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# Norrisolide: Total Synthesis and Related Studies

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**Abstract:** A stereoselective synthesis of (+)-norrisolide is presented. This natural product belongs to a family of marine spongiane diterpenes the structure of which is characterized by a fused γ-lactone–γ-lactol ring system attached to a bicyclic hydrophobic core. Our studies led to the development of a expedient synthesis of such γ-lactone–γ-lactol motifs based on ring expansion of a fused cyclopropyl ester. Highlights of the synthetic strategy toward norrisolide include the coupling of the two bicyclic systems by constructing a sterically demanding C9–C10 bond and the installation of the C19 oxygen at the last step of the synthesis via a Baeyer–Villiger oxidation.

**Keywords:** natural products · oxidation · synthetic methods · terpenoids · total synthesis

## Introduction

Nudibranchs (nudibranchia) are a class of shell-less, brightly collored sea slugs that comprise one of the largest groups of marine molluscs with over 3000 species described to-date.[1] Their name, a combination of the Latin word *nudus* (naked) and the Greek word *branchia* (gills), appropriately describes their shell-less, seemingly vulnerable appearance. To avoid their natural predators, these marine animals have developed an alternative "chemical shell", consisting of toxic and antifeedant substances that are concentrated in their skin.[2] Further studies indicated that these metabolites are acquired from the nudibranch's dietary habits that include generally praying on sponges and bryozoans. With or without further chemical modifications, these metabolites are stored in the animal's dorsal mantle and excreted when the animal is in danger, thus protecting it from its natural predators.

As a part of a program on molluscan chemical defenses, Faulkner and co-workers isolated norrisolide (**1**) from the skin extracts of the nudibranch *Chromodoris norrisi*.[3] Subsequent studies led to the isolation of **1** from the marine sponges *Dendrilla sp.* and *Dysidea sp.*, providing additional evidence of the feeding patterns of this animal.[4] Spectroscopic and crystallographic studies established that norrisolide belongs to a family of rearranged spongiane diterpenes[5,6] that also includes macfarlandin C (**2**),[7] dendrillolide A (**3**),[8] shahamin K (**4**)[9] and chromodorolide A (**5**)[10] (Figure 1). The biological profile of these family members includes antifungal, antimicrobial, antifeedant, antiviral and antitumor properties as well as $PLA_2$ inhibition.[11] The structural diversity of these compounds is proposed to originate from the spongiane skeleton (**6**) following a series of ring oxidations and skeletal rearrangements. In the case of **1**, **2** and **3**, such a process produces an unusual motif highlighted by a fused γ-lactone–γ-lactol ring system attached to a hydrophobic core. The degree of oxygenation and pattern of functionalities encountered in this side chain confer to

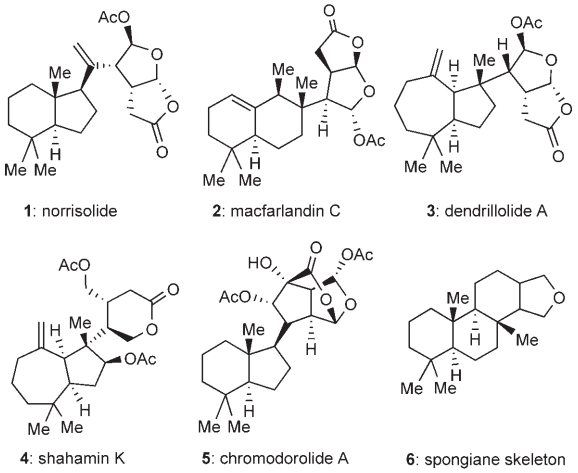


Figure 1. Representative structures of rearranged spongiane diterpenes.

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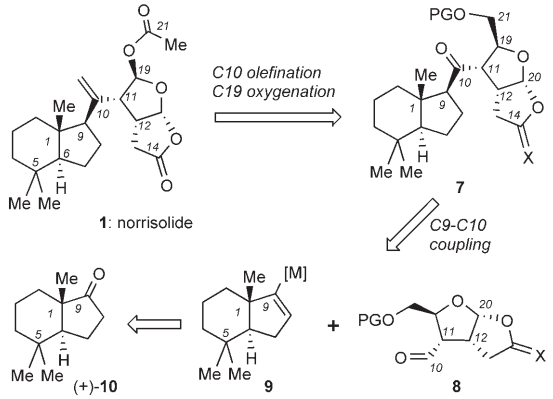
these molecules a high degree of chemical reactivity, the biological significance of which remains largely unexplored.[12]

The combination of interesting structural features and unexplored biological profile of **1** prompted us to develop a stereocontrolled approach to this natural product.[13] Herein we present a full account of our studies toward this goal, culminating in an expedient and stereoselective synthesis of (+)-norrisolide.[14] These studies establish the absolute stereochemistry of this natural product and pave the way for a more precise study of its structure–activity relationship.[15]

## Results and Discussion

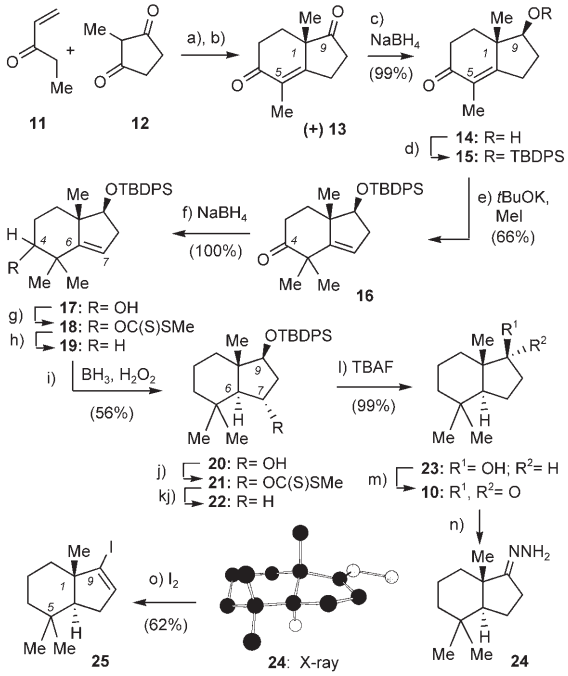
**Retrosynthetic analysis and strategic bond disconnections**: The retrosynthetic analysis toward norrisolide (**1**) is shown in Scheme 1. To avoid any issues related to the reactivity and fragility of the of the γ-lactone–γ-lactol ring system, we




Scheme 1. Strategic bond disconnections of **1** (PG, X indicate protecting groups).

chose to adjust its oxygenation pattern during the last steps of the synthesis. This analysis led us to consider compound **7** as an appropriate synthetic precursor of **1**. In the forward direction, we envisioned that **7** could lead to **1** via a sequence of reactions that include olefination of the C10 carbonyl group and oxidation at the C14 and C19 centers. The latter functionalization could be achieved via a Baeyer–Villiger oxidation that was projected to install the C19 oxygen in a regio- and stereoselective manner.[16] Compound **7** could be formed by connecting fragments **8** and **9** representing the side chain and the core of norrisolide. The *trans*-fused hydrindane motif of **9** could be traced to enantiomerically enriched ketone (+)-**10**. The synthesis of norrisolide based on these considerations is presented in the following schemes.

**Synthesis of the hydrindane core fragment of norrisolide**: An enantioselective synthesis of ketone **10** has been previously reported by Paquette starting from the well known Wieland–Miescher enone.[17] In the course of our studies we developed an alternative route to ketone **10** which proved to be advantageous during scale-up. This approach is highlighted in Scheme 2 and began with an asymmetric Robinson annulation of enone **11** with diketone **12**.[18] Use of D-CSA and L-phenylalanine during this reaction led to an




Scheme 2. a) 1.5 equiv $Et_3N$, EtOAc, 25 °C, 12 h, 89 %; b) 0.6 equiv D-CSA, 0.8 equiv L-Phe, acetonitrile, 25 → 70 °C, 5 d, 60 % (after recrystallization); c) 0.33 equiv $NaBH_4$, EtOH, −25 °C, 0.5 h, 99 %; d) 2.5 equiv imidazole, 2.0 equiv TBDPSCl, 0.1 equiv DMAP, DMF, 25 °C, 4 h, 77 %; e) 2.0 equiv *t*BuOK, DMF, 0 → 25 °C, 1 h, then 2.0 equiv MeI, 0 °C, 1 h, 66 % f) 1.2 equiv $NaBH_4$, MeOH, 0 °C, 1 h, 100 %; g) 1.2 equiv *n*BuLi, 0 °C, 0.5 h, 10 equiv $CS_2$, 2 h, then 3.0 equiv MeI, THF, 0.5 h, 95 %; h) 2.5 equiv $nBu_3SnH$, 0.1 equiv AIBN, toluene, 120 °C, 0.5 h, 86 %; i) 3.0 equiv $BH_3$·THF, THF, 0 °C, 12 h, then 20 equiv 3 M NaOH (aq), 20 equiv $H_2O_2$, 25 °C, 12 h, 78 % (56 % of *trans* and 24 % of *cis*); j) 1.2 equiv *n*BuLi, 0 °C, 0.5 h, 10 equiv $CS_2$, 2 h, then 3.0 equiv MeI, THF, 0 °C, 0.5 h; k) 2.5 equiv $nBu_3SnH$, 0.1 equiv AIBN, toluene, 120 °C, 0.5 h, 92 % (over 2 steps); l) 3.0 equiv TBAF, THF, 60 °C, 8 h, 99 %; m) 4.5 equiv PCC, Celite, $CH_2Cl_2$, 25 °C, 1 h, 92 %; n) 30 equiv $N_2H_4$·$H_2O$, 5.0 equiv $Et_3N$, EtOH, reflux, 5 h, 99 %; o) $I_2$ (until $N_2$ evolution ceased), 10 equiv DBU, THF, 25 °C, 0.25 h, 62 %.

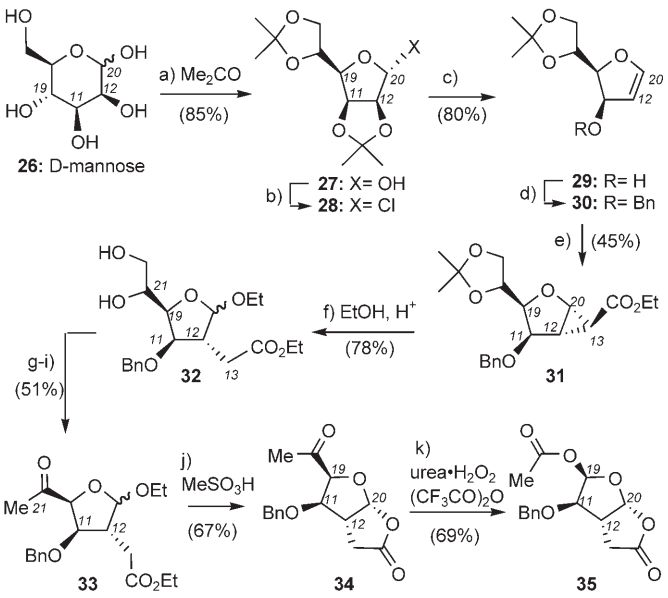
enantioselective synthesis of the desired ketone (+)-**13**, which, after one recrystallization, was isolated in 60 % yield and greater than 95 % *ee*. Selective reduction of the more reactive C9 carbonyl group, followed by silylation of the resulting alcohol afforded compound **15** (76 % yield over two steps). Treatment of **15** with *t*BuOK produced the extended enolate that upon methylation gave rise to ketone **16** in 66 % yield.[19] Reduction of the C4 carbonyl group of **16**, followed by a Barton–McCombie radical deoxygenation of the resulting alcohol, produced alkene **19** in 82 % yield (over three steps).[20] Several methods were examined for the conversion of alkene **19** to the *trans*-fused bicycle **20**. All hydrogenation conditions produced a mixture of *cis* (major product) and *trans* bicycles which were difficult to separate by

using standard chromatographic techniques. We found, however, that hydroxylation of **19** ($BH_3$·THF/$H_2O_2$) afforded the *trans*-bicycle **20** as the major isomer in 56% yield (*trans*/*cis* 2.3:1). The diastereomeric outcome of this hydroxylation was found to be dependant upon the size of the C9 silyl ether, and in the case of the bulky TBDPS group it produced the best ratio of *trans* to *cis* isomers that were easily separated by column chromatography. Radical deoxygenation of alcohol **20**, followed by deprotection of the C9 silyl ether and oxidation of the resulting alcohol, produced ketone **10** in 84% yield (over four steps). Treatment of **10** with hydrazine produced hydrazone **24** that upon reaction with $I_2$/$Et_3N$/DBU produced vinyl iodide **25** in 61% yield (over two steps).[21] The *trans* junction of the bicyclic scaffold of **25** was unambiguously determined by a single-crystal X-ray diffraction analysis of hydrazone **24**.[22]

**Synthesis of the side chain motif of norrisolide**: Having developed an efficient synthesis of the core fragment of norrisolide, we turned our attention to the synthesis of the bicyclic side chain motif of **1**. At the onset of our investigation, we chose to pursue this synthesis by creating the fused γ-lactone ring from ring expansion of an appropriately substituted cyclopropyl ester (see conversion of **31** to **34**, Scheme 3). It is well established that the strained three-membered ring of cyclopropanes can lead, upon activation, to a variety of ring cleavage and ring expansion reactions.[23] Based on this, we expected that the presence of both electron withdrawing and electron donating substituents at vicinal positions of the cyclopropyl ring of **31** would allow the cleavage of the anomeric bond to occur under mild acidic conditions.[24] This approach appeared advantageous since compound **31** could be constructed by a substrate-directed cyclopropanation of a chiral dihydrofuran, such as **30**, the stereochemistry of which could be traced to D-mannose (**26**). In this manner, the chirality inherent in **26** could be translated to the desired stereochemistry of all stereocenters of the side chain of **1**. Scheme 3 highlights these efforts.[14a]

Conversion of D-mannose (**26**) to the known bisacetonide **27** was accomplished by a modification of the reported procedure in which $I_2$ was used as the catalyst (instead of $H_2SO_4$).[25] This modification led to isolation of **27** in 85% yield after a simple filtration and recrystallization (Scheme 3). Treatment of **27** with TsCl and $Et_3N$ afforded glycosyl chloride **28**, which upon slow addition to a stirring mixture of sodium naphthalenide in THF gave rise to glycal **29** (48%, over two steps).[26] Compound **29** was labile upon standing and was immediately benzylated to produce benzyl ether **30** in 90% yield. Rhodium acetate-catalyzed cyclopropanation of **30** produced ester **31** as a single isomer at the C12 center.[27,28] As expected, the bulky acetonide group at C19 in conjunction with the benzyl ether group at C11 were able to direct this sterically demanding cyclopropanation from the α-face of the dihydrofuran ring. During optimization attempts we found that the yield of cyclopropanation depended upon the reagent concentration; for example under dilute conditions we observed formation of increased




Scheme 3. a) 0.1 M D-mannose in acetone, 0.2 equiv $I_2$, 25 °C, 2 h, 85%; b) 0.6 equiv DMAP, 1.2 equiv TsCl, 1.0 equiv $Et_3N$, $CH_2Cl_2$, 25 °C, 2 h, 60%; c) 3.0 equiv naphthalene, 10 equiv Na, THF, 0 → 25 °C, 10 min, 80%; d) 1.2 equiv BnBr, 1.2 equiv NaH, 0.5 equiv $nBu_4N^+I^-$, 0 °C to 25 °C, 2 h, 90%; e) 0.01 equiv $Rh_2(OAc)_4$, 1.1 equiv $N_2CHCO_2Et$ (0.1 M in $CH_2Cl_2$, syringe pump addition), $CH_2Cl_2$, 25 °C, 14 h, 45%; f) EtOH, 0.8 M $H_2SO_4$, 25 °C, 48 h, 78%; g) 3.0 equiv $NaIO_4$, THF/$H_2O$ 1:1, 20 min, 25 °C; h) 1.0 equiv $TiCl_4$, 3.0 equiv $Ti(OiPr)_4$, THF, 0 °C; 4.0 equiv MeLi, 1 h, 0 → 25 °C, 1 h, 63% (2 steps); i) 4.0 equiv $(COCl)_2$, 5.0 equiv DMSO, −78 °C, 0.5 h, $CH_2Cl_2$; $Et_3N$, −40 °C, 10 min, 79%; j) 6.0 equiv $MeSO_3H$ in $CH_2Cl_2$, −5 → 0 °C, 12 h, 67%; k) urea/hydrogen peroxide, trifluoroacetic anhydride, 40 min, 0 °C, $CH_2Cl_2$, 25 °C, 2 h, 69%.

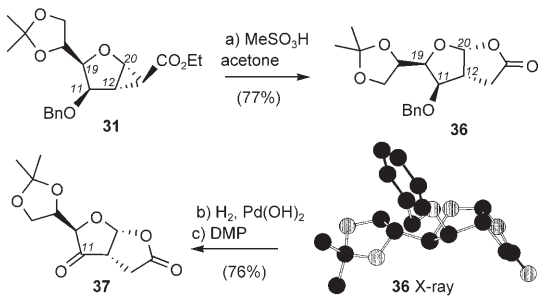
amounts of byproducts arising from dimerization of ethyl diazoacetate. Best results were obtained upon syringe pump addition of ethyl diazoacetate (0.1 M in $CH_2Cl_2$) into a concentrated mixture of **30** (2 M in $CH_2Cl_2$) and rhodium acetate at 25 °C, producing cyclopropyl ester **31** in 45% yield. In this case we observed the formation of two diasteromers at the C13 center (4:1 in favor of the *exo* adduct), which were both subjected to the next reaction.

