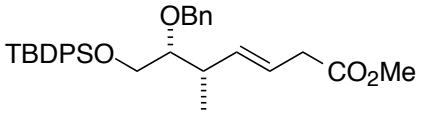
Supporting Information
Total Synthesis of Epothilone A

Bin Zhu and James S. Panek

Department of Chemistry and the Center for Streamlined Synthesis,
Metcalf Center for Science and Engineering,
Boston University, 590 Commonwealth Avenue, Boson, MA 02215

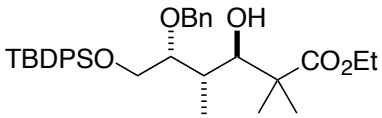
General Information. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 400 MHz and 75.0 MHz respectively unless specified otherwise. Chemical shifts are reported in parts per million using the solvent resonance internal standard (chloroform, 7.24 and 77.0 ppm, unless specified otherwise). Data are reported as follows: chemical shift, multiplicity (app = apparent, par obsc = partially obscured, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, ABq = ab quartet), integration, and coupling constant. Ratios of diastereomers were determined by ^{1}H NMR (400 MHz) operating at a signal/noise ratio of >200:1. Infrared Resonance spectra were recorded on a Perkin-Elmer 7700 series FTIR spectrophotometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are reported as $[\alpha]_D$ (concentration in grams/100 mL solvent). High resolution mass spectra were obtained on a Fingan MAT-90 spectrometer in the Boston University Mass Spectrometry Laboratory. Methylene chloride (CH_2Cl_2), benzene, toluene and dimethyl sulfoxide (DMSO) were distilled from calcium hydride; and tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone prior to use. Titanium tetrachloride ($TiCl_4$) was freshly distilled from copper powder before each use. BF_3•OEt_2 and TMSOTf were distilled under an argon atmosphere before use. TMSCl was freshly distilled from quinoline before each use. All other reagents were used as supplied. All reactions were carried out in oven-dried glassware under argon atmosphere unless otherwise noted. Analytical thin layer chromatography was performed on Whatman Reagent 0.25 mm

silica gel 60-Å plates. Flash chromatography was performed on E. Merck silica gel 230-400 mesh.



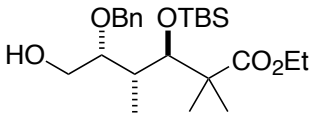
8

Preparation of Compound 8. A stirred solution of aldehyde **7** (10.0 g, 33.6 mmol) and benzyloxytrimethylsilane (TMSOBn) (14.0 mL, 71.2 mmol) in dry CH_2Cl_2 (110 mL) was cooled to –78 ºC, to which trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.6 mL, 3.3 mmol) was added. The reaction mixture was slowly warmed up to –50 ºC for 16 h, before crotylsilane reagent *S*-**3** (8.80 g, 33.6 mmol) was added followed by BF_3•Et_2O (9.0 mL, 73.1 mmol). The resulting solution was allowed to further warm up to –30 ºC for 24 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (300 mL x 2). The organic layer was washed with saturated aqueous NaCl (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (silica, 5% EtOAc in hexane) afforded crotylation product **8** (14.4 g, 83%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 2H, *J* = 8 Hz), 7.65 (d, 2H, *J* = 8 Hz), 7.43-7.25 (m, 11H), 5.49 (m, 2H), 4.68 and 4.47 (Abq, 2H, *J* = 11.6 Hz), 3.71 (d, 2H, *J* = 4.8 Hz), 3.61 (s, 3H), 3.32 (dt, 1H, *J* = 5.2 Hz, 6 Hz), 2.95 (d, 2H, *J* = 5.6Hz), 2.51 (ddq, 1H, *J* = 6.4 Hz, 6.4 Hz, 6.8 Hz), 1.03 (s, 9H), 0.99 (d, 3H, *J*sher, H. S. ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 139.0, 137.1, 135.6, 133.6, 129.6, 128.2, 127.6, 127.4, 121.5, 83.6, 72.8, 64.6, 51.7, 38.4, 38.3, 38.0, 26.9, 19.2, 15.4; IR (neat) νmax 2956, 2931, 2858, 1741, 1472, 1429, 1255, 1166, 1113; $[\alpha]^{23}_D$ = +14.1° (*c* = 1.35, CH_2Cl_2).



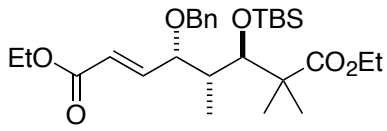
10

Preparation of Compound 10. To a solution of homoallylic ether **8** (8.3 g, 16.1 mmol) and pyridine (1.3 mL, 16.1 mmol) in MeOH (120 mL)/CH_2Cl_2 (60 mL) at –78 ºC was bubbled ozone gas for 30 min. Methyl sulfide (11.8 mL, 161 mmol) was then added to the resulting blue solution. The dry ice bath was removed and the reaction was allowed to stirred at room temperature under argon for 16 h. The solvent was removed in vacuo, and the residue was diluted with CH_2Cl_2 (300 mL), washed with H_2O (50 mL x 2) and saturated aqueous NaCl (50 mL), and dried over $MgSO_4$. The CH_2Cl_2 was removed in vacuo to afford the aldehyde as colorless oil (6.3 g, 88%). This aldehyde (6.3 g, 14.1 mmol) was dissolved in dry CH_2Cl_2 (45 mL) and the resulting solution was cooled to –78 ºC. To this stirred solution was added freshly distilled $TiCl_4$ (1.70 mL, 15.5 mmol), followed by silyl ketene acetal **9** (3.9 mL, 18.7 mmol) after 20 min. The reaction was stirred at –78 ºC for 45 min before being quenched with EtOAc (10 mL) and H_2O (50 mL). The mixture was extracted with CH_2Cl_2 (150 mL x 2). The organic layer was washed with saturated aqueous NaCl (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (silica, 5% EtOAc in hexane) to give alcohol **10** as colorless oil (6.6 g, 83%, *anti*/*syn* = 6:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.43-7.35 (m, 6H), 7.34-7.25 (m, 5H), 4.69 and 4.54 (ABq, 2H, *J* = 11.2 Hz), 4.06 (dq, 2H, *J* = 2 Hz, 7.2 Hz), 3.92 (dd, 1H, *J* = 6.4 Hz, 10.8 Hz), 3.86-3.80 (m, 2H), 3.70 (dd, 1H, *J* = 5 Hz, 6.2 Hz), 3.35(d, 1H, *J* = 4.4Hz), 1.97 (ddq, 1H, *J* = 2.4 Hz, 7.2 Hz, 7.2 Hz), 1.19 (s, 3H), 1.18 (t, 3H, *J* = 7.2 Hz), 1.12 (s, 3H), 1.04 (s, 9H), 0.77 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 138.4, 135.6, 133.3, 129.8, 128.4, 127.7, 127.6, 82.4, 78.1, 77.2, 72.4, 64.1, 60.3, 47.0, 36.9, 26.8, 23.7, 19.2, 18.9, 14.1, 13.1; IR (neat) νmax 3472, 2943, 2866, 1717, 1464, 1388, 1258, 1113; CIHRMS $[M+H]^+$ calculated for $C_{34}H_{47}SiO_5$ 563.3193, found: 563.3228; $[\alpha]^{23}_D$ = +8.0° (*c* = 0.5, CH_2Cl_2).



