Supporting Information

Unified Total Synthesis of Pteriatoxins and their Diastereomers

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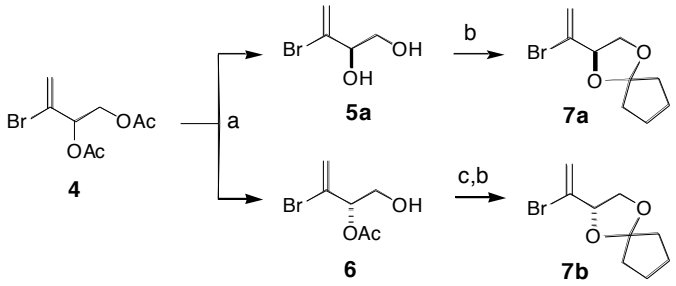
General methods. Unless otherwise noted, all reactions were carried out under positive argon pressure using oven-dried glassware and standard syringe, cannula and septa techniques. Tetrahydrofuran (THF), benzene, toluene and diethyl ether were distilled over Na / benzophenone ketyl under nitrogen immediately prior to use. Dichloromethane, acetonitrile, triethylamine, and diisopropylamine (DIPA) were distilled from CaH_2 under nitrogen prior to use. Dess-Martin periodinane was purchased from OmegaChem Inc. (Canada). Unless otherwise stated, all chemicals were used as received. Flash chromatography purifications were performed using Baker silica gel 60 (40 μm) and the solvents indicated. After chromatography, solvents were evaporated using a Büchi rotary evaporator, followed by further treatment under high vacuum, unless otherwise indicated. Analytical TLC was performed using 0.25 mm EM silica gel 60 F_{254} plates that were analyzed by fluorescence upon 254 nm irradiation or by staining with anisaldehyde reagent (900 mL of 95% EtOH, 50 mL of conc. H_2SO_4, 50 mL of acetic acid and 5 mL of anisaldehyde).

NMR spectra were recorded on a Varian Inova-600 (600MHz), Varian Inova-500 (500 MHz) or Varian Mercury-400 (400MHz) spectrometer. Chemical shifts are reported in parts per million (ppm). For ^1H NMR spectra the residual solvent peak was used as the internal reference (7.26 ppm, $CDCl_3$; 7.15 ppm, C_6D_6; 3.06 ppm, CD_3OD), while the central solvent peak was used as the reference (77.0 ppm for CDCl3) for ^{13}C NMR spectra. For ^1H NMR multiplicity (singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), multiplet (m)) and coupling constant(s) were reported whenever possible. ^{13}C NMR spectra were recorded with complete proton decoupling. Low resolution EI mass spectra were obtained using an AX-505H mass spectrometer (JEOL USA, Inc., Peabody, MA). High resolution EI mass spectra were obtained by using a SX-102A mass spectrometer (JEOL USA, Inc., Peabody, MA) using a mass resolution of 10,000.

Experimental for Scheme 1.



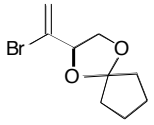
Scheme 1. Reagents. a. lipase PS800 (**5**: 46%; **6**: 41%). b. cyclopentanone, *p*-TsOH (79%). c. LiOH (97%).

Diol 5a and 5b. To a mixture of racemic diacetate **4** (Petrow, A. A. *Zh. Obshch. Khim.* **1940**, *10*, 1013) (7.25 g, 28.9 mmol) in toluene (94 mL) and water (54 mL) was added Amano lipase PS800 (1.88 g). The biphasic mixture was stirred vigorously for 2 h with the addition of solid NaH_2PO_4 portionwise to keep the pH close to 4.5. The mixture was filtered through a pad of silica gel (eluent: EtOAc) to remove enzyme. The filtrate was dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 5:1, then 1:1) to obtain diol (*R*)-**5a** (2.20 g, >96% ee, $[\alpha]_D^{20}$ –9.4 (*c* 0.85, benzene), 46%), monoacetate (*S*)-**6** (3.64 g, 41%, 88% ee) and unreacted racemic diacetate (0.871 g, 12%).

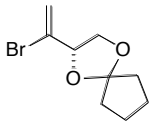
To a mixture of (*S*)-**6** (1.97 g, 9.42 mmol, 88% ee) and racemic diacetate **4** (600 mg, 2.39 mmol) in toluene (25 mL) and water (14 mL) was added Amano lipase PS800 (500 mg). The reaction was performed as same as the above procedure (however, the stirring was prolonged to 7 h) to afford optically pure monoacetate (*S*)-**6** (1.91 g, 77%, >96% ee): ^{1}H NMR (400 MHz, $CDCl_3$) 6.00 (dd, J = 2.8, 1.3 Hz, 1H), 5.74 (d, J = 2.8 Hz, 1H), 5.35 (t, J = 6.5 Hz, 1H), 3.86 (d, J = 6.5 Hz, 2H), 2.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 191.3, 148.7, 141.8, 98.5, 84.1, 42.5 ppm.

To a mixture of (*S*)-monoacetate **6** (1.70 g, 8.13 mmol) and water (0.5 mL) in THF (2.0 mL) at rt was added LiOH (384 mg, 16.0 mmol). The mixture was stirred for 2 h and poured into two-layer mixture of EtOAc and water. The separated aqueous phase

was saturated by NaCl and extracted with EtOAc (three times). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 1:1) gave (*S*)-**5b** (1.31 g, 97%) as a pale yellow oil; $[\alpha]_D^{20}$ +9.2 (*c* 0.44, PhH).



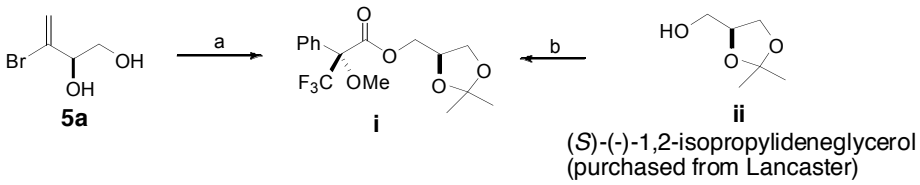
7a



7b

Vinyl bromide 7a and 7b. A mixture of diol (*R*)-**5a** (1.35 g, 8.10 mmol), cyclopentanone (1.34 g, 16.0 mmol) and *p*-TsOH·H_2O (307 mg, 1.62 mmol) in benzene (25 mL) was stirred at rt. After 12 h of stirring, cyclopentanone (1.34 g, 16.0 mmol) and $MgSO_4$ (3.0 g) was added and the mixture was stirred for an additional 6 h, and quenched by sat. aq. $NaHCO_3$. The mixture was partitioned between EtOAc and water, and the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O =20:1) to obtain vinyl bromide (*R*)-**7a** (1.50 g, 79%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): 6.02 (s, 1H), 5.58 (s, 1H), 4.57 (dd, *J* = 6.5, 6.4 Hz, 1H), 4.13 (dd, *J* = 13.0, 6.5Hz, 1H), 3.86 (dd, *J* = 13.0, 6.5 Hz, 1H), 1.98-1.64 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 131.6, 128.5, 120.9, 117.1, 78.8, 69.2, 36.7, 36.5, 23.8, 23.7 ppm; IR (film) 2960, 2875, 1635, 1337, 1106, 1042, 897 cm^{-1}; HRMS (EI) calcd for $C_9H_{13}BrO_2$ $[M]^+$ 232.0099, found 232.0096; $[\alpha]_D^{20}$ +10.4° (*c* 1.07, PhH). Vinyl bromide (*S*)-**7b** (1.99 g) was prepared in the same fashion from (*S*)-**5b** (2.20 g, 13.2 mmol) in 65% yield; $[\alpha]_D^{20}$ -10.2 (*c* 0.84, PhH).

Experimental for Scheme I.



Scheme I. Reagents . (a) 1. TsOH, $MeC(OMe)_2Me$. 2. O_3, then $NaBH_4$. 3. (*S*)-MTPACl. (b) (*S*)-MTPACl.

Ester i. To a stirred solution of the diol (*R*)-**5a** (790 mg, 4.756 mmol) in 2,2-dimethoxypropane (10 mL) at rt was added $TsOH{\cdot}H_2O$ (90 mg). After stirring at rt overnight, the mixture was quenched by addition of Et_3N (0.5 mL) and evaporated. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 20:1 then 10:1) to give the corresponding acetonide (820 mg, 84 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): 6.05 (t, *J* = 1.2 Hz, 1H), 5.60 (t, *J* = 1.2 Hz, 1H), 4.62 (t, *J* =6.4 Hz, 1H), 4.20 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.89 (dd, *J* = 8.4, 6.0 Hz, 1H), 1.49 (s, 3H), 1.41 (s, 3H) ppm.

To a stirred solution of the above acetonide (250 mg, 1.213 mmol) in CH_2Cl_2/MeOH (1:1, 12 mL) at -78 ^{0}C was bubbled through O_3 for 20 min. After removing excess O_3 by bubbling N_2 for 15 min, $NaBH_4$ (500 mg x 2) was added. After 2 h of stirring at rt, the reaction was quenched with H_2O, extracted with Et_2O, died over anhydrous $MgSO_4$, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 1:1, 1:4, then Et_2O) to provide the corresponding alcohol (128 mg, 80 %) as a colorless oil: ^{1}H NMR (400 MHz, CD_3OD): 4.15 (m, 1H), 4.03 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.72 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.55 (d, *J* = 5.2 Hz, 2H), 1.37 (s, 3H), 1.32 (s, 3H) ppm.

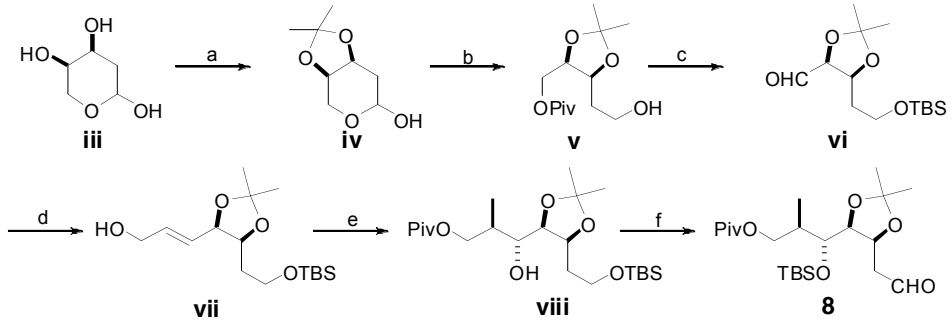
To a stirred solution of the above alcohol (2 mg), DMAP (0.2 mg), and Et_3N (20 μL) in CH_2Cl_2 (0.2 mL) was added (*S*)-MTPACl (5 μL) and stirred at rt for overnight. The reaction mixture was diluted with Et_2O, washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated in vacuo to provide crude ester **i**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.51-7.55 (m, 2H), 7.37-7.46 (m, 3H), 4.42 (dd, *J* = 10.4, 4.8 Hz, 1H), 4.35 (m, 1H), 4.28 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.04 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.73 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.54-3.57 (m, 3H), 1.38 (s, 3H), 1.34 (s, 3H) ppm.

To a stirred solution of (*S*)-(-)-1,2-isopropylideneglycerol (**ii**, purchased from Lancaster, 2 mg), DMAP (0.2 mg), and Et_3N (20 μL) in CH_2Cl_2 (0.2 mL) was added (*S*)-MTPACl (5 μL) and stirred at rt for overnight. The reaction mixture was diluted with Et_2O, washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated in vacuo to provide crude ester **i**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.51-7.55 (m, 2H), 7.37-7.46 (m, 3H), 4.42 (dd, *J* = 10.4, 4.8 Hz, 1H), 4.35 (m, 1H), 4.28 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.04 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.73 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.54-3.57 (m, 3H), 1.38 (s, 3H), 1.34 (s, 3H) ppm. The spectrum matched that of the same ester prepared from diol (*R*)-**5**, therefore proving the stereochemical assignment of diol (*R*)-**5** is correct.

The stereochemistry of diol (*S*)-**5** was proved via the same sequence.

Synthesis of Aldehyde 8 (Scheme II).

The aldehyde **8** was synthesized from 2-dexoy-D-ribose as summarized in Scheme II. This synthesis was originally developed by Drs. Kazuo Nagasawa, John A. McCauley, and Vito Guagnano of this laboratory, in conjunction with the synthesis of the natural antipode of PnTX A.

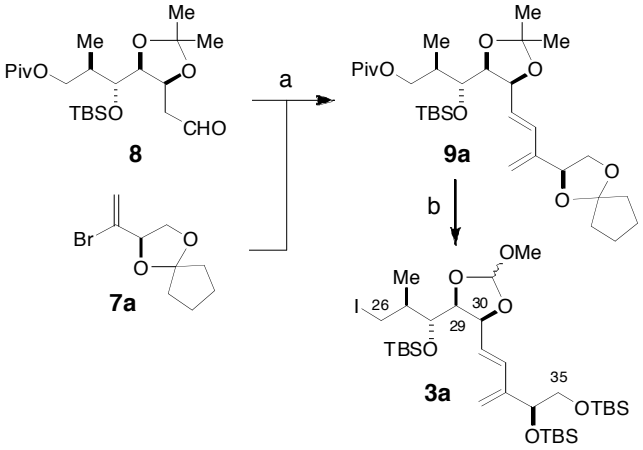


Scheme II. Reagents. (a) PPTS, $MeC(OMe)_2Me$, THF, 0 °C to rt, 77%. (b) 1. *n*BuLi, Ph_3PCH_3Br, THF, 0 °C to rt; then PivCl, 0 °C to rt, 76%. 2. O_3, $MeOH/CH_2Cl_2$, -78 °C; $NaBH_4$, -78 °C to 0 °C, 76%. (c) 1. TBSCl, imidazole, CH_2Cl_2, 0 °C to rt. 2. DIBAL, CH_2Cl_2, -78 °C. 3. DMSO, oxalyl chloride, NEt_3, CH_2Cl_2, -78 °C. (d) 1. $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C to rt. 2. DIBAL, CH_2Cl_2, -78 °C; 75% (5 steps). (e) 1. $Ti(OiPr)_4$, (+)-DET, $tBuO_2H$, 4 ÅMS, CH_2Cl_2, 94%. 2. MeLi, CuI, Et_2O, 0 °C to rt. 3. PivCl, CH_2Cl_2, 0 °C to rt; 77% (2 steps). (f) 1. TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%. 2. HF•pyr/pyr/THF (1:4:10), THF, 0 °C to rt, 85%. 3. Dess-Martin oxidation, 98%.

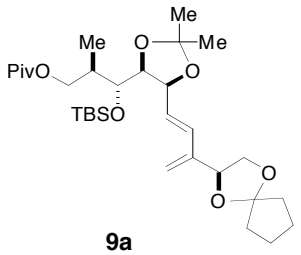
Spectroscipic Data of Aldehyde 8 (colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$) 9.82 (dd, *J* = 3.2, 2.0 Hz, 1H), 4.66 (ddd, *J* = 10.0, 5.6, 3.2 Hz, 1H), 4.21 (dd, *J* = 10.8,

7.6 Hz, 1H), 4.18 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.97 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.93 (dd, *J* = 8.4, 3.6 Hz, 1H), 2.55-2.62 (m, 2H), 2.11-2.19 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.22 (s, 9H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 201.1, 178.3, 109.1, 73.0, 70.2, 66.5, 45.1, 38.8, 38.7, 28.2, 27.2, 25.8, 25.7, 18.1, 11.0, -3.68, -4.52 ppm; IR (film) 2959, 1730, 1475, 1467, 1376, 1255, 1161, 1087, 839, 776, 668 cm^{-1}; HRMS (ES) calcd for $C_{22}H_{42}O_6Si$ $[M+H]^+$ 431.2829, found 431.2823; $[\alpha]_D^{20}$ –56.5 (*c* 1.16, $CHCl_3$).

Experimental for Scheme 2.



Scheme 2. Reagents. a. 1. **7a**, $NiCl_2$, $CrCl_2$, 86%. 2. Ac_2O, Py. 93%, 3. $Pd(OAc)_2$, $CaCO_3$, 97%. b. 1. TFA, H_2O, CH_2Cl_2, 91%, 2. Ac_2O, Py. 99%. 3. TFA, H_2O, CH_2Cl_2, 93%. 4. $CH(OMe)_3$, PPTS, 70%. 5. K_2CO_3, MeOH. 6. TBSCl, DMAP, 98% over 3 steps. 7. DIBAL, 82%. 8. MeI, DEAD, PPh_3, 88%.

