CHAPTER 4

Progress Toward the Total Synthesis of Acutumine[†]

4.1. Introduction

Acutumine arguably represents one of the most structurally complex propellane alkaloids. As was discussed in the previous chapter, its promising biological properties and densely functionalized architecture render this molecule an attractive, yet formidable synthetic target. A comparison of the studies discussed in Section 3.4 reveals two significant, commonly encountered challenges in the synthesis of acutumine: the efficient construction of the two vicinal, all-carbon quaternary stereocenters, and stereoselective installation of the chloride. With these considerations in mind, an efficient route to acutumine that utilizes the diastereoselective 1,2-addition to benzoquinone-derived sulfinimines developed in our laboratory was envisioned. Our synthetic plan is discussed in detail below.

[†] Portions of this chapter have been reproduced from published studies (see reference 5) and the supporting information found therein. The research presented in this chapter was completed in collaboration with John R. Butler, a postdoctoral scholar in the Reisman group.

4.2. Synthetic Approach

In a retrosynthetic sense, acutumine (**133**) was simplified to diol **193**, an intermediate envisioned to arise from lactol **195** by a retro-aldol/aldol sequence (Figure 1). In this key reaction, the strained nature of the cyclobutane embedded within pentacycle **195** was expected to facilitate cleavage of the C4-C5 bond to give keto-aldehyde **194**, which could then undergo intramolecular aldol ring closure. While on first inspection, lactol **195** appears to be a complex structural framework, we hypothesized that its cyclobutane core could be constructed in a straightforward fashion by a photochemical [2+2] cycloaddition. This disconnection reduces our target to dihydroindolone **197**, a structural motif readily obtained using the previously developed sulfinimine chemistry.

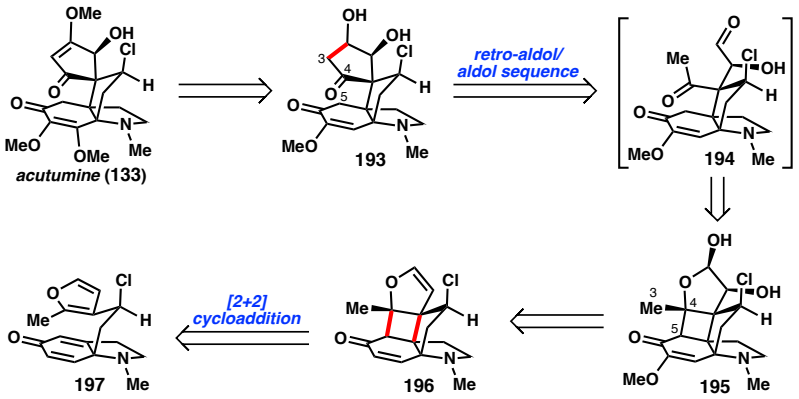


Figure 1. Retrosynthetic analysis of acutumine.

Alternatively, we recognized that isomeric dihydroindolone **202** could also be a viable intermediate en route to acutumine (Figure 2). Indeed, [2+2] cycloaddition and oxidation of this substrate would deliver diol **200**, which can undergo the retro-aldol fragmentation to afford α-hydroxyketone **199**. Intramolecular aldol reaction of **199** would

produce cyclopentanone **198**, a structural isomer of **193** also anticipated to be amenable to the synthesis of acutumine.

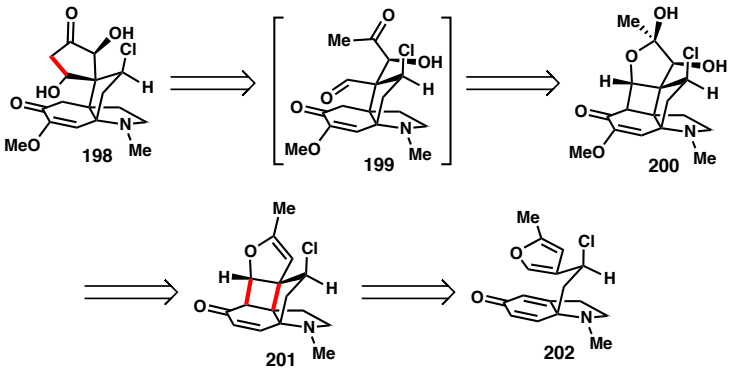


Figure 2. Alternative retro-aldol/aldol precursor.

The synthesis of dihydroindolones **197** and **202** raises questions regarding a key component to our synthetic planning: installation of the stereogenic C–Cl bond. Specifically, the preparation of **197** and **202** using our 1,2-addition methodology necessitates the use of a nucleophile bearing an appropriate functional handle to advance to the chloride. It was envisioned that addition of a furan-derived enolate (**203**) to bromosulfinimine **96c** (Figure 3). Addition of such nucleophiles to *t*-butanesulfinimines is not unprecedented: Ellman and coworkers have demonstrated that 1,2-addition of simple enolates to sulfinyl ketimines generates β-amino acid derivatives in excellent yield and diastereoselectivity.[1] If successful, the resulting ketone-containing sulfinamides could be elaborated to **197** and **202** following our previously optimized cross-coupling/acid cyclization sequence.[2,3]

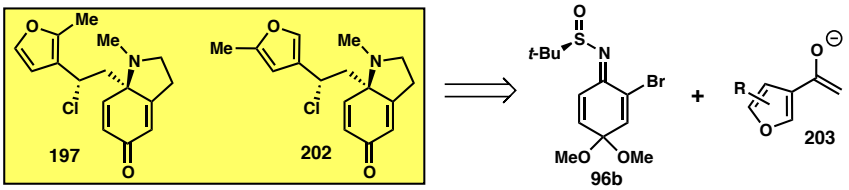


Figure 3. A diastereoselective enolate addition approach for **197** and **202**.

Alternatively, it was anticipated that the [2+2] cycloaddition/retro-aldol/aldol strategy could be assessed by exploring the synthesis of des-chloro dihydroindolones **207** and **208** (Figure 4). Importantly, these substrates were expected to be readily accessible by addition of the appropriate furan-containing Grignard reagent to bromosulfinimine **96c** and elaboration using our previously established conditions. In addition to simplifying substrate preparation, this retrosynthetic modification also presents an opportunity to evaluate a late-stage chlorination via C–H activation chemistry (**204** to **193**). While reports of C–H activation occurring at secondary positions are limited, intermediates such as **204** represent an exciting new platform to develop novel C–H functionalization reactions.

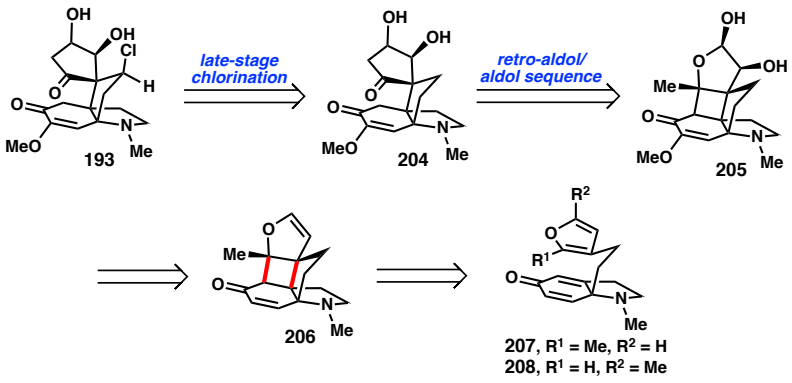


Figure 4. A late-stage chlorination approach.

4.3. Synthetic Investigations

4.3.1. An Enolate 1,2-Addition Strategy. To ascertain the potential utility of an enolate 1,2-addition strategy, initial studies sought to explore the reactivity of ketofuran **209**. We were pleased to find that exposure of **96c** to the sodium enolate of **209** at –78 °C affords sulfinamide **210** in 98% yield and excellent diastereoselectivity (Figure 5). Unfortunately, quenching the sulfinamide anion with MeI and HMPA under our previously optimized conditions[3] delivered an intractable mixture of products. Attempts to alkylate the sulfinamide in a separate step with a variety of methylating reagents revealed that **210** is unstable under basic conditions. On the other hand, cross-coupling of sulfinamide **210** with stannane **105** proceeded without incident; however, subjection of **211** to our optimal cyclization conditions (HCl, THF, 0 °C) led to significant decomposition.

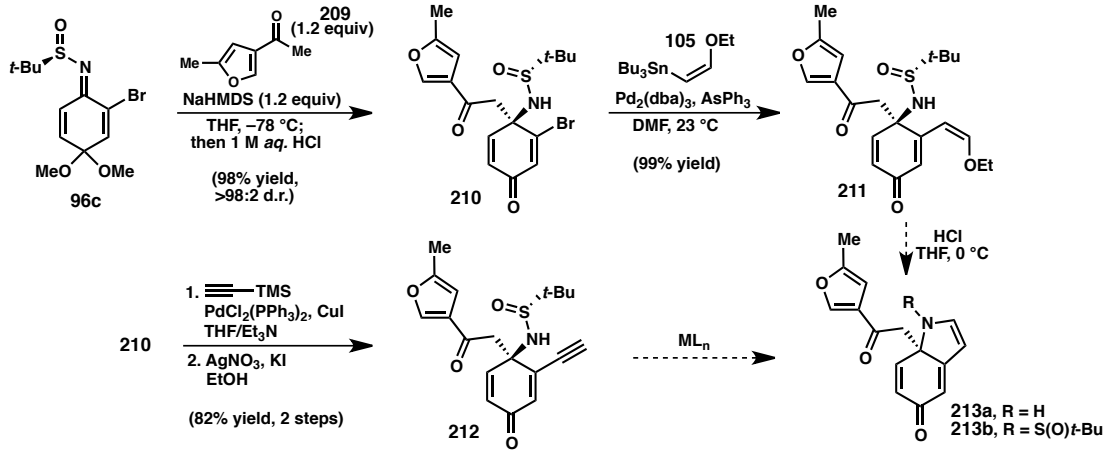


Figure 5. Attempts to prepare indolone **213**.

Moving forward, it was hypothesized that the requisite pyrrolidine ring could potentially be installed via an intramolecular hydroamination of alkyne-bearing

sulfinamide **212** (Figure 4). Importantly, a number of strategies have emerged that accomplish this type of transformation under mild reaction conditions.[4] To evaluate this approach, **212** was prepared in two steps from **210** following Sonogashira coupling with trimethylsilylacetylene and deprotection of the silyl-protected alkyne. To our dismay, attempts to promote the hydroamination with a number of transition metal catalysts only returned starting material or led to decomposition.

4.3.2. An Alkyl Grignard Addition Approach. Based on these initial challenges, we turned our attention to the preparation of des-chloro dihydroindolones **207** and **208** (Figure 6). To this end, we examined the use of furan-containing Grignard reagents **214** and **216** in the sulfinimine methodology. Exposure of bromosulfinimine **96c** to Grignard reagent **214** at –78 °C resulted in the expected 1,2-addition reaction; however, upon purification by flash chromatography, the major product was enol ether **215** (Figure 6).[5] Presumably, the mildly acidic silica gel mediates an intramolecular Friedel–Crafts conjugate addition. Although it might be possible to identify purification conditions that allow for isolation of the 1,2-addition product, the acid sensitivity of this substrate suggests it would not be amenable to pyrrolidine formation using the previously established conditions. We hypothesized that in the analogous 2,3-disubstituted furanyl substrate (**216**), the C2 methyl group should mitigate this type of reactivity and allow for isolation of the corresponding 1,2-addition product. This hypothesis was validated when, upon treatment of sulfinimine **96c** with Grignard reagent **216** followed by in situ methylation, sulfinamide **217** was isolated in 68% yield as a single diastereomer.

Sulfinamide **217** was elaborated to dihydroindolone **207** following our optimized three-step protocol for pyrrolidine formation. Thus, Pd-catalyzed cross-coupling of

sulfinamide **217** with stannane **105** proceeded smoothly to give enol ether **218**. Acid-mediated cyclization furnished an enamine intermediate, which was then selectively reduced to afford dihydroindolone **207** in 61% yield over three steps.

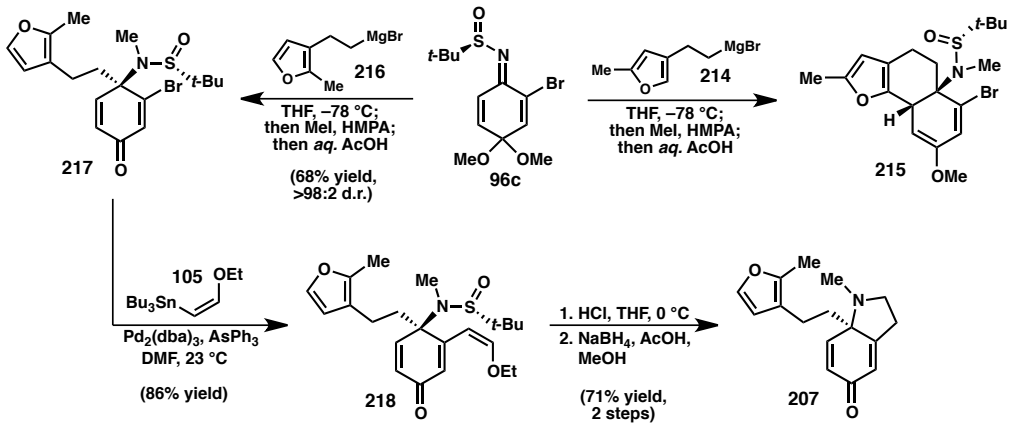


Figure 6. Preparation of a [2+2] cycloaddition substrate.

4.3.3. Evaluation of a Photo [2+2] Cycloaddition. With **207** hand, we were poised to study the key photochemical [2+2] cycloaddition reaction to establish the propellane core of acutumine. While we were confident we could obtain the desired linear [2+2] product, it was also noted we could generate the analogous crossed product, in which the cycloaddition occurs across the other face of the furan olefin (Figure 7, **206** versus **219**). Further, it was evident that issues of chemoselectivity might arise, given the different combinations of potential [2+2] coupling partners (e.g., formation of **220**).

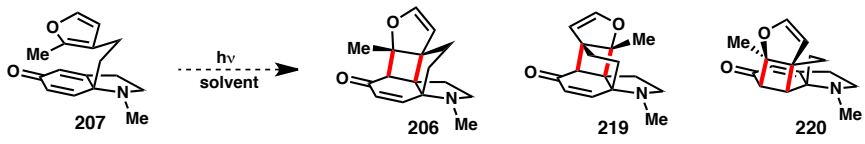


Figure 7. Possible products from photo [2+2] cycloaddition of **207**.