Treatment of **31** with a dilute ethanolic solution of $H_2SO_4$ induced acetonide deprotection and concomitant opening of the cyclopropyl ring leading to compound **32** in 78% yield (Scheme 3).[29] Conversion of **32** to **33** was accomplished via a sequence of three steps that included: a) oxidative cleavage of the 1,2-diol of **32** ($NaIO_4$); b) methylation of the resulting aldehyde using $MeTi(OiPr)_4$;[30] and Swern oxidation of the resulting alcohol (51% yield over three steps). It is worth mentioning that the titanium-induced methylation proceeded with excellent chemoselectivity (no interference with the ester functionality) and diastereoselectivity (about 10:1 mixture of isomers at the C21 center, presumably arising from a chelation-controlled addition). Formation of the bicyclic system **34** was achieved under acidic conditions. Although a variety of Brönsted acids and Lewis acids could effect this transformation, we found that best yields were obtained by using methanesulfonic acid, which at 0 °C produced compound **34** as a single isomer in 67% yield.[31]

With bicyclic lactone **34** in hand, we decided to test the crucial Baeyer–Villiger oxidation in order to install the C19 oxygen (Scheme 3). Both *m*CPBA/NaOH and urea/hydrogen peroxide in combination with trifluoroacetic anhydride produced the desired structure **35**. This conversion was cleaner using the urea-hydrogen peroxide conditions, leading to formation of **35** in 69% yield. As predicted, a single isomer was obtained during this oxidation having the desired stereochemistry at the C19 center, as established by a combination of spectroscopic techniques (COSY and NOE experiments).

Encouraged by the positive results of the Baeyer–Villiger oxidation, we sought to optimize further the above strategy. One of its main drawbacks was the rather cumbersome and multistep sequence developed for the conversion of cyclopropyl ester **31** to lactone **34**. The problem with this conversion was due to the presence of the labile acetonide, that underwent deprotection under the acidic conditions employed ($H_2SO_4$ in EtOH). To circumvent this problem we performed this reaction using $MeSO_3H$ in acetone. Under the modified conditions, we were able to suppress entirely the acetonide deprotection and achieve conversion of cyclopropyl ester **31** to lactone **36** in one step and 77% yield (Scheme 4).[14c] The stereochemistry of **36** was established




Scheme 4. a) $MeSO_3H$/acetone 1:10, 25°C, 12 h, 77%; b) 10% $Pd(OH)_2$, $H_2$, $CH_2Cl_2$, 25°C, 24 h, 82%; c) 1.2 equiv DMP, 25°C, 12 h, 93%.

unambiguously by a single-crystal X-ray diffraction analysis, thus also confirming the outcome of the cyclopropanation sequence.[22]

Reductive debenzylation of **36** produced, after oxidation of the resulting alcohol, ketone **37** in 76% yield (over two steps). Unfortunately, all efforts to homologate this carbonyl group met with failure. Only low yields were obtained with a variety of Wittig ylids, while, under harsh conditions, substantial amounts of decomposition were observed. We hypothesized that the steric hindrance imposed by the bicyclic motif of **37** together with the reactivity of the lactone functionality were responsible for the side products obtained during these reactions. We also attempted to homologate the C11 center in compound **31** but this was similarly problematic, suggesting that a different strategy may be needed for the synthesis of norrisolide.

Despite the disappointing outcome, the strategy presented in Schemes 3 and 4 allowed us to draw several conclusions that are summarized here: a) we found that the Baeyer–Villiger oxidation was reliable and could be used during the last steps of the norrisolide synthesis (conversion of **34** to **35**); b) we established that an appropriately substituted dihydrofuran could be converted to the desired γ-lactone–γ-lactol motif (conversion of **30** to **34**) and we developed a one-pot ring expansion protocol (conversion of **31** to **36**); and c) we found that homologation of the C11 carbonyl group was problematic, at least in the presence bicycles **31** and **37**, indicating that this one carbon extension had to be performed prior to the formation of the bicyclic system. These conclusions paved the way for the development of a second generation strategy toward norrisolide.

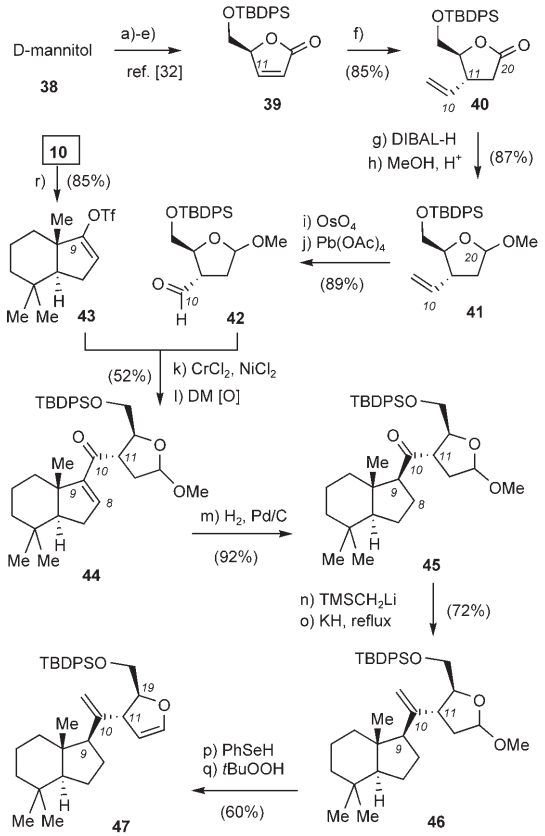
**Synthesis of fragment 47**: Evaluation of the above information led us to consider butenolide **39** as a synthetic precursor of the norrisolide side chain (Scheme 5). We envisioned that this compound would be suitable for the one carbon extension at the C11 center and it could also be converted to a dihydrofuran (such as **47**), a presumed substrate for the key cyclopropanation reaction. Reduction of this plan to practice is shown in Scheme 5.

Enantiomerically pure butenolide **39** was prepared from D-mannitol (**38**) as described in the literature.[32] Reaction of **39** with vinyl magnesium bromide in the presence of catalytic copper(I) bromide produced adduct **40** in 85% yield.[33] This 1,4-addition proceeded exclusively *anti* to the bulky TBDPS silyl ether, setting the desired stereochemistry at C11. DIBAL-H reduction of lactone **40**, followed by an acid-catalyzed protection of the resulting lactol, produced methyl acetal **41** as an unseparable mixture of anomers.[34] Osmium-catalyzed dihydroxylation of **41** afforded, after oxidative cleavage of the resulting diol, aldehyde **42**, which was immediately subjected to coupling with **43**.

Kishi–Nozaki coupling[35] of freshly prepared vinyl triflate **43** with aldehyde **42** followed by Dess–Martin periodinane (DMP) oxidation of the resulting alcohol, produced enone **44** in 52% yield over two steps (Scheme 5). Hydrogenation of the C8–C9 double bond proceeded exclusively from the more accessible α-face of the bicyclic core to form ketone **45** in 92% yield. Standard olefination procedures (Wittig and Tebbe)[36] failed to convert **45** into **46**, presumably due to the steric hindrance of the C10 carbonyl group. We found however, that this reaction could be achieved by a modified Peterson olefination procedure ($TMSCH_2Li$; KH reflux),[37] which produced alkene **45** in 72% yield (over two steps).

Treatment of methyl acetal **46** with phenyl selenol in the presence of $BF_3{\cdot}Et_2O$ produced, after oxidation, enol ether **47** thus setting the stage for the crucial cyclopropanation reaction. Much to our disappointment, however, in sharp contrast to the conversion of **30** to **31** (Scheme 3), this reaction proved to be problematic. Both rhodium- and copper-catalyzed cyclopropanation procedures were tested but resulted in very low conversion of the starting material and low yields of complex product mixtures. The differences in the reactivity profiles between **30** and **47** could be due to the stereochemistry of the C11 and C19 centers. In the case of




Scheme 5. a) 0.01 equiv $SnCl_2$, 2,2-dimethoxypropane/DME 2:3, reflux, 4 h, 78%; b) 2.0 equiv $NaIO_4$, saturated aqueous $NaHCO_3/CH_2Cl_2$ 1:20, 0°C, 2 h, 73%; c) 1.5 equiv $Ph_3P{=}CHCO_2Me$, MeOH, 0°C, 16 h, 70%; d) conc. $H_2SO_4$/MeOH 1:100, 25°C, 1 h, 90%; e) 1.2 equiv TBDPSCl, 5.0 equiv $NH_4NO_3$, DMF, 25°C, 12 h, 92%; f) 1.1 equiv $CH_2{=}CHMgBr$, 10% CuBr·$Me_2S$, THF, −78°C, 15 min then **39**, 45 min, 85%; g) 1.05 equiv DIBAL-H $CH_2Cl_2$, −78°C, 30 min, 99%; h) cat. HCl (~1%), MeOH, 25°C, 1 h, 88%; i) 2.5% $OsO_4$, 1.1 equiv NMO, 0.1 mL pyridine, acetone/$H_2O$ 95:5, 12 h, 97%; j) 1.1 equiv $Pb(OAc)_4$, $CH_2Cl_2$, 25°C, 0.5 h, 92%; k) 5.0 equiv $CrCl_2$, 0.05 equiv $NiCl_2$, DMF, 25°C, 6 h, 53%; l) DMP, $CH_2Cl$, 25°C, 12 h, 99%; m) 10% Pd/C, $H_2$, MeOH, 25°C, 12 h, 92%; n) 3 equiv TMSMeLi, THF, 0 → 25°C, 1 h, 81%; o) 10 equiv KH, THF, reflux, 2 h, 89%; p) 1.5 equiv PhSeH, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 0°C, 0.5 h, 90%; q) 1.8 equiv $Et_3N$, 2.3 equiv *t*BuOOH, 0.3 equiv $Ti(O\mathit{i}Pr)_4$, $CH_2Cl_2$, 0°C, 45 min, 67%; r) 1.1 equiv NaHMDS, 1.1 equiv $PhNTf_2$, THF, −78°C, 4 h, 85%.

dihydrofuran **30** these substituents are *syn* to each other and both shield the β-face of the dihydrofuran directing the cyclopropanation from the α-face. In the case of **47** these substituents are *anti* hindering substantially both faces of the enol ether. The presence of an additional alkene in **47** could also interfere and complicate the results of this cyclopropanation.

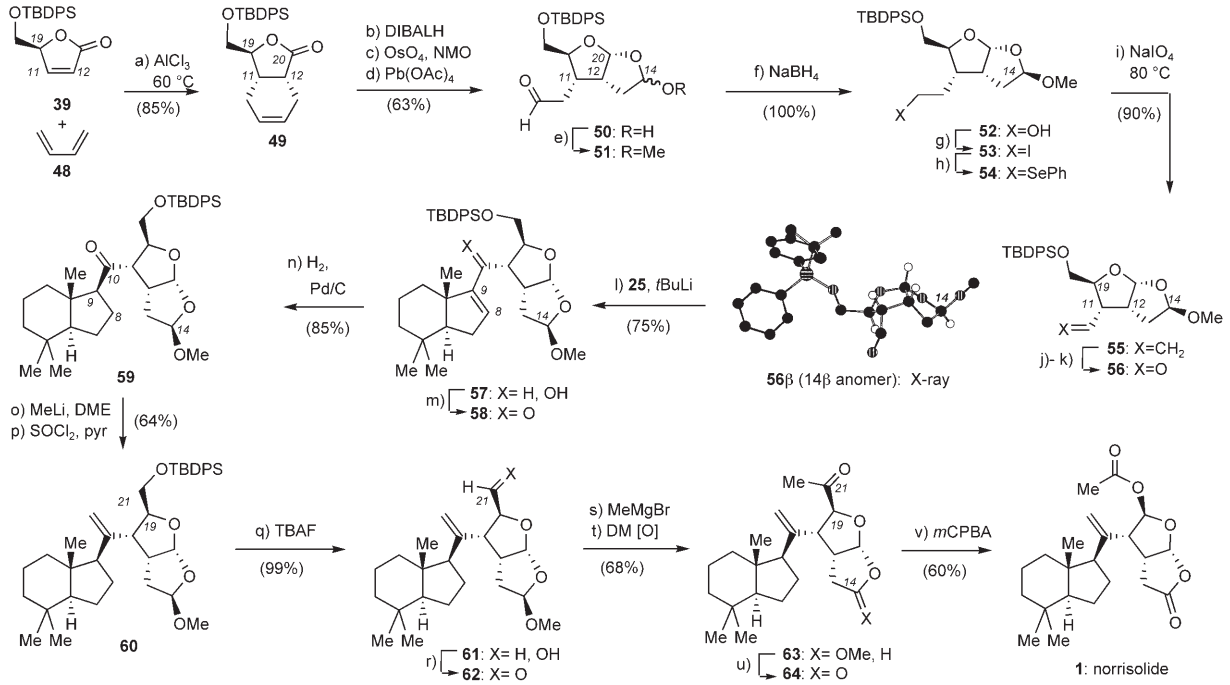
The above studies led us to conclude that the C12 stereocenter should be functionalized prior to constructing the C9–C10 bond. Such a functionality should be able to withstand strong nucleophilic conditions that are required for the installation of the alkene at the C10 center. In the other hand, we were able to construct C9–C10 bond and found also conditions that led to the formation of the terminal alkene. These findings led to our successful campaign toward the synthesis of norrisolide.

**Total synthesis of norrisolide**: Re-evaluation of the above results led us to install the functionalities at the C11 and C12 centers early in the synthesis. Since these substituents needed to be *syn* to each other, we decided to start our strategy with a Diels–Alder reaction between butenolide **39** and butadiene (**48**).[38] Under $AlCl_3$ catalysis this reaction proceeded exclusively from the opposite face of the bulky TBDPS group and afforded **49** in 85% yield as a single enantiomer (Scheme 6).[39] Reduction of the C20 lactone of **49** (DIBAL-H) produced, after oxidative cleavage of the double bond ($OsO_4$, NMO; $Pb(OAc)_4$), lactol **50** in 63% yield as a 1:1 mixture of isomers at the C14 center. Further treatment of **50** with MeOH in the presence of acid catalysis,[40] afforded the isomeric methyl ethers **51** that were easily separable by standard chromatographic techniques. After separation, both C14 anomers of **51** were employed toward the synthesis of norrisolide. Unambiguous stereochemical assignment for these isomers was established at a later stage via a crystal structure of anomer **56**β (see Scheme 6 for X-ray of **56**β). Aldehyde **51** was then converted to selenide **54**, via intermediates **52** and **53**, that, after oxidation ($NaIO_4$) and elimination, produced alkene **55** (61% overall yield from **51**).[41] Dihydroxylation of compound **55** ($OsO_4$, NMO), followed by oxidative cleavage of the resulting diol, gave rise to aldehyde **56** (94% yield over two steps). As mentioned above, the C14β anomer of aldehyde **56** was crystalline and a single-crystal X-ray diffraction analysis confirmed the relative and absolute stereochemistry of all chiral centers.[22]

Guided by our previous results, we attempted the Kishi–Nozaki coupling between aldehyde **56** and vinyl triflate **43**. Unfortunately, this reaction produced the coupled product in less than 10% yield, accompanied by substantial amounts of the reduced *trans*-hydrindane. Suspecting that the reduced reactivity of aldehyde **56** was due to the steric hindrance of its concave bicyclic motif, we decided to alter the size of the vinyl nucleophile. With this in mind, we attempted this coupling using a vinyl lithium as the corresponding nucleophile. As shown in Scheme 2, ketone **10** could be easily converted to vinyl iodide **25** that, upon treatment with *t*Buli and quenching of the anion with aldehyde **56**, afforded the desired coupling product **57**. The resulting allylic alcohol was then oxidized to enone **58** by using Dess–Martin periodinane (71% yield, over two steps, Scheme 6). Compound **58** was hydrogenated across the C8–C9 bond, exclusively from the α-face of the hydrindane core, producing ketone **59** in 85% yield. Interestingly, treatment of the C14α anomer of **58** under the same reaction conditions led to inversion of configuration at the C14 center and isolation of **59**β as the major adduct.

As expected, ketone **59** did not convert to alkene **60** under the standard Wittig conditions. Moreover, the previously explored Peterson olefination reaction was also ineffective, resulting in complete recovery of the starting materi-




Scheme 6. a) 0.33 equiv $AlCl_3$, $CH_2Cl_2$, 60 °C, 6 d, 85%; b) 1.2 equiv DIBAL-H, $CH_2Cl_2$, −78 °C, 0.5 h, 98%; c) 0.01 equiv $OsO_4$, 1.1 equiv NMO, 3 drops pyridine, acetone/$H_2O$ 10:1, 25 °C, 8 h; d) 1.2 equiv $Pb(OAc)_4$, $CH_2Cl_2$, 0 °C, 0.5 h, 64% (over 2 steps); e) 1.2 equiv MeOH, Amberlyst 15, 3 Å MS, $Et_2O$, 25 °C, 10 h, 77% (**51**α/**51**β 1:1); f) 1.5 equiv $NaBH_4$, MeOH, 25 °C, 0.5 h; g) 2.2 equiv imid, 1.1 equiv $PPh_3$, 1.2 equiv $I_2$, THF, 25 °C, 0.5 h, 93% (over 2 steps); h) 0.55 equiv $(PhSe)_2$, 1.5 equiv $NaBH_4$, EtOH, 25 °C, 0.5 h, 92%; i) 1.6 equiv $NaIO_4$, MeOH/$H_2O$ 5:2, 25 °C, 1 h, then $Et_3N$/PhH 1:1, reflux, 0.5 h, 78%; j) 0.05 equiv $OsO_4$, 1.1 equiv NMO, 3 drops pyridine, acetone/$H_2O$ 10:1, 25 °C, 10 h; k) 1.2 equiv $Pb(OAc)_4$, $CH_2Cl_2$, 0 °C, 0.5 h, 94% (over 2 steps); l) 1.5 equiv **25**, 3.0 equiv *t*BuLi, THF, −78 to −40 °C, 0.5 h, then **56**, THF, −78 °C, 1 h, 75%; m) 8.0 equiv DMP, $CH_2Cl_2$, 25 °C, 10 h, 95%; n) 10% Pd/C, $H_2$, MeOH, 25 °C, 10 h, 85%; o) 5.0 equiv MeLi, THF/DME 1:3, 0 °C, 0.5 h, 75%; p) 10.0 equiv $SOCl_2$, 20.0 equiv pyridine, $CH_2Cl_2$, 0 °C, 0.5 h, 85%; q) 2.0 equiv TBAF, THF, 25 °C, 8 h, 99%; r) 3.0 equiv IBX, MeCN, 80 °C, 2 h, 96%; s) 10.0 equiv MeMgBr, THF, 0 °C, 0.5 h, 72%; t) 2.5 equiv DMP, $CH_2Cl_2$, 25 °C, 6 h, 94%; u) 10 equiv $CrO_3$, AcOH/$H_2O$ 2:1, 25 °C, 6 h, 80%; v) 2.5 equiv *m*CPBA, 2.5 equiv $NaHCO_3$, $CH_2Cl_2$, 0 °C, 4 h, 60%.

al. Neither increased temperature nor excess of reagent could overcome the sluggish reactivity of the severely hindered carbonyl group of **59**. However, this ketone could be reduced to the corresponding alcohol with $NaBH_4$, suggesting that it was not completely inert. After substantial experimentation we found that excess MeLi in the presence of 1,2-dimethoxyethane was sufficiently reactive to methylate ketone **59**, affording the corresponding tertiary alcohol in good yield (75%). The latter compound underwent smooth elimination when exposed to 10 equivalents of thionyl chloride in the presence of excess pyridine, to afford terminal alkene **60** as the sole product (85% yield).[42] Fluoride-induced deprotection of the silyl ether and oxidation of the resulting alcohol **61**, furnished aldehyde **62** in 93% combined yield. This compound was rather labile and was treated immediately after a short filtration with excess methyl Grignard producing, after oxidation of the ensuing alcohol, ketone **63** (68% yield, over two steps). Treatment of **63** with $CrO_3$ in aqueous acetic acid produced lactone **64** in 80% yield. Finally, Baeyer–Villiger oxidation of **64** with *m*CPBA in the presence of $NaHCO_3$ led to insertion of the oxygen between the C19 and C21 centers with complete retention of configuration, producing norrisolide (**1**) in 60% yield. The spectra of the final product were identical with that of an authentic sample. Moreover, both samples exhibited dextrorotatory optical rotation and identical biological activity.

