Total Synthesis of Apoptolidin A

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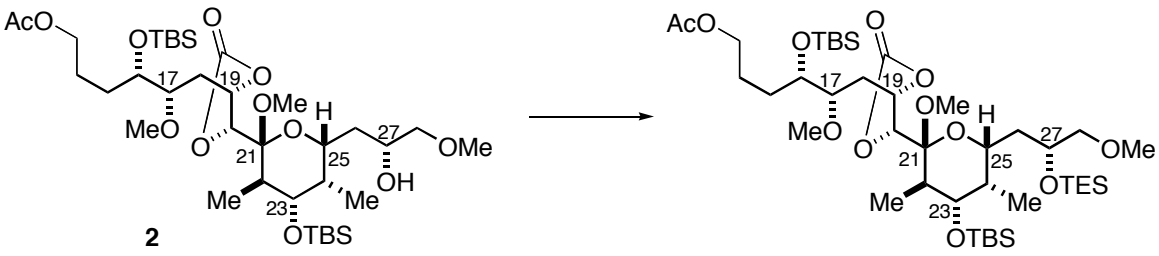
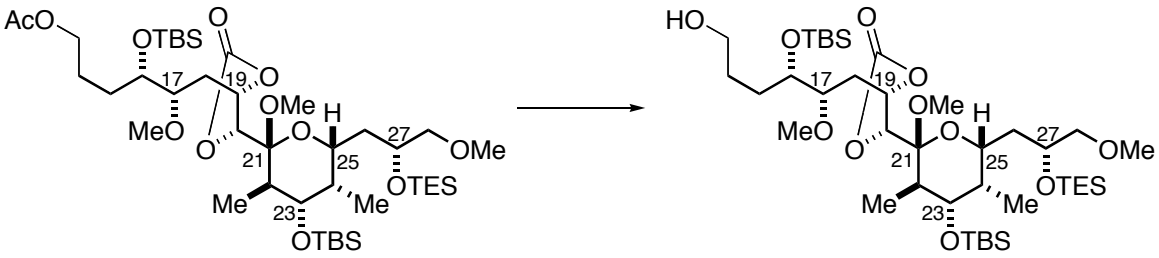
Supporting Information: Experimental Procedures

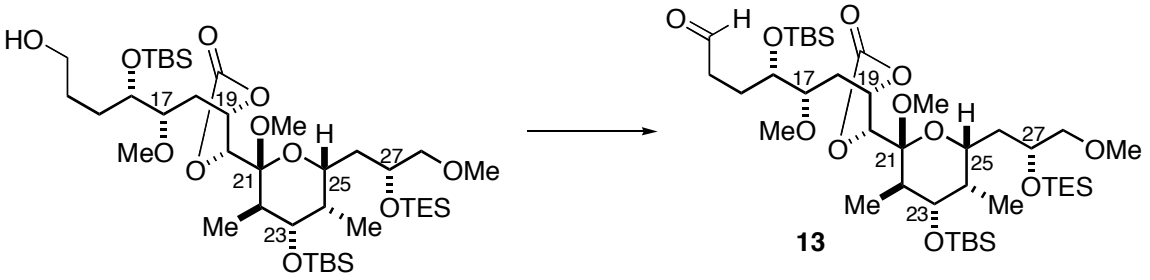


Conversion of Alcohol 2 to the triethylsilylether. A solution of alcohol **2** (536 mg, 0.714 mmol) and Et_3N (0.150 mL, 1.08 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C. To the stirring solution was added triethylsilyl chloride (0.145 mL, 0.864 mmol), and then DMAP (4.0 mg, 0.033 mmol). The solution became cloudy as a dense white precipitate formed. After 30 min saturated $NaHCO_3$ solution was added and the mixture was stirred vigorously. The mixture was diluted with H_2O and CH_2Cl_2 then the layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x). The combined organic solution was dried (Na_2SO_4) and evaporated. Chromatography, eluting with 14:86 EtOAc/hexanes, afforded 579 mg (94%) of the TES ether as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.09 (s, 3H), 0.53-0.66 (band, 6H), 0.84 (d, J = 7.0, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 0.94 (t, J = 8.0, 9H), 0.98 (d, J = 6.5, 3H), 1.22-1.32 (m, 1H), 1.48 (ddd, J = 14.0, 8.0, 3.5, 1H), 1.54-1.83 (band, 6H), 1.90-2.00 (band, 2H), 2.04 (s, 3H), 3.24 (dd, J = 9.5, 6.0, 1H), 3.25 (s, 3H), 3.27-3.32 (m, 1H), 3.30 (s, 3H), 3.35-3.40 (m, 1H), 3.39 (s, 3H), 3.71 (dd, J = 10.5, 4.5, 1H), 3.83-3.93 (band, 3H), 4.01-4.09 (band, 2H), 4.35 (d, J = 5.0, 1H), 4.89 (ddd, J = 10.5, 4.5, 2.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.9, -4.7, -4.40, -4.36, 4.9, 5.3, 6.9, 11.6, 17.9, 18.0, 20.9, 25.4, 25.7, 25.8, 27.1, 34.5, 35.2, 38.3, 39.5, 48.8, 58.3, 58.7, 64.4, 69.0, 69.3, 70.2, 73.4, 75.5, 77.6, 79.3, 80.7, 100.0, 153.9, 171.0; IR (thin film) ν 2954(s), 2884(s), 2858(s), 1816(s), 1741(s), 1463(m), 1364(m), 1249(s), 1072(s); $[\alpha]^{20}_D$ = +11 (*c* 4.5, CH_2Cl_2); MS (ESI) calculated for $C_{42}H_{84}NaO_{12}Si_3$ $[MNa]^+$: *m/z* 887.5, found: *m/z* 887.4.

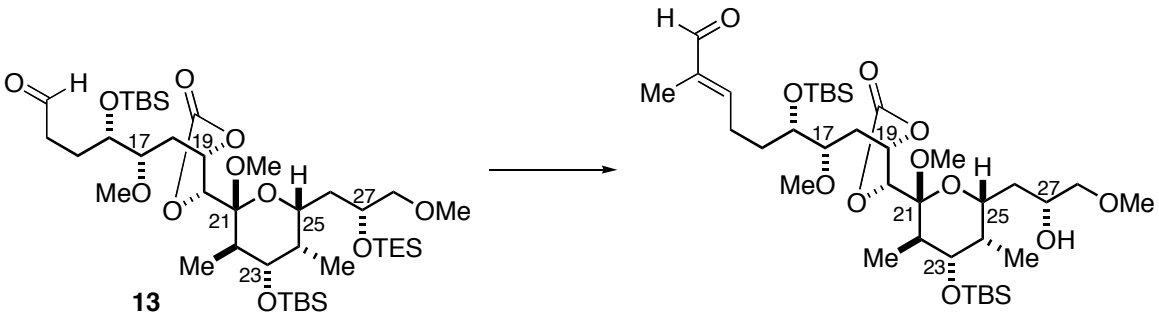


Cleavage of the C12 Acetate. A solution of the C12 acetate from the previous reaction (575 mg, 0.664 mmol) in MeOH (5 mL) and THF (5 mL) was cooled in an ice-water bath. Powdered K_2CO_3 (500 mg, 3.62 mmol) was added in one portion and the resulting heterogeneous mixture stirred vigorously. After 3 h at 0 °C TLC analysis indicated that the desired reaction was complete. Saturated $NaHCO_3$ solution, H_2O, and CH_2Cl_2 were added and the mixture was shaken and the layers were separated. The aqueous solution was extracted with CH_2Cl_2 (3x) and the combined organic solution was dried (Na_2SO_4)

