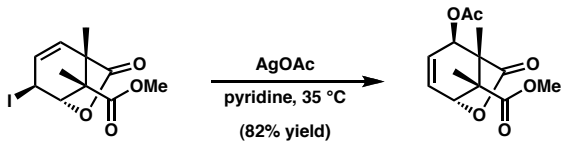


226 *242* *247*

Iodolactone 247. To a solution of diene **226** (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 (39.1mL, 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 **242** solidified and was typically used immediately in the next step without purification: R_f 0.19 (30% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80–5.45 (m, 4H), 3.66 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz,

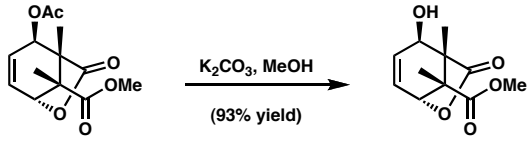
$CDCl_3$) δ 180.5, 175.1, 131.6, 131.5, 121.9, 121.8, 52.1, 48.4, 48.1, 20.2 (2C); IR (Neat film NaCl) 2985, 2954, 1731, 1700, 1258, 1240, 1132, 1102, 702 cm^{-1}; HRMS (EI) $[M]^+$ *m/z* calc'd for $[C_{11}H_{14}O_4]^+$: 210.0892, found 210.0898; $[\alpha]_D^{26}$ –10.94 (c 1.03, $CHCl_3$, 50% ee) from reaction with stoichiometric quinine. HPLC analysis (Chirapak AD 4.6 x 25 mm, 5.0% IPA in 95% hexane with 0.1% TFA, 1.0 mL/min, λ = 254 nm) of the asymmetric reaction performed with a catalytic amount of menthol derivative **246** showed carboxylic acid **242** to be of 85% ee (t_{fast} = 10.11 min, major; t_{slow} = 12.13 min, minor).

The above residue containing carboxylic acid **242** (theoretical yield: 96.6 mmol, 1.00 equiv) was dissolved in ACN (380 mL) and H_2O (380 mL) and treated with $NaHCO_3$ (24.3 g, 290 mmol, 3.00 equiv), KI (43.3 g, 261 mmol, 2.70 equiv), and I_2 (66.2 g, 261 mmol, 2.70 equiv) and the flask was wrapped in foil to exclude light. After 10 h, the reaction mixture was quenched in the dark with sat. aq. $Na_2S_2O_3$ until colorless, diluted with EtOAc (650 mL), extracted with EtOAc (2 x 300 mL), washed with brine (200 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to provide iodolactone **247** (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); ^1H NMR (300 MHz, C_6D_6) δ 5.33 (ddd, *J* = 1.5, 3.0, 9.3 Hz, 1H), 4.86 (dd, *J* = 1.5, 9.3 Hz, 1H), 4.63 (app. t, *J* = 2.1 Hz, 1H), 4.29 (m, 1H), 3.13 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 175.3, 173.0, 133.0, 130.1, 80.4, 53.6, 52.5, 47.0, 16.9, 16.0, 15.0; IR (Neat film NaCl) 2953, 1795, 1732, 1450, 1293, 1247, 1141, 1107, 1062, 969 cm^{-1}; HRMS (EI) $[M]^+$ *m/z* calc'd for $[C_{11}H_{14}O_4I]^+$: 336.9937, found 336.9930.



247 *247a*

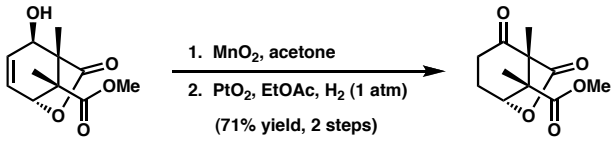
Allylic Acetate 247a. To a solution of iodolactone **247** (23.0 g, 68.5 mmol, 1.00 equiv) in pyridine (140 mL) was added AgOAc (34.3 g, 206 mmol, 3.00 equiv). The reaction mixture was wrapped in foil to exclude light and heated to 35 °C. After 3.5 d, the reaction mixture was concentrated (~ 5 torr at 50 °C), diluted with H_2O (500 mL) and CH_2Cl_2 (300 mL), and extracted with CH_2Cl_2 (7 x 150 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography on silica gel (15 to 35% EtOAc in hexanes) to provide allylic acetate **247a** (15.2 g, 82% yield) as an oil: R_f 0.57 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddd, J = 1.0, 5.6, 9.1 Hz, 1H), 5.98 (ddd, J = 1.0, 3.5, 9.0 Hz, 1H), 5.35 (dd, J = 1.5, 3.5 Hz, 1H), 4.85 (dd, J = 1.0, 6.0 Hz, 1H), 3.75 (s, 3H), 2.11 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 173.0, 169.6, 131.1, 129.5, 76.8, 69.9, 54.7, 52.7, 50.0, 20.7, 15.6, 13.6; IR (Neat film NaCl) 2986, 2953, 1788, 1735, 1373, 1257, 1219, 1024, 962 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{13}H_{16}O_6+H]^+$: 269.1025, found 269.1014.



247a *248*

Allylic Alcohol 211. To a solution of allylic acetate **210** (15.2 g, 56.2, 1.00 equiv) in MeOH (275 mL) was added K_2CO_3 (1.55 g, 11.3 mmol, 0.20 equiv) and the reaction was vigorously stirred. After 10 min, TLC analysis indicated consumption of the starting material, and the reaction mixture was quenched with H_2O (200 mL), brine (300 mL), and CH_2Cl_2 (200 mL). The pH of the aqueous layer was adjusted to pH 7 with 3 M HCl

(~ 8 mL) [*Caution: gas evolution!*] and extracted with CH_2Cl_2 (10 x 50 mL). The combined organics were washed with brine (100 mL), concentrated, and purified by flash chromatography on silica gel (25 to 35% EtOAc in hexanes) to provide allylic alcohol **211** (11.9 g, 93% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from Et_2O/heptanes at ambient temperature: mp 94.5–95.5 °C (Et_2O/heptane); R_f 0.38 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (ddd, J = 1.5, 5.8, 9.3 Hz, 1H), 6.04 (ddd, J = 1.0, 3.3, 9.3 Hz, 1H), 4.79 (dd, J = 1.0, 5.5 Hz, 1H), 4.15 (dd, J = 1.0, 3.5 Hz, 1H), 3.72 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 173.6, 134.8, 127.3, 77.4, 69.8, 54.7, 52.6, 50.8, 15.5, 13.7; IR (Neat film NaCl) 3484, 2954, 1773, 1731, 1454, 1259, 1137, 1110, 1049, 1031, 983, 955 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{11}H_{14}O_5+H]^+$: 227.0919, found 227.0924.

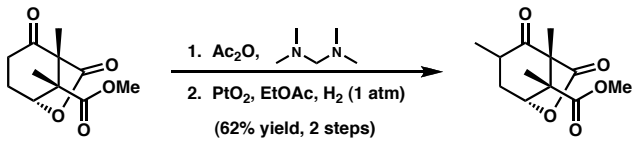


248 *249*

Ketone 249. To a solution of allylic alcohol **248** (2.23 g, 9.86 mmol, 1.00 equiv) in acetone (100 mL) was added activated MnO_2 (17.1 g, 197 mmol, 20.0 equiv) and the reaction mixture was stirred at ambient temperature for 1.25 h. The reaction mixture was filtered, washed with acetone, and concentrated to an oil.

To a solution of this crude material in EtOAc (60 mL) was added PtO_2 (67.1 mg, 0.296 mmol, 0.03 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 1.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (30 to 50% EtOAc in hexanes) to provide ketone **249** (1.59 g, 71% yield) as an amorphous solid: R_f 0.38 (50% EtOAc in hexanes); ^{1}H NMR (300

MHz, $CDCl_3$) δ 4.89 (dd, *J* = 1.2, 3.9 Hz, 1H), 3.75 (s, 3H), 2.62–2.56 (m, 2H), 2.47–2.37 (m, 1H), 2.15–2.01 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 173.4, 171.3, 79.4, 62.4, 56.5, 53.0, 33.9, 24.9, 14.3, 9.3; IR (Neat film NaCl) 2989, 2955, 1790, 1732, 1343, 1267, 1227, 1152, 1089, 1018, 966 cm^{-1}; HRMS (EI) $[M]^+$ *m/z* calc'd for $[C_{11}H_{14}O_5]^+$: 226.0841, found 226.0847.

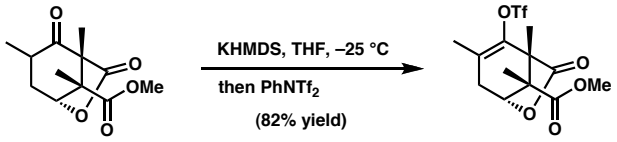


249 ***250***

Methyl ketone 250. To a cooled (15 °C) solution of ketone **249** (1.31 g, 5.77 mmol, 1.00 equiv) and Ac_2O (6.55 mL, 69.3 mmol, 12.0 equiv) was added *N*,*N*,*N*',*N*'-tetramethyldiaminomethane (4.73 mL, 34.6 mmol, 6.00 equiv) in a dropwise manner over 30 min. At the end of the addition, the reaction was allowed to come to ambient temperature. After 4 h, additional Ac_2O (6.00 mL, 63.5 mmol, 11.0 equiv) and *N*,*N*,*N*',*N*'-tetramethyldiaminomethane (7.00 mL, 51.3 mmol, 8.89 equiv) were added and the reaction was warmed to 32 °C for 12 h. The reaction mixture was then cooled, concentrated in vacuo, quenched into water (40 mL), sat. aq. $NaHCO_3$ (20 mL), and ice (40 g), and extracted with CH_2Cl_2 (4 x 40 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude solid which was used immediately in the next step.

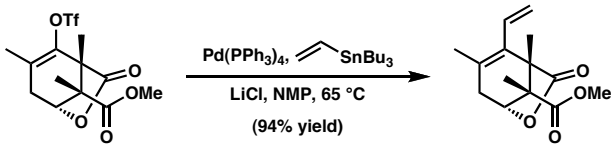
To a solution of the crude material in EtOAc (100 mL) was added PtO_2 (131 mg, 0.577 mmol, 0.10 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 5.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (20 to 40% EtOAc in hexanes) to provide a single diastereomer of methyl ketone **250** (854 mg, 62% yield) as an amorphous solid: R_f 0.57, 0.29 (50% EtOAc in

hexanes, 50% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, $CDCl_3$) δ 4.87 (m, 1H), 3.75 (s, 3H), 2.75–2.56 (m, 2H), 1.82–1.66 (m, 1H), 1.27 (s, 3H), 1.14 (d, J = 6.3 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 174.1, 171.3, 79.4, 62.0, 57.3, 53.0, 38.9, 34.0, 14.7, 13.9, 9.6; IR (Neat film NaCl) 2987, 2954, 1788, 1726, 1259, 1154, 1077, 1038 cm^{-1}; HRMS (EI) $[M]^+$ m/z calc'd for $[C_{12}H_{16}O_5]^+$: 240.0998, found 240.0996.