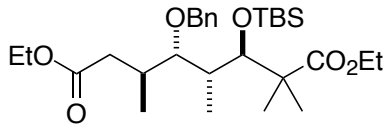
11

Preparation of compound 11. To a solution of the alcohol **10** (0.80 g, 1.42 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added successively 2,6-lutidine (0.50 mL, 4.3 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (0.50 mL, 2.18 mmol). After 2 h, the reaction was poured into CH_2Cl_2 (50 mL), washed with 1 **N** HCl (5 mL) and saturated aqueous NaCl (10 mL), and dried over $MgSO_4$. Purification by flash chromatography (silica, 2% EtOAc in hexane) afforded TBS ether (914 mg, 95%). This di-silyl ether (914 mg, 1.35 mmol) was dissolved in THF (10 mL), and a 1:1 mixture of tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 2.70 mL, 2.70 mmol) and acetic acid (AcOH) (0.155 mL, 2.70 mmol) was added. The reaction was stirred at room temperature for 24 h, before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (20 mL x 2), and the organic layer was washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (silica, 10% EtOAc in hexane) to give the alcohol **11** (545 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.59 (s, 2H), 4.08 (dq, 2H, *J* = 2.8 Hz, 4 Hz), 3.94 (d, 1H, *J* = 4.4 Hz), 3.77 (m, 1H), 3.61 (m, 1H), 3.50 (dt, 1H, *J* = 4 Hz, 7.2 Hz), 1.92 (ddq, 1H, *J* = 4 Hz, 4 Hz, 7.2 Hz), 1.88 (t, 1H, *J* = 6.2 Hz), 1.23 (t, 3H, *J* = 7 Hz), 1.18 (s, 3H), 1.14 (s, 3H), 1.06 (d, 3H, *J* = 7.2 Hz), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 138.6, 128.4, 127.6, 127.5, 79.9, 79.8, 72.3, 63.3, 60.5, 48.5, 38.3, 26.2, 24.3, 19.6, 18.4, 16.1, 14.0, -3.0, -4.2; IR (neat) νmax 3496, 2930, 2858, 1727, 1473, 1388, 1256, 1065; CIHRMS $[M+H]^+$ calculated for $C_{24}H_{43}SiO_5$: 439.2880, found: 439.2885; $[\alpha]^{23}_D$ = -4.8° (*c* = 0.42, CH_2Cl_2).



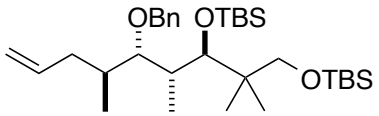
12

Preparation of Compound 12. To a solution of $(COCl)_2$ (0.73 mL, 8.36 mmol) in dry CH_2Cl_2 (60 mL) at –78 ºC was added dropwise DMSO (1.37 mL, 19.34 mmol). The solution was stirred at –78 ºC for 30 min, before a solution of alcohol **11** (2.83 g, 6.46 mmol) in 5 mL dry CH_2Cl_2 was added. The reaction was kept at –78 ºC for another 45 min, and Et_3N (4.5 mL, 32.3 mmol) was then added in. The dry ice bath was removed, and the reaction mixture was stirred at room temperature for 1.5 h before being quenched with H_2O (50 mL). The resulting mixture was poured into hexane (300 mL). The organic layer was separated and washed with H_2O (50 mL x 2) and saturated aqueous NaCl (50 mL). The aqueous layers were combined and re-extracted with hexane (50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give the crude aldehyde as a light yellow oil. The crude aldehyde was dissolved in dry benzene (50 mL), and PPh_3=$CHCO_2Et$ (95%, 2.8 g, 7.63 mmol) was added. The resulting solution was heated under reflux for 4 h before being cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (silica, 5% EtOAc in hexane) afforded the α,β-unsaturated ester **12** as colorless oil (2.98 g, 91% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.98 (dd, 1H, J = 5.6 Hz, 15.6 Hz), 5.98 (dd, 1H, J = 1.2 Hz, 16 Hz), 4.53 and 4.34 (ABq, 2H, J = 11.6 Hz), 4.20 (m, 1H), 4.18 (q, 2H, J = 7.2 Hz), 4.11 (d, 1H, J = 5.6 Hz), 4.05 (dq, 2H, J =2 Hz, 7.2 Hz), 1.70 (m, 1H), 1.28 (t, 3H, J = 7.2 Hz), 1.19 (t, 3H, J = 7.2 Hz), 1.16 (s, 3H), 1.09 (s, 3H), 0.96 (d, 3H, J = 7.2 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.006 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 166.3, 148.8, 138.6, 128.2, 127.3, 127.1, 121.6, 78.2, 77.8, 70.6, 60.4, 48.0, 43.8, 26.3, 26.2, 18.6, 18.4, 14.2, 14.1, 14.0, 12.8, -3.1, -3.6; IR (neat) νmax; 2930, 2857, 1722, 1473, 1367, 1174, 1077; CIHRMS $[M+H]^+$ calculated for $C_{28}H_{47}SiO_6$ 507.3142:, found: 507.3141; $[\alpha]^{23}_D$ = -11.5° (*c* = 1.5, CH_2Cl_2).



13

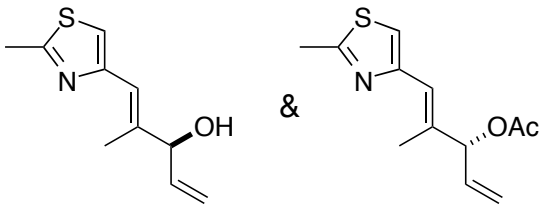
Preparation of Compound 13. To a stirred suspension of CuI (3 g, 15.4 mmol) in THF (80 mL) at 0 ºC was slowly added MeLi•LiBr (1.5 **M** in Et_2O, 20.5 mL, 30.8 mmol). The resulting clear solution was stirred at 0 ºC for 10 min before being cooled to –78 ºC. To the cooled solution of Me_2CuLi was added successively TMSCl (8 mL, 63 mmol) and a solution of α,β-unsaturated ester **12** in 5 mL THF. The reaction was stirred at –78 ºC for 4 h before being quenched with a 1:1 mixture of 30% aqueous ammonium hydroxide and saturated aqueous NH_4Cl (60 mL). The mixture was extracted with EtOAc (150 mL) and the organic layer was washed with H_2O (50 mL), saturated aqueous NaCl (30 mL) and dried over $MgSO_4$. Purification by flash chromatography (silica, 5% EtOAc in hexane) afforded ester **13** as colorless oil (1.26 g, 94%, C-7/C-8 *anti*/*syn* ratio > 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.68 and 4.53 (ABq, 2H, *J* = 11.2 Hz), 4.12 (d, 1H, *J* = 6 Hz), 4.14-4.00 (m, 4H), 3.49 (dd, 1H, *J* = 4 Hz, 6 Hz), 2.56 (dd, 1H, *J* = 4 Hz, 14.8 Hz), 2.26 (m, 1H), 2.15 (dd, 1H, *J* = 9.6 Hz, 14.8 Hz), 1.83 (m, 1H), 1.21 (t, 3H, *J* = 7 Hz), 1.20 (s, 3H), 1.19 (t, 3H, *J* = 6.8 Hz), 1.15 (s, 3H), 0.97 (d, 3H, *J* = 6.4 Hz), 0.95 (d, 3H, *J* = 6.8 Hz), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 173.4, 139.1, 128.2, 127.2, 127.1, 82.0, 79.0, 73.7, 60.4, 60.1, 48.0, 41.6, 37.3, 34.5, 26.7, 26.4, 18.7, 18.4, 17.8, 14.2, 14.0, 12.6, -1.7, -3.9; IR (neat) νmax; 2958, 2858, 1733, 1473, 1464, 1388, 1256, 1176, 1070; CIHRMS $[M+H]^+$ calculated for $C_{29}H_{51}SiO_6$: 523.3454, found: 523.3495; $[\alpha]^{23}_D$ = -18.6° (*c* = 0.7, CH_2Cl_2).