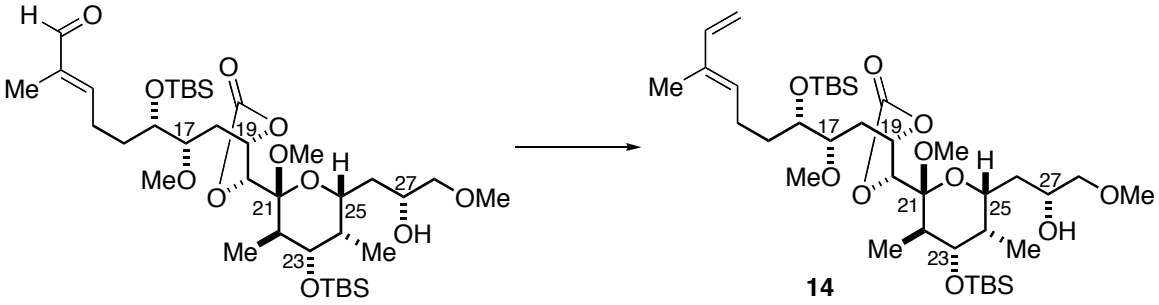
and concentrated in vacuo. The residue was purified by chromatography eluting with 1:3 EtOAc/hexanes afforded 522 mg (95%) of the C12 alcohol as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.53-0.65 (band, 6H), 0.84 (d, *J* = 7.0, 3H), 0.876 (s, 9H), 0.881 (s, 9H), 0.94 (t, *J* = 8.0, 9H), 0.97 (d, *J* = 6.5, 3H), 1.26-1.34 (m, 1H), 1.44-1.78 (band, 8H), 1.89-2.00 (band, 2H), 3.25 (dd, *J* = 9.5, 6.0, 1H), 3.25 (s, 3H), 3.30 (dd, *J* = 9.5, 4.5, 1H), 3.31 (s, 3H), 3.36-3.40 (m, 1H), 3.39 (s, 3H), 3.61-3.66 (band, 2H), 3.71 (dd, *J* = 10.5, 4.5, 1H), 3.84-3.93 (band, 3H), 4.34 (d, *J* = 5.0, 1H), 4.89 (ddd, *J* = 10.5, 5.0, 2.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.9, -4.7, -4.42, -4.36, 4.9, 5.3, 6.9, 11.6, 17.9, 18.0, 25.7, 25.8, 27.1, 29.4, 34.6, 35.1, 38.3, 39.5, 48.8, 58.3, 58.7, 62.9, 69.0, 69.2, 70.6, 73.4, 75.5, 77.6, 79.4, 80.7, 100.0, 153.9; IR (thin film) ν 3435(br), 2954(s), 2884(s), 2858(s), 1816(s), 1463(m), 1385(m), 1255(m), 1071(s); $[\alpha]^{21}_D$ = +13 (*c* 4.3, CH_2Cl_2); MS (ESI) calculated for $C_{40}H_{82}NaO_{11}Si_3$ $[MNa]^+$: *m*/*z* 845.5, found: *m*/*z* 845.4.



Aldehyde 13. A stirring solution of dimethyl sulfoxide (0.020 mL, 0.28 mmol) in CH_2Cl_2 (0.500 mL) was cooled in a dry ice/acetone bath. Oxalyl chloride (0.080 mL of a 2.0 M solution in CH_2Cl_2, 0.16 mmol) was added over 2 min. After stirring at -78 °C for 30 min the primary alcohol obtained from the reaction above (41.3 mg, 0.0501 mmol) was added as a solution in CH_2Cl_2 (0.25 mL + 2x0.1 mL rinses) over 5 min. After stirring at -78 °C for 30 min, Et_3N (0.070 mL, 0.50 mmol) was added and the reaction mixture was stirred for 15 min at -78 °C before being allowed to warm to rt. The reaction mixture was shaken with 0.5 N $NaHSO_4$ (2 mL) and the layers were separated. The aqueous solution was extracted with CH_2Cl_2 (3x) and the combined organic solution wsa dried (Na_2SO_4) and concentrated. The reside was purified by flash chromatography, eluting with 13:87 EtOAc/hexanes, affording 37.9 mg (92%) of aldehyde **13** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.057 (s, 3H), 0.064 (s, 3H), 0.09 (s, 3H), 0.54-0.66 (band, 6H), 0.85 (d, *J* = 7.0, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 0.95 (t, *J* = 8.0, 9H), 0.99 (d, *J* = 7.0, 3H), 1.46-1.57 (band, 2H), 1.62-1.74 (band, 3H), 1.87-2.02 (band, 3H), 2.44-2.52 (m, 1H), 2.54-2.62 (m, 1H), 3.256 (dd, *J* = 9.5, 6.0, 1H), 3.260 (s, 3H), 3.31 (dd, *J* = 9.5, 4.5, 1H), 3.32 (s, 3H), 3.396 (ddd, *J* = 11.0, 4.0, 1.0, 1H), 3.403 (s, 3H), 3.72 (dd, *J* = 10.0, 4.5, 1H), 3.87-3.94 (band, 3H), 4.35 (d, *J* = 5.0, 1H), 4.90 (ddd, *J* = 10.5, 7.5, 2.5, 1H), 9.79 (t, *J* = 1.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.8, -4.7, -4.4, -4.3, 4.9, 5.3, 6.9, 11.6, 17.9, 18.1, 23.0, 25.7, 25.8, 34.4, 35.2, 38.3, 39.5, 40.5, 48.8, 58.3, 58.8, 69.0, 69.28, 69.34, 73.4, 75.4, 77.7, 79.2, 80.7, 100.0, 153.9, 202.0; IR (thin film) ν 2954(s), 2885(s), 2858(s), 1815(s), 1727(m), 1463(m), 1387(m), 1255(m), 1073(s); $[\alpha]^{22}_D$ = +12 (*c* 1.5, CH_2Cl_2); MS (ESI) calculated for $C_{40}H_{80}NaO_{11}Si_3$ $[MNa]^+$: *m*/*z* 843.4, found: *m*/*z* 843.3.