## Conclusion

In conclusion, we present herein our studies toward the synthesis of norrisolide (**1**), a marine diterpene with an uncommon chemical structure and unexplored biological properties. The compact and sterically cumbersome structure of **1** led to several unsuccessful reactions and several modifications of the overall synthetic strategy. Nonetheless, exploration of each strategy led to conclusions that were critical to the design of the successful strategy. Moreover, novel approaches for the synthesis of the uncommon γ-lactone–γ-lactol motif of **1** were developed. The synthetic approach is stereoselective and allows construction of analogues of **1** that could be used to evaluate the biological mode of action of this natural product.

## Experimental Section

**General techniques**: All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purifica-

tion except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mm Hg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether ($Et_2O$), dichloromethane ($CH_2Cl_2$), toluene ($PhCH_3$) and benzene (PhH) were purified by passage through a bed of activated alumina. *N,N*-Diisopropylethylamine (DIPEA), diisopropylamine, pyridine, triethylamine (TEA) and boron trifluoride etherate were distilled from calcium hydride prior to use. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mm Hg) and stored over 4 Å molecular sieves until needed. Yields refer to chromatographically and spectroscopically ($^1$H NMR, $^{13}$C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in $cm^{-1}$ units. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: $[\alpha]_\lambda^T$ (*c*: g per 100 mL, solvent). High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

**Enone 13**: Enone **13** was prepared as described in ref. [19b]. $[\alpha]_D^{25} = +285.1$ ($c = 2.1$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 2.94$–$2.71$ (m, 3H), 2.59–2.35 (m, 3H), 2.05 (dd, $J = 13.6$, 5.2 Hz, 1H), 1.82 (dt, $J = 13.6$, 6.0 Hz, 1H), 1.76 (s, 3H), 1.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta =$ 217.2, 197.5, 162.2, 129.6, 48.9, 35.5, 32.8, 28.9, 24.6, 21.3, 10.9.

**Alcohol 14**: Sodium borohydride (5.4 g, 135 mmol) was added, in four portions to enone **13** (48 g, 263 mmol) in methanol (125 mL) cooled to 0 °C, and the reaction was stirred for 30 min. The reaction was quenched by a dropwise addition of saturated aqueous ammonium chloride (500 mL). The mixture was extracted with $Et_2O$ (3 × 200 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum to afford analytically pure alcohol **14** (47 g, 97%). $R_f = 0.2$ (100% $Et_2O$); $[\alpha]_D^{25} = +55.2$ ($c = 1.3$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 3.82$ (dd, $J = 10.4$, 7.6 Hz, 1H), 2.59–2.51 (m, 2H), 2.44–2.37 (m, 2H), 2.15–2.03 (m, 2H), 1.85–1.75 (m, 2H), 1.64 (s, 3H), 1.10 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 198.8$, 167.8, 129.0, 81.0, 45.0, 33.9, 33.3, 29.5, 25.6, 15.2, 10.7; IR (film): $\nu_{max} = 3411$, 2925, 1642, 1448, 1418, 1376, 1330, 1099, 1022 $cm^{-1}$; HRMS: *m/z*: calcd for $C_{11}H_{16}O_2$: 203.1049, found: 203.1051 $[M+Na]^+$.

**Enone 15**: Imidazole (18.4 g, 270 mmol), DMAP (3.3 g, 27 mmol) and TBDPS chloride (72.6 g, 265 mmol) were added sequentially to a solution of alcohol **14** (47 g, 261 mmol) in anhydrous DMF (200 mL) cooled to 0 °C. The ice bath was removed and the mixture was stirred at 35 °C for 12 h under an argon atmosphere. The mixture was diluted with $Et_2O$ (250 mL) and water (300 mL). The aqueous phase was extracted with $Et_2O$ (3 × 300 mL) and the combined organic phases were dried over magnesium sulfate. The solvent was concentrated on the rotary evaporator and the residue was purified using silica gel chromatography (5% $Et_2O$ in hexanes) to yield protected alcohol **15** (84 g, 77%). $R_f = 0.7$ (40% $Et_2O$ in hexanes); $[\alpha]_D^{25} = -40.2$ ($c = 2.77$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$–$7.66$ (m, 4H), 7.40–7.38 (m, 6H), 3.74 (dd, $J = 7.2$, 10.4 Hz, 1H), 2.58–2.19 (m, 6H), 1.97 (ddd, $J = 1.6$, 5.2, 12.8 Hz, 1H), 1.91–1.69 (m, 3H), 1.57 (s, 3H), 1.46 (dt, $J = 5.2$, 14 Hz, 1H), 1.08 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 198.8$, 167.6, 135.9, 135.8, 134.8, 129.6, 127.7, 127.6, 127.5, 81.6, 45.7, 34.0, 33.4, 29.7, 27.0, 19.3, 15.8, 10.5; HRMS: *m/z*: calcd for $C_{27}H_{34}O_2Si$: 441.2211, found 441.2201 $[M+Na]^+$.

**Ketone 16**: Ketone **15** (20 g, 47.7 mmol) was dissolved in DMF (80 mL) under an argon atmosphere and cooled to 0 °C by means of an ice bath. Potassium *tert*-butoxide (10.6 g, 95 mmol) was added to the mixture and it was stirred at 0 °C for 15 min. The ice bath was removed and the mixture was stirred for an additional 45 min. The mixture was again cooled to 0 °C and iodomethane (13.4 g, 95 mmol) was added to the reaction over a five-minute period and the ice bath was removed. The reaction was stirred for 1 h, diluted with $Et_2O$ (350 mL) and washed with aqueous saturated ammonium chloride (400 mL). The aqueous phase was extracted $Et_2O$ (2 × 200 mL) and the combined organic phases were dried over magnesium sulfate, concentrated on the rotary evaporator, and subjected to silica gel chromatography (100% hexanes) to yield **16** (13.6 g, 66%) and starting material **15** (5 g, 25%). $R_f = 0.7$ (50% $Et_2O$ in hexanes); $[\alpha]_D^{25} = -10.6$ ($c = 2.0$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$–$7.68$ (m, 4H), 7.46–7.36 (m, 6H), 5.28 (dd, $J = 3.6$, 1.6 Hz, 1H), 3.96 (dd, $J = 9.2$, 7.6 Hz, 1H), 2.53–2.45 (m, 1H), 2.33 (dd, $J = 14.8$, 8.8 Hz, 1H), 2.17–2.05 (m, 2H), 1.78–1.72 (m, 1H), 1.51–1.44 (m, 1H), 1.32 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H), 1.12 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta =$ 214.9, 153.6, 135.7, 134.2, 133.6, 129.6, 129.5, 127.5, 127.3, 119.8, 81.8, 48.4, 47.1, 37.7, 35.1, 33.5, 28.1, 27.1, 23.7, 19.5, 18.2; IR (film): $\nu_{max} =$ 3070, 2964, 2931, 2857, 1714, 1460, 1427, 1112, 1039, 820, 702 $cm^{-1}$; HRMS: *m/z*: calcd for $C_{28}H_{36}O_2Si$: 455.2383, found: 455.2368 $[M+Na]^+$.

**Alcohol 17**: Ketone **16** (49 g, 113 mmol) was dissolved in methanol (250 mL) and cooled to 0 °C. Sodium borohydride (1.5 g, 37.6 mmol) was added in four portions. The reaction was stirred at 0 °C for 20 min then diluted with $Et_2O$ followed by careful addition of aqueous saturated ammonium chloride (350 mL). The aqueous phase was extracted with $Et_2O$ (3 × 200 mL), dried over magnesium sulfate, filtered and concentrated on the rotary evaporator to yield analytically pure alcohol (48 g, 98%). $R_f =$ 0.3 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25} = -31.9$ ($c = 1.6$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$–$7.66$ (m, 4H), 7.42–7.36 (m, 6H), 5.18 (dd, $J = 3.2$, 1.2 Hz, 1H), 3.82 (dd, $J = 9.2$, 7.2 Hz, 1H), 3.16 (dd, $J = 11.6$, 3.6 Hz, 1H), 2.17 (dd, $J = 14.4$, 8.8 Hz, 1H), 1.96 (dd, $J = 14.8$, 7.2 Hz, 1H), 1.77–1.68 (m, 2H), 1.63–1.57 (m, 1H), 1.20 (s, 3H), 1.07 (s, 9H), 1.06 (s, 3H), 1.06–1.02 (m, 1H), 1.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 155.4$, 136.0, 135.9, 134.7, 134.0, 129.6, 129.5, 127.5, 127.4, 118.6, 84.3, 47.4, 39.4, 37.9, 37.0, 27.8, 27.0, 25.5, 21.5, 19.4, 17.9; IR (film): $\nu_{max} = 3393$, 3069, 3050, 2962, 2932, 2856, 1468, 1427, 1112, 1037, 820, 702 $cm^{-1}$; HRMS: calcd for $C_{28}H_{38}O_2Si$: 457.2540, found: 457.2561 $[M+Na]^+$.

**Xanthate 18**: A solution of alcohol **17** (8.68 g, 20 mmol) in THF (200 mL) under an argon atmosphere was cooled to 0 °C by means of an ice bath. *n*-Butyllithium (16 mL, 40 mmol, 2.5 M in hexanes) was added dropwise and the solution was stirred for 45 min at 0 °C followed by the slow addition of carbon disulfide (4.6 mL, 100 mmol). The solution was stirred for 90 min and iodomethane (7 mL, 120 mmol) was slowly added to the reaction mixture and stirring was continued for an additional 90 min at 0 °C. The reaction was diluted with $Et_2O$ and quenched with saturated ammonium chloride. The aqueous phase was extracted with $Et_2O$ (3 × 100 mL), dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was purified by silica gel chromatography (5% $Et_2O$ in hexanes) to yield xanthate **18** (10.1 g, 95%), as an orange oil. $R_f = 0.9$ (100% hexanes); $[\alpha]_D^{25} = -15.4$ ($c = 3.50$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$–$7.65$ (m, 4H), 7.40–7.38 (m, 6H), 5.24 −5.20 (m, 2H), 3.87 (dd, $J = 9.2$, 7.6 Hz, 1H), 2.54 (s, 3H), 2.17 (dd, $J =$ 14.8, 9.2 Hz, 1H), 1.96 (dd, $J = 15.2$, 7.6 Hz, 1H), 1.91–1.84 (m, 2H), 1.77 (dt, $J = 13.2$, 3.2 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.20–1.09 (m, 1H), 1.08 (s, 9H), 1.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 154.0$, 135.9, 135.8, 134.6, 133.8, 129.7, 129.5, 127.6, 127.4, 119.6, 89.4, 84.1, 47.3, 39.3, 37.8, 36.4, 27.0, 25.5, 23.6, 23.3, 19.4, 18.7, 18.0; IR (film): $\nu_{max} = 3070$, 2964, 2931, 2856, 1233, 1215, 1112, 1063, 1041 $cm^{-1}$; HRMS: *m/z*: calcd for $C_{30}H_{40}O_2S_2Si$: 547.2137, found 547.2119 $[M+Na]^+$.

**Alkene 19**: Tributyl tin hydride (17.5 g, 60 mL) and AIBN (0.5 g, 3 mmol) was added to a solution of xanthate **18** (10.1 g, 19 mmol) in toluene (100 mL). The mixture was rapidly brought to reflux by immersing

into a silicon oil bath preheated to 150 °C and heated under reflux for 20 min. The reaction was cooled to room temperature and the solvent removed on the rotary evaporator. The residue was purified by silica gel chromatography (100 % hexanes) to yield **19** (6.6 g, 86 %) as a clear oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.82 (dd, J = 7.6, 2.0 Hz, 4H), 7.53–7.44 (m, 6H), 5.21 (dd, $J$ = 3.2, 1.6 Hz, 1H), 3.99 (dd, $J$ = 9.2, 8.0 Hz, 1H), 2.25 (dd, $J$ = 14.8, 9.2 Hz, 1H), 2.04 (dd, $J$ = 14.4, 7.2 Hz, 1H), 1.91–1.87 (m, 1H), 1.82 (dt, $J$ = 13.6, 3.6 Hz, 1H), 1.57–1.46 (m, 2H), 1.33 (s, 3H), 1.22 (s, 9H), 1.22–1.12 (m, 1H), 1.18 (s, 3H), 1.10 (s, 3H), 1.06–0.98 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 155.8, 135.9, 135.8, 134.7, 134.0, 129.4, 129.3, 127.3 (2), 116.1, 84.6, 47.6, 40.6, 39.7, 36.9, 34.0, 30.5, 28.8, 27.2, 19.6, 19.3, 18.1; HRMS: $m/z$: calcd for $C_{28}H_{38}OSi$: 441.2590, found 441.2568 $[M+Na]^+$.

**Alcohol 20**: Alkene **19** (21 g, 50 mmol) was dissolved in anhydrous THF (250 mL). The solution was cooled to 0 °C and borane/dimethyl sulfide complex (6 mL, 60 mmol, 10 M in THF) was added and the ice bath removed. The solution was stirred for 5 h at which time the temperature was increased to 30 °C and the reaction was stirred for 12 h. The reaction was cooled to 0 °C and treated with a mixture of 30 % aqueous $H_2O_2$/3 M NaOH solution (1 L, 1:1), slowly added maintaining the reaction temperature below 35 °C. The solution was removed from the ice bath and stirred for 6 h at 25 °C. The reaction was judged complete by the disappearance of the borane adduct (by TLC analysis) and the formation of compound **20** ($R_f$ = 0.65, 50 % $Et_2O$ in hexanes) together with the *cis*-fused isomer ($R_f$ = 0.70, 50 % $Et_2O$ in hexanes). The reaction was quenched by the careful addition of saturated sodium thiosulfate at 0 °C, maintaining the internal temperature below 30 °C. The solution was stirred for 12 h after which time it was diluted with $Et_2O$ and the aqueous phase was extracted with $Et_2O$ (3 × 100 mL). The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated to give an oily residue that was purified using silica gel chromatography (100 % hexanes → 50 % $Et_2O$ in hexanes) to yield the *cis* isomer (4.4 g) and **20** (12.7 g, 78 %, 2.28:1 *trans*/*cis*). $R_f$ = 0.65 (50 % $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +26.3 ($c$ = 2.52, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.72–7.69 (m, 4H), 7.47–7.38 (m, 6H), 4.21 (dt, $J$ = 10.0, 3.2 Hz, 1H), 3.83 (t, $J$ = 8.8 Hz, 1H), 2.06 (dt, $J$ = 14.0, 9.2 Hz, 1H), 1.69–1.16 (m, 6H), 1.12 (s, 9H), 1.01 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.92 (d, J = 10.0 Hz, 1H), 0.79 (dt, $J$ = 12.8, 3.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.8, 135.7, 134.0, 129.6, 129.5, 127.4, 80.1, 70.6, 45.4, 42.3, 42.0, 38.0, 33.9, 33.2, 27.1, 21.8, 19.5, 19.4, 14.3; IR (film): $\nu_{max}$ = 3390, 3071, 3049, 2928, 2858, 1112, 703 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{28}H_{40}O_2Si$: 459.2695, found 459.2701 $[M+Na]^+$.

**Xanthate 21**: A solution of alcohol **20** (18 g, 41 mmol) in THF (350 mL) under an argon atmosphere was cooled to 0 °C and treated with *n*-butyllithium (34 mL, 85 mmol, 2.5 M in hexanes), added dropwise over 45 min, followed by a slow addition of carbon disulfide (15.2 g, 200 mmol). After stirring for 90 min, iodomethane (19 mL, 300 mmol) was slowly added and the reaction was stirred for an additional 90 min at 0 °C. The reaction was diluted with $Et_2O$ and quenched with saturated ammonium chloride. The aqueous phase was extracted with $Et_2O$ (3 × 100 mL), dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was purified by silica gel chromatography (5 % $Et_2O$ in hexanes) to yield xanthate **21** (22.1 g, 100 %) as an orange oil. $R_f$ = 0.3 (50 % $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +9.4 ($c$ = 1.9, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.68–7.62 (m, 4H), 7.46–7.35 (m, 6H), 5.81 (dt, $J$ = 9.6, 2.8 Hz, 1H), 3.76 (t, $J$ = 8.8 Hz, 1H), 2.49 (s, 3H), 2.23 (dt, $J$ = 14.4, 9.2 Hz, 1H), 1.63–1.51 (m, 4H), 1.44–1.36 (m, 3H), 1.07 (s, 9H), 1.03 (s, 3H), 0.95 (s, 3H), 0.81 (s, 3H), 0.74–0.68 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.8, 135.7, 134.1, 133.7, 129.5, 127.4, 82.8, 80.1, 56.2, 44.8, 41.7, 38.7, 37.8, 33.3, 33.0, 27.1, 21.9, 19.5, 19.4, 19.0; IR (film): $\nu_{max}$ = 3070, 2954, 2927, 2857, 1461, 1233, 1201, 1113, 1052, 702 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{30}H_{42}O_2S_2Si$: 549.2293, found 549.2289 $[M+Na]^+$.