We nevertheless conducted a screen of photochemical reaction conditions, varying both the solvent and the irradiation wavelength.[6] Irradiation of **207** at 350 nm in benzene afforded trace amounts of the desired [2+2] product as determined by ^{1}H NMR analysis. However, following characterization by NMR and IR spectroscopy and HRMS, the major product of this reaction was assigned as diketone **223** (Figure 8). Diketone **223** is hypothesized to arise by a photolytic oxa-di-π-methane rearrangement,[7] which, following C–C bond fragmentation, generates the unstable iminium ion **222**. Nucleophilic addition of adventitious water results in iminium hydrolysis and intramolecular conjugate addition to produce **223**.

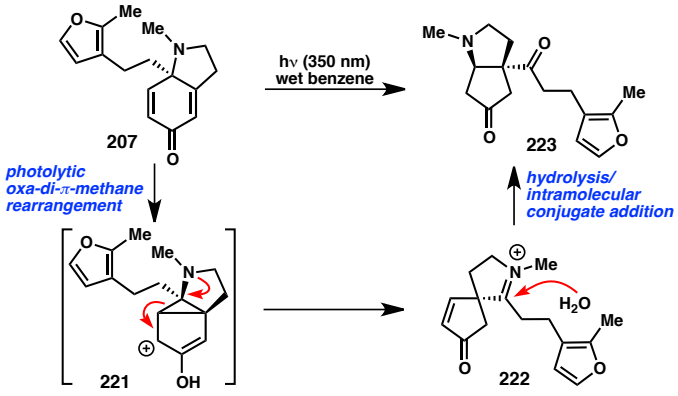


Figure 8. [2+2] photocycloaddition of dihydroindolone **207**.

To circumvent this type of undesired reactivity, the C7-C8 enone functionality was masked as its epoxide under nucleophilic epoxidation conditions (Figure 9). We were pleased to find that photochemical [2+2] cycloaddition of enone **224** proved more fruitful: a brief screen of reaction parameters revealed that irradiation of **224** at 350 nm in pentane was optimal, delivering dihydrofuran **225** in 72% yield. Notably, this reaction

exhibits a high degree of regioselectivity (for the linear vs. crossed product) and installs the vicinal all-carbon quaternary centers of acutumine in a single step.

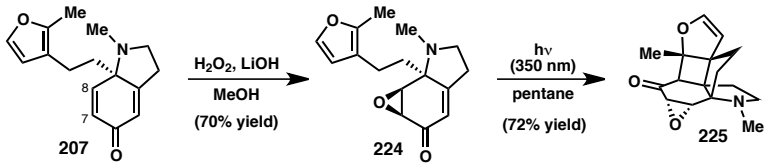


Figure 9. Photocycloaddition of epoxyenone **224**.

4.3.4. Examination of a Retro-Aldol/Aldol Reaction. Having successfully prepared the propellane core of acutumine, attention turned to investigating the second key retrosynthetic disconnection: the retro-aldol/aldol sequence. In particular, we anticipated that oxidation of dihydrofuran **225** would initially generate lactol **226** (Figure 10). At the outset of these studies, it was unclear if this lactol would be an isolable intermediate. Given the strain embedded within the cyclobutane moiety, it was hypothesized that C–C bond scission would be facile and may even occur under the oxidation conditions to deliver aldehyde **227**. Exposure of **227** to acidic or basic conditions was then expected to facilitate intramolecular aldol reaction to afford spirocyclic cyclopentanone **229**.

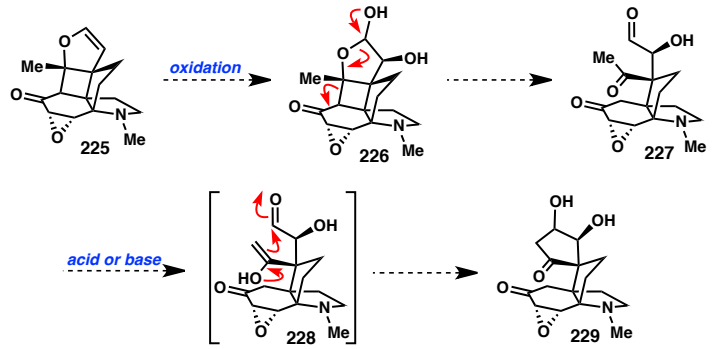


Figure 10. A retro-aldol/adol strategy for cyclopentenone synthesis.

We first examined the conversion of the dihydrofuran to a lactol-containing substrate using standard electrophilic epoxidation conditions. Whereas exposure of **225** to dimethyldioxirane, *m*-chloroperoxybenzoic acid, or simple oxaziridines led to *N*-oxidation, treatment with *N*-bromosuccinimide in aqueous THF[8] afforded bromohydrin **230** in excellent yield as a ~3:1 mixture of diastereomers at the lactol carbon (Figure 11). The bromohydrin proved to be a surprisingly stable intermediate that could be easily purified by silica gel chromatography. Single-crystal X-ray diffraction of **230** confirmed the regiochemical outcome of the photocycloaddition, which generates the linear [2+2] product. To our dismay, attempts to facilitate a retro-aldol fragmentation of **230** under mildly acidic or basic conditions led to significant decomposition and failed to produce detectable quantities of **232** or similar fragmentation products.

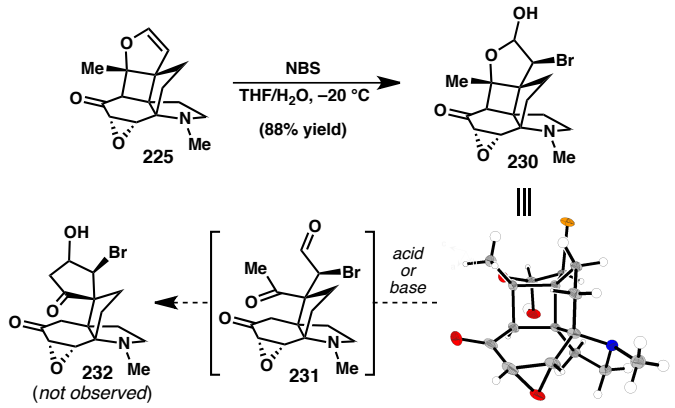


Figure 11. Attempted fragmentation of bromohydrin **230**.

In light of these results, we suspected that the epoxide moiety of **230** might be a source of undesired reactivity under our retro-aldol conditions. Thus, attention turned to the construction of dihydrofuran **234**, an intermediate in which the C7-C8 alkene has

been reduced (Figure 12). To this end, Cu-catalyzed conjugate reduction of **207** furnished enone **233**, a substrate that performed well under the previously optimized photo [2+2] reaction conditions to give dihydrofuran **234** in 71% yield. After an extensive screen of oxidation conditions, dihydrofuran **234** was found to undergo dihydroxylation under Upjohn conditions[9] to provide diol **235** in good yield. Like its bromohydrin analog, **235** proved to be remarkably stable to silica gel chromatography.

With access to lactol **235**, a number of conditions were evaluated for their ability to cleave the C4-C5 bond by a retro-aldol reaction. Unfortunately, as was observed with bromohydrin **230**, a variety of acidic or basic conditions failed to deliver the desired product. However, a benzene stock solution of diol **235** used for TLC analysis was found to slowly develop a single, new spot over the course of several days. To our surprise, isolation and single-crystal X-ray diffraction of this compound identified it as hemiketal **238**.

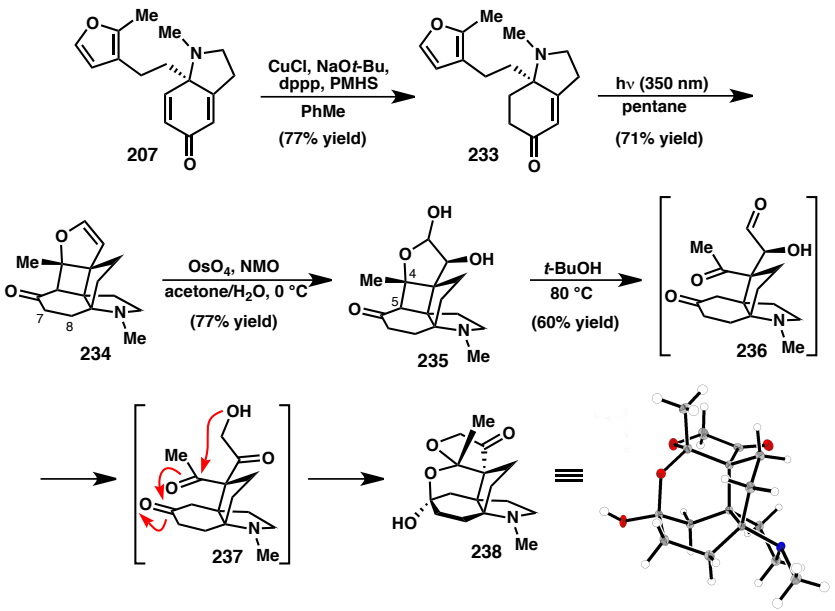


Figure 12. Isolation of ketal rearrangement product **238**.

It is proposed that aldehyde **236**, the product directly formed by retro-aldol fragmentation of **235**, readily tautomerizes to keto-alcohol **237**. Formation of this primary alcohol triggers an intramolecular cyclization cascade, leading to hemiketal **238**. A brief solvent screen identified *t*-BuOH as the optimal solvent for this rearrangement, which could be achieved in 60% yield when the reaction mixture was heated to 80 °C. Ketal **238** has thus far proven recalcitrant in our efforts toward further elaboration to **133**. Nevertheless, the isolation of **238** confirmed the viability of the [2+2] cycloaddition/retro-aldol sequence to prepare the aza-propellane core of acutumine.

4.3.5. A Lactone Fragmentation Strategy. Given the intermediacy of retro-aldol product **236**, we next sought to access an isolable cyclobutane fragmentation intermediate that could be advanced to the natural product. Specifically, it was envisioned that a deleterious tautomerization/ketalization event would be precluded in the corresponding lactone substrate (**239**, Figure 13). Indeed, nucleophilic ring opening of lactone **239** would deliver α-hydroxyester **240**, an intermediate without an accessible tautomerization pathway. Moreover, a Dieckmann cyclization between the methyl ketone and ester moieties of **240** would deliver an acutumine precursor (**241**) bearing the appropriate oxidation pattern about its cyclopentenone ring.

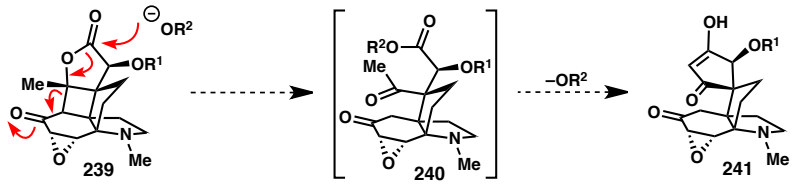


Figure 13. A retro-Dieckmann/retro-aldol approach.

The preparation of a suitable lactone substrate commenced with dihydrofuran **225** (Figure 14). Exposure of **225** to the previously identified dihydroxylation conditions delivered lactol **242** as an inconsequential 3:1 mixture of diastereomers. A screen of numerous oxidation conditions revealed that treatment with chromic acid was optimal, generating lactone **243** in 60% yield over 2 steps. Remarkably, **243** is the exclusive oxidation product formed in this reaction. At this point, we sought to protect the free alcohol of **243** as its benzyl ether; however, reaction of **243** with Cs_2CO_3 and benzyl bromide[10] (BnBr) did not afford the desired product. Instead, 1 and 2D NMR analysis identified the major product as cyclobutane **245**, which was obtained in 40% yield. It is hypothesized that this unusual product results from an initial base-mediated elimination of the lactone to deliver carboxylate anion **244**. This intermediate then reacts with BnBr and undergoes olefin isomerization to produce **245**.

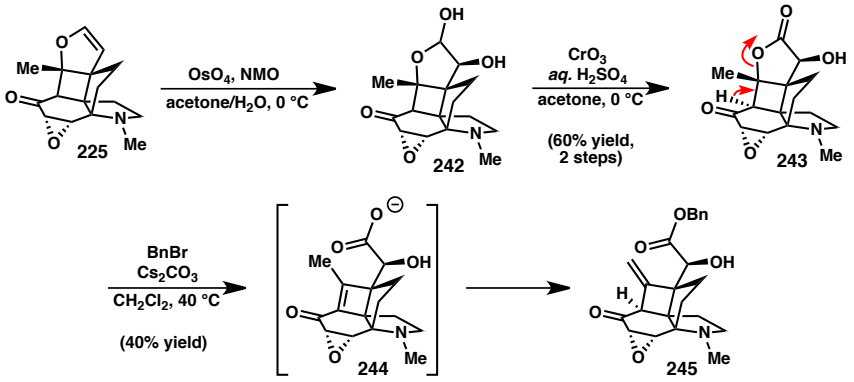


Figure 14. Isolation of cyclobutane **245**.

To mitigate the reactivity of the cyclobutane moiety, the use of more mild protection conditions was examined. To our delight, exposure of lactone **243** to TBSCl and *i*Pr_2NEt in refluxing CH_2Cl_2 furnished silyl ether **246** in 66% yield (Figure 15). With **246** in hand,

a nucleophile-mediated lactone opening/fragmentation reaction of **246** was investigated. Unfortunately, addition of numerous alcohol, amine, and thiol nucleophiles to **246** failed to give the desired product; under most reaction conditions, a complex mixture of products was observed. Interestingly, treatment of lactone **246** with K_2CO_3 in MeOH cleanly afforded a single product by ^{1}H NMR. Isolation and extensive 2D NMR characterization revealed the product to be ketal **248**. It is proposed that methanolysis of **246** generates epoxyketone **247**, which reacts further in a methoxide-mediated cyclization cascade to provide the observed ketal product.[11]

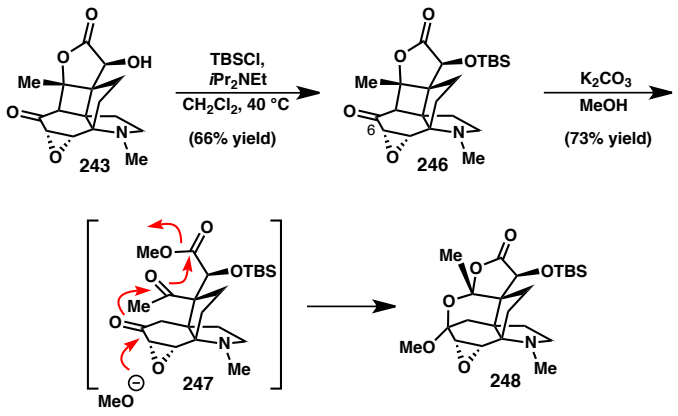


Figure 15. Fragmentation of lactone **246**.