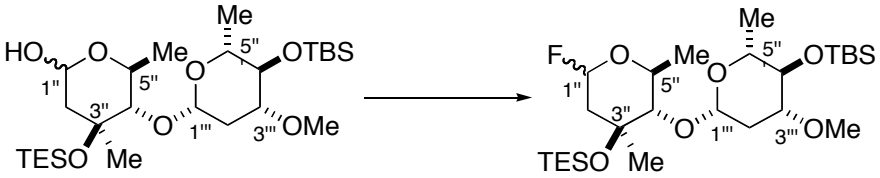


Wittig olefination of aldehyde 13. A stirring mixture of aldehyde **13** (37.9 mg, 0.0461 mmol) and (α-formylethylidene)triphenylphosphorane (44.0 mg, 0.138 mmol) in chlorobenzene (0.40 mL) was heated at 95 °C (the solution became homogeneous at this temperature). After 15 h ^{1}H NMR analysis indicated that the reaction was complete. The solution was allowed to cool, and was then evaporated to dryness. The orange/brown solid was boiled in hexanes and after cooling the solid was filtered off and washed with hexanes. The combined hexanes solution was evaporated. The residual oil was purified by flash chromatography, eluting with 35:65 EtOAc/hexanes providing 26.1 mg (76%) of the desired unsaturated aldehyde as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.84 (d, *J* = 7.0, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 0.97 (d, *J* = 7.0, 3H), 1.33 (ddd, *J* = 14.0, 10.5, 1.5, 1H), 1.41 (dddd, *J* = 14.5, 10.0, 10.0, 5.0, 1H), 1.55-1.78 (band, 4H), 1.75 (s, 3H), 1.90-2.03 (band, 2H), 2.29 (m, 1H), 2.36 (br. d, *J* = 3.0, 1H), 2.52 (m, 1H), 3.19 (dd, *J* = 9.0, 8.0, 1H), 3.27 (s, 3H), 3.37 (s, 3H), 3.36-3.47 (band, 2H), 3.42 (s, 3H), 3.76 (dd, *J* = 10.5, 5.0, 1H), 3.90 (ddd, *J* = 9.0, 4.0, 1.0, 1H), 3.95 (tm, *J* = 7.5, 1H), 4.06 (dm, *J* = 11.0, 1H), 4.32 (d, *J* = 5.0, 1H), 4.96 (ddd, *J* = 11.0, 5.0, 2.5, 1H), 6.48,(ddd, *J* = 7.0, 7.0, 1.0, 1H), 9.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, -4.29, -4.26, 5.0, 9.2, 11.6, 17.9, 18.1, 25.7, 25.8, 25.9, 29.6, 34.5, 35.4, 36.2, 39.3, 48.8, 58.5, 59.1, 66.8, 67.6, 70.3, 73.2, 75.1, 77.4, 79.3, 81.1, 100.0, 139.6, 153.9, 195.0; IR (thin film) ν 3502(br), 2953(s), 2929(s), 2889(s), 2857(s), 1812(s), 1686(s), 1645(w), 1463(m), 1383(m), 1255(m), 1073(s); $[\alpha]^{25}_D$ = +12 (*c* 1.9, CH_2Cl_2); MS (ESI) calculated for $C_{37}H_{70}NaO_{11}Si_2$ $[MNa]^+$: *m/z* 769.4, found: *m/z* 769.2.

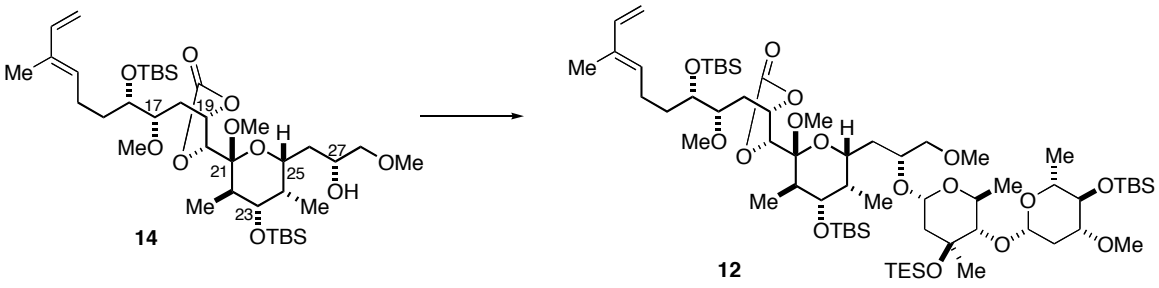


Diene 14. A stirring suspension of methyltriphenylphosphonium bromide (357 mg, 1.00 mmol) in THF (1 mL) was cooled in an ice bath. A solution of KO*t*-Bu (112 mg, 1.00 mmol) in THF (1 mL) was added, dropwise. The yellow methylenetriphenylphosphorane solution was stirred at rt for 0.5 h. Methylenetriphenylphosphorane solution was added dropwise to a stirring solution of the unsaturated aldehyde from the reactionabove (205 mg, 0.274 mmol) in THF (2.0 mL), until a bright yellow color persisted. The reaction

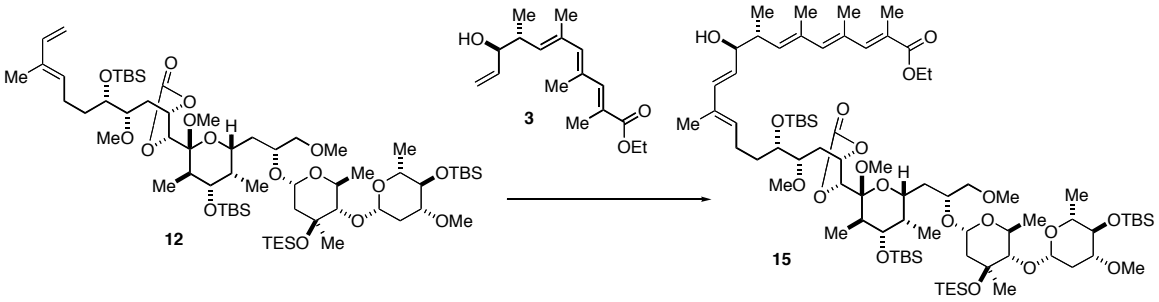
mixture was diluted with saturated NH_4Cl solution and CH_2Cl_2. The mixture was shaken and separated. The aqueous solution was extracted with CH_2Cl_2 (3x) and the combined organic solution was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography, eluting with 1:3 EtOAc/hexanes, affording 163 mg (81%) of diene **14** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.84 (d, *J* = 6.5, 3H), 0.886 (s, 9H), 0.894 (s, 9H), 0.98 (d, *J* = 7.0, 3H), 1.24-1.37 (band, 2H), 1.55-1.72 (band, 4H), 1.74 (s, 3H), 1.92-2.00 (band, 2H), 2.07 (m, 1H), 2.31 (m, 1H), 2.35 (d, *J* = 3.0, 1H), 3.19 (dd, *J* = 9.0, 8.0, 1H), 3.27 (s, 3H), 3.36-3.42 (band, 2H), 3.37 (s, 3H), 3.40 (s, 3H), 3.76 (dd, *J* = 10.0, 4.5, 1H), 3.86 (ddd, *J* = 9.0, 4.0, 3.0, 1H), 3.95 (m, 1H), 4.05 (dm, *J* = 11.0, 1H), 4.33 (d, *J* = 5.0, 1H), 4.93 (d, *J* = 11.0, 1H), 4.95 (ddd, *J* = 11.0, 5.0, 2.5, 1H), 5.09 (d, *J* = 17.5, 1H), 5.47 (t, *J* = 7.0, 1H), 6.34 (dd, *J* = 17.5, 11.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.8, -4.7, -4.34, -4.25, 5.0, 11.6, 11.7, 17.97, 18.06, 25.0, 25.77, 25.81, 30.6, 34.6, 35.4, 36.1, 39.3, 48.7, 58.4, 59.0, 66.7, 67.6, 70.4, 73.2, 75.3, 77.3, 79.4, 81.0, 100.0, 110.7, 132.4, 134.4, 141.3, 154.0; IR (thin film) ν 3486(br), 2929(s), 2890(s), 2857(s), 1815(s), 1606(w), 1463(m), 1387(m), 1255(m), 1074(s); $[\alpha]^{22}_D$ = +11 (*c* 2.0, CH_2Cl_2); MS (ESI) calculated for $C_{38}H_{72}NaO_{10}Si_2$ $[MNa]^+$: *m/z* 767.5, found: *m/z* 767.2.