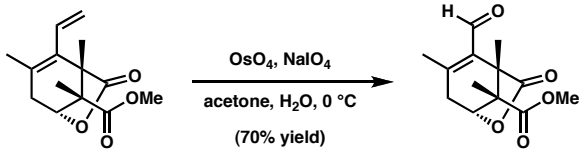
250 ***251***

Triflate 251. To a cooled (–25 °C) solution of KHMDS (339 mg, 1.70 mmol, 1.20 equiv) in THF (12 mL) was added methyl ketone **250** (340 mg, 1.42 mmol, 1.00 equiv) in THF (10 mL) in a dropwise manner over 10 min. After 1.5 h at –25 °C, $PhNTf_2$ (708 mg, 1.98 mmol, 1.40 equiv) in THF (5 mL) was added, and the reaction was maintained for an additional 30 min at –25°C. The reaction mixture quenched into half-saturated brine (40 mL) and EtOAc (40 mL), and extracted with EtOAc (4 x 15 mL). The combined organics were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 40% EtOAc in hexanes) to provide triflate **251** (435 mg, 82% yield) as an oil: R_f 0.20 (50% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (app. t, J = 2.7 Hz, 1H), 3.75 (s, 3H), 2.63–2.47 (m, 2H), 1.86 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 172.1, 138.2, 128.2, 118.4 (app. d, $J_{C\text{-}F}$ = 319 Hz), 77.2, 54.6, 53.0, 50.4, 35.0, 17.2, 12.6, 10.0; IR (Neat film NaCl) 2956, 1790, 1727, 1408, 1208, 1138, 824 cm^{-1}; HRMS (EI) $[M+H]^+$ m/z calc'd for $[C_{13}H_{15}O_7F_3S+H]^+$: 373.0569, found 373.0550.



251 *251a*

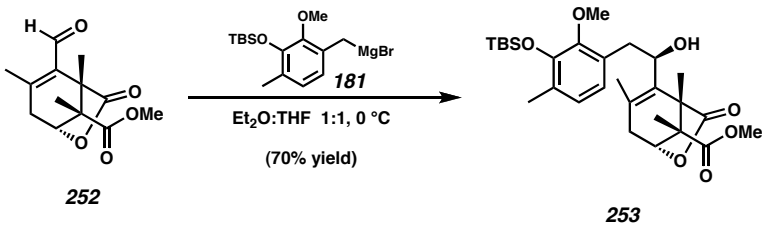
Diene 251a. To a solution of triflate **251** (865 mg, 2.32 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (134.2 mg, 0.116 mmol, 0.05 equiv), and LiCl (295 mg, 6.97 mmol, 3.00 equiv) in NMP (18 mL) was added tributyl(vinyl)tin (1.02 mL, 3.48 equiv, 1.50 equiv), and the mixture was heated to 65 °C for 9.5 h. The reaction mixture was cooled to ambient temperature, quenched with H_2O (50 mL) and Et_2O (50 mL), and extracted with Et_2O (5 x 30 mL). The combined organics were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (5 to 25% EtOAc in hexanes) to provide diene **251a** (545 mg, 94% yield) as an oil: R_f 0.63, 0.80 (50% Et_2O in hexanes developed thrice, 50% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (ddd, J = 1.2, 11.3, 17.6 Hz, 1H), 5.34 (dd, J = 2.0, 11.3 Hz, 1H), 5.02 (dd, J = 2.3, 17.6 Hz, 1H), 4.53 (app. t, J = 2.7 Hz, 1H), 3.70 (s, 3H), 2.37 (s, 2H), 1.72 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ□176.7, 173.7, 132.3, 131.5, 130.2, 120.6, 77.7, 53.6, 52.5, 49.3, 35.3, 20.0, 12.9, 12.5; IR (Neat film NaCl) 2985, 2951, 2911, 1782, 1730, 1267, 1198, 1144, 1089, 1035, 972 cm^{-1}; HRMS (EI) $[M]^+$ *m/z* calc'd for $[C_{14}H_{18}O_4]^+$: 250.1205, found 250.1204.



251a *252*

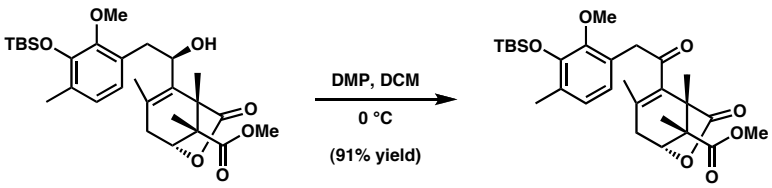
Enal 252. To a cooled (0 °C) solution of diene **251a** (271 mg, 1.08 mmol, 1.00 equiv) in acetone (8.00 mL) and H_2O (8.00 mL) was added OsO_4 (27.5 mg, 0.108 mmol, 0.10 equiv) and $NaIO_4$ (511 mg, 2.38 mmol, 2.20 equiv). After 8.5 h at 0°C, the reaction

mixture was quenched with brine (30 mL) and EtOAc (30 mL), and extracted with EtOAc (5 x 30 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (25 to 50% EtOAc in hexanes) to provide enal **252** (191 mg, 70% yield) as a solid: R_f 0.48 (50% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 4.54 (app. t, J = 2.4 Hz, 1H), 3.72 (s, 3H), 2.57 (d, J = 1.8 Hz, 2H), 2.07 (s, 3H), 1.49 (s, 2H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 176.0, 172.8, 151.0, 131.6, 76.7, 53.9, 52.7, 48.2, 37.5, 19.2, 12.5, 12.3; IR (Neat film NaCl) 2952, 1786, 1729, 1681, 1333, 1273, 1250, 1201, 1136, 1082, 1034, 969 cm^{-1}; HRMS (EI) $[M]^+$ *m/z* calc'd for $[C_{13}H_{16}O_5]^+$: 252.0998, found 252.0984.



Allylic alcohol 252. A flame-dried two-neck round bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (1.03 g, 42.4 mmol, 32.4 equiv) and Et_2O (12 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (150 μL, 1.74 mmol, 1.33 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (677 mg, 1.96 mmol, 1.50 equiv) in Et_2O (7.0 mL) was added in a dropwise manner over 30 min and heating was continued for an additional 30 min. The Grignard reagent was then cooled (0 °C) and added to a cooled (0 °C) solution of enal **252** (330 mg, 1.31 mmol, 1.00 equiv) in Et_2O (10 mL) and THF (30 mL). After 1 h at 0 °C, the reaction mixture was allowed to come to ambient temperature, and after an additional 30 min, the reaction was quenched with ice-cold H_2O (50 mL), 2 M HCl (2.0 mL), and

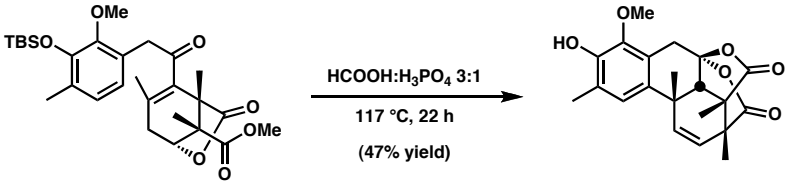
Et_2O (20 mL), and extracted with Et_2O (4 x 40 mL). The combined organics were washed with brine (2 x 30 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 50% EtOAc in hexanes) to give allylic alcohol **253** (477 mg, 70% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from EtOAc/heptanes at ambient temperature: mp 154–155 °C (EtOAc/heptane); R_f 0.50 (35% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 7.7 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 4.75 (bs, 1H), 4.52 (app. t, J = 2.6 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.00–2.80 (m, 2H), 2.76–2.54 (bs, 1H), 2.36 (m, 2H), 2.20 (s, 3H), 1.78 (s, 3H), 1.50 (s, 3H), 1.29 (s, 3H), 1.02 (s, 9H), 0.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 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]$^+$ m/z calc'd for [$C_{28}H_{42}SiO_7$+Na]$^+$: 541.2598, found 541.2571.



253 *255*

Enone 255. To a cooled (0 °C) solution of allylic alcohol **253** (129 mg, 0.248 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (210 mg, 0.496 mmol, 2.00 equiv) and the resulting mixture was stirred for 1 h. The reaction mixture was diluted with Et_2O (75 mL), filtered, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (15 to 40% EtOAc in hexanes) to give enone **255** (117 mg, 91% yield) as a foam: R_f 0.57 (35% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 4.61 (app. t,

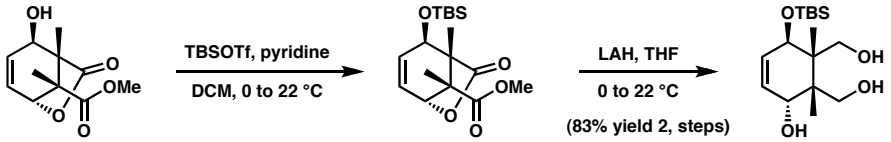
J = 2.4 Hz, 1H), 3.94 (d, *J* = 17.7 Hz, 1H), 3.76 (d, *J* = 17.7 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.46 (dd, *J* = 2.7, 18.9 Hz, 1H), 2.35 (dd, *J* = 1.5, 18.9 Hz, 1H), 2.20 (s, 3H), 1.66 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.02 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 176.2, 173.1, 150.0, 146.9, 135.4, 130.6, 130.0, 125.7, 124.4, 123.3, 77.8, 59.8, 53.5, 52.7, 47.8, 46.2, 34.3, 26.0, 18.8, 18.4, 17.0, 12.5, 11.7, –4.3; IR (Neat film NaCl) 2953, 2930, 2858, 1785, 1732, 1463, 1421, 1286, 1252, 1236, 840 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{28}H_{40}SiO_7+H]^+$: 517.2622, found 517.2631.



255 ***256***

Bisacetoxyacetal 256. A solution of enone **255** (58.5 mg, 0.113 mmol, 1.00 equiv) in formic acid (2.40 mL) and 85% H_3PO_4 (800 μL) was fitted with a reflux condenser and heated at 117 °C for 22 h. The reaction mixture was cooled to ambient temperature, diluted with ice cold H_2O (60 mL) and extracted with Et_2O (5 x 15 mL). The combined organics were dried ($MgSO_4$) and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 40% EtOAc in hexanes) to give bisacetoxyacetal **256** (19.6 mg, 47% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from Et_2O/hexanes at ambient temperature: mp 185–190 °C decomp. (Et_2O/hexanes); R_f 0.32 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.14 (dd, *J* = 0.9, 9.3 Hz, 1H), 5.62 (bs, 1H), 5.42 (d, *J* = 9.3 Hz, 1H), 3.77 (s, 3H), 3.61 (d, *J* = 15.9 Hz, 1H), 3.02 (dd, *J* = 0.9, 15.9 Hz, 1H), 2.48 (s, 1H), 2.52 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 169.5, 145.9, 144.4, 137.4, 130.8, 126.0, 124.9, 124.7, 121.8, 105.7, 60.9, 53.0, 45.9, 38.0, 32.2, 31.5, 16.3,

16.2, 15.8; IR (Neat film NaCl) 3468, 2978, 2942, 1801, 1757, 1360, 1213, 1057, 937, 914, 732 cm^{-1}; HRMS (EI) $[M]^+$ *m/z* calc'd for $[C_{21}H_{22}O_6]^+$: 370.1416, found 370.1410.

