CHAPTER FIVE

A Convergent Approach to Ineleganolide[i]

5.1 Retrosynthetic Analysis for Ineleganolide[ii]

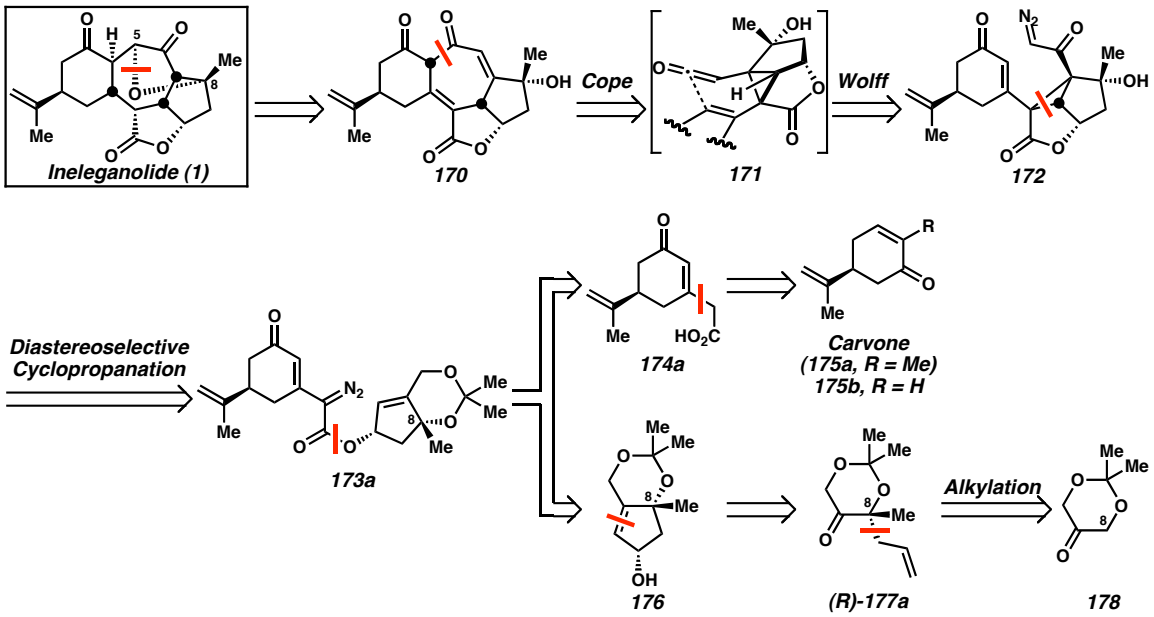
At the outset of this project, we planned to construct the seven-membered ring core of ineleganolide (**1**) through a Wolff/Cope rearrangement (Scheme 5.1.1).[1,2] Initial retrosynthetic simplification of the C(8)–C(5) ether revealed cycloheptadienone **170**, which we sought to assemble from a Cope rearrangement of ketene **171**, generated in situ by Wolff rearrangement of α-diazoketone **172a**. The cyclopropane in α-diazoketone **172a** would arise from vinyldiazoester **173a**, which itself would be the coupling product of carboxylic acid **174** and alcohol **176**. Carboxylic acid **174** would be accessed from carvone (**175a**, via *des*-methyl carvone (**175b**)[3]). Embedded within alcohol **176** was a tertiary stereocenter at C(8), which we targeted through enantioselective alkylation starting from dioxanone **178**.

---

[i] The enantioselective total synthesis of ineleganolide has been pursued in collaboration with Dr. Amanda Jones, a post-doctoral associate in the Stoltz group, who joined efforts toward the total synthesis of ineleganolide in December 2007.

[ii] This section is comprised of excerpts from Chapter 3.1 and 3.2. It has been included to enable this chapter to function as a self-contained description of our efforts toward an asymmetric total synthesis of ineleganolide.

Scheme 5.1.1 Retrosynthetic analysis for ineleganolide

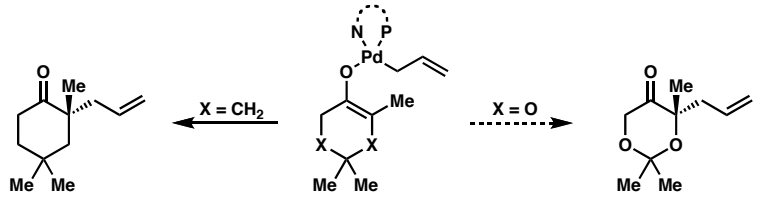


5.2 Enantioselective Alkylation to Access Tertiary Alcohol ent-176[iii]

From the beginning of this project, we sought to overcome the challenges of the enantioselective installation of the C(8) tertiary alcohol and the subsequent construction of the highly substituted cycloheptanone core (Scheme 5.2.1). To install the C(8) stereocenter, we found inspiration in recent work within the group to establish quaternary stereocenters through the enantioselective decarboxylative alkylation of cyclic enolates.[4] If this method could be employed with α-oxygenation, we would be able to access the C(8) center embedded within alcohol **176** (see Chapter 4). At the time, there was limited evidence that α-heteroatoms might be tolerated in the reaction.

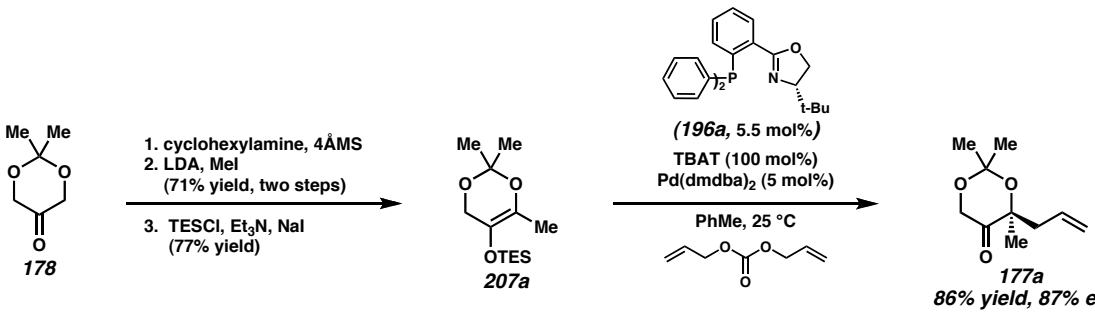
[iii] Section 5.2 includes substantial excerpts from Section 4.8.

Scheme 5.2.1 Decarboxylative alkylation to form tetrasubstituted oxygenated systems



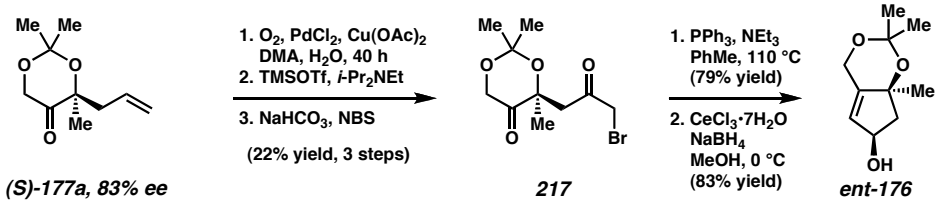
We chose to assemble this center with enantioselective alkylation of silyl enol ether **207a**, which is available in three steps from dioxanone **178** (Section 4.4, summarized in Scheme 5.2.2). Exposure of triethylsilyl ether **207a** to $Pd(dmdba)_2$ (5 mol%), (*S*)-*t*-BuPHOX (**196a**, 5.5 mol%),[5] and diallyl carbonate (1.05 equiv) with an equivalent of TBAT in PhMe at 25 °C, provided tetrasubstituted ether (*S*)-**177a** in 86% yield and 87% ee.

Scheme 5.2.2 Synthesis of enantioenriched ketone (*S*)-**177a**



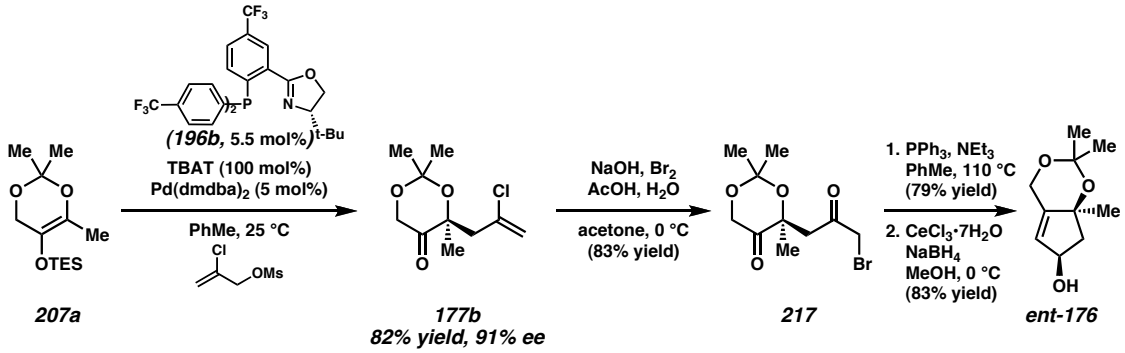
Our initial plan was to process enantioenriched ketone (*S*)-**177a** to cyclopentenol ent-**176** by a Wacker oxidation, Aldol ring closure, and a Luche reduction (Scheme 5.2.3). The Aldol ring closure did not proceed; however, Wacker oxidation could be followed by bromination, Wittig olefination and Luche reduction. Unfortunately, low yields and decomposition plagued processing of enantioenriched ketone (*S*)-**177a** by this route. Thus, we elected to use an allyl transfer unit in a higher oxidation state.

Scheme 5.2.3 Access to cyclopentenol ent-**176**



In our modified approach, palladium-catalyzed enantioselective alkylation furnishes chloroallyl dioxanone **177b**, which can be transformed to alcohol ent-**176** under mild conditions. On treatment with $Pd(dmdba)_2$ (5 mol%), tris(CF_3)-(*S*)-*t*-BuPHOX (**196b**, 5.5 mol%),[5] and chlorallyl mesylate (1.05 equiv) with an equivalent of TBAT in PhMe at 25 °C, triethylsilyl ether **207a** generates tetrasubstituted ether **177b** in 82% yield and 91% ee (for optimization, see Section 4.4). While olefin **177a** can be converted to α-bromoketone **217** in 22% yield over three steps, chloroalkene **177b** can be efficiently converted to α-bromoketone **217** by mild oxidation in up to 83% yield over a single step (Scheme 5.2.4). Unfortunately, this mild oxidative bromination does not scale well, and the bromide decomposes readily. Consequently, the two-step oxidative bromination/Wittig olefination sequence has been run more than 40 times, each time beginning with 0.300 g of chloroolefin **177b**. This alteration significantly improves access to alcohol ent-**176**.

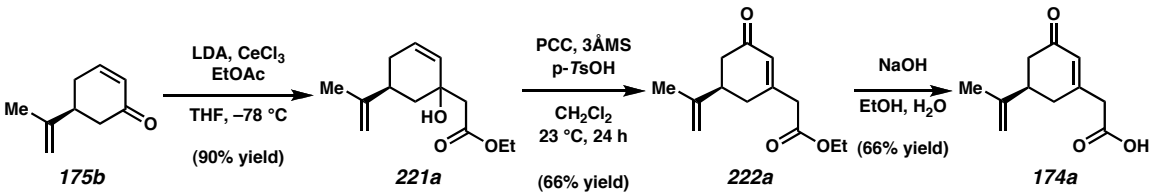
Scheme 5.2.4 Synthesis of cyclopentenol ent-**176** via chloroallyl mesylate alkylation



5.3 Construction of a cyclohexenone coupling partner

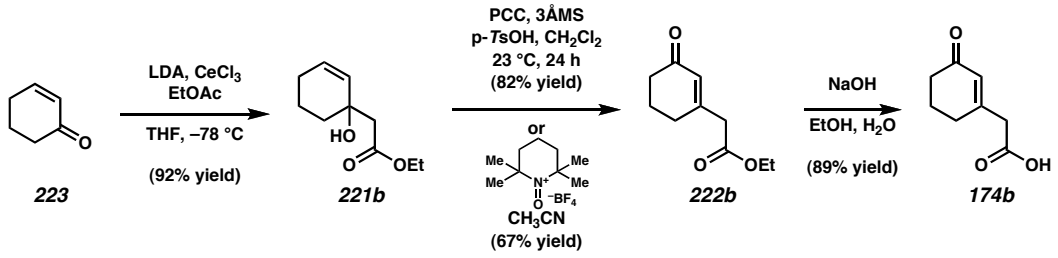
With enantioenriched cyclopentenol ent-**176** in hand, we turned our attention toward construction of its coupling partner, carboxylic acid **174a** (Scheme 5.3.1). Conversion of *des*-methyl carvone (**175a**)[6] to tertiary alcohol **221a** by addition of the lithium enolate of EtOAc proceeded efficiently in the presence of $CeCl_3$.[6] Oxidative rearrangement with allylic transposition to enone **222a** with pyridinium chlorochromate (PCC)[7] and saponification furnished carboxylic acid **174a** in 59% overall yield.

Scheme 5.3.1 Toward the cyclohexenone portion of ineleganolide



We also assembled carboxylic acid **174b** as a more direcly accessible model (Scheme 5.3.2). In case derivatives of isopropenyl **174a** could not withstand transformations in the developed route, then isopropenyl functionality could be installed at a later stage. Cyclohexenone **223** was converted to carboxylic acid **174b** in good yields by a route analogous to that used to access isopropenyl-containing acid **174a**. Notably, $TEMPO^+BF_4^-$ could be used as an environmentally benign alternative to effect the same oxidative rearrangement, albeit in slightly lower yield (**221b→222b**).[8]

Scheme 5.3.2 Toward the cyclohexenone portion of ineleganolide

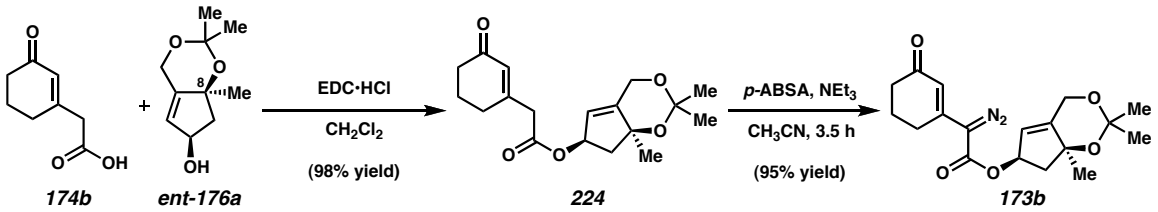


5.4 Advancing Toward an Enantioenriched [5–3]-Fused Lactone

5.4.1 First-Generation Approach

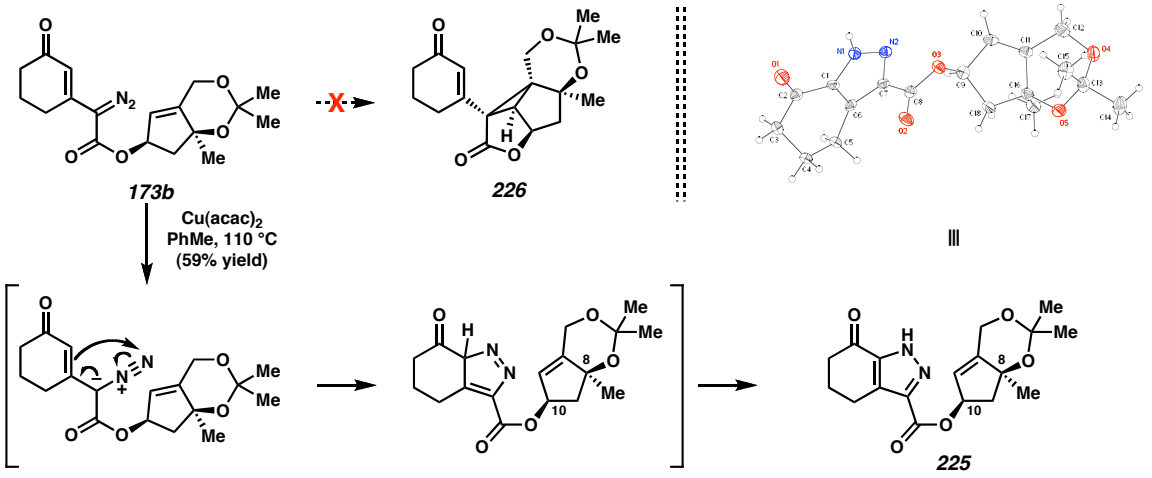
To set-up the key Wolff/Cope rearrangement, we coupled ent-**176** and carboxylic acid **174b** with DCC in 85% yield (Scheme 5.4.1). Subsequently, diazo transfer was accomplished upon treatment with *p*-ABSA to furnish the targeted cyclopropanation precursor (**173b**) in excellent yield.

Scheme 5.4.1 Toward the targeted cyclopropanation substrate (**173b**)



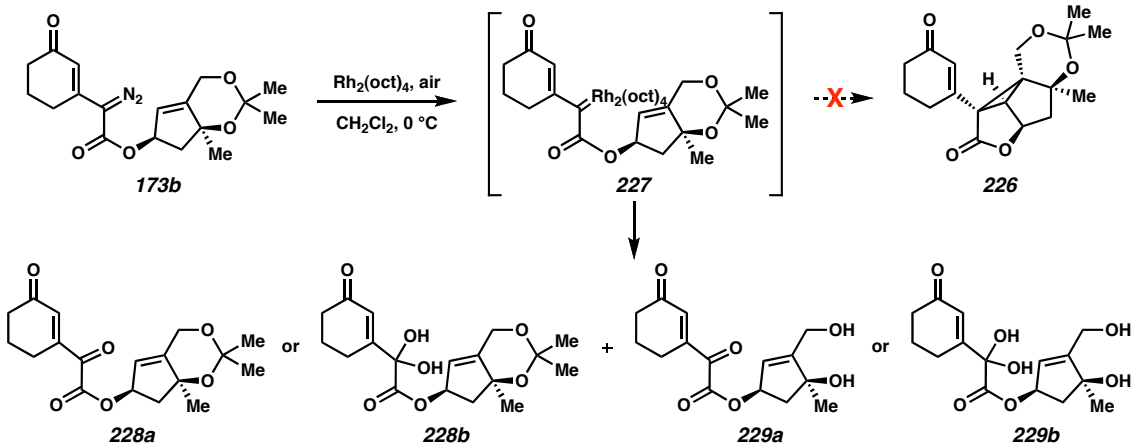
Unfortunately, treatment of diazoester **173b** under standard cyclopropanation conditions did not lead to the desired cyclopropane (**226**). Rather, a thermal rearrangment occurred to form pyrazole **225** in 59% yield (Scheme 5.4.2). Reports of pyrazole formation on thermolysis of vinyl diazo substrates appeared as early as 1935.[9] Padwa proposed that pyrazole formation proceeds through a 1,5-cyclization followed by a proton shift.[9f] Indeed, this undesired pyrazole formed cleanly when diazoester **173b** was heated in benzene at reflux, in the absence of copper(II) acetoacetate. This structure has been solved X-ray crystallographic analysis, which confirms the *syn*-arrangement of C(8) and C(10) oxygenation.

Scheme 5.4.2 Thermal formation of pyrazole **225**



At lower temperatures, neither cyclopropane **226** nor pyrazole **225** formed. One potential explanation for the lack of reactivity at these temperatures was that diazoester **173b** did not form the requisite metal carbenoid (**227**). To disprove this potentially detrimental hypothesis, we exposed diazoester **173b** to $Rh_2(oct)_4$ to ambient air at 0 °C, anticipating that oxygen would intercept a generated metal carbenoid and form an oxidation product (Scheme 5.4.3). Indeed, under these conditions, oxidized **228** formed along with its acetonide-cleaved analogue (**229**), suggesting that a carbenoid formed upon exposure of diazoester **173b** to $Rh_2(oct)_4$, but that it failed to undergo cyclopropanation.

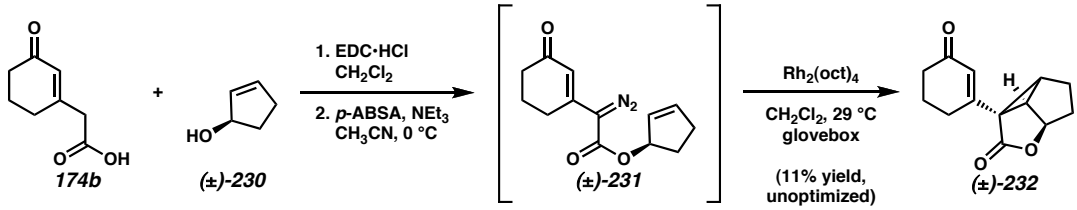
Scheme 5.4.3 Evidence of carbene generation



5.4.2 Probing the Influence of Steric Interactions on Cyclopropanation

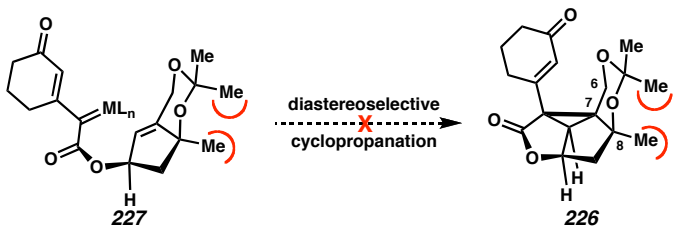
Cyclopropanations rarely involve precursors with tetrasubstituted olefins or vinyldiazoesters. To verify that a similar vinyldiazoester would be viable in cyclopropanation, we assembled vinyldiazoester **231** (Scheme 5.4.4). Coupling known alcohol **230** with carboxylic acid **174b**, and subsequent diazotization provided diazoester **231**. Gratifyingly, exposure of diazoester **231** to rhodium octanoate formed cyclopropane **232**. Application of these conditions to diazoester **173b** did not form cyclopropane **226**. This showed that the vinyldiazoester in acetonide **173b** did not prevent cyclopropanation.

Scheme 5.4.4 Successful cyclopropanation of a model substrate (e.g., **231**)



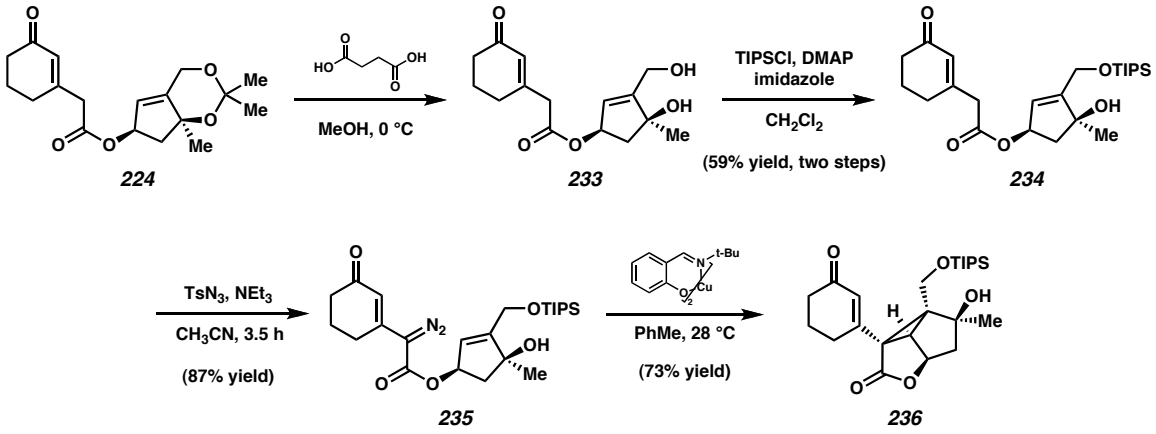
Having discovered that this vinyldiazoester functionality could be incorporated into competent cyclopropanation precursors, we turned our attention to probing the impact of cyclopentene functionalization in diazoester **173b** on cyclopropanation. Close examination of cyclopropane **226** revealed a 1,3-diaxial interaction that likely disfavored cyclopropanation (Scheme 5.4.5). This interaction was necessarily enhanced in cyclopropane **226**, relative to diazoester **173b**.

Scheme 5.4.5 A possible model to explain the unsuccessful cyclopropanation reactions



To avoid this strain, we constructed silyl ether **235** from ester **224** (Scheme 5.4.6). Wary of the possibility of olefin isomerization, we turned to De Waard's catalytic conditions for ketal cleavage. De Waard found that ketal cleavage was effected without olefin isomerization when catalysis involved acids with a pKa around 3.[10] Adaptation of these conditions to our system enabled cleavage of acetonide **224** with fumaric acid in methanol at 0 °C.[10] Silylation with TIPSCl provided ready access to silyl ether **234**, which was treated with TsN_3 to provide diazoester **235**. To our delight, copper *tert*-butyl salicylaldimine ($Cu(tbs)_2$) was uniquely effective in this cyclopropanation, forming **236** in 74% yield over 5 days under an inert atmosphere (glovebox).

Scheme 5.4.6 Successful cyclopropanation of silyl ether **235**

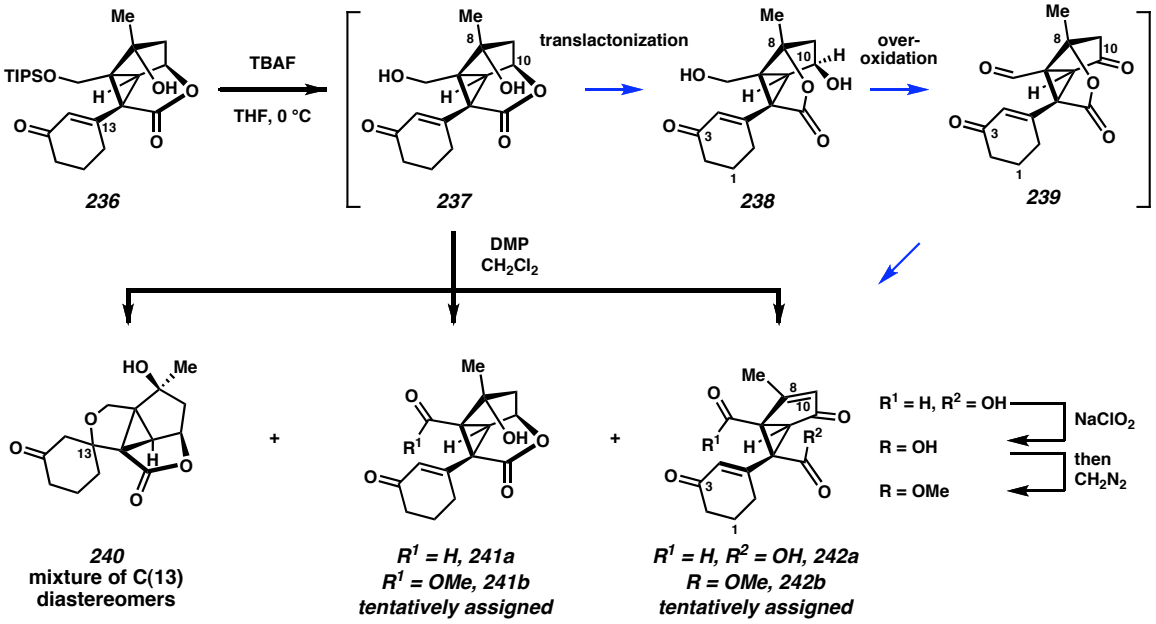


5.5 Efforts Toward a Wolff/Cope Precursor

With the cyclopropane successfully installed, we sought to advance intermediate **236** to an appropriately functionalized Wolff/Cope precursor (Scheme 5.5.1). Desilylation of cyclopropane **236** occurred readily; however, oxidation provided an array of products under a range of oxidation conditions. While a range of oxidants were tested, Dess-Martin periodinane was among the most promising. Upon oxidation with Dess-Martin periodinane, dihydropyran **240** was observed as the major product (Scheme

5.5.1). Presumably, this product arose by conjugate addition of the primary alcohol into the enone functionality. When the crude desilylation products were immediately subjected to oxidation conditions, two aldehydes could be observed (e.g., **241a** and **242a**, tentatively assigned). These aldehydes were not stable to isolation. Further oxidation of these crude aldehydes, and subsequent methylation provided trace amounts of two products, tentatively assigned as methyl ester **241b** and diester **242b**. We hypothesized that α,β-unsaturated ketone **242b** was formed by translactonization of the C(8) alcohol to release the C(10) alcohol (e.g., **237** → **238** → **239**), which could be oxidized by Dess-Martin periodinane. Subsequent elimination of the C(8) oxygenation could provide carboxylic acid **242a**.