Fluoride 4. A solution of hemiacetal **10** (113 mg, 0.211 mmol) in CH_2Cl_2 (3.0 mL) was cooled to 0 ˚C and (diethylamino)sulfur trifluoride (DAST) (0.055 mL, 0.42 mmol) was added via syringe. After 10 min TLC analysis indicated that the starting material had been consumed. After 30 min saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic solution was dried (Na_2SO_4) then evaporated. The unpurified fluoride **4** (>10:1 α:β) was used directly for the next transformation. ^{1}H NMR (400 MHz, C_6D_6) δ 0.12 (s, 3H), 0.21 (s, 3H), 0.42-0.55 (band, 6H), 0.92 (t, *J* = 8.0, 9H), 1.00 (s, 9H), 1.37 (d, *J* = 6.5, 3H), 1.54 (s, 3H), 1.55-1.70 (m, 2H), 1.61 (d, *J* = 6.0, 3H), 1.96 (dd, *J* = 14.0, 4.5, 1H), 2.51 (ddd, *J* = 12.5, 5.0, 2.0, 1H), 3.10 (s, 3H), 3.15 (ddd, *J* = 13.0, 8.5, 5.0, 1H), 3.27 (t, *J* = 9.0, 1H), 3.30-3.38 (m, 1H), 3.63 (d, *J* = 10.0, 1H), 4.05 (m, 1H), 5.01 (dd, *J* = 9.5, 1.5, 1H), 5.41 (dd, *J* = 53.5, 2.5, 1H).



Diene 12. Fluoride **4** (crude from the above procedure) and diene **14** (160 mg, 0.215 mmol) were dissolved in CH_2Cl_2, and the solvent was evaporated from a 10-mL round-bottomed flask. The mixture was dissolved in Et_2O (3 mL) and freshly activated 4 Å molecular sieve powder (1.00 g) was added and the mixture was stirred vigorously for 0.5 h. The mixture was cooled to 0 ˚C and powdered $SnCl_2$ (0.230 g, 1.21 mmol) was added in one portion. After stirring at 0 ˚C for 2 h, Et_3N (0.20 mL, 1.51 mmol) was added and, after stirring for another 30 min, Celite (~0.5 g) was added. The mixture was filtered through a pad of Celite with repeated washing with EtOAc. The combined organic solution was washed with 2:1 H_2O/saturated $NaHCO_3$, and the aqueous solution was extracted with EtOAc (3x). The combined organic solution was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography, eluting with 9:91-1:3 EtOAc/hexanes, affording 170 mg (64%) of disaccharide **12** as a colorless oil, 25.3 mg (9.5%) of the β-anomer and 34.1 mg (21%) of recovered diene **14**. **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.056 (s, 3H), 0.060 (s, 3H), 0.072 (s, 3H), 0.074 (s, 3H), 0.09 (s, 3H), 0.53-0.62 (band, 6H), 0.84 (d, *J* = 7.5, 3H), 0.877 (s, 9H), 0.887 (s, 18H), 0.96 (t, *J* = 8.0, 9H), 0.98 (d, *J* = 7.0, 3H), 1.23 (d, *J* = 6.0, 3H), 1.24 (d, *J* = 6.0, 3H), 1.25-1.37 (band, 2H), 1.40 (s, 3H), 1.52-1.76 (band, 5H), 1.73 (s, 3H), 1.86 (dd, *J* = 13.0, 4.0, 1H), 1.90-2.00 (band, 3H), 2.06 (m, 1H), 2.31 (m, 1H), 2.39 (ddd, *J* = 12.0, 4.5, 1.5, 1H), 2.99 (ddd, *J* = 16.5, 8.0, 5.0, 1H), 3.07-3.18 (band, 2H), 3.22 (s, 3H), 3.28 (s, 3H), 3.29 (s, 3H), 3.32 (d, *J* = 10.0, 1H), 3.35-3.43 (band, 3H), 3.39 (s, 3H), 3.65-3.73 (band, 3H), 3.78 (dm, *J* = 8.0, 1H), 3.86 (m, 1H), 4.32 (d, *J* = 5.0, 1H), 4.76 (dd, *J* = 9.5, 1.5, 1H), 4.85-4.90 (band, 2H), 4.91 (d, *J* = 11.0, 1H), 5.07 (d, *J* = 17.5, 1H), 5.46 (t, *J* = 7.0, 1H), 6.34 (dd, *J* = 17.5, 11.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.9, -4.8, -4.7, -4.4, -4.3, -4.0, 4.9, 6.9, 7.1, 11.6, 11.7, 17.9, 18.0, 18.30, 18.32, 18.5, 23.4, 25.0, 25.7, 25.8, 26.0, 30.5, 34.6, 35.1, 35.2, 35.7, 39.3, 45.1, 48.6, 56.0, 58.3, 59.0, 66.4, 69.2, 70.1, 72.5, 73.3, 74.3, 75.2, 75.3, 75.4, 76.8, 79.3, 80.6, 81.3, 85.7, 96.6, 100.2, 101.0, 110.7, 132.4, 134.3, 141.3, 153.8; IR (thin film) ν 2955(s), 2931(s), 2884(s), 2858(s), 1818(s), 1606(w), 1463(m), 1386(m), 1254(m), 1161(s), 1101(s), 1074(s); $[\alpha]^{22}_D$ = -34 (*c* 1.4, CH_2Cl_2); HRMS (ESI) calculated for $C_{64}H_{124}NaO_{16}Si_4$ $[MNa]^+$: *m*/*z* 1283.7864, found: *m*/*z* 1283.7857