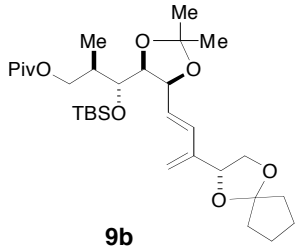


Diene 9a. To a mixture of aldehyde **8** (485 mg, 1.14 mmol) and vinyl bromide (*R*)-**7a** (308 mg, 1.32 mmol) in degassed DMF (3.0 mL) was added 1% $NiCl_2/CrCl_2$ (353 mg, 2.40 mmol) in a glove box. The reaction mixture (deep-green suspension) was stirred vigorously at rt for 2 h before a solution of *D*/*L*-serine in sat. aq. $NaHCO_3$ (1.0 M,

10 mL) was added outside of the glove box. The resulting purple two-layer mixture was stirred vigorously for an additional 6 h and extracted with EtOAc (5 x 30 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4, filtered, concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 5:1) to afford the corresponding allylic alcohol (581 mg, 86%) as a 1.2:1 diastereomeric mixture; IR (film) 3489, 2960, 1729, 1472, 1160, 1095, 839 cm^{-1}; HRMS (ES) calcd for $C_{31}H_{57}O_8Si$ $[M+H]^+$ 585.3822, found 585.3806. Both diastereomers can be separated by further SiO_2 column chromatography (hexanes / EtOAc = 10:1). Major isomer: ^1H NMR (500 MHz, $CDCl_3$) 5.25 (s, 1H), 5.20 (s, 1H), 4.61 (t, *J* = 7.0 Hz, 1H), 4.57 (t, *J* = 5.5 Hz, 1H), 4.48 (m, 1H), 4.25 (dd, *J* = 11.0, 7.5 Hz, 1H), 4.16-4.13 (m, 2H), 4.01-3.98 (m, 2H), 3.68 (t, *J* = 8.0 Hz, 1H), 2.16 (m, 1H), 1.92-1.70 (m, 8H), 1.44 (s, 3H), 1.36 (s, 3H), 1.24 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 178.0, 149.9, 118.9, 110.8, 107.9, 77.5, 76.1, 74.5, 70.0, 69.8, 69.1, 66.7, 38.83, 38.81, 36.5, 36.3, 36.2, 28.5, 27.3, 26.1, 26.0, 25.9, 23.7, 23.5, 18.2, 11.3, -3.68, -4.18 ppm; $[\alpha]_D^{20}$ -18.4° (*c* 1.12, PhH). Minor isomer: ^1H NMR (400 MHz, $CDCl_3$) 5.32 (s, 1H), 5.15 (s, 1H), 4.54 (t, *J* = 7.5 Hz, 1H), 4.36-4.31 (m, 2H), 4.21 (dd, *J* = 8.0, 10.5 Hz, 1H), 4.17 (dd, *J* = 6.0, 7.5 Hz, 1H), 4.10 (dd, *J* = 5.5, 8.5 Hz, 1H), 3.99 (dd, *J* = 3.0, 9.0 Hz, 1H), 3.96 (dd, *J* = 7.5, 11.5 Hz, 1H), 3.62 (t, *J* = 8.0 Hz, 1H), 2.17 (m, 1H), 1.92-1.66 (m, 8H), 1.46 (s, 3H), 1.32 (s, 3H), 1.21 (s, 9H), 1.02 (d, *J* = 7.5 Hz, 3H), 0.85 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 178.0, 148.8, 118.8, 110.3, 108.8, 78.8, 76.8, 76.1, 72.6, 70.3, 69.8, 66.6, 38.9, 36.7, 36.4, 35.5, 29.8, 27.4, 25.93, 25.90, 23.7, 23.5, 18.2, 10.9, -3.35, -4.42 ppm; $[\alpha]_D^{20}$ -4.2 (*c* 0.85, PhH).

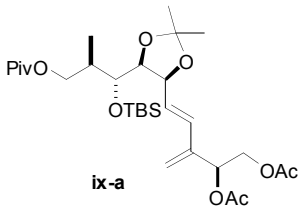
To a mixture of the above allylic alcohol (mixture of diastereomers at C32 position, 580 mg, 0.993 mmol), DMAP (57.0 mg, 0.471 mmol) and pyridine (148 mg, 1.88 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added Ac_2O (115 mg, 1.13 mmol). After 2 h of stirring at 0 °C, the reaction was quenched by several pieces of crushed ice and the mixture was stirred vigorously at rt for 1 h. The whole mixture was poured into two-layer mixture of EtOAc-sat. aq. $NaHCO_3$ and the separated organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 10:1) to provide the corresponding allylic acetate (580 mg, 93%) as a mixture of diastereomers.

A mixture of the above allylic acetate (580 mg, 0.926 mmol), $Pd(OAc)_2$ (10.5 mg, 0.0468 mmol), PPh_3 (85 mg, 0.33 mmol) and $CaCO_3$ (3.0 g, 30.0 mmol) in toluene (10 mL) was stirred at 110 °C for 2 h. The light-yellow solution was purified directly by SiO_2 column chromatography (hexanes / EtOAc = 100:0, 20:1, 10:1) to obtain 1,3-diene **9a** (505 mg, 97%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): 6.27 (d, *J* = 16.5 Hz, 1H), 5.78 (dd, *J* = 8.0, 16.5 Hz, 1H), 5.39 (s, 1H), 5.17 (s, 1H), 4.71 (t, *J* = 7.0 Hz, 1H), 4.57 (dd, *J* = 6.0, 6.5 Hz, 1H), 4.21 (dd, *J* = 7.0, 10.5 Hz, 1H), 4.17 (t, *J* = 7.0 Hz, 1H), 4.14 (dd, *J* = 5.5, 8.0 Hz, 1H), 3.98 (dd, *J* = 7.0, 11.0 Hz, 1H), 3.91 (dd, *J* = 3.5, 8.0 Hz, 1H), 3.57 (t, *J* = 8.0 Hz, 1H), 2.13 (m, 1H), 1.96-1.69 (m, 8H), 1.46 (s, 3H), 1.35 (s, 3H), 1.21 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 178.3, 143.2, 132.7, 126.2, 119.2, 115.3, 108.4, 79.2, 78.5, 75.2, 70.8, 69.6, 66.6, 38.8, 38.6, 36.3, 36.0, 28.1, 27.2, 25.9, 25.4, 23.8, 23.4, 18.1, 11.5, -3.80, -4.40 ppm; IR (film) 2958, 1730, 1481, 1370, 1161, 1092, 837, 777 cm^{-1}; HRMS (ES) calcd for $C_{31}H_{54}O_7Si$ $[M+NH_4]^+$ 584.3983, found 584.3975; $[\alpha]_D^{20}$ -7.9 (*c* 1.11, PhH).



9b

Diene **9b** was prepared according to the above procedure from (*S*)-**7b**: ^{1}H NMR (400 MHz, $CDCl_3$) 6.26 (d, *J* = 16.0 Hz, 1H), 5.68 (dd, *J* = 16.0, 8.8 Hz, 1H), 5.42 (s, 1H), 5.16 (s, 1H), 4.71 (t, *J* = 6.8 Hz, 1H), 4.53 (dd, *J* = 8.8, 5.6 Hz, 1H), 4.24 (dd, *J* = 11.2, 7.2 Hz, 1H), 4.18 (dd, *J* = 8.0, 6.8 Hz, 1H), 4.14 (dd, *J* = 8.4, 5.2 Hz, 1H), 3.96 (dd, *J* = 10.8, 6.8 Hz, 1H), 3.94 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.58 (t, *J* = 7.2 Hz, 1H), 2.09-2.16 (m, 1H), 1.88-1.97 (m, 1H), 1.78-1.84 (m, 3H), 1.68-1.75 (m, 4H), 1.43 (s, 3H), 1.34 (s, 3H), 1.22 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H) ppm; IR (film) 2958,1731, 1472, 1249, 1159, 1106, 837 cm^{-1}; $[\alpha]_D^{20}$ –40.7 (*c* 1.50, PhH).

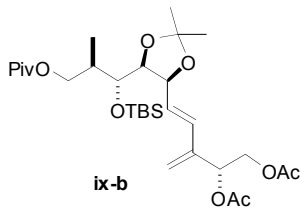


ix-a

Diacetate ix-a. Acetonide **9a** (1.352g, 2.385 mmol) was dissolved in TFA-CH_2Cl_2-H_2O (15 mL, prepared by mixing 20 mL of CH_2Cl_2, 10 mL of H_2O and 5 mL of CF_3CO_2H, and the organic layer was used), and stirred at rt for 2h. The mixture was poured into the mixture of Et_2O, sat. aq. $NaHCO_3$, and solid $NaHCO_3$. The organic phase was extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 1:1, then 1:2) to afford unreacted **9a** (76 mg, 15%) and the corresponding 1,2-diol (311 mg, 70%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) 6.24 (d, *J* = 16.0 Hz, 1H), 5.91 (dd, *J* = 16.0, 8.0 Hz, 1H), 5.36 (s, 1H), 5.25 (s, 1H), 4.57 (t, *J* = 7.0 Hz, 1H), 4.54 (dd, *J* = 8.0, 3.5 Hz, 1H), 4.30 (dd, *J* = 9.0, 7.0 Hz, 1H), 4.16 (dd, *J* = 7.5, 6.0 Hz, 1H), 3.93 (dd, *J* = 7.0, 4.0 Hz, 1H), 3.89 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.75 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.56 (dd, *J* = 11.0, 7.5 Hz, 1H), 2.11 (m, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.20 (s, 9H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H) ppm; IR (film) 3443, 2953, 1730, 1163, 1090, 837 cm^{-1}; LRMS (ES) calcd for $C_{30}H_{52}O_9Si$ $[M+Na]^+$ 523.3, found 523.2.

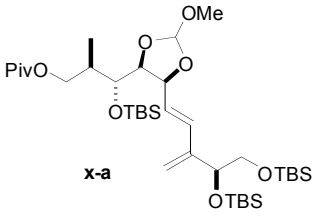
To a solution of the above diol (2.210 g, 4.41 mmol) in CH_2Cl_2 (22 mL) was added NEt_3 (4.92 mL, 35.3 mmol), DMAP (108 mg, 0.88 mmol), Ac_2O (1.66 mL, 17.7 mmol) sequentially at 0 °C. The mixture was allowed to warm to rt and stirred overnight, quenched by sat. aq. NH_4Cl, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 4:1) to give acetate **ix-a** (2.560 g, 99%) as colorless oil: ^{1}H NMR (400 MHz, C_6D_6) 6.35 (dd, *J* = 6.4, 16.0 Hz, 1H), 6.28 (d, *J* = 16.4 Hz, 1H), 6.07 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.15 (s, 1H), 5.05 (s, 1H), 4.65 (t, *J* = 5.2 Hz, 1H), 4.58 (dd, *J* = 6.8, 11.2 Hz, 1H), 4.48 (dd, *J* = 2.8, 12.0 Hz, 1H), 4.15-4.22 (m, 3H), 4.05 (dd, *J* = 8.4, 11.6 Hz, 1H), 2.31 (dq, *J* = 2.4, 6.8 Hz, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.17 (s, 9H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H) ppm; ^{13}C NMR (100 MHz, C_6D_6) 177.5, 169.9, 169.0, 141.6, 131.9, 116.7, 108.7, 79.2, 79.1, 71.4, 70.8, 66.9, 65.3, 39.3,

38.7, 28.1, 27.3 (3x), 26.1 (3x), 25.6, 20.4, 20.2, 18.3, 11.6, -3.7, -4.3 ppm; HRMS (ES) calcd for $C_{30}H_{52}O_9Si$ $[M+NH_4]^+$ 602.3724, found 602.3715; $[\alpha]_D^{20}$ -41.8 (*c* 0.23, PhH).



ix-b

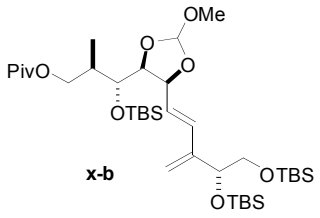
Diacetate **ix-b** was prepared according to the above procedure from acetonide **9b**: ^{1}H NMR (400 MHz, C_6D_6) 6.35 (dd, *J* = 8.0, 16.0 Hz, 1H), 6.20 (d, *J* = 16.0 Hz, 1H), 6.03 (dd, *J* = 2.4, 8.8 Hz, 1H), 5.16 (s, 1H), 5.00 (s, 1H), 4.60 (dd, *J* = 4.8, 8.8 Hz, 1H), 4.56 (dd, *J* = 7.6, 11.2 Hz, 1H), 4.49 (dd, *J* = 2.8, 12.0 Hz, 1H), 4.16-4.24 (m, 3H), 3.92 (dd, *J* = 8.8, 12.0 Hz, 1H), 2.33 (dq, *J* = 2.4, 7.2 Hz, 1H), 1.64 (s, 3H), 1.63 (s, 3H), 1.23 (s, 9H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, C_6D_6) 177.5, 169.9, 168.9, 141.7, 132.8, 117.0, 108.7, 80.0, 78.9, 70.9, 70.7, 66.8, 65.4, 39.2, 38.8, 28.3, 27.4 (3x), 26.1 (3x), 25.7, 20.3, 20.2, 18.3, 11.4, -3.9, -4.2 ppm; HRMS (ES) calcd for $C_{30}H_{52}O_9Si$ $[M+NH_4]^+$ 602.3724, found 602.3699; $[\alpha]_D^{20}$ -19.2 (*c* 0.23, PhH).



x-a

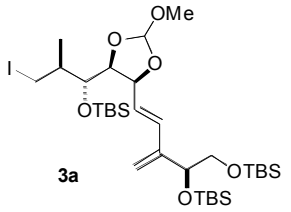
Bis-TBS ether x-a. To a solution of diacetate **ix-a** (2.342 g, 4.0 mmol) in CH_2Cl_2 (100 mL) was added freshly mixed TFA / CH_2Cl_2 / H_2O (4:4:1, v/v/v, 10 mL) at 0 °C. After 40 min of stirring at 0 °C, the reaction was quenched with sat. aq. $NaHCO_3$, extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 4:1, then 1:1) to give the corresponding diol (1.560 g) and recovered acetonide **ix-a** (574 mg), which was re-submitted to the same reaction conditions twice to give additional diol (2.030 g in total, 93%).

To a solution of the above diol (2.030 g, 3.73 mmol) in CH_2Cl_2 (30 mL) were added $CH(OMe)_3$ (8.2 mL, 111 mmol), and PPTS (46.8 mg, 0.19 mmol) at rt. After 8 h of stirring at rt, the reaction was quenched by addition of NEt_3 (2 mL), concentrated to afford the corresponding crude orthoester, which was dissolved in MeOH (30 mL), and was added K_2CO_3 (2.575 g, 18.6 mmol) at rt. After 5 h of stirring at rt, the reaction mixture was filtered through a pad of basic alumina with Et_2O. The solvent was removed to give the corresponding crude diol, which was dissolved in CH_2Cl_2 (30 mL). To this solution were added NEt_3 (5.2 mL, 37.3 mmol), DMAP (4.553 g, 37.3 mmol), TBSCl (2.798 g, 18.6 mmol) sequentially at rt. After 36 h of stirring at rt, the reaction was quenched by sat. aq. $NaHCO_3$, extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 20:1) to afford orthoester **x-a** (2.682 g, 98% over 3 steps) as *ca*. 2:1 mixture of diastereomers. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) 6.24 (d, J = 15.5 Hz, 1H), 5.95 (dd, J = 7.0, 15.5 Hz, 1H), 5.78 (s, 1H), 5.29 (s, 1H), 5.22 (s, 1H), 4.81 (t, J = 6.5 Hz, 1H), 4.36 (m, 1H), 4.32 (t, J = 6.0 Hz, 1H), 4.17 (dd, J = 7.0, 12.5 Hz, 1H), 4.02 (m, 1H), 3.90 (dd, J = 5.0, 7.0 Hz, 1H), 3.56 (dd, J = 4.0, 11.0 Hz, 1H), 3.43 (s, J = 7.5 Hz, 1H), 3.34 (s, 3H), 3.28-3.24 (m, 1H), 2.12 (m, 1H), 1.19 (s, 9H), 1.01 (d, J = 7.0 Hz, 3H), 0.88-0.86 (m, 27H), 0.08 (s, 6H), 0.06 (s, 6H), 0.02 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 178.4, 145.3, 132.9, 123.9, 115.8, 115.1, 78.9, 77.6, 74.6, 71.5, 68.3, 66.2, 52.1, 37.8, 29.7, 27.2, 26.0, 25.9, 25.8, 18.4, 18.3, 18.2, 12.4, -4.00, -4.26, -4.71, -4.84, -5.23, -5.38 ppm; IR (film) 2929, 1731, 1254, 1083, 837, 777 cm^{-1}; LRMS (FAB) calcd for $C_{37}H_{74}O_8Si_3$ $[M+Na]^+$ 753, found 753.



Orthoester **x-b** was prepared according to the above procedure from acetonide **ix-b**. Major diastereomer: ^{1}H NMR (500 MHz, C_6D_6) 6.26 (d, J = 19.0 Hz, 1H), 6.19 (dd, J = 12.0. 8.5 Hz, 1H), 5.81 (s, 1H), 5.49 (s, 1H), 5.19 (s, 1H), 4.77 (t, J = 7.5 Hz, 1H), 4.65 (broad d, J = 7.0 Hz, 1H), 4.48 (dd, J = 10.5, 5.5 Hz, 1H), 4.48-4.52 (m, 1H), 4.20 (dd, J

= 10.5, 6.5 Hz, 1H), 4.16-4.19 (m, 1H), 3.89 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.63 (dd, *J* = 10.5, 6.0 Hz, 2H), 3.08 (s, 3H), 2.20-2.26 (m, 1H), 1.20 (s, 9H), 1.03 (s, 9H), 0.97 (s, 9H), 0.93 (s, 9H), 0.22 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.09 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 178.3, 145.1, 134.1, 123.9, 117.5, 116.1, 79.6, 79.5, 77.4, 74.1, 70.3, 68.4, 66.2, 52.1, 50.1, 38.8, 38.2, 27.2, 26.0, 25.9, 25.8, 25.6, 18.4, 18.2, 18.1, 11.6, -3.8, -4.2, -4.4, -4.7, -4.8, -5.3 ppm.

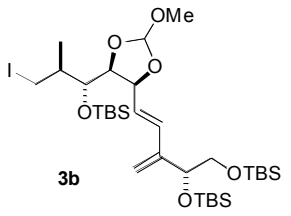


3a

Iodide 3a. To a stirred solution of ester **x-a** (733.5 mg, 1.004 mmol) in CH_2Cl_2 (10 ml) at -78 °C was added DIBAL (1 *M* in toluene 2.5 mL) and stirred for 15 min. The reaction was quenched by sequential addition of MeOH, sat. aq. sodium potassium tartrate, stirred at rt for 2 h, extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 9:1, 4:1, then 2:1, all solvents contains 0.1% Et_3N) to furnish the corresponding alcohol as a mixture of diastereomers (535 mg, 82.4 %).

