Chapter 3

Synthetic Studies towards the C_{19}-Diterpenoid Alkaloid Talatisamine

3.1 INTRODUCTION

The diterpenoid alkaloids have garnered much attention from the synthetic community due to their structural complexity and compelling biological activity.[1] Early efforts in the 1960s were directed towards classic targets such as C_{20} veatchine[2] and atisine type alkaloids,[3] and later, pioneering work towards C_{19} aconitine type alkaloids.[4] More recently, synthetic studies towards more complex C_{20} hetidine and hetisine type alkaloids have sparked a new interested in the field,[5] specifically towards the C_{18} and C_{19} natural products. This chapter reviews completed total syntheses of natural products that bear the aconitine core (*e.g.* C_{18}- and C_{19}-diterpenoid alkaloids), as well as syntheses of related C_{20}-diterpenoid alkaloids employing divergent strategies. Lastly, a detailed account of our own progress towards talatisamine, a C_{19} aconitine type alkaloid, is

presented, as well as a unified strategy to access C_{20} denudatine and napelline type alkaloids in a non-biomimetic manner.

3.2 STRUCTURAL AND BIOSYNTHETIC CONSIDERATIONS

A major challenge in the synthesis of diterpenoid alkaloids is construction of the highly caged polycyclic framework. The C_{18}- and C_{19}-diterpenoid alkaloids possess a complex hexacyclic skeleton that is abundantly decorated with oxygenated functionality (Figure 3.1). Specifically, a piperidyl E-ring bridges the hydrindane AF-ring system, that is adjoined to a bicyclo[3.2.1] CD-rings through the central cyclohexyl B-ring. The A-F/B-C rings also constitute a 6/7/5-ring system rearranged from a 6/6/6-phenanthrene core. The natural products possess at least 11 contiguous stereocenters that include two quaternary centers at C4 and C11 at the bridgehead positions of the AE bicycle.

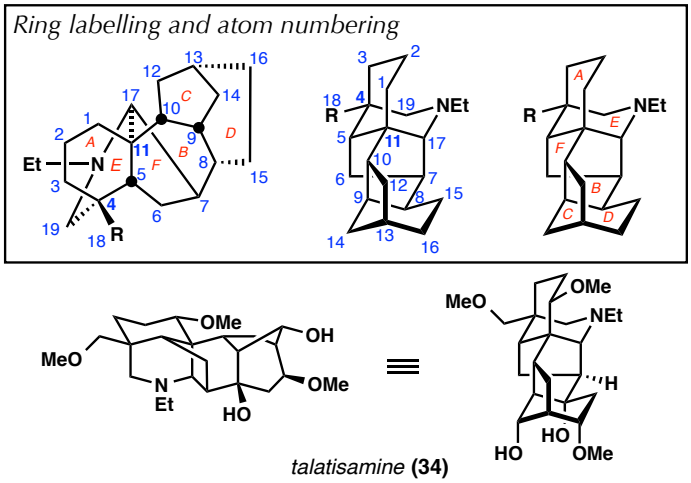


Figure 3.1. Structural depictions of C_{19}-Diterpenoid Alkaloids

Although there have only been a handful of completed syntheses of C_{19}- and C_{18}-diterpenoid alkaloids, several reports, most of which detail approaches to the AEF or CD

rings, have been published.[6] A majority of the successful syntheses have employed Diels–Alder cycloadditions to form a [2.2.2]-bicycle and Wagner–Meerwein rearrangement to generate the [3.2.1]-bicyclic CD-ring system. These strategies have relied on the biomimetic rearrangement of the C_{20} denudatine skeleton into the C_{19} aconitine framework. Chemical evidence for this transformation was first demonstrated by Johnston and Overton, who were able to convert atisine to derivative **80**, containing a tosylate leaving group (Figure 3.2).[7] Gas phase pyrolysis at 500 °C successfully converted the [2.2.2]-bicycle into the [3.2.1]-bicycle of **81** in 77% yield. Wiesner also achieved a solution phase Wagner–Meerwein rearrangement several years later, in a tricyclic model system.[4b] Under solvolytic conditions, tosylate **82** underwent rearrangement to tricycles **83** as a 1:1 mixture of olefins. This biomimetic conversion was key to their strategy to access C_{19} aconitine and C_{20} napelline type alkaloids.

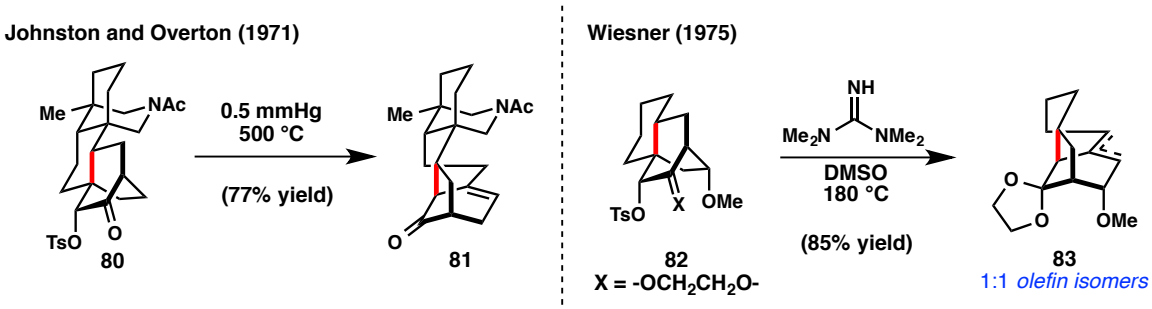


Figure 3.2. Chemical support for biomimetic Wagner–Meerwein rearrangements.

3.3 PRIOR TOTAL SYNTHESES

3.3.1 *Wiesner's Synthesis of C_{19}- and C_{20}-Diterpenoid Alkaloids*

Wiesner's landmark synthesis of talatisamine (**34**) in 1974 constitutes the first total synthesis of a C_{19}-diterpenoid alkaloid.[4a] Implementation of the Wagner–Meerwein

rearrangement in the more complex context of total synthesis proved challenging, but was eventually accomplished during the late stage of the synthesis. The synthesis begins with an initial Diels–Alder cycloaddition between bicycle **84** and diene **85** afforded two diastereomeric tricycles that were independently advanced to sulfonamide **86** (Figure 3.3).[4b] Deprotonation by sodium hydride and cyclization afforded the piperidine ring, and after mesylate reduction and methylation, provided aromatic intermediate **87**. At this stage, a dissolving metal reduction, amine acylation, and olefin isomerization afforded enone **88**, which readily underwent [2 + 2] cycloaddition with allene to furnish cyclobutane **89**. Another three steps involving oxidative cleavage of the exocyclic olefin, generated cyclobutanol **90**, and upon exposure to Brønsted acid, underwent a retro-aldol reaction to ketoaldehyde **91** and intramolecular aldol cyclization to provide the [2.2.2]-bicycle of atisine framework **92**. A further seven steps were required to install the tosylate leaving group of **93** in the requisite stereochemical configuration.

With tosylated atisine analogue **93**, the biomimetic Wagner–Meerwein rearrangement would forge the [3.2.1]-bicyclic CD-rings of talatisamine (**34**). Under previously described conditions employing a tetramethylguanidine base at elevated temperatures, **93** underwent rearrangement to presumably produce carbocationic intermediate **94**, and subsequently, an equimolar mixture of olefinic isomers **95** and **96** (Figure 3.4). Although the rearrangement proceeded in good overall yield, isomer **95** could not be advanced in a productive manner; only isomer **96** was carried forward to pentacycle **97**. Upon mercuric acetate-mediated oxidation, a biomimetic aza-Prins cyclization formed the last C7–C17 bond, completing the first total synthesis of a C_{19}-diterpenoid alkaloid, talatisamine (**34**).

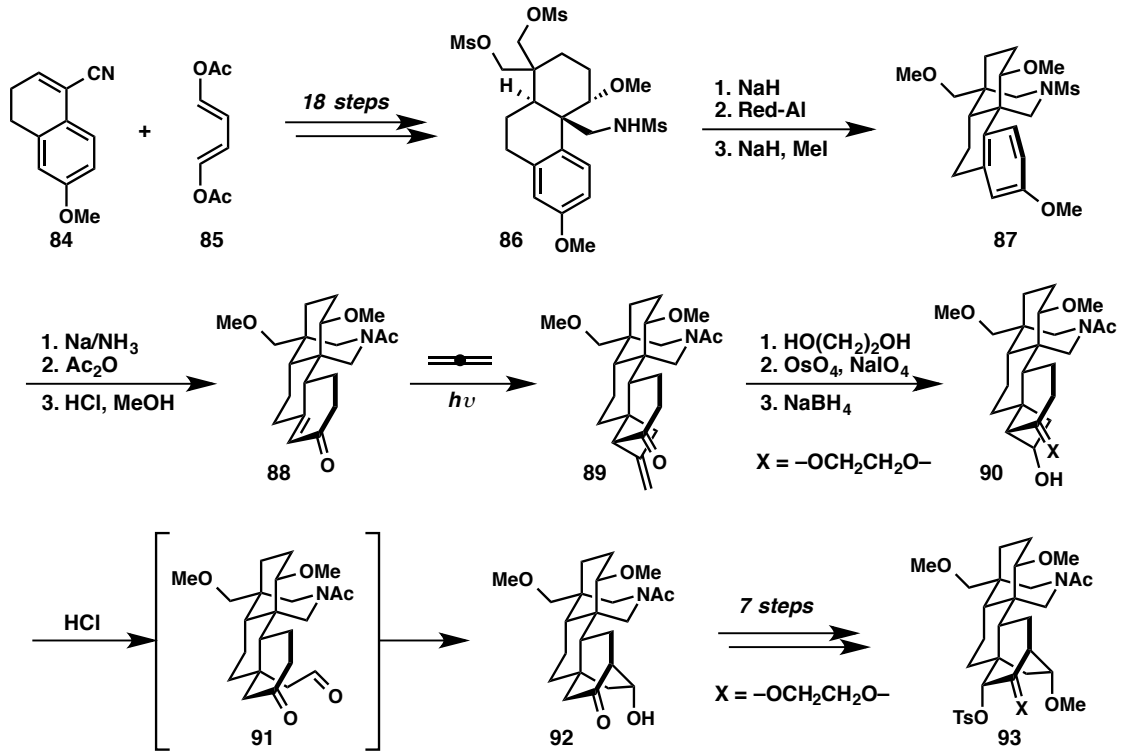


Figure 3.3. Synthesis of Wagner–Meerwein rearrangement precursor **93**.

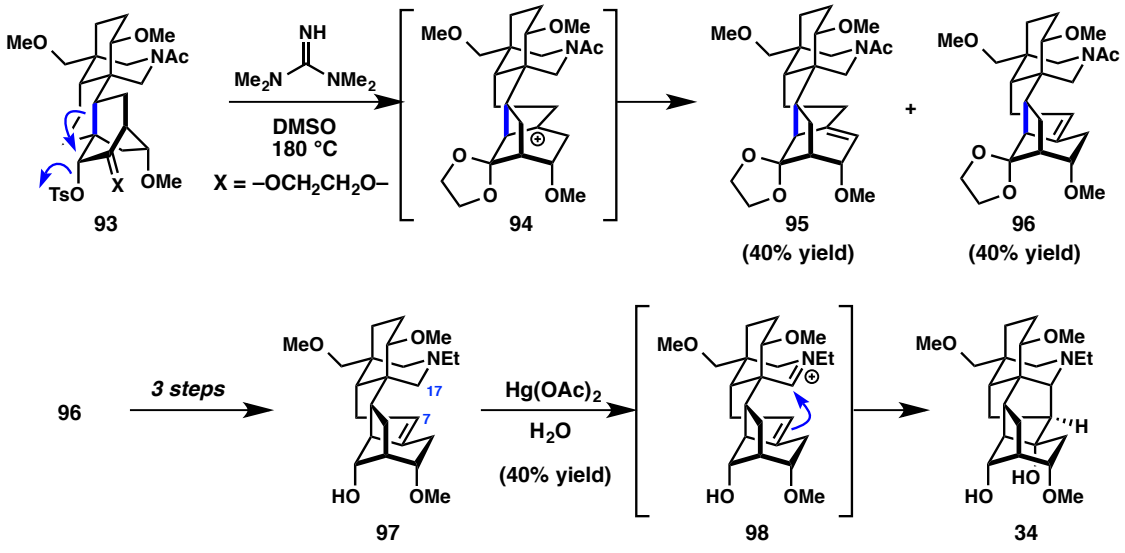


Figure 3.4. Wiesner's total synthesis of talatisamine (**34**).

In an effort to improve the synthesis, Wiesner and coworkers hypothesized that performing the biomimetic rearrangement with the C7–C17 bond in place would preclude the unproductive, strained olefin isomer **95**. Accordingly, they began synthetic efforts towards 13-desoxydelphonine (**99**), which possesses a C6-methoxy group. Olefin **100** was synthesized in 11 steps from *o*-cresol, and then engaged in an aziridination and aza-semipinacol rearrangement of **101** to form the C7–C17 bond (aconitine numbering) of acetamide **102** (Figure 3.5). A 20-step sequence appended a cyclohexyl ring bearing a methyl ester (**103**), and another 5 steps involving lactam formation provided aromatic intermediate **104**. Most importantly, this intermediate (**104**) possesses the C7–C17 bond that was absent in their first generation synthesis of talatisamine (**34**).

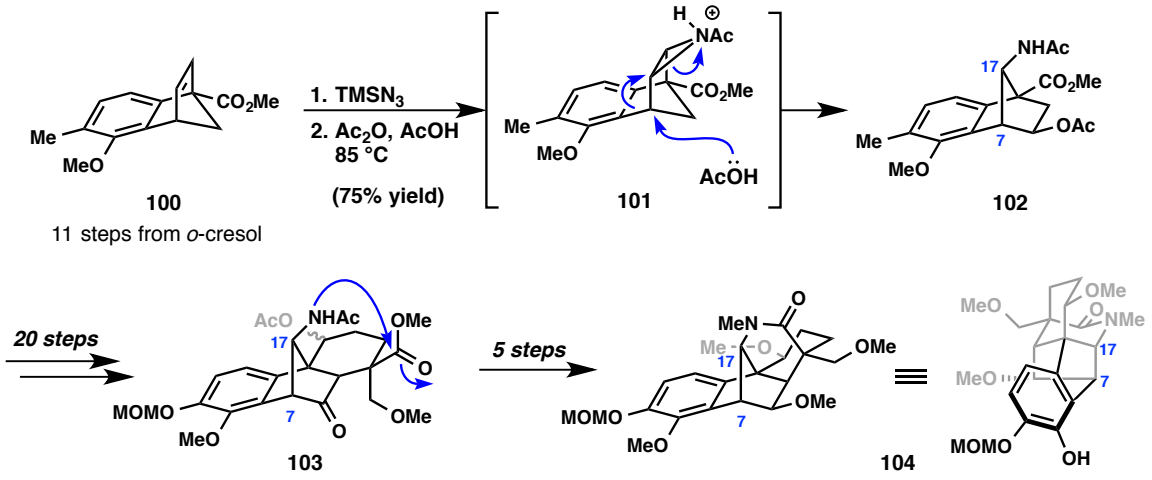


Figure 3.5. Synthesis of pentacyclic aromatic intermediate **104**.

From aromatic intermediate **104**, the endgame strategy mirrors that of their synthesis of talatisamine (**34**), however with the C7–C17 bond in place, significant improvements were observed. Rather than a reductive dearomatization, three steps involving oxidative dearomatization of arene **104** provided diene **105** as a mixture of

diastereomers and brominated/unbrominated products (Figure 3.6). The mixture of products underwent an intermolecular Diels–Alder cycloaddition with benzyl vinyl ether, and after global reduction with zinc metal, afforded a single hexacyclic product **106** that comprises the C_{20} denudatine framework. Elaboration of **106** to hexacyclic intermediate **107** required 12 steps, thereby installing a bromide leaving group for the crucial rearrangement. Under previously described conditions, the Wagner–Meerwein rearrangement of bromide **107** proceeded smoothly to afford aconitine framework **108** as a single isomer in 89% yield. This rearrangement is a significant improvement from their previous synthesis, which provided a 1:1 mixture of olefinic isomers. A final four steps involving deprotection, reductions, and hydrations provided 13-desoxydelphonine (**99**). The fourth generation synthetic strategy obviated the low yielding aza-Prins cyclization, since the C7–C17 bond was formed at a relatively early stage in the synthesis. This seminal work leveraged the conversion of denudatine framework **107** into the aconitine framework **108**, a finding that would be pivotal for the success of future syntheses.

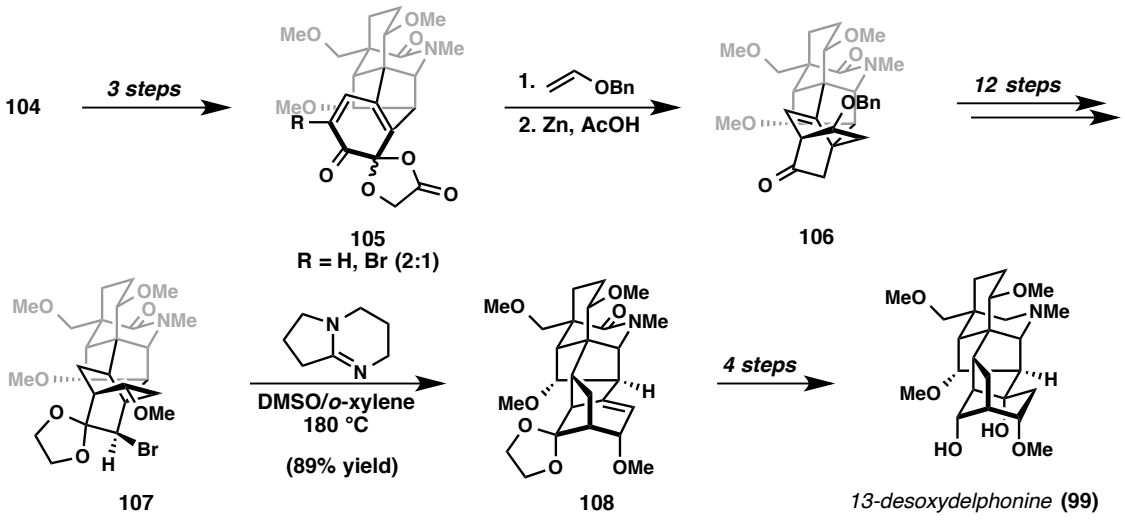


Figure 3.6. Wiesner's total synthesis of 13-desoxydelphonine (**99**).

During the course of Wiesner's work towards C_{19} aconitine type alkaloids, his group also explored the biomimetic conversion of the denudatine scaffold to the napelline scaffold through a similar Wagner–Meerwein rearrangement (Figure 3.7).[8] Denudatine framework **109** was synthesized in a fashion analogous to the previously described synthesis of 13-desoxydelphonine (**99**). By installing a leaving group at C13 instead of C15, rearrangement of mesylate **109** occurred readily under reflux in acetic acid to furnish triacetate **110**. This was advanced three steps to triketone **111**, which constituted a formal synthesis of napelline (**29**) based on their earlier work.[8c]

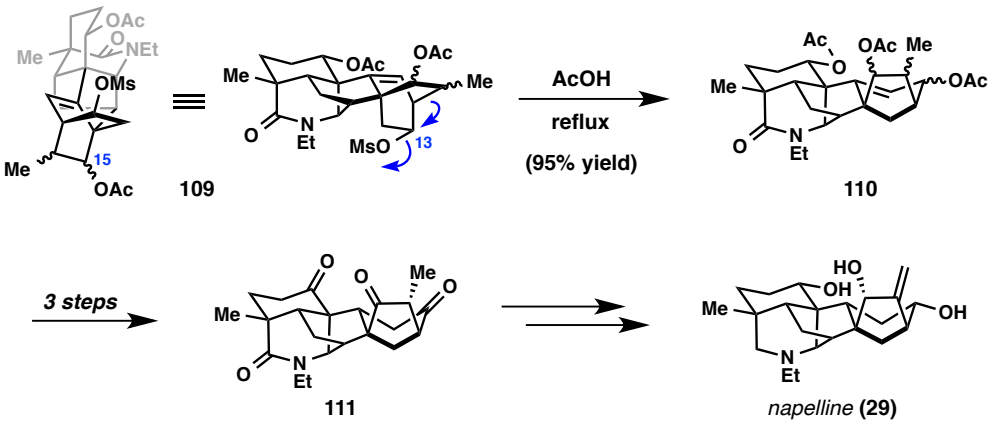


Figure 3.7. Wiesner's total synthesis of napelline (**29**).

Wiesner's work towards the synthesis of C_{19}- and C_{20}-diterpenoid alkaloids was initially part of a structural elucidation effort, but undoubtedly inspired future syntheses that also feature elegant use of Wagner–Meerwein rearrangements for conversions of denudatine scaffolds to aconitine scaffolds. Although Wiesner's syntheses cannot be held to the same standards as modern total synthesis, their influence on the field is incredibly significant, as the diterpenoid alkaloids remain formidable targets for total synthesis, even with modern synthetic methods.

3.3.2 *Gin's Synthesis of Neofinaconitine*

The next total synthesis of a diterpenoid alkaloid possessing the aconitine core came nearly four decades after Wiesner's work. In Gin's posthumous synthesis of the C_{18}-diterpenoid alkaloid neofinaconitine (**112**), a convergent strategy was employed to assemble the aconitine scaffold and to access to synthetic material for stereochemical/structural confirmation.[9] Notably, the synthesis did not utilize the same Wagner–Meerwein rearrangement as the past and future syntheses. In their retrosynthetic analysis, Gin and coworkers envisioned forming the C7–C8 bond of neofinaconitine (**112**) through a radical cyclization and the C11 quaternary center through an intramolecular Mannich reaction at C17 (Figure 3.8). The deconstructed polycycle **113** could be accessed in a convergent manner by Diels–Alder cycloaddition of dihydroazepinone **114** and siloxydiene **115**. The fused cyclopropane of **115** could be prepared by another unusual Diels–Alder cycloaddition between siloxydiene **116** and cyclopropene **117**.

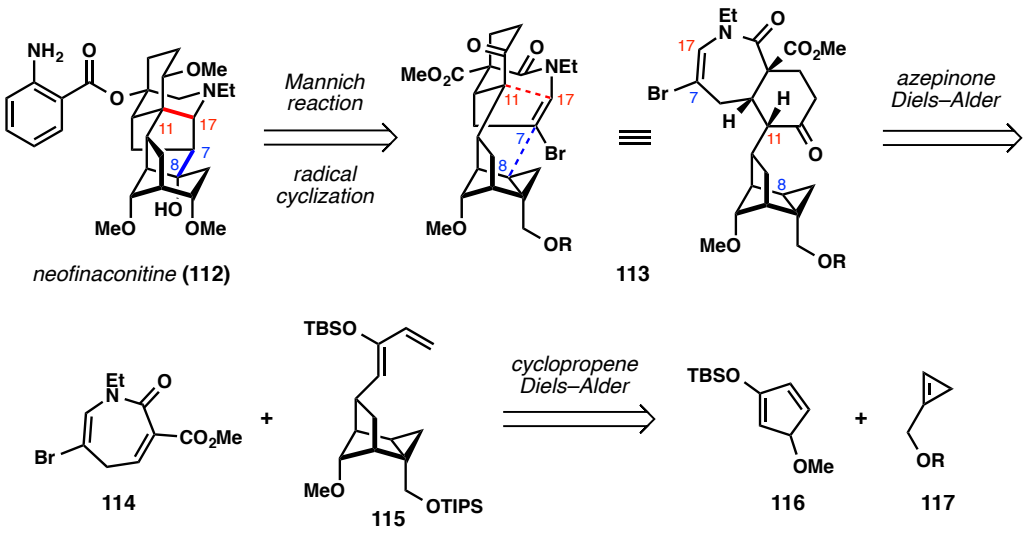


Figure 3.8. Gin's retrosynthetic analysis of neofinaconitine (**112**).

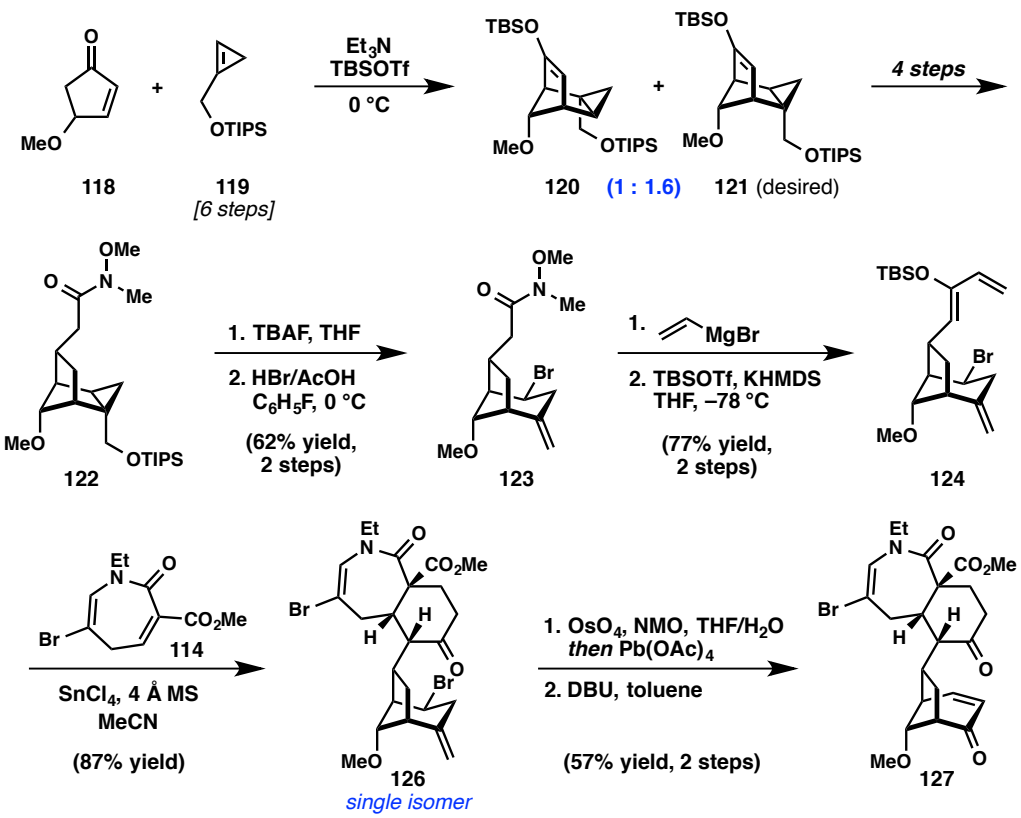


Figure 3.9. Convergent assembly of Mannich cyclization precursor **127**.

The C/D bicycle was generated at an early stage in the synthesis through a Diels–Alder cycloaddition between cyclopropene **119** and a siloxydiene generated *in situ* from cyclopentene **118** (Figure 3.9). This produced two isomeric cycloadducts **120** and **121** in a 1:1.6 ratio, in favor of the desired isomer. This mixture was advanced four steps to Weinreb amide **122**, which was ultimately isolable as a single isomer. Since the cyclopropylmethyl silyl ether moiety of **122** was detrimental to diastereoselectivity of the ensuing azepinone Diels–Alder, it was converted to homoallyl bromide **123**, which served as an α,β-unsaturated ketone precursor. Addition of vinyl-Grignard and silyl ether formation provided siloxydiene **124** as a single olefin isomer. With the homoallylic bromide of **124**, it was suspected that the sterically large bromine atom would hinder the

"back" face of the diene and restrict rotation, thereby improving the diastereofacial selectivity. Remarkably, Diels–Alder cycloaddition with azepinone **114** in the presence of tin tetrachloride provided cycloadduct **126** in 87% yield as a single product. Lastly, homoallyl bromide **126** was converted to enone **127** by oxidative scission of the exocyclic olefin, followed by β-elimination of the bromide.

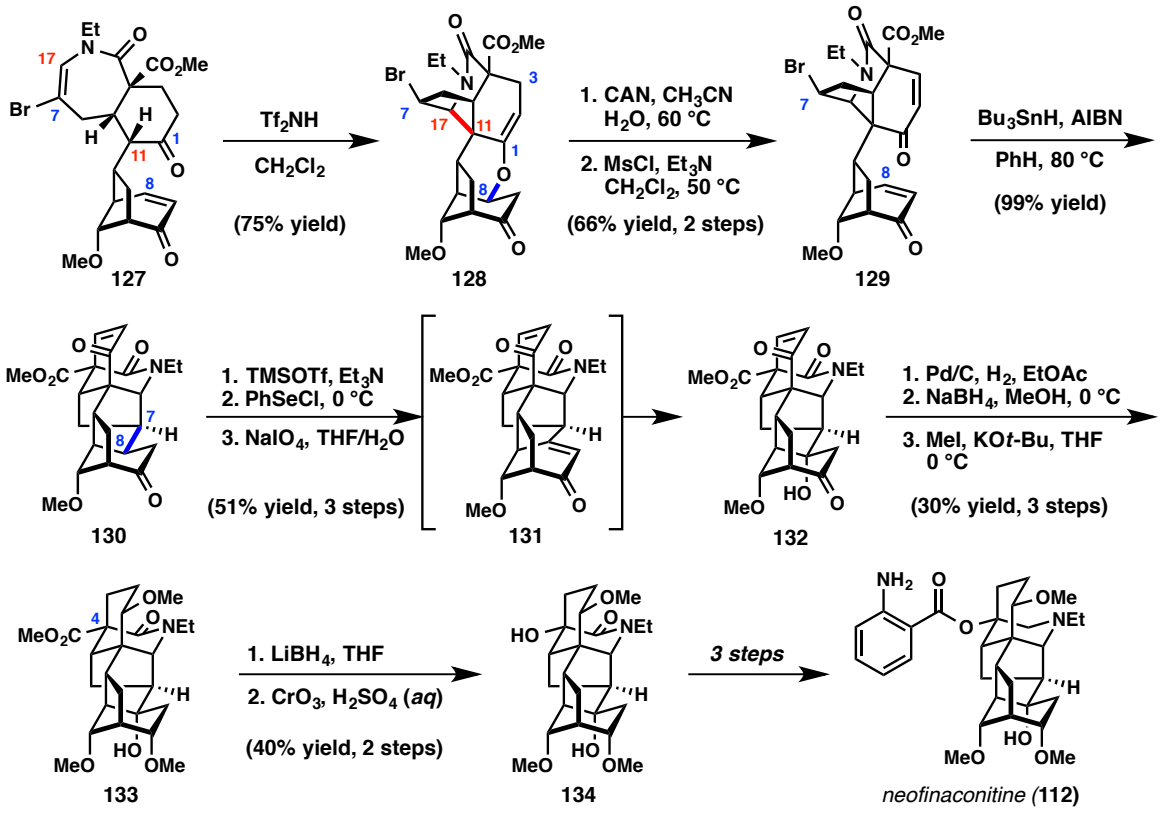


Figure 3.10. Gin's total synthesis of neofinaconitine (**112**).

The assembly of the aconitine core required two crucial C–C bond formations. The C11–C17 bond was to be formed by an intramolecular Mannich-type *N*-acyliminium cyclization, and the C7–C8 bond was to be formed by an intramolecular radical cyclization. Protonation of enamide **127** with triflimide produced an *N*-acyliminium ion that underwent Mannich reaction with a C1–C11 enol to forge the desired C11–C17 bond

(Figure 3.10). Unfortunately, the C1 ketone underwent cyclization onto the D-ring enone to forge the unproductive C8–O bond of **128**. Cleavage of this undesired C8–O bond required three steps, and was accomplished by allylic oxidation at C3, followed by mesylation and elimination to produce bis-enone **129**. Remarkably, the radical cyclization proceeded smoothly to construct the C7–C8 bond of the aconitine core (**130**) in quantitative yield. To date, this remains the most expedient synthesis of the full aconitine scaffold.

The remainder of the synthesis necessitated functional group interconversions to establish alcohol and methyl ether stereocenters, oxidative truncation of the C4 methyl ester, and selective acylation of the resulting C4 alcohol. The tertiary alcohol at C8 was introduced utilizing the D-ring ketone of **130** (Figure 3.10). Silyl enol formation and selenation provided an α-selenide that underwent oxidation/elimination by treatment with sodium *meta*-periodate. The transiently generated bridgehead olefin (**131**) readily underwent hydration to provide tertiary alcohol **132**. Hydrogenation, borohydride reduction, and methylation provided **133** in 30% yield over three steps. Although this sequence terminated with a low yielding, non-selective *bis*-methylation, an efficient protocol involving global methylation and formal C8-OMe demethylation was developed in subsequent semisynthetic studies. From C_{19} acontine scaffold **133**, borohydride reduction of the methyl ester was followed by oxidative truncation to provide the C4 alcohol of the C_{18}-diterpenoid alkaloids (**134**). Finally, amide reduction and acylation provided neofinaconitine (**112**) in an additional three steps. Structural assignment of the synthetic material was also confirmed through relay synthesis from the C_{19}-diterpenoid alkaloid condelphine. Gin's synthesis of neofinaconitine (**112**) showcases the advantages

of a non-biomimetic, convergent strategy for the synthesis of highly caged, polycyclic frameworks.

3.3.3 *Sarpong's Unified Strategy towards C_{20}-, C_{19}-, and C_{18}-Diterpenoid Alkaloids*

Wiesner's landmark syntheses of C_{19} aconitine type and C_{20} napelline type alkaloids demonstrated the viability of biomimetic conversions of denudatine scaffolds to napelline and aconitine scaffolds in total synthesis. These conversions would be employed once again in the synthesis of weisaconitine D (**135**) and liljestrandinine (**154**), which Sarpong reported as the first strategy to access both C_{18}- and C_{19}-diterpenoid alkaloids.[10] In contrast to Gin's synthesis of neofinaconitine (**112**), which oxidatively truncates the C4–C18 bond of a C_{19}-framework,[9] Sarpong's synthesis excludes C18 for the synthesis of **135**, and modularly constructs the C4–C18 bond of C_{19}-diterpenoid alkaloid **154**. In their retrosynthetic analysis of **135**, the B-ring was identified as the maximally bridged ring, and was disconnected, along with the C/D-rings, to arene-olefin **136** (Figure 3.11). The maximally bridged piperidine E-ring of **136** was disconnected at the C19–N bond to arrive at hydrindane **137**. This bicycle would serve as the divergence point for C_{19}- and C_{20}-diterpenoid alkaloids, which require quaternization at C4. Bicycle **137** would arise from a Diels–Alder cycloaddition between diene **138** and enone **139**.

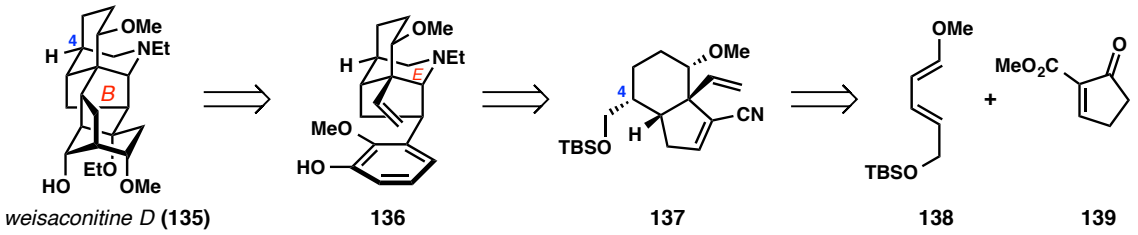


Figure 3.11. Sarpong's retrosynthetic analysis of weisaconitine D (**135**).

The synthesis of weisaconitine D (**135**) proceeded in 30 steps from diene **138**, which itself is available in five steps from commercial materials (Figure 3.12). A Diels–Alder cycloaddition between **138** dienophile **139** provided a cycloadduct that was hydrogenated to give bicycle **140**. The ketone of **140** was converted to the vinyl triflate, which underwent cross-coupling with sodium cyanide to yield α,β-unsaturated nitrile **131** in 70% yield over the two steps. Next, a Rh-catalyzed conjugate addition with *in situ* generated lithium boronate **142** simultaneously generated two adjacent stereocenters in **143**. The nitrile was stereospecifically converted to the carbamate through a Hoffmann rearrangement, with additional steps providing mesylate **144**. Subjection to potassium *tert*-butoxide then effected intramolecular alkylation to forge the piperidine ring of **145** in 76% yield. Methoxymethyl ether cleavage and oxidative dearomatization afforded the intramolecular Diels–Alder substrate **146**.

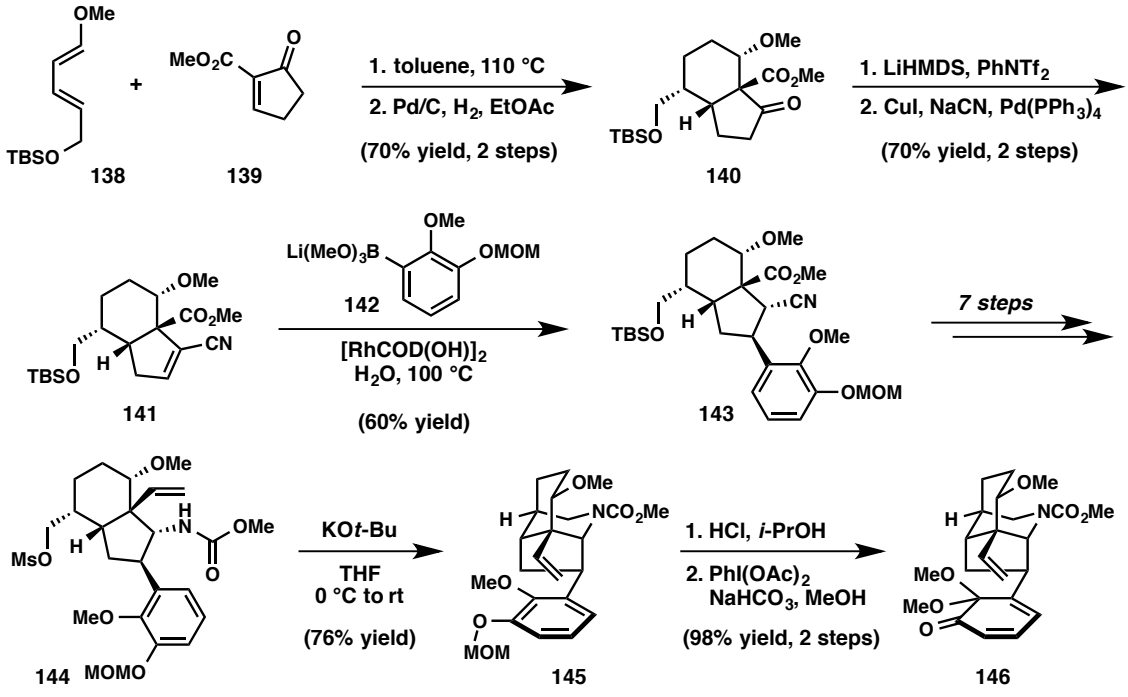


Figure 3.12. Preparation of intramolecular Diels–Alder precursor **146**.

Dienone **146** readily underwent cycloaddition in refluxing *para*-xylene to produce the bicyclo[2.2.2] moiety of **147** (Figure 3.13). Four functional group manipulations provided alcohol **148**, and exposure to triflic anhydride generated an intermediate triflate that underwent the key Wagner–Meerwein rearrangement to forge the [3.2.1]-bicycle of **149**. The rearrangement produced a single product, even though two isomeric alcohols are possible; presumably, the allylic isomer of **149** is precluded due to ring strain from a bridgehead olefin. Another eight steps were required to install the final C–O bond, the *N*-ethyl group, and the C16 methoxy group of weisaconitine D (**135**).

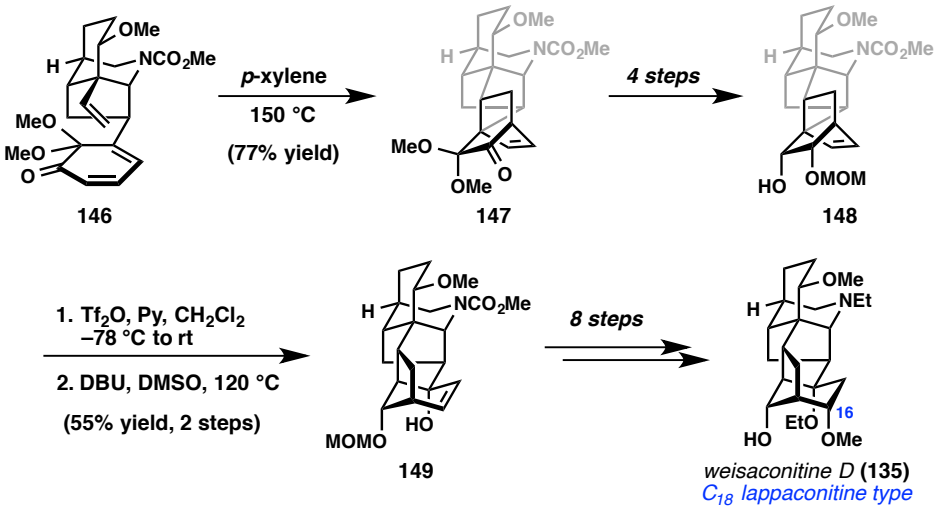


Figure 3.13. Sarpong's total synthesis of weisaconitine D (**135**).

