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Synthesis of the Spirocyclic Framework of Sesterterpenoid Natural Products

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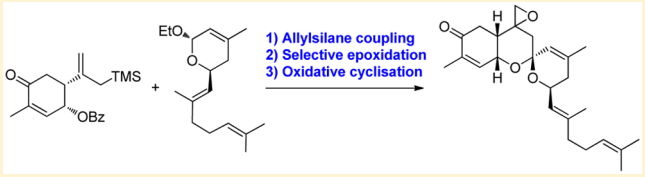
Supporting Information

ABSTRACT: A convergent synthetic route to the sesterterpenoid framework of the bioactive phorbaketal and alotaketal natural product families has been established. The synthetic approach hinges on a Hosomi−Sakurai coupling of complex acetal and allylsilane coupling partners, followed by DDQ-promoted oxidative cyclization of highly unsaturated advanced intermediates. This robust synthetic approach enables further investigations into the members of these natural product families and readily provides access to analogues for biological testing.



INTRODUCTION

The phorbaketals and alotaketals are structurally related sesterterpenoid natural products that exhibit diverse biological activity. Phorbaketal A (**1**) and alotaketal A (**2**) (Figure 1) are

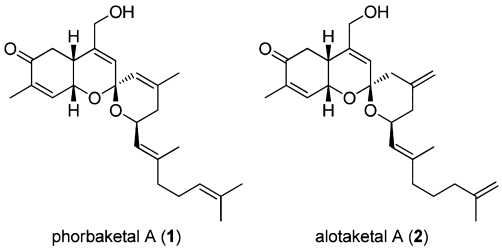


Figure 1. Related natural products phorbaketal A and alotaketal A.

prototypical members of these families; a range of oxidized or reduced derivatives have been isolated. Phorbaketal A was isolated from the marine sponge *Phorbas* sp. collected off the coast of Gageo Island, South Korea.[1] It was found to promote osteogenic differentiation in human mesenchymal stem cells, mediated by the transcription factor Runx2 and its transcriptional coactivator TAZ, and also displays inhibition of adipocyte differentiation, mast cell activity, and fatty acid synthesis in the liver.[2−6] Alotaketal A was isolated from the marine sponge *Hamigera* sp., collected near Milne Bay in Papua New Guinea.[7] It was shown to activate the cAMP signaling pathway in HEK293 cells at nanomolar concentrations (EC_{50} = 18 nM). Two total syntheses of **2** have been reported to date, the first by Yang et al.[8,9] followed closely by that by Dalby and co-workers.[10] The specific structure of the phorbaketal family has not yet been prepared via chemical synthesis.

Inspired by the challenging structural architecture and the array of promising biological activity, we undertook investigations into the synthesis of this family of compounds. The results of these studies are reported herein.

RETROSYNTHETIC ANALYSIS

Phorbaketal A (**1**) was chosen as a representative member of the phorbaketal and alotaketal families, with the view to establishing an efficient and reliable synthetic route that could be adapted for the synthesis of related natural products or the generation of biologically active analogues. During the previous syntheses of alotaketal A (**2**), the carbon skeleton was assembled via the coupling of a bicyclic lactone and an acyclic allyl halide, with subsequent spirocyclization and then construction of the C-ring (Scheme 1).[8−10] In contrast, we envisaged that the union of two similarly sized monocyclic coupling partners, followed by cyclization to construct the B-ring, would improve the overall convergence of the synthesis.

With this in mind, we aimed to install the key allylic alcohol moiety using a late-stage epoxide opening, following the oxidative spirocyclization of **5**. The free hydroxyl group would be exploited for the selective epoxidation of the 2,2-disubstituted double bond resulting from the coupling of allylsilane (−)-**6** with acetal **7**. A second strategy was also devised to allow for unexpected issues that might arise during the final transformations due to the presence of the alkenyl side chain. Accordingly, it was envisaged that, following construction of the tricyclic core **8**, the side chain could be installed via an olefination reaction.

RESULTS AND DISCUSSION

Our investigations began with the synthesis of the allylsilane coupling partner **6**. As described in a recent report from our group, two parallel approaches were developed for the synthesis of **6** (Scheme 2).[11] The first began from chiral pool starting material carvone **10** to give allylsilane (+)-**6** in eight steps. This approach, however, was not conducive to large-scale synthesis of **6** due to the challenges involved in the installation of the γ-

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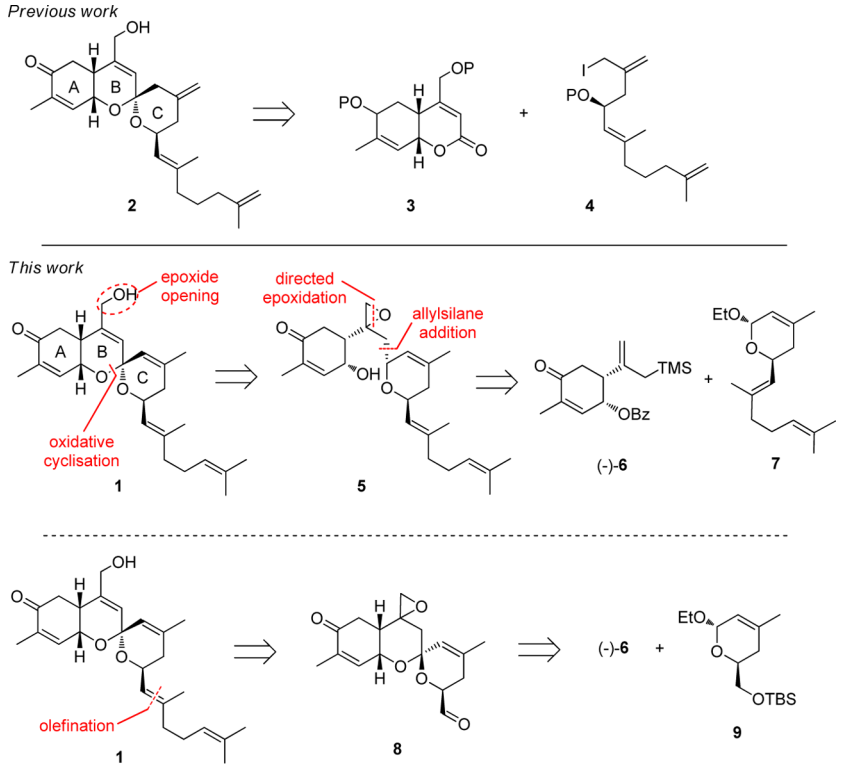
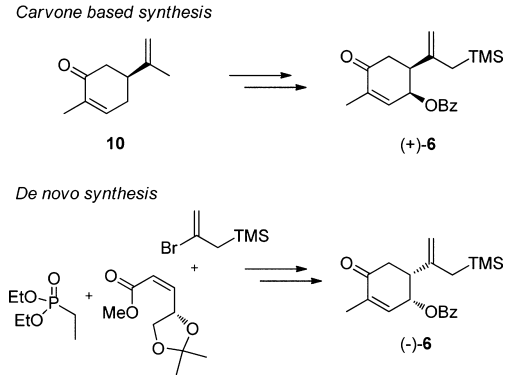
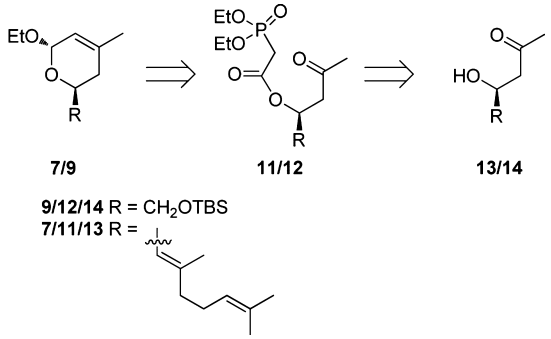
Scheme 1. Retrosynthetic Analysis of Phorbaketal A[8−10]



Scheme 2. Synthesis of Allylsilane Coupling Partner 6[11]



Scheme 3. Retrosynthetic Analysis of Acetal Coupling Partners 7 and 9



hydroxyl group. An alternative approach was then developed in which (−)-**6** was constructed from simpler starting materials in a six-step sequence via a diastereoselective conjugate addition, nucleophilic phosphonate addition, and a benzoyl transfer−intramolecular Horner−Wadsworth−Emmons (HWE) sequence to construct the cyclohexenone ring.[11] The latter approach was significantly more robust than the former, providing adequate material for subsequent synthetic investigations.

Synthesis of Acetal Coupling Partners 7 and 9. A common synthetic strategy was devised for the synthesis of acetal coupling partners **7** and **9** (Scheme 3). It was envisaged that intramolecular HWE olefination of phosphonates **11** and **12** followed by reduction and acetalization would provide the required ethyl acetals. Phosphonates **11** and **12** would in turn be available from the corresponding *β*-hydroxy ketones **13** and **14**.