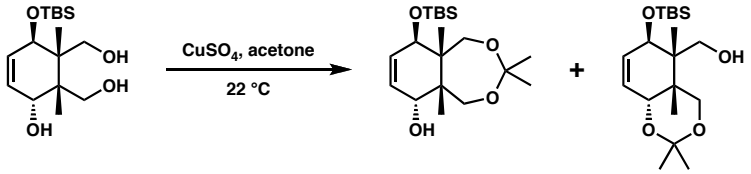


248 ***257*** ***258***

Triol 258. To cooled (0 °C) solution of allylic alcohol **248** (4.37 g, 19.3 mmol, 1.00 equiv) and pyridine (3.12 mL, 38.7 mmol, 2.00 equiv) in CH_2Cl_2 (19 mL) was added TBSOTf (6.66 mL, 29.0 mmol, 1.50 equiv) in a dropwise manner. At the end of the addition, the reaction was allowed to warm to ambient temperature and stirred for 15 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), quenched with sat. aq. NH_4Cl (75 mL), and extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to give crude silyl ether **257**, which was typically used without purification in the next step: R_f 0.69 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.19 (ddd, *J* = 1.0, 6.0, 9.0 Hz, 1H), 5.89 (ddd, *J* = 1.0, 3.5, 9.0 Hz, 1H), 4.78 (d, *J* = 5.5 Hz, 1H), 4.08 (dd, *J* = 1.0, 3.5 Hz, 1H), 3.72 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 173.7, 134.8, 126.9, 77.3, 70.5, 54.9, 52.5, 51.3, 25.6, 17.9, 15.7, 14.7, −4.5, −5.1; IR (Neat film NaCl) 2952, 2933, 2857, 1779, 1737, 1725, 1454, 1374, 1254, 1095, 1065, 957, 841, 780 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{17}H_{28}SiO_5+H]^+$: 341.1784, found 341.1781.

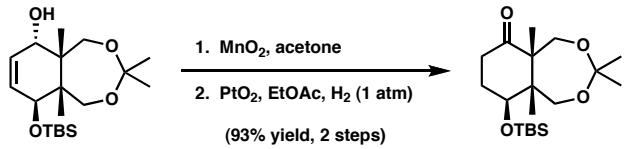
The above residue containing silyl ether **257** (theoretical yield: 19.3 mmol, 1.00 equiv) was dissolved in THF (193 mL), cooled (0 °C), and treated with LAH (2.20 g, 58.0 mmol, 3.00 equiv) in portions. At the end of the addition, the reaction was allowed to come to ambient temperature, and stirred for 18 h. The cooled (0 °C) reaction mixture was quenched by the careful dropwise addition of EtOAc (66 mL) until out gassing ceased, addition of Celite (7.0 g), and finally careful addition of sat. aq. Na_2SO_4 (33 mL).

The resulting slurry was filtered, dried (Na_2SO_4), and concentrated to give triol **258** (5.05 g, 83% yield, 2 steps) as a white solid of ~ 95% purity. Analytically pure material could be obtained by recrystallization from 1% EtOAc in benzene: mp 130.5–132.0 °C (EtOAc/benzene); R_f 0.22 (30% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68–5.62 (m, 2H), 4.45 (s, 1H), 4.20 (s, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.69 (d, *J* = 11.5 Hz, 1H), 3.50 (d, *J* = 12.0 Hz, 1H), 1.15 (s, 3H), 0.89 (s, 9H), 0.84 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.3, 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+) $[M+H]^+$ *m/z* calc'd for $[C_{16}H_{32}SiO_4+H]^+$: 317.2148, found 317.2162.



1,3-Dioxepane 259 and Acetonide 260. To a solution of triol **258** (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 **259** (1.48 g, 35% yield) as a waxy solid: R_f 0.66 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (dt, *J* = 2.1, 10.2 Hz, 1H), 5.49 (dt, *J* = 2.1, 10.2 Hz, 1H), 4.99 (s, 1H), 4.23 (app. q, *J* = 2.4 Hz, 1H), 3.73 (d, *J* = 12.3 Hz, 1H), 3.58 (d, *J* = 12.6 Hz, 1H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.19 (d, *J* = 12.6 Hz, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.71 (s,

3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 131.7, 129.2, 101.8, 73.5, 68.1, 63.8, 63.0, 46.9, 46.3, 26.5, 25.7, 25.4, 18.8, 18.7, 11.7, −3.7, −4.5; IR (Neat film NaCl) 3446, 2983, 2954, 2858, 1472, 1372, 1253, 1221, 1085, 1070, 1044, 835, 775 cm^{-1}; HRMS (FAB+) $[M–H_2+H]^+$ calc'd for $[C_{19}H_{35}SiO_4]^+$: *m/z* 355.2305, found 355.2317 and acetonide **260** (2.25 g, 53% yield) as an oil: R_f 0.76 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 4.4, 9.6 Hz, 1H), 5.69 (dd, *J* = 4.8, 9.9 Hz, 1H), 4.12 (d, *J* = 4.5 Hz, 1H), 4.01 (d, *J* = 12.9 Hz, 1H), 3.91 (s, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.64 (d, *J* = 10.2 Hz, 1H), 3.56 (d, *J* = 12.9 Hz, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 124.4, 98.6, 71.7, 70.9, 68.9, 65.2, 43.8, 35.1, 28.4, 25.7, 20.9, 20.0 (bs), 17.9, 15.3, −4.1, −5.1; IR (Neat film NaCl) 3451, 2955, 2931, 2886, 2858, 1379, 1256, 1104, 1056, 836, 775 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{19}H_{36}SiO_4+H]^+$: 357.2461, found 357.2478.

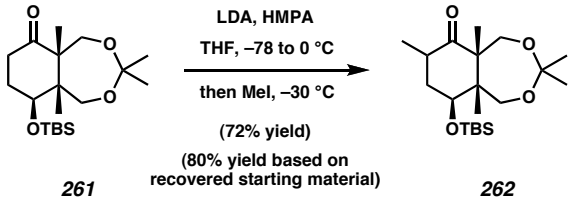


259 ***261***

Ketone 261. To a solution of 1,3-dioxepane **259** (798 mg, 2.24 mmol, 1.00 equiv) in acetone (23 mL) was added activated MnO_2 (3.89 g, 44.7 mmol, 20.0 equiv), and the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was filtered, washed with acetone, and concentrated to an oil.

To a solution of this crude material in EtOAc (28 mL) was added PtO_2 (16.0 mg, 67.2 μmol, 0.03 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 1.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide ketone **261** (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+) $[M+H]^+$ *m/z* calc'd for $[C_{19}H_{36}O_4Si+H]^+$: 357.2461, found 357.2473.



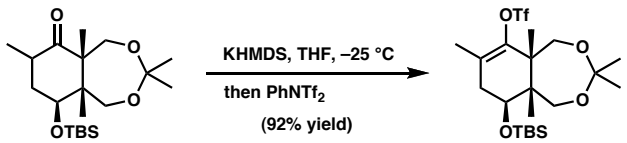
261 *262*

Methyl Ketones 262. 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 **261** (879 mg, 2.47 mmol, 1.00 equiv) in THF (30.0 mL) was added in a dropwise manner, and the reaction mixture was stirred at –78 °C for 30 min. HMPA (1.07 mL, 6.17 mmol, 2.50 equiv) was added and the reaction mixture brought to 0 °C for 1 h. After cooling again to –78 °C, the reaction mixture was treated with MeI (200 μL, 3.21 mmol, 1.30 equiv), and after 15 min allowed to warm to –30 °C. The reaction was allowed to warm to 0 °C slowly over 10 h, quenched with H_2O (150 mL) and EtOAc (75 mL), and extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to give recovered ketone **261** (90.9 mg, 10% yield), methyl ketone **262a** (219

mg, 24% yield, high R_f diastereomer), and methyl ketone **262b** (436 mg, 48% yield, low R_f diastereomer) as an oil.

High R_f diastereomer 262a: R_f 0.65 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (dd, *J* = 4.7, 12.2 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 3.49 (d, *J* = 12.6 Hz, 1H), 3.34 (d, *J* = 12.3 Hz, 1H), 2.93 (d, *J* = 11.7 Hz, 1H), 2.41 (dq, *J* = 6.3, 19.8 Hz, 1H), 1.98 (dt, *J* = 5.1, 12.9 Hz, 1H), 1.53 (d, *J* = 13.2 Hz, 1H), 1.34 (s, 3H), 1.10 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.55 (s, 3H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 101.9, 67.0, 65.5, 63.9, 56.8, 48.1, 41.0, 38.6, 25.8, 24.8, 24.5, 18.0, 15.7, 14.7, 11.3, −4.3, −5.1; IR (Neat film NaCl) 2984, 2955, 2935, 2858, 1709, 1220, 1095, 1072, 1044, 868, 837, 776 cm^{-1}; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{20}H_{38}O_4Si+H]^+$: *m/z* 371.2618, found 371.2607.

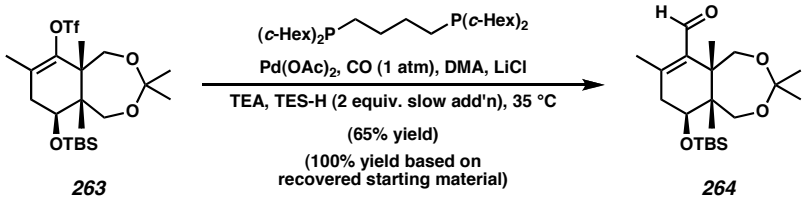
High R_f diastereomer 262b: R_f 0.36 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (d, *J* = 12.6 Hz, 1H), 3.60 (d, *J* = 12.0 Hz, 1H), 3.58 (bs, 1H), 3.41 (d, *J* = 12.6 Hz, 1H), 3.02–2.80 (m, 2H), 1.91 (ddd, *J* = 4.2, 5.6, 14.0 Hz, 1H), 1.58 (m, 1H), 1.30 (s, 3H), 1.24 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 101.2, 73.0, 67.8, 64.3, 54.4, 47.0, 37.7, 35.3, 25.8, 25.0, 23.9, 19.4, 18.1, 16.9, 14.7, −4.6, −5.0; IR (Neat film NaCl) 2933, 2858, 1709, 1255, 1222, 1078, 1046, 838, 775 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{20}H_{38}O_4Si+H]^+$: 371.2618, found 371.2625.