Scheme 5.5.1 Byproducts formed in the desilylation–oxidation sequence

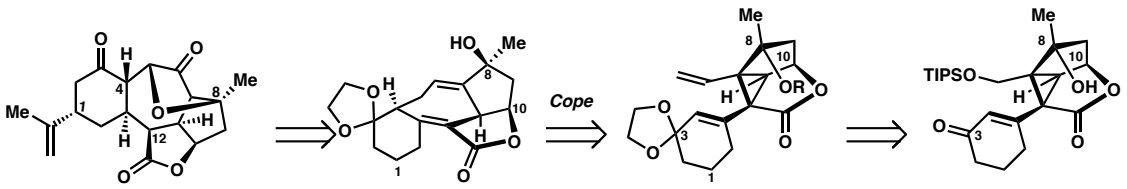


5.6 A Second-Generation Approach to Ineleganolide

Having struggled with oxidation to provide the targeted Wolff/Cope precursor (e.g., silyl **236** → ester **241b**, Scheme 5.5.1), we considered a Cope strategy to form the

seven-membered ring of ineleganolide (Scheme 5.6.1). Thus, we targeted cycloheptadiene **243**, which we expected to assemble by way of a [3,3]-sigmatropic rearrangement of divinylcyclopropane **244**. To limit byproduct formation during oxidation, we have chosen to mask the problematic C(8) tertiary alcohol and the C(3) ketone in cyclopropane **236**.

Scheme 5.6.1 Retrosynthetic analysis involving a Cope rearrangement

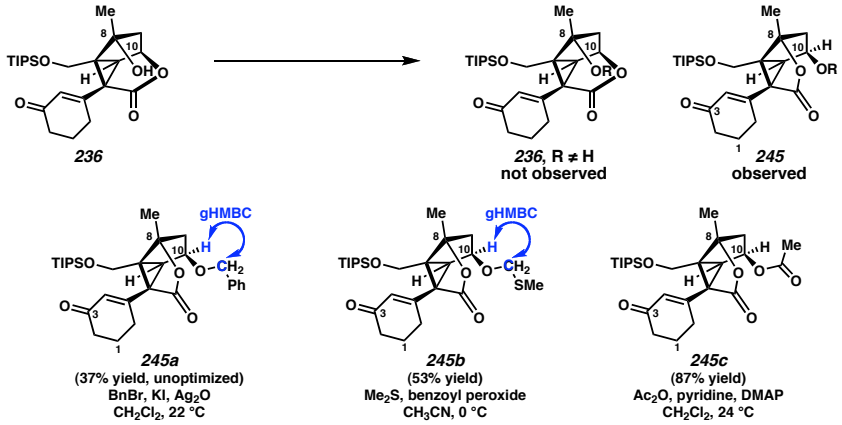


5.7 Masking the C(8) Tertiary Alcohol in Ineleganolide

Initially, we targeted formation of benzyl, MTM, and acetyl C(8)-ethers (e.g., **236**, R≠H; Scheme 5.7.1). Facile ether formation was achieved under a variety of acid- and base-promoted conditions. By standard analytical measurements (e.g., ^{1}H- and ^{13}C-NMR and IR spectroscopy, and HRMS), the formed products matched expectations for C(8)-ethers (e.g., **236**, R≠H).

To our surprise, gradient-heteronuclear multiple bond correlation (gHMBC) spectroscopy revealed that all efforts to alkylate the C(8) alcohol result in translactonization[11] to furnish a C(8) lactone and a C(10) ether (e.g., **236** → **245**). Smooth benzylation of the C(10) alcohol was achieved on treatment of C(8) alcohol **236** with BnBr, KI, and Ag_2O at room temperature. Similarly, the secondary MTM ether formed on exposure of C(8) alcohol **236** to dimethyl sulfate and benzoyl peroxide at 0 °C. Finally, upon base-mediated acetylation (Ac_2O, pyridine, DMAP), the translactonized product contained a C(8) lactone and a C(10) acetate.[12]

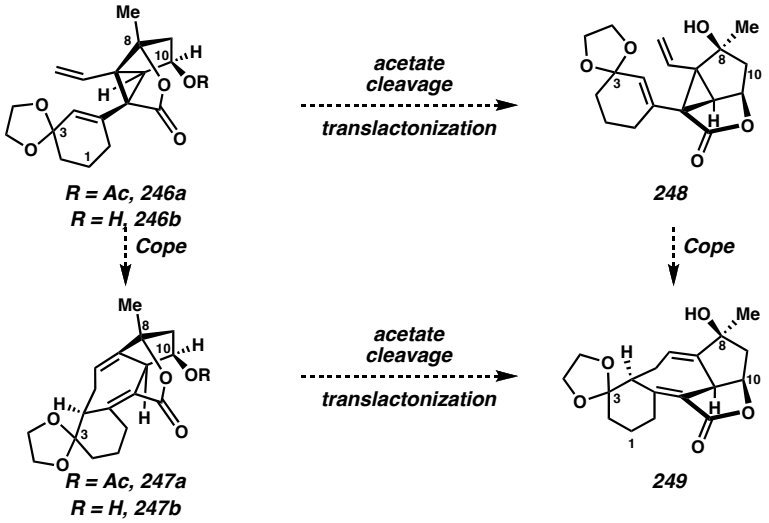
Scheme 5.7.1 Translactonization to form benzyl, MTM, and acetyl ethers



5.8 Masking the α,β-Unsaturated Ketone: Ketalization with Olefin Isomerization

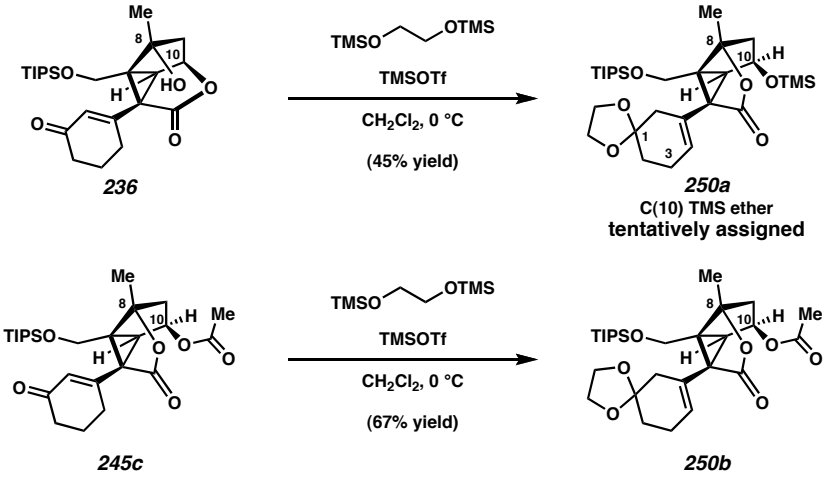
While these translactonized products were not originally targeted, we anticipated that they could still be converted to ineleganolide (**1**) through an acetate-cleavage/retro-translactonization/Cope rearrangement (Scheme 5.8.1). In keeping with our earlier commitment to mask the problematic C(3) ketone, divinylcyclopropane **246a** was targeted as a suitable precursor for this tandem transformation. We expected that both translactonization and Cope rearrangement would be thermodynamically governed transformations. In the case where the C(10) alcohol of divinylcyclopropane **246a** was exposed (e.g., **246b**), then the reaction would funnel to the lowest energy product, namely less-strained cycloheptadiene **249**. Direct Cope rearrangement of the C(8) lactone (**246**) would form highly-strained **247**, a compound possessing two anti-Bredt, bridgehead olefins. Were this to form, it would undergo translactonization to cycloheptadiene **249**.

Scheme 5.8.1 Proposals to access to cycloheptadiene **249**



As we began our efforts to access a more oxidized framework, we postulated that the electrophilic C(3) ketone would need to be masked to prevent side reactions during oxidation. Under many standard ketalization conditions, ketones **236** and **245c** either decomposed, or formed complex product mixtures (Scheme 5.8.2). Furthermore, these ketones were unreactive toward mild conditions that are designed to prevent alkene isomerization (TMSOTf, $(TMSOCH_2)_2$, CH_2Cl_2, –78 °C, multiple days). At higher temperatures (0 °C), ketalization proceeded, albeit with the concomitant undesired olefin isomerization (e.g., **236** → **250** and **245c** → **250**).

Scheme 5.8.2 Ketalization with undesired olefin isomerization

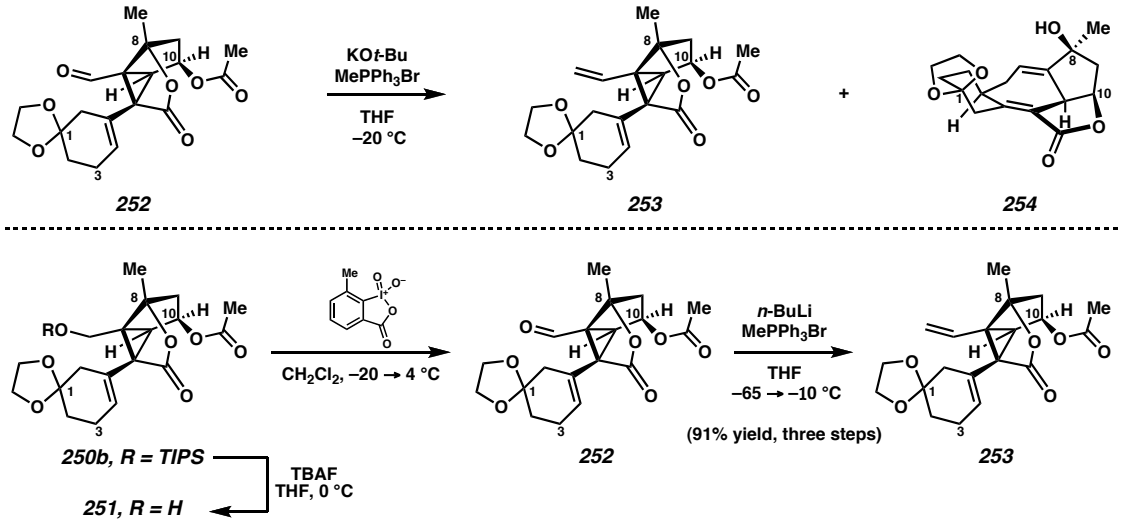


Although this olefin isomer was not originally designed into our synthetic approach to ineleganolide, we anticipated that ketal **250** would be an appropriate precursor for a tandem translactonization/Cope rearrangement. We imagined that more limited oxidation of the primary alcohol to an aldehyde could facilitate methylenation to generate divinylcyclopropane **253**, an appropriate Cope precursor (Scheme 5.8.3). In an initially promising result, Dess-Martin periodinane slowly oxidized primary alcohol **251** to an aldehyde with byproducts. To improve upon these conditions, we turned to 3-methyl-2-iodoxybenzoic acid (Me-IBX). Calculations by Su and Goddard[13] identified Me-IBX as a more reactive oxidant. We[iv] found that Me-IBX to be more soluble in a broader range of solvents. To our delight, oxidation with Me-IBX at –20 to 4 °C in CH_2Cl_2 provided a single aldehyde (**252**) that was used without purification in the next reaction.

[iv] Roizen, J. L.; Stoltz, B. M.; McFadden, R., unpublished results.

Careful selection of temperature and base are required to achieve efficient methylenation (Scheme 5.8.3). The crude aldehyde formed a modest amount of divinylcyclopropane **253** on methylenation with Wittig reagents generated from $MePPh_3Br$ with KO*t*-Bu (in reactions at –20 or 24 °C) or *n*-BuLi (in reactions at 24 °C). Interestingly, alongside olefin **253**, a small amount of cycloheptadiene **254** was also formed in these reactions. Ultimately, smooth methylenation was achieved on treatment of crude aldehyde **252** in THF at –65 to –10 °C with the Wittig reagent generated from $MePPh_3Br$ and *n*-BuLi. In the best case, TBAF-mediated desilylation could be followed by carefully optimized conditions for oxidation and Wittig olefination to deliver divinylcyclopropane **253**.

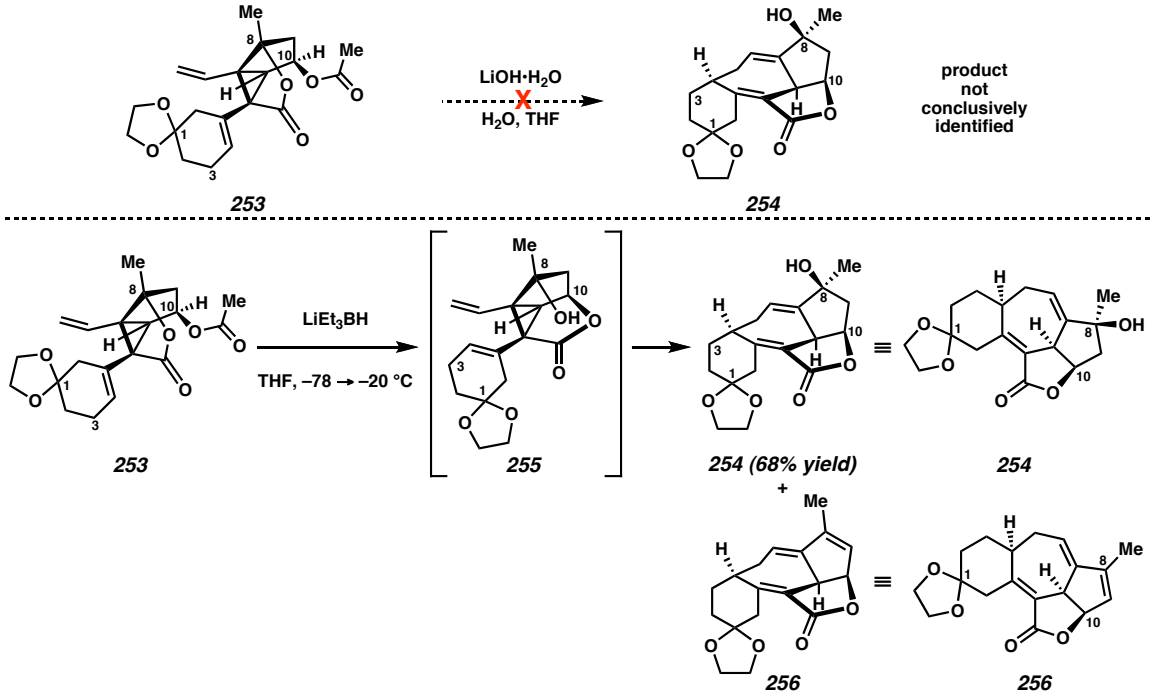
Scheme 5.8.3 Access to divinylcyclopropane **253**



With divinylcyclopropane **253** in hand,[14] we envisioned that initial acetate cleavage could be followed by translactonization to C(10) lactone **255** and then undergo the desired Cope rearrangement to less strained cycloheptadiene **254**. Along these lines, base-mediated acetate cleavage furnished a single product displaying a ^{1}H-NMR spectrum that included an additional vinyl proton and non-equivalent ketal protons, and

could not be assigned to cycloheptadiene **254** (Scheme 5.8.4). Interestingly, divinylcyclopropane **253** reacted at low temperature with nucleophilic super-hydride to form desired cycloheptadiene **254**, along with dehydration product **256** in variable yields. Presumably, acetate cleavage enabled translactonization to a divinylcyclopropane that spontanously underwent a Cope rearrangement. Importantly, this translactonization/Cope rearrangement constituted the first synthesis of the [6-7-5-5] core of ineleganolide.

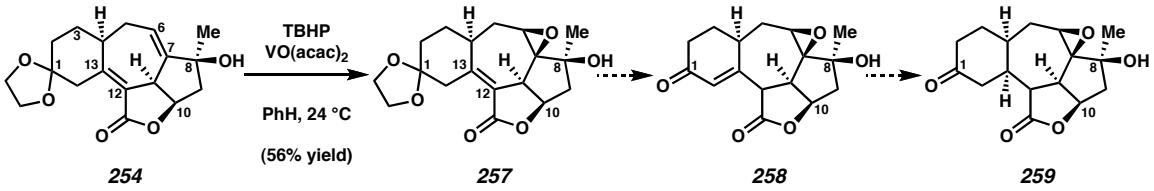
Scheme 5.8.4 Deacetylation-induced translactonization/Cope rearrangement



Having established a route to the carbon scaffold of ineleganolide, we turned our attention to installation of oxygenation C(6) and reduction of the tetrasubstitued C(12)–C(13) olefin. We were pleased to find that the tertiary C(8) alcohol in cycloheptadiene **254** directed diastereoselective epoxidation of the C(6)–C(7) olefin upon treatment with $VO(acac)_2$ and TBHP to generate epoxide **257** (Scheme 5.8.5). Anticipating that direct reduction of the tetrasubstitued C(12)–C(13) olefin would be challanging, we chose to

pursue deketalization of cycloheptadiene **257**, which would likely induce olefin isomerization to form enone **258**. We imagined that the ketone in enone **258** would serve as a C(1) handle to facilitate olefin reduction. Unfortunately, ketal **257** proved recalcitrant to a broad range of ketal cleavage conditions. Ketal cleavage and olefin reduction continue to be areas of active research.

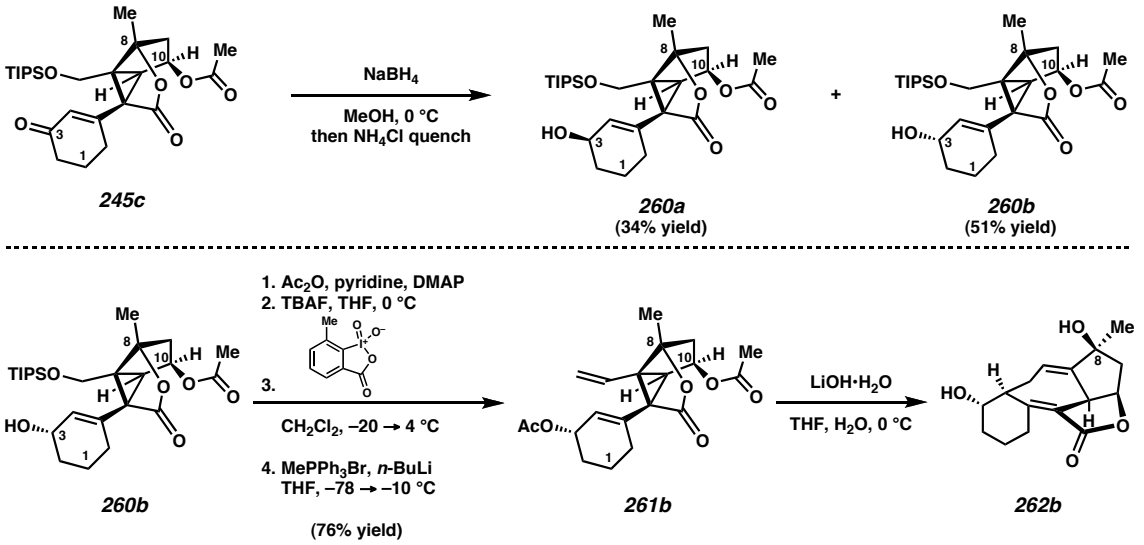
Scheme 5.8.5 Olefin differentiation from cycloheptadiene **254**



5.9 Masking the α,β-Unsaturated Ketone: C(3) Reduction

Given the challenges encountered during our examination of the deketalization process, we next sought to mask the ketone as an ether (Scheme 5.9.6). We found that Luche reduction of ketone **245c** furnished 1:1.5 ratio of diastereomeric alcohols **260a** and **b**. These diastereomers were separated and carried in parallel through the subsequent reactions. Secondary alcohol **260b** was masked as an acetate, then the primary alcohol was desilylated, oxidized to an aldehyde, and subjected to Wittig olefination to provide divinylcyclopropane **261b** in 76% yield over four steps. Lithium hydroxide-mediated acetate cleavage of divinylcyclopropane **261b** promoted a translactonization/Cope rearrangement cascade to deliver cycloheptadiene **262b**, with minimal elimination of the C(8) alcohol. Research is underway to advance cycloheptadienes **262** to ineleganolide.

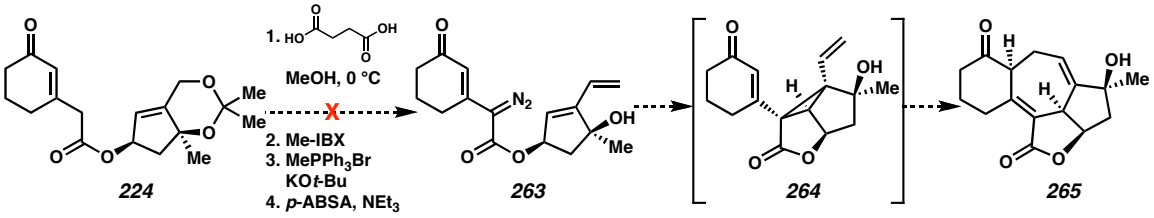
Scheme 5.9.6 Access to cycloheptadiene **262**



5.10 Formal Cyclopropanation/Cope Approach to Ineleganolide

Concurrent with the sequence described in Sections 5.6–5.9, a tandem cyclopropanation/Cope strategy was pursued to form the scaffold of ineleganolide. To investigate this strategy, we targeted diazoester **263** as the precursor to our key tandem cyclopropanation/Cope rearrangement (Scheme 5.10.1). Unfortunately, we were unable to convert acetonide **224** to diazoester **263**. We postulated that the electrophilic cyclohexenone portion of acetonide **224** interfered with the requisite olefination.

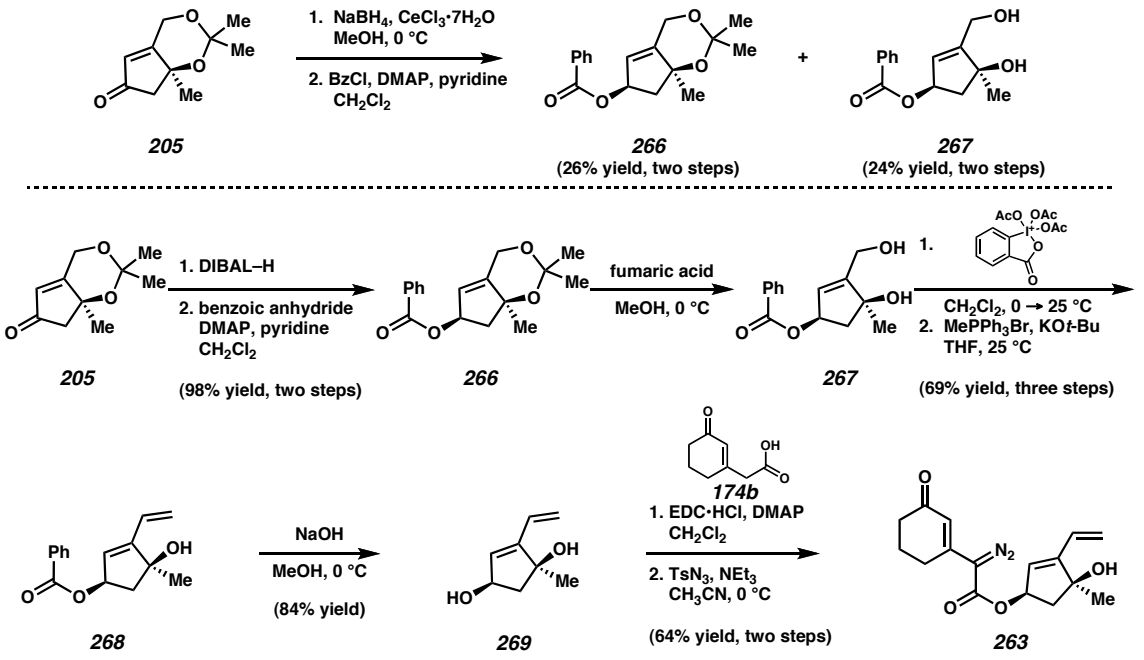
Scheme 5.10.1 Plan to access to diazoester **263**



To enable methylenation, we carried out the necessary manipulations on the cyclopentene fragment prior to coupling with the cyclohexenone carboxylic acid. Thus, cyclopentenone **205** was converted to allylic benzoyl ester **266**. Reduction and

benzoylation provided a mixture of desired benzoyl ester **266** and diol **267**, whose isolation was accompanied by degradation. Fortunately, acetonide-cleavage was suppressed in the presence of excess base, to allow access to readily isolable benzoyl ester **266** in 98% yield over two-steps. Benzoyl ester **266** was then deketalized, oxidized with Dess-Martin periodinane and methylenated to deliver diene **268**. Alkoxide-mediated debenzoylation furnished alcohol **269**, which was coupled with carboxylic acid **174b** and diazotizatized to provide the targeted diazoester **263**.

