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Total Synthesis of Marine Eicosanoid (−)-Hybridalactone

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Abstract: (−)-Hybridalactone (**1**) is a marine eicosanoid isolated from the red alga *Laurencia hybrida*. This natural product contains cyclopropane, cyclopentane, 13-membered macrolactone and epoxide ring systems incorporating seven stereogenic centers. Moreover, this compound has an acid-labile skipped *Z*,*Z*-diene motif. In this paper, we report on the total synthesis of (−)-hybridalactone (**1**). The unique eicosanoid (−)-hybridalactone (**1**) was synthesized starting from optically active γ-butyrolactone **2** in a linear sequence comprising 21 steps with an overall yield of 21.9%. A key step in the synthesis of (−)-hybridalactone (**1**) is the methyl phenylsulfonylacetate-mediated one-pot synthesis of the *cis*-cyclopropane-γ-lactone derivative. This reaction provided an efficient and stereoselective access to *cis*-cyclopropane-γ-lactone **12**. Further elaboration of the latter compounds through desulfonylation, epoxidation, oxidation, Wittig olefination and Shiina macrolactonization afforded (−)-hybridalactone.

Keywords: hybridalactone · macrolactone · natural products · one-pot synthesis · total synthesis

Introduction

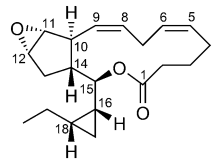
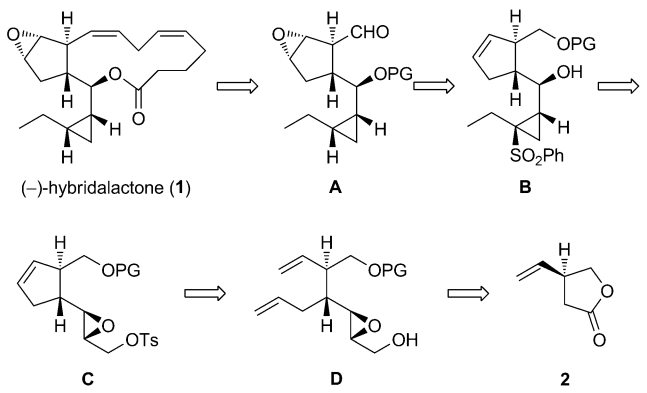


Figure 1. Structure and numbering of (−)-hybridalactone.

Hybridalactone (**1**) is a structurally unique eicosanoid first isolated in 1981 from antibacterial extracts of the red alga *Laurencia hybrida* by Higgs and coworkers (Figure 1).[1] The overall structure of hybridalactone was demonstrated on the basis of spectral analysis and chemical conversion. Although the relative configurations of the cyclopentane (C-10 to C-14) and cyclopropane (C-16 to C-18) moieties were assigned by the coupling constants obtained from the ^{1}H NMR spectrum, the relative configuration at C-15 and the absolute structure of this compound were not elaborated. The complete stereochemistry was then determined based on consideration of a combined analysis of molecular mechanic calculations and the reported ^{1}H NMR data in 1984 by Corey and co-workers. Moreover, the absolute configuration of hybridalactone was determined by X-ray crystallographic analysis of a saturated lactone bromohydrin derived from an authentic sample.[2] The first total synthesis of hybridalactone was achieved based on the above results by Corey's group.[3] Hybridalactone possesses a tetracyclic ring system comprising cyclopropane, cyclopentane, 13-membered lactone and epoxide moieties, contains seven contiguous stereogenic centers and a skipped *Z*,*Z*-configured 1,4-diene motif, the overall composition of which makes it a challenging synthetic target. Recently, the protecting group-free total synthesis of **1** using molybdenum alkylidene-catalyzed ring-closing alkyne metathesis as a key step was reported by Fürstner's group.[4]

Our synthetic strategy for (−)-hybridalactone (**1**) features the stereocontrolled one-pot synthesis of the cyclopropane derivative employing alkyl phenyl sulfone and epoxide developed by the authors.[5] Our retrosynthetic analysis is briefly outlined in Scheme 1. We envisioned that the skipped *Z*,*Z*-configured 1,4-diene motif on the macrolactone ring should be constructed in the latter stages of the synthesis due to sensitivity of the 1,4-diene moiety to both acidic and oxidative conditions. Therefore, we set aldehyde **A** for fur-



Scheme 1. Retrosynthetic analysis of (−)-hybridalactone (**1**).

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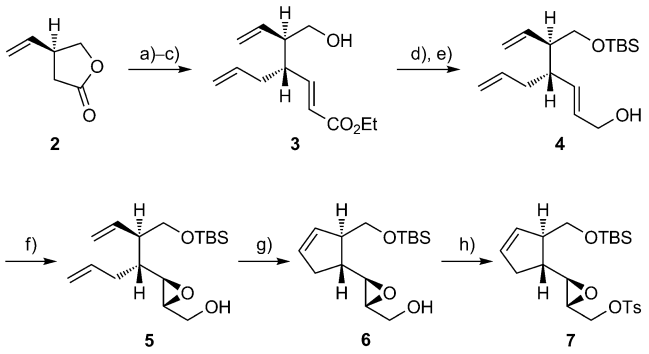
ther elaboration toward **1**. Aldehyde **A** was expected to be generated from cyclopentene **B** through desulfonylation, vanadium-catalyzed epoxidation and oxidation of the primary hydroxy group. Key intermediate **B** would be constructed by our developed stereocontrolled one-pot synthesis of cyclopropane derivative using epoxy tosylate **C** and phenyl propyl sulfone. The cyclopentene ring in epoxy tosylate **C** was surmised to be constructed by the ring-closing metathesis of epoxy alcohol **D**. Epoxy alcohol **D** could easily be prepared from known optically active γ-butyrolactone **2**.[6]

Results and Discussion

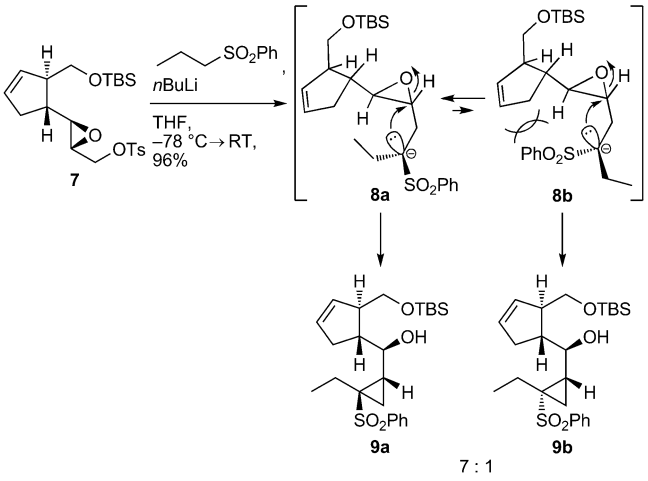
The synthesis of (−)-hybridalactone (**1**) commenced with allylation at the α-position of optically active γ-butyrolactone **2**[6] (>99.5% *ee*). γ-Butyrolactone **2** was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C and then with 3-iodopropene to give the *trans*-lactone in a stereoselective manner (Scheme 2).[7] Subsequent