The formation of **248** is not unlike the rearrangement observed in the retro-aldol fragmentation of **235** (see Figure 12): in both transformations, the electrophilicity of the C6 ketone enables the formation of thermodynamically stable ketal products. Moving forward, it was hypothesized that preparation of a lactone substrate bearing a tethered nucleophile could facilitate the desired fragmentation reaction under more mild reaction conditions, thereby attenuating the reactivity of the resulting epoxyketone intermediate.

To this end, carbamate **249** was prepared by exposure of **243** to ethyl isocyanate and DMAP in MeCN (Figure 16). We were pleased to find that addition of K_2CO_3 to a solution of **249** in MeOH generates the carbamate anion, which triggers a lactone opening/retro-aldol sequence to initially deliver diketone **251**; unfortunately, this intermediate readily undergoes intramolecular aldol ring closure to produce **252** in 75% yield.

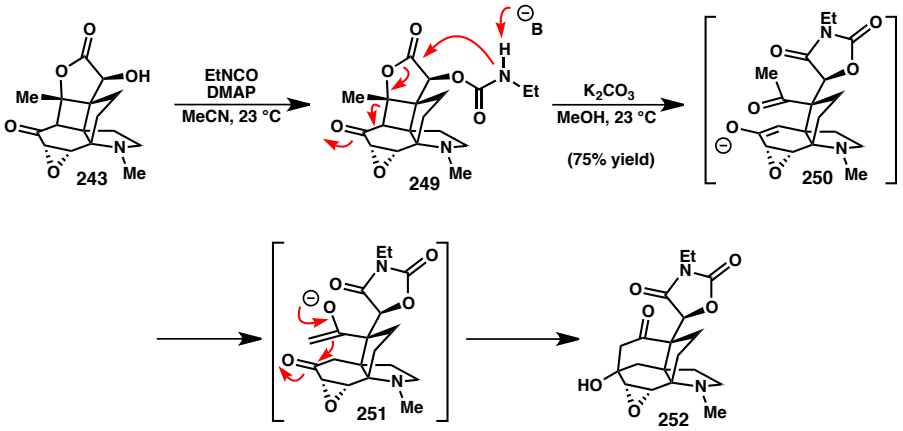


Figure 16. Functionalization of carbamate-tethered lactone **249**.

Taken collectively, our attempts to prepare the cyclopentenone of acutumine via base-mediated cyclization reactions illustrate that the C6 ketone is too reactive under a number of conditions. To circumvent these challenges, we examined a one-pot fragmentation/silylation of **249** in which the transiently formed enolate (**250**) could be trapped as its silyl ether. To our delight, exposure of **249** to LiHMDS followed by addition of HMPA and TBSOTf at –78 °C afforded silyl enol ether **253** in 63% yield (Figure 17). With Dieckmann cyclization precursor **253** in hand, a small screen of reaction parameters was conducted. Under carefully optimized conditions, methyl ketone

253 could be converted to spirocycle **254** using 1.1 equivalents of KO*t*-Bu in THF at –20 °C. Notably, **254** possesses the carbocyclic core of acutumine and presents appropriate functional handles to elaborate to the natural product.

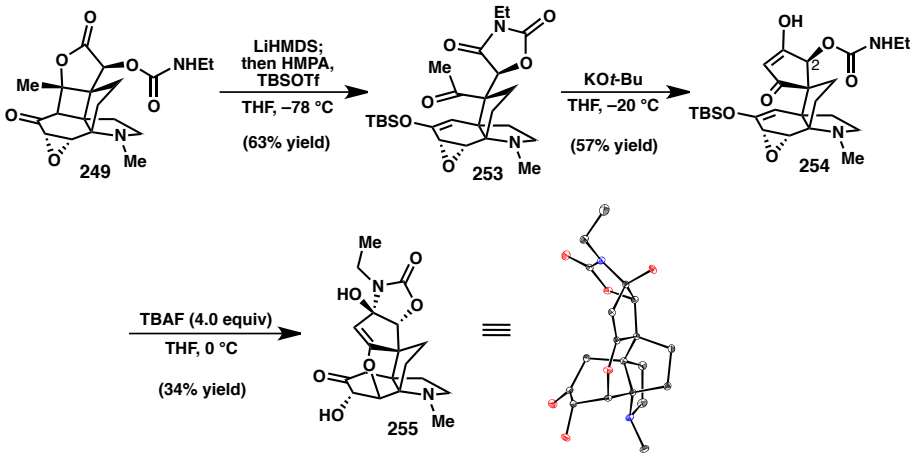


Figure 17. Construction of the carbocyclic core of acutumine.

Spirocycle **254** represents our most advanced intermediate in our synthesic efforts toward acutumine. While we were pleased with our ability to access the acutumine framework, we sought to corroborate our structural assignment by X-ray analysis of a cyclopentenone-containing intermediate. Toward this goal, treatment of **254** with excess TBAF afforded a new, crystalline solid in 34% yield. Single crystal X-ray diffraction of this compound confirmed the formation of hexacyclic aminal **255**. In addition to undergoing the desired desilylation reaction, this peculiar product results from (1) intramolecular epoxide opening by the enol of the cyclopentenone, (2) epimerization of the C2 carbinol, and (3) cyclization of the carbamate onto the enone carbonyl. Although this type reactivity was not expected, the formation of **255** ultimately presents a potential

avenue by which to elaborate the epoxide of **254** to the dimethoxyenone of the natural product.

4.4. Future Directions

Having prepared spirocycle **254**, our immediate objective is to advance this intermediate to dechloroacutumine (**134**, Figure 18). As such, exposure of enol ether **249** to mild methylation conditions should deliver methoxyenone **256**. Oxidative epoxide opening[12] of this intermediate should give an α-hydroxy ketone, which upon exhaustive methylation is expected to yield diene **257**. Finally, desilyation and deprotection of the carbamate should deliver **134**.

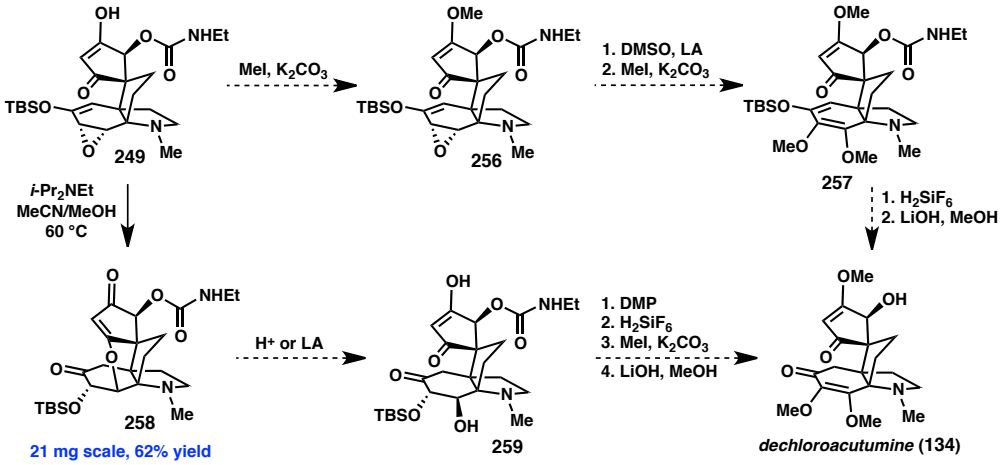


Figure 18. Proposed end-game strategy for dechloroacutumine.

In the event this synthetic route proves unsuccessful, we envision pursuing an alternative strategy that takes advantage of the reactivity observed in the formation of **255** (see Figure 17). Specifically, preliminary studies have demonstrated that exposure of **249** to *i*-Pr$_2$NEt in MeCN/MeOH at 60 °C facilitates an intramolecular epoxide opening

reaction to give pentacycle **258** in 56% isolated yield (Figure 18). To advance this intermediate to **134**, Brønsted or Lewis acid-mediated hydrolysis of the enol ether will furnish alcohol **259**. This intermediate can undergo an oxidation/desilylation/methylation sequence to install the dimethoxyenone, followed by carbamate deprotection to yield the natural product.

In accord with the long-term goals of this project, we also plan to thoroughly investigate installation of the stereogenic chloride. While our preliminary studies regarding an early-stage C–Cl bond formation were not fruitful, we have begun to pursue alternative [2+2] substrates using the enolate 1,2-addition protocol described in section 4.3.1. Alternatively, we are poised to exploit the carbamate functionality of **249** to implement a directed, late-stage C–H activation reaction for chloride installation.[13] In this regard, our synthesis is amenable to the preparation of a number of directing group-bearing substrates from the divergent functionalization of lactone **243**.

4.5. Concluding Remarks

In summary, we have developed a synthesis of the carbocyclic framework of acutumine in only 12 steps from commercially available starting materials. Key to the success of our approach is a photochemical [2+2] cycloaddition to install the vicinal all-carbon quaternary stereocenters and a lactone fragmentation/Dieckmann cyclization sequence to construct the spirocyclic cyclopentenone. These investigations were ultimately enabled by the versatility of our highly diastereoselective 1,2-addition reaction. Notably, by changing the nature of the nucleophile employed, we have the power to explore a number of different strategies en route to acutumine. We are confident

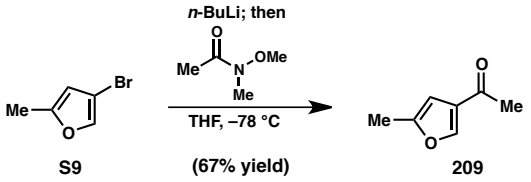
the studies discussed above will lead to the construction of more appropriately oxidized propellane intermediates, which will facilitate our synthetic endeavors towards the completion of the natural product.

4.6. Experimental Section

4.6.1. Materials and Methods. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), acetonitrile (MeCN), and toluene (PhMe) were dried by passing through activated alumina columns. MeOH was distilled over magnesium oxide and triethylamine (Et_3N) was 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, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al. (Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925) using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to internal $CHCl_3$ (^{1}H, δ = 7.26; ^{13}C, δ = 77.0). Data for ^{1}H 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), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

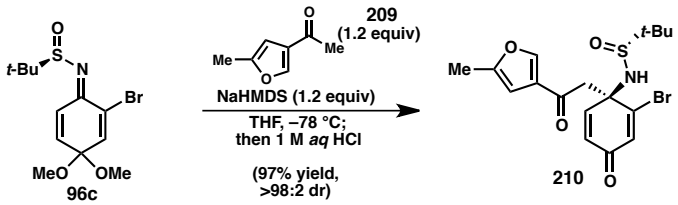
4.6.2. Procedures and Spectroscopic Data

Preparation of ketofuran 209.



To a solution of **S9**[14] (343 mg, 2.13 mmol) in THF (7 mL) at –78 °C was added *n*-BuLi (0.93 mL, 2.29 M solution in Hexanes, 2.13 mmol) dropwise by syringe. The resulting pale yellow solution was stirred 10 minutes at –78 °C, then *N*-methoxy-*N*-methylacetamide (226 μL, 2.13 mmol) was added dropwise by syringe. The reaction was allowed to stir at –78 °C for 2 hours, then quenched by the addition of a solution of AcOH (150 μL) in Et_2O (5 mL). The reaction was removed from the –78 °C bath, water (4 mL) was added, and was allowed to warm to room temperature. The organic layer was washed with with water (2 x 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure, *being careful to keep the pressure above ~120 torr*. The crude material was purified by flash chromatography (10 to 20% Et_2O in Pentane) to afford ketofuran **209** (178 mg, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 6.33 (t, J = 1.0 Hz, 1H), 2.38 (s, 3H), 2.29 (d, J = 1.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.7, 154.3, 146.2, 128.9, 104.2, 27.52, 13.37. FTIR (NaCl, thin film) 3127, 2925, 1678, 1544, 1395, 1354, 1296, 1142, 936, 910, 824 cm^{-1}.

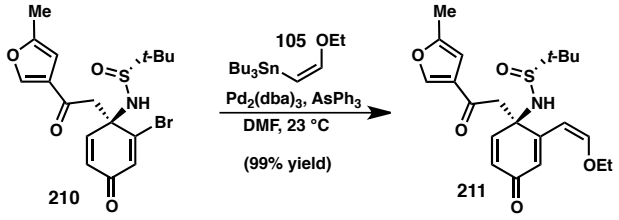
Preparation of sulfinamide 210.



To a solution of **209** (247 mg, 1.99 mmol) in THF (6 mL) at –78 °C was added a solution of NaHMDS (0.9 M solution in THF, 2.2 mL, 2.0 mmol) dropwise by syringe. The reaction was allowed to stir 1 hour at –78 °C, then a solution of **96b** (558 mg, 1.66 mmol) in THF (1 mL) was added dropwise by syringe. The resulting orange solution was stirred at –78 °C for 3 hours, then quenched by the addition of 1 N HCl (8 mL). The

reaction was warmed to room temperature and stirred vigorously for 20 minutes. The reaction mixture was diluted with EtOAc (30 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a tan oil. The diastereoselectivity was determined to be >98:2 by ^{1}H NMR. Flash chromatography (40% to 60% EtOAc in Hexanes) afforded sulfinamide **210** (667 mg, 97% yield) as a pale yellow foam. $[\alpha]_D^{25}$ –92.3° (*c* 0.88, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.0 Hz, 1H), 7.38 (d, *J* = 10.1 Hz, 1H), 6.85 (d, *J* = 1.8 Hz, 1H), 6.33 (t, *J* = 1.1 Hz, 1H), 6.30 (dd, *J* = 10.1, 1.8 Hz, 1H), 5.99 (s, 1H), 3.47 (d, *J* = 16.2 Hz, 1H), 2.93 (d, *J* = 16.2 Hz, 1H), 2.31 (d, *J* = 1.1 Hz, 3H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.3, 182.8, 155.3, 150.5, 148.5, 147.1, 135.7, 128.5, 126.7, 103.9, 60.6, 57.1, 47.5, 22.7, 13.4. FTIR (NaCl, thin film) 3246, 2960, 2924, 1670, 1599, 1543, 1293, 1144, 1070, 956, 910, 731 cm^{-1}; HRMS (ESI+) calc'd for $C_{17}H_{20}NO_4SBr$ $[M+H]^+$ 416.0369, found 416.0373.

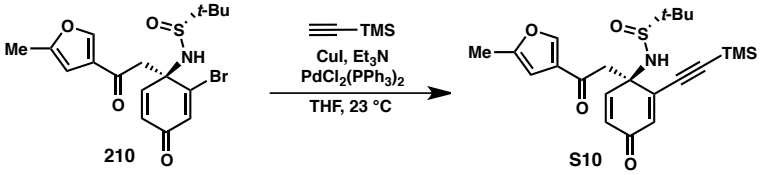
Preparation of enol ether 211.