Extension of this strategy to the synthesis of C_{19}- and C_{20}-diterpenoid alkaloids necessitated quaternization at C4. To this end, alcohol **150** was oxidized under Swern conditions to the aldehyde (not shown) to facilitate α-functionalization (Figure 3.14). Unfortunately, attempts to alkylate the aldehyde were unfruitful, leading to decomposition or alkylation from the undesired α-face. Ultimately, an aldol-Cannizzaro sequence was developed to access a 1,3-diol that was subsequently mesylated to afford

bis-mesylate **151** with the C4 stereocenter ablated. At this stage, intramolecular *N*-alkylation provided the piperidine ring of tetracycle **152**, and mesylate displacement with methoxide afforded the C18 methoxy group of **153**. This was advanced to C_{19}-diterpenoid alkaloid liljestrandinine (**154**) in a further 12 steps analogous to the weisaconitine D (**135**) synthesis.

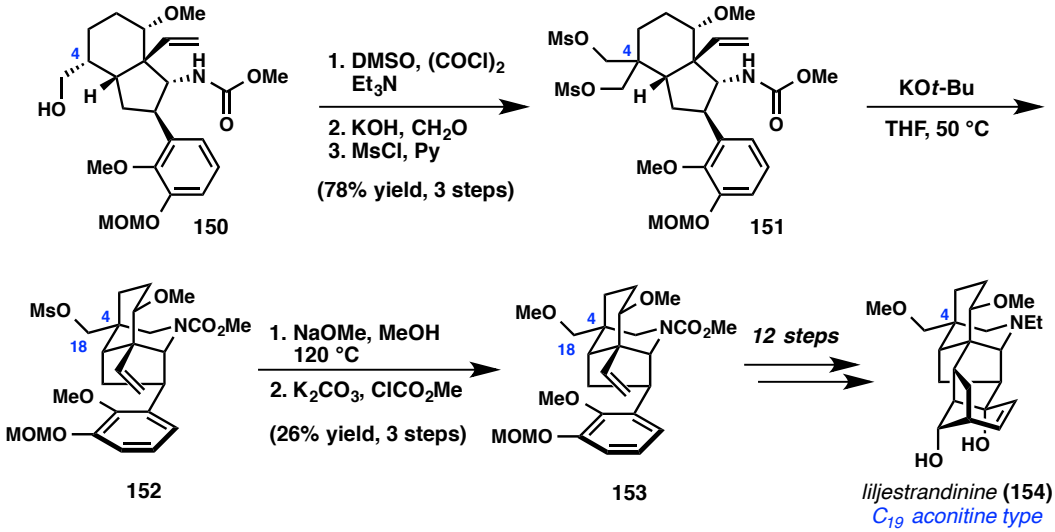


Figure 3.14. Sarpong's total synthesis of liljestrandinine (**154**).

By establishing a protocol to functionalize C4, bis-mesylate **151** is well suited for advancement to C_{20} denudatine type alkaloids.[11] Optimal conditions for piperidine ring formation were identified using potassium hydride instead of potassium *tert*-butoxide, providing **154** in a substantially improved 83% yield (Figure 3.15). Reductive cleavage of the C18 mesylate to the methyl group and oxidative dearomatization/intramolecular Diels–Alder cycloaddition were accomplished in four steps to furnish hexacycle **155**, which possesses the bicyclo[2.2.2] moiety of the denudatine type alkaloids. A final seven

steps of functional group interconversions provided cochlearenine (**156**), as well as *N*-oxidized and C17-veratroylated natural analogues.

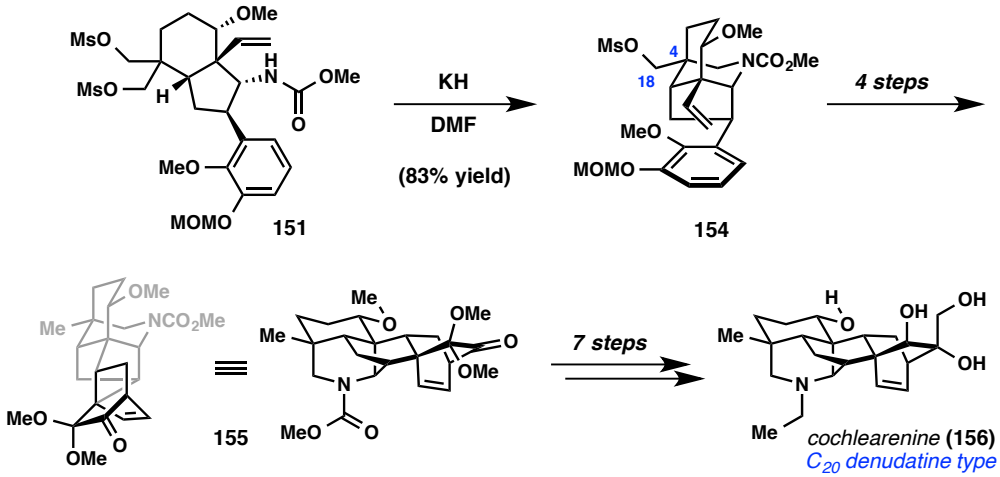


Figure 3.15. Sarpong's total synthesis of cochlearenine (**156**).

The installation of stereocenters relies completely on diastereocontrol from stereocenters established in the initial Diels–Alder cycloaddition that forms the hydrindane unit. Thus, an enantioselective variant of the transformation would render the syntheses asymmetric. For this purpose, dienophile **157** was synthesized and utilized in a Cu-catalyzed enantioselective Diels–Alder cycloaddition with diene **138**, providing cycloadduct **158** in 92% enantiomeric excess. The carbonylcarbamate functionality could be converted to the methyl ester by subjection to bismuth(III) triflate in methanol, and after re-protection of the silyl ether in the same pot, provides hydrindane **159** thereby intercepting an early intermediate in the syntheses.

Sarpong's synthetic strategy targets C_{18}-, C_{19}-, and C_{20}-diterpenoid alkaloids in a modular fashion through C4 quaternization and biomimetic Wagner–Meerwein rearrangements of denudatine frameworks to aconitine frameworks. Specifically, by

diverging at an early stage in the synthesis through arene olefin **150** (see Figure 3.14), the strategy demonstrate that C_{18} variants need not necessarily derive from C_{19} or C_{20} variants through C4–C18 bond scission. These syntheses also highlight the potential of *de novo* syntheses to access biogenetically related diterpenoid alkaloids.

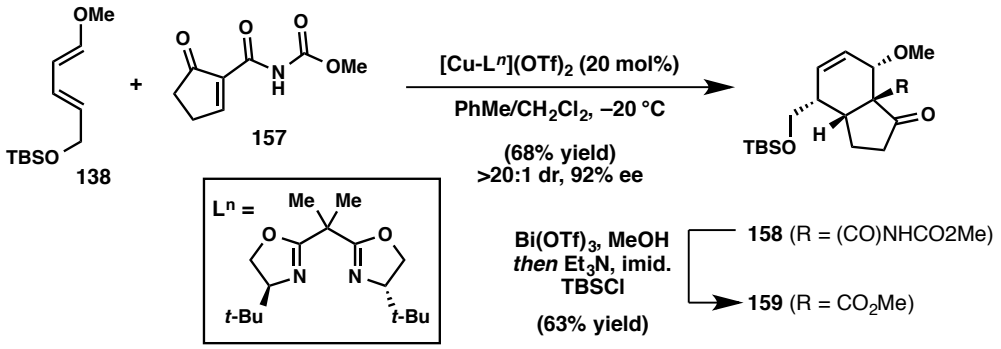


Figure 3.16. Enantioselective [4 + 2] for the synthesis of hydrindane **159**.

3.3.4 *Fukuyama's Synthesis of C_{19}- and C_{20}-Diterpenoid Alkaloids*

In 2014, Fukuyama reported the first total synthesis of a C_{20} denudatine type alkaloid, lepenine (**160**).[12] In their follow up study, an intermediate in their synthesis was advanced to the C_{19} aconitine type alkaloid, cardiopetaline (**162**), by employing a microwave-assisted Wagner–Meerwein rearrangement.[13] Both lepenine (**160**) and cardiopetaline (**162**) were accessed from common intermediate **161** (Figure 3.17). Retrosynthetically, lepenine (**160**) was proposed to arise from arene **163**. Ultimately, their sequence for installing the bicyclo[2.2.2] moiety mirrored that of Wiesner's fourth generation synthesis of 13-desoxydelphonine (**99**, see Figure **3.6**). The C7–C20 bond (denudatine numbering) of **163** could be constructed by an intramolecular Mannich cyclization between the ketone of **164** and an *in situ* generated iminium ion.

Coincidentally, the analogous C11–C17 bond of neofinaconitine (**112**) is also constructed by an intramolecular Mannich cyclization in Gin's synthesis.[9] The tricyclic core of **164** could be stereoselectively generated by an intramolecular Diels–Alder cycloaddition of **165**, which possesses only a single stereogenic center.

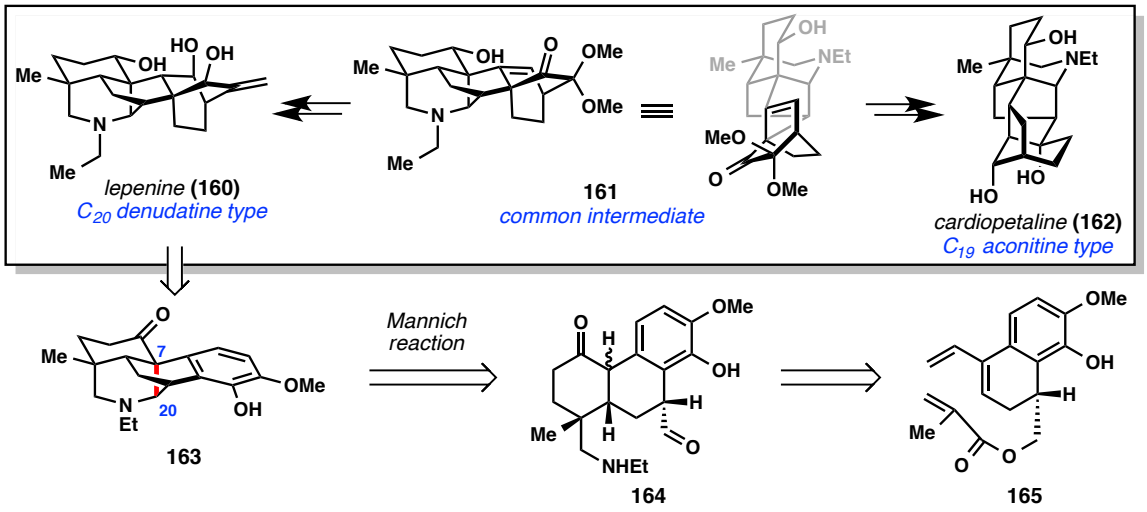


Figure 3.17. Divergent strategy for lepenine (**160**) and cardiopetaline (**162**).

The first stereogenic center is derived from L-lactic acid methyl ester. In two steps (not shown), allylic alcohol **166** was synthesized, and a tandem Johnson–Claisen rearrangement/Claisen rearrangement occurred upon refluxing in triethylorthoacetate to afford *trans*-olefin **167** in 85% yield (Figure 3.18). Mesylation, ozonolysis/reduction, and pivaloylation provided pivalate **168**, which was determined to have an enantiomeric excess of 91%, indicating successful chirality transfer during the Claisen rearrangement. Friedel–Crafts acylation of an intermediate carboxylic acid afforded tetralone **169**, which was advanced four steps to Diels–Alder precursor **170**. In the subsequent cycloaddition, heating in the presence of a radical scavenger successfully constructed the phenanthrene

core of **171**. At this stage, crystallization of intermediate **171** provided enantiomerically pure material.

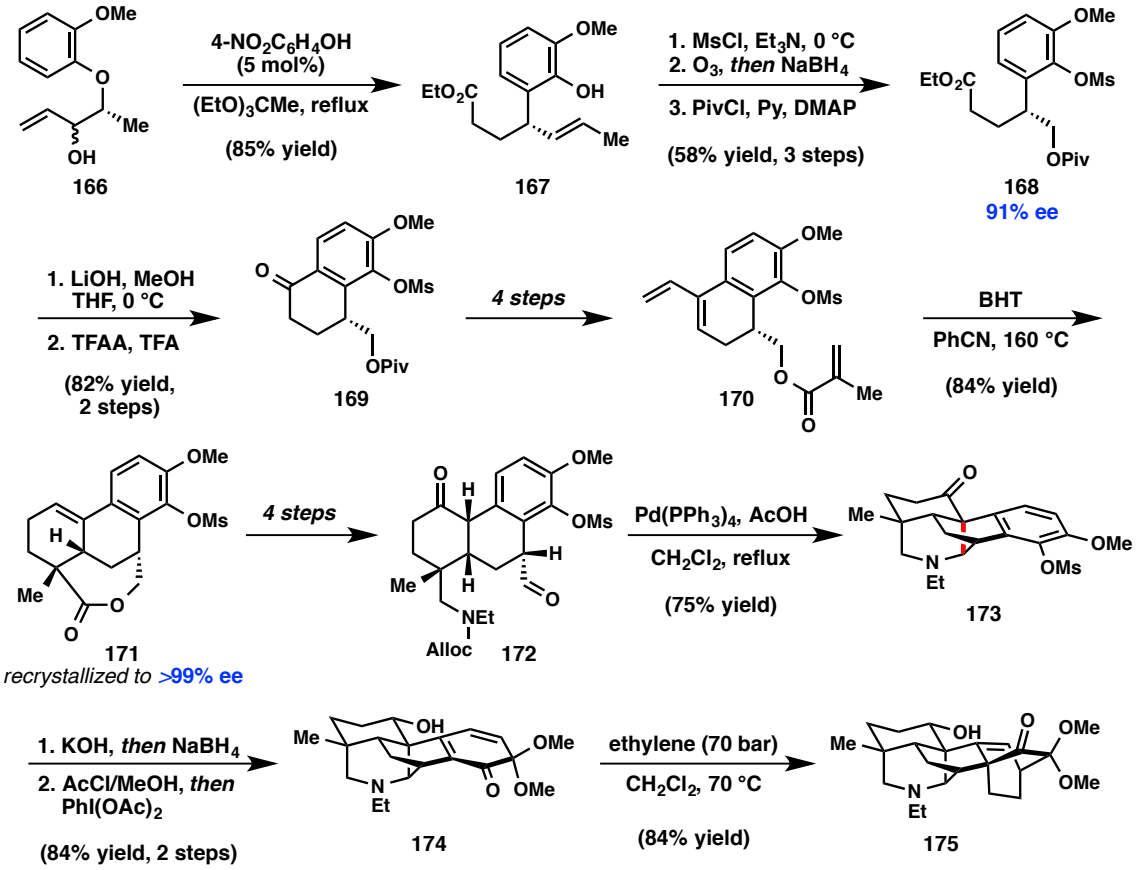


Figure 3.18. Synthesis of denudatine core **175**.

In four steps, the olefin of **171** was hydrated, and the bridging lactone is converted to aminoaldehyde **172**. Upon Pd-catalyzed removal of the Alloc group, an intramolecular Mannich reaction occurred to provided pentacycle **173** in 75% yield. This single step constructs two bridged ring systems in the piperidine ring and bicyclo[2.2.1] moiety. From **173**, cleavage of the mesylate, *in situ* borohydride reduction, and oxidative dearomatization then afforded *ortho*-quinone monoketal **174**. Heating **174** under an

ethylene atmosphere smoothly furnished the bicyclo[2.2.2] system of **175**, which constitutes the C_{20} denudatine core.

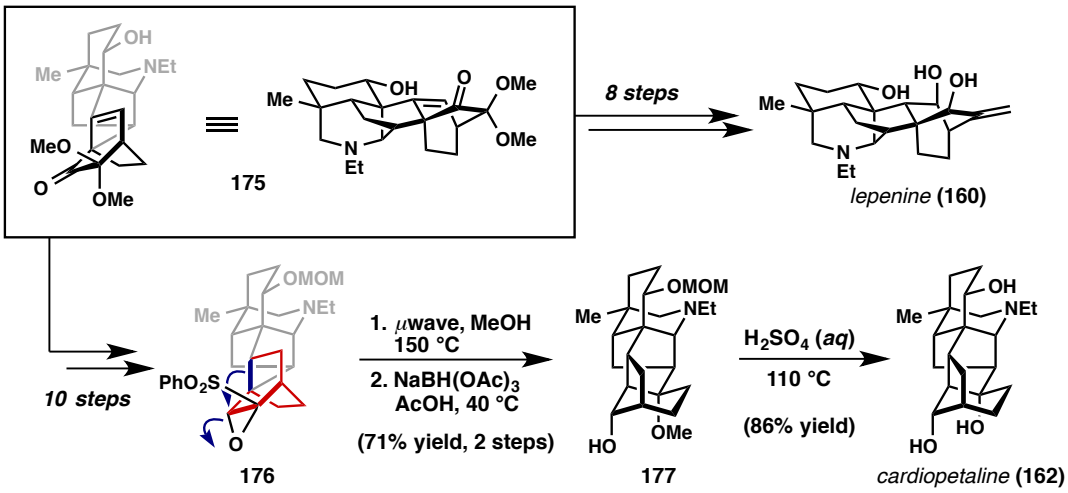


Figure 3.19. Fukuyama's total syntheses of lepenine (**160**) and cardiopetaline (**162**).

With the denudatine core **175** in place, eight steps of standard functional group manipulations including hydration of the olefin and methylenation provided C_{20} denudatine type alkaloid, lepenine (**160**, Figure 3.19). In order to access the C_{19}-diterpenoid alkaloid scaffold, **175** was converted to sulfonyloxirane **176** in 10 steps. The epoxide underwent a microwave-assisted Wagner–Meerwein rearrangement, and upon reduction, provided the alcohol of aconitine core **177**. Finally, methoxymethyl ether cleavage and formal demethylation at C8 was accomplished by heating in aqueous sulfuric acid, providing cardiopetaline **162** in 86% yield. Although Fukuyama's studies appear to draw heavily from Wiesner's fourth generation methods,[4f] synthesis of the analogous aromatic intermediate was significantly improved, and the strategy successfully transferred asymmetry from the chiral pool. Additionally, a new additive-

free method for the Wagner–Meerwein rearrangement was identified for sulfonyloxirane **176**.

3.3.5 *Summary of Previous Synthetic Strategies*

Wiesner's pioneering studies heavily influenced future syntheses. The salient transformation of Wiesner's, Sarpong's, and Fukuyama's syntheses is a biomimetic Wagner–Meerwein rearrangement that transforms a denudatine scaffold to an aconitine scaffold. The requisite bicyclo[2.2.2] systems were constructed using inter- and intramolecular Diels–Alder cycloadditions. However, as demonstrated in the three syntheses, stereoselective installation of the necessary leaving groups required long sequences of minimally productive functional group manipulations. Thus, syntheses that construct the CD-[3.2.1]-bicycle in a non-biomimetic fashion may circumvent these issues. Although Gin's synthesis of neofinaconitine (**112**) certainly addresses these challenges, the initial cyclopropene [4 + 2] cycloaddition proceeds with poor regioselectively, providing a 1:1.6 mixture of inseperable isomers. Our group's synthetic strategy, described in the next sections, represents a distinct approach to the aconitine core.

3.4 SYNTHETIC APPROACH TO DITERPENOID ALKALOIDS

A majority of the diterpenoid alkaloids possess a common structural motif in the AEF tricycle (Figure 3.20). This motif is comprised of a hydrindane framework (A/F rings) that is bridged by a substituted piperidyl ring (E ring). This tricycle is conjoined to a [3.2.1]-bicycle in the aconitine and napelline type alkaloids (*e.g.* **34** and **29**) and a

[2.2.2]-bicycle in the denudatine type alkaloids (*e.g.* **160**). We sought to identify a synthetic approach that would access these highly bridged polycyclic structures with a unified strategy. Talatisamine (**34**) was chosen as an initial target due to its compelling biological activity as a selective voltage-gated K^+ channel blocker. In a convergent manner, the central 6-membered B ring can be retrosynthetically disconnected to two polycycles of similar complexity: the AEF-rings (**178**) and the CD-[3.2.1]-bicycle (**179**). Analogous disconnections are envisioned for napelline (**29**), which possesses a [3.2.1]-bicycle with different relative connectivity to the AEF tricycle, and lepenine (**160**), which possesses a [2.2.2]-bicycle. Notably, the C_{20}-diterpenoid alkaloids bear an additional quaternary center at C8 that represents another major synthetic challenge for attachment to the F-ring. Nevertheless, we anticipate that development of a convergent synthesis of talatisamine (**34**), specifically through conjoining the two polycycles **178** and **179**, will be highly informative for the synthesis of C_{20} napelline and denudatine type alkaloids.

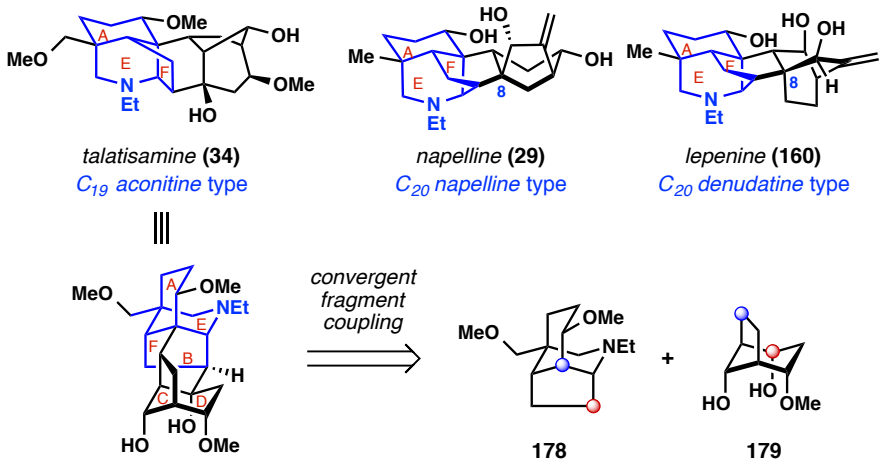


Figure 3.20. Synthetic strategy to convergently access diterpenoid alkaloids.

In order to achieve a truly convergent fragment coupling, enantioselective syntheses of both fragments must be developed. Furthermore, in addition to the bridged polycyclic structure, another major challenge for the synthesis of talatisamine (**34**) are the 12 contiguous stereocenters, including two quaternary centers at C4 and C11. In our retrosynthetic analysis, a key disconnection of the piperidine E-ring, through a lactam intermediate, to secondary amine **180** simplifies the construction of the C4 quaternary center to the facile α-functionalization of a diester (Figure 3.21). The secondary amine of **180** could be introduced via reductive amination of ketone **181**, which provides a functional handle to bisect the central B-ring at both α-positions of the ketone. Specifically, it was envisioned that an intramolecular aldol of diketone **182** would close the central B-ring, and a semipinacol rearrangement would construct the hindered C10–C11 bond and C11 quaternary center of **182** via epoxy alcohol **183**. Epoxy alcohol **183** is the direct product of a convergent fragment coupling between vinyl lithium **184** and epoxyketone **185**. This strategy streamlines the synthesis of bridged polycyclic compounds by enabling the coupling of two relatively complex fragments through the robust chemistry of 1,2-additions into ketones. The subsequent semipinacol rearrangement exploits the enthalpically favorable ring-opening of epoxides as a driving force for the formation of a hindered quaternary center,[14] and in this case, ultimately enables the crucial retrosynthetic disconnection of the C10–C11 bond, resulting in a highly convergent synthetic plan.

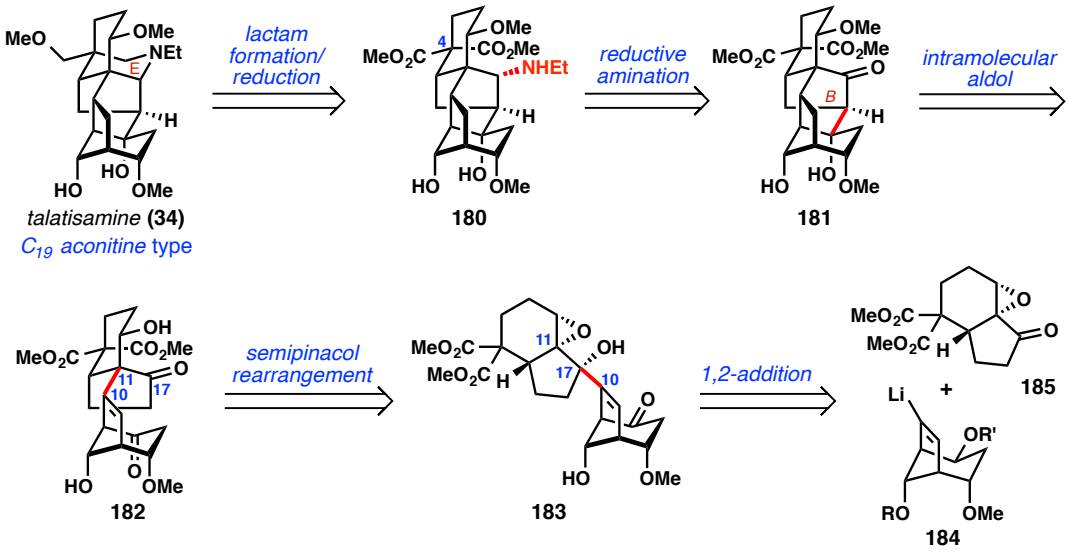


Figure 3.21. Retrosynthetic analysis of talatisamine (**34**).

3.5 FORWARD SYNTHETIC EFFORTS

In the following sections, our synthetic efforts towards C_{19}-diterpenoid alkaloid talatisamine (**34**) are described. A racemic route to epoxyketone **185** was developed first, and this was used in a model system to explore the 1,2-addition/semipinacol rearrangement sequence as well as the intramolecular aldol and reductive amination steps. Subsequently, enantioselective routes to epoxyketone **185** and [3.2.1]-bicycles were developed and employed in the 1,2-addition/semipinacol rearrangement sequence to convergently couple both fragments. Lastly, efforts to complete the total synthesis of talatisamine (**34**) are detailed.

3.5.1 *Semipinacol Rearrangement Model Studies towards a Tetracyclic Analogue*

Our first task was to establish proof of concept for a convergent fragment coupling towards diterpenoid alkaloids beginning with the synthesis of the AEF tricycle.

Thus, a racemic route to epoxyketone **185** was devised (Figure 3.22). Beginning with dimethyl malonate (**186**), alkylation with commercially available alkyl bromide **187** followed by Michael addition with 2-cyclopenten-1-one (**188**) forged the first quaternary center of **189** in modest yield. Exposure to aqueous hydrochloric acid at elevated temperature resulted in ketal deprotection and intramolecular aldol condensation to afford enone **190** in 84% yield. This three-step procedure efficiently constructs the hydrindane framework (AF rings) from cheap and readily available starting materials in a scalable manner.

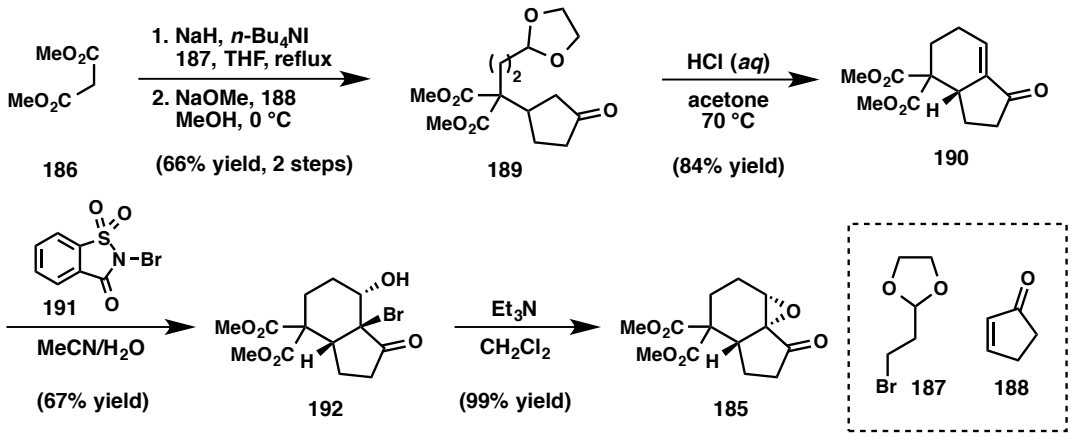


Figure 3.22. Racemic synthesis of epoxyketone **185**.

In order to establish the epoxide stereochemistry with the *trans*-fused ring junction, enone **190** was converted to bromohydrin **182** by treatment with *N*-bromosaccharin (**191**) in the presence of water.[15] This transformation presumably occurs by initial formation of a bromonium ion on the β-face, followed by nucleophilic addition of water from the α-face at the less substituted position. Other brominating reagents, such as *N*-bromosuccinimide, tetrabutylammonium tribromide, pyridinium tribromide, and bromine, were unsuccessful in activating the olefin of **190**; *N*-bromosaccharin

appears to be electrophilic enough to activate the non-nucleophilic olefin of **190**. Although this transformation did not occur with perfect regio- or stereocontrol, the major isomer **192** was separated from other isomers during purification by crystallization. Attempts to improve the selectivity by modifying reaction parameters (temperature, equivalents of water, *etc.*) were also unfruitful. Nonetheless, the bromohydration of enone **190** was easily scalable and permitted the diastereoselective synthesis of epoxyketone **185**. The last transformation was accomplished by simple exposure to triethylamine base to facilitate epoxide ring closure. Nucleophilic epoxidation of enone **190** was also explored, but did not provide isolable products; this method would also hypothetically produce the undesired *cis*-ring junction.

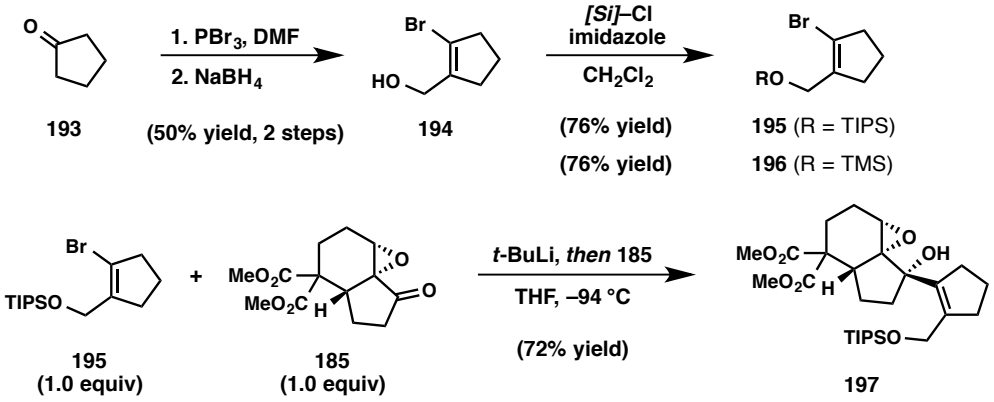
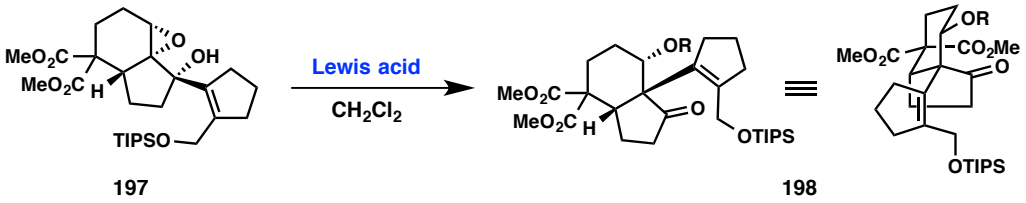


Figure 3.23. Synthesis of semipinacol rearrangement precursor **197**.

Vinyl halides readily undergo lithium-halogen exchange and addition into carbonyls, and vinylic functionality is known to have good migratory aptitude. Therefore, vinyl bromide **195** was chosen as an appropriate model compound, as it possesses a 5-membered ring that resembles the aconitine C-ring as well as a pendant silyl ether for the intramolecular aldol step (Figure 3.23). The synthesis of vinyl bromide **195** commenced

with a known two-step procedure engaging cyclopentanone (**193**) with Vilsmeier salt and *in situ* vinyl-bromide formation, followed by borohydride reduction to produce vinyl bromide **194**.[16] The allylic alcohol was then silyl protected to afford the corresponding silyl ethers **195** and **196** in good yield. Lithium-halogen exchange of vinyl bromide **195** using *tert*-butyllithium at low temperature provided the alkenyllithium, and addition of one equivalent of epoxyketone **185** afforded tertiary alcohol **197** as a single diastereomer in 72% yield. It was crucial to perform the 1,2-addition by inverse addition at –94 °C, as exposing the *in situ* generated vinyllithium to higher temperatures resulted in competing Wurtz dimerization. Nevertheless, cyclopentene **195** was successfully coupled to epoxyketone **185** while simultaneously establishing the requisite *anti*-relationship between the migrating cyclopentene and the epoxide of **197**.



197 **198**

Entry	Lewis acid	Additive	Temperature	Result
1	$ZnBr_2$	--	rt	no reaction
2	$AlMe_3$	--	–78 °C to rt	no reaction
3	$AlMe_2Cl$	--	–78 °C to rt	chlorohydrin
4	$EtAlCl_2$	--	–78 °C to rt	chlorohydrin
5	$BF_3{\bullet}OEt_2$	--	–45 °C	fluorohydrin
6	$TiCl_4$	--	–78 °C to rt	decomposition
7	$Yb(OTf)_3$	--	rt	desilylation
8	$Sc(OTf)_3$	--	–78 °C to rt	decomposition
9	TMSOTf	--	–78 °C	decomposition
10	TMSOTf	2,6-lutidine	0 °C	90% yield (R = TMS)

Table 3.1. Screen of Lewis acids for semipinacol rearrangement of **197**.

With an established protocol for the coupling of vinyl halides with epoxyketone **185**, we investigated the key semipinacol rearrangement to determine the feasibility of the proposed strategy to construct the challenging C11 quaternary center. For this purpose, a broad screen of common Lewis acids was conducted on epoxy alcohol **197** in dichloromethane (Table 3.1). Several common Lewis acids failed to promote reactivity (entries 1 and 2), while others promoted non-specific decomposition of the substrate (entries 6, 8, and 9) or desilylation (entry 7). Interestingly, alkylaluminum chlorides and boron trifluoride resulted in nucleophilic epoxide ring opening to halohydrins instead of semipinacol rearrangement (entries 3–5). In an attempt to protect the tertiary alcohol of **197**, it was discovered that subjection to TMSOTf in the presence of 2,6-lutidine directly afforded the desired rearrangement product **198** in 90% yield (entry 10). Presumably, the amine base acts to buffer the triflic acid formed in the alcohol protection step, and excess TMSOTf facilitates semipinacol rearrangement of the *in situ* generated silyl ether. The use of a stronger base, such as triethylamine, resulted in further conversion of ketone **198** to the silyl enol ether.

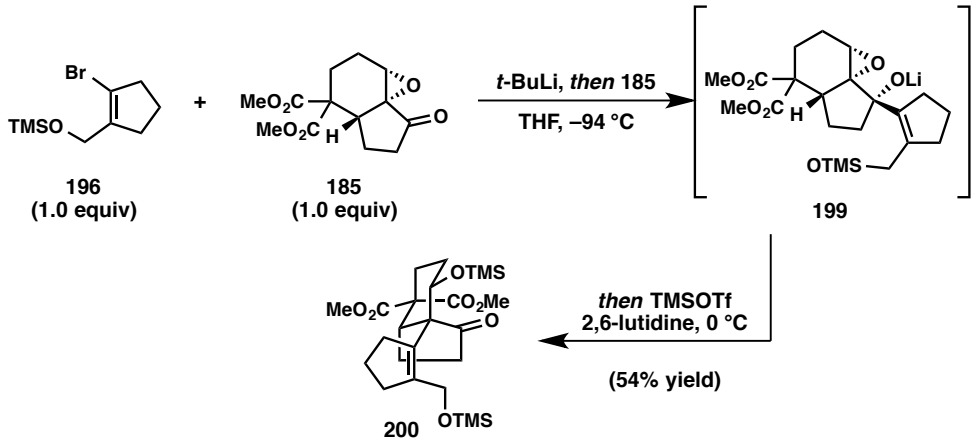


Figure 3.24. One pot 1,2-addition and semipinacol rearrangement.

Further highlighting the utility of this convergent fragment coupling strategy, the 1,2-addition and semipinacol rearrangement could be performed in a single vessel (Figure 3.24). Thus, lithium-halogen exchange of vinyl bromide **196** with *tert*-butyllithium followed by addition of epoxyketone **185** produces intermediate lithium alkoxide **199**. After warming the reaction temperature to 0 °C, TMSOTf and 2,6-lutidine are added to the reaction mixture, resulting in rapid semipinacol rearrangement to afford 54% yield of **200** in a single step. This remarkable transformation provides rearrangement product **200** as a *single diastereomer* from one equivalent of each coupling partner. This method enables the efficient construction of the aconitine C11 quaternary center directly from vinyl halides and epoxyketone **185**, and demonstrates potential for the synthesis of C_{20}-diterpenoid alkaloids as well.

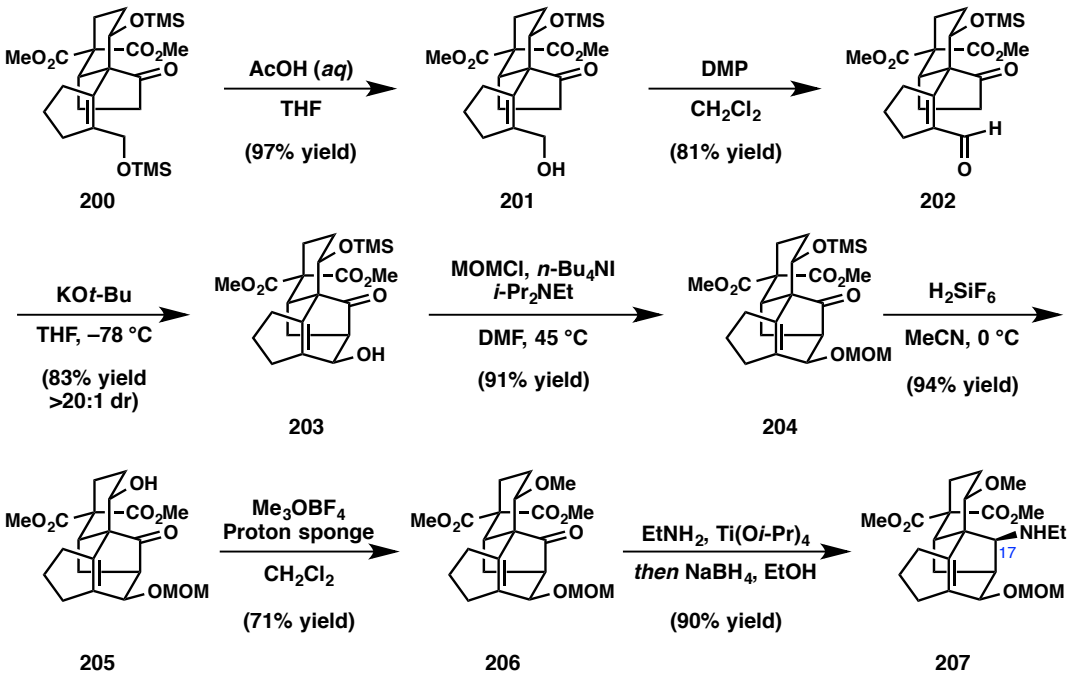


Figure 3.25. Investigations on intramolecular aldol and reductive amination steps.

We next attempted to investigate the intramolecular aldol and reductive amination steps. Because difficulty was encountered in differentiating the primary triisopropyl (TIPS) ether and secondary trimethylsilyl (TMS) ether of **198**, bis-TMS ether **200** was used for further model studies (Figure 3.25). Exposure of **200** to aqueous acetic acid in tetrahydrofuran resulted in selective deprotection of the primary silyl ether to alcohol **201** in excellent yield. Oxidation using Dess–Martin periodinane provided ketoaldehyde **202**, which was poised to undergo intramolecular aldol reaction. Treatment of ketoaldehyde **202** with hexamethyldisilazide bases produced aldol product **203** in variable diasteomeric ratios, but nevertheless forging the central B-ring in good yield. The yield and diastereomeric ratio was improved when potassium *tert*-butoxide was employed, providing aldol product **203** in 83% yield and >20:1 diastereoselectivity. However, the relative configuration was not determined at this stage since β-hydroxyketone **203** underwent spontaneous epimerization upon standing (likely through a retro-aldol/aldol process) and desilylation.