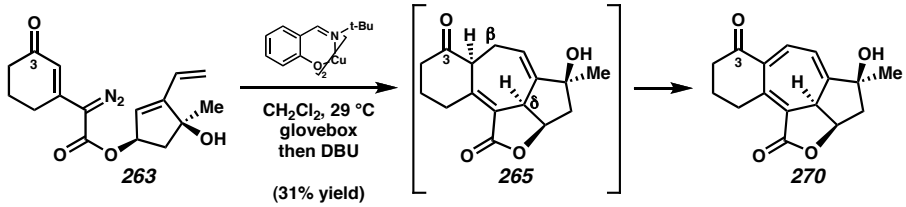
Scheme 5.10.2 Access to diazoester **263**



With this cyclopropanation precursor in hand, we sought to examine conditions to induce a tandem cyclopropanation/Cope cascade, allowing access to cycloheptadiene **265** directly. Davies and co-workers pioneered the tandem cyclopropanation/Cope[15,16] rearrangement for diastereoselective intramolecular reactions.[17,18,19,20] In the event, treatment of diazoester **263** with $Cu(tbs)_2$ under N_2-atmosphere in a glovebox resulted in the formation of a compound possessing three olefins, instead of two as in desired

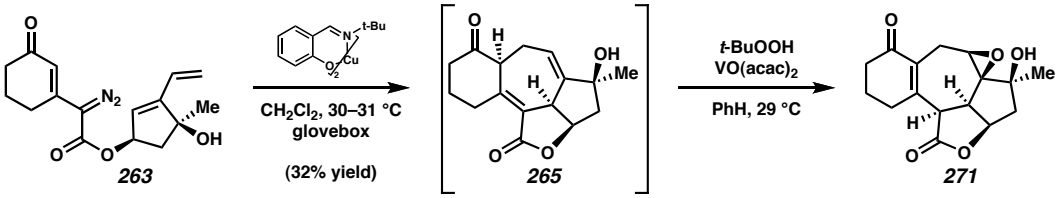
product **265**. After careful analytical examination we were surprised to identify cycloheptatriene **270** as the major product of this reaction. Cycloheptatriene **270** likely arose from oxidation of cycloheptadiene **265** that was copper-mediated during the reaction, or air-accelerated during work-up. Presumably, the acidic β- and δ-protons of the C(3) ketone helped to facilitate this undesired oxidation reaction.

Scheme 5.10.3 Successful cyclopropanation/Cope rearrangement of diazoester **263**



To our delight, we could avoid this over-oxidation by employing lower $Cu(tbs)_2$-loadings, as visible by ^1H NMR spectrum of the crude mixture that had never been exposed to air. With lower catalyst loadings, the intermediate cycloheptadiene (**265**) could be intercepted prior to exposure to air through diastereoselective epoxidation of its C(6)–C(7) olefin with $VO(acac)_2$ and TBHP at room temperature to generate epoxide **271** in 32% yield for a formal cyclopropanation, Cope rearrangement, epoxidation sequence. Investigations are underway to advance epoxide **271** toward ineleganolide (**1**).

Scheme 5.10.4 Successful cyclopropanation/Cope rearrangement and epoxidation



5.11 Concluding Remarks

In the best case, we will merge the asymmetric ketone alkylation and a tandem translactonization/Cope or cyclopropanation/Cope rearrangement into the synthesis of

ineleganolide (**1**). Already, we have developed the previously unknown palladium-catalyzed asymmetric alkylation of dioxanones. The resultant chloroalkene can be advanced through a mild oxidative bromination and Wittig olefination sequence to rapidly access enantioenriched cyclopentenol ent-**176**, following reduction. These alcohols can be coupled with cyclohexenone acid **174a**. These flexible vinylogous β-ketoesters can be advanced to rigid cyclopropanes. By necessity, we have created a rich body of chemistry exploring translactonizations in *cis*-substituted cyclopentane diols, including a translactonization/Cope cascade. We have also been able to access the carbon framework of ineleganolide via a formal cyclopropanation/Cope/epoxidation sequence. Both of these cascade sequences provide access to the rigid [6–7–5–5]-fused scaffold of ineleganolide (**1**).

5.12 Experimental Section

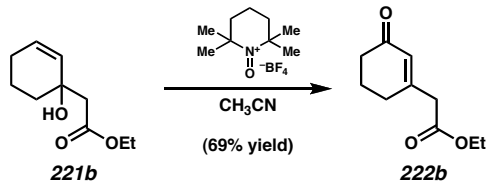
5.12.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tetrabutylammonium triphenyldifluorosilicate (TBAT) was purchased from Sigma-Aldrich Chemical Company and azeotropically dried five times from acetonitrile prior to use. Trimethylsilyl chloride (TMSCl), pyridine, and triethylamine (NEt_3) were distilled from sodium hydride immediately prior to use. Sodium iodide was dried by heating at 90 °C (2 torr) for 12 h. $TEMPO^+BF_4^-$,[8] *p*-acetamidobenzenesulfonyl azide (*p*ABSA),[26] TsN_3,[21] bis(*N-tert*-butylsalicylaldehydiminato) copper (II, $Cu(tbs)_2$),[22] Dess-Martin periodinane (DMP),[23] diazomethane,[24] and Amberlyst A26 ($S_2O_3^{2-}$)[25] were prepared by known methods. Other

reagents were used without further purification. Molecular sieves were purchased from Sigma Aldrich Chemical Company as activated 5 μm powder and stored in a 120 °C drying oven until immediately prior to use unless otherwise noted. Rhodium octanoate was purchased from Strem. *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC•HCl) and 4-(dimethyl amino)pyridine (DMAP) and *N*,*N'*-dicyclohexylcarbodiimide (DCC) were purchased from Sigma Aldrich Chemical Company. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or CAM staining. Florisil® (100–200 mesh) and ICN Silica gel (particle size 0.032–0.063 mm) were used for flash chromatography. Chiral HPLC analysis was performed with an Agilent 1100 Series HPLC utilizing chiralpak AD or chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm or 220 nm. Chiral GC anaylsis was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25 cm) column (1.0 mL/min carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300, 500, or 600 NMR spectrometer (at 300, 500, or 600 MHz, and 75, or 125 MHz, respectively), and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). If carbons were not recorded in a particular spectrum, then the missing carbons were noted by italicizing the absent carbon in a partial formula at the beginning of the spectrum. IR spectra were recorded on a Perkin

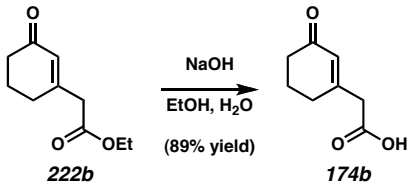
Elmer Paragon 1000 spectrometer and are reported in wavenumbers (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility, or acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

5.12.2 Preparative Procedures



221b *222b*

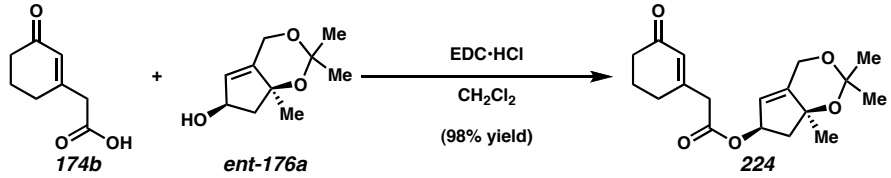
Ethyl 2-(3-oxocyclohex-1-enyl)acetate (222b).[8] To a 0.17 M acetonitrile solution of known allylic alcohol **221b**[6] (1.14 g, 6.19 mmol) at ambient temperature was added $TEMPO^{+}BF_4^{-}$ (1.49 g, 6.15 mmol). After stirring for 1 hour, the orange solution was poured onto H_2O (30 mL) and Et_2O (100 mL). The organic and aqueous phases were separated and the aqueous layer further extracted with Et_2O (2 x 100 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (1:10→1:4→1:1 EtOAc:hexanes) to yield known[6] cyclohexenone **222b** (0.77 g, 69% yield) as a colorless liquid. ^{1}H NMR of this compound was as reported in the literature.[6]



222b *174b*

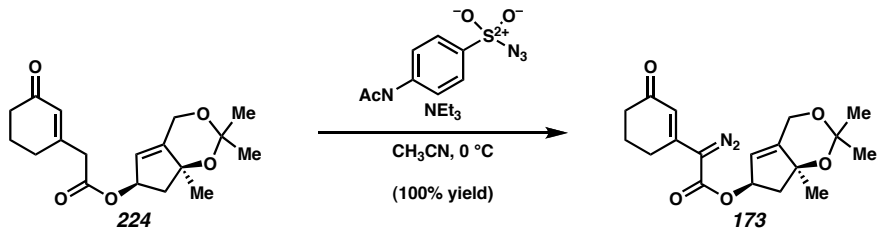
2-(3-Oxocyclohex-1-enyl)acetic acid (174b). To a 1:1 EtOH/H_2O solution (0.14 M) of ester **222b** [6] (0.76 g, 4.2 mmol) cooled in an ice water bath was added NaOH (aq) (1.8

mL, 3.04 M, 5.47 mmol) dropwise. The bright yellow solution was allowed to warm to room temperature and stirred for 5 hours. The solution was quenched with 10% HCl (aq) (15 mL) and extracted with EtOAc (5 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (3:1→1:1→0:1 hexanes/EtOAc eluent) to yield carboxylic acid **174b** (0.57 g, 89% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (m, 1H), 3.28 (d, J = 0.7, 2H), 2.43–2.39 (m, 4H), 2.03 (dt, J = 13.1, 6.3, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.07, 174.54, 157.10, 129.13, 43.07, 37.02, 29.76, 22.60; IR (thin film/NaCl) 3445, 2950, 1722, 1652, 1415, 1377, 1351, 1328, 1260, 1197, 1130, 974, 884 cm^{-1}; HRMS-MM: ESI–APCI *m/z* calc'd for $C_8H_{10}O_3$ $[M+H]^+$: 155.0703, found 155.0704.



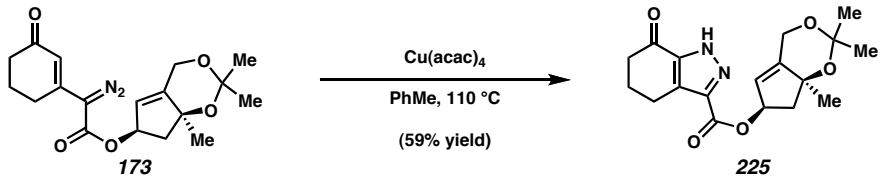
Ester 224. A concentration flask was charged with a yellow mixture of acid **174b** (1.303 g, 8.4 mmol, 3 equiv), alcohol ent-**176a** (from 2.95 mmol ketone **205**, 1 equiv) and EDC•HCl (1.131g, 5.9 mmol, 2 equiv) in CH_2Cl_2 (29.5 mL, 0.1 M). The suspension was cooled to 0 °C (ice water bath) and treated with DMAP (72 mg, 0.59 mmol, 0.2 equiv). The suspension was allowed to gradually warm to room temperature (ca. 25 °C) as the ice bath melted. After 3.5 hours, the reaction was treated with additional EDC•HCl (1.131g, 5.9 mmol, 2 equiv). After 1.5 hours, the solution was cooled to 0 °C (ice water bath) and treated with 0.1 N HCl (6 mL). The layers were separated, and the organics were further rinsed with 0.1 N HCl (6 mL), 5% K_2CO_3 (aq, 6 mL x 2), and brine (6 mL)

in succession. Each aqueous layer was further extracted with EtOAc (12 mL x 10). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give ester **224** as a yellow oil (0.923 g, 98% yield). R_f 0.72 (EtOAc; UV active; visualized with anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (d, J = 0.7, 1H), 5.59–5.52 (m, 1H), 5.51 (dd, J = 3.2, 1.7, 1H), 4.67–4.63 (m, 2H), 3.21 (s, 2H), 2.56 (dd, J = 12.9, 6.7, 1H), 2.40–2.32 (m, 4H), 2.00 (dt, J = 12.7, 6.5, 2H), 1.92 (dd, J = 12.8, 6.6, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.51, 169.42, 157.12, 147.15, 129.10, 121.26, 100.40, 80.97, 77.04, 60.38, 49.29, 43.63, 37.35, 30.07, 29.81, 28.60, 25.84, 22.77; IR (thin film/NaCl) 3440, 2929, 2863, 1732, 1667, 1427, 1327, 1257, 1169, 1127, 974 cm^{-1}; HRMS–EI *m/z* calc'd for $C_{18}H_{24}O_5$ $[M+]^+$: 320.1624, found 320.1613; $[\alpha]_D^{24.1}$ 28.4° (*c* 0.11, $CHCl_3$, derived from ketone **205** with 91% ee).



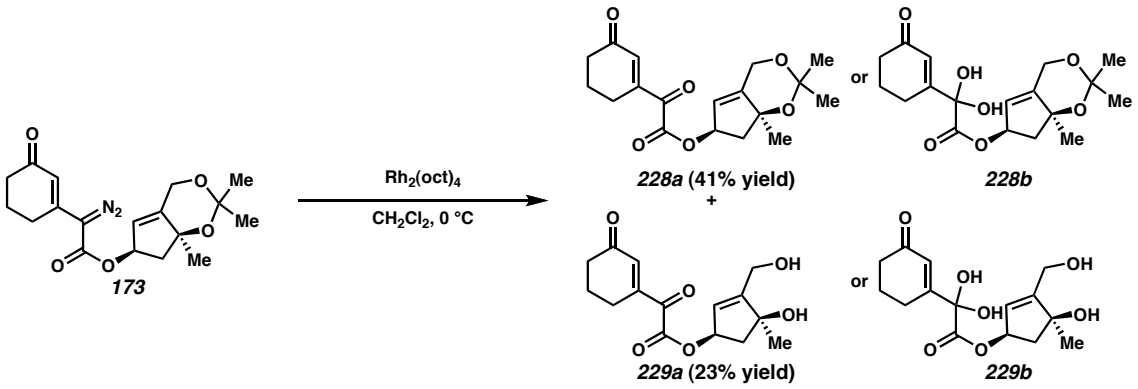
Diazoester 173. A vial beneath N_2(g) was charged with ester **224** (32 mg, 0.1 mmol, 1 equiv), CH_3CN (0.5 mL, 0.2 M) and *p*ABSA (31 mg, 0.13 mmol, 3 equiv).[26] The solution turned deep yellow upon dropwise addition of NEt_3 (0.04 mL, 0.3 mmol, 3 equiv). After six hours, the yellow mixture was treated with Et_2O and filtered through a plug of SiO_2 (ca. 1 mL) with copious elution. The yellow solution was concentrated under reduced pressure. The residue was diluted with EtOAc and purified by flash chromatography (SiO_2 (ca. 14 mL), 1:3 → 1:2 EtOAc:hexanes eluent) to give diazoester **173** as a yellow

oil (37 mg, 100% yield). R_f 0.38 (1:1 EtOAc:hexanes; visualized with UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.67 (dddd, J = 8.5, 6.7, 3.4, 1.9, 1H), 5.54 (dd, J = 3.5, 1.5, 1H), 4.69–4.65 (m, 1H), 4.65–4.61 (m, 1H), 2.58 (dd, J = 12.8, 6.9, 1H), 2.54–2.49 (m, 2H), 2.41–2.36 (m, 2H), 2.06 (dt, J = 12.7, 6.3, 2H), 1.97 (dd, J = 12.9, 6.5, 1H), 1.43 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, $-C{=}N_2$ or $-C(CH_3)_2$) δ 197.37, 162.66, 147.45, 147.22, 121.27, 120.85, 100.45, 80.98, 77.45, 60.35, 49.36, 36.99, 30.01, 28.61, 26.78, 25.90, 22.49; IR (CH2Cl2) 2989, 2939, 2866, 2101, 1708, 1580, 1370, 1352, 1329, 1229, 1191, 1137, 1110, 1064, 994, 847, 744 cm^{-1}; HRMS–EI *m/z* calc'd for $C_{18}H_{22}O_5N_2$ $[M+]^+$: 346.1529, found 346.1524; $[\alpha]_D^{24.4}$ 47.9° (*c* 0.11, $CHCl_3$, derived from ketone **205** with 91% ee).



Pyrazole 225. A flask fitted with a reflux condenser was charged with diazoester **173** (20 mg, 0.054 mmol, 1 equiv) and PhMe (8 mL, 0.00675 M). The yellow solution was treated with a warm (previously refluxing) solution of copper(II) acetylacetonate (2.8 mg, 0.011 mmol, 0.2 equiv) in PhMe (2 mL, with 10 mL wash, 0.054 M in diazoester **173**). The solution was heated in an oil bath at 110 °C. After 40 minutes, the solution was removed from heat and concentrated under reduced pressure. The residue was diluted with 1:1 EtOAc:hexanes and purified by flash chromatography (SiO_2 ~ 8 mL; 1:1 EtOAc:hexanes eluent) to give pyrazole **225** as a white solid (10 mg, 59% yield). Colorless crystals could be obtained by slow diffusion of PhH into a solution of pyrazole **225** in $CHCl_3$. Melting point analysis resulted in crystals yellowing at 149–150 °C and

then converting to a red liquid as gas evolved at 170–172 °C. R_f 0.26 (1:1 EtOAc:hexanes; visualized with UV or anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.40 (s, 1H), 5.80 (ddtd, J = 6.8, 5.0, 3.4, 1.9, 1H), 5.67 (dt, J = 3.0, 1.5, 1H), 4.70 (ddd, J = 15.7, 3.3, 2.4, 1H), 4.68–4.63 (m, 1H), 3.01 (t, J = 6.1, 2H), 2.68 (dd, J = 12.7, 6.8, 1H), 2.60 (dd, J = 7.3, 5.6, 2H), 2.14 (ddt, J = 12.8, 7.3, 3.5, 3H), 1.63 (s, 2H), 1.47 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, –*C*=O, –*CC*(O)OR) δ 147.18, 131.82, 121.42, 110.22, 100.44, 81.03, 77.15, 60.42, 49.46, 38.70, 30.07, 29.91, 28.64, 25.86, 24.56, 21.51; IR (thin film/NaCl) 3286, 2990, 2937, 2861, 1716, 1689, 1512, 1461, 1380, 1369, 1356, 1339, 1299, 1258, 1188, 1172, 1094, 1042, 994, 851, 832, 766 cm^{-1}; HRMS–EI *m/z* calc'd for $C_{18}H_{23}O_5N_2$ $[M+H]^+$: 347.1607, found 347.1596; $[\alpha]_D^{27.4}$ +45.6° (*c* 0.59, acetone, derived from ketone **205** with derived from ketone **205** with 91% ee).

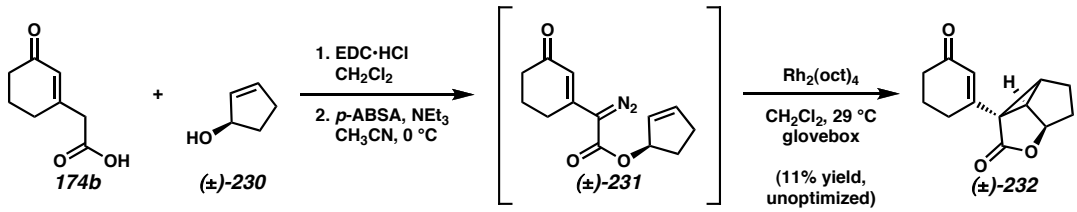


Oxidized 228a, or **228b**, and **229a**, or **229b**.[27] As a note of clarification, one set of data has been acquired for compound **228**, and another for compound **229**. ^{13}C and IR spectra support their assignment as ketones **228a** and **229a**, respectively, while HRMS data supports their assignment as hydrates **228b** and **229b**, respectively. It is likely that these hydrates form under the conditions used to obtain HRMS data.

A vial was charged with rhodium octanoate dimer ($Rh_2(oct)_4$, 0.6 mg, 0.0007 mmol, 0.01 equiv) and CH_2Cl_2 (0.2 mL, 0.375 M relative to diazoester **173**). The pale green solution was cooled to 0 °C (ice water bath). To it was added dropwise diazoester **173** (28 mg, 0.075 mmol, 1 equiv) in CH_2Cl_2 (0.22 mL, 0.341 M). After 25 minutes, the yellow solution was treated with additional $Rh_2(oct)_4$ (0.4 mg, 0.0005 mmol, 0.007 equiv). After an additional 18 hours, the yellow solution was treated with a third portion of $Rh_2(oct)_4$ (0.4 mg, 0.0005 mmol, 0.007 equiv). After an additional two hours, the reaction was diluted with EtOAc (10 mL), filtered through a plug of celite and concentrated under reduced pressure. The residue was diluted with EtOAc (10 mL), filtered and concentrated. This residue was purified by flash chromatography (SiO_2 ~ 16 mL; 1:40 → 1:20 → 1:5 → 1:0 EtOAc:CH_2Cl_2 then 1:20 MeOH:EtOAc elution) to give oxidized **228a** (9.8 mg, 41% yield). R_f 0.61 (1:5 EtOAc:CH_2Cl_2; UV/Vis); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (t, J = 1.7, 1H), 5.75–5.70 (m, 1H), 5.58 (dd, J = 3.7, 1.7, 1H), 4.70–4.62 (m, 2H), 2.64 (dd, J = 12.9, 6.9, 1H), 2.54 (td, J = 6.1, 1.8, 2H), 2.52–2.47 (m, 2H), 2.11–2.02 (m, 3H), 1.44 (d, J = 0.5, 3H), 1.41 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.04, 188.67, 162.67, 149.98, 148.57, 137.01, 120.17, 100.56, 80.98, 78.98, 60.34, 49.00, 38.24, 30.09, 28.73, 25.73, 22.99, 21.90; IR (thin film/NaCl) 3384, 2934, 2871, 1732, 1682, 1455, 1429, 1416, 1373, 1350, 1317, 1257, 1195, 1148, 1110, 1065, 1030, 978, 949, 902, 849, 735 cm^{-1}; HRMS–ES *m/z* calc'd for **228** $C_{18}H_{24}O_7$ $[M+H]^+$: 353.1600, found 353.1631; $[\alpha]_D^{26.6}$ +30.4° (*c* 0.15, $CHCl_3$, derived from ketone **205** with derived from ketone **205** with 91% ee).

Chromatography also furnished slightly impure acetonide-cleaved **229a** or **229b**. Acetonide-cleaved **229a** or **229b** was purified by flash chromatography (SiO_2 ~ 2 mL;

4:1 EtOAc:hexanes elution) to give acetonide-cleaved **229a** (4.8 mg, 23% yield). R_f 0.40 (EtOAc; UV active, visualized with anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (t, J = 1.7, 1H), 5.85 (d, J = 1.3, 1H), 5.70–5.64 (m, 1H), 4.48–4.31 (m, 2H), 2.60 (dd, J = 14.7, 7.2, 2H), 2.53 (ddd, J = 10.9, 8.5, 6.7, 2H), 2.51–2.43 (m, 2H), 2.44 (s, 1H), 2.16 (dd, J = 14.6, 3.3, 1H), 2.13–2.03 (m, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.23, 188.61, 172.82, 162.61, 155.18, 137.07, 124.38, 81.42, 78.75, 59.25, 47.87, 38.21, 26.59, 22.97, 21.90; IR (thin film/NaCl) 3382, 2968, 2935, 2872, 1732, 1682, 1455, 1428, 1415, 1373, 1349, 1318, 1259, 1193, 1110, 1092, 1065, 1030, 979, 949, 903, 854, 797, 734 cm^{-1}; HRMS (ES+) *m/z* calc'd for **229** $C_{15}H_{18}O_6$ $[M+H]^+$: 295.1182, found 295.1195; HRMS–ES *m/z* calc'd for **229** $C_{15}H_{20}O_7$ $[M+H]^+$: 313.1287, found 313.1286; $[\alpha]_D^{24.9}$ +48.8° (*c* 0.09, $CHCl_3$, derived from ketone **205** with derived from ketone **205** with 91% ee).



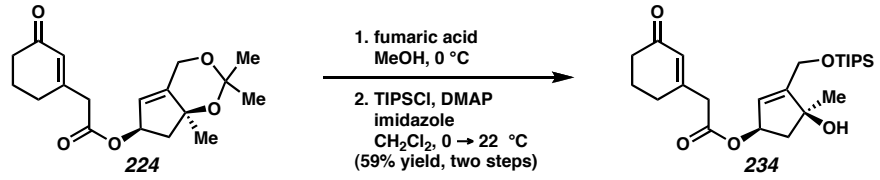
Cyclopropane 232. A flask was charged with 2-cyclopentenol[28] (**230**, 0.235 g, 2.8 mmol, 1 equiv), carboxylic acid **174b** (0.637 g, 4.2 mmol, 1.5 equiv), CH_2Cl_2 (28 mL, 0.1 M) and DCC (0.749 g, 3.6 mmol, 1.3 equiv). The pale yellow solution was cooled to 0 °C (ice water bath). The cold solution was treated with DMAP (68 mg, 0.56 mmol, 0.2 equiv), and the solution became a deep orange suspension. The mixture was allowed to gradually warm to room temperature (ca. 25 °C). After 24.5 hours, the brown mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL), filtered through SiO_2 (ca. 5 mL), concentrated under reduced pressure, and purified by

flash chromatography (SiO_2 ~ 60 mL; 1:1:4 EtOAc:CH_2Cl_2:hexanes elution) to give a yellow residue (99 mg, ≤18% yield). R_f 0.78 (EtOAc; UV active; visualized with anisaldehyde stain).

A flask was charged with a yellow solution of the residue (80 mg, 0.40 mmol, 1 equiv), CH_3CN (2 mL, 0.2 M) and *p*ABSA (0.125 g, 0.52 mmol, 1.3 equiv). The solution was treated with NEt_3 (0.17 mL, 1.2 mmol, 3 equiv) to produce a deeper yellow solution, which became a suspension with time. After 21 hours, the suspension was concentrated under reduced pressure. The residue was dissolved in EtOAc and flash chromatographed (SiO_2 ~ 16 mL; 1:4 → 1:3 → 1:2 EtOAc:hexanes eluent) to give diazoester **231** and slightly impure diazoester **231**. R_f 0.38 (1:1 EtOAc: hexanes; UV/Vis).