To a solution of sulfinamide **210** (100 mg, 0.24 mmol) in DMF (2.4 mL) was added $Pd_2(dba)_3$ (11 mg, 0.012 mmol), $AsPh_3$ (15 mg, 0.048 mmol) and stannane **105** (0.089 mL, 0.27 mmol). The solution was degassed with N_2 for 30 minutes, then stirred at room temperature for an additional 30 minutes. The solution was passed through a short plug of Celite, diluted with EtOAc (20 mL), and washed with H_2O (3 x 10 mL). The combined aqueous layers were back extracted with EtOAc (20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a brown oil. Flash chromatography (50% to 75% EtOAc in Hexanes) gave enol ether **211** (97 mg, 99% yield) as an inseparable mixture of >1:10 E/Z isomers. $[\alpha]_D^{25}$ –93.0° (*c* 0.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 0.9 Hz, 1H), 7.18–7.13 (m, 2H), 6.58 (d, *J* = 7.2 Hz, 1H), 6.31 (t, *J* = 1.0 Hz, 1H), 6.22 (dd, *J* = 10.2, 2.0 Hz,

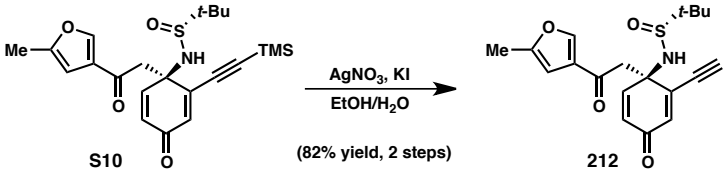
1H), 5.94 (s, 1H), 5.05 (d, J = 7.2 Hz, 1H), 4.12–4.00 (m, 2H), 3.13 (d, J = 16.1 Hz, 1H), 2.85 (d, J = 16.0 Hz, 1H), 2.29 (d, J = 1.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.25 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.6, 186.2, 155.1, 154.1, 152.2, 150.1, 147.1, 128.7, 127.6, 127.4, 104.0, 99.4, 70.8, 58.3, 56.4, 48.3, 22.7, 15.4, 13.4. FTIR (NaCl, thin film) 3245, 2979, 2926, 1654, 1624, 1577, 1543, 1388, 1326, 1290, 1144, 1101, 1058, 911, 897, 731 cm^{-1}; HRMS (ESI+) calc'd for $C_{21}H_{27}NO_5S$ $[M+H]^+$ 406.1683, found 406.1682.

Preparation of enyne S10.



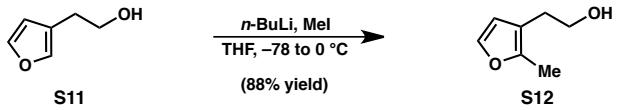
A round bottom flask was charged with sulfinamide **210** (300 mg, 0.724 mmol), $PdCl_2(PPh_3)_2$ (25 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol), and THF (3.5 mL). The resulting yellow solution was degassed with N_2 for 20 minutes. Then, Et_3N (3.5 mL) and ethynyltrimethylsilane (113 μL, 0.797 mmol) were sequentially added, and the reaction mixture was allowed to stir 1 hour at room temperature. The mixture was filtered through Celite, rinsed with EtOAc, and concentrated under reduced pressure to give a yellow oil. The crude product was used in the following step without further purification. A small sample was purified by flash chromatography (40 to 75% EtOAc in Hexanes) for characterization purposes: $[\alpha]_D^{25}$ –61.3° (*c* 0.72, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.20 (d, J = 10.3 Hz, 1H), 6.56 (d, J = 2.0 Hz, 1H), 6.33 (s, 1H), 6.26 (dd, J = 10.3, 2.0 Hz, 1H), 5.84 (s, 1H), 3.41 (d, J = 16.1 Hz, 1H), 2.95 (d, J = 16.1 Hz, 1H), 2.31 (s, 3H), 1.26 (s, 9H), 0.21 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.8, 184.4, 155.2, 150.5, 147.1, 141.6, 135.3, 128.7, 127.6, 108.1, 104.0, 100.5, 58.3, 56.6, 47.6, 22.7, 13.4, -0.5. FTIR (NaCl, thin film) 3245, 2959, 1661, 1544, 1390, 1311, 1251, 1144, 1068, 897, 847, 761 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{29}NO_4SiS$ $[M+H]^+$ 432.1659, found 432.1664.

Preparation of enyne 212.



To a solution of **S10** (0.724 mmol) in EtOH (48 mL) and H_2O (12 mL) was added $AgNO_3$ (148 mg, 0.869 mmol). The reaction was allowed to stir for 3 hours, then KI (156 mg, 0.941 mmol) was added, and the reaction was stirred for an additional 30 minutes. The resulting mixture was filtered through Celite, rinsed with EtOAc, concentrated under reduced pressure, and purified by flash chromatography (50 to 75% EtOAc in Hexanes) to afford enyne **212** (213 mg, 82% yield) as pale brown solid. $[\alpha]_D^{25}$ –84.2° (*c* 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.0 Hz, 1H), 7.25 (d, *J* = 10.3 Hz, 1H), 6.62 (d, *J* = 1.9 Hz, 1H), 6.33 (t, *J* = 1.0 Hz, 1H), 6.28 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.86 (s, 1H), 3.54 (d, *J* = 0.6 Hz, 1H), 3.47 (d, *J* = 16.3 Hz, 1H), 2.97 (d, *J* = 16.3 Hz, 1H), 2.31 (d, *J* = 1.1 Hz, 3H), 1.26 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.5, 184.1, 155.2, 150.7, 147.0, 140.8, 136.16, 128.5, 127.5, 103.9, 88.9, 79.7, 58.3, 56.7, 47.4, 22.6, 13.4. FTIR (NaCl, thin film) 3246, 2961, 2093, 1662, 1624, 1543, 1391, 1313, 1287, 1144, 1063, 909, 731 cm^{-1}; HRMS (ESI+) calc'd for $C_{19}H_{21}NO_4S$ $[M+H]^+$ 360.1264, found 360.1262.

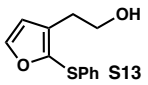
Synthesis of furanyl alcohols:



Preparation of alcohol S12. To a solution of 2-(3-furanyl)ethanol[15] (**S11**) (1.85 g, 16.5 mmol) in THF (80 mL) at –78 °C was added *n*-BuLi (2.32 M solution in Hexanes, 14.2 mL, 33.0 mmol) dropwise by syringe, and the resulting solution was allowed to stir at –78 °C for 30 minutes. Upon warming to 0 °C and stirring an additional 30 minutes, MeI (2.1 mL, 33.0 mmol) was added dropwise by syringe. The reaction mixture was allowed to stir 1 hour at 0 °C, then quenched by the addition of H_2O (30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography

(25% EtOAc in Hexanes) to afford alcohol **S12** (1.83 g, 88% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 1.4 Hz, 1H), 6.22 (d, *J* = 1.2 Hz, 1H), 3.74 (t, *J* = 6.5 Hz, 2H), 2.60 (t, *J* = 6.5 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 140.2, 114.9, 111.4, 62.7, 28.3, 11.5; FTIR (NaCl, thin film) 3400, 2921, 1740, 1512, 1374, 1202, 1166, 1129, 1046, 939, 893, 731 cm^{-1}; HRMS (ESI+) calc'd for $C_7H_{10}O_2$ $[M+H]^+$ 126.0681, found 126.0649.

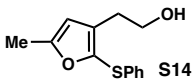
Preparation of furanyl alcohol S13.



S13

Prepared from 8.92 mmol of 2-(3-furanyl)ethanol (**S11**) using the above general procedure with diphenyl disulfide (3.89 g, 17.8 mmol) as the electrophile (added in one solid portion). The crude product was purified by flash chromatography (25% EtOAc in Hexanes) to give alcohol **S13** (1.78 g, 75% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 2.0 Hz, 1H), 7.28–7.21 (m, 2H), 7.21–7.11 (m, 1H), 7.14–7.06 (m, 2H), 6.50 (d, *J* = 2.0 Hz, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 2.81 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 140.1, 136.7, 130.2, 129.1, 126.9, 126.1, 112.9, 62.4, 29.3; FTIR (NaCl, thin film) 3338, 2947, 2879, 1582, 1478, 1440, 1142, 1067, 1024, 890, 738 cm^{-1}; HRMS (ESI+) calc'd for $C_{12}H_{12}O_2S$ $[M+H]^+$ 221.0631, found 221.0627.

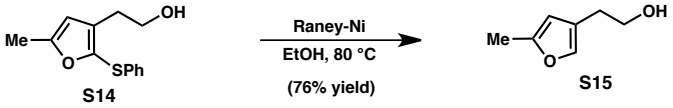
Preparation of furanyl alcohol S14.



S14

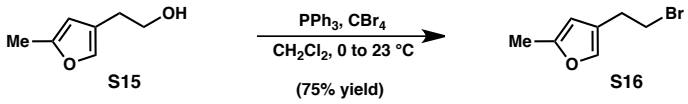
Prepared from 6.81 mmol of alcohol **S13** using the above general procedure. The crude product was purified by flash chromatography (25% EtOAc in Hexanes) to give alcohol **S14** (1.43 g, 89% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 7.17 – 7.12 (m, 1H), 7.12 – 7.07 (m, 2H), 6.11 (d, *J* = 1.1 Hz, 1H), 3.76 (q, *J* = 6.2 Hz, 2H), 2.75 (t, *J* = 6.5 Hz, 2H), 2.32 (d, *J* = 1.0 Hz, 3H), 1.42 (t, *J* = 5.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 137.34, 137.33, 131.8, 129.0, 126.50, 125.9, 109.3, 62.5, 29.4, 14.1. FTIR (NaCl, thin film) 3338, 2947, 2923, 2878, 1605, 1583, 1478, 1440, 1248, 1116, 1048, 1024, 956, 808, 739 cm^{-1}; HRMS (ESI+) calc'd for $C_{13}H_{14}O_2S$ $[M+H]^+$ 235.0787, found 235.0791.

Preparation of furanyl alcohol S15.



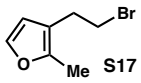
To a solution of furanyl alcohol **S14** (775 mg, 3.31 mmol) in EtOH (50 mL) was added Raney-Ni (1.50 g, 200 wt %), and the resulting suspension was heated to 80 °C. The reaction was allowed to stir a total of 2 hours and 30 minutes at 80 °C, adding additional portions of Raney-Ni (1.50 g, 200 wt %) every 30 minutes (for a total of 6 g Raney-Ni). The reaction was cooled to room temperature, filtered through a pad of Celite®, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (25% EtOAc in Hexanes) to provide alcohol **S15** (319 mg, 76% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, J = 1.0 Hz, 1H), 5.90 (t, J = 1.1 Hz, 1H), 3.75 (t, J = 6.3 Hz, 2H), 2.62 (td, J = 6.4, 0.9 Hz, 2H), 2.26 (d, J = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 138.0, 122.0, 107.0, 62.4, 28.4, 13.5. FTIR (NaCl, thin film) 3367, 2922, 2880, 1617, 1554, 1448, 1383, 1266, 1119, 1050, 1021, 920, 805 cm^{-1}; HRMS (ESI+) calc'd for $C_7H_{10}O_2$ $[M+H]^+$ 126.0681, found 126.0635.

Synthesis of furanyl bromide substrates:



Preparation of bromide S16. To a solution of alcohol **S15** (318 mg, 2.52 mmol) and CBr_4 (1.00 g, 3.02 mmol) in CH_2Cl_2 (11 mL) at 0 °C was added PPh_3 (793 mg, 3.02 mmol) in one portion. The resulting solution was allowed to stir at 0 °C for 5 minutes, then warmed to room temperature and stirred an additional 30 minutes. The reaction mixture was dry loaded onto silica gel (6 g) and purified by flash chromatography (0 to 2% Et_2O in Hexanes) to give bromide **S16** (360 mg, 75% yield) as a colorless oil. Bromide **S6** is a fairly unstable intermediate and was immediately converted to its Grignard reagent upon preparation.

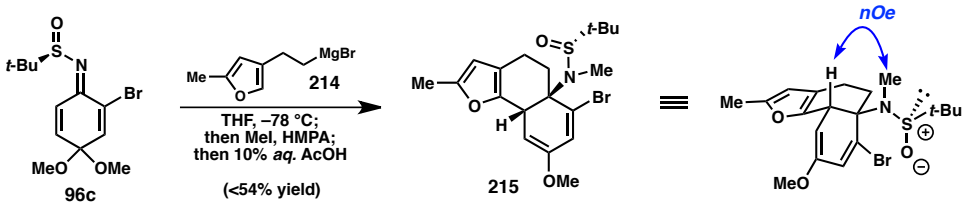
Preparation of bromide S17.



Prepared from 14.5 mmol alcohol **S12** using the above general procedure. The reaction mixture was dry loaded onto silica gel (40 g) and purified by flash chromatography (0 to 2% Et_2O in Hexanes) to give bromide **S17** (1.91

g, 70% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 1.9 Hz, 1H), 6.23 (d, *J* = 1.9 Hz, 1H), 3.46 (t, *J* = 7.5 Hz, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 140.2, 116.2, 111.0, 32.6, 28.9, 11.5. FTIR (NaCl, thin film) 2922, 2860, 1624, 1513, 1449, 1437, 1281, 1224, 1156, 1135, 939, 893, 731 cm^{-1}; HRMS (ESI+) calc'd for C_7H_9OBr $[M+H]^+$ 187.9837, found 187.9830.

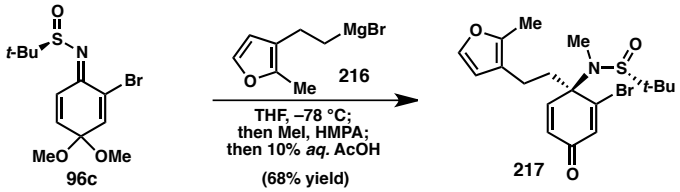
Preparation of enol ether 215.