The synthesis of acetal **7** began with a Nagao aldol reaction[12] of acetylated auxiliary **15**[13] and geranial **16**[14] to install the required (4*S*)-stereochemistry (Scheme 4). Generation of the titanium enolate of **15** and subsequent reaction with **16** afforded a separable 6:1 diastereomeric mixture of alcohols, with the required diastereomer **17** isolated in 70% yield. Major diastereomer **17** was assigned on the basis of previously reported stereochemical assignment and comparison of the ^{1}H NMR spectrum with those of structurally related compounds.[8] The thiazolidine thione auxiliary was readily exchanged with *N*-methoxymethylamine in the presence of imidazole to produce Weinreb amide **18**, followed by the nucleophilic addition of methylmagnesium bromide to furnish *β*-hydroxy ketone **13** in excellent yield. Treatment of **13** with bromoacetyl bromide and pyridine afforded ester **19**, which was converted to phosphonate **11** in quantitative yield using a Michaelis−Arbuzov reaction.[15,16] The intramolecular HWE reaction proceeded cleanly with sodium hydride as the base to furnish lactone **20** in good yield. Finally, a reduction/acetalization sequence effected the conversion of lactone **20** into the desired acetal coupling partner **7**.

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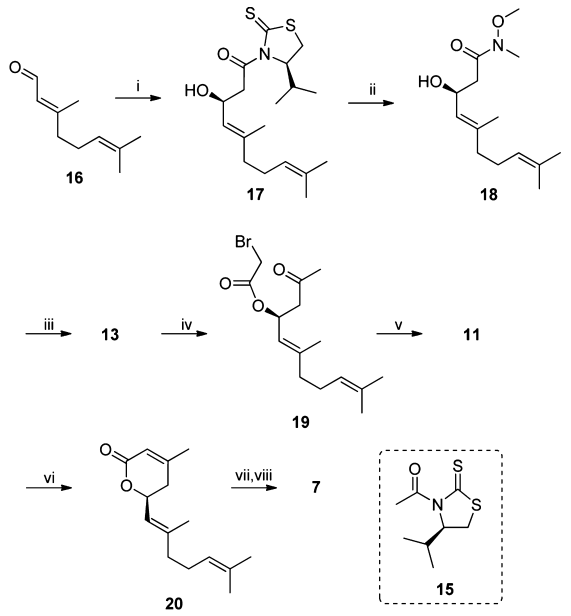
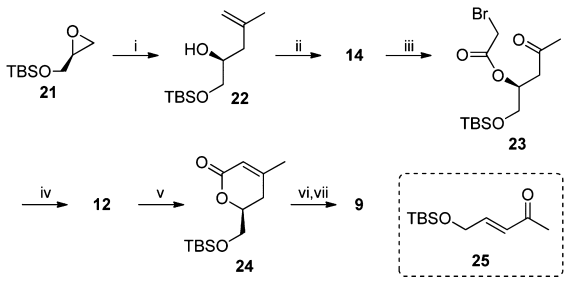
Scheme 4. Synthesis of Acetal Coupling Partner 7[a]



[a]Reagents and conditions: (i) **15**, $TiCl_4$, DIPEA, CH_2Cl_2, −78 °C, 70%; (ii) Me(OMe)NH·HCl, imidazole, CH_2Cl_2, rt, 85%; (iii) MeMgBr, Et_2O, 0 °C to rt, 94%; (iv) bromoacetyl bromide, py, CH_2Cl_2, 0 °C to rt, 89%; (v) $P(OEt)_3$, 95 °C, 100%; (vi) NaH, THF, 0 °C to rt, 75%; (vii) DIBAL-H, CH_2Cl_2, −10 to 0 °C; (viii) PPTS, PhMe/EtOH (2:1), rt, 74% over two steps.

An alternative route was established for the synthesis of the *β*-hydroxy ketone intermediate required to prepare acetal coupling partner **9** (Scheme 5). The chirality was derived from

Scheme 5. Synthesis of Acetal Coupling Partner 9[a]

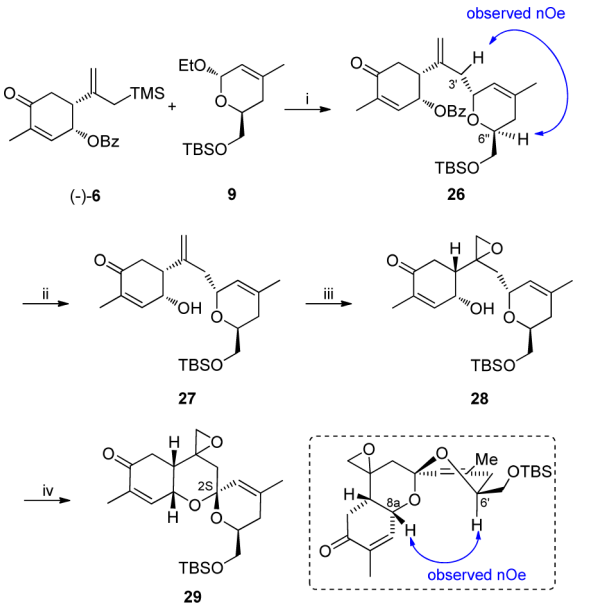


[a]Reagents and conditions: (i) isopropenyl-MgBr, CuI, THF, −40 to −10 °C, 73%; (ii) OsO_4, NMO, 2,6-lutidine, acetone/H_2O (10:1), rt, then $PhI(OAc)_2$, 92%; (iii) bromoacetyl bromide, py, CH_2Cl_2, 0 °C to rt, 85%; (iv) $P(OEt)_3$, 100 °C, 94%; (v) LiO^{t}Bu, THF, 40 °C, 84%; (vi) DIBAL-H, CH_2Cl_2, −10 to 0 °C; (vii) PPTS, PhMe/EtOH (2:1), rt, 84% over two steps

known (*S*)-epoxide **21**,[17] which was opened with isopropenylmagnesium bromide in the presence of catalytic copper(I) iodide to afford alkene **22**.[18] The one-pot procedure for dihydroxylation/oxidative cleavage developed by Nicolaou and co-workers was then employed for the conversion of alkene **22** to ketone **14**.[19] Analogous to the synthesis of **11**, acetylation and a Michaelis−Arbuzov reaction then provided phosphonate **12** in preparation for the intramolecular HWE olefination.[15,16] When the previously successful HWE conditions (sodium hydride in THF) were applied to **12**, significant elimination of the ester group was observed, forming unsaturated ketone **25**. Similar undesired elimination was observed by Ardisson and co-workers, who found that employing lithium *tert*-butoxide as the base in THF at 40 °C greatly improved selectivity for the HWE product.[20] Pleasingly, when these conditions were applied to the intramolecular HWE reaction of phosphonate **12**, the desired lactone **24** was isolated in 84% yield with minimal elimination observed. Reduction and subsequent acetalization of lactone **24** provided acetal coupling partner **9** in good yield.

Construction of the Sesterterpenoid Skeleton. Gratified with the synthesis of the desired coupling partners **6**, **7**, and **9**, attention turned to the Hosomi−Sakurai-type coupling to construct the core carbon skeleton. Initial investigations focused on the coupling of **6** and **9**, with the view that the final transformation would prove less problematic in the absence of the alkenyl side chain (Scheme 6). On the basis of

Scheme 6. Synthesis of the Spiroketal Core of Phorbaketal A[a]



[a]Reagents and conditions: (i) $InCl_3$, CH_2Cl_2, 0 °C to rt, 81%; (ii) K_2CO_3, MeOH/THF (1:1), rt, 91%; (iii) V(O)(acac)$_2$, TBHP, CH_2Cl_2, rt, 45%; (iv) DDQ, 2,6-dichloropyridine, $LiClO_4$, 4 Å molecular sieves, DCE, rt, 21%.

previous success in using $InCl_3$ for transformations of spiroketal systems within our group,[21] this Lewis acid was initially employed and found to effectively promote the desired coupling under mild conditions. Treatment of **6** and **9** with $InCl_3$ (1.1 equiv) in dichloromethane at 0 °C followed by warming to room temperature afforded the coupled product **26** in 81% yield. **26** was produced exclusively as the 2″,6″-*anti* diastereomer, confirmed by a characteristic NOE correlation between H-3′ and H-6″. Attempts to employ a catalytic loading of $InCl_3$ were unsuccessful as the reaction no longer proceeded to completion. The success of this coupling reaction was particularly satisfying as it was readily achieved in the presence of the unprotected ketone, negating the need for additional protection or redox steps.

Following removal of the benzoyl protecting group, epoxidation of alcohol **27** was explored. The use of vanadyl acetylacetonate/*tert*-butyl hydroperoxide-based conditions for the selective epoxidation of terpenoid substrates was first

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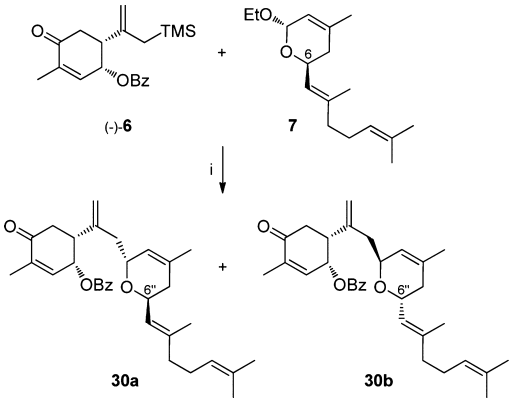
demonstrated by Sharpless and co-workers.[22] These conditions were applied to effect the epoxidation of alcohol **27**, providing epoxide **28** in 45% yield as a 10:1 mixture of diastereomers. The relative stereochemistry of the epoxide center was not able to be elucidated by analysis of the NOESY spectrum.