To a solution of the above alcohol (530 mg, 0.819 mmol), PPh_3 (645 mg, 2.457 mmol), and 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide (Sumilizer, 57 mg, 0.164 mmol) in benzene (N_2 bubbling for 15min, 8 mL) at 0 °C was added MeI (0.153 mL, 2.457 mmol) and DEAD (0.387 mL, 2.457 mmol), successively. The mixture was stirred at rt overnight, directly charged to a SiO_2 column (hexane / Et_2O = 20:1, contains 0.1% Et_3N) to furnish iodide **3a** (544 mg, 88%) as a mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) 6.25 (d, *J* = 16.0 Hz, 1H), 5.86 (dd, *J* = 16.0, 7.2 Hz, 1H), 5.80 (s, 1H), 5.33 (s, 1H), 5.24 (d, *J* = 1.2 Hz, 1H), 4.81 (t, *J* = 6.4 Hz, 1H), 4.39 (dd, *J* = 7.2, 2.8 Hz, 1H), 4.28 (t, *J* = 7.2 Hz, 1H), 3.92 (dd, *J* = 7.2, 4.0 Hz, 1H), 3.58 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.48-3.40 (m, 2H), 3.34 (s, 3H), 3.18 (dd, *J* = 9.2, 6.8 Hz, 1H), 1.95 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 18 H), 0.88 (s, 9H), 0.104 (s, 3H), 0.093 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 145.3, 133.2, 123.6, 116.6, 115.1, 79.1, 77.9, 72.8, 68.3, 52.1, 41.0, 26.0,

25.90, 25.87, 18.4, 18.3, 18.2, 15.7, 14.7, 12.2, –3.80, –4.18, –4.68, –4.77, –5.15, –5.33 ppm; IR (film) 2929, 1472, 1463, 1255, 1124, 1082, 836, 776 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{65}IO_6Si_3$ $[M+Na]^+$ 779.3031, found 779.3021; $[\alpha]_D^{20}$ –46.0 (*c* 1.03, PhH).

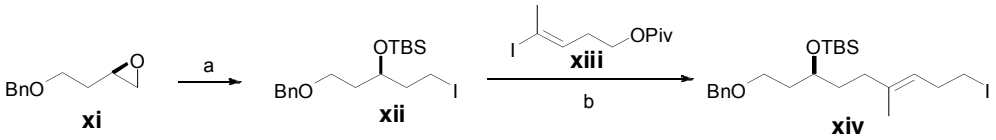


3b

Iodide **3b** was prepared according to the above procedure from ester **x-b**. Major Diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) 6.27 (d, *J* = 12.8 Hz, 1H), 5.87 (dd, *J* = 12.8, 7.2 Hz, 1H), 5.74 (s, 1H), 5.38 (s, 1H), 5.21 (s, 1H), 4.54 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.45 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.29 (t, *J* = 5.2 Hz, 1H), 3.97 (dd, *J* = 4.8, 3.2 Hz, 1H), 3.64 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.38-3.53 (m, 2H), 3.33 (s, 3H), 3.25 (dd, *J* = 7.6, 4.7 Hz, 1H), 1.85-1.92 (m, 1H), 1.06 (d, *J* = 5.2 Hz, 3H), 0.89 (s, 18H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H), 0.04 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 145.1, 134.4, 124.2, 117.5, 116.0, 80.0 (x2), 77.7, 74.1, 71.6, 68.5, 51.8, 42.0, 26.0 (x6), 25.8, (x3), 18.4, 18.2, 18.0, 15.9, 14.5, 10.9, -3.8, -4.1, -4.6, -4.7, -5.2, -5.3 ppm; IR (film) 2929, 1472, 1253, 1081, 836, 777 cm^{-1}; LRMS (ESI) calcd for $C_{32}H_{65}IO_6Si_3$ $[M+Na]^+$ 778, found 778.

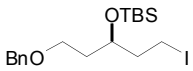
Significant modifications/improvements have been made on the original synthesis of dithiane **1** (McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647). The improved synthesis is summarized in Schemes III, IV, V, and VI.

Experimental for Scheme III.



xi **xii** **xiv**

Scheme III. Reagents. a. 1. vinyl magnesium bromide, CuI, -25 °C to 0 °C, 100%. 2. TBSCl, imidazole, DMF, rt. 3. O_3; then $NaBH_4$. 4.Ph_3P, I_2, imidazole, CH_2Cl_2. b. 1. **xiii**, Negishi coupling. 2. DIBAL, -78 °C, CH_2Cl_2. 3. Ph_3P, I_2, imidazole, CH_2Cl_2.



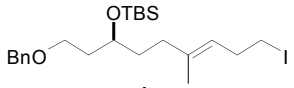
xii

Iodide xii. To a stirred suspension of CuI (3.42 g, 17.95 mmol) in THF (200 mL) under N_2 at -78 ^oC was added vinyl magnesium bromide (1.0 M in THF, 220 mL) and epoxide **xi** (32.0 g, 179.5 mmol) in THF (50 mL) successively. The brown solution was stirred at -25 to -20 ^oC overnight, then at 0 ^oC for another 1 h. The reaction was quenched by sat. aq. NH_4Cl, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 15:1, 9:1, 3:1) to give the corresponding allylic alcohol (37.2 g, 100%): ^1H NMR (400 MHz, $CDCl_3$) 7.25-7.37 (m, 5H), 5.79-5.89 (m, 1H), 5.08-5.14 (m, 2H), 4.53 (s, 2H), 3.85-3.91 (m, 1H), 3.66-3.75 (m, 1H), 3.62-3.65 (m, 1H), 2.23-2.27 (m, 2H), 1.75-1.80 (m, 2H) ppm.

To a stirred solution of the above allylic alcohol (38.0 g, 184 mmol) in DMF (100 mL) was added imidazole (16.0 g, 221 mmol) and TBSCl (30.5 g, 202 mmol). The reaction mixture was stirred at rt overnight and quenched by H_2O. The mixture was extracted with Et_2O, and the combined organic layers was washed by 1*N* HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give the corresponding crude silylated alcohol: ^1H NMR (400 MHz, $CDCl_3$) 7.26-7.33 (m, 5H), 5.76-5.85 (m, 1H), 5.00-5.05 (m, 2H), 4.48 (ABq, J = 12.0 Hz, 2H), 3.88-3.92 (m, 1H), 3.52-3.57 (m, 2H), 2.20-2.52 (m, 2H), 1.66-1.84 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm.

The above crude olefin was dissolved in CH_2Cl_2/MeOH (1:1, 800 mL), and O_3 was bubbled through for 45 min until the solution turned to blue. N_2 was bubbled through for 15 min before $NaBH_4$ (15.0 g, 395 mmol) was added slowly. The reaction mixture was stirred at 0 ^oC for 3 h and quenched by sat. aq. NH_4Cl (300 mL), extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 15:1, 9:1, 3:1) to give the corresponding primary alcohol (50.2 g, 84 %) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) 7.28-7.37 (m, 5H), 4.48 (ABq, J = 12.0 Hz, 2H), 4.09-4.14 (m, 1H), 3.80-3.86 (m, 1H), 3.72(m, 1H) 3.52 (t, J = 6.4 Hz, 2H), 2.40 (dd, J = 5.6, 4.4 Hz, 1H), 1.80-1.92 (m, 3H), 1.63-1.69 (m, 1H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H) ppm.

To a stirred solution of PPh_3 (17.2 g, 65.412 mmol) and imidazole (5.5 g, 81 mmol) in CH_2Cl_2 (200 mL) at 0 ^oC was added I_2 (16.6 g, 65 mmol) in one portion, and stirred at rt for 30 min. To the pale brown suspension was added a solution of the above alcohol (20.2 g, 62.3 mmol) in CH_2Cl_2 (50 mL) via cannula at 0 ^oC. The reaction mixture was stirred at rt for 1 h and filtered through a pad of SiO_2 (hexanes / EtOAc = 100:0, 9:1) to give iodide **xii** (24.3 g): ^1H NMR (400 MHz, $CDCl_3$) 7.27-7.37 (m, 5H), 4.49 (ABq, 2H, *J* =12.0 Hz, 2H), 3.96 (m, 1H), 3.52 (t, *J* =6.4 Hz, 2H), 3.16-3.25 (m, 2H), 1.96-2.03 (m, 2H), 1.78 (dd, *J* =12.0, 6.0Hz, 2H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H) ppm.



xiv

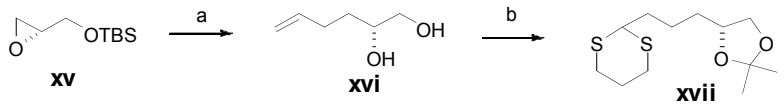
Iodide xiv. To a mixture of Zn (24 g) and $Cu(OAc)_2 \cdot H_2O$ (2.4 g) was added AcOH (120 mL). The resulting mixture was heated to reflux for 5 min. After cooled to rt, AcOH was removed by glass pipette. This procedure was repeated three times. The resulting black Zn-Cu was washed by Et_2O (5 x 100 mL) and dried under high vacuum overnight to furnish a pale purple gray powder, which was placed in one-liter three-necked flask containing a solution of alkyl iodide **xii** (28.3 g, 65.1 mmol) in benzene (dried over 4 Å molecular sieves before use, 120 mL) and DMF (15 mL). N_2 was bubbled through the suspension for 15 min before heated to 55 - 60 ^oC for 2 h (iodide **xii** was almost consumed, checked by TLC). A solution of vinyl iodide **xiii** (ca 30 g) in benzene (100 mL) and $Pd(PPh_3)_4$ (5.0 g) were added at this temperature. The resulting mixture was stirred at the same temperature overnight before quenched by sat. aq. NH_4Cl, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 100:0, 15:1, 9:1) to give the corresponding crude coupling product.

The above crude product mixture was dissolved in CH_2Cl_2 (dried over 4 Å molecular sieves before use, 300 mL) and cooling to -78 ^oC. DIBAL (1.0 *M* in toluene, 140 mL) was added, and the resulting mixture was stirred for 15 min before quenched by MeOH and 1 *N* HCl at -78 ^oC. The reaction was warmed to rt and stirred for 30 min, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 10:1, 6:1, 3:1,

2:1) to give the corresponding homo allylic alcohol (14.21 g, 55.6% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.37 (m, 5H), 5.12 (dt, *J* =7.2, 1.2 Hz, 1H), 4.48 (ABq, *J* =12.0 Hz, 2H), 3.81-3.84 (m, 1H), 3.60 (t, *J* =7.2 Hz, 2H), 3.53 (t, *J* =5.6 Hz, 2H), 2.24-2.29 (m, 2H), 1.97-2.11 (m, 2H), 1.78-1.84 (m, 1H), 1.65-1.74 (m, 1H), 1.63 (s, 3H), 1.52-1.58 (m, 2H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm.

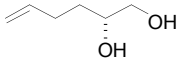
To a stirred solution of PPh_3 (1.4 g, 5.3 mmol) and imidazole (450 mg, 6.6 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C was added I_2 (1.354 g, 5.3 mmol). The reaction mixture was stirred at rt for 30 min before a solution of the above alcohol (1.995 g, 5.1 mmol) in CH_2Cl_2 (5 mL) was added. After stirring at rt for 2 h, the reaction was quenched by sat. aq. NH_4Cl and aq. Na_2SO_3, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 9:1) to furnish iodide **xiv** (2.553 g, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.37 (m, 5H), 5.08 (t, *J* =6.8 Hz, 1H), 4.49 (ABq, *J* =12.0 Hz, 2H), 3.81-3.88 (m, 1H), 3.54 (t, *J* =6.4 Hz, 2H), 3.09 (t, *J* =7.2 Hz, 2H), 2.57 (q, *J* =7.2 Hz, 2H), 1.87-2.03 (m, 2H), 1.71-1.82 (m, 2H), 1.59 (s, 3H), 1.52-1.58 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm.

Experimental for Scheme IV.



xv **xvi** **xvii**

Scheme IV. Reagents. a. 1. H_2C=$CHCH_2MgBr$, Li_2CuCl_4, THF/Et_2O, -30 °C. 2. TBAF, THF, rt. b. 1. $MeC(OMe)_2Me$, TsOH, acetone, rt. 2. O_3; then $NaBH_4$. 3. PPh_3, I_2, imidazole, CH_2Cl_2. 4. 1,3-dithiane, *t*BuLi, THF, -78 °C.

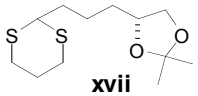


xvi

Diol xvi. To a stirred solution of epoxide **xv** (26 g, 138.0 mol) in Et_2O (200 mL) at -30 ^{o}C was added Li_2CuCl_4 (0.1 M in THF, 34.5 mL) and allylmagnesium bromide (1 M in Et_2O, 165 mL) successively. The mixture was stirred at -30 ^{o}C for 30 min then at rt for 2 h. After quenched with sat. aq. NH_4Cl, the mixture was extracted with Et_2O, dried

over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 50:1, 20:1, 15:1, 10:1) to furnish the corresponding alcohol (25.04 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) 5.80-5.88 (m, 1H), 5.04 (ddd, *J* =14.4, 2.4, 1.2 Hz, 1H), 4.97 (dd, *J* =8.4, 1.6Hz, 1H), 3.62-3.68 (m, 2H), 3.41 (dd, J=7.6, 6.0 Hz, 1H), 2.20-2.27 (m, 1H), 2.10-2.17 (m, 1H), 1.44-1.58 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H) ppm.

To a stirred solution of the above alcohol (1.665 g, 7.2 mmol) in THF (5mL) was added TBAF (1 M in THF, 8 mL) and stirred at rt overnight. The volatile was removed in vacuo, and the residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 4:1, EtOAc / MeOH = 4:1) to give diol **xvi** (1.078 g, this compound is volatile): ^{1}H NMR (500 MHz, $CDCl_3$) 5.84 (ddt, *J* = 14.0, 10.0, 6.5 Hz, 1H), 5.07 (ddd, *J* = 15.0, 3.0, 1.5 Hz, 1H), 4.99 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.73-3.78 (m, 1H), 3.67 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.46 (dd, *J* =11.5, 8.0 Hz, 1H), 2.12-2.54 (m, 2H), 1.51-1.59 (m, 2H) ppm.



xvii

Dithiane xvii. To a solution of diol **xvi** (1.078 g) in acetone (1 mL) were added 2,2-dimethoxypropane (2 mL) and $TsOH{\cdot}H_2O$ (27 mg, 0.145 mmol). The mixture was stirred at rt overnight. Et_3N was added, and the volatile was removed in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 100:0, 20:1, then 12:1) to furnish the corresponding acetonide (968 mg, 86% over 2 steps, this compound is volatile): ^{1}H NMR (400 MHz, $CDCl_3$) 5.77-5.87 (m, 1H), 5.04 (dt, *J* =17.2, 2.0 Hz, 1H), 4.98 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.02-4.13 (m, 3H), 3.52 (t, *J* = 7.2 Hz, 1H), 2.06-2.21 (m, 2H), 1.71-1.80 (m, 1H), 1.55-1.64 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H) ppm.

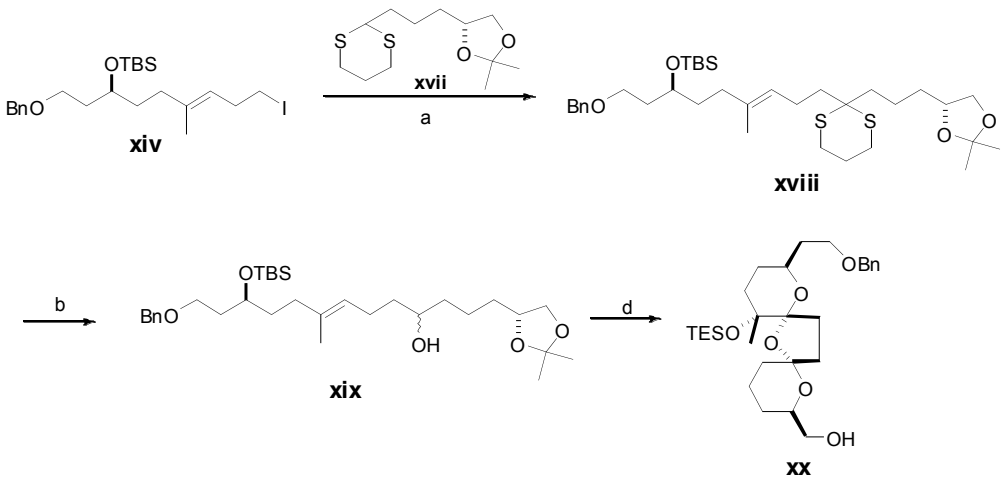
To a stirred solution of the above olefin (15.24 g, 97.5 mmol) in CH_2Cl_2 (150 mL) and MeOH (150 mL) at -78 ^{o}C was bubbled with O_3 until the color of the solution changed to pale blue. After bubbling N_2 for 15 min, $NaBH_4$ (10 g) was added, and the mixture was allowed to warm to rt and stirred overnight. The reaction mixture was quenched by sat. aq. NH_4Cl, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 4:1, 1:1, 1:3, 0:100) to furnish the corresponding alcohol (11.76g,

77% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) 4.27 (quintet, J = 6.4 Hz, 1H), 4.09 (dd, J = 8.0, 6.4 Hz, 1H), 3.77-3.84 (m, 2H), 3.60 (t, J = 7.6 Hz, 1H), 2.18 (t, J = 5.2 Hz, 1H), 1.82 (q, J = 5.6 Hz, 2H), 1.43 (s, 3H), 1.36 (s, 3H) ppm.

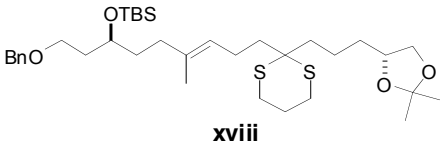
To a stirred solution of PPh_3 (19.8 g, 75.6 mmol) and imidazole (6 g, 88.1 mmol) in CH_2Cl_2 (250 mL) at 0 ^oC was added I_2 (19.2 g, 75.6 mmol). A solution of the above alcohol (11.76g, 73.4 mmol) in CH_2Cl_2 (100 mL) was added via cannula and the mixture was stirred at rt for 3 h. After quenched with sat. aq. $NaHCO_3$ and sat. aq. Na_2SO_3, the mixture was extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a pad of SiO_2 to give the corresponding iodide (18.379 g, 93%).