Scheme 2. Synthesis of epoxy tosylate **7**. a) LDA, 3-iodopropene, THF, −78 °C; b) DIBAH, CH_2Cl_2, −78 °C, 85% (2 steps); c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux, 88%; d) TBSCl, Et_3N, DMAP, CH_2Cl_2, RT; e) DIBAH, CH_2Cl_2, −78 °C, 96% (2 steps); f) TBHP, D-(−)-DIPT, $Ti(OiPr)_4$, 4 Å MS, CH_2Cl_2, −20 °C, 93%; g) Grubbs 1st cat., CH_2Cl_2, RT, 93%; h) TsCl, Et_3N, CH_2Cl_2, reflux, 86%.

reduction of the *trans*-lactone by diisobutylaluminum hydride (DIBAH) afforded the hemiacetal as a mixture of diastereomers (d.r. 3:2) in 85% yield for two steps from **2**. The resulting hemiacetal was then treated with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 under reflux to afford (*E*)-α,β-unsaturated ester **3** in 88% yield as a single compound. In this reaction, when the reaction temperature was raised further, the oxy-Michael adduct was predominantly obtained. Protection of the primary hydroxy group in **3**, and subsequent reduction of the ester moiety with DIBAH, cleanly generated allylic alcohol **4** in 96% yield for two steps from **3**. Asymmetric epoxidation of allylic alcohol **4** according to the Sharpless procedure[8] gave epoxy alcohol **5** in 93% yield as a sole product. Ring-closing metathesis of epoxy alcohol **5** using Grubbs first-generation catalyst[9] afforded cyclopentene **6** in 93% yield. Tosylation of the primary hydroxy group in cyclopentene **6** gave epoxy tosylate **7** in 86% yield. Epoxy tosylate **7** is a substrate of the one-pot synthesis of the cyclopropane derivative.

The sulfonyl carbanion prepared from phenyl propyl sulfone[10] (2.3 equiv) and *n*BuLi (2.2 equiv) was treated with epoxy tosylate **7** at −78 °C to room temperature over 12 h to give β-sulfone **9a** and α-sulfone **9b** as a diastereomeric mixture at C-18[11] in a ratio of 7:1 in 96% yield (Scheme 3).



Scheme 3. One-pot synthesis of cyclopropanes **9a** and **9b**.

These cyclopropanes were easily separated by silica gel chromatography, and the relative configurations of **9a** and **9b** were determined by NOESY analysis (Figure 2). The *cis* configuration of the cyclopropane in **9a** was determined by NOE correlation between the methine proton at C-15 and

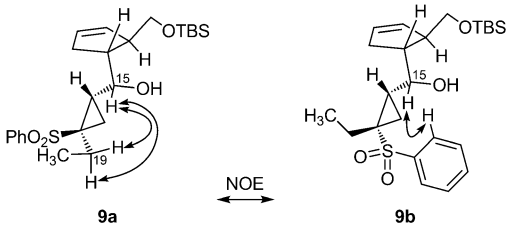
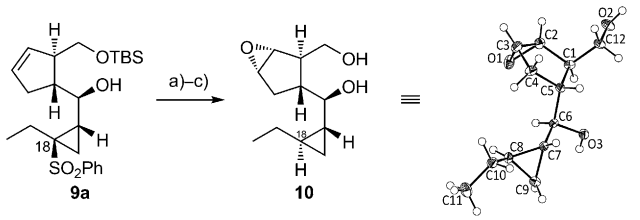


Figure 2. Selected NOE correlations of **9a** and **9b**.

the methylene protons at C-19. In the same way, the *trans* configuration of the cyclopropane in **9b** was determined by NOE correlation between the methine proton at C-15 and the sp^2-methine proton at the *ortho* position of the sulfonyl group. The diastereoselectivity of this reaction was presumably derived from steric hindrance between the phenylsulfonyl group and the cyclopentene ring (**8a** and **8b**), which might favor attack of the sulfonylcarbanion on the epoxide from the less hindered side.

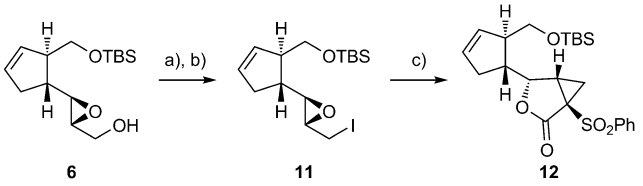
The phenylsulfonyl group in β-sulfone **9a** was removed by treatment with Na(Hg) and Na_2HPO_4 to give cyclopropane as a sole product (Scheme 4). However, the relative configuration at C-18 could not be determined. Determination of



Scheme 4. Desulfonylation of **9a** and ORTEP drawing of *trans*-cyclopropane **10**. a) Na(Hg), Na_2HPO_4, MeOH, RT; b) TBHP, $VO(acac)_2$, CH_2Cl_2, RT; c) TBAF, THF, RT, 86% (3 steps).

the cyclopropane stereochemistry was performed in a later step. The aforementioned desulfonylated product was treated with TBHP in the presence of catalytic $VO(acac)_2$[12] to give the α-epoxide, and deprotection of the TBS group with TBAF furnished diol **10** as crystalline solid in 86% yield for three steps from **9a**. The structure of diol **10** was determined by single-crystal X-ray diffraction, and unfortunately the C-18 stereochemistry of the cyclopropane moiety is the result of epimerization under the desulfonylation conditions employed. With respect to this unanticipated epimerization, we hypothesized that repulsion between the side chains of cyclopropane is the main factor driving for conversion to the *trans* configuration. In order to avoid the inversion of C-18, it is necessary to modify the initial synthetic plans for (−)-hybridalactone (**1**).

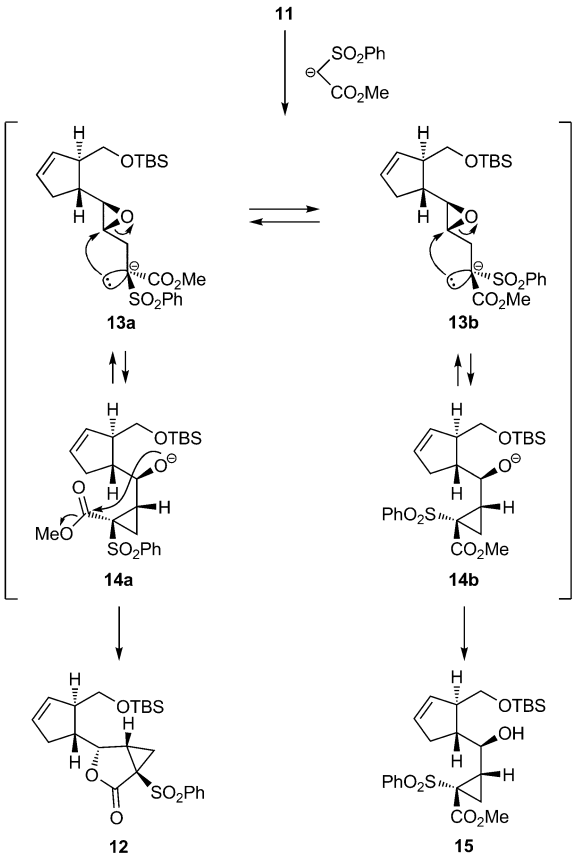
We envisioned that the cyclopropane moiety could be assembled in a *cis*-fused manner using a methyl phenylsulfonylacetate-mediated one-pot synthesis of the *cis*-cyclopropane-γ-lactone derivative. To implement this strategy, cyclopentene **6** was treated with MsCl and Et_3N to give the corresponding mesylate (Scheme 5). The resulting mesylate was