Investigations into the oxidative cyclization of **28** to construct the spiroketal core of phorbaketal A (**1**) began by exploring DDQ-based conditions commonly employed by Floreancig and co-workers.[23] Accordingly, treatment of cyclization precursor **28** with excess DDQ (2 equiv), 2,6-dichloropyridine (4 equiv), and catalytic lithium perchlorate furnished spiroketal **29** in an unoptimized 21% yield. Spiroketal **29** was isolated as the single (2*S*)-diastereoisomer, assigned on the basis of a characteristic NOE correlation observed between H-8a and H-6′.

Satisfied that the key Hosomi–Sakurai coupling, selective epoxidation, and oxidative cyclization had been successfully carried out, the overall approach toward **1** was now carefully reconsidered. A model study, as well as observations made in unrelated work, had demonstrated that obtaining good stereoselectivity and yield using a Julia olefination to append the alkenyl side chain to an aldehyde derived from **29** would be very challenging. Trisubstituted alkenes in general are not easily formed using Julia methodology. It was also clear that using acetal **7**, with the side chain already in place, would increase the overall efficiency of the synthesis. Therefore, while the synthesis of spiroketal **29** might be an important intermediate for generation of analogues of **1** in the future, endeavors toward the target compound were refocused to include fully functionalized acetal **7**.

The previously successful $InCl_3$-promoted Hosomi–Sakurai conditions were next applied to the coupling of allylsilane **6** and acetal **7** (Scheme 7). Surprisingly, under these reaction

Scheme 7. Hosomi–Sakurai Coupling of Allylsilane 6 and Acetal 7[a]

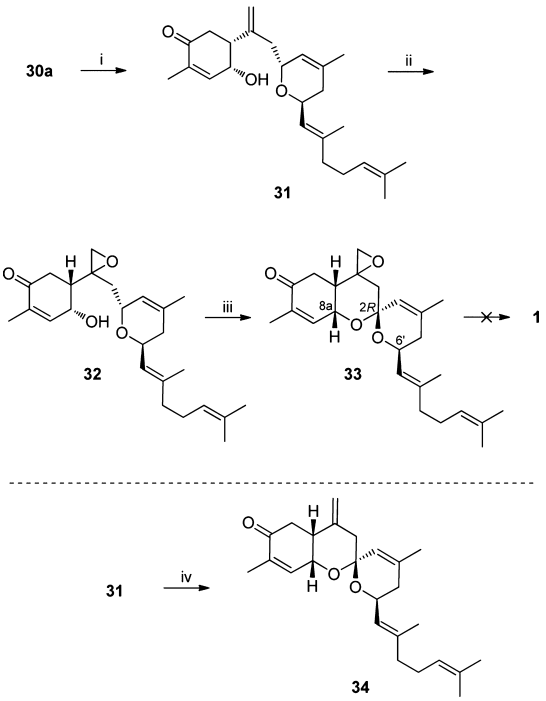


[a]Reagents and conditions: (i) $InCl_3$ (1.1 equiv), CH_2Cl_2, 0 °C, 72%, 2:1 **30a**/**30b** or (TMS)OTf (1.1 equiv), CH_2Cl_2, −78 °C, 75% **30a**.

conditions the diastereomeric products **30a** and **30b** were produced in a 2:1 ratio, resulting from some unexpected epimerization of the C-6 stereocenter.[24] Pleasingly, when (TMS)OTf (1.1 equiv) was employed as the Lewis acid at −78 °C, only the desired diastereomer **30a** was obtained in 75% yield. Use of (TMS)OTf at higher temperatures resulted in the formation of complex mixtures, and no reaction took place when $InCl_3$ was used at temperatures below −10 °C.

Following benzoyl deprotection, selective epoxidation of **31** was carried out under conditions analogous to those employed for **27**, providing **32** in 52% yield (Scheme 8). After further

Scheme 8. Synthesis of Spiroketals 33 and 34[a]



[a]Reagents and conditions: (i) K_2CO_3, MeOH–THF (1:1), rt, 76%; (ii) V(O)(acac)$_2$, TBHP, Et_2O–MeCN (1:1), rt, 60–65%; (iii) DDQ, acetone, rt, 53%; (iv) DDQ, acetone, rt, 44%.

screening a range of solvents for this transformation, it was found that a mixture of diethyl ether and acetonitrile (1:1) was optimal, giving rise to improved 60–65% yields of **32**. The stereochemistry of the resultant epoxide was not able to be assigned on the basis of analysis of the NOESY spectrum.

Attention next turned to the oxidative cyclization of **32** to construct the spiroketal core, a significant challenge considering the numerous potential sites for oxidation. Investigations began by employing the previously successful conditions (DDQ/2,6-dichloropyridine/$LiClO_4$), which provided the desired spiroketal **33** in 20% yield.[23] TLC analysis of small-scale reactions indicated that, in the absence of 2,6-dichloropyridine or $LiClO_4$, or both, the reaction was not adversely affected. By changing the solvent to benzene and using a larger excess of DDQ (3 equiv), the yield was slightly improved to 34%. When acetone was employed as the solvent, the desired spiroketal **33** was isolated in 53% yield. Once again, the NOE correlation between H-8a and H-6′ confirmed the *R* configuration of the spirocenter of **33**, which is consistent with the stereochemistry of phorbaketal A (**1**). The *exo* olefinic spiroketal skeleton **34** was also constructed by cyclization of intermediate **31** under the optimized conditions.

With access to the desired sesterterpenoid scaffold secured, investigations into the epoxide opening step required for preparation of phorbaketal A were also undertaken. Despite examination of a wide range of conditions (see the Supporting Information) reported to promote allylic alcohol formation from epoxides,[25−30] it has not yet been possible to effect the desired transformation for this complex substrate.

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The synthetic studies reported herein have led to the development of a convergent synthetic approach toward the core structure of phorbaketal A and the wider family of structurally related natural products. Our approach included a robust Hosomi−Sakurai coupling reaction with highly complex substrates and a selective DDQ-promoted oxidative spirocyclization of a sensitive, highly unsaturated cyclization precursor. This synthetic study provides a solid foundation for future endeavors into the synthesis of the natural product family and importantly will enable preparation of structural analogues for biological testing and structure−activity relationship studies.

EXPERIMENTAL SECTION

General Procedures. Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen using standard techniques. Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl. CH_2Cl_2 was freshly distilled from calcium hydride. All other reagents were used as received unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as the visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Silica gel (60, 230−400 mesh) was used for flash column chromatography. NMR spectra were recorded at room temperature in $CDCl_3$ solution on either a spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or a spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million on the δ scale, and coupling constants, J, are in hertz. Multiplicities are reported as "s" (singlet), "br s" (broad singlet), "d" (doublet), "dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), "t" (triplet), and "m" (multiplet). Where distinct from those due to the major diastereomer, resonances due to minor diastereomers are denoted by an asterisk. ^{1}H and ^{13}C NMR resonances were assigned using a combination of DEPT 135, COSY, HSQC, HMBC, and NOESY spectra. Infrared (IR) spectra were recorded using a thin film on a composite of zinc selenide and diamond crystal on an FT-IR system transform spectrometer. Melting points are uncorrected. High-resolution mass spectrometry (HRMS) was performed using a spectrometer operating at a nominal accelerating voltage of 70 eV or a TOF-Q mass spectrometer.

(*S*,*E*)-3-Hydroxy-1-((*R*)-4-isopropyl-2-thioxothiazolidin-3-yl)-5,9-dimethyldeca-4,8-dien-1-one (17). $TiCl_4$ (5.6 mL, 51.1 mmol) was added dropwise over 10 min to a solution of **15** (9.40 g, 46.2 mmol) in CH_2Cl_2 (300 mL) at 0 °C. The reaction mixture was stirred for 10 min and cooled to −78 °C, and DIPEA (9.0 mL, 51.1 mmol) was added dropwise. The mixture was stirred at −78 °C for 2 h, and then a solution of aldehyde **16** (4.68 g, 30.7 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 30 min. After the resulting mixture was stirred for 2 h, water (200 mL) was added, and the mixture was allowed to warm to rt and extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (4:1 to 2:1) as the eluent afforded title compound **17** (7.56 g, 70%) as a yellow oil: $[\alpha]_D^{20}$ −354.4 (c 1.17, $CHCl_3$); IR (film) ν_{max} 3420, 2964, 2927, 1690, 1443, 1353, 1305, 1278, 1254, 1154, 1092, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.24 (d, J = 8.5, Hz, 1H, H-4), 5.17−5.14 (m, J = 6.6, 6.6 Hz, 1H), 5.10−5.05 (m, 1H), 4.91 (ddd, J = 8.7, 8.5, 2.9 Hz, 1H), 3.55−3.49 (m, 2H), 3.32 (dd, J = 17.6, 8.7 Hz, 1H), 3.03 (dd, J = 11.5, 1.0 Hz, 1H), 2.62 (br s, 1H), 2.42−2.33 (m, 1H), 2.12−1.99 (m, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.0, 172.9, 139.4, 131.8, 125.4, 123.9, 71.5, 65.2, 45.7, 39.5, 31.0, 30.7, 26.4, 25.8, 19.2, 17.9, 17.8, 16.8; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{18}H_{29}NNaO_2S_2$ 378.1532, found 378.1530.