**Silyl ether 22**: Xanthate **21** (22 g, 41 mmol) was dissolved in toluene (175 mL). Tributyl tin hydride (35 g, 120 mmol) and AIBN (0.7 g, 4 mmol) were added and the mixture was rapidly brought to reflux by immersing it in a pre-heated silicon oil bath and reflux continued for 20 min. The reaction was cooled to room temperature and diluted with $Et_2O$ and quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted with $Et_2O$ (3 × 100 mL), dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was purified by silica gel chromatography (5 % $Et_2O$ in hexanes) to yield silyl ether **22** (22.1 g, 100 %) as an orange oil. $R_f$ = 0.9 (100 % hexanes); $[\alpha]_D^{25}$ = +4.6 ($c$ = 1.10, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.73–7.70 (m, 4H), 7.47–7.38 (m, 6H), 3.58 (t, $J$ = 7.6 Hz, 1H), 1.75–1.33 (m, 8H), 1.12 (s, 9H), 1.00 (s, 3H), 0.99–0.85 (m, 2H), 0.89 (s, 3H), 0.78 (s, 3H), 0.77–0.70 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.9, 135.8, 134.8, 134.2, 129.3, 129.2, 127.2 (2), 83.0, 52.3, 43.6, 41.7, 37.8, 33.1, 32.7, 29.9, 27.2, 20.8, 20.4, 19.7, 19.5, 12.5; IR (film): $\nu_{max}$ = 3070, 2954, 2928, 2859, 1111, 702 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{28}H_{40}OSi$: 443.2746, found 443.2761 $[M+Na]^+$.

**Alcohol 23**: Compound **22** (15 g, 35.7 mmol) was dissolved in THF (100 mL) at 25 °C and treated with TBAF (100 mL, 100 mmol, 1 M in THF). The mixture was stirred for 8 h, concentrated on the rotary evaporator and purified by silica gel chromatography to afford alcohol **23** (6.4 g, 99 %). $R_f$ = 0.3 (50 % $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +11.8 ($c$ = 6, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.53 (m, 1H), 2.01 (m, 1H), 1.71–1.30 (m, 6H), 1.06–0.87 (m, 3H), 0.87 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 82.5, 53.1, 42.7, 41.6, 37.3, 33.0, 32.7, 29.4, 20.7, 20.1, 19.5, 11.7; IR (film): $\nu_{max}$ = 3044, 2923, 2867, 2844, 1459, 1383, 1104, 1064, 1020, 702 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{12}H_{22}ONa$: 205.1568, found 205.1572 $[M+Na]^+$.

**Ketone 10**: Alcohol **23** (6.4 g, 35.1 mmol) was dissolved in $CH_2Cl_2$ (200 mL). Celite (20 g) followed by PCC (19.7 g, 93 mmol) were added and the heterogeneous mixture was stirred for 12 h at 25 °C. The reaction mixture was filtered through Celite and concentrated to a residue on the rotary evaporator. The residue was purified by silica gel chromatography (5 % $Et_2O$ in hexanes) to afford ketone **10** (5.8 g, 92 %). $R_f$ = 0.6 (50 % $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +107.0 ($c$ = 3.80, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.40 (dd, $J$ = 19.2, 8.8 Hz, 1H), 2.09–1.99 (m, 1H), 1.91–1.84 (m, 1H), 1.73–1.56 (m, 4H), 1.47 (dt, $J$ = 13.6, 3.2 Hz, 1H), 1.30–1.03 (m, 3H), 0.94 (s, 3H), 0.92 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 221.3, 54.1, 48.1, 41.3, 35.4, 34.0, 32.4, 32.1, 21.5, 19.2, 19.1, 15.8; IR (film): $\nu_{max}$ = 1739, 1474, 1459, 1369, 1120, 1020 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{12}H_{20}ONa$: 203.1412, found 203.1431 $[M+Na]^+$.

**Hydrazone 24**: Ketone **10** (503 mg, 2.7 mmol) was dissolved in ethanol (10 mL) and treated with hydrazine monohydrate (4.2 mL, 86.5 mmol) and triethylamine (2.2 mL, 15.8 mmol). The reaction was stirred at reflux for 12 h. The reaction was cooled to 25 °C and the solvent removed under vacuum. The residue was taken up in ethyl acetate and was washed with water to neutrality, the combined organic phases were dried over sodium sulfate and concentrated on the rotary evaporator. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.65 (br s, 2H), 2.21–2.02 (m, 2H), 1.77–1.70 (m, 2H), 1.59–1.37 (m, 4H), 1.22–1.01 (m, 3H), 0.88 (s, 3H), 0.83 (s, 6H). This compound was recrystallized from ethanol/$H_2O$ and the structure was confirmed by X-ray analysis.

**Vilyl iodide 25**: Crude hydrazone **24** (524 mg, 2.7 mmol) was dissolved in $Et_2O$ (100 mL) and treated with DBU (4.1 g, 27 mmol). Iodine, dissolved in $Et_2O$, was added dropwise to the stirring solution until a light brown color persists (observed nitrogen evolution). Excess saturated sodium thiosulfate was added and the mixture was stirred vigorously for 10 min. The aqueous phase was extracted with $Et_2O$ (3 × 50 mL) and washed with brine. The organic phases were collected, dried over sodium sulfate, and the solvent removed on the rotary evaporator. The residue was purified on silica gel with 100 % hexane to yield vinyl iodide **25** (510 mg, 62 %). $R_f$ = 0.9 (100 % hexanes); $[\alpha]_D^{25}$ = −5.93 ($c$ = 4.85, $CH_2Cl_2$); $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ = 5.97 (t, $J$ = 2.4 Hz, 1H), 1.83–1.73 (m, 2H), 1.53–1.39 (m, 4H), 1.28–1.24 (m, 2H), 1.09–1.02 (m, 1H), 0.94–0.87 (m, 2H), 0.79 (s, 3H), 0.77 (s, 3H), 0.75 (s, 3H); $^{13}$C NMR (100 MHz, $C_6D_6$): $\delta$ = 137.1, 114.4, 58.0, 50.5, 41.5, 37.3, 33.2, 32.6, 31.3, 21.4, 20.3, 17.4; IR (film): $\nu_{max}$ = 2997, 2928, 2863, 1457, 1373, 987, 847, 803, 680 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{12}H_{19}I$: 291.0569, found 291.0551 $[M+H]^+$.

**Acetonide 27**: Iodine (14.21 g, 0.056 mol) was added to a suspension of D-mannose (**26**) (50 g, 0.28 mol) in acetone (2.5 L) and the mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched at 0 °C with sodium thiosulfate and sodium bicarbonate and the organic residues extracted with chloroform. After washing with sodium bicarbonate (3 ×

200 mL), the organic layer was dried over $MgSO_4$, concentrated and recrystallized from acetone/hexane to produce **27** (60 g, 0.24 mol, 85%) as a colorless solid. $R_f = 0.33$ (silica gel, 50% $Et_2O$ in hexanes); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.38 (d, $J = 2.4$ Hz, 1H), 4.81 (dd, $J = 3.6$, 6 Hz, 1H), 4.62 (d, $J = 6.0$ Hz, 1H), 4.40 (m, 1H), 4.18 (dd, $J = 3.6$, 7.2 Hz, 1H), 4.06 (m, 2H), 2.57 (brs, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 112.4, 108.9, 100.9, 85.3, 79.9, 79.5, 73.2, 66.3, 26.7, 25.8, 25.1, 24.4.

**Chloride 28**: A solution of compound **27** (20 g, 0.077 mol) in dry methylene chloride (200 mL) was treated sequentially with DMAP (5.64 g, 0.046 mol), tosyl chloride (16.32 g, 0.092 mol) and triethylamine (10.7 mL, 0.077 mol). The reaction mixture was stirred at 25°C until TLC showed completion of reaction (approx. 2 h) at which time the solution was washed with aqueous copper sulfate, sodium bicarbonate and extracted with $Et_2O$. The organic layer was extracted with sodium chloride ($3 \times 200$ mL), dried over $MgSO_4$, concentrated and purified by chromatography (silica gel, 10–50% $Et_2O$ in hexanes) to afford **10** (13.5 g, 46.2 mmol, 60%) as a viscous, amber-colored oil. $R_f = 0.80$ (50% $Et_2O$ in hexanes); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.07 (s, 1H), 4.96 (d, $J$ = 5.6 Hz, 1H), 4.89 (m, 1H), 4.44 (m, 1H), 4.21 (dd, $J = 3.6$, 11.2 Hz, 1H), 4.10 (dd, $J = 6.0$, 8.8 Hz, 1H), 4.02 (dd, $J = 4.4$, 8.8 Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 113.2, 109.4, 97.5, 89.1, 82.3, 78.5, 72.3, 66.7, 27.0, 25.9, 25.2, 24.7.

**Benzyl ether 30**: Napthalene (4.8 g, 37.5 mmol) was dissolved in THF (200 mL) under an argon atmosphere. Sodium (2.9 g, 125 mmol) was added over a period of 45 min and the solution was stirred at ambient temperature until a deep green color was observed. Chloride **28** (3.5 g, 12.5 mmol) dissolved in THF (100 mL) was added to the naphthalene/sodium mixture over a period of 4 h, taking care that the green color persisted through the entire addition. The reaction was judged complete by consumption of the starting material (TLC) and the solution was carefully filtered through a plug of Celite. The solution was diluted with $Et_2O$ (300 mL) and washed with water (300 mL) and by brine (300 mL). The organic phase was dried over magnesium sulfate and the solvent was removed on the rotary evaporator. The residue was purified by flash chromatography ($R_f = 0.3$; 70% $Et_2O$ in hexanes) and the semi pure glycal **29** was taken to the next step directly. A solution of glycal **29** (2.0 g, 10 mmol) in THF (5 mL) at 0°C was treated under argon with sodium hydride (283 mg, 12 mmol), benzyl bromide (2.02 g, 12 mmol), and tetrabutyl ammonium iodide (0.198 g, 0.54 mmol). The reaction mixture was allowed to warm up to 25°C and stirred for 2 h at which time the TLC showed disappearance of the starting material. The reaction was quenched with brine and extracted with $Et_2O$. The organic layer was washed with brine ($3 \times 50$ mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, 5–30% $Et_2O$ in hexanes) to produce compound **30** (2.5 g, 9 mmol, 90%) as a viscous, bright-yellow oil. $R_f = 0.65$ (30% $Et_2O$ in hexanes); $[\alpha]_D^{25} = -103.4$ ($c$ = 1.0, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.32 (m, 5H), 6.62 (d, $J$ = 2.4 Hz, 1H), 5.29 (t, $J = 2.8$ Hz, 1H), 4.66 (m, 1H), 4.55 (m, 3H), 4.44 (dd, $J = 4.4$, 5.2 Hz, 1H), 4.12 (m, 1H), 3.99 (m, 1H), 1.47 (s, 3H), 1.40 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 150.3, 138.2, 128.1, 127.4, 127.3, 108.5, 101.7, 83.9, 79.1, 73.0, 70.9, 65.9, 26.6, 25.3; IR (film): $\nu_{max}$ = 2978, 2925, 1606, 1064.

**Cyclopropyl ester 31**: Benzyl ether **30** (7.75 g, 0.028 mol) was dissolved in $CH_2Cl_2$ (30 mL) and a catalytic amount of rhodium acetate (0.023 g, 0.01 equiv) was added to give a blue-green colored solution. As the solution was being stirred, ethyl diazoacetate (3.52 g, 0.031 mol), dissolved in $CH_2Cl_2$ (40 mL) was added via syringe pump over a period of 14 h. The reaction was carried out at 25°C and open to the atmosphere. After the completion of addition, the mixture was allowed to stir for another 3 h and then concentrated to reveal a blue, viscous oil. After silica gel separation the two isomeric cyclopropyl esters (3.7 g, 0.013 mmol, 45%) (4:1 ratio at the C13 center) were isolated together and were taken forward to the remaining steps. Major isomer: $R_f = 0.75$ (50% $Et_2O$ in hexanes); $[\alpha]_D^{25} = -4.95$ ($c = 0.93$, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35 (m, 5H), 4.71 (d, $J = 11.6$ Hz, 1H), 4.59 (d, $J = 12$ Hz, 1H), 4.35 (m, 2H), 4.18 (d, $J = 4.8$ Hz, 1H), 4.07 (m, 3H), 3.95 (dd, $J = 6.0$, 8.4 Hz, 1H), 3.68 (m, 1H), 2.34 (t, $J = 4.4$, 4.8 Hz, 1H), 1.89 (d, $J = 2.8$ Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 1.24 (t, $J = 6.8$, 7.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.6, 137.5, 128.2, 127.6, 127.5, 108.6, 81.9, 78.8, 72.7, 72.1, 66.5, 64.9, 60.7, 28.5, 26.7, 25.4, 21.4, 14.3; IR (film): $\nu_{max}$ = 2984, 2935, 1715, 1268, 1187, 1097 $cm^{-1}$; HRMS: $m/z$: calcd for $C_{20}H_{26}O_6Na$: 385.1627, found 385.1623 $[M+Na]^+$.

**Diol 32**: A solution of cyclopropyl ester **31** (2.5 g, 6.90 mmol) in EtOH (75 mL) was treated with sulfuric acid (1.0 mL) and the reaction was stirred vigorously for 24 h. The reaction was quenched with triethylamine and concentrated under reduced pressure. The mixture was taken up again in ethyl acetate and washed with brine ($1 \times 100$ mL). The compound was dried over magnesium sulfate, filtered and concentrated in vacuo. Silica gel column chromatography (0–60% ethyl acetate in hexanes) yielded diol **32** (1.98 g, 78%, 5.78 mmol) as a clear foam. $R_f = 0.2$ (80% $Et_2O$ in hexanes); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.30–7.25 (m, 5H), 4.78 (d, $J = 5.6$ Hz, 1H), 4.55 (d, $J = 5.6$ Hz, 1H), 4.38 (d, $J = 3.4$ Hz, 1H), 4.25 (d, $J = 3.6$ Hz, 1H), 4.22–4.12 (m, 5H), 3.91 (brs, 1H), 3.88–3.58 (m, 6H), 2.8 (brs, 1H), 2.38 (m, 1H), 1.85 (m, 1H), 1.26–1.18 (m, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ = 171.01, 138.30, 128.07, 127.76, 127.35, 125.45, 108.84, 87.32, 80.15, 79.15, 71.15, 69.78, 64.52, 62.15, 60.71, 28.85, 22.15, 19.05, 16.17.

**Ketone 34**: A solution of diol **32** (0.126 g, 0.33 mmol) in 1:1 mixture of THF and water (5 mL each) was treated at 25°C with sodium periodate (0.211 g, 0.989 mmol) for 30 min. The reaction turned cloudy after some time and was quenched, when TLC showed completion of reaction, with sodium thiosulfate and sodium bicarbonate. The reaction was extracted with ethyl acetate ($3 \times 30$ mL), dried over magnesium sulfate and concentrated under reduced pressure and dried under high vacuum. The residue was treated with THF (5 mL) and $MeTi(OiPr)_3$ (5 mL, 5 mmol, 0.5 M) at 0°C. The reaction was brought up to 25°C after 30 min and stirred for another 3 h. Afterwards, the reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate ($3 \times 30$ mL) and dried with magnesium sulfate. After concentration, the compound (0.080 g, 0.31 mmol) was run through a quick silica gel column and subjected to Dess–Martin periodinane oxidation conditions. The reaction took 1 h to go to completion at which time it was quenched with sodium thiosulate and sodium bicarbonate. After extraction with ethyl acetate ($3 \times 25$ mL) the organic solution was dried over magnesium sulfate and concentrated in vacuo. Column chromatography gave **33** (0.060 g, 0.165 mmol) as a light yellow oil that was subjected to the next step. A solution of ester **33** (0.929 g, 2.64 mmol) in dry $CH_2Cl_2$ (90 mL) was cooled to −20°C and treated under argon with methanesulfonic acid (1 mL, 6 equiv) added dropwise via syringe. The temperature of the reaction mixture was allowed to rise to −5°C where it was stirred for 6 h. During this time the reaction mixture changed from a light yellow to a dark brown color. At the end of 6 h, the dry-ice bath was exchanged for an ice-water bath and allowed to stir for another 6 h. Upon completion of the reaction (TLC test, the cyclized product is distinctly more polar than the starting material) the reaction was quenched with a mixture of triethylamine and sodium bicarbonate and extracted with $Et_2O$. The organic layer was washed with sodium bicarbonate ($3 \times 50$ mL), dried over $MgSO_4$ and concentrated. The resulting crude solid was purified by chromatography (silica gel, 30–80% $Et_2O$ in hexanes) to afford ketone **34** (0.491 g, 1.76 mmol, 67%) as a light yellow solid. $R_f = 0.40$ (80% $Et_2O$ in hexanes); $[\alpha]_D^{25} = -53.5$ ($c = 0.85$, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34 (t, $J = 7.2$, 10 Hz, 3H), 7.23 (d, $J = 6.4$ Hz, 2H), 6.33 (d, $J = 5.6$ Hz, 1H), 4.54 (m, 2H), 4.46 (d, $J = 11.6$ Hz, 1H), 4.15 (d, $J = 4$ Hz, 1H), 3.23 (q, $J = 5.6$, 6.0 Hz, 1H), 2.84 (dd, $J = 19.2$, 11.6 Hz, 1H), 2.33 (dd, $J = 5.2$, 18.8 Hz, 1H), 2.27 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 204.8, 173.5, 136.2, 128.5, 128.2, 127.6, 107.4, 85.4, 85.1, 72.2, 44.3, 31.1, 28.4; IR (film): $\nu_{max}$ = 3634, 3528, 2918, 2861, 1780, 1731 $cm^{-1}$; HRMS: $m/z$: calcd for $C_{15}H_{16}O_5Cs$: 409.0049, found: 409.0055 $[M+Cs]^+$.