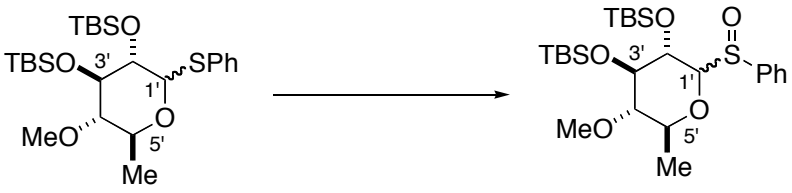
Pentaene 15. To a solution of diene **12** (164 mg, 0.130 mmol) and tetraene **3** (80.0 mg, 0.287 mmol) in CH_2Cl_2 (2.00 mL) was added Grubbs second generation catalyst[2] ($Cl_2(PCy_3)(IMes)Ru=CHPh$) (10.0 mg, 0.0117 mmol). The homogeneous solution was allowed to stand, under an argon atmosphere, at rt for 2.5 h. The solution was then

stirred in the air for 2 h before being evaporated. The residual dark oil was purified flash chromatography, eluting with 1:3 EtOAc/hexanes, affording 75.5 mg (46%) of recovered diene **12** (first eluted) and 77.6 mg (39%) of pentaene **15** as colorless oils. The recovered diene was recycled as follows: To a solution of diene **12** (75.5 mg, 0.0598 mmol) and tetraene **3** (38.0 mg, 0.136 mmol) in CH_2Cl_2 (1.00 mL) was added Grubbs second generation catalyst[2] ($Cl_2(PCy_3)(IMes)Ru{=}CHPh$) (5.0 mg, 0.0058 mmol). The homogeneous solution was allowed to stand, under an argon atmosphere, at rt for 2.5 h. The solution was then stirred in the air for 2 h before being concentrated. The residual dark oil was purified flash chromatography, eluting with 1:3 EtOAc/hexanes, affording 27.5 mg (14% of initial) of recovered diene **12** and 41.1 mg (21%) of pentaene **15.** Overall 119 mg (60%) of pentaene **15**. An analytical sample of pentaene **15** was obtained after HPLC purification (Gradient elution 10-15% EtOAc in hexanes), the major impurities were not isomers of **15**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.065 (s, 3H), 0.071 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.54-0.63 (band, 6H), 0.86 (d, *J* = 6.5, 3H), 0.882 (s, 9H), 0.888 (s, 9H), 0.891 (s, 9H), 0.96 (t, *J* = 8.0, 9H), 0.98 (d, *J* = 6.5, 3H), 1.04 (d, *J* = 6.5, 3H), 1.24 (d, *J* = 6.0, 3H), 1.25 (d, *J* = 6.0, 3H), 1.30 (t, *J* = 7.0, 3H), 1.28-1.37 (band, 1H), 1.40 (s, 3H), 1.53-1.77 (band, 7H), 1.72 (s, 3H), 1.79 (d, *J* = 1.0, 3H), 1.86 (dd, *J* = 13.0, 4.0, 1H), 1.90-2.00 (band, 3H), 1.96 (s, 3H), 2.02 (d, *J* = 1.0, 3H), 2.08 (m, 1H), 2.30 (m, 1H), 2.39 (ddd, *J* = 12.0, 4.5, 1.5, 1H), 2.69 (dddd, *J* = 14.0, 10.5, 7.0, 7.0, 1H), 3.00 (ddd, *J* = 11.5, 8.0, 5.0, 1H), 3.07-3.18 (band, 2H), 3.22 (s, 3H), 3.29 (s, 3H), 3.30 (s, 3H), 3.32 (d, *J* = 9.5, 1H), 3.36-3.44 (band, 3H), 3.40 (s, 3H), 3.65-3.73 (band, 3H), 3.79 (dm, *J* = 7.5, 1H), 3.85 (dm, *J* = 9.0, 1H), 4.05 (m, 1H), 4.20 (q, *J* = 7.0, 2H), 4.32 (d, *J* = 5.0, 1H), 4.77 (dd, *J* = 10.0, 1.5, 1H), 4.87 (d, *J* = 4.5, 1H), 4.89 (ddd, *J* = 10.5, 5.0, 2.5, 1H), 5.26 (d, *J* = 10.0, 1H), 5.45 (t, *J* = 7.0, 1H), 5.58 (dd, *J* = 15.5, 6.5, 1H), 6.01 (s, 1H), 6.22 (d, *J* = 15.5, 1H), 7.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.84, -4.79, -4.7, -4.34, -4.25, -4.0, 4.9, 6.9, 7.1, 11.6, 12.5, 14.1, 14.3, 16.5, 17.3, 18.0, 18.1, 18.26, 18.32, 18.34, 18.5, 23.4, 24.9, 25.76. 25.79, 26.0, 30.6, 34.7, 35.1, 35.2, 35.7, 39.3, 39.4, 45.1, 48.7, 56.0, 58.4, 59.0, 60.6, 66.4, 69.3, 70.3, 72.5, 73.3, 74.4, 75.2, 75.3, 75.4, 76.8, 77.0, 79.3, 80.7, 81.4, 85.7, 96.7, 100.2, 101.0, 125.9, 127.3, 131.8, 132.6, 133.0, 133.3, 133.7, 136.1, 138.8, 143.6, 153.9, 169.1; IR (thin film) ν 3502(br), 2955(s), 2931(s), 2857(s), 1817(s), 1704(m), 1462(m), 1386(m), 1253(s), 1101(s), 1074(s); $[\alpha]^{25}_D$ = +7.0 (*c* 0.98, CH_2Cl_2); HRMS (ESI) calculated for $C_{79}H_{146}NaO_{19}Si_4$ $[MNa]^+$: *m/z* 1533.9433, found: *m/z* 1533.9430.

8 **9**

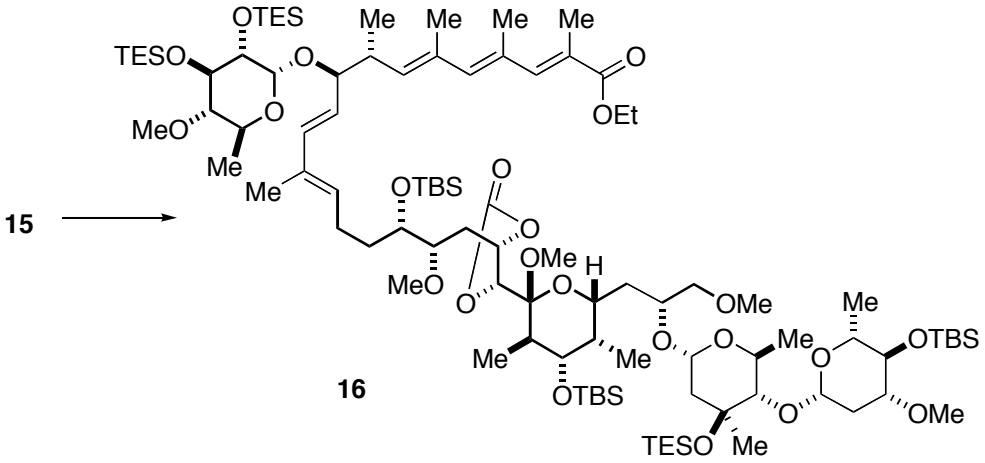
Thioether 9. To a solution of hemiacetal **8** (295 mg, 0.725 mmol) in CH_2Cl_2 (5 mL) was added ZnI_2 (695 mg, 2.18 mmol), *n*-Bu_4NI (268 mg, 0.726 mmol), and $PhSSiMe_3$ (0.690 mL, 3.64 mmol) and the heterogeneous mixture was stirred at rt for 2 h. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added and the resulting mixture was shaken then the layers were separated. The aqueous solution was extracted with CH_2Cl_2 (3x) and the

