General Access to Concave-Substituted cis-Dioxabicyclo[3.3.0]octanones: Enantioselective Total Syntheses of Macfarlandin C and Dendrillolide A.

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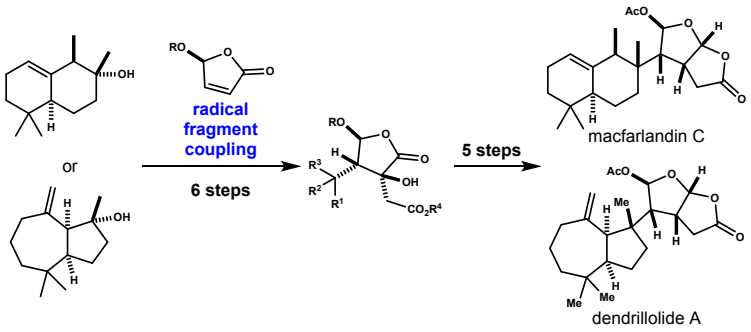
ABSTRACT: The evolution of a strategy to access the family of rearranged spongian diterpenoids harboring a concave-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment is described. The approach involves late-stage fragment coupling of a tertiary-carbon radical and an electron-deficient double bond to form vicinal quaternary and tertiary stereocenters with high fidelity. A stereoselective Mukaiyama hydration is the key step in the subsequent elaboration of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one moiety. This strategy was utilized in enantioselective total syntheses of (−)-macfarlandin C and (+)-dendrillolide A. An efficient construction of enantiopure tetramethyloctahydronaphthalenes was developed during the construction of (−)-macfarlandin C.



INTRODUCTION

A *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one (**1**) is a common structural motif in a diverse group of diterpenoids.[1] This structure can be decorated in multitude ways, such as being incorporated into a polycyclic framework or appended to a complex lipophilic substituent. The second subset contains several marine-derived diterpenoids that are characterized by a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one appended at C-6 to a quaternary carbon of a 14-carbon bicyclic fragment (Figure 1). The hydrocarbon substituent can be attached to either the convex or concave face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one, with the latter being more common. Macfarlandin C (**3**)[2] and dendrillolide A (**4**)[3] exemplify this latter group. The linkage that joins the two fragments is freely rotatable, making identification of the relative configurations of these natural products challenging. X-ray crystallographic analysis and chemical synthesis have proven to be the only methods of establishing the relative and absolute configurations of this group of diterpenoids.[1–8] For many of these natural products, stereochemical assignments are based solely on their presumed biosynthetic relationship to the spongian diterpenoid skeleton (**2**).[9]

The Golgi-altering activity of macfarlandin E, a rearranged spongian diterpenoid harboring a 2,7-dioxabicyclo[3.2.1]octan-3-one, was the original impetus for our interest in this class of natural products.[10] The unique mode of action elicited by macfarlandin E could be recapitulated with simplified 2,7-dioxabicyclo[3.21]octan-3-one or *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one congeners.[10,11]

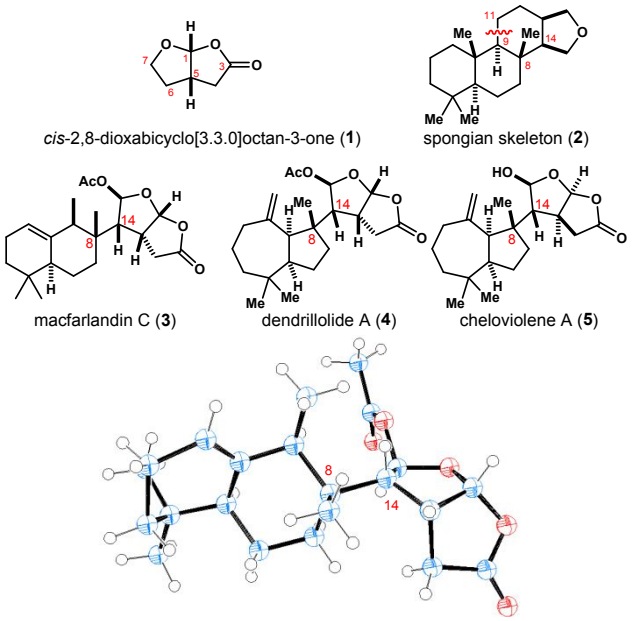
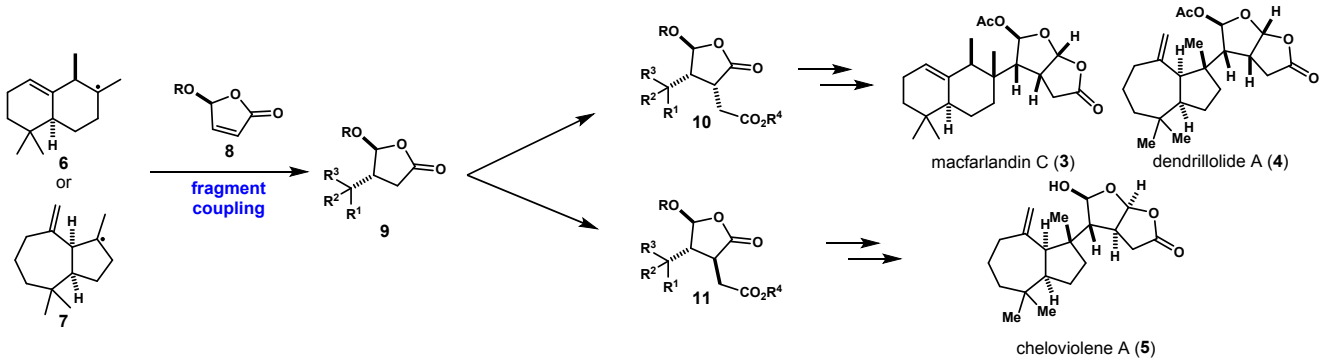


Figure 1: The *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one ring system, three rearranged-spongian diterpenoids harboring this fragment, and the spongian skeleton, which is the presumed biosynthetic precursor of these diterpenoids. An ORTEP ball-and-stick representation of the X-ray model of (−)-macfarlandin C showing the unusually long (1.577 Å) C-8/C-14 σ-bond linking the two chiral fragments.

Treatment of cells with these structures results in irreversible fragmentation of the Golgi apparatus with the resi-

Scheme 1



dual components remaining localized in the pericentriolar region of the cell.[10,11] Investigations revealed that both the bridged and fused dioxabicyclooctanone subunits convert to pyrrole products in the presence of primary amines, most likely via 1,4-dialdehyde intermediates that arise from fragmentation of these oxabicyclic agents. This degradation pathway is postulated to be significant in eliciting the Golgi phenotype of these natural products.[10-12]

Formation of the σ-bond that joins the two chiral fragments in a stereocontrolled fashion is a principal challenge in the chemical synthesis of the rearranged spongian diterpenoids depicted in Figure 1. In members having the bulky hydrocarbon fragment on the concave face of the *cis*2,8-dioxabicyclo[3.3.0]octan-3-one, such as macfarlandin C (**3**) and dendrillolide A (**4**), the difficulty of this bond construction is amplified. The extent of steric congestion in these structures, which is not readily apparent in two dimensional drawings, is obvious in the X-ray model of macfarlandin C (**3**) (Figure 1).[2] The central C-8/C-14 σ-bond of **3** is abnormally long at 1.577 Å, in stark contrast to cheloviolene A whose corresponding bond is quite standard (1.546 Å).[4a,6b,13]

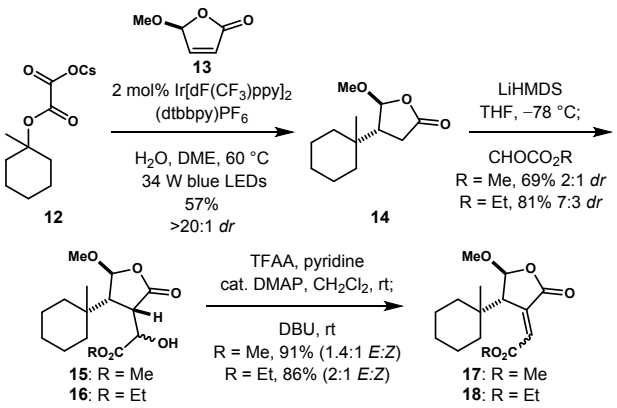
From the outset our synthetic strategy was to forge the challenging C-8/C-14 σ-bond by the coupling of tertiary radicals **6** or **7**, which embody the octahydronaphthalene and *cis*-methyleneperhydroazulene fragments of macfarlandin C and dendrillolide A, with an enantiopure 5-alkoxybutenolide **8** (Scheme 1). This approach would exploit the high efficiency and typical high diastereoselectivity of tertiary radical/alkene fragment couplings,[14] and our earlier success in employing this step to prepare cheloviolenes A (**5**) and B.[6] In these previous syntheses, elaborating coupling product **9** to the targeted diterpenoids was fairly straightforward, as the remaining two carbons could be installed stereoselectively by the direct alkylation of the lithium enolate of **9** with an iodoacetic acid ester to yield intermediate **11**.[6] To synthesize the related diterpenoids in this series that display the bulky hydrocarbons substituent on the more-hindered concave face, **9** would need to be elaborated to a butyrolactone intermediate such as **10.** The successful development of the divergent synthetic strategy outlined in Scheme 1, and its use to accomplish enantioselective total syntheses of macfarlandin C (**3**) and dendrillolide A (**4**) are the subject of this report.[7]

RESULTS AND DISCUSSION

A. Exploratory Investigations in Model Systems to Develop a Synthesis of *cis*-2,8-Dioxabicyclo[3.3.0]octan-3-ones Harboring an Endo C-6 Substituent.

Initial Attempts. Our studies began with butyrolactone **14**, which is readily available from the union of tertiary-radical precursor **12** and 5-methoxybutenolide (**13**) (Scheme 2).[6b] We anticipated that the carboxymethyl side chain could be installed *cis* to the bulky methylcyclohexyl substituent by diastereoselective hydrogenation of a 3-alkylidene fragment. To access such an intermediate, lactone **14** was deprotonated with LHMDS and the resulting enolate allowed to react with methyl (or ethyl) glyoxylate at −78 °C in THF to provide epimeric aldol adducts, which were directly dehydrated to provide alkylidene products **17** or **18** as mixtures of *E* and *Z* stereoisomers. The aldol step proceeded in variable yields with methyl glyoxylate, likely reflecting the purity of this reagent. Fortunately, changing to ethyl glyoxylate resulted in the aldol step being more efficient and reproducible.

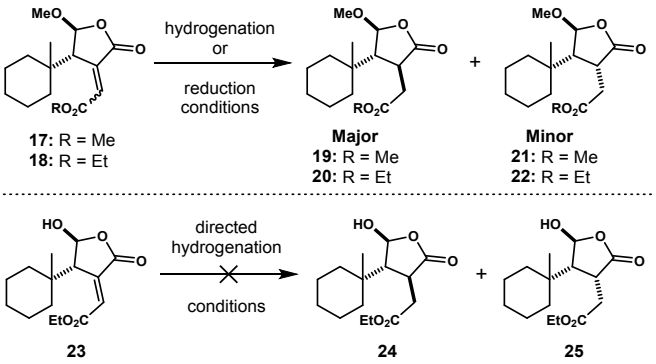
Scheme 2



The reduction of alkylidene butyrolactones **17** and **18** under a variety of conditions was examined (Scheme 3). Several heterogenous catalysts were explored with the

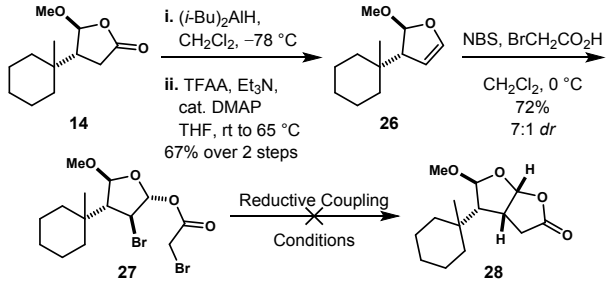
anticipation that the *Re* face of the double bond would approach the metal surface in order to minimize steric interactions with the 1-methylcyclohexyl substituent. However, under both the homogenous and heterogeneous hydrogenation conditions that we examined the undesired all-*trans* products **19** or **20** were formed preferentially (see supporting information for details). The use of nucleophilic metal-hydride reagents allowed for facile reduction of the electron deficient double bond. Within this reaction manifold, we explored a variety of proton sources with the hope of influencing facial selectivity for protonation of the *in situ*-generated lactone enolate. However, all conditions examined proved to be either unselective or returned the all-*trans* products selectively. Partial epimerization of the desired (less stable) hydrogenation product **19** (**20**) under some of the reduction conditions was observed.[6b,15] We also explored briefly the potential of directed hydrogenation by employing lactol **23**, but the conditions examined resulted in no reaction or decomposition of the starting material.

Scheme 3



Another approach that we examined attempted to capitalize on the recent advances in transition metal catalyzed cross-electrophile coupling (Scheme 4).[16] In this study, radical coupling product **14** was first transformed to dihydrofuran **26** by sequential reaction with di-isobutylaluminum hydride (DIBALH) and trifluoroacetic anhydride and base. Exposure of this intermediate to NBS and bromoacetic acid afforded bromoacetal **27** with high diastereoselectivity. With this intermediate in hand, a wide variety of Ni-catalyzed cross coupling conditions were explored with no success.[17] The desired butyrolactone product **28** was only observed in trace amounts, with either ester hydrolysis and/or reductive debromination of the ester side chain being the products detected by ^{1}H NMR analysis. Presumably, the steric bulk of the 1-methylcyclohexyl substituent limits the ability of the nickel catalyst to effectively engage the secondary bromide. In addition to the approaches outlined in Schemes 3 and 4, several other strategies were examined without success and have been described elsewhere.[18]

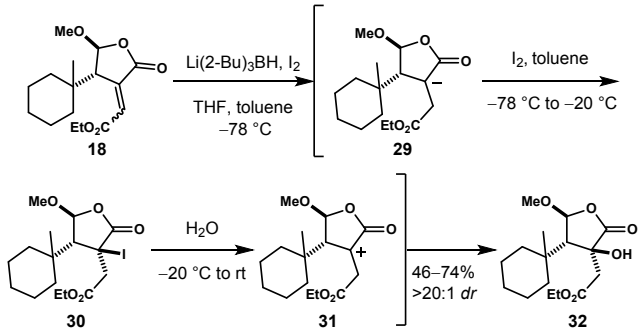
Scheme 4



Discovery of the α-Hydroxy Blocking Group Strategy and Successful Synthesis of *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one 36 Having a C-6 Tertiary Substituent on the Concave Face. The approach that was finally successful resulted from a study whose objective was to position the vicinal alkyl substituents of a butyrolactone intermediate cis, by first forming a lactone enolate from alkylidene precursor **18**, and quenching this enolate with a halogen electrophile which was expected to react from the enolate face opposite the 1-methylcyclohexyl substituent (Scheme 5). To our surprise, when iodine was employed in the trapping step and the reaction was quenched by adding water at –20 °C, α-hydroxy lactone **32** was isolated as the major product in variable yields. That this product had the desired cis orientation of the alkyl substituents at C-3 and C-4 was confirmed by X-ray crystallographic analysis. Alcohol **32** might result from ionization of the expected iodination product **30** upon warming in aqueous THF to form α-acyloxy carbenium ion **31**, which is trapped from the face opposite the 1-methylcyclohexyl substituent to form alcohol **32**; however, alternate pathways proceeding by radical intermediates cannot be excluded.[19,20] Unfortunately, this synthesis of alcohol **32** was capricious, with the reduction byproduct **20** being formed in significant and variable yields.

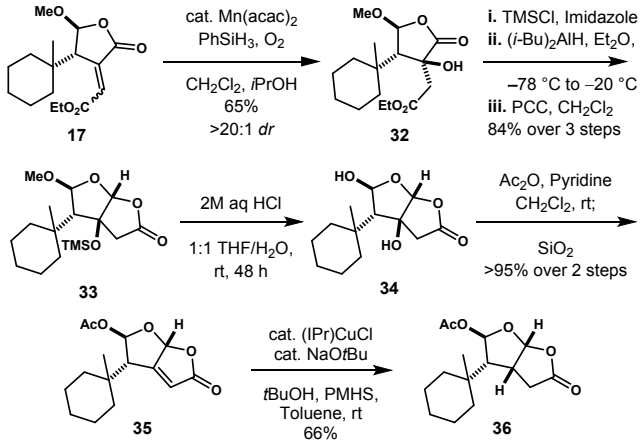
In order to develop a more reliable route to alcohol **32**, we examined the possibility of obtaining this product by Mukaiyama hydration of alkylidene lactone **18**.[21] It seemed likely that hydrogen-atom addition to **18** would occur at the less-substituted alkylidene carbon,[21d] and considerable precedent existed that C–O bond-formation would take place from the sterically more accessible face of the radical intermediate.[22] Using standard conditions first reported by Mukaiyama,[21b] **18** was transformed with high regio- and stereoselectivity to α-hydroxylactone **32** (Scheme 6). Although the yield was modest (65%), this reaction was sufficiently reproducible to allow us to proceed ahead to see whether **32** would be a viable precursor to the desired endo-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one product.

Scheme 5



With a reliable method of establishing the *cis* relationship between the carboxymethyl and 1-methylcyclohexyl substituents in hand, we explored ways to transform alcohol **32** into the elusive concave-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one **36**. Reaction of alcohol **32** with a variety of hydride reducing agents led to inconsistent results,[6b] with significant amounts of the starting alcohol being recovered unchanged. This issue was circumvented by first protecting the alcohol as its trimethylsilyl ether. Reduction of this intermediate with excess DIBALH at –78 to –20 °C, followed by oxidation of the resulting mixture of lactols with pyridinium chlorochromate (PCC) afforded *cis*-dioxabicyclooctanone **33** in high yield.

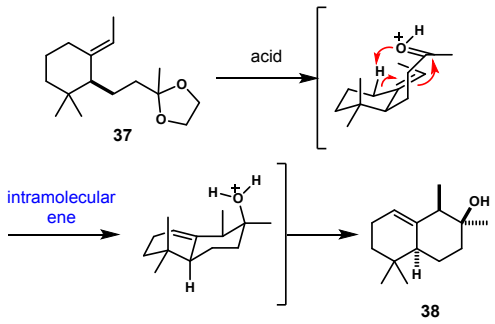
Scheme 6



Exposure of this intermediate to dilute HCl at rt cleaved the silyl ether and methoxy groups giving diol **34**. This product was then allowed to react with excess acetic anhydride and pyridine in the presence of DMAP to yield a mixture of the corresponding diacetate and its elimination product **35**. During chromatographic purification of this product mixture on silica gel, the diacetate was observed to partially convert into the elimination product **35**. In subsequent experiments, this crude product was adsorbed on silica gel at rt, and after standing for 16 h, chromatography on silica gel gave bicyclic butenolide **35** in nearly quantitative yield. Conjugate-silane reduction using an N-heterocyclic carbene copper complex, as described by Buchwald and coworkers, afforded *cis*-2,8-bicyclo[3.3.0]octan-3-one **36** in 66% yield.[23]

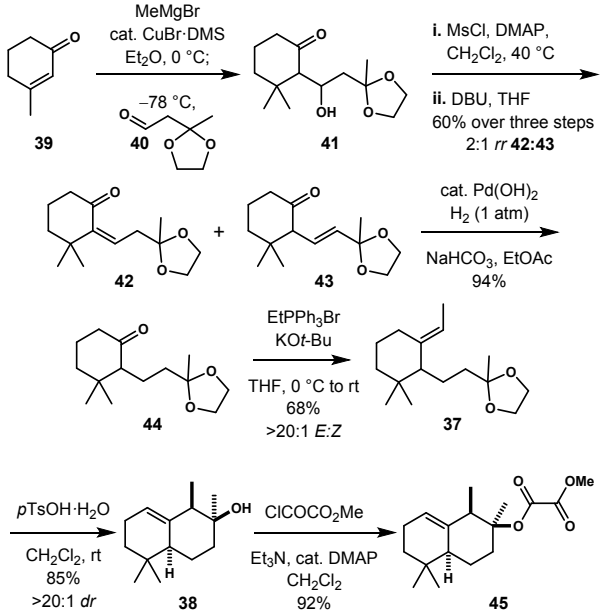
B. Developing the Enantioselective Total Synthesis of (–)-Macfarlandin C.