The alcohol was promptly protected as the methoxymethyl ether (**204**) and desilylated using hexafluorosilicic acid to reveal the C1 alcohol (**205**). Reductive amination on ketone **205** proved to be intractable at the time, possibly due to the free alcohol at C1; we therefore sought to methylate the alcohol to the methyl ether present in talatisamine (**34**). Methylation attempts under basic conditions were met with limited success, resulting in decomposition likely stemming from retro-aldol of the β-hydroxyketone. The use of trimethyloxonium tetrafluoroborate and Proton sponge provided methyl ether **206** in 71% yield. With ketone **206** in hand, treatment with ethylamine in the presence of a titanium tetraisopropoxide led to complete conversion to

an intermediate iminium ion (observed by LCMS). Dilution of the reaction mixture with ethanol and addition of sodium borohydride resulted in reduction to secondary amine **207**. Rigorous analysis of 2D NMR data revealed that the newly formed C17 stereocenter possessed the undesired configuration for lactam ring closure to the piperidine E-ring. Although unexpected, this finding can be rationalized by steric encumberance imposed by the pseudoaxial MOM-ether.

The model studies discussed thus far validated our synthetic approach and demonstrated that both C4 and C11 quaternary centers could be accessed in a rapid sequence from commercially available starting materials. Specifically, hydrindane **185** was readily available in just five steps from dimethyl malonate (**186**) using operationally simple chemistry. With the model system (vinyl bromide **196**), 1,2-addition and semipinacol rearrangement were accomplished in a single step, thereby establishing an efficient means to couple both fragments in a convergent fashion and directly forge the challenging C11 quaternary center. This short sequence also enabled important investigations of subsequent key steps, including an intramolecular aldol cyclization to create the central B-ring and reductive amination to afford the secondary amine, albeit in the undesired configuration. Ultimately, tetracyclic analogue **207** possesses four of the six rings present in talatisamine (**34**), and was synthesized in 12 steps from dimethyl malonate (**186**). Although these studies were compelling, they did not yet address the challenge of [3.2.1]-bicyclic CD-ring system or the enantioselective syntheses of both fragments described in the retrosynthetic analysis.

3.5.2 *Enantioselective Syntheses of Two Bicyclic Fragments*

The most straightforward manner to render the epoxyketone (**185**) route asymmetric was to employ an enantioselective Michael addition between α-substituted malonate **208** and cyclopenten-1-one (**188**) to intercept ketone **189** (Figure 3.26). Only one such method has been reported, by the Shibasaki group, utilizing an elaborate lanthanum-bound linked-BINOL catalyst.[17] Attempts to utilize this chemistry were met with initial success, but reproducibility issues hampered future use since the catalyst quality varied depending on the batch of lanthanum from commercial vendors. Another limiting factor was the high catalyst loading (10 mol%) of the non-recoverable linked-BINOL ligand, which was synthesized in seven steps from (*S*)-BINOL.

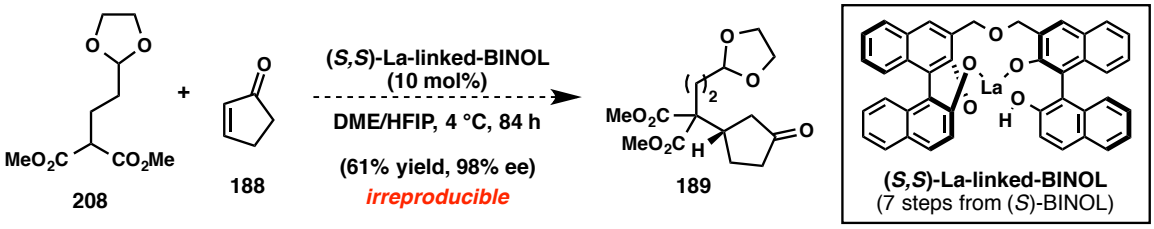


Figure 3.26. Catalytic enantioselective Michael addition of **208** and **188**.

An alternative route utilized another procedure developed by Shibasaki (Figure 3.27).[18] An enantioselective Michael addition between dimethyl malonate (**186**) and cyclopenten-1-one (**188**) was catalyzed by GaNa-(*S*)-BINOL and sodium *tert*-butoxide to deliver α-functionalized malonate **209** in 92% yield and 91% enantiomeric excess. The reaction is proposed to occur through attack of a sodium enolate onto the bimetallic catalyst, coordination of the α,β-unsaturated ketone to the Ga center, and Michael addition via an organized transition state to generate the new stereogenic center. This

reaction was reproducible and scalable, and also did not require cryogenic temperatures. The remainder of the sequence resembles the racemic route with minimal adjustments. Protection of ketone **209** under standard conditions provided ketal **210**, which was alkylated with alkyl bromide **187** to forge the C4 quaternary center of bis-ketal **211**. Heating in aqueous hydrochloric acid and acetone resulted in ketal deprotection and intramolecular deprotection to intercept enone **190**. Bromohydration was again achieved with *N*-bromosaccharin (**191**) and water. Notably, purification by recrystallization effectively enriched the enantiomeric excess to >99%, thereby providing enantiopure material. Epoxide ring closure proceeded uneventfully to afford epoxyketone **185** in six steps from dimethyl malonate (**186**).

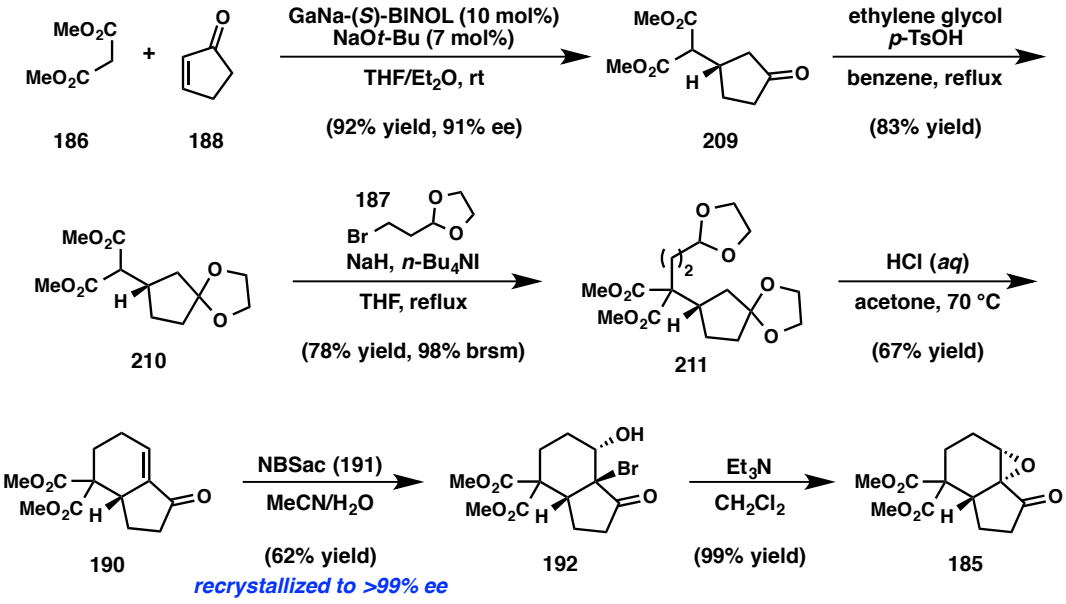


Figure 3.27. Alternative enantioselective route to epoxyketone **185**.

We envisioned utilizing a *meta*-photocycloaddition for the synthesis of the bicyclo[3.2.1]octane fragment, as it is an established method for the construction of

bicyclic compounds in total synthesis.[19] However, intermolecular *meta*-photocycloadditions, particularly with anisole (**212**) and electron rich olefins (*e.g.* **213**) are known to react with poor regioselectivity in the cyclopropane ring-forming step as well as poor endo/exo selectivity, forming up to four isomeric products (Figure 3.28).[20] Sugimura *et al.* have devised a valuable solution to this problem by joining the arene and olefin reactants with a chiral tether as in **216**.[21] Irradiation of arene olefin **216** at 254 nm resulted in photocycloaddition to initially produce the 6-substituted product **217**, which subsequently underwent vinyl-cyclopropane rearrangement to form the 7-substituted product **218**. In typical systems, these two isomeric products undergo photoequilibration. However, 6-substituted photoadduct **217** absorbs more strongly at 254 nm, resulting in a complete shift in equilibrium to produce 7-substituted photoadduct **218** in 70% isolated yield. Sugimura advanced cyclopropane **218** to enantiomerically pure bicyclo[3.2.1]octane **220** in a five step sequence involving cyclopropane ring-opening.

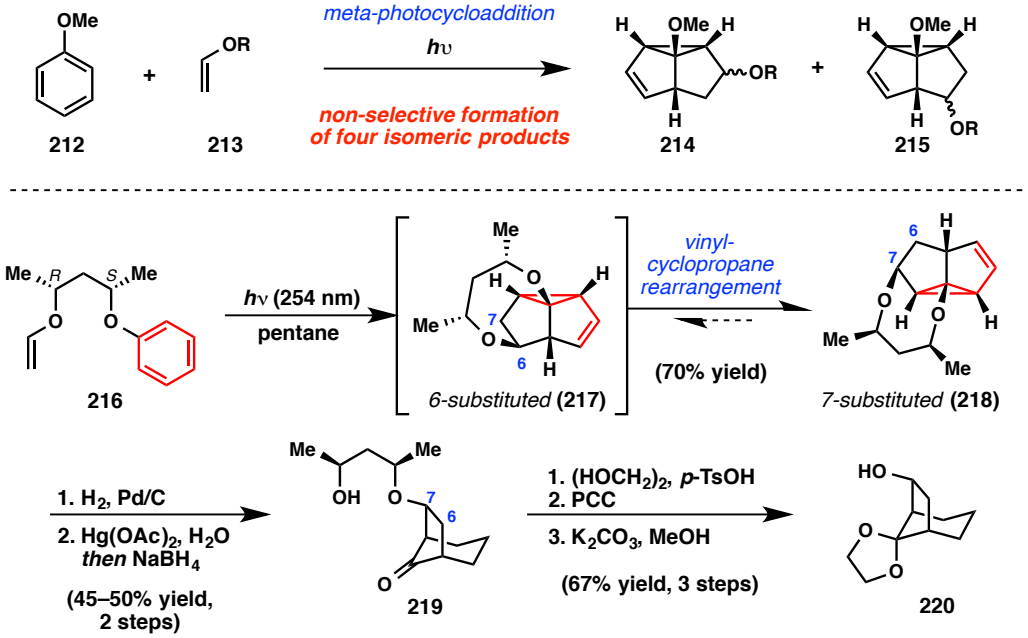


Figure 3.28. Sugimura's diastereoselective *meta*-photocycloaddition.

We sought to employ Sugimura's method for construction of enantiopure [3.2.1]-bicycles for the synthesis of talatisamine (**34**). Rather than reducing the olefin of photoadduct **218**, we plan to instead engage it in an electrophilic ring opening of the neighboring cyclopropane, which would also be assisted by the ether substituent (Figure 3.29). Photoadduct **218** can therefore undergo Grob fragmentation to produce oxocarbenium ion **221**, which would hydrolyze to form ketone **222**. Tether cleavage would proceed identically to Sugimura's sequence, and functional group interconversions of the resulting alcohol would produce vinyl bromide **223**. This sequence could potentially provide access to a variety of enantiopure [3.2.1]-bicycles bearing a vinylic anion (*e.g.* **224–226**) for 1,2-addition and semipinacol rearrangement into epoxyketone **185**, and functionality on the 3-carbon bridge to facilitate B-ring formation.

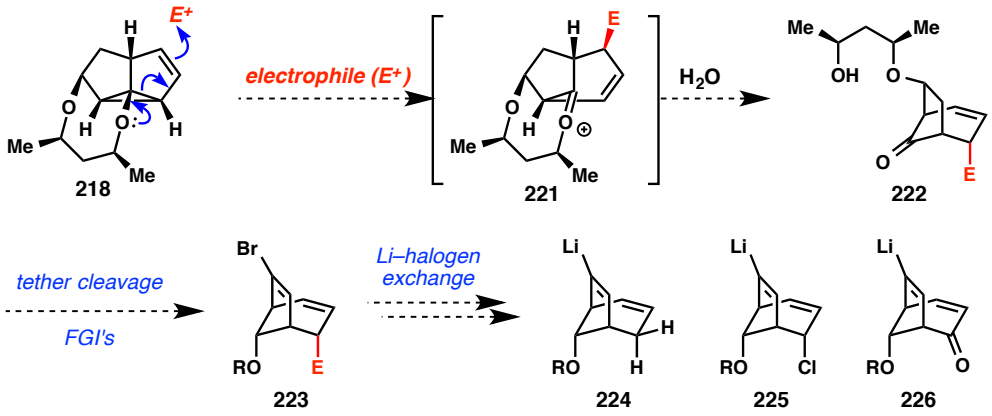


Figure 3.29. Forward plan for elaborating photoadduct **218**.

The synthesis of photoadduct **218** was performed using procedures modified from Sugimura's initial report.[21a] Beginning with commercially available (*2R,4R*)-pentanediol (**227**), a Mitsunobu reaction with phenol provided the aryl ether, and Hg(II)-catalyzed vinylation with ethyl vinyl ether provided arene olefin **216** (Figure 3.30). Although

Sugimura's studies were conducted on small scale, we were able to obtain comparable yields of the *meta*-photocycloaddition on 1.5 g scale after optimization of the reaction setup. Because the reaction profiles were generally clean, reactions could be run in 1.5 g batches, concentrated to crude mixtures, and combined with future batches for a single purification to provide multigram quantities of photoadduct **218**.

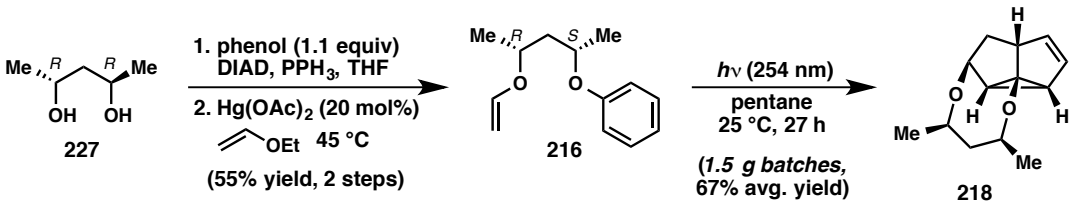


Figure 3.30. Scalable synthesis of photoadduct **218**.

Our first attempts to advance photoadduct **218** were through protonation of the olefin with Brønsted acid (Figure 3.31). The 6-substituted product **217** could be isolated at partial conversions of the *meta*-photocycloaddition, and subjection to aqueous hydrochloric acid at elevated temperatures provided ketone **228** in 37% yield. However, attempts to optimize this reaction were unfruitful, and ultimately this substrate was not pursued because the photocycloaddition could not be easily optimized for selective synthesis of 6-substituted adduct **217**. Under similar conditions, the 7-substituted adduct **218** surprisingly afforded diene **229**. Although one can surmise this occurs by elimination of the tether to form a C6–C7 olefin, evidence supported the intermediacy of cyclopropylcarbinyl cation **230**. For instance, diene **229** was not observed in acidolysis of the 6-substituted adduct **217**, as one would expect from elimination at C6/C7. At room temperature, ketalization of the ketone of **229** was observed, indicating that the free alcohol of intermediate **230** can ketalize prior to hydrolysis. Similar results were reported

by Fenton and Gilbert, who found that treatment of 7-acetate-substituted *meta*-photoadducts with acidic methanol resulted in formation of ketone **229** as well.[22] In an attempt to harness this reactivity, vinyl bromide **230**, the product of *meta*-photocycloaddition of aryl bromide **231**, could potentially undergo acidolysis to directly afford bicyclo[3.2.1]octane **232**. This would significantly shorten the synthetic route, as it effects tether cleavage and vinyl bromide formation in a single step to provide a functionalized fragment that can be used directly in the 1,2-addition/semipinacol rearrangement sequence. Unfortunately, preliminary experiments with aryl bromide **230** did not deliver photoadduct **231**, and instead resulted in significant polymer formation. Future studies are still warranted, particularly with other aryl functionalities that can be rapidly advanced to a vinyl anion equivalent.

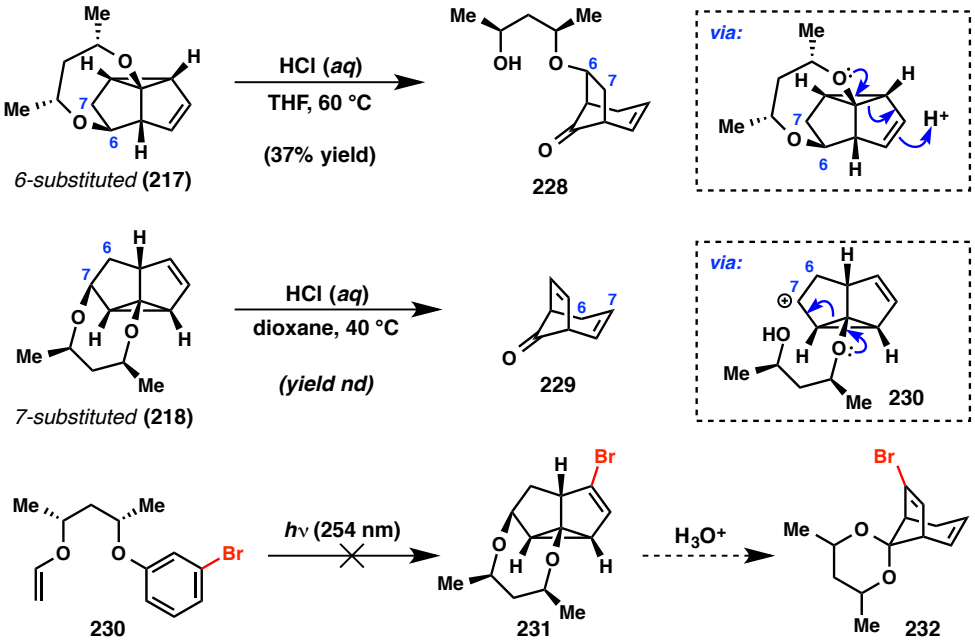


Figure 3.31. Acidolysis of *meta*-photoadducts.

Subsequent attempts to functionalize photoadduct **218** involved halogenation of the olefin (Figure 3.32). Treatment with *N*-chlorosaccharin in THF and water resulted in formation of allylic chloride **233** in 84% yield. Protection of the ketone and oxidation of the tether provided ketone **234** in 80% yield over two steps. Cleavage of the tether required low temperatures to prevent further fragmentation of the [3.2.1]-bicycle, and was accomplished with potassium hexamethyldisilazide at –78 °C to afford alcohol **235**. DMP oxidation then delivered ketone **236**. Unfortunately, ketone **236** could not be advanced to vinyl bromide **237** due to the labile allylic chloride, and therefore this substrate was not further pursued.

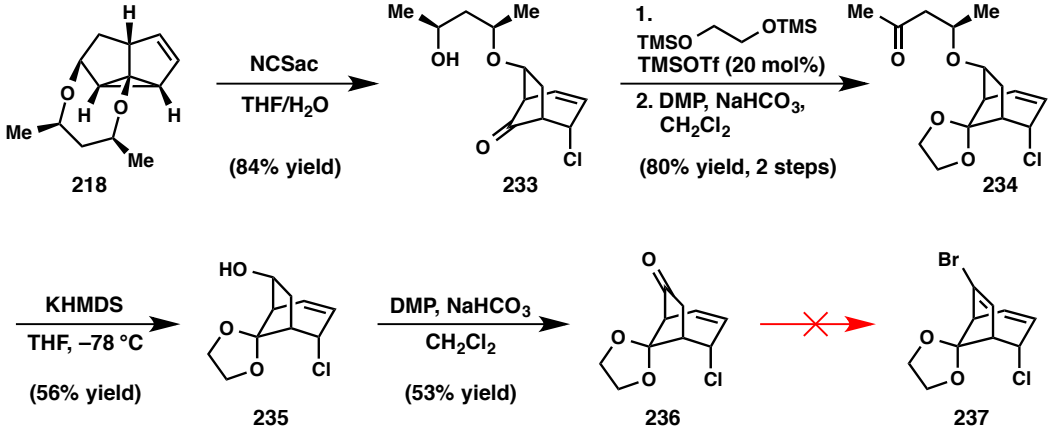


Figure 3.32. Synthesis of a chlorinated bicyclo[3.2.1]octane.

In hopes that an allylic ether would be less labile than the chloride, photoadduct **218** was epoxidized with *m*-CPBA produced an intermediate epoxide (**238**) that was immediately activated with Brønsted acid to furnish allylic alcohol **239** in 79% yield (Figure 3.33).[23] In order to differentiate both secondary alcohols of **239**, the allylic alcohol would be selectively protected as part of a 1,3-diol. Therefore, reduction with sodium borohydride in the presence of cerium trichloride furnished 1,3-diol **240** as a

single diastereomer in 91% yield. Interestingly, borohydride reduction of **239** in the absence of cerium trichloride provided a 1 : 2.3 mixture of diols **240** and **244**, favoring the *anti*-diastereomer **244**. The formation of **244** could proceed by directed delivery of the hydride by the allylic alcohol of **239**. The oxophilic cerium salt likely chelates to the hydroxyl groups, thereby preventing the directed hydride delivery and providing triol **240** as a single diastereomer. Attempts to protect the *syn*-diastereomer **240** as the acetonide were met with complications relating to hydrolysis of the allylic alcohol under acidic conditions, resulting in non-selective formation of allyl ethers **241** and **242**, and further fragmentation to arene **243**. Efforts to synthesize other acetals were largely unfruitful due to the tendency of the allyl alcohol to undergo hydrolysis and fragmentation.

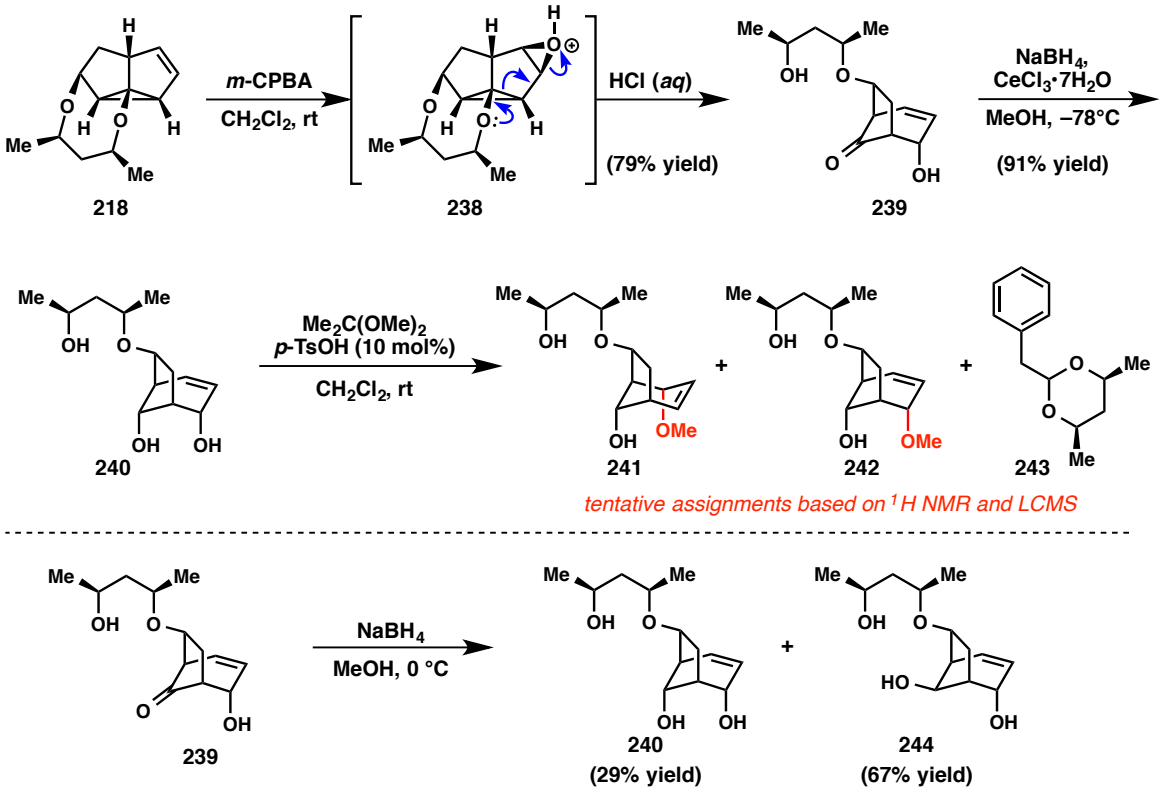


Figure 3.33. Epoxidation of photoadduct **218** and elaboration to triol **240**.

In order to circumvent the lability of allyl alcohol **240**, silylene protection at low temperatures mitigated hydrolysis, providing siliconide **245** in 91% yield (Figure 3.34). Oxidation of the tether with DMP, elimination mediated by KHMDS, and another oxidation afforded bicyclic ketone **248**, which was also converted to triflate **249** under standard conditions for subsequent investigations.

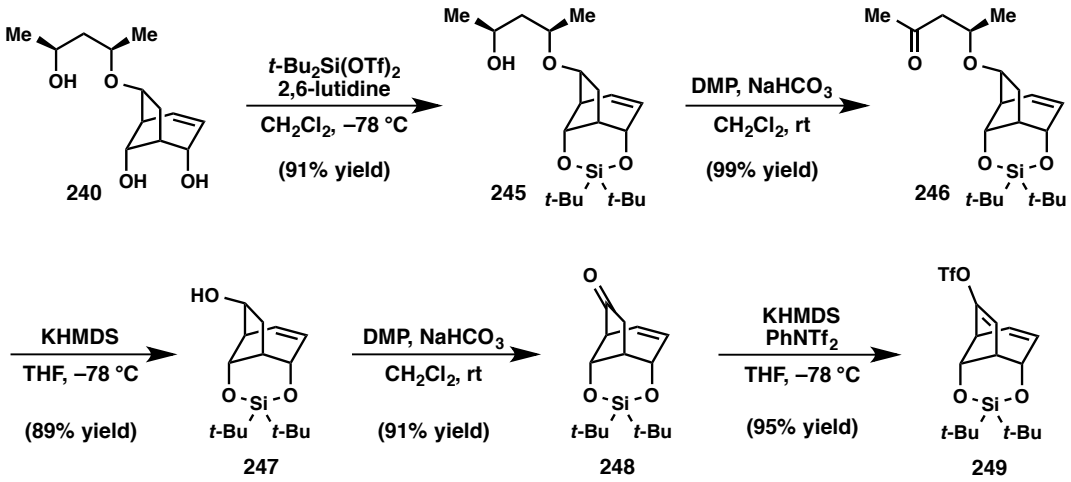


Figure 3.34. Silylene protection and advancement to bicyclic triflate **249**.

With the functionalized bicyclo[3.2.1]octane in place, efforts were directed towards conversion to a vinyl anion precursor for the following 1,2-addition. For ketone **248**, Shapiro conditions and triphenyl phosphite-halogen-based conditions failed to provide isolable samples of vinyl bromide **250**.[24,25] Barton's method for preparation of vinyl iodides by oxidation of intermediate hydrazones successfully delivered vinyl iodide **251**, albeit in a modest 39% yield.[26] Vinyl triflate **249** could also be used for the preparation of vinyl bromide **250** and vinyl stannane **252**. Under Pd-catalyzed conditions reported by Buchwald, vinyl bromide **250** was formed in low yield, possibly due to competing deprotection of the silylene group at high temperature.[27] Coupling of the vinyl

triflate with stannyl cuprates provided tributylstannane **252** in a moderate 50% yield, but was hampered by scalability issues.[28] Ultimately, the highest yielding procedure employed a Pd-catalyzed Stille cross-coupling with hexamethylditin to produce vinyl stannane **253**.[29] Although this stannane could be used directly in the 1,2-addition, the crude material was converted to vinyl iodide **251** due to safety concerns regarding volatile tetra-alkylstannane byproducts. Nevertheless, this two-step procedure efficiently and reliably provided multigram quantities of vinyl iodide **251** to enable subsequent investigations on the 1,2-addition and semipinacol rearrangement.

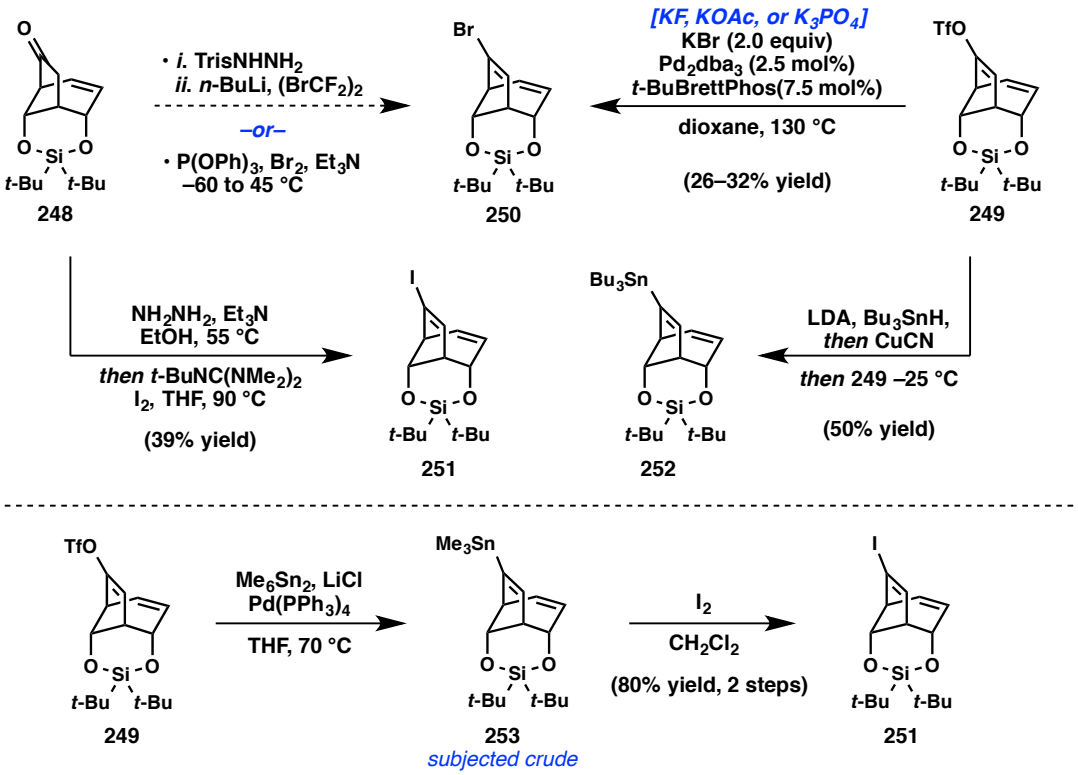


Figure 3.35. Preparation bicyclic vinyl anion precursors.

3.5.3 *Convergent Fragment Coupling*

In consideration of the fragment coupling between bicyclic vinyllithium **254** and epoxyketone **185**, 1,2-addition should provide epoxyalcohol **255**, and semipinacol rearrangement should generate rearranged product **256** (Figure 3.36). Based on earlier model studies, we anticipated that the allyl ether moiety of **256** might undergo ionization to allyl cation **257**, which upon enol ether formation, is poised to undergo cationic cyclization to furnish the carbocyclic core (**258**) of the aconitine alkaloids. This hypothesis was supported by investigations of epoxy alcohol **259**, which underwent rearrangement with concomitant elimination of the allyl ether moiety, presumably through allyl cation **260**, to provide diene products such as **261**.

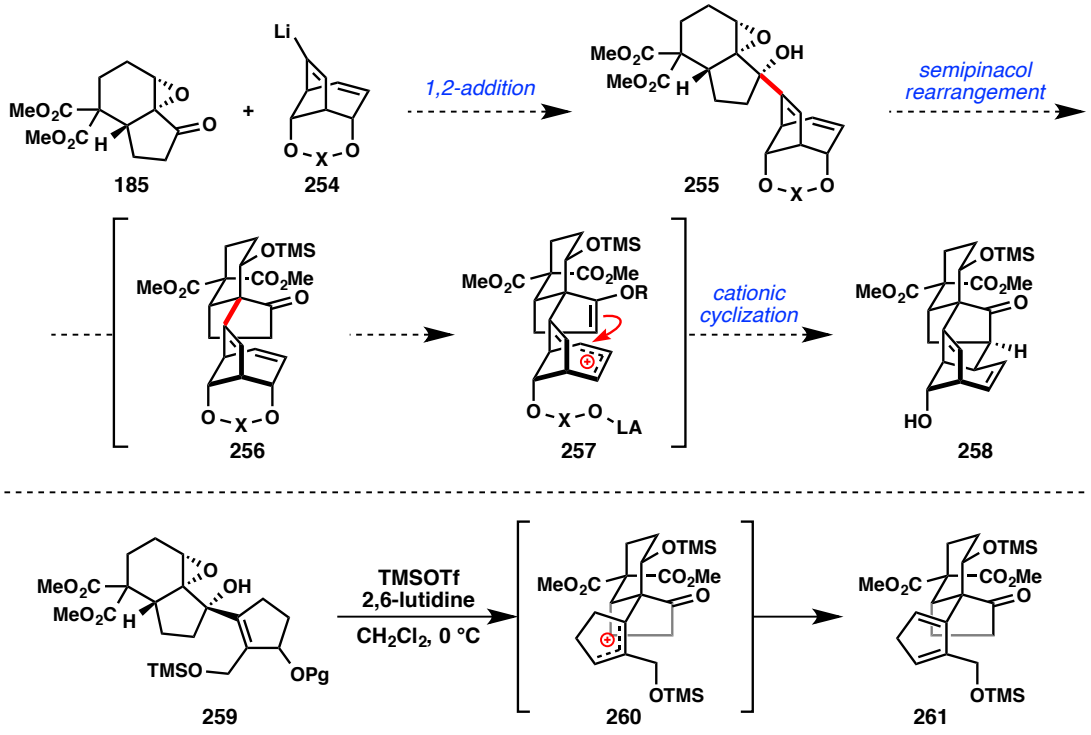
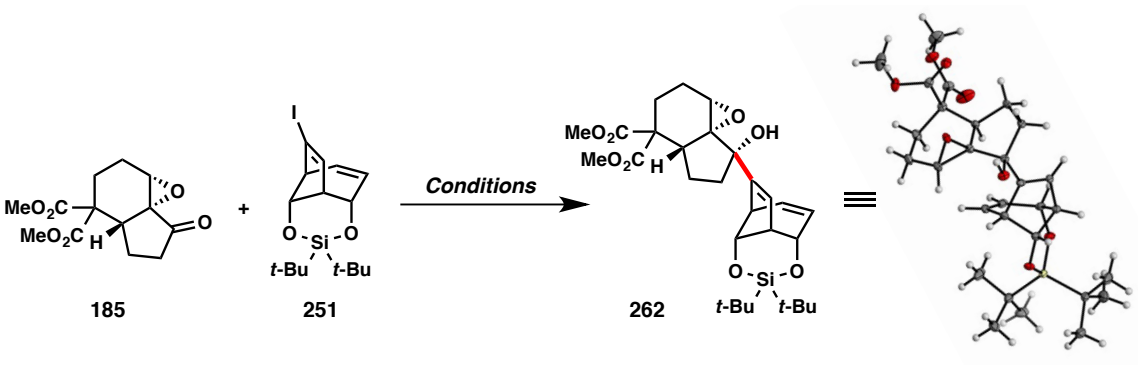


Figure 3.36. Proposed cationic cyclization for carbocyclic core **258**.



Entry	Conditions	Yield 262 (%)	Notes
1	*t*-BuLi (2.0 equiv), THF, –78 °C; *then* **185**, –94 °C	55	inverse addition[a]
2	PhLi (2.0 equiv), THF, –78 °C; *then* **185**, –94 °C	50	inverse addition[a]
3	*t*-BuLi (3.0 equiv) added into **185** and **251**, THF, –94 °C	50	"one-pot" conditions[b]
4	*t*-BuLi (2.0 equiv), THF, –78 °C; solution added to **185**, –94 °C	72	normal addition[c]
5	*t*-BuLi (2.0 equiv), THF, –78 °C; *then* HMPA, **185**, –94 °C	0	only protodehalogenation
6	*t*-BuLi (2.0 equiv), THF, –78 °C; added to $CeCl_3$/THF; *then* **185**	51	--
7	*t*-BuLi (2.0 equiv), TMEDA/THF, –78 °C; *then* **185**, –94 °C	47	--
8	*t*-BuLi (2.0 equiv), TMEDA/hexane, –78 °C; *then* **185**, toluene, –94 °C	0	only protodehalogenation
9	*i*-PrMgCl•LiCl (1.1 equiv), THF, rt; *then* **185**, –94 °C	0	only protodehalogenation
10	*i*-PrMgCl•LiCl (1.1 equiv), toluene, rt; *then* **185**, rt	0	only protodehalogenation

[a] Inverse addition: epoxyketone **185** added to pre-stirred solution of vinyllithium (*t*-BuLi/**251**). [b] "One-pot" conditions: *t*-BuLi added directly to solution of **185** and **251**. [c] Normal addition: pre-stirred solution of vinyllithium (*t*-BuLi/**251**) added to epoxyketone **185.**

Table 3.2. 1,2-addition optimization for tertiary alcohol **262**.

Under previously developed conditions for 1,2-addition into epoxyketone **185**, reaction with bicyclic vinyl iodide **251** furnished epoxy alcohol **262** in 55% yield (Entry 1, Table 3.2). Other reagents for lithium-halogen exchange such as phenyllithium failed to increase the yield, as did single pot conditions in which *tert*-butyllithium was added directly to a mixture of epoxyketone **185** and vinyl iodide **251** (Entries 2 and 3). Although the conditions in Entry 1 were developed to prevent Wurtz coupling of the model system discussed in Section 3.5.1, it was discovered that bicycle **251** did not undergo the same dimerization and thus did not require inverse addition. Normal addition of the intermediate vinyllithium into a pre-cooled solution of epoxyketone **185** at –94 °C delivered epoxy alcohol **262** in 72% yield on a 1.6 g scale (entry 4). A survey of additives including HMPA, $CeCl_3$, and TMEDA provided lower yields or protodehalogenation (Entries 6–8). Iodine/magnesium exchange with "turbo Grignard" also exclusively resulted in protodehalogenation of **251**, likely by α-deprotonation of epoxyketone **185** (Entries 9 and 10).[30]

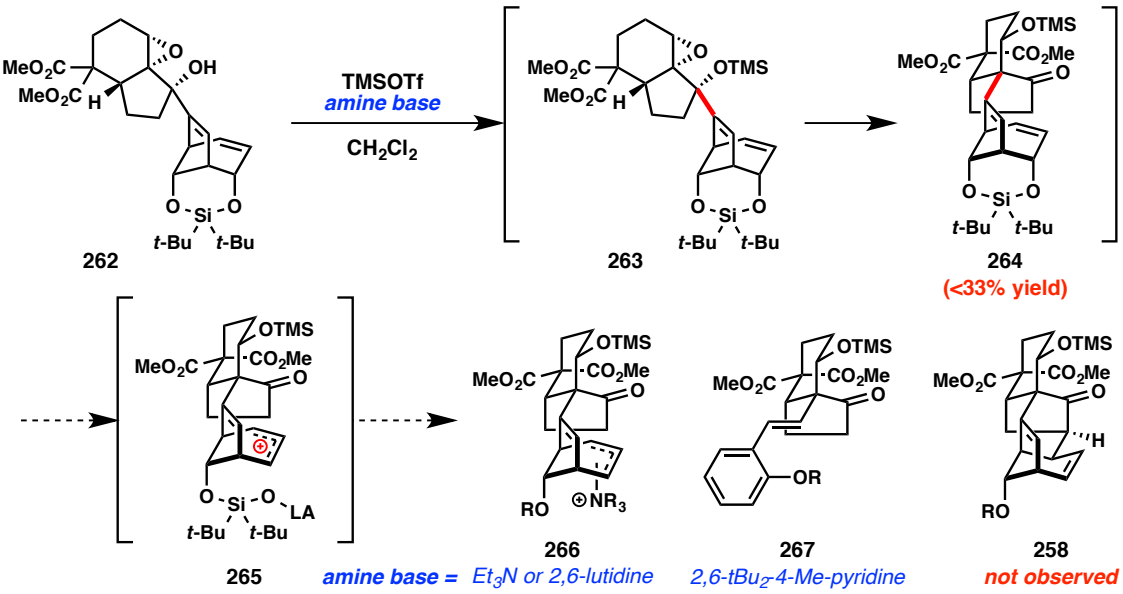


Figure 3.37. Semipinacol rearrangement of **262** and side product formation.

At this juncture, extensive efforts were directed to achieve the proposed cationic cyclization. Standard conditions for semipinacol rearrangement necessitated TMSOTf as the Lewis acid, and an amine base to buffer the reaction media from triflic acid generated *in situ*. At low temperatures (below 0 °C), rapid protection of tertiary alcohol **262** to the silyl ether **263** occurred (Figure 3.37). Approaching room temperature, semipinacol rearrangement to **264** was observed; however, this was formed as a mixture with other side-products, and purification returned <33% yield of semipinacol product **264**. When the reactions were allowed to reach full conversion, tentatively assigned products **266** and **267** were observed. These products are proposed to arise from the intermediate allyl cation **265**. With triethylamine or 2,6-lutidine as bases, ammonium/lutidinium products **266** were observed by ^{1}H NMR; we speculate that these may arise from non-regioselective attack of the base onto allyl cation **265**. With the non-nucleophilic base 2,6-di*tert*-butyl-4-methylpyridine, *ortho*-substituted styrene **267** was observed by ^{1}H NMR; this may occur by rearrangement of allyl cation **265** through an elaborate mechanism in which the [3.2.1]-bicycle is fragmented (as in Figure 3.33). Unfortunately, no products containing silyl enol ethers or cationic cyclization product **258** were observed during the course of these studies.