262 *263*

Triflate 263. 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 **262b** (1.04 g,

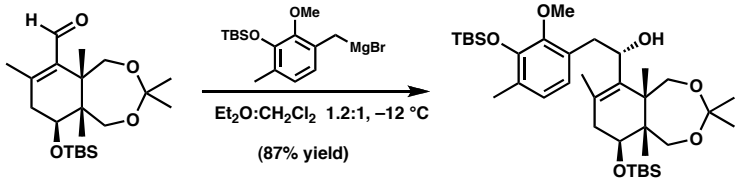
2.79 mmol, 1.00 equiv) in THF (20 mL) in a dropwise manner over 10 min. After 2 h at –25 °C, $PhNTf_2$ (1.30 g, 3.63 mmol, 1.30 equiv) in THF (20 mL) was added, and the reaction was maintained for an additional 30 min at –25°C. The reaction mixture was quenched into half-saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL), and extracted with EtOAc (5 x 50 mL). The combined organics were washed with brine (1 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (0 to 10% EtOAc in hexanes) to provide triflate **263** (1.30 g, 92% yield) as an oil: R_f 0.69 (10% Et_2O in hexanes); ^1H NMR (300 MHz, C_6D_6) δ 4.18 (dd, J = 6.3, 9.9 Hz, 1H), 3.79 (d, J = 12.3 Hz, 1H), 3.65 (d, J = 12.9 Hz, 1H), 3.41 (d, J = 12.3 Hz, 1H), 3.33 (d, J = 12.6 Hz, 1H), 2.08 (dd, J = 6.5, 17.6 Hz, 1H), 1.91 (ddd, J = 1.1, 9.9, 17.6 Hz, 1H), 1.61 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 0.98 (s, 9H), 0.49 (s, 3H), 0.15 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.9, 127.1, 119.7 (q, $J_{C\text{-}F}$ = 318 Hz), 102.0, 65.4, 65.2, 62.7, 47.4, 45.9, 38.2, 26.5, 25.0, 24.9, 18.6, 18.3, 17.0, 11.0, –3.8, –4.6; IR (Neat film NaCl) 2988, 2954, 2858, 1405, 1213, 1141, 1078, 879 cm^{-1}; HRMS (FAB+) $[M+H]^+$ m/z calc'd for $[C_{21}H_{37}SSiO_6F_3+H]^+$: 503.2110, found 503.2094.



263 *264*

Enal 264. 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 **263** (1.71 g, 3.40 mmol, 1.00

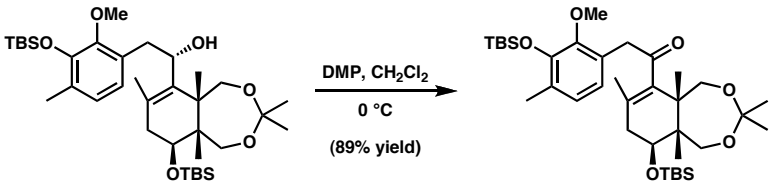
equiv) in DMA (20 mL). A solution of Et_3SiH (1.09 mL, 6.80 mmol, 2.0 equiv) in DMA (10.0 mL) was added by syringe pump to the reaction over 10 h. After an additional 14 h at 40 °C, the reaction mixture was cooled to ambient temperature, poured into H_2O (100 mL) and Et_2O (100 mL), and extracted with Et_2O (5 x 50 mL). The combined organic layers were washed with H_2O (20 mL), brine (2 x 20 mL), dried (Na_2SO_4), and concentrated to give an oil, which was purified by flash chromatography on silica gel (2 to 10% EtOAc in hexanes) to give recovered triflate **263** (606 mg, 35% yield) and enal **264** (841 mg, 65% yield) as a pale yellow oil: R_f 0.50, 0.55 (10% EtOAc in hexanes developed twice, 25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 4.19 (dd, *J* = 7.1, 9.2 Hz, 1H), 3.73 (d, *J* = 12.3 Hz, 1H), 3.60 (d, *J* = 12.0 Hz, 1H), 3.57 (d, *J* = 12.3 Hz, 1H), 3.34 (d, *J* = 12.3 Hz, 1H), 2.32–2.22 (m, 2H), 2.09 (s, 3H), 1.31 (s, 3H), 1.24 (s, 6H), 0.89 (s, 9H), 0.53 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 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+) $[M-H_2+H]^+$ *m/z* calc'd for $[C_{20}H_{37}O_5]^+$: 385.2410, found 385.2412.



264 *265*

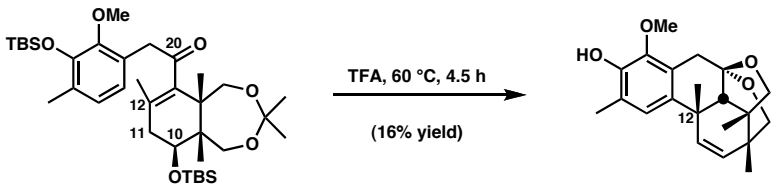
Allylic alcohol 265. A flame-dried two-neck round bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (3.00 g, 123 mmol, 56.1 equiv) and Et_2O (45 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (75.0 μL, 0.870 mmol, 0.40 equiv) in a dropwise manner. [*Caution: gas evolution!*] When gas evolution ceased, a solution of benzyl bromide **151** (1.37 g, 3.96 mmol, 1.80 equiv) in Et_2O (18.0 mL) was added in a dropwise manner over

30 min and heating was continued for an additional 30 min. The Grignard reagent was then cooled (0 °C), and added to a cooled (–12 °C) solution of enal **264** (841 mg, 2.20 mmol, 1.00 equiv) in Et_2O (45 mL) and CH_2Cl_2 (90 mL). After 1 h at –12 °C, the reaction was quenched with H_2O (150 mL), 2 M citric acid (20 mL), brine (20 mL), and EtOAc (50 mL), and extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 12.5% Et_2O in hexanes) to give allylic alcohol **265** (1.24 g, 87% yield) as a foam consisting of a 10:1 mixture diastereomers. Only the major component (stereochemistry shown above) could be isolated in pure form: R_f 0.41, 0.29 (25% Et_2O in hexanes, 10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 4.46 (d, J = 10.2 Hz, 1H), 4.16 (dd, J = 7.1, 9.5 Hz, 1H), 3.71 (s, 3H), 3.62 (d, J = 12.6 Hz, 1H), 3.53 (d, J = 12.3 Hz, 1H), 3.39 (d, J = 12.3 Hz, 1H), 3.32 (bs, 1H), 3.27 (dd, J = 10.7, 14.0 Hz, 1H), 2.59 (dd, J = 3.0, 14.1 Hz, 1H), 2.46 (s, 1H), 2.20 (s, 3H), 2.10–2.00 (m, 2H), 1.98 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.03 (s, 9H), 0.90 (s, 9H), 0.56 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 147.2, 134.6, 132.2, 130.8, 129.4, 126.4, 123.1, 100.8, 72.6, 66.1, 65.7, 62.2, 60.0, 47.1, 43.6, 40.0, 38.4, 26.0, 25.9, 24.7(2C), 20.9, 18.6, 18.1, 17.8, 17.0, 10.9, –4.0, –4.2, –4.3, –5.1; IR (Neat film NaCl) 3479, 2955, 2931, 2858, 1463, 1253, 1221, 1074, 838, 780 cm^{-1}; HRMS (FAB+) $[M\text{-}H_2+H]^+$ m/z calc'd for $[C_{36}H_{63}Si_2O_6]^+$: 647.4163, found 647.4156.



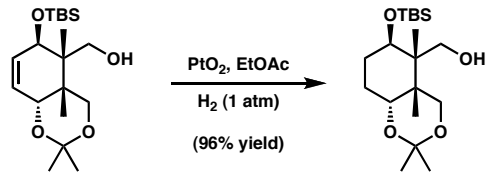
265 *266*

Enone 266. To a cooled (0 °C) solution of allylic alcohol **265** (1.24 g, 1.91 mmol, 1.00 equiv) in CH_2Cl_2 (120 mL) was added Dess-Martin periodinane (1.21 g, 2.86 mmol, 1.50 equiv) and the resulting mixture was stirred for 2 h. The reaction mixture was concentrated to ~ 40 mL, diluted with Et_2O (250 mL), filtered, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (2.5 to 5% EtOAc in hexanes) to give enone **266** (1.10 g, 89% yield) as a foam: R_f 0.43, 0.69 (10% EtOAc in hexanes, 10% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 4.28 (dd, J = 7.1, 9.5 Hz, 1H), 3.92 (d, J = 18.3 Hz, 1H), 3.80 (d, J = 18.0 Hz, 1H), 3.75 (d, J = 11.4 Hz, 1H), 3.64 (s, 3H), 3.52 (d, J = 12.6 Hz, 1H), 3.39 (d, J = 12.3 Hz, 1H), 2.20 (s, 3H), 2.12–1.98 (m, 2H), 1.72 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.13 (s, 3H), 1.02 (s, 9H), 0.90 (s, 9H), 0.66 (s, 3H), 0.15 (s, 6H), 0.09 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 150.1, 147.0, 138.2, 129.9 (2C), 125.8, 125.3, 123.2, 101.1, 65.9, 65.5, 61.5, 60.0, 47.1, 45.3, 42.9, 37.9, 26.1, 25.9, 24.7 (2C), 20.7, 18.6, 18.1, 17.1, 11.1, −4.2 (2C), −4.4, −5.1; IR (Neat film NaCl) 2954, 2930, 2858, 1699, 1463, 1252, 1221, 1099, 1073, 864, 836, 780 cm^{-1}; HRMS (FAB+) $[M+H]^+$ m/z calc'd for $[C_{36}H_{63}Si_2O_6+H]^+$: 647.4163, found 647.4140.



266 *270*

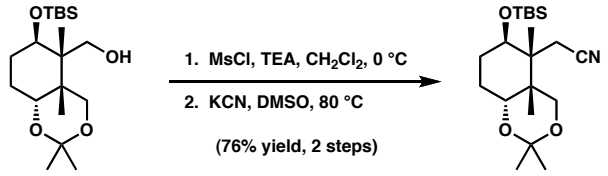
Acetal 270. A solution of enone **266** (67.8 mg, 0.1047 mmol, 1.0 equiv) in TFA (3.5 mL, 0.03 M) was heated to 65 °C for 5 h, then cooled to ambient temperature. The solvent was removed by rotary evaporation and benzene was added and removed by rotary evaporation (3x). The crude oil was purified by flash chromatography (5% to 25% EtOAc/hexanes, slow gradient) to afford acetal **270** (5.9 mg, 0.0172 mmol, 16% yield). R_f 0.30 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 5.97 (dd, *J* = 1.0, 9.5 Hz, 1H), 5.55 (s, 1H), 5.33 (d, *J* = 9.5 Hz, 1H), 4.18 (d, *J* = 8.5, 1H), 3.74 (s, 3H), 3.60 (d, *J* = 8.5 Hz, 1H), 3.55 (d, *J* = 11.5 Hz, 1H), 3.25 (d, *J* = 16.0, 1H), 3.09 (d, *J* = 11.5, 1H), 2.76 (d, *J* = 15.5, 1H), 2.23 (s, 3H), 1.76 (s, 1H), 1.42 (s, 3H), 1.15 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 144.1, 135.4, 135.1, 130.0, 124.7, 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}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{21}H_{26}O_4+H]^+$: 343.1909, found 343.1922.