Scheme 7



Initial Syntheses of the Octahydronaphthalene Fragment of Macfarlandin C. With a successful strategy to access the concave-substituted *cis*-2,8-bicyclo[3.3.0]octan-3-one fragment available, we turned our attention to the total synthesis of (–)-macfarlandin C (**3**). Octahydronapthalene alcohol **38** was envisaged as the precursor of tertiary radical **6** in the fragment-coupling step depicted in Scheme 1.[24] The axial alcohol epimer **38** was initially targeted because of its anticipated formation from (E)-ethylidenecyclohexane acetal **37** by the intramolecular carbonyl-ene cyclization depicted in Scheme 7. Carbonyl-ene cyclizations of this type have long been used to form octahydronapthalene products, and the cyclization of a related methylidene analogue of **37** had been reported.[25,26]

Scheme 8

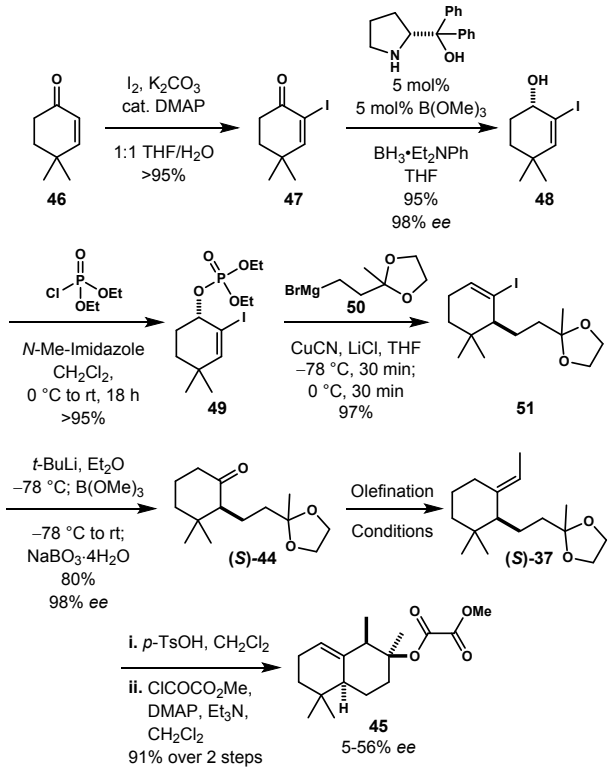


Our initial exploration of this route was carried out in the racemic series and is summarized in Scheme 8. The approach commenced with a copper-catalyzed conjugate addition of MeMgBr to 3-methylcyclohexenone (**39**), followed by reaction of the *in situ* generated enolate with aldehyde **40** to give aldol adduct **41** as a mixture of stereoisomers. This crude material was dehydrated to afford alkenes **42** and **43** as an inseparable mixture. Hydrogenation of this mixture, followed by Wittig

olefination delivered the desired cyclization precursor ***rac*-37** with high *E* stereoselectivity. Exposure of this intermediate to catalytic amounts of *p*-toluenesulfonic acid in wet CH_2Cl_2 resulted in hydrolysis of the ketal and subsequent intramolecular carbonyl-ene cyclization to give octahydronapthalene ***rac*-38** as the sole detected product. We were pleased to find that alcohol ***rac*-38** could be converted into tertiary-homoallylic oxalate derivative **45** without the formation of diene elimination byproducts.

As the projected fragment-coupling step would require the union of enantioenriched fragments, we turned to develop an enantioselective synthesis of alcohol **38**. We were attracted initially to the possibility that enantioselective hydrogenation of enone **42** might allow the route we had already developed to be employed.[27] However, this approach was rendered impractical by our inability to produce useful amounts of pure enone **42** from the mixture of aldol products.

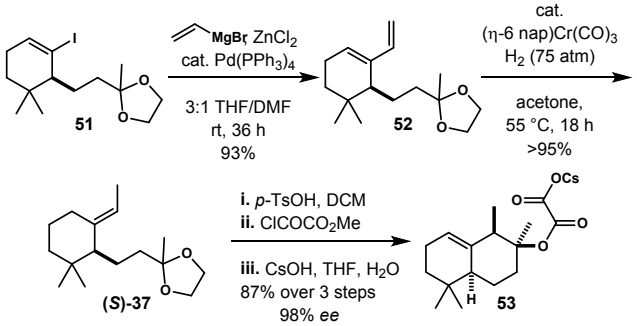
Scheme 9



We turned to develop an alternate synthesis in which the neopentylic stereocenter of the cyclohexanone intermediate would be formed by a stereoselective S_N2' displacement reaction (Scheme 9). Particularly appealing was the synthesis of enantiopure α-substituted cyclohexanones by *anti*-S_N2' displacement of allylic phosphate intermediates developed by Knochel and coworkers, which had been shown to be useful for preparing enantioenriched 2-alkyl-3,3-dimethylcyclohexanones.[28] The sequence began with (*S*)-2-iodocyclohexenol **48**, whose synthesis by Corey-Bakshi-Shibata reduction had been described earlier in the enantiomeric series.[28b,29] After converting alcohol **48** to the corresponding allylic phosphate, reaction of **49** with an excess of the organocuprate generated *in situ* from Grignard reagent **50** and CuCN produced vinyl iodide **51** with complete stereospecificity,[28] as confirmed by enantioselective HPLC analysis. Transformation of **51** to ketone (*S*)-**44** was accomplished without loss of enantiopurity by Knochel's procedure.[28] Wittig olefination of (*S*)-**44**, as carried out in the racemic series, gave ethylidene product **37**, which was transformed to oxalate diester **45** in high yield. However, the enantiomeric purity of **45** was quite low, and epimerization of the labile α-stereocenter during the Wittig olefination was identified as the culprit of this erosion of enantiopurity. A wide variety of Wittig reaction conditions were then explored in attempts to suppress epimerization, including salt- and base-free conditions.[30] Unfortunately, substantial racemization was observed under all the conditions surveyed.

The high efficiency and high enantiomeric purity of the synthesis of vinyl iodide **51** led us to explore alternative methods of converting this intermediate to the (*E*)-ethylidene cyclization precursor (*S*)-**37**. We reasoned that installation of a vinyl unit, followed by stereocontrolled 1,4-reduction of the resultant diene would be a viable way to access this intermediate (Scheme 10). The required 1,3-diene **52** was readily prepared in high yield by Negishi vinylation.[31] The most direct method to access (*S*)-**37** from diene **52** would be a selective 1,4-delivery of hydrogen. Regio- and stereocontrolled hydrogenations of this type have been known for some time and are affected by use of chromium η^6-arene tricarbonyl complexes.[32] In the event, hydrogenation of **52** in the presence of 20 mol % of (η^6-napthalene)chromium tricarbonyl at high pressures of hydrogen occurred in nearly quantitative yield to give (*E*)-ethylidene product **(*S*)-37**. Advancing this material over two steps furnished methyl oxalate **45** of high enantiomeric purity (>97% ee). Saponification of **45** with aqueous cesium hydroxide provided oxalate salt **53**, finally positioning us to explore the critical fragment-coupling step.

Scheme 10

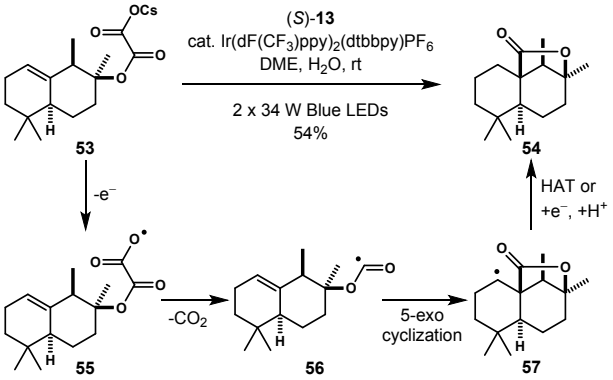


Fragment Coupling is Undermined by Cyclization of an Alkoxyacyl Intermediate and Synthesis of the Epimeric Octahydronaphthalene Tertiary Alcohol. Following coupling procedures developed in our earlier studies,[6] cesium oxalate **53** was irradiated with blue LEDs in the presence of 1 mol % of the iridium photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and 1 equiv of (*S*)-5-methoxybutenolide (*S*)-**13** (Scheme 11). However, no trace of the desired coupling product was observed; the only product observed was the tricyclic butyrolactone **54**. This

tricyclic lactone would be the result of 5-exo-cyclization of the intermediate alkoxycarbonyl radical **56**, produced from oxalate radical **55** in the initial rapid decarboxylation event. Although 5-exo cyclizations of alkoxyacyl radicals are well known,[33–35] we had hoped that bond formation at the β,β-disubstituted alkene center would have been retarded. As moderating the rate of this intramolecular process appeared impossible, another precursor of octahydronapthalene tertiary radical **6** depicted in Scheme 1 would be required.

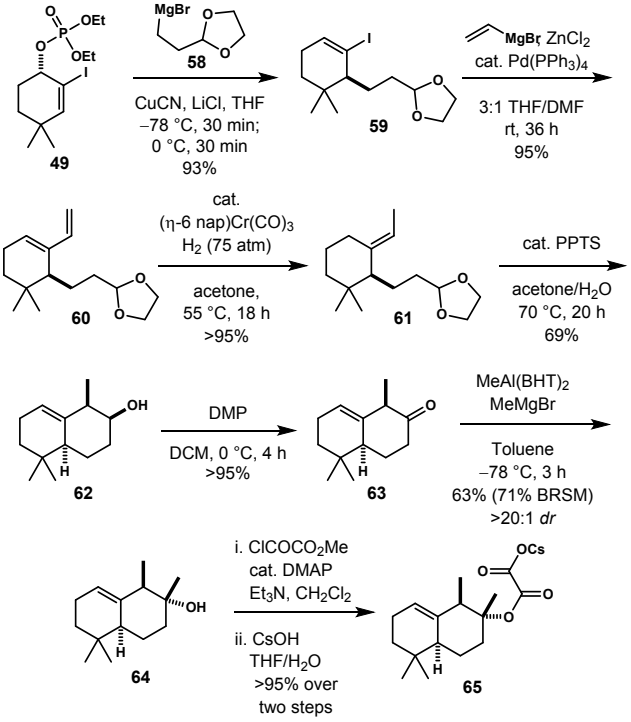
To preclude cyclization of an alkoxycarbonyl radical intermediate, we turned to develop a synthesis of the epimeric octahydronapthalene tertiary alcohol, which would tether an oxalate fragment in a pseudoequatorial orientation. Using the same sequence that we had employed to prepare tertiary alcohol **38**, the related octahydronapthalene secondary alcohol **62**, was prepared in four steps and 57% overall yield from allylic phosphate **49** and Grignard reagent **58** (Scheme 12).

Scheme 11



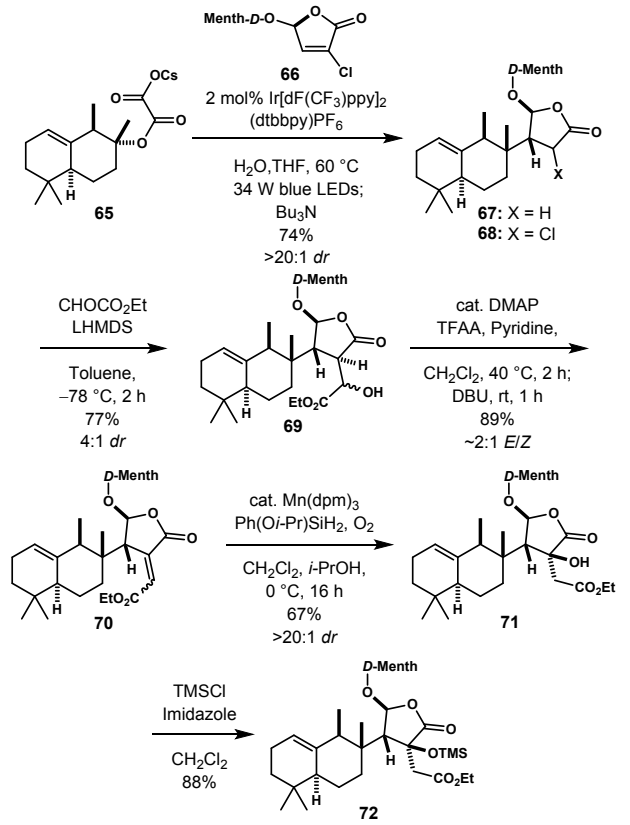
Oxidation of **62** with Dess-Martin periodinane[36] gave β,γ-unsaturated ketone **63**, a labile oil that was prone to autoxidation. To no surprise, reaction of this ketone with MeLi or MeMgBr afforded predominantly the undesired axial tertiary alcohol **38**. In order to reverse the selectivity, we employed Yamamoto's bulky bis[2,6-bis(1,1-dimethylethyl)-4-methylphenolato] methylaluminum (MAD), which is thought to coordinate with the carbonyl oxygen and favor nucleophilic addition from the axial vector.[37] In the event, addition of MeMgBr to a solution of MAD (6 equiv) and ketone **63** in toluene at –78 °C delivered equatorial tertiary alcohol **64** in 63% yield (70 % corrected for recovered **63**) and superb 20:1 facial selectivity. Alkoxyacylation of **64** with methyl chlorooxalate and selective saponification of the resulting diester with aqueous CsOH provided cesium oxalate **65** in high yield.

Scheme 12



Successful Fragment Coupling and Total Synthesis of (–)-Macfarlandin C. With the epimeric tertiary oxalate **65** in hand, we examined its participation in the pivotal fragment-coupling step with (*R*)-chlorobutenolide **66** (Scheme 13). This coupling partner was chosen for its higher reactivity with nucleophilic tertiary radicals.[6]

Scheme 13

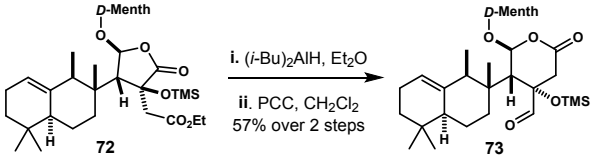


To our delight, irradiation of oxalate **65** with 34 W blue (465 nm) LEDs in the presence of 1 mol % of the iridium photocatalyst and 1 equiv of chlorobutenolide **66** gave as the major products the coupled lactone **67** and its chloro analogue **68**. *In situ* reductive dechlorination of **68** could be achieved by addition of tributylamine and continued irradiation. Using this procedure, lactone **67** was isolated in 74% yield and >20:1 diastereoselectivity from oxalate salt **65**.

Lactone **67** was elaborated by the aldol-dehydration sequence optimized in the model system to access vinylogous α-alkoxyacyl esters **70**. Treatment of these electron-deficient alkenes under Mukaiyama hydration conditions provided tertiary alcohol **71** with high regio- and stereoselectivity. A small screen of manganese catalysts and silane reductants showed that optimal yields of alcohol **71** were achieved with the more active catalytic system reported by Shenvi and coworkers.[38] Under these conditions, competitive hydration of the more electron rich trisubstituted alkene was relatively minor and only observed under forcing conditions. Tertiary alcohol **71** was then derivatized as its trimethylsilyl silyl ether prior to attempting cyclization to form the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one ring system.

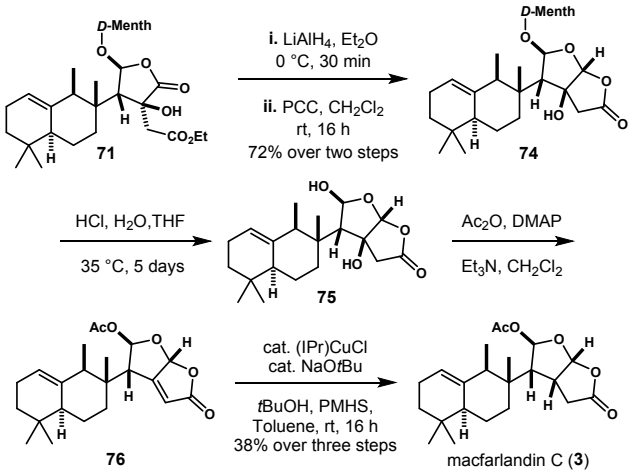
At this stage, we encountered an unexpected hurdle. When lactone ester **72** was exposed to excess DIBALH followed by oxidation with PCC, the desired *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one was not formed (Scheme 14). The presence of an aldehyde signal in the ^{1}H NMR spectrum and a six-membered lactone carbonyl peak at 1720 cm^{-1} in the IR spectra indicated that the major product was valerolactone **73**. Presumably, a Lewis acidic aluminum species facilitated skeletal rearrangement prior to the oxidation step. We briefly considered if it was possible to induce a rearrangement of **73** into its *cis* 2,8-dioxabicyclo[3.3.0]octan-3-one analogue, and screened several potential Lewis and Bronsted acid catalysts to no avail.

Scheme 14



These setbacks forced us to explore other reducing agents in the hope of restoring the desired reduction/cyclization sequence (Scheme 15). Surprisingly, both silyl ether **72** and tertiary alcohol **71** were stable to a variety of reducing agents.[39] Finally we found that exposing alcohol **71** to 5 equiv of $LiAlH_4$ in Et_2O at 0 °C, followed by oxidation of the resulting products with PCC gave rise to a mixture of the desired *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one **74** and recovered **71**. Increasing the amount of $LiAlH_4$ to 15 equiv, prior to oxidation with PCC resulted in complete. and, more importantly, consistent conversion to *cis*-dioxabicyclooctanone **74**.

Scheme 15

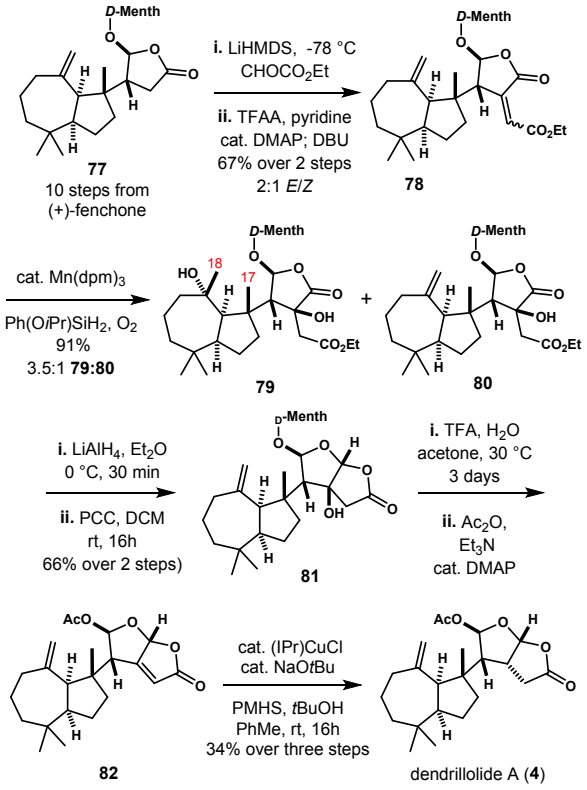


With a reliable method of constructing **74** in hand we were poised to complete the total synthesis of (–)-macfarlandin C. The menthol auxiliary was removed by exposing **74** to dilute HCl at 35 °C for several days. Increasing the temperature above 35 °C in order to accelerate the conversion to the corresponding diol resulted in extensive decomposition. The crude diol **75** was then peracetylated by reaction with excess acetic anhydride in the presence of DMAP. An intermediate diacetate could be observed in ^{1}H NMR spectra of reaction aliquots, however in this case extended exposure of the crude products to silica gel resulted in decomposition. This issue could be circumvented if the peracetylation step was accomplished in the presence of Et_3N, which promotes acetate elimination *in situ* affording exclusively butenolide **76**. Without purification, this product was reduced to deliver (–)-macfarlandin C (**3**), $[\alpha]^{21}_D$ –28 (*c* = 0.4, $CHCl_3$), in 38% yield over the three steps. Spectroscopic properties of synthetic (–)-macfarlandin C were fully consistent with those reported for the natural isolate, as was its optical rotation.[2]

C. Generalization of the Alcohol-Blocking Route Enables the Total Synthesis of (+)-Dendrillolide A

In order to probe the generality of our approach to concave-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones, we turned to access (+)-dendrillolide A by a related sequence (Scheme 16). The synthesis began with tricyclic lactone **77**, which had been prepared previously from (+)-fenchone.[6] This lactone was advanced through the aldol-dehydration sequence without issue. However, under Mukaiyama hydration conditions both exocyclic double bonds of intermediate **78** reacted at comparable rates affording a 3–4:1 mixture of diol **79** and alcohol **80**.[40] Fortunately, this selectivity issue proved irrelevant because carrying these products individually or as a mixture through the reduction-oxidation sequence delivered bicyclic lactone **81** exclusively. We postulate that the destabilizing *syn*-pentane interaction between the C-17 and C-18 methyl groups facilitates elimination of the C-18 acetate intermediate under the mildly acidic conditions of the PCC oxidation.