(*S*,*E*)-3-Hydroxy-*N*-methoxy-*N*,5,9-trimethyldeca-4,8-dienamide (18). A solution of aldol **17** (7.60 g, 21.4 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (6.22 g, 64.2 mmol), and imidazole (7.28 g, 0.11 mol) in CH_2Cl_2 (210 mL) was stirred at rt for 18 h. Saturated aqueous NH_4Cl (150 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (4:1 to 2:1) as the eluent afforded title compound **18** (4.64 g, 85%) as a colorless oil: $[\alpha]_D^{20}$ −53.9 (c 1.18, $CHCl_3$); IR (film) ν_{max} 3437, 2972, 2921, 1642, 1438, 1384, 1180, 1107, 1023, 991 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.22 (d, J = 8.4 Hz, 1H), 5.08−5.03 (m, 1H), 4.81−4.76 (m, 1H), 3.72 (br s, 1H), 3.66 (s, 3H), 3.17 (s, 3H), 2.58−2.56 (m, 2H), 2.09−1.96 (m, 4H), 1.66 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 138.6, 131.6, 125.7, 123.9, 65.1, 61.2, 39.4, 38.5, 31.8, 26.3, 25.6, 17.6, 16.6; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{14}H_{25}NNaO_3$ 278.1727, found 278.1733.

(*S*,*E*)-4-Hydroxy-6,10-dimethylundeca-5,9-dien-2-one (13). MeMgBr (2.5 M in Et_2O, 18.0 mL, 45.0 mmol) was added dropwise to a solution of amide **17** in Et_2O (80 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 1 h. Saturated aqueous NH_4Cl (100 mL) was added, and the mixture was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (4:1) as the eluent afforded title compound (*S*)-**13** (3.58 g, 94%) as a colorless oil: $[\alpha]_D^{20}$ −19.4 (c 1.29, $CHCl_3$); IR (film) ν_{max} 3409, 2967, 2917, 2857, 1708, 1669, 1438, 1376, 1358, 1264, 1157, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.17 (d, J = 8.5 Hz, 1H), 5.09−5.05 (m, 1H), 4.83−4.79 (m, 1H), 2.79 (d, J = 3.4 Hz, 1H), 2.65 (dd, J = 17.1, 8.5 Hz, 1H), 2.55 (dd, J = 17.1, 3.6 Hz, 1H), 2.16 (s, 3H), 2.11−1.98 (m, 4H), 1.66 (s, 6H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.3, 138.9, 131.6, 125.6, 123.8, 64.7, 50.3, 39.4, 30.8, 26.3, 25.6, 17.6, 16.6; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{13}H_{22}NaO_2$ 233.1512, found 233.1516.

(*S*,*E*)-6,10-Dimethyl-2-oxoundeca-5,9-dien-4-yl 2-Bromoacetate (19). Bromoacetyl bromide (0.35 mL, 4.13 mmol) was added dropwise to a solution of alcohol **13** (0.58 g, 2.76 mmol) and pyridine (0.40 mL, 5.52 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The reaction was stirred for 1 h and then warmed to rt for a further 1 h. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (9:1) as the eluent afforded title compound **19** (0.81 g, 89%) as a colorless oil: $[\alpha]_D^{20}$ +6.0 (c 1.17, $CHCl_3$); IR (film) ν_{max} 2966, 2920, 2859 1727, 1274, 1157, 110.6, 1032, 922 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.93 (ddd, J = 9.3, 7.7, 5.5 Hz, 1H), 5.09 (d, J = 9.3 Hz, 1H), 5.02−4.98 (m, 1H), 3.77 (s, 2H), 2.88 (dd, J = 16.4, 7.7 Hz, 1H), 2.64 (dd, J = 16.4, 5.5 Hz, 1H), 2.17 (s, 3H), 2.07−1.95 (m, 4H), 1.79 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.6, 166.0, 142.7, 131.8, 123.5, 121.1, 69.7, 48.1, 39.4, 30.6, 26.2, 26.1, 25.6, 17.6, 16.8; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{15}H_{23}BrNaO_3$ 353.0723, found 353.0722.

(*S*,*E*)-6,10-Dimethyl-2-oxoundeca-5,9-dien-4-yl 2-(Diethoxyphosphoryl)acetate (11). A mixture of bromide **19** (0.80 g, 2.42 mmol) and triethyl phosphite (0.50 mL, 2.89 mmol) was heated at 70 °C for 1 h and then 95 °C for 3 h. The reaction mixture was cooled to rt and purified directly by flash chromatography using hexanes−EtOAc (4:1 to EtOAc only) as the eluent to afford title compound **11** (0.94 g, quantitative) as a pale yellow oil: $[\alpha]_D^{20}$ −0.6 (c 1.03, $CHCl_3$); IR (film) ν_{max} 2980, 2921, 1729, 1260, 1023, 964 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.90 (ddd, J = 9.3, 7.4, 5.9 Hz, 1H), 5.07 (d, J = 9.3 Hz, 1H), 5.03−4.98 (m, 1H), 4.12 (dq, J = 7.6 Hz, $^3J_{HP}$ = 8.0 Hz, 4H), 2.89 (d, $^2J_{HP}$ = 14.4 Hz, 2H), 2.84 (dd, J = 16.2, 7.4 Hz), 2.59 (dd, J = 16.2, 5.9 Hz, 1H), 2.13 (s, 3H), 2.06−1.91 (m, 4H), 1.75 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.31 (t, J = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.8, 164.8 (d, $^2J_{CP}$ = 6.2 Hz), 142.3, 131.9, 123.7, 121.7, 69.1, 62.8, 48.4, 39.6, 34.6, 30.7, 26.3, 25.7, 17.7,

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17.0, 16.4 (d, $^2J_{CP}$ = 6.1 Hz), 16.2 (d, $^2J_{CP}$ = 6.6 Hz); HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{19}H_{33}NaO_6P$ 411.1907, found 411.1912.

(*S*,*E*)-6-(2,6-Dimethylhepta-1,5-dien-1-yl)-4-methyl-5,6-dihydro-2*H*-pyran-2-one (20). NaH (60% in paraffin oil, 0.11 g, 2.66 mmol) was slowly added to a solution of phosphonate **11** (0.86 g, 2.21 mmol) in THF (44 mL) at 0 °C. The mixture was warmed to rt and stirred for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the mixture extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (9:1 to 4:1) as the eluent afforded title compound **20** (0.39 g, 75%) as a pale yellow oil: $[\alpha]_D^{20}$ −40.9 (*c* 1.05, $CHCl_3$); IR (film) ν_{max} 2969, 2919, 2856, 1713, 1382, 1243, 1041, 989, 848 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (s, 1H), 5.34−5.30 (m, 1H), 5.13−5.04 (m, 2H), 2.42−2.33 (m, 1H), 2.20 (dd, J = 18.0, 4.0 Hz, 1H), 2.13−2.01 (m, 4H), 1.98 (s, 3H), 1.71 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 157.0, 142.5, 132.0, 123.6, 121.9, 116.7, 74.2, 39.4, 35.2, 26.2, 25.7, 23.0, 17.7, 16.8; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{15}H_{22}NaO_2$ 257.1512, found 257.1520.

(2*S*,6*S*)-2-((*E*)-2,6-dimethylhepta-1,5-dien-1-yl)-6-ethoxy-4-methyl-3,6-dihydro-2*H*-pyran (7). DIBAL (1 M in toluene, 1.0 mL, 1.02 mmol) was added dropwise over 15 min to a solution of lactone **20** (0.20 g, 0.85 mmol) in CH_2Cl_2 (13 mL) at −10 °C. The reaction mixture was stirred for 45 min at −10 to 0 °C, followed by the addition of MeOH (1.0 mL) and saturated aqueous potassium sodium tartrate (15 mL). CH_2Cl_2 was removed in vacuo and the resultant mixture extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated aqueous potassium sodium tartrate (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was not purified prior to the next step.