To a stirred solution of 1,3-dithiane (5.758 g, 47.9 mmol) in THF (70 mL) and HMPA (distilled from Na and stored in the presence of activated 4 Å molecular sieves, 3.5 mL) at -30 ^oC was added ^{t}BuLi (1.4 M in pentane, 31 mL), The mixture was cooled to -78 ^oC. After 30 min at -78 ^oC, a solution of the above iodide (6.187 g, 22.9 mmol) in THF (15 mL) was added via cannula. The resulting mixture was stirred for 30 min at same temperature, quenched by sat. aq. NH_4Cl, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 20:1, 15:1, 9:1, 4:1 then 3:1) to furnish dithiane **xvii** (6.12 g, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) 4.03-4.10 (m, 1H), 4.04 (dd, J = 8.0, 6.0 Hz, 1H), 3.51 (t, J = 7.5 Hz, 1H), 2.80-2.90 (m, 4H), 2.09-2.15 (m, 1H), 1.84-1.91 (m, 1H), 1.77-1.83 (m, 2H), 1.60-1.69 (m, 2H), 1.49-1.57 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H) ppm.

Experimental for Scheme V.



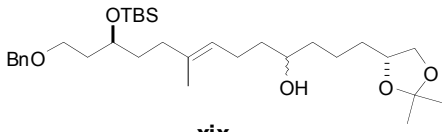
Scheme V. Reagents. a. ^{t}BuLi, **xvii**, THF, -78 °C to 0 °C. b. 1. PIFA, $SrCO_3$, MeCN/H_2O, 0 °C. 2. $NaBH_4$, EtOH, 0 °C. c. 1. $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSONH_2$, $K_2OsO_2{\cdot}2H_2O$, tBuOH/H_2O. 2. Swern oxidation. 3. CSA, MeOH, rt. d. 1. TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. 2. TBAF, THF, 0 °C.



xviii

Dithiane xviii. To a solution of dithiane **xvii** (7.8 g, 29.7 mmol, azeotropically dried with PhH three times) in THF (freshly distilled from $LiAlH_4$, 70 mL) at -78 °C was added ^{t}BuLi (1.7 *M* in pentane, 18 mL) via syringe. The resulting yellow solution was warmed to 0 °C for 30 min before cooled back to -78 °C. To the mixture was added a solution of iodide **xiv** (18 g, 35.8 mmol) in THF (20 mL) over 25 min via cannula (yellow suspension formed after addition). The mixture was warmed to 0 °C, stirred for 30 min before quenched by sat. aq. NH_4Cl. The mixture was extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 9:1, then hexanes / PhH / ^{t}BuOMe = 4:1:1) to afford the recovered iodide **xiv** and the coupling product **xviii**. Another cycle of this reaction using the recovered iodide **xiv** gave more coupling product **xviii** (18.70 g in total, 72 % based on dithiane **xvii**): ^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.36 (m, 5H), 5.11 (t, *J* =4.0 Hz, 1H), 4.49 (ABq, *J* =12.0 Hz, 2H), 4.03-4.13 (m, 2H), 3.80-3.85 (m, 1H), 3.49-3.56 (m, 3H), 2.75-2.86 (m, 4H), 2.05-2.13 (m, 2H), 1.86-2.00 (m, 8H), 1.71-1.81

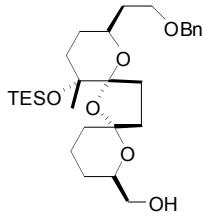
(m, 8H), 1.43-1.66 (m, 6H), 1.54 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm.



xix

Alcohol xix. To a stirred suspension of dithiane **xviii** (18.70 g, 29.4 mmol) and $SrCO_3$ (53 g) in CH_3CN (260 mL) and H_2O (26 mL) at 0 ^oC was added PIFA (28 g, 64.6 mmol). The reaction mixture was stirred at 0 ^oC for 30 min. $NaHCO_3$ (50 g), H_2O (200 mL), and Na_2SO_3 (15 g) were added successively. After stirred at rt for 30 min, the mixture was extracted with hexane / Et_2O = 4:1, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 100:0, 9:1, 4:1, 2:1) to furnish the corresponding ketone (12.02 g, 74.9 %): ^1H NMR (500 MHz, $CDCl_3$) 7.26-7.35 (m, 5H), 5.05 (dt, J =11.5, 1.0 Hz, 1H), 4.48 (ABq, J =11.5 Hz, 2H), 4.07 (quintet, J = 5.5 Hz, 1H), 4.03 (t, J=5.5 Hz, 1H), 3.82 (quintet, J = 5.5 Hz, 1H), 3.53 (t, J = 6.0 Hz, 1H), 3.51 (dd, J = 14.5, 7.0 Hz, 2H), 2.43 (t, J = 7.0 Hz, 2H), 2.40 (t, J =4.5 Hz, 2H), 2.24 (q, J =7.5 Hz, 2H), 1.92-2.04 (m, 2H), 1.67-1.79 (m, 3H), 1.54 (s, 3H), 1.48-1.61 (m, 5H), 1.40 (s, 3H), 1.34 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm.

To a solution of the above ketone (12.02 g, 22.0 mmol) in EtOH (70 mL) at 0 ^oC was added $NaBH_4$ (850 mg) and stirred at rt for 1h. The reaction was quenched by sat. aq. NH_4Cl followed by sat. aq. $NaHCO_3$ until pH = 9. The mixture was extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 6:1, 3:1, 2:1, 1:1) to furnish alcohol **xix** as an inseparable 1:1 mixture (11.84 g, 98%): ^1H NMR (600 MHz, $CDCl_3$) 7.26-7.35 (m, 5H), 5.13 (t, J =6.6 Hz, 1H), 4.49 (ABq, J =11.4 Hz, 2H), 4.06-4.10 (m, 1H), 4.04 (t, J =6.6 Hz, 1H), 3.82 (quintet, J =4.8 Hz, 1H), 3.57-3.63 (m, 1H), 3.54 (t, J =6.6 Hz, 2H), 3.51 (dt, J =7.2, 2.4 Hz, 1H), 1.94-2.13 (m, 4H), 1.70-1.80 (m, 2H), 1.62-1.67 (m, 1H), 1.57 (s, 3H), 1.43-1.54 (m, 9H), 1.41 (s, 3H), 1.35 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm.



xx

Alcohol xx. To a stirred suspension of alcohol **xix** (11.84 g, 21.6 mmol), $(DHQD)_2PHAL$ (840 mg, 1.079 mmol), $K_3Fe(CN)_6$ (21.3 g, 64.7 mmol), K_2CO_3 (8.94 g, 64.7 mmol), and $MeSONH_2$ (2.05 g, 21.6 mmol) in ^tBuOH (110 mL) and H_2O (110 mL) at 0 ^oC was added $K_2OsO_4 \cdot 2H_2O$ (80 mg, 0.216 mmol). The resulting mixture was allowed to warm to rt without remove the ice-water bath and stirred for 17 h. K_2CO_3 (9g) and $Na_2S_2O_3 \cdot 5H_2O$ (20 g) were added to the reaction mixture and stirred at rt for 30 min. The mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 4:1, 2:1, 1:1, 1:4, 1:9, 0:100, then EtOAc / MeOH = 20:1) to furnish the corresponding triol (12.2 g, 87%): ^1H NMR (600 MHz, $CDCl_3$) 7.26-7.35 (m, 5H), 4.48 (ABq, J =11.4 Hz, 2H), 4.06-4.10 (m, 1H), 4.04 (t, J =7.8 Hz, 1H), 3.88-3.94 (m, 1H), 3.68(broad m, 1H), 3.61 (broad m, 1H), 3.48-3.52 (m, 3), 3.39 (d, J =10.2 Hz, 1H), 3.16 (br, 1H), 2.86 (br, 1H), 2.22 (br, 1H), 1.79 (q, J = 6.6 Hz, 2H), 1.60-1.76 (m, 4H), 1.44-1.58 (m, 10H), 1.46 (s, 3H), 1.35 (s, 3H), 1.08 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H) ppm.

To a stirred solution of $(COCl)_2$ (0.87 mL, 1.75 mmol) in CH_2Cl_2 (2 mL) at -78 ^oC was added a solution of DMSO (0.19mL, 2.625 mmol) in CH_2Cl_2 (0.8 mL). After 10 min, a solution of the above triol (102 mg, 0.175 mmol) in CH_2Cl_2 (0.6 mL), and Et_3N (0.6 mL, 4.301 mmol) were added successively. The mixture was warmed to rt and stirred for 1h. After quenched with H_2O, the mixture was extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 2:1) to furnish the corresponding diketone (93.8 mg, 92 %): ^1H NMR (400 MHz, $CDCl_3$) 7.26-7.34 (m, 5H), 4.47 (ABq, J =12.0 Hz, 2H), 4.01-4.10 (m, 1H), 3.83-3.89 (m, 1H), 3.49-3.53 (m, 3), 2.59-2.90 (m, 4H), 2.52 (t, J =6.8 Hz, 2H), 1.69-1.78 (m, 6H), 1.48-1.66 (m, 4H), 1.39 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ppm.

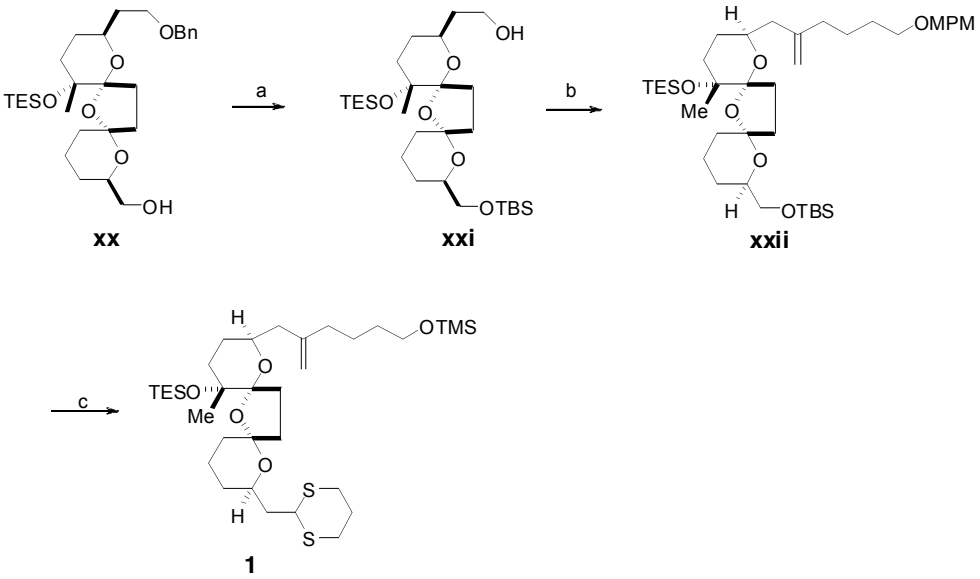
To a stirred solution of the above diketone (52.3 mg, 0.0903 mmol) in MeOH (1 mL) was added CSA (0.6 mg) and stirred at rt overnight. After addition of Et_3N (0.1 mL), the mixture was concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 5:1, 2:1, 1:1, 1:2 then 1:5) to give the corresponding desired spiroketal (16 mg, 43.6%), undesired epimer (7.5 mg, 20.4%), and other undetermined stereoisomers. All undesired isomers were recycled three times under the same conditions twice to give more desired spiroketal (25.7 mg in total, 70%). Desired spiroketal: ^{1}H NMR (600 MHz, $CDCl_3$) 7.32-7.36 (m, 4H), 7.26-7.30 (m, 1H), 4.50 (ABq, *J* = 12.6 Hz, 2H), 3.94-4.04 (m, 2H), 3.63-3.66 (m, 1H), 3.50 (dt, *J* = 9.0, 6.6 Hz, 1H), 3.39 (dt, *J* = 7.2, 1.2 Hz, 2H), 2.56 (t, *J* = 6.0 Hz, 1H), 2.16-2.22 (m, 2H), 1.77-1.92 (m, 5H), 1.64-1.75 (m, 4H), 1.56-1.61 (m, 1H), 1.42-1.48 (m, 1H), 1.40 (dd, *J* = 19.8, 5.4 Hz, 1H), 1.25 (s, 3H), 1.21-1.28 (m, 2H) ppm. Undesired epimer: ^{1}H NMR (600 MHz, $CDCl_3$) 7.26-7.35 (m, 5H), 4.47 (s, 2H), 3.96-4.02 (m, 1H), 3.66-3.74 (m, 2H), 3.49-3.56 (m, 3H), 2.32 (dt, *J* = 13.2, 7.8 Hz, 1H), 2.21 (dd, *J* =12.6, 7.2 Hz, 1H), 1.91 (dt, *J* = 13.2, 4.2 Hz, 1H), 1.78-1.85 (m, 2H), 1.64-1.76 (m, 4H), 1.58-1.62 (m, 1H), 1.44-1.56 (m, 3H), 1.38-1.42 (m, 1H), 1.34-1.36 (m, 2H), 1.25 (s, 3H) ppm.

To a stirred solution of the above desired ketal (64.8 mg, 0.159 mmol) in CH_2Cl_2 (3 mL) at 0 ^{o}C was added 2,6-lutidine (0.185 mL) and TESOTf (0.18 mL). After 2 h at 0 ^{o}C, the reaction was quenched sat. aq. $NaHCO_3$, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexane / Et_2O = 100:0, 20:1 then 10:1) to give the corresponding bis-TES compound (128 mg, 91%) as a mixture of epimers. The undesired epimer (25.7 mg, 0.0632 mmol) was subjected to the same conditions to provide more desired protected ketal. See the PnTX A synthesis (McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647) for the details on this isomerization process.

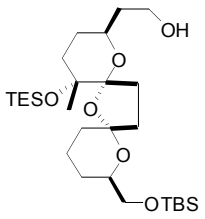
To a stirred solution of the above bis-TES spiroketal mixture (128 mg, 0.202 mmol) in THF (1 mL) at 0 ^{o}C was added TBAF (1 M in THF, 0.22 mL). After 10 min, the mixture was quenched with H_2O, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 10:1, 5:1 then 2:1) to give desired epimeric alcohol **xx** (96 mg, 92%) and undesired epimeric alcohol (4 mg, 4%). Desired epimer **xx**: ^{1}H

NMR (500 MHz, $CDCl_3$) 7.26-7.34 (m, 5H), 4.49 (ABq, *J* = 14.5 Hz, 2H), 4.07-4.13 (m, 1H), 3.93-3.98 (m, 1H), 3.63-3.68 (m, 1H), 3.52 (dt, *J* = 10.0, 5.5 Hz, 1H), 3.38 (t, *J* = 6.0 Hz, 2H), 2.44 (t, *J* = 6.5 Hz, 1H), 2.15-2.30 (m, 2H), 2.00-2.08 (m, 1H), 1.90 (ddt, *J* =17.0, 13.5, 3.5 Hz, 1H), 1.70-1.84 (m, 4H), 1.55-1.69 (m, 3H), 1.50 (dt, 1H, *J* = 13.5, 4.5 Hz, 1H), 1.37-1.47 (m, 2H), 1.30 (s, 3H), 1.22 (dq, *J* = 12.5, 4.0 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 9H), 0.57 (q, *J* = 8.0 Hz, 6H) ppm. Undesired epimer: ^{1}H NMR (500 MHz, $CDCl_3$): 7.26-7.35 (m, 5H), 4.46 (ABq, *J* = 11.5 Hz, 2H), 3.98-4.04 (m, 1H), 3.76-3.83 (m, 2H), 3.49-3.56 (m, 2H), 3.45 (dd, *J* = 9.5, 7.5 Hz, 1H), 2.94-2.98 (m, 1H), 2.30 (q, *J* = 8.0 Hz, 1H), 2.05-2.14 (m, 2H), 1.91-1.96 (m, 1H), 1.81-1.89 (m, 1H), 1.73-1.80 (m, 1H), 1.54-1.72 (m, 7H), 1.37-1.49 (m, 3H), 1.34 (s, 3H), 0.97 (t, *J* = 7.5 Hz, 9H), 0.64 (q, *J* = 8.0 Hz, 6H) ppm.

Experimental for Scheme VI.