Scheme 16



Somewhat to our surprise, one of the final steps in the synthesis of dendrillolide A required modification. Specifically, removal of the menthol fragment from acetal **81** required more forcing conditions, as the dilute HCl conditions used in the macfarlandin C series resulted in little reaction of acetal **81**. Eventually, it was found that in a solution containing equal volumes of TFA/H_2O/acetone at 30 °C the desired hydrolysis was slowly, yet efficiently realized. It is of interest that identical treatment of macfarlandin C precursor **74** results in its complete decomposition. The two final steps proceeded without complications to provide (+)-dendrillolide A (**4**), $[\alpha]^{22}_D$ +64 (*c* = 1.0, $CHCl_3$) of ca. 90% purity in 34% yield over the three-step sequence. The spectroscopic properties of synthetic dendrillolide A and optical rotation agreed with those reported for the natural isolate.[3, 41]

Conclusion

The first synthesis of *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones that display a bulky C-6 hydrocarbon substituent on the sterically congested concave face has been developed. The general route is exemplified by enantioselective total syntheses of the rearranged spongian diterpenoids (–)-macfarlandin C (**3**) and (+)-dendrillolide A (**4**), with the synthesis of **4** rigorously establishing the absolute configuration of natural (+)-dendrillolide A.[9] The ancillary investigations discussed in this account provide insight into the evolution of the ultimately successful synthetic strategies.

Our approach to these marine natural products builds on our prior studies in the area[6] and now allows for divergent access to either convex- or concave-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one products. The newly developed sequence relies on a highly regio- and diastereoselective Mukaiyama hydration reaction that orient vicinal carbon side chains cis on a butyrolactone precursor of the *cis*-dioxabicyclooctanone fragment. In both syntheses, the hydrocarbon and lactone fragments were united by an efficient stereoselective fragment coupling between a tertiary alcohol-derived tertiary radical and an electron-deficient alkene resulting in the formation of a new quaternary and tertiary carbon stereocenter.[14] In the total synthesis of macfarlandin C, we developed a nine-step enantioselective route to the octahydronaphthalene fragment, which relied on a key carbonyl-ene cyclization to fashion the decalin framework. We anticipate that aspects of these studies will prove useful in future synthetic endeavors in this and related areas.

EXPERIMENTAL SECTION

Unless stated otherwise, reactions were conducted in oven-dried glassware under an atmosphere of argon. Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), dimethylformamide (DMF), toluene, dichloromethane (CH_2Cl_2), and methanol (MeOH) were dried by passage through activated alumina. Commercial solutions of ethyl glyoxylate were distilled over P_2O_5 immediately prior to use. All other commercial reagents were used as received unless otherwise noted. Reaction temperatures were controlled using a temperature modulator, and unless stated otherwise, reactions were performed at rt (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm), or staining with p-anisaldehyde, ceric ammonium molybdate (CAM), or $KMnO_4$. Silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded at 500 or 600 MHz and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded at 125 or 150 MHz. IR spectra were recorded on a ThermoFisher Nicolet iS5 FT-IR spectrometer with an iD7 ATR accessory and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility with a Micromass LCT spectrometer. The instrument utilized for crystallographic data collection was a three-circle, sealed-tube, Mo radiation, Bruker SMART APEX II CCD based system. Optical rotation readings were obtained using JASCO P-1010 polarimeter. Kessil KSH150B LED Grow Light 150, Blue (34 W blue LED lamps) were purchased from http://www.amazon.com. Enantiomeric excess for compounds **45**, **48**, **51**, and **59** was determined by HPLC analysis using an Agilent 1100 series analytical HPLC. Abbreviations commonly used are: IPA (isopropyl alcohol), Hex (hexanes), DMAP (4-dimethylaminopyridine), EtOAc (ethyl acetate), rt (room temperature); For others, see: JOC Standard Abbreviations and Acronyms: http://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf.

Preparation of Alcohol 15: A solution of lactone **14** (500 mg, 2.36 mmol)[6] in THF (12 mL) was cooled to –78 °C and a solution of LHMDS (2.8 mL, 2.8 mmol, 1.2 equiv, 1 M in THF) was added dropwise. The resulting yellow solution was maintained at –78 °C for 15 min, after which a solution of freshly prepared and distilled methyl glyoxylate (30 mL, 24.0 mmol, 0.81 M in THF) was added.[42] The reaction mixture was maintained at –78 °C for 1 h and was subsequently quenched by the addition of saturated aqueous NH_4Cl solution (7 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, 3:1→1.5:1 Hex/EtOAc) to obtain alcohol **15** (492 mg, 1.64 mmol, 69%) as a colorless oil and as an inseparable 2:1 mixture of diastereomers. R_f = 0.36 (3:1 Hex/EtOAc, visualized with $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.22 (br s, 0.33H, minor), 5.16 (d,

J = 3.1 Hz, 0.66H, major), 4.67 (dd, *J* = 9.4, 3.1 Hz, 0.33H, minor), 4.37–4.34 (m, 0.66H, major), 3.84 (s, 2H, major), 3.75 (s, 1H, minor), 3.50 (s, 1H, minor), 3.49 (s, 2H, major), 3.48–3.47 (m, 0.33H, minor), 3.26 (d, *J* = 4.3 Hz, 0.66H, major), 3.06 (dd, *J* = 6.5, 3.2 Hz, 0.66H, major), 2.91–2.89 (m, 0.33H, minor), 2.38–2.33 (m, 0.66H, major), 2.11–2.07 (m, 0.33H, minor), 1.60–1.16 (m, 10H, major and minor), 0.90 (s, 2H, major), 0.81 (s, 1H, minor); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, mixture of diastereomers) δ (Major) 174.8, 172.9, 106.0, 70.6, 57.3, 53.2, 52.3, 45.9, 35.6, 35.4, 34.5, 26.0, 21.4, 21.3, 20.3 (Minor) 176.2, 172.8, 105.4, 70.8, 56.9, 52.6, 52.1, 45.5, 34.9, 34.6, 34.0, 25.9, 21.45, 21.38, 19.5; IR (thin film) 2929, 2854, 1777, 1747, 1446, 1124, 964 cm^{-1}; HRMS (CI-TOF) *m/z*: $(M+H)^+$ calcd for $[C_{15}H_{25}O_6]$ 301.1651; found 301.1658.

Preparation of Alcohol 16: A flame dried 250 mL round-bottom flask was charged with lactone **14** (1.37 g, 6.44 mmol) and THF (64 mL, 0.1 M). The solution was cooled to –78 °C and a solution of LHMDS (7.3 mL, 7.3 mmol, 1.15 equiv, 1 M in THF) was added dropwise. The reaction was maintained at –78 °C for 1 h. During the enolate formation, ethyl glyoxylate (50 wt% in toluene) was distilled over P_2O_5 under argon (10–15 min at 110 °C then over 10 min warmed to 140 °C and over 10 min warmed to 200 °C); the yellow distillate was used immediately. Freshly distilled ethyl glyoxylate (6.4 mL, 32 mmol, 5 equiv) was added, the reaction mixture was maintained at –78 °C for 1.5 h, and then subsequently quenched by the addition of H_2O (50 mL) and allowed to warm to rt. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine (40 mL) and dried over $MgSO_4$. The organic layer was filtered and concentrated to an orange oil. The residue was purified by flash column chromatography (SiO_2, 20:1→4:1 Hex/EtOAc) to afford alcohol **16** (1.64 g, 5.22 mmol, 81%) as a colorless oil and as a ~7:3 mixture of alcohol epimers. R_f = 0.3 (4:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$): δ 5.23 (d, *J* = 1.2 Hz, 0.3H, minor), 5.17 (d, *J* = 3.0 Hz, 0.7H, major), 4.66 (dd, *J* = 3.0, 8.9, 0.3H, minor), 4.39-4.25 (m, 2.4H, major and minor), 4.18-4.10 (m, 0.3H, minor), 3.52 (s, 0.9H, minor), 3.51 (s, 2.1H, major), 3.48-3.44 (m, 0.3H, minor), 3.25 (d, *J* = 4.1 Hz, 0.7H, major), 3.08 (dd, *J* = 3.0, 6.5 Hz, 0.7H, major), 3.07 (app t, *J* = 3.4 Hz, 0.3H, minor), 2.40 (dd, *J* = 3.1, 6.2 Hz, 0.7H, major), 2.15-2.11 (m, 0.3H, minor), 1.64-1.51 (m, 3H), 1.50-1.41 (m, 2H), 1.38-1.21 (m, 5H), 1.35 (t, *J* = 7.0 Hz, 2.1H, major), 1.31 (t, *J* = 7.1 Hz, 0.9H, minor), 0.93 (s, 2.1H, major), 0.84 (s, 0.9H, minor); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ (Major) 174.6, 172.4, 105.9, 70.5, 62.6, 57.2, 45.8, 35.6, 35.4, 34.4, 31.6, 25.9, 21.4, 21.3, 20.3, 14.0, (Minor) 176.1, 172.3, 105.3, 70.7, 62.0, 56.8, 45.4, 34.9, 34.6, 33.9, 29.7, 25.9, 21.37, 21.33, 19.5, 14.0; IR (thin film) 3475, 2927, 2852, 1773, 1737, 1446, 1371, 1263, 1220, 1184, 1121 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{16}H_{26}O_6Na]^+$ 337.1627; found 337.1614

Preparation of Alkenes 17: A scintillation vial containing a stir bar was charged with alcohol **15** (486 mg, 1.62 mmol), DMAP (20 mg, 0.16 mmol) and 1,2-dichloromethane (11 mL) under argon. After sequential addition of pyridine (520 µL, 6.48 mmol) and trifluoroacetic anhydride (460 µL, 3.24 mmol), the reaction mixture was maintained at rt for 45 min when complete consumption of the starting material was observed by TLC analysis. After this time, DBU (1.45 mL, 9,72 mmol) was added by syringe and the reaction mixture was stirred at rt for 1 h. The reaction mixture was then quenched by the addition of saturated aqueous NH_4Cl solution (6 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic layers were washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered through cotton and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, 4:1 Hex/EtOAc) to provide alkenes **17** (415 mg, 1.47 mmol, 91%) as a colorless oil and as a 1.5:1 mixture of alkene isomers: R_f = 0.68 and 0.50 (3:1 Hex/EtOAc); ^1H NMR (500 MHz, $CDCl_3$, mixture of alkene isomers) δ 6.90 (s, 0.6H, major), 6.28 (s, 0.4H, minor), 5.39 (s, 0.6H, major), 5.27 (s, 0.4H, minor), 3.83 (s, 1.2H, minor), 3.78 (s, 1.8H, major), 3.49–3.46 (m, 0.6H), 3.48 (s, 1.2H, minor), 3.47 (s, 1.8H, major), 2.70 (s, 0.4H, minor), 1.64–1.04 (m, 10H, major and minor), 0.93 (s, 1.8H, major), 0.86 (s, 1.2H, minor); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, mixture of diastereomers) δ (Major) 170.5, 165.7, 141.7, 127.6, 105.1, 56.6, 55.9, 52.2, 38.1, 35.1, 34.3, 25.9, 21.7, 21.6, 19.8 (Minor) 167.3, 165.6, 133.5, 130.2, 104.2, 56.6, 55.6, 52.6, 35.8, 35.3, 34.6, 26.0, 21.50, 21.4, 20.5; IR (thin film) 2931, 2858, 1774, 1731, 1214, 938, 911 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{15}H_{22}O_5Na]^+$ 305.1365; found 305.1362.

Preparation of Alkenes 18: A 100 mL round-bottom flask was charged with alcohol **16** (1.63 g, 5.2 mmol), DMAP (63 mg, 0.52 mmol, 10 mol%), and CH_2Cl_2 (25 mL, 0.2 M). After sequential addition of pyridine (1.67 mL, 20.8 mmol, 4 equiv) and trifluoroacetic anhydride (1.4 mL, 10 mmol, 2 equiv), the reaction mixture was maintained at 40 °C for 1 h when complete consumption of the starting material was observed by TLC analysis. The reaction was cooled to rt and DBU (4.6 mL, 31 mmol, 6 equiv) was added via syringe. The mixture was stirred at rt for 1 h and then quenched by the addition of H_2O (20 mL). The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 20 mL). The combined organic layers were then washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to a brown oil. This residue was purified by flash column chromatography (SiO_2, 20:1→10:1 Hex/EtOAc) to afford **(*E*)-18** (865 mg, 2.91 mmol, 56%) and **(*Z*)-18** (459 mg, 1.56 mmol, 30%) as colorless oils. R_f = 0.60 and 0.45 (4:1 Hex/EtOAc), respectively; **(*E*)-18:** ^1H NMR (600 MHz, $CDCl_3$): δ 6.90 (d, *J* = 1.6 Hz, 1H), 5.39 (s, 1H), 4.31-4.19 (m, 2H), 3.51 (d, *J* = 1.6 Hz, 1H), 3.48 (s, 3H), 1.66-1.59 (m, 1H), 1.56-1.50 (m, 2H), 1.49-1.35 (m, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.29-1.18 (m, 3H), 1.15-1.06 (m, 1H), 0.94 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 170.4, 165.2, 141.2, 127.9, 104.9, 61.2, 56.47, 55.7, 38.0, 35.0, 34.2, 25.8, 21.6, 21.5, 19.6, 14.1; IR (thin film) 2927, 2851, 1776, 1724, 1465, 1446, 1372, 1353, 1255, 1206, 1113, 1065, 1024, 999, 929, 786, 673; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{16}H_{24}NaO_5]^+$ 319.1521; found 319.1533; **(Z)-18:** ^1H NMR (600 MHz, $CDCl_3$): δ 6.27 (d, *J* = 1.6 Hz, 1H), 5.27 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.48 (s, 3H), 2.69 (s, 1H), 1.60-1.37 (m, 8H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.31-1.22 (m, 2H), 0.87 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 167.1, 165,1, 133.0, 130.6, 104.1, 61.7, 56.5, 55.5, 35.7, 35.2, 34.6, 25.9, 21.44, 21.40, 20.5, 14.0; IR (thin film) 2927, 2851, 1772, 1732, 1465, 1446, 1367, 1328, 1219, 1176, 1090, 1025, 942, 674 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{16}H_{24}NaO_5]^+$ 319.1521; found 319.1533.

Preparation of Lactol 23: A 10 mL round-bottom flask was charged with alkene **(*Z*)-18** (160 mg, 0.54 mmol) in THF (3 mL, 0.18M) and cooled to 0 °C. Then concentrated HCl (3 mL) was added dropwise. The reaction was allowed to warm to rt and stirred for 24 hrs. The reaction was then cooled to 0 °C and diluted with H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were then dried over $MgSO_4$, filtered and concentrated to an orange oil. The crude residue was purified by flash column chromatography (SiO_2, 5:1 Hex/EtOAc) to afford **23** (132 mg, 87%) as a yellow oil. R_f = 0.32 (5:1 Hex/EtOAc); ^1H NMR (600 MHz, $CDCl_3$) δ 6.93 (d, *J* = 1.6 Hz, 1H), 5.95 (s, 1H), 4.31-4.20 (m, 2H), 3.54 (d, *J* = 1.6 Hz, 1H), 1.64-1.59 (m, 1H), 1.55-1.50 (m, 2H), 1.49-1.35 (m, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.29-1.19 (m, 3H), 1.15-1.06 (m, 1H), 0.94 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.4, 165.4, 141.1, 128.6, 98.4, 61.3, 56.3, 38.1, 35.0, 34.2, 25.9, 21.6, 21.5, 19.7, 14.1; IR (thin film) 3402, 2927, 2858, 1774, 1724, 1446, 1372, 1253, 1206, 1107, 1025, 940; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{15}H_{22}O_5Na]^+$ 305.1365; found 305.1371.

Preparation of Dihydrofuran 26: A flame-dried 10 mL round bottom flask was charged with lactone **14** (100 mg, 0.47 mmol) and CH_2Cl_2 (4.7 mL, 0.1 M). The solution was cooled to –78 °C and DIBAL (0.52 mL, 0.52 mmol, 1.1 equiv, 1 M in hexanes) was added dropwise. The reaction was then stirred at –78 °C for 1 h, quenched by the addition of acetone (1 mL), and stirred for 5 min. A saturated aqueous solution of Rochelle's salt (2 mL) was added and the reaction mixture was allowed to warm to rt and stirred for 40 min. This mixture was then extracted with Et_2O (2 x 10 mL) and the organic extracts were washed with brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to a colorless oil, which was used without further purification.

A 10 mL flask was charged with the crude lactol dissolved in THF (2.4 mL, 0.2 M) and cooled to 0 °C. DMAP (6 mg, 0.047 mmol, 10 mol%) was added followed by Et_3N (0.26 mL, 1.88 mmol, 4 equiv) and TFAA (0.13 mL, 0.94 mmol, 2 equiv). The mixture was then warmed to 65 °C for 1 h. The reaction mixture was cooled to rt and quenched with the addition of sat. aq. NH_4Cl (20 mL). The mixture was then extracted with Et_2O (2 x 10 mL) and the organic layer were washed with brine (20 mL). The organic layer were then dried over $MgSO_4$, filtered, and concentrated to a yellow oil. The crude residue was purified by flash column chromatograpy (SiO_2 neutralized with 1% Et_3N in Hex, 1:0→20:1→10:1 Hex/EtOAc) to afford dihydrofuran **26** (64 mg, 67% over two steps) as a colorless oil. R_f = 0.88 (4:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (500 MHz, $CDCl_3$): δ 6.36 (dd, *J* = 1.8, 2.5 Hz, 1H), 5.15 (d, *J* = 2.5 Hz, 1H), 4.97 (t, *J* = 2.8 Hz, 1H), 3.46 (s, 3H), 2.61-2.55 (m, 1H), 1.60-1.20 (m, 10 H), 0.80 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz,

$CDCl_3$) δ 143.8, 107.6, 101.0, 59.5, 55.5, 35.6, 35.4, 34.3, 26.4, 21.7, 21.6, 20.4; IR (thin film) 2923, 2851, 1619, 1445, 1379, 1218, 1140, 1105, 1053, 1034, 961, 928, 902 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{12}H_{20}O_2Na]^+$ 197.1542; found 197.1550.

Preparation of Bromoester 27: A flame-dried 10 mL flask was charged with dihydrofuran **26** (55 mg, 0.28 mmol) in CH_2Cl_2 (3 mL, 0.1 M) and cooled to 0 °C. Bromoacetic acid (58 mg, 0.42 mmol, 1.5 equiv) was added followed by NBS (58 mg, 0.32 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 1 h. TLC analysis indicated the starting material had been consumed. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was then washed with sat. aq. $Na_2S_2O_3$ (10 mL) , dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:0→9:1 Hex/EtOAc) to afford bromoester **27** (83 mg, 72%%) as a colorless oil as a 7:1 mixture of partially separable diastereomers. R_f = 0.55 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$) δ 6.44 (d, *J* = 2.1 Hz, 1H), 5.04 (d, *J* = 4.2 Hz, 1H), 4.04 (dd, *J* = 2.1, 4.4 Hz, 1H), 3.84 (s, 2H), 3.47 (s, 3H), 2.60 (t, *J* = 4.2 Hz, 1H), 1.61–1.25 (m, 10H), 0.95 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 165.6, 108.2, 104.3, 62.9, 56.5, 46.7, 36.4, 36.1, 34.7, 26.0, 25.4, 21.5, 21.4, 21.3; IR (thin film) 2925, 2850, 1756, 1446, 1395, 1268, 1097, 1030, 951, 901, 877 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{14}H_{22}O_4Br_2Na]^+$ 434.9782, 436.9763, 438.9745 (1:2:1); found 434.9784, 436.9751, 438.9742 (1:2:1).

Preparation of Alcohol 32: A 25 mL round bottom flask containing a stir bar was charged with alkene **18** (281 mg, 0.95 mmol) and toluene (9 mL, 0.1 M) under argon. The solution was cooled to −78 °C and a solution of L-selectride (1.4 mL, 1.4 mmol, 1 M in THF) was added dropwise. The resulting solution was maintained at −78 °C for 1 h, after which a solution of iodine (1.2 g, 4.75 mmol) in toluene (5 mL) was added. The reaction mixture was allowed to warm to −20 °C and then quenched by the addition of H_2O (5mL). This mixture was stirred at rt for 30 min. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (2 x 30 mL) and then brine (2 x 30 mL), dried over $MgSO_4$, filtered through cotton and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, 10:1→4:1 Hex/EtOAc) to provide tertiary alcohol **32** (220 mg, 0.70 mmol, 74%) as a colorless solid.