4

Preparation of Compound 4. To a solution of ester **13** (270 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) at –78 ºC was added DIBAL-H (1.0 M in hexane, 2.6 mL, 2.6 mmol). The resulting solution was stirred at –78 ºC for 15 min before being quench with MeOH (1 mL) followed by 1N HCl (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x 2). The organic extracts were combined, washed with saturated aqueous NaCl (5 mL) and concentrated in vacuo to give the crude hydroxyl aldehyde **14**. The crude **14** was dissolved in dry DMF (1 mL). The solution was cooled to 0 ºC, and imidazole (141 mg, 2.08 mmol) and TBSCl (157 mg, 1.04 mmol) was added successively. The reaction was kept at 0 ºC for 2 h before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (15 mL x 2). The organic layers were combined and washed with H_2O (5 mL), saturated aqueous NaCl (5 mL) and dried over $MgSO_4$. Purification by flash chromatography (silica, 5 % EtOAc in hexane) afforded the aldehyde as colorless oil (193 mg, 68% for two steps). To a suspension of CH_3PPh_3Br (320 mg, 0.90 mmol) in THF (5 mL) was added $NaN(TMS)_2$ (1.0 **M** in THF, 0.78 mL, 0.78 mmol). The resulting yellow mixture was stirred for 30 min before being cooled to 0 ºC. To this mixture was added a solution of above prepared aldehyde (193 mg, 0.35 mmol) in 1 mL THF. The reaction was stirred at 0 ºC for 15 min before being quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with hexane (30 mL). The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica, 2% EtOAc in hexane) afforded olefin **4** as colorless oil (173 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.77 (m, 1H), 5.01 (d, 1H, J = 18 Hz), 4.97 (d, 1H, J =11.6 Hz), 4.63 and 4.54 (ABq, 2H, J = 11.6 Hz), 3.77 (d, 1H, J = 3.2 Hz), 3.45 (d, 1H, J = 7.2 Hz), 3.38 and 3.08 (ABq, 2H, J = 9.2 Hz), 2.29 (m, 1H), 2.08 (m, 1H), 1.96 (m, 2H), 1.12 (d, 3H, J = 7.2 Hz), 0.97 (d, 3H, J = 6 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.004 (s, 3H), 0.002 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 139.5, 138.1, 128.2, 127.1, 115.6, 84.7, 76.4, 74.5, 70.7, 42.0, 41.5, 36.1, 34.9, 26.3, 26.0, 21.9, 21.5, 18.6, 18.3, 17.3, 14.9, -2.7, -4.7, -5.3, -5.5; IR (neat) νmax; 2957, 2858, 1641, 1472, 1361, 1256, 1088; CIHRMS $[M+H]^+$ calculated for $C_{32}H_{60}Si_2O_3$: 548.4081, found: 548.4035; $[\alpha]^{23}_D$ = -5.3° (*c* = 0.6, CH_2Cl_2).



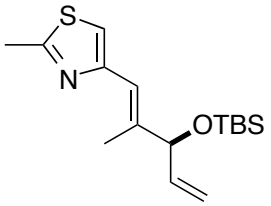
S-**16** R-**17**

Synthesis and Lipase Promoted Kinetic Resolution of *rac*-16. To a solution of aldehyde **15** (3.4 g, 20.1 mmol) in THF (70 mL) at –78 °C was added vinyl magnesiumbromide (1.0 **M** in THF, 24 mL, 24 mmol). The reaction was then stirred at –78 °C for 30 min before being quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (100 mL x 3). The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica, 20 to 33% EtOAc in hexane) afforded racemic alcohol *rac*-**16** as light yellow oil (3.6 g, 90%). To a stirred solution of *rac*-**16** (3.6 g, 18.3 mmol) in hexane/vinyl acetate (10:1. 187 mL) at room temperature was added lipase AK powder (1.80 g, 50wt%, Amano Pharmaceutical Co., Inc.). The progress of the reaction was monitored by ^{1}H NMR measuring the integration of the methine proton adjacent to the hydroxyl group and the methine proton adjacent to the acetate group. When the ratio of acetate and remaining alcohol in the reaction mixture reached 1:1 (*ca.* 72 h), the insoluble enzyme was removed by filtration, and washed with diethyl ether (200 mL). Concentration of the filtrate in vacuo and purification by flash chromatography (silica gel) afforded the acetate *R*-**17** as light yellow oil (15% EtOAc in hexane, 2.1 g, 48%) and

the unreacted alcohol *S*-**16** as light yellow oil (35% EtOAc in hexane, 1.73 g, 48%, 90% ee).[1]

Compound *S*-16. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.60 (s, 1H), 5.89 (ddd, 1H, J = 5.6 Hz, 10 Hz, 16.8 Hz), 5.34 (d, 1H, J = 17.6 Hz), 5.19 (d, 1H, J = 10.4 Hz), 4.66 (bs, 1H), 2.69 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 152.7, 140.8, 136.7, 119.1, 115.4, 78.1, 19.0, 14.5; IR (neat) νmax; 3346, 2979, 2855, 1639, 1508, 1440, 1379, 1269, 1189; CIHRMS $[M+H]^+$ calculated for $C_{10}H_{14}NOS$: 196.0796, found: 196.0808; $[\alpha]^{23}_D$ = +6.9° (*c* = 0.8, CH_2Cl_2).

Compound *R*-17. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.57 (s, 1H), 5.84 (ddd, 1H, *J* = 6.4 Hz, 10.8 Hz, 17.2 Hz), 5.71 (d, 1H, *J* = 6Hz), 5.31 (d, 1H, *J* = 16.8 Hz), 5.23 (d, 1H, *J* = 10.4 Hz), 2.69 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 164.4, 152.3, 136.4, 134.7, 120.7, 117.1, 116.2, 79.0, 21.0, 19.0, 14.8; IR (neat) νmax; 1739, 1370, 1235, 1183, 1019; CIHRMS $[M+H]^+$ calculated for $C_{12}H_{16}NO_2S$: 238.0902, found: 238.0930; $[\alpha]^{23}_D$ = +35° (*c* = 0.7, CH_2Cl_2).

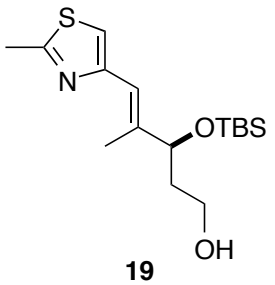


18

Preparation of Compound 18. To a solution of *S*-**16** (0.79 g, 4.0 mmol) in dry DMF (8 mL) at 0 ºC was added successively imidazole (0.82 g, 12.0 mmol) and TBSCl (0.9 g, 6.0 mmol), and the reaction was stirred at 0 ºC for 2 h. The reaction mixture was then poured into H_2O (20 mL) and extracted with CH_2Cl_2 (30 mL x 2). The organic layer was washed with H_2O (20 mL), saturated aqueous NaCl (20 mL) and dried over $MgSO_4$. Concentration in vacuo and purification by flash chromatography (silica, 5% EtOAc in hexane) afforded silyl ether **18** as colorless oil (1.2 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.54 (s, 1H), 5.78 (ddd, 1H, *J* =4.8 Hz, 10.4 Hz, 17.2 Hz), 5.29

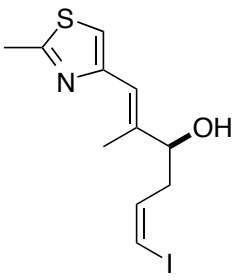
[1] The ee was determined by mandelate ester formation: (a) Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, *2*, 199. (b) Dale, J.A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. The absolute C15 stereochemistry was assigned by comparing the optical rotation data of compound **5** with the reported data.

(dt, 1H, J = 17.2 Hz, 1.6 Hz), 5.08 (dt, 1H, J = 1.6 Hz, 10 Hz), 4.59 (d, 1H, J = 4.8 Hz), 2.69 (s, 3H), 1.93 (d, 3H, J = 1.2 Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 153.2, 144.3, 139.8, 118.6, 115.2, 114.2, 79.1, 25.8, 19.1, 18.3, 14.0, -4.8; IR (neat) νmax; 2956, 2857, 1639, 1504, 1472, 1360, 1252, 1182, 1031; CIHRMS $[M+H]^+$ calculated for $C_{16}H_{28}NOSSi$: 310.1661, found: 310.1666; $[\alpha]^{23}_D$ = -28.6° (c = 1.8, CH_2Cl_2).