To a solution of sulfinimine **96c** (71 mg, 0.21 mmol) in THF (0.4 mL) at –78 °C was added a solution of Grignard reagent **214** (0.5 M solution in THF, 0.47 mL, 0.23 mmol)[16] dropwise by syringe. The resulting solution was then stirred at –78 °C for 1 hour, then MeI (39 μL, 0.63 mmol) and HMPA (110 μL, 0.63 mmol) were sequentially added dropwise by syringe, and the solution stirred at –78 °C for ten minutes. The reaction was then warmed to 23 °C and stirred for 12 hours, then quenched by the addition of aqueous AcOH (10% v/v, 0.8 mL). After 3 hours, the mixture was diluted with EtOAc (10 mL) and washed with H_2O (3 x 4 mL). The aqueous layer was back extracted with EtOAc (10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (25% to 60% EtOAc in Hexanes) to afford tricycle **215** (49 mg, 54% yield) as a pale yellow foam. The purified intermediate co-eluted with ~10% of an unidentified impurity. A small sample was further purified by preparative TLC (40% EtOAc in Hexanes) for characterization purposes: $[\alpha]_D^{25}$ +431.4° (c = 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (d, *J* = 2.1 Hz, 1H), 5.75 (d, *J* = 1.1 Hz, 1H), 5.12 (dd, *J* = 6.2, 2.2 Hz, 1H), 3.82 (d, *J* = 6.2 Hz, 1H), 3.56 (s, 3H), 2.64 (dt, *J* = 13.0, 4.0 Hz, 1H), 2.58 (s, 3H), 2.56–2.50 (m, 1H), 2.39 (dt, *J* = 16.2, 3.7 Hz, 1H), 2.22 (s, 3H), 2.03 (ddd, *J* = 12.9, 10.6, 5.1 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 150.9, 147.3, 132.0, 127.6, 116.6, 105.6, 93.8, 66.5, 59.0, 54.8, 39.2, 32.6, 26.4, 24.6, 19.0, 13.6; FTIR (NaCl, thin film) 2952, 2922, 2863, 1657, 1577, 1453, 1362, 1251, 1218,

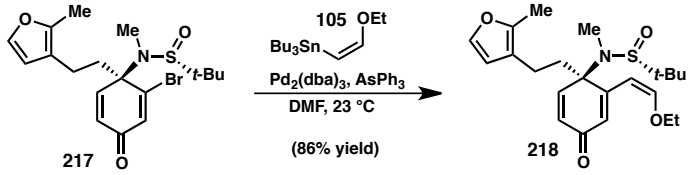
1175, 1072, 1024, 950, 806, 736 cm^{-1}; HRMS (ESI+) calc'd for $C_{19}H_{26}NO_3SBr$ $[M+H]^+$ 428.0897, found 428.0890.

Preparation of sulfinamide 217.



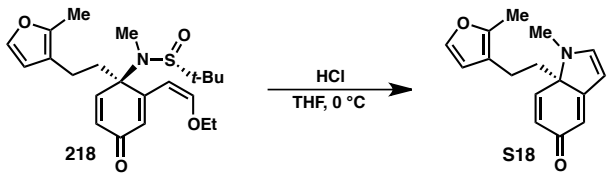
To a solution of sulfinimine **96c** (2.22 g, 6.60 mmol) in THF (13 mL) at –78 °C was added a solution of Grignard reagent **216** (0.64 M solution in THF, 12.4 mL, 7.92 mmol) dropwise by syringe. The solution was then stirred at –78 °C for 1 hour, then MeI (1.2 mL, 19 mmol) and HMPA (3.3 mL, 19 mmol) were sequentially added dropwise by syringe, and the solution stirred at –78 °C for 10 minutes. The solution was then warmed to 23 °C and stirred for 12 hours, then quenched by the addition of aqueous AcOH (10% v/v, 30 mL). After 3 hours, the mixture was diluted with Et_2O (40 mL) and washed with H_2O (3 x 20 mL). The aqueous layer was back extracted with Et_2O (50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale brown oil. The diastereoselectivity was determined to be >98:2 by ^1H NMR. Flash chromatography (20% to 60% EtOAc in Hexanes) afforded sulfinamide **217** as a pale yellow foam (1.76 g, 68% yield). $[\alpha]_D^{25}$ +6.4° (*c* 0.98, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 1.8 Hz, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 6.80 (d, *J* = 10.0 Hz, 1H), 6.44 (dd, *J* = 10.0, 1.8 Hz, 1H), 6.14 (d, *J* = 1.8 Hz, 1H), 2.71 (ddd, *J* = 12.9, 11.4, 5.6 Hz, 1H), 2.46 (s, 3H), 2.16 (s, 3H), 2.13–2.02 (m, 2H), 1.73 (ddd, *J* = 12.9, 11.6, 5.7 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 150.7, 150.0, 147.6, 140.2, 136.4, 129.7, 116.6, 111.1, 68.7, 59.2, 36.9, 26.7, 24.2, 19.5, 11.5; FTIR (NaCl, thin film) 2923, 1669, 1594, 1296, 1271, 1139, 1076, 949, 893 cm^{-1}; HRMS (ESI+) calc'd for $C_{18}H_{24}NO_3SBr$ $[M+H]^+$ 414.0733, found 414.0729.

Preparation of trienone 218.



To a solution of sulfinamide **218** (1.50 g, 3.61 mmol) in DMF (20 mL) was added $Pd_2(dba)_3$ (170 mg, 0.18 mmol), $AsPh_3$ (220 mg, 0.72 mmol) and stannane **105** (1.32 mL, 3.97 mmol). The solution was degassed with N_2 for 30 minutes, then stirred at room temperature for an additional 30 minutes. The solution was passed through a short plug of Celite, diluted with EtOAc (100 mL), and washed with H_2O (3 x 40 mL). The combined aqueous layers were back extracted with EtOAc (100 mL), and the organic layers were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a brown oil. The product was obtained as a >10:1 mixture of *Z*:*E* olefin isomers. Flash chromatography (50% to 100% EtOAc in Hexanes) afforded enol ether **218** (1.26 g, 86% yield) as a tan foam. $[\alpha]_D^{25}$ –72.1° (c = 1.31, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 1.9 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 6.60 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 10.0 Hz, 1H), 6.36 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.09 (d, *J* = 1.8 Hz, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 4.08–3.99 (m, 2H), 2.43 (s, 3H), 2.37 (ddd, *J* = 12.7, 11.2, 5.7 Hz, 1H), 2.10 (s, 3H), 2.09–2.03 (m, 2H), 1.75 (ddd, *J* = 12.6, 11.2, 5.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6, 154.7, 153.5, 149.4, 147.3, 139.9, 130.5, 128.9, 117.4, 111.2, 98.7, 70.7, 66.5, 58.9, 37.2, 27.1, 24.5, 24.4, 19.5, 15.4, 11.3; FTIR (NaCl, thin film) 2974, 2925, 1660, 1622, 1576, 1456, 1384, 1264, 1122, 1068, 954, 893 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{31}NO_4S$ $[M+H]^+$ 406.2047, found 406.2044.

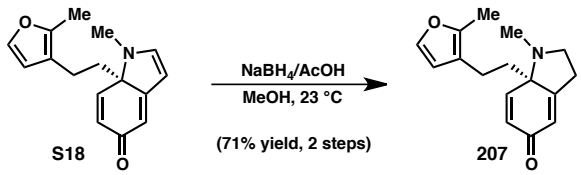
Preparation of enamine S18.



To a solution of enol ether **218** (778 mg, 1.92 mmol) in THF (38 mL) at 0 °C was added a solution of HCl (2.0 M solution in Et_2O, 19 mL, 38 mmol) dropwise by syringe over 1 minute. The reaction was allowed to stir an additional 2 minutes at 0 °C and

quenched by the addition of aqueous NaOH (10% w/v, 25 mL). The reaction was warmed to room temperature and stirred for an additional 5 minutes. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude enamine **S18** as a red oil, which was used immediately in the following step without further purification. A small sample was purified by flash chromatography (15 to 100% EtOAc in CH_2Cl_2) for characterization purposes: $[\alpha]_D^{25}$ –1847.5° (c = 0.63, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 1.8 Hz, 1H), 6.96 (dd, *J* = 9.8, 0.6 Hz, 1H), 6.88 (d, *J* = 3.3 Hz, 1H), 6.14 (dd, *J* = 9.8, 1.6 Hz, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.86 (d, *J* = 1.6 Hz, 1H), 5.45 (dd, *J* = 3.3, 0.4 Hz, 1H), 3.03 (s, *J* = 4.5 Hz, 3H), 2.20–2.07 (m, 2H), 2.11 (s, 3H), 1.96 – 1.89 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7, 174.5, 153.4, 147.4, 140.0, 139.9, 131.1, 116.7, 111.1, 109.8, 99.6, 72.5, 44.2, 31.5, 18.5, 11.3. FTIR (NaCl, thin film) 2918, 1630, 1568, 1516, 1314, 1246, 1138, 1088, 1041, 884, 830 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{17}NO_2$ $[M+H]^+$ 256.1332, found 256.1332.

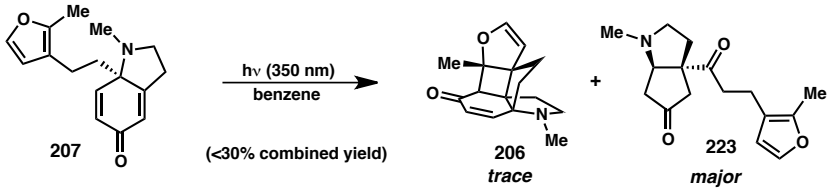
Preparation of dihydroindolone 207.



To a solution of crude enamine **S18** (1.92 mmol) in MeOH (38 mL) was added a premixed solution of $NaBH_4$ (145 mg, 3.84 mmol) in AcOH (13 mL), dropwise by syringe. The solution was stirred at room temperature for 1 hour, then another portion of $NaBH_4$ (145 mg, 3.84 mmol) in AcOH (13 mL) was added. After stirring an additional 30 minutes, the reaction was slowly poured into a solution of KOH (50% w/v, 60 mL) at 0 °C. The mixture was then diluted and extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (50 to 100% EtOAc in CH_2Cl_2) to afford dihydroindolone **207** (349 mg, 71% yield, 2 steps) as a red oil. $[\alpha]_D^{25}$ +54.6° (c = 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 10.0 Hz, 1H), 6.32 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.18 (dt, *J* = 3.3, 1.6 Hz, 1H), 6.10 (d, *J* = 1.9 Hz,

1H), 3.17 (ddd, *J* = 10.5, 8.3, 4.6 Hz, 1H), 3.07–2.99 (m, 1H), 2.77 – 2.69 (m, 2H), 2.40 (s, 3H), 2.16–2.05 (m, 1H), 2.12 (s, 3H), 1.99 (ddd, *J* = 14.1, 11.2, 5.8 Hz, 1H), 1.81–1.67 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6, 166.9, 147.2, 145.9, 140.0, 130.2, 123.3, 117.5, 111.0, 66.4, 51.5, 36.4, 30.6, 27.8, 19.1, 11.4. FTIR (NaCl, thin film) 2919, 2849, 1669, 1643, 1607, 1512, 1452, 1272, 1176, 1139, 892, 732 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{19}NO_2$ $[M+H]^+$ 258.1489, found 258.1490.

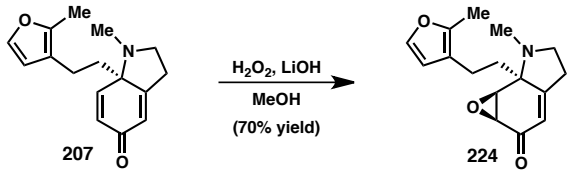
Photochemical [2+2] reaction of dihydroindolone 207.



A solution of dihydroindolone **207** (70 mg, 0.27 mmol) in benzene (36 mL) was divided into six 6 mL portions, which were each placed in 13x100 mm borosilicate test tubes. The reaction tubes were irradiated in a Luzchem photoreactor fitted with λ ≈ 350 nm lamps and a merry-go-round apparatus. After irradiating for 2 hours, the reaction mixtures were combined and concentrated under reduced pressure. The crude residue was purified by flash chromatography (1 to 3% MeOH in CH_2Cl_2) to give a mixture of dihydrofuran **206**, diketone **223**, and small amounts (~10%) of other unidentified products (21 mg total, <30% yield). This mixture of products was further purified by preparative TLC for characterization purposes. Spectral data[17] for dihydrofuran **206**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 10.5 Hz, 1H), 6.43 (d, *J* = 2.9 Hz, 1H), 6.07 (d, *J* = 10.5 Hz, 1H), 4.84 (d, *J* = 2.9 Hz, 1H), 3.29 (s, 1H), 2.67 (dt, *J* = 8.7, 6.7 Hz, 1H), 2.58 (dt, *J* = 9.0, 6.9 Hz, 1H), 2.47 (s, 3H), 2.36–2.22 (m, 2H), 1.89–1.78 (m, 1H), 1.78–1.63 (m, 3H), 1.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.4, 151.5, 147.0, 128.7, 103.5, 89.0, 70.5, 66.9, 61.5, 57.1, 54.3, 35.8, 34.6, 32.2, 28.8, 16.3. Characterization data for diketone **223**: $[\alpha]_D^{25}$ +45.1° (c = 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.9 Hz, 1H), 6.13 (d, *J* = 1.9 Hz, 1H), 3.16 (ddd, *J* = 9.3, 8.0, 1.2 Hz, 1H), 2.89 (d, *J* = 18.6 Hz, 1H), 2.85 (d, *J* = 5.6 Hz, 1H), 2.78–2.62 (m, 4H), 2.42 (td, *J* = 9.7, 8.2 Hz, 1H), 2.35–2.15 (m, 4H), 2.26 (s, 3H), 2.20 (s, 3H), 1.88 (ddd, *J* = 13.4, 9.8, 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.5, 209.7, 147.8, 140.2, 117.2, 111.1, 69.2, 62.2, 56.7,

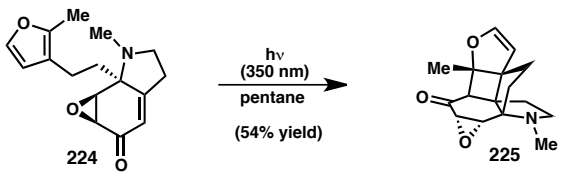
47.3, 41.9, 39.7, 38.9, 34.9, 19.5, 11.4; FTIR (NaCl, thin film) 2919, 2848, 2785, 1745, 1700, 1513, 1452, 1395, 1351, 1252, 1138, 1045, 893, 735 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{21}NO_3$ $[M+H]^+$ 276.1594, found 276.1591.

Preparation of epoxide 224.