Preparation of Alcohol 32 by Mukaiyama Hydration: A 25 mL round-bottom flask was charged with alkenes **18** (169 mg, 0.57 mmol) and *i*-PrOH (6 mL, 0.1 M). The mixture was sparged with O_2 for 5 min. Then $Mn(acac)_2$ (23.5 mg, 0.092 mmol, 15 mol%) and $PhSiH_3$ (0.28 mL, 2.26 mmol, 4 equiv) were added. The mixture was gently warmed with a heat gun until the reaction turned yellow and started to bubble. The reaction was then allowed to cool to rt and stirred at rt for 24 h. The reaction was then concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 10:1→4:1 Hex/EtOAc) to afford alcohol **32** (116 mg, 65%) as a colorless oil, which solidifies over time. X-ray quality crystals were obtained from slow evaporation of CH_2Cl_2. R_f = 0.3 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$): δ 5.31 (d, *J* = 7.3 Hz, 1H), 4.68 (s, 1H), 4.26-4.16 (m, 2H), 3.57 (s, 3H), 2.98 (d, *J* = 15.1 Hz, 1H), 2.68 (d, *J* = 15.0 Hz, 1H), 2.48 (d, *J* = 7.4 Hz, 1H), 1.70-1.64 (m, 1H), 1.63-1.57 (m, 1H), 1.55-1.48 (m, 2H), 1.48-1.38 (m, 5H), 1.32-1.24 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 175.1, 170.5, 104.4, 77.0, 61.7, 58.2, 57.5, 39.2, 38.2, 36.3, 34.4, 25.8, 22.3, 21.4, 21.3, 14.0; IR (thin film) 3448, 2930, 2854, 1782, 1735, 1448, 1392, 1373, 1298, 1216, 1175, 1135, 1044, 922 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{16}H_{27}O_6]^+$ 315.1808; found 315.1811.

Preparation of TMS-protected Alcohol S1: A 10 mL round-bottom flask was charged with alcohol **32** (113 mg, 0.358 mmol) and CH_2Cl_2 (3 mL, 0.1 M). Imidazole (148 mg, 2.17 mmol, 6 equiv) was added, followed by freshly distilled TMSCl (0.14 mL, 1.1 mmol, 3 equiv). The reaction was then stirred at rt for 3 h, at which time TLC analysis indicated consumption of starting material. The reaction was quenched by the addition of H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were then dried over $MgSO_4$, filtered, and concentrated to afford lactone **S1** (127 mg, 92%) as a pale-yellow oil that was used without further purification. R_f = 0.66 (4:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, C_6D_6): δ 5.32 (d, *J* = 7.7 Hz, 1H), 3.93 (dq, *J* = 7.1, 11.0 Hz, 1H), 3.79 (dq, *J* = 7.1, 11.0 Hz, 1H), 3.13 (s, 3H), 3.10 (d, *J* = 16.4 Hz, 1H), 2.93 (d, *J* = 16.4 Hz, 1H), 2.58 (d, *J* = 7.7 Hz, 1H), 1.67-1.58 (m, 1H), 1.55-1.43 (m, 3H), 1.43-1.30 (m, 4H), 1.30-1.25 (m, 1H), 1.24-1.14 (m, 1H), 0.93 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.33 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6): δ 174.3, 169.0, 104.2, 79.7, 61.5, 60.4, 56.6, 42.9, 38.0, 36.5, 34.3, 25.9, 21.8, 21.6, 21.4, 13.6, 1.6; IR (thin film) 2925, 2850, 1780, 1739, 1373, 1339, 1248, 1132, 954, 844 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{19}H_{34}NaO_6Si]^+$ 409.2022; found 409.2013.

Preparation of Dioxabicyclo[3.3.0]octan-3-one 33: A 10 mL round-bottom flask was charged with lactone **S1** (19 mg, 0.05 mmol) and Et_2O (1.5 mL, 0.03 M). The mixture was cooled to −78 °C and DIBAL (0.25 mL, 0.25 mmol, 5 equiv, 1 M in hexanes) was added. The reaction was then stirred at −78 °C for 2 h and then allowed to warm passively over an hour to −20 °C. The reaction was stirred at −20 °C for 30 min and then quenched by the addition of a saturated aqueous solution of Rochelle's salt (2 mL) and saturated aqueous $NaHCO_3$ (2 mL). The mixture was then vigorously stirred for 30 min. The reaction mixture was then extracted with Et_2O (3 x 10 mL). The organic extracts were then dried over $MgSO_4$, filtered and concentrated to afford the crude lactols as a colorless oil.

A 10 mL round-bottom flask was charged with the crude lactols and CH_2Cl_2 (1.5 mL, 0.03 M). PCC (22 mg, 0.10 mmol, 2 equiv) was added and the reaction mixture was stirred at rt for 16 h. Celite® (2 g) was added to the reaction mixture followed by dilution with 10 mL of 4:1 hexane/EtOAc. The mixture was then filtered through a SiO_2 plug with 4:1 hexanes/EtOAc (30 mL). The filtrate was concentrated to afford dioxabicyclo[3.3.0]octanone **33** (16 mg, 91% over two steps) as a colorless oil: R_f = 0.35 (9:1 hexanes/EtOAc, visualized with $KMnO_4$). This material was taken on without further purification, as the TMS-protecting group was quite labile. A small sample was purified by flash column chromatography for characterization purposes. ^1H NMR (600 MHz, C_6D_6): δ 5.71 (s, 1H), 4.55 (d, *J* = 6.4 Hz, 1H), 3.16 (s, 3H), 2.63 (d, *J* = 17.4 Hz, 1H), 2.43 (d, *J* = 6.3 Hz, 1H), 2.28 (d, *J* = 17.4 Hz, 1H), 1.53-1.03 (m, 10H), 0.70 (s, 3H), 0.01 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6): δ 174.2, 106.8, 105.0, 85.3, 55.4, 39.0, 37.4, 37.0, 34.2, 25.9, 21.6, 21.3, 1.2; IR (thin film) 2924, 2850, 1803, 1254, 1162, 1129, 1111, 1054, 1031, 946, 913, 844 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{17}H_{30}NaO_5Si]^+$ 365.1760; found 365.1761.

Preparation of Dioxabicyclo[3.3.0]oct-4-en-3-one 35: A 10 mL round-bottom flask was charged with lactone **33** (12 mg, 0.035 mmol) and THF (1 mL, 0.03 M). Aqueous HCl (1 mL, 4 M aqueous, 110 equiv) was added, and the reaction mixture was stirred at rt for 48 h. The reaction was then diluted with H_2O (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated to afford lactol **34** as colorless oil.

A 10 mL round-bottom flask was charged with the crude lactol **34**, DMAP (1.5 mg, 0.012 mmol, 35 mol%) and CH_2Cl_2 (2 mL, 0.01 M). Then freshly distilled pyridine (60 µL, 0.75 mmol, 20 equiv) was added followed by Ac_2O (50 µL, 0.53 mmol, 15 equiv). The reaction mixture was then stirred at rt for 24 h. The reaction was quenched by the addition of H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and filtered. SiO_2 (2 g) was added to the filtrate and the mixture was concentrated to give a colorless solid, which was allowed to sit at rt under vacuum for 16 h. The material was then purified by column chromatography (SiO_2, 4:1 Hex/EtOAc) to afford butenolide **35** (10 mg, >95%) as a colorless oil. R_f = 0.26 (4:1 Hex/EtOAc, visualized with $KMnO_4$).; ^1H NMR (600 MHz, $CDCl_3$): δ 6.48 (d, *J* = 3.9 Hz, 1H), 6.16 (s, 1H), 5.97 (d, *J* = 2.1 Hz, 1H), 3.25-3.21 (m, 1H), 2.13 (s, 3H), 1.54-1.48 (m, 4H), 1.47-1.35 (m, 3H), 1.34-1.27 (m, 3H), 1.01 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 171.0, 169.3, 167.5, 115.4, 104.1, 100.5, 53.7, 36.2, 36.1, 34.3, 25.9, 21.5, 21.3, 21.2, 20.7; IR (thin film) 2925, 2851, 1790, 1749, 1660, 1446, 1368, 1215, 1164, 1133, 1043, 987, 973, 944, 863 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{15}H_{20}NaO_5]^+$ 303.1208; found 303.1214.

Preparation of Dioxabicyclo[3.3.0]octan-3-one 36: A 5 mL round-bottom flask was charged with (*i*Pr)CuCl (2.3 mg, 0.0047 mmol, 15 mol%), NaO*t*Bu (0.05 mL, 0.1 M in toluene, 15 mol%), and toluene (0.5 mL). PMHS (7 µL, 0.1 mmol, 4 equiv) was added as a solution in toluene (0.1 mL). The reaction mixture was then stirred for 5 min. Then a solution of butenolide **35** (8.1 mg, 0.029 mmol) and *t*-BuOH (11 µL, 0.12 mmol, 4 equiv) in toluene (0.5 mL) was added to the reaction. The mixture was then stirred at rt for 16 h. The reaction was quenched by the addition of H_2O (5 mL) and allowed to stir for 5 min. The mixture was then extracted with EtOAc (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated to a colorless solid. This material was purified by flash column chromatography (SiO_2, 4:1

hexanes/EtOAc) to afford lactone **36** (5.3 mg, 66%) as a colorless solid. R_f: = 0.36 (4:1 hexanes/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$): δ 6.41 (d, *J* = 7.1 Hz, 1H), 6.04 (d, *J* = 4.0 Hz, 1H), 3.07 (dddd, *J* = 4.4, 6.4, 9.2, 10.2 Hz, 1H), 2.72 (dd, *J* = 10.2, 17.5 Hz, 1H), 2.55 (dd, *J* = 9.1, 17.6 Hz, 1H), 2.57-2.53 (m, 1H), 2.09 (s, 3H), 1.56-1.51 (m, 2H), 1.51-1.43 (m, 3H), 1.37-1.31 (m, 3H), 1.29-1.21 (m, 2H), 1.03 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 175.5, 169.9, 105.1, 96.7, 54.1, 41.3, 38.0, 37.4, 34.0, 29.7, 25.8, 22.7, 21.7, 21.3, 21.2; IR (thin film) 2925, 2851, 1795, 1749, 1376, 1228, 1163, 1016, 984, 939, 865 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{15}H_{22}O_5Na]^+$ 305.1365; found 305.1375.

Preparation of Alkenes 42 and 43: A flame-dried 250 mL round bottom was charged with CuBr·DMS (180 mg, 0.87 mmol, 10 mol%) and suspended in Et_2O (54 mL, 0.16 M). MeMgBr (3.3 mL, 11 mmol, 1.2 equiv, 3.31 M in Et_2O) was added to the suspension and the mixture was stirred for 15 min at rt then cooled to 0 °C. 3-Methylcyclohexenone (**39**) (1.02 mL, 9 mmol) was added dropwise at 0 °C and stirring was continued for 30 min until TLC showed full consumption of the starting material. The reaction was then cooled to −78 °C and a solution of aldehyde **40** (1.93 g, 14.8 mmol, 1.65 equiv)[43] in Et_2O (15 mL) was added slowly. The reaction was allowed to warm to rt overnight. Then sat. aqueous NH_4Cl (70 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated. The crude aldol product **41** was obtained as yellowish oil, which was directly used in the subsequent step.

To a solution of crude alcohol **41** in CH_2Cl_2 (90 mL, 0.1 M), DMAP (5.5 g, 45 mmol, 5 equiv) and MsCl (1.75 mL, 22.5 mmol, 2.5 equiv) were added. The reaction was then heat at reflux overnight. The mixture was then concentrated under reduced pressure (ca. 20 mL volume) and flushed through a SiO_2 plug with EtOAc (150 mL). The solvent was removed and the crude mesylates were taken up in THF (70 mL, 0.13 M) followed by the dropwise addition of DBU (4.71 mL, 31.5 mmol, 3.5 equiv). The mixture was maintained at rt overnight, after which time it was concentrated to 10% of its original volume. Et_2O (100 mL) was added and the organic phase was washed with water (25 mL) and brine (25 mL). After drying over Na_2SO_4 and removal of all volatiles, the crude product was purified by flash column chromatography (SiO_2, 10:1→4:1 Hex/EtOAc). The desired compound was obtained as colorless oil and as a 2:1 mixture of **42**:**43** (1.3 g, 5.5 mmol, 61% over three steps); Diagnostic ^1H-NMR (600 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 9.8, 15.5 Hz, 0.3H), 5.59 (t, *J* = 7.1 Hz, 0.7H), 5.39 (d, *J* = 15.5 Hz, 0.3H), 3.97-3.90 (m, 4H), 2.75 (d, *J* = 9.8 Hz, 0.3H), 2.57 (d, *J* = 7.4 Hz, 1.4H), 2.43 (t, *J* = 6.7 Hz, 1.4H), 2.37 (dt, *J* = 5.7, 13.6 Hz, 0.3H), 2.29-2.22 (m, 0.3H), 1.94-1.82 (m, 2H), 1.70-1.62 (m, 2H), 1.47 (s, 0.9), 1.29 (s, 2.1H), 1.08 (s, 4.2H), 0.96 (s, 0.9), 0.83 (s, 0.9H) ppm.

Preparation of *rac*-Ketone 44: The mixture of alkene isomers **42** and **43** (1.3 g, 5.5 mmol, 1 equiv) was dissolved in EtOAc (55 mL, 0.1 M) and $Pd(OH)_2$ (309 mg, 0.44 mmol, 0.08 equiv, 20 wt%) and $NaHCO_3$ (462 mg, 5.5 mmol, 1 equiv) were added in one portion. The reaction vessel was evacuated and backfilled with a hydrogen balloon (three times). With the balloon attached the reaction was stirred under a hydrogen atmosphere overnight after which time TLC showed full consumption of the starting materials. The solids were removed by filtration over Celite® and washing with the solids with EtOAc (100 mL). The filtrate was then concentrated under reduced pressure to afford ketone **44** (1.22 g, 5.1 mmol, 93%) as colorless oil. R_f = 0.36 (4:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$) δ 3.97-3.90 (m, 4H), 2.35-2.32 (m, 1H), 2.28-2.23 (m, 1H), 2.12 (app. d, *J* = 11.2 Hz, 1H), 1.91-1.87 (m, 1H), 1.84-1.80 (m, 1H), 1.77-1.65 (m, 2H), 1.64-1.59 (m, 2H), 1.47-1.38 (m, 2H), 1.32 (s, 3H), 1.05 (s, 3H), 0.79 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 213.6, 110.1, 64.7, 64.6, 61.1, 41.2, 39.8, 39.0, 37.8, 29.5, 23.8, 23.3, 22.5, 18.9; IR (thin film) 2962, 2874, 1708, 1459, 1370, 1259, 1222, 1058, 868 cm^{-1}; HRMS (CI-TOF) *m/z*: $(M+H)^+$ calcd for $[C_{12}H_{25}O_3]^+$ 241.1804; found 241.1798.

Preparation of *rac*-Alkene 37: A suspension of $EtPPh_3Br$ (1.53 g, 4.13 mmol, 8.25 equiv) and KO*t*-Bu (421 mg, 3.75 mmol, 7.5 equiv) in THF (6.5 mL) was stirred for 30 min at rt. The reaction was then cooled to 0 °C and a solution of ketone **44** (121 mg, 0.5 mmol, 1 eq.) in THF (5 mL) was added dropwise. The reaction was allowed to warm to rt overnight and was then heated to 60 °C for 5 h. The reaction was quenched with sat. aqueous NH_4Cl (20 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The crude product was dissolved in acetone (3 mL) followed by the addition of Merrifield resin (253 mg, 4.38 Cl/g) and NaI (150 mg, 1 mmol, 2 equiv). The suspension was stirred at rt overnight, after which time the mixture was filtered over Celite® and the solids were washed with THF (15 mL), CH_2Cl_2 (15 mL), H_2O (15 mL), acetone (15 mL), MeOH (15 mL). This washing cycle was repeated three times. The biphasic mixture was concentrated under reduced pressure, followed by the addition of Et_2O (50 mL). The organic phase was washed with water (10 mL) then brine (10 mL) and dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 30:1 Hex/Et_2O) to afford alkene **37** as a colorless oil (116 mg, 0.46 mmol, 92%). R_f = 0.46 (10:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$) δ 5.07 (q, *J* = 6.7 Hz, 1H), 3.95-3.90 (m, 4H), 2.25 (dt, *J* = 14.1, 3.5 Hz, 1H), 1.78-1.74 (m, 1H), 1.60 (d, *J* = 6.6 Hz, 3H),1.55-1.50 (m, 5H), 1.45-1.39 (m, 2H), 1.35-1.34 (m, 1H), 1.32 (s, 3H), 1.20-1.18 (m, 1H), 0.88 (s, 3H), 0.86 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 139.2, 117.7, 110.6, 64.7, 64.7, 55.9, 37.9, 35.8, 34.9, 28.3, 27.9, 24.0, 23.9, 23.0, 21.1, 12.8; IR (thin film) 2953, 2926, 2864, 1449, 1376, 1238, 1220, 1063, 864, 825 cm^{-1}; HRMS (CI-TOF) *m/z*: $(M+H)^+$ calcd for $[C_{16}H_{29}O_2]^+$ 253.2168; found 253.2161.

Preparation of Alcohol 38: In a 100 mL round bottom flask, ketal **37** (594 mg, 2.03 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (83 mL, 0.025 M). *Para*-toluenesulfonic acid monohydrate (77 mg, 0.41 mmol, 20 mol%) was added and the reaction was maintained at rt for 3 h. After TLC showed complete consumption of the starting material, water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 15:1→10:1 Hex/EtOAc) to yield alcohol **38** as a yellowish oil (358 mg, 1.73 mmol, 85%). R_f = 0.35 (hexanes/EtOAc, 10:1); ^1H NMR (600 MHz, $CDCl_3$) δ 5.44 (br s, 1H), 2.09-2.04 (m, 3H), 1.77-1.70 (m, 2H), 1.63 (s, 1H), 1.53 (td, *J* = 13.4, 4.3 Hz, 1H), 1.47 (br d, *J* = 12.9 Hz, 1H), 1.43-1.38 (m, 1H), 1.28-1.22 (m, 1H), 1.21 (s, 3H), 1.18-1.15 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 3H), 0.88 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 141.9, 119.0, 72.5, 49.2, 47.9, 40.7, 31.9, 31.3, 27.6, 27.5, 26.7, 26.5, 23.1, 10.7; IR (thin film) 2925, 2866, 1454, 1380, 1363, 1271, 1246, 999, 948, 909, 724 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ calcd for $[C_{14}H_{25}O]^+$ 209.1905; found 209.1907; Optical Rotation $[\alpha]^{25}_D$ −78.6, $[\alpha]^{25}_{577}$ −83.2, $[\alpha]^{25.0}_{546}$ −95.0, $[\alpha]^{25}_{435}$ −163.8, $[\alpha]^{25}_{405}$ −200.1 (*c* = 1.24, $CHCl_3$).