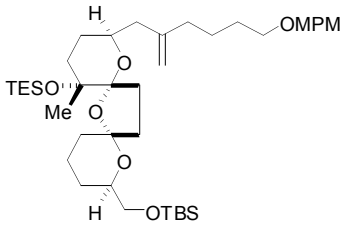


Scheme VI. Reagents. a. 1. TBSCl, imidazole, DMF, rt. 2. H_2, $Pd(OH)_2/C$, THF/MeOH. b. 1. Swern oxidaiton. 2. *t*BuLi, $I(CH_2)_4OMPM$, Et_2O, -78 °C. 3. Swern oxidation. 4. $Ph_3P{=}CH_2$, PhMe, 0 °C to rt. c. 1.HF·pyr, pyr, THF, 0 °C. 2. PPh_3, I_2, dimidazole, PhH/CH_2Cl_2, rt. 3. 1,3-dithiane, *t*BuLi, -78 °C to 0 °C, THF/HMPA. 4. DDQ, CH_2Cl_2/H_2O, 0 °C. 5. TMSCl, NEt_3, CH_2Cl_2. 0 °C.



xxi

Alcohol xxi. To a stirred solution of alcohol **xx** (91 mg, 0.175 mmol) in DMF (1 mL) was added imidazole (36 mg) and TBSCl (53 mg, 0.356 mmol) at rt. The mixture was stirred overnight, quenched with H_2O, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was dissolved in THF-MeOH (4:1, 3 mL) and stirred in the presence of $Pd(OH)_2/C$ (43mg) at rt under H_2 atmosphere for 2 h. The reaction mixture was filtered through a pad of celite and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 8:1) to give alcohol **xxi** (72 mg, 76% over 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) 4.20-4.26 (m, 1H), 3.97-4.02 (m, 1H), 3.75-3.81 (m, 1H), 3.74 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.63-3.68 (m, 1H), 3.46-3.51 (m, 1H), 3.21 (dd, *J* = 7.5, 3.5 Hz, 1H), 2.16-2.25 (m, 2H), 1.94-2.01 (m, 1H), 1.91 (ddt, *J* = 26.0, 13.0, 4.0 Hz, 1H), 1.75-1.84 (m, 4H), 1.44-1.69 (m, 7H), 1.31 (s, 3H), 1.19 (dq, *J* = 13.5, 4.0 Hz, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 9H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.07 (s, 6H) ppm.



xxii

MPM ether xxii. To a stirred solution of $(COCl)_2$ (2 M in CH_2Cl_2, 5.2 mL) in CH_2Cl_2 (50 mL) at -78 ^oC was added successively DMSO (1 mL) in CH_2Cl_2 (5mL), alcohol **xxi** (3.76 g, 6.9 mmol, in 10 mL of CH_2Cl_2), and Et_3N (3 mL). The mixture was stirred at -78 ^oC for 30 min, then 0 ^oC for 30 min. The reaction mixture was quenched with H_2O, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short SiO_2 pad (hexanes / EtOAc = 5:1) to

furnish the corresponding crude aldehyde (2.530 g, 94%), which was used in next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) 9.74 (s, 1H), 4.44-4.50 (m, 1H), 3.90-3.95 (m, 1H), 3.62 (dd, *J* =9.5, 4.5 Hz, 1H), 3.45 (dd, *J* =10.5, 7.0 Hz, 1H), 3.45 (dd, *J* = 10.5, 7.0 Hz, 1H), 2.40 (dd, *J* = 6.0, 2.0 Hz, 2H), 2.13-2.24 (m, 2H), 1.99-2.05 (m, 1H), 1.90 (ddt, *J* = 14.0, 9.0, 4.0 Hz, 1H), 1.74-1.83 (m, 4H), 1.60-1.68 (m, 3H), 1.49 (dq, *J* = 13.0, 4.0 Hz, 2H), 1.30 (s, 3H), 1.18-1.27 (m, 1H), 0.95 (t, *J* =8.0 Hz, 9H), 0.89 (s, 9H), 0.57 (q, *J* =8.0 Hz, 6H), 0.50 (s, 6H) ppm.

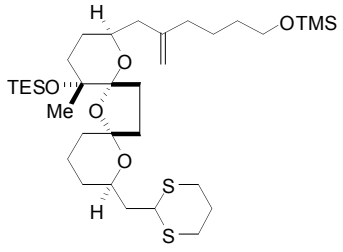
Note: Although 2 eq. of ^{t}BuLi should be needed to generate alkyl lithium theoretically, using 1 eq. of ^{t}BuLi showed better results in this case. To a stirred solution of alkyl iodide $ICH_2CH_2CH_2CH_2OMPM$ (2.9 g, 9.0 mmol) in Et_2O (25 mL) at -78 ^{o}C was added ^{t}BuLi (1.7 M in pentane, 5.1 mL). The mixture was stirred for 15 min (slightly cloudy) at -78 ^{o}C, then at rt for 3 min (clear solution). The mixture was cooled to -78 ^{o}C again (yellow solution) before a solution of the above crude aldehyde (2.23 g, 4.107 mmol, in 5 mL of Et_2O) via cannula. The reaction mixture was warmed to 0 ^{o}C over 30 min, quenched with H_2O, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short SiO_2 pad (hexanes / EtOAc = 20:1, 10:1, then 5:1) to give the corresponding alcohol as a mixture of inseparable diasteromers (3.034 g, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) 7.25 (d, *J* = 7.0 Hz, 2H), 6.87 (d, *J* = 6.5 Hz, 2H), 4.41 (s, 2H), 4.15-4.24 (m, 1H), 3.92-4.02 (m, 1H), 3.82 (s, 1.5H), 3.80 (s, 1.5H), 3.83-3.88 (m, 0.5H), 3.71-3.76 (m, 0.5H), 3.78 (dd, *J* = 10.0, 4.0 Hz, 0.5H), 3.70 (dd, *J* = 10.0, 4.0 Hz, 0.5H), 3.49 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.42-3.44 (m, 2H), 3.33 (d, *J* = 4.0 Hz, 1H), 2.13-2.24 (m, 2H), 1.86-2.03 (m, 2H), 1.75-1.85 (m, 4H), 1.44-1.68 (m, 11H), 1.36-1.42 (m, 2H), 1.30 (s, 3H), 1.17-1.26 (m, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.89 (s, 9H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.07, 0.05, 0.04 (each s, total 6H) ppm.

To a stirred solution of $(COCl)_2$ (2 M in CH_2Cl_2, 6 mL) in CH_2Cl_2 (25 mL) at -78 ^{o}C was added successively DMSO (1.26 mL), the above alcohol (3.00 g in 5 mL of CH_2Cl_2), and Et_3N (4.2 mL). The mixture was stirred at -78 ^{o}C for 30 min, then 0 ^{o}C for 30 min. The reaction mixture was quenched with H_2O, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short SiO_2 pad (hexanes / EtOAc = 5:1) to furnish the corresponding crude ketone (2.876g): ^{1}H NMR (500 MHz, $CDCl_3$) 7.24 (d, *J* = 10.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz,

2H), 4.41 (s, 2H), 4.26-4.32 (m, 1H), 3.88-3.93 (m, 1H), 3.80 (s, 3H), 3.66 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.44 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.42 (t, *J* = 6.0 Hz, 1H), 2.44-2.55 (m, 3H), 2.39 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.12-2.20 (m, 2H), 1.98 (dt, *J* = 12.5, 7.5 Hz, 1H), 1.89 (ddt, *J* = 21.5, 14.0, 4.0 Hz, 1H), 1.70-1.81 (m, 4H), 1.56-1.66 (m, 7H), 1.36-1.47 (m, 2H), 1.27 (s, 3H), 1.19-1.30 (m, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.89 (s, 9H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.05 (s, 3H), 0.04 (s, 3H) ppm.

To a stirred suspension of methyl triphenylphosphonium bromide salt (24 g, dried under high vacuum at 115 ^{o}C under P_2O_5 overnight) in toluene (freshly distilled over LAH, 150 mL) at 0 ^{o}C was added ^{n}BuLi (2.49 M in hexane, 21 mL). The mixture was stirred at rt for 1 h (orange suspension). After stirring was stopped, the mixture was allowed to stand for 1 h. Use the supernatant as a solution of salt free ylide (0.4 M).

To a stirred solution of the above salt free ylide (40 mL) at 0 ^{o}C was added a solution of the above ketone (2.876 g, 3.9 mmol) in toluene (freshly distilled over LAH, 7mL) via cannula. The mixture was stirred at rt for 1h, filtered through the pad of SiO_2 (hexanes / Et_2O = 1:1) and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 20:1, 15:1, 9:1, 6:1, 3:1 then 1:1) to give olefin **xxii** (2.184 g, 76%) and recovered ketone (325 mg, 11%). The recovered ketone could be recycled in the same manner to provide additional olefine **xxii**: ^{1}H NMR (600 MHz, $CDCl_3$) 7.25 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.86 (s, 1H), 4.75 (s, 1H), 4.42 (s, 2H), 4.02-4.08 (m, 1H), 3.90-3.95 (m, 1H), 3.80 (s, 3H), 3.66 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.42-3.45 (m, 3H), 2.12-2.22 (m, 3H), 1.99-2.08 (m, 4H), 1.89 (ddt, *J* = 22.5, 11.0, 3.0 Hz, 1H), 1.72-1.82 (m, 4H), 1.62-1.67 (m, 1H), 1.53-1.61 (m, 4H), 1.42-1.52 (m, 3H), 1.37 (dq, *J* = 15.5, 3.5 Hz, 1H), 1.28 (s, 3H), 1.18-1.30 (m, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 9H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H) ppm.



1

TMS ether 1. To a stirred solution of TBS ether **xxii** (2.177 g, 2.969 mmol) in THF (20 mL) at 0 °C was added a solution of HF·py/py/THF (2:8:20, v/v/v, 16.5 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (slow addition), extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 5:1 then 2:1) to give the corresponding alcohol (1.822 g): ^{1}H NMR (500 MHz, $CDCl_3$) 7.26 (d, *J* = 7.0 Hz, 2H), 6.87 (d, *J* = 7.0 Hz, 2H), 4.84 (s, 1H), 4.75 (s, 1H), 4.42 (s, 2H), 4.02-4.07 (m, 1H), 3.97-4.01 (m, 1H), 3.80 (s, 3H), 3.53 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.45 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.44 (t, *J* = 5.0 Hz, 2H), 2.28 (dd, *J* = 17.5, 7.5 Hz, 1H), 2.15-2.23 (m, 1H), 2.07-2.12 (m, 1H), 1.98-2.05 (m, 3H), 1.91 (ddt, *J* = 33.0, 16.5, 5.0 Hz, 1H), 1.74-1.84 (m, 3H), 1.64-1.69 (m, 1H), 1.55-1.62 (m, 4H), 1.46-1.54 (m, 5H), 1.25-1.40 (m, 2H), 1.29 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.56 (q, *J* = 8.0 Hz, 6H) ppm.

To a stirred solution of the above alcohol (1.847 g, 2.985 mmol) in PhH/CH_2Cl_2 (1:1, 50 mL) were added imidazole (3.043 g, 44.760 mmol), PPh_3 (4.735 g, 18.053 mmol) and I_2 (4.544 g, 17.906 mmol) at rt. The mixture was wrapped with alumina foil and stirred overnight. The mixture was quenched by sat. aq. $NaHCO_3$, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 40:1, 10:1 then 2:1) to give the corresponding iodide (1.827g, 84 %) and recovered starting material (261 mg, 14%): ^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (d, *J* = 10.0 Hz, 2H), 6.87 (d, *J* = 10.5 Hz, 2H), 4.82 (s, 3H), 4.76 (s, 3H), 4.43 (s, 2H), 3.96-4.03 (m, 1H), 3.80 (s, 3H), 3.76-3.84 (m, 1H), 3.45 (t, *J* = 8.5 Hz, 2H), 3.16 (dd, *J* = 13.0, 7.0 Hz, 1H), 3.11 (dd, *J* = 13.0, 8.5 Hz, 1H), 2.30 (dd, *J* = 17.5, 7.0Hz, 1H), 2.14-2.23 (m, 1H), 2.00-2.11 (m, 4H), 1.77-1.96 (m, 4H), 1.40-1.74 (m, 10H), 1.28-1.38 (m, 1H), 1.29 (s, 3H), 1.15-1.26 (m, 1H), 0.94 (t, *J* = 10.0 Hz, 9H), 0.56 (q, *J* = 10.0 Hz, 6H) ppm.

To a stirred solution of 1,3-dithiane (1.65g, 13.734 mmol) in THF (freshly distilled over LAH, 25ml) and HMPA (distilled over Na and stored in the presence of activated 4 Å molecular sieves, 2.5 mL) at -40-30 °C was added ^{t}BuLi (1.7 *M* in pentane, 7.3 mL). The mixture was stirred for 30 min (yellow solution) before cooled to -78 °C. A pre-cooled (-78 °C) solution of the above iodide (1.82 g, 2.497 mmol) in THF (7 mL) was added via cannula. The mixture was gradually warmed to 0 °C over 2 h, quenched

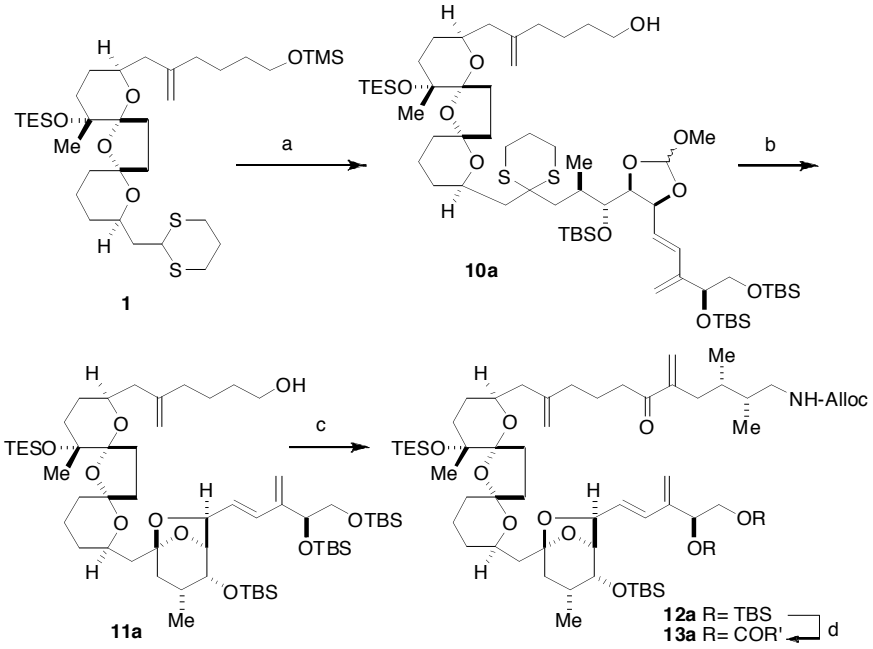
by sat. aq. NH_4Cl, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / Et_2O = 100:0, 50:1, 20:1, 15:1, 9:1, 6:1, 4:1) to give the corresponding dithiane (1.748g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.93 (s, 1H), 4.81 (s, 1H), 4.43 (s, 2H), 4.12-4.20 (m, 3H), 3.80 (s, 3H), 3.45 (t, *J* = 7.0 Hz, 2H), 2.70-2.87 (m, 4H), 2.28 (dd, *J* = 6.5, 15.0 Hz, 1H), 2.13-2.21 (m, 2H), 2.00-2.08 (m, 5H), 1.85-1.95 (m, 2H), 1.73-1.84 (m, 5H), 1.48-1.66 (m, 7H), 1.31-1.44 (m, 2H), 1.28 (s, 3H), 1.16-1.26 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 9H), 0.56 (q, *J* = 7.5 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 159.0, 146.3, 130.7, 129.1, 113.6, 111.0, 110.2, 107.8, 73.4, 72.4, 70.0, 68.85, 68.82, 55.2, 42.9, 42.6, 42.2, 37.4, 36.9, 34.3, 34.0, 31.0, 30.7, 30.1, 29.7, 29.6, 29.5, 25.9, 24.22, 24.15, 19.4, 7.08, 6.70 ppm; IR (film) 2936, 1612, 1513, 1247, 1038, 743 cm^{-1}; HRMS (ES) calcd for $C_{39}H_{64}O_6S_2Si$ $[M+H]^+$ 721.3992, found 721.3988.

To a mixture of the above MPM ether (243 mg, 0.337 mmol) and H_2O (0.5 mL) in CH_2Cl_2 (2.0 mL) at 0 °C was added a solution of DDQ (80.0 mg, 0.354 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred vigorously at rt for 1 h, quenched with sat. aq. $NaHCO_3$ and sat. aq. Na_2SO_3, extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 10:1, then 1:2) to give the corresponding alcohol (188 mg, 93%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) 4.92 (s, 1H), 4.82 (s, 1H), 4.18-4.12 (m, 3H), 3.66 (t, *J* = 6.0 Hz, 2H), 2.74-2.88 (m, 4H), 2.27 (dd, *J* = 15.0, 3.0 Hz, 1H), 2.13-2.20 (m, 2H), 2.04-2.10 (m, 5H), 1.73-1.96 (m, 6H), 1.50-1.68 (m, 8H), 1.34-1.44 (m, 2H), 1.28 (s, 3H), 1.17-1.26 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 9H), 0.56 (q, *J* = 8.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 146.4, 111.2, 110.2, 107.9, 73.4, 69.0, 68.8, 62.8, 43.0, 42.5, 42.3, 37.4, 36.6, 34.3, 34.1, 32.5, 30.8, 30.7, 30.0, 29.8, 29.7, 25.9, 24.3, 23.7, 19.4, 7.1, 6.7 ppm; IR (film) 3427, 2934, 1728, 1643 1139, 1039, 743 cm^{-1}; HRMS (ES) calcd for $C_{31}H_{56}O_5S_2Si$ $[M+H]^+$ 601.3417, found 601.3417.

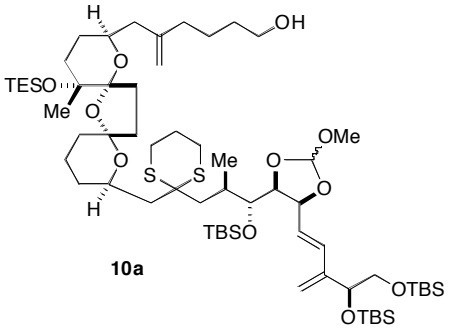
To a solution of the above alcohol (188 mg, 0.313 mmol) and pyridine (2.0 g, 25.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TMSCl (108 mg, 1.26 mmol). After 6 h of stirring at rt, the reaction mixture was added dropwise into a vigorously stirred ice-cooled mixture of EtOAc and saturated aq. $NaHCO_3$. The separated organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated.