260 *272*

Alcohol 272. To a solution of acetonide **260** (5.64 g, 15.8 mmol, 1.00 equiv) in EtOAc (198 mL) was added PtO_2 (108 mg, 0.475 mmol, 0.03 equiv), and the reaction mixture was sparged with a stream of H_2 gas for 4 h. The reaction mixture was concentrated (~ 10 mL), filtered through a plug of silica gel, and concentrated to give hydrogenated

alcohol **272** (5.47 g, 96% yield) as an oil: R_f 0.76 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (dd, *J* = 5.5, 12.0 Hz, 1H), 3.98 (dd, *J* = 5.0, 10.3 Hz, 1H), 3.88 (d, *J* = 13.0 Hz, 1H), 3.79 (app. t, *J* = 3.0 Hz, 1H), 3.45 (s, 1H), 3.32 (d, *J* = 12.0 Hz, 1H), 3.04 (app. t, *J* = 11.0 Hz, 1H), 2.12 (app. tt, *J* = 3.8, 14.3 Hz, 1H), 1.86 (app. tt, *J* = 3.0, 14.0 Hz, 1H), 1.48 (s, 3H), 1.47–1.37 (m, 1H), 1.42 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.5, 75.0, 74.4, 69.5, 66.8, 43.5, 35.0, 29.5, 25.9, 25.1, 21.9, 20.2, 18.8, 18.0, 17.2, –4.6, –5.0; IR (Neat film NaCl) 3497, 2953, 2936, 2883, 2858, 1472, 1379, 1257, 1196, 1083, 1060, 1034, 1005, 866, 834, 774 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{19}H_{38}SiO_4+H]^+$: 359.2618, found 359.2632.

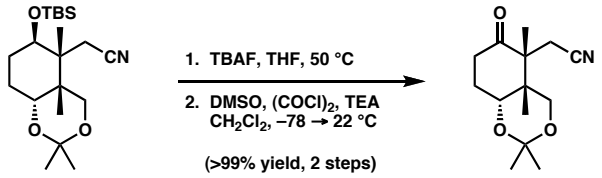


272 ***273***

Nitrile 273. To a cooled (0 °C) solution of alcohol **272** (880 mg, 2.45 mmol, 1.00) and TEA (1.02 mL, 7.36 mmol, 3.00 equiv) in CH_2Cl_2 (25 mL) was added methanesulfonyl chloride (228 μL, 2.95 mmol, 1.20 equiv) in a dropwise manner. After 30 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (40 mL), ice cold H_2O (50 mL), and brine (25 mL), and extracted with CH_2Cl_2 (3 x 35 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), and concentrated to a waxy solid that was used in the next step immediately.

The above residue was dissolved in DMSO (25 mL) and treated with KCN (400 mg, 6.14 mmol, 2.50 equiv) at 80 °C for 4 h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc (50 mL) and H_2O (150 mL), and extracted with EtOAc (7 x 40 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4),

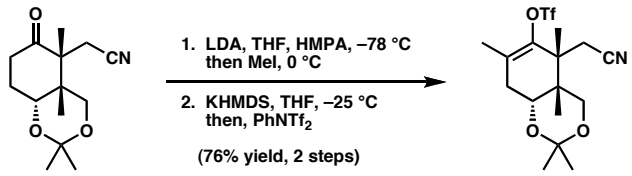
concentrated, and purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide nitrile **273** (682 mg, 76% yield) as a solid : R_f 0.42 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (d, *J* = 8.7 Hz, 1H), 3.83 (d, *J* = 8.4 Hz, 1H), 3.70–3.60 (m, 2H), 3.49 (d, *J* = 8.1 Hz, 1H), 3.46 (d, *J* = 8.7 Hz, 1H), 2.18–2.04 (m, 1H), 1.74–1.45 (m, 3H), 1.55 (s, 6H), 1.14 (s, 3H), 0.90 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.7, 78.8, 76.1, 74.8, 71.0, 70.1, 50.8, 48.8, 28.8 (2C), 27.6 (2C), 25.8, 22.6, 18.0, 9.5, –3.9, –5.0; IR (Neat film NaCl) 2956, 2934, 2882, 2860, 1460, 1254, 1183, 1080, 1047, 916, 868, 835, 772 cm^{-1}; HRMS (FAB+) $[M\text{-}H_2+H]^+$ *m/z* calc'd for $[C_{20}H_{36}NO_3Si]^+$: 366.2464, found 366.2459.



Ketone 274. To a solution of nitrile **273** (889.8 mg, 2.421 mmol, 1.00 equiv) in THF (14.5 mL) was added a 1.0 M solution of TBAF (7.26 μL, 7.262 mmol, 3.00 equiv) in THF, and the reaction mixture was heated to 50 °C for 12 h. The reaction mixture was cooled to ambient temperature, quenched with sat. NH_4Cl aq. (75 mL) and diluted with CH_2Cl_2 (125 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$, and concentrated into an oil, which was used without further purification.

A solution of DMSO (1.37 mL, 19.4 mmol, 8.0 equiv) in CH_2Cl_2 (100 mL) was cooled to –78 °C and oxalyl chloride (1.48 mL, 16.9 mmol, 7.00 equiv) was added in a dropwise manner. After 30 min at –78 °C, a solution of the crude alcohol generated above in CH_2Cl_2 (10 mL, + 2 x 2 mL rinse) was added in a dropwise manner down the wall of the flask. After 1.5 h at –78 °C, TEA 6.75 mL, 48.4 mmol, 20.0 equiv) was added and the

reaction mixture was allowed to warm slowly to ambient temperature, diluted with half-saturated NH_4Cl (100 mL), and extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were washed with saturated $NaHCO_3$ (75 mL), dried ($MgSO_4$), concentrated to an oil, and purified by flash chromatography on silica gel (20 to 35% EtOAc in hexanes) to provide ketone **274** (617 mg, 2.45 mmol, > 99% yield, 2 steps) as an oil: R_f 0.49 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (d, J = 8.7 Hz, 1H), 4.01 (dd, J = 4.4, 10.7 Hz, 1H), 3.95 (d, J = 9.3 Hz, 1H), 3.50 (d, J = 9.3 Hz, 1H), 3.41 (d, J = 8.1 Hz, 1H), 2.68–2.41 (m, 2H), 2.41–2.24 (m, 1H), 2.10–1.90 (m, 1H), 1.61 (s, 6H), 1.23 (s, 3H), 1.14 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 121.3, 77.5, 75.0, 74.1, 70.7, 58.0, 50.4, 35.6, 28.6, 27.7, 27.5, 21.4, 16.7; IR (Neat film NaCl) 2983, 2881, 2254, 1714, 1387, 1373, 1171, 1052, 907, 729, 651 cm^{-1}; HRMS (EI) $[M]^+$ *m/z* calc'd for $[C_{14}H_{21}NO_3]^+$: 251.1521, found 251.1518.

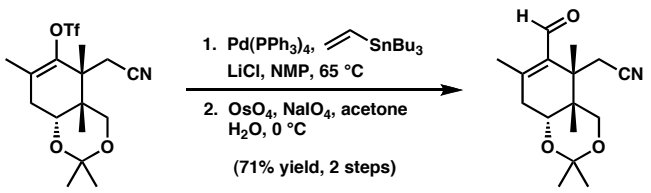


274 *276*

Triflate 276. 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 **274** (347 mg, 1.38 mmol, 1.00 equiv) in THF (15.0 mL) was added in a dropwise manner, and the reaction mixture was stirred at –78 °C for 2 h. HMPA (552 μL, 3.18 mmol, 2.30 equiv) was added and the reaction mixture was brought to 0 °C for 1 h. After cooling again to –78 °C, the solution containing the enolate was added to a solution of MeI (258 μL, 4.14 mmol, 3.00 equiv) in THF (4.00 mL) at –30 °C in a dropwise manner over 25 min. After 6 h at –25 °C, the

reaction mixture was quenched with H_2O (30 mL) and CH_2Cl_2 (30 mL), and extracted with CH_2Cl_2 (5 x 30 mL). The combined organics were washed, dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give to an inseparable mixture of diastereomeric methyl ketones (286 mg, 78% yield).

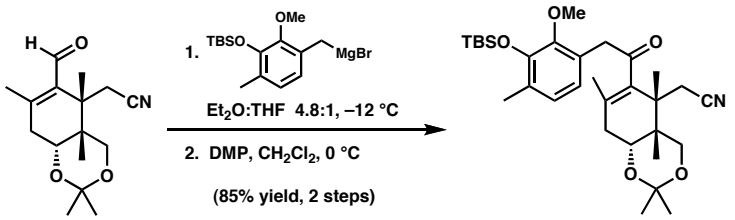
To a cooled (–25 °C) solution of KHMDS (300 mg, 1.50 mmol, 1.40 equiv) in THF (17 mL) was added the above mixture of methyl ketones (286 mg, 1.07 mmol, 1.00 equiv) in THF (15 mL) in a dropwise manner over 10 min. After 2.5 h at –25 °C, $PhNTf_2$ (614 mg, 1.72 mmol, 1.60 equiv) in THF (10.7 mL) was added, and the reaction maintained for an additional 30 min at –25°C. The reaction mixture was quenched into half-saturated $NaHCO_3$ (100 mL) and extracted with EtOAc (4 x 70 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 25% Et_2O in hexanes) to provide triflate **276** (420 mg, 98% yield, 76% yield for 2 steps) as an oil: R_f 0.41 (50% Et_2O in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 4.16 (d, J = 8.7 Hz, 1H), 3.95 (d, J = 9.3 Hz, 1H), 3.52 (dd, J = 6.2, 8.6 Hz, 1H), 3.46 (d, J = 9.0 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 2.17 (dd, J = 6.0, 18.0 Hz, 1H), 1.95 (dd, J = 8.1, 18.0 Hz, 1H), 1.50 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.7, 125.1, 121.5, 119.5 (app. d, $J_{C\text{-}F}$ = 296 Hz), 75.2, 74.7, 74.3, 71.0, 51.2, 50.4, 36.1, 28.2, 27.4, 21.6, 18.1, 16.4; IR (Neat film NaCl) 2988, 2942, 2884, 1403, 1211, 1141, 1053, 990, 874 cm^{-1}; HRMS (EI) $[M]^+$ m/z calc'd for $[C_{16}H_{22}NO_5F_3S]^+$: 397.1171, found 397.1179.