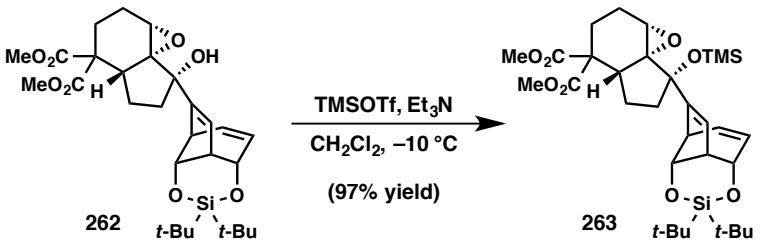
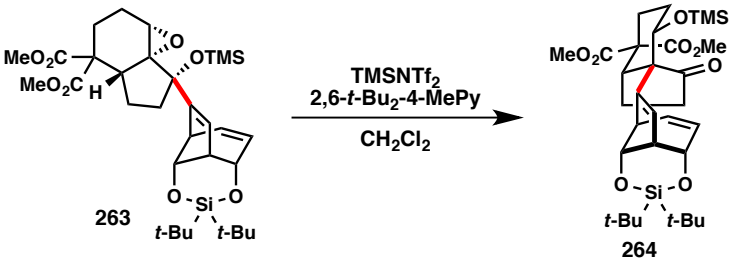


Figure 3.38. Trimethylsilyl protection of epoxy alcohol **263**.

Although we were initially discouraged by these results, we remained optimistic since the semipinacol rearrangement occurred readily at room temperature. We elected to devise a procedure for efficient preparation of semipinacol product **264**. For these studies, epoxy alcohol **262** was protected as silyl ether **263** with TMSOTf at –10 °C (Figure 3.38). Since this reaction was clean and high yielding, we posited that low temperatures mitigated ionization of the allyl ether moiety. To this effect, we optimized the semipinacol rearrangement of silyl ether **263** at low temperatures using a stronger Lewis acid, $TMSNTf_2$, and non-nucleophilic base, 2,6-di*tert*-butyl-4-methylpyridine, to preclude *N*-silylation (Table 3.3).[31] At –78 °C, low yields of rearrangement product **264** were obtained at extended reaction times, but the reaction profile and yield improved with shorter reaction times (Entries 1 and 2). Lowering the reaction temperature and time even further provided improved yields of up to 90% (Entries 3 and 4). However, with one equivalent of Lewis acid, the reaction scaled poorly, and the yield diminished to as low as 59% on a 280 mg scale (Entries 5–7). We reasoned that use of silyl ether **263** as the rearrangement substrate negated the need for a full equivalent of $TMSNTf_2$, which could in fact be regenerated *in situ*. Using catalytic amounts of Lewis acid successfully delivered semipinacol product **264** in quantitative yield, and tolerated elevated temperatures and extended reaction times (Entry 8). Additionally, this reaction was highly scalable, providing semipinacol product **264** in 97% yield on a 1.2 g scale (Entry 9).

The coupling epoxyketone **185** with bicyclo[3.2.1]octane **251** currently proceeds in three steps. However, the sequence is efficient, occurring in an overall 67% yield. The ability to reliably advance multigram quantities of epoxyketone **185** and bicycle **251**

to semipinacol product **264** proved to be crucial for enabling subsequent studies towards talatisamine (**34**).



Entry	Scale	Equivs $TMSNTf_2$	Temperature (°C)	Time	Isolated yield 264 (%)
1	10 mg	1.0	–78	45 min	<25
2	10 mg	1.0	–78	60 sec	50
3	10 mg	1.0	–94	85 sec	82
4	10 mg	1.0	–94	10 sec	90
5	75 mg	1.0	–94	10 sec	88
6	150 mg	1.0	–94	10 sec	82
7	280 mg	1.0	–94	10 sec	59
8	10 mg	0.10	–70 to 0	2.5 hr	99
9	1.2 g	0.10	–70	15 min	97

Table 3.3. Semipinacol rearrangement optimization of silyl ether **263**.

3.5.4 *Assembly of the Carbocyclic Core of Talatisamine*

At this juncture, several options were explored to advance semipinacol rearrangement product **264** to the carbocyclic core of talatisamine (**34**), which required construction of the final C7–C8 bond to complete the central B-ring. We first explored a radical cyclization of α-bromoketone **268** onto the D-ring olefin (Figure 3.39).

Deprotonation of ketone **264** with LiHMDS and addition of NBS provided bromoketone **268** in 82% yield. To our dismay, an extensive survey of reaction conditions to effect the desired 6-*exo* radical cyclization failed to deliver carbocyclic core **269**. Instead, all attempts returned starting material (**268**) or the hydrodebromination product (**264**). It was unclear to us at that juncture whether cyclization to radical **271** was unfavorable due to resonance-stabilized radical **270**, or if cyclization suffered from poor polarity matching.

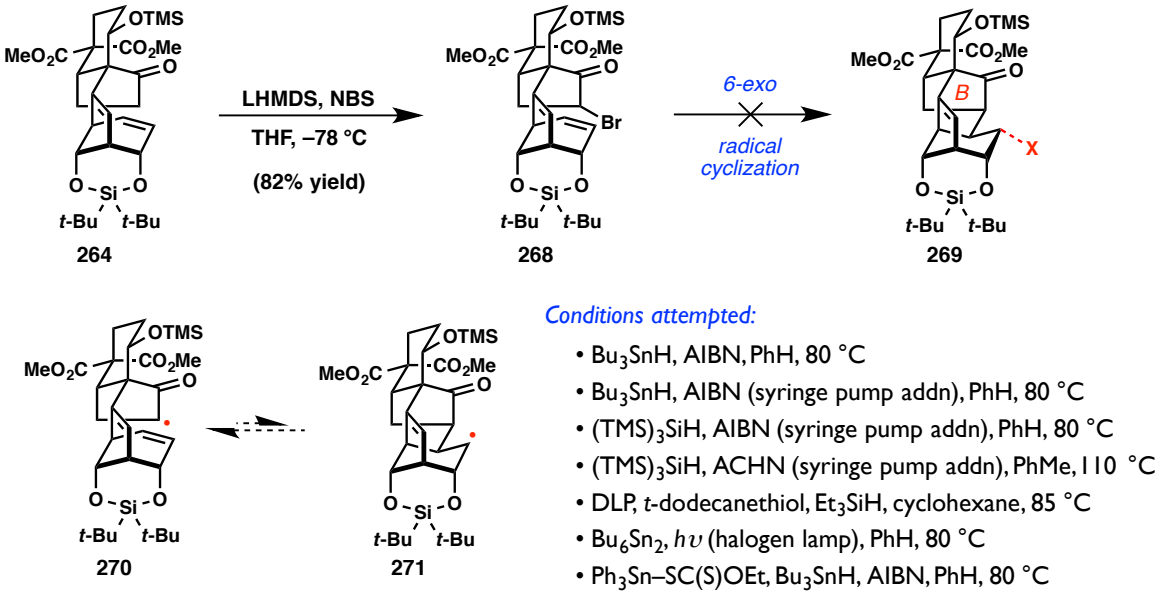


Figure 3.39. Survey of 6-*exo* radical cyclization conditions for pentacycle **269**.

Reflecting on the success of the intramolecular aldol reaction in the model system (see Section 3.5.1), we elected to perform an intramolecular Michael addition to complete the aconitine carbocyclic core. To this end, selective deprotection of silylene **264** was accomplished using HF•pyridine to deliver diol **272** in 98% yield (Figure 3.40). Under conditions developed by Steves and Stahl, allylic oxidation occurred to afford α,β-

unsaturated ketone **273** in good yield, although over-oxidation to the diketone was occasionally observed at prolonged reaction times, resulting in slightly diminished yields.[32] Protection of the secondary alcohol provided the corresponding methoxymethyl ether of **274** in 84% yield. Treatment of **274** with *tert*-butoxide base at low temperature resulted in an intramolecular Michael addition to furnish pentacycle **275**, thereby completing the central B-ring of the aconitine carbocycle.

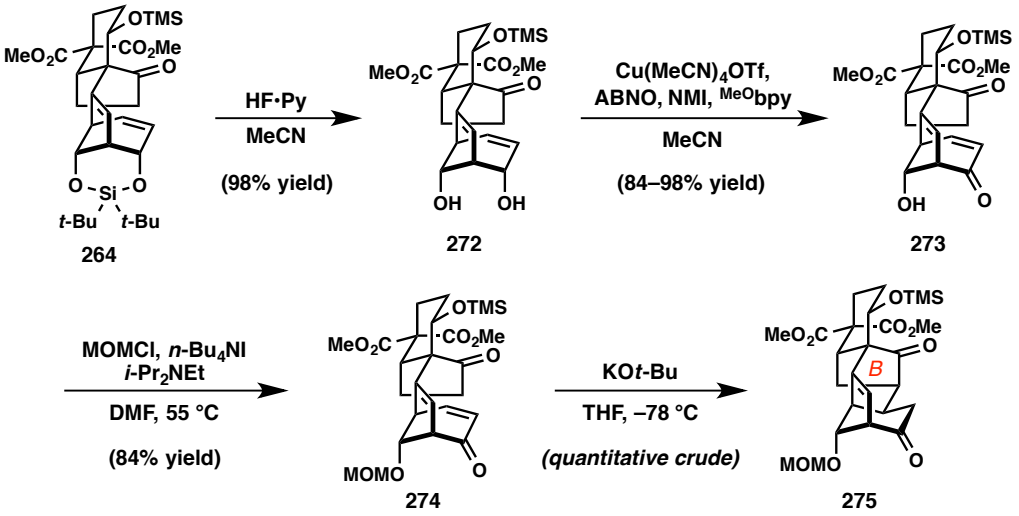


Figure 3.40. Intramolecular Michael addition for carbocyclic core **275**.

Completion of the aconitine carbocycle **275** marks the successful implementation of our convergent fragment coupling strategy. In our retrosynthetic analysis, the principle disconnections were bisection across the central B-ring. We have thus demonstrated that the aconitine core can be assembled in a convergent manner by constructing the C10–C11 bond via semipinacol rearrangement and the C7–C8 bond via intramolecular Michael addition.

3.5.5 *Endgame Efforts*

From aconitine carbocycle **275**, the remaining hurdles for the total synthesis of talatisamine (**34**) include hydrogenation of the bridgehead olefin, installation of the C8 alcohol, and construction of the piperidine E-ring. Guided by Gin's synthesis of neofinaconitine (**112**), we elected to install the C8 alcohol through oxy-Michael addition of an intermediate α,β-unsaturated ketone.[9] Deprotonation of diketone **275** occured chemoselectively α to the C16 ketone to afford α-selenide **276** in 80% yield (Figure 3.41). Oxidation of a selenide possessing a free C1 alcohol resulted in rupture of the central B-ring through the C7–C8 bond via a retro-aldol process. However, with the C1 TMS-ether, β-hydroxyketone **277** was furnished in 44% yield. As in Gin's system, we propose that selenoxide elimination occurs to generate an intermediate enone, which is rapidly hydrated to relieve strain in the bridgehead olefin.

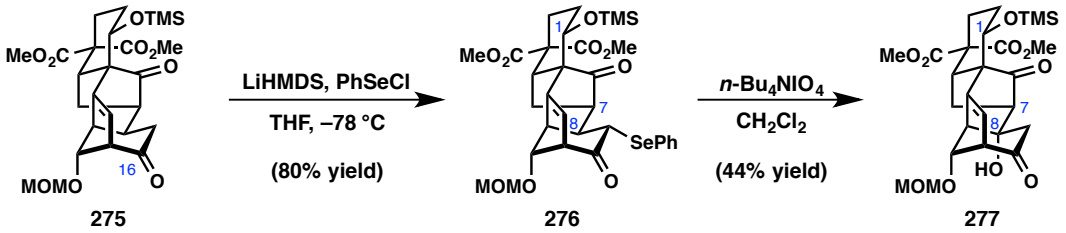


Figure 3.41. Initial investigation of oxy-Michael addition for the C8-alcohol.

During these studies, we observed that the C1 silyl ether was labile and occasionally underwent spontaneous deprotection. For this reason, silyl ether **275** was converted to lactone **278** by exposure to trifluoroacetic acid (Figure 3.42). Hydrogenation of the bridgehead olefin proceeded smoothly under standard conditions to provide saturated product **279** in 96% yield over two steps.[33] Selenation of the ketone

afforded α-selenide **280**, and oxidation with sodium *meta*-periodate yielded tertiary alcohol **281** in moderate yield. However, because the substrate lacks alkene functionality, oxidation of the selenide could proceed under ozonolytic conditions without complication. This also allowed the use of methanol as both the solvent and nucleophile for the oxy-Michael addition. As such, ozonolysis of **280** in methanol followed by addition of pyridine, which accelerated selenoxide elimination, furnished C8-methyl ether **282** in 88% yield. The methyl ether would serve as a protecting group for the C8 alcohol of talatisamine (**34**), since selective formal demethylation at the position is known to occur through a carbocation intermediate.[34]

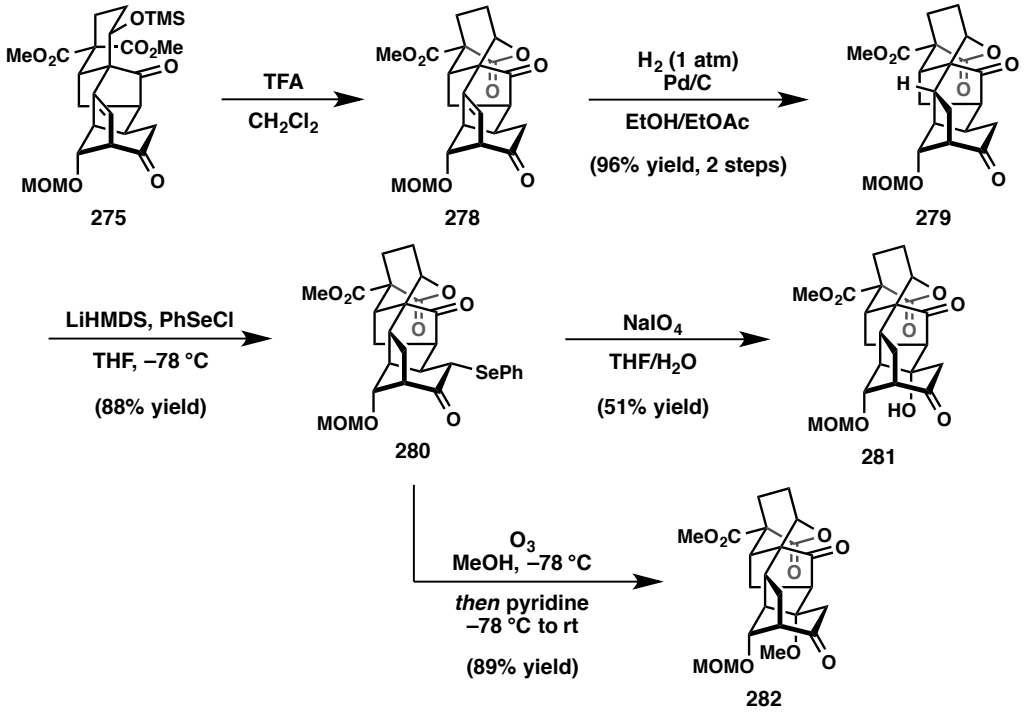


Figure 3.42. Functionalization to C8-methoxylated lactone **282**.

Alongside several functional group manipulations, the last challenge is to install the piperidine E-ring of talatisamine (**34**). The original proposal was to implement a

reductive amination of the C17 ketone. Unfortunately, preliminary experiments showed that chemoselective reduction of the C17 ketone of **282** proceeded stereoselectively from the α-face, providing alcohol **283** in 66% yield (Figure 3.43). The diastereoselectivity of this reduction is conflicting with lactam formation, since hypothetical reduction of C17 imine **284** would provide β-disposed secondary amine **285**, which is geometrically unable to undergo cyclization with the lactone carbonyl to form lactam **286**. This outcome forced us to devise a new scheme for installing the piperidine E-ring.

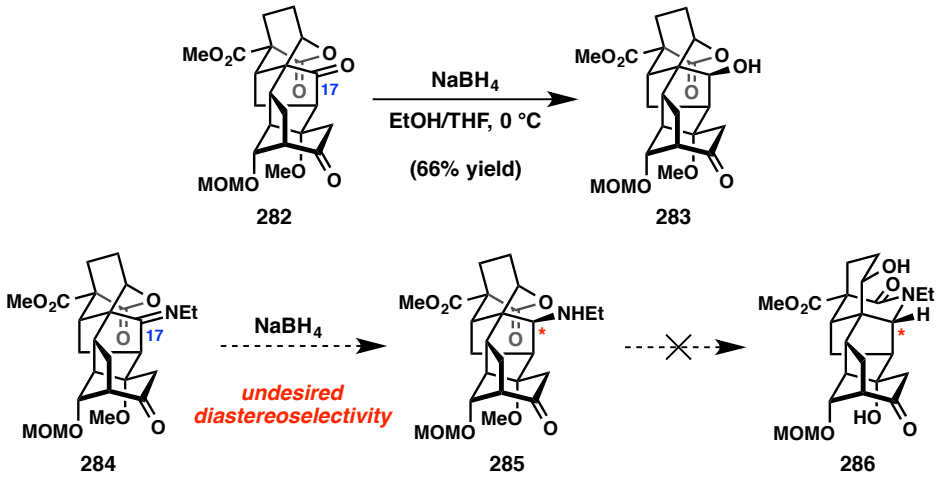


Figure 3.43. Unexpected diastereoselectivity for reduction of the C17 ketone.

An important note regarding the lactone functionality is that it differentiates the C18 and C19 carbonyls, which were formerly both methyl esters. As part of the oxabicyclo[2.2.2] system, the lactone also bears an substantial degree of ring strain. We therefore sought to engage the lactone in an aminolysis reaction with ethylamine. When treated with ethylamine in THF at room temperature, lactone **282** underwent aminolysis to afford amide **287** in 69% yield (Figure 3.44). Alternatively, the aminolysis could be performed in the same pot as the selenoxide elimination reaction, affording amide **287** in

87% yield from α-selenide **280**. From amide **287**, a final C17–N bond formation through a nucleophilic displacement would complete the full framework of talatisamine (**34**). The C17 ketone of **287** could again be chemo- and diastereoselectively reduced with sodium borohydride to produce diol **288**. However, we were unable to mesylate the C17 alcohol of **288**, as mesylation of the C1 alcohol and amide activation often occurred competitively.

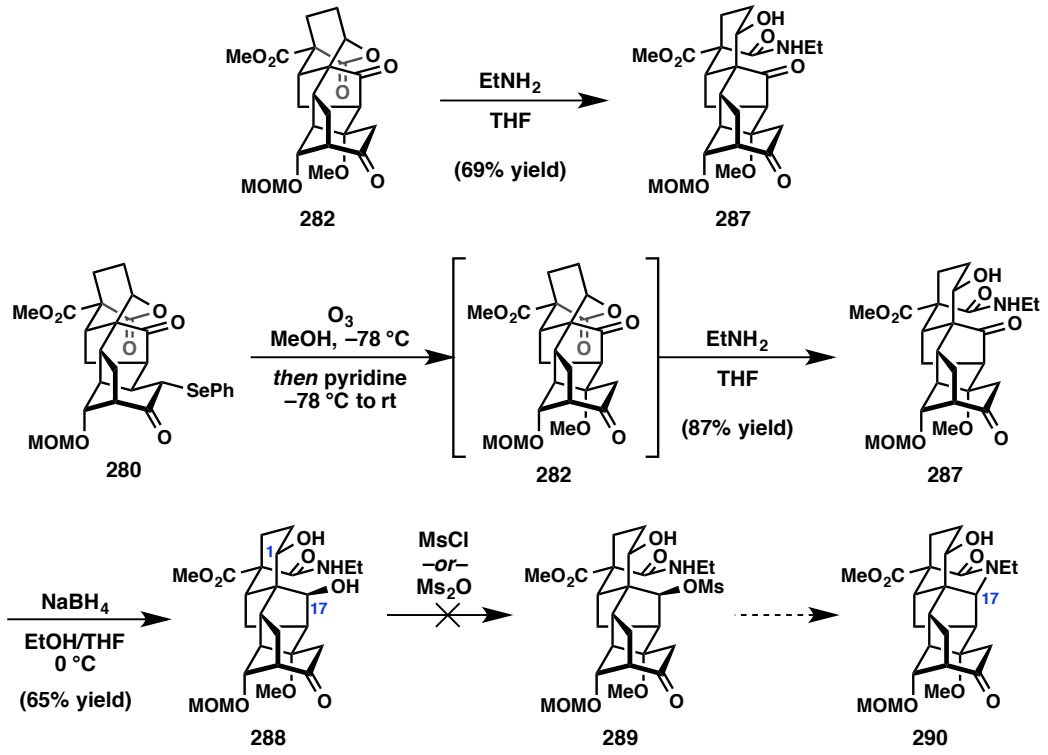


Figure 3.44. Initial investigations on lactone aminolysis.

Due to the difficulties encountered with diol **288**, alcohol **283** was mesylated instead, as it lacks the problematic the C1 alcohol and C18 amide (Figure 3.45). Standard mesylation conditions employing triethylamine or pyridine with mesyl chloride or mesyl anhydride in dichloromethane provided no reaction at room temperature, and returned

intractable reaction profiles at prolonged reaction times or higher temperatures. Interestingly, the use of *n*-butyllithium or LiHMDS at low temperatures for alkoxide formation prior to mesylation resulted in conversion to cyclic mesyl acetal **291**, which was disappointingly inert to aminolysis conditions. Switching to a potassium counterion in KO*t*-Bu and KHMDS provided moderate conversions to desired mesylate **293**. These results are promising, and further optimization of this mesylation step is required.

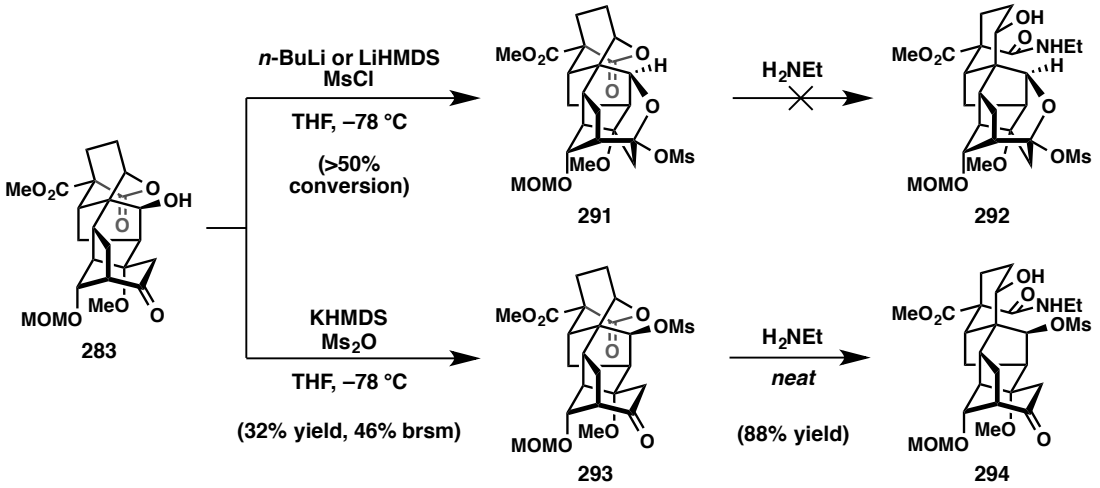


Figure 3.45. Preliminary results for mesylation and aminolysis of lactone **283**.

With mesylate **293** in hand, subjection to neat ethylamine in a sealed vessel produced aminolysis product **294** in 88% yield. Amide **294** is poised to undergo intramolecular cyclization and mesylate displacement to produce aconitine core. A preliminary screen of conditions has thus far proved unsuccessful. If accomplished, the resulting lactam possesses all the functionality required for advancement to talatisamine (**34**), and remaining steps include global reduction of the carbonyl functional groups, global methylation, and deprotection of the MOM ether and C8-methoxy group; all of these transformations are well precedented based on previous syntheses. Preliminary

investigations to forge aconitine core **290** have revealed a surprising reluctance of amide **293** to undergo intramolecular cyclization. Basic conditions have led to side products arising from enolization and elimination of the C8-methoxy group, while acidic conditions have failed to induce reactivity in **293**. Preliminary experiments have also suggested that solvolytic conditions, such as those employed by Wiesner and Sarpong, may result in ionization of the mesylate and lactam formation.[4,10] Further efforts to this end are required for the total synthesis of talatisamine (**34**).

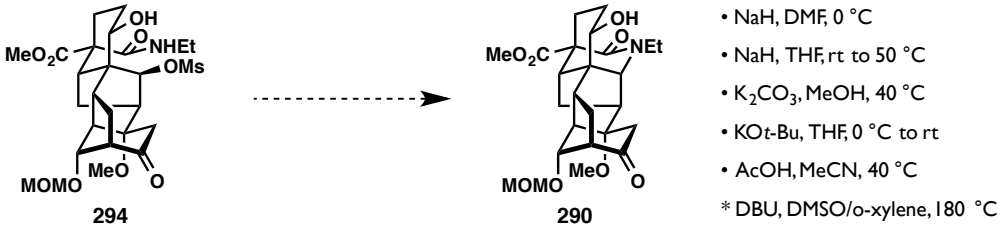


Figure 4.46. Preliminary investigations on lactam ring closure.

3.6 FUTURE DIRECTIONS

Immediate objectives will focus on the final challenge of amide cyclization of mesylate **294** to form lactam **290**, as well as optimization of the mesylation step (Figure 3.47). Should these efforts be successful, the remaining steps to access talatisamine (**34**) are straightforward. Global reduction with lithium aluminum hydride in refluxing dioxane should provide triol **295**, and subsequent methylation should afford protected intermediate **296**. Lastly, as demonstrated by Pelletier, Gin, and Fukuyama, subjection to aqueous sulfuric acid at high temperature should result in cleavage of the methoxymethyl ether and formal demethylation at C8 to produce talatisamine (**34**).[34]

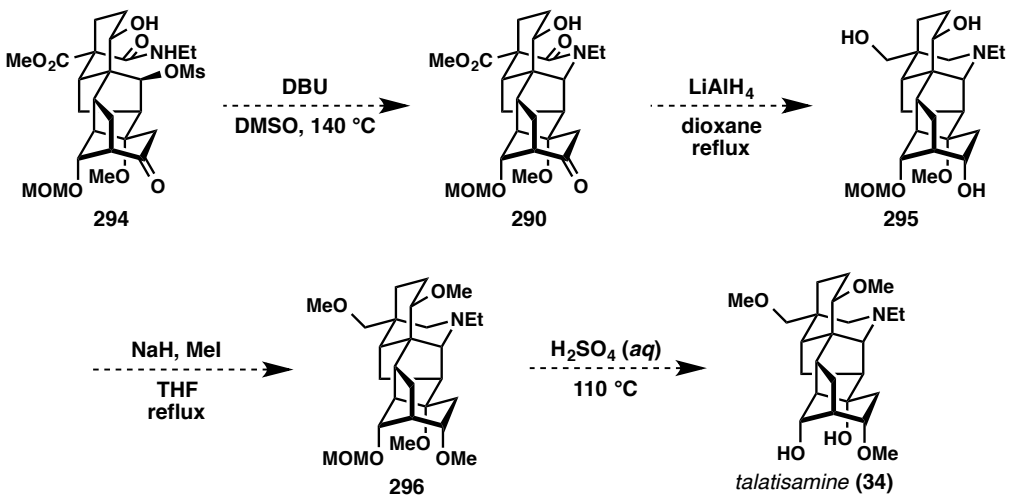


Figure 3.47. Proposed completion of talatisamine (**34**).

As a long-term objective, we propose to implement the convergent fragment coupling strategy in the synthesis of denudatine and napelline type C_{20}-diterpenoid alkaloids. The piperidine rings of napelline (**29**) and lepenine (**160**) can be retrosynthetically deconstructed to amides **297** and **299**, respectively. Scission across the central ring through the bonds shown in red lead to [3.2.1]- and [2.2.2]-bicyclic vinyllithiums **298** and **300**. Enantioselective syntheses of both bicyclic fragments also require development, but epoxyketone **185** can serve as the precursor to the AF rings of napelline (**29**) and lepenine (**160**). Successful syntheses of these alkaloids would validate the approach as a unified strategy to access C_{19}- and C_{20}-diterpenoid alkaloids, and access to C_{18}-diterpenoid alkaloids may also be possible by oxidative scission of the C4–C18 bond as demonstrated in Gin's synthesis of neofinaconitine (**112**).[9]

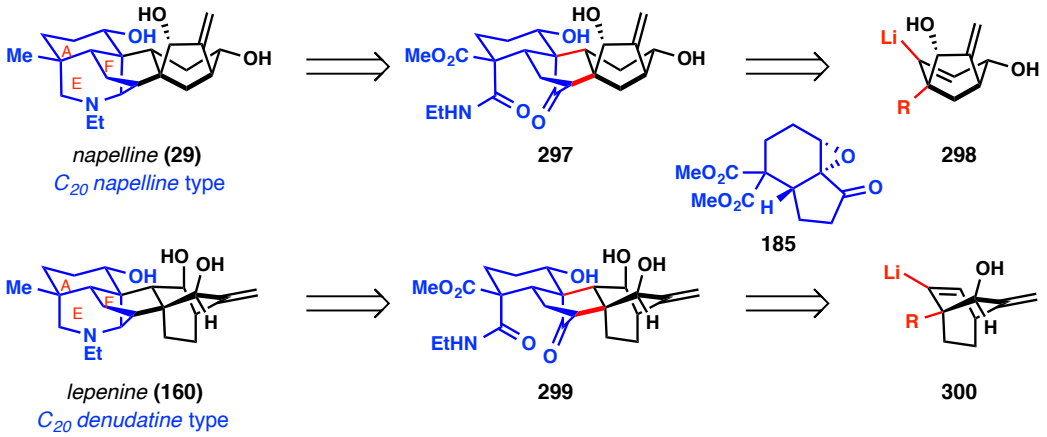


Figure 3.47. Retrosynthetic analysis of C_{20}-diterpenoid alkaloids.

3.7 CONCLUDING REMARKS

The C_{19}-diterpenoid alkaloids represent highly challenging targets for total synthesis and test the limits of current state-of-the-art methods and strategies. Syntheses by Wiesner, Sarpong, and Fukuyama have thoroughly established the [4 + 2] cycloaddition and biomimetic Wagner–Meerwein rearrangement as a viable method to construct the aconitine skeleton.[4,10,13] These syntheses have also shown that biogenetically related C_{20}-diterpenoid alkaloids can be accessed via common intermediates. On the other hand, Gin's synthesis of the C_{18} neofinaconitine (**112**) has demonstrated that a non-biomimetic approach can lead to a relatively expedient synthesis of the aconitine core.[9]

Our approach to talatisamine (**34**) showcases the advantages of a convergent strategy to couple two relatively complex, chiral fragments. Scalable and enantioselective syntheses of epoxyketone **185** and bicyclo[3.2.1]octane **251** have been developed, and novel application of a 1,2-addition/semipinacol rearrangement sequence has successfully constructed the hindered C11 quaternary center of the diterpenoid alkaloids. This

approach has enabled efficient access to the carbocyclic core of the C_{19} aconitine type alkaloids, with requisite functionalities in place for advancement to talatisamine (**34**). Additionally, the coupling of additional bicyclic fragments with epoxyketone **185** via the 1,2-addition/semipinacol rearrangement method can possibly provide access to a range of C_{20}-diterpenoid alkaloids possessing a common AEF tricycle, as in napelline (**29**) and lepenine (**160**).

3.8 EXPERIMENTAL SECTION

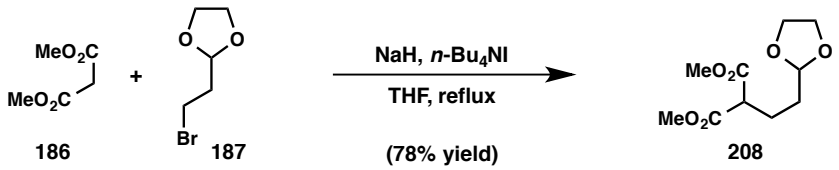
3.8.1 *Materials and Methods*

Unless otherwise stated, reactions were performed under an inert atmosphere (dry N_2 or Ar) with freshly dried solvents utilizing standard Schlenk techniques. Glaswarewas oven-dried at 120 °C for a minimum of four hours, or flame-dried utilizing a Bunsen burner under high vacuum. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), *tert*-butyl methyl ether (TBME), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) and *N*,*N*-diisopropylethylamine (DIPEA) were distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, $KMnO_4$, or CAM staining. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 microns [230 to 400 mesh]) purchased from Silicycle. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz respectively), a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$) and $CDCl_3$ (^{13}C, $\delta = 77.0$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR

spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), or mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility in fast-atom bombardment mode (FAB).

3.8.2 *Preparative Procedures and Spectroscopic Data*

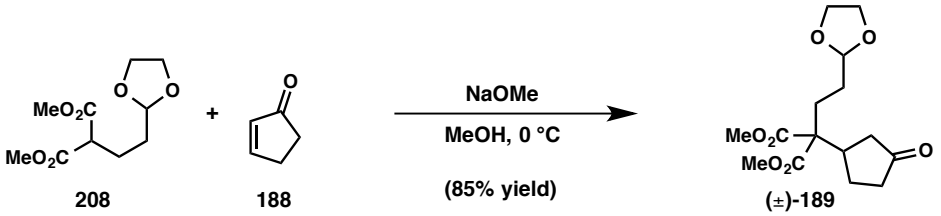
Preparation of diester 208:



In a 250-mL, round-bottomed flask equipped with a reflux condenser, NaH (60% dispersion in mineral oil, 1.05 g, 43.7 mmol, 1.17 equiv) was suspended in THF (44 mL) and cooled to 0 °C. To this suspension was added dimethyl malonate (**186**, 5.0 mL, 43.7 mmol, 1.17 equiv) dropwise with a vent needle to allow pressure release caused by H_2 evolution. The reaction was then warmed to room temperature with stirring for 30 minutes, after which *n*-Bu_4NI (1.38 g, 3.74 mmol, 0.10 equiv) and 2-(2-bromoethyl)-1,3-dioxolane (**187**, 4.4 mL, 37.4 mmol, 1.0 equiv) was added. The solution was heated to reflux and stirred for 4 h, and then quenched by addition of sat. NH_4Cl (100 mL). The aqueous phase was extracted with Et_2O (3 x 200 mL), and the combined organic extracts were washed with 1 N HCl (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (20 to 23% EtOAc in hexanes) provided diester **208** (6.76 g, 29.1 mmol, 78% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.88 (t, *J* = 4.5 Hz, 1H), 4.00 – 3.91 (m, 2H), 3.90 – 3.80 (m, 2H), 3.74 (s, 6H), 3.47 (t, *J* = 7.5 Hz, 1H), 2.08 – 2.01 (m, 2H), 1.74 – 1.68 (m, 2H).

Preparation of racemic ketal 189:



In a 500-mL, round-bottomed flask, Na (2.18 g, 94.9 mmol, 1.1 equiv) was added to MeOH (110 mL). After consumption of the solid Na, the solution was cooled to 0 °C, and a solution of diester **208** (20.0 g, 86.3 mmol, 1.0 equiv) in MeOH (30 mL) was added via cannula, followed by dropwise addition of a solution of 2-cyclopenten-1-one (**188**, 7.95 mL, 94.9 mmol, 1.1 equiv) in MeOH (30 mL) over 20 minutes. The reaction was stirred for an additional 2 h, and then quenched with sat. NH_4Cl (300 mL). The mixture was concentrated *in vacuo* to remove MeOH, and the resulting solution was extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (20% acetone in hexanes) afforded ketal **189** (23.1 g, 73.5 mmol, 85% yield) as a white solid.

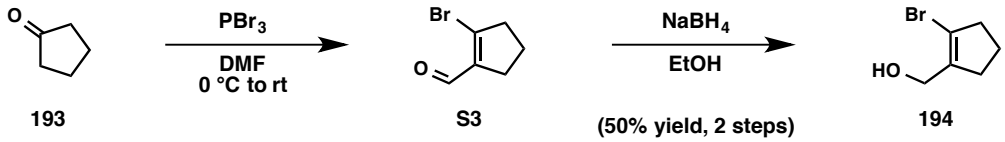
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (td, *J* = 4.4, 0.9 Hz, 1H), 4.01 – 3.91 (m, 2H), 3.89 – 3.80 (m, 2H), 3.74 – 3.73 (m, 6H), 2.85 – 2.74 (m, 1H), 2.48 (dd, *J* = 18.5, 7.6 Hz, 1H), 2.31 (dd, *J* = 17.2, 8.4 Hz, 1H), 2.25 – 2.11 (m, 3H), 2.08 – 2.03 (m, 2H), 1.73 – 1.58 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 217.4, 170.9, 170.8, 103.7, 59.4, 52.4, 52.4, 41.1, 40.2, 38.5, 28.9, 27.7, 24.9.

FTIR (NaCl, thin film): 2956, 2890, 1743, 1730, 1451, 1435, 1407, 1222, 1147, 1036 cm^{-1}.

HRMS: (FAB) calc'd for $C_{15}H_{23}O_7$ $[M + H]^+$ 315.1444, found 315.1438.

Preparation of allylic alcohol 194:



193 S3 (50% yield, 2 steps) 194

In a 1-L, round-bottomed flask, PBr_3 (14.3 mL, 153 mmol, 2.7 equiv) was added via syringe to a solution of DMF (14.0 mL, 181 mmol, 3.2 equiv) in CH_2Cl_2 (80 mL) at 0 °C. After stirring for 1 h, a solution of cyclopentanone (**193**, 5.0 mL, 56.5 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL, 10 mL rinse) was added via cannula. The reaction was allowed to warm to ambient temperature, and stirred for an additional 21 h. The reaction was cooled again to 0 °C, and quenched *carefully* with sat. $NaHCO_3$ (500 mL). Solid $NaHCO_3$ was added periodically as needed until bubbling ceased. The resulting mixture was extracted with Et_2O (3 x 250 mL), and the combined organic extracts were washed with H_2O (2 x 500 mL) and brine (500 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (15% EtOAc in hexanes) to afford bromoenal **S3** (ca. 5.8 g), which was used in the next step without rigorous removal of solvent.

In a 500-mL, round-bottomed flask, bromoenal **S3** (ca. 5.8 g) was dissolved in EtOH (33 mL) and cooled to 0 °C. $NaBH_4$ (1.5 g, 39.8 mmol, 1.2 equiv) was added, and

the reaction was stirred for 1 h. The reaction was quenched with H_2O (200 mL), and the mixture was concentrated *in vacuo* to remove ethanol. The resulting aqueous solution was extracted with Et_2O (3 x 200 mL), and the combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (15% EtOAc in hexanes) afforded allylic alcohol **194** (5.05 g, 28.5 mmol, 50% yield over two steps) as a colorless oil. Spectroscopic data for bromoenal **S3** and allylic alcohol **194** matched that reported in the literature.[16]

Caution: Bromoenal **S3** was found to decompose exothermically upon standing for several hours. It could be safely stored as a solution in Et_2O in a –20 °C freezer, but in most cases was immediately used in subsequent reactions.

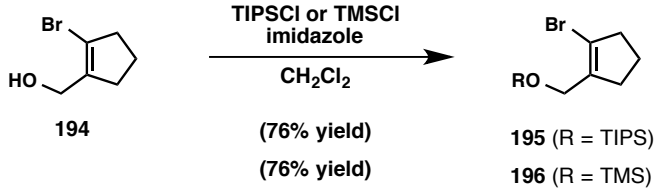
Bromoenal S3:

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 2.94 – 2.86 (m, 4H), 2.57 – 2.49 (m, 4H), 2.02 (pd, J = 7.9, 1.1 Hz, 4H).

Allylic alcohol 194:

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29 – 4.21 (m, 2H), 2.73 – 2.59 (m, 2H), 2.54 – 2.40 (m, 2H), 1.97 (tt, *J* = 8.3, 6.6 Hz, 2H).

Preparation of silyl ethers 195 and 196:



In a 200-mL, round-bottomed flask, allylic alcohol **194** (5.05 g, 28.5 mmol, 1.0 equiv) and imidazole (4.66 g, 68.5 mmol, 2.4 equiv) were dissolved in DMF (57 mL). To this solution was added TMSCl (4.34 mL, 34.2 mmol, 1.2 equiv), and the reaction was stirred for 12 h. The reaction was quenched with sat. $NaHCO_3$ (100 mL) and H_2O (100 mL), and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with H_2O (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (0.5% Et_3N/5% EtOAc in hexanes) to afford TMS ether **196** (5.44 g, 21.8 mmol, 76% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24 (tt, *J* = 1.6, 1.0 Hz, 2H), 2.67 – 2.61 (m, 2H), 2.46 – 2.38 (m, 2H), 1.99 – 1.90 (m, 2H), 0.13 (s, 9H).