PPTS (21 mg, 0.085 mmol) was added to a solution of the crude hemiacetal in toluene/EtOH (2:1, 6 mL) at rt. After the resulting mixture was stirred for 3 h at rt, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexane−EtOAc (9:1) as the eluent afforded title compound **20** (0.17 g, 74% over two steps) as a colorless oil: $[\alpha]_D^{20}$ −22.4 (*c* 1.09, $CHCl_3$); IR (film) ν_{max} 2971, 2915, 1878, 1444, 1381, 1136, 1061, 1008, 974 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.48−5.47 (m, 1H), 5.23 (d, *J* = 8.3 Hz, 1H), 5.12−5.08 (m, 1H), 4.99−4.98 (m, 1H), 4.69−4.63 (m, 1H), 3.86 (dq, *J* = 9.6, 7.1, 1H), 3.53 (dq, *J* = 9.6, 7.1, 1H), 2.15−2.00 (m, 5H), 1.80 (dd, *J* = 17.4, 3.5 Hz, 1H), 1.74 (s, 3H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.4, 137.6, 131.7, 124.8, 124.1, 119.8, 95.2, 63.6, 63.2, 39.6, 35.8, 26.5, 25.8, 22.9, 17.8, 16.8, 15.5; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{17}H_{28}NaO_2$ 287.1982, found 287.1990.

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-methylpent-4-en-2-ol (22). Isopropenylmagnesium bromide (0.5 M in THF, 23 mL, 11.7 mmol) was added to a stirred suspension of epoxide **21** (2.0 g, 10.6 mmol) and CuI (0.20 g, 1.06 mmol) in THF (27 mL) at −40 °C. After 1 h the reaction was allowed to warm to −10 °C and stirred for a further 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and the mixture extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (40 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (30:1) as the eluent afforded title compound **22** (1.90 g, 73%) as a colorless oil: $[\alpha]_D^{20}$ +2.5 (*c* 1.09, $CHCl_3$) [lit.[31] $[\alpha]_D^{25}$ −1.86 (*c* 1.30, $CHCl_3$), for opposite enantiomer]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.83 (s, 1H), 4.78 (s, 1H), 3.85−3.78 (m, 1H), 3.61 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.46 (dd, *J* = 9.9, 6.8 Hz, 1H), 2.37 (d, *J* = 3.5 Hz, 1H), 2.17 (d, *J* = 6.3 Hz, 2H), 1.77 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H,); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.4, 113.0, 69.7, 66.9, 41.7, 26.0, 22.6, 18.4, −5.21, −5.25. The spectroscopic data were in agreement with literature values.[18]

(*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxypentan-2-one (14). 2,6-Lutidine (3.0 mL, 26.0 mmol), NMO (2.28 g, 19.5 mmol), and OsO_4 (0.66 mL, 0.065 mmol, 2.5% in *tert*-butyl alcohol) were added to a solution of alkene **22** (3.00 g, 13.0 mmol) in acetone/water (10:1, 130 mL) at rt. The resulting mixture was stirred at rt for 2.5 h, and (diacetoxyiodo)benzene (6.28 g, 19.5 mmol) was added in one portion. After a further 2 h at rt, the reaction was quenched with saturated aqueous $Na_2S_2O_4$ (100 mL) and the mixture extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated aqueous $CuSO_4$ (2 × 80 mL) and brine (80 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (9:1 to 4:1) as the eluent afforded title compound **14** (2.78 g, 92%) as a colorless oil: $[\alpha]_D^{20}$ −16.0 (*c* 1.19, $CHCl_3$) (lit.[30] synthesis racemic); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.13−4.04 (m, 1H), 3.59 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.53 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.87 (d, *J* = 4.4 Hz, 1H), 2.61 (d, *J* = 6.1 Hz, 2H), 2.19 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.6, 68.3, 66.4, 46.6, 30.9, 25.9, 18.4, −5.2, −5.3. The spectroscopic data were in agreement with literature values.[32]

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-oxopent-2-yl 2-Bromoacetate (23). Bromoacetyl bromide (0.45 mL, 5.16 mmol) was added dropwise to a solution of alcohol **14** (0.80 g, 3.47 mmol) and pyridine (0.54 mL, 6.88 mmol) in CH_2Cl_2 (7.0 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min, then warmed to rt, and stirred for 30 min. Water (30 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (15:1) as the eluent afforded title compound **23** (1.04 g, 85%) as a colorless oil: $[\alpha]_D^{20}$ −19.2 (*c* 1.04, $CHCl_3$); IR (film) ν_{max} 2955, 2930, 2857, 1739, 1718, 1472, 1463, 1360, 1277, 1256, 1103, 833, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.33−5.26 (m, 1H), 3.79 (s, 2H), 3.77−3.67 (m, 1H), 2.88−2.73 (m, 2H), 2.17 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.1, 166.6, 72.6, 63.4, 43.8, 30.5, 25.9, 25.9, 18.3, −5.3; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{13}H_{25}BrNaO_4Si$ 375.0598, found 375.0595.

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-oxopent-2-yl 2-(Diethoxyphosphoryl)acetate (12). A mixture of bromide **23** (2.50 g, 7.08 mmol) and triethyl phosphite (1.5 mL, 8.49 mmol) was heated at 70 °C for 30 min, 80 °C for 30 min, and then 100 °C for 2 h. The reaction mixture was purified directly by flash chromatography using hexanes−EtOAc (4:1 to 1:3) as the eluent to afford title compound **12** (2.74 g, 94%) as a pale yellow oil: $[\alpha]_D^{20}$ −15.4 (*c* 1.11, $CHCl_3$); IR (film) ν_{max} 2955, 2931, 2858, 1737, 1719, 1473, 1390, 1361, 1254, 1109, 1047, 1022, 969, 834, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.29−5.22 (m, 1H), 4.18−4.07 (m, 4H), 3.73 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.63 (dd, *J* = 10.9, 4.8 Hz, 1H), 2.90 (dd, *J* = 1.2 Hz, $^2J_{HP}$ = 21.6 Hz, 2H), 2.81 (dd, *J* = 17.0, 6.1 Hz, 1H), 2.71 (dd, *J* = 17.0, 6.8 Hz, 1H,), 2.14 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 6H), 0.84 (s, 9H), 0.01 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.2, 165.1 (d, $^2J_{CP}$ = 6.1 Hz), 71.9, 63.3, 62.76 (d, $^2J_{CP}$ = 6.1 Hz), 62.73 (d, $^2J_{CP}$ = 6.1 Hz), 43.9, 34.4 (d, J_{CP} = 133.4 Hz), 30.4, 25.8, 18.2, 16.42, 16.36, −5.4; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{17}H_{35}NaO_7PSi$ 433.1782, found 433.1786.

6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-methyl-5,6-dihydro-2*H*-pyran-2-one (24). LiO^tBu (0.12 g, 1.44 mmol) was added to a solution of phosphonate **12** (0.59 g, 1.44 mmol) in THF (32 mL) at 40 °C. The reaction mixture was stirred for 1 h, quenched with saturated aqueous NH_4Cl (40 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (20:1 to 9:1) as the eluent afforded title compound **24** (0.31 g, 84%) as a pale yellow oil: $[\alpha]_D^{20}$ −92.4 (*c* 1.06, $CHCl_3$); IR (film) ν_{max} 2953, 2929, 2857, 1720, 1387, 1245, 1124, 832, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.77 (s, 1H), 4.44−4.36 (m, 1H), 3.83−3.73 (m, 2H), 2.49 (dd, *J* = 18.0, 10.9 Hz, 1H), 2.25 (dd, *J* = 18.0, 4.2 Hz, 1H), 1.98 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 157.1, 116.3, 77.2, 64.3, 31.1, 25.9, 23.1,

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18.4, −5.2, −5.3; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{13}H_{24}NaO_3Si$ 279.1387, found 279.1390.

(2*S*,6*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-ethoxy-4-methyl-3,6-dihydro-2*H*-pyran (9). To a solution of lactone **24** (1.28 g, 4.99 mmol) in CH_2Cl_2 (75 mL) at −10 °C was added DIBAL (1 M in cyclohexane, 6.0 mL, 5.99 mmol) dropwise over 15 min. The reaction mixture was stirred for 45 min at −10 to 0 °C, followed by the addition of MeOH (4 mL) and saturated aqueous potassium sodium tartrate (70 mL). The mixture was stirred for 1 h and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed with saturated aqueous potassium sodium tartrate (70 mL) and brine (70 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was not purified prior to the next step.

To a solution of crude hemiacetal in toluene/EtOH (2:1, 38 mL) was added PPTS (0.30 g, 1.19 mmol) at rt. After 2 h, saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (20:1) as the eluent afforded title compound **9** (1.21 g, 84% over two steps) as a pale yellow oil: $[\alpha]_D^{20}$ −35.8 (*c* 1.06, $CHCl_3$); IR (film) ν_{max} 2929, 2858, 1683, 1472, 1463, 1383, 1251, 1127, 1093, 1063, 1001, 834, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.46 (s, 1H), 4.97 (s, 1H), 4.01−3.94 (m, 1H), 3.84 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.71 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.63 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.49 (dq, *J* = 9.5, 7.1 Hz, 1H), 2.00−1.92 (m, 1H), 1.78 (dd, *J* = 17.2, 3.5 Hz, 1H), 1.73 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.1, 119.9, 95.0, 67.5, 66.2, 62.9, 31.9, 26.0, 23.0, 18.4, 15.5, −5.1, −5.2; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{15}H_{30}NaO_3Si$ 309.1856, found 309.1848.