The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 1:1, then 1:2) to obtain TMS ether **1** (210 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) 4.93 (s, 1H), 4.82 (s, 1H), 4.19 (dd, *J* = 8.5, 6.0 Hz, 1H), 4.18-4.14 (m, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.85 (dddd, *J* = 14, 14, 11, 2.0 Hz, 2H), 2.76 (dddd, *J* = 15, 14, 4.5, 4.5 Hz, 2H), 2.28 (dd, *J* = 15, 6.5 Hz, 1H), 2.19 (dd, *J* = 8, 8 Hz, 1H), 2.16 (dd, *J* =9, 9 Hz, 1H), 2.09-2.01 (m, 4H), 1.86-1.74 (m, 4H), 1.65-1.45 (m, 11H), 1.42 (dd, *J* = 13, 3.5 Hz, 1H), 1.37 (dd, *J* = 15, 4.0 Hz, 1H), 1.29 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.57 (q, *J* = 8.0 Hz, 6H), 0.11 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 146.5, 111.0, 110.3, 107.8, 73.5, 68.9, 68.8, 62.6, 43.0, 42.7, 42.3, 37.5, 36.9, 34.4, 34.1, 32.5, 31.0, 30.8, 30.2, 29.8, 29.6, 25.9, 24.3, 23.8, 19.5, 7.13, 6.75, -0.45 ppm; IR (film) 3071, 2951, 1643, 1458, 1249, 841, 744 cm^{-1}; HRMS (ES) calcd for $C_{34}H_{64}O_5S_2Si_2$ $[M+H]^+$ 673.3812, found 673.3835; $[\alpha]_D^{20}$ +5.90 (*c* 1.09, $CHCl_3$).

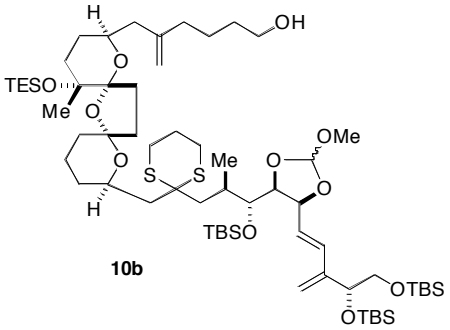
Experimental for Scheme 3.



Scheme 3. Reagents. (a). 3a, *t*BuLi, HMPA/THF. 2. K_2CO_3, MeOH, 73% over 2 steps. (b). 1. PPTS. 2. K_2CO_3, MeOH, 73% over 2 steps. 3. PIFA, 74%. (c). 1. SO_3•pyr, DMSO, 83%. 2. Ni/Cr-coupling with C_1-C_5 vinyl iodide 2, 84%. 3. Dess-Martin oxidation, 79%. (d). 1. HF•pyr, pyr. 2. R'COCl, NEt_3, DMAP, CH_2Cl_2.

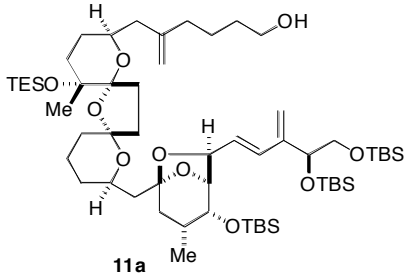


Dithiane 10a. To a solution of dithiane **1** (113 mg, 0.168 mmol) in THF/HMPA (2.5 mL, 9:1, v/v) at -78 °C was added ^{t}BuLi (1.7 *M* in pentane, 0.12 mL, 0.210 mmol) and the orange solution was stirred at -78 °C for 20 min. A pre-cooled (-78 °C) solution of alkyl iodide **3a** (72 mg, 0.0951 mmol) in THF (1.0 mL) was added via cannula and the mixture was stirred at -78 °C for an additional 30 min. The reaction was quenched with phosphate buffer (1.0 *M*, pH = 7, 2.0 mL) and the whole mixture was diluted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in MeOH / CH_2Cl_2 (10 mL, 1:1, v/v) and K_2CO_3 (5 mg) was added, the mixture was stirred at rt for 2 h, and the whole mixture was evaporated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 9:1, 5:1 then 3:1) to afford dialkylated dithiane **10a** (85 mg, 73 %) as a mixture of diasteromers (*ca.* 5:1). Major isomer: ^{1}H NMR (500 MHz, C_6D_6) 6.54 (d, *J* = 15.5 Hz, 1H), 6.11 (dd, *J* = 15.5, 5.0 Hz, 1H), 5.91 (s, 1H), 5.34 (s, 1H), 5.30 (s, 1H), 5.03 (s, 1H), 5.00 (m, 1H), 4.96 (s, 1H), 4.70 (d, *J* = 7.0 Hz, 1H), 4.45-4.32 (m, 3H), 4.20 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.85 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.64 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.51-3.42 (m, 3H), 3.20 (m, 3H), 2.76-1.74 (m, 19H), 1.63-1.26 (m, 20H), 1.17-0.97 (m, 36H), 0.61 (q, *J* = 8.0 Hz, 6H), 0.44 (s, 3H), 0.38 (s, 3H), 0.27 (s, 3H), 0.24 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H) ppm; IR (film) 3461, 2953, 2278, 1465, 1375, 1252, 1134, 1079, 1041, 977, 837, 778 cm^{-1}; LRMS (ES) calcd for $C_{68}H_{120}O_{11}S_2Si_4$ $[M+Na]^+$ 1251.7; found 1251.7; $[\alpha]_D^{20}$ -5.04 (*c* 1.07, $CHCl_3$).



10b

Dithiane **10b** was prepared according to the above procedure from alkyl iodide **3b**. Major isomer: ^{1}H NMR (500 MHz, C_6D_6) 6.23 (d, J = 12.8 Hz, 1H), 5.76 (dd, J = 12.8, 6.4 Hz, 1H), 5.75 (s, 1H), 5.33 (s, 1H), 5.18 (s, 1H), 4.82 (s, 1H), 4.78 (s, 1H), 4.72 (dd, J = 5.6, 4.4 Hz, 1H), 4.38-4.42 (m, 1H), 4.20-4.26 (m, 3H), 3.94 (dd, J = 7.2, 2.0 Hz, 1H), 3.62-3.67 (m, 3H), 3.40 (dd, J = 7.8, 5.6 Hz, 1H), 3.32 (s, 3H), 2.64-2.91 (m, 4H), 2.33-2.45 (m, 2H), 1.87-2.30 (m, 11H), 1.68-1.85 (m, 4 H), 1.48-1.64 (m, 8H), 1.28 (s, 3H), 1.24-1.40 (m, 4H), 1.11 (d, J = 5.2 Hz, 3H), 0.94 (t, J = 8.5 Hz, 9H), 0.89 (s, 18H), 0.86 (s, 9H), 0.57 (q, J = 6.0 Hz, 6H), 0.16 (s, 3H), 0.14 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H) ppm; $[\alpha]_D^{20}$ -5.04 (*c* 1.07, $CHCl_3$).

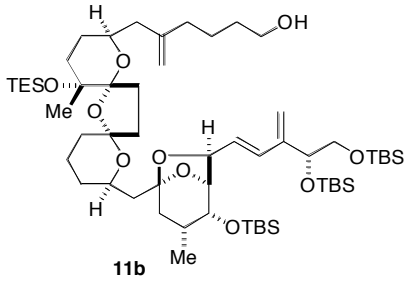


11a

Bicycloketal 11a. To a stirred solution of orthoester **10a** (621 mg, 0.506 mmol) in wet CH_2Cl_2 (prepared by mixing CH_2Cl_2 and H_2O in a separatory funnel, then use CH_2Cl_2 phase, 62 mL) was added PPTS (62 mg) and stirred at rt for 5h. The mixture was poured into Et_2O, sat. aq. $NaHCO_3$, stirred for 30 min, and extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (20 ml) and MeOH (20 ml), K_2CO_3 (7.5 mg) was added. The mixture was stirred at rt for 30 min, treated with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / PhH / EtOAc = 4:1:2) to give the corresponding diol (435 mg, 73 %): ^{1}H NMR (500 MHz,

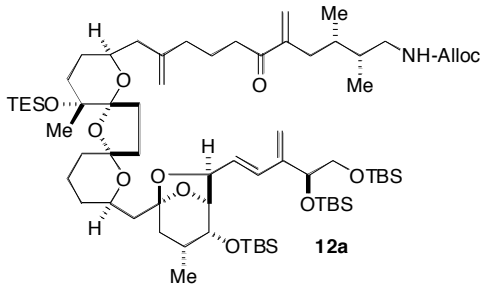
$CDCl_3$) 6.33 (d, *J* = 16.5 Hz, 1H), 5.95 (dd, *J* = 17.0, 7.0 Hz, 1H), 5.29 (s, 1H), 5.19 (s, 1H), 4.81 (s, 1H), 4.78 (s, 1H), 4.43 (dd, *J* = 6.5, 3.0 Hz, 1H), 4.40-4.50 (m, 3H), 3.77 (dd, *J* = 7.5, 3.0 Hz, 1H), 3.59-3.66 (m, 4H), 3.44 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.22 (broad d, *J* = 4.0 Hz, 1H), 2.70-2.90 (m, 5H), 2.42 (dd, *J* = 15.5, 3.0 Hz, 1H), 2.33 (dd, *J* = 15.0, 5.0 Hz, 1H), 2.15-2.21 (m, 4H), 2.00-2.09 (m, 4H), 1.71-1.98 (m, 8H), 1.46-1.62 (m, 8H), 1.28 (s, 3H), 1.26-1.39 (m, 4H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.91 (s, 9H), 0.892 (s, 9H), 0.887 (s, 9H), 0.57 (q, *J* = 8.0 Hz, 6H), 0.18 (s, 3H), 0.15 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, C_6D_6) 146.8, 146.3, 131.7, 115.5, 111.5, 110.6, 108.1, 79.1, 75.1, 75.0, 74.0, 73.5, 70.1, 69.0, 68.9, 62.4, 54.0, 46.8, 42.7, 42.6, 37.8, 36.9, 34.8, 34.6, 34.3, 33.0, 32.5, 31.5, 29.9, 29.5, 26.5, 26.3, 26.1 (x3), 26.0 (x3), 25.9 (x3), 25.1, 24.3, 24.1, 20.0, 18.4, 18.3, 18.2, 18.1, 7.2, 6.9 (x2), -3.6, -4.3, -4.6, -4.8, -5.2, -5.3 ppm; LRMS (ESI) calcd for $C_{61}H_{118}O_{10}S_2Si_4$ $[M+NH_4]^+$ 1204; found 1205; $[\alpha]_D^{20}$ +9.30 (*c* 0.28, PhH).

To a stirred solution of the above diol (148 mg, 0.125 mmol) in CH_2Cl_2 (1.0 mL) and CH_3CN / H_2O (9:1, v/v, 1.3 mL) at 0 °C was added $SrCO_3$ (170 mg, 1.152 mmol) and PIFA (123 mg, 0.287 mmol) successively. The mixture was stirred at 0 °C for 30 min, charged directly to a SiO_2 column (hexanes / EtOAc = 20:1, 10:1, 5:1) to give ketal **11a** (100 mg, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) 6.32 (d, *J* = 16.0 Hz, 1H), 5.88 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.29 (s, 1H), 5.17 (s, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 4.51 (t, *J* = 5.5 Hz, 1H), 4.38 (dd. *J* = 7.0, 3.5 Hz, 1H), 4.06-4.16 (m, 3H), 3.62 (broad d, *J* = 4.5 Hz, 2H), 3.56 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.46 (dt, *J* = 7.5, 3.0 Hz, 2H), 2.26 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.13-2.19 (m, 2H), 1.98-2.10 (m, 9H), 1.65-1.94 (m, 8H), 1.32-1.60 (m, 4H), 1.29 (s, 3H), 1.20-1.30 (m, 2H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.91 (s, 9H), 0.889 (s, 9H), 0.885 (s, 9H), 0.85 (d, *J* = 6.0 Hz, 3H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.07 (s, 3H), 0.05 (s, 3H), 0.042 (s, 3H), 0.039 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, C_6D_6) 147.0, 145.7, 132.7, 124.0, 116.9, 111.6, 110.6, 109.0, 108.0, 81.8, 79.5, 75.1, 73.7, 69.3, 68.9, 68.6, 62.3, 45.0, 42.6, 39.6, 38.0, 36.6, 34.8, 34.4, 32.9, 32.3, 31.0, 29.9, 29.0, 25.9 (x3), 25.0 (x3), 25.8 (x3), 24.5, 24.2, 20.2, 18.3, 18.3, 18.3, 17.0, 7.2, 7.0 (x2), -4.5, -4.8 (x2), -4.9, -5.3, -5.4 ppm; HRMS (ESI) calcd for $C_{58}H_{110}O_{10}Si_4$ $[M+H]^+$ 1079.7254 found 1079.7247; $[\alpha]_D^{20}$ +50.0 (*c* 0.16, PhH).



11b

Ketal **11b** was prepared according to the above procedure from orthoester **10b**: ^{1}H NMR (500 MHz, $CDCl_3$) 6.31 (d, *J* = 16.0 Hz, 1H), 5.93 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.26 (s, 1H), 5.17 (s, 1H), 4.81 (s, 1H), 4.79 (s, 1H), 4.51 (t, *J* = 5.5 Hz, 1H), 4.38 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.15 (dd, *J* = 5.0, 2.0 Hz, 1H), 4.06-4.13 (m, 2H), 3.62 (t, *J* = 5.5 Hz, 2H), 3.55 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.45-3.48 (m, 2H), 2.25 (dd, *J* = 6.5, 14.0 Hz, 1H), 1.98-2.20 (m, 11H), 1.86-1.93 (m, 1H), 1.72-1.85 (m, 7H), 1.68 (dd, *J* = 13.0, 5.0 Hz, 1H), 1.32-1.60 (m, 4H), 1.29 (s, 3H), 1.20-1.30 (m, 2H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.91 (s, 9H), 0.89 (s, 18H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.56 (q, *J* = 8.0 Hz, 6H),0.06 (s, 3H), 0.04 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 146.8, 145.8, 133.1, 123.7, 116.8, 111.6, 110.5, 108.7, 108.1, 81.9, 79.4, 77.4, 75.0, 73.7, 69.4, 68.7, 68.7, 63.0, 44.7, 42.4, 39.1, 37.9, 36.6, 34.7, 32.8, 32.0, 31.0, 29.9, 29.2, 26.2 (x3), 26.1 (x6), 24.7, 24.0, 20.0, 18.7, 18.53, 18.49, 17.2, 7.4, 7.0 (x2), -4.2, -4.50, -4.54, -4.6, -4.9, -5.1 ppm; HRMS (ESI) calcd for $C_{58}H_{110}O_{10}Si_4$ $[M+H]^+$ 1079.7254 found 1079.7234; $[\alpha]_D^{20}$ +4.4 (*c* 0.47, $CHCl_3$).



12a

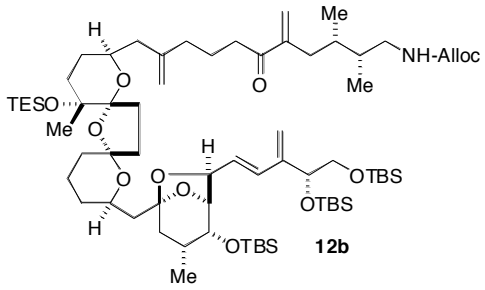
Bis-TBS ether 12a. To a stirred solution of alcohol **11a** (123 mg, 0.114 mmol) and Et_3N (0.41 mL) in CH_2Cl_2 (2.2 mL) at 0 °C was added a solution of SO_3·Pyr (236 mg, 1.481 mmol) in DMSO (0.5 mL) via cannula. The mixture was stirred at rt for 30 min, directly charged to a SiO_2 column (hexanes / EtOAc = 20:1 then 10:1) to give the corresponding aldehyde (102 mg, 83 %): ^{1}H NMR (500 MHz, $CDCl_3$) 9.75 (s, 1H), 6.32

(d, *J* = 16.5 Hz, 1H), 5.87 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.29 (s, 1H), 5.17 (s, 1H), 4.87 (s, 1H), 4.78 (s, 1H), 4.49 (t, *J* = 5.5 Hz, 1H), 4.38 (dd. *J* = 7.5, 4.0 Hz, 1H), 4.06-4.16 (m, 3H), 3.56 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.45-3.52 (m, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 1.96-2.24 (m, 12H), 1.72-1.91 (m, 7H), 1.67 (dd, *J* = 13.0, 5.5 Hz, 1H), 1.35-1.62 (m, 3H), 1.18-1.31 (m, 2H), 1.28 (s, 3H), 0.94 (t, *J* = 8.5 Hz, 9H), 0.91 (s, 9H), 0.88 (s, 18H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.56 (q, *J* = 7.5 Hz, 6H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; $[\alpha]_D^{20}$ +31.9 (*c* 0.185, PhH).

To a stirred solution of the above aldehyde (88 mg, 0.082 mmol) and vinyl iodide **2** (172 mg, 0.49 mmol) in DMF (1.1 mL) was added 0.5% $NiCl_2/CrCl_2$ (113 mg, 0.921 mmol) and stirred at rt for 4 h in a glove box. The reaction was taken out of the box and the mixture was poured into a serine solution (5% in sat. aq. $NaHCO_3$) and stirred at rt overnight. The mixture was extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 10:1, 7:1, 5:1, 3:1 then 2:1) to give the corresponding adduct (88 mg, 84 %) as a mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) 6.32 (d, *J* = 16.5 Hz, 1H), 5.84-5.96 (m, 2H), 5.30 (d, *J* = 15.5 Hz, 1H), 5.29 (s, 1H), 5.20 (d, *J* = 10.0 Hz, 1H), 5.17 (s, 1H), 5.07 (s, 1H), 4.81 (s, 2H), 4.77 (s, 1H), 4.59 (broad, 1H), 4.55 (d, *J* = 5.0 Hz, 2H), 4.50 (t, *J* = 5.0 Hz, 1H), 4.28-4.41 (m, 1H), 4.00-4.16 (m, 4H), 3.56 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.45-3.51 (m, 2H), 3.00-3.16 (m, 2H), 2.21-2.28 (m, 1H), 1.95-2.20 (m, 7H), 1.66-1.93 (m, 8H), 1.36-1.62 (m, 5H), 1.28 (s, 3H), 1.16-1.32 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 7.5 Hz, 3H), 0.56 (q, *J* = 8.5 Hz, 6H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H) ppm.