^{13}C NMR (126 MHz,$CDCl_3$): δ 139.8, 116.8, 60.4, 40.3, 32.4, 21.5, -0.4.

FTIR (NaCl, thin film): 2953, 2922, 2852, 1655, 1443, 1319, 1246, 1091, 1023 cm^{-1}.

HRMS: (FAB) calc'd for $C_9H_{17}BrOSiNa$ $[M + Na]^+$ 271.0130, found 217.0144.

The same procedure was used to prepare TIPS ether **195**:

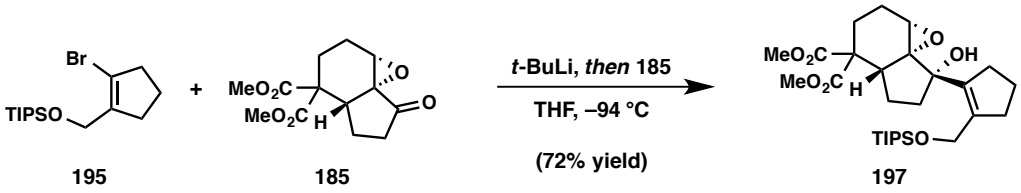
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.35 (tq, *J* = 1.7, 0.9 Hz, 2H), 2.68 – 2.62 (m, 2H), 2.52 – 2.45 (m, 2H), 1.99 – 1.91 (m, 2H), 1.18 – 1.10 (m, 3H), 1.10 – 1.04 (m, 18H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 140.7, 115.2, 61.4, 40.2, 32.3, 21.5, 18.0, 12.0.

FTIR (NaCl, thin film): 2960, 2941, 2892, 2866, 1657, 1463, 1383, 1369, 1104, 1066 cm^{-1}.

HRMS: (FAB) calc'd for $C_{15}H_{28}BrOSi$ $[M + H - H_2]^+$ 331.1093, found 331.1089.

Preparation of epoxy alcohol 197:



195 185 197

In a 10-mL, round-bottomed flask, a solution of vinyl bromide **195** (54.3 mg, 0.186 mmol, 1.0 equiv) in THF (0.93 mL) was added to a solution of *t*-BuLi (220 µL, 0.373 mmol, 2.0 equiv) in THF (0.93 mL) at –94 °C. After stirring for 15 min, a solution of epoxyketone **185** (50.0 mg, 0.186 mmol, 1.0 equiv) in THF (0.93 mL) was added. The reaction was stirred for an additional hour, and then quenched with H_2O (5 mL). The mixture was extracted with Et_2O (3 x 5 mL), and the combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude residue by silica gel chromatography (11% EtOAc in hexanes) afforded epoxy alcohol **197** (64.5 mg, 0.134 mmol, 72% yield) as a colorless oil.

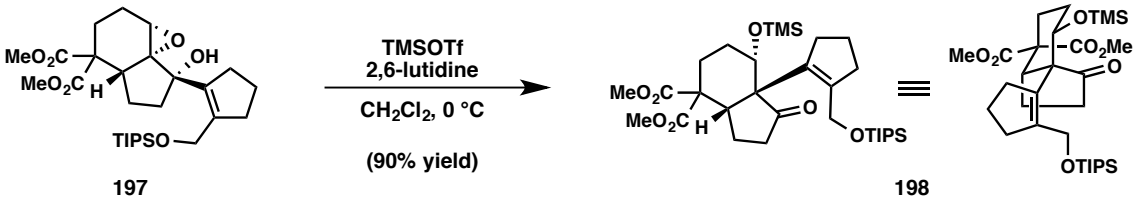
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.58 (dt, J = 2.8, 1.5 Hz, 2H), 3.75 (s, 3H), 3.71 (s, 3H), 3.29 (d, J = 3.6 Hz, 1H), 2.99 (s, 1H), 2.65 (dd, J = 12.3, 5.7 Hz, 1H), 2.57 – 2.49 (m, 2H), 2.49 – 2.24 (m, 6H), 2.06 – 1.91 (m, 4H), 1.86 – 1.70 (m, 2H), 1.63 – 1.54 (m, 1H), 1.14 – 1.07 (m, 3H), 1.07 – 1.03 (m, 18H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9, 170.2, 139.4, 136.5, 77.1, 72.1, 60.6, 57.5, 55.0, 52.9, 52.1, 46.3, 39.5, 35.4, 35.0, 29.0, 24.6, 22.0, 21.5, 18.0, 12.0.

FTIR (NaCl, thin film): 3493, 2946, 2888, 2865, 1740, 1730, 1463, 1434, 1368, 1305, 1245, 1092, 1062 cm^{-1}.

HRMS: (ESI) calc'd for $C_{28}H_{46}NaO_7Si$ $[M + Na]^+$ 545.2905, found 545.2906.

Preparation of ketone 198:



In a 10-mL, round-bottomed flask, epoxy alcohol **197** (94.2 mg, 0.180 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. 2,6-lutidine (63 μL, 0.541 mmol, 3.0 equiv) was added, followed by TMSOTf (65 μL, 0.360 mmol, 2.0 equiv). The reaction was stirred for 15 min, and then quenched with sat. $NaHCO_3$ (5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (7% EtOAc in hexanes) afforded ketone **198** (95.8 mg, 0.161 mmol, 90% yield) as a colorless oil.

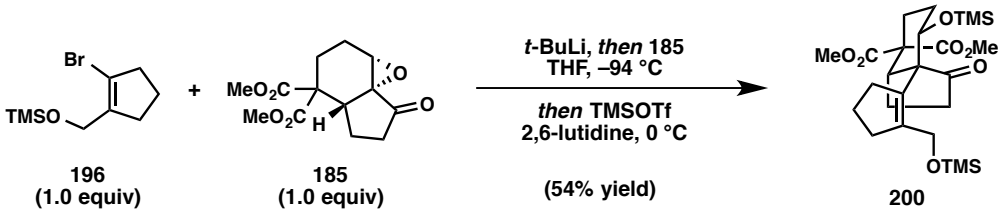
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (s, 1H), 4.12 (d, J = 12.2 Hz, 1H), 3.98 (d, J = 12.2 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.44 (dd, J = 12.7, 7.5 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.45 (dt, J = 15.7, 7.5 Hz, 2H), 2.39 – 2.08 (m, 6H), 1.94 – 1.76 (m, 3H), 1.77 – 1.64 (m, 2H), 1.14 – 1.08 (m, 3H), 1.08 – 1.04 (m, 18H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 220.1, 170.9, 170.8, 139.2, 135.4, 70.3, 61.4, 57.3, 56.1, 52.6, 52.5, 45.7, 38.7, 36.5, 35.0, 28.3, 23.5, 21.5, 19.0, 17.9, 11.9, -0.1.

FTIR (NaCl, thin film): 2950, 2892, 2866, 1743, 1462, 1405, 1278, 1278, 1252, 1208, 1169, 1094, 1070, 1020 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{33}O_6Si$ $[M - OTIPS]^+$ 421.2041, found 421.2031.

Preparation of ketone 200 directly from epoxyketone 185:



In a 50-mL, round-bottomed flask, vinyl bromide **196** (130 mg, 0.522 mmol, 1.0 equiv) was dissolved in THF (5.2 mL) and cooled to –94 °C (acetone/liquid N_2). *t*-BuLi (0.61 mL, 1.7 M in pentane, 1.04 mmol, 2.0 equiv) was added, and the reaction was stirred for 10 min. In a separate flask, a solution of epoxyketone **185** (140 mg, 0.522 mmol, 1.0 equiv) in THF (5.2 mL) was prepared and added slowly, down the side of the flask, to the first reaction flask. The reaction was stirred for 30 min while allowing the acetone/liquid N_2 bath to expire (not exceeding 0 °C). The cooling bath was replaced with an ice bath (0 °C), and then 2,6-lutidine (0.18 mL, 1.57 mmol, 3.0 equiv) was added, followed by TMSOTf (0.19 mL, 1.04 mmol, 2.0 equiv). The reaction was stirred for 20 min, and then another portion of 2,6-lutidine (0.18 mL, 1.57 mmol, 3.0 equiv) was added, followed by another portion of TMSOTf (0.19 mL, 1.04 mmol, 2.0 equiv). The reaction was stirred an additional 20 min, then quenched with sat. $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic extracts were dried

over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (5 to 7% EtOAc in hexanes) to provide ketone **200** (142.7 mg, 0.279 mmol, 54% yield) as a colorless oil.

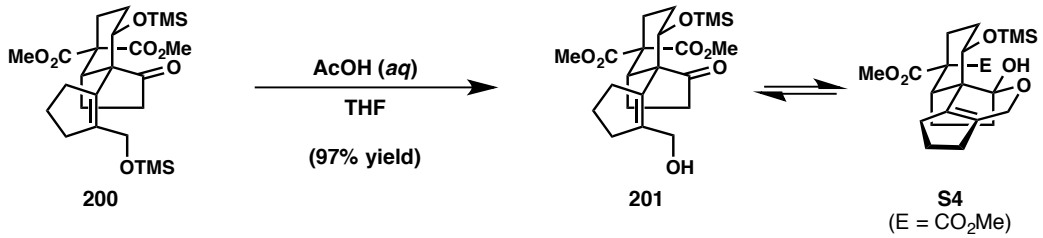
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (s, 1H), 3.98 (d, *J* = 12.6 Hz, 1H), 3.88 (d, *J* = 12.8 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.38 (dd, *J* = 12.8, 7.5 Hz, 1H), 2.48 – 2.25 (m, 6H), 2.25 – 2.08 (m, 3H), 1.93 – 1.64 (m, 5H), 0.11 (s, 9H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 220.0, 170.8, 170.8, 138.6, 136.0, 70.4, 60.4, 57.3, 56.1, 52.6, 52.6, 45.8, 38.8, 36.7, 35.2, 28.3, 23.5, 21.6, 19.0, -0.1, -0.6.

FTIR (NaCl, thin film): 2954, 2904, 2848, 1743, 1460, 1434, 1405, 1252, 1209, 1169, 1072, 1021 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{33}O_6Si$ $[M - OTMS]^+$ 421.2041, found 421.2045.

Preparation of allylic alcohol 201:



In a 10-mL, round-bottomed flask, bis-silyl ether **200** (120 mg, 0.235 mmol, 1.0 equiv) was dissolved in THF (2.4 mL). Aqueous AcOH (0.7 mL, 1.0 M, 0.700 mmol, 3.0 equiv) was added, and the reaction was stirred for 45 min. The reaction was then quenched by addition of sat. $NaHCO_3$ (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and

concentrated *in vacuo*. Purification by silica gel chromatography (33% EtOAc in hexanes) afforded an equilibrium mixture of allylic alcohol **201** and cyclic hemiketal **S4** (100 mg, 0.228 mmol, 97% yield) as a white foam.

FTIR (NaCl, thin film): 3479, 2953, 2847, 1739, 1734, 1643, 1445, 1434, 1402, 1251, 1172, 1099, 1075 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{33}O_6Si$ $[M - OH]^+$ 421.2041, found 421.2043.

Key NMR signals for allylic alcohol **201**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.31 (d, *J* = 16.5 Hz, 1H), 4.17 (dt, *J* = 16.1, 2.7 Hz, 1H), 3.87 (t, *J* = 5.5 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.09 (t, *J* = 9.1 Hz, 1H), 0.15 (s, 9H).

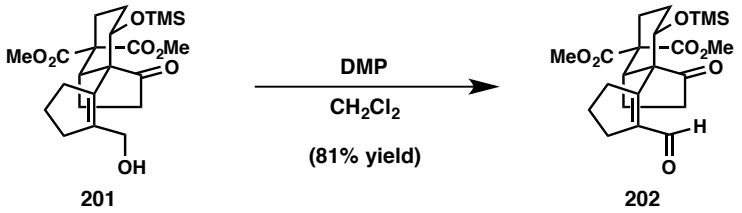
^{13}C NMR (126 MHz, $CDCl_3$): δ 221.8, 171.9, 170.9, 134.1, 134.1, 0.4.

Key NMR signals for cyclic hemiketal **S4**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25 (s, 1H), 3.99 (dd, *J* = 12.4 6.1 Hz, 1H), 3.89 (dd, *J* = 14.0, 4.8 Hz), 3.76 (s, 3H), 3.71 (s, 3H), 3.36 (dd, *J* = 12.8, 7.5 Hz, 1H), 0.09 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.0, 170.5, 139.3, 138.1, 106.9, 0.1.

Preparation of ketoaldehyde 202:



201 202

In a 25-mL, round-bottomed flask, allylic alcohol **201** (203.4 mg, 0.464 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4.6 mL). Dess–Martin periodinane (393.4 mg, 0.927 mmol, 2.0 equiv) was added, and the reaction was stirred for 1 h. The reaction was then quenched by addition of sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude residue by silica gel chromatography (25% EtOAc in hexanes) afforded ketoaldehyde **202** (163.7 mg, 0.375 mmol, 81% yield) as a colorless oil.

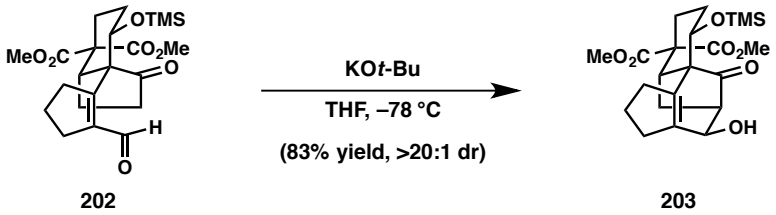
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 4.39 (s, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.45 (dd, *J* = 12.6, 7.7 Hz, 1H), 2.78 – 2.63 (m, 3H), 2.60 – 2.34 (m, 4H), 2.25 – 2.07 (m, 2H), 1.95 – 1.72 (m, 4H), 1.67 (tdd, *J* = 14.4, 3.5, 2.0 Hz, 1H), 0.07 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 218.6, 188.4, 171.0, 170.4, 162.1, 138.6, 70.1, 58.9, 56.5, 52.8, 52.7, 47.6, 38.9, 38.8, 31.8, 28.2, 23.8, 21.7, 19.2, -0.1.

FTIR (NaCl, thin film): 2954, 2851, 2756, 1740, 1660, 1594, 1579, 1460, 1434, 1252, 1171, 1099, 1060, 1023 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{33}O_7Si$ $[M + H]^+$ 437.1990, found 437.1982.

Preparation of tetracycle 203:



202 203

In a 10-mL, round-bottomed flask, ketoaldehyde **202** (40.0 mg, 91.6 μmol, 1.0 equiv) was dissolved in THF (1.8 mL) and cooled to –78 °C. To this solution was added KO*t*-Bu (101 μL, 1 M in THF, 0.101 mmol, 1.1 equiv), and the reaction was stirred for 5 min at –78 °C. The reaction was quenched by addition of sat. $NaHCO_3$ (2 mL), and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (40% EtOAc in hexanes) to afford alcohol **203** (33.1 mg, 75.8 μmol, 83% yield) as a white solid.

Note: The aldol product **203** is unstable to long term storage, as it slowly undergoes epimerization at the allylic alcohol (likely through retro-aldol/aldol) and cleavage of the silyl ether. It is also unstable to un-neutralized $CDCl_3$, and thus NMR's are often contaminated with epimeric/diol side products. The direct aldol product **203** was most often carried onto the next step crude without purification.

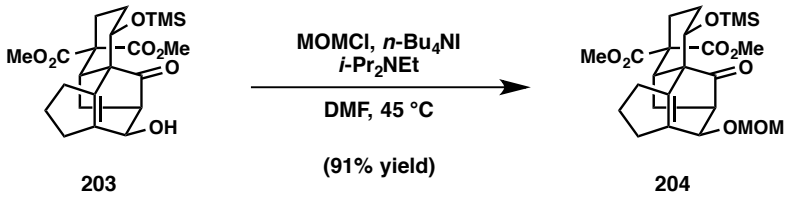
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (s, 1H), 3.99 (dd, *J* = 9.1, 6.6 Hz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 2.62 – 2.50 (m, 3H), 2.52 – 2.42 (m, 1H), 2.42 (dd, *J* = 9.9, 2.3 Hz, 1H), 2.28 – 2.12 (m, 3H), 2.01 – 1.89 (m, 4H), 1.81 – 1.73 (m, 2H), 1.63 (ddd, *J* = 14.3, 10.0, 1.9 Hz, 1H), 0.12 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.7, 172.2, 170.5, 147.1, 138.1, 78.1, 70.7, 57.3, 55.1, 52.9, 52.3, 51.7, 44.4, 32.6, 31.6, 29.5, 27.4, 26.7, 23.1, 0.9.

FTIR (NaCl, thin film): 3445, 2954, 2851, 1738, 1732, 1652, 1435, 1252, 1059, 841 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{33}O_7Si$ $[M + H]^+$ 437.1990, found 437.1994.

Preparation methoxymethyl ether 204:



203 **204**

In a 1-dram vial, allylic alcohol **203** (8.4 mg, 19.2 μmol, 1.0 equiv) was dissolved in DMF (0.20 mL). To this solution was sequentially added *n*-Bu_4NI (1.4 mg, 3.9 μmol, 0.20 equiv), *i*-Pr_2NEt (20 μL, 0.115 mmol, 6.0 equiv), and MOMCl (7.3 μL, 96.2 μmol, 5.0 equiv). The reaction was heated to 45 °C and stirred for 13 h, and then quenched with sat. $NaHCO_3$ (2 mL). The mixture was extracted with CH_2Cl_2 (3 x 1 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (40% EtOAc in hexanes) to afford methoxymethyl ether **204** (8.4 mg, 17.5 μmol, 91% yield) as a colorless oil.

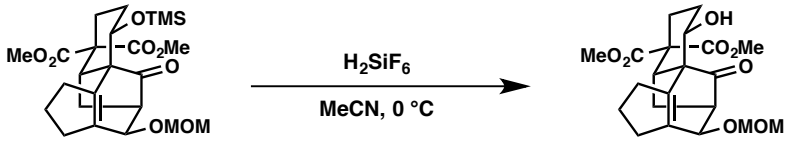
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (d, *J* = 7.1 Hz, 1H), 4.69 (d, *J* = 7.1 Hz, 1H), 4.25 (t, *J* = 2.5 Hz, 1H), 4.00 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.43 (s, 3H), 2.63 (ddd, *J* = 8.6, 3.2, 1.9 Hz, 1H), 2.60 – 2.41 (m, 4H), 2.25 – 2.10 (m, 3H), 2.00 – 1.90 (m, 3H), 1.88 – 1.71 (m, 2H), 1.63 – 1.56 (m, 1H), 0.10 (s, 9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 209.5, 172.3, 170.4, 147.4, 135.7, 95.5, 82.5, 70.2, 57.3, 55.4, 54.6, 52.9, 52.3, 47.7, 44.5, 32.9, 31.6, 29.1, 27.3, 26.3, 23.0, 0.9.

FTIR (NaCl, thin film): 2953, 2847, 1755, 1732, 1462, 1453, 1434, 1251, 1150, 1099, 1024 cm^{-1}.

HRMS: (ESI) calc'd for $C_{24}H_{36}KO_8Si$ $[M + K]^+$ 519.1811, found 519.1813.

Preparation of alcohol 205:



204 **205**

In a 1-dram vial, silyl ether **204** (8.4 mg, 17.5 μmol, 1.0 equiv) was dissolved in MeCN (0.35 mL) and cooled to 0 °C. H_2SiF_6 (20–25 wt%, 11.2 μL, 17.5 μmol, 1.0 equiv) was added, and the reaction was stirred for 10 minutes before quenching with sat. $NaHCO_3$ (1 mL). The mixture was extracted with CH_2Cl_2 (3 x 1 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford pure alcohol **205** (6.7 mg, 16.4 μmol, 94% yield) as a white solid.

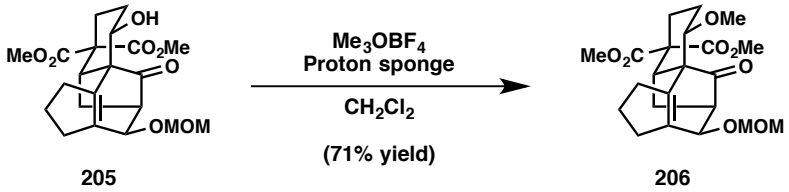
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (d, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.33 – 4.26 (m, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 3.82 (td, *J* = 11.6, 5.1 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.44 (s, 3H), 2.82 – 2.69 (m, 2H), 2.65 – 2.51 (m, 1H), 2.51 – 2.41 (m, 1H), 2.37 (ddd, *J* = 14.5, 8.6, 1.8 Hz, 1H), 2.27 – 2.13 (m, 3H), 2.10 – 1.91 (m, 3H), 1.86 (td, *J* = 14.0, 2.7 Hz, 1H), 1.64 (ddd, *J* = 14.4, 9.9, 2.0 Hz, 1H), 1.46 (qd, *J* = 13.7, 2.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 217.5, 171.7, 170.8, 147.4, 136.8, 95.6, 82.8, 71.4, 57.7, 55.5, 53.8, 52.8, 52.5, 47.9, 45.0, 32.9, 31.9, 30.2, 28.1, 27.6, 22.7.

FTIR (NaCl, thin film): 3491, 2953, 2892, 2849, 1741, 1732, 1453, 1435, 1298, 1286, 1260, 1215, 1151, 1098, 1080, 1056, 1035, 1024 cm^{-1}.

HRMS: (ESI) calc'd for $C_{19}H_{23}O_6$ $[M - OCH_2OCH_3]^+$ 347.1489, found 347.1484.

Preparation of methyl ether 206:



205 **206**

In an N_2-filled glovebox, alcohol **205** (30.0 mg, 73.4 μmol, 1.0 equiv), Me_3OBF_4 (32.6 mg, 0.220 mmol, 3.0 equiv), and Proton sponge (63.0 mg, 0.294 mmol, 4.0 equiv) were dissolved in CH_2Cl_2 (0.5 mL) in a 1-dram vial. The vial was sealed with a Teflon cap, brought out of the glovebox, and stirred for 36 h. The reaction mixture was then filtered directly through a short plug of silica, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (60% EtOAc in hexanes) to afford methyl ether **206** (22.1 mg, 52.3 μmol, 71% yield) as a colorless oil.

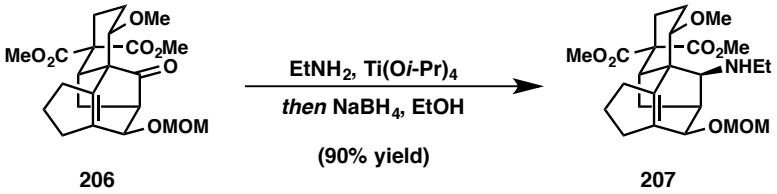
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (d, *J* = 7.1 Hz, 1H), 4.65 (d, *J* = 7.1 Hz, 1H), 4.26 (s, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 3.44 – 3.39 (m, 4H), 3.35 (s, 3H), 2.71 (ddd, *J* = 8.6, 3.5, 2.0 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.53 – 2.45 (m, 1H), 2.38 (dd, *J* = 9.9, 2.1 Hz, 1H), 2.34 – 2.15 (m, 3H), 2.09 – 1.90 (m, 3H), 1.85 (ddd, *J* = 14.3, 12.5, 3.3 Hz, 1H), 1.66 – 1.51 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 209.6, 172.1, 170.3, 146.9, 136.3, 95.4, 82.1, 79.2, 57.7, 57.1, 55.5, 54.5, 52.9, 52.3, 47.6, 44.8, 33.1, 31.7, 30.0, 26.7, 22.7, 22.0.

FTIR (NaCl, thin film): 2952, 2849, 1752, 1732, 1452, 1437, 1258, 1238, 1214, 1149, 1105, 1024 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{30}NaO_8$ $[M + Na]^+$ 445.1833, found 445.1844.

Preparation of amine 207:



206 **207**

In a ½-dram vial, $EtNH_2$ (36 μL, 2.0 M in THF, 72 μmol, 3.0 equiv) and Ti(O*i*-Pr)$_4$ (37 μL, 0.125 mmol, 6.0 equiv) were added to ketone **206** (10.0 mg, 23.7 μmol, 1.0 equiv). After stirring for 2 h, the mixture was diluted with EtOH (0.47 mL), and $NaBH_4$ (9.0 mg, 0.238 mmol, 10 equiv) was added. The reaction mixture was stirred for an additional 2 h, and then concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 and quenched by addition of sat. $NaHCO_3$ (1 mL) and Rochelle's salt (ca. 30 mg), and then stirred for 1 h. The layers were separated, and the aqueous phase was extracted CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford amine **207** (9.6 mg, 21.3 μmol, 90% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 3.74 (s, 3H), 3.73 – 3.68 (m, 1H), 3.70 – 3.56 (m, 4H), 3.38 (s, 3H), 3.23 (s, 3H), 3.20 – 3.11

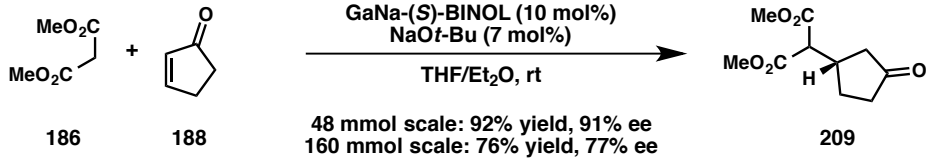
(m, 1H), 2.79 – 2.56 (m, 4H), 2.56 – 2.45 (m, 3H), 2.33 – 2.03 (m, 4H), 1.89 (p, J = 7.4 Hz, 2H), 1.72 – 1.59 (m, 2H), 1.37 (dd, J = 13.7, 9.7 Hz, 1H), 1.04 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 170.8, 145.6, 133.5, 95.2, 77.4, 76.0, 61.5, 56.6, 56.4, 55.3, 52.9, 52.4, 49.0, 47.6, 42.8, 38.7, 33.4, 31.1, 28.9, 24.0, 21.7, 21.5, 15.3.

FTIR (NaCl, thin film): 3346, 2951, 2888, 2847, 2824, 1738, 1732, 1463, 1457, 1436, 1372, 1262, 1236, 1198, 1148, 1096, 1029, 988, 917 cm^{-1}.

HRMS: (ESI) calc'd for $C_{24}H_{38}NO_7$ $[M + H]^+$ 452.2643, found 452.2634.

Preparation of diester 209:



Preparation of GaNa-(*S*)-BINOL solution (0.05 M in 9:1 THF:Et_2O):[18] In a 500-mL, round-bottomed flask, a solution of NaO*t*-Bu (3.29 g, 34.2 mmol, 4.0 equiv) in THF (60 mL) was added to a solution of (*S*)-BINOL (4.90 g, 17.1 mmol, 2.0 equiv) in THF (52 mL), and the resulting mixture was stirred for 30 minutes. This was then cannulated into a solution of $GaCl_3$ (1.51 g, 8.55 mmol, 1.0 equiv) in THF (43 mL) and Et_2O (17 mL). This mixture was stirred for 2 h, and then allowed to stand un-agitated for at least 22 h.

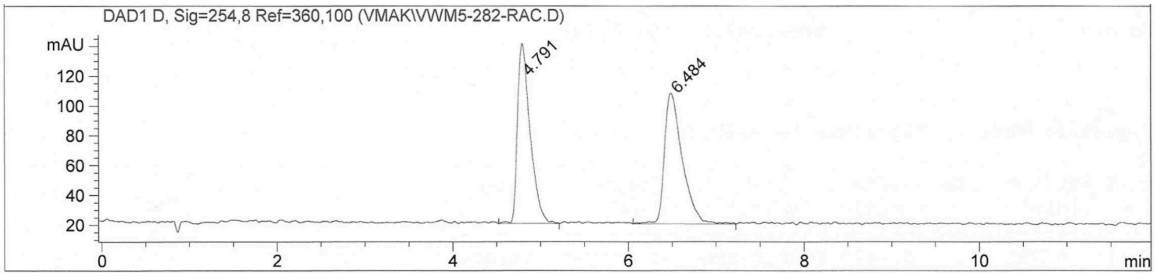
Enantioselective Michael addition: A solution of GaNa-(*S*)-BINOL (96 mL, 0.05 M in 9:1 THF:Et_2O, 4.80 mmol, 0.10 equiv) was transferred via syringe to a 500-mL, round-bottomed flask. To this was added a solution of NaO*t*-Bu (323 mg, 3.36 mmol. 0.07 equiv) in THF (7.5 mL), followed by dimethyl malonate (**186**, 5.5 mL, 48

mmol, 1.0 equiv) and 2-cyclopenten-1-one (**188**, 4.0 mL, 48 mmol, 1.0 equiv). The reaction was stirred for 37 h, then quenched with 1 N HCl (300 mL). The mixture was extracted with EtOAc (3 x 200 mL), and the combined organic extracts were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacou*. Vacuum distillation of the crude residue afforded diester **209** (9.44 g, 44.1 mmol, 92% yield) as a colorless oil. Spectroscopic data matched that reported in the literature.[35]

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.75 (s, 3H), 3.38 (d, *J* = 9.4 Hz, 1H), 2.95 – 2.78 (m, 1H), 2.51 (dd, *J* = 18.4, 7.7 Hz, 2H), 2.43 – 2.13 (m, 3H), 2.01 (ddd, *J* = 18.4, 11.1, 1.3 Hz, 1H), 1.74 – 1.59 (m, 1H).

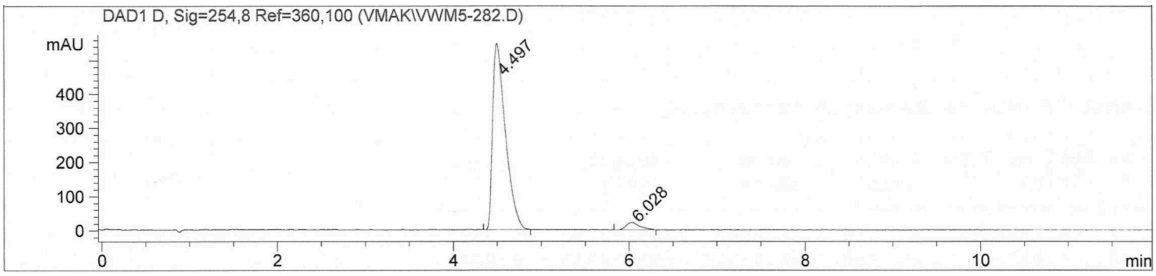
Diester **209** was carried forward to enone **190**, where enantiomeric excess was determined to be 91%:

SFC data for racemic enone 190:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.791	VV	0.1489	1209.87744	120.72012	49.2621
2	6.484	VV	0.2134	1246.12061	87.90836	50.7379

SFC data for enantioenriched enone 190 (three steps from diester 209):

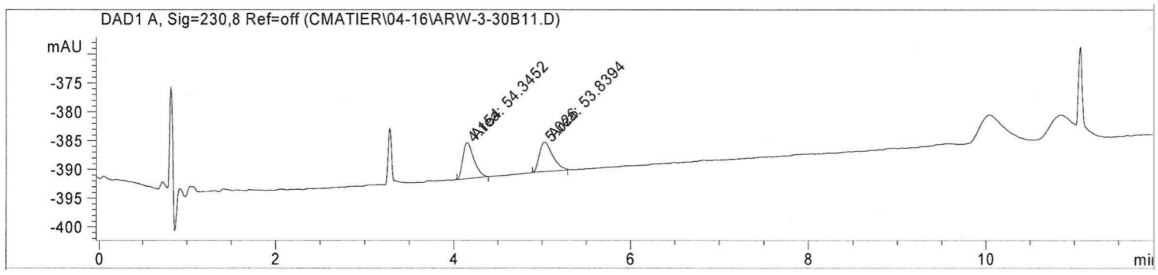


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.497	BB	0.1512	5494.35840	546.90161	95.9901
2	6.028	BB	0.1575	229.52094	21.68033	4.0099

Large-scale preparation of diester 209: The above protocol was reproduced using 160 mmols of dimethyl malonate (**186**) and 160 mmols of 2-cyclopenten-1-one (**188**), affording a 76% yield of diester **209** in 77% ee.

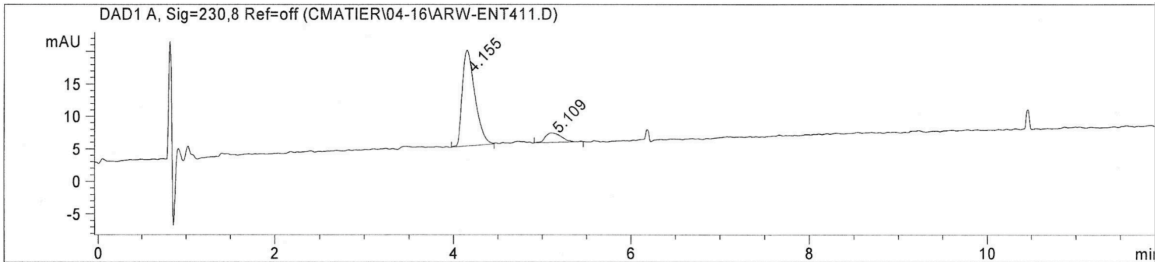
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –46° (*c* = 0.84, $CHCl_3$).

SFC data for racemic diester 209:



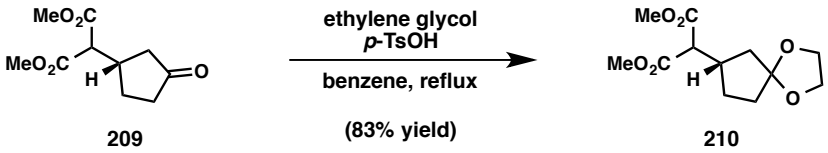
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.154	MM	0.1434	54.34519	6.31819	50.2337
2	5.026	MM	0.1737	53.83944	5.16645	49.7663

SFC data for enantioenriched diester 209 prepared on 160 mmol scale:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.155	BB	0.1512	145.44695	14.72653	88.5103
2	5.109	BB	0.1910	18.88070	1.47825	11.4897

Preparation of ketal 210:



209 210

In a 50-mL, round-bottomed flask equipped with a reflux condenser and Dean–Stark trap, ketone **209** (1.33 g, 6.19 mmol, 1.0 equiv) was dissolved in toluene (21 mL). To this solution was added ethylene glycol (0.70 mL, 12.4 mmol, 2.0 equiv) and *p*-TsOH•H_2O (120 mg, 0.619 mmol, 0.10 equiv), and the reaction was heated to reflux for 48 h. The reaction was then cooled to room temperature and washed with sat. $NaHCO_3$ (2 x 50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (25% EtOAc in hexanes) provided ketal **210** (1.33 g, 5.15 mmol, 83% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 – 3.84 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.31 (d, *J* = 10.2 Hz, 1H), 2.75 – 2.62 (m, 1H), 2.08 (ddd, *J* = 13.7, 8.0, 1.2 Hz, 1H), 1.99 – 1.86 (m, 2H), 1.85 – 1.75 (m, 1H), 1.56 (dd, *J* = 13.6, 9.5 Hz, 1H), 1.48 – 1.36 (m, 1H).

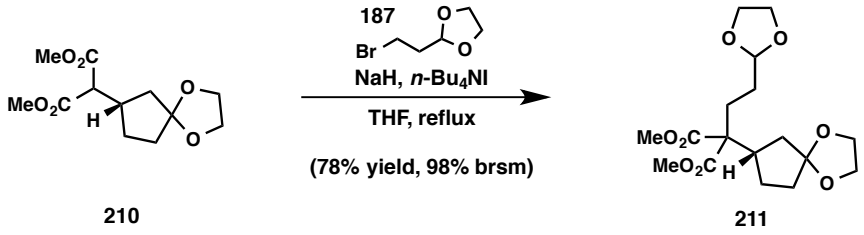
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 168.9, 117.0, 64.3, 64.2, 56.7, 52.4, 52.4, 40.6, 36.8, 35.5, 28.2.

FTIR (NaCl, thin film): 2956, 2885, 1754, 1734, 1435, 1316, 1216, 1151, 1079, 1017, 947 cm^{-1}.

HRMS: (PMM) calc'd for $C_{12}H_{19}O_6$ $[M + H]^+$ 259.1176, found 259.1169.

$[\alpha]_D^{25}$ = +2.2° (*c* = 1.4, $CHCl_3$).

Preparation of bis-ketal 211:



210 **211**

In a 250-mL, round-bottomed flask equipped with a reflux condenser, NaH (60% dispersion in mineral oil, 1.42 g, 35.6 mmol, 1.2 equiv) was washed with hexanes (3 x 10 mL), then cooled to 0 °C. A solution of diester **210** (7.66 g, 29.6 mmol, 1.0 equiv) in THF (70 mL, followed by 3 x 10 mL rinse) was added, and the reaction was heated to 70 °C with stirring for 25 min. *n*-Bu_4NI (1.09 g, 2.96 mmol, 0.10 equiv) and 2-(2-bromoethyl)-1,3-dioxolane (**187**, 5.22 mL, 44.5 mmol, 1.5 equiv) were added sequentially, and the reaction was heated to reflux for 15 h. The reaction was then quenched by addition of sat. NH_4Cl (50 mL) and H_2O (50 mL). The mixture was

extracted with CH_2Cl_2 (3 x 250 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (35 to 40% EtOAc in hexanes) afforded recovered starting material **210** (1.56 g, 20% recovery) and bis-ketal **211** (7.26 g, 23.1 mmol, 78% yield, 98% based on recovered starting material) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.83 (td, *J* = 4.5, 1.9 Hz, 1H), 3.97 – 3.81 (m, 8H), 3.71 (s, 3H), 3.71 (s, 3H), 2.70 – 2.60 (m, 1H), 2.05 – 1.95 (m, 3H), 1.91 – 1.80 (m, 2H), 1.80 – 1.66 (m, 2H), 1.64 – 1.50 (m, 3H).

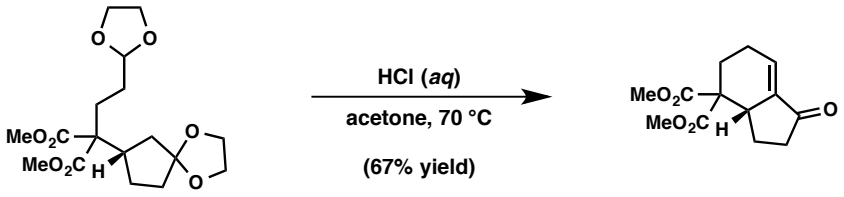
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 171.1, 116.6, 103.9, 64.9, 64.9, 64.2, 64.1, 59.8, 52.2, 52.1, 40.4, 38.0, 35.3, 29.0, 27.9, 25.4.

FTIR (NaCl, thin film): 2954, 2915, 2877, 1728, 1434, 1227, 1141, 1024 cm^{-1}.

HRMS: (FAB) calc'd for $C_{17}H_{27}O_8$ $[M + H]^+$ 359.1706, found 359.1716.

$[\alpha]_D^{25}$ = –0.69° (*c* = 0.60, $CHCl_3$).

Preparation of enone 190:



211 190

In a 200-mL, round-bottomed flask equipped with a reflux condenser, bis-ketal **211** (7.26 g, 23.1 mmol, 1.0 equiv) was dissolved in acetone (92 mL). Aqueous HCl (23.1 mL, 2 N, 46.2 mmol, 2.0 equiv) was added, and the reaction was heated to 70 °C with stirring for 7 h. The reaction was then quenched with sat. $NaHCO_3$ (100 mL) and

partially concentrated *in vacuo* to remove acetone. The resulting mixture was extracted with CH_2Cl_2 (3 x 150 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (25% EtOAc in hexanes) to afford enone **190** (3.91 g, 15.5 mmol, 67% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (q, *J* = 3.8 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.11 (qdd, *J* = 7.4, 3.5, 2.1 Hz, 1H), 2.53 – 2.37 (m, 4H), 2.32 – 2.22 (m, 2H), 2.11 – 2.00 (m, 1H), 1.99 – 1.90 (m, 1H).

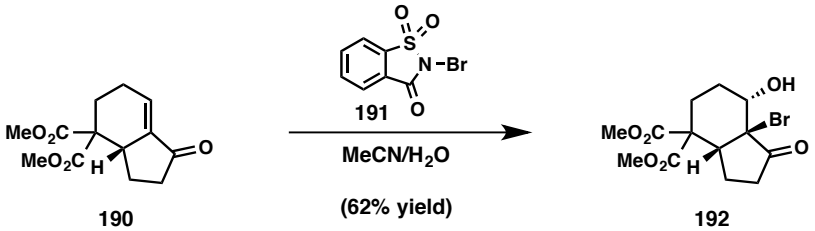
^{13}C NMR (126 MHz, $CDCl_3$): δ 204.6, 171.9, 169.5, 137.1, 131.3, 55.1, 52.7, 52.2, 42.8, 37.8, 29.4, 23.9, 23.3.

FTIR (NaCl, thin film): 3022, 2956, 2898, 2848, 1732, 1659, 1451, 1434, 1283, 1256, 1214, 1174, 1143, 1064 cm^{-1}.