(4*R*,5*R*)-5-(3-((2*R*,6*S*)-6-(((*tert*-Butyldimethylsilyl)oxy)-methyl)-4-methyl-5,6-dihydro-2*H*-pyran-2-yl)prop-1-en-2-yl)-4-(benzoyloxy)-2-methylcyclohex-2-enone (26). $InCl_3$ (0.14 g, 0.64 mmol) was added to a solution of silane **6** (0.20 g, 0.58 mmol) and acetal **9** (0.18 g, 0.64 mmol) in CH_2Cl_2 (7.3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, quenched with water (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (20:1) as the eluent afforded title compound **26** (0.24 g, 81%) as a yellow oil: $[\alpha]_D^{20}$ −229.7 (*c* 1.12, $CHCl_3$); IR (film) ν_{max} 2954, 2928, 2857, 1718, 1683, 1451, 1262, 1104, 1095, 833, 776, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 6.91−6.88 (m, 1H), 5.77 (dd, *J* = 5.4, 3.3 Hz, 1H), 5.34−5.32 (m, 1H), 5.07 (s, 1H), 4.94 (s, 1H), 4.27−4.21 (m, 1H), 3.79−3.73 (m, 1H), 3.65 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.51 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.20−3.14 (m, 1H), 2.98 (dd, *J* = 16.2, 13.0 Hz, 1H), 2.62 (dd, *J* = 16.2, 3.4 Hz, 1H), 2.45 (dd, *J* = 14.8, 8.5 Hz, 1H), 2.18 (dd, *J* = 14.8, 4.7 Hz, 1H), 1.90−1.88 (m, 2H), 1.85 (s, 3H), 1.67 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.4, 165.8, 144.9, 139.2, 138.7, 133.2, 131.9, 130.0, 129.7, 128.5, 122.6, 114.1, 72.8, 68.9, 66.4, 65.9, 43.1, 39.6, 38.1, 31.8, 26.0, 23.3, 18.5, 15.7, −5.1, −5.2; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{30}H_{42}NaO_5Si$ 533.2694, found 533.2693.

(4*R*,5*R*)-5-(3-((2*R*,6*S*)-6-(((*tert*-Butyldimethylsilyl)oxy)-methyl)-4-methyl-5,6-dihydro-2*H*-pyran-2-yl)prop-1-en-2-yl)-4-hydroxy-2-methylcyclohex-2-enone (27). K_2CO_3 (0.19 g, 1.41 mmol) was added to a solution of **26** (0.24 g, 0.47 mmol) in MeOH/THF (1:1, 10 mL) at rt. The reaction mixture was stirred for 4 h, saturated aqueous NH_4Cl (10 mL) was added. and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (5:1) as the eluent afforded title compound **27** (0.17 g, 91%) as a pale yellow oil: $[\alpha]_D^{20}$ −100.6 (*c* 1.02, $CHCl_3$); IR (film) ν_{max} 3446, 2928, 2857, 1678, 1472, 1446, 1380, 1361, 1252, 1093, 1043, 937, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.74−6.71 (m, 1H), 5.40−5.37 (m, 1H), 5.16 (s, 1H), 4.97 (s, 1H), 4.46 (br s, 1H), 4.40−4.32 (m, 1H), 3.84−3.76 (m, 1H), 3.63 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.55 (dd, *J* = 10.5, 4.6 Hz, 1H), 2.93−2.79 (m, 2H), 2.52 (dd, *J* = 14.2, 10.3 Hz, 1H), 2.31 (d, *J* = 12.1 Hz, 1H), 2.22 (dd, *J* = 14.2, 4.4 Hz, 1H), 1.83 (d, *J* = 6.6 Hz, 2H), 1.80 (s, 3H), 1.71 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.5, 144.3, 142.4, 136.9, 131.7, 122.8, 116.6, 71.0, 69.0, 66.3, 64.3, 44.8, 42.1, 38.0, 31.5, 26.1, 23.3, 18.6, 15.6, −5.19, −5.22; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{23}H_{38}NaO_4Si$ 429.2432, found 429.2438.

(4*R*,5*S*)-5-(2-(((2*R*,6*S*)-6-(((*tert*-Butyldimethylsilyl)oxy)-methyl)-4-methyl-5,6-dihydro-2*H*-pyran-2-yl)methyl)oxiran-2-yl)-4-hydroxy-2-methylcyclohex-2-en-1-one (28). *tert*-Butyl hydroperoxide (5.5 M in decane, 2 drops) was added to a green solution of alcohol **27** (26 mg, 0.064 mmol) and vanadyl acetylacetonate (17 mg, 0.064 mmol) in CH_2Cl_2 (0.8 mL) at rt. The reaction mixture immediately became dark red and was stirred at rt until the color faded back to a dark green, at which time additional *tert*-butyl hydroperoxide (5.5 M in decane, 1 drop) was added. This process was repeated until complete consumption of **27** was observed by TLC (6 h). Saturated aqueous $Na_2S_2O_4$ (1 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (6:1) as the eluent afforded title compound **28** (12.1 mg, 45%) as a yellow oil: $[\alpha]_D^{20}$ −57.1 (*c* 2.01, $CHCl_3$); IR (film) ν_{max} 3419, 2928, 2857, 1678, 1472, 1428, 1381, 1361, 1251, 1102, 935, 834, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.69 (qd, *J* = 5.7, 1.3 Hz, 1H), 5.27−5.26 (m, 1H), 4.61−4.57 (m, 1H), 4.16−4.11 (m, 1H), 3.83−3.77 (m, 1H), 3.65 (dd, *J* = 10.4, 7.0 Hz, 1H), 3.55 (dd, *J* = 10.4, 4.5 Hz, 1H), 2.98 (d, *J* = 4.0 Hz, 1H), 2.76 (d, *J* = 4.0 Hz, 1H), 2.71 (dd, *J* = 16.2, 12.7 Hz, 1H), 2.44−2.29 (m, 3H), 1.84−1.81 (m, 2H), 1.79 (s, 3H), 1.72−1.57 (m, 5H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.0, 142.6, 136.9, 132.3, 122.6, 69.0, 68.7, 66.1, 65.2, 59.5, 50.3, 43.1, 36.4, 35.1, 31.5, 26.1, 23.3, 18.7, 15.7, −5.1; HRMS [EI, (M + Na)$^+$] m/z calcd for $C_{23}H_{38}NaO_5Si$ 445.2381, found 445.2396.

(4a′*S*,6″*S*,8a′*R*)-6″-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4″,7′-dimethyl-4a′,5″,6″,8a′-tetrahydro-3′*H*-dispiro[oxirane-2,4′-chromene-2′,2″-pyran]-6′(5′*H*)-one (29). 2,6-Dichloropyridine (28 mg, 0.19 mmol), $LiClO_4$ (0.5 mg, 4.73 μmol), and DDQ (21 mg, 95.2 μmol) were added to a suspension of alcohol **28** (20 mg, 47.1 μmol) and 4 Å molecular sieves in DCE (0.5 mL) at rt. After 6 h, NEt_3 (2 drops) was added, and the resulting mixture was filtered through a plug of silica, washing with CH_2Cl_2 (2 × 3 mL), and the filtrate was concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (15:1 to 9:1) as the eluent afforded title compound **29** (4.2 mg, 21%) as a pale yellow oil: $[\alpha]_D^{20}$ −45.0 (*c* 0.44, $CHCl_3$); IR (film) ν_{max} 2926, 2856, 1684, 1462, 1444, 1380, 1361, 1250, 1125, 1085, 1007, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.64 (dq, *J* = 5.8, 1.5 Hz, 1H), 5.42 (s, 1H), 4.66 (dd, *J* = 5.8, 3.1 Hz, 1H), 4.09−4.02 (m, 1H), 3.71-.363 (m, 2H), 2.86−2.73 (m, 3H), 2.51 (dd, *J* = 16.2, 4.3 Hz, 1H), 2.26 (d, *J* = 13.4 Hz, 1H), 1.95 (dd, *J* = 17.2, 11.3 Hz, 1H), 1.85−1.78 (m, 5H), 1.75 (s, 3H), 1.33 (d, *J* = 13.4 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.9, 139.5, 139.4, 137.9, 122.9, 97.0, 69.4, 65.9, 63.3, 56.7, 56.4, 39.9, 38.0, 34.3, 31.4, 25.9, 22.9, 18.4, 16.0, −5.2; HRMS [EI, (M + Na)$^+$] m/z calcd for 443.2224 $C_{23}H_{36}NaO_5Si$, found 443.2210.