**Lactone 35**: A suspension of urea/30% hydrogen peroxide (0.447 g, 4.75 mmol) in dry $CH_2Cl_2$ (20 mL) was cooled to 0°C and treated with trifluoroacetic anhydride (0.336 mL, 2.38 mmol) added dropwise over a 5-min period. The reaction mixture was brought up to 25°C, allowed to stir for 30 min and added via cannula to a solution of ketone **34** (0.164 g, 0.594 mmol) in dry $CH_2Cl_2$ (5 mL). After stirring at 25°C for 2 h (completion by TLC), the reaction was quenched with sodium thiosulfate and

sodium bicarbonate at 0 °C and stirred for 0.5 h. The organic layer was diluted with $Et_2O$ and washed with sodium bicarbonate (3×20 mL). The organic layer was collected, dried over $MgSO_4$, concentrated and purified (silica gel, 20–60% $Et_2O$ in hexanes) to afford compound **35** (0.12 g, 69%) as a white powdery solid. $R_f$=0.30 (70% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +68.1 ($c$=0.7, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35 (t, $J$= 7.2, 9.2 Hz, 3H), 7.30 (d, $J$=7.6 Hz, 2H), 6.45 (d, $J$=4.0 Hz, 1H), 6.04 (d, $J$=6.0 Hz, 1H), 4.63 (d, $J$=11.6 Hz, 1H), 4.49 (d, $J$=11.6 Hz, 1H), 3.88 (qr, $J$=4 Hz, 1H), 3.10 (m, 1H), 2.79 (dd, $J$=9.2, 18.8 Hz, 1H), 2.48 (dd, $J$=1.6, 18.8 Hz, 1H), 2.12 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.7, 169.2, 136.5, 128.6, 128.4, 127.8, 105.3, 95.1, 81.9, 73.5, 41.7, 33.2, 21.1; IR (film): $\nu_{max}$ = 2919, 2854, 1788, 1745, 1374, 1235, 1138 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{15}H_{16}O_6Na$: 315.0845, found: 315.0859 $[M+Na]^+$.

**Lactone 36**: 10% methanesulfonic acid solution (1.0 mL) in acetone at 25 °C was added to a solution of the cyclopropyl ester **31** (0.44 mmol) in acetone (1 mL). The reaction mixture was stirred overnight, quenched by triethylamine (0.26 mL) in an ice bath and then stirred for 30 min. The solution was concentrated in vacuo and purified by column chromatography (20 → 60% $Et_2O$ in petroleum ether) to give the γ-lactone **36** as a white powdery solid. $[\alpha]_D^{25}$ = −21.7 ($c$=1.68, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.31 (m, 5H), 6.16 (d, $J$=5.6 Hz, 1H), 4.63 (d, $J$=1.6 Hz, 2H), 4.43 (q, $J$=7.6 Hz, 1H), 4.14 (dd, $J$=8.8, 6.0 Hz, 1H), 4.02–3.99 (m, 2H), 3.91 (d, $J$=2.8 Hz, 1H), 3.22–3.19 (m, 1H), 2.84 (dd, $J$=18.8, 11.6 Hz, 1H), 2.35 (dd, $J$=18.8, 5.2 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.4, 137.3, 128.5, 128.0, 127.6, 109.3, 107.2, 83.4, 81.9, 72.1, 67.2, 45.0, 31.4, 26.8, 25.4; HRMS: $m/z$: calcd for $C_{18}H_{22}O_6Na$: 357.1314, found 357.1330 $[M+Na]^+$.

**Ketone 37**: Benzyl alcohol **36** (200 mg, 0.6 mmol) was dissolved in THF (10 mL), treated with activated 10% $Pd(OH)_2$ (25 mg) and stirred under an atmosphere of hydrogen for 24 h. The solution was filtered through a plug of celite, concentrated on the rotary evaporator and the residue was applied to silica gel chromatography (60% $Et_2O$ in hexanes) to afford of the corresponding alcohol **37a** (120 mg, 82%). $R_f$=0.3 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = −20 ($c$=0.66, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 6.20 (d, $J$=6 Hz, 1H), 4.32 (m, 1H), 4.25 (m, 1H), 4.20 (m, 1H), 3.98 (m, 1H), 3.95 (dd, $J$=2.8, 8 Hz, 1H), 3.17 (m, $J$=5.6 Hz, 1H), 2.90 (dd, $J$=11.6, 19.2 Hz, 1H), 2.46 (d, $J$=3.2 Hz, 1H), 2.42 (d, $J$=5.2 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 174.4, 109.8, 107.5, 82.2, 76.7, 73.0, 67.7, 47.3, 31.5, 26.9, 25.1; HRMS: $m/z$: calcd for $C_{11}H_{16}O_6Na$: 267.0845, found: 267.0865 $[M+Na]^+$. A solution of alcohol **37a** (120 mg, 0.5 mmol) in $CH_2Cl_2$ (25 mL) was treated with DMP (266 mg, 0.6 mmol) at 25 °C for 12 h. The solution was diluted with saturated aqueous sodium thiosulfate (20 mL) and saturated sodium hydrogen carbonate (20 mL) and stirred vigorously until the biphasic mixture was visibly clear. The aqueous phase was extracted with $CH_2Cl_2$ (3× 20 mL). The combined organic phases were dried over sodium sulfate and concentrated on the rotary evaporator. The residue was purified on silica gel (50% $Et_2O$ in hexanes) to yield ketone **37** (107 mg, 93%). $R_f$= 0.5 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +76 ($c$=0.61, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.43 (d, $J$=5.6 Hz, 1H), 4.43 (m 1H), 4.24 (s, 1H), 4.09 (m, 2H), 3.28 (m, 1H), 2.88 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 209.5, 171.9, 110.5, 104.8, 79.2, 75.5, 64.2, 46.7, 31.4, 25.9, 25.2; HRMS: $m/z$: calcd for $C_{11}H_{16}O_6Na$: 265.0688, found: 265.0691 $[M+Na]^+$.

**Butenolide 39**: Hydroxymethyl butenolide (3.0 g, 26.3 mmol) and ammonium nitrate (6.4 g, 80.0 mmol) were dissolved in DMF (100 mL) under an atmosphere of argon and cooled to 0 °C. TBDPSCl (7.4 g, 27.0 mmol) was added and the reaction was stirred 30 min, the ice bath was then removed and the reaction stirred for an additional 12 h. The mixture was diluted with $Et_2O$ (150 mL) and washed with $H_2O$ (300 mL). The aqueous phase was extracted with $Et_2O$ (3×50 mL) and the combined organic phases were dried over magnesium sulfate and concentrated on the rotary evaporator. The crude residue was purified on silica gel (20% $Et_2O$ in hexanes) to yield compound **39** (8.8 g, 95%). $R_f$=0.8 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = −80.7 ($c$=3.95, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.66–7.64 (m, 4H), 7.46–7.39 (m, 7H), 6.18 (dd, $J$=6.0, 2.0 Hz, 1H), 5.08 (m, 1H), 3.91–3.89 (m, 2H), 1.05 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 154.0, 135.5, 135.4, 132.7, 132.4, 129.9, 127.8, 122.6, 83.2, 63.2, 26.6, 19.1.

**Lactone 40**: Copper bromide/dimethyl sulfide complex (3.5 g, 10.2 mmol) was dissolved in THF (20 mL) under an argon atmosphere and cooled to −78 °C (dry ice/acetone). Vinylmagnesium bromide (11 mL, 11 mmol, 1 M in THF) was added via syringe and the solution was stirred at −78 °C for 15 min. Butenolide **39** (2.9 g, 8.2 mmol) dissolved in THF (20 mL) was added to the stirring solution via syringe. When the addition was complete the dry ice bath was replaced with an ice water bath and the solution was stirred for 1 h. The solution was diluted with $Et_2O$ (75 mL) and saturated aqueous ammonium chloride (150 mL). The aqueous phase was extracted with $Et_2O$ (3×75 mL). The combined organic phases were dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was purified on silica gel (40% $Et_2O$ in hexanes) to afford (3.5 g, 85%). $R_f$=0.4 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +38.3 ($c$=2.3, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.69–7.66 (m, 4H), 7.24–7.37 (m, 6H), 5.76 (m, 1H), 5.14 (s, 1H), 5.09 (d, $J$=17.6 Hz, 1H), 4.26 (m, $J$=3.2 Hz, 1H), 3.93 (dd, $J$=2.8, 11.6 Hz, 1H), 3.73 (dd, $J$=3.2, 11.6 Hz, 1H), 3.21 (m, $J$=7.6 Hz, 1H), 2.83 (dd, $J$=9.2, 17.6 Hz, 1H), 2.45 (dd, $J$=8.4, 17.6 Hz, 1H), 1.07 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.9, 136.4, 135.6, 135.5, 132.9, 132.5, 129.9, 127.8, 117.4, 84.5, 63.3, 40.7, 35.0, 26.7, 19.2; HRMS: $m/z$: calcd for $C_{23}H_{28}O_3SiNa$: 403.1706, found: 403.1729 $[M+Na]^+$.

**Alkene 41**: Lactone **40** (2.2 g, 5.8 mmol) was dissolved in $CH_2Cl_2$ (75 mL) and cooled to −78 °C (dry ice/acetone). DIBAL (5.9 mL, 5.9 mmol, 1 M in $CH_2Cl_2$), was added dropwise over 5 min, and the solution was stirred for 30 min. Methanol (10 mL) was added and the dry ice bath was removed. Stirring was continued as the reaction warmed to 25 °C (30 min). Saturated aqueous ammonium chloride (100 mL) was added and the mixture was stirred for an additional 30 min then filtered through Celite. The aqueous phase was extracted with $CH_2Cl_2$ (3×75 mL). The combined organic phases were dried over sodium sulfate. The solvent was removed on the rotary evaporator and the residue was thoroughly dried under high vacuum for 12 h to give analytically pure product (2.2 g) which was carried directly to the next step. The crude lactol was dissolved in methanol (30 mL). In a separate vial four drops of diphenyldichlorosilane was added to methanol (3 mL). The acidic methanol solution was added to the lactol solution and the reaction mixture was stirred at 25 °C. The reaction, judged complete after 30 min (TLC), was quenched with pyridine (0.5 mL), concentrated on the rotary evaporator, and purified by silica gel chromatography (15% $Et_2O$ in hexanes) to afford the protected lactol as a mixture of anomers (2.0 g). $R_f$=0.8 (50% $Et_2O$ in hexanes); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.73–7.71 (m, 8H), 7.42–7.39 (m, 12H), 5.90–5.67 (m, 2H), 5.09–4.95 (m, 6H), 3.91–3.70 (m, 6H), 3.99 (s, 3H), 3.90 (s, 3H), 2.96 (m, 1H), 2.72 (m, $J$=8.4 Hz, 1H), 2.37 (m, 1H), 2.09 (dd, $J$=12.4, 16 Hz, 1H), 1.88 (dt, $J$=4.8, 12 Hz, 1H), 1.76 (dq, $J$=2.4, 6.8 Hz, 1H), 1.08 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 139.2, 138.2, 135.7, 135.6, 135.5, 134.8, 133.6, 133.5, 130.4, 129.6, 127.9, 127.6, 116.1, 115.5, 105.2, 104.9, 85.1, 83.0, 65.9, 64.3, 54.9, 54.4, 50.9, 44.2, 43.4, 39.8, 26.8, 19.3; HRMS: $m/z$: calcd for $C_{24}H_{32}O_3SiNa$: 419.2019, found: 419.2039 $[M+Na]^+$.

**Aldehyde 42**: Compound **41** (2.0 g, 5.1 mmol) was dissolved in wet acetone (50 mL) and treated with osmium tetroxide (75 mg, 0.3 mmol), followed by NMO (620 mg, 5.3 mmol) and pyridine (0.1 mL). The reaction was stirred for 12 h at 25 °C. The mixture was concentrated and filtered through a plug of silica gel (100% $Et_2O$). $Et_2O$ was removed on the rotary evaporator and the residue was dissolved in $CH_2Cl_2$ (25 mL) and treated with lead tetraacetate (2.4 g, 5.2 mmol). The reaction mixture was stirred for 15 min at 25 °C and quenched with excess ethylene glycol, the solvent was removed on the rotary evaporator and the residue was applied to silica gel chromatography (40% $Et_2O$ in hexanes) to yield aldehyde **42** as a mixture of anomers (1.8 g, 89%). $R_f$=0.4 (50% $Et_2O$ in hexanes); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.73 (s, 1H), 9.67 (s, 1H), 7.67–7.63 (m, 8H), 7.44–7.35 (m, 12H), 5.07 (dd, $J$=3.2, 5.6 Hz, 1H), 5.10 (d, $J$=4.8 Hz, 1H), 4.44 (q, $J$=4.4 Hz, 1H), 4.31 (m, 1H), 3.85 (dd, $J$=10.4, 5.2 Hz, 1H), 3.77 (d, $J$=4 Hz, 2H), 3.66 (dd, $J$=9.6, 7.6 Hz, 1H), 3.29 (s, 3H), 3.25 (m, 1H), 3.23 (s, 3H), 2.95 (m, 1H), 2.26 (m, 3H), 2.85 (dd, $J$=12.8, 8.0 Hz, 1H), 1.05 (s, 18H); $^{13}$C NMR (100 MHz,

$CDCl_3$): $\delta$ = 201.8, 200.2, 135.6, 135.5, 129.8, 127.7, 105.2, 105.0, 80.1, 78.2, 66.5, 65.2, 54.7, 53.2, 51.7, 34.2, 33.8, 26.8, 19.2; HRMS: *m*/*z*: calcd for $C_{23}H_{30}O_4SiNa$: 421.1811, found: 421.1835 $[M+Na]^+$.

**Triflate 43**: Ketone **10** (620 mg, 3.4 mmol) was dissolved in anhydrous THF (30 mL) and cooled to −78 °C (dry ice/acetone) under an argon atmosphere. NaHMDS (3.7 mL, 3.7 mmol, 1 M in THF) was added by syringe and the mixture was stirred for 30 min at −78 °C. $Tf_2NPh$ (920 mg, 3.7 mmol) dissolved in THF (15 mL) was added to the enolate by syringe. The reaction was stirred for 15 min at which time the dry ice/acetone bath was replaced with an ice-water bath. Stirring was continued for 2 h at 0 °C. The reaction was diluted with $Et_2O$ (100 mL) and quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted with $Et_2O$ (3×75 mL) and the combined organic phases were dried over magnesium sulfate. The solvent was removed on the rotary evaporator and the residue was purified on silica gel (5% $Et_2O$ in hexanes) to afford triflate **43** (2.9 g, 85%). $[\alpha]_D^{25}$ = (*c* = 4.85, $CH_2Cl_2$); $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ = 5.29 (m, 1H), 1.67–1.62 (m, 2H), 1.46–1.43 (m, 1H), 1.37–1.25 (m, 3H), 1.22–1.13 (m, 1H), 0.83–0.79 (m, 2H), 0.81 (s, 3H), 0.69 (s, 3H), 0.63 (s, 3H); $^{13}$C NMR (100 MHz, $C_6D_6$): $\delta$ = 158.9, 114.6, 57.0, 45.4, 41.1, 33.3, 32.6, 32.0, 30.4, 26.7, 21.0, 19.5, 17.0; IR (film): $\nu_{max}$ = 2997, 2928, 2863, 1457, 1373, 987, 847, 803, 680 $cm^{-1}$; HRMS: *m*/*z*: calcd for $C_{13}H_{19}F_3O_3S$: 313.1085, found: 313.1004 $[M+H]^+$.

**Enone 44**: Chromium(II) chloride (640 mg, 5.2 mmol) and nickel(II) chloride (3 mg) were dissolved in anhydrous DMF (10 mL) under an argon atmosphere. The heterogenous solution was sonicated for 15 min and stirred for an additional 15 min. Aldehyde **42** (460 mg, 1.2 mmol) dissolved in DMF (5 mL) was added to the chromium/nickel/DMF mixture and stirred for 10 min. Vinyl triflate **43** (420 mg, 1.4 mmol) dissolved in DMF (5 mL) was added to the reaction via syringe and the solution was stirred for 6 h. The reaction was quenched with $Et_2O$ (75 mL). The solution was filtered through Celite and the celite was washed with additional portions of $Et_2O$. The combined organic phases were washed with saturated sodium hydrogen carbonate (100 mL), dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was dissolved in $CH_2Cl_2$ (50 mL) and treated with DMP (850 mg, 2 mmol), and the mixture was stirred for 4 h. The reaction was quenched with saturated sodium thiosulfate (75 mL) and saturated sodium hydrogen carbonate (50 mL) and the mixture was vigorously stirred until visibly clear. The solution was extracted with $CH_2Cl_2$ (3×75 mL). The combined organic phases were dried over sodium sulfate, concentrated on the rotary evaporator and purified on silica gel (20% $Et_2O$ in hexanes) to afford the α,β-unsaturated ketone **44** as a mixture of anomers (355 mg, 52%, two steps). $R_f$ = 0.7 (50% $Et_2O$ in hexanes); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.77–7.64 (m, 8H), 7.42–7.37 (m, 12H), 6.94 (brs, 1H), 6.70 (brs, 1H), 5.06(d, *J* = 7.2 Hz, 1H), 5.03 (d, *J* = 4.8 Hz,1H), 4.49 (m, 1H), 4.42 (q, *J* = 5.6 Hz, 1H), 3.91(m, 1H), 3.77–3.70 (m, 4H), 3.29–3.25 (m, 4H), 3.28 (s, 3H), 2.35–2.03 (m, 8H), 1.75–0.89 (m, 14H), 1.06 (s, 9H), 1.05 (s, 9H), 0.97 (s, 12H), 0.90 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 197.6, 197.0, 155.0, 145.2, 143.8, 135.6, 135.5, 133.3, 131.3, 129.7, 127.6, 105.2, 104.6, 82.4, 79.4, 65.8, 64.2, 59.0, 54.6, 47.4, 46.9, 41.2, 38.3, 35.3, 33.1, 32.7, 29.9, 26.8, 21.0, 19.9, 19.2, 17.6; IR (film): $\nu_{max}$ = 3070, 3049, 2930, 2859, 1665, 1587, 1471, 1428, 1365, 1306, 1261, 1205, 1109, 1049, 741, 703 $cm^{-1}$; HRMS: *m*/*z*: calcd for $C_{35}H_{48}O_4SiNa$: 583.3214, found: 583.3212 $[M+Na]^+$.