To a solution of dienone **207** (213 mg, 0.828 mmol) in MeOH (8 mL) was added LiOH (40.0 mg, 1.66 mmol), followed by aqueous H_2O_2 (101 μL of a 50 wt % H_2O solution, 1.66 mmol). The reaction was allowed to stir at room temperature for 1 hour, then H_2O (8 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (50 to 75% EtOAc in Hexanes) provided epoxide **224** (158 mg, 70% yield) as a yellow oil. $[\alpha]_D^{25}$ – 235.9° (c = 0.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.9 Hz, 1H), 6.13 (d, *J* = 1.8 Hz, 1H), 5.87 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.62 (d, *J* = 4.1 Hz, 1H), 3.42 (dd, *J* = 4.1, 1.8 Hz, 1H), 3.15 (ddd, *J* = 9.4, 7.7, 4.6 Hz, 1H), 2.85 (td, *J* = 9.3, 6.6 Hz, 1H), 2.74–2.66 (m, 2H), 2.56 (s, 3H), 2.20–2.05 (m, 5H), 1.84 (ddd, *J* = 13.8, 11.3, 5.8 Hz, 1H), 1.74 (ddd, *J* = 13.9, 12.0, 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.0, 162.6, 147.2, 140.1, 118.5, 117.3, 110.8, 65.4, 53.5, 53.3, 50.9, 35.0, 29.7, 28.5, 19.5, 11.4. FTIR (NaCl, thin film) 2918, 2848, 1676, 1512, 1448, 1273, 1171, 1137, 1055, 893 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{19}NO_3$ $[M+H]^+$ 274.1438, found 274.1438.

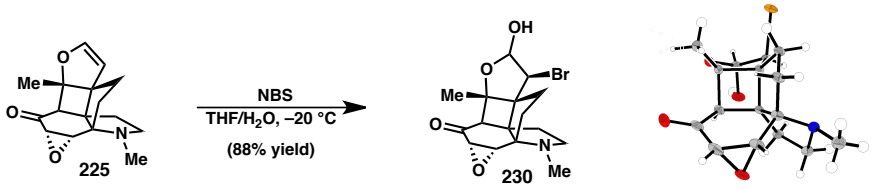
Preparation of dihydrofuran 225.



A solution of enone **224** (38 mg, 0.14 mmol) in a 50:1 mixture of pentane/benzene (24 mL) was divided into four 6 mL portions, which were each placed

in 13x100 mm borosilicate test tubes. The reaction tubes were irradiated in a Luzchem photoreactor fitted with λ ≈ 350 nm lamps and a merry-go-round apparatus. After irradiating for 50 minutes, the reaction mixtures were combined and concentrated under reduced pressure. The crude residue was purified by flash chromatography (50 to 75% EtOAc in Hexanes) to give dihydrofuran **225** (20 mg, 52% yield) as a pale yellow solid. $[\alpha]_D^{25}$ +55.1° (*c* 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.8 Hz, 1H), 4.65 (d, *J* = 2.8 Hz, 1H), 3.64 (d, *J* = 4.3 Hz, 1H), 3.24 (d, *J* = 4.3 Hz, 1H), 3.18 (s, 1H), 2.97 (td, *J* = 8.6, 5.6 Hz, 1H), 2.77 (ddd, *J* = 8.5, 7.7, 5.6 Hz, 1H), 2.48 (s, 3H), 2.31 (ddd, *J* = 13.1, 7.6, 5.7 Hz, 1H), 2.11 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.95 (ddd, *J* = 13.4, 8.4, 5.6 Hz, 1H), 1.84 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.74 (td, *J* = 13.3, 7.6 Hz, 1H), 1.56 (td, *J* = 13.3, 7.6 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 147.4, 103.0, 89.0, 71.0, 65.5, 62.1, 60.0, 55.8, 55.7, 54.6, 34.6, 32.0, 31.6, 29.8, 16.8. FTIR (NaCl, thin film) 2949, 2930, 2889, 2786, 1699, 1606, 1448, 1187, 1136, 1027, 883, 872 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{19}NO_3$ $[M+H]^+$ 274.1438, found 274.1438.

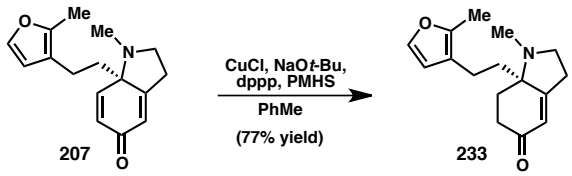
Preparation of bromohydrin 230.



To a solution of dihydrofuran **225** (19 mg, 0.070 mmol) in a 10:1 mixture of THF:H_2O (1.4 mL total) at –20 °C was added *N*-bromosuccinimide (13 mg, 0.075 mmol). The reaction mixture was allowed to stir 30 minutes at –20 °C and then quenched with saturated aqueous $Na_2S_2O_3$ (2 mL). After stirring for 10 minutes and warming to room temperature, the mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (30 to 40% EtOAc in Hexanes) to furnish bromohydrin **230** (23 mg, 88% yield) as a white solid. A small portion of **230** was recrystallized from Et_2O/Hexanes to give crystals suitable for single crystal X-ray diffraction: $[\alpha]_D^{25}$ –7.5° (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3:1 mixture of inseparable diastereomers, major diastereomer is designated by *, minor

diastereomer denoted by [§]) δ 5.85 (s, 1H[*]), 5.14 (s, 1H[§]), 4.45 (s, 1H[§]), 4.44 (s, 1H[*]), 3.65 (d, *J* = 4.5 Hz, 1H[§]), 3.64 (d, *J* = 4.4 Hz, 1H[*]), 3.31 (s, 1H[*]), 3.23 (d, *J* = 4.4 Hz, 1H[§]), 3.21 (d, *J* = 4.3 Hz, 1H[*]), 3.03 – 2.98 (t, *J* = 6.9 Hz, 2H[§]), 2.97 – 2.91 (m, 1H[*]), 2.97 – 2.91 (m, 2H[§]), 2.54 (dt, *J* = 14.6, 7.4 Hz, 1H[*]), 2.49 (s, 3H[*]), 2.48 (s, 3H[§]), 2.20 – 2.06 (m, 1H[*], 2H[§]), 2.06 – 1.98 (m, 2H[*], 2H[§]), 1.93 (ddd, *J* = 14.3, 7.6, 5.4 Hz, 1H[*]), 1.44 (ddd, *J* = 14.0, 12.8, 7.5 Hz, 1H[*]), 1.39 (ddd, *J* = 14.1, 12.9, 7.4 Hz, 1H[§]), 1.29 (s, 3H[*], 3H[§]), 0.88 (m, 1H[§]); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8[*], 203.9[§], 106.5[*], 95.6[§], 89.2[*], 83.9[§], 73.54[*], 73.48[§], 64.4[*], 63.5[*], 63.0[§], 58.6[*], 58.1[§], 57.6[§], 57.0[*], 56.3[*], 56.1[§], 55.1[§], 54.58[§], 54.57[*], 54.51[*], 54.3[§], 34.5[*], 34.3[§], 32.8[*], 32.0[*], 31.8[§], 30.02[§], 29.96[*], 29.87[§], 18.8[*], 18.2[§]. FTIR (NaCl, thin film) 3413, 2937, 2854, 1701, 1449, 1379, 1255, 1215, 1177, 1021, 930, 877, 737 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{20}NO_4Br$ $[M+H]^+$ 370.0648, found 370.0641.

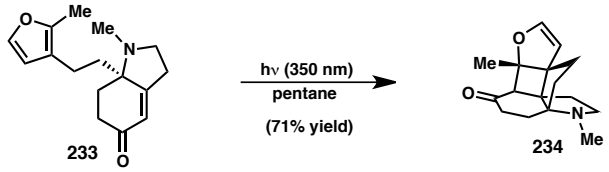
Preparation of enone 233.



In a glove box, a round bottom flask was charged with CuCl (8.6 mg, 0.087 mmol), NaO*t*-Bu (8.4 mg, 0.087 mmol), dppp (36 mg, 0.087 mmol), and degassed PhMe (5.7 mL), and the mixture was stirred for 20 minutes. The reaction was brought out onto the benchtop, placed under an atmosphere of N_2, and polymethylhydrosiloxane (58 μL, 0.96 mmol) was added, followed by a solution of dihydroindolone **207** (225 mg, 0.87 mmol) in degassed PhMe (3 mL). The reaction was allowed to stir 2 hours, then quenched by the addition of aqueous 1 N NaOH (9 mL) and stirred vigorously for 20 minutes. The mixture was extracted with EtOAc (2 x 30 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0 to 3% MeOH in CH_2Cl_2) to give enone **233** (170 mg, 75% yield) as a yellow oil. $[\alpha]_D^{25}$ –115.9° (*c* 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 1.8 Hz, 1H), 6.15 (d, *J* = 1.8 Hz, 1H), 5.87 – 5.83 (m, *J* = 1.5 Hz, 1H), 3.02 – 2.92 (m, 2H), 2.73 (dddd, *J* = 17.7, 8.1, 5.9, 2.3 Hz, 1H), 2.65 (dddd, *J* = 17.8, 7.4, 5.9, 1.4 Hz, 1H), 2.49 – 2.41 (m, 3H), 2.46 (s, 3H), 2.41 – 2.30 (m, 1H), 2.25

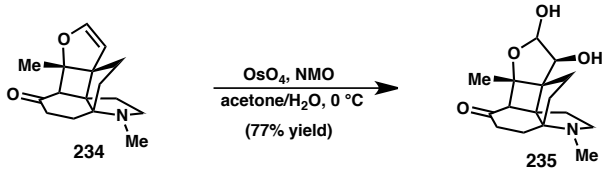
(ddd, *J* = 12.8, 5.0, 2.4 Hz, 1H), 2.19 (s, 3H), 1.87 (td, *J* = 13.0, 7.0, 1H), 1.82 (ddd, *J* = 14.2, 12.4, 4.8 Hz, 1H), 1.68 (ddd, *J* = 14.3, 12.7, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 172.7, 147.0, 140.0, 121.5, 118.4, 111.0, 63.2, 51.7, 35.0, 33.6, 33.3, 31.6, 30.3, 21.4, 11.5; FTIR (NaCl, thin film) 2923, 2784, 1669, 1448, 1270, 1198, 1137, 892, 729 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{21}NO_2$ $[M+H]^+$ 260.1645, found 260.1645.

Preparation of dihydrofuran 234.



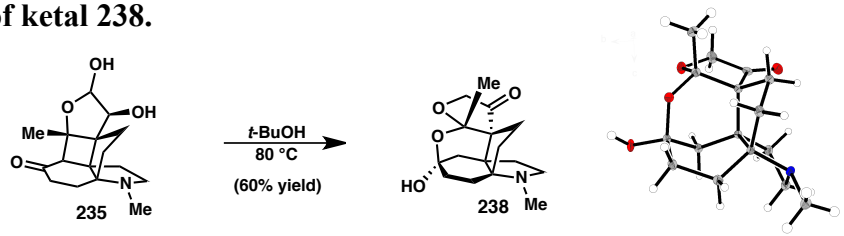
A solution of enone **233** (170 mg, 0.66 mmol) in a 50:1 mixture of pentane/benzene (65 mL) was divided into ten 6.5 mL portions, which were each placed in 13x100 mm borosilicate test tubes. The reaction tubes were irradiated in a Luzchem photoreactor fitted with λ ≈ 350 nm lamps and a merry-go-round apparatus. After irradiating for 6 hours, the reaction mixtures were combined and concentrated under reduced pressure. The crude residue was purified by flash chromatography (2 to 8% MeOH in CH_2Cl_2) to give dihydrofuran **234** (120 mg, 71% yield) as a pale yellow solid. $[\alpha]_D^{25}$ +207.6° (*c* 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.8 Hz, 1H), 4.74 (d, *J* = 2.8 Hz, 1H), 3.10 (s, 1H), 2.76 – 2.65 (m, 2H), 2.52 – 2.43 (m, 1H), 2.35 – 2.23 (m, 2H), 2.28 (s, 3H), 1.97 – 1.84 (m, 3H), 1.83 – 1.72 (m, 3H), 1.64 (ddd, *J* = 13.9, 8.2, 6.7 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.9, 146.6, 104.1, 88.5, 71.1, 65.3, 62.3, 60.2, 53.0, 37.0, 34.5, 31.5, 30.7, 29.6, 24.1, 16.9; FTIR (NaCl, thin film) 2925, 2864, 2783, 1696, 1600, 1457, 1379, 1169, 1139, 1031, 879, 755 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{21}NO_2$ $[M+H]^+$ 260.1645, found 260.1644.

Preparation of diol 235.



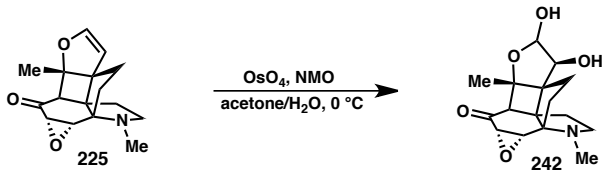
To a solution of dihydrofuran **234** (93 mg, 0.36 mmol) in acetone (6.4 mL) at 0 °C was added OsO_4 (23 μL of a 4 wt % solution in H_2O, 3.6 μmol), followed by a solution of *N*-methylmorpholine-*N*-oxide (46 mg, 0.39 mmol) in H_2O (0.6 mL). The resulting solution was allowed to stir 45 minutes at 0 °C. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (6 mL), and the resulting mixture was stirred at 0 °C for 20 minutes. The biphasic mixture was warmed to room temperature and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (5 to 20% MeOH in CH_2Cl_2) to provide diol **235** (81 mg, 77% yield) as an off-white foam. $[\alpha]_D^{25}$ +116.4° (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2:1 mixture of inseparable diastereomers[4], major diastereomer is designated by *, minor diastereomer denoted by §) δ 5.50 (s, 1H§), 5.37 (d, *J* = 2.9 Hz, 1H*), 4.23 (s, 1H§), 3.92 (d, *J* = 2.8 Hz, 1H*), 3.30 (s, 1H§), 2.99–2.82 (m, 1H*, 1H§), 2.85 (s, 1H*), 2.79 (td, *J* = 9.3, 6.0 Hz, 1H*), 2.76–2.69 (m, 1H§), 2.60–2.54 (m, 1H§), 2.54–2.45 (m, 1H*, 1H§), 2.37–2.20 (m, 2H*, 1H§), 2.32 (s, 3H§), 2.31 (s, 3H*), 2.18 (ddd, *J* = 14.1, 8.2, 6.0 Hz, 1H*), 1.97–1.82 (m, 3H*, 3H§), 1.82–1.71 (m, 2H*, 2H§), 1.71–1.59 (m, 1H*, 1H§), 1.20 (s, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.6§, 209.3*, 106.1§, 97.7*, 88.3§, 84.3*, 79.4§, 74.0*, 73.3§, 72.8*, 64.6§, 62.5*, 61.7§, 59.8*, 54.9§, 54.1*, 53.0§, 52.9*, 36.31§, 36.27*, 34.7§, 34.6*, 31.4§, 30.0*, 29.7§, 29.1*, 29.0§, 26.1*, 22.2*, 21.8§, 18.8§, 18.6*; FTIR (NaCl, thin film) 3369, 2935, 2864, 2788, 1691, 1448, 1183, 1146, 1125, 1049, 1022, 979, 914, 875, 754 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{23}NO_4$ $[M+H]^+$ 294.1700, found 294.7001.