combined organic solution was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography, eluting with 3:97 EtOAc/hexanes, to afford 219 mg (61%) of a mixture of isomers (~5:1 α:β) as a colorless oil. Known thioether **9**[3] is the major component. This mixture was used for the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.096 (s, 3H), 0.101 (s, 1.2H), 0.12 (s, 3H), 0.124 (s, 0.6H), 0.13 (s, 3H), 0.16 (s, 3H), 0.27 (s, 0.6H), 0.94 (s, 9H), 0.95 (s, 9H), 1.01 (s, 1.8H), 1.12 (d, *J* = 6.0, 0.6H), 1.27 (d, *J* = 6.5, 3H), 2.74 (dd, *J* = 9.5, 8.5, 1H), 3.43 (s, 0.6H), 3.50 (s, 3H), 3.61 (m, 0.45H), 3.73 (dd, *J* = 8.5, 8.5, 1H), 3.84 (dd, *J* = 9.0, 5.5, 1H), 4.07 (m, 0.2H), 4.21 (m, 1H), 4.36 (m, 0.2H), 4.98 (m, 0.2H), 5.42 (d, *J* = 5.5, 1H), 7.17-7.34 (band, 3.6H), 7.44 (d, *J* = 7.0, 2H), 7.60 (d, *J* = 7.5, 1.2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.3, -4.1, -3.9 (minor), -3.6, -3.5 (minor), -3.3, 18.0, 18.2, 18.3, 18.4 (minor), 26.1 (minor), 26.29, 26.30, 59.9 (minor), 61.1, 61.2 (minor), 68.0, 69.2 (minor), 74.2, 74.4 (minor), 74.5, 78.3 (minor), 85.0 (minor), 87.1, 89.3, 126.8, 126.9 (minor), 127.1 (minor), 128.80, 128.82 (minor), 128.9 (minor), 131.3 (minor), 131.4 (minor), 131.6, 135.1, 135.2 (minor).



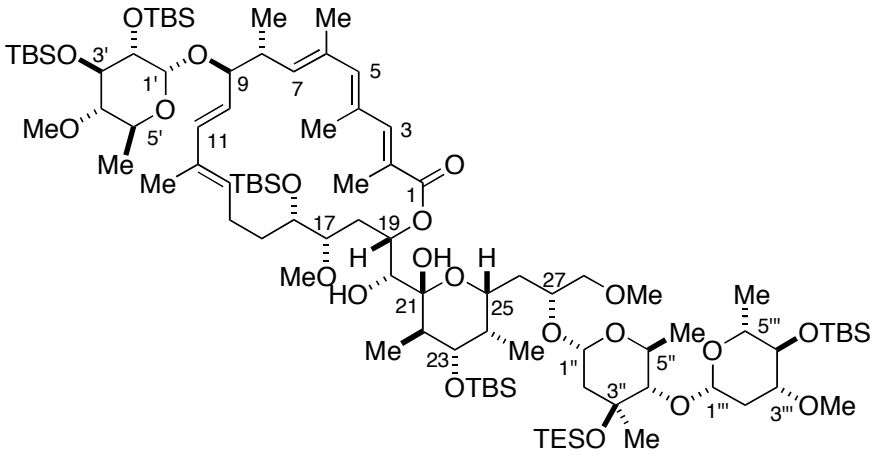
9 **5**

Sulfoxide 5. A solution of thioether **9** (an isomeric mixture)(152 mg, 0.305 mmol) in CH_2Cl_2 (4 mL) was cooled to -78 ˚C. Solid *m*-CPBA (75%) (120 mg, 0.575 mmol) was added in one portion to the stirring solution. After 45 min more *m*-CPBA (200 mg, 0.958 mmol) was added. After a further 15 min saturated Na_2SO_3 solution (1.00 mL) was added dropwise and the vigorously stirring solution was allowed to warm to rt. The mixture was diluted with H_2O, saturated $NaHCO_3$ solution, and CH_2Cl_2. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2x). The combined organic solution was dried (Na_2SO_4) and evaporated. The residual oil was purified by flash chromatography, eluting with 1:9 EtOAc/hexanes, to provide 113 mg (72%) of sulfoxide **5** as a mixture of isomers (~2.5:1) as a colorless oil. This mixture was used for the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (band, 6H), 0.14 (s, 1.2H), 0.17 (band, 2.4H), 0.20 (s, 4.2H), 0.30 (s, 3H), 0.84 (s, 9H), 0.94 (s, 3.6H), 0.99 (s, 9H), 1.01 (s, 3.6H), 1.06 (d, *J* = 8.0, 1.2 H), 1.22 (d, *J* = 8.0, 3H), 2.66 (dd, *J* = 11.5, 11.0, 0.4H), 2.87 (d, *J* = 10.5, 1H), 3.40 (s, 3H), 3.45 (s, 1.2H), 4.04 (m, 1H), 4.06 (m, 0.4H), 4.22 (dd, *J* = 7.0, 7.0, 1H), 4.26 (dd, *J* = 8.0, 7.5, 0.4H), 4.36 (d, *J* = 4.5, 1H), 4.41 (dd, *J* = 4.5, 4.0, 1H), 4.56 (dd, *J* = 11.0, 10.5, 0.4H), 4.74 (dddd, *J* = 15.5, 11.5, 7.5, 7.5, 0.4H), 7.47-7.61 (band, 4.2H), 7.67-7.72 (band, 2.8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.2, -4.7, -4.4, -4.1, -4.0 (minor), -3.6 (minor), -3.1 (minor), 17.8, 18.0 (minor), 18.2, 18.3 (minor), 18.6 (minor), 19.4, 25.7, 25.8, 26.3 (minor), 26.4 (minor), 57.7, 60.8 (minor), 69.0, 70.6 (minor), 71.2, 73.4 (minor), 74.1, 74.7 (minor), 86.6 (minor), 87.2, 94.5, 95.7 (minor), 124.8 (minor), 125.5, 128.6, 128.9 (minor), 130.5 (minor), 130.8, 141.4 (minor), 142.7.