**Ketone 45**: 10% palladium on carbon (20 mg) was added to a solution of ketone **44** (175 mg, 0.31 mmol) in methanol (50 mL). The flask was evacuated and filled with hydrogen by means of a balloon. The heterogeneous solution was stirred at 25 °C under an atmosphere of hydrogen for 16 h. The solution was filtered through a plug of Celite, concentrated and applied to silica gel chromatography (5% $Et_2O$ in hexanes) to afford compound **45** as mixture of anomers (165 mg, 92%). $R_f$ = 0.7 (50% $Et_2O$ in hexanes); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.70–7.66 (m, 8H), 7.44–7.37 (m, 12H), 5.08–5.05 (m, 1H), 5.03 (d, *J* = 6 Hz, 1H), 4.21–4.17 (m, 1H), 4.10 (q, *J* = 5.2 Hz, 1H), 3.86–3.68 (m, 4H), 3.47–3.39 (m, 1H), 3.36 (s, 3H), 3.31–3.25 (m, 1H), 3.26 (s, 3H), 2.63 (t, *J* = 8.8 Hz, 1H), 2.45 (t, *J* = 8.7 Hz, 1H), 2.33–0.9 (m, 26H), 1.08 (s, 9H), 1.07 (s, 9H), 0.86 (s, 6H), 0.84 (s, 6H), 0.66 (s, 3H), 0.63 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 211.9, 210.5, 135.6, 135.6, 133.3, 133.2, 129.7, 127.8, 127.8, 127.7, 105.7, 105.2, 84.0, 81.3, 66.8, 65.1, 65.0, 64.7, 58.6, 54.6, 52.7, 52.3, 45.1, 45.0, 41.2, 41.1, 39.9, 36.5, 36.0, 33.4, 33.3, 26.9, 26.8, 22.1, 21.7, 20.8, 20.6, 20.5, 19.8, 19.3, 15.3, 15.1; HRMS: calcd for $C_{35}H_{50}O_4SiNa$: 585.3370, found: 585.3368 $[M+Na]^+$.

**Alkene 46**: A solution of ketone **45** (150 mg, 0.27 mmol) in THF (15 mL) was cooled to 0 °C and treated with trimethylsilylmethyllithium (0.9 mL, 0.9 mmol, 1 M in pentane) for 30 min. The solution was diluted with $Et_2O$ (50 mL) and the organic phase was washed with saturated ammonium chloride (100 mL). The aqueous phase was back extracted with $Et_2O$ (2× 50 mL). The organic phase was dried over magnesium sulfate and concentrated on the rotary evaporator. The crude material was thoroughly dried on the high vacuum and dissolved in THF (25 mL). KH (116 mg, 2.9 mmol) was added and the solution was heated under reflux for 30 min. The solution was diluted with $Et_2O$ (50 mL) and washed with water (100 mL). The aqueous phase was back extracted with $Et_2O$ (2× 50 mL). The combined organic layers were dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was purified on silica gel (100% hexanes) to give alkene **46** as a mixture of anomers (110 mg, 72%, two steps). $R_f$ = 0.8 (30% $Et_2O$ in hexanes); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.71–7.65 (m, 8H), 7.42–7.38 (m, 12H), 5.07–4.96 (m, 3H), 4.89 (s, 1H), 3.95–3.58 58 (m, 8H), 3.42 (s, 3H), 3.31 (s, 3H), 3.13 (q, *J* = 8 Hz, 1H), 2.89–2.80 (m, 1H), 2.29–1.73 (m, 6H), 1.65–0.77 (m, 22H), 1.08 (s, 9H), 1.07 (s, 9H), 0.86 (s, 6H), 0.84 (s, 9H), 0.61(s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 148.2, 135.6, 133.7, 129.6, 127.6, 119.8, 112.3, 110.4, 105.2, 88.6, 83.9, 66.9, 65.8, 58.8, 58.5, 57.9, 54.6, 54.4, 45.4, 45.2, 41.5, 40.9, 40.5, 38.3, 38.5, 36.7, 33.3, 33.2, 30.3, 25.3, 24.9, 21.3, 21.1, 20.5, 20.2, 19.3, 19.2, 18.5, 13.9, 12.5; IR (film): $\nu_{max}$ = 2930, 2857, 1470, 1363, 1109, 1046, 703 $cm^{-1}$; HRMS: *m*/*z*: calcd for $C_{36}H_{52}O_3SiNa$: 593.3578, found: 593.3568 $[M+Na]^+$.

**Alkene 47**: Alkene **46** (425 mg, 1.1 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and cooled to 0 °C. Phenyl selenol (235 mg, 1.15 mmol) was added followed by $BF_3{\cdot}Et_2O$ (~0.1 mL) and stirred for 15 min. The reaction was quenched with pyridine (0.2 mL) and diluted with $CH_2Cl_2$ (20 mL). The organic phase was washed with saturated sodium hydrogen carbonate. The aqueous phase was back extracted with $CH_2Cl_2$ (2× 20 mL) and the combined organic layers were dried over sodium sulfate. The solvent was removed on the rotary evaporator and the residue filtered through a short plug of silica gel with hexane to afford the crude phenyl selenide as a mixture of anomers (530 mg, 90%). The product was taken directly to the next step without further purification. **47a**: $R_f$ = 0.8 (40% $Et_2O$ in hexanes); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.72–7.70 (m, 8H), 7.63–7.60 (m, 12H), 7.42–7.37 (m, 6H), 7.37–7.26 (m, 4H), 5.96–5.91 (m, 2H), 5.15(s, 1H), 5.07 (s, 1H), 4.94 (s, 1H), 4.90 (s, 1H), 4.00–3.66 (m, 6H), 2.79–2.68 (m, 2H), 2.48–2.90 (m, 2H), 2.10–1.99 (m, 4H), 1.69–0.95 (m, 22H), 1.07 (s, 18H), 0.85 (s, 12H), 0.62 (s, 6H).

Phenylselenide **47a** (530 mg, 0.77 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and cooled to 0 °C. Triethylamine (202 mg, 2 mmol), *tert*-butyl peroxide (0.74 mL, 2 mmol, 2.7 M in toluene), and titanium isopropoxide (340 mg, 1.2 mmol) were added successively to the stirring, cooled solution. The mixture was stirred for 45 min, diluted with $CH_2Cl_2$ (50 mL) and washed with saturated sodium hydrogen carbonate (100 mL). The aqueous phase was back extracted twice with $CH_2Cl_2$ (50 mL). The combined organic layers were dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was purified on silica gel (100% hexanes) to yield enol ether **47** (279 mg, 67%). $R_f$ = 0.7 ($Et_2O$/hexanes 2:3); $[\alpha]_D^{25}$ = +19.4 (*c* = 0.1, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.71–7.68 (m, 4H), 7.42–7.39 (m, 6H), 6.37 (dd, *J* = 2.8, 2.0 Hz, 1H), 5.07 (s, 1H), 4.91 (s, 1H), 4.81 (d, *J* = 2.8 Hz, 1H), 4.22 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.76 (m, 1H), 3.66 (m, 1H), 3.26 (m, 1H), 1.91 (dd, *J* = 10.8, 8.0 Hz, 1H), 1.71–0.97 (m, 15H), 1.07 (s, 9H), 0.85 (s, 6H), 0.64 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 151.4 145.4, 135.6, 133.4, 131.5, 129.7, 129.6, 129.2, 127.7, 111.7, 103.0, 88.8, 66.2, 58.5, 57.2, 50.7, 43.2, 41.4, 39.7, 33.2, 28.8, 25.6, 20.5, 20.0, 19.3, 14.0; IR (film): $\nu_{max}$ = 3070, 2928, 2855, 1616, 1471, 1427, 1111, 702 $cm^{-1}$; HRMS: *m*/*z*: calcd for $C_{36}H_{52}O_3SiNa$: 551.3321, found: 551.3379 $[M+Na]^+$.

**Lactone 49**: Butenolide **39** (5.0 g, 14.2 mmol) was dissolved in $CH_2Cl_2$ (50 mL) in a high pressure tube, aluminum chloride (0.62 g, 4.6 mmol) and excess butadiene (20 mL) were added and the tube was sealed and

heated to 60°C for 6 d. The reaction was cooled to −78°C (dry ice/acetone) prior to opening the tube and the solution was filtered through a short plug of Celite. The solvent was removed on the rotary evaporator and the residue was purified by silica gel chromatography (25% $Et_2O$ in hexanes) to give compound **49** (4.9 g, 85%). $R_f$=0.7 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +19.4 ($c$=3.40, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.66–7.64 (m, 4H), 7.41–7.39 (m, 6H), 5.84–5.76 (m, 2H), 4.14 (q, $J$= 4.0 Hz, 1H), 3.85 (dd, $J$=11.6, 4.0 Hz, 1H), 3.74 (dd, $J$=11.2, 3.6 Hz, 1H), 3.00 (td, $J$=8.8, 4.4 Hz, 1H), 2.72–2.65 (m, 1H), 2.43–2.21 (m, 3H), 1.93–1.86 (m, 1H), 1.04 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 179.5, 135.6, 135.5, 132.8, 129.9, 127.8, 126.4, 125.6, 84.8, 64.2, 37.4, 34.0, 26.7, 25.5, 22.5, 19.1; IR (film): $\nu_{max}$ = 3070, 3043, 2932, 2857, 1775, 1112, 704 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{25}H_{30}O_3SiNa$: 429.1862, found: 429.1891 $[M+Na]^+$.

**Lactol 50**: A solution of lactone **49** (12.9 g, 31.6 mmol) in $CH_2Cl_2$ (150 mL) was treated at −78°C with DIBAL-H (33 mL, 33 mmol, 1 M in toluene), added dropwise over a period of 5 min. After 30 min, the reaction was quenched with methanol (10 mL) and the solution was brought to ambient temperature over a 45 minute period. Saturated ammonium chloride (100 mL) was added and the solution was filtered through celite. The solvent was removed in vacuo to yield analytically pure lactol (4.1 g) which was carried to the next step directly. **49a**: $[\alpha]_D^{25}$ = −16.9 ($c$=1.93, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.71–7.69 (m, 4H), 7.46–7.39 (m, 6H), 5.73–5.70 (m, 1H), 5.61–5.59 (m, 1H), 5.08 (d, $J$=5.5 Hz, 1H), 3.86–3.81 (m, 2H), 3.64–3.61 (m, 1H), 3.02 (d, $J$=6.0 Hz, 1H), 2.73 (q, $J$=7.5 Hz, 1H), 2.30–2.16 (m, 3H), 1.84–1.80 (m, 2H), 1.09 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 135.7, 135.6, 133.0, 132.9, 129.8, 127.8, 125.2, 123.9, 103.0, 83.4, 64.5, 41.6, 32.1, 26.9, 23.3, 22.8, 19.2; HRMS: $m/z$: calcd for $C_{25}H_{32}O_3SiNa$: 431.2019, found: 431.2030 $[M+Na]^+$.

The crude lactol (~31.60 mmol) was dissolved in acetone and water 9:1 (150 mL). Osmium tetroxide (2.5 wt% in *tert*-butanol, 3.9 g, 0.38 mmol) and *N*-methyl morpholine oxide (4.22 g, 36 mmol) were added and the mixture was stirred for 10 h at 25°C. The reaction mixture was quenched with saturated aqueous sodium thiosulfate (100 mL) and stirred for 30 min. The mixture was extracted with $Et_2O$ (3×75 mL). The solution was dried over sodium sulfate and concentrated to give the crude triol which was carried forward to the next step without purification. Triol **49b**: $R_f$=0.2 ($Et_2O$); $[\alpha]_D^{25}$ = +2.86 ($c$=1.43, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.70–7.66 (m, 4H), 7.44–7.37 (m, 6H), 5.04 (d, $J$=3.6 Hz, 1H), 3.96–3.91 (m, 2H), 3.81 (dd, $J$=11.2, 3.6 Hz, 1H), 3.67–3.59 (m, 2H), 3.31 (d, $J$=4.8 Hz, 1H), 2.71–2.66 (m, 1H), 2.49–2.21 (m, 3H), 2.03–1.85 (m, 2H), 1.55–1.50 (m, 1H), 1.39–1.32 (m, 1H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.5, 132.6, 129.8, 129.7, 127.7, 102.3, 81.7, 68.7, 67.9, 65.0, 40.7, 35.0, 30.0, 27.0, 26.9, 26.3, 19.3; HRMS: $m/z$: calcd for $C_{25}H_{34}O_5SiNa$: 465.2073, found: 465.2091 $[M+Na]^+$.

The crude triol (~31.6 mmol) was dissolved in $CH_2Cl_2$ (250 mL) and treated with lead tetraacetate (14.2 g, 32 mmol). The reaction was stirred for 15 min then quenched with excess ethylene glycol. The reaction was concentrated on the rotary evaporator and thoroughly dried. The residue was purified on silica gel (50% $Et_2O$ in hexanes) to afford compound **50** as mixture of anomers (8.9 g, 64%, four steps). $R_f$=0.4 (50% $Et_2O$ in hexanes); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.71 (s, 1H), 9.69 (s, 1H), 7.67–7.63 (m, 8H), 7.44–7.35 (m, 12H), 5.89 (d, $J$=5.2 Hz, 1H), 5.87 (d, $J$=5.2 Hz, 1H), 5.65 (t, $J$=2.8 Hz, 1H), 5.49 (dd, $J$=5.2, 2.4 Hz, 1H), 4.09 (dt, $J$=10.0, 4.0 Hz, 1H), 3.85–3.72 (m, 3H), 3.43 (s, 1H), 3.40–3.36 (m, 1H), 3.27 (s, 1H), 3.21–3.17 (m, 1H), 2.82–2.74 (m, 2H), 2.67–2.49 (m, 3H), 2.44–2.36 (m, 1H), 2.01–1.94 (m, 1H), 1.81–1.69 (m, 3H), 1.30–1.19 (m, 2H), 1.08 (s, 9H), 1.07 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 200.5, 199.5, 135.5, 135.4, 133.1, 133.0, 132.9, 129.7, 129.6, 127.6, 127.5, 110.2, 108.1, 99.2, 97.9, 81.2, 64.2, 63.8, 44.3, 43.9, 43.0, 41.7, 36.8, 36.5, 33.7, 32.5, 31.6, 27.0, 26.9, 19.4; HRMS: $m/z$: calcd for $C_{25}H_{32}O_5SiNa$: 463.1917, found: 463.1929 $[M+Na]^+$.

**Aldehyde 51**: Anhydrous methanol (0.98 mL, 24 mmol), followed by of Amberlyst 15 ion-exchange resin (0.50 g) was added to a solution of aldehyde **50** (8.88 g, 20.2 mmol) in anhydrous $Et_2O$ (100 mL) containing activated 3 Å molecular sieves (1.50 g) and the solution was stirred for 10 h. The reaction mixture was filtered through Celite and concentrated on the rotary evaporator. The residue was purified on silica gel (15% $Et_2O$ in hexanes) to afford α-isomer (**51**α; 3.5 g, 38.5%) and β-isomer (**51**β; 3.5 g, 38.5%).

Compound **51**α: $R_f$=0.67 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +61.7 ($c$= 3.14, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.70 (s, 1H), 7.72–7.68 (m, 4H), 7.43–7.37 (m, 6H), 5.91 (d, $J$=5.6 Hz, 1H), 4.93 (d, $J$=5.2 Hz, 1H), 3.92–3.77 (m, 3H), 3.32 (s, 3H), 3.17–3.10 (m, 1H), 2.74 (dd, $J$= 17.6, 10.4 Hz, 1H), 2.63–2.51 (m, 2H), 1.99–1.92 (m, 1H), 1.72 (dd, $J$= 14.4, 1.2 Hz, 1H), 1.11 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 200.3, 135.3, 133.0, 129.4, 127.4, 109.9, 103.9, 81.0, 64.4, 54.2, 43.7, 42.9, 36.5, 33.2, 26.8, 19.2; HRMS: $m/z$: calcd for $C_{26}H_{34}O_5SiNa$: 477.2073, found: 477.2049 $[M+Na]^+$.

Compound **51**β: $R_f$=0.62 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = −13.4 ($c$= 2.51, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.71 (s, 1H), 7.68–7.64 (m, 4H), 7.44–7.37 (m, 6H), 5.79 (d, $J$=5.0 Hz, 1H), 5.13 (d, $J$=4.0 Hz, 1H), 3.85–3.82 (m, 1H), 3.77–3.69 (m, 2H), 3.33 (s, 3H), 3.31–3.26 (m, 1H), 2.76–2.71 (m, 1H), 2.53 (dd, $J$=17.5, 4.5 Hz, 1H), 2.41 (dd, $J$=17.5, 10.0 Hz, 1H), 1.83–1.72 (m, 2H), 1.06 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 199.8, 135.6, 135.5, 133.1, 133.0, 129.8, 129.7, 127.7, 108.0, 105.5, 81.1, 63.7, 54.8, 44.0, 41.6, 36.8, 31.6, 26.8, 19.2; HRMS: $m/z$: calcd for $C_{26}H_{34}O_5SiNa$: 477.2073, found: 477.2061 $[M+Na]^+$.

**Alcohol 52**α: A solution of aldehyde **51**α (3.51 g, 7.72 mmol) in methanol (50 mL) was treated with sodium borohydride (0.70 g, 18.13 mmol). The solution was stirred for 20 min then carefully quenched with a few drops of acetic acid/methanol 1':10, diluted with $CH_2Cl_2$ (100 mL) and washed with saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2×100 mL), dried over magnesium sulfate, concentrated, and applied to silica gel chromatography (40% $Et_2O$ in hexanes) to yield the corresponding alcohol (3.5 g, ~100%). $[\alpha]_D^{25}$ = +64.0 ($c$= 2.17, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.71–7.69 (m, 4H), 7.44–7.37 (m, 6H), 5.86 (d, $J$=5.0 Hz, 1H), 5.00 (d, $J$=4.5 Hz, 1H), 3.95–3.88 (m, 2H), 3.74 (dd, $J$=11.0, 4.0 Hz, 1H), 3.65–3.60 (m, 1H), 3.58–3.53 (m, 1H), 3.33 (s, 3H), 2.94–2.88 (m, 1H), 2.31–2.24 (m, 1H), 2.05–1.94 (m, 2H), 1.70–1.56 (m, 3H), 1.07 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 135.7, 135.6, 133.6, 133.4, 129.6, 127.6, 109.7, 104.9, 81.9, 64.3, 61.5, 54.6, 44.4, 38.4, 32.5, 30.5, 26.8, 19.3; HRMS: $m/z$: calcd for $C_{26}H_{36}O_5SiNa$: 479.2230, found: 479.2235 $[M+Na]^+$.