Scheme 5. Synthesis of *cis*-cyclopropane-γ-lactone **12**. a) MsCl, Et_3N, CH_2Cl_2, 0°C; b) NaI, $NaHCO_3$, acetone, 40°C, 85% (2 steps); c) methyl phenylsulfonylacetate, K_2CO_3, DMF, RT, 93%.

converted to epoxy iodide **11** by treatment with NaI and $NaHCO_3$ in 85% yield for two steps from **6**. Epoxy iodide **11** is the substance generated for the one-pot synthesis of the *cis*-cyclopropane-γ-lactone derivative. Thus, under optimized conditions, epoxy iodide **11** was treated with methyl phenylsulfonylacetate[13] and K_2CO_3 in dry *N*,*N*-dimethylformamide (DMF) at room temperature for 36 h to afford the desired *cis*-cyclopropane-γ-lactone **12** in 93% yield as a single isomer.

A plausible mechanism for the formation of *cis*-cyclopropane-γ-lactone **12** is given in Scheme 6. The carbanion of methyl phenylsulfonylacetate reacted with epoxy iodide **11**



Scheme 6. A plausible mechanism for the formation of *cis*-cyclopropane-γ-lactone **12**.

to form the epoxy sulfone, which is rapidly converted into the corresponding sulfonylcarbanions **13a** and **13b**. Intramolecular alkylation of sulfonylcarbanions **13a** and **13b** gave diastereomeric cyclopropanes **14a** and **14b**, respectively. These intramolecular alkylations are reversible reactions. Therefore, an equilibrium is established between cyclopropanes **14a** and **14b** via epoxides **13a** and **13b**. However, only cyclopropane **14a** can further cyclize to an ester moiety to give *cis*-cyclopropane-γ-lactone **12**. In order to confirm this hypothesis, we performed the following investigation. Epoxy iodide **11** was treated with methyl phenylsulfonylacetate and K_2CO_3 in DMF at room temperature for a shorter reaction time to afford *cis*-cyclopropane-γ-lactone **12** together with cyclopropane **15** derived from sulfonylcarbanion **14b**. The relative configuration of cyclopropane **15** was determined by NOESY analysis (Figure 3). The *trans* configuration of the cyclopropane in **15** was determined by NOE correlation between the methine proton at C-15 and the sp^2-methine proton at the *ortho* position of the sulfonyl group. Cyclopropane **15** was treated with K_2CO_3 in DMF for 36 h again to give *cis*-cyclopropane-γ-lactone **12** in 92% yield as a sole product. This result clearly supports our proposed reaction mechanism.

Reductive desulfonylation of **12** with Mg in MeOH[14] at 50°C afforded the γ-lactone (Scheme 7). The resulting γ-lac-

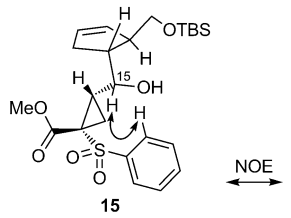
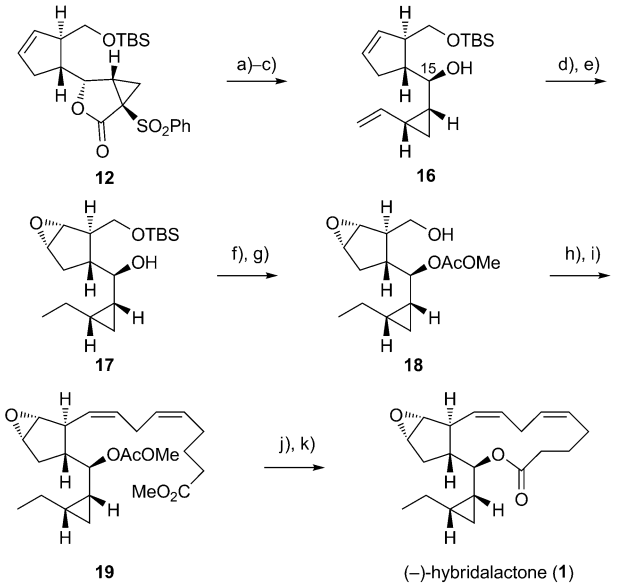


Figure 3. Selected NOE correlations of **15**.



Scheme 7. Total synthesis of (−)-hybridalactone (**1**). a) Mg, MeOH, 50 °C; b) DIBAH, CH_2Cl_2, −78 °C; c) Ph_3PCH_3Br, *t*BuOK, THF/toluene, RT, 86% (3 steps): d) TBHP, $VO(acac)_2$, CH_2Cl_2, RT; e) $H_2NNH_2{\cdot}H_2O$, O_2, riboflavin tetrabutyrate, CH_3CN, RT, 81% (2 steps); f) MeOAcCl, Py, RT; g) TBAF, AcOH, THF, RT, 94% (2 steps); h) IBX, DMSO/THF, RT; i) (*Z*)-(8-methoxy-8-oxooct-3-enyl)triphenylphosphonium bromide, LiHMDS, HMPA, THF, −78 °C; j) 0.2 M LiOH aq., THF, RT; k) MNBA, DMAP, CH_2Cl_2, RT, 68% (4 steps).