Trisaccharide 16. A mixture of sulfoxide **5** (18.0 mg, 0.0349 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (30.0 mg, 0.146 mmol), and freshly activated 4 Å molecular sieve powder (~300 mg) in Et_2O (1 mL) was stirred at rt for 0.5 h and then cooled to -78 °C. Freshly distilled trifluoromethanesulfonic anhydride (0.0055 mL, 0.033 mmol) was added dropwise. After stirring the mixture at -78 °C for 10 min (solution brown colored), a mixture of alcohol **15** (41.1 mg, 0.0271 mmol) and 4 Å molecular sieve powder (~100 mg) was added (via syringe) as a suspension in Et_2O (0.50 mL + 2 x 0.3 rinses). After stirring at -78 °C for 1.5 h, the mixture was allowed to warm to 0 °C and saturated $NaHCO_3$, H_2O, CH_2Cl_2, and Celite were added. The resulting mixture was filtered through a pad of Celite washing with CH_2Cl_2. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (3x). The combined organic solution was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography, eluting with 1:9 EtOAc/hexanes, to give 20.4 mg (40%) of trisaccharide **16** as a colorless oil. An analytical sample was obtained after HPLC purification (gradient elution 5_12% EtOAc in hexanes), the anomer ratio was estimated to be >10:1 α:β. **16:** ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 6H), 0.07 (s, 3H), 0.081 (s, 3H), 0.086 (s, 3H), 0.089 (s, 3H), 0.11 (s, 3H), 0.55-0.64 (band, 6H), 0.86 (d, *J* = 7.0, 3H), 0.88-0.90 (band, 27H), 0.90 (s, 9H), 0.92 (s, 9H), 0.97 (t, *J* = 7.5, 9H), 0.98 (d, *J* = 7.0, 3H), 1.02 (d, *J* = 6.5, 3H), 1.24 (d, *J* = 6.0, 3H), 1.25 (d, *J* = 6.0, 3H), 1.28 (d, *J* = 6.5, 3H), 1.31 (t, *J* = 7.0, 3H), 1.40 (s, 3H), 1.53-1.78 (band, 4H), 1.69 (s, 3H), 1.82 (s, 3H), 1.87 (dd, *J* = 13.5, 4.5, 1H), 1.91-2.02 (band, 3H), 1.96 (d, *J* = 0.5, 3H), 2.02 (d, *J* = 1.0, 3H), 2.09 (m, 1H), 2.23-2.33 (m, 1H), 2.40 (ddd, *J* = 12.5, 4.5, 1.5, 1H), 2.64 (t, *J* = 9.0, 1H), 2.77 (m, 1H), 3.00 (ddd, *J* = 12.0, 7.0, 4.5, 1H), 3.10 (dd, *J* = 8.0, 1H), 3.11-3.18 (m, 1H), 3.23 (s, 3H), 3.29 (s, 3H), 3.30 (s, 3H), 3.33 (d, *J* = 10.0, 1H), 3.36-3.42 (band, 3H), 3.41 (s, 3H), 3.46-3.50 (m, 1H), 3.48 (s, 3H), 3.61-3.74 (band, 4H), 3.79 (dm, *J* = 7.5, 1H), 3.84 (t, *J* = 9.0, 2H), 3.87 (dd, *J* = 9.0, 5.5, 1H), 4.21 (q, *J* = 7.0, 2H), 4.33 (d, *J* = 5.0, 1H), 4.71 (d, *J* = 3.0, 1H), 4.77 (dd, *J* = 10.0, 2.0, 1H), 4.87 (d, *J* = 4.0, 1H), 4.90 (ddd, *J* = 10.5, 4.5, 2.5, 1H), 5.22 (d, *J* = 10.0, 1H), 5.31 (dd, *J* = 15.5, 9.0, 1H), 5.43 (br. t, *J* = 7.0, 1H), 5.99 (s, 1H), 6.17 (d, *J* = 15.5, 1H), 7.15 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.83, -4.78, -4.65, -4.31, -4.24, -4.21, -4.1, -4.0, -3.7, -3.1, 4.9, 6.9, 7.1, 11.6, 12.5, 14.1, 14.3, 17.3, 17.6, 17.96, 18.04, 18.07, 18.12, 18.33, 18.36, 18.38, 18.43, 18.5, 23.4, 24.8, 25.77, 25.80, 26.0, 26.3, 26.4, 30.4, 34.6, 35.2, 35.3, 35.7, 38.0, 39.3,

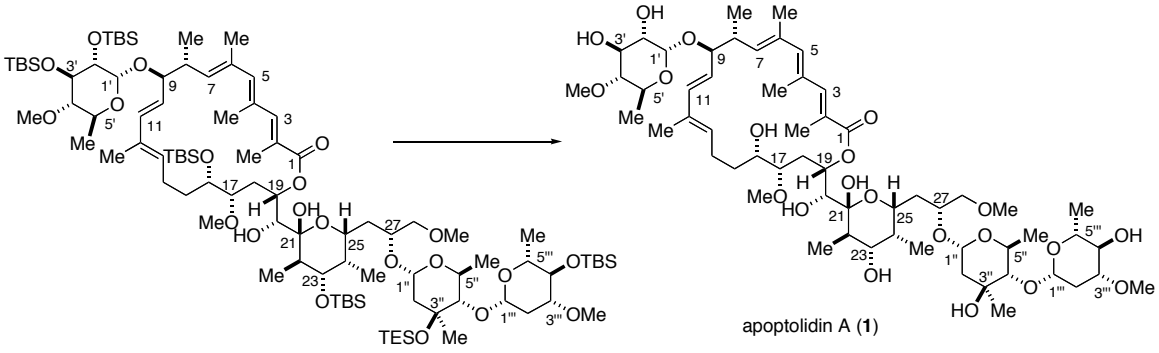
45.1, 48.8, 56.0, 58.4, 59.0, 60.6, 61.2, 66.4, 67.2, 69.3, 70.1, 72.5, 73.3, 73.7, 74.2, 74.4, 75.2, 75.3, 75.4, 76.8, 79.3, 79.9, 80.8, 81.4, 85.7, 87.5, 94.4, 96.7, 100.2, 101.0, 123.3, 125.7, 131.5, 132.5, 133.0, 133.2, 134.3, 139.1, 140.3, 143.9, 153.9, 169.2; IR (thin film) ν 2955(s), 2931(s), 2857(s), 1818(s), 1705(s), 1615(w), 1462(s), 1381 (s), 1253(s), 1101(s); $[\alpha]^{24}_{D}$ = -27 (*c* 0.23, CH_2Cl_2); MS (ESI) calculated for $C_{98}H_{186}NaO_{23}Si_6$ $[MNa]^+$: *m*/*z* 1922.2, found: *m*/*z* 1922.8

16 

Macrocyclic Lactone . To a solution of ester **16** (14.2 mg, 0.00747 mmol) in a mixture of THF (0.60 mL) and MeOH (0.20 mL) was added LiOH-H_2O (0.10 mL of a 1M solution in H_2O, 0.1 mmol). The solution was stirred vigorously at 10 °C for 7 d before being diluted with NH_4Cl solution and then extracted with EtOAc (5x). The combined organic solution was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography, eluting with 1:4 EtOAc/hexanes to give 7.8 mg (57%) of the carboxylic acid as a colorless oil. The carboxylic acid was not further characterized.