Preparation of Oxalate 45: Tertiary alcohol **38** (81 mg, 0.38 mmol) and DMAP (4.6 mg, 0.038 mmol, 10 mol%) were dissolved in CH_2Cl_2 (4 mL, 0.1 M) in a scintillation vial under argon. After the addition of Et_3N (64 µL, 0.46 mmol, 1.2 equiv) and methyl chlorooxacetate (42 µL, 0.46 mmol, 1.2 equiv), the vial was sealed with a Teflon-coated cap and was placed in an aluminum block preheated to 40 °C. The homogeneous mixture was maintained at this temperature for 2 h. After this time, the vial was removed from the block and allowed to cool to rt. Additional portions of Et_3N (64 µL, 0.46 mmol, 1.2 equiv) and methyl chlorooxacetate (42 µL, 0.46 mmol, 1.2 equiv) were added, and the vial was capped, placed in the aluminum heating block at 40 °C, and maintained at this temperature for a further 3 h. The vial was then allowed to cool to rt and the reaction mixture was quenched with saturated aqueous NH_4Cl solution (2 mL). The biphasic mixture was transferred to a separatory funnel and diluted with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered through cotton, and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, 20:1 Hex/EtOAc) to provide methyl oxalate ester **45** (105 mg, 0.35 mmol, 92%) as a colorless oil. R_f = 0.45 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.45 (s, 1H), 3.83 (s, 3H), 2.85 (br d, *J* = 15.0 Hz, 1H), 2.07-2.00 (m, 2H), 2.00-1.96 (m, 1H), 1.69-1.64 (m, 1H), 1.63-1.55 (m, 1H), 1.60 (s, 3H), 1.50 (td, *J* = 14.4, 3.7 Hz, 1H), 1.38-1.31 (m, 1H), 1.20-1.14 (m, 2H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H), 0.82 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.2, 157.2, 138.5, 119.2, 88.7, 53.2, 48.4, 48.0, 35.2, 33.7, 31.5, 28.2, 25.8, 24.7, 24.3, 23.0, 10.9; IR (thin film) 2951, 2919, 1766, 1739, 1452, 1331, 1208, 1164, 1100, 873 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{17}H_{26}O_4Na]^+$ 317.1729; found 317.1736; Optical Rotation $[\alpha]^{25}_D$ −12.9, $[\alpha]^{25}_{577}$ −13.3, $[\alpha]^{25}_{546}$ −14.9, $[\alpha]^{25}_{435}$ −20.3, $[\alpha]^{25}_{405}$ −29.3 (c = 1.15, $CHCl_3$); Analysis by HPLC confirmed that the compound was obtained in 98% *ee*: AD

column, 1% IPA/*n*-hexane, 0.5 mL/min. t_R: 9.7 min (major), 10.9 min (minor).

Preparation of Dioxolane 51: A solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (6.00 g, 30.9 mmol, 3 equiv)[44] and 1,2-dibromoethane (0.6 mL) in THF (20 mL) was added to a suspension of Mg turnings (2.25 g, 92.8 mmol, 9 equiv) in THF (45 mL, 0.5 M overall). The mixture was briefly warmed with a heat gun for 10 seconds, and was then stirred for 2 h at rt. The resulting black suspension of **50** was transferred via cannula to a round-bottom flask containing a stir bar under argon. The mixture was cooled to −78 °C and a homogeneous solution of CuCN (2.77 g, 30.9 mmol, 3 equiv) and LiCl (2.62 g, 61.85 mmol, 6 equiv) in THF (31 mL) was added via syringe. After stirring vigorously for 15 min at −78 °C, a solution of phosphate **49** (4.00 g, 10.3 mmol) in THF (20 mL) was added. The suspension was stirred for 30 min at −78 °C, then was allowed to warm to 0 °C while stirring for an additional 30 min. Saturated aqueous NH_4Cl solution (150 mL) was added and the biphasic mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3 x 200 mL) and the combined organic layers were washed with brine (2 x 300 mL), dried over $MgSO_4$, filtered and concentrated. The residue obtained was purified by flash column chromatography (SiO_2, 15:1 Hex/EtOAc) to provide vinyl iodide **51** (3.49 g, 9.97 mmol, 97%) as a colorless oil. Spectral data acquired for the compound matched those previously reported.[28b] Optical Rotation $[\alpha]^{27}_D$ −58.5, $[\alpha]^{27}_{577}$ −61.8, $[\alpha]^{27}_{546}$ −70.7, $[\alpha]^{27}_{435}$ −123.2, $[\alpha]^{27}_{405}$ −152.6 (c = 0.58, CH_2Cl_2). Analysis by HPLC confirmed that the compound was present in 99% *ee*: AD column, 215 nm, 0.5% IPA/n-hexane, 0.15 mL/min. t_R: 36.528 min (major), 39.080 min (minor).

Preparation of (*S*)-Ketone 44: A 100 mL round-bottom flask was charged with vinyl iodide **51** (1.50 g, 4.28 mmol) and Et_2O (14 mL, 0.3 M) under Ar. The reaction mixture was cooled to −78 °C and a solution of *t*-BuLi (6.0 mL, 9.00 mmol, 2.1 equiv, 1.5 M in pentane) was added slowly. The homogeneous solution was maintained at this temperature for 45 min, after which $B(OMe)_3$ (1.2 mL, 10.71 mmol, 2.5 equiv) was added in one portion. The reaction mixture was then allowed to warm to rt and was maintained at this temperature for 3 h. After this time, THF (15 mL), $NaBO_3$•4 H_2O (6.59 g, 42.85 mmol, 10 equiv) and H_2O (15 mL) were added sequentially. The heterogeneous mixture was stirred at rt for 24 h, after which it was diluted with H_2O (40 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL) and dried over $MgSO_4$. The suspension was filtered through cotton to remove the drying agent and the filtrate was concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, 9:1→6:1 Hex/EtOAc) to provide (*S*)-ketone **44** (830 mg, 3.45 mmol, 80%) as a colorless oil: R_f = 0.36 (3:1 Hex/EtOAc, visualized with $KMnO_4$). Spectral data for (*S*)-**44** matched that of the racemic material reported above. Optical Rotation $[\alpha]^{25}_D$ +11.3, $[\alpha]^{25}_{577}$ +12.6, $[\alpha]^{25}_{546}$ +14.9, $[\alpha]^{25}_{435}$ +47.5, $[\alpha]^{25}_{405}$ +75.6 (c = 1.00, $CHCl_3$).

Wittig olefination of enantioenriched (*S*)-**44** under the conditions reported for the formation of **rac-37** followed subsequent conversion to oxalate **45**, provides **45** in significantly diminished enantiopurity as determined by chiral HPLC analysis.

Preparation of Diene 52: A solution of vinylmagnesium bromide (4.6 mL, 2.9 mmol, 2equiv, 0.62 M in THF) was added to a solution of $ZnCl_2$ (8.6 mL, 4.3 mmol, 3 equiv, 0.5 M in THF) at −78 °C. The suspension was then allowed to warm to rt while stirring for 1.5 h. After this time, a solution of iodide **51** (500 mg, 1.43 mmol) and $Pd(PPh_3)_4$ (165 mg, 0.143 mmol, 10 mol%) in THF (3.3 mL) and DMF (3.3 mL) was added slowly. The reaction mixture was stirred at rt for 36 h, and saturated aqueous NH_4Cl solution (10 mL) and Et_2O (50 mL) were added. The organic layer was separated, washed with brine (2 x 40 mL), dried over $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, 30:1→20:1 Hex/EtOAc) to provide diene **52** (333 mg, 1.33 mmol, 93%) as a colorless oil: R_f = 0.49 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 17.8, 11.0 Hz, 1H), 5.61 (t, *J* = 3.8 Hz, 1H), 5.05 (d, *J* = 17.8 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 3.95–3.86 (m, 4H), 2.15–2.10 (m, 2H), 1.90–1.86 (m, 1H), 1.79–1.65 (m, 2H), 1.64–1.52 (m, 2H), 1.41–1.32 (m, 1H), 1.28 (s, 3H), 1.18–1.12 (m, 1H), 0.99 (s, 3H), 0.84 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 140.05, 140.04, 127.3, 109.9, 109.1, 63.94, 63.92, 42.3, 32.0, 30.0, 28.4, 26.7, 26.3, 23.5, 23.0; IR (thin film) 3088, 2953, 2872, 1375, 1060 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ calcd for $[C_{16}H_{27}O_2]^+$ 251.2011; found 251.1920; Optical Rotation $[\alpha]^{25}_D$ −72.0, $[\alpha]^{25}_{577}$ −75.4, $[\alpha]^{25}_{546}$ −85.5, $[\alpha]^{25}_{435}$ −146.5, $[\alpha]^{25}_{405}$ −177.8 (c = 1.14, $CHCl_3$).

Preparation of (*S*)-Alkene 37: In a glove box under a N_2 atmosphere, a stainless-steel Parr bomb containing a stir bar was charged with (η^6-naphthalene)chromium tricarbonyl (106 mg, 0.40 mmol, 20 mol%), diene **52** (500 mg, 2.00 mmol) and acetone (20 mL, degassed in a Schlenk tube by 3 freeze-pump-thaw cycles prior to bringing into the glove box, 0.1 M). The Parr bomb was sealed, removed from the glove box, and quickly purged with H_2 gas three times before being pressurized to 75 atm (~1100 psi) H_2. The apparatus was then placed in a sand bath preheated to 55 °C and was maintained at this temperature while stirring for 18 h. The H_2 pressure was released and the reaction mixture was transferred to a round bottom flask and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 50:1→20:1 Hex/EtOAc) provided exocyclic alkene (*S*)-**37** (496 mg, 1.97 mmol, 98%) as a colorless oil. Spectral data acquired for the compound matched those reported above. Optical Rotation $[\alpha]^{25}_D$ +24.7, $[\alpha]^{25}_{577}$ +24.9, $[\alpha]^{25}_{546}$ +27.7, $[\alpha]^{25}_{435}$ +45.3, $[\alpha]^{25}_{405}$ +56.1 (c = 1.04, $CHCl_3$).

Preparation of Cesium Oxalate 53: A 1-dram vial containing a stir bar was charged with methyl oxalate ester **45** (101 mg, 0.340 mmol) and THF (340 µL, 1.0 M). To this colorless solution was added dropwise aqueous 1 N CsOH (340 µL, 0.340 mmol, 1equiv) with vigorous stirring. The progress of the reaction was monitored by TLC during addition of the aqueous CsOH solution. After complete addition of the aqueous CsOH solution, the reaction mixture was transferred to a round-bottom flask and was concentrated under reduced pressure at 50 °C to yield cesium oxalate salt **53** (133 mg, 0.322 mmol, 95%) as a colorless powder. The oxalate was dried under vacuum for 18 h before use. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.27 (br s, 1H), 2.74–2.69 (m, 1H), 1.95–1.86 (m, 2H), 1.85–1.78 (m, 1H), 1.56–1.47 (m, 2H), 1.41 (s, 3H), 1.34 (dt, *J* = 13.8, 3.6 Hz, 1H), 1.29–1.23 (m, 1H), 1.22–1.14 (m, 1H), 1.31–1.08 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 3H), 0.75 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 168.0, 163.7, 139.5, 117.3, 81.6, 47.7, 47.3, 34.8, 34.2, 31.1, 28.5, 24.84, 24.76, 23.4, 22.4, 10.8; HRMS (ESI-TOF) *m/z*: (M-Cs)$^-$calcd for $[C_{16}H_{23}O_4]^-$ 279.1596; found279.1588.

Preparation of Tricyclic Butyrolactone 54: To a 1-dram vial was added sequentially (*S*)-5-methoxyfuranone (**13**) (13 mg, 0.11 mmol, 1equiv), cesium oxalate salt **53** (50 mg, 0.12 mmol, 1.1 equiv), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (1 mg, 0.001 mmol, 1 mol%), DME (550 µL, 0.2 M) and H_2O (20 µL, 1.1 mmol, 10 equiv). The yellow reaction mixture was sparged with argon for 5 min, after which it was placed on a stir plate equipped with 2 x 34 W blue (465 nm peak intensity, unfiltered) LED lamps approximately 4 cm from the lamps and stirred vigorously. The vial was irradiated for 36 h and air was blown on the vial to prevent an increase in temperature due to the LED lamps. After 36 h, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and flushed through a pipette plug of Na_2SO_4. The yellow solution was then concentrated under reduced pressure to obtain a crude residue that was purified by flash column chromatography (SiO_2, 30:1 Hex/EtOAc), providing lactone **54** (16 mg, 0.066 mmol, 54% based on the cesium oxalate) as a colorless oil: R_f = 0.44 (9:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13–2.02 (m, 1H), 1.95–1.87 (m, 3H), 1.71 (q, *J* = 7.1 Hz, 1H), 1.63–1.57 (m, 2H), 1.52–1.43 (m, 2H), 1.34 (dd, *J* = 12.2, 5.0 Hz, 1H), 1.28 (s, 3H), 1.18–1.08 (m, 2H), 0.91–0.88 (m, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 180.2, 83.6, 53.8, 50.5, 50.4, 41.8, 36.5, 34.1, 32.2, 29.3, 21.9, 21.6, 20.3, 18.7, 10.4; IR (thin film) 2932, 1754, 1136 cm^{-1}; HRMS (CI-TOF) *m/z*: $(M+NH_4)^+$ calcd for $[C_{15}H_{28}NO_2]^+$ 254.2120; found 254.2111; Optical Rotation $[\alpha]^{25}_D$ −3.4, $[\alpha]^{25}_{577}$ −3.2, $[\alpha]^{25}_{546}$ −3.9, $[\alpha]^{25}_{435}$ −4.8, $[\alpha]^{25}_{405}$ −3.3 (c = 1.29, $CHCl_3$).

Preparation of dioxolane 59: A solution of 2-(2-bromoethyl)-1,3-dioxolane (6.96 g, 38.7 mmol, 3equiv) and 1,2-dibromoethane (0.7 mL, 8 mmol, 0.65equiv) in THF (25 mL) was added to a suspension of Mg turnings (2.82 g, 116 mmol, 9equiv) in THF (55 mL). The mixture was briefly warmed with the heat gun for 10 sec, and was then stirred for 2 h at rt. The resulting black suspension of Grignard reagent **58** was then transferred via cannula to a round-bottom flask containing a stir bar under argon. The mixture was cooled to −78 °C and a homogenous solution of CuCN (3.46 g, 38.7 mmol, 3equiv) and LiCl (3.28 g, 77.3 mmol, 6 eq) in THF (40 mL) was added via syringe. After stirring vigorously for 15 min at −78 °C, a solution of phosphate **49** (5.00 g, 12.8 mmol) in THF (25 mL) was added. The resulting suspension was stirred for 30 min at −78 °C and then was allowed to warm to 0 °C while stirring

for an additional 30 min. Saturated aqueous NH_4Cl solution (150 mL) was added and the biphasic mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3 x 200 mL) and the combined organic layers were washed with brine (2 x 300 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (SiO_2, 20:1 Hex/EtOAc) to afford vinyl iodide **59** (4.03 g, 11.9 mmol, 93%) as a colorless oil. Spectral data acquired for the compound matched those previously reported for the enantiomer.[28b] $[\alpha]^{25}_D$ –59.2, $[\alpha]^{25}_{577}$ –62.6, $[\alpha]^{25}_{546}$ –70.5, $[\alpha]^{25}_{435}$ –126.5, $[\alpha]^{25}_{405}$ –156 (*c* = 1.02, $CHCl_3$). Analysis of a comparable sample ($[\alpha]^{27}_D$ –58.5) by HPLC confirmed that the enantiomeric purity of this sample was 99% ee: AD column, 215 nm, 0.5% IPA/n-hexane, 0.15 mL/min. t_R: 36.5 min (major), 39.0 min (minor).

Preparation of diene 60: A solution of vinyl magnesium bromide (22.5 mL, 22.5 mmol, 2 equiv, 1 M in THF) was added to a solution of $ZnCl_2$ (48 mL, 34 mmol, 3 equiv, 0.7 M in THF) and THF (19 mL) at –78 °C. The suspension was then allowed to warm over 1.5 h to rt while stirring. A solution of iodide **59** (3.78 g, 11.2 mmol) and $Pd(PPh_3)_4$ (1.30 g, 1.12 mmol, 10 mol%) in THF (25 mL) and DMF (25 mL) was added slowly. The reaction mixture was allowed to stir at rt for 36 h, after which saturated aqueous NH_4Cl solution (100 mL) was added. The mixture was extracted with Et_2O (3 x 150 mL), and the organic layer was separated, washed with brine (2 x 200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 30:1 → 15:1 Hex/EtOAc) to provide diene **60** (2.54 g, 10.7 mmol, 95%) as a colorless oil: R_f = 0.61 (9:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.64-5.61 (m, 1H), 5.06 (d, *J* = 17.7 Hz, 1H), 4.88 (d, *J* = 11.1 Hz, 1H), 4.75 (t, *J* = 4.8 Hz, 1H), 3.98-3.91 (m, 2H), 3.84-3.79 (m, 2H), 2.15-2.10 (m, 2H), 1.96-1.92 (m, 1H), 1.76-1.69 (m, 2H), 1.66-1.57 (m, 2H), 1.42-1.34 (m, 1H), 1.18-1.12 (m, 1H), 1.00 (s, 3H), 0.85 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 140.5, 140.2, 127.9, 109.8, 105.1, 64.95, 64.92, 43.0, 34.7, 32.5, 20.5, 28.8, 27.0, 26.8, 23.7; IR (thin film) 2954, 2870, 1647, 1406, 1139, 1034, 893 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+NH_4)^+$ calcd for $[C_{15}H_{28}NO_2]^+$ 254.2120; found 254.2129; Optical Rotation $[\alpha]^{22}_D$ –87.4, $[\alpha]^{22}_{577}$ –93.7, $[\alpha]^{22}_{546}$ –105, $[\alpha]^{22}_{435}$ –183, $[\alpha]^{22}_{405}$ –219 (*c* = 1.02, $CHCl_3$).

Preparation of ethylidene 61: In a glove box under a N_2 atmosphere, a stainless steel Parr bomb containing a stir bar was charged with (η^6-naphthalene)chromium tricarbonyl (560 mg, 2.1 mmol, 13 mol %), diene **60** (3.94 g, 16.7 mmol) and acetone (170 mL, 0.1 M, degassed in a Schlenk tube by three freeze-pump-thaw cycles prior to bringing into the glove box). The Parr bomb was sealed, removed from the glove box, and quickly purged with H_2 gas three times before being pressurized to 75 atm (~1100 psi) H_2. The apparatus was then placed in a sand bath preheated to 55 °C and was maintained at this temperature while stirring for 60 h. The H_2 pressure was released and the reaction mixture was transferred to a round-bottom flask and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 50:1 Hex/EtOAc) to afford (*E*)-ethylidene acetal **61** (3.97 g, 16.6 mmol, >95%) as a colorless oil: R_f = 0.67 (9:1 Hex/EtOAc).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.08 (q, *J* = 6.4 Hz, 1H), 4.82 (t, *J* = 4.4 Hz, 1H), 3.98-3.95 (m, 2H), 3.87-3.82 (m, 2H), 2.28-2.25 (m, 1H), 1.76-1.71 (m, 1H), 1.59 (dd, *J* = 6.7, 1.0 Hz, 3H), 1.56-1.34 (m, 8H), 1.19-1.14 (m, 1H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.9, 118.0, 105.2, 65.0, 64.9, 55.7, 35.6, 34.8, 32.8, 28.2, 28.0, 23.8, 22.9, 21.2, 12.8; IR (thin film) 2951, 2926, 2460, 1408, 1382, 1364, 1140, 1037, 955, 891, 907, 824 cm^{-1}; HRMS (CI-TOF) *m/z*: (M^+) calcd for $[C_{15}H_{26}O_2]^+$ 238.1933; found 238.1942; Optical Rotation $[\alpha]^{23}_D$ +32.8, $[\alpha]^{23}_{577}$ +33.3, $[\alpha]^{23}_{546}$ +38.2, $[\alpha]^{23}_{435}$ +60.8, $[\alpha]^{23}_{405}$ +74.5 (*c* = 0.96, $CHCl_3$).

Preparation of alcohol 62: A round-bottom flask was charged with ethylidene acetal **61** (3.97 g, 16.6 mmol), acetone (150 mL, 0.1 M), and H_2O (57 mL, 220 equiv). To the mixture was added pyridine *p*-toluenesulfonate (PPTS, 1.26 g, 5.01 mmol, 30 mol %), and the flask was placed in a sand bath pre-heated to 70 °C. The reaction was stirred at this temperature for 20 h, after which it was allowed to cool to rt. The mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 9:1 Hex/EtOAc) to afford alcohol **62** (2.23 g, 11.5 mmol, 69%) as a colorless oil which solidified upon storage at –20 °C: R_f = 0.40 (9:1 Hex/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.38 (br s, 1H), 3.82-3.72 (m, 1H), 2.28-2.24 (m, 1H), 2.05-2.02 (m, 2H), 1.92 (dq, *J* = 13.7, 3.2 Hz, 1H), 1.69-1.65 (m, 1H), 1.60 (tdd, *J* = 2.4, 4.5, 13.6 Hz, 1H), 1.53-1.50 (m, 1H), 1.41-1.34 (m, 2H), 1.32 (qd, *J* = 4.0, 12.9 Hz, 1H), 1.17 (dt, *J* = 4.7, 13.0 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 140.0, 119.6, 72.4, 49.1, 43.7, 33.9, 32.7, 31.4, 27.8, 27.0, 24.4, 23.0, 14.3; IR (thin film) 2911, 2867, 2360, 2340, 1452, 1382, 1363, 1186, 1093, 969, 940, 714 cm^{-1}; HRMS (CI-TOF) *m/z*: (M^+) calcd for $[C_{13}H_{22}O]^+$ 194.1671; found 194.1672; Optical Rotation $[\alpha]^{22.5}_D$ –84.8, $[\alpha]^{22}_{577}$ –89.2, $[\alpha]^{22}_{546}$ –101, $[\alpha]^{22}_{435}$ –174, $[\alpha]^{22}_{405}$ –208 (*c* = 1.1, $CHCl_3$).