(4*R*,5*R*)-5-(3-((2*R*,6*S*)-6-((*E*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4-methyl-5,6-dihydro-2*H*-pyran-2-yl)prop-1-en-2-yl)-4-(benzoyloxy)-2-methylcyclohex-2-enone (30a) and (4*R*,5*R*)-5-(3-((2*S*,6*R*)-6-((*E*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4-methyl-5,6-dihydro-2*H*-pyran-2-yl)prop-1-en-2-yl)-4-(benzoyloxy)-2-methylcyclohex-2-enone (30b). *Method A.* $InCl_3$ (16.3 mg, 0.074 mmol) was added to a solution of silane (−)-**6** (23 mg, 0.067 mmol) in CH_2Cl_2 (0.7 mL) and acetal **7** (20 mg, 0.074 mmol) at 0 °C. The reaction was stirred for 1 h at 0 °C and for 30 min at rt. Saturated aqueous $NaHCO_3$ (1 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (20:1) as the eluent afforded title compounds **30a** (16.0 mg, 49%) and **30b** (7.5 mg, 23%) as pale yellow oils.

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Method B. (TMS)OTf (0.16 mL, 0.87 mmol) was added dropwise to a solution of silane (−)-**6** (0.25 g, 0.72 mmol) and acetal **7** (0.23 g, 0.87 mmol) in CH_2Cl_2 (7.3 mL) at −78 °C. The reaction was stirred at −78 °C for 2 h, saturated aqueous $NaHCO_3$ (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (30:1) as the eluent afforded title compound **30a** (0.27 g, 75%) as a pale yellow oil.

Data for ***30a:*** R_f 0.30 (EtOAc−hexanes, 20:1); $[\alpha]_D^{20}$ −227.0 (*c* 0.94, $CHCl_3$); IR (film) ν_{max} 2920, 1718, 1684, 1448, 1379, 1266, 1103, 1069, 914 711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.88−6.85 (m, 1H), 5.75 (dd, *J* = 5.7, 3.0 Hz, 1H), 5.35 (s, 1H), 5.17 (d, *J* = 7.8 Hz, 1H), 5.09−5.04 (m, 2H), 4.92 (s, 1H), 4.46 (ddd, *J* = 7.8, 7.8, 4.7 Hz, 1H), 4.23 (br s, 1H), 3.22 (br d, *J* = 13.0 Hz, 1H), 2.97 (dd, *J* = 16.4, 13.0 Hz, 1H), 2.60 (dd, *J* = 16.4, 3.4 Hz, 1H), 2.50 (dd, *J* = 14.6, 8.4 Hz, 1H), 2.22 (dd, *J* = 14.6, 4.9 Hz, 1H), 2.07−1.88 (m, 6H), 1.84 (s, 3H), 1.70 (s, 3H), 1.67 (s, 6H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.5, 165.9, 145.2, 139.4, 139.1, 138.7, 133.2, 132.2, 131.7, 130.1, 129.8, 128.5, 125.0, 124.0, 122.8, 113.9, 72.5, 66.5, 65.7, 42.9, 39.9, 39.6, 38.0, 35.5, 26.6, 25.8, 23.3, 17.8, 16.9, 15.7; HRMS [EI, $(M + Na)^+$] *m*/*z* calcd for $C_{32}H_{40}NaO_4$ 511.2819, found 511.2818.

Data for ***30b:*** R_f 0.26 (EtOAc−hexanes, 20:1); $[\alpha]_D^{20}$ −186.1 (*c* 0.75, $CHCl_3$); IR (film) ν_{max} 2970, 2918, 2855, 1718, 1683, 1448, 1266, 1104, 1069, 916, 711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.89 (dq, *J* = 5.7, 1.4 Hz, 1H), 5.76 (dd, *J* = 5.7, 2.9 Hz, 1H), 5.34 (s, 1H), 5.17 (d, *J* = 7.8 Hz, 1H), 5.09−5.04 (m, 2H), 4.97 (s, 1H), 4.41 (ddd, *J* = 7.8, 7.8 4.4 Hz, 1H), 4.30 (br s, 1H), 3.09−2.95 (m, 2H), 2.62 (dd, *J* = 15.5, 2.8 Hz, 1H), 2.44 (dd, *J* = 14.6, 8.8 Hz, 1H), 2.30 (dd, *J* = 14.6, 4.9 Hz, 1H), 2.08−1.82 (m, 9H), 1.67 (s, 6H), 1.62 (s, 3H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.4, 165.9, 143.8, 140.0, 139.1, 138.8, 133.3, 132.2, 131.7, 130.0, 129.8, 128.5, 124.9, 124.1, 122.8, 114.9, 70.4, 66.7, 65.4, 42.8, 40.2, 39.6, 38.1, 35.5, 26.5, 25.8, 23.3, 17.8, 16.8, 15.7; HRMS [EI, $(M + Na)^+$] *m*/*z* calcd for $C_{32}H_{40}NaO_4$ 511.2819, found 511.2802.

(4*R*,5*R*)-5-(3-((2*R*,6*S*)-6-((*E*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4-methyl-5,6-dihydro-2*H*-pyran-2-yl)prop-1-en-2-yl)-4-hydroxy-2-methylcyclohex-2-enone (31). K_2CO_3 (7.6 mg, 0.055 mmol) was added to a solution of ester **30a** (9.0 mg, 0.018 mmol) in MeOH/THF (1:1, 0.4 mL). The reaction mixture was stirred at rt for 24 h, water (0.5 mL) was added, and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (4:1) as the eluent afforded title compound **31** (5.4 mg, 76%) as a colorless oil: $[\alpha]_D^{20}$ −81.7 (*c* 0.59, $CHCl_3$); IR (film) ν_{max} 3426 (br), 2916, 1677, 1444, 1379, 1104, 1039, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.73−6.71 (m, 1H), 5.39−5.38 (m, 1H), 5.20−5.17 (m, 2H), 5.08−5.04 (m, 1H), 4.98 (s, 1H), 4.49 (ddd, *J* = 7.5, 7.5 4.4 Hz, 1H), 4.40−4.39 (m, 1H), 4.35−4.30 (m, 1H), 2.86−2.84 (m, 2H), 2.66 (br s, 1H), 2.49 (dd, *J* = 14.2, 9.3 Hz, 1H), 2.36−2.26 (m, 2H), 2.10−1.99 (m, 5H), 1.89−1.84 (m, 1H), 1.81 (s, 3H), 1.72 (s, 3H), 1.68−1.66 (m, 6H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.2, 145.0, 142.0, 140.5, 137.2, 132.1, 131.8, 124.4, 124.0, 122.7, 116.2, 70.7, 66.0, 64.1, 45.1, 41.6, 39.6, 37.7, 35.2, 26.5, 25.8, 23.4, 17.8, 16.8, 15.7; HRMS [EI, $(M + Na)^+$] *m*/*z* calcd for $C_{25}H_{36}NaO_3$ 407.2557, found 407.2561.

(4*R*,5*S*)-5-((*R*)-2-(((2*R*,6*S*)-6-((*E*)-2,6-dimethylhepta-1,5-dien-1-yl)-4-methyl-5,6-dihydro-2*H*-pyran-2-yl)methyl)oxiran-2-yl)-4-hydroxy-2-methylcyclohex-2-enone (32). *tert*-Butyl hydroperoxide (5.5 M in decane, 78 μL) was added to a green solution of alcohol **31** (30 mg, 0.078 mmol) and vanadyl acetylacetonate (21 mg, 0.078 mmol) in Et_2O/MeCN (1:1, 0.8 mL) at rt. After the resulting solution was stirred at rt for 30 min, saturated aqueous $Na_2S_2O_4$ (1 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (4:1 to 2:1) as the eluent afforded title compound **32** (20 mg, 65%) as a colorless solid: mp 64−66 °C; $[\alpha]_D^{20}$ −30.0 (*c* 0.22, $CHCl_3$); IR (film) ν_{max} 3439 (br), 2961, 2923, 2855, 1723, 1678, 1450, 1375, 1108, 1044, 935 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.71 (dq, *J* = 5.6, 1.8 Hz, 1H), 5.26 (s, 1H), 5.17 (d, *J* = 7.9 Hz, 1H), 5.08−5.03 (m, 1H), 4.62−4.60 (m, 1H), 4.50−4.44 (m, 1H), 4.20−4.14 (m, 1H), 3.49 (d, *J* = 3.8 Hz, 1H), 2.77 (s, 2H), 2.66 (dd, *J* = 15.7, 12.2 Hz, 1H), 2.45 (ddd, *J* = 12.2, 3.6, 3.6 Hz, 1H), 2.39−2.30 (m, 2H), 2.08−1.97 (m, 5H), 1.86−1.77 (m, 4H), 1.69 (s, 6H), 1.67 (s, 3H), 1.59−1.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.0, 142.8, 140.6, 137.0, 132.4, 131.8, 124.4, 123.9, 122.6, 68.3, 66.2, 65.1, 59.9, 49.6, 42.3, 39.5, 38.2, 35.1, 35.0, 26.5, 25.8, 23.3, 17.8, 16.8, 15.7; HRMS [EI, $(M + Na)^+$] *m*/*z* calcd for $C_{25}H_{36}NaO_4$ 423.2506, found 423.2497.