Preparation of ketal 238.



A 20-mL vial was charged with diol **235** (30 mg, 0.10 mmol) and *t*-BuOH (3 mL), sealed, and heated to 80 °C for 5 days. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by flash chromatography (2 to 8% MeOH in CH_2Cl_2) to give ketal **238** (18 mg, 60% yield) as a pale yellow solid. $[\alpha]_D^{25}$ +47.9° (*c* 0.47, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (d, *J* = 17.7 Hz, 1H), 3.90 (d, *J* = 17.7 Hz, 1H), 2.97 (s, 1H), 2.88 (q, *J* = 8.6 Hz, 1H), 2.67 (td, *J* = 9.5, 2.3 Hz, 1H), 2.28 – 2.20 (m, 1H), 2.25 (s, 3H), 2.18 (dd, *J* = 13.4, 1.7 Hz, 1H), 2.01–1.94 (m, 1H), 1.93 (d, *J* = 13.4 Hz, 1H), 1.88–1.71 (m, 3H), 1.69–1.61 (m, 2H), 1.59–1.49 (m, 1H), 1.42–1.36 (m, 1H), 1.35 (s, 3H), 1.04 (ddd, *J* = 12.7, 7.1, 2.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 109.8, 97.3, 73.1, 69.2, 60.4, 55.4, 51.2, 36.2, 35.2, 34.1, 31.3, 29.4, 26.6, 24.3, 24.2; FTIR (NaCl, thin film) 3066, 2966, 2938, 2804, 1744, 1452, 1353, 1313, 1240, 1185, 1129, 1074, 1055, 1002, 900, 876, 859 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{23}NO_4$ $[M+H]^+$ 294.1700, found 294.1705.

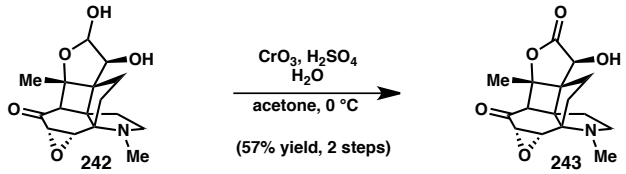
Preparation of diol 242.



To a solution of dihydrofuran **225** (400 mg, 1.46 mmol) in acetone (27 mL) at 0 °C was added OsO_4 (150 µL of a 2.5 wt % solution in *t*-BuOH, 14.6 µmol), followed by a solution of NMO (175 mg, 1.49 mmol) in H_2O (2 mL). The reaction was allowed to stir for 1 hour at 0 °C, quenched by the addition of saturated aqueous $Na_2S_2O_3$ (15 mL), and stirred at 0 °C for an additional 20 minutes. The mixture was warmed to room temperature and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a pale yellow oil. The crude product was used in the following step without further purification.

A small sample was purified by flash chromatography (4 to 10% MeOH in CH_2Cl_2) to provide diol **242** as a white foam: $[\alpha]_D^{25}$ +21.9° (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, compound exists as a 1.5:1 mixture of inseparable diastereomers) δ 5.47 (s, 1H), 5.40 (d, *J* = 3.0 Hz, 1H), 4.20 (s, 1H), 3.89 (d, *J* = 3.0 Hz, 1H), 3.66 (d, *J* = 4.4 Hz, 1H), 3.66 (d, *J* = 4.3 Hz, 1H), 3.28 (s, 1H), 3.23 (d, *J* = 4.4 Hz, 1H), 3.20 (d, *J* = 4.3 Hz, 1H), 3.06–2.91 (m, 4H), 2.86 (s, 1H), 2.61–2.46 (m, 1H), 2.50 (s, 3H), 2.49 (s, 3H), 2.19–2.02 (m, 5H), 2.02–1.79 (m, 4H), 1.55–1.36 (m, 2H), 1.22 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.2, 204.4, 105.9, 97.8, 88.7, 84.8, 79.3, 74.1, 73.3, 73.0, 64.7, 62.4, 58.5, 58.4, 57.1, 55.1, 54.8, 54.7, 54.52, 54.47, 54.4, 54.0, 34.9, 34.7, 31.2, 30.7, 30.5, 30.3, 26.8, 19.1, 18.8; FTIR (NaCl, thin film) 3369, 2935, 2864, 2788, 1691, 1448, 1183, 1146, 1125, 1049, 1022, 979, 914, 875, 754 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{21}NO_5$ $[M+H]^+$ 308.1492, found 308.1494.

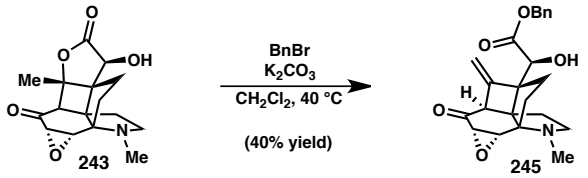
Preparation of lactone 243.



To a solution of diol **242** (1.46 mmol) in acetone (30 mL) at 0 °C was added a solution of chromic acid (3.1 M based on CrO_3, 1.9 mL) dropwise by syringe over 1 minute. The reaction was allowed to stir at 0 °C for an additional 7 minutes, then quenched by the sequential addition of *i*-PrOH (0.5 mL) and saturated aqueous $NaHCO_3$ (15 mL). The mixture was warmed to room temperature and stirred vigorously for 5 minutes, then diluted and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (2 to 4% MeOH in CH_2Cl_2) to deliver lactone **243** (253 mg, 57% yield, 2 steps) as a white foam: $[\alpha]_D^{25}$ –42.2° (*c* 0.60, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.06 (s, 1H), 3.73 (d, J = 4.6 Hz, 1H), 3.36 (ddd, J = 9.6, 7.2, 5.1 Hz, 1H), 3.32 (d, J = 4.6 Hz, 1H), 3.02 (ddd, J = 9.6, 8.6, 7.4 Hz, 1H), 2.93 (s, 1H), 2.50 (s, 3H), 2.31 (ddd, J = 14.7, 12.9, 8.1 Hz, 1H), 2.16 (dd, J = 14.3, 8.0 Hz, 1H), 2.13–2.05 (m, 2H), 1.86 (dd, J = 14.7, 7.6 Hz, 1H), 1.47–1.36 (m,

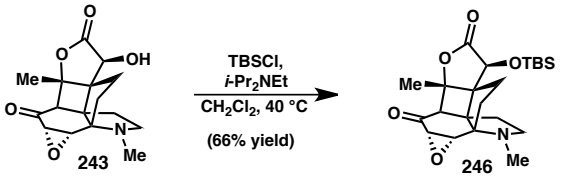
1H), 1.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 176.0, 90.4, 74.0, 71.6, 59.1, 57.9, 56.7, 54.9, 54.4, 34.5, 30.6, 30.1, 25.5, 18.0; FTIR (NaCl, thin film) 3421, 2944, 2860, 1773, 1707, 1449, 1384, 1256, 1171, 1081, 953, 873, 737 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{19}NO_5$ $[M+H]^+$ 306.1336, found 306.1341.

Preparation of cyclobutane 245.



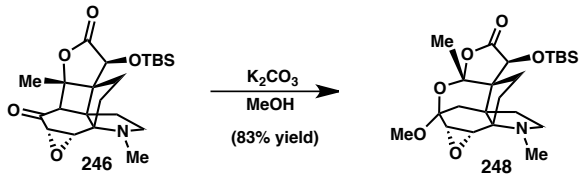
To a solution of lactone **243** (10 mg, 0.033 mmol) in CH_2Cl_2 (0.7 mL) was added BnBr (8 μL, 0.07 mmol), followed by Cs_2CO_3 (22 mg, 0.07 mmol). The reaction was heated to 40 °C and allowed to stir 5 hours. The reaction was cooled to room temperature, then quenched with saturated aqueous NH_4Cl (1 mL). The mixture was extracted with EtOAc (3 x 2 mL), and the combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by preparative TLC (80% EtOAc in Hexanes) to generate cyclobutane **245** (5.2 mg, 40% yield) as a white solid: $[\alpha]_D^{25}$ –15.8° (*c* 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.32 (m, 5H), 5.23 (dd, *J* = 3.0, 1.1 Hz, 1H), 5.20 (m, 2H), 4.81 (dd, *J* = 3.5, 1.1 Hz, 1H), 4.34 (s, 1H), 3.65 (d, *J* = 4.4 Hz, 1H), 3.36 (t, *J* = 3.2 Hz, 1H), 3.22 (dd, *J* = 4.3, 0.5 Hz, 1H), 3.04 (td, *J* = 8.7, 3.9 Hz, 1H), 2.89 (td, *J* = 9.1, 8.7, 6.1 Hz, 1H), 2.51–2.43 (m, 1H), 2.48 (s, 3H), 2.09 (td, *J* = 12.4, 7.0 Hz, 1H), 2.01–1.90 (m, 2H), 1.58 (dd, *J* = 12.6, 6.9 Hz, 1H), 1.47 (ddd, *J* = 13.4, 12.3, 6.9 Hz, 1H), 1.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.3, 172.9, 145.0, 134.6, 128.9, 128.8, 128.7, 111.3, 72.0, 71.6, 67.6, 63.1, 58.5, 58.0, 54.4, 54.3, 51.2, 34.3, 30.8, 30.3, 29.6; FTIR (NaCl, thin film) 3493, 2924, 2853, 1735, 1706, 1455, 1262, 1216, 1195, 1105, 1071, 909, 879, 754 cm^{-1}; HRMS (ESI+) calc'd for $C_{23}H_{25}NO_5$ $[M+H]^+$ 396.1805, found 396.1809.

Preparation of silyl ether 246.



To a solution of **243** (70 mg, 0.23 mmol) in CH_2Cl_2 (1.2 mL) was added TBSCl (42 mg, 0.28 mmol), followed by *i*-Pr_2NEt (80 μL, 0.46 mmol). The reaction was heated to 40 °C and stirred for 4 hours, then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (2 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude residue was purified by flash chromatography (25 to 33% EtOAc in Hexanes) to give silyl ether **246** (63 mg, 66% yield) as a colorless oil: $[\alpha]_D^{25}$ –28.1° (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 1H), 3.68 (d, *J* = 4.5 Hz, 1H), 3.31 (d, *J* = 4.6 Hz, 1H), 2.99 (td, *J* = 9.1, 5.0 Hz, 1H), 2.95–2.88 (m, 1H), 2.90 (s, 1H), 2.47 (s, 3H), 2.18–2.05 (m, 2H), 2.04–1.87 (m, 2H), 1.83 (ddd, *J* = 14.4, 7.4, 1.0 Hz, 1H), 1.40 (s, 3H), 1.32 (ddd, *J* = 14.0, 12.8, 7.4 Hz, 1H), 0.86 (s, 9H), 0.15 (d, *J* = 5.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.2, 174.4, 90.2, 73.2, 73.1, 59.7, 59.0, 56.2, 55.8, 54.5, 54.1, 34.4, 30.4, 29.9, 26.9, 25.6, 18.2, 17.8, -4.7, -5.3; FTIR (NaCl, thin film) 2955, 2930, 2857, 1781, 1709, 1472, 1383, 1255, 1171, 1090, 1044, 946, 840, 781 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{33}NO_5Si$ $[M+H]^+$ 420.2201, found 420.2203.

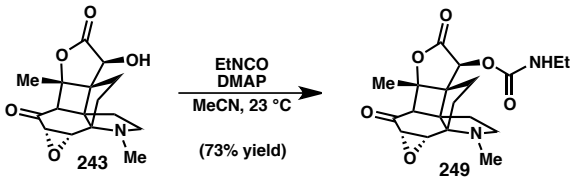
Preparation of ketal 248.



To a solution of silyl ether **246** (17 mg, 0.040 mmol) in MeOH (1.3 mL) at 0 °C was added K_2CO_3 (11 mg, 0.079 mmol) in one portion. The solution was warmed to room temperature and stirred for 2 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (25 to 40% EtOAc in Hexanes) to give ketal **248** (15

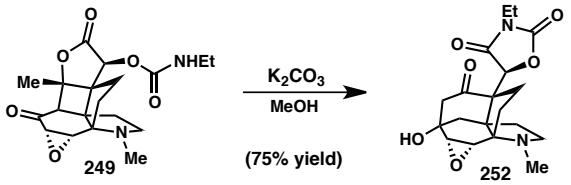
mg, 83% yield) as a colorless oil: $[\alpha]_D^{25}$ –52.3° (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (s, 1H), 3.42 (s, 3H), 3.30 (dd, *J* = 4.8, 1.5 Hz, 1H), 3.24 (d, *J* = 4.8 Hz, 1H), 2.91 (dd, *J* = 8.8, 6.3 Hz, 1H), 2.81 (ddd, *J* = 11.7, 8.8, 4.2 Hz, 1H), 2.59 (s, 3H), 2.07 (d, *J* = 14.0 Hz, 1H), 2.01–1.92 (m, 2H), 1.78 (td, *J* = 11.5, 6.5 Hz, 1H), 1.68 (s, 3H), 1.65 (dd, *J* = 14.0, 1.6 Hz, 1H), 1.62–1.54 (m, 1H), 1.48–1.31 (m, 2H), 0.88 (s, 9H), 0.16 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 112.4, 99.7, 75.2, 71.3, 60.2, 56.2, 55.0, 53.9, 53.7, 50.0, 36.0, 35.6, 33.4, 27.2, 26.3, 25.6, 25.5, 18.1, -4.6, -5.2; FTIR (NaCl, thin film) 2929, 2855, 1783, 1469, 1379, 1274, 1257, 1186, 1123, 1040, 1024, 994, 928, 843, 781 cm^{-1}; HRMS (ESI+) calc'd for $C_{23}H_{37}NO_6Si$ $[M+H]^+$ 452.2463, found 452.2471.

Preparation of carbamate 249.