tone was reduced with DIBAH to the hemiacetal, which was then treated with Wittig reagent ($Ph_3P{=}CH_2$) to afford diene **16** in 86% yield for three steps from **12**. Diene **16** was treated with TBHP in the presence of a catalytic amount of $VO(acac)_2$ to give the α-epoxide as a sole product. The regioselectivity of this epoxidation can be explained by differences in the electron density of the two double bonds. That is, since the reaction proceeds in preference to a more electron-rich endocyclic alkene, the desired product was obtained. Furthermore, the stereoselectivity may be accounted for by invoking a process involving coordination of the hydroxy group at C-15 to the reagent. The terminal olefin moiety in α-epoxide was hydrogenated by a flavin-catalyzed aerobic reduction according to the method developed by Naota and co-workers.[15] Thus, treatment of the α-epoxide with riboflavin tetrabutyrate and hydrazine monohydrate in dry acetonitrile using a balloon of O_2 at room temperature furnished the desired secondary alcohol **17** in 81% yield for two steps from **16**. In this reduction, when hydrogenation was performed using palladium catalyst, cleavage of the cyclopropane ring was observed. Protection of the secondary hydroxy group in **17** with methoxyacetyl chloride (MeOAcCl) and pyridine, followed by deprotection of TBS with tetrabutylammonium fluoride (TBAF), furnished primary alcohol **18** in 94% yield for two steps from **17**. Initial attempts to protect the secondary hydroxy group using a variety of ether protecting groups resulted in decomposition of the 1,4-skipped diene moiety during deprotection. Therefore, an ester protecting group was selected, although use of an acetyl group led to decomposition of the epoxide moiety owing to the strongly basic conditions for deprotection, and a formyl group was not tolerated in the following oxidation. Eventually, the methoxyacetyl group was found to be an efficient protecting group due to its moderate stability. Subsequent attempts to oxidize the primary hydroxy group in **18** under various conditions were met with limited success due to instability of the generated aldehyde. This transformation was best achieved by oxidation with 2-iodoxybenzoic acid (IBX[16]) in dimethylsulfoxide (DMSO)/THF to give the aldehyde. The aldehyde was then treated with phosphonium ylide derived from (*Z*)-(8-methoxy-8-oxooct-3-enyl)triphenylphosphonium bromide[17] and lithium hexamethyldisilazide (LiHMDS) in the presence of HMPA to give the skipped *Z*,*Z*-configured 1,4-diene **19** as a sole product. To complete the total synthesis, hydrolysis of the methyl ester and methoxyacetyl group using aqueous LiOH gave the corresponding hydroxycarboxylic acid. Finally, macrolactonization of hydroxycarboxylic acid with 2-methyl-6-nitrobenzoic anhydride (MNBA[18]) and 4-*N*,*N*-dimethylaminopyridine (DMAP) furnished (−)-hybridalactone (**1**) in 68% yield for four steps from **18**. Physical data of synthetic (−)-hybridalactone (**1**) were consistent with that of reported data.[1–3]

Conclusion

In summary, we have achieved the enantioselective total synthesis of (−)-hybridalactone (**1**) in 21.9% overall yield via a 21-step linear sequence from inexpensive γ-butyrolactone **2**. Essential to the development of this route was exploitation of the one-pot synthesis of the *cis*-cyclopropane-γ-lactone derivative sequence to furnish *cis*-cyclopropane-γ-lactone **12**.

Experimental Section

General: All reagents (Aldrich, Kanto, TCI and Wako) and solvents were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography on glass plates coated with a fluorescent indicator with a 254 nm excitation wavelength (Merck-5554-7). Flash column chromatography was performed using Kanto Chemical Silica Gel 60N (spherical, natural) 40–50 μm. Melting points (m.p.) were measured using the Yanaco melting point apparatus MP-S3 and are uncorrected. Optical rotations were measured with a JASCO P-1030 polarimeter. IR spectra were recorded with a JASCO FT-IR/620 spectrometer. UV spectra were recorded using a JASCO V-550 spectrophotometer. X-

ray diffraction data were collected on a Bruker SMART APEX II Ultra diffractometer with APEX II CCD area detector, comprising a Bruker TXS fine-focus rotating anode and Bruker Helios multilayer confocal mirror. The data collection, cell refinement, and data reduction were performed using Bruker Suite software package.[19] The structures were solved by the direct method and refined on F^2 by using SHELX-97. [20] The non-hydrogen atoms were refined anisotropically. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker DRX-400 or Bruker Biospin AV-600 spectrometer. Chemical shifts are given on the δ (ppm) scale using tetramethylsilane (TMS) as the internal standard (s, singlet; d, doublet; t, triplet; q, quartet; quint., quintet; m, multiplet; br, broad). High resolution ESIMS (HRESIMS) spectra were obtained using a Micromass LCT spectrometer. Elemental analysis data were obtained using an Elementar Vario EL.

CCDC-858852 (**10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*E*)-α,β-Unsaturated ester 3: *n*BuLi (1.56 M solution in hexane, 0.660 mL, 1.03 mmol) was added to a solution of diisopropylamine (0.156 mL, 1.11 mmol) in THF (9.00 mL) at −78 °C and the resulting mixture was stirred at 0 °C for 30 min. After cooling to −78 °C, a solution of γ-butyrolactone **2** (96.4 mg, 0.860 mmol) in THF (2.30 mL) was introduced and stirring continued at this temperature for 30 min prior to addition of 3-iodopropene (0.120 mL, 1.31 mmol). After an additional 20 min, the reaction mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo to give a crude product which was used for the next step without further purification.

To a stirred solution of the crude product in CH_2Cl_2 (8.23 mL) was added DIBAH (1.04 M solution in hexane, 0.870 mL, 0.905 mmol) over 5 min at −78 °C. After stirring for 20 min, the reaction mixture was diluted with Et_2O and $Na_2SO_4{\cdot}10H_2O$ (1.00 g) was slowly added. The mixture was then allowed to warm to room temperature. After stirring for 12 h, the mixture was diluted with AcOEt, passed through a pad of Na_2SO_4, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 3:1) to give a diastereomeric mixture of the hemiacetal (3:2, 113 mg, 85 % over two steps) as a colorless oil. R_f=0.25 (hexane/AcOEt 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.90–5.73 (m, 1.6H), 5.66–5.57 (m, 0.4H), 5.39 (t, J=3.8 Hz, 0.4H), 5.21 (t, J=3.4 Hz, 0.6H), 5.14–4.98 (m, 4H), 4.20 (t, J=8.6 Hz, 0.4H), 3.99 (t, J=8.5 Hz, 0.6H), 3.81 (t, J=8.5 Hz, 0.6H), 3.59 (t, J=8.6 Hz, 0.4H), 2.93 (brs, 1H), 2.80–2.71 (m, 0.6H), 2.53 (quint, J=8.6 Hz, 0.4H), 2.31–2.12 (m, 2H), 2.00–1.93 (m, 0.6H), 1.91–1.83 ppm (m, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 137.7 (t), 137.7 (t), 136.8 (t), 135.9 (t), 117.3 (d), 116.7 (d), 116.6 (d), 115.8 (d), 103.3 (t), 98.7 (t), 72.0 (d), 71.3 (d), 52.2 (t), 49.9 (t), 49.7 (t), 46.8 (t), 35.5 (d), 31.2 ppm (d); IR (neat): $\tilde{\nu}$ = 3408, 3078, 2978, 2937, 1642 cm^{-1}; HRMS (ESI): m/z: calcd for $C_9H_{14}O_2+Na^+$: 177.0891 [M+Na$^+$]; found: 177.0890; elemental analysis calcd (%) for $C_9H_{14}O_2$: C 70.10, H 9.15; found: C 69.89, H 8.98.