Alcohol **52**β was prepared similarly to compound **52**α starting from aldehyde **51**β. $[\alpha]_D^{25}$ = −19.9 ($c$=0.78, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.70–7.67 (m, 4H), 7.43–7.37 (m, 6H), 5.77 (d, $J$=5.0 Hz, 1H), 5.14 (br s, 1H), 3.89 (dd, $J$=11.5, 3.0 Hz, 1H), 3.78–3.59 (m, 4H), 3.34 (s, 3H), 3.13–3.07 (m, 1H), 2.43–2.41 (m, 1H), 1.88 (d, $J$=9.0 Hz, 2H), 1.65–1.48 (m, 3H), 1.06 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 135.7, 135.6, 133.4, 133.2, 129.7, 127.7, 127.6, 108.0, 105.7, 82.0, 63.8, 61.6, 54.8, 44.2, 39.0, 31.6, 29.8, 26.8, 19.3; HRMS: $m/z$: calcd for $C_{26}H_{36}O_5SiNa$: 479.2230, found: 479.2239 $[M+Na]^+$.

**Iodide 53**: Imidazole (1.64 g, 23.9 mmol), triphenyl phosphine (3.14 g, 11.9 mmol) and iodine (3.02 g, 11.9 mmol) were added to a solution of alcohol **52**α (5 g, 11 mmol) in THF (100 mL) and the mixture was stirred for 30 min. The reaction was quenched with saturated sodium thiosulfate and extracted with $Et_2O$ (3×100 mL). The combined organic phases were dried over magnesium sulfate, concentrated and purified on silica gel to afford iodide **53**α (3.02 g, over two steps, 74%). $[\alpha]_D^{25}$ = +77.3 ($c$=3.68, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.70–7.66 (m, 4H), 7.40–7.37 (m, 6H), 5.86 (d, $J$=5.6 Hz, 1H), 4.98 (d, $J$=5.2 Hz, 1H), 3.90 (dt, $J$= 10.4, 3.6 Hz, 1H), 3.81 (dd, $J$=11.6, 3.2 Hz, 1H), 3.70 (dd, $J$=11.2, 4.0 Hz, 1H), 3.30 (s, 3H), 3.18–3.12 (m, 1H), 2.99 (q, $J$=8.0 Hz, 1H), 2.94–2.87 (m, 1H), 2.32–2.24 (m, 1H), 2.06–1.84 (m, 4H), 1.06 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.7, 135.6, 133.5, 133.4, 129.7, 129.6, 127.7 (2), 109.7, 104.7, 81.3, 64.3, 54.6, 43.4, 43.3, 32.4, 31.6, 26.9, 19.3, 3.7; IR (film): $\nu_{max}$ = 3070, 2956, 2929, 2857, 1111, 1092, 997, 703 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{26}H_{35}O_4ISi$: 567.1427, found: 567.1429 $[M+H]^+$.

Iodide **53**β (1.55 g, over two steps from **7**, 70%) was prepared similarly to compound **53**α starting from alcohol **52**β. $[\alpha]_D^{25}$ = +2.14 ($c$=2.70, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.71–7.68 (m, 4H), 7.44–7.37 (m, 6H), 5.79 (d, $J$=5.2 Hz, 1H), 5.15 (d, $J$=4.0 Hz, 1H), 3.85 (dd, $J$= 11.2, 3.6 Hz, 1H), 3.78 (dt, $J$=9.6, 3.2 Hz, 1H), 3.70 (dd, $J$=10.8, 3.2 Hz, 1H), 3.35 (s, 3H), 3.26–3.20 (m, 1H), 3.17–3.11 (m, 1H), 3.09–3.02 (m, 1H), 2.53–2.45 (m, 1H), 2.04–1.95 (m, 1H), 1.93–1.83 (m, 2H), 1.82–1.70

(m, 1H), 1.07 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.5, 135.4, 133.2, 133.0, 129.6, 129.5, 127.6, 127.5, 107.9, 105.6, 81.3, 63.7, 54.8, 43.6, 43.3, 31.2, 31.1, 27.0, 19.4, 3.3; IR (film): $\nu_{max}$ = 3067, 2952, 2927, 2851, 1109, 1089, 992, 701 cm$^{-1}$; HRMS: *m/z*: calcd for $C_{26}H_{35}O_4ISi$: 567.1427, found: 567.1439 $[M+H]^+$.

**Phenyl selenide 54α**: Sodium borohydride (0.33 g, 8.6 mmol) was added to diphenyl selenide (0.89 g, 2.8 mmol) in ethanol (50 mL) under an argon atmosphere. The mixture was stirred for 20 min at room temperature. Iodide **53**α (3.00 g, 5.30 mmol) in ethanol (50 mL) was added to the above mixture and the reaction was stirred at 25 °C for 45 min. The solution was diluted with $Et_2O$ (100 mL) and washed with saturated aqueous ammonium chloride (100 mL). The aqueous phase was extracted with $Et_2O$ (3×75 mL). The combined organic layers were dried over magnesium sulfate, concentrated and purified on silica gel to afford the corresponding selenide (2.88 g, 91 %). $[\alpha]_D^{25}$ = +78.1 (*c*=4.54, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.67 (m, 4H), 7.37–7.36 (m, 8H), 7.22–7.20 (m, 3H), 5.84 (d, *J*=5.6 Hz, 1H), 4.97 (d, *J*=4.8 Hz, 1H), 3.87 (dt, *J*=10.0, 3.6 Hz, 1H), 3.80 (dd, *J*=11.2, 2.8 Hz, 1H), 3.67 (dd, *J*=11.2, 4.0 Hz, 1H), 3.29 (s, 3H), 2.91–2.82 (m, 1H), 2.78–2.71 (m, 1H), 2.34–2.26 (m, 1H), 1.98 (dd, *J*=11.2, 5.6 Hz, 1H), 1.95 (dd, *J*=10.4, 5.6 Hz, 1H), 1.84 (dd, *J*=14.0, 2.0, 1H), 1.76 (q, *J*=7.6 Hz, 2H), 1.05 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.7, 135.6, 133.6, 133.5, 132.7, 129.6 (2), 129.0, 127.6 (2), 126.9, 109.7, 104.8, 81.8, 64.3, 54.5, 43.8, 42.1, 32.3, 27.9, 26.8, 26.1, 19.3; IR (film): $\nu_{max}$ = 3070, 2955, 2929, 2857, 1111, 1091, 996, 703 cm$^{-1}$.

Isomeric selenide **54**β (3.02 g, 95 %) was prepared accordingly, starting from **53**β. $[\alpha]_D^{25}$ = +6.92 (*c*=4.32, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.69–7.64 (m, 4H), 7.48–7.35 (m, 8H), 7.24–7.22 (m, 3H), 5.76 (d, *J*=5.2 Hz, 1H), 5.11 (dd, *J*=4.0, 1.6 Hz, 1H), 3.82 (dd, *J*=10.8, 2.8 Hz, 1H), 3.71–3.63 (m, 2H), 3.34 (s, 3H), 3.12–3.04 (m, 1H), 2.97–2.90 (m, 1H), 2.82–2.75 (m, 1H), 2.51–2.43 (m, 1H), 1.82–1.73 (m, 3H), 1.65–1.56 (m, 1H), 1.04 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 135.6, 135.5, 133.3, 133.1, 132.7, 129.7, 129.6, 129.0, 127.6, 126.9, 108.0, 107.9, 105.6, 81.7, 63.5, 54.7, 43.5, 42.3, 31.0, 27.4, 26.7, 25.9, 19.2; IR (film): $\nu_{max}$ = 3073, 2954, 2927, 2856, 1113, 1090, 997, 703 cm$^{-1}$.

**Alkene 55**: Compound **54**α (2.88 g, 4.83 mmol) was dissolved in THF/$H_2O$/MeOH 1:1:2 (150 mL). Sodium periodate (5.24 g, 24.3 mmol) was added in three portions over a 15 min period. The solution was allowed to stir until the starting material was consumed (30 min as judged by TLC), the reaction was diluted with $CH_2Cl_2$ (100 mL) and the sodium periodate quenched with saturated aqueous sodium thiosulfate (100 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2×75 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated on the rotary evaporator to yield alkene product **55**α (1.7 g, 82 %) and recovered starting material (0.35 g, 9 %) after purification on silica gel (20 % $Et_2O$ in hexanes). $[\alpha]_D^{25}$ = +59.4 (*c*=1.1, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.69–7.68 (m, 4H), 7.38–7.35 (m, 6H), 5.91 (d, *J*=5.2 Hz, 1H), 5.81–5.72 (m, 1H), 5.09–5.01 (m, 2H), 4.99 (d, *J*=5.6 Hz, 1H), 4.10–4.06 (m, 1H), 3.85 (dd, *J*=11.2, 2.0 Hz, 1H), 3.67 (dd, *J*=11.6, 4.4 Hz, 1H), 3.33 (s, 3H), 2.97–2.90 (m, 1H), 2.86 (q, *J*=9.2 Hz, 1H), 2.05 (dd, *J*=14.0, 2.0 Hz, 1H), 1.99–1.92 (m, 1H), 1.05 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.7, 135.6, 133.7, 133.6, 129.5, 127.6, 118.1, 110.1, 104.8, 81.5, 63.6, 54.5, 46.5, 46.0, 33.2, 26.8, 19.3; IR (film): $\nu_{max}$ = 3071, 2957, 2930, 2858, 1111, 1093, 997, 704 cm$^{-1}$.

The above procedure was used for the conversion of selenide **54**β to alkene **55**β (1.85 g, 83 %). $[\alpha]_D^{25}$ = −11.5 (*c*=1.93, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.74–7.69 (m, 4H), 7.43–7.37 (m, 6H), 5.85 (d, *J*=4.8 Hz, 1H), 5.73–5.64 (m, 1H), 5.18–5.11 (m, 3H), 3.98 (dt, *J*=6.4, 2.8 Hz, 1H), 3.91 (dd, *J*=11.2, 2.4 Hz, 1H), 3.70 (dd, *J*=11.2, 3.6 Hz, 1H), 3.38 (s, 3H), 3.19–3.11 (m, 1H), 3.05 (dd, *J*=18.0, 8.0 Hz, 1H), 2.03–1.96 (m, 1H), 1.94–1.88 (m, 1H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.5, 135.4, 133.7, 133.4, 133.1, 129.4, 127.5, 127.4, 118.5, 108.1, 105.6, 81.1, 63.1, 54.8, 46.3, 45.7, 32.4, 26.8, 19.4.

**Aldehyde 56**: Osmium tetroxide (0.51 g, 0.050 mmol), NMO (0.63 g, 5.2 mmol), and catalytic amount of pyridine (three drops) were added to a solution of alkene **55**α (1.90 g, 4.33 mmol) in acetone/water 10:1 (110 mL). The reaction mixture was stirred for 10 h at room temperature and then quenched with saturated aqueous sodium thiosulfate (125 mL). The aqueous phase was extracted with $Et_2O$ (3×100 mL). The combined organic layers were dried over magnesium sulfate and concentrated on the rotary evaporator to afford the ~2 g of the crude diol which was dried under high vacuum. A solution of the crude diol in $CH_2Cl_2$ (100 mL) was cooled to 0 °C and treated with lead(IV) tetraacetate (2.63 g, 5.64 mmol). The solution was stirred for 30 min at 0 °C, quenched with excess ethylene glycol and the organic phase was washed twice with water (100 mL). The aqueous phase was back extracted with $CH_2Cl_2$ (2×100 mL) and the combined organic phases were dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was purified by silica gel chromatography (50 % $Et_2O$ in hexanes) to yield aldehyde **56**α (1.8 g, 92 %). $[\alpha]_D^{25}$ = +62.9 (*c*=1.33, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.77 (d, *J*=2.4 Hz, 1H), 7.67–7.63 (m, 4H), 7.40–7.38 (m, 6H), 5.93 (d, *J*=5.2 Hz, 1H), 5.01 (dd, *J*=4.8, 0.8 Hz, 1H), 4.64–4.60 (m, 1H), 3.88–3.79 (m, 2H), 3.34 (s, 3H), 3.24–3.17 (m, 1H), 3.07–3.01 (m, 1H), 2.14–2.01 (m, 2H), 1.04 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 201.8, 135.6, 135.5, 133.2, 129.7, 127.7, 110.4, 104.7, 78.5, 64.6, 54.6, 54.5, 43.2, 33.7, 26.8, 19.2; IR (film): $\nu_{max}$ = 301, 2931, 2858, 1721, 1112, 998, 704 cm$^{-1}$; HRMS: *m/z*: calcd for $C_{25}H_{32}O_5Si$: 441.2097, found: 441.2071 $[M+H]^+$.

The above procedure was used for the conversion of alkene **55**β to aldehyde **56**β (1.75 g, 94 %); $[\alpha]_D^{25}$ = −28.7 (*c*=4.18, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.78 (s, 1H), 7.69–7.66 (m, 4H), 7.45–7.38 (m, 6H), 5.86 (d, *J*=5.0 Hz, 1H), 5.18 (d, *J*=5.0 Hz, 1H), 4.47–4.44 (m, 1H), 3.91 (dd, *J*=11.0, 4.0 Hz, 1H), 3.82 (dd, *J*=11.0, 3.0 Hz, 1H), 3.42–3.35 (m, 2H), 3.35 (s, 3H), 2.04 (ddd, *J*=13.5, 9.0 Hz, 1H), 1.91–1.86 (m, 1H), 1.06 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 199.2, 135.5, 135.4, 133.0, 132.8, 129.7, 127.7, 127.6, 108.3, 105.9, 77.8, 63.6, 55.2, 54.8, 42.4, 32.9, 26.7, 19.1; HRMS: *m/z*: calcd for $C_{25}H_{32}O_5Si$: 441.2097, found: 441.2081 $[M+H]^+$.

**Alcohol 57**: Vinyl iodide **25** (200 mg, 0.69 mmol) was dissolved in anhydrous THF (15 mL), cooled to −78 °C (dry ice/acetone) under an argon atmosphere and treated with *tert*-butyllithium (0.82 mL, 1.4 mmol, 1.7 M in pentane) and the solution was stirred at −78 °C for 30 min. The anion was brought to 0 °C for ~1 min and then returned to the −78 °C bath and stirred for an additional 10 min. Aldehyde **56**α (200 mg, 0.45 mmol) in anhydrous THF (3 mL) was added dropwise to the vinyl lithium solution and the reaction was stirred at −78 °C for 30 min. The reaction was quenched by diluting with $Et_2O$ (25 mL) followed by saturated ammonium chloride (100 mL). The aqueous phase was extracted with $Et_2O$ (3×35 mL), the combined organic layers were dried over sodium sulfate, and concentrated on the rotary evaporator. The residue was purified by silica gel chromatography (40 % $Et_2O$ in hexanes) to afford pure allylic alcohol **57**α (221 mg, 54 %). $R_f$=0.55 (50 % $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +45.5 (*c*=3.50, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.69 (m, 4H), 7.41–7.38 (m, 6H), 5.85 (d, *J*=5.6 Hz, 1H), 5.70 (s, 1H), 5.00 (d, *J*=4.0 Hz, 1H), 4.32–4.29 (m, 2H), 3.94 (dd, *J*=11.2, 3.6 Hz, 1H), 3.78 (dd, *J*=10.8, 2.8 Hz, 1H), 3.37 (s, 3H), 2.94–2.89 (m, 1H), 2.69–2.63 (m, 1H), 2.05–1.98 (m, 4H), 1.75–1.26 (m, 7H), 1.07 (s, 9H), 1.02 (s, 3H), 0.97 (s, 3H), 0.86 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 155.7, 135.7, 135.6, 133.4, 133.2, 129.7, 127.7, 127.6, 125.5, 109.6, 104.5, 80.7, 66.7, 65.8, 60.2, 47.1, 46.2, 44.8, 41.4, 35.2, 33.7, 33.2, 32.8, 28.6, 26.9, 21.4, 19.9, 19.2, 18.2; IR (film): $\nu_{max}$ = 3437, 3070, 3049, 2930, 2857, 1112, 999, 703 cm$^{-1}$; HRMS: *m/z*: calcd for $C_{37}H_{52}O_5SiNa$: 627.3482, found: 627.3491 $[M+Na]^+$.

The above procedure was used for the conversion of aldehyde **56**β to alcohol **57**β (201 mg, 51 %). $[\alpha]_D^{25}$ = −13.7 (*c*=0.85, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.69–7.67 (m, 4H), 7.44–7.36 (m, 6H), 5.79 (br s, 1H), 5.71 (d, *J*=4.0 Hz, 1H), 5.13 (d, *J*=4.0 Hz, 1H), 4.13–4.06 (m, 2H), 3.93–3.87 (m, 2H), 3.34 (s, 3H), 3.01–2.97 (m, 1H), 2.73 (q, *J*=6.8 Hz, 1H), 2.43 (d, *J*=4.4 Hz, 1H), 2.07 (dd, *J*=8.4, 1.6 Hz, 2H), 1.98–1.92 (m, 1H), 1.76 (dd, *J*=12.0, 9.5 Hz, 3H), 1.62–1.56 (m, 1H), 1.48–1.42 (m, 1H), 1.26–1.20 (m, 2H), 1.10–1.03 (m, 1H), 1.07 (s, 9H), 1.06 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 155.7, 135.7, 135.6, 133.0, 132.8, 129.8 (2), 127.8, 127.7, 126.7, 107.6, 105.9, 81.8, 67.1, 65.4, 60.2, 54.9, 47.9, 47.2, 45.1, 41.4, 35.2, 33.2, 32.8, 31.9, 28.8, 26.9, 21.4, 19.9, 19.2, 18.5; HRMS: *m/z*: calcd for $C_{37}H_{52}O_5SiNa$: 627.3482, found: 627.3499 $[M+Na]^+$.