19

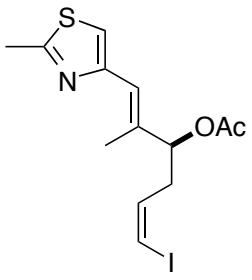
Preparation of Compound 19. To BH_3•THF (1.0 **M** in THF, 5.8 mL, 5.8 mmol) at 0 ºC was added cyclohexene (1.17 mL, 11.6 mmol), and the reaction was stirred at 0 ºC for 1h. To the resulting mixture at 0 ºC was added a solution of olefin **18** in THF (2 mL). The reaction was allowed to slowly warm up to room temperature for 3 h, before 2.5 M aqueous NaOH (4.6 mL) and 30% aqueous H_2O_2 (1.8 mL) was added. Stirring was kept for 45 min and the reaction mixture was then extracted with EtOAc (30 mL x 3). The organic layer was washed with H_2O (20 mL), saturated aqueous NaCl (10 mL) and dried over MgSO4. Concentration in vacuo and purification by flash chromatography (silica, 20 to 33% EtOAc in hexane) afforded alcohol **19** as colorless oil (1.14 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.50 (s, 1H), 4.37 (dd, 1H, J = 4.4 Hz, 7.2 Hz), 3.73 (m, 2H), 2.69 (s, 3H), 2.00 (s, 3H), 3.79-3.68 (m, 2H), 0.89 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 153.0, 141.6, 118.8, 115.4, 77.2, 60.5, 38.2, 25.8, 19.2, 18.2, 14.4, -4.6, -5.2; IR (neat) νmax: 3363, 2954, 2929, 2885, 2856, 1658, 1507, 1472, 1361, 1255, 1072; CIHRMS $[M+H]^+$ calculated for $C_{16}H_{30}NO_2SSi$: 328.1767, found: 328.1742; $[\alpha]^{23}_D$ = -27.7° (c = 0.7, CH_2Cl_2).



20

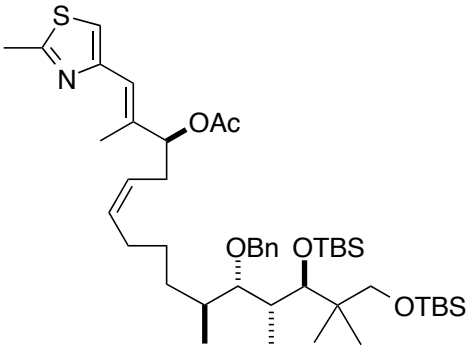
Preparation of Compound 20. To a solution of alcohol **19** (0.64 g, 1.95 mmol) in CH_2Cl_2 (40 mL) was added Dess-Martin periodinane (1.2 g, 2.83 mmol). The resulting mixture was stirred at room temperature for 15 min before being quenched with H_2O (30 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x 2). The organic layers were combined, washed with saturated aqueous NaCl (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was diluted with hexane (100 mL) and filtered through a pad of Celite . Removal of solvent in vacuo gave crude aldehyde as light yellow oil. To a suspension of CH_2IPPh_3I (2.6 g, 4.9 mmol) in THF (20 mL) was added $NaN(TMS)_2$ (1.0 **M** solution in THF, 4.4 mL, 4.4 mmol). The resulting red solution was stirred at room temperature for 15 min before being cooled to –78 ºC. To this cooled solution was added a solution of above prepared aldehyde in THF (2 mL), and the reaction mixture was then warmed to 0 ºC for 20 min. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with hexane (100 mL). The organic layer was washed with H_2O (20 mL), saturated aqueous NaCl (10 mL), and dried over $MgSO_4$. Removal of solvent afforded the crude vinyl iodide as light yellow oil. This crude vinyl iodide was dissolved in CH_3CN (15 mL) in a plastic vial, and 48% aqueous HF (3 mL) was added slowly to the resulting solution. The reaction was stirred for 16 h before being poured into saturated aqueous Na_2CO_3 (30 mL). The aqueous layer was extracted with EtOAc (30 mL x 3). The organic layer was combined, washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Concentration under reduced pressure and purification by flash chromatography (silica gel, 30% EtOAc in hexane) afforded vinyl iodide **20** as light yellow oil (0.42 g, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.55 (s, 1H), 6.33-6.25 (m, 2H), 4.30 (t, 1H, J = 6.4 Hz), 2.69 (s, 3H), 2.49 (m, 2H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 164.7, 152.5, 141.3, 137.5, 119.2, 115.7, 84.4, 75.9, 40.6, 19.1, 14.4; IR (neat) νmax: 3347, 2920, 1734, 1654, 1608, 1437, 1375, 1292, 1190, 1045; CIHRMS $[M+H]^+$ calculated for $C_{11}H_{15}NOSI$: 335.9917, found: 335.9921; $[\alpha]^{23}_D$ = -19.4° (*c* = 0.35, CH_2Cl_2).



5

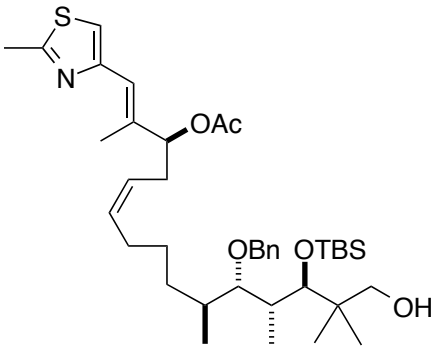
Preparation of Compound 5. To a solution of alcohol **20** (310 mg, 0.93 mmol) and DMAP (34 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) at 0 ºC was added Et_3N (0.26 mL, 1.87 mmol) and Ac_2O (0.13 mL, 1.38 mmol). The reaction was stirred for 2 h at 0 ºC before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL x 2), and the organic layer was washed with H_2O (5 mL), saturated aqueous NaCl (5 mL) and dried over $MgSO_4$. Removal of solvent under reduced pressure and purification by flash chromatography (silica, 10% EtOAc in hexane) afforded vinyl iodide **5** as light yellow oil (330 mg, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.52 (s, 1H), 6.33 (dt, 1H, *J* = 1.2 Hz, 7.6 Hz), 6.16 (dt, 1H, *J* = 7.2 Hz, 7.2 Hz), 5.38 (t, 1H, *J* = 6.4 Hz), 2.69 (s, 3H), 2.64-2.51 (m, 2H), 2.08 (d, 3H, *J* = 1.6 Hz), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 164.6, 152.3, 136.6, 136.2, 120.8, 116.4, 85.1, 76.8, 38.4, 21.1, 19.2, 14.9; IR (neat) νmax: 2923, 1736, 1611, 1505, 1435, 1370, 1235, 1183, 1020; CIHRMS $[M+H]^+$ calculated for $C_{13}H_{17}INO_2S$: 378.0023, found: 378.0060; $[\alpha]^{23}_D$ = -28.3° (*c* = 0.90, $CHCl_3$).