To a THF solution (1.00 mL) of the carboxylic acid from above (7.8 mg, 0.00422 mmol) and Et_3N (0.022 mL, 0.16 mmol) was added 2,4,6-trichlorobenzoyl chloride (0.016 mL, 0.10 mmol), dropwise over 5 min. The cloudy solution was stirred at rt for 15 h. The reaction mixture was diluted with toluene (1.00 mL) and the resulting cloudy solution was added, using a syringe pump, over 1.5 h [followed by two toluene rinses (0.50 mL), added over 20 min and 10 min], to a stirring solution of DMAP (100 mg, 0.819 mmol) in toluene (300 mL) at rt. After stirring for 24 h, the solution was concentrated to 100 mL and NH_4Cl solution, H_2O, and EtOAc were added. The mixture was shaken and then separated. The aqueous solution was extracted with EtOAc (2x), and the combined organic solution was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography, eluting with 13:87 EtOAc/hexanes, to give 5.7 mg (74%) of the macrolactone as a colorless oil. An analytical sample was obtained after HPLC purification (gradient elution 9-15% EtOAc in hexanes). ^{1}H NMR (500 MHz, C_6D_6) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.10 (s, 6H), 0.12 (s, 3H), 0.18 (s, 3H), 0.21 (s, 3H), 0.23 (s, 3H), 0.28 (s, 3H), 0.35 (s, 3H), 0.56-0.63 (band, 6H), 0.967 (s, 9H), 0.972 (s, 9H), 0.96-

1.03 (band, 6H), 1.00 (s, 9H), 1.06 (s, 9H), 1.12 (s, 9H), 1.21 (d, J = 6.5, 3H), 1.27 (d, J = 7.0, 3H), 1.25-1.37 (band), 1.41 (s, 3H), 1.42 (s, 3H), 1.48 (d, J = 6.5, 3H), 1.57 (s, 3H), 1.71 (d, J = 6.5, 3H), 1.748 (s, 3H), 1.752 (s, 3H), 1.81 (s, 3H), 2.12 (s, 3H), 1.58-2.21 (band, 9H), 2.27 (m, 1H), 2.58-2.65 (band,1H), 2.70 (t, J = 9.0, 1H), 2.99 (br. t, J = 9.0, 1H), 3.115 (s, 3H), 3.117 (s, 3H), 3.12-3.15 (m, 1H), 3.20 (m, 1H), 3.28-3.36 (m, 1H), 3.26 (s, 3H), 3.36 (s, 3H), 3.38-3.45 (band, 2H), 3.48 (dd, J = 10.0, 5.5, 1H), 3.54 (br. t, J = 9.5, 1H), 3.56 (s, 3H), 3.71 (dd, J = 9.0, 3.5, 1H), 3.76 (d, J = 9.5, 1H), 3.90 (m, 1H), 3.95 (m, 1H), 4.00 (t, J = 9.0, 1H), 4.03-4.13 (band, 4H), 4.23 (t, J = 9.0, 1H), 4.96-5.03 (band, 2H), 5.10-5.15 (band, 2H), 5.34 (dd, J = 16.0, 1H), 5.45 (br. t, J = 8.0, 1H), 6.01 (dd, J = 10.0, 8.0, 1H), 6.13 (s, 1H), 6.15 (d, J = 16.0, 1H), 7.49 (s, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ -4.2, -4.0, -3.6, -3.44, -3.40, -3.11, -3.09, -3.0, -2.9, -2.0, 6.4, 7.9, 8.0, 12.5, 14.9, 16.8, 18.3, 18.92, 18.98, 19.02, 19.1, 19.2, 19.5, 19.6, 24.5, 26.2, 26.7, 27.0, 27.3, 27.4, 30.8, 36.3, 36.8, 37.0, 37.7, 38.8, 39.3, 40.8, 46.4, 48.5, 56.3, 59.4, 61.6, 61.9, 67.5, 68.4, 70.2, 71.6, 73.7, 74.1, 75.0, 75.4, 75.6, 76.2, 76.5, 76.8, 77.3, 78.1, 82.4, 82.8, 83.6, 86.1, 88.7, 96.3, 97.7, 101.7, 102.9, 125.2, 126.3, 132.5, 133.1, 133.5, 133.8, 141.2, 141.5, 145.0, 145.8, 170.0; IR (thin film) ν 2955(s), 2930(s), 2857(s), 1702 (s), 1604(w), 1462(s), 1386(s), 1252(s), 1102(s); $[\alpha]^{23}_{D}$ = -15 (*c* 0.15, CH_2Cl_2); HRMS (ESI) calculated for $C_{95}H_{182}NaO_{21}Si_6$ $[MNa]^+$: *m/z* 1850.1687, found: *m/z* 1850.1692.



Apoptolidin A. In a polypropylene vial, a solution of the macrolactone from the previous reaction (4.5 mg, 0.0024 mmol) in acetonitrile (0.30 mL) and THF (0.10 mL) was cooled to -25 °C. A solution of H_2SiF_6 (20-25 wt.% in H_2O)(3 drops from a 22G needle) was added to the lactone solution. The reaction mixture was stirred at -9 °C for 95 h. The reaction mixture was cooled to -25 °C and $NaHCO_3$ (sat. aq) solution (2 mL) added dropwise. After warming to room temperature the mixture was extracted with EtOAc (5x1 mL). The combined organic solution was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography, eluting with 9:1 CH_2Cl_2/MeOH, affording 1.0 mg (30%) of apoptolidin (~80% purity (by ^{1}H NMR)). ^{1}H NMR (500 MHz, CD_3OD) δ 0.89 (d, J = 7.0, 3H), 1.02 (*d*, J = 6.5, 3H), 1.13 (*d*, J = 6.5, 3H), 1.26 (d, J = 6.5, 3H), 1.27 (d, J = 6.0, 3H), 1.32 (s, 3H), 1.33-1.52 (band, 3H), 1.55-1.62 (m, 1H), 1.68 (s, 3H), 1.70-1.83 (band, 3H), 1.91-1.97 (m, 1H), 1.94 (s, 3H), 2.0-2.19 (band, 3H), 2.11 (s, 3H), 2.18 (s, 3H), 2.41-2.52 (band, 2H), 2.68-2.80 (band, 2H), 2.72 (t, J = 9.0, 1H), 2.97 (t, J = 9.0, 1H), 3.14-3.24 (band, 2H), 3.27 (s, 3H), 3.28-3.33 (region obscured by CD_2HOD peak), 3.33-3.50 (band, 4H), 3.36 (s, 3H), 3.42 (s, 3H), 3.53 (m,

1H), 3.58 (s, 3H), 3.63-3.77 (band, 4H), 3.83 (t, J = 9.0, 1H), 3.95 (m, 1H), 4.80-4.86 (band, 2H), 4.88 (water signal), 4.94 (d, J = 4.0, 1H), 5.20-5.26 (band, 2H), 5.29 (d, J = 11.0, 1H), 5.68 (dd, J = 7.0, 6.0, 1H), 6.18 (d, J = 16.0, 1H), 6.20 (s, 1H), 7.39 (s, 1H). HRMS (ESI) calculated for $C_{58}H_{96}NaO_{21}$ $[MNa]^+$: m/z 1151.6342, found: m/z. 1151.6355. HPLC co-injection of synthetic and natural apoptolidin A showed a single component.

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