HRMS: (FAB) calc'd for $C_{13}H_{17}O_5$ $[M + H]^+$ 253.1076, found 253.1076.

$[\alpha]_D^{25}$ = –34° (*c* = 1.7, $CHCl_3$).

Preparation bromohydrin 192:



A 250-mL, round-bottomed flask was charged with enone **190** (3.91 g, 15.5 mmol, 1.0 equiv), MeCN (64 mL), and H_2O (12 mL), followed lastly by *N*-

bromosaccharin (**191**, 5.28 g, 20.1 mmol, 1.3 equiv). The reaction was stirred for 6.5 h, then quenched by addition of sat. $Na_2S_2O_3$ (150 mL). The mixture was extracted with Et_2O (3 x 250 mL), and the combined organic extracts were washed with sat. $NaHCO_3$ (2 x 150 mL), brine (150 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a crude white solid. This was dissolved in Et_2O (600 mL) at 35 °C. Ca. 300 mL was concentrated off, and then hexanes (300 mL) was added. The solution was concentrated until ca. 300 mL of solvent remained, with white solids suspended within. The solvent was decanted into a Büchner funnel, washing the flask carefully with hexanes. The residual solids in the flask were collected, affording bromohydrin **192** (3.37 g, 9.65 mmol, 62% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 – 4.32 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.10 (ddd, *J* = 12.2, 5.8, 1.5 Hz, 1H), 2.80 – 2.68 (m, 2H), 2.58 – 2.45 (m, 1H), 2.43 – 2.32 (m, 2H), 2.32 – 2.16 (m, 2H), 2.11 – 1.96 (m, 2H).

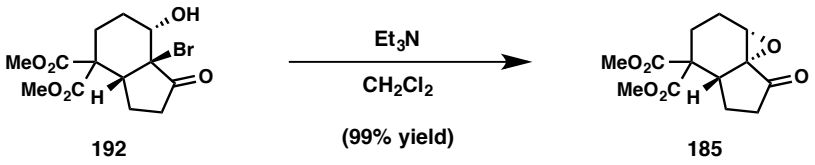
^{13}C NMR (101 MHz, $CDCl_3$): δ 211.6, 171.3, 171.1, 76.5, 55.5, 53.0, 52.5, 47.9, 42.2, 36.2, 28.2, 27.6, 21.3.

FTIR (NaCl, thin film): 3436, 2998, 2955, 2847, 1748, 1732, 1435, 1403, 1252, 1213, 1152, 1091, 1073, 1056, 980 cm^{-1}.

HRMS: (FAB) calc'd for $C_{13}H_{18}BrO_6$ $[M + H]^+$ 349.0287, found 349.0275.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –49° (*c* = 0.17, $CHCl_3$).

Preparation of epoxyketone 185:



192 185

In a 250-mL, round-bottomed flask, bromohydrin **192** (3.35 g, 9.59 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (96 mL). Et_3N (1.60 mL, 11.5 mmol, 1.2 equiv) was added, and the reaction was stirred for 9 h. The mixture was loaded directly onto a column of silica gel (slurried in hexanes), and purification by chromatography (100% hexanes, then 40% EtOAc in hexanes) afforded epoxyketone **185** (2.54 g, 9.47 mmol, 99% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 1H), 3.76 – 3.73 (m, 4H), 2.93 (dd, *J* = 12.5, 5.8 Hz, 1H), 2.67 (qd, *J* = 11.7, 7.4 Hz, 1H), 2.58 (ddd, *J* = 18.7, 7.6, 1.6 Hz, 1H), 2.48 – 2.28 (m, 4H), 2.12 – 2.01 (m, 1H), 1.72 – 1.61 (m, 1H).

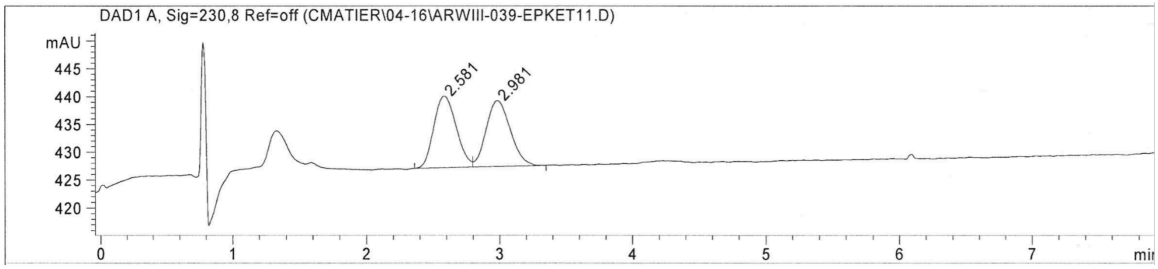
^{13}C NMR (126 MHz, $CDCl_3$): δ 212.0, 171.4, 169.8, 63.0, 56.1, 55.2, 53.1, 52.4, 43.8, 38.4, 29.3, 23.0, 21.7.

FTIR (NaCl/thin film): 3006, 2956, 2903, 2848, 1755, 1732, 1453, 1434, 1408, 1372, 1306, 1251, 1214, 1176, 1139, 1058, 890 cm^{-1}.

HRMS: (FAB) calc'd for $C_{13}H_{17}O_6$ $[M + H]^+$ 269.1025, found 269.1050.

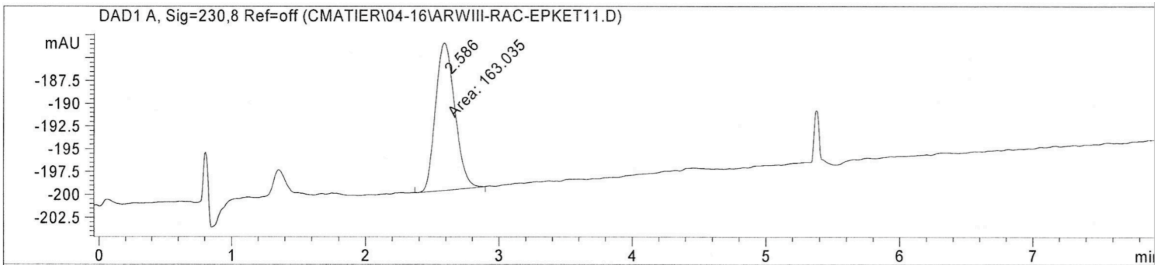
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –171° (*c* = 0.60, $CHCl_3$).

SFC data for racemic epoxyketone 185:



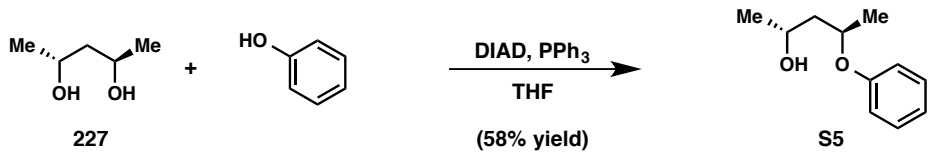
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.581	BV	0.1844	151.12083	12.92222	50.1015
2	2.981	VB	0.1999	150.50854	11.87293	49.8985

SFC data for enantiopure epoxyketone 185:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.586	MM T	0.1680	163.03540	16.17313	100.0000

Preparation of aryl ether S5:

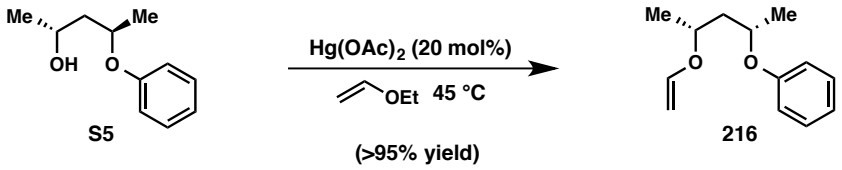


In a 1-L, round-bottomed flask equipped with an addition funnel, (2*R*, 4*R*)-pentanediol (**227**, 7.39 g, 71.0 mmol, 1.0 equiv), phenol (7.35 g, 78.1 mmol, 1.1 equiv), and PPh_3 (22.3 g, 85.1 mmol, 1.2 equiv) were dissolved in THF (375 mL). A solution of

DIAD (16.8 mL, 85.1 mmol, 1.2 equiv) in THF (100 mL) was prepared in another flask, and transferred to the addition funnel. The DIAD solution was added dropwise to the vigorously stirring reaction over 25 min, and the resulting solution was stirred for an additional 24 h and concentrated *in vacuo*. Purification of the crude residue by silica gel chromatography (15% EtOAc in hexanes) afforded arene **S5** (7.4 g, 41 mmol, 52% yield). Spectroscopic data matched that reported by Sugimura *et al.*[21]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H), 6.99 – 6.91 (m, 3H), 4.61 (dqd, *J* = 8.6, 6.0, 4.4 Hz, 1H), 4.06 (dqt, *J* = 8.9, 6.1, 2.7 Hz, 1H), 2.56 (s, 1H), 1.95 (dt, *J* = 14.4, 8.8 Hz, 1H), 1.70 (ddd, *J* = 14.4, 4.5, 3.1 Hz, 1H), 1.31 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.2 Hz, 3H).

Preparation of arene olefin 216:

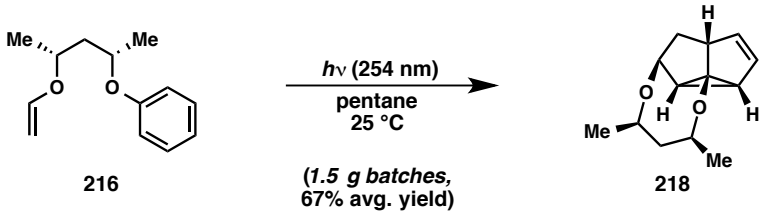


In a 250-mL, round-bottomed flask equipped with a reflux condenser, arene **S5** (3.90 g, 21.6 mmol, 1.0 equiv) was dissolved in ethyl vinyl ether (108 mL), and $Hg(OAc)_2$ (689 mg, 2.16 mmol, 0.10 equiv) was added. The mixture was heated to reflux and stirred for 18 h, at which point another portion of $Hg(OAc)_2$ (689 mg, 2.16 mmol, 0.10 equiv) was added. After stirring for another 15 h at reflux, the reaction was quenched by addition of sat. $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 200 mL). The combined organic extracts

were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by filtering over a short plug of silica (eluting with 10% EtOAc/1% Et_3N in hexanes) to provide arene olefin **216** (4.5 g, 21.8 mmol, 100% yield) as a colorless oil. Spectroscopic data matched that reported by Sugimura *et al.*[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 2H), 6.97 – 6.86 (m, 3H), 6.34 (dd, *J* = 14.2, 6.6 Hz, 1H), 4.52 (h, *J* = 6.2 Hz, 1H), 4.33 (dd, *J* = 14.2, 1.6 Hz, 1H), 4.12 (h, *J* = 6.3 Hz, 1H), 4.03 (dd, *J* = 6.7, 1.6 Hz, 1H), 2.20 (dt, *J* = 13.9, 6.9 Hz, 1H), 1.65 (dt, *J* = 14.0, 6.0 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H).

Preparation of 7-substituted *meta*-photoadduct 218:

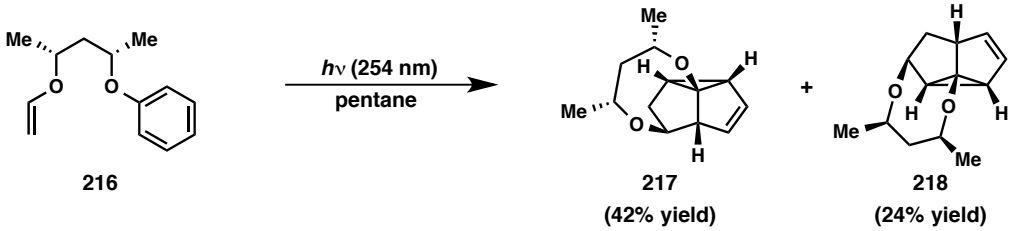


In a 1-L, round-bottomed quartz flask, arene olefin **216** (1.5 g, 7.3 mmol, 1.0 equiv) was dissolved in pentane (700 mL). This solution was sparged with Ar for 75 min, then irradiated with stirring using a Honeywell 254 nm lamp for 27 h. The temperature was deliberately maintained at 25 °C using ventilation fans. Upon completion, the reaction was concentrated *in vacuo* to afford a crude residue. *This procedure was repeated for a total of 5 batches*. All 5 crude batches were combined and purified by silica gel chromatography (9% EtOAc in hexanes) to afford 7-substituted

photoadduct **218** (5.0 g, 24.2 mmol, 67% average yield over 5 batches) as a white solid. Spectroscopic data matched that reported by Sugimura *et al.*[21]

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.63 (ddt, *J* = 5.5, 2.7, 1.0 Hz, 1H), 5.44 (dd, *J* = 5.5, 1.7 Hz, 1H), 4.49 (dd, *J* = 7.0, 2.5 Hz, 1H), 4.31 (p, *J* = 6.5 Hz, 1H), 4.06 (p, *J* = 6.5 Hz, 1H), 3.26 (dd, *J* = 8.4, 2.8 Hz, 1H), 2.52 – 2.42 (m, 3H), 2.34 (dt, *J* = 17.4, 7.4 Hz, 1H), 2.10 (ddd, *J* = 14.6, 7.0, 0.9 Hz, 1H), 1.60 (d, *J* = 17.5 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 6H).

Preparation of 6-substituted *meta*-photoadduct 217:



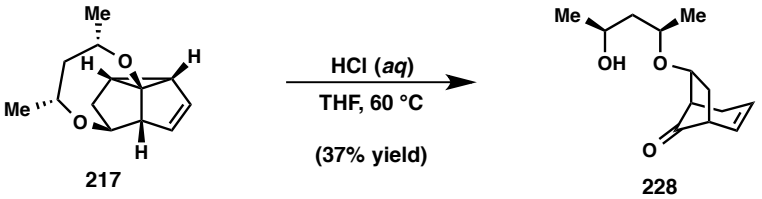
A 500-mL, round-bottomed quartz flask was charged with arene olefin **216** (244 mg, 1.18 mmol, 1.0 equiv) and pentane (250 mL). The solution was degassed by sparging with argon for 30 minutes. The reaction was then irradiated with stirring using a Honeywell 254 nm lamp for 21.5 h. The reaction was then concentrated *in vacuo*, and purified by silica gel chromatography (7 to 9% EtOAc in hexanes) to provide 6-substituted photoadduct **217** (101.3 mg, 0.491 mmol, 42% yield) and 7-substituted photoadduct **218** (59.1 mg, 0.287 mmol, 24% yield). Spectroscopic data matched that reported by Sugimura *et al.*[21]

Note: No extra precautions were taken to prevent heating of this reaction by the irradiation lamp. This caused polymeric material to form on the inner wall of the flask,

which interfered with light penetration, and thereby effectively diminished conversion of **217** to **218** via vinyl cyclopropane rearrangement to allow isolation of 6-substituted photoadduct **217**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.59 (ddd, *J* = 5.6, 2.4, 0.7 Hz, 1H), 5.42 (ddd, *J* = 5.7, 2.8, 1.6 Hz, 1H), 4.25 (dtd, *J* = 9.9, 7.3, 6.8, 5.7 Hz, 1H), 4.16 – 4.07 (m, 1H), 4.02 (tt, *J* = 7.4, 5.6 Hz, 1H), 3.85 (t, *J* = 2.6 Hz, 2H), 2.34 (ddt, *J* = 8.2, 2.2, 1.2 Hz, 1H), 2.09 (ddt, *J* = 8.4, 6.3, 1.1 Hz, 1H), 1.95 – 1.80 (m, 2H), 1.59 (d, *J* = 15.3 Hz, 1H), 1.50 (ddd, *J* = 13.9, 3.0, 1.4 Hz, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.4 Hz, 3H).

Preparation of [3.2.1]-bicycle 228:

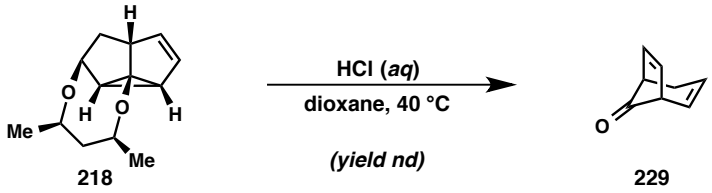


217 228

To a 1-dram vial containing 6-substituted photoadduct **217** (18.0 mg, 87.3 μmol, 1.0 equiv) was added THF (0.87 mL) and aqueous HCl (3 M, 0.15 mL, 0.436 mmol, 5.0 equiv). The vial was sealed and heated to 60 °C for 16 h, then quenched by addition of sat. $NaHCO_3$ (3 mL). The mixture was extracted with CH_2Cl_2 (3 x 3 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (40% EtOAc in hexanes) provided [3.2.1]-bicycle **228** (7.3 mg, 32.5 μmol, 37% yield) as a colorless oil. Spectroscopic data matched that reported by Sugimura *et al.*[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (dddd, *J* = 9.4, 7.0, 2.5, 1.0 Hz, 1H), 5.48 (dddd, *J* = 9.2, 3.7, 2.8, 0.8 Hz, 1H), 4.10 (dd, *J* = 8.5, 4.4 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.73 – 3.62 (m, 1H), 2.97 (ddt, *J* = 17.9, 5.2, 2.6 Hz, 1H), 2.86 (s, 1H), 2.68 (dd, *J* = 13.3, 8.4 Hz, 1H), 2.65 – 2.57 (m, 2H), 2.39 (dt, *J* = 4.6, 2.0 Hz, 1H), 1.92 (dt, *J* = 13.1, 5.5 Hz, 1H), 1.67 – 1.58 (m, 1H), 1.50 (ddd, *J* = 14.5, 4.1, 2.7 Hz, 1H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H).

Preparation of [3.2.1]-bicycle 229:

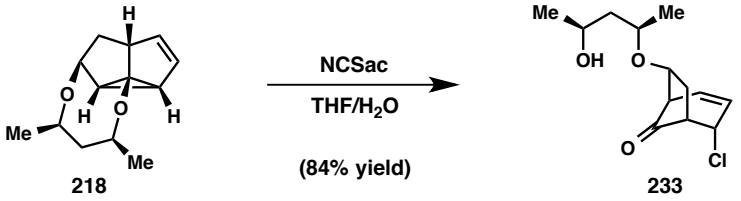


218 229

To a 1-dram vial containing 7-substituted photoadduct **218** (4.2 mg, 20.4 μmol, 1.0 equiv) was added dioxane (0.20 mL) and aqueous HCl (3 M, 70 μL, 0.204 mmol, 10.0 equiv). The vial was sealed and heated to 40 °C for 3 h, then quenched by addition of sat. $NaHCO_3$ (1 mL). The mixture was extracted with CH_2Cl_2 (3 x 1 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. ^{1}H NMR of the crude residue showed signals for a major product that were consistent with those reported for known [3.2.1]-bicycle **229**.[36]

Diagnostic signals in crude ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68 (dd, *J* = 6.8, 3.0 Hz, 1H), 6.21 (dd, *J* = 6.9, 3.0 Hz, 1H), 6.07 – 6.01 (m, 2H), 5.51 – 5.46 (m, 1H) 2.82 – 2.74 (m, 3H), 2.52 – 2.46 (m, 1H).

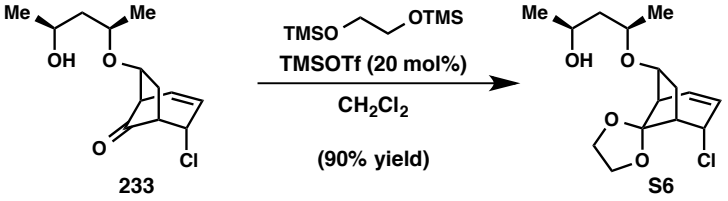
Preparation of allylic chloride 233:



In a 50-mL, round-bottomed flask, photoadduct **218** (250 mg, 1.21. mmol, 1.0 equiv) was dissolved in THF (10 mL) and H_2O (2 mL). *N*-chlorosaccharin (317 mg, 1.45 mmol, 1.2 equiv) was added, and the reaction was stirred for 1.5 h. The reaction was then quenched by addition of sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (45 to 50% EtOAc in hexanes) to afford allylic chloride **233** (267 mg, 1.03 mmol, 84% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (dd, *J* = 9.1, 7.2 Hz, 1H), 5.79 (ddd, *J* = 9.0, 3.9, 1.3 Hz, 1H), 4.88 (dd, *J* = 3.8, 3.2 Hz, 1H), 4.04 (dd, *J* = 7.3, 1.2 Hz, 1H), 3.90 (dqt, *J* = 9.2, 6.2, 3.0 Hz, 1H), 3.70 (dqd, *J* = 8.6, 6.0, 4.6 Hz, 1H), 2.80 (dt, *J* = 7.4, 1.2 Hz, 1H), 2.73 (ddq, *J* = 8.0, 3.1, 1.5 Hz, 1H), 2.30 (d, *J* = 2.8 Hz, 1H), 2.25 (ddd, *J* = 15.0, 7.4, 1.7 Hz, 1H), 2.15 (ddt, *J* = 14.9, 8.2, 1.3 Hz, 1H), 1.64 (dt, *J* = 14.4, 8.7 Hz, 1H), 1.48 (ddd, *J* = 14.4, 4.6, 3.3 Hz, 1H), 1.17 (d, *J* = 3.1 Hz, 3H), 1.15 (d, *J* = 3.0 Hz, 3H).

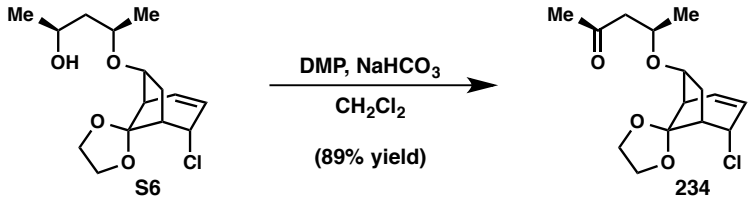
Preparation of ketal S6:



In a 25-mL, round-bottomed flask, ketone **233** (267 mg, 1.03 mmol, 1.0 equiv) and 1,2-bis(trimethylsiloxy)ethane (0.50 mL, 2.06 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (10 mL). To this solution was added TMSOTf (37 μL, 0.206 mmol, 0.20 equiv). The reaction was stirred for 15 h, and then quenched with sat. $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide pure ketal **S6** (282 mg, 0.931 mmol, 90% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (ddd, *J* = 9.5, 7.1, 0.8 Hz, 1H), 5.75 (ddd, *J* = 9.3, 3.6, 1.4 Hz, 1H), 4.48 – 4.42 (m, 1H), 4.44 (s, 1H), 4.09 – 3.99 (m, 4H), 4.00 – 3.88 (m, 1H), 3.72 (dd, *J* = 8.3, 3.0 Hz, 1H), 3.65 (dqd, *J* = 11.9, 5.9, 2.7 Hz, 1H), 2.48 (td, *J* = 7.5, 1.8 Hz, 2H), 2.11 (ddd, *J* = 14.7, 8.6, 3.2 Hz, 1H), 1.95 (dd, *J* = 14.7, 8.3 Hz, 1H), 1.66 – 1.52 (m, 1H), 1.49 (dt, *J* = 14.8, 2.1 Hz, 1H), 1.15 (dd, *J* = 6.3, 1.0 Hz, 3H), 1.11 (d, *J* = 5.9 Hz, 3H).

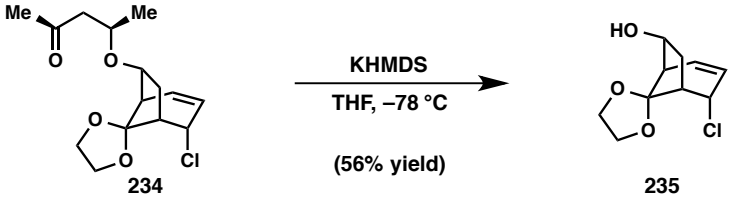
Preparation of ketone 234:



A 25-mL, round-bottomed flask was charged with alcohol **S6** (282 mg, 0.931 mmol, 1.0 equiv), $NaHCO_3$ (313 mg, 3.73 mmol, 4.0 equiv), and CH_2Cl_2 (9.3 mL). To this solution was added Dess–Martin periodinane (790 mg, 1.86 mmol, 2.0 equiv). The reaction was stirred for 12 h, and then quenched with sat. $NaHCO_3$ (10 mL) and sat. $Na_2S_2O_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude residue by silica gel chromatography (40% EtOAc in hexanes) afforded ketone **234** (249 mg, 0.828 mmol, 89% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (ddd, *J* = 9.4, 7.4, 0.9 Hz, 1H), 5.71 (ddd, *J* = 9.4, 3.5, 1.4 Hz, 1H), 4.45 (ddd, *J* = 3.5, 2.0, 0.9 Hz, 1H), 4.03 – 3.94 (m, 4H), 3.89 (dqd, *J* = 8.2, 6.1, 4.6 Hz, 1H), 3.65 (dd, *J* = 8.2, 3.5 Hz, 1H), 2.78 (dd, *J* = 15.8, 8.2 Hz, 1H), 2.50 (dd, *J* = 7.4, 1.9 Hz, 1H), 2.44 (ddt, *J* = 7.8, 3.0, 1.7 Hz, 1H), 2.35 (dd, *J* = 15.8, 4.6 Hz, 1H), 2.20 (s, 3H), 2.03 (dddd, *J* = 14.3, 7.8, 3.5, 0.8 Hz, 1H), 1.94 (dd, *J* = 14.4, 8.2 Hz, 1H), 1.13 (d, *J* = 6.1 Hz, 3H).

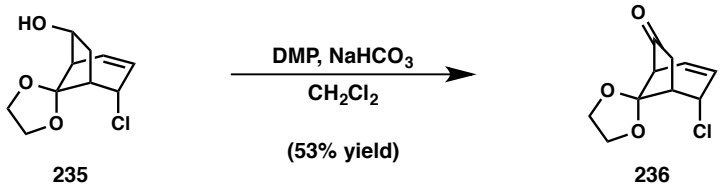
Preparation of alcohol 235:



In a 25-mL, round-bottomed flask, ketone **234** (249 mg, 0.828 mmol, 1.0 equiv) was dissolved in THF (8.3 mL) and cooled to –78 °C. KHMDS (2.5 mL, 0.5 M in toluene, 1.24 mmol, 1.5 equiv) was added, and then reaction was warmed to 0 °C. After stirring for 30 min, the reaction was quenched with sat. NH_4Cl (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (40% EtOAc in hexanes) afforded alcohol **235** (100 mg, 0.462 mmol, 56% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (ddd, *J* = 9.5, 7.2, 0.8 Hz, 1H), 5.72 (ddd, *J* = 9.4, 3.7, 1.5 Hz, 1H), 4.44 (ddd, *J* = 3.8, 2.2, 0.8 Hz, 1H), 4.12 – 3.99 (m, 4H), 3.91 (ddd, *J* = 12.3, 5.7, 4.1 Hz, 1H), 3.22 (d, *J* = 12.3 Hz, 1H), 2.53 – 2.48 (m, 1H), 2.41 (dd, *J* = 7.2, 1.9 Hz, 1H), 2.02 (dd, *J* = 5.5, 4.0 Hz, 2H).

Preparation of ketone 236:



235 **236**

A 25-mL, round-bottomed flask was charged with alcohol **235** (98.0 mg, 0.452 mmol, 1.0 equiv), $NaHCO_3$ (152 mg, 1.81 mmol, 4.0 equiv), and CH_2Cl_2 (5 mL). To this solution was added Dess–Martin periodinane (384 mg, 0.905 mmol, 2.0 equiv). The reaction was stirred for 15 h, and then quenched with sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude residue by silica gel chromatography (25% EtOAc in hexanes) afforded ketone **236** (51.7 mg, 0.241 mmol, 53% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (ddd, *J* = 9.2, 3.6, 0.8 Hz, 1H), 5.89 (dd, *J* = 9.3, 7.5 Hz, 1H), 4.64 (dd, *J* = 3.6, 1.3 Hz, 1H), 4.17 – 3.96 (m, 4H), 2.94 (dtt, *J* = 7.5, 1.4, 0.7 Hz, 1H), 2.82 – 2.72 (m, 2H), 2.20 (dt, *J* = 19.0, 4.6 Hz, 1H).

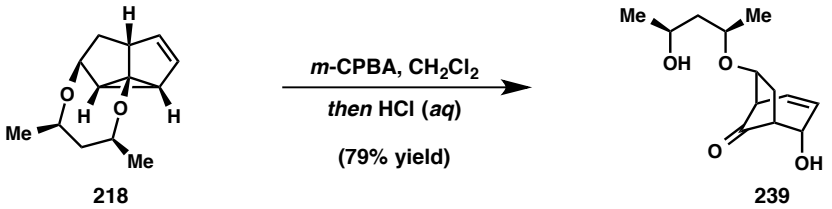
^{13}C NMR (101 MHz, $CDCl_3$): δ 204.4, 128.7, 125.9, 110.3, 65.4, 64.3, 60.1, 53.8, 44.9, 41.9.

FTIR (NaCl, thin film): 3043, 2965, 2895, 1753, 1628, 1478, 1407, 1380, 1346, 1312, 1213, 1146, 1097, 1055, 1003, 948, 918 cm^{-1}.

HRMS: (FAB) calc'd for $C_{10}H_{12}ClO_3$ $[M + H]^+$ 215.0475, found 215.0454.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +544° (*c* = 1.0, $CHCl_3$).

Preparation of allylic alcohol 239:



218 239

A 1-L, round-bottomed flask was charged with photoadduct **218** (7.26 g, 35.2 mmol, 1.0 equiv) and CH_2Cl_2 (350 mL), and cooled to 0 °C. *m*-CPBA (7.89 g, 35.2 mmol, 1.0 equiv) was added, and the reaction was stirred for 30 min at 0 °C, then warmed to room temperature. After stirring for an additional 90 min at room temperature, 2 N HCl (70 mL, 140 mmol, 4.0 equiv) was added, and the biphasic mixture was stirred vigorously. After 30 min, the reaction was quenched by careful addition of sat. $NaHCO_3$ (200 mL), and stirred until bubbling ceased (ca. 30 min). The layers were separated, and the aqueous phase was extracted with EtOAc (8 x 300 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by silica gel chromatography (45 to 50% acetone in hexanes) afforded allylic alcohol **239** (6.7 g, 28 mmol, 79% yield) as a colorless oil.

Note: The product is highly water soluble, and thus requires rigorous extraction with a polar solvent such as EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (dd, *J* = 9.0, 7.2 Hz, 1H), 5.77 (ddd, *J* = 9.0, 3.8, 1.2 Hz, 1H), 4.59 (s, 1H), 4.02 (dd, *J* = 6.1, 2.2 Hz, 1H), 3.90 (dqd, *J* = 9.2, 6.2, 3.0 Hz, 1H), 3.70 (dqd, *J* = 8.8, 6.0, 4.3 Hz, 1H), 2.79 (dd, *J* = 7.2, 1.5 Hz, 1H), 2.67 – 2.53 (m,

2H), 2.31 (br s, 1H), 2.18 – 2.05 (m, 2H), 1.62 (dt, *J* = 14.4, 8.9 Hz, 1H), 1.48 (ddd, *J* = 14.5, 4.4, 3.1 Hz, 1H), 1.16 (d, *J* = 3.8 Hz, 3H), 1.14 (d, *J* = 4.1 Hz, 3H).

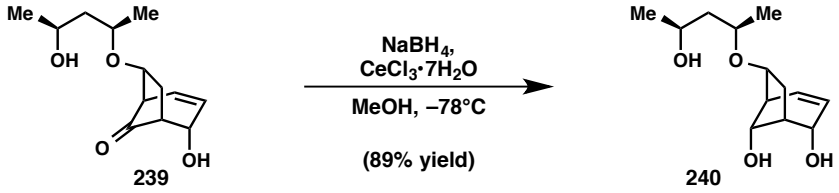
^{13}C NMR (101 MHz, $CDCl_3$): δ 213.9, 131.4, 129.6, 81.1, 75.2, 73.9, 67.0, 51.6, 49.5, 45.9, 32.2, 23.6, 20.0.

FTIR (NaCl, thin film): 3400, 2969, 2933, 1753, 1458, 1447, 1376, 1329, 1120, 1080, 1048, 926 cm^{-1}.

HRMS: (FAB) calc'd for $C_{13}H_{21}O_4$ $[M + H]^+$ 241.1440, found 241.1421.

$[\alpha]_D^{25}$ = –6.2° (*c* = 1.0, $CHCl_3$).

Preparation of triol 240:



In a 1-L, round-bottomed flask, ketone **239** (6.7 g, 28 mmol, 1.0 equiv) and $CeCl_3$•$7H_2O$ (15.6 g, 41.8 mmol, 1.5 equiv) were dissolved in MeOH (280 mL). The solution was then cooled to –78 °C, and $NaBH_4$ (1.27 g, 33.5 mmol, 1.2 equiv) was added. After stirring for 2 h at –78 °C, the reaction was quenched with 1 M NaOH (200 mL), and concentrated *in vacuo* to remove MeOH. The aqueous phase was extracted with EtOAc (8 x 250 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Filtration of the crude residue over a short plug of silica (eluting with 50% acetone in hexanes) afforded triol **240** (6.1 g, 25 mmol, 89% yield) as a white solid.

Note: The product is highly water soluble, and thus requires rigorous extraction with a polar solvent such as EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (ddt, *J* = 9.9, 3.7, 1.7 Hz, 1H), 5.74 (dd, *J* = 9.4, 7.0 Hz, 1H), 4.46 (s, 1H), 3.97 (dqd, *J* = 8.9, 6.3, 2.7 Hz, 1H), 3.85 (br s, 1H), 3.77 – 3.67 (m, 3H), 3.62 (br s, 2H), 2.63 – 2.58 (m, 1H), 2.46 (appar s, 1H), 1.77 (td, *J* = 4.7, 4.1, 1.7 Hz, 2H), 1.63 – 1.47 (m, 2H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H).

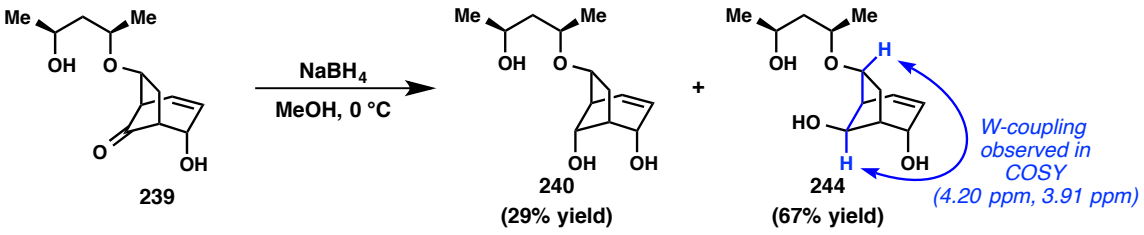
^{13}C NMR (101 MHz, $CDCl_3$): δ 129.7, 126.5, 78.3, 75.4, 72.0, 71.7, 68.1, 45.5, 45.4, 40.8, 33.8, 23.4, 20.1.

FTIR (NaCl, thin film): 3369, 3032, 2967, 2934, 1757, 1642, 1447, 1420, 1376, 1318, 1180, 1084, 1033, 970, 934 cm^{-1}.

HRMS: (FAB) calc'd for $C_{13}H_{23}O_4$ $[M + H]^+$ 243.1596, found 243.1616.

$[\alpha]_D^{25}$ = –6.2° (*c* = 1.0, $CHCl_3$).

Preparation of triol 244:



In a 1-dram vial, ketone **239** (9.2 mg, 38 μmol, 1.0 equiv) was dissolved in MeOH (0.38 mL) and cooled to 0 °C. $NaBH_4$ (2.9 mg, 77 μmol, 2.0 equiv) was added, and the reaction was stirred for 15 minutes, then diluted with acetone (1 mL) and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (2 mL) and washed with 1 N

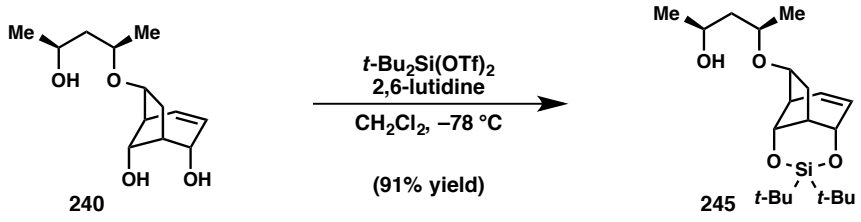
NaOH (2 mL). The aqueous phase was extracted with EtOAc (3 x 2 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (50 to 55% acetone in hexanes) to provide 1,3-*syn*-diol **240** (2.7 mg, 11 μmol, 29% yield) and *anti*-1,3-diol **244** (6.2 mg, 26 μmol, 67% yield).

Spectroscopic data for 1,3-*anti*-diol **244**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (dd, *J* = 9.3, 7.4 Hz, 1H), 5.53 (ddd, *J* = 9.3, 3.8, 1.5 Hz, 1H), 4.20 (s, 1H), 4.00 (t, *J* = 3.3 Hz, 1H), 3.94 (ddd, *J* = 9.5, 6.4, 2.9 Hz, 1H), 3.91 (d, *J* = 7.1 Hz, 1H), 3.75 – 3.66 (m, 1H), 2.69 (d, J = 7.3 Hz, 1H), 2.58 (br s, 3H), 2.50 (d, *J* = 7.7 Hz, 1H), 2.04 (ddd, *J* = 14.6, 8.2, 1.7 Hz, 1H), 1.80 (dd, *J* = 14.7, 7.2 Hz, 1H), 1.64 (dt, *J* = 14.5, 9.0 Hz, 1H), 1.47 (ddd, *J* = 14.5, 4.3, 2.6 Hz, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 132.1, 127.7, 81.0, 74.5, 74.3, 74.1, 67.2, 49.1, 47.3, 45.8, 33.5, 24.0, 19.9.

Preparation of siliconide 245:



A 500-mL, round-bottomed flask was charged with triol **240** (6.1 g, 25 mmol, 1.0 equiv), 2,6-lutidine (7.0 mL, 60 mmol, 2.4 equiv), and CH_2Cl_2 (250 mL), and then cooled to –78 °C. To this solution was added *t*-$Bu_2Si(OTf)_2$ (9.8 mL, 30 mmol, 1.2 equiv), and

the reaction was stirred for 1 h. The reaction was quenched with sat. $NaHCO_3$ (100 mL) and H_2O (100 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 250 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (25% EtOAc in hexanes) to afford siliconide **245** (8.75 g, 22.9 mmol, 91% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (ddd, *J* = 9.5, 4.4, 1.6 Hz, 1H), 5.74 (ddd, *J* = 9.6, 6.3, 1.2 Hz, 1H), 4.59 (t, *J* = 4.8 Hz, 1H), 4.04 – 3.91 (m, 2H), 3.80 – 3.70 (m, 2H), 3.39 (s, 1H), 2.78 (dd, *J* = 6.3, 4.1 Hz, 1H), 2.77 – 2.67 (m, 1H), 1.82 (ddd, *J* = 15.2, 7.5, 1.3 Hz, 1H), 1.71 (dd, *J* = 15.0, 7.9 Hz, 1H), 1.60 (dt, *J* = 14.5, 9.2 Hz, 1H), 1.52 (ddd, *J* = 14.5, 4.0, 2.6 Hz, 1H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 9H), 0.96 (s, 9H).

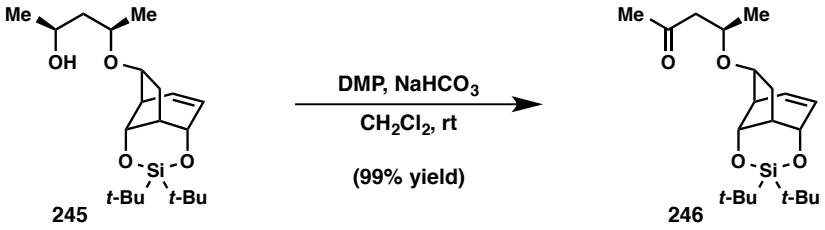
^{13}C NMR (101 MHz, $CDCl_3$): δ 129.8, 129.1, 76.4, 74.7, 73.7, 71.0, 67.6, 46.4, 45.9, 38.6, 33.0, 28.7, 28.2, 23.6, 21.2, 20.7, 20.0.

FTIR (NaCl, thin film): 3436, 3032, 2968, 2934, 2900, 2859, 1476, 1388, 1364, 1326, 1196, 1174, 1058, 1036, 1019, 998, 826 cm^{-1}.

HRMS: (FAB) calc'd for $C_{21}H_{39}O_4Si$ $[M + H]^+$ 383.2618, found 383.2630.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +59° (*c* = 0.90, $CHCl_3$).