21

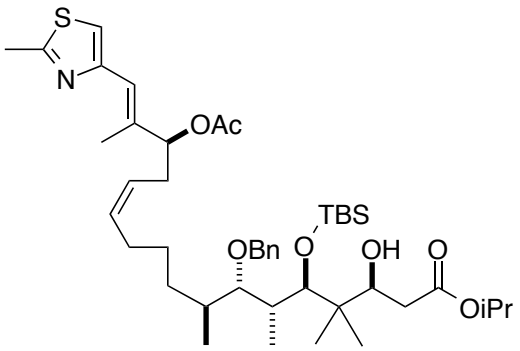
Preparation of Compound 21. To olefin **4** (200 mg, 0.365 mmol) was added 9-BBN (0.5 **M** solution in THF, 1.5 mL, 0.75 mmol), and the reaction was stirred for 4 h at room temperature. In a separate flask, vinyl iodide **5** (170 mg, 0.451 mmol) was dissolved in DMF (5 mL). Under vigorous stirring, Cs_2CO_3 powder (240 mg, 0.736 mmol) was added to the resulting solution, followed by $AsPh_3$ (17 mg, 0.056 mmol), $PdCl_2$(dppf) (30 mg, 0.037 mmol) and H_2O (0.24 mL, 13.3 mmol) successively. The resulting mixture was stirred for 5 min before the borane solution was added. The reaction was then stirred for 1.5 h, and the color of the mixture turned from dark brown to yellow. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with CH_2Cl_2 (30 mL x 3). The organic layer was then washed with H_2O (15 mL) and saturated aqueous NaCl (10 mL), and dried over $MgSO_4$. Purification by flash chromatography (silica, 5 to 10% EtOAc in hexane) afforded coupling product **21** as light yellow oil (175 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.91 (s, 1H), 6.50 (s, 1H), 5.48 (m, 1H), 5.28 (m, 1H), 5.25 (t, 1H, *J* = 6.8 Hz), 4.56 (ABq, 2H, *J* = 11.2 Hz), 3.75 (d, 1H, *J* = 3.2 Hz), 3.40 (dd, 1H, *J* = 2 Hz, 8.8 Hz), 3.38 and 3.05 (ABq, 2H, *J* = 9.4 Hz), 2.68 (s, 3H), 2.44 (m, 2H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (m, 2H), 1.80-1.65 (m, 2H), 1.50-1.38 (m, 2H), 1.30-1.19 (m, 2H), 1.11 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 0.89 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 164.8, 152.3, 139.6, 137.8, 132.8, 128.2, 127.2, 127.1, 123.9, 120.2, 116.1, 85.1, 78.5, 76.2, 74.3, 70.8, 42.0, 41.7, 36.3, 31.1, 30.2, 29.7, 28.1, 26.3, 26.0, 25.7, 21.9, 21.4, 21.2, 19.1, 18.5, 18.2, 17.3, 14.9, 14.6, -2.8, -4.7, -5.3, -5.5; IR (neat) νmax: 2928, 1741, 1653, 1507, 1472, 1371, 1240, 1064; CIHRMS

[M+H]$^+$ calculated for $C_{45}H_{78}NSSi_2O_5$: 800.5140, found: 800.5071; $[\alpha]^{23}_D$ = -11.3° (*c* = 0.80, CH_2Cl_2).



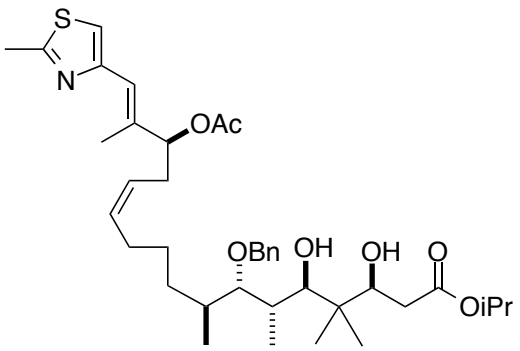
22

Preparation of Compound 22. To a solution of silyl ether **21** (140 mg, 0.175 mmol) in THF (8 mL) in a plastic vial was added pyridine buffered HF•pyridine solution (8 mL, prepared from 5 mL THF, 2 mL pyridine and 1mL HF•pyridine). The reaction was stirred at room temperature for 36 h before being quenched with saturated aqueous Na_2CO_3 (15 mL). The mixture was extracted with EtOAc (20 mL x 3). The combined organic layer was then washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica, 10 to 20% EtOAc in hexane) afforded alcohol **22** as white solid (112 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.93 (s, 1H), 6.52 (s, 1H), 5.48 (m, 1H), 5.29 (m, 1H), 5.24 (t, 1H, *J* = 6.6 Hz), 4.55 (s, 2H), 3.68 and 3.21 (ABq, 2H, J = 10.6 Hz), 3.61 (d, 1H, *J* = 2.8 Hz), 3.45 (dd, 1H, *J* = 2 Hz, 6.8 Hz), 2.70 (s, 3H), 2.45 (m, 2H), 2.34-1.98 (m, 2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.83 (m, 1H), 1.47 (m, 2H), 1.30-1.20 (m, 3H), 1.16 (d, 3H, *J* = 7.2 Hz), 1.04 (s, 3H), 0.97 (d, 3H, *J* = 6.8 Hz), 0.90 (s, 9H), 0.88 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 164.8, 152.2, 139.4, 137.8, 132.8, 128.2, 127.1, 124.0, 120.3, 116.1, 84.2, 81.4, 78.5, 73.6, 70.9, 41.1, 40.8, 36.4, 31.1, 29.7, 28.0, 26.3, 24.0, 22.1, 21.2, 19.1, 18.5, 16.9, 14.7, 14.1, -2.8, -4.8; IR (neat) νmax: 3447, 2928, 2856, 1736, 1463, 1370, 1238, 1060; CIHRMS [M]$^+$ calculated for $C_{39}H_{63}NSSiO_5$: 685.4196, found: 685.4227; $[\alpha]^{23}_D$ = -9.7° (*c* = 0.70, CH_2Cl_2).



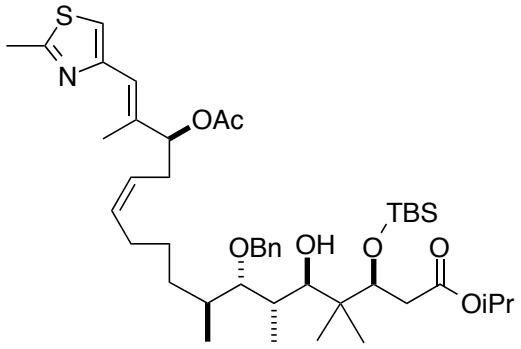
23

Preparation of Compound 23. To a solution of alcohol **22** (152 mg, 0.222 mmol) in CH_2Cl_2 (4 mL) was added Dess-Martin periodinane (190 mg, 0.448 mmol). The resulting mixture was stirred at room temperature for 1 h, before being transferred to a column of silica gel and eluted with 20% EtOAc in hexane. Removal of solvent afforded aldehyde as light yellow oil (140 mg, 92%). A solution of this aldehyde (140 mg, 0.205 mmol) in CH_2Cl_2 (1 mL) was treated with silyl ketene acetal **6** (0.08 mL, 0.41 mmol) and $TiCl_4$ (0.03 mL, 0.274 mmol) at –78 ºC for 15 min. The reaction was quenched with EtOAc (3 mL) and H_2O (3 mL) and the mixture was extracted with EtOAc (15 mL x 3). The organic layer was washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Purification by flash chromatography (silica, 20% EtOAc in hexane) afforded alcohol **23** as light yellow oil (140 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.92 (s, 1H), 6.50 (s, 1H), 5.48 (m, 1H), 5.29 (m, 1H), 5.25 (t, 1H, *J* = 7 Hz), 4.98 (qq, 1H, J = 6.2 Hz, 6.2 Hz), 4.60 and 4.52 (ABq, 2H, J = 11.6 Hz), 3.70 (d, 1H, J = 2.8 Hz), 3.56 (dd, 1H, J = 2.8 Hz, 6 Hz), 3.21 (bs, 1H), 2.68 (s, 3H), 2.54-2.30 (m, 4H), 2.13 (m, 1H), 2.08-1.96 (m,2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.83 (m,1H), 1.46 (m, 2H), 1.23 (m, 2H), 1.21 (d, 3H, J = 6.4 Hz), 1.18 (d, 3H, J = 6.4 Hz), 1.12 (d, 3H, J = 7.2 Hz), 0.94 (d, 3H, J = 8.8 Hz), 0.93 (s, 3H), 0.91 (s, 9H), 0.85 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 170.1, 164.5, 152.6, 139.8, 137.4, 132.8, 128.1, 126.9, 124.0, 120.6, 116.2, 83.3, 79.8, 78.6, 73.1, 71.5, 68.2, 43.7, 40.2, 37.1, 36.7, 31.1, 31.0, 28.0, 27.9, 26.5, 26.4, 21.8, 21.2, 20.9, 19.5, 19.2, 18.7, 16.8, 14.8, -2.4, -4.6; IR (neat) νmax: 3516, 2930, 1737, 1464, 1373, 1237, 1109, 1062; CIHRMS $[M+H]^+$ calculated for $C_{44}H_{72}NSSiO_7$: 786.4799, found: 786.4771; $[\alpha]^{23}_D$ = -13.2° (*c* = 1.05, CH_2Cl_2).