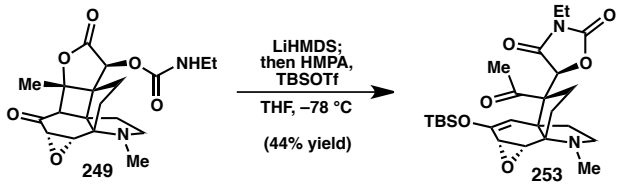
To a solution of lactone **243** (350 mg, 1.15 mmol) in MeCN (6 mL) was sequentially added ethyl isocyanate (200 μL, 2.52 mmol) and DMAP (140 mg, 1.15 mmol). The reaction was allowed to stir for 4 hours, then concentrated under reduced pressure and loaded directly onto a silica gel column. Flash chromatography (80 to 100% EtOAc in Hexanes) afforded carbamate **249** (314 mg, 73% yield) as a white foam: $[\alpha]_D^{25}$ –46.0° (*c* 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (s, 1H), 4.80 (t, *J* = 5.9 Hz, 1H), 3.67 (d, *J* = 4.4 Hz, 1H), 3.32 (d, *J* = 4.4 Hz, 1H), 3.28–3.17 (m, 2H), 3.05–2.96 (m, 2H), 2.93 (s, 1H), 2.46 (s, 3H), 2.23–2.08 (m, 3H), 1.89 (ddd, *J* = 14.0, 12.8, 7.6 Hz, 1H), 1.77 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.46 – 1.33 (m, 1H), 1.40 (s, 3H), 1.14 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 172.4, 154.5, 89.8, 72.6, 71.9, 59.1, 58.1, 57.1, 55.8, 54.1, 53.8, 36.3, 34.3, 30.5, 30.2, 26.1, 17.5, 15.0; FTIR (NaCl, thin film) 3370, 2939, 1777, 1730, 1708, 1525, 1450, 1382, 1239, 1173, 1138, 1085, 1027, 959, 872, 732 cm^{-1}; HRMS (ESI+) calc'd for $C_{19}H_{24}N_2O_6$ $[M+H]^+$ 377.1707, found 377.1711.

Preparation of alcohol 252.



To a solution of carbamate **249** (4.0 mg, 0.011 mmol) in MeOH (0.8 mL) was added K_2CO_3 (3 mg, 0.02 mmol) in one portion. The reaction was allowed to stir at room temperature for 3 hours, then quenched with saturated aqueous NH_4Cl (1 mL). The mixture was diluted and extracted with EtOAc (3 x 2 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (1 to 3% MeOH in CH_2Cl_2) to deliver alcohol **252** (3.0 mg, 75% yield) as a white solid: $[\alpha]_D^{25}$ +139.2° (*c* 0.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19–4.97 (m, 1H), 4.57 (s, 1H), 3.98 (d, *J* = 4.5 Hz, 1H), 3.68–3.52 (m, 2H), 3.39 (ddd, *J* = 10.1, 8.4, 4.7 Hz, 1H), 3.11–3.04 (m, 1H), 2.93 (d, *J* = 19.4 Hz, 1H), 2.80–2.68 (m, 2H), 2.67–2.58 (m, 1H), 2.47 (d, *J* = 19.4 Hz, 1H), 2.40 (s, 3H), 2.31 (ddd, *J* = 15.1, 9.7, 2.3 Hz, 1H), 2.17–2.03 (m, 2H), 1.80 (ddd, *J* = 13.7, 8.4, 6.6 Hz, 1H), 1.65 (dt, *J* = 15.7, 9.8 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 207.1, 172.5, 154.9, 80.8, 75.7, 72.3, 67.8, 58.2, 52.7, 52.7, 49.1, 44.5, 39.4, 37.0, 35.3, 33.0, 30.1, 28.1, 12.2; FTIR (NaCl, thin film) 2947, 1810, 1733, 1697, 1449, 1420, 1350, 1220, 1055, 1017, 958, 765, 734 cm^{-1}; HRMS (ESI+) calc'd for $C_{19}H_{24}N_2O_6$ $[M+H]^+$ 377.1707, found 377.1718.

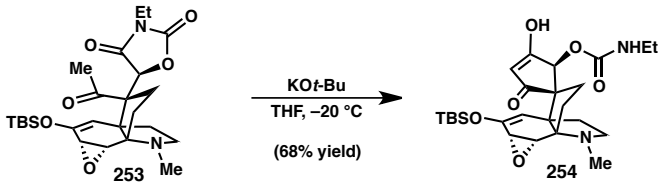
Preparation of silyl enol ether 253.



To a solution of carbamate **249** (47.0 mg, 0.125 mmol) in THF (1.6 mL) at –78 °C was added LiHMDS (137 µL, 0.137 mmol) dropwise via syringe. The reaction was stirred at –78 °C for 20 minutes, then HMPA (239 µL, 1.37 mmol) and TBSOTf (34 µL, 0.15 mmol) were sequentially added via syringe. The resulting mixture was stirred for an

additional 20 minutes at –78 °C before quenching with 2,6-lutidine (14 μL, 0.125 mmol) followed by aqueous buffer solution (pH= 7, 2 mL). The mixture was allowed to warm to room temperature, diluted with additional buffer solution (5 mL), then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography on Florisil (40 to 60% EtOAc in Hexanes) to afford silyl enol ether **253** (27 mg, 44% yield) as a white foam: $[\alpha]_D^{25}$ –111.3° (*c* 1.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03 (d, *J* = 2.1 Hz, 1H), 4.75 (s, 1H), 3.68–3.53 (m, 2H), 3.42 (d, *J* = 4.2 Hz, 1H), 3.10 (dd, *J* = 4.2, 2.1 Hz, 1H), 2.95 (ddd, *J* = 9.5, 8.6, 5.8 Hz, 1H), 2.79 (ddd, *J* = 8.7, 6.9, 2.0 Hz, 1H), 2.65 (s, 3H), 2.42–2.21 (m, 3H), 2.14–2.05 (m, 1H), 2.10 (s, 3H), 2.00 (ddd, *J* = 13.9, 12.2, 7.9 Hz, 1H), 1.89 (ddd, *J* = 12.8, 5.8, 2.0 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.22–0.07 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.5, 172.1, 155.6, 146.2, 111.4, 83.1, 71.8, 70.9, 60.1, 56.3, 52.7, 50.0, 36.6, 35.6, 35.1, 34.3, 33.0, 29.6, 25.6, 18.0, 12.2, -4.60, -4.62; FTIR (NaCl, thin film) 2956, 2931, 2858, 1813, 1739, 1699, 1668, 1449, 1417, 1381, 1355, 1255, 1221, 1117, 1008, 938, 900, 868, 838, 738 cm^{-1}; HRMS (ESI+) calc'd for $C_{25}H_{38}N_2O_6Si$ $[M+H]^+$ 491.2572, found 491.2579.

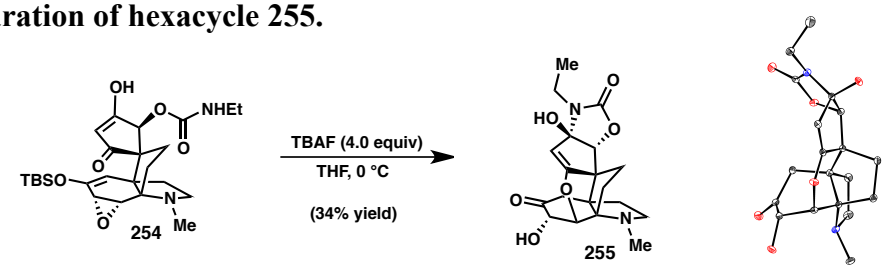
Preparation of cyclopentenone 254.



To a solution of silyl enol ether **253** (44 mg, 0.090 mmol) in THF (3 mL) at –20 °C was added a solution of KO*t*-Bu (99 μL, 1.0 M in THF, 0.099 mmol) dropwise by syringe. The reaction was allowed to stir at –20 °C for 20 minutes, then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was warmed to room temperature and extracted with a 4:1 mixture of EtOAc/CH_2Cl_2 (9 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (50 to 60% EtOAc in Hexanes) to furnish cyclopentenone **254** (30 mg, 68% yield) as a white solid: $[\alpha]_D^{25}$ +6.4° (*c* 0.76, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (s, 1H), 5.12 (s, 1H), 4.86 (s, 1H), 4.82 (t, *J* = 5.8 Hz,

1H), 4.75 (d, *J* = 3.2 Hz, 1H), 4.70 (s, 1H), 3.76 (d, *J* = 3.2 Hz, 1H), 3.34–3.19 (m, 3H), 2.64–2.48 (m, 2H), 2.35 (s, 3H), 2.26–2.14 (m, 1H), 2.08 (td, *J* = 13.5, 12.9, 3.5 Hz, 1H), 1.91 (ddd, *J* = 13.4, 9.9, 3.4 Hz, 1H), 1.68 (ddd, *J* = 13.7, 10.0, 6.5 Hz, 1H), 1.61–1.51 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.12 (d, *J* = 13.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 191.6, 155.7, 150.0, 109.2, 106.8, 86.1, 75.5, 70.1, 69.9, 59.7, 53.0, 53.0, 37.1, 36.3, 30.9, 30.2, 25.7, 24.0, 18.1, 15.2, -4.20, -4.32; FTIR (NaCl, thin film) 3305, 2930, 2858, 1728, 1698, 1597, 1537, 1463, 1382, 1251, 1211, 1168, 1137, 1086, 1032, 951, 856, 838, 782, 733 cm^{-1}; HRMS (ESI+) calc'd for $C_{25}H_{38}N_2O_6Si$ $[M+H]^+$ 491.2572, found 491.2575.

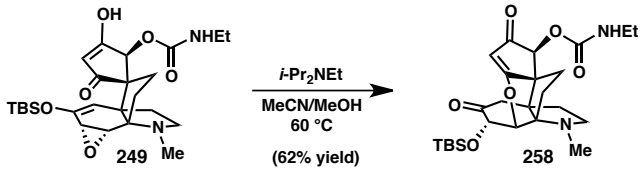
Preparation of hexacycle 255.



To a solution of cyclopentenone **254** (12.6 mg, 0.026 mmol) in THF (2.5 mL) at 0 °C was added TBAF (1.0 M in THF, 103 μL, 0.10 mmol) dropwise by syringe. The reaction was stirred for 30 minutes, then quenched by the addition of saturated aqueous Na_2SO_4 (2 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with saturated aqueous Na_2SO_4 (4 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (50 to 80% EtOAc in Hexanes) to deliver hexacycle **255** (3.3 mg, 34% yield) as a white solid. A portion of this material was recrystallized from $CHCl_3$ to give crystals suitable for single crystal X-ray diffraction: $[\alpha]_D^{25}$ +87.1° (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (d, *J* = 0.7 Hz, 1H), 4.55 (s, 1H), 4.48 (d, *J* = 0.7 Hz, 1H), 3.76 (s, 1H), 3.41 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.27 (dq, *J* = 14.5, 7.3 Hz, 1H), 3.16 (dt, *J* = 9.9, 8.2 Hz, 1H), 2.93 (s, 1H), 2.60 (ddd, *J* = 11.3, 10.0, 3.0 Hz, 1H), 2.40–2.30 (m, 2H), 2.30–3.21 (m, 1H), 2.22 (s, 3H), 2.13–1.99 (m, 2H), 1.94–1.79 (m, 2H), 1.61 (ddd, *J* = 13.9, 10.1, 6.2 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.8, 162.8, 155.4, 100.73, 96.5, 89.3, 86.2, 75.2, 69.4, 59.8, 55.8, 51.7, 43.5, 36.1, 35.9, 32.9, 32.7, 22.3, 14.8; FTIR (NaCl, thin film) 3332, 2924, 2853, 1720, 1656, 1461, 1376, 1251, 1200,

1091, 1052, 959, 923, 820, 761, 733 cm^{-1}; HRMS (ESI+) calc'd for $C_{19}H_{24}N_2O_6$ $[M+H]^+$ 377.1707, found 377.1716.

Preparation of pentacycle 258.



To a solution of cyclopentenone **249** (21.2 mg, 0.043 mmol) in MeCN/MeOH (4:1, 2 mL total) was added *i*-Pr_2NEt (30 μL, 0.173 mmol). The reaction was heated to 60 °C and allowed to stir for 64 hours at that temperature, then cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (40 to 60% EtOAc in Hexanes) afforded pentacycle **258** (13.1 mg, 62% yield) as a white foam: $[\alpha]_D^{25}$ +25.9° (*c* 0.66, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (s, 1H), 5.16 (s, 1H), 4.98 (t, *J* = 5.7 Hz, 1H), 4.75 (s, 1H), 3.82 (s, 1H), 3.22 (m, 2H), 3.14 (ddd, *J* = 9.7, 8.5, 7.4 Hz, 1H), 2.62–2.49 (m, 2H), 2.39 (d, *J* = 15.9 Hz, 1H), 2.22 (s, 3H), 2.12 (td, *J* = 12.1, 7.1 Hz, 1H), 2.05 (d, *J* = 16.0 Hz, 1H), 2.00 (ddd, *J* = 13.6, 10.1, 3.6 Hz, 1H), 1.92 (ddd, *J* = 13.8, 12.3, 3.6 Hz, 1H), 1.63 (ddd, *J* = 14.0, 10.1, 6.4 Hz, 1H), 1.49 (ddd, *J* = 13.3, 8.5, 3.2 Hz, 1H), 1.15 (t, *J* = 7.3 Hz, 3H), 0.91 (s, 10H), 0.13 (d, *J* = 27.9 Hz, 6H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 204.3, 199.3, 190.8, 155.3, 107.2, 95.8, 75.6, 74.9, 69.2, 58.4, 53.8, 51.5, 44.6, 36.2, 35.9, 32.9, 32.0, 25.8, 22.1, 18.4, 15.1, -4.37, -5.56; FTIR (NaCl, thin film) 3342, 2953, 2930, 2855, 1720, 1601, 1535, 1472, 1462, 1380, 1248, 1172, 1144, 1032, 926, 842, 781, 733 cm^{-1}; HRMS (ESI+) calc'd for $C_{25}H_{38}N_2O_6Si$ $[M+H]^+$ 491.2572, found 491.2574.

4.7. Notes and References

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(5) Enol ether **215** was isolated in 54% yield as a difficult to separate 9:1 mixture with an unidentified side product. Analytically pure material was obtained by multiple purifications. See: Navarro, R.; Reisman, S.E. *Org. Lett.* **2012**, *14*, 4354–4357.

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(11) Attempts to control the equivalents of the alkoxide nucleophile did not prove fruitful; in these reactions, an intractable mixture of products was observed.

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(16) Grignard reagent **214** was prepared as follows: To a suspension of magnesium turnings (1.60 g, 65.8 mmol) in THF (8 mL) was added diisobutylaluminum hydride (60 μL, 0.34 mmol). The resulting suspension was heated to reflux, and a solution of bromide **S16** (7.58 g, 40.1 mmol) in THF (42 mL) was added dropwise. The reaction was maintained at reflux for 1 hour, then cooled to room temperature. The resulting Grignard reagent was titrated and stored in a Schlenk tube.

(17) Less than 1 mg of analytically pure dihydrofuran **206** was isolated; as such, some carbon signals were extrapolated from HMBC spectral data. See Appendix 3.