A flask in an N_2-filled glovebox was charged with a solution of rhodium octanoate (0.4 mg, 0.0005 mmol, 0.015 equiv) in CH_2Cl_2 (0.1 mL, 0.35 M relative to diazoester) at 29 °C. To this was added diazoester **231** (8.5 mg, 0.035 mmol, 1 equiv) in CH_2Cl_2 (0.75 mL, 0.047 M). After 4 h, the reaction was removed from the glovebox and concentrated under reduced pressure. It was partially purified by pipette column (3:1 hexanes:THF eluent), followed by further purification by pipette column (3:1 PhH:EtOAc eluent), and finally purification by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; 1:1 PhH:EtOAc elution x 3) to give cyclopropane **232** (0.8 mg, 11% yield) as a yellow oil. R_f 0.36 (1:1 EtOAc:PhH; UV active; visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (t, J = 1.6, 1H), 5.00 (dd, J = 3.9, 1.3, 1H), 3.17 (dd, J = 6.5, 4.4, 1H), 2.74 (dddd, J = 18.5, 6.9, 5.3, 1.6, 1H), 2.49–2.42 (m, 1H), 2.36 (dd, J = 7.5, 6.0, 2H), 2.31–2.19 (m, 3H), 2.09 (dd, J = 13.0, 6.0, 1H), 2.06–1.96 (m, 3H), 1.96–1.88 (m, 2H), 1.83–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$,

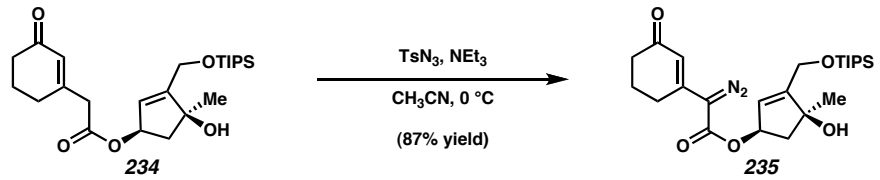
–*C*=O) δ 157.92, 126.64, 82.54, 42.96, 41.22, 40.59, 37.58, 37.28, 31.20, 28.03, 23.91, 22.81; IR (thin film/NaCl) 3494, 2928, 1760, 1668, 1610, 1337, 1255, 1192, 1103, 994, 964 cm^{-1}; HRMS–EI *m/z* calc'd for $C_{13}H_{14}O_3$ $[M+H]^+$: 218.0943, found 218.0940.



Silyl ether 234. A flask was charged with acetonide **224** (0.451 g, 1.41 mmol, 1 equiv) in MeOH (30 mL, 0.047 M), and the solution was cooled to 0 °C (ice water bath). The solution was treated dropwise with a solution of fumaric acid (59 mg, 0.50 mmol, 0.36 equiv) in MeOH (10 mL, 0.14 M total relative to acetonide). After 3 days, the reaction was quenched by addition of a 1:1 solution of H_2O and saturated aq $NaHCO_3$ (40 mL each), and extracted with EtOAc (300 mL, and then 200 mL x 5). The organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a golden/orange oil.

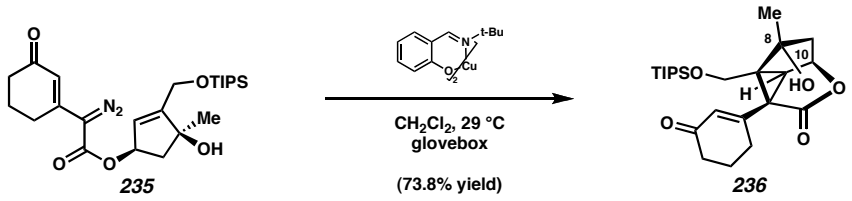
The resultant oil was dissolved in CH_2Cl_2 (35 mL, 0.040 M), placed beneath an Ar(g) atmosphere, and cooled to 0 °C (ice water bath). The solution was treated dropwise with imidazole (0.303 g, 4.46 mmol, 3.16 equiv) in CH_2Cl_2, followed by TIPSCl (0.91 mL, 4.25 mmol, 3.01 equiv) and DMAP (20 mg, 0.16 mmol, 0.11 equiv) in CH_2Cl_2. After 17 hours, the solution was quenched with saturated aq NH_4Cl (50 mL), and extracted with EtOAc (150 mL x 3). The organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The reaction was purified by flash chromatography (1:19 → 1:9 EtOAc:CH_2Cl_2 eluent) to give silyl ether **234** (0.371 g, 59% yield over two steps) as a yellow oil. R_f 0.76 (EtOAc, UV/Vis, visualized with

anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (t, J = 1.0, 1H), 5.70 (dd, J = 3.5, 1.7, 1H), 5.47 (dtd, J = 7.2, 3.6, 1.8, 1H), 4.56–4.35 (m, 2H), 3.20 (s, 2H), 2.78 (s, 1H), 2.49 (dd, J = 14.4, 7.3, 1H), 2.39–2.32 (m, 4H), 2.08–1.88 (m, 3H), 1.38 (s, 3H), 1.18–1.07 (m, 3H), 1.06–1.02 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.61, 169.49, 157.34, 153.60, 129.07, 124.49, 81.10, 76.91, 60.40, 48.00, 43.73, 37.35, 29.77, 26.79, 22.76, 18.20, 12.03; IR (thin film/NaCl) 3440, 2943, 2890, 2866, 1733, 1668, 1462, 1368, 1325, 1255, 1192, 1165, 1127, 1107, 1055, 994, 883, 683 cm^{-1}; HRMS (mixed EIC+) *m/z* calc'd for $C_{24}H_{40}O_5Si$ $[M+Na]^+$: 459.2537, found 459.2539; $[\alpha]_D^{18.9}$ +44.8° (*c* 0.93, $CHCl_3$, derived from ketone **205** with 91% ee).



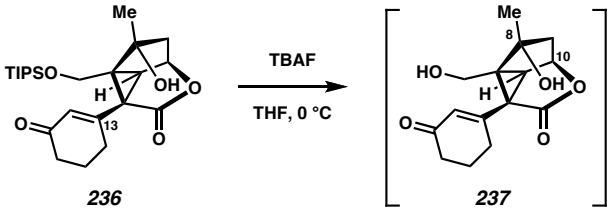
Diazoester 235. A flask was charged with a pale yellow solution of ester **234** (53 mg, 0.121 mmol, 1 equiv) in CH_3CN (4.7 mL, 0.026 M) with TsN_3 (0.600 g, 0.535 mmol, 4.4 equiv), and cooled to 0 °C (ice water bath). CAUTION!!! TsN_3 is SHOCK SENSITIVE AND POTENTIALLY EXPLOSIVE. The solution was treated with Et_3N (0.03 mL, 0.22 mmol, 1.8 equiv) dropwise, and immediately turned deeper yellow in color. After 24 hours, the reaction was concentrated under reduced pressure. The crude yellow mixture was purified by flash chromatography (SiO_2 ~ 16 mL; 1:5 EtOAc:PhH eluent) to give diazoester **235** (48.9 mg, 87% yield) as a yellow oil. R_f 0.48 (1:2 EtOAc:PhH; visualized with UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.71 (dd, J = 3.3, 1.6, 1H), 5.59 (ddd, J = 7.3, 3.7, 1.9, 1H), 2.82 (s, 1H), 2.58–2.49 (m, 3H), 2.41–2.35 (m, 2H), 2.10–2.00 (m, 3H), 1.40 (s, 3H), 1.13 (tt, J = 12.2, 6.9, 3H), 1.08–1.03 (m, 21H); ^{13}C NMR

(125 MHz, $CDCl_3$, $-C{=}N_2$) δ 197.48, 162.70, 153.74, 147.50, 124.41, 120.65, 81.05, 77.43, 60.40, 48.22, 36.98, 26.97, 26.76, 22.47, 18.19, 12.03; IR (thin film/NaCl) 3407, 2943, 2891, 2866, 2101, 1709, 1645, 1578, 1463, 1387, 1354, 1326, 1255, 1231, 1191, 1138, 1106, 1061, 993 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{24}H_{39}N_2O_5Si$ $[M+H]^+$: 463.2628, found 463.2640; $[\alpha]_D^{23.4}$ +48.5° (*c* 0.175, $CHCl_3$, derived from ketone **205** with 91% ee).



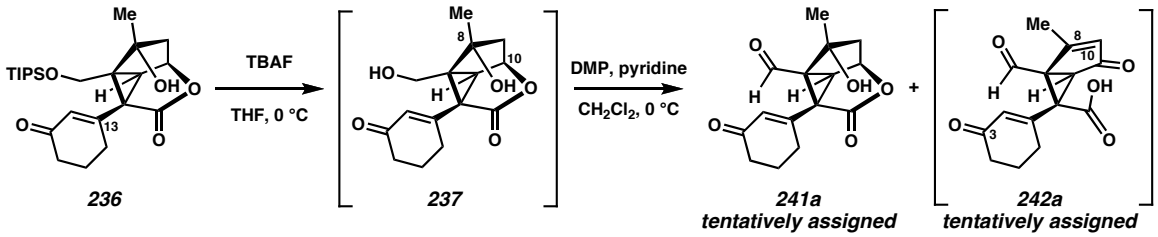
Cyclopropane 236. In the glovebox, a flask was charged with $Cu(tbs)_2$ (92.2 mg, 0.22 mmol, 1.1 equiv) and CH_2Cl_2 (20 mL, 0.01 M). This solution was treated with diazoester **235** (93.2 mg, 0.20 mmol, 1 equiv) in CH_2Cl_2 (8 mL, 0.025 M). After 7 days, the reaction was removed from the glovebox and concentrated under reduced pressure to yield a brown residue, which was purified by flash chromatography (SiO_2 ~ 16 mL; 1:1 EtOAc:hexanes eluent) to give cyclopropane **236** as a yellow oil (62.8 mg, 73.8% yield). R_f 0.18 (1:1 EtOAc:hexanes; UV active; visualized with anisaldehyde stain); ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (s, 1H), 4.91 (td, J = 6.2, 2.9, 1H), 4.11 (d, J = 11.5, 1H), 3.53 (d, J = 11.5, 1H), 2.72–2.64 (m, 1H), 2.63 (d, J = 5.9, 1H), 2.49–2.27 (m, 2H), 2.21–2.01 (m, 3H), 1.97–1.87 (m, 1H), 1.78 (s, 1H), 1.53 (s, 3H), 1.15–0.80 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.67, 173.11, 156.45, 130.05, 93.76, 70.61, 59.86, 59.59, 53.75, 48.04, 42.84, 37.59, 29.48, 22.85, 19.09, 18.20, 12.08; IR (thin film/NaCl) 3427, 2943, 2893, 2867, 1759, 1668, 1626, 1463, 1382, 1346, 1322, 1291, 1258, 1192, 1175, 1122, 1085, 1065, 1028, 997, 966, 883, 797 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{24}H_{39}O_5Si$

$[M+H]^+$: 435.2567, found 435.2586; $[\alpha]_D^{21.2}$ –12.6° (*c* 0.125, $CHCl_3$, derived from ketone **205** with 91% ee).



236 *237*

Diol 237. A flask was charged with a colorless solution of silyl ether **236** (0.7 mg, 0.00165 mmol, 1 equiv) in THF (0.2 mL, 0.00825 M) at 0 °C (ice water bath). The solution was treated with TBAF (1M in THF, 2 μL, 0.002 mmol, 1.2 equiv), and the solution turned yellow in color. After 30 min, the reaction was filtered through SiO_2 (ca. 1 mL; EtOAc elution), and concentrated under reduced pressure to give a crude white paste, assigned as crude diol **237**. R_f 0.14 (EtOAc; UV/Vis active); ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (s, 1H), 4.93 (t, J = 6.3, 1H), 3.94 (d, J = 11.9, 1H), 3.66 (d, J = 12.0, 1H), 2.74–2.65 (m, 2H), 2.69 (d, J = 6.0, 1H), 2.47–2.34 (m, 3H), 2.31–2.23 (m, 2H), 2.19 (dd, J = 14.0, 7.0, 1H), 2.13 (d, J = 13.5, 1H), 2.11–2.01 (m, 2H), 1.99–1.89 (m, 2H), 1.69 (s, 3H); HRMS–EI *m/z* calc'd for $C_{15}H_{18}O_5$ $[M+^{\bullet}]^+$: 278.1154, found 278.1143.

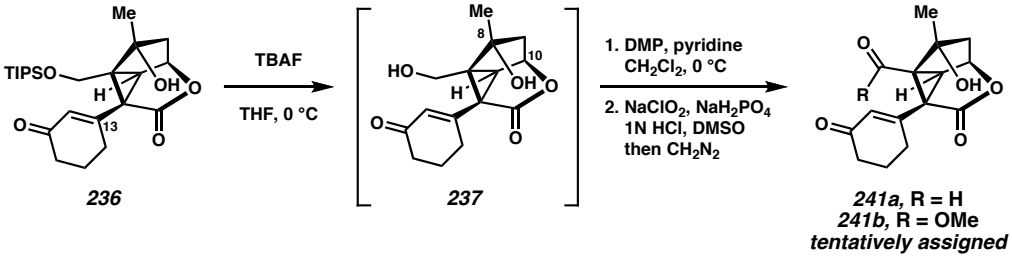


236 *237* ***241a*** ***tentatively assigned*** ***242a*** ***tentatively assigned***

Aldehyde 241a. A flask was charged with a colorless solution of silyl ether **236** (8.2 mg, 0.019 mmol, 1 equiv) in THF (0.2 mL, 0.095 M) at 0 °C (ice water bath). The solution was treated with TBAF (1M in THF, 6.4 μL, 0.0064 mmol, 0.34 equiv), and the solution turned yellow in color. After 13, 26, and 40 minutes, additional TBAF solution (5.0 μL,

0.005 mmol, 0.26 equiv per addition) was added to the reaction. After 53 min, the reaction was filtered through SiO_2 (ca. 0.5 mL; EtOAc elution), and concentrated under reduced pressure to give crude diol **237** as a yellow oil (4.6 mg, ≤85% yield).

A flask was charged with a yellow solution of crude diol **237** (4.6 mg, ≤0.0165 mmol, ≤0.85 equiv) in CH_2Cl_2 (0.8 mL, 0.023 M) and pyridine (0.04 mL, 0.49 mmol, 26 equiv) at 0 °C (ice water bath). The solution was treated with DMP (7 mg, 0.017 mmol, 0.89 equiv). CAUTION! DMP is a HEAT- and SHOCK-SENSITIVE COMPOUND, showing exotherms when heated (>130 °C). Operations should be conducted behind a blast shield. After 17 h at this temperature, the mixture was diluted with EtOAc (ca. 10 mL) and concentrated under reduced pressure. ^{1}H NMR was used as a qualitative measure of conversion, and showed a ratio of diol **237**:aldehyde **241a**:aldehyde **242a** of 1.1:1:0.5. The desired aldehyde (**241a**) was isolated through thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; EtOAc x 2 elution, R_f 0.35). Neither the diol (**237**), nor the over-oxidized aldehyde (**242a**) could be recovered from this purification. R_f 0.50 (EtOAc; visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 6.12 (s, 1H), 4.99 (td, J = 6.1, 1.5, 1H), 3.44 (d, J = 5.9, 1H), 2.64 (d, J = 22.4, 1H), 2.53–2.36 (m, 2H), 2.32–2.22 (m, 2H), 2.17 (s, 1H, O*H*), 2.14–2.01 (m, 2H), 1.97 (ddd, J = 16.5, 8.5, 4.1, 1H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, –O_2*CC*(*C*=)*CC*(O)H) δ 191.79, 131.96, 91.95, 69.63, 54.29, 46.82, 37.58, 29.29, 22.64, 20.01; HRMS–EI *m/z* calc'd for $C_{15}H_{16}O_5$ $[M+^{\bullet}]^+$: 276.0998, found 276.1007.

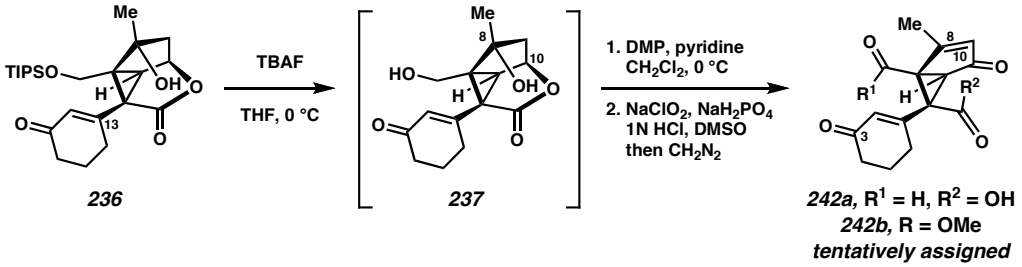


Ester 241b. For a representative desilylation procedure, see silyl ether **236** → diol **237**. Desilylation was carried out beginning with silyl ether **236** (0.9 mg, 0.0021 mmol, 1 equiv).

A flask was charged with a yellow solution of crude diol **237** in CH_2Cl_2 (0.2 mL, 0.0105 M) with pyridine (1 μL, 0.013 mmol, 6 equiv) at 0 °C (ice water bath). The solution was treated with DMP (1.2 mg, 0.0028 mmol, 1.3 equiv). CAUTION! DMP is a HEAT- and SHOCK-SENSITIVE COMPOUND, showing exotherms when heated (>130 °C). All operations should be carried out behind a blast shield. After 42 h at this temperature, the mixture was diluted with EtOAc (ca. 10 mL), filtered through SiO_2 (ca. 0.5 mL) and concentrated under reduced pressure. ^{1}H NMR was used as a qualitative measure of conversion, and showed a ratio of diol: desired aldehyde **241a** of 1:1, with an indeterminant amount of over-oxidized aldehyde (**242a**).

A flask was charged with a mixture including the crude aldehyde (**241a**) in DMSO (0.16 mL, 0.263 M) and saturated aq NaH_2PO_4 with 1N HCl (3:1, 0.03 mL, 0.135 M). The mixture was treated with $NaClO_2$ (1.8 mg, 0.02 mmol, 8.4 equiv). After 26 m, the solution was treated with CH_2N_2 (ca. 3 mL of a 1.7 M solution in Et_2O). Excess diazomethane was allowed to evaporate over several hours, at which point the reaction was carefully concentrated under reduced pressure. ^{1}H NMR was used as a qualitative measure of conversion, and showed a ratio of diol:methyl ester **241b**:bis-methyl ester

242b of 0.36:1:0.32. This mixture was combined with similar mixtures from other reactions, and purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall) with EtOAc elution. The desired methyl ester was removed from the plate at R_f 0.21, slightly impure. This mixture was further purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; 1:20 MeOH: Et_2O x 2 elution). The desired methyl ester (**241b**) was removed from the plate at R_f 0.27, still slightly impure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (s, 1H), 5.00–4.94 (m, 1H), 3.69 (s, 3H), 3.24 (d, J = 6.0, 1H), 2.662.58 (m, 2H), 2.47–2.39 (m, 2H), 2.30 (dd, J = 14.2, 7.3, 1H), 2.12–2.02 (m, 1H), 1.92 (ddd, J = 13.4, 8.0, 4.3, 2H), 1.51 (s, 3H); HRMS–EI *m/z* calc'd for $C_{16}H_{19}O_6$ $[M+^{\bullet}]^+$: 307.1182, found 307.1180. Note: This data has been recorded on a slightly impure sample, and is therefore not conclusive, but suggestive.



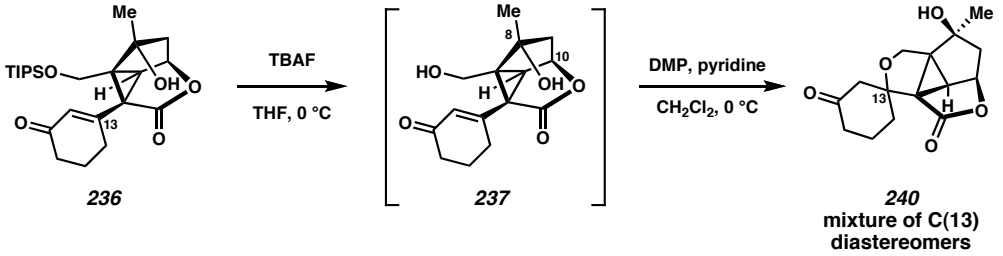
236 *237* ***242a,*** **R^1 = H, R^2 = OH** ***242b,*** **R = OMe** ***tentatively assigned***

Diester 242b. For a representative desilylation procedure, see silyl ether **236** → diol **237**. Desilylation was carried out beginning with silyl ether **236** (1.8 mg, 0.0042 mmol, 1 equiv).

A flask was charged with a mixture of crude diol **237** and DMP (7.3 mg, 0.017 mmol, 4 equiv) at 0 °C (ice water bath). CAUTION! DMP is a HEAT- and SHOCK-SENSITIVE COMPOUND, showing exotherms when heated (>130 °C). All operations should be carried out behind a blast shield. The mixture was treated with CH_2Cl_2 (0.4 mL, 0.0105 M). After 2 days at this temperature, the mixture was diluted with EtOAc (ca.

10 mL), filtered through SiO_2 (ca. 1 mL) and concentrated under reduced pressure to give a white solid, presumed to be aldehyde **242a**.

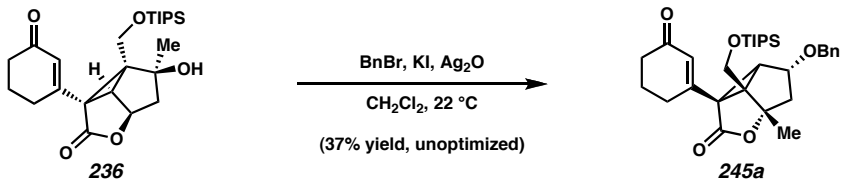
For a representative procedure for $NaClO_2$ oxidation and methylation, see silyl ether **236** → methyl ester **241b**. The reaction was purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; EtOAc elution). The targeted methyl ester (**242b**) was removed from the plate at R_f 0.46. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (d, J = 1.3, 1H), 5.61–5.58 (m, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.00 (d, J = 0.7, 1H), 2.50 (dddd, J = 18.3, 8.6, 4.8, 1.9, 1H), 2.46–2.31 (m, 6H), 2.08–1.89 (m, 3H).



Dihydropyran 240. For a representative desilylation procedure, see silyl ether **236** → diol **237**. Desilylation was carried out beginning with silyl ether **236** (5.6 mg, 0.013 mmol, 1 equiv).

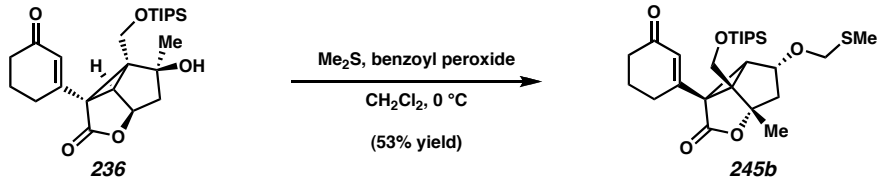
A flask was charged with a solution of crude diol **237**, CH_2Cl_2 (1.1 mL, 0.012 M) and pyridine (0.02 mL, 0.159 mmol, 12 equiv) at 0 °C (ice water bath), which was subsequently treated with DMP (7.9 mg, 0.018 mmol, 1.4 equiv). CAUTION! DMP is a HEAT- and SHOCK-SENSITIVE COMPOUND, showing exotherms when heated (>130 °C). ALL OPERATIONS SHOULD BE CONDUCTED BEHIND A BLAST SHIELD. After 2 days at this temperature, the mixture was diluted with EtOAc (ca. 10 mL), and concentrated under reduced pressure. The resultant semi-solid was treated with CH_2Cl_2 (ca. 1 mL) and Amberlyst A26 ($S_2O_3^{2-}$) (19.6 mg). After 6.5 h, the mixture was treated

with JandaJel (2.3 mmol/g, 17.2 mg, 0.0396 mmol, 3.0 equiv). After an additional 17.5 h, the mixture was filtered through SiO_2 (ca. 0.2 mL; EtOAc elution), and concentrated under reduced pressure. The diastereomeric mixture was purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; Et_2O x 2 elution). The desired diastereomeric mixture was removed from the plate at R_f 0.10. The diastereomeric mixture of dihydropyrans (**240**) was further purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; 1:1 EtOAc:PhH elution). The diastereomeric mixture was removed from the plate at R_f 0.27, as a white solid. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (app. dd, J = 7.8, 3.7, 1H), 4.01 (d, J = 9.4, 1H), 3.89 (d, J = 9.4, 1H), 3.18 (d, J = 4.8, 1H), 2.77 (ddd, J = 14.2, 11.6, 5.1, 1H), 2.70 (d, J = 14.1, 1H), 2.43–2.28 (m, 2H), 2.26 (dd, J = 14.1, 2.3, 1H), 2.18 (dd, J = 14.3, 2.0, 1H), 2.08–2.03 (m, 1H), 2.04–1.86 (m, 3H), 1.76–1.70 (m, 1H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.52, 172.90, 84.71, 80.50, 78.02, 64.66, 55.70, 53.05, 45.93, 45.65, 43.73, 40.87, 31.51, 27.84, 20.18. Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (app. dd, J = 7.8, 3.7, 1H), 4.10 (d, J = 9.6, 1H), 3.87 (d, J = 9.6, 1H), 3.58 (d, J = 15.1, 1H), 3.18 (d, J = 4.8, 1H), 2.77 (ddd, J = 14.2, 11.6, 5.1, 1H), 2.58 (d, J = 15.1, 1H), 2.43–2.28 (m, 2H), 2.18 (dd, J = 14.3, 2.0, 1H), 2.08–2.03 (m, 1H), 2.04–1.86 (m, 3H), 1.76–1.70 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.69, 173.02, 84.75, 80.54, 78.15, 64.70, 56.61, 52.83, 48.55, 45.65, 43.86, 40.58, 31.17, 27.80, 21.51. Diastereomeric Mixture: IR (thin film/NaCl) 3460, 3059, 2964, 2874, 1756, 1712, 1456, 1423, 1372, 1348, 1412, 1259, 1172, 1109, 1073, 1047, 1012, 982, 925, 867, 855, 810, 770, 733 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+Na]^+$ calc'd for $C_{15}H_{19}O_5$, 301.1046; found, 301.1067.