Preparation of ketone 246:



A 500-mL, round-bottomed flask was charged with alcohol **245** (8.5 g, 22 mmol, 1.0 equiv), $NaHCO_3$ (5.60 g, 66.6 mmol, 3.0 equiv), and CH_2Cl_2 (225 mL). Dess–Martin periodinane (12.2 g, 28.9 mmol, 1.3 equiv) was added, and the reaction was stirred for 17 h, after which the reaction was filtered through a plug of silica (eluting with 50% EtOAc in hexanes). The filtrate was concentrated *in vacuo*, and then diluted in CH_2Cl_2 (100 mL), washed with sat. $NaHCO_3$ (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide ketone **246** (8.5 g, 22 mmol, 99% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (ddd, *J* = 9.5, 4.4, 1.6 Hz, 1H), 5.73 (ddd, *J* = 9.5, 6.2, 1.2 Hz, 1H), 4.55 (t, *J* = 4.8 Hz, 1H), 3.99 (td, *J* = 4.0, 0.8 Hz, 1H), 3.92 (h, *J* = 6.1 Hz, 1H), 3.65 (d, *J* = 7.1 Hz, 1H), 2.74 – 2.64 (m, 3H), 2.42 (dd, *J* = 16.0, 5.9 Hz, 1H), 2.16 (s, 3H), 1.76 (ddd, *J* = 14.9, 7.0, 1.4 Hz, 1H), 1.67 (ddt, *J* = 14.8, 7.7, 1.3 Hz, 1H), 1.11 (d, *J* = 6.1 Hz, 3H), 1.05 (s, 9H), 0.96 (s, 9H).

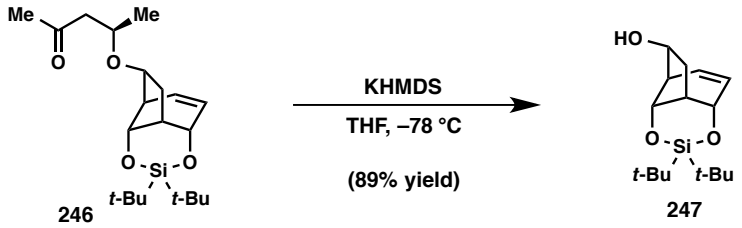
^{13}C NMR (101 MHz, $CDCl_3$): δ 207.2, 129.5, 129.4, 76.9, 73.8, 71.1, 70.2, 51.0, 46.7, 38.5, 32.7, 31.2, 28.7, 28.2, 21.2, 20.7, 20.0.

FTIR (NaCl, thin film): 3012, 2970, 2934, 2888, 2859, 1719, 1476, 1388, 1364, 1327, 1176, 1087, 1046, 1018, 999, 826 cm^{-1}.

HRMS: (FAB) calc'd for $C_{21}H_{37}O_4Si$ $[M + H]^+$ 381.2461, found 381.2465.

$[\alpha]_D^{25}$ = +67° (*c* = 1.6, $CHCl_3$).

Preparation of alcohol 247:



A 500-mL, round-bottomed flask was charged with ketone **246** (8.5 g, 22 mmol, 1.0 equiv) and THF (225 mL), and cooled to –78 °C. KHMDS (58 mL, 0.5 M in toluene, 29 mmol, 1.3 equiv) was added, and the resulting solution was warmed to 0 °C and stirred for 2.5 h. The reaction was then quenched with sat. NH_4Cl (100 mL) and H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (20% EtOAc in hexanes) to provide alcohol **247** (5.9 g, 20 mmol, 90% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (ddd, *J* = 9.4, 4.3, 1.6 Hz, 1H), 5.77 (ddd, *J* = 9.5, 6.1, 1.2 Hz, 1H), 4.78 (dd, *J* = 5.5, 4.1 Hz, 1H), 4.06 (dd, *J* = 6.6, 1.6 Hz, 1H), 4.01 (t, *J* = 3.9 Hz, 1H), 2.81 – 2.72 (m, 1H), 2.63 (ddd, *J* = 6.0, 4.3, 1.2 Hz, 1H), 1.81 (dd, *J* = 14.8, 6.8 Hz, 1H), 1.71 (ddt, *J* = 15.0, 7.9, 1.2 Hz, 1H), 1.07 (s, 9H), 0.98 (s, 9H).

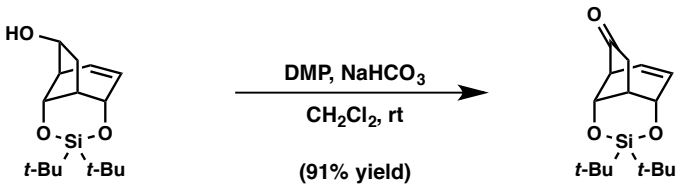
^{13}C NMR (101 MHz, $CDCl_3$): δ 129.6, 129.0, 73.6, 71.8, 71.0, 50.4, 38.7, 34.1, 28.7, 28.2, 21.2, 20.7.

FTIR (NaCl, thin film): 3401, 3033, 2968, 2935, 2896, 2860, 1476, 1442, 1388, 1364, 1321, 1280, 1224, 1175, 1032, 998, 920, 825 cm^{-1}.

HRMS: (FAB) calc'd for $C_{16}H_{27}O_3Si$ $[M + H - H_2]^+$ 295.1747, found 295.1730.

$[\alpha]_D^{25}$ = +89° (*c* = 1.3, $CHCl_3$).

Preparation of ketone 248:



247 248

A 500-mL, round-bottomed flask was charged with alcohol **247** (6.0 g, 20 mmol, 1.0 equiv), $NaHCO_3$ (5.1 g, 60 mmol, 3.0 equiv), and CH_2Cl_2 (200 mL). Dess–Martin periodinane (10.3 g, 24.3 mmol, 1.2 equiv) was added, and the reaction was stirred for 4 h, after which the reaction was filtered through a plug of silica (eluting with 67% EtOAc in hexanes). The filtrate was concentrated *in vacuo*, and then diluted in CH_2Cl_2 (100 mL), washed with sat. $NaHCO_3$ (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide ketone **248** (5.40 g, 18.3 mmol, 91% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08 (ddd, *J* = 9.3, 4.6, 1.6 Hz, 1H), 5.76 (ddd, *J* = 9.2, 6.9, 1.4 Hz, 1H), 4.59 (ddt, *J* = 5.6, 4.1, 1.1 Hz, 1H), 4.27 (ddd, *J* = 4.5, 3.4, 0.9 Hz, 1H), 3.14 (dddd, *J* = 6.8, 4.2, 1.4, 0.7 Hz, 1H), 3.02 (dddq, *J* = 6.8, 5.0, 3.3, 1.6 Hz, 1H), 2.37 – 2.31 (m, 1H), 2.28 (dd, *J* = 19.4, 6.4 Hz, 1H), 1.09 (s, 9H), 0.99 (s, 9H).

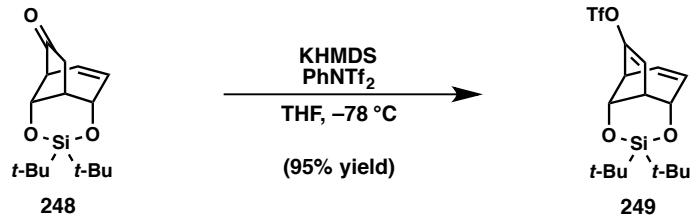
^{13}C NMR (101 MHz, $CDCl_3$): δ 206.7, 131.3, 124.8, 71.7, 69.8, 55.1, 38.5, 37.6, 28.6, 28.2, 21.1, 20.8.

FTIR (NaCl, thin film): 3036, 2968, 2935, 2859, 1743, 1629, 1476, 1404, 1387, 1365, 1298, 1221, 1187, 1145, 1115, 997, 790 cm^{-1}.

HRMS: (FAB) calc'd for $C_{16}H_{27}O_3Si$ $[M + H]^+$ 295.1730, found 295.1731.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +510° (*c* = 1.1, $CHCl_3$).

Preparation of vinyl triflate 249:



248 249

A 250-mL, round-bottomed flask was charged with ketone **248** (3.00 g, 10.2 mmol, 1.0 equiv), which was subsequently dissolved in THF (60 mL) and cooled to –78 °C. KHMDS (22.4 mL, 0.5 M in toluene, 11.2 mmol, 1.1 equiv) was added, and the reaction was stirred for 15 minutes. In a separate flask, a solution of $PhNTf_2$ (4.00 g, 11.2 mmol, 1.1 equiv) in THF (40 mL) was prepared and cannulated into the first reaction flask. The resulting mixture was stirred for an additional hour, and then quenched with sat. NH_4Cl (50 mL) and H_2O (50 mL). This mixture was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude residue by silica gel chromatography (9% EtOAc in hexanes) afforded vinyl triflate **249** (4.13 g, 9.68 mmol, 95% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (ddd, *J* = 9.6, 6.0, 1.1 Hz, 1H), 5.84 (dddd, *J* = 9.6, 4.5, 2.0, 0.8 Hz, 1H), 5.49 (dd, *J* = 4.1, 0.8 Hz, 1H), 4.69 (tt, *J* = 4.8, 1.0 Hz, 1H), 4.28 (ddd, *J* = 4.0, 2.9, 0.8 Hz, 1H), 3.13 (ddddd, *J* = 4.8, 3.9, 2.8, 1.9, 0.9 Hz, 1H), 2.91 (ddq, J = 5.6, 4.7, 0.9 Hz, 1H), 1.08 (s, 9H), 1.01 (s, 9H).

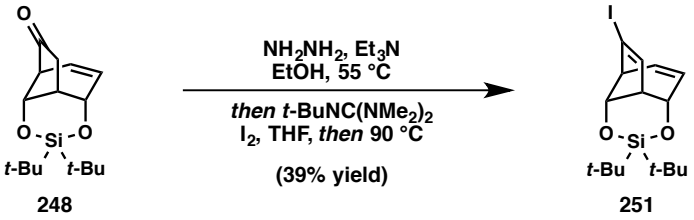
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3, 131.7, 130.8, 113.2, 75.7, 65.0, 45.2, 44.2, 28.8, 28.2, 21.1, 20.7.

FTIR (NaCl, thin film): 3042, 2976, 2938, 2906, 2852, 1640, 1478, 1429, 1380, 1365, 1258, 1249, 1214, 1141, 1123, 1074, 1001, 926, 901 cm^{-1}.

HRMS: (FAB) calc'd for $C_{17}H_{26}F_3SSiO_5$ $[M + H]^+$ 427.1222, found 427.1205.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +20° (*c* = 1.2, $CHCl_3$).

Preparation of vinyl iodide 251 from ketone 248:



248 251

To a 1-dram vial containing ketone **248** (10.0 mg, 34.0 μmol, 1.0 equiv) was added hydrazine hydrate (16 μL, 0.340 mmol, 10 equiv), Et_3N (47 μL, 0.340 mmol, 10 equiv), and absolute ethanol (0.34 mL). The reaction was heated to 55 °C for 90 minutes, then concentrated *in vacuo*, azeotroping with benzene (3 x 1 mL). The crude hydrazone was dissolved in THF (0.4 mL) and used in the next step

In separate vial, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (47 μL, 0.238 mmol, 7.0 equiv) was added to a solution of I_2 (18.1 mg, 71.3 μmol, 2.1 equiv) in THF (0.4 mL). To this solution was added the prepared hydrazone solution in a dropwise fashion, and

the reaction turns from brown to colorless. After stirring for 20 minutes, the solution was concentrated *in vacuo*, and the resulting crude residue was heated to 90 °C for 5 h. After cooling to room temperature, purification by silica gel chromatography (25 to 30% CH_2Cl_2 in hexanes) afforded vinyl iodide **251** (5.3 mg, 13 μmol, 39% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.23 (ddd, *J* = 9.6, 6.0, 1.1 Hz, 1H), 6.21 (d, *J* = 3.9 Hz, 1H), 4.63 (tt, *J* = 4.7, 1.0 Hz, 1H), 4.21 (ddd, *J* = 4.4, 3.0, 0.8 Hz, 1H), 2.98 (ddddd, *J* = 4.8, 3.7, 2.8, 1.9, 0.7 Hz, 1H), 2.87 (ddq, *J* = 5.9, 4.5, 0.7 Hz, 1H), 1.07 (s, 9H), 1.00 (s, 9H).

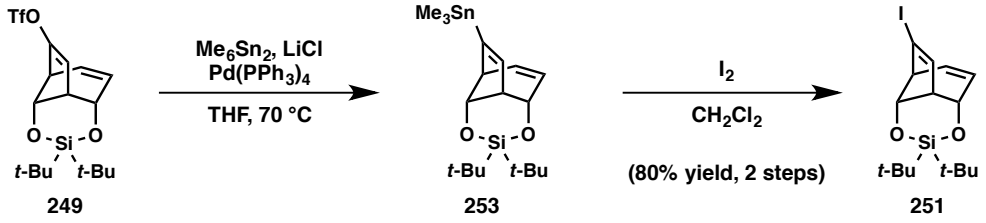
^{13}C NMR (101 MHz, $CDCl_3$): δ 137.3, 133.0, 130.2, 106.7, 76.8, 65.2, 54.5, 48.5, 28.8, 28.2, 21.2, 20.7.

FTIR (NaCl, thin film): 3043, 2971, 2931, 2888, 2856, 1578, 1476, 1382, 1364, 1314, 1286, 1248, 1200, 1119, 1082, 1001, 809 cm^{-1}.

HRMS: (FAB) calc'd for $C_{16}H_{26}IO_2Si$ $[M + H]^+$ 405.0747, found 405.0747.

$[\alpha]_D^{25}$ = +21° (*c* = 0.96, $CHCl_3$).

Preparation of vinyl iodide 251 from vinyl triflate 249:



In an N_2-filled glovebox, LiCl (635 mg, 15.0 mmol, 3.0 equiv) and $Pd(PPh_3)_4$ (230 mg, 0.200 mmol, 0.04 equiv) were a 250-mL Schlenk tube containing vinyl triflate

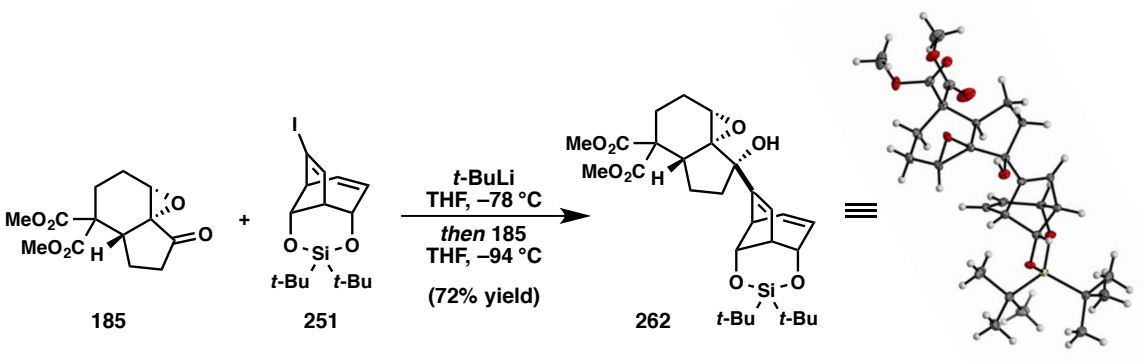
249 (2.13 g, 4.99 mmol, 1.0 equiv). The contents were dissolved in THF (25 mL), and then Me_6Sn_2 (1.04 mL, 4.99 mmol, 1.0 equiv) was added. The walls of the tube were rinsed with THF (25 mL), and then the tube was sealed and brought out of the glovebox. The reaction was heated to 70 °C with vigorous stirring for 15 h, then cooled to room temperature, diluted with hexanes (ca. 100 mL), and quenched with H_2O (50 mL). The solution was extracted with hexanes (3 x 100 mL), and then the combined organic extracts were washed with H_2O (50 mL), 10% NH_4OH (50 mL), and H_2O (50 mL) again. After drying over Na_2SO_4 and filtration, the filtrate was concentrated *in vacuo* to afford crude vinyl stannane **253**. A small sample was purified by silica gel chromatography (1% EtOAc in hexanes) to afford an analytically pure sample:

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07 (ddd, *J* = 9.5, 6.1, 1.1 Hz, 1H), 5.97 (d, *J* = 3.5 Hz, 1H), 5.59 (ddd, *J* = 9.5, 4.5, 1.9 Hz, 1H), 4.47 (t, *J* = 4.7 Hz, 1H), 4.23 (ddd, *J* = 4.3, 3.0, 0.6 Hz, 1H), 3.04 – 2.93 (m, 1H), 2.89 (dd, *J* = 6.2, 4.3 Hz, 1H), 1.08 (s, 9H), 1.01 (s, 9H), 0.14 (s, 9H).

The crude vinyl stannane **253** was dissolved in CH_2Cl_2 (20 mL) and cooled to –20 °C. To this solution was cannulated a solution of I_2 (1.25 g, 4.92 mmol, 1.05 equiv) in CH_2Cl_2 (30 mL). After stirring for 1 h, the reaction was quenched with sat. $Na_2S_2O_3$ (50 mL), and diluted with H_2O (25 mL) and CH_2Cl_2 (25 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the

crude residue by silica gel chromatography (25 to 30% CH_2Cl_2 in hexanes) provided vinyl iodide **251** (1.522 g, 3.76 mmol, 80% yield) as a white solid.

Preparation of epoxy alcohol 262:



In a 250-mL, round-bottomed flask, vinyl iodide **251** (1.62 g, 4.01 mmol, 1.0 equiv) was dissolved in THF (40 mL) and cooled to –78 °C. To this solution was added *t*-BuLi (4.7 mL, 1.7 M in pentane, 8.01 mmol, 2.0 equiv) slowly down the side of the flask over 5 minutes, and the resulting mixture was stirred for an additional 15 minutes at –78 °C. This solution was then cannulated over 10 minutes into a pre-cooled solution of epoxyketone **185** (1.40 g, 5.21 mmol, 1.3 equiv) in THF (40 mL) at –94 °C (acetone/liquid N_2 bath). The reaction was stirred for an additional 2 h while allowing the acetone/liquid N_2 bath to expire, and then quenched with sat. $NaHCO_3$ (100 mL). This was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (10 to 12% acetone in hexanes) to afford epoxy alcohol **262** (1.58 g, 2.89 mmol, 72% yield) as a white solid. A small sample was recrystallized in hexanes/diethyl ether to obtain crystals suitable for X-ray crystallography.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (ddd, *J* = 9.6, 6.1, 1.1 Hz, 1H), 5.70 (ddd, *J* = 9.4, 4.3, 1.6 Hz, 1H), 5.65 (d, *J* = 3.8 Hz, 1H), 4.48 (t, *J* = 4.7 Hz, 1H), 4.25 (ddd, *J* = 4.0, 3.0, 0.8 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.32 (d, *J* = 3.6 Hz, 1H), 3.05 – 3.01 (m, 1H), 2.83 (ddd, *J* = 6.1, 4.4, 0.8 Hz, 1H), 2.71 (dd, *J* = 10.7, 7.5 Hz, 1H), 2.53 – 2.42 (m, 1H), 2.47 (s, 1H), 2.42 – 2.29 (m, 2H), 2.10 – 1.98 (m, 2H), 1.97 – 1.86 (m, 2H), 1.61 – 1.47 (m, 1H), 1.08 (s, 9H), 1.02 (s, 9H).

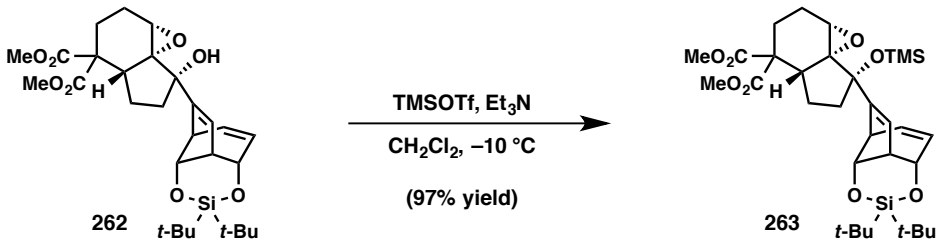
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 170.2, 161.6, 134.5, 129.2, 123.4, 77.7, 75.3, 71.2, 66.1, 56.5, 55.0, 52.9, 52.2, 45.6, 45.2, 44.4, 37.3, 29.3, 28.9, 28.3, 23.3, 21.6, 21.2, 20.7.

FTIR (NaCl, thin film): 3496, 3032, 2950, 2860, 1732, 1476, 1458, 1434, 1383, 1364, 1306, 1244, 1176, 1108, 991 cm^{-1}.

HRMS: (PPM) calc'd for $C_{29}H_{43}O_8Si$ $[M + H]^+$ 547.2722, found 547.2713.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –5.1° (*c* = 0.30, $CHCl_3$).

Preparation of silyl ether 263:



In a 100-mL, round-bottomed flask, epoxy alcohol **262** (1.06 g, 1.94 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL) and cooled to –10 °C. Et_3N (0.81 mL, 5.82 mmol, 3.0 equiv) was added, followed by TMSOTf (0.42 mL, 2.33 mmol, 1.2 equiv). The reaction was stirred for 15 minutes, then quenched by addition of sat. $NaHCO_3$ (20

mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (10 to 12% EtOAc in hexanes) to afford silyl ether **263** (1.17 g, 1.89 mmol, 97% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (ddd, *J* = 9.6, 6.1, 1.1 Hz, 1H), 5.68 (dddd, *J* = 9.7, 4.5, 1.9, 0.7 Hz, 1H), 5.57 (d, *J* = 3.7 Hz, 1H), 4.48 (t, *J* = 4.7 Hz, 1H), 4.26 (ddd, *J* = 4.1, 3.0, 0.7 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.30 (d, *J* = 3.5 Hz, 1H), 3.08 – 3.03 (m, 1H), 2.90 (ddd, *J* = 6.3, 4.3, 0.9 Hz, 1H), 2.74 (dd, *J* = 9.8, 8.8 Hz, 1H), 2.61 (dddd, *J* = 12.9, 11.0, 8.9, 3.9 Hz, 1H), 2.43 – 2.25 (m, 2H), 2.12 (ddd, *J* = 12.7, 8.7, 3.9 Hz, 1H), 2.08 – 2.01 (m, 1H), 1.96 (ddd, *J* = 15.1, 8.2, 3.7 Hz, 1H), 1.89 – 1.77 (m, 1H), 1.45 (ddd, *J* = 13.3, 10.1, 8.4 Hz, 1H), 1.09 (s, 9H), 1.02 (s, 9H), 0.05 (s, 9H).

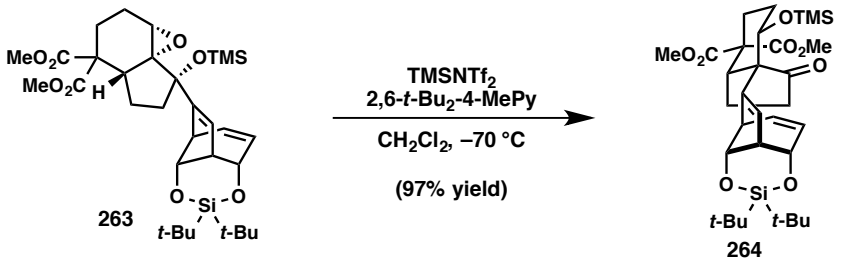
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 170.4, 163.2, 135.1, 129.0, 122.5, 77.7, 77.6, 70.1, 66.1, 55.0, 54.0, 52.8, 52.1, 45.8, 44.9, 41.4, 34.5, 29.7, 28.9, 28.3, 22.2, 21.6, 21.2, 20.7, 2.2.

FTIR (NaCl, thin film): 3028, 2952, 2904, 2860, 1732, 1477, 1462, 1434, 1364, 1250, 1175, 1110, 1058, 992, 881, 842 cm^{-1}.

HRMS: (PPM) calc'd for $C_{32}H_{51}O_8Si_2$ $[M + H]^+$ 619.3117, found 619.3106.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +36° (*c* = 0.35, $CHCl_3$).

Preparation of ketone 264:



A 100-mL, round-bottomed flask was charged with silyl ether **263** (1.168 g, 1.89 mmol, 1.0 equiv) and CH_2Cl_2 (40 mL), and the solution was cooled to –70 °C in a dry ice/acetone bath. In an N_2-filled glovebox, a 100-mL microsyringe was filled with $TMSNTf_2$ (67 mg, 0.189 mmol, 0.10 equiv), plugged with a rubber stopper, and removed from the glovebox. The $TMSNTf_2$ was immediately added in one portion to the reaction mixture. After stirring for an additional 15 minutes at –70 °C, the reaction was quenched with sat. $NaHCO_3$ (30 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL), and the organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by silica gel chromatography (10% EtOAc in hexanes) to afford ketone **264** (1.13 g, 1.83 mmol, 97% yield) as a white solid.

Note: If the starting material is not rigorously dry, the reaction may not reach full conversion. It is possible that trace amounts of water can quench $TMSNTf_2$ and result in early termination. In this case, the crude product can simply be resubjected to the reaction conditions. In order to ensure the starting material is sufficiently free of water, it can be azeotroped with toluene or benzene (1–3x) prior to the reaction.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (ddd, *J* = 9.5, 6.1, 1.1 Hz, 1H), 5.65 (ddd, *J* = 9.5, 4.3, 1.9 Hz, 1H), 5.40 (d, *J* = 3.8 Hz, 1H), 4.66 (t, *J* = 4.7 Hz, 1H), 4.31 (br s, 1H), 4.23 (appar t, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.40 (dd, *J* = 11.7, 7.3 Hz, 1H), 3.03 – 2.94 (m, 2H), 2.48 (td, *J* = 14.1, 3.4 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.17 – 2.05 (m, 3H), 1.80 – 1.71 (m, 1H), 1.65 – 1.60 (m, 1H), 1.52 (tdd, *J* = 14.3, 2.9, 1.9 Hz, 1H), 1.08 (s, 9H), 1.00 (s, 9H), 0.05 (s, 9H).

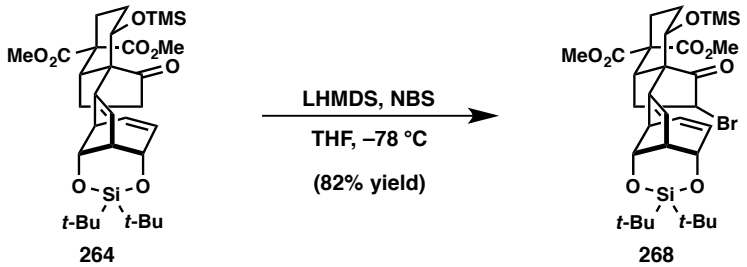
^{13}C NMR (126 MHz, $CDCl_3$): δ 215.9, 170.7, 170.6, 158.9, 134.8, 128.2, 124.4, 76.7, 69.9, 66.2, 58.0, 56.2, 52.8, 52.6, 46.2, 46.1, 41.8, 38.8, 28.9, 28.3, 27.4, 23.7, 21.2, 20.7, 19.3, 0.0.

FTIR (NaCl, thin film): 3032, 2952, 2896, 2859, 1741, 1477, 1462, 1443, 1384, 1363, 1252, 1170, 1097, 991, 840 cm^{-1}.

HRMS: (PMM) calc'd for $C_{32}H_{51}O_8Si_2$ $[M + H]^+$ 619.3117, found 619.3105.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +92° (*c* = 0.73, $CHCl_3$).

Preparation of α-bromoketone 268:



264 268

A 5-mL, round-bottomed flask was charged with ketone **264** (31.6 mg, 51.1 μmol, 1.0 equiv) and THF (0.8 mL), and cooled to –78 °C. LiHMDS (61.0 μL, 61.0 μmol, 1.2 equiv) was added, and the reaction was stirred for 25 minutes, after which a solution of NBS (11.8 mg, 66.4 μmol, 1.3 equiv) in THF (0.5 mL) was prepared and added. The

reaction was stirred at –78 °C for an additional 40 minutes, and then quenched by addition of sat. $Na_2S_2O_3$ (2 mL) and H_2O (2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 1 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (9% EtOAc in hexanes) to afford a-bromoketone **268** (29.3 mg, 42.0 μmol, 82% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (ddd, *J* = 9.6, 6.1, 1.1 Hz, 1H), 5.68 (ddd, *J* = 9.5, 4.3, 1.8 Hz, 1H), 5.41 (d, *J* = 3.8 Hz, 1H), 4.71 (ddt, *J* = 5.3, 4.4, 1.0 Hz, 1H), 4.34 (br s, 1H), 4.25 – 4.21 (m, 2H), 3.80 (dd, *J* = 13.5, 6.3 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.13 (dd, J = 6.1, 4.4 Hz, 1H), 3.05 – 2.96 (m, 1H), 2.77 (ddd, *J* = 14.1, 13.0, 6.6 Hz, 1H), 2.41 (td, *J* = 14.0, 3.6 Hz, 1H), 2.15 (d, *J* = 14.8 Hz, 1H), 1.93 (dd, *J* = 14.1, 6.7 Hz, 1H), 1.69 – 1.48 (m, 2H), 1.08 (s, 9H), 1.00 (s, 9H), 0.03 (s, 9H).

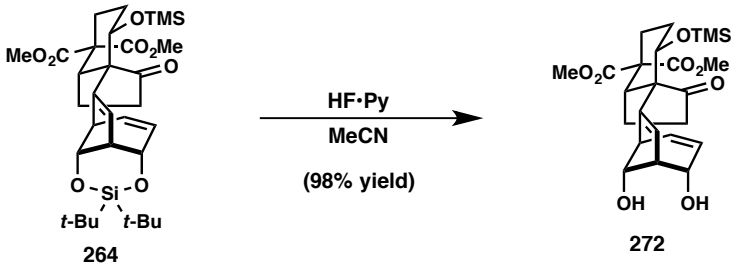
^{13}C NMR (101 MHz, $CDCl_3$): δ 208.1, 170.3, 170.2, 158.2, 135.5, 128.0, 125.5, 76.6, 70.1, 65.8, 58.0, 55.6, 53.0, 52.9, 47.0, 46.4, 46.2, 39.1, 35.0, 28.9, 28.3, 27.0, 21.3, 20.7, 19.4, -0.0.

FTIR (NaCl, thin film): 2952, 2941, 2896, 2859, 1755, 1741, 1476, 1460, 1434, 1254, 1230, 1175, 1104, 1054, 994, 894 cm^{-1}.

HRMS: (ESI) calc'd for $C_{29}H_{41}BrO_7Si$ $[M – OSiMe_3]^+$ 607.1721, found 607.1731.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +127° (*c* = 0.45, $CHCl_3$).

Preparation of diol 272:



A 125-mL Teflon Erlenmeyer flask was charged with silylene **264** (714 mg, 1.15 mmol, 1.0 equiv) and MeCN (55 mL) and cooled to 0 °C with an ice bath. A solution of HF•Py (pyridine ~30%, HF ~70%, 570 mg) in MeCN (3 mL) was added, and the ice bath was removed to allow the reaction to reach ambient temperature. After stirring for 1.5 h, the solution was filtered through a plug of silica (eluting with EtOAc) and concentrated *in vacuo* to provide pure diol **272** (540 mg, 1.13 mmol, 98% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 – 5.75 (m, 2H), 5.47 (d, *J* = 3.6 Hz, 1H), 4.61 (q, *J* = 5.2 Hz, 1H), 4.28 (br s, 1H), 3.94 (appar d, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.38 (dd, *J* = 12.1, 7.3 Hz, 1H), 2.91 (t, *J* = 4.5 Hz, 1H), 2.88 – 2.70 (m, 2H), 2.69 – 2.65 (m, 1H), 2.48 (td, *J* = 14.3, 3.6 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.19 – 2.02 (m, 3H), 1.80 – 1.56 (m, 2H), 1.48 (tdd, *J* = 14.1, 2.8, 2.0 Hz, 1H), 0.03 (s, 9H).

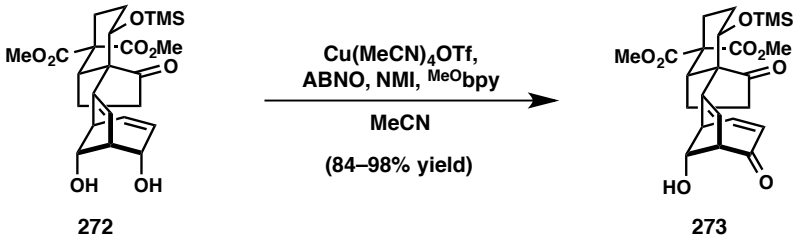
^{13}C NMR (101 MHz, $CDCl_3$): δ 215.9, 170.7, 170.6, 157.0, 130.9, 129.5, 124.8, 74.3, 69.7, 65.7, 57.8, 56.3, 52.9, 52.7, 47.5, 44.3, 41.8, 38.9, 27.4, 23.6, 19.3, -0.0.

FTIR (NaCl, thin film): 3401, 3025, 2954, 1738, 1434, 1404, 1336, 1313, 1252, 1194, 1171, 1074, 1058, 1020, 980, 892, 862, 842 cm^{-1}.

HRMS: (PMM) calc'd for $C_{24}H_{33}O_7Si$ $[M - OH]^+$ 461.1990, found 461.1980.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +92° (*c* = 1.3, $CHCl_3$).

Preparation of enone 273:



272 **273**

To a 100 mL, round-bottomed flask was added diol **272** (540.0 mg, 1.13 mmol, 1.0 equiv), $Cu(MeCN)_4OTf$ (21.0 mg, 56.4 μmol, 0.05 equiv), 4,4'-dimethoxy-2,2'-bipyridine (^{MeO}bpy, 12.2 mg, 56.4 μmol, 0.05 equiv), *N*-methylimidazole (9.0 μL, 0.113 mmol, 0.10 equiv), and MeCN (25 mL). Lastly, ABNO (7.9 mg, 56.4 μmol, 0.05 equiv) was added, and the clear brownish reaction mixture was stirred until slightly yellow-green (ca. 80 min), at which point the solution was filtered through a short plug of silica and concentrated *in vacuo*. Purification of the crude residue by silica gel chromatography (60 to 70% EtOAc in hexanes) afforded enone **273** (454.0 mg, 0.953 mmol, 84% yield) as a white solid.

Note: On a 62 mg scale of diol **272**, this same procedure provided enone **273** (60.9 mg) in 98% yield. On larger scale, over-oxidation to the 1,3-diketone occurs to a larger extent and provides diminished yields (lowest of 84% on 540 mg scale).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (ddd, *J* = 9.7, 6.4, 1.6 Hz, 1H), 5.89 (ddd, *J* = 9.7, 2.0, 1.2 Hz, 1H), 5.62 (d, *J* = 3.9 Hz, 1H), 5.06 – 4.96 (m, 1H), 4.23 (br s, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 3.41 (dd, *J* = 12.2, 7.3 Hz, 1H), 3.27 (t, *J* = 5.5 Hz, 1H), 3.26 – 3.18 (br

m, 1H), 2.62 – 2.41 (m, 2H), 2.38 – 2.25 (m, 1H), 2.23 – 2.07 (m, 3H), 1.82 – 1.59 (m, 2H), 1.48 (tdd, J = 14.3, 3.5, 1.9 Hz, 1H), 0.02 (s, 9H).

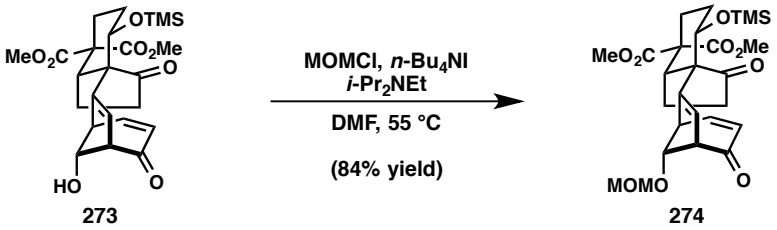
^{13}C NMR (101 MHz, $CDCl_3$): δ 215.7, 195.3, 170.8, 170.4, 156.0, 148.7, 127.5, 124.5, 84.3, 69.6, 61.4, 57.9, 56.2, 53.0, 52.8, 47.1, 41.7, 38.8, 27.5, 23.5, 19.3, -0.1.

FTIR (NaCl, thin film): 3467, 3009, 3955, 1738, 1674, 1435, 1376, 1314, 1253, 1230, 1172, 1076, 1060, 1021, 981, 843 cm^{-1}.

HRMS: (PMM) calc'd for $C_{24}H_{33}O_8Si$ $[M + H]^+$ 477.1939, found 477.1952.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +281° (c = 1.1, $CHCl_3$).

Preparation of MOM-ether 274:



A 50-mL, round-bottomed flask was charged with alcohol **273** (454 mg, 0.953 mmol, 1.0 equiv), *n*-Bu_4NI (70.0 mg, 0.191 mmol, 0.20 equiv), *i*-Pr_2NEt (1.0 mL, 5.72 mmol, 6.0 equiv), and DMF (10 mL), followed lastly by MOMCl (0.36 mL, 4.76 mmol, 5.0 equiv). The reaction mixture was heated to 55 °C with stirring for 15 h, then cooled to room temperature and diluted with H_2O (10 mL) and Et_2O (10 mL). The layers thoroughly mixed, separated, and then the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with water (3 x 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude residue by silica gel chromatography (30 to 33% EtOAc in hexanes) afforded methoxymethyl ether **274** (417.5 mg, 0.802 mmol, 84% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (ddd, *J* = 9.8, 6.3, 1.6 Hz, 1H), 5.82 (d, *J* = 10.1 Hz, 1H), 5.64 (d, *J* = 3.8 Hz, 1H), 4.75 (td, *J* = 4.6, 1.6 Hz, 1H), 4.71 (s, 2H), 4.25 (br s, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.43 (dd, *J* = 12.3, 7.3 Hz, 1H), 3.38 – 3.27 (m, 2H), 3.32 (s, 3H), 2.52 (td, *J* = 14.2, 3.3 Hz, 1H), 2.39 – 2.26 (m, 1H), 2.23 – 2.08 (m, 3H), 1.81 – 1.59 (m, 2H), 1.48 (tdd, *J* = 14.3, 3.3, 1.9 Hz, 1H), 0.03 (s, 9H).

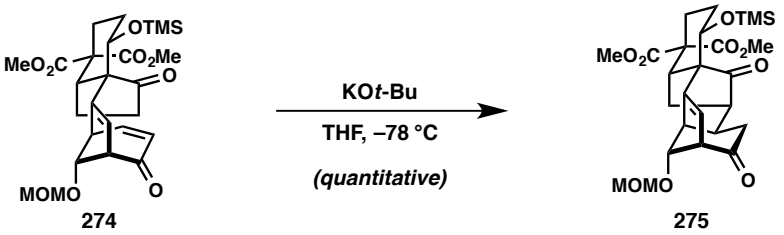
^{13}C NMR (101 MHz, $CDCl_3$): δ 215.5, 195.7, 170.7, 170.4, 155.9, 148.5, 126.7, 124.4, 96.6, 90.5, 69.7, 60.2, 57.8, 56.2, 56.1, 52.9, 52.8, 45.7, 41.7, 38.8, 27.5, 23.5, 19.3, -0.1.

FTIR (NaCl, thin film): 3009, 2954, 1738, 1681, 1462, 1435, 1253, 1230, 1172, 1059, 1040, 981 cm^{-1}.

HRMS: (PMM) calc'd for $C_{26}H_{37}O_9Si$ $[M + H]^+$ 521.2201, found 521.2207.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +258° (*c* = 1.3, $CHCl_3$).

Preparation of pentacycle 275:



A 50-mL, round-bottomed flask was charged with enone **274** (417.5 mg, 0.802 mmol, 1.0 equiv), followed by THF (8 mL), and this solution was cooled to –78 °C. KO*t*-Bu (1.04 mL, 1.0 M in THF, 1.04 mmol, 1.3 equiv) was added to the reaction, which was allowed to stir for 70 minutes. The reaction was quenched by addition of sat. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic

extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide pentacycle **275** (417.3 mg, 0.801 mmol, quantitative yield) as a white solid. This was used in following reactions without further purification.

Note: Purification of Michael addition product **275** led to slightly diminished yields. Crude material was deemed pure by NMR and used in following reactions without further purification for practical purposes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (d, *J* = 2.6 Hz, 1H), 4.68 (s, 2H), 4.59 (t, *J* = 5.5 Hz, 1H), 4.31 (dd, *J* = 6.5, 3.8 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.36 (s, 3H), 3.32 (dd, *J* = 5.0, 2.6 Hz, 1H), 3.06 (t, *J* = 5.5 Hz, 1H), 2.91 (dd, *J* = 10.2, 5.5 Hz, 1H), 2.61 (dd, *J* = 19.4, 8.7 Hz, 1H), 2.51 – 2.44 (m, 1H), 2.36 – 2.23 (m, 4H), 2.20 (ddd, *J* = 13.3, 7.5, 5.6 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.72 – 1.54 (m, 2H), 0.10 (s, 9H).

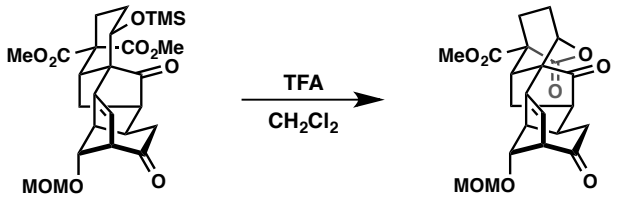
^{13}C NMR (101 MHz, $CDCl_3$): δ 203.7, 202.7, 173.0, 170.5, 146.8, 122.6, 96.3, 78.6, 66.4, 60.5, 59.0, 56.6, 56.1, 53.1, 51.9, 51.2, 42.4, 41.4, 37.9, 36.0, 27.1, 26.1, 25.1, 0.3.