**Enone 58**: DMP reagent (1.8 g, 4.4 mmol) was added to a solution of allylic alcohol **57**α (200 mg, 0.33 mmol) in $CH_2Cl_2$ (5 mL) and the reaction was stirred for 1 h. Saturated aqueous sodium thiosulfate (15 mL) and $NaHCO_3$ (5 mL) were added and the mixture was stirred until the organic layer was clear (45 min). The aqueous layer was extracted with $CH_2Cl_2$ (3×50 mL), dried over sodium sulfate, and concentrated on the rotary evaporator. The residue was purified on silica gel (30% $Et_2O$ in hexanes) to yield enone **58**α (196 mg, 99%). $R_f$=0.6 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +58.3 ($c$=0.30, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.68–7.60 (m, 4H), 7.40–7.34 (m, 6H), 6.72 (m, 1H), 5.90 (d, $J$=5.6 Hz, 1H), 5.02 (dd, $J$=5.6, 1.2 Hz, 1H), 4.73 (dt, $J$=10.0, 2.4 Hz, 1H), 3.95 (dd, $J$=12.0, 2.4 Hz, 1H), 3.88 (t, $J$=9.6 Hz, 1H), 3.71 (dd, $J$=11.6, 3.2 Hz, 1H), 3.35 (s, 3H), 3.16–3.09 (m, 1H), 2.31–2.15 (m, 3H), 2.07–1.99 (m, 1H), 1.79–1.45 (m, 6H), 1.11 (m, 1H), 1.04 (s, 3H), 1.03 (s, 9H), 0.98 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 195.7, 155.7, 143.6, 135.6, 135.5, 133.6, 133.4, 131.9, 129.5, 127.6, 109.3, 105.5, 78.3, 63.2, 59.2, 50.4, 47.1, 46.0, 41.2, 35.1, 33.8, 33.1, 32.7, 30.0, 26.8, 21.1, 19.8, 19.4, 17.7; HRMS: $m/z$: calcd for $C_{37}H_{50}O_5Si$: 603.3505, found: 603.3520 $[M+H]^+$.

The above procedure was used for the conversion of alcohol **57**β to enone **58**β. $[\alpha]_D^{25}$ = −38.1 ($c$=0.40, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.67–7.61 (m, 4H), 7.43–7.32 (m, 6H), 6.77 (dd, $J$=3.6, 2.0 Hz, 1H), 5.84 (d, $J$=5.2 Hz, 1H), 5.13 (dd, $J$=4.0, 0.8 Hz, 1H), 4.48 (dt, $J$=9.6, 2.8 Hz, 1H), 3.96–3.88 (m, 2H), 3.73–3.69 (m, 1H), 3.34 (s, 3H), 3.30–3.24 (m, 1H), 2.27–2.19 (m, 3H), 1.77–1.43 (m, 6H), 1.26–1.04 (m, 2H), 1.03 (s, 12H), 0.97 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 195.5, 155.2, 144.1, 135.5, 135.3, 133.3, 133.0, 129.5, 127.5, 107.9, 105.6, 79.1, 78.6, 63.1, 59.2, 55.0, 50.3, 45.4, 41.3, 35.1, 33.2, 32.8 (2), 30.1, 26.9, 21.2, 19.9, 19.4, 17.9; HRMS: $m/z$: calcd for $C_{37}H_{50}O_5Si$: 603.3505, found: 603.3511 $[M+H]^+$.

**Ketone 59**: Enone **58**α (192 mg, 0.32 mmol) in methanol (25 mL) was treated with 10% activated palladium on carbon (30 mg) and stirred for 16 h under an atmosphere of hydrogen. The solution was filtered through Celite, concentrated and applied to silica gel chromatography to afford **59**α (15 mg, 6%) and anomer **59**β (144 mg, 75%).

Treatment of enone **58**β under identical reaction conditions led to isolation of **59**β as the sole product isolated in 83% yield. **59**α: $R_f$=0.6 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +78.9 ($c$=1.09, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.68–7.63 (m, 4H), 7.41–7.36 (m, 6H), 5.87 (d, $J$=5.2 Hz, 1H), 5.06 (dd, $J$=4.8, 2.4 Hz, 1H), 4.56 (dt, $J$=10.0, 2.4 Hz, 1H), 3.90 (dd, $J$=11.6, 2.4 Hz, 1H), 3.65 (dd, $J$=11.6, 3.2 Hz, 1H), 3.52 (dd, $J$=10.0, 8.4 Hz, 1H), 3.36 (s, 3H), 3.21–3.14 (m, 1H), 2.34 (t, $J$=9.6 Hz, 1H), 2.06–1.97 (m, 3H), 1.68–1.12 (m, 10H), 1.05 (s, 9H), 0.86 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H). **59**β: $R_f$=0.6 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +18.3 ($c$=0.63, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.66–7.61 (m, 4H), 7.39–7.36 (m, 6H), 5.8 (d, $J$=5.5 Hz, 1H), 5.15 (d, $J$=4.5 Hz, 1H), 4.33–4.29 (m, 1H), 3.90–3.84 (m, 2H), 3.73 (dd, $J$=12.5, 3.0 Hz, 1H), 3.34 (s, 3H), 2.66–2.60 (m, 1H), 2.22–2.16 (m, 1H), 1.86 (dd, $J$=12.0, 7.0 Hz, 1H), 1.78–1.04 (m, 12H), 1.04 (s, 9H), 0.89 (s, 3H), 0.87 (s, 3H), 0.73 (s, 3H); HRMS: $m/z$: calcd for $C_{37}H_{52}O_5SiNa$: 627.3482, found: 627.3491 $[M+Na]^+$.

**Alkene 60**: Ketone **59**β (125 mg, 0.21 mmol) in DME/THF 3:1 (5 mL) was cooled to 0°C and treated with methyl lithium (1 mL, 1.6 mmol, 1.6 M in $Et_2O$). The reaction was stirred for 30 min at 0°C then diluted with $Et_2O$ (15 mL), quenched with saturated ammonium chloride solution and extracted with $Et_2O$ (3×15 mL). The solvent was removed on the rotary evaporator and purified by silica gel chromatography (hexanes/$Et_2O$ 7:3) to give the corresponding alcohol (98 mg, 75%). **60a**: $R_f$=0.5 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = −14.1 ($c$=1.0, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.72–7.66 (m, 4H), 7.42–7.37 (m, 6H), 5.74 (d, $J$=4.4 Hz, 1H), 5.18 (d, $J$=5.2 Hz, 1H), 4.34 (d, $J$=8.8 Hz, 1H), 4.00 (d, $J$=10.4 Hz, 1H), 3.67 (dd, $J$=11.2, 2.0 Hz, 1H), 3.40 (s, 3H), 3.06–3.03 (m, 1H), 2.77 (dd, $J$=8.4, 6.4 Hz, 1H), 2.69–2.62 (m, 1H), 2.04–1.99 (m, 2H), 1.85 (t, $J$=10.0 Hz, 1H), 1.74–1.07 (m, 10H), 1.24 (s, 3H), 1.07 (s, 9H), 1.02 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.5, 135.4, 133.4, 133.0, 129.5 (2), 127.6, 127.5, 107.3, 107.2, 78.3, 65.9, 58.9, 57.9, 55.1, 48.8, 44.7, 44.5, 42.0, 41.2, 33.9, 33.1, 32.8, 26.9, 25.2, 23.7, 21.0, 20.9, 19.9, 19.4, 16.3; IR (film): $\nu_{max}$ = 3464 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{38}H_{56}O_5SiNa$: 643.3795, found: 643.3771 $[M+Na]^+$.

To a solution of the above alcohol (90 mg, 0.14 mmol) in $CH_2Cl_2$ (5 mL) at 25°C was added pyridine (0.3 mL, 2.8 mmol), followed by thionyl chloride (0.5 mL, 1 mmol, 2 M in $CH_2Cl_2$). The reaction was stirred for 30 min then diluted with $CH_2Cl_2$ (10 mL), washed with water, extracted with $CH_2Cl_2$ (3×15 mL), dried over sodium sulfate and concentrated on the rotary evaporator. The residue was purified on silica gel (hexanes/$Et_2O$ 95:5) to afford alkene **60** (70 mg, 85%). $R_f$=0.8 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +10.25 ($c$=0.625, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.69 (m, 4H), 7.38–7.36 (m, 6H), 5.82 (d, $J$=4.0 Hz, 1H), 5.11 (d, $J$=4.0 Hz, 1H), 4.98 (s, 1H), 4.73 (s, 1H), 4.04 (d, $J$=8.4 Hz, 1H), 3.89 (d, $J$=9.6 Hz, 1H), 3.67 (dd, $J$=9.6, 2.8 Hz, 1H), 3.37 (s, 3H), 3.12–3.10 (m, 1H), 2.88 (dd, $J$=8.8, 6.4 Hz, 1H), 2.03–1.95 (m, 2H), 1.73–0.80 (m, 12H), 1.06 (s, 9H), 0.83 (s, 6H), 0.64 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 144.4, 135.6, 135.5, 133.5, 133.2, 129.4, 127.4, 113.9, 108.0, 105.4, 81.2, 63.0, 59.5, 58.3, 54.9, 47.2, 44.4, 44.1, 41.7, 39.0, 33.2, 33.1, 26.9, 24.9, 20.6, 19.9, 19.4, 14.1; IR (film): $\nu_{max}$ = 3071, 3049, 2929, 2859, 1460, 1428, 1107 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{38}H_{54}O_4SiNa$: 625.3683, found 625.3667 $[M+Na]^+$.

**Alcohol 61**: A solution of silyl ether **60** (70 mg, 0.12 mmol) in THF (5 mL) was treated with TBAF (0.2 mL, 0.2 mmol, 1 M THF) and stirred at 25°C for 12 h. The solution was concentrated and applied to silica gel chromatography ($Et_2O$/hexanes 4:1) to afford alcohol **61** (43 mg, 99%). $R_f$=0.2 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = +6.25 ($c$=1.00, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.78 (d, $J$=5.2 Hz, 1H), 5.11 (d, $J$=4.8 Hz, 1H), 5.05 (s, 1H), 4.84 (s, 1H), 4.10–4.05 (m, 1H), 3.87 (dd, $J$=12.0, 2.0 Hz, 1H), 3.55 (dd, $J$=12.4, 4.0 Hz, 1H), 3.36 (s, 3H), 3.18–3.09 (m, 1H), 2.77 (dd, $J$=10.8, 8.0 Hz, 1H), 2.08–0.81 (m, 14H), 0.85 (s, 6H), 0.69 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 144.2, 114.1, 107.8, 105.5, 80.2, 61.7, 59.3, 58.1, 55.0, 46.7, 44.7, 44.4, 41.7, 38.9, 33.3 (2), 32.9, 24.5, 20.7, 20.6, 19.8, 14.0; IR (film): $\nu_{max}$ = 3462, 1025, 998 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{22}H_{36}O_4Na$: 387.3581, found 387.3599 $[M+Na]^+$.

**Aldehyde 62**: Alcohol **61** (32 mg, 0.09 mmol) in acetonitrile (5 mL) was treated with IBX (76 mg, 0.27 mmol) and stirred at reflux for 1 h. The reaction was cooled to 0°C and the solids were removed by filtration and the filter cake was washed with $Et_2O$ (3×10 mL). The solvent was removed on the rotary evaporator and the residue was dried under high vacuum for 2 h to yield crude aldehyde **62** (30 mg, 91%) which was found to be unstable on silica gel and therefore carried forward without purification. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.55 (dd, $J$=3.2, 1.6 Hz, 1H), 5.88 (d, $J$=7.2 Hz, 1H), 5.13–5.08 (m, 3H), 4.38 (dd, $J$=14.8, 3.2 Hz, 1H), 3.35 (s, 3H), 3.24–3.18 (m, 1H), 2.88 (dd, $J$=14.8, 10.4 Hz, 1H), 2.06–1.94 (m, 3H), 1.76–0.91 (m, 11H), 0.83 (s, 6H), 0.62 (s, 3H).

**Ketone 63**: Crude aldehyde **62** (30 mg, 0.88 mmol) in anhydrous THF (5 mL) was cooled to 0°C and treated with methyl magnesium bromide (0.2 mL, 0.28 mmol, 1.4 M, THF/toluene) for 1 h. The reaction was diluted with $Et_2O$ (5 mL) and saturated aqueous ammonium chloride (15 mL), extracted with $Et_2O$ (3×10 mL), dried over magnesium sulfate and concentrated on the rotary evaporator. The crude mixture of diastereomers was oxidized with DMP (424 mg, 1 mmol) in $CH_2Cl_2$ at 25°C for 4 h. The reaction was diluted with saturated sodium thiosulfate (10 mL) and $NaHCO_3$ (10 mL) and the heterogenous mixture was vigorously stirred until the solution was visibly clear. The aqueous layer was extracted with $CH_2Cl_2$ (3×10 mL), dried over sodium sulfate and concentrated on rotary evaporator. The residue was purified by silica chromatography to afford the corresponding ketone (14 mg; 43% overall isolated, three steps). $R_f$=0.3 (50% $Et_2O$ in hexanes); $[\alpha]_D^{25}$ = −4.51 ($c$=0.52, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.89 (d, $J$=5.2 Hz, 1H), 5.14 (s, 1H), 5.12 (d, $J$=4.8 Hz, 1H), 5.06 (s, 1H), 4.40 (d, $J$=10.4 Hz, 1H), 3.37 (s, 3H), 3.22–3.14 (m, 1H), 2.84 (dd, $J$=10.4, 8.0 Hz, 1H), 2.21 (s, 3H), 2.06–2.01 (m, 2H), 1.75–0.85 (m, 12H), 0.85 (s, 6H), 0.64 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 206.0, 142.7, 115.5, 108.4, 105.6, 84.0, 59.3, 58.1, 55.1, 50.4, 44.9, 44.4, 41.6, 38.9, 33.3 (2), 33.0, 26.5, 24.6, 20.7, 20.6, 19.8, 13.9; IR (film): $\nu_{max}$ = 2923, 1720, 1005 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{23}H_{36}O_4$: 377.2691, found 377.2670 $[M+H]^+$.

**Lactone 64**: A solution of ketone **63** (6 mg, 0.016 mmol) in acetone (0.2 mL) was treated with a solution of chromic acid (15 mg, 0.15 mmol)

in acetic acid (1.5 mL) with water (0.5 mL), and stirred for 6 h at room temperature. The solution was diluted with $CH_2Cl_2$ (5 mL) and washed with water (10 mL) followed by aqueous sodium hydrogen carbonate (10 mL). The organic solvent was dried over sodium sulfate and concentrated on the rotary evaporator. The residue was purified on silica gel to yield the corresponding lactone (4.5 mg, 80%). $R_f = 0.6$ (hexanes/$Et_2O$/$CH_2Cl_2$ 1:1:0.02); $[\alpha]_D^{25} = +22.4$ ($c = 0.16$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.22 (d, $J = 5.6$ Hz, 1H), 5.31 (s, 1H), 5.04 (s, 1H), 4.46 (d, $J = 10.8$ Hz, 1H), 3.32–3.25 (m, 1H), 2.93 (t, $J = 10.4$ Hz, 1H), 2.74 (dd, $J = 18.8$, 4.0 Hz, 1H), 2.56 (dd, $J = 19.2$, 10.8 Hz, 1H), 2.25 (s, 3H), 2.08 (t, $J = 9.2$ Hz, 1H), 1.72–1.02 (m, 11H), 0.86 (s, 6H), 0.65 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 204.1, 174.2, 142.9, 117.4, 107.3, 85.2, 59.6, 58.1, 49.6, 44.5, 42.2, 41.5, 38.9, 33.3, 33.2, 30.5, 27.0, 24.7, 20.7, 20.6, 19.8, 14.2; IR (film): $\nu_{max}$ = 2924, 1788, 1721, 992 cm$^{-1}$; HRMS: $m/z$: calcd for $C_{22}H_{32}O_4$: 361.2378, found 361.2391 $[M+H]^+$.

**(+)-Norrisolide (1)**: Solid $NaHCO_3$ (84 mg, 0.5 mmol) was added at 0°C to a solution of lactone **64** (4.5 mg, 0.012 mmol) in $CH_2Cl_2$ (3 mL) and the heterogeneous mixture was stirred for 5 min. *m*CPBA (3.5 mg, 0.020 mmol) dissolved in $CH_2Cl_2$ (1 mL) was added to the reaction flask and the mixture was stirred at 0°C for 45 min. The reaction was quenched by the addition of saturated aqueous sodium thiosulfate (10 mL) and stirred for an additional 30 min. The mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3×5 mL). The combined organic phases were dried over sodium sulfate and the solvent removed on the rotary evaporator. The compound was purified on silica gel to yield norrisolde as a white solid (1.5 mg). $R_f = 0.6$ (hexanes/$Et_2O$ 3:7); $[\alpha]_D^{25} = +3.5$ ($c = 0.13$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ = 6.63 (dd, $J = 4.0$, 1.6 Hz, 1H), 5.66 (dd, $J = 6.4$, 1.6 Hz, 1H), 4.90 (s, 1H), 4.77 (s, 1H), 2.70 (dd, $J = 8.8$, 3.6 Hz, 1H), 2.40–2.33 (m, 1H), 2.15 (dd, $J = 18.0$, 4.0 Hz, 1H), 1.76 (dd, $J = 18.4$, 10.8 Hz, 1H), 1.58 (s, 3H), 1.45–0.60 (m, 12H), 0.85 (s, 3H), 0.79 (s, 3H), 046 (s, 3H); $^{13}$C NMR (100 MHz, $C_6D_6$): $\delta$ = 173.5, 168.5, 143.4, 116.9, 107.1, 101.8, 58.7, 57.7, 50.0, 45.0, 41.7, 40.5, 38.6, 33.4, 33.3, 30.5, 24.2, 21.2, 20.7, 20.4, 19.9, 14.1; HRMS: $m/z$: calcd for $C_{22}H_{32}O_5$: 316.2038, found 316.2051 $[M-AcOH]^+$.

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