276 *278*

Enal 278. To a solution of triflate **276** (1.41 g, 3.54 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (307 mg, 0.266 mmol, 0.075 equiv), and LiCl (450 mg, 10.6 mmol, 3.00 equiv) in NMP (59 mL) was added tributyl(vinyl)stannane (1.55 mL, 5.31 equiv, 1.50 equiv), and the mixture was heated to 65 °C for 0.5 h. The reaction mixture was cooled to ambient temperature, quenched with H_2O (300 mL) and Et_2O (200 mL), and extracted with Et_2O (4 x 125 mL). The combined organics were washed with brine (170 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide the intermediate diene (1.04 g, quantitative yield) as a viscous oil containing a small amount of solvent.

To a cooled (0 °C) solution of the intermediate diene (116.7 mg, 0.42 mmol, 1.00 equiv) in acetone (5.30 mL) and H_2O (5.30 mL) was added OsO_4 (10.8 mg, 42.3 μmol, 0.10 equiv) and $NaIO_4$ (227 mg, 1.06 mmol, 2.50 equiv). After 3.5 h at 0°C, the reaction mixture was diluted with H_2O (35 mL) and EtOAc (35 mL), and extracted with EtOAc (5 x 15 mL). The combined organics from four such reactions were washed with brine (200 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (20 to 35% EtOAc in hexanes) to provide enal **278** (332 mg, 71% yield, 2 steps) as an oil: R_f 0.28 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 4.21 (d, *J* = 9.0 Hz, 1H), 3.87 (d, *J* = 9.3 Hz, 1H), 3.85 (d, *J* = 8.4 Hz, 1H), 3.70 (d, *J* = 9.0 Hz, 1H), 3.51 (d, *J* = 8.7 Hz, 1H), 2.78 (dd, *J* = 6.0, 19.8 Hz, 1H), 2.49 (dd, *J* = 9.0, 19.8 Hz, 1H), 2.16 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 153.2, 136.8, 121.5, 76.0, 74.2, 74.1, 70.4, 48.7, 48.0, 38.7, 28.7, 27.3, 20.7, 19.0, 18.0; IR (Neat film NaCl) 2982, 2938, 2880, 1671, 1628, 1386, 1177, 1050 cm^{-1}; HRMS (EI) $[M]^+$ *m/z* calc'd for $[C_{16}H_{23}NO_3]^+$: 277.1678, found 277.1677.

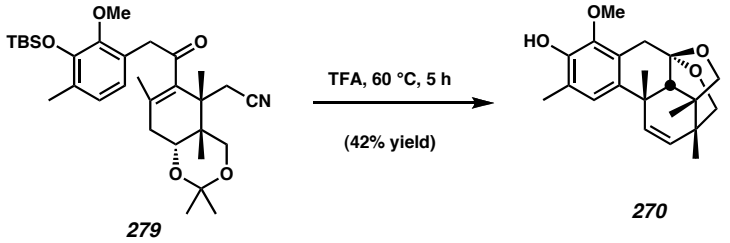


278 *279*

Enone 279. A flame-dried two-neck round bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (1.66 g, 68.4 mmol, 57.0 equiv) and Et_2O (27 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (120 μL, 1.39 mmol, 1.16 equiv) in a dropwise manner. [*Caution: gas evolution!*] When gas evolution ceased, a solution of benzyl bromide **151** (1.24 g, 3.60 mmol, 3.00 equiv) in Et_2O (8.0 mL) was added in a dropwise manner over 30 min, and heating was continued for an additional 20 min. The Grignard reagent was then cooled (0 °C), and added to a cooled (0 °C) solution of enal **278** (332 mg, 1.20 mmol, 1.00 equiv) in THF (12 mL). After 1 h at 0 °C, the reaction was quenched with 0.5 M citric acid (40 mL), and EtOAc (40 mL), and extracted with EtOAc (5 x 25 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give a separable 3:1 mixture of diastereomeric allylic alcohols (533.3 mg, 85% yield).

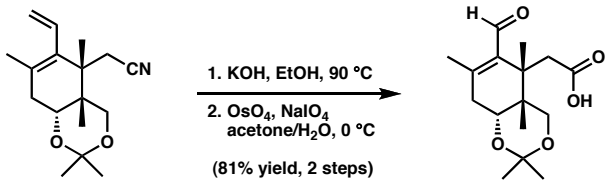
To a cooled (0 °C) solution of the above allylic alcohol (76.0 mg, 0.140 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL) was added Dess-Martin periodinane (89.1 mg, 0.211 mmol, 1.50 equiv) and the resulting mixture was stirred for 2 h. The reaction mixture was diluted with Et_2O (35 mL), filtered, concentrated to an oil, and purified by flash chromatography on silica gel (5 to 20% EtOAc in hexanes) to give enone **279** (75.7 mg, 100% yield, 85% yield 2 steps) as an oil: R_f 0.47 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 7.8 Hz, 1H), 4.16 (d, J = 8.7 Hz, 1H), 4.08 (d, J = 9.0 Hz, 1H), 3.87 (dd, J = 6.0, 8.4 Hz, 1H), 3.86 (s, 2H), 3.64 (s, 3H), 3.53

(d, *J* = 8.7 Hz, 1H), 3.52 (d, *J* = 9.0 Hz, 1H), 2.54 (dd, *J* = 6.0, 17.7 Hz, 1H), 2.30 (dd, *J* = 8.3, 18.2 Hz, 1H), 2.21 (s, 3H), 1.79 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.02 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 150.0, 147.0, 138.7, 130.0, 128.2, 125.8, 125.2, 123.3, 121.6, 75.5 (2C), 75.2, 70.5, 59.9, 49.7, 47.2, 47.1, 35.5, 28.7, 27.6, 26.0, 21.1, 20.8, 18.5, 18.2, 17.1, –4.2; IR (Neat film NaCl) 2932, 2859, 1699, 1464, 1422, 1286, 1073, 1047, 856, 841 cm^{-1}; HRMS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{31}H_{47}NSiO_5+H]^+$: 542.3302, found 542.3296.



279 *270*

Acetal 270. A solution of enone **279** (29.9 mg, 55.2 μmol, 1.00 equiv) in trifluoroacetic acid (4.00 mL) was heated to 60 °C for 5 h. The reaction mixture was then cooled to ambient temperature, concentrated to an oil, and purified by flash chromatography on silica gel (5 to 50% EtOAc in hexanes) to give acetal **270** (7.9 mg, 23.1 μmol, 42% yield) as an off-white solid.

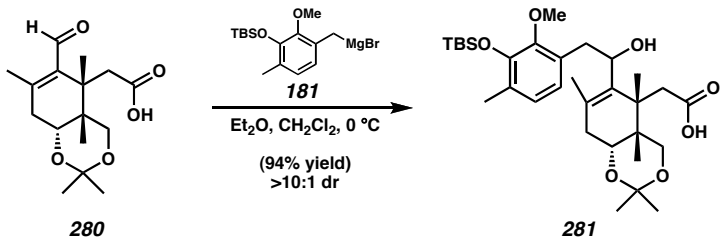


277 *280*

Enal 280. To a stirred solution of nitrile **277** (370.3 mg, 1.35 mmol, 1 equiv) in EtOH (26.9 mL, 0.05 M) was added KOH aq. (26.9 mL, 5 wt% in H_2O, 0.05 M). The reaction was then heated to 80 °C for 44 hours. The reaction was then cooled to ambient temperature and the EtOH was removed by rotary evaporation. The resulting aqueous

solution was diluted with 60 mL CH_2Cl_2, 26.9 mL HCl (2M), and further extracted with CH_2Cl_2 (5 x 40 mL). The organic layers were dried over $MgSO_4$ and concentrated to an oil (406.7 mg, 1.38 mmol, > 99% yield), which was carried on to the next step without further purification.

To a solution of the carboxylic acid intermediate (133.2 mg, 0.4525 mmol, 1 equiv) in acetone (5.7 mL, 0.08 M) and water (5.7 mL, 0.08 M) at 0 °C was added OsO_4 (11.5 mg, 45.25 μmol, 0.1 M) and $NaIO_4$ (241.7 mg, 1.13 mmol, 2.5 equiv). The reaction mixture was stirred at 0 °C for 1 h then diluted with H_2O (25 mL), EtOAc (25 mL), further extracted with EtOAc (3 x 15 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (30% to 60% acetone/hexanes, with 3 drops AcOH per 100 mL eluent during the last half of the column) afforded enal **280** (111.5 mg, 0.3762 mmol, 83% yield) as a white amorphous solid. R_f 0.28 (40% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 4.06 (d, J = 9.0 Hz, 1H), 4.01 (d, J = 9.0 Hz, 1H), 3.89 (d, J = 9.0 Hz, 1H), 3.88 (t, J = 3.7 Hz, 1H), 3.76 (d, J = 9.3 Hz, 1H), 2.63 (comp. m, 1H), 2.27 (dd, J = 19.3, 4.0 Hz, 1 H), 2.18 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H), 1.26 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 175.9 150.1, 138.5, 80.9, 78.2, 76.2, 74.2, 47.4, 45.2, 38.1, 26.8, 23.0, 21.7, 19.3, 18.2; IR (Neat film NaCl) 3600–2500, 2981, 2939, 2882, 1731, 1668, 1385, 1175, 1154, 1049, 918 cm^{-1}; MS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{16}H_{24}O_5+H]^+$: 297.1702, found 297.1697.



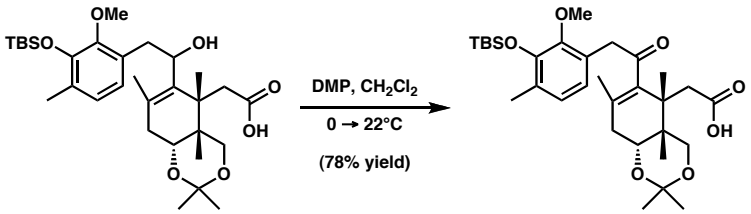
280 281

Allylic alcohol 281. A flame-dried two-neck round bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (1.03 g, 42.4 mmol,

32.4 equiv) and Et_2O (12 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (150 μL, 1.74 mmol, 1.33 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (677 mg, 1.96 mmol, 1.50 equiv) in Et_2O (7.0 mL) was added in a dropwise manner over 30 min and heating was continued for an additional 30 min. The Grignard reagent was then cooled to 0 °C and 3 equivalents were added dropwise to a cooled (0 °C) solution of enal **280** (100 mg, 0.337 mmol, 1.00 equiv) in Et_2O (3.8 mL) and CH_2Cl_2 (7.4 mL) (1:2 ratio, 0.03 M overall). After 15 min at 0 °C, the reaction was quenched with H_2O (5 mL) and 2 M citric acid (2.0 mL) and allowed to come to ambient temperature. The mixture was diluted with H_2O (30 mL) and Et_2O (30 mL), and extracted with Et_2O (50 mL then 3 x 10 mL). The combined organics were washed with brine (30 mL), dried over Na_2SO_4, and concentrated to an oil. Purification by flash chromatography on silica gel (15 to 65% EtOAc in hexanes with 3 drops AcOH per 100 mL eluent for last half of column) provided allylic alcohol **281** (178.3 mg, 0.3168 mmol, 94% yield, > 10:1 dr) as a partially separated mixture of two diastereomers **281a** and **281b**.