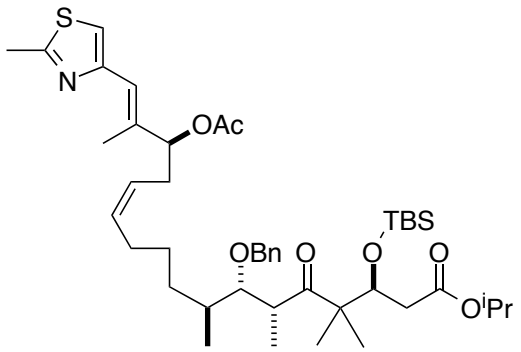
24

Preparation of Compound 24. To a solution of silyl ether **23** (130 mg, 0.166 mmol) in THF (5 mL) at 0 ºC was added tetrabutylammonium fluoride (TBAF) (1.0 **M** solution in THF, 0.5 mL, 0.5 mmol). The reaction was kept at 0 ºC for 10 min before being quenched with saturated aqueous NH_4Cl (3 mL). The resulting mixture was extracted with EtOAc (20 mL x 3). The organic layer was washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Purification by flash chromatography (silica, 30% EtOAc in hexane) afforded diol **24** as light yellow oil (99 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.92 (s, 1H), 6.50 (s, 1H), 5.47 (m, 1H), 5.30 (m, 1H), 5.25 (t, 1H, *J* = 6.8 Hz), 5.02 (qq, 1H, *J* = 6.4 Hz, 6.4 Hz), 4.61 and 4.47 (ABq, 2H, *J* = 11.2 Hz), 4.05 (bs, 1H), 4.00 (dd, 1H, *J* = 2.8 Hz, 10 Hz), 3.73 (d, 1H, *J* = 6.4 Hz)), 3.50 (d, 1H, *J* = 3.6 Hz), 2.68 (s, 3H), 2.52-2.32 (m, 4H), 2.10-1.88 (m, 3H), 2.04 (s, 6H), 1.66-1.42 (m,2H), 1.34-1.12 (m, 3H), 1.22 (d, 3H, *J* = 6.4 Hz), 1.22 (d, 3H, *J* = 7.2 Hz), 1.08 (d, 3H, *J* = 6.8 Hz), 0.97 (s, 3H), 0.94 (d, 3H, *J* = 6.8 Hz), 0.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 170.1, 164.6, 152.5, 138.4, 137.3, 132.5, 128.4, 127.6, 127.5, 124.2, 120.6, 116.2, 83.7, 83.5, 78.5, 75.8, 71.7, 68.0, 41.7, 37.3, 35.7, 35.2, 32.8, 31.1, 27.7, 27.6, 27.5, 21.8, 21.2, 19.2, 16.5, 16.1, 14.8; IR (neat) νmax: 3461, 2975, 2933, 1736, 1498, 1454, 1373, 1238, 1181, 1109; CIHRMS $[M]^+$ calculated for $C_{38}H_{57}NSO_7$: 671.3855, found: 671.3882; $[\alpha]^{23}_D$ = -7.2° (*c* = 0.25, CH_2Cl_2).



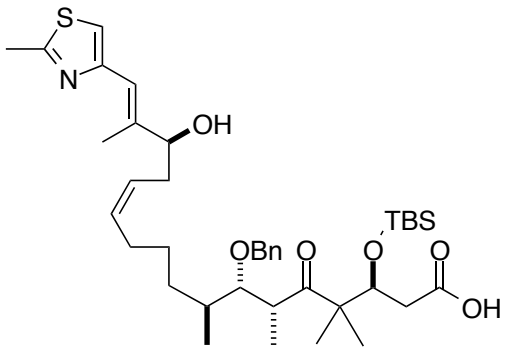
25

Preparation of Compound 25. To a solution of diol **24** (99 mg, 0.148 mmol) in DMF (1 mL) was added imidazole (0.30 g, 4.41 mmol) followed by TBSCl (0.33 g, 2.19 mmol). The resulting solution was stirred at room temperature for 36 h before being quenched by addition of H_2O (5 mL). The mixture was extracted with EtOAc (20 mL x 3), and the organic layer was washed with H_2O (5 mL), saturated aqueous NaCl (5 mL), and dried over $MgSO_4$. Purification by flash chromatography (silica, 20 % EtOAc in hexane) afforded silyl ether **25** as light yellow oil (105 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 6.92 (s, 1H), 6.50 (s, 1H), 5.47 (m, 1H), 5.28 (m, 1H), 5.25 (t, 1H, *J* = 6.8 Hz), 4.95 (qq, 1H, *J* = 6.4 Hz, 6.4 Hz), 4.59 and 4.53 (ABq, 2H, *J* = 11.2 Hz), 4.14 (t, 1H, *J* = 4.8 Hz), 3.70 (d, 1H, *J* = 6.8 Hz)), 3.42 (s, 1H), 2.75 (dd, 1H, *J* = 4.8 Hz, 17.2 Hz), 2.68 (s, 3H), 2.53-2.35 (m, 2H), 2.26 (dd, 1H, *J* = 5.2 Hz, 16.8 Hz), 2.04 (s, 6H), 2.10-1.90 (m, 3H), 1.84 (m, 1H), 1.65-1.40 (m, 2H), 1.35-1.20 (m, 2H), 1.20 (d, 3H, *J* = 6.4 Hz), 1.17 (d, 3H, *J* = 6 Hz), 1.04 (d, 3H, *J* = 6.8 Hz), 0.93 (s, 3H), 0.90 (d, 3H, *J* = 6.4 Hz), 0.85 (s, 9H), 0.84 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 170.1, 164.5, 152.6, 139.1, 137.4, 132.7, 128.3, 127.3, 124.0, 120.6, 116.1, 83.8, 78.9, 78.6, 75.1, 72.4, 67.9, 43.6, 39.9, 36.2, 36.1, 32.8, 31.1, 27.8, 27.5, 26.0, 21.8, 21.7, 21.2, 20.2, 19.6, 19.2, 18.2, 16.5, 15.0, 14.8, -4.2, -4.9; IR (neat) νmax: 3410, 2929, 2857, 1738, 1463, 1370, 1237, 1182, 1067; CIHRMS $[M+H]^+$ calculated for $C_{44}H_{72}NSSiO_7$: 786.4799, found: 786.4770; $[\alpha]^{23}_D$ = -9.0° (*c* = 0.67, CH_2Cl_2).