To a stirred solution of the above hemiacetal (226 mg, 1.47 mmol) in CH_2Cl_2 (7.40 mL) was added Ph_3P=$CHCO_2Et$ (2.56 g, 7.35 mmol) at room temperature. The mixture was then refluxed for 96 hr. After cooling to room temperature, the mixture was passed through a pad of silica gel and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 1:1) to give **3** (291 mg, 88 %) as a colorless oil. R_f=0.22 (hexane/AcOEt 2:1); $[\alpha]_D^{25}$ = +27.6 (c=1.20 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 6.75 (dd, J=15.6, 9.2 Hz, 1H), 5.80 (d, J=15.6 Hz, 1H), 5.71–5.60 (m, 2H), 5.28 (dd, J=10.3, 1.7 Hz, 1H), 5.20 (dd, J=17.1, 1.7 Hz, 1H), 5.02–4.98 (m, 2H), 4.19 (q, J=7.1 Hz, 2H), 3.63 (m, 1H), 3.41 (m, 1H), 2.37–2.23 (m, 3H), 2.08 (m, 1H), 1.43 (m, 1H), 1.29 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 166.2 (q), 149.8 (t), 137.4 (t), 135.4 (t), 122.8 (t), 119.4 (d), 117.0 (d), 63.6 (d), 60.3 (d), 50.2 (t), 43.5 (t), 36.2 (d), 14.2 ppm (s); IR (neat): $\tilde{\nu}$ = 3442, 3077, 2979, 1714, 1651 cm^{-1}; UV/Vis (MeOH): λ_{max} (ε)=209 nm (3900) (200 000 mol^{-1}m^{3}cm^{-1}); HRMS (ESI): m/z: calcd for $C_{13}H_{20}O_3+H^+$: 225.1491 [M+H$^+$]; found: 225.1494; elemental analysis calcd (%) for $C_{13}H_{20}O_3$: C 69.61, H 8.99; found: C 69.55, H 8.86.

Allylic alcohol 4: To a stirred solution of (*E*)-α,β-unsaturated ester **3** (3.54 g, 15.8 mmol) in CH_2Cl_2 (15.8 mL) were added Et_3N (2.70 mL, 19.4 mmol), DMAP (1.93 g, 15.8 mmol) and TBSCl (3.33 g, 22.1 mmol) at room temperature. After stirring for 15 min, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O and brine, and then concentrated in vacuo. The residue was passed through a pad of silica gel (hexane/AcOEt 6:1) and then concentrated in vacuo to give a crude product.

To a stirred solution of the crude product in CH_2Cl_2 (158 mL) was added DIBAH (1.04 M solution in hexane, 38.0 mL, 39.5 mmol) over 15 min at −78 °C. After stirring for 15 min, $Na_2SO_4{\cdot}10H_2O$ (30.0 g) was slowly added. The mixture was then allowed to warm to room temperature. After stirring for 12 h, the mixture was passed through a pad of Na_2SO_4 and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 6:1) to give allylic alcohol **4** (4.50 g, 96 % over two steps) as a colorless oil. R_f=0.38 (hexane/AcOEt 3:1); $[\alpha]_D^{25}$ = +2.29 (c=1.44 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.76–5.60 (m, 3H), 5.48 (ddd, J=15.4, 8.8, 1.6 Hz, 1H), 5.10–4.95 (m, 4H), 4.10 (d, J=5.8 Hz, 2H), 3.61 (dt, J=5.1, 9.9 Hz, 1H), 3.58 (dt, J=5.8, 9.9 Hz, 1H), 3.53 (brs, 1H), 2.32–2.25 (m, 2H), 2.14 (m, 1H), 1.97 (m, 1H), 0.88 (s, 9H), 0.01 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 138.7 (t), 137.1 (t), 134.7 (t), 130.4 (t), 116.7 (d), 115.7 (d), 64.4 (d), 63.7 (d), 50.4 (t), 42.6 (t), 36.3 (d), 25.9×3 (s), 18.3 (q), −5.4 (s), −5.4 ppm (s); IR (neat): $\tilde{\nu}$ = 3348, 3076, 2954, 2929, 2858, 1641 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{32}O_2Si+Na^+$: 319.2069 [M+Na$^+$]; found: 319.2082; elemental analysis calcd (%) for $C_{17}H_{32}O_2Si$: C 68.86, H 10.88; found: C 68.58, H 10.66.

Epoxy alcohol 5: To a cold (−20 °C) suspension of 4 Å molecular sieves (3.86 g) in CH_2Cl_2 (12.7 mL) were added D-(−)-DIPT (0.164 mL, 0.784 mmol), Ti(O*i*Pr)$_4$ (0.193 mL, 0.653 mmol) and TBHP (6.54 M solution in CH_2Cl_2, 2.99 mL, 19.6 mmol). After stirring for 10 min at the same temperature, a solution of allylic alcohol **4** (1.93 g, 6.53 mmol) in CH_2Cl_2 (20.0 mL) was added over 1 h. After stirring at −20 °C for 2 h, NaOH (30 % solution in brine, 0.446 mL) was added. The mixture was diluted with Et_2O, warmed to room temperature, and stirred for 10 min. Magnesium sulfate (408 mg) and Celite (41.0 mg) were then added, and after stirring for 15 min the mixture was passed through a pad of Celite and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 5:1) to give epoxy alcohol **5** (1.90 g, 93 %) as a colorless oil. R_f=0.20 (hexane/AcOEt 4:1); $[\alpha]_D^{25}$ = +11.8 (c=0.29 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.74 (m, 1H), 5.69 (dt, J=17.9, 9.4 Hz, 1H), 5.17–4.99 (m, 4H), 3.87 (d, J=12.4 Hz, 1H), 3.73 (dd, J=10.2, 7.2 Hz, 1H), 3.63 (dd, J=10.2, 6.5 Hz, 1H), 3.59 (m, 1H), 2.91 (dt, J=4.3, 2.5 Hz, 1H), 2.80 (dd, J=9.0, 2.5 Hz, 1H), 2.52 (m, 1H), 2.33 (m, 1H), 1.99 (m, 1H), 1.60 (brs, 1H), 1.52 (m, 1H), 0.88 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 137.0 (t), 136.7 (t), 117.9 (d), 116.3 (d), 64.1 (d), 61.7 (d), 59.0 (t), 57.7 (t), 48.6 (t), 41.5 (t), 32.4 (d), 25.9× 3 (s), 18.3 (q), −5.3 (s), −5.4 ppm (s); IR (neat): $\tilde{\nu}$ = 3442, 3077, 2928, 2858, 1641 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{32}O_3Si+H^+$: 313.2199 [M+H$^+$]; found: 313.2199; elemental analysis calcd (%) for $C_{17}H_{32}O_3Si$: C 65.33, H 10.32; found: C 65.07, H 10.18.