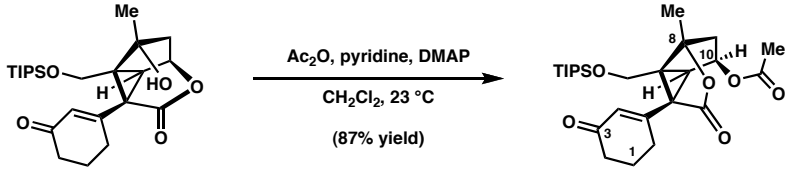
Benzyl ether 245a.[29] A flask was charged with a solution of silyl ether **236** (1.1 mg, 0.0026 mmol, 1 equiv) in PhMe (0.2 mL, 0.013 M) beneath an Ar(g) atmosphere at room temperature (22.5 °C). The solution was treated with KI (0.9 mg, 0.0054 mmol, 2.1 equiv) and Ag_2O (0.9 mg, 0.0039 mmol, 1.5 equiv), followed by BnBr (10 μL, 0.084 mmol, 32 equiv). After 2 days, the yellow mixture was heated in an oil bath at 40 °C for 22 hours, at which point additional BnBr (10 μL, 0.084 mmol, 32 equiv) was added to the reaction. After 24 h, the suspension was treated with Ag_2O (3.0 mg, 0.013 mmol, 5 equiv) and KI (4.6 mg, 0.028 mmol, 10.6 equiv). After an additional 27 h, additional BnBr (10 μL, 0.084 mmol, 32 equiv) was added to the reaction. After an additional 27 h, the reaction was diluted with EtOAc (10 mL), filtered through SiO_2, and concentrated under reduced pressure. The mixture was purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; 1:10 acetone:CH_2Cl_2 elution) to give benzoyl ester **245a** (0.5 mg, 37% yield, R_f 0.69). R_f 0.22 (1:1 Et_2O:heptanes, UV/Vis, visualized with anisaldehyde stain); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.32 (m, 4H), 7.29–7.26 (m, 1H), 5.92 (t, J = 1.4, 1H), 4.63 (d, J = 11.7, 1H), 4.52 (dd, J = 7.5, 5.6, 1H), 4.37 (d, J = 11.6, 1H), 4.16 (d, J = 11.5, 1H), 3.56 (d, J = 11.5, 1H), 2.79–2.72 (m, 1H), 2.60 (d, J = 5.6, 1H), 2.47 (ddd, J = 16.6, 9.2, 4.7, 1H), 2.39 (ddd, J = 12.1, 7.9, 4.7, 1H), 2.28 (d, J = 13.9, 1H), 2.21–2.08 (m, 2H), 2.14 (dd, J = 13.9, 7.6, 1H), 1.95 (tdd, J = 13.8, 9.3, 4.6, 1H), 1.70 (s, 3H), 1.12–0.90 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.21, 172.56, 156.26, 137.48, 129.72, 128.70, 128.20, 128.03, 93.15, 76.92, 71.45, 59.91, 59.38, 52.08,

48.09, 40.27, 37.65, 29.51, 22.86, 19.05, 18.22, 12.10; IR (thin film/NaCl) 3063, 3032, 2944, 2892, 2867, 1760, 1674, 1626, 1498, 1455, 1428, 1416, 1383, 1345, 1319, 1300, 1259, 1190, 1177, 1125, 1086, 1039, 1014, 996, 962, 935, 918, 883, 797, 737 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{31}H_{44}O_5Si$, 525.3031; found, 525.3023; $[\alpha]_D^{22.9}$ +5.9° (*c* 0.20, $CHCl_3$, derived from ketone **205** with 91% ee).



MTM-ether 245b. A vial was charged with a solution of alcohol **236** (2.0 mg, 0.0046 mmol, 1 equiv) in CH_3CN (0.3 mL) and dimethyl sulfide (4.5 μL, 0.061 mmol, 13.2 equiv) at 0 °C (ice water bath). Benzoyl peroxide (10.9 mg, 0.045 mmol, 9.8 equiv) was added to the solution in portions over 23 minutes. After 6.25 hours, the solution was extracted with Et_2O (5 mL x 4). The organic extracts were rinsed sequentially with 1N NaOH (0.9 mL), then brine (ca. 1 mL x 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The oil was purified by thin layer chromatography on a 250 μm plate (1:4 Et_2O:PhH x 2 elution; R_f 0.44) to give a mixture of desired **245b** and an aromatic compound. The mixture was loaded onto a plug of SiO_2 (ca. 1 mL), and rinsed with PhH, and eluted with EtOAc to provide MTM-ether **245b** as a yellow oil (1.2 mg, 53% yield). R_f 0.77 (1:1 EtOAc:hexanes, UV/Vis, visualized with anisaldehyde stain); ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (d, J = 1.5, 1H), 4.83 (t, J = 6.0, 1H), 4.66 (d, J = 11.8, 1H), 4.60 (d, J = 11.8, 1H), 4.16 (d, J = 11.5, 1H), 3.55 (d, J = 11.5, 1H), 2.71 (ddd, J = 17.8, 7.2, 3.7, 1H), 2.65 (d, J = 5.7, 1H), 2.46 (ddd, J = 16.9, 9.2, 4.8, 1H), 2.38 (ddd, J = 17.7, 8.3, 5.1, 1H), 2.23 (dd, J = 13.9, 0.9, 1H), 2.18

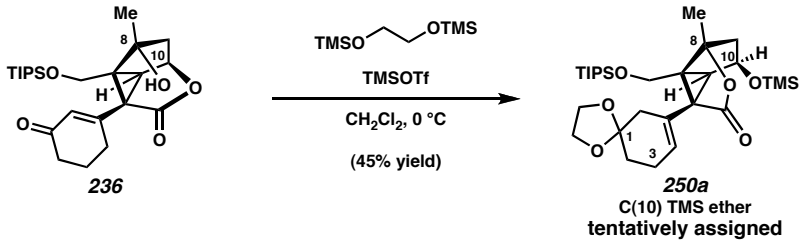
(dd, J = 13.9, 7.2, 2H), 2.12 (s, 3H), 2.14–2.05 (m, 1H), 1.99–1.90 (m, 1H), 1.70 (s, 3H), 1.12–0.94 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$, –*C*O_2R) δ 199.13, 156.01, 129.83, 93.36, 74.60, 73.79, 59.85, 59.14, 51.79, 48.14, 40.43, 37.63, 29.47, 22.86, 18.99, 18.22, 14.13, 12.10; IR (thin film/NaCl) 2943, 2867, 1760, 1674, 1627, 1463, 1430, 1383, 1323, 1297, 1257, 1190, 1173, 1125, 1081, 1036, 1014, 995, 960, 935, 915, 884, 797, 751, 726 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: [M+Na]$^+$ calc'd for $C_{26}H_{42}O_5SSi$, 517.2414; found, 517.2412; $[\alpha]_D^{18.8}$ +12.5° (*c* 0.13, $CHCl_3$, derived from ketone **205** with 91% ee).



236 ***245c***

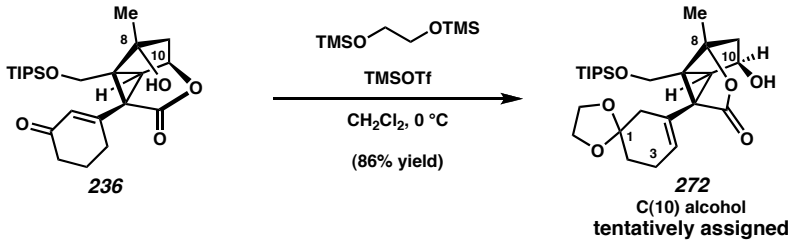
Secondary acetate 245c. A flask charged with CH_2Cl_2 (0.96 mL, 0.027 M), tertiary alcohol **236** (11.2 mg, 0.0258 mmol, 1 equiv), Ac_2O (0.03 mL, 0.33 mmol, 13 equiv) and pyridine (0.03 mL, 0.38 mmol, 15 equiv) at room temperature (23 °C) was treated with DMAP (0.4 mg, 0.003 mmol, 0.13 equiv). After 1 h 10 m, the solution was extracted with EtOAc (10 mL x 4), and rinsed successively with 1N HCl (3 mL) and brine (3 mL x 2). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a secondary acetate **245c** (11.7 mg, 87.3% yield) as a pale yellow oil. R_f 0.64 (1:1 EtOAc:hexanes, UV/Vis, visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, C_6D_6) δ 6.17 (t, J = 1.5, 1H), 5.11 (dd, J = 7.7, 5.9, 1H), 3.77 (d, J = 11.6, 1H), 3.40 (d, J = 11.6, 1H), 2.62 (d, J = 5.9, 1H), 2.46 (dddd, J = 9.4, 7.3, 5.0, 1.7, 1H), 2.11–1.96 (m, 4H), 1.80–1.72 (m, 4H), 1.58–1.44 (m, 2H), 1.42 (s, 3H), 0.93 (d, J = 1.9, 18H), 0.95–0.88 (m, 3H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (t, J = 1.5, 1H), 5.41 (td, J = 6.0, 2.1, 1H), 4.19 (d, J = 11.4, 1H), 3.53 (d, J = 11.5, 1H), 2.81 (d, J = 5.9, 1H), 2.54 (dddd, J

= 18.1, 7.3, 4.9, 1.5 1H), 2.45–2.29 (m, 2H), 2.24 (d, J = 0.9, 1H), 2.24 (d, J = 5.0, 1H), 2.21–2.13 (m, 1H), 2.09–2.01 (m, 1H), 2.00 (s, 3H), 1.99–1.89 (m, 1H), 1.70 (s, 3H), 1.10–0.92 (m, 3H), 1.02 (d, J = 3.8, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ 197.27, 171.93, 170.82, 154.60, 130.84, 92.53, 73.83, 60.38, 58.66, 50.92, 48.36, 41.98, 37.85, 29.55, 23.19, 20.58, 19.17, 18.46, 12.47; IR (film) 2943, 2867, 1769, 1740, 1675, 1628, 1463, 1374, 1323, 1241, 1191, 1173, 1127, 1082, 1064, 1025, 883, 796, 684 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{26}H_{40}O_6Si$, 477.2667; found, 477.2667; $[\alpha]_D^{17.9}$ –11.6° (*c* 0.35, CH_3CN, derived from ketone **205** with 91% ee).



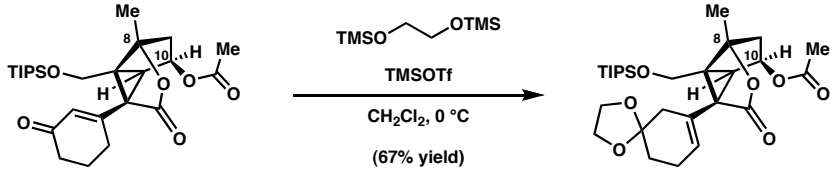
Ketal 250a. A flask was charged with ketone **236** (5.4 mg, 0.013 mmol, 1 equiv) in CH_2Cl_2 (1 mL, 0.013 M) and 1,2-bis(trimethylsilyloxy)ethane (0.06 mL, 0.26 mmol, 20 equiv) at 0 °C (ice water bath). The a pale yellow solution was treated with a 1% (v/v) solution of TMSOTf in CH_2Cl_2 (45 μL, 0.0025 mmol, 0.19 equiv). After 48 hours at this temperature, the yellow solution was quenched through addition of pyridine (0.03 mL, 0.0037 mmol, 0.28 equiv), and then concentrated under reduced pressure. The yellow oil was purified by flash chromatography (SiO_2 ~ 2.2 mL; 3:17 EtOAc:hexanes eluent). The desired material was further purified by flash chromatography (SiO_2 ~ 2.2 mL; 1:20 → 1:10 EtOAc:hexanes eluent). The desired material was purified by thin layer chromatography on a 250 μm plate (1:1 EtOAc:hexanes eluent, R_f 0.69) to give pure TMS-ether **250a** (3.2 mg, 45% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 5.63 (s, 1H), 4.75

(dd, J = 7.0, 6.0, 1H), 4.26 (d, J = 11.5, 1H), 3.56 (ddd, J = 7.8, 6.8, 4.7, 1H), 3.51–3.43 (m, 4H), 3.06 (dd, J = 16.9, 2.2, 1H), 2.63 (d, J = 5.9, 1H), 2.12 (app d, J = 13.1, 3H), 2.01–1.92 (m, 2H), 1.71–1.57 (m, 2H), 1.53 (s, 3H), 1.11–0.92 (m, 21H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.18, 130.16, 127.58, 108.50, 91.77, 71.58, 64.75, 64.62, 60.48, 57.54, 55.37, 49.16, 43.57, 39.58, 31.27, 25.08, 19.56, 18.53, 12.55, 0.451; IR (thin film/NaCl) 3512, 3044, 2944, 2892, 2867, 1766, 1674, 1464, 1433, 1382, 1366, 1321, 1298, 1252, 1202, 1175, 1127, 1084, 1062, 1023, 996, 972, 954, 926, 897, 883, 843, 801, 762, 735, 705 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: [M+Na]$^+$ calc'd for $C_{29}H_{50}O_6Si$, 573.3038; found, 573.3033; $[\alpha]_D^{15.9}$ –3.1° (*c* 0.32, CH_2Cl_2, derived from ketone **205** with 91% ee).



Ketal 272. For a representative ketalization procedure, see ketone **236** → ketal **250**. Ketalization was carried out beginning with silyl ether **236** (2.6 mg, 0.0061 mmol, 1 equiv) over 8 days. The resultant ketal was purified by thin layer chromatography on a 250 μm plate (EtOAc elution; R_f 0.39) to give pure ketal **272** (2.1 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74–5.70 (m, 1H), 4.89 (td, J = 6.9, 3.0, 1H), 4.30 (d, J = 11.5, 1H), 4.03–3.85 (m, 4H), 3.41 (d, J = 11.5, 1H), 2.62 (d, J = 6.0, 1H), 2.57 (dd, J = 16.8, 2.0, 1H), 2.37–2.29 (m, 1H), 2.29–2.20 (m, 1H), 2.17 (dd, J = 13.8, 7.3, 1H), 2.10 (d, J = 13.7, 1H), 1.82–1.74 (m, 1H), 1.73–1.66 (m, 1H), 1.65 (s, 3H), 1.13–0.96 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6, –*C*O_2R) δ 128.80, 128.49, 107.96, 93.20, 71.17, 64.67,

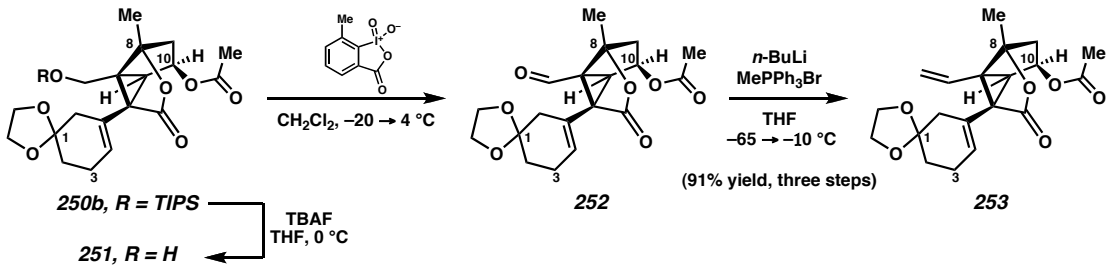
64.51, 59.81, 57.87, 59.81, 57.87, 54.32, 48.45, 43.14, 38.47, 30.66, 24.65, 19.06, 18.15, 12.07; IR (thin film/NaCl) 3446, 2942, 2867, 1760, 1464, 1382, 1325, 1257, 1176, 1115, 1082, 1062, 1022, 946, 882, 854, 797 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+Na]^+$ calc'd for $C_{26}H_{42}O_6Si$, 501.2643; found, 501.2640; $[\alpha]_D^{21.1}$ –3.5° (*c* 0.21, $CHCl_3$, derived from ketone **205** with 91% ee).



245c *250b*

Ketal 250b. A flask was charged with a colorless solution of ketone (7.0 mg, 0.015 mmol, 1 equiv), CH_2Cl_2 (2 mL, 0.0073 M), and 1,2-bis(trimethylsilyloxy)ethane (0.10 mL, 0.41 mmol, 28 equiv). The solution was cooled to 0 °C (ice water bath), and treated dropwise with a 1% v/v solution of TMSOTf in CH_2Cl_2 (150 μL, 0.000008 mmol, 0.0005 equiv). After two days, the solution was treated sequentially with CH_2Cl_2 (0.5 mL, 0.0294 M), 1,2-bis(trimethylsilyloxy)ethane (0.10 mL, 0.41 mmol, 28 equiv) and TMSOTf (150 μL of a solution containing TMSOTf (10 μL) in CH_2Cl_2 (1 mL), 0.000008 mmol, 0.0005 equiv). After an additional 12 h, the reaction was quenched through addition of pyridine (0.3 mL, 0.0037 mmol, 0.25 equiv), and then concentrated under reduced pressure. The resultant yellow oil was purified by thin layer chromatography on a 250 μm plate (12 cm x 20 cm; 1:1 Et_2O:hexanes, then 2:1 Et_2O:pentane elution) to furnish ketal **250b** (5.1 mg, 67% yield) as a colorless oil. R_f 0.64 (1:2 EtOAc:PhH, visualized with anisaldehyde stain); ^1H NMR (600 MHz, $CDCl_3$) δ 5.68 (tt, J = 3.5, 1.6, 1H), 5.39 (ddd, J = 5.6, 5.6, 2.8, 1H), 4.30 (d, J = 11.4, 1H), 3.99–3.88 (m, 3H), 3.88–3.82 (m, 1H), 3.39 (d, J = 11.5, 1H), 2.81 (d, J = 6.0, 1H), 2.46 (d, J = 16.8, 1H), 2.35–

2.26 (m, 1H), 2.24–2.15 (m, 3H), 1.99 (s, 3H), 1.74 (dddd, J = 16.8, 9.2, 4.8, 1.2, 2H), 1.69–1.61 (m, 4H), 1.56–1.51 (m, 3H), 1.10–0.98 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.10, 171.39, 129.52, 127.88, 107.90, 92.79, 73.86, 64.68, 64.50, 59.65, 57.19, 51.15, 48.51, 42.18, 38.39, 30.58, 24.61, 20.99, 18.87, 18.17, 12.06; IR (thin film/NaCl) 2943, 2867, 2892, 1763, 1739, 1463, 1432, 1373, 1323, 1298, 1243, 1201, 1173, 1131, 1115, 1079, 1062, 1045, 1023, 962, 948, 920, 903, 882, 852, 796, 737, 683, 657, 614 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{28}H_{44}O_7Si$, 521.2925; found, 521.2929; $[\alpha]_D^{21.0}$ +16.8° (*c* 0.37, $CHCl_3$, derived from ketone **205** with 91% ee).



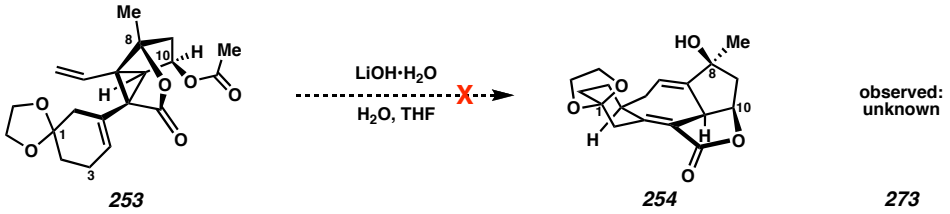
Divinylcyclopropane 253. A flask was charged with silyl ether **250b** (15.0 mg, 0.027 mmol, 1 equiv) in THF (2.3 mL, 0.012 M) at 0 °C (ice water bath). The colorless solution was treated dropwise with TBAF (1M in THF, 40 μL, 0.040 mmol, 1.5 equiv), generating a yellow solution. After 1.5 h, the solution was diluted with EtOAc (to 40 mL), filtered through SiO_2 (ca. 0.1 mL) and concentrated under reduced pressure to give primary alcohol **251** as a yellow oil. This yellow oil had already been characterized analytically as a byproduct in the ketalization reaction. R_f 0.07 (1:1 EtOAc:hexanes, visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (dd, J = 5.9, 3.3, 1H), 5.39 (td, J = 6.7, 1.6, 1H), 4.01 (dd, J = 6.1, 2.2, 1H), 4.00 (d, J = 6.1, 1H), 3.93 (d, J = 6.1, 1H), 3.91 (dd, J = 6.1, 1.3, 1H), 3.84 (d, J = 12.9, 1H), 3.81 (d, J = 13.0, 1H), 2.94 (d, J = 6.0, 1H), 2.74–2.67 (m, 1H), 2.39–2.31 (m, 1H), 2.27–2.18 (m, 3H), 2.01 (s, 3H),

1.96 (app d, J = 16.7, 1H), 1.77 (dd, J = 9.3, 6.6, 1H), 1.82–1.72 (m, 2H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.92, 171.28, 128.11, 127.08, 108.28, 92.71, 73.54, 64.79, 64.58, 58.60, 57.78, 50.91, 47.82, 41.01, 38.81, 30.04, 24.65, 20.94, 18.71; IR (thin film/NaCl) 3464, 2932, 1738, 1373, 1242, 1046, 1021 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{19}H_{24}O_7$, 365.1595; found, 365.1598; $[\alpha]_D^{22.5}$ +36.7° (*c* 0.13, $CHCl_3$, derived from ketone **205** with 91% ee).

The crude alcohol **251** was thrice concentrated from PhH (0.15 mL each), and backfilled with Ar(g). The diol **251** was diluted with CH_2Cl_2 (16 mL, 0.0017 M), cooled to –15 °C (cryocool temperature), and treated with crushed Me-IBX (15 mg, 0.051 mmol, 1.9 equiv). After 5 min, the solution was allowed to warm gradually to 4 °C (cold room temperature). After 18, 24, 30, 45, and 55 h, additional portions were added of crushed Me-IBX (67.4 mg total, 0.23 mmol, 8.5 equiv). After 65 h, the reaction was diluted with EtOAc (to ca. 25 mL), filtered through SiO_2 (ca. 0.2 mL), and concentrated under reduced pressure to give crude aldehyde **252**.

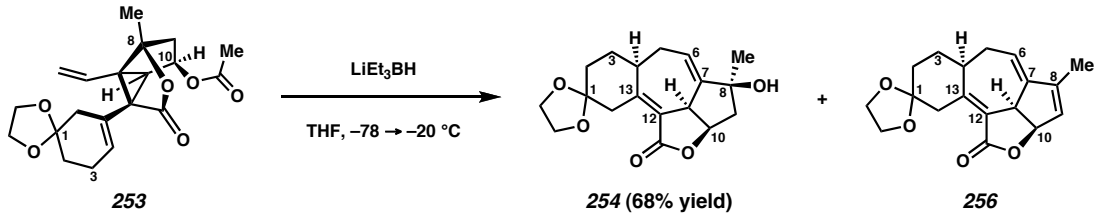
A flask was charged with a mixture of Ph_3PMeBr (0.129 g, 0.36 mmol, 13 equiv) in THF (9 mL, 0.003 M) at room temperature (ca. 24 °C). The mixture was treated dropwise with *n*-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol, 12.0 equiv), generating an orange solution. After 55 min, the orange solution had been cooled to –78 °C (acetone / dry ice) and was treated dropwise with crude aldehyde **252** in THF (0.3 mL x 2). The solution was allowed to gradually warm to –10 °C (over 1.33 h), at which point it was treated with acetone (0.3 mL). The reaction was rinsed with 1:1 brine:H_2O (ca. 1 mL), and extracted with EtOAc (to ca. 50 mL). Extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The mixture was purified by thin layer chromatography on 250

μm plates (10 cm x 20 cm; EtOAc x 2 elution) to furnish the desired divinylcyclopropane (**253**, R_f 0.79, 7.9 mg including ca. 5% other, 91% yield of slightly impure material) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (ddd, J = 17.1, 10.5, 0.5, 1H), 5.73 (tt, J = 3.5, 1.7, 1H), 5.39 (dd, J = 6.9, 5.9, 1H), 5.16 (dd, J = 10.5, 1.1, 1H), 5.03 (dd, J = 17.1, 1.1, 1H), 4.01–3.90 (m, 4H), 3.04 (d, J = 5.9, 1H), 2.32 (app ddd, J = 10.3, 6.0, 2.2, 2H), 2.23 (app dd, J = 14.3, 0.6, 2H), 2.16 (dd, J = 14.4, 7.6, 1H), 2.03 (s, 3H), 1.91 (dd, J = 10.1, 8.4, 1H), 1.75 (ddd, J = 14.0, 6.9, 3.9, 1H), 1.64–1.58 (m, 1H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, $-CO_2R$) δ 171.39, 130.16, 127.82, 127.03, 118.51, 107.92, 92.40, 73.45, 64.58, 64.49, 58.06, 50.54, 49.77, 40.98, 37.59, 30.72, 24.51, 20.98, 20.05; IR (thin film/NaCl) 2932, 1759, 1738, 1433, 1373, 1329, 1244, 1196, 1123, 1100, 1046, 1024, 958, 851, 734 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+Na]^+$ calc'd for $C_{20}H_{24}O_6$, 383.1465; found, 383.1466; $[\alpha]_D^{20.4}$ –11.2° (*c* 0.17, $CHCl_3$, derived from ketone **205** with 91% ee).



Unknown 273. A flask was charged with divinylcyclopropane **253** (1.4 mg, 0.0039 mmol, 1 equiv) and THF (1 mL, 0.0039 M), and cooled to 0 °C (ice water bath). The solution was treated dropwise with LiOH•H_2O (3.5 mg, 0.083 mmol, 21.5 equiv) in H_2O (0.35 mL). After 23 h, the solution was extracted with EtOAc (50 mL) and rinsed with 1:1 brine:H_2O (ca. 1 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. This product was combined with that from a similar reaction that had been performed with divinylcyclopropane **253** (0.5 mg). The

mixture was purified by thin layer chromatography on 250 μm plates (11 cm x 20 cm; 1:1 acetone:petroleum ether elution) to furnish unknown **273** (R_f 0.24) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 1.7, 1H), 5.62 (app dt, J = 5.1, 2.6, 1H), 4.88 (app dt, J = 9.3, 7.2, 1H), 4.30–4.26 (m, 1H), 4.10–4.06 (m, 1H), 4.03–3.99 (m, 1H), 3.93–3.89 (m, 1H), 3.22–3.16 (m, 1H), 2.52 (dd, J = 13.1, 7.3, 1H), 2.53–2.49 (m, 1H), 2.42–2.38 (m, 1H), 2.24–2.08 (m, 3H), 1.82–1.68 (m, 3H), 1.28 (d, J = 1, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2, –CO_2R) δ 152.79, 147.72, 118.77, 95.67, 79.28, 76.32, 69.81, 61.43, 48.86, 43.56, 35.27, 30.31, 30.26, 28.42, 28.31, 25.11; IR (thin film/NaCl) 3397, 2925, 1717, 1602, 1204, 1188, 1098, 1037 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+^{\bullet}]^+$ calc'd for $C_{18}H_{21}O_5$, 317.1384; found, 317.1391. Rotation not recorded.