FTIR (NaCl, thin film): 3017, 2954, 2904, 2828, 1747, 1732, 1714, 1589, 1461, 1434, 1406, 1361, 1251, 1215, 1152, 1111, 1043, 866 cm^{-1}.

HRMS: (PMM) calc'd for $C_{26}H_{37}O_9Si$ $[M + H]^+$ 521.2201, found 521.2186.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +168° (*c* = 1.2, $CHCl_3$).

Preparation of lactone 278:



275 **278**

In a 50-mL, round-bottomed flask, diester **275** (417.3 mg, 0.802 mmol, 1.0 equiv) was dissolved in wet CH_2Cl_2 (8.0 mL). To this solution was added TFA (0.31 mL, 4.05 mmol, 5.0 equiv). The reaction was stirred for 21 h, and then quenched with sat. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude lactone **278** (<350 mg) as a white foam. This crude material was deemed pure by NMR and used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (d, *J* = 2.6 Hz, 1H), 5.20 (dd, J = 4.7, 0.8 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.63 (t, *J* = 5.5 Hz, 1H), 3.82 (s, 3H), 3.38 (dd, *J* = 4.9, 2.6 Hz, 1H), 3.36 (s, 3H), 3.11 (t, *J* = 5.7 Hz, 1H), 2.99 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.73 (dd, *J* = 19.3, 9.1 Hz, 1H), 2.64 (dtd, *J* = 9.0, 4.5, 1.8 Hz, 1H), 2.47 – 2.22 (m, 5H), 2.10 – 1.99 (m, 2H), 1.82 (dddd, *J* = 13.8, 11.3, 5.0, 1.0 Hz, 1H), 4.66 – 4.59 (m, 1H).

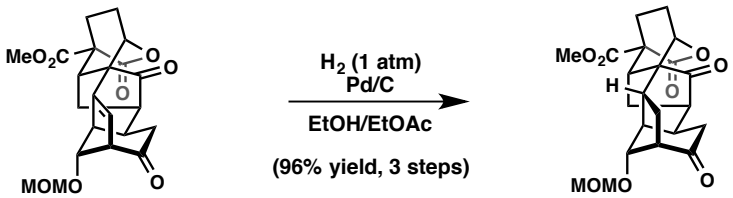
^{13}C NMR (101 MHz, $CDCl_3$): δ 203.8, 200.6, 169.2, 169.1, 143.3, 121.9, 96.6, 78.3, 72.0, 62.2, 60.8, 56.2, 52.8, 52.8, 51.3, 43.7, 43.0, 38.8, 36.0, 28.5, 28.0, 21.2.

FTIR (NaCl, thin film): 3009, 2954, 1749, 1711, 1444, 1367, 1298, 1264, 1220, 1153, 1108, 1068, 1047, 997 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{24}KO_8$ $[M + K]^+$ 455.1103, found 455.1096.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +183° (*c* = 0.67, $CHCl_3$).

Preparation of carbocycle 279:



To a 50-mL, round-bottomed flask containing crude lactone **278** (<350 mg) under N_2 was added Pd/C (10 wt%, 333 mg), followed by absolute EtOH (6 mL) and EtOAc (6 mL). The reaction vessel was purged with H_2 for 5 minutes via a double-walled balloon, and stirred for another 22 h under H_2 (1 atm). The H_2 balloon was then removed, and the flask was purged with N_2 for 15 minutes. The suspension was filtered through a plug of silica (eluting with EtOAc), and the resulting solution was concentrated *in vacuo* to provide carbocycle **279** (322.6 mg, 0.771 mmol, 96% yield over 3 steps from enone **274**) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (dd, *J* = 4.5, 1.2 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.19 (t, *J* = 4.6 Hz, 1H), 3.82 (s, 3H), 3.34 (s, 3H), 2.88 – 2.73 (m, 5H), 2.65 – 2.53 (m, 1H), 2.47 (dd, *J* = 14.9, 9.7 Hz, 1H), 2.39 (ddd, *J* = 13.5, 11.8,

4.8 Hz, 1H), 2.34 (d, *J* = 18.1 Hz, 1H), 2.23 – 2.09 (m, 2H), 2.05 – 1.86 (m, 3H), 1.80 (dddd, *J* = 14.1, 11.1, 4.2, 1.2 Hz, 1H), 1.46 (ddd, *J* = 14.8, 6.6, 0.9 Hz, 1H).

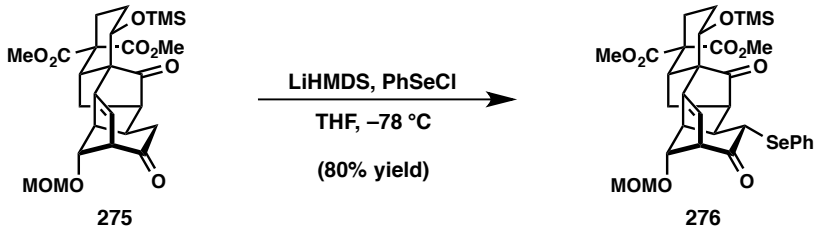
^{13}C NMR (101 MHz, $CDCl_3$): δ 213.9, 210.2, 169.3, 169.1, 96.3, 79.2, 74.1, 56.1, 55.9, 53.1, 52.8, 52.8, 51.5, 49.6, 45.3, 39.9, 39.0, 37.6, 28.2, 27.9, 24.2, 19.8.

FTIR (NaCl, thin film): 2953, 2915, 2854, 1740, 1711, 1458, 1449, 1377, 1298, 1262, 1151, 1103, 1048, 992, 753 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{28}NO_8$ $[M + NH_4]^+$ 436.1966, found 436.1963.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +32° (*c* = 1.0, $CHCl_3$).

Preparation of α-selenide 276:



275 276

In a 1-dram vial, pentacycle **275** (15.0 mg, 28.8 μmol, 1.0 equiv) was dissolved in THF (0.3 mL) and cooled to – 78°C. LiHMDS (35 μL, 1.0 M in THF, 34.6 μmol, 1.2 equiv) was added, and the resulting solution was stirred for 15 minutes. In a separate 1-dram vial, a solution of PhSeCl (7.2 mg, 37.5 μmol, 1.3 equiv) in THF (0.3 mL) was prepared, and added to the reaction mixture at –78 °C. After stirring for an additional 2 h, the reaction was quenched with sat. $NaHCO_3$ (1 mL), extracted with CH_2Cl_2 (3 x 1 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography

(30% EtOAc in hexanes) to afford α-selenide **276** (15.6 mg, 23.1 μmol, 80% yield) as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.67 (m, 2H), 7.30 – 7.25 (m, 3H), 5.59 (d, *J* = 2.6 Hz, 1H), 4.58 (s, 2H), 4.53 (t, *J* = 5.5 Hz, 1H), 4.29 (dd, *J* = 6.7, 4.1 Hz, 1H), 3.76 (s, 3H), 3.68 (d, *J* = 4.1 Hz, 1H), 3.64 (s, 3H), 3.50 (dd, *J* = 5.1, 2.6 Hz, 1H), 3.36 (s, 3H), 3.05 (t, *J* = 5.5 Hz, 1H), 2.92 (dd, *J* = 10.2, 5.5 Hz, 1H), 2.69 (q, *J* = 4.7 Hz, 1H), 2.43 (dd, *J* = 7.3, 4.7 Hz, 1H), 2.31 – 2.09 (m, 3H), 1.90 – 1.77 (m, 1H), 1.68 – 1.53 (m, 2H), 0.09 (s, 9H).

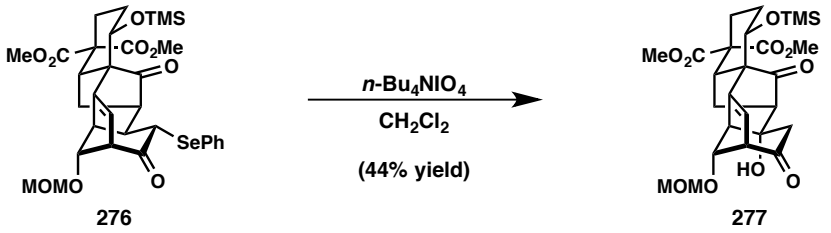
^{13}C NMR (101 MHz, $CDCl_3$): δ 203.7, 201.6, 172.9, 170.4, 145.9, 135.2, 129.7, 129.0, 127.9, 122.9, 96.0, 78.5, 66.6, 60.8, 59.1, 56.6, 56.3, 53.1, 52.0, 50.1, 48.1, 46.7, 43.4, 41.4, 27.1, 26.0, 25.0, 0.3.

FTIR (NaCl, thin film): 3051, 2953, 2896, 1740, 1730, 1579, 1436, 1360, 1250, 1216, 1108, 1039, 931, 869, 841, 753 cm^{-1}.

HRMS: (PMM) calc'd for $C_{32}H_{41}O_9SeSi$ $[M + H]^+$ 677.1680, found 677.1696.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +89° (*c* = 1.1, $CHCl_3$).

Preparation of β-hydroxyketone 277:



To a 1-dram vial containing α-selenide **276** (15.0 mg, 22.2 μmol, 1.0 equiv) was added *n*-Bu_4NIO_4 (38.0 mg, 0.0888 μmol, 4.0 equiv) and wet CH_2Cl_2 (0.44 mL). The reaction was sealed and stirred for 25 h, then diluted with CH_2Cl_2 (1 mL) and quenched with sat. $NaHCO_3$ (0.5 mL) and sat. $Na_2S_2O_3$ (1 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by preparative thin-layer chromatography (50% acetone in hexanes) to afford 3°-alcohol **277** (5.2 mg, 9.69 μmol, 44% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62 (d, *J* = 2.7 Hz, 1H), 4.76 – 4.69 (m, 3H), 4.34 (dd, *J* = 7.0, 4.6 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.52 (dd, *J* = 4.9, 2.7 Hz, 1H), 3.50 (br s, 1H), 3.38 (s, 3H), 3.07 – 2.95 (m, 3H), 2.67 (d, *J* = 20.0 Hz, 1H), 2.36 (d, *J* = 7.1 Hz, 1H), 2.32 – 2.13 (m, 3H), 2.03 (dt, *J* = 14.5, 6.4 Hz, 1H), 1.87 (dddd, *J* = 13.7, 8.6, 6.9, 1.8 Hz, 1H), 1.71 – 1.59 (m, 1H), 0.10 (s, 9H).

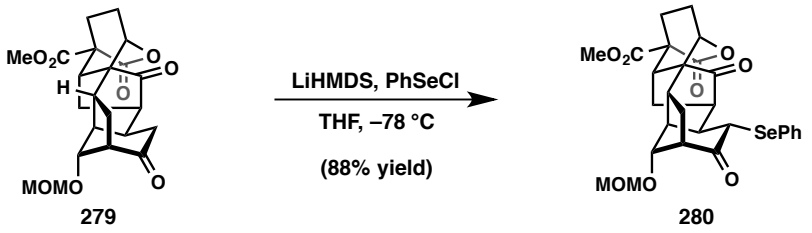
^{13}C NMR (101 MHz, $CDCl_3$): δ 201.6, 200.9, 172.9, 170.4, 144.1, 125.4, 96.6, 79.8, 73.5, 66.5, 60.5, 58.0, 57.6, 56.7, 56.3, 53.2, 52.1, 49.0, 49.0, 41.4, 27.2, 24.9, 23.2, 0.3.

FTIR (NaCl, thin film): 3524, 2954, 2919, 2854, 1734, 1458, 1434, 1362, 1251, 1211, 1110, 1040, 841, 754 cm^{-1}.

HRMS: (ESI) calc'd for $C_{26}H_{37}O_{10}Si$ $[M + H]^+$ 537.2151, found 537.2167.

$[\alpha]_D^{25}$ = +166° (*c* = 0.37, $CHCl_3$).

Preparation of α-selenide 280:



279 280

A 50-mL, round-bottomed flask was charged with diketone **279** (168 mg, 0.401 mmol, 1.0 equiv), which was dissolved in THF (4 mL) and cooled to –78 °C. In a separate flask, a solution of PhSeCl (123 mg, 0.642 mmol, 1.6 equiv) in THF (4 mL) was prepared. LiHMDS (0.60 mL, 1.0 M in THF, 0.60 mmol, 1.5 equiv) was added to the solution of diketone **279**, and the resulting mixture was stirred for 30 minutes at –78 °C. The THF solution of PhSeCl was then added, and the mixture was stirred for another 2 hours. The reaction was quenched with sat $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (90% ethyl acetate in hexanes) to afford α-selenide **280** as a yellow foam (201.5 mg, 0.351 mmol, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 – 7.68 (m, 2H), 7.31 – 7.27 (m, 3H), 4.75 (dd, *J* = 4.4, 1.0 Hz, 1H), 4.58 (d, *J* = 6.9 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 1H), 4.22 (t, *J* = 5.0 Hz, 1H), 3.81 (s, 1H), 3.76 (d, *J* = 4.5 Hz, 1H), 3.38 (s, 3H), 3.11 (dtd, *J* = 6.8, 4.4, 2.2 Hz,

1H), 3.05 (dd, *J* = 8.4, 5.4 Hz, 1H), 2.85 (q, *J* = 5.3 Hz, 1H), 2.72 (dd, *J* = 9.8, 7.3 Hz, 1H), 2.59 – 2.53 (m, 1H), 2.41 (dd, *J* = 15.1, 9.8 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.21 (dd, *J* = 6.7, 4.1 Hz, 1H), 2.16 (ddt, *J* = 14.3, 11.8, 4.5 Hz, 1H), 2.02 – 1.91 (m, 3H), 1.78 (ddd, *J* = 14.7, 11.4, 4.1 Hz, 1H), 1.50 (dd, *J* = 15.2, 7.2 Hz, 1H).

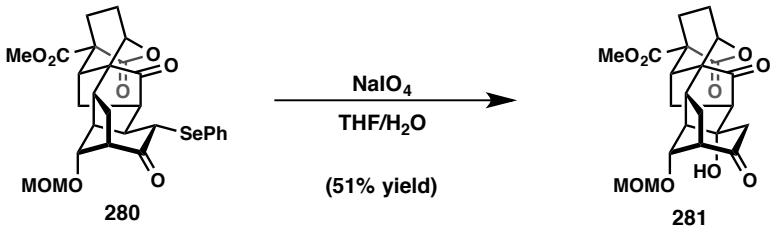
^{13}C NMR (126 MHz, $CDCl_3$): δ 214.0, 207.8, 169.2, 168.9, 134.9, 130.1, 129.1, 128.2, 96.0, 78.7, 73.9, 56.3, 56.2, 53.2, 53.0, 52.8, 51.6, 50.3, 49.2, 47.8, 45.4, 39.5, 28.3, 27.5, 24.4, 19.7.

FTIR (NaCl, thin film): 3017, 2952, 2896, 2854, 1755, 1739, 1713, 1477, 1464, 1438, 1377, 1298, 1262, 1103, 1052, 989 cm^{-1}.

HRMS: (ESI) calc'd for $C_{28}H_{34}NO_8Se$ $[M + NH_4]^+$ 592.1444, found 592.1424.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +13° (*c* = 0.60, $CHCl_3$).

Preparation of β-hydroxyketone 281:



To a 1-dram vial was added α-selenide **280** (10.4 mg, 18.1 μmol, 1.0 equiv), $NaIO_4$ (19.4 mg, 90.7 μmol, 5.0 equiv), THF (0.3 mL), and H_2O (60 μL). The reaction was allowed to stir for 10 h, and then quenched by addition of sat. $NaHCO_3$ (1 mL). The aqueous phase was extracted with EtOAc (3 x 1 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel

chromatography (40% acetone in hexanes) afforded β-hydroxyketone **281** (4.0 mg, 9.2 μmol, 51% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (dd, *J* = 4.3, 0.9 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.37 (t, *J* = 4.9 Hz, 1H), 3.83 (s, 3H), 3.39 – 3.35 (m, 1 H), 3.36 (s, 3H), 2.99 (d, *J* = 20.1 Hz, 1H), 2.92 (dd, *J* = 8.2, 5.0 Hz, 1H), 2.85 (dd, *J* = 15.1, 9.9 Hz, 1H), 2.75 (d, *J* = 5.6 Hz, 1H), 2.74 (d, *J* = 19.9 Hz, 1H), 2.66 (dd, *J* = 9.9, 7.4 Hz, 1H), 2.48 – 2.37 (m, 2H), 2.35 (d, *J* = 6.5 Hz, 1H), 2.24 – 2.15 (m, 1H), 2.02 – 1.84 (m, 3H), 1.79 (dddd, *J* = 14.3, 11.2, 4.3, 1.2 Hz, 1H), 1.41 (dd, *J* = 15.0, 6.8 Hz, 1H).

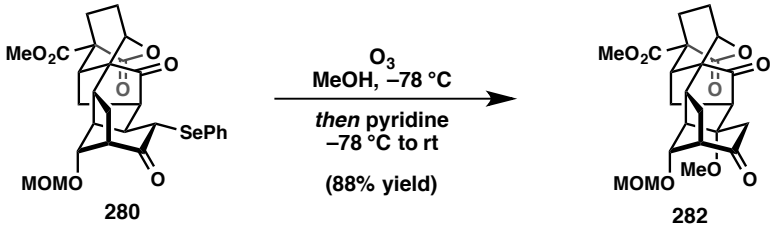
^{13}C NMR (101 MHz, $CDCl_3$): δ 210.7, 207.7, 169.1, 168.9, 96.6, 79.7, 76.7, 73.8, 57.8, 56.5, 56.2, 53.0, 52.8, 52.2, 50.8, 47.6, 45.5, 43.9, 28.3, 24.3, 23.8, 20.1.

FTIR (NaCl, thin film): 3468, 2960, 2915, 2851, 1745, 1717, 1464, 1445, 1379, 1298, 1272, 1104, 1051 cm^{-1}.

HRMS: (FAB) calc'd for $C_{22}H_{27}O_9$ $[M + H]^+$ 435.1655, found 435.1639.

$[\alpha]_D^{25}$ = +16° (*c* = 0.21, $CHCl_3$).

Preparation of β-methoxyketone 282:



A 25-mL, round-bottomed flask was charged with α-selenide **280** (90.6 mg, 0.158 mmol, 1.0 equiv), CH_2Cl_2 (4 mL), and methanol (4 mL). The flask was cooled to –78 °C,

at which time ozone (as a mixture with O_2) was gently bubbled through the solution (O_2 flow rate = 1/4 L/min, 2 setting on ozone generator) for 20 min. The solution was then sparged with Ar for 15 minutes, and pyridine (64 μL, 0.790 mmol, 5 equiv) was added. The reaction was allowed to warm to ambient temperature, and stirred for a further 48 h. The methanol solvent and pyridine were then removed by concentration *in vacuo*, and the crude residue was purified by silica gel chromatography (44% acetone in hexane) to afford β-methoxyketone **282** as a white solid (62.3 mg, 0.139 mmol, 88% yield) with a small amount of inseperable arene impurity (<10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 4.0 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 1H), 4.23 (t, *J* = 4.6 Hz, 1H), 3.81 (s, 3H), 3.32 (s, 3H), 3.11 (s, 3H), 2.98 (d, *J* = 17.9 Hz, 1H), 2.79 (dd, *J* = 7.4, 4.5 Hz, 1H), 2.72 (q, *J* = 6.0 Hz, 1H), 2.69 – 2.58 (m, 3H), 2.55 (d, *J* = 6.7 Hz, 1H), 2.45 (dt, *J* = 11.2, 6.5 Hz, 1H), 2.42 – 2.34 (m, 1H), 2.23 – 2.09 (m, 1H), 2.03 – 1.70 (m, 4H), 1.39 (ddd, *J* = 14.9, 6.1, 2.8 Hz, 1H).

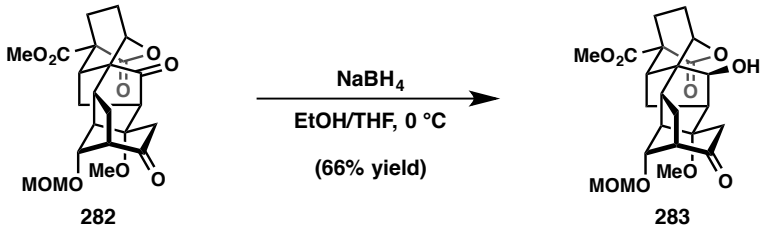
^{13}C NMR (101 MHz, $CDCl_3$): δ 211.5, 208.3, 169.1, 169.1, 95.7, 81.0, 76.9, 74.1, 56.6, 55.8, 53.8, 53.0, 52.8, 52.6, 48.9, 45.8, 45.0, 44.6, 44.5, 28.0, 24.2, 24.2, 20.1.

FTIR (NaCl, thin film): 2954, 2915, 2832, 1746, 1711, 1462, 1443, 1375, 1298, 1262, 1221, 1152, 1103, 1049, 916, 753 cm^{-1}.

HRMS: (FAB) calc'd for $C_{23}H_{29}O_9$ $[M + H]^+$ 449.1811, found 449.1801.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –14° (*c* = 0.24, $CHCl_3$).

Preparation of alcohol 283:



282 **283**

A solution of **282** (17.0 mg, 37.9 μmol, 1.0 equiv) in absolute EtOH (0.28 mL) and THF (0.28 mL) was cooled to 0 °C in a 5-mL round-bottomed flask. $NaBH_4$ (3.6 mg, 94.8 μmol, 2.5 equiv) was added, and three more equal portions of $NaBH_4$ were added each successive hour. An hour after the fourth portion was added, the reaction was quenched with sat. $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3% MeOH in CH_2Cl_2) to afford alcohol **283** as a clear oil (11.2 mg, 24.9 μmol, 66% yield).

Note: Extended reaction time leads to over-reduction of the methyl ester. Remarkably, the methyl ester undergoes facile reduction, while the C16 ketone remains inert.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.82 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 4.2 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.20 (td, *J* = 4.9, 1.6 Hz, 1H), 4.16 (dd, *J* = 4.8, 3.9 Hz, 1H), 3.78 (s, 3H), 3.35 (s, 3H), 3.15 (s, 3H), 2.93 (d, *J* = 16.9 Hz, 1H), 2.77 (ddd, *J* = 7.3, 4.0, 1.3 Hz, 1H), 2.71 (d, *J* = 16.9 Hz, 1H), 2.64 – 2.60 (m, 1H), 2.45 (ddd, *J* = 6.4, 4.9, 1.3 Hz, 1H), 2.39 (t, *J* = 5.5 Hz, 1H), 2.35 – 2.23 (m, 3H), 2.22 – 2.10 (m, 2H), 2.06 (dd, *J* = 9.7, 7.5 Hz, 1H), 1.97 – 1.86 (m, 2H), 1.71 – 1.63 (m, 1H), 1.56 (ddd, *J* = 14.5, 7.5, 5.9 Hz, 1H).

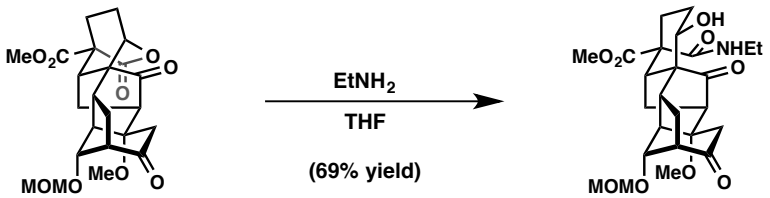
^{13}C NMR (101 MHz, $CDCl_3$): δ 212.6, 171.2, 169.4, 95.8, 78.1, 76.0, 74.4, 72.0, 55.7, 53.5, 53.0, 52.6, 48.5, 48.4, 47.7, 47.5, 43.9, 43.3, 40.6, 28.6, 26.6, 25.4, 20.5.

FTIR (NaCl, thin film): 3436, 2951, 2854, 2832, 1738, 1730, 1713, 1468, 1449, 1375, 1330, 1287, 1251, 1115, 1050 cm^{-1}.

HRMS: (ESI) calc'd for $C_{22}H_{25}O_8$ $[M - OMe]^+$ 419.1700, found 419.1709.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –10° (*c* = 0.53, $CHCl_3$).

Preparation of amide 287:



To a 1-dram vial containing lactone **282** (4.6 mg, 10.3 μmol, 1.0 equiv) was added ethylamine (0.30 mL, 2.0 M in THF, 0.60 mmol). The resulting solution was stirred for 72 h at room temperature, then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (50% acetone in hexanes) to afford amide **287** as a colorless oil (3.5 mg, 7.1 μmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (t, *J* = 5.5 Hz, 1H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 1H), 4.29 (t, *J* = 4.8 Hz, 1H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.82 (s, 3H), 3.61 (td, *J* = 9.9, 6.0 Hz, 1H), 3.34 (s, 3H), 3.32 – 3.16 (m, 2H), 3.06 (s, 3H), 2.88 – 2.61 (m, 6H), 2.44 – 2.30 (m, 2H), 2.19 (ddd, *J* = 15.8, 11.3, 8.0 Hz, 1H), 2.03 (ddd, *J* = 13.8, 6.1, 4.6 Hz, 1H), 1.98 – 1.87 (m, 2H), 1.84 – 1.63 (m, 3H), 1.10 (t, *J* = 7.3 Hz, 3H).

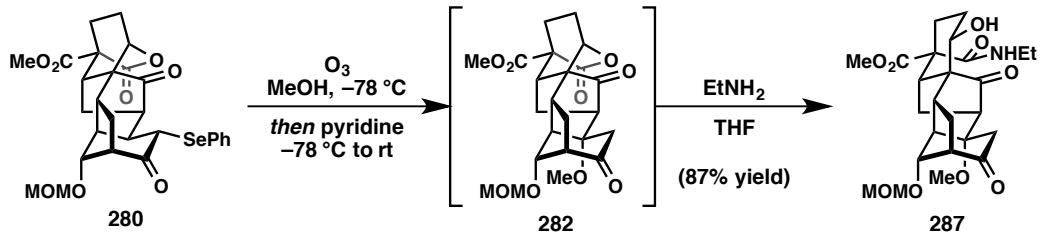
^{13}C NMR (101 MHz, $CDCl_3$): δ 216.1, 209.1, 174.6, 169.0, 95.5, 81.9, 77.3, 73.6, 58.3, 55.8, 53.6, 53.3, 52.7, 52.6, 51.3, 48.9, 44.1, 43.2, 42.2, 34.7, 30.3, 29.0, 26.3, 24.8, 14.7.

FTIR (NaCl, thin film): 3370, 2952, 2900, 2824, 1720, 1657, 1529, 1452, 1236, 1152, 1046, 753 cm^{-1}.

HRMS: (ESI) calc'd for $C_{25}H_{36}NO_9$ $[M + H]^+$ 494.2385, found 494.2381.

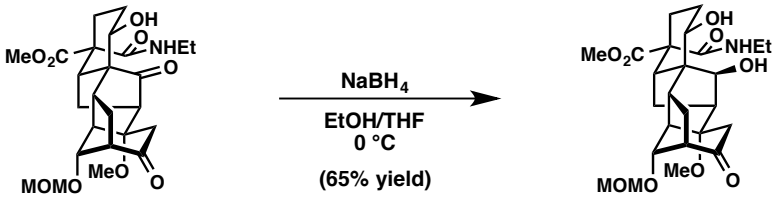
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –30° (*c* = 0.47, $CHCl_3$).

One-pot preparation amide 287:



A 25-mL, round-bottomed flask was charged with α-selenide **280** (30.0 mg, 52.3 μmol, 1.0 equiv) and methanol (3 mL). The flask was cooled to –78 °C, at which time ozone (as a mixture with O_2) was gently bubbled through the solution (O_2 flow rate = 1/4 L/min, 2 setting on ozone generator) for 10 min. The solution was sparged with Ar for 10 minutes, and then pyridine (85 μL, 1.05 mmol, 20 equiv) was added. The reaction was allowed to warm to ambient temperature, and stirred for a further 17 h. The methanol solvent and pyridine were then removed by concentration *in vacuo*, and ethylamine (3 mL, 2.0 M in THF) was added. After stirring for 72 h, the reaction mixture was concentrated *in vacuo*, and the resulting crude residue was purified by silica gel chromatography (50% acetone in hexanes) to provide amide **287** as a white solid (22.4 mg, 45.4 μmol, 87% yield).

Preparation of diol amide 288:



A 25-mL, round-bottomed flask was charged with ketone **287** (20.0 mg, 40.5 μmol, 1.0 equiv), absolute EtOH (1 mL), and THF (1 mL). The resulting solution was cooled to 0 °C, and three portions of $NaBH_4$ (8 mg, 0.211 mmol, 5 equiv) were added over one hour (one portion every 20 minutes, total of 24 mg added). The reaction was then quenched with sat. $NaHCO_3$ (5 mL) and stirred for an additional 15 minutes. The biphasic mixture was concentrated *in vacuo* to remove ethanol and THF. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (4% MeOH in CH_2Cl_2) to afford diol amide **288** as a white solid (13.1 mg, 26.4 μmol, 65% yield).

Note: Extended reaction time leads to over-reduction of the methyl ester. Remarkably, the methyl ester undergoes facile reduction, while the C16 ketone remains inert.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (t, *J* = 5.4 Hz, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.43 (d, *J* = 5.2 Hz, 1H), 4.16 (t, *J* = 4.4 Hz, 1H), 3.84 (q, *J* = 6.3 Hz, 1H), 3.77 (s, 3H), 3.48 (br s, 1H), 3.36 (s, 3H), 3.26 (qdd, *J* = 7.3, 5.4, 2.9 Hz, 2H), 3.12 (s, 3H), 2.86 (d, *J* = 17.0 Hz, 1H), 2.80 – 2.73 (m, 1H), 2.73 (d, *J* = 17.1 Hz, 1H), 2.60 –

2.52 (m, 2H), 2.53 – 2.42 (m, 3H), 2.26 – 1.84 (m, 6H), 1.83 – 1.71 (m, 1H), 1.32 (ddd, *J* = 14.2, 8.2, 6.4 Hz, 1H), 1.12 (t, *J* = 7.3 Hz, 3H).

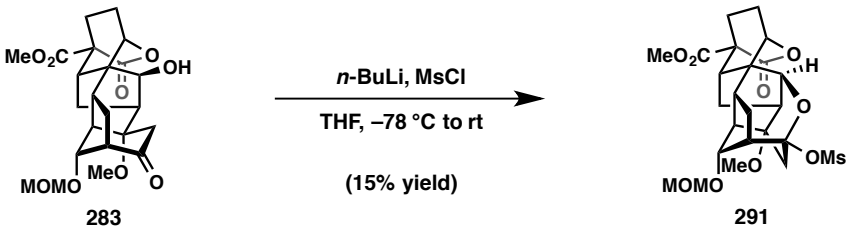
^{13}C NMR (101 MHz, $CDCl_3$): δ 213.0, 175.8, 169.6, 95.7, 78.1, 74.8, 74.5, 70.7, 55.8, 55.7, 53.5, 53.3, 48.3, 47.7, 46.1, 45.9, 45.3, 43.4, 43.0, 34.9, 29.4, 27.1, 23.2, 22.1, 14.5.

FTIR (NaCl, thin film): 3369, 2934, 2896, 2847, 2824, 1726, 1708, 1660, 1640, 1545, 1530, 1464, 1449, 1221, 1166, 1115, 1044 cm^{-1}.

HRMS: (ESI) calc'd for $C_{25}H_{38}NO_9$ $[M + H]^+$ 496.2541, found 496.2540.

$[\alpha]_D^{25}$ = –96° (*c* = 0.23, $CHCl_3$).

Preparation of mesyl acetal 291:

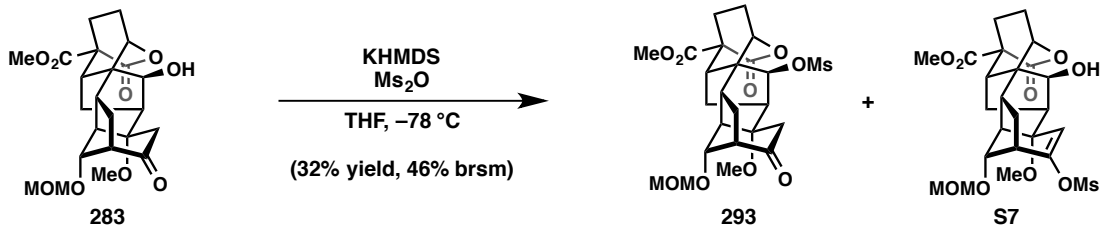


In a 1-dram vial, *n*-BuLi (3.2 μL, 2.5 M solution in hexane, 8.06 μmol, 1.1 equiv) was added to a solution of alcohol **283** (3.3 mg, 7.33 μmol, 1.0 equiv) in THF (0.30 mL) at –78 °C. After stirring for 20 minutes, MsCl (3.0 μL, 38.7 μmol, 5.3 equiv) was added. The reaction was allowed to warm to room temperature overnight, and then quenched with sat. $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by preparative thin-layer chromatography (5% MeOH in CH_2Cl_2) to afford mesyl acetal **291** (0.6 mg, 1 μmol, 15% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (d, *J* = 4.2 Hz, 1H), 4.74 (d, *J* = 6.5 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 3.86 (dd, *J* = 4.0, 2.3 Hz, 1H), 3.79 (s, 3H), 3.40 (s, 3H), 3.27 (d, *J* = 11.2 Hz, 1H), 3.22 (s, 3H), 3.12 (s, 3H), 2.88 (br s, 1H), 2.50 (t, *J* = 5.9 Hz, 1H), 2.44 – 2.24 (m, 4H), 2.22 – 2.05 (m, 3H), 1.95 (d, *J* = 12.6 Hz, 1H), 1.91 – 1.84 (m, 2H), 1.43 – 1.30 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 169.3, 113.3, 96.2, 81.1, 81.0, 77.4, 75.8, 55.8, 53.1, 52.7, 52.0, 49.5, 49.2, 47.7, 44.9, 42.8, 42.3, 42.2, 38.6, 27.3, 24.7, 24.6, 20.6.

Preparation of mesylate 293:



In a flame-dried 5-mL, round-bottomed flask, alcohol **283** (24.2 mg, 53.6 μmol, 1.0 equiv) was dissolved in THF (0.8 mL) and cooled to –78 °C. KHMDS (130 μL, 0.5 M in PhMe, 65.0 mmol, 1.2 equiv) was added, and the resulting solution was stirred for 10 minutes. In a separate 1-dram vial, Ms_2O (20.5 mg, 0.118 mmol, 2.2 equiv) was dissolved in THF (0.2 mL) and added to the alkoxide solution. After stirring for an additional 40 minutes, the reaction was quenched with sat. $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by preparative thin-layer chromatography (5% MeOH in CH_2Cl_2) to afford mesylate **293** (9.0 mg, 17 μmol, 32%

yield) as a colorless oil, mesyl enol ether **S7** (5.3 mg, 10 μmol, 19% yield) as a colorless oil, and starting material **283** (7.4 mg, 16 μmol, 30% recovery).

Data for mesylate 293:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (dd, *J* = 5.2, 1.6 Hz, 1H), 4.84 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 4.3 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.20 (t, *J* = 4.4 Hz, 1H), 3.80 (s, 3H), 3.36 (s, 3H), 3.16 (s, 3H), 3.08 (s, 3H), 3.02 (d, *J* = 17.2 Hz, 1H), 2.84 (ddd, *J* = 7.0, 4.0, 1.3 Hz, 1H), 2.71 (d, *J* = 17.3 Hz, 1H), 2.66 (t, *J* = 5.6 Hz, 1H), 2.51 (ddd, *J* = 6.5, 5.0, 1.3 Hz, 1H), 2.41 (dd, *J* = 14.7, 9.9 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.28 – 2.12 (m, 3H), 1.99 – 1.88 (m, 3H), 1.78 (ddd, *J* = 14.3, 12.1, 7.5 Hz, 1H), 1.70 (ddd, *J* = 14.6, 7.8, 5.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.0, 169.5, 169.0, 95.7, 75.6, 74.9, 73.9, 55.8, 53.4, 52.8, 52.8, 48.7, 47.8, 47.3, 46.7, 43.7, 41.9, 40.5, 38.2, 28.3, 25.9, 25.1, 20.4.

FTIR (NaCl, thin film): 3017, 2952, 2839 1756, 1736, 1709, 1466, 1450, 1335, 1287, 1256, 1218, 1177, 1112, 1085, 959, 839 cm^{-1}.

HRMS: (PMM) calc'd for $C_{24}H_{36}NO_{11}S$ $[M + NH_4]^+$ 546.2004, found 546.2011.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +61° (*c* = 0.70, $CHCl_3$).

Data for mesyl enol ether S7:

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95 (t, *J* = 1.4 Hz, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 4.72 (d, *J* = 4.1 Hz, 1H), 4.62 (d, *J* = 6.9 Hz, 1H), 4.04 (t, *J* = 3.6 Hz, 1H), 3.96 (t, *J* = 4.4 Hz, 1H), 3.78 (s, 3H), 3.38 (s, 3H), 3.22 (s, 3H), 3.17 (s, 3H), 2.78 (dd, *J* = 6.2, 4.6 Hz, 1H),

2.64 (dd, *J* = 13.3, 5.5 Hz, 1H), 2.47 (t, *J* = 5.4 Hz, 1H), 2.35 – 2.17 (m, 4H), 2.12 – 2.00 (m, 3H), 2.00 – 1.88 (m, 2H), 1.74 (ddd, J = 13.3, 11.4, 6.4 Hz, 1H), 1.69 – 1.60 (m, 1H).

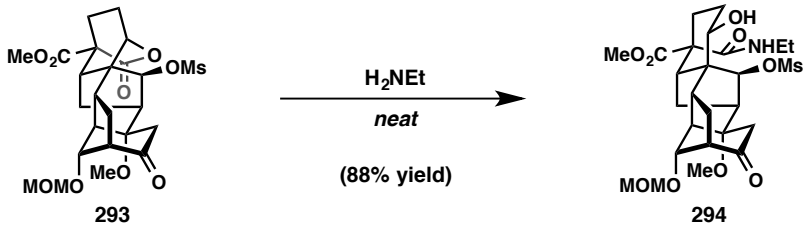
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 169.4, 150.5, 115.1, 95.6, 77.4, 76.0, 74.0, 72.2, 55.7, 53.0, 52.6, 49.2, 47.4, 47.1, 44.0, 43.8, 42.9, 39.9, 38.1, 28.9, 28.9, 25.0, 20.4.

FTIR (NaCl, thin film): 2952, 2930, 2851, 2828, 1738, 1730, 1668, 1466, 1451, 1360, 1301, 1180, 1151, 1054, 971 cm^{-1}.

HRMS: (ESI) calc'd for $C_{23}H_{29}O_{10}S$ $[M - OMe]^+$ 497.1476, found 497.1462.

$[\alpha]_D^{25}$ = –2.6° (*c* = 0.40, $CHCl_3$).

Preparation of mesylate amide 294:



To a 1-dram vial containing lactone **293** (7.0 mg, 13.2 μmol, 1.0 equiv) was added neat ethylamine (~0.3 mL, distilled from a 70% solution in water and stored over KOH). The vial was sealed with a Teflon cap and allowed to stir for 72 h at room temperature. The reaction was then opened to the atmosphere to allow evaporation of ethylamine. The resulting residue was dissolved in dichloromethane, and further concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (45% acetone in hexanes) to afford amide **294** as a white solid (6.7 mg, 11.7 μmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (t, *J* = 5.3 Hz, 1H), 5.20 (dd, *J* = 5.4, 1.1 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.18 (t, *J* = 4.4 Hz, 1H), 3.78 (s, 3H), 3.72 (td, *J* = 8.8, 5.7 Hz, 1H), 3.36 (s, 3H), 3.26 (qd, *J* = 7.3, 5.5 Hz, 2H), 3.12 (s, 3H), 3.09 (s, 3H), 2.99 (d, *J* = 17.2 Hz, 1H), 2.89 (d, *J* = 8.9 Hz, 1H), 2.80 (ddd, *J* = 7.7, 4.2, 1.2 Hz, 1H), 2.74 – 2.59 (m, 4H), 2.31 – 2.20 (m, 3H), 2.19 – 2.06 (m, 2H), 2.06 – 1.90 (m, 2H), 1.85 (dtd, *J* = 14.1, 9.0, 1.7 Hz, 1H), 1.43 (ddd, *J* = 14.3, 7.9, 6.3 Hz, 1H), 1.13 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.9, 175.3, 169.0, 95.7, 77.4, 77.4, 74.0, 69.8, 56.2, 55.7, 53.4, 53.3, 48.5, 47.8, 45.6, 44.9, 44.7, 43.0, 42.6, 38.4, 34.9, 28.5, 26.1, 22.4, 21.9, 14.5.

FTIR (NaCl, thin film): 3387, 2940, 2900, 2851, 2832, 1710, 1660, 1647, 1529, 1464, 1331, 1220, 1172, 1044, 948, 852 cm^{-1}.

HRMS: (ESI) calc'd for $C_{26}H_{40}NO_{11}S$ $[M + H]^+$ 574.2317, found 574.2302.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –14° (*c* = 0.45, $CHCl_3$).

3.9 NOTES AND REFERENCES

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