Cyclopentene 6: To a stirred solution of **5** (1.14 g, 3.65 mmol) in CH_2Cl_2 (730 mL) was added Grubbs 1st catalyst (300 mg, 0.365 mmol). After stirring for 2 hr, the reaction mixture was diluted with Et_2O, passed through a pad of silica gel, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 3:1) to give cyclopentene **6** (969 mg, 93 %) as a colorless oil. R_f=0.33 (hexane/AcOEt 2:1); $[\alpha]_D^{25}$ = −65.5 (c=0.20 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.70 (ddt, J=5.8, 4.0, 1.9 Hz, 1H), 5.63 (ddt, J=5.8, 4.0, 2.0 Hz, 1H), 3.90 (m, 1H), 3.62 (m, 1H), 3.56 (dt, J=6.0, 9.7 Hz, 1H), 3.53 (dt, J=6.4, 9.7 Hz, 1H), 3.02–2.96 (m, 2H), 2.80 (m, 1H), 2.50 (ddq, J=16.8, 8.9, 2.3 Hz, 1H), 2.14 (m, 1H), 2.06 (m, 1H), 1.76 (brs, 1H), 0.88 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 131.6 (t), 130.2 (t), 66.2 (d), 61.7 (d), 58.7 (t), 57.1 (t), 52.3 (t), 41.1 (t), 34.5 (d), 25.9×3 (s), 18.3 (q), −5.4 (s), −5.4 ppm (s); IR

(neat): $\tilde{\nu}$ = 3433, 3054, 2930, 2856, 1620 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{15}H_{28}O_3Si+H^+$: 285.1886 [$M+H^+$]; found: 285.1885; elemental analysis calcd (%) for $C_{15}H_{28}O_3Si$: C 63.33, H 9.92; found: C 63.12, H 9.89.

Epoxy iodide 11: To a stirred solution of cyclopentene **6** (2.45 g, 8.61 mmol) in CH_2Cl_2 (86.1 mL) were added Et_3N (3.60 mL, 25.8 mmol) and MsCl (0.800 mL, 10.3 mmol) at 0 °C. After stirring for 15 min, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo to give a crude product which was used for the next step without further purification.

To a stirred solution of the crude product in acetone (86.1 mL) were added $NaHCO_3$ (3.60 g, 43.1 mmol) and NaI (6.50 g, 43.1 mmol) at room temperature. The resulting mixture was then heated to 40 °C. After stirring for 13 h, the reaction mixture was diluted with Et_2O, filtered through silica gel, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 15:1) to give epoxy iodide **11** (2.89 g, 85 % over two steps) as a colorless oil. R_f = 0.65 (hexane/AcOEt 6:1); $[\alpha]_D^{25}$ = −110.3 (*c* = 0.11 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.71 (ddt, *J* = 5.8, 2.1, 2.1 Hz, 1H), 5.64 (ddt, *J* = 5.8, 2.1, 2.1 Hz, 1H), 3.54 (dt, *J* = 6.4, 9.7 Hz, 1H), 3.52 (dt, *J* = 6.2, 9.7 Hz, 1H), 3.28 (dd, *J* = 9.1, 5.0 Hz, 1H), 3.04 (ddd, *J* = 6.8, 5.0, 2.1 Hz, 1H), 3.01 (dd, *J* = 9.0, 7.2 Hz, 1H), 2.84 (dd, *J* = 6.8, 1.8 Hz, 1H), 2.81 (m, 1H), 2.51 (ddq, *J* = 16.9, 8.0, 2.4 Hz, 1H), 2.18 (m, 1H), 2.03 (m, 1H), 0.89 (s, 9H), 0.34 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 131.5 (t), 130.3 (t), 66.1 (d), 65.4 (t), 57.1 (t), 52.5 (t), 41.4 (t), 34.5 (d), 25.9×3 (s), 18.3 (q), 5.0 (d), −5.3 (s), −5.4 ppm (s); IR (neat): $\tilde{\nu}$ = 3054, 2953, 2929, 2855 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{15}H_{27}IO_2Si+H^+$: 395.0903 [$M+H^+$]; found: 395.0903; elemental analysis calcd (%) for $C_{15}H_{27}IO_2Si$: C 45.68, H 6.90; found: C 45.53, H 6.91.

***cis*-Cyclopropane-γ-lactone 12**: To a stirred solution of epoxy iodide **11** (915 mg, 2.32 mmol) and methyl phenylsulfonylacetate (1.99 g, 9.28 mmol) in DMF (23.2 mL) was added K_2CO_3 (3.21 g, 23.2 mmol) at room temperature. After stirring for 36 hr, the reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 7:1) to give *cis*-cyclopropane-γ-lactone **12** (1.04 g, 93 %) as a white needle-like crystalline solid. R_f = 0.47 (hexane/AcOEt 3:1); m.p. 185–186 °C; $[\alpha]_D^{25}$ = −145.1 (*c* = 0.76 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 8.08–8.04 (m, 2H), 7.69 (m, 1H), 7.62–7.56 (m, 2H), 5.69 (ddt, *J* = 5.8, 2.0, 1.9 Hz, 1H), 5.65 (ddt, *J* = 5.8, 2.0, 1.9 Hz, 1H), 4.46 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.58 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.41 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.14 (dt, *J* = 7.7, 5.4 Hz, 1H), 2.80 (m, 1H), 2.60 (m, 1H), 2.10–2.04 (m, 3H), 1.53 (t, *J* = 5.4 Hz, 1H), 0.84 (s, 9H), 0.02 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 167.1 (q), 138.3 (q), 134.3 (t), 132.3 (t), 129.2 (t), 129.1×2 (t), 129.1×2 (t), 80.6 (t), 65.2 (d), 52.4 (t), 47.2 (q), 41.4 (t), 34.3 (d), 29.7 (t), 25.8×3 (s), 18.2 (q), 16.4 (d), −5.4 (s), −5.4 ppm (s); IR (KBr): $\tilde{\nu}$ = 3073, 2930, 2857, 1782 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{23}H_{32}O_5SSi+H^+$: 449.1818 [$M+H^+$]; found: 449.1832; elemental analysis calcd (%) for $C_{23}H_{32}O_5SSi$: C 61.57, H 7.19; found: C 61.58, H 7.08.

***cis*-Cyclopropane-γ-lactone 12 and cyclopropane 15**: To a stirred solution of epoxy iodide **11** (9.7 mg, 0.0247 mmol) and methyl phenylsulfonylacetate (15.9 mg, 0.0742 mmol) in DMF (0.494 mL) was added K_2CO_3 (17.1 mg, 0.124 mmol) at room temperature. After stirring for 12 h, the reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 7:1) to give *cis*-cyclopropane-γ-lactone **12** (9.6 mg, 87 %) as a white needle-like crystalline solid and cyclopropane **15** (1.4 mg, 12 %) as a colorless oil. cyclopropane **15**: R_f = 0.13 (hexane/AcOEt 3:1); $[\alpha]_D^{25}$ = −11.1 (*c* = 1.05 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 7.96–7.93 (m, 2H), 7.61 (m, 1H), 7.54–7.50 (m, 2H), 5.74 (ddt, *J* = 5.7, 2.3, 2.1 Hz, 1H), 5.52 (ddt, *J* = 5.7, 2.3, 2.1 Hz, 1H), 4.34 (ddd, *J* = 0.8, 2.1, 6.8 Hz, 1H), 4.06 (d, *J* = 2.1 Hz, 1H), 3.73 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.55 (s, 3H), 3.43 (dd, *J* = 9.6, 8.8 Hz, 1H), 2.92 (m, 1H), 2.56–2.52 (m, 2H), 2.33 (dd, *J* = 8.8, 4.9 Hz, 1H), 2.24 (m, 1H), 2.16 (ddd, *J* = 10.0, 8.8, 6.1 Hz, 1H), 1.96 (dd, *J* = 10.0, 4.9 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 167.1 (q), 140.8 (q), 133.6 (t), 131.4 (t), 130.4 (t), 128.9×2 (t), 128.7×2 (t), 69.5 (t), 67.6 (d), 52.8 (t), 52.4 (s), 49.7 (t), 49.7 (q), 39.1 (t), 35.9 (d), 26.0×3 (s), 20.6 (d), 18.4 (q), −5.4 (s), −5.4 ppm (s); IR (neat): $\tilde{\nu}$ = 3528, 3406, 3058, 2953, 2929, 2856, 1735 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{24}H_{36}O_6SSi+Na^+$: 503.1900 [$M+Na^+$]; found: 503.1882; elemental analysis calcd (%) for $C_{24}H_{36}O_6SSi$: C 59.97, H 7.55; found: C 60.01, H 7.39.