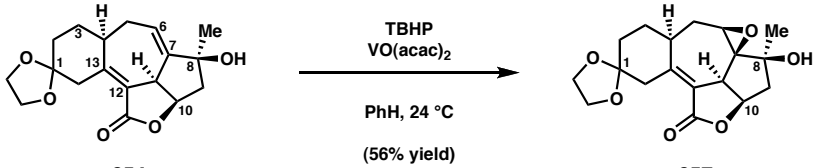


Cycloheptadiene 254. A flask was charged with acetate **253** (2.0 mg, 0.0055 mmol, 1 equiv) in THF (2.0 mL, 0.0028 M) at –78 °C (acetone, dry ice bath). The colorless solution was treated dropwise with $LiEt_3BH$ (0.5 M solution in THF, 24 μL, 2.2 equiv). After 10 min, the solution was allowed to warm to –20 °C (cryocool temperature). After an additional 6 h, the reaction was treated with H_2O (0.02 mL), allowed to warm to room temperature (ca. 24 °C), diluted with EtOAc (to 10 mL), filtered through SiO_2 (ca. 0.2 mL), and concentrated under reduced pressure. The product was combined with product from two equivalent reactions that had been run with acetate **253** (0.4 and 1.0 mg, respectively). The reactions were purified by thin layer chromatography on a 250 μm

plate (10 cm x 20 cm; EtOAc elution) to furnish the desired cycloheptadiene (**254**, R_f 0.34, slightly impure material). The material was further purified by thin layer chromatography on a 250 μm plate (10 cm x 20 cm; 1:5 acetone:CH_2Cl_2 elution) to furnish the desired cycloheptadiene (**254**, R_f 0.29, 1.8 mg, 68% yield). R_f 0.56 (EtOAc, UV/Vis, visualized with anisaldehyde stain); ^{1}H NMR (600 MHz, C_6D_6) δ 5.34 (ddd, J = 2.8, 5.0, 5.0 Hz, 1H), 4.12 (ddd, J = 7.1, 8.0, 9.2 Hz, 1H), 3.66 (ddd, J = 6.2, 6.8, 6.8 Hz, 1H), 3.62 (ddd, J = 5.1, 6.9, 6.9 Hz, 1H), 3.50 (br d, J = 15 Hz, 1H), 3.47 (ddd, J = 4.8, 6.9, 6.9 Hz, 1H), 3.42 (ddd, J = 5.9, 6.9, 6.9 Hz, 1H), 3.36 (d, J = 15.4 Hz, 1H), 3.27 (br d, J = 9 Hz, 1H), 2.15 (dddd, J = 4.5, 4.5, 8.9, 8.9 Hz, 1H), 1.92 (dd, J = 7.1, 12.8 Hz, 1H), 1.89 (dddd, J = 3.6, 3.6, 5.4, 16.7 Hz, 1H), 1.85 (dddd, J = 1.0, 4.3, 6.0, 13.7 Hz, 1H), 1.73 (ddd, J = 4.9, 10.8, 13.9 Hz, 1H), 1.67 (dddd, J = 2.4, 4.8, 9.5, 16.7, 1H), 1.43 (dddd, J = 5.4, 5.4, 5.4, 13.6 Hz, 1H), 1.37 (dddd, J = 4.2, 9.0, 10.6, 13.5 Hz, 1H), 1.34 (qdd, J = 0.9, 7.9, 12.8 Hz, 1H), 0.85 (d, J = 0.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.63, 156.01, 149.87, 124.54, 119.13, 109.85, 78.82, 76.30, 65.03, 64.84, 48.92, 43.65, 39.63, 35.56, 34.34, 30.80, 28.50, 28.47; IR (thin film/NaCl) 3446, 2927, 1738, 1647, 1362, 1288, 1256, 1197, 1125, 1044, 955 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{18}H_{22}O_5$, 319.1540; found, 319.1530; $[\alpha]_D^{23.8}$ +23.3° (*c* 0.18, CH_2Cl_2, derived from ketone **205** with 91% ee).

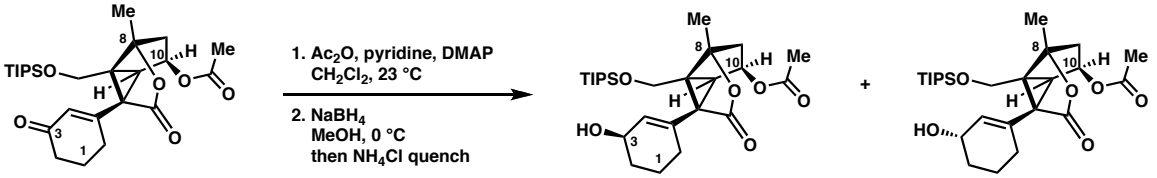
Dehydration product **256**. R_f 0.68 (1:5 acetone:PhH; visualized with anisaldehyde stain); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 5.88 (s, 1H), 5.58 (dt, J = 2.2, 6.0, 1H), 5.35 (app ddd, J = 1.2, 1.1, 7.4, 1H), 4.32 (m, 1H) 3.96–3.91 (m, 2H), 3.90–3.83 (m, 2H), 2.87 (ddd, J = 16.1, 5.0, 5.0, 1H), 2.68 (m, 1H), 2.45 (dd, J = 14.2, 2.2, 1H), 2.17 (dddd, J = 15.9, 6.5, 6.5 1.1, 1H), 1.83 (s, 3H), 1.85–1.73 (m, 3H), 1.63–1.71 (m, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 170.07, 154.02, 150.83, 145.74, 129.98, 123.12, 117.00, 109.36, 81.57, 64.58, 64.30, 43.58, 40.15, 36.05, 34.77, 30.84, 29.25, 12.09; IR (thin film/NaCl) 3456 (br), 2934, 1738, 1733, 1645, 1443, 1339, 1246, 1194, 1167, 1118, 1089, 1069, 1021, 974, 955, 845, 774, 708 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{18}H_{20}O_4$, 301.1434; found, 301.1439; $[\alpha]_D^{25.8}$ –25.5° (*c* 0.22, CH_2Cl_2, derived from ketone **205** with 91% ee).



Epoxide 257. A flask was charged with cycloheptadiene **254** (0.9 mg, 0.0028 mmol, 1 equiv) and $VO(acac)_2$ (0.2 mg, 0.00075 mmol, 0.27 equiv) in PhH (0.4 mL). The pale green solution was treated with TBHP, 5.5 M in decane (ca. 10 μL, 1 drop), and then turned burgundy in color. After 12 minutes, the solution was treated with saturated aq Na_2SO_3 (0.04 mL), diluted with EtOAc (to 10 mL), filtered through SiO_2 (ca. 0.2 mL), and concentrated under reduced pressure. This compound was combined with the crude product from an analogous reaction carried out with cycloheptadiene **254** (1.8 mg, 0.0056 mmol). The reactions were purified by thin layer chromatography on a 250 μm plate (10 cm x 20 cm; 1:5 acetone:CH_2Cl_2 elution) to furnish epoxide **257** (1.6 mg, 56% yield, R_f 0.34) as a colorless oil. R_f 0.40 (EtOAc, visualized by UV/Vis, or with anisaldehyde stain); ^1H NMR (500 MHz, CD_2Cl_2) δ 4.83 (ddd, J = 8.7, 7.5, 6.6, 1H), 4.03–3.85 (m, 5H), 3.34 (t, J = 3.0, 1H), 3.28 (d, J = 15.0, 1H), 3.07 (dt, J = 15.1, 1.1, 1H), 2.70–2.62 (m, 1H), 2.52 (dd, J = 13.5, 7.5, 1H), 2.27 (s, 1H), 2.07–2.03 (m, 1H), 2.05 (d, J = 2.6, 1H), 1.90–1.77 (m, 3H), 1.73–1.67 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

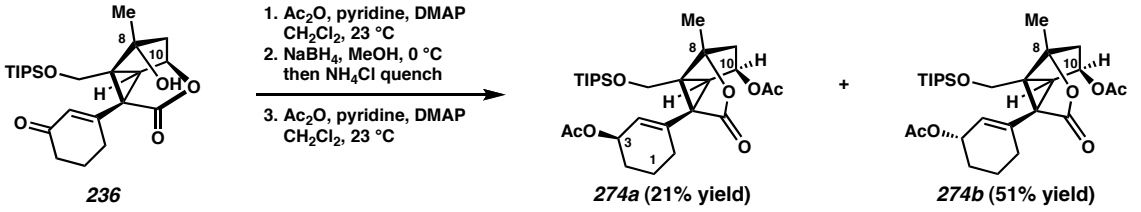
169.34, 156.46, 120.06, 109.51, 75.85, 74.84, 68.72, 65.07, 64.84, 55.86, 47.65, 42.82, 39.42, 35.33, 34.02, 29.25, 29.10, 23.73; IR (thin film/NaCl) 3473, 2974, 2935, 2893, 1739, 1662, 1444, 1360, 1327, 1288, 1268, 1247, 1211, 1189, 1120, 1090, 1043, 1020, 962, 803, 734 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{18}H_{22}O_6$, 335.1489; found, 335.1483; $[\alpha]_D^{22.1}$ +28.6° (*c* 0.16, CH_2Cl_2, derived from ketone **205** with 91% ee).



236 ***260a* (34% yield)** ***260b* (51% yield)**

Alcohol 260. Alcohol **236** (57.2 mg, 0.131 mmol, 1 equiv) was converted to acetate **245c**, as described above. The crude **245c** as a pale yellow oil was dissolved in MeOH (12.0 mL, 0.011 M), cooled to 0 °C (ice water bath) and treated with $NaBH_4$ (18.6 mg, 0.491 mmol, 3.75 equiv). After 24 m, the yellow solution was treated with a saturated aq solution of NH_4Cl (0.70 mL). The mixture was diluted with EtOAc (125 mL), filtered through SiO_2 (ca. 2 mL) and concentrated under reduced pressure to an off-white solid. The solid was purified by preparative thin layer chromatography on a 250 μm analytical plate (2:1 CH_2Cl_2:EtOAc x 2 elution) to give alcohol **260a** (21.4 mg, 34% yield) as a colorless oil and alcohol **260b** (32.2 mg, 51% yield) as a colorless oil. Alcohol **260a**: R_f 0.65 (1:1 EtOAc:hexanes, visualized by UV/Vis, or with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (app dt, J = 3.1, 1.7, 1H), 5.38 (dt, J = 5.9, 4.1, 1H), 4.24 (d, J = 11.4, 2H), 3.45 (dd, J = 11.4, 8.7, 1H), 2.77 (d, J = 5.9, 1H), 2.25–2.16 (m, 2H), 2.16–2.07 (m, 1H), 2.00 (s, 3H), 1.88 (tdd, J = 7.8, 4.8, 3.1, 1H), 1.77–1.72 (m, 1H), 1.70 (ddd, J = 7.6, 4.3, 2.2, 1H), 1.67 (s, 3H), 1.65–1.59 (m, 1H), 1.47 (dddd, J = 12.5, 9.4, 6.5, 3.2, 1H), 1.41 (s, 1H), 1.12–0.92 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.19, 171.32,

133.73, 132.96, 93.00, 73.83, 65.90, 60.02, 57.50, 51.00, 48.28, 41.86, 31.58, 28.08, 20.93, 19.34, 18.90, 18.23, 12.09; IR (film) 3482, 2941, 2866, 1760, 1740, 1462, 1374, 1242, 1080, 1065, 882, 683 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+NH_4]^+$ calc'd for $C_{26}H_{42}O_6Si$, 496.3089; found, 496.3071; $[\alpha]_D^{27.2}$ +8.7° (*c* 1.52, $CHCl_3$, derived from ketone **205** with 91% ee). Alcohol **260b**: R_f 0.61 (1:1 EtOAc:hexanes, UV/Vis, visualized with anisaldehyde stain); ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (dt, J = 3.3, 1.6, 1H), 5.39 (dt, J = 5.9, 4.1, 1H), 4.23 (d, J = 11.4, 1H), 4.14 (app s, 1H), 3.40 (d, J = 11.4, 1H), 2.74 (d, J = 5.9, 1H), 2.20 (d, J = 4.1, 1H), 2.19–2.14 (m, 2H), 1.99 (s, 3H), 1.80–1.70 (m, 3H), 1.66 (s, 3H), 1.63–1.48 (m, 2H), 1.10–0.92 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.16, 171.26, 133.91, 132.61, 92.96, 73.74, 65.77, 59.95, 57.22, 51.05, 48.27, 41.67, 31.70, 28.12, 20.92, 19.35, 18.86, 18.20, 12.07; IR (thin film/NaCl) 3447, 2941, 2866, 1763, 1740, 1462, 1374, 1242, 1080, 1064, 882, 683 cm^{-1}; HRMS-EI *m/z*: $[M+NH_4]^+$ calc'd for $C_{26}H_{42}O_6Si$, 496.3089; found, 496.3099; $[\alpha]_D^{26.8}$ +33.1° (*c* 1.01, $CHCl_3$, derived from ketone **205** with 91% ee).

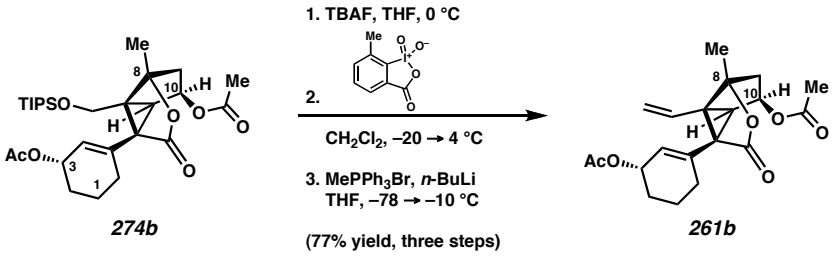


236 ***274a* (21% yield)** ***274b* (51% yield)**

Bisacetates 274. For representative acetylation and reduction procedures, see acetylation of tertiary alcohol **236** to **245c**, and reduction of **245c** to **260**. Alcohols **260** can be acetylated without attempting their purification or separation. Bisacetates **274** can be separated by preparative thin layer chromatography on a 250 μm analytical plate (eluent: 20:1 CH_2Cl_2:EtOAc x 2) to give bisacetate **274b** as a colorless oil (6.3 mg, 51% yield over three steps) and bisacetate **274a** as a white solid (2.6 mg, 21% yield over three

steps). Alternatively, bisacetates **274** can be formed by acylation in parallel. Alcohol **260b** (20.0 mg, 0.042 mmol, 1 equiv) furnished bisacetate **274b** (21.7 mg, 99% yield), while alcohol **260a** (13.9 mg, 0.029 mmol, 1 equiv) provided bisacetate **274a** (12.1 mg, 80% yield). In this case, bisacetates were carried on without further purification. Bisacetate **274a**: R_f 0.41 (1:20 EtOAc:CH_2Cl_2 x 2, visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (app dt, J = 3.5, 1.6, 1H), 5.40 (dd, J = 10.0, 4.1, 1H), 5.31–5.25 (m, 1H), 4.24 (d, J = 11.4, 1H), 3.42 (d, J = 11.4, 1H), 2.79 (d, J = 6.0, 1H), 2.25–2.17 (m, 3H), 1.99 (d, J = 5.7, 6H), 1.86 (tt, J = 7.3, 5.4, 1H), 1.78–1.69 (m, 1H), 1.66 (s, 3H), 1.69–1.63 (m, 2H), 1.63–1.55 (m, 1H), 1.12–0.94 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.78, 171.26, 170.65, 135.92, 128.28, 92.96, 73.68, 68.01, 59.78, 57.64, 51.08, 48.42, 41.46, 28.08 (2C), 21.46, 20.92, 19.09, 18.89, 18.23, 12.10; IR (thin film/NaCl) 2944, 2867, 1770, 1738, 1732, 1667, 1463, 1433, 1373, 1321, 1297, 1241, 1200, 1172, 1129, 1100, 1080, 1065, 1045, 1025, 965, 947, 918, 901, 883, 792, 748, 730 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H–OAc]^+$ calc'd for $C_{28}H_{44}O_7Si$, 461.2718; found, 461.2740; $[\alpha]_D^{25.8}$ +72.4° (*c* 0.19, $CHCl_3$, derived from ketone **205** with 91% ee). Bisacetate **274b**: R_f 0.56 (1:20 EtOAc:CH_2Cl_2 x 2, visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (app dt, J = 3.5, 1.8, 1H), 5.40 (ddd, J = 5.9, 4.9, 3.4, 1H), 5.23–5.18 (m, 1H), 4.23 (d, J = 11.4, 1H), 3.43 (d, J = 11.4, 1H), 2.69 (d, J = 6.0, 1H), 2.26–2.18 (m, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.83–1.73 (m, 3H), 1.70–1.63 (m, 1H), 1.66 (s, 3H), 1.63–1.55 (m, 1H), 1.11–0.93 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.80, 171.25, 170.95, 136.13, 128.13, 92.90, 73.71, 68.13, 60.13, 57.33, 51.07, 48.14, 41.62, 28.07, 27.93, 21.53, 20.94, 19.37, 18.89, 18.21, 12.09; IR (film) 2943, 2867, 1770, 1738, 1463, 1373, 1321, 1241, 1199, 1129, 1098, 1080, 1064, 1045, 1025, 963, 917, 883,

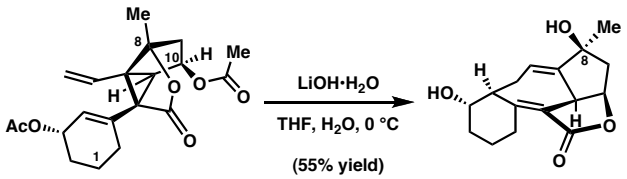
810, 791, 684, 657 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H–OAc]^+$ calc'd for $C_{28}H_{44}O_7Si$, 461.2718; found, 461.2732; $[\alpha]_D^{26.0}$ –28.5° (*c* 0.16, $CHCl_3$, derived from ketone **205** with 91% ee).



Divinylcyclopropane 261b. *Desilylation*. A flask charged with THF (4.8 mL, 0.012 M) and bisacetate **274b** (30.0 mg, 0.0576 mmol, 1 equiv) was cooled to 0 °C (ice-water bath) and treated dropwise with TBAF (1 M in THF, 0.09 mL, 0.09 mmol, 1.56 equiv). After 30 m, the yellow solution was diluted with EtOAc (to 25 mL), filtered through SiO_2 (ca. 0.3 mL) and concentrated under reduced pressure to give desilylated compound as an oil (R_f 0.11 (1:1 EtOAc:hexanes, visualized with anisaldehyde stain)).

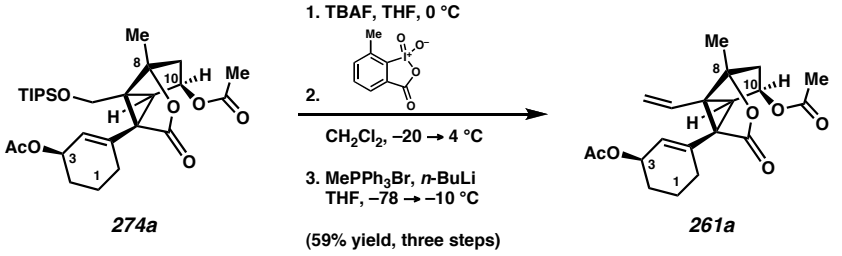
Oxidation. The crude oil was taken up in CH_2Cl_2 (30 mL), cooled to –20 °C (cryocool) beneath an Ar atmosphere, and treated with crushed Me-IBX (34 mg, 0.12 mmol, 2.0 equiv). After 10 m, the mixture was allowed to gradually warm to 4 °C (cold room). Two additional portions of crushed Me-IBX (34.6 and 29.5 mg, 0.12 and 0.10 mmol, 2.0 and 1.7 equiv) were added to the mixture ca. 6 and ca. 9 hours after the initial addition. On completion of the reaction (ca. 21 h), the mixture was diluted with EtOAc (to 100 mL) and filtered through SiO_2 (ca. 2 mL). The organics were concentrated under reduced pressure to give aldehyde as a cream-colored solid (R_f 0.31 (1:1 EtOAc:hexanes, visualized with anisaldehyde stain)). The solid was placed under an argon atmosphere and quickly dissolved in THF (0.5 mL).

Wittig olefination. A room temperature (ca. 24 °C) flask charged with a mixture of $MePPh_3Br$ (0.230 g, 0.643 mmol, 11.1 equiv) and THF (30 mL, 0.0019 M) beneath an Ar atmosphere was treated dropwise with *n*-BuLi (2.5 M in hexanes, 0.40 mL, 1 mmol, 17 equiv). The yellow solution was stirred for 30 min, and then cooled to –65 °C (*i*-PrOH / dry ice bath). The yellow solution was treated dropwise with aldehyde in THF (0.5 mL x 2). The solution was allowed to warm to –10 °C over ca. 1 h, at which point it was quenched by addition of acetone (1 mL). The white mixture was rinsed with 1:1 H_2O: brine (ca. 5 mL) and extracted with EtOAc (to 75 mL). The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was dissolved in EtOAc (10 mL), filtered through SiO_2 (ca. 0.3 mL), and concentrated under reduced pressure. The semi-solid was purified by preparatory thin layer chromatography on a 250 μm plate (1:15 EtOAc:CH_2Cl_2 x 2 eluent) to give divinylcyclopropane **261b** as a colorless oil (16.0 mg, 77% yield). R_f 0.17 (1:15 EtOAc:CH_2Cl_2, visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (dd, J = 17.0, 10.6, 1H), 5.65–5.59 (m, 1H), 5.41 (t, J = 6.6, 1H), 5.27–5.19 (m, 1H), 5.14 (d, J = 10.5, 1H), 4.98 (d, J = 17.0, 1H), 3.00 (d, J = 5.9, 1H), 2.21 (d, J = 14.1, 2H), 2.15 (dd, J = 14.4, 7.5, 2H), 2.03 (s, 3H), 2.01 (s, 3H), 1.81–1.60 (m, 4H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.42, 171.21, 171.06, 135.36, 128.72, 126.99, 118.75, 92.56, 73.20, 68.17, 58.31, 50.77, 49.80, 40.05, 28.07, 27.75, 21.59, 20.93, 19.99, 19.44; IR (film) 2937, 1760, 1738, 1733, 1373, 1242, 1178, 1066, 1046, 1022, 959, 915 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M–H]^-$ calc'd for $C_{20}H_{24}O_6$, 359.1500; found, 359.1513; $[\alpha]_D^{22.8}$ –48.0° (*c* 0.13, $CHCl_3$, derived from ketone **205** with 91% ee).

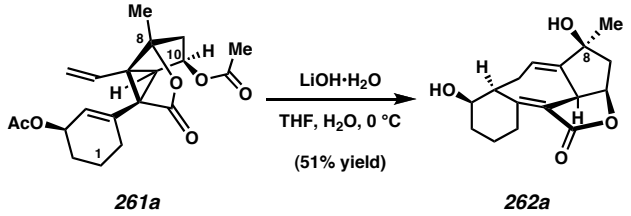


261b *262b*

Cycloheptadiene 262b. A flask charged with bisacetate **261b** (7.3 mg, 0.020 mmol, 1 equiv) in THF (5.2 mL, 0.0039 M) at 0 °C (ice water bath) was treated dropwise with a solution of LiOH•H_2O (9.1 mg, 0.22 mmol, 10.8 equiv) in H_2O (0.91 mL, 0.022 M). After 9 h, the solution was diluted with EtOAc (to 40 mL), filtered through SiO_2 (ca. 0.4 mL) and concentrated under reduced pressure. The semi-solid was purified by preparatory thin layer chromatography on a 250 μm plate (1:3 acetone:CH_2Cl_2 elution) to give cycloheptadiene **262b** (3.1 mg, 55% yield, R_f 0.14) as a white solid. R_f 0.45 (EtOAc, UV/Vis, stained blue in anysaldehyde); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 5.71 (app td, J = 5.2, 2.7, 1H), 4.82 (dd, J = 16.7, 7.5, 1H), 4.23 (d, J = 9.0, 1H), 3.69 (td, J = 8.3, 3.8, 1H), 3.13–3.05 (m, 1H), 2.84–2.75 (m, 1H), 2.66 (t, J = 8.0, 1H), 2.57–2.50 (m, 1H), 2.44 (dd, J = 12.8, 7.1, 1H), 2.32 (dddd, J = 16.3, 9.2, 4.9, 2.2, 1H), 1.91 (ddd, J = 12.6, 9.2, 5.2, 1H), 1.84–1.76 (m, 1H), 1.74 (dd, J = 12.8, 7.9, 1H), 1.60–1.52 (m, 3H), 1.48 (ddd, J = 18.8, 12.9, 5.3, 1H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2, –lactone carbon, –disubstituted carbon of trisubstituted olefin) δ 158.4, 123.4, 118.9, 78.8, 76.1, 72.0, 49.0, 48.7, 43.7, 32.6, 28.7, 27.2, 26.1, 21.0; IR (film) 3393, 2929, 1719, 1653, 1448, 1359, 1289, 1206, 1114, 1036, 966, 734 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{16}H_{20}O_4$, 277.1434; found, 277.1427; $[\alpha]_D^{28.1}$ +33.5° (*c* 0.17, CH_2Cl_2, derived from ketone **205** with 91% ee).

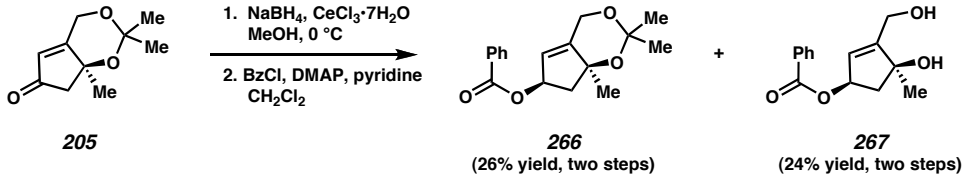


Divinylcyclopropane 261a. For a representative procedure, see silyl ether **274b** → divinylcyclopropane **261b**. 59% yield over three steps. R_f 0.35 (1:20 acetone:CH_2Cl_2, visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (dd, J = 17.1, 10.5, 1H), 5.64 (dt, J = 3.5, 1.7, 1H), 5.39 (dd, J = 7.1, 6.1, 1H), 5.27 (dddd, J = 7.3, 5.5, 3.7, 1.8, 1H), 5.16 (dd, J = 10.5, 1.1, 1H), 5.00 (dd, J = 17.1, 1.1, 1H), 3.03 (d, J = 5.9, 1H), 2.22 (d, J = 14.1, 1H), 2.15 (dd, J = 14.4, 7.5, 1H), 2.13–2.05 (m, 1H), 2.01 (s, 3H), 2.00 (s, 3H), 1.85 (ddd, J = 17.8, 9.6, 5.6, 1H), 1.78–1.70 (m, 1H), 1.62 (dt, J = 12.4, 6.2, 2H), 1.57 (s, 3H), 1.51–1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 171.2, 170.7, 135.3, 129.3, 127.1, 118.5, 92.6, 73.3, 68.4, 58.5, 50.8, 49.7, 40.6, 28.0, 27.7, 21.5, 20.9, 20.0, 19.2; IR (film) 2937, 2868, 1759, 1738, 1733, 1375, 1242, 1180, 1066, 1046, 1023, 960, 915 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M - H]^-$ calc'd for $C_{20}H_{24}O_6$, 359.1500; found, 359.1488; $[\alpha]_D^{23.7}$ +30.4° (*c* 0.18, $CHCl_3$, derived from ketone **205** with 91% ee).