Preparation of ketone 63: A round-bottom flask was charged with alcohol **62** (808 mg, 4.16 mmol) and CH_2Cl_2 (40 mL, 0.1 M) under argon. The solution was cooled to 0 °C and Dess-Martin periodinane (DMP, 2.11 g, 4.99 mmol, 1.2equiv) was added in one portion. The reaction mixture was then allowed to warm to rt and was maintained at this temperature for 2 h. TLC analysis indicated starting material was still present, so an additional portion of DMP (0.35 g, 0.82 mmol, 0.2equiv) was added. The reaction was stirred for an additional 2 h, after which TLC analysis indicated that the starting material was consumed. The reaction mixture was then diluted with Et_2O (40 mL) and the solution was flushed through a pad of Celite®. The pad of Celite® was washed with Et_2O (300 mL), and the filtrate was concentrated under reduced pressure. The oily solid residue was suspended in 9:1 Hex/EtOAc (20 mL) and flushed through a small plug of silica gel. The plug of silica gel was eluted with 9:1 Hex/EtOAc (300 mL), and the filtrate was concentrated to afford ketone **63** (777 mg, 4.04 mmol, >95%) as a colorless oil. β,γ-Unsaturated ketone **63** was prone to double bond isomerization during storage and was used immediately in the next step: R_f = 0.48 (9:1 Hex/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.41 (br s, 1H), 3.04-3.00 (m, 1H), 2.48 (ddd, *J* = 3.5, 5.1, 14.5 Hz, 1H), 2.41 (dddd, *J* = 1.0, 6.2, 12.3, 14.6 Hz, 1H), 2.11-2.04 (m, 2H), 2.04-1.98 (m, 2H), 1.48-1.42 (m, 1H), 1.41-1.36 (m, 1H), 1.23 (dt, *J* = 5.1, 13.1 Hz, 1H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.00 (s, 3H), 0.92 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 210.9, 139.0, 118.5, 52.2, 48.0, 41.1, 32.9, 31.8, 28.1, 27.7, 26.5, 23.1, 10.5; IR (thin film) 2953, 2869, 1717, 1673, 1453, 1365, 1337, 1174, 953, 849 cm^{-1}; HRMS (EI-TOF) *m/z*: (M^+) calcd for $[C_{13}H_{20}O]^+$ 192.1514; found 192.1519. Optical Rotation $[\alpha]^{22}_D$ –139, $[\alpha]^{22}_{577}$ –148, $[\alpha]^{22}_{546}$ –171, $[\alpha]^{22}_{435}$ –333, $[\alpha]^{22}_{405}$ –72.8 (*c* = 1.05, $CHCl_3$).

Preparation alcohol 64: A round-bottom flask was charged with 2,6-di-*tert*-butyl-4-methylphenol (5.34 g, 24.2 mmol, 6 equiv) and toluene (40 mL) under argon. A solution of $AlMe_3$ (6.1 mL, 12 mmol, 3equiv, 2 M in toluene) was added slowly via syringe at rt and vigorous gas evolution was observed. The homogenous light-yellow solution was maintained at rt for 1 h, after which it was cooled to –78 °C. Ketone **63** (777 mg, 4.04 mmol) was added slowly as a solution in toluene (16 mL) and the resulting solution was maintained at –78 °C for 10 min. A solution of MeMgBr (4.0 mL, 12 mmol, 3equiv, 3.0 M in Et_2O) was added slowly, and the solution was maintained at –78 °C for 1.5 h. The reaction mixture was then allowed to slowly warm to –20 °C overnight (16 h). After this time, the solution was then allowed to warm to 0 °C over 20 min. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (40 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 50 mL), and the combined organic layers were washed with brine (2 x 40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 9:1 Hex/EtOAc) to afford alcohol **64** (532 mg, 2.55 mmol, 63%) as a colorless solid: R_f = 0.30 (9:1 Hex/EtOAc) and recovered ketone **63** (64.3 mg, 0.33 mmol, 8%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (br s, 1H), 2.07-1.98 (m, 3H), 1.84 (dt, *J* = 3,7, 12.8 Hz, 1H), 1.76 (dq, *J* = 4.4, 13.3 Hz, 1H), 1.61-1.53 (m, 2H), 1.45-1.35 (br s, 1H), 1.35-1.29 (m, 1H), 1.20-1.15 (m, 1H), 1.11 (qd, *J* = 4.0, 13.1 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.96 (s, 3H), 0.91 (s, 3H), 0.83 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 140.9, 117.8, 74.5, 48.9, 48.5, 42.8, 34.0, 31.4, 28.4, 26.0, 23.0, 20.2, 10.6; IR (thin film) 3307, 2947, 2922, 2845, 1454, 1374, 1126, 1001, 948 cm^{-1}; HRMS Several attempts to acquire HRMS data for alcohol **64** using ESI-TOF and CI-TOF ionization techniques were unsuccessful; Optical Rotation $[\alpha]^{22}_D$ –88.5, $[\alpha]^{22}_{577}$ –91.6, $[\alpha]^{22}_{546}$ –109, $[\alpha]^{22}_{435}$ –181, $[\alpha]^{22}_{405}$ –212 (*c* = 0.04, $CHCl_3$).

Preparation of Methyl Oxalate S2: A round-bottom flask was charged with alcohol **64** (558 mg, 2.67 mmol), DMAP (33 mg, 0.27 mmol, 10 mol %) and CH_2Cl_2 (14 mL, 0.2 M) under argon. After sequential addition of Et_3N (0.75 mL, 5.4 mmol, 2 equiv) and methyl chlorooxacetate (0.49 mL, 5.3 mmol, 2equiv), the reaction was maintained at rt for 5 h, after which time TLC analysis indicated

complete conversion. The reaction mixture was diluted with saturated aqueous NH_4Cl solution (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers were washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 30:1 Hex/EtOAc) to afford methyl oxalate ester **S2** (773 mg, 2.62 mmol, >95%) as a colorless oil: R_f = 0.57 (9:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (s, 1H), 3.86 (s, 3H), 2.65-2.55 (m, 2H), 2.03-1.98 (m, 2H), 1.89 (td, *J* = 13.2, 4.0 Hz, 1H), 1.83-1.77 (m, 1H), 1.64-1.57 (m, 1H), 1.33 (s, 3H), 1.32-1.28 (m, 1H), 1.23-1.16 (m, 1H), 1.16-1.07 (m, 1H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 3H), 0.82 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.2, 156.8, 139.3, 119.7, 91.2, 53.4, 48.2, 46.1, 36.7, 34.0, 31.4, 28.4, 25.7, 25.4, 23.0, 17.3, 10.9; IR (thin film) 2951, 2919, 1772, 1741, 1200, 1168 cm^{-1}; HRMS (ESI-TOF) *m/z*: (M+Na)$^+$ calcd for $[C_{17}H_{26}O_4Na]^+$ 317.1729; found 317.1732; Optical Rotation $[\alpha]^{22}_D$ −103, $[\alpha]^{22}_{577}$ −101, $[\alpha]^{22}_{546}$ −108, $[\alpha]^{22}_{435}$ −187, $[\alpha]^{22}_{405}$ −222 (*c* = 0.22, $CHCl_3$).

Preparation of Cesium Oxalate 65: A round-bottom flask was charged with methyl oxalate ester **S2** (379 mg, 1.29 mmol) and THF (2.6 mL). A solution of CsOH (1.29 mL, 1.29 mmol, 1 M in H_2O) was added slowly. The reaction was then stirred at rt for 1 h, after which TLC analysis indicated that starting material had been consumed. The reaction was then carefully concentrated under reduced pressure at 50 °C. The residue was then dried under vacuum overnight to produce cesium oxalate salt **65** (525 mg, 1.27 mmol, 99%) as a colorless powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.36 (br s, 1 H), 2.56-2.52 (m, 1H), 2.41-2.35 (m, 1H), 2.00-1.93 (m, 1H), 1.84 (td, *J* = 3.5, 13.6 Hz, 1H), 1.75-1.69 (m, 1H), 1.61-1.55 (m, 1H), 1.33-1.26 (m, 1H), 1.18-1.14 (m, 1H), 1.12 (s, 3H), 1.05 (qd, *J* = 3.8, 13.7 Hz, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 3H), 0.80 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 167.5, 163.4, 139.8, 118.0, 83.7, 47.6, 45.3, 36.4, 33.6, 30.9, 28.1, 25.3, 24.8, 22.4, 17.5, 10.5; IR (thin film) 2943, 2907, 2866, 2843, 1705, 1689, 1644, 1605, 1381, 1221, 1089, 898, 780, 764, 749 cm^{-1}; HRMS (ESI-TOF) *m/z*: (M-Cs)$^-$ calcd for $C_{16}H_{23}O_4$ 279.1596; found 279.1602.

Preparation of Lactone 67: Cesium oxalate **65** (414 mg, 1.00 mmol), chlorobutenolide **66** (274 mg, 1.00 mmol, 1 equiv)[6], $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (22.8 mg, 0.02 mmol, 2 mol %), H_2O (0.18 mL, 10 mmol, 10), and THF (2 mL, 0.5 M) were divided equally into four 2-dram vials. The vials were then sparged with argon for 15 min. The vials were then placed on a stir plate equipped with two 34 W blue (465 nm peak intensity, unfiltered) LEDs and a cardboard box (to block light pollution from entering the lab) with double-sided tape inside to hold the vials. The vials were placed in a square pattern approximately 4 cm from the lamps and stirred vigorously. The samples were irradiated by the lamps for 20 h inside the closed box, allowing the temperature of the reaction to rise to 60 °C and the air inside the box to 40–45°C because of the heat given off from the LEDS. Then *n*-Bu_3N (0.30 mL, 1.3 mmol, 5 equiv) was added to each vial and irradiation was continued for another 6 h. The reactions were then poured into a separatory funnel and diluted with H_2O (15 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were then dried over $MgSO_4$, filtered, and concentrated to an orange oil. The residue was then purified by flash column chromatography (SiO_2, 30:1→20:1 Hex/EtOAc) to afford lactone **67** (320 mg, 74%) as a colorless solid. R_f = 0.45 (9:1 Hex/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.68 (d, *J* = 1.3 Hz, 1H), 5.33 (dd, *J* = 2.2, 3.5 Hz, 1H), 3.52 (dt, *J* = 4.1, 10.5 Hz, 1H), 2.72 (dd, *J* = 9.8, 18.3 Hz, 1H), 2.49 (ddd, *J* = 1.3, 3.3, 10.1 Hz, 1H), 2.36 (dd, *J* = 3.5, 18.2 Hz, 1H), 2.18-2.12 (m, 1H), 2.11-2.05 (m, 2H), 2.05-2.00 (m, 2H), 1.73-1.60 (m, 3H), 1.51-1.45 (m, 1H), 1.42 (dt, *J* = 3.1, 12.6 Hz, 1H), 1.40-1.33 (m, 2H), 1.28 (dt, *J* = 3.8, 8.9 Hz, 1H), 1.24-1.14 (m, 3H), 1.05-0.97 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.92-0.81 (m, 2H), 0.91 (s, 3H), 0.88 (d, *J* = 7.1 Hz, 3H), 0.84 (s, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.66 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 177.1, 140.6, 118.3, 101.0, 76.7, 49.1, 48.8, 47.9, 43.3, 39.7, 39.2, 34.3, 33.3, 32.4, 31.4, 31.3, 29.7, 28.0, 26.3, 25.4, 24.5, 23.1, 22.9, 22.3, 20.9, 17.3, 15.6, 11.1; IR (thin film) 2952, 2920, 2867, 1788, 1455, 1384, 1168, 1091, 1015, 970, 945 cm^{-1}; HRMS (ESI-TOF) *m/z*: (M+Na)$^+$ calcd for $[C_{28}H_{46}O_3Na]^+$ 453.3345; found 453.3342; Optical Rotation $[\alpha]^{22.2}_D$ +27.4, $[\alpha]^{22.3}_{577}$ +28.3, $[\alpha]^{22}_{546}$ +29.0, $[\alpha]^{22}_{435}$ +39.9, $[\alpha]^{22}_{405}$ +46.5 (*c* = 0.75, $CHCl_3$).

Preparation of Alcohols 69: A flame dried 100 mL round-bottom flask was charged with lactone **67** (712 mg, 1.65 mmol) and toluene (17 mL, 0.1 M). The solution was cooled to −78 °C and a solution of LHMDS (2.5 mL, 2.5 mmol, 1.5 eq, 1 M in THF) was added dropwise. The reaction was maintained at −78 °C for 1 h. During the enolate formation, ethyl glyoxylate (50 wt% in toluene) was distilled over P_2O_5 under argon (10–15 min at 110 °C , over 10 min warm to 140 °C, and then warm to 200 °C); the obtained yellow distillate was used immediately. The freshly distilled ethyl glyoxylate (1.6 mL, 8.2 mmol, 5 eq) was added dropwise to the cold enolate solution. The reaction mixture was maintained at −78 °C for 2 h and then quenched by the addition of H_2O (20 mL) and allowed to warm to rt. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (40 mL) and dried over $MgSO_4$. After filtration, concentration of the filtrate gave a yellow oil, which was purified immediately by flash column chromatography (SiO_2, 20:1→9:1 Hex/EtOAc) to afford alcohols **69** (678 mg, 77%) as a colorless oil and an inseparable ~4:1 mixture of alcohol epimers. R_f = 0.3 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.67 (m, 0.2H, minor), 5.66 (d, *J* = 2.6 Hz, 0.8H, major), 5.37-5.34 (m, 0.8H, major), 5.34-5.31 (m, 0.2H, minor), 4.66 (dd, *J* = 3.7, 9.7 Hz, 0.2H, minor), 4.40-4.30 (m, 1.6H, major), 4.30-4.25 (m, 0.2H, minor), 4.24 (dd, *J* = 3.2, 4.4 Hz, 0.8H, major), 4.14-4.05 (m, 0.2H, minor), 3.52 (dt, *J* = 4.0, 10.8 Hz, 1H), 3.27 (d, *J* = 9.7 Hz, 0.2H, minor), 3.23 (d, *J* = 4.7 Hz, 0.8H, major), 3.08 (dd, *J* = 3.0, 6.0 Hz, 0.8H, major), 2.84 (app t, *J* = 3.3 Hz, 0.2H, minor), 2.64 (dd, *J* = 2.6, 6.0 Hz, 0.8H, major), 2.39 (app d, *J* = 2.8 Hz, 0.2H, minor), 2.24-2.15 (m, 1H), 2.10-2.00 (m, 4H), 1.75-1.70 (m, 1H), 1.69-1.60 (m, 3H), 1.53-1.46 (m, 2H), 1.41-1.31 (m, 3.6H), 1.34 (t, *J* = 7.1 Hz, 2.4H, major), 1.31-1.12 (m, 4.4H), 1.29 (t, *J* = 7.2 Hz, 0.6H, minor), 0.99 (d, *J* = 6.7 Hz, 3H), 0.95-0.90 (m, 6H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.85 (s, 2.4H, major), 0.83 (s, 0.6H, minor), 0.73 (s, 2.4H, major), 0.55 (s, 0.6H, minor); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (only major listed) 175.0, 172.5, 140.3, 118.6, 103.3, 100.2, 77.5, 71.2, 62.5, 51.2, 49.1, 47.9, 46.3, 43.2, 40.0, 39.5, 34.4, 33.3, 32.6, 31.5, 31.4, 28.0, 26.4, 25.0, 24.5, 23.0, 22.4, 21.0, 17.3, 15.5, 14.2, 11.3; IR (thin film) 3500, 2952, 2920, 2868, 1775, 1738, 1662, 1454, 1382, 1369, 1320, 1297, 1266, 1239, 1180, 1114, 1097, 945, 732 cm^{-1}; HRMS (ESI-TOF) *m/z*: (M+Na)$^+$ calcd for $[C_{32}H_{52}NaO_6]^+$ 555.3661; found 555.3676.

Preparation of Alkenes (*E*)-70 and (*Z*)-70: A 50 mL round-bottom flask containing a stir bar was charged with the mixture of alcohol epimers **69** (678 mg, 1.27 mmol), DMAP (19 mg, 0.15 mmol, ~10 mol %) and CH_2Cl_2 (13 mL, 0.1 M) under argon. After sequential addition of pyridine (0.42 mL, 5.2 mmol, 4 equiv) and trifluoroacetic anhydride (0.36 mL, 2.6 mmol, 2 equiv), the reaction mixture was maintained at 40 °C for 1.5 h at which time complete consumption of the starting material was obsd by TLC analysis. After this time, DBU (1.1 mL, 7.7 mmol, 6 eq) was added by syringe and the reaction mixture was stirred at rt for 16 h. The reaction mixture was then quenched by the addition of H_2O (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with 1 M HCl (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The orange residue was purified by flash column chromatography (SiO_2, 1:0→30:1→20:1 Hex/EtOAc) to provide (*E*)-**70** (375 mg, 0.73 mmol, 57%) as a colorless foam: R_f = 0.65 (4:1 hexanes/EtOAc, visualized with $KMnO_4$) and (*Z*)-**70** (206 mg, 0.40 mmol, 32%) as a colorless oil: R_f = 0.40 (4:1 hexanes/EtOAc). **(E)-70:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.84 (d, *J* = 1.7 Hz, 1H), 5.79 (s, 1H), 5.34 (bs, 1H), 4.27-4.19 (m, 2H), 3.82 (d, *J* = 1.6 Hz, 1H), 3.51 (dt, *J* = 4.2, 10.7 Hz, 1H), 2.28-2.24 (m, 1H), 2.06-2.01 (m, 3H), 1.94-1.89 (m, 1H), 1.67-1.58 (m, 4H), 1.50-1.47 (m, 1H), 1.40-1.28 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.22-1.13 (m, 4H), 1.03 (d, J = 7.0 Hz, 3H), 1.01-0.95 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.80 (s, 3H), 0.72 (d, *J* = 6.9 Hz, 3H), 0.67 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 170.6, 165.4, 143.2, 140.4, 127.0, 118.6, 100.1, 77.1, 61.1, 51.8, 49.2, 47.5, 43.7, 43.6, 39.8, 34.3, 33.7, 33.4, 31.4, 31.3, 28.0, 26.2, 25.3, 24.2, 23.2, 22.9, 22.3, 20.8, 16.0, 15.6, 14.2, 11.4; IR (thin film) 2952, 2920, 2850, 1777, 1727, 1455, 1370, 1254, 1209, 1111, 1026, 918 cm^{-1}; HRMS (ESI-TOF) *m/z*: (M+Na)$^+$ calcd for $[C_{32}H_{50}NaO_5]^+$ 537.3556; found 537.3576; Optical Rotation $[\alpha]^{21}_D$ +0.7, $[\alpha]^{21}_{577}$ +0.4, $[\alpha]^{21}_{546}$ −0.8, $[\alpha]^{21}_{435}$ −12.8, $[\alpha]^{21}_{405}$ −20.9 (*c* = 1.0, $CHCl_3$). **(Z)-70:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.28 (d, *J* = 1.6 Hz, 1H), 5.72 (s, 1H), 5.35 (bs, 1H), 4.33-4.22 (m, 2H), 3.55 (dt, *J* = 4.2, 10.7 Hz, 1H), 2.87 (d, *J* = 1.3 Hz, 1H), 2.21 (q, *J* = 6.6 Hz, 1H), 2.09-1.98 (m, 4H), 1.69-1.57 (m, 4H), 1.51-1.46 (m, 1H), 1.40-1.26 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.26-1.10 (m, 4H), 1.03-0.97 (m, 1H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 3H), 0.85 (d, *J* = 7.1 Hz, 3H), 0.82 (s, 3H), 0.81 (s, 3H), 0.76 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 167.3, 165.3, 140.3, 134.9, 129.7, 118.8, 98.6, 76.7,

61.5, 54.8, 49.1, 47.8, 43.3, 41.2, 39.7, 34.3, 33.42, 33.39, 31.41, 31.39, 28.0, 26.2, 25.4, 24.3, 23.2, 22.9, 22.3, 20.9, 16.6, 15.7, 13.9, 11.2; IR (thin film) 2954, 2922, 2867, 1775, 1733, 1667, 1455, 1367, 1325, 1241, 1180, 1087, 1029, 933 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{32}H_{50}NaO_5]^+$ 537.3556; found 537.3576; Optical Rotation $[\alpha]^{22}_D$ +27.3, $[\alpha]^{22}_{577}$ +28.4, $[\alpha]^{22}_{546}$ +30.9, $[\alpha]^{22}_{435}$ +52.4, $[\alpha]^{22.2}_{405}$ +64.2 (*c* = 1.0, $CHCl_3$).