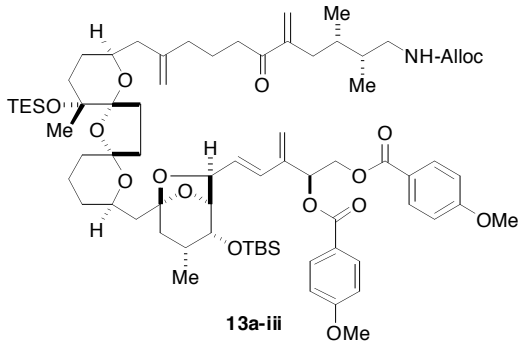
To a stirred solution of the above adduct (102 mg, 0.079 mmol) and pyridine (0.4 mL) in CH_2Cl_2 (4 mL) was added Dess-Martin reagent (84 mg, 0.198 mmol). After 20 min of stirring at rt, the mixture was charged directly to a SiO_2 column (hexanes / EtOAc = 10:1, 8:1, the 6:1) to give ketone **12a** (80 mg, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) 6.32 (d, *J* = 16.5 Hz, 1H), 6.01 (s, 1H), 5.88-5.91 (m, 1H), 5.87 (dd, *J* = 16.0, 7.5 Hz, 1H), 5.69 (s, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 5.28 (s, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 5.16 (s, 1H), 4.94 (broad, 1H), 4.85 (s, 1H), 4.78 (s, 1H), 4.57 (broad, 1H), 4.55 (d, *J* = 4.5 Hz, 1H), 4.49 (t, *J* = 5.0 Hz, 1H), 4.38 (dd, *J* = 7.5, 4.0 Hz, 1H), 4.12-4.18 (m, 2H), 4.05-4.12 (m, 1H), 3.56 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.44-3.50 (m, 2H), 3.14-3.22 (m, 1H), 3.06-3.13

(m, 1H), 2.59-2.70 (m, 2H), 2.41 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.21 (dd, *J* = 14.5, 7.0 Hz, 1H), 2.10-2.18 (m, 2H), 1.94-2.09 (m, 7H), 1.79-1.92 (m, 3H), 1.70-1.78 (m, 4H), 1.66 (dd, *J* = 13.0, 5.5 Hz, 1H), 1.53-1.62 (m, 3H), 1.36-1.52 (m, 3H), 1.27 (s, 3H), 1.19-1.32 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.85 (d, *J* = 6.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.56 (q, *J* = 7.5 Hz, 6H), 0.07 (s, 3H), 0.04 (s, 3H), 0.038 (s, 3H), 0.034 (s, 3H), 0.023 (s, 3H), 0.015 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 202.1, 156.4, 147.5, 145.9, 145.4, 133.1, 132.7, 125.3, 123.2, 117.4, 117.0, 111.7, 110.2, 108.4, 107.9, 81.6, 79.1, 74.8, 73.3, 69.2, 68.8, 68.3, 65.8, 65.3, 45.1, 44.4, 41.9, 38.9, 37.4, 37.2, 36.5, 36.3, 34.5, 34.2, 33.4, 31.9, 29.7, 28.8, 26.0, 25.8, 25.7, 24.3, 22.3, 19.7, 18.4, 18.3, 18.2, 16.9, 15.2, 14.2, 12.7, 7.10, 6.75, -4.46, -4.74, -4.81, -4.90, -5.19, -5.39 ppm; IR (film) 2954, 1728, 1679, 1462, 1250, 1136, 1012, 835, 776 cm^{-1}; LRMS (ES) calcd for $C_{76}H_{127}NO_{12}Si_4$ $[M+Na]^+$ 1308.9, found 1308.9; $[\alpha]_D^{20}$ +22.8 (*c* 0.70, $CHCl_3$).



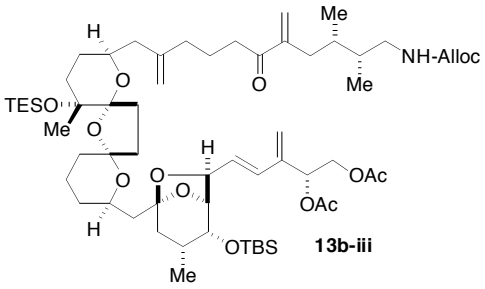
Enone **12b** was prepared according to the above procedure from **11b**: ^{1}H NMR (600 MHz, $CDCl_3$) 6.32 (d, *J* = 16.2 Hz, 1H), 6.02 (s, 1H), 5.92 (dd, *J* = 17.4, 6.6 Hz, 1H), 5.88-5.96 (m, 1H), 5.70 (s, 1H), 5.30 (dd, *J* = 17.4, 1.8 Hz, 1H), 5.26 (s, 1H), 5.20 (d, *J* = 10.2 Hz, 1H), 5.17 (s, 1H), 4.93-4.98 (m, 1H), 4.85 (s, 1H), 4.77 (s, 1H), 4.59 (broad, 1H), 4.55 (d, *J* = 4.2 Hz, 1H), 4.94 (t, *J* = 5.4 Hz, 1H), 4.38 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.11-4.17 (m, 2H), 4.05-4.10 (m, 1H), 3.55 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.48 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.44-3.47 (m, 1H), 3.14-3.21 (m, 1H), 3.07-3.12 (m, 1H), 2.65 (dd, *J* = 15.0, 7.2 Hz, 2H), 2.42 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.10-2.22 (m, 3H), 1.93-2.09 (m, 7H), 1.79-1.92 (m, 3H), 1.71-1.78 (m, 4H), 1.62-1.66 (m, 1H), 1.53-1.60 (m, 3H), 1.36-1.52 (m, 3H), 1.19-1.28 (m, 2H), 1.27 (s, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.90 (s, 9H), 0.88 (s, 18H), 0.85 (d, *J* = 6.6 Hz, 6H), 0.74 (d, *J* = 6.0 Hz, 3H), 0.56 (q, *J* = 7.8 Hz, 6H), 0.06 (s, 3H), 0.04 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 202.2, 156.4, 147.5, 146.0, 145.5, 133.1, 132.7, 125.3, 123.5, 117.4, 116.6, 111.7, 110.2, 108.3,

107.9, 81.5, 79.0, 74.9, 73.3, 69.3, 68.8, 68.4, 68.3, 65.3, 45.1, 44.4, 41.9, 38.9, 37.6, 37.4, 37.3, 36.5, 36.3, 34.5, 34.2, 33.4, 31.8, 30.7, 29.7, 28.9, 26.0, 25.8, 25.7, 24.3, 22.3, 19.7, 18.4, 18.3, 18.2, 16.9, 14.3, 12.7, 7.1, 6.7, -4.5, -4.8, -4.8, -4.9, -5.2, -5.4 ppm; IR (film) 2955, 1717, 1458, 1250, 1137, 1042, 836 cm^{-1}; LRMS (ES) calcd for $C_{76}H_{127}NO_{12}Si_4$ $[M+NH_4]^+$ 1303.9, found 1304.2; $[\alpha]_D^{20}$ +1.47 (*c* 0.75, $CHCl_3$).



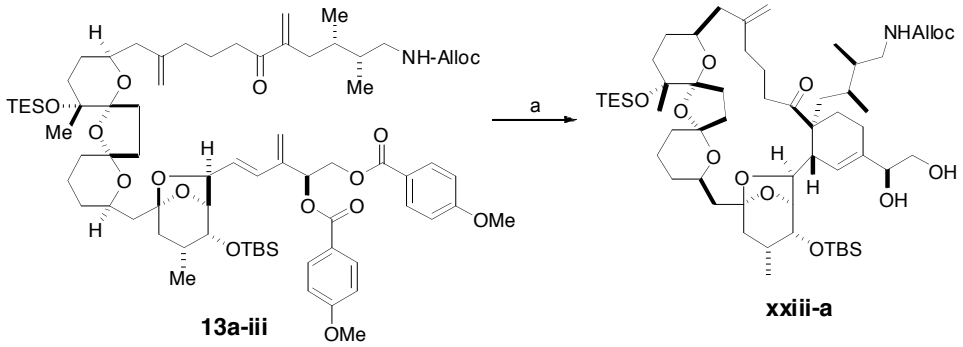
Diester 13a-iii. To a plastic tube containing enone **12a** (123 mg, 95.6 μmol) was added a mixture of HF·py / py / CH_3CN / Et_2O (1:5:10:1, v/v/v/v, 12 mL) at rt. The mixture was stirred for 6 h before quenched by slow addition of sat. aq. $NaHCO_3$, extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes /EtOAc = 5:1, 3:1 then 1:1) to give the corresponding diol and recovered starting material, which was re-submitted to the same reaction conditions three times to give additional diol (75 mg, 73%).

To a flask containing the above diol (246 mg, 0.232 mmol) was added py / *p*-methoxybenzoyl chloride (10 mL, 10:1, v/v) at 0 °C. The reaction mixture was allowed to warm to rt overnight. The volatile was removed by high vacuum, and the residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 5:1, then 3:1) to give diester **13a-iii** (237 mg, 89%).



Diacetate **13b-iii** was prepared according to the above procedure from **12b**.

Experimental for Scheme VII.



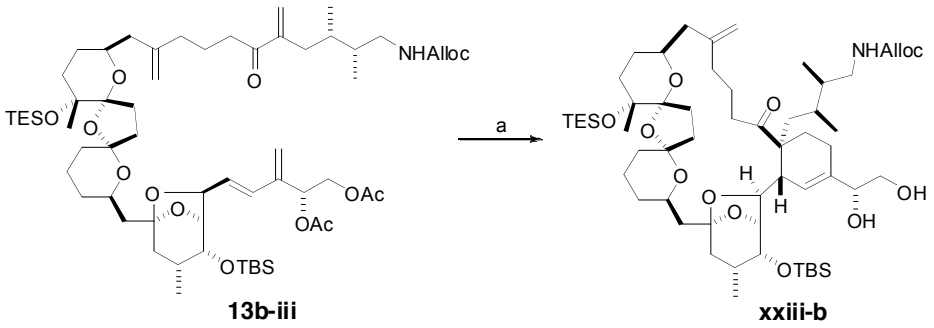
Scheme VII. Reagents. a. 1. sumilizer, dodecane, 160 °C. 2. K_2CO_3, MeOH, rt.

Diol xxiii-a. A mixture of Diels-Alder precursor **13a-iii** (40.0 mg, 35.1 μmol), 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide (Sumilizer, 8.0 mg), and dodecane (40 mL) was placed in a Schlenk tube (soaked in 40% KOH in 2-propanol over 24 h, washed and dried before use) and degassed by freeze-thaw methods for three times. The mixture was stirred for 12 h at 157 °C. After cooling to rt, the combined reaction mixture were filtered through a pad of basic alumina to remove dodecane (hexanes then EtOAc) to afford crude Diels-Alder cycloadducts as a mixture of diastereomers, which was purified by SiO_2 column chromatography (hexanes / EtOAc = 8:1, 7:1, 6:1 then 5:1) to give desired exo adduct **14a-iii** (20.4 mg, 51%) and other undesired stereoisomers (14.8 mg, 37%).

To a solution of Diels-Alder adduct (20 mg, 17.5 μmol) in CH_2Cl_2 / MeOH (4 mL, 1:1, v/v) was added excess K_2CO_3 at rt. After stirring at rt overnight, the reaction mixture was diluted with Et_2O, filtered through a short pad of SiO_2 to give the crude

product, which was purified again by SiO_2 column chromatography (hexanes /EtOAc = 2:1 then 1:1) to give the corresponding diol **xxiii-a** (18.6 mg, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) 5.86-5.95 (m, 1H), 5.31 (d, J = 8.0 Hz, 1H), 5.29 (s, 1H), 5.22 (d, J = 10.5 Hz, 1H), 4.85 (broad, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 4.54 (d, J = 4.5 Hz, 2H), 4.10-4.17 (m, 2H), 4.03-4.09 (m, 1H), 33.96-4.02 (m, 1H), 3.81 (dd, J = 11.5, 4.5 Hz, 1H), 3.67-3.71 (m, 1H), 3.60-3.62 (m, 1H), 3.53-3.59 (m, 1H), 2.96-3.11 (m, 2H), 2.85 (broad d, J = 11.0 Hz, 1H), 2.50-2.62 (m, 2H), 2.42 (broad, 1H), 1.19-2.32 (m, 39H), 0.94 (d, J = 8.0 Hz, 9H), 0.92 (s, 9H), 0.88 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 7.5 Hz, 3H), 0.77 (d, J = 6.0 Hz, 3H), 0.56 (q, J = 8.0 Hz, 6H), 0.06 (s, sH), 0.08 (s, 3H) ppm; IR (film) 2928, 1700, 1459, 1248, 1041, 776 cm^{-1}; LRMS (ESI) calcd for $C_{58}H_{99}NO_{12}Si_2$ $[M+Na]^+$ 1080.7, found 1080.5.

Experimental for Scheme VIII.



13b-iii **xxiii-b**

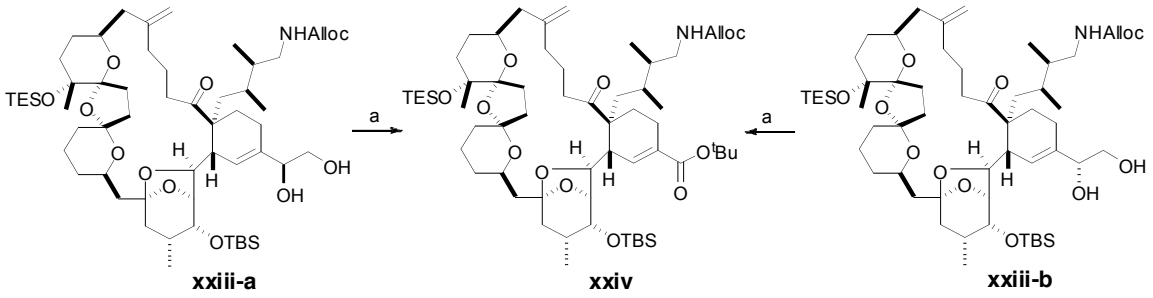
Scheme VIII. Reagents. a. 1. sumilizer, dodecane, 160 °C. 2. K_2CO_3, MeOH, rt.

Diol xxiii-b. A mixture of Diels-Alder precursor **13b-iii** (40.0 mg, 35.1 mmol), 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide (sumilizer, 8.0 mg), and dodecane (40 mL) was placed in a Schlenk tube (soaked in 40% KOH in 2-propanol over 24 h, washed and dried before use) and degassed by freeze-thaw methods for three times. The mixture was stirred for 12 h at 157 °C. After cooling to rt, the combined reaction mixture were filtered through a pad of basic alumina to remove dodecane (hexanes then EtOAc) to afford crude Diels-Alder cycloadducts as a mixture of diastereomers, which was purified by SiO_2 column chromatography (hexanes / EtOAc = 8:1, 7:1, 6:1 then 5:1) to give desired exo adduct **14b-iii** (14.4 mg, 36%) and other undesired stereoisomers (17.6 mg, 44%).

To a solution of Diels-Alder adduct (20 mg, 17.5 mmol) in CH_2Cl_2 / MeOH (4 mL, 1:1, v/v) was added excess K_2CO_3 at rt. After stirring at rt overnight, the reaction mixture was diluted with Et_2O, filtered through a short pad of SiO_2 to give the crude product, which was purified again by SiO_2 column chromatography (hexanes / EtOAc = 2:1 then 1:1) to give the corresponding diol **xxiii-b** (18.6 mg, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) 5.86-5.95 (m, 1H), 5.31 (s, 1H), 5.30 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.22 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.90 (broad, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 4.54 (d, *J* = 6.0 Hz, 2H), 4.16-4.17 (m, 1H), 4.12 (broad m, 1H), 3.98-4.04 (m, 1H), 3.82 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.62-3.72 (m, 3H), 3.08-3.12 (m, 1H), 2.94-2.98 (m, 1H), 2.85 (broad d, *J* = 11.5 Hz, 1H), 2.52-2.64 (m, 2H), 2.24-2.37 (m, 2H), 1.20-2.18 (m, 38 H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.91 (s, 9H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H), 0.56 (q, *J* = 7.5 Hz, 6H), 0.09 (s, 3H), 0.06 (s, 3H) ppm.

The stereochemical correlation between **xxiii-a/b** and **xxiv** was carried out as shown in Scheme IX. Note that **xxiv** is a known compound in the original PnTX A synthesis (McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647).

Experimental for Scheme IX.



Scheme IX. Reagents. a. 1. $NaIO_4$. 2. $NaClO_2$, 3. ^{t}BuOH, EDC, DMAP

Ester xxiv. To a solution of diol xxiii-a (0.6 mg) in 10% aq. THF (0.3 mL) at 0 ^{o}C was added $NaIO_4$ (10 mg). After 30 min of stirring at 0 ^{o}C, the mixture was diluted with EtOAc, washed with sat. aq. $NaHCO_3$/$Na_2S_2O_3$ solution, water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was

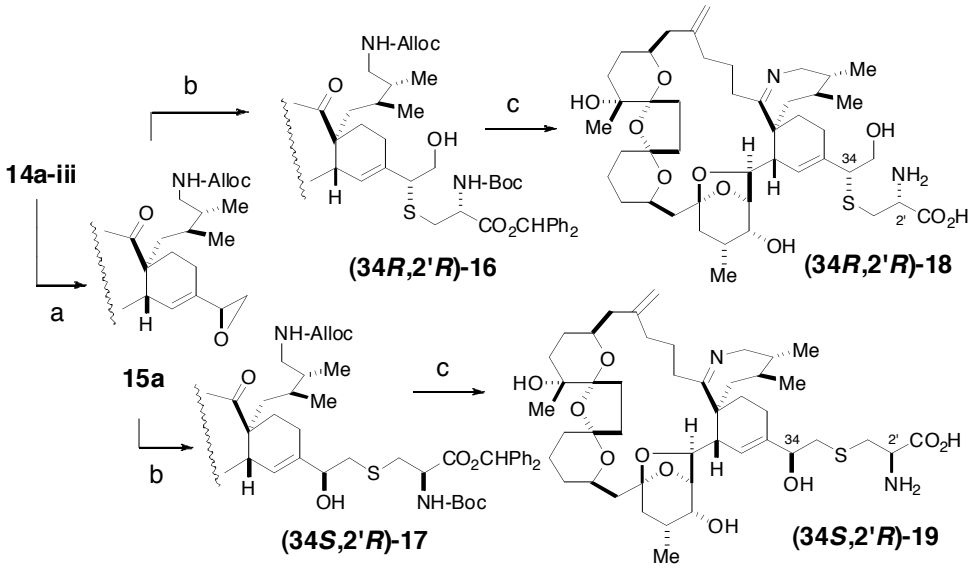
filtered through a pad of silica gel (hexanes / EtOAc = 4:1) to give the corresponding crude aldehyde.