(2′*R*,4a*S*,6′*S*,8a*R*)-6-((*E*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4,7-dimethyl-4a,5,6,8a-tetrahydro-3*H*-dispiro[oxirane-2,4-chromene-2,2-pyran]-6(5*H*)-one (33). DDQ (39 mg, 0.17 mmol) was added to a suspension of alcohol **32** (23 mg, 0.057 mmol) in acetone (0.6 mL) at rt. The mixture was stirred for 24 h, then 1 M aqueous sodium hydroxide (3 mL) was added, and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (9:1) as the eluent afforded title compound **33** (12.1 mg, 53%) as a pale yellow oil: $[\alpha]_D^{20}$ −39.7 (*c* 0.22, $CHCl_3$); IR (film) ν_{max} 2963, 2922, 1726, 1685, 1445, 1380, 1287, 1223, 1170, 1109, 1012, 983, 948 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.65 (d, *J* = 5.8, Hz, 1H), 5.42 (s, 1H), 5.23 (d, *J* = 8.2 Hz, 1H), 5.12−5.08 (m, 1H), 4.71−4.65 (m, 1H), 4.55 (dd, *J* = 5.8, 3.2 Hz, 1H), 2.86−2.75 (m, 3H), 2.50 (dd, *J* = 16.1, 4.1 Hz, 1H), 2.24 (d, *J* = 13.5 Hz, 1H), 2.14−1.97 (m, 5H,), 1.86−1.79 (m, 5H), 1.74 (s, 3H), 1.71 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.35 (d, *J* = 13.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 139.6, 139.4, 139.2, 138.4, 131.9, 125.0, 123.9, 122.8, 97.1, 65.4, 63.5, 56.5, 56.4, 39.9, 39.6, 38.2, 35.4, 34.3, 26.4, 25.8, 23.0, 18.0, 17.0, 16.1; HRMS [EI, $(M + Na)^+$] *m*/*z* calcd for $C_{25}H_{34}NaO_4$ 421.2349, found 421.2351.

(2*R*,4a*R*,6′*S*,8a*R*)-6′-((*E*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4′,7-dimethyl-4-methylene-3,4,4a,5′,6′,8a-hexahydrospiro-[chromene-2,2′-pyran]-6(5*H*)-one (34). DDQ (35 mg, 0.16 mmol) was added to a suspension of alcohol **31** (20 mg, 0.052 mmol) in acetone (0.5 mL) at rt. The mixture was stirred for 24 h, then 1 M aqueous sodium hydroxide (3 mL) was added, and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes−EtOAc (15:1) as the eluent afforded title compound **34** (8.8 mg, 44%) as a pale yellow oil: $[\alpha]_D^{20}$ −12.5 (*c* 0.88, $CHCl_3$); IR (film) ν_{max} 2981, 2885, 1683, 1446, 1382, 1230, 1167, 1104, 1009, 981 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.63 (dq, *J* = 5.9, 1.3 Hz, 1H), 5.42 (s, 1H), 5.26 (d, *J* = 8.5 Hz, 1H), 5.11−5.06 (m, 1H), 4.93 (t, *J* = 1.8 Hz, 1H), 4.87 (t, *J* = 1.8 Hz, 1H), 4.71−4.65 (m, 1H), 4.45−4.43 (m, 1H), 2.91 (dd, *J* = 15.7, 13.6 Hz, 1H), 2.77 (ddd, *J* = 13.6, 3.6, 3.6 Hz, 1H), 2.50 (dt, *J* = 14.5, 2.0 Hz, 1H), 2.31−2.25 (m, 2H), 2.13−2.00 (m, 5H), 1.83−1.78 (m, 4H), 1.75 (s, 3H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.7, 142.2, 140.4, 139.4, 138.9, 138.2, 131.8, 124.9, 124.0, 123.1, 112.8, 96.2, 65.4, 64.1, 41.1, 39.8, 39.6, 38.6, 35.6, 26.5, 25.8, 22.9, 17.8, 16.8, 16.0; HRMS [EI, $(M + Na)^+$] *m*/*z* calcd for $C_{25}H_{34}NaO_3$ 405.2400, found 405.2410.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of compounds **7**, **9**, **11**−**14**, **17**−**20**, **22**−**24**, and **26**−**34**, proposed mechanism of C-6 epimerization, and table of conditions investigated in attempted transformation of epoxide **33** to phorbaketal A (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Rho, J.-R.; Hwang, B.; Sim, C.; Joung, S.; Lee, H.-Y.; Kim, H.-J. *Org. Lett.* **2009**, *11*, 5590−5593.
(2) Byun, M.; Kim, A.; Hwang, J.-H.; Sung, M.; Lee, Y.; Hwang, B.; Rho, J.-R.; Hwang, E.; Hong, J.-H. *FEBS Lett.* **2012**, *586*, 1086−1092.
(3) Kang, H.; Rho, J.-R.; Hong, J.-H.; Park, S.-B.; Shin, C.-S.; Lee, J.-H.; Hong, J.-Y.; Kim, E.-O.; Kim, J.-A.; Oh, S.-M. WO 2010/050783 A2, 2010.
(4) Kang, H.; Won, D.-H.; Yang, I.; Kim, E. O.; Kim, J. A.; Giri, A. G.; Mallepally, V. R. WO 2012/033353 A2, 2012.
(5) Kang, H.; Won, D. H.; Yang, I. H.; Kim, E. O.; Kim, J. A.; Giri, A. G.; Mallepally, V. R. US 2013/0274212, 2013.
(6) Byun, M. R.; Lee, C. H.; Hwang, J.-H.; Kim, A. R.; Moon, S. A.; Sung, M. K.; Roh, J.-R.; Hwang, E. S.; Hong, J.-H. *Eur. J. Pharmacol.* **2013**, *718*, 181−187.
(7) Forestieri, R.; Merchant, C.; de Voogd, N.; Matainaho, T.; Kieffer, T.; Andersen, R. *Org. Lett.* **2009**, *11*, 5166−5169.
(8) Huang, J.; Yang, J.; Zhang, J.; Yang, J. *J. Am. Chem. Soc.* **2012**, *134*, 8806−8809.
(9) Huang, J.; Yang, J.; Zhang, J.; Yang, J. *Org. Biomol. Chem.* **2013**, *11*, 3212−3222.
(10) Xuan, M.; Paterson, I.; Dalby, S. *Org. Lett.* **2012**, *14*, 5492−5495.
(11) Hubert, J. G.; Furkert, D. P.; Brimble, M. A. *J. Org. Chem.* **2015**, *80*, 2231−2239.
(12) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391−2393.
(13) Galvez, E.; Romea, P.; Urpi, F. *Org. Synth.* **2009**, *86*, 70.
(14) Kumpulainen, E. T. T.; Koskinen, A. M. P. *Chem.—Eur. J.* **2009**, *15*, 10901−10911.
(15) Michaelis, A.; Kaehne, R. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1048−1055.
(16) Arbuzov, A. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687.
(17) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.
(18) Huang, X.; Shao, N.; Palani, A.; Aslanian, R.; Buevich, A. *Org. Lett.* **2007**, *9*, 2597−2600.
(19) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552−1555.
(20) Fleury, E.; Sorin, G.; Prost, E.; Pancrazi, A.; Sautel, F.; Massiot, G.; Lannou, M.-I.; Ardisson, J. *J. Org. Chem.* **2013**, *78*, 855−864.
(21) Aitken, H. R. M.; Furkert, D. P.; Hubert, J. G.; Wood, J. M.; Brimble, M. A. *Org. Biomol. Chem.* **2013**, *11*, 5147−5155.
(22) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.
(23) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184−4187.
(24) As this unexpected epimerization was *not* observed in similar coupling of acetal **9** (Scheme 6), it is likely that the additional resonance stabilization of the allyl side chain is required for this to occur. A plausible mechanism for the epimerization is included in the Supporting Information. The site of epimerization was confirmed by careful NMR studies involving (6*S*)-**7** and (±)-**7**.
(25) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843−2859.
(26) Kitahara, T.; Kurata, H.; Matsuoka, T.; Mori, K. *Tetrahedron* **1985**, *41*, 5475−5485.
(27) Kato, T.; Hirukawa, T.; Suzuki, T.; Tanaka, M.; Hoshikawa, M.; Yagi, M.; Tanaka, M.; Takagi, S.; Saito, N. *Helv. Chim. Acta* **2001**, *84*, 47−68.
(28) Paquette, L. A.; Lo, H. Y. *J. Org. Chem.* **2003**, *68*, 2282−2289.
(29) Brennan, N. K.; Guo, X.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 732−734.
(30) Liu, P.; Wang, J.; Zhang, J.; Qiu, F. G. *Org. Lett.* **2011**, *13*, 6426−6428.
(31) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160−10161.
(32) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440−11441.

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