Preparation of Tertiary Alcohol 71: A 50 mL round-bottom flask was charged with alkenes **70** (103 mg, 0.20 mmol) and $Mn(dpm)_3$ (12 mg, 0.02 mmol, 10 mol%) dissolved in 1:1 CH_2Cl_2/*i*PrOH (20 mL, 0.01 M) at 0 °C. The system was then sparged with oxygen for 10 min. Then Ph(O-*i*Pr)SiH_2 (0.07 mL, 0.39 mmol, ~2 eq) in CH_2Cl_2 (0.5 mL) was added via syringe pump over 1 h while sparging continued. The reaction was then allowed to slowly warm to rt overnight (16 h). The reaction mixture was then quenched with saturated $Na_2S_2O_3$ (10 mL) and stirred for 10 min. The reaction mixture was then diluted with H_2O (30 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were then dried over $MgSO_4$, filtered, and concentrated to a brown oil. The residue was then purified by flash column chromatography (SiO_2, 1:0→9:1→4:1 Hex/EtOAc) to afford alcohol **71** (71.5 mg, 67%) as a colorless oil: R_f = 0.3 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$) δ 5.78 (d, *J* = 5.4 Hz, 1H), 5.33 (broad s, 1H), 4.79 (s, 1H), 4.26-4.13 (m, 2H), 3.61 (dt, *J* = 3.4, 10.4 Hz, 1H), 2.89 (d, *J* =15.4 Hz, 1H), 2.78 (d, *J* = 15.4 Hz, 1H), 2.69 (d, *J* = 5.2 Hz, 1H), 2.36-2.29 (m, 1H), 2.22-2.10 (m, 2H), 2.06-1.98 (m, 2H), 1.70-1.62 (m, 3H), 1.61-1.56 (m, 2H), 1.53-1.49 (m, 1H), 1.45-1.31 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.25-1.20 (m, 2H), 1.20-1.14 (m, 1H), 1.03-0.98 (m, 1H), 0.97-0.92 (m, 6H), 0.91 (s, 3H), 0.89 (s, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.83 (s, 3H), 0.79 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.3, 170.9, 140.3, 118.9, 99.6, 78.3, 76.8, 61.5, 56.7, 49.4, 47.8, 44.8, 39.9, 39.5, 39.0, 34.7, 34.2, 33.3, 31.5, 31.3, 28.0, 26.2, 25.3, 24.7, 23.0, 22.9, 22.3, 21.0, 16.7, 15.7, 14.0, 11.6; IR (thin film) 3457, 2950, 2920, 2867, 1778, 1734, 1453, 1370, 1333, 1201, 1153, 1137, 1035, 919, 733 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{32}H_{52}NaO_6]^+$ 555.3661; found 555.3665; Optical Rotation $[\alpha]^{22}_D$ +37.9, $[\alpha]^{22}_{577}$ +39.5, $[\alpha]^{22}_{546}$ +44.4, $[\alpha]^{22}_{435}$ +68.2, $[\alpha]^{22}_{405}$ +79.5 (*c* = 1.0, $CHCl_3$).

Preparation of Silyl Ether 72: A round bottom flask was charged with **71** alcohol (69.4 mg, 0.13 mmol) and CH_2Cl_2 (1.5 mL, ~0.1 M). Imidazole (55 mg, 0.80 mmol, 6 eq) was added followed by freshly distilled TMSCl (0.05 mL, 0.4 mmol, 3 eq). The reaction mixture was then stirred at rt for 16 h. TLC indicated consumption of starting material. The reaction was then diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were then dried over $MgSO_4$, filtered, and concentrated to an orange oil. The crude residue was purified by flushing through a neutralized SiO_2 plug (neutralized before use with 2% Et_3N in hexanes, flush with 50 mL of 9:1 Hex/EtOAc) and concentrated to afford lactone **72** (69.6 mg, 88%) as a colorless oil. R_f = 0.5 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, C_6D_6) δ 6.05 (d, *J* = 8.1 Hz, 1H), 5.37-5.34 (m, 1H), 3.96 (dq, *J* = 7.1, 10.8 Hz, 1H), 3.83 (dq, *J* = 7.1, 10.8 Hz, 1H), 3.65 (dt, *J* = 4.1, 10.6 Hz, 1H), 3.19 (d, *J* = 16.4 Hz, 1H), 3.05 (d, *J* = 16.4 Hz, 1H), 2.93 (d, *J* = 8.1 Hz, 1H), 2.67-2.59 (m, 1H), 2.45 (dp, *J* = 2.6, 6.8 Hz, 1H), 2.15-2.09 (m, 1H), 2.05-1.92 (m, 2H), 1.74-1.59 (m, 2H), 1.53-1.28 (m, 7H), 1.26-1.18 (m, 2H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.14-1.09 (m, 1H), 1.03 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.94 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.89-0.86 (m, 1H), 0.84 (s, 3H), 0.82-0.76 (m, 1H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.39 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6) δ 174.3, 169.2, 140.7, 118.2, 98.8, 79.9, 77.6, 60.4, 58.6, 49.8, 47.9, 44.9, 43.3, 40.0, 39.9, 35.2, 33.9, 32.7, 31.0, 30.9, 27.5, 26.6, 25.7, 25.3, 23.1, 21.9, 20.8, 16.0, 15.7, 13.7, 11.8, 1.5; IR (thin film) 2952, 2921, 2868, 1780, 1740, 1455, 1371, 1341, 1249, 1151, 1128, 1107, 947, 862, 844 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{35}H_{60}O_6SiNa]^+$ 627.4057; found 627.4061; Optical Rotation $[\alpha]^{23}_D$ +6.1, $[\alpha]^{23}_{577}$ +6.8, $[\alpha]^{23}_{546}$ +7.1, $[\alpha]^{23}_{435}$ +7.9, $[\alpha]^{23}_{405}$ +10.0 (*c* = 1.5, $CHCl_3$).

Preparation of Valerolactone 73: In a 10 mL flame-dried round bottom flask, a solution of lactone **72** (50 mg, 0.082 mmol) in Et_2O (2.8 mL, 0.03 M) was cooled to −78 °C. DIBAL (0.41 mL, 0.41 mmol, 5 eq) was added and the mixture was stirred at −78 °C for 2 h. The reaction mixture was then warmed to −20 °C slowly over an hour and then stirred at this temperature for 30 min. The reaction was then quenched with sat. aqueous Rochelle's salt (2 mL) and 1M NaOH (0.41 mL). The mixture was then stirred for 20 min at rt then diluted with H_2O (10 mL). The mixture was extracted with Et_2O (3 x 10 mL) and the organic layer were dried over $MgSO_4$, filtered and concentrated to a colorless oil. This material was used immediately in the next step.

A 10 mL round bottom flask was charged with the crude lactols dissolved in CH_2Cl_2 (2.8 mL, 0.03 M), PCC (35.4 mg, 0.164 mmol, 2 eq) was added, and the mixture was stirred at rt for 16 h. Celite® (0.5 g) was added to the reaction and it was diluted with 4:1 Hex/EtOAc (10 mL). The mixture was then filtered through a neutralized SiO_2 plug (neutralized with 2% Et_3N in hexanes, flushed with 30 mL of 4:1 Hex/EtOAc). The filtrate was concentrated to afford lactone **73** (26.4 mg, 57%) as a light brown foam. R_f = 0.45 (4:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, C_6D_6) δ 10.01 (dd, *J* = 1.5, 3.0 Hz, 1H), 5.38 (d, *J* = 8.0 Hz, 1H), 5.33-5.29 (m, 1H), 3.52 (dt, *J* = 4.1, 10.7 Hz, 1H), 2.76 (dd, *J* = 1.5, 15.6 Hz, 1H), 2.73 (d, *J* = 8.0 Hz, 1H), 2.5-2.44 (m, 1H), 2.35 (dp, *J* = 2.5, 7.0 Hz, 1H), 2.29 (dd, *J* = 3.0, 15.6 Hz, 1H), 2.05-1.93 (m, 3H), 1.51-1.22 (m, 11H), 1.18-1.09 (m, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.30 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6) δ 198.6, 174.3, 140.5, 118.4, 98.4, 80.1, 77.9, 57.3, 49.8, 49.6, 47.8, 44.9, 40.0, 39.7, 35.0, 33.8, 32.8, 31.1, 31.0, 27.6, 26.5, 25.8, 25.0, 23.2, 22.9, 21.9, 20.7, 16.0, 15.4, 11.8, 1.3; IR (thin film) 2953, 2919, 2850, 1777, 1722, 1632, 1455, 1251, 1125, 942 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{33}H_{56}O_5SiNa]^+$ 583.3795; found 583.3779; Optical Rotation $[\alpha]^{23}_D$ +45.6, $[\alpha]^{23}_{577}$ +47.6, $[\alpha]^{23}_{546}$ +53.8, $[\alpha]^{23}_{435}$ +86.1, $[\alpha]^{23}_{405}$ +101 (*c* = 1.0, $CHCl_3$).

Preparation of Dioxabicyclo[3.3.0]octan-3-one 74: A 10 mL round-bottom flask was charged with lactone **71** (14.2 mg, 0.0266 mmol), which was dissolved in Et_2O (5 mL, 0.005 M) and cooled to 0 °C. Solid $LiAlH_4$ (16 mg, 0.43 mmol, 15 eq) was added in one portion. The mixture was then allowed to stir at 0 °C for 30 min and then quenched by the Fieser method (0.02 mL of H_2O, then 0.02 mL of 15% aqueous NaOH, then 0.06 mL of H_2O). The mixture was then warmed to rt and stirred for 1 h or until the residual gray color of $LiAlH_4$ had been fully converted to colorless solids. Then $MgSO_4$ was added and the mixture was filtered. The filtered solids were washed with Et_2O (30 mL) and the filtrate was concentrated to afford a mixture of lactol epimers, as a colorless foam, which was carried on without further purification.

A 10 mL round-bottom flask was charged with the crude lactols and dissolved in CH_2Cl_2 (5 mL, 0.005 M) at rt. PCC (12mg, 0.056 mmol, 2.1 equiv) was then added to the reaction and the mixture was stirred at rt overnight (~16 h). Celite® (100 mg) was then added to the reaction and the mixture was concentrated. The solids were then suspended in 4:1 hexanes/EtOAc (10 mL) and filtered through a SiO_2 plug, which was washed with 4:1 hexanes/EtOAc (30 mL). The filtrate was then concentrated to afford lactone **74** (9.4 mg, 72%) as a colorless oil, which was used without further purification: R_f = 0.3 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$) 5.61 (s, 1H), 5.46 (d, *J* = 5.8 Hz, 1H), 5.33-5.28 (m, 1H), 3.54 (dt, *J* = 3.9, 10.5 Hz, 1H), 3.09 (d, *J* = 17.5 Hz, 1H), 2.55 (d, *J* = 17.5 Hz, 1H), 2.55 (d, *J* = 5.9 Hz, 1H), 2.20-2.11 (m, 2H), 2.10-2.05 (m, 1H), 2.05-1.98 (m, 2H), 1.74-1.69 (m, 1H), 1.68-1.65 (m, 1H), 1.65-1.62 (m, 2H), 1.62-1.60 (m, 1H), 1.43 (s, 1H), 1.40-1.32 (m, 3H), 1.29-1.24 (m, 3H), 1.23-1.20 (m, 1H), 1.20-1.18 (m, 1H), 1.18-1.13 (m, 1H), 1.03-0.98 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 174.7, 140.4, 118.3, 108.8, 100.0, 83.6, 76.2, 58.4, 49.4, 47.9, 44.5, 40.0, 39.7, 38.6, 35.3, 34.4, 32.7, 31.4, 31.2, 27.7, 26.8, 25.7, 25.2, 23.2, 23.0, 22.3, 21.0, 18.0, 15.8, 11.6; IR (thin film) 3403, 2921, 2867, 1792, 1455, 1383, 1219, 1163, 1104, 1035, 924, 772 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{30}H_{48}O_5Na]^+$ 511.3399; found 511.3399; Optical Rotation $[\alpha]^{23}_D$ +23.7, $[\alpha]^{23}_{577}$ +24.4, $[\alpha]^{23}_{546}$ +24.4, $[\alpha]^{23}_{435}$ +34.3, $[\alpha]^{23}_{405}$ +39.7 (*c* = 0.6, $CHCl_3$).

Preparation of (–)-macfarlandin C (3): Aqueous HCl (4 M, 1.5 mL, 0.06 M overall) was added to a solution of acetal **74** (9.1 mg, 0.019 mmol) in THF (1.5 mL). The reaction was then warmed to 35 °C and stirred at this temperature for 5 days. The reaction was then cooled to rt and diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated to afford the intermediate lactol alcohol **75** as a pale-yellow oil, which was carried on without further purification.

The crude lactol alcohol **75** was dissolved in CH_2Cl_2 (3 mL, 0.06 M) and DMAP (2.2 mg, 0.019 mmol, 1 eq) and Et_3N (0.06 mL, 0.4 mmol, 20 eq) were added, followed by Ac_2O (0.03 mL, 0.3 mmol, 20 eq). The reaction was then stirred at rt overnight (~16 h) and then quenched by the addition of H_2O (5 mL) and saturated aq. $NaHCO_3$ (5 mL). The

mixture was then extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration and concentration of the filtrate gave a yellowish solid. This residue was taken up in 4:1 hexanes/EtOAc (5 mL) and flushed through a SiO_2 plug (neutralized with 10 mL of 5% Et_3N in hexanes) with 25 mL of 4:1 hexanes/EtOAc. The filtrate was then concentrated to afford butenolide **76** as a pale-yellow oil, which was used immediately without further purification.[46]

A flame-dried 10 mL flask was charged with (IPr)CuCl (2.2 mg, 0.0046 mmol, 25 mol%) and toluene (0.5 mL). To this solution, NaO*t*-Bu (2.3 µL, 2 M in THF, 0.0046 mmol, 25 mol%) was added followed by PMHS (3.3 µL, 0.056 mmol, 3 equiv). The resulting yellow solution was stirred at rt for 5 min. Then crude butenolide **76** and *t*-BuOH (3.5 µL, 0.037 mmol, 2 equiv) as a solution in toluene (1.5 mL, 0.01 M final concentration) were added to the reaction. The mixture was then stirred at rt overnight (~16 h). The reaction was then quenched with H_2O (5 mL) and vigorously stirred for 5 min. The mixture was then diluted with brine (5 mL) and poured into a separatory funnel. The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were then dried over $MgSO_4$, filtered, and concentrated to a green oil. The residue was then purified by preparative TLC (SiO_2, 4:1 Hex/EtOAc) to afford (–)-macfarlandin C (**3**) (2.7 mg, 38% over three steps) as a colorless solid:[47] R_f = 0.29 (4:1 Hex/EtOAc, visualized with $KMnO_4$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.53 (d, *J* = 7.3 Hz, 1H), 6.04 (d, *J* = 4.1 Hz, 1H), 5.31 (br. t, *J* = 3.7 Hz, 1H), 3.06-3.00 (m, 1H), 2.81 (app t, *J* = 6.8 Hz, 1H), 2.74 (dd, *J* = 10.4, 17.4 Hz, 1H), 2.55 (dd, *J* = 8.9, 17.4 Hz, 1H), 2.09 (s, 3H), 2.05-1.98 (m, 2H), 1.89 (bq, *J* = 7.0 Hz, 1H), 1.76-1.69 (m, 1H), 1.66-1.57 (m, 2H), 1.43-1.37 (m, 1H), 1.36-1.31 (m, 1H), 1.25-1.19 (m, 1H), 1.15 (dt, *J* = 4.8, 12.8 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 175.4, 169.7, 140.3, 118.4, 104.8, 96.1, 51.7, 49.0, 44.4, 42.1, 39.7, 35.5, 32.6, 31.2, 30.2, 27.6, 26.8, 25.2, 23.0, 21.2, 18.9, 11.6; IR (thin film) 2921, 2851, 1799, 1750, 1455, 1375, 1225, 999 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{22}H_{32}O_5Na]^+$ 399.2148; found 399.2159; Optical Rotation $[\alpha]^{21}_D$ –27.7, $[\alpha]^{21}_{577}$ –29.5, $[\alpha]^{21}_{546}$ –43.1, $[\alpha]^{21}_{435}$ –112, $[\alpha]^{21}_{405}$ –125 (*c* = 0.4, $CHCl_3$); $[\alpha]_D$ –29.1 (c = 0.75, $CHC1_3$) is reported for the natural isolate.[2a]

Preparation of Alcohol S3: A flame dried 100 mL round bottom flask was charged with lactone **77** (882 mg, 2.04 mmol)[6] and toluene (20 mL, 0.1 M). The solution was cooled to –78 °C and a solution of LiHMDS (3.1 mL, 3.1 mmol, 1.55 eq, 1 M in THF) was added dropwise. The reaction was maintained at –78 °C for 1 h. During the enolate formation, ethyl glyoxylate (50 wt% in Toluene, ~5.04 M) was distilled over P_2O_5 under Argon (10–15 min at 110 °C, then warm over 10 min to 140 °C then warm to 200 °C). The obtained yellow distillate was used immediately. The freshly distilled ethyl glyoxylate (2.0 mL, 10 mmol, 5 equiv) was added. The reaction mixture was maintained at –78 °C for 2 h and then quenched by the addition of H_2O (20 mL) and allowed to warm to rt. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were then washed with brine (50 mL) and dried over $MgSO_4$. The organic layer were filtered and concentrated to a dark yellow oil, which was purified immediately.[45] The residue was purified by column chromatography (SiO_2, 20:1→9:1 Hex/EtOAc) to afford alcohol **S3** (931 mg, 85%) as a colorless oil and an inseparable 4:1 mixture of diastereomers. R_f = 0.3 (9:1 Hex/EtOAc, visualized with $KMnO_4$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.51-5.50 (m, 0.2H, minor), 5.49 (d, *J* = 2.2 Hz, 0.8H, major), 4.83 (d, *J* = 1.7 Hz, 0.8H, major), 4.81 (d, *J* = 1.6 Hz, 0.2H, minor), 4.69-4.66 (m, 0.8H, major), 4.65 (dd, *J* = 3.8, 9.6 Hz, 0.2H, minor), 4.61-4.58 (m, 0.2H, minor), 4.40-4.30 (m, 1.8H, major and minor), 4.32 (dd, *J* = 2.7, 4.3 Hz, 0.8H, major), 4.13 (dq, *J* = 7.1, 10.8 Hz, 0.2H, minor), 3.56 (dt, *J* = 4.3, 10.7 Hz, 0.2H, minor), 3.53 (dt, *J* = 4.1, 10.6 Hz, 0.8H, major), 3.30 (d, *J* = 9.5 Hz, 0.2H, minor), 3.23 (d, *J* = 4.5 Hz, 0.8H, major), 3.10 (dd, *J* = 2.6, 5.2 Hz, 0.8H, major), 2.86 (app t, *J* = 3.2 Hz, 0.2H, minor), 2.64 (d, *J* = 9.0 Hz, 0.8H, major), 2.51 (dd, *J* = 2.2, 5.2 Hz, 0.8H, major), 2.39-2.33 (m, 1H, major and minor), 2.30 (m, 0.2H, minor), 2.22 (dp, *J* = 2.5, 7.0 Hz, 0.8H, major), 2.17 (dp, *J* = 2.2, 6.9 Hz, 0.2H, minor), 2.13-2.07 (m, 1H, major and minor), 1.93 (q, *J* = 9.4 Hz, 1H), 1.83 (t, *J* = 12.9 Hz, 1H), 1.79-1.70 (m, 3H), 1.68-1.57 (m, 4H), 1.43-1.32 (m, 2.4H, major and minor), 1.35 (t, *J* = 7.1 Hz, 2.4H, major), 1.30 (t, *J* = 7.2 Hz, 0.6H, minor), 1.29-1.24 (m, 2.6H, major and minor), 1.03-0.98 (m, 1H), 0.97 (s, 3H), 0.95 (s, 3H), 0.94 (d, *J* = 3.6 Hz, 0.6H, minor), 0.93 (d, *J* = 6.5 Hz, 2.4H, major), 0.91 (s, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (Major) 175.1, 172.4, 153.4, 114.8, 102.0, 77.5, 71.7, 62.6, 55.1, 55.0, 54.2, 48.0, 47.8, 47.4, 39.9, 37.8, 37.2, 37.0, 36.2, 34.4, 34.3, 31.5, 28.6, 26.2, 25.7, 25.0, 22.9, 22.4, 21.5, 21.0, 15.4, 14.1, (Minor, not all peaks visible) 176.4, 172.6, 153.3, 114.7, 102.3, 78.3, 71.0, 62.0, 54.9, 52.1, 47.63, 47.61, 47.5, 40.2, 37.7, 37.3, 37.1, 34.2, 31.6, 28.61, 26.1, 24.8, 22.6, 22.3, 21.1, 15.1, 14.0; IR (thin film) 3502, 2950, 2921, 2868, 1775, 1738, 1454, 1386, 1367, 1264, 1240, 1178, 1112, 1093, 1022, 959, 933, 909, 731 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{32}H_{52}O_6Na]^+$ 555.3661; found 555.3679.