***cis*-Cyclopropane-γ-lactone 12**: To a stirred solution of cyclopropane **15** (1.4 mg, 0.00290 mmol) in DMF (0.0970 mL) was added K_2CO_3 (1.2 mg, 0.00868 mmol) at room temperature. After stirring for 36 h, the reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 8:1) to give *cis*-cyclopropane-γ-lactone **12** (1.2 mg, 92 %).

Diene 16: To a stirred solution of *cis*-cyclopropane-γ-lactone **12** (101 mg, 0.226 mmol) in MeOH (11.3 mL) was added Mg (565 mg, 23.2 mmol) at room temperature. The resulting mixture was then heated to 50 °C. After stirring for 30 min, the reaction mixture was diluted with Et_2O and extracted by centrifugation. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was passed through a pad of silica gel (hexane/AcOEt 5:1) and then concentrated in vacuo to give a crude product.

To a stirred solution of the crude product in CH_2Cl_2 (4.50 mL) was added DIBAH (1.03 M solution in hexane, 0.260 mL, 0.268 mmol) over 5 min at −78 °C. After stirring for 5 min, $Na_2SO_4{\cdot}10H_2O$ (1.00 g) was slowly added to the reaction mixture. The mixture was allowed to warm to room temperature. After stirring for 1.5 h, the mixture was passed through a pad of anhydrous Na_2SO_4, and then concentrated in vacuo to give a crude product which was used for the next step without further purification.

To a stirred suspension of Ph_3PCH_3Br (323 mg, 0.903 mmol) in toluene (4.50 mL) was added *t*BuOK (88.7 mg, 0.791 mmol) at room temperature. After stirring for 1.5 h, a solution of the above crude product in THF (4.50 mL) was added to the mixture. After stirring for 15 min at room temperature, the reaction mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 5:1) to give diene **16** (60.0 mg, 86 % over three steps) as a colorless oil. R_f = 0.55 (hexane/AcOEt 3:1); $[\alpha]_D^{25}$ = −69.3 (*c* = 0.49 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.73 (m, 1H), 5.61 (dt, *J* = 17.0, 10.1 Hz, 1H), 5.44 (m, 1H), 5.10 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.96 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.83 (ddd, *J* = 9.6, 4.4, 1.9 Hz, 1H), 3.76 (d, *J* = 1.9 Hz, 1H), 3.34 (t, *J* = 9.6 Hz, 1H), 3.21 (dt, *J* = 8.7, 9.6 Hz, 1H), 2.83 (m, 1H), 2.54 (m, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 1.61 (m, 1H), 1.11 (dq, *J* = 8.5, 6.2 Hz, 1H), 0.99 (dt, *J* = 4.9, 8.5 Hz, 1H), 0.92 (s, 9H), 0.66 (dd *J* = 10.9, 5.2 Hz, 1H), 0.10 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 139.1 (t), 131.7 (t), 129.8 (t), 114.1 (d), 73.9 (t), 67.9 (d), 53.2 (t), 51.6 (t), 36.2 (d), 26.0×3 (s), 24.8 (t), 21.1 (t), 18.4 (q), 9.9 (d), −5.5×2 ppm (s); IR (neat): $\tilde{\nu}$ = 3437, 3052, 2929, 2857, 1633 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{18}H_{32}O_2Si+H^+$: 309.2250 [$M+H^+$]; found: 309.2260; elemental analysis calcd (%) for $C_{18}H_{32}O_2Si$: C 70.07, H 10.45; found: C 69.99, H 10.46.

Secondary alcohol 17: To a stirred solution of diene **16** (121 mg, 0.392 mmol) in CH_2Cl_2 (7.80 mL) were added $VO(acac)_2$ (10.4 mg, 0.0392 mmol) and TBHP (5.26 M solution in CH_2Cl_2, 0.370 mL, 1.95 mmol) at room temperature. After stirring for 3 h, dimethylsulfide was added to the reaction mixture. The mixture was filtered through silica gel and then concentrated in vacuo. The residue was passed through a pad of silica gel (hexane/AcOEt 5:1) and then concentrated in vacuo to give a crude product.

To a stirred solution of the crude product in CH_3CN (3.90 mL) were added riboflavin tetrabutyrate (5.2 mg, 0.00790 mmol) and hydrazine monohydrate (0.0380 mL, 0.783 mmol) under an oxygen atmosphere at room temperature. After stirring for 12 h, the reaction mixture was concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 5:1) to give secondary alcohol **17** (104 mg, 81 % over two steps) as a white needle-like crystalline solid. R_f = 0.33 (hexane/AcOEt 4:1); m.p. 68–69 °C; $[\alpha]_D^{25}$ = −30.1 (*c* = 0.48 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 3.72 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.60 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.57 (m, 1H), 3.53 (m, 1H),

3.49 (d, J=2.7 Hz, 1H), 3.10 (m, 1H), 2.68 (m, 1H), 2.21 (m, 1H), 2.17 (m, 1H), 1.99 (d, J=13.9 Hz, 1H), 1.55 (m, 1H), 1.10 (m, 1H), 0.99 (t, J=7.1 Hz, 3H), 0.90 (s, 9H), 0.83–0.68 (m, 3H), 0.14 (m, 1H), 0.06 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 74.2 (t), 64.4 (d), 61.7 (t), 59.3 (t), 45.6 (t), 43.1 (t), 32.9 (d), 25.8×3 (s), 22.4 (d), 21.7 (t), 18.2 (q), 18.0 (t), 14.5 (s), 9.2 (d), −5.5 (s), −5.6 ppm (s); IR (KBr): $\tilde{\nu}$ = 3422, 2962, 2932, 2900, 2864 cm^{-1}; HRMS (ESI): m/z calcd for $C_{18}H_{34}O_3Si+H^+$: 327.2355 [M+H$^+$]; found: 327.2369; elemental analysis calcd (%) for $C_{18}H_{34}O_3Si$: C 66.21, H 10.49; found: C 66.23, H 10.46.