High R_f diastereomer 281a: R_f 0.72 (50% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, J = 7.8 Hz, 1 H), 6.72 (d, J = 7.8 Hz, 1H), 4.56 (d, J = 9.3 Hz, 1H), 4.04 (d, J = 8.5 Hz, 1H), 3.89 (app. t, J = 8.8 Hz, 2H), 3.81 (t, J = 4.2 Hz, 1H), 3.78 (d, J = 8.8 Hz, 1H), 3.72 (s, 3H), 3.09 (dd, J = 13.9, 10.5 Hz, 1 H), 2.79 (dd, J = 13.9, 2.4 Hz, 1H), 2.41 (dd, J = 18.1, 3.9 Hz, 1H), 2.21 (s, 3H), 2.05 (dd, J = 18.1, 4.2 Hz, 1H), 1.52 (s, 3H), 1.03 (s, 9H), 1.01 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 149.4, 147.3, 135.9, 130.4, 129.8, 126.4, 123.2, 78.0, 76.4, 75.0, 73.6, 60.0, 47.3, 39.2, 36.7, 26.7, 26.0, 23.1, 20.6, 18.6, 17.0, –4.0, –4.1; IR (Neat film NaCl) 3426, 2956, 2932, 2859, 1731, 1464, 1419, 1286, 1253, 1178, 1074, 1046, 918, 840, 782, 733 cm^{-1}; MS (FAB+) $[M+H-H_2]^+$ calc'd for $[C_{31}H_{49}O_7Si]^+$: m/z 561.3248, found 561.3253.

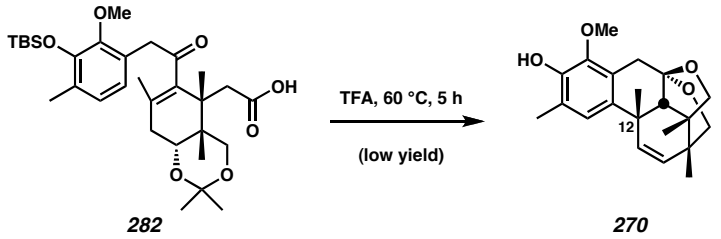
Low R_f diastereomer 281b: R_f 0.61 (50% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.27 (dd, *J* = 10.3, 2.7 Hz, 1H), 4.14 (d, *J* = 8.3 Hz, 1H), 3.98 (d, *J* = 9.8 Hz, 1H), 3.81 (app. t, *J* = 5.9 Hz, 1H), 3.74 (d, *J* = 8.3 Hz, 1H), 3.71 (d, *J* = 8.8 Hz, 1H), 3.70 (s, 3H), 3.14 (dd, *J* = 13.9, 10.3 Hz, 1H), 2.81 (dd, *J* = 13.9, 2.7 Hz, 1H), 2.38 (dd, *J* = 18.1, 4.9 Hz, 1H), 2.21 (s, 3H), 2.13 (dd, *J* = 17.8, 6.1 Hz, 1H), 1.98 (s, 3H), 1.52 (s, 6H), 1.18 (s, 3H), 1.06 (s, 3H), 1.03 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 149.5, 147.3, 136.0, 130.4, 129.7, 126.3, 123.2, 78.1, 76.1, 74.1, 73.7, 60.0, 49.9, 47.1, 38.1, 37.4, 26.0, 25.8, 23.7, 21.1, 20.7, 19.9, 18.6, 17.0, −4.0, −4.1; IR (Neat film NaCl) 3600–2500, 2930, 2859, 1722, 1464, 1419, 1286, 1253, 1178, 1074, 1045, 918, 840, 734 cm^{-1}; MS (FAB+) $[M+H-H_2]^+$ *m/z* calc'd for $[C_{31}H_{49}O_7Si]^+$: 561.3248, found 561.3225.



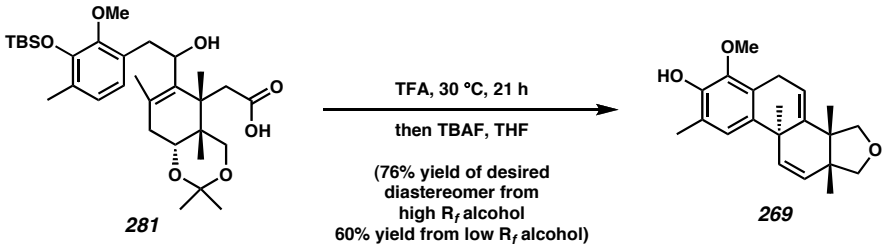
281 *282*

Enone 282. To a cooled (0 °C) solution of allylic alcohol **281** (35 mg, 0.062 mmol, 1.0 equiv) was added Dess-Martin periodinane (40.8 mg, 0.093 mmol, 1.5 equiv). The resulting solution was stirred at 0 °C for 1.5 h then was diluted with 10 mL Et_2O, filtered thru #2 Whatman paper, concentrated, and purified by flash column chromatography (10 to 50% EtOAc/hexanes) to provide enone **282** (27.1 mg, 0.048 mmol, 78% yield): R_f 0.42 (30% acetone in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 4.32 (d, *J* = 8.2 Hz, 1H), 3.98–3.62 (m, 6H), 3.65 (s, 3H), 2.43 (dd, *J* = 18.2, 2.9 Hz, 1H), 2.21 (s, 3H), 2.13 (dd, *J* = 17.6, 3.5 Hz, 1H), 1.78 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H), 1.14 (s, 3H), 1.02 (s, 9H), 1.00 (s, 3H), 0.15 (app. d, *J* = 2.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 176.2, 149.9, 147.0, 138.4, 130.1, 126.9, 125.9, 125.0,

123.3, 80.6, 78.3, 76.5, 74.8, 59.9, 46.8, 35.4, 26.8, 26.1, 23.1, 21.9, 21.2, 18.5, 17.7, 17.1, −4.19, −4.22; IR (Neat film NaCl) 3695–2398, 2932, 2859, 1735, 1699, 1464, 1421, 1286, 1073, 919, 840, 782, 733 cm^{-1}; MS (FAB+) $[M+H]^+$ *m/z* calc'd for $[C_{31}H_{48}O_7Si+H]^+$: 561.3248, found 561.3220.



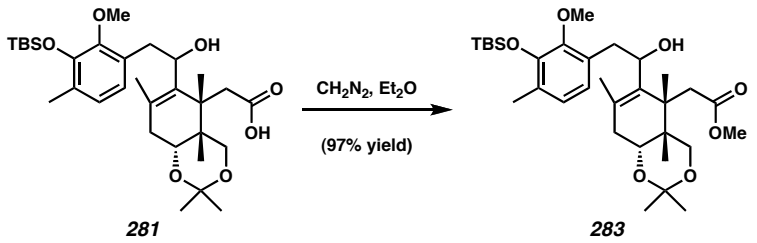
Acetal 270 from enone 282: A solution of enone **282** (20.4 mg, .036 mmol, 1.0 equiv) in TFA (2.0 mL, 0.018 M) was heated to 65 °C for 5 h, then cooled to ambient temperature. The solvent was removed by rotary evaporation and benzene was added and removed by rotary evaporation (3x). The crude oil was purified by preparative thin-layer chromatography (30% EtOAc/hexanes) to afford a small amount of acetal **270**.



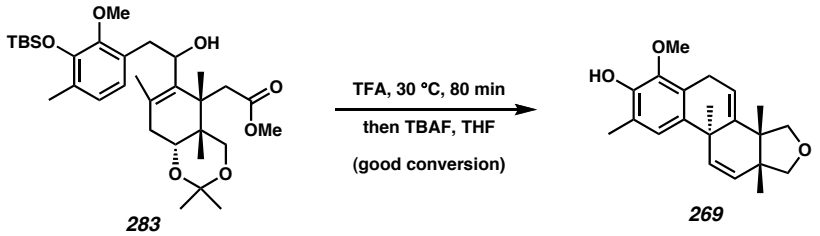
Tetracycle 269. A solution of allylic alcohol **281a** (30 mg, 0.053 mmol, 1.0 equiv) in TFA (3 mL, 10 mg/mL) was warmed to 30 °C and stirred for 21 h (reaction times as low as 30 min provide similar results) before cooling to ambient temperature. TFA was removed by rotary evaporation, diluted with benzene and concentrated to an oil (3x) then redissolved in THF (2 mL, 0.025 M). A solution of TBAF (54 μL, 0.106 mmol, 2.0 equiv) in THF (2.0 M) was added, and the reaction mixture was stirred for 3 h, quenched

with H_2O (20 mL), extracted with CH_2Cl_2 (5 x 20 mL), dried over $MgSO_4$, and purified by flash chromatography (10 to 20% EtOAc in hexanes) to provide tetracycle **269** (13.3 mg, 0.041 mmol, 76% yield) as a yellow solid.

A solution of allylic alcohol **281b** (30 mg, 0.053 mmol, 1.0 equiv) in TFA (3 mL, 10 mg/mL) was warmed to 30 °C and stirred for 21 h (reaction times as low as 30 min provide similar results) before cooling to ambient temperature. TFA was removed by rotary evaporation, diluted with benzene and concentrated to an oil (3x) then redissolved in THF (2 mL, 0.025 M). A solution of TBAF (54 μL, 0.106 mmol, 2.0 equiv) in THF (2.0 M) was added, and the reaction mixture was stirred for 3 h, quenched with H_2O (20 mL), extracted with CH_2Cl_2 (5 x 20 mL), dried over $MgSO_4$, and purified by flash chromatography (10 to 20% EtOAc in hexanes) to provide tetracycle **269** (10.4 mg, 0.032 mmol, 60% yield) as a yellow solid. Crystals suitable for X-ray analysis were obtained by crystallization from Et_2O/heptanes at ambient temperature: mp 150–153 °C (Et_2O/heptane); R_f 0.39 (30% acetone in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.18 (d, J = 10.3 Hz, 1H), 6.14 (d, J = 6.4 Hz, 1H), 5.69 (d, J = 10.3 Hz, 1H), 5.54 (s, 1H), 4.33 (d, J 7.6 Hz, 1H), 3.86 (s, 2H), 3.63 (dd, J = 19.9, 7.0 Hz, 3.49 (d, J = 7.3 Hz, 1H), 3.16 (d, J = 19.6 Hz, 1H), 2.24 (s, 3H), 1.26 (s, 3H), 1.20 (s, 3H), 0.76 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 143.4, 143.1 138.8, 134.1, 131.4, 125.8, 123.9, 121.8, 120.7, 80.1, 78.1, 77.2, 60.9, 48.7, 46.6, 39.0, 28.9, 25.0, 20.6, 17.1, 15.8; IR (Neat film NaCl) 3368, 2961, 2925, 1871, 1485, 1462, 1421, 1320, 1211, 1070, 907, 733 cm^{-1}; MS (FAB+) $[M+H-H_2]^+$ m/z calc'd for $[C_{21}H_{25}O_3]^+$: 325.1799, found 325.1804.