Cycloheptadiene 262a (white solid). For a representative procedure see, divinylcyclopropane **261b** → cycloheptadiene **262b**. 51% yield. R_f 0.44 (EtOAc, visualized by UV/Vis or with anisaldehyde stain); ^{1}H NMR (500 MHz, C_6D_6) δ 5.55 (s, 1H), 4.22 (dd, J = 16.1, 7.8, 1H), 3.50 (dd, J = 12.2, 6.7, 1H), 3.43 (d, J = 7.7, 1H), 3.32–

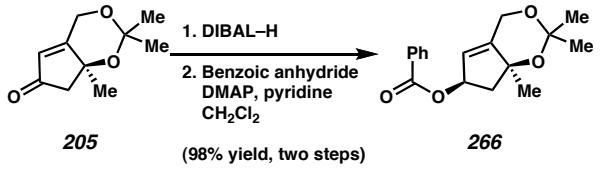
3.09 (m, 1H), 2.91 (app s, 1H), 2.56 (dd, J = 10.0, 4.6, 1H), 2.44 (ddd, J = 17.3, 8.6, 4.2, 1H), 1.99 (dd, J = 12.6, 7.3, 1H), 1.76–1.63 (m, 1H), 1.56 (dq, J = 19.2, 6.4, 1H), 1.46–1.11 (m, 6H), 0.93 (s, 3H).; ^{13}C NMR (125 MHz, C_6D_6) δ 168.7, 157.1, 148.5, 125.4, 119.4, 78.6, 75.7, 71.6, 48.9, 44.8, 43.2, 30.7, 28.3, 25.2, 24.4, 21.6; IR (film) 3369, 2929, 1724, 1654, 1449, 1357, 1289, 1208, 1098, 1038 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{16}H_{20}O_4$, 277.1434; found, 277.1445; $[\alpha]_D^{26.6}$ +100.0° (*c* 0.16, acetone, derived from ketone **205** with 91% ee).



205 ***266*** (26% yield, two steps) ***267*** (24% yield, two steps)

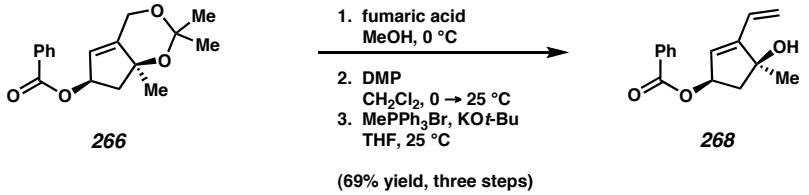
Benzoyl ester 266. A flask charged with CH_2Cl_2 (3.4 mL, 0.24 M), alcohol **176** (prepared from 0.82 mmol of enone **205**, 1 equiv) and pyridine (0.20 mL, 2.4 mmol, 3 equiv) was cooled to 0 °C (ice-water bath) and treated dropwise with benzoyl chloride (0.13 mL, 1.1 mmol, 1.3 equiv). The reaction was allowed to warm to room temperature over approx. 20 h. The reaction was treated with saturated aq NH_4Cl (ca. 10 mL) and extracted with EtOAc (ca. 40 mL x 5). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was flash chromatographed (SiO_2 ~ 16 mL; 1:2 CH_2Cl_2:hexanes → CH_2Cl_2 → EtOAc eluent) to give benzoyl ester **266** (63 mg, 26% yield over two steps), and acetonide-cleaved **267** (49 mg, 24% yield over two steps). Benzoylated **266**. R_f 0.66 (1:1 EtOAc:hexanes, visualized by UV/Vis, or with anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 6.6, 2H), 7.56 (t, J = 7.3, 1H), 7.43 (t, J = 6.6, 2H), 5.82–5.75 (m, 1H), 5.68–5.66 (m, 1H), 4.71–4.68 (m, 2H), 2.68 (dd, J = 6.9, 12.8, 1H), 2.12 (dd, J = 6.9, 12.9, 1H), 1.49 (s, 6H), 1.42 (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 166.6, 146.5, 133.2, 130.4, 129.8, 128.5, 122.0, 100.3, 81.0, 76.6, 60.4, 49.2, 30.0, 28.6, 25.9; IR (thin film/NaCl) 2990, 2939, 2862, 1715, 1602, 1451, 1369, 1268, 1158 cm^{-1}; HRMS-EI *m/z*: $[M+H]^+$ calc'd for $C_{17}H_{20}O_4$, 288.1362; found, 288.1366; $[\alpha]_D^{24.7}$ +74.2° (*c* 1.0, $CHCl_3$, derived from ketone **205** with 91% ee). Acetonide-cleaved **267**. R_f 0.28 (1:1 EtOAc:hexanes, UV/Vis); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.6, 1.1, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.41 (app t, J = 7.8, 2H), 5.89 (app d, J = 1.5, 1H), 5.73–5.66 (m, 1H), 4.45 (d, J = 14.2, 1H), 4.37 (d, J = 14.3, 1H), 2.66 (dd, J = 14.3, 7.3, 1H), 2.44 (app s, 1H), 2.18 (dd, J = 14.3, 3.8, 1H), 1.6 (app s, 1H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.59, 153.07, 133.28, 130.33, 129.84, 128.59, 126.18, 81.65, 76.32, 59.38, 48.53, 26.59; IR (thin film/NaCl) 3382, 3065, 2973, 2932, 2863, 1714, 1694, 1602, 1584, 1452, 1357, 1316, 1275, 1210, 1178, 1112, 1070, 1227, 953, 854, 713 cm^{-1}; HRMS-EI *m/z*: $[M^{\bullet}]^+$ calc'd for $C_{14}H_{16}O_4$, 248.1049; found, 248.1040; $[\alpha]_D^{24.7}$ +100.8° (*c* 0.55, $CHCl_3$, derived from ketone **205** with 91% ee).



Benzoyl ester 266. A dilute solution of enone **205** in Et_2O was concentrated at 150 torr to 0.645 g of a 30% (w/w) solution as determined by ^1H NMR (0.19 g enone, 1.04 mmol) and dissolved in THF (8 mL, 0.13 M). [The volatility of the starting enone precluded preparation of fully concentrated samples without significant loss of material.] The solution was cooled in a dry ice/acetone bath and to it was added DIBALH (2.3 mL, 1 M toluene, 2.3 mmol). The starting material was consumed within 10 minutes according to TLC. The solution was warmed to room temperature and quenched with saturated aq

sodium potassium tartrate (20 mL) and saturated aq NH_4Cl (20 mL) and stirred vigorously for 2 h. The solution was extracted with Et_2O (6 x 50 mL) and the combined organic phases dried with Na_2SO_4, filtered and concentrated at 150 torr. The crude material was purified by flash chromatography (1:1 pentane:Et_2O), concentrated at 150 torr and dissolved immediately in CH_2Cl_2 (17 mL, 0.06 M) for use in the next step. The CH_2Cl_2 solution of allylic alcohol was cooled in an ice water bath and to it was added DMAP (0.27 g, 2.2 mmol) and Et_3N (1.3 mL, 9.38 mmol) followed by benzoic anhydride (0.472 g, 2.1 mmol). The solution was stirred for 4 hr with warming to ambient temperature, then quenched with saturated aq NH_4Cl (20 mL) and extracted with EtOAc (3 x 75 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (2:1 hexanes:CH_2Cl_2 with 2% Et_3N) to yield benzoate ester **266** (0.294 g, 98% yield, 2 steps) as a colorless oil. See above for characterization data.

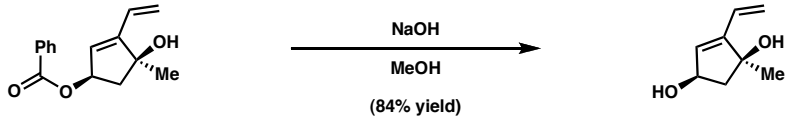


Allylic benzoyl ester 268. To a MeOH (3 mL, 0.037 M) solution of acetonide **266** (0.031 g, 0.11 mmol), cooled in an ice water bath, was added trimethyl orthoformate (0.16 mL, 0.96 mmol) followed by a MeOH (1.5 mL) solution of fumaric acid (0.032 g, 0.28 mmol). The solution was allowed to gradually warm to ambient temperature and stirred an additional 10 hr. The solution was quenched with saturated aq $NaHCO_3$ (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried

with $MgSO_4$, filtered and concentrated in vacuo to yield crude diol **267** (0.028 g, 100% yield) as a colorless oil, which was used immediately.

Crude diol **267** (0.028, 0.11 mmol) was dissolved in CH_2Cl_2 (2 mL, 0.055 M) and cooled in an ice water bath. To the solution was added DMP (0.11 g, 0.27 mmol). CAUTION! DMP is a HEAT- and SHOCK-SENSITIVE COMPOUND, showing exotherms when heated (>130 °C). All operations should be carried out behind a blast shield. The solution was stirred for an additional two hr (with warming to ambient temperature) and quenched with saturated aq $NaHCO_3$ (3 mL) and saturated aq $Na_2S_2O_3$ (6 ml). The two phases were stirred vigorously for 5 min and then extracted with EtOAc (6 x 25 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude aldehyde was used immediately as is. A solution of methylenetriphenylphosphorane was prepared in THF (8 mL, 0.06 M) from triphenylphosphonium bromide (0.17 g, 0.48 mmol) and potassium *t*-butoxide (0.053 g, 0.47 mmol). The yellow solution was cooled in an ice water bath after stirring for 30 min at ambient temperature, and to it added crude aldehyde dropwise as a solution in THF (4 mL). The reaction was complete within 10 min according to TLC. The brown solution was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (1:20 EtOAc:hexanes elution) to yield allylic benzoyl ester **268** as a pale yellow oil (0.019 g, 69% yield, 3 steps). R_f 0.62 (1:2 EtOAc:hexanes, visualized with anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dt, J = 8.4, 1.5, 2H), 7.56 (app t, J = 7.4, 1H), 7.44 (app t, J = 7.7, 2H), 6.36 (dd, J = 17.9, 11.3, 1H), 5.94 (d, J = 2.2, 1H), 5.84–5.77 (m, 1H), 5.75 (ddd, J = 7.0, 4.7, 2.0, 1H),

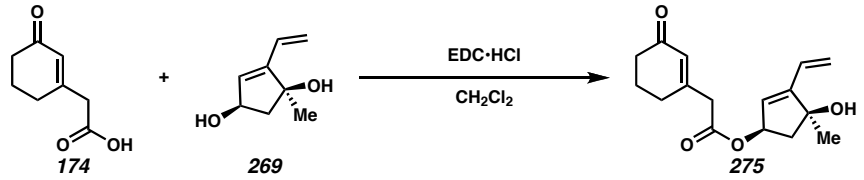
5.34 (dd, J = 11.3, 1.6, 1H), 2.75 (dd, J = 14.1, 7.3, 1H), 2.16 (dd, J = 14.1, 4.7, 1H), 1.91 (s, 1H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, $-CO_2Ph$) δ 151.34, 133.25, 130.42, 129.84, 129.22, 128.59, 127.24, 119.37, 81.28, 76.12, 49.49, 26.98; IR (thin film/NaCl) 3436 (br), 3063, 2974, 2931, 2865, 1715, 1602, 1585, 1452, 1356, 1316, 1273, 1213, 1177, 1112, 1070, 1026, 993, 955, 924, 859, 713 cm^{-1}; HRMS-EI *m/z*: [M+•]$^+$ calc'd for $C_{15}H_{16}O_3$, 244.1100; found, 244.1101; $[\alpha]_D^{27.3}$ +150.0° (*c* 0.13, $CHCl_3$, derived from ketone **205** with 91% ee).



268 ***269***

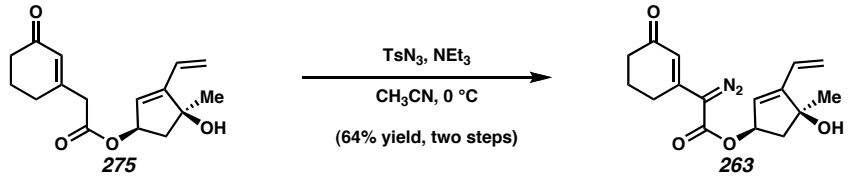
Alcohol 269. To a MeOH (5 mL, 0.05 M) solution of allylic benzoyl ester **268** (0.062 g, 0.25 mmol) was added a MeOH solution of sodium hydroxide (0.85 mL, 0.64 M, 0.54 mmol) dropwise. The solution was stirred at ambient temperature for 3 hours, quenched with H_2O (10 mL) and extracted with EtOAc (6 x 25 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (4:1 CH_2Cl_2:EtOAc → 1:1 hexanes/EtOAc elution) to yield alcohol **269** as a white solid (0.030 g, 84% yield). R_f 0.13 (1:5 EtOAc:CH_2Cl_2, visualized with anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (dd, J = 17.8, 11.3, 1H), 5.82 (d, J = 2.1, 1H), 5.73 (dd, J = 17.9, 1.7, 1H), 5.26 (dd, J = 11.2, 1.7, 1H), 4.65 (dd, J = 11.5, 5.1, 1H), 2.54 (dd, J = 13.6, 6.8, 1H), 1.85 (app dd, J = 13.6, 4.8, 2H), 1.68 (d, J = 6.6, 1H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.52, 131.34, 129.52, 118.63, 81.32, 73.03, 53.07, 26.81; IR (thin film/NaCl) 3287, 3252, 2968, 2930, 2873, 1587, 1481, 1445, 1370, 1341, 1316, 1124, 1088, 1056, 1032, 987, 945, 926 cm^{-1};

HRMS-EI *m/z*: $[M+^{\bullet}]^+$ calc'd for $C_8H_{12}O_2$, 140.0837; found, 140.0859; $[\alpha]_D^{24.2}$ +100.0° (*c* 0.085, MeOH, derived from ketone **205** with 91% ee).



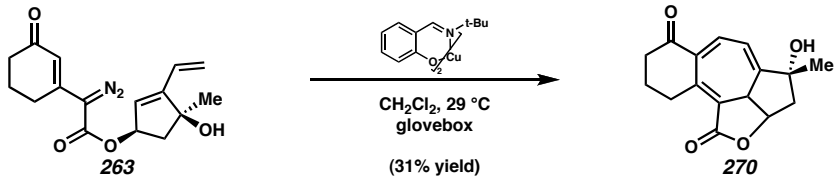
Ester 275. A CH_2Cl_2 (15 mL, 0.026 M) solution of alcohol **269** (0.054 g, 0.39 mmol) with carboxylic acid **174** (0.16 g, 1.1 mmol) was cooled in an ice water bath. EDC•HCl (0.21 g, 1.1 mmol) was added followed by DMAP (0.011 g, 0.09 mmol). The deep yellow solution was allowed to warm to ambient temperature and stirred an additional 1 hour. The solution was quenched with aq HCl (20 mL, 0.12 M) and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with aq HCl (20 mL, 0.12 M), aq K_2CO_3 (2 x 20 mL 5 % w/v), brine (20 mL), and saturated aq NH_4Cl (20 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated to provide crude ester **275** (0.125 g, 117% crude yield) as an orange oil. The crude ester was used without further purification. An analytical sample was obtained at another point, upon purification by preparatory thin layer chromatography with Et_2O x 2 as the eluent. R_f 0.21 (1:5 EtOAc:CH_2Cl_2, visualized with anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (dd, J = 17.9, 11.3, 1H), 5.94–5.91 (m, 1H), 5.78 (d, J = 2.2, 1H), 5.81–5.72 (m, 1H), 5.53–5.47 (m, 1H), 5.32 (dd, J = 11.3, 1.1, 1H), 3.21 (s, 2H), 2.62 (dd, J = 14.1, 7.3, 1H), 2.42–2.32 (m, 4H), 2.06–1.93 (m, 3H), 1.84 (s, 1H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.61, 169.42, 157.18, 151.66, 129.08, 128.98, 126.48, 119.68, 81.14, 76.49, 49.18, 43.66, 37.32, 29.80, 26.97, 22.74; IR (thin film/NaCl) 3417, 2925, 2853, 1732, 1661, 1415, 1326, 1259, 1165, 1063, 959, 887 cm^{-1}; HRMS-EI *m/z*: $[M^{\bullet}]^+$ calc'd

for $C_{16}H_{20}O_4$, 276.1362; found, 276.1363; $[\alpha]_D^{23.2}$ +45.6° (*c* 0.20, $CHCl_3$, derived from ketone **205** with 91% ee).

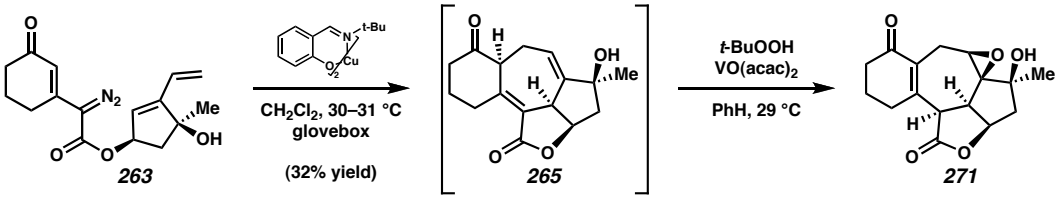


Diazoester 263. To a CH_3CN (42 mL, 0.01 M) solution of ester **275** (≤0.125 g, 0.385 mmol) was added TsN_3 (0.670 g, 3.4 mmol) dropwise using a flame-dulled pipette. CAUTION!!! TsN_3 is SHOCK SENSITIVE AND POTENTIALLY EXPLOSIVE. The flask was equipped with an argon balloon and cooled in an ice water bath. Et_3N (0.8 mL, 5.8 mmol) was added dropwise causing the solution to become deep orange in color. The solution was allowed to warm to ambient temperature and stirred an additional 11 hr. The solution was concentrated in vacuo and purified using flash chromatography (4:1 CH_2Cl_2:EtOAc) to yield diazoester **263** (0.746 g, 64% yield, 2 steps) as a bright yellow oil. R_f 0.18 (1:5 EtOAc:CH_2Cl_2, UV/Vis, visualized with anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (s, 1H), 6.33 (dd, J = 17.9, 11.3, 1H), 5.81 (d, J = 2.1, 1H), 5.81 (dd, J = 9.8, 7.7, 1H), 5.66–5.61 (m, 1H), 5.35 (d, J = 11.4, 1H), 2.68 (dd, J = 14.0, 7.3, 1H), 2.54 (d, J = 5.6, 1H), 2.53 (d, J = 5.6, 1H), 2.43 (d, J = 5.6, 1H), 2.41 (d, J = 5.6, 1H), 2.08 (app dd, J = 12.9, 6.4, 2H), 2.05 (dd, J = 14.1, 4.8, 1H), 1.89 (s, 1H), 1.46 (s, 3H); ^{1}H NMR (500 MHz, C_6D_6) 6.75 (t, J = 1.3, 1H), 6.15 (dd, J = 17.8, 11.3, 1H), 5.72 (dd, J = 17.8, 1.8, 1H), 5.60 (d, J = 2.0, 1H), 5.44 (t, J = 6.2, 1H), 5.11 (dd, J = 11.3, 1.8, 1H), 2.32 (dd, J = 13.7, 7.3, 1H), 2.16–2.07 (m, 2H), 1.82 (dd, J = 13.7, 5.2, 1H), 1.64 (dd, J = 8.8, 3.5, 2H), 1.39 (dt, J = 12.4, 6.2, 2H), 1.37–1.20 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6, –*C*N_2) δ 197.40, 162.72, 151.78, 147.19, 128.98, 126.36, 120.88,

119.77, 81.08, 76.94, 49.34, 36.96, 27.16, 26.78, 22.46; IR (thin film/NaCl) 3407, 2930, 2103, 1707, 1644, 1577, 1430, 1387, 1353, 1328, 1310, 1254, 1230, 1190, 1138, 1063, 992, 744 cm^{-1}; HRMS-EI *m/z*: $[M+H]^+$ calc'd for $C_{16}H_{18}N_2O_4$, 303.1345; found, 303.1339; $[\alpha]_D^{20.4}$ +67.0° (*c* 0.24, $CHCl_3$, derived from ketone **205** with 91% ee).

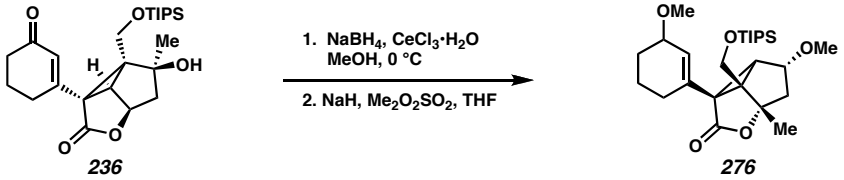


Cycloheptatriene 270. To a CH_2Cl_2 (2.4 mL) solution of $Cu(tbs)_2$ (0.035 g, 0.084 mmol, 3.2 eq.) in a moisture-free, oxygen-free glovebox was added diazoester **263** (0.008 g, 0.026 mmol) as a solution in CH_2Cl_2 (5.6 mL). The deep maroon solution was stirred for 5 days at 29 °C and removed from the glove box. DBN (0.01 mL, 0.08 mmol) was added and the solution stirred for 2 hr. The solution was diluted with EtOAc, filtered over a sort silica plug, concentrated in vacuo and purified by preparatory thin layer chromatography (2:1 EtOAc/benzene) to yield cycloheptatriene **270** (0.0022 g, 31% yield) as a pale yellow solid. R_f 0.50 (1:2 EtOAc:PhH, UV/Vis, visualized with anisaldehyde stain); ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 6.4, 1H), 6.53(d, J = 6.4, 2.2, 1H), 5.17(ddd, J = 7.9, 6.6, 4.5, 1H), 3.58(m, 1H), 3.20 (d, J = 7.9, 1H), 2.94 (dm, J = 17.5, 1H), 2.61(m, 2H), 2.51(dd, J = 14.5, 6.6, 1H), 2.26 (dd, J = 14.5, 4.4, 1H), 1.97 (m, 2H), 1.76 (s, 1H), 1.5(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 168.4, 156.3, 144.9, 139.8, 139.2, 117.3, 115.3, 79.2, 78.2, 48.3, 46.4, 39.6, 28.1, 26.5, 20.9; IR (thin film/NaCl) 3416 (br), 2956, 2925, 2853, 1739, 1734, 1682, 1610, 1525, 1455, 1375, 1354, 1264, 1181, 1098, 1044, 802 cm^{-1}; HRMS-LC/MS: TOF *m/z*: $[M+H]^+$ calc'd for $C_{16}H_{17}O_4$: 273.1121, found; 273.1131; $[\alpha]_D^{25}$ –86.9 (*c* 0.43, CH_2Cl_2, derived from ketone **205** with 91% ee).



To a CH_2Cl_2 (2 mL) solution of $Cu(tbs)_2$ (0.0062 g, 0.015 mmol, 0.4 eq.) in a moisture-free, oxygen-free glove box was added diazoester **263** (0.0108 g, 0.036 mmol) as a solution in CH_2Cl_2 (2.5 mL). The deep maroon solution was stirred for 5 days at 30–31 °C and then concentrated in vacuo (predominantly diene, R_f 0.36 in 2:1 EtOAc:benzene, visualized by UV/Vis, or with anisaldehyde stain). PhH (3 mL) was added and the solution removed from the glovebox. $VO(acac)_2$ (0.010 g, 0.038 mmol) followed by *t*-BuOOH (0.05 mL, 5.5 M decane, 0.275 mmol). Upon addition of *t*-BuOOH the solution turns an even deeper maroon and over the course of 20 minutes, after which time starting material has been consume by TLC, the solution gradually becomes a light tan color. The solution was diluted with EtOAc, filtered over a short silica plug, concentrated in vacuo and purified by preparatory TLC (2:1 EtOAc/ benzene) to yield epoxide **271** (0.0033 g, 32% yield) as an off-white solid. R_f 0.23 (1:2 EtOAc:PhH, UV/Vis, visualized with $KMnO_4$ stain); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.84 (t, J = 5.1 Hz, 1H), 3.82 (dd, J = 18.4, 6.1 Hz, 1H), 3.52 (d, J = 6 Hz, 1H), 3.41 (t, J = 5.6 Hz, 1H), 3.38 (d, J = 6.4 Hz, 1H), 3.22 (m, 1H), 2.54 (ddd, *J* = 16.9, 7.5, 4.8 Hz, 1H), 2.51 (s, 1H), 2.41 (m, 3 H), 2.18 (m, 1H), 2.08 (m, 1H), 1.95 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 172.3, 150.0, 130.0, 80.0, 75.0, 70.4, 54.4, 51.1, 46.2, 43.8, 37.9, 32.7, 26.9, 22.1, 21.8; IR (thin film/NaCl) 3472 (br), 2960, 2933, 2857, 1766, 1661, 1626, 1371, 1266, 1231, 1186, 1148, 1105, 976, 919, 785, 731, 556, 527 cm^{-1}; HRMS-MM: ESI–APCI *m/z*: $[M+H]^+$ calc'd for $C_{16}H_{18}O_5$, 291.1227, found, 291.1228;

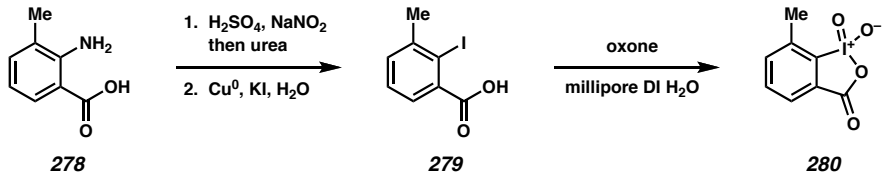
m/z [M–H]$^-$: calc'd for $C_{16}H_{18}O_5$, 289.1081, found, 289.1086; $[\alpha]_D^{25.4}$ +86.2 (*c* 0.16, CH_2Cl_2, derived from ketone **205** with 91% ee).



Methyl ether 276. A flask was charged with cyclopropane **236** (3.7 mg, 0.0087 mmol, 1 equiv) in MeOH (0.2 mL) at 0 °C (ice water bath). The solution was treated with $CeCl_3 \bullet H_2O$ (2.0 mg, 0.0054 mmol, 0.62 equiv) followed by $NaBH_4$ (2.3 mg, 0.061 mmol, 7 equiv). After 28 min, the cold solution was diluted with EtOAc (to ca. 1 mL), and treated with NaOH (3.08 M solution, 2 drops, ca. 20 μL). After 5 min, the mixture was filtered through SiO_2 (ca. 0.2 mL) with EtOAc (to 15 mL), and concentrated under reduced pressure. The semi-solid was dry loaded onto a pipette column and eluted with CH_2Cl_2 then (f. 12) EtOAc. An early isomer eluted in f. 1–7 (**277**, 0.7 mg, 19% yield), while the later isomer eluted in f. 12-22 with other compounds (3.4 mg, <91% yield of impure material). Diol **277**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (d, J = 4.0, 1H), 5.14 (dd, J = 7.2, 6.3, 1H), 4.67 (dd, J = 7.9, 3.9, 1H), 3.89 (d, J = 11.7, 1H), 3.65 (d, J = 11.7, 1H), 2.93 (d, J = 6.1, 1H), 2.35 (ddd, J = 8.9, 4.2, 4.2, 2H), 2.09 (dd, J = 13.8, 7.4, 1H), 1.95 (d, J = 13.8, 1H), 1.89–1.69 (m, 3H), 1.63–1.54 (m, 2H), 1.53 (s, 3H), 1.26 (s, 3H), 1.14–0.94 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.86, 135.10, 129.76, 93.19, 71.30, 65.35, 60.07, 57.82, 53.18, 48.47, 41.88, 29.90, 27.99, 19.37, 18.92, 18.33, 12.16; IR (thin film/NaCl) 2941, 2866, 1766, 1463, 1423, 1383, 1352, 1315, 1302, 1259, 1231, 1198, 1176, 1129, 1079, 1035, 1013, 995, 964, 945, 914, 882, 794, 743, 740 cm^{-1};

HRMS-MM: ESI–APCI, *m/z* calc'd for $C_{24}H_{40}O_5Si$ $[M+Na]^+$: 459.2537, found; 459.2538; $[\alpha]_D^{18.8}$ –35.4 (*c* 0.13, CH_2Cl_2).