Primary alcohol 18: To a stirred solution of secondary alcohol **17** (29.7 mg, 0.0910 mmol) in pyridine (0.460 mL) was added methoxyacetyl chloride (0.0130 mL, 0.137 mmol) at room temperature. After stirring for 45 min, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo to give a crude product. The residue was passed through a pad of silica gel (hexane/AcOEt 7:1) and then concentrated in vacuo to give a crude product.

To a stirred solution of the crude product in THF (1.80 mL) were added acetic acid (0.0520 mL, 0.910 mmol) and TBAF (1.00 M solution in THF, 0.460 mL, 0.460 mmol). After stirring for 4 h, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 1:4) to give primary alcohol **18** (24.2 mg, 94% over two steps) as a colorless oil. R_f=0.23 (hexane/AcOEt 1:2); $[\alpha]_D^{25}=-2.37$ (c= 0.46 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 4.65 (t, J= 9.2 Hz, 1H), 4.02 (s, 2H), 3.60–3.56 (m, 2H), 3.47 (m, 1H), 3.44 (s, 3H), 3.41 (d, J=2.3 Hz, 1H), 2.24–2.12 (m, 3H), 2.00–1.82 (m, 2H), 1.68 (m, 1H), 1.12 (m, 1H), 1.02 (t, J=7.2 Hz, 3H), 0.92–0.82 (m, 2H), 0.61 (dt, J=5.6, 8.3 Hz, 1H), 0.10 ppm (dd, J=10.5, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 170.1 (q), 79.8 (t), 70.1 (d), 63.4 (d), 59.6 (t), 59.3 (s), 58.0 (t), 45.3 (t), 45.0 (t), 29.3 (d), 23.0 (d), 20.8 (t), 20.2 (t), 14.1 (s), 9.0 ppm (d); IR (neat): $\tilde{\nu}$ = 3458, 2930, 2873, 1743 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{24}O_5+Na^+$: 307.1521 [M+Na$^+$]; found: 307.1520; elemental analysis calcd (%) for $C_{15}H_{24}O_5$: C 63.36, H 8.51; found: C 63.27, H 8.48.

(−)-Hybridalactone (1): To a solution of IBX (34.5 mg, 0.123 mmol) in DMSO (1.20 mL) was added a solution of primary alcohol **18** (17.6 mg, 0.0619 mmol) in THF (1.20 mL). After stirring for 13 h at room temperature, H_2O was added to the mixture. The mixture was filtered through Celite, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was passed through a pad of silica gel (hexane/AcOEt 1:4) and then concentrated in vacuo to give a crude product.

To a stirred suspension of (*Z*)-(8-methoxy-8-oxooct-3-enyl)triphenylphosphonium bromide (122 mg, 0.246 mmol) in THF (1.10 mL) were added LiHMDS (1.00 M solution in THF, 0.220 mL, 0.220 mmol) and HMPA (0.110 mL, 0.615 mmol) dropwise at 0 °C and the resulting mixture was stirred for 30 min at same temperature. The mixture was cooled to −78 °C. A solution of the above crude product in THF (1.00 mL) was then added to the mixture. After stirring for 10 min at room temperature, the reaction mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was passed through a pad of silica gel (hexane/AcOEt 4:1) and then concentrated in vacuo to give a crude product.

To a stirred solution of the crude ester in THF (1.30 mL) was added LiOH (0.20 M solution in H_2O, 15.4 mL, 3.08 mmol) at room temperature. After stirring for 1.5 h, the mixture was diluted with $Et_2O/CHCl_3$ (3:1), washed with saturated aqueous NH_4Cl, H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was passed through a pad of silica gel (hexane/AcOEt 1:1) and then concentrated in vacuo to give a crude product.

To a stirred solution of MNBA (22.7 mg, 0.0660 mmol) and DMAP (16.2 mg, 0.132 mmol) in CH_2Cl_2 (2.40 mL) was added a solution of the above crude product in CH_2Cl_2 (23.0 mL) dropwise over 4 h at room temperature. The mixture was cooled to 0 °C, and then saturated aqueous $NaHCO_3$ was added. After stirring for 5 min, the reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt 15:1) to give (−)-hybridalactone (**1**) (13.3 mg, 68% over four steps) as a white semi-solid. R_f=0.23 (hexane/AcOEt 10:1); $[\alpha]_D^{25}=-55.3$ (c=0.20 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.51 (dt, J=4.6, 10.8 Hz, 1H), 5.47 (ddd, J=10.8, 3.9, 1.2 Hz, 1H), 5.27 (ddt, J=3.2, 1.7, 10.8 Hz, 1H), 5.07 (dt, J=2.0, 10.8 Hz, 1H), 4.72 (t, J=10.2 Hz, 1H), 3.51 (d, J= 1.8 Hz, 1H), 3.37 (dt, J=14.7, 10.8 Hz, 1H), 3.17 (d, J=1.8 Hz, 1H), 2.96 (d, J=10.5 Hz, 1H), 2.40–2.20 (m, 5H), 2.05 (t, J=10.2 Hz, 1H), 2.02–1.90 (m, 3H), 1.72 (m, 1H), 1.48 (m, 1H), 1.17 (m, 1H), 1.03 (t, J= 7.1 Hz, 3H), 0.89 (m, 1H), 0.76 (m, 1H), 0.57 (dt, J=4.7, 8.5 Hz, 1H), 0.05 ppm (dd, J=8.5, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ = 173.2 (q), 129.0 (t), 128.5 (t), 128.2 (t), 127.1 (t), 79.0 (t), 60.9 (t), 58.2 (t), 49.0 (t), 41.6 (t), 32.8 (d), 28.6 (d), 26.4 (d), 25.8 (d), 24.0 (d), 23.2 (d), 21.2 (t), 20.4 (t), 14.2 (s), 8.5 ppm (d); IR (KBr): $\tilde{\nu}$ = 2954, 2926, 1725 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{28}O_3+Na^+$: 339.1936 [M+Na$^+$]; found: 339.1934; elemental analysis calcd (%) for $C_{20}H_{28}O_3$: C 75.91, H 8.92; found: C 76.18, H 8.93.

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Natural Products

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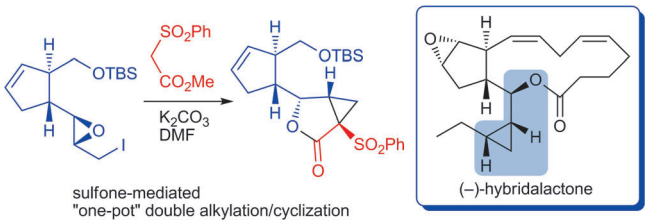
Total Synthesis of Marine Eicosanoid (−)-Hybridalactone



Natural product synthesis: The asymmetric total synthesis of a marine eicosanoid (−)-hybridalactone) was achieved with the methyl phenylsulfonylacetate-mediated one-pot synthesis of *cis*-cyclopropane-γ-lactone derivative as a key reaction for the construction of *cis*-cyclopropane moiety.