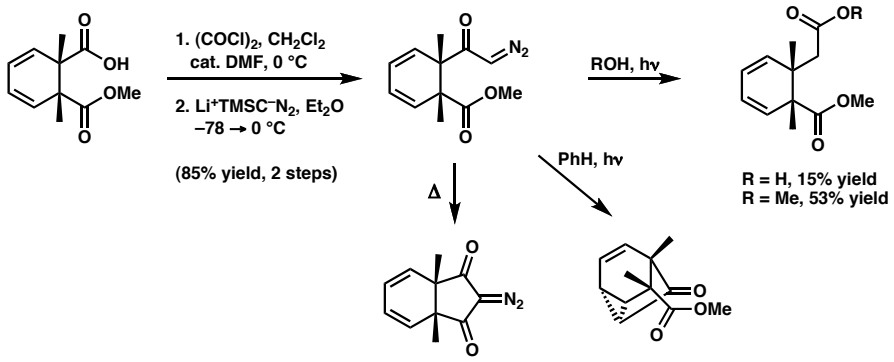
Methyl ester 283. To a solution of acid **281** (10 mg, 0.018 mmol, 1.0 equiv) in Et_2O (0.5 mL) was added CH_2N_2 in Et_2O (2 mL, ~ 1–2 M). The solution was stirred, open to air, until no further yellow color was visible. The solvent was removed by rotary evaporation to provide pure methyl ester **283** (9.9 mg, 0.017 mmol, 97% yield) as a clear oil: R_f 0.47 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 4.21 (d, J = 9.4 Hz, 1H), 4.07 (d, J = 9.1 Hz, 1H), 4.02 (d, J = 8.2 Hz, 1H), 3.77 (d, J = 7.9 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.58 (d, J = 5.6 Hz, 1H), 3.55 (d, J = 5.0 Hz, 1H), 3.16 (dd, J = 14.1, 10.5 Hz, 1H), 2.79 (dd, J = 14.1, 1.8 Hz, 1H), 2.44 (br s, 1H), 2.21 (s, 3H), 2.17 (d, J = 8.2 Hz, 1H), 1.97 (s, 3H), 1.42 (s, 3H), 1.25 (s. 3H), 1.11 (s. 3H), 1.07 (s, 9H), 0.17 (app. d, J = 1.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 149.5, 147.3, 135.1, 130.8, 129.6, 129.2, 126.4, 76.7, 74.8, 74.2, 73.6, 71.8, 60.0, 51.9, 51.7, 47.3, 38.2, 37.9, 26.3, 26.0, 24.3, 21.1, 21.0, 18.6, 17.8, 17.0, –4.1, –4.06; IR (Neat film NaCl) 3444, 2931, 2858, 1734, 1464, 1285, 1142, 1044, 1004, 919, 840, 782, 732 cm^{-1}; MS (FAB+) $[M+H]^+$ m/z calc'd for $[C_{32}H_{52}O_7Si+H]^+$: 577.3561, found 577.3544.

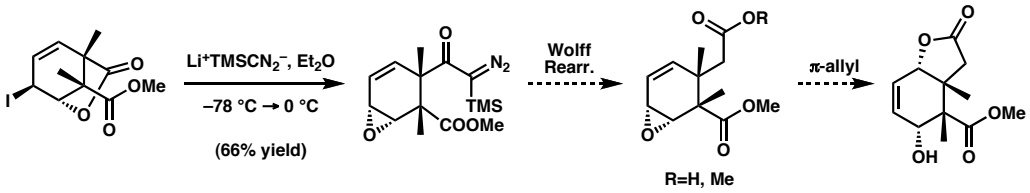


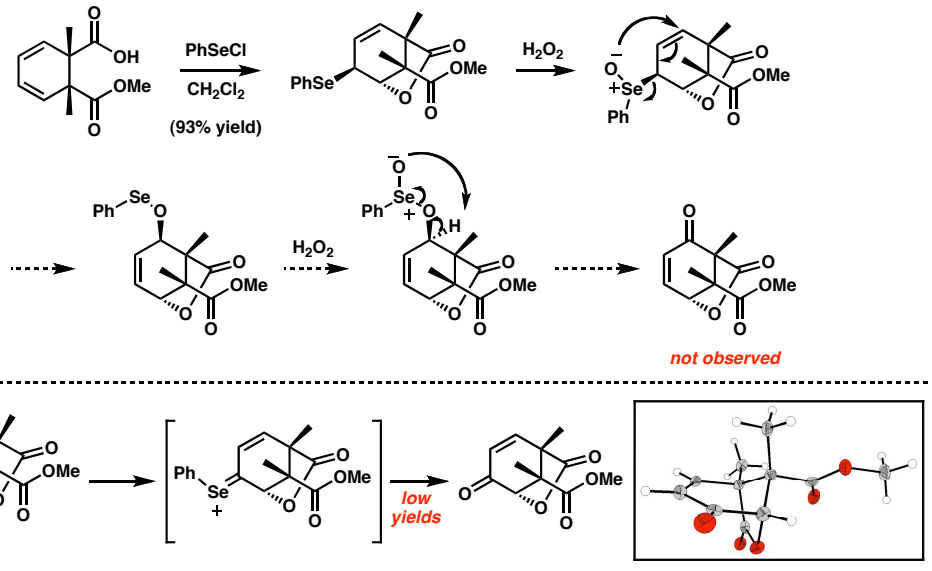
Tetracycle 269 from methyl ester 283. A solution of allylic alcohol **283** (9.9 mg, 17.7 μmol, 1.0 equiv) in TFA (700 μL, 0.025 M) was warmed to 30 °C and stirred for 80 min before cooling to ambient temperature. TFA was removed by rotary evaporation,

diluted with benzene and concentrated to an oil (3x). ^{1}H NMR analysis indicated the formation of tetracycle **269** as the major product.

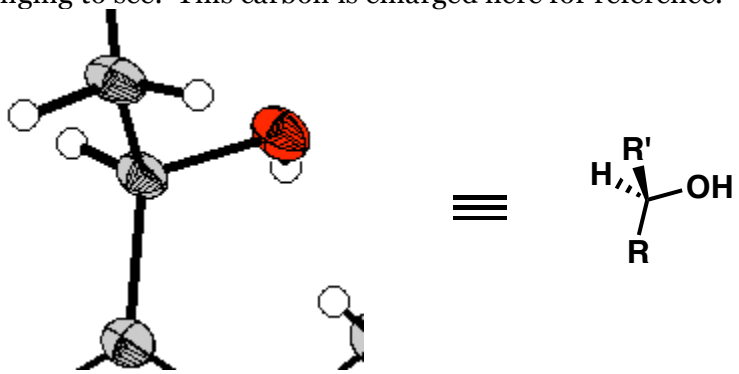
References

1. Birman, V. B.; Danishefsky, S. J., *J. Am. Chem. Soc.* **2002,** *124*, 2080–2081.
2. Interestingly, the yield of this reaction varies consistently with scale. The optimal yield was achieved using 19 g of the *endo* substrate, and the result was repeated several times on this scale.
3. a) For a review, see: Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965–2983. b) For an application in synthesis, see: Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793–8794.
4. Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A., *J. Org. Chem.* **2000,** *65*, 6984–6991.
5. A sample of this compound was graciously donated to us by Prof. Li Deng at Brandeis University.
6. 1.1 equiv quinine. 0.1 M PhMe, and 3 equiv: EtOH (47% ee), BnOH (0% ee), *i*–PrOH (NR), *n*–PrOH (46% ee), PhOH (NR).
7. 

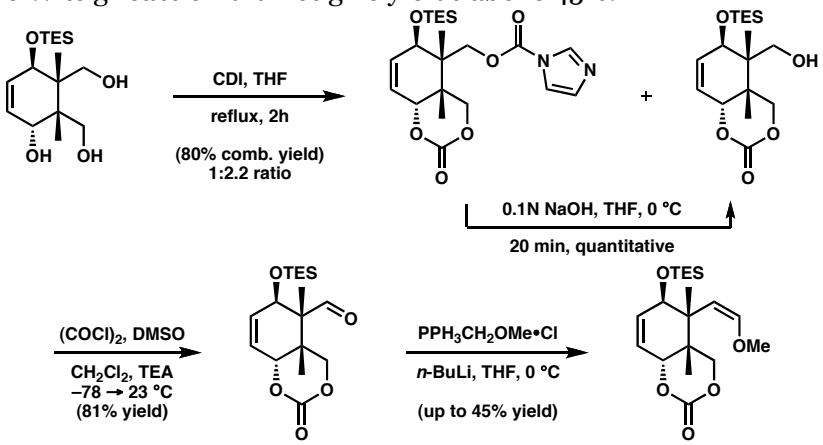
8. 

9. 

10. Ball, S.; Goodwin, T. W.; Morton, R. A., *Biochem. J.* **1948**, *42*, 516–523.
11. Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955–5956.
12. Bhattacharya, A.; Segmuller, B.; Y. A. *Synth. Commun.* **1996**, *26*, 1775–1784.
13. See Chapter 2 for details.
14. When the ORTEP image was shrunk, the stereochemistry at the center of interest became challenging to see. This carbon is enlarged here for reference.

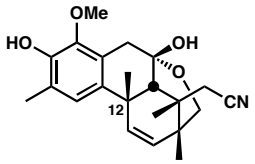


15. Attempts were made to access the opposite alcohol diastereomer. Mitsunobu attempts led either to recovered starting alcohol or to decomposition. Additionally, enone **255** was reduced under Luche conditions, but led to the same diastereomer of allylic alcohol **253**.
16. Silylation with TBSCl, DMAP, Imidazole, and DMF only proceeded to 10% conversion upon heating for extensive time scales.
17. Miljkovic, M.; Hagel, P. *Carbohydr. Res.* **1983**, *111*, 319–324. b) Morgenlie, S. *Carbohydr. Res.* **1975**, *41*, 77–83.
18. Brewster, A. G.; Leach, A. *Tetrahedron Lett.* **1986**, *27*, 2539–2542.
19. The 7-membered acetal can be accessed exclusively via selective oxidation of the secondary alcohol to the enone followed by acetal formation. The 7-membered acetal can be converted to the 6-membered acetal with 50% conversion and 100% mass recovery.
20. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7278.
21. A similar strategy was conducted in the below system. Once again, the methoxy methylene Wittig reaction did not give yields above 45%.



22. a) Okamoto, Y.; Yano, T. *Tetrahedron Lett.* **1971**, 4285–4287. b) Fraser, G. M.; Hoffmann, H. M. R. *Chem. Commun.* **1967**, 561–563.

23. The structure of this compound has been verified by extensive 2D NMR analysis. It should be noted that the compound was originally reported in D. Behenna's thesis as the following hemiacetal:



24. Efforts to determine the stereochemistry of the major isomer are ongoing.
25. Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3458.