To a solution of the above aldehyde in ^{t}BuOH (0.5 mL) was added 2-methyl-2-butene (0.3 mL), a solution of NaH_2PO_4 (excess) and $NaClO_2$ (excess) in H_2O (0.6 mL) at 0 ^oC. After 30 min of stirring at 0 ^oC, the mixture was directly applied to silica gel column (EtOAc) to afford the corresponding crude carboxylic acid.

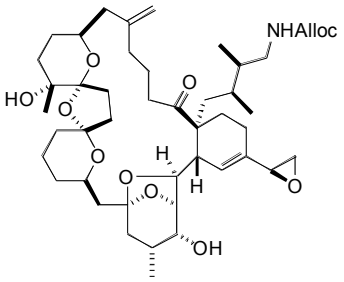
To a mixture of the above crude acid, ^{t}BuOH (0.1 mL) and DMAP (0.1 mg) in CH_2Cl_2 (0.3 mL) was added EDCI (excess). After stirring overnight at rt, the mixture was diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 flash chromatography (hexanes / EtOAc = 4:1) to afford *t*-butyl ester **xxiv**. Comparison of the ^{1}H NMR spectrum of **xxiv** with that of the authentic sample (McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647) established that **xxiii-a** has the desired stereochemistry.

The stereochemistry of **xxiii-b** was established employing the same procedure.

Experimental for Scheme 4.



Scheme 4. Reagents. (a) 1. K_2CO_3. 2. HF•py, pr, 74% over 2 steps. 2. TsCl. 3. K_2CO_3, 78% over 2 steps. (b) N-Boc-L-Cys(SH)-OCHPh$_2$ (an inseparable mixture of **16** and **17**), 85%. (c) 1. $Pd(PPh_3)_4$, AcOH, 72%. 2. 1,3,5-(i-Pr)$_3$C$_6$H$_2$CO$_2$H-Et$_3$N salt, 80 °C, xylene. 3. TFA, CH_2Cl_2, followed by HPLC separation of **18** and **19**.



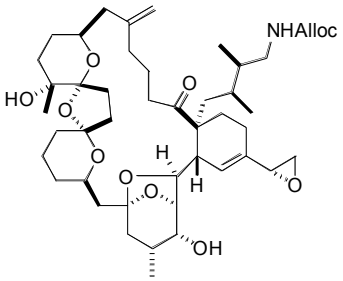
15a

Epoxide 15a. To a stirred solution of the diol **xxiii-a** (10.5 mg, 7.9 mmol) in CH_3CN (0.8 mL) and Et_2O (5 drops) at rt was added 30 % HF·py in pyridine (6 drops) and HF·py (2 drops). After the mixture was stirred at rt overnight, HF·py (4 drops) was added for every 12h (total 6 drops of 30% HF·py in pyridine and 10 drops of HF·py were added). The reaction mixture was filtered through a small SiO_2 column, eluted with EtOAc/MeOH (10:1). The filtrate was concentrated and purified by SiO_2 flash chromatography (hexanes / EtOAc = 1:1, EtOAc, then EtOAc / MeOH = 10:1) to afford the corresponding tetraol (5.0 mg, 74 %) as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) 5.73-5.81 (m, 1H), 5.15 (d, *J* = 17.5 Hz, 1H), 5.10 (s, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 4.94 (s, 1H), 4.88 (s, 1H), 4.49 (broad d, *J* = 4.5 Hz, 2H), 4.38 (broad, 1H), 4.19-4.34 (m, 3H), 3.91 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.84 (broad, 1H), 3.53-3.60 (m, 2H), 3.46-3.52 (m, 1H), 2.81-2.91 (m, 2H), 2.59-2.67 (m, 2H), 2.38-2.46 (m, 1H), 1.18-2.36 (m, 36H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.66 (d, *J* = 6.5 Hz, 3H) ppm; HRMS (ESI) calcd for $C_{46}H_{71}NO_{12}$ $[M+NH_4]^+$ 847.5320, found 847.5333; $[\alpha]_D^{20}$ +8.4 (*c* 0.25, PhH).

To a stirred solution of the above tetraol (5.0 mg, 6.0 μmol) in CH_2Cl_2 (0.4 mL) at rt was added Et_3N (0.4 ml), DMAP (0.19 mg), and TsCl (1.9 mg). After 30 min of stirring at rt, the mixture was charged directly to a SiO_2 column (hexanes / EtOAc = 1:2, 1:4, then EtOAc / MeOH = 4:1) to afford the corresponding tosylate and recovered tetraol. After repeating this process twice, tosylate (5.5 mg) and recovered tetraol (0.2 mg) were obtained as a colorless oil: HRMS (FAB) calcd for $C_{58}H_{77}NO_{14}S$ $[M+Na]^+$ 1006.4962, found 1006.4971.

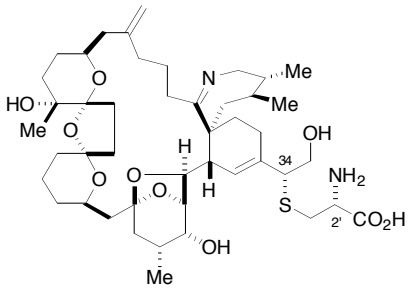
To a stirred solution of the above tosylate (5.5 mg) in CH_2Cl_2/MeOH (1:1, v/v, 0.3 mL) was added K_2CO_3 (5 mg) and stirred at rt for 30 min. The mixture was filtered through a pad of SiO_2 and concentrated. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 1:1, 1:2, then 1:10) to afford epoxide **15a** (3.8 mg, 78 % over 2 steps) as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) 5.76-5.84 (m, 1H), 5.16

(d, *J* = 17.0 Hz, 1H), 5.10 (s, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 4.94 (s, 1H), 4.88 (s, 1H), 4.51-4.56 (m, 2H), 4.25-4.39 (m, 3H), 4.18 (broad d, *J* = 2.0 Hz, 1H), 4.10 (t, *J* = 6.0 Hz, 1H), 3.83 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.53 (broad d, *J* = 10.0 Hz, 1H), 2.89-2.92 (m, 1H), 2.77-2.84 (m, 1H), 2.68-2.76 (m, 3H), 2.63 (dd, *J* = 12.5, 3.5 Hz, 1H), 2.50 (t, *J* = 5.0 Hz, 1H), 2.24-2.40 (m, 4H), 1.10-2.19 (m, 32H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.64 (d, *J* = 7.0 Hz, 3H) ppm; HRMS (ESI) calcd for $C_{58}H_{75}NO_{11}$ $[M+H]^+$ 812.4949, found 812.4943; $[\alpha]_D^{20}$ +20.0 (*c* 0.16, PhH).

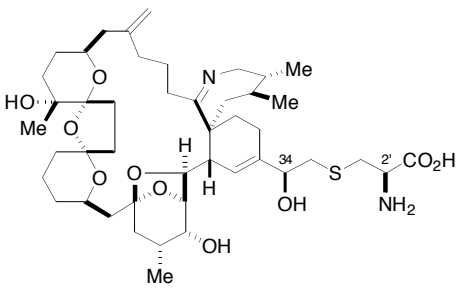


15b

Epoxide **15b** was prepared according to the same procedure from **xxiii-b**: ^{1}H NMR (500 MHz, C_6D_6) 5.77-5.85 (m, 1H), 5.16 (dd, *J* = 18.5, 1.5 Hz, 1H), 5.12 (s, 1H), 5.01 (dd, *J* = 10.0, 1.0 Hz, 1H), 4.92 (s, 1H), 4.86 (s, 1H), 4.51-4.58 (m, 2H), 4.26-4.36 (m, 3H), 4.18-4.20 (m, 1H), 4.14 (broad t, *J* = 6.0 Hz, 1H), 3.87 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.50 (broad d, *J* = 11.0 Hz, 1H), 2.95-3.10 (m, 1H), 2.88 (broad s, 1H), 2.68-2.78 (m, 3H), 2.60 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.36-2.46 (m, 3H), 2.26-2.33 (m, 4H), 1.26-2.18 (m, 30H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.69 (d, *J* = 6.0 Hz, 3H) ppm; HRMS (ESI) calcd for $C_{58}H_{75}NO_{11}$ $[M+H]^+$ 812.4949, found 812.4943; $[\alpha]_D^{20}$ +12.3 (*c* 0.13, PhH).



(34*R*, 2'*R*)-18a



(34*S*, 2'*R*)-19a

Pteriatoxin B/C (34*R*, 2'*R*)-18a and Pteriatoxin A (34*S*, 2'*R*)-19a. To a stirred solution of epoxide **15a** (1.9 mg, 2.3 μmol) in ^{i}PrOH (0.4 mL) and THF (0.05 mL) at rt was added Et_3N (0.1 mL) and Boc-*L*-Cys(SH)-$OCHPh_2$ (22 mg). After stirring overnight at rt, the reaction mixture was concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexanes / EtOAc = 3:1, 2:1, 1:1, 1:2 then 0:100) to afford sulfide **(34*R*, 2'*R*)-16a** and **(34*S*, 2'*R*)-17a** (2.4 mg, 85%) as a TLC inseparable mixture of the regioisomers.

To a stirred solution of sulfide **16a** and **17a** (1.8 mg, 1.5 μmol) in toluene / AcOH (100:1, v/v, 0.3 mL) at rt was added $Pd(PPh_3)_4$ (0.1 mg). After 1 h of stirring at rt, the mixture was directly charged to a SiO_2 column (EtOAc, $CHCl_3$ / MeOH = 9:1, then $CHCl_3$ / MeOH / H_2O = 16:8:1) to afford the corresponding ketoamine (1.2 mg, 72%) as an inseparable mixture of regioisomers: LRMS (ESI) calcd for $C_{63}H_{90}N_2O_{13}S$ $[M+H]^+$ 1115.6, found 1115.8.

The mixture of the above ketoamines (1.0 mg, 0.90 μmol) was dissolved in 1% (w/v) 1,3,5-triisopropylbenzoic acid - triethylamine salt in xylene (1 mL, prepared by dissolving 100 mg of 1,3,5-triisopropylbenzoic acid in 10 mL of xylene, followed by addition of 1 eq. of NEt_3 relative to the acid) and stirred at 80 °C for 40 h. The reaction mixture was directly charged to a SiO_2 column (hexanes / EtOAc = 3:1, 1:1, 1:5, 0:100, then EtOAc / MeOH = 9:1, 5:1) to afford the corresponding imine as a TLC inseparable mixture of regioisomers and 1,3,5-triisopropylbenzoic acid: LRMS (ESI) calcd for $C_{63}H_{88}N_2O_{12}S$ $[M+H]^+$ 1097.6, found 1097.4.

The mixture of the above imines and 1,3,5-triisopropylbenzoic acid was dissolved in TFA / CH_2Cl_2 (1:1, v/v, 3 mL) and stirred at rt for 10 min. The reaction mixture was poured into the toluene and concentrated. The residue was washed with Et_2O and separated by reversed phase HPLC (YMC-Pack ODS-A, 250x10 mm, H_2O / CH_3CN = 3:1, v/v, containing 0.1% TFA) to afford pure PtTX B/C **(34*R*, 2'*R*)-18a** (0.50 mg, 59%) and PtTX A **(34*S*, 2'*R*)-19a** (0.32 mg, 36%). LRMS (ESI) calcd for $C_{45}H_{70}N_2O_{10}S$ $[M+H]^+$ 831.5, found 831.1. Secondary alcohol: LRMS (ESI) calcd for $C_{45}H_{70}N_2O_{10}S$ $[M+H]^+$ 831.5, found 831.1. For ^{1}H NMR spectra see the supporting information of the accompanying paper.

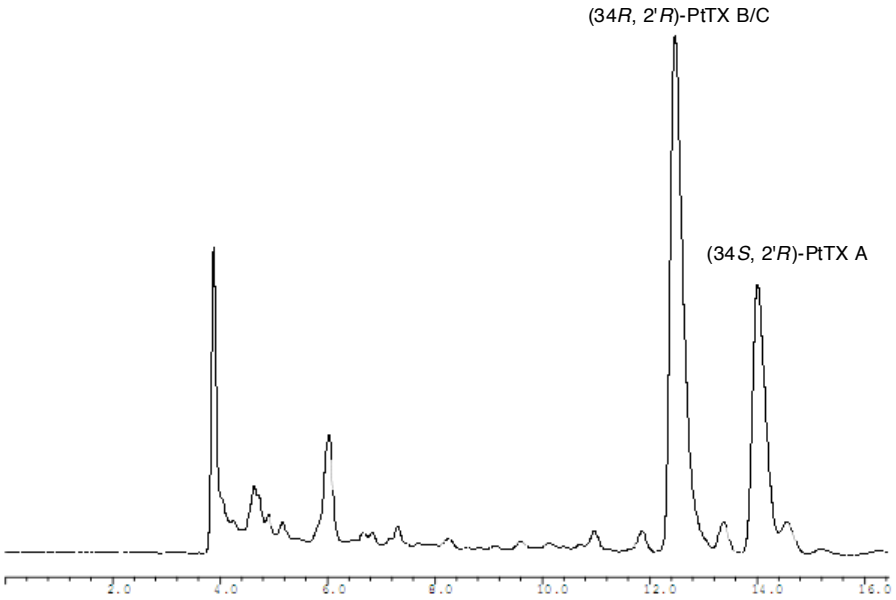
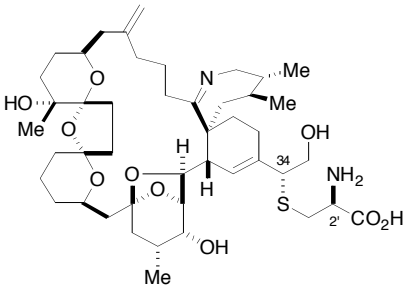
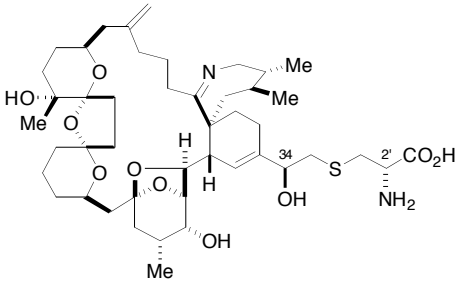


Figure I. HPLC Trace for Separation of **(34*R*, 2'*R*)**-PtTX B/C and **(34*S*, 2'*R*)**-PtTX A

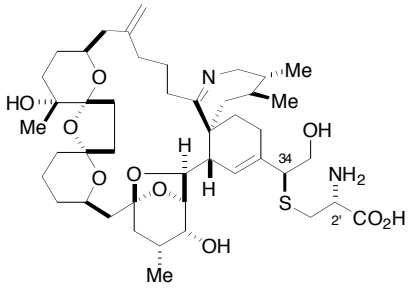


(34*R*, 2'*S*)-18a

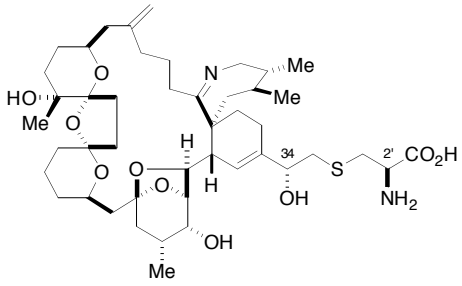


(34*S*, 2'*S*)-19a

Pteriatoxin B/C (34*R*, 2'*S*)-18a and Pteriatoxin A (34*S*, 2'*S*)-19a were prepared according to the same procedure from epoxide **15a** and Boc-*D*-Cys(SH)-OCHPh$_2$. For ^{1}H NMR spectra see the supporting information of the accompanying paper.

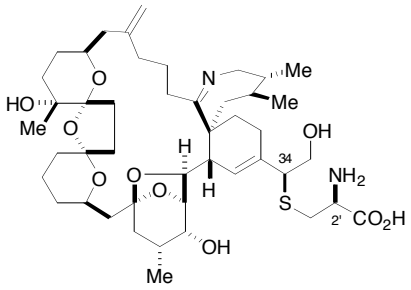


(34*S*, 2'*R*)-18a

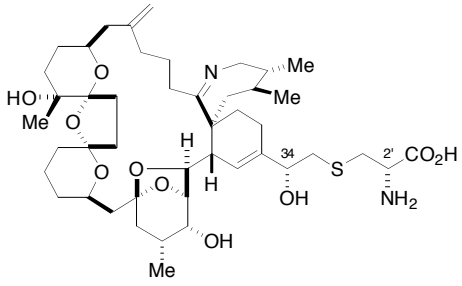


(34*R*, 2'*R*)-19a

Pteriatoxin B/C (34*S*, 2'*R*)-18a and Pteriatoxin A (34*R*, 2'*R*)-19a were prepared according to the same procedure from epoxide **15b** and Boc-*L*-Cys(SH)-$OCHPh_2$. For ^1H NMR spectra see the supporting information of the accompanying paper.



(34*S*, 2'*S*)-18a



(34*R*, 2'*S*)-19a

Pteriatoxin B/C (34*S*, 2'*S*)-18a and Pteriatoxin A (34*R*, 2'*S*)-19a were prepared according to the same procedure from epoxide **15b** and Boc-*D*-Cys(SH)-$OCHPh_2$. For ^1H NMR spectra see the supporting information of the accompanying paper.