Dehydration to Alkenes (*E*)-and (*Z*)-78: A flame dried 25 mL round-bottom flask was charged with alcohol **S3** (270 mg, 0.507 mmol) in CH_2Cl_2 (5 mL, 0.1 M). DMAP (6.2 mg, 0.051 mmol, 10 mol%), pyridine (0.17 mL, 2.1 mmol, 4 equiv), and TFAA (0.14 mL, 1.00 mmol, 2 equiv) were added in that order. The reaction mixture was then placed in a sand bath that was preheated to 35 °C, and stirred at this temperature for 1.5 hr. The reaction was then cooled to rt and DBU (0.43 mL, 3.0 mmol, 6 eq) was added, and the reaction was stirred at rt for 1 h. The reaction was then quenched by the addition of H_2O (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were then dried over $MgSO_4$, filtered, and concentrated to an orange oil. The residue was purified by flash column chromatography (SiO_2, 1:0→95:5→9:1 Hex/EtOAc) to afford **(*E*)-78** as a colorless foam (148 mg, 57%): R_f = 0.7 (9:1 Hex/EtOAc) and **(*Z*)-78** as colorless oil (77 mg, 29%): R_f = 0.48 (9:1 Hex/EtOAc). **(*E*)-78:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (d, *J* = 1.5 Hz, 1H), 5.62 (s, 1H), 4.78 (d, *J* = 1.9 Hz, 1H), 4.49 (d, *J* = 1.6 Hz, 1H), 4.28-4.19 (m, 2H), 3.68 (d, *J* =1.5 Hz, 1H), 3.54 (dt, *J* = 4.2, 10.7 Hz, 1H), 2.62 (d, *J* = 8.7 Hz, 1H), 2.31 (dd, *J* = 4.2, 12.1 Hz, 1H), 2.13-2.04 (m, 2H), 1.93 (dp, *J* = 2.5, 7.0 Hz, 1H), 1.80-1.69 (m, 4H), 1.69-1.58 (m, 5H), 1.51-1.45 (m, 1H), 1.43-1.33 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.27-1.18 (m, 2H), 1.02-0.96 (m,1H), 0.96 (s, 3H), 0.95 (s, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.89-0.84 (m, 1H), 0.83 (d, *J* =7.1 Hz, 3H), 0.77 (s, 3H), 0.73 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.7, 165.4, 152.8, 143.1, 127.4, 114.9, 102.0, 77.1, 61.1, 54.4, 53.6, 53.5, 50.8, 47.5, 40.0, 37.7, 37.2, 36.9, 36.1, 34.3, 34.2. 31.5, 28.6, 26.2, 25.5, 25.4, 23.2, 22.4, 22.3, 20.8, 15.6, 14.1; IR (thin film) 2953, 2923, 2868, 1777, 1724, 1455, 1371, 1253, 1208, 1092, 1026, 936 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{32}H_{50}O_5Na]^+$ 537.3556; found 537.3542; Optical Rotation $[\alpha]^{21}_D$ +56.2, $[\alpha]^{21}_{577}$ +60.0, $[\alpha]^{21}_{546}$ +67.3, $[\alpha]^{21}_{435}$ +104.4, $[\alpha]^{21}_{405}$ +121 (*c* = 1.0, $CHCl_3$); **(*Z*)-78:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.35 (d, *J* = 1.2 Hz, 1H), 5.54 (s, 1H), 4.83 (d, *J* = 1.6 Hz, 1H), 4.60 (d, *J* = 1.4 Hz, 1H), 4.33-4.25 (m, 2H), 3.58 (dt, *J* = 4.2, 10.7 Hz, 1H), 2.72 (s, 1H), 2.69 (d, *J* = 8.5 Hz, 1H), 2.34 (dd, *J* = 5.1, 12.7 Hz, 1H), 2.11-2.06 (m, 1H), 2.06-1.99 (m, 1H), 1.97-1.91 (m, 1H), 1.83-1.71 (m, 4H), 1.70-1.58 (m, 5H), 1.56-1.51 (m, 1H), 1.43-1.34 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.29-1.24 (m, 1H), 1.23-1.16 (m, 1H), 1.04-0.99 (m, 1H), 0.98 (s, 3H), 0.94 (s, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.84 (s, 3H), 0.76 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 167.4, 165.2, 152.3, 134.4, 130.3, 115.3, 100.6, 76.8, 61.6, 55.6, 53.9, 53.8, 49.1, 47.8, 39.9, 37.6, 37.0, 36.9, 36.2, 34.3, 34.2, 31.4, 28.6, 26.0, 25.9, 25.4, 23.2, 22.3, 22.1, 20.9, 15.7, 13.9; IR (thin film) 2952, 2923, 2867, 1775, 1733, 1454, 1365, 1324, 1241, 1184, 1091, 1026, 976, 942, 923, 889 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{30}H_{50}O_5Na]^+$ 537.3556; found 537.3542; Optical Rotation $[\alpha]^{22}_D$ +69.2, $[\alpha]^{22}_{577}$ +71.9, $[\alpha]^{22}_{546}$ +82.4, $[\alpha]^{22}_{435}$ +137, $[\alpha]^{23}_{405}$ +166 (*c* = 1.0, $CHCl_3$).

Preparation of Diol 79 and Alcohol 80: A 50 mL round-bottom flask was charged with alkene **78** (76.9 mg, 0.1493 mmol) and $Mn(dpm)_3$ (8.7 mg, 0.014 mmol, 10 mol%) dissolved in 1:1 CH_2Cl_2/*i*-PrOH (14 mL, 0.01M). The reaction mixture was then sparged with O_2 for 10 min and then cooled to 0 °C. Then Ph(O*i*Pr)SiH_2 (0.11 mL, 0.61 mmol, 4 equiv) in CH_2Cl_2 (1 mL) was added via syringe pump over 1h. The reaction was then allowed to slowly warm to rt overnight (16 h). The reaction was then quenched with saturated $Na_2S_2O_3$ (10 mL) and stirred for 30 min. The mixture was then diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated to a brown oil. The residue was purified by flash column chromatography (SiO_2, 9:1→4:1 Hex/EtOAc) to afford diol **79** (57.3 mg, 70%) as a colorless foam: R_f = 0.23 (4:1 Hex/EtOAc, visualized with $KMnO_4$) and alcohol **80** (17.1 mg, 21%) as a colorless oil: R_f = 0.69 (4:1 Hex/EtOAc, visualized with $KMnO_4$); **Diol 79:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1H), 5.63 (d, *J* = 7.7 Hz, 1H), 4.50 (s, 1H), 4.23-4.14 (m, 2H), 3.61 (dt, *J* = 4.1, 10.6 Hz, 1H), 3.11 (d, *J* = 7.6 Hz, 1H), 2.91 (d, *J* = 14.9 Hz 1H), 2.87 (d, *J* = 11.5 Hz, 1H), 2.60 (d, *J* = 14.9 Hz, 1H), 2.25-2.17 (m, 1H), 2.16-2.09 (m, 2H), 1.82-1.63 (m, 6H), 1.62-1.57 (m, 1H), 1.54 (s, 3H), 1.50-1.44 (m, 2H), 1.42-1.35 (m, 1H), 1.39 (s, 3H), 1.35-1.29 (m, 1H), 1.29-1.18 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.10 (s, 3H), 1.08-0.99 (m, 2H), 0.98-0.95 (m, 6H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.81

(d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 175.0, 170.4, 99.4, 88.7, 78.0, 77.4, 61.7, 56.9, 55.0, 54.6, 48.4, 47.3, 44.5, 43.2, 41.2, 39.8, 38.7, 36.0, 35.6, 34.3, 31.4, 27.8, 25.9, 25.5, 24.0, 23.2, 22.4, 22.0, 21.0, 20.9, 16.0, 14.1; IR (thin film) 3440, 2952, 2924, 2869, 1776, 1734, 1454, 1371, 1332, 1299, 1200, 1134, 1037, 931, 849 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{32}H_{54}O_7Na]^+$ 573.3767; found 573.3751; Optical Rotation $[\alpha]^{23}_D$ +94.1, $[\alpha]^{23}_{577}$ +97.0, $[\alpha]^{23}_{546}$ +112.5, $[\alpha]^{23}_{435}$ +184.5, $[\alpha]^{23}_{405}$ +220.2 (*c* = 1.0, $CHCl_3$); **Alcohol 80:** ^1H NMR (600 MHz, $CDCl_3$) δ 5.63 (d, *J* = 7.3 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 4.72 (bs, 1H), 4.69 (d, *J* = 1.8 Hz, 1H), 4.25-4.14 (m, 2H), 3.61 (dt, *J* = 4.2, 10.7 Hz, 1H), 3.33 (d, *J* = 8.7 Hz, 1H), 3.00 (d, *J* = 15.0 Hz, 1H), 2.61 (d, *J* = 15.0 Hz, 1H), 2.57 (d, *J* = 7.3 Hz, 1H), 2.36 (dd, *J* = 5.3, 12.8 Hz, 1H), 2.19 (dp, *J* = 2.3, 7.0 Hz, 1H), 2.15-2.10 (m, 1H), 2.06 (q, *J* = 9.6 Hz, 1H), 1.97 (dt, *J* = 6.6, 12.7 Hz, 1H), 1.79-1.59 (m, 8H), 1.46-1.35 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.25-1.20 (m, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.87-0.83 (m, 1H), 0.81 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 175.1, 170.8, 153.6, 115.0, 99.5, 77.9, 77.3, 61.7, 57.1, 53.5, 52.6, 48.1, 47.1, 40.1, 39.2, 39.0, 37.8, 37.6, 36.2, 34.3, 31.5, 29.7, 28.8, 25.8, 25.6, 25.5, 23.3, 22.9, 22.4, 20.9, 16.0, 14.0; IR (thin film) 3447, 2951,2922, 2868, 1781, 1734, 1455, 1371, 1336, 1219, 1138, 1031,924 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{32}H_{52}O_6Na]^+$ 555.3661; found 555.3646; Optical Rotation $[\alpha]^{21}_D$ +103, $[\alpha]^{21}_{577}$ +107, $[\alpha]^{21}_{546}$ +121, $[\alpha]^{21}_{435}$ +200, $[\alpha]^{21}_{405}$ +238 (*c* = 1.0, $CHCl_3$).

Preparation of Dioxabicyclo[3.3.0]octan-3-one 81: A 25 mL round bottom flask was charged with a solution of lactone **79** (27 mg, 0.049 mmol) in Et_2O (10 mL, 0.005M) and cooled to 0 °C. Then $LiAlH_4$ (28 mg, 0.72 mmol, 15 equiv) was added in 3 portions. The mixture was then stirred for 10 min at 0 °C. The reaction was then quenched by the Fieser method (0.05 mL of H_2O, then 0.05 mL of 15% aqueous NaOH, then 0.15 mL of H_2O) and stirred for 1 h or until the residual gray color of $LiAlH_4$ had been fully converted to colorless solids. Solid $MgSO_4$ was added and the mixture was filtered. The filtered solids were washed with Et_2O (30 mL) and the combined filtrates were concentrated to afford a mixture of lactols as a colorless foam, which was carried on without further purification.

The crude lactols were then dissolved in CH_2Cl_2 (9 mL, 0.005M) and PCC (29 mg, 0.13 mmol, 2.7 equiv) was added. The mixture was stirred at rt overnight (16 h). Then Celite® (100 mg) was added and the mixture was stirred for 10 min. The CH_2Cl_2 was then removed from the reaction mixture and the residual solids were suspended in 4:1 Hex/EtOAc (10 mL) and filtered through a neutralized SiO_2 plug (washed with 5% Et_3N in hexanes, 10 mL). The solids were washed with 4:1 Hex/EtOAc (20 mL). The filtrate was then concentrated to afford lactone **81** (15.5 mg, 66%) as a pale-yellow oil, which was used without further purification: R_f = 0.32 (4:1 Hex/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, $CDCl_3$) δ 5.60 (s, 1H), 5.22 (d, *J* = 4.3 Hz, 1H), 4.80 (d, *J* = 1.5 Hz, 1H), 4.64 (d, *J* = 1.6 Hz, 1H), 3.54 (dt, *J* = 4.0, 10.6 Hz, 1H), 3.06 (d, *J* = 17.7 Hz, 1H), 2.95-2.90 (m, 1H), 2.50 (d, *J* = 17.7 Hz, 1H), 2.41-2.35 (m, 2H), 2.22-2.14 (m, 1H), 2.09-2.03 (m, 1H), 1.84 (app t, *J* = 12.6 Hz, 1H), 1.78-1.60 (m, 8H), 1.59-1.54 (m, 2H), 1.42-1.32 (m, 3H), 1.31-1.26 (m, 1H), 1.24-1.17 (m, 1H), 1.06-1.00 (m, 1H), 1.02 (s, 3H), 0.95 (s, 6H), 0.93-0.90 (m, 6H), 0.89-0.86 (m, 1H), 0.83 (d, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 175.0, 153.1, 114.6, 108.6, 100.8, 84.0, 76.1, 61.5, 54.9, 54.2, 48.0, 47.7, 40.5, 38.1, 38.0, 37.3, 37.2, 36.1, 34.5, 34.4, 31.5, 28.2, 27.3, 25.9, 25.7, 24.0, 23.0, 22.4, 21.1, 15.5; IR (thin film) 3441, 2950, 2922, 2867, 1798, 1455, 1376, 1219, 1180, 1088, 1061, 1031, 945, 849 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{30}H_{48}O_5Na]^+$ 511.3399; found 511.3395; Optical Rotation $[\alpha]^{21}_D$ +77.5, $[\alpha]^{21}_{577}$ +80.7, $[\alpha]^{21}_{546}$ +89.6, $[\alpha]^{21}_{435}$ +143, $[\alpha]^{21}_{405}$ +168 (*c* = 0.7, $CHCl_3$).

Preparation of (+)-dendrillolide A (4): To a solution of acetal **81** (5.6 mg, 0.0114 mmol) in acetone (0.7 mL) and H_2O (0.7 mL) at 0 °C, TFA (0.7 mL, 0.005M overall concentration) was added dropwise. The reaction was stirred at this temperature for 10 min and then warmed to 30 °C and stirred at this temperature for 3 days. The reaction was then cooled to rt and concentrated to a brown oil under reduced pressure. Water (5 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated to a brown oil, which was carried on without further purification.

The crude lactol was then dissolved in CH_2Cl_2 (3 mL, 0.06M) and DMAP (1.4 mg, 0.0114 mmol, 1 eq) and Et_3N (0.04 mL, 0.2856 mmol, 25 eq) were added to the mixture, followed by Ac_2O (0.02 mL, 0.2115 mmol, ~19 eq). The reaction was then stirred at rt overnight (~16 h). The reaction was then quenched by the addition of H_2O (5 mL) and sat. aq. $NaHCO_3$ (5 mL). The mixture was then extracted with CH_2Cl_2 (3 x 5 mL) and the organic layer were dried over $MgSO_4$. The solids were filtered out and the filtrate was concentrated to a yellow solid. The crude mixture was taken up in 4:1 hexanes/EtOAc (5 mL) and flushed through a SiO_2 plug (neutralized with 10 mL of 5% Et_3N in hexanes) with 25 mL of 4:1 hexanes/EtOAc. The filtrate was then concentrated to afford butenolide **82** as a pale-yellow oil, which was used immediately without further purification.

A flame-dried 10 mL flask was charged with (IPr)CuCl (1.4 mg, 0.0028 mmol, 25 mol%) and toluene (0.25 mL). To this solution, Na*O*t-Bu (1.4 μL, 2 M in THF, 0.0028 mmol, 25 mol%) was added followed by PMHS (2.0 μL, 16 M neat, 0.034 mmol, 3 equiv). The resulting yellow solution was stirred at rt for 5 min. Then crude butenolide **82** and *t*-BuOH (2.1 μL, 0.023 mmol, 2 eq) as a solution in toluene (0.75 mL, 0.01 M final concentration) was added to the reaction. The mixture was then stirred at rt overnight (~16 h). The reaction was then quenched with H_2O (5 mL) and vigorously stirred for 5 min. The mixture was then diluted with brine (5 mL) and poured into a separatory funnel. The mixture was extracted with EtOAc (3 x 10 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to a light green oil. This residue was then purified by preparative TLC (SiO_2, 9:1 Pentanes/EtOAc) to afford dendrillolide A (**4**) (1.5 mg, 34% over three steps) as a colorless oil:[47] R_f = 0.43 (4:1 Hex/EtOAc, visualized with $KMnO_4$); R_f = 0.15 (9:1 Pentanes/EtOAc, visualized with $KMnO_4$); ^1H NMR (600 MHz, C_6D_6) δ 6.45 (d, *J* = 6.3 Hz, 1H), 5.57 (d, *J* = 4.3 Hz, 1H), 4.71 (d, *J* = 2.0 Hz, 1H), 4.42 (d, *J* = 2.0 Hz, 1H), 2.45 (d, *J* = 9.3 Hz, 1H), 2.23-2.16 (m, 3H), 2.14 (dd, *J* = 10.1, 17.4 Hz, 1H), 1.99-1.92 (m, 1H), 1.78 (dd, *J* = 9.2, 17.4 Hz, 1H), 1.66 (s, 3H), 1.61-1.52 (m, 3H), 1.45-1.36 (m, 4H), 1.21-1.13 (m, 1H), 1.09-1.02 (m, 1H), 0.96 (s, 3H), 0.92 (s, 3H), 0.51 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6) δ 174.8, 169.0, 153.8, 114.3, 105.0, 97.1, 55.7, 54.9, 54.5, 46.7, 41.9, 38.1, 37.7, 37.6, 36.0, 34.5, 28.8, 28.7, 27.1, 25.7, 24.1, 20.7; IR (thin film) 2951, 2925, 2856, 1797, 1751, 1454, 1374, 1224, 988 cm^{-1}; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $[C_{22}H_{32}O_5Na]^+$ 399.2148; found 399.2148; Optical Rotation $[\alpha]^{22}_D$ +64.0, $[\alpha]^{22}_{577}$ +63.5, $[\alpha]^{22}_{546}$ +69.2, $[\alpha]^{22}_{435}$ +88.9, $[\alpha]^{22}_{405}$ +133 (*c* = 1.0, $CHCl_3$); $[\alpha]^{20}_D$ +83.5 (c = 3.8, $CHCl_3$) is reported for the natural isolate.[3,41]

ASSOCIATED CONTENT

Supporting Information. Conditions explored for the hydrogenation of **17** and **18**, HAT conditions explored for the hydrogenation of **18**, comparisons of ^1H and ^{13}C NMR data for synthetic and natural (–)-macfarlandin C and (+)-dendrollide A, and CIF files and X-ray model of compound **32**. "This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

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47. Macfarlandin C (**3**) and dendrillolide A (**4**) decompose under mildly acidic conditions such as prolonged exposure to silica gel or $CDCl_3$, resulting in the growth of a difficult to separate decomposition product showing a diagnostic broad multiplet at 1.25 ppm (^{1}H NMR, $CDCl_3$) and peaks at 29.7, 29.4 and 14.1 ppm (^{13}C{^{1}H} NMR, $CDCl_3$).