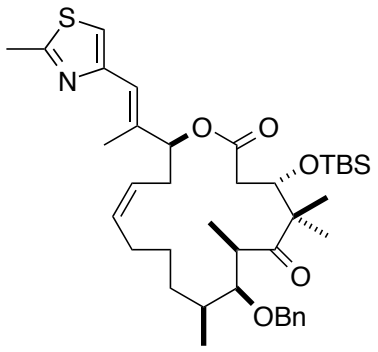
26

Preparation of Compound 26. The alcohol **25** (100 mg, 0.127 mmol) was dissolved in CH_2Cl_2 (4 mL), and Dess-Martin periodinane (162 mg, 0.382 mmol) was added. After 2 h at room temperature, the reaction mixture was transferred to a silica gel column and washed with 10% and 20% EtOAc in hexane. The solvent was removed in vacuo to give ketone **26** as light yellow oil (95 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 6.91 (s, 1H), 6.49 (s, 1H), 5.44 (m, 1H), 5.29 (m, 1H), 5.25 (t, 1H, *J* = 7.2 Hz), 4.98 (qq, 1H, *J* = 6 Hz, 6 Hz), 4.56 and 4.48 (ABq, 2H, *J* = 10.6 Hz), 4.36 (dd, 1H, *J* = 3.2 Hz, 6.4 Hz), 3.44 (dd, 1H, *J* = 4 Hz, 6.4 Hz)), 3.29 (dq, 1H, *J* = 6.6 Hz, 6.6 Hz), 2.68 (s, 3H), 2.52-2.34 (m, 3H), 2.21 (dd, 1H, *J* = 6 Hz, 12.8 Hz), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (m, 2H), 1.54-1.34 (m, 3H), 1.30-1.16 (m, 2H), 1.24 (s, 3H), 1.22 (d, 3H, *J* = 6.4 Hz), 1.21 (d, 3H, *J* = 6.4 Hz), 1.12 (d, 3H, *J* = 6.8 Hz), 1.06 (s, 3H), 0.93 (s, 3H), 0.95 (d, 3H, *J* = 6.8 Hz), 0.85 (s, 9H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.7, 171.5, 170.1, 164.6, 152.6, 138.9, 137.4, 132.7, 128.3, 127.8, 127.4, 124.1, 120.6, 116.2, 85.0, 78.5, 75.3, 74.21, 67.9, 53.5, 44.8, 40.6, 37.5, 31.1, 30.9, 29.7, 27.9, 27.6, 26.0, 23.3, 21.9, 21.8, 21.2, 20.0, 19.2, 18.2, 17.8, 14.8, 14.0, -4.4, -4.6; IR (neat) νmax: 2933, 1735, 1695, 1471, 1373, 1237, 1090; CIHRMS $[M+H]^+$ calculated for $C_{44}H_{70}NSSiO_7$: 784.4628, found: 784.4635; $[\alpha]^{23}_{D}$ = -29.8° (*c* = 0.33, CH_2Cl_2).



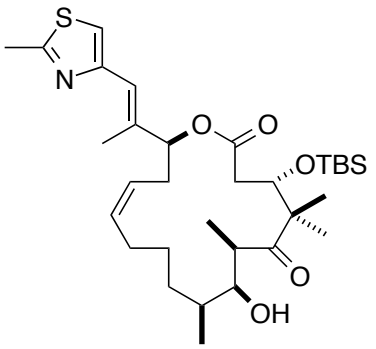
27

Preparation of Compound 27. To a solution of ketone **26** (90 mg, 0.115 mmol) in MeOH (10 mL) was added 2 **N** NaOH aqueous solution (5 mL). The resulting mixture was stirred at room temperature for 10 min before being heated under reflux condition for 1.5 h. The solution was cooled to room temperature and MeOH was partially removed under reduced pressure. The solution was then acidified with 1 **N** HCl aqueous solution to pH = 3~4 and the mixture was extracted with EtOAc (15 mL x 4). The organic layer was washed with saturated aqueous NaCl (5 mL) and dried over $MgSO_4$. Purification by flash chromatography (silica, 2% MeOH in CH_2Cl_2) afforded hydroxyl acid **26** as light yellow oil (50 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.22 (m, 5H), 6.93 (s, 1H), 6.63 (s, 1H), 5.53 (m, 1H), 5.38 (m, 1H), 5.25 (t, 1H, *J* = 7.2 Hz), 4.58 and 4.50 (ABq, 2H, *J* = 10.8 Hz), 4.41 (dd, 1H, *J* = 3.6 Hz, 6.4 Hz), 4.16 (t, 1H, *J* = 6.2 Hz), 3.47 (dd, 1H, *J* = 4 Hz, 7.2 Hz)), 3.29 (dq, 1H, *J* = 6.8 Hz, 6.8 Hz), 2.69 (s, 3H), 2.54-2.26 (m, 4H), 2.16-1..95 (m, 2H), 1.99 (s, 3H), 1.75-1.40 (m, 3H), 1.26-1.10 (m, 2H), 1.19 (s, 3H), 1.15 (d, 3H, *J* = 6.8 Hz), 1.13 (s, 3H), 0.86 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.8, 175.0, 165.0, 152.6, 141.8, 138.9, 133.4, 128.2, 127.7, 127.4, 124.9, 118.8, 115.2, 84..8, 77.2, 75.1, 73.5, 54.0, 44.3, 40.0, 37.3, 33.5, 30.9, 27.9, 27.6, 26.0, 23.4, 19.1, 18.8, 18.2, 17.6, 14.7, 14.6, -4.1, -4.6; IR (neat) νmax: 3400, 2930, 2857, 1696, 1472, 1255, 1191, 1091; CIHRMS $[M+H]^+$ calculated for $C_{39}H_{62}NSSiO_6$: 700.4067, found: 700.4012; $[\alpha]^{23}_D$ = -38.2° (*c* = 0.55, CH_2Cl_2).



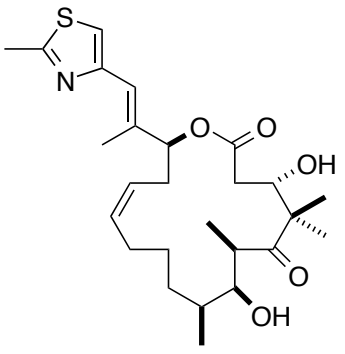
28

Macrolactonization to Produce Compound 28. To a solution of hydroxyl acid **27** (10 mg, 0.014 mmol) in THF (0.5 mL) was added Et_3N (0.02 mL, 0.144 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.015 mL, 0.096 mmol). The resulting solution was stirred at 0 °C for 15 min before being diluted with toluene (2 mL), and added dropwise to a solution of DMAP (26 mg, 0.21 mmol) in toluene (8 mL). The mixture was then stirred at room temperature for 30 min and concentrated in vacuo. Purification by flash chromatography (silica, 20% EtOAc in hexane) afforded lactone **28** as light yellow oil (7.1 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.93 (s, 1H), 6.51 (s, 1H), 5.52 (dt, 1H, J = 3.2 Hz, 11.2 Hz), 5.36 (dt, 1H, J = 6.8 Hz, 10 Hz), 4.98 (d, 1H, *J* = 10.4 Hz), 4.69 and 4.60 (ABq, 2H, *J* = 10.8 Hz), 4.00 (d, 1H, *J* = 10 Hz), 3.69 (d, 1H, *J* = 9.6 Hz), 3.14 (dq, 1H, *J* = 7.2 Hz, 9.6 Hz), 2.82-2.60 (m, 2H), 2.69 (s, 3H), 2.36 (m, 1H), 2.08 (s, 3H), 2.05-1.97 (m, 1H), 1.85 (m, 1H), 1.68-1.52 (m, 3H), 1.32-0.98 (m, 3H), 1.19 (d, 3H, *J* = 6.4 Hz), 1.18 (s, 3H), 1.14 (s, 3H), 1.06 (d, 3H, *J* = 7.2 Hz), 0.84 (s, 9H), 0.11 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 171.1, 164.7, 152.5, 139.1, 138.4, 135.0, 128.3, 127.6, 127.4, 122.7, 119.8, 116.3, 87.1, 79.8, 77.2, 76.1, 53.4, 47.8, 38.9, 37.0, 31.8, 31.5, 29.3, 28.3, 26.2, 24.9, 24.0, 20.1, 19.2, 18.7, 17.1, 14.8, -3.1, -5.7; IR (neat) νmax: 2929, 1740, 1696, 1464, 1379, 1256, 1160, 1097; CIHRMS $[M]^+$ calculated for $C_{39}H_{59}NSSiO_5$: 681.3883, found: 681.3825; $[\alpha]^{23}_D$ = -10.4° (*c* = 0.45, CH_2Cl_2).