A room temperature (21.9 °C) flask was charged with a colorless solution of the mixture containing the later diastereomer (3.4 mg, ≤0.008 mmol, 1 equiv) in THF (0.4 mL, 0.02 M). The solution was treated with NaH, 60% in mineral oil (3.1 mg, 0.078 mmol, 9.7 equiv). After 8 min, the white mixture was treated with dimethyl sulfate (6.5 μL, 0.07 mmol, 2.6 equiv). After 14 h, the white mixture was diluted with EtOAc (to 25 mL), filtered through SiO_2 (ca. 0.2 mL) and concentrated under reduced pressure. The desired methyl ether (**276**) was isolated through thin layer chromatography on a 250 μm silica gel plate (12 cm x 20 cm; 10:1 CH_2Cl_2:acetone x 2 elution, R_f 0.62). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.33 (dd, J = 7.1, 5.6, 1H), 4.25 (d, J = 11.4, 1H), 3.80 (s, 1H), 3.43 (d, J = 11.4, 1H), 3.35 (d, J = 1.6, 3H), 3.30 (s, 3H), 2.48 (d, J = 5.5, 1H), 2.38–2.28 (m, 1H), 2.18 (d, J = 13.7, 1H), 2.10 (dd, J = 13.7, 7.4, 1H), 1.87–1.75 (m, 3H), 1.65 (s, 3H), 1.64–1.58 (m, 1H), 1.55 (t, J = 2.5, 3H), 1.11–0.95 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.10, 134.47, 129.50, 92.41, 79.44, 74.82, 60.24, 57.68, 56.57, 55.76, 52.44, 47.94, 39.77, 28.37, 27.74, 19.96, 19.02, 18.21, 12.11; IR (thin film/NaCl) 2941, 2866, 1766, 1463, 1382, 1318, 1301, 1259, 1209, 1162, 1091, 1065, 1035, 1000, 957, 883, 804, 760 cm^{-1}; HRMS-MM: ESI–APCI, *m/z* calc'd for $C_{26}H_{44}O_5Si$ $[M+Na]^+$: 487.2850, found; 487.2854; $[\alpha]_D^{22.8}$ +3.8 (*c* 0.20, CH_2Cl_2).

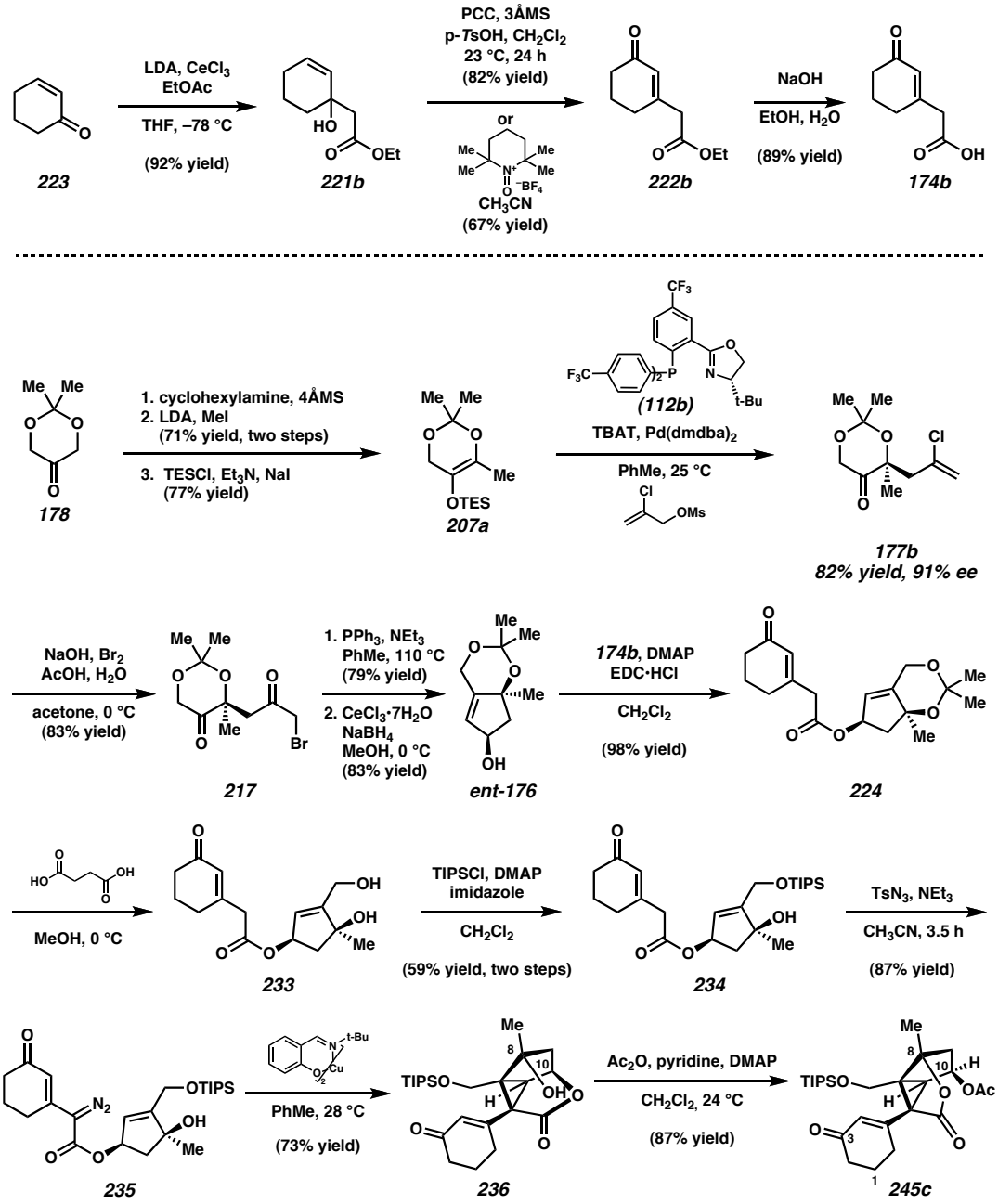


278 *279* *280*

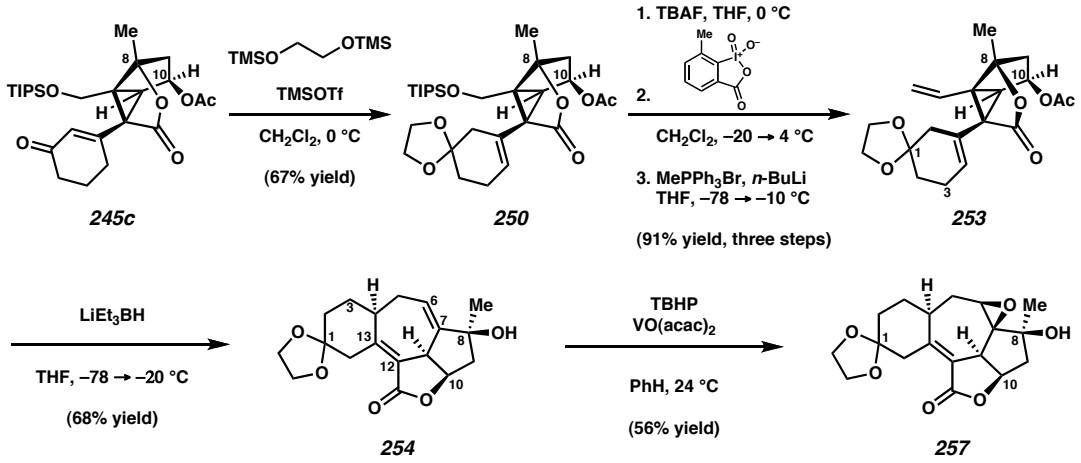
3-Methyl-2-iodoxybenzoic acid 280. 3-Methylanthranilic acid (**278**) was converted to 3-methyl-2-iodobenzoic acid (**279**) on the basis of precedent by Suda.[30] Almost colorless crystals of 3-methyl-2-iodobenzoic acid **279** were accessed by dissolving the solid product mixture in a minimal amount of hot EtOAc, and triturating the yellow solution with hexanes. 3-Methyl-2-iodobenzoic acid (**279**) was converted to 3-methyl-2-iodoxybenzoic acid (**280**) by the method of Santagostino.[23a] ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.89 (d, J = 7.32, 1H), 7.65 (t, J = 7.32, 1H), 7.61 (d, J = 7.32, 1H), 2.79 (s, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 167.93, 147.59, 139.21, 137.99, 132.82, 132.10, 128.85, 19.75; IR (thin film/NaCl) 1669, 1618, 1561, 1455 1364, 1281, 752, 724 cm^{-1}; HRMS-MM: ESI–APCI *m/z* calc'd for $C_8H_6O_4I$ $[M+H]^+$: xx, found; xx.

5.13 Summary of Synthetic Efforts

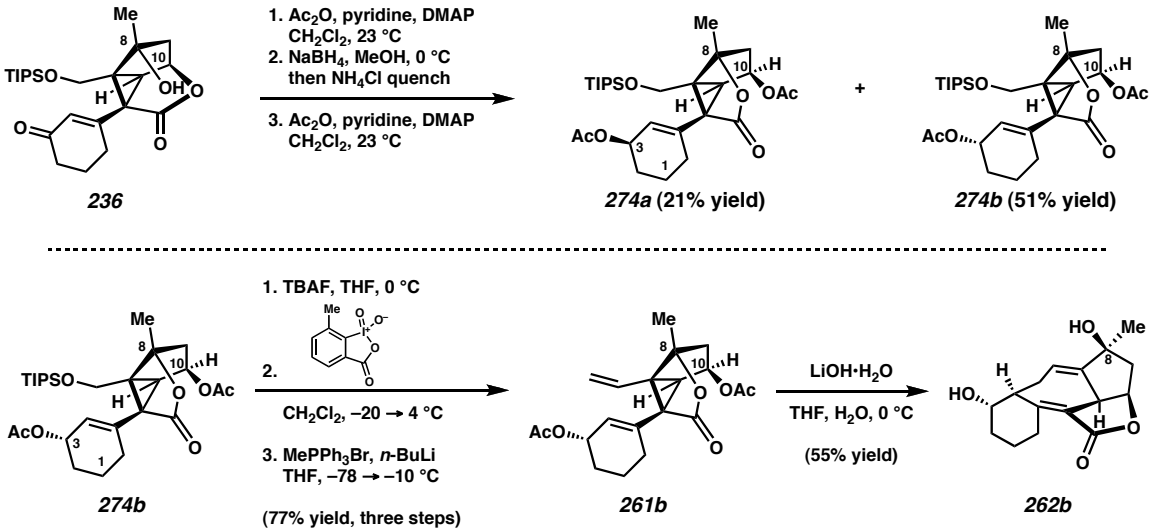
5.13.1 Summary of Progress Toward Secondary Acetate 245c



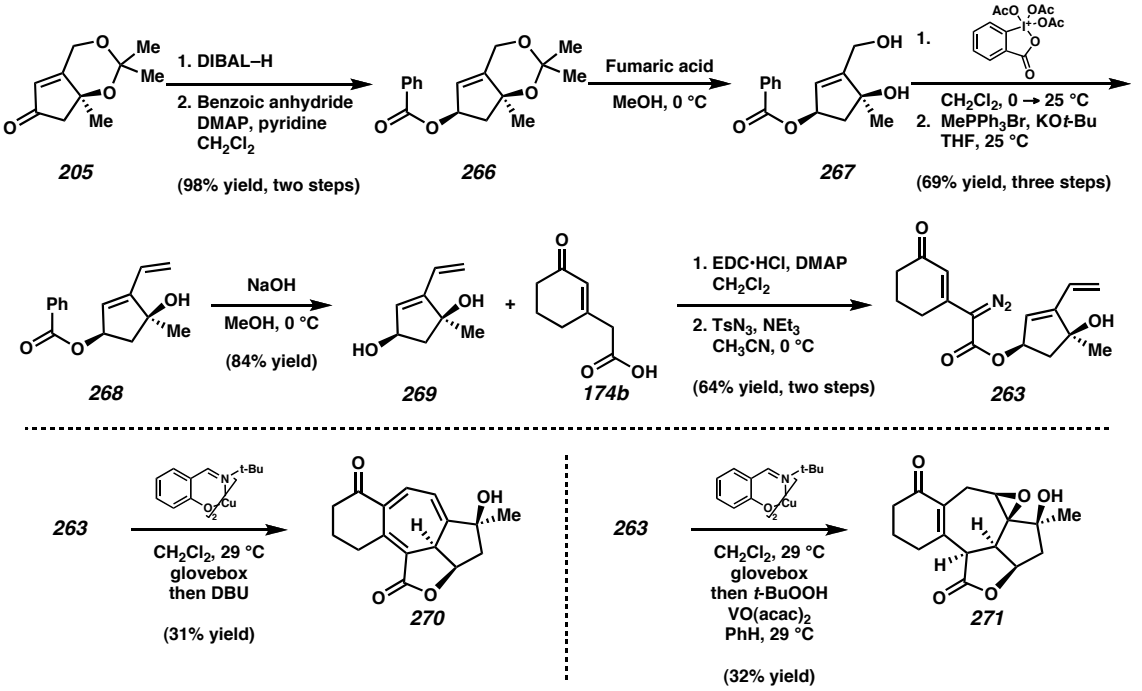
5.13.2 Summary of Progress Toward Ketal 257



5.13.3 Summary of Progress Toward Diol 262



5.13.4 Summary of Progress Toward Ineleganolide via a Cyclopropanation/Cope Rearrangement



5.14 Notes and References

(1) Sarpong, R.; Su, J. T.; Stoltz, B. M. The Development of a Facile Tandem Wolff/Cope Rearrangement for the Synthesis of Fused Carbocyclic Skeletons *J. Am. Chem. Soc.* **2003**, *125*, 13624–13625.

(2) Su, J. T.; Sarpong, R.; Stoltz, B. M.; Goddard, W. A. III. Substituent Effects and Nearly Degenerate Transition States: Rational Design of Substrates for the Tandem Wolff/Cope Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 24–25.

(3) Chen, J.; Marx, J. N. A Stereoselective Total Synthesis of (–)-Rishitin. *Tetrahedron Lett.* **1997**, *38*, 1889–1892.

(4) (a) Mohr, J. T.; Stoltz, B. M. Enantioselective Tsuji Allylations. *Chem.–Asian J.* **2007**, *2*, 1476–1491; (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. Deracemization of Quaternary Stereocenters by Pd-Catalyzed Enantioconvergent Decarboxylative Allylation of Racemic β-Ketoesters. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927; (c) Behenna, D. C.; Stoltz, B. M. The Enantioselective Tsuji Allylation. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

(5) (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. A Facile and Modular Synthesis of Phosphinooxazoline Ligands. *Org. Lett.* **2007**, *9*, 2529–2531; (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. Preparation of (S)-*tert*-ButylPHOX. *Org. Synth.* **2009**, *86*, 181–193; (c) Helmchen, G.; Pfaltz, A. Phosphinooxazolines — A New Class of Versatile, Modular P,N-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 336–345; (d) Williams, J. M. J. The Ups and Downs of Allylpalladium Complexes in Catalysis. *Synlett* **1996**, 705–710, and references therein.

(6) Liu, H.-J.; Zhu, B.-Y. Efficient Addition of Cerium(III) Enolate of Ethyl Acetate to Ketones: Application to the Synthesis of β-Ethoxycarbonylmethyl α,β-Unsaturated Ketones. *Can. J. Chem.* **1991**, *69*, 2008–2013.

(7) Herscovici, J.; Egron, M.-J.; Antonakis, K. New Oxidative Systems for Alcohols: Molecular Sieves with Chromium (VI) Reagents. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1967–1973.

(8) For similar transformations, see: Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. Oxidative Rearrangement of Tertiary Allylic Alcohols Employing Oxoammonium Salts. *J. Org. Chem.* **2008**, *73*, 4750–4752.

(9) Pyrazole formation has been previously reported in thermolysis of vinyl diazo compounds: (a) Doyle, M. P.; Yan, M.; Gao, H.-M.; Blossey, E. C. Catalysts with Mixed Ligands on Immobilized Supports. Electronic and Steric Advantages. *Org. Lett.* **2003**, *5*, 561–563; (b) Doyle, M. P.; Yan, M. Effective and Highly Stereoselective Coupling with Vinyldiazomethanes To Form Symmetrical Trienes. *J. Org. Chem.* **2002**, *67*, 602–604; (c) Hutchinson, I. S.; Matlin, S. A.; Mete, A. The synthesis of 3-diazo-2-nitromethylenepiperidine. *Tetrahedron Lett.* **2001**, *42*, 1773–1776; (d) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. The Reaction of α-Diazo-β-hydroxy Esters with Boron Trifluoride Etherate: Generation and Rearrangement of Destabilized Vinyl Cations. A Detailed Experimental and Theoretical Study. *J. Am. Chem. Soc.* **1993**, *118*, 1–12; (e) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. α-Hydroxy Esters as Chiral Auxiliaries in Asymmetric Cyclopropanations by Rhodium(II)-Stabilized Vinylcarbenoids. *J. Am. Chem. Soc.* **1993**, *115*, 9468–9479; (f) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. Reaction of Carbonyl Compounds with Ethyl Lithiodiazoacetate. Studies Dealing with the Rhodium(II)-Catalyzed Behavior of the Resulting Adducts. *J. Org. Chem.* **1990**, *55*, 4144–4153; (g) Bailey, R. J.; Card, P. J.; Shechter, H. Chemistry of 8-

Substituted 1-Naphthylmethylenes and 2-Substituted Benzylidenes. A Simple Entry to 1*H*-Cyclobuta[*de*]naphthalenes. *J. Am. Chem. Soc.* **1983**, *105*, 6096–6103; (h) Hurd, C. D.; Lui, S. C. Vinyldiazomethane. *J. Am. Chem. Soc.* **1935**, *57*, 2656–2657.

(10) De Leeuw, J. W.; De Waard, E. R.; Beetz, T.; Huisman, H. O. α,β-Unsaturated Acetals. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 1047–1052.

(11) For related examples involving intramolecular translactonization of γ-lactones, see: (a) Raffaelli, B.; Pohjoispää, M.; Hase, T.; Cardin, C. J.; Gan, Y.; Wähälä, K. Stereochemistry and rearrangement reactions of hydroxylignanolactones. *Org. Biomol. Chem.* **2008**, *6*, 2619–2627; (b) Mulzer, J.; Giester, G.; Gilbert, M. Toward a Total Synthesis of Macrocyclic Jatrophane Diterpenes – Concise Route to a Highly Functionalized Cyclopentane Key Intermediate. *Helv. Chim. Acta* **2005**, *88*, 1560–1579; (c) Duret, P.; Figadère, B.; Hocquemiller, R.; Cavé, A. Epimerization of Annonaceous Acetogenins under Basic Conditions. *Tetrahedron Lett.* **1997**, *38*, 8849–8852; (d) Clardy, J.; Springer, J. P.; Buechi, G.; Matsuo, K.; Wightman, R. Tryptoquivaline and tryptoquivalone, two tremorgenic metabolites of Aspergillus clavatus. *J. Am. Chem. Soc.* **1975**, *97*, 663–665.

(12) The immediate product of acetylation does not demonstrate the necessary gHMBC correlations; however, ketone reduction generates two diastereomers, one of which exhibits diagnostic gHMBC correlations.

(13) Su, J. T.; Goddard, W. A. G., III. Enhancing 2-Iodobenzoic Acid Reactivity by Exploiting a Hypervalent Twist. *J. Am. Chem. Soc.* **2005**, *127*, 14146–14147.

(14) Thermal reactions of divinylcyclopropane **171** did not provide strained **173**. Therefore, attention was focused on acetate cleavage reactions.

(15) (a) Tei, T.; Sugimura, T.; Katagiri, T.; Tai, A.; Okuyama, T. Application of modified hydroxy-directed diastereodifferentiating Simmons-Smith reaction to an unreactive conjugated triene. Stereocontrolled tandem cyclopropanation–Cope rearrangement-cyclopropanation. *Tetrahedron: Asymmetry* **2001**, *12*, 2727–2730; (b) Davies, H. M. L.; Calvo, R. L.; Townsend, R. J.; Ren, P.; Churchill, R. M. An Exploratory Study of Type II [3+4] Cycloadditions Between Vinylcarbenoids and Dienes. *J. Org. Chem.* **2000**, *65*, 4261–4268; (c) Davies, H. M. L. Tandem Cyclopropanation/Cope Rearrangement: A General Method for the Construction of Seven-Membered Rings. *Tetrahedron* **1993**, *49*, 5203–5223; (d) Davies, H. M. L.; Clark, T. J.; Smith, H. D. Stereoselective Synthesis of Seven-Membered Carbocycles by a Tandem Cyclopropanation/Cope Rearrangement Between Rhodium(II)-Stabilized Vinylcarbenoids and Dienes. *J. Org. Chem.* **1991**, *56*, 3817–3824; (e) Cantrell, W. R., Jr.; Davies, H. M. L. Stereoselective Convergent Synthesis of Hydroazulenes via an Intermolecular Cyclopropanation/Cope Rearrangement. *J. Org. Chem.* **1991**, *56*, 723–727; (f) Davies, H. M. L.; Clark, D. M.; Smith, T. K. [3+4] Cycloaddition Reactions of Vinyl Carbenoids with Furans. *Tetrahedron Lett.* **1985**, *26*, 5659–5662.

(16) Davies, H. M. L.; Smith, H. D.; Korkor, O. Tandem Cyclopropanation/Cope Rearrangement Sequence. Stereospecific [3+4] Cycloaddition Reaction of Vinylcarbenoids with Cyclopentadiene. *Tetrahedron Lett*. **1987**, *28*, 1853–1856.

(17) (a) Davies, H. M. L.; McAfee, M .J.; Oldenburg, C. E. M. Scope and Stereochemistry of the Tandem Intramolecular Cyclopropanation/Cope Rearrangement Sequence. *J. Org. Chem*. **1989**, *54*, 930–936; (b) Davies, H. M. L.; Oldenburg, C. E. M.; McAfee, M. J.; Nordahl, J. G.; Henretta, J. P.; Romines, K. R. Novel Approach to Seven-membered Rings by the Intramolecular Tandem Cyclopropanation/Cope Rearrangement Sequence. *Tetrahedron Lett*. **1988**, *29*, 975–978.

(18) For intermolecular cascades, see: (a) Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. Tandem Asymmetric Cyclopropanation/Cope Rearrangement. A Highly Diastereoselective and Enantioselective Method for the Construction of 1,4-Cycloheptadienes. *J. Am. Chem. Soc*. **1998**, *120*, 3326–3331; (b) Davies, H. M. L.; Peng, Z.-Q.; Houser, J. H. Asymmetric Synthesis of 1,4-Cycloheptadienes and Bicyclo[3.2.1]octa-2,6-dienes by Rhodium(II) N-(p-(*tert*-butyl)phenylsulfonyl)prolinate Catalyzed Reactions Between Vinyldiazomethanes and Dienes. *Tetrahedron Lett*. **1994**, *35*, 8939–8942.

(19) Davies, H. M. L.; Doan, B. D. Enantioselective Synthesis of Fused Cycloheptadienes by a Tandem Intramolecular Cyclopropanation/Cope Rearrangement Sequence. *J. Org. Chem*. **1999**, *64*, 8501–8508.

(20) For asymmetric intramolecular cascades, see: (a) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. Asymmetric Synthesis of Highly Functionalized 8-Oxabicyclo[3.2.1]octane Derivatives. *J. Am. Chem. Soc.* **1996**, *118*, 10774–10782. For related uses of chiral auxiliaries in cyclopropanation/Cope reactions, see: (b) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. Enantioselective Synthesis of Functionalized Tropanes by Rhodium(II) Carboxylate-Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Pyrroles. *J. Org. Chem.* **1997**, *62*, 1095–1105.

(21) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. An Improved Method for the Synthesis of α-Diazo Ketones. *J. Org. Chem.* **1990**, *55*, 1959–1964.

(22) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. Homogeneous catalysis in the decomposition of the diazo compounds by copper chelates: Asymmetric carbenoid reactions. *Tetrahedron* **1968**, *24*, 3655–3669.

(23) (a) Frigerio, M.; Santagostino, M.; Sputore, S. A User-Friendly Entry to 2-Iodoxybenzoic Acid (IBX). *J. Org. Chem.* **1999**, *64*, 4537–4538; (b) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. The Dess-Martin Periodinane: 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one. *Org. Syn.* **2000**, *77*, 141–146.

(24) de Boer, Th. J.; Backer, H. J. Diazomethane. *Org. Syn.* **1963**, *Coll. Vol. 4*, 250–253.

(25) Parlow, J. J.; Case, B. L.; South, M. S. High-Throughput Purification of Solution-Phase Periodinane Mediated Oxidation Reactions Utilizing a Novel Thiosulfate Resin. *Tetrahedron* **1999**, *55*, 6785–6796.

(26) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. Diazotransfer Reactions with *p*-Acetamidobenzenesulfonyl Azide. *Synth. Comm.* **1987**, *17*, 1709–1716.

(27) Based on a procedure within reference 17a.

(28) Larock, R. C.; Yum, E. K.; Yang, H. Palladium-Catalyzed Intermolecular Arylation of Funcationally-Substituted Cycloalkenes by Aryl Iodides. *Tetrahedron* **1994**, *50*, 305–321.

(29) This procedure has been influenced by: Bouzide, A.; Sauvé, G. Highly Selective Silver(I) Oxide Mediated Monoprotection of Symmetrical Diols. *Tetrahedron Lett.* **1997**, *38*, 5945–5948.

(30) Kanoh, S.; Muramoto, H.; Kobayashi, N.; Motoi, M.; Suda, H. Practical Method for the Synthesis and Optical Resolution of Axially Dissymmetric 6,6'-Dimethylbiphenyl-2,2'-dicarboxylic Acid. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3659–3662.