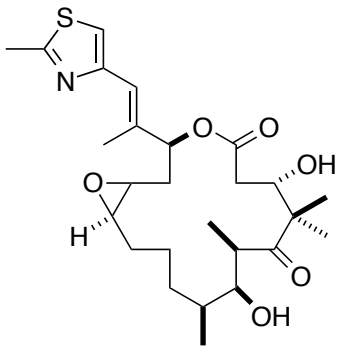
29

Preparation of Compound 29. To a solution of lactone **28** (28 mg, 0.041 mmol) in CH_2Cl_2 (4 mL) was added H_2O (1 mL), followed by 2,3-dichloro-5,6-dicyano-1,4-bennzoquinone (DDQ) (100 mg, 0.44 mmol). The reaction was vigorously stirred for 2.5 h before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (15 mL x 2) and diethyl ether (10 mL), and the organic layers were combined and dried over $MgSO_4$. Purification by flash chromatography (silica gel, 30% EtOAc in hexane) afforded lactone **29** as white solid (20 mg, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.55 (s, 1H), 5.44 (dt, 1H, J = 3.2 Hz, 11.2 Hz), 5.33 (m, 1H), 5.01 (d, 1H, *J* = 9.6 Hz), 4.04 (dd, 1H, *J* = 5.6 Hz, 6.8 Hz), 3.92 (bs, 1H), 3.04 (dq, 1H, *J* = 2.8 Hz, 6.8 Hz), 2.98 (bs, 1H), 2.79 (d, 2H, J = 7.2 Hz), 2.76-2.67 (m, 1H), 2.70 (s, 3H), 2.34 (m, 1H), 2.16-2.05 (m, 1H), 2.09 (s, 3H), 1.95 (m, 1H), 1.76 (m, 1H), 1.62 (m, 1H), 1.45 (m, 1H), 1.30-1.10 (m, 2H), 1.15 (s, 6H), 1.12 (d, 3H, *J* = 6.4 Hz), 1.00 (d, 3H, *J* = 6.8 Hz), 0.81 (s, 9H), 0.10 (s, 3H), -0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.9, 170.8, 164.6, 152.5, 138.3, 134..6, 124.1, 119.6, 116.1, 79.1, 76.3, 73.3, 53.6, 43.1, 39.2, 38.8, 33.6, 32..0, 28..4, 27.9, 26.2, 24.7, 23.0, 19.2, 18.6, 16.5, 15.3, 14.1, -3.6, -5.4; IR (neat) νmax: 3462, 2927, 2855, 1740, 1695, 1507, 1464, 1389, 1261, 1182, 1098; CIHRMS $[M]^+$ calculated for $C_{32}H_{53}NSSiO_5$: 591.3413, found: 591.3412; $[\alpha]^{23}_D$ = -44.3° (*c* = 0.30, CH_2Cl_2).



30

Preparation of Compound 30. To a solution of lactone **29** (18 mg, 0.030 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (TFA) (0.5 mL). The reaction was stirred at room temperature for 2.5 h before being concentrated under reduced pressure. The residue was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 33% EtOAc in hexane) afforded dihydroxy lactone **30** as white foam (13 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.58 (s, 1H), 5.41 (ddt, 1H, J = 4.4 Hz, 10 Hz, 10 Hz), 5.34 (ddt, 1H, J = 4.8 Hz, 10 Hz, 10 Hz), 5.27 (dd, 1H, *J* = 1.2 Hz, 9.6 Hz), 4.22 (d, 1H, *J* = 10.8 Hz), 3.71 (bs, 1H), 3.32 (bs, 1H), 3.12 (dq, 1H, *J* = 2 Hz, 6.8 Hz), 3.03 (bs, 1H), 2.71-2.62 (m, 1H), 2.68 (s, 3H), 2.48 (dd, 1H, *J* = 11.6 Hz, 15.2 Hz), 2.33 (dd, 1H, *J* = 2.8 Hz, 15.2 Hz), 2.28-2.12 (m, 2H), 2.06 (d, 3H, *J* = 0.8 Hz), 2.04-1.96 (m, 1H), 1.74 (m, 1H), 1.67 (m, 1H), 1.38-1.28 (m, 1H), 1.31 (s, 3H), 1.26-1.14 (m, 2H), 1.16 (d, 3H, *J* = 6.8 Hz), 1.06 (s, 3H), 0.98 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.4, 170.3, 165.0, 152.1, 138.6, 133.5, 125.0, 119.5, 115.9, 78.5, 74.1, 72.5, 53.3, 41.9, 39.3, 38.5, 32.4, 31.8, 27.6, 27.5, 22.6, 19.1, 18.8, 15.8, 15.6, 13.5; IR (neat) νmax: 3409, 2923, 1734, 1686, 1464, 1260, 1152, 1092; CIHRMS $[M+H]^+$ calculated for $C_{26}H_{40}NSO_5$: 478.2627, found: 478.2640; $[\alpha]^{23}_D$ = -82.1° (*c* = 0.28, CH_2Cl_2).



epothilone A (**1**)

Preparation of Epothilone A (1). To a solution of di-hydroxyl lactone **30** (7 mg, 0.0147 mmol) in MeOH (0.3 mL) was added CH_3CN (0.03 mL, 0.575 mmol), $KHCO_3$ (5 mg, 0.05 mmol) and 30% aqueous H_2O_2 (0.03 mL, 0.265 mmol). The reaction was stirred at room temperature for 4 h before additional CH_3CN (0.03 mL, 0.575 mmol), $KHCO_3$ (5 mg, 0.05 mmol) and 30% aqueous H_2O_2 (0.03 mL, 0.265 mmol) was added. Another portion of above reagents was added after 12 h, and the reaction was stirred for another 8 h. The reaction mixture was then passed through a short column of silica gel and eluted with 4:1 EtOAc/hexane. Concentration and purification by flash chromatography (silica gel, 40% EtOAc in hexane) afforded recovered di-hydroxy lactone **30** (2 mg) and epothilone A (**1**) (3 mg, 60% based on recovered starting material). ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.56 (s, 1H), 5.39 (dd, 1H, *J* = 2 Hz, 9.2 Hz), 4.17 (ddd, 1H, *J* = 3.2 Hz, 6.4 Hz, 9.6 Hz), 3.74 (ddd, 1H, *J* = 4 Hz, 4 Hz, 4.8 Hz), 3.67 (d, 1H, *J* = 6.8 Hz), 3.20 (dq, 1H, *J* = 4.8 Hz, 6.8 Hz), 3.00 (dt, 1H, *J* = 8.8 Hz, 4 Hz), 2.88 (dt, 1H, *J* = 8 Hz, 4 Hz), 2.68 (s, 3H), 2.51-2.45 (m, 2H), 2.39 (dd, 1H, *J* = 3.2 Hz, 14.4 Hz), 2.14-2.06 (m, 1H), 2.09 (d, 3H, *J* = 0.8 Hz), 1.86 (dt, 1H, *J* = 14.8 Hz, 8.8 Hz), 1.76-1.66 (m, 2H), 1.58-1.35 (m, 1H), 1.38-1.28 (m, 4H), 1.35 (s, 3H), 1.15 (d, 3H, *J* = 6.8 Hz), 1.07 (s, 3H), 0.99 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.4, 171.1, 165.8, 152.7, 138.3, 120.4, 116.9, 77.4, 75.1, 73.7, 58.0, 55.3, 53.9, 44.0, 39.8, 37.0, 32.3, 31.1, 30.3, 28.0, 24.1, 22.2, 20.5, 19.5, 17.5, 15.8, 14.5; IR (neat) νmax; 3464, 2926, 1737, 1689, 978; CIHRMS $[M+H]^+$ calculated for $C_{26}H_{40}NO_6S$: 494.2576, found: 494.2553; $[\alpha]^{23}_D$ = -42.05° (*c* = 